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Divergent total syntheses of pyrroloiminoquinone alkaloids enabled by the development of a Larock/Buchwald–Hartwig annulation/cyclization†

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Pyrroloiminoquinone alkaloids are a large class of natural products that display a wide range of biological activities. Synthetic approaches to these natural products typically rely on a common late-stage C10-oxygenated pyrroloiminoquinone intermediate, but these strategies often lead to lengthy synthetic sequences that are not amenable to divergent syntheses. We devised an alternative approach aimed at the early introduction of the C10 nitrogen, which we hypothesized would enable late-stage diversification. This strategy hinged upon a Larock/Buchwald–Hartwig annulation/cyclization to quickly access the core of these alkaloids. We report the development of this cascade process, which was facilitated by a dual ligand system in addition to selective functionalization of the key intermediate, to provide efficient syntheses of makaluvamines A, C, and D and isobatzelline B, and the first total synthesis of makaluvamine N.

Pyrroloiminoquinone alkaloids are a large class of marine- and fungal-derived natural products that have received significant attention within the scientific community for over 30 years.[1] This is in part due to their broad biological activities such as antitumor, antiviral, and antimicrobial activities, among many others.[2] Structurally, pyrroloiminoquinone alkaloids are defined by a conserved pyrrolo[4,3,2-*de*]quinoline ring system and differ by the functionality appended to this central ring. These natural products typically contain other complex ring systems and a variety of heteroatoms, as exemplified by aleutianamine (**1**, Fig. 1A).[3] Their complex and unique structures have inspired synthetic efforts for decades and several successful total syntheses of these alkaloids have been reported.[4,5] Strategies typically utilize a common late-stage C10-oxygenated pyrroloiminoquinone intermediate **2**, with amination serving to introduce the final nitrogen atom. While this approach has proved successful, there is limited divergency from this common iminoquinone intermediate, and other functionality appended to the central core (*i.e.*, R^1–R^4) must be introduced earlier in the synthesis. This lack of divergency could explain the paucity of structure–activity relationship (SAR) studies of pyrroloiminoquinone alkaloids.[6] Additionally, access to the common intermediate **2** typically necessitates lengthy synthetic sequences due to the linear nature of arene functionalization steps (see ESI† for a detailed discussion of synthetic strategies toward the common intermediate **2**).

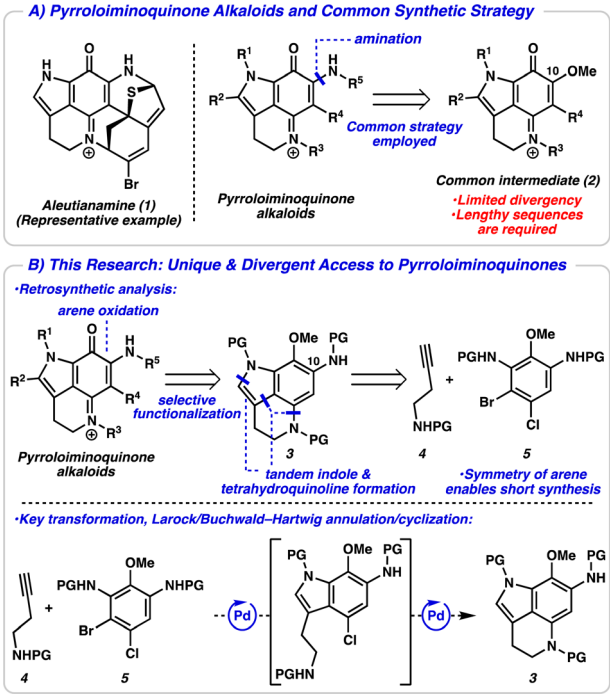

Fig. 1 (A) Representative pyrroloiminoquinone and the common strategy employed toward these alkaloids. (B) Our strategy toward pyrroloiminoquinones and the key transformation to realize this strategy.

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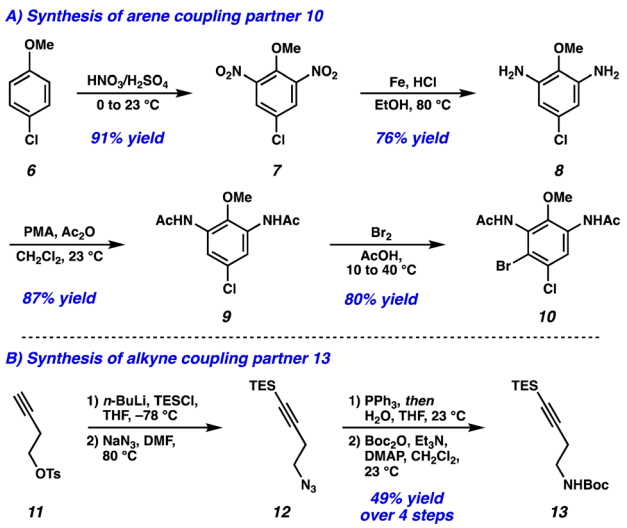
We devised an alternative approach in order to address the issues of divergence and step count, envisioning a direct arene oxidation state adjustment leading back to an aminoindole (**3**), an uncommon disconnection that avoids the use of the common intermediate **2** (Fig. 1B).[7] We hypothesized that with judicious choice of nitrogen protecting groups, selective functionalization of all five possible positions of the pyrroloiminoquinone scaffold (R^1–R^5) could be achieved. We next disconnected both the indole and tetrahydroquinoline, revealing a pseudo symmetric arene (**5**). We imagined that the symmetry of this highly substituted arene would simplify its synthesis, precluding the need for a lengthy synthetic sequence. Critical to the success of this strategy is the indolization/tetrahydroquinoline formation step. We envisioned that the development of a tandem Larock/Buchwald–Hartwig annulation/cyclization could enable this approach. While both the Larock indole synthesis and Buchwald–Hartwig amination are well documented independently,[8,9] to the best of our knowledge a tandem Larock/Buchwald–Hartwig annulation/cyclization has yet to be reported. To this end, we set out to access the Larock/Buchwald–Hartwig annulation/cyclization substrates.

Dinitration of 4-chloroanisole (**6**) proceeded smoothly to provide dinitro arene **7**, which underwent reduction to the corresponding dianiline (**8**) (Scheme 1A). Phosphomolybdic acid (PMA)-mediated acetylation[10] then yielded diacetanilide **9**. Finally, monobromination served as the desymmetrizing step to provide the first Larock/Buchwald–Hartwig cyclization substrate **10** in just 4 steps. The synthesis of the alkyne coupling partner commenced from commercially available alkyne **11**, which was silylated followed by substitution of the tosyl group with NaN_3 to afford azide **12** (Scheme 1B). Azide **12** was then converted to the amine *via* Staudinger reduction, which was subsequently Boc protected to provide alkyne coupling partner **13** in 4 total steps.

We next turned our attention to the development of the key Larock/Buchwald–Hartwig annulation/cyclization. Since Larock's original disclosure of the palladium-mediated indolization of alkynes and *o*-iodoanilines, the scope has been expanded to *o*-bromoanilines through catalyst and ligand design.[9] Despite these efforts, examples of substrates bearing bis *ortho* substitution with respect to the halide are rare, so we anticipated that this would be a difficult transformation to realize. We first tested the conditions reported by Reisman and coworkers,[11] which employ $Pd[P(t\text{-}Bu)_3]_2$ as the catalyst and ligand source along with a soluble amine base (Cy_2NMe), but these led to no detectable product formation and primarily protodebromination of arene **10** (Table 1, entry 1). We next evaluated the conditions reported by Boger and coworkers[12] which again utilize a Pd (0) precatalyst, now in combination with the electron rich 1,1′-bis(di-*tert*-butylphosphino)ferrocene (D*t*-BPF) ligand and Et_3N as the base, but protodebromination was similarly observed with no desired product formation (entry 2). Utilizing modified conditions reported by Senanayake and coworkers,[13] which implement a Pd(II) precatalyst and D*t*-BPF as the ligand, now using an inorganic base (K_2CO_3), we were encouraged to isolate 15% yield of desired tricycle **14** (entry 3). This represents a powerful transformation, as 3 bonds and 2 rings are formed in a single synthetic step. This yield could be improved to 32% by increasing the catalyst and ligand loading, using higher equivalents of alkyne **13**, and freshly drying the K_2CO_3 (entry 4). After extensive investigation, we discovered that the addition of another ligand (XPhos) to the system improved the yield to 69% (entry 5, see ESI† for additional optimization details). Lastly, the addition of 4 Å molecular sieves addressed issues with reproducibility, likely caused by the presence of water. Overall, this transformation represents the first example of a tandem Larock/Buchwald–Hartwig annulation/cyclization and provides access to the core of the pyrroloiminoquinone alkaloids in a longest linear sequence (LLS) of just 5 steps, which to the best of our knowledge is the shortest synthetic sequence to such a tricyclic intermediate.

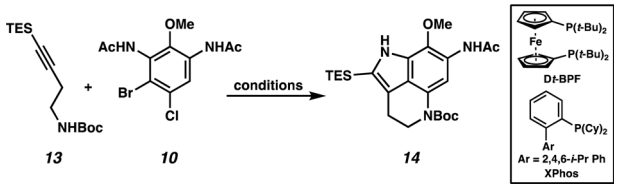


Scheme 1 (A) Synthesis of arene coupling partner **10**. (B) Synthesis of alkyne coupling partner **13**.

We were next interested into gaining insight on how the dual ligand system was uniquely effective in this transformation. First, we investigated the effects of the ligand stoichiometry under the optimal reaction conditions. The ratio of D*t*-BPF : XPhos was varied, while keeping the total ligand percentage at 30 mol% (2 equivalents with respect to Pd). If an excess of D*t*-BPF was used in respect to XPhos, the efficiency of the annulation/cyclization was diminished (Table 2, entries 1–3). In these cases, a large portion of the remaining mass balance was the intermediate indole product (*vide infra*). Efficient formation of tricyclic product **14** was restored under the optimal reaction conditions consisting of a 1 : 1 D*t*-BPF : XPhos ratio (entry 4). Interestingly, a 1 : 2 D*t*-BPF : XPhos mixture was also effective, providing **14** in a 64% yield (entry 5). However, once a larger excess of XPhos was employed the yield of **14** decreased (entries 6 and 7). In these cases, the reaction profile was more complicated with unidentifiable side/decomposition products.

To gain further insight, we studied each step of the tandem process individually while adjusting the ligand stoichiometry. We first studied the Larock indolization process by monitoring the consumption of bromoarene **10** by LC/MS. We found that either D*t*-BPF or XPhos on their own could facilitate the Larock

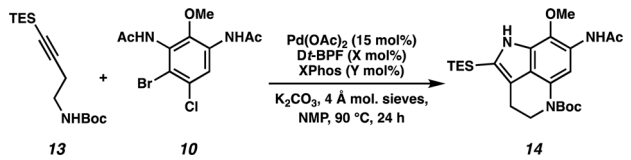
Table 1 Investigation of Larock/Buchwald–Hartwig annulation/cyclization



Entry	Catalyst	Ligand	Base	Solvent	Temp/time	Yield (%)
1[a]	$Pd[P(t\text{-}Bu)_3]_2$ (10 mol%)	—	Cy_2NMe	1,4-Dioxane	80 °C, 24 h	0
2[a]	$Pd_2(dba)_3$ (10 mol%)	D*t*-BPF (20 mol%)	Et_3N	DMF	130 °C, 30 h	0
3[a]	$Pd(OAc)_2$ (5 mol%)	D*t*-BPF (10 mol%)	K_2CO_3	NMP	110 °C, 24 h	15
4[b]	$Pd(OAc)_2$ (15 mol%)	D*t*-BPF (30 mol%)	K_2CO_3	NMP	110 °C, 24 h	32
5[c]	$Pd(OAc)_2$ (15 mol%)	D*t*-BPF (15 mol%) + XPhos (15 mol%)	K_2CO_3	NMP	90 °C, 24 h	69

Reactions performed on a 0.1 mmol scale at 0.1 M. Yields refer to isolated yields. [a] 2.0 equiv. of alkyne **13**, 2.5 equiv. of base. [b] 5.0 equiv. of alkyne **13**, 5.0 equiv. of freshly dried powdered K_2CO_3. [c] 0.44 mmol scale, 5.0 equiv. of alkyne **13**, 5.0 equiv. of freshly dried granular K_2CO_3, freshly activated 4 Å mol. sieves.

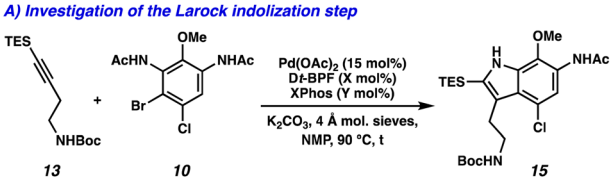
Table 2 Ligand stoichiometry effects on the tandem Larock/Buchwald–Hartwig annulation/cyclization



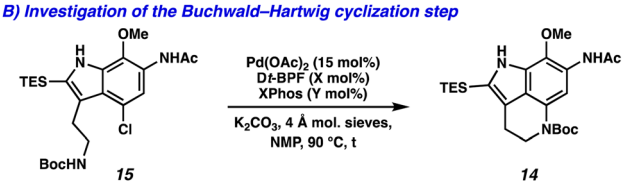
Entry	D*t*-BPF mol%	XPhos mol%	Yield[a] (%)
1	30	0	3
2	25	5	8
3	20	10	10
4	15	15	72
5	10	20	64
6	5	25	47
7	0	30	36

[a] Yields were determined by LC/MS using 1,3,5-trimethoxy benzene as an internal standard.

Table 3 (A) Investigation of the Larock indolization step. (B) Investigation of the Buchwald–Hartwig cyclization step



Entry	D*t*-BPF mol%	XPhos mol%	Time	Yield[a] (%)
1	30	0	20 h	45
2	15	15	8 h	62
3	0	30	11 h	44

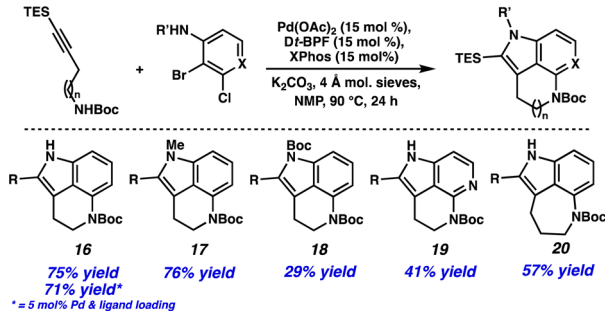


Entry	D*t*-BPF mol%	XPhos mol%	Time	Yield[a] (%)
1	30	0	24 h	20
2	15	15	16 h	87
3	0	30	8 h	88[b]

[a] Yields were determined by LC/MS using 1,3,5-trimethoxy benzene as an internal standard. [b] Isolated yield.

indolization with similar efficiencies, although a significant reaction rate difference was observed (Table 3A, entries 1 and 3). Interestingly, the yield of indole **15** was increased when a 1 : 1 D*t*-BPF : XPhos ratio was employed, suggesting a synergistic effect of the dual ligand system on the Larock indolization process (entry 2). The lower yield of just the Larock indolization process (Table 3A, entry 2) compared to the tandem process (Table 1, entry 5) is likely due to quenching of intermediates on the catalytic cycle, as the reaction was stopped as soon as bromoarene **10** was consumed.‡ We next studied the Buchwald–Hartwig step by subjecting indole **15** to different ligand mixtures. D*t*-BPF on its own only provided a 20% yield of tricycle **14** (Table 3B, entry 1). However, the addition of XPhos formed **14** in a 87% yield (entry 2). A similar result was obtained when XPhos was used on its own, however the rate of product formation was faster compared to the 1 : 1 D*t*-BPF : XPhos mixture (entry 3). These results suggest that XPhos facilitates the Buchwald–Hartwig amination step of the tandem annulation/cyclization process.

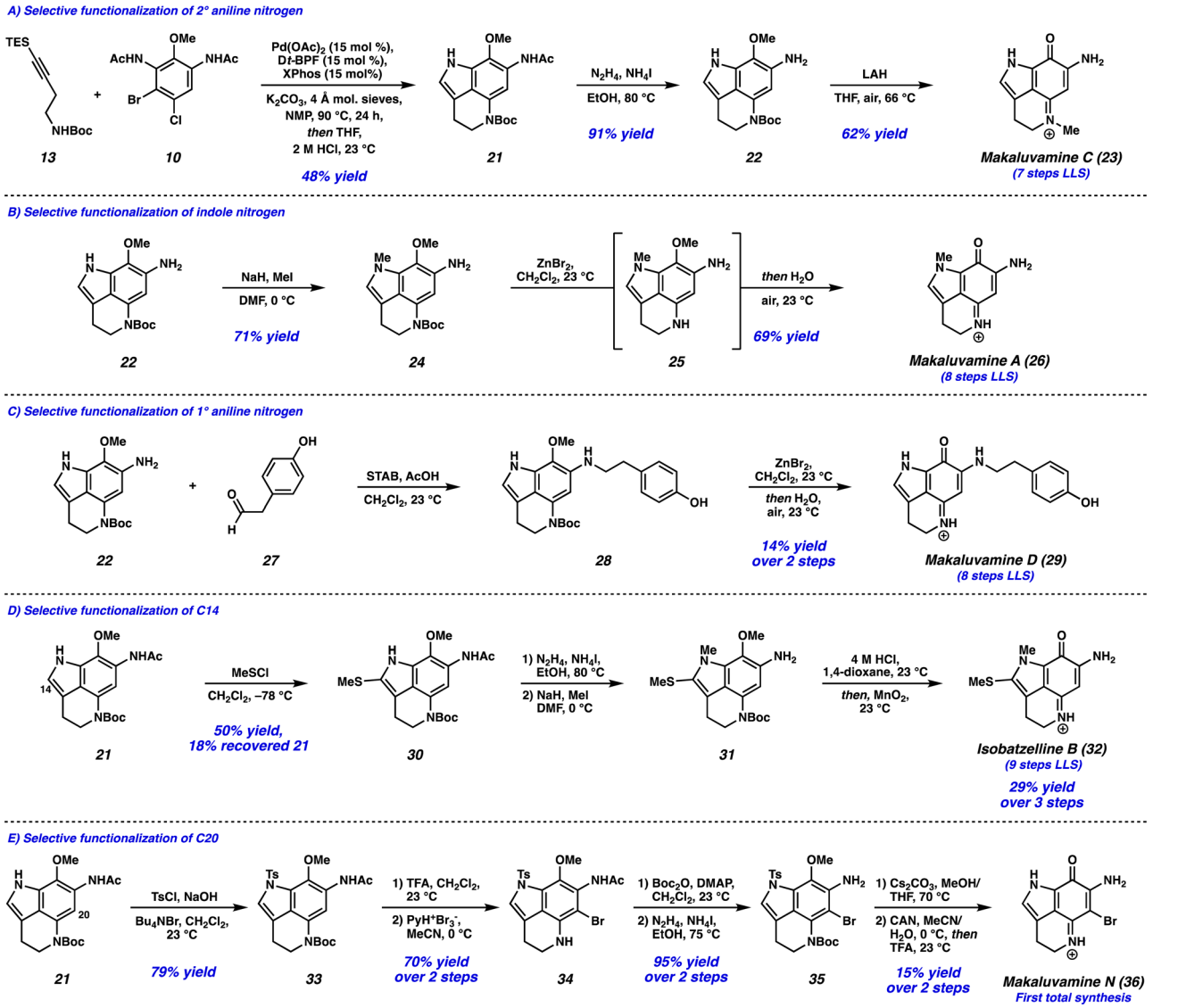
Taken together, we hypothesize that under the optimal reaction conditions a dynamic ligand exchange process



Scheme 2 Selected substrate scope. R = TES.

between D*t*-BPF and XPhos on the palladium center gives rise to a synergistic effect on the Larock indolization, a phenomenon that has been well documented for mixed ligand systems in palladium catalysis.[14] Additionally, the ligand exchange allows for XPhos to facilitate the Buchwald–Hartwig amination step efficiently. This transformation highlights the utility of mixed ligand systems in palladium catalysis and suggests it should be explored more generally in reaction optimization.

With these results in hand, we were interested to see if this method could be applied more generally. Using commercially available 2-bromo-3-chloroaniline resulted in a 75% yield of tricycle **16** (Scheme 2). Additionally, the catalyst and ligand loading could be lowered to 5 mol% without a significant decrease in yield (*i.e.*, 71% yield). *N*-Substitution on the aniline was tolerated, providing both *N*-Me (**17**) and *N*-Boc (**18**) cyclization products. Excitingly, employing 3-bromo-2-chloropyridine resulted in a 41% yield of azaindole derivative **19**, demonstrating the compatibility of heterocyclic substrates in the transformation. Finally, an alkyne coupling partner with



Scheme 3 Divergent syntheses of 5 pyrroloiminoquinone natural products from key tricyclic intermediate **21**. (A) Selective functionalization of the 2° aniline nitrogen. (B) Selective functionalization of the indole nitrogen. (C) Selective functionalization of the 1° aniline nitrogen. (D) Selective functionalization of C14. (E) Selective functionalization of C20.

a longer carbon chain could be used to provide the 5,6,7-tricyclic product **20** in 57% yield.

With the successful development of the Larock/Buchwald–Hartwig annulation/cyclization, we turned our attention toward selectively functionalizing all five positions on tricycle **14** to access an array of pyrroloiminoquinone natural products. To this end, the Larock/Buchwald–Hartwig annulation/cyclization could be followed by an acidic workup to provide desilylated tricycle **21** (Scheme 3A). Employing modified conditions from Ohshima and coworkers,[15] the acetamide could be selectively removed in the presence of the carbamate, yielding aniline **22**. Finally, lithium aluminum hydride (LAH) reduction of the carbamate to the *N*-Me moiety was accompanied by spontaneous aerobic oxidation to yield makaluvamine C (**23**) in just 7 steps (LLS).

We next investigated the selective functionalization of the indole nitrogen (Scheme 3B). Starting with aniline **22**, selective *N*-methylation of the indole nitrogen was achieved under basic conditions to give tricycle **24**. We attempted canonical arene oxidation conditions to pyrroloiminoquinones such as CAN, Fremy's salt, or MnO_2, but unfortunately non-specific decomposition of tricycle **24** was observed under these conditions. Excitingly, when the Boc group was first removed using $ZnBr_2$,[16] the resulting highly electron-rich aniline intermediate **25** underwent spontaneous aerobic oxidation, providing makaluvamine A (**26**) in 8 steps (LLS).

Next, we targeted the selective functionalization of the 1° aniline nitrogen (Scheme 3C). This was achieved using a reductive amination between aniline **22** and aldehyde **27**, to yield *N*-alkylated aniline **28**. Then, our mild arene oxidation protocol was employed to yield makaluvamine D (**29**) in 8 steps (LLS).

We then turned our attention to functionalizing the indole C14 position (Scheme 3D). Using modified conditions reported by Joule and coworkers,[4i] treatment of tricycle **21** with freshly prepared MeSCl (generated from Me_2S_2 and SO_2Cl_2) at −78 °C lead to selective thiomethylation at the C14 position, yielding sulfide **30**. The use of an excess of Me_2S_2 to quantitively generate MeSCl, and performing the reaction at low temperatures was critical to suppressing arene chlorination or difunctionalization. From thiomethylated arene **30**, acetamide cleavage followed by indole *N*-methylation provided tricycle **31**. Unfortunately, this substrate performed poorly in the $ZnBr_2/O_2$ deprotection/oxidation step. Instead, we found that the Boc deprotection could be achieved using anhydrous HCl in dioxane, and the resulting intermediate (not shown) could undergo arene oxidation with MnO_2 in the same flask to provide isobatzelline B (**32**) in 9 steps (LLS).§

Finally, we set out to selectively functionalize the C20 position of tricycle **21** (Scheme 3E). The indole nitrogen was first protected as a sulfonamide to yield tricycle **33**, which then underwent Boc removal and selective C20 bromination to provide bromo-tricycle **34**. Unfortunately, direct acetamide cleavage of this compound proved unsuccessful. Instead, the 2° aniline nitrogen of bromo-tricycle **34** was reprotected as the carbamate, which was followed by acetamide removal to yield bromoaniline **35**. The tosyl group was then removed under basic conditions, and arene oxidation using CAN followed by Boc deprotection yielded makaluvamine N (**36**) in 12 steps (LLS), representing the first total synthesis of this natural product to date.

Conclusions

In summary, we devised a unique approach to five pyrroloiminoquinone alkaloids, which could likely be applied to additional natural products and analogs. Our strategy was enabled by the development of a novel Larock/Buchwald–Hartwig annulation/cyclization to rapidly access the core of these natural products. Critical to the success of this transformation was the employment of a dual ligand system. By judicious choice of nitrogen protecting groups, the key tricyclic intermediate was selectively functionalized in 5 different positions to provide efficient total syntheses of makaluvamines A (**26**), C (**23**), and D (**29**) and isobatzelline B (**32**), and the first total synthesis of makaluvamine N (**36**). We believe that this strategy will facilitate analog synthesis and the advancement of pyrroloiminoquinones as therapeutic candidates, which has historically been a challenge due to the lack of divergent synthetic routes. Additionally, we aim to use the key tricyclic intermediate **14** prepared by our tandem annulation/cyclization strategy to access more complex pyrroloiminoquinone natural products.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

S. P. R. conceived of and performed experiments. J. F., H. Y., Z. P. S., and S. C. V. also performed experiments. B. M. S. supported and supervised the research. S. P. R. wrote the original draft of the manuscript, which was edited by all authors.

Conflicts of interest

There are no conflicts to declare.

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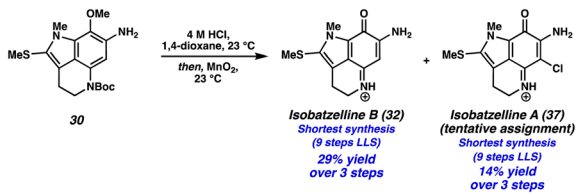
Notes and references

‡ This is supported by observation of large amounts of protodebromination (*i.e.* **9**) and other unidentifiable by-products in the LC/MS trace, which is not the case when the reaction is allowed to proceed for 24 h (*i.e.* optimized conditions).

§ Interestingly, we also isolated isobatzelline A (**37**) from the reaction mixture, representing a 9 step synthesis (LLS) of this natural product. We report this as a tentative assignment as decomposition was observed during the ^{13}C NMR experiment, although the ^{1}H NMR spectra was in good agreement with those previously reported[4n] (see the ESI for additional details). We hypothesize that isobatzelline A (**37**) forms from isobatzelline B (**32**) under the reaction conditions through an oxidative nucleophilic substitution of hydrogen (ONSH) type transformation, wherein Cl^- addition into isobatzelline B (**32**) is followed by oxidation. Alternatively, Cl_2 could be generated from HCl and MnO_2, which then chlorinates the pyrroloiminoquinone double bond in isobatzelline B (**32**), followed by elimination to provide isobatzelline A (**37**). For an example of ONSH with chloride nucleophiles see ref. 17.



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Supporting Information For Divergent Total Syntheses of Pyrroloiminoquinone Alkaloids Ena-bled by the Development of a Larock/Buchwald–Hartwig Annulation/Cyclization

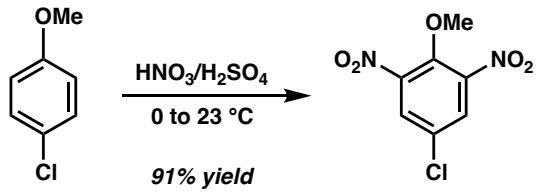
Table of Contents:

Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under a nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under Ar. Reagents were purchased from commercial sources and used as received. K_2CO_3 was freshly flame-dried under vacuum prior to use. 4Å molecular sieves were activated via microwave heating (1100 W, full power, 45 s X 4), cooled under N_2, and stored in a N_2 filled glovebox. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin- layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 pre-coated plates (250 μm) and visualized by UV fluorescence quenching, potassium permanganate staining, or p- anisaldehyde staining. Silicycle SiliaFlash P60 Academic Silica gel (particle size 40–63 μm) was used for flash chromatography. Preparative HPLC was performed on an Agilent 1100 Series HPLC system using a 9.4 x 250 mm Agilent Eclipse XDB-C18 column, or on an Agilent 1200 Series HPLC system using a 9.4 x 250 mm Agilent Zorbax Rx-SIL column. ^{1}H and ^{13}C NMR spectra were recorded on Varian Inova 500 (500 and 125 MHz, respectively), Varian Inova 600 (600 and 150 MHz, respectively), and Bruker 400 (400 and 100 MHz, respectively) spectrometers and are reported in terms of chemical shift relative to $CHCl_3$ (δ 7.26 and 77.16 ppm, respectively), DMSO (δ 2.50 and 39.52 ppm, respectively), or CH_3OH (δ 3.31 and 49.01 ppm, respectively). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant, integration). Abbreviations are used as follows: br s = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. IR spectra were obtained from thin films deposited on NaCl plates using a Perkin Elmer Spectrum BXII spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+), GC field ionization (GCFI+), or electron ionization (EI+) mode, or using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+).

List of Abbreviations

TLC – thin-layer chromatography, LC/MS – liquid chromatography/mass spectrometry, EtOAc – ethyl acetate, TFA – trifluoroacetic acid, THF – tetrahydrofuran, EtOH – ethanol, MeOH – methanol, DCM – dichloromethane, Ac_2O – acetic anhydride, AcOH – acetic acid, TESCl – chlorotriethylsilane, *n*-BuLi – *n*-butyllithium, DMF – dimethylformamide, Boc_2O – di-tert-butyl decarbonate, Et_3N – triethylamine, DMAP – 4-dimethylaminopyridine, XPhos – 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, DtBPF – 1,1′-Bis(di-*tert*-butylphosphino)ferrocene, MeLi – methyl lithium, MeI – iodomethane, NaHMDS – Sodium bis(trimethylsilyl)amide, NMP – *N*-methyl-2-pyrrolidone, STAB – sodium triacetoxy borohydride, TsCl – *p*-toluenesulfonyl chloride, CAN – ceric ammonium nitrate.



6 ***7***

5-chloro-2-methoxy-1,3-dinitrobenzene (7): *Caution! Fuming nitric acid is extremely corrosive and oxidizing. Standard latex and nitrile gloves should not be used when using fuming nitric acid. Wear neoprene based gloves. All operations using fuming nitric acid should be conducted behind a safety shield.*

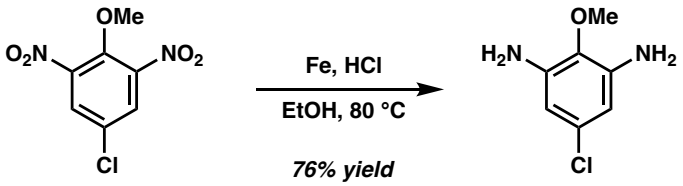
Behind a safety shield, a flame dried 500 mL 3-neck round-bottom flask equipped with a 100 mL additional funnel was charged with fuming nitric acid (40 mL) and brought to 5 °C. 4-chloroanisole (***6***, Combi-Blocks, 20.0 g, 140.27 mmol, 1.0 equiv) was added dropwise such that the temperature was kept below 30 °C (~ 30 min). The reaction mixture was then brought to 0 °C and concentrated sulfuric acid (20 mL) was added dropwise such that the temperature was kept below 20 °C (~ 30 min). The reaction mixture was then brought to 5 °C and fuming nitric acid (20 mL) was added dropwise such that the temperature was kept below 20 °C (~ 20 min). The reaction mixture was then stirred for 10 min at 23 °C. The reaction mixture was then poured onto ice (100 mL) and the yellow precipitate was collected via vacuum filtration. The yellow solid was rinsed with cold water and dried under vacuum for 16 h. This yellow solid was taken forward without additional purification. A small sample was purified by column chromatography (SiO_2, 5% EtOAc/Hexanes) for analytical characterization.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 2H), 4.07 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.5, 145.7, 129.6, 129.3, 65.2.

IR (Neat Film, NaCl): 3082, 2964, 2324, 1608, 1531, 1475, 1421, 1401, 1363, 1254, 1172, 1097, 976, 922, 888, 806, 778, 754, 721 cm^1.

HRMS (GCFI+): *m/z* calc'd for $C_7H_5ClN_2O_5$ $[M]^{+\bullet}$: 231.9887, found 231.9876.



7 ***8***

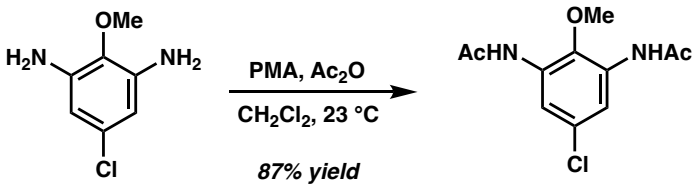
5-chloro-2-methoxybenzene-1,3-diamine (8): A flame dried 500 mL 3-neck round-bottom flask equipped with a reflux condenser was charged with dinitro arene **7** (15.0 g, 64.5 mmol, 1.0 equiv) in EtOH (184 mL, 0.35 M) and 1.5% aq. HCl (64.5 mL, 1 M). Iron (21.6 g, 387.0 mmol, 6 equiv) was added in 5 portions over 5 minutes. The reaction mixture was heated to 80 °C for 6 h, at which point TLC indicated consumption of the starting material. The crude reaction mixture was pushed through a pad of celite with EtOAc (200 mL). The filtrate was diluted with water (300 mL) and the product was extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 40%-50%-75% EtOAc/Hexanes) to afford the title compound (8.44 g, 76% yield) as an off white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.15 (s, 2H), 3.78 – 3.72 (m, 7H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.9, 133.0, 130.1, 106.2, 58.6.

IR (Neat film, NaCl): 3308, 2361, 1675, 1598, 1504, 1435, 1292, 1237, 991, 683 cm^1.

HRMS (ESI+): *m/z* calc'd for $C_7H_{10}ClN_2O$ $[M+H]^+$: 173.0476, found 173.0478.



8 ***9***

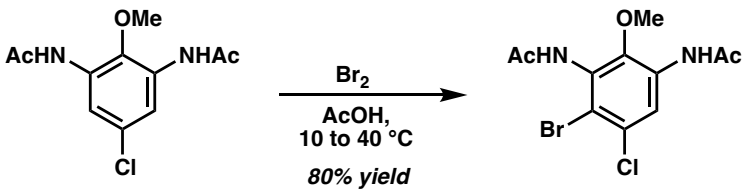
***N,N'*-(5-chloro-2-methoxy-1,3-phenylene)diacetamide (9)**: Prepared using a modified literature procedure.[17] A flame dried 100 mL round-bottom flask was charged with dianline **8** (2.0 g, 11.6 mmol, 1.0 equiv) in CH_2Cl_2 (23 mL, 0.5 M). Acetic anhydride (2.4 mL, 25.52 mmol, 2.2 equiv) and phosphomolybdic acid (PMA, 423.0 mg, 0.23 mmol, 0.02 equiv) were then added. The reaction mixture was stirred at 23 °C for 3 h, at which point TLC indicated complete consumption of the starting material. The reaction mixture was diluted with water (100 mL) and ethyl acetate (150 mL) and the product was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title compound (2.57 g, 87% yield) as a brown solid which was taken forward without additional purification**.**

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 2H), 7.47 (s, 2H), 3.77 (s, 3H), 2.23 (s, 6H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 169.3, 139.4, 132.9, 127.1, 116.8, 60.5, 23.9.

IR (Neat film, NaCl): 3413, 3342, 3317, 3220, 2979, 1635, 1592, 1505, 1442, 1322, 1227, 1150, 1023, 985, 889, 816, 763, 714, 678 cm[1].

HRMS (ESI+): *m/z* calc'd for $C_{11}H_{14}ClN_2O_3$ $[M+H]^+$: 257.0687, found 257.0689.



9 ***10***

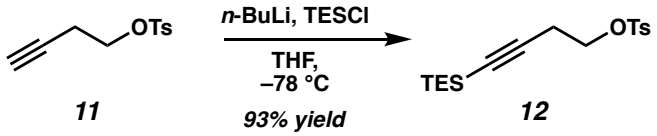
***N,N'*-(4-bromo-5-chloro-2-methoxy-1,3-phenylene)diacetamide (10):** A flame dried 50 mL round-bottom flask was charged with diacetamide **9** (2.57 g, 10.0 mmol, 1.0 equiv) in glacial acetic acid (14.0 mL, 0.73M). The solution was cooled to 10 °C and Br_2 (0.77 mL, 30.0 mmol, 3.0 equiv) was added dropwise over 2 min. The reaction mixture was warmed to 23 °C over 1 h and was then heated to 40 °C for 16 h, at which point LC/MS analysis indicated complete consumption of the starting material. The reaction mixture was poured into ice water (50 mL) and the precipitate was collected via vacuum filtration. The crude product was purified by column chromatography (SiO_2, 100% EtOAc) to afford the title compound (2.7 g, 80% yield) as a brown solid.

^{1}H NMR (600 MHz, DMSO-d_6): δ 9.74 (s, 1H), 9.60 (s, 1H), 8.31 (s, 1H), 3.67 (s, 3H), 2.14 (s, 3H), 2.07 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 169.5, 168.6, 146.7, 132.4, 132.4, 128.0, 120.9, 117.9, 60.9, 23.9, 22.6.

IR (Neat film, NaCl): 3902, 3735**,** 3182, 3002, 2335,1665, 1583, 1514, 1458, 1399, 1370, 1267, 1227, 1165, 1086, 995, 911, 871, 835, 817, 770, 755, 700, 680, 612 cm^1.

HRMS (ESI+): *m/z* calc'd for $C_{11}H_{13}BrClN_2O_3$ $[M+H]^+$: 334.9793, found 334. 9794.



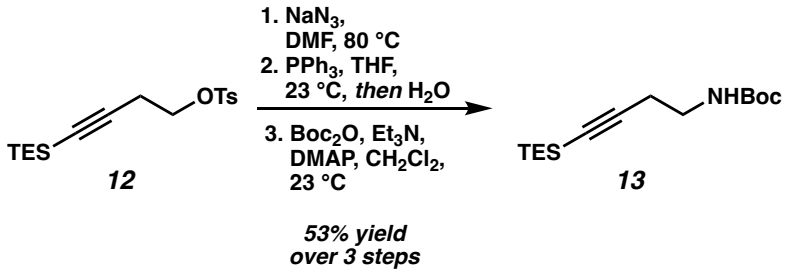
4-(triethylsilyl)but-3-yn-1-yl 4-methylbenzenesulfonate (12): A flame dried 250 mL round-bottom flask was charged with but-3-yn-1-yl 4-methylbenzenesulfonate (**11**, 7.35 g, 32.77 mmol, 1.0 equiv) and THF (82.5 mL, 0.4 M). The solution was cooled to –78 °C and *n*-BuLi (15.73 mL, 39.33 mmol, 1.2 equiv) was added dropwise over 10 min. The solution was stirred at –78 °C for 30 min, at which point TESCl (6.6 mL, 39.33 mmol, 1.2 equiv) was added dropwise over 5 min. The reaction was stirred at –78 °C for 2 h, at which point TLC analysis indicated consumption of the starting material. The reaction mixture was warmed to 23 °C and saturated aq. NH_4Cl (100 mL) and EtOAc (100 mL) were added. The product was extracted with EtOAc (3 x 150 mL), the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title compound (10.27 g, 93% yield) as a yellow oil which was taken forward without additional purification. A small sample was purified via column chromatography (SiO_2, 5% EtOAc/Hexanes) for characterization.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.80 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 4.10 (t, J = 7.3 Hz, 2H), 2.62 (t, J = 7.3 Hz, 2H), 2.45 (s, 3H), 0.94 (t, J = 7.9 Hz, 9H), 0.54 (q, J = 7.9 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.0, 133.1, 130.0, 128.1, 101.5, 84.9, 67.8, 21.8, 20.9, 7.5, 4.4.

IR (Neat film, NaCl): 3859, 3552, 2955, 2911, 2875, 2732, 2178, 1598, 1494, 1458, 1413, 1367, 1307, 1290, 1237, 1189, 1179, 1097, 1062, 1018, 984, 905, 814, 763, 737, 686, 665 cm^1.

HRMS (GCFI+): *m/z* calc'd for $C_{17}H_{27}O_3SSi$ $[M+H]^+$: 339.1450, found 339.1450.



***tert*-butyl (4-(triethylsilyl)but-3-yn-1-yl)carbamate (13):** A flame dried 100 mL round-bottom flask was charged with tosylated alkyne **12** (10.27 g, 30.34 mmol, 1.0 equiv), DMF, (30.34 mL, 1.0 M), and NaN_3 (2.96 g, 45.5 mmol, 1.5 equiv). The reaction mixture was heated at 80 °C for 5h, at which point TLC analysis indicated consumption of the starting material. The reaction mixture was diluted with Et_2O (100 mL) and H_2O (200 mL). The product was extracted with Et_2O (3 x 150 mL), the combined organic layers were washed with 1M aq. LiCl (5 x 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to near dryness to afford the title compound in a solution of Et_2O (~15 mL), which was taken forward to the next step without additional purification.

A flame dried 250 mL round-bottom flask was charged with a solution of the intermediate azide in Et_2O (15 mL, not shown) and THF (90 mL, 0.3 M). PPh_3 (11.94 g, 45.5 mmol, 1.5 equiv) was added in 5 portions over 5 min at 23 °C. The reaction mixture was stirred for 2 h at 23 °C, at which point ^1H NMR analysis indicated consumption of the azide. H_2O (6 mL, 5 M) was added and the reaction mixture was further stirred at 23 °C for 12 h. The reaction mixture was diluted with Et_2O (100 mL) and H_2O (200 mL). The product was extracted with Et_2O (3 x 150 mL), the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to near dryness to afford the title compound in a solution of Et_2O (~15 mL), which was taken forward to the next step without additional purification.

A flame dried 250 mL round-bottom flask was charged with a solution of the intermediate primary amine in Et_2O (15 mL, not shown), Boc_2O (7.28 g, 33.37 mmol, 1.1 equiv), CH_2Cl_2 (90 mL, 0.3 M), Et_3N (6.3 mL, 45.5 mmol, 1.5 equiv), and DMAP (366.0 mg, 3 mmol, 0.1 equiv). The reaction mixture was stirred at 23 °C for 12 h, at which point TLC analysis indicated consumption of the primary amine. The reaction mixture was diluted with Et_2O (200 mL) and H_2O (200 mL). The product was extracted with Et_2O (3 x 150 mL), the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product

was purified by column chromatography (SiO_2, 5% EtOAc/Hexanes) to afford the title compound (4.56 g, 53% yield over 3 steps) as a yellow oil.

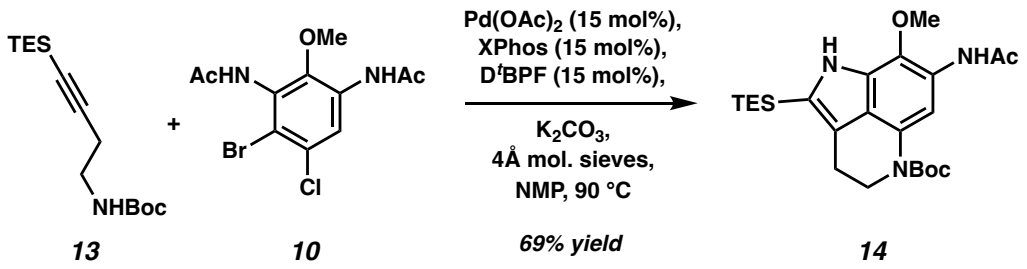
Additionally, we found that after isolation, another drying process of alkyne **13** led to better yields in the subsequent cyclization/annulation. This was achieved by first dissolving alkyne **13** in EtOAc and adding $MgSO_4$. This solution was then passed through a short plug of basic alumina followed by concentration under reduced pressure.

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.81 (br s, 1H), 3.27 (q, J = 6.5 Hz, 2H), 2.43 (t, J = 6.6 Hz, 2H), 1.44 (s, 9H), 0.98 (t, J = 7.9 Hz, 9H), 0.58 (q, J = 7.9 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9, 105.3, 83.8, 79.5, 39.5, 28.5, 21.4, 7.6, 4.6.

IR (Neat film, NaCl): 3354, 2954, 2912, 2875, 2173, 1696, 1520, 1458, 1391, 1365, 1248, 1176, 1072, 1004, 971, 870, 719, 738, cm^1.

HRMS (GCFI+): *m/z* calc'd for $C_{15}H_{30}NO_2Si$ $[M+H]^+$: 284.2046, found 284.2041.



General procedure A: Larock/Buchwald–Hartwig annulation/cyclization.

Note: This reaction was found to be water sensitive. It is critical to use freshly flame-dried K_2CO_3, freshly activated 4Å molecular sieves, and anhydrous NMP (Sigma-Aldrich, item# 328634).

***tert*-butyl 7-acetamido-8-methoxy-2-(triethylsilyl)-3,4-dihydropyrrolo[4,3,2-*de*]quinoline-5(1*H*)-carboxylate (14):** In a nitrogen filled glovebox, to a flame dried 8 mL vial equipped with a magnetic stir bar was sequentially added K_2CO_3 (granular, freshly flame-dried, 303.4 mg, 2.2 mmol, 5.0 equiv), 4Å molecular sieves (powdered, freshly activated, 150 mg, 50 wt% with respect to K_2CO_3), $Pd(OAc)_2$ (Strem, 14.8 mg, 0.066 mmol, 0.15 equiv), XPhos (Combi Blocks, 31.4 mg, 0.066 mmol, 0.15 equiv), D*t*BPF (TCI, 31.3 mg, 0.066 mmol, 0.15 equiv), aryl bromide **10** (147.7 mg, 0.44 mmol, 1.0 equiv), alkyne **13** (622.6 mg, 2.2 mmol, 5.0 equiv), and NMP (4.4 mL, 0.1 M). The vial was sealed with a PTFE cap, removed from the glovebox, stirred at 1000 rpm, and heated at 90 °C for 24 h at which point LC/MS indicated consumption of the starting material. The reaction mixture was pushed through a short pad of celite with EtOAc (20 mL) and was diluted with 1 M aq. LiCl (30 mL). The product was extracted with EtOAc (5 x 30 mL). The combined organic layers were washed with 1M aq. LiCl (x3, 30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 50%-60-70% EtOAc/Hexanes) to afford the title compound (139.7 mg, , 69% yield) as a brown solid. Additionally, unreacted alkyne **13** could be recovered in the first few collected fractions (483 mg, 90% recovery).

^{1}H NMR (600 MHz, CD_3OD): δ 10.10 (s, 1H), 7.54 (s, 1H), 3.98 (t, J = 5.7 Hz, 2H), 3.89 (s, 3H), 2.99 (t, J = 5.6 Hz, 2H), 2.18 (s, 3H), 1.56 (s, 9H), 1.00 (t, J = 7.7 Hz, 9H), 0.91 (q, J = 8.0 Hz, 6H).

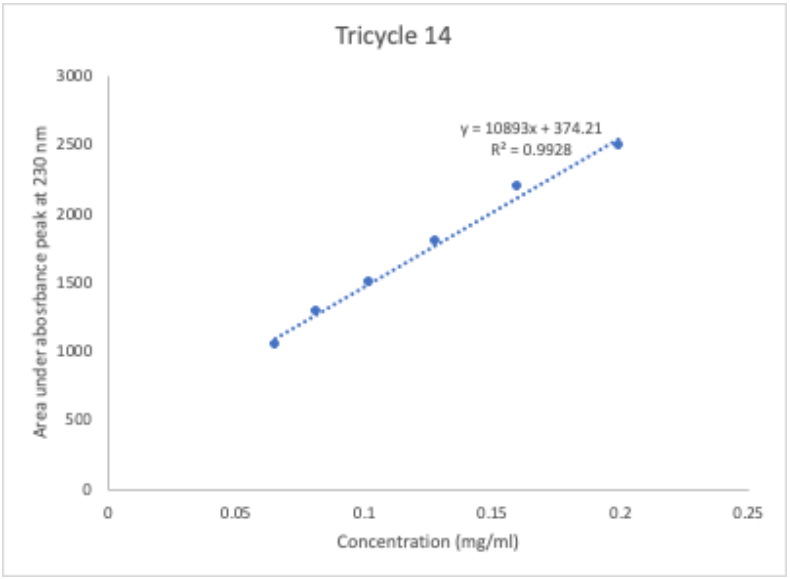
Note: Two carbon signals are observed as a doublet due to hindered rotation about the C–N bond of the carbamate.

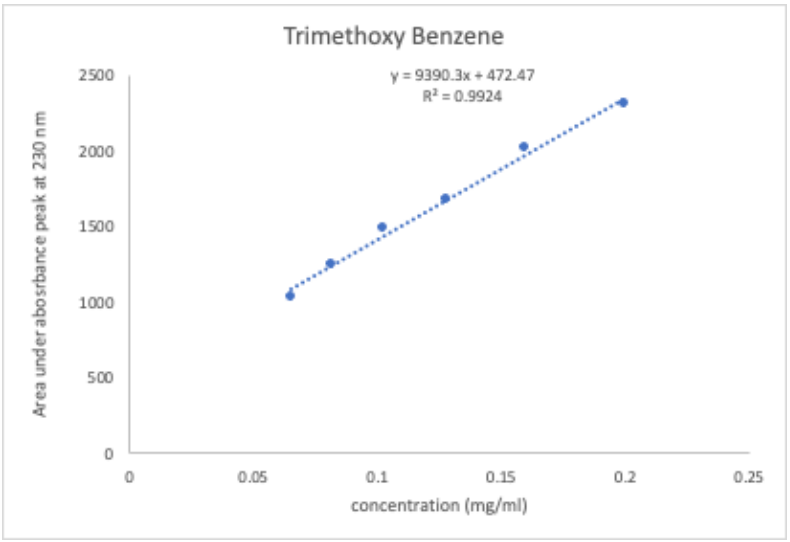
^{13}C NMR (100 MHz, CD_3OD): δ 172.3, 155.4, 136.0, 131.2 (d, J = 15.0 Hz), 129.8 (d, J = 16.7 Hz), 128.9, 125.0, 123.2, 121.7, 109.2, 82.4, 61.3, 46.8, 28.7, 25.6, 23.3, 7.7, 4.4.

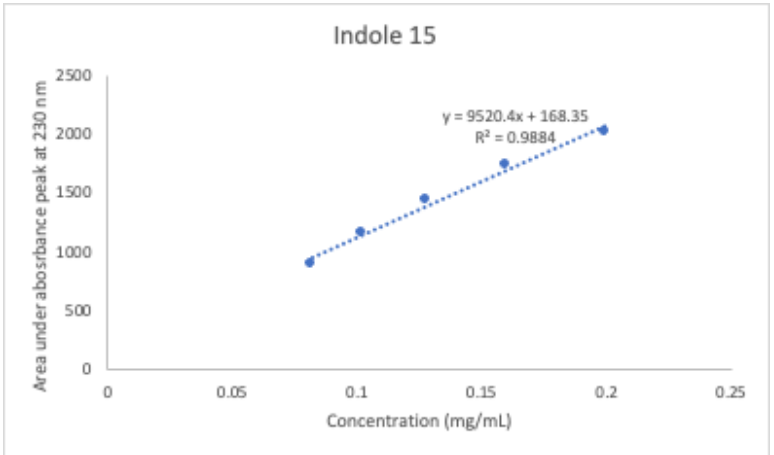
IR (Neat film, NaCl): 3307, 2952, 2930, 2873, 2485, 1667, 1622, 1539, 1516, 1456, 1388, 1368, 1312, 1364, 1160, 1077, 1050, 1003, 977, 855, 737 cm^{1}.

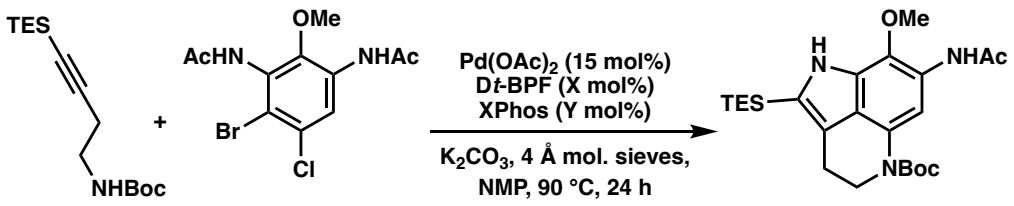
HRMS (ESI+): *m/z* calc'd for $C_{24}H_{38}N_3O_4Si$ $[M+H]^+$: 460.2626, found 460.2625.

Figure S1. Calibration curve for LC/MS assay for ligand stoichiometry experiments.







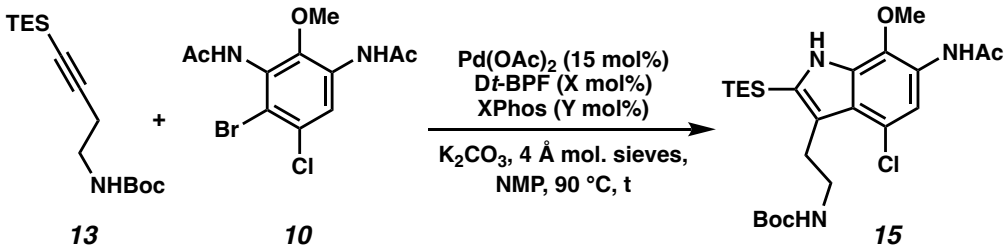


13 ***10*** ***14***

Entry	D*t*-BPF mol %	XPhos mol%	Yield[a]
1	30	0	3%
2	25	5	8%
3	20	10	10%
4	15	15	72%
5	10	20	64%
6	5	25	47%
7	0	30	36%

Ligand stoichiometry experiments: The reactions were set up according to general procedure A on 0.05 mmol scale, using the following modifications: A stock solution of XPhos was prepared in CH_2Cl_2 and the necessary amount was added to each vial via Hamilton syringe. The CH_2Cl_2 was evaporated by blowing air into the vial using a pipette. After the CH_2Cl_2 was evaporated, the vial was charged with K_2CO_3 and 4 Å mol. sieves. Stock solutions of bromoarene **10**, D*t*-BPF, and $Pd(OAc)_2$ were prepared in NMP, and added to the reaction vial via Hamilton syringe. Alkyne **13** was then added. After 24 h, 0.05 mmol of 1,3,5-trimethoxybenzene was added to the reaction vial. It was sealed and stirred for 20 seconds to ensure mixing. A pipette tip of the reaction mixture was then added to an LC/MS vial which was further diluted with 1 mL of MeCN. Yields were calculated based on the areas under the curve at 230 nM using the calibration curves shown on the previous page.

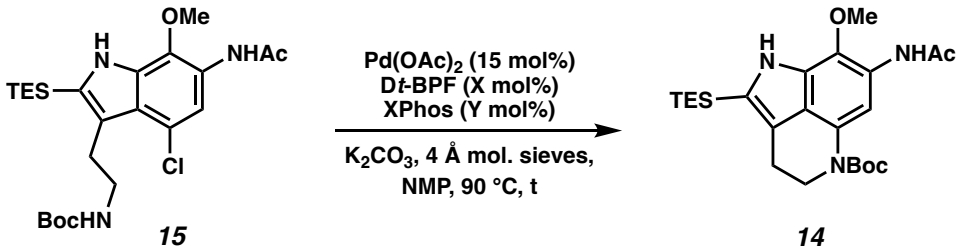
A) Investigation of the Larock indolization step



13 ***10*** ***15***

Entry	D*t*-BPF mol %	XPhos mol%	Time	Yield[a]
1	30	0	20 h	45%
2	15	15	8 h	62%
3	0	30	11 h	44%

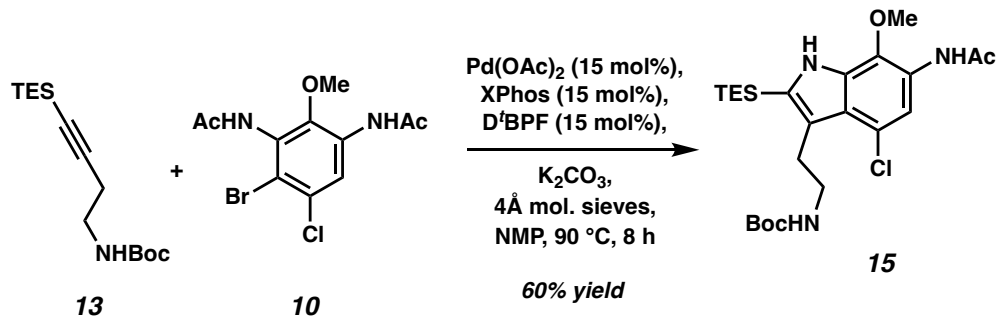
B) Investigation of the Buchwald–Hartwig cyclization step



15 ***14***

Entry	D*t*-BPF mol %	XPhos mol%	Time	Yield[a]
1	30	0	24 h	20%
2	15	15	16 h	87%
3	0	30	8 h	88%[b]

Ligand stoichiometry experiments of each individual step of the tandem annulation/cyclization: These experiments were set up following the procedure described on the previous page with the following modification: Reaction vials were sealed with a red septa cap and connected to a nitrogen line. Aliquots were taken every 1 h until bromoarene **10** was fully consumed, at which point the reaction vial was opened to air and yields were obtained as described on the previous page.



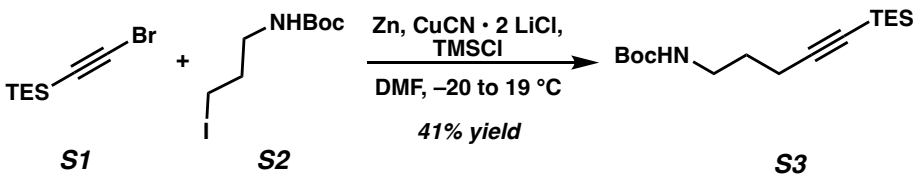
***tert*-butyl (2-(6-acetamido-4-chloro-7-methoxy-2-(triethylsilyl)-1*H*-indol-3-yl)ethyl)carbamate (15):** Prepared according to general procedure A, except the reaction was monitored by LC/MS every hour until bromo arene **10** was consumed. Purification by column chromatography (SiO_2, 40-50-60% ethyl acetate/hexanes) afforded the title compound (60% yield) as an off white foam.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.61 (s, 1H), 9.40 (s, 1H), 7.43 (s, 1H), 6.97 (t, J = 5.6 Hz, 1H), 3.78 (s, 3H), 3.17 3.11 (m, 2H), 3.01 – 2.97 (m, 2H), 2.10 (s, 3H), 1.38 (s, 9H), 0.94 – 0.92 (m, 15H).

^{13}C NMR (100 MHz DMSO-d_6): δ 168.7, 155.5, 136.2, 134.2, 133.4, 124.6, 123.3, 122.5, 118.3, 116.4, 77.3, 60.6, 43.5, 28.3, 26.8, 23.6, 7.4, 3.1.

IR (Neat film, NaCl): 3298, 2954, 2874, 2173, 1693, 1618, 1585, 1506, 1366, 1249, 1169, 1062, 1002, 962, 856, 734, 683 cm^1.

HRMS (ESI+): *m/z* calc'd for $C_{20}H_{31}ClN_3O_4Si$ $[M+H]^+$: 440.1767, found 440.1773.



***tert*-butyl (5-(triethylsilyl)pent-4-yn-1-yl)carbamate (S3):** Alkyl iodide **S2** and bromo alkyne **S1** were prepared as previously described[25], then coupled by the conditions by Baran and coworkers[26]. Briefly, a flame-dried flask was charged with zinc dust (235 mg, 3.6 mmol, 3.6 equiv), DMF (1.5 mL), and 1,2-dibromoethane (0.017 mL, 0.2 mmol, 0.2 equiv). The suspension was heated at 80 °C for 30 minutes. After cooling to 19 °C, trimethylsilylchloride (0.013 mL, 0.1 mmol, 0.1 equiv, freshly distilled over CaH_2) was added and the suspension was stirred an additional 30 minutes at 19 °C. To this suspension was slowly added (ca. 2 min) a DMF solution of the alkyl iodide **S2** (285.1 mg, 1 mmol, 1 equiv, 0.1 mL DMF) which resulted in an exotherm. After returning to 19 °C, stirring was ceased and the alkyl zinc reagent was transferred dropwise via cannula to a cooled (–20 °C) DMF solution of CuCN (80.6 mg, 0.9 mmol, 0.9 equiv) and LiCl (76.3 mg, 1.8 mmol, 1.8 equiv) in DMF (2.5 mL; 0.25 M, total volume relative to alkyl iodide).

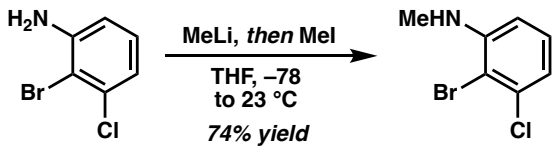
After a period of 15 minutes, neat bromo acetylene **S1** (306.6 mg, 1.4 mmol, 1.4 equiv) was added dropwise to the reaction mixture at –20 °C. The reaction mixture was then allowed to slowly warm to 19 °C over a 3 hour period, and was further stirred at that temperature for an additional 8 hours. At this time the reaction was quenched by the addition of brine (20 mL) and extracted with Et_2O (4 × 50 mL). The organic extracts were washed with brine (5 x 100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified using silica gel flash column chromatography (5 to 15% EtOAc/hexanes) to afford the title compound (168 mg, 41 %) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.78 (s, 1H), 3.23 (q, J = 6.5 Hz, 2H), 2.29 (t, J = 6.9 Hz, 2H), 1.74 – 1.67 (m, 2H), 1.43 (s, 9H), 0.97 (t, J = 7.9 Hz, 9H), 0.56 (q, J = 7.9 Hz, 6H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 107.6, 82.7, 79.3, 40.0, 28.9, 28.5, 17.7, 7.6, 4.6;

IR (Neat film, NaCl): 3351, 2925, 2171, 1684, 1404, 1298, 1169, 1112, 983, 739 cm[1].

HRMS (GCFI+): *m/z* calc'd for $C_{16}H_{32}NO_2Si$ $[M+H]^+$: 298.2202, found 298.2200.



S4 ***S5***

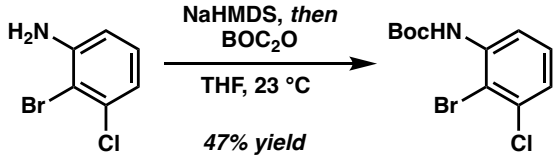
2-bromo-3-chloro-*N*-methylaniline (S5): A flame dried round-bottom flask was charged with 2-bromo-3-chloroaniline (**S4,** 300.0 mg, 1.45 mmol, 1.0 equiv) in THF (14.5 mL, 0.1 M). The solution was cooled to –78 °C and MeLi (3.1 M in diethoxymethane, 4.68 mL, 1.45 mmol, 1.0 equiv) was added dropwise over 1 h. The resultant solution was stirred for 30 min at –78 °C, at which point MeI (0.118 mL, 1.89 mmol, 1.3 equiv) in THF (0.63 mL) was added dropwise over 1 min. The resultant solution was stirred for 1 h at –78 °C, and was then warmed to 23 °C. The reaction was diluted with EtOAc (50 mL) and water (50 mL) and the product was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 5%-10% EtOAc/Hexanes) to afford the title compound (234.5 mg, 74% yield) as a yellow oil.

^{1}H NMR (400 MHz, MeOD): δ 7.13 (t, *J* = 8.1 Hz, 1H), 6.75 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.54 (dd, *J* = 8.3, 1.4 Hz, 1H), 2.85 (s, 3H).

^{13}C NMR (100 MHz, MeOD): δ 149.6, 135.7, 129.8, 118.2, 109.5, 109.4, 30.8.

IR (Neat film, NaCl): 3423, 3075, 2988, 2934, 2901, 2821, 1906, 1715, 1595, 1508, 1457, 1426, 1390, 1319, 1281, 1171, 1135, 1100, 1070, 1019,862, 762, 718, 697 cm^1.

HRMS (ESI+): m/z calc'd for C_7H_8BrClN [M+H$^+$]: 219.9523, found 219.9517.



S4 ***S6***

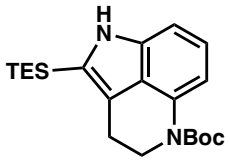
***tert*-butyl (2-bromo-3-chlorophenyl)carbamate (S6):** A flame dried round-bottom flask was charged with 2-bromo-3-chloroaniline (**S4,** 300.0 mg, 1.45 mmol, 1.0 equiv) in THF (10.0 mL, 0.145 M). NaHMDS (531.0 mg, 2.9 mmol, 2.0 equiv) in THF (3.0 mL) was added dropwise over 2 min at 23 °C. The resulting solution was allowed to stir for 20 min. BOC_2O (348.0 mg, 1.6 mmol, 1.1 equiv) in THF (2 mL) was then added dropwise over 2 min, and the reaction mixture was stirred for 2 h. The reaction was diluted with EtOAc (50 mL) and water (50 mL) and the product was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 1-2-3-5% EtOAc/Hexanes) to afford the title compound (207.2 mg, 47% yield) as an orange solid.

^{1}H NMR (400 MHz, MeOD): δ 7.73 (dd, *J* = 7.2, 2.4 Hz, 1H), 7.33 – 7.22 (m, 2H), 1.52 (s, 9H).

^{13}C NMR (100 MHz, MeOD): δ 154.8, 139.9, 135.9, 129.5, 126.6, 122.9, 117.3, 82.0, 28.5.

IR (Neat film, NaCl): 3140, 3106, 2997, 2930, 1849, 1721, 1570, 1520, 1453, 1400, 1368, 1329, 1297, 1232, 1178, 1165, 1063, 1024, 878, 772, 758, 697, 622 cm^1.

HRMS (GCFI+): m/z calc'd for $C_{11}H_{13}NO_2ClBr$ $[M]^{+\bullet}$: 304.9818, found 304.9805.



16

***tert*-butyl 2-(triethylsilyl)-3,4-dihydropyrrolo[4,3,2-*de*]quinoline-5(1*H*)-carboxylate (16)**: Prepared according to general procedure A using 2-bromo-3-chloroaniline **S4** (Combi Blocks, 20.6 mg, 0.1 mmol) and alkyne **13**. Purification by column chromatography (SiO_2, 2-5% EtOAc/Hexanes) afforded the title compound (27.6 mg, 75% yield) as a white solid.

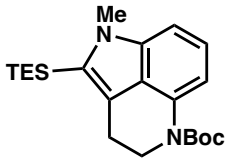
Additionally, this compound could be prepared according to general procedure A with only 5 mol% catalyst and ligand loading to afford the title compound in 71% yield (26.5 mg).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.29 (s, 1H), 7.11 (t, J = 7.9 Hz, 1H), 7.02 (d, J = 8.1 Hz, 1H), 4.10 – 4.06 (m, 2H), 3.05 – 3.03 (m, 2H), 1.58 (s, 9H), 1.00 (t, J = 7.8 Hz, 9H), 0.85 (q, J = 7.8 Hz, 6H).

^{13}C NMR (100 MHz, MeOD): δ 155.6, 139.4, 133.7, 128.4, 123.6, 122.9, 120.5, 110.0, 107.1, 82.2, 46.9, 28.7, 25.7, 7.7, 4.5.

IR (Neat film, NaCl): 3356, 2953, 2877, 2505, 1673, 1594, 1391, 1313, 1232, 1210, 1165, 1005, 9811, 845, 765, 737, 720 cm^1.

HRMS (ESI+): *m/z* calc'd for $C_{21}H_{33}N_2O_2Si$ $[M+H]^+$: 373.2306, found 373.2303.



17

***tert*-butyl-1-methyl-2-(triethylsilyl)-3,4-dihydropyrrolo[4,3,2-*de*]quinoline-5(1*H*)-carboxylate (17)**: Prepared according to general procedure A using 2-bromo-3-chloro-*N*-methylaniline (**S5**, 22.0 mg, 0.1 mmol) and alkyne **13**. Purification by column chromatography (SiO_2, 2-4-6-8% EtOAc/Hexanes), followed by preparative TLC (10% EtOAc/Hexanes) afforded the title compound (29.4 mg, 76% yield) as a white solid.

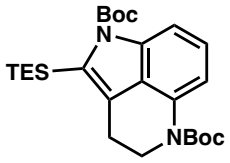
^{1}H NMR (400 MHz, MeOD): δ 7.22 (m, 1H), 7.08 (t, *J* = 7.9 Hz, 1H), 6.96 (d, *J* = 8.2, 1H), 3.98 (t, *J* = 5.6 Hz, 2H), 3.78 (s, 3H), 3.03 (t, *J* 5.7 Hz, 2H), 1.55 (s, 9H), 1.01 – 0.91 (m, 15H).

Note: The product was observed as a mixture of rotamers in the ^{13}C NMR.

^{13}C NMR (100 MHz, MeOD): δ 169.3, 155.4, 140.6, 133.9, 133.6, 132.4, 130.6, 129.8, 124.1, 122.4, 122.2, 110.1, 105.0, 82.3, 69.1, 46.8, 40.1, 33.6, 31.6, 30.1, 28.7, 26.2, 24.9, 24.0, 14.4, 11.4, 7.8, 5.2.

IR (Neat film, NaCl): 2952, 2926, 2874, 1694, 1598, 1463, 1454, 1388, 1352, 1316, 1293, 1227, 1162, 1129, 103, 938, 834, 811, 779, 764, 734.

HRMS (ESI+): *m/z* calc'd for $C_{18}H_{21}N_2O_2Si$ (- *t*-Bu) $[M+H]^+$: 331.1836, found 331.1835.



18

di-*tert*-butyl 2-(triethylsilyl)-3,4-dihydropyrrolo[4,3,2-*de*]quinoline-1,5-dicarboxylate (18): Prepared according to general procedure A using *tert*-butyl (2-bromo-3-chlorophenyl)carbamate (arene **S6**, 30.6 mg, 0.1 mmol) and alkyne **13**. Purification by column chromatography (SiO_2, 2% to 3% to 5% ethyl acetate/hexanes) afforded the title compound (13.5 mg, 29% yield) as a white solid.

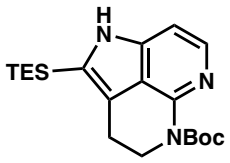
^{1}H NMR (400 MHz, MeOD): δ 7.53 (d, *J* = 8.2 Hz, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.20 (t, *J* = 8.1 Hz, 1H), 4.00 – 3.93 (m, 2H), 3.04 (dd, *J* = 6.4, 5.3 Hz, 2H), 1.70 (s, 9H), 1.57 (s, 9H), 0.96 – 0.93 (m, 15H).

Note: The product was observed as a mixture of rotamers in the ^{13}C NMR.

^{13}C NMR (100 MHz, MeOD): δ 155.0, 153.1, 137.9, 134.3, 132.4, 131.5, 129.9, 129.2, 126.5, 124.3, 114.6, 111.4, 84.9, 82.7, 69.1, 46.2, 40.2, 28.6, 28.5, 8.3, 5.9.

IR (Neat film, NaCl): 3124, 3052, 2932, 2856, 1726, 1595, 1508, 1449, 1365, 1265, 1147, 1107, 1056, 996, 739, 703, 661 cm^1.

HRMS (ESI+): *m/z* calc'd for $C_{22}H_{33}N_2O_4Si$ (- *t*-Bu) $[M+H]^+$: 417. 2204, found 417.2200.



19

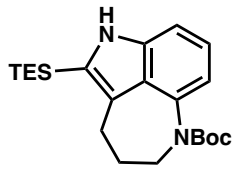
***tert*-butyl5-(triethylsilyl)-6,7-dihydropyrrolo[2,3,4-*de*][1,8]naphthyridine-8(4*H*)-carboxylate (19):** Prepared according to general procedure A using 4-amino-3-bromo-2-chloropyridine (Combi Blocks, 20.7 mg, 0.1 mmol) and alkyne **13**. Purification by column chromatography (SiO_2, 4% acetone/hexanes) afforded the title compound (15.1 mg, 41% yield) as a brown solid.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.11 (s, 1H) 8.09 (d, *J* = 5.8 Hz, 1H), 6.94 (d, *J* = 5.9 Hz, 1H), 4.14 (t, *J* = 5.7 Hz, 2H), 3.02 (t, *J* = 5.7 Hz, 2H), 1.57 (s, 9H), 0.99 (t, *J* = 7.9 Hz, 9H), 0.85 (q, *J* = 7.8 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 148.2, 141.1, 140.9, 128.5, 121.9, 117.4, 102.7, 81.4, 47.0, 28.5, 24.5, 7.5, 3.6.

IR (Neat film, NaCl): 3302, 2954, 1700, 1600, 1380, 1311, 1244, 1153, 1052, 1007, 982, 906, 729 cm^1.

HRMS (ESI+): *m/z* calc'd for $C_{16}H_{24}N_3O_2Si$ (- *t*-Bu) $[M+H]^+$: 318.1632, found 318.1646.



20

***tert*-butyl-5-(triethylsilyl)-2,3,4,6-tetrahydro-1*H*-azepino[4,3,2-*cd*]indole-1-carboxylate (20):** Prepared according to general procedure A using 2-bromo-3-chloroaniline (**S4**, 20.6 mg, 0.1 mmol) and alkyne **S3**. Purification by column chromatography (SiO_2, 4% acetone/hexanes) afforded the title compound (22.0 mg, 57% yield) as a white solid.

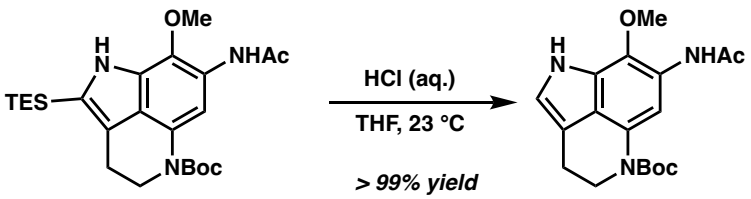
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.84 (s, 1H), 7.14 – 7.05 (m, 2H), 7.01 (d, J = 7.5 Hz, 1H), 3.87 (t, J = 6.2 Hz, 2H), 3.01 (t, J = 6.9 Hz, 2H), 2.17 (tt, J = 6.9, 6.2 Hz, 2H), 1.52 (s, 9H), 1.01 (t, J = 7.8 Hz, 9H), 0.87 (q, J = 7.8 Hz, 6H).

Note: This compound was observed as a mixture of rotamers in the ^{13}C NMR spectrum.

^{13}C NMR (100 MHz, MeOD): δ 156.5, 141.7, 141.6, 137.4, 131.1, 131.0, 126.3, 126.2, 124.7, 124.6, 115.8, 109.5, 109.5, 81.5, 50.9, 29.5, 24.9, 7.8, 4.6.

IR (Neat film, NaCl): 3344, 2952, 2874, 2496, 1667, 1609, 1581, 1453, 1392, 1366, 1324, 1219, 1172, 1107, 1003, 982, 735 cm^1.

HRMS (ESI+): *m/z* calc'd for $C_{18}H_{27}N_2O_2Si$ (- *t*-Bu) $[M+H]^+$: 331.1836, found 331.1836.



14 ***21***

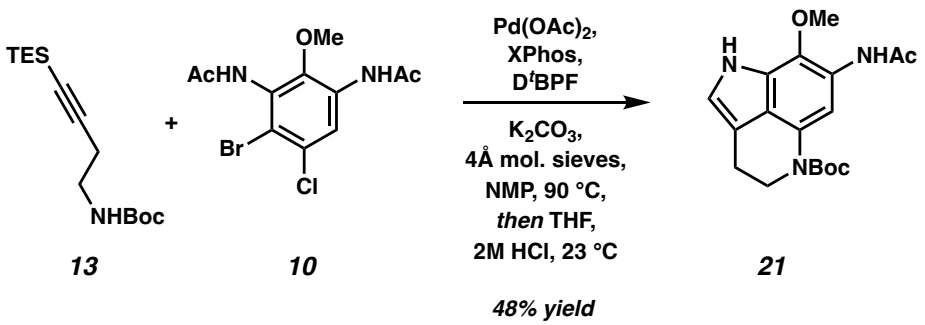
***tert*-butyl 7-acetamido-8-methoxy-3,4-dihydropyrrolo[4,3,2-*de*]quinoline-5(1*H*)-carboxylate (21):** To a 20 mL vial under an ambient atmosphere was added tricycle **14** (134.0 mg, 0.29 mmol, 1.0 equiv), THF (2.9 mL, 0.1 M), and 2 M aq. HCl (2.9 mL, 0.1 M). The reaction mixture was stirred at 23 °C for 4 h, at which point LC/MS analysis indicated complete consumption of the starting material. Aq. saturated $NaHCO_3$ (10 mL) was added, and the reaction mixture was transferred to a separatory funnel with EtOAc. The mixture was further diluted with EtOAc (30 mL) and water (30 mL). The product was extracted with EtOAc (3 x 30 mL), the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title compound (97.1 mg, quantitative yield) as a brown solid, which was taken directly forward without further purification.

^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (s, 1H), 6.88 (s, 1H), 3.97 (t, J = 5.6 Hz, 2H), 3.92 (s, 3H), 2.92 (t, J = 5.7 Hz, 2H), 2.17 (s, 3H), 1.56 (s, 9H).

^{13}C NMR (100 MHz, CD_3OD): δ 172.3, 155.4, 136.4, 128.9, 127.7, 124.2, 122.5, 119.4, 111.2, 109.6, 82.4, 60.9, 46.6, 28.7, 23.8, 23.3.

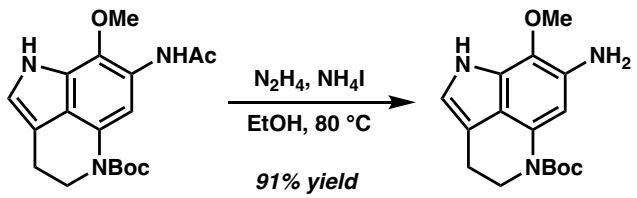
IR (Neat film, NaCl): 3317, 2972, 2929, 2444, 1668, 1510, 1389, 1367, 1326, 1264, 1247, 1206, 1160, 1125, 1037, 969, 873 cm^1.

HRMS (ESI+): *m/z* calc'd for $C_{14}H_{16}N_3O_4$ (loss of *t*Bu) $[M+H]^+$: 290.1135, found 290.1135.



One-step Larock/Buchwald-Hartwig/silyl deprotection procedure.

Prepared according to general procedure A using 100 mg of bromo arene **10** (0.298 mmol). After 24 h of stirring at 90 °C, LC/MS analysis indicated consumption of the starting material and formation of direct Larock/Buchwald-Hartwig product **14** (not shown). The reaction mixture was cooled to 23 °C and THF (3.0 mL, 0.1 M) and aq. 2 M HCl (3.0 mL, 0.1 M) were added. The reaction mixture was stirred at 23 °C for 5 h, at which point LC/MS analysis indicated complete formation of the desilylated product. The reaction mixture was transferred to a separatory funnel with EtOAc, and further diluted with saturated aq. $NaHCO_3$ (20 mL), 1 M aq. LiCl (30 mL) and EtOAc (30 mL). The product was extracted with EtOAc (5 x 30 mL). The combined organic layers were washed with 1 M aq. LiCl (x 3), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 60-70%-80%-90% EtOAc/Hexanes) to afford the title compound (**21**, 49.1 mg, 48% yield) as a brown solid.



21 ***22***

***tert*-butyl 7-amino-8-methoxy-3,4-dihydropyrrolo[4,3,2-*de*]quinoline-5(1*H*)-carboxylate (22):** Prepared using a modified procedure.[20] Under an ambient atmosphere, a flame dried 4 mL vial was charged with indole **21** (66.3 mg, 0.19 mmol, 1.0 equiv). EtOH (1.9 mL, 0.1M), N_2H_4•H_2O (0.288 mL, 5.76 mmol, 30.0 equiv), and NH_4I (275.5 mg, 1.9 mmol, 10.0 equiv) were then added. The solution was degassed with argon for 1 minute and sealed with a PTFE cap. The reaction mixture was heated at 80 °C for 24 h, at which point LC/MS analysis indicated complete consumption of the starting material. The reaction mixture was concentrated under reduced pressure to near dryness. Ethyl acetate (10 mL) was used to transfer the mixture to a separatory funnel. Water (10 mL) was then added and the product was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 60% EtOAc/Hexanes) to afford the title compound (52.7 mg, 91% yield) as a brown solid.

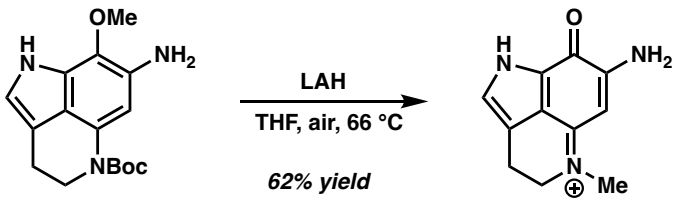
^{1}H NMR (600 MHz, CD_3OD): δ 6.93 (s, 1H), 6.67 (s, 1H), 3.96 – 3.91 (m, 2H), 3.88 (s, 3H), 2.90 – 2.85 (m, 2H), 1.56 (s, 9H);

^{13}C NMR (100 MHz, CD_3OD): δ 155.4, 134.3, 130.7, 129.6, 128.8, 118.3, 116.8, 111.1, 103.8, 82.1, 60.1, 46.9, 28.7, 23.9.

IR (Neat film, NaCl): 3345, 2916, 2849, 1684, 1635, 1524, 1443, 1589, 1364, 1241, 1217, 1160, 1127, 963, 835 cm^1.

HRMS (ESI+): *m/z* calc'd for $C_{16}H_{22}N_3O_3$ $[M+H]^+$: 304.1656, found 304.1652.

Note: This compound is stable under ambient conditions (i.e., air atmosphere) frozen in benzene at –20 °C for up to 1 month. However, this compound is indefinitely stable when stored at room temperature in a nitrogen filled glovebox.



22 ***Makaluvamine C (23)***

Makaluvamine C (23): Under an ambient atmosphere, a flame dried 4 mL vial was charged lithium aluminum hydride (LAH, 406 mg, 10.7 mmol, 30.0 equiv) and THF (3.57 mL, 0.1M). This solution was cooled to 0 °C and stirred for 1 minute. Amino indole **22** (108.2 mg, 0.357 mmol, 1.0 equiv) in THF (0.8 mL) was then added dropwise. This solution was stirred at 0 °C for 5 minutes. The vial was sealed with a PTFE cap and heated to 66 °C for 36 h, at which point LC/MS analysis indicated complete consumption of the starting material. The reaction mixture was then cooled to 0 °C and Rochelle's salt (6 mL) was added dropwise. This mixture was stirred for 5 minutes at 0 °C and then transferred to a separatory funnel with ethyl acetate (20 mL). Water (20 mL) was then added and the product was extracted with EtOAc (8 x 20 mL). The combined organic layers were directly dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 10% MeOH/CH_2Cl_2, 1% TFA) to afford Makaluvamine C as a brown solid. This solid was dissolved in MeOH (1 mL) and TFA (5 drops) was added. The resulting purple solution was concentrated under reduced pressure to yield the TFA salt of Makaluvamine C (**23**, 70.0 mg, 62% yield) as a purple solid.

^{1}H NMR (600 MHz, DMSO-*d*6): δ 13.09 (s, 1H), 9.42 (s, 1H), 8.65 (s, 1H), 7.28 (s, 1H), 5.71 (s, 1H), 3.89 (t, J = 7.6 Hz, 2H), 3.31 (s, 3H), 2.91 (t, J = 7.6 Hz, 2H).

^{13}C NMR (100 MHz, DMSO-*d*6): δ 167.5, 156.6, 155.8, 126.7, 123.4, 123.3, 118.1, 85.4, 52.7, 18.9. *Note: The carbon signal at 39.0 was obscured by the DMSO peak.*

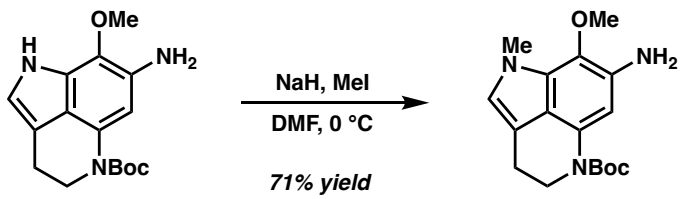
^{1}H NMR (600 MHz, MeOD): δ 7.11 (s, 1H), 5.71 (s, 1H), 3.94 (t, J = 7.6 Hz, 2H), 3.38 (s, 3H), 3.00 (t, J = 7.6 Hz, 2H).

^{13}C NMR (100 MHz, MeOD): δ 167.1, 157.1, 156.8, 125.5, 123.6, 123.4, 118.1, 85.3, 52.9, 38.2, 18.9.

IR (Neat film, NaCl): 3742, 3136, 3045, 2921, 2852, 2364, 1610, 1435, 1409, 1401, 1036, 730.

HRMS (ESI+): *m/z* calc'd for $C_{11}H_{12}N_3O$ $[M]^+$: 202.0975, found 202.0975.

These characterization data are in good agreement with those previously reported.[21a,b]



22 ***24***

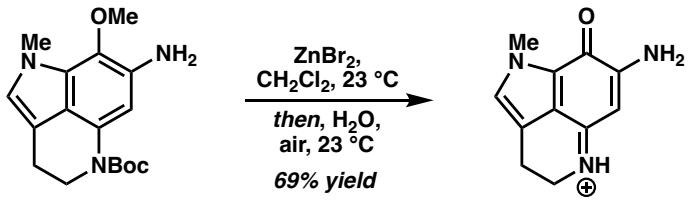
***tert*-butyl 7-amino-8-methoxy-1-methyl-3,4-dihydropyrrolo[4,3,2-*de*]quinoline-5(1*H*)-carboxylate (24):** A flame dried 4 mL vial was charged with NaH (12.0 mg, 0.3 mmol, 1.5 equiv), DMF (0.5 mL, 2.5 M), and brought to 0 °C. Aniline **22** (60.8 mg, 0.2 mmol, 1.0 equiv) in DMF (4.0 mL, 0.05M) was then added dropwise. The solution was stirred at 0 °C for 30 min, at which point MeI (0.0125 mL, 0.2 mmol, 1.0 equiv) was added. The solution was stirred for 30 min at 0 °C, at which point LC/MS analysis indicated complete consumption of the starting material. Saturated aq. NH_4Cl (2 mL), water (20 mL) and EtOAc (20 mL) were added, and the product was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with 1M aq. LiCl (x2), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 40%-50% EtOAc/Hexanes) to afford the title compound (44.8 mg, 71% yield) as a brown foam.

^{1}H NMR (400 MHz, CD_3OD): δ 6.91 (s, 1H), 6.50 (s, 1H), 3.93 – 3.88 (m, 2H), 3.87 (s, 3H), 3.81 (s, 3H), 2.86 – 2.81 (m, 2H), 1.56 (s, 9H).

^{13}C NMR (100 MHz, CD_3OD): δ 155.4, 135.8, 131.2, 130.1, 129.5, 122.1, 118.6, 110.6, 103.9, 82.2, 61.8, 46.7, 34.6, 28.7, 23.8.

IR (Neat film, NaCl): 3356, 2929, 2500, 2218, 2068, 1693, 1623, 1518, 1454, 1389, 1375, 1268, 1255, 1215, 1160, 1123, 1017, 960, 847, 765 cm^1.

HRMS (ESI+): *m/z* calc'd for $C_{17}H_{24}N_3O_3$ $[M+H]^+$: 318.1812, found 318.1817.



24 ***Makaluvamine A (26)***

Makaluvamine A (26): To a flame dried 20 mL scintillation vial in a nitrogen filled glove box were added amino indole **24** (44.8 mg, 0.14 mmol, 1.0 equiv), anhydrous $ZnBr_2$ (252.2 mg, 1.12 mmol, 8.0 equiv), and CH_2Cl_2 (1.4 mL, 0.1M). The vial was sealed with a red septum, removed from the glovebox, and stirred under N_2 at 23 °C for 2 h. Water (4.0 mL, 0.035 M) was then added, and the mixture was stirred at 23 °C for 10 min. The red septum was removed and a gas dispersion tube connected to a compressed air line was fitted onto the vial and lowered into the solution. The mixture was further stirred at 23 °C with air bubbling into the solution for 20 min, at which point LC/MS analysis indicated consumption of most of the starting material and formation of the product. The reaction mixture was diluted with saturated aq. $NaHCO_3$ (20 mL) and a 4:1 CH_3Cl:MeOH mixture (20 mL). The product was extracted with a 4:1 CH_3Cl:MeOH mixture (20 mL x 15). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 10% MeOH/DCM + 1% TFA). The combined product fractions were concentrated under reduced pressure, were redissolved in MeOH (2 mL) and TFA (0.1 mL), and concentrated under reduced pressure to afford the TFA salt of makaluvamine A (**26**, 30.4 mg, 69% yield) as a brown/purple solid.

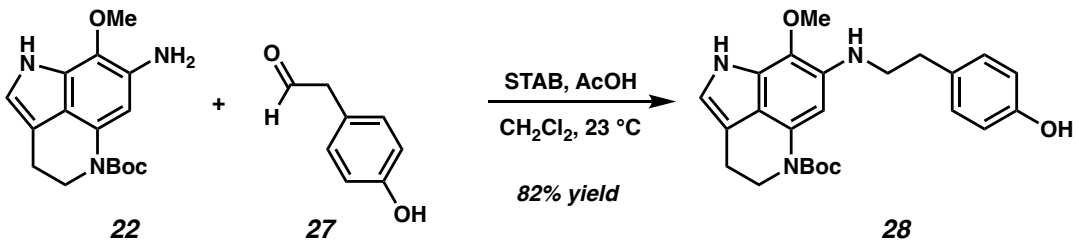
^{1}H NMR (400 MHz, DMSO-*d6*): δ 10.64 (s, 1H), 9.15 (s, 1H), 8.35 (s, 1H), 7.30 (s, 1H), 5.64 (s, 1H), 3.88 (s, 3H), 3.74 (td, J = 7.7, 2.8 Hz, 2H), 2.82 (t, J = 7.6 Hz, 2H); **(600 MHz, MeOD):** δ 7.11 (s, 1H), 5.62 (s, 1H), 3.96 (s, 3H), 3.82 (t, J = 7.6 Hz, 2H), 2.92 (t, J = 7.6 Hz, 2H).

^{13}C NMR (100 MHz, DMSO-*d6*): δ 168.4, 156.8, 156.0, 131.1, 123.1, 122.4, 117.9, 86.6, 42.1, 35.9, 18.0.

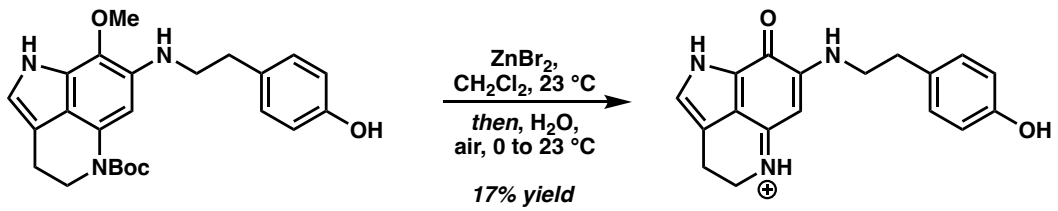
IR (Neat film, NaCl): 2914, 1667, 1601, 1527, 1430, 1392, 1320, 1251, 1169, 801, 708 cm^1.

HRMS (ESI+): *m/z* calc'd for $C_{11}H_{12}N_3O$ $[M]^+$: 202.0975, found 202.0976.

The characterization data are in good agreement with those previously reported.[21a,c]



***tert*-butyl 7-((4-hydroxyphenethyl)amino)-8-methoxy-3,4-dihydropyrrolo[4,3,2-*de*]quinoline-5(1*H*)-carboxylate (28):** A flame dried 4 mL vial was charged with aniline **22** (41.8 mg, 0.138 mmol, 1.0 equiv), and CH_2Cl_2 (1.4 mL, 0.1M). Aldehyde **27**[22] (18.76 mg, 0.138 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL), sodium triacetoxyborohydride (STAB, 58.5 mg, 0.276 mmol, 2.0 equiv), and AcOH (0.004 mL, 0.276 mmol, 2.0 equiv) were then added. The reaction mixture was stirred at 23 °C for 30 min, at which point LC/MS analysis indicated consumption of the starting material. The reaction mixture was transferred to a separatory funnel with EtOAc, and further diluted with EtOAc (10 mL) and saturated aq. $NaHCO_3$ (10 mL). The product was extracted with EtOAc (10 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude brown solid (48.1 mg, 82% yield) was taken directly to the next step without further purification.



28 ***Makaluvamine D (29)***

Makaluvamine D (29): To a flame dried 20 mL scintillation vial in a nitrogen filled glove box was added amino indole **28** (32.0 mg, 0.076 mmol, 1.0 equiv), anhydrous $ZnBr_2$ (136.0 mg, 0.6 mmol, 8.0 equiv), and CH_2Cl_2 (1.5 mL, 0.05M). The vial was sealed with a red septum, removed from the glovebox, and stirred under N_2 at 23 °C for 2 h. Water (7.6 mL, 0.01 M) was then added, and the mixture was stirred at 23 °C for 10 min. The red septum was removed and a gas dispersion tube connected to a compressed air line was fitted onto the vial and lowered into the solution. The mixture was further stirred at 23 °C with air bubbling into the solution for 1 h, at which point LC/MS analysis indicated consumption of most of the starting material and formation of the product. The reaction mixture was diluted with saturated aq. $NaHCO_3$ (20 mL) and a 4:1 CH_3Cl:*i*-PrOH mixture (20 mL). The product was extracted with a 4:1 CH_3Cl: *i*-PrOH mixture (20 mL x 10). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 10% MeOH/DCM + 1% TFA). The combined product fractions were concentrated under reduced pressure, were redissolved in MeOH (2 mL) and TFA (0.1 mL), and concentrated under reduced pressure to afford the TFA salt of makaluvamine D (**29**, 4.0 mg, 17% yield) as a brown/purple solid.

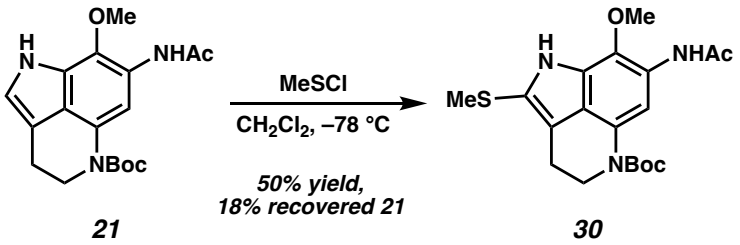
^{1}H NMR (600 MHz, CD_3OD): δ 7.15 (s, 1H), 7.07 (d, J = 8.4 Hz, 2H), 6.72 (d, J = 8.5 Hz, 2H), 5.38 (s, 1H), 3.84 (t, J = 7.6 Hz, 2H), 3.55 (t, J = 7.3 Hz, 2H), 2.95 (t, J = 7.5 Hz, 2H), 2.88 (t, J = 7.3 Hz, 2H).

^{13}C NMR (100 MHz, CD_3OD): δ 168.5, 159.7, 157.4, 155.1, 130.9, 130.0, 127.2, 125.5, 124.0, 120.2, 116.5, 85.2, 46.5, 44.2, 34.4, 19.5.

IR (Neat film, NaCl): 3442, 2921, 2368, 1688, 1440, 1211, 1143, 1025, 835, 737, 727, 629 cm^1.

HRMS (ESI+): *m/z* calc'd for $C_{18}H_{18}N_3O_2$ $[M]^+$: 308.1394, found 308.1391.

The characterization data are in good agreement with those previously reported.[23]



***tert*-butyl 7-acetamido-8-methoxy-2-(methylthio)-3,4-dihydropyrrolo[4,3,2-*de*]quinoline-5(1*H*)-carboxylate (30):** Prepared using a modified procedure.[24] To a flame dried 4 mL vial was added CH_2Cl_2 (1 mL, 0.56 M) and Me_2S_2 (0.15 mL, 1.72 mmol, 4.0 equiv). The solution was cooled to 0 °C and SO_2Cl_2 (0.035 mL, 0.43 mmol, 1.0 equiv) was added. The reaction mixture was stirred at 0 °C for 1 h to provide a 0.86 M solution of MeSCl in CH_2Cl_2.

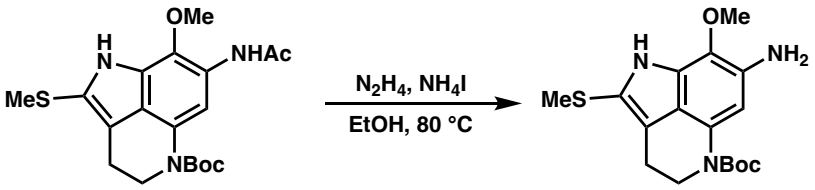
To a separate flame dried 4 mL vial was added indole **21** (43.0 mg, 0.125 mmol, 1.0 equiv) and CH_2Cl_2 (2.5 mL, 0.05 M). The solution was cooled to –78 °C, and freshly prepared 0.86 M MeSCl solution in CH_2Cl_2 (0.145 mL, 0.125 mmol, 1.0 equiv) was added dropwise over 2 min. The reaction mixture was stirred for 5 min at –78 °C, at which point LC/MS analysis indicated near complete consumption of the starting material. Saturated aq. $Na_2S_2O_3$ solution (1 mL) was added at –78 °C, and the reaction mixture was warmed to 23 °C. The reaction mixture was transferred to a separatory funnel with EtOAc, and further diluted with EtOAc (30 mL) and H_2O (30 mL). The product was extracted with EtOAc (3 x 30 mL), the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified via preparative TLC (2 plates, SiO_2, 80% EtOAc/hexanes) to afford the title compound (24.6 mg, 50% yield) as a yellow foam. 7.9 mg of indole **21** was re-isolated (18% recovered SM).

^{1}H NMR (600 MHz, CD_3OD): δ 7.58 (s, 1H), 3.98 (t, J = 5.6 Hz, 2H), 3.90 (s, 3H), 2.91 (t, J = 5.7 Hz, 2H), 2.41 (s, 3H), 2.18 (s, 3H), 1.56 (s, 9H).

^{13}C NMR (100 MHz, CD_3OD): δ 172.3, 155.3, 128.7, 128.6, 125.3, 125.0, 122.5, 115.9, 110.6, 109.7, 82.5, 61.1, 46.4, 28.7, 23.6, 23.3, 19.6.

IR (Neat film, NaCl): 3280, 2977, 2926, 1674, 1537, 1385, 1317, 1265, 1248, 1157, 1131, 1084, 1046, 1026, 958, 853, 737 cm^1.

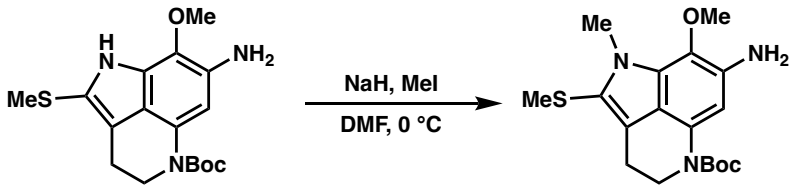
HRMS (ESI+): *m/z* calc'd for $C_{19}H_{25}N_3O_4SNa$ $[M+Na]^+$: 414.1458, found 414.1464.



30 ***S7***

***tert*-butyl 7-amino-8-methoxy-2-(methylthio)-3,4-dihydropyrrolo[4,3,2-*de*]quinoline-5(1*H*)-carboxylate (S7):** Under an ambient atmosphere, a flame dried 8 mL vial was charged with indole **30** (51.0 mg, 0.13 mmol, 1.0 equiv). EtOH (1.3 mL, 0.1M), N_2H_4•H_2O (0.122 mL, 3.9 mmol, 30.0 equiv), and NH_4I (188.5 mg, 0.1.3 mmol, 10.0 equiv) were then added. The solution was degassed with argon for 1 minute and sealed with a PTFE cap. The reaction mixture was heated at 80 °C for 16 h, at which point TLC analysis indicated complete consumption of the starting material. The reaction mixture was concentrated under reduced pressure to near dryness. Ethyl acetate (10 mL) was used to transfer the mixture to a separatory funnel. Water (10 mL) was then added and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the titled compound (45.1 mg, crude) as a brown solid which was used directly in the next step without further purification.

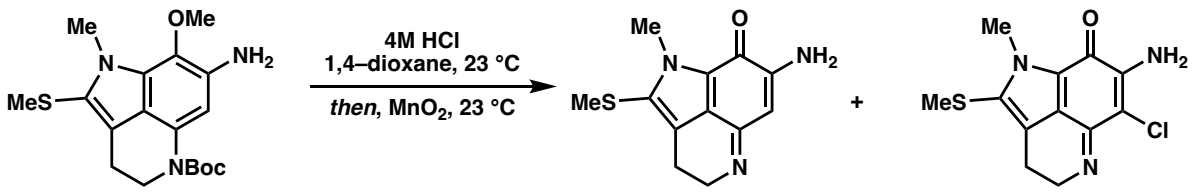
Note: This compound was found to be unstable upon standing in air for >1 h, and was thus carried immediately forward after its preparation.



S7 ***31***

***tert*-butyl 7-amino-8-methoxy-1-methyl-2-(methylthio)-3,4-dihydropyrrolo[4,3,2-*de*]quinoline-5(1*H*)-carboxylate (31):** A flame dried 4 mL vial was charged with NaH (2.2 mg, 0.055 mmol, 1.5 equiv), DMF (0.074 mL, 0.5 M), and brought to 0 °C. Aniline **S7** (12.9 mg, 0.037 mmol, 1.0 equiv) in DMF (0.74 mL, 0.05M) was then added dropwise. The solution was stirred at 0 °C for 30 min, at which point MeI (0.0023 mL, 0.037 mmol, 1.0 equiv) was added. The solution was stirred for 30 min at 0 °C, at which point TLC analysis indicated complete consumption of the starting material. Saturated aq. NH_4Cl (2 mL), water (2 mL) and EtOAc (2 mL) were added, and the product was extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with 1M aq. LiCl (x2), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title compound (9.2 mg, crude) as a brown solid which was used directly in the next step without further purification.

Note: This compound was found to be unstable upon standing in air for >1 h, and was thus carried immediately forward after its preparation



31 ***Isobatzelline B (32)*** ***Isobatzelline A (37) (tentative assignment)***

29% yield over 3 steps ***14% yield over 3 steps***

Isobatzelline B (32) and Isobatzelline A (37): A flame dried 8 mL vial was charged with sulfide **31** (15.0 mg, 0.041 mmol, 1.0 equiv) and 4M HCl in dioxane (2.5 mL, 0.0165M). The reaction was stirred at 23 °C for 2 hours, at which point MnO_2 (35.7 mg, 0.41 mmol, 10.0 equiv) was added in one portion. The reaction was further stirred for 5 minutes, at which point saturated aq. $NaHCO_3$ (3 mL) was added. The reaction mixture was transferred to a separatory funnel and saturated aq. $NaHCO_3$ was added until the pH of the mixture was 7. The products were extracted with 4:1 $CHCl_3$:iso-propanol (10 mL X 10). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude brown solid was purified by preparatory TLC (4 plates, 9:1 DCM:MeOH) to afford isobatzelline B (4.4 mg, 29% yield over three steps) as a red/brown solid and isobatzelline A (2.3 mg, 14% yield over three steps) as red solid.

Isobatzelline B (32):

^{1}H NMR (600 MHz, 1:1 CD_3OD:$CDCl_3$): δ 5.71 (s, 1H), 3.98 (s, 3H), 3.89 (t, J = 7.7 Hz, 2H), 2.87 (t, J = 7.7 Hz, 2H), 2.34 (s, 3H).

^{1}H NMR (600 MHz, CD_3OD, TFA salt): δ 5.65 (s, 1H), 4.01 (s, 3H), 3.86 (t, J = 7.6 Hz, 2H), 2.98 (t, J = 7.6 Hz, 2H), 2.40 (s, 3H).

^{13}C NMR (100 MHz, CD_3OD, TFA salt): δ 169.1, 159.2, 158.0, 136.5, 126.3, 124.5, 123.0, 87.7, 43.8, 33.7, 19.8, 18.4.

IR (Neat film, NaCl): 3214, 2921, 2853, 1665, 1616, 1463, 1265, 1122, 736 cm^1.

HRMS (ESI+): *m/z* calc'd for $C_{12}H_{14}N_3OS$ $[M+H]^+$: 248.0852, found 248.0855.

The characterization data are in good agreement with those previously reported.[25]

Isobatzelline A (37):

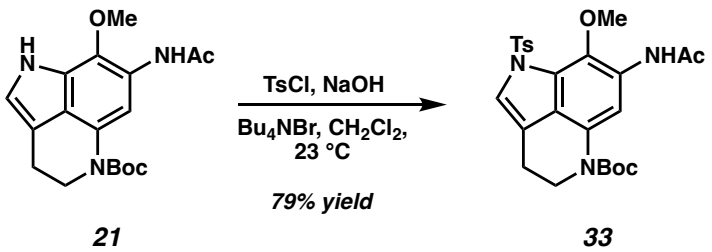
^{1}H NMR (600 MHz, 1:1 CD_3OD:$CDCl_3$): δ 4.05 (t, J = 7.8 Hz, 2H), 3.95 (s, 3H), 2.75 (d, J = 7.7 Hz, 2H), 2.31 (s, 3H). This data is in good agreement with those previously reported.[25]

Note: Decomposition of isobatzelline A was observed when acquiring the ^{13}C NMR, thus we have reported this as a tentative assignment.

^{13}C NMR (100 MHz, 1:1 CD_3OD:$CDCl_3$): δ 169.5, 153.2, 142.5, 133.4, 131.7, 129.3, 127.4, 123.5, 121.9, 113.2, 68.8, 39.4, 32.9, 30.2, 23.2, 19.0.

IR (Neat film, NaCl): 3332, 3222, 2921, 2358, 1666, 1591, 1525, 1425, 1401, 1266, 1233, 1000, 721 cm^1.

HRMS (ESI+): *m/z* calc'd for $C_{12}H_{13}ClN_3OS$ $[M+H]^+$: 282.0462, found 282.0463.



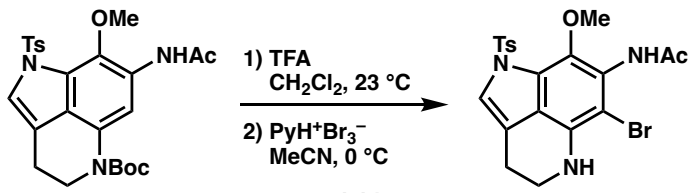
***tert*-butyl 7-acetamido-8-methoxy-1-tosyl-3,4-dihydropyrrolo[4,3,2-*de*]quinoline-5(1*H*)-carboxylate (33):** A flame-dried 1 dram vial was charged with indole **21** (25 mg, 0.0724 mmol, 1.0 equiv), TsCl (28 mg, 0.145 mmol, 2.0 equiv), Bu_4NBr (2.4 mg, 0.00724 mmol, 0.1 equiv), and powdered KOH (13 mg, 0.217 mmol, 3.0 equiv). The vial was evacuated and backfilled with nitrogen, then CH_2Cl_2 (0.72 mL, 0.1M) was added, and the resulting suspension was stirred at 23 °C for 30 min. The reaction was diluted with CH_2Cl_2 (5 mL) and water (5 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3x3 mL), the combined organic extracts were dried with Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (15% EtOAc/hexanes to 50% EtOAc/hexanes) to afford the title compound (28.5 mg, 0.0571 mmol, 79%) as a yellow solid.

^{1}H NMR (400 MHz, C_6D_6): δ 9.11 (s, 1H), 7.85 (d, J = 8.3 Hz, 2H), 7.33 – 7.20 (m, 2H), 6.65 (d, J = 8.3 Hz, 2H), 3.76 (t, J = 5.7 Hz, 2H), 3.66 (s, 3H), 2.29 (m, 2H), 1.67 (s, 3H), 1.64 – 1.46 (m, 12H).

^{13}C NMR (100 MHz, C_6D_6): δ 167.1, 153.5, 144.4, 144.3, 136.6, 132.8, 130.9, 130.5, 129.7, 125.8, 121.7, 121.6, 117.0, 110.5, 81.8, 61.6, 44.3, 28.5, 24.3, 22.5, 21.1.

IR (Neat film, NaCl): 3301, 3133, 2978, 2933, 1693, 1681, 1613, 1530, 1470, 1370, 1328, 1306, 1271, 1168, 1094, 849, 800, 766, 735, 703, 681, 667.

HRMS (FD+): *m/z* calc'd for $C_{25}H_{29}N_3O_6S$ $[M+H]^+$: 500.1855, found 500.1866.



33 ***34***

***N*-(6-bromo-8-methoxy-1-tosyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinolin-7-yl)acetamide (34):** A flame-dried 1 dram vial was charged with indole **33** (28.5 mg, 0.0571 mmol, 1.0 equiv), CH_2Cl_2 (0.57 mL, 0.1M), and TFA (0.13 mL, 1.71 mmol, 30 equiv). The resulting mixture was stirred at 23 °C for 2 h, at which point LC/MS analysis showed full consumption of starting material. The reaction was diluted with CH_2Cl_2 (7 mL), washed with sat. $NaHCO_3$ (3x5 mL), and dried over Na_2SO_4, and concentrated under reduced pressure afford the intermediate secondary aniline (not shown) which was used directly without further purification.

A 20 mL flame-dried vial containing intermediate secondary aniline (not shown, *ca.*0.0571 mmol, 1.0 equiv) was charged with MeCN (4.0 mL, 0.14M). The resulting solution was cooled to 0 °C with ice/water bath, and pyridinium tribromide ($PyHBr_3$, 16.4 mg, 0.0514 mmol, 0.9 equiv) in MeCN (1.7 mL) was then added. The mixture was stirred at 0 °C for 30 min, at which point LC/MS indicated near full consumption of the starting material. The reaction mixture was concentrated under reduced pressure, and resulting residue was purified by preparatory TLC (100% EtOAc) to afford the title compound (19.3 mg, 0.0404 mmol, 70% over 2 steps) as a brown oil.

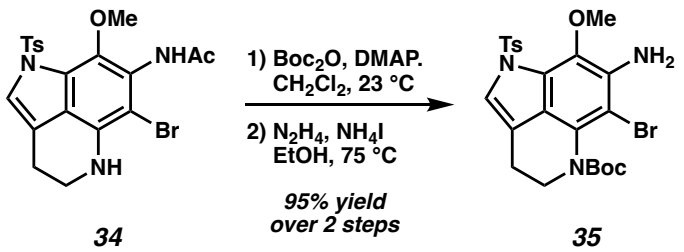
Note: This compound was observed as a mixture of rotamers due to hindered rotation about the amide C–N bond.

^{1}H NMR (400 MHz, C_6D_6): δ 7.97 – 7.79 (m, 2H), 7.31 (s, 1H), 6.73 – 6.57 (m, 2H), 3.87 (s, 1H), 3.79 – 3.71 (m, 3H), 2.66 – 2.52 (m, 2H), 2.32 – 2.44 (m, 2H), 1.74 – 1.61 (m, 6H).

^{13}C NMR (100 MHz, C_6D_6): δ 172.5, 168.0, 144.3, 137.7, 137.4, 136.8, 136.1, 129.7, 129.6, 126.2, 122.0, 121.7, 121.2, 115.5, 115.0, 100.9, 99.8, 62.1, 61.8, 42.0, 22.9, 22.2, 21.0.

IR (Neat film, NaCl): 2919, 1813, 1688, 1504, 1353, 1288, 1167, 1138, 1106, 1055, 814, 665.

HRMS (FD+): *m/z* calc'd for $C_{20}H_{21}BrN_3O_4S$ $[M+H]^+$: 478.0436, found 478.0441.



34 *35*

***tert*-butyl 7-amino-6-bromo-8-methoxy-1-tosyl-3,4-dihydropyrrolo[4,3,2-*de*]quinoline-5(1*H*)-carboxylate (35):** A flame-dried 1 dram vial was charged with bromoindole **34** (19.3 mg, 0.0403 mmol, 1.0 equiv), DMAP (0.5 mg, 0.00403 mmol, 0.1 equiv), Boc_2O (26.4 mg, 0.121 mmol, 3.0 equiv), and CH_2Cl_2 (4 mL, 0.1M). The resulting mixture was stirred at 23 °C, and after 1 h the mixture was concentrated under reduced pressure to afford crude *N*-Boc bromoaniline (not shown), which was used directly without further purification.

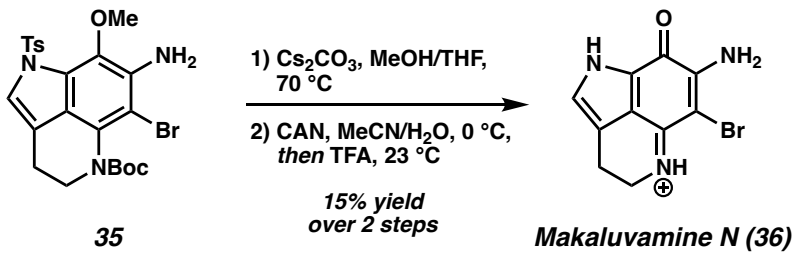
A flame-dried ½ dram vial was charged with *N*-Boc bromoaniline (not shown, *ca*. 0.0403 mmol, 1.0 equiv), NH_4I (175 mg, 1.21 mmol, 30 equiv), EtOH (0.4 mL, 0.1M) and $N_2H_4 \cdot H_2O$ (0.26 mL, 4.03 mmol, 100 equiv). The resulting mixture was stirred at 75 °C for 2 days, at which point LC/MS analysis showed full consumption of the starting material. The reaction mixture was diluted with H_2O (2 mL) and extracted with CH_2Cl_2 (4x4 mL). The combined organic extracts was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by preparatory TLC (65% EtOAc/Hex) to the title compound (20.4 mg, 0.0382 mmol, 95% over 2 steps) as a brown solid.

^{1}H NMR (400 MHz, C_6D_6): δ 7.92 (d, J = 8.4 Hz, 2H), 7.30 (s, 1H), 6.69 (d, J = 7.9 Hz, 2H), 5.69 (s, 1H), 3.89 (s, 3H), 3.82, (s, 1H), 2.53 (t, J = 5.9 Hz, 2H), 2.24 (t, J = 6.0, 2H), 1.70 (s, 3H), 1.43 (s, 9H).

^{13}C NMR (100 MHz, C_6D_6): δ 154.0, 144.2, 137.7, 137.0, 135.9, 129.7 (2C), 126.1, 121.5, 120.9, 115.2, 101.3, 79.6, 61.9, 42.0, 28.4, 22.2, 21.1. (*Note: an additional ^{13}C resonance associated with the tosyl group is likely obscured by the solvent signal).*

IR (Neat film, NaCl): 2921, 1722, 1688, 1633, 1501, 1350, 1286, 1228, 1171, 1106, 850, 813, 664, 611.

HRMS (FD+): *m/z* calc'd for $C_{23}H_{27}BrN_3O_5S$ $[M+H]^+$: 536.0855, found 536.0852.



35 ***Makaluvamine N (36)***

Makaluvamine N (36): A flame-dried 1 dram vial was charged with bromoaniline **35** (19.1 mg, 0.0356 mmol, 1.0 equiv), Cs_2CO_3 (116 mg, 0.356 mmol, 10 equiv), MeOH (0.3 mL, 0.1M), and THF (0.6 mL, 0.05M), and the resulting mixture was stirred at 70 °C for 1.5 h. The reaction mixture was diluted with H_2O (5 mL), and extracted with CH_2Cl_2 (3x3 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to afford the intermediate deprotected indole (not shown) as a brown solid which was used immediately in the next reaction without purification.

To a 20 mL vial containing deprotected indole (*ca.* 0.0356 mmol, 1.0 equiv) under nitrogen was added MeCN (2.0 mL). The resulting solution was cooled to 0 °C, then added CAN (25.4 mg, 0.0463 mmol, 1.3 equiv) in H_2O (1 mL). The reaction mixture was stirred at 0 °C for 5 min at which point LC/MS analysis showed full consumption of starting material. The reaction was diluted with H_2O (5 mL), extracted with DCM (3x5 mL). The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure, and the resulting residue was dissolved in TFA (1.8 mL). The mixture was allowed to stand at 23 °C for 10 min before being concentrated *in vacuo* to afford crude makaluvaine N (**36**). The crude product was purified by preparative reverse-phase HPLC (Eclipse XDB-C18, 5 μm, 9.4 x 250 mm, MeCN-H_2O (0.1% TFA) = 0:100 to 100:0, linear gradient for 6 min, flow rate = 5 mL/min) to afford makaluvamine N (**36**) as the TFA salt (2 mg, 0.00526 mmol, 15% over 2 steps).

^{1}H NMR (400 MHz, MeOD): δ 7.17 (s, 1H), 3.94 (t, *J* = 7.6 Hz, 2H), 2.99 (t, *J* = 7.6 Hz, 2H).
^{13}C NMR (100 MHz, MeOD): δ 166.4, 157.1, 155.5, 127.5, 125.1, 123.7, 120.9, 82.1, 45.0, 19.5.

IR (Neat film, NaCl): 3386, 3111, 1681, 1612, 1409, 1206, 721.

HRMS (FD+): *m/z* calc'd for $C_{10}H_9BrN_3O$ $[M+H]^+$: 265.9929, found 265.9930.

The characterization data are in good agreement with those previously reported.[26]

Table of comparison of ^{1}H resonance signals of synthetic vs natural[26] makaluvamine N (**36**).

Natural (δ)	**Synthetic** (δ)
2.98 (2H, t, *J* = 7.5 Hz)	2.99 (t, *J* = 7.6 Hz, 2H).
3.93 (2H, t, *J* = 7.5 Hz)	3.94 (t, *J* = 7.6 Hz, 2H),
7.15 (1H, s,)	7.17 (s, 1H),

*Spectra acquired in MeOD.

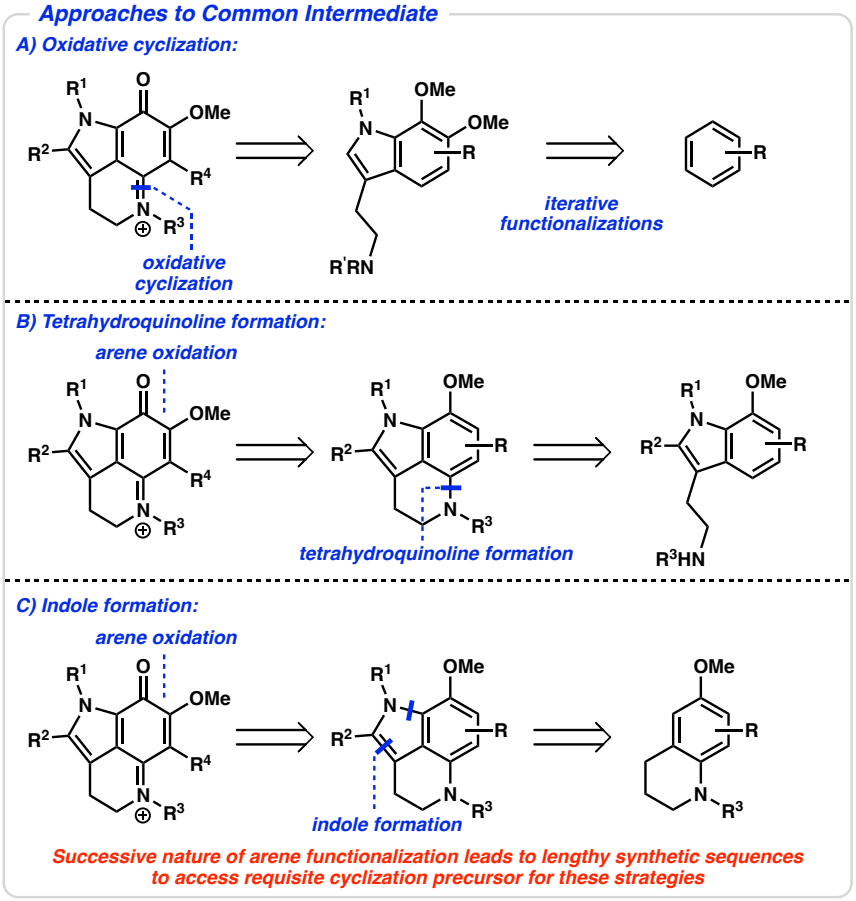
Table of comparison of ^{13}C resonance signals of synthetic vs natural[26] makaluvamine N (**36**).

Natural (δ)	**Synthetic** (δ)
19.5	19.5
45.1	45.0
82.3	82.1
121.0	120.9
123.7	123.7
125.1	125.1
127.6	127.5
155.4	155.5
157.2	157.1
166.3	166.4

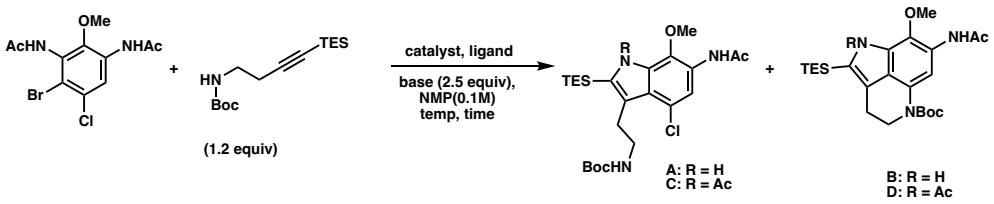
*Spectra acquired in MeOD.

Discussion on Strategies to Access Common Intermediate 10:

Given that most syntheses of pyrroloiminoquinones proceed through the common iminoquinone intermediate, much of the research in the field has focused on its construction, which has resulted in three major strategies. The first utilizes an oxidative cyclization strategy, wherein the iminoquinone is constructed from a tryptamine through a sequential arene oxidation and nitrogen cyclization (Figure S1). This tryptamine in turn is accessed through iterative arene functionalizations from a simple arene starting material. The second is a tetrahydroquinoline formation approach, in which the iminoquinone oxidation state is first adjusted back to an anisole derivative. The tetrahydroquinoline C–N bond is then forged through a cyclization event, once again tracing back to a tryptamine derivative. The third approach focuses on an indole formation, where again arene oxidation state adjustment leads back to an anisole type intermediate. The indole is then disconnected tracing back to a tetrahydroquinoline derivative which is accessed through iterative functionalizations from a simple arene starting material. Although these approaches have proved successful in numerous syntheses, the successive nature of arene functionalization leads to lengthy synthetic sequences in order to access the requisite cyclization precursor. Refer to references 4 and 5 in the main text for examples of these strategies.

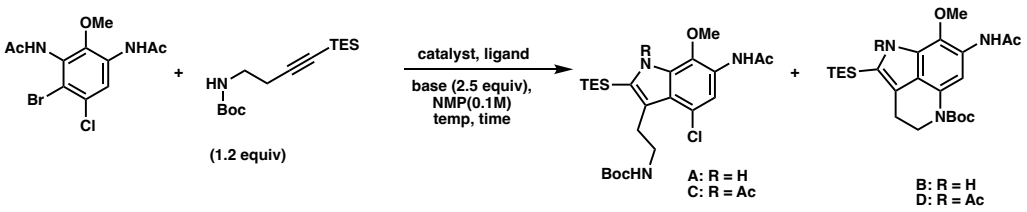


Additional Larock/Buchwald–Hartwig Annulation/Cyclization Optimization:



Entry	Catalyst	Ligand	Base	Temp	Time	Yield
1	$Pd(OAc)_2$ (7 mol%)	D^tBPF (10 mol%)	K_2CO_3	110 °C	24h	15% B
2 (3 equiv of alkyne)	$Pd(OAc)_2$ (5 mol%)	D^tBPF (8 mol%)	K_2CO_3	110 °C	24h	19% B
3	$Pd(OAc)_2$ (11 mol%)	D^tBPF (12 mol%)	Cs_2CO_3	110 °C	24h	0% just SM
4	$Pd(OAc)_2$ (8 mol%)	XPhos (7 mol%)	K_2CO_3	110 °C	24h	11% B
5	$Pd(OAc)_2$ (7 mol%)	D^tBPF (10 mol%)	K_2CO_3	110 °C	24h	25% A
6	XPhos Pd G3 (10 mol%)	-	K_2CO_3	110 °C	24h	22% A + 8% B
7	$Pd(OAc)_2$ (10 mol%)	D^tBPF (25 mol%)	K_2CO_3	110 °C	24h	7% A + 18% B
8	$Pd(OAc)_2$ (10 mol%)	xanthphos (17 mol%)	K_2CO_3	110 °C	24h	0%, just SM
9	$Pd(OAc)_2$ (15 mol%)	D^tBPF (30 mol%)	K_2CO_3 (5 equiv)	110 °C	48h	19% B
10	$Pd(OAc)_2$ (10 mol%)	D^tBPF (20 mol%)	K_2CO_3 + LiCl (1equiv)	110 °C	48h	31% A w/ impurity
11 (toluene instead of NMP)	$Pd(OAc)_2$ (10 mol%)	D^tBPF (23 mol%)	K_2CO_3 (5 equiv)	110 °C	48h	0%, mostly proto-debromination
12 (DMA instead of NMP)	$Pd(OAc)_2$ (8 mol%)	D^tBPF (19 mol%)	K_2CO_3 (5 equiv)	110 °C	48h	3% A
13 -freshly dried K_2CO_3	$Pd(OAc)_2$ (9 mol%)	D^tBPF (18 mol%)	K_2CO_3	110 °C	48h	19% A + 19% B
14 -freshly dried K_2CO_3	*t*-BuXPhos Pd G3 (8 mol%)	-	K_2CO_3	110 °C	48h	11% A
15 -freshly dried K_2CO_3 -5 equiv alkyne	$Pd(OAc)_2$ (15 mol%)	D^tBPF (30 mol%)	K_2CO_3 (5 equiv)	110 °C	48h	32% B
16 -freshly dried K_2CO_3 -9 equiv alkyne	$Pd(OAc)_2$ (15 mol%)	D^tBPF (30 mol%)	K_2CO_3 (5 equiv)	110 °C	48h	15% B

Reactions conducted on 0.1 mmol scale. Yields refer to LC/MS yields using 1,3,5-trimethoxy benzene as an internal standard.



Entry	Catalyst	Ligand	Base	Temp	Time	Yield
17 -freshly dried K_2CO_3 -5 equiv alkyne -4 Å mol sieves	$Pd(OAc)_2$ (15 mol%)	D^tBPF (30 mol%)	K_2CO_3 (5 equiv)	110 °C	48h	41% B
18 -freshly dried K_2CO_3 -5 equiv alkyne -4 Åmol sieves 20 mg scale	$Pd(OAc)_2$ (15 mol%)	D^tBPF (30 mol%)	K_2CO_3 (5 equiv)	110 °C	48h	26% B
19 -freshly dried K_2CO_3 -2 equiv alkyne -AuCl (20 mol%)	$Pd(OAc)_2$ (15 mol%)	XPhos (30 mol%)	K_2CO_3 (5 equiv)	110 °C	48h	23% B
20 -freshly dried K_2CO_3 -2.5 equiv alkyne -CuI (10 mol%)	$Pd(OAc)_2$ (15 mol%)	XPhos (30 mol%)	K_2CO_3 (5 equiv)	110 °C	48h	trace B
21 (dioxane instead of NMP)	$Pd(P(t\text{-}Bu)_3)_2$ (10 mol%)	-	Cy_2NMe (2.5 equiv)	80 °C	6d	trace A
22	$Pd(OAc)_2$ (16 mol%)	D^tBPF (22 mol%)	K_2CO_3 (3.5 equiv)	130 °C	30h	trace B
23	$Pd(OAc)_2$ (10 mol%)	pheynyl urea (40 mol%)	K_2CO_3 (3 equiv)	130 °C	30h	SM + decomp
24 (dioxane instead of NMP)	$Pd(P(t\text{-}Bu)_3)_2$ (5 mol%)	-	Cy_2NMe (2.5 equiv)	130 °C	30h	proto-debromination
25 (DMF instead of NMP)	$Pd_2(DBA)_3$ (10 mol%)	D^tBPF (20 mol%)	TEA (2.5 equiv)	130 °C	30h	proto-debromination + trace C
26 (DMF instead of NMP)	$Pd(OAc)_2$ (10 mol%)	D^tBPF (20 mol%)	TEA (2.5 equiv)	130 °C	30h	proto-debromination + trace C
27	$Pd(OAc)_2$ (15 mol%)	D^tBPF (20 mol%)	K_3PO_4 (2.5 equiv)	130 °C	30h	trace A
28	$Pd(OAc)_2$ (16 mol%)	D^tBPF (26 mol%)	K_2CO_3 (2.5 equiv)	110 °C	5h	8% A 2% B
29	$Pd(OAc)_2$ (6 mol%)	D^tBPF (7 mol%)	Cy_2NMe (2.5 equiv)	110 °C	24h	sm + proto-debromination
30 (DMF instead of NMP)	$Pd(OAc)_2$ (5 mol%)	D^tBPF (7 mol%)	K_2CO_3 (2.5 equiv)	110 °C	24h	trace A
31	$Pd(P(t\text{-}Bu)_3)_2$ (5 mol%)	-	K_2CO_3 (2.5 equiv)	110 °C	24h	trace B

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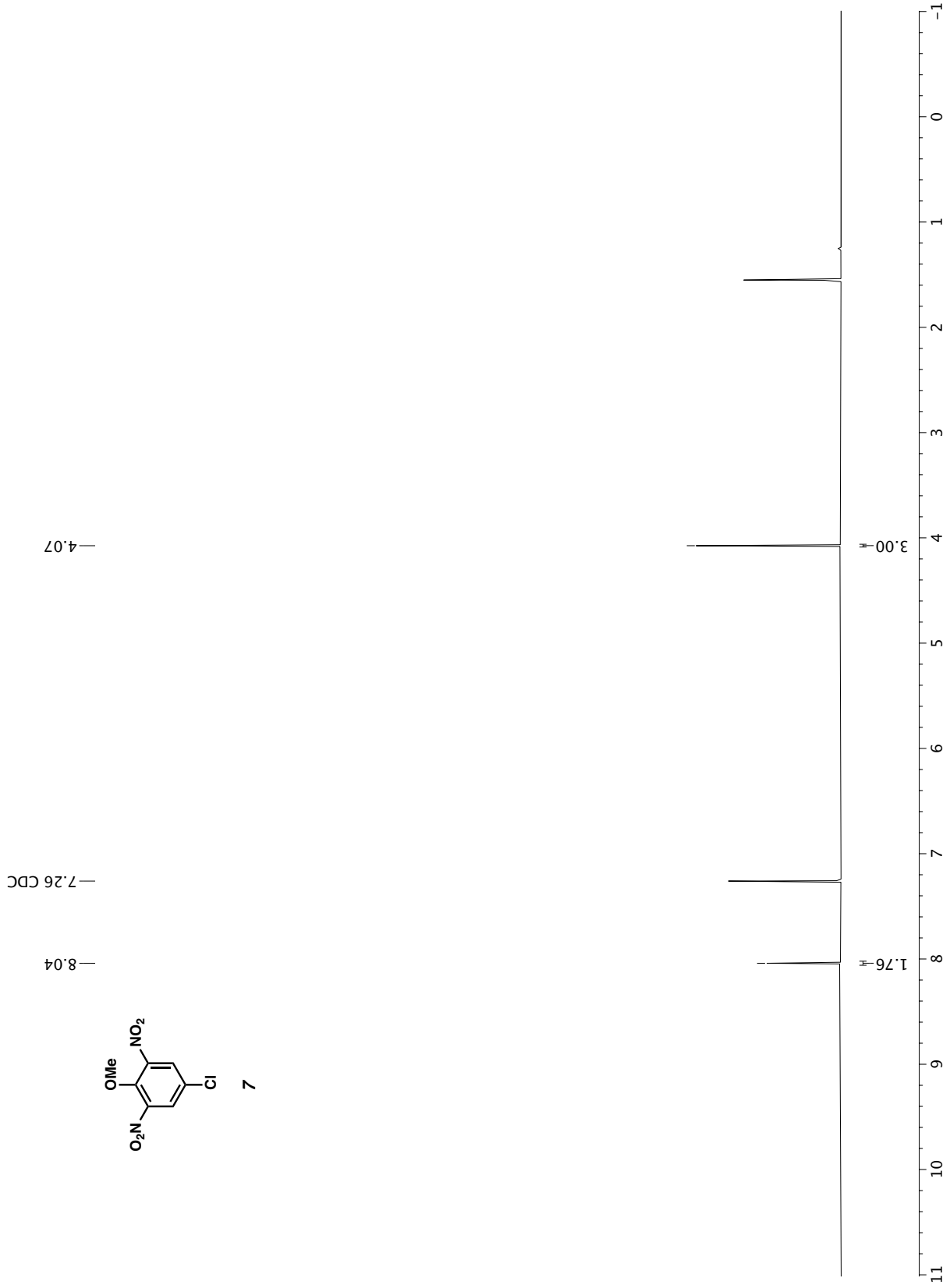
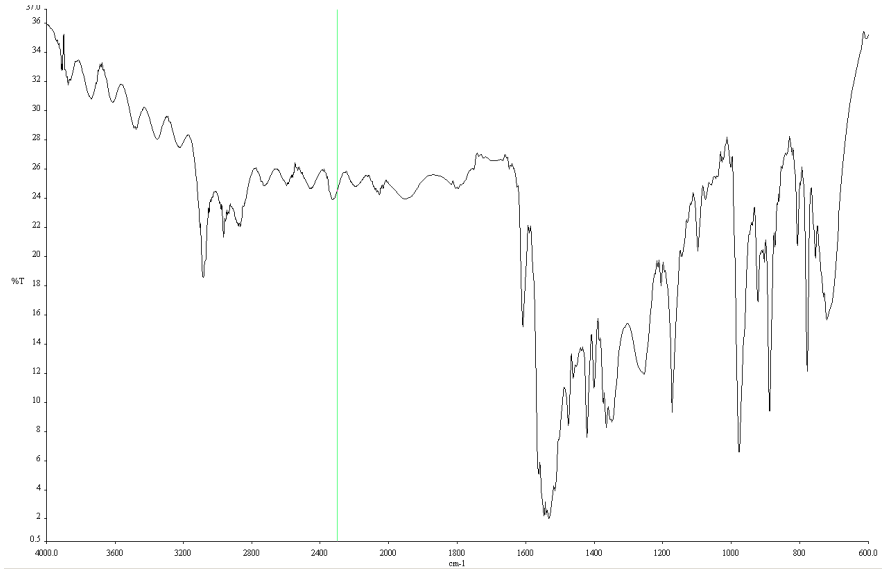
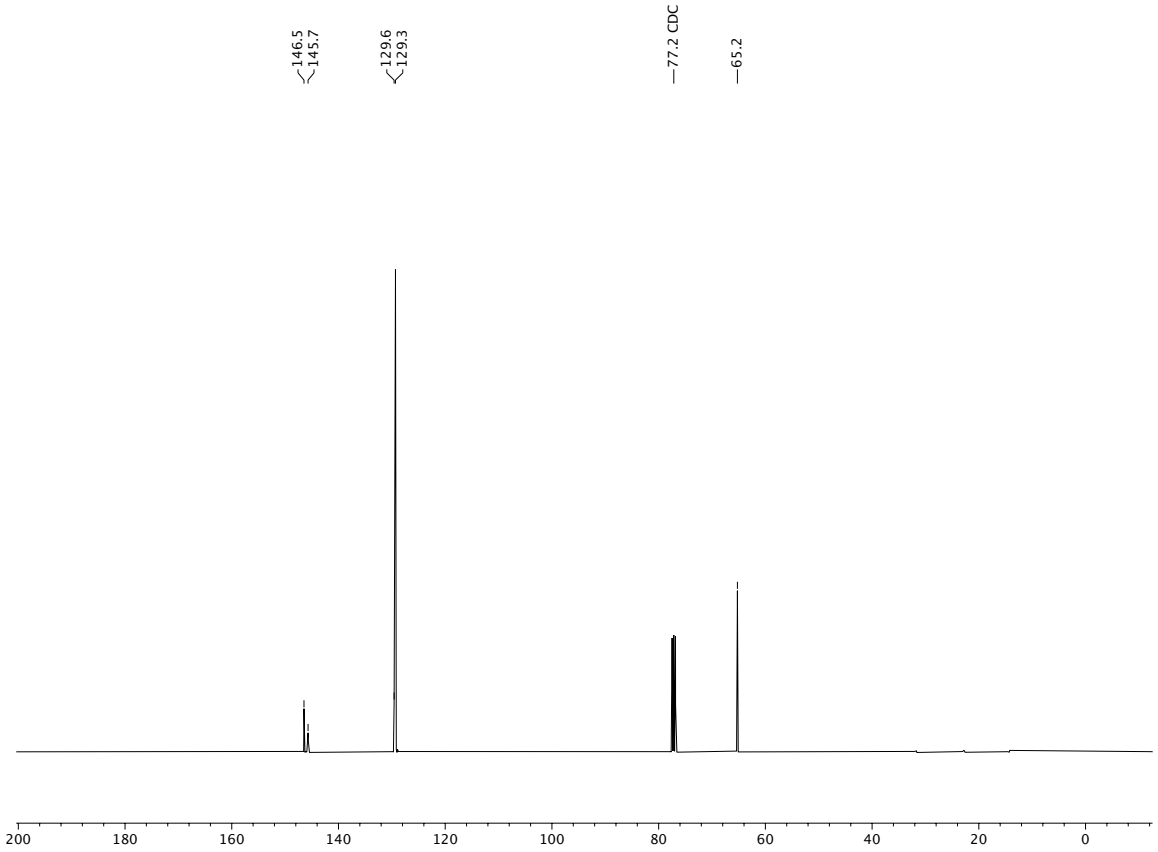


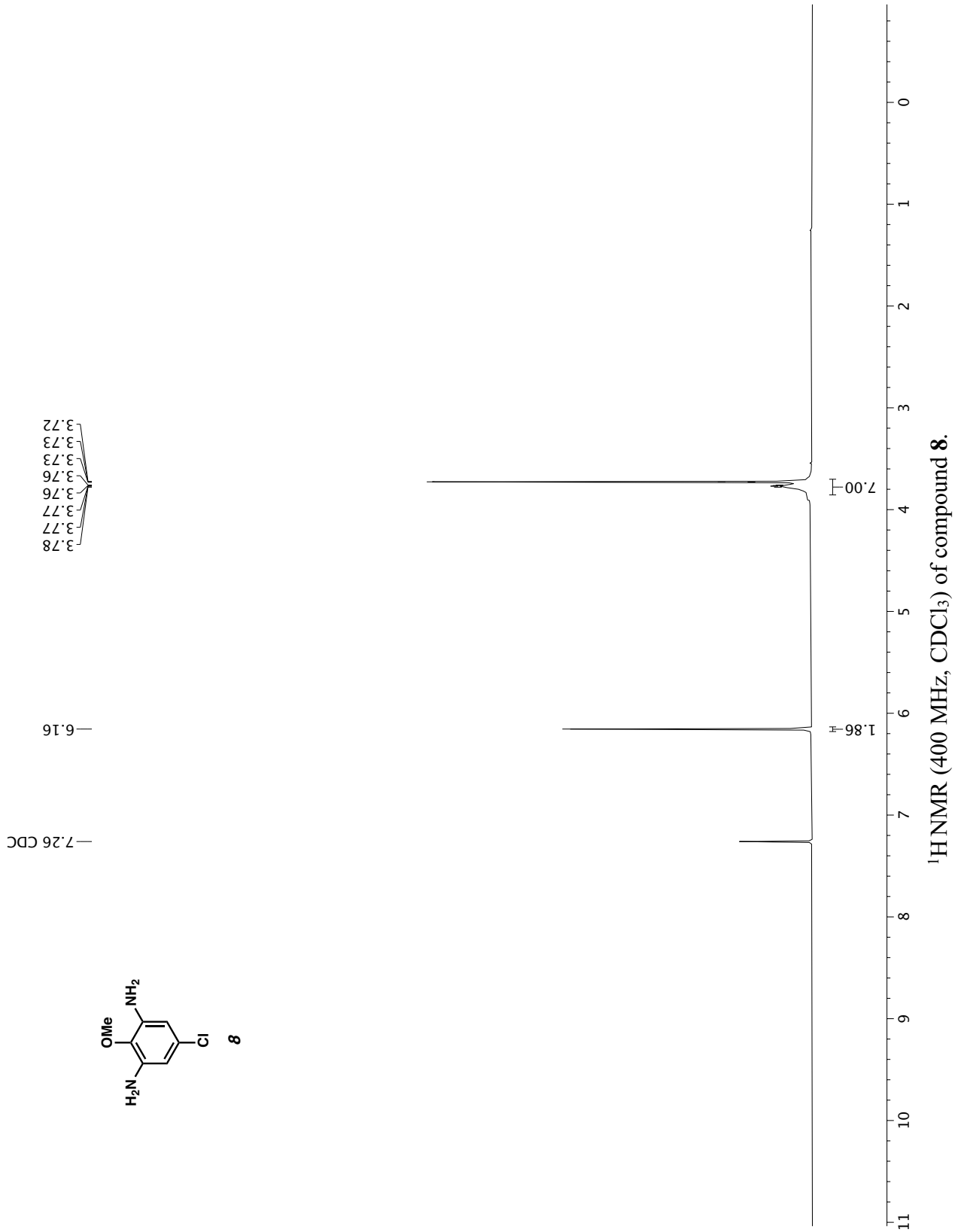
^{1}H NMR (400 MHz, $CDCl_3$) of compound **7**.



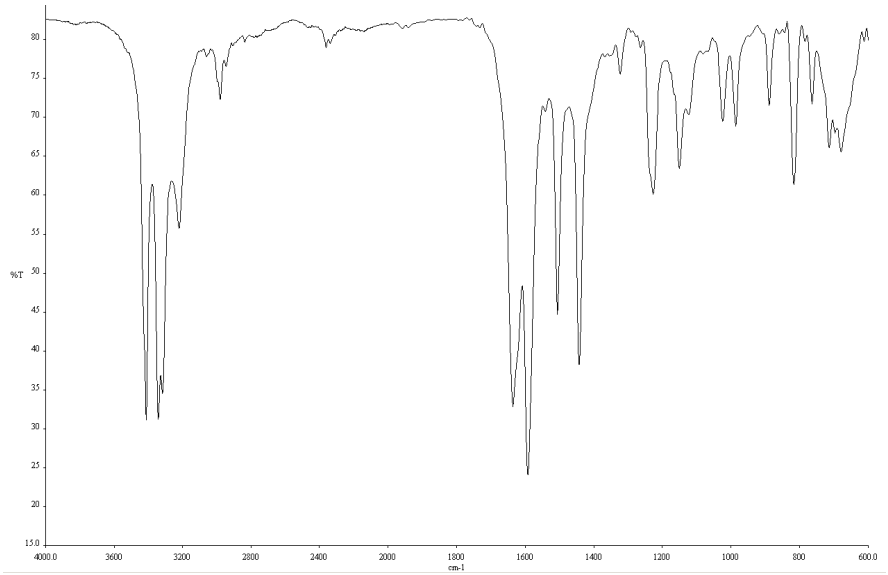
Infrared spectrum (Thin Film, NaCl) of compound **7**.



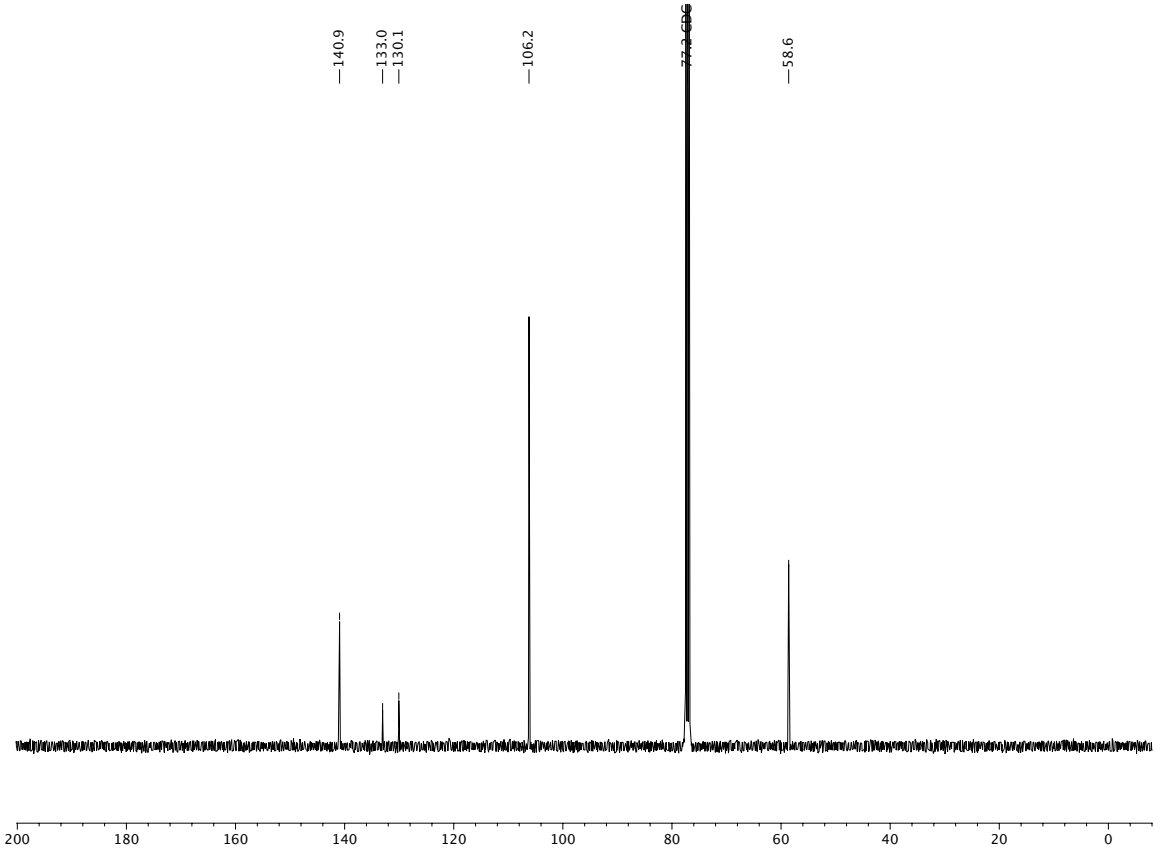
^{13}C NMR (100 MHz, $CDCl_3$) of compound **7**.



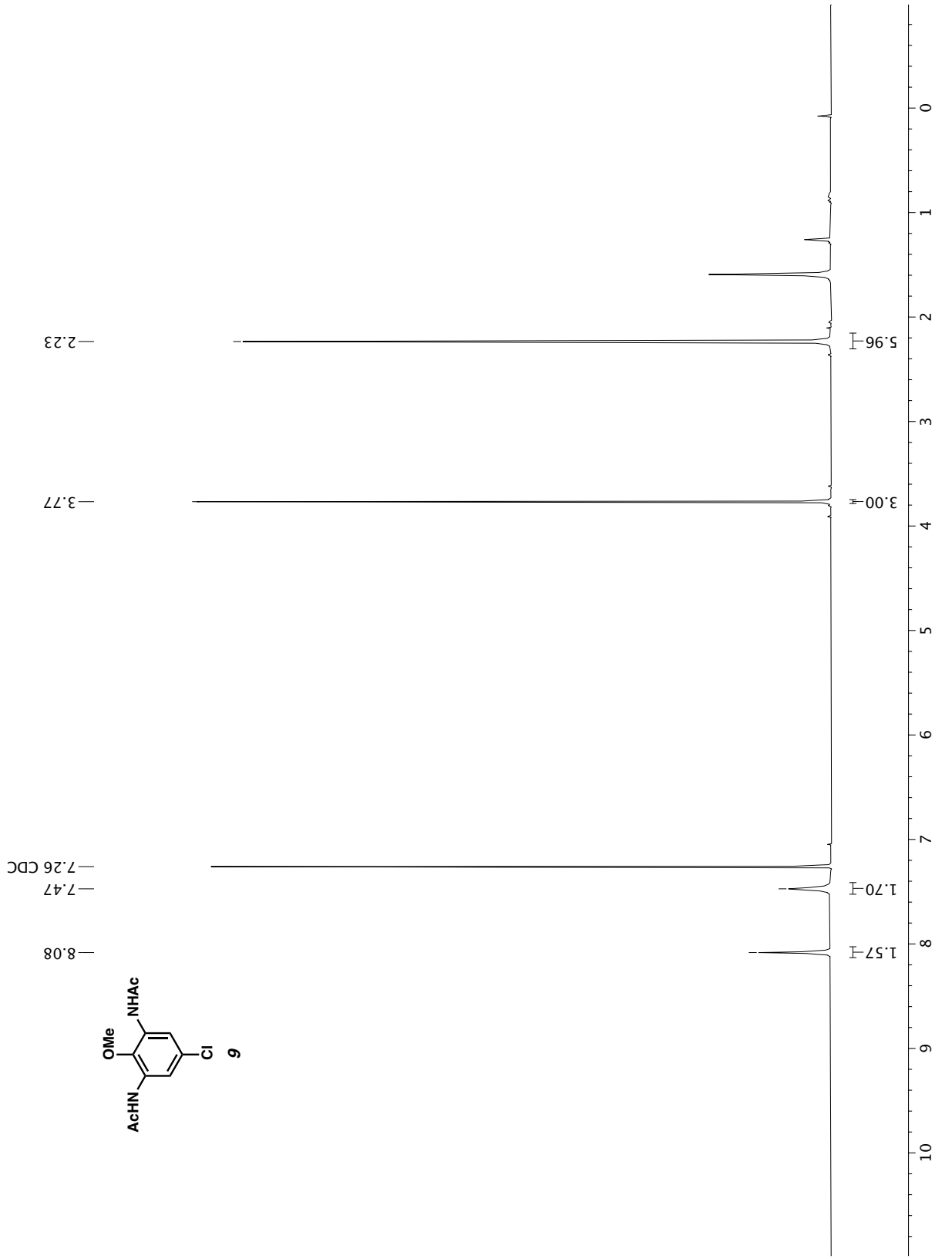
^{1}H NMR (400 MHz, $CDCl_3$) of compound **8**.



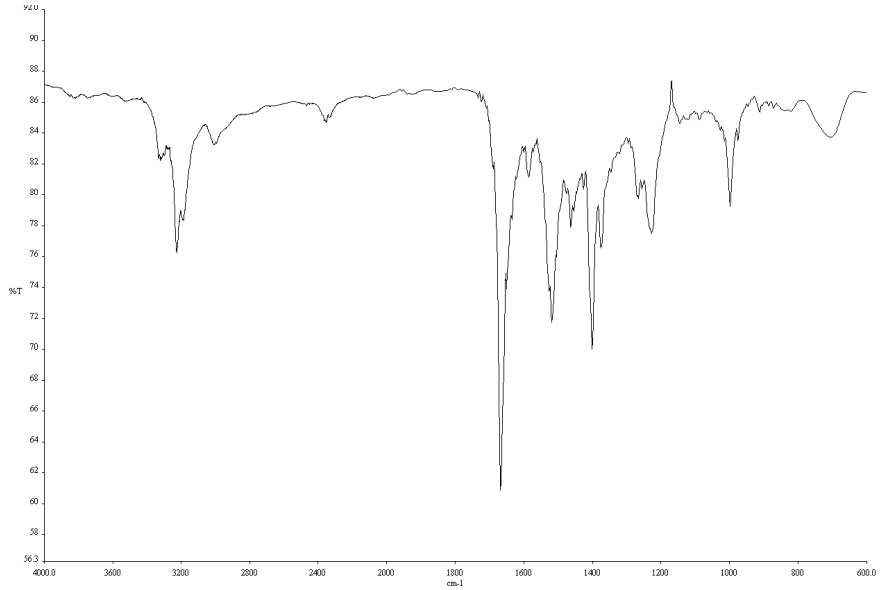
Infrared spectrum (Thin Film, NaCl) of compound **8**.



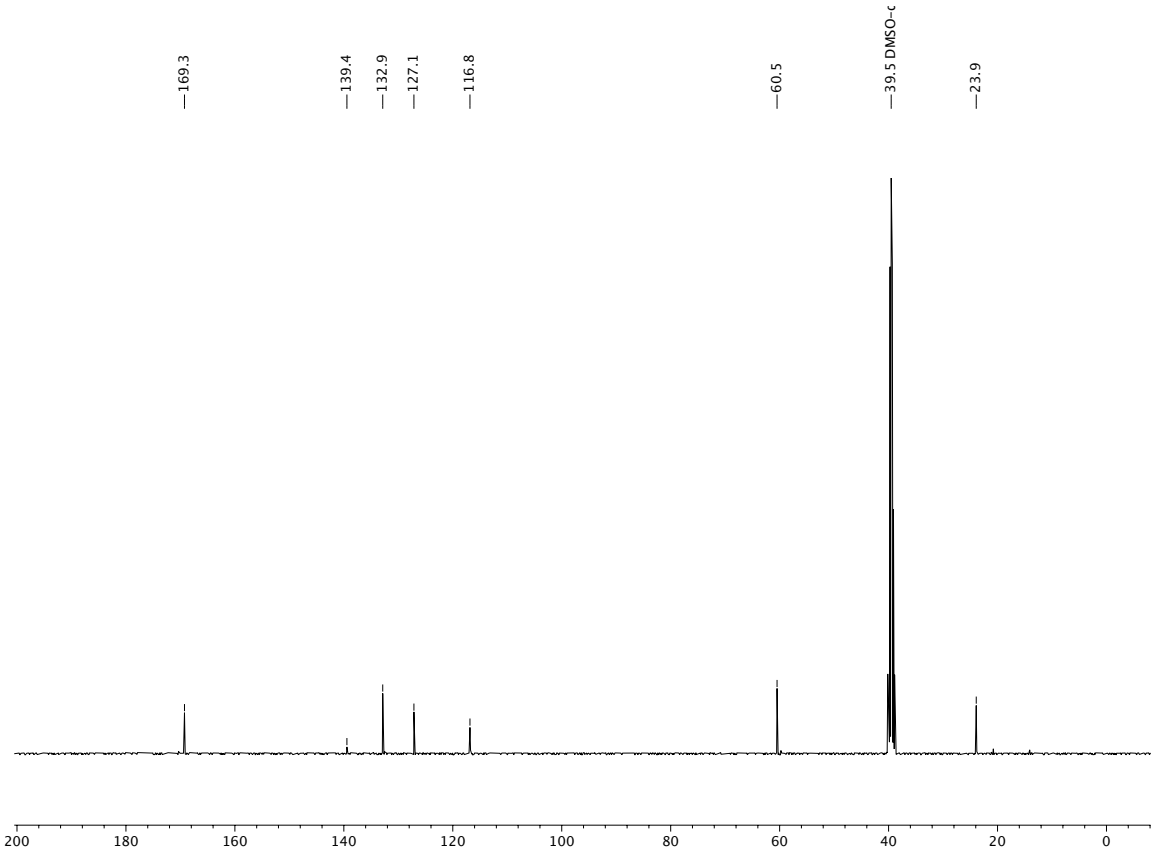
^{13}C NMR (100 MHz, $CDCl_3$) of compound **8**.



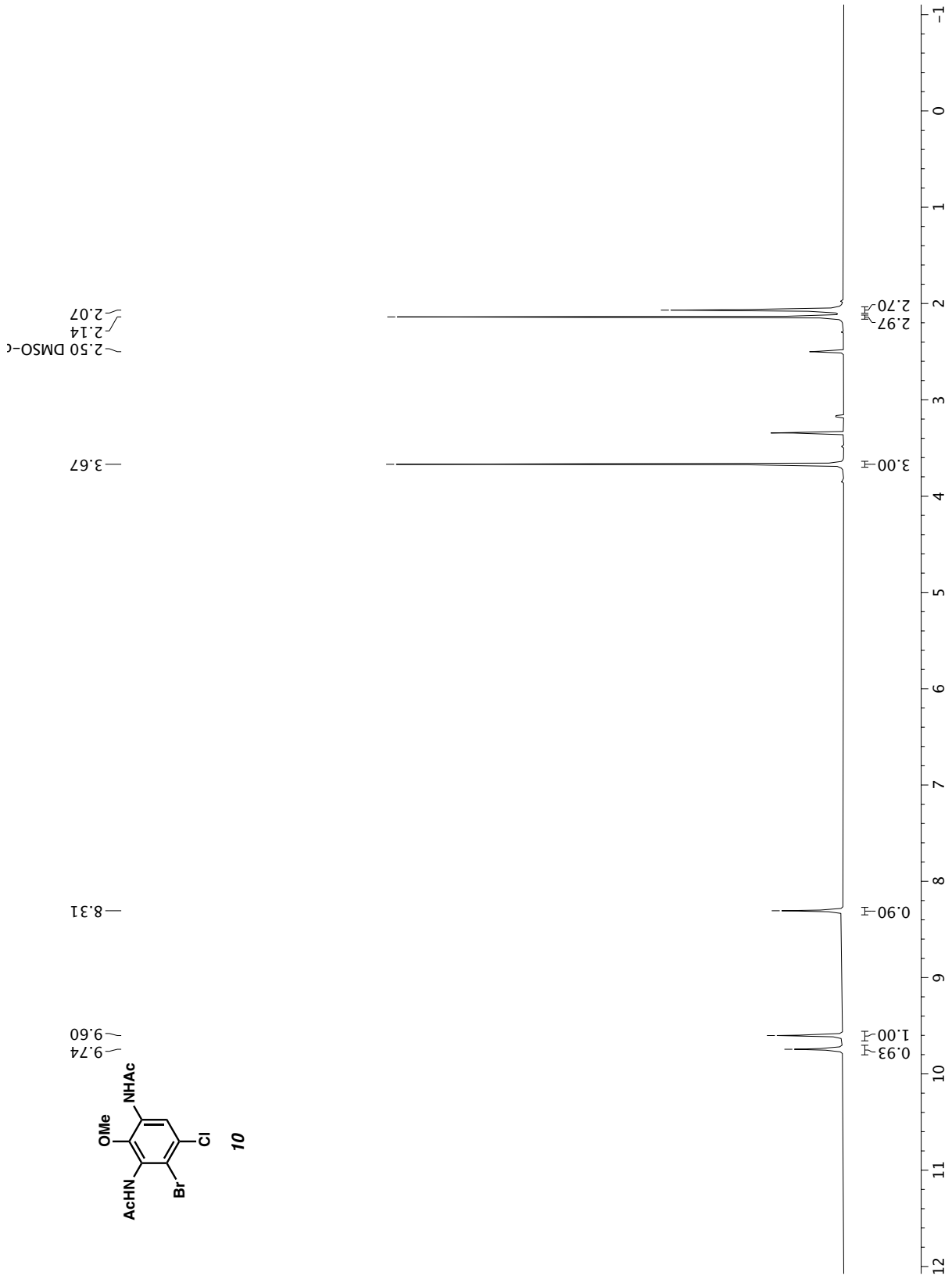
^{1}H NMR (400 MHz, $CDCl_3$) of compound **9**.



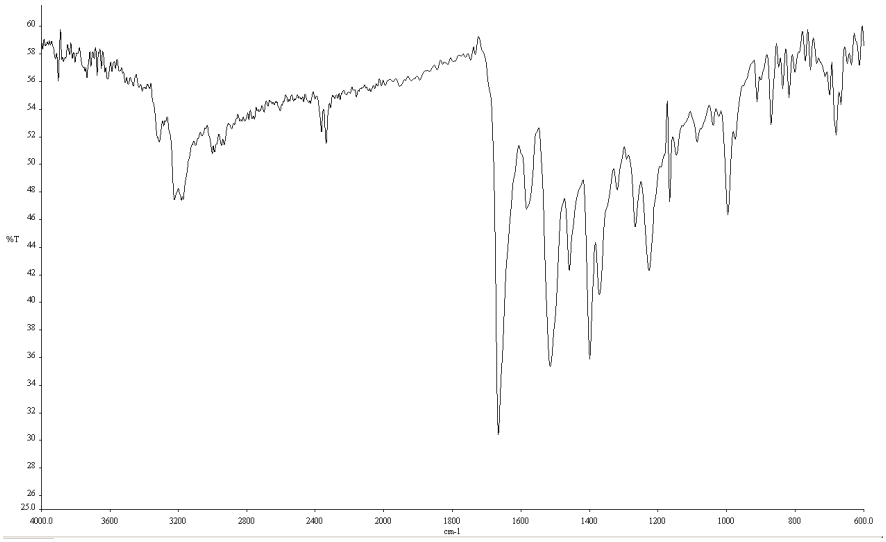
Infrared spectrum (Thin Film, NaCl) of compound **9**.



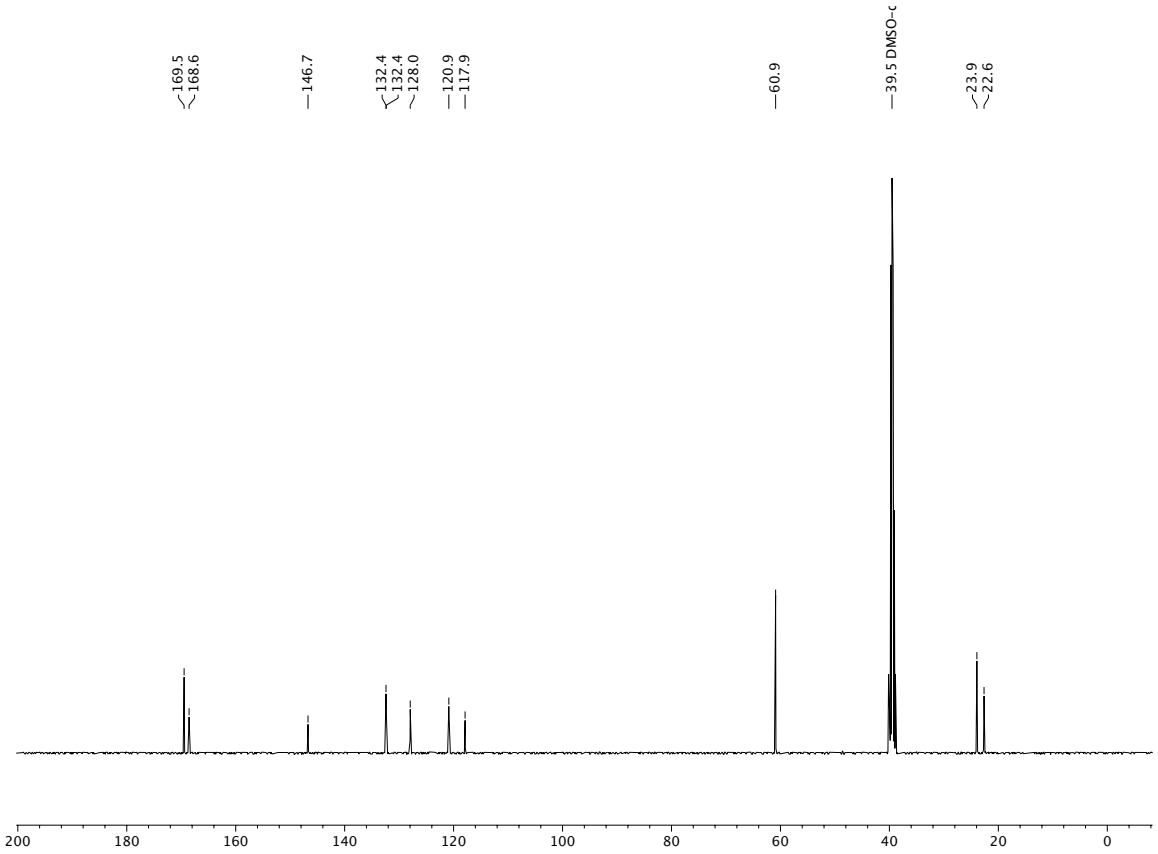
^{13}C NMR (100 MHz, DMSO-d_6) of compound **9**.



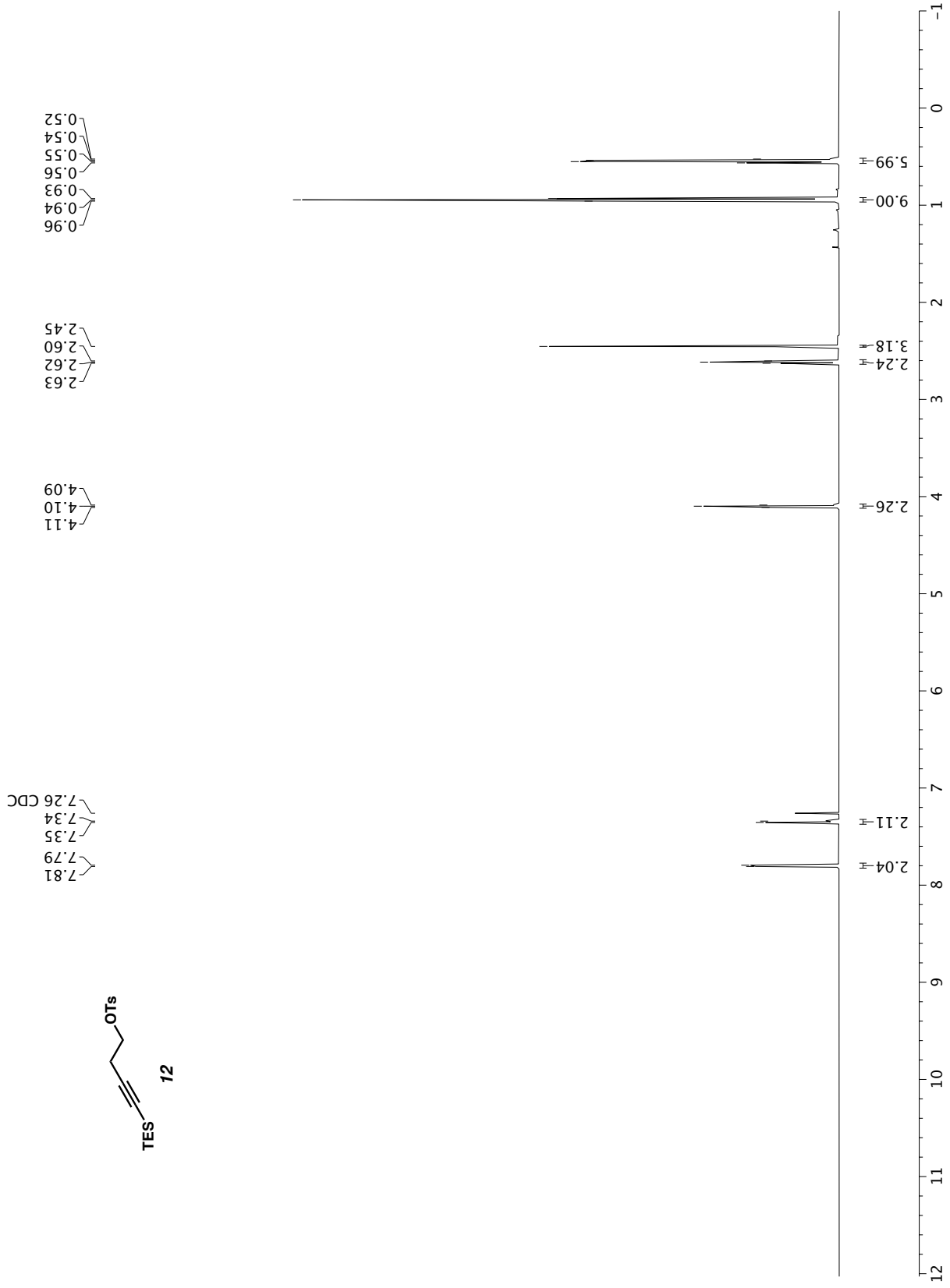
^{1}H NMR (600 MHz, DMSO-d_6) of compound **10**.



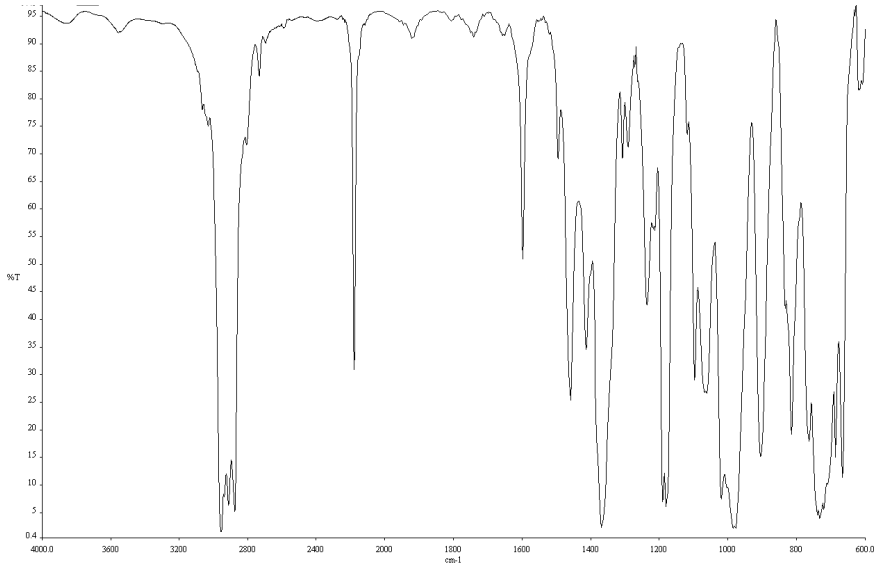
Infrared spectrum (Thin Film, NaCl) of compound **10**.



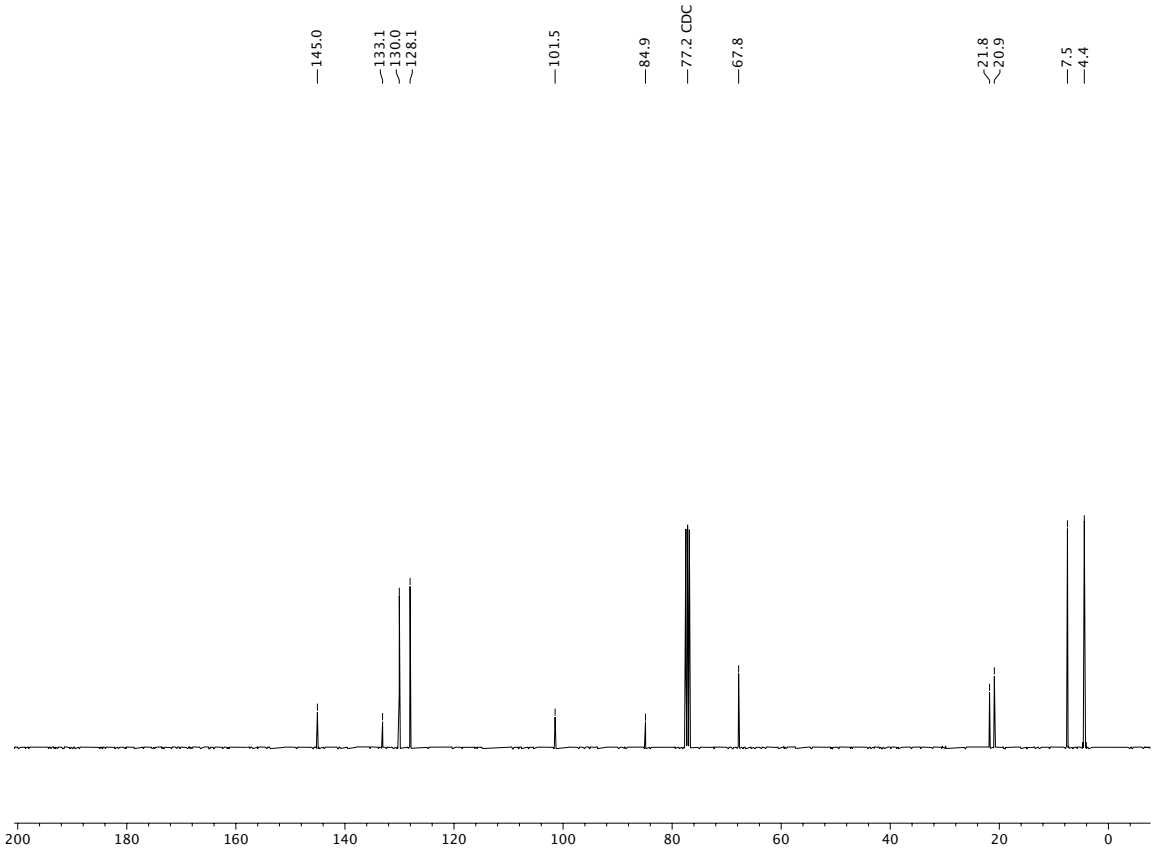
^{13}C NMR (100 MHz, DMSO-d_6) of compound **10**.



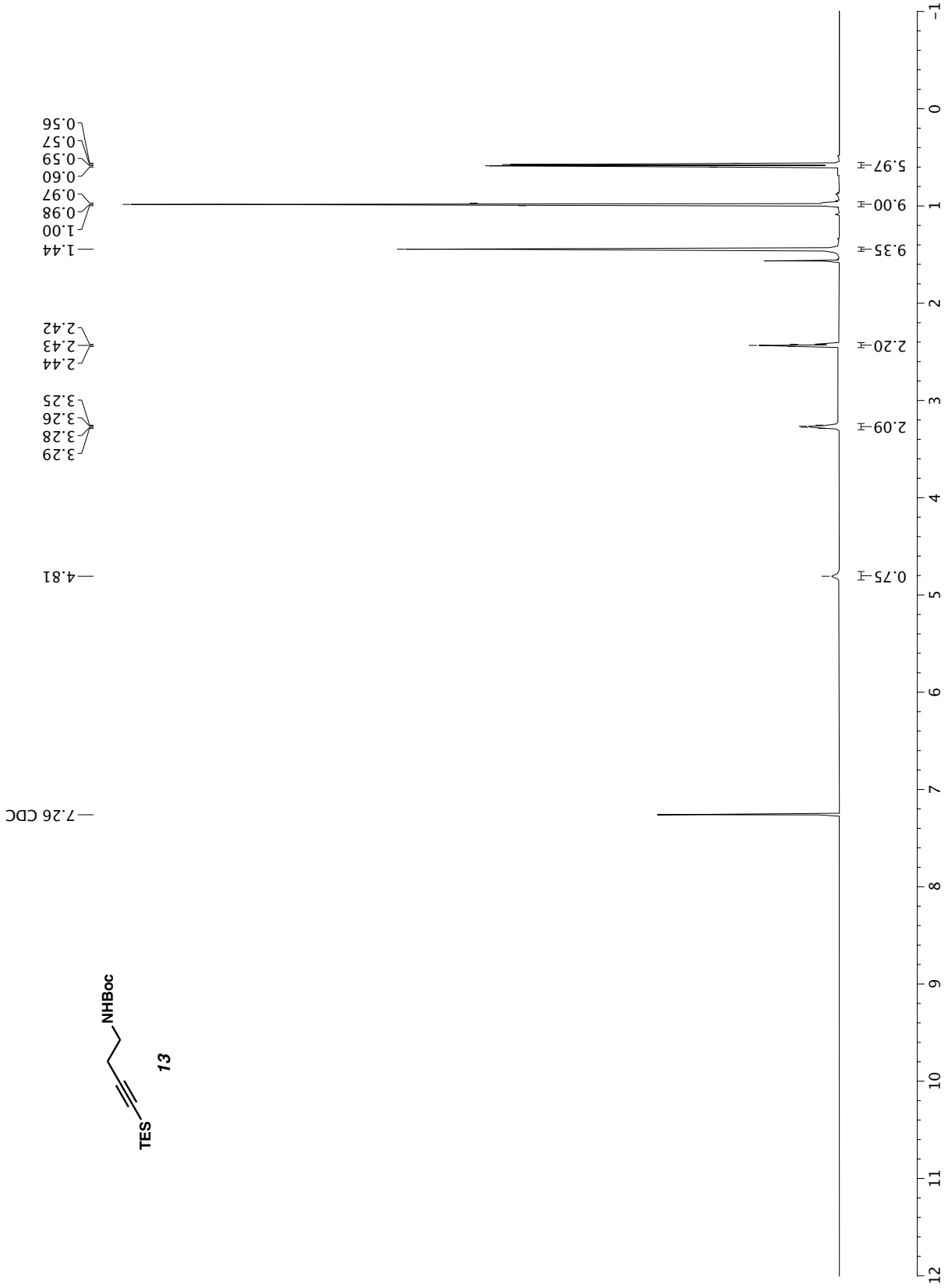
^{1}H NMR (600 MHz, $CDCl_3$) of compound **12**.



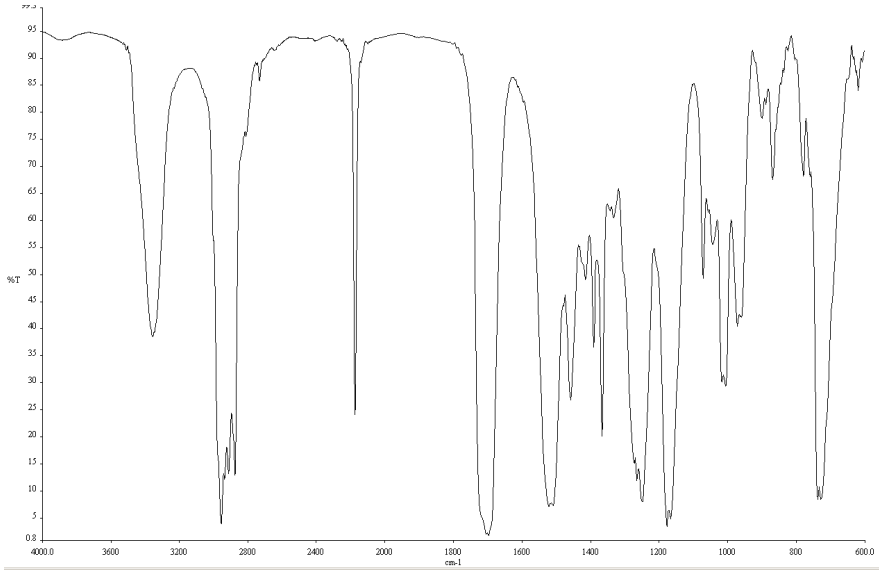
Infrared spectrum (Thin Film, NaCl) of compound **12**.



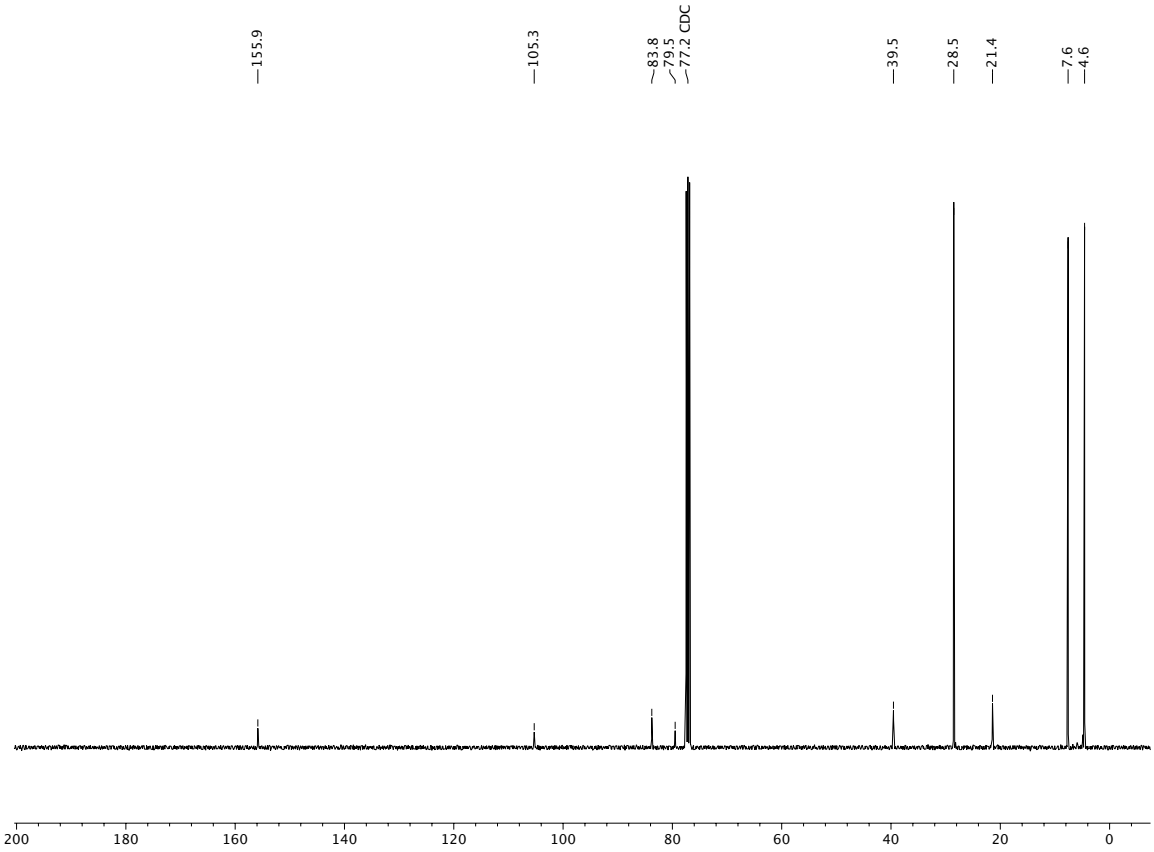
^{13}C NMR (100 MHz, $CDCl_3$) of compound **12**.



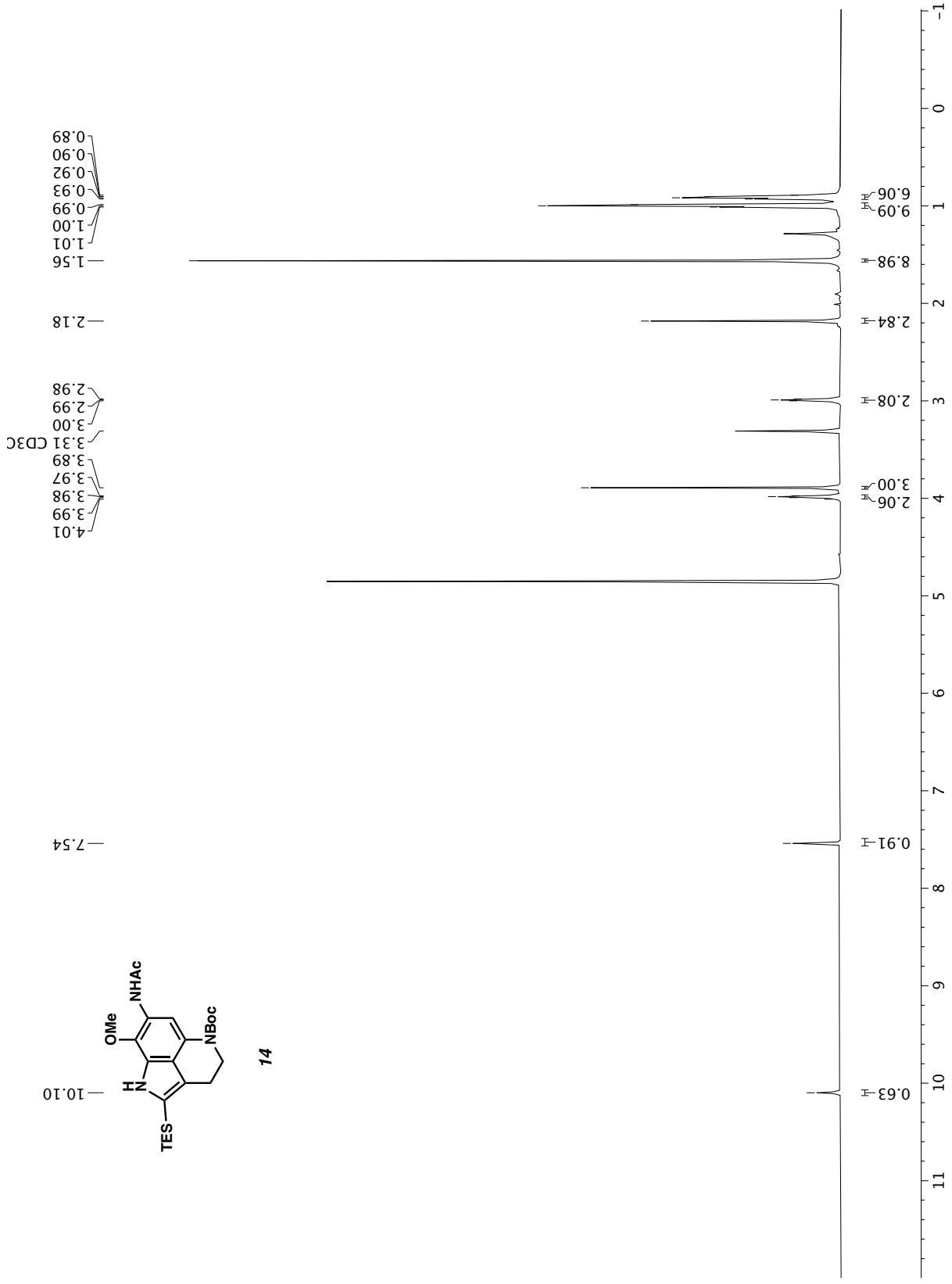
^{1}H NMR (600 MHz, $CDCl_3$) of compound **13**.



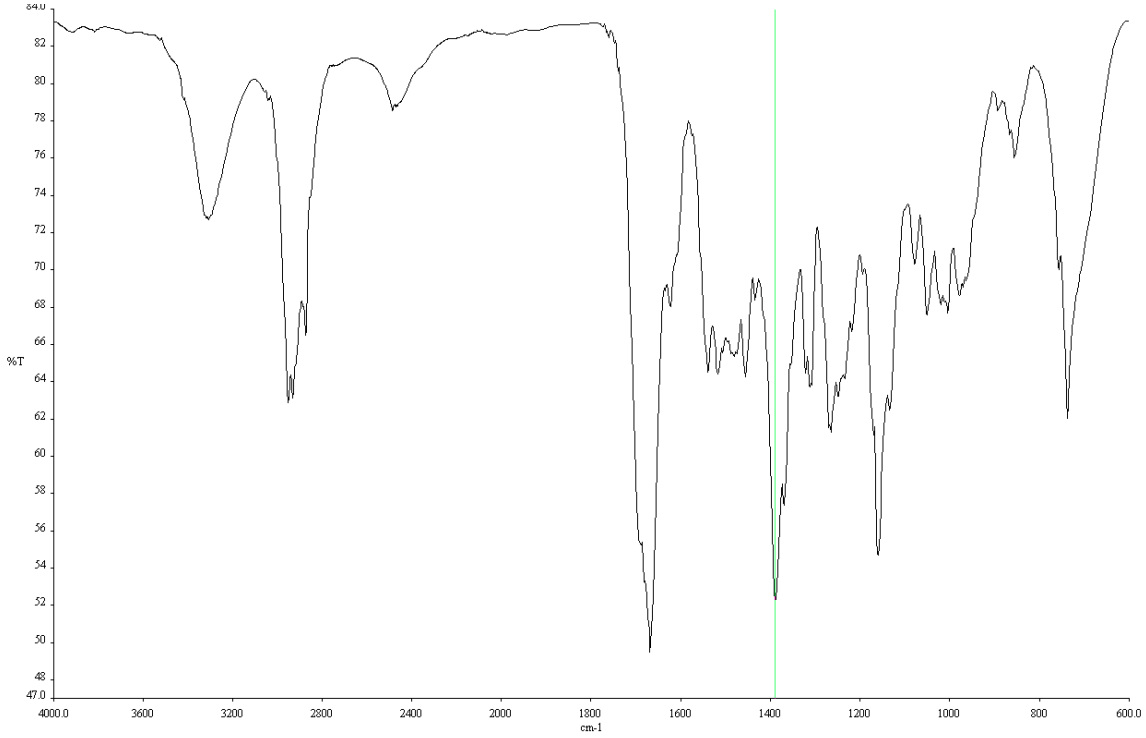
Infrared spectrum (Thin Film, NaCl) of compound **13**.



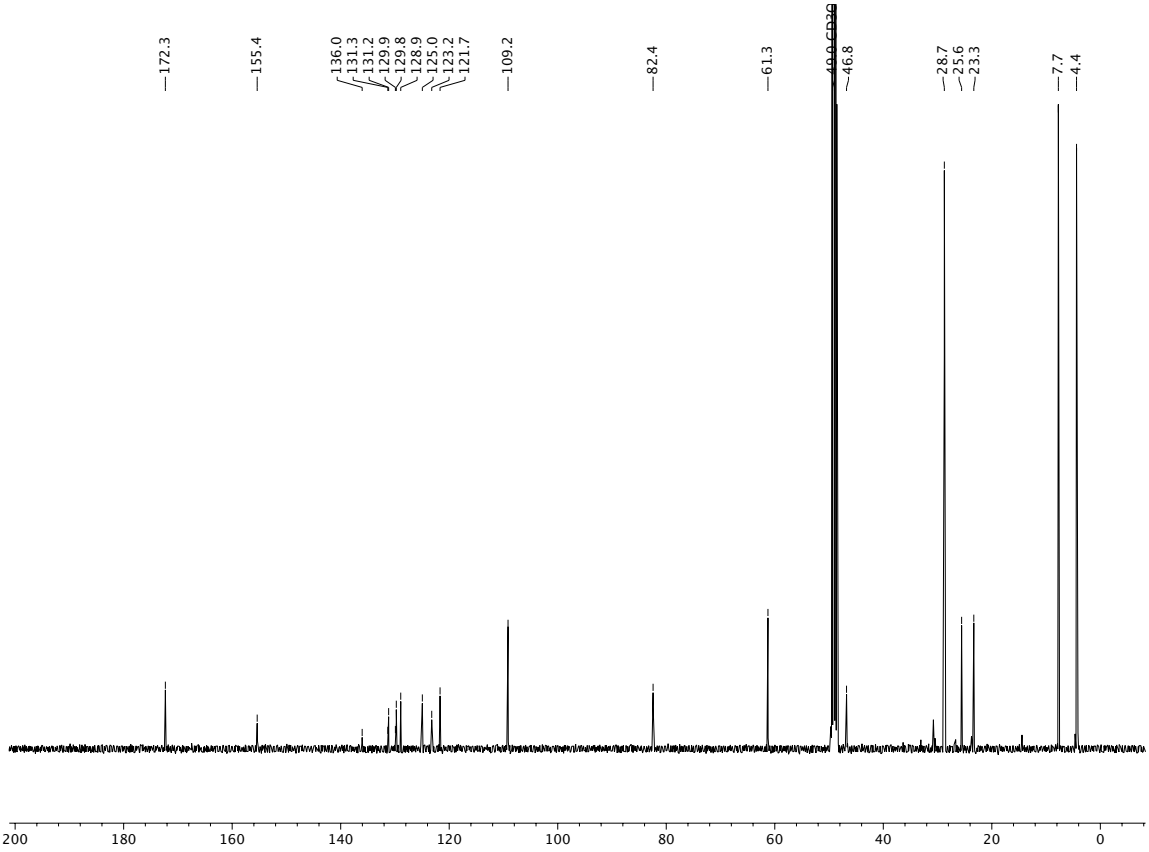
^{13}C NMR (100 MHz, $CDCl_3$) of compound **13**.



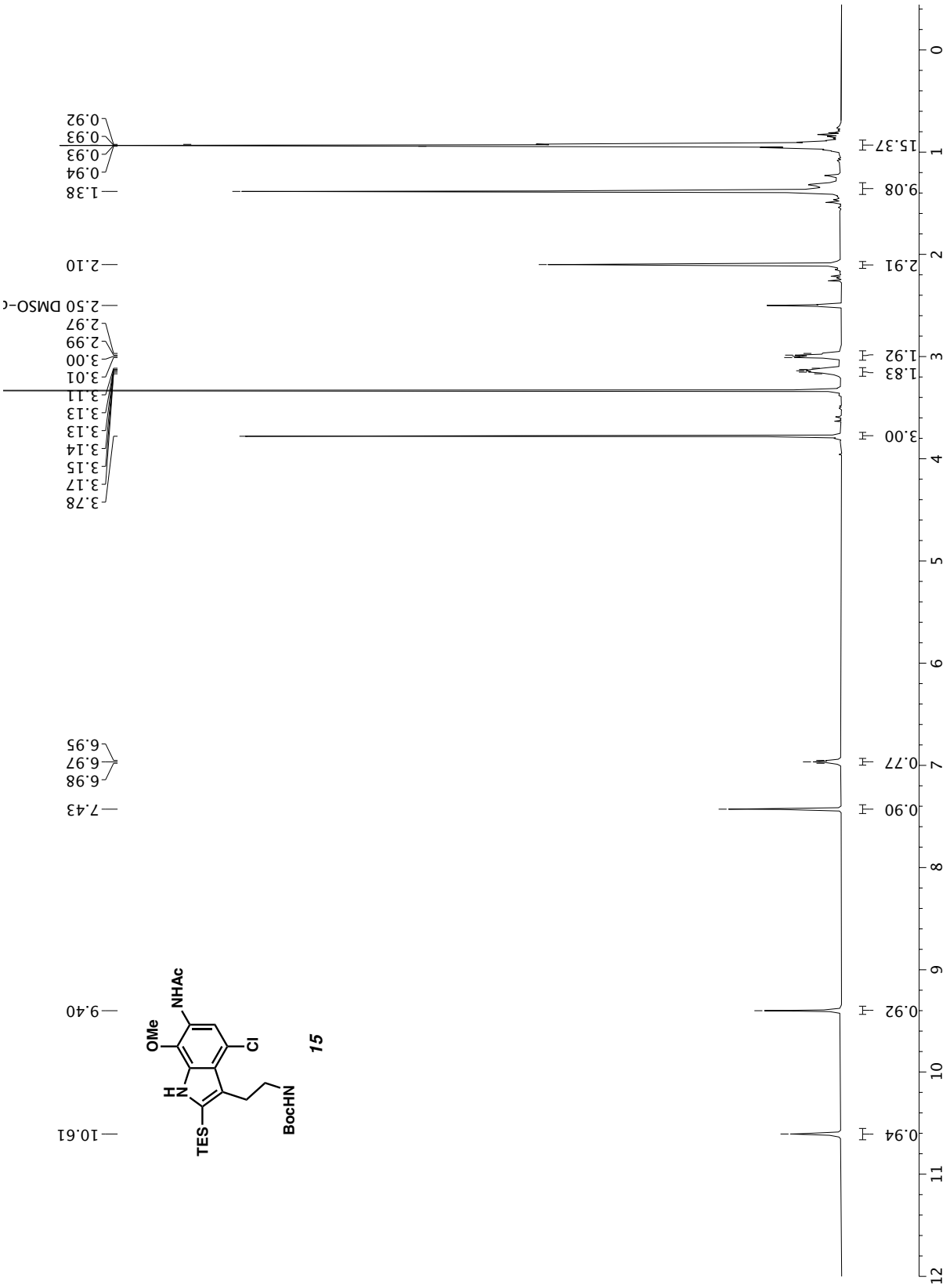
^{1}H NMR (600 MHz, MeOD) of compound **14**.



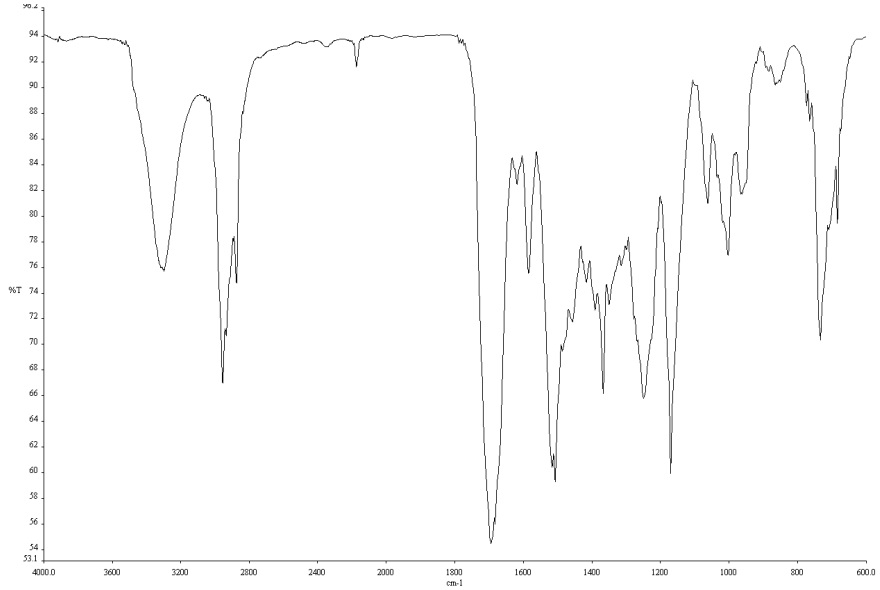
Infrared spectrum (Thin Film, NaCl) of compound **14**.



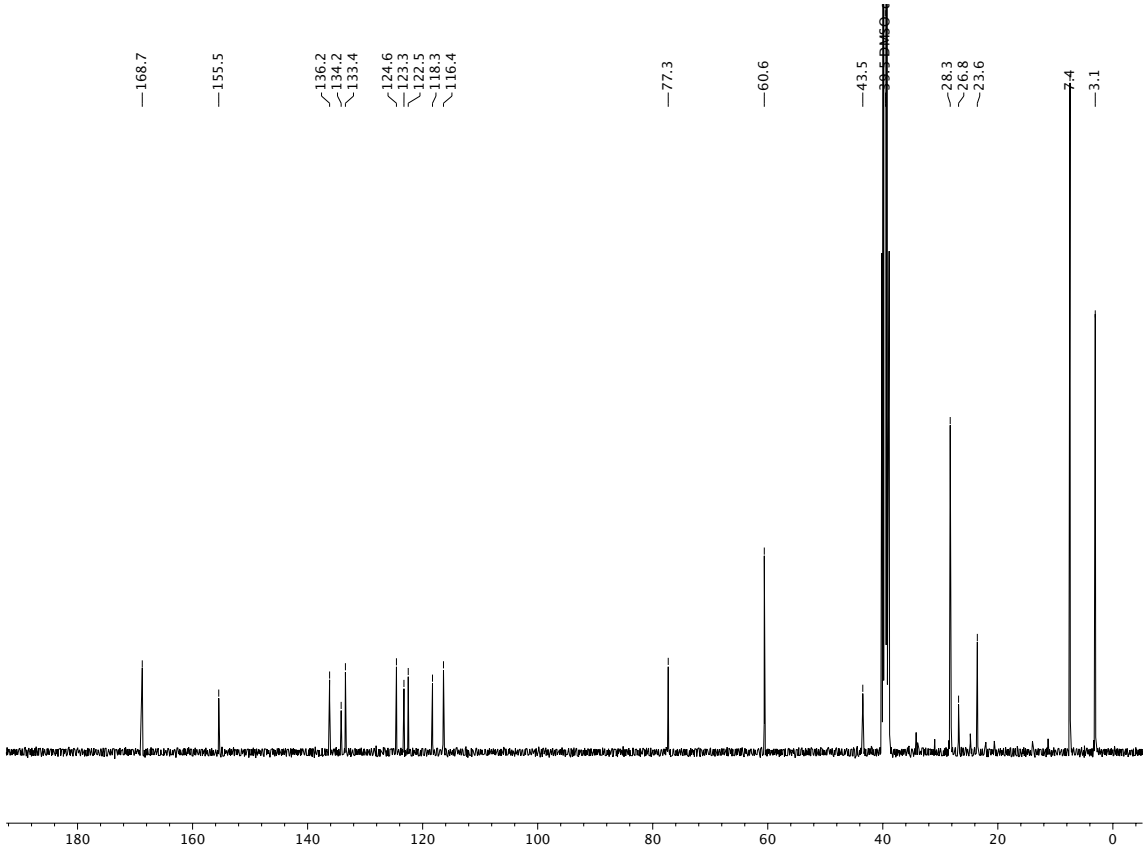
^{13}C NMR (100 MHz, MeOD) of compound **14**.



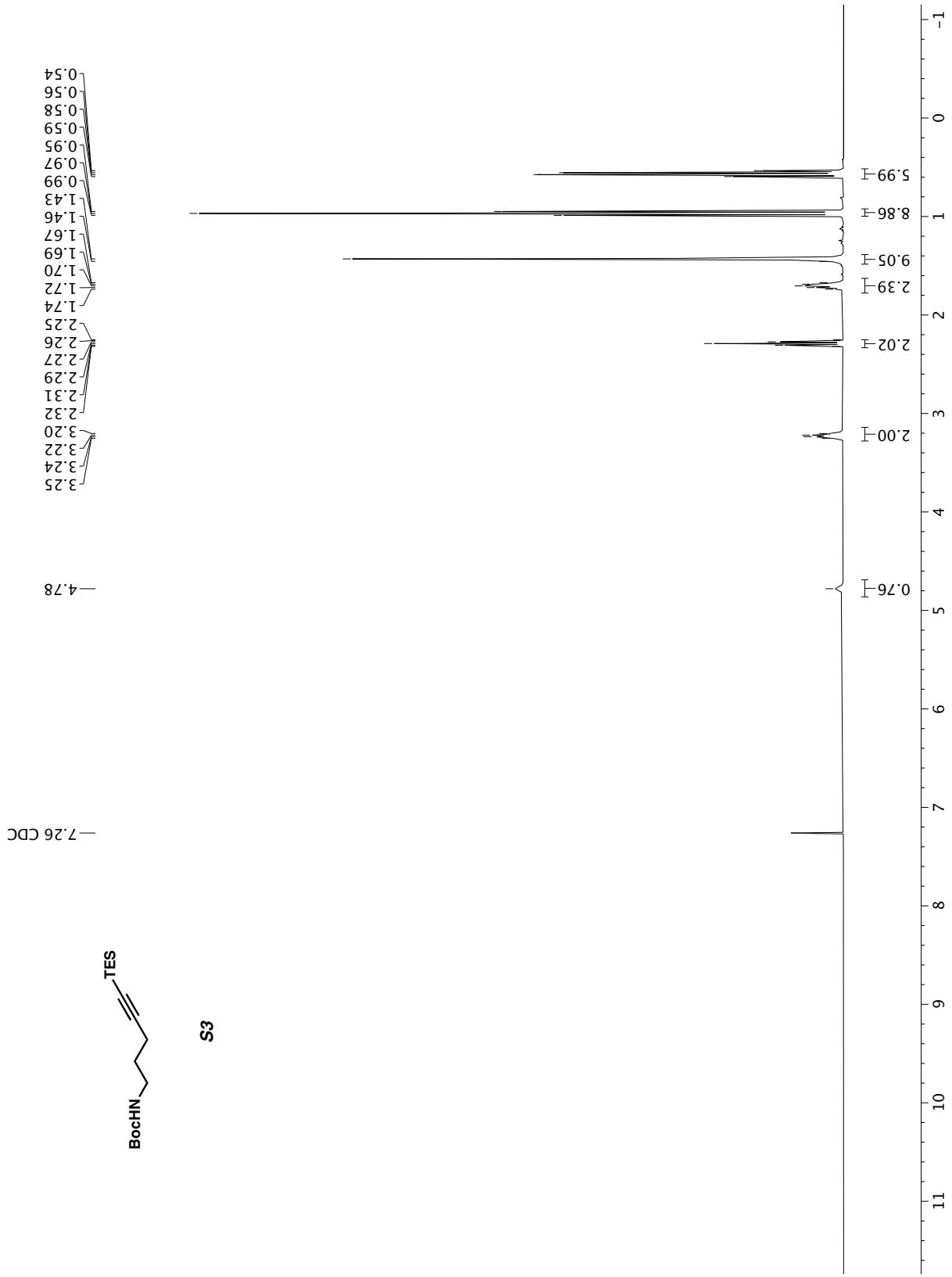
^{1}H NMR (400 MHz,DMSO-*d6*) of compound **15**.



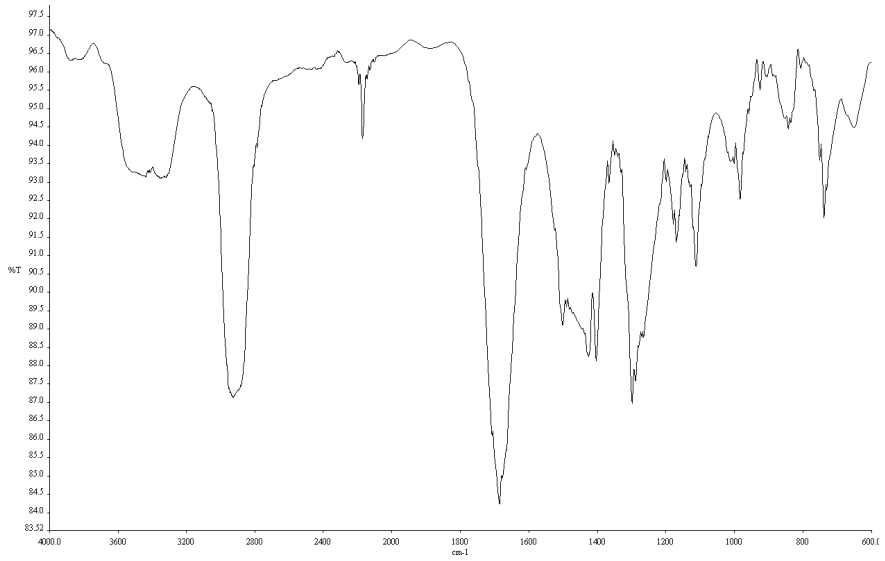
Infrared spectrum (Thin Film, NaCl) of compound **15**.



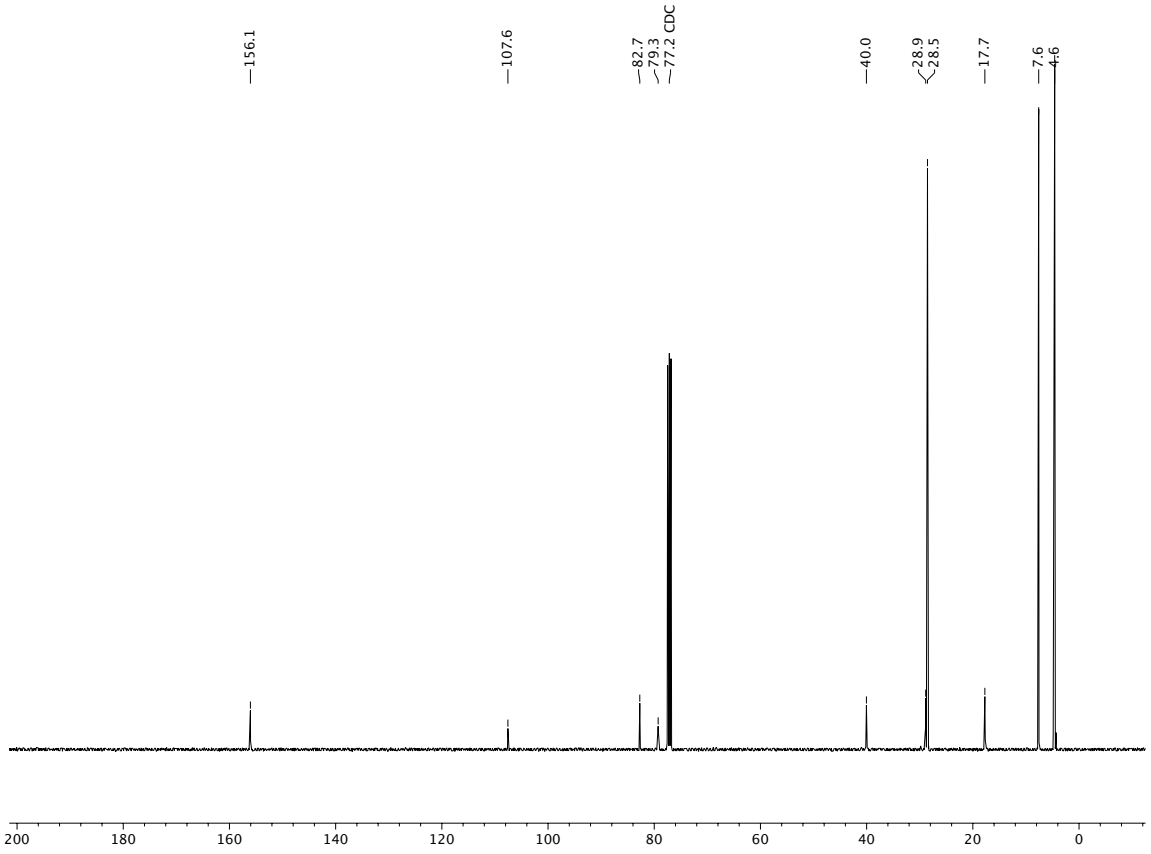
^{13}C NMR (100 MHz, DMSO) of compound **15**.



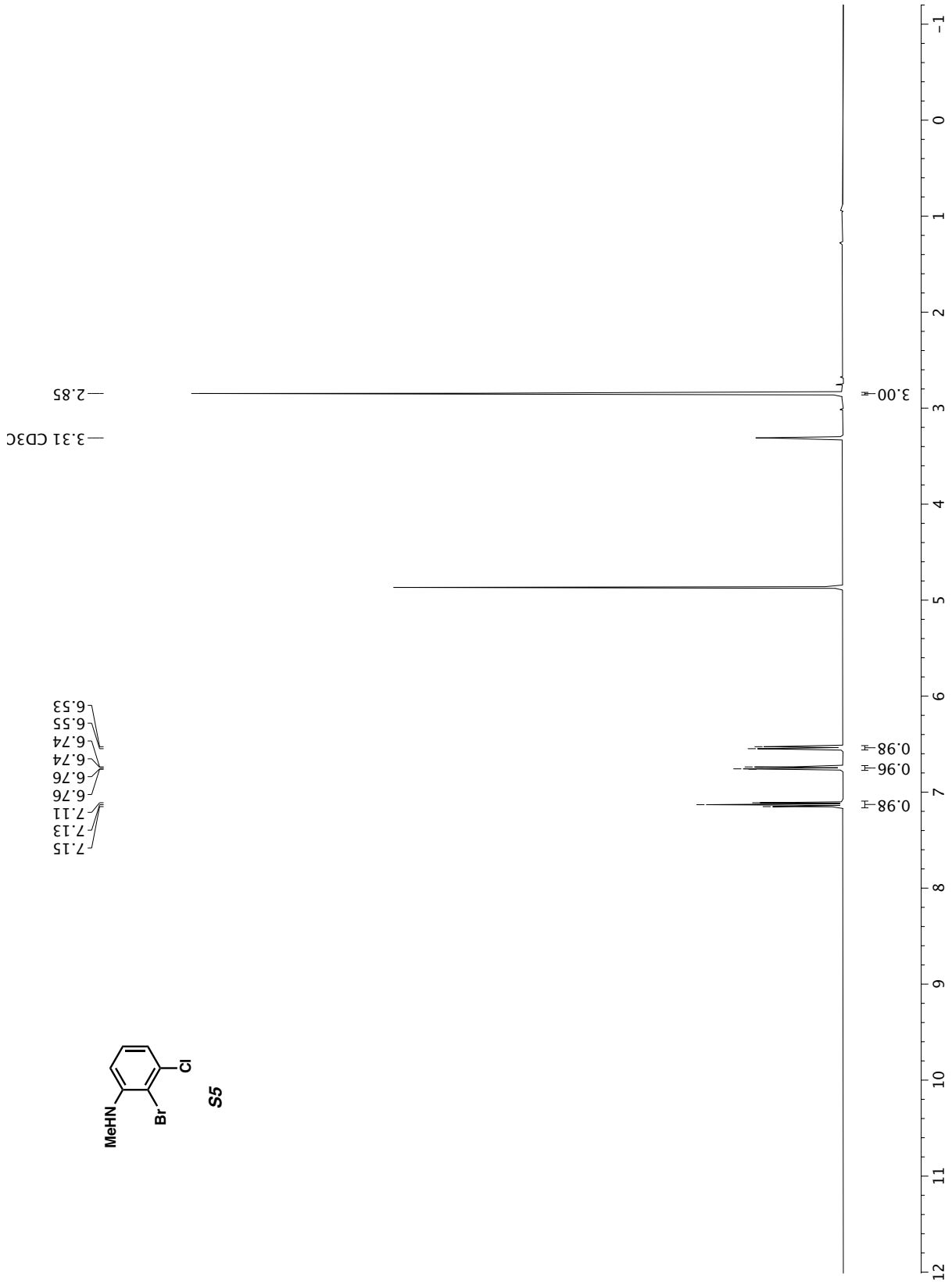
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S3**.



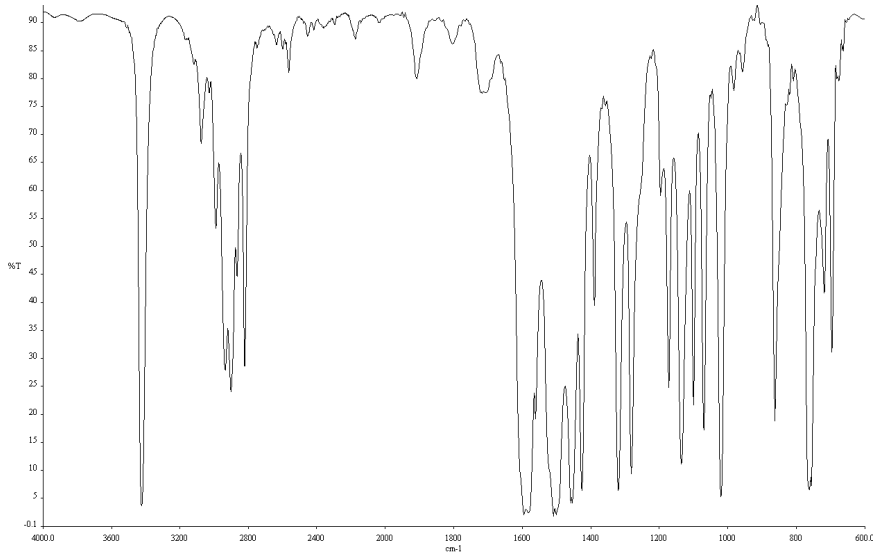
Infrared spectrum (Thin Film, NaCl) of compound **S3**.



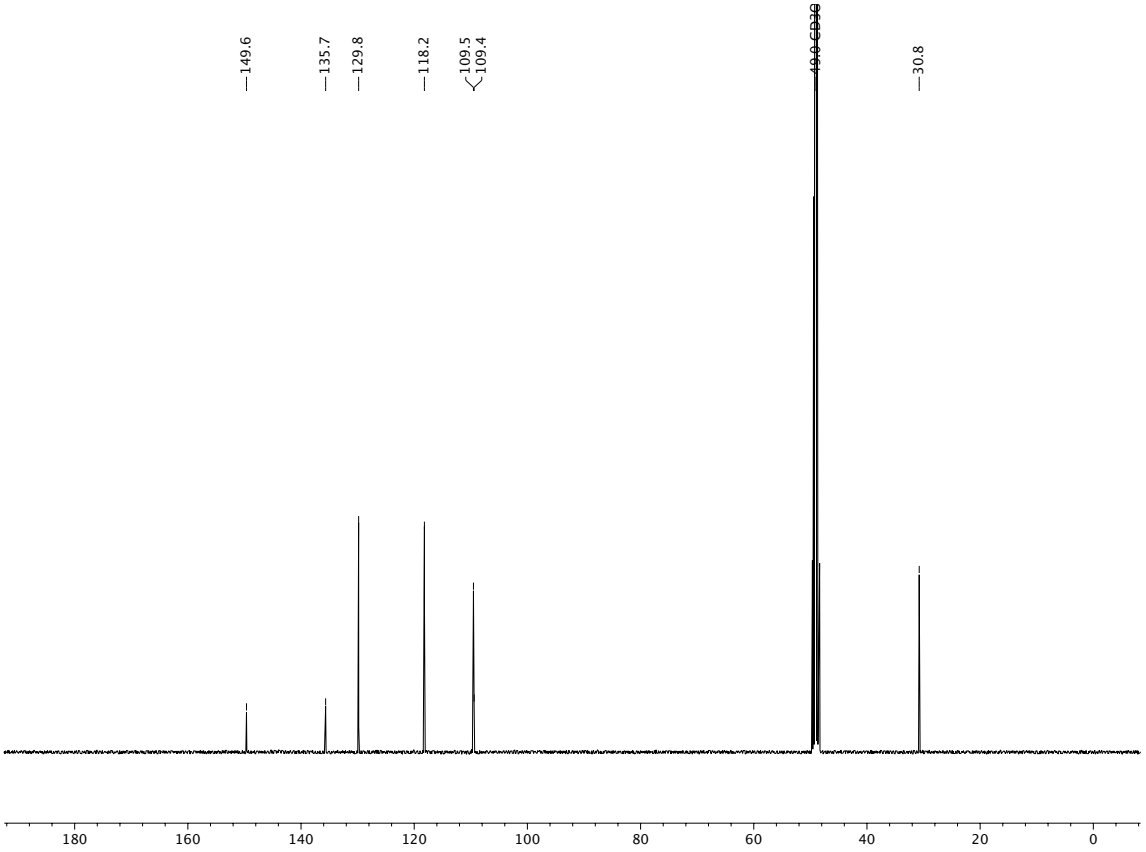
^{13}C NMR (100 MHz, $CDCl_3$) of compound **S3**.



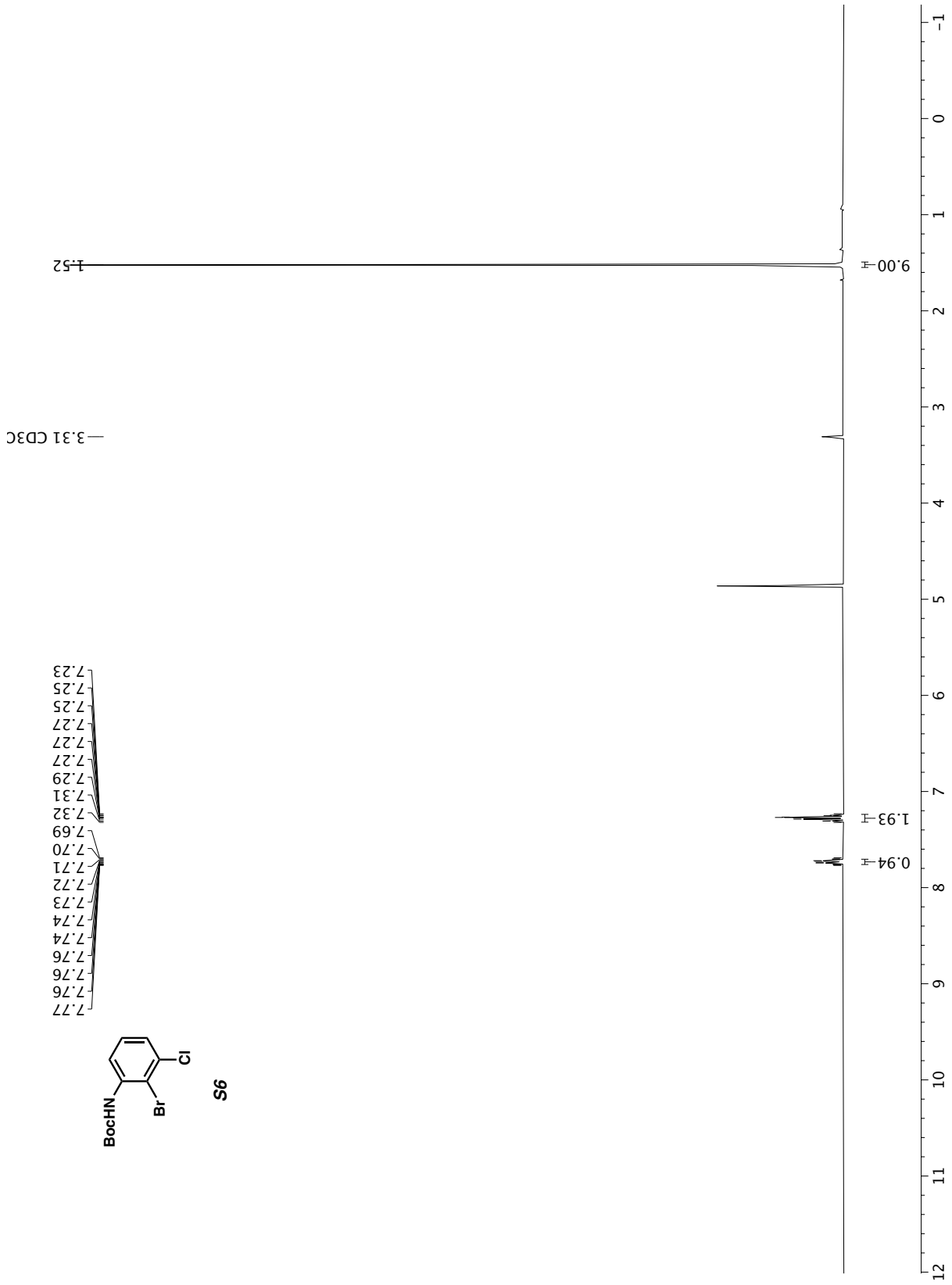
^{1}H NMR (600 MHz, MeOD) of compound **S5**.



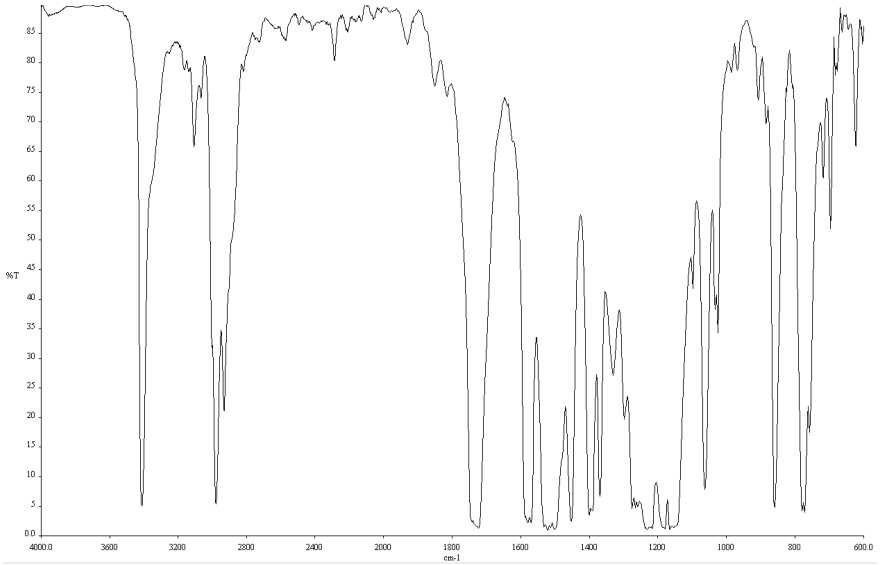
Infrared spectrum (Thin Film, NaCl) of compound **S5**.



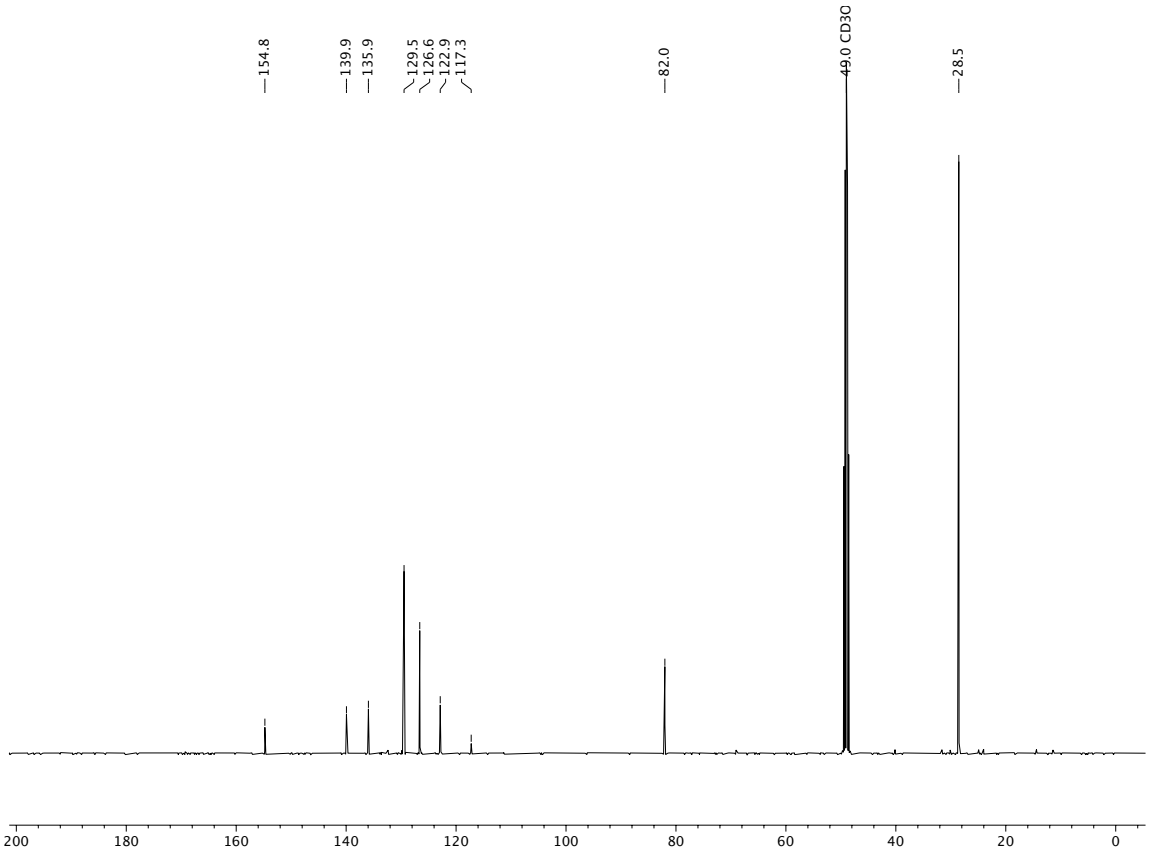
^{13}C NMR (100 MHz, MeOD) of compound **S5**.



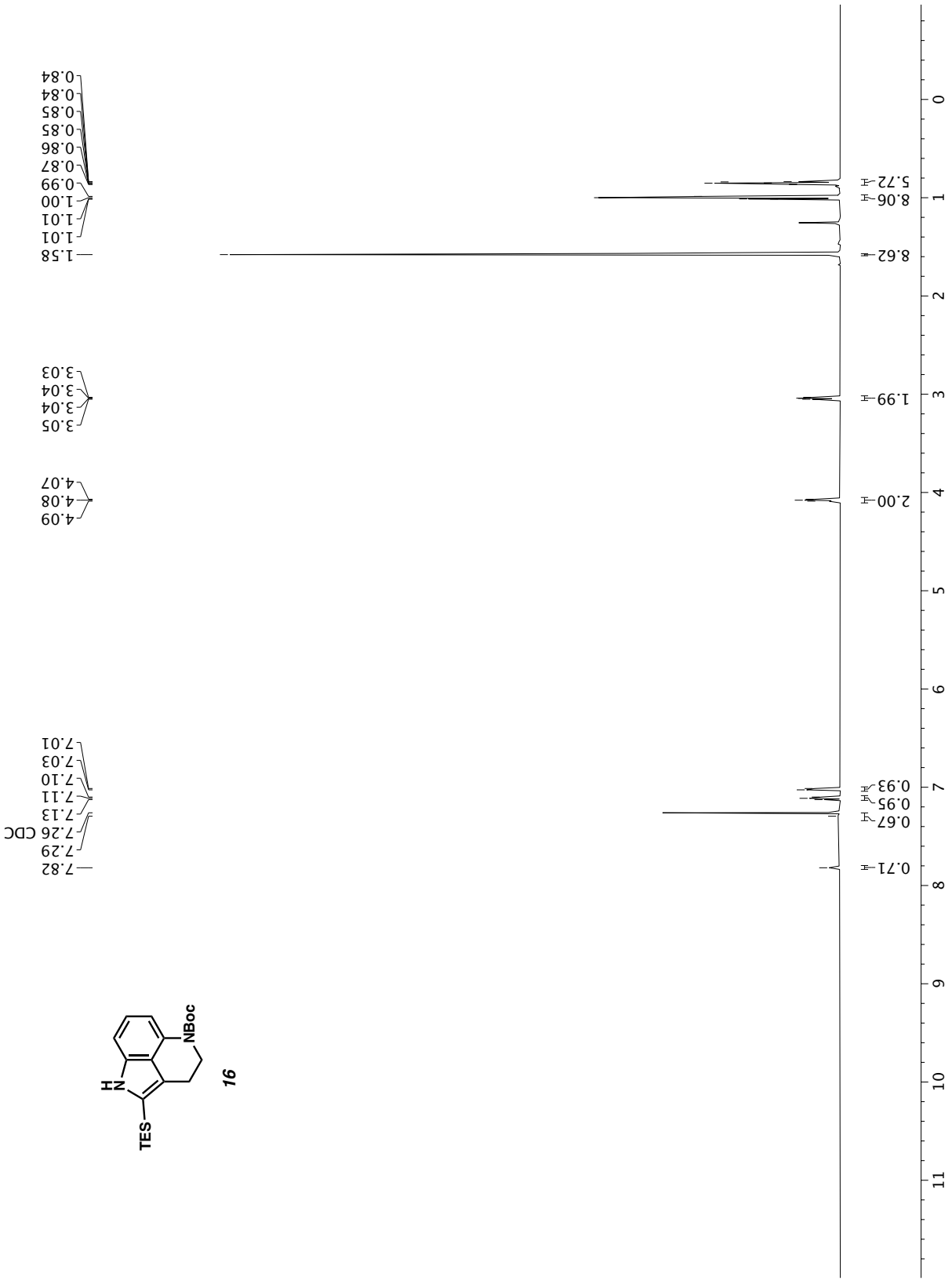
^{1}H NMR (400 MHz, MeOD) of compound **S6**.



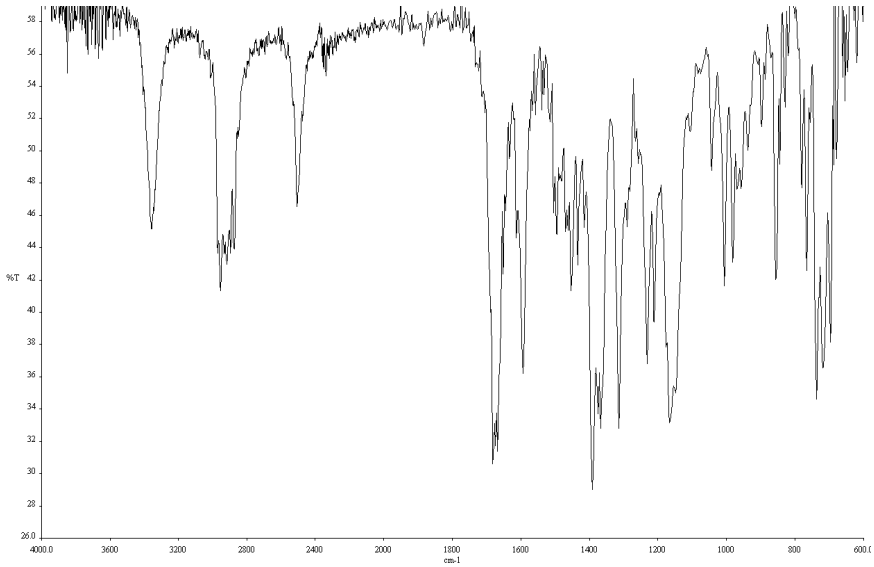
Infrared spectrum (Thin Film, NaCl) of compound **S6**.



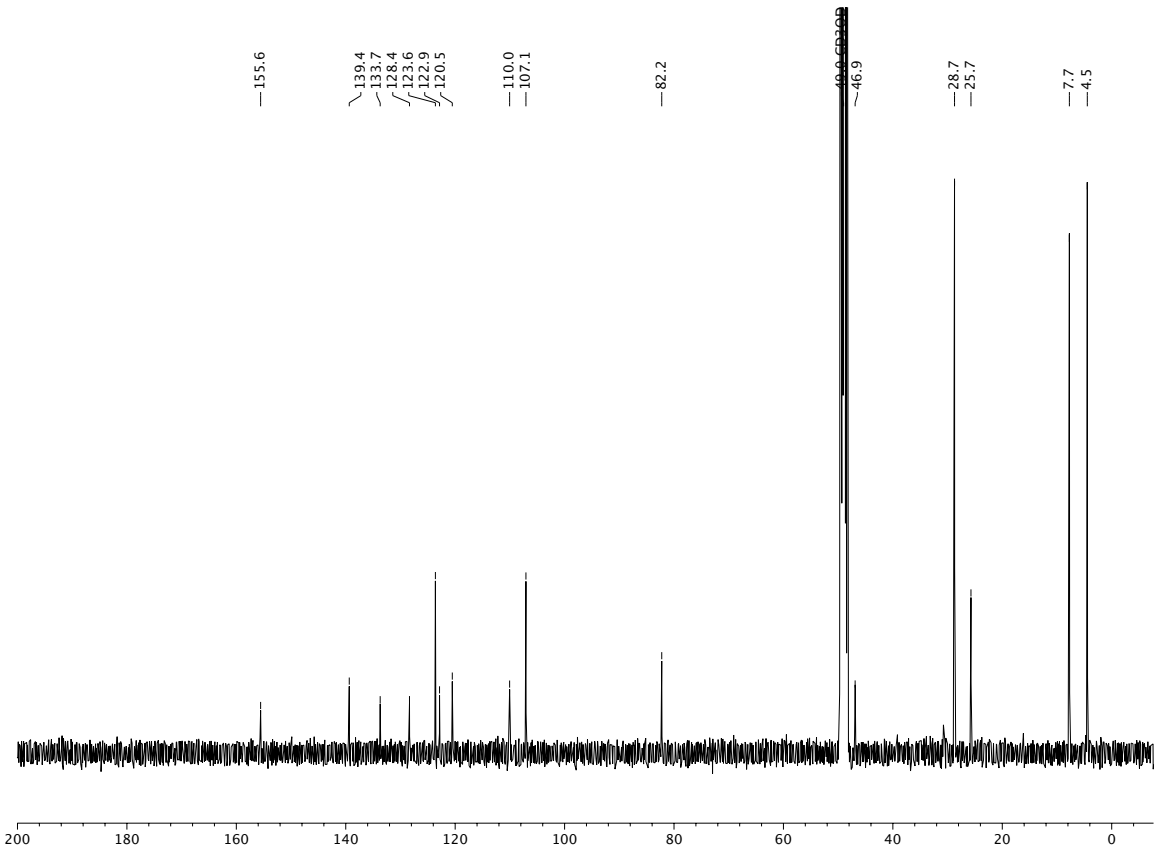
^{13}C NMR (100 MHz, MeOD) of compound **S6**.



^{1}H NMR (600 MHz, $CDCl_3$) of compound **16**.

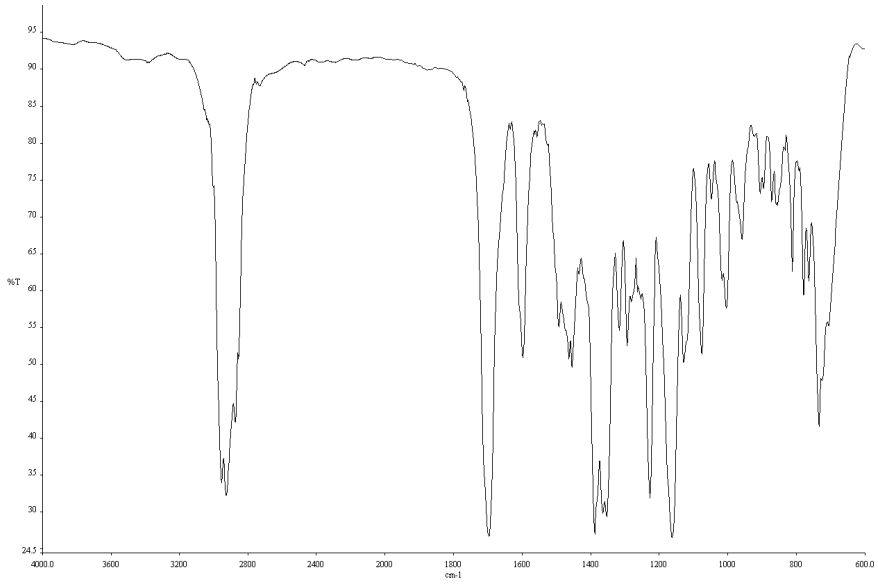


Infrared spectrum (Thin Film, NaCl) of compound **16**.

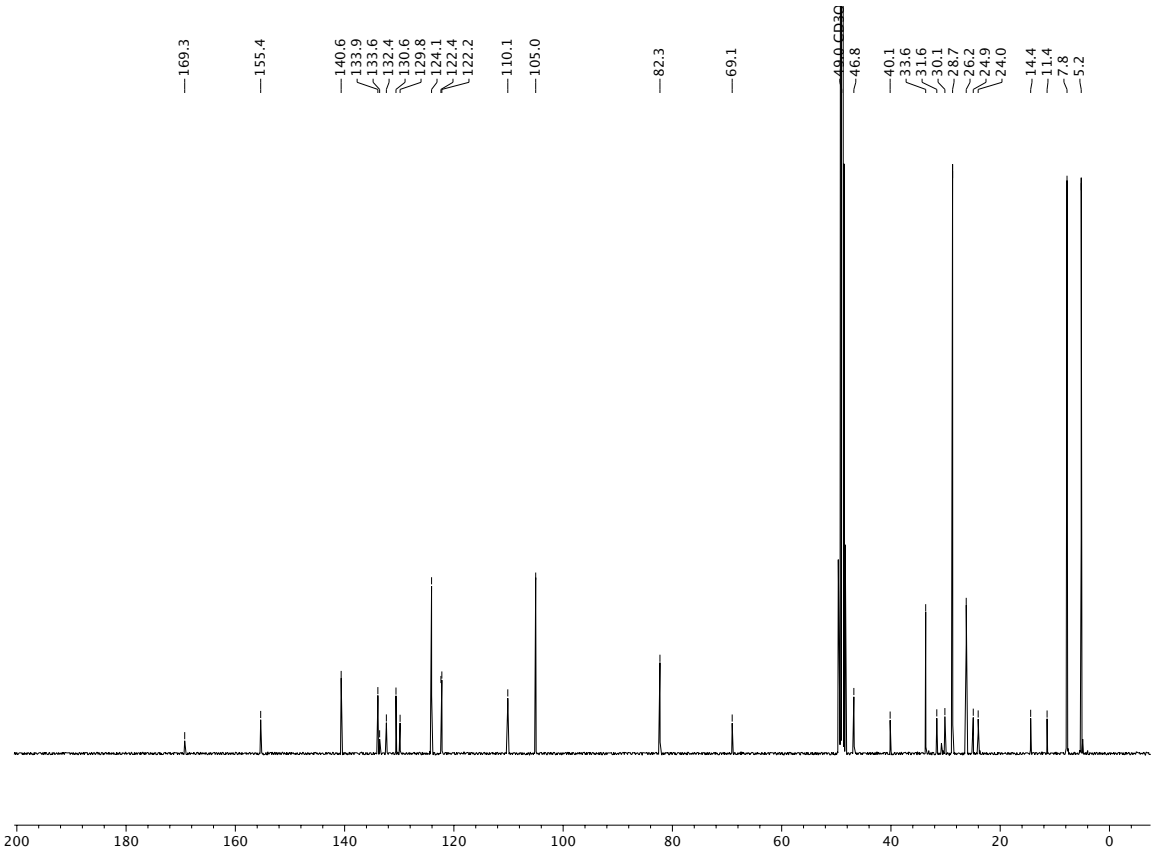


^{13}C NMR (100 MHz, MeOD) of compound **16**.

^{1}H NMR (400 MHz, MeOD) of compound **17**.

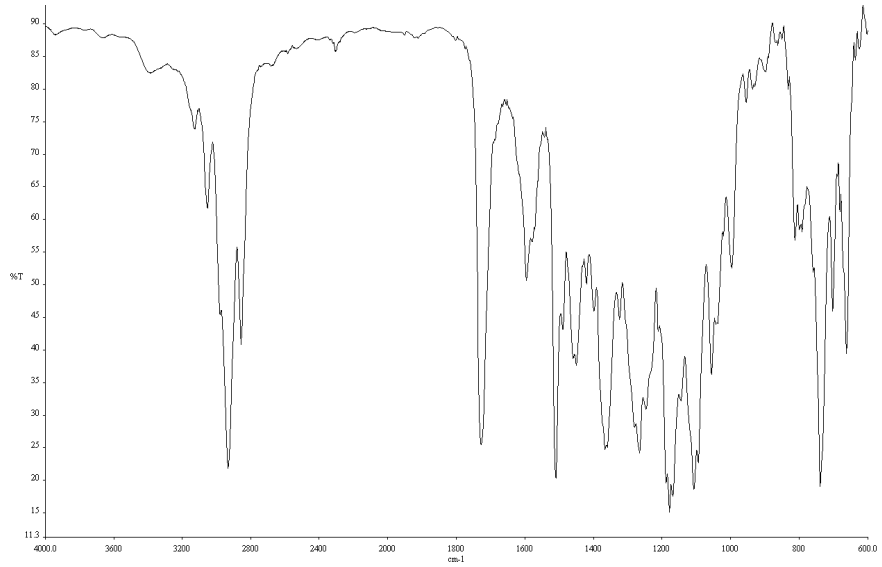


Infrared spectrum (Thin Film, NaCl) of compound **17**.

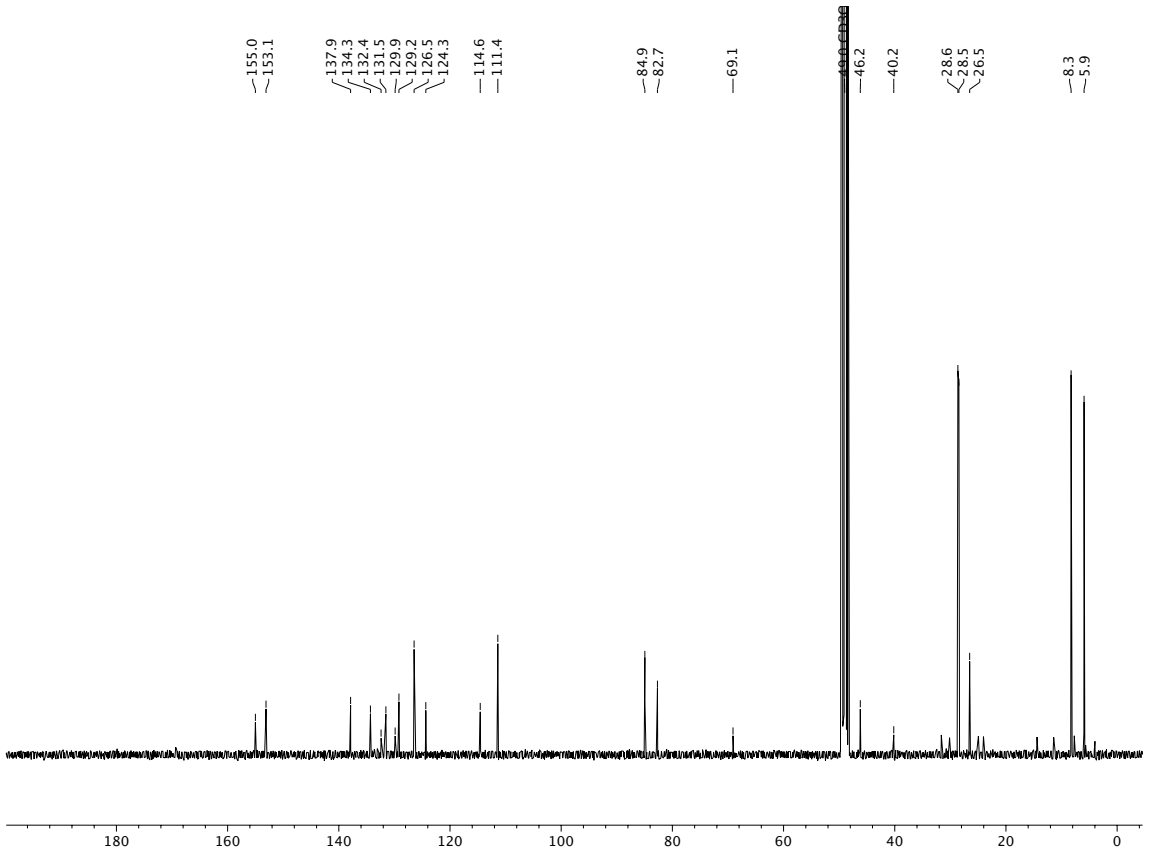


^{13}C NMR (100 MHz, MeOD) of compound **17**.

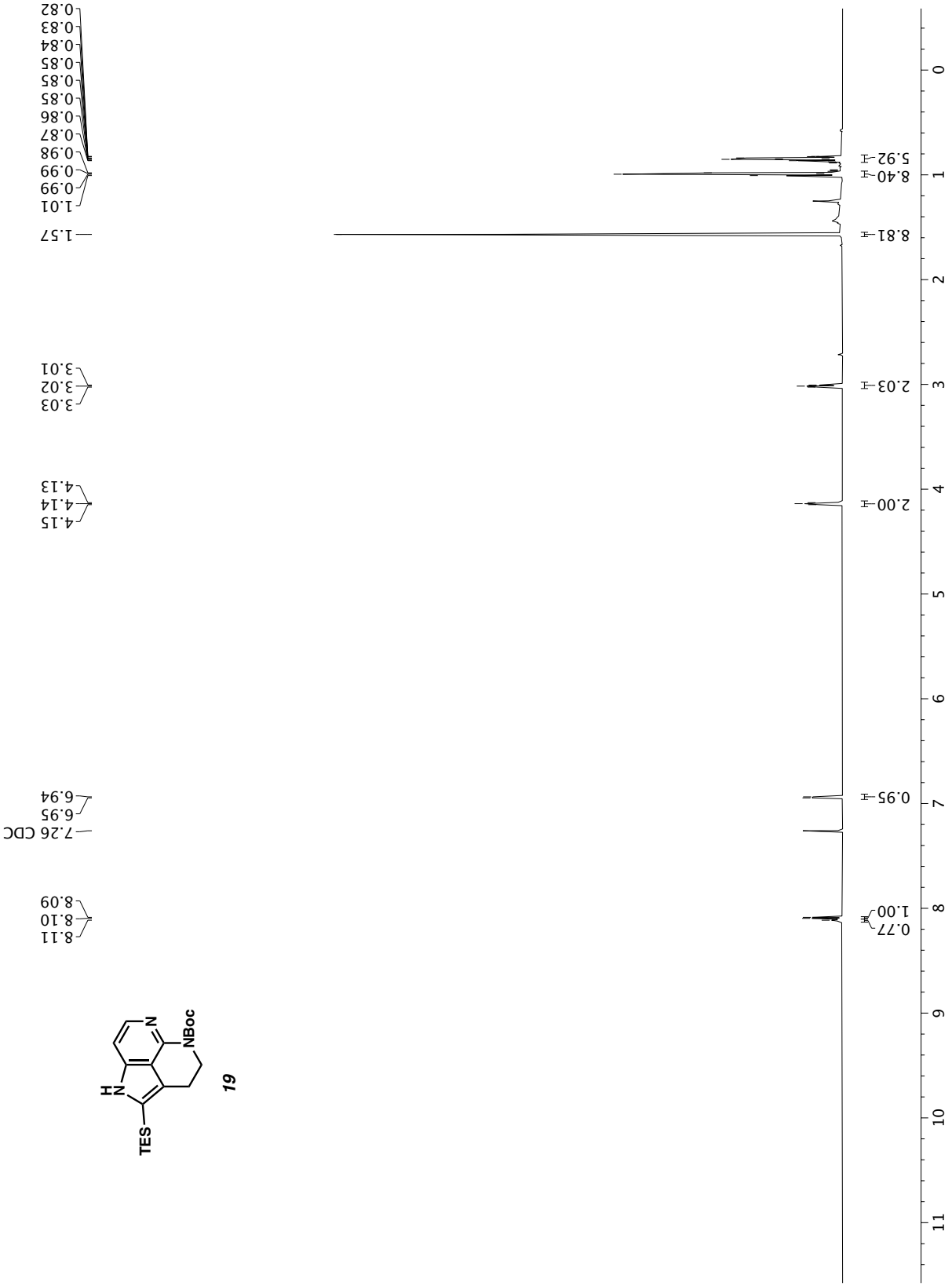
^{1}H NMR (400 MHz, MeOD) of compound **18**.



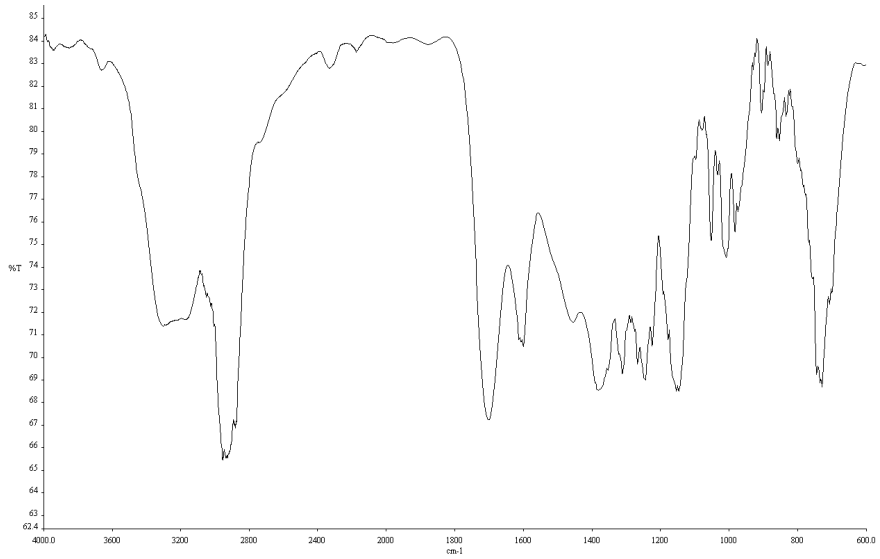
Infrared spectrum (Thin Film, NaCl) of compound **18**.



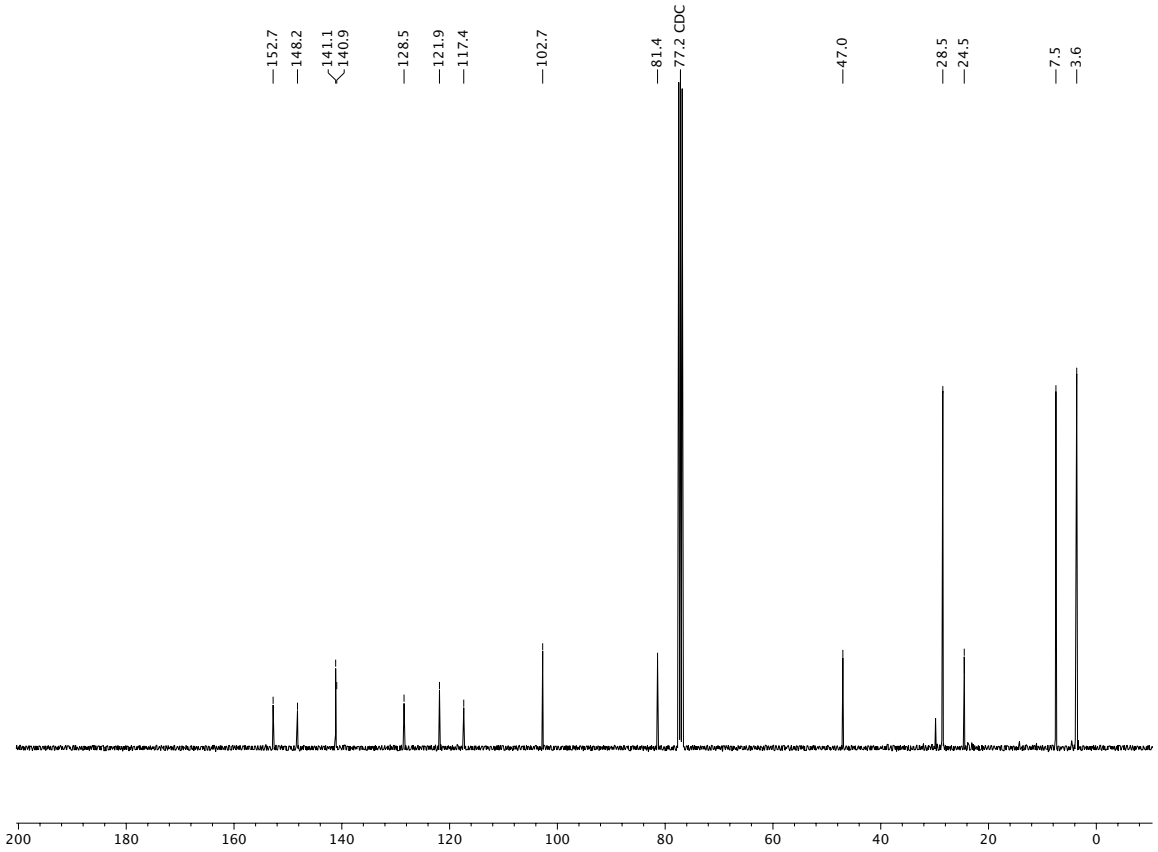
^{13}C NMR (100 MHz, MeOD) of compound **18**.



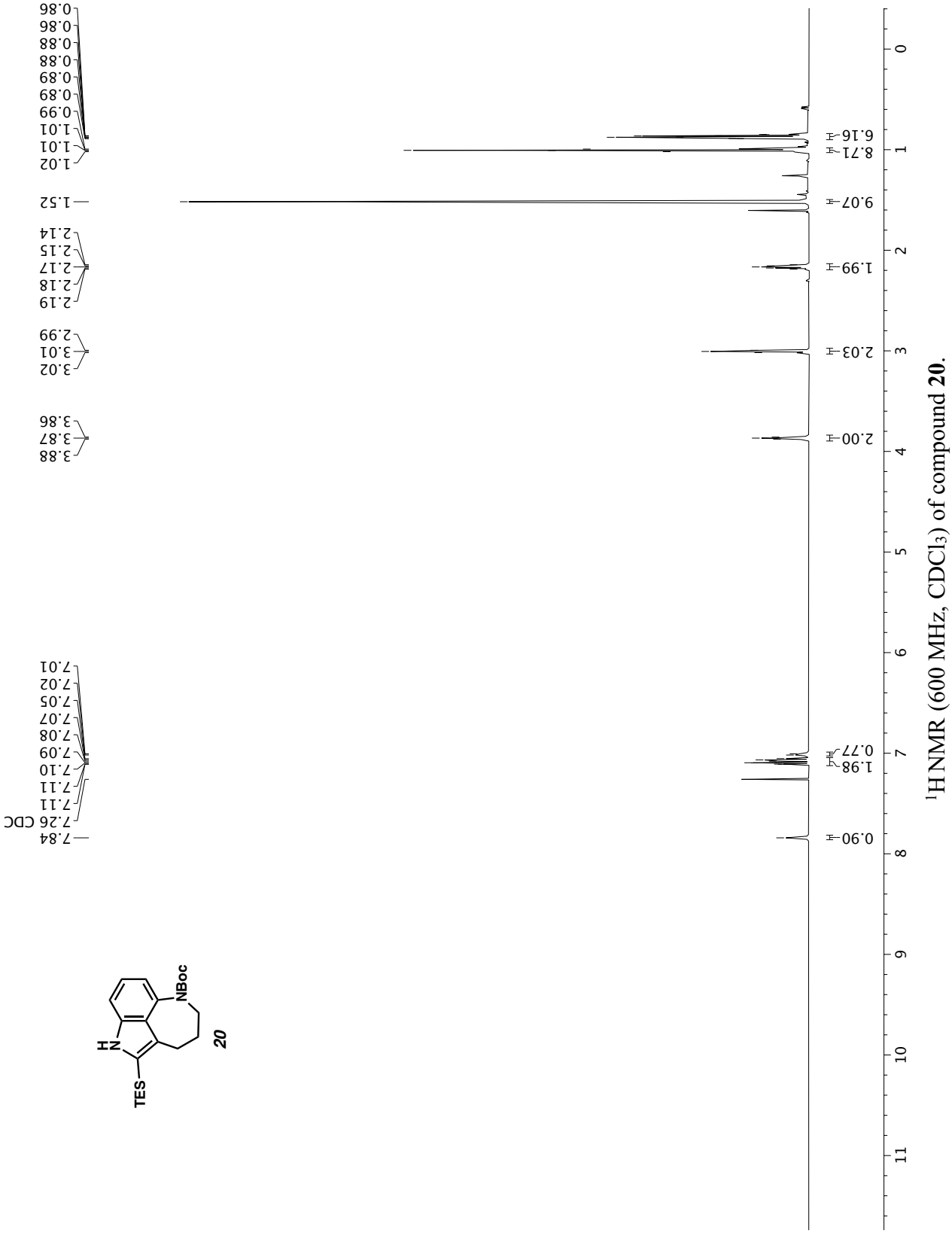
^{1}H NMR (600 MHz, $CDCl_3$) of compound **19**.



Infrared spectrum (Thin Film, NaCl) of compound **19**.



^{13}C NMR (100 MHz, $CDCl_3$) of compound **19**.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3.88
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7.02
7.05
7.07
7.08
7.09
7.10
7.11
7.11
7.26 CDC
7.84
0.90
1.98
0.77
2.00
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8.71
6.16
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H
N
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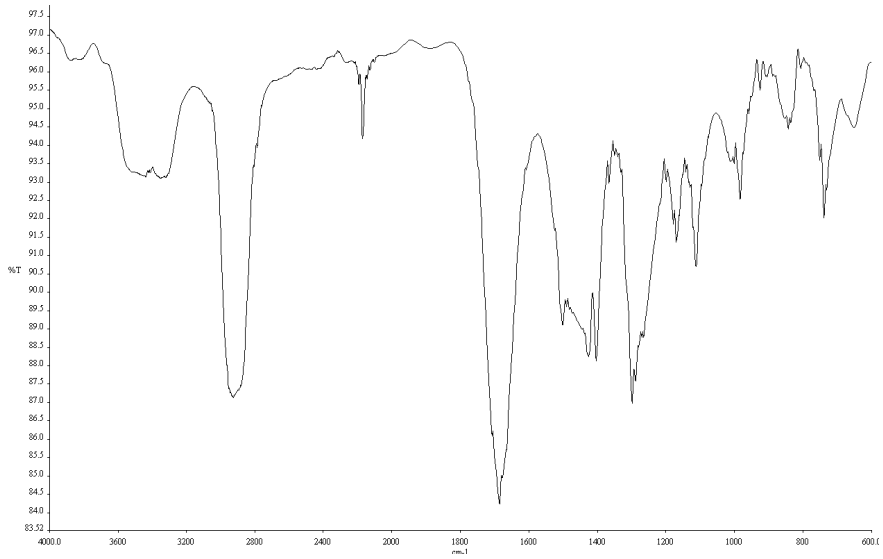
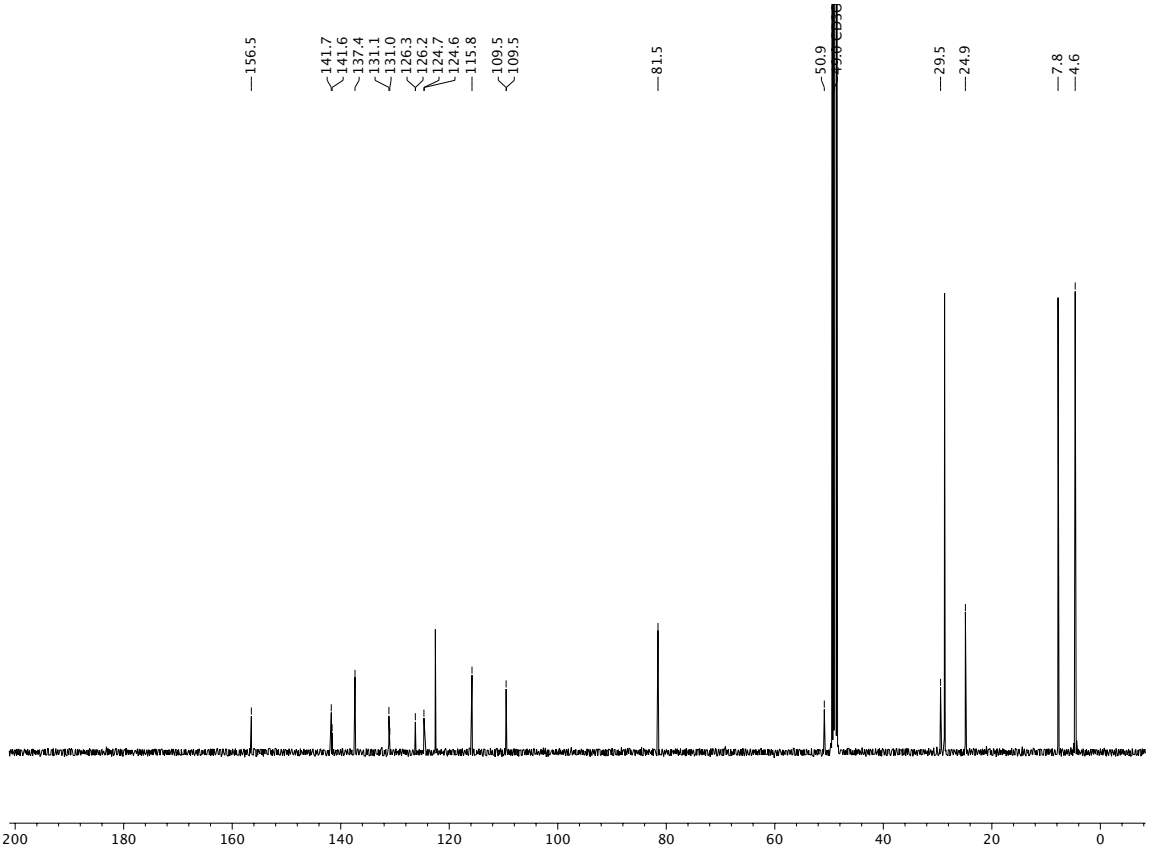
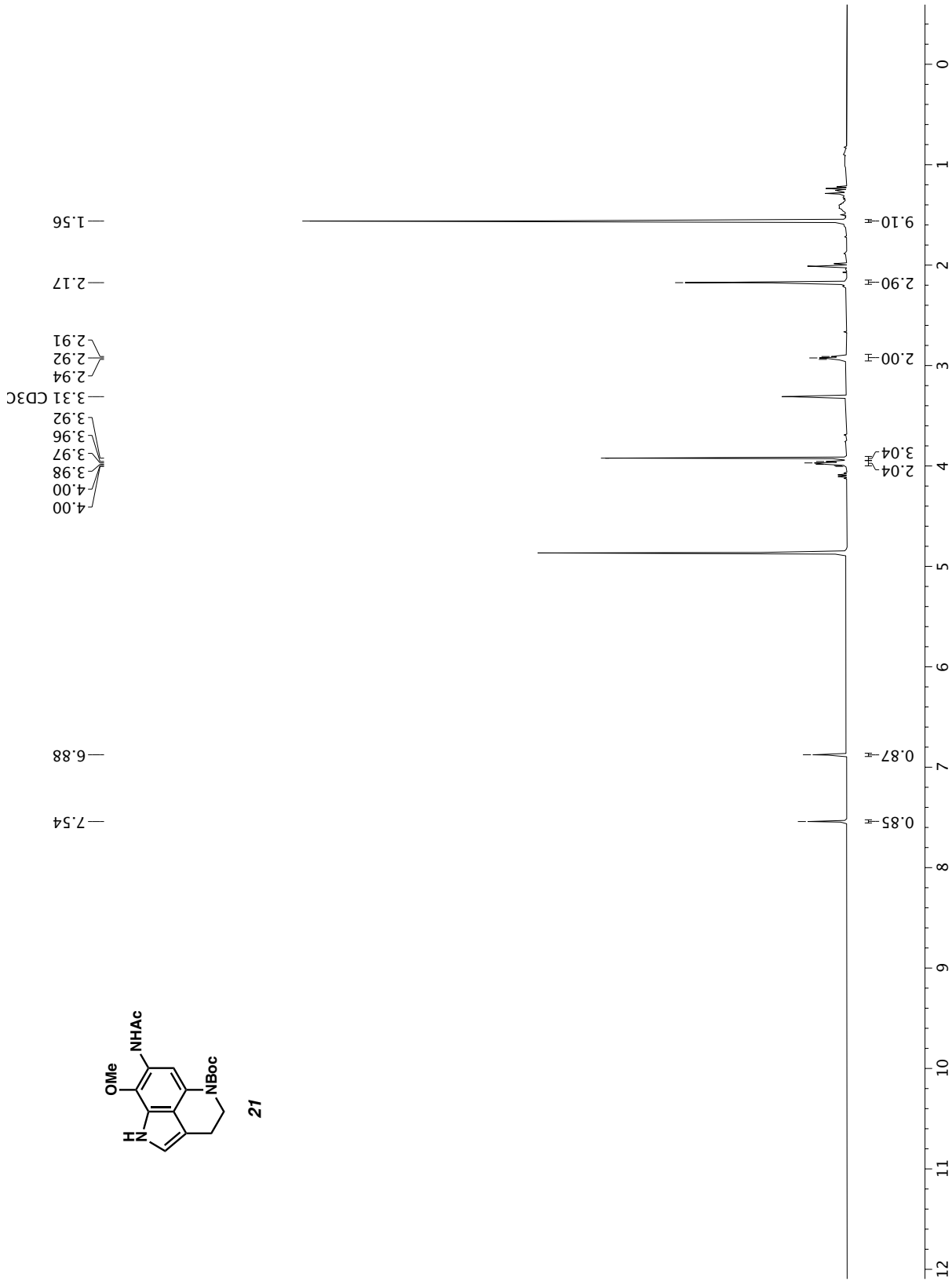
20
^{1}H NMR (600 MHz, $CDCl_3$) of compound **20**.



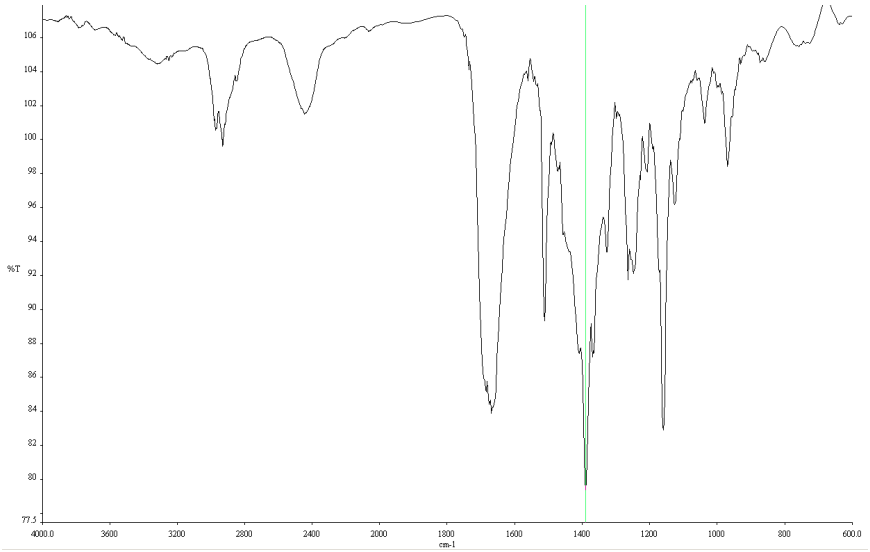
Infrared spectrum (Thin Film, NaCl) of compound **20**.



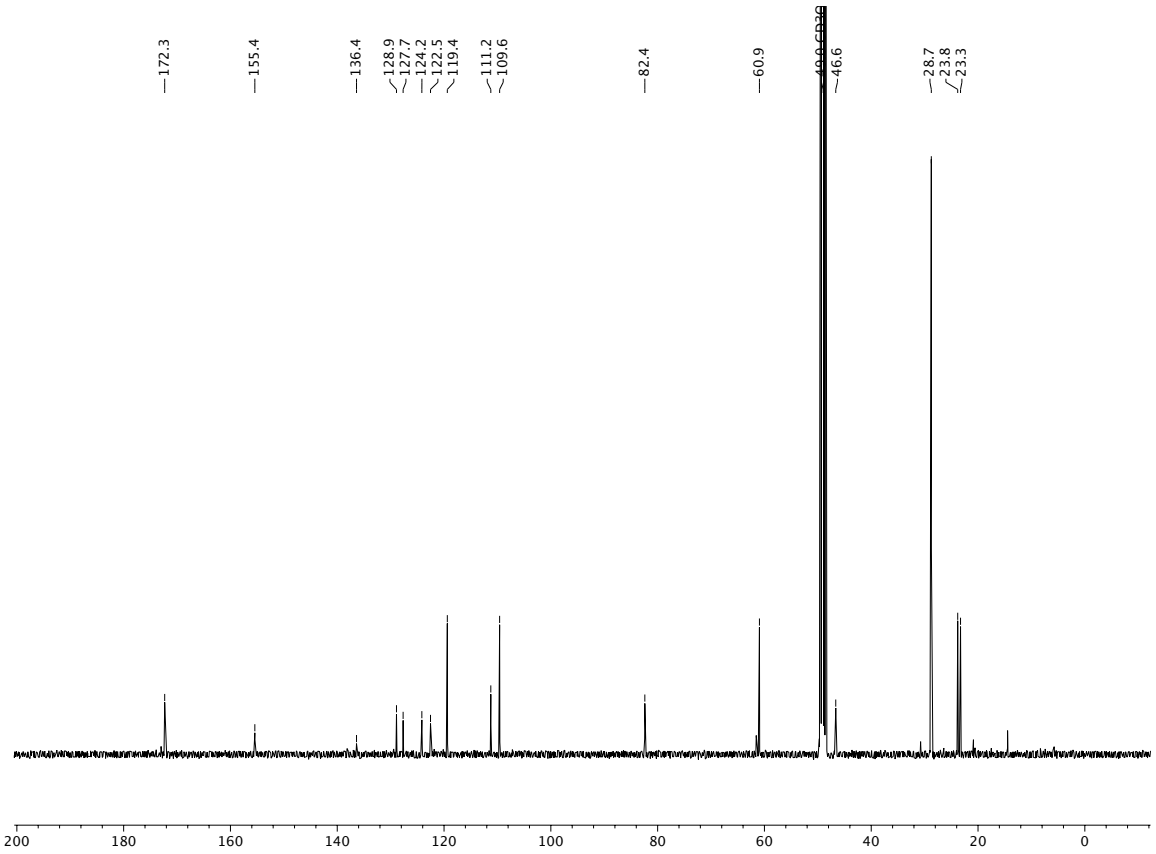
^{13}C NMR (100 MHz, CD_3OD) of compound **20**.



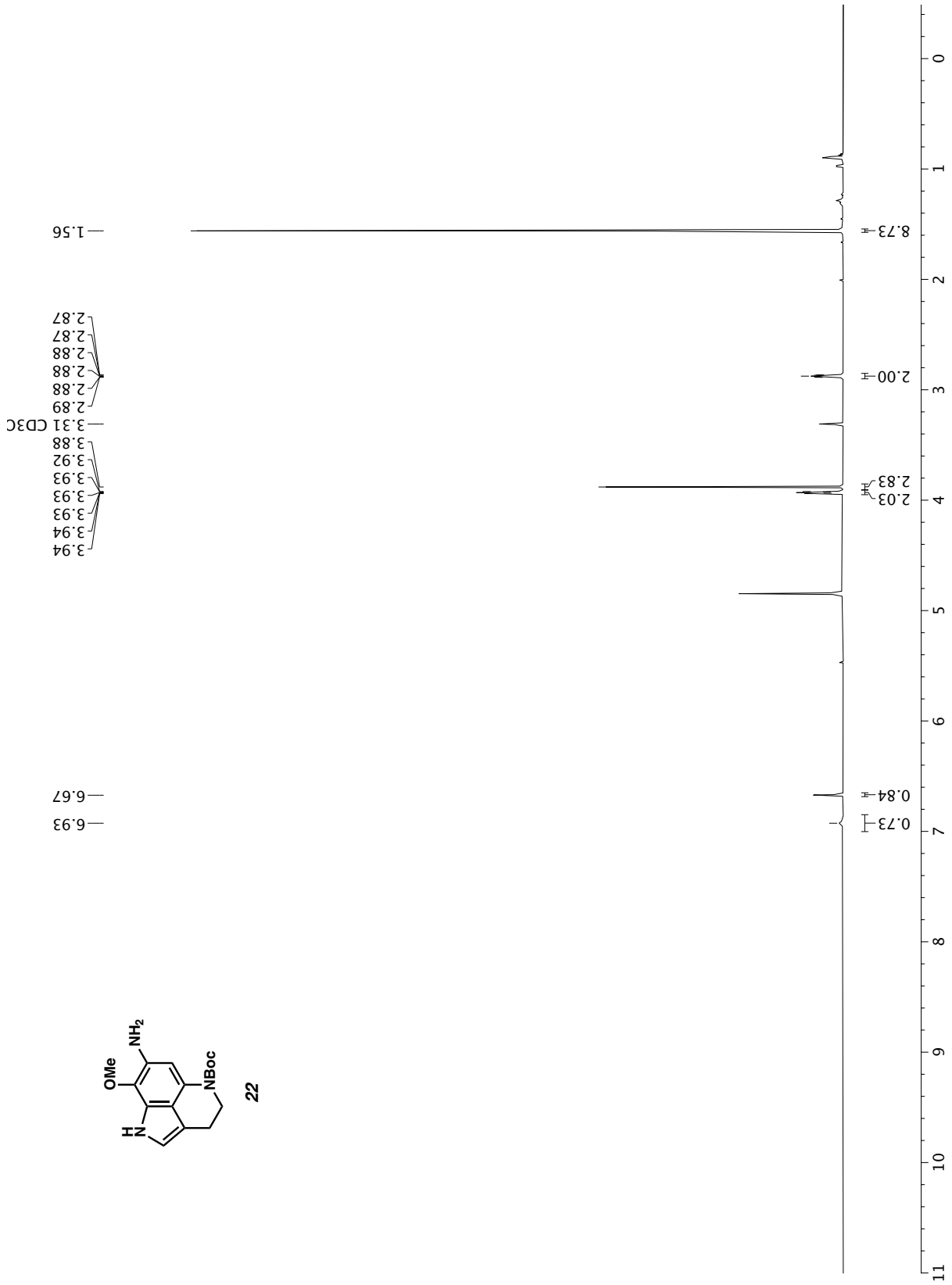
^{1}H NMR (400 MHz, MeOD) of compound **21**.



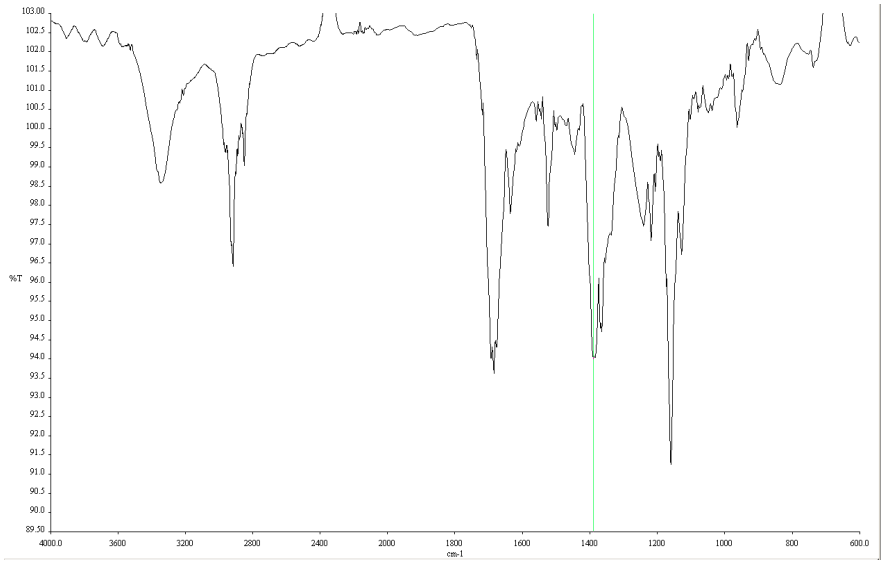
Infrared spectrum (Thin Film, NaCl) of compound **21**.



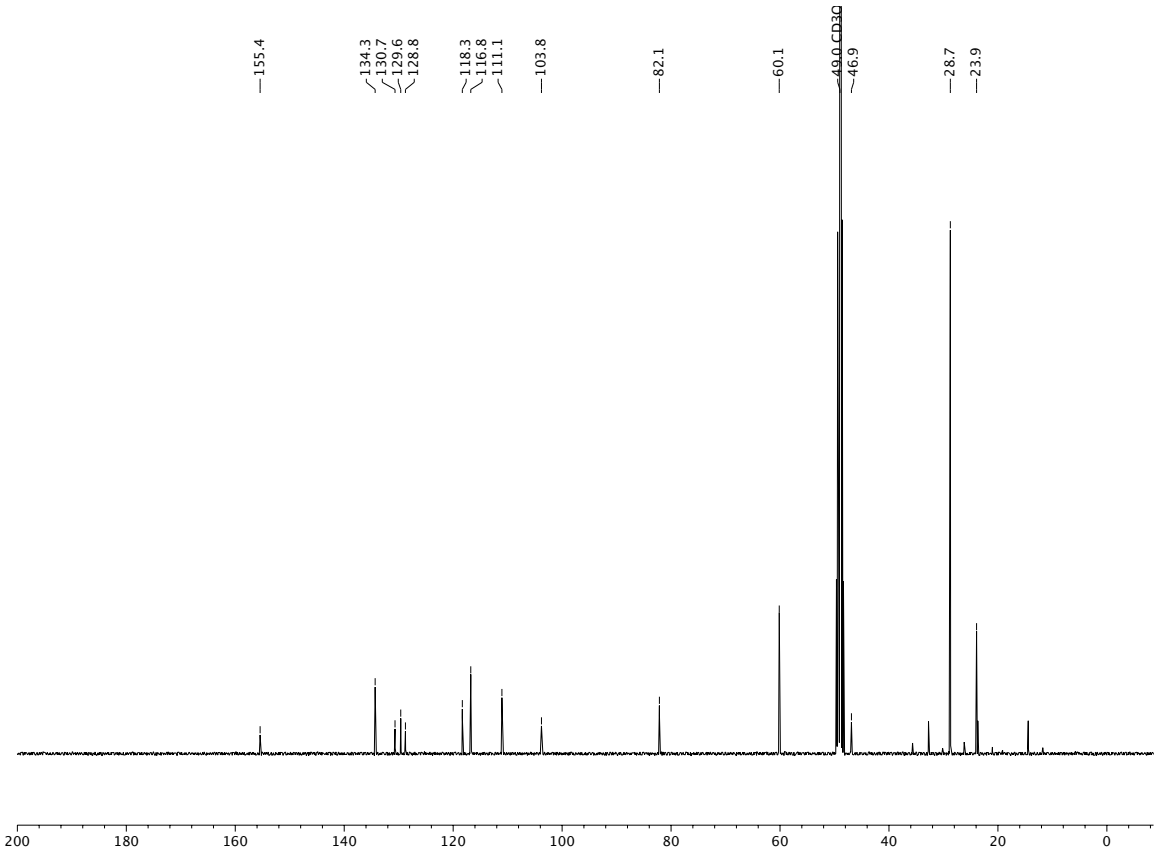
^{13}C NMR (100 MHz, MeOD) of compound **21**.



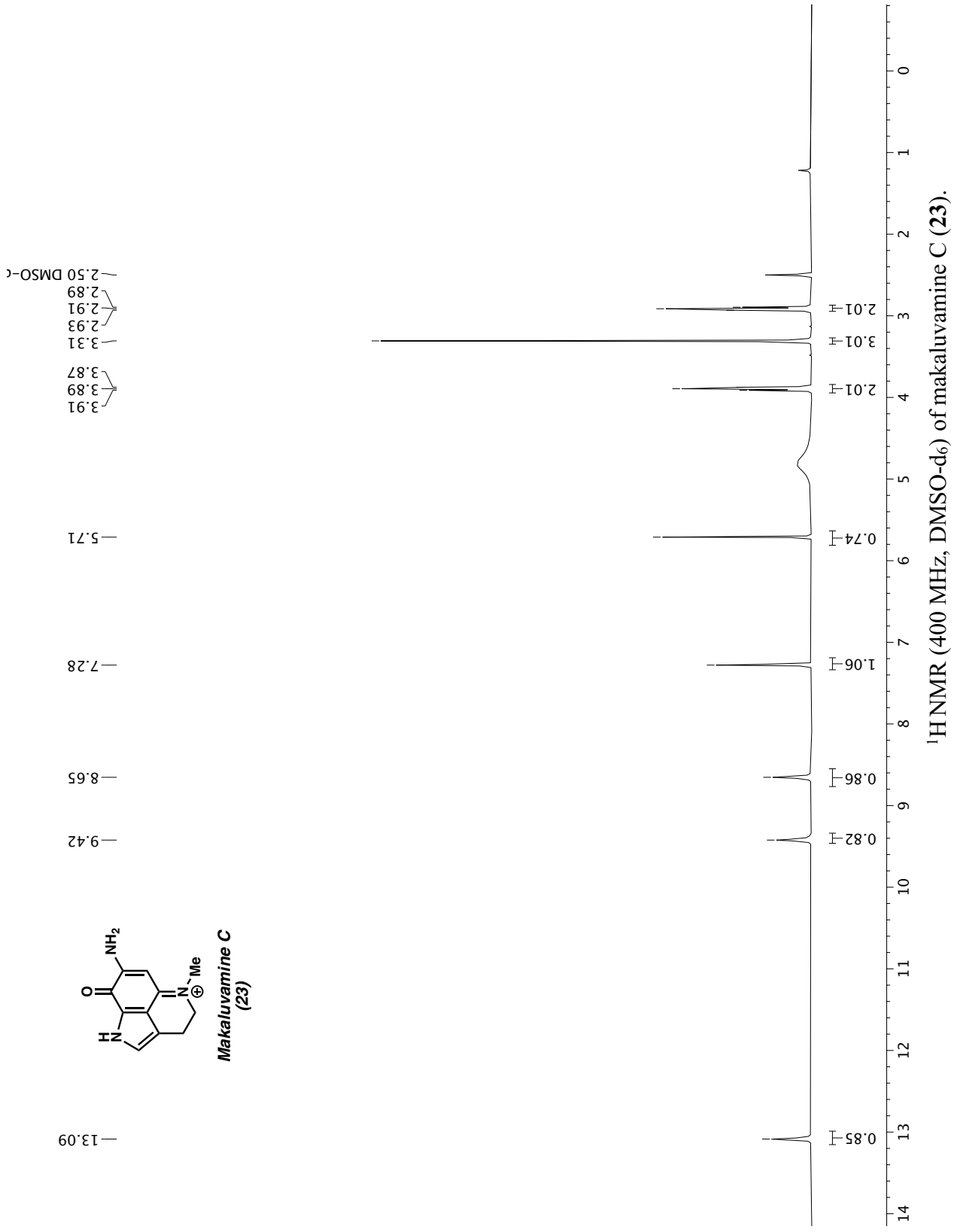
^{1}H NMR (600 MHz, MeOD) of compound **22**.



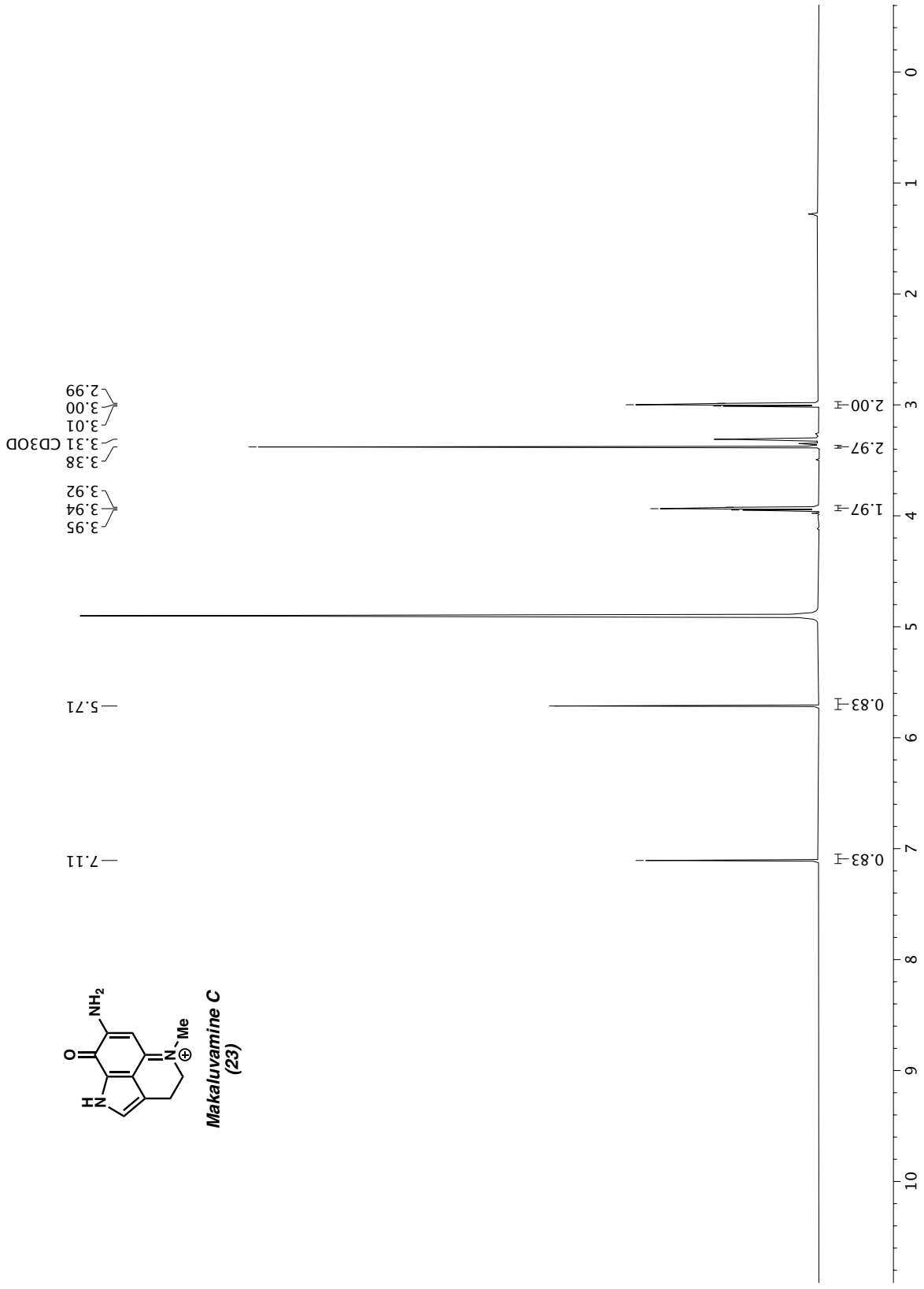
Infrared spectrum (Thin Film, NaCl) of compound **22**.



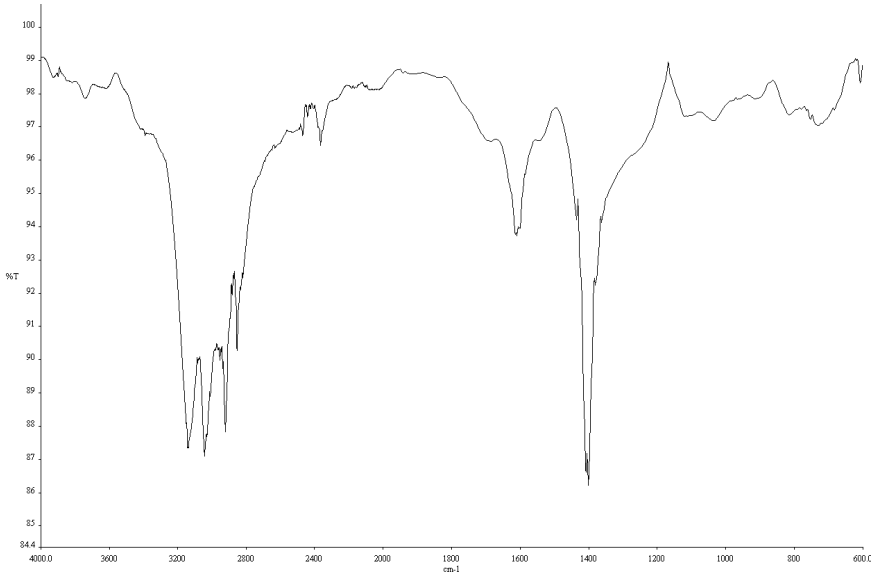
^{13}C NMR (100 MHz, MeOD) of compound **22**.



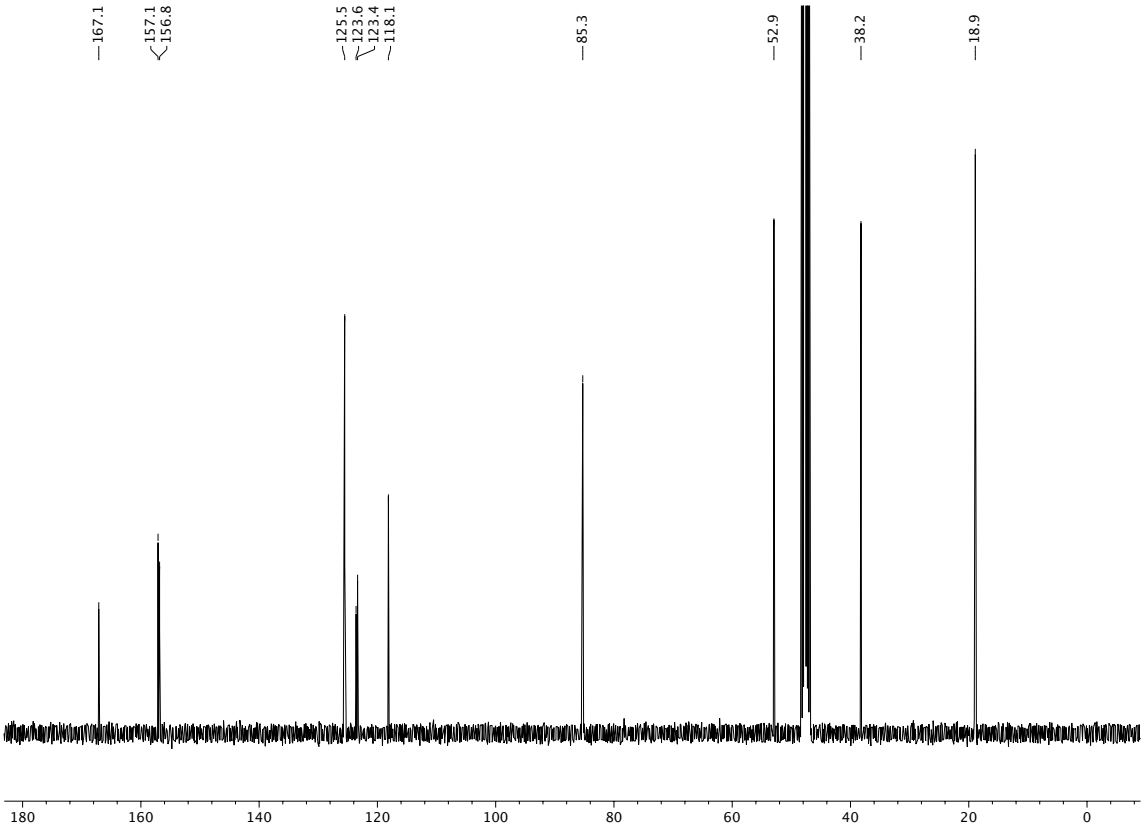
^{1}H NMR (400 MHz, DMSO-d_6) of makaluvamine C (**23**).



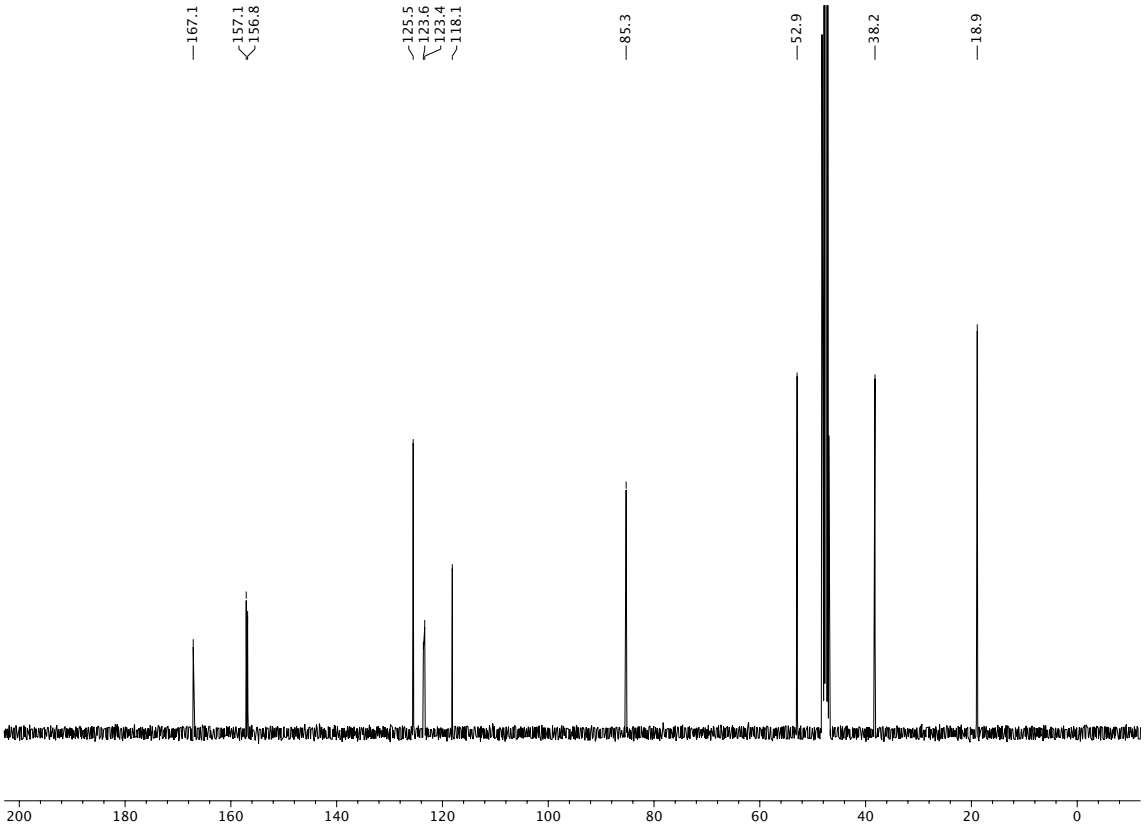
^{1}H NMR (600 MHz, MeOD) of makaluvamine C (**23**).



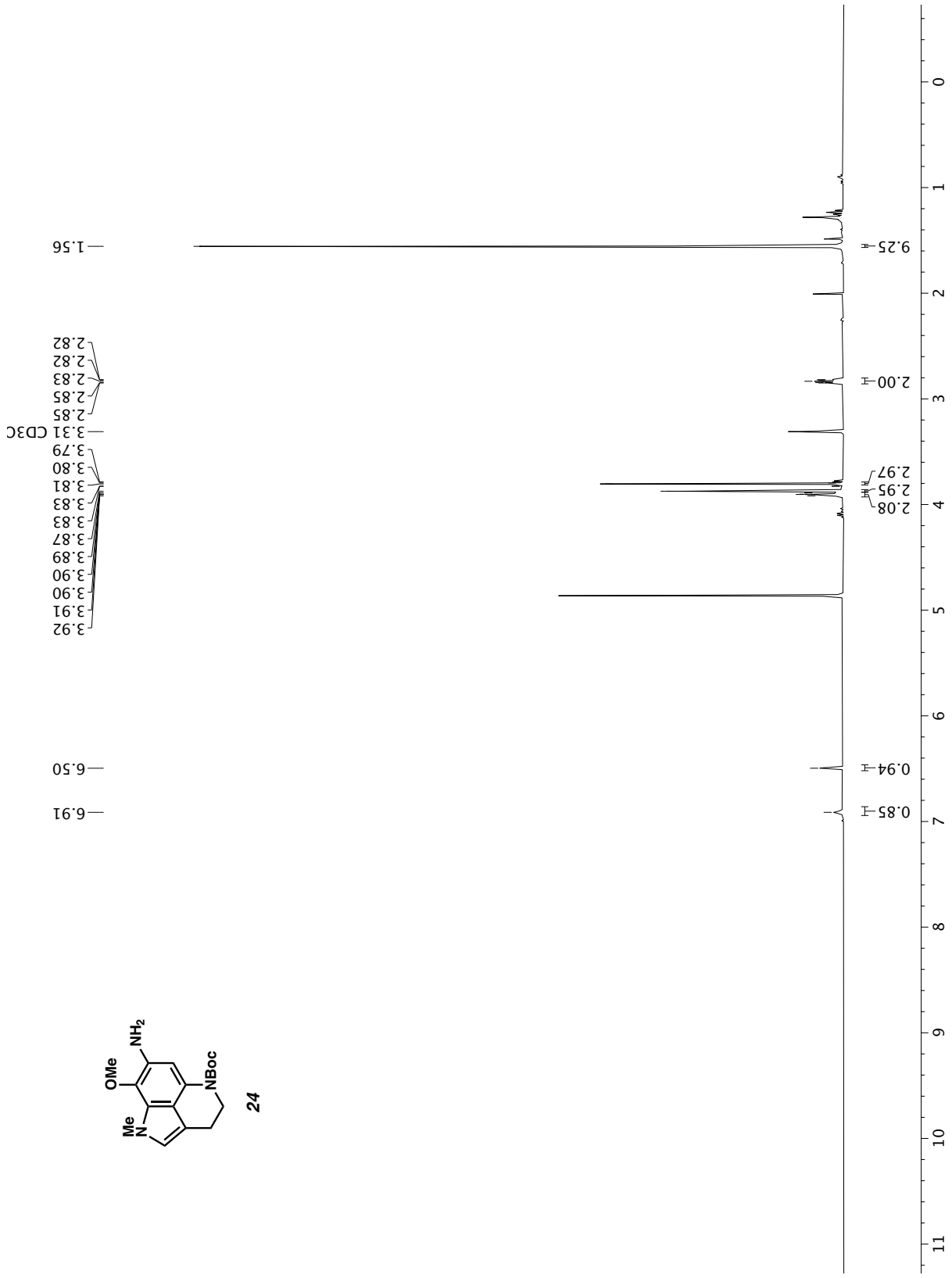
Infrared spectrum (Thin Film, NaCl) of Makaluvamine C (**23**).



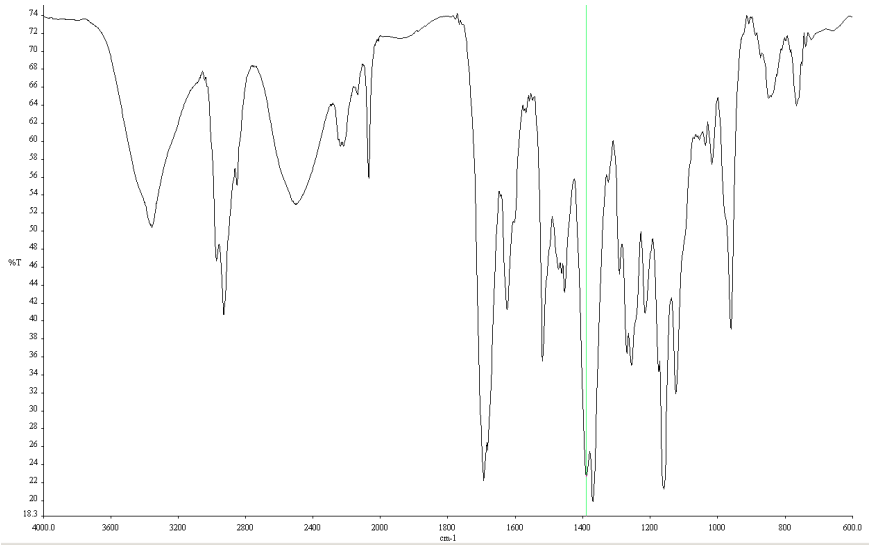
^{13}C NMR (100 MHz, DMSO-d_6) of makaluvamine C (**23**).



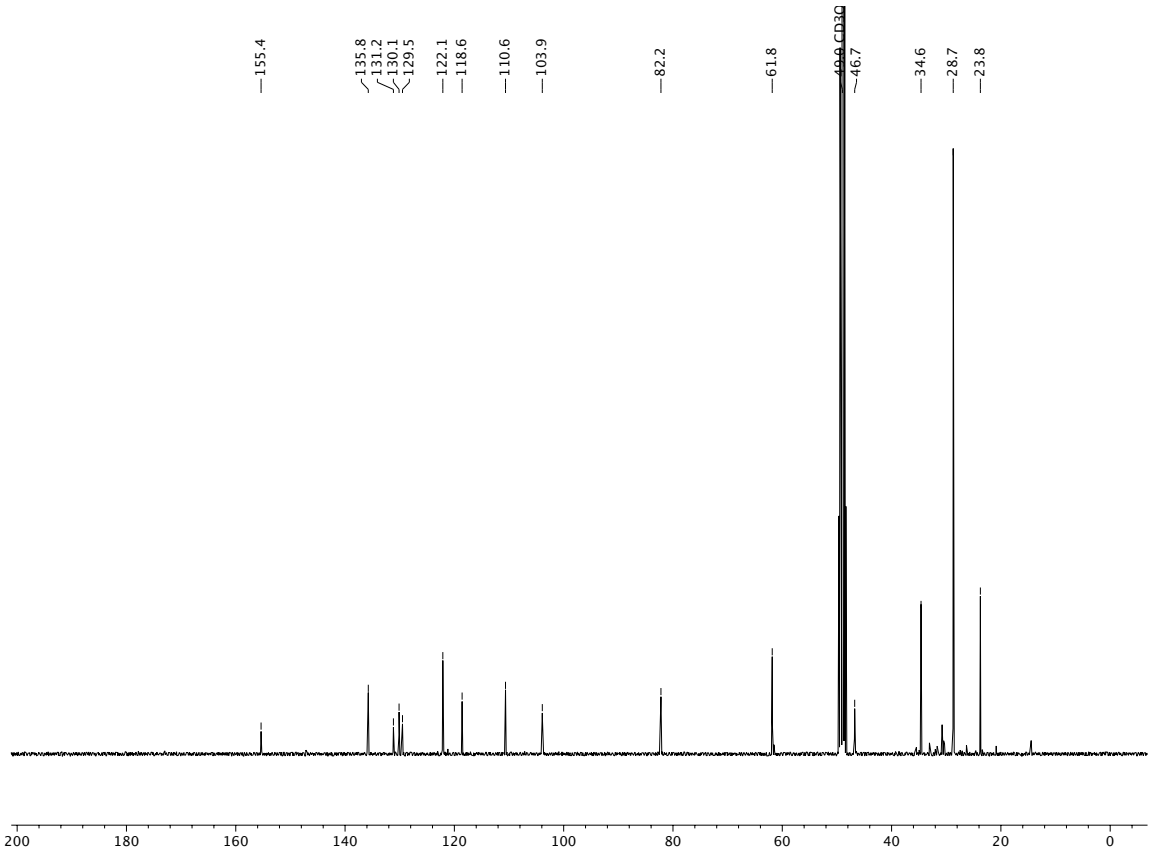
^{13}C NMR (100 MHz, MeOD) of makaluvamine C (**23**).



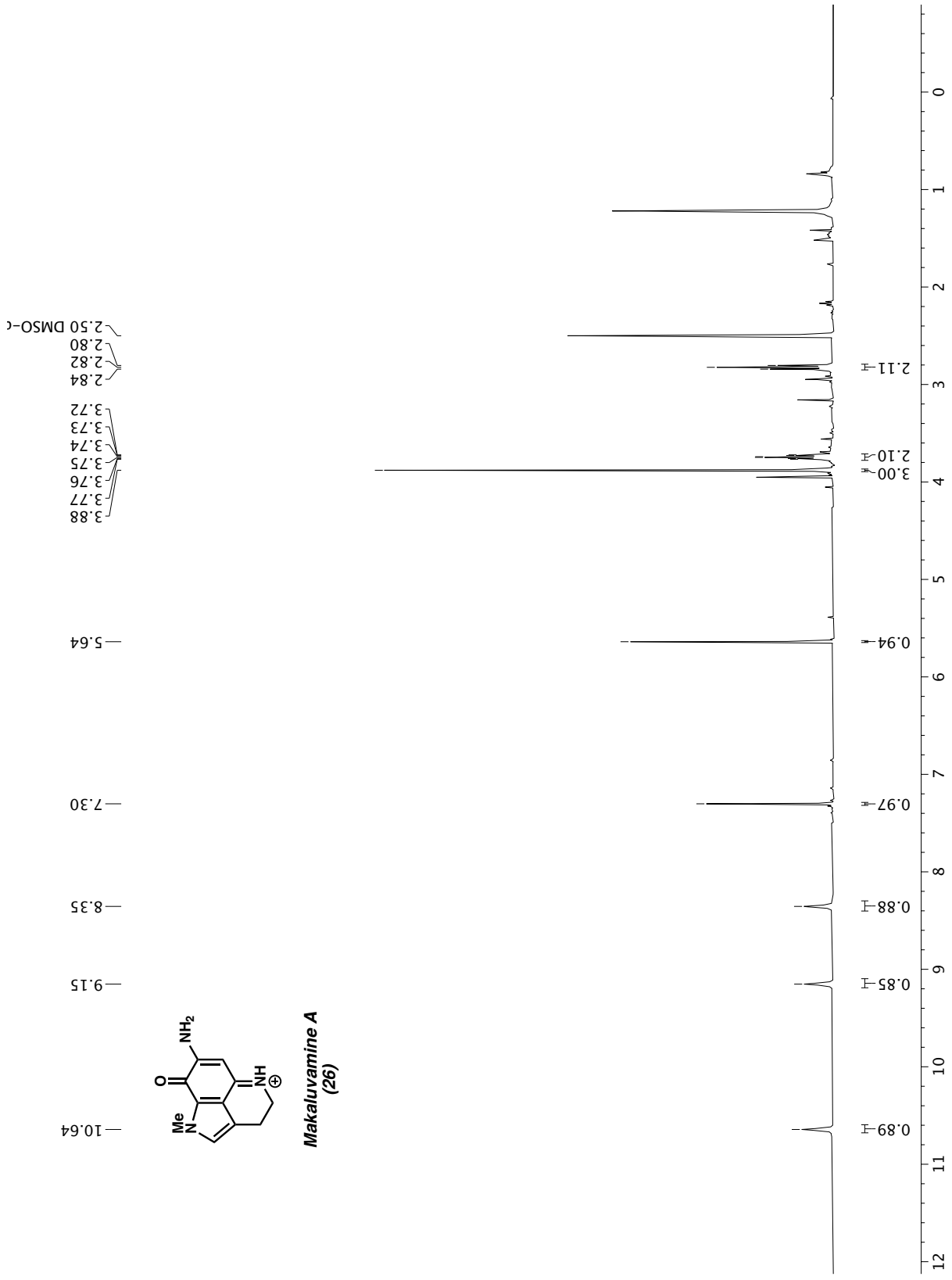
^{1}H NMR (400 MHz, MeOD) of compound **24**.



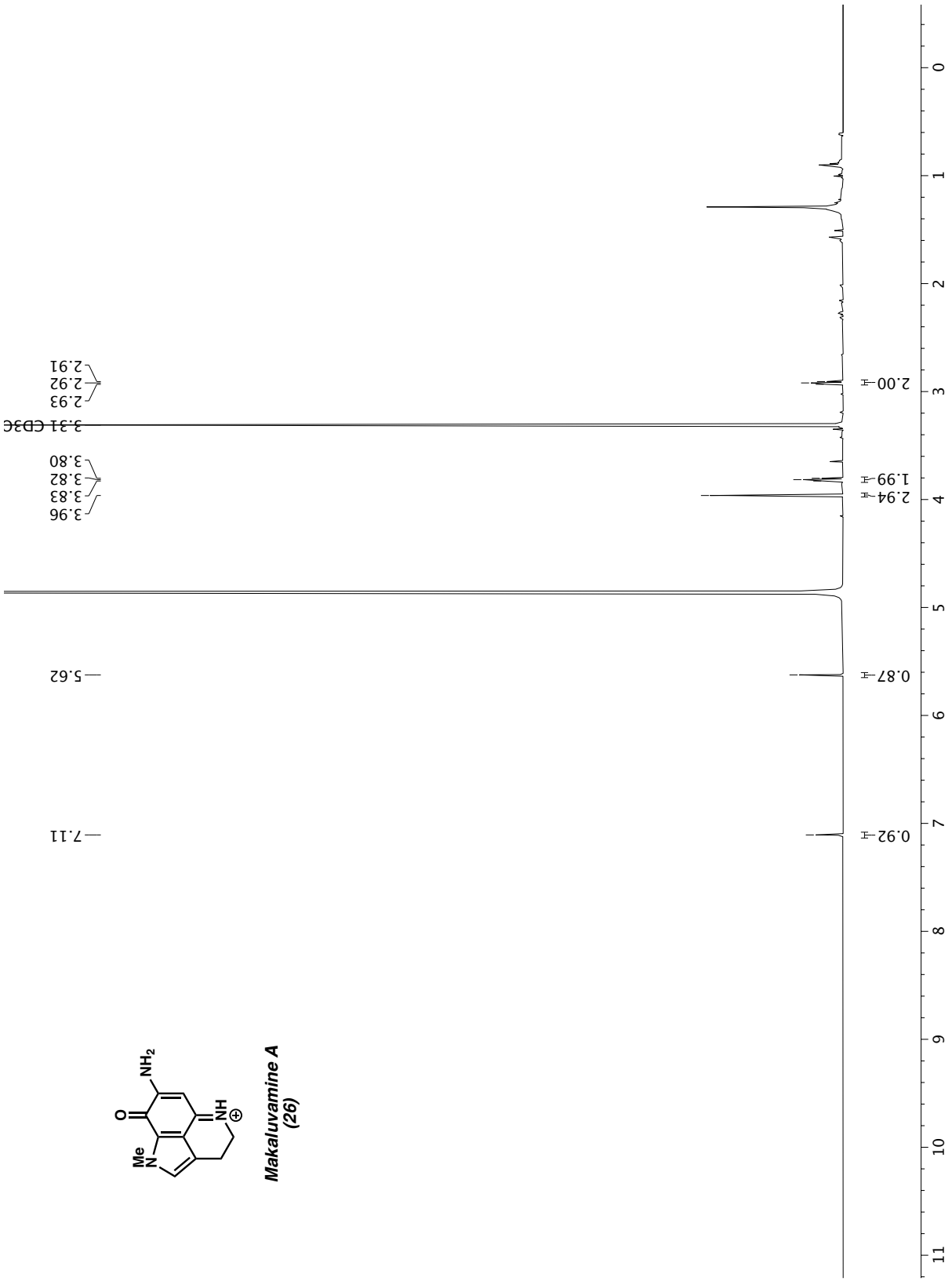
Infrared spectrum (Thin Film, NaCl) of compound **24**.



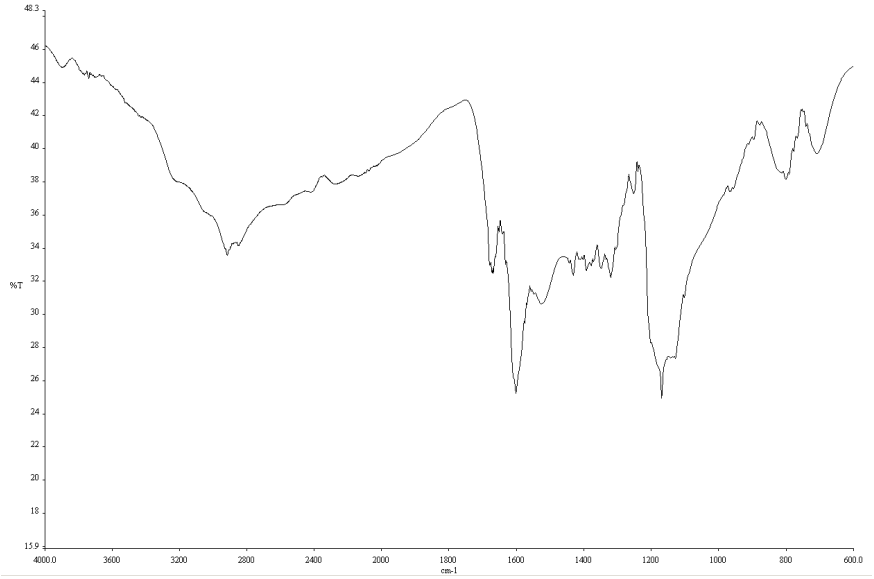
^{13}C NMR (100 MHz, MeOD) of compound **24**.



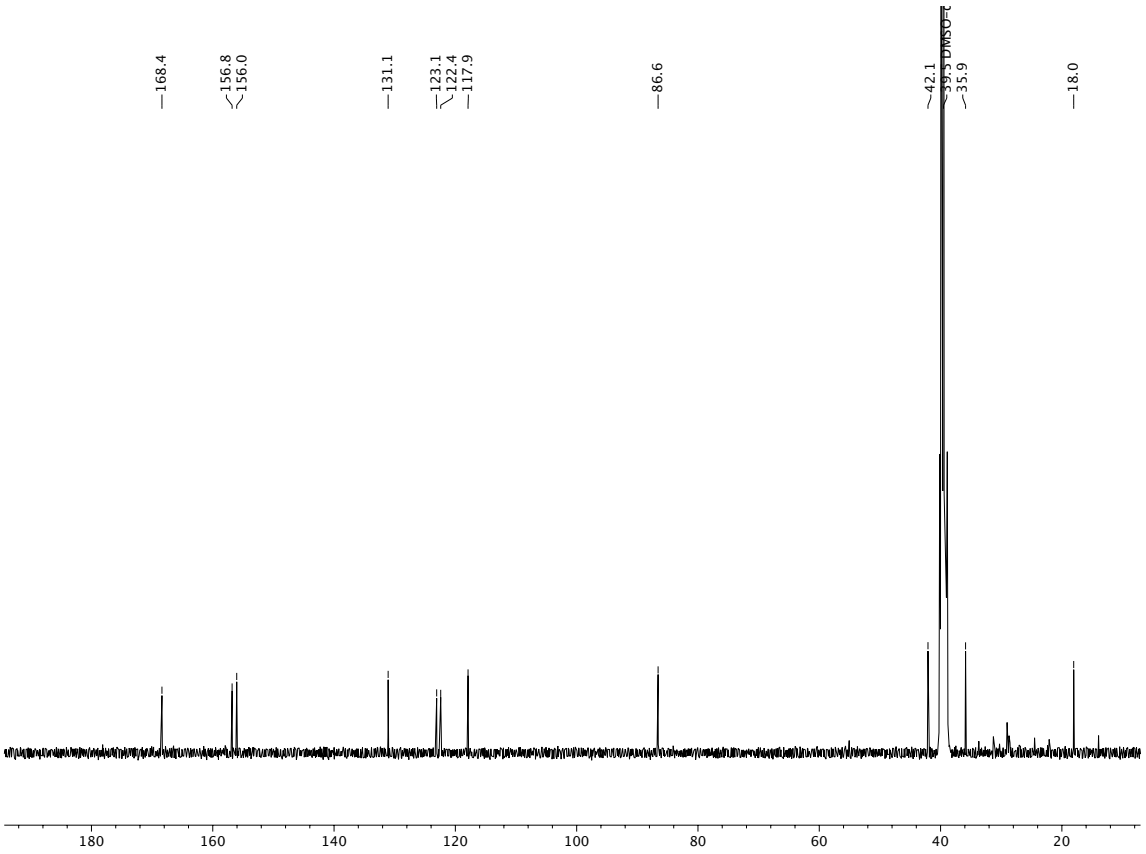
^{1}H NMR (400 MHz, DMSO-d_6) of makaluvamine A (**26**).



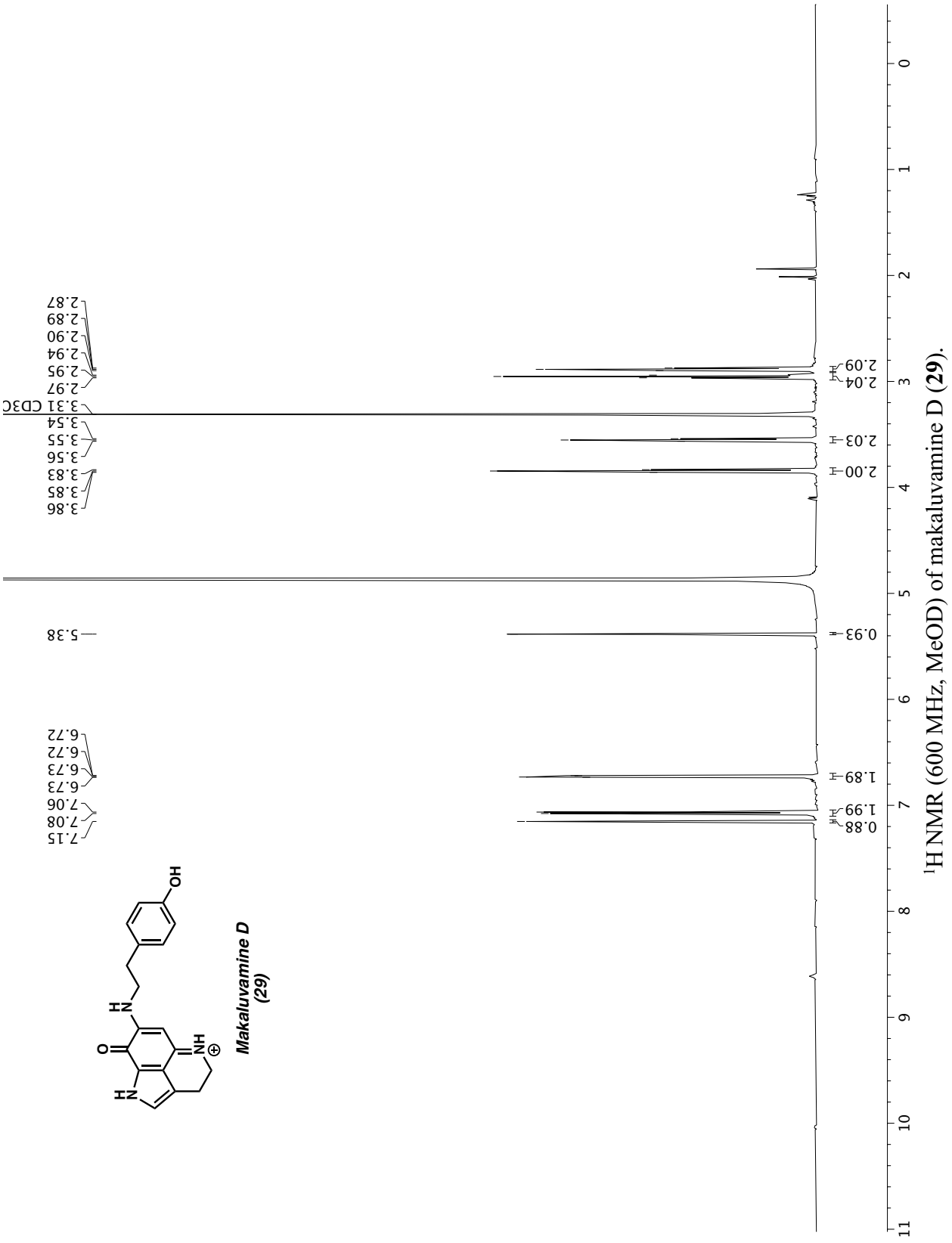
^{1}H NMR (600 MHz, MeOD) of makaluvamine A (**26**).



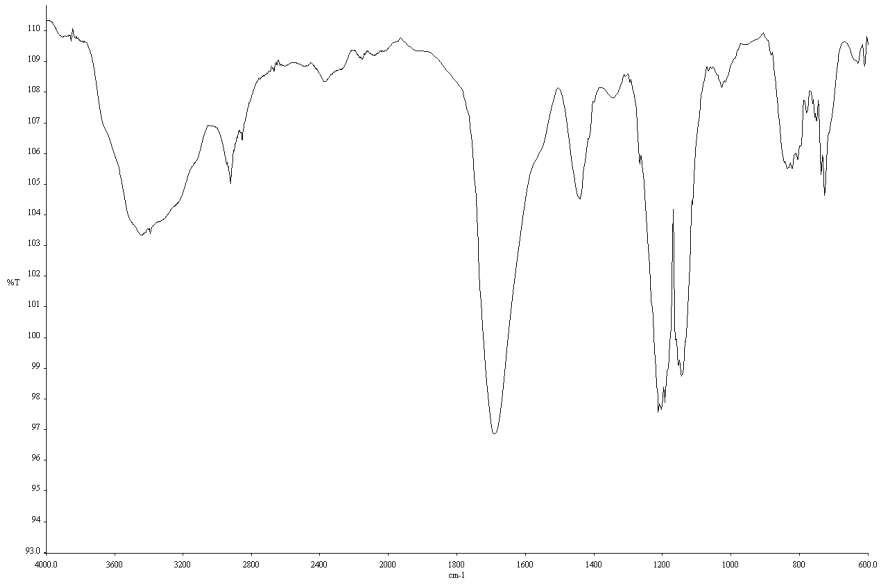
Infrared spectrum (Thin Film, NaCl) of makaluvamine A (**26**).



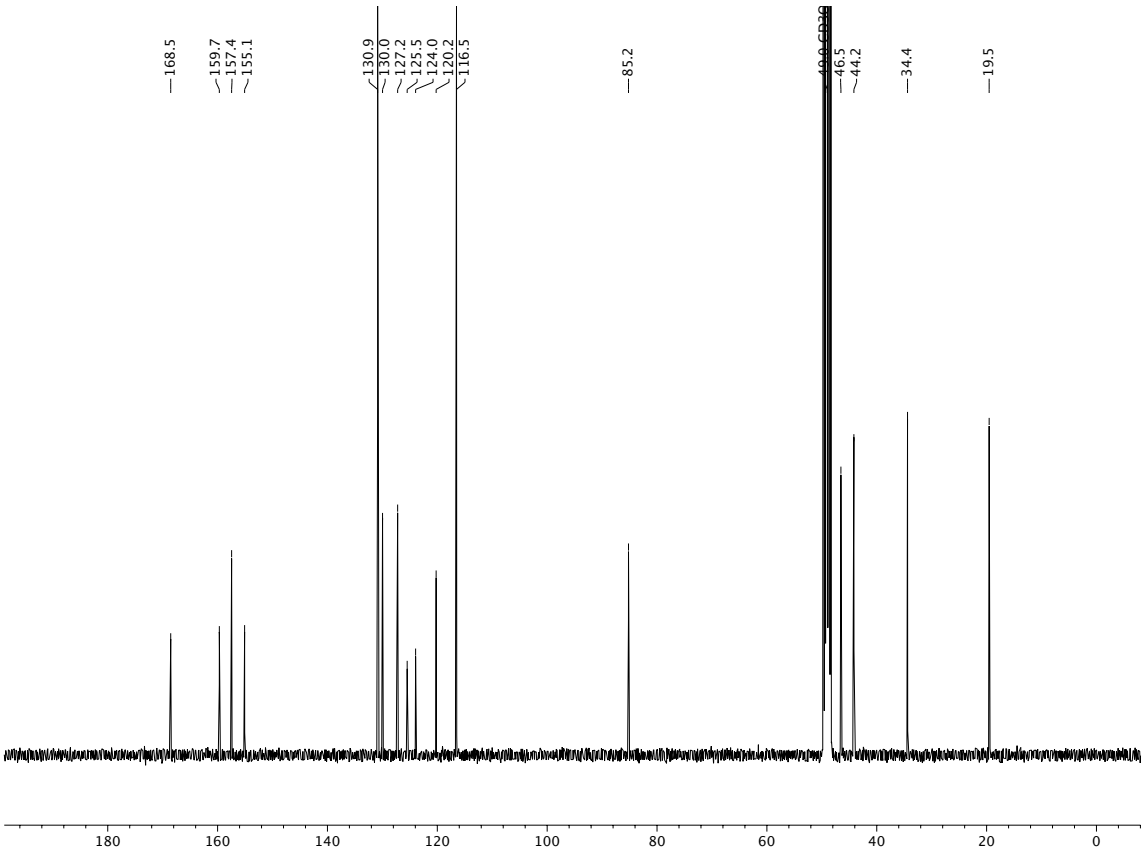
^{13}C NMR (100 MHz, DMSO-d_6) of makaluvamine A (**26**).



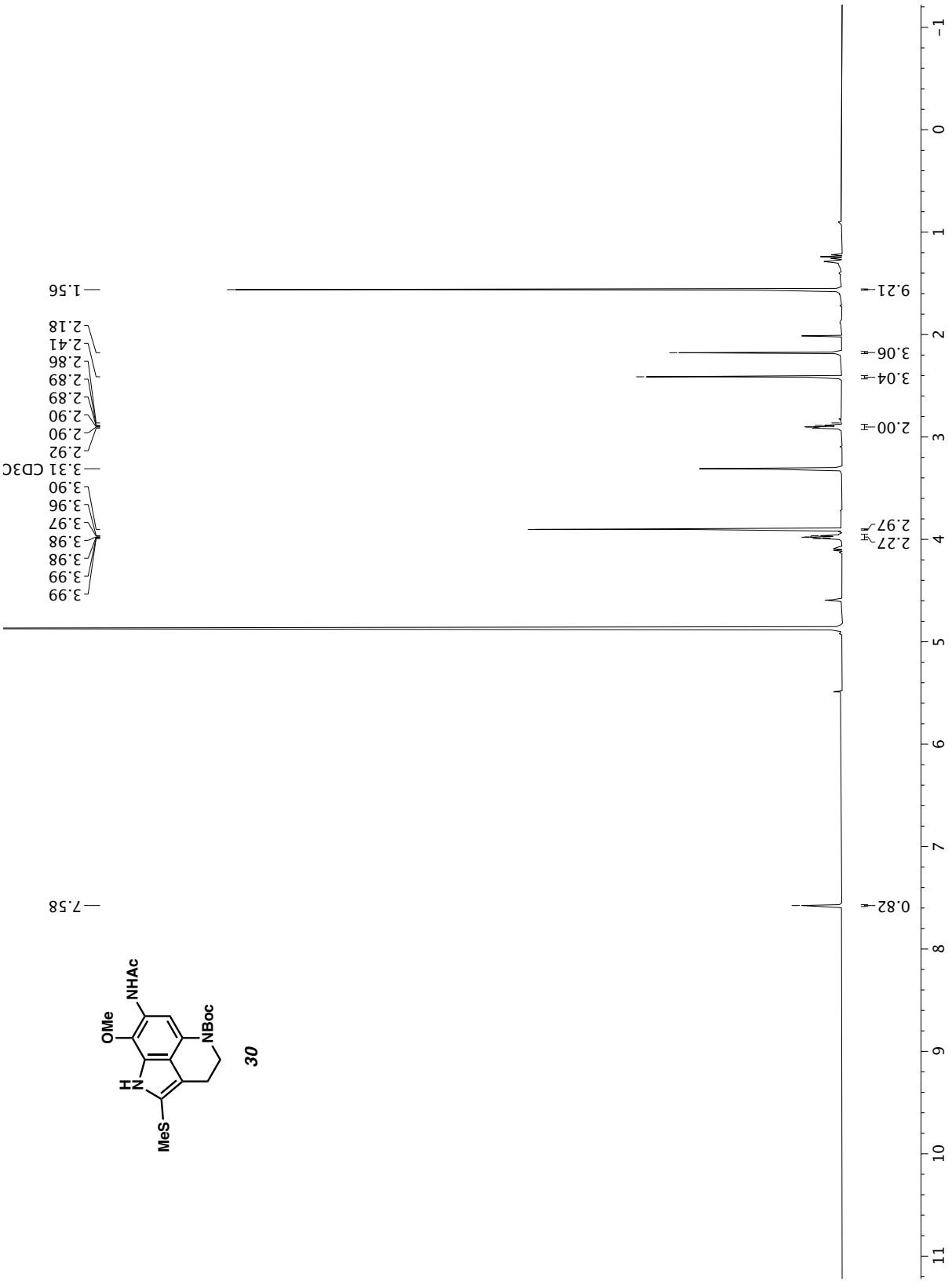
^{1}H NMR (600 MHz, MeOD) of makaluvamine D (**29**).



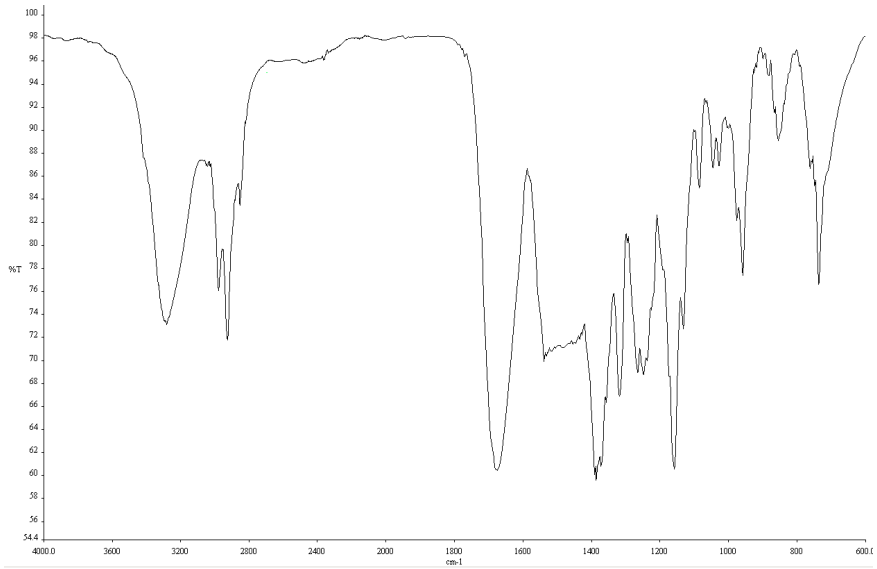
Infrared spectrum (Thin Film, NaCl) of makaluvamine D (**29**).



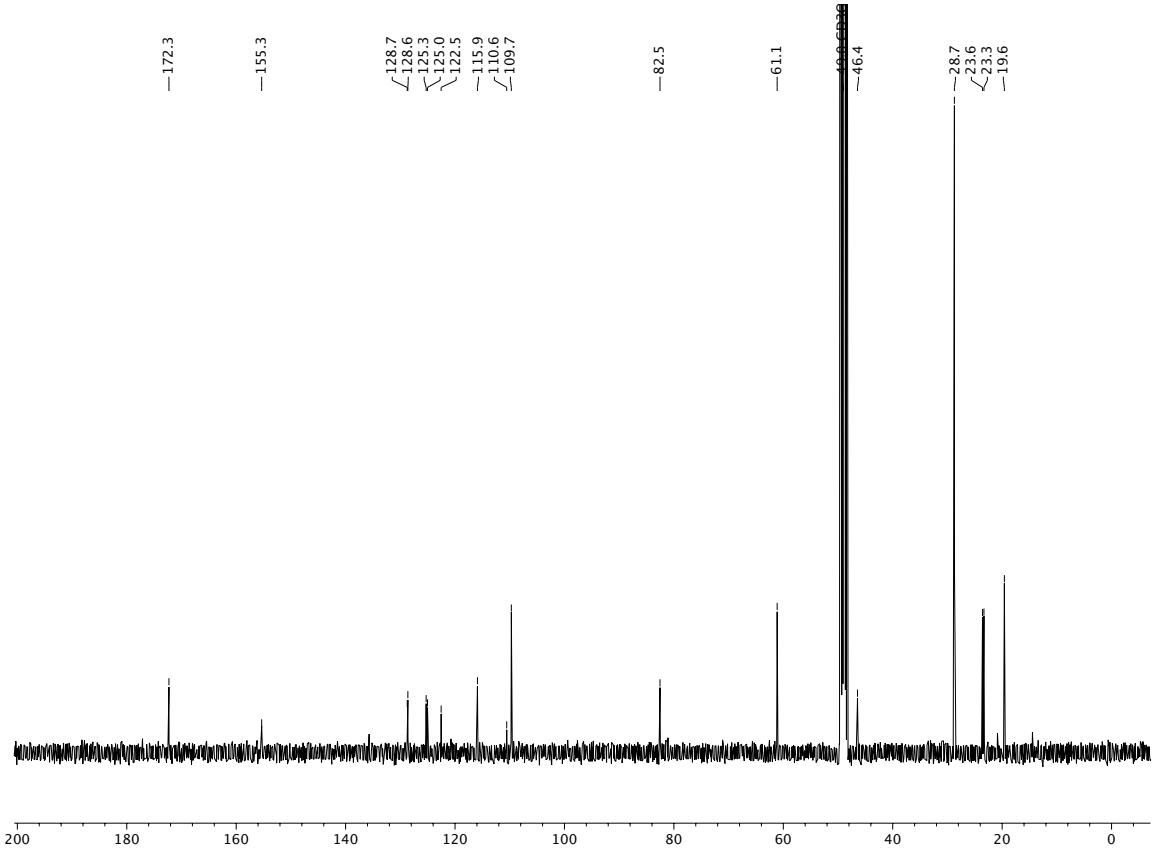
^{13}C NMR (100 MHz, MeOD) of makaluvamine D (**29**).



^{1}H NMR (600 MHz, MeOD) of compound (**30**).

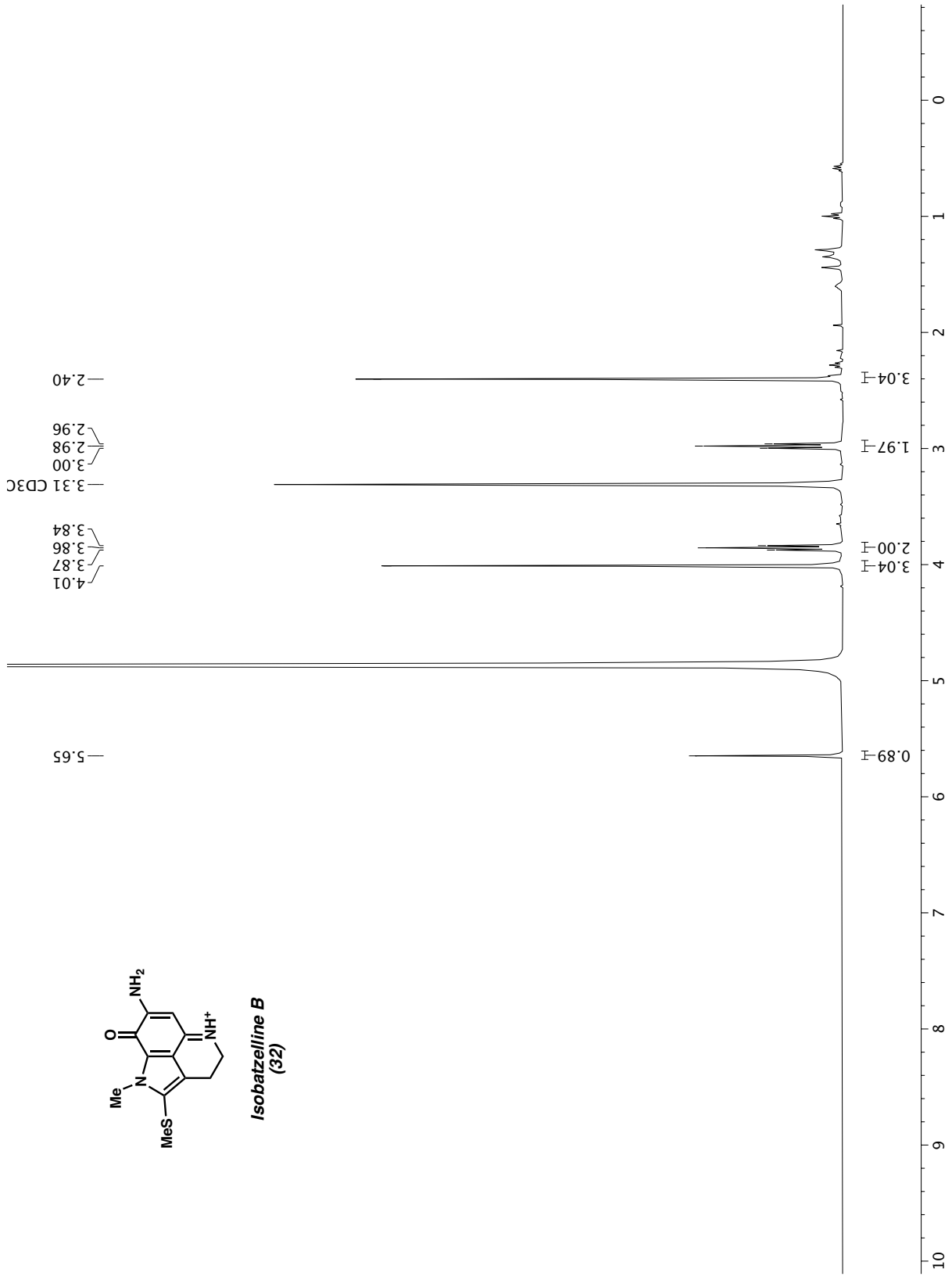


Infrared spectrum (Thin Film, NaCl) of compound (**30**).

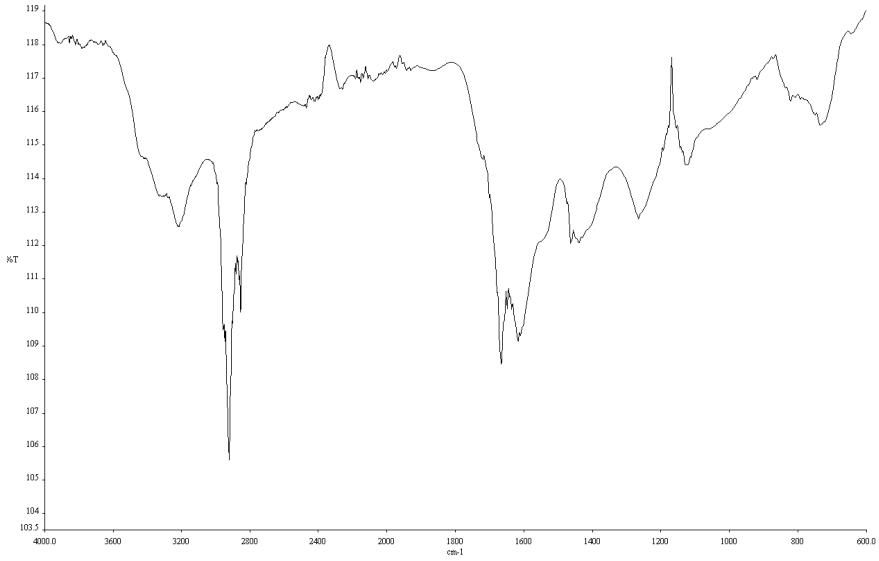


^{13}C NMR (100 MHz, MeOD) of compound (**30**).

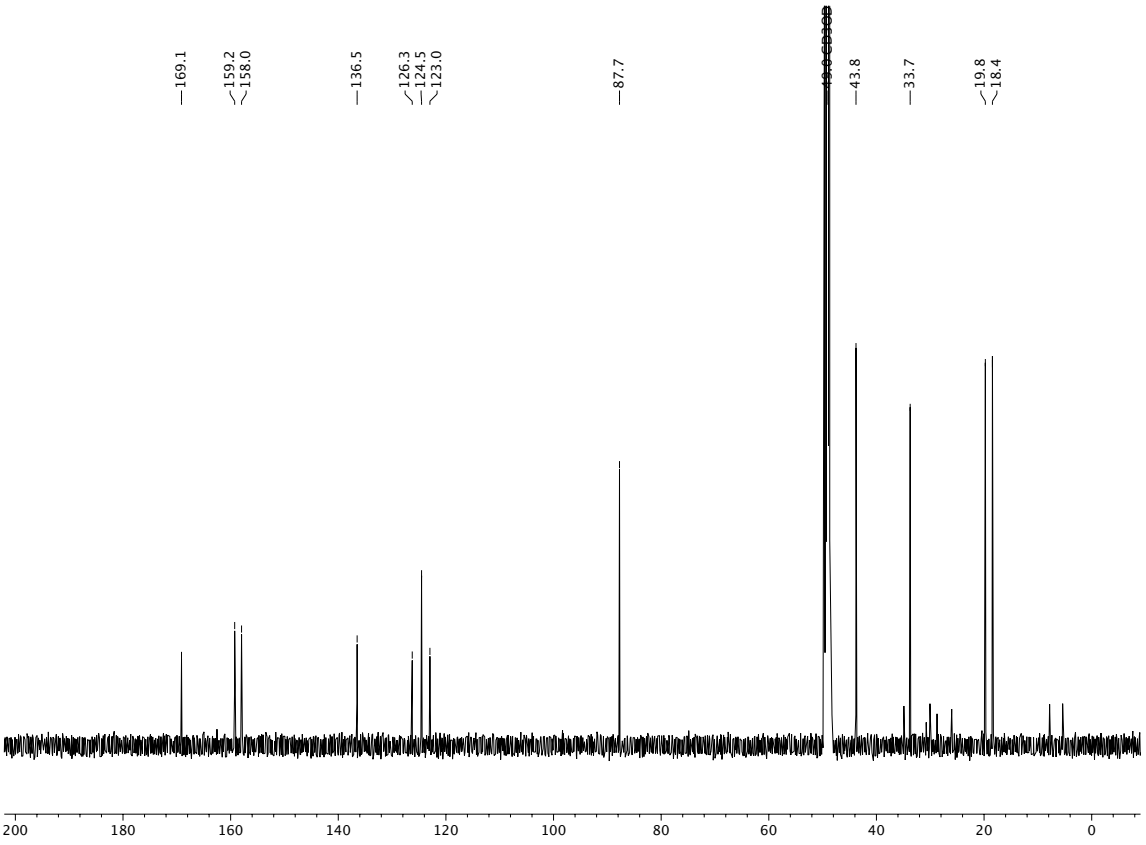
^{1}H NMR (400 MHz, 1:1 MeOD:$CDCl_3$) of isobatzelline B(**32**).



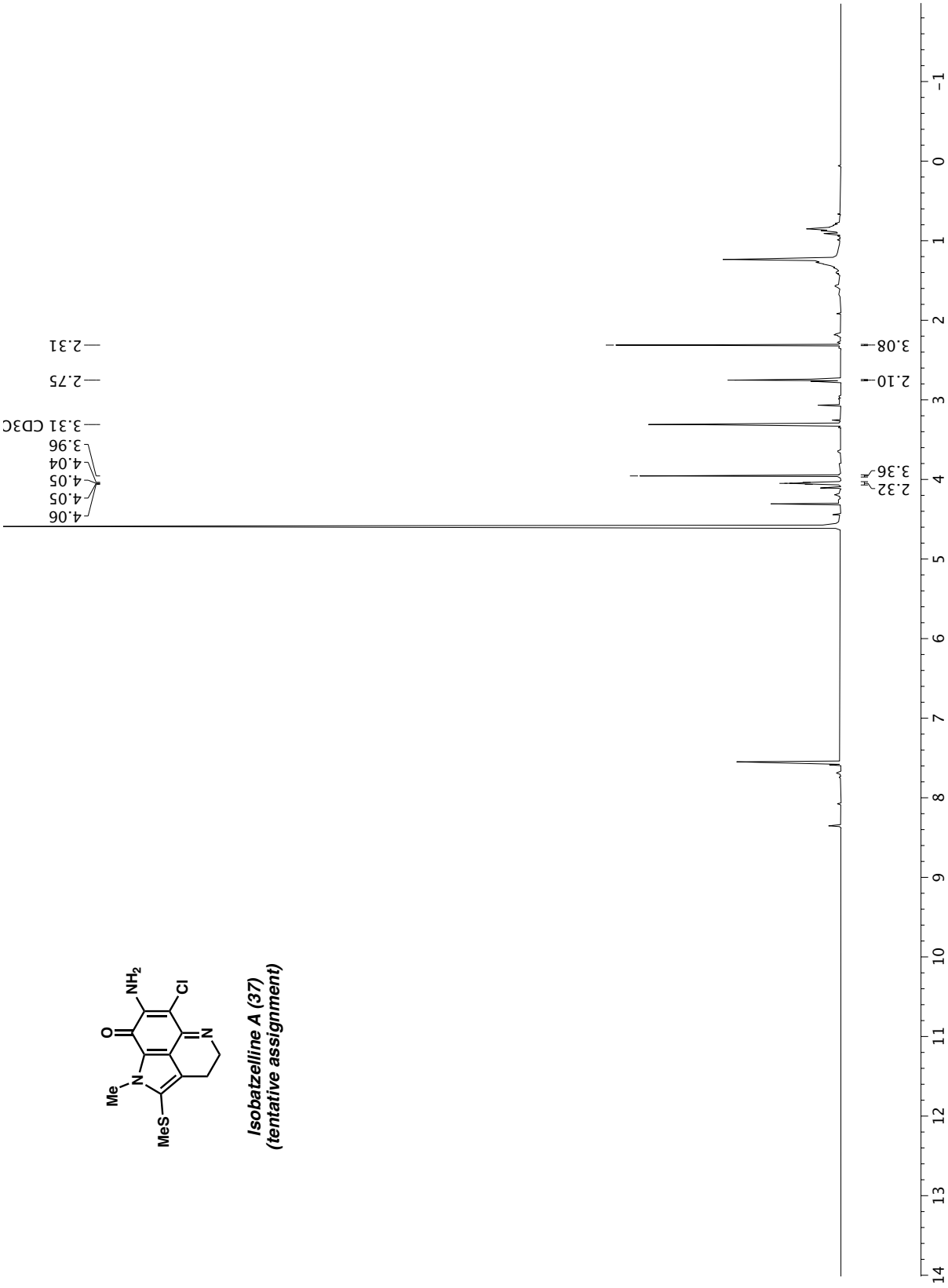
^{1}H NMR (400 MHz, MeOD) of isobatzelline B TFA salt (**32**).



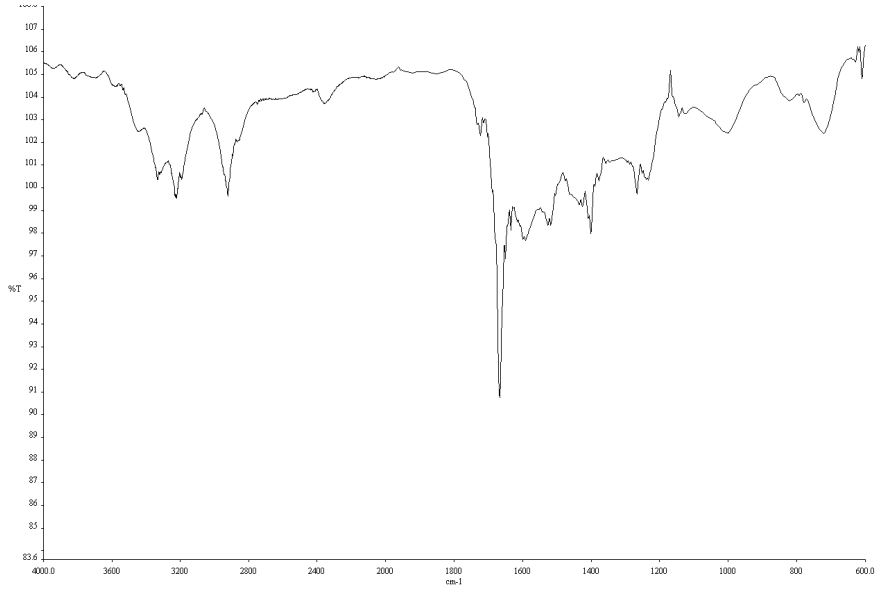
Infrared spectrum (Thin Film, NaCl) of isobatzelline B (**32**).



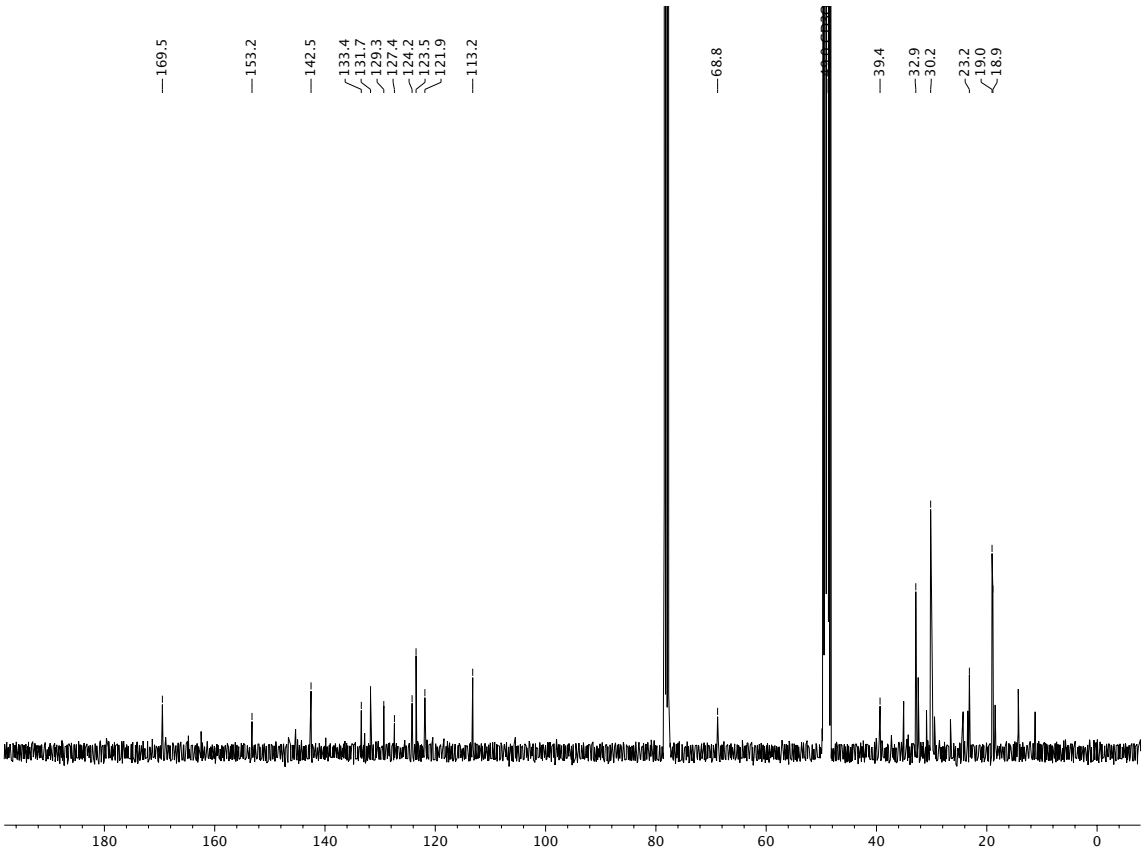
^{13}C NMR (100 MHz, MeOD) of isobatzelline B TFA salt (**32**).



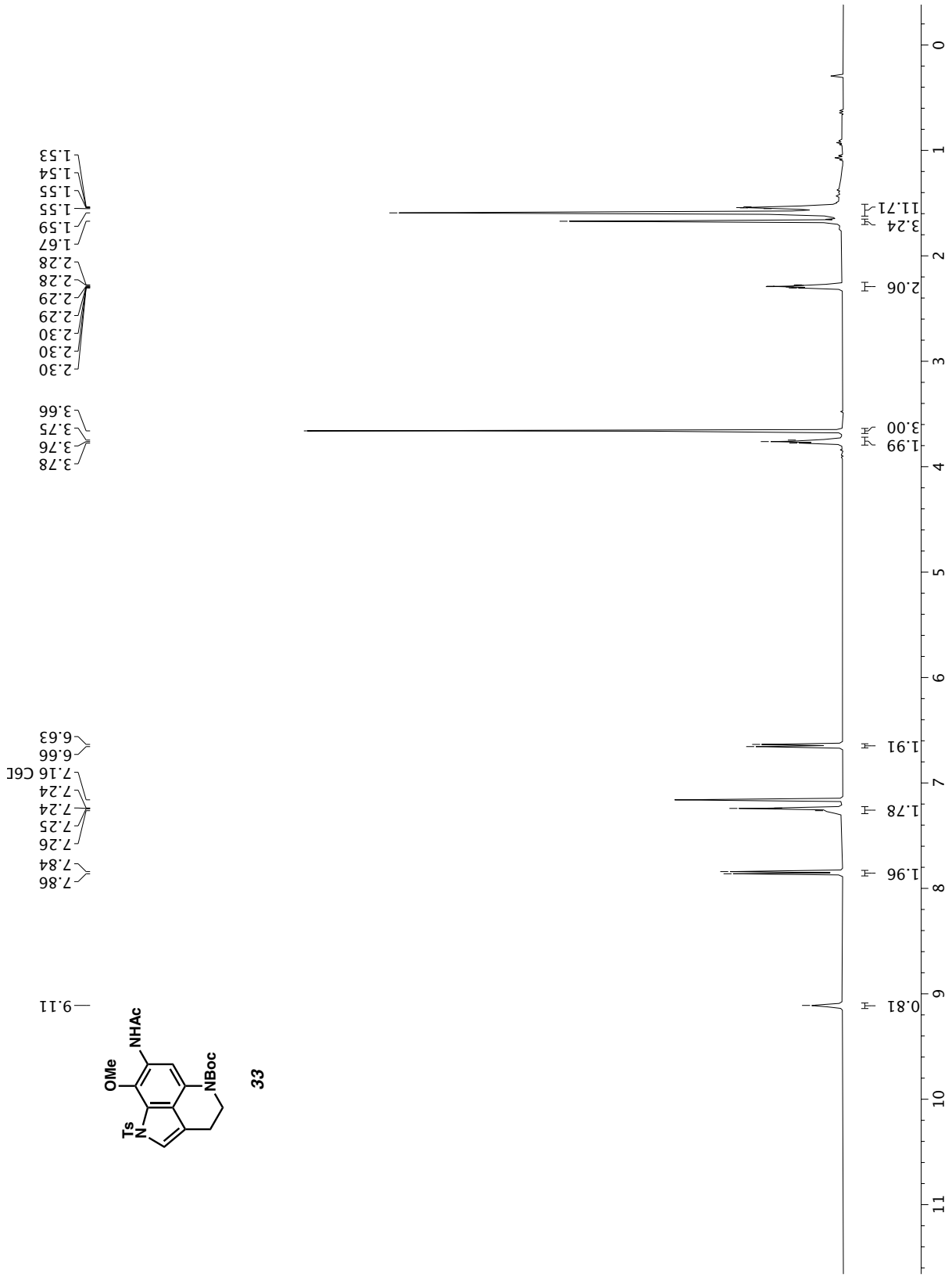
^{1}H NMR (400 MHz, 1:1 MeOD:$CDCl_3$) of isobatzelline *A* (**37**).



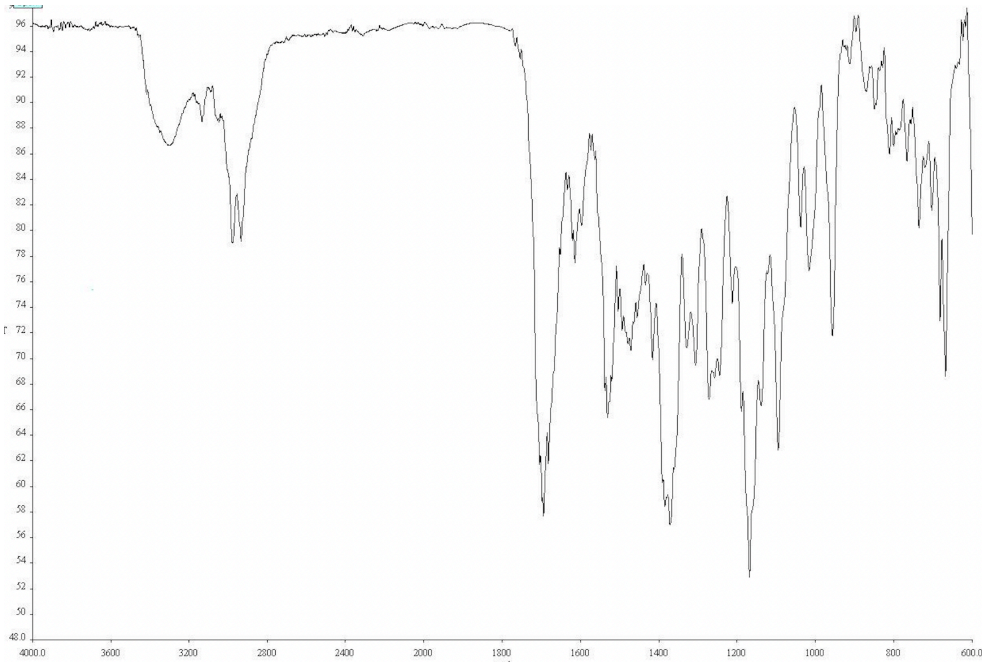
Infrared spectrum (Thin Film, NaCl) of isobatzelline A (**37**).



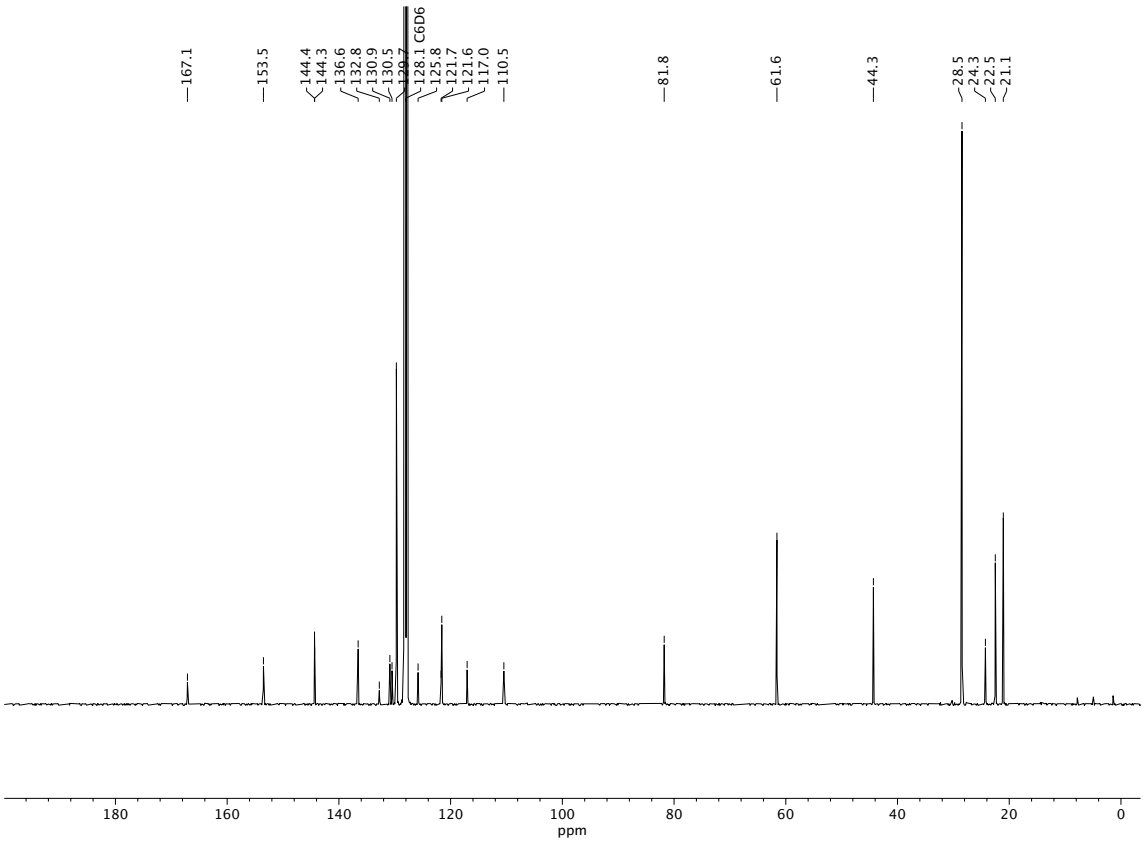
^{13}C NMR (100 MHz, 1:1 MeOD:$CDCl_3$) of decomposed isobatzelline A (**37**).



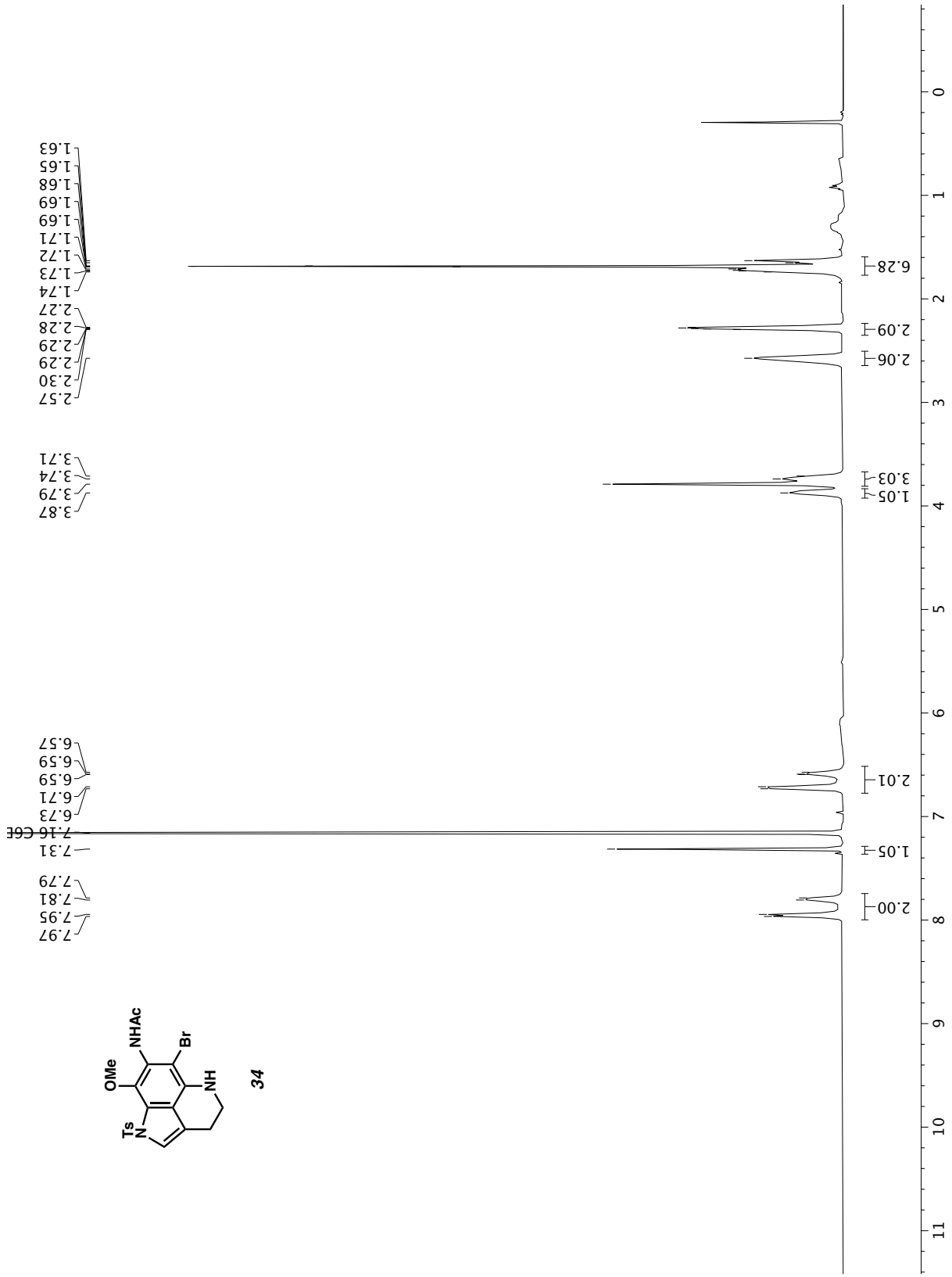
^{1}H NMR (400 MHz, C_6D_6) of compound (**33**).



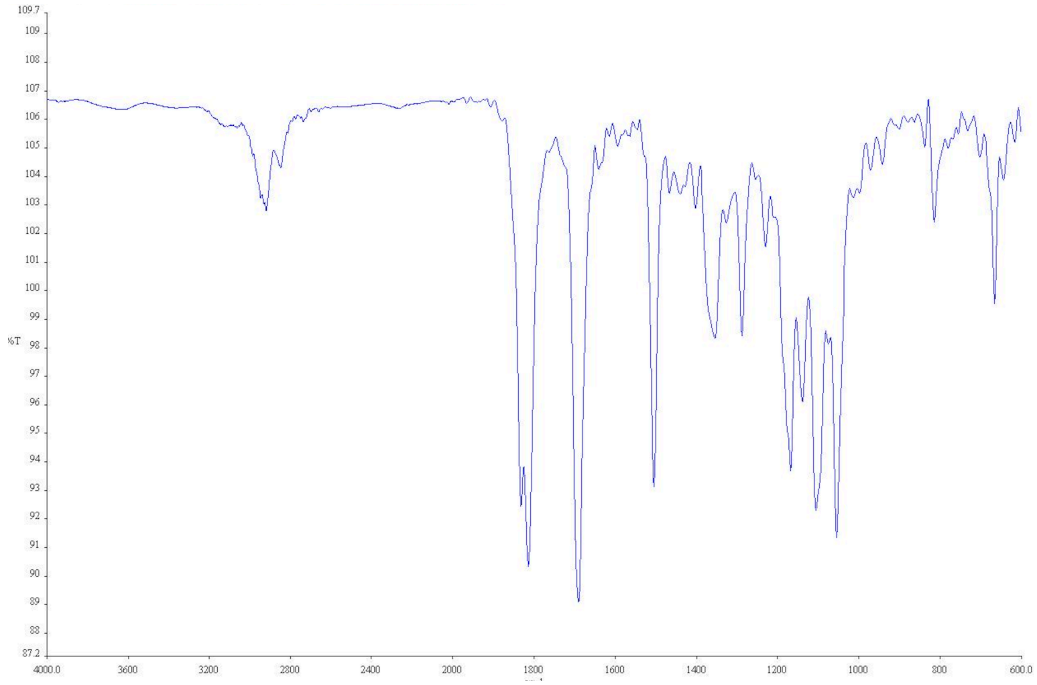
Infrared spectrum (Thin Film, NaCl) of compound **33**.



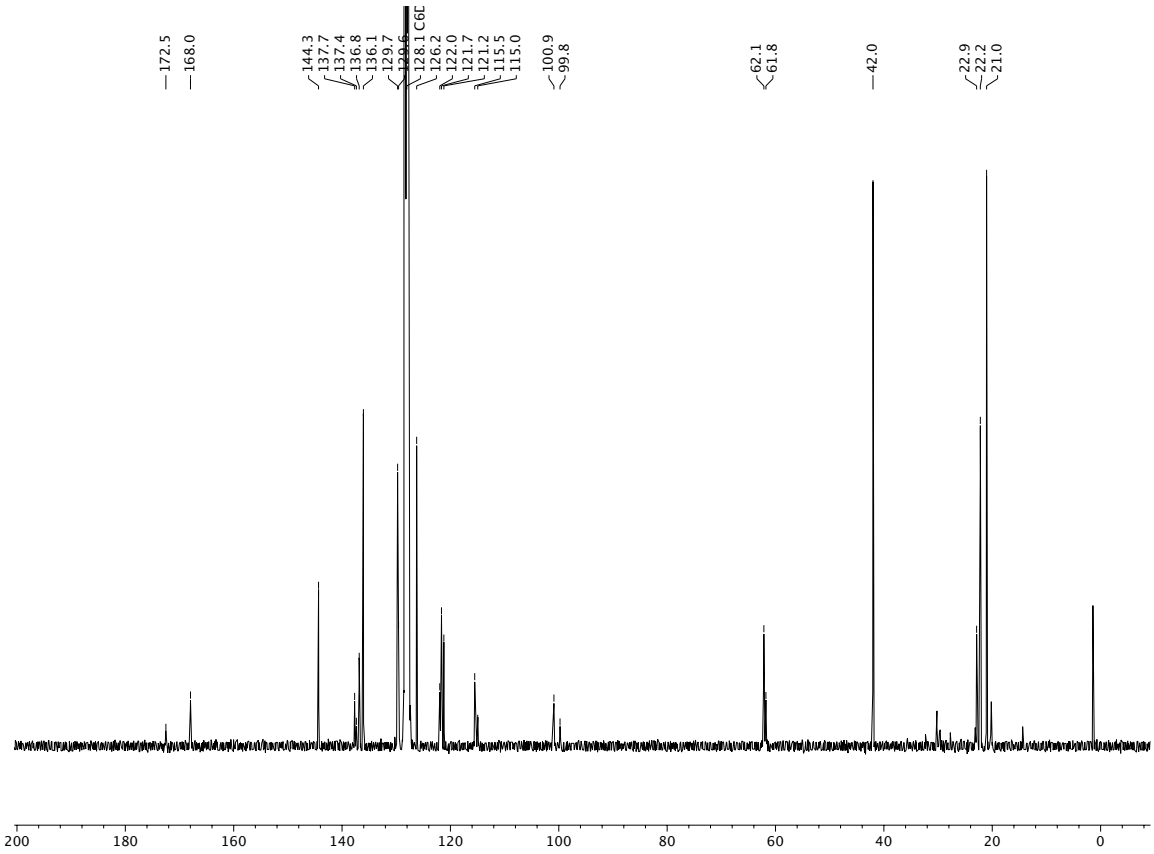
^{13}C NMR (100 MHz, C_6D_6) of compound **33**.



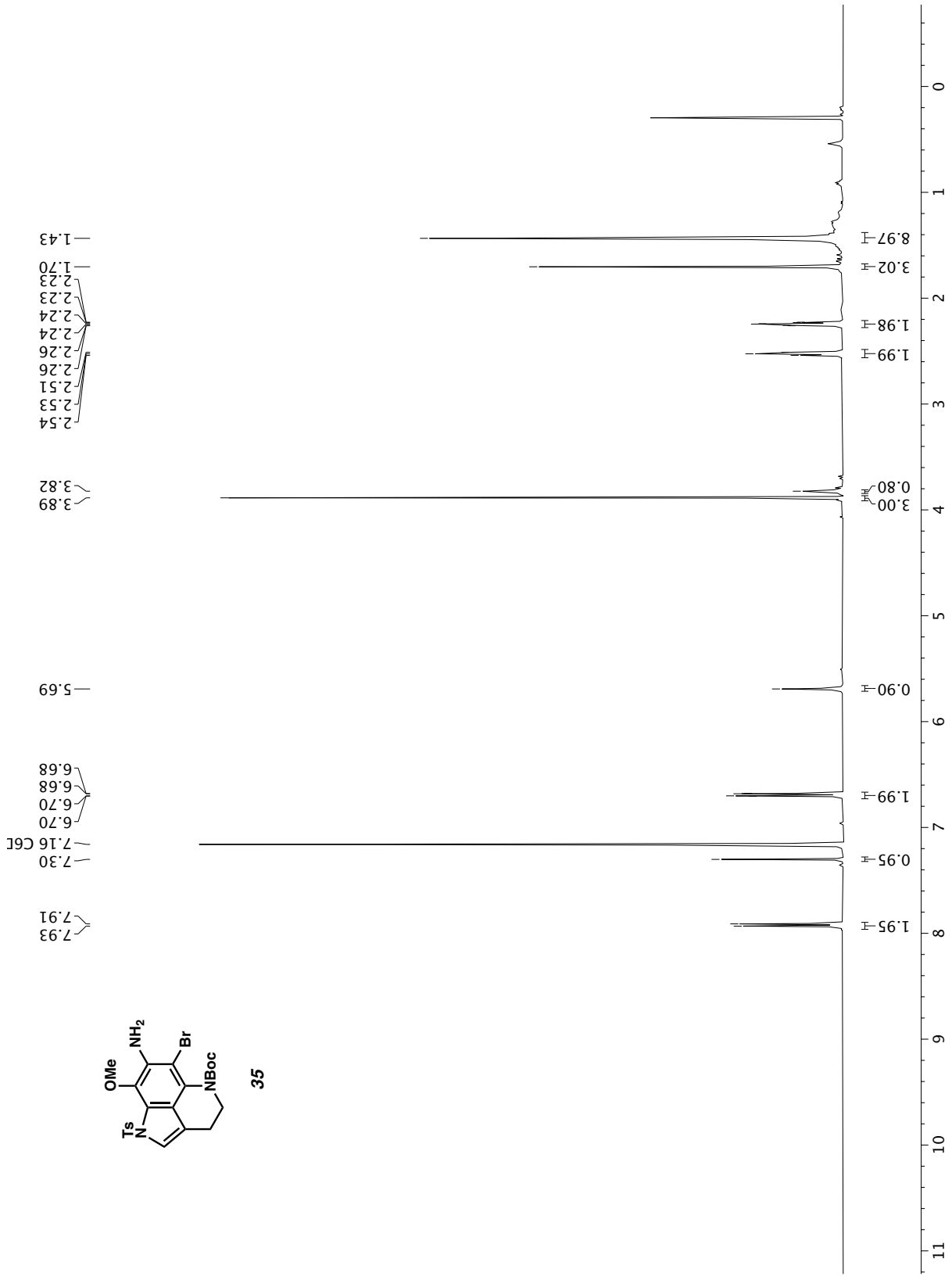
^{1}H NMR (400 MHz, C_6D_6) of compound (**34**).



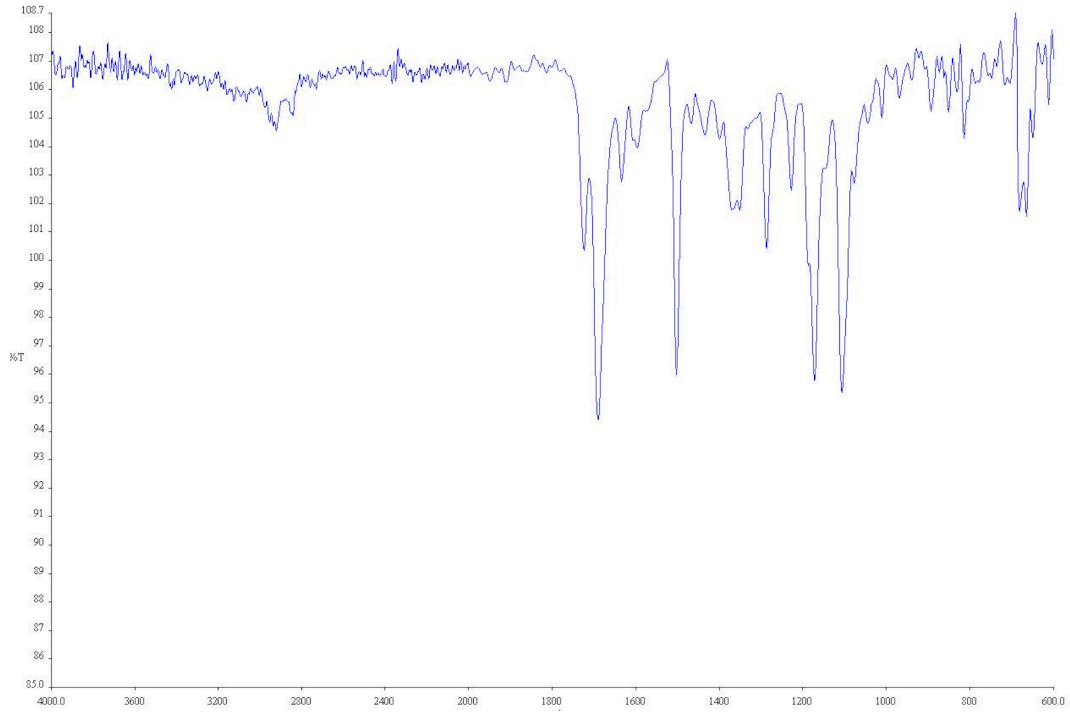
Infrared spectrum (Thin Film, NaCl) of compound **34**.



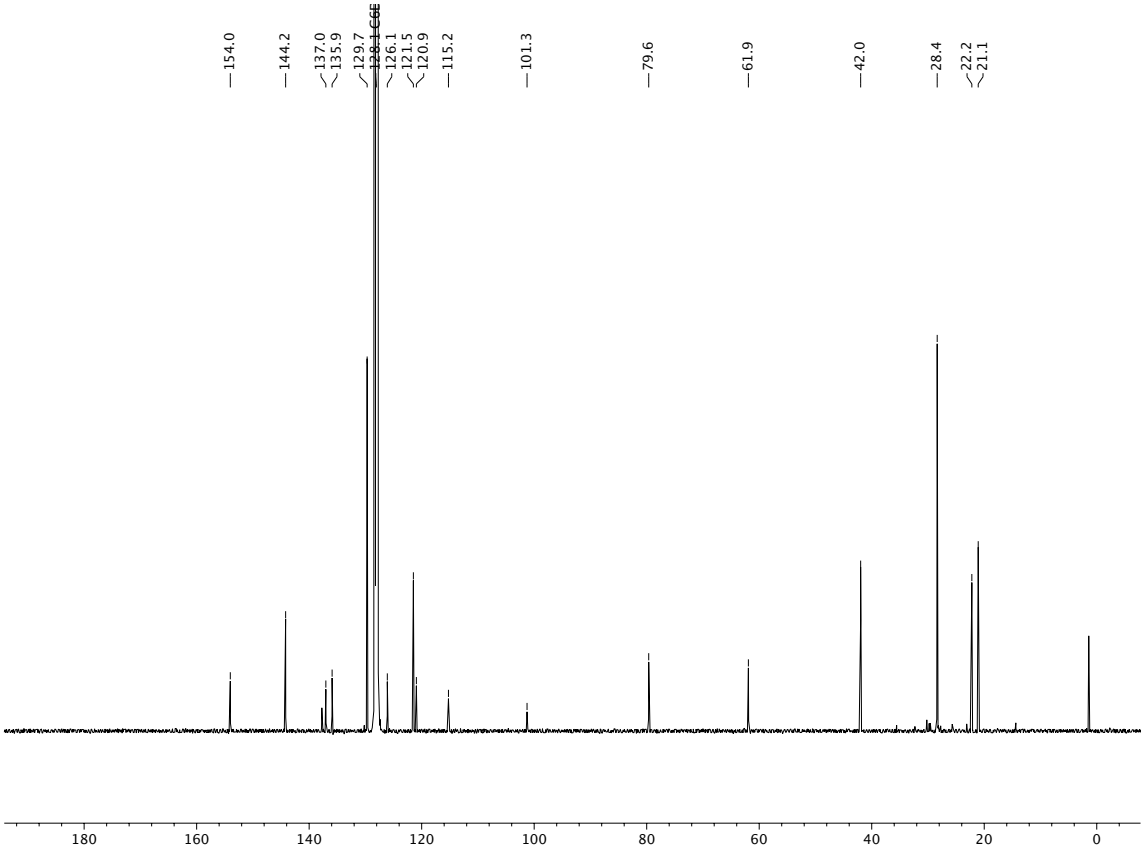
^{13}C NMR (100 MHz, C_6D_6) of compound **34**.



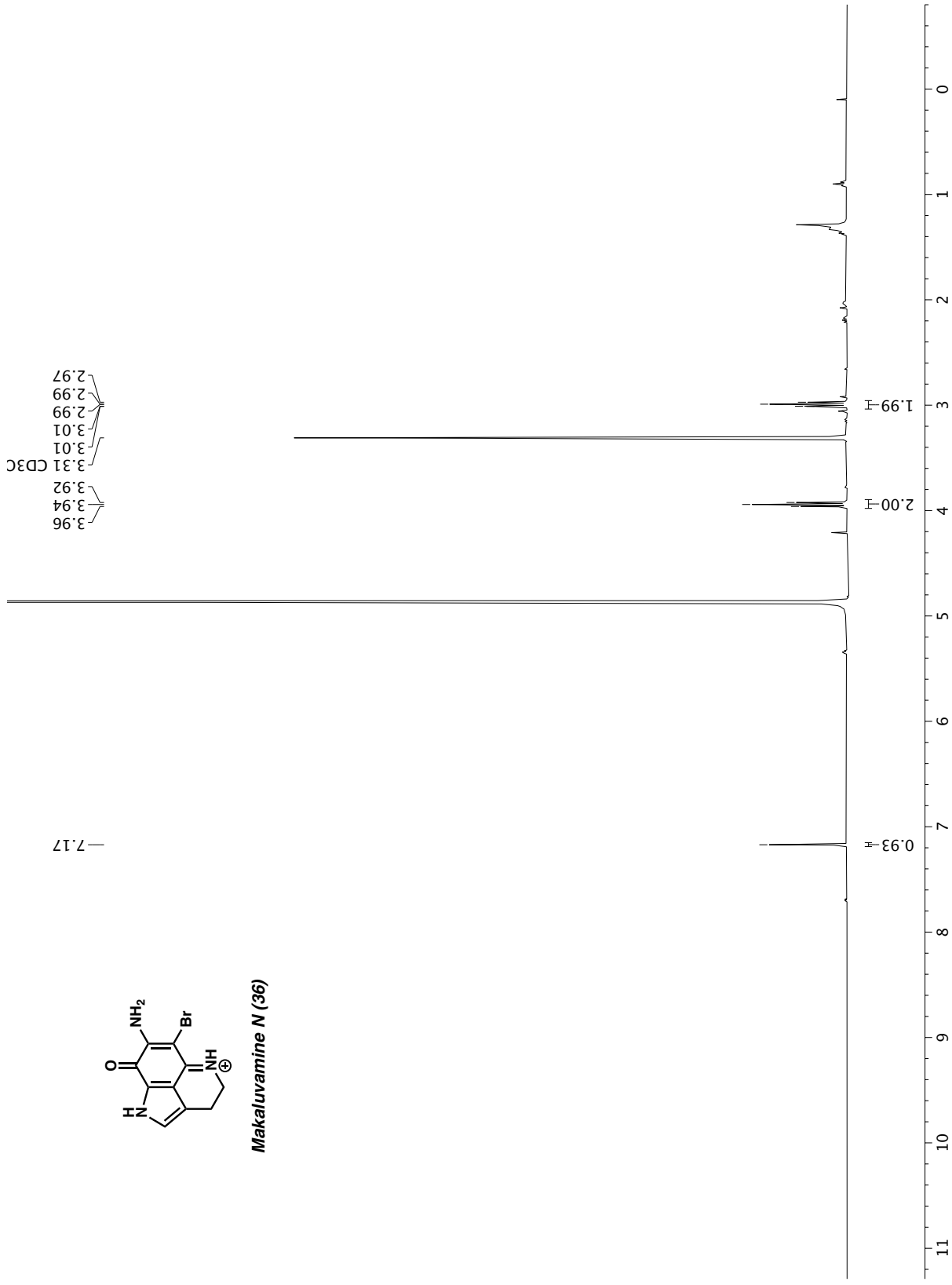
^{1}H NMR (400 MHz, C_6D_6) of compound (**35**).



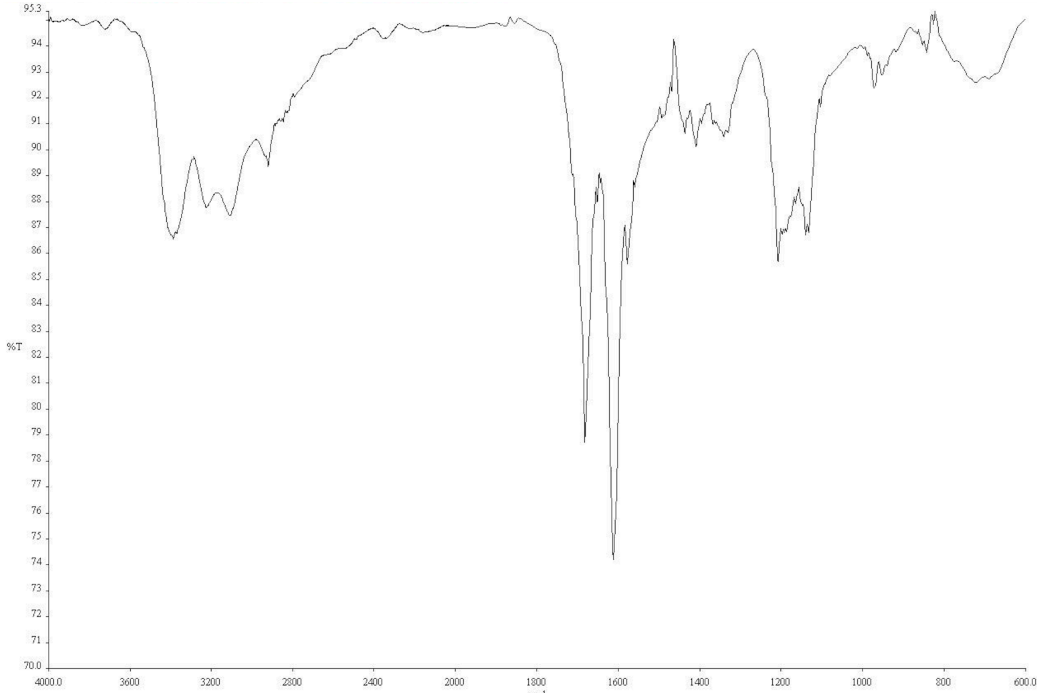
Infrared spectrum (Thin Film, NaCl) of compound **35**.



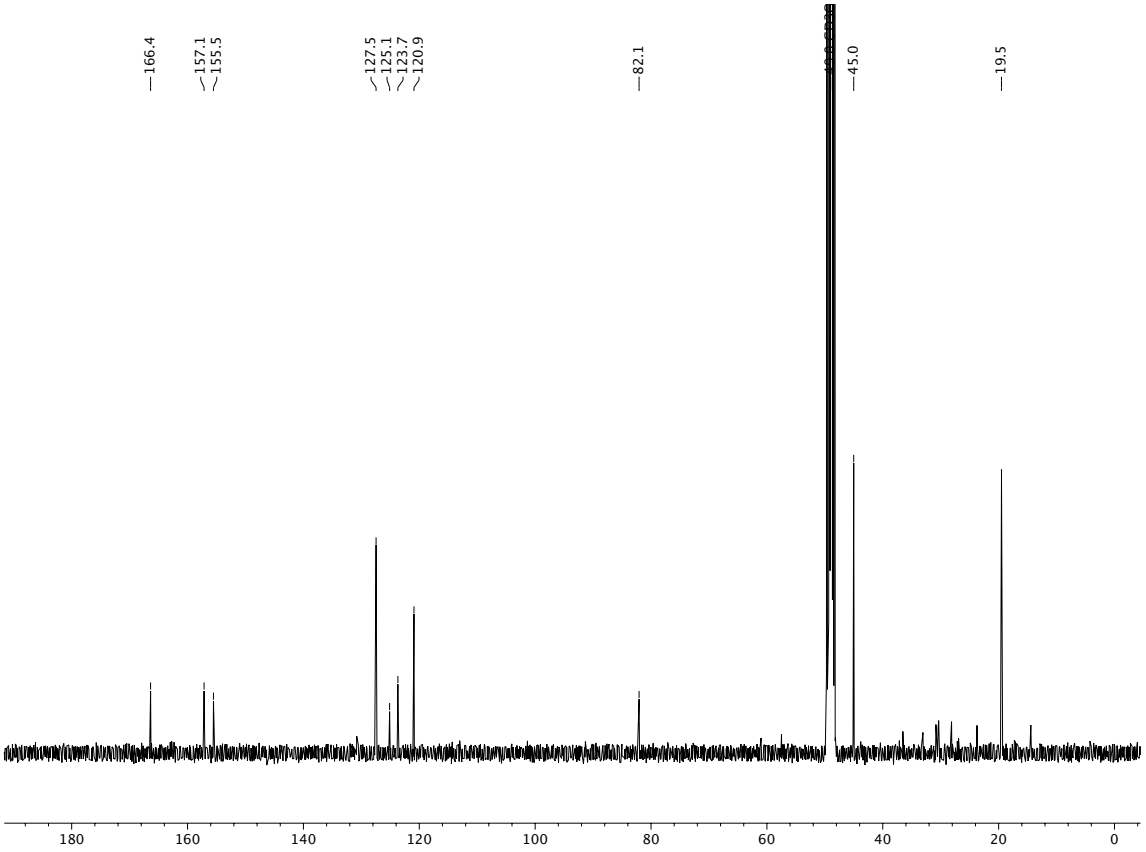
^{13}C NMR (100 MHz, C_6D_6) of compound **35**.



^{1}H NMR (400 MHz, MeOD) of makaluvamine N (**36**).



Infrared spectrum (Thin Film, NaCl) of makaluvamine N (**36**).



^{13}C NMR (100 MHz, MeOD) of makaluvamine N (**36**).