**A concise synthesis of (+)-batzelladine B from simple pyrrole-based starting materials.**

Brendan T. Parr, Christos Economou, and Seth B. Herzon*

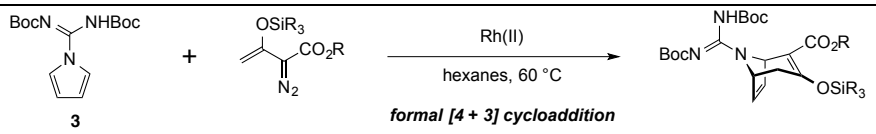
Department of Chemistry, Yale University, 225 Prospect Street, New Haven, CT 06520-8107

*Nature*

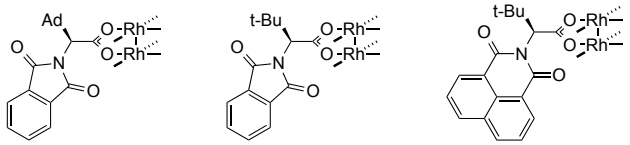
Supporting Information

## Index

**Table S1.** Optimization of the formal [4+3] cycloaddition.[a]




| entry | $SiR_3$ | OR | $Rh_2$[(*S*)-lig]$_4$ (mol%) | yield[c] | er[d] (or dr[e]) |
|---|---|---|---|---|---|
| 1 | TBS | $CH_3$ | ptad (1) | 91% | 86:14 |
| 2 | TBS | $CH_3$ | pttl (1) | 93% | 80:20 |
| 3 | TIPS | $CH_3$ | ptad (1) | 73% | 80:20 |
| 4 | TIPS | $CH_3$ | pttl (1) | 93% | 90:10 |
| 5 | TIPS | $CH_3$ | nttl (1) | —[f] | —[f] |
| 6 | TBS | *t*-Bu | ptad (1) | 66% | 85:15 |
| 7 | TBS | *t*-Bu | pttl (1) | 71% | 88:12 |
| 8 | TIPS | Et | pttl (1) | 45% | 93:7 |
| ***9***[b] | ***TBS*** | ***(S)-pantolactonyl (9)*** | ***pttl (0.5)*** | ***93%* (10)** | ***>95:5*** |
| 10[b] | TBS | (*R*)-pantolactonyl | pttl (0.5) | 81% (**10**) | 76:24 |




$Rh_2$[(*S*)-ptad]$_4$ $Rh_2$[(*S*)-pttl]$_4$ $Rh_2$[(*S*)-nttl]$_4$

[a]All reactions employed 250 μmol of **3** and 2.00 equiv of diazoester. [b]Reaction conducted in pentanes at 36 °C and employed 250 μmol of diazoester and 1.10 equiv **3**. [c]Isolated yield after purification by flash-column chromatography. [d]Enantiomeric ratio (er) was determined by chiral stationary phase supercritical fluid chromatography. [e]Diastereomeric ratio (dr) was determined by $^1$H NMR analysis of the unpurified product mixture. [f]Product not formed.

**General Experimental Procedures.** All reactions were performed in single-neck, flame-dried, round-bottomed flasks fitted with rubber septa under a positive pressure of argon unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula, or were handled in a nitrogen-filled drybox (working oxygen level <10 ppm). Organic solutions were concentrated by rotary evaporation at 28–32 °C. Flash-column chromatography was performed as described by Still et al.,[1] employing silica gel (60 Å, 40–63 μm particle size) purchase from Sorbent Technologies (Atlanta, GA). Analytical thin-layered chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm, 60 Å pore size) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) and/or submersion in aqueous ceric ammonium molybdate solution (CAM) or aqueous potassium permanganate solution ($KMnO_4$), followed by brief heating on a hot plate (120 °C, 10–15 s).

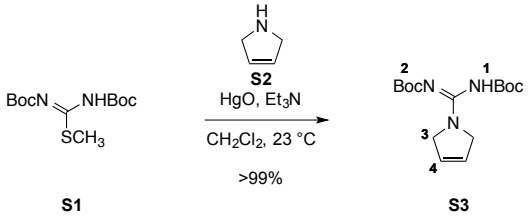
**Materials.** Commercial solvents and reagents were used as received with the following exceptions. Benzene, dichloromethane, pentane, and toluene were purified according to the method of Pangborn et al.[2] Triethylamine was distilled from calcium hydride under an atmosphere of argon immediately before use. Di-*iso*-propylamine was distilled from calcium hydride and was stored under nitrogen. Tetrahydrofuran was distilled from sodium–benzophenone under an atmosphere of nitrogen immediately before use. The molarity of *n*-butyllithium solutions was determined by titration against a standard solution of menthol and 1,10-phenanthroline in tetrahydrofuran (average of three determinations).[3] Potassium *tert*-butoxide was stored and handled in a nitrogen-filled drybox. Dimethyl sulfoxide (ACS reagent grade) was purchased from Macron Fine Chemicals. Trimethylsilyl trifluoromethanesulfonate was purified by short path distillation and stored at –30 °C under argon. *t*ert-Butyldimethylsilyl trifluoromethanesulfonate was purified by short path distillation and was stored at –30 °C under argon. 2,6-Lutidine was distilled from calcium hydride and was stored under argon. *N*-Methyl-2-pyrrolidinone was distilled and deoxygenated by sparging with dinitrogen before use. Water employed in the reductive hydration reaction (**25→27**) was deoxygenated by sparging with dinitrogen before use. Formic acid was degassed by three freeze–pump–thaw cycles before use. Trifluoroacetic acid employed in the final step (**28→1**) was fractionally-distilled and degassed by three freeze–pump–thaw cycles immediately before use. 1,3-Dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU) was distilled from calcium hydride and stored under argon. Molecular sieves were activated by heating to 200 °C under vacuum (<1 Torr) for 12 h, and were stored in an oven at >160 °C. *p*-Acetamidobenzenesulfonyl azide,[4] the ruthenium catalyst **26**,[5] (*R*)-4,4-dimethyl-2-oxotetrahydrofuran-3-yl 3-((*tert*-butyldimethylsilyl)oxy)-2-diazobut-3-enoate (**9**),[6] 1-((trimethylsilyl)ethynyl)-1,2-benzoiodaoxol-3(1*H*)-one,[7] *tert*-butyl 2-(1*H*-pyrrol-2-yl)acetate (**S6**),[8] the guanyl alcohol (**24**),[9] and benzyl octanoate[10] were prepared according to published procedures.

**Instrumentation.** Proton nuclear magnetic resonance spectra ($^1$H NMR ) were recorded at 500 or 600 MHz at 24 °C, unless otherwise noted. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CDCl_3$, δ 7.26; $CD_3OD$, δ 3.31). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quarter, m = multiplet and/or multiple resonances, br = broad, app = apparent), coupling constant in Hertz, integration, and assignment. Proton-decoupled carbon nuclear magnetic resonance spectra ($^{13}$C NMR) were recorded at 125 MHz at 24 °C, unless otherwise noted. Chemical shifts are expressed in parts per million (ppm,

δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$, δ 77.0; $CD_3OD$, δ 49.0). Distortionless enhancement by polarization transfer spectra [DEPT (135)] were recorded at 125 or 150 MHz at 24 °C, unless otherwise noted. $^{13}C$ NMR and DEPT (135) data are combined and represented as follows: chemical shift, carbon type [obtained from DEPT (135) experiments]. Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectra were obtained using a Thermo Electron Corporation Nicolet 6700 FTIR spectrometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption ($cm^{-1}$), intensity of absorption (s = strong, m = medium, w = weak, br = broad). Analytical ultra high-performance liquid chromatography/mass spectrometry (UPLC/MS) was performed on a Waters UPLC/MS instrument equipped with a reverse-phase $C_{18}$ column (1.7 μm particle size, 2.1 × 50 mm), dual atmospheric pressure chemical ionization (API)/electrospray (ESI) mass spectrometry detector, and photodiode array detector. Samples were eluted with a linear gradient of 5% acetonitrile–water containing 0.1% formic acid→100% acetonitrile containing 0.1% formic acid over 0.75 min, followed by 100% acetonitrile containing 0.1% formic acid for 0.75 min, at a flow rate of 800 μL/min. High-resolution mass spectrometry (HRMS) were obtained on a Waters UPLC/HRMS instrument equipped with a dual API/ESI high-resolution mass spectrometry detector and photodiode array detector. Unless otherwise noted, samples were eluted over a reverse-phase $C_{18}$ column (1.7 μm particle size, 2.1 × 50 mm) with a linear gradient of 5% acetonitrile–water containing 0.1% formic acid→95% acetonitrile–water containing 0.1% formic acid for 1 min, at a flow rate of 600 μL/min. Preparatory high-performance liquid chromatography (HPLC) was carried out on a Waters 2545 Binary Solvent Manager equipped with a Waters Sunfire™ preparatory reverse-phase $C_{18}$ column (5 μm particle size, 10 × 150 mm), a Waters 2998 Photodiode Array (PDA) detector (280 nm), and a Waters 2767 Sample Manager. Optical rotations were measured on a Perkin Elmer polarimeter equipped with a sodium (589 nm, D) lamp. Optical rotation data are represented as follows: specific rotation ($[\alpha]_\lambda^T$), concentration (mg/mL), and solvent.

**Synthetic Procedures.**

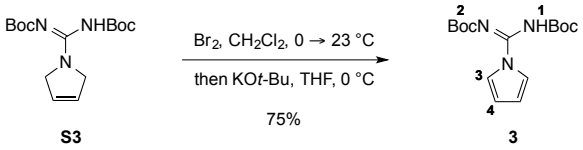
*Synthesis of the guanylpyrroline **S3**:*




Mercury oxide (7.68 g, 35.5 mmol, 1.10 equiv) and triethylamine (13.4 mL, 96.1 mmol, 3.00 equiv) were added in sequence to a solution of 3-pyrroline **S2** (2.42 g, 33.6 mmol, 1.04 equiv) and 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea **S1** (9.90 g, 32.4 mmol, 1 equiv) in dichloromethane (240 mL) at 23 °C, with exclusion of light. The resulting orange suspension was stirred for 20 h at 23 °C, with exclusion of light. The product mixture was filtered through a pad of celite (2.5 × 4.5 cm). The filter cake was washed with ethyl acetate (3 × 50 mL). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes initially, grading to 33% ethyl acetate–hexanes, one step) to afford the guanylpyrroline **S3** as a crystalline, colorless solid (10.1 g, >99%).

$R_f$ = 0.39 (25% ethyl acetate–hexanes; UV, $KMnO_4$). $^1H$ NMR (500 MHz, $CDCl_3$): δ 10.28 (bs, 1H, $H_1$), 5.80 (s, 2H, $H_4$), 4.40 (s, 4H, $H_3$), 1.50 (s, 18H, $H_2$). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 154.0 (C), 124.8 (CH), 55.1 ($CH_2$), 28.1 ($CH_3$). The carbamate carbonyl and *tert*-butyl quaternary carbons were not observed due to line broadening. IR (ATR-FTIR), $cm^{-1}$: 2984 (m), 1741 (s), 1638 (s), 1596 (s). HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{15}H_{26}N_3O_4$, 312.1918; found, 312.1920.

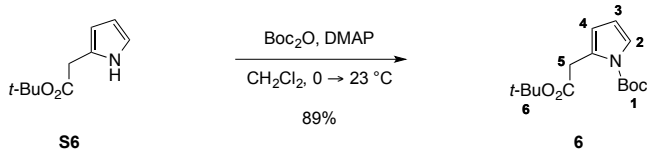
*Synthesis of the amidinylpyrrole **3**:*




Bromine (433 μL, 8.40 mmol, 1.05 equiv) was added dropwise via syringe to a solution of the guanylpyrroline **S3** (2.49 g, 8.00 mmol, 1 equiv) in dichloromethane (32 mL) at 0 °C. The resulting red mixture was then allowed to warm over 2 h to 23 °C. The reaction mixture was stirred for 12 h at 23 °C. The mixture was then cooled to 0 °C. The cold solution was transferred to a suspension of potassium *tert*-butoxide (3.59 g, 32.0 mmol, 4.00 equiv) in tetrahydrofuran (32 mL) at 0 °C via cannula. Chilled (0 °C) tetrahydrofuran (10 mL) was added to the empty reaction flask, and the rinse was transferred to the potassium *tert*-butoxide suspension via cannula. The resulting suspension was stirred for 2 h at 0 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (50 mL) and ethyl acetate (100 mL). The diluted product mixture was then transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed sequentially with saturated aqueous ammonium chloride solution (50 mL), water (50 mL), and saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes). The fractions containing product (TLC analysis) were collected and the collected fractions were concentrated. The resulting residue was triturated with pentane (10 mL) to afford the amidinylpyrrole **3** as a colorless, crystalline solid (1.85 g, 75%)

$R_f$ = 0.34 (25% ether–hexanes; UV, CAM). $^1$H NMR (500 MHz, $CDCl_3$): δ 9.44 (bs, 1H, $H_1$), 7.18 (t, J = 2.0 Hz, 2H, $H_3$), 6.27 (t, J = 2.0 Hz, 2H, $H_4$), 1.51 (s, 18H, $H_2$). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 148.2 (C), 120.9 (CH), 112.6 (CH), 27.9 ($CH_3$). The carbamate carbonyl and *tert*-butyl quaternary carbons were not observed due to line broadening. IR (ATR-FTIR), cm$^{-1}$: 3231 (m), 2983 (m), 1757 (s), 1705 (s). HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{15}H_{24}N_3O_4$, 310.1761; found, 310.1754.

*Synthesis of the pyrrolyl acetate **6***:

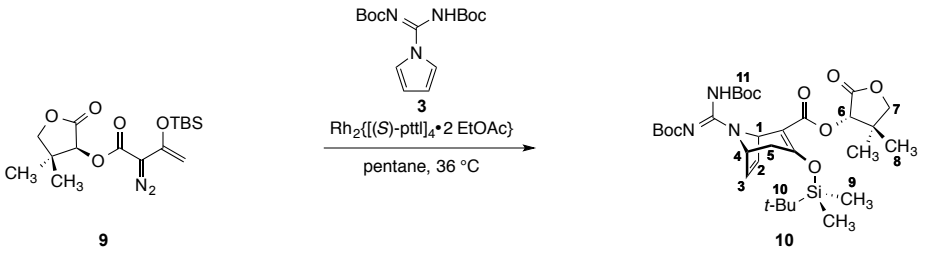



Di-*tert*-butyl-dicarbonate (5.23 g, 24.0 mmol, 1.20 equiv) and 4-(dimethylamino)pyridine (245 mg, 2.00 mmol, 0.100 equiv) were added in sequence to a solution of the pyrrole **S6** (3.62 g, 20.0 mmol, 1 equiv) in dichloromethane (100 mL) at 0 °C. The reaction mixture was allowed to warm over 1 h to 23 °C. The reaction mixture was stirred for 20 h at 23 °C. The product mixture was then diluted with ethyl acetate (200 mL). The diluted mixture was washed sequentially with saturated aqueous ammonium chloride solution (50 mL) and saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 100% hexanes initially, grading to 5% ethyl acetate–hexanes, one step) to furnish the pyrrolyl acetate **6** as a colorless solid (5.01 g, 89%).

$R_f$ = 0.51 (10% ethyl acetate–hexanes; UV). $^1$H NMR (500 MHz, $CDCl_3$): δ 7.22–7.20 (m, 1H, $H_2$), 6.09 (t, J = 2.9 Hz, 1H, $H_3$), 6.06–6.04 (m, 1H, $H_4$), 3.78 (s, 2H, $H_5$), 1.57 (s, 9H, $H_1$), 1.44 (s, 9H, $H_6$). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 170.1 (C), 149.3 (C), 128.1 (C), 121.4 (CH), 113.8 (CH), 109.8 (CH), 83.4 (C), 80.6 (C), 35.9 ($CH_2$), 28.0 ($CH_3$), 27.9 ($CH_3$). IR (ATR-FTIR), cm$^{-1}$: 2978 (m), 2933 (w), 1736 (s). HRMS-CI (m/z): $[M + Na]^+$ calcd for $C_{15}H_{23}NNaO_4$, 304.1519; found, 304.1522.

*Synthesis of the alkyne **12**:*

*Step 1: Synthesis of the dehydrotropane **10**:*




Dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate] ethyl acetate adduct (105 mg, 73.7 μmol, 0.0050 equiv) was added to a suspension of the amidinylpyrrole **3** (4.89 g, 15.8 mmol, 1.10 equiv) in *n*-pentane (850 mL) at 23 °C. The reaction vessel was fitted with a reflux condenser and then heated in a mantle to a vigorous reflux. The resulting green suspension was stirred and refluxed for 15 min, to allow thorough deoxygenation. A solution of (*S*)-4,4-dimethyl-2-oxotetrahydrofuran-3-yl 3-((*tert*-butyldimethylsilyl)oxy)-2-diazobut-3-enoate **9** (4.99 g, 14.1 mmol, 1 equiv) in *n*-pentane (50 mL) was then added dropwise over 2 h via syringe pump. Over the course of the addition, the green suspension became homogeneous, indicating partial consumption of **3**. Upon completion of the addition, the reaction mixture was stirred at reflux for an additional 15 min. The product mixture was cooled over 30 min to 24 °C. The cooled product mixture was concentrated. $^1$H NMR analysis of the unpurified product indicated >95:5 dr. The residue was purified by flash-column chromatography (eluting with 11% ethyl acetate–hexanes initially, grading to 33% ethyl acetate–hexanes, one step) to provide the dehydrotropane **10** as a crystalline, colorless solid (8.31 g, 93%).

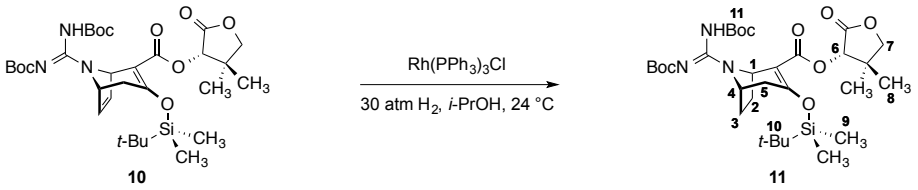
An identical experiment employing dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate] ethyl acetate adduct (1.4 mg, 1.0 μmol, 0.0010 equiv), the amidinylpyrrole **3** (340 mg, 1.10 mmol, 1.10 equiv), and (*S*)-4,4-dimethyl-2-oxotetrahydrofuran-3-yl 3-((*tert*-butyldimethylsilyl)oxy)-2-diazobut-3-enoate **9** (356 g, 1.00 mmol, 1 equiv) provided the product **10** as a crystalline, colorless solid (528 mg, 87%).

An identical experiment employing dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate] ethyl acetate adduct (35.5 mg, 21.7 μmol, 0.0050 equiv), the amidinyl pyrrole **3** (1.54 g, 5.00 mmol, 1.00 equiv), and (*S*)-4,4-dimethyl-2-oxotetrahydrofuran-3-yl 3-((*tert*-butyldimethylsilyl)oxy)-2-diazobut-3-enoate **9** (1.77 g, 5.00 mmol, 1 equiv) was conducted. The unpurified product was used directly in the following step.

$R_f$ = 0.30 (25% ethyl acetate–hexanes; UV, CAM). $^1$H NMR (500 MHz, $CD_3OD$, 60 °C): δ 6.54 (dd, J = 6.0, 2.6 Hz, 1H, $H_2$), 6.10 (dd, J = 6.0, 2.6 Hz, 1H, $H_3$), 5.47 (s, 1H, $H_6$), 5.40 (bs, 1H, $H_1$), 4.84 (dd, J = 5.6, 2.3 Hz, 1H, $H_4$), 4.10 (app q, J = 8.9 Hz, 2H, $H_7$), 3.22 (dd, J = 18.2, 5.8 Hz, 1H, $H_5$), 1.99 (d, J = 18.2 Hz, 1H, $H_5$), 1.47 (s, 18H, $H_{11}$), 1.20 (s, 3H, $H_8$), 1.12 (s, 3H, $H_8$), 0.94 (s, 9H, $H_{10}$), 0.22 (s, 3H, $H_9$), 0.21 (s, 3H, $H_9$). $^{13}$C NMR (125 MHz, $CD_3OD$, 60 °C): δ 174.8 (C), 163.4 (C), 162.8 (C), 152.4 (C), 150.4 (2 × C), 138.1 (CH), 129.5 (CH), 114.0 (C), 83.0 (C), 80.6 (C), 77.6 ($CH_2$), 75.8 (CH), 59.0 (CH), 58.8 (CH), 41.3 (C), 34.3 ($CH_2$), 28.6

($CH_3$), 28.5 ($CH_3$), 26.3 ($CH_3$), 23.3 ($CH_3$), 20.5 ($CH_3$), 19.3 (C), –3.4 (2 × $CH_3$). IR (ATR-FTIR), $cm^{-1}$: 2974 (w), 1794 (m), 1749 (m), 1729 (m). HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{31}H_{50}N_3O_9Si$, 636.3311; found, 636.3364. $[\alpha]_D^{20}$ −4.4 (*c* 13.5, $CH_3OH$).

*Step 2: Synthesis of the tropane **11**:*

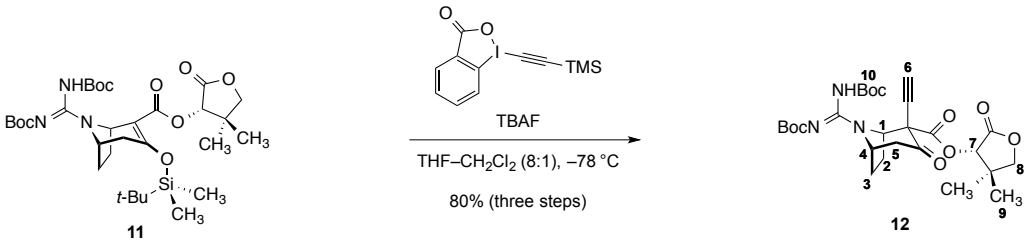



Chloro tris(triphenylphosphine)rhodium (95.1 mg, 102 μmol, 0.020 equiv) was added to a stirred solution of the unpurified dehydrotropane **10** obtained in the preceding step (nominally 3.18 g, 5.00 mmol, 1 equiv) in *iso*-propanol (49 mL) in a 200-mL beaker. The reaction vessel was sealed in a stainless steel hydrogenation chamber. The chamber was flushed with dihydrogen (3 × 30 atm) and then charged to 30 atm. The reaction mixture was stirred for 24 h at 23 °C under 30 atm of dihydrogen. The product mixture was concentrated. The unpurified material was dried by azeotropic distillation with toluene (3 × 10 mL) and the residue obtained was used directly in the following step.

An analytically-pure sample of the tropane **11** was obtained by flash-column chromatography (eluting with 17% ethyl acetate–hexanes).

$R_f$ = 0.35 (25% ethyl acetate–hexanes; UV). $^1$H NMR (500 MHz, $CD_3OD$, 50 °C): δ 5.48 (s, 1H, $H_6$), 5.04 (bs, 1H, $H_1$), 4.55 (bs, 1H, $H_4$), 4.15–4.04 (m, 2H, $H_7$), 3.22 (dd, J = 17.8, 4.1 Hz, 1H, $H_5$), 2.32–2.18 (m, 2H, $H_{2,3}$), 2.15–1.98 (m, 2H, $H_{2,5}$), 1.82–1.72 (m, 1H, $H_3$), 1.47 (s, 18H, $H_{11}$), 1.20 (s, 3H, $H_8$), 1.09 (s, 3H, $H_8$), 0.96 (s, 9H, $H_{10}$), 0.24 (s, 3H, $H_9$), 0.22 (s, 3H, $H_9$). $^{13}$C NMR (125 MHz, $CD_3OD$, 50 °C): δ 174.9 (C), 163.6 (C), 163.0 (C), 152.7 (C), 151.5 (2 × C), 113.7 (C), 83.0 (C), 80.6 (C), 77.6 ($CH_2$), 75.7 (CH), 56.7 (CH), 54.5 (CH), 41.5 (C), 41.3 ($CH_2$), 35.7 ($CH_2$), 30.0 ($CH_2$), 28.6 ($CH_3$), 28.5 ($CH_3$), 26.3 ($CH_3$), 23.2 ($CH_3$), 20.5 ($CH_3$), 19.3 (C), –3.4 ($CH_3$), –3.5 ($CH_3$). IR (ATR-FTIR), cm$^{-1}$: 2957 (m), 1796 (m), 1748 (m), 1731 (m). HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{31}H_{52}N_3O_9Si$, 638.3467; found, 636.3470. $[\alpha]_D^{20}$ –6.4 (*c* 6.30, $CH_3OH$).

*Step 3: Synthesis of alkyne **12**:*

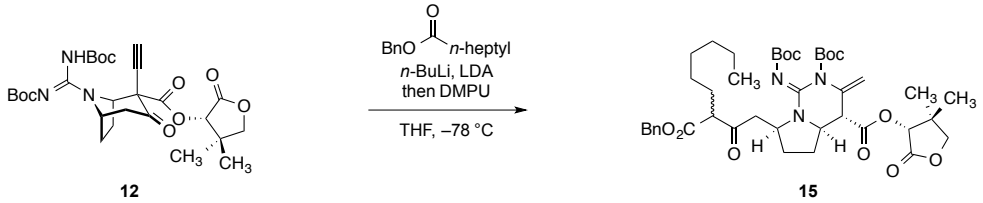



A solution of the unpurified tropane **11** obtained in the preceding step (nominally 3.19 g, 5.00 mmol, 1 equiv) in tetrahydrofuran (83 mL) was cooled to –78 °C for 30 min. A solution of tetrabutylammonium fluoride in tetrahydrofuran (1.0 M, 12.0 mL, 12.0 mmol, 2.40 equiv) was then added dropwise over 15 min via syringe pump. The reaction mixture was stirred for 1 h at –78 °C. A solution of 1-((trimethylsilyl)ethynyl)-1,2-benzoiodaoxol-3(1*H*)-one (2.07 g, 6.00 mmol, 1.20 equiv) in tetrahydrofuran–dichloromethane (2:1, 45 mL) at –78 °C was then added dropwise over 30 min via syringe pump. Upon completion of the addition, the reaction mixture was stirred for 3 h at –78 °C. The product mixture was diluted with saturated aqueous ammonium chloride solution (100 mL). The diluted product mixture was allowed to warm over 30 min to 23 °C, with stirring. The warmed, biphasic mixture was transferred to a separatory funnel and extracted with ethyl acetate (3 × 50 mL). The organic layers were combined and the combined organic layers were washed sequentially with saturated aqueous sodium bicarbonate solution (5 × 50 mL) and saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 25% ethyl acetate–hexanes initially, grading to 35% ethyl acetate–hexanes, one step) to afford the alkyne **12** as a light tan, powdered solid (2.19 g, 80% over three steps).

$R_f$ = 0.21 (33% ethyl acetate–hexanes; UV). $^1$H NMR (500 MHz, $CD_3OD$, 50 °C): δ 5.57 (s, 1H, $H_7$), 4.97 (bs, 1H, $H_1$), 4.69 (bs, 1H, $H_4$), 4.15 (d, J = 8.9 Hz, 1H, $H_8$), 4.09 (d, J = 8.9 Hz, 1H, $H_8$), 3.62 (dd, J = 13.5, 3.5 Hz, 1H, $H_5$), 3.07 (s, 1H, $H_6$), 2.37 (dd, J = 13.5, 2.0 Hz, 1H, $H_5$), 2.32–2.22 (m, 2H, $H_{2,3}$), 2.13–2.02 (m, 1H, $H_2$), 1.76–1.65 (m, 1H, $H_3$), 1.49 (s, 18H, $H_{10}$), 1.23 (s, 3H, $H_9$), 1.13 (s, 3H, $H_9$). $^{13}$C NMR (125 MHz, $CD_3OD$, 50 °C): δ 198.6 (C), 173.4 (C), 166.7 (C), 79.6 (2 × C), 78.2 ($CH_2$), 77.9 (C), 77.5 (CH), 64.0 (CH), 63.1 (C), 57.0 (CH), 45.4 ($CH_2$), 41.7 (C), 29.0 ($CH_2$), 28.6 (2 × $CH_3$), 26.6 ($CH_2$), 22.8 ($CH_3$), 20.2 ($CH_3$). The carbamate carbonyl and guanidinyl carbons were not observed due to line broadening. IR (ATR-FTIR), cm$^{-1}$: 3256 (w), 2976 (m), 1791 (m), 1746 (s). HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{27}H_{38}N_3O_9$, 548.2603; found, 548.2594. $[\alpha]_D^{20}$ −293.6 (*c* 3.10, $CH_3OH$).

*Synthesis of the ketone **16**:*

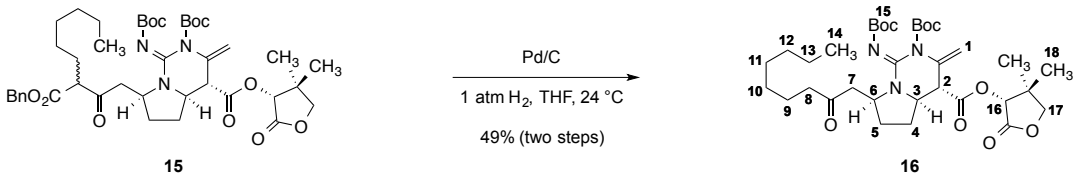
*Step 1: Synthesis of the β-keto ester **15**:*




A solution of *n*-butyllithium in hexanes (2.4 M, 765 μL, 1.83 mmol, 1.00 equiv) was added dropwise over 5 min to conical flask containing a solution of the alkyne **12** (1.00 g, 1.83 mmol, 1 equiv) in tetrahydrofuran (8.0 mL) that had been precooled to –78 °C for 15 min. In a separate round-bottomed flask, a solution of di-*iso*-propylamine (477 μL, 3.38 mmol, 1.85 equiv) in tetrahydrofuran (17 mL) was cooled to –78 °C. A solution of *n*-butyllithium in hexanes (2.4 M, 1.41 mL, 3.39 mmol, 1.85 equiv) was added dropwise over 5 min to the solution of di-*iso*-propylamine. After stirring for 30 min at –78 °C, a solution of benzyl octanoate (770 mg, 3.29 mmol, 1.80 equiv) in tetrahydrofuran (16 mL) was added to the freshly prepared lithium di-*iso*-propylamide solution dropwise over 10 min at –78 °C. Upon completion of the addition, the mixture was stirred for 15 min at –78 °C. The cold solution of deprotonated **12** was then added to the solution of lithium benzyl octanoate via cannula over 5 min at –78 °C. The conical flask containing deprotonated **12** was rinsed with tetrahydrofuran (1.0 mL) and the residual solution was cooled for to –78 °C for 5 min before being transferred via cannula to the solution lithium benzyl octanoate. The reaction mixture was stirred for 3 h at –78 °C. 1,3-Dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (3.0 mL) was then added to the reaction over 5 min at –78 °C and the resulting mixture was stirred for 30 min. The product mixture was diluted with saturated aqueous ammonium chloride solution (25 mL). The diluted product mixture was warmed over 30 min to 23 °C. The warmed mixture was diluted with ethyl acetate (75 mL) and the resulting solution was transferred to a separatory funnel. The layers that formed were separated, and the aqueous layer was discarded. The organic layer was washed sequentially with saturated aqueous ammonium chloride solution (25 mL), water (3 × 25 mL), and saturated aqueous sodium chloride solution (25 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated.

Attempted purification of the β-keto ester **15** by flash-column chromatography under a variety of conditions resulted in isolation of a complex mixture of unidentified decomposition products. Accordingly, the unpurified residue was used directly in the following step.

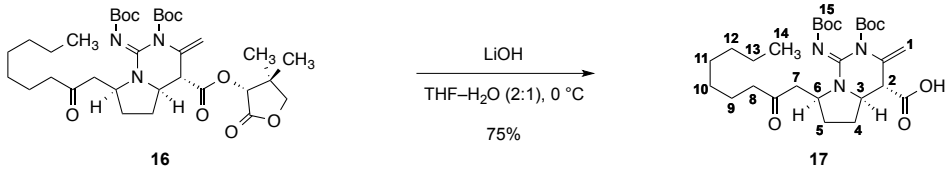
*Step 2: Synthesis of the ketone **16**:*




Palladium (5 wt% on carbon, 390 mg, 183 μmol, 0.100 equiv) was added in a single portion to a solution of the unpurified β-keto ester **15** obtained in the preceding step (nominally 1.43 g, 1.83 mmol, 1 equiv) in tetrahydrofuran (36 mL) at 23 °C. The reaction vessel was fitted with a rubber septum and the septum was penetrated with a needle. A balloon of dihydrogen was fixed to the vessel and the headspace was purged with dihydrogen. The needle and emptied balloon were removed and the suspension was stirred under a fresh balloon of dihydrogen for 3 h, at which time complete hydrogenolysis of the benzyl group was observed (UPLC/MS analysis). The headspace in the reaction vessel was replaced with argon and the reaction mixture was stirred for until complete decarboxylation of the intermediate ketoacid was observed (~3 h, UPLC/MS analysis). The product mixture was filtered through a bed of celite (2.5 × 2.5 cm) and the filter cake was washed with ethyl acetate (3 × 25 mL). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was purified by flash-column chromatography (eluting with 25% ethyl acetate–hexanes initially, grading to 35% ethyl acetate–hexanes, one step) to provide the ketone **16** as a crystalline, colorless solid (578 mg, 49% over 2 steps, 10:1 mixture of C-2 diastereomers).

$R_f$ = 0.15 (35% ethyl acetate–hexanes; UV). $^1$H NMR (500 MHz, $CD_3OD$): δ 5.60 (s, 1H, $H_1$), 5.48 (s, 2H, $H_{1,16}$), 4.51–4.44 (m, 1H, $H_6$), 4.16 (d, J = 8.9 Hz, 1H, $H_{17}$), 4.11 (d, J = 8.9 Hz, 1H, $H_{17}$), 4.04 (td, J = 9.3, 6.2 Hz, 1H, $H_3$), 3.96 (d, J = 9.7 Hz, 1H, $H_2$), 2.87 (dd, J = 16.7, 3.6 Hz, 1H, $H_7$), 2.65 (dd, J = 16.7, 9.3 Hz, 1H, $H_7$), 2.45 (t, J = 7.4 Hz, 2H, $H_8$), 2.33–2.26 (m, 1H, $H_4$), 2.23–2.13 (m, 1H, $H_5$), 1.95–1.81 (m, 2H, $H_{4,5}$), 1.56–1.52 (m, 2H, $H_9$), 1.47 (s, 9H, $H_{15}$), 1.46 (s, 9H, $H_{15}$), 1.32–1.26 (m, 8H, $H_{10–13}$), 1.23 (s, 3H, $H_{18}$), 1.16 (s, 3H, $H_{18}$), 0.90 (t, J = 6.8 Hz, 3H, $H_{14}$). $^{13}$C NMR (125 MHz, $CD_3OD$): 210.0 (C), 174.1 (C), 170.2 (C), 160.7 (C), 152.0 (C), 151.3 (C), 137.2 (C), 115.5 ($CH_2$), 84.5 (C), 80.4 (C), 77.4 (CH), 77.4 ($CH_2$), 59.4 (CH), 57.1 (CH), 55.6 (CH), 45.7 ($CH_2$), 44.0 ($CH_2$), 41.6 (C), 32.9 ($CH_2$), 30.6 ($CH_2$), 30.3 ($CH_2$), 30.2 ($CH_2$), 30.1 ($CH_2$), 28.7 ($CH_3$), 28.3 ($CH_3$), 24.8 ($CH_2$), 23.7 ($CH_2$), 22.8 ($CH_3$), 20.3 ($CH_3$), 14.4 ($CH_3$). IR (ATR-FTIR), cm$^{-1}$: 2930 (m), 1792 (m), 1733 (s), 1603 (s). HRMS-CI (m/z): [M + H]$^+$ calcd for $C_{34}H_{54}N_3O_9$, 648.3855; found, 648.3851. $[\alpha]_D^{20}$ +23.9 (*c* 23.0, $CH_3OH$).

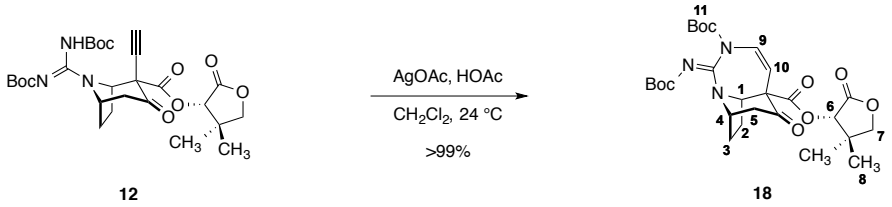
*Synthesis of the acid **17**:*




Aqueous lithium hydroxide solution (1.0 N, 6.24 mL, 6.24 mmol, 10.0 equiv) was added dropwise over 5 min with stirring to a solution of the pantolactone ester **16** (404 mg, 624 μmol, 1 equiv) in tetrahydrofuran (12 mL) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C. The pH of the solution was adjusted to ~3 by the dropwise addition of aqueous hydrogen chloride solution (1.0 N) at 0 °C. The acidified product mixture was transferred to a separatory funnel. The biphasic mixture was extracted with ethyl acetate (3 × 15 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (3 × 15 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% methanol–dichloromethane) to afford the acid **17** as a colorless, crystalline solid (251 mg, 75%).

$R_f$ = 0.15 (5% methanol–dichloromethane; UV). $^1$H NMR (500 MHz, $CDCl_3$): δ 5.46 (s, 1H, $H_1$), 5.38 (s, 1H, $H_1$), 4.50 (t, J = 9.0 Hz, 1H, $H_6$), 3.93 (td, J = 9.6, 6.4 Hz, 1H, $H_3$), 3.52 (d, J = 9.6 Hz, 1H, $H_2$), 3.02 (dd, J = 16.5, 3.2 Hz, 1H, $H_7$), 2.43 (dd, J = 16.5, 9.6 Hz, 1H, $H_7$), 2.37 (td, J = 7.5, 5.5 Hz, 2H, $H_8$), 2.27–2.20 (m, 1H, $H_4$), 2.16–2.06 (m, 1H, $H_5$), 1.86 (dd, J = 13.3, 7.1 Hz, 1H, $H_5$), 1.78–1.67 (m, 1H, $H_4$), 1.54–1.50 (m, 2H, $H_9$), 1.48 (s, 9H, $H_{15}$), 1.43 (s, 9H, $H_{15}$), 1.32–1.19 (m, 8H, $H_{10–13}$), 0.86 (t, J = 7.0 Hz, 3H, $H_{14}$). $^{13}$C NMR (125 MHz, $CDCl_3$): 209.1 (C), 173.5 (C), 159.3 (C), 149.8 (C), 149.6 (C), 135.5 (C), 113.7 ($CH_2$), 83.0 (C), 79.3 (C), 57.8 (CH), 56.6 (CH), 54.0 (CH), 44.8 ($CH_2$), 43.4 ($CH_2$), 31.6 ($CH_2$), 29.4 ($CH_2$), 29.4 ($CH_2$), 29.1 ($CH_2$), 29.0 ($CH_2$), 28.3 ($CH_3$), 27.9 ($CH_3$), 23.7 ($CH_2$), 22.6 ($CH_2$), 14.0 ($CH_3$). IR (ATR-FTIR), cm$^{-1}$: 2929 (m), 2857 (w), 1731 (s), 1713 (s). HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{28}H_{46}N_3O_7$, 536.3330; found, 536.3351. $[\alpha]_D^{20}$ +44.4 (*c* 4.50, $CH_3OH$).

*Synthesis of the diazepine **18**:*

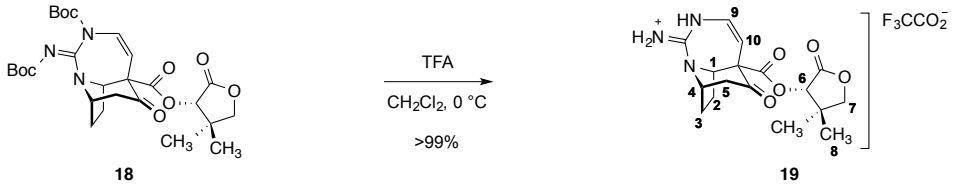



12 18

Silver acetate (0.7 mg, 4 μmol, 0.2 equiv) and acetic acid (5 μL, 80 μmol, 4 equiv) were added in sequence to a solution of the alkyne **12** (15.9 mg, 19.7 μmol, 1 equiv) in dichloromethane (200 μL) at 24 °C. The mixture was stirred for 24 h at 23 °C. The product solution was then purified directly by preparatory thin-layer chromatography (eluting with 40% ethyl acetate–hexanes) to afford the diazepine **18** as a colorless, powdered solid (15.8 mg, >99%).

$R_f$ = 0.45 (50% ethyl acetate–hexanes; UV). $^1$H NMR (500 MHz, $CDCl_3$, 50 °C): δ 6.88 (d, J = 9.3 Hz, 1H, $H_9$), 5.44 (s, 1H, $H_6$), 5.09 (d, J = 9.2 Hz, 1H, $H_{10}$), 4.96–4.90 (m, 1H, $H_4$), 4.81 (d, J = 5.9 Hz, 1H, $H_1$), 4.09–4.01 (m, 2H, $H_7$), 2.99 (dd, J = 17.1, 5.3 Hz, 1H, $H_5$), 2.72–2.63 (m, 1H, $H_3$), 2.40 (d, J = 17.1 Hz, 1H, $H_5$), 2.33–2.26 (m, 2H, $H_{2,3}$), 1.79–1.72 (m, 1H, $H_2$), 1.52 (s, 9H, $H_{11}$), 1.49 (s, 9H, $H_{11}$), 1.27 (s, 3H, $H_8$), 1.13 (s, 3H, $H_8$). $^{13}$C NMR (125 MHz, $CDCl_3$, 50 °C): δ 199.8 (C), 171.4 (C), 167.8 (C), 159.3 (C), 151.5 (C), 150.0 (C), 128.1 (CH), 110.7 (CH), 84.1 (C), 80.0 (C), 76.6 (CH), 76.4 ($CH_2$), 66.4 (C), 58.1 (CH), 55.6 (CH), 46.0 ($CH_2$), 40.6 (C), 28.3 ($CH_3$), 28.2 ($CH_3$), 27.3 ($CH_2$), 26.7 ($CH_2$), 23.0 ($CH_3$), 19.9 ($CH_3$). IR (ATR-FTIR), cm$^{-1}$: 2978 (w), 2932 (w), 1783 (m), 1742 (s), 1693 (m), 1603 (m). HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{27}H_{38}N_3O_9$, 548.2603; found, 548.2581. $[\alpha]_D^{20}$ −147.7 (*c* 13.0, $CH_3OH$).

*Synthesis of the diazepenium ion **19**:*

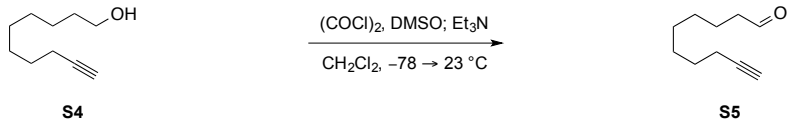



Trifluoroacetic acid (500 μL) was added dropwise over 5 min to a solution of the diazepine **18** (15.8 mg, 28.9 μmol, 1 equiv) in dichloromethane (500 μL) at 0 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm to 23 °C. The reaction mixture was stirred for 2 h at 23 °C. The product mixture was concentrated, and excess trifluoroacetic acid was removed by azeotropic distillation with benzene (3 × 500 μL) to afford the diazepenium ion **19** as a colorless, crystalline solid (13.3 mg, >99%).

Crystals of **19** that were suitable for X-ray analysis were grown by vapor diffusion from acetonitrile with diethyl ether as antisolvent.

$^1$H NMR (500 MHz, $CD_3OD$, 50 °C): δ 6.36 (d, J = 10.0 Hz, 1H, $H_9$), 5.65 (s, 1H, $H_6$), 5.37 (d, J = 10.0 Hz, 1H, $H_{10}$), 4.97 (app t, J = 5.5 Hz, 1H, $H_4$), 4.22 (d, J = 7.3 Hz, 1H, $H_1$), 4.16 (d, J = 8.9 Hz, 1H, $H_7$), 4.10 (d, J = 8.9 Hz, 1H, $H_7$), 2.78 (ddd, J = 13.9, 9.4, 4.1 Hz, 1H, $H_3$), 2.69 (ddd, J = 17.9, 5.5, 1.8 Hz, 1H, $H_5$) 2.62 (dd, J = 17.9 Hz, 1.5 Hz, 1H, $H_5$), 2.52–2.42 (m, 1H, $H_2$), 2.39–2.26 (m, 1H $H_3$), 1.93–1.85 (m, 1H, $H_2$), 1.24 (s, 3H, $H_8$), 1.09 (s, 3H, $H_8$). $^{13}$C NMR (125 MHz, $CD_3OD$): δ 201.4 (C), 174.0 (C), 168.7 (C), 156.7 (C), 126.4 (CH), 109.9 (CH), 78.1 ($CH_2$), 77.5 (CH), 68.9 (C), 61.6 (CH), 61.3 (CH), 46.8 ($CH_2$), 41.8 (C), 28.8 ($CH_2$), 28.2 ($CH_2$), 22.6 ($CH_3$), 20.2 ($CH_3$). IR (ATR-FTIR), cm$^{-1}$: 2971 (w), 1784 (s), 1751 (s), 1716 (s), 1661 (s). HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{17}H_{22}N_3O_5$, 348.1554; found, 348.1564. $[\alpha]_D^{20}$ −377.8 (*c* 3.6, $CH_3OH$).

*Synthesis of 9-decynal (**S5**):*

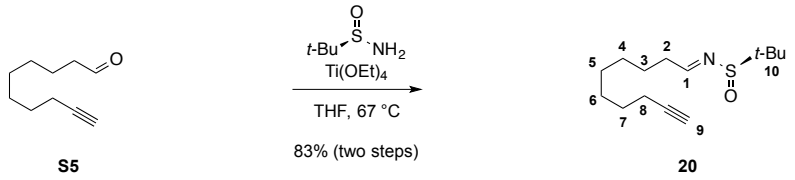



**S4** **S5**

Oxalyl chloride (4.20 mL, 48.1 mmol, 1.48 equiv) was added dropwise via syringe to a solution of dimethylsulfoxide (7.00 mL, 98.5 mmol, 3.04 equiv) and 9-decyn-1-ol **S4** (5.75 mL, 16.2 mmol, 1 equiv) in dichloromethane (180 mL) at –78 °C. The resulting white suspension was stirred for 1 h at –78 °C. Triethylamine (23.0 mL, 162 mmol, 5.09 equiv) was then added dropwise via syringe pump over 20 min. The resulting suspension was stirred for 2 h at –78 °C. The reaction flask was then removed from the cooling bath and the mixture was warmed over 30 min to 23 °C. The warmed reaction mixture was stirred for 2.5 h at 23 °C. The yellow product mixture was diluted sequentially with water (100 mL) and ethyl acetate (500 mL) and the diluted product mixture was transferred to a separatory funnel. The diluted product mixture was then washed with saturated aqueous sodium chloride solution (300 mL). The organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by elution over a short pad of silica gel (6.0 × 8.0 cm, eluting with 10% ethyl acetate–hexanes). The filtrate was collected and concentrated. The residue obtained was used directly in the following step.

$^{1}$H and $^{13}$C NMR spectroscopic data for 9-decynal (**S5**) obtained in this way were in agreement with those published.[11]

*Synthesis of the sulfinylimine **20**:*

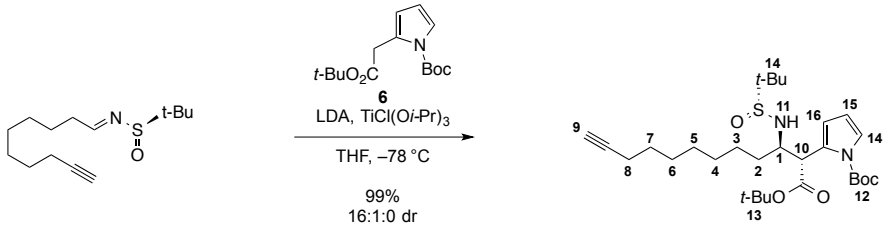



**S5** **20**

Titanium ethoxide (12.2 mL, 58.9 mmol, 2.00 equiv) was added to a solution of the unpurified 9-decynal **S5** obtained in the preceding step (nominally 4.92 g, 32.4 mmol, 1.10 equiv) and (*S*)-2-methylpropane-2-sulfinamide (3.60 g, 29.5 mmol, 1 equiv) in tetrahydrofuran (110 mL) at 23 °C. The reaction flask was then fitted with a reflux condenser and placed in an oil bath that had been preheated to 67 °C. The reaction mixture was stirred and heated for 13 h at 67 °C. The reaction flask was then removed from the heating bath and the product mixture was allowed to cool over 45 min to 23 °C. The cooled product mixture was then poured into a stirring solution of saturated aqueous sodium chloride (150 mL) and was then diluted with ethyl acetate (500 mL). The diluted suspension was stirred for 1 h at 23 °C. The resulting white suspension was filtered through a pad of Celite (4.0 × 8.0 cm). The filter cake was washed with ethyl acetate (2 × 100 mL). The filtrates were collected and combined, and the combined filtrates were transferred to a separatory funnel. The layers that formed were separated and the organic layer was washed with saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate. The dried organic layer was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes) to provide the sulfinimine **20** as a light yellow oil (6.29 g, 83% over two steps).

$R_f$ = 0.16 (10% ethyl acetate–hexanes; UV, CAM). $^1$H NMR (500 MHz, $CDCl_3$): δ 8.06 (t, J = 4.7 Hz, 1H, $H_1$), 2.51 (td, J = 7.4, 4.8 Hz, 2H, $H_2$), 2.18 (td, J = 7.1, 2.6 Hz, 2H, $H_8$), 1.93 (t, J = 2.6 Hz, 1H, $H_9$), 1.66–1.60 (m, 2H, $H_3$), 1.57–1.49 (m, 2H, $H_7$), 1.43–1.30 (m, 6H, $H_{4–6}$), 1.19 (s, 9H, $H_{10}$). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 169.8 (CH), 84.7 (C), 68.3 (CH), 56.7 (C), 32.2 ($CH_2$), 29.2 ($CH_2$), 29.0 ($CH_2$), 28.7 ($CH_2$), 28.5 ($CH_2$), 25.6 ($CH_2$), 22.5 ($CH_3$), 18.5 ($CH_2$). IR (ATR-FTIR), cm$^{-1}$: 3309 (m), 2930 (s), 2858 (m), 1622 (s). HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{14}H_{26}NOS$, 256.1730; found, 256.1727. $[\alpha]_D^{20}$ −63.6 (*c* 28.0, $CH_3OH$).

*Synthesis of the Mannich addition product **21**:*

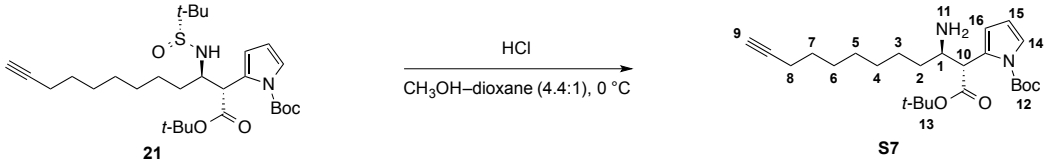



A solution of *n*-butyllithium in hexanes (2.50 M, 8.92 mL, 22.3 mmol, 2.10 equiv) was added dropwise via syringe pump over 20 min to a solution of di-*iso*-propylamine (3.30 mL, 23.4 mmol, 2.20 equiv) in tetrahydrofuran (75 mL) at –78 °C. The resulting mixture was stirred for 30 min at –78 °C. A solution of the pyrrolyl acetate **6** (3.12 g, 12.3 mmol, 2.00 equiv) in tetrahydrofuran (5.0 mL) was then added dropwise via syringe. The resulting mixture was stirred for 30 min at –78 °C. A solution of chloro tri-*iso*-propoxytitanium in tetrahydrofuran (1.60 M, 25.0 mL, 40.0 mmol, 3.77 equiv) was then added dropwise via syringe pump over 20 min at –78 °C. The resulting dark red solution was stirred for 30 min at –78 °C. A solution of the sulfinimine **20** (2.72 g, 10.6 mmol, 1 equiv) in tetrahydrofuran (5.0 mL) was then added dropwise via syringe pump over 20 min at –78 °C. The reaction mixture was stirred for 2 h at –78 °C. The cold product mixture was diluted with saturated aqueous ammonium chloride solution (10 mL). The reaction vessel was immediately removed from the cooling bath and diluted sequentially with ethyl acetate (500 mL) and saturated aqueous sodium chloride solution (200 mL). The diluted product mixture was warmed over 30 min to 23 °C, with stirring. The warmed product mixture was transferred to a separatory funnel and the layers that formed separated. The organic layer was washed with saturated aqueous sodium chloride solution (200 mL). The aqueous layers were combined and the combined aqueous layers were extracted with ethyl acetate (300 mL). The organic layers were combined and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to afford the Mannich addition product **21** as a pale yellow oil (5.63 g, 99%, ~16:1 mixture of C-10 diastereomers).

$R_f$ = 0.10 (20% ethyl acetate–hexanes; UV, CAM). $^1$H NMR (500 MHz, $CDCl_3$): δ 7.20 (dd, J = 3.2, 1.6 Hz, 1H, $H_{14}$), 6.23–6.19 (m, 1H, $H_{16}$), 6.11 (t, J = 3.2 Hz, 1H, $H_{15}$), 4.66 (d, J = 6.2 Hz, 1H, $H_{11}$), 4.26 (d, J = 8.3 Hz, 1H, $H_{10}$), 3.77–3.69 (m, 1H, $H_1$), 2.16 (td, J = 7.1, 2.6 Hz, 2H, $H_8$), 1.92 (t, J = 2.6 Hz, 1H, $H_9$), 1.70–1.61 (m, 1H, $H_2$), 1.55 (s, 9H, $H_{12}$), 1.53–1.46 (m, 3H, $H_{2,7}$), 1.44 (s, 9H, $H_{13}$), 1.41–1.23 (m, 8H, $H_{3–6}$), 1.16 (s, 9H, $H_{14}$). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 170.8 (C), 149.6 (C), 130.6 (C), 121.8 (CH), 112.5 (CH), 110.0 (CH), 84.6 (C), 83.7 (C), 81.3 (C), 68.1 (CH), 59.3 (C), 55.9 (CH), 50.5 (CH), 34.2 ($CH_2$), 29.1 ($CH_2$), 28.9 ($CH_2$), 28.6 ($CH_2$), 28.4 ($CH_2$), 28.0 ($CH_3$), 27.9 ($CH_3$), 25.8 ($CH_2$), 22.8 ($CH_3$), 18.3 ($CH_2$). IR (ATR-FTIR), $cm^{-1}$: 3309 (w), 2932 (m), 1739 (s). HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{29}H_{49}N_2O_5S$, 537.3357; found, 537.3353. $[\alpha]_D^{20}$ −8.5 (*c* 11.8, $CH_3OH$).

*Synthesis of the urea **22**:*

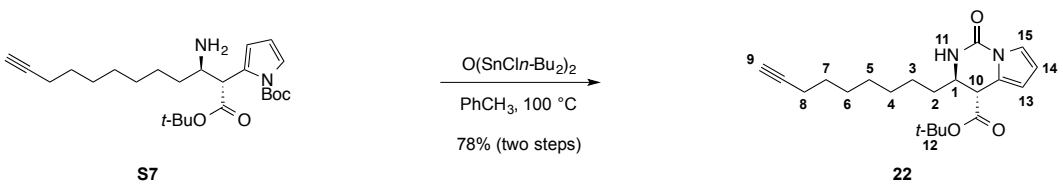
*Step 1: Synthesis of the amine **S7**:*




A solution of hydrogen chloride in 1,4-dioxane (4 N, 7.90 mL, 31.6 mmol, 3.01 equiv) was added dropwise via syringe pump over 10 min to a solution of the Mannich addition product **21** (5.63 g, 10.5 mmol, 1 equiv) in methanol (40 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. Saturated aqueous sodium bicarbonate solution (35 mL) was then added dropwise via syringe pump over 10 min to the product mixture at 0 °C. The diluted product mixture was then transferred to a separatory funnel and diluted with water (50 mL). The resulting emulsion was then extracted with dichloromethane (1 × 100 mL, 3 × 30 mL). The organic layers were combined and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate concentrated. The unpurified residue was dried by azeotropic distillation from toluene (4 × 20 mL) and used directly in the following step.

Attempted purification of the amine **S7** by flash-column chromatography resulted in isolation of a mixture of the amine **S7**, the urea **22**, and uncharacterized decomposition products.

*Step 2: Synthesis of the urea **22**:*

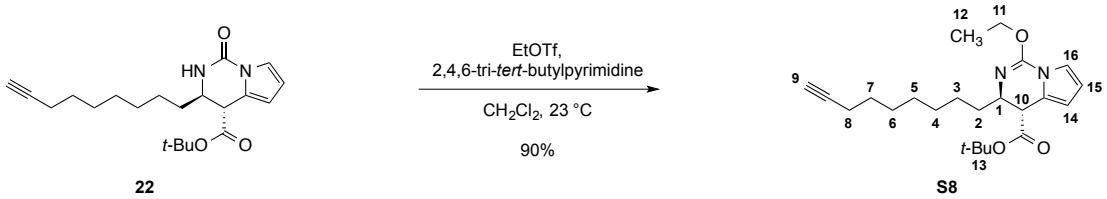



**S7** **22**

Bis(dibutylchlorotin) oxide (1.16 g, 2.10 mmol, 0.200 equiv) was added to a solution of the unpurified amine **S7** obtained in the preceding step (nominally 4.54 g, 10.5 mmol, 1 equiv) in toluene (120 mL) at 23 °C. The reaction flask was sealed with a rubber septum and placed in an oil bath that had been preheated to 100 °C. The reaction mixture was stirred and heated for 1.5 h at 100 °C. The product mixture was then cooled over 30 min to 23 °C. The cooled product mixture was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 14% ethyl acetate–hexanes) to provide the urea **22** as a pale yellow solid (2.94 g, 78% over two steps).

$R_f$ = 0.41 (25% ethyl acetate–hexanes; UV, CAM). $^1$H NMR (500 MHz, $CDCl_3$): δ 7.31 (dd, J = 3.1, 1.4 Hz, 1H, $H_{15}$), 6.19 (app t, J = 3.1 Hz, 1H, $H_{14}$), 6.12 (s, 1H, $H_{11}$), 6.09–6.04 (m, 1H, $H_{13}$), 3.92–3.74 (m, 1H, $H_1$), 3.63 (d, J = 6.7 Hz, 1H, $H_{10}$), 2.16 (td, J = 7.1, 2.6 Hz, 2H, $H_8$), 1.93 (t, J = 2.6 Hz, 1H, $H_9$), 1.56 (app q, J = 7.5 Hz, 2H, $H_2$), 1.52–1.47 (m, 2H, $H_7$), 1.46 (s, 9H, $H_{12}$), 1.43–1.25 (m, 8H, $H_{3–6}$). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 169.1 (C), 149.8 (C), 125.8 (C), 117.9 (CH), 111.0 (CH), 109.7 (CH), 84.5 (C), 82.2 (C), 68.2 (CH), 53.2 (CH), 45.3 (CH), 34.1 ($CH_2$), 29.1 ($CH_2$), 28.8 ($CH_2$), 28.5 ($CH_2$), 28.3 ($CH_2$), 27.9 ($CH_3$), 25.3 ($CH_2$), 18.3 ($CH_2$). IR (ATR-FTIR), cm$^{-1}$: 3285 (m), 3126 (w), 2931 (m), 1709 (s). HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{21}H_{31}N_2O_3$, 359.2329; found, 359.2329. $[\alpha]_D^{20}$ −46.1 (*c* 30.4, $CH_3OH$).

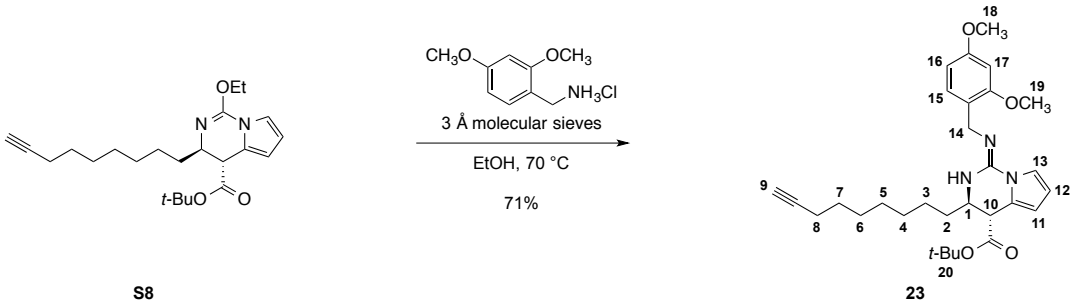
*Synthesis of the ethoxy pyrimidine **S8**:*




2,4,6-Tri-*tert*-butylpyrimidine (4.07 g, 16.4 mmol, 2.00 equiv) was added to a solution of the urea **22** (2.94 g, 8.20 mmol, 1 equiv) in dichloromethane (3.3 mL) at 23 °C. Ethyl trifluoromethanesulfonate (1.27 mL, 9.80 mmol, 1.20 equiv) was then added dropwise via syringe at 23 °C. The reaction mixture was stirred vigorously for 43 h at 23 °C. The product mixture was then transferred to an Erlenmeyer flask and diluted with ether (150 mL). The stirred suspension was cooled to 0 °C. Aqueous sodium bicarbonate solution (5 wt%, 50 mL) was added to the diluted product mixture via syringe pump over 10 min at 0 °C. The mixture was then transferred to a separatory funnel and the layers that formed separated. The aqueous layer was discarded. The organic layer was washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% ethyl acetate–hexanes) to provide the ethoxy pyrimidine **S8** as a colorless oil (2.86 g, 90%).

$R_f$ = 0.32 (6% ethyl acetate–hexanes; UV, CAM). $^1$H NMR (500 MHz, $CDCl_3$): δ 7.00 (dd, J = 3.0, 1.4 Hz, 1H, $H_{16}$), 6.13 (app t, J = 3.2 Hz, 1H, $H_{15}$), 6.03–5.99 (m, 1H, $H_{14}$), 4.29 (q, J = 7.1 Hz, 2H, $H_{11}$), 3.88–3.81 (m, 1H, $H_1$), 3.49 (d, J = 6.8 Hz, 1H, $H_{10}$), 2.16 (td, J = 7.1, 2.6 Hz, 2H, $H_8$), 1.92 (t, J = 2.6 Hz, 1H, $H_9$), 1.55–1.47 (m, 3H, $H_{2,7}$), 1.47–1.42 (m, 12H, $H_{2,3,13}$), 1.41–1.33 (m, 5H, $H_{4,12}$), 1.33–1.26 (m, 4H, $H_{5,6}$). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 170.8 (C), 145.4 (C), 127.0 (C), 115.6 (CH), 109.6 (CH), 107.8 (CH), 84.7 (C), 81.2 (C), 68.0 (CH), 62.6 ($CH_2$), 56.6 (CH), 44.9 (CH), 35.2 ($CH_2$), 29.3 ($CH_2$), 29.0 ($CH_2$), 28.6 ($CH_2$), 28.4 ($CH_2$), 27.9 ($CH_3$), 25.8 ($CH_2$), 18.3 ($CH_2$), 14.2 ($CH_3$). IR (ATR-FTIR), cm$^{-1}$: 3309 (w), 2931 (s), 1731 (s), 1673 (s). HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{23}H_{35}N_2O_3$, 387.2642; found, 387.2644. $[\alpha]_D^{20}$ +58.9 (*c* 83.6, $CH_3OH$).

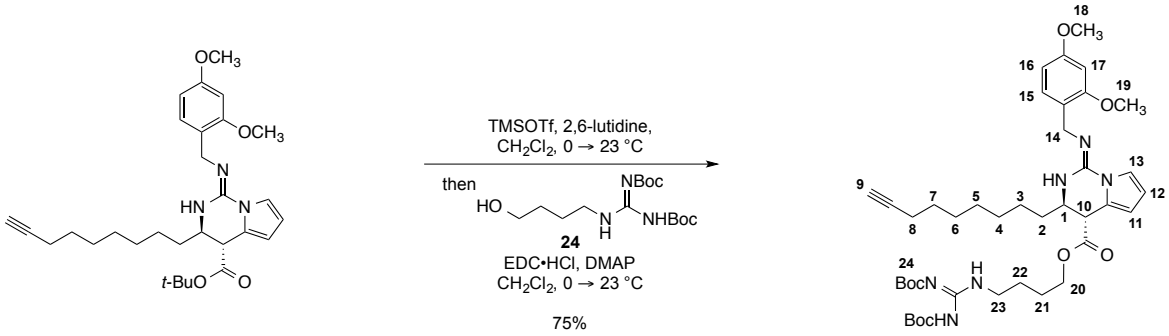
*Synthesis of the amino pyrimidine **23**:*




A screw-capped pressure vessel equipped with a stir bar was charged with activated 3 Å molecular sieves (2.92 g, 102 wt%, powdered). 2,4-Dimethoxybenzylamine hydrochloride (1.66 g, 8.14 mmol, 1.10 equiv) and a solution of the ethoxy pyrimidine **S8** (2.86 g, 7.40 mmol, 1 equiv) in ethanol (8.5 mL) were then added in sequence. The reaction vessel was sealed and the sealed vessel was immersed in an oil bath that had been preheated to 70 °C. The reaction mixture was stirred for 5 d at 70 °C. The product mixture was then cooled over 30 min to 23 °C. Potassium carbonate (1.24 g, 8.97 mmol, 1.21 equiv) was then added in one portion to the product mixture at 24 °C. The resulting suspension was stirred for 20 min at 24 °C. The mixture was filtered through a sintered glass funnel and the solids were washed with ethyl acetate (3 × 40 mL). The filtrates were collected and combined, and the combined filtrates were concentrated. The residue obtained was purified by flash-column chromatography (eluting with 1% triethylamine–10% ethyl acetate–hexanes initially, grading to 1% triethylamine–25% ethyl acetate–hexanes, one step) to afford the amino pyrimidine **23** as a light orange oil (2.65 g, 71%, 4:1 mixture of C-10 diastereomers).

$R_f$ = 0.26 (1% triethylamine–25% ethyl acetate–hexanes; UV, CAM). $^1$H NMR (500 MHz, $CD_3OD$, * denotes second diastereomer): δ 7.22 (d, J = 8.3 Hz, 1H, $H_{15*}$), 7.17–7.16 (m, 2H, $H_{13,13*,15}$), 6.53–6.52 (m, 1H, $H_{17,17*}$), 6.46–6.26 (m, 1H, $H_{16,16*}$), 6.17 (t, J = 3.2 Hz, 1H, $H_{12}$), 6.15–6.13 (m, 1H, $H_{12*}$), 6.04 (d, J = 2.0 Hz, 1H, $H_{11,11*}$), 4.42–4.19 (m, 2H, $H_{14,14*}$), 3.84–3.83 (m, 3H, $H_{18,18*}$), 3.77–3.76 (m, 4H, $H_{1,1*,19,19*}$), 3.63–3.60 (m, 1H, $H_{10,10*}$), 2,16–2.11 (m, 3H, $H_{8,8*,9,9*}$), 1.53–1.44 (m, 2H, $H_{2,2*}$), 1.41 (s, 9H, $H_{20}$), 1.40 (s, 9H, $H_{20*}$), 1.37–1.21 (m, 10H, $H_{3-7,3-7*}$). $^{13}$C NMR (125 MHz, $CD_3OD$): δ 172.9 (C), 161.6 (C), 159.6 (C), 146.6 (C), 129.9 (CH), 127.4 (C), 120.5 (C), 116.8 (C), 110.9 (CH), 110.0 (CH), 105.2 (CH), 99.2 (CH), 85.1 (C), 82.5 (C), 69.4 (CH), 56.5 (CH), 55.9 ($CH_3$), 55.8 ($CH_3$), 45.9 (CH), 41.8 (CH), 36.0 ($CH_2$), 30.4 ($CH_2$), 20.0 ($CH_2$), 29.7 (2 × $CH_2$), 28.2 ($CH_2$), 27.0 ($CH_3$), 19.0 ($CH_2$). IR (ATR-FTIR), cm$^{-1}$: 3409 (w), 3295 (w) 2932 (s), 1725 (s) 1654(s). HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{30}H_{42}N_3O_4$, 508.3170; found, 508.3183. $[\alpha]_D^{20}$ +19.4 (*c* 3.10, $CH_3OH$).

*Synthesis of the bis(guanidine)* ***25****:*



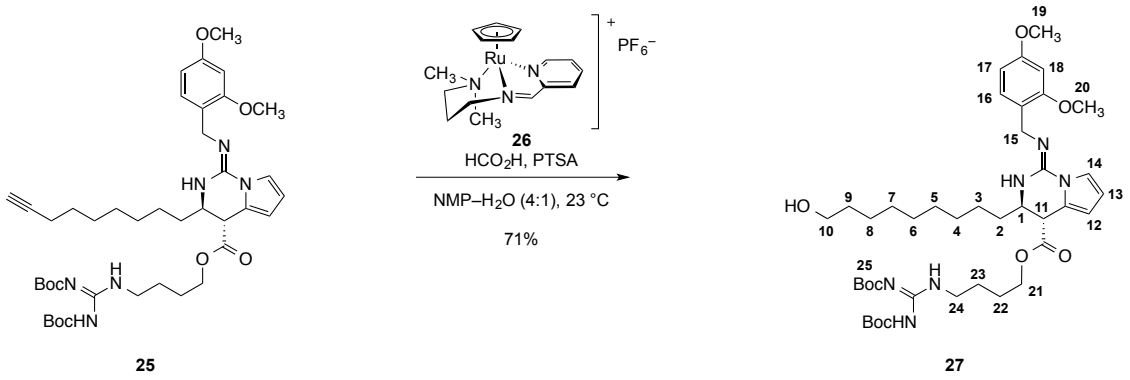

**23** **25**

Trimethylsilyl trifluoromethanesulfonate (4.10 mL, 22.6 mmol, 10.0 equiv) was added dropwise via syringe pump over 5 min to a solution of 2,6-lutidine (2.62 mL, 22.6 mmol, 10.0 equiv) and the ester **23** (1.15 g, 2.26 mmol, 1 equiv) in dichloromethane (11 mL) at 0 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm over 20 min to 23 °C. The reaction mixture was stirred for 40 h at 23 °C. The product mixture was then cooled to 0 °C. Saturated aqueous sodium chloride solution (25 mL) was then added slowly to the product mixture at 0 °C. The resulting biphasic mixture was transferred to a separatory funnel and diluted with ethyl acetate (50 mL). The layers that formed were separated and the aqueous layer was discarded. The organic layer was washed with saturated aqueous sodium chloride solution (25 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was then dried by azeotropic distillation with toluene (3 × 10 mL) and the dried residue was dissolved in dichloromethane (23 mL). The resulting solution was cooled to 0 °C. The alcohol **24** (749 mg, 2.26 mmol, 1 equiv), 4-(dimethylamino)pyridine (27.6 mg, 226 μmol, 0.10 equiv), and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (650 mg, 3.39 mmol, 1.50 equiv) were added in sequence to the solution at 0 °C. The reaction vessel was removed from the cooling bath and was allowed to warm over 30 min to 23 °C. The mixture was stirred for 1 h at 23 °C. The product mixture was then rapidly diluted with saturated aqueous sodium chloride solution (20 mL). The resulting biphasic mixture was transferred to a separatory funnel and diluted with ethyl acetate (75 mL). The layers that formed were separated and the aqueous layer was discarded. The organic layer was washed with saturated aqueous sodium chloride solution (3 × 20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 1% triethylamine–25% ethyl acetate–hexanes) to afford the bis(guanidine) **25** as an amorphous, colorless solid (1.30 g, 75%).

$R_f$ = 0.50 (1% triethylamine–50% ethyl acetate–hexanes; UV, CAM). $^1$H NMR (500 MHz, $CD_3OD$): δ 7.21 (m, 1H, $H_{13}$), 7.15 (d, J = 8.3 Hz, 1H, $H_{15}$), 6.52 (d, J = 2.2 Hz, 1H, $H_{17}$), 6.45 (dd, J = 8.3 Hz, 2.2 Hz, 1H, $H_{16}$), 6.19 (t, J = 3.2 Hz, 1H, $H_{12}$), 6.12–6.09 (m, 1H, $H_{11}$), 4.41 (d, J = 15.3 Hz, 1H, $H_{14}$), 4.30 (d, J = 15.3 Hz, 1H, $H_{14}$), 4.18–4.04 (m, 2H, $H_{20}$), 3.83–3.81 (m, 5H, $H_1$, $H_{10,18}$), 3.77 (s, 3H, $H_{19}$), 3.28 (td, = 7.0, 2.6 Hz, 2H, $H_{23}$), 2.18–2.11 (m, 3H, $H_{8,9}$), 1.67–1.57 (m, 4H, $H_{21,22}$), 1.52 (s, 9H, $H_{24}$), 1.52 (s, 9H, $H_{24}$), 1.39–1.21 (m, 12H, $H_{2–6}$). $^{13}$C NMR

(125 MHz, $CD_3OD$): δ 173.5 (C), 164.6 (C), 161.7 (C), 159.6 (C), 157.5 (C), 154.2 (C), 146.6 (CH), 130.0 (CH), 126.9 (C), 120.4 (C), 117.0 (C), 110.9 (CH), 110.4 (C), 105.2 (CH), 99.2 (CH), 85.1 (C), 84.5 (C) 80.4 (C), 69.4 ($CH_2$), 66.0 (CH), 56.6 (CH), 55.9 ($CH_3$), 55.8 ($CH_3$), 44.8 ($CH_2$), 41.7 (CH), 41.4 ($CH_2$), 35.9 ($CH_2$), 30.4 ($CH_2$) 30.0 ($CH_2$), 29.7 (2 × $CH_2$), 28.6 ($CH_3$), 28.3 ($CH_3$), 27.1 ($CH_2$), 27.0 ($CH_2$), 26.9 ($CH_2$), 19.0 ($CH_2$). IR (ATR-FTIR), $cm^{-1}$: 3290 (w), 2931 (m), 1718 (s), 1640 (s), 1615 (s). HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{41}H_{61}N_6O_8$, 765.4545; found, 765.4533. $[\alpha]_D^{20}$ +9.6 (*c* 5.20, $CH_3OH$).

*Synthesis of the alcohol **27**:*

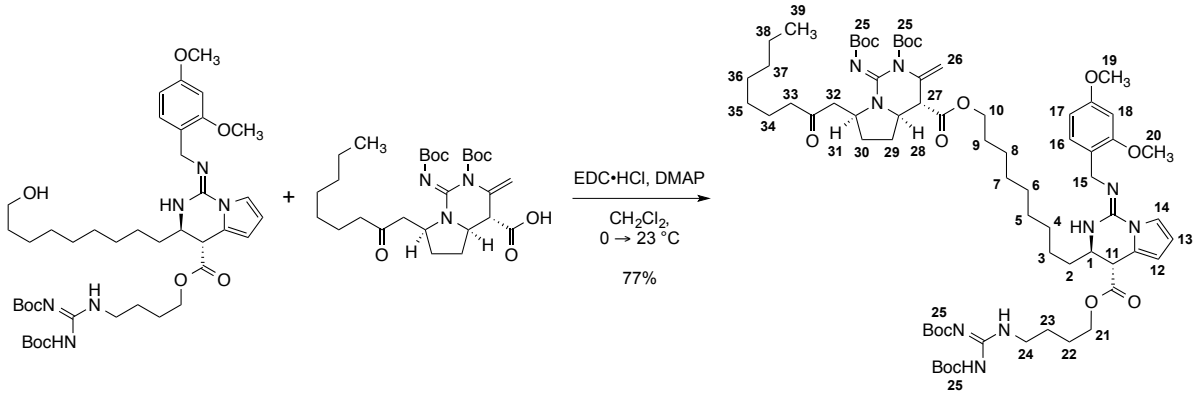



A screw-capped pressure vessel was charged with the bis(guanidine) **25** (112 mg, 147 μmol, 1 equiv), *para*-toluenesulfonic acid monohydrate (28.7 mg, 151 μmol, 1.03 equiv), and the catalyst **26** (11.3 mg, 22.0 μmol, 0.150 equiv) at 23 °C. The vessel was outfitted with a rubber septum and the headspace in the vessel was evacuated. The headspace was back-filled with argon. This process was repeated three times. A deoxygenated solution of *N*-methyl-2-pyrrolidinone and water (4:1, 600 μL) and degassed formic acid (22.0 μL, 588 μmol, 4.00 equiv) were added in sequence to the reaction vessel under argon at 23 °C. The vessel was then sealed. The reaction vessel was immersed in a sonicating bath until the reaction mixture became homogeneous. The resulting crimson solution was stirred for 3 d at 23 °C. The reaction vessel was then vented (*CAUTION*: pressure build-up). The brown product mixture was transferred to a separatory funnel and diluted with saturated aqueous sodium bicarbonate solution (5 mL). The diluted solution was extracted with ether (5 × 30 mL). The organic layers were combined and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 1% triethylamine–50% ethyl acetate–hexanes). The fractions containing product (TLC analysis) were collected and concentrated. The resulting residue was partitioned into eight portions and each portion was purified by preparatory thin-layer chromatography (eluting first with 1% triethylamine–33% ethyl acetate–hexanes, then 1% triethylamine–50% ethyl acetate–hexanes) to provide separately the alcohol **32** as a colorless solid (59.0 mg, 51%) and its C-11 diastereomer (23 mg, 20%).

$R_f$ = 0.23 (1% triethylamine–50% ethyl acetate–hexanes; UV, CAM). $^1$H NMR (500 MHz, $CD_3OD$): δ 7.21 (bs, 1H, $H_{14}$), 7.15 (d, J = 8.4 Hz, 1H, $H_{16}$), 6.51 (d, J = 2.3 Hz, 1H, $H_{18}$), 6.44 (dd, J = 8.3, 2.4 Hz, 1H, $H_{17}$), 6.18 (t, J = 3.3 Hz, 1H, $H_{13}$), 6.09 (d, J = 3.4 Hz, 1H, $H_{12}$), 4.40 (d, J = 15.4 Hz, 1H, $H_{15}$), 4.30 (d, J = 15.3 Hz, 1H, $H_{15}$), 4.16–4.07 (m, 2H, $H_{21}$), 3.85–3.78 (m, 2H, $H_{1,11}$), 3.82 (s, 3H, $H_{19}$), 3.77 (s, 3H, $H_{20}$), 3.53 (t, J = 6.7 Hz, 2H, $H_{10}$), 3.27 (t, J = 7.0 Hz, 2H, $H_{24}$), 1.67–1.60 (m, 2H, $H_{22}$), 1.60–1.54 (m, 2H, $H_{23}$), 1.54–1.48 (m, 11H, $H_{9,25}$), 1.47 (s, 9H, $H_{25}$), 1.34–1.20 (m, 14H, $H_{2–8}$). $^{13}$C NMR (125 MHz, $CD_3OD$): δ 173.5 (C), 164.6 (C), 161.6 (C), 159.6 (C), 157.5 (C), 154.2 (C), 146.6 (C), 129.9 (CH), 126.8 (C), 120.4 (C), 117.0 (CH), 110.9 (CH), 110.4 (CH), 105.1 (CH), 99.1 (CH), 84.4 (C), 80.4 (C), 66.0 ($CH_2$), 63.0 ($CH_2$), 56.6 (CH), 55.8 ($CH_3$), 55.8 ($CH_3$), 44.7 ($CH_2$), 41.6 (CH), 41.4 ($CH_2$), 35.9 ($CH_2$), 33.7 ($CH_2$), 30.7 ($CH_2$), 30.6 ($CH_2$), 30.6 ($CH_2$), 28.6 ($CH_3$), 28.3 ($CH_3$), 27.2 ($CH_2$), 27.0 ($CH_2$), 26.9 ($CH_2$), 26.9 ($CH_2$). One methylene carbon was not observed, which is believed to be due to coincidence with

an additonal resonance. IR (ATR-FTIR), $cm^{-1}$: 3329 (w), 2929 (s), 1722 (s), 1641 (s), 1615 (s). HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{41}H_{65}N_6O_9$, 785.4808; found, 785.4814. $[\alpha]_D^{20}$ +13.0 (*c* 20.0, $CH_3OH$).

*Synthesis of the penultimate intermediate **28**:*



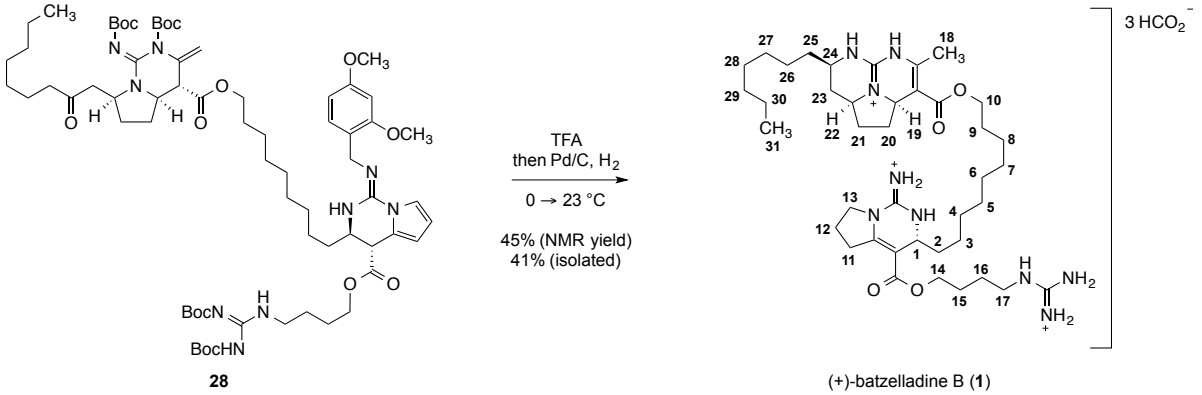

**27** **17** **28**

The carboxylic acid **17** (36.2 mg, 67.6 μmol, 1 equiv) was added to a stirred solution of the alcohol **27** (54.2 mg, 69.0 μmol, 1.02 equiv) in dichloromethane (1.4 mL) at 23 °C. The solution was then cooled to 0 °C for 15 min. 4-(Dimethylamino)pyridine (6.1 mg, 50 μmol, 0.74 equiv) and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (19.4 mg, 101 μmol, 1.50 equiv) were then added in sequence at 0 °C. The reaction mixture was warmed over 2 h to 23 °C, and was stirred for an additional 12 h at 23 °C. The product mixture was cooled to 0 °C for 15 min. The cooled product solution was diluted with saturated aqueous sodium chloride solution (10 mL). The diluted product solution was warmed over 15 min to 23 °C. The warmed biphasic mixture was transferred to a separatory funnel. The mixture was extracted with dichloromethane (3 × 5 mL). The organic layers were combined and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 1% triethylamine–33% ethyl acetate–hexanes) to afford the penultimate intermediate **28** as a colorless, powdered solid (67.4 mg, 77%).

$R_f$ = 0.19 (1% triethylamine–33% ethyl acetate–hexanes; UV, CAM). $^1$H NMR (500 MHz, $CD_3OD$): δ 7.21 (bs, 1H, $H_{14}$), 7.15 (d, J = 8.4 Hz, 1H, $H_{16}$), 6.52 (d, J = 2.2 Hz, 1H, $H_{18}$), 6.45 (dd, J = 8.2, 2.5 Hz, 1H, $H_{17}$), 6.18 (app t, J = 3.3 Hz, 1H, $H_{13}$), 6.10 (d, J = 3.4 Hz, 1H, $H_{12}$), 5.38 (s, 1H, $H_{26}$), 5.36 (s, 1H, $H_{26}$), 4.48–4.42 (m, 1H, $H_{31}$), 4.40 (d, J = 15.2 Hz, 1H, $H_{15}$), 4.31 (d, J = 15.3 Hz, 1H, $H_{15}$), 4.20–4.07 (m, 4H, $H_{10,21}$), 4.01–3.94 (m, 1H, $H_{28}$), 3.86–3.79 (m, 2H, $H_{1,11}$), 3.83 (s, 3H, $H_{19}$), 3.77 (s, 3H, $H_{20}$), 3.72 (d, J = 9.5 Hz, 1H, $H_{27}$), 3.30–3.25 (m, 2H, $H_{24}$), 2.86 (dd, J = 16.8, 3.6 Hz, 1H, $H_{32}$), 2.61 (dd, J = 16.7, 9.3 Hz, 1H, $H_{32}$), 2.43 (t, J = 7.4 Hz, 2H, $H_{33}$), 2.24–2.08 (m, 2H, $H_{29,30}$), 1.87–1.75 (m, 2H, $H_{29,30}$), 1.69–1.61 (m, 4H, $H_{9,22}$), 1.60–1.52 (m, 4H, $H_{23,34}$), 1.52 (s, 9H, $H_{25}$), 1.47 (s, 9H, $H_{25}$), 1.46 (s, 9H, $H_{25}$), 1.44 (s, 9H, $H_{25}$), 1.38–1.20 (m, 22H, $H_{2–8,35–38}$), 0.89 (t, J = 6.5 Hz, 3H, $H_{39}$). $^{13}$C NMR (125 MHz, $CD_3OD$): δ 210.9 (C), 173.3 (C), 171.0 (C), 164.5 (C), 161.7 (C), 160.8 (C), 159.6 (C), 157.5 (C), 154.2 (C), 151.9 (C), 151.3 (C), 146.7 (C), 137.6 (C), 130.1 (CH), 126.9 (C), 120.2 (C), 117.1 (CH), 114.1 ($CH_2$), 111.2 (CH), 110.6 (CH), 105.2 (CH), 99.2 (CH), 84.5 (C), 84.2 (C), 80.4 (C), 80.4 (C), 66.8 ($CH_2$), 66.1 ($CH_2$), 59.3 (CH), 57.5 ($CH_2$), 56.4 (CH), 55.9 ($CH_3$), 55.8 ($CH_3$), 55.5 (CH), 45.7 ($CH_2$), 44.7 (CH), 44.0 ($CH_2$), 41.7 (CH), 41.4 ($CH_2$), 35.9 ($CH_2$), 32.9 ($CH_2$), 30.6 ($CH_2$), 30.5 ($CH_2$), 30.4 ($CH_2$), 30.3 ($CH_2$), 30.2 ($CH_2$), 30.1 ($CH_2$), 29.6 ($CH_2$), 28.7 ($CH_3$), 28.6 ($CH_3$), 28.4

($CH_2$), 28.3 ($CH_3$), 28.3 ($CH_3$), 27.1 ($CH_2$), 27.0 ($CH_2$), 26.9 ($CH_2$), 24.8 ($CH_2$), 23.7 ($CH_2$), 14.4 ($CH_3$). Two methylene carbons are not observed, which is believed to be due to coincidence with another resonance. IR (ATR-FTIR), $cm^{-1}$: 3332 (w), 2930 (m), 2856 (w), 1718 (s), 1612 (s). HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{69}H_{108}N_9O_{15}$, 1302.7959; found, 1302.8019. $[\alpha]_D^{20}$ +8.9 (*c* 18.0, $CH_3OH$).

*Synthesis of (+)-batzelladine B (**1**)*:

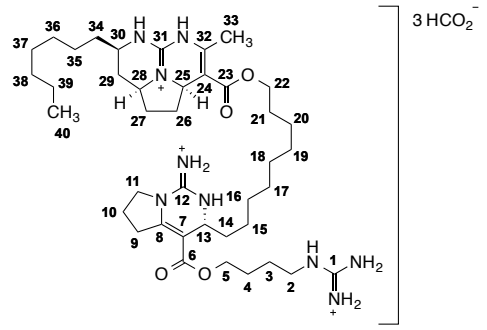



A one-dram vial was charged with the penultimate intermediate **28** (20.0 mg, 15.4 μmol, 1 equiv) and palladium (5 wt% on carbon, 9.5 mg, 4.6 μmol, 0.30 equiv). The vessel was sealed with a rubber septum and the headspace was evacuated. The evacuated vessel was back-filled with argon (1 atm). This process was repeated three times. The vessel was then cooled in an ice bath to 0 °C. Chilled (−15 °C), degassed, and freshly-distilled trifluoroacetic acid (300 μL) was added to the vessel under argon at 0 °C. The reaction vessel was immediately removed from the ice bath and the reaction mixture allowed to warm over 20 min to 23 °C. The reaction mixture was stirred for 1 h at 23 °C under argon. The reaction mixture was cooled to –78 °C. The headspace in the reaction vessel was then evacuated. The reaction mixture was allowed to warm to 23 °C under static vacuum. The headspace in the reaction vessel was then back-filled with dihydrogen (1 atm). This process was repeated twice. The reaction mixture was then stirred for 15 h at 23 °C under dihydrogen. The product mixture was then cooled over 30 min to 0 °C. The balloon of dihydrogen was replaced with a balloon of argon. The mixture was then diluted with methanol (deoxygenated by sparging with dinitrogen, 1.0 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C. The diluted mixture was then warmed over 15 min to 23 °C. The resulting suspension was filtered through a pad of celite (0.5 cm × 2.0 cm). The filter cake was washed with methanol (3 × 1.0 mL). The filtrates were combined and the combined filtrates were concentrated. $^1$H NMR analysis of the residue against an internal standard (1,3,5-trimethoxybenzene) indicated a 45% yield of product. The residue obtained from this mixture was purified by preparatory high-performance liquid chromatography (eluting with 0.1% trifluoroacetic acid–10% acetonitrile–water initially, grading to 0.1% trifluoroacetic acid–50% acetonitrile–water over 70 min, 40 injections). The fractions containing product (UPLC/MS analysis) were combined and the combined fractions were lyophilized. The residue obtained was further purified by preparatory thin-layer chromatography (eluting with 3.5% formic acid–10% methanol–35% acetone–dichloromethane) to furnish (+)-batzelladine B (**1**) as a colorless solid (5.5 mg, 40%).

$^1$H NMR (600 MHz, $CD_3OD$): δ 4.50 (dd, J = 10.0, 6.0 Hz, 1H, $H_{19}$), 4.38 (t, J = 5.9 Hz, 1H, $H_1$), 4.21 (t, J = 6.3 Hz, 1H, $H_{14}$), 4.20–4.09 (m, 2H, $H_{10}$), 3.84–3.75 (m, 2H, $H_{13,22}$), 3.70–3.63 (m, 1H, $H_{13}$), 3.53–3.48 (m, 1H, $H_{24}$), 3.34–3.32 (m, 1H, $H_{11}$), 3.22 (t, J = 7.0 Hz, 2H, $H_{17}$), 2.98 (dt, J = 18.9, 9.7 Hz, 1H, $H_{11}$), 2.54–2.48 (m, 1H, $H_{20}$), 2.41 (ddd, J = 13.2, 5.2, 2.7 Hz, 1H, $H_{23}$), 2.30 (s, 3H, $H_{18}$), 2.26–2.19 (m, 1H, $H_{12}$), 2.18–2.05 (m, 2H, $H_{12,21}$), 1.79–1.71 (m, 4H, $H_{15,16}$),

1.70–1.65 (m, 3H, $H_{9,20}$), 1.64–1.58 (m, 3H, $H_{21,25}$), 1.59–1.53 (m, 2H, $H_2$), 1.50–1.40 (m, 4H, $H_{3,8}$), 1.40–1.25 (m, 19H, $H_{4–7,23,26–30}$), 0.91 (t, J = 6.6 Hz, 3H, $H_{31}$). $^{13}$C NMR (150 MHz, $CD_3OD$): δ 166.9 (C), 166.2 (C), 158.8 (C), 153.3 (C), 152.9 (C), 147.6 (C), 144.9 (C), 103.1 (C), 102.5 (C), 65.5 ($CH_2$), 65.2 ($CH_2$), 58.2 (CH), 57.1 (CH), 51.4 (CH), 51.1 (CH), 42.0 ($CH_2$), 37.5 ($CH_2$), 34.7 ($CH_2$), 34.0 ($CH_2$), 33.9 ($CH_2$), 32.9 ($CH_2$), 32.0 ($CH_2$), 30.5 ($CH_2$), 30.5 ($CH_2$), 30.5 ($CH_2$), 30.3 ($CH_2$), 30.3 ($CH_2$), 29.7 ($CH_2$), 27.6 ($CH_2$), 27.2 ($CH_2$), 27.0 ($CH_2$), 26.7 ($CH_2$), 26.2 ($CH_2$), 25.2 ($CH_2$), 23.7 ($CH_2$), 22.9 ($CH_2$), 17.5 ($CH_3$), 14.4 ($CH_3$). Two methylene carbons are not observed: one is obfuscated by the solvent signal and the other is believed to be coincident with another signal at 30.3–30.5 ppm. IR (ATR-FTIR), $cm^{-1}$: 3357 (w), 3189 (w), 2920 (s), 2851 (s), 1660 (m), 1633 (m). HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{40}H_{68}N_9O_4$, 738.5394; found, 738.5388; Natural: $[\alpha]_D^{25}$ +44.3 (*c* 3.7, solvent not reported).[12] Synthetic: $[\alpha]_D^{20}$ +6.3 (*c* 1.6, $CH_3OH$).

Comparison of $^1$H NMR Data of Natural and Synthetic (+)-Batzelladine B (**1**).[a]



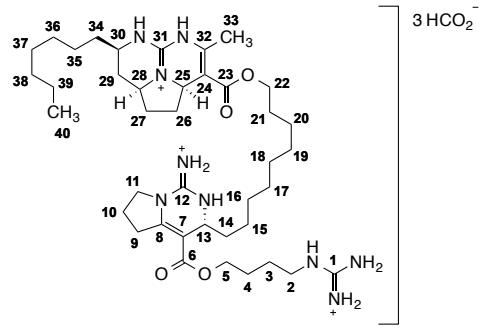

(+)-batzelladine B (**1**)

| Position | $^1$H NMR Synthetic **1** (methanol-$d_4$) | $^1$H NMR Natural **1** (methanol-$d_4$) |
|---|---|---|
| 2 | 3.22 (t, 7.0) | 3.21 (t, 7.1) |
| 3 | 1.79–1.71 (m) | 1.69 (m) |
| 4 | 1.79–1.71 (m) | 1.75 (m) |
| 5 | 4.21 (t, 6.3) | 4.20 (t, 6.0) |
| 9α | 2.98 (dt, 18.9, 9.7) | 2.96 (m) |
| 9β | 3.34–3.32 (m) | 3.32 (m) |
| 10α | 2.18–2.05 (m) | 2.11 (m) |
| 10β | 2.26–2.19 (m) | 2.21 (m) |
| 11α | 3.70–3.63 (m) | 3.63 (m) |
| 11β | 3.84–3.75 (m) | 3.79 (m) |
| 13 | 4.38 (t, 5.9) | 4.38 (t, 6.0) |
| 14 | 1.59–1.53 (m) | 1.55 (m) |
| 15 | 1.50–1.40 (m) | 1.47 (m) |
| 16 | 1.40–1.25 (m) | 1.29 (bs) |
| 17 | 1.40–1.25 (m) | 1.29 (bs) |
| 18 | 1.40–1.25 (m) | 1.29 (bs) |
| 19 | 1.40–1.25 (m) | 1.29 (bs) |
| 20 | 1.50–1.40 (m) | 1.42 (m) |
| 21 | 1.71–1.64 (m) | 1.63 (m) |
| 22 | 4.20–4.09 (m) | 4.14 (m) |
| 25 | 4.50 (dd, 10.0, 6.0) | 4.50 (dd, 6.0, 4.0) |
| 26α | 1.71–1.64 (m) | 1.67 (m) |
| 26β | 2.54–2.48 (m) | 2.48 (m) |
| 27α | 1.64–1.59 (m) | 1.57 (m) |
| 27β | 2.18–2.05 (m) | 2.10 (m) |
| 28 | 3.84–3.75 (m) | 3.75 (m) |
| 29α | 1.40–1.25 (m) | 1.32 (m) |
| 29β | 2.41 (ddd, 13.2, 5.2, 2.7) | 2.37 (m) |
| 30 | 3.53–3.48 (m) | 3.46 (m) |
| 33 | 2.30 (s) | 2.30 (s) |
| 34 | 1.64–1.59 (m) | 1.60 (m) |

| | | |
|---|---|---|
| 35 | 1.40–1.25 (m) | 1.30 (m) |
| 36 | 1.40–1.25 (m) | 1.29 (bs) |
| 37 | 1.40–1.25 (m) | 1.29 (bs) |
| 38 | 1.40–1.25 (m) | 1.29 (bs) |
| 39 | 1.40–1.25 (m) | 1.29 (bs) |
| 40 | 0.91 (t, 6.6) | 0.88 (t, 6.0) |

[a] Data for natural (+)-batzelladine B (**1**) were obtained from the following reference: Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; De Brosse, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, C.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Potts, B. C. M. *J. Org. Chem.* **1995**, *60*, 1182–1188.

Comparison of $^{13}$C NMR Data of Natural and Synthetic (+)-Batzelladine B (**1**).[a]




(+)-batzelladine B (**1**)

| Position | $^{13}$C NMR Synthetic **1** (methanol-$d_4$) | $^{13}$C NMR Natural **1** (methanol-$d_4$)[b] |
|---|---|---|
| 1 | 158.7 | 158.7 |
| 2 | 42.0 | 42.0 |
| 3 | 26.7 | 26.6 |
| 4 | 27.0 | 27.0 |
| 5 | 65.2 | 65.1 |
| 6 | 166.2 | 166.2 |
| 7 | 103.1 | 103.1 |
| 8 | 152.9 | 152.8 |
| 9 | 32.0 | 31.9 |
| 10 | 22.9 | 22.9 |
| 11 | [c] | 48.8 |
| 12 | 153.3 | 153.2 |
| 13 | 51.4 | 51.4 |
| 14 | 37.5 | 37.5 |
| 15 | 25.2 | 25.2 |
| 16 | 30.3–30.5 | 30.3–30.6 |
| 17 | 30.3–30.5 | 30.3–30.6 |
| 18 | 30.3–30.5 | 30.3–30.6 |
| 19 | 30.3–30.5 | 30.3–30.6 |
| 20 | 27.2 | 27.1 |
| 21 | 29.7 | 29.7 |
| 22 | 65.5 | 65.5 |
| 23 | 166.9 | 166.9 |
| 24 | 102.5 | 102.6 |
| 25 | 58.2 | 58.9 |
| 26 | 34.0 | 34.0 |
| 27 | 27.6 | 27.6 |
| 28 | 57.1 | 57.1 |
| 29 | 33.9 | 33.9 |
| 30 | 51.1 | 51.1 |
| 31 | 147.6 | 147.6 |
| 32 | 144.9 | 144.8 |
| 33 | 17.5 | 17.5 |
| 34 | 34.7 | 34.7 |

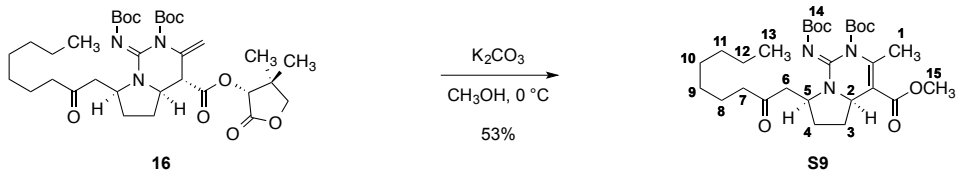
| | | |
|---|---|---|
| 35 | 26.2 | 25.9 |
| 36 | 30.3–30.5 | 30.3–30.6 |
| 37 | 30.3–30.5 | 30.3–30.6 |
| 38 | 32.9 | 33.0 |
| 39 | 23.7 | 23.7 |
| 40 | 14.4 | 14.4 |

[a] Data for natural (+)-batzelladine B (**1**) were obtained from the following reference: Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; De Brosse, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, C.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Potts, B. C. M. *J. Org. Chem.* **1995**, *60*, 1182–1188. [b] In the isolation report, the chemical shifts for **1** are mislabeled as belonging to (+)-batzelladine A. [c] Signal was buried under the solvent ($CD_3OD$) signal.

**Determination of the Diastereoselectivity in the Hydrogenation of the Vessel Fragment.**

The diastereoselectivity in the reduction of the vessel fragment in the final step of the sequence (**28→1**) could not be readily determined. Consequently, the selectivity was determined using the vessel analog **S9** as a model system.

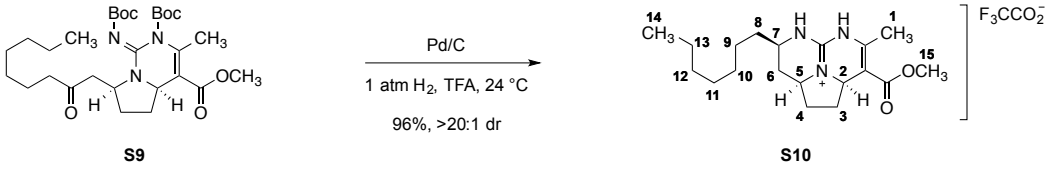
*Synthesis of the methyl ester **S9**:*




A solution of the pantolactone ester **16** (134 mg, 207 μmol, 1 equiv) in methanol (4.2 mL) was cooled to 0 °C for 30 min. Potassium carbonate (145 mg, 1.05 mmol, 5.07 equiv) was then added in a single portion. The resultant pale yellow suspension was stirred for 14 h at 0 °C. The product mixture was diluted with saturated aqueous ammonium chloride solution (10 mL) at 0 °C. The diluted mixture was transferred to a separatory funnel and extracted with dichloromethane (3 × 5 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (5 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to afford the methyl ester **S9** as a colorless, powdered solid (59.1 mg, 53%).

$R_f$ = 0.24 (25% ethyl acetate–hexanes). $^1$H NMR (500 MHz, $CD_3OD$): δ 4.47–4.39 (m, 1H, $H_5$), 4.33–4.24 (m, 1H, $H_2$), 3.80 (s, 3H, $H_{15}$), 3.00 (dd, J = 16.6, 3.0 Hz, 1H, $H_6$), 2.49–2.40 (m, 3H, $H_{6,7}$), 2.38 (s, 3H, $H_1$), 2.18–2.07 (m, 1H, $H_3$), 1.93–1.84 (m, 1H, $H_4$), 1.84–1.77 (m, 1H, $H_4$), 1.56–1.51 (m, 3H, $H_{3,8}$), 1.50 (s, 9H, $H_{14}$), 1.48 (s, 9H, $H_{14}$), 1.33–1.28 (m, 8H, $H_{9–12}$), 0.89 (t, J = 6.8 Hz, 3H, $H_{13}$). $^{13}$C NMR (125 MHz, $CD_3OD$): δ 209.7 (C), 165.0 (C), 159.6 (C), 148.6 (C), 148.0 (C), 145.6 (C), 123.5 (C), 84.2 (C), 79.0 (C), 56.9 (CH), 54.6 (CH), 50.7 ($CH_3$), 43.4 ($CH_2$), 42.5 ($CH_2$), 31.5 ($CH_2$), 29.0 ($CH_2$), 28.8 ($CH_2$), 28.8 ($CH_2$), 28.0 ($CH_2$), 27.3 ($CH_3$), 26.9 ($CH_3$), 23.5 ($CH_2$), 22.2 ($CH_2$), 17.7 ($CH_3$), 13.0 ($CH_3$). IR (ATR-FTIR), cm$^{-1}$: 2928 (s), 2856 (m), 1719 (s), 1611 (s). HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{29}H_{48}N_3O_7$, 550.3487; found, 550.3489. $[\alpha]_D^{20}$ +40.0 (*c* 11.0, $CH_3OH$).

*Synthesis of the vessel analog **S10**:*




**S9** **S10**

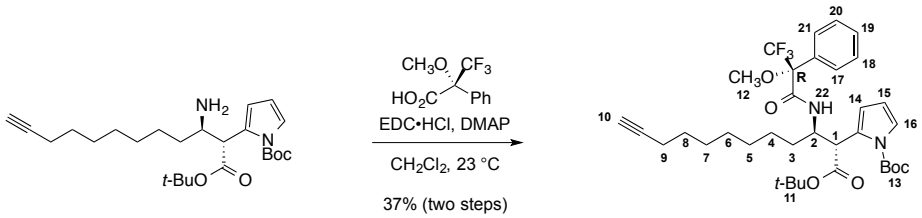
A 1-dram vial equipped with a stir bar was charged sequentially with the methyl ester **S9** (8.7 mg, 16 μmol, 1 equiv) and palladium (5 wt% on carbon, 6.7 mg, 3.3 μmol, 0.20 equiv). The vessel was fitted with a rubber septum and evacuated. The vessel was kept under static vacuum and then fixed with a balloon of dihydrogen. Cold (~0 °C), degassed, freshly-distilled trifluoroacetic acid (350 μL) was then added. The resulting suspension was stirred for 3 h at 23 °C. The product mixture was cooled to 0 °C fin an ice bath for 15 min. The cooled product mixture was diluted rapidly with methanol (deoxygenated by sparging with dinitrogen, 1.0 mL). The balloon of dihydrogen was removed and the mixture was placed under a positive pressure of argon for 30 min at 0 °C. The reaction vessel was removed from the ice bath and the solution was filtered through a pad of celite (0.5 × 1.0 cm). The filter cake was washed with methanol (3 × 1.00 mL). The filtrates were collected and combined. The combined filtrates were concentrated to afford the vessel methyl ester **S10** (6.8 mg, 96%). $^{1}$H NMR analysis of the unpurified product residue indicated a single C-7 diastereomer had been formed.

$^{1}$H NMR (500 MHz, $CD_3OD$): δ 4.53 (dd, J = 10.0, 6.1 Hz, 1H, $H_2$), 3.85–3.78 (m, 1H, $H_5$), 3.74 (s, 3H, $H_{15}$), 3.52 (dtd, J = 11.0, 6.6, 2.8 Hz, 1H, $H_7$), 2.52 (dddd, J = 12.2, 9.0, 6.0, 3.2 Hz, 1H, $H_3$), 2.42 (ddd, J = 13.3, 5.2, 2.8 Hz, 1H, $H_6$), 2.30 (s, 3H, $H_1$), 2.17 (app dq, J = 12.7, 8.7 Hz, 1H, $H_4$), 1.78–1.66 (m, 2H, $H_{3,8}$), 1.65–1.57 (m, 2H, $H_{4,8}$), 1.49–1.27 (m, 11H, $H_{6,9–13}$), 0.91 (t, J = 6.6 Hz, 3H, $H_{14}$). $^{13}$C NMR (125 MHz, $CD_3OD$): δ 167.0 (C), 147.3 (C), 144.1 (C), 103.1 (C), 58.3 (CH), 57.2 (CH), 51.8 ($CH_3$), 51.5 (CH), 34.9 ($CH_2$), 33.9 ($CH_2$), 33.8 ($CH_2$), 32.9 ($CH_2$), 30.4 ($CH_2$), 30.3 ($CH_2$), 27.5 ($CH_2$), 26.2 ($CH_2$), 23.7 ($CH_2$), 17.7 ($CH_3$), 14.4 ($CH_3$). IR (ATR-FTIR, $cm^{-1}$: 2928 (m), 2858 (w), 1689 (s), 1533 (w). HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{19}H_{32}N_3O_2$, 334.2489; found, 334.2490. $[\alpha]_D^{20}$ +84 (*c* 0.93, $CH_3OH$)

**Determination of Stereochemistry of the Mannich Addition Product 21.**

The C-2 stereochemistry of the Mannich addition product **21** was determined by deprotection (**21**→**S7**), followed by Mosher ester analysis.[13]

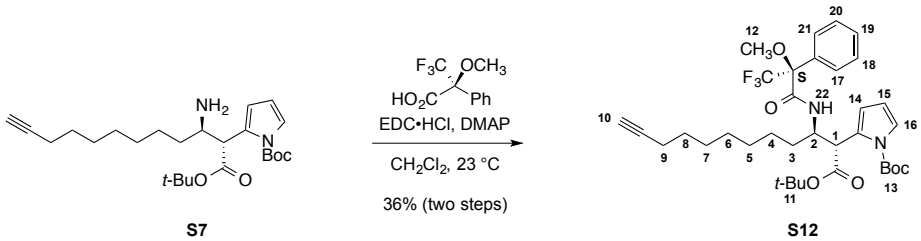
*Synthesis of the (R)-Mosher amide **S11**:*




1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (40.5 mg, 211 μmol, 3.30 equiv) and 4-(dimethylamino)pyridine (24.1 mg, 197 μmol, 3.08 equiv) were added in sequence to a solution of the amine **S7** (nominally 27.4 mg, 64.0 μmol, 1 equiv) and (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (45.4 mg, 194 μmol, 3.02 equiv) in dichloromethane (1.0 mL) at 23 °C. The reaction mixture was stirred for 2.5 h at 23 °C. An additional portion of 4-(dimethylamino)pyridine (4.6 mg, 38 μmol, 0.59 equiv) was added to the reaction mixture at 23 °C. The reaction mixture was stirred for an additional 12.5 h at 23 °C. The product mixture was diluted with ethyl acetate (10 mL). The diluted product mixture was washed sequentially with water (2.0 mL), saturated aqueous ammonium chloride solution (2.0 mL), and saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparatory thin-layer chromatography (eluting with 1% triethylamine–10% ethyl acetate–hexanes) to furnish the (*R*)-Mosher amide **S11** (15.5 mg, 37% from **21**) as a light yellow oil.

$R_f$ = 0.36 (1% triethylamine–10% ethyl acetate–hexanes; UV, CAM). $^1$H NMR (500 MHz, $CDCl_3$): δ 7.52–7.50 (m, 2H, $H_{17,21}$), 7.36–7.33 (m, 3H, $H_{18–20}$), 7.16–7.15 (m, 1H, $H_{16}$), 7.08 (d, J = 9.6 Hz, 1H, $H_{22}$), 6.30–6.29 (m, 1H, $H_{14}$), 6.10 (t, J = 3.3 Hz, 1H, $H_{15}$), 4.62 (qd, J = 9.4, 2.9 Hz, 1H, $H_2$), 4.55 (d, J = 8.0 Hz, 1H, $H_1$), 3.25 (s, 3H, $H_{12}$), 2.15 (td, J = 7.1, 2.5 Hz, 2H, $H_9$), 1.93 (t, J = 2.5 Hz, 1H, $H_{10}$), 1.68 (ddd, J = 15.7, 10.1, 5.5 Hz, 1H, $H_3$), 1.59 (s, 9H, $H_{13}$), 1.51–1.43 (m, 10H, $H_{3,11}$), 1.39–1.15 (m, 10H, $H_{4–8}$). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 170.3 (C), 165.7 (C), 150.0 (C), 133.4 (C), 130.3 (C), 129.4 (CH), 128.4 (CH), 127.5 (CH), 121.9 (CH), 113.1 (CH), 110.6 (CH), 84.8 (C), 84.3 (C), 81.7 (C), 68.3 (CH), 54.9 ($CH_3$), 51.4 (CH), 49.0 (CH), 33.8 ($CH_2$), 29.3 ($CH_2$), 29.1 ($CH_2$), 28.7 ($CH_2$), 28.6 ($CH_2$), 28.1 ($CH_3$), 28.0 ($CH_3$), 26.0 ($CH_2$), 18.5 ($CH_2$). IR (ATR-FTIR), cm$^{-1}$: 3410 (w), 3311 (w), 2934 (m), 1729 (s), 1699 (s). HRMS-CI (m/z): $[M + Na]^+$ calcd for $C_{35}H_{47}F_3N_2NaO_6$, 671.3278; found, 671.3322. $[\alpha]_D^{20}$ +6.1 (*c* 9.80, $CH_3OH$).

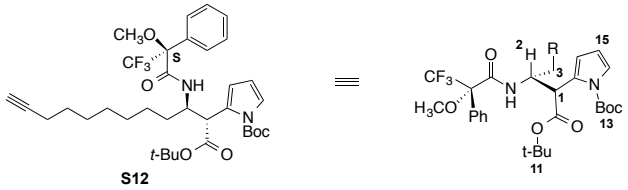
*Synthesis of (S)-Mosher amide **S12**:*

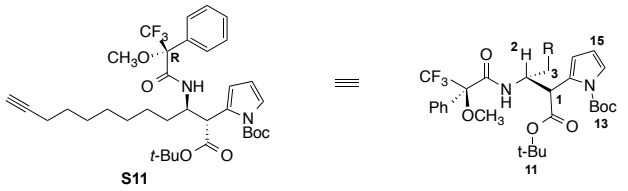



1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (38.6 mg, 201 μmol, 3.15 equiv) and 4-(dimethylamino)pyridine (31.1 mg, 255 μmol, 3.98 equiv) were added in sequence to a solution of the amine **S7** (nominally 27.4 mg, 63.3 μmol, 1 equiv) and (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (47.0 mg, 201 μmol, 3.15 equiv) in dichloromethane (1.0 mL) at 23 °C. The reaction mixture was stirred for 15 h at 23 °C. The product mixture was then diluted with ethyl acetate (10 mL). The diluted product mixture was washed sequentially with water (2.0 mL), saturated aqueous ammonium chloride solution (2.0 mL), and saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparatory thin-layer chromatography (eluting with 1% triethylamine–10% ethyl acetate–hexanes) to furnish the (*S*)-Mosher amide **S12** (14.8 mg, 36%) as a light yellow oil.

$R_f$ = 0.26 (1% triethylamine–10% ethyl acetate–hexanes; UV, CAM). $^1$H NMR (500 MHz, $CDCl_3$): δ 7.36 (d, J = 9.9 Hz, 1H, $H_{22}$), 7.33–7.26 (m, 3H, $H_{18–20}$), 7.20 (d, J = 7.6 Hz, 2H, $H_{17,21}$), 7.01–7.00 (m, 1H, $H_{16}$), 6.29–6.28 (m, 1H, $H_{14}$), 6.07 (t, J = 3.4 Hz, 1H, $H_{15}$), 4.63 (qd, J = 9.1, 2.9 Hz, 1H, $H_2$), 4.53 (d, J = 8.3 Hz, 1H, $H_1$), 3.30 (s, 3H, $H_{12}$), 2.17 (td, J = 7.1, 2.6 Hz, 2H, $H_9$), 1.93 (t, J = 2.6 Hz, 1H, $H_{10}$), 1.73 (ddd, J = 12.7, 8.6, 5.7 Hz, 1H, $H_3$), 1.60–1.25 (m, 29H, $H_{3,4–8,11,13}$). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 170.3 (C), 165.6 (C), 150.0 (C), 132.6 (C), 130.3 (C), 129.1 (CH), 128.6 (CH), 128.0 (CH), 121.8 (CH), 113.1 (CH), 110.5 (CH), 84.9 (C), 84.3 (C), 81.2 (C), 68.2 (CH), 54.9 ($CH_3$), 51.5 (CH), 49.2 (CH), 34.4 ($CH_2$), 29.4 ($CH_2$), 29.1 ($CH_2$), 28.8 ($CH_2$), 28.6 ($CH_2$), 28.1 ($CH_3$), 28.0 ($CH_3$), 25.7 ($CH_2$), 18.5 ($CH_2$). IR (ATR-FTIR), $cm^{-1}$: 3401 (w), 3310 (w), 2934 (m), 2858 (w), 1728 (s), 1698 (s). HRMS-CI (m/z): $[M + Na]^+$ calcd for $C_{35}H_{47}F_3N_2NaO_6$, 671.3278; found, 671.3362. $[\alpha]_D^{20}$ +4.7 (*c* 27.8, $CH_3OH$).

*Comparison of $^1$H NMR data between the (R)-Mosher amide **S11** and the (S)-Mosher amide **S12**:*




| H | $\delta_S$ (ppm) | $\delta_R$ (ppm) | $\Delta\delta_{S-R}$ (ppm) |
|---|---|---|---|
| $H_{13}$ | 1.55 | 1.59 | -0.04 |
| $H_{15}$ | 6.07 | 6.10 | -0.03 |
| $H_1$ | 4.53 | 4.55 | -0.02 |
| $H_{11}$ | 1.43 | 1.44 | -0.01 |
| $H_2$ | 4.63 | 4.62 | +0.01 |
| $H_{3a}$ | 1.73 | 1.68 | +0.05 |

**Crystallographic Data for the Diazepenium 19:**

Single crystals of $C_{19}H_{22}F_3N_3O_7$ spider-15033 were grown by vapor diffusion crystallization from acetonitrile with diethyl ether as anti-solvent. For the structure of spider-15033, low-temperature diffraction data (ω-scans) were collected on a Rigaku R-AXIS RAPID diffractometer coupled to an R-AXIS RAPID imaging plate detector with Mo Kα radiation (λ = 0.71073 Å). All structures were solved by direct methods using SHELXT and were refined against $F^2$ on all data by full-matrix least squares with SHELXL.[14] All non-hydrogen atoms were refined anisotropically. Unless stated otherwise, hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). Hydrogen atoms H2, H1A, and H1B were found in the difference map and semi-freely refined. These hydrogen atoms were also refined as a part of donor-acceptor hydrogen bond interactions. The full numbering scheme of spider-15033 can be found in the Supporting Information. Full details of the X-ray structure determination are located in the CIF, also included in the Supporting Information. CCDC number 1400311 (spider-15033) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

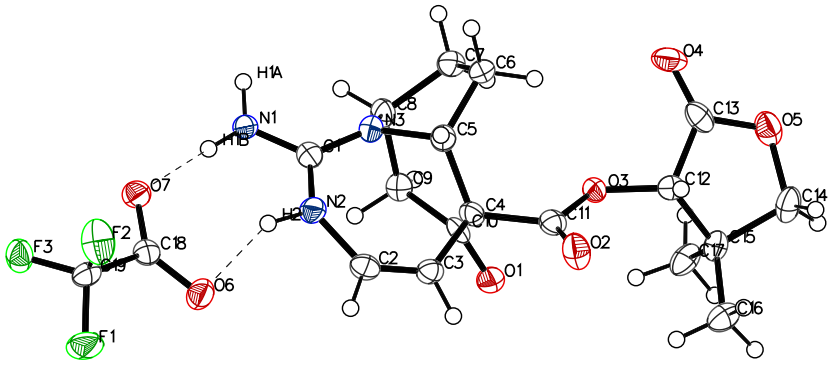



**Figure S1.** The full numbering scheme of spider-15033. All atoms shown are depicted with 50% thermal contours. The hydrogen atoms are shown as spheres. Atom C4 has S chirality, C5 has R; C8 has S; C12 has R.

**Table S2**. Crystal data and structure refinement for spider-15033.

| | | |
|---|---|---|
| Identification code | spider-15033 | |
| Empirical formula | $C_{19}H_{22}F_3N_3O_7$ | |
| Formula weight | 461.39 | |
| Temperature | 93(2) K | |
| Wavelength | 0.71075 Å | |
| Crystal system | Monoclinic | |
| Space group | $P\,2_1$ | |
| Unit cell dimensions | a = 9.4094(3) Å | α = 90°. |
| | b = 11.7301(3) Å | β = 99.289(7)°. |
| | c = 9.5007(6) Å | γ = 90°. |
| Volume | 1034.87(8) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.481 $Mg/m^3$ | |
| Absorption coefficient | 0.130 $mm^{-1}$ | |
| F(000) | 480 | |
| Crystal size | 0.200 x 0.190 x 0.180 $mm^3$ | |
| Crystal color and habit | Colorless Block | |
| Diffractometer | Rigaku R-AXIS RAPID imaging plate | |
| Θ range for data collection | 3.318 to 25.010°. | |
| Index ranges | $-11 \le h \le 11$, $-13 \le k \le 13$, $-11 \le l \le 11$ | |
| Reflections collected | 33505 | |
| Independent reflections | 3647 [R(int) = 0.0830] | |
| Observed reflections (I > 2σ(I)) | 3299 | |
| Completeness to θ = 25.010° | 99.7 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.977 and 0.873 | |
| Solution method | SHELXT-2014/5 (Sheldrick, 2014) | |
| Refinement method | SHELXL-2014/7 (Sheldrick, 2014) | |
| Data / restraints / parameters | 3647 / 1 / 303 | |
| Goodness-of-fit on $F^2$ | 1.162 | |
| Final R indices [I>2σ(I)] | R1 = 0.0510, wR2 = 0.0721 | |
| R indices (all data) | R1 = 0.0573, wR2 = 0.0736 | |
| Absolute structure parameter | -0.1(4) | |
| Largest diff. peak and hole | 0.211 and -0.178 $e.Å^{-3}$ | |

**Table S3**. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for spider-15033. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| F(1) | 3692(3) | 5060(2) | 7176(3) | 56(1) |
| F(2) | 2825(3) | 3895(3) | 8560(3) | 47(1) |
| F(3) | 4129(2) | 3280(2) | 7076(3) | 37(1) |
| O(6) | 1034(3) | 4789(2) | 5821(3) | 35(1) |
| O(7) | 1375(3) | 2891(2) | 5792(3) | 29(1) |
| C(18) | 1703(4) | 3886(4) | 6151(4) | 25(1) |
| C(19) | 3097(4) | 4032(4) | 7229(4) | 29(1) |
| O(1) | 5001(3) | 5444(2) | 573(3) | 29(1) |
| O(2) | 3718(3) | 6281(3) | 3957(3) | 38(1) |
| O(3) | 2665(3) | 5138(2) | 2182(3) | 23(1) |
| O(4) | 279(3) | 3698(3) | 2070(3) | 37(1) |
| O(5) | -1060(3) | 5193(3) | 1203(3) | 36(1) |
| N(1) | 8641(4) | 2256(3) | 3983(4) | 26(1) |
| N(2) | 8207(4) | 4077(3) | 4699(4) | 27(1) |
| N(3) | 6340(3) | 3013(3) | 3451(4) | 24(1) |
| C(1) | 7730(4) | 3109(4) | 4036(4) | 24(1) |
| C(2) | 7678(5) | 5192(4) | 4369(4) | 28(1) |
| C(3) | 6451(4) | 5546(4) | 3652(4) | 25(1) |
| C(4) | 5152(4) | 4846(3) | 3004(4) | 24(1) |
| C(5) | 5180(4) | 3709(3) | 3848(4) | 25(1) |
| C(6) | 3905(4) | 2901(4) | 3443(5) | 27(1) |
| C(7) | 4204(5) | 2310(4) | 2069(5) | 30(1) |
| C(8) | 5795(4) | 2564(4) | 1992(4) | 27(1) |
| C(9) | 5954(4) | 3557(3) | 984(4) | 26(1) |
| C(10) | 5303(4) | 4665(4) | 1403(4) | 23(1) |
| C(11) | 3798(4) | 5525(4) | 3111(4) | 26(1) |
| C(12) | 1286(4) | 5627(3) | 2253(4) | 24(1) |
| C(13) | 169(5) | 4707(4) | 1866(4) | 29(1) |
| C(14) | -834(5) | 6417(4) | 1074(5) | 36(1) |
| C(15) | 800(4) | 6558(4) | 1161(4) | 27(1) |
| C(16) | 1297(5) | 7758(4) | 1643(5) | 34(1) |
| C(17) | 1250(5) | 6266(4) | -285(4) | 34(1) |

**Table S4**. Bond lengths [Å] and angles [°] for spider-15033.

| | |
|---|---|
| F(1)-C(19) | 1.334(5) |
| F(2)-C(19) | 1.340(5) |
| F(3)-C(19) | 1.338(5) |
| O(6)-C(18) | 1.246(5) |
| O(7)-C(18) | 1.241(5) |
| C(18)-C(19) | 1.537(5) |
| O(1)-C(10) | 1.210(5) |
| O(2)-C(11) | 1.206(5) |
| O(3)-C(11) | 1.349(5) |
| O(3)-C(12) | 1.430(4) |
| O(4)-C(13) | 1.201(5) |
| O(5)-C(13) | 1.351(5) |
| O(5)-C(14) | 1.460(5) |
| N(1)-C(1) | 1.324(5) |
| N(1)-H(1A) | 0.93(5) |
| N(1)-H(1B) | 0.88(5) |
| N(2)-C(1) | 1.341(5) |
| N(2)-C(2) | 1.416(5) |
| N(2)-H(2) | 0.95(5) |
| N(3)-C(1) | 1.341(5) |
| N(3)-C(5) | 1.460(5) |
| N(3)-C(8) | 1.495(5) |
| C(2)-C(3) | 1.309(6) |
| C(2)-H(2A) | 0.9500 |
| C(3)-C(4) | 1.518(5) |
| C(3)-H(3) | 0.9500 |
| C(4)-C(11) | 1.520(6) |
| C(4)-C(5) | 1.554(5) |
| C(4)-C(10) | 1.565(6) |
| C(5)-C(6) | 1.529(6) |
| C(5)-H(5) | 1.0000 |
| C(6)-C(7) | 1.543(6) |
| C(6)-H(6A) | 0.9900 |
| C(6)-H(6B) | 0.9900 |
| C(7)-C(8) | 1.539(6) |
| C(7)-H(7A) | 0.9900 |
| C(7)-H(7B) | 0.9900 |
| C(8)-C(9) | 1.531(5) |
| C(8)-H(8) | 1.0000 |
| C(9)-C(10) | 1.516(5) |
| C(9)-H(9A) | 0.9900 |
| C(9)-H(9B) | 0.9900 |
| C(12)-C(13) | 1.511(6) |
| C(12)-C(15) | 1.525(6) |

| | |
|---|---|
| C(12)-H(12) | 1.0000 |
| C(14)-C(15) | 1.535(6) |
| C(14)-H(14A) | 0.9900 |
| C(14)-H(14B) | 0.9900 |
| C(15)-C(16) | 1.530(6) |
| C(15)-C(17) | 1.540(6) |
| C(16)-H(16A) | 0.9800 |
| C(16)-H(16B) | 0.9800 |
| C(16)-H(16C) | 0.9800 |
| C(17)-H(17A) | 0.9800 |
| C(17)-H(17B) | 0.9800 |
| C(17)-H(17C) | 0.9800 |
| O(7)-C(18)-O(6) | 129.5(4) |
| O(7)-C(18)-C(19) | 115.8(3) |
| O(6)-C(18)-C(19) | 114.5(4) |
| F(1)-C(19)-F(3) | 106.0(3) |
| F(1)-C(19)-F(2) | 106.8(3) |
| F(3)-C(19)-F(2) | 106.0(3) |
| F(1)-C(19)-C(18) | 113.2(3) |
| F(3)-C(19)-C(18) | 114.2(3) |
| F(2)-C(19)-C(18) | 110.1(3) |
| C(11)-O(3)-C(12) | 117.5(3) |
| C(13)-O(5)-C(14) | 109.2(3) |
| C(1)-N(1)-H(1A) | 119(3) |
| C(1)-N(1)-H(1B) | 115(3) |
| H(1A)-N(1)-H(1B) | 123(4) |
| C(1)-N(2)-C(2) | 126.8(3) |
| C(1)-N(2)-H(2) | 116(3) |
| C(2)-N(2)-H(2) | 113(3) |
| C(1)-N(3)-C(5) | 124.5(3) |
| C(1)-N(3)-C(8) | 125.4(3) |
| C(5)-N(3)-C(8) | 106.1(3) |
| N(1)-C(1)-N(2) | 119.3(4) |
| N(1)-C(1)-N(3) | 121.0(4) |
| N(2)-C(1)-N(3) | 119.7(4) |
| C(3)-C(2)-N(2) | 131.0(4) |
| C(3)-C(2)-H(2A) | 114.5 |
| N(2)-C(2)-H(2A) | 114.5 |
| C(2)-C(3)-C(4) | 128.6(4) |
| C(2)-C(3)-H(3) | 115.7 |
| C(4)-C(3)-H(3) | 115.7 |
| C(3)-C(4)-C(11) | 108.5(3) |
| C(3)-C(4)-C(5) | 108.0(3) |
| C(11)-C(4)-C(5) | 111.1(3) |
| C(3)-C(4)-C(10) | 105.9(3) |
| C(11)-C(4)-C(10) | 110.2(3) |

| | |
|---|---|
| C(5)-C(4)-C(10) | 112.9(3) |
| N(3)-C(5)-C(6) | 100.2(3) |
| N(3)-C(5)-C(4) | 107.3(3) |
| C(6)-C(5)-C(4) | 117.1(3) |
| N(3)-C(5)-H(5) | 110.6 |
| C(6)-C(5)-H(5) | 110.6 |
| C(4)-C(5)-H(5) | 110.6 |
| C(5)-C(6)-C(7) | 104.4(3) |
| C(5)-C(6)-H(6A) | 110.9 |
| C(7)-C(6)-H(6A) | 110.9 |
| C(5)-C(6)-H(6B) | 110.9 |
| C(7)-C(6)-H(6B) | 110.9 |
| H(6A)-C(6)-H(6B) | 108.9 |
| C(8)-C(7)-C(6) | 105.4(3) |
| C(8)-C(7)-H(7A) | 110.7 |
| C(6)-C(7)-H(7A) | 110.7 |
| C(8)-C(7)-H(7B) | 110.7 |
| C(6)-C(7)-H(7B) | 110.7 |
| H(7A)-C(7)-H(7B) | 108.8 |
| N(3)-C(8)-C(9) | 105.0(3) |
| N(3)-C(8)-C(7) | 102.4(3) |
| C(9)-C(8)-C(7) | 111.8(3) |
| N(3)-C(8)-H(8) | 112.4 |
| C(9)-C(8)-H(8) | 112.4 |
| C(7)-C(8)-H(8) | 112.4 |
| C(10)-C(9)-C(8) | 113.8(3) |
| C(10)-C(9)-H(9A) | 108.8 |
| C(8)-C(9)-H(9A) | 108.8 |
| C(10)-C(9)-H(9B) | 108.8 |
| C(8)-C(9)-H(9B) | 108.8 |
| H(9A)-C(9)-H(9B) | 107.7 |
| O(1)-C(10)-C(9) | 122.6(4) |
| O(1)-C(10)-C(4) | 118.8(4) |
| C(9)-C(10)-C(4) | 118.4(3) |
| O(2)-C(11)-O(3) | 123.8(4) |
| O(2)-C(11)-C(4) | 124.9(4) |
| O(3)-C(11)-C(4) | 111.2(3) |
| O(3)-C(12)-C(13) | 107.6(3) |
| O(3)-C(12)-C(15) | 115.5(3) |
| C(13)-C(12)-C(15) | 103.0(3) |
| O(3)-C(12)-H(12) | 110.1 |
| C(13)-C(12)-H(12) | 110.1 |
| C(15)-C(12)-H(12) | 110.1 |
| O(4)-C(13)-O(5) | 122.4(4) |
| O(4)-C(13)-C(12) | 128.8(4) |
| O(5)-C(13)-C(12) | 108.8(4) |

| | |
|---|---|
| O(5)-C(14)-C(15) | 105.0(3) |
| O(5)-C(14)-H(14A) | 110.7 |
| C(15)-C(14)-H(14A) | 110.7 |
| O(5)-C(14)-H(14B) | 110.7 |
| C(15)-C(14)-H(14B) | 110.7 |
| H(14A)-C(14)-H(14B) | 108.8 |
| C(12)-C(15)-C(16) | 114.3(3) |
| C(12)-C(15)-C(14) | 98.5(3) |
| C(16)-C(15)-C(14) | 111.7(4) |
| C(12)-C(15)-C(17) | 110.6(3) |
| C(16)-C(15)-C(17) | 110.9(4) |
| C(14)-C(15)-C(17) | 110.2(4) |
| C(15)-C(16)-H(16A) | 109.5 |
| C(15)-C(16)-H(16B) | 109.5 |
| H(16A)-C(16)-H(16B) | 109.5 |
| C(15)-C(16)-H(16C) | 109.5 |
| H(16A)-C(16)-H(16C) | 109.5 |
| H(16B)-C(16)-H(16C) | 109.5 |
| C(15)-C(17)-H(17A) | 109.5 |
| C(15)-C(17)-H(17B) | 109.5 |
| H(17A)-C(17)-H(17B) | 109.5 |
| C(15)-C(17)-H(17C) | 109.5 |
| H(17A)-C(17)-H(17C) | 109.5 |
| H(17B)-C(17)-H(17C) | 109.5 |

Symmetry transformations used to generate equivalent atoms:

**Table S5**. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for spider-15033. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| F(1) | 46(2) | 26(1) | 86(2) | 6(2) | -20(2) | -12(1) |
| F(2) | 40(2) | 72(2) | 27(2) | -6(1) | -1(1) | 8(2) |
| F(3) | 27(1) | 34(2) | 49(2) | -11(1) | 0(1) | 2(1) |
| O(6) | 32(2) | 26(2) | 45(2) | -1(2) | -5(2) | 4(1) |
| O(7) | 30(2) | 26(2) | 30(2) | 0(1) | -3(1) | -3(1) |
| C(18) | 26(2) | 27(3) | 22(2) | 2(2) | 6(2) | 0(2) |
| C(19) | 32(2) | 19(2) | 35(3) | -1(2) | 6(2) | 0(2) |
| O(1) | 28(2) | 28(2) | 30(2) | 5(1) | 4(1) | -1(1) |
| O(2) | 27(2) | 42(2) | 42(2) | -19(2) | 2(2) | 0(2) |
| O(3) | 18(1) | 23(2) | 28(2) | -1(1) | 2(1) | -1(1) |
| O(4) | 38(2) | 29(2) | 44(2) | 1(2) | 9(2) | -11(2) |
| O(5) | 24(2) | 41(2) | 43(2) | -9(2) | 2(1) | 0(2) |
| N(1) | 21(2) | 23(2) | 31(2) | 4(2) | -3(2) | 0(2) |
| N(2) | 26(2) | 25(2) | 28(2) | 4(2) | -3(2) | -1(2) |
| N(3) | 22(2) | 24(2) | 25(2) | 0(2) | 4(2) | 3(2) |
| C(1) | 22(2) | 30(3) | 20(2) | 6(2) | 1(2) | 0(2) |
| C(2) | 30(2) | 25(2) | 29(3) | -3(2) | 4(2) | -3(2) |
| C(3) | 27(2) | 23(2) | 27(2) | -3(2) | 7(2) | -1(2) |
| C(4) | 22(2) | 23(3) | 27(2) | -3(2) | 3(2) | -3(2) |
| C(5) | 24(2) | 29(2) | 21(2) | 3(2) | 5(2) | 3(2) |
| C(6) | 26(2) | 24(2) | 31(2) | 7(2) | 4(2) | 2(2) |
| C(7) | 28(2) | 26(2) | 36(3) | 2(2) | 1(2) | -2(2) |
| C(8) | 22(2) | 29(3) | 28(3) | -3(2) | 0(2) | 0(2) |
| C(9) | 27(2) | 28(2) | 22(2) | -3(2) | 2(2) | 1(2) |
| C(10) | 16(2) | 29(2) | 23(2) | 0(2) | 2(2) | -4(2) |
| C(11) | 26(2) | 26(2) | 26(2) | 0(2) | 9(2) | -1(2) |
| C(12) | 26(2) | 25(2) | 22(2) | -1(2) | 6(2) | 0(2) |
| C(13) | 27(3) | 36(3) | 28(3) | -5(2) | 12(2) | -4(2) |
| C(14) | 32(3) | 33(3) | 42(3) | -8(2) | 1(2) | 10(2) |
| C(15) | 26(2) | 30(2) | 24(2) | 0(2) | 2(2) | 5(2) |
| C(16) | 44(3) | 25(2) | 35(3) | -1(2) | 9(2) | 3(2) |
| C(17) | 44(3) | 32(3) | 27(3) | 8(2) | 6(2) | 10(2) |

**Table 6**. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for spider-15033.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1A) | 8280(50) | 1520(40) | 3810(50) | 41(14) |
| H(1B) | 9540(50) | 2400(40) | 4360(50) | 44(15) |
| H(2) | 9180(50) | 4070(50) | 5160(50) | 53(15) |
| H(2A) | 8323 | 5785 | 4730 | 34 |
| H(3) | 6363 | 6347 | 3519 | 31 |
| H(5) | 5348 | 3858 | 4898 | 30 |
| H(6A) | 2986 | 3329 | 3264 | 33 |
| H(6B) | 3858 | 2336 | 4208 | 33 |
| H(7A) | 4040 | 1478 | 2116 | 36 |
| H(7B) | 3571 | 2621 | 1223 | 36 |
| H(8) | 6330 | 1869 | 1762 | 32 |
| H(9A) | 6990 | 3681 | 959 | 31 |
| H(9B) | 5488 | 3347 | 9 | 31 |
| H(12) | 1254 | 5915 | 3238 | 29 |
| H(14A) | -1180 | 6835 | 1859 | 43 |
| H(14B) | -1350 | 6706 | 152 | 43 |
| H(16A) | 983 | 7931 | 2554 | 52 |
| H(16B) | 876 | 8314 | 924 | 52 |
| H(16C) | 2349 | 7799 | 1759 | 52 |
| H(17A) | 2303 | 6227 | -174 | 51 |
| H(17B) | 895 | 6857 | -983 | 51 |
| H(17C) | 839 | 5527 | -618 | 51 |

**Table S7**. Torsion angles [°] for spider-15033.

| | |
|---|---|
| O(7)-C(18)-C(19)-F(1) | 156.0(4) |
| O(6)-C(18)-C(19)-F(1) | -27.3(5) |
| O(7)-C(18)-C(19)-F(3) | 34.5(5) |
| O(6)-C(18)-C(19)-F(3) | -148.8(4) |
| O(7)-C(18)-C(19)-F(2) | -84.6(4) |
| O(6)-C(18)-C(19)-F(2) | 92.1(4) |
| C(2)-N(2)-C(1)-N(1) | 149.7(4) |
| C(2)-N(2)-C(1)-N(3) | -31.0(6) |
| C(5)-N(3)-C(1)-N(1) | 158.3(4) |
| C(8)-N(3)-C(1)-N(1) | -47.3(6) |
| C(5)-N(3)-C(1)-N(2) | -21.0(6) |
| C(8)-N(3)-C(1)-N(2) | 133.4(4) |
| C(1)-N(2)-C(2)-C(3) | 19.4(7) |
| N(2)-C(2)-C(3)-C(4) | 3.8(8) |
| C(2)-C(3)-C(4)-C(11) | 145.5(4) |
| C(2)-C(3)-C(4)-C(5) | 25.0(6) |
| C(2)-C(3)-C(4)-C(10) | -96.2(5) |
| C(1)-N(3)-C(5)-C(6) | -154.0(4) |
| C(8)-N(3)-C(5)-C(6) | 47.4(4) |
| C(1)-N(3)-C(5)-C(4) | 83.3(5) |
| C(8)-N(3)-C(5)-C(4) | -75.3(4) |
| C(3)-C(4)-C(5)-N(3) | -72.6(4) |
| C(11)-C(4)-C(5)-N(3) | 168.5(3) |
| C(10)-C(4)-C(5)-N(3) | 44.2(4) |
| C(3)-C(4)-C(5)-C(6) | 175.8(3) |
| C(11)-C(4)-C(5)-C(6) | 56.9(5) |
| C(10)-C(4)-C(5)-C(6) | -67.4(4) |
| N(3)-C(5)-C(6)-C(7) | -37.2(4) |
| C(4)-C(5)-C(6)-C(7) | 78.4(4) |
| C(5)-C(6)-C(7)-C(8) | 14.7(4) |
| C(1)-N(3)-C(8)-C(9) | -79.6(5) |
| C(5)-N(3)-C(8)-C(9) | 78.6(4) |
| C(1)-N(3)-C(8)-C(7) | 163.5(4) |
| C(5)-N(3)-C(8)-C(7) | -38.2(4) |
| C(6)-C(7)-C(8)-N(3) | 13.0(4) |
| C(6)-C(7)-C(8)-C(9) | -98.9(4) |
| N(3)-C(8)-C(9)-C(10) | -50.9(4) |
| C(7)-C(8)-C(9)-C(10) | 59.3(5) |
| C(8)-C(9)-C(10)-O(1) | -160.9(4) |
| C(8)-C(9)-C(10)-C(4) | 25.0(5) |
| C(3)-C(4)-C(10)-O(1) | -77.1(4) |
| C(11)-C(4)-C(10)-O(1) | 40.0(5) |
| C(5)-C(4)-C(10)-O(1) | 164.9(3) |
| C(3)-C(4)-C(10)-C(9) | 97.3(4) |

| | |
|---|---|
| C(11)-C(4)-C(10)-C(9) | -145.6(3) |
| C(5)-C(4)-C(10)-C(9) | -20.8(5) |
| C(12)-O(3)-C(11)-O(2) | -2.5(6) |
| C(12)-O(3)-C(11)-C(4) | 174.4(3) |
| C(3)-C(4)-C(11)-O(2) | -22.8(6) |
| C(5)-C(4)-C(11)-O(2) | 95.8(5) |
| C(10)-C(4)-C(11)-O(2) | -138.3(4) |
| C(3)-C(4)-C(11)-O(3) | 160.3(3) |
| C(5)-C(4)-C(11)-O(3) | -81.0(4) |
| C(10)-C(4)-C(11)-O(3) | 44.8(4) |
| C(11)-O(3)-C(12)-C(13) | -146.6(3) |
| C(11)-O(3)-C(12)-C(15) | 99.0(4) |
| C(14)-O(5)-C(13)-O(4) | -178.0(4) |
| C(14)-O(5)-C(13)-C(12) | 1.6(4) |
| O(3)-C(12)-C(13)-O(4) | 31.6(6) |
| C(15)-C(12)-C(13)-O(4) | 154.1(5) |
| O(3)-C(12)-C(13)-O(5) | -148.0(3) |
| C(15)-C(12)-C(13)-O(5) | -25.6(4) |
| C(13)-O(5)-C(14)-C(15) | 22.9(4) |
| O(3)-C(12)-C(15)-C(16) | -88.0(4) |
| C(13)-C(12)-C(15)-C(16) | 155.0(4) |
| O(3)-C(12)-C(15)-C(14) | 153.5(3) |
| C(13)-C(12)-C(15)-C(14) | 36.5(4) |
| O(3)-C(12)-C(15)-C(17) | 38.1(5) |
| C(13)-C(12)-C(15)-C(17) | -78.9(4) |
| O(5)-C(14)-C(15)-C(12) | -36.5(4) |
| O(5)-C(14)-C(15)-C(16) | -157.0(3) |
| O(5)-C(14)-C(15)-C(17) | 79.3(4) |

Symmetry transformations used to generate equivalent atoms:

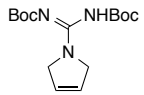
**Table S8.** Hydrogen bonds for spider-15033 [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| C(6)-H(6A)...O(3) | 0.99 | 2.36 | 3.039(5) | 125.3 |
| N(1)-H(1A)...O(6)#1 | 0.93(5) | 2.14(5) | 2.913(5) | 139(4) |
| C(8)-H(8)...F(1)#1 | 1.00 | 2.35 | 3.059(5) | 127.0 |
| N(1)-H(1B)...O(7)#2 | 0.88(5) | 2.10(5) | 2.950(5) | 163(4) |
| N(2)-H(2)...O(6)#2 | 0.95(5) | 1.95(5) | 2.828(5) | 153(5) |

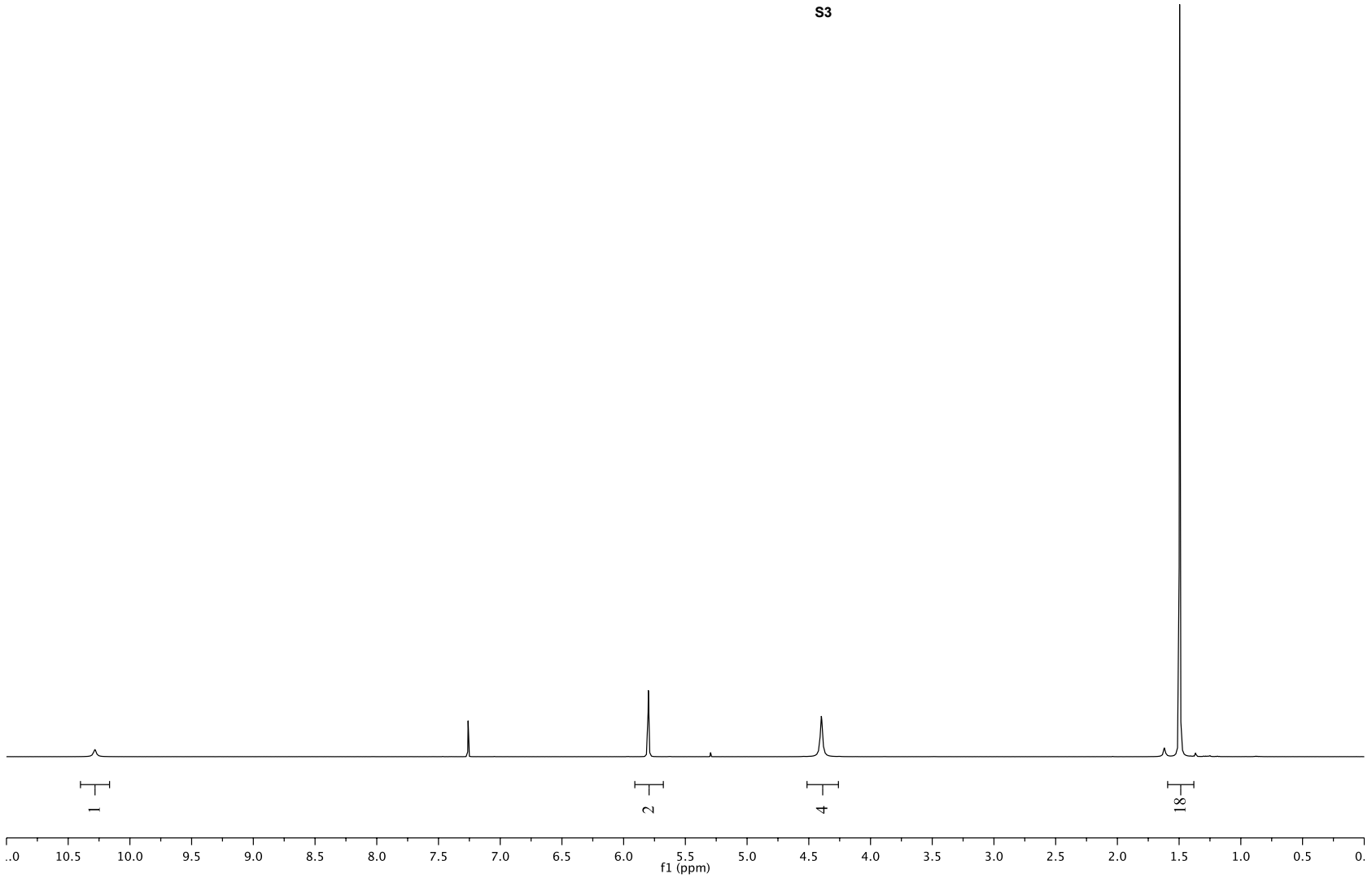
Symmetry transformations used to generate equivalent atoms:
#1 -x+1,y-1/2,-z+1 #2 x+1,y,z

**Catalog of Nuclear Magnetic Resonance and Infrared Spectra.**

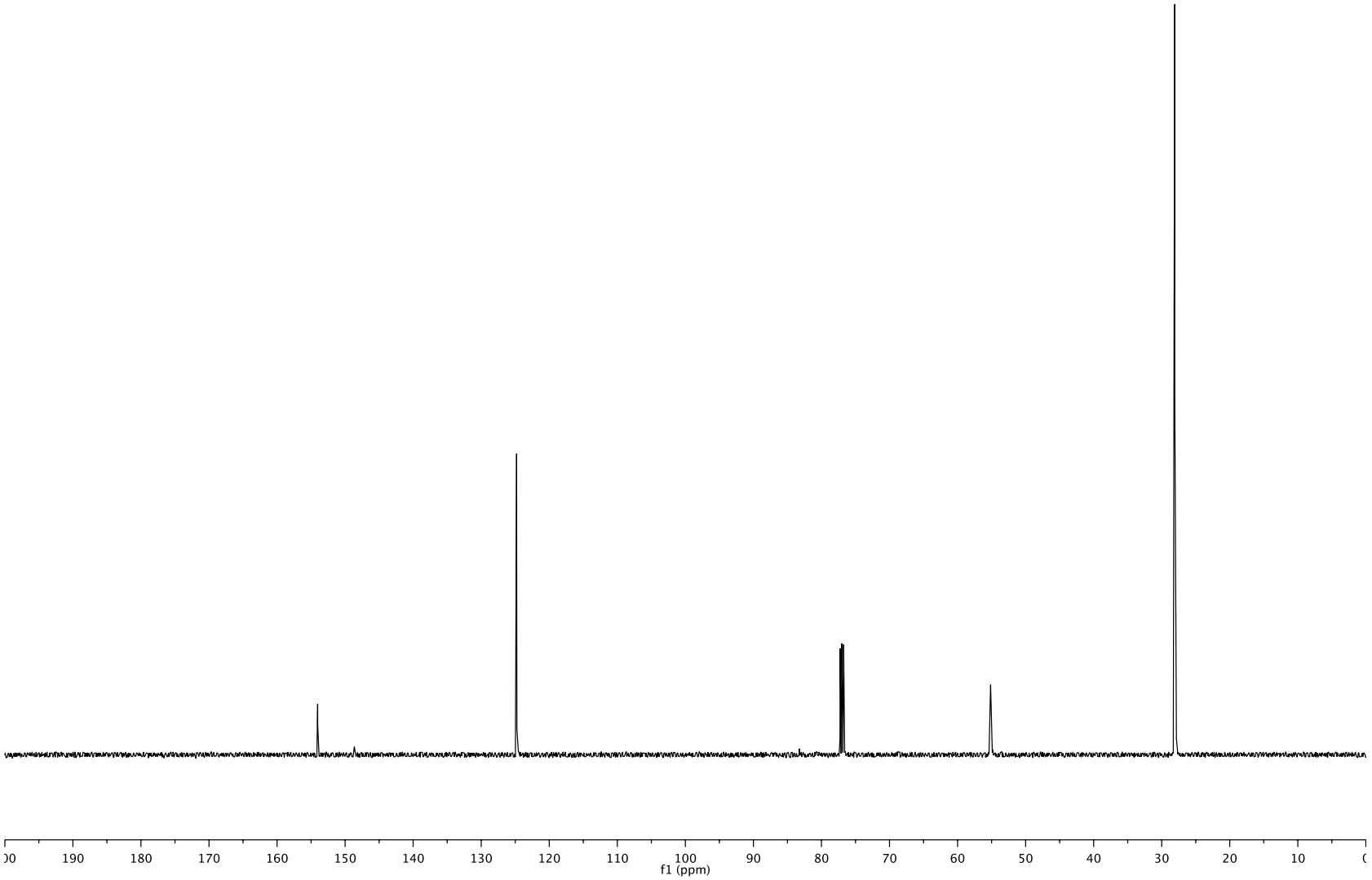
$^1$H NMR, 500 MHz, $CDCl_3$

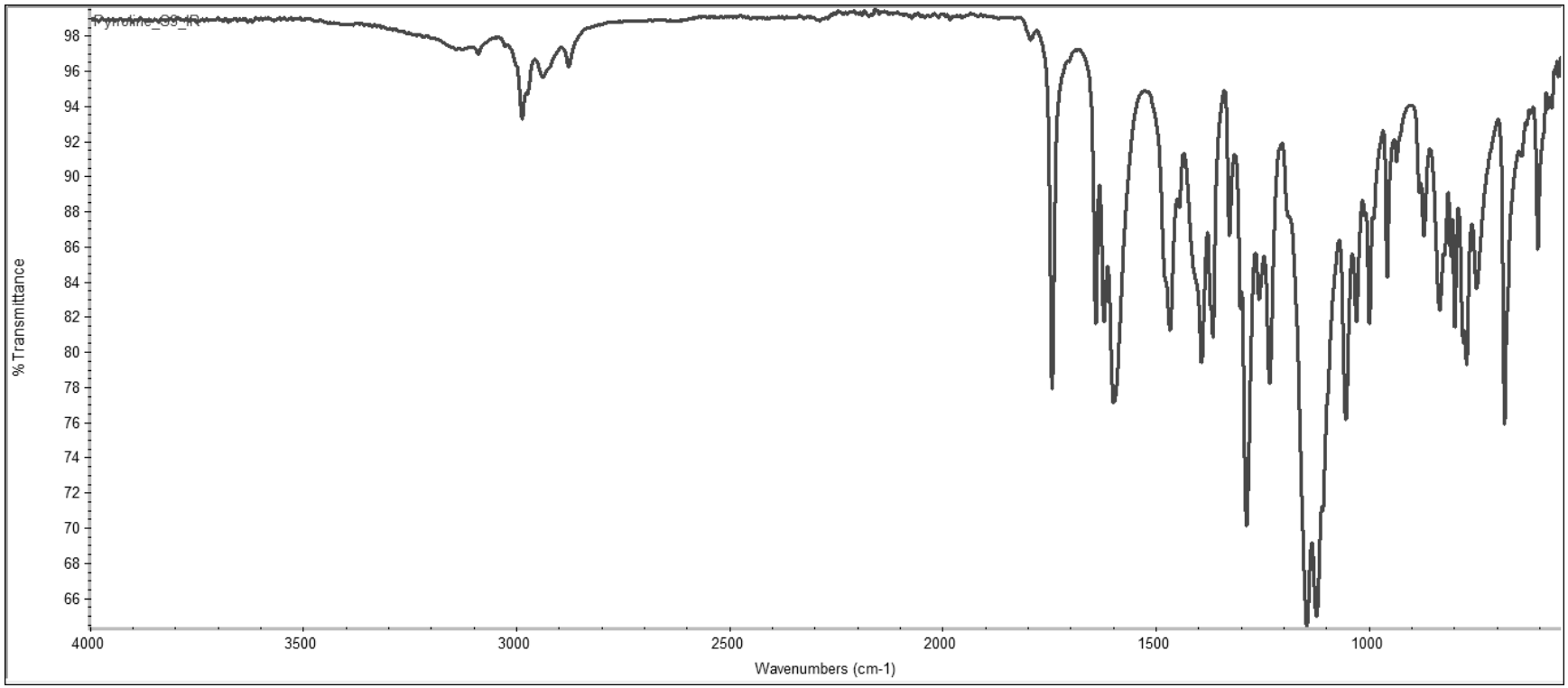



**S3**

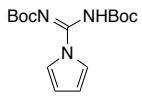


$^{13}C$ NMR, 125 MHZ, $CDCl_3$

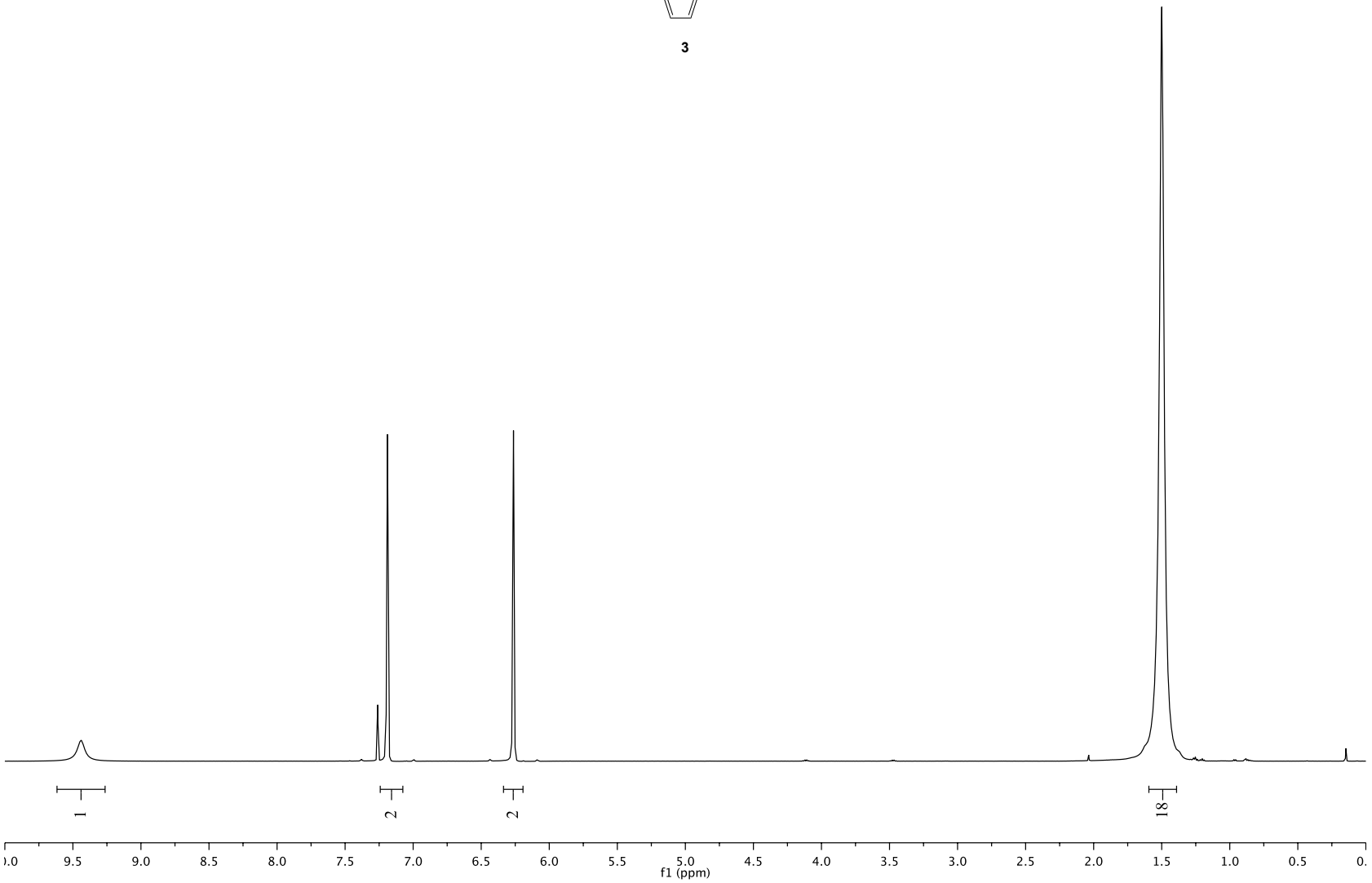



% Transmittance
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

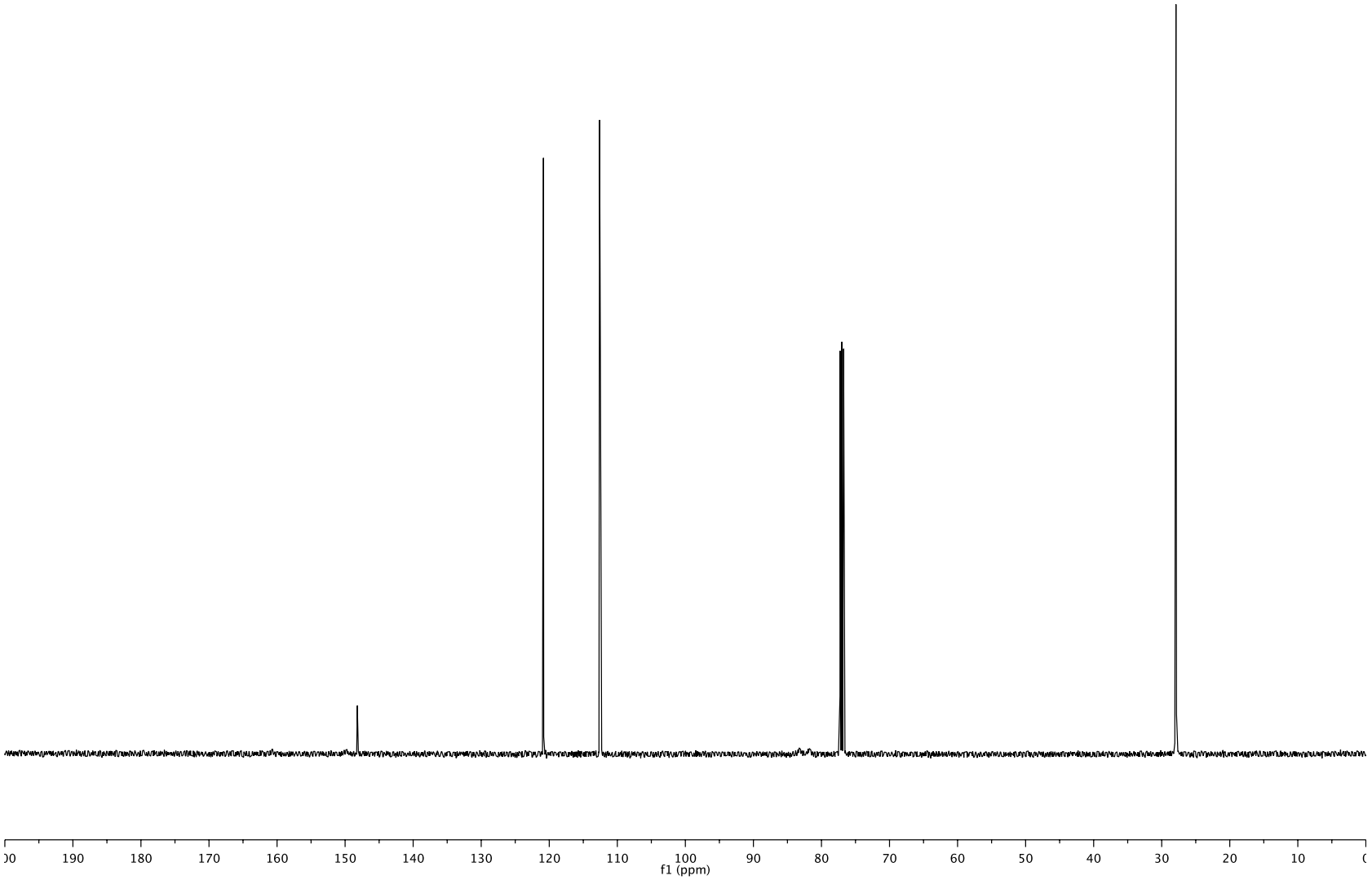
$^1$H NMR, 500 MHz, $CDCl_3$

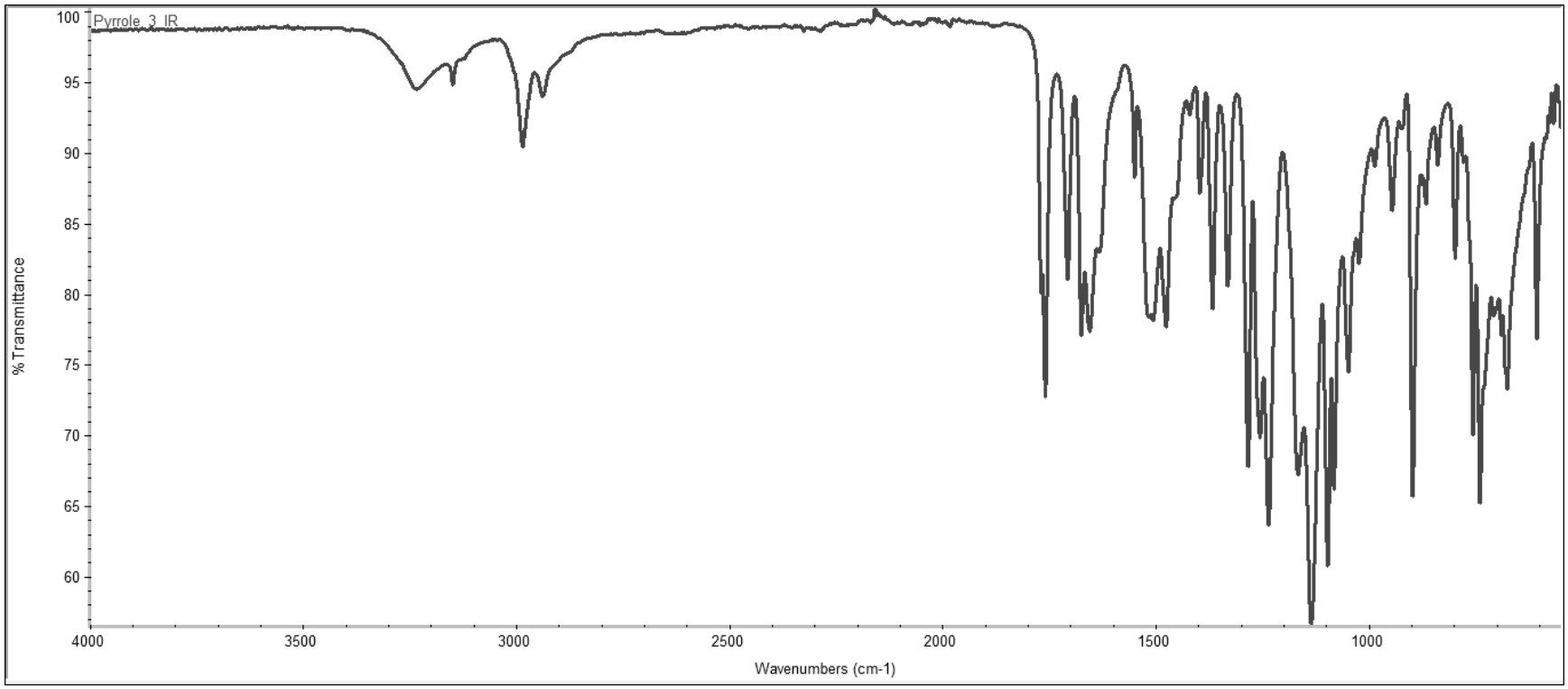



**3**

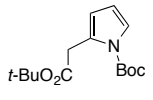


$^{13}C$ NMR, 125 MHz, $CDCl_3$

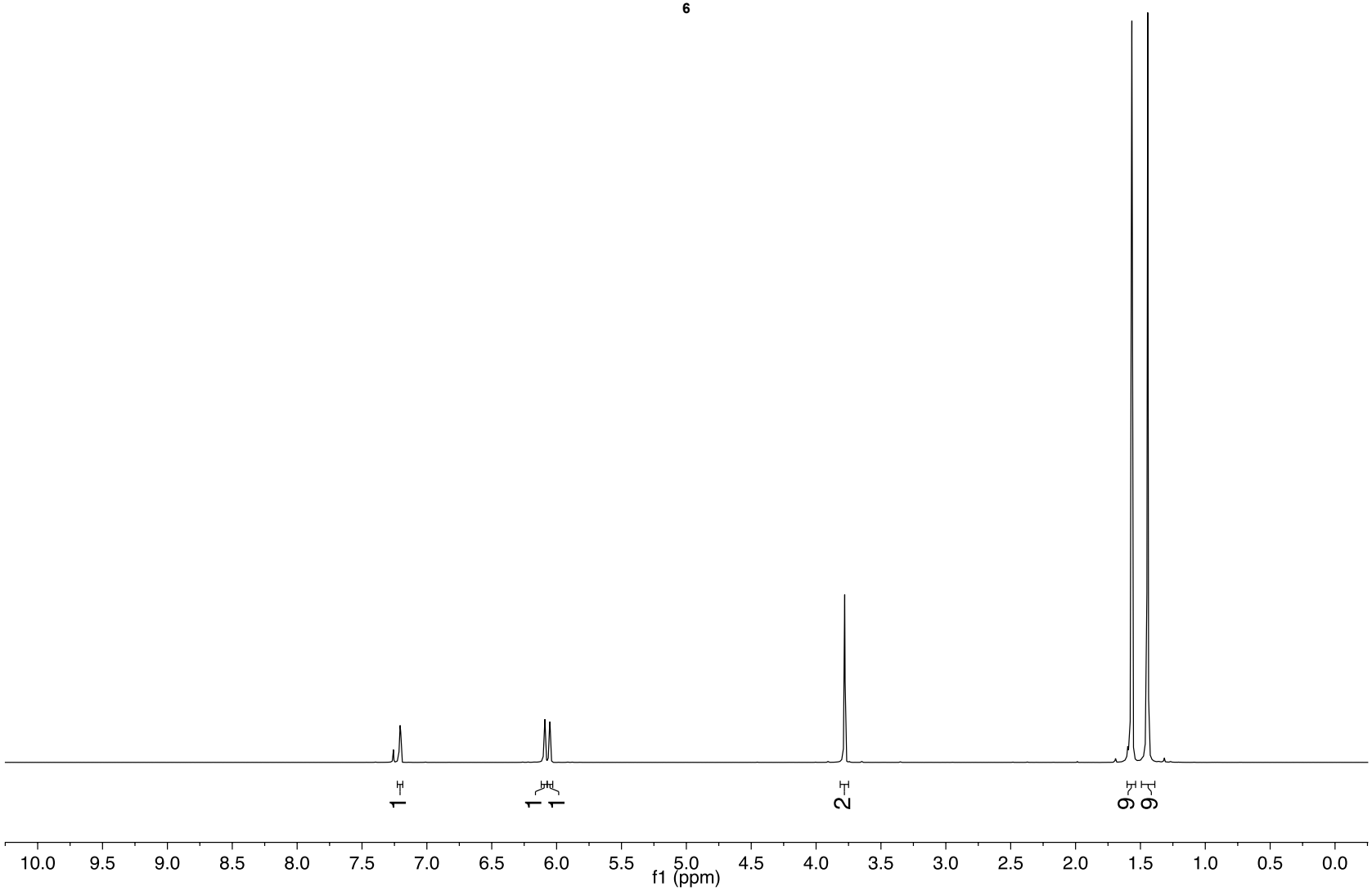



Pyrrole_3_IR
100
95
90
85
80
75
70
65
60
% Transmittance
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

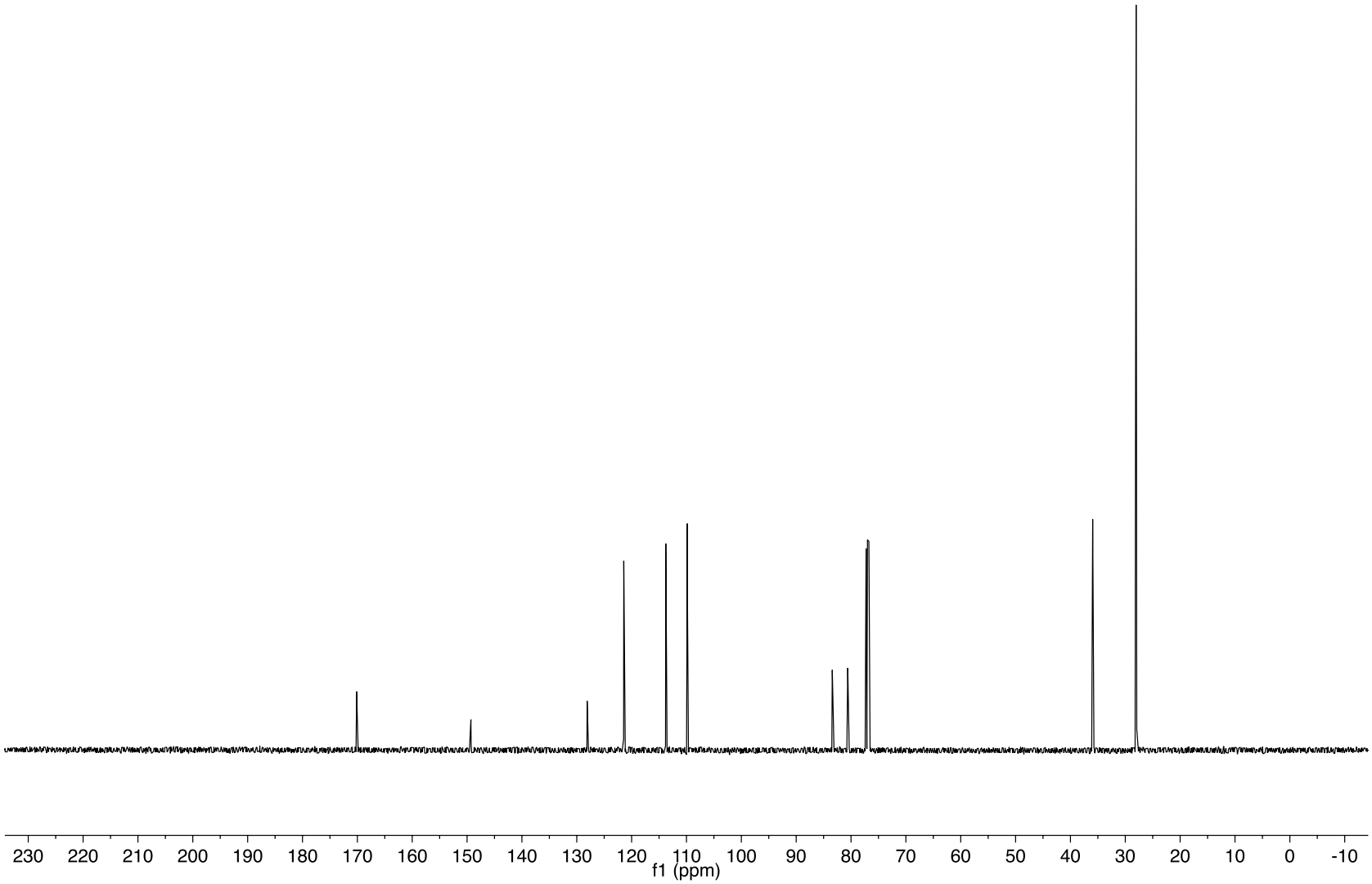
$^1$H NMR, 500 MHz, $CDCl_3$

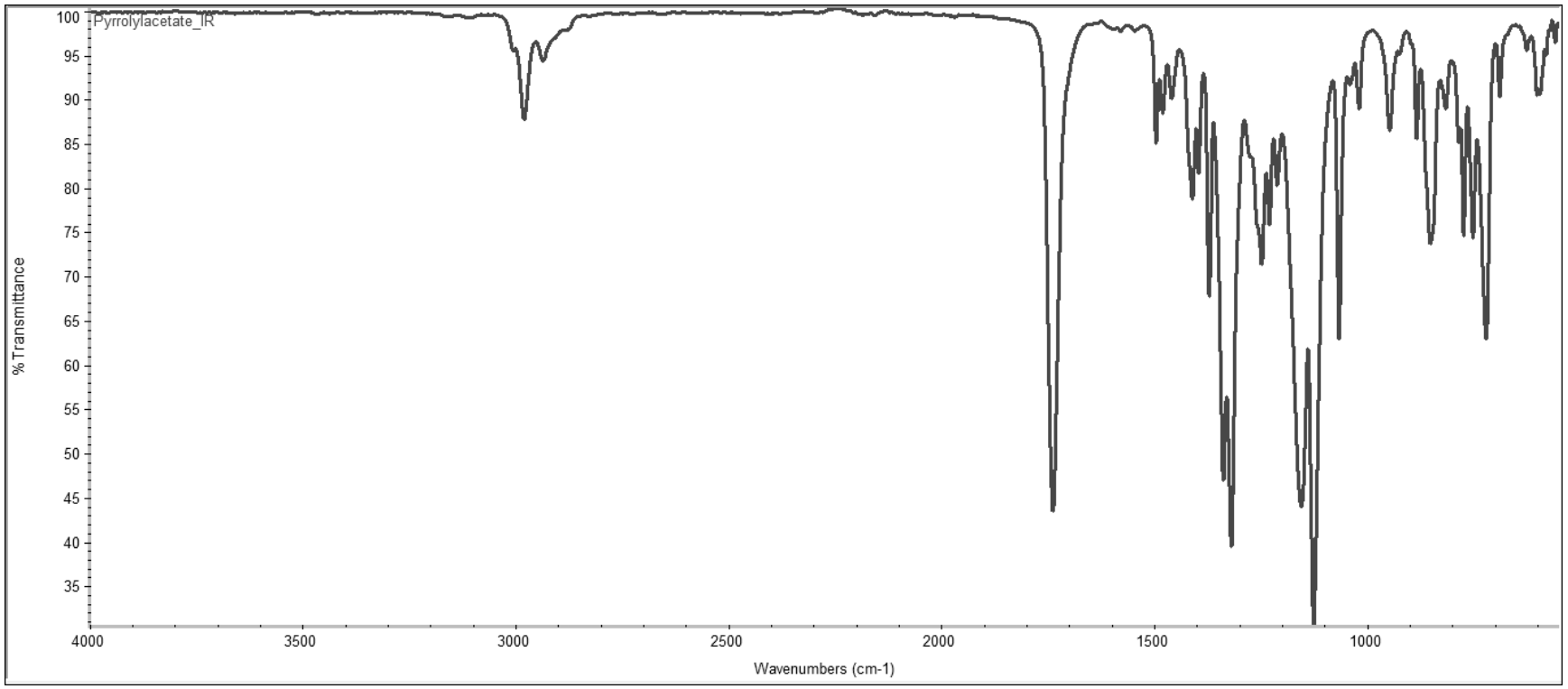



**6**

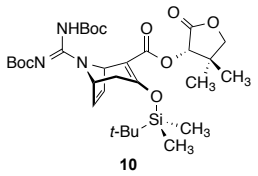


$^{13}C$ NMR, 125 MHz, $CDCl_3$

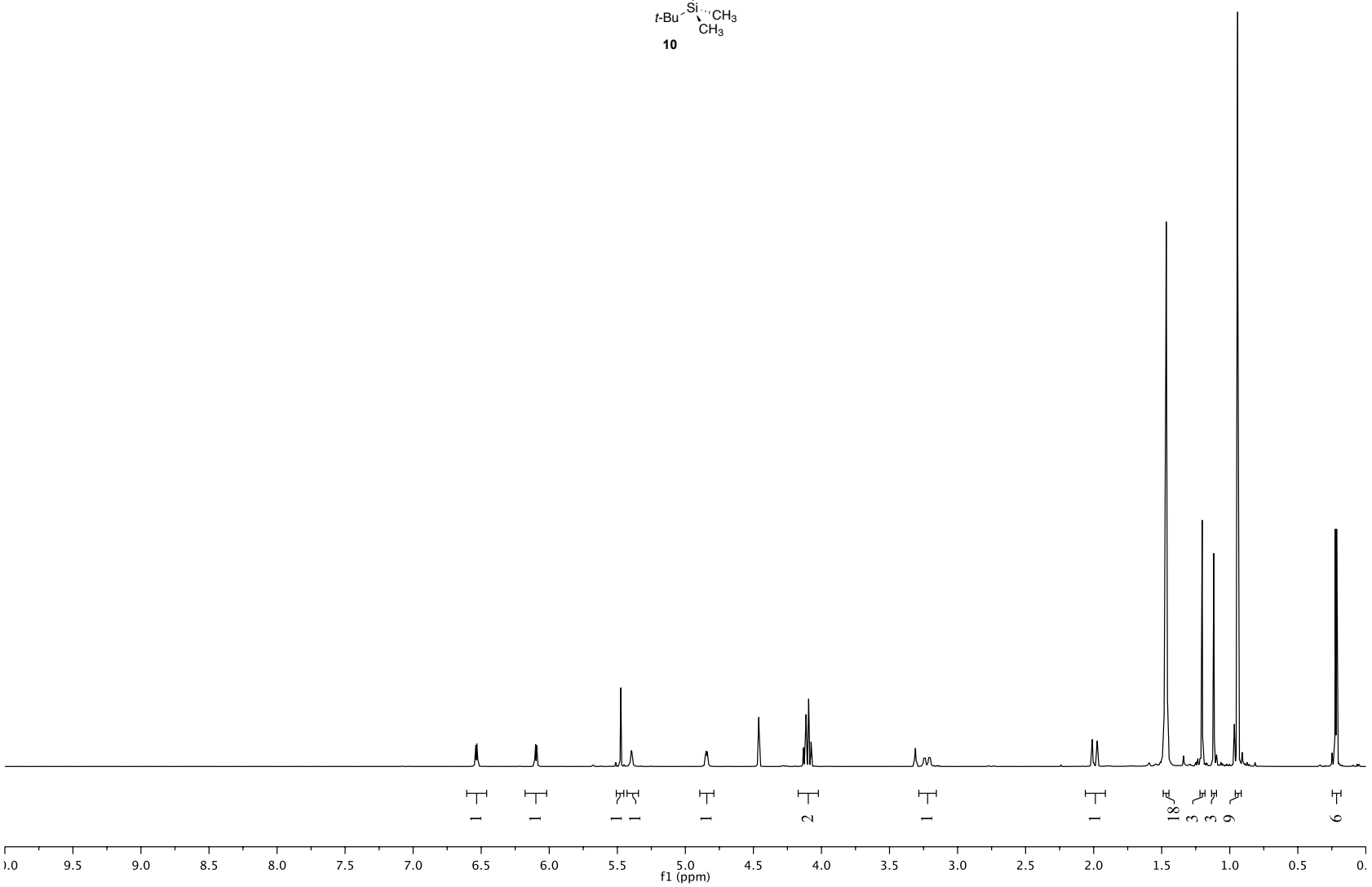


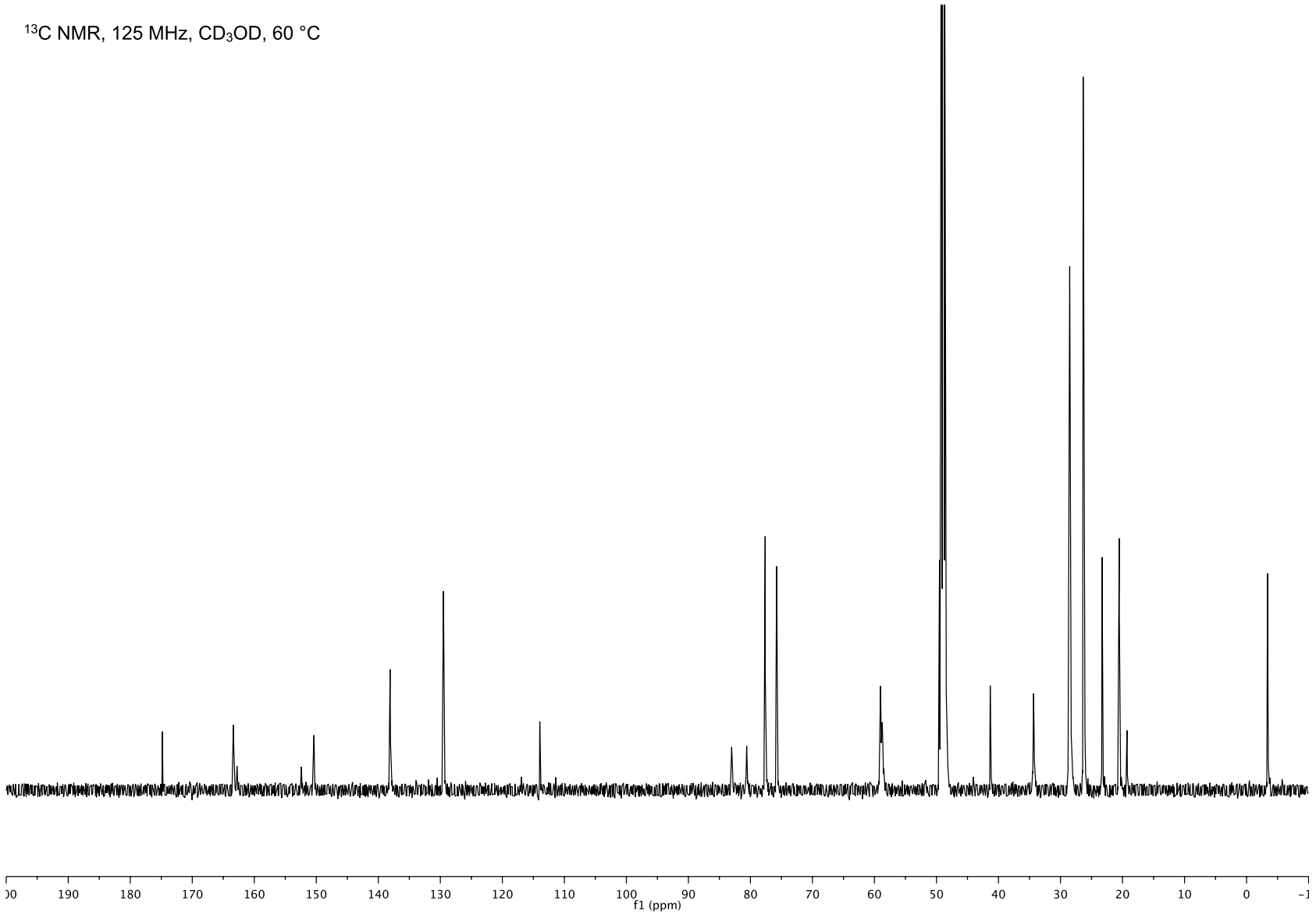

Pyrrolylacetate_IR
% Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
35
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

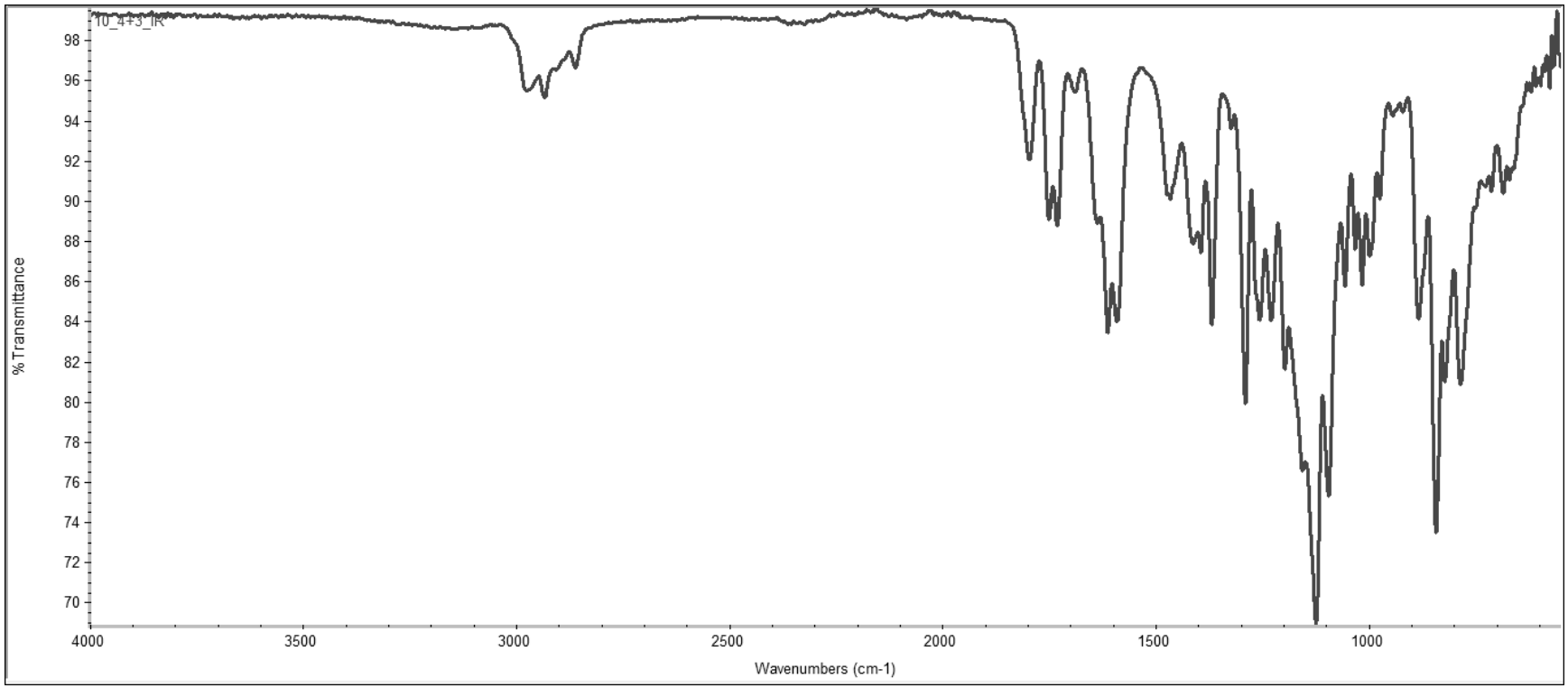
$^1$H NMR, 500 MHz, $CD_3OD$, 60 °C



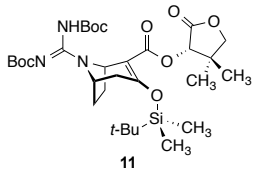

**10**




$^{13}$C NMR, 125 MHz, $CD_3OD$, 60 °C
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


10_4+3_IR
% Transmittance
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

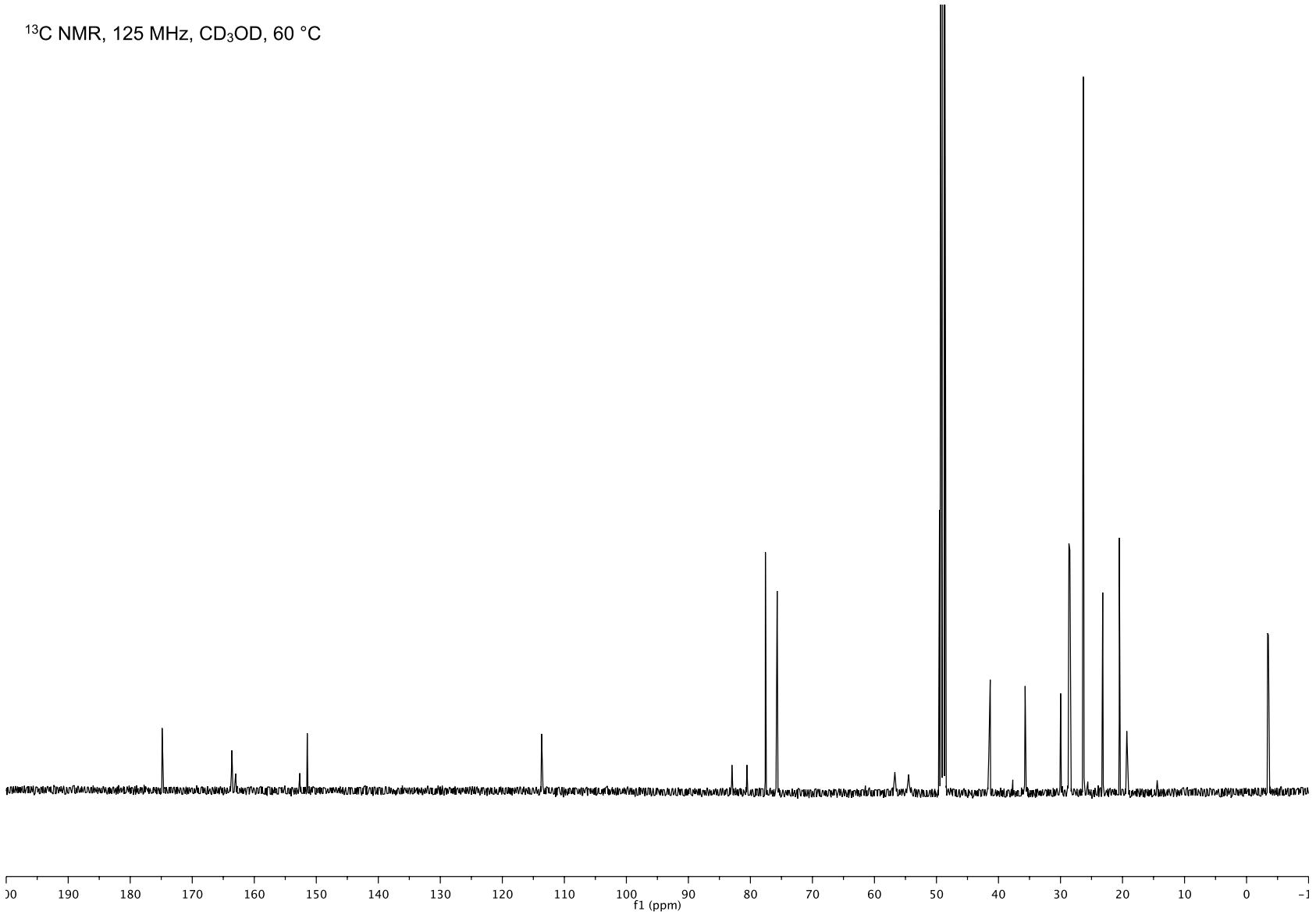
$^1$H NMR, 500 MHz, $CD_3OD$, 60 °C

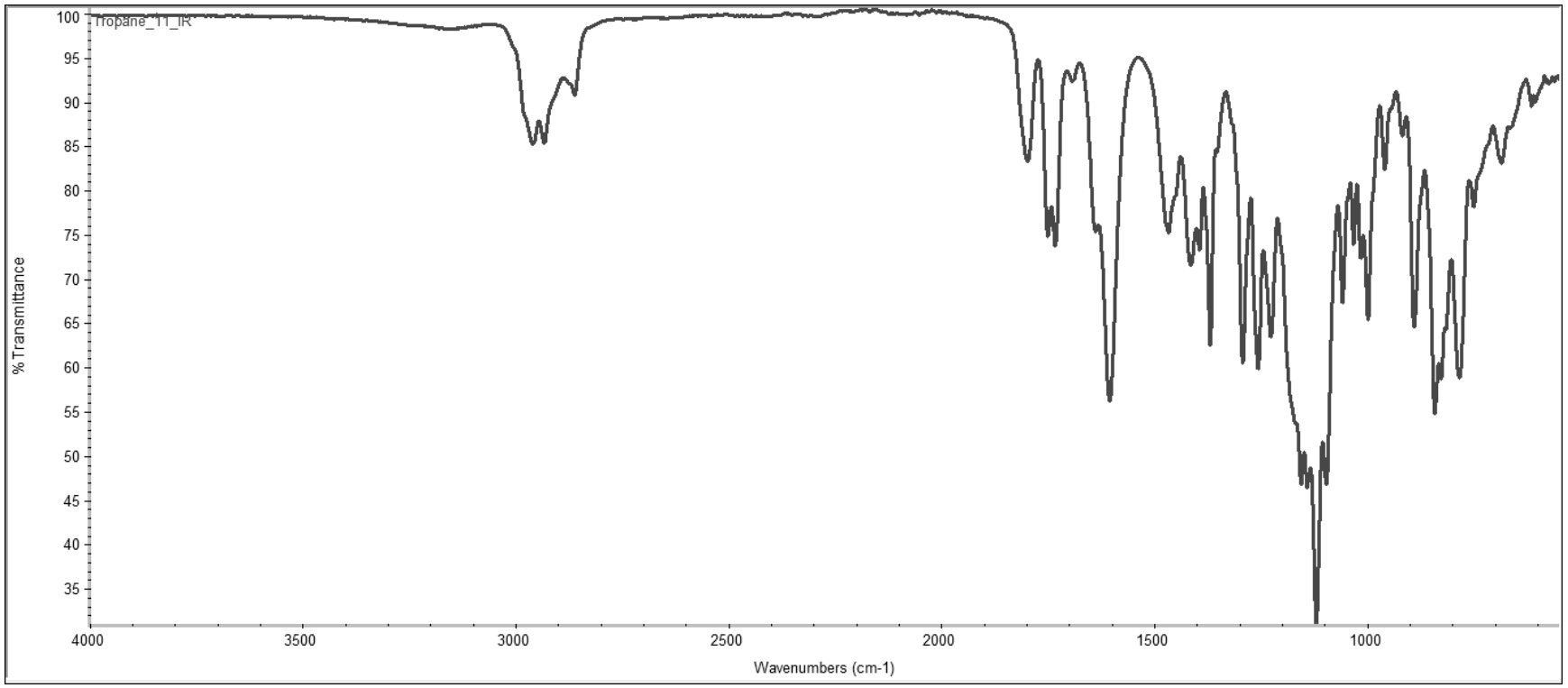


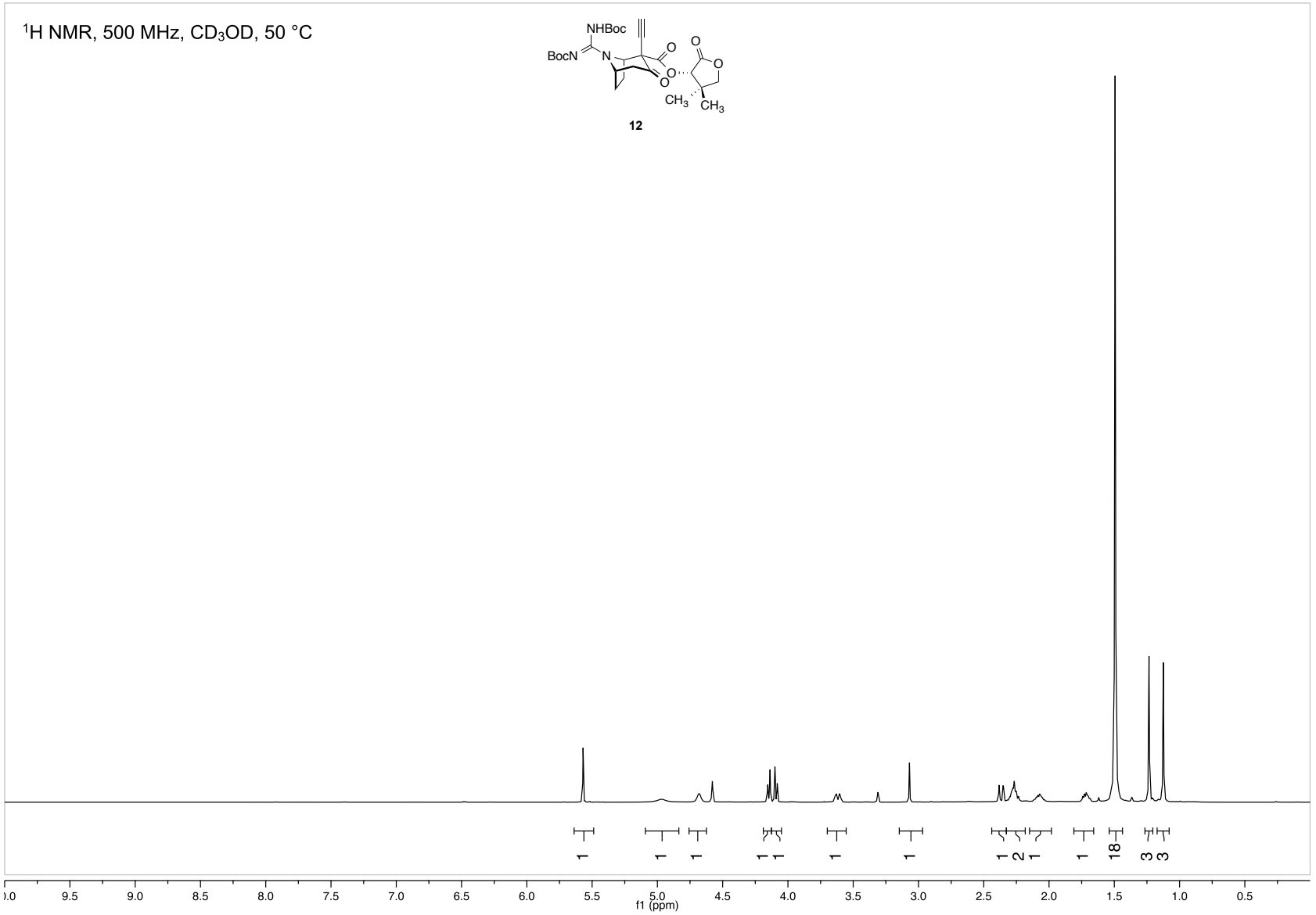

**11**

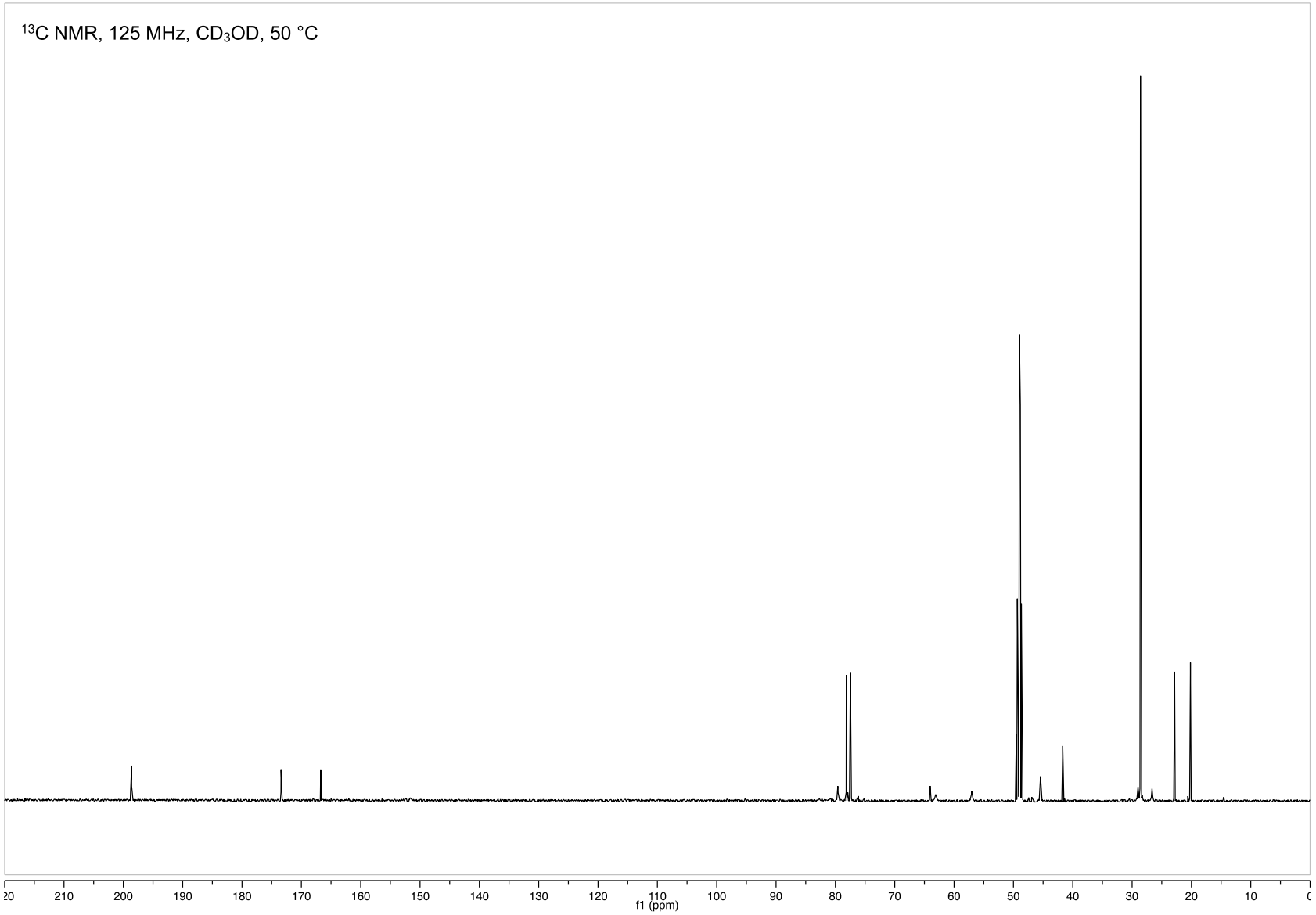


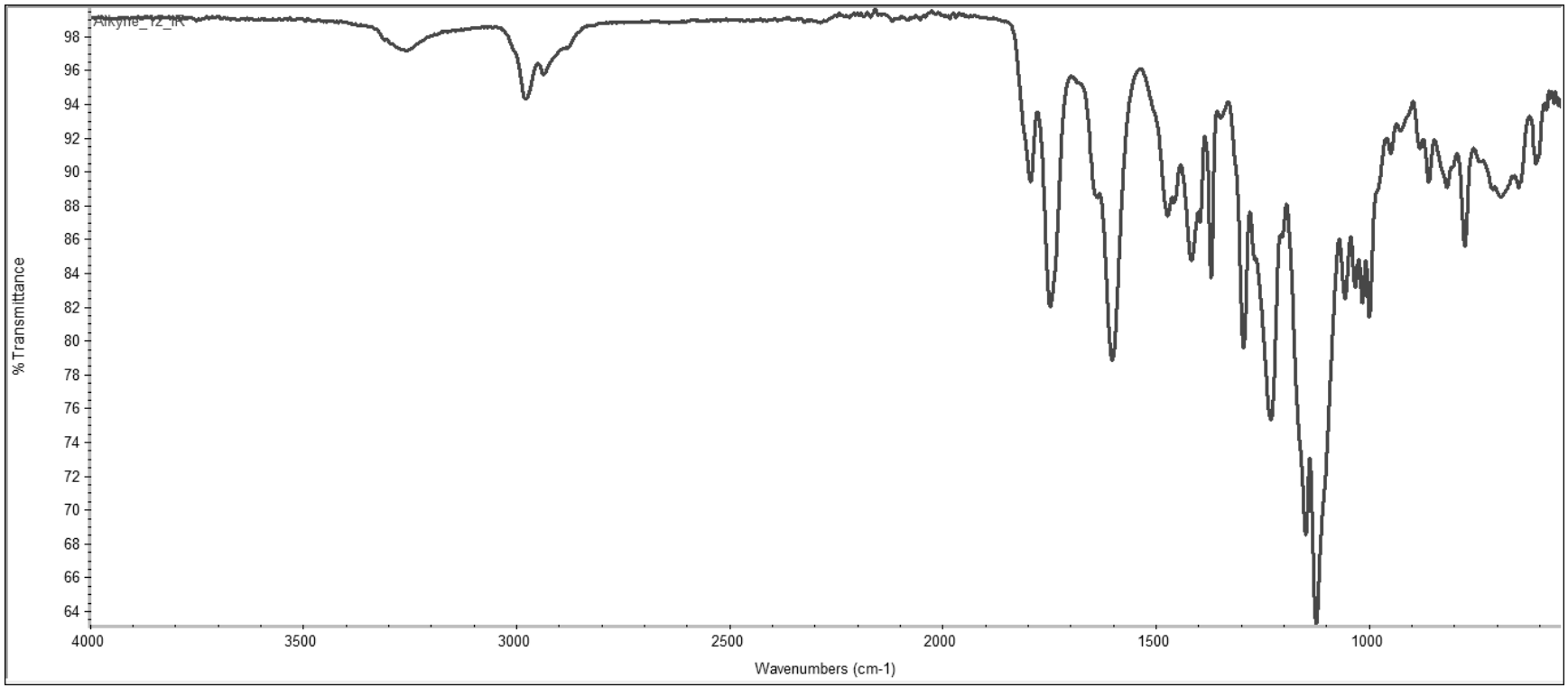

Parr, Economou, and Herzon "A concise synthesis of (+)-batzelladine B from simple pyrrole-based starting materials" *Nature*

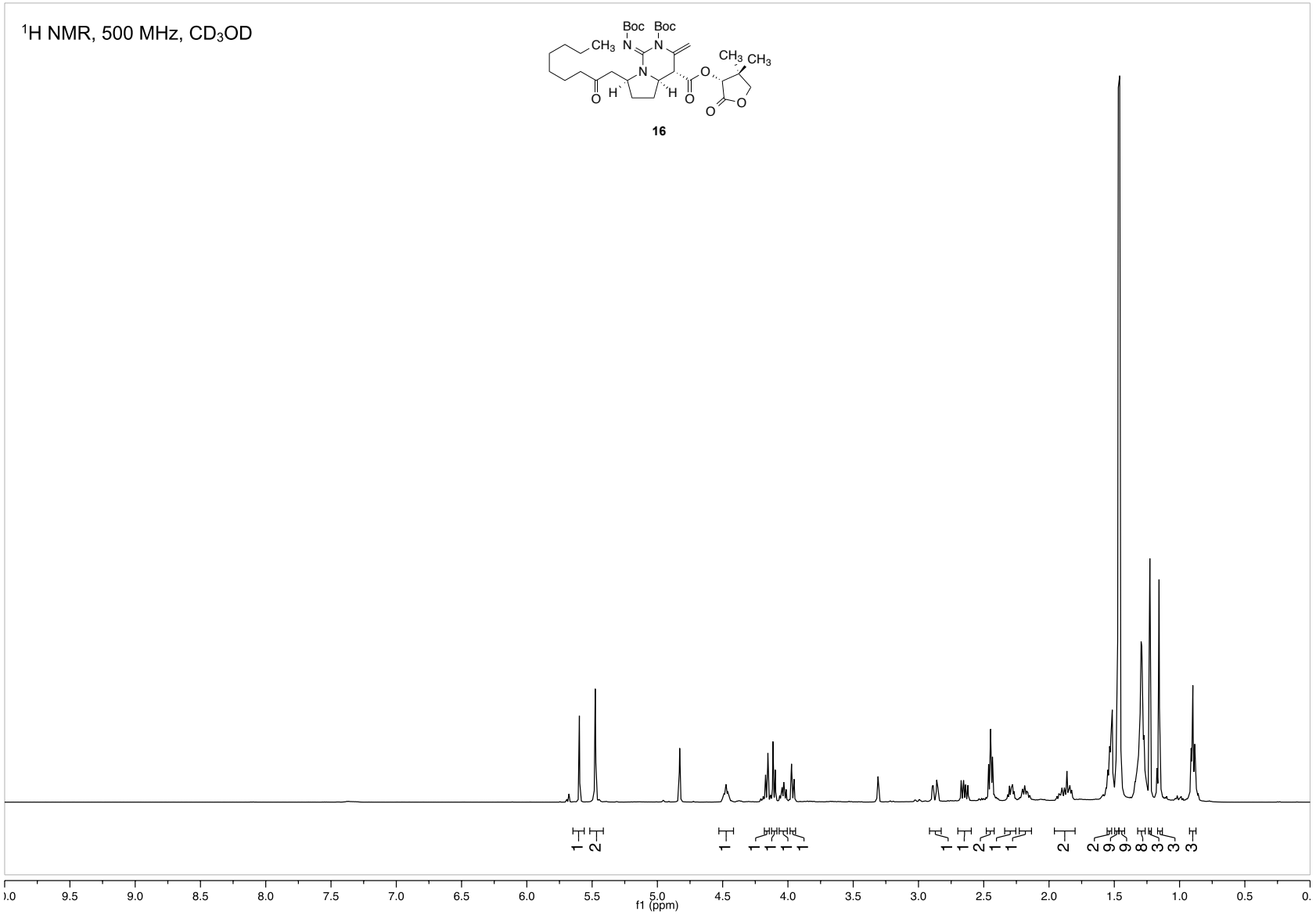

$^{13}$C NMR, 125 MHz, $CD_3OD$, 60 °C
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Tropane_11_IR
% Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
35
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

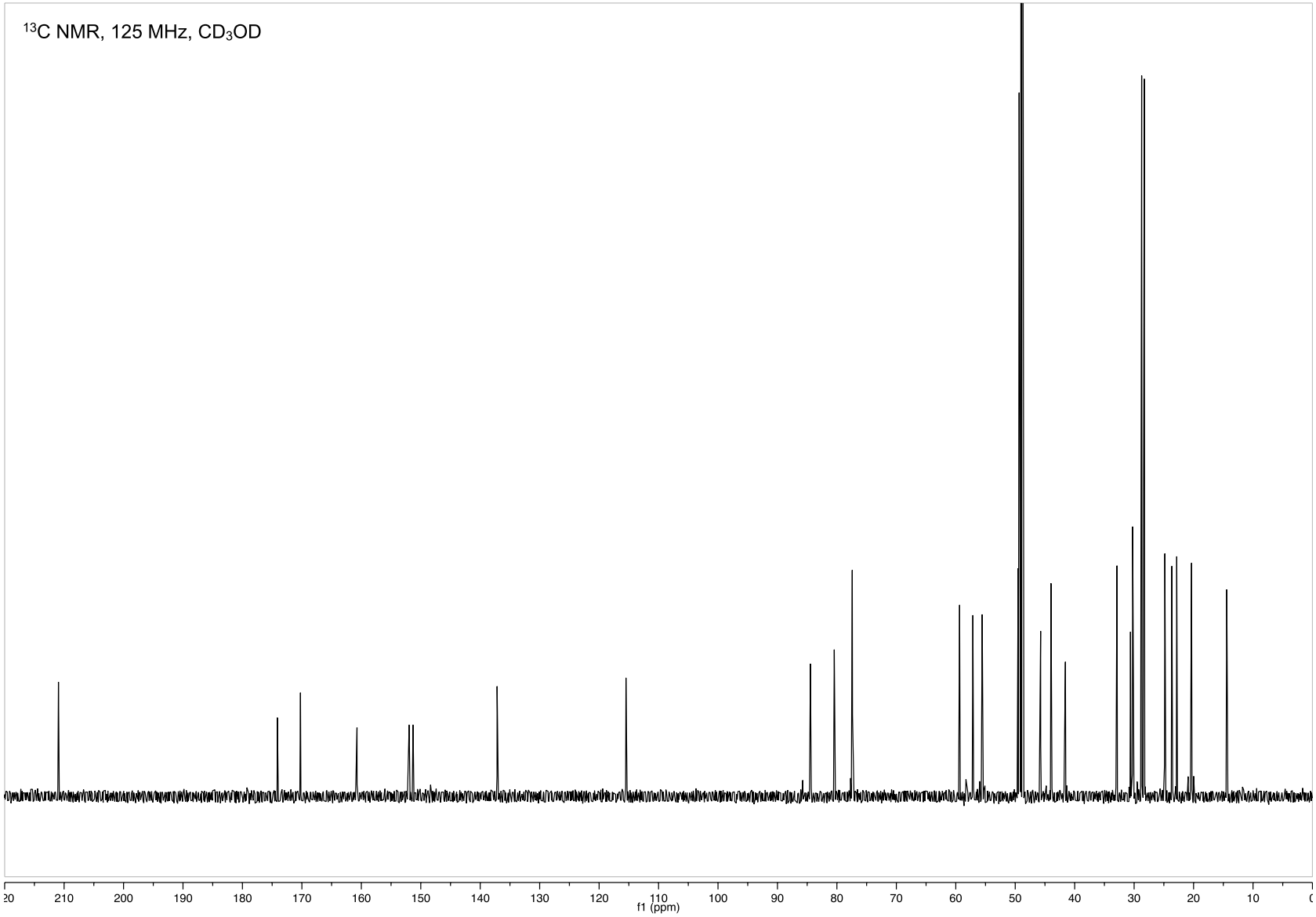

1H NMR, 500 MHz, CD3OD, 50 °C
NHBoc
BocN
N
O
O
O
O
O
CH3
CH3
12
1
1
1
1
1
1
1
1
2
1
1
18
3
3
f1 (ppm)

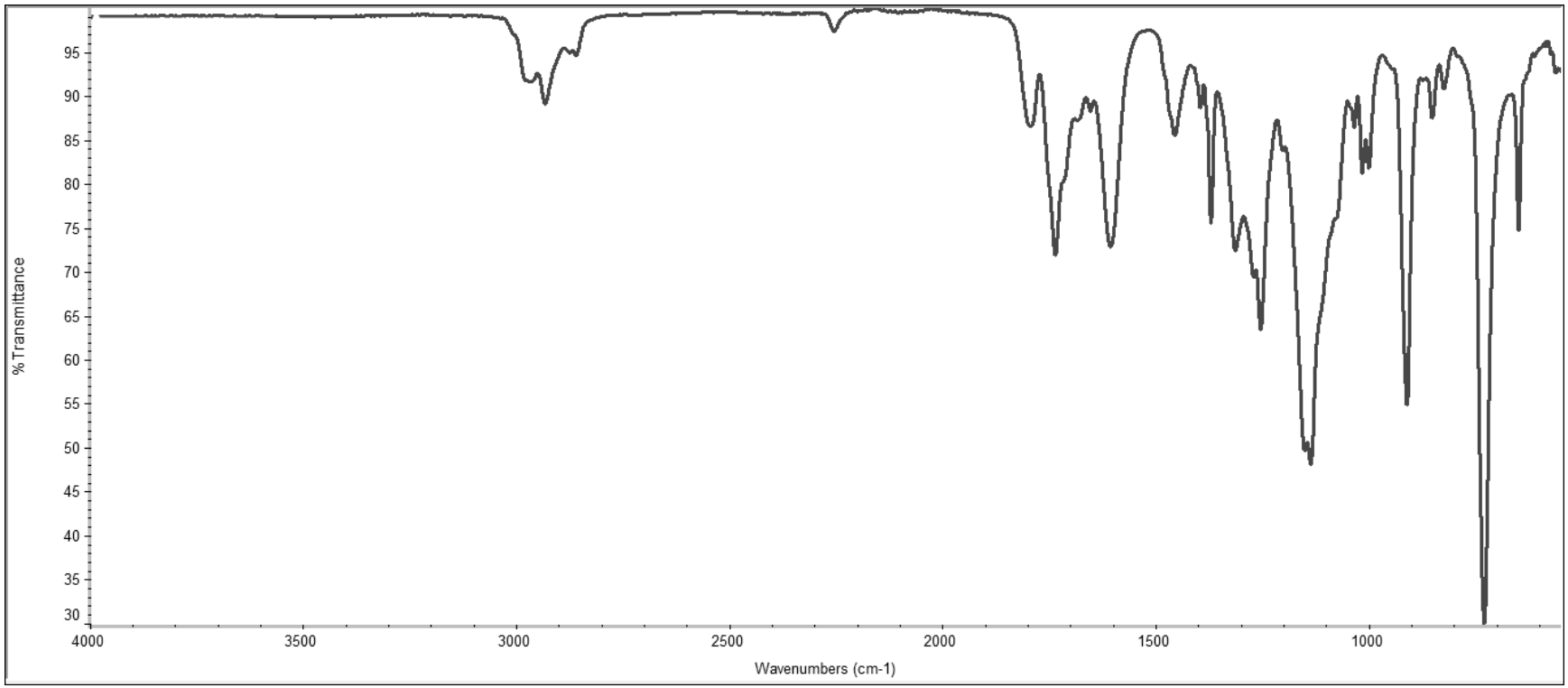

$^{13}$C NMR, 125 MHz, $CD_3OD$, 50 °C
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

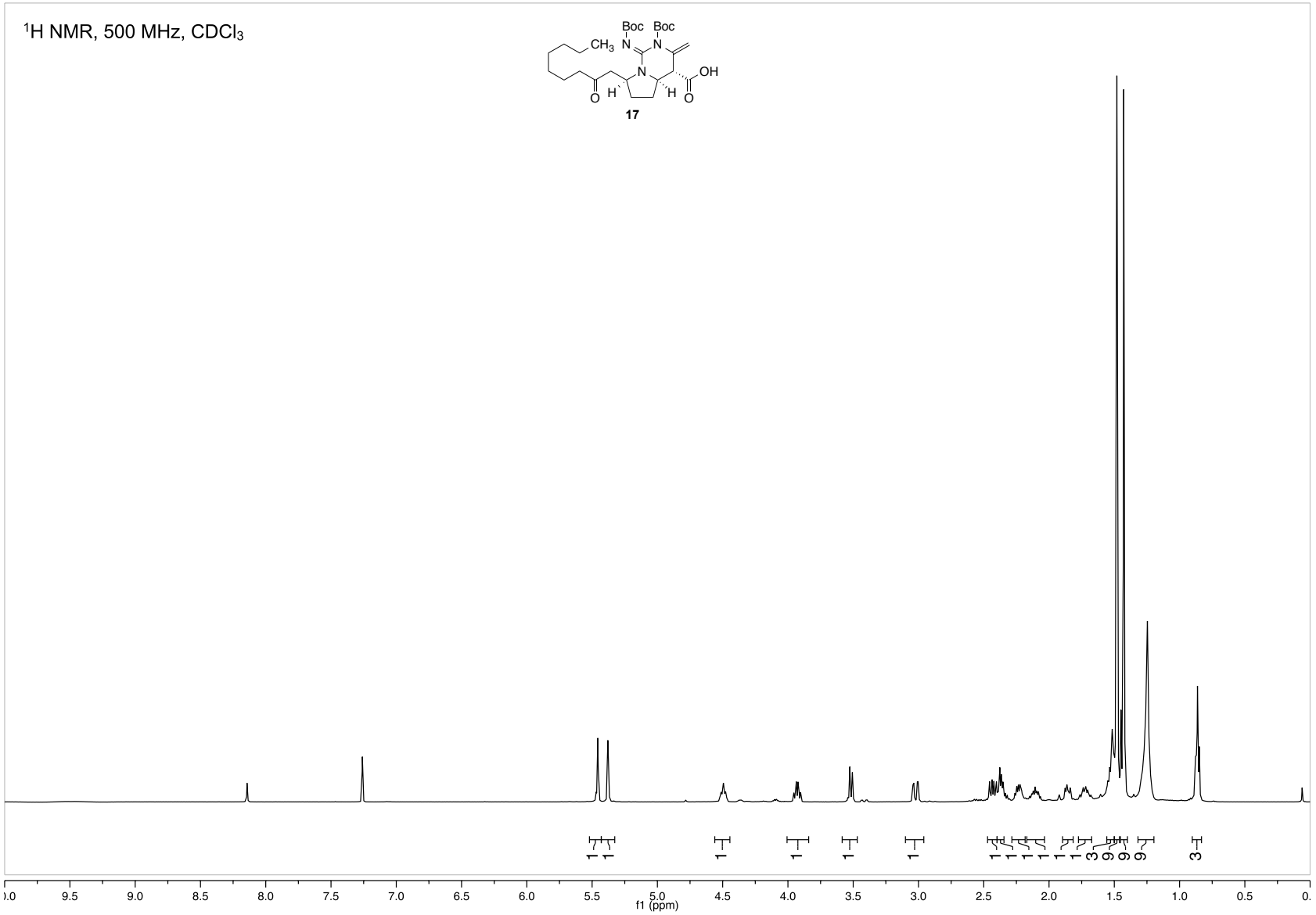

Alkyne_1Z_IR
% Transmittance
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

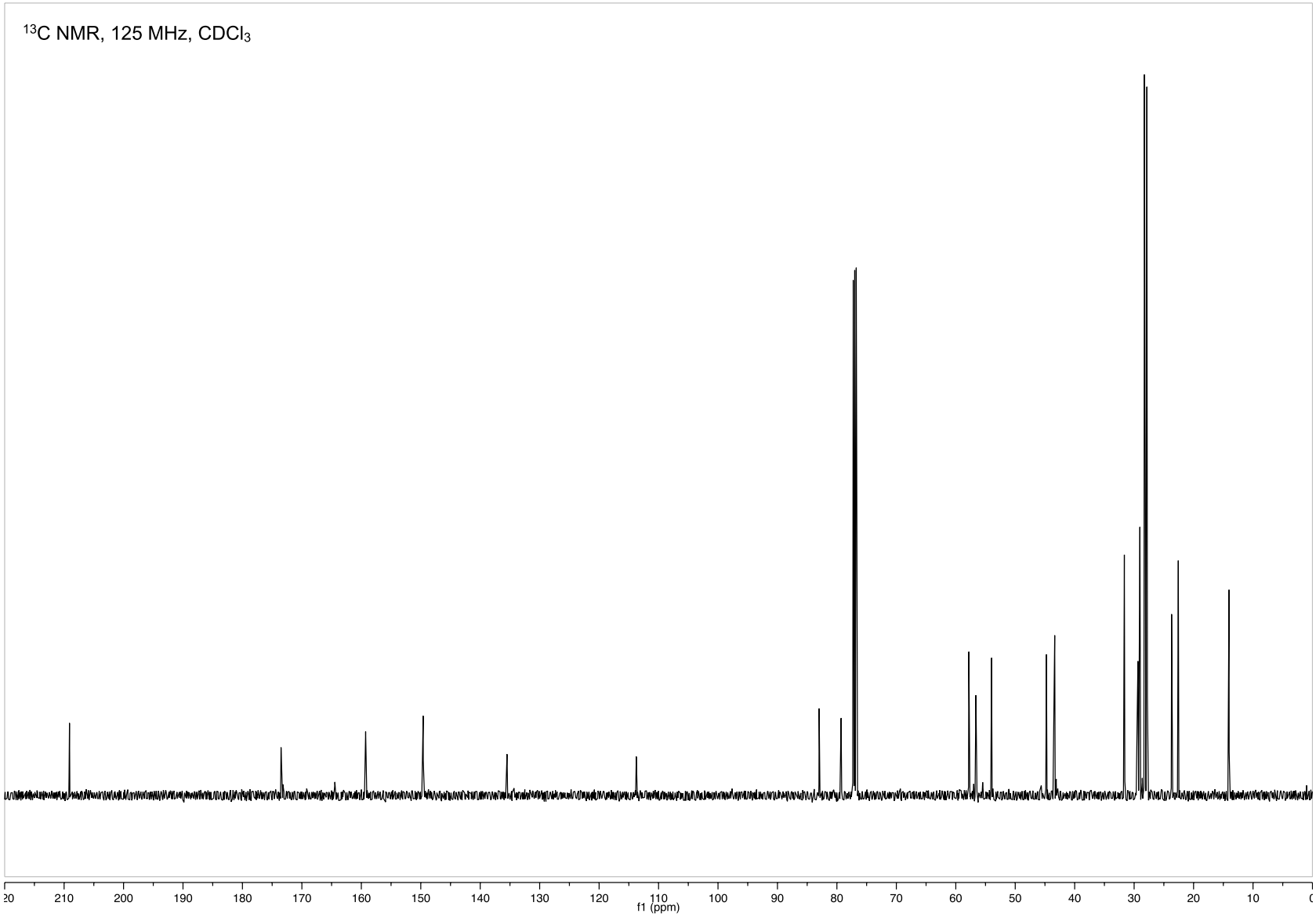


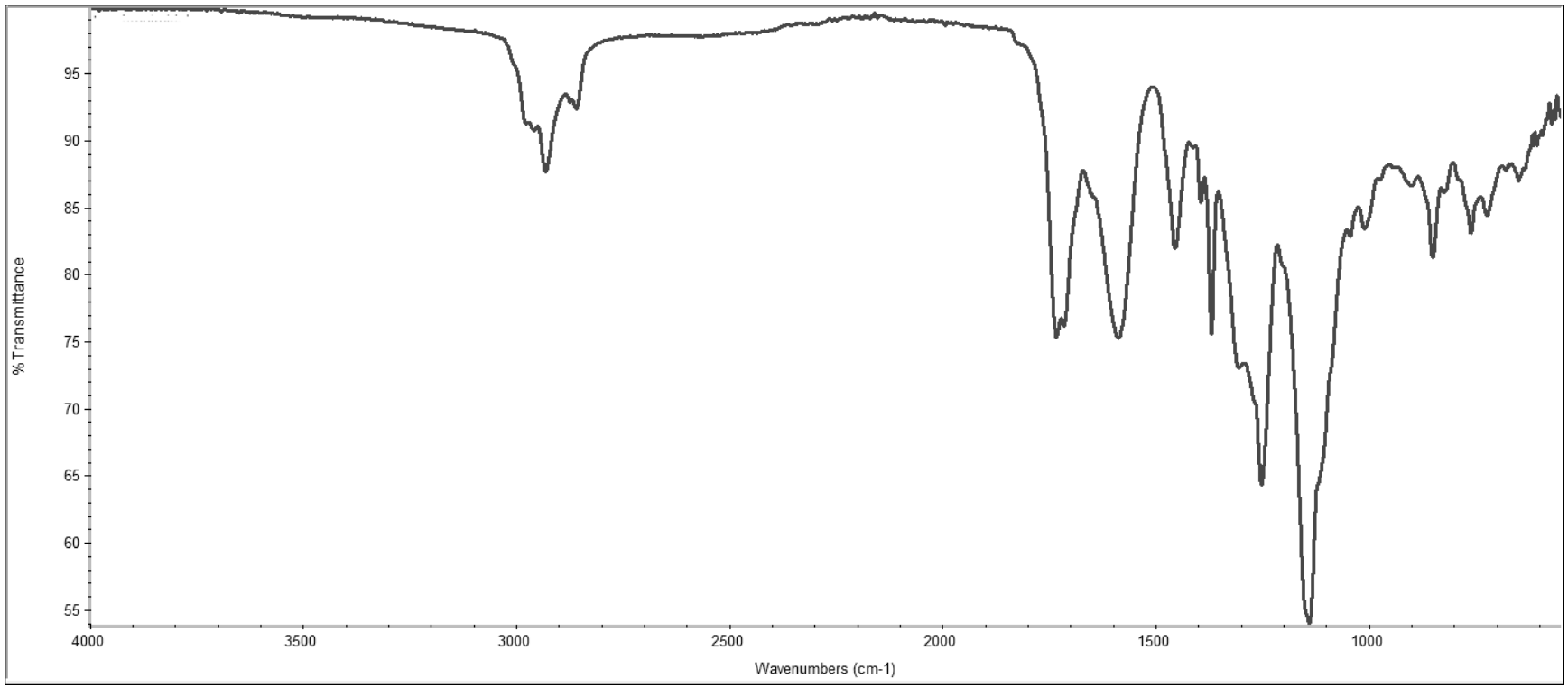

Parr, Economou, and Herzon "A concise synthesis of (+)-batzelladine B from simple pyrrole-based starting materials" *Nature*

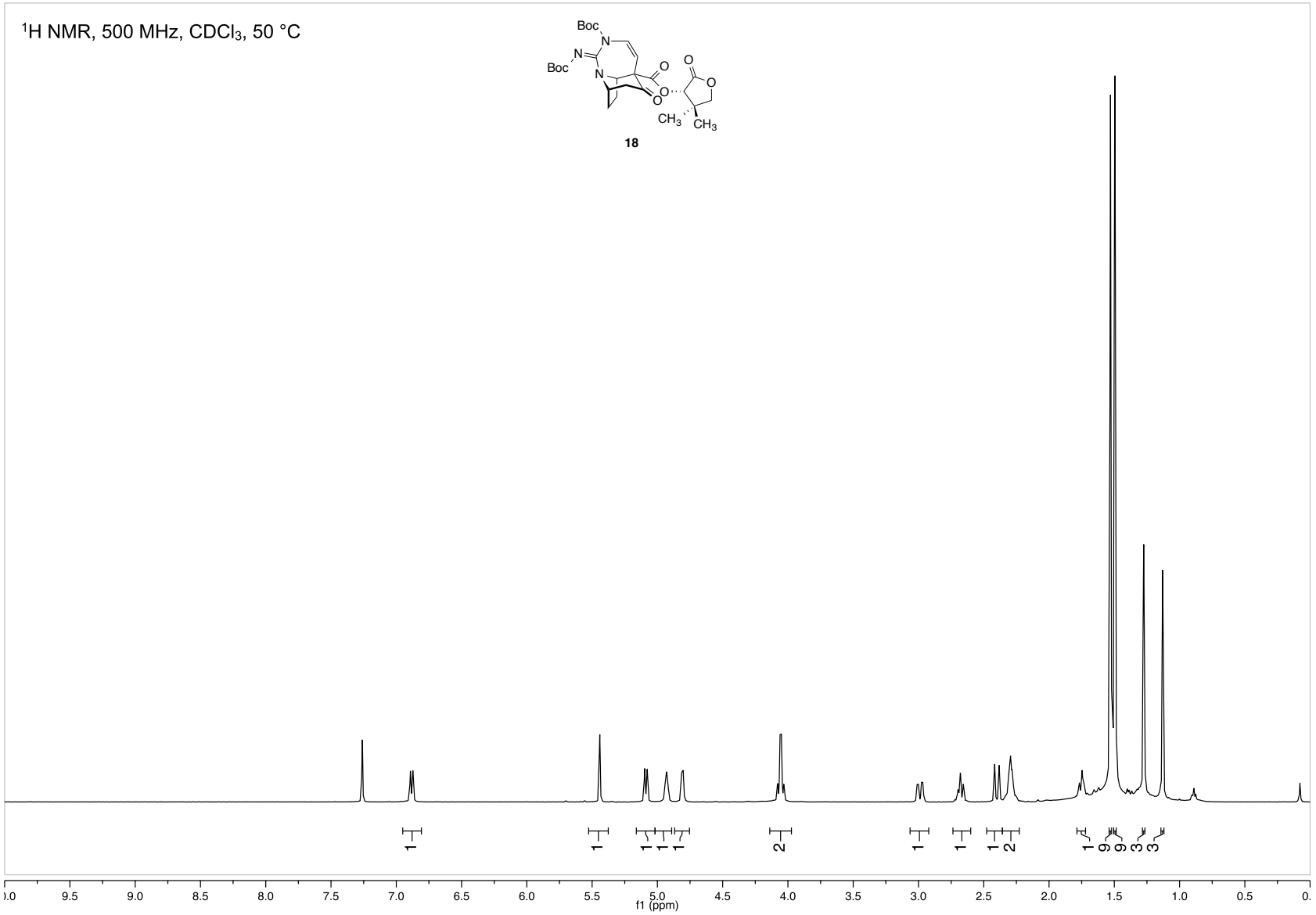

$^{13}$C NMR, 125 MHz, $CD_3OD$
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

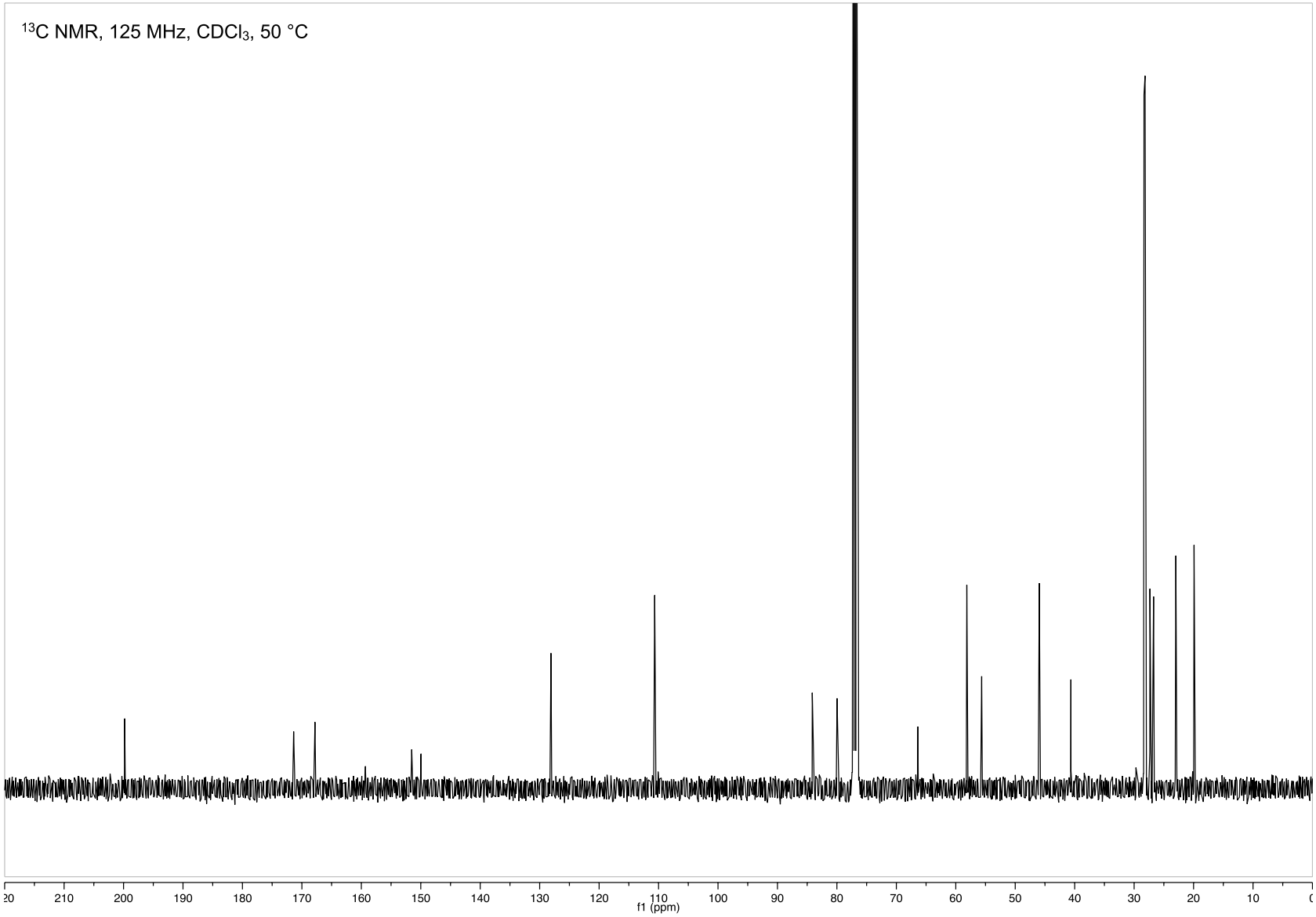

% Transmittance
95
90
85
80
75
70
65
60
55
50
45
40
35
30
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

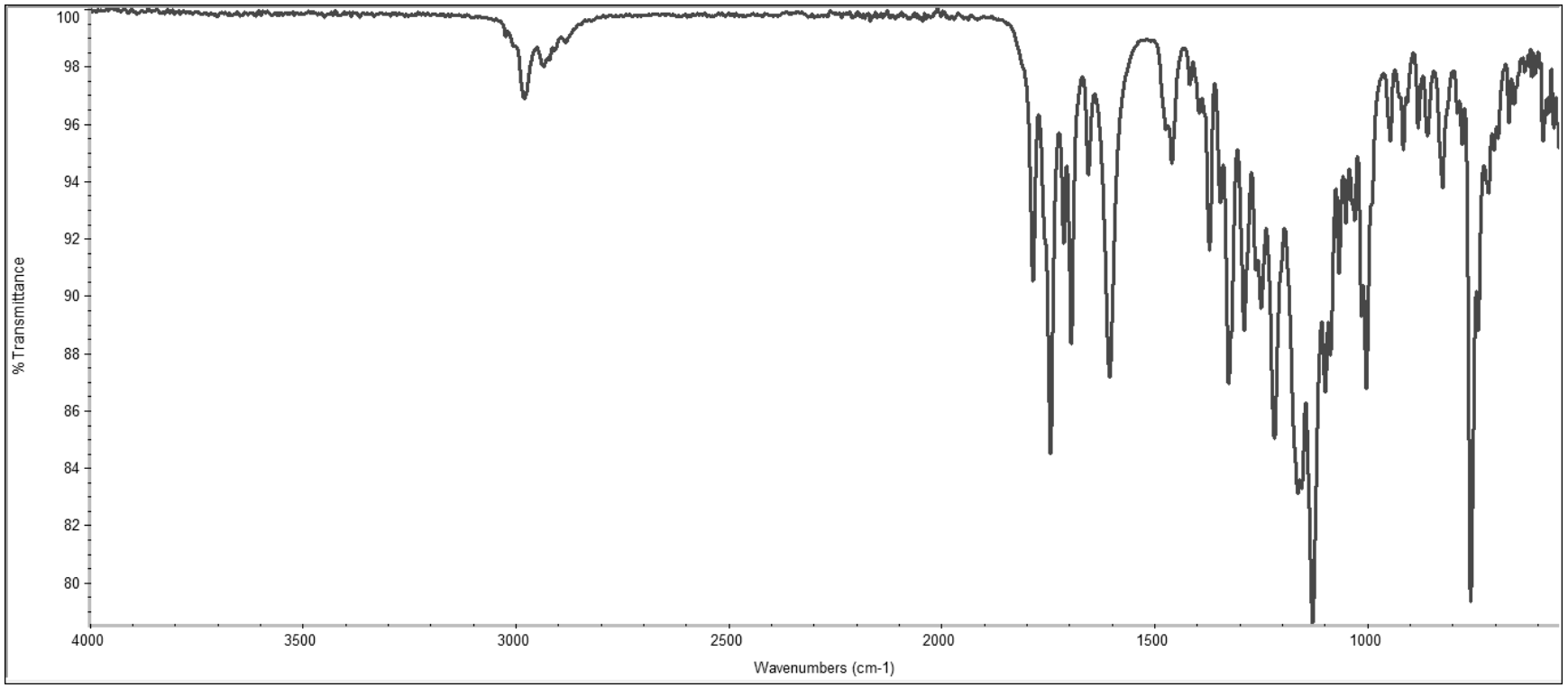

1H NMR, 500 MHz, CDCl3
Boc
Boc
CH3
N
N
N
OH
O
H
H
O
17
1.7
1.1
1.0
1.0
1.0
1.0
1.2
1.4
1.7
1.5
3.5
9.5
9.6
9.7
3.7
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

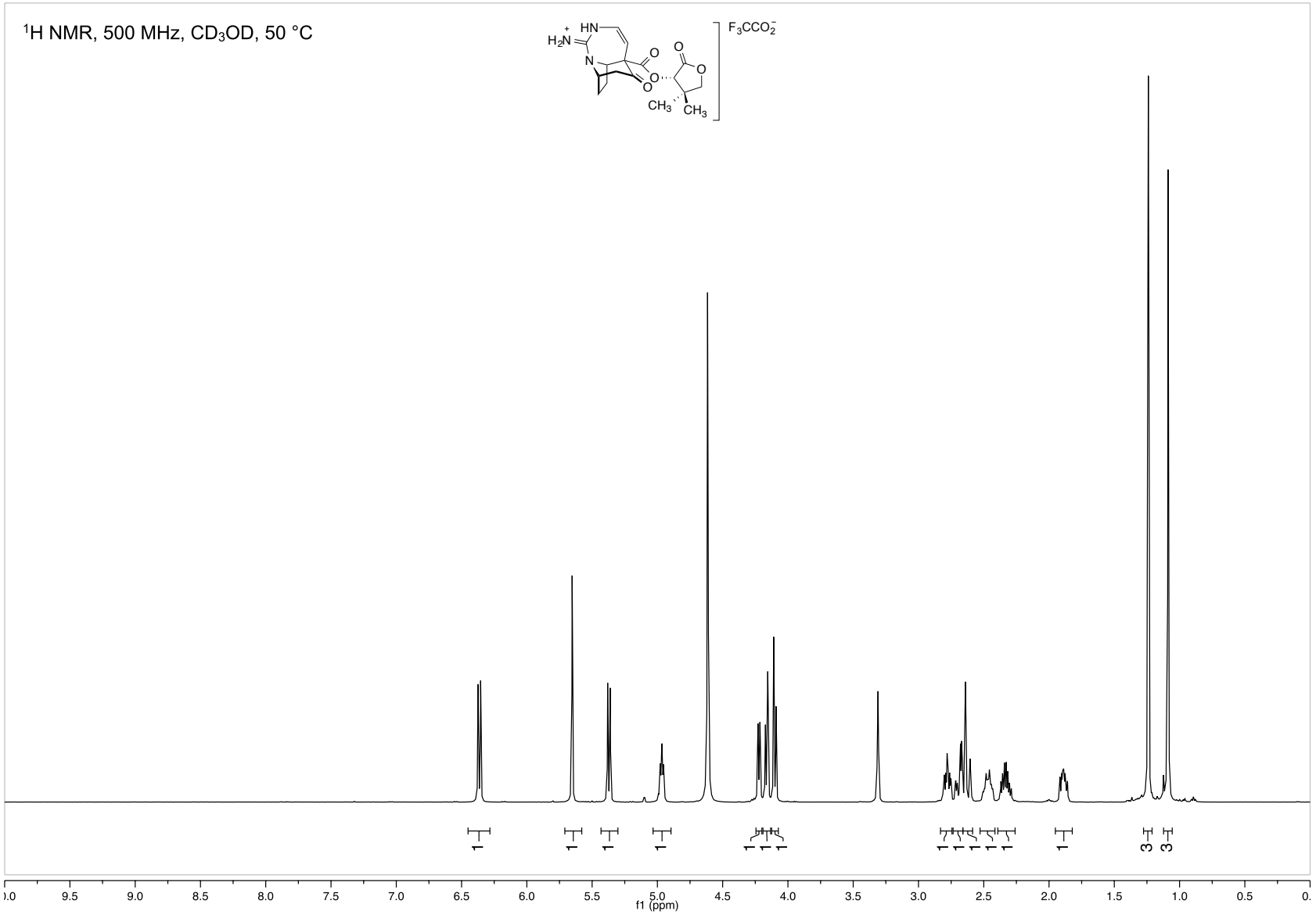

$^{13}$C NMR, 125 MHz, $CDCl_3$
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


% Transmittance
95
90
85
80
75
70
65
60
55
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

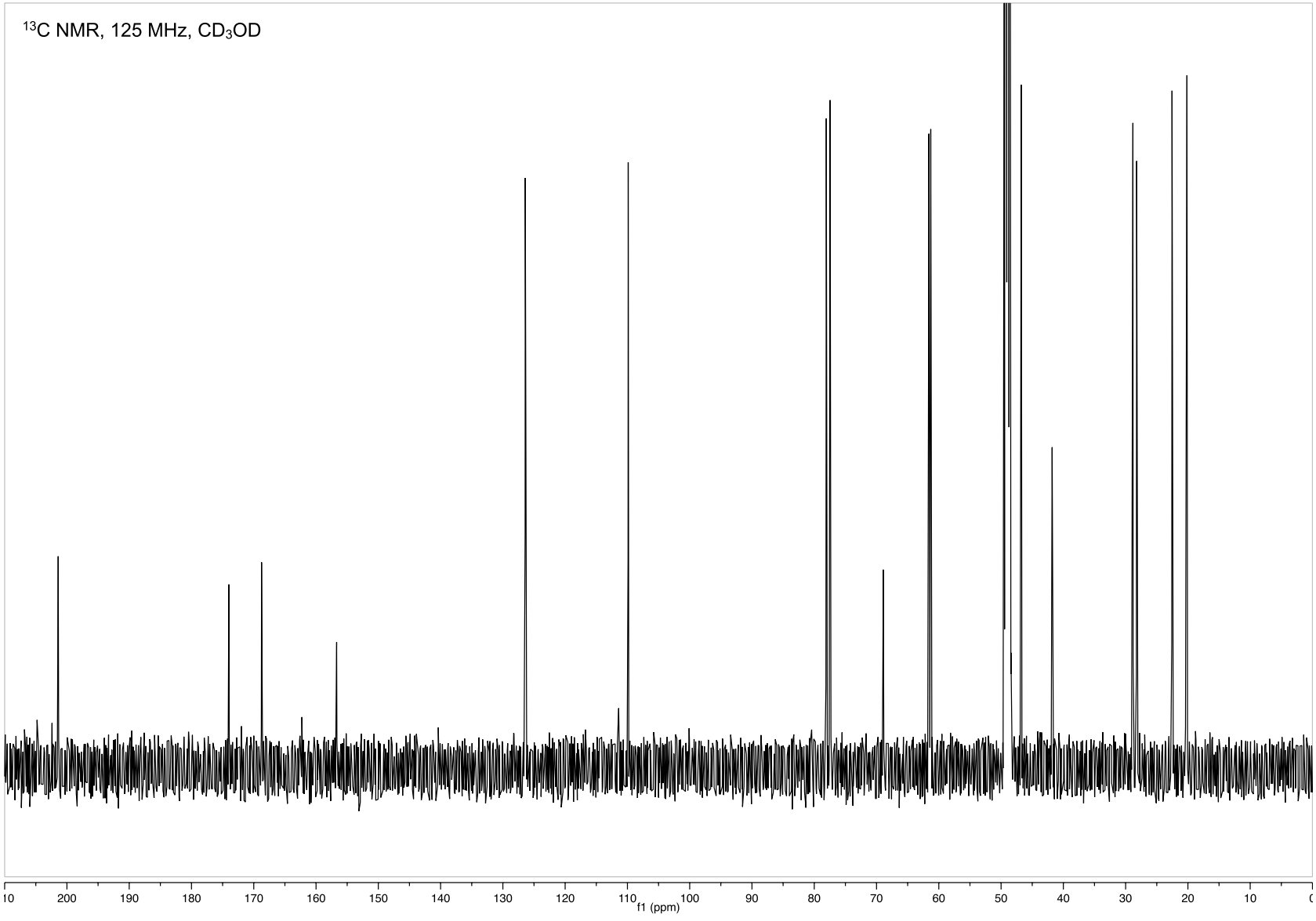

1H NMR, 500 MHz, CDCl3, 50 °C
Boc
N
N
Boc
N
O
O
O
O
O
CH3
CH3
18
1
1
1
1
1
2
1
1
1
2
1
9
9
3
3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

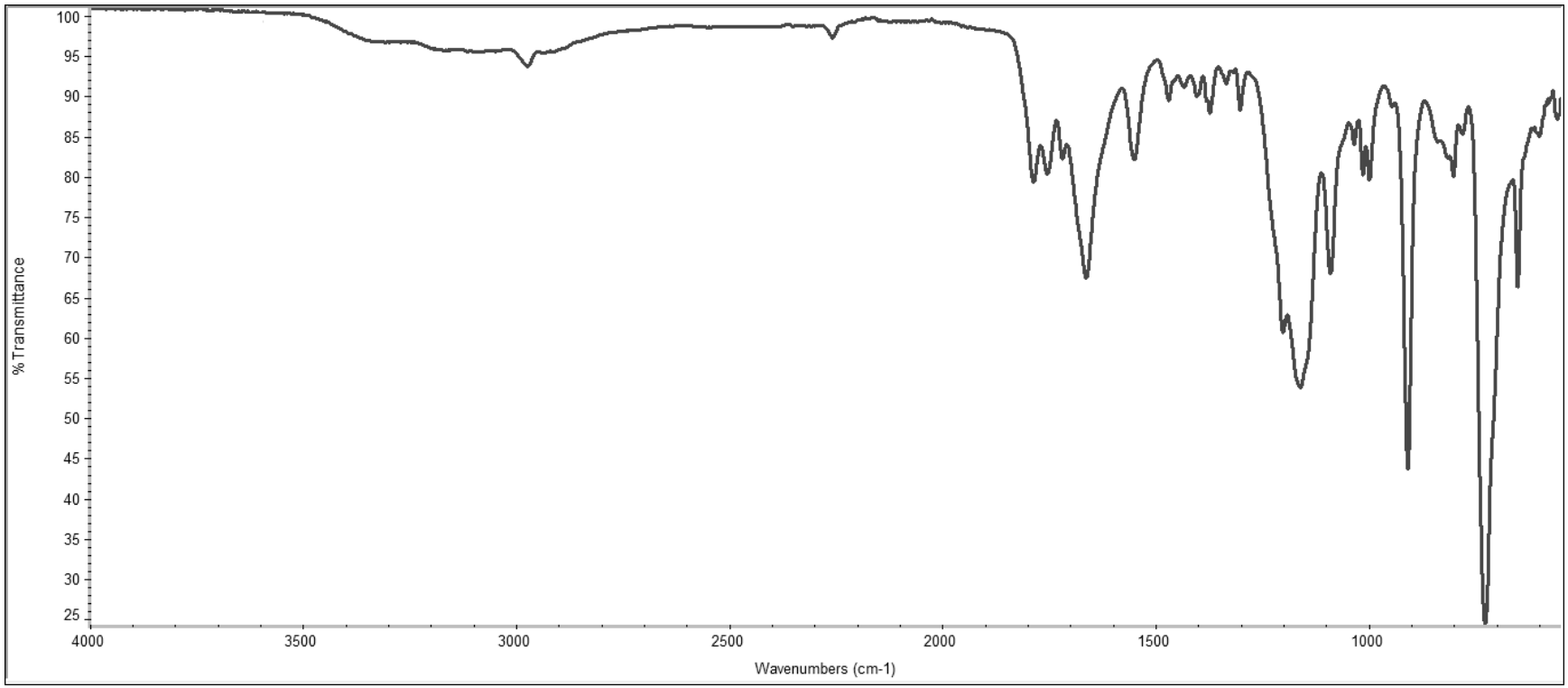

$^{13}$C NMR, 125 MHz, $CDCl_3$, 50 °C
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


100
98
96
94
92
90
88
86
84
82
80
% Transmittance
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

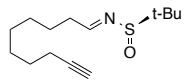



Parr, Economou, and Herzon "A concise synthesis of (+)-batzelladine B from simple pyrrole-based starting materials" *Nature*

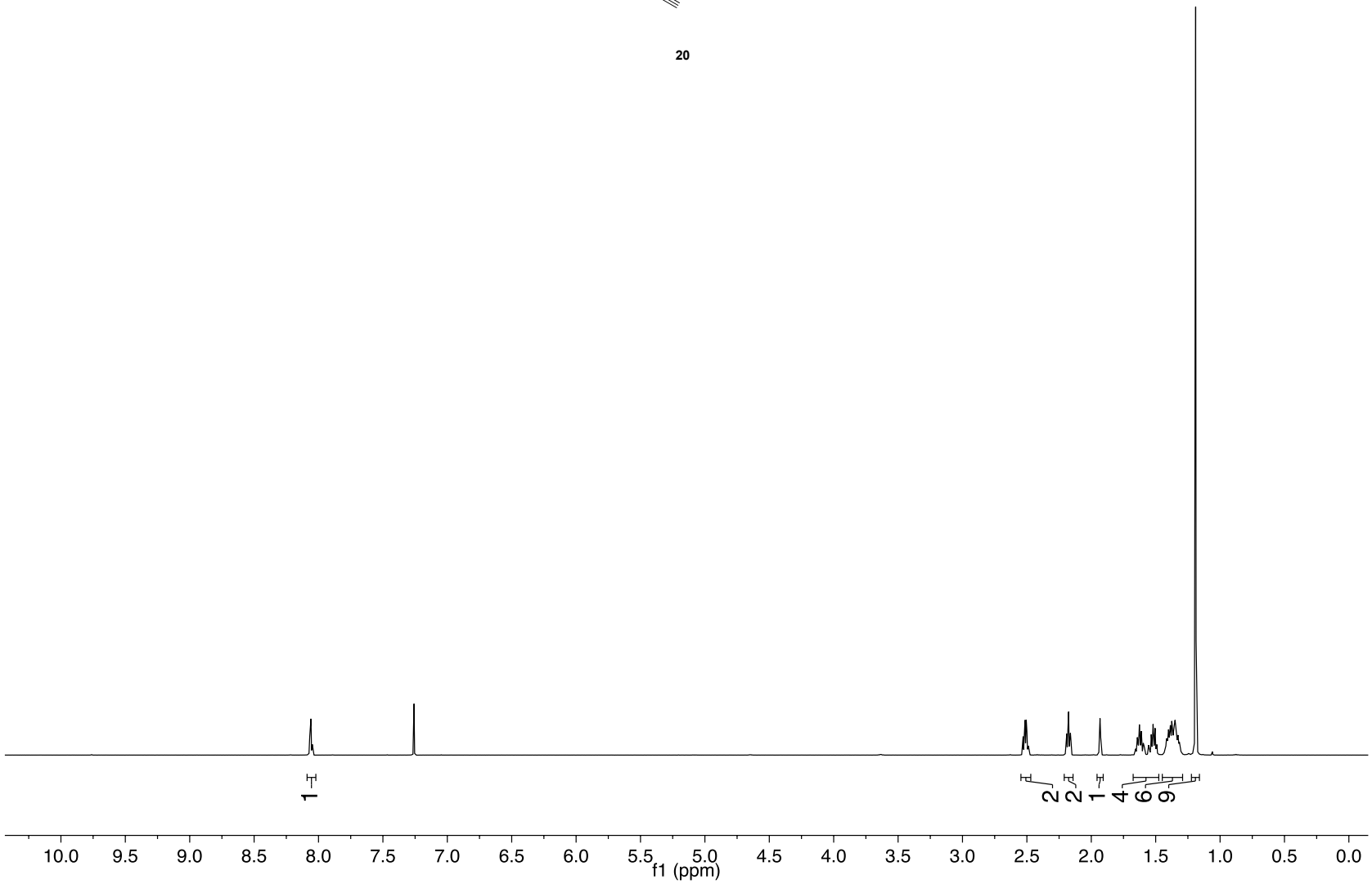

$^{13}$C NMR, 125 MHz, $CD_3OD$
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


% Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

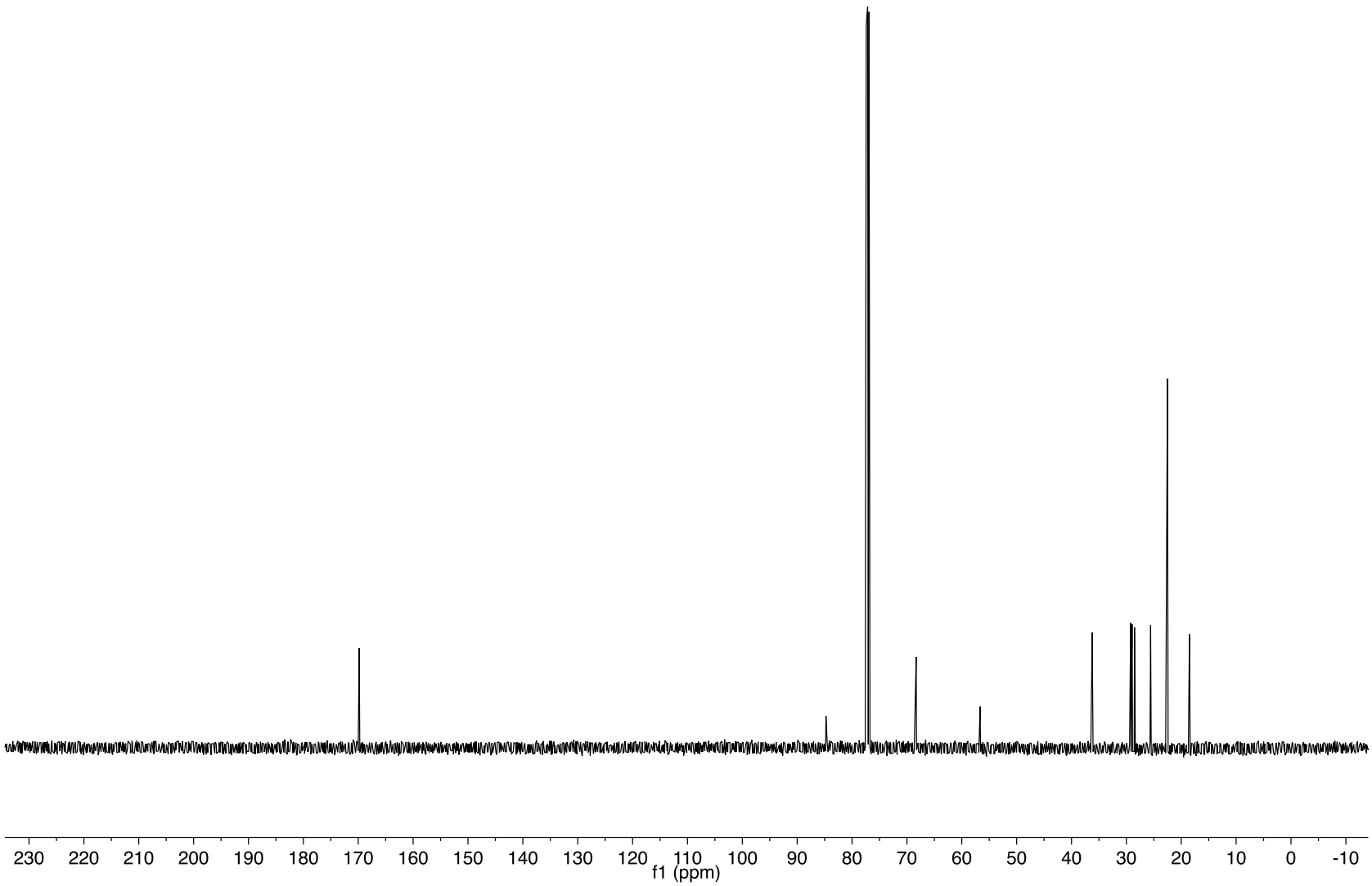
$^1$H NMR, 500 MHz, $CDCl_3$

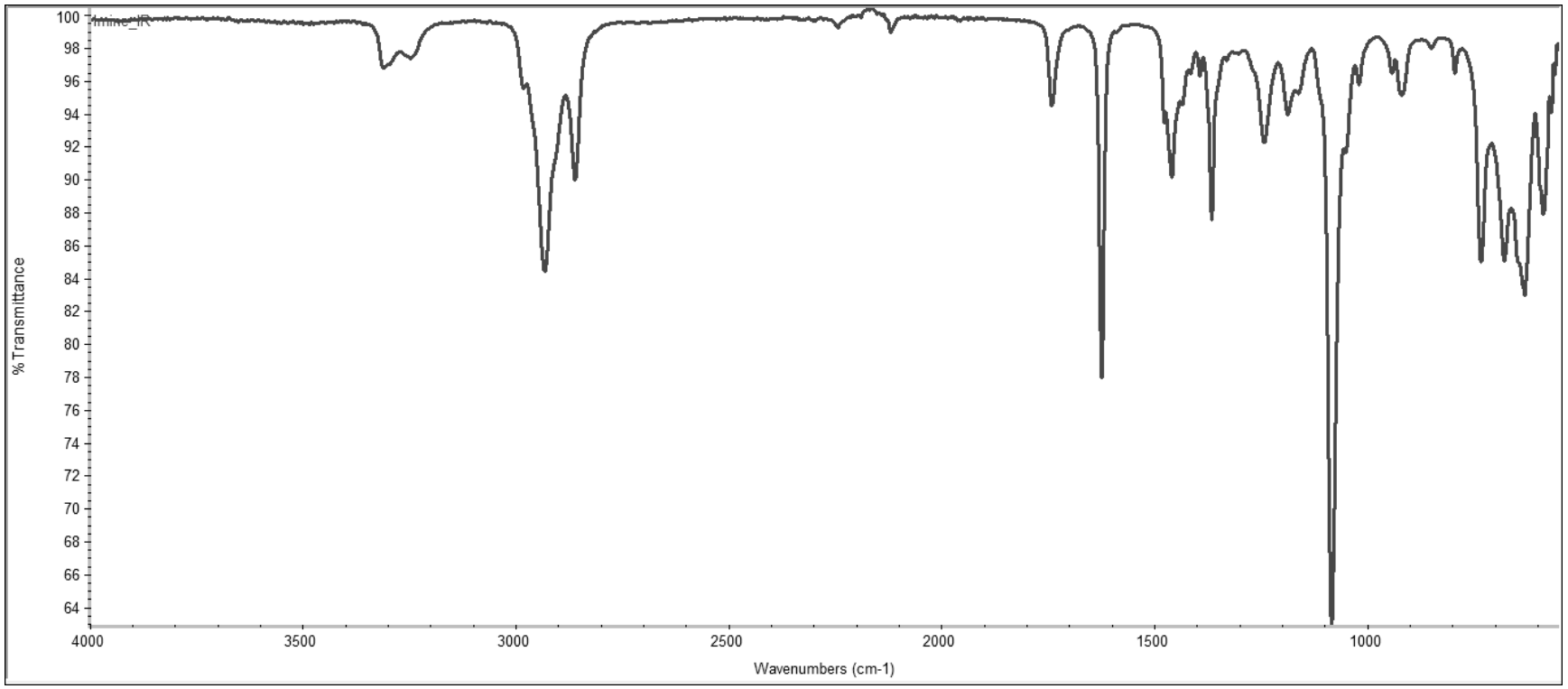



**20**

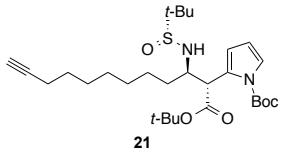


$^{13}C$ NMR, 125 MHz, $CDCl_3$



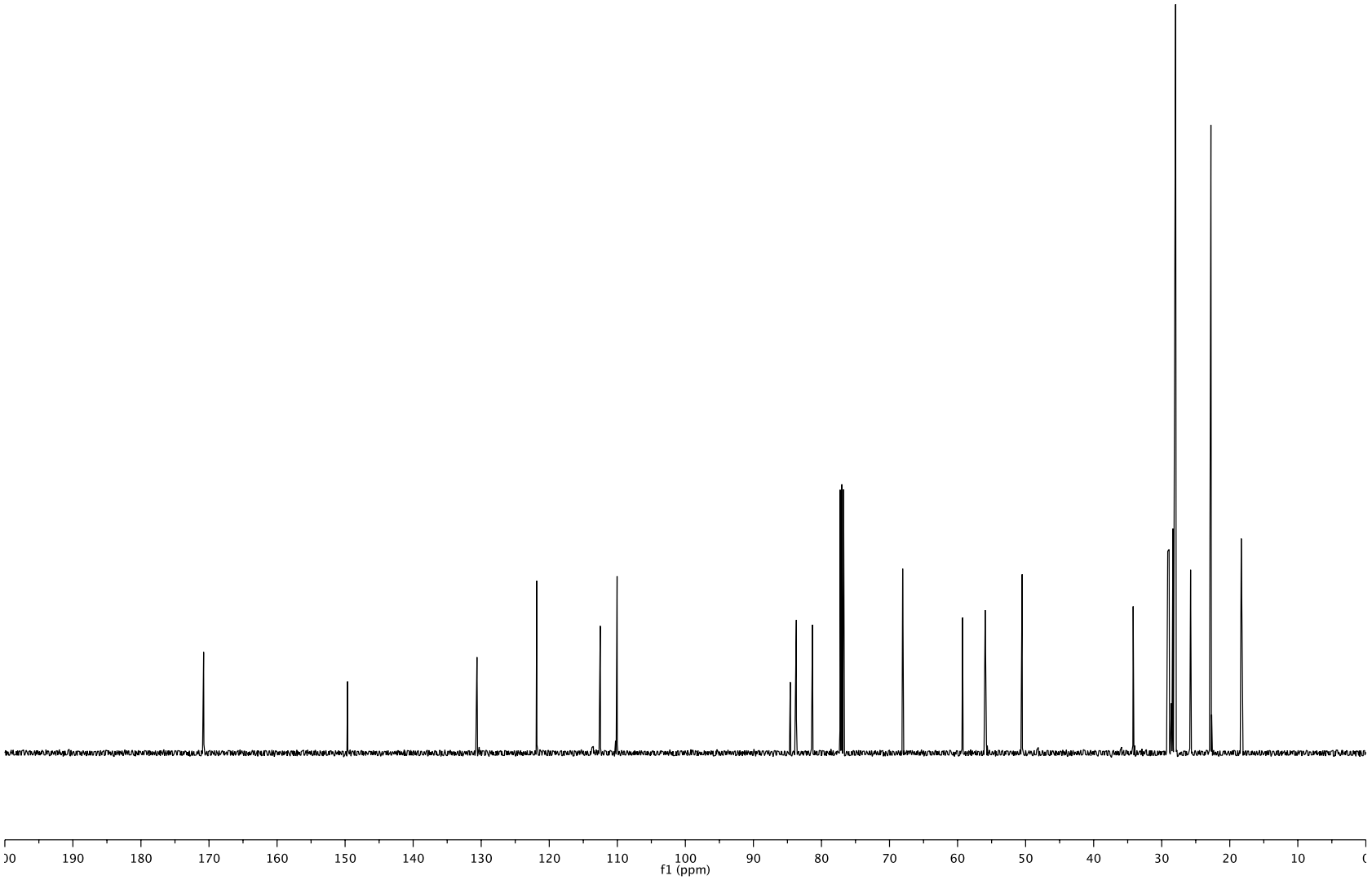

% Transmittance
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

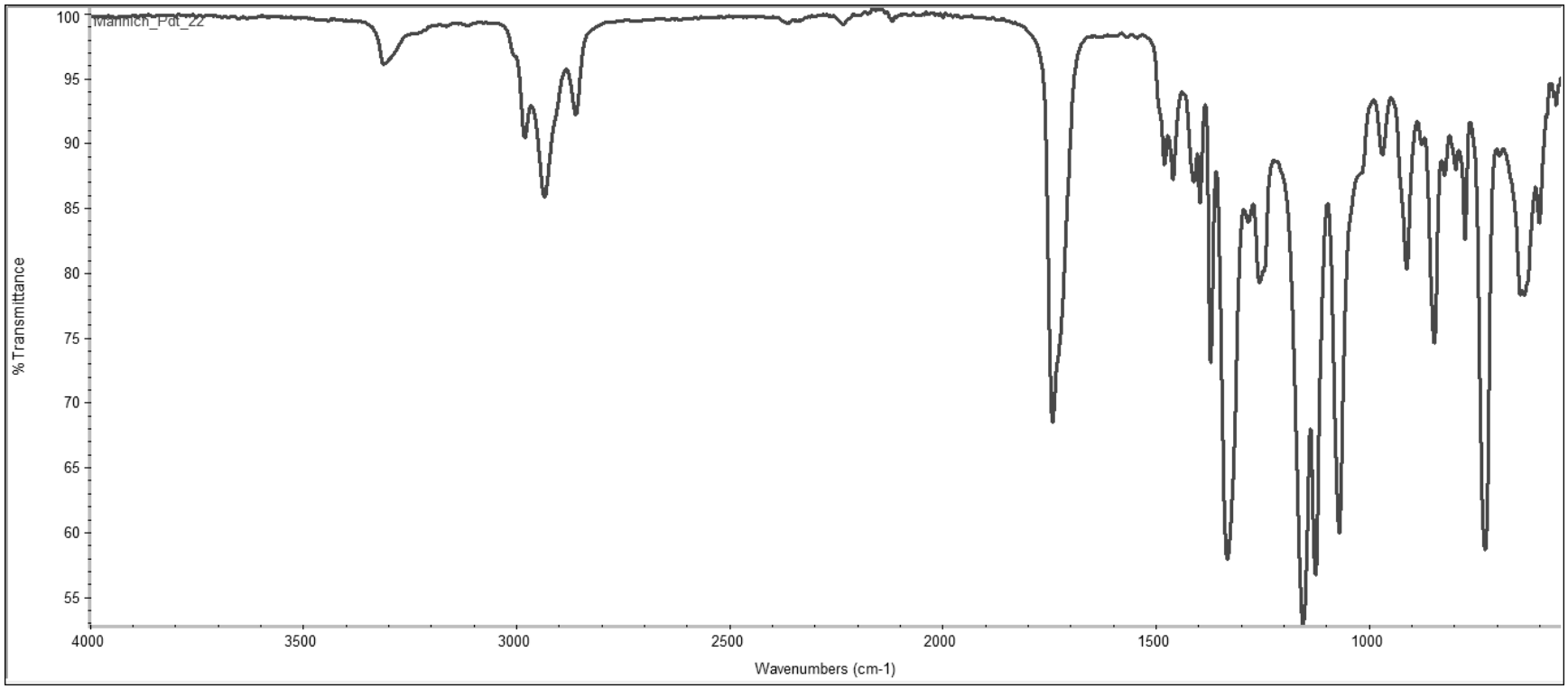
$^1$H NMR, 500 MHz, $CDCl_3$



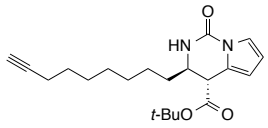

**21**

$^{13}C$ NMR, 125 MHz, $CDCl_3$

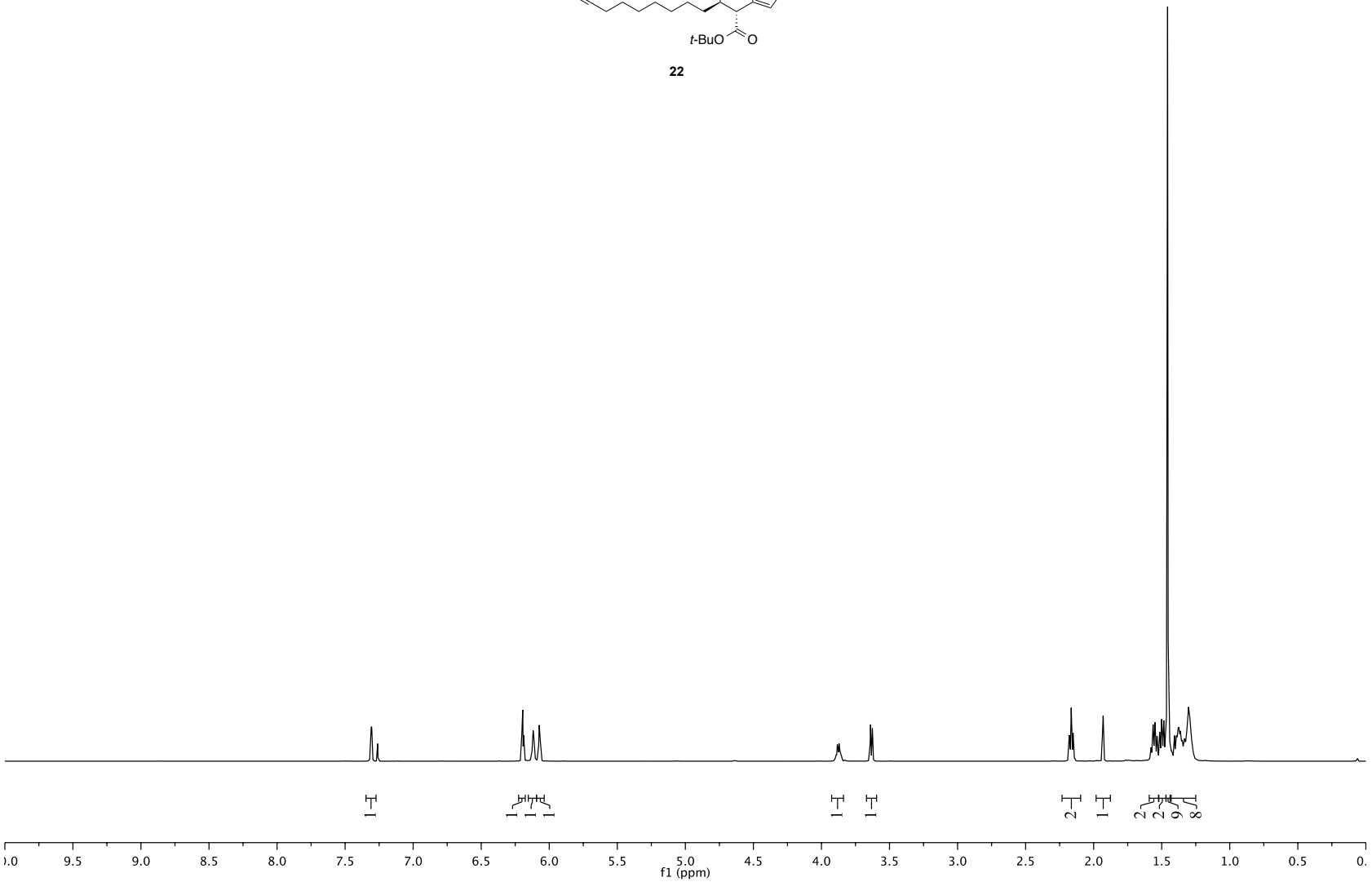



Mannich_Pdt_22
% Transmittance
100
95
90
85
80
75
70
65
60
55
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

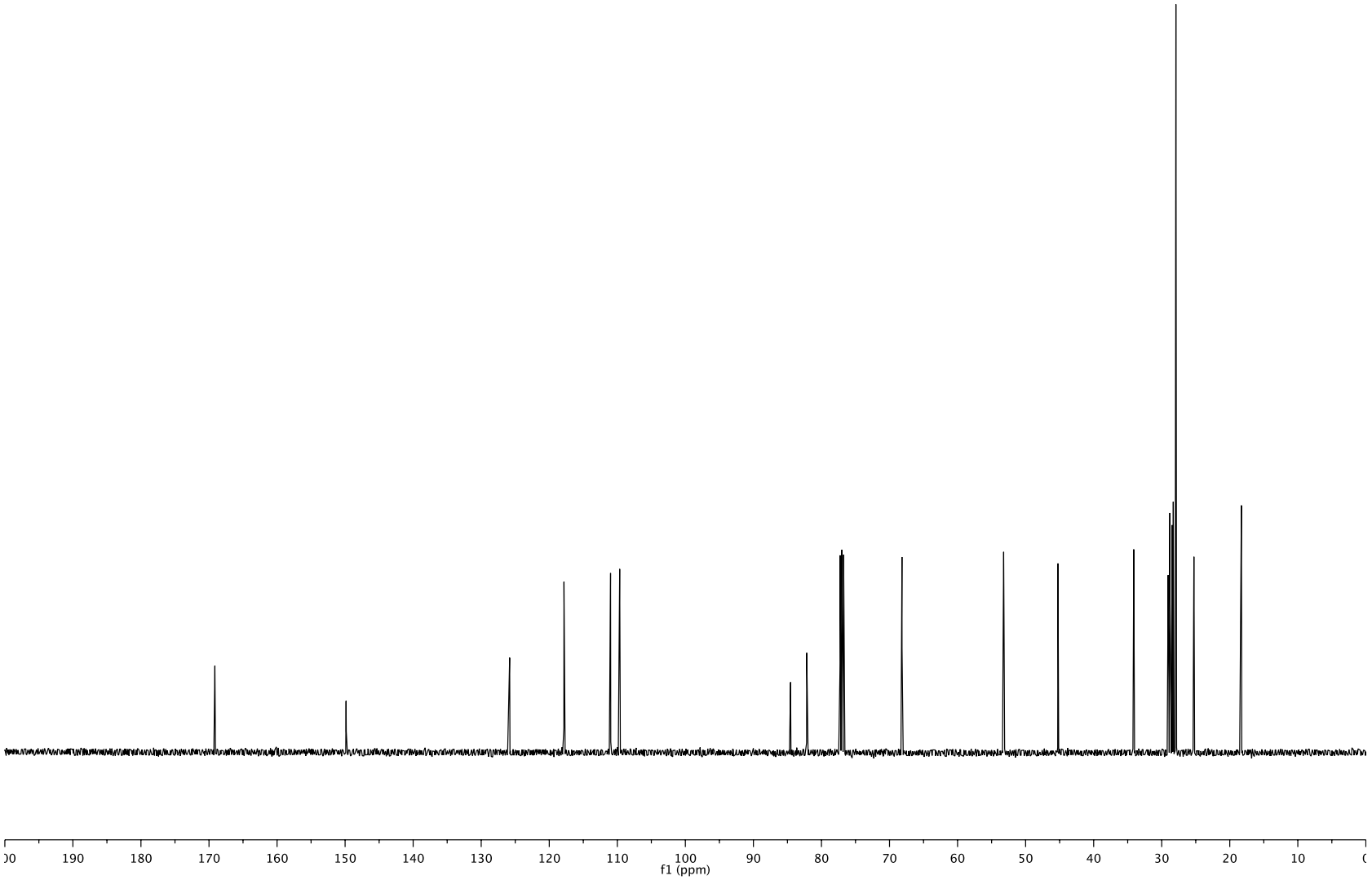
$^1$H NMR, 500 MHz, $CDCl_3$

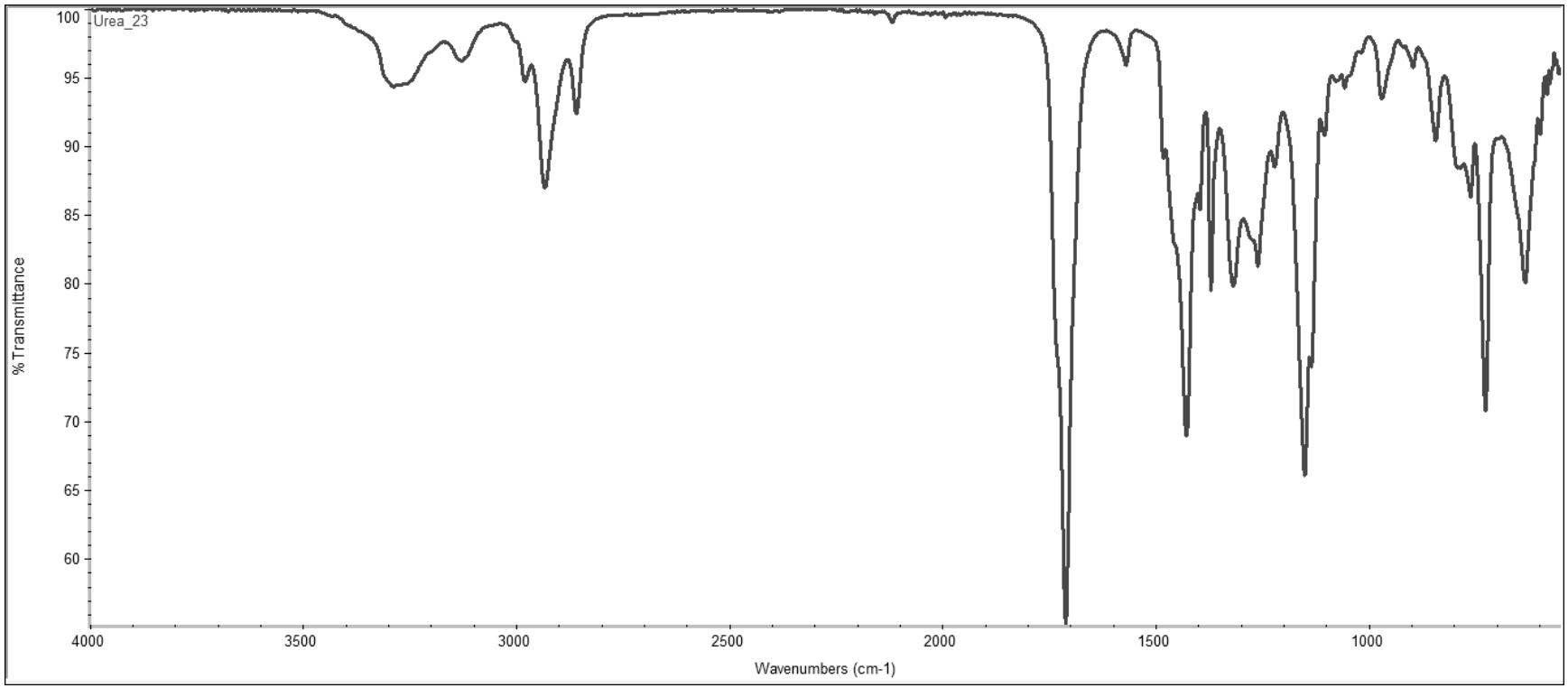



**22**

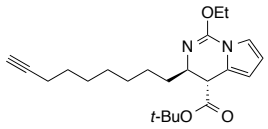


$^{13}C$ NMR, 125 MHz, $CDCl_3$

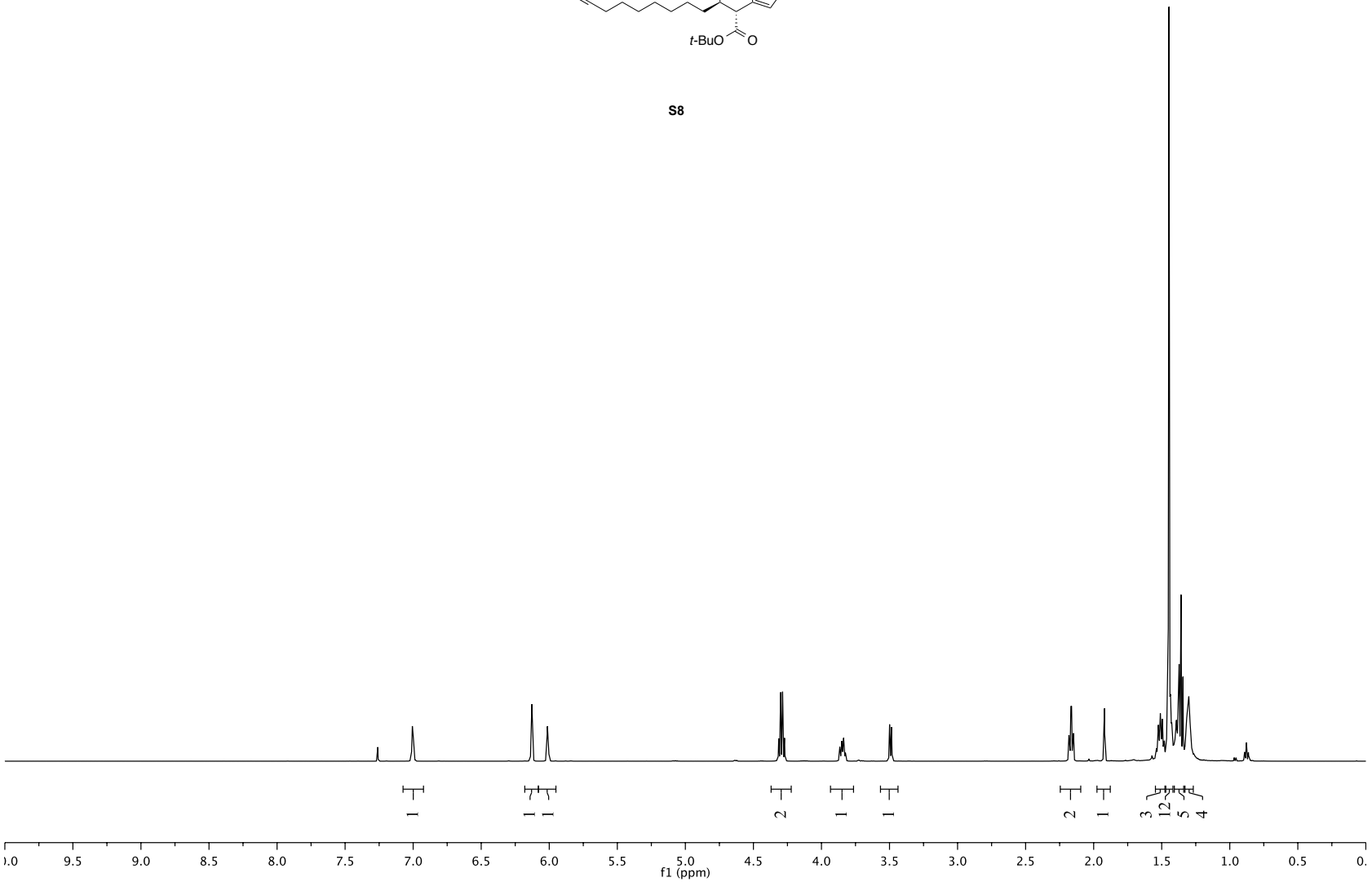



Urea_23
100
95
90
85
80
75
70
65
60
% Transmittance
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

$^1$H NMR, 500 MHz, $CDCl_3$

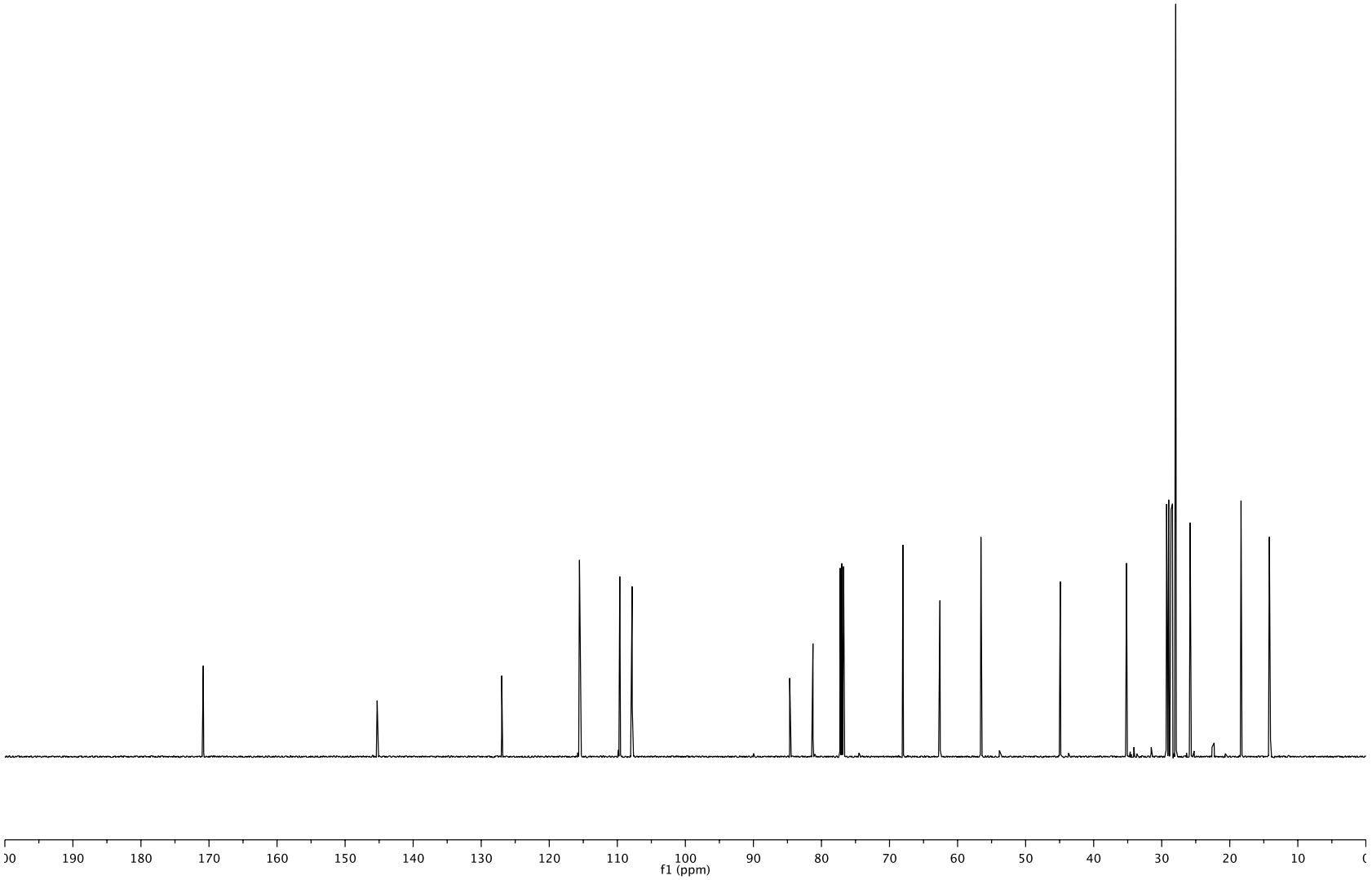


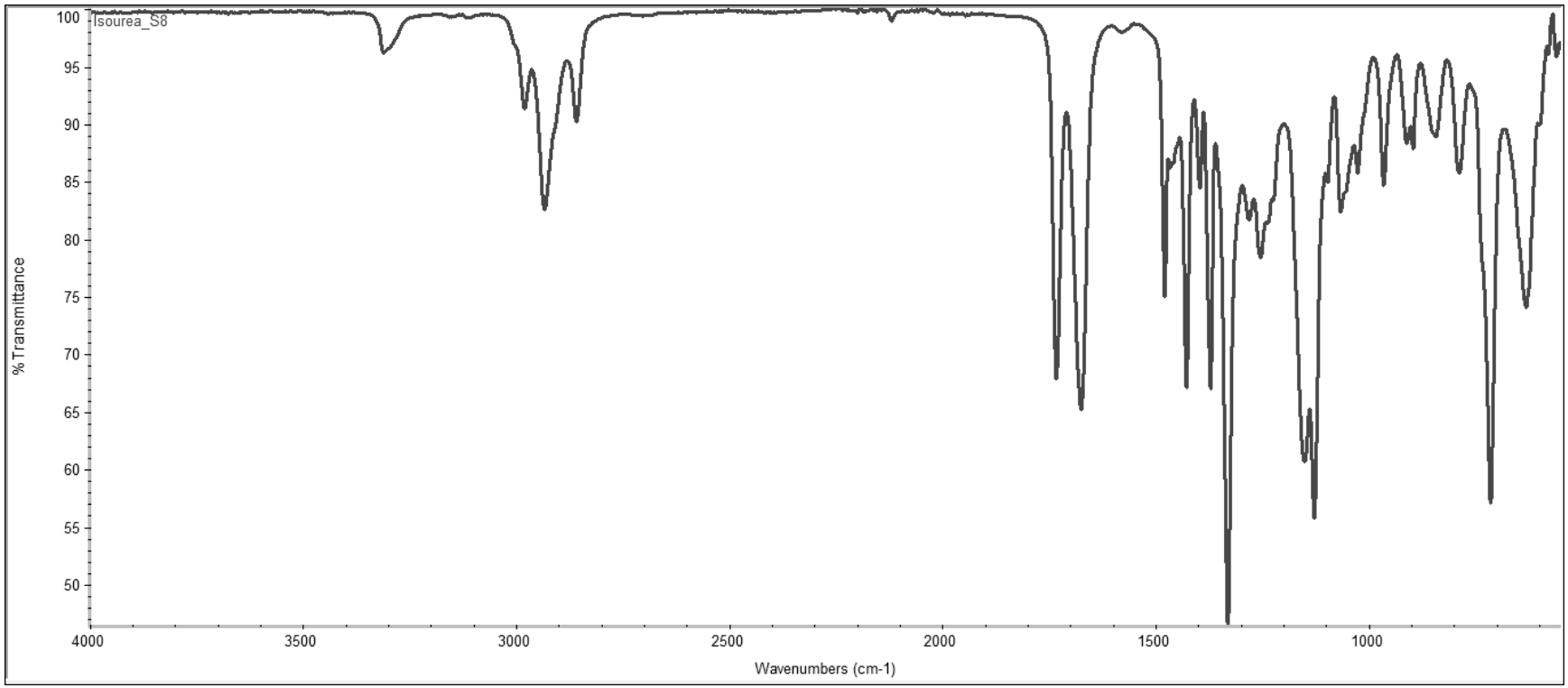

**S8**



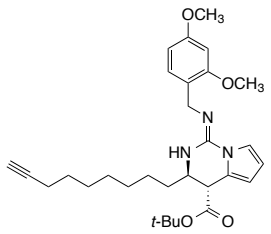

Parr, Economou, and Herzon "A concise synthesis of (+)-batzelladine B from simple pyrrole-based starting materials" *Nature*

$^{13}C$ NMR, 125 MHz, $CDCl_3$

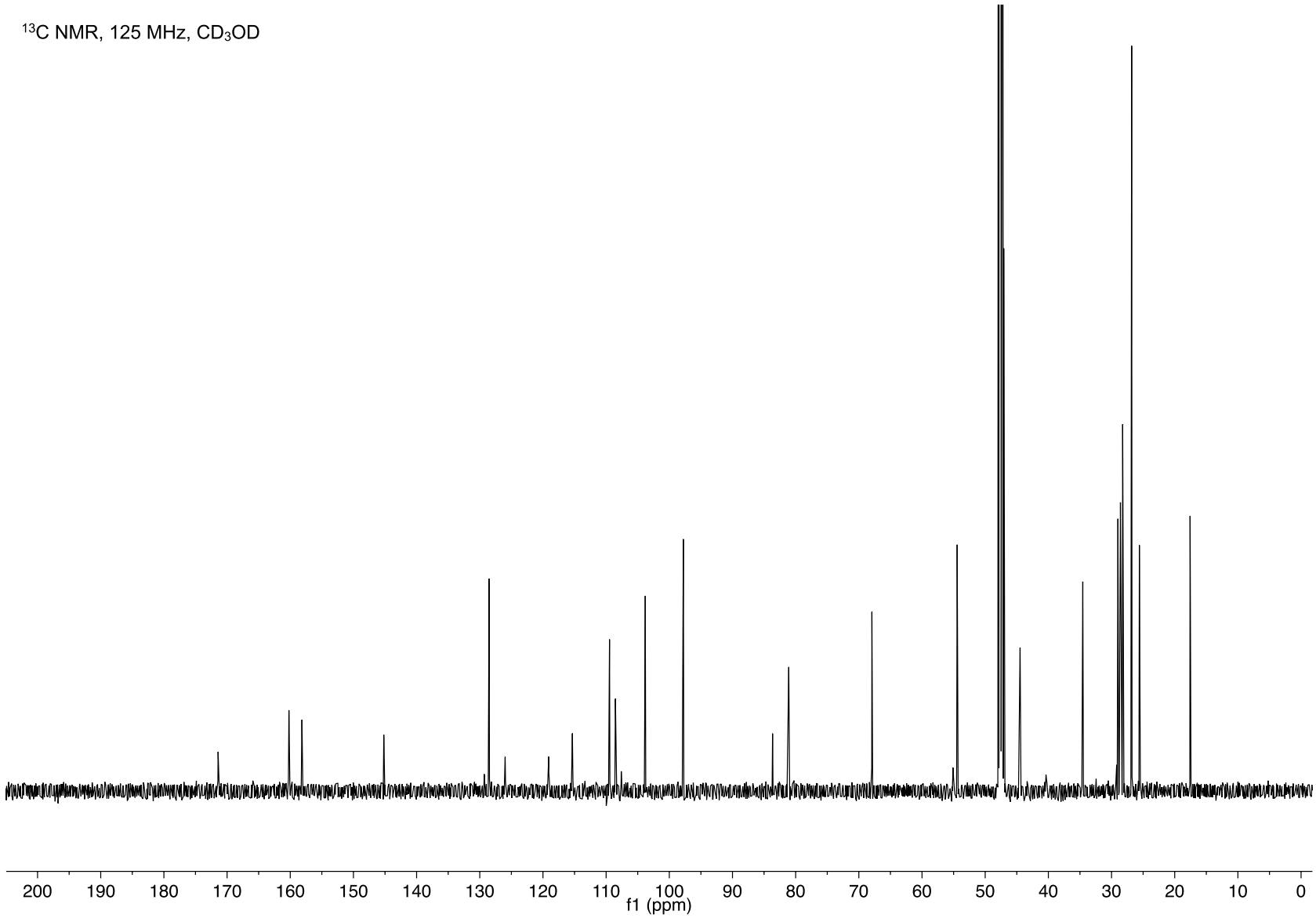


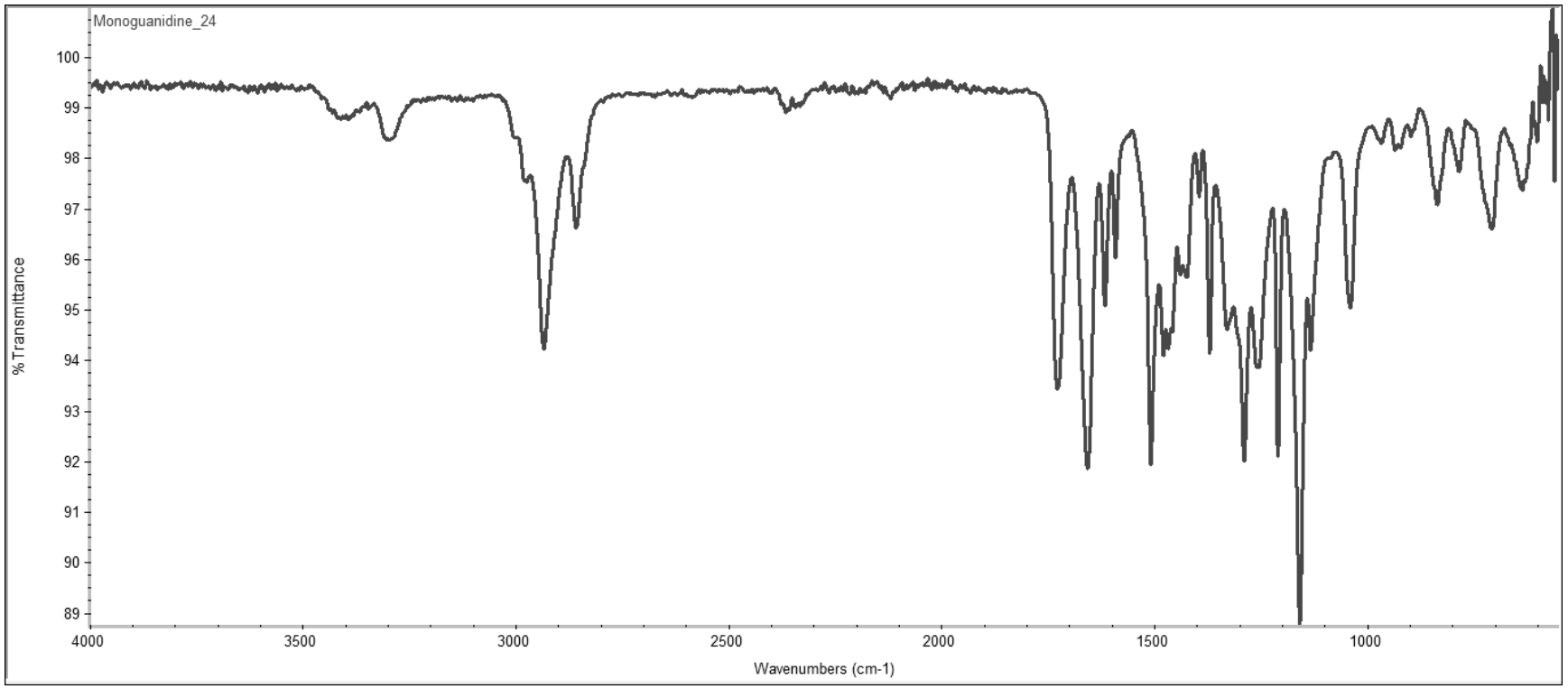

Isourea_S8
% Transmittance
100
95
90
85
80
75
70
65
60
55
50
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

$^1$H NMR, 500 MHz, $CD_3OD$

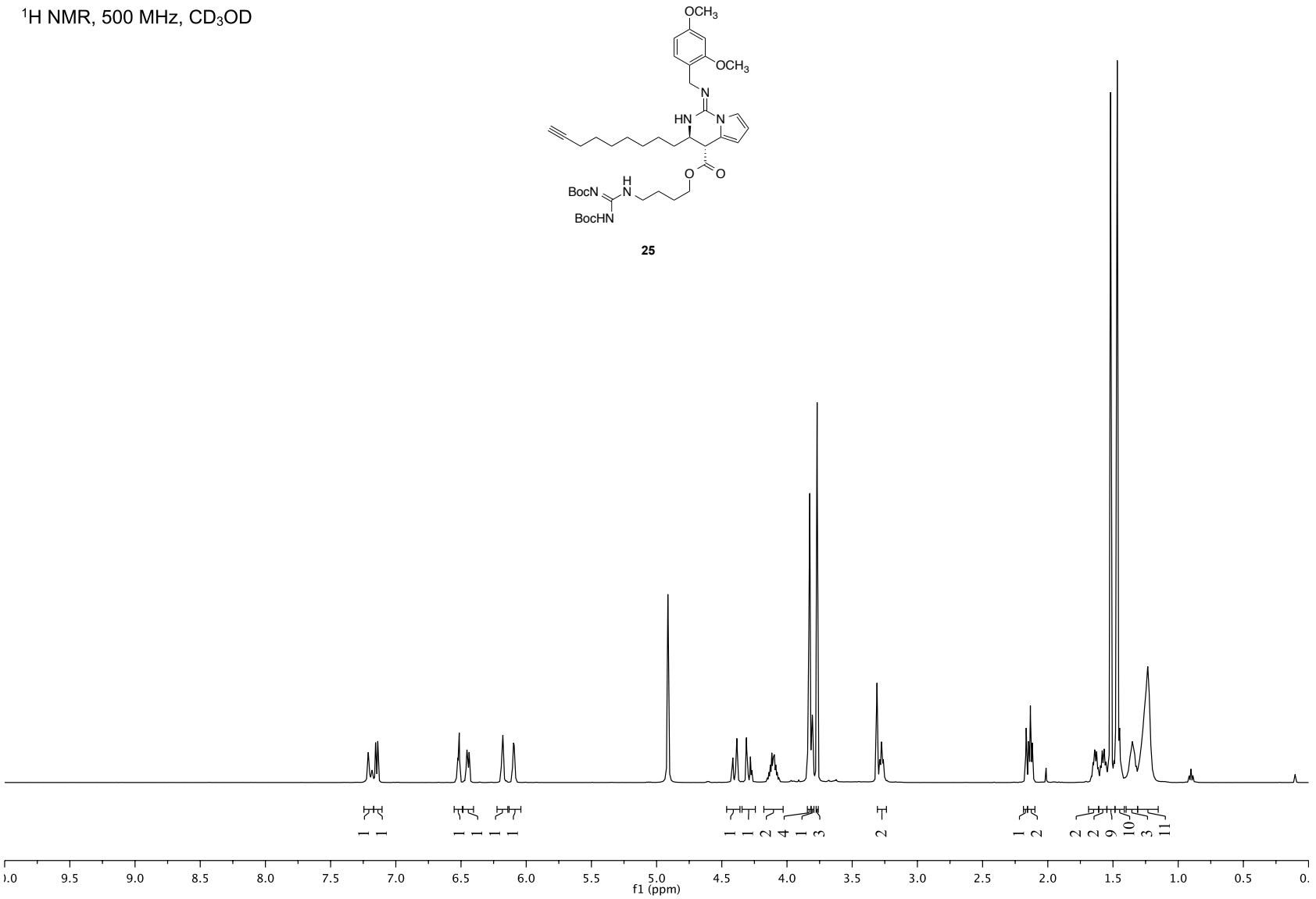


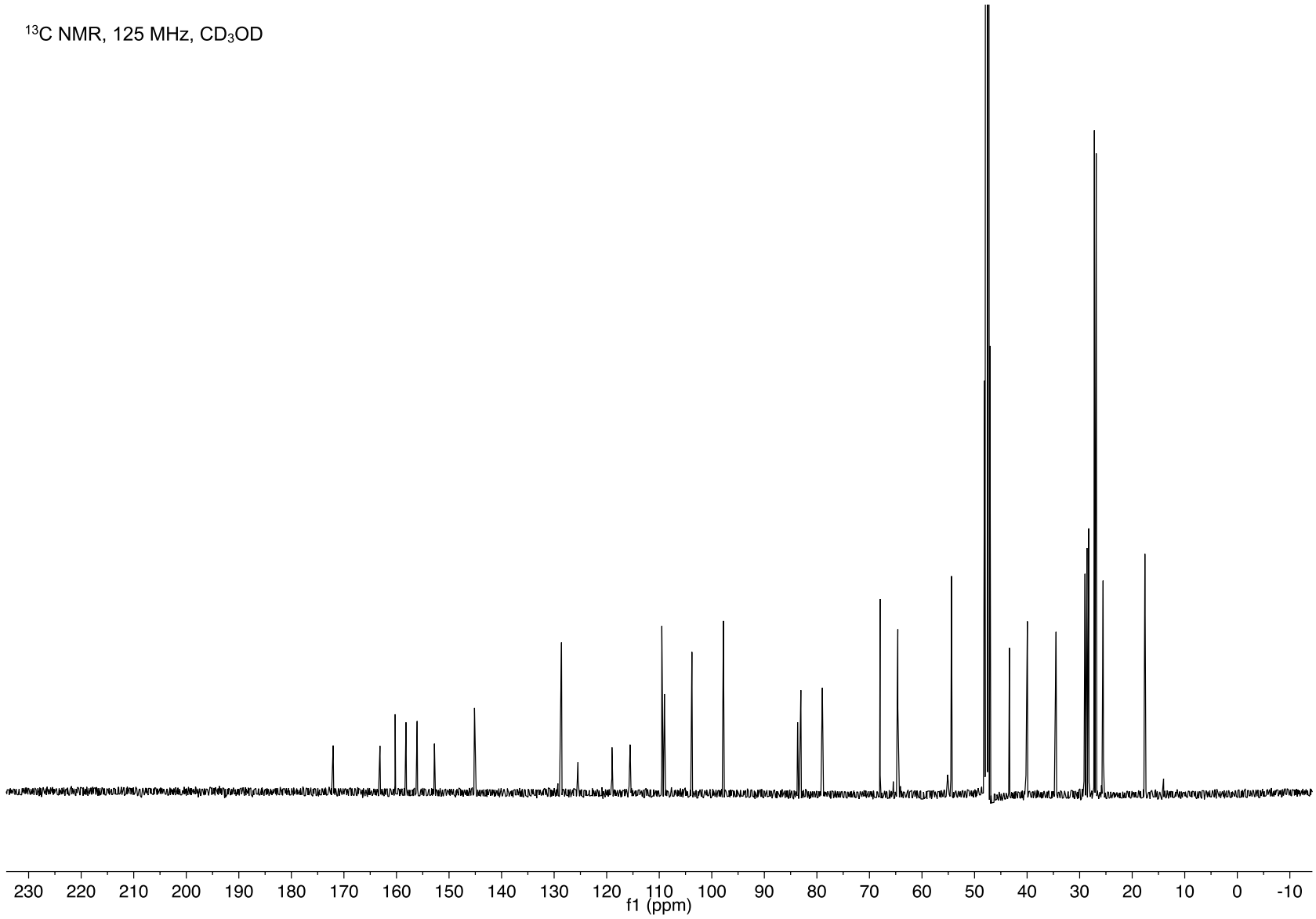

**23**

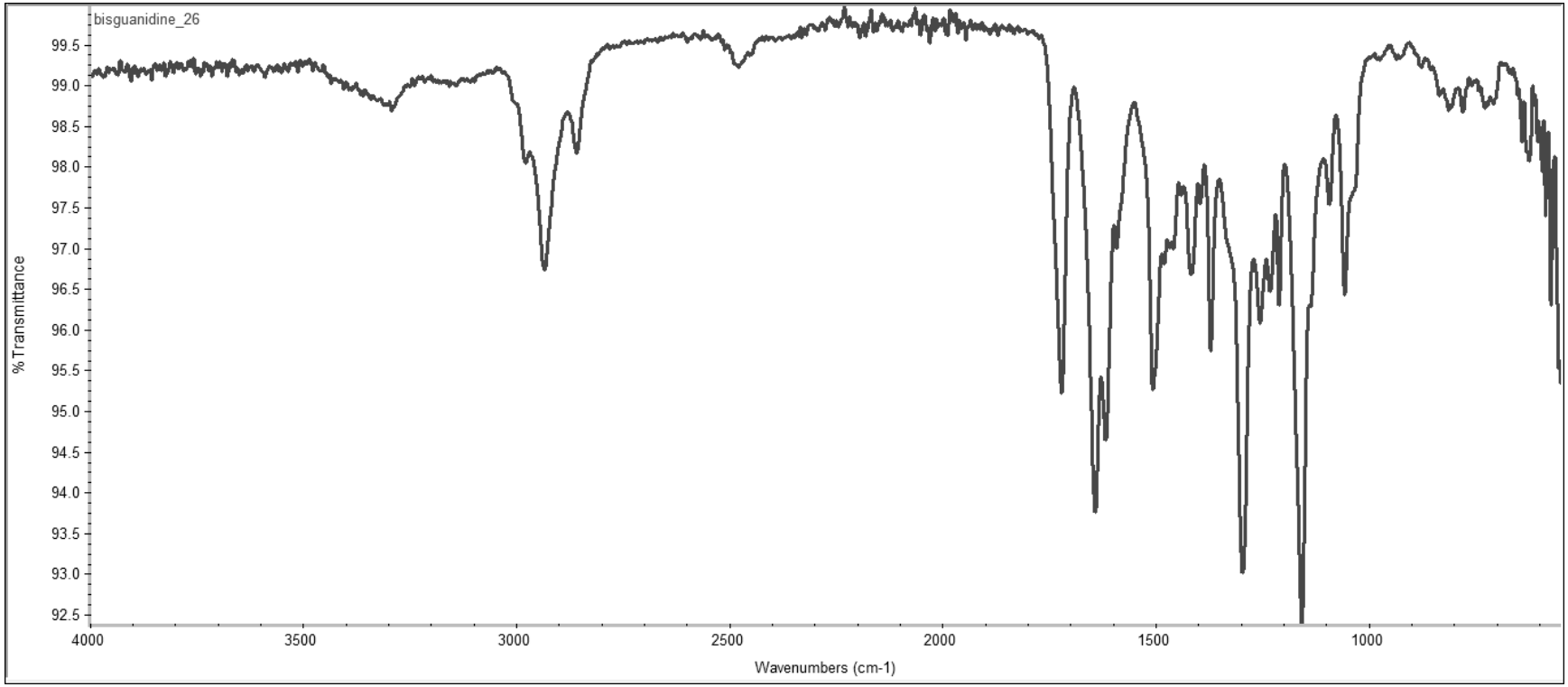

$^{13}$C NMR, 125 MHz, $CD_3OD$
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Monoguanidine_24
% Transmittance
100
99
98
97
96
95
94
93
92
91
90
89
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

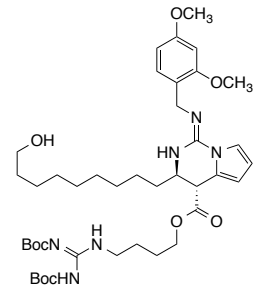
$^1$H NMR, 500 MHz, $CD_3OD$



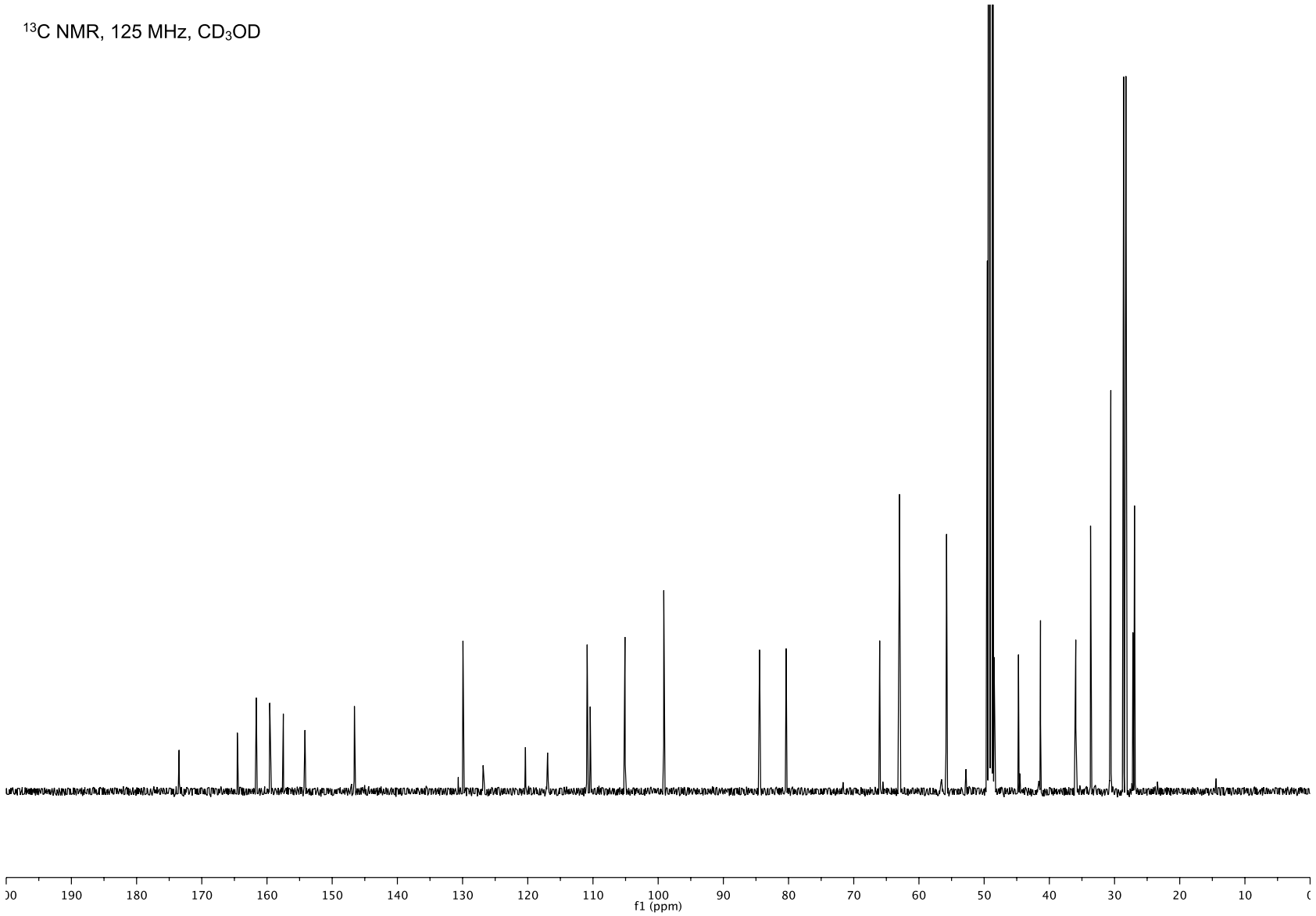

$^{13}$C NMR, 125 MHz, $CD_3OD$
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

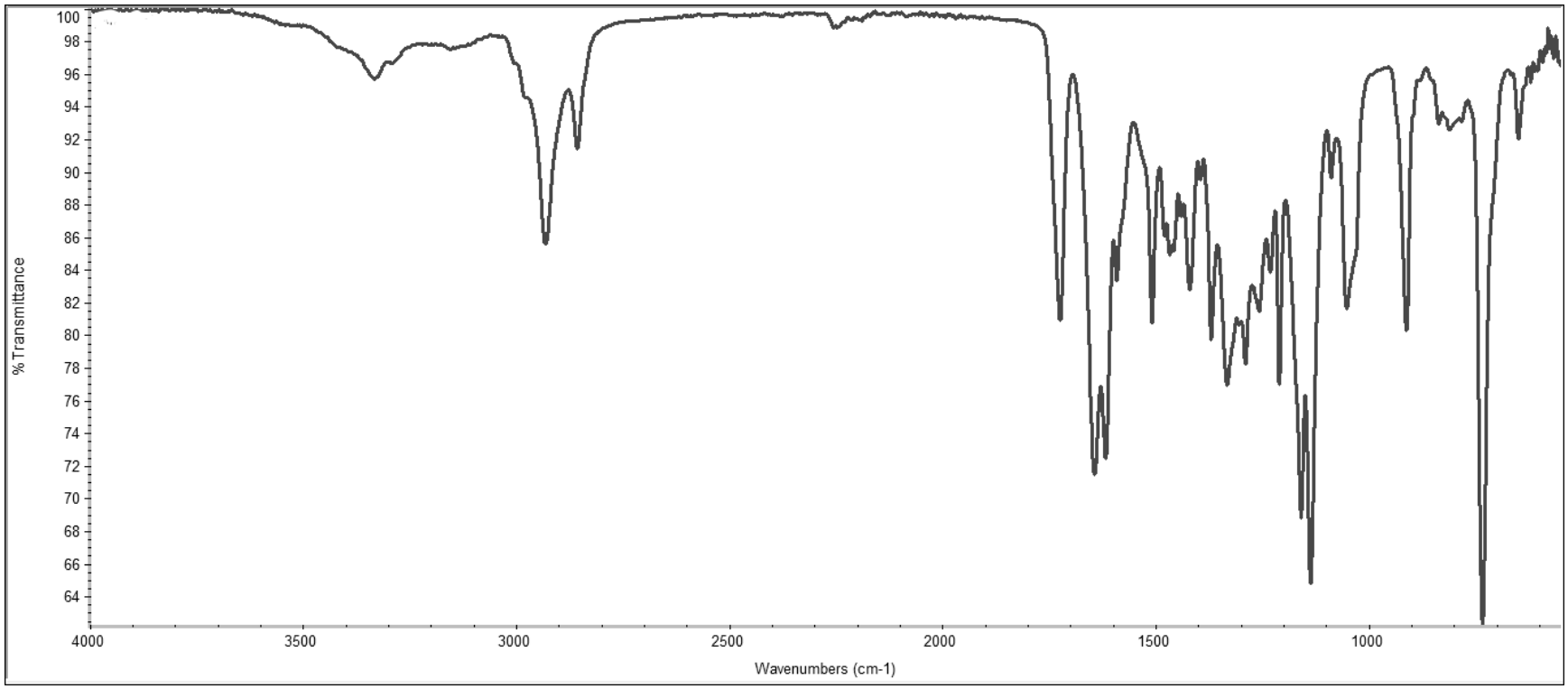

bisguanidine_26
% Transmittance
99.5
99.0
98.5
98.0
97.5
97.0
96.5
96.0
95.5
95.0
94.5
94.0
93.5
93.0
92.5
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

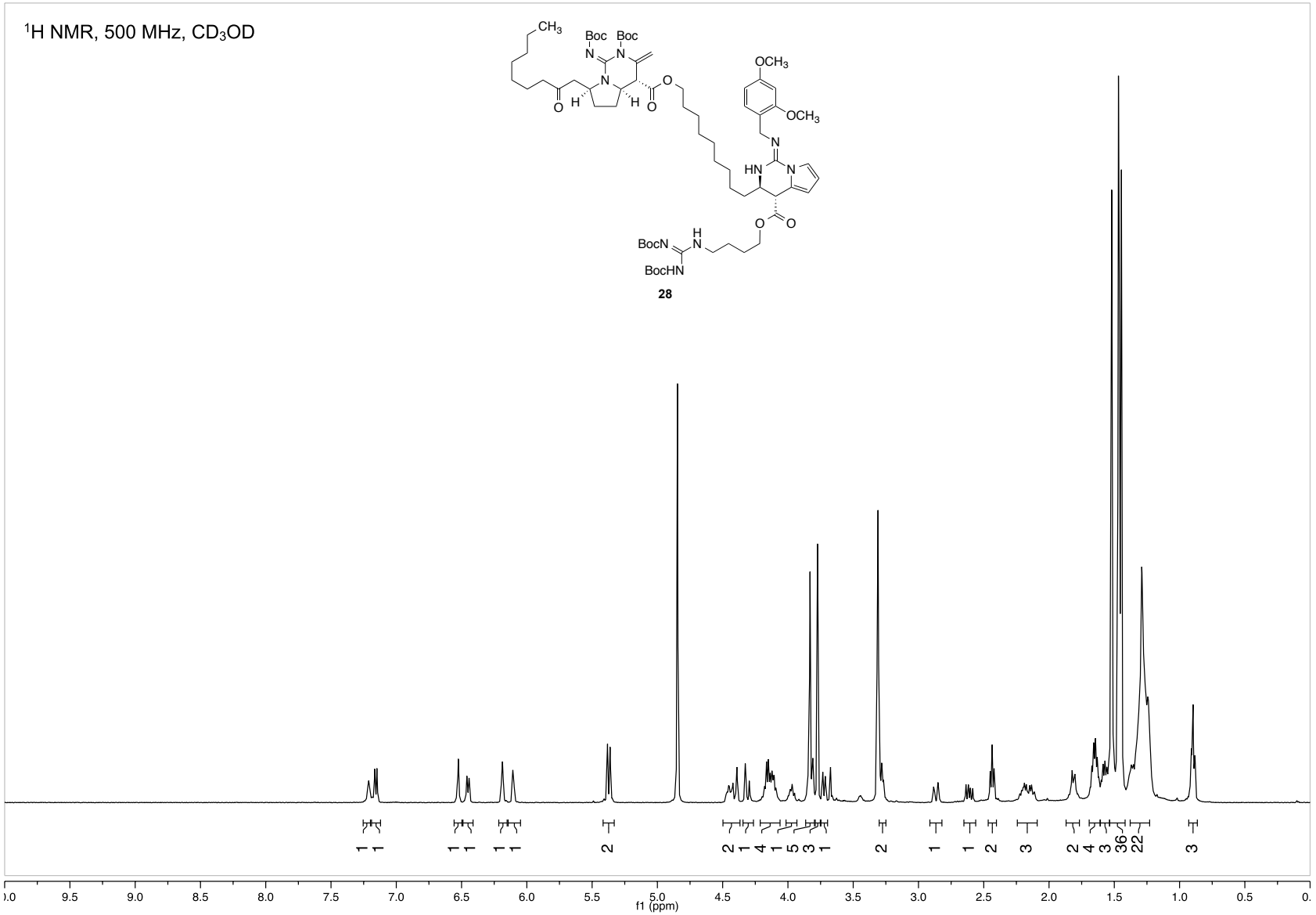
$^1$H NMR, 500 MHz, $CD_3OD$



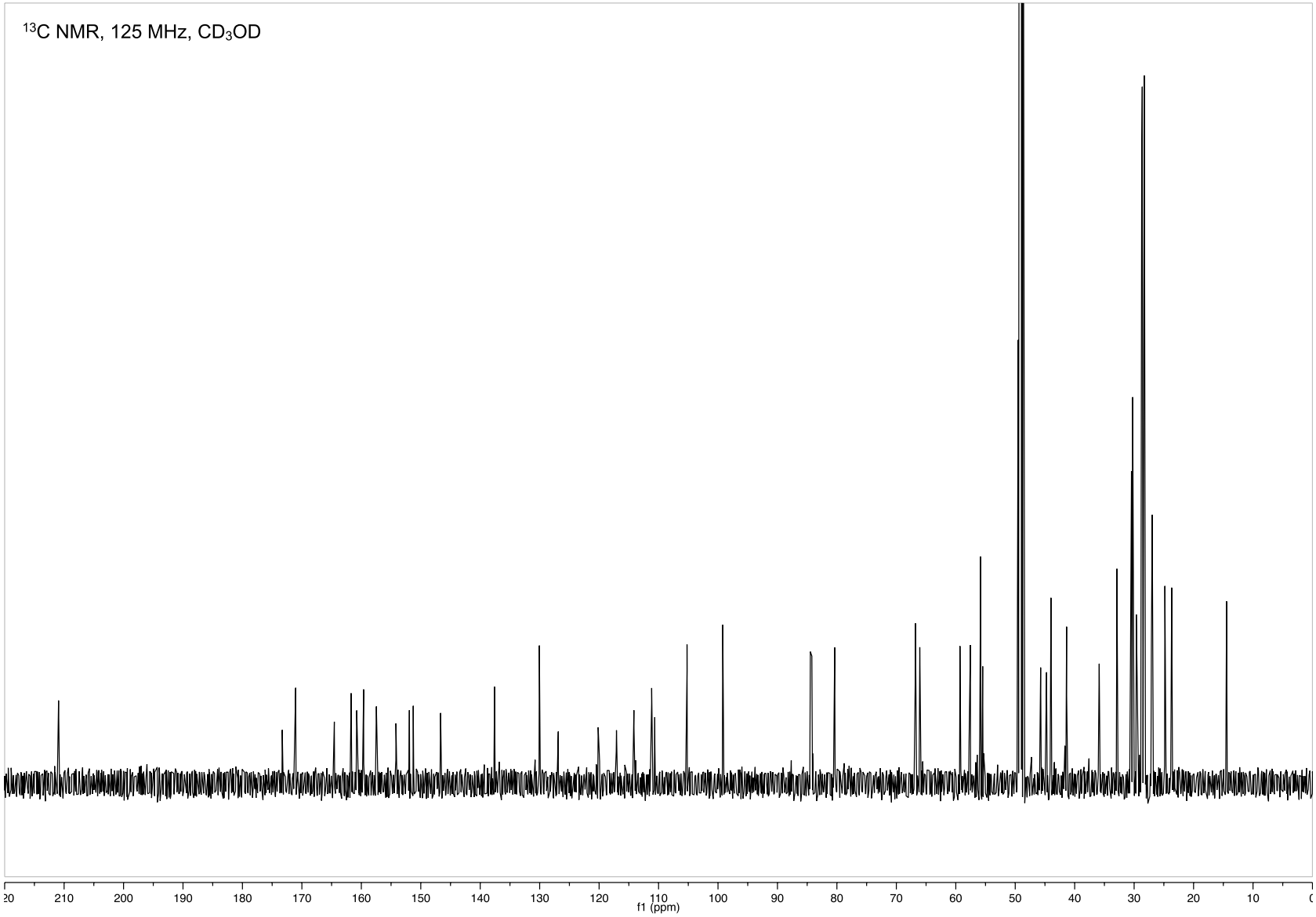

**27**

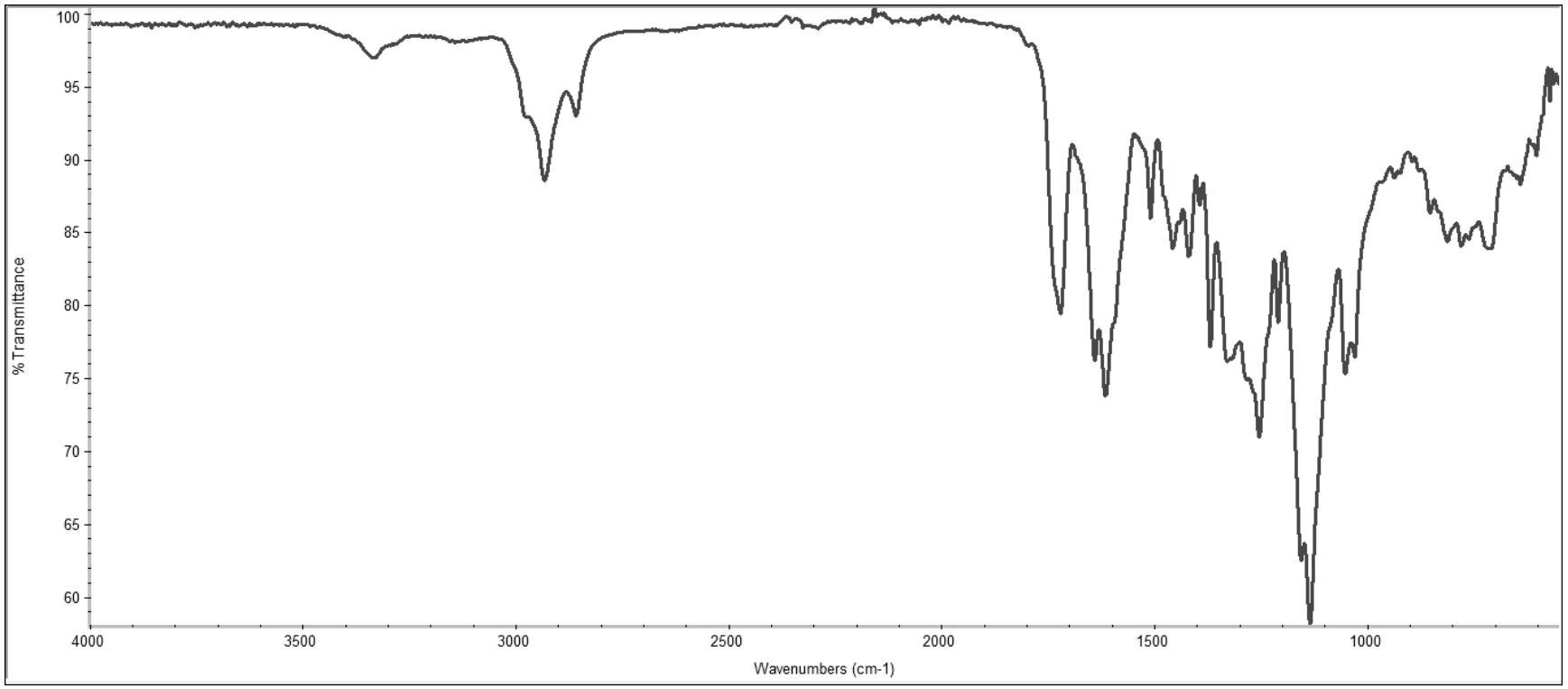

$^{13}$C NMR, 125 MHz, $CD_3OD$
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

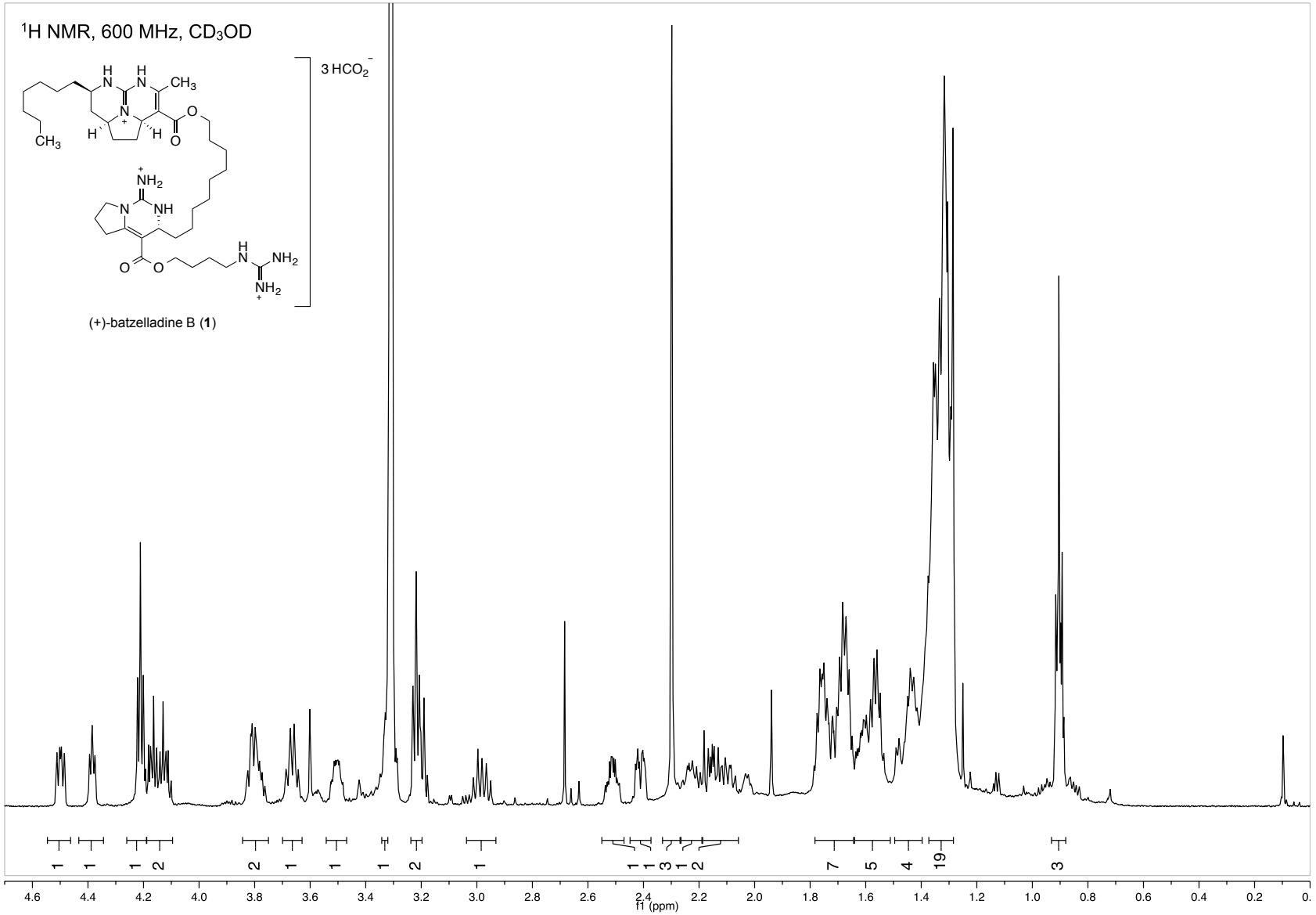

% Transmittance
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)




Parr, Economou, and Herzon "A concise synthesis of (+)-batzelladine B from simple pyrrole-based starting materials" *Nature*

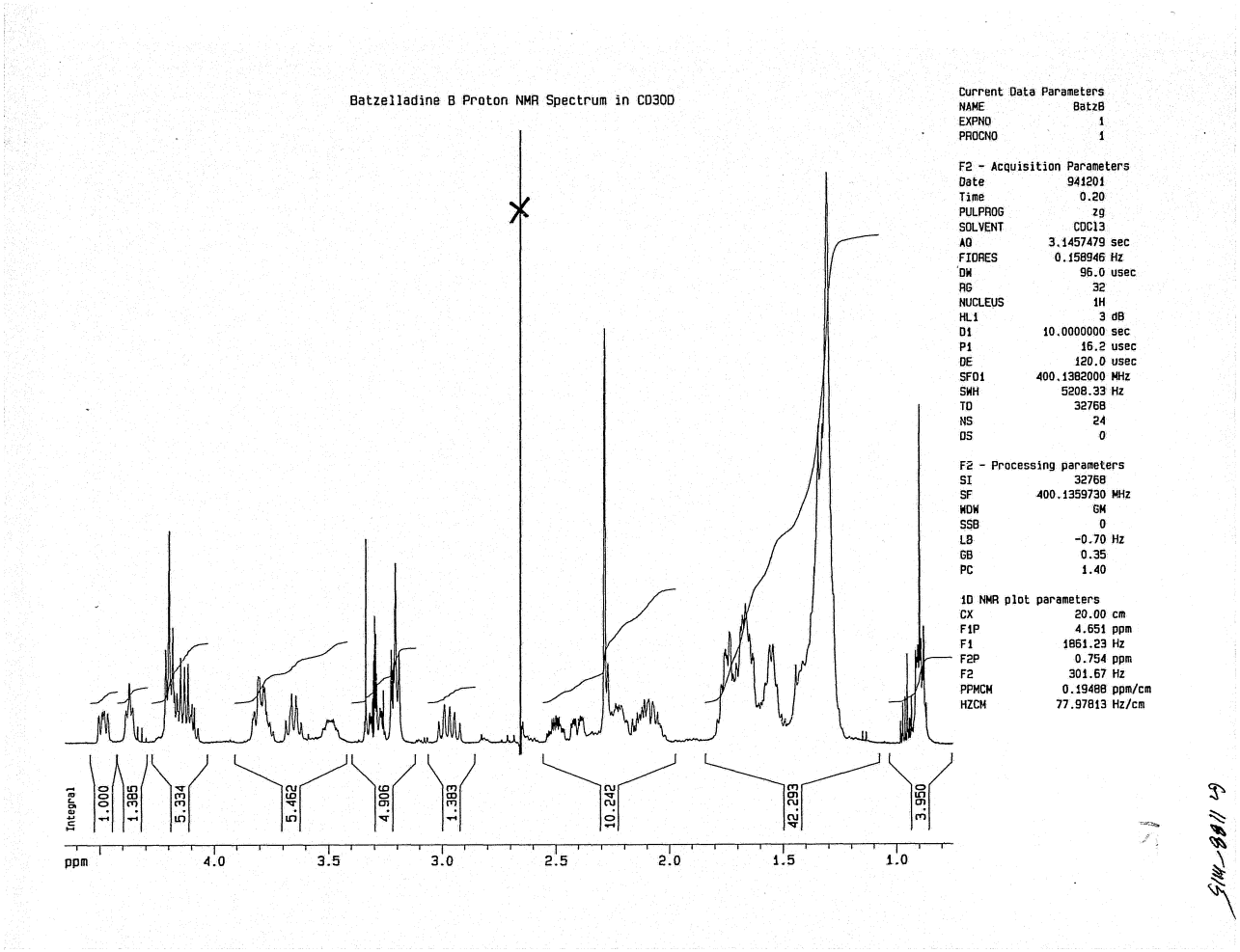

$^{13}$C NMR, 125 MHz, $CD_3OD$
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

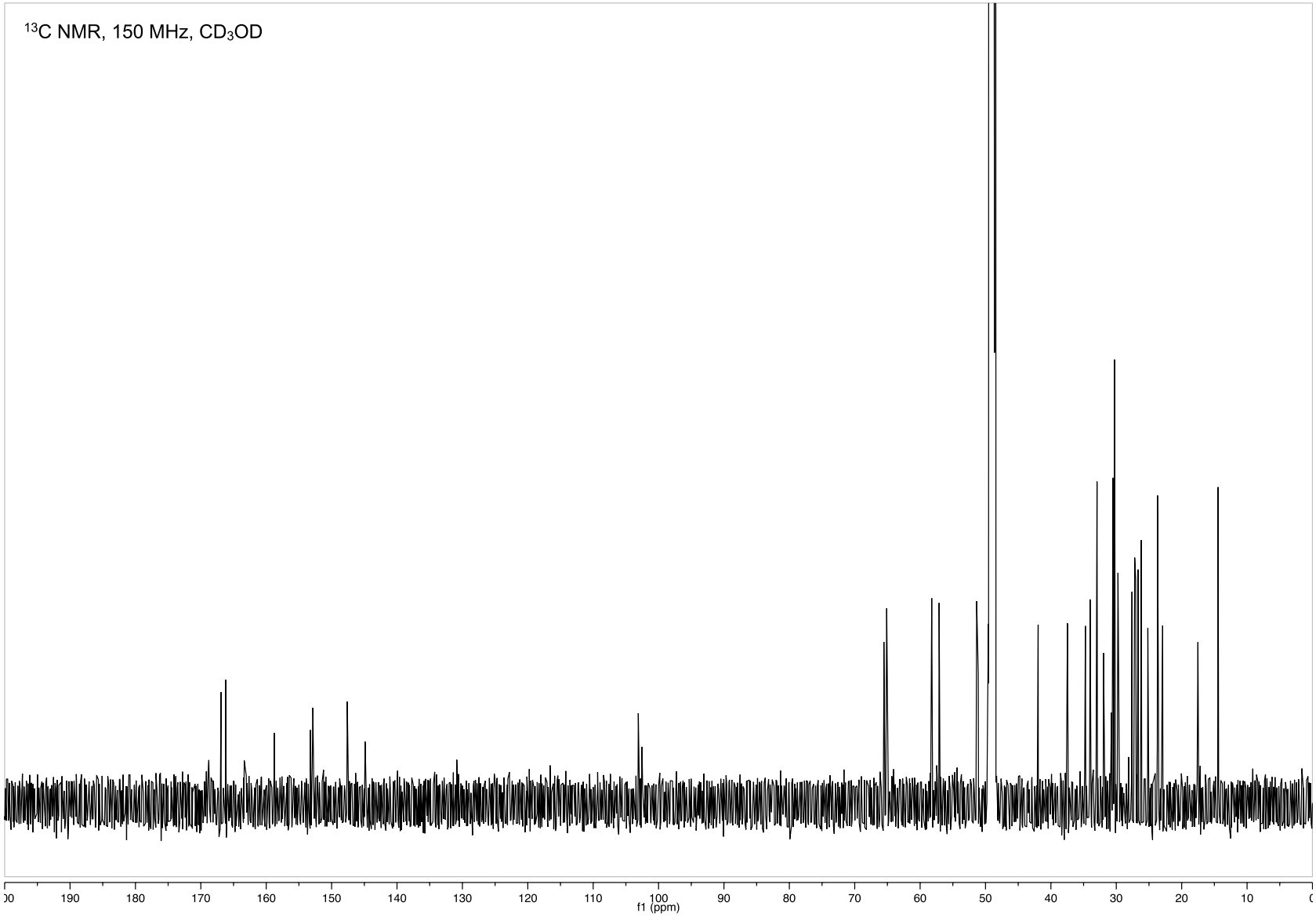

100
95
90
85
80
75
70
65
60
% Transmittance
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)



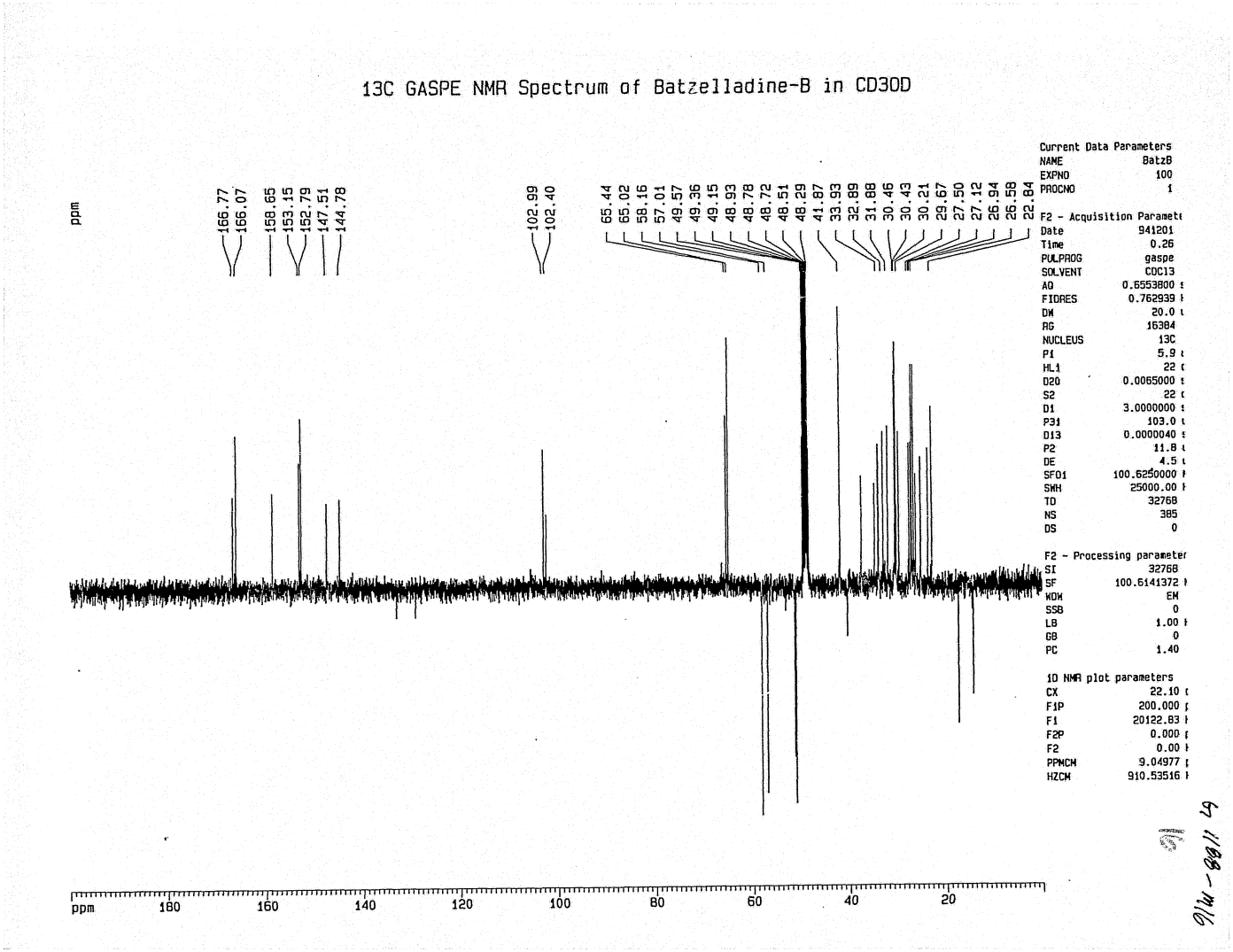

Parr, Economou, and Herzon "A concise synthesis of (+)-batzelladine B from simple pyrrole-based starting materials" *Nature*

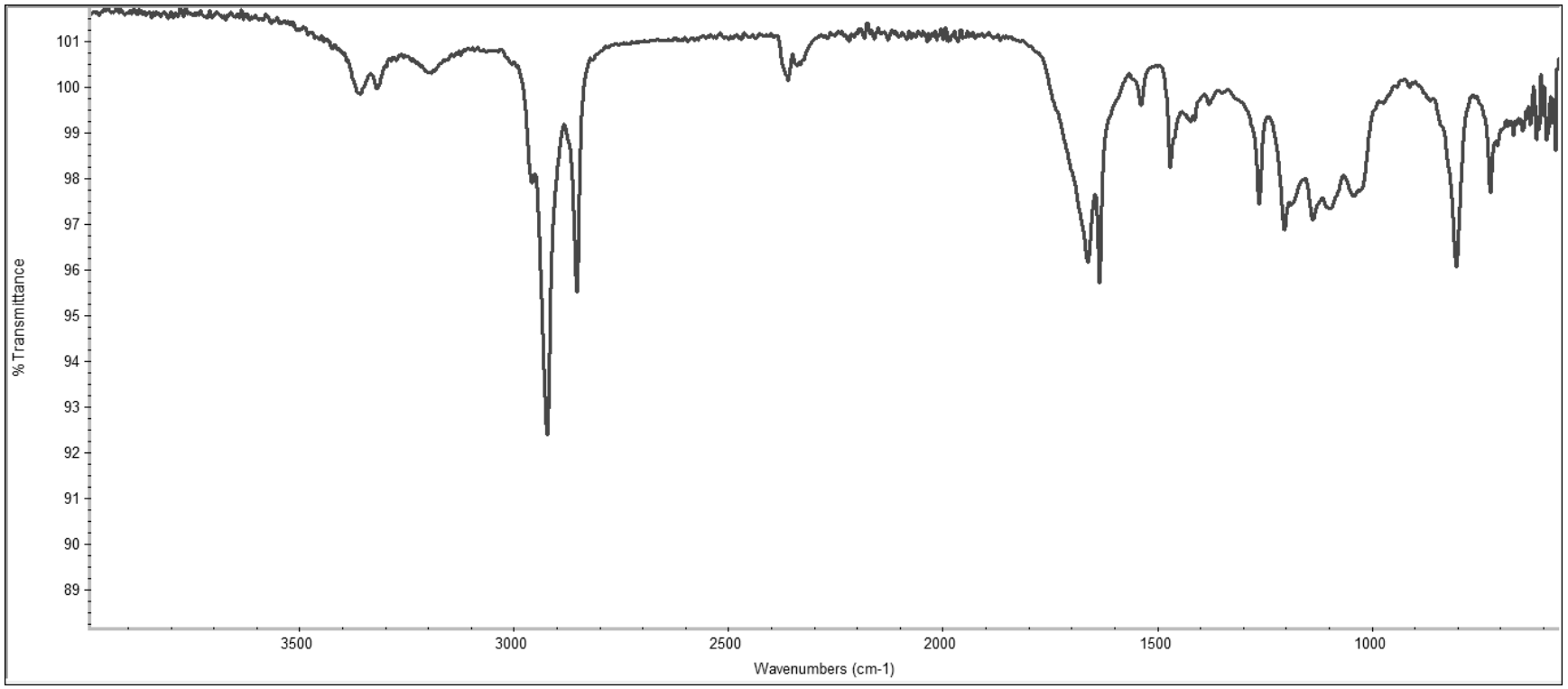
The $^{1}$H NMR spectrum of natural (+)-batzelladine B (**1**) below was reproduced from the following reference: Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; De Brosse, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, C.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Potts, B. C. M. *J. Org. Chem.* **1995**, *60*, 1182–1188.

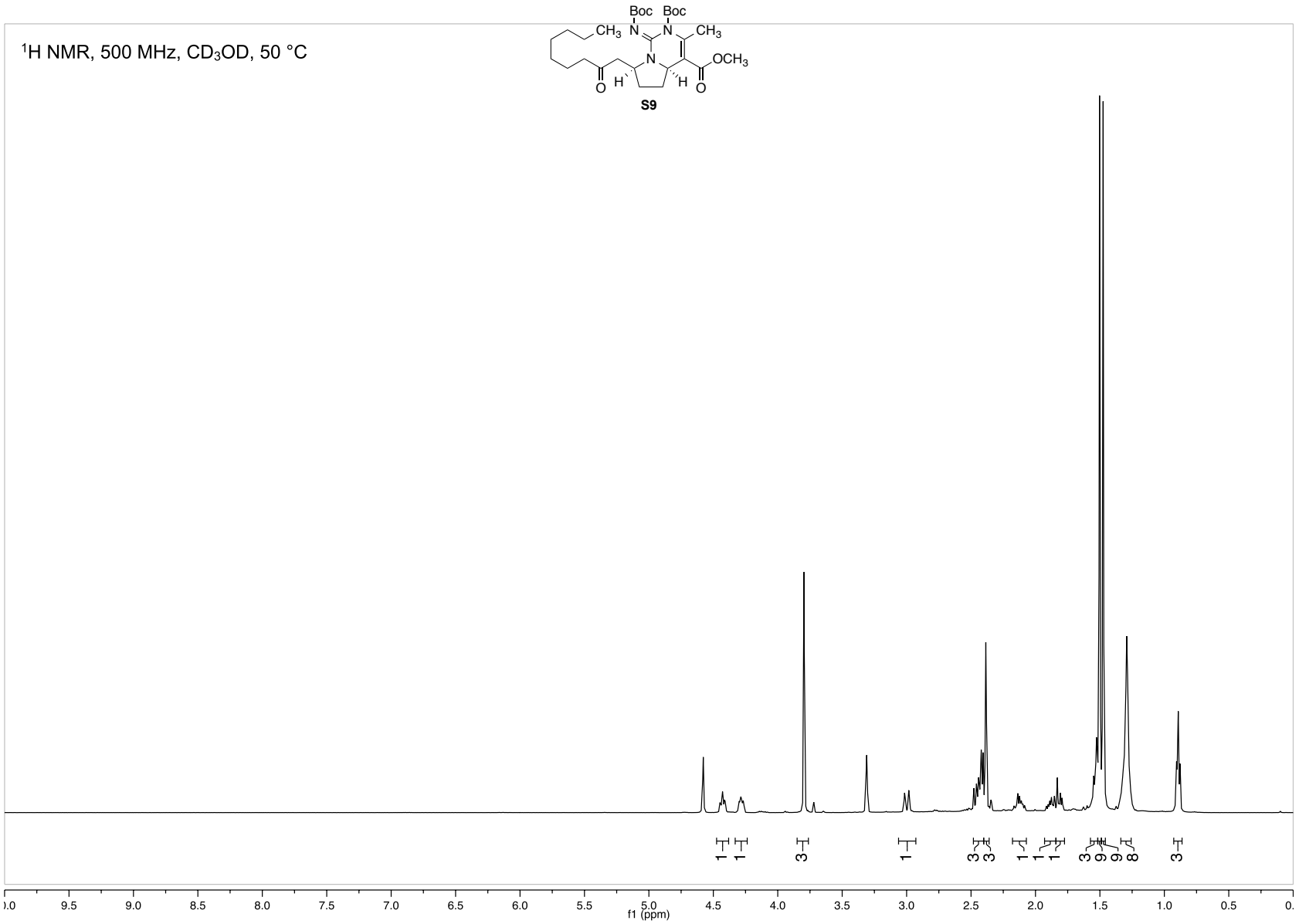


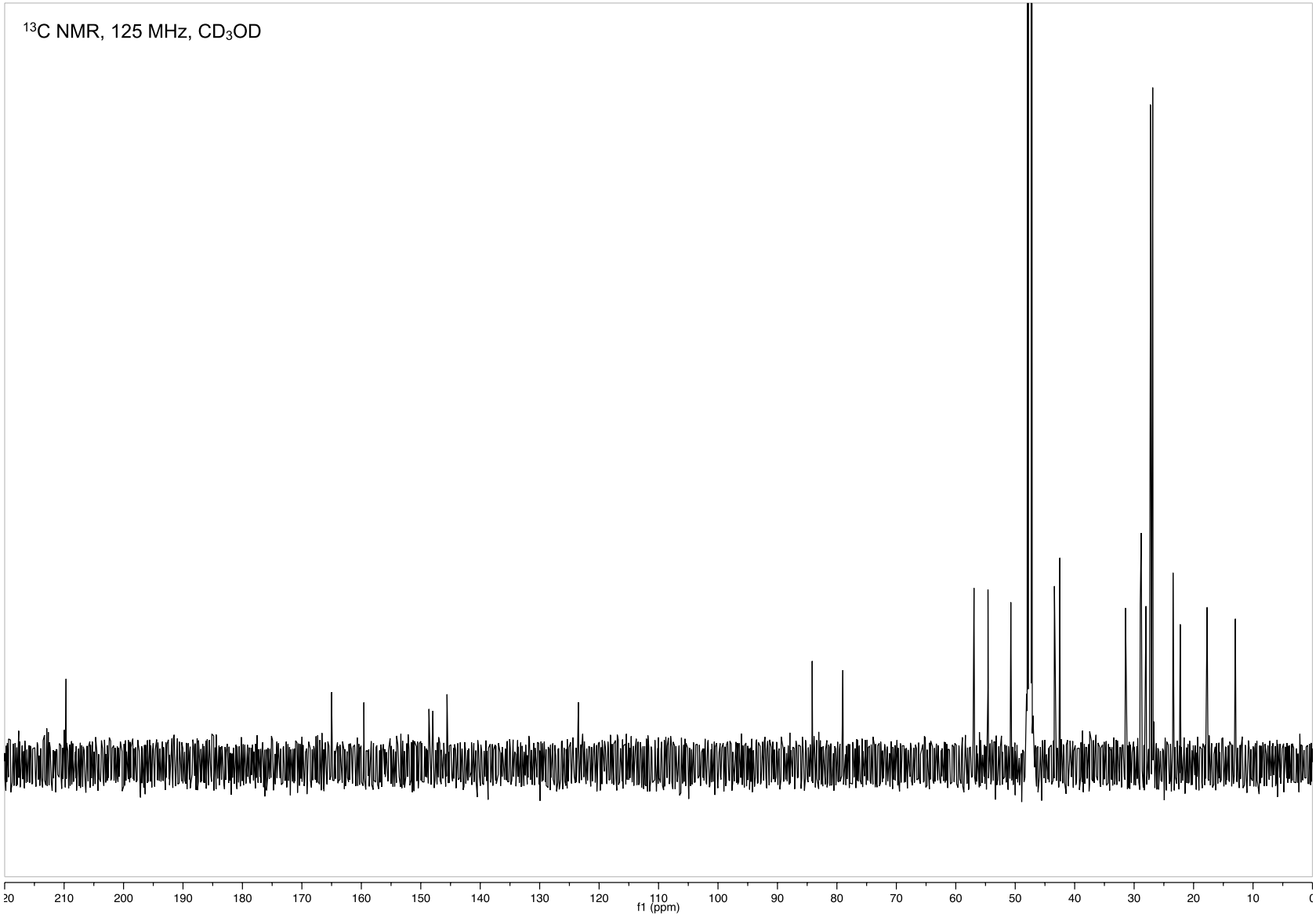

$^{13}$C NMR, 150 MHz, $CD_3OD$
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

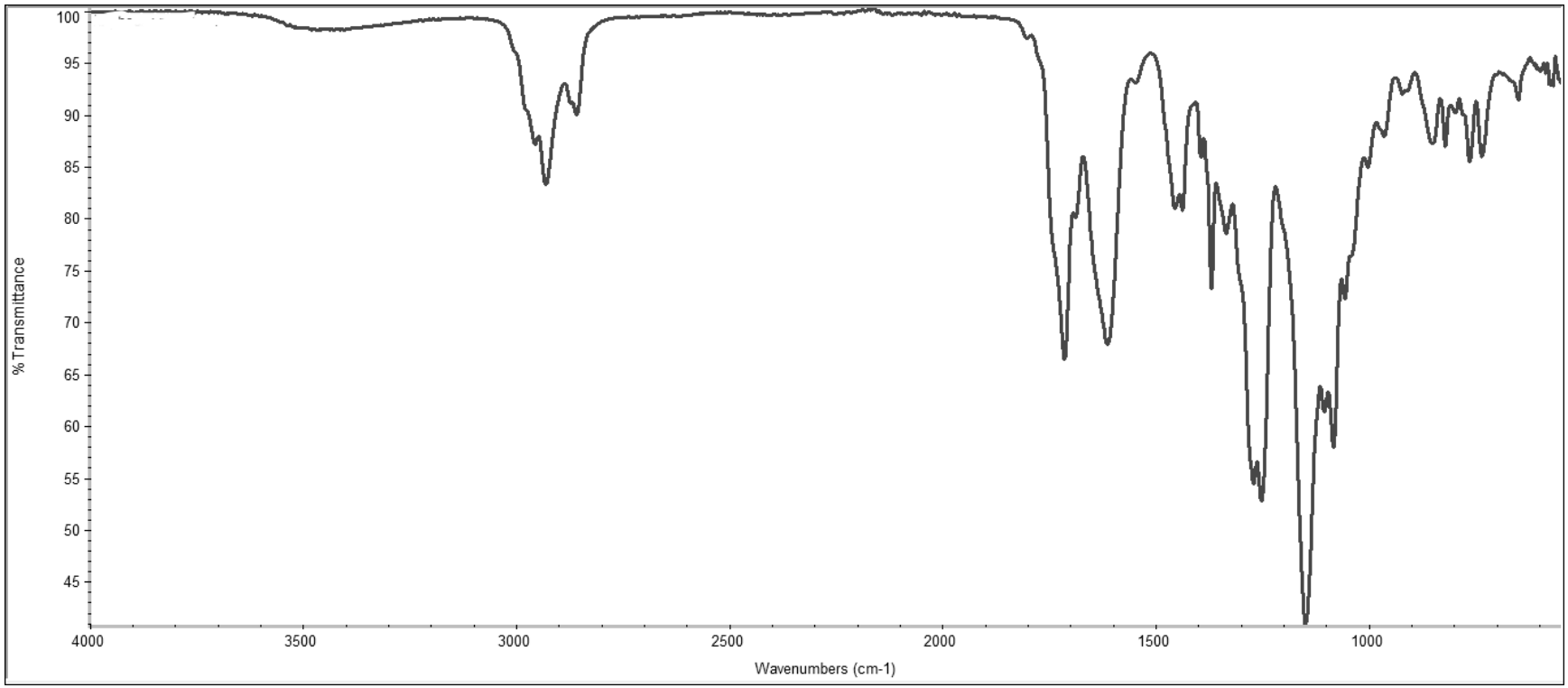
The $^{13}C$ NMR spectrum of natural (+)-batzelladine B (**1**) below was reproduced from the following reference: Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; De Brosse, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, C.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Potts, B. C. M. *J. Org. Chem.* **1995**, *60*, 1182–1188.

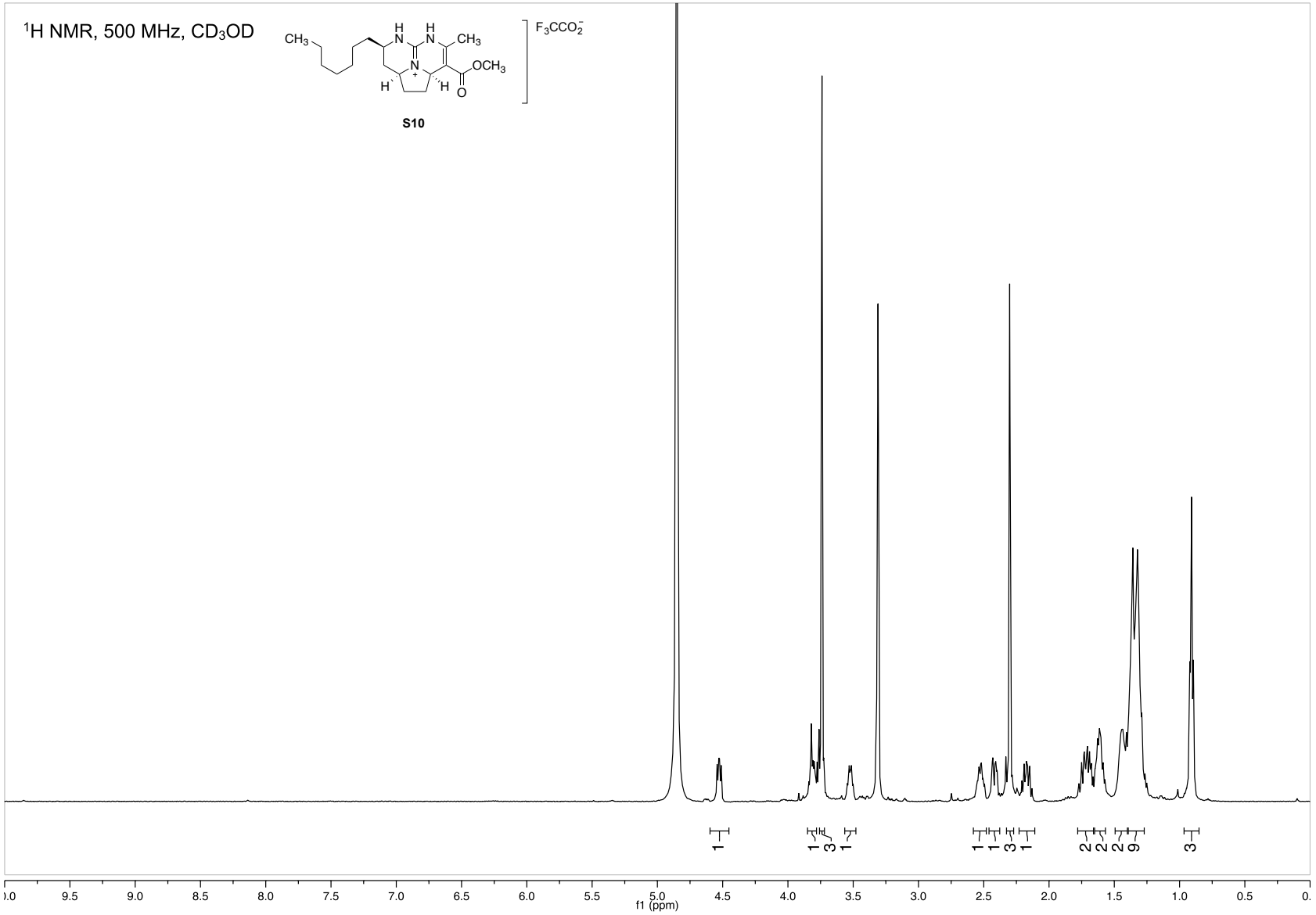



% Transmittance
101
100
99
98
97
96
95
94
93
92
91
90
89
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

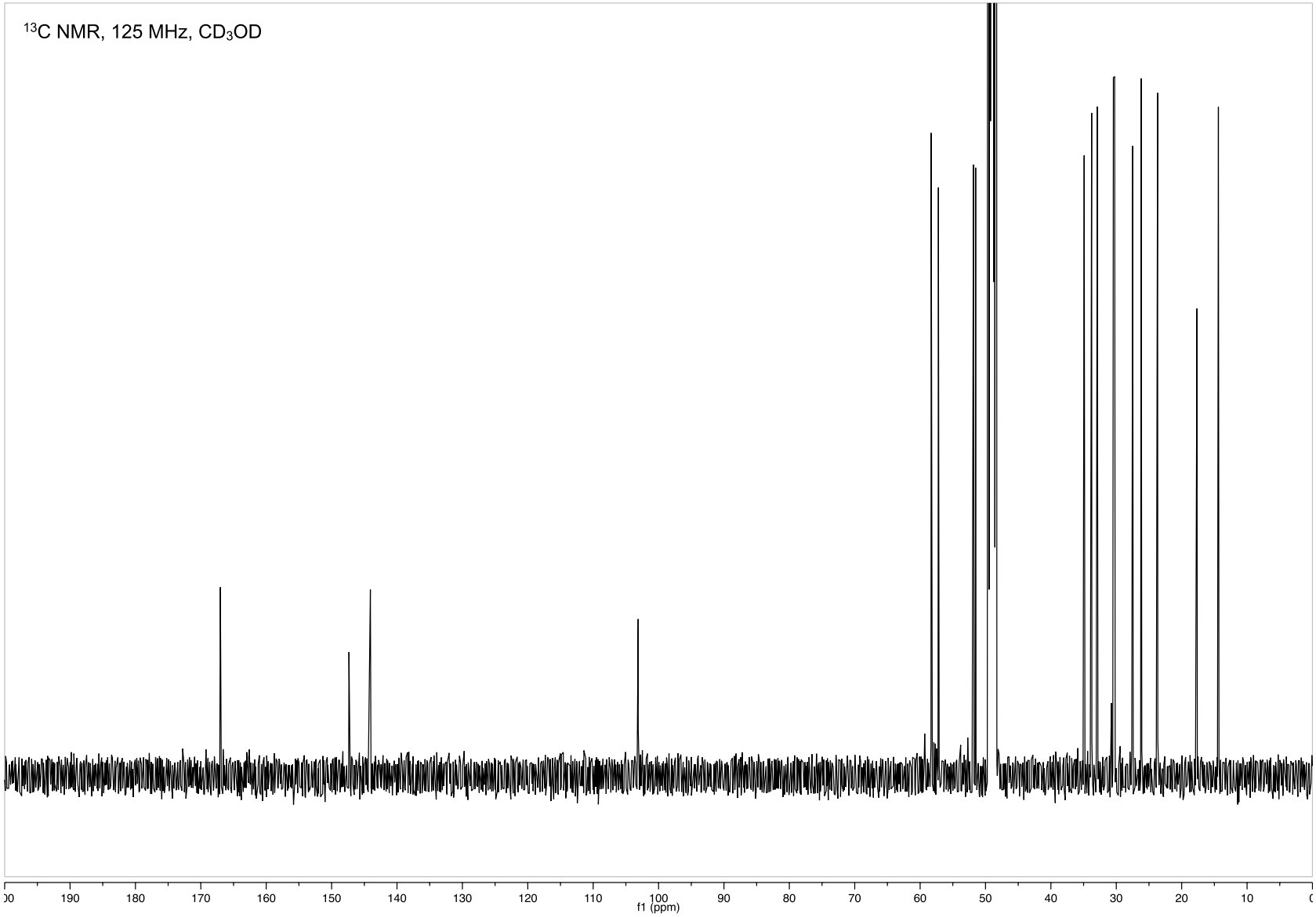

1H NMR, 500 MHz, CD3OD, 50 °C
Boc Boc
CH3 N N CH3
N
OCH3
O H H O
S9
1 1 3 1 3 3 1 1 1 3 9 8 3
f1 (ppm)

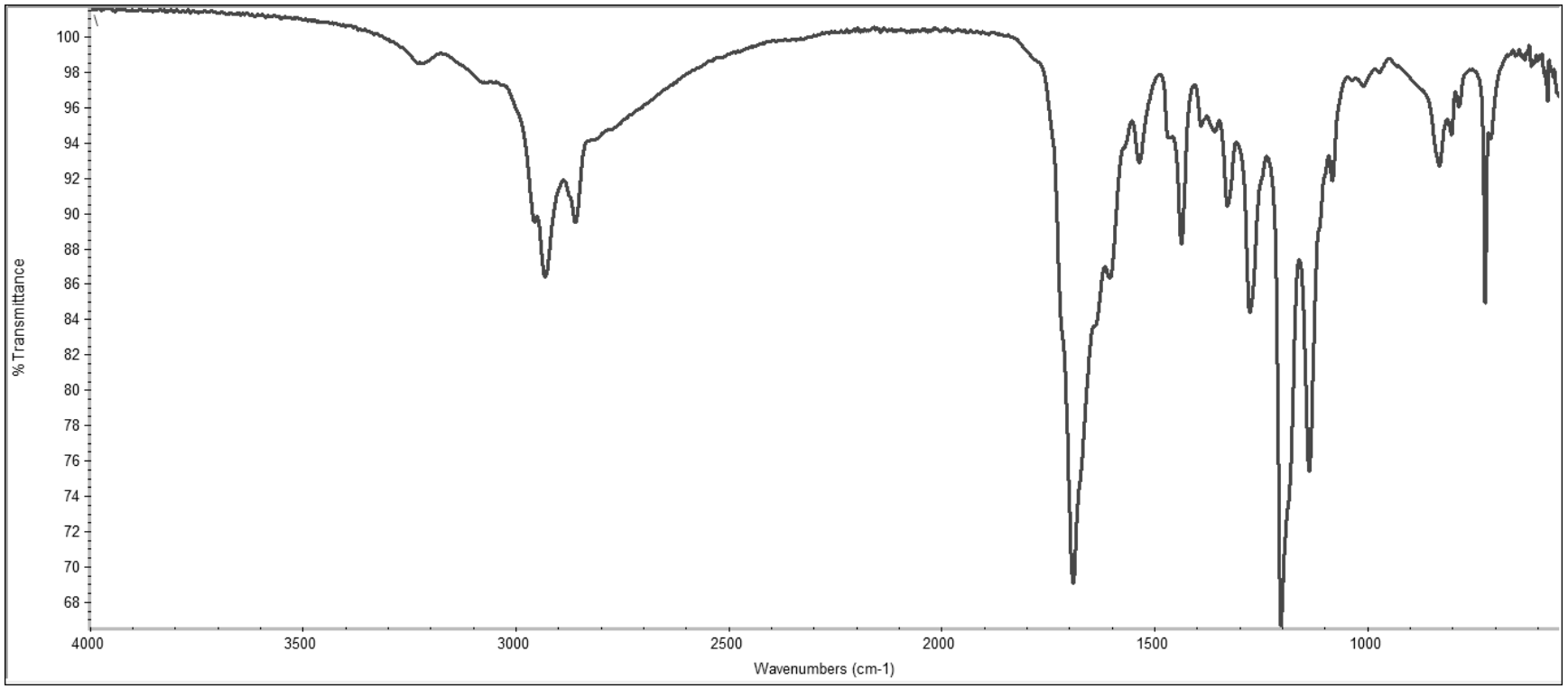

$^{13}$C NMR, 125 MHz, $CD_3OD$
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


100
95
90
85
80
75
70
65
60
55
50
45
% Transmittance
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

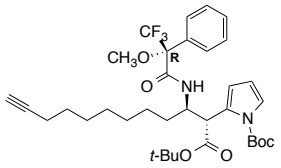



Parr, Economou, and Herzon "A concise synthesis of (+)-batzelladine B from simple pyrrole-based starting materials" *Nature*


$^{13}$C NMR, 125 MHz, $CD_3OD$
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

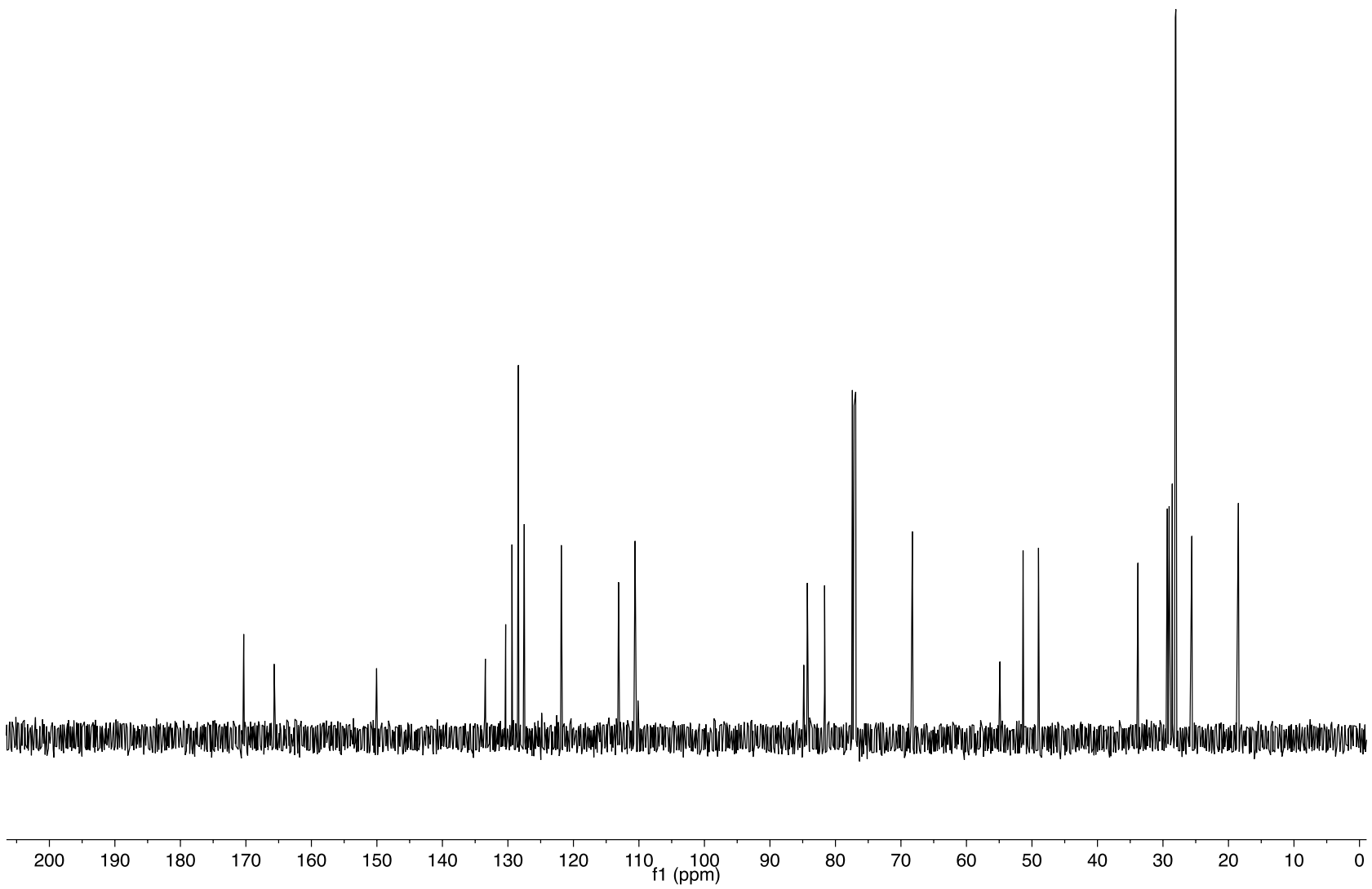

% Transmittance
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

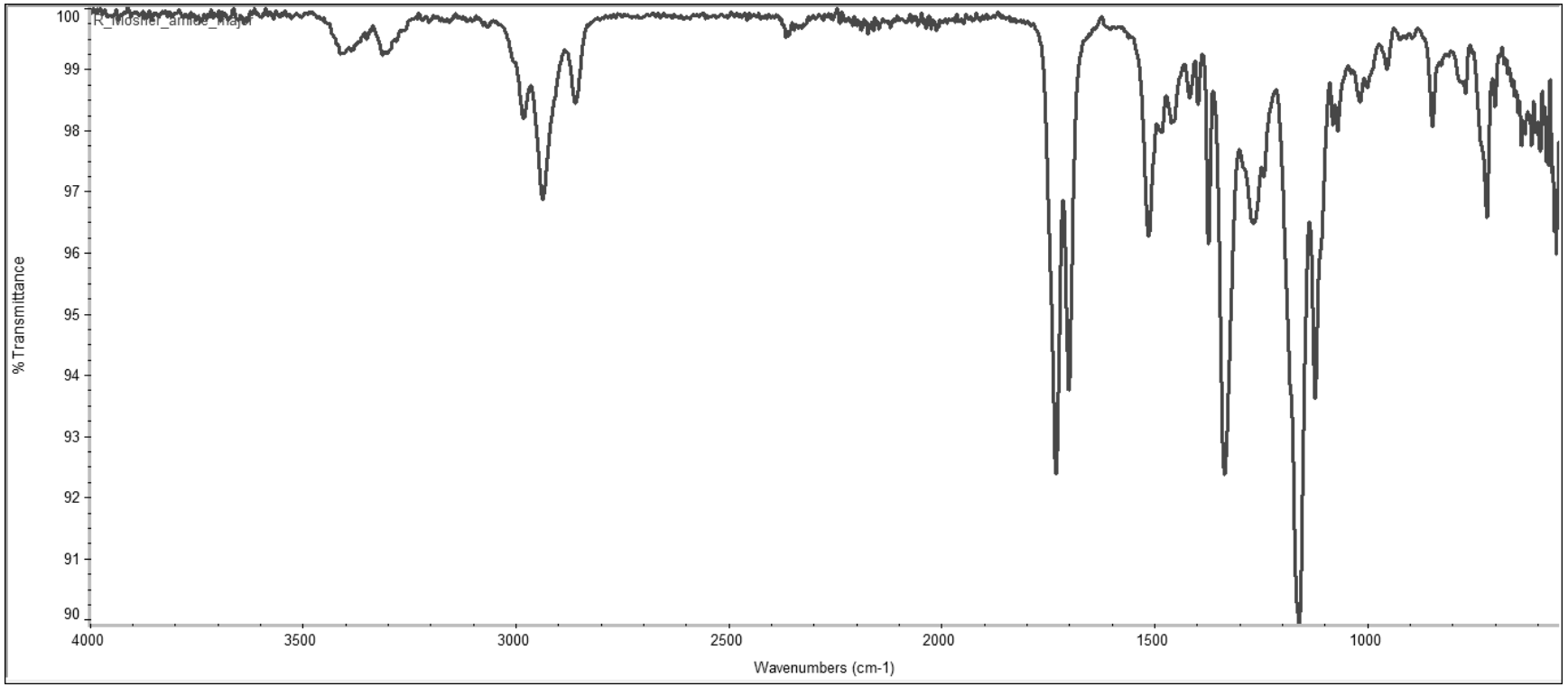
$^1$H NMR, 500 MHz, $CDCl_3$



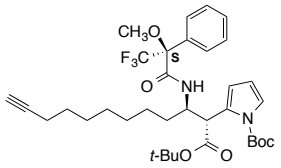

**S11**

$^{13}$C NMR, 125 MHz, $CDCl_3$




100
99
98
97
96
95
94
93
92
91
90
% Transmittance
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

$^1$H NMR, 500 MHz, $CDCl_3$

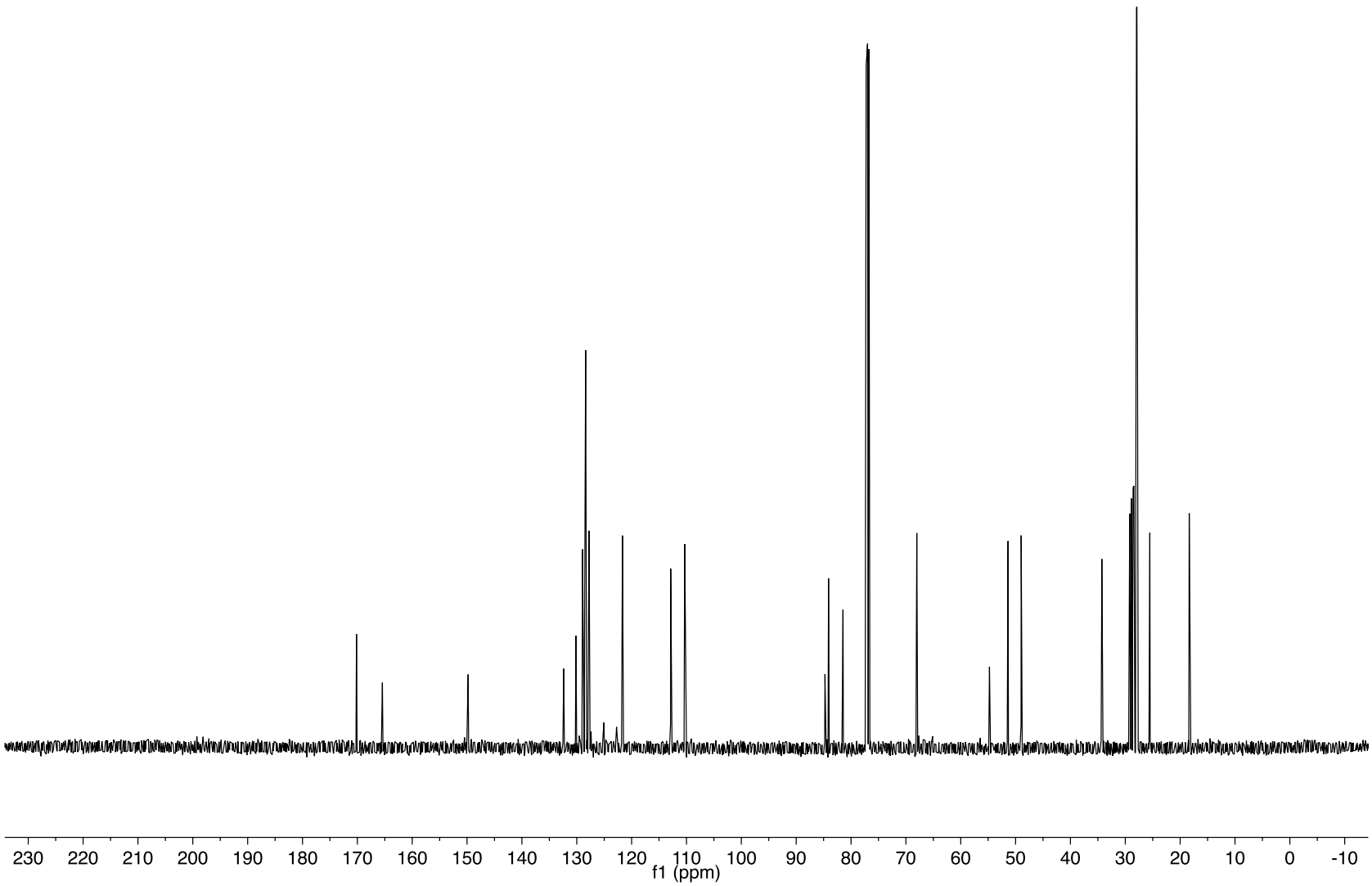


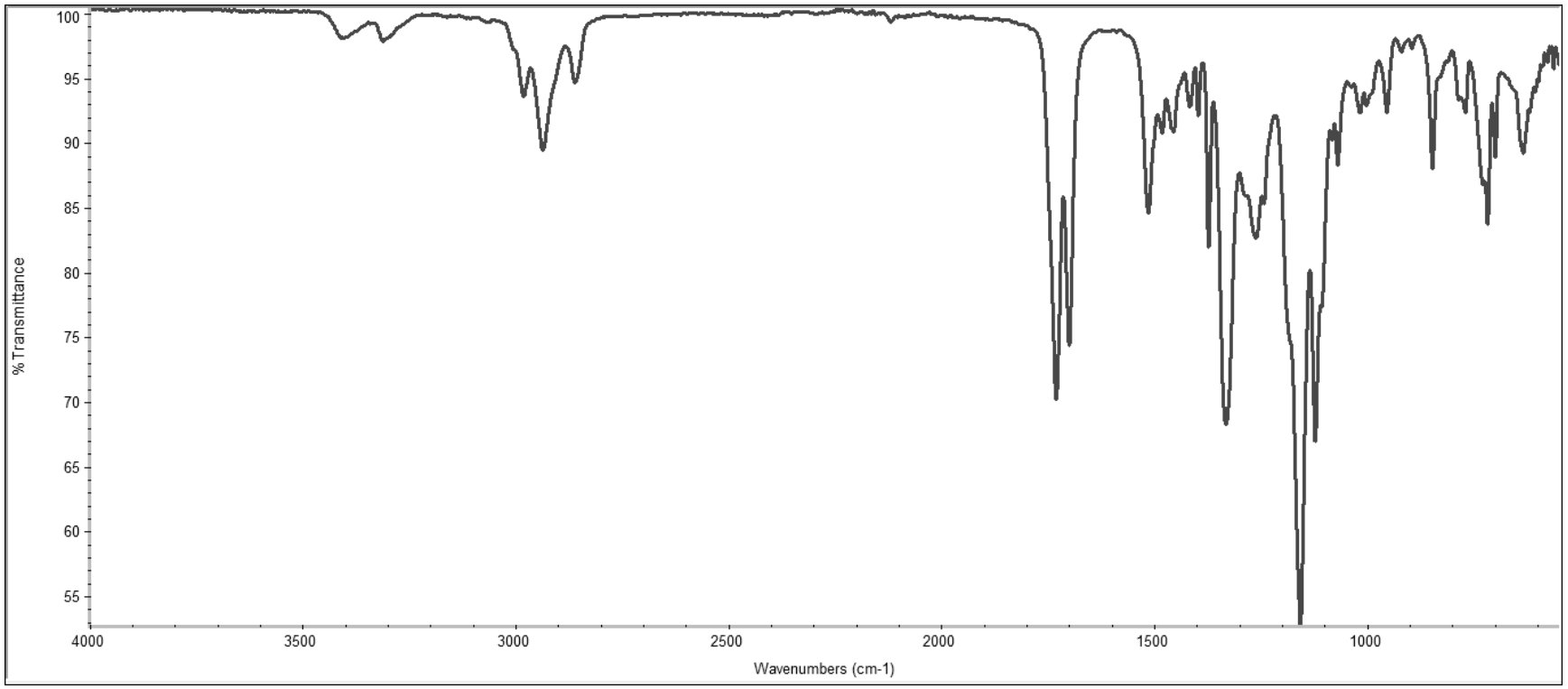

**S12**




Parr, Economou, and Herzon "A concise synthesis of (+)-batzelladine B from simple pyrrole-based starting materials" *Nature*

$^{13}$C NMR, 125 MHz, $CDCl_3$




100
95
90
85
80
75
70
65
60
55
% Transmittance
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

**Bibliography.**


1. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
2. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
3. Lin, H.-S.; Paquette, L. A. *Synth. Commun.* **1994**, *24*, 2503.
4. Davies, H. M. L.; Cantrell, W. R., Jr.; Romines, K. R.; Baum, J. S. *Org. Synth.* **1992**, *70*, 93.
5. Zeng, M.; Li, L.; Herzon, S. B. *J. Am. Chem. Soc.* **2014**, *136*, 7058.
6. Xu, J.; Caro-Diaz, E. J.; Batova, A.; Sullivan, S. D.; Theodorakis, E. A. *Chem. – Asian J.* **2012**, *7*, 1052.
7. Fernández González, D.; Brand, J. P.; Waser, J. *Chem. –Eur. J.* **2010**, *16*, 9457.
8. Schloemer, G. C.; Greenhouse, R.; Muchowski, J. M. *J. Org. Chem.* **1994**, *59*, 5230.
9. Botta, M.; Corelli, F.; Maga, G.; Manetti, F.; Renzulli, M.; Spadari, S. *Tetrahedron* **2001**, *57*, 8357.
10. Otera, J.; Yano, T.; Kawabata, A.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 2383.
11. Ghosh, B.; Amado-Sierra, M. D. R. I.; Holmes, D.; Maleczka, R. E. *Org. Lett.* **2014**, *16*, 2318.
12. Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; Brosse, C. D.; Mai, S.; Truneh, A.; Carte, B. *J. Org. Chem.* **1995**, *60*, 1182.
13. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
14. Sheldrick, G. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2008**, *64*, 112.