Supporting Information

Catalytic Enantioselective Electrocyclization-Mediated Cascades

Eleanor E. Maciver, Peter C. Knipe, Andrew P. Cridland, Amber L. Thompson and Martin D. Smith

Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford, OX1 3TA, UK

Fax: 44 (0) 1865 285002; Tel: 44 (0) 1865 285103; E-mail: martin.smith@chem.ox.ac.uk

1. General Information

All reactions were carried out under a positive pressure of argon in washed and oven-dried glassware unless otherwise stated.

1.1 Solvents and Reagents

Tetrahydrofuran, dichloromethane, diethyl ether, methanol and toluene were purified by pressurized filtration through activated silica columns, employing the method of Grubbs *et. al.*[1] Other solvents were used as supplied (analytical or HPLC grade) without prior purification. Petroleum ether refers to the fraction of petroleum ether boiling in the range 40-60 °C. Where mixtures of solvents are specified, the stated ratios are volume:volume. Triethylamine was distilled over calcium hydride and stored over potassium hydroxide under an inert argon atmosphere.

Unless otherwise indicated, all aqueous solutions used were saturated.

Reagents were used directly as supplied by major chemical suppliers, or following purification procedures described by Perrin and Armarego.[2]

1.2 Chromatography

Flash column chromatography was carried out using VWR silica gel (40 – 63 μm particle size).

Analytical thin-layer chromatography was carried out on Merck Kieselgel 60 F_{254} 0.25 mm precoated aluminium plates. Visualization was carried out by viewing under ultra-violet radiation (254 nm) and appropriate heating with ammonium molybdate or ninhydrin. The ammonium molybdate solution was made by dissolving ammonium molybdate (5 g) and ceric sulfate (0.2 g) in 5 % aqueous sulphuric acid (100 mL). The ninhydrin solution was made by dissolving ninhydrin (0.3 g) in *n*-butanol (100 mL) and adding acetic acid (3 mL).

1.3 NMR Spectroscopy

NMR spectra were recorded on a Bruker AV400 (^{1}H: 400 MHz, ^{13}C: 101 MHz), Bruker Avance Cryo 500 (^{1}H: 500 MHz, ^{13}C: 126 MHz), Bruker AVB500 (^{1}H: 500 MHz, ^{13}C: 126 MHz) or Bruker DPX300 (^{1}H: 300 MHz, ^{13}C: 75 MHz) spectrometer. Chemical shifts are quoted in ppm, are referenced to the residual non-deuterated solvent peak and are quoted based on appearance rather than interpretation. ^{1}H spectra are reported as follows: δ_H (*spectrometer frequency*, *solvent*): *ppm* (*number of protons, multiplicity, J-coupling constant(s), assignment*). ^{13}C spectra are reported as

follows: δ_C (*spectrometer frequency*, *solvent*): *ppm* (*assignment*). Spectral assignment was aided by the results of DEPT, COSY, HMBC and HSQC experiments where appropriate.

1.4 IR Spectroscopy

IR spectra were recored on a Bruker Tensor 27 FTIR spectrometer equipped with an attenuated total reflectance attachment with internal calibration. Absorbtion maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}).

1.5 Mass Spectrometry

Mass spectra were recorded on a Micromass LCT Premier spectrometer under conditions of electrospray ionization (ESI). Accurate masses (HRMS) were recorded on Bruker MicroTOF and Micromass GCT spectrometers under conditions of ESI and field ionization (FI) respectively. Values are reported as a ration of mass to charge in Daltons.

1.6 Polarimetry

Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a path length of 1 dm.

1.7 Melting Points

All melting points were measured on a Gallenkamp MF-370 melting point apparatus and are uncorrected. Solvents are reported in parentheses where solids were purified by recrystallization.

1.7 HPLC

Analytical chiral HPLC was performed on a Dionex Ultimate 3000 HPLC system comprising a Dionex LPG-3400A pump, WPS-3000SL autosampler, TCC-3000SD column compartment, DAD-3000 diode array detector and the appropriate Daicel Chiralpak column.

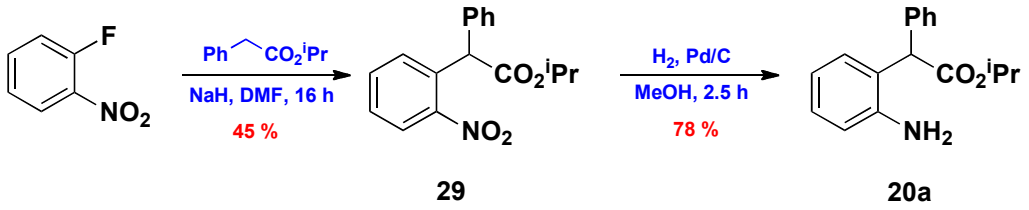
1.8 Naming and Numbering of Compounds

Where given, systematic compound names are those generated by ChemBioDraw Ultra 12.0 following IUPAC conventions. The numbering of atoms for spectral assignment purposes is arbitrary and not necessarily consistent with the IUPAC name.

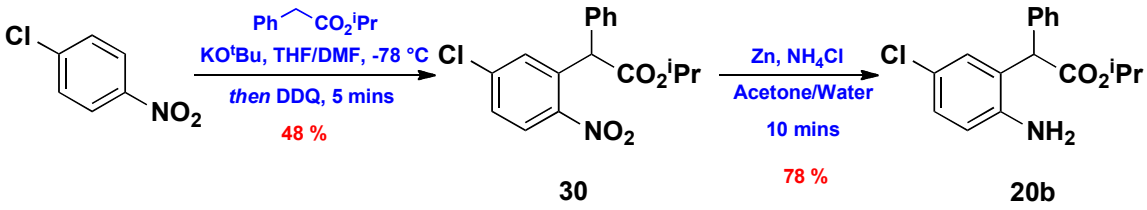
2. General Schemes for Substrate Synthesis

2.1 Anilines

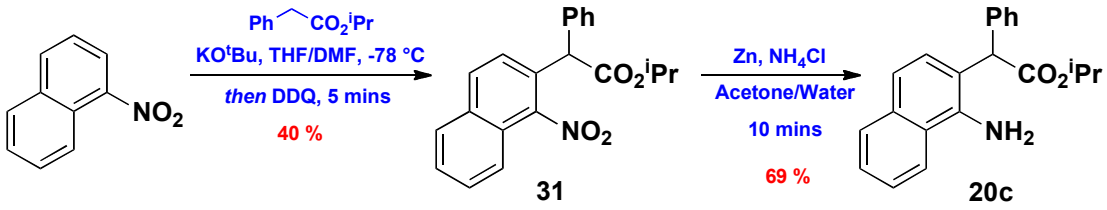
Malonyl anilines **1** and **28** were prepared as previously reported.[3] α-Phenyl ester anilines **20a**, **20b** and **20c** were prepared by nucleophilic aromatic substitution or by the vicarious nucleophilic substitution (VNS) method of Mąkosza *et. al*,[4] followed by reduction of the aromatic nitro group:



Scheme S 1 Synthesis of aniline *via* S_NAr and H_2 reduction.



Scheme S 2 Synthesis of chloroaniline *via* VNS and zinc reduction.

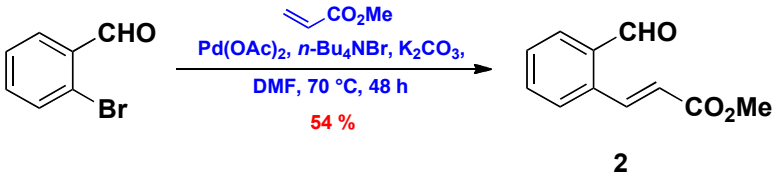


Scheme S 3 Synthesis of naphthalen-1-amine *via* VNS and zinc reduction.

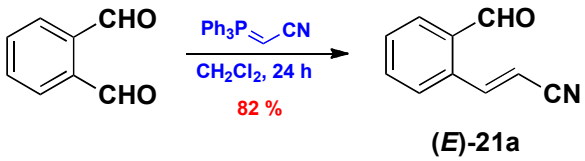
2.2 Aldehydes

2.2.1 Cinnamyl Aldehydes

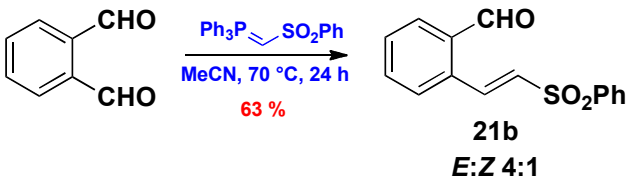
Cinnamyl aldehydes **2**, **21a** and **21b** were prepared via the Heck[6] and Wittig procedures outlined:



Scheme S 4 Synthesis of cinnamic ester aldehyde *via* Heck reaction.



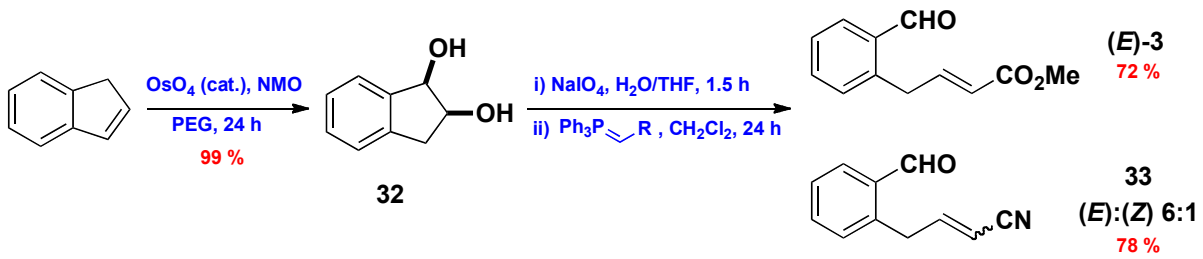
Scheme S 5 Synthesis of cinnamonitrile aldehyde *via* Wittig reaction.



Scheme S 6 Synthesis of sulfonyl aldehyde *via* Wittig reaction.

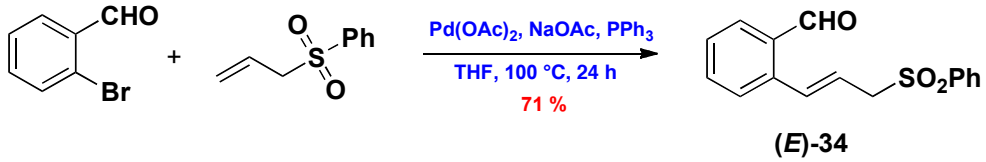
2.2.2 Homocinnamyl Aldehydes

Homocinnamyl aldehydes **3** and **33** were prepared *via* a tandem oxidative cleavage-Wittig protocol[11] from *cis*-indane-1,2-diol **32**, formed by dihydroxylation of indene:[9]



Scheme S 7 Synthesis of homocinnamyl aldehydes *via* oxidative cleavage-Wittig protocol

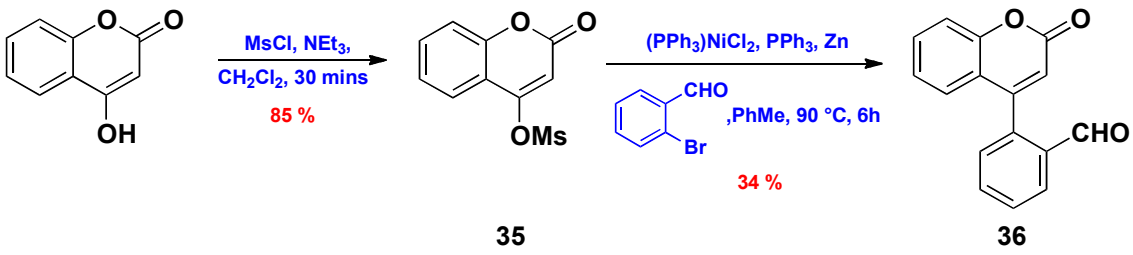
Aldehyde **34** was prepared from 2-bromobenzaldehyde in a Heck procedure reported to result in the double bond lying in conjugation with the sulfone.[12] In our hands, however, only the compound with the double bond in the styrenic position was isolated:



Scheme S 8 Synthesis of sulfonyl homostyryl aldehyde *via* Heck reaction.

2.2.3 o-(4-Coumaryl)benzaldehyde

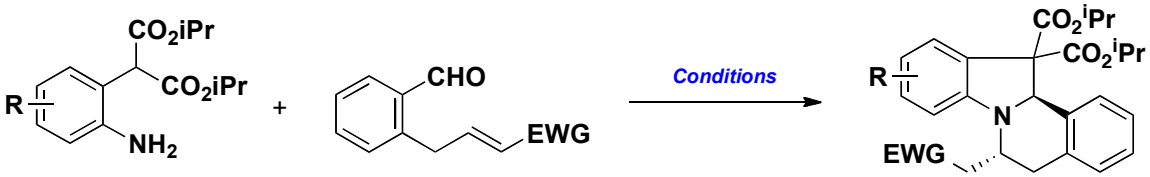
The coumaryl aldehyde **36** was formed by mesylation of 4-hydroxycoumarin,[15] and subsequent reductive cross-coupling with 2-bromobenzaldehyde:[16]



Scheme S 9 Synthesis of coumaryl aldehyde *via* reductive cross-coupling.

3 Experimental Procedures

3.1 General Procedures for the Cascade Cyclization of Malonate Substrates



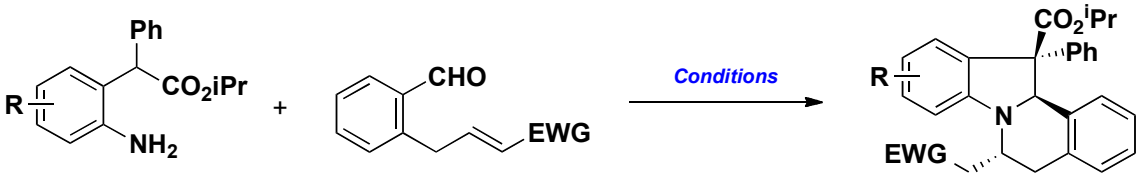
General Procedure 1 *(asymmetric).* The appropriate aniline (1.0 eq.), aldehyde (1.0 eq.) and magnesium sulfate (5.0 eq.) were stirred for 16 h at RT in toluene (0.1 M concentration of aniline). The resulting mixture was filtered and concentrated *in vacuo.* The imine was redissolved in toluene (0.05 M concentration of imine), (8*S*, 9*R*)-*N*-benzylcinchonidinium chloride **11** (0.1 eq.) was added and the solution was stirred at -15 ˚C for 30 mins. Pre-cooled potassium carbonate (33 % aq., 0.25 mL / mL toluene) was added to the reaction and stirred for 16 h before quenching with ammonium chloride (sat. aq., 50 mL/mmol imine) and extracting with dichloromethane (3 x 50 mL/mmol imine). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography.

General Procedure 2 *(asymmetric).* The appropriate aniline (1.0 eq.), aldehyde (1.0 eq.) and magnesium sulfate (5.0 eq.) were stirred for 16 h at RT in toluene (0.1 M concentration of aniline). The resulting mixture was filtered and concentrated *in vacuo*. The imine was redissolved in toluene (0.05 M concentration of imine), (8*S*, 9*R*)-*N*-benzylcinchonidinium chloride **11** (0.1 eq.) was added and the mixture was cooled to -78 ˚C for 30 mins before adding anhydrous freshly-ground potassium hydroxide (10 eq.). The reaction was stirred at -78 ˚C for 16 h and then allowed to warm to RT for 6 h before quenching with ammonium chloride (sat. aq., 50 mL/mmol imine) and extracting with dichloromethane (3 x 50 mL/mmol imine). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography.

General Procedure 3 *(racemic).* The appropriate aniline (1.0 eq.), aldehyde (1.0 eq.) and magnesium sulfate (5.0 eq.) were stirred for 16 h at RT in toluene (0.1 M concentration of aniline). The resulting mixture was filtered and concentrated *in vacuo*. The imine was redissolved in toluene (0.05 M concentration of imine), tetrabutylammonium chloride (0.1 eq.) and $CsOH{\cdot}H_2O$ (10.0 eq.) were added and the reaction stirred for 24 h. The mixture was then diluted with ammonium chloride (sat. aq., 50 mL/mmol imine) and extracted with dichloromethane (3 x 50 mL/mmol imine). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography.

General Procedure 4 *(racemic).* The appropriate aniline (1.0 eq.), aldehyde (1.0 eq.) and magnesium sulfate (5.0 eq.) were stirred for 16 h at RT in toluene (0.1 M concentration of aniline). The resulting mixture was filtered and concentrated *in vacuo*. The imine was redissolved in toluene (0.05 M concentration of imine), tetrabutylammonium chloride (0.1 eq.) and anhydrous freshly-ground potassium hydroxide (10 eq.) were added and the reaction stirred for 16 h. The mixture was then quenched with ammonium chloride (sat. aq., 50 mL/mmol imine) and extracted with dichloromethane (3 x 50 mL/mmol imine). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography.

3.2 General Procedures for the Cascade Cyclization of α-Phenyl Ester Substrates



General Procedure 5 *(racemic).* The appropriate aniline (1.0 eq.), aldehyde (1.0 eq.) and magnesium sulfate (5.0 eq.) were stirred for 16 h at RT in toluene (0.1 M concentration of aniline). The resulting mixture was filtered over Celite® and concentrated *in vacuo*. The crude imine was then redissolved in toluene (0.1 M concentration of imine), cooled to ***T*** °C and (8*S*,9*R*)-*N*-benzylcinchonidinium chloride **11** (0.1 eq.) and anhydrous freshly-ground potassium hydroxide (10 eq.) added. After 16 h the mixture was allowed to warm to RT and stirred for a further 6 h. The reaction was quenched with ammonium chloride (sat. aq., 50 mL/mmol imine) and diluted with dichloromethane (50 mL/mmol imine). The aqueous layer was extracted with dichloromethane (3 x 50 mL/mmol imine), and the combined organic extracts dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography.

General Procedure 6 *(racemic).* The appropriate aniline (1.0 eq.), aldehyde (1.0 eq.) and magnesium sulfate (5.0 eq.) were stirred for 16 h at RT in toluene (0.1 M concentration of aniline). The resulting mixture was filtered over Celite® and concentrated *in vacuo*. The crude imine was then redissolved in tetrahydrofuran (0.1 M concentration of imine) and potassium *tert*-butoxide (2.0 eq.) was added to the stirred solution at RT. After 45 mins the reaction was quenched with ammonium chloride (sat. aq., 50 mL/mmol imine) and diluted with dichloromethane (50 mL/mmol imine). The aqueous layer was extracted with dichloromethane (3 x 50 mL/mmol imine), and the combined organic

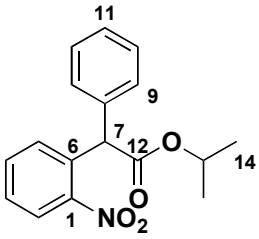
extracts dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography to afford the racemic cyclized product.*

* *Note that diastereomeric products formed under racemic reaction conditions that were not formed under asymmetric conditions were not spectroscopically assigned.*

3.3 Full Procedures and Characterization Data

3.3.1 Synthesis of Anilines

Iso-propyl 2-(2-nitrophenyl)-2-phenylacetate (**29**)



Sodium hydride (60 % dispersion in mineral oil, 1.10 g, 27.5 mmol) was added in three portions over 30 mins to a stirred solution of *iso*-propyl 2-phenylacetate (5.0 g, 28 mmol) in *N,N*-dimethylformamide (50 mL) at 0 °C. After a further 30 mins 2-fluoronitrobenzene (1.95 mL, 18.5 mmol) was added dropwise and the solution allowed to rise to RT. After 16 h the reaction was diluted with diethyl ether (200 mL), quenched with ammonium chloride (sat. aq., 50 mL) and the organic phase washed with 10 % aqueous magnesium sulfate solution (3 x 50 mL). The aqueous washes were back-extracted once with diethyl ether (50 mL), and the combined organic layers dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography (silica gel, petroleum ether : ethyl acetate, 50 : 1) and subsequent recrystallization (petroleum ether/ethyl acetate) to afford **29** (2.48 g, 45 %) as a white crystalline solid. The data obtained is consistent with that reported in the literature.4

δH (400 MHz, $CDCl_3$): 8.03 (1H, dd, *J* 8.0, 1.4, H2), 7.50 (1H, td, *J* 7.6, 1.4, H4), 7.44-7.32 (4H, m, H3, H10, H11), 7.27 (2H, d, *J* 6.6, H9), 7.13 (1H, dd, *J* 7.8, 1.0, H5), 5.63 (1H, s, H7), 5.11 (1H, septet, *J* 6.3, H13), 1.30 (3H, d, *J* 6.1, H14), 1.18 (3H, d, *J* 6.3 , H14').

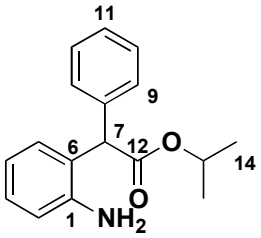
δC (101 MHz, $CDCl_3$): 170.8 (C12), 148.9 (C1), 136.8 (C8), 134.2 (C6), 133.1 (C4), 131.6 (C5), 129.2 (C10), 129.0 (C9), 128.1 (C3), 127.8 (C11), 124.8 (C2), 69.2 (C13), 53.4 (C7), 21.7 (C14), 21.4 (C14').

ν_{max} (neat): 2980, 2360, 1727 (C=O), 1524 (NO_2), 1453 cm^{-1}.

HRMS (ES+): found 322.1049; $C_{17}H_{17}NO_4Na$, $[M+Na]^+$ requires 322.1050.

MP: 69-74 °C (petroleum ether/ethyl acetate).

Iso-propyl 2-(2-aminophenyl)-2-phenylacetate (**20a**)



A RT suspension of nitroarene **29** (3.57 g, 11.9 mmol) and palladium on activated carbon (350 mg) in degassed methanol (35 mL) was stirred vigorously under an atmosphere of hydrogen (balloon pressure). After 2.5 h the reaction mixture was filtered over Celite® and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, petroleum ether : diethyl ether, 10 : 1) and subsequent recrystallization (diethyl ether/petroleum ether) to afford aniline **20a** (2.50 g, 78 %) as an off-white crystalline solid.

δH (300 MHz, $CDCl_3$): 7.29-7.15 (5H, m, H9, H10 & H11), 7.08-7.00 (2H, m, H3 & H5), 6.70 (1H, td, *J* 7.5, 1.1, H4), 6.61 (1H, d, *J* 7.9, H2), 5.03 (1H, septet, *J* 6.3, H13), 4.90 (1H, s, H7), 3.59 (2H, br s, NH_2), 1.17 (6H, t, *J* 6.7, H14).

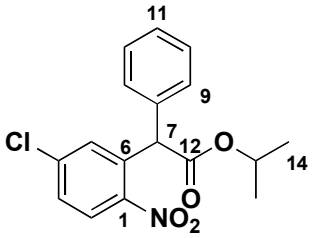
δC (75 MHz, $CDCl_3$): 172.1 (C12), 144.6 (C1), 137.1 (C8), 129.3 (C5), 128.8 (C9/C10), 128.6 (C9/C10), 128.4 (C3/C11), 127.4 (C3/C11), 123.5 (C6), 118.9 (C4), 116.8 (C2), 68.8 (C13), 53.5 (C7), 21.8 (C14), 21.7 (C14').

ν_{max} (neat): 3442, 2982, 2935, 1722 (C=O), 1637 (Ar C=C), 1451 cm^{-1}.

HRMS (ES+): found 292.1313; $C_{17}H_{19}NO_2Na$, $[M+Na]^+$ requires 292.1313.

MP: 74-78 °C (diethyl ether/petroleum ether).

Iso-propyl 2-(5-chloro-2-nitrophenyl)-2-phenylacetate (**30**)



According to a literature procedure[4] *iso*-propyl phenylacetate (2.26 g, 12.7 mmol) in tetrahydrofuran (25 mL) was added to a stirred suspension of potassium *tert*-butoxide (1.42 g, 12.7 mmol) in tetrahydrofuran (100 mL) at -78 °C, and the resulting yellow solution stirred for three minutes. 1-Chloro-4-nitrobenzene (4.00 g, 25.4 mmol) in tetrahydrofuran (25 mL) was added over a period of one minute, and the solution stirred for a further 3 minutes. DDQ (3.45 g, 15.2 mmol) in *N,N*-dimethylformamide (25 mL) was added and the solution stirred for a further 5 minutes before the reaction mixture was quenched with ammonium chloride (sat. aq., 50 mL) and allowed to warm to RT. The crude mixture was poured into water (1 L) and extracted with ethyl acetate (3 x 250 mL), the combined organic extracts washed with brine (250 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography (silica gel, petroleum ether : ethyl acetate, 50 : 1) and subsequent recrystallization (ethyl acetate/petroleum ether) to afford nitroarene **30** (2.03 g, 48 %) as a white crystalline solid. The data obtained is consistent with that reported in the literature.4

δH (400 MHz, $CDCl_3$): 8.02 (1H, d, *J* 8.7, H2), 7.46-7.35 (4H, m), 7.28-7.24 (2H, m), 7.05 (1H, d, *J* 2.2, H5), 5.63 (1H, s, H7), 5.10 (1H, septet, *J* 6.3, H13), 1.29 (3H, d, *J* 6.2, H14), 1.17 (3H, d, *J* 6.2, H14').

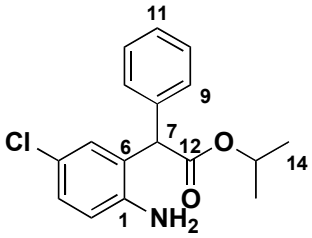
δC (101 MHz, $CDCl_3$): 170.4 (C12), 147.1 (C1), 139.8 (C4), 136.3 & 135.9 (C6 & C8), 131.8 (Ar CH) 129.2 & 129.1 (C9 & C10), 128.3 (Ar CH), 128.2 (Ar CH), 126.4 (Ar CH), 69.5 (C13), 53.5 (C7), 21.7 (C14), 21.4 (C14').

HRMS (ES+): found 356.0652; $C_{17}H_{16}{}^{35}ClNO_4Na$, $[M(^{35}Cl)+Na]^+$ requires 326.0660.

ν_{max} (neat): 2981, 1731 (C=O), 1516 (NO_2) 1339 (NO_2), 1106, 713 cm^{-1}.

MP: 94-99 °C (ethyl acetate/petroleum ether).

Iso-propyl 2-(2-amino-5-chlorophenyl)-2-phenylacetate (**20b**)



According to a literature procedure[5] zinc dust (2.43 g, 37.1 mmol) and ammonium chloride (2.93 g, 54.8 mmol) were added to a stirred RT solution of nitroarene **30** (1.25 g, 3.75 mmol) in 5:1 acetone:water (100 mL). After 10 minutes the heterogeneous reaction mixture was filtered over Celite®, and diluted with ethyl acetate (100 mL). The crude mixture was washed with water (100 mL) and the aqueous layer extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude product was purified by recrystallization (ethyl acetate/petroleum ether) to afford aniline **20b** (888 mg, 78 %) as a pale yellow crystalline solid.

δH (400 MHz, $CDCl_3$): 7.39-7.26 (5H, m, H9, H10 &H11), 7.13 (1H, s, H5), 7.08 (1H, d, *J* 8.4, H3), 6.62 (1H, d, *J* 8.6, H2), 5.12 (1H, sept, *J* 6.1, H13), 4.93 (1H, s, H7), 3.80 (2H, br s, NH_2), 1.29-1.24 (6H, m, H14).

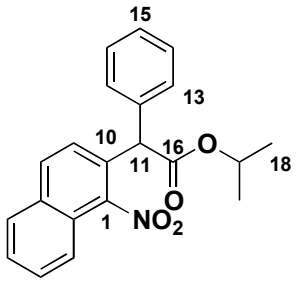
δC (101 MHz, $CDCl_3$): 171.5 (C12), 143.3 (C1), 136.3 (C8), 129.1 (C5), 128.8 & 128.7 (C9 & C10), 128.2 (C3), 127.7 (C11), 124.9 (C6), 123.5 (C4), 117.8 (C2), 69.1 (C13), 53.4 (C7), 21.7 & 21.6 (C14 & C14').

HRMS (ES+): found 326.0906; $C_{17}H_{18}{}^{35}ClNO_2Na$, $[M(^{35}Cl)+Na]^+$ requires 326.0918.

ν_{max} (neat): 3477 (N-H), 3374 (N-H), 2983, 2932, 1720 (C=O), 1493, 1201, 1093, 813, 698 cm^{-1}.

MP: 118-121 °C (ethyl acetate/petroleum ether).

Iso-propyl 2-(1-nitronaphthalen-2-yl)-2-phenylacetate (**31**)



According to a literature procedure[4] *iso*-propyl phenylacetate (2.26 g, 12.7 mmol) in tetrahydrofuran (25 mL) was added to a stirred suspension of potassium *tert*-butoxide (1.42 g, 12.7 mmol) in tetrahydrofuran (100 mL) at -78 °C, and the resulting yellow solution stirred for three minutes. 1-Nitronaphthalene (4.32 g, 25.4 mmol) in tetrahydrofuran (25 mL) was added over a period of one minute, and the solution stirred for a further 3 minutes. DDQ (3.45 g, 15.2 mmol) in *N,N*-dimethylformamide (25 mL) was added and the solution stirred for a further 5 minutes before the reaction mixture was quenched with ammonium chloride (sat. aq., 50 mL) and allowed to warm to RT. The crude mixture was poured into water (1 L) and extracted with ethyl acetate (3 x 250 mL), the combined organic extracts washed with brine (250 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography (silica gel, petroleum ether : ethyl acetate, 35 : 1) and subsequent recrystallization (ethyl acetate/petroleum ether) to afford **31** (1.76 g, 40 %) as a pale pink crystalline solid. The data obtained is consistent with that reported in the literature.4

δH (500 MHz, $CDCl_3$): 7.90 (1H, d, *J* 8.8, H8), 7.87 (1H, d, *J* 8.0, H6), 7.76 (1H, d, *J* 8.4, H3), 7.63 (1H, t, *J* 7.6, H4), 7.58 (1H, t, *J* 7.5, H5), 7.52 (1H, d, *J* 8.5, H9), 7.30-7.40 (5H, m, H13, H14 & H15), 5.23 (1H, s, H11), 5.14 (1H, sept, *J* 6.3, H17), 1.28 (3H, d, *J* 6.3, H18), 1.26 (3H, d, *J* 6.3, H18').

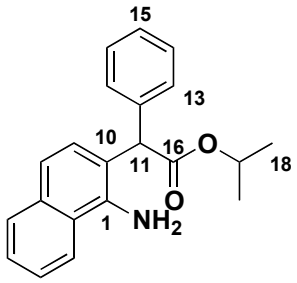
δC (126 MHz, $CDCl_3$): 170.3 (C16), 147.6 (C1), 137.0 (C10), 132.8 (C7), 130.5 (C8), 128.9 (C14), 128.7 (C4), 128.4 (C13), 128.1 (C12), 128.0 (C6), 127.7 (C15), 127.5 (C5), 126.4 (C9), 124.2 (C2), 121.8 (C3), 69.5 (C17), 51.8 (C11), 21.6 & 21.6 (C18 & C18').

ν_{max} (neat): 3028, 2985, 1716 (C=O), 1497 (NO_2), 1289 (NO_2), 1239, 1097, 748, 697 cm^{-1}.

HRMS (ES+): found 372.1198; $C_{21}H_{19}NO_4Na$, $[M+Na]^+$ requires 372.1206.

MP: 152-159 °C (ethyl acetate/petroleum ether).

Iso-propyl 2-(1-aminonaphthalen-2-yl)-2-phenylacetate (**20c**)



According to a literature procedure[5] zinc dust (1.89 g, 29.1 mmol) and ammonium chloride (2.28 g, 43.0 mmol) were added to a stirred RT solution of nitroarene **31** (1.00 g, 2.87 mmol) in 5:1 acetone:water (60 mL). After 10 minutes the heterogeneous reaction mixture was filtered over Celite®, and diluted with ethyl acetate (60 mL). The crude mixture was washed with water (60 mL) and the aqueous layer extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography (silica gel, petroleum ether : ethyl acetate, 15:1) to afford **20c** (633 mg, 69 %) as a white solid.

δH (400 MHz, $CDCl_3$): 7.82-7.77 (2H, m, H3 & H6), 7.49-7.43 (2H, m, H4 & H5), 7.38-7.25 (7H, m, H8, H9, H13, H14 & H15), 5.21 (1H, s, H11), 5.15 (1H, sept, *J* 6.1, H17), 4.35 (2H, br s, NH_2), 1.29 (3H, d, *J* 6.3, H18), 1.24 (3H, d, *J* 6.2, H18').

δC (101 MHz, $CDCl_3$): 172.2 (C16), 140.0 (C1), 137.3 (C12), 133.6 (C7), 128.7 & 128.6 (C13 & C14), 128.5 (C6), 127.5 (Ar CH), 127.3 (Ar CH), 125.8 (Ar CH), 125.1 (Ar CH), 123.9 (C2), 120.6 (C3), 118.5 (C8), 117.0 (C10), 68.9 (C17), 53.9 (C11), 21.8 (C18), 21.7 (C18').

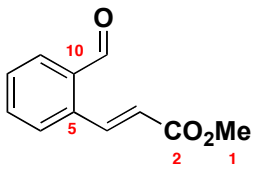
HRMS (ES+): found 320.1641; $C_{21}H_{22}NO_2$, $[M+H]^+$ requires 320.1645.

ν_{max} (neat): 3481 (NH_2), 3397 (NH_2), 3059, 2981, 2930, 1712 (C=O), 1699, 1641, 1198, 1098, 801, 738, 709 cm^{-1}.

MP: 109-111 °C.

3.3.2 Synthesis of Aldehydes

(*E*)-Methyl 3-(2-formylphenyl)acrylate (**2**)



According to a literature procedure[6] 2-bromobenzaldehyde (500 mg, 2.7 mmol) in DMF (1.6 mL) was added to a stirring solution of methyl acrylate (1.20 mL, 13.5 mmol), palladium(II) acetate (61 mg, 0.3 mmol), tetra-*n*-butylammonium bromide (222 mg, 0.7 mmol) and potassium carbonate (298 mg, 2.2 mmol). The resulting mixture was heated to 70 °C for 48 h, cooled to RT, then filtered over Celite® and washed with ethyl acetate. The organic layer was washed with water (100 mL) and the aqueous layer extracted with ethyl acetate (3 x 100 mL), dried over anhydrous magnesium sulfate, concentrated *in vacuo* and purified by flash column chromatography (silica gel, petroleum ether : ethyl acetate, 50 : 1) to afford aldehyde **(*E*)-2** (278 mg, 54 %) as a pale yellow solid. The data obtained is consistent with that reported in the literature.6

δ_H (500 MHz, $CDCl_3$): 10.23 (1H, s, H11), 8.53 (1H, d, *J* 16.0, H4), 7.88 (1H, d, *J* 7.6, H9), 7.66-7.54 (3H, m H6, H7, H8), 6.39 (1H, d, *J* 16.0, H3), 3.84 (3H, s, H1).

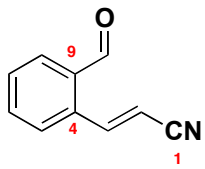
δ_C (126 MHz, $CDCl_3$) 191.8 (C11), 166.6 (C2), 141.3 (C4), 136.5 (C10), 133.9 (C6/C7/C8), 133.8 (C5), 132.4 (C9), 129.9 (C6/C7/C8), 128.0 (C6/C7/C8), 122.7 (C3), 51.9 (C1).

ν_{max} (neat) 3068, 3002, 2953, 1719, 1635, 1596, 1569 cm^{-1}.

HRMS (ES+): found 213.0530; $C_{11}H_{10}O_3Na$ $[M+Na]^+$ requires 213.0522.

MP: 51-52 °C.

(*E*)-3-(2-Formylphenyl)acrylonitrile (**21a**)



(Triphenylphosphoranylidene)acetonitrile (780 mg, 2.6 mmol) was added to a stirring RT solution of phthaldialdehyde (347 mg, 2.6 mmol) in dichloromethane (4 mL). After 24 h the solution was diluted with diethyl ether (20 mL) and filtered. The filtrate was concentrated *in vacuo* and the resulting crude solid was purified by flash column chromatography (silica gel, petroleum ether : ethyl acetate, 25:1) to afford aldehyde **(*E*)-21a** (332 mg, 82 %) as a white solid. The data obtained is consistent with that reported in the literature.[7]

δ_H (400 MHz, $CDCl_3$): 10.11 (1H, s, H10), 8.03 (1H, d, *J* 11.9, H3), 7.91 (1H, d, *J* 7.6 H5), 7.89 (1H, d, *J* 7.6, H8), 7.71 (1H, dd, *J* 7.6, 7.6, H6), 7.65 (1H, dd, *J* 7.6, 7.6, H7), 5.66 (1H, d, *J* 11.9, H2).

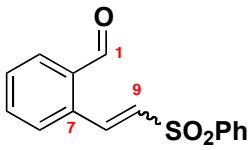
δ_C (101 MHz, $CDCl_3$): 192.7 (C10), 148.2 (C3), 134.6 (C6), 134.4 (C4), 134.1 (C8), 133.6 (C9), 130.5 (C7), 129.5 (C5), 116.7 (C1), 99.3 (C2).

HRMS (ES+): found 180.0419; $C_{10}H_7NONa$ $[M+Na]^+$ requires 180.0420.

ν_{max} (neat): 3068, 3057, 2857, 2761, 2220, 1725, 1683, 1645, 1612, 1597 cm^{-1}.

MP: 82-85 °C.

2-(2-(Phenylsulfonyl)vinyl)benzaldehyde (**21b**)



Triphenyl((phenylsulfonyl)methylene)phosphorane[8] (1.7 g, 4.2 mmol) was added to a stirred solution of phthaldialdehyde (557 mg, 4.2 mmol) in acetonitrile (10 mL) and heat to 70 °C for 72 h before being cooled, diluted with diethyl ether (20 mL) and filtered. The filtrate was concentrated *in vacuo* and the resulting solid was purified by flash column chromatography (silica gel, petroleum ether : ethyl acetate, 5 : 1) to afford aldehyde **21b** (707 mg, 63 %) as an inseparable 4:1 mixture of *E*:*Z* isomers.

(*E*)-21b

δ_H (500 MHz, $CDCl_3$): 10.22 (1H, s, H1), 8.56 (1H, d, *J* 15.4, H8), 8.04 (2H, d, *J* 7.4, H11), 7.90-7.85 (1H, m, H3), 7.69-7.52 (6H, m, H4, H5, H6, H12, H13), 6.82 (1H, d, *J* 15.4, H9).

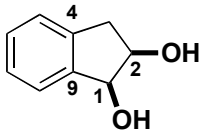
δ_C (126MHz, $CDCl_3$): 191.8 (C1), 140.3 (C10), 140.3 (C9) 134.1 (C2/C7), 134.1 (C2/C7), 134.0 (C8), 133.6 (C5/C13), 133.5 (C5/C13), 131.7 (C3/C4/C6/C11/C12), 130.7 (C3/C4/C6/C11/C12), 129.4 (C3/C4/C6/C11/C12), 128.4 (C3/C4/C6/C11/C12), 128.0 (C3/C4/C6/C11/C12).

HRMS (ES+): found 295.0406; $C_{15}H_{12}O_3SNa$ $[M+Na]^+$ requires 295.0399.

ν_{max} (neat): 3066, 2959, 1774, 1697, 1615, 1595, 1568 cm^{-1}.

MP: 98-104 °C.

2,3-Dihydro-1*H*-indene-1,2-diol (**32**)



According to a literature procedure[9] indene (1.0 g, 8.6 mmol), *N*-methylmorpholine-*N*-oxide (1.3 g, 11.2 mmol) and osmium tetroxide (22 mg, 0.1 mmol) were stirred for 24 h in PEG (mw 400, 10 g). Diethyl ether (20 mL) was added to the reaction and stirred vigorously before allowing to settle and decanting the diethyl ether layer. This process was repeated twice, the organic layers were combined, concentrated *in vacuo* and purified by column chromatography (chloroform : methanol, 97 : 3) to afford diol **32** (1.29 g, 99 %) as a white solid. The data obtained is consistent with that reported in the literature.9

δ_H (300 MHz, $CDCl_3$): 7.44 – 7.36 (1H, m, Ar-H), 7.32 – 7.20 (3H, m, Ar-H), 4.92 (1H, s, H1), 4.46-4.36 (1H, m, H2), 3.17 (1H, br s, OH), 3.14-2.99 (2H, m, H3 & OH), 2.92 (1H, dd, *J* 16.3, 3.6, H3').

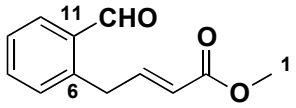
δ_C (126 MHz, $CDCl_3$): 142.0 (C4/C9), 140.2 (C4/C9), 128.8 (C5/C6/C7/C8), 127.2 (C5/C6/C7/C8), 125.3 (C5/C6/C7/C8), 125.0 (C5/C6/C7/C8), 76.0 (C1), 73.5 (C2), 38.5 (C3).

HRMS (ES+): found 173.0573; $C_9H_{10}O_2Na$ $[M+Na]^+$ requires 173.0573.

ν_{max} (neat): 3418 (br), 1642.

MP: 100-105 °C.

(*E*)-Methyl 4-(2-formylphenyl)but-2-enoate (**3**)



According to a literature procedure[11] sodium metaperiodate (1.19 g, 5.56 mmol) in water (50 mL) was added to a stirred RT solution of diol **32** (700 mg, 4.67 mmol) in tetrahydrofuran (25 mL). After 90 mins the organic solvent was removed *in vacuo* and the remaining aqueous solution saturated with sodium chloride. The aqueous layer was extracted with ethyl acetate (3 x 25 mL) and the combined organic layers dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford crude *iso*-chroman-1,3-diol, which was immediately redissolved in dichloromethane (50 mL) and stirred with anhydrous magnesium sulfate (2.5 g). After 2 h the mixture was filtered and concentrated *in vacuo* to afford crude homophthaldialdehyde (pure by ^{1}H NMR) in quantitative yield. The crude aldehyde was dissolved in dichloromethane (5 mL) and added to a stirred RT solution of methyl triphenylphosphoranylidene acetate (1.57 g, 4.70 mmol) in dichloromethane (5 mL). After 24 h the solvent was removed *in vacuo* and the crude mixture purified by flash column chromatography (silica gel, petroleum ether : diethyl ether, 15 : 1) to afford aldehyde **(*E*)-3** (686 mg, 72 %) as a pale yellow oil. The data obtained is consistent with that reported in the literature.[10]

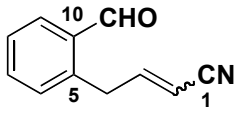
δH (500 MHz, $CDCl_3$): 10.15 (1H, s, H12), 7.84 (1H, d, *J* 7.6, H7), 7.56 (1H, dd, *J* 7.6, 7.5, H9), 7.47 (1H, t, *J* 7.5, H8), 7.28 (1H, d, *J* 7.6, H10), 7.15 (1H, dt, *J* 15.6, 6.5, H4), 5.73 (1H, d, *J* 15.6, H3), 3.99 (2H, d, *J* 6.5, H5), 3.70 (3H, s, H1).

δC (126 MHz, $CDCl_3$): 192.5 (C12), 166.7 (C2), 147.0 (C11), 139.6 (C4), 134.0 (C9), 133.8 (C7), 133.7 (C6), 131.4 (C10), 127.5 (C8), 122.2 (C3), 51.5 (C1), 35.3 (C5).

ν_{max} (neat): 2734, 2860, 2851, 1723, 1697, 1655, 1600, 1575 cm^{-1}.

HRMS (ES+): found 227.0697; $C_{12}H_{12}O_3Na$, $[M+Na]^+$ requires 227.0679.

4-(2-Formylphenyl)but-2-enenitrile (**33**)



According to a literature procedure[11] sodium metaperiodate (2.55 g, 11.9 mmol) in water (100 mL) was added to a stirred RT solution of diol **32** (1.50 g, 10 mmol) in tetrahydrofuran (50 mL). After 90 mins the organic solvent was removed *in vacuo* and the remaining aqueous solution saturated with sodium chloride. The aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford crude *iso*-chroman-1,3-diol, which was immediately redissolved in dichloromethane (100 mL) and stirred with anhydrous magnesium sulfate (5 g). After 2 h the mixture was filtered and concentrated *in vacuo* to afford crude homophthaldialdehyde (pure by ^{1}H NMR) in quantitative yield. The crude aldehyde was dissolved in dichloromethane (10 mL) and added to a stirred RT solution of triphenylphosphylidene acetonitrile (3.38 g, 11 mmol) in dichloromethane (10 mL). After 24 h the solvent was removed *in vacuo* and the crude mixture purified by flash column chromatography (silica gel, petroleum ether : diethyl ether, 15 : 1) to afford aldehydes **(*E*)-33** (1.15 g, 67 %) and **(*Z*)-33** (192 mg, 11 %) as colourless oils.

(*E*)-33

δH (500 MHz, $CDCl_3$): 10.09 (1H, s, H11), 7.84 (1H, dd, *J* 7.5, 1.6, H6), 7.59 (1H, td, *J* 7.5, 1.6, H8) 7.53 (1H, td, *J* 7.5, 1.0, H7), 7.27 (1H, dd, *J* 6.9, 1.6, H9), 6.90 (1H, dt, *J* 16.4, 6.5, H3), 5.25 (1H, dt, *J* 16.4, 1.8, H2), 3.99 (2H, dd, *J* 6.5, 1.8, H4).

δC (126 MHz, $CDCl_3$): 192.8 (C11), 153.3 (C3), 137.9 (C10), 135.4 (C6), 134.1 (C7), 133.7 (C5), 131.5 (C9), 128.0 (C8), 117.2 (C1), 100.9 (C2), 36.6 (C4).

ν_{max} (neat): 3057, 3925, 2859, 2360, 2342, 1697, 1631, 1601 cm^{-1}.

HRMS (ES+): found 194.0575; $C_{11}H_9NONa$, $[M+Na]^+$ requires 194.0576.

(*Z*)-33

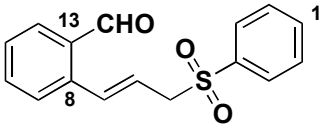
δH (500 MHz, $CDCl_3$): 10.15 (1H, s, H11), 7.83 (1H, dd, *J* 7.5, 0.9, H6), 7.59 (1H, td, *J* 7.5, 1.3, H8), 7.51 (1H, t, *J* 7.5, H7), 7.40 (1H, d, *J* 7.5, H9), 6.71 (1H, dt, *J* 10.8, 7.5, H3), 5.39 (1H, d, *J* 10.8, H2), 4.19 (2H, d, *J* 7.5, H4).

δC (126 MHz, $CDCl_3$): 193.1 (C11), 152.2 (C3), 138.4 (C10), 135.2 (C6), 134.3 (C8), 133.6 (C5), 131.6 (C9), 127.8 (C7), 116.0 (C1), 100.1 (C2), 35.7 (C4).

ν_{max} (neat): 3021, 2917, 2849, 2360, 2342, 1697, 1602 cm^{-1}.

HRMS (ES+): found 194.0578; $C_{11}H_9NONa$, $[M+Na]^+$ requires 194.0576.

(*E*)-2-(3-(Phenylsulfonyl)prop-1-en-1-yl)benzaldehyde (**34**)



According to a literature procedure[12] a mixture of 2-bromobenzaldehyde (1.0 g, 5.4 mmol), allylphenylsulfone (980 mg, 5.4 mmol), sodium acetate (1.3 g, 16.2 mmol), triphenylphosphine (140 mg, 0.5 mmol) and palladium(II) acetate (60 mg, 0.3 mmol) in tetrahydrofuran (10 mL) was stirred in a sealed tube at 100 °C for 24 h. The resulting mixture was filtered through Celite®, concentrated *in vacuo* and purified by flash column chromatography (silica gel, petroleum ether : ethyl acetate, 5 : 1) to afford aldehyde **34** (1.1 g, 71 %) as a yellow solid.[*]

δH (500 MHz, $CDCl_3$): 10.00 (1H, s, H14), 7.90 (2H, d, *J* 7.8, H3), 7.77 (1H, d, *J* 7.8, H9/H12), 7.65 (1H, t, *J* 7.7, H1), 7.58-7.45 (5H, m, Ar C-*H*), 7.27 (1H, d, *J* 15.7, H7), 6.11 (1H, dt, *J* 15.7, 7.7, H6), 4.05 (2H, d, *J* 7.7, H5).

δC (126 MHz, $CDCl_3$): 192.2 (C14), 138.3 (C4/C8), 137.9 (C4/C8), 135.8 (C7), 133.9 (C1), 133.9 (Ar CH), 132.7 (C13), 132.5 (Ar CH), 129.2 (C2/C3), 128.6 (Ar CH), 128.4 (C2/C3), 127.7 (Ar CH), 120.4 (C6), 60.6 (C5).

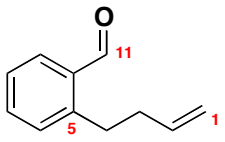
ν_{max} (neat): 3064, 2730, 1694, 1596, 1568 cm^{-1}.

HRMS (ES+): found 309.0558; $C_{16}H_{14}O_3SNa$ $[M+Na]^+$ requires 309.0556.

MP: 72-75 °C.

[*] *Although the reference reports the synthesis of the isomeric compound where the alkene sits in conjugation with the sulfone, in our hands only the styrenic compound was isolated.*

2-(But-3-en-1-yl)benzaldehyde (**37**)



According to a literature procedure[13] allylmagnesium bromide (6.5 mL, 1 M in tetrahydrofuran, 6.5 mmol) was added dropwise over 30 mins to a stirred RT solution of 2-bromobenzylbromide (1.0 g, 4.37 mmol) in tetrahydrofuran (3 mL). The resulting solution was heated to reflux for 2 h before being allowed to cool to RT. The reaction was quenched with ammonium chloride (sat. aq., 30 mL) and the aqueous layer was extracted with diethyl ether (3 x 50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The clear liquid was redissolved in tetrahydrofuran (4 mL) at -78 °C and *n*-butyllithium (4.1 mL, 1.6 M in hexanes, 6.56 mmol) was added dropwise over 30 mins followed by *N,N*-DMF (0.8 mL, 10.9 mmol) in tetrahydrofuran (1.5 mL) over 30 mins. The resulting solution was allowed to warm to RT overnight before quenching with ammonium chloride (sat. aq., 50 mL). The aqueous layer was extracted with diethyl ether (3 x 50 mL), dried over anhydrous magnesium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography (petroleum ether : diethyl ether, 50 : 1) to afford aldehyde **37** (517 mg, 68 %) as a colourless oil. The data obtained is consistent with that reported in the literature.[13]

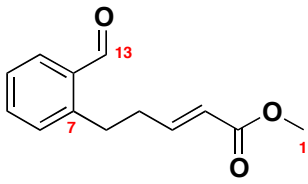
δ_H (400 MHz, $CDCl_3$): 10.28 (1H, s, H11), 7.84 (1H, d, *J* 7.7, H9), 7.52 (1H, td, *J* 7.5, 1.2, H7), 7.39 (1H, t, *J* 7.5, H8), 7.29 (1H, d, *J* 7.5, H6), 5.94-5.90 (1H, m, H2), 5.10-4.97 (2H, m, H1), 3.15 (2H, t, *J* 7.6, H4), 2.43-2.34 (2H, m, H3).

δ_C (101 MHz, $CDCl_3$): 192.4 (C11), 144.7 (C10), 137.4 (C2), 133.7 (C7), 132.0 (C9), 131.1 (C6), 130.1 (C5), 126.6 (C8), 115.5 (C1), 35.9 (C3), 32.0 (C4).

HRMS (FI): found 160.0888; $C_{11}H_{12}O$ $[M\bullet]^+$ requires 160.0888.

ν_{max} (neat): 3066, 2959, 1774, 1697, 1615, 1595, 1568 cm^{-1}.

(*E*)-Methyl 5-(2-formylphenyl)pent-2-enoate (**4**)



Hoveyda-Grubbs second-generation catalyst (18 mg, 0.03 mmol) was added to a stirred solution of aldehyde **37** (100 mg, 0.58 mmol) and methyl acrylate (104 μL, 1.16 mmol) in dichloromethane (3 mL) and stirred for 16 h at RT. The resulting solution was concentrated *in vacuo* and purified by flash column chromatography (silica gel, petroleum ether : ethyl acetate, 25 : 1) to afford aldehyde **(*E*)-4** (121 mg, 90 %) as a pale oil. The data obtained is consistent with that reported in the literature.[14]

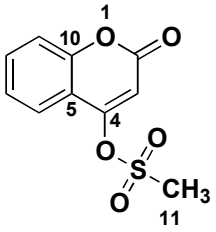
δ_H (400 MHz, $CDCl_3$): 10.14 (1H, s, H13), 7.79 (1H, d, *J* 7.6, H11), 7.50 (1H, t, *J* 7.4, H9), 7.39 (1H, t, *J* 7.4, H10), 7.25 (1H, d, *J* 7.5, H8), 7.00 (1H, dt, *J* 15.7, *J* 7.0, H4), 5.82 (1H, d, *J* 15.7, H3), 3.69 (3H, s, H1), 3.17 (2H, t, *J* 7.7, H6), 2.52 – 2.45 (2H, m, H5).

δ_C (101 MHz, $CDCl_3$): 192.7 (C13), 166.9 (C2), 147.9 (C4), 143.1 (C12), 133.8 (C9), 133.8 (C11), 133.7 (C7), 131.1 (C10), 127.0 (C8), 121.7 (C3), 51.4 (C1), 33.8 (C5), 31.5 (C6).

HRMS (ES+): found 241.0830; $C_{13}H_{14}O_3Na$ $[M+Na]^+$ requires 241.0835.

ν_{max} (neat): 2952, 2738, 1721, 1696, 1657 cm^{-1}.

2-Oxo-2*H*-chromen-4-yl methanesulfonate (**35**)



According to a literature procedure[15] methanesulfonyl chloride (2.63 mL, 34 mmol), was added in one portion to a stirred RT solution of 4-hydroxycoumarin (5.0 g, 31 mmol) and triethylamine (6.4 mL, 46 mmol) in dichloromethane (120 mL). After 30 mins the reaction was diluted with dichloromethane (200 mL), quenched with water (100 mL) and the organic layer washed with hydrochloric acid (1 M, 100 mL), sodium bicarbonate (sat. aq., 100 mL) and brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting solid residue was purified by a single recrystallization from hot toluene to afford 4-hydroxycoumarin methanesulfonate **36** (6.36 g, 85 %) as a white crystalline solid.*

δH (400 MHz, $CDCl_3$): 7.74 (1H, dd, *J* 7.9, 1.5, H6), 7.64 (1H, ddd, *J* 8.5, 7.2, 1.4, H8), 7.40-7.32 (2H, m, H7 & H9), 6.53 (1H, s, H3), 3.40 (3H, s, H11).

δC (101 MHz, $CDCl_3$): 160.5 (C4), 157.2 (C2), 153.6 (C10), 133.5 (C8), 124.7 (C7), 122.9 (C6), 117.2 (C9), 114.7 (C5), 103.5 (C3), 39.2 (C11).

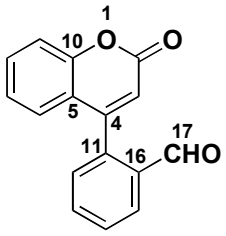
ν_{max} (neat): 3070, 3035, 3011, 2933, 1720 (C=O), 1368 (S=O), 1330 (S=O), 1173, 899, 867 cm^{-1}.

HRMS (ES+): found 262.9981; $C_{10}H_8O_5SNa$, $[M+Na]^+$ requires 262.9985.

MP: 113 – 117 °C (toluene).

* *Note: trace amounts of this compound were observed to cause irritation on contact with skin.*

2-(2-Oxo-2*H*-chromen-4-yl)benzaldehyde (**36**)



According to a literature procedure[16] a stirred suspension of 4-methoxycoumarin methanesulfonate **35** (500 mg, 2.08 mmol), bis(triphenylphosphine)nickel(II) chloride[17] (272 mg, 0.42 mmol), triphenylphosphine (217 mg, 0.84 mmol) and zinc dust (340 mg, 5.2 mmol) in dry toluene (12 mL) was warmed to 90 °C. 2-Bromobenzaldehyde (0.29 mL, 2.5 mmol) was added dropwise over 3 h and the mixture stirred for a further 3 h until the starting material was consumed. The reaction mixture was allowed to cool to RT, diluted with dichloromethane (50 mL), filtered over Celite®, quenched with hydrochloric acid (5 % aq., 25 mL) and the aqueous layer extracted with dichloromethane (3 x 25 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude mixture was purified by flash column chromatography (silica gel, petroleum ether : ethyl acetate, 4 : 1) to afford aldehyde **36** (175 mg, 34 %) as an off-white crystalline solid.

δH (400 MHz, $CDCl_3$): 9.91 (1H, s, H17), 8.11 (1H, dd, *J* 7.7, 1.2, H15), 7.78 (1H, app. td, *J* 7.5, 1.5, H13), 7.71 (1H, app. t, *J* 7.9, H14), 7.56 (1H, ddd, *J* 8.4, 7.2, 1.4, H8), 7.42 (2H, app. t, *J* 8.5, H6 & H12), 7.18 (1H, ddd, *J* 7.9, 7.3, 0.9, H7), 7.01 (1H, dd, *J* 7.9, 1.5, H9), 6.40 (1H, s, H3).

δC (101 MHz, $CDCl_3$): 190.0 (C17), 160.0 (C2), 153.5 & 153.3 (C4 & C10), 137.2 (C11), 134.5 (C13), 133.8 (C16), 132.4 (C7), 130.1 (C14), 129.9 (C6), 129.7 (C15), 126.5 (C9), 124.6 (C8), 120.0 (C5), 117.4 (C12), 116.5 (C3).

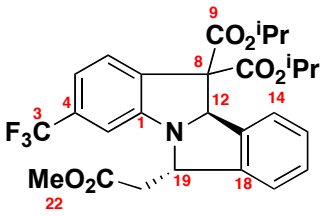
ν_{max} (neat): 2857, 2759, 1698 (C=O), 1605, 1370, 1183, 937, 866, 775, 752 cm^{-1}.

HRMS (ES+): found 273.0522; $C_{16}H_{10}O_3Na$, $[M+Na]^+$ requires 273.0522.

MP: 107-111 °C.

3.3.3 Phase transfer catalyzed cyclizations

Pyrrolizidine **8**



Asymmetric. Prepared according to *general procedure 1*: 100 mg aniline **1** (0.29 mmol), 66 mg aldehyde **(*E*)-2** (0.29 mmol), chromatography (silica gel, petroleum ether : ethyl acetate, 20:1), 119 mg, 79 %, 88 % ee, >20:1 dr.

Racemic. Prepared according to *general procedure 3*: 100 mg aniline **1** (0.29 mmol), 66 mg aldehyde **(*E*)-2** (0.29 mmol), chromatography (silica gel, petroleum ether : ethyl acetate, 20:1), 89 mg, 59 %.

δ_H (400 MHz, $CDCl_3$): 7.65 (1H, d, *J* 7.8, H6), 7.50 – 7.47 (1H, m, H15), 7.34 – 7.30 (2H, m, H14, H16), 7.22 – 7.17 (2H, m, H17, H5), 7.04 (1H, s, H2), 6.15 (1H, s, H12), 5.52 (1H, t, *J* 6.4, H19), 5.29 (1H, sept, *J* 6.3, H10), 4.61 (1H, sept, *J* 6.3, H10), 3.75 (3H, s, H22), 3.01 (1H, dd, *J* 16.8, 6.4, H20), 2.37 (1H, dd, *J* 16.8, 6.4, H20), 1.42 (6H, d, *J* 6.3, H11), 0.84 (6H, d, *J* 6.3, H11).

δ_C (101 MHz, $CDCl_3$): 172.7 (C9/C21), 168.3 (C9/C21), 167.0 (C9/C21), 149.5 (C1/C7/C13/C18), 144.2 (C1/C7/C13/C18), 135.9 (C1/C7/C13/C18), 135.0 (C1/C7/C13/C18), 131.7 (q, *J* 32, C4), 128.8 (C14/C15/C16/C17), 127.8 (C14/C15/C16/C17), 126.6 (C6), 124.5 (C14/C15/C16/C17), 123.9 (q, *J* 282, C3), 122.9 (C14/C15/C16/C17), 118.1 (q, *J* 4, C5), 122.2 (q, *J* 4, C2), 76.3 (C12), 70.2 (C10), 70.1 (C10), 66.9 (C8), 61.0 (C19), 51.8 (C22), 39.0 (C20), 21.7 (C11), 21.6 (C11), 21.1 (C11), 21.0 (C11).

δ_F (376 MHz, $CDCl_3$): – 62.5.

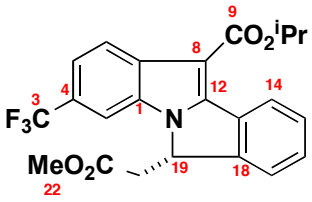
HRMS (ES+): found 542.1741; $C_{27}H_{28}F_3NO_6Na$ $[M+Na]^+$ requires 542.1761.

ν_{max} (neat): 2983, 1729, 1632 cm^{-1}.

Chiral HPLC (Chiralpak OD-H, 1.5 % IPA, 98 % hexane, 1.0 $mL.min^{-1}$, λ = 271) t_R (major) = 6.9, t_R (minor) = 9.1.

$[\alpha]_D^{25}$ +14 (*c* = 1.36, $CHCl_3$).

Indole **39**



This compound was formed during the purification of indoline **8** by flash column chromatography in a variety of yields depending on the solvent system. Less polar solvent systems resulted in a larger yield of the indole **39** due to the greater length of time on silica. This compound is a bright yellow oil.

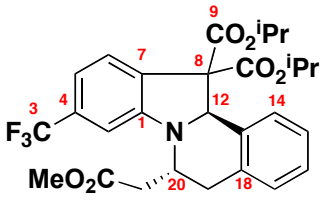
δ_H (500 MHz, $CDCl_3$): 8.84 (1H, d, *J* 7.2, H14), 8.37 (1H, d, *J* 8.5, H6), 7.65 (1H, s, H2), 7.58 – 7.54 (2H, m, H15, H16), 7.53 – 7.47 (2H, m, H5, H17), 5.85 (1H, dd, *J* 7.5, *J* 5.3, H19), 5.42 (1H, sept, *J* 6.3, H10), 3,81 (3H, s, H22), 3.23 (1H, dd, *J* 16.5, *J* 5.3, H20), 2.85 (1H, dd, *J* 16.5, *J* 7.5, H20), 1.52 (6H, d, *J* 6.3, H11).

δ_C (126 MHz, $CDCl_3$): 170.7 (C9/C21), 164.6 (C9/C21), 150.2 (C12), 146.6 (C18), 133.7 (C1), 132.0 (C7), 130.5 (C13), 129.8 (C17), 129.3 (C15/C16), 126.3 (C14), 124.9 (q, *J* 31.1 C4), 124.8 (q, *J* 271, C3), 123.5 (C6), 122.8 (C15/C16), 118.5 (q, *J* 4, C5), 107.1 (q, *J* 4, C2), 100.8 (C8), 67.7 (C10), 57.5 (C19), 52.4 (C22), 39.2 (C20), 22.4 (C11).

HRMS (ES+): found 454.1227; $C_{23}H_{20}F_3NO_4Na$ $[M+Na]^+$ requires 454.1237.

ν_{max} (neat): 2984, 2939, 1731, 1634, 1615 cm^{-1}.

Indolizidine **9**



Asymmetric. Prepared according to *general procedure 2*: 50 mg aniline **1** (0.14 mmol), 28 mg aldehyde **(*E*)-3** (0.14 mmol), chromatography (silica gel, petroleum ether : ethyl acetate, 10:1), 68 mg, 88 %, 91 % ee, >20:1 dr.

Racemic. Prepared according to *general procedure 3*: 25 mg aniline **1** (0.07 mmol), 14 mg aldehyde **(*E*)-3** (0.07 mmol), chromatography (silica gel, petroleum ether : ethyl acetate, 10:1), 29 mg, 57 %.

δ_H (500 MHz, $CDCl_3$): 7.64 (1H, d, *J* 7.9, H6), 7.44 (1H, d, *J* 6.6, H14), 7.30 – 7.22 (3H, m, H15, H16, H17), 6.94 (1H, d, *J* 7.9, H5), 6.72 (1H, s, H2), 5.52 (1H, s, H12), 5.28 (1H, sept, *J* 6.3, H10), 4.82 (1H, sept, *J* 6.3, H10), 4.53 – 4.46 (1H, m, H20), 3.70 (3H, s, H23), 3.18 (1H, dd, *J* 15.1, *J* 5.2, H19), 3.04 (1H, dd, *J* 15.1, *J* 1.9, H19), 2.53 (1H, d, *J* 15.8, H21), 2.12 (1H, dd, *J* 15.9, *J* 10.3, H21), 1.40 (3H, d, *J* 6.3, H11), 1.38 (3H, d, *J* 6.3, H11), 0.95 (3H, d, *J* 6.3, H11), 0.81 (3H, d, *J* 6.3, H11).

δ_C (126 MHz, $CDCl_3$): 172.2 (C22), 168.4 (C9), 166.8 (C9), 148.3 (C7), 134.5 (C18), 133.4 (C13), 132.2 (q, *J* 32, C4), 130.3 (C1), 128.9 (C15/C16/C17), 127.3 (C15/C16/C17), 126.5 (C15/C16/C17), 126.0 (C6), 125.3 (C14), 124.3 (q, *J* 272, C3), 114.3 (q, *J* 4, C5), 103.4 (q, *J* 4, C2), 70.3 (C10), 69.8 (C10), 65.5 (C8), 65.2 (C12), 51.7 (C23), 47.8 (C20), 36.6 (C21), 33.6 (C19), 21.7 (C11), 21.6 (C11), 21.2 (C11), 21.1 (C11).

δ_F (376 MHz, $CDCl_3$): – 62.6.

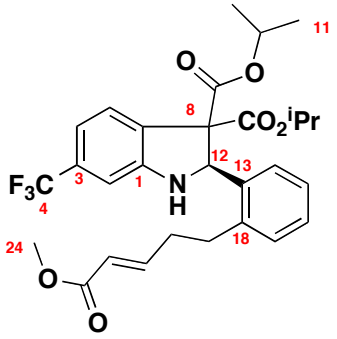
HRMS (ES+): found 556.1916; $C_{28}H_{30}NF_3O_6Na$ $[M+Na]^+$ requires 556.1917.

ν_{max} (neat): 2984, 2939, 1732, 1614 cm^{-1}.

Chiral HPLC (Chiralpak IC, 1 % IPA, 99 % hexane, 1.0 mL.min^{-1}, λ = 288) t_R (major) = 12.5, t_R (minor) = 17.7.

$[\alpha]_D^{25}$ + 8 (*c* = 1.10, $CHCl_3$).

Indoline **38**



***Asymmetric*:** Aniline **1** (21 mg, 0.06 mmol), aldehyde **4** (13 mg, 0.06 mmol) and magnesium sulfate (38 mg, 0.31 mmol) were stirred for 16 h at RT in toluene (0.5 mL). The resulting mixture was filtered and concentrated *in vacuo.* The imine was then redissolved in toluene (0.6 mL), (8*S*, 9*R*)-*N*-benzylcinchonidinium chloride **11** (4 mg, 0.01 mmol) was added and the solution was stirred at RT for 30 minutes. Potassium carbonate (33 % aq., 0.3 mL) was added to the reaction and stirred for 70 h. The mixture was quenched with ammonium chloride (sat. aq., 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, petroleum ether : ethyl acetate, 10 : 1) to afford compound **38** (71 %, 94 % ee) as a yellow oil.

***Racemic*:** Aniline **1** (28 mg, 0.08 mmol), aldehyde **4** (18 mg, 0.08 mmol) and magnesium sulfate (51 mg, 0.41 mmol) were stirred for 16 h at RT in toluene (0.5 mL). The resulting mixture was filtered and concentrated *in vacuo*. The imine was then redissolved in toluene (0.6 mL), tetrabutylammonium chloride (2 mg, 0.01 mmol) and potassium carbonate (33 % aq., 3 mL) were added and the reaction stirred for 16 h. The mixture was then quenched with ammonium chloride (sat. aq., 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, petroleum ether : ethyl acetate, 10 : 1) to afford **38** (29 mg, 64 %).

δ_H (500 MHz, $CDCl_3$): 7.51 (1H, d, *J* 8.0, ArH), 7.20 (2H, t, *J* 7.6, ArH), 7.15 – 6.98 (4H, m, ArH/H21), 6.86 (1H, s, H2), 6.14 (1H, s, H12), 5.92 (1H, d, *J* 15.7, H22), 5.14 – 5.04 (2H, m, H10), 3.75 (3H, s, H24), 3.18 – 3.09 (1H, m, H20), 2.87 – 2.77 (1H, m, H20), 2.66 – 2.49 (2H, m, H19), 1.31 – 1.20 (12H, m, H11).

δ_C (126 MHz, $CDCl_3$): 167.8 (C9), 167.6 (C9), 167.1 (C23), 150.8 (C1/C7/C13/C18), 148.0 (C21), 146.0 (C1/C7/C13/C18), 139.1 (C1/C7/C13/C18), 138.1 (C1/C7/C13/C18), 132.2 (q, *J* 32, C3), 129.3 (C6/C14/C15/C16/C17), 128.8 (C6/C14/C15/C16/C17), 128.5 (C6/C14/C15/C16/C17), 127.4

(C6/C14/C15/C16/C17), 127.0 (C6/C14/C15/C16/C17), 124.2 (q, *J* 272, C4), 121.7 (C22), 115.4 (q, *J* 4, C5), 105.3 (q, *J* 4, C2), 70.3 (C10), 69.9 (C10), 69.0 (C8), 62.0 (C12), 51.5 (C24), 34.0 (C19), 31.4 (C20), 21.4 (C11), 21.3 (C11).

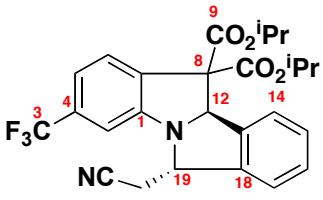
δ_F (470 MHz, $CDCl_3$): – 62.6.

ν_{max} (neat): 3375, 2984, 2936, 1725, 1656, 1618 cm^{-1}.

HRMS (ES+): found 548.2250; $C_{29}H_{33}F_3NO_6$ $[M+H]^+$ requires 548.2254.

Chiral HPLC (Chiralpak OD-H, 3 % IPA, 97 % hexane, 1.0 $mL.min^{-1}$, λ = 272) t_R (major) = 18.1, t_R (minor) = 14.7.

Pyrrolizidine **14**



Asymmetric. Prepared according to *general procedure 1*: 50 mg aniline **1** (0.14 mmol), 23 mg aldehyde **(*E*)-21a** (0.14 mmol), chromatography (silica gel, petroleum ether : ethyl acetate, 20:1), 70 %, 97 % ee, >20:1 dr.

Racemic. Prepared according to *general procedure XXC*: 25 mg aniline **1** (0.07 mmol), 12 mg aldehyde **(*E*)-21a** (0.07 mmol), chromatography (silica gel, petroleum ether : ethyl acetate, 20:1), 32 mg, 91 %.

δ_H (500 MHz, $CDCl_3$): 7.59 (1H, d, *J* 8.0, H6), 7.45 (1H, d, *J* 7.1, H14), 7.41 – 7.33 (2H, m, H15, H16), 7.32 (1H, d, *J* 7.6, H17), 7.27 (1H, s, H2), 7.21 (1H, d, *J* 8.0, H5), 6.21 (1H, d, *J* 2.3, H12), 5.26 (1H, sept, *J* 6.3, H10), 4.91 (1H, td, *J* 5.6, *J* 2.4, H19), 4.57 (1H, sept, *J* 6.3, H10), 2.98 (1H, dd, *J* 16.7, *J*, 5.6, H20), 2.92 (1H, dd, *J* 16.7, *J* 5.6, H20) 1.42 (3H, d, *J* 6.3, H11), 1.38 (3H, d, *J* 6.3, H11), 0.91 (3H, d, *J* 6.3, H11), 0.68 (3H, d, *J* 6.3, H11).

δ_C (126 MHz, $CDCl_3$): 168.0 (C9), 167.0 (C9), 153.0 (C1), 140.6 (C18), 137.3 (C13), 133.6 (C7), 132.4 (q, *J* 32, C4), 129.1 (C15/C16), 128.8 (C15/C16), 127.0 (C6), 124.2 (C14), 124.0 (q, *J* 273, C3), 122.5 (C17), 118.9 (q, *J* 4, C5), 117.5 (C21), 109.4 (q, *J* 4, C2), 74.0 (C12), 70.5 (C10), 70.0 (C10), 67.9 (C8), 66.6 (C19), 27.5 (C20), 21.7 (C11), 21.6 (C11), 21.2 (C11), 20.8 (C11).

δ_F (376 MHz, $CDCl_3$): – 62.5.

HRMS (ES+): found 509.1647; $C_{26}H_{25}F_3N_2O_4Na$ $[M+Na]^+$ requires 509.1659.

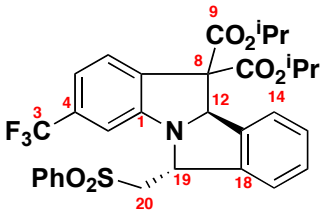
ν_{max} (neat): 2984, 2938, 2252, 1727, 1616, 1593 cm^{-1}.

Chiral HPLC (Chiralpak OD-H, 2 % IPA, 98 % hexane, 1.0 $mL.min^{-1}$, λ = 221) t_R (major) = 16.8, t_R (minor) = 18.6.

$[\alpha]_D^{25}$ – 7 (*c* = 0.75, $CHCl_3$).

MP: 109 – 111 ˚C (dichloromethane : petroleum ether).

Pyrrolizidine **15**



Asymmetric. Prepared according to *general procedure 1*: 79 mg aniline **1** (0.23 mmol), 62 mg aldehyde **21b** (0.23 mmol), chromatography (silica gel, petroleum ether : ethyl acetate, 15:1), *major*: 80 mg, 58 %, 85 % ee, *minor*: 39 mg, 29 %, 91 % ee.

Racemic. Prepared according to *general procedure 3*: 25 mg aniline **1** (0.07 mmol), 20 mg aldehyde **21b** (0.07 mmol), chromatography (silica gel, petroleum ether : ethyl acetate, 15:1), *major*: 19 mg, 47 %, *minor*: 7 mg, 17 %.

Major

δ_H (500 MHz, $CDCl_3$): 7.98 (2H, d, *J* 7.2, H22), 7.64 (1H, t, *J* 7.5, H24), 7.54 (2H, t, *J* 7.6, H23), 7.47 (1H, d, *J* 8.0, H6), 7.37 (1H, d, *J* 7.5, H14), 7.33 – 7.24 (3H, m, H15, H16, H17), 7.23 (1H, s, H2), 7.13 (1H, d, *J* 8.0, H5), 5.99 (1H, s, H12), 5.26 (1H, t, *J* 6.7, H19), 5.16 (1H, sept, *J* 6.3, H10), 4.74 (1H, sept, *J* 6.3, H10), 3.71 (1H, dd, *J* 15.7, *J* 6.7, H20), 3.57 (1H, dd, *J* 15.7, *J* 6.7, H20), 1.38 (3H, d, *J* 6.3, H11), 1.29 (3H, d, *J* 6.3, H11), 1.05 (3H, d, *J* 6.3, H11), 0.79 (3H, d, *J* 6.3, H11).

δ_C (126 MHz, $CDCl_3$): 167.8 (C9), 166.7 (C9), 152.9 (C1), 141.1 (C18), 140.0 (C21), 137.5 (C13), 133.9 (C24), 132.2 (q, *J* 32, C4), 131.6 (C7), 129.3 (C23), 129.1 (C16), 128.8 (C15), 127.8 (C22), 127.0 (C6), 124.0 (q, *J* 273, C3), 123.5 (C17), 123.2 (C14), 118.1 (q, *J* 4, C5), 109.4 (q, *J* 4, C2), 74.0 (C12), 70.3 (C10), 70.0 (C10), 67.4 (C8), 64.4 (C19), 63.2 (C20), 21.6 (C11), 21.5 (C11), 21.3 (C11), 20.9 (C11).

δ_F (376 MHz, $CDCl_3$): – 62.3.

HRMS (ES+): found 624.1620; $C_{31}H_{30}F_3NO_6SNa$ $[M+Na]^+$ requires 624.1638.

ν_{max} (neat): 2984, 1730, 1618, 1590 cm^{-1}.

Chiral HPLC (Chiralpak OD-H, 2 % IPA, 98 % hexane, 1.0 $mL.min^{-1}$, λ = 262) t_R (major) = 34.2, t_R (minor) = 25.9.

$[\alpha]_D^{25}$ – 18 (*c* = 0.60, $CHCl_3$).

Mp: 144 – 146 ˚C (petroleum ether : diethyl ether).

***Minor*:**

δ_H (500 MHz, $CDCl_3$): 8.00 (2H, d, *J* 7.3, H22), 7.74 – 7.67 (2H, m, H14, H24), 7.65 – 7.59 (3H, m, H6, H23), 7.50 (1H, d, *J* 7.2, H17), 7.42 (1H, t, *J* 7.2, H16), 7.34 (1H, t, *J* 7.2, H15), 7.19 (1H, d, *J* 8.0, H5), 6.85 (1H, s, H2), 6.08 (1H, s, H12), 5.52 (1H, d, *J* 7.0, H19), 5.29 (1H, sept, *J* 6.3, H10), 4.50 (1H, sept, *J* 6.3, H10), 3.76 (1H, dd, *J* 15.6, *J* 1.5, H20), 3.01 (1H, dd, *J* 15.5, *J* 7.0, H20), 1.42 (3H, d, *J* 6.3, H11), 1.41 (3H, d, *J* 6.3, H11), 0.95 (3H, d, *J* 6.3, H11), 0.77 (3H, d, *J* 6.3, H11).

δ_C (126 MHz, $CDCl_3$): 167.9 (C9), 166.9 (C9), 148.4 (C1), 144.1 (C18), 139.1 (C21), 136.5 (C7), 134.3 (C13/C24), 134.0 (C13/C24), 132.0 (q, *J* 32, C4), 129.6 (C23), 129.6 (C16), 128.1 (C22), 128.0 (C15), 126.6 (C6), 124.2 (C14/C17), 124.1 (C14/C17), 123.9 (q, *J* 273, C3), 118.7 (q, *J* 4, C5), 112.0 (q, *J* 4, C2), 75.9 (C12), 70.2 (C10), 66.6 (C8), 58.6 (C20), 57.7 (C19), 21.7 (C11), 21.6 (C11), 21.2 (C11), 21.1 (C11).

δ_F (376 MHz, $CDCl_3$): – 62.3.

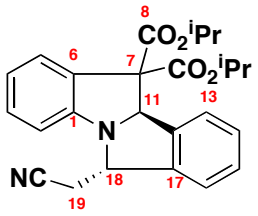
HRMS (ES+): found 624.1628; $C_{31}H_{30}F_3NO_6SNa$ $[M+Na]^+$ requires 624.1638.

ν_{max} (neat): 2985, 2938, 1726, 1641 cm^{-1}.

Chiral HPLC (Chiralpak OD-H, 2 % IPA, 98 % hexane, 1.0 $mL.min^{-1}$, λ = 217) t_R (major) = 11.8, t_R (minor) = 13.9.

$[\alpha]_D^{25}$ – 85 (*c* = 0.10, $CHCl_3$).

Pyrrolizidine **16**



***Asymmetric*.**[*] Aniline **28** (50 mg, 0.18 mmol), aldehyde **(*E*)-21a** (28 mg, 0.18 mmol) and magnesium sulfate (108 mg, 0.90 mmol) were stirred for 16 h at RT in toluene (1 mL). The resulting mixture was filtered and concentrated *in vacuo.* The imine was redissolved in toluene (1 mL), (8*S*, 9*R*)-*N*-benzylcinchonidinium chloride **11** (8 mg, 0.02 mmol) was added and the solution was stirred at – 30 ˚C for 30 minutes. Anhydrous powdered potassium hydroxide (81 mg, 1.44 mmol) was added to the reaction and stirred for 16 h at – 30 ˚C before quenching with ammonium chloride (sat aq., 10 mL) and extracting with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel, petroleum ether : ethyl acetate, 15 : 1) to afford compound **16** (67 mg, 89 %, 73 % ee, >20:1 dr).

***Racemic*.** Prepared according to *general procedure 3*: 25 mg aniline **28** (0.09 mmol), 13 mg aldehyde **(*E*)-21a** (0.09 mmol), chromatography (silica gel, petroleum ether : ethyl acetate, 15:1), 36 mg, 96 %.

δ_H (500 MHz, $CDCl_3$): 7.50 (1H, d, *J* 7.7, H5), 7.46 (1H, d, *J* 6.5, H13), 7.37 – 7.32 (2H, m, H14, H15), 7.32 – 7.28 (2H, m, H3, H16), 7.10 (1H, d, *J* 7.9, H2), 6.96 (1H, td, *J* 7.6, *J* 0.9, H4), 6.16 (1H, d, *J* 2.4, H11), 5.25 (1H, sept, *J* 6.3, H9), 4.87 (1H, td, *J* 5.8, *J* 2.5, H18), 4.54 (1H, sept, *J* 6.3, H9), 2.93 (1H, d, *J* 5.8, H19), 2.92 (1H, d, *J* 5.8, H19), 1.41 (3H, d, *J* 6.3, H10), 1.37 (3H, d, *J* 6.3, H10), 0.89 (3H, d, *J* 6.3, H10), 0.68 (3H, d, *J* 6.3, H10).

δ_C (126 MHz, $CDCl_3$): 168.7 (C8), 167.7 (C8), 152.7 (C6), 141.1 (C12), 137.8 (C17), 130.0 (C1/C3/C16), 129.9 (C1/C3/C16), 128.9 (C14/C15), 128.5 (C14/C15), 126.6 (C5), 124.2 (C13), 122.4 (C3/C16), 122.1 (C4), 117.9 (C20), 113.0 (C2), 74.8 (C11), 70.0 (C9), 69.5 (C9), 68.3 (C7), 66.8 (C18), 27.5 (C19), 21.7 (C10), 21.6 (C10), 21.2 (C10), 20.8 (C10).

HRMS (ES+): found 441.1784; $C_{25}H_{26}N_2O_4Na$ $[M+Na]^+$ requires 441.1785.

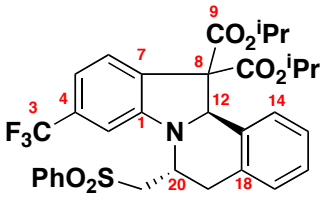
[*] *Due to low solubility of the substrate in toluene this cyclization could not be enacted* via *the methods outlined in the General Procedures.*

ν_{max} (neat): 2982, 2936, 2361, 2342, 1725, 1625, 1600 cm^{-1}.

Chiral HPLC (Chiralpak IA, 3 % IPA, 97 % hexane, 1.0 $mL.min^{-1}$, λ = 272) t_R (major) = 23.8, t_R (minor) = 18.4.

$[\alpha]_D^{25}$ + 43 (*c* = 2.1, $CHCl_3$).

Indolizidine **17**



Asymmetric. Prepared according to *general procedure 2*: 50 mg aniline **1** (0.14 mmol), 47 mg aldehyde **(*E*)-34** (0.14 mmol), chromatography (silica gel, petroleum ether : ethyl acetate, 10:1), *major* (as drawn): 47 mg, 53 %, 83 % ee, *minor*: 34 mg, 38 %, 87 % ee.

Racemic. Prepared according to *general procedure 3*: 50 mg aniline **1** (0.14 mmol), 47 mg aldehyde **(*E*)-34** (0.14 mmol), chromatography (silica gel, petroleum ether : ethyl acetate, 10:1), *major*: 24 mg, 27 %, *minor*: 13 mg, 15 %.

***Major*:**

δ_H (500 MHz, $CDCl_3$): 7.78 (2H, dd, *J* 8.0, *J* 0.8, H23), 7.57 (1H, t, *J* 7.4, H25), 7.46 – 7.37 (4H, m, H6, H17, H24), 7.22 – 7.16 (2H, m, H15, H16), 7.07 – 7.03 (1H, m, H14), 6.96 (1H, d, *J* 7.9, H5), 6.87 (1H, s, H2), 5.20 (1H, sept, *J* 6.3, H10), 5.11 (1H, s, H12), 4.63 – 4.56 (1H, m, H20), 4.39 (1H, sept, *J* 6.3, H10), 3.32 (1H, dd, *J* 14.8, *J* 8.4, H21), 3.16 (1H, dd, *J* 14.8, *J* 5.3, H21), 3.10 (1H, dd, *J* 15.5, *J* 5.5, H19), 2.72 (1H, d, *J* 15.5, H19), 1.38 (3H, d, *J* 6.3, H11), 1.36 (3H, d, *J* 6.3, H11), 0.76 (3H, d, *J* 6.3, H11), 0.61 (3H, d, *J* 6.3, H11).

δ_C (126 MHz, $CDCl_3$): 168.2 (C9), 166.9 (C9), 150.0 (C1), 139.4 (C7), 133.7 (C25), 132.7 (C18), 132.2 (C22), 131.4 (C13), 130.8 (q, *J* 263, C3), 130.2 (C4), 129.4 (C14), 129.0 (C24), 128.1 (C17), 127.9 (C15/C16), 127.5 (C23), 126.9 (C15/C16), 126.0 (C6), 115.4 (C5), 105.5 (C2), 70.3 (C10), 69.8 (C10), 68.1 (C8), 63.3 (C12), 57.8 (C21), 49.7 (C20), 33.1 (C19), 21.7 (C11), 21.5 (C11), 20.8 (C11), 20.7 (C11).

δ_F (376 MHz, $CDCl_3$): – 62.6.

HRMS (ES+): found 616.1820; $C_{32}H_{33}NF_3O_6S$ $[M+H]^+$ requires 616.1981.

ν_{max} (neat): 3070, 2983, 2933, 1724, 1667, 1614 cm^{-1}.

Chiral HPLC (Chiralpak IA, 3 % IPA, 97 % hexane, 1.0 $mL.min^{-1}$, λ = 209) t_R (major) = 21.6, t_R (minor) = 17.4.

$[\alpha]_D^{25}$ + 11 (*c* = 1.25, $CHCl_3$).

***Minor*:**

δ_H (500 MHz, $CDCl_3$): 7.91 (2H, d, *J* 8.6, H23), 7.72 (1H, t, *J* 7.5, H25), 7.64 – 7.58 (3H, m, H6, H24), 7.41 (1H, d, *J* 7.6, H17), 7.35 – 7.23 (3H, m, H14, H15, H16), 6.96 (1H, d, *J* 7.9, H5), 6.24 (1H, s, H2), 5.51 (1H, s, H12), 5.27 (1H, sept, *J* 6.3, H10), 4.77 (1H, sept, *J* 6.3, H10), 4.50 – 4.45 (1H, m, H20), 3.58 (1H, dd, *J* 15.2, *J* 1.9, H19), 3.18 (1H, dd, *J* 15.2, *J* 4.9, H19), 3.03 (1H, d, *J* 14.6, H21), 2.87 (1H, dd, *J* 14.6, *J* 10.3, H21), 1.39 (3H, d, *J* 6.3, H11), 1.37 (3H, d, *J* 6.3, H11), 0.91 (3H, d, *J* 6.3, H11), 0.80 (3H, d, *J* 6.3, H11).

δ_C (126 MHz, $CDCl_3$): 168.2 (C9), 167.0 (C9), 147.4 (C1), 139.1 (C7), 134.2 (C13/C22), 134.1 (C25), 132.5 (C13/C22), 132.2 (C18), 130.8 (C4), 129.6 (C24), 129.5 (C15), 127.8 (C23), 127.6 (C14), 126.8 (C16), 126.2 (C6), 125.3 (C17), 124.0 (q, *J* 272, C3), 115.3 (C5), 103.7 (C2), 70.5 (C10), 69.9 (C10), 65.7 (C8), 64.6 (C12), 56.0 (C21), 46.1 (C20), 32.9 (C19), 21.6 (C11), 21.6 (C11), 21.2 (C11), 21.2 (C11).

δ_F (376 MHz, $CDCl_3$): – 62.5.

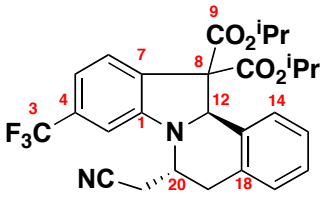
HRMS (ES+): found 638.1789; $C_{32}H_{32}NF_3O_6SNa$ $[M+Na]^+$ requires 638.1795.

ν_{max} (neat): 2984, 2924, 1725, 1668 cm^{-1}.

Chiral HPLC (Chiralpak IA, 4 % IPA, 96 % hexane, 1.0 $mL.min^{-1}$, λ = 335) t_R (major) = 14.8, t_R (minor) = 13.2.

$[\alpha]_D^{25}$ + 36 (*c* = 1.85, $CHCl_3$).

Indolizidine **18**



Asymmetric. Prepared according to *general procedure 2*: 50 mg aniline **1** (0.14 mmol), 25 mg aldehyde **(*E*)-33** (0.14 mmol), chromatography (silica gel, petroleum ether : ethyl acetate, 20:1), *major* (as drawn): 41 mg, 57 %, 93 % ee, *minor*: 30 mg, 42 %, 90 % ee.

Racemic. Prepared according to *general procedure 3*: 25 mg aniline **1** (0.07 mmol), 12 mg aldehyde **(*E*)-33** (0.07 mmol), chromatography (silica gel, petroleum ether : ethyl acetate, 20:1), *major*: 14 mg, 40 %, *minor*: 5 mg, 15 %.

Major (as drawn):

δ_H (500 MHz, $CDCl_3$): 7.57 (1H, d, *J* 7.0, H17), 7.53 (1H, d, *J* 7.9, H6), 7.29 – 7.22 (2H, m, H15, H16), 7.11 (1H, d, *J* 6.7, H14), 7.02 (1H, d, *J* 7.9, H5), 6.97 (1H, s, H2), 5.98 (1H, s, H12), 5.28 (1H, sept, *J* 6.3, H10), 4.47 (1H, sept, *J* 6.3, H10), 4.42 – 4.36 (1H, m, H20), 3.17 (1H, dd, *J* 15.5, *J* 5.2, H19), 2.76 (1H, d, *J* 15.5, H19), 2.55 (1H, dd, *J* 16.8, *J* 7.0, H21), 2.45 (1H, dd, *J* 16.8, *J* 7.3, H21) 1.42 (3H, d, *J* 6.3, H11), 1.38 (3H, d, *J* 6.3, H11), 0.85 (3H, d, *J* 6.3, H11), 0.63 (3H, d, *J* 6.3, H11).

δ_C (126 MHz, $CDCl_3$): 168.3 (C9), 167.0 (C9), 150.7 (C1), 132.5 (C7), 131.9 (C18), 131.0 (C13), 130.7 (C4), 129.6 (C17), 128.6 (C14), 128.1 (C15/C16), 127.1 (C15/C16), 126.2 (C6), 124.1 (q, *J* 273, C3), 117.8 (C22), 115.9 (C5), 105.6 (C2), 70.5 (C10), 69.9 (C10), 68.2 (C8), 63.9 (C12), 51.9 (C20), 32.4 (C19), 21.7 (C11), 21.6 (C11), 21.6 (C21), 21.0 (C11), 20.7 (C11).

δ_F (376 MHz, $CDCl_3$): – 62.6.

HRMS (ES+): found 523.1816; $C_{27}H_{27}N_2F_3O_4Na$ $[M+Na]^+$ requires 523.1815.

ν_{max} (neat): 2984, 2934, 2360, 2342, 1731, 1699, 1668, 1624 cm^{-1}.

Chiral HPLC (Chiralpak OD-H, 3 % IPA, 97 % hexane, 1.0 $mL.min^{-1}$, λ = 219) t_R (major) = 12.8, t_R (minor) = 9.8.

$[\alpha]_D^{25}$ – 11 (*c* = 0.95, $CHCl_3$).

MP: 93 – 95 ˚C (diethyl ether : petroleum ether).

***Minor*:**

δ_H (500 MHz, $CDCl_3$): 7.67 (1H, d, *J* 7.9, H6), 7.46 (1H, d, *J* 7.3, H17), 7.35 (1H, d, *J* 7.0, H14), 7.33 – 7.27 (2H, m, H15, H16), 7.02 (1H, d, *J* 7.9, H5), 6.74 (1H, s, H2), 5.52 (1H, s, H12), 5.29 (1H, sept, *J* 6.3, H10), 4.83 (1H, sept, *J* 6.3, H10), 4.50 – 4.46 (1H, m, H20), 3.28 (2H, br s, H19), 2.57 (1H, dd, *J* 17.0, *J* 3.3, H21), 2.11 (1H, dd, *J* 17.0, *J* 10.6, H21), 1.41 (3H, d, *J* 6.3, H11), 1.39 (3H, d, *J* 6.3, H11), 1.02 (3H, d, *J* 6.3, H11), 0.92 (3H, d, *J* 6.3, H11).

δ_C (126 MHz, $CDCl_3$): 168.2 (C9), 167.1 (C9), 147.7 (C7), 133.8 (C13), 132.6 (C1), 131.9 (C18), 130.7 (C4), 129.2 (C14), 127.7 (C15/C16), 127.0 (C15/C16), 126.4 (C6), 125.6 (C17), 125.1 (C3), 117.7 (C22), 115.6 (C5), 103.9 (C2), 70.5 (C10), 70.1 (C10), 65.5 (C12), 65.0 (C8), 48.1 (C20), 33.0 (C19), 21.7 (C11), 21.6 (C11), 21.3 (C11), 21.3 (C11), 20.1 (C21).

δ_F (376 MHz, $CDCl_3$): – 61.0.

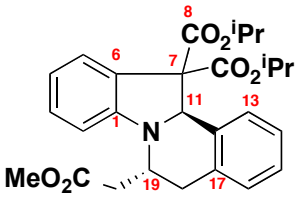
HRMS (ES+): found 523.1816; $C_{27}H_{27}N_2F_3O_4Na$ $[M+Na]^+$ requires 523.1815.

ν_{max} (neat): 2986, 2936, 2851, 2360, 2339, 1792, 1646 cm^{-1}.

Chiral HPLC (Chiralpak OD-H, 3 % IPA, 97 % hexane, 1.0 $mL.min^{-1}$, λ = 216) t_R (major) = 7.2, t_R (minor) = 19.0.

$[\alpha]_D^{25}$ + 83 (*c* = 1.20, $CHCl_3$).

Indolizidine **19**



Asymmetric. Prepared according to *general procedure 2*: 50 mg aniline **28** (0.18 mmol), 37 mg aldehyde **(*E*)-3** (0.18 mmol), chromatography (silica gel, petroleum ether : ethyl acetate, 20:1), 36 mg, 45 %, 75 % ee.

Racemic. Prepared according to *general procedure 4*: 25 mg aniline **28** (0.09 mmol), 18 mg aldehyde **(*E*)-3** (0.09 mmol), chromatography (silica gel, petroleum ether : ethyl acetate, 20:1), 15 mg, 36 %.

δ_H (500 MHz, $CDCl_3$): 7.56 (1H, d, *J* 7.7, H5), 7.48 – 7.43 (1H, m, H13), 7.27 – 7.18 (4H, m, H3, H14, H15, H16), 6.71 (1H, t, *J* 7.7, H4), 6.60 (1H, d, *J* 7.8, H2), 5.53 (1H, s, H11), 5.28 (1H, sept, *J* 6.3, H9), 4.81 (1H, sept, *J* 6.3, H9), 4.51 – 4.45 (1H, m, H19), 3.69 (3H, s, H22), 3.19 (1H, dd, *J* 15.0, *J* 5.2, H18), 3.01 (1H, dd, *J* 15.0, *J* 1.9, H18), 2.57 (1H, d, *J* 15.7, H20), 2.09 (1H, dd, *J* 15.7, *J* 10.6, H20), 1.40 (3H, d, *J* 6.3, H10), 1.38 (3H, d, *J* 6.3, H10), 0.93 (3H, d, *J* 6.3, H10), 0.80 (3H, d, *J* 6.3, H10).

δ_C (126 MHz, $CDCl_3$): 172.6 (C21), 169.2 (C8), 167.9 (C8), 148.2 (C1), 135.0 (C12), 133.5 (C17), 129.8 (C3), 128.9 (C14/C15/C16), 127.0 (C14/C15/C16), 126.9 (C6), 126.5 (C14/C15/C16), 126.0 (C5), 125.5 (C13), 117.7 (C4), 107.8 (C2), 69.9 (C9), 69.3 (C9), 66.1 (C7), 64.8 (C11), 51.6 (C22), 48.0 (C19), 36.6 (C20), 33.7 (C18), 21.7 (C10), 21.6 (C10), 21.3 (C10), 21.1 (C10).

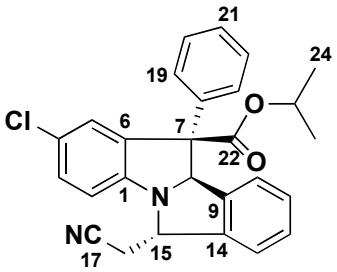
HRMS (ES+): 488.2038 found; $C_{27}H_{31}NO_6Na$ $[M+Na]^+$ requires 488.2044.

Chiral HPLC (Chiralpak IA, 3 % IPA, 97 % hexane, 1.0 mL.min^{-1}, λ = 272) t_R (major) = 6.6, t_R (minor) = 7.0.

$[\alpha]_D^{25}$ + 6 (*c* = 0.3, $CHCl_3$).

ν_{max} (neat): 2982, 2952, 1731, 1664, 1601 cm^{-1}.

Pyrrolizidine **22**



Asymmetric. Prepared according to *general procedure 5*: 50 mg aniline **20b** (0.165 mmol), 26 mg aldehyde **(*E*)-21a** (0.165 mmol), T = -30 °C, chromatography (silica gel, hexane : ethyl acetate, 10:1), 64 mg, 87 %, 97 % ee, >20:1 dr.

Racemic. Prepared according to *general procedure 6*: 50 mg aniline **20b** (0.165 mmol), 26 mg aldehyde **(*E*)-21a** (0.165 mmol), chromatography (silica gel, hexane : ethyl acetate, 10:1), 72 mg, 95 % combined yield of diastereomers, 14 mg, 19 % yield of desired diastereoisomer.

δH (400 MHz, $CDCl_3$): 7.58 (2H, d, *J* 7.4, H19), 7.48-7.41 (3H, m), 7.40-7.31 (4H, m), 7.25 (1H, dd, *J* 8.4, 2.1, H3), 7.12 (1H, d, *J* 2.1, H5), 7.07 (1H, d, *J* 8.5, H2), 5.69 (1H, d, *J* 2.3, H8), 4.88 (1H, td, *J* 5.7, 2.3, H15), 4.64 (1H, sept, *J* 6.3, H23), 2.93 (1H, dd, *J* 16.7, 5.3, H16), 2.84 (1H, dd, *J*, 16.7, 6.2, H16), 0.86 (3H d, *J* 6.2, H24), 0.54 (3H, d, *J* 6.3, H24').

δC (101 MHz, $CDCl_3$): 169.9 (C22), 151.8 (C1), 141.9 (Ar C), 140.7 (Ar C), 138.7 (Ar C), 136.1 (Ar C), 129.4 (C3), 128.8 (Ar CH), 128.7 (Ar CH), 128.7 (C20), 128.2 (C19), 127.5 (Ar CH), 126.5 (Ar C), 126.4 (C5), 123.3 (Ar CH), 122.6 (Ar CH), 118.0 (C17), 113.5 (C2), 82.1 (C8), 68.8 (C23), 66.9 (C15), 66.8 (C7), 27.3 (C16), 21.1 (C24), 20.6 (C24').

HRMS (ES+): found 465.1327; $C_{27}H_{23}{}^{35}ClN_2O_2Na$, $[M(^{35}Cl)+Na]^+$ requires 465.1340.

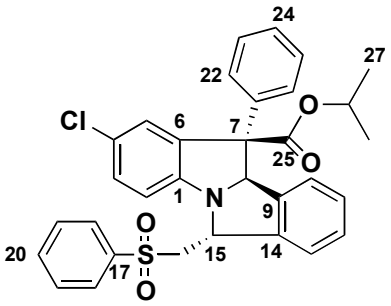
ν_{max} (neat): 3060, 3029, 2981, 2934, 2881, 2250 (C≡N), 1723 (C=O), 1475, 1218, 1105, 757, 700 cm^{-1}.

MP: 142-151 °C.

Chiral HPLC (Chiralpak IA, 3 % IPA, 97 % hexane, 1.0 $mL.min^{-1}$, λ = 245) t_R (major) = 22.2, t_R (minor) = 20.3.

$[\alpha]_D^{25.0}$ -9.0 (*c* = 2.1, $CHCl_3$).

Pyrrolizidine **23**



Asymmetric. Prepared according to *general procedure 5*: 50 mg aniline **20b** (0.165 mmol), 45 mg aldehyde **21b** (0.165 mmol), T = 0 °C, chromatography (silica gel, hexane : ethyl acetate, 20:1), *major*: 53 mg, 58 %, 94 % ee, *minor*: 29 mg, 31 %.*

Racemic. Prepared according to *general procedure 6*: 50 mg aniline **20b** (0.165 mmol), 45 mg aldehyde **21b** (0.165 mmol), chromatography (silica gel, hexane : ethyl acetate, 20:1), 68 mg, 74 % combined yield of diastereomers, 7 mg, 8 % yield of desired diastereoisomer.

Major (as drawn)

δH (400 MHz, $CDCl_3$): 7.89 (2H, d, *J* 7.3, H18), 7.51 (1H, t, *J* 6.9, H20), 7.41-7.34 (3H, m, H11 & H19), 7.33-7.21 (7H, m), 7.20-7.13 (3H, m, H2 & 2 x Ar CH), 5.35-5.30 (2H, m, H8 & H15), 4.89 (1H, septet, *J* 6.3, H26), 3.58 (1H, dd, *J* 15.0, 8.3, H16), 3.52 (1H, dd, *J* 14.9, 4.3, H16'), 1.09 (3H, d, *J* 6.3, H27), 0.76 (3H, d, *J* 6.2, H27').

δC (101 MHz, $CDCl_3$): 169.8 (C25), 151.1 (C1), 142.8 (Ar C), 140.7 (Ar C), 140.3 (Ar C), 138.8 (Ar C), 133.7 (Ar C), 133.6 (C20), 129.1 (Ar CH), 129.0 (C19), 129.0 (Ar CH), 128.5 (Ar CH), 128.3 (Ar CH), 127.7 (C18), 127.3 (Ar CH), 127.2 (Ar CH), 126.6 (Ar CH), 125.9 (C4), 123.8 (C11), 123.0 (Ar CH), 113.8 (C2), 80.0 (C8), 69.3 (C26), 65.2 (C15), 65.1 (C7), 62.3 (C16), 21.4 (C27), 21.0 (C27').

HRMS (ES+): found 580.1322; $C_{32}H_{28}{}^{35}ClNO_4SNa$, $[M(^{35}Cl)+Na]^+$ requires 580.1320.

ν_{max} (neat): 3036, 2987, 2931, 1731 (C=O), 1598, 1299 (S=O), 1077, 690, 607 cm^{-1}.

MP: 192-194 °C.

Chiral HPLC (Chiralpak OD-H, 20 % IPA, 80 % hexane, 1.0 $mL.min^{-1}$, λ = 245) t_R (major) = 13.0, t_R (minor) = 11.2.

---

* *The ee of the minor diastereoisomer could not be determined since a racemic sample of this isomer was not generated.*

$[\alpha]_D^{25.0}$ +64.2 (*c* = 0.85, $CHCl_3$).

Minor*

δH (500 MHz, $CDCl_3$): 8.01 (2H d, *J* 7.3, H18), 7.74 (1H, t, *J* 7.4, H20), 7.65 (2H, t, *J* 7.6, H19), 7.46-7.41 (4H, m, H22 & H23), 7.40-7.30 (3H, m, H12, H13 & H24), 7.30-7.25 (1H, m, H11), 7.20 (1H, dd, *J* 8.4, 2.2, H3), 7.18 (1H, d, *J* 2.2, H10), 7.12 (1H, d, *J* 2.2, H5), 6.60 (1H, d, *J* 8.5, H2), 5.55 (1H, d, H8), 5.49 (1H, d, *J* 6.6, H15), 4.68 (1H, septet, *J* 6.3, H26), 3.65 (1H, dd, *J* 15.4, 1.7, H16), 3.22 (1H, dd, *J* 15.4, 6.7, H16'), 0.91 (3H, d, *J* 6.3, H27), 0.82 (3H, d, *J* 6.3, H27').

δC (126 MHz, $CDCl_3$): 170.1 (C25), 146.2 (C1), 143.7 (Ar C), 141.3 (Ar C), 139.4 (Ar C), 138.7 (Ar C), 136.2 (Ar C), 134.0 (C20), 129.5 (C19), 129.4 (C3), 128.7 (C23), 128.3 (C18), 127.9 (C11), 127.8 (C22), 127.6 (C12/C24), 127.0 (C5), 126.5 (C4), 123.7 (C13), 122.5 (C10), 116.0 (C2), 81.9 (C8), 68.7 (C26), 66.7 (C7), 58.7 (C16), 57.7 (C15), 21.3 (C27), 21.0 (C27').†

HRMS (ES+): found 580.1320; $C_{32}H_{28}{}^{35}ClNO_4SNa$, $[M(^{35}Cl)+Na]^+$ requires 580.1320.

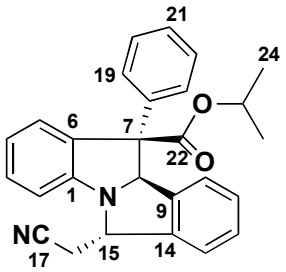
ν_{max} (neat): 3063, 2980, 1723 (C=O), 1600, 1472, 1308 (S=O), 1210, 1103, 911 cm^{-1}.

---

* *The ee of the minor diastereoisomer could not be determined since a racemic sample of this isomer was not generated.*

† *Note that a ^{13}C peak corresponding to either C12 or C24 was not observed, presumably due to overlap with another peak.*

Pyrrolizidine **24**



Asymmetric. Prepared according to *general procedure 5*: 50 mg aniline **20a** (0.186 mmol), 26 mg aldehyde **(*E*)-21a** (0.184 mmol), T = -78 °C, chromatography (silica gel, dichloromethane : hexane, 1:1), 61 mg, 80 %, 93 % ee, >20:1 dr.

Racemic. Prepared according to *general procedure 6*: 50 mg aniline **20a** (0.186 mmol), 26 mg aldehyde **(*E*)-21a** (0.184 mmol), chromatography (silica gel, dichloromethane : hexane, 1:1), 48 mg, 64 % combined yield of diastereomers, 18 mg, 24 % yield of desired diastereoisomer.

δH (400 MHz, $CDCl_3$): 7.60 (2H, d, *J* 7.4, H19), 7.48-7.39 (3H, m), 7.38-7.32 (4H, m), 7.29 (1H, t, *J* 8.2, H3), 7.13 (2H, t, *J* 6.9, H2 & H5), 6.95 (1H, t, *J* 7.5, H4), 5.65 (1H, d, *J* 2.4, H8), 4.91 (1H, td, *J* 5.7, 2.5, H15), 4.60 (1H, septet, *J* 6.2, H23), 2.95 (1H, dd, *J* 16.6, 5.6, H16), 2.89 (1H, dd, *J* 16.7, 5.8, H16'), 0.79 (3H, d, *J* 6.2, H24), 0.49 (3H, d, *J* 6.3, H24').

δC (101 MHz, $CDCl_3$): 170.4 (C22), 153.2 (C1), 142.5 (Ar C), 140.9 (Ar C), 139.2 (Ar C), 134.2 (C6), 129.4 (C3), 128.6 (Ar CH), 128.6 (Ar CH), 128.5 (Ar CH), 128.5 (C19), 127.3 (Ar CH), 126.4 (C5), 123.1 (Ar CH), 122.6 (Ar CH), 121.8 (C4), 118.0 (C17), 112.7 (C2), 81.8 (C8), 68.4 (C23), 67.0 (C7), 66.9 (C15), 27.4 (C16), 21.0 (C24), 20.6 (C24').

HRMS (ES+): found 431.1727; $C_{27}H_{24}N_2O_2Na$, $[M+Na]^+$ requires 431.1730.

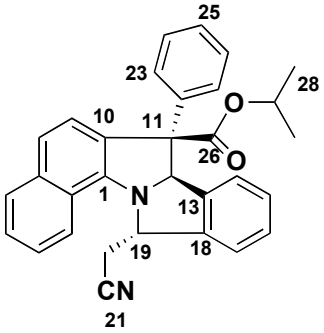
ν_{max} (neat): 3029, 2979, 2933, 2162, 1719 (C=O), 1599, 1479, 1210, 1103, 754, 699 cm^{-1}.

MP: 61-64 °C.

Chiral HPLC (Chiralpak IA, 10 % IPA, 90 % hexane, 1.0 $mL.min^{-1}$, λ = 207) t_R (major) = 22.2, t_R (minor) = 14.3.

$[\alpha]_D^{25.0}$ -29.8 (*c* = 0.57, $CHCl_3$).

Pyrrolizidine **25**



Asymmetric. Prepared according to *general procedure 5*: 50 mg aniline **20c** (0.156 mmol), 25 mg aldehyde **(*E*)-21a** (0.159 mmol),[*] T = 0 °C, chromatography (silica gel, hexane : ethyl acetate, 20:1), 37 mg, 52 %, 90 % ee, >20:1 dr.

Racemic. Prepared according to *general procedure 6*: 50 mg aniline **20c** (0.156 mmol), 25 mg aldehyde **(*E*)-21a** (0.156 mmol), chromatography (silica gel, hexane : ethyl acetate, 20:1), 31 mg, 43 % combined yield of diastereomers.[†]

δH (500 MHz, $CDCl_3$): 8.00 (1H, d, *J* 8.3, H3), 7.90 (1H, d, *J* 8.0, H6), 7.59-7.54 (2H, m, H4 & Ar CH), 6.54-7.47 (4H, m, H24, H25 & Ar CH), 7.42-7.32 (5H, m, H23 & 3 x Ar CH), 7.31-7.26 (2H, m, 2 x Ar CH), 5.94 (1H, s, H12), 5.36 (1H, t, *J* 4.5, H19), 4.74 (1H, septet, *J* 6.3, H27), 3.26-3.16 (2H, m, H20 & H20'), 0.98 (3H, d, *J* 6.2, H28), 0.52 (3H, d, *J* 6.3, H28').

δC (126 MHz, $CDCl_3$): 170.5 (C26), 148.4 (C1), 143.8 (C22), 140.4 (Ar C), 139.2 (Ar C), 135.0 (C7), 129.2 (C6), 128.8 (Ar CH), 128.7 (Ar CH), 128.4 (C23), 128.1 (C24), 127.2 (Ar CH), 125.9 (Ar CH), 125.6 (Ar CH), 124.3 (Ar CH), 123.6 (C10), 123.5 (Ar CH), 122.8 (C3), 122.6 (Ar CH), 122.6 (Ar CH), 117.3 (C21), 82.3 (C12), 68.9 (C27), 66.6 (C11), 65.6 (C19), 28.1 (C20), 21.3 (C28), 20.7 (C28').[‡]

HRMS (ES+): found 481.1875; $C_{31}H_{26}N_2O_2Na$, $[M+H]^+$ requires 481.1886.

ν_{max} (neat): 3056, 2979, 2916, 2248 (C≡N), 1718 (C=O), 1573, 1341, 1178, 1095, 1086, 761, 693 cm^{-1}.

MP: 158-163 °C.

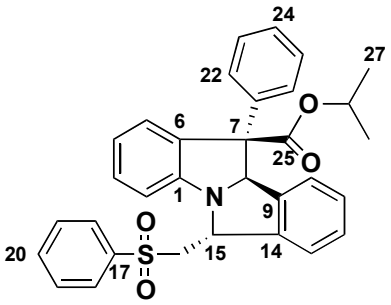
---

[*] *Note that this substrate was stirred for 72 h during the imine formation stage.*
[†] *In this case a pure racemic sample of the diastereomer formed in the asymmetric reaction could not be isolated, but it was possible to identify the relevant enantiomers from the chiral HPLC trace of the mixture of diastereomers.*
[‡] *One fully substituted aromatic C not observed and assumed to be overlapping with another peak.*

Chiral HPLC (Chiralpak OD-H, 10 % IPA, 90 % hexane, 1.0 mL.min^{-1}, λ = 251) t_R (major) = 10.5, t_R (minor) = 11.8.

$[\alpha]_D^{25.0}$ -84.6 (*c* = 1.3, $CHCl_3$).

Pyrrolizidine **26**



Asymmetric. Prepared according to *general procedure 5*: 50 mg aniline **20a** (0.186 mmol), 51 mg aldehyde **21b** (0.187 mmol), T = RT, chromatography (silica gel, petroleum ether : ethyl acetate, 10:1), *major*: 69 mg, 70 %, 89 % ee, 8.5:1 dr.*

Racemic. Prepared according to *general procedure XX*: 50 mg aniline **20a** (0.186 mmol), 51 mg aldehyde **21b** (0.187 mmol), chromatography (silica gel, petroleum ether : ethyl acetate, 10:1), 58 mg, 60 % combined yield of diastereomers, 12 mg, 12 % yield of desired diastereoisomer.

δH (400 MHz, $CDCl_3$): 7.91 (2H, d, *J* 7.3, H18), 7.49 (1H, app. t, *J* 7.5, H20), 7.41 (1H, d, *J* 7.4, H10), 7.39-7.33 (3H, m, H11 & H19), 7.33-7.24 (7H, m, H12, H13, H22, H23 & H24), 7.22 (1H, d, *J* 7.0, H3), 7.17 (2H, app. d, *J* 8.4, H2 & H5), 6.89 (1H, app. td, *J* 7.4, 0.9, H4), 5.36 (1H, dd, *J* 7.4, 4.7, H15), 5.31 (1H, s, H8), 4.85 (1H, septet, *J* 6.3, H26), 3.63 (1H, dd, *J* 14.8, 7.9, H16). 3.55 (1H, dd, *J* 14.9, 4.5, H16'), 1.03 (3H, d, *J* 6.2, H27), 0.70 (3H, d, *J* 6.2, H27').

δC (101 MHz, $CDCl_3$): 170.4 (C25), 152.6 (C1), 143.4 (Ar C), 141.1 (Ar C), 140.3 (Ar C), 139.3 (Ar C), 133.5 (C20), 132.1 (C17), 129.1 (Ar CH), 128.9 (Ar CH), 128.7 (Ar CH), 128.3 (Ar CH), 128.2 (Ar CH), 127.7 (Ar CH), 127.6 (Ar CH), 127.0 (Ar CH), 126.6 (C5), 123.6 (C10), 123.1 (C11), 121.1 (C4), 112.9 (C2), 80.0 (C8), 68.9 (C26), 65.4 (C7), 65.1 (C15), 62.6 (C16), 21.4 (C27), 21.0 (C27').

HRMS (ES+): found 524.1886; $C_{32}H_{30}NO_4S$, $[M+H]^+$ requires 524.1890.

ν_{max} (neat): 3036, 2987, 2931, 1731 (C=O), 1598, 1299 (S=O), 1077, 690, 607 cm^{-1}.

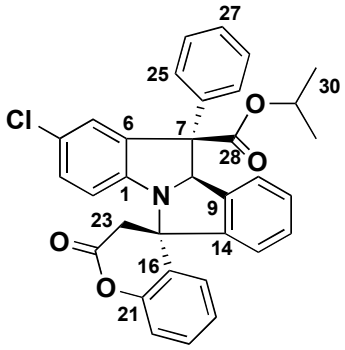
MP: 142-144 °C.

Chiral HPLC (Chiralpak IA, 10 % IPA, 90 % hexane, 1.0 $mL.min^{-1}$, λ = 239) t_R (major) = 19.5, t_R (minor) = 13.7.

* Diastereomeric ratio determined by integration of characteristic H16 peaks in the crude ^1H NMR spectrum.

$[\alpha]_D^{25.0}$ +41.3 (*c* = 0.45, $CHCl_3$).

Pyrrolizidine **27**



Asymmetric. Prepared according to *general procedure XX*: 50 mg aniline **20b** (0.165 mmol), 41 mg aldehyde **36** (0.164 mmol), T = 0 °C, chromatography (silica gel, petroleum ether : ethyl acetate, 20:1), 40 mg, 48 %, 97 % ee, >20:1 dr.

Racemic. Prepared according to *general procedure XX*: 50 mg aniline **20b** (0.165 mmol), 41 mg aldehyde **36** (0.164 mmol), chromatography (silica gel, petroleum ether : ethyl acetate, 20:1), 45 mg, 51 % combined yield of diastereomers.*

δH (500 MHz, $CDCl_3$): 7.69 (1H, dd, *J* 7.7, 1.6, H17), 7.58-7.51 (4H, m, H25 & H26), 7.45 (1H, app. tt, *J* 7.2, 1.6, H27), 7.43-7.39 (1H, m, H19), 7.39-7.27 (6H, m, H5, H11-H13, H20), 7.24-7.17 (3H, m, H3, H10, H18), 6.52 (1H, d, *J* 8.4, H2), 5.94 (1H, s, H8), 4.91 (1H, septet, *J* 6.3, H29), 3.49 (1H, d, *J* 15.4, H23), 2.89 (1H, d, *J* 15.8, H23'), 1.04 (3H, d, *J* 6.3, H30), 0.93 (3H, d, *J* 6.4, H30').

δC (126 MHz, $CDCl_3$): 170.2 (C28), 167.4 (C22), 150.1 (C1), 146.0 (C21), 145.0 (Ar C), 142.4 (Ar C), 138.6 (Ar C), 135.5 (Ar C), 129.7 (C19), 129.3 (Ar C), 129.1 (C3), 129.0 (Ar CH), 128.9 (C26), 128.5 (Ar CH), 127.7 (C25), 127.6 (Ar CH), 127.6 (C27), 127.2 (C4), 126.5 (C17), 125.2 (C18), 123.4 (Ar CH), 122.4 (C10), 117.5 (C20), 115.7 (C2), 82.4 (C8), 69.4 (C29), 67.8 (C7/C15), 66.5 (C7/C15), 38.7 (C23), 21.2 (C30), 21.0 (C30').

HRMS (ES+): found 558.1440; $C_{33}H_{26}{}^{35}ClNO_4Na$, $[M(^{35}Cl)+Na]^+$ requires 558.1443.

ν_{max} (neat): 3028, 2981, 2929, 1776 (C=O), 1724 (C=O), 1471, 1227, 1193, 758 cm^{-1}.

MP: 133-135 °C.

* *In this case a pure racemic sample of the diastereomer formed in the asymmetric reaction could not be isolated, but it was possible to identify the relevant enantiomers from the chiral HPLC trace of the mixture of diastereomers.*

Chiral HPLC (Chiralpak IC, 3 % IPA, 97 % hexane, 1.0 mL.min^{-1}, λ = 245) t_R (major) = 10.5, t_R (minor) = 16.4.

$[\alpha]_D^{25.0}$ +158.6 (*c* = 0.43, $CHCl_3$).

4 References

[1] A. B. Pangborn, M. A. Gairdello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics*, 1996, **15**, 1518.

[2] D. D. Perrin, W. L. F. Armarego, *Purification of Laboratory Chemicals*; Pergamon Press, 2nd Edition; Oxford, 1980.

[3] E. E. Maciver, S. Thompson, M. Smith, *Angew. Chem. Int. Ed.*, 2009, **48**, 9979.

[4] M. J. Mąkosza, K. Kamieńska-Trela, M. Paszewski, M. Bechcicka, *Tetrahedron*, 2005, **61**, 11952.

[5] K. S. Macmillan, T. Nguyen, I. Hwang, D. L. Boger, *J. Am. Chem. Soc.* 2009, **131**, 1187.

[6] M. Freiria, A. J. Whitehead, D. A. Tocher, W. B. Motherwell, *Tetrahedron*, 2004, **60**, 2673.

[7] C. S. Bryan, M. Lautens, *Org. Lett.*, 2010, **12**, 2754.

[8] This compound was prepared according to A. M. Van Leusen, B. A. Reith, A. J. W. Iedema, J. Strating, *Recueil des Travaux Chimique des Pays-Bas*, 1972, **91**, 37.

[9] S. Chandrasekhar, C. Narsihmulu, S. S. Sultana, N. R. Reddy, *Chem. Commun.,* 2003, 1716.

[10] W. F. K. Schnatter, Ö. Almarsson, T. C. Bruice, *Tetrahedron*, 1991, **47**, 8687.

[11] Oxidative cleavage of diol: B. Wünsch, M. Zott, *Synthesis*, 1992, 927.

[12] C. S. Cho, D. K. Lim, J. Q. Zhang, T.-J. Kim, S. C. Shim, *Tetrahedron Letters*, 2004, **45**, 5653.

[13] I. D. G. Watson, S. Ritter, F. D. Toste, *J. Am. Chem. Soc.*, 2009, **131**, 2056.

[14] K. Yoshikai, T. Hayama, K. Nishimura, K.-I. Yamada, K. Tomioka, *J. Org. Chem.*, 2005, **70**, 681.

[15] A. L. Hansen, T. Skrydstrup, *Org. Lett.*, 2005, **7**, 5585.

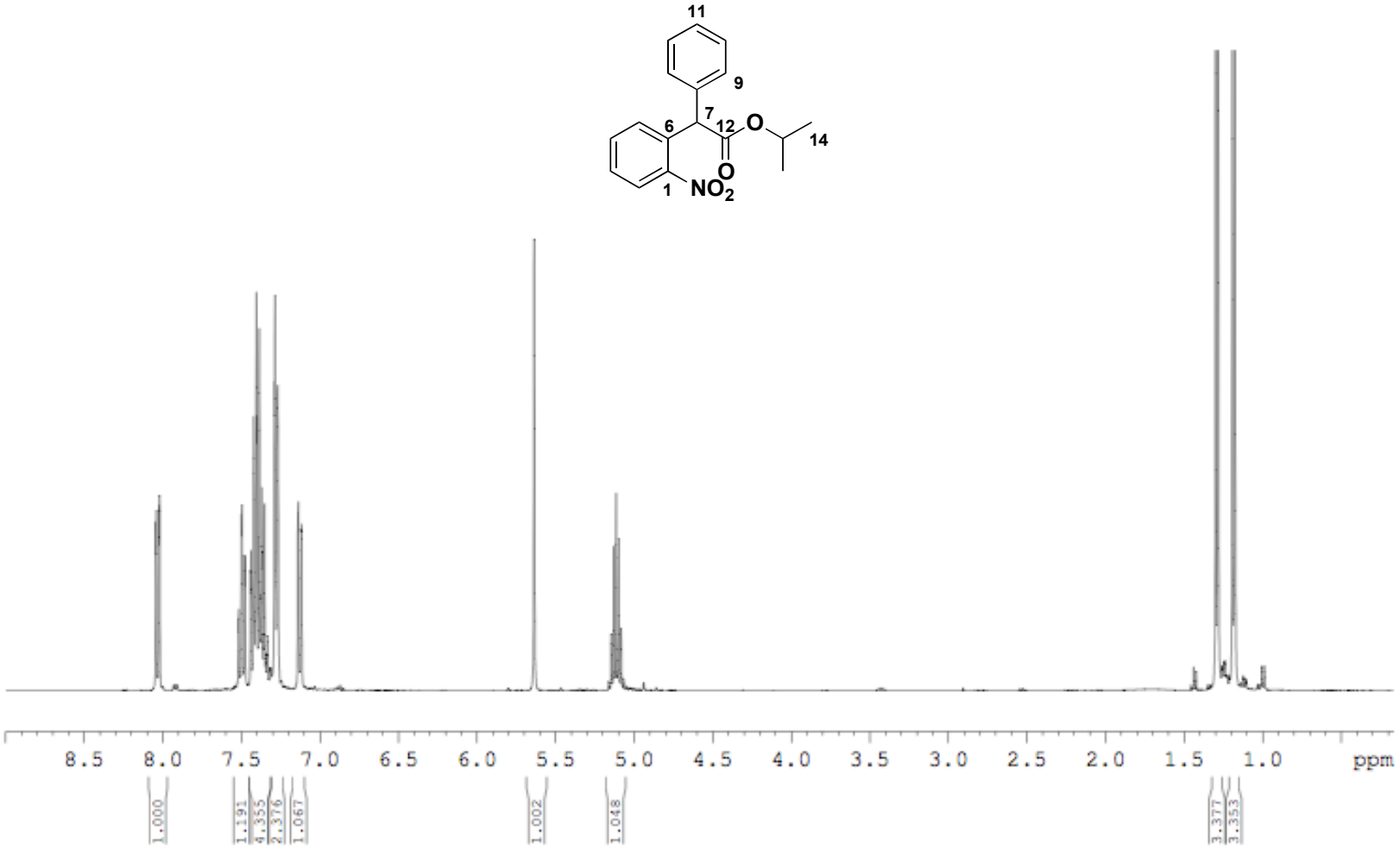
[16] J.-G. Lei, M.-H. Xu, G.-Q. Lin *Synlett*, 2004, 2364.

[17] This compound was prepared according to L. M. Venanzi, *J. Chem. Soc.*, 1958, 719.

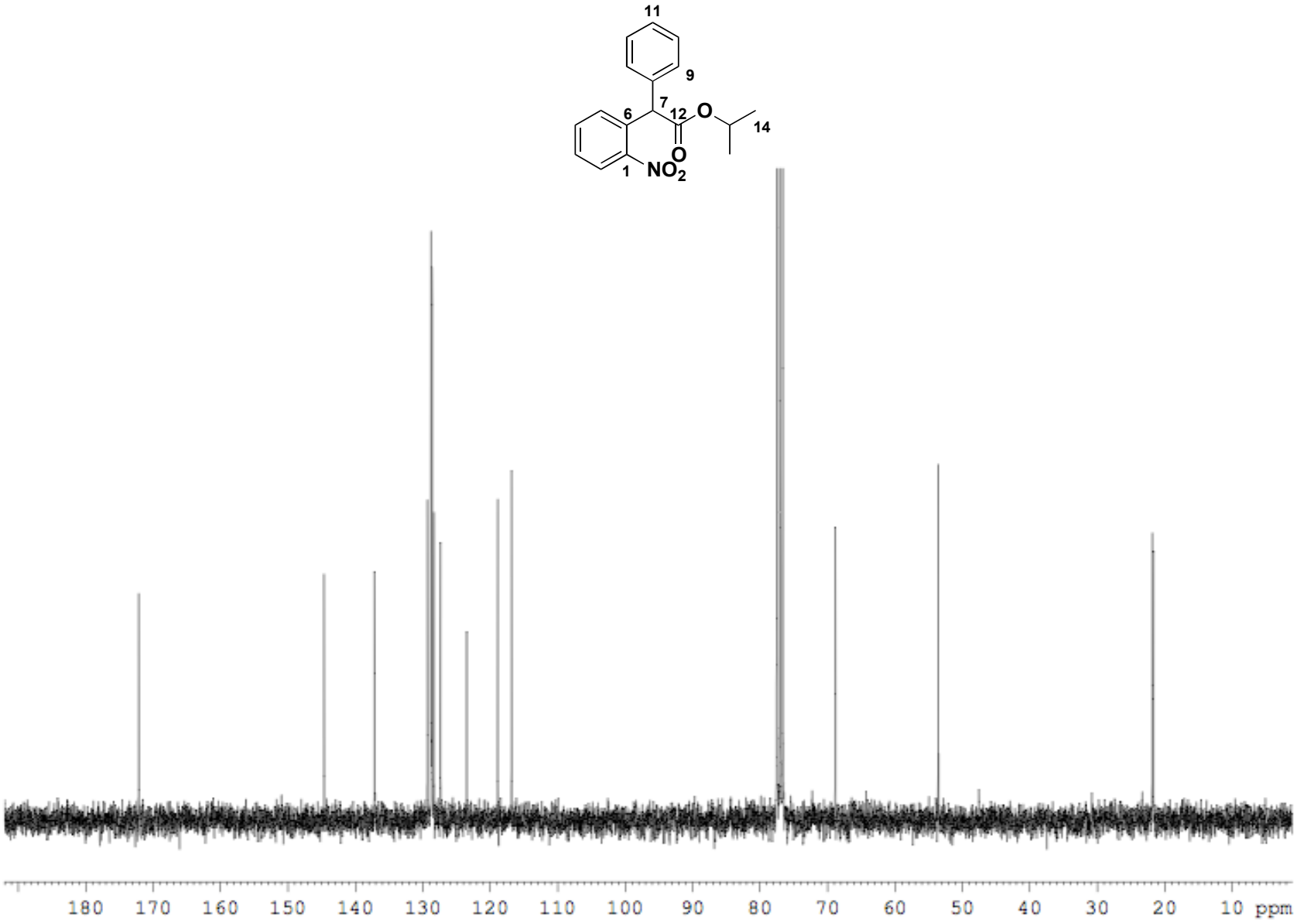
5 NMR Spectra

5.1 Anilines and precursors

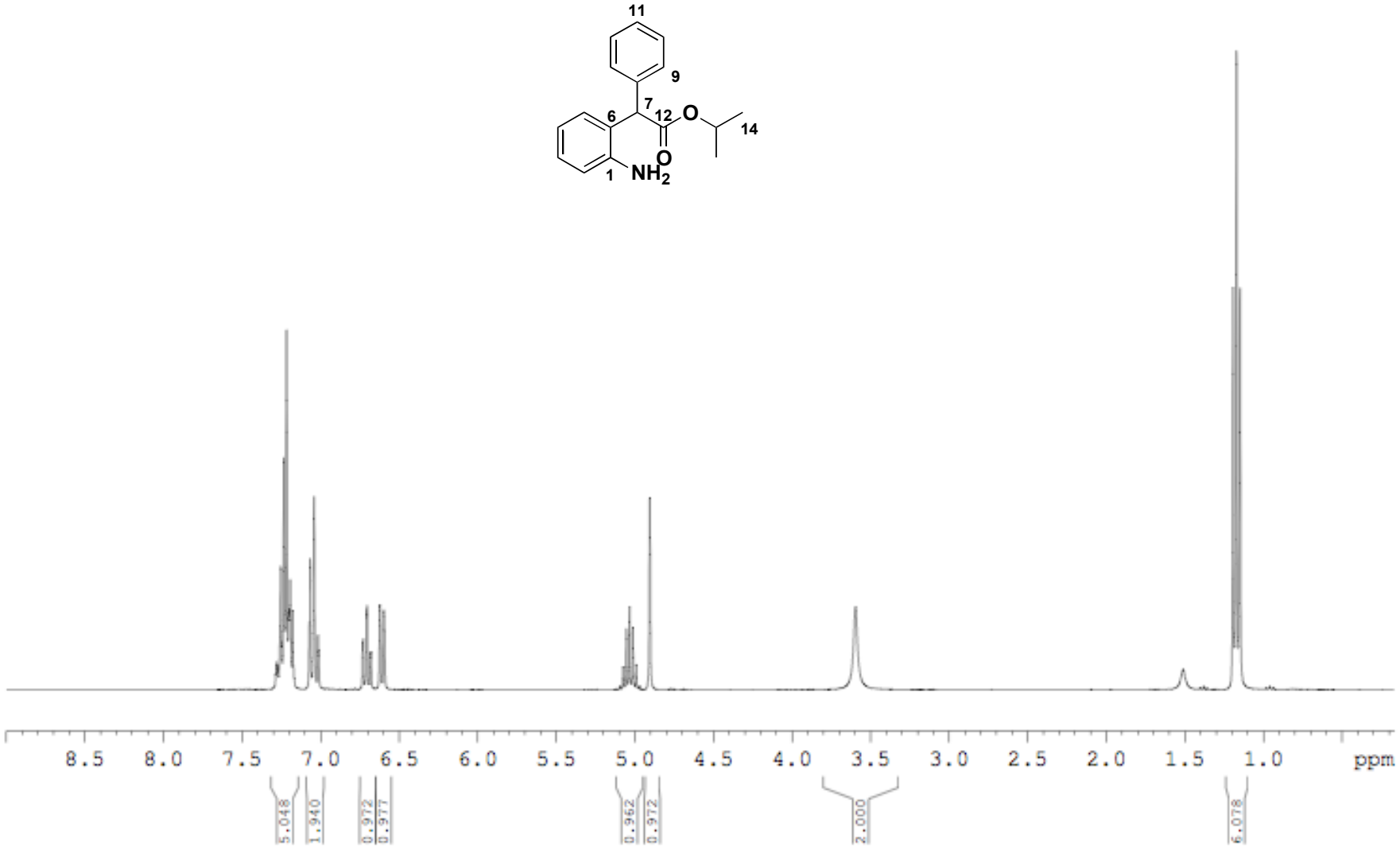
Iso-propyl 2-(2-nitrophenyl)-2-phenylacetate (**29**)



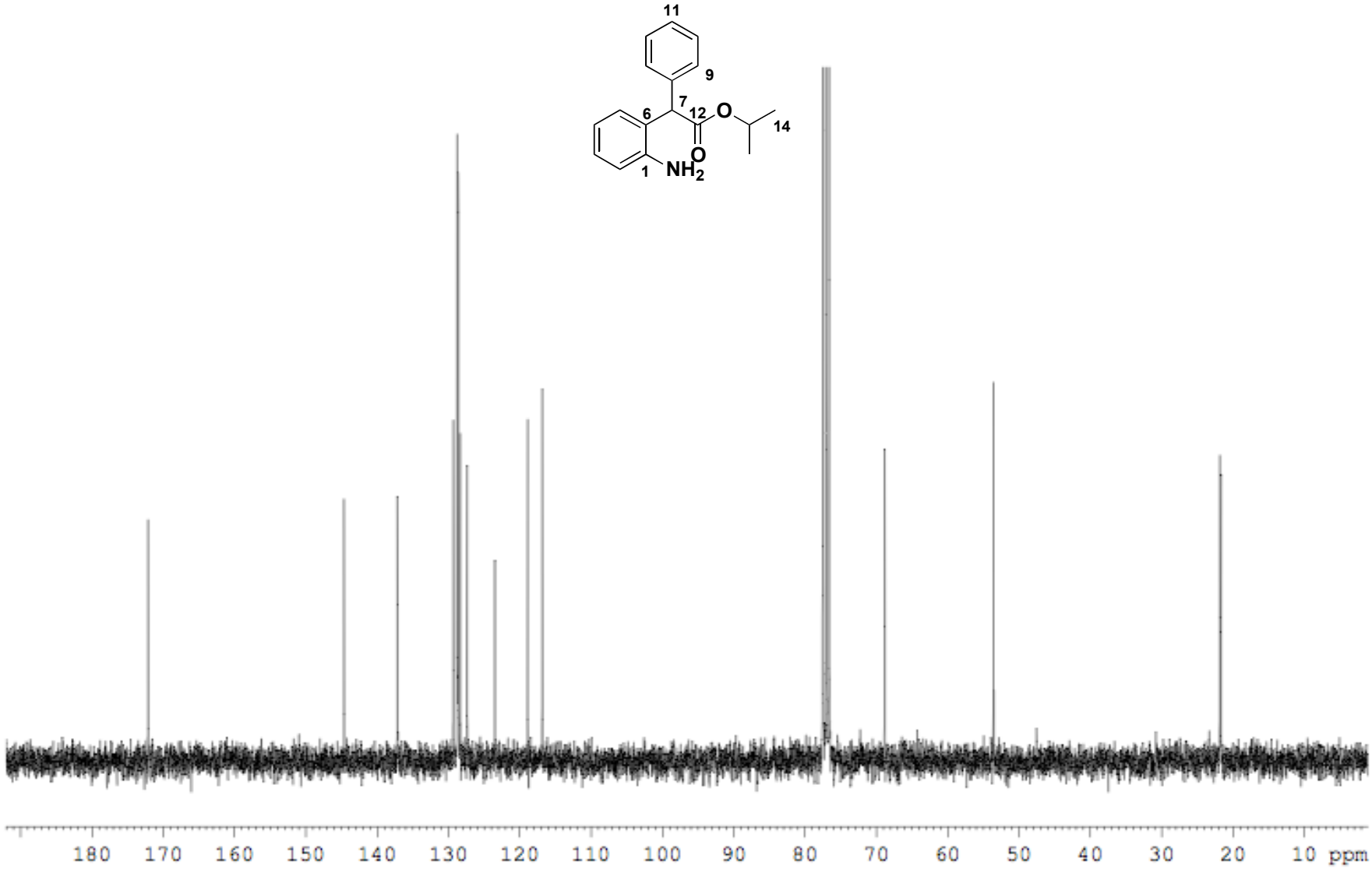
Iso-propyl 2-(2-nitrophenyl)-2-phenylacetate (**29**)



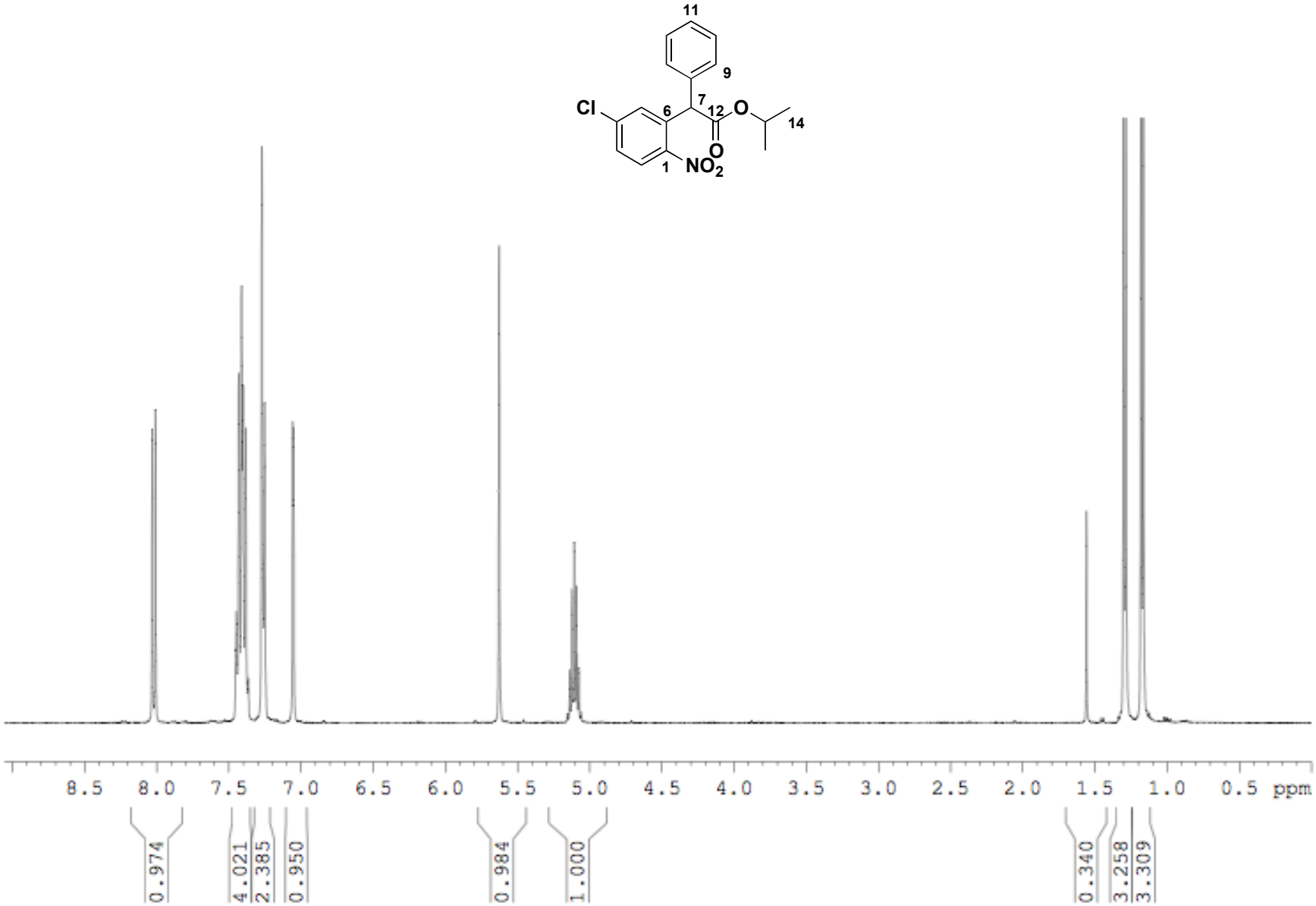
Iso-propyl 2-(2-aminophenyl)-2-phenylacetate (**20a**)



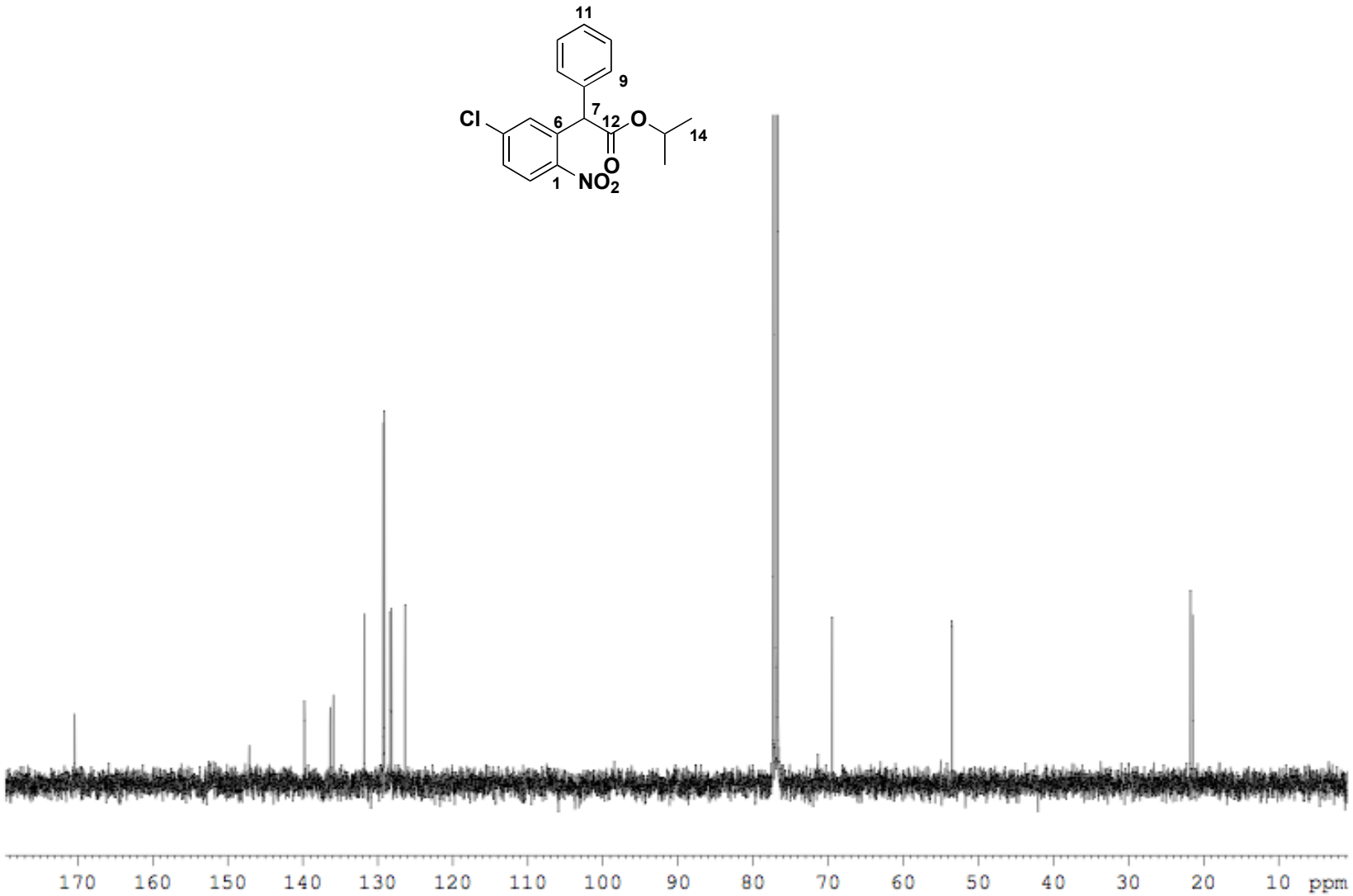
Iso-propyl 2-(2-aminophenyl)-2-phenylacetate (**20a**)



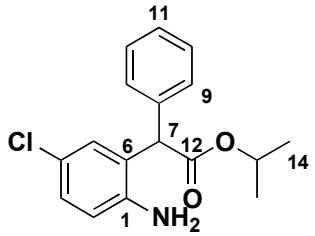
Iso-propyl 2-(5-chloro-2-nitrophenyl)-2-phenylacetate (**30**)

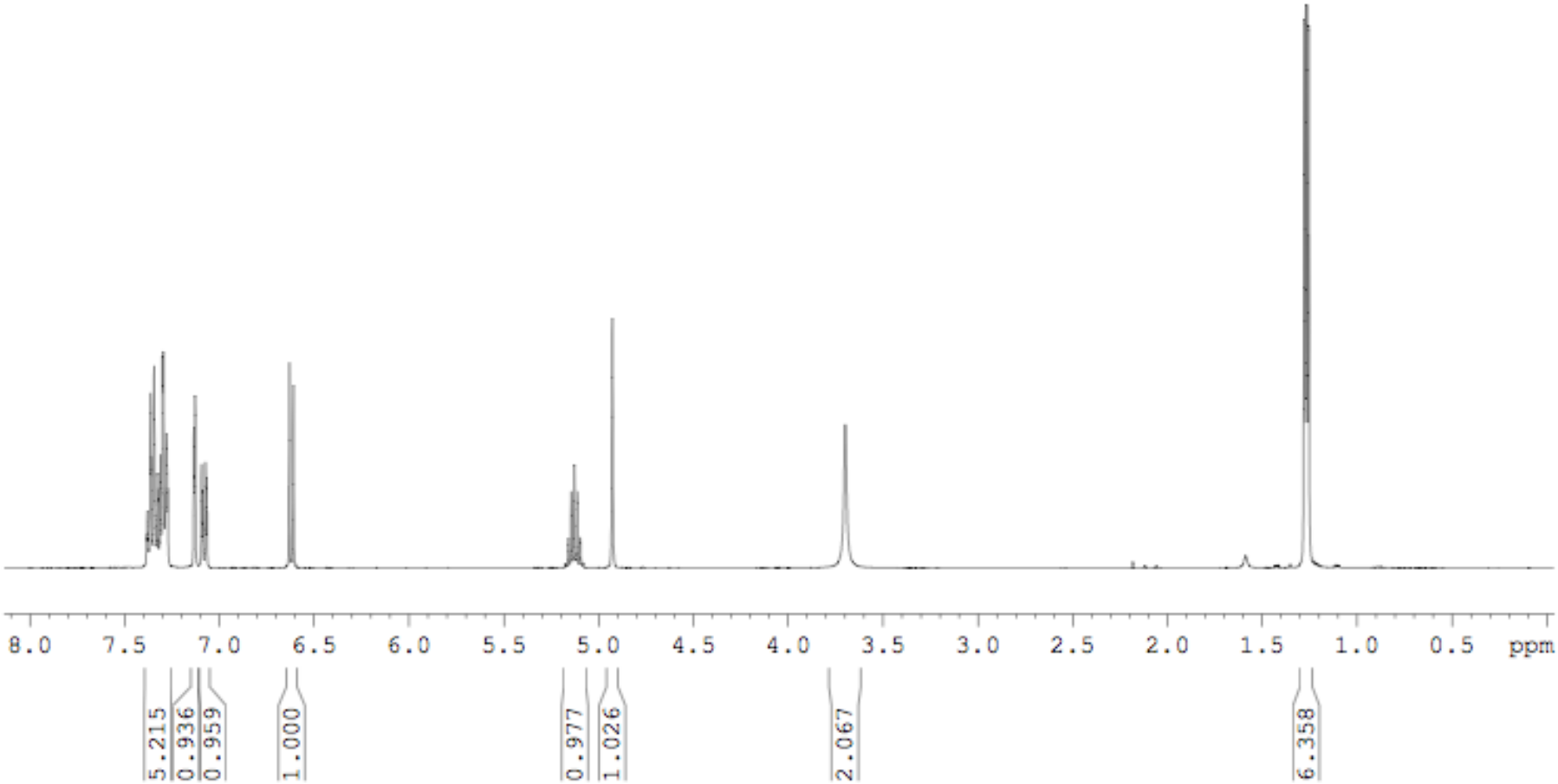


Iso-propyl 2-(5-chloro-2-nitrophenyl)-2-phenylacetate (**30**)

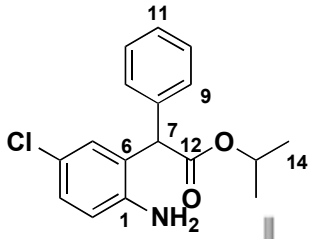


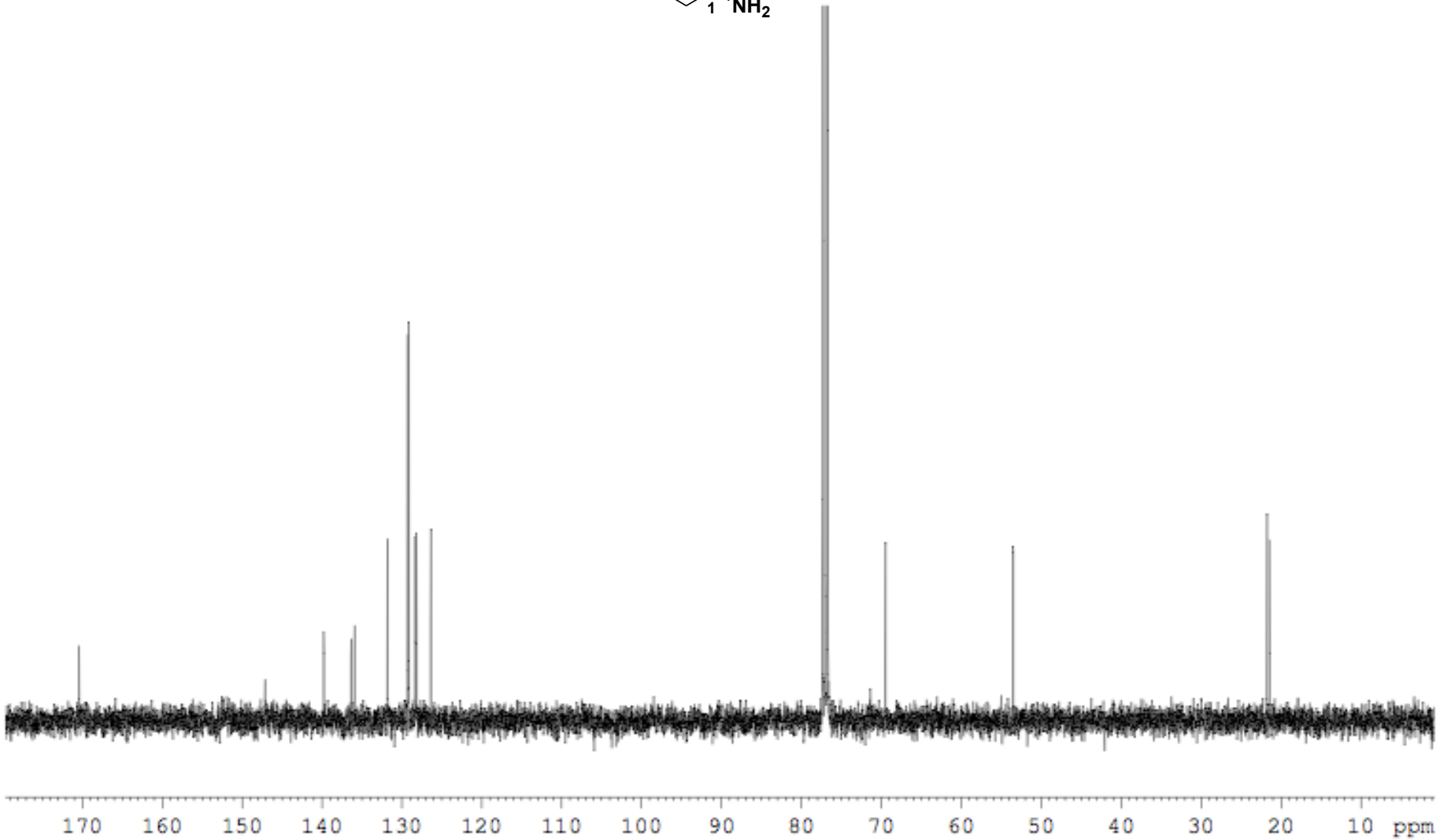
Iso-propyl 2-(2-amino-5-chlorophenyl)-2-phenylacetate (**20b**)



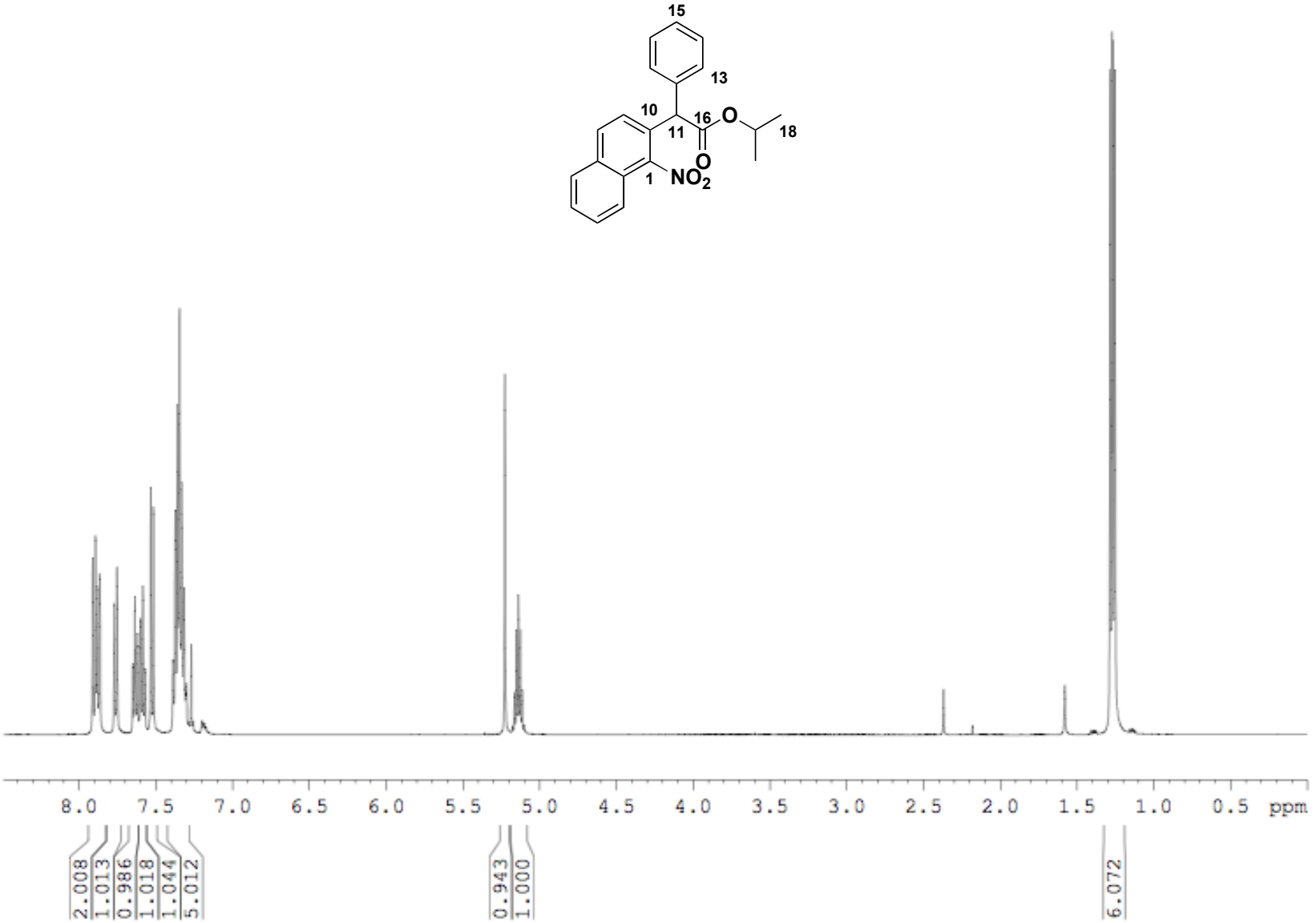


Iso-propyl 2-(2-amino-5-chlorophenyl)-2-phenylacetate (**20b**)

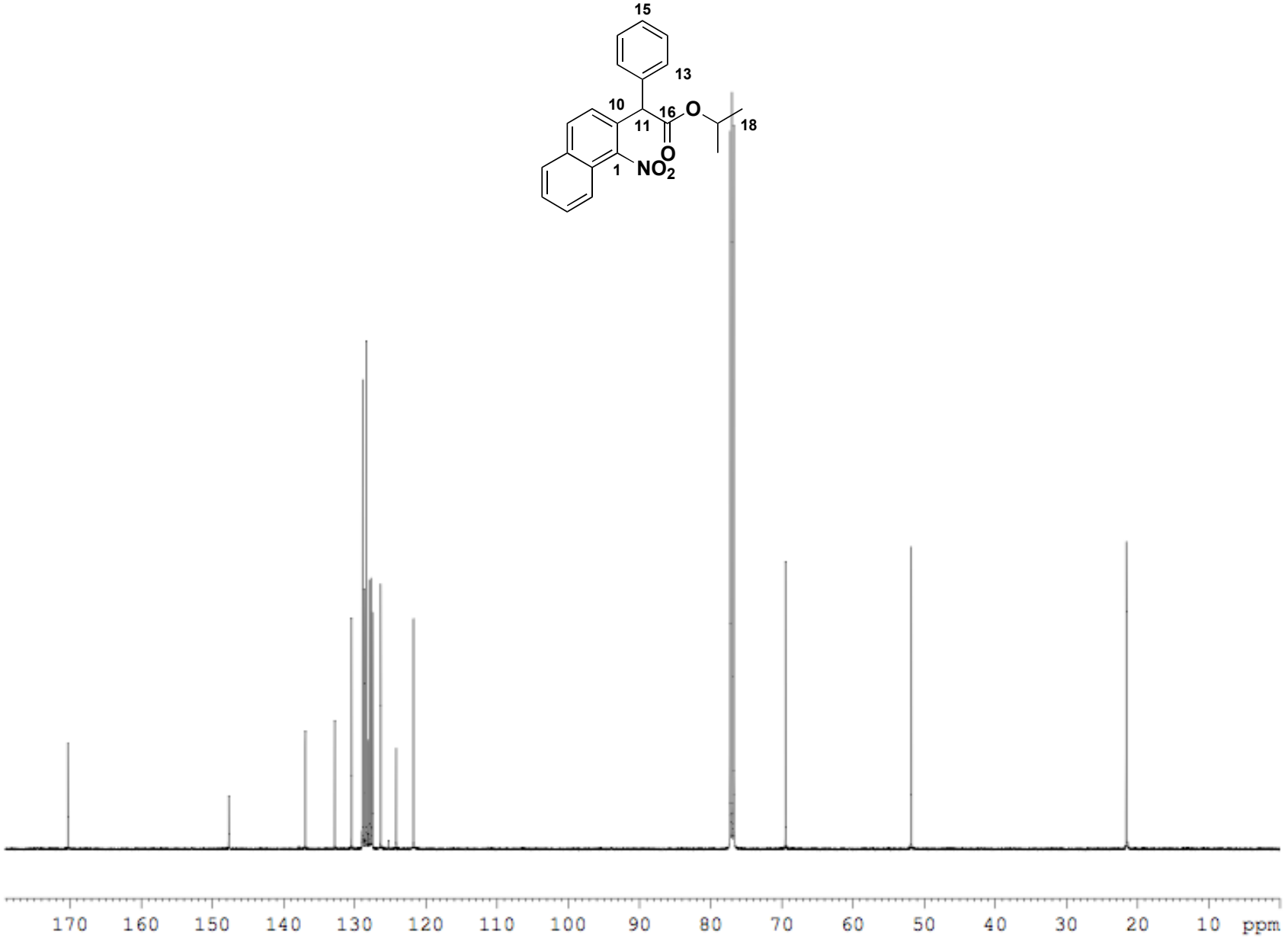




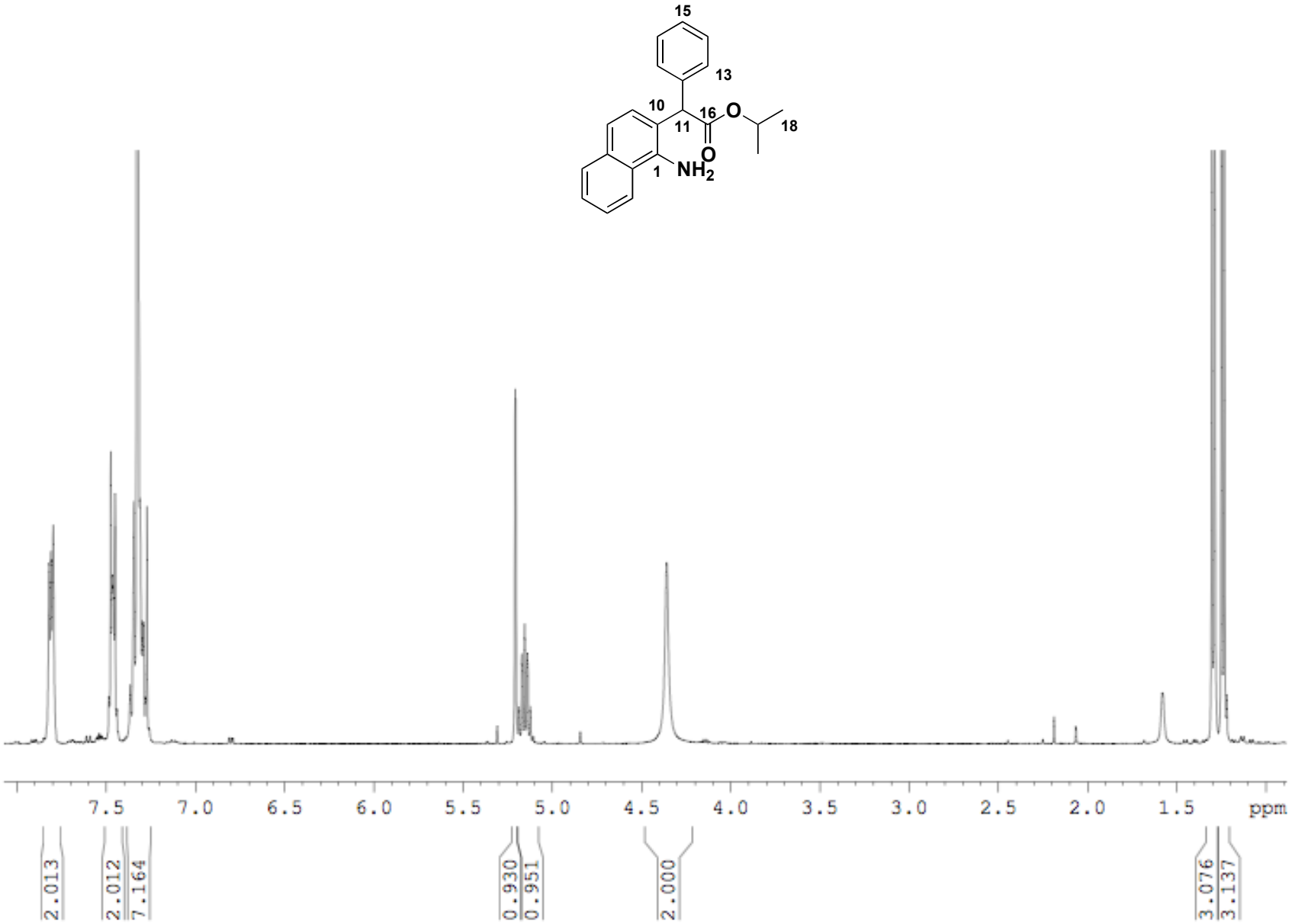
Iso-propyl 2-(1-nitronaphthalen-2-yl)-2-phenylacetate (**31**)



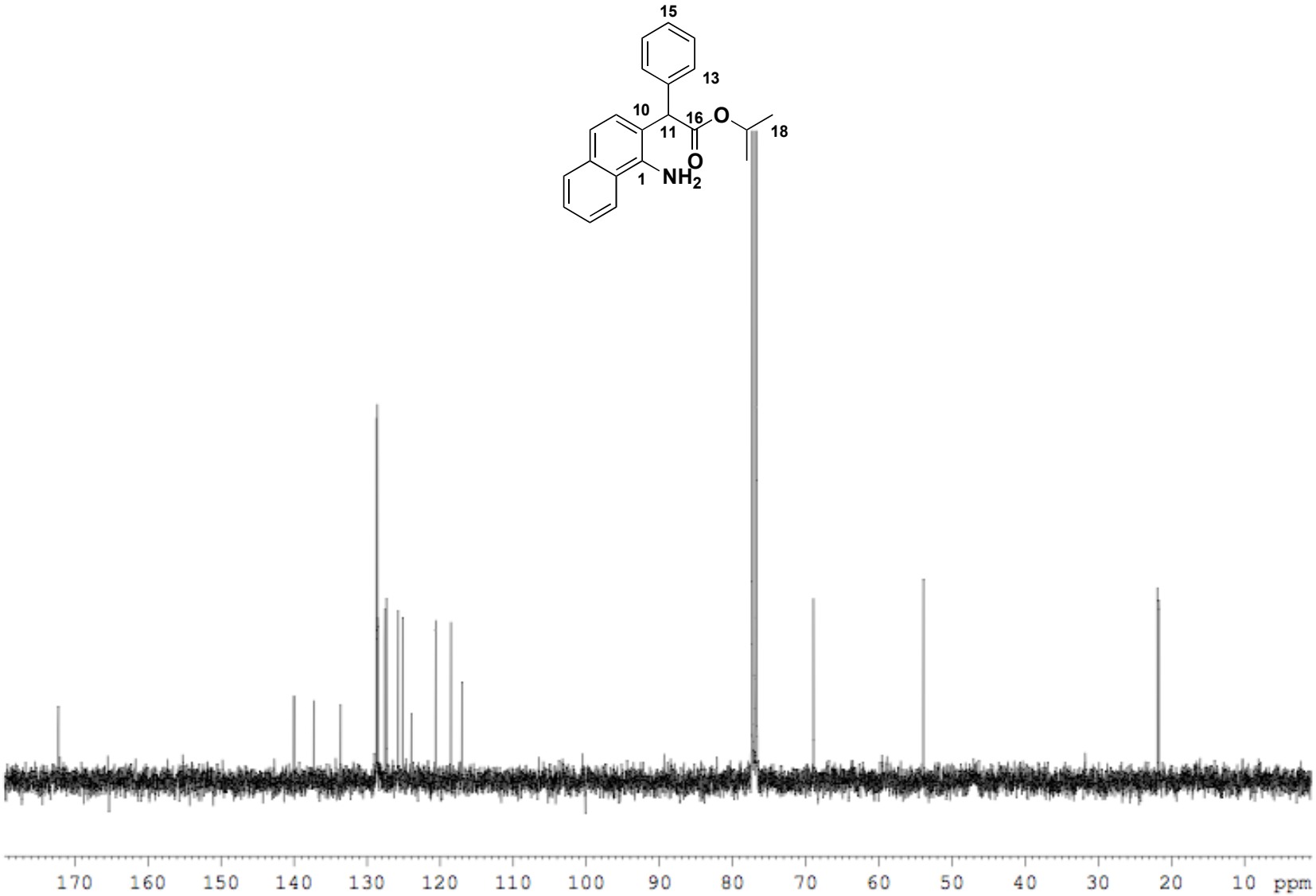
Iso-propyl 2-(1-nitronaphthalen-2-yl)-2-phenylacetate (**31**)



Iso-propyl 2-(1-aminonaphthalen-2-yl)-2-phenylacetate (**20c**)

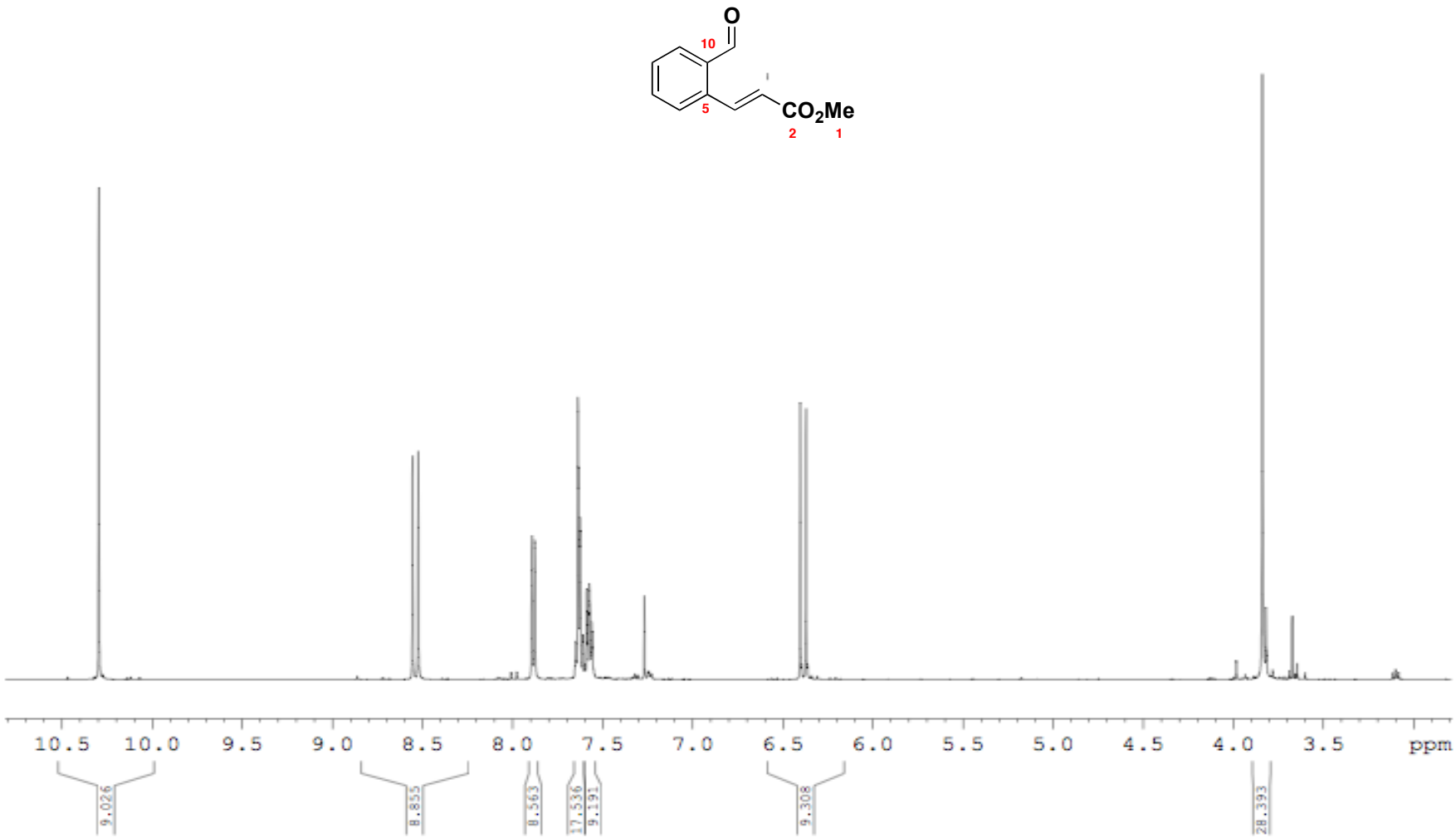


Iso-propyl 2-(1-aminonaphthalen-2-yl)-2-phenylacetate (**20c**)

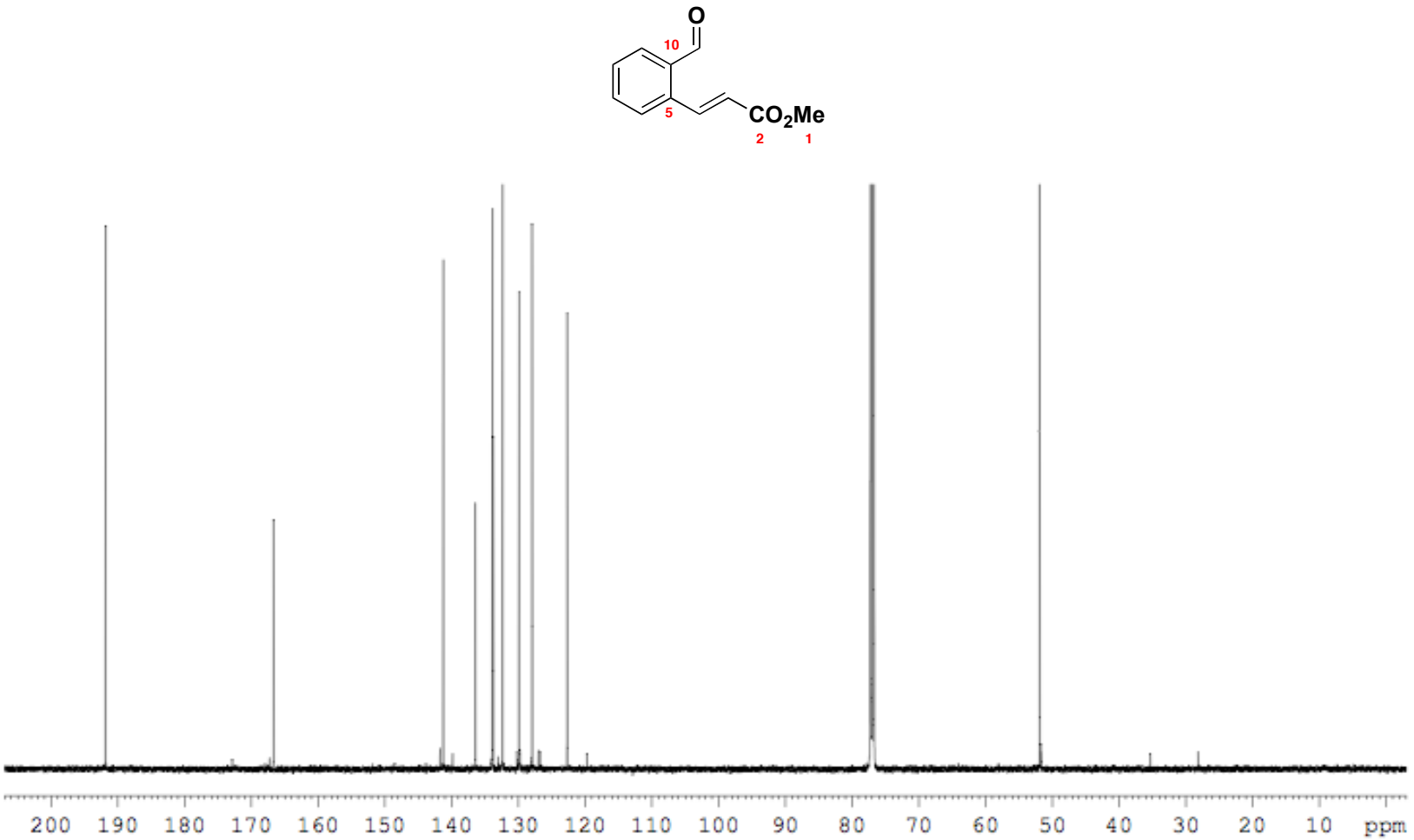


5.2 Aldehydes and precursors

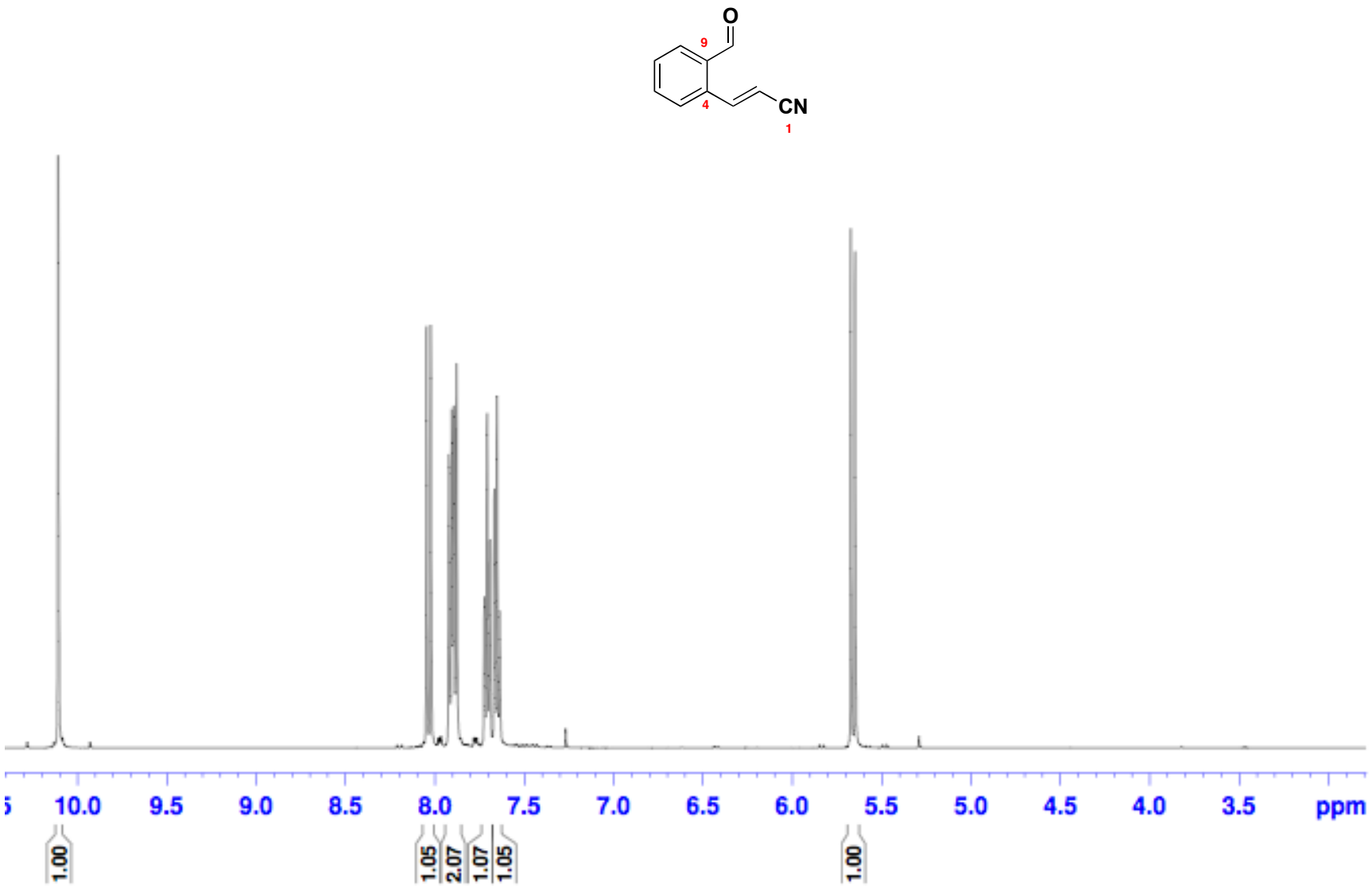
(*E*)-Methyl 3-(2-formylphenyl)acrylate (**2**)



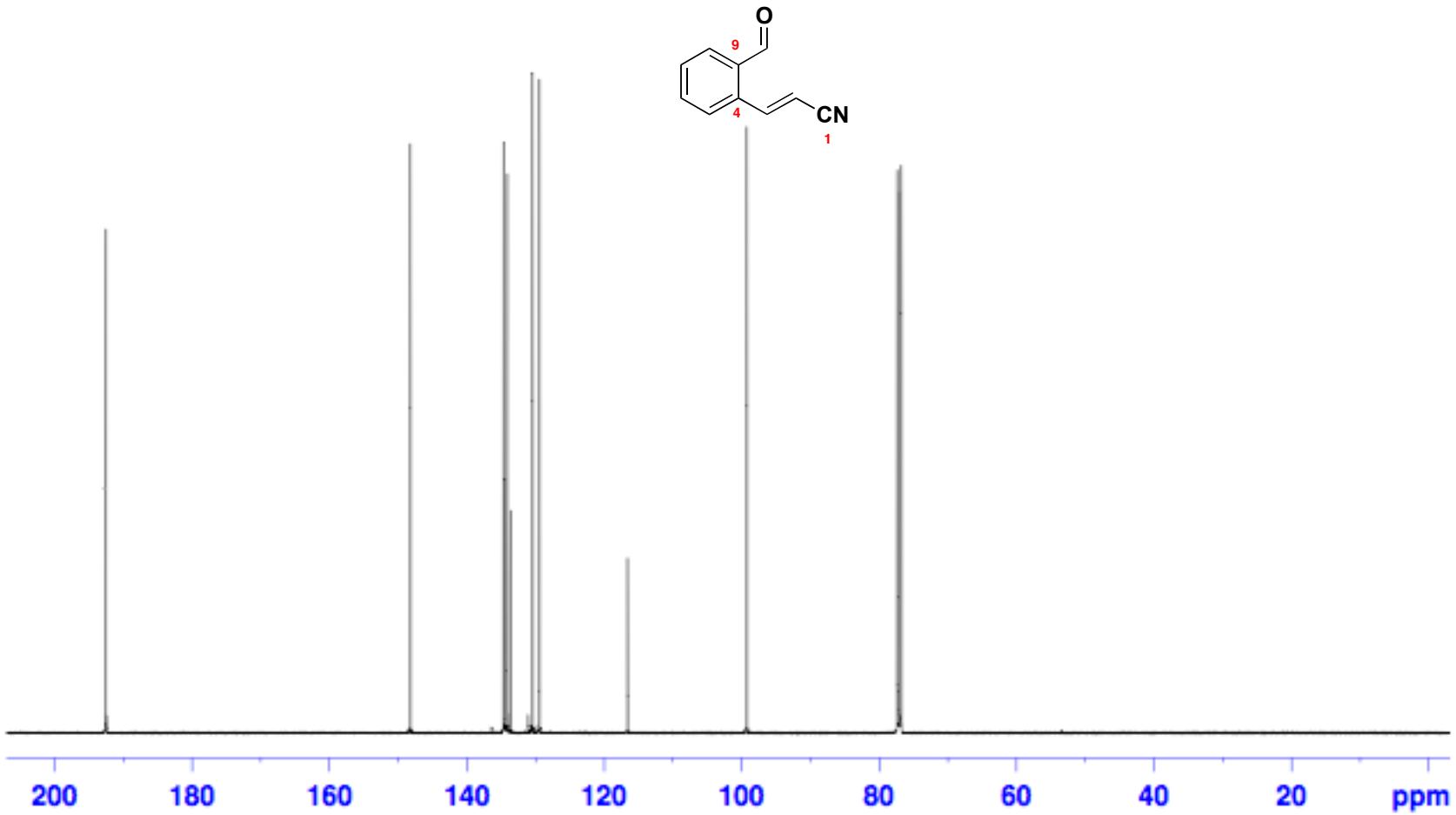
(*E*)-Methyl 3-(2-formylphenyl)acrylate (**2**)



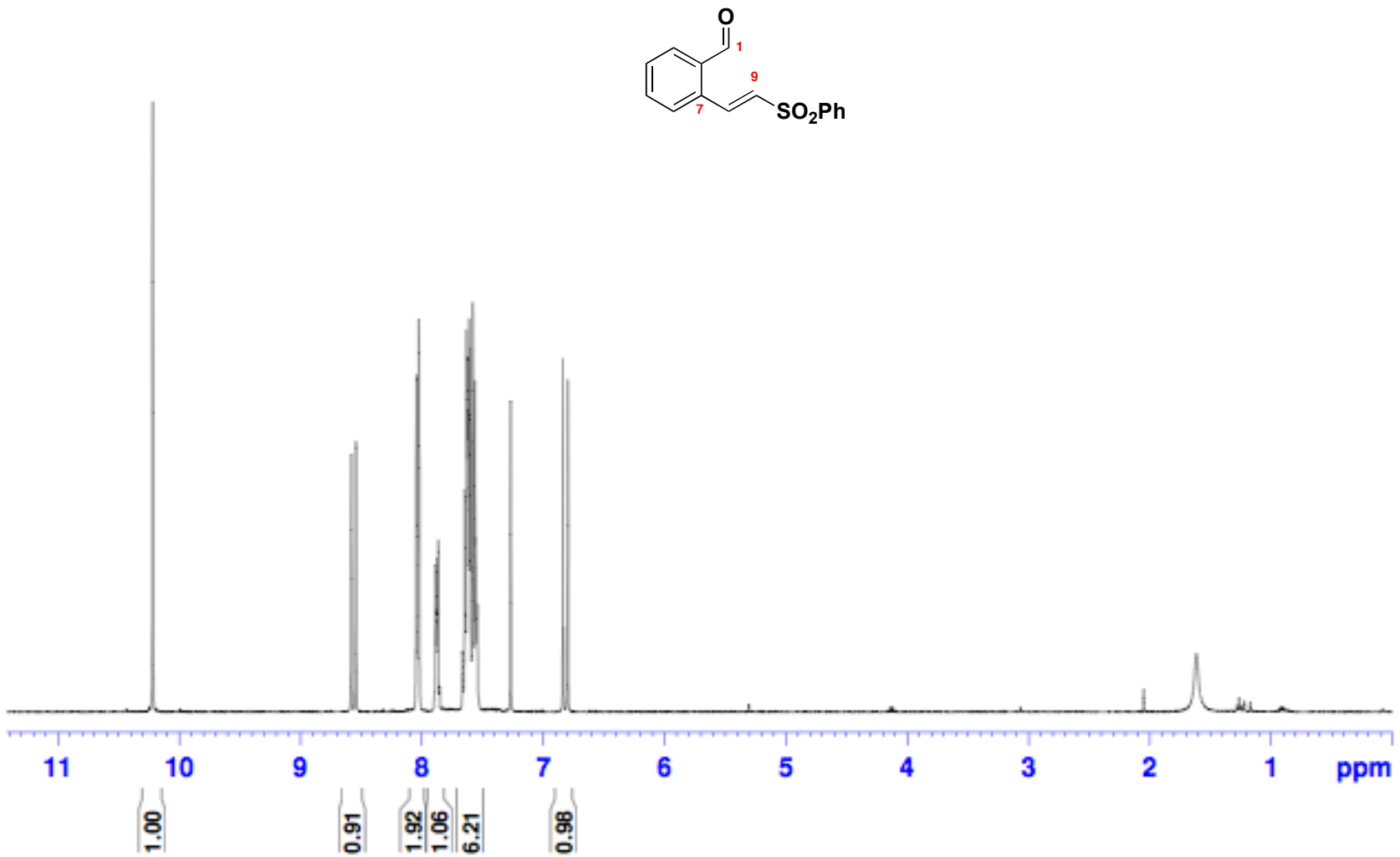
(*E*)-3-(2-Formylphenyl)acrylonitrile (**21a**)



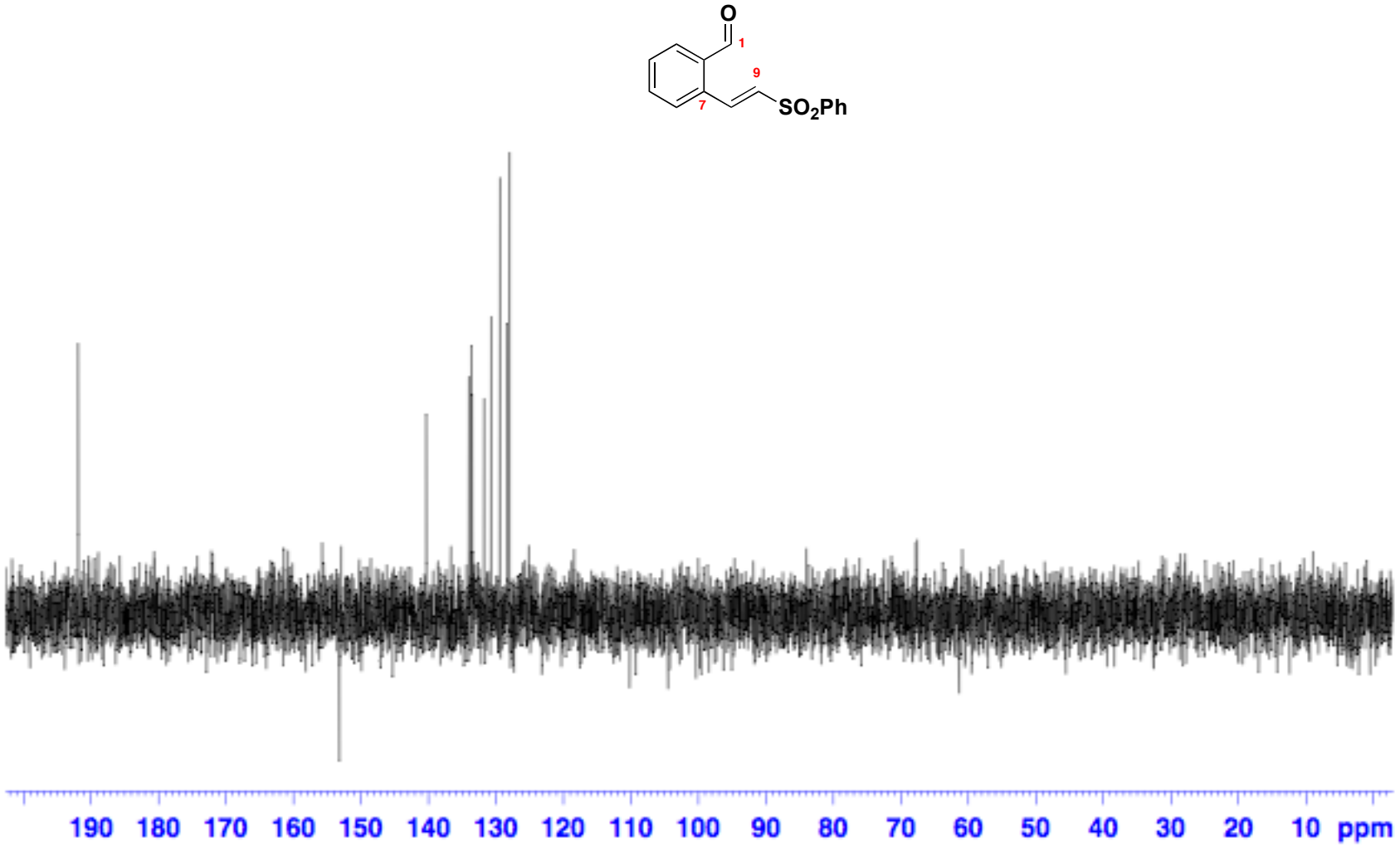
(*E*)-3-(2-Formylphenyl)acrylonitrile (**21a**)



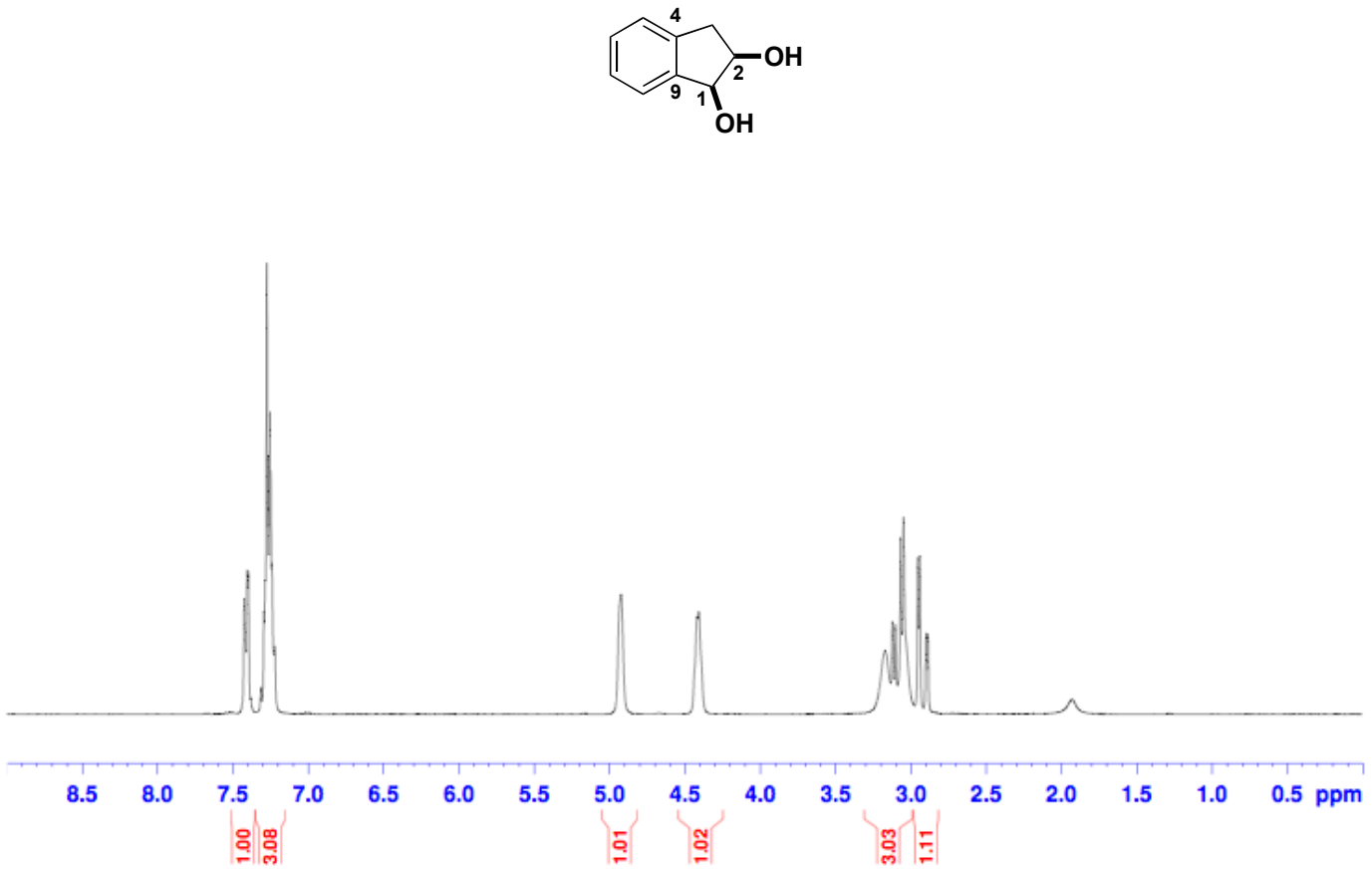
2-(2-(Phenylsulfonyl)vinyl)benzaldehyde (**21b**)



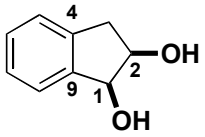
2-(2-(Phenylsulfonyl)vinyl)benzaldehyde (**21b**)

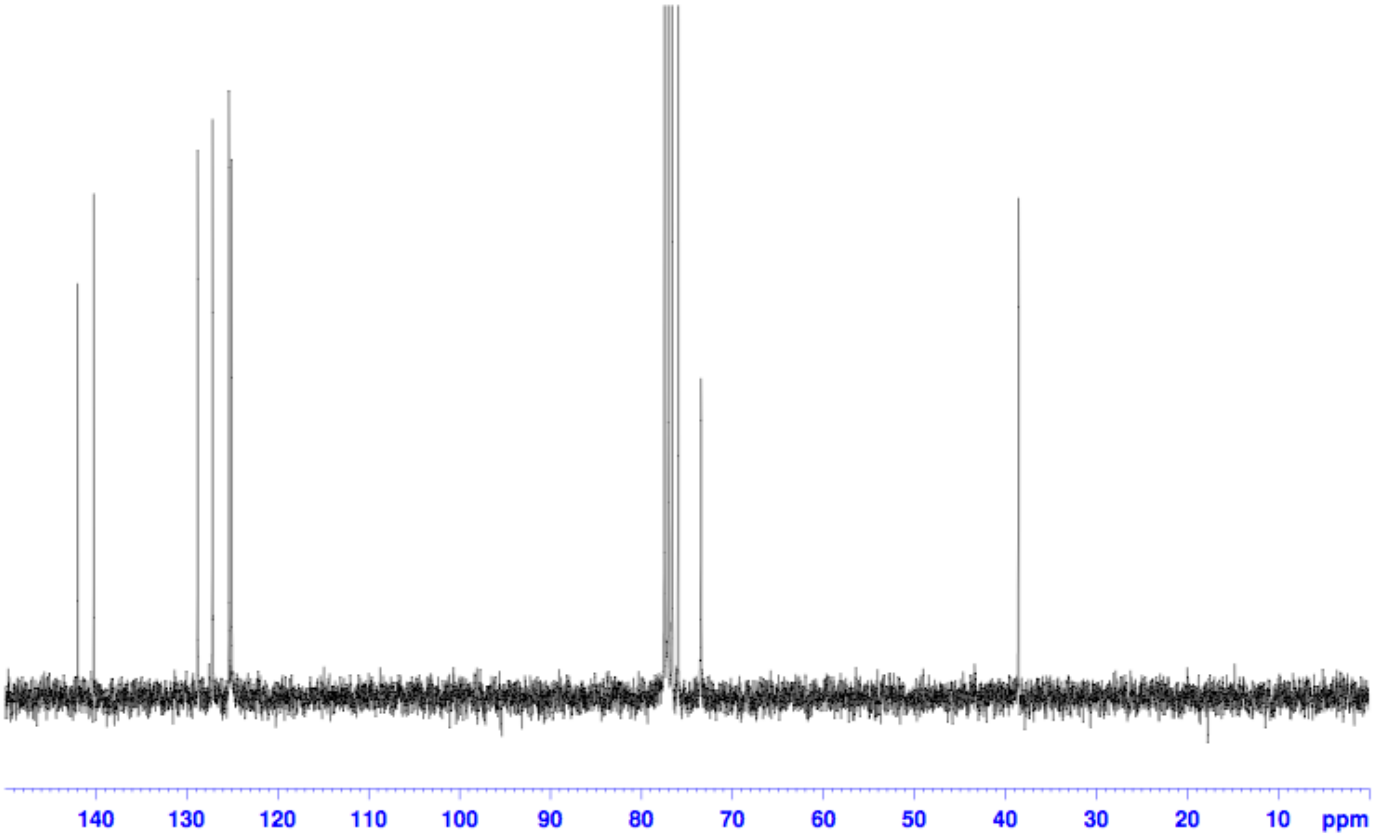


2,3-Dihydro-1*H*-indene-1,2-diol (**32**)

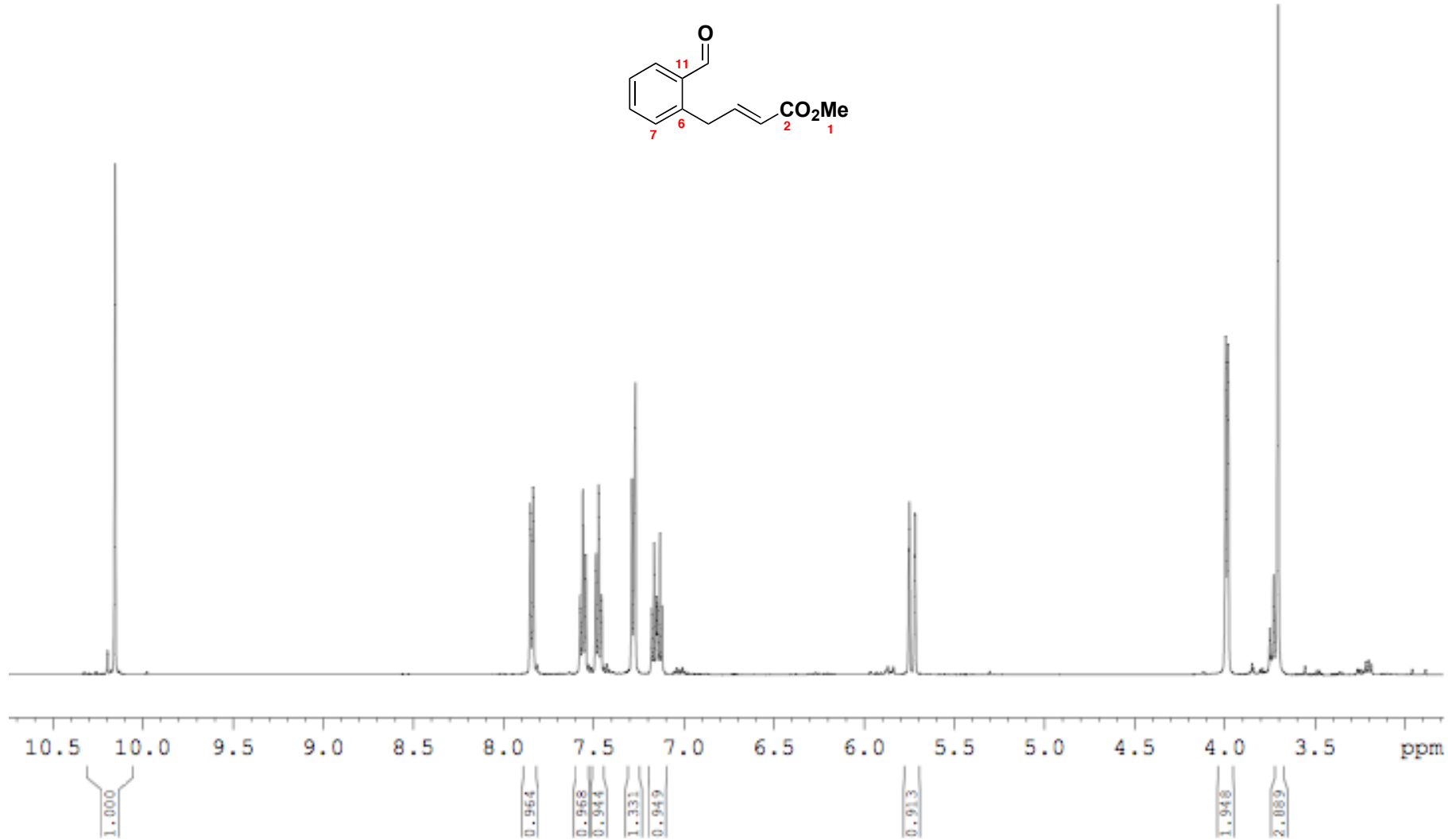


2,3-Dihydro-1*H*-indene-1,2-diol (**32**)

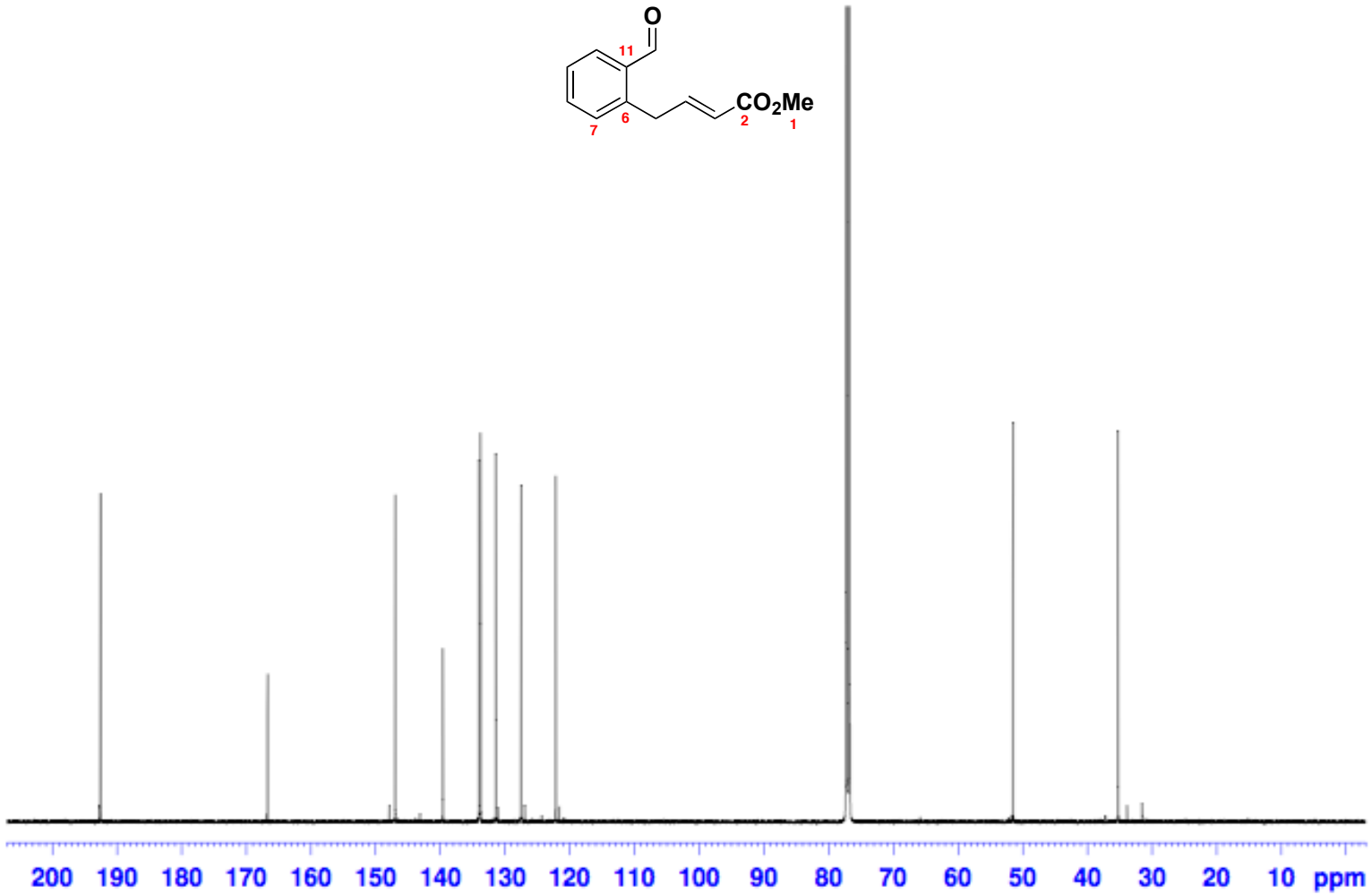




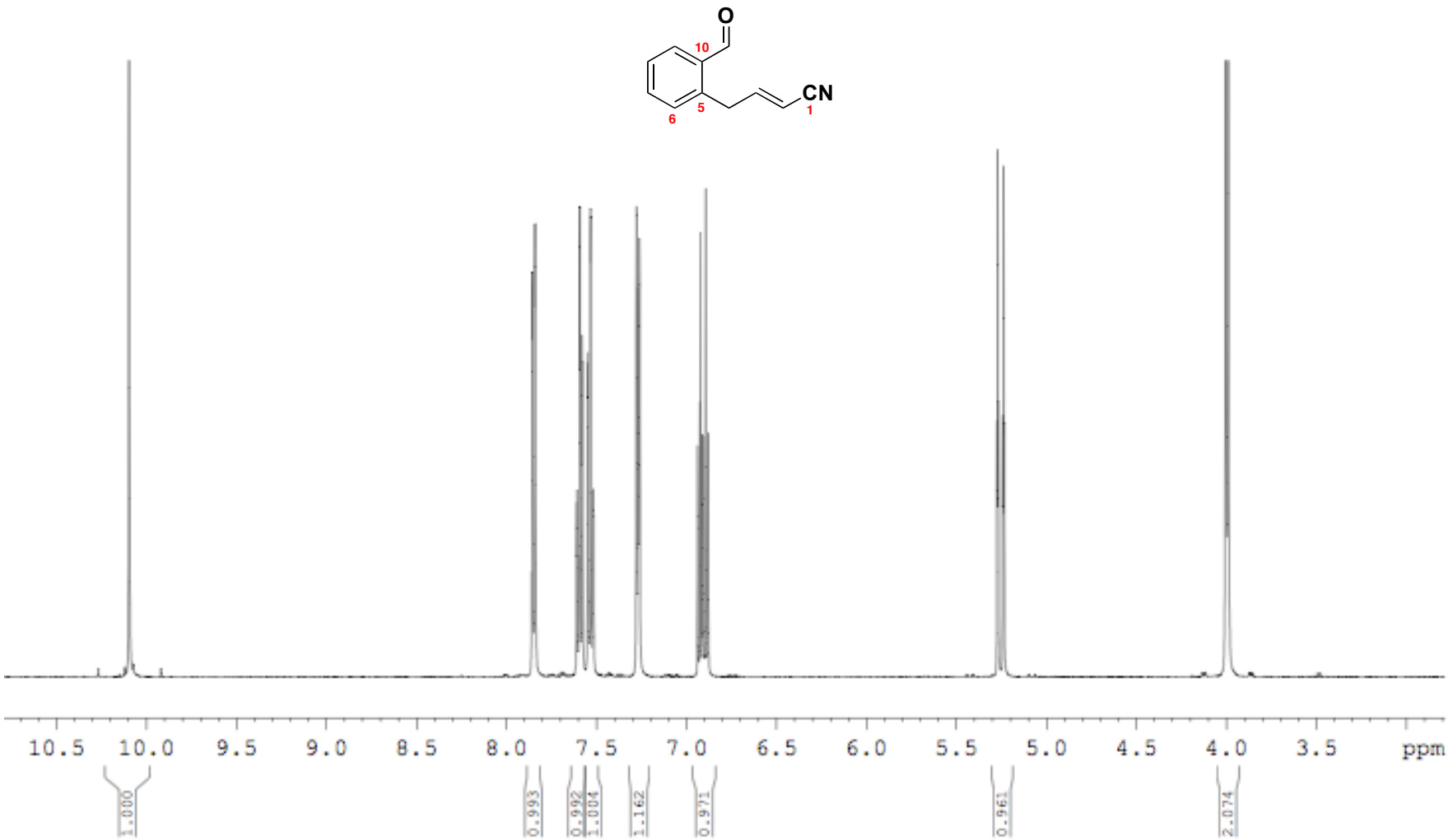
(*E*)-Methyl 4-(2-formylphenyl)but-2-enoate (**3**)



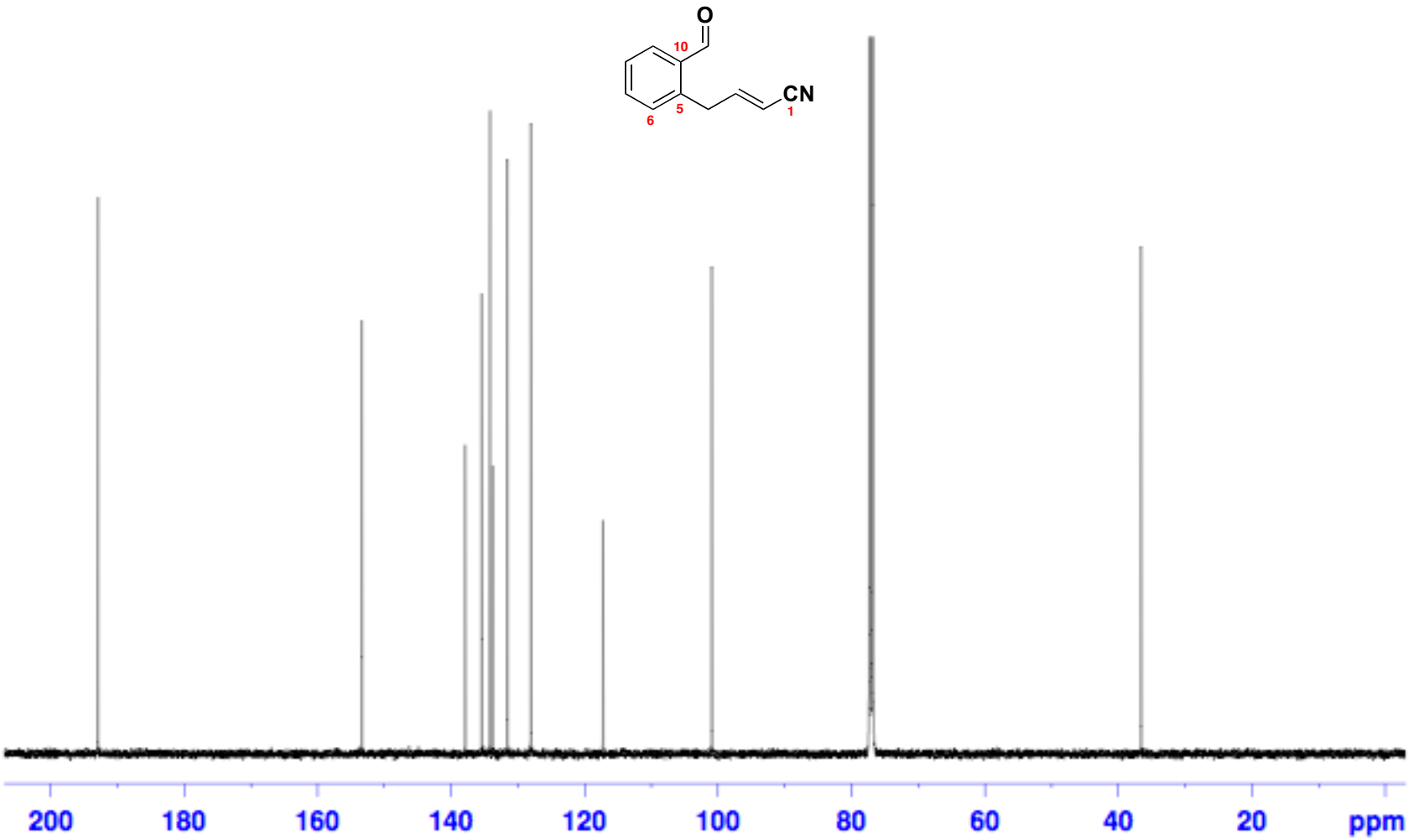
(*E*)-Methyl 4-(2-formylphenyl)but-2-enoate (**3**)



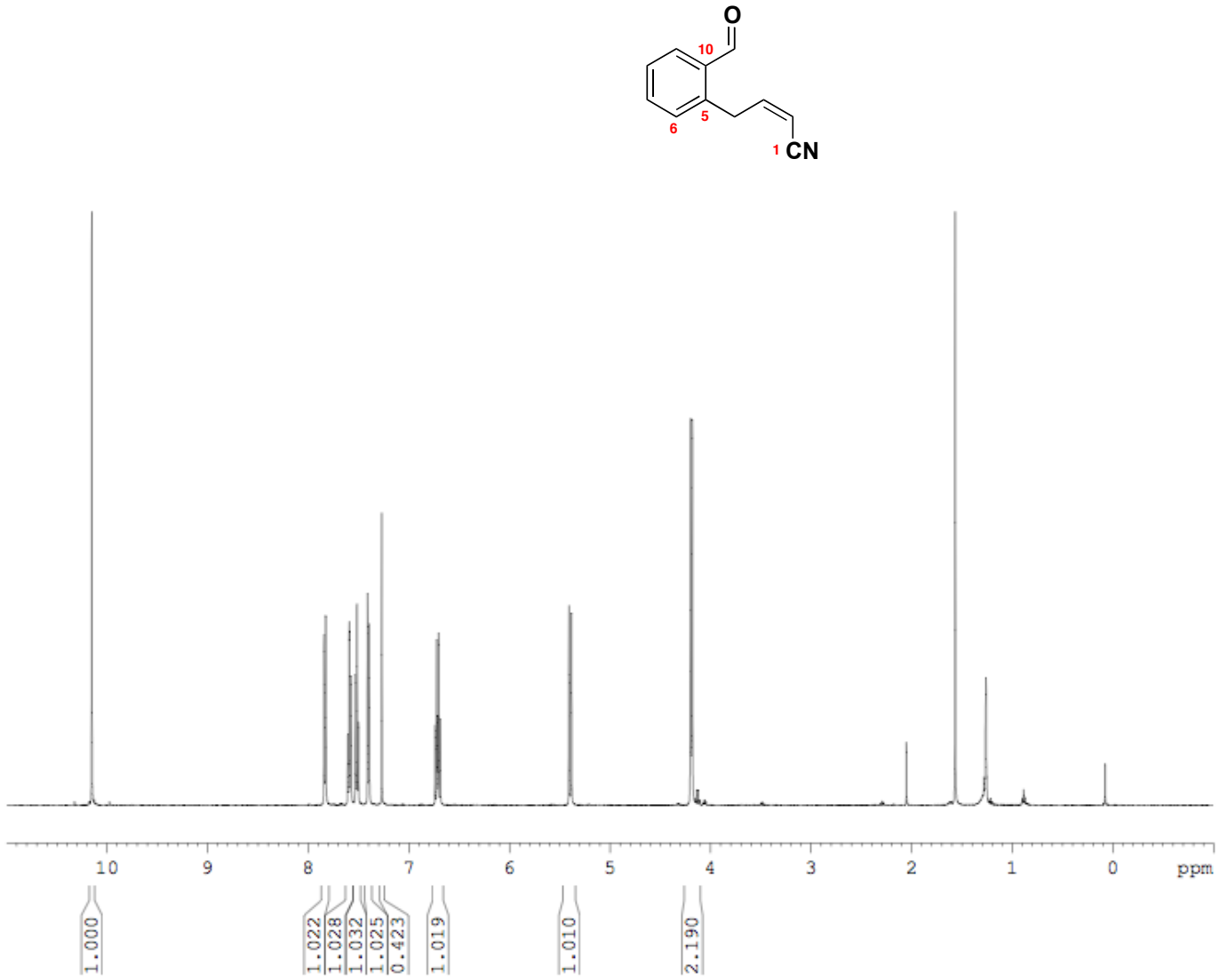
(*E*)-4-(2-Formylphenyl)but-2-enenitrile (**33**)



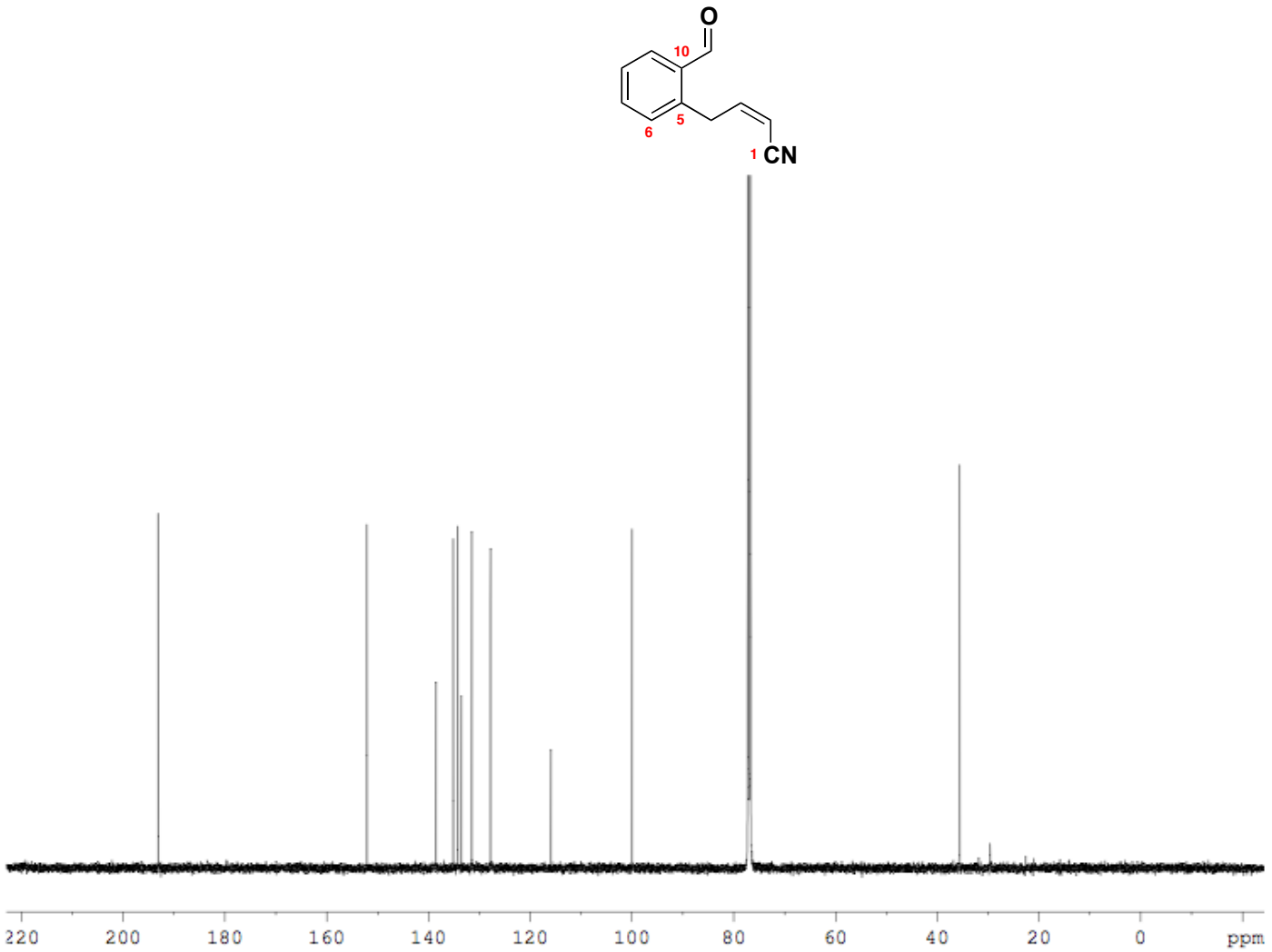
(*E*)-4-(2-Formylphenyl)but-2-enenitrile (**33**)



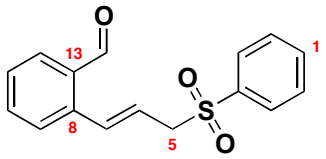
(*Z*)-4-(2-Formylphenyl)but-2-enenitrile (**33**)

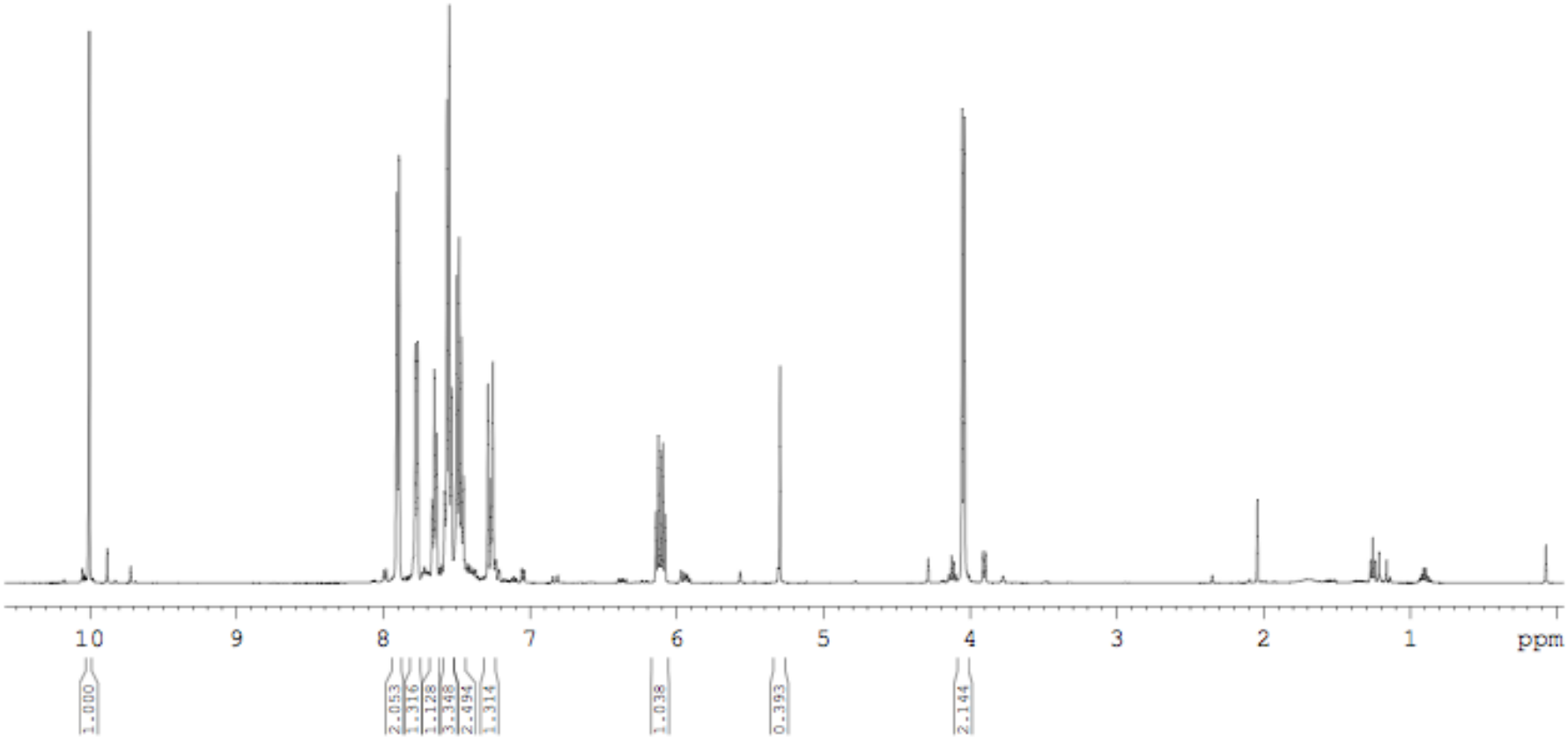


(*Z*)-4-(2-Formylphenyl)but-2-enenitrile (**33**)

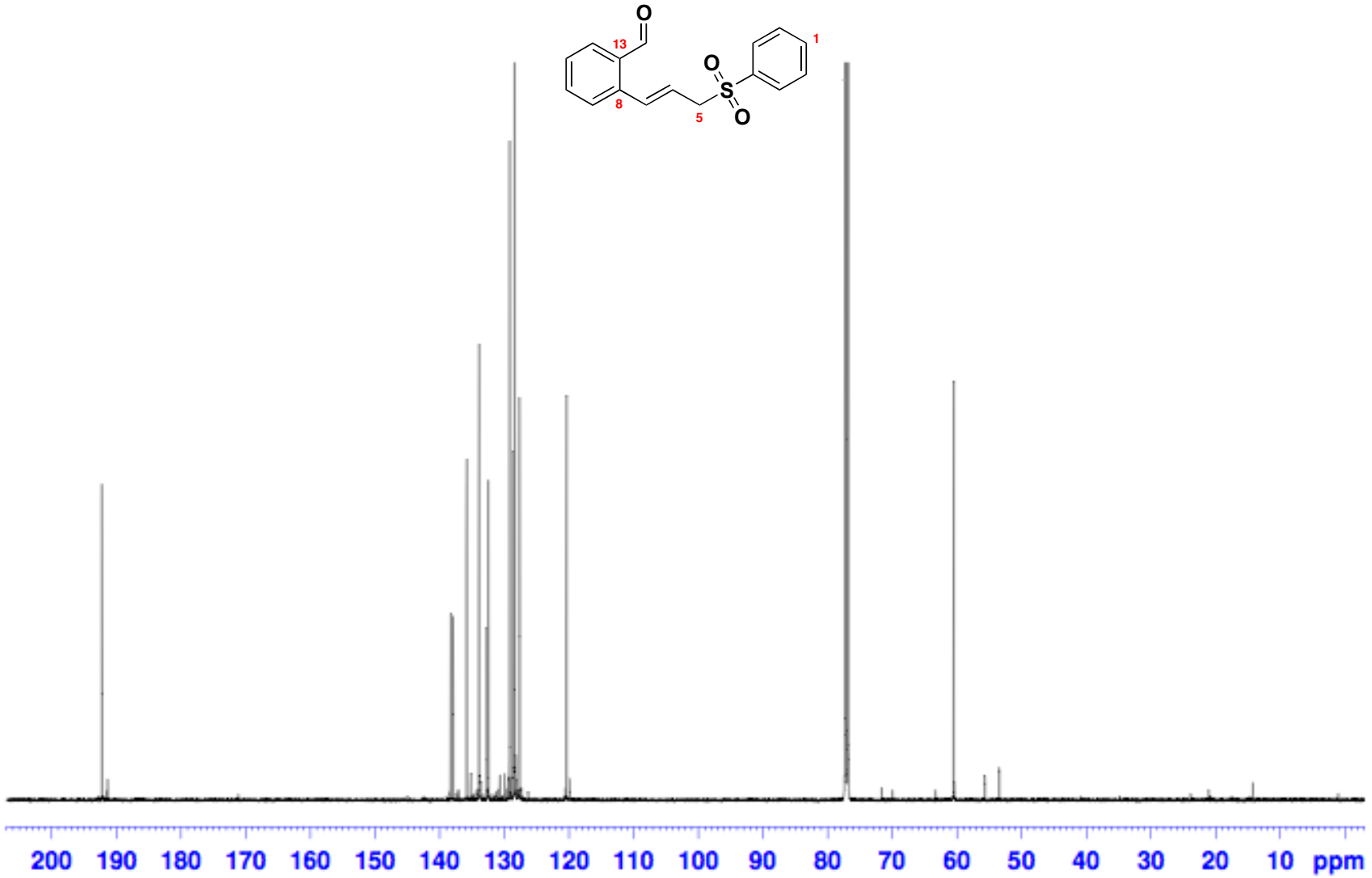


(*E*)-2-(3-(Phenylsulfonyl)prop-1-en-1-yl)benzaldehyde (**34**)

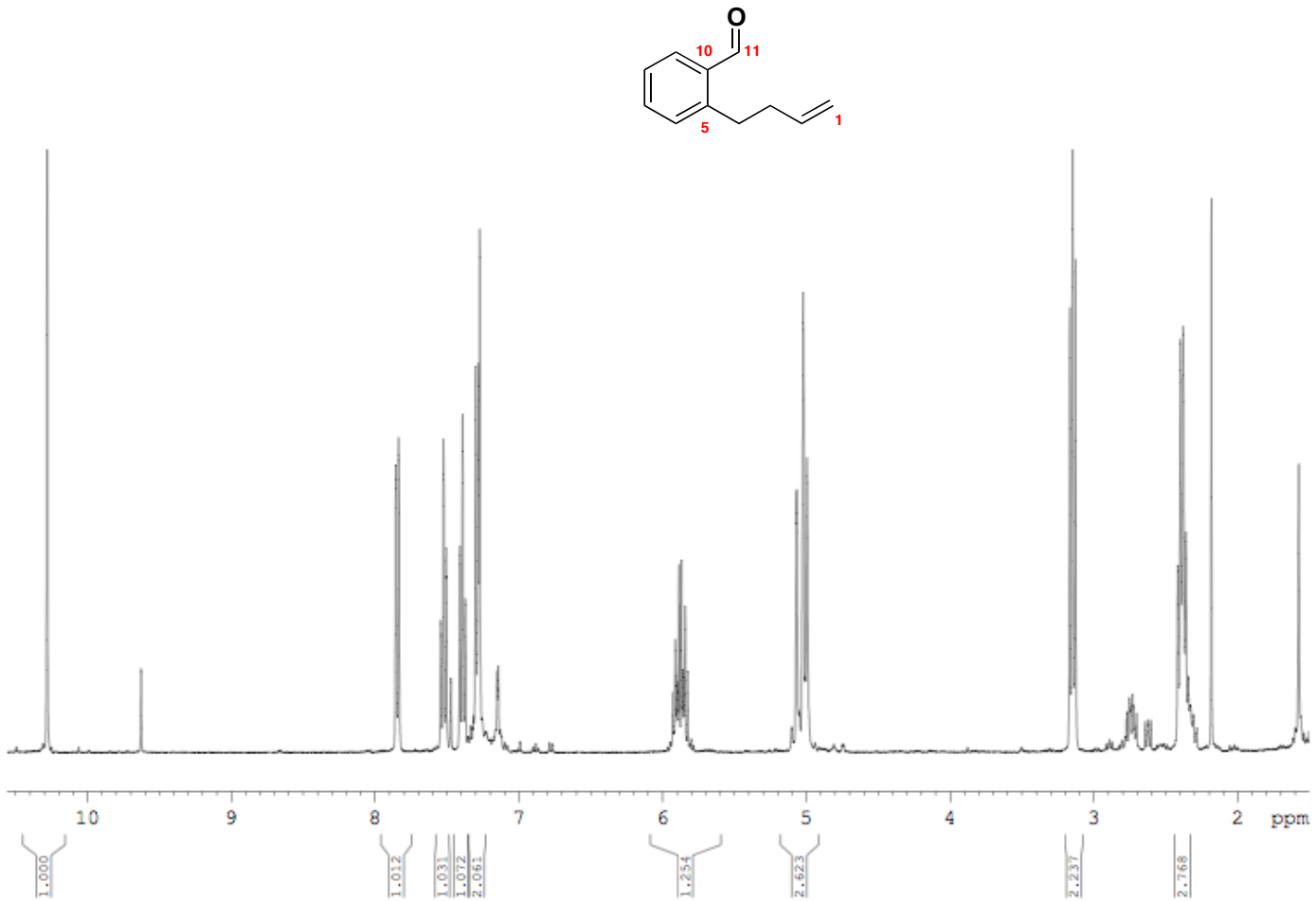




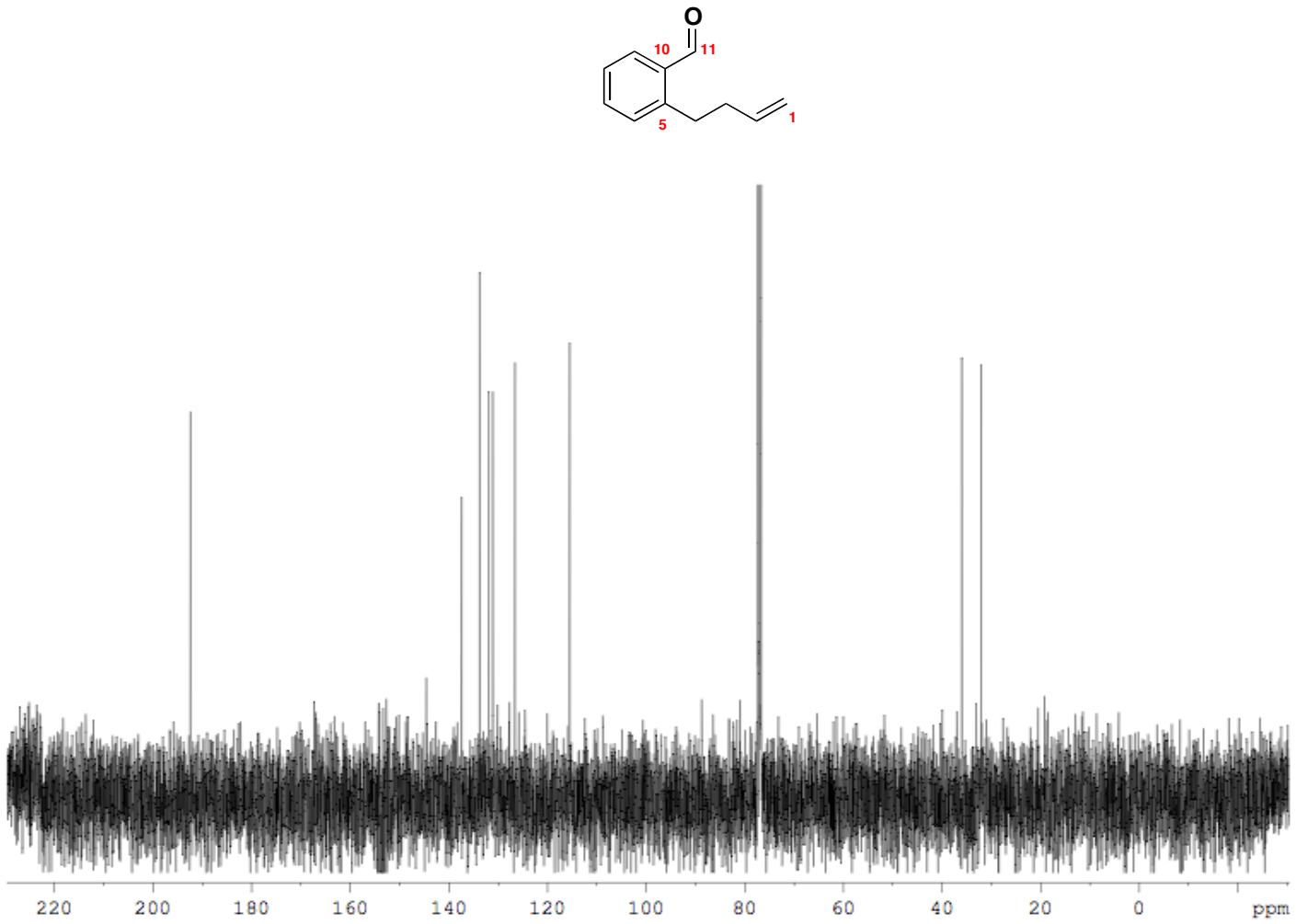
(*E*)-2-(3-(Phenylsulfonyl)prop-1-en-1-yl)benzaldehyde (**34**)



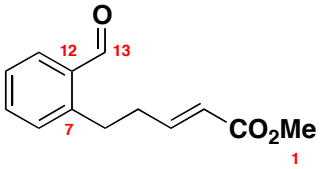
2-(But-3-en-1-yl)benzaldehyde (**37**)

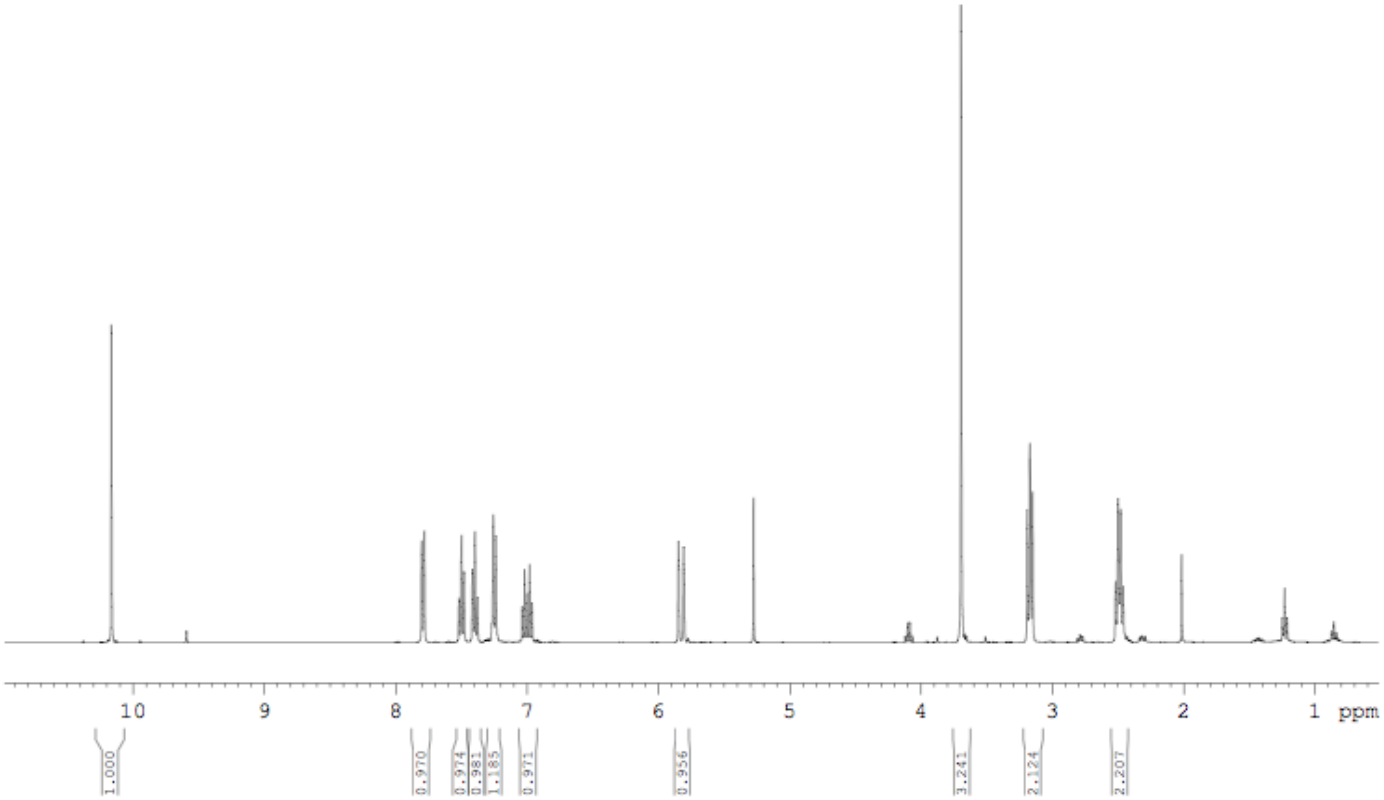


2-(But-3-en-1-yl)benzaldehyde (**37**)

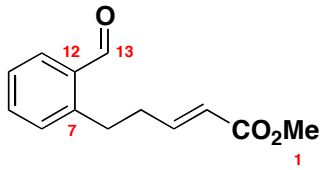


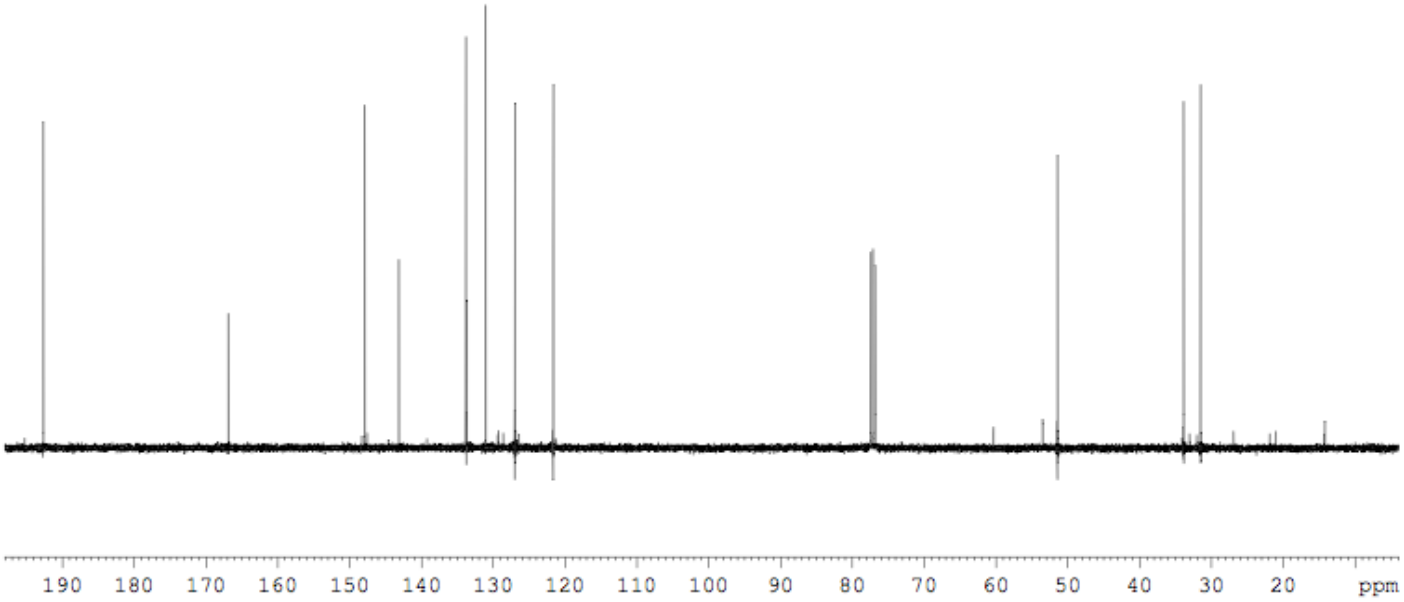
(*E*)-Methyl 5-(2-formylphenyl)pent-2-enoate (**4**)



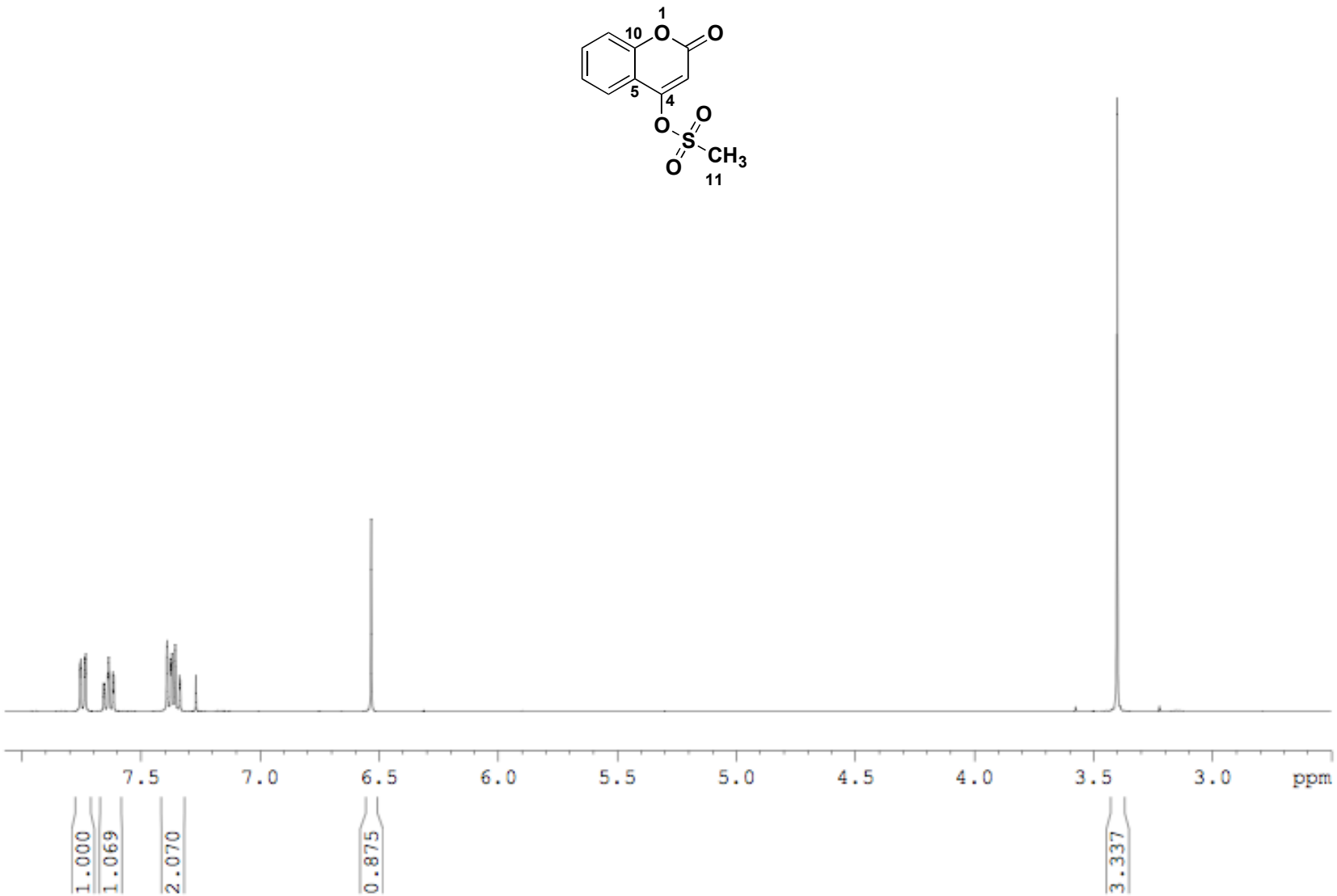


(*E*)-Methyl 5-(2-formylphenyl)pent-2-enoate (**4**)

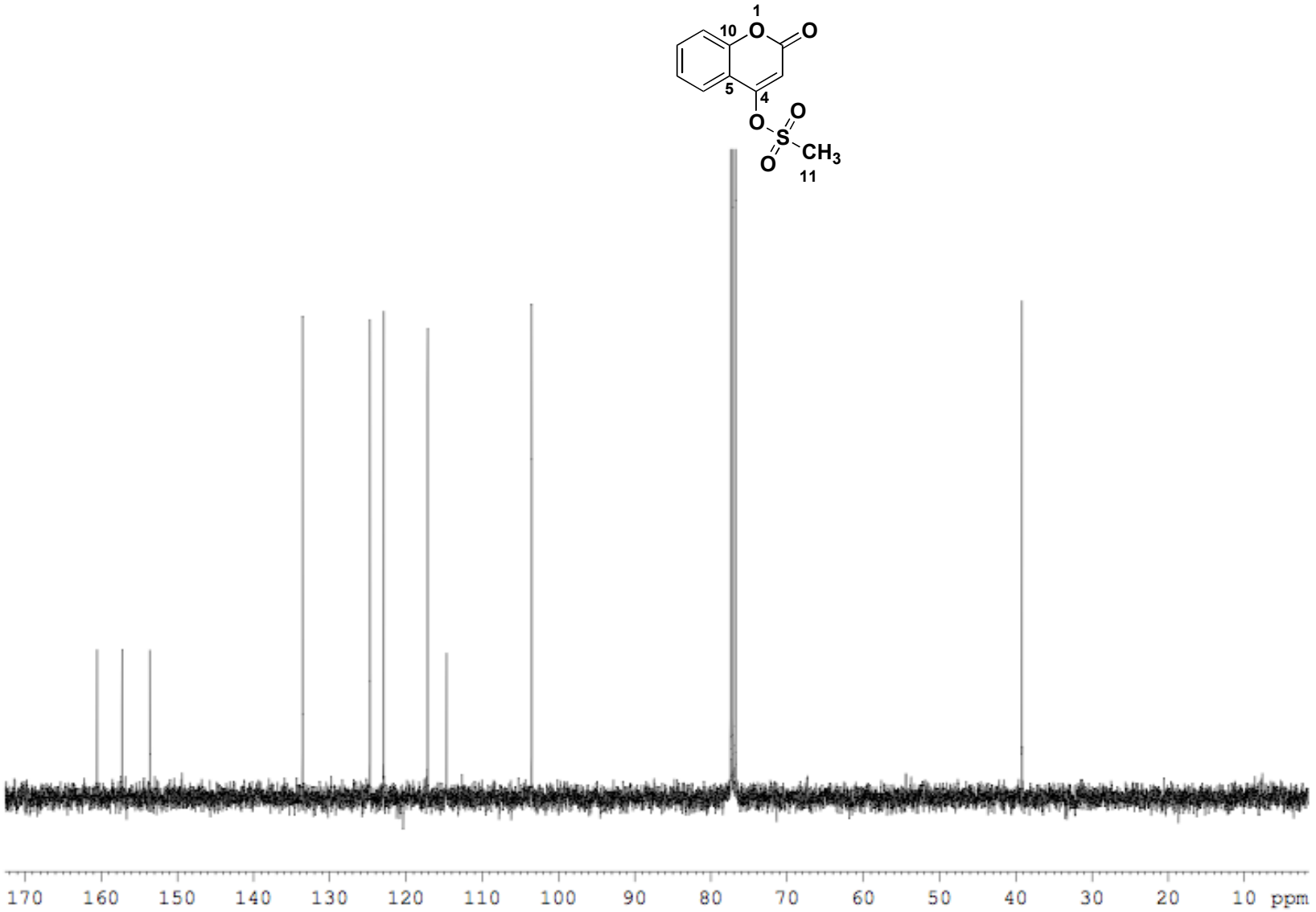




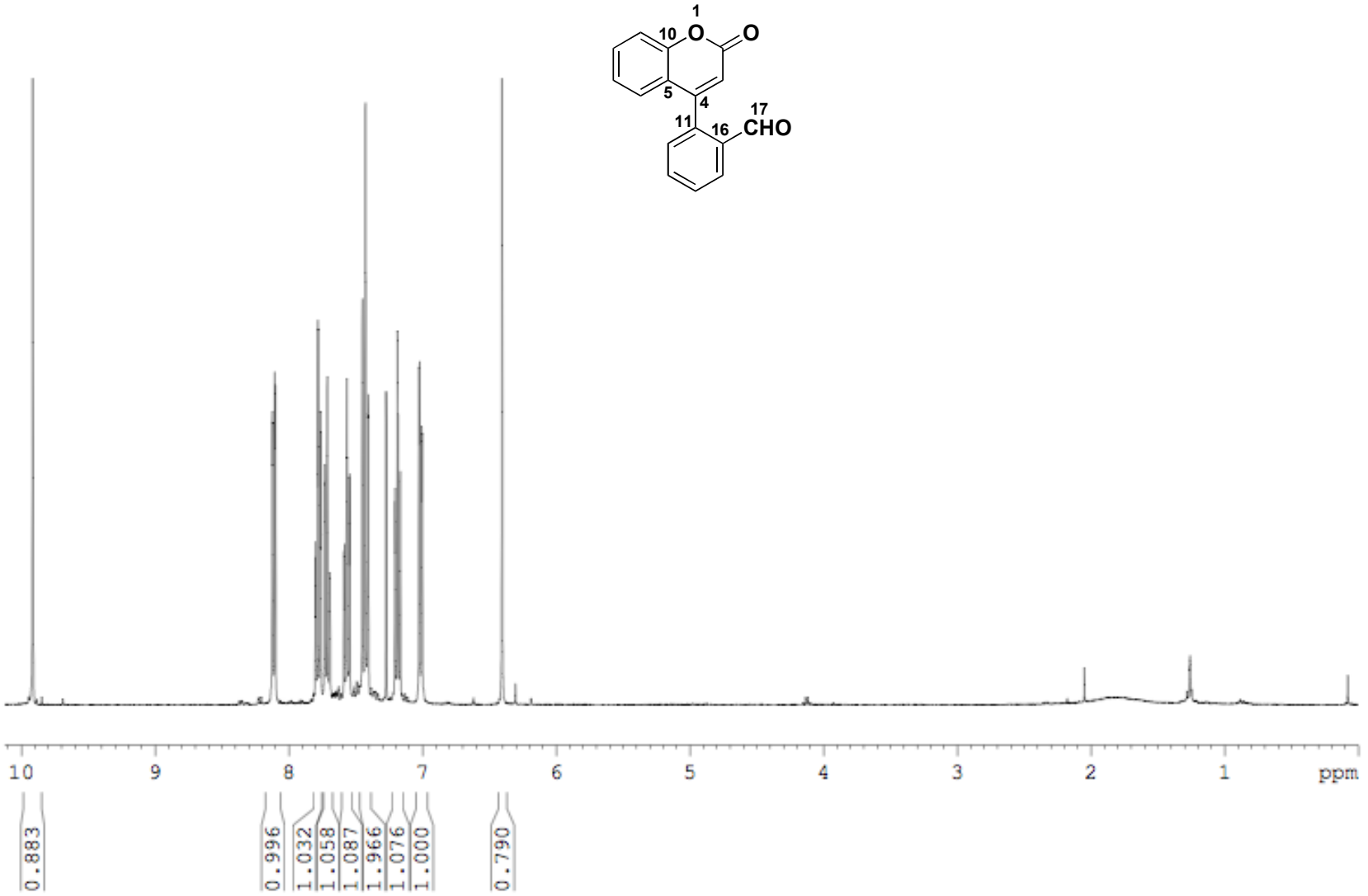
2-Oxo-2*H*-chromen-4-yl methanesulfonate (**35**)



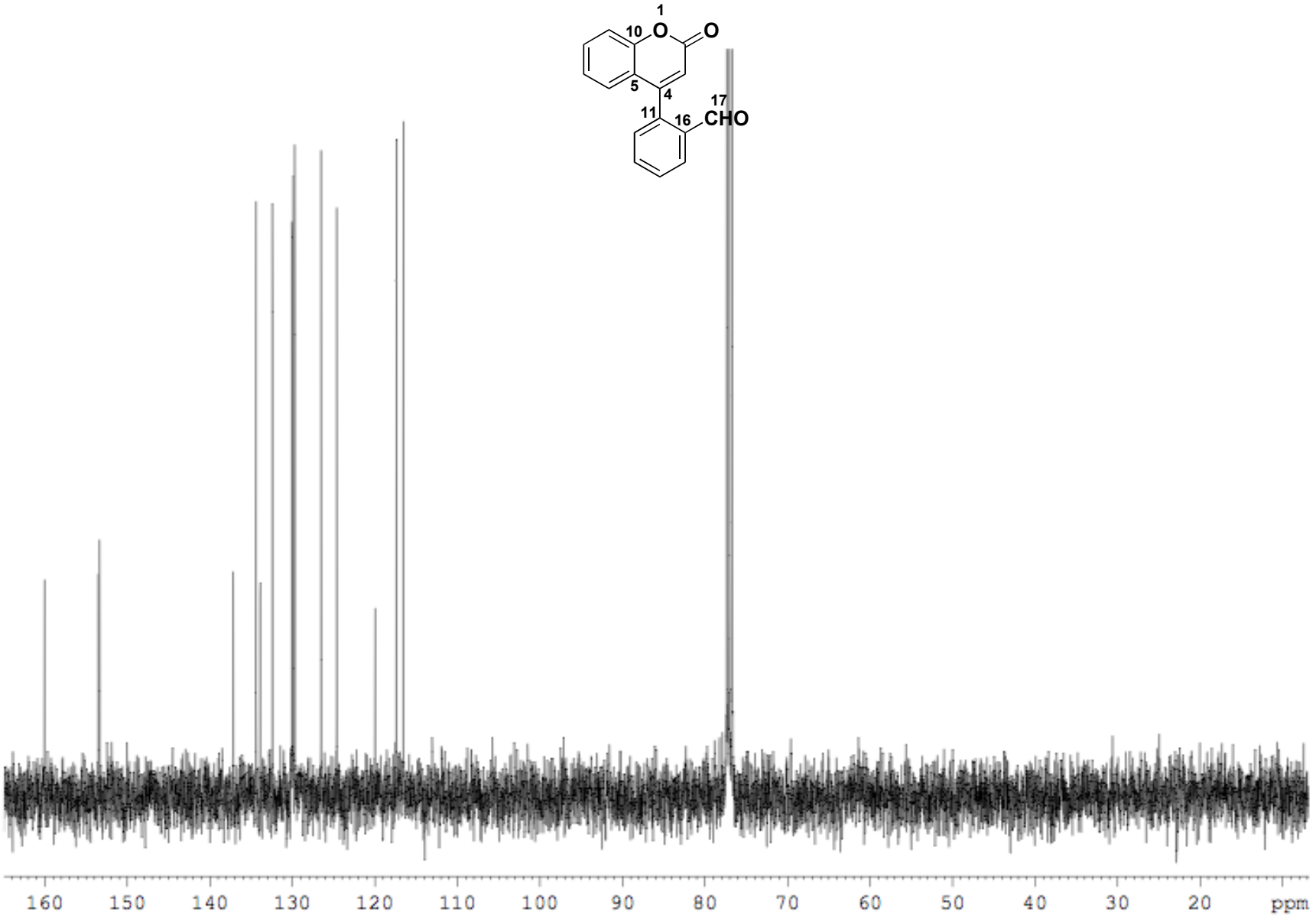
2-Oxo-2*H*-chromen-4-yl methanesulfonate (**35**)



2-(2-Oxo-2*H*-chromen-4-yl)benzaldehyde (**36**)

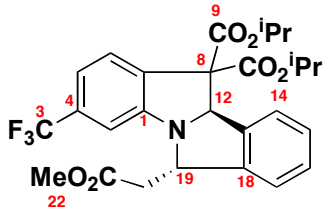


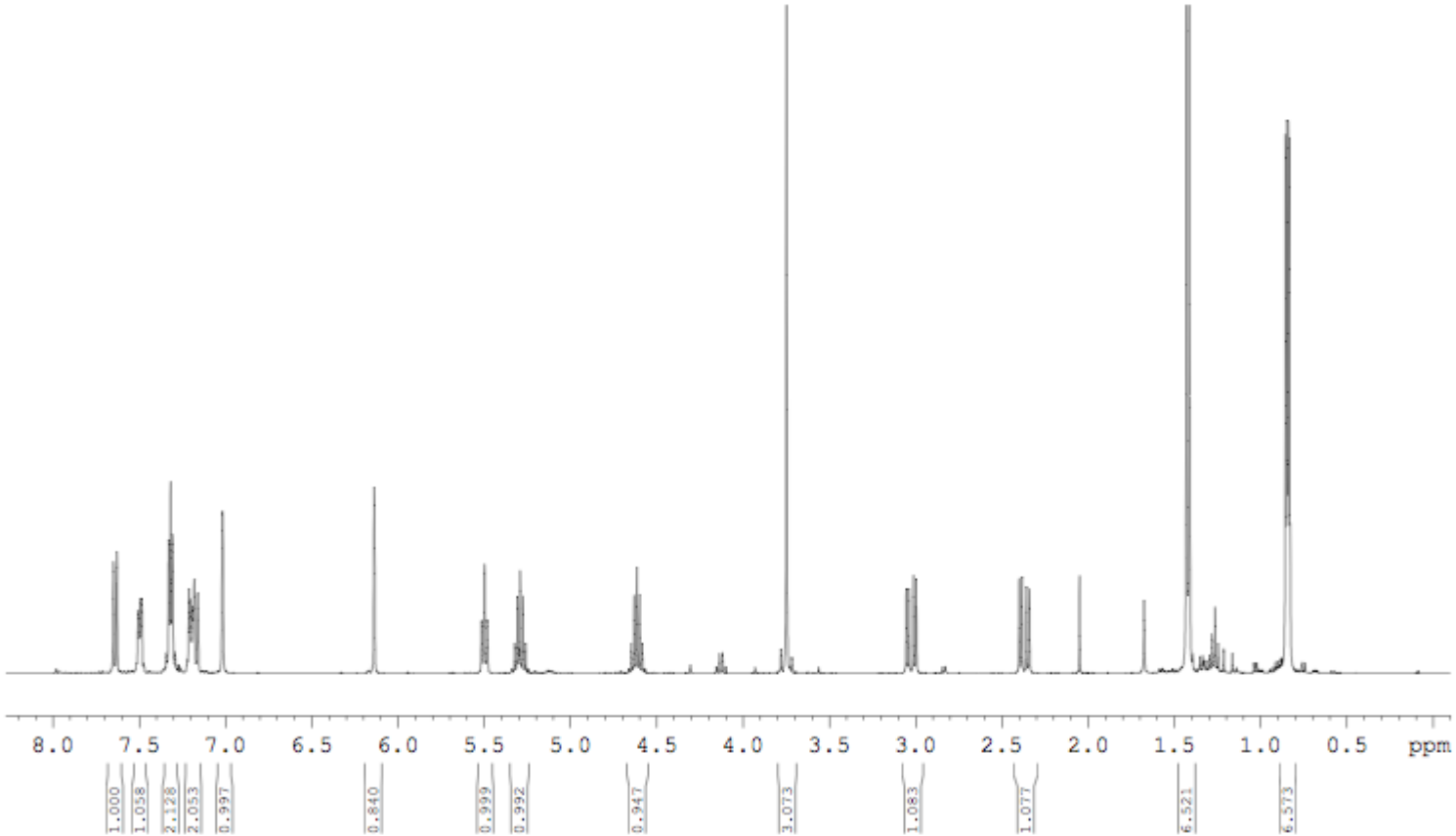
2-(2-Oxo-2*H*-chromen-4-yl)benzaldehyde (**36**)



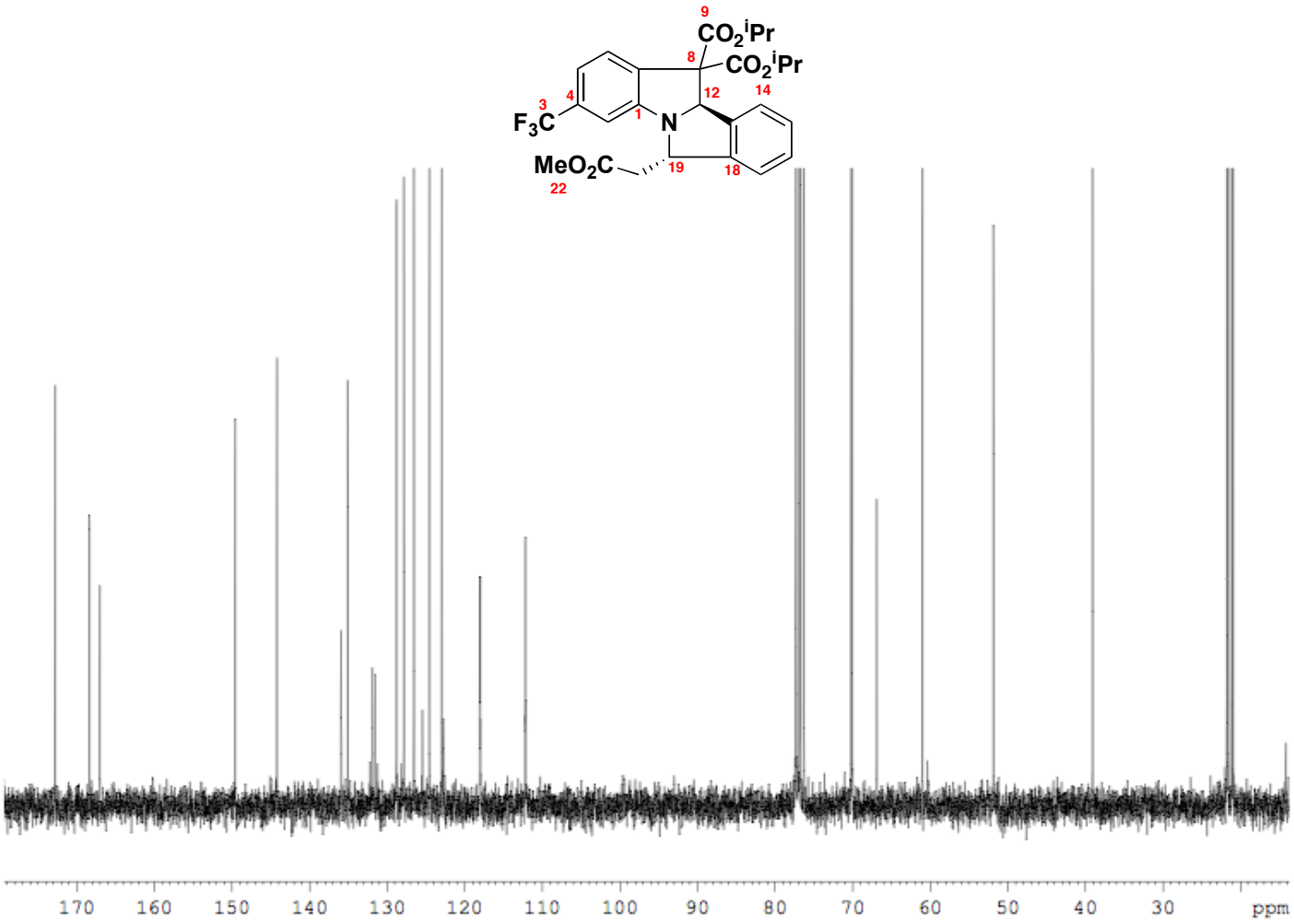
5.3 Cascade Products

Pyrrolizidine **8**

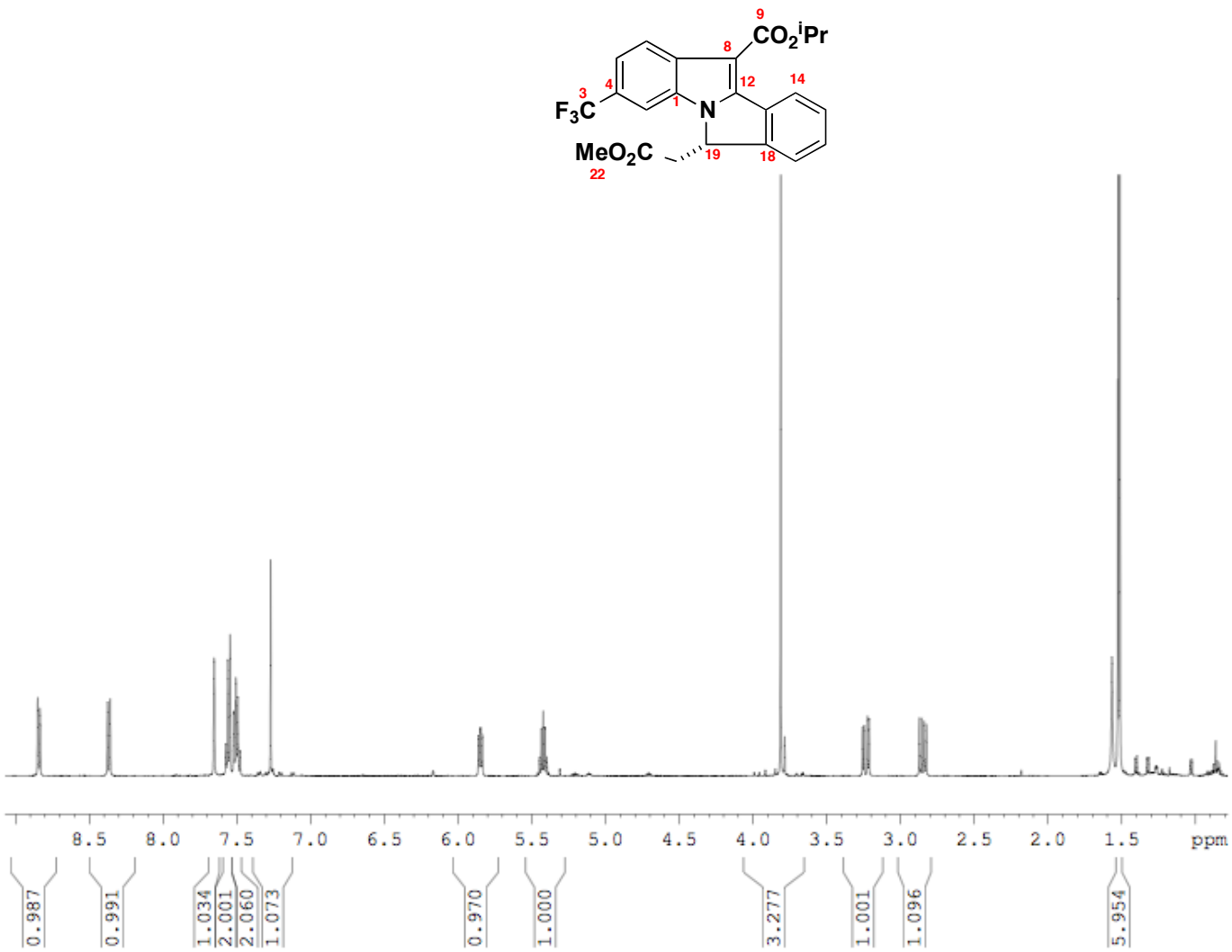




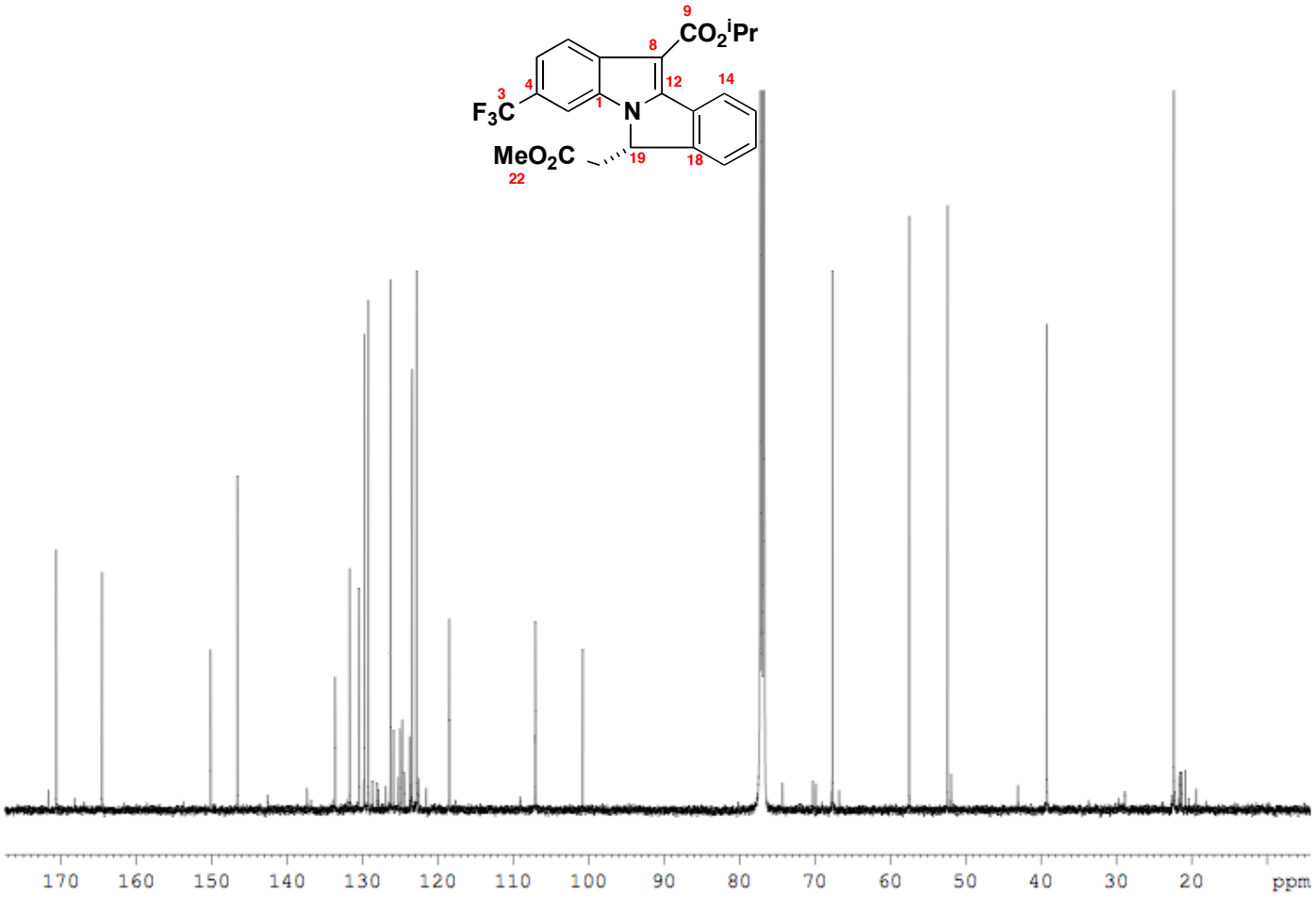
Pyrrolizidine **8**



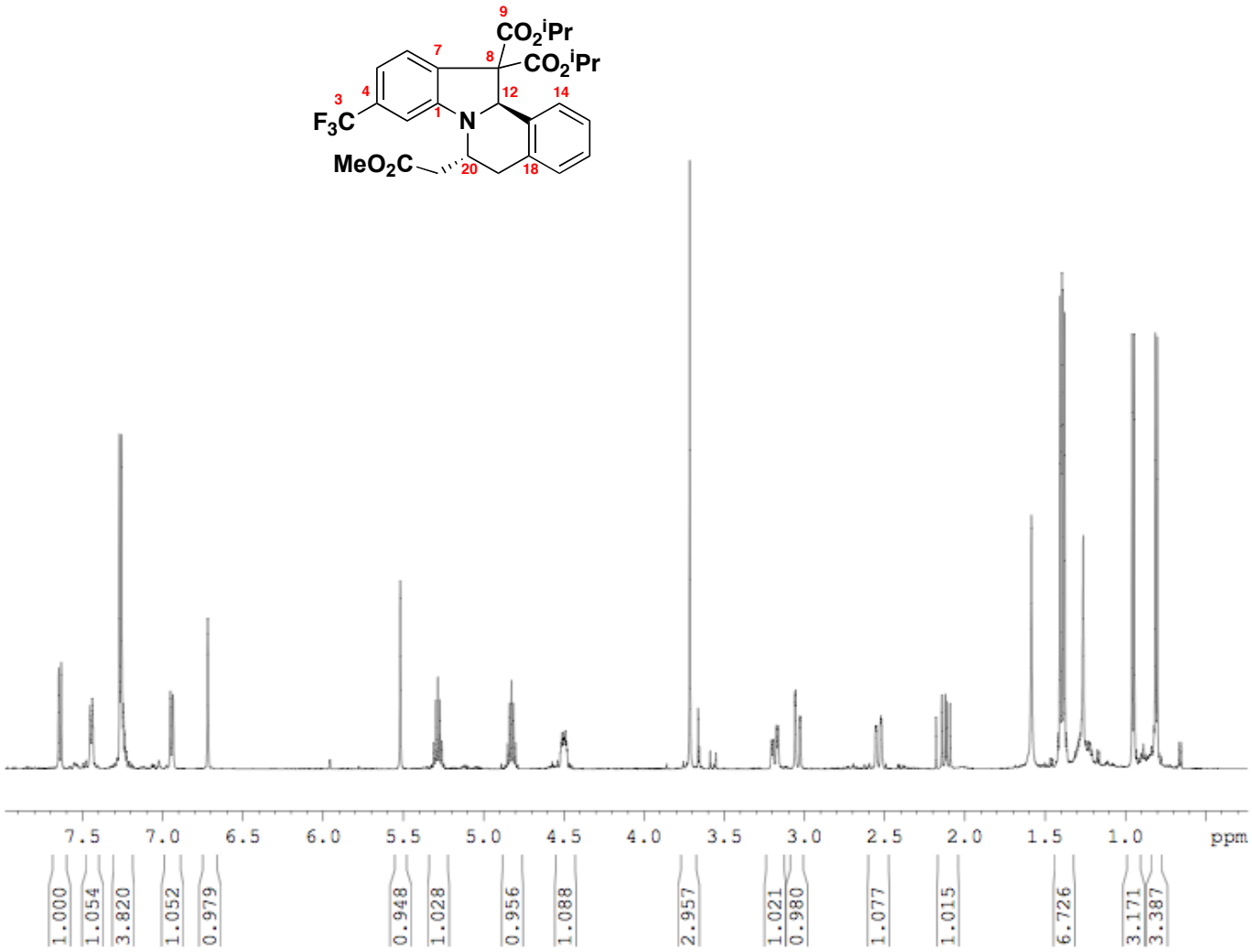
Indole **39**



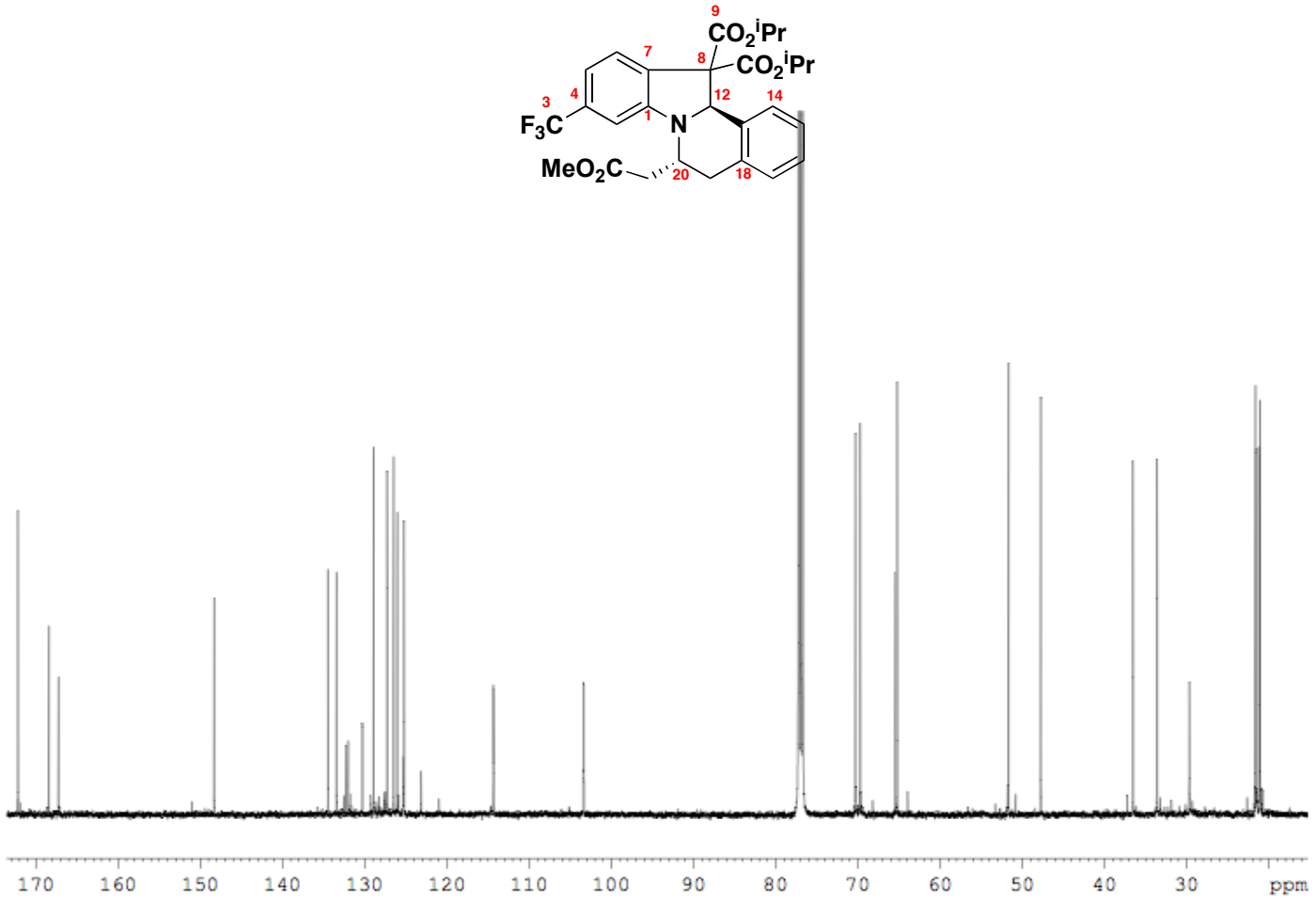
Indole **39**



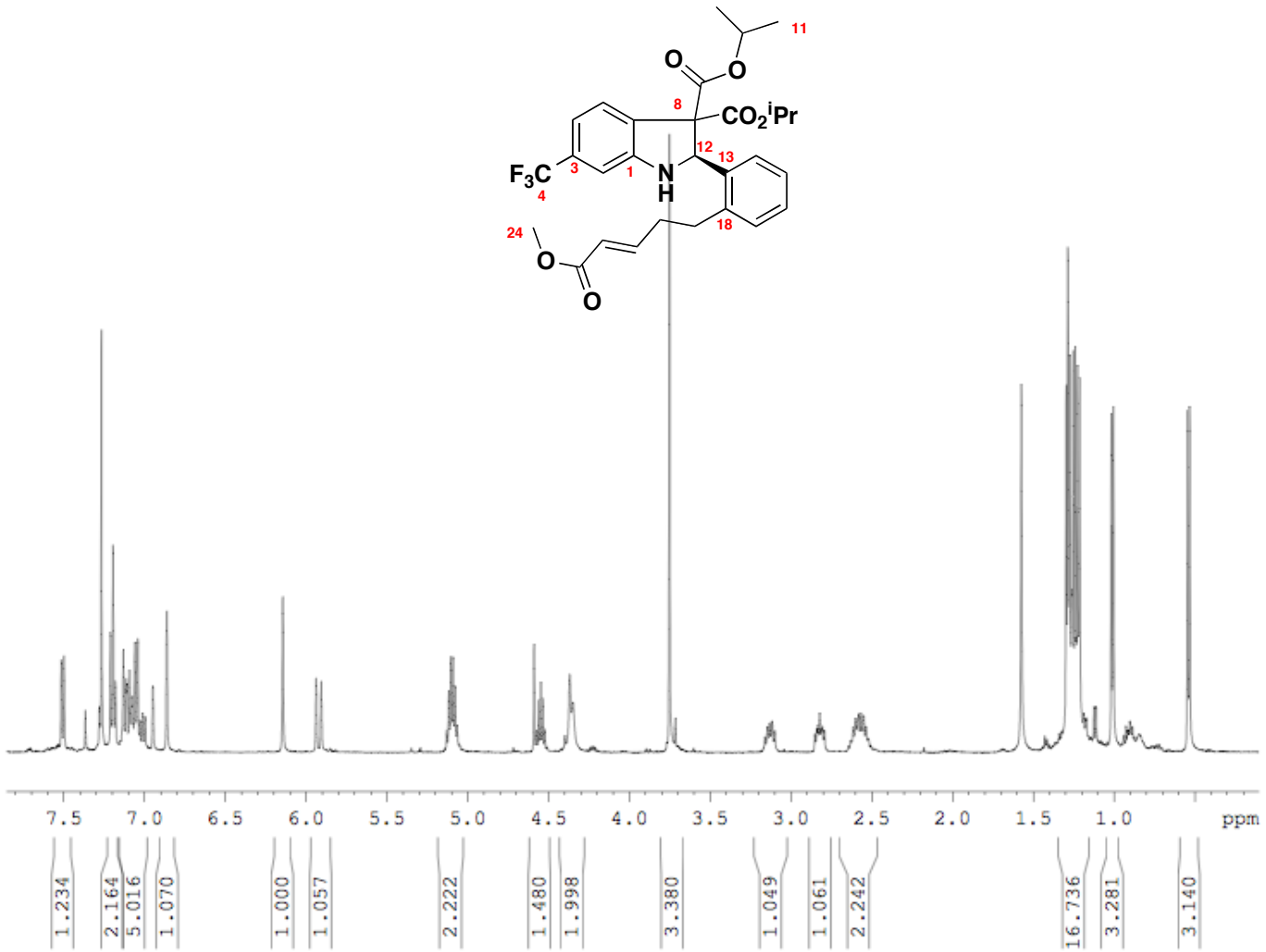
Indolizidine **9**



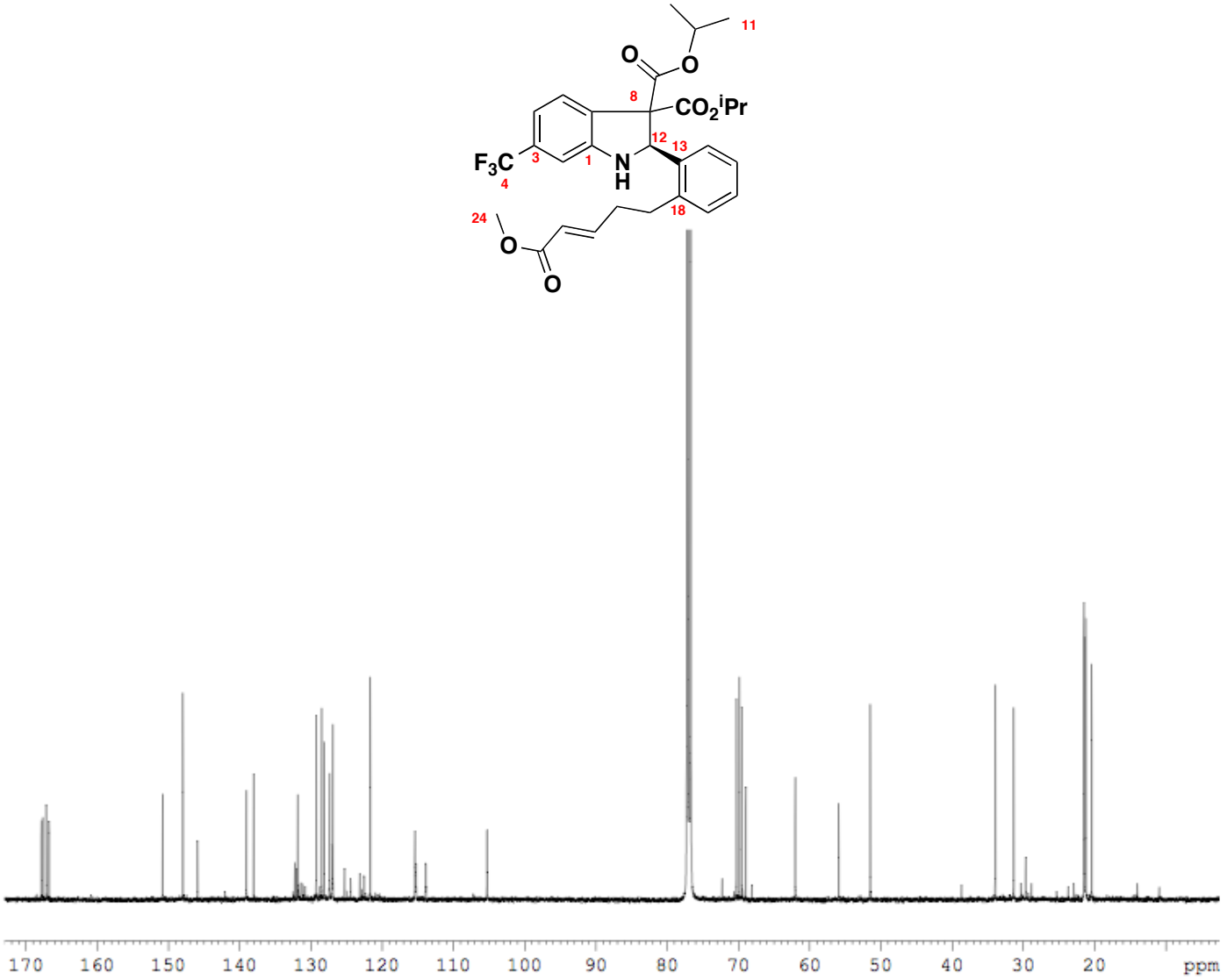
Indolizidine **9**



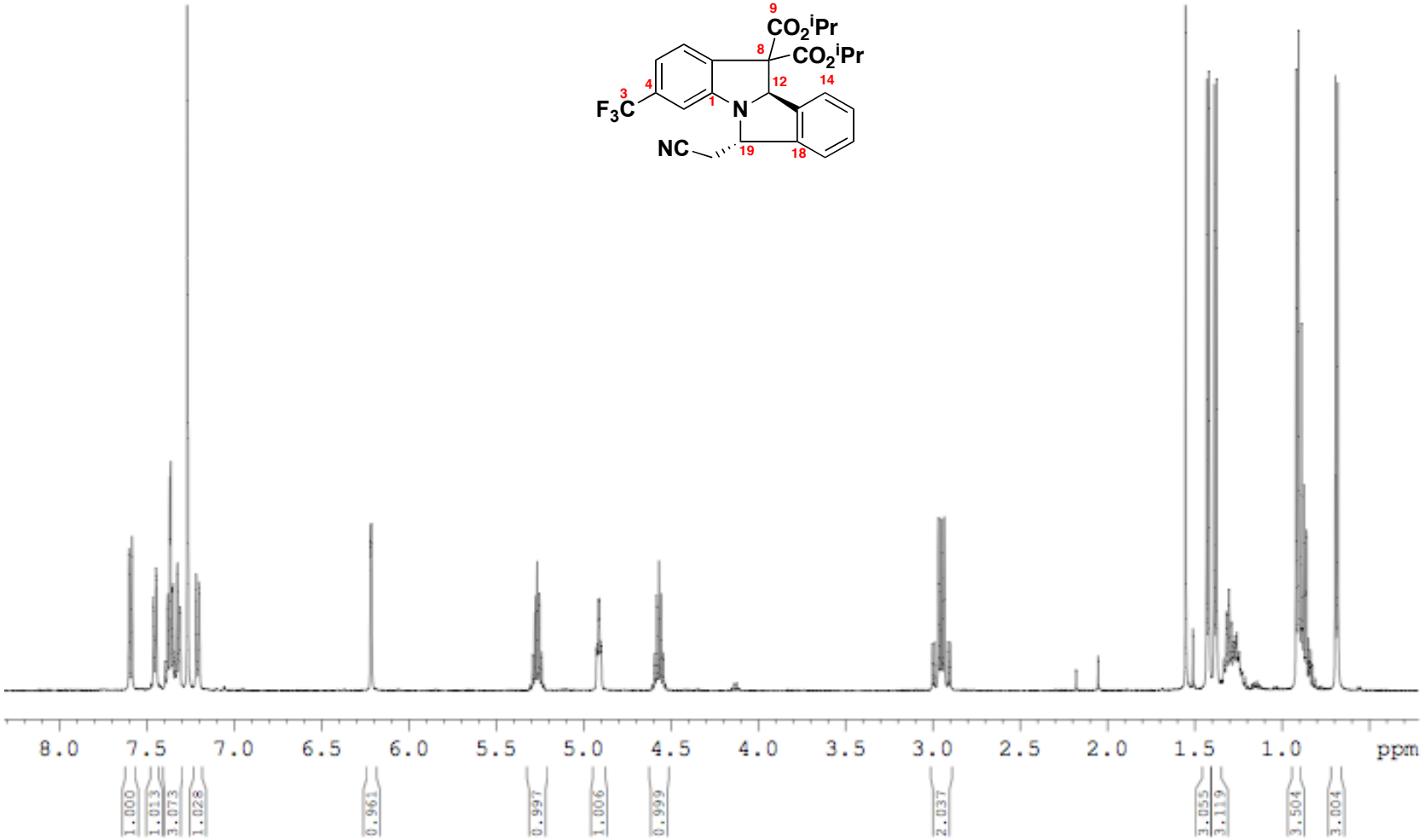
Indoline **38**



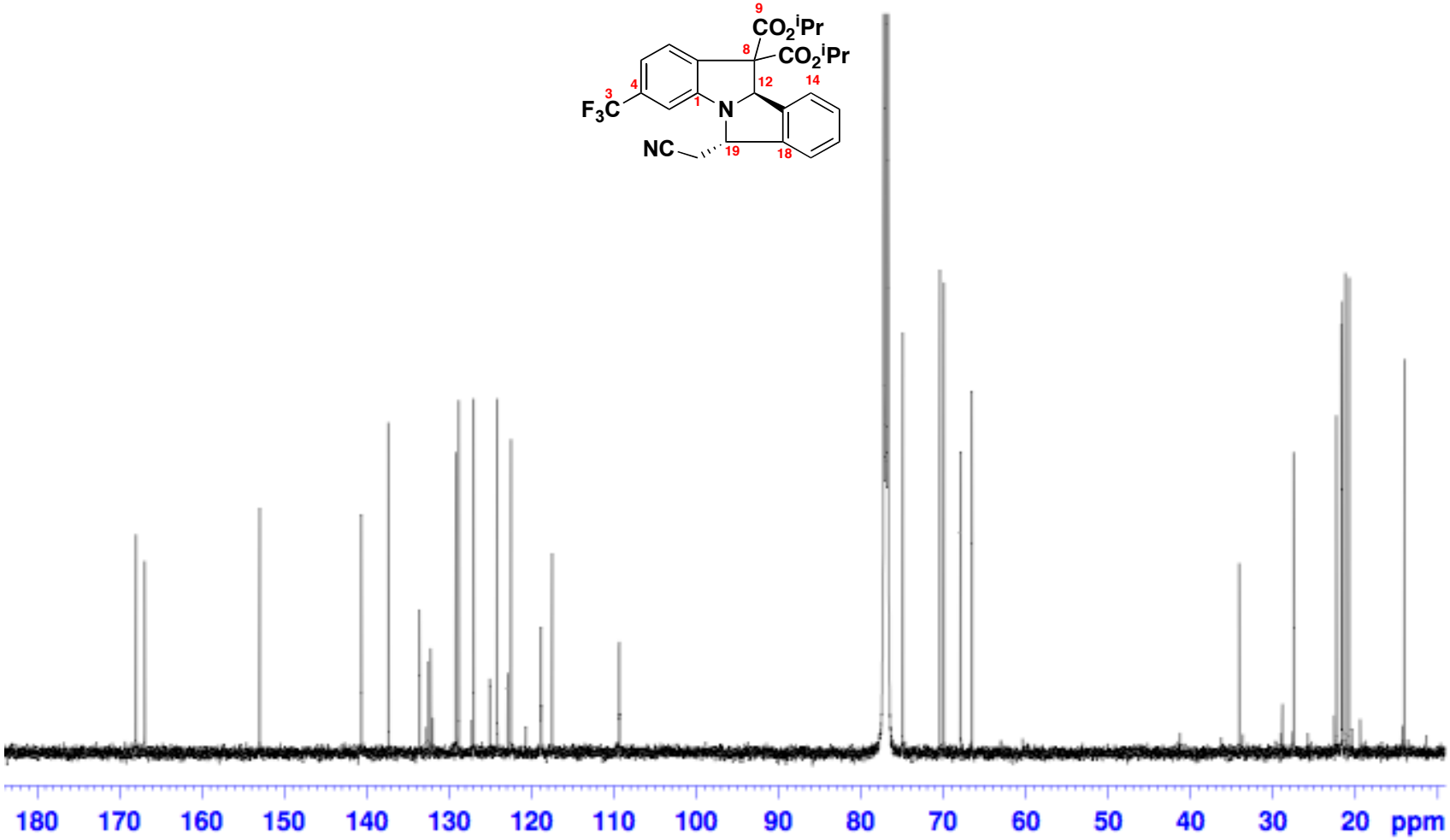
Indoline **38**



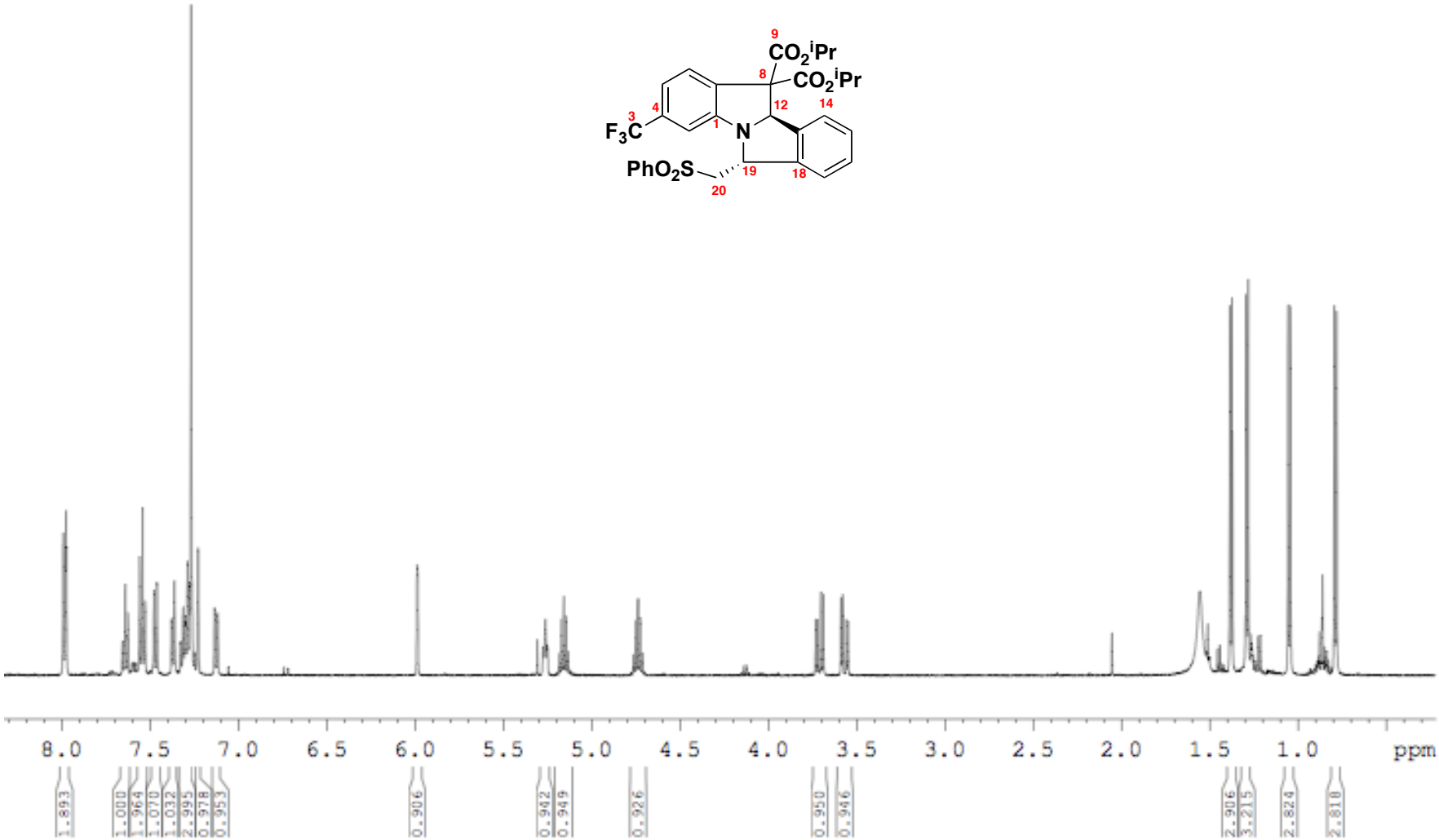
Pyrrolizidine **14**



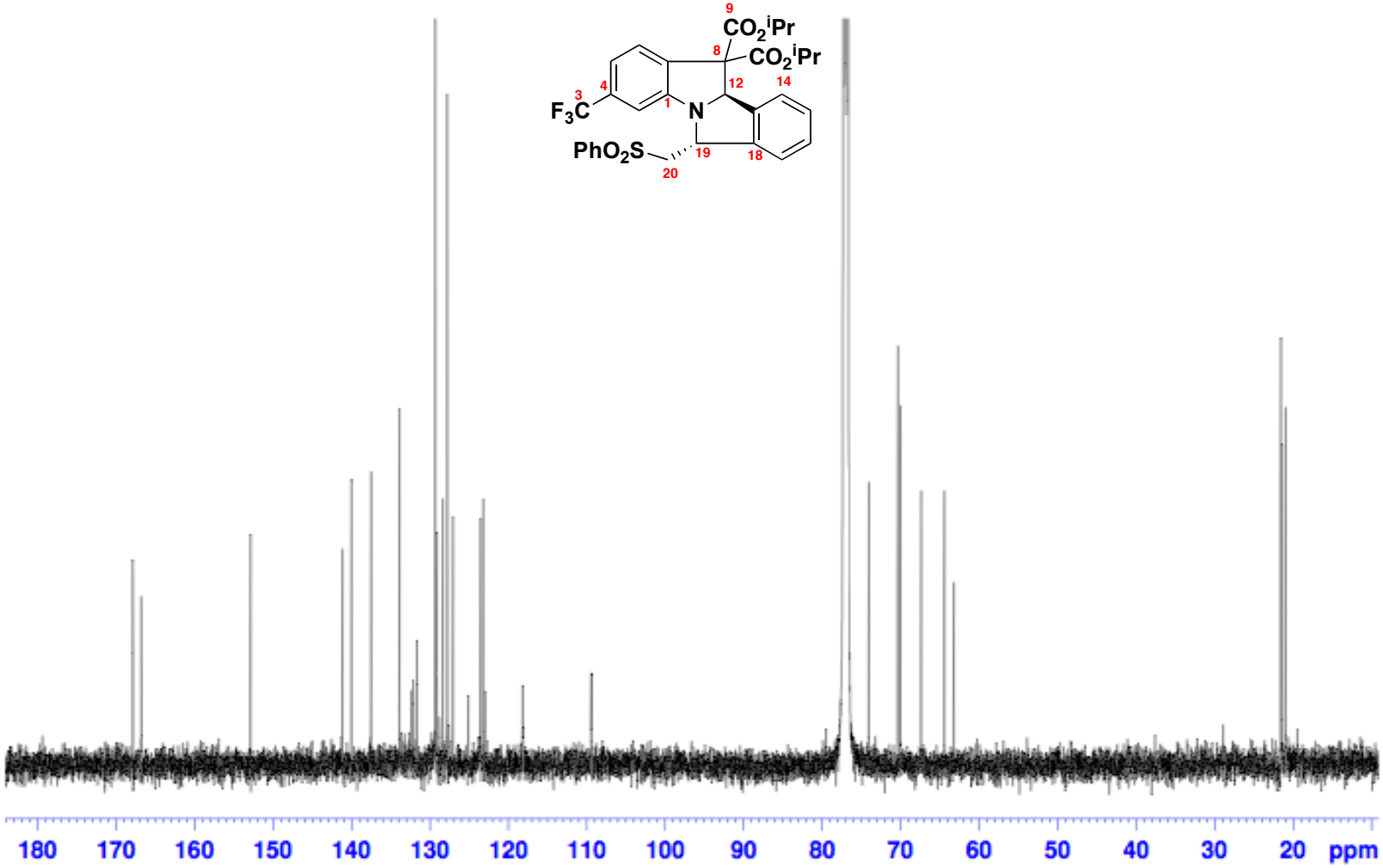
Pyrrolizidine **14**



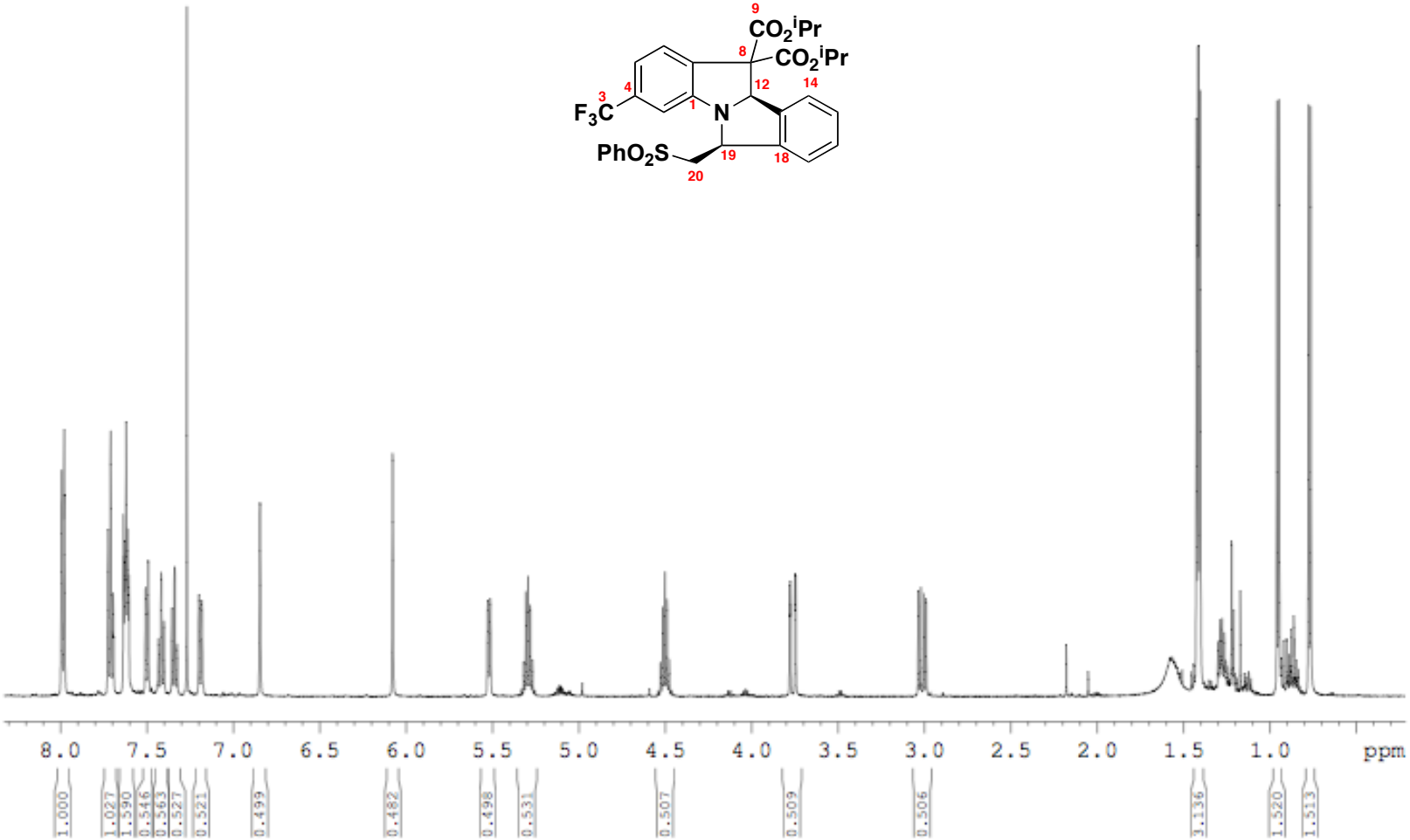
Pyrrolizidine **15 (major)**



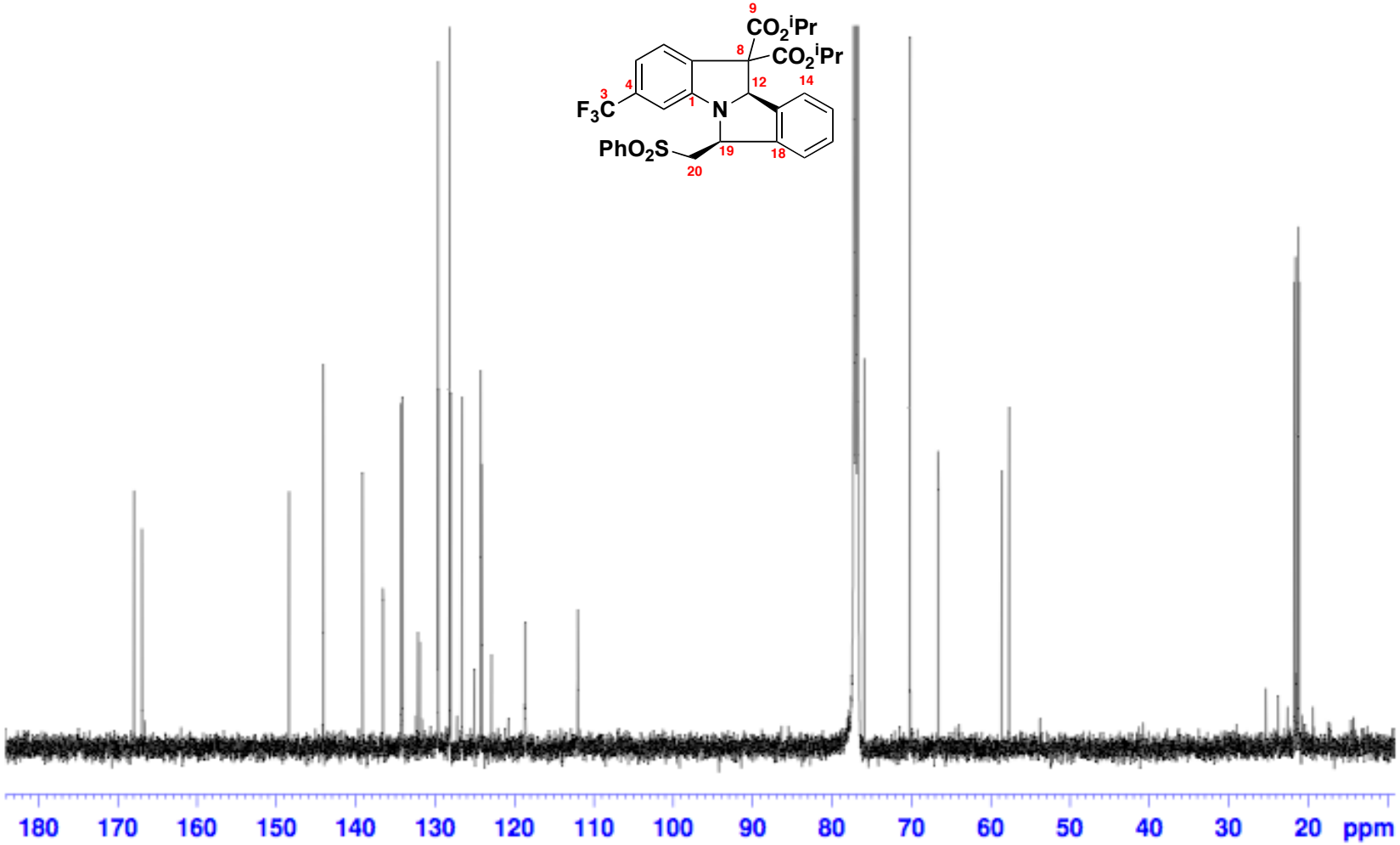
Pyrrolizidine **15 (major)**



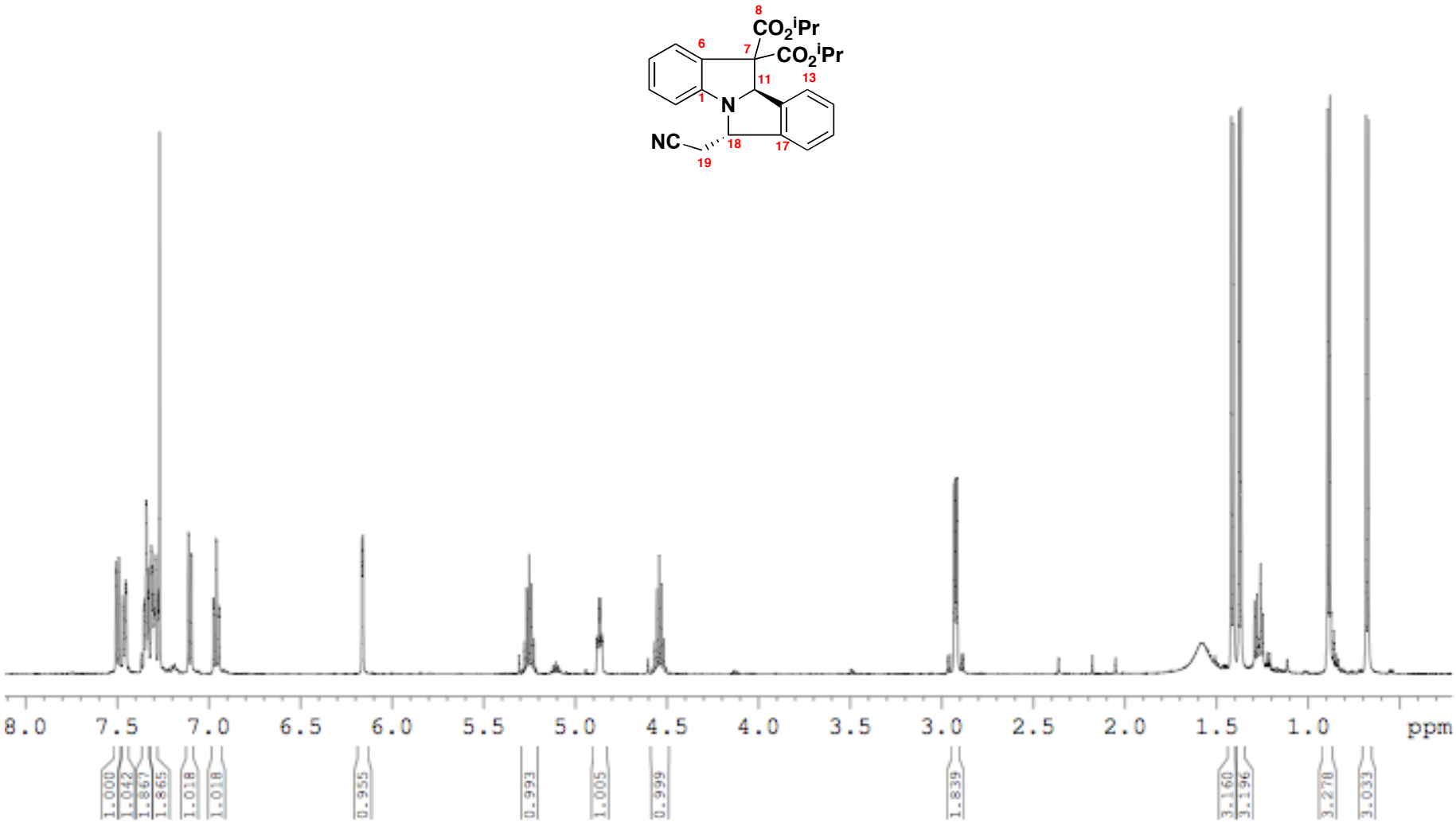
Pyrrolizidine **15 (minor)**



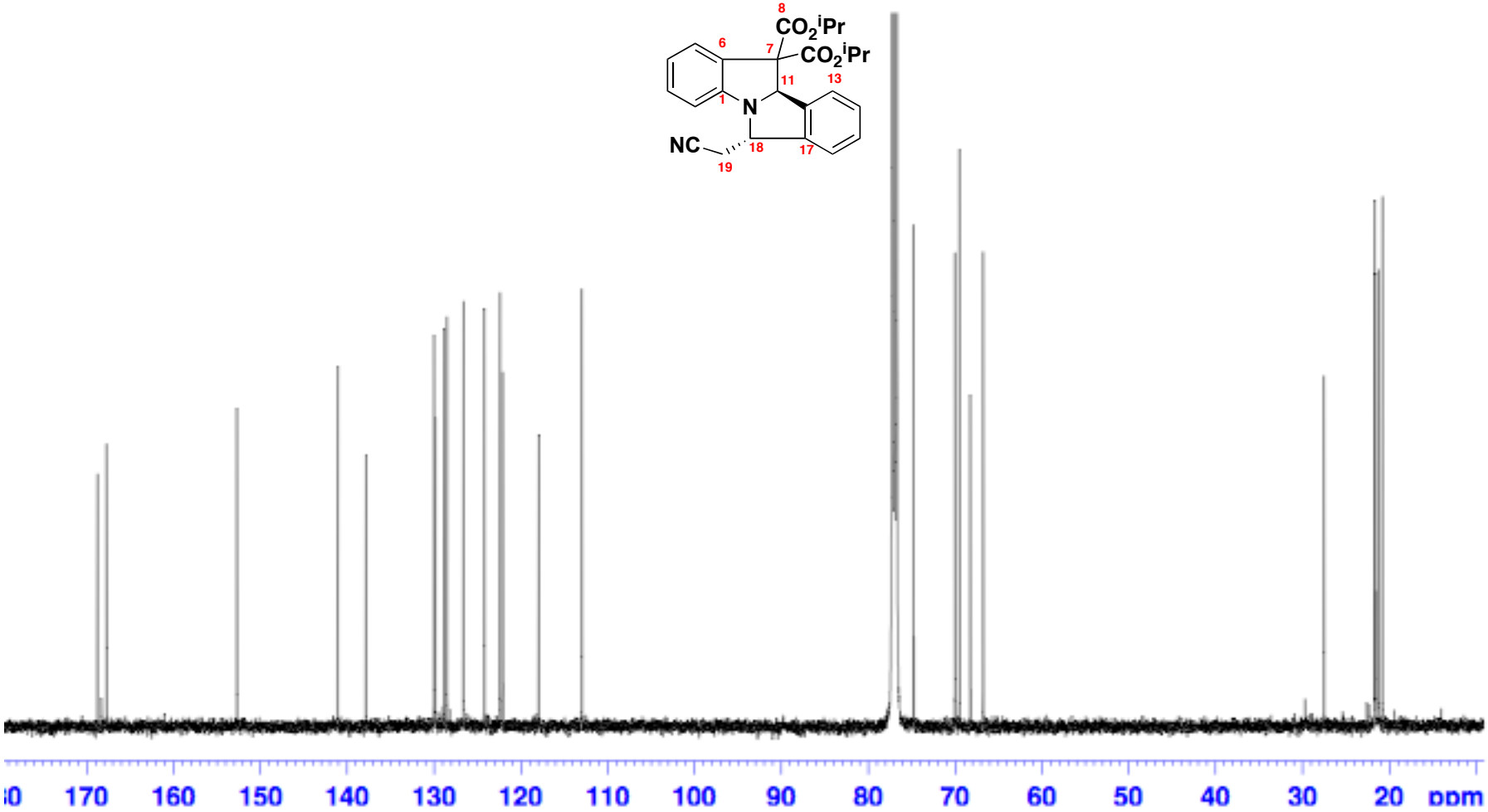
Pyrrolizidine **15 (minor)**



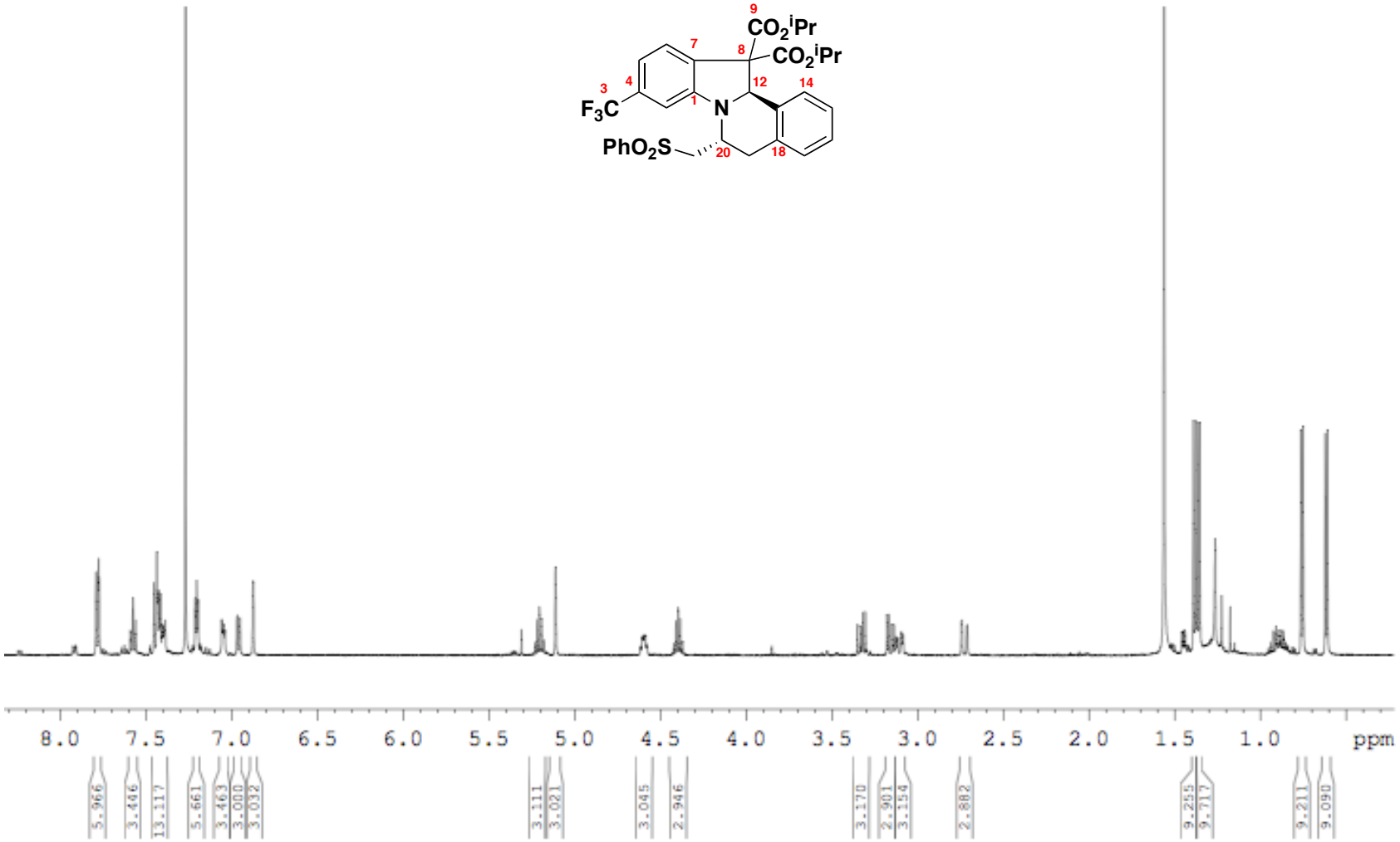
Pyrrolizidine **16**



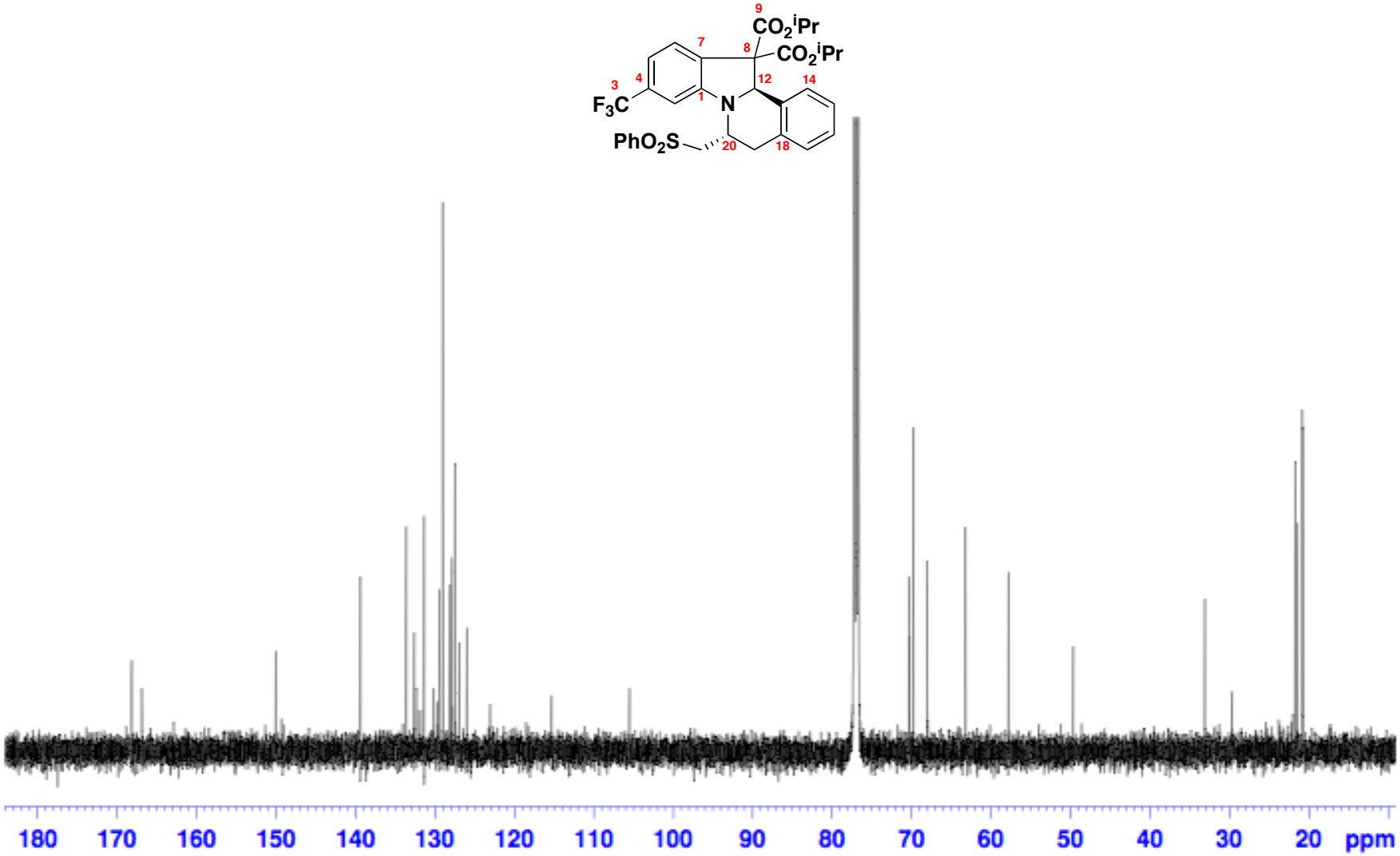
Pyrrolizidine **16**



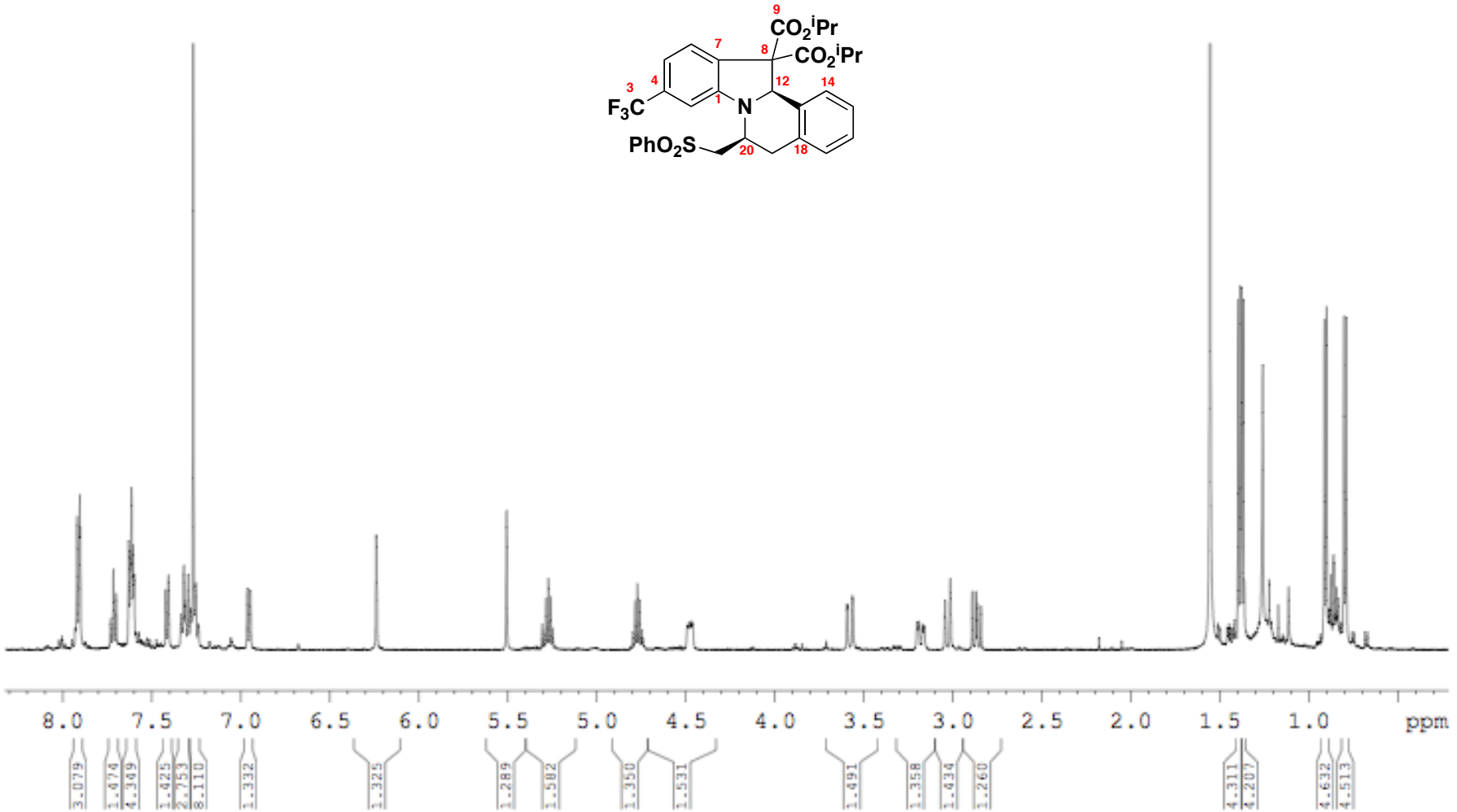
Indolizidine **17 (major)**



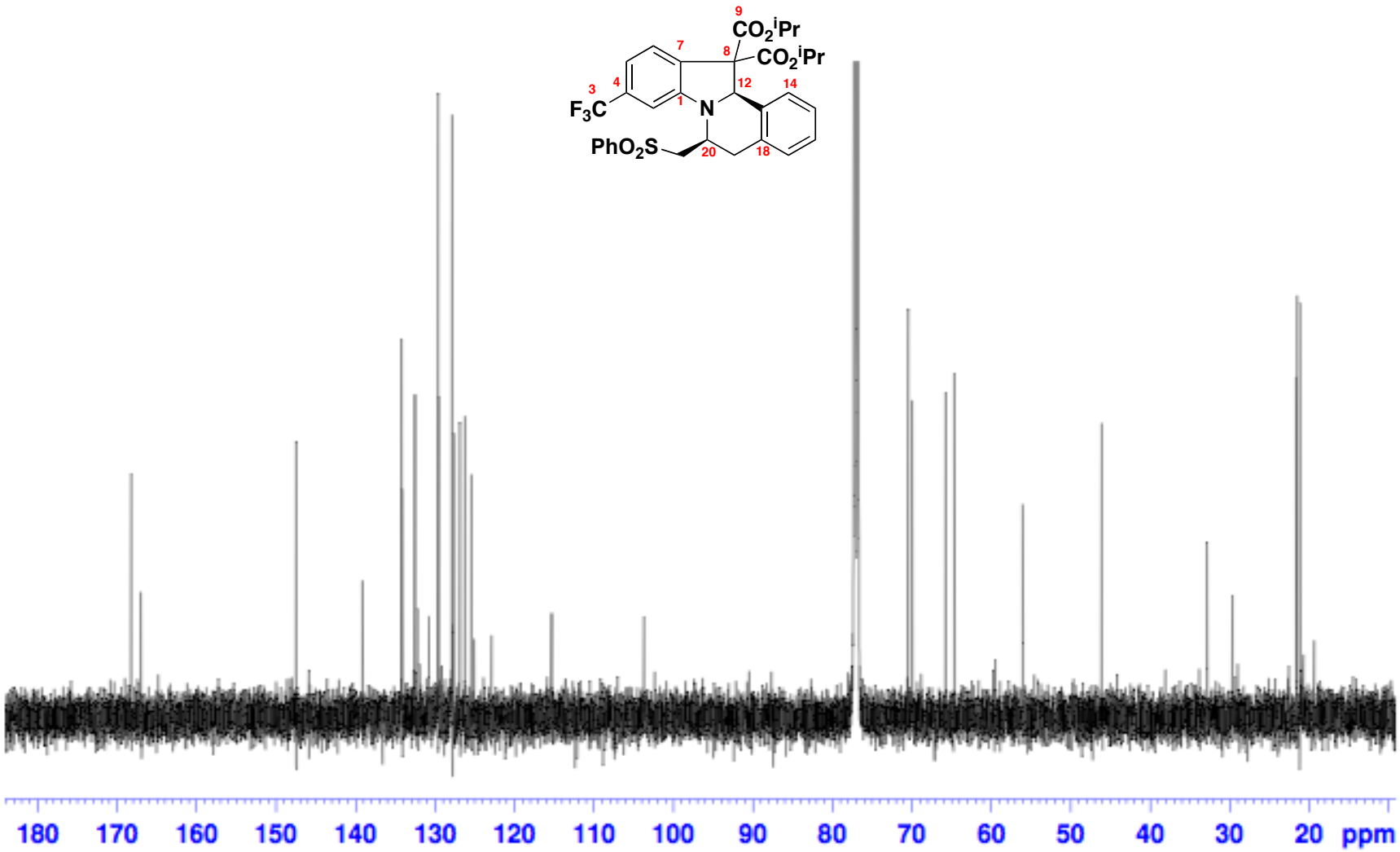
Indolizidine **17 (major)**



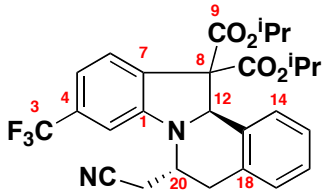
Indolizidine **17 (minor)**



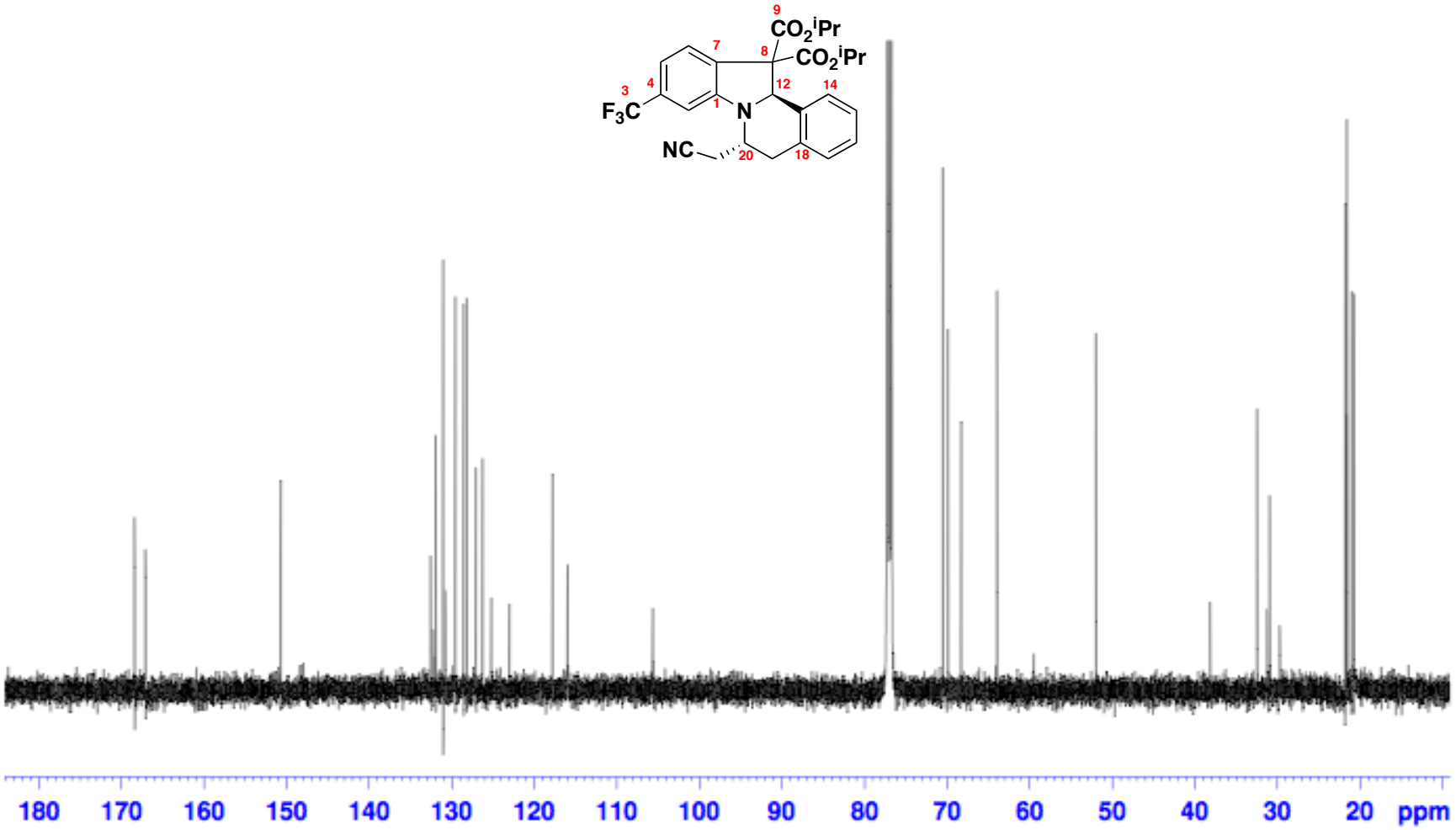
Indolizidine **17 (minor)**



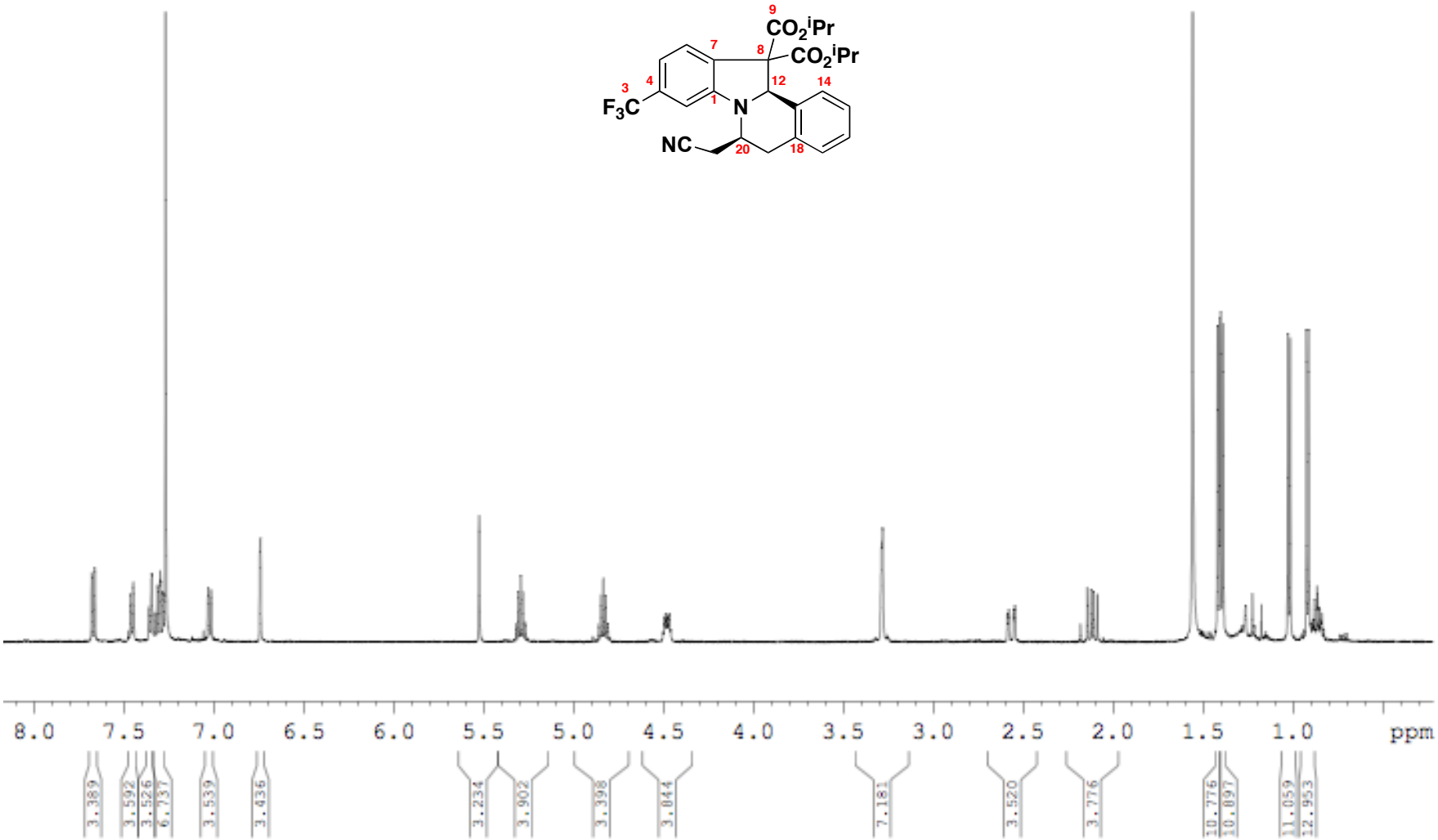
Indolizidine **18 (major)**



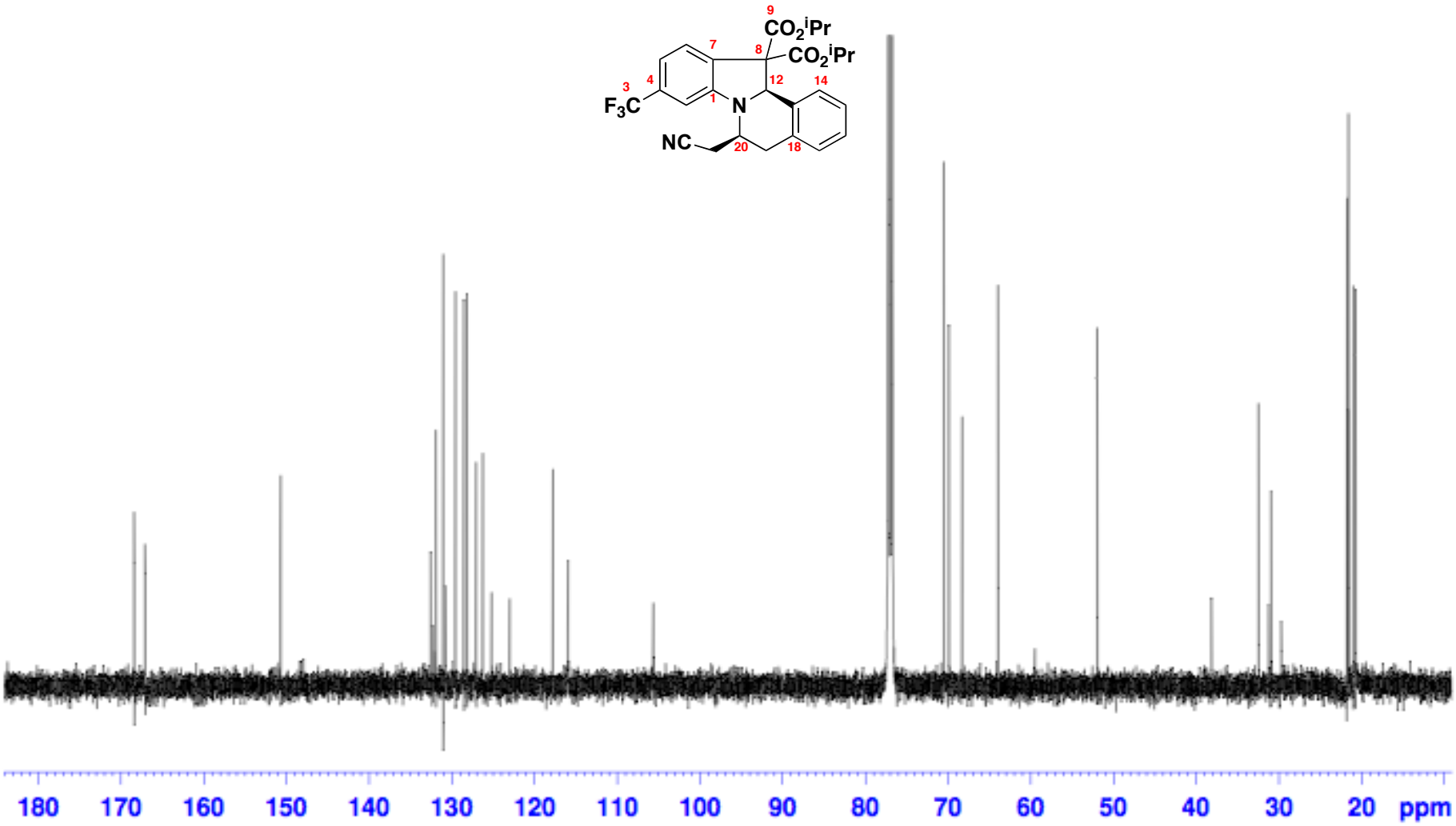
Indolizidine **18 (major)**



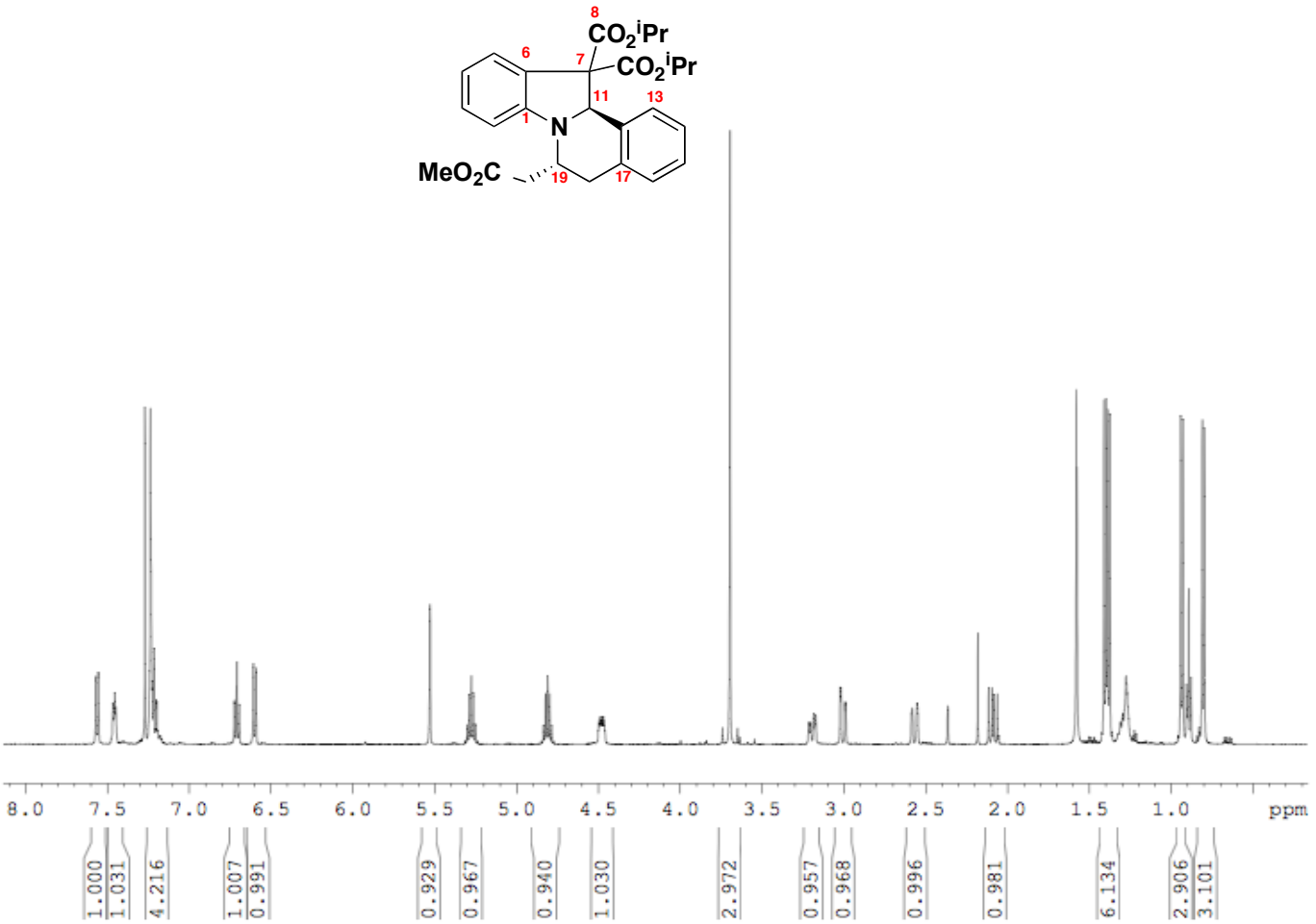
Indolizidine **18 (minor)**



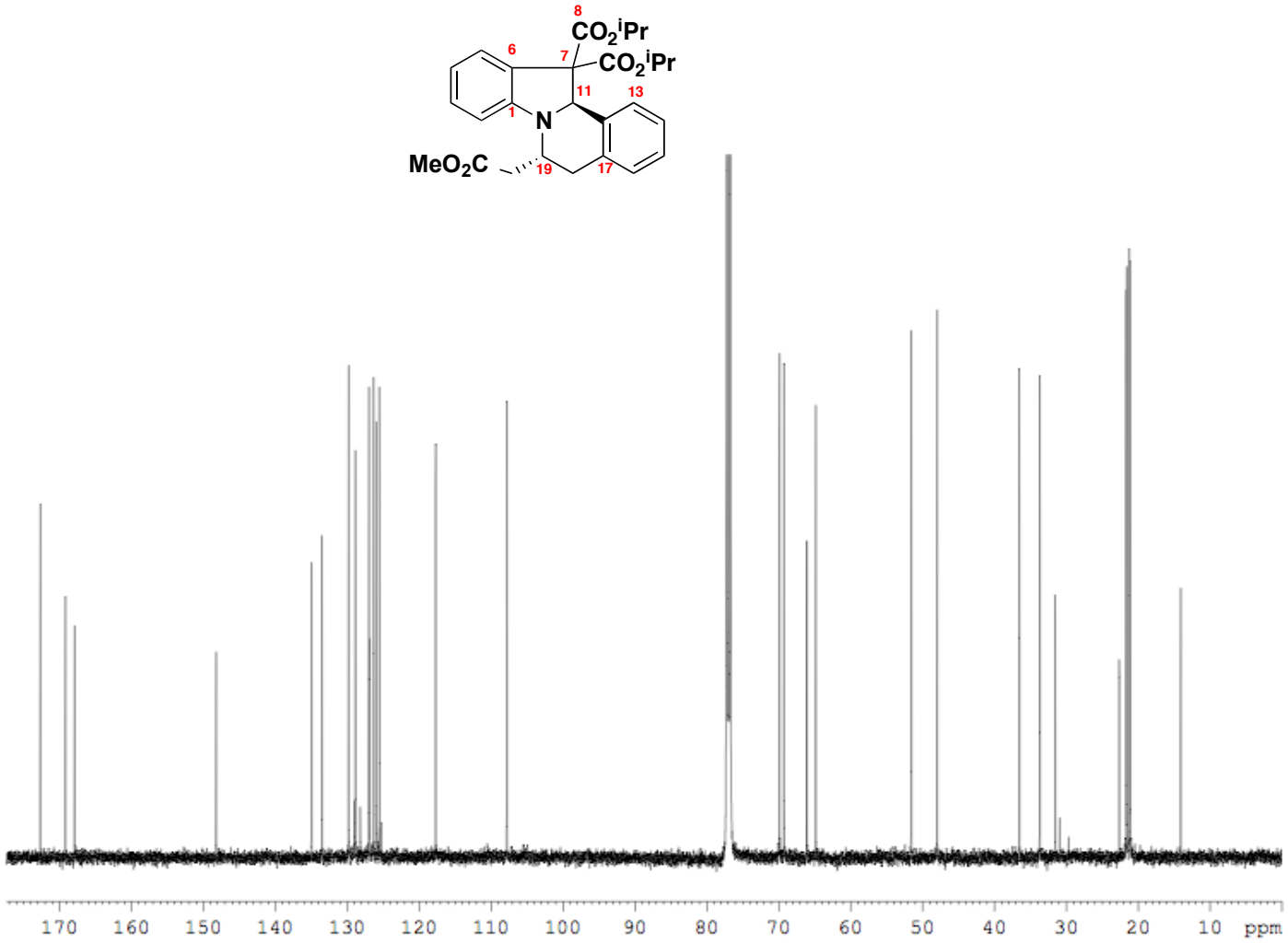
Indolizidine **18 (minor)**



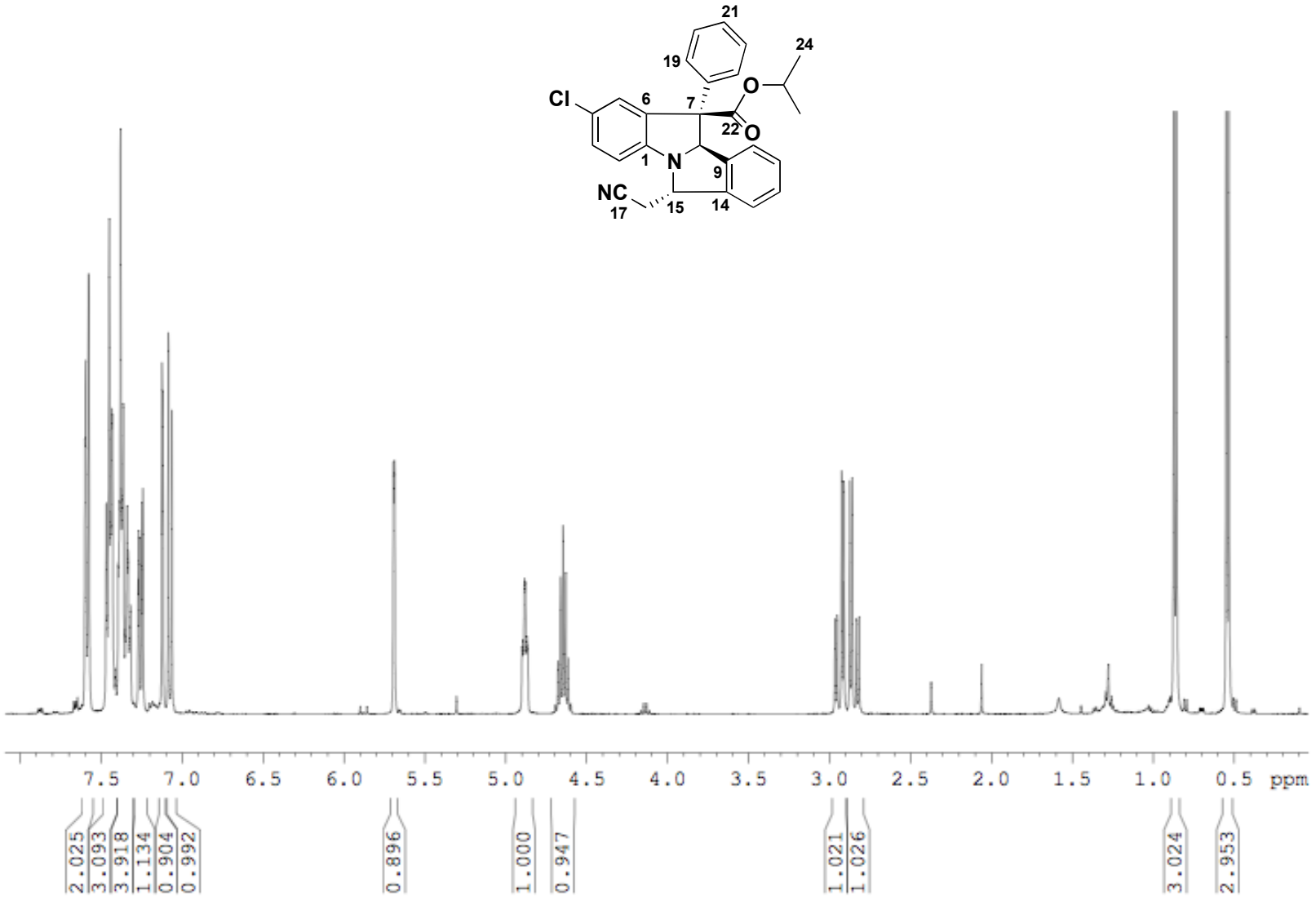
Indolizidine **19**



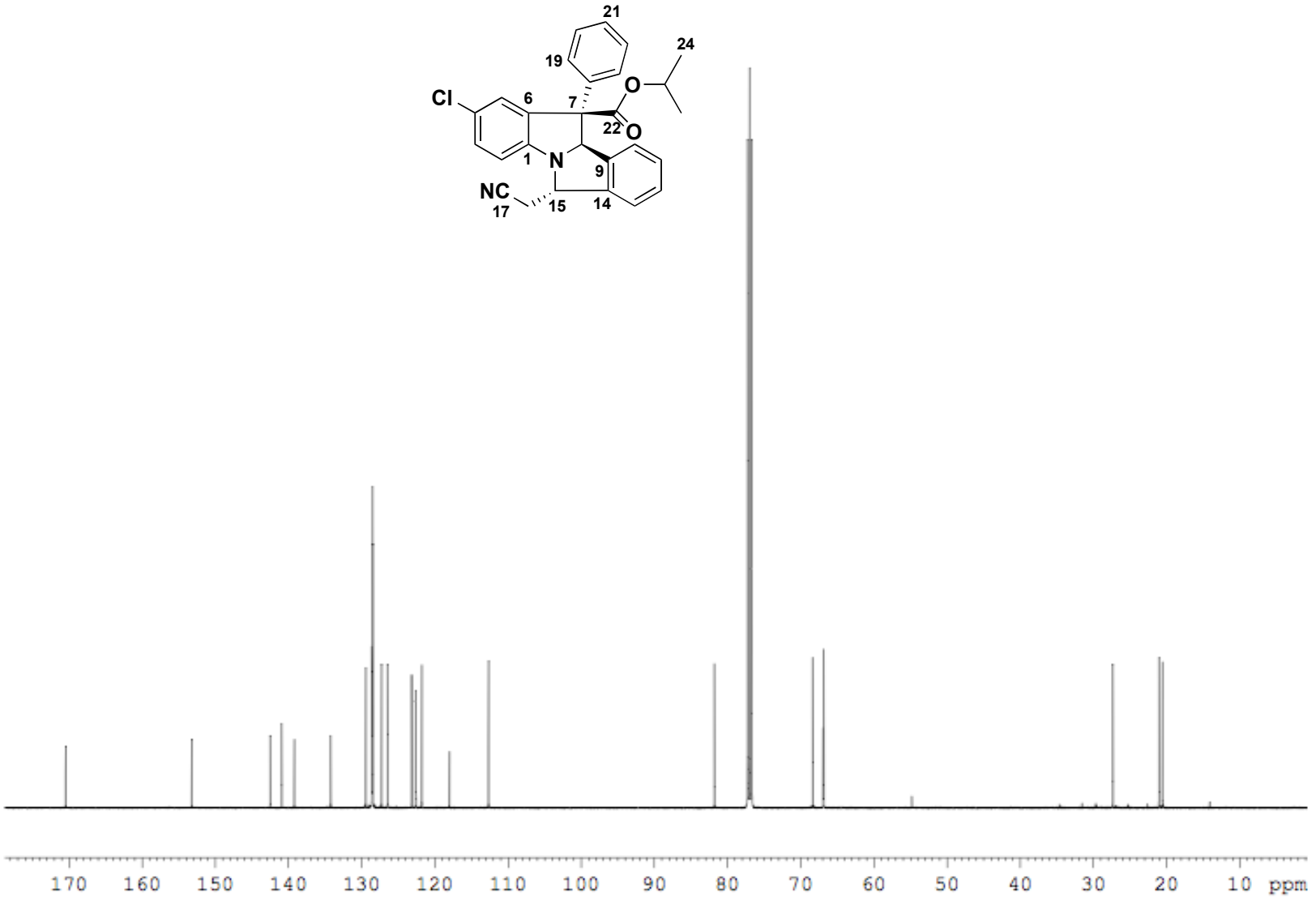
Indolizidine **19**



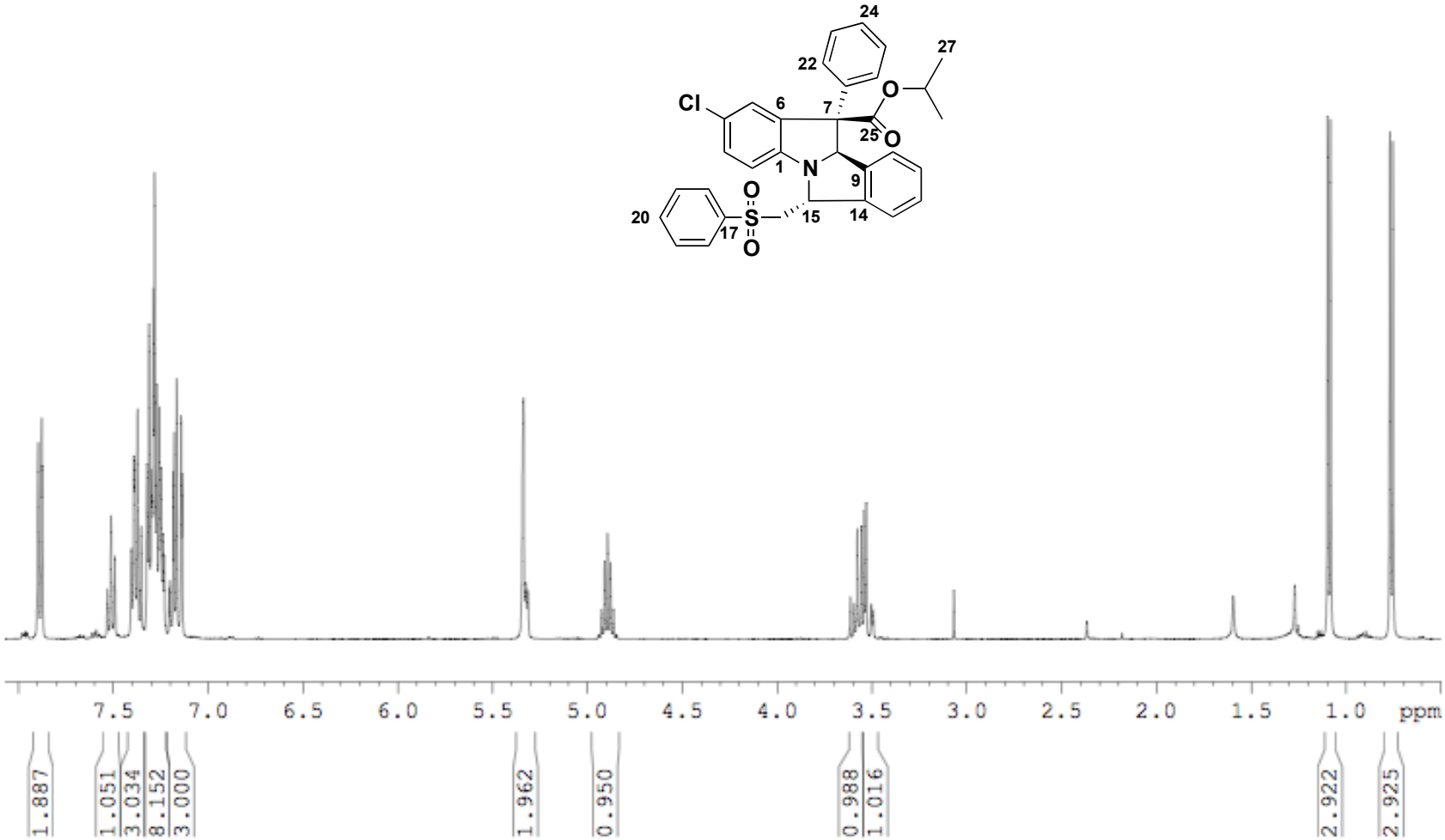
Pyrrolizidine **22**



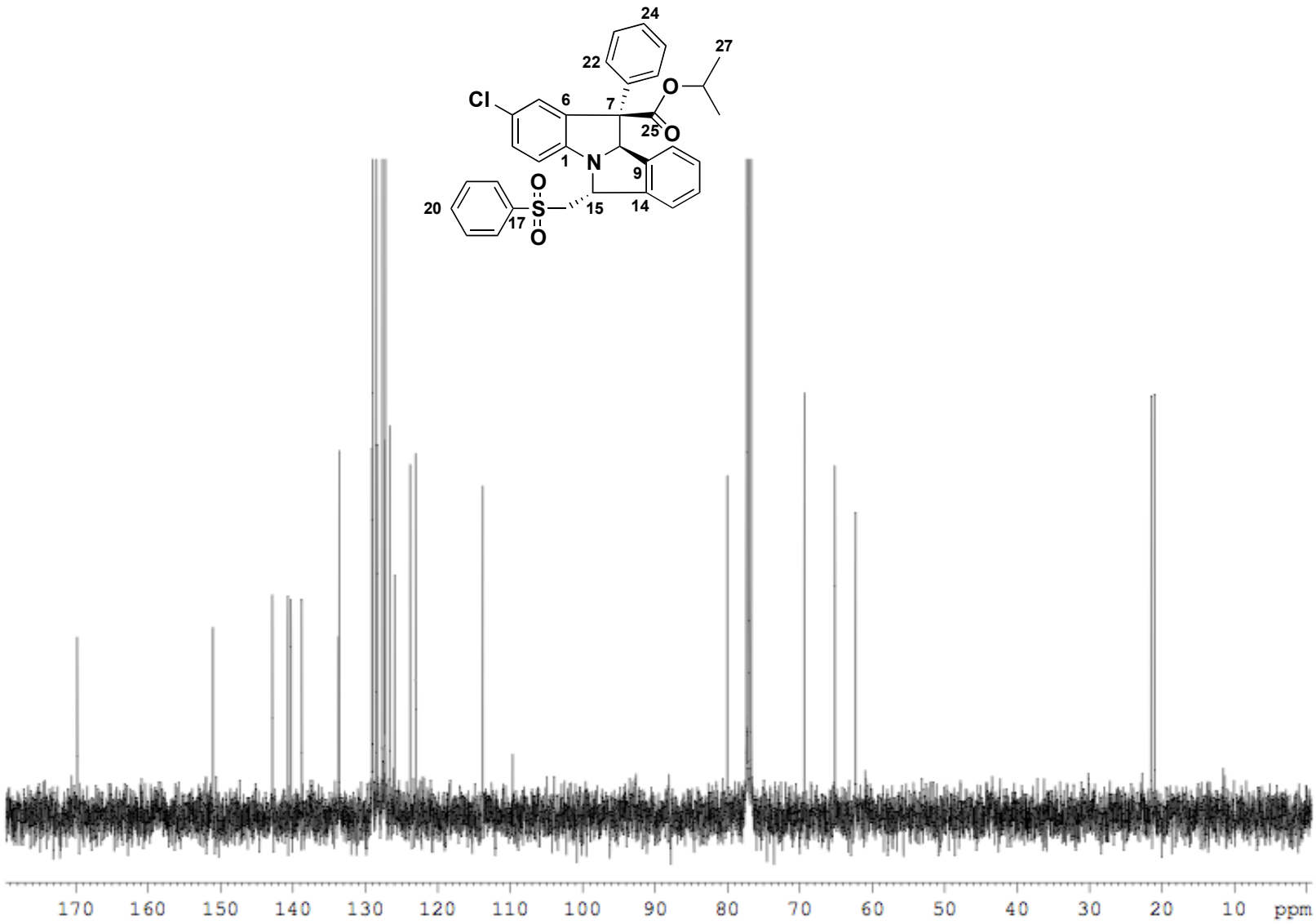
Pyrrolizidine **22**



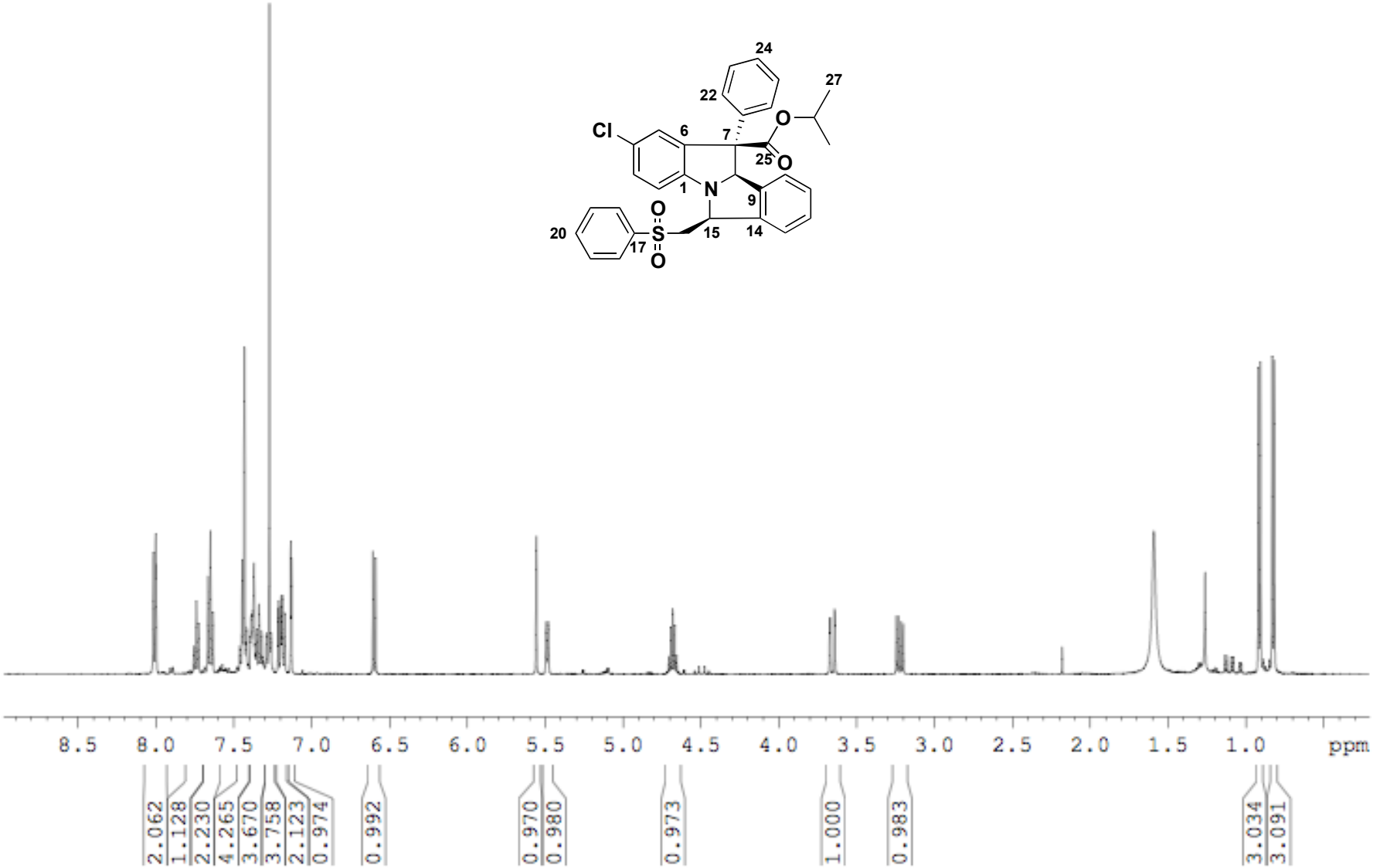
Pyrrolizidine **23 (major)**



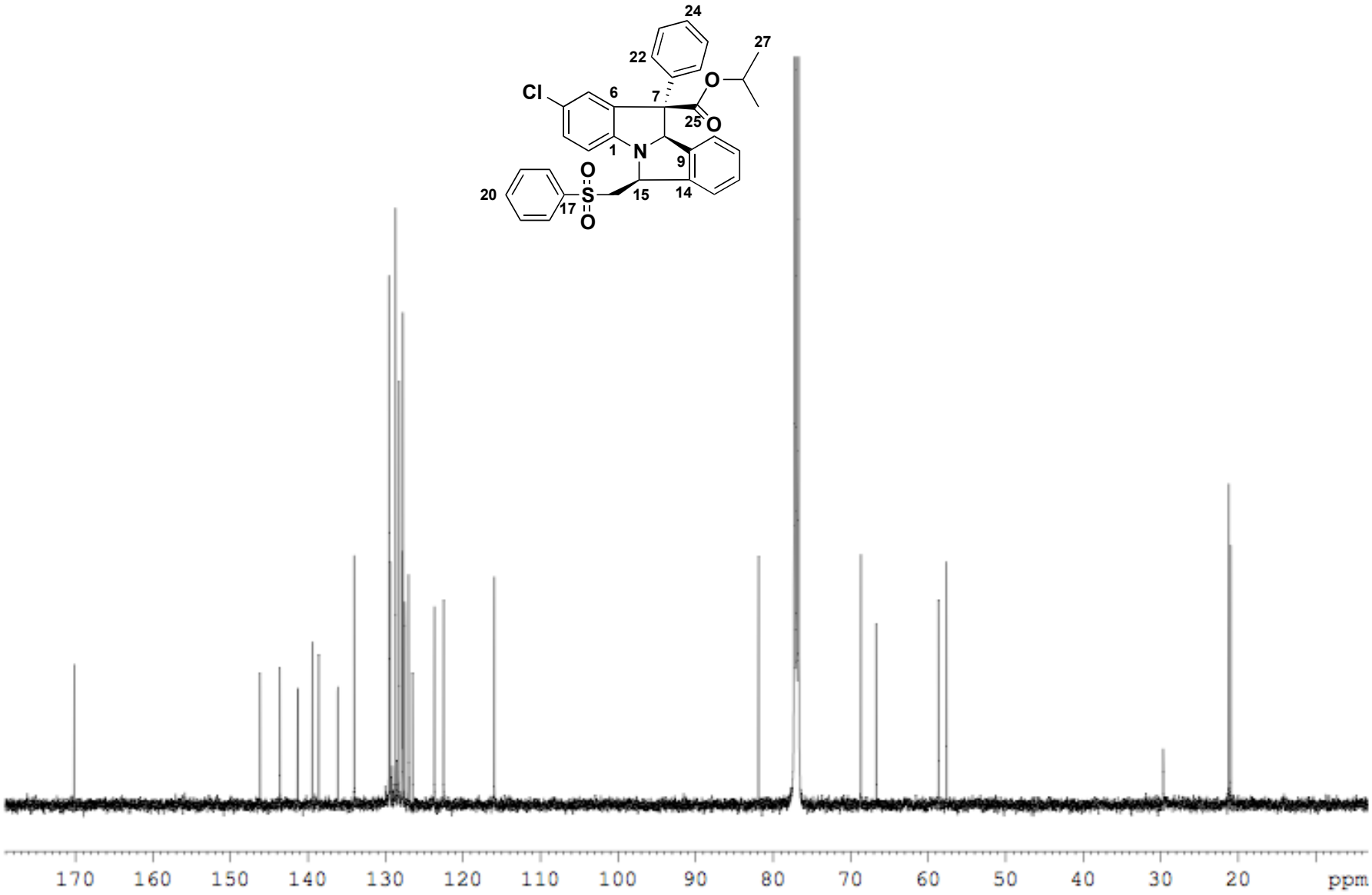
Pyrrolizidine **23 (major)**



Pyrrolizidine **23 (minor)**

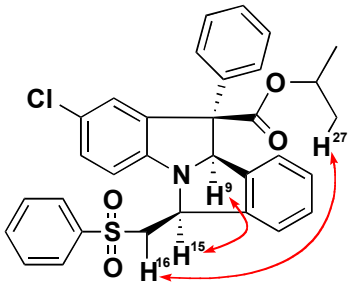


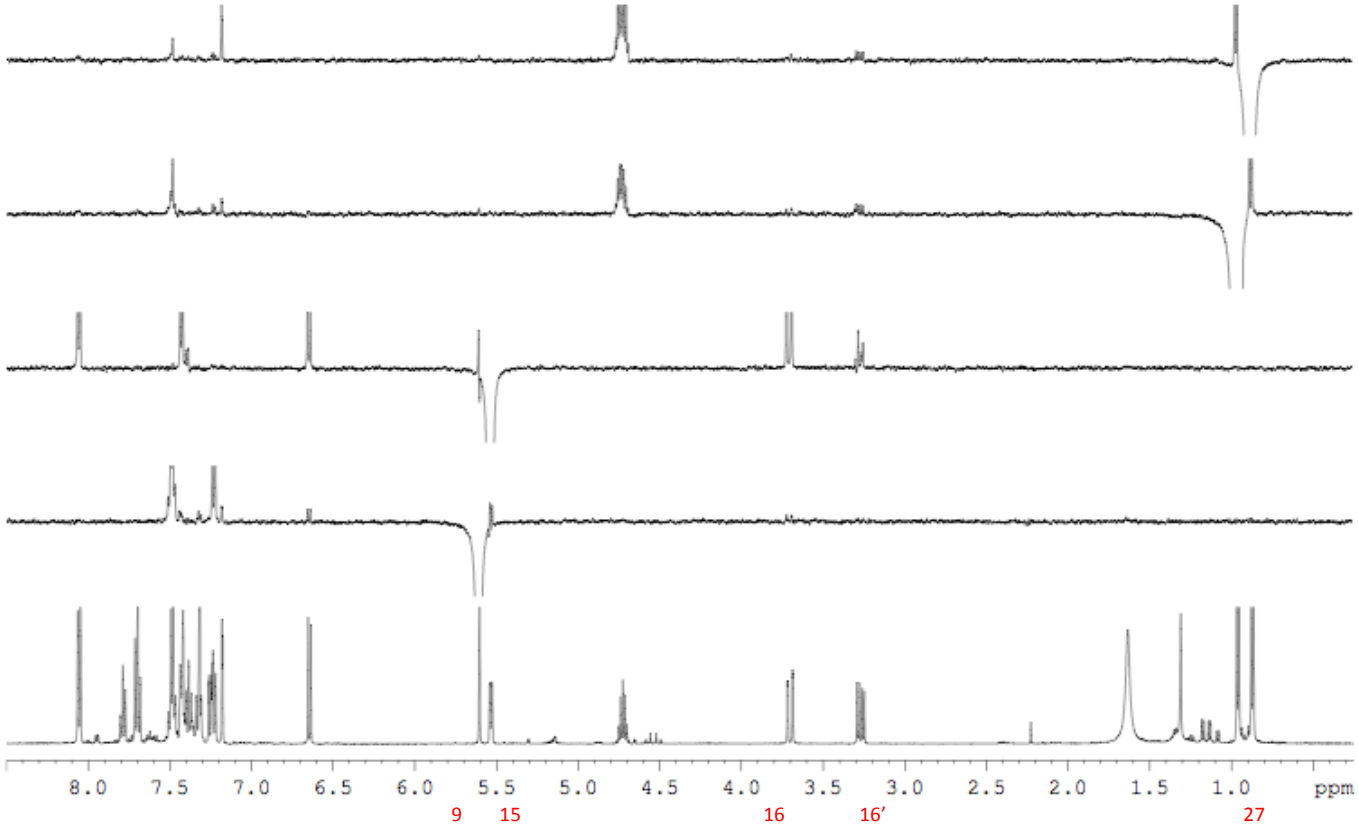
Pyrrolizidine **23 (minor)**



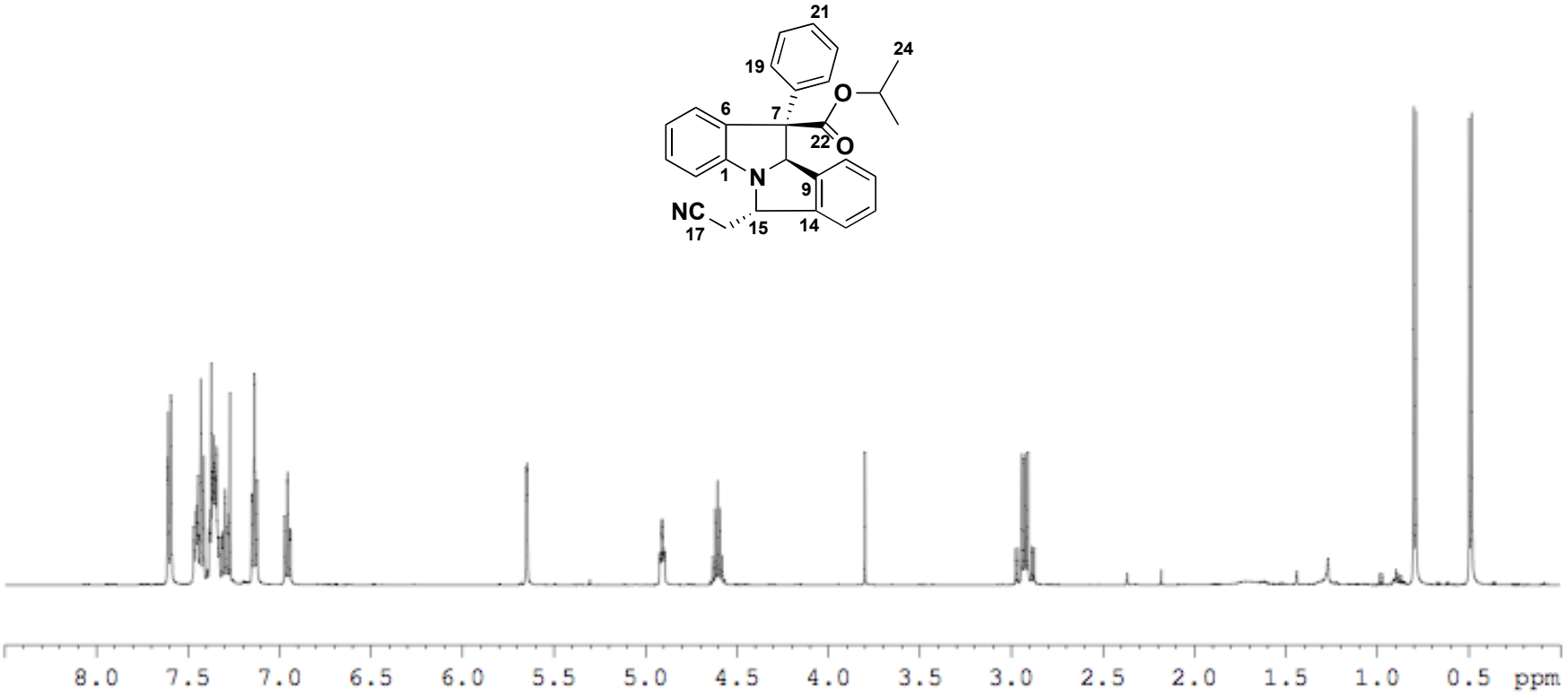
Pyrrolizidine **23 (minor)**

Key nOe Data

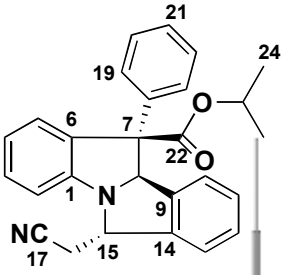


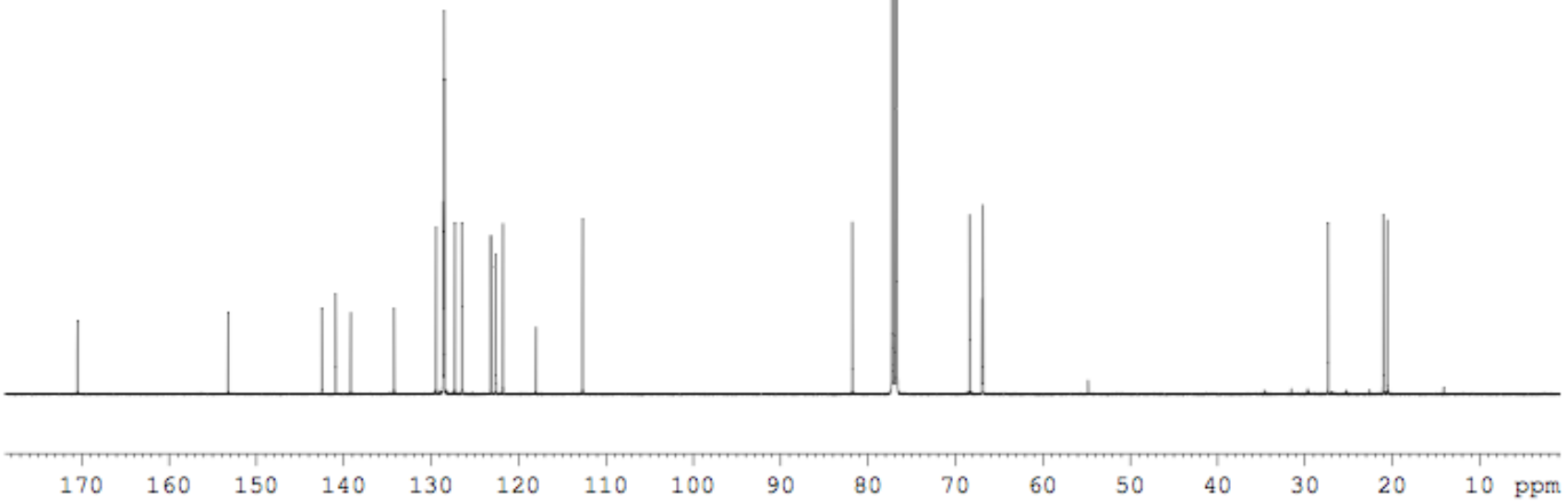


Pyrrolizidine **24**



Pyrrolizidine **24**

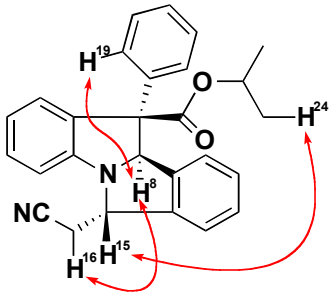


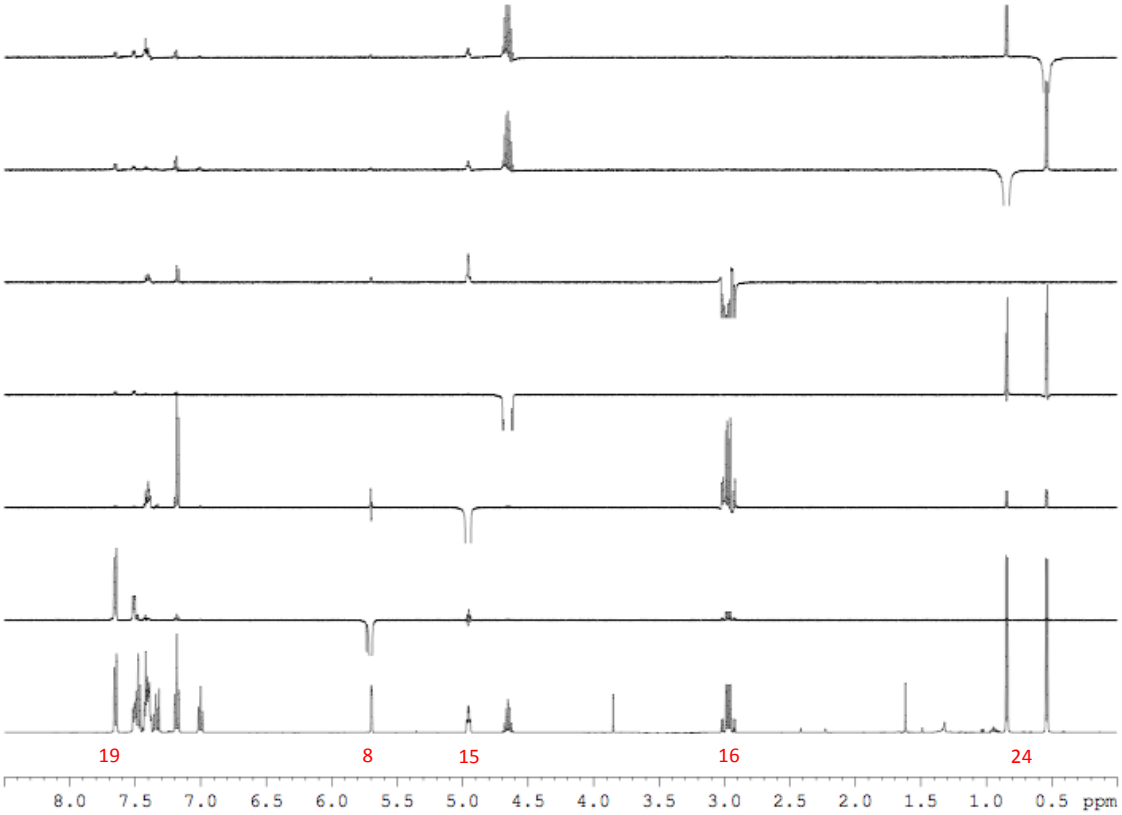


Key

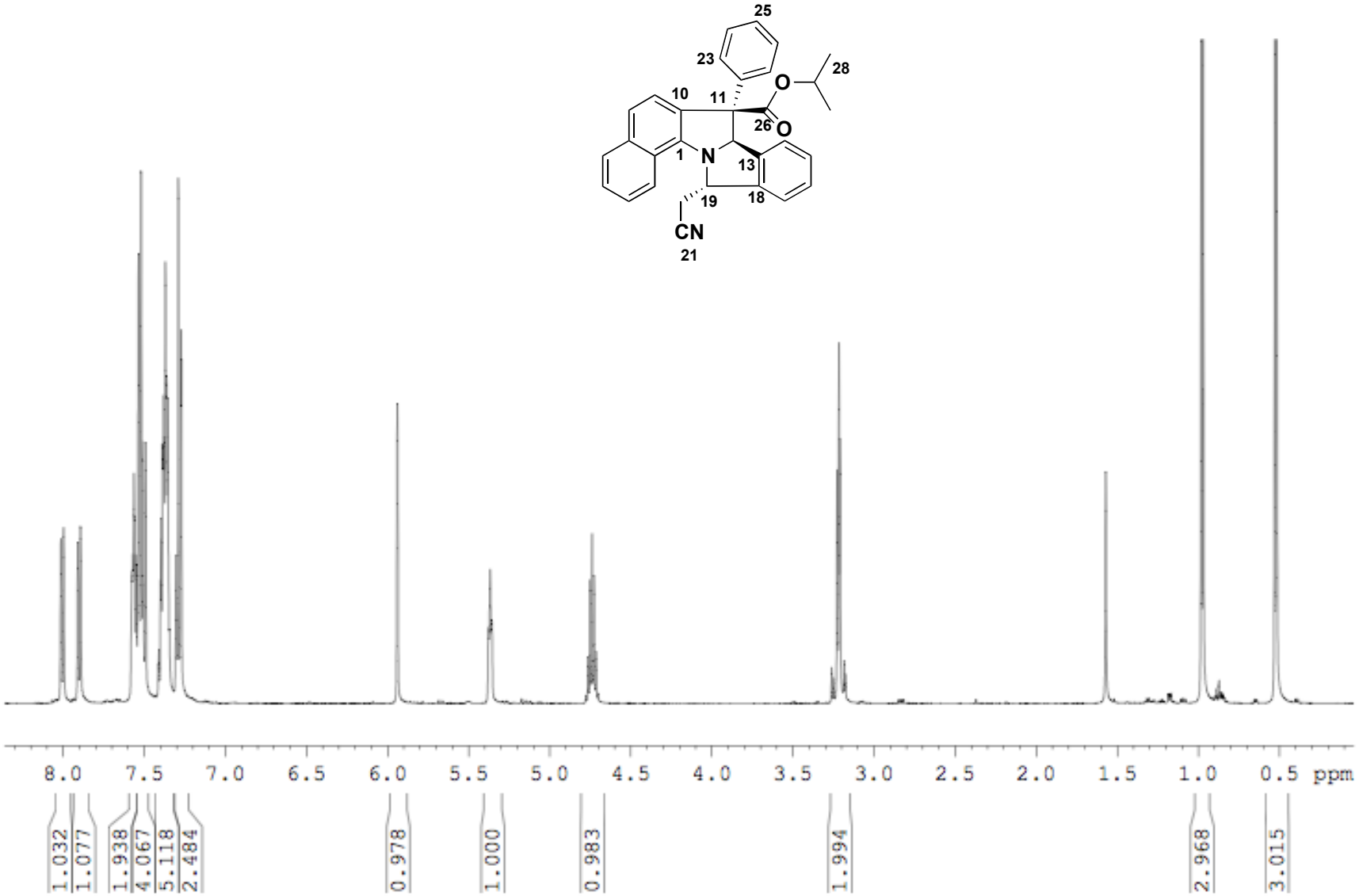
Pyrrolizidine **24**

Key nOe Data

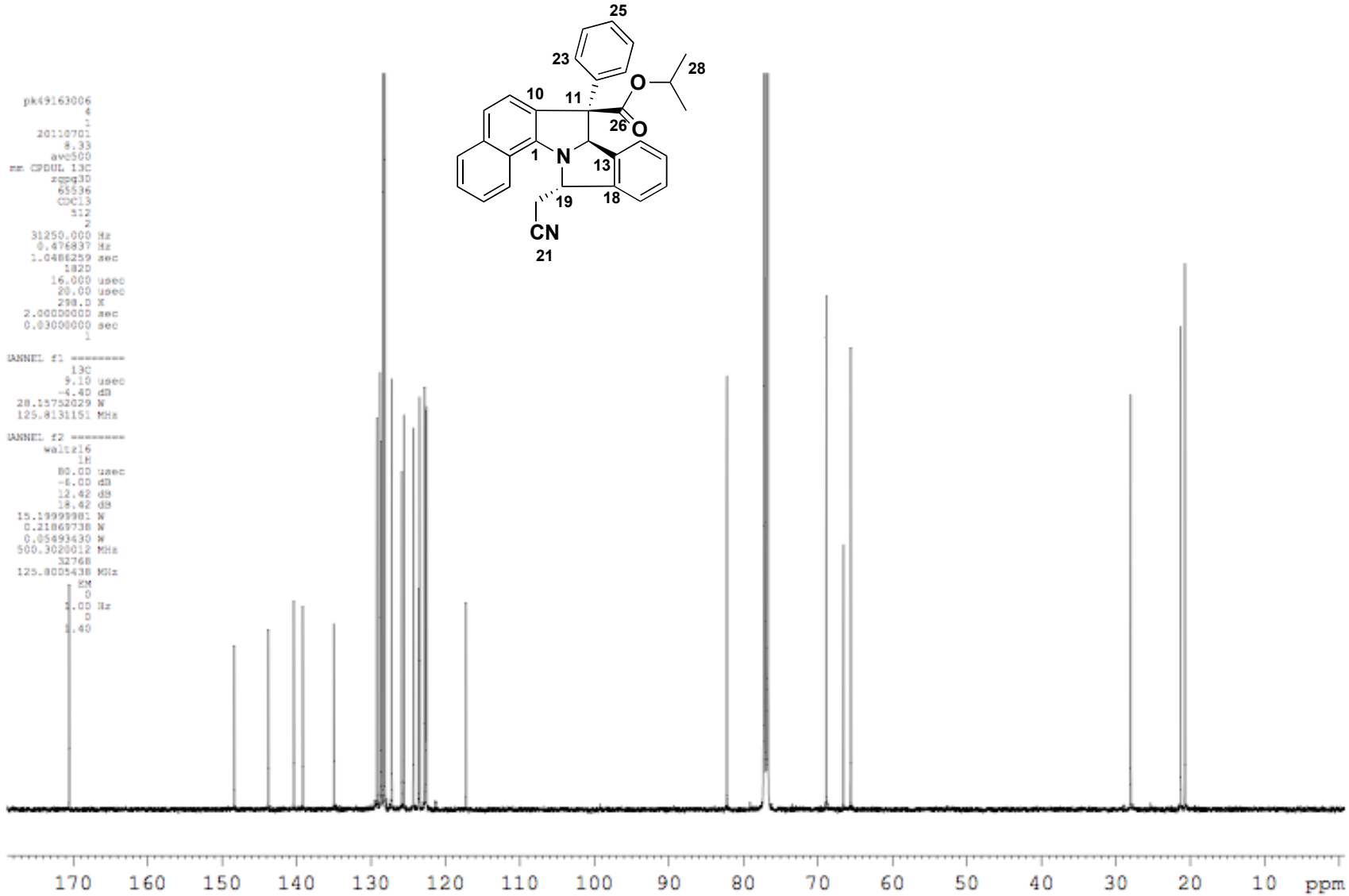




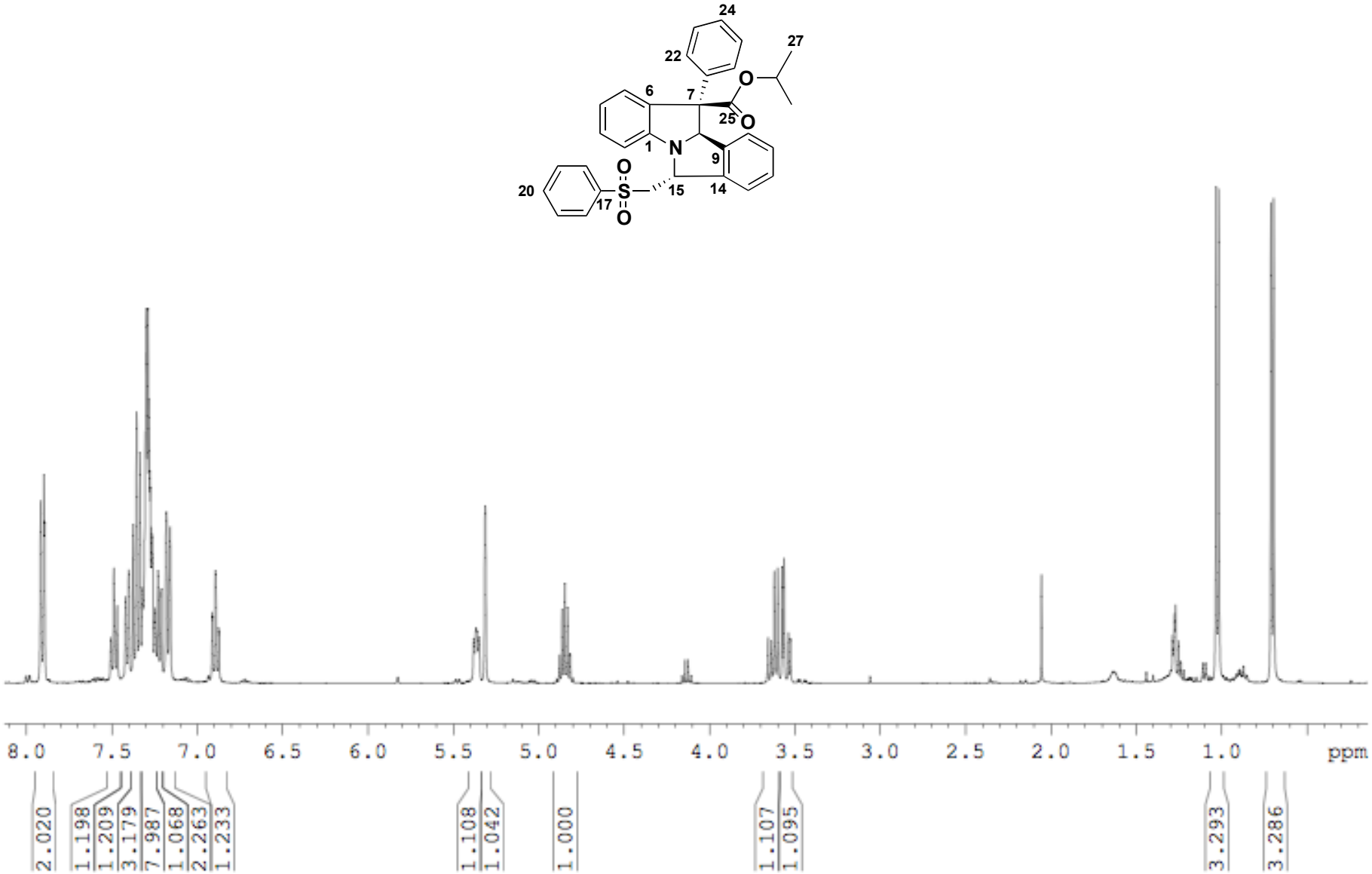
Pyrrolizidine **25**



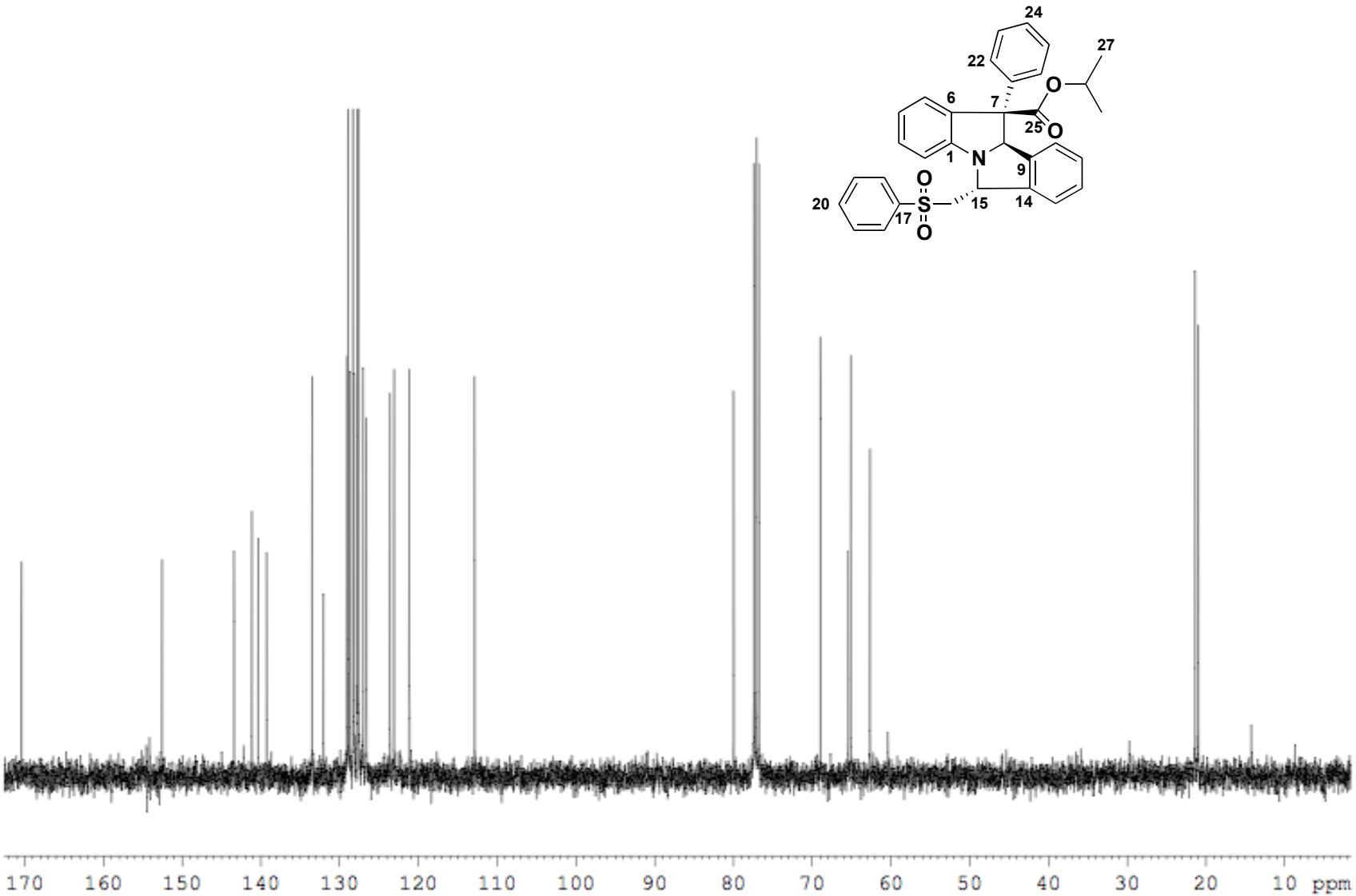
Pyrrolizidine **25**



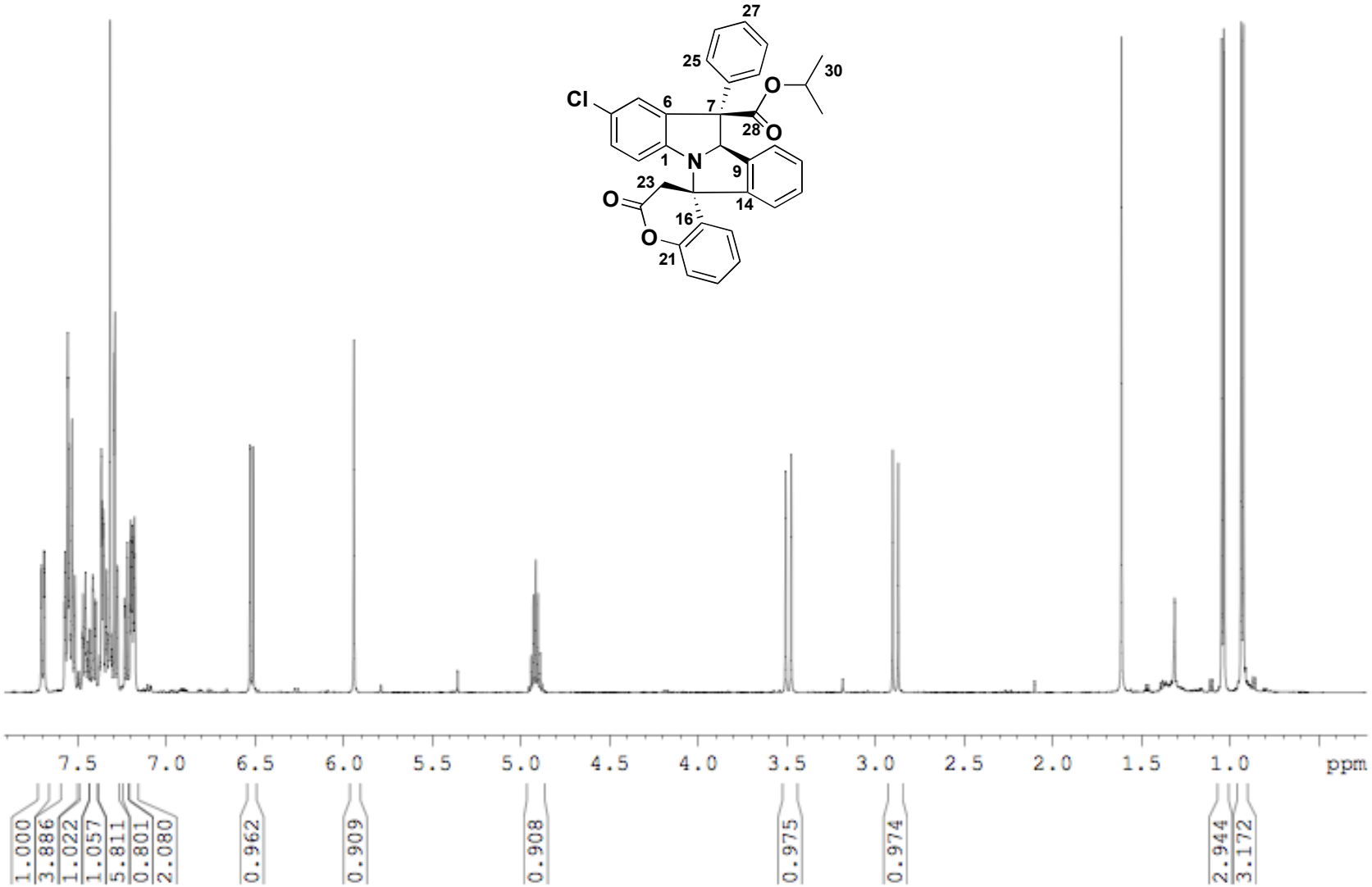
Pyrrolizidine **26**



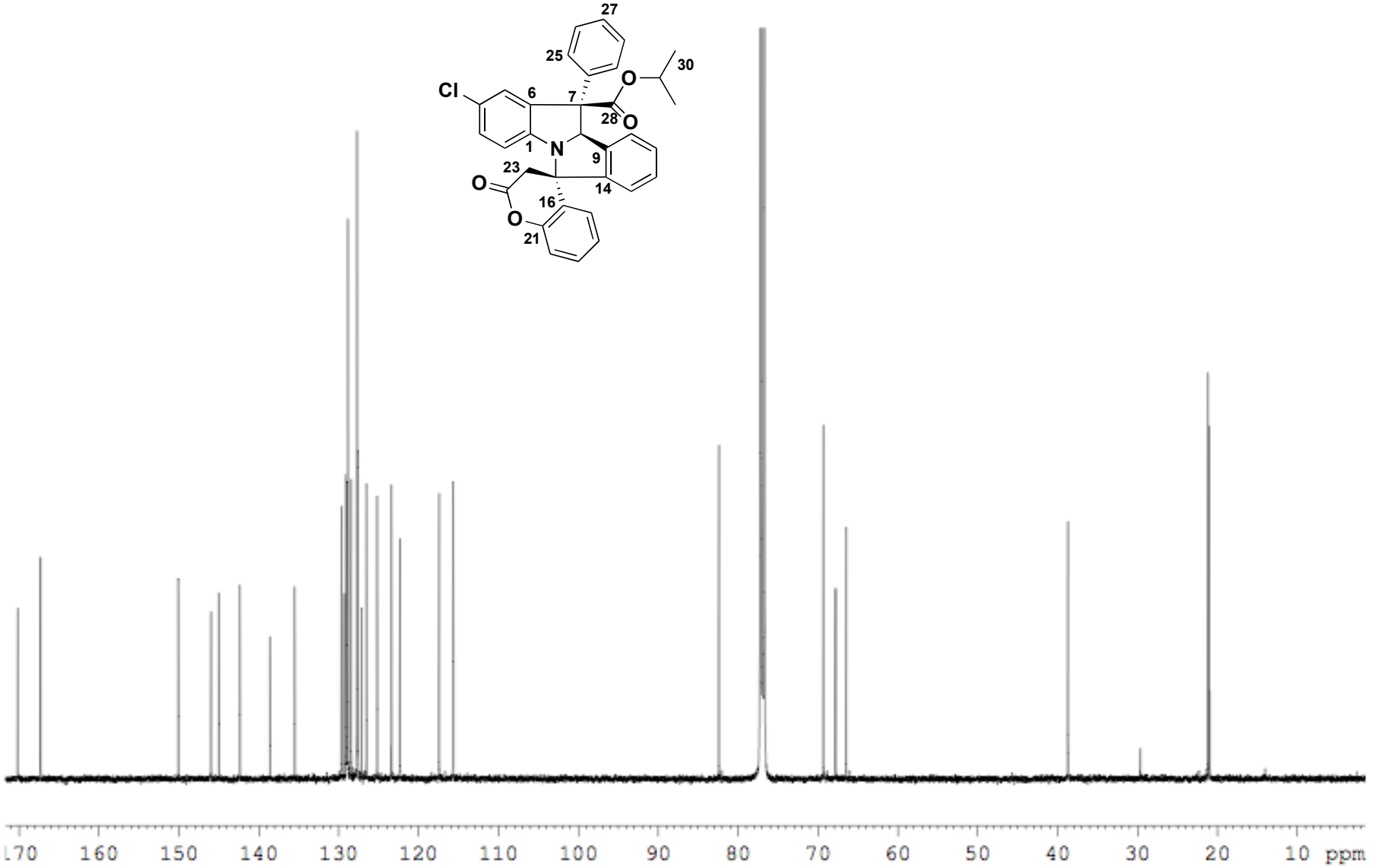
Pyrrolizidine **26**



Pyrrolizidine **27**

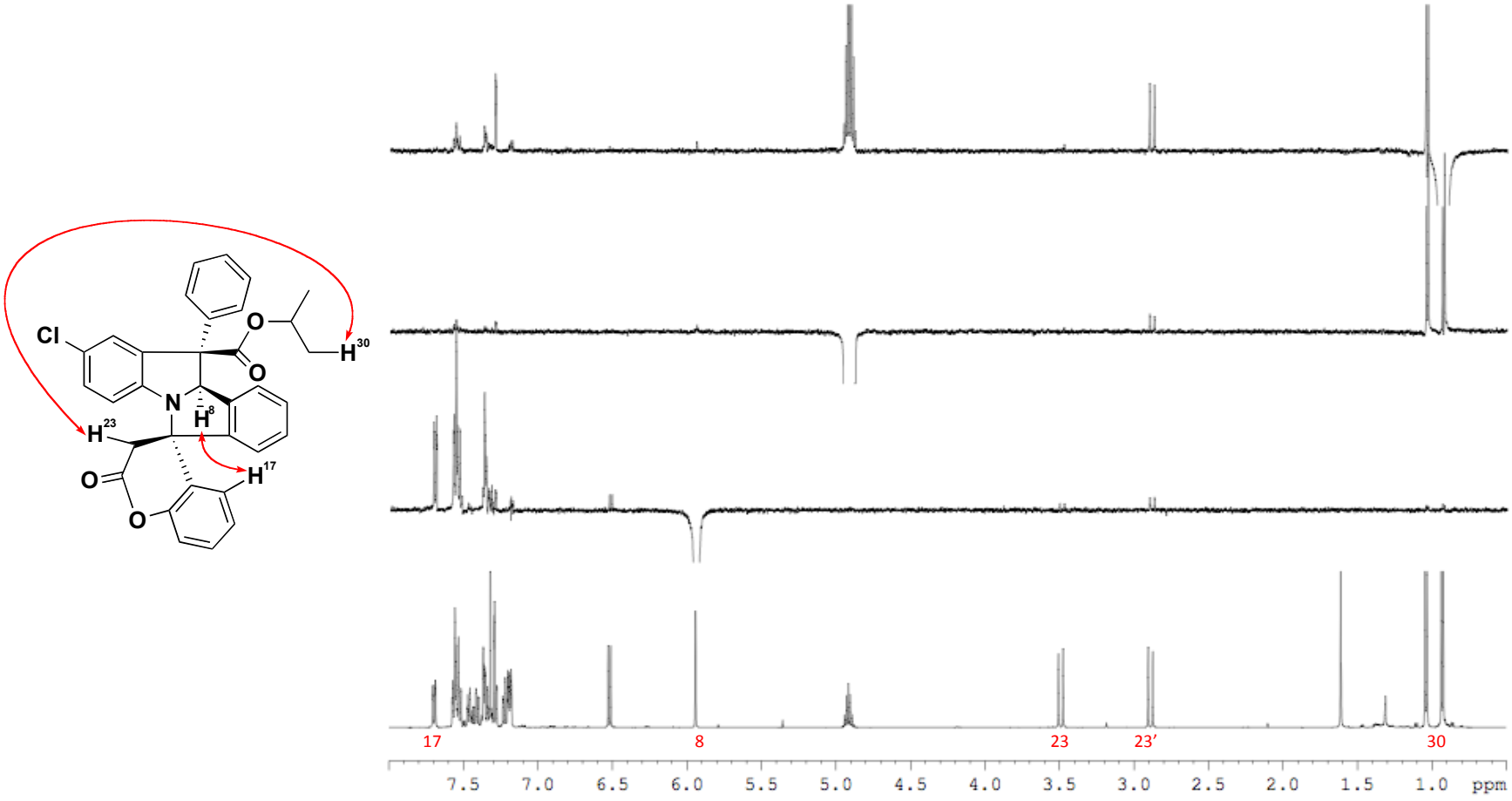


Pyrrolizidine **27**

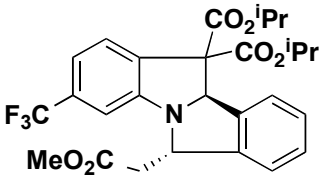


Key nOe Data

Pyrrolizidine **27**

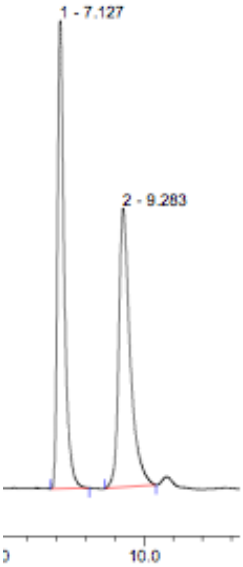


6 HPLC Data

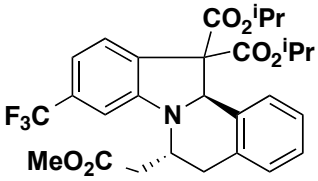


Pyrrolizidine **8**. Chiral HPLC (Chiralpak OD-H, 1.5 % IPA in hexanes, 1.0 mL/min, λ = 271, 5 μL injection) t_R (major) = 6.9, t_R (minor) = 9.1

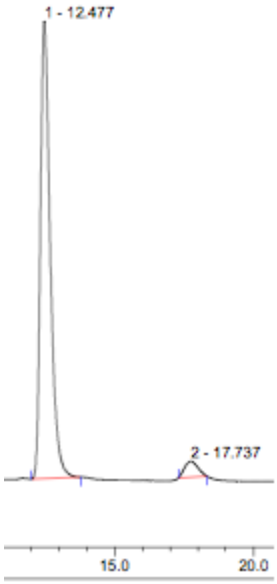
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	6.92	n.a.	38.602	12.578	93.72	n.a.	BMB
2	9.09	n.a.	1.732	0.843	6.28	n.a.	BMB*
Total:			40.334	13.421	100.00	0.000	



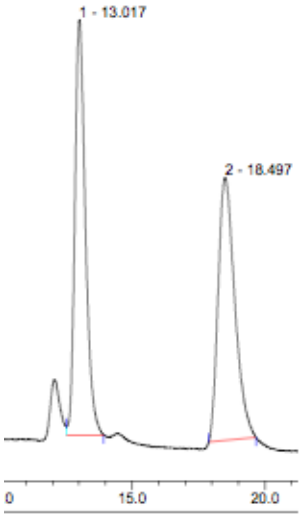
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.13	n.a.	95.346	25.658	50.00	n.a.	BMB
2	9.28	n.a.	56.881	25.656	50.00	n.a.	BMB



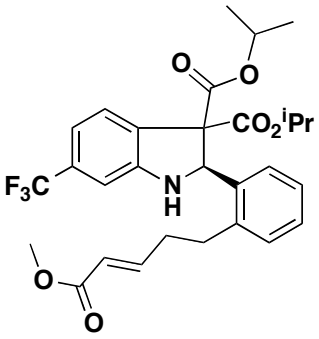
Indolizidine **9**. Chiral HPLC (Chiralpak IC, 1 % IPA in hexanes, 1.0 mL/min, λ = 288, 5 μL injection) t_R (major) = 12.5, t_R (minor) = 17.7



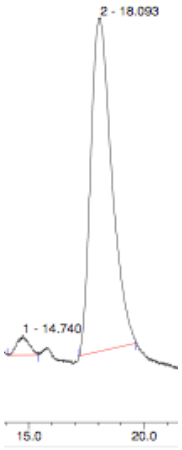
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12.48	n.a.	130.577	53.310	95.48	n.a.	BMB
2	17.74	n.a.	4.563	2.525	4.52	n.a.	BMB*



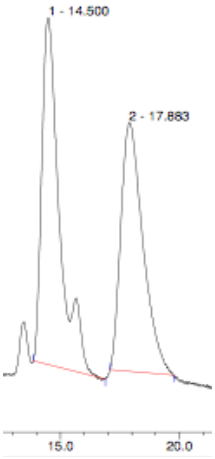
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13.02	n.a.	13.881	6.373	50.07	n.a.	MB*
2	18.50	n.a.	8.782	6.355	49.93	n.a.	BMB*



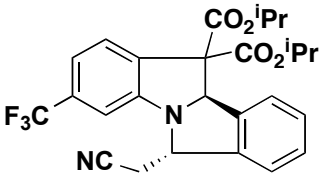
Indoline **38**. Chiral HPLC (Chiralpak OD-H, 3 % IPA in hexanes, 1.0 mL/min, λ = 272, 5 μL injection) t_R (major) = 18.1, t_R (minor) = 14.7.



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14.74	n.a.	0.227	0.130	3.15	n.a.	BMB*
2	18.09	n.a.	3.792	3.982	96.85	n.a.	BMB
Total:			4.019	4.111	100.00	0.000	

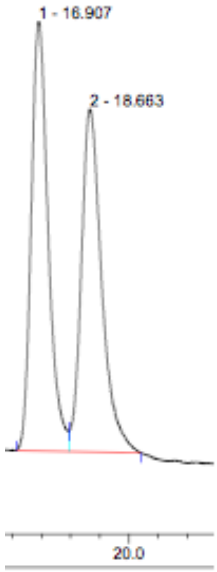


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14.50	n.a.	4.658	4.004	52.67	n.a.	BMB*
2	17.88	n.a.	3.342	3.599	47.33	n.a.	BMB*
Total:			8.000	7.603	100.00	0.000	

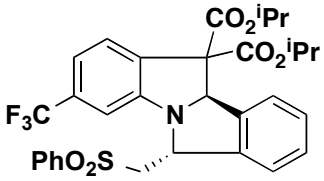


Pyrrolizidine **14**. Chiral HPLC (Chiralpak OD-H, 2 % IPA in hexanes, 1.0 mL/min, λ = 221, 5 μL injection) t_R (major) = 16.8, t_R (minor) = 18.6

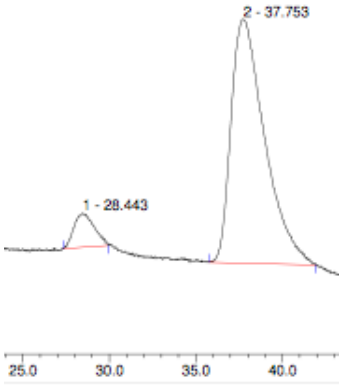
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	16.83	n.a.	22.497	15.529	98.34	n.a.	BMB*
2	18.59	n.a.	0.459	0.263	1.66	n.a.	BMB*



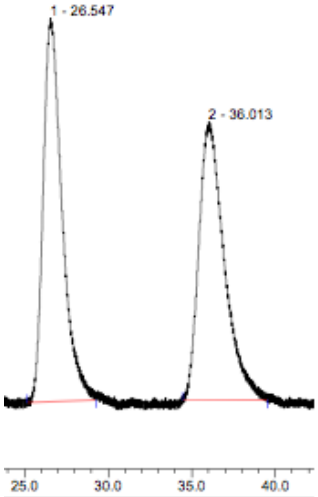
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	16.91	n.a.	14.501	9.734	50.85	n.a.	BM
2	18.66	n.a.	11.590	9.407	49.15	n.a.	MB



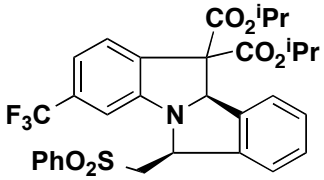
Pyrrolizidine **15** (***major***). Chiral HPLC (Chiralpak OD-H, 2 % IPA in hexanes, 1.0 mL/min, λ = 262, 5 μL injection) t_R (major) = 34.2, t_R (minor) = 25.9



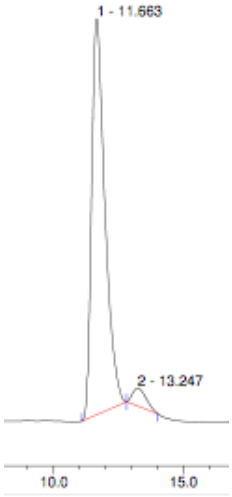
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	28.44	n.a.	0.656	0.887	7.76	n.a.	BMB*
2	37.75	n.a.	4.658	10.545	92.24	n.a.	BMB*
Total:			5.315	11.432	100.00	0.000	



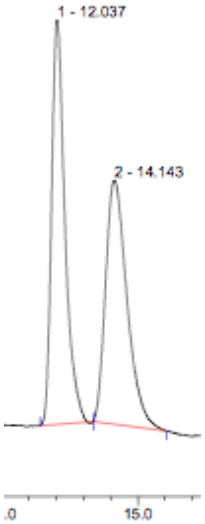
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	26.55	n.a.	3.014	3.930	50.58	n.a.	BMB*
2	36.01	n.a.	2.185	3.839	49.42	n.a.	BMB*



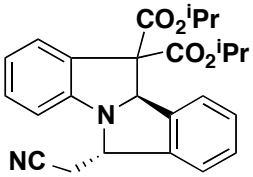
Pyrrolizidine **15 (minor)**. Chiral HPLC (Chiralpak OD-H, 2 % IPA in hexanes, 1.0 mL/min, λ = 217, 5 μL injection) t_R (major) = 11.8, t_R (minor) = 13.9



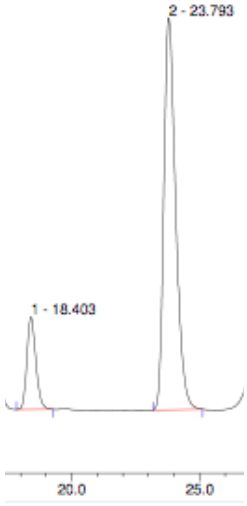
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.66	n.a.	121.850	72.581	95.53	n.a.	BMb*
2	13.25	n.a.	5.494	3.395	4.47	n.a.	bMB*
Total:			127.344	75.975	100.00	0.000	



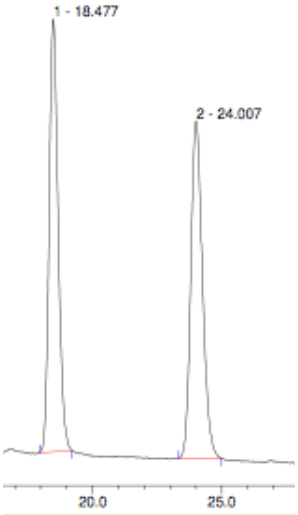
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12.04	n.a.	25.846	14.658	50.85	n.a.	BMb*
2	14.14	n.a.	15.598	14.168	49.15	n.a.	bMB*



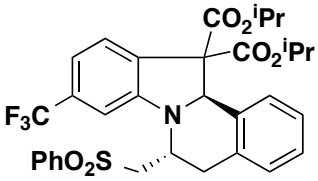
Pyrrolizidine **16**. Chiral HPLC (Chiralpak IA, 3 % IPA in hexanes, 1.0 mL/min, λ = 272, 5 μL injection) t_R (major) = 23.8, t_R (minor) = 18.4.



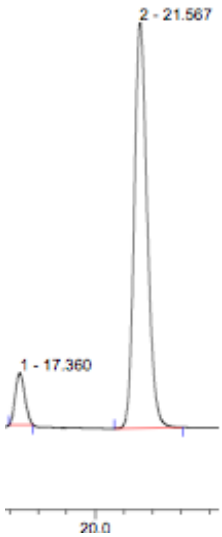
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	18.40	n.a.	14.156	5.728	15.19	n.a.	BMB
2	23.79	n.a.	59.949	31.989	84.81	n.a.	BMB
Total:			74.105	37.717	100.00	0.000	



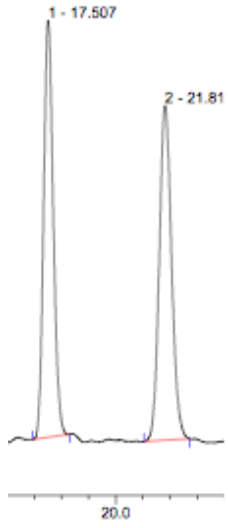
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	18.48	n.a.	16.584	6.691	49.80	n.a.	BMB
2	24.01	n.a.	12.927	6.745	50.20	n.a.	BMB
Total:			29.511	13.437	100.00	0.000	



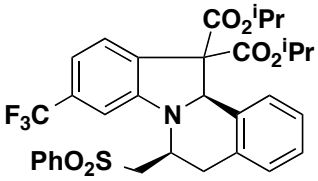
Indolizidine **17 (major)**. Chiral HPLC (Chiralpak IA, 3 % IPA in hexanes, 1.0 mL/min, λ = 209, 5 μL injection) t_R (major) = 21.6, t_R (minor) = 17.4



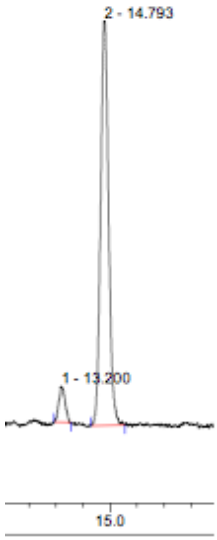
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	17.36	n.a.	31.643	12.107	8.53	n.a.	BMB*
2	21.57	n.a.	247.533	129.828	91.47	n.a.	BMB



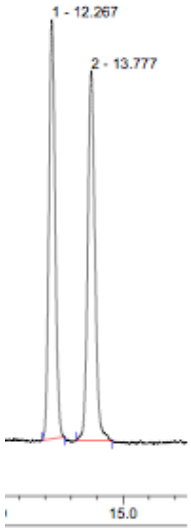
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	17.51	n.a.	37.951	15.556	49.38	n.a.	BMB*
2	21.81	n.a.	30.491	15.949	50.62	n.a.	BMB



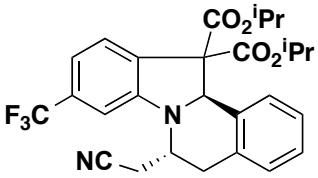
Indolizidine **17 (minor)**. Chiral HPLC (Chiralpak IA, 4 % IPA in hexanes, 1.0 mL/min, λ = 335, 5 μL injection) t_R (major) = 14.8, t_R (minor) = 13.2



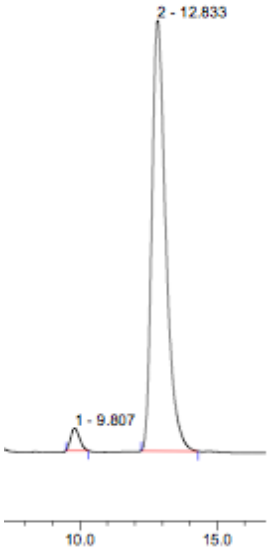
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13.20	n.a.	0.455	0.121	6.47	n.a.	BMB*
2	14.79	n.a.	5.136	1.758	93.53	n.a.	BMB*



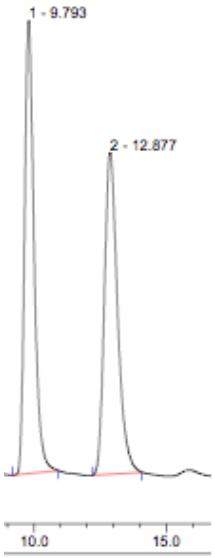
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12.27	n.a.	7.156	1.973	49.47	n.a.	BMB
2	13.78	n.a.	6.300	2.016	50.53	n.a.	BMB*



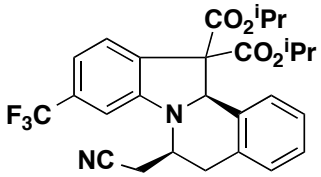
Indolizidine **18 (major)**. Chiral HPLC (Chiralpak OD-H, 3 % IPA in hexanes, 1.0 mL/min, λ = 219, 5 μL injection) t_R (major) = 12.8, t_R (minor) = 9.8



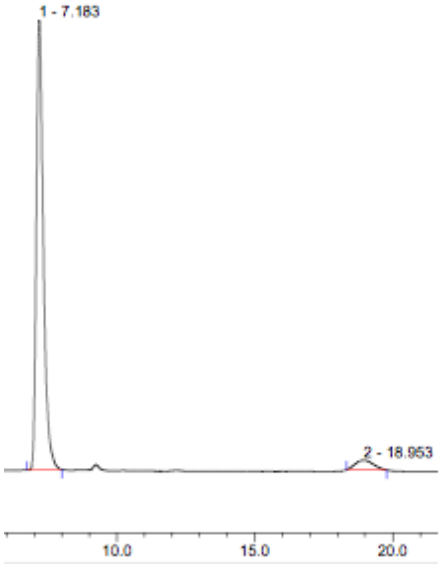
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	9.81	n.a.	33.156	12.396	3.28	n.a.	BMB*
2	12.83	n.a.	621.943	364.950	96.72	n.a.	BMB*



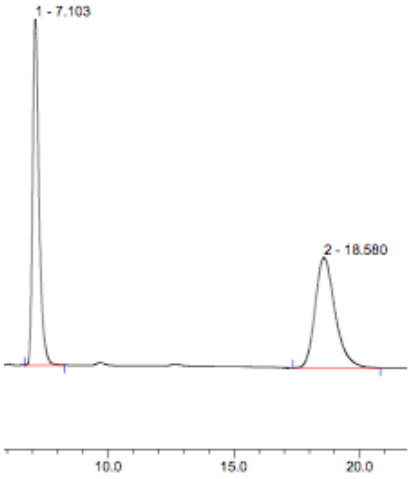
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	9.79	n.a.	187.651	77.472	50.29	n.a.	BMB*
2	12.88	n.a.	133.232	76.581	49.71	n.a.	BMB*



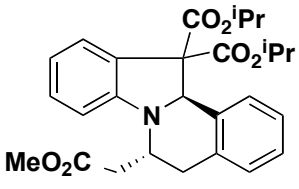
Indolizidine **18 (minor)**. Chiral HPLC (Chiralpak OD-H, 3 % IPA in hexanes, 1.0 mL/min, λ = 216, 5 μL injection) t_R (major) = 7.2, t_R (minor) = 19.0



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.18	n.a.	363.712	107.013	94.77	n.a.	BMB*
2	18.95	n.a.	7.799	5.905	5.23	n.a.	BMB*

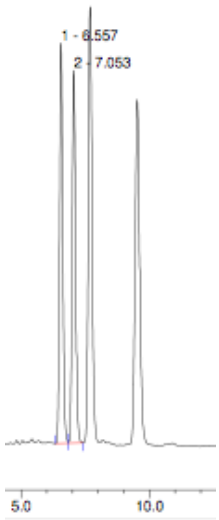


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.10	n.a.	204.246	60.025	50.06	n.a.	BMB
2	18.58	n.a.	65.042	59.884	49.94	n.a.	BMB

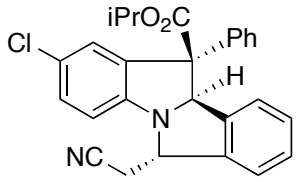


Indolizidine **19**. Chiral HPLC (Chiralpak IA, 3 % IPA in hexanes, 1.0 mL/min, λ = 272, 5 μL injection) t_R (major) = 6.5, t_R (minor) = 7.0

No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	6.55	n.a.	784.774	112.674	87.37	n.a.	BMB*
2	7.04	n.a.	108.810	16.295	12.63	n.a.	Rd
Total:			893.584	128.968	100.00	0.000	

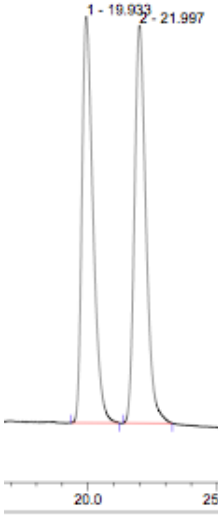


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	6.56	n.a.	42.181	5.979	50.13	n.a.	BM *
2	7.05	n.a.	39.235	5.949	49.87	n.a.	MB*
Total:			81.416	11.928	100.00	0.000	

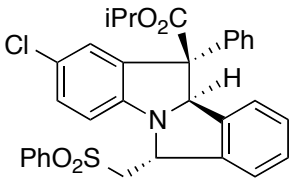


Pyrrolizidine **22**. Chiral HPLC: (Chiralpak IA, 3 % IPA in hexanes, 1.0 mL/min, λ = 245 nm, 5 μL injection) t_R (major) = 22.2 mins, t_R (minor) = 20.3 mins.

No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	20.30	n.a.	1.207	0.705	1.58	n.a.	BMB
2	22.15	n.a.	83.268	43.903	98.42	n.a.	BMB
Total:			84.475	44.607	100.00	0.000	

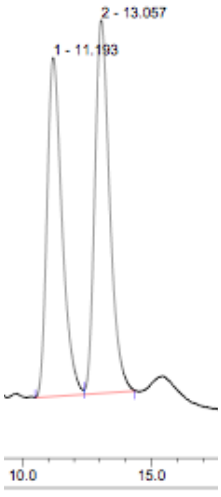


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	19.93	n.a.	27.283	13.593	49.70	n.a.	BMB
2	22.00	n.a.	26.694	13.759	50.30	n.a.	BMB
Total:			53.977	27.352	100.00	0.000	

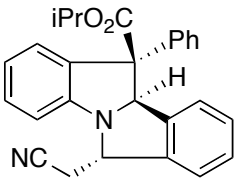


Pyrrolizidine **23 (major)**. Chiral HPLC: (Chiralpak OD-H, 20 % IPA in hexanes, 1.0 mL/min, λ = 245 nm, 5 μL injection) t_R (major) = 13.0 mins, t_R (minor) = 11.2 mins.

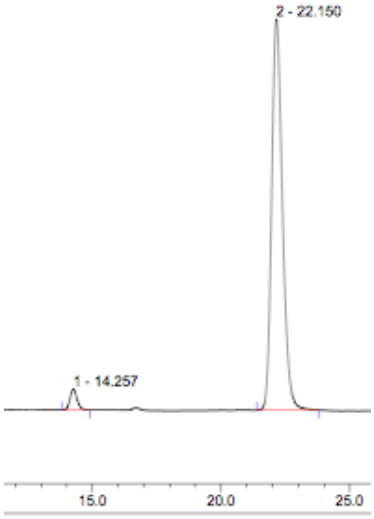
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.19	n.a.	0.662	0.417	3.13	n.a.	BMB*
2	13.01	n.a.	19.285	12.916	96.87	n.a.	BMB
Total:			19.947	13.334	100.00	0.000	



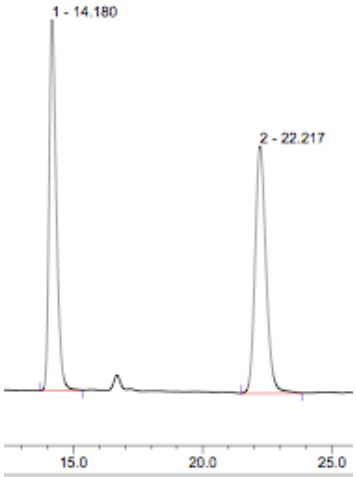
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.19	n.a.	10.393	7.012	47.88	n.a.	BM
2	13.06	n.a.	11.434	7.633	52.12	n.a.	MB
Total:			21.828	14.645	100.00	0.000	



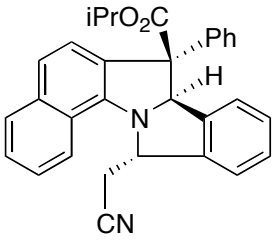
Pyrrolizidine **24**. Chiral HPLC: (Chiralpak IA, 10 % IPA in hexanes, 1.0 mL/min, λ = 207 nm, 5 μL injection) t_R (major) = 22.2 mins, t_R (minor) = 14.3 mins.



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14.26	n.a.	27.948	8.688	3.31	n.a.	BMB
2	22.15	n.a.	523.543	253.993	96.69	n.a.	BMB
Total:			551.491	262.682	100.00	0.000	

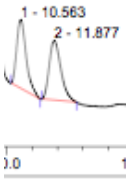


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14.18	n.a.	320.512	103.161	49.79	n.a.	BMB
2	22.22	n.a.	213.195	104.050	50.21	n.a.	BMB
Total:			533.707	207.211	100.00	0.000	

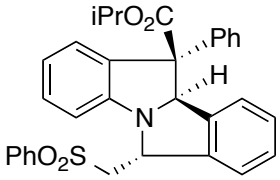


Pyrrolizidine **25**. Chiral HPLC: (Chiralpak OD-H, 10 % IPA in hexanes, 1.0 mL/min, λ = 251 nm, 5 μL injection) t_R (major) = 10.5 mins, t_R (minor) = 11.8 mins.

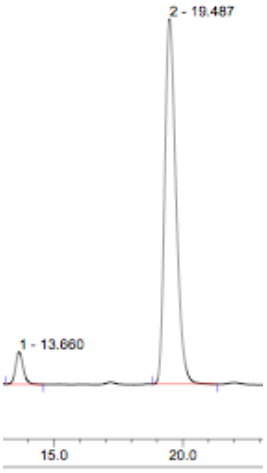
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.51	n.a.	252.588	115.653	94.78	n.a.	BM *
2	11.83	n.a.	11.149	6.366	5.22	n.a.	MB*
Total:			263.737	122.020	100.00	0.000	



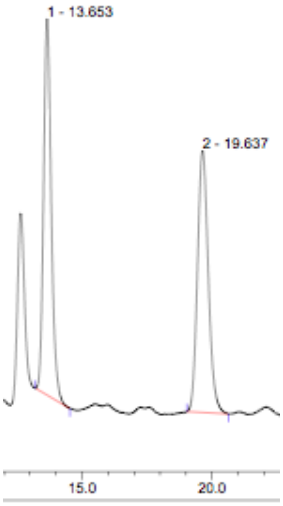
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.56	n.a.	6.552	2.818	48.42	n.a.	BMB*
2	11.88	n.a.	5.686	3.002	51.58	n.a.	BMB*
Total:			12.238	5.819	100.00	0.000	



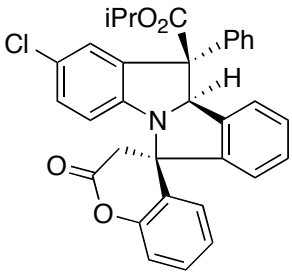
Pyrrolizidine **26**. Chiral HPLC: (Chiralpak IA, 10 % IPA in hexanes, 1.0 mL/min, λ = 239 nm, 5 μL injection) t_R (major) = 19.5 mins, t_R (minor) = 13.6 mins.



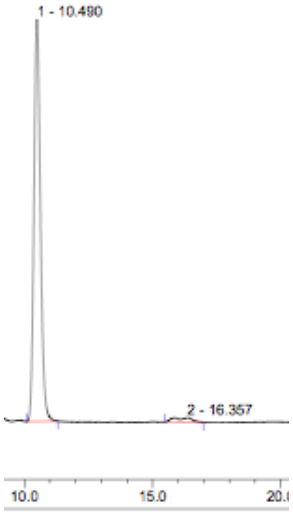
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13.66	n.a.	29.536	10.131	5.67	n.a.	BMB*
2	19.49	n.a.	333.724	168.680	94.33	n.a.	BMB
Total:			363.260	178.810	100.00	0.000	



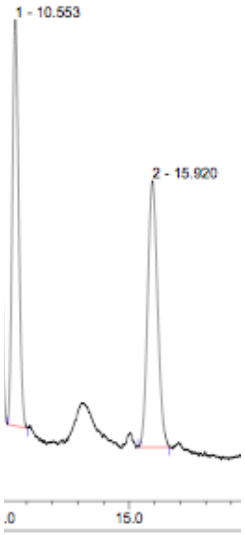
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13.65	n.a.	11.905	4.070	50.40	n.a.	BMB*
2	19.64	n.a.	8.281	4.006	49.60	n.a.	BMB
Total:			20.186	8.076	100.00	0.000	



Pyrrolizidine **27**. Chiral HPLC: (Chiralpak IC, 3 % IPA in hexanes, 1.0 mL/min, λ = 245 nm, 1.5 μL injection) t_R (major) = 10.5 mins, t_R (minor) = 16.4 mins.



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.49	n.a.	69.345	20.373	97.01	n.a.	BMB
2	16.36	n.a.	0.737	0.628	2.99	n.a.	BMB*
Total:			70.083	21.001	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.55	n.a.	4.678	1.335	49.35	n.a.	BMB*
2	15.92	n.a.	3.063	1.370	50.65	n.a.	BMB
Total:			7.741	2.705	100.00	0.000	