Concise total syntheses of (–)-Jorunnamycin A and (–)-Jorumycin enabled by asymmetric catalysis

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The bis-tetrahydroisoquinoline (bis-THIQ) natural products have been studied intensively over the past four decades for their exceptionally potent anticancer activity, in addition to strong gram-positive and -negative antibiotic character. Synthetic strategies toward these complex polycyclic compounds have relied heavily on electrophilic aromatic chemistry, such as the Pictet-Spengler reaction, that mimics their biosynthetic pathways. Herein we report an approach to two bis-THIQ natural products, jorunnamycin A and jorumycin, that instead harnesses the power of modern transition-metal catalysis for the three major bond-forming events and proceeds with high efficiency (15 and 16 steps, respectively). By breaking from biomimicry, this strategy allows for the preparation of a more diverse set of non-natural analogs.

The bis-tetrahydroisoquinoline (bis-THIQ) natural products have been studied intensively by chemists and biologists alike during the 40+ years since their initial discovery due to their intriguing chemical structures, potent biological activities, and unique mechanisms of action (*1*, *2*). Jorumycin (**1**, Fig. 1) and its congeners ecteinascidin 743 (Et 743, **2**) and jorunnamycin A (**3**) possess a pentacyclic carbon skeleton, highly oxygenated ring termini, and a central pro-iminium ion (manifested either as a carbinolamine or an α-aminonitrile motif). This latter functionality serves as an alkylating agent *in vivo*, resulting in covalent modification of DNA in a process that ultimately leads to cell death (*3*). The promise of these natural products as anticancer agents has been realized in the case of Et 743 (Yondelis®, trabectedin), which has been approved in the US, Europe, and elsewhere for the treatment of a variety of drug-resistant and unresectable soft-tissue sarcomas and ovarian cancer (*3*). Unfortunately, although **2** is available from nature, isolation of one gram of the drug would require more than one ton of biological material. For this reason, the successful application of **2** as an antitumor agent has necessitated its large-scale chemical synthesis, a 21-step process that begins with cyanosafracin A, a fermentable and fully functionalized bis-THIQ natural product (*4*). This has restricted medicinal chemistry endeavors via this route to the production of only compounds with a high degree of similarity to the natural products themselves.

Intriguingly, although **1** and **3** possess quinone rings, these moieties are rapidly reduced in cells to their hydroquinone oxidation states, more closely resembling those of **2** (*5*). These highly electron-rich functional groups are key components in the biosynthetic pathways of the bis-THIQ's, which are forged by the action of Pictet–Spenglerase enzymes (*6*, *7*). Previously reported chemical syntheses of bis-THIQ natural products feature elegant and creative application of electrophilic aromatic substitution (EAS) chemistry for the construction of one or more of the THIQ motifs. Though highly enabling, this approach has also limited the synthesis of non-natural analogs to highly natural product-like derivatives. As a key example, despite the scores of analogs produced over the past few decades (*8–11*), the majority of the derivatives focus on substitution of the heteroatom moiety appended to the B-ring (cf. structure **4**, Fig. 1), and only a select few possess significant structural and substitutional variation around the aromatic or quinone A- and E-rings (*8–11*). Furthermore, derivatives possessing electron-withdrawing groups on these rings are inaccessible using biomimetic approaches, as these would inhibit the EAS chemistry used to construct the THIQs. This latter point is significant, as studies have indicated that the smaller bis-THIQ natural products such as **1** and **3** are more susceptible to metabolic degradation than Et 743 and other larger bis-THIQs (*12*, *13*), and the installation of electron-withdrawing groups is a commonly employed strategy to improve a drug molecule's metabolic stability (*14*).

Jorumycin has been the target of four total syntheses (*15–18*) and two semisyntheses (*19*, *20*) since its isolation in 2000 (*21*), and jorunnamycin A has frequently been prepared en route. Jorumycin displays IC_{50}'s of 0.24 nM vs. A549 lung cancer, 0.49 nM vs. DU145 prostate cancer, and 0.57 nM vs. HCT116 colon cancer (*17*, *19*, *21*), among others, thus offering immense therapeutic potential. Furthermore, jorumycin and jorunnamycin A are appealing targets for further synthetic elaboration: the oxygen substitution appended to the B-ring (cf. structure **4**, X = OH, Fig. 1) could allow rapid diversification to the ecteinascidin, saframycin, safracin, and renieramycin scaffolds (*1*). To overcome the limitations of the current state of the art with respect to analog diversity, we sought an alternative, non-biomimetic route to these natural products.

Specifically, we envisioned the retrosynthetic strategy shown in Fig. 2A. We posited that a late stage oxygenation event to provide jorumycin (**1**) would greatly simplify the construction of the precursor, pentacycle **6**. We then considered disconnection of the central C-ring (cf. Fig. 1) through cleavage of the lactam moiety in **6**, providing bis-THIQ compound **7**. Critically, bis-THIQ structure **7** was recognized as a potential product of an enantioselective hydrogenation of bis-isoquinoline **8**. The central biaryl bond of **8** could be formed through a C–H cross-coupling reaction, leading to isoquinoline monomers **9** and **10**, thus greatly simplifying the synthetic challenge. As a key advantage, isoquinolines **9** and **10** could be prepared through the application of any known method, not limited only to those requiring highly electron-rich and α-nucleophilic species. Crucially, this approach would allow access to the natural products themselves, as well as derivatives featuring substantial structural and/or electronic variation.

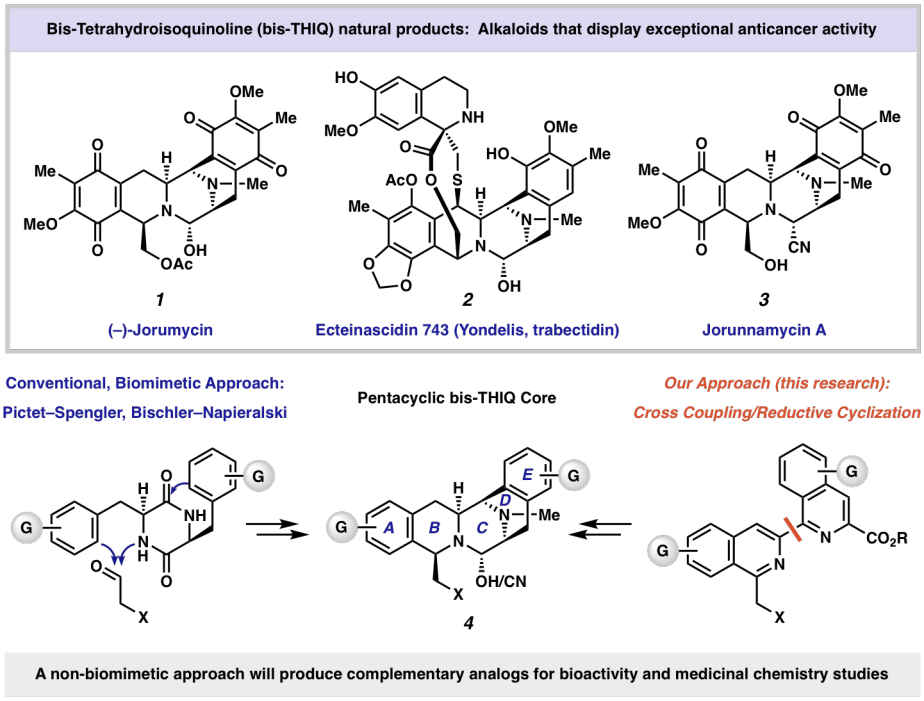


Fig. 1. bis-Tetrahydroisoquinoline natural products. Jorumycin (1), ecteinascidin 743 (2), and jorunnamycin A (3). Me, methyl; Ac, acetyl; COAc, pyruvyl; X, oxygen or nitrogen substitution; G, oxygen or carbon substitution; R, generic alkyl substitution.

As shown in Fig. 2B, we initiated our synthetic studies with the Sonogashira coupling of aryl bromide **11** (available in two steps from 3,5-dimethoxybenzaldehyde, see Supplementary Materials) with *tert*-butyldimethylsilyl propargyl ether (**12**); simply adding solid hydroxylamine hydrochloride to the reaction mixture after the coupling provided oxime-bearing alkyne **13** in 99% yield. Catalytic silver(I) triflate activated the alkyne toward nucleophilic attack by the oxime, directly generating isoquinoline *N*-oxide **9** in 77% yield on up to a 12-gram scale (*22*). Next, we began our synthesis of isoquinoline triflate **10** by using aryne-based methodology developed in our laboratories (*23*). Silyl aryl triflate **14** (available in 3 steps from 2,3-dimethoxytoluene, see Supplementary Materials) was treated with cesium fluoride to generate the corresponding aryne intermediate *in situ* (not shown), which underwent aryne acyl-alkylation with *in situ* condensation to provide 3-hydroxy-isoquinoline **16** in 45% yield. Reaction with trifluoromethanesulfonic anhydride provided electrophilic coupling partner **10** in 94% yield.

With working routes to both isoquinoline monomers in hand, we turned our attention to the palladium-catalyzed cross-coupling reaction which would be used to construct the carbon skeleton of jorumycin. We were pleased to find that isoquinolines **9** and **10** were efficiently coupled under modified conditions developed by Fagnou and co-workers to provide bis-isoquinoline **18** in 94% yield on a 7-gram scale (*24*). This large-scale application of C–H activation likely proceeds through a transition state similar to **17** and allows for the direct construction of **18** without the need for prefuctionalization (*25*). The excess of *N*-oxide **9** required to achieve maximum levels of efficiency appears to be only a kinetic factor, as all excess **9** was recovered after the reaction.

At this stage, we sought to install the level of oxidation necessary to initiate our hydrogenation studies (Fig. 2C). Specifically, this required selective oxidation of the nitrogen-adjacent methyl and methylene groups on the B- and D-rings, respectively. We attempted a double-Boekelheide rearrangement to transpose the *N*-oxidation to both *C*–positions simultaneously, effecting formal C–H oxidation reactions (*26*). Unfortunately, after oxidation to intermediate bis-*N*-oxide **19**, only the B-ring azine underwent rearrangement. Despite this setback, we found that it was possible to parlay this reactivity into a one-pot protocol by adding acetic anhydride upon complete oxidation, providing differentially protected diol **20** in 62% yield. N–O bond cleavage and oxyl-mediated oxidation provided bis-isoquinoline **8** in two additional steps. To date, we have produced more than 5 grams of bisisoquinoline **8**.

With a scaleable route to isoquinoline **8** in hand, we turned our attention to the key hydrogenation event. If successful, this strategic disconnection would add four molar equivalents of hydrogen, create four new stereocenters, and form the central C-ring lactam. Although the enantioselective hydrogenation of nitrogen-based heterocycles is a well-studied reaction, isoquinolines are possibly the most challenging and least investigated substrates (*27*). To our knowledge only four reports existed prior to our studies that describe asymmetric isoquinoline hydrogenation, and only one appears to tolerate 1,3-disubstitution patterns (*28–31*).

We nonetheless noted that metal-catalyzed imine and carbonyl reduction is a comparatively successful and well-studied transformation (*32*, *33*). We were drawn to the iridium catalyst developed by scientists at Ciba-Geigy (now Syngenta) for asymmetric ether-directed imine reduction in the preparation of Metolachlor (*34*). Considering the positioning of the hydroxymethyl group appended

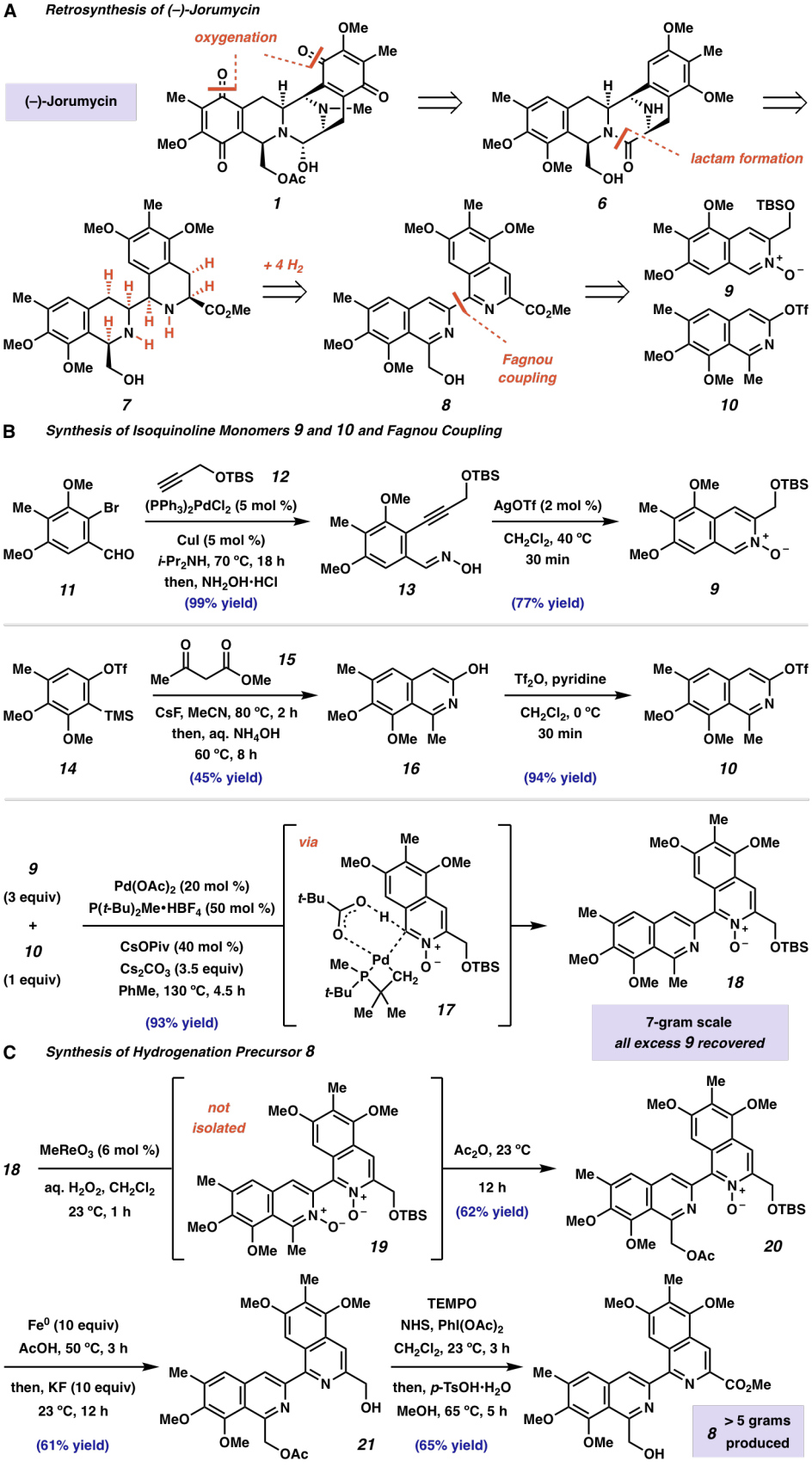
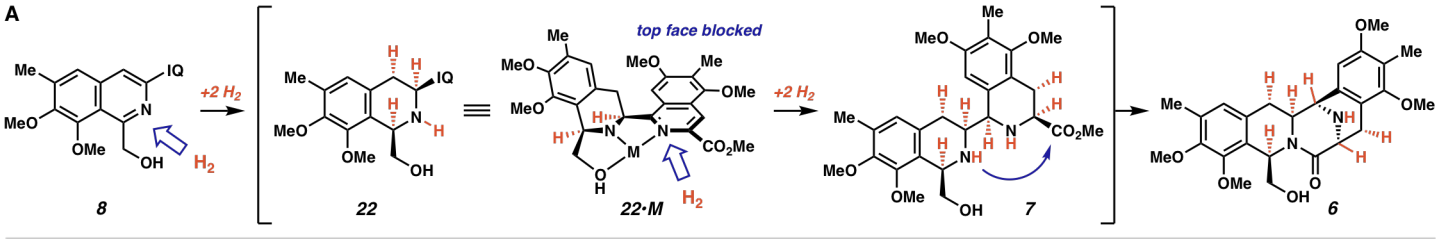


Fig. 2. Considerations for an orthogonal synthesis of jorunnamycin A and jorumycin. (**A**) Retrosynthetic analysis leading to a synthesis of jorumycin that deviates from previous synthetic strategies. (**B**) Isoquinoline **9** and **10** were synthesized in two steps each from aryl bromide **11** and *ortho*-silyl aryl triflate **14**, respectively. (**C**) Boekelheide rearrangement provided an efficient and scalable route to bis-isoquinoline **8** under mild conditions. TBS, *tert*-butyldimethylsilyl; Ph, phenyl; *i*-Pr, isopropyl; aq., aqueous; Tf, trifluoromethanesulfonyl, TMS, trimethylsilyl; MeCN, acetonitrile; *t*-Bu, *tert*-butyl; Piv, trimethyl-acetyl; equiv, molar equivalent; TEMPO, 2,2,6,6-tetramethylpiperidine-*N*-oxyl; NHS, *N*-hydroxysuccinimide; *p*-TsOH•H_2O, *para*-toluenesulfonic acid monohydrate.

to the B-ring of **8** and the electronic similarity of the adjacent C1–N □-bond to that of an imine, we posited that a similar catalytic system might be used to direct the initial reduction to this position (Fig 3). Furthermore, the chelation mode was attractive as a scaffolding element to enable enantioselective *Si*-face reduction. In keeping with previous observations (*28–31*), we anticipated that full B-ring reduction would provide *cis*-mono-THIQ **22** as the major product. We believed that **22** would then act as a tridentate ligand for a metal ion (although not necessarily the catalytically active species), and the three-dimensional coordination environment of metal-bound **22•M** would direct D-ring hydrogenation from the same face. Finally, the all-*syn* nature of **7** places the ester moiety in proximity to B-ring secondary amine, and we expected lactamization to be rapid. If successful, this self-reinforcing diastereoselectivity model would allow for control over the four new stereocenters and produce the bis-THIQ core in a single step.

Upon beginning our enantioselective hydrogenation studies, we found that we could identify trace amounts of conversion to mono-THIQ product **22** by using the catalyst mixture developed at Ciba-Geigy (*34*), thus confirming the accelerating effects of the pendent hydroxy directing group. Under these general conditions, we then performed a broad evaluation of more than 60 chiral ligands commonly used in enantioselective catalysis protocols (see Supplementary Materials). From this survey, we identified three ligands that provided **22** in at least 80% enantiomeric excess (ee) and with uniformly excellent diastereoselectivity (all >20:1 diastereomeric ratio, dr): (*S*)-(CF$_3$)-*t*-BuPHOX (**23**, Entry 2, 22% yield, –82% ee), (*S*,*S*)-Et-FerroTANE (**24**, Entry 3, 26% yield, –87% ee), and (*S*,*R*$_P$)-Xyliphos (**25**, Entry 4, 30% yield, 80% ee). After evaluating these ligand classes further, we identified (*S*,*R*$_P$)-BTFM-Xyliphos (**26**) (*35*) as a strongly activating ligand that provided mono-THIQ **22** in 83% yield, >20:1 dr, and in a remarkable 94% ee (Entry 5). Moreover, we were elated to find that ligand **26** formed a catalyst that provided pentacycle **6** as a single diastereomer in 10% yield. Further evaluation of the reaction parameters revealed that increasing temperature provided higher levels of reactivity, albeit at the expense of enantioselectivity (Entry 6, 31% yield of **22**, 87% ee, 43% yield of **6**). The best results were achieved by performing the reaction at 60 °C for 18 hours and then increasing the temperature to 80 °C for 24 hours. Under these conditions, **6** was isolated in 59% yield with >20:1 dr and 88% ee (Entry 7) (*36*). In the end, doubling the catalyst loading allowed us to isolate **6** in 83% yield, also with



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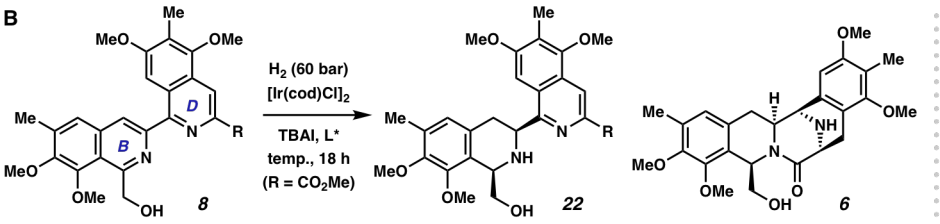


entry	catalyst loading	ligand	temperature	yield *22**	ee *22*†	yield *6**	dr *6*‡	ee *6*†
1	5 mol %	25	23 °C	2%	ND	0%	--	--
2	5 mol %	23	60 °C	22%	–82%	0%	--	--
3	5 mol %	24	60 °C	26%	–87%	0%	--	--
4	5 mol %	25	60 °C	30%	80%	0%	--	--
5	5 mol %	26	60 °C	83%	94%	10%	>20:1	ND
6	5 mol %	26	80 °C	31%	87%	43%	>20:1	ND
7	5 mol %	26	60 °C → 80 °C§	7%	94%	59%¶	>20:1	88%
8	10 mol %	26	60 °C → 80 °C§	3%	94%	83%¶	>20:1	88% (>99%)#

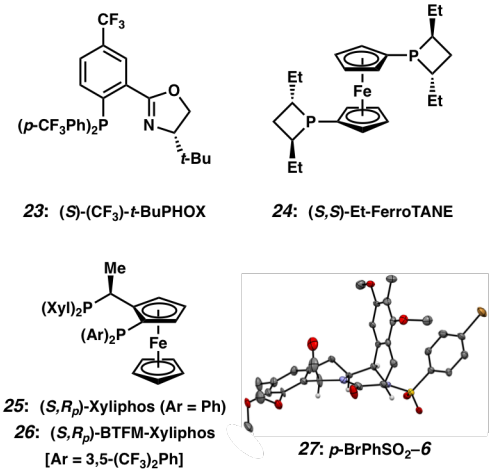


Fig 3. Development of the enantioselective hydrogenation. (A) Stereochemical rationale for the enantio- and diastereoselective hydrogenation of bis-isoquinoline **8**. **(B)** Optimization of the hydrogenation reaction. Unless otherwise noted, all reactions were performed in 9:1 toluene:acetic acid (0.02 M) using a 1.2:1 ligand:metal ratio and a 3:1 iodide:metal ratio under a hydrogen atmosphere (60 bar) for 18 h. *Measured by UHPLC-MS UV absorption vs. 1,3,5-trimethoxybenzene internal standard unless otherwise noted. †Measured by chiral HPLC analysis. ‡Measured by ^{1}H-NMR analysis of the crude reaction mixture. §Reaction performed at 60 ºC for 18 h, then the temperature was raised to 80 ºC and maintained at that temperature for 24 h. ¶Yield of isolated product after column chromatography using 10.5 mol % **26** in entry 7 and 21 mol % **26** in entry 8. #After one recrystallization. IQ, 3-carbomethoxy-5,7-dimethoxy-6-methylisoquinolin-1-yl; dr, diastereomeric ratio (major isomer vs. all others); ee, enantiomeric excess; cod, 1,5-cyclooctadiene; TBAI, tetra-*n*-butylammonium iodide; ND, not determined; Et, ethyl; Xyl, 3,5-dimethylphenyl; Ar, aryl; BTFM, 3,5-bis-trifluoromethylphenyl.

>20:1 dr and 88% ee (Entry 8) on greater than 1 mmol scale. bis-THIQ **6** could be easily accessed in enantiopure form (>99% ee by HPLC) by crystallization from a slowly evaporating acetonitrile solution, and we were able to confirm the relative and absolute stereochemistry by obtaining an x-ray crystal structure on corresponding 4-bromophenyl sulfonamide **27**. Within the context of this synthesis, the relatively high catalyst loading (20 mol % Ir) is mitigated by the substantial structural complexity generated in this single transformation.

At this stage, we were poised to investigate the third and final key disconnection from our retrosynthetic analysis, namely, late-stage C–H oxidation of the arenes (Fig. 4). To set up this chemistry the piperazinone N–H of **6** was methylated under reductive amination conditions in quantitative yield. Despite numerous attempts to effect catalytic C–H oxidation on this advanced intermediate, we found that a two-step procedure was necessary instead. We were able to chlorinate both of the remaining aromatic positions, providing bis-THIQ **28** in 68% yield. From here, we once again turned to catalysis, this time for the oxygenation of aryl halides. After extensive investigation, we found that Stradiotto and coworkers' recently developed protocol for the hydroxylation of aryl halides was uniquely effective (*37*). Further optimization revealed that the combination of adamantyl BippyPhos ligand with Buchwald's cyclometalated palladium(II) dimer was ideal (*38*), providing dihydroxylated bis-THIQ **29** in 46% yield, an impressive result for such a challenging coupling reaction on a sterically large, electron-rich, and Lewis-basic substrate in the final stages of the synthesis. Partial lactam reduction with cyanide trapping proceeded in 50% yield, and oxidation of the phenols provided jorunnamycin A (**3**) in only 15 linear steps. We isolated hemiacetal **30** in 33% yield, which was surprising given the generally low stability of acyclic hemiacetals. Finally, we developed conditions for the conversion of jorunnamycin A into jorumycin in a single step, providing **1** in 68% yield in 16 linear steps (*1*). Jorunnamycin A (**3**) and jorumycin (**1**) are produced in 0.24% and 0.17% yield, respectively, from commercially available materials, but key bis-THIQ **6**, the branching point for derivative synthesis, is accessed over 10 steps in 5.0% overall yield on greater than 500 mg scale. These efforts are similar to Zhu and coworkers' elegant synthesis of jorumycin with regard to brevity (*16*).

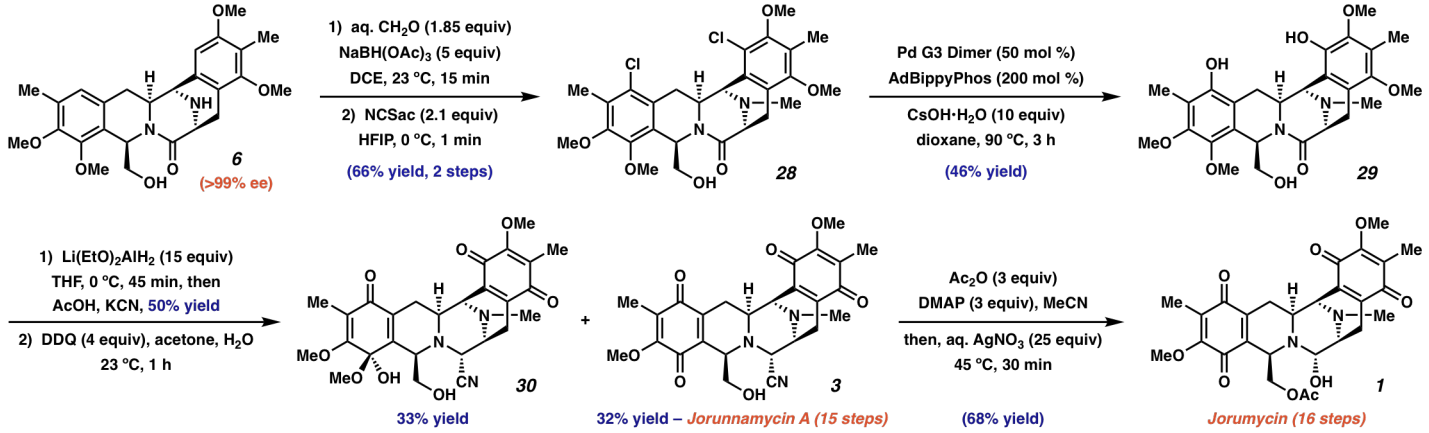


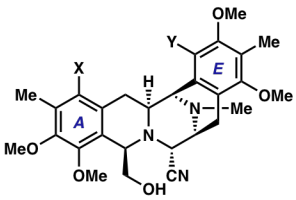
Fig. 4. Completion of jorunnamycin A and jorumycin. After the reductive cyclization, five and six steps, including a palladium-catalyzed hydroxylation event, were required for the complete synthesis of jorunnamycin A (**3**) and jorumycin (**1**), respectively. DCE, 1,2-dichloroethane; NCSac, *N*-chlorosaccharine; HFIP, 1,1,1,3,3,3-hexafluoroisopropanol; Ad, 1-adamantyl; Pd G3 Dimer, (2'-Amino-1,1'-biphenyl-2-yl)methanesulfonatopalladium(II) dimer; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMAP, 4-dimethylaminopyridine.

Central to the anticancer activity of the bis-THIQ natural products is the capacity to alkylate DNA upon loss of water or cyanide from the central carbinolamine or α-cyanoamine, respectively (*39*). After alkylation, compelling evidence suggests formation of reactive oxygen species (*5*) or DNA-protein cross-links (*8*, *40*) leads to cell-cycle arrest or cell death. We therefore synthesized analogs **31**–**34**, which feature the non-oxygenated framework as well as all permutations of partial and full oxygenation. The activity of this series would allow us to determine the relative importance of the location and degree of oxygenation on the A- and E-rings, the structure-activity relationships of which have not previously been explored.

With the backdrop that preclinical efficacy studies are complex and demanding, we conducted very preliminary studies to probe the relative cytotoxicity of synthetic analogues **31**–**34** and established that modifying one site on the scaffold greatly diminishes cytotoxicity, whereas other modifications conserved cytotoxicity. The cytostatic and cytotoxic properties of **31**–**34** were determined using long-term, growth-maximizing assay conditions against 29 cancer cell lines known to be responsive in vitro to other general cytotoxics (Fig. 5, see Supplementary Materials) (*41*, *42*). Cells were routinely assessed for mycoplasma contamination using a multiplex PCR method and STR profiling for cell-line authentication. This methodology differs markedly from the standard 72-hour, luminescence-based cytotoxicity assays employed most commonly for in vitro quantification of drug response. This approach was chosen as it is specifically well suited to determine the activity of compounds wherein anti-proliferative effects occur over a longer time period than standard cytotoxic agents. Perhaps not surprisingly, removal of both phenolic oxygens resulted in a complete loss in activity (i.e., **31,** all IC50's > 1 μM),

while fully oxygenated bis-THIQ **34** showed cytotoxicity. The most notable results were provided by **32** and **33**, which possess A- and E-ring monohydroxylation, respectively. While compound **32**, which is devoid of E-ring oxygenation, showed diminished activity, we were surprised to find that compound **33** featuring only E-ring oxygenation maintained a similar activity profile to fully oxygenated **34** (see Supplementary Materials). At the moment, we believe these data to be the result of general cytotoxicity, as opposed to cancer cell-specific activity. As a reference, three out of four previously known anticancer agents that function through general cytotoxicity showed similar levels of activity in our model. While more sophisticated studies are necessary to determine actual efficacy, the ability to delete one oxygen atom and retain activity is both intriguing and unrexpected.

The use of catalysis, rather than native reactivity, is a key advantage to our synthesis, allowing us to expedite access to both the natural products themselves, and also biologically relevant derivatives.



31: X = Y = H → both rings partially deoxygenated
32: X = OH, Y = H → E-ring partially deoxygenated
33: X = H, Y = OH → A-ring partially deoxygenated
34: X = Y = OH → both rings fully oxygenated

Selective, partial oxygenation allows basic SAR development

Compound	Mean IC_{50} (nM)	Description
31	≥1000	full deoxygenation
32	708	partial (E-ring) deoxygenation
33	233	partial (A-ring) deoxygenation
34	397	full oxygenation
Carfilzomib	4	Proteosome inhibitor
Cisplatin	202	DNA binder
MK8745	360	Aurora kinase inhibitor
MMAE	438	tubulin binder

· Cytotoxicity diminished upon E-ring deoxygenation · · Cytotoxicity maintained upon A-ring deoxygenation ·

Fig. 5. Biological evaluation of non-natural analogs. Leveraging the non-biomimetic approach to A- and E-ring construction allows for the production of previously inaccessible bis-THIQ analogs. Data reported are IC_{50}'s measured from whole cells treated for 6 days using a 1:5 dilution series to cover a range of concentrations from 0–1 μM from an initial 10 mM DMSO stock solution of the analog in question. The IC_{50} of each compound was calculated as a function of population doublings from baseline. MMAE, monomethyl auristatin E.

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34. *S*,R_P-BTFM-Xyliphos (**27**) is produced and sold by Solvias AG and is licensed to Sigma-Aldrich Co., and Strem Chemicals under the name SL-J008-2.
35. The lower ee measured on isolated **6** as compared to isolated **22** can be rationalized by competitive (although minor), non-selective D-ring reduction leading to the same major diastereomer. See Supplementary Materials.
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SUPPLEMENTARY MATERIALS
Materals and Methods
Tables S1 to S13
Figures S1 to S4
NMR Spectra
References (*43-52*)

A Catalytic, Asymmetric Total Synthesis of (–)-Jorunnamycin A and (–)-Jorumycin

Eric R. Welin, Aurapat Ngamnithiporn, Max Klatte, Guillaume Lapointe, Christopher D. Gilmore, Pamela M. Tadross, Gerit M. Pototschnig, Martina S. J. McDermott, Dylan Conklin, Christopher K. Haley, Kenji Negoro, Emil Glibstrup, Christian U. Grünanger, Scott C. Virgil, Dennis J. Slamon, and Brian M. Stoltz*

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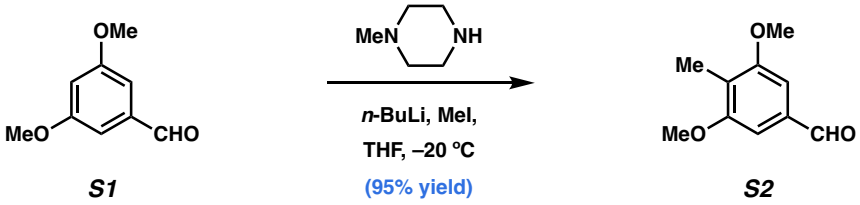
Supplementary Materials

Supplementary Materials

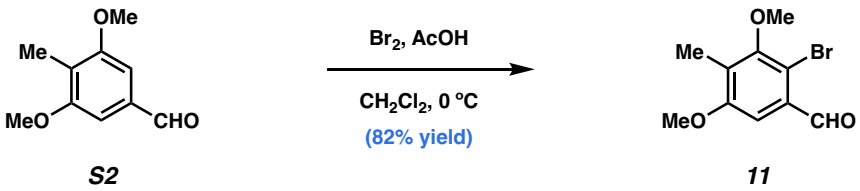
General Information. Unless stated otherwise, reactions were performed at ambient temperature (23 °C) in flame-dried glassware under an argon atmosphere using dry, deoxygentated solvents (distilled or passed over a column of activated alumina) (*43*). Commercially available reagents were used as received. Reactions requiring external heat were modulated to the specified temperatures using an IKAmag temperature controller. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 pre-coated plates (250 nm) and visualized by UV fluorescence quenching or potassium permanganate staining. Silicycle SiliaFlash P60 Academic Silica gel (particle size 40–63 nm) was used for flash chromatography. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. ^{1}H and ^{13}C NMR spectra were

recorded on a Varian Inova 500 (500 MHz and 126 MHz, respectively) and a Bruker AV III HD spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe (400 MHz and 101 MHz, respectively) and are reported in terms of chemical shift relative to $CHCl_3$ (δ 7.26 and 77.16, respectively). ^{19}F and ^{31}P NMR spectra were recorded on a Varian Inova 300 (282 MHz and 121 MHz, respectively). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant, integration). Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). Analytical chiral SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system with Chiralpak (AD-H) or Chiracel (OD-H) columns obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Center for Catalysis and Chemical Synthesis using an Agilent 6200 series TOF with an Agilent G1978A Multimode source in mixed (Multimode ESI/APCI) ionization mode. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. For X-Ray structure determination, low-temperature diffraction data (-and -scans) were collected on a Bruker AXS D8 VENTURE KAPPA diffractometer coupled to a PHOTON 100 CMOS detector with *K* radiation (= 1.54178 Å) from an IμS micro-source for the structure of compound P17208. The structure was solved by direct methods using SHELXS (*44*) and refined against F^2 on all data by full-matrix least squares with SHELXL-2014 (*45*) using established refinement techniques (*46*). All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the *U* value of the atoms they are linked to (1.5 times for methyl groups). Unless otherwise noted, all disordered atoms were refined with the help of similarity restraints on the 1,2- and 1,3-distances and displacement parameters as well as rigid bond restraints for anisotropic displacement parameters. Compound P17208 crystallizes in the orthorhombic space group $P2_12_12$ with one molecule in the asymmetric unit along with two molecules of isopropanol. The hydroxide group and both isopropanol molecules were disordered over two positions. The Flack parameter refines to be 0.138(9).

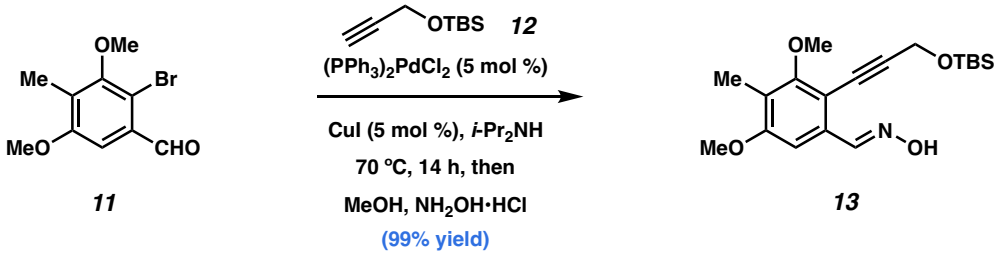
Synthesis of Isoquinoline-*N*-Oxide 9.



3,5-dimethoxy-4-methylbenzaldehyde (S2). The procedure was adapted from the method of Comins *et al.* (*47*). *N*-methylpiperazine (670 µL, 6.6 mmol, 1.1 equiv) was dissolved in 20 mL THF and cooled to –20 ºC. *n*-Butyllithium (2.4 M, 2.65 mL, 6.3 mmol, 1.05 equiv) was added in a dropwise fashion, resulting in an orange solution. The solution was stirred at this temperature 15 min before a solution of 3,5-dimethoxybenzaldehyde (**S1**, 1.00 g, 6.0 mmol, 1 equiv) in 3 mL THF was added in a dropwise fashion, causing a color change to yellow. The solution was stirred at this temperature 30 min before a second portion of *n*-butyllithium (2.4 M, 7.5 mL, 18.1 mmol, 3 equiv) was added in a dropwise fashion. At this point, the flask was stored in a –20 ºC freezer for 24 h. The flask was re-submerged in a –20 ºC bath, and freshly distilled methyl iodide (2.25 mL, 36.1 mmol, 6 equiv) was added in a dropwise fashion, resulting in a mild exotherm. The solution was stirred 30 min at –20 ºC and was removed from its bath, warming to room temperature. After 30 min the reaction was quenched by the addition of 20 mL 0.5 M HCl, and the solution was stirred 30 min open to air. The layers were separated and the aqueous phase was saturated with sodium chloride. The aqueous phase was extracted with Et_2O, dried over $MgSO_4$ and concentrated. The product was purified by column chromatography (10% EtOAc/hex). Colorless solid, 1.03 g, 5.72 mmol, 95% yield**.** NMR spectra were identical to the previously reported compound (*47*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.03 (s, 2H), 3.87 (s, 6H), 2.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0, 158.7, 135.1, 122.5, 104.7, 55.9, 9.0. **Note:** This procedure could be readily increased to 10 g scale with minimal loss in yield (>90% yield).

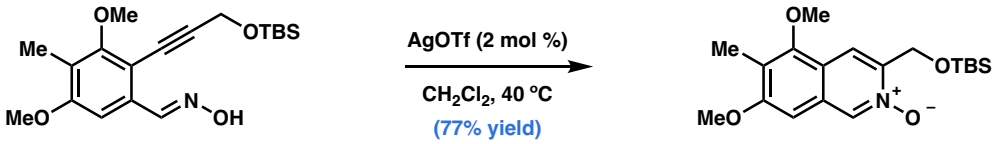


2-Bromo-3,5-dimethoxy-4-methylbenzaldehyde (11). Aldehyde **S2** (8.62 g, 47.8 mmol, 1 equiv) was dissolved in CH_2Cl_2 (100 mL, 0.5 M) and acetic acid (30 µL, 0.5 mmol, 0.01 equiv) was added. The solution was cooled to 0 ºC before bromine was added in a slow, dropwise fashion. The solution was stirred 30 min after complete addition at 0 ºC, at which time TLC (10% EtOAc/hex) showed complete conversion. The reaction was quenched by the addition of 10% aqueous sodium thiosulfate and saturated $NaHCO_3$ solution. The layers were separated and the aqueous phase was extracted with $CHCl_3$. The combined organic phases were washed with water, dried over $MgSO_4$ and concentrated. The product was purified by dissolving in ~50 mL boiling hexanes, under which conditions the trace amounts of dibromide are insoluble. The solution was filtered while boiling, providing the pure product. Colorless solid, 10.13 g, 39.1 mmol, 82% yield. NMR spectra were identical to the previously reported compound (*48*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 7.21 (s, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.8, 158.2, 156.2, 132.2, 129.5, 114.9, 106.0, 60.8, 56.1, 10.6.



(*E*)-2-(3-((tert-butyldimethylsilyl)oxy)prop-1-yn-1-yl)-3,5-dimethoxy-4-methylbenzaldehyde oxime (13). Bromide **11** (19.4 g, 74.9 mmol, 1 equiv), $(PPh_3)_2PdCl_2$ (2.6 g, 3.70 mmol, 0.05 equiv), and CuI (714 mg, 3.75 mmol, 0.05 equiv) were slurried in diisopropylamine (300 mL, 0.25 M, freshly distilled from CaH_2) in a 2 liter 3-necked roundbottom flask, and the orange suspension was sparged with N_2 for 10 min. *O-tert*-butyldimethylsilyl propargyl alcohol (**12**, 17.3 g, 101 mmol, 1.35 equiv) (*49*) was added in one portion, causing the suspension to darken as the palladium catalyst was reduced. The suspension was sparged with N_2 for a further 1 min,

then heated to 70 ºC for 24 h. At this stage, TLC and LCMS indicated complete conversion of bromide **11**, so the suspension was cooled to 50 ºC and 200 mL MeOH was added. Hydroxylamine hydrochloride (6.24 g, 89.8 mmol, 1.2 equiv) was added in one portion and the solution was heated to reflux (85 ºC) for 2 h. At this stage, TLC and LCMS indicated complete conversion to the product. The solution was cooled to room temperature and celite (~100 g) was added. The suspension was filtered through a pad of celite, topped with sand, eluting with ethyl acetate. The filtrate was concentrated and purified by column chromatography (15% EtOAc/hex). Colorless solid, 26.9 g, 74.1 mmol, 99% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.46 (s, 1H), 7.10 (s, 1H), 4.62 (s, 2H), 3.86 (s, 6H), 2.15 (s, 3H), 0.95 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.5, 158.8, 149.5, 132.8, 122.5, 110.3, 101.9, 96.2, 78.2, 61.0, 55.9, 52.6, 26.0, 18.5, 9.3, –5.0; IR (thin film, NaCl): 3270.1, 3092.6, 2997.3, 1953.8, 2932.4, 2896.1, 2857.0, 2221.2, 1611.1, 1591.7, 1560.0, 1463.8, 1402.9, 1383.9, 1331.8, 1281.5, 1255.3, 1217.9, 1191.5, 1164.3, 1136.9, 1121.1, 1101.2, 1080.0, 1034.8, 977.1, 903.5, 837.9, 779.7, 722.1, 704.2, 671.8; HRMS (ESI-TOF) calc'd for [M^+] $C_{19}H_{29}NO_4Si$ = 363.1866, found 363.1939.

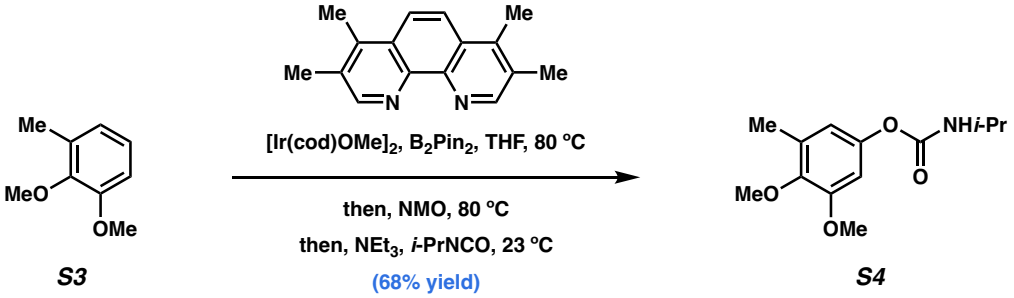


13 *9*

3-(((tert-butyldimethylsilyl)oxy)methyl)-5,7-dimethoxy-6-methylisoquinoline-*N*-oxide (9). Oxime **13** (15.92 g, 45.7 mmol, 1 equiv) was dissolved in CH_2Cl_2 (460 mL, 0.1 M) and the flask was vacuum purged and refilled with nitrogen five times, then heated to reflux. AgOTf (235 mg, 0.91 mmol, 0.02 equiv) was added in one portion to the refluxing solution, resulting in a rapid and mildly exothermic reaction. The reaction flask was shielded from light and maintained at reflux for 15 min, at which time LCMS indicated full conversion to the product. The solution was filtered through a 1 inch pad of silica with 500 mL CH_2Cl_2 and 1 L 10% MeOH/EtOAc. Silica gel (40 mL) was added to the second portion of filtrate, which was then concentrated. The product was purified by column chromatography using a 6 inch pad of silica (30–50–100% EtOAc/CH_2Cl_2; then 2–5–10–20% MeOH/EtOAc + 1% NEt_3). Colorless solid, 12.27 g, 33.8 mmol, 77% yield. The product is initially isolated as a black solid that is spectroscopically pure,

and can be recrystallized to a colorless solid from minimal boiling heptanes. Very little mass is lost during this process (less than 50 mg from a 12 g batch), indicating the presence of very minor yet highly colored impurities. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.02 (s, 1H), 6.71 (s, 1H), 5.01 (d, J = 1.4 Hz, 2H), 3.92 (s, 3H), 3.87 (s, 3H), 2.27 (s, 3H), 1.00 (s, 9H), 0.15 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 153.7, 145.9, 135.2, 128.4, 123.6, 120.1, 115.0, 97.4, 61.7, 60.1, 55.9, 26.0, 18.4, 9.8, -5.3; IR (thin film, NaCl): 3390.3, 3073.7, 2998.1, 2953.8, 2892.2, 2857.2, 1637.3, 1613.4, 1567.8, 1470.6, 1390.6, 1371.6, 1341.4, 1308.3, 1254.2, 1209.7, 1185.3, 1148.0, 1116.4, 1020.7, 1007.1, 957.4, 899.7, 838.8, 808.0, 777.9, 701.7, 669.8, 637.7; HRMS (ESI-TOF) calc'd for [M^+] $C_{19}H_{29}NO_4Si$ = 363.1866, found 363.1863.

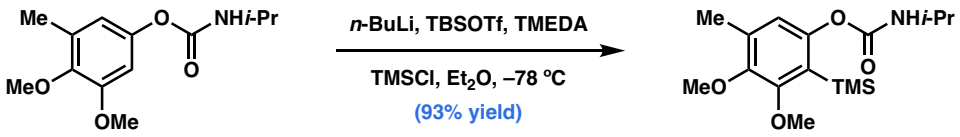
Synthesis of Isoquinoline Triflate 10.



S3 *S4*

3,4-Dimethoxy-5-methylphenyl isopropylcarbamate (S4). In a nitrogen-filled glovebox, $[Ir(cod)OMe]_2$ (22.3 mg, 0.034 mmol, 0.005 equiv) and 3,4,7,8-tetramethyl-1,10-phenanthroline (15.9 mg, 0.067 mmol, 0.01 equiv) were dissolved in 5 mL THF and stirred 30 min. In the meantime, 2,3-dimethoxytoluene (1.00 mL, 6.73 mmol, 1 equiv) and B_2Pin_2 (1.28 g, 5.05 mmol, 0.75 equiv) were weighed into a 20 mL sealable microwave vial (also in the glovebox) with a teflon-coated stir bar and 5 mL THF was added. Upon complete dissolution, the catalyst solution was transferred to the microwave vial, which was sealed prior to removing from the glovebox. The vial was then placed in a preheated 80 ºC oil bath and stirred 48 h, at which time TLC (20% EtOAc/hex) revealed complete conversion to a single borylated product. The vial was cooled to room temperature and the cap was removed. *N*-methylmorpholine-*N*-oxide (2.37 g, 20.2 mmol, 3 equiv) was added in a few small portions and the vial was resealed and returned to the 80 ºC oil bath for 3 h, at which time TLC (20% EtOAc/hex) indicated complete oxidation to the interme-

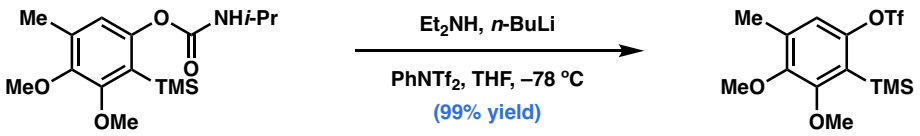
diate phenol. Triethylamine (4.7 mL, 33.7 mmol, 5 equiv) and isopropyl isocyanate (2.6 mL, 26.9 mmol, 4 equiv) were added at 23 ºC and the solution was stirred 16 h, at which time TLC (50% EtOAc/hex) indicated complete conversion to carbamate **S4**. The contents of the vial were transferred to a 100 mL roundbottom flask and 10% aq. $Na_2S_2O_3$ was added to quench the remaining oxidant and citric acid hydrate (4.5 g, >3 equiv) was added to chelate the boron. This solution was stirred 1 h, and concentrated HCl was added 1 mL at a time until an acidic pH was achieved. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic phases were then washed with aqueous K_2CO_3, dried over $MgSO_4$ and concentrated. The product was purified by column chromatography (25% EtOAc/hex). Colorless solid, 1.16 g, 4.6 mmol, 68% yield. NMR spectra were identical to the previously reported compound (*49*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (d, *J* = 2.6 Hz, 1H), 6.52 (d, *J* = 2.8 Hz, 1H), 4.84 (d, *J* = 7.8 Hz, 1H), 3.88 (ddd, *J* = 16.1, 13.9, 7.6 Hz, 1H), 3.82 (s, 3H) 3.76 (s, 3H), 2.24 (s, 3H), 1.23 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0, 153.0, 146.8, 144.7, 132.3, 115.4, 104.3, 60.3, 55.9, 43.6, 23.0, 16.0.



S4 ***S5***

3,4-Dimethoxy-5-methyl-2-(trimethylsilyl)phenyl isopropylcarbamate (S5). *Note: Vigorous stirring was required throughout the course of the reaction due to the formation of insoluble triflate salts.* Carbamate **S4** (17.30 g, 68.2 mmol, 1 equiv) was dissolved in Et_2O (340 mL, 0.2 M) *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, 11.3 mL, 75.1 mmol, 1.1 equiv) was added and the solution was cooled to 0 ºC before *tert*-butyldimethylsilyl triflate (TBSOTf, 17.25 mL, 75.1 mmol, 1.1 equiv) was added in a slow stream. The solution was stirred 10 min at 0 ºC, removed from the ice bath and stirred at 23 ºC for 30 min. A second portion of TMEDA (41 mL, 273 mmol, 4 equiv) was added and the solution was cooled to –78 ºC. *n*-Butyllithium (2.4 M, 114 mL, 274 mmol, 4 equiv) was added in a dropwise fashion through a flame-dried addition funnel over the course of 1 h, being sure to not let the temperature rise significantly. The resulting yellow suspension was stirred vigorously for 4 h at –78 ºC, taking care not to let the temperature

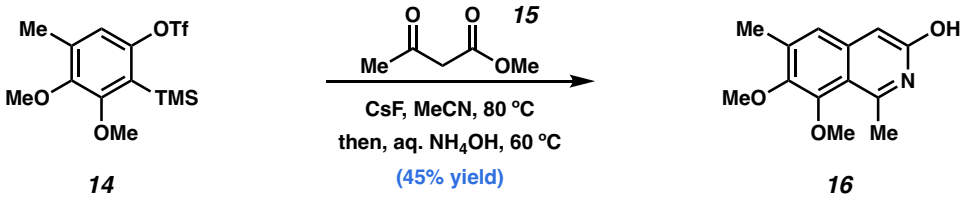
rise. Trimethylsilyl chloride (61 mL, 478 mmol, 7 equiv) was then added dropwise via the addition funnel over the course of 30 min and the suspension was stirred at –78 ºC for 30 min, then was removed from the dry ice bath and stirred at 23 ºC for 16 h. The reaction was quenched by the addition of 300 mL aqueous NH_4Cl (30 mL saturated solution diluted to 300 mL) through an addition funnel, the first 50 mL of which were added dropwise, followed by the addition of the remainder in a slow stream. The aqueous phase was then further acidified by the addition of small portions of concentrated HCl until an acidic pH was achieved (~30 mL required). The layers were separated and the aqueous phase was extracted twice with Et_2O. The combined organic phases were washed with saturated aqueous NH_4Cl, dried over $MgSO_4$ and concentrated. The product was purified by column chromatography (20–30% Et_2O/hex). Colorless solid, 20.61 g, 63.3 mmol, 93% yield. NMR spectra were identical to the previously reported compound (*49*). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 (s, 1H), 4.69 (d, J = 8.1 Hz, 1H), 3.96–3.85 (m, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 2.23 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H), 0.30 (s, 9H); 157.9, ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.9, 154.2, 150.5, 148.5, 134.6, 123.0, 120.1, 60.5, 59.8, 43.5, 23.1, 16.1, 1.3.



S5 ***14***

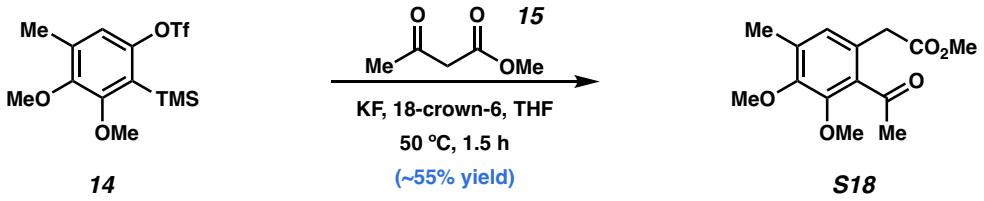
3,4-Dimethoxy-5-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (14). *Note: Arene **14** can be isolated as a colorless oil, but undergoes decomposition and should be used within the day of its isolation.* Carbamate **S5** (8.08 g, 24.8 mmol, 1 equiv) was dissolved in THF (100 mL, 0.25 M) and diethylamine (3.85 mL, 37.2 mmol, 1.5 equiv) was added and the solution was cooled to –78 ºC. *n*-Butyllithium (2.5 M, 15 mL, 37.5 mmol, 1.5 equiv) was added slowly over the course of 15 min. The solution was stirred at that temperature for 30 min, then removed from its bath and stirred at 23 ºC for 30 min. *N*-Phenyl triflimide (10.6 g, 29.8 mmol, 1.2 equiv) was added in one portion and the solution was stirred 30 min. A second portion of diethylamine (4.6 mL, 44.7 mmol, 1.8 equiv) was added and the solution was stirred 2 h. The solution was filtered through a 1 inch pad of silica gel with 50% Et_2O/hex and concentrated. The product was purified by column chromatography (10% Et_2O/hex). Colorless oil, 9.15 g, 24.6 mmol, 99%

yield. NMR spectra were identical to the previously reported compound (*49*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 2.28 (d, J = 0.7 Hz, 3H), 0.38 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 150.4, 149.0, 135.6, 124.2, 118.7 (q, J = 320.6 Hz), 117.7, 60.6, 59.8, 16.3, 1.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ -73.1 (s, 3F).

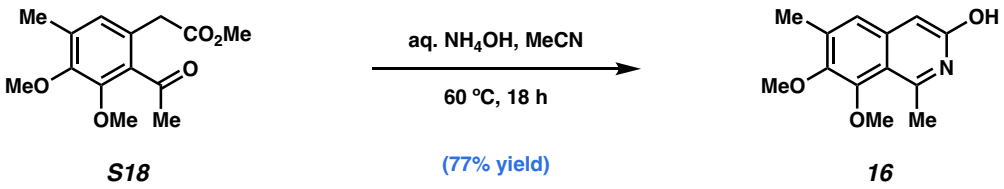


7,8-Dimethoxy-1,6-dimethyl-3-hydroxyisoquinoline (16). Cesium fluoride (204 mg, 1.34 mmol, 2.5 equiv) was dissolved in acetonitrile (5.4 mL, 0.1 M) in a 20 mL microwave vial and water (9.7 µL, 0.537 mmol, 1.0 equiv) and methyl acetoacetate (58 µL, 0.537 mmol, 1.0 equiv) were added. Aryne precursor **14** (250 mg, 0.671 mmol, 1.25 equiv) was added neat via syringe, and the vial was placed in a preheated 80 ºC oil bath. After 2 h, TLC revealed complete consumption of **14**, so NH_4OH (28–30%, 5.4 mL) was added in one portion. The vial was moved to a preheated 60 ºC oil bath and stirred for 8 h. The solution was poured into brine inside a separatory funnel and the solution was extracted with EtOAc (2x 30 mL). The aqueous phase was brought to pH 7 by the addition of concentrated HCl and was extracted with EtOAc (2x 30 mL). The aqueous phase was discarded. The organic phase was then extracted with 2M HCl (5x 20 mL). The organic phase was checked by LCMS to confirm that all of product **16** had transferred to the aqueous phase and was subsequently discarded. The aqueous phase was then brought back to pH 7 by the addition of 100 mL 2M NaOH and was extracted with EtOAc (5x 20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated, providing the product. Yellow solid, 56.9 mg, 0.243 mmol, 45% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (d, J = 0.7 Hz, 1H), 6.51 (s, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 3.03 (d, J = 0.7 Hz, 3H), 2.28 (d, J = 1.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.8, 149.5, 145.9, 142.6, 140.4, 121.4, 113.1, 104.8, 60.5, 60.2, 21.1, 17.3; IR (thin film, NaCl): 3327.0, 2937.6, 2608.7, 1651.7, 1455.4, 1324.2, 1226.8, 1177.9, 1147.2, 1089.5, 1062.3, 1034.8, 1000.5, 960.0, 937.7, 892.4, 861.7, 813.2, 724.1, 682.8, 662.3; HRMS (ESI-TOF) calc'd for [M^+] $C_{13}H_{15}NO_3$ = 233.1052, found 233.1057. *Note: When performed on multi-gram scale, this reaction proved highly vari-*

able due to unknown factors. Yields typically dropped into the 20–30% range. We have therefore developed the two-step procedure below that requires extensive column chromatography and generates significantly more organic waste, but that does provide hydroxyisoquinoline ***16*** *in higher overall yield.*

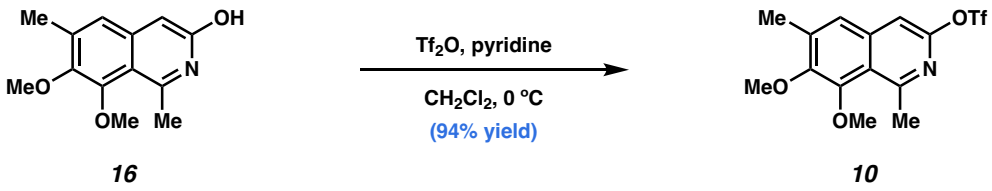


Methyl 2-(2-acetyl-3,4-dimethoxy-5-methylphenyl)acetate (S18). Anhydrous potassium fluoride (7.0 g, 120.5 mmol, 3.3 equiv) and 18-crown-6 (31.0 g, 117.3 mmol, 3.2 equiv) were weighed into a flame-dried 1L recovery flask inside a nitrogen-filled glovebox to minimize exposure to atmospheric water. The flask was removed from the glovebox, anhydrous THF (370 mL, 0.1 M in **14**) was added and the resulting slurry was heated to 50 °C in an oil bath. Aryne precursor **14** (13.67 g, 36.7 mmol, 1.0 equiv) was dissolved in anhydrous THF (30 mL) and added to the warm fluoride solution in a slow, dropwise fashion via cannula over 1 h, followed by a 10 mL rinse of the flask and cannula, added rapidly. After stirring 1 h at 50 °C, TLC revealed complete consumption of **14** and the appearance of at least five new products (the product has an $R_f = 0.35$ in 20% EtOAc/hex, major middle spot). The crude reaction was filtered through a 1" pad of SiO_2 using 1L of 30% EtOAc/hex and the filtrate was concentrated. The product was purified by column chromatography [4x10" SiO_2, 2L 5% EtOAc/hex (collected in Erlenmeyer flasks)–1.5L 10%–1.5L 20%–1L 30%–600 mL 50% EtOAc/hex]. The product could not be completely purified from the reaction mixture, but using the above conditions **S18** could be obtained in roughly 80% purity as estimated by ^{1}H NMR. Colorless oil, 6.70 g isolated, ~5.36 g **S18** adjusted for purity, ~20.1 mmol, ~55% yield. NMR spectra were identical to the previously reported compound (*50*). Because of the low purity, only ^{1}H NMR spectra were recorded for this compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (q, J = 0.7 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 4H), 3.68 (s, 3H), 3.62 (s, 2H), 2.55 (s, 3H), 2.24 (d, J = 0.7 Hz, 3H).



S18 *16*

7,8-Dimethoxy-1,6-dimethyl-3-hydroxyisoquinoline (16). In a 250 mL flask equipped with a Kontes valve, arene **S18** was dissolved in MeCN (15 mL) and NH_4OH (28–30%, 30 mL), the flask was sealed to prevent loss of gaseous ammonia and was placed in a preheated 60 °C oil bath. Within 1 h yellow **16** began to precipitate from the reaction solution. After stirring at 60 ºC for 18 h, the flask was cooled to room temperature, then placed in a –25 °C freezer for 3 h, after which time the suspension was filtered. The yellow filter cake was washed with cold (–25 °C) MeCN until the filtrate was no longer yellow. The filter cake was allowed to dry on the filter paper for 15 min, then was transferred to a vial and dried at high vacuum for 24 h to provide the analytically pure product. Yellow solid, 3.61 g, 15.5 mmol, 77% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (d, J = 0.7 Hz, 1H), 6.51 (s, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 3.03 (d, J = 0.7 Hz, 3H), 2.28 (d, J = 1.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.8, 149.5, 145.9, 142.6, 140.4, 121.4, 113.1, 104.8, 60.5, 60.2, 21.1, 17.3; IR (thin film, NaCl): 3327.0, 2937.6, 2608.7, 1651.7, 1455.4, 1324.2, 1226.8, 1177.9, 1147.2, 1089.5, 1062.3, 1034.8, 1000.5, 960.0, 937.7, 892.4, 861.7, 813.2, 724.1, 682.8, 662.3; HRMS (ESI-TOF) calc'd for [M^+] $C_{13}H_{15}NO_3$ = 233.1052, found 233.1057.

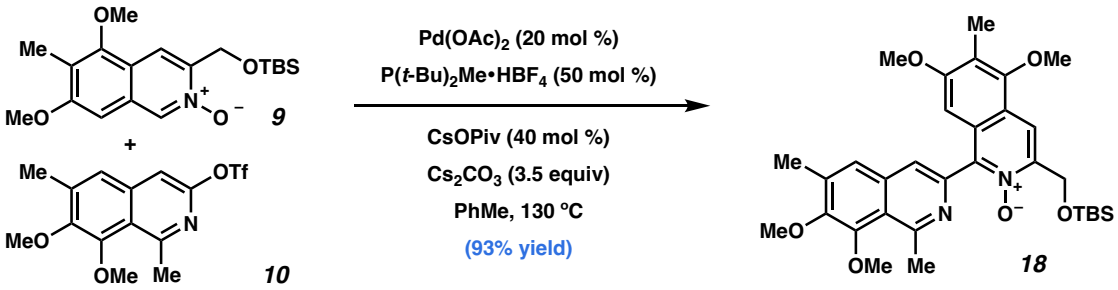


16 *10*

7,8-Dimethoxy-1,6-dimethyl-3-(trifluoromethanesulfonyloxy)isoquinoline (10). Hydroxyisoquinoline **16** (2.60 g, 11.1 mmol, 1 equiv) was dissolved in CH_2Cl_2 (70 mL, 0.16 M) and pyridine (11.4 mL, 140.6 mmol, 12.7 equiv) was added and the solution was cooled to 0 ºC. Trifluoromethanesulfonic anhydride (Tf_2O, 3.00 mL, 17.8 mmol, 1.6 equiv) was added dropwise, causing the yellow solution to turn dark red. After 30 min TLC (10% EtOAc/hex) revealed complete conversion, so the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (70 mL).

The solution was stirred vigorously until bubbling ceased, at which time the layers were separated. The organic phase was extracted with CH_2Cl_2 and the combined organic phases were dried over Na_2SO_4 and concentrated. The product was purified by column chromatography (10% Et_2O/hex). Yellow oil, 3.82 g, 10.5 mmol, 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 1.0 Hz, 1H), 7.21 (s, 1H), 3.98 (s, 3H), 3.93 (s, 3H), 3.07 (d, *J* = 0.7 Hz, 3H), 2.44 (d, *J* = 1.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 151.0, 150.5, 149.9, 139.2, 136.8, 123.6, 122.9, 118.8 (q, *J* = 320.5 Hz), 107.6, 60.8, 60.2, 26.7, 17.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ -72.99; IR (thin film, NaCl): 3436.0, 2939.4, 1605.5, 1553.6, 1493.7, 1415.9, 1381.0, 1351.9, 1332.9, 1248.8, 1209.3, 1133.6, 1097.0, 1059.9, 1009.8, 983.4, 966.2, 940.7, 892.0, 834.7, 768.1, 695.0, 649.3, 608.2; HRMS (ESI-TOF) calc'd for [M^+] $C_{14}H_{14}F_3NO_5S$ = 365.0545, found 365.0547.

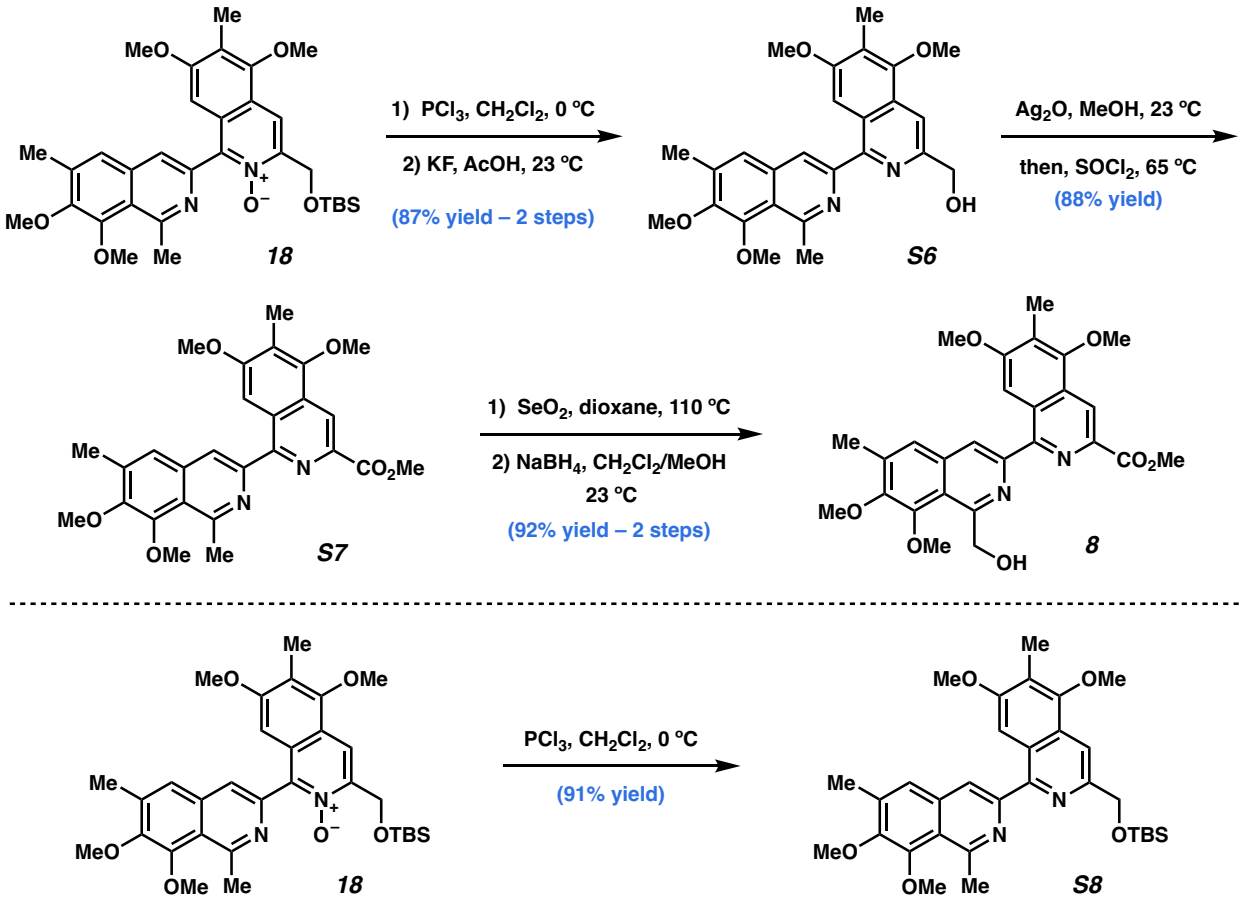
Fagnou Cross-Coupling Reaction.



3-(((tert-butyldimethylsilyl)oxy)methyl)-5,7,7',8'-tetramethoxy-1',6,6'-trimethyl-[1,3'-biisoquinoline] 2-oxide (18). Palladium acetate (347 mg, 1.54 mmol, 0.20 equiv), di-*tert*-butyl (methyl)phosphonium tetrafluoroborate (957 mg, 3.86 mmol, 0.50 equiv), and cesium carbonate (1.26 g, 3.41 mmol, 0.50 equiv) were weighed into a 100 mL pear-shaped flask and brought into a nitrogen-filled glovebox and cesium pivalate (CsOPiv, 722 mg, 3.09 mmol, 0.40 equiv) was added to the flask. In the glovebox, degassed toluene (80 mL) was added, the flask was sealed with a rubber septum and removed from the glovebox, to be placed in a 60 ºC preheated oil bath, where it was stirred for 30 min and allowed to cool to room temperature. In the meantime, *N*-oxide **9** (8.42 g, 23.1 mmol, 3 equiv) and cesium carbonate (7.54 g, 23.1 mmol, 3 equiv) were weighed into a 250 mL sealable flask equipped with a Kontes valve, to which 50 mL toluene was added, and this suspension was sparge-degassed with nitrogen for 10 min. Isoquinoline triflate

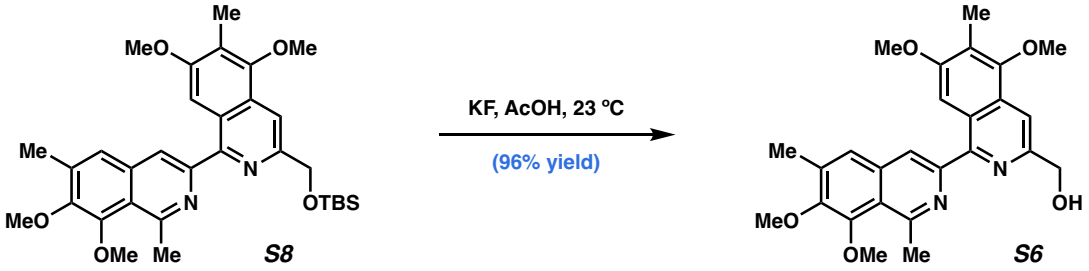
10 (2.77 g, 6.82 mmol, 1.00 equiv) was dissolved in 10 mL toluene, which was sparge-degassed with nitrogen for 10 min. The solution of isoquinoline triflate **10** was then added via cannula to the cooled catalyst solution, rinsing the flask with 5 mL degassed toluene. The catalyst/triflate solution was then added via cannula to the 250 mL sealable flask, rinsing with 10 mL degassed toluene. The flask was sealed and placed in a 130 ºC preheated oil bath for 4.5 h. The flask was then allowed to cool to room temperature and Celite (10 g) was added. This suspension was then filtered through a 1 inch pad of Celite that was topped with sand, rinsing with CH_2Cl_2 and acetone (500 mL each). The solution was concentrated, providing the crude product. ^{1}H NMR of the crude reaction mixture showed a 2:1 mixture of bis-isoquinoline **18** and *N*-oxide **9** at this point, indicating complete conversion to product. The product was purified by column chromatography (10–20% EtOAc/hex, then 20–50–100% EtOAc/hex + 1% NEt_3, then 10–20% MeOH/EtOAc + 1% NEt_3. bis-Isoquinoline **18** elutes during the 50–100% EtOAc/hex portion, and remaining *N*-oxide **9** elutes during the 10–20% MeOH/EtOAc portion). Colorless foam, 3.88 g, 6.70 mmol, 98% yield. An analogous coupling performed with 2.39 g isoquinoline triflate **10** provided 3.30 g of product (87% yield), together providing 7.18 g bis-isoquinoline **18** in 93% average yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 0.9 Hz, 1H), 7.81 (s, 1H), 7.42 (d, J = 1.1 Hz, 1H), 6.60 (s, 1H), 5.06 (d, J = 1.4 Hz, 2H), 4.01 (s, 3H), 3.97 (s, 3H), 3.90 (s, 3H), 3.65 (s, 3H), 3.17 (s, 3H), 2.45 (d, J = 0.9 Hz, 3H), 2.28 (s, 3H), 1.03 (s, 9H), 0.17 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 157.8, 153.8, 151.3, 149.6, 146.0, 143.7, 142.0, 137.6, 134.8, 128.2, 124.3, 122.7, 122.5, 121.5, 120.4, 114.5, 98.6, 61.8, 60.9, 60.4, 60.3, 55.7, 27.2, 26.1, 18.5, 17.1, 9.7, –5.2; IR (thin film, NaCl): 3417.9, 2954.4, 2856.9, 1614.6, 1567.0, 1463.4, 1392.7, 1328.6, 1255.0, 1213.2, 1189.5, 1139.2, 1117.7, 1089.2, 1057.0, 1008.0, 961.2, 936.5, 897.0, 839.1, 815.5, 778.4, 734.4, 701.8, 634.2; HRMS (ESI-TOF) calc'd for [M^+] $C_{32}H_{42}N_2O_6Si$ = 578.2812, found 578.2796.

First-Generation Synthesis of bis-Isoquinoline 8.

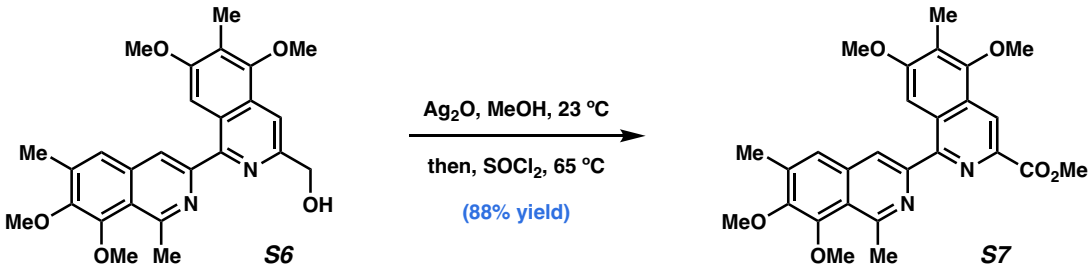


3-(((Tert-butyldimethylsilyl)oxy)methyl)-5,7,7',8'-tetramethoxy-1',6,6'-trimethyl-1,3'-biisoquinoline (S8). Bis-isoquinoline-*N*-oxide **18** (6.16 g, 10.6 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (210 mL, 0.05 M) and the solution was cooled to 0 ºC. Neat phosphorus trichloride (1.86 mL, 21.3 mmol, 2.00 equiv) was added at a dropwise pace over 5 minutes, causing the solution to immediately turn dark purple. After 30 min, TLC revealed complete conversion to the product, so the reaction was quenched with saturated aqueous K_2CO_3 and diluted with water. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated (note: a brine wash caused a significant emulsion regardless of extraction solvent, and was avoided). The product was purified by column chromatography (10% EtOAc/hex + 1% NEt_3). Yellow solid, 5.44 g, 9.67 mmol, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (q, J = 1.1 Hz, 1H), 8.00 (s, 1H), 7.87 (s, 1H), 7.47 (d, J = 0.6 Hz, 1H), 5.08 (d, J = 1.2 Hz, 2H), 4.02 (s, 3H), 3.98 (s, 3H), 3.92 (s, 3H), 3.85 (s, 3H),

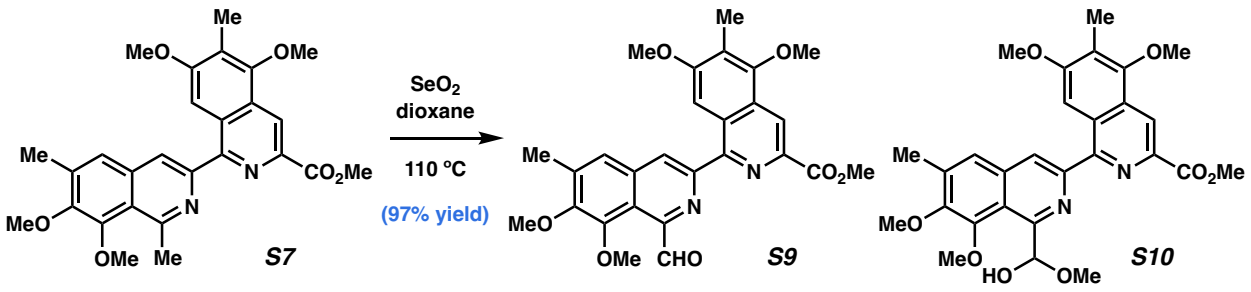
3.21 (s, 3H), 2.47 (d, J = 0.9 Hz, 3H), 2.36 (s, 3H), 1.04 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4, 156.1, 155.5, 153.6, 152.2, 150.9, 150.6, 149.6, 137.4, 135.5, 129.0, 125.9, 124.6, 124.2, 122.1, 119.8, 110.4, 101.2, 66.4, 61.6, 60.9, 60.4, 55.6, 27.2, 26.2, 18.6, 17.1, 9.8, –5.2.



(5,7,7',8'-Tetramethoxy-1',6,6'-trimethyl-[1,3'-biisoquinolin]-3-yl)methanol (S6). Bis-isoquinoline **S8** (5.44 g, 9.7 mmol, 1.00 equiv) was dissolved in acetic acid (40 mL, 0.25 M) and solid potassium fluoride (2.81 g, 48.0 mmol, 5.00 equiv) was added in one portion. The solution was stirred 30 min at room temperature, at which time LCMS showed complete conversion to the product. The solution was diluted with CH_2Cl_2 and ice and the solution was stirred vigorously as a solution of sodium hydroxide (25 g, 0.625 mol, 0.9 equiv relative to 40 mL AcOH) in 70 mL water was added slowly. The rest of the acetic acid was quenched by the addition of saturated aqueous K_2CO_3. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated. The product was purified by column chromatography (1–2–3–4–5% MeOH/CH_2Cl_2 + 1% NEt_3). Colorless solid, 4.17 g, 9.31 mmol, 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 8.03 (s, 1H), 7.79 (d, J = 0.9 Hz, 1H), 7.49 (d, J = 1.1 Hz, 1H), 4.94 (s, 2H), 4.03 (s, 3H), 3.97 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.22 (s, 3H), 2.47 (d, J = 1.0 Hz, 3H), 2.35 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 156.0, 155.2, 153.5, 151.1, 150.3, 149.7, 149.6, 137.6, 135.4, 129.0, 126.2, 124.7, 124.6, 122.2, 119.9, 111.3, 101.3, 65.0, 61.7, 60.9, 60.3, 55.6, 27.2, 17.1, 9.9; IR (thin film, NaCl): 3352.3, 3128.9, 2936.6, 2855.0, 1620.4, 1594.1, 1556.8, 1484.4, 1462.2, 1454.9, 1416.4, 1392.3, 1355.0, 1331.4, 1303.1, 1243.0, 1218.0, 1195.9, 1133.0, 1117.1, 1090.7, 1059.8, 1008.2, 963.5, 906.0, 884.5, 841.2, 795.7, 732.6, 645.8; HRMS (ESI-TOF) calc'd for [M+] $C_{26}H_{28}N_2O_5$ = 448.1998, found 448.1992.

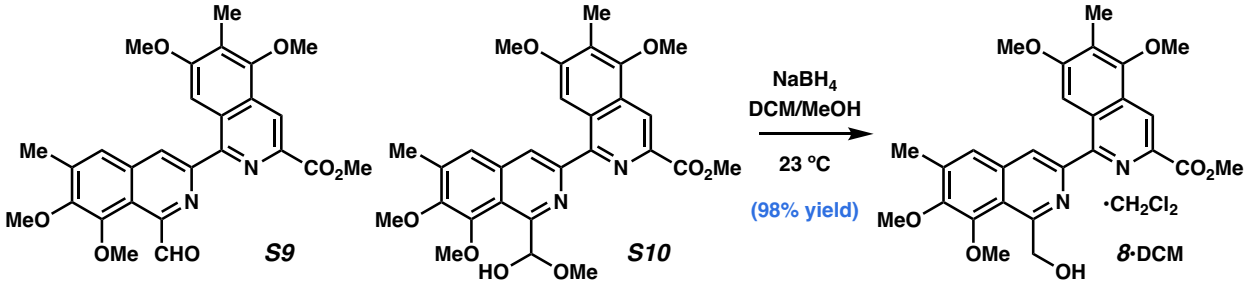


Methyl 5,7,7',8'-tetramethoxy-1',6,6'-trimethyl-[1,3'-biisoquinoline]-3-carboxylate (S7). bis-Isoquinoline **S6** (1.50 g, 3.34 mmol, 1.00 equiv) and silver(I) oxide (3.88 g, 16.7 mmol, 5.00 equiv) were slurried in MeOH (35 mL, 0.1 M). After 30 min, the solution appeared to be fully homogeneous and deep red in color. After 4 h, LCMS showed full conversion to a mixture of methyl ester **S7** and the corresponding carboxylic acid. Thionyl chloride (1.21 mL, 16.7 mmol, 5.00 equiv) was added through the top of a reflux condenser, and following the complete addition the solution was heated to reflux After 1.5 h, LCMS showed complete conversion to methyl ester **S7**. The solution was cooled to room temperature and celite was added, and the solution was filtered through more celite, rinsing with EtOAc. The solution was concentrated, then redissolved in CH_2Cl_2 and washed with dilute aqueous K_2CO_3 and brine. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated. The product was purified by column chromatography (25% EtOAc/hex + 1% NEt_3). White solid, 1.40 g, 2.94 mmol, 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, J = 0.9 Hz, 1H), 8.19 (s, 1H), 8.13 (s, 1H), 7.52 (d, J = 1.1 Hz, 1H), 4.05 (s, 3H), 4.01 (s, 3H), 3.97 (s, 3H), 3.94 (s, 3H), 3.90 (s, 3H), 3.20 (s, 3H), 2.46 (d, J = 1.0 Hz, 3H), 2.36 (s, 3H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 167.0, 160.0, 156.0, 155.8, 154.9, 151.1, 149.9, 149.5, 139.0, 137.5, 135.6, 128.6, 128.0, 125.0, 124.7, 122.3, 120.5, 118.6, 101.9, 62.3, 60.9, 60.3, 55.8, 52.8, 27.1, 17.1, 9.9; IR (thin film, NaCl): 3443.0, 2948.7, 1714.1, 1614.7, 1454.4, 1407.2, 1384.3, 1330.3, 1304.7, 1270.1, 1226.4, 1136.9, 1088.6, 1057.2, 1008.0, 870.5, 786.0, 733.2; HRMS (ESI-TOF) calc'd for [M^+] $C_{27}H_{28}N_2O_6$ = 476.1947, found 476.1952.



Methyl 1'-formyl-5,7,7',8'-tetramethoxy-6,6'-dimethyl-[1,3'-biisoquinoline]-3-carboxylate (S8) and methyl 1'-(hydroxy(methoxy)methyl)-5,7,7',8'-tetramethoxy-6,6'-dimethyl-[1,3'-biisoquinoline]-3-carboxylate (S9) and methyl 1'-(hydroxy(methoxy)methyl)-5,7,7',8'-tetramethoxy-6,6'-dimethyl-[1,3'-biisoquinoline]-3-carboxylate (S10). bis-Isoquinoline **S7** (1.40 g, 2.94 mmol, 1.00 equiv) and selenium dioxide (652 mg, 5.88 mmol, 2.00 equiv) was slurried in dioxane and the flask was fitted with a reflux condenser. The flask was vacuum purged/refilled with N_2 five times, then heated to reflux. At about 80 ºC the solution became fully homogeneous. After 1 h at reflux, the flask was cooled to room temperature and LCMS showed full conversion to aldehyde **S9**. Celite was added to the crude reaction and the resulting slurry was filtered through more celite, rinsing with EtOAc. SiO_2 was added to the filtrate and the solution was concentrated. Due to the insolubility of the products, a mixture of MeOH and CH_2Cl_2 was required during purification by column chromatography (10% MeOH/DCM + 1% NEt_3). During this process, the highly electrophilic aldehyde moiety is converted to the hemiacetal in a thermodynamic 85:15 mixture favoring the hemiacetal. The two products can neither be interconverted nor separated, and as such was characterized as a mixture. White solid, total mass = 1.47 g, 85:15 molar ratio of **S10**:**S9** by ^{1}H NMR, corresponding to 1.25 g hemiacetal **S10** (2.39 mmol, 82% yield) and 220 mg **S9** (0.45 mmol, 15% yield), 2.84 mmol total, 97% combined yield. *Aldehyde **S9**:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.92 (s, 1H), 8.78 (s, 1H), 8.72 (s, 1H), 8.56 (s, 1H), 7.68 (d, J = 1.2 Hz, 1H), 4.07 (s, 3H), 4.04 (s, 3H), 4.02 (s, 3H), 3.95 (s, 3H), 3.70 (s, 3H), 2.51 (d, J = 1.0 Hz, 3H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.4, 160.6, 154.8, 154.1, 151.8, 151.3, 151.0, 147.1, 139.2, 135.8, 128.7, 128.1, 125.3, 125.0, 124.1, 121.6, 119.1, 102.0, 67.2, 60.7, 60.6, 56.3, 46.1, 17.4. *Hemiacetal **S10**:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, J = 0.8 Hz, 1H), 8.44 (s, 1H), 7.97 (s, 1H), 7.61 (d, J = 1.1 Hz, 1H), 6.52 (d, J = 10.6 Hz, 1H), 6.41 (d, J = 10.6 Hz, 1H), 4.10 (s, 3H), 4.06 (s, 3H), 3.98 (s, 3H), 3.98 (s, 3H), 3.92 (s, 3H),

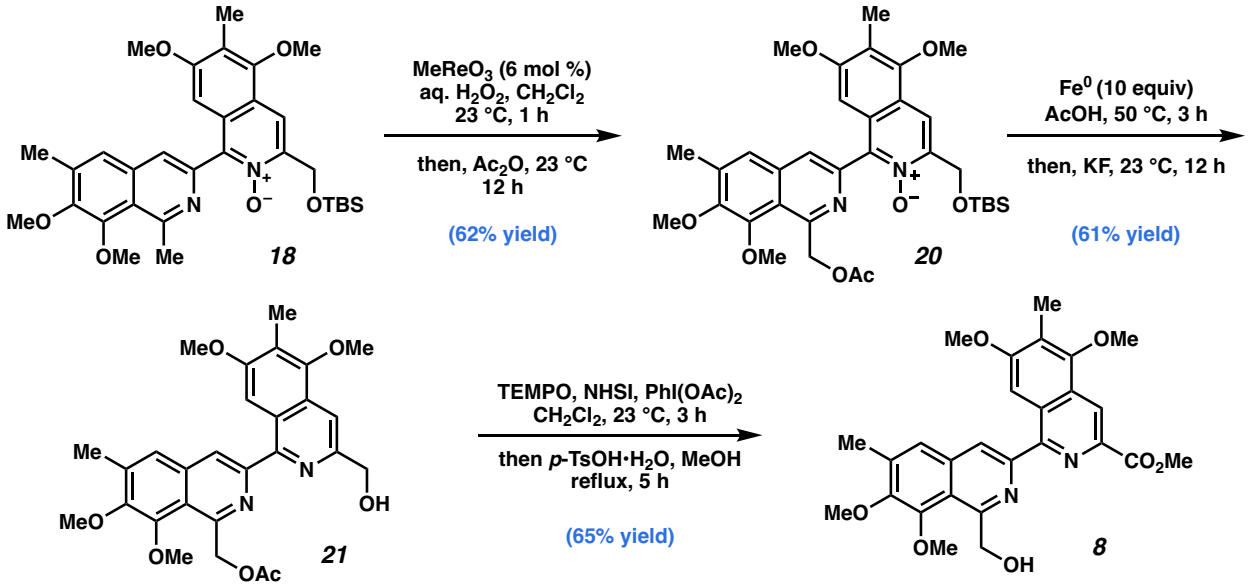
3.63 (s, 3H), 2.48 (d, J = 1.0 Hz, 3H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 160.3, 155.2, 154.9, 152.9, 151.5, 148.6, 148.2, 138.9, 138.6, 136.5, 128.5, 127.9, 125.2, 124.9, 123.4, 120.1, 118.9, 101.5, 95.2, 62.3, 60.8, 60.3, 56.0, 55.2, 52.8, 17.3, 10.0. IR (thin film, NaCl): 3436.7, 2948.9, 2846.9, 1737.7, 1711.2, 1619.9, 1462.1, 1386.6, 1304.0, 1272.2, 1228.6, 1136.2, 1086.2, 1001.8, 900.5, 734.1; HRMS (ESI-TOF) for aldehyde **S9** calc'd for [M^+] $C_{27}H_{26}N_2O_7$ = 490.1740, found 490.1742; HRMS (ESI-TOF) for hemiacetal **S10** calc'd for [M^+] $C_{28}H_{30}N_2O_8$ = 522.2002, found 522.2005.

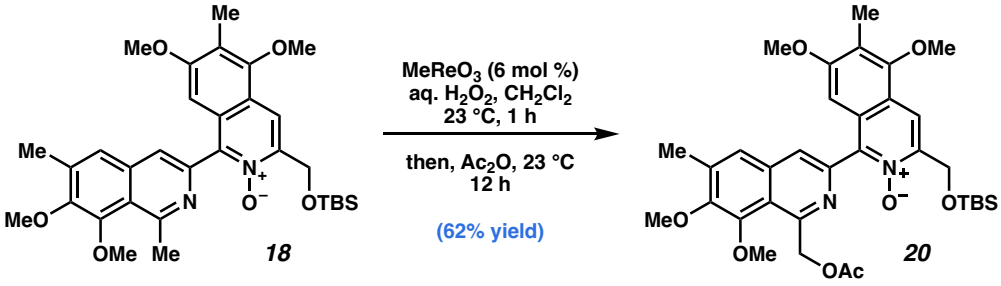


Methyl 1'-(hydroxymethyl)-5,7,7',8'-tetramethoxy-6,6'-dimethyl-[1,3'-biisoquinoline]-3-carboxylate dichloromethane solvate (8•CH_2Cl_2). *Note: Aldehyde **S7** and hemiacetal **S9** appear to be in thermal equilibrium at 23 °C in a 4:1 v/v mixture of CH_2Cl_2:MeOH in a 1:3 ratio of **S9**:**S10**. When excess $NaBH_4$ is utilized, competitive reduction of the methyl ester was observed; however, when $NaBH_4$ was employed in substoichiometric fashion, selective reduction of the aldehyde was observed. Presumably the reaction proceeds to completion as a manifestation of Le Châtelier's principle.* A mixture of bis-isoquinolines **S9** and **S10** (2.84 mmol in total, 1.00 equiv) was dissolved in CH_2Cl_2 (24 mL) and MeOH (6 mL, 0.1 M) and sodium borohydride (36.0 mg, 0.946 mmol, 0.33 equiv) was added. Gas evolution observed for ~1 minute, then stopped. 5 minutes after the addition of sodium borohydride LCMS showed complete and selective reduction to desired product **8**. The reaction was quenched by the addition of citric acid monohydrate (594 mg, 2.84 mmol, 1.00 equiv) and water and the solution was stirred at 1500 rpm for 10 min, then is basified by the addition of saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated. The product was purified by column chromatography using a 1:1 mixture of CH_2Cl_2:EtOAc as the polar solvent (20–30–40–50–60–100% polar solvent/

hex + 1% NEt_3). Colorless solid, 1.55 g, 2.68 mmol, 98% yield. Note: A stoichiometric amount of dichloromethane could not be removed from the product despite extensive time on high vacuum (10 mTorr), leading to the conclusion that the product is isolated as a stoichiometric dichloromethane monosolvate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, J = 0.8 Hz, 1H), 8.30 (s, 1H), 7.90 (s, 1H), 7.59 (d, J = 0.5 Hz, 1H), 5.55 (t, J = 3.5 Hz, 1H), 5.39 (d, J = 3.5 Hz, 2H), 5.30 [s, 2H (CH_2Cl_2)], 4.06 (s, 3H), 4.06 (s, 3H), 3.99 (s, 3H), 3.96 (s, 3H), 3.90 (s, 3H), 2.49 (d, J = 0.9 Hz, 3H), 2.38 (s, 3H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 166.9, 160.2, 155.8, 155.6, 155.0, 151.1, 149.1, 148.5, 139.0, 138.4, 135.5, 128.5, 127.9, 125.3, 124.8, 121.6, 120.3, 118.8, 101.3, 64.7, 62.4, 60.9, 60.3, 56.1, 53.4, 52.9, 17.2, 10.0; IR (thin film, NaCl): 3364.8, 3130.4, 2930.2, 2856.2, 1690.6, 1620.8, 1594.3, 1556.6, 1462.3, 1413.2, 1391.8, 1356.6, 1330.7, 1302.1, 1258.7, 1196.3, 1130.7, 1088.7, 1058.5, 1010.1, 964.2, 885.9, 838.1, 801.9, 777.4, 734.0; HRMS (ESI-TOF) calc'd for [M^+] $C_{27}H_{28}N_2O_7$ = 492.1897, found 492.1894.

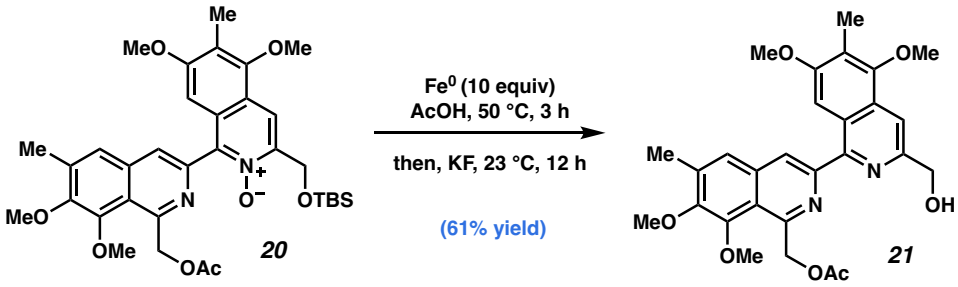
Second-Generation Synthesis of bis-Isoquinoline 8.



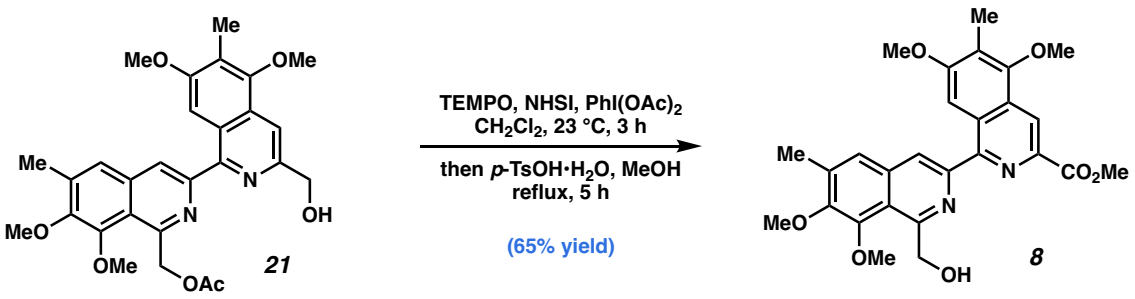


1'-(acetoxymethyl)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5,7,7',8'-tetramethoxy-6,6'-dimethyl-[1,3'-biisoquinoline] 2-oxide (20). *Note: Addition of the catalyst in a single portion resulted in rapid over-oxidation, but addition in 3 portions, at least 20 minutes apart resulted in clean conversion. Furthermore, bis-N-oxide* ***19*** *was not stable to Na_2SO_4, $MgSO_4$, or SiO_2, and as such it was neither dried nor purified by column chromatography, but the clean reaction profile did not necessitate purification.* Bis-isoquinoline-*N*-oxide **18** (150 mg, 0.259 mmol, 1 equiv) and methyl trioxorhenium (1.3 mg, 0.0052 mmol, 0.02 equiv) were dissolved in CH_2Cl_2 (2.6 mL, 0.1 M) and 35% aqueous hydrogen peroxide (40 µL, 0.454 mmol, 1.75 equiv) was added. The solution was stirred at 1300 rpm for 30 min, at which point a second portion of $MeReO_3$ (1.3 mg, 0.0052 mmol, 0.02 equiv) was added. After 30 min, a third and final portion of $MeReO_3$ (1.3 mg, 0.0052 mmol, 0.02 equiv) was added. After a further 30 min, LCMS showed complete consumption of the bis-isoquinoline-*N*-oxide, so acetic anhydride (0.122 ml, 1.30 mmol, 5 equiv) was then added and the reaction mixture was stirred at 23 °C. After 12 hours, LCMS showed complete consumption of the bis-N-oxide. The reaction was quenched with water and basified with aqueous K_2CO_3. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and azeotroped with benzene twice. The crude product was purified by column chromatography (35% EtOAc/hex + 1% NEt_3). Yellow foam, 102.0 mg, 0.160 mmol, 62% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.05 (s, 1H), 7.49 (s, 1H), 6.64 (s, 1H), 5.85 (s, 2H), 5.05 (s, 2H), 4.04 (s, 3H), 3.96 (s, 3H), 3.92 (s, 3H), 3.73 (s, 3H), 2.46 (s, 3H), 2.29 (s, 3H), 1.99 (s, 3H), 1.04 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 159.1, 153.2, 145.8, 138.2, 134.9, 128.3, 124.4, 123.8, 122.9, 114.7, 98.8, 68.1, 61.8, 60.9, 60.4, 60.2, 55.8, 26.1, 21.1, 18.5, 17.1, 9.8, –5.2. IR (thin film, NaCl): 2931.8, 2856.3, 1742.2, 1613.9, 1556.5, 1462.7, 1454.2, 1359.3,

1316.3, 1236.4, 1137.2, 1090.0, 1006.4, 896.6, 838.7, 754.5; HRMS (ESI-TOF) calc'd for $[M+H]^+$ $C_{34}H_{45}N_2O_8Si$ = 637.2940, found 637.2944.

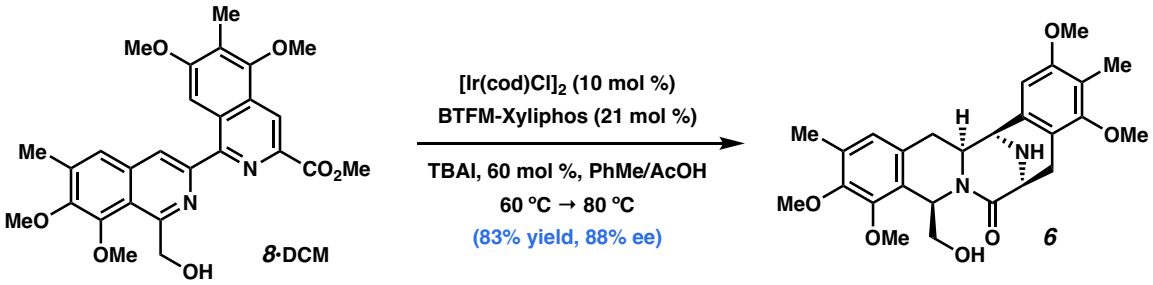


(3-(hydroxymethyl)-5,7,7',8'-tetramethoxy-6,6'-dimethyl-[1,3'-biisoquinolin]-1'-yl)methyl acetate (21). To a solution of bis-isoquinoline-N-oxide **21** (99.0 mg, 0.155 mmol, 1 equiv) in acetic acid (1.6 mL), Fe powder (86.8 mg, 1.55 mmol, 10 equiv) was added at 23 °C. The reaction mixture was stirred at 50 °C for 3 hours, at which point the LCMS showed complete consumption of the starting material. The reaction mixture was then cooled to room temperature and KF (90.1 mg, 1.55 mmol, 10 equiv) was added. After 12 hours, LCMS showed complete consumption of the TBS-protected alcohol intermediate, so the reaction was diluted with CH_2Cl_2 and washed with aqueous K_2CO_3. The aqueous layer was separated and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude was purified by column chromatography (50% EtOAc/CH_2Cl_2 + 1% Et_3N). Pale yellow solid, 48.1 mg, 0.095 mmol, 61% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.85 (s, 1H), 7.74 (d, J = 0.9 Hz, 1H), 7.47 (d, J = 1.1 Hz, 1H), 5.84 (s, 2H), 4.87 (d, J = 0.9 Hz, 2H), 3.99 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 2.41 (d, J = 1.0 Hz, 3H), 2.29 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 157.9, 155.1, 153.5, 151.6, 151.0, 150.5, 149.5, 148.6, 138.1, 135.7, 129.0, 126.3, 124.8, 124.6, 121.5, 121.1, 111.5, 101.3, 68.3, 64.9, 61.8, 60.9, 60.2, 55.8, 21.2, 17.1, 10.0; IR (thin film, NaCl): 3417.7, 2939.0, 1738.2, 1594.6, 1556.7, 1454.6, 1417.6, 1303.0, 1237.5, 1130.7, 1091.1, 1006.3, 888.4, 754.5; HRMS (ESI-TOF) calc'd for $[M+H]^+$ $C_{28}H_{31}N_2O_7$ = 507.2126, found 507.2130.



Methyl 1'-(hydroxymethyl)-5,7,7',8'-tetramethoxy-6,6'-dimethyl-[1,3'-biisoquinoline]-3-carboxylate (8). Alcohol **21** (29.5 mg, 0.058 mmol, 1 equiv), TEMPO (4.5 mg, 0.029 mmol, 0.5 equiv), N-hydroxysuccinimide (7.4 mg, 0.064 mmol, 1.1 equiv), and (diacetoxyiodo)benzene (75.0 mg, 0.233 mmol, 4 equiv) were dissolved in CH_2Cl_2 (1.2 mL, 0.05 M) and stirred at room temperature. After 3 hours, LCMS showed complete consumption of the alcohol. Methanol (1.2 mL) and *p*-toluenesulfonic acid monohydrate (110.7 mg, 0.582 mmol, 10 equiv) were added and the reaction heated at reflux for 5 hours. The solution was concentrated, then redissolved in CH_2Cl_2 and was washed with dilute aqueous K_2CO_3 and brine. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated. The product was purified by column chromatography using a 1:1 mixture of CH_2Cl_2:EtOAc as the polar solvent (20–30–40–50–60–100% polar solvent/hex + 1% NEt_3). Pale yellow solid, 18.6 mg, 0.038 mmol, 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, J = 0.8 Hz, 1H), 8.30 (s, 1H), 7.90 (s, 1H), 7.59 (d, J = 0.5 Hz, 1H), 5.55 (t, J = 3.5 Hz, 1H), 5.39 (d, J = 3.5 Hz, 2H), 4.06 (s, 3H), 4.06 (s, 3H), 3.99 (s, 3H), 3.96 (s, 3H), 3.90 (s, 3H), 2.49 (d, J = 0.9 Hz, 3H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 160.2, 155.8, 155.6, 155.0, 151.1, 149.1, 148.5, 139.0, 138.4, 135.5, 128.5, 127.9, 125.3, 124.8, 121.6, 120.3, 118.8, 101.3, 64.7, 62.4, 60.9, 60.3, 56.1, 53.4, 52.9, 17.2, 10.0; IR (thin film, NaCl): 3364.8, 3130.4, 2930.2, 2856.2, 1690.6, 1620.8, 1594.3, 1556.6, 1462.3, 1413.2, 1391.8, 1356.6, 1330.7, 1302.1, 1258.7, 1196.3, 1130.7, 1088.7, 1058.5, 1010.1, 964.2, 885.9, 838.1, 801.9, 777.4, 734.0; HRMS (ESI-TOF) calc'd for [M^+] $C_{27}H_{28}N_2O_7$ = 492.1897, found 492.1894.

Asymmetric Hydrogenation of bis-Isoquinoline 8.



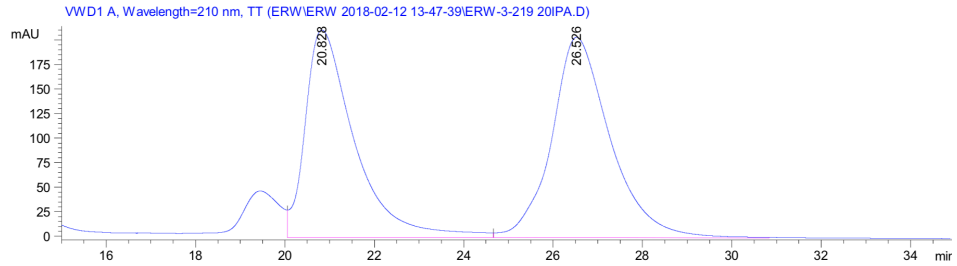
(6*S*,9*R*,14a*S*,15*R*)-9-(hydroxymethyl)-2,4,10,11-tetramethoxy-3,12-dimethyl-5,6,9,14,14a,15-hexahydro-7H-6,15-epiminobenzo[4,5]azocino[1,2-b]isoquinolin-7-one (6). *Note: Due to the air-sensitivity of the phosphine ligand and the low-valent iridium complex, the preparation of the catalyst and the reaction mixture was performed inside a nitrogen-filled glovebox. The reaction was performed in a 100 mL roundbottom flask with a teflon-coated, egg-shaped stir bar, which was placed inside a Parr bomb. Said bomb was also brought into the glovebox for reaction set-up, with the exception of the pressure gauge. A piece of electrical tape was used to seal the bomb immediately upon its removal via the large antechamber, and care was taken to minimize the time between the removal of the tape and the replacement of the gauge.* bis-Isoquinoline **8** (620 mg, 1.07 mmol, 1 equiv) was weighed in air into a 100 mL roundbottom flask with a teflon-coated stir bar and the flask was brought into a nitrogen-filled glovebox. Solid tetra-*n*-butylammonium iodide (238 mg, 0.644 mmol, 0.6 equiv, 3 equiv relative to Ir) was added to the flask. $[Ir(cod)Cl]_2$ (72.1 mg, 0.107 mmol, 0.1 equiv, 20 mol% Ir) and BTFM-Xyliphos (a.k.a. SL-J008-2, 205 mg, 0.225 mmol, 0.21 equiv) were dissolved in 10 mL toluene in a scintillation vial and the resulting solution was allowed to stand for 10 min. 28.3 mL of toluene was added to the flask containing bis-isoquinoline **8**, followed by the addition of 5.4 mL AcOH, resulting in a yellow solution of protonated **8**. The iridium-ligand solution was then added to the flask with two 5 mL rinses, bringing the final volume to 53.7 mL of 9:1 PhMe:AcOH (0.02 M in **8**). The flask was sealed with a rubber septum that was then pierced with three 16 gauge (purple) needles, each bent at a 90º angle. The flask was placed inside the bomb, which was then sealed prior to removal from the glovebox via the large antechamber. At this stage, the tape was removed from the top of the bomb and the pressure gauge was quickly screwed in place and tightened. With

200 rpm stirring, the bomb was charged to 10 bar of H_2 and slowly released. This process was repeated twice, before charging the bomb to 60 bar of H_2, at which time it was placed in a pre-heated 60 ºC oil bath. The bath was maintained at this temperature for 18 h, then raised to 80 ºC for 24 h. At this time, the bomb was removed from the oil bath and the hydrogen pressure was vented. The flask was removed from the bomb and the solution was transferred to a 250 mL roundbottom flask and basified by the careful addition of saturated aqueous K_2CO_3 and water until pH > 7. The solution was transferred to a separatory funnel and the layers were separated. The aqueous phase was extracted 5x with EtOAc, and the combined organic phases were washed twice with water and once with brine, dried over Na_2SO_4, and concentrated. The product was purified by column chromatography (15x1", 1% MeOH/DCM + 1% NEt_3). At this stage, ^{1}H NMR determined the purity of the product to be 90% as a brown foam. 469 mg, 422 mg adjusted for purity, 0.899 mmol, 83% yield, 88% ee. Enantiomeric excess was determined by chiral HPLC analysis [AD, 20% IPA, 280 nm, 1.0 mL/min: t_R(minor) = 21.6 min, t_R(minor) = 26.9 min]. The product could then be crystallized to analytical and optical purity (>99% ee) by dissolving the brown foam in acetonitrile and allowing the solution to slowly evaporate under a stream of N_2. The crystals were washed 3x with 500 µL portions of –40 ºC acetonitrile. The resulting crystals were dried *in vacuo*, providing 203 mg of enantiopure (>99% ee) bis-tetrahydroisoquinoline **6**. The mother liquor could be purified by preparative SFC (AD-H, 20% IPA/CO_2, 210 nm, flow rate = 40 mL/min, t_R(minor) = 25.0 min, t_R(major) = 30.0 min) to provide the remaining material in enantiopure fashion. The crystals isolated above were used to collect the following characterization data. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.73 (s, 1H), 6.35 (s, 1H), 5.79 (dd, *J* = 6.7, 3.8 Hz, 1H), 4.12 – 4.10 (m, 2H), 3.93 (dt, *J* = 12.7, 2.9 Hz, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 3.70 (s, 3H), 3.43 (d, *J* = 10.6 Hz, 1H), 3.22 – 3.10 (m, 3H), 3.03 (dd, *J* = 17.2, 6.6 Hz, 1H), 2.74 (dd, *J* = 14.5, 2.6 Hz, 1H), 2.67 – 2.60 (m, 1H), 2.25 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 157.7, 156.6, 150.0, 149.7, 131.8, 131.2, 130.9, 125.0, 124.4, 119.8, 119.7, 106.1, 69.0, 61.7, 60.7, 60.4, 60.0, 55.9, 55.0, 54.4, 52.8, 33.2, 30.1, 15.9, 9.2; IR (thin film, NaCl): 3301.7, 3052.7, 2940.2, 2859.4, 2835.6, 1621.9, 1614.0, 1486.0, 1463.1, 1455.0, 1410.0, 1352.8, 1324.3, 1273.8, 1233.6, 1190.8, 1124.8, 1082.0, 1000.5, 957.7, 925.7, 894.4, 849.2,

816.5, 788.5, 734.8, 703.2; HRMS (ESI-TOF) calc'd for [M^+] $C_{26}H_{32}N_2O_6$ = 468.2260, found 468.2255; $[\alpha]_D$ = –56.9º (c = 0.5, $CHCl_3$).

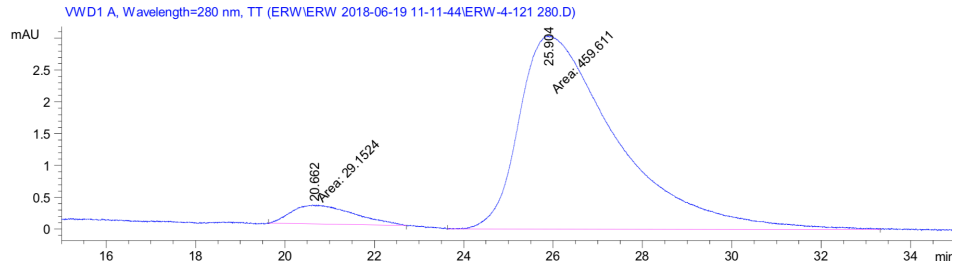
HPLC Traces of Racemic, Enantioenriched, and Enantiopure 6

Racemic **6**:



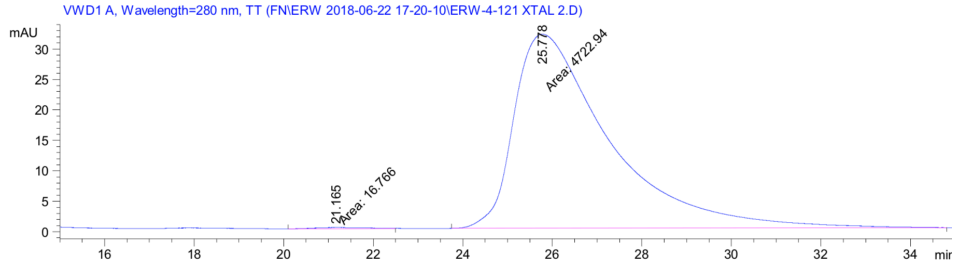
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	20.828	VV	1.1381	1.62981e4	211.43427	46.6229
2	26.526	VB	1.3510	1.86592e4	204.29330	53.3771

Enantioenriched **6**:



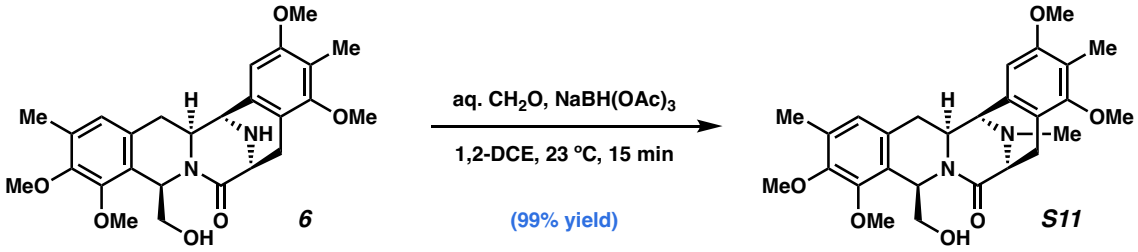
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	20.662	MM	1.6178	29.15240	3.00330e-1	5.9645
2	25.904	MM	2.5301	459.61133	3.02761	94.0355

Enantiopure **6**:



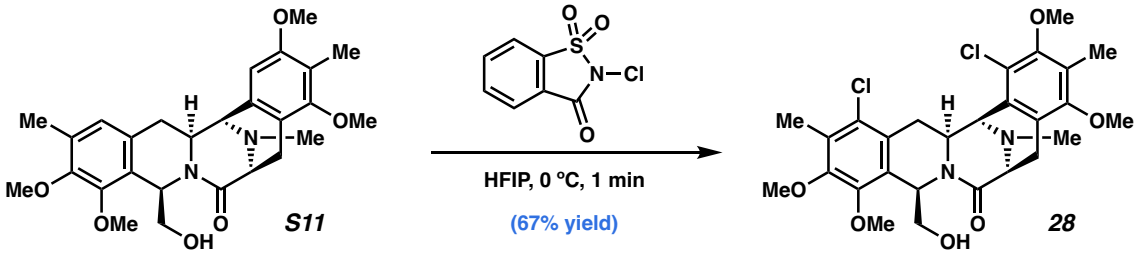
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	21.165	MM	1.3378	16.76600	2.08876e-1	0.3537
2	25.778	MM	2.4698	4722.94482	31.87181	99.6463

Endgame Synthesis of Jorumycin (1).



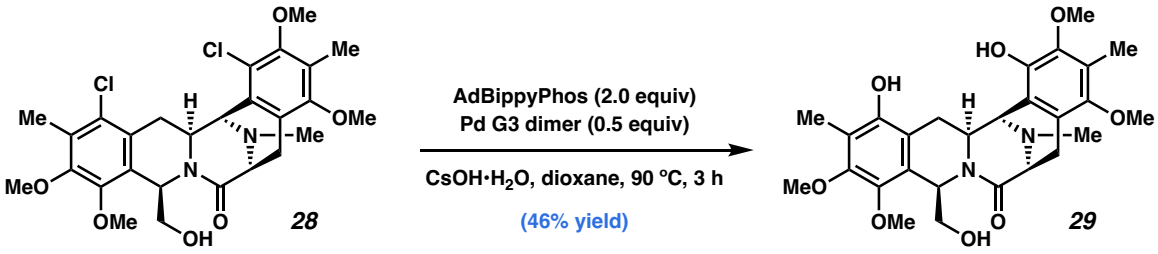
(6*S*,9*R*,14a*S*,15*R*)-9-(hydroxymethyl)-2,4,10,11-tetramethoxy-3,12,16-trimethyl-5,6,9,14,14a,15-hexahydro-7H-6,15-epiminobenzo[4,5]azocino[1,2-b]isoquinolin-7-one (S11). Enantiopure bis-tetrahydroisoquinoline **6** (120 mg, 0.256 mmol, 1 equiv) was dissolved in 1,2-dichloroethane (1,2-DCE, 5.1 mL, 0.05 M) and 37% aqueous formaldehyde (35 µL, 0.474 mmol, 1.85 equiv) was added. The solution was stirred at 800 rpm for 10 min before sodium triacetoxyborohydride (307 mg, 1.45 mmol, 5 equiv) was added. This solution was stirred at 23 ºC for 15 min, at which time LCMS showed full conversion to the product. Citric acid monohydrate (404 mg, 1.92 mmol, 7.5 equiv) was added to the solution, followed by 20 mL water. This solution was stirred for 10 min before the slow addition of saturated aqueous K_2CO_3 until pH > 7. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated. The product was purified by column chromatography (1% MeOH/DCM + 1% NEt_3). Colorless solid, 123 mg, 0.255 mmol, quantitative yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (s, 1H), 6.34 (s, 1H), 5.77 (dd, *J* =

6.5, 3.8 Hz, 1H), 4.00 (dt, *J* = 12.4, 3.0 Hz, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 3.80 – 3.76 (m, 2H), 3.78 (s, 3H), 3.70 (s, 3H), 3.44 (ddd, J = 8.6, 7.1, 6.0 Hz, 1H), 3.22 – 3.15 (m, 2H), 3.14 (dd, J = 17.6, 6.5 Hz, 1H), 2.96 (br s, 1H), 2.94 (dd, *J* = 17.6, 1.2 Hz, 1H), 2.67 (dd, *J* = 14.5, 2.6 Hz, 1H), 2.62 – 2.53 (m, 1H), 2.47 (s, 3H), 2.24 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 157.4, 156.7, 150.0, 149.7, 131.7, 131.5, 128.8, 125.0, 124.4, 119.7, 119.0, 106.9, 69.1, 61.4, 60.7, 60.4, 60.3, 60.0, 58.4, 55.9, 52.8, 40.1, 33.0, 24.2, 15.9, 9.1; IR (thin film, NaCl): 3382.5, 2938.3, 2862.0, 1633.4, 1608.1, 1485.1, 1462.9, 1445.8, 1410.0, 1359.5, 1325.2, 1271.9, 1232.7, 1189.7, 1123.5, 1080.0, 1015.0, 1001.3, 962.6, 910.0, 847.7, 803.5, 646.4; HRMS (ESI-TOF) calc'd for [M^+] $C_{27}H_{34}N_2O_6$ = 482.2417, found 482.2414; $[\alpha]_D$ = –76.2° (c = 0.5, $CHCl_3$).



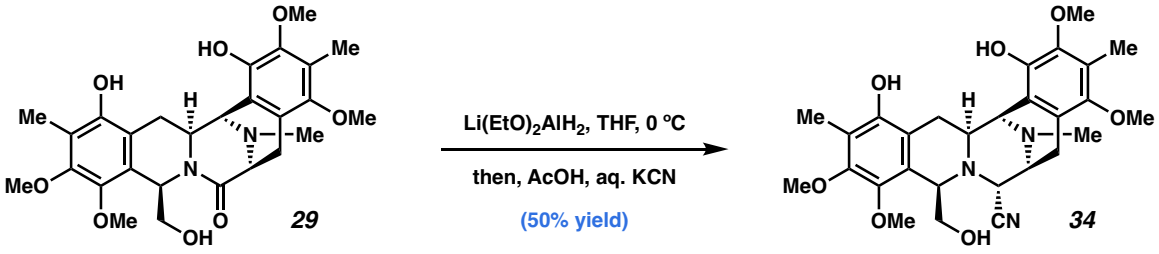
(6*S*,9*R*,14a*S*,15*R*)-1,13-dichloro-9-(hydroxymethyl)-2,4,10,11-tetramethoxy-3,12,16-trimethyl-5,6,9,14,14a,15-hexahydro-7H-6,15-epiminobenzo[4,5]azocino[1,2-b]isoquinolin-7-one (28). bis-Tetrahydroisoquinoline **S11** (179.9 mg, 0.372 mmol, 1.0 equiv) was dissolved in HFIP (16.6 mL, 0.02 M after complete addition) and the solution was cooled to 0 ºC. *N*-Chlorosaccharine (170 mg, 0.782 mmol, 2.1 equiv) was dissolved in 2 mL HFIP and this solution was added at a slow dropwise pace, allowing the orange color to dispel after each addition, and the resulting yellow solution was stirred at 0 ºC. An LCMS sample taken 1 min after complete addition showed full conversion to the dichloride product, so the reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$. The resulting mixture was transferred to a separatory funnel with and diluted with CH_2Cl_2 and water, creating a triphasic system with HFIP on bottom, CH_2Cl_2 in the middle, and the aqueous phase on top. The bottom two phases were collected directly in a 250 mL roundbottom flask. The aqueous phase was basified with K_2CO_3 and extracted with CH_2Cl_2, draining the organic phase directly into the flask. The flask was concentrated and azeotropically dried twice with toluene. The product was then purified by column chromatography (1% MeOH/CH_2Cl_2 + 1% NEt_3). White solid, 138.3 mg, 0.251 mmol, 67% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (dd, *J* = 7.2, 4.1 Hz, 1H), 4.47 (dd, *J* = 3.7, 1.1 Hz, 1H), 4.04 (ddd, *J* = 12.8, 3.7, 2.6 Hz, 1H), 3.90 (s, 3H), 3.82 (dd, *J* = 15.6, 2.6 Hz, 1H), 3.82 (s, 3H), 3.78 – 3.76 (m, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 3.42 (dt, *J* = 10.8, 4.8 Hz, 1H), 3.18 (dd, *J* = 7.0, 4.8 Hz, 1H), 3.13 (dd, *J* = 18.2, 6.7 Hz, 1H), 3.13 – 3.08 (m, 1H), 3.00 (dd, *J* = 18.1, 1.3 Hz, 1H), 2.45 (s, 3H), 2.31 (s, 3H), 2.27 (s, 3H), 2.17 (dd, *J* = 15.6, 12.8 Hz, 1H); 173.3, 156.1, 153.8, 150.4, 148.3, 130.7, 129.8, 128.0, 127.9, 126.2, 125.6, 124.5, 123.9, 69.1, 60.9, 60.5, 60.4, 60.4, 59.5, 58.8, 57.6, 52.1, 40.3, 29.5, 24.7, 13.8, 10.1; IR (thin film, NaCl): 3417.7, 2939.6, 1643.6, 1633.8, 1462.1, 1454.8, 1403.6, 1360.5, 1329.7, 1272.2, 1236.1, 1224.0, 1191.6, 1146.7, 1105.6, 1081.9, 1004.6, 951.2, 931.7, 833.0, 793.8, 767.9, 736.2, 702.5; HRMS (ESI-TOF) calc'd for [M^+] $C_{27}H_{32}N_2O_6Cl_2$ = 550.1637, found 550.1637; $[\alpha]_D$ = –119.0º (c = 0.5, $CHCl_3$).



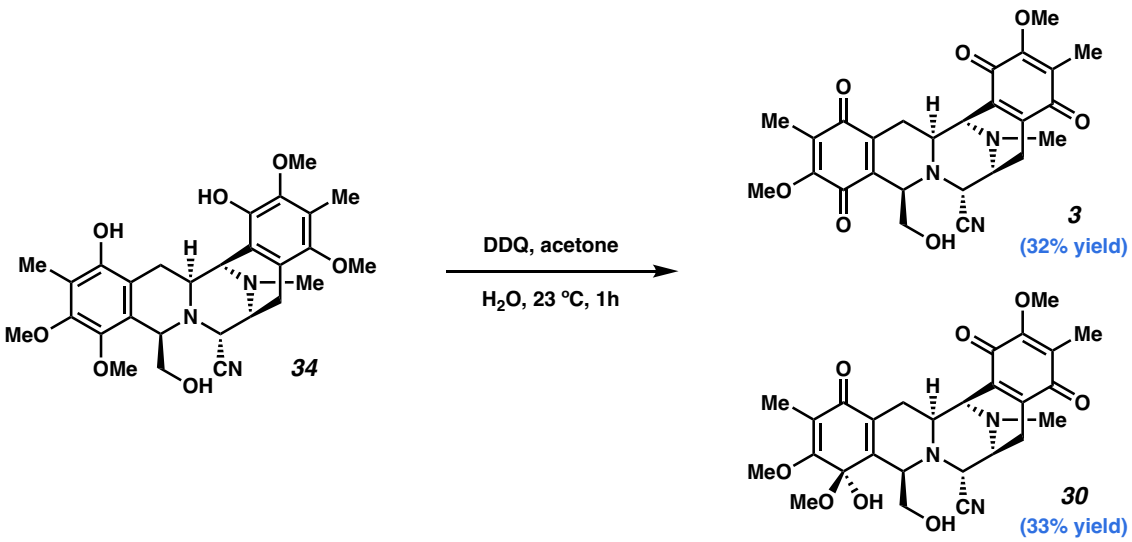
(6S,9R,14aS,15R)-1,13-dihydroxy-9-(hydroxymethyl)-2,4,10,11-tetramethoxy-3,12,16-trimethyl-5,6,9,14,14a,15-hexahydro-7H-6,15-epiminobenzo[4,5]azocino[1,2-b]isoquinolin-7-one (29). *Note: If the reaction vessel is prematurely exposed to air at elevated tempearture, aerobic oxidation leads to the formation of quinones, which undergo hydrolysis of the vinylogous ester in the presence of CsOH. The solution must be fully cooled to room temperature prior to breaking the seal. The bisphenol product is otherwise not sensitive to aerobic oxidation, in the solid state or in solution.* In a nitrogen-filled glovebox, (2′-Amino-1,1′-biphenyl-2-yl)methanesulfonatopalladium(II) dimer (Buchwald's dimer, 33.5 mg, 0.0453 mmol, 0.500 equiv) and 5-[di(1-adamantyl)phosphino]-1′,3′,5′-triphenyl-1′H-[1,4′]bipyrazole (AdBippyPhos, 120.2 mg, 0.181 mmol, 2.00 equiv) were weighed into a scintillation vial and dioxane (8.1 mL) was added. The vial was sealed with electrical tape and removed from the glovebox, sonicated briefly, and returned to the glovebox. The resulting tan solution was then transferred to a 20 mL microwave vial containing bis-tetrahydroisoquinoline **28** (50.0 mg, 0.0907 mmol, 1.00 equiv) and $CsOH•H_2O$ (152.3 mg, 0.907 mmol, 10.0 equiv), followed by a 1 mL rinse (9.1 mL total volume,

0.01 M in **28**). The vial was sealed, removed from the glovebox, and placed in a preheated 90 ºC oil bath. After 3 h, the vial was removed and allowed to cool fully to room temperature prior to removing the seal. Acetic acid (46.5 µL, 0.813 mmol, 9 equiv) was added to quench remaining CsOH and the contents of the vial were transferred to a roundbottom flask, to which silica gel and solid $KHCO_3$ (to quench excess acetic acid) were added directly to dry load the crude mixture onto a silica gel column. The solution was concentrated, and the product was purified by column chromatography (2–4–6–8–10% MeOH + CH_2Cl_2: 200 mL portions, no NEt_3 added, product elutes in the 6% portion). Tan solid, 21.4 mg, 0.0416 mmol, 46% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (dd, *J* = 7.2, 4.2 Hz, 1H), 4.34 (d, *J* = 2.0 Hz, 1H), 3.96 (dt, *J* = 12.3, 2.5 Hz, 1H), 3.81 (s, 3H), 3.80 (dd, *J* = 6.0, 1.0 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.65 (s, 3H), 3.52 (br s, 1H), 3.47 – 3.40 (m, *2*H), 3.23 (dd, *J* = 10.8, 7.2 Hz, 1H), 3.14 (dd, *J* = 18.1, 6.7 Hz, 1H), 3.02 (d, *J* = 18.0 Hz, 1H), 2.45 (s, 3H), 2.21 (s, 3H), 2.14 (s, 3H), 2.09 (dd, *J* = 15.2, 12.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 150.0, 149.7, 146.8, 144.1, 143.5, 143.4, 124.6, 123.7, 122.6, 118.6, 118.3, 115.9, 69.2, 61.0, 60.9, 60.4, 60.3, 59.6, 59.0, 55.3, 52.5, 40.1, 25.2, 24.5, 9.7, 9.3; IR (thin film, NaCl): 3332.3, 2937.3, 1613.3, 1462.2, 1453.3, 1413.6, 1353.2, 1302.2, 1191.4, 1108.8, 1068.0, 1005.9, 910.3, 836.1, 806.3, 730.6; HRMS (ESI-TOF) calc'd for [M^+] $C_{27}H_{34}N_2O_8$ = 514.2315, found 514.2311; $[\alpha]_D$ = –91.6º (c = 0.5, $CHCl_3$).

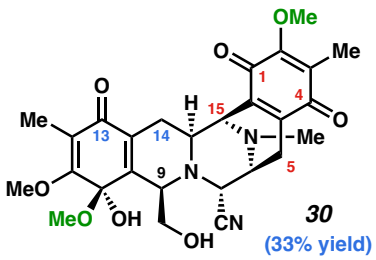


(6S,7R,9R,14aS,15R)-1,13-dihydroxy-9-(hydroxymethyl)-2,4,10,11-tetramethoxy-3,12,16-trimethyl-6,7,9,14,14a,15-hexahydro-5H-6,15-epiminobenzo[4,5]azocino[1,2-b]isoquinoline-7-carbonitrile (34). In an oven-dried vial, $LiAlH_4$ solution (1.0 M in THF, 2 mL, 2.0 mmol) was cooled to 0 ºC. A solution of ethyl acetate (230 µL, 2.35 mmol) in 2 mL THF was added slowly, and the resulting solution was stirred 30 min at 0 ºC, providing a 0.47 M solution of $Li(EtO)_2AlH_2$ in THF. bis-Tetrahydroisoquinoline **29** (49.0 mg, 0.095 mmol, 1.0 equiv) was dissolved in THF (4.8 mL, 0.02 M) and the resulting solution was cooled to 0 ºC. A solution of

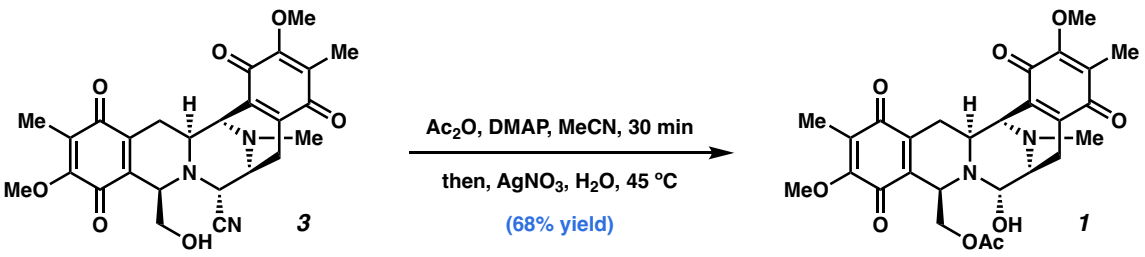
$Li(EtO)_2AlH_2$ (0.47 M in THF, 3.0 mL, 1.43 mmol, 15.0 equiv) was added slowly, resulting in extensive evolution of H_2. After stirring 50 min, the reaction was quenched with acetic acid (115 µL, 2.00 mmol, 21 equiv) and aqueous potassium cyanide (4.8 M, 120 µL, 0.571 mmol, 6.0 equiv) was added, followed by celite and anhydrous Na_2SO_4 (roughly 1 g each). The solution was diluted with 8 mL THF and stirred 10 h, warming to room temperature. More celite was added, and the suspension was filtered through celite, rinsing with EtOAc. The filtrate was transferred to a roundbottom flask and was concentrated. At this stage, LCMS revealed a ~4:1 mixture of product **34** and starting material **29**, so the crude mixture was resubjected to the reduction conditions, using 3 mL THF as the reaction solvent and 1 mL of freshly prepared $Li(EtO)_2AlH_2$ solution. After 10 min, LCMS showed minimal conversion of the remaining starting material, with some over-reduced product (m/z = 501). The reaction mixture was quenched and worked up as described above. The product was purified by column chromatography (50–75–100% EtOAc/hex, 200 mL each; product elutes in the 75% portion). Colorless solid, 25.2 mg, 47.9 µmol, 50% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (dD, *J* = 2.7, 1.1 Hz, 1H), 4.00 – 4.05 (m, 2H), 3.81 (s, 3H), 3.751 (s, 3H), 3.749 (s, 3H), 3.70 (s, 3H), 3.56 (dd, *J* = 10.9, 4.4 Hz, 1H), 3.40 (ddd, *J* = 7.5, 2.5, 1.2 Hz, 1H), 3.31 (dt, *J* = 12.1, 2.7 Hz, 1H), 3.18 (d, *J* = 9.4 Hz, 1H), 3.13 (dd, *J* = 15.6, 2.7 Hz, 1H), 3.10 (dd, *J* = 18.6, 7.8 Hz, 1H), 2.51 (d, *J* = 18.6 Hz, 1H), 2.34 (s, 3H), 2.22 (s, 3H), 2.09 (s, 3H), 1.85 (dd, *J* = 15.6, 12.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6, 148.7, 146.6, 143.7, 143.4, 143.1, 125.4, 123.5, 122.7, 118.1, 118.0, 117.1, 116.7, 66.2, 61.2, 61.0, 60.8, 60.4, 60.2, 58.5, 57.1, 56.7, 55.2, 41.9, 25.4, 21.7, 9.8, 9.0; IR (thin film, NaCl): 3427.6, 2936.1, 2832.7, 2228.1, 1606.8, 1463.2, 1412.1, 1384.5, 1349.9, 1319.9, 1300.9, 1251.3, 1218.1, 1191.3, 1150.7, 1107.7, 1070.1, 1001.7, 981.7, 907.7, 875.4, 829.8, 754.4; HRMS (ESI-TOF) calc'd for $[M^+]$ $C_{28}H_{35}N_3O_7$ = 525.2475, found 525.2471; $[\alpha]_D$ = +22.9º (c = 0.5, $CHCl_3$).



(–)-Jorunnamycin A (3). bis-Tetrahydroisoquinoline **34** (22.0 mg, 41.9 µmol, 1.0 equiv) and 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (DDQ, 38.0 mg, 167 µmol, 4.0 equiv) were weighed into a roundbottom flask and 8.4 mL of a 9:1 mixture of acetone and water was added (0.005 M). The purple solution gradually turned blood red. After 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated. The product was purified using reverse-phase (C_{18}) preparative HPLC (MeCN/0.4% acetic acid in water, 5.0 mL/min, monitor wavelength = 254 nm, 20–70% MeCN over 5 min, hold at 70% for 3 min, hold at 95% for 3 min. Product **3** has t_R = 7.2 min). Yellow film, 6.6 mg, 13.4 µmol, 32% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.11 (d, *J* = 2.6 Hz, 1H), 4.08 (dd, *J* = 3.0, 1.0 Hz, 1H), 4.03 (s, 3H), 3.99 (s, 3H), 3.90 (app q, *J* = 3.1 Hz, 1H), 3.71 (dd, *J* = 11.3, 3.4 Hz, 1H), 3.50 (br s, 1H), 3.42 (ddd, *J* = 7.4, 2.6, 1.5 Hz, 1H), 3.18 (dt, *J* = 11.4, 2.9 Hz, 1H), 2.93 (ddd, *J* = 17.4, 2.8, 0.9 Hz, 1H), 2.83 (dd, *J* = 21.0, 7.5 Hz, 1H), 2.31 (s, 3H), 2.26 (d, *J* = 21.0 Hz, 1H), 1.95 (s, 3H), 1.94 (s, 3H), 1.41 (ddd, *J* = 17.5, 11.5, 2.7 Hz, 1H); IR (thin film, NaCl): 3508.5, 2943.0, 2226.8, 1651.8, 1620.8, 1447.2, 1373.6, 1310.6, 1277.4, 1236.0, 1190.6, 1151.1, 1098.1, 1077.8, 963.7, 886.8, 775.3; HRMS (ESI-TOF) calc'd for [M^+] $C_{26}H_{27}N_3O_7$ = 493.1849, found 493.1848; $[\alpha]_D$ = –94.3° (c = 0.35, $CHCl_3$).

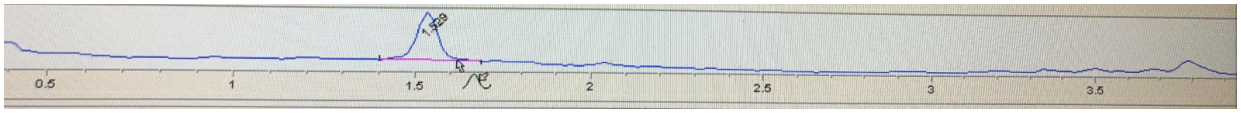


(6S,7R,9R,10R,14aS,15R)-10-hydroxy-9-(hydroxymethyl)-2,10,11-trimethoxy-3,12,16-trimethyl-1,4,13-trioxo-1,5,6,7,9,10,13,14,14a,15-decahydro-4H-6,15-epiminobenzo[4,5]azocino[1,2-b]isoquinoline-7-carbonitrile (30). Product **30** was also isolated from the preparative HPLC method described above, with t_R = 9.3 min. Yellow film, 7.3 mg, 13.9 μmol, 33% yield. The structure was assigned using diagnostic nOe correlations (highlighted methoxy groups) and HMBC correlations (C13 to C14 but not C9, C1 to C15 and C5, C4 to C15 and C5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (t, *J* = 7.7 Hz, 1H), 4.16 (dd, *J* = 3.8, 1.5 Hz, 1H), 4.08 (s, 3H), 4.00 (s, 3H), 3.74 (dd, *J* = 7.8, 5.8 Hz, 1H), 3.66 (d, *J* = 2.6 Hz, 1H), 3.43 (ddd, *J* = 7.8, 2.8, 1.7 Hz, 1H), 3.29 (dt, *J* = 10.8, 4.2 Hz, 1H), 3.13 (s, 3H), 2.82 (dd, *J* = 20.9, 7.8 Hz, 1H), 2.62 (ddd, *J* = 18.6, 4.6, 3.0 Hz, 1H), 2.28 (s, 3H), 2.13 (d, *J* = 20.9 Hz, 1H), 1.93 (s, 3H), 1.75 (s, 3H), 1.68 (br s, 1H, OH), 1.52 (ddd, *J* = 18.5, 10.7, 3.1 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 186.6, 185.2, 182.7, 160.4, 155.9, 143.2, 141.2, 136.2, 128.5, 127.7, 117.9, 116.0, 99.0, 74.2, 61.2, 60.5, 59.1, 56.0, 55.6, 54.6, 53.9, 51.8, 41.9, 26.0, 21.5, 8.8, 7.9; IR (thin film, NaCl): 3445.7, 3013.6, 2952.6, 2853.8, 2226.1, 1643.9, 1615.0, 1455.3, 1412.8, 1373.4, 1318.1, 1272.0, 1247.5, 1189.2, 1153.9, 1091.9, 1060.9, 1025.7, 990.6, 973.3, 950.1, 895.6, 878.0, 759.4, 720.6, 666.1; HRMS (ESI-TOF) calc'd for $[M–OH]^+$ $C_{27}H_{29}N_3O_7$ = 493.1849, found 493.1848; $[\alpha]_D$ = –94.3° (c = 0.35, $CHCl_3$).

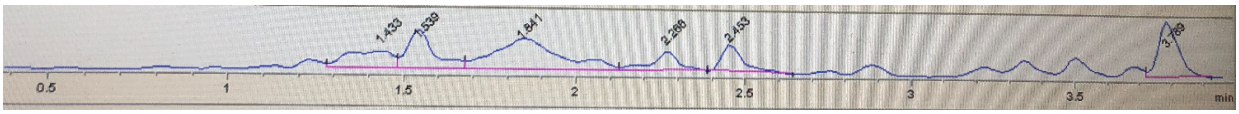


(–)-Jorumycin (1). In a 1-dram vial, Jorunnamycin A (**3**, 6.6 mg, 13.4 µmol, 1.0 equiv) and 4-dimethylaminopyridine (DMAP, 4.9 mg, 40.1 µmol, 3.0 equiv) were dissolved in acetonitrile (400 µL, 0.03 M) and acetic anhydride (3.8 µL, 40.1 µmol, 3.0 equiv) was added neat. The brown solution immediately turned yellow. After 30 minutes, LCMS showed complete conversion to the acetylated intermediate. At this stage, silver nitrate (57.0 mg, 334 µmol, 25.0 equiv) and water (260 µL) were added in rapid succession. The vial was resealed and placed in a pre-heated 45 ºC heating block, then protected from light with aluminum foil. After 30 minutes, LCMS showed complete conversion to (–)-jorumycin (**1**), so the solution was filtered to remove AgCN and silver black, and the crude reaction mixture was purified directly using preparative HPLC (MeCN/0.4% acetic acid in water, 5.0 mL/min, monitor wavelength = 265 nm, 10–55% MeCN over 7 min, ramp to 95% MeCN over 0.2 min, hold at 95% for 1.8 min for a total run time of 9 min. Product has t_R = 6.6 min). Yellow film, 4.8 mg, 9.12 µmol, 68% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.44 (dd, *J* = 11.2, 3.5 Hz, 1H), 4.44 (br s, 1H), 4.37 (d, *J* = 3.1 Hz, 1H), 4.01 (s, 3H), 3.99 (s, 3H), 3.92 (br s, 1H), 3.82 (dd, *J* = 11.3, 3.4 Hz, 1H), 3.21 – 3.16 (m, 1H), 3.14 (dd, *J* = 7.3, 4.7 Hz, 1H), 2.84 (dd, *J* = 16.6, 2.4 Hz, 1H), 2.66 (dd, *J* = 21.1, 7.6 Hz, 1H), 2.27 (s, 3H), 2.23 (d, *J* = 21.0 Hz, 1H), 1.96 (s, 3H), 1.94 (s, 3H), 1.76 (s, 3H), 1.24 (ddd, *J* = 16.6, 11.3, 2.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.0, 181.4, 170.2, 155.8, 155.4, 142.1, 142.0, 137.4, 128.9, 128.5, 83.1, 64.4, 61.19, 61.17, 57.6, 54.4, 52.9, 51.1, 41.6, 25.7, 20.74, 20.69, 8.9, 8.8; IR (thin film, NaCl): 3478.3, 2923.5, 2850.7, 1738.4, 1651.6, 1620.8, 1449.0, 1373.6, 1309.4, 1260.4, 1233.9, 1188.7, 1149.6, 1096.2, 1083.0, 1013.2, 901.9, 871.7, 839.6, 801.2, 730.2; HRMS (ESI-TOF) calc'd for [M^+] $C_{27}H_{30}N_2O_9$ = 526.1951, found 526.1956; $[\alpha]_D$ = –86.8º (c = 0.1, $CHCl_3$).

Note: After purification via the method as described above (preparative HPLC using MeCN and 0.4% AcOH in H_2O with lyophilization of the product-containing fractions), we obtained jorumycin as a yellow solid in high purity as determined from the following LCMS trace (TIC):



Following this method of purification, a sample was prepared for NMR spectroscopy using $CDCl_3$ that had been freshly distilled from flame-dried K_2CO_3, and a ^1H spectrum was recorded within minutes of preparing the sample. Despite all of our precautions, significant impurities were present in the spectrum at 1.25 ppm, 2–2.25 ppm, and 5–6 ppm. The sample was immediately tested for purity using the same LCMS method as above and provided the following chromatogram (TIC):



Many attempts to repurify our samples were made, including repurification via the method described above, preparative HPLC with MeCN and H_2O in the absence of AcOH, column chromatography with 1% MeOH in CH_2Cl_2 in the presence or absence of NEt_3, and column chromatography on SiO_2 or basic alumina with EtOAc in the absence of NEt_3. In all cases, spectra containing the impurities described above were obtained, independent of the method of purification. This leads us to conclude that jorumycin is not stable in chloroform; this is also consistent to observations made in the isolation report (21). The optical rotation listed above was measured by repurifying the product as originally described and dissolving the sample in $CHCl_3$ that had been freshly distilled from flame-dried K_2CO_3 immediately prior to recording its optical rotation to minimize decomposition, and this method provided a value in good agreement with previous literature (15–20); however, a ^1H NMR spectrum of this sample showed the same impurities described above. We therefore conclude that future synthetic endeavors should avoid the use of chloroform as a solvent for analytical characterization (*51, 52*). *We are currently working to obtain the requisite data in a solvent such as benzene or acetonitrile.*

Tabulated NMR Data for Hemiacetal 30, Jorunnamycin A (3), and Jorumycin (1).

	^{1}H NMR	^{13}C NMR
Hydroxymethyl	4.54 (t, *J* = 7.7 Hz, 1H)	186.6
C15	4.16 (dd, *J* = 3.8, 1.5 Hz, 1H)	185.2
OMe	4.08 (s, 3H)	182.7
OMe	4.00 (s, 3H)	160.4
Hydroxymethyl	3.74 (dd, *J* = 7.8, 5.8 Hz, 1H)	155.9
C7	3.66 (d, *J* = 2.6 Hz, 1H)	143.2
C6	3.43 (ddd, *J* = 7.8, 2.8, 1.7 Hz, 1H)	141.2
α-amino (between C14 and C15)	3.29 (dt, *J* = 10.8, 4.2 Hz, 1H)	136.2
Hemiacetal OMe	3.13 (s, 3H)	128.5
C5	2.82 (dd, *J* = 20.9, 7.8 Hz, 1H)	127.7
C1	2.62 (ddd, *J* = 18.6, 4.6, 3.0 Hz, 1H)	117.9
NMe	2.28 (s, 3H)	116.0
C4	2.13 (d, *J* = 20.9 Hz, 1H)	99.0
Me	1.93 (s, 3H)	74.2
Me	1.75 (s, 3H)	61.2
OH	1.63 (br s, 1H, OH),	60.5
C1	1.52 (ddd, *J* = 18.5, 10.7, 3.1 Hz, 1H)	59.1
		56.0
		55.6
		54.6
		53.9
		51.8
		41.9
		26.0
		21.5
		8.8
		7.9

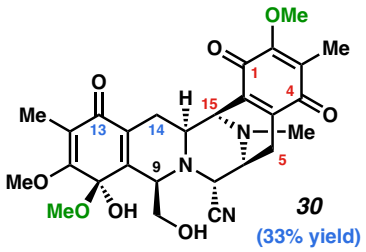
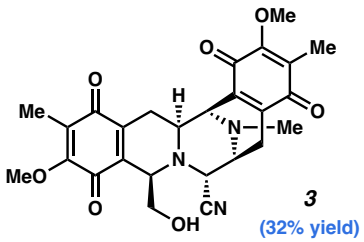


Table S1. Tabulated NMR data and assignments for hemiacetal **30**.

Jorunnamycin A (3)

Synthetic Jorunnamycin A, ^{1}H NMR	Authentic Jorunnamycin A (Ref. 15), ^{1}H NMR	Synthetic Jorunnamycin A, ^{13}C NMR	Authentic Jorunnamycin A (Ref. 15), ^{13}C NMR
4.11 (d, *J* = 2.6 Hz, 1H)	4.08 (d, J = 2.3 Hz, 1H)	186.4	186.5
4.08 (dd, *J* = 3.0, 1.0 Hz, 1H)	4.06 (app d, J = 2.1 Hz, 1H)	185.6	185.7
4.03 (s, 3H)	4.01 (s, 3H)	182.4	182.5
3.99 (s, 3H)	3.97 (s, 3H)	181.5	181.6
3.90 (app q, *J* = 3.1 Hz, 1H)	3.87 (ddd, J = 5.8, 3.0, 3.0 Hz, 1H)	155.6	155.7
3.71 (dd, *J* = 11.3, 3.4 Hz, 1H)	3.69 (dt, J = 11.5, 2.8 Hz, 1H)	155.5	155.6
3.50 (br s, 1H)	3.48 (m, 1H)	141.8	141.8
3.42 (ddd, *J* = 7.4, 2.6, 1.5 Hz, 1H)	3.39 (app d, J = 7.5 Hz, 1H)	141.5	141.6
3.18 (dt, *J* = 11.4, 2.9 Hz, 1H)	3.15 (dt, J = 11.5, 2.8 Hz, 1H)	136.2	136.3
2.93 (ddd, *J* = 17.4, 2.8, 0.9 Hz, 1H)	2.91 (dd, J = 17.5, 2.6 Hz, 1H)	135.8	135.8
2.83 (dd, *J* = 21.0, 7.5 Hz, 1H)	2.81 (dd, J = 20.9, 7.5 Hz, 1H)	129.1	129.1
2.31 (s, 3H)	2.28 (s, 3H)	128.8	128.8
2.26 (d, *J* = 21.0 Hz, 1H)	2.23 (d, J = 21.1 Hz, 1H)	117.0	117.0
1.95 (s, 3H)	1.93 (s, 3H)	64.1	64.2
1.94 (s, 3H)	1.92 (s, 3H)	61.3	61.3
1.41 (ddd, *J* = 17.5, 11.5, 2.7 Hz, 1H)	1.38 (ddd, J = 17.3, 11.5, 2.6 Hz, 1H)	61.3	61.3
		59.1	59.2
		58.1	58.2
		54.6	54.7
		54.4	54.5
		54.4	54.4
		41.8	41.8
		25.5	25.6
		21.6	21.7
		9.0	9.0
		8.9	8.9

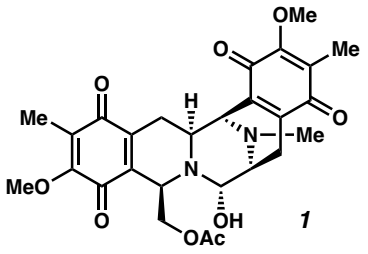


3
(32% yield)

Table S2. Tabulated NMR data for (–)-Jorunnamycin A (**3**).

Jorumycin (1)

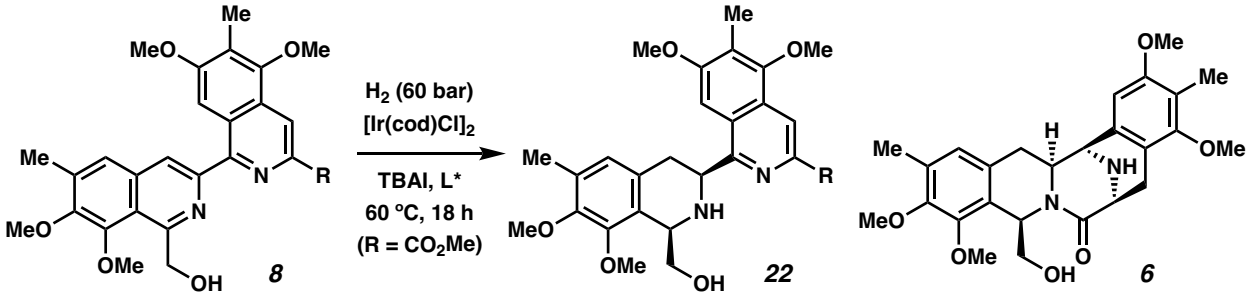
Synthetic Jorumycin, ^{1}H NMR	Authentic Jorumycin (Ref. 15), ^{1}H NMR	Synthetic Jorumycin, ^{13}C NMR	Authentic Jorumycin (Ref. 15), ^{13}C NMR
4.47 – 4.41 (m, 1H)	4.41 (dd, *J* = 11.1, 3.4 Hz, 1H),	186.7	186.8
4.44 (dd, *J* = 11.2, 3.5 Hz, 1H)	4.41 (d, *J* = 11.1 Hz, 1H),	186.0	186.1
4.36 (q, *J* = 3.6, 3.2 Hz, 1H)	4.35 (ddd, *J* = 5.5, 2.8, 2.8 Hz, 1H),	186.7	182.8
4.00 (s, 3H)	3.98 (s, 3H),	181.5	181.6
3.98 (s, 3H)	3.96 (s, 3H),	170.2	170.3
3.90 (app d, *J* = 2.5 Hz, 1H)	3.88 (app d, *J* = 2.7 Hz, 1H),	155.8	155.9
3.88 (br s, 1H, C21-OH)	3.86 (d, *J* = 10.9 Hz, 1H, C21-OH),	155.4	155.5
3.81 (dd, *J* = 11.2, 3.3 Hz, 1H)	3.80 (dd, *J* = 11.1, 3.2 Hz, 1H),	142.1	142.2
3.20 – 3.12 (m, 2H)	3.16 (m, 1H),	142.0	142.1
	3.14 (m, 1H),	137.4	137.5
2.84 (dd, *J* = 16.7, 2.2 Hz, 1H)	2.82 (dd, *J* = 16.8, 2.3 Hz, 1H),	134.6	134.7
2.65 (dd, *J* = 21.0, 7.5 Hz, 1H)	2.63 (dd, *J* = 21.1, 7.5 Hz, 1H),	128.9	129.0
2.26 (s, 3H)	2.24 (s, 3H),	128.5	128.6
2.23 (d, *J* = 18.8 Hz, 1H)	2.22 (d, *J* = 20.0 Hz, 1H),	83.2	83.2
1.96 (s, 3H)	1.94 (s, 3H),	64.3	64.4
1.93 (s, 3H)	1.91 (s, 3H),	61.2	61.2
1.76 (s, 3H)	1.74 (s, 3H),	61.2	61.2
1.28 (dd, *J* = 11.5, 2.6 Hz, 1H)	1.24 (ddd, *J* = 16.6, 11.3, 2.6 Hz, 1H)	57.6	57.7
		54.3	54.4
		52.9	52.9
		51.2	51.3
		41.6	41.7
		25.8	25.8
		20.7	20.8
		20.6	20.7
		9.0	9.0
		8.8	8.9



1

Table S3. Tabulated data for (–)-Jorumycin (**1**).

Optimization of the Enantioselective Hydrogenation.

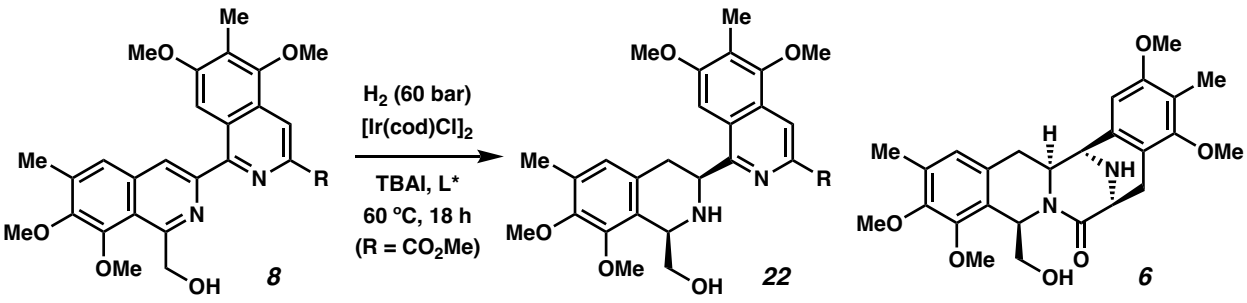


Entry	Ligand	Yield 22	ee 22	Yield 6
L1	SL-J001-1	—	—	—
L2	SL-J002-1	—	—	—
25	Xyliphos	26%	80%	—
L3	SL-J216-1	—	—	—
L4	SL-J404-1	68%	–15%	—
L5	SL-J006-1	—	—	—
26	BTFM-Xyliphos	83%	94%	10%
L6	SL-J007-1	—	—	—
L7	SL-J013-1	—	—	—
L8	SL-J418-1	30%	–77%	—
L9	SL-J212-1	—	—	—
L10	SL-J015-1	22%	–16%	—
L11	SL-J003-2	—	—	—
L12	SL-J009-1	—	—	—
L13	SL-J004-1	—	—	—
L14	SL-J502-1	—	—	—
L15	SL-J505-1	—	—	—
L16	SL-W002-1	—	—	—
L17	SL-W006-1	—	—	—
L18	SL-W001-1	2%	ND	—
L19	SL-W005-1	6%	ND	—
L20	SL-W003-1	4%	ND	—

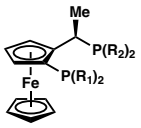
Entry	Ligand	Yield 22	ee 22	Yield 6
L21	SL-W008-1	2%	ND	—
L22	SL-W009-1	—	—	—
L23	SL-W022-1	—	—	—
L24	BINAP	—	—	—
L25	BINAPINE	6%	ND	—
L26	MeO-BIBOP	<1%	ND	—
L27	DTB-MeOBIPHEP	—	—	—
L28	DTBM-MeOBIPHEP	—	—	—
L29	SEGPHOS	<1%	ND	—
L30	DM-SEGPHOS	—	—	—
L31	C_3-TunePhos	—	—	—
L32	DIFLUORPHOS	14%	62%	—
L33	SYNPHOS	—	—	—
L34	SL-M001-2	23%	32%	—
L35	SL-M012-2	6%	ND	—
L36	SL-M003-2	55%	–27%	—
L37	SL-T001-1	88%	–17%	—
L38	SL-T002-1	—	—	—
L39	SL-N004-1	—	—	—
L40	*t*-Bu-PHOX	1%	ND	—
23	(CF_3)-*t*-BuPHOX	22%	–82%	—
L41	QUINAP	6%	ND	—
L42	Me-BPE	30%	26%	—
L43	Et-BPE	31%	16%	—
L44	*i*-Pr-BPE	2%	ND	—
L45	Me-DUPHOS	11%	ND	—
L46	Et-DUPHOS	12%	ND	—
L47	DuanPhos	3%	ND	—
L48	catASium MNXyl(S)	36%	0%	—
L49	catasium MNXylF(S)	12%	ND	—
24	Et-FerroTANE	26%	87%	—

Entry	Ligand	Yield 22	ee 22	Yield 6
L50	Me-Ferrocelane	<1%	ND	—
L51	*i*-Pr-Ferrocelane	—	—	—
L52	DIOP	16%	6%	—
L53	SolPhos	—	—	—
L54	P-Phos	7%	46%	—
L55	PhanePhos	31%	10%	—
L56	Xyl-PhanePhos	15%	58%	—
L57	SDP	4%	ND	—
L58	SKP	—	—	—
L59	Chiraphos	48%	13%	—
L60	BDPP	8%	ND	—
L61	catASium D	20%	47%	—
L62	BPPM	8%	ND	—
L63	NorPhos	65%	38%	—

Table S4. Results of 66 ligands tested in the asymmetric hydrogenation of **8**.

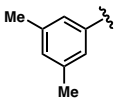


Josiphos lig.	R_1	R_2	yield and ee of *22*
L1: SL-J001-1	Ph	Cy	--
L2: SL-J002-1	Ph	*t*-Bu	--
25: SL-J005-2	Ph	Xyl	26%, 80% ee
L3: SL-J216-1	1-Nap	*t*-Bu	--
L4: SL-J404-1	1-Nap	Xyl	68%, –15% ee
L5: SL-J006-1	BTFM	Cy	--
26: SL-J008-1	*BTFM*	*Xyl*	*83%, 94% ee*
L6: SL-J007-1	DMM-Ph	Cy	--
L7: SL-J013-1	DMM-Ph	*t*-Bu	--
L8: SL-J418-1	DMM-Ph	Xyl	30%, –77% ee
L9: SL-J212-1	2-fur	*t*-Bu	--
L10: SL-J015-1	2-fur	Xyl	22%, –16% ee
L11: SL-J003-2	Cy	Cy	--
L12: SL-J009-1	Cy	*t*-Bu	--
L13: SL-J004-1	Cy	Ph	--
L14: SL-J502-1	*t*-Bu	Ph	--
L15: SL-J505-1	*t*-Bu	*o*-Tol	--



Josiphos framework (-1 enantiomer)

Xyl:



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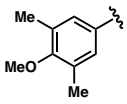

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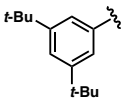
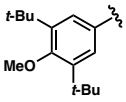
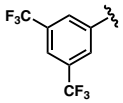


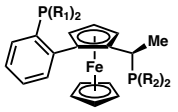
DTBM:



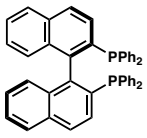
BTFM:



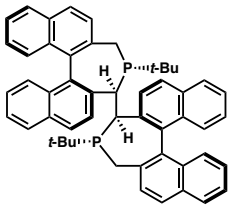
Walphos lig.	R_1	R_2	yield and ee of *22*
L16: SL-W002-1	Ph	Ph	--
L17: SL-W006-1	Ph	Xyl	--
L18: SL-W001-1	Ph	BTFM	2%, ee ND
L19: SL-W005-1	DMM-Ph	BTFM	6%, ee ND
L20: SL-W003-1	Ph	Cy	4%, ee ND
L21: SL-2008-1	Cy	BTFM	2%, ee ND
L22: SL-W009-1	Xyl	Xyl	--
L23: SL-W022-1	Ph	norbornyl	--



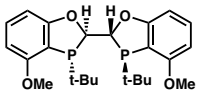
Walphos framework (-1 enantiomer)



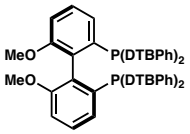
L24: BINAP
--



L25: BINAPINE
6%, ee ND



L26: MeO-BIBOP
<1 %, ee ND



L27: DTB-MeOBIPHEP
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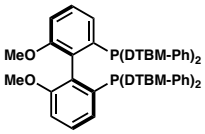

L28: DTBM-MeOBIPHEP
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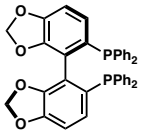
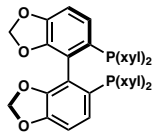
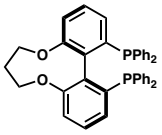


L29: SEGPHOS
<1 %, ee ND



L30: DM-SEGPHOS
--



L31: C_3-TunePhos
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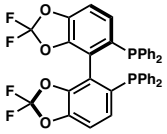
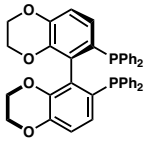


L32: Difluorphos
14%, 62% ee



L33: SYNPHOS
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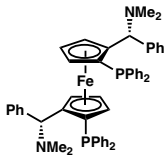
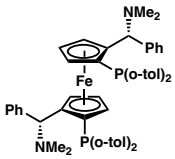


L34: SL-M001-2
23%, 32% ee



L35: SL-M012-2
6%

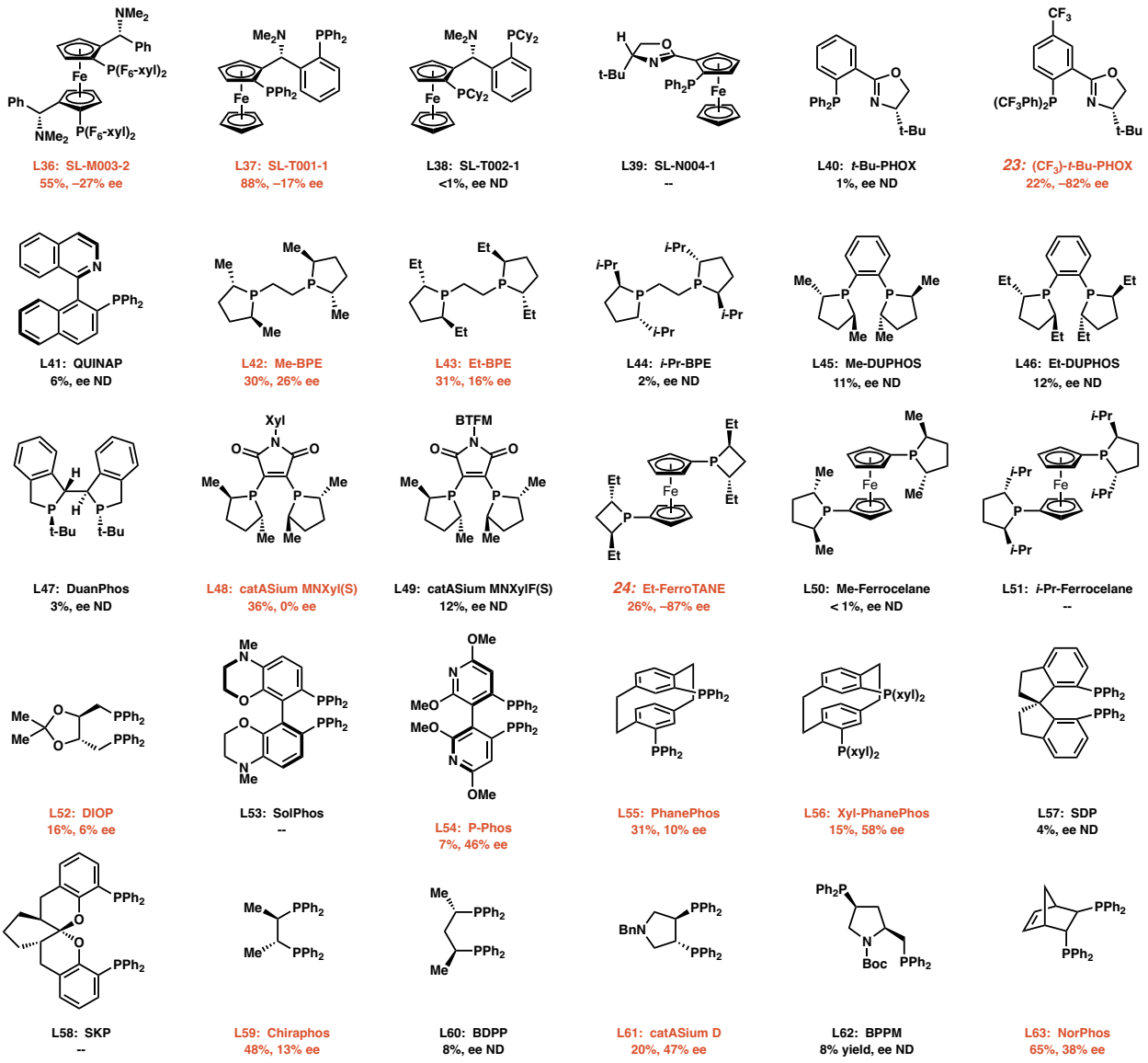


Figure S1. Results of 66 ligands tested in the asymmetric hydrogenation of **8**, including the ligands' structures.

Explanation of Selectivity Differences Between Products 22 and 6.

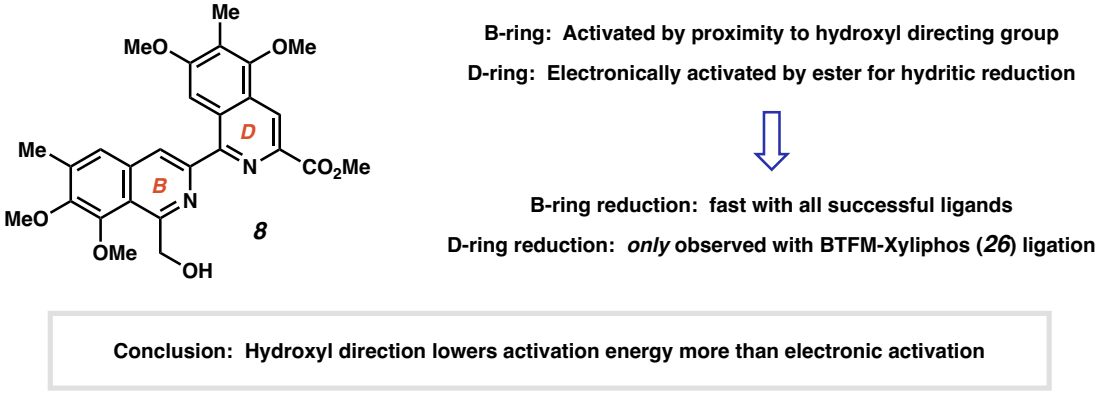


Figure S2. While the D-ring is electronically activated to receive nucleophilic hydritic M–H bonds, the directing affect of the hydroxymethyl group appended to the B-ring appears to be a more strongly activating group.

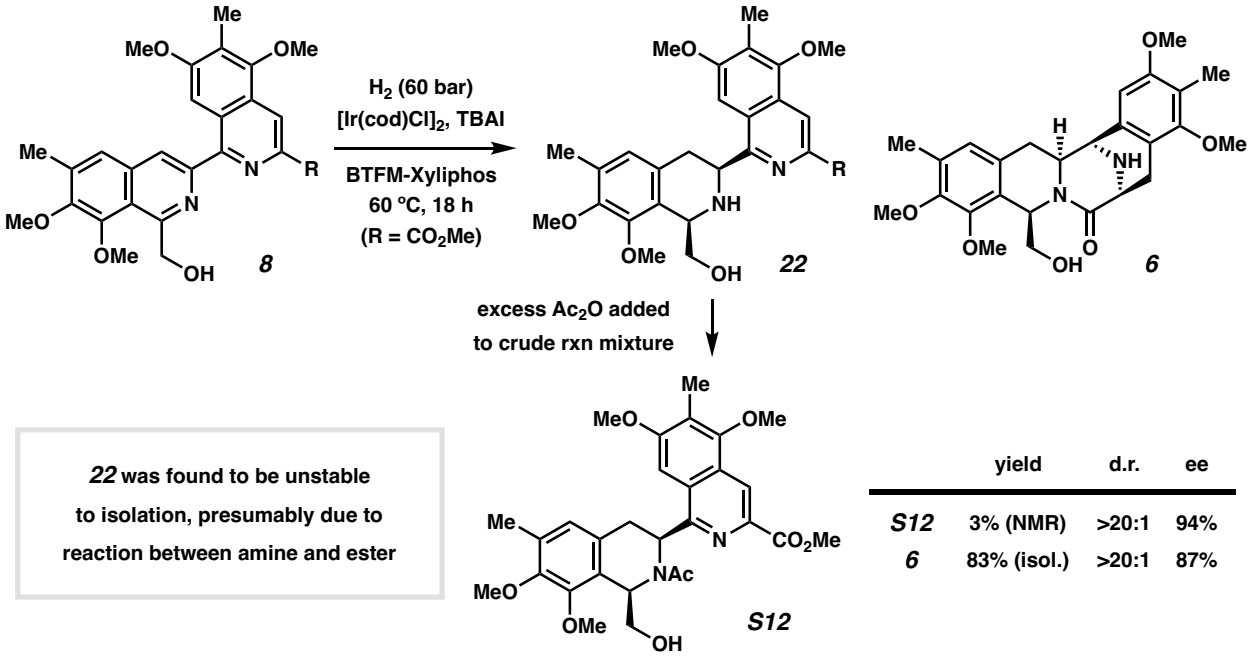


Figure S3. Of all the ligands tested, only BTFM-Xyliphos enables the further reduction of **22** to **6** following lactamization. Intriguingly, the product **22** shows a 94% ee, while product **6** only shows 87% ee. We propose that the discrepancy in enantioenrichment of the products is due to competitive D-ring reduction with lower enantioselectivity than that observed when the B-ring is reduced first. Because no other diastereomers are observed, global reduction via this route also appears to be fully diastereoselective.

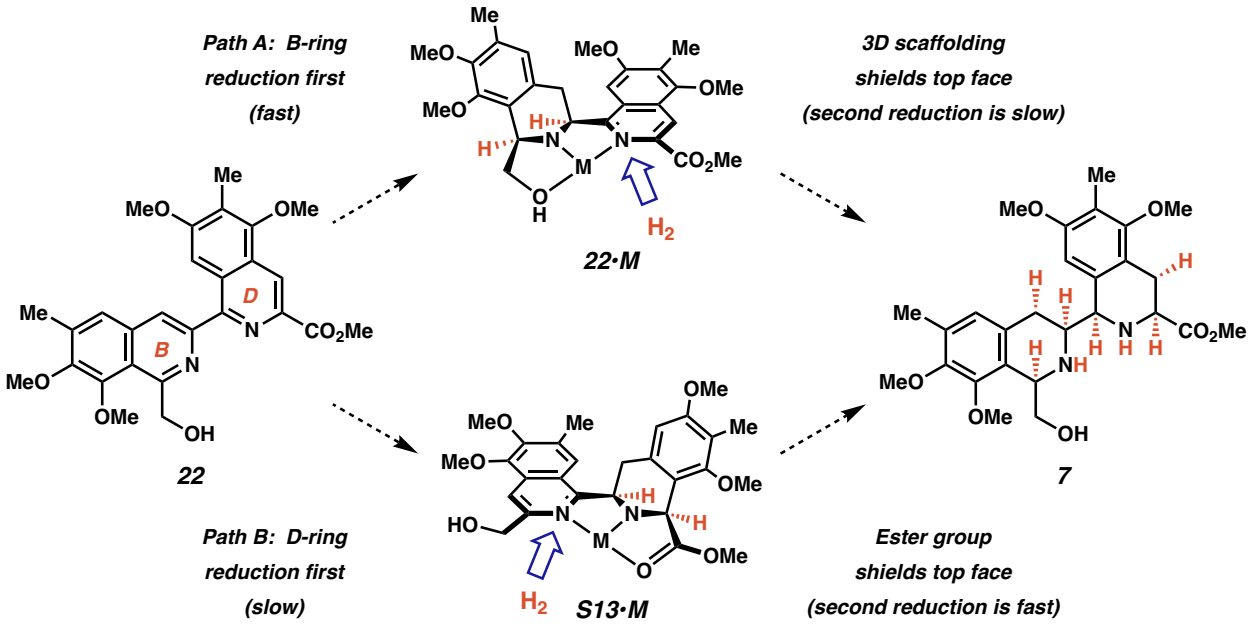
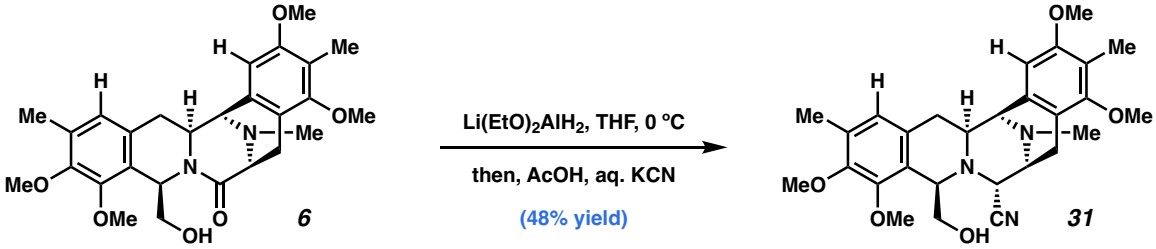


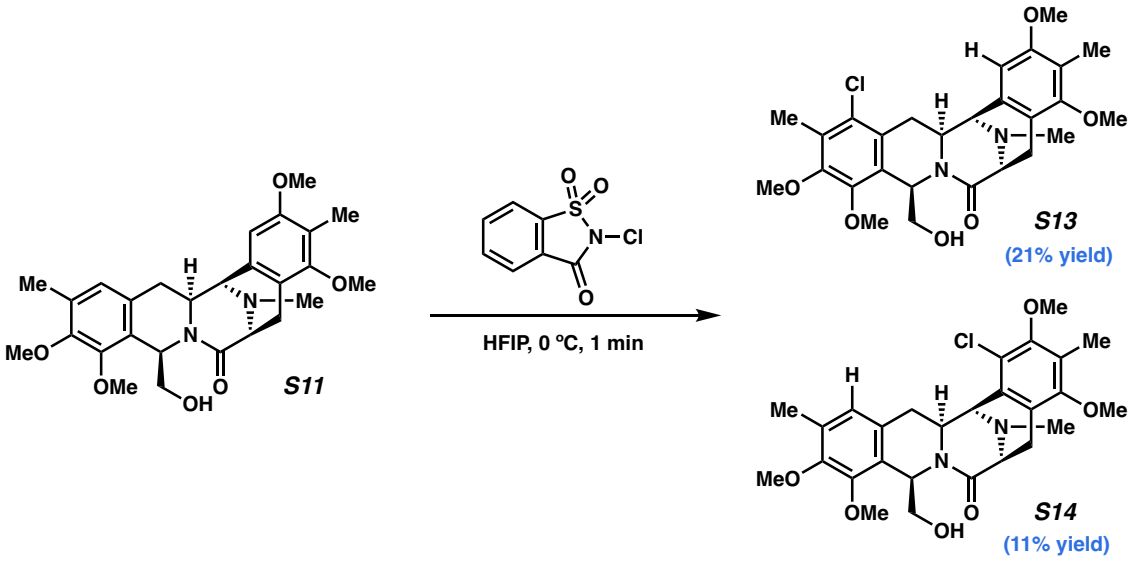
Figure S4. Path A is faster than Path B for all ligands to such an extent that Path B is only observed when the most activating ligand, BTFM-Xyliphos, is used. Both partially reduced intermediates are expected to form tridentate chelates to the metal to form **22•M** and **S13•M** (with **M** not necessarily being the catalytically active metal), with the three dimensional structures of each leading to the all-*syn* product as the major diastereomer. Furthermore, because B-ring reduction appears to be faster than D-ring reduction in all cases, intermediate **22** can be isolated (after *N*-protection) while intermediate **S12** has never been directly observed. The discrepancy in enantiomeric excess between intermediate **22** and fully hydrogenated intermediate **7** (as manifested by the enantiomeric excess of **S12** and bis-THIQ **6**, respectively) can be explained if the enantioselectivity of Path B is significantly lower than that of Path A. As the two paths converge onto the same product, in this scenario the enantiopurity of **6** would be expected to be less than that of **22**.

Synthesis of Derivatives 31–34.



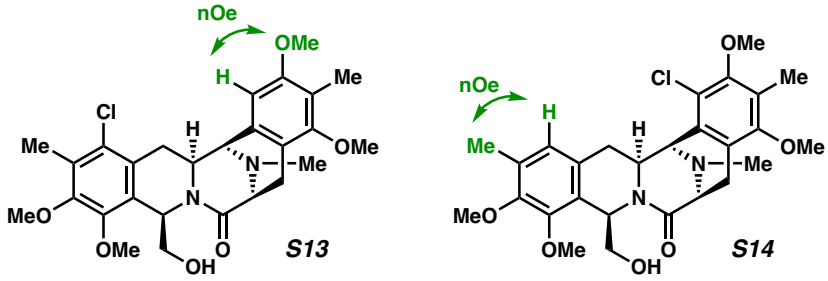
(6*S*,7*R*,9*R*,14a*S*,15*R*)-9-(hydroxymethyl)-2,4,10,11-tetramethoxy-3,12,16-trimethyl-6,7,9,14,14a,15-hexahydro-5*H*-6,15-epiminobenzo[4,5]azocino[1,2-*b*]isoquinoline-7-carbonitrile (31). In an oven-dried vial, $LiAlH_4$ solution (1.0 M in THF, 2 mL, 2.0 mmol) was cooled to 0 ºC. A solution of ethyl acetate (230 µL, 2.35 mmol) in 2 mL THF was added slowly, and the resulting solution was stirred 30 min at 0 ºC, providing a 0.47 M solution of $Li(EtO)_2AlH_2$ in THF. bis-Tetrahydroisoquinoline **6** (8.0 mg, 16.6 µmol, 1.0 equiv) was dissolved in THF (0.75 mL, 0.02 M) and the resulting solution was cooled to 0 ºC. A solution of $Li(EtO)_2AlH_2$ (0.47 M in THF, 0.47 mL, 0.21 mmol, 15.0 equiv) was added slowly, resulting in extensive evolution of H_2. After stirring 45 min, the reaction was quenched with acetic acid (17.7 µL, 0.31 mmol, 21 equiv) and aqueous potassium cyanide (4.8 M, 18.4 µL, 88.4 µmol, 6.0 equiv) was added, followed by celite and anhydrous Na_2SO_4 (roughly 300 mg each). The solution was diluted with 1 mL THF and stirred 10 h, warming to room temperature. More celite was added, and the suspension was filtered through celite, rinsed with EtOAc, and concentrated. The product was purified by preparative HPLC (MeCN/0.4% acetic acid in water, 5.0 mL/min, monitor wavelength = 230 nm, 35–95% MeCN over 8 min, hold at 95% for 1 min for a total run time of 9 min. Product **31** has t_R = 6.5 min). Colorless solid, 3.9 mg, 7.9 µmol, 48% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (s, 1H), 6.23 (s, 1H), 4.02 (d, *J* = 2.4 Hz, 1H), 3.99 (t, *J* = 4.4 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.69 (s, 3H), 3.66 (s, 3H), 3.55 – 3.51 (m, 1H), 3.48 (d, *J* = 10.4 Hz, 1H), 3.36 (d, *J* = 7.7 Hz, 1H), 3.25 (dt, *J* = 12.1, 2.6 Hz, 1H), 3.13 – 3.07 (m, 1H), 3.05 (dd, *J* = 18.4, 7.8 Hz, 1H), 2.49 – 2.39 (m, 2H), 2.31 (s, 3H), 2.25 – 2.16 (m, 1H), 2.13 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 148.5, 148.1, 130.0, 129.2, 124.9, 124.2, 123.5, 118.1, 117.7, 116.9, 107.3, 106.2, 64.9, 62.4, 61.3, 60.1, 59.3, 58.9, 57.5, 55.5, 54.8, 54.6, 40.7, 31.8, 20.6, 14.7, 8.0;

IR (thin film, NaCl): 3440.8, 2961.2, 2928.4, 2855.0, 1607.1, 1455.7, 1410.2, 1325.6, 1260.8, 1190.0, 1122.9, 1082.1, 1029.4, 912.2, 864.5, 801.0, 733.7; HRMS (ESI-TOF) calc'd for [M^+] $C_{28}H_{35}N_3O_5$ = 493.2577, found 493.2579; $[\alpha]_D$ = –43.3° (c = 0.05, $CHCl_3$).



(6*S*,9*R*,14a*S*,15*R*)-13-chloro-9-(hydroxymethyl)-2,4,10,11-tetramethoxy-3,12,16-trimethyl-5,6,9,14,14a,15-hexahydro-7*H*-6,15-epiminobenzo[4,5]azocino[1,2-*b*]isoquinolin-7-one (S13) and (6*S*,9*R*,14a*S*,15*R*)-1-chloro-9-(hydroxymethyl)-2,4,10,11-tetramethoxy-3,12,16-trimethyl-5,6,9,14,14a,15-hexahydro-7*H*-6,15-epiminobenzo[4,5]azocino[1,2-*b*]isoquinolin-7-one (S14). bis-Tetrahydroisoquinoline **S11** (112.0 mg, 0.232 mmol, 1.0 equiv) was dissolved in HFIP (11.6 mL, 0.02 M after complete addition) and the solution was cooled to 0 °C. *N*-Chlorosaccharine (55.6 mg, 0.255 mmol, 1.1 equiv) was dissolved in 1.6 mL HFIP and this solution was added at a slow dropwise pace, allowing the orange color to dispel after each addition, and the resulting yellow solution was stirred at 0 °C. An LCMS sample taken 1 min after complete addition showed a 2.5:1.7:1.0:1.5 mixture of starting material **S11**:**S13**:**S14**: dichlorinated product **28**. The reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ and transferred to a separatory funnel with CH_2Cl_2 and water, creating a triphasic system with HFIP on bottom, CH_2Cl_2 in the middle, and the aqueous phase on top. The bottom two phases were collected. The aqueous phase was basified with K_2CO_3 and extracted with CH_2Cl_2. The combined organic phases were concentrated and azeotropically dried twice with benzene. Products **S13**

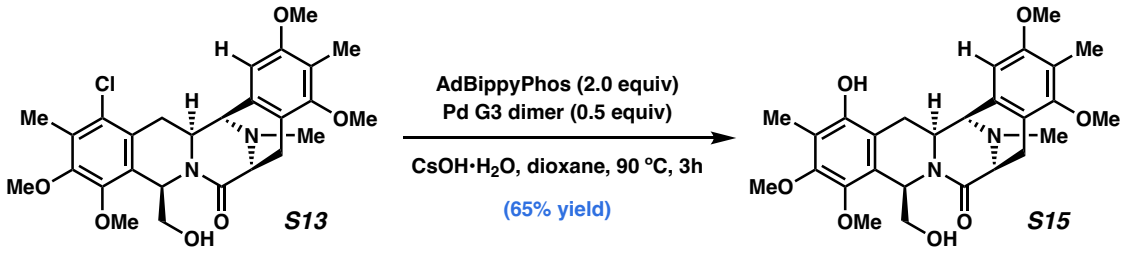
and **S14** were isolated using preparative HPLC (MeCN/0.4% acetic acid in water, 5.0 mL/min, monitor wavelength = 235 nm, 50–80% MeCN over 10 min, ramp to 95% MeCN over 0.5 min, hold at 95% for 2.5 min for a total run time of 13 min. Starting material **S11**, product **S13**, and **S14** has t_R = 3.1, 5.1, and 6.7 min, respectively). Starting material **S11** was recovered as a colorless solid, 24.3 mg, 0.050 mmol, 22% yield. **S13** was isolated as a white solid, 25.2 mg, 0.049 mmol, 21% yield, and 27% yield based on recovered starting material. **S14** is a white solid, 13.7 mg, 0.026 mmol, 11% yield, 15% yield based on recovered starting material. The structures of **S13** and **S14** were assigned using diagnostic nOe correlations (highlighted methoxy or methyl groups).



Product **S13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (s, 1H), 5.75 (dd, *J* = 6.4, 4.0 Hz, 1H), 3.95 (ddd, *J* = 12.6, 3.6, 2.5 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.84 – 3.78 (m, 2H), 3.77 (s, 3H), 3.69 (s, 3H), 3.40 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.26 (dd, *J* = 15.2, 2.5 Hz, 1H), 3.18 (dd, *J* = 10.9, 6.4 Hz, 2H), 3.12 (d, *J* = 6.6 Hz, 1H), 2.94 (dd, *J* = 17.7, 1.3 Hz, 1H), 2.47 (s, 3H), 2.41 (dd, *J* = 15.2, 12.6 Hz, 1H), 2.31 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 157.4, 156.8, 150.4, 148.5, 130.6, 129.7, 128.5, 127.5, 126.2, 119.8, 118.7, 107.0, 68.8, 61.1, 60.9, 60.4, 60.4, 60.1, 57.6, 55.9, 52.7, 40.0, 30.6, 24.0, 13.8, 9.1; IR (thin film, NaCl): 3387.5, 2938.1, 1634.1, 1455.8, 1407.0, 1330.2, 1123.8, 1081.0, 1013.2, 754.4; HRMS (ESI-TOF) calc'd for $[M+H]^+$ $C_{27}H_{34}ClN_2O_6$ = 517.2100, found 517.2082; $[\alpha]_D$ = –73.6º (c = 0.89, $CHCl_3$).

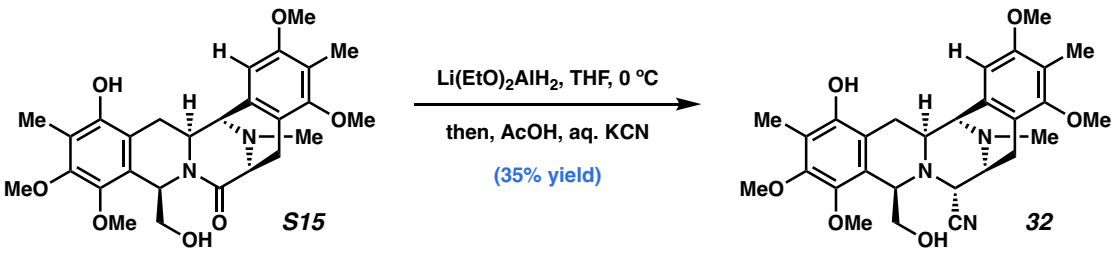
Product **S14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (s, 1H), 5.85 (dd, *J* = 7.5, 4.2 Hz, 1H), 4.46 – 4.39 (m, 1H), 4.08 (dt, *J* = 12.9, 2.9 Hz, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 3.77 (s, 4H), 3.71 (s, 4H), 3.44 (dd, *J* = 10.8, 4.2 Hz, 1H), 3.22 – 3.06 (m, 3H), 3.00 (dd, *J* = 18.1, 1.3 Hz, 1H), 2.43 (s, 3H), 2.39 – 2.29 (m, 1H), 2.26 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 156.0, 153.6, 149.8, 149.4, 131.7, 131.3, 127.8, 126.1, 124.8, 124.4, 124.2, 123.5, 69.0, 60.6,

60.4, 60.3, 59.9, 59.3, 59.2, 57.6, 52.0, 40.1, 31.7, 24.8, 15.7, 10.0; IR (thin film, NaCl): 3418.3, 2939.3, 2870.0, 1643.7, 1633.8, 1454.9, 1446.2, 1325.6, 1224.2, 1105.8, 1080.7, 1004.5, 931.9, 755.2; HRMS (ESI-TOF) calc'd for $[M+H]^+$ $C_{27}H_{34}ClN_2O_6$ = 517.2100, found 517.2101; $[\alpha]_D$ = –114.0º (c = 0.86, $CHCl_3$).



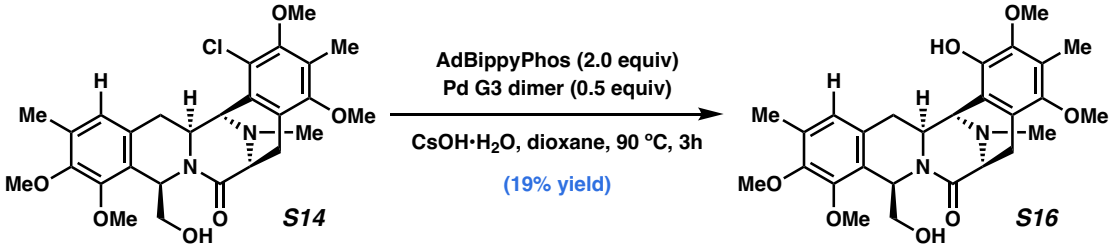
(6*S*,9*R*,14a*S*,15*R*)-13-hydroxy-9-(hydroxymethyl)-2,4,10,11-tetramethoxy-3,12,16-trimethyl-5,6,9,14,14a,15-hexahydro-7*H*-6,15-epiminobenzo[4,5]azocino[1,2-*b*]isoquinolin-7-one (S15). In a nitrogen-filled glovebox, Buchwald's dimer (16.4 mg, 0.022 mmol, 0.50 equiv) and 5-[di(1-adamantyl)phosphino]-1′,3′,5′-triphenyl-1′H-[1,4′]bipyrazole (AdBippyPhos, 58.9 mg, 0.089 mmol, 2.00 equiv) were weighed into a scintillation vial and dioxane (4.0 mL) was added. The vial was sealed with electrical tape and removed from the glovebox, sonicated briefly, and returned to the glovebox. The resulting tan solution was then transferred to a scintillation vial containing bis-tetrahydroisoquinoline **S13** (23.0 mg, 0.045 mmol, 1.00 equiv) and CsOH•H_2O (74.7 mg, 0.045 mmol, 10.0 equiv), followed by a 0.5 mL rinse (4.5 mL total volume, 0.01 M). The vial was sealed, removed from the glovebox, and placed in a preheated 90 ºC oil bath. After 3 h, the vial was removed and allowed to cool fully to room temperature prior to removing the seal. Acetic acid (23 µL, 0.401 mmol, 9 equiv) was added to quench remaining CsOH and the contents of the vial were transferred to a roundbottom flask, to which silica gel was added directly to dry load the crude mixture onto a silica gel column. The solution was concentrated, and the product was purified by column chromatography (2–4–6–8% MeOH + CH_2Cl_2: no NEt_3 added). Colorless solid, 14.4 mg, 0.029 mmol, 65% yield. *Note: Based on the ^{1}H NMR spectrum of the isolated product, there is approximately 20% of an additional side product.* ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.55 (s, 1H), 5.85 (dd, *J* = 6.7, 4.1 Hz, 1H), 4.15 – 3.98 (m, 2H), 3.94 (d, *J* = 2.5 Hz, 7H), 3.89 (s, 4H), 3.81 (s, 4H), 3.50 (dd, *J* = 11.0, 4.2 Hz, 1H), 3.34 – 3.22 (m, 3H), 3.07 (dd, *J* = 17.6, 1.2 Hz, 1H), 2.60 (s, 3H), 2.37 (dd, *J* = 14.9, 12.6 Hz, 1H), 2.28 (s, 3H), 2.26 (s, 3H); ^{13}C

NMR (101 MHz, $CDCl_3$) δ 173.3, 157.3, 156.8, 150.0, 146.3, 143.7, 128.7, 125.3, 119.8, 118.8, 118.3, 117.4, 107.2, 69.1, 61.3, 60.9, 60.4, 60.2, 60.2, 58.1, 56.0, 52.6, 40.0, 29.8, 26.1, 24.0, 9.1; IR (thin film, NaCl): 3318.3, 2935.3, 1621.7, 1607.9, 1587.1, 1463.4, 1455.5, 1354.7, 1272.0, 1123.1, 1068.6, 755.2; HRMS (ESI-TOF) calc'd for $[M+H]^+$ $C_{27}H_{35}N_2O_7$ =499.2439, found 499.2449; $[\alpha]_D$ = –87.2º (c = 1.03, $CHCl_3$).



(6*S*,7*R*,9*R*,14a*S*,15*R*)-13-hydroxy-9-(hydroxymethyl)-2,4,10,11-tetramethoxy-3,12,16-trimethyl-6,7,9,14,14a,15-hexahydro-5*H*-6,15-epiminobenzo[4,5]azocino[1,2-*b*]isoquinoline-7-carbonitrile (32). In an oven-dried 1-dram vial, $LiAlH_4$ solution (1.0 M in THF, 1 mL, 1.0 mmol) was cooled to 0 ºC. A solution of ethyl acetate (115 µL, 1.18 mmol) in 1 mL THF was added slowly, and the resulting solution was stirred 30 min at 0 ºC, providing a 0.47 M solution of $Li(EtO)_2AlH_2$ in THF. bis-Tetrahydroisoquinoline **S15** (14.4 mg, 28.9 µmol, 1.0 equiv) was dissolved in THF (1.5 mL, 0.02 M) and the resulting solution was cooled to 0 ºC. A solution of $Li(EtO)_2AlH_2$ (0.47 M in THF, 0.92 mL, 0.43 mmol, 15.0 equiv) was added slowly, resulting in extensive evolution of H_2. After stirring 20 min, LCMS showed complete consumption of **S15**, so the reaction was quenched with acetic acid (34.7 µL, 0.607 mmol, 21 equiv) and aqueous potassium cyanide (4.8 M, 36.1 µL, 0.173 mmol, 6.0 equiv) was added, followed by celite and anhydrous Na_2SO_4 (roughly 500 mg each). The solution was diluted with 3 mL THF and stirred for 12 h, warming to room temperature. At this stage, LCMS revealed some unreacted starting material, so the reaction was stirred at 50°C for an additional 3 hours. ~1 g of K_2CO_3 was added, followed by celite. The suspension was filtered through celite, rinsed with EtOAc, and concentrated. The product was purified by preparative HPLC (MeCN/0.4% acetic acid in water, 5.0 mL/min, monitor wavelength = 230 nm, 40–60% MeCN over 7 min, ramp to 95% MeCN over 0.5 min, hold at 95% for 2.5 min for a total run time of 10 min. Product **32** has t_R = 5.1 min). Colorless solid, 5.1 mg, 10.0 µmol, 35% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.37 (s, 1H), 4.09 (d, *J* =

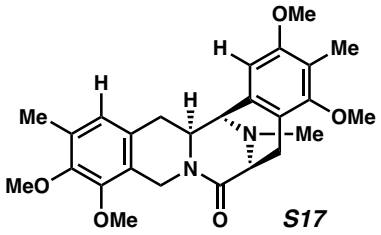
2.4 Hz, 1H), 4.07 (t, J = 4.6 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.77 (s, 3H), 3.73 (s, 3H), 3.65 – 3.62 (m, 1H), 3.53 (dd, J = 10.9, 4.5 Hz, 1H), 3.43 (dt, J = 7.8, 1.5 Hz, 1H), 3.27 (dt, J = 12.0, 2.7 Hz, 1H), 3.16 – 3.09 (m, 2H), 2.94 (dd, J = 15.1, 2.7 Hz, 1H), 2.50 (d, J = 18.2 Hz, 1H), 2.39 (s, 3H), 2.13 (s, 3H), 2.12 (s, 3H), 2.10 (d, J = 12.3 Hz, 1H), 1.99 (dd, J = 15.1, 12.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6, 156.1, 149.6, 146.3, 143.3, 130.4, 125.8, 119.3, 118.9, 118.1, 117.8, 116.1, 107.6, 66.2, 63.6, 61.4, 60.8, 60.5, 60.1, 58.5, 56.4, 55.9, 55.8, 41.9, 26.1, 21.8, 9.2, 8.9; IR (thin film, NaCl): 3443.9, 2937.0, 2359.2, 1606.3, 1463.3, 1417.5, 1354.4, 1263.8, 1190.8, 1122.4, 1070.4, 983.0, 911.3, 732.7; HRMS (ESI-TOF) calc'd for [M^+] $C_{28}H_{36}N_3O_6$ = 510.2599, found 510.2589; $[\alpha]_D$ = +36.4° (c = 0.36, $CHCl_3$).



(6*S*,9*R*,14a*S*,15*R*)-1-hydroxy-9-(hydroxymethyl)-2,4,10,11-tetramethoxy-3,12,16-trimethyl-5,6,9,14,14a,15-hexahydro-7*H*-6,15-epiminobenzo[4,5]azocino[1,2-*b*]isoquinolin-7-one (S16). In a nitrogen-filled glovebox, Buchwald's dimer (6.8 mg, 9.2 μmol, 0.50 equiv) and 5-[di(1-adamantyl)phosphino]-1′,3′,5′-triphenyl-1′H-[1,4′]bipyrazole (AdBippyPhos, 24.4 mg, 0.037 mmol, 2.00 equiv) were weighed into a scintillation vial and dioxane (1.6 mL) was added. The vial was sealed with electrical tape and removed from the glovebox, sonicated briefly, and returned to the glovebox. The resulting tan solution was then transferred to a 1-dram vial containing bis-tetrahydroisoquinoline **S14** (9.5 mg, 0.018 mmol, 1.00 equiv) and CsOH•H_2O (30.9 mg, 0.184 mmol, 10.0 equiv), followed by a 0.2 mL rinse (1.8 mL total volume, 0.01 M). The vial was sealed, removed from the glovebox, and placed in a preheated 90 °C oil bath. After 3 h, the vial was removed and allowed to cool fully to room temperature prior to removing the seal. Acetic acid (9.5 μL, 0.166 mmol, 9 equiv) was added to quench remaining CsOH and the contents of the vial were transferred to a scintillation vial, to which silica gel was added directly to dry load the crude mixture onto a silica gel column. The solution was concentrated, and the product was purified by column chromatography (2–4–6–8% MeOH + CH_2Cl_2: no NEt_3 added).

Due to a significant amount of impurities present in the sample, the isolated product was repurified using preparative HPLC (MeCN/0.4% acetic acid in water, 5.0 mL/min, monitor wavelength = 235 nm, 25–55% MeCN over 10 min, ramp to 95% MeCN over 0.5 min, hold at 95% for 2.5 min for a total run time of 13 min. Product **S16** has t_R = 5.1 min). White solid, 1.7 mg, 3.41 μmol, 19% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 1H), 5.81 (dd, *J* = 7.2, 3.6 Hz, 1H), 5.65 (s, 1H), 4.27 (dd, *J* = 3.7, 1.3 Hz, 1H), 4.02 (dt, *J* = 12.7, 2.9 Hz, 1H), 3.90 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.76–3.73 (m, 1H), 3.68 (s, 3H), 3.45 (dd, *J* = 11.0, 4.1 Hz, 1H), 3.22 (dd, *J* = 10.6, 7.2 Hz, 1H), 3.13 (dd, *J* = 18.0, 6.7 Hz, 1H), 3.07 – 2.93 (m, 2H), 2.47 – 2.32 (m, 4H), 2.24 (s, 3H), 2.23 – 2.20 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 149.9, 149.8, 149.6, 143.7, 143.0, 132.2, 131.7, 124.8, 124.7, 123.4, 123.0, 115.9, 69.4, 61.1, 60.7, 60.5, 60.0, 59.7, 59.2, 55.2, 52.7, 40.2, 31.8, 24.8, 15.9, 9.8; IR (thin film, NaCl): 3423.5, 2936.4, 1628.4, 1438.5, 1412.0, 1325.6, 1259.5, 1235.8, 1109.0, 1080.0, 1052.4, 1006.2, 730.9; HRMS (ESI-TOF) calc'd for $[M+H]^+$ $C_{27}H_{35}N_2O_7$ =499.2439, found 499.2439; $[\alpha]_D$ = –45.8º (c = 0.10, $CHCl_3$).

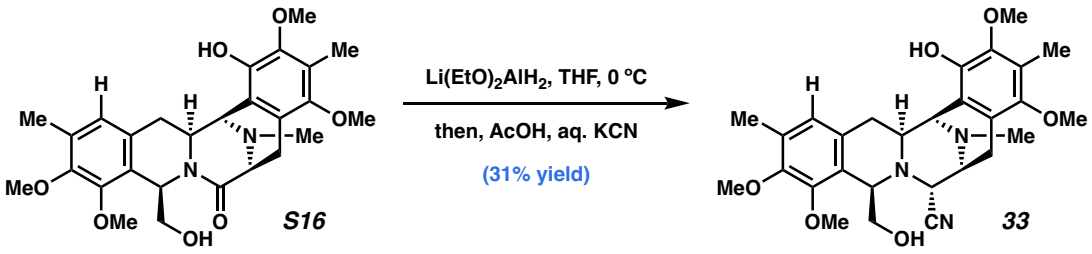
*Note: In addition to the desired product **S16**, we were also able to isolate and assign the structure of side product* **S17**. **S17** *presumably arises from palladium-mediate oxidative deformylation. Similar byproducts have been identified by LCMS in other runs, but have neither been isolated nor quantified.*



S17

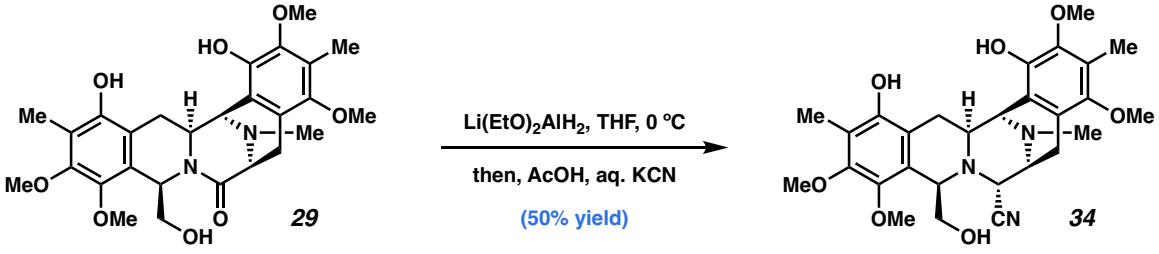
(6*S*,14a*S*,15*R*)-2,4,10,11-tetramethoxy-3,12,16-trimethyl-5,6,9,14,14a,15-hexahydro-7*H*-6,15-epiminobenzo[4,5]azocino[1,2-*b*]isoquinolin-7-one (S17). Isolated from preparative HPLC as described above. Product **S17** has t_R = 11.3 min. Colorless solid, 0.9 mg, 1.99 μmol, 11% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (s, 1H), 6.38 (s, 1H), 4.66 (d, *J* = 18.7 Hz, 1H), 4.55 (d, *J* = 18.7 Hz, 1H), 4.05 (ddd, *J* = 12.2, 4.8, 2.7 Hz, 1H), 3.87 (dd, *J* = 4.7, 1.2 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 4H), 3.78 (s, 3H), 3.70 (s, 3H), 3.10 (dd, *J* = 17.9, 7.1 Hz, 1H), 2.97 – 2.88

(m, 1H), 2.69 (dd, J = 15.0, 2.7 Hz, 1H), 2.48 (s, 3H), 2.45 – 2.34 (m, 1H), 2.21 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 157.3, 156.6, 149.7, 130.6, 129.5, 129.1, 124.7, 123.4, 119.6, 119.1, 107.0, 60.7, 60.2, 59.5, 55.9, 55.8, 40.6, 40.1, 33.7, 22.8, 15.8, 9.1; IR (thin film, NaCl): 2935.3, 2857.5, 2361.9, 2344.3, 1653.9, 1638.1, 1609.7, 1458.2, 1448.3, 1412.7, 1327.2, 1123.8, 1078.4, 1000.9, 731.2; HRMS (ESI-TOF) calc'd for $[M+H]^+$ $C_{26}H_{33}N_2O_5$ =453.2384, found 453.2379; $[\alpha]_D$ = –123.4º (c = 0.06, $CHCl_3$).



(6*S*,7*R*,9*R*,14a*S*,15*R*)-1-hydroxy-9-(hydroxymethyl)-2,4,10,11-tetramethoxy-3,12,16-trimethyl-6,7,9,14,14a,15-hexahydro-5*H*-6,15-epiminobenzo[4,5]azocino[1,2-*b*]isoquinoline-7-carbonitrile (33). In an oven-dried 1-dram vial, $LiAlH_4$ solution (1.0 M in THF, 1 mL, 1.0 mmol) was cooled to 0 ºC. A solution of ethyl acetate (115 µL, 1.18 mmol) in 1 mL THF was added slowly, and the resulting solution was stirred 30 min at 0 ºC, providing a 0.47 M solution of $Li(EtO)_2AlH_2$ in THF. bis-Tetrahydroisoquinoline **S16** (2.2 mg, 4.41 µmol, 1.0 equiv) was dissolved in THF (0.2 mL, 0.02 M) and the resulting solution was cooled to 0 ºC. A solution of $Li(EtO)_2AlH_2$ (0.47 M in THF, 141 µL, 66.2 µmol, 15.0 equiv) was added slowly, resulting in extensive evolution of H_2. After stirring 20 min, LCMS showed complete consumption of **S16**, so the reaction was quenched with acetic acid (5.3 µL, 92.7 µmol, 21 equiv). Aqueous potassium cyanide (4.8 M, 5.5 µL, 26.5 µmol, 6.0 equiv) was added, followed by celite, anhydrous Na_2SO_4 (roughly 100 mg each), and 0.4 mL of THF. The reaction was warmed to room temperature at stirred for 12 h. ~150 mg of K_2CO_3 and celite were added. The suspension was filtered through celite, rinsed with EtOAc, and concentrated. The product was purified by preparative HPLC (MeCN/0.4% acetic acid in water, 5.0 mL/min, monitor wavelength = 230 nm, 40–70% MeCN over 10 min, ramp to 95% MeCN over 0.5 min, hold at 95% for 2.5 min for a total run time of 13 min. Product **33** has t_R = 4.7 min). Colorless solid, 0.7 mg, 1.4 µmol, 31% yield. ^{1}H NMR (400

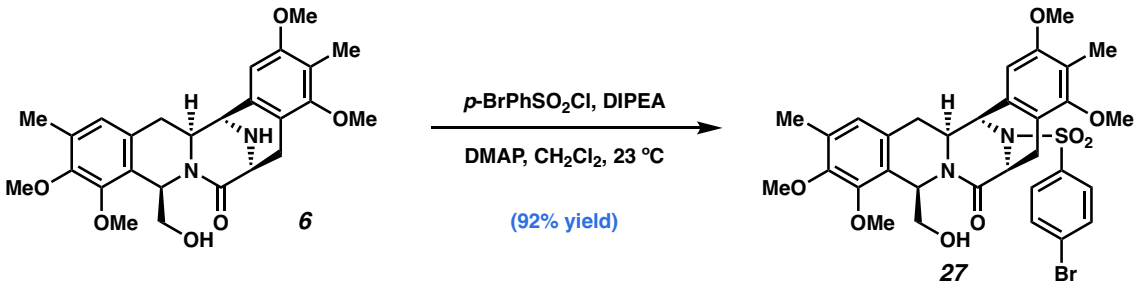
MHz, $CDCl_3$) δ 6.65 (s, 1H), 5.52 (s, 1H), 4.15 (s, 1H), 4.07 (d, *J* = 3.0 Hz, 2H), 3.87 (s, 3H), 3.75 (t, *J* = 0.9 Hz, 7H), 3.70 (s, 3H), 3.56 (d, *J* = 8.6 Hz, 2H), 3.43 – 3.31 (m, 2H), 3.10 (dd, *J* = 18.5, 7.8 Hz, 1H), 2.80 (dd, *J* = 15.4, 2.5 Hz, 1H), 2.50 (d, *J* = 18.5 Hz, 1H), 2.34 (s, 3H), 2.23 (s, 3H), 2.20 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 149.2, 148.7, 143.6, 143.3, 142.1, 131.8, 131.2, 125.2, 124.9, 123.5, 118.1, 116.9, 66.0, 61.1, 61.1, 60.5, 60.2, 60.1, 58.7, 57.5, 56.6, 55.3, 41.9, 32.0, 21.8, 15.8, 9.8; IR (thin film, NaCl): 3400.3, 2930.0, 2858.5, 2350.5, 2250.0, 1663.8, 1458.2, 1411.7, 1327.3, 1308.1, 1261.2, 1105.8, 1080.3, 1056.6, 1009.6, 910.8, 800.7, 733.4; HRMS (ESI-TOF) calc'd for [M^+] $C_{28}H_{36}N_3O_6$ = 510.2599, found 510.2596; $[\alpha]_D$ = –21.8º (c = 0.05, $CHCl_3$).



(6S,7R,9R,14aS,15R)-1,13-dihydroxy-9-(hydroxymethyl)-2,4,10,11-tetramethoxy-3,12,16-trimethyl-6,7,9,14,14a,15-hexahydro-5H-6,15-epiminobenzo[4,5]azocino[1,2-b]isoquinoline-7-carbonitrile (34). In an oven-dried vial, $LiAlH_4$ solution (1.0 M in THF, 2 mL, 2.0 mmol) was cooled to 0 ºC. A solution of ethyl acetate (230 µL, 2.35 mmol) in 2 mL THF was added slowly, and the resulting solution was stirred 30 min at 0 ºC, providing a 0.47 M solution of $Li(EtO)_2AlH_2$ in THF. bis-Tetrahydroisoquinoline **29** (49.0 mg, 0.095 mmol, 1.0 equiv) was dissolved in THF (4.8 mL, 0.02 M) and the resulting solution was cooled to 0 ºC. A solution of $Li(EtO)_2AlH_2$ (0.47 M in THF, 3.0 mL, 1.43 mmol, 15.0 equiv) was added slowly, resulting in extensive evolution of H_2. After stirring 45 min, the reaction was quenched with acetic acid (115 µL, 2.00 mmol, 21 equiv) and aqueous potassium cyanide (4.8 M, 120 µL, 0.571 mmol, 6.0 equiv) was added, followed by celite and anhydrous Na_2SO_4 (roughly 1 g each). The solution was diluted with 8 mL THF and stirred 10 h, warming to room temperature. More celite was added, and the suspension was filtered through celite, rinsing with EtOAc. The filtrate was transferred to a roundbottom flask and was concentrated. At this stage, LCMS revealed a ~4:1 mixture of product **34** and starting material **29**, so the crude mixture was resubjected to the re-

duction conditions, using 3 mL THF as the reaction solvent and 1 mL of freshly prepared $Li(EtO)_2AlH_2$ solution. After 10 min, LCMS showed very little conversion of the remaining starting material, with some over-reduced product (m/z = 501). The reaction mixture was quenched and worked up as described above. The product was purified by column chromatography (50–75–100% EtOAc/hex, 200 mL each; product elutes in the 75% portion). Colorless solid, 25.2 mg, 47.9 μmol, 50% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (dD, *J* = 2.7, 1.1 Hz, 1H), 4.00 – 4.05 (m, 2H), 3.81 (s, 3H), 3.751 (s, 3H), 3.749 (s, 3H), 3.70 (s, 3H), 3.56 (dd, *J* = 10.9, 4.4 Hz, 1H), 3.40 (ddd, *J* = 7.5, 2.5, 1.2 Hz, 1H), 3.31 (dt, *J* = 12.1, 2.7 Hz, 1H), 3.18 (d, *J* = 9.4 Hz, 1H), 3.13 (dd, *J* = 15.6, 2.7 Hz, 1H), 3.10 (dd, *J* = 18.6, 7.8 Hz, 1H), 2.51 (d, *J* = 18.6 Hz, 1H), 2.34 (s, 3H), 2.22 (s, 3H), 2.09 (s, 3H), 1.85 (dd, *J* = 15.6, 12.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6, 148.7, 146.6, 143.7, 143.4, 143.1, 125.4, 123.5, 122.7, 118.1, 118.0, 117.1, 116.7, 66.2, 61.2, 61.0, 60.8, 60.4, 60.2, 58.5, 57.1, 56.7, 55.2, 41.9, 25.4, 21.7, 9.8, 9.0; IR (thin film, NaCl): 3427.6, 2936.1, 2832.7, 2228.1, 1606.8, 1463.2, 1412.1, 1384.5, 1349.9, 1319.9, 1300.9, 1251.3, 1218.1, 1191.3, 1150.7, 1107.7, 1070.1, 1001.7, 981.7, 907.7, 875.4, 829.8, 754.4; HRMS (ESI-TOF) calc'd for [M^+] $C_{28}H_{35}N_3O_7$ = 525.2475, found 525.2471; $[\alpha]_D$ = +22.9° (c = 0.5, $CHCl_3$).

Preparation and Crystal Structure Analysis of 27 (sample No.: P17208).



(6S,9R,14aS,15R)-16-((4-bromophenyl)sulfonyl)-9-(hydroxymethyl)-2,4,10,11-tetramethoxy-3,12-dimethyl-5,6,9,14,14a,15-hexahydro-7H-6,15-epiminobenzo[4,5]azocino[1,2-b]isoquinolin-7-one (27). bis-Tetrahydroisoquinoline **6** (45 mg, 0.096 mmol, 1.0 equiv, 88% ee), 4-dimethylaminopyridine (DMAP, 1.2 mg, 0.0096 mmol, 0.10 equiv), and *p*-bromophenylsulfonyl chloride (27 mg, 0.105 mmol, 1.10 equiv) were dissolved in CH_2Cl_2 (2 mL, 0.05 M) and

diisopropylethylamine (DIPEA, 33 μL, 0.192 mmol, 2.0 equiv) was added. The solution was stirred 2 h, at which time LCMS revealed full conversion to product **27**. The reaction was quenched by the addition of 1M HCl. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated. The product was purified by column chromatography (1% MeOH/CH_2Cl_2 + 1% NEt_3). Colorless solid, 61.0 mg, 0.089 mmol, 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.7 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 6.73 (s, 1H), 6.35 (s, 1H), 5.70 (dd, *J* = 6.3, 4.3 Hz, 1H), 5.07 (dd, *J* = 3.5, 1.6 Hz, 1H), 4.74 (dt, *J* = 7.0, 1.3 Hz, 1H), 4.01 (dt, *J* = 12.7, 2.9 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 3.77 (s, 3H), 3.49 (s, 3H), 3.41 (dt, *J* = 10.4, 4.9 Hz, 1H), 3.19 (dt, *J* = 11.2, 5.6 Hz, 1H), 3.03 (dd, *J* = 17.6, 1.3 Hz, 1H), 2.77 (dd, *J* = 14.4, 2.6 Hz, 1H), 2.71 (dd, *J* = 17.6, 6.9 Hz, 1H), 2.62 (t, *J* = 13.4 Hz, 1H), 2.49 (t, *J* = 5.6 Hz, 1H), 2.24 (s, 3H), 2.09 (s, 3H). X-ray quality crystals were obtained by allowing the slow evaporation of an isopropanol solution of **27**. The major enantiomer of the mixture is shown below.

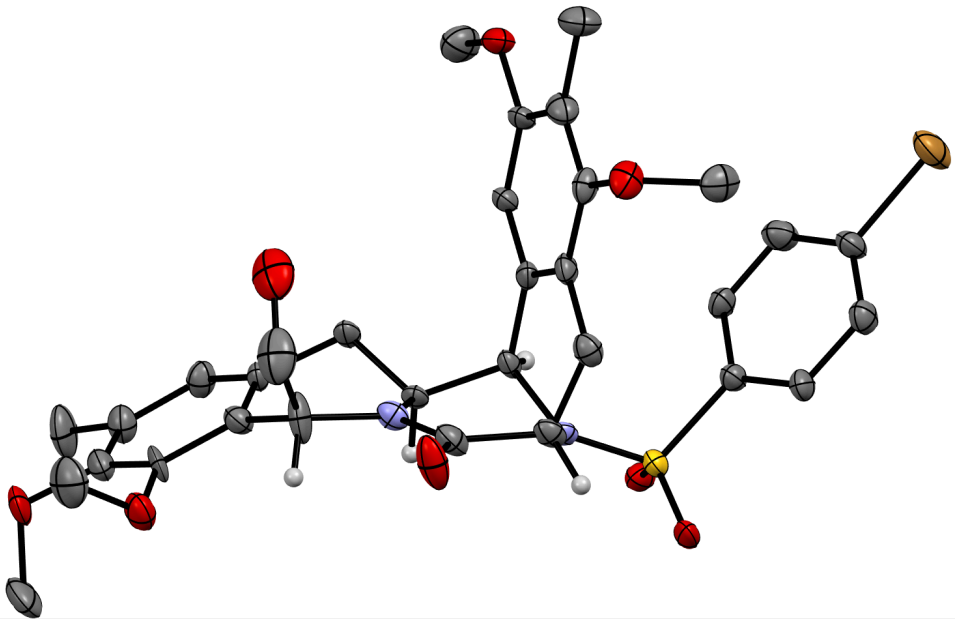


Table S5. Crystal data and structure refinement for P17208_sq.

Identification code	P17208_sq	
Empirical formula	C32 H35 Br N2 O8 S	
Formula weight	687.59	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12$	
Unit cell dimensions	a = 29.7321(15) Å	a= 90°.
	b = 10.3172(5) Å	b= 90°.
	c = 12.6857(5) Å	g = 90°.
Volume	3891.4(3) $Å^3$	
Z	4	
Density (calculated)	1.174 Mg/m^3	
Absorption coefficient	2.307 mm^{-1}	
F(000)	1424	
Crystal size	0.250 x 0.150 x 0.050 mm^3	
Theta range for data collection	2.972 to 74.895°.	
Index ranges	-37<=h<=37, -12<=k<=12, -15<=l<=13	
Reflections collected	45082	
Independent reflections	7958 [R(int) = 0.0739]	
Completeness to theta = 67.679°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7538 and 0.5857	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7958 / 70 / 430	
Goodness-of-fit on F^2	1.116	
Final R indices [I>2sigma(I)]	R1 = 0.0560, wR2 = 0.1328	
R indices (all data)	R1 = 0.0611, wR2 = 0.1354	
Absolute structure parameter	0.140(9)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.650 and -0.545 $e.Å^{-3}$	

Cell Culture and Proliferation Assays

Cell lines, cell culture, and reagents:

A panel of 29 cell lines, representing 4 major cancer types (lung, colon breast and ovarian), was assayed for response to THIQ agents. Cells were cultured in appropriate culture media (e.g., RPMI 1640, DMEM, L-15) supplemented with 10% to 15% heat-inactivated fetal bovine serum (FBS), 2 mmol/L glutamine, and 1% penicillin G-streptomycin-fungizone solution (PSF, Irvine Scientific) as previously described (*41*). Cells were routinely assessed for mycoplasma contamination using a multiplex PCR method and STR profiling by the GenePrint 10 System (Promega) was used for cell-line authentication.

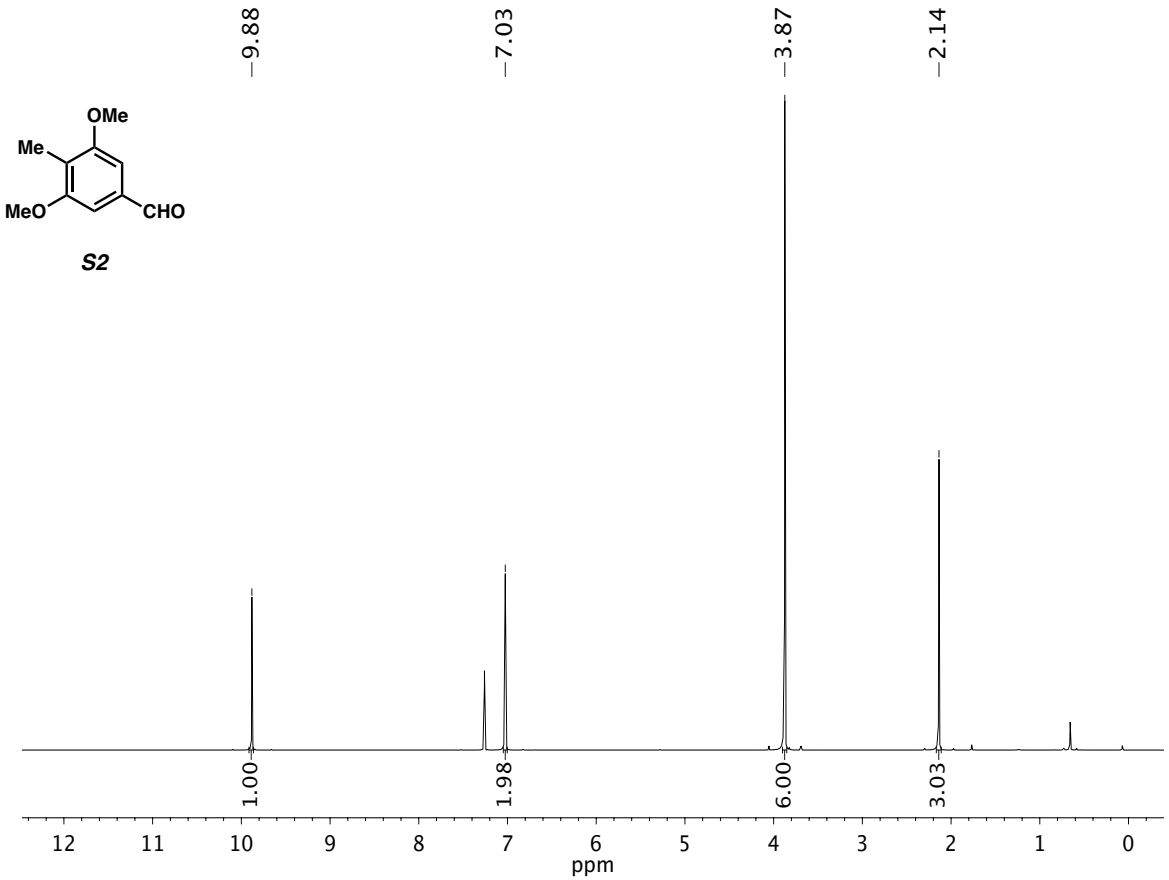
In vitro proliferation assays:

Response to THIQ agents was measured by a six-day proliferation assay. Stock solutions of THIQ agents were prepared at 10 mM in DMSO. Cells were seeded in 48-well plates at a seeding density previously determined to maximize growth over a 6-day treatment window. After 24 hours, the cells were treated with six 1:10 (**34**) or 1:5 (**30**–**33**) dilutions of inhibitor starting at 1 μM. Control wells were imaged at this time for baseline cell counts. After six days of treatment cells were counted on a custom automation platform designed by Tecan. This robotic system trypsinizes adherent cells, centrifuges cells to the bottom of the wells and counts cells via brightfield image segmentation on a Synentec Cellavista imaging system. IC_{50} values for each molecule were calculated by fitting curves to data points from each dose–response assay using the Proc NLIN function in SAS for Windows version 9.2 (SAS Institute, Inc.).

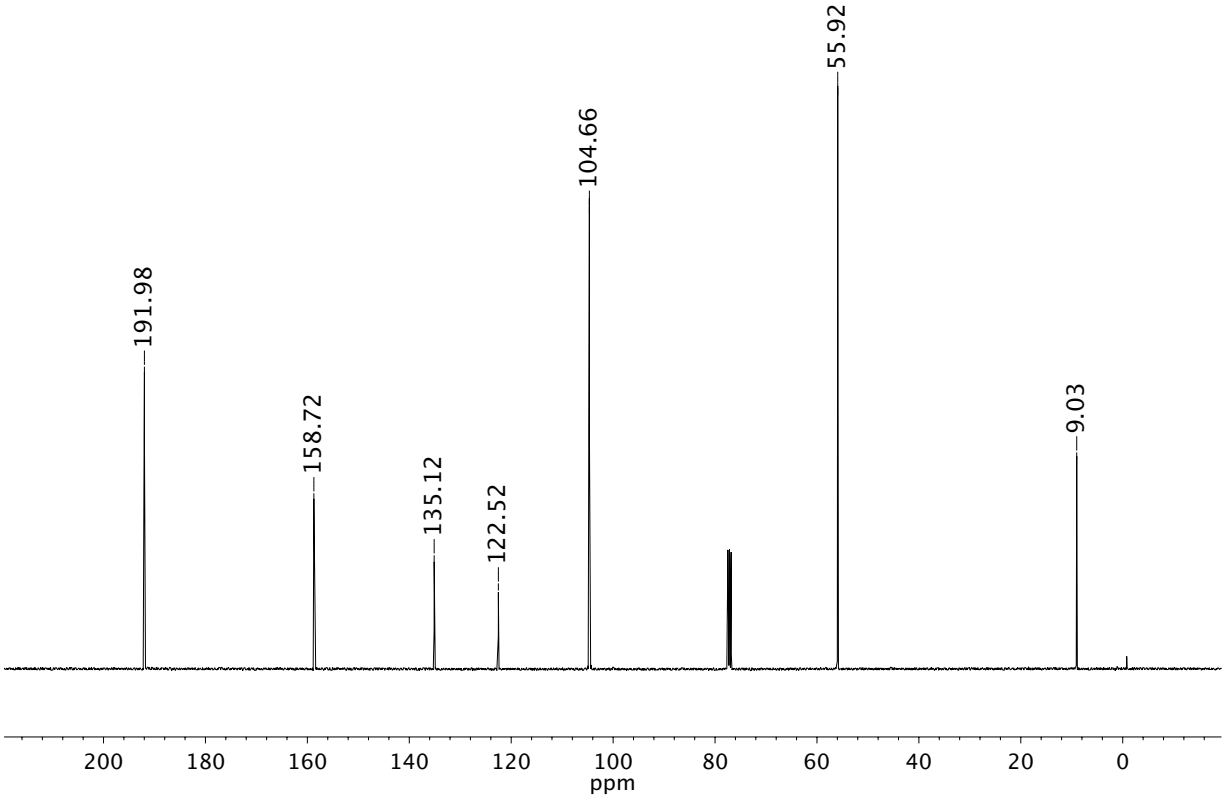
Biological Evaluation of Non-Natural Analogs

		30	31	32	33	34
H810	Lung	260	ND	260	210	110
A427	Lung	660	1000	880	210	340
H1836	Lung	470	1000	700	280	490
H226	Lung	1000	ND	770	210	660
H441	Lung	1000	ND	980	270	740
H1437	Lung	1000	ND	1000	740	760
H647	Lung	1000	1000	1000	540	770
NCIH747	Colon	1000	1000	290	150	120
SW837	Colon	910	1000	890	140	230
SW480	Colon	1000	ND	720	190	370
LS174t	Colon	1000	1000	1000	260	610
SNUC1	Colon	1000	ND	820	500	730
SKCO1	Colon	1000	1000	1000	790	780
SW48	Colon	1000	1000	720	120	810
OVCAR3	Ovarian	1000	1000	1000	150	120
ES2	Ovarian	1000	1000	410	200	170
OV207	Ovarian	1000	1000	970	250	170
OVTOKO	Ovarian	1000	1000	860	210	420
RMG1	Ovarian	1000	1000	990	200	520
RMUGS	Ovarian	1000	1000	1000	300	550
OVCAR5	Ovarian	1000	ND	310	220	650
EFO21	Ovarian	1000	1000	1000	240	780
MB468	Breast	1000	ND	470	140	210
ZR751	Breast	1000	ND	330	180	230
EFM19	Breast	460	ND	1000	140	230
MB453	Breast	260	ND	1000	250	350
HCC1806	Breast	1000	ND	560	190	380
T47D	Breast	1000	ND	1000	210	540
COLO824	Breast	230	ND	260	200	790

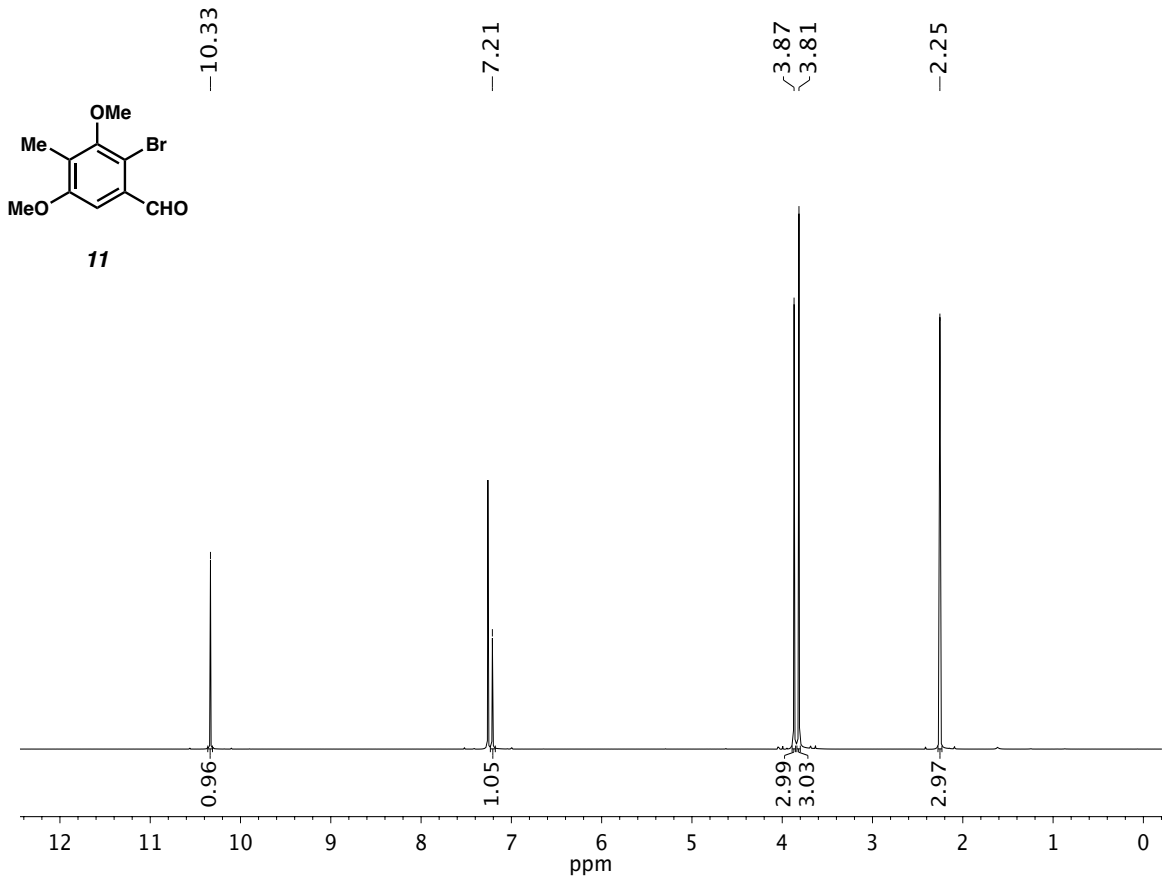
Table S12. IC_{50}'s (nM) of compounds **30**–**34** (all data in μM; data listed as 1000 μM are ≥1000 μM).



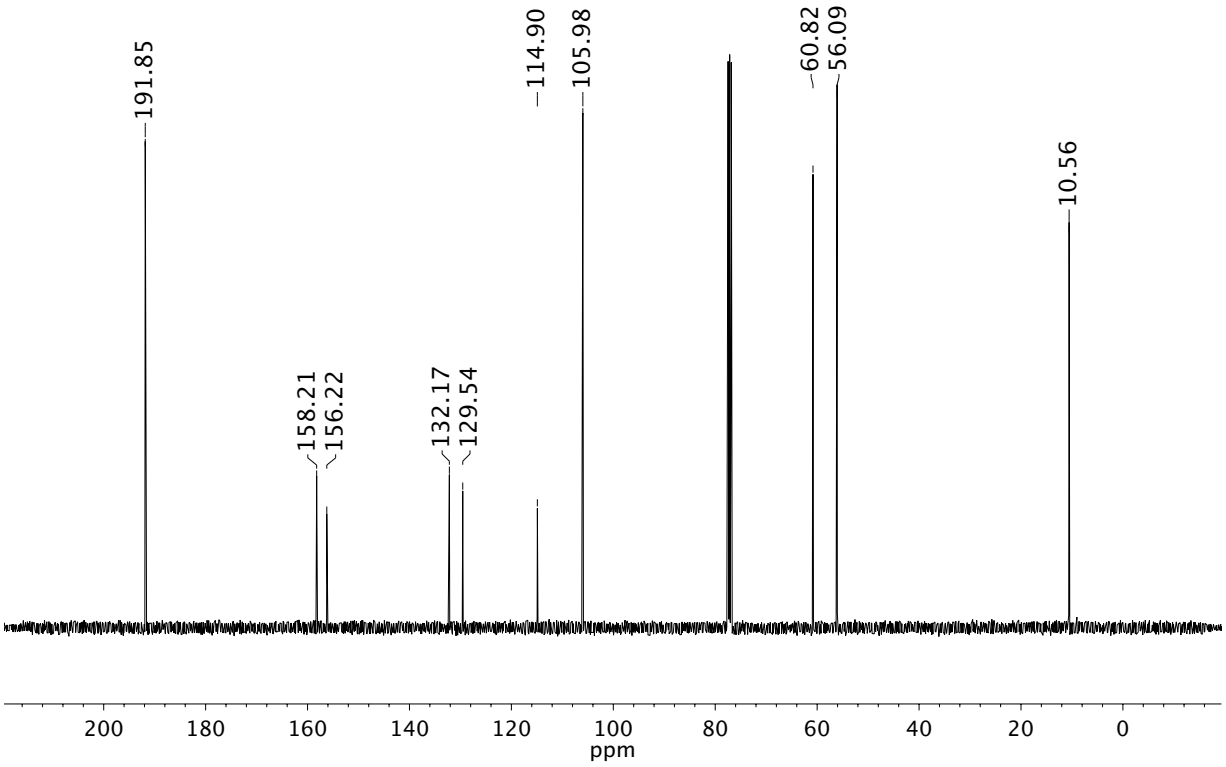
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S2**.



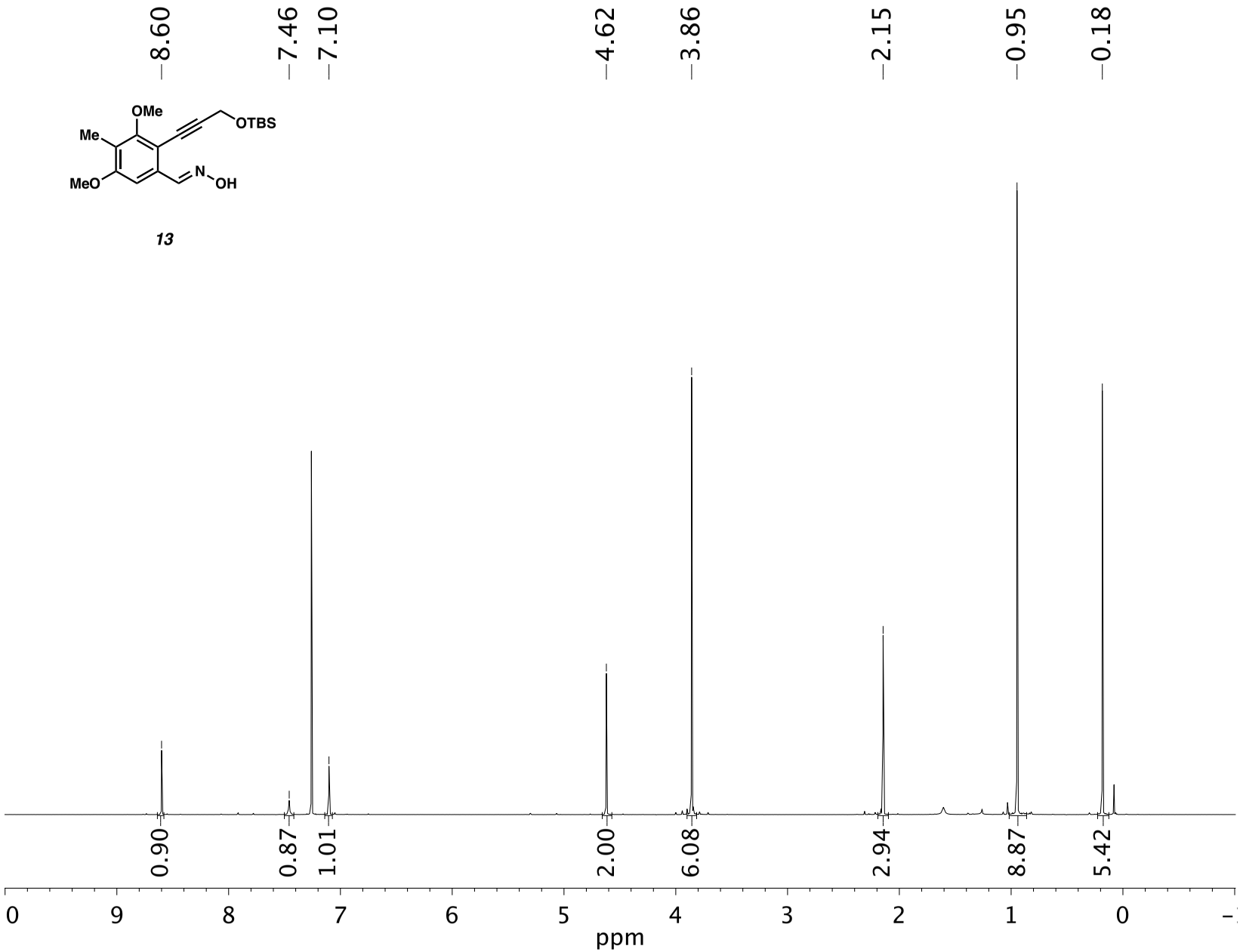
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S2**.



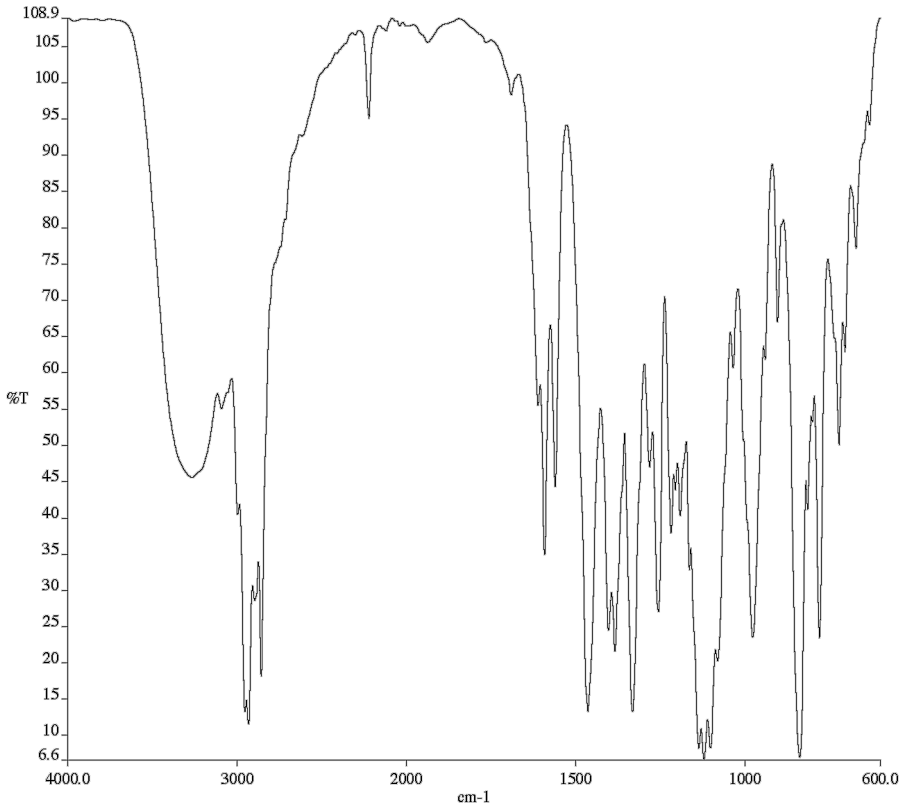
^{1}H NMR (400 MHz, $CDCl_3$) of compound **11**.



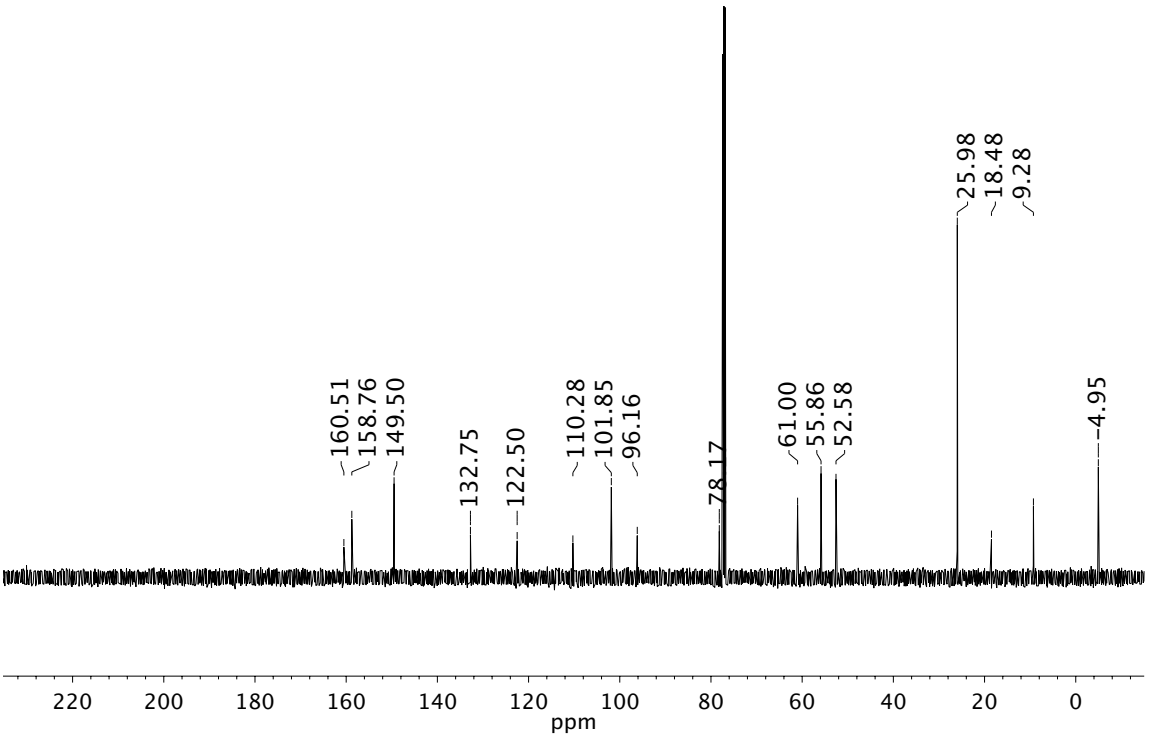
^{13}C NMR (101 MHz, $CDCl_3$) of compound **11**.



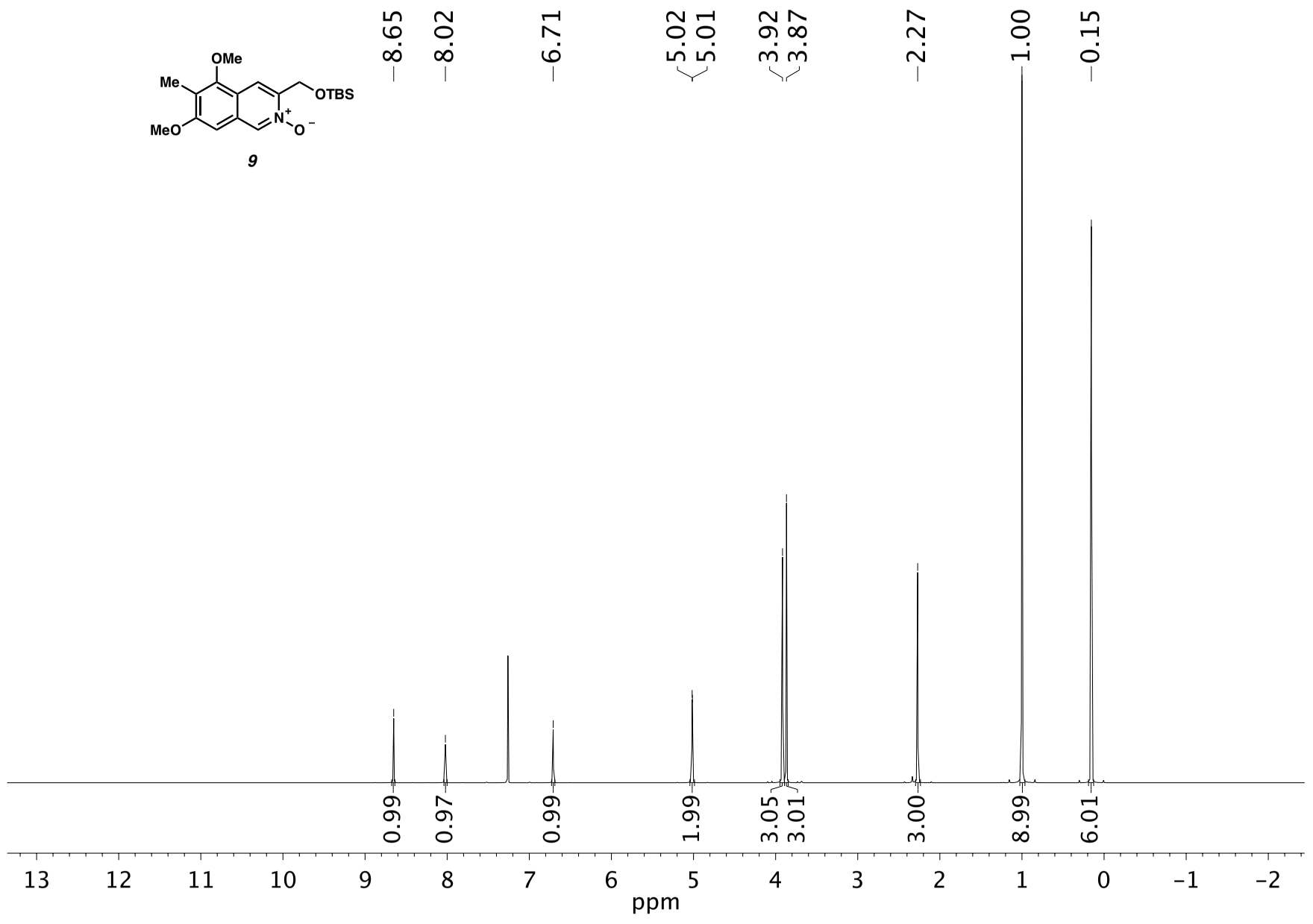
^{1}H NMR (500 MHz, $CDCl_3$) of compound **13**.



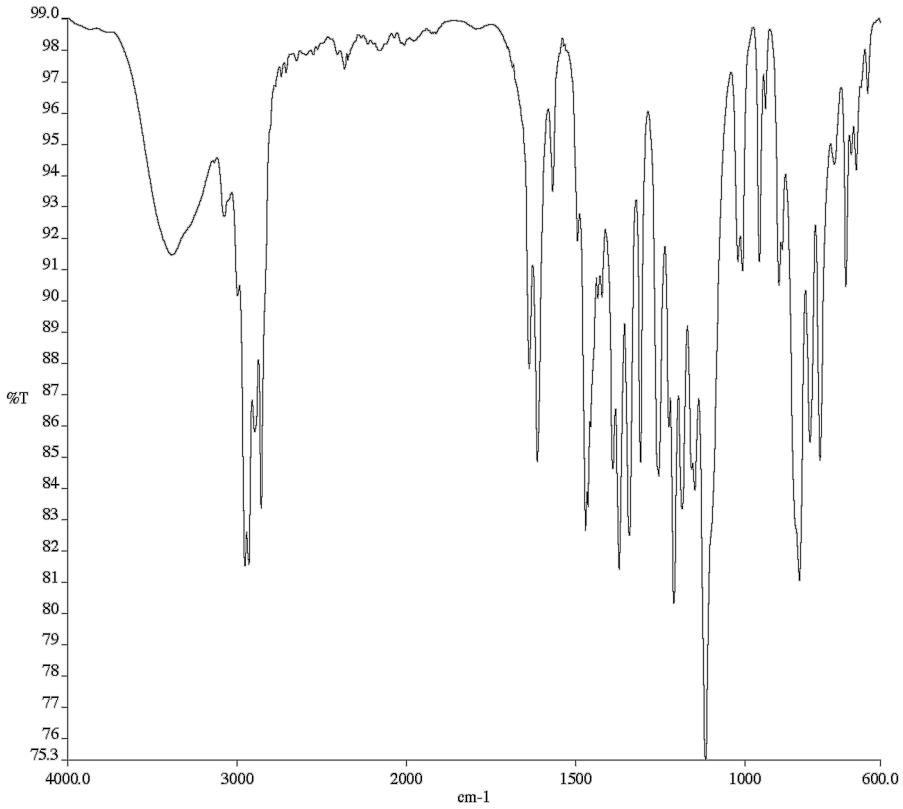
Infrared spectrum (Thin Film, NaCl) of compound **13**.



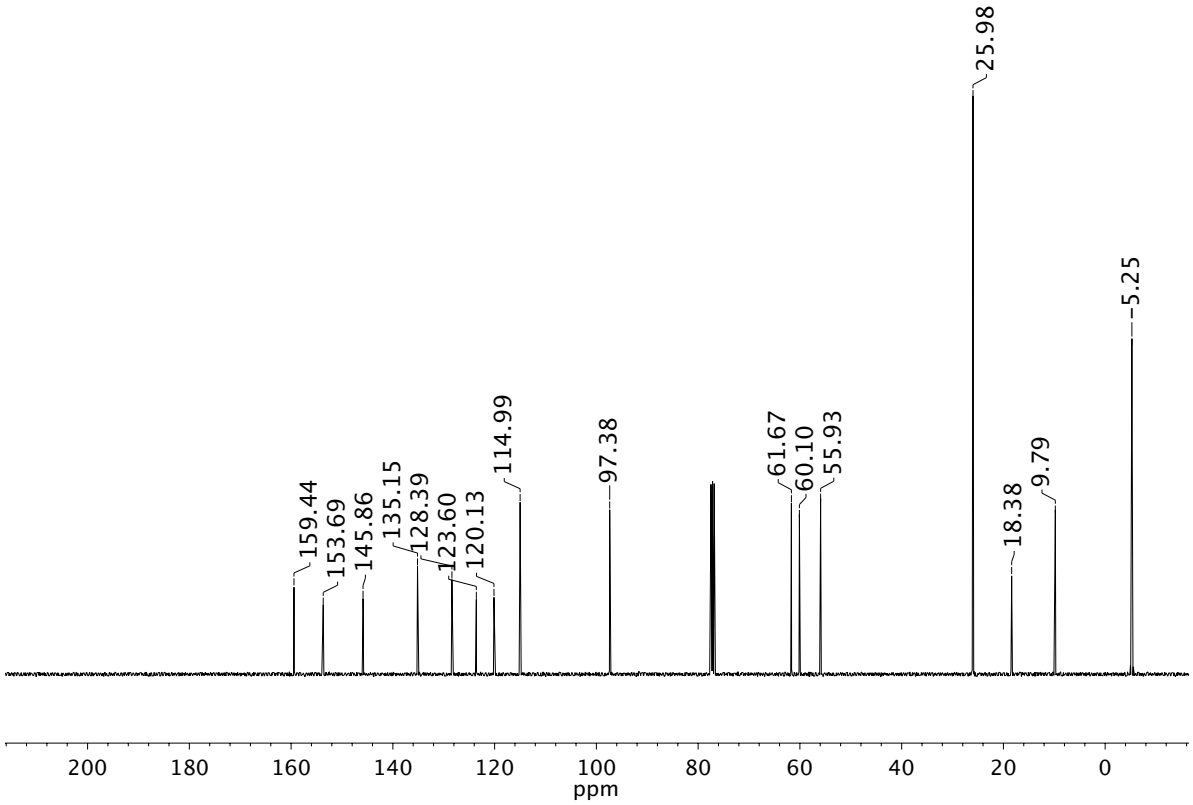
^{13}C NMR (126 MHz, $CDCl_3$) of compound **13**.



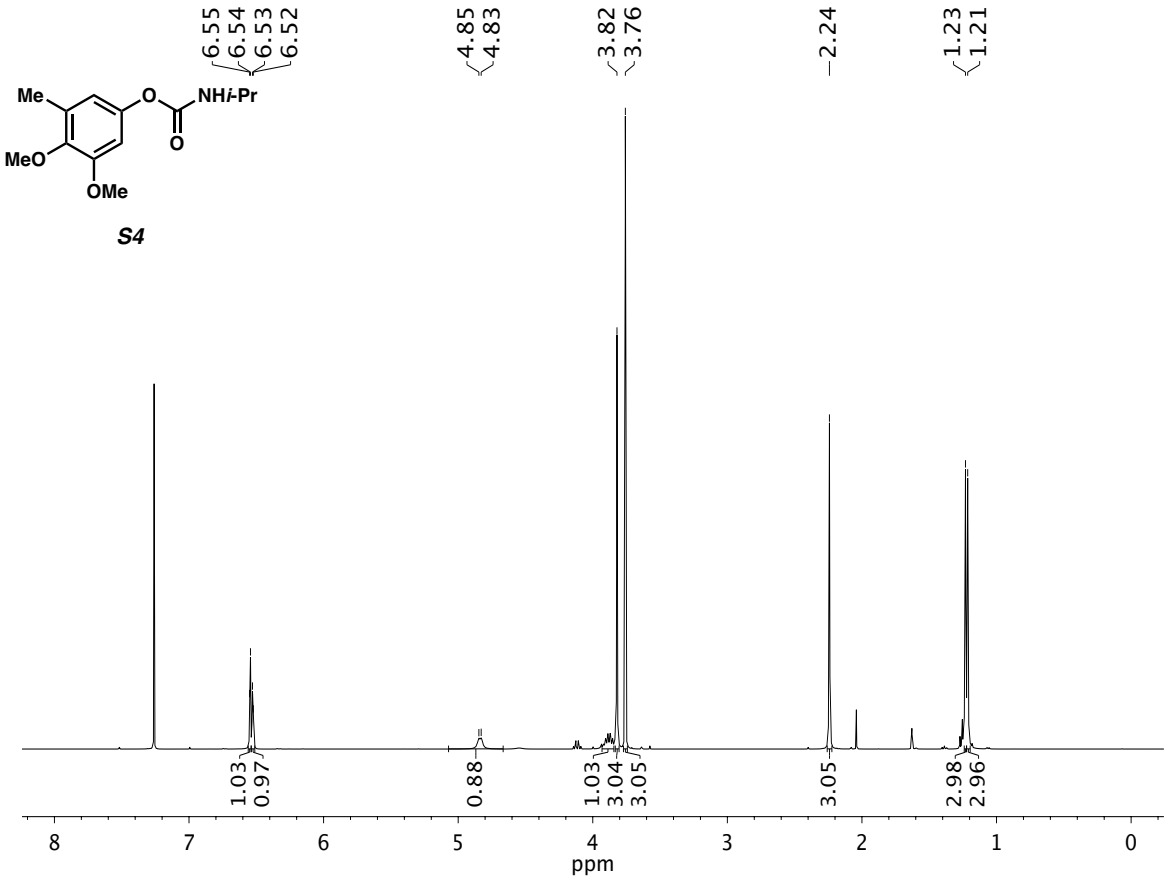
^{1}H NMR (400 MHz, $CDCl_3$) of compound **9**.



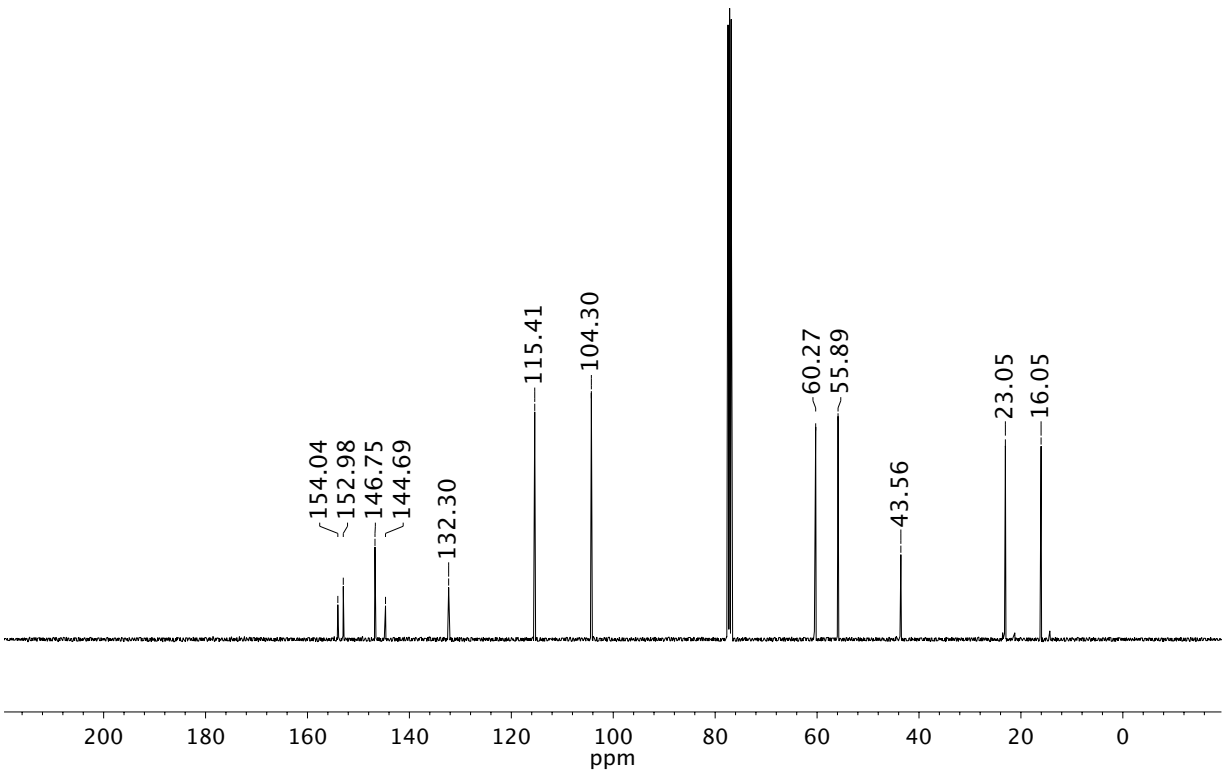
Infrared spectrum (Thin Film, NaCl) of compound **9**.



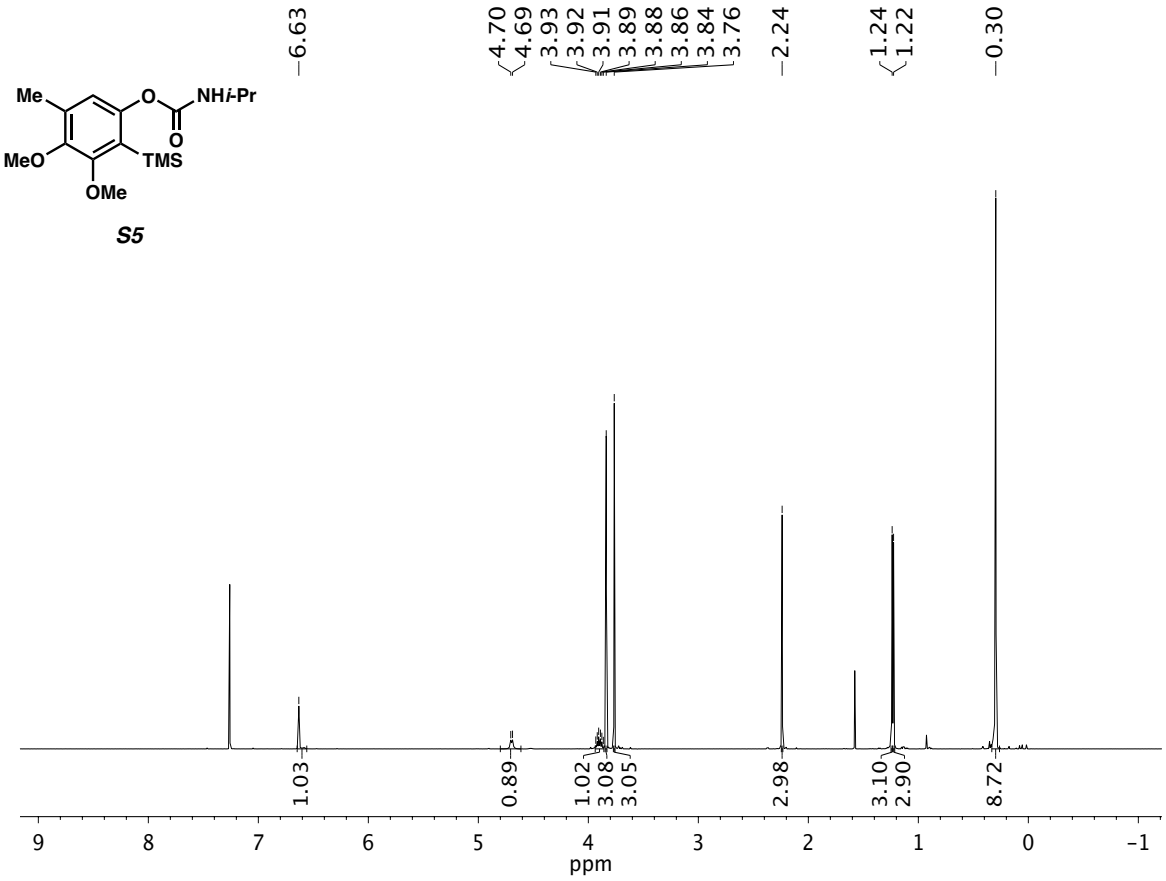
^{13}C NMR (101 MHz, $CDCl_3$) of compound **9**.



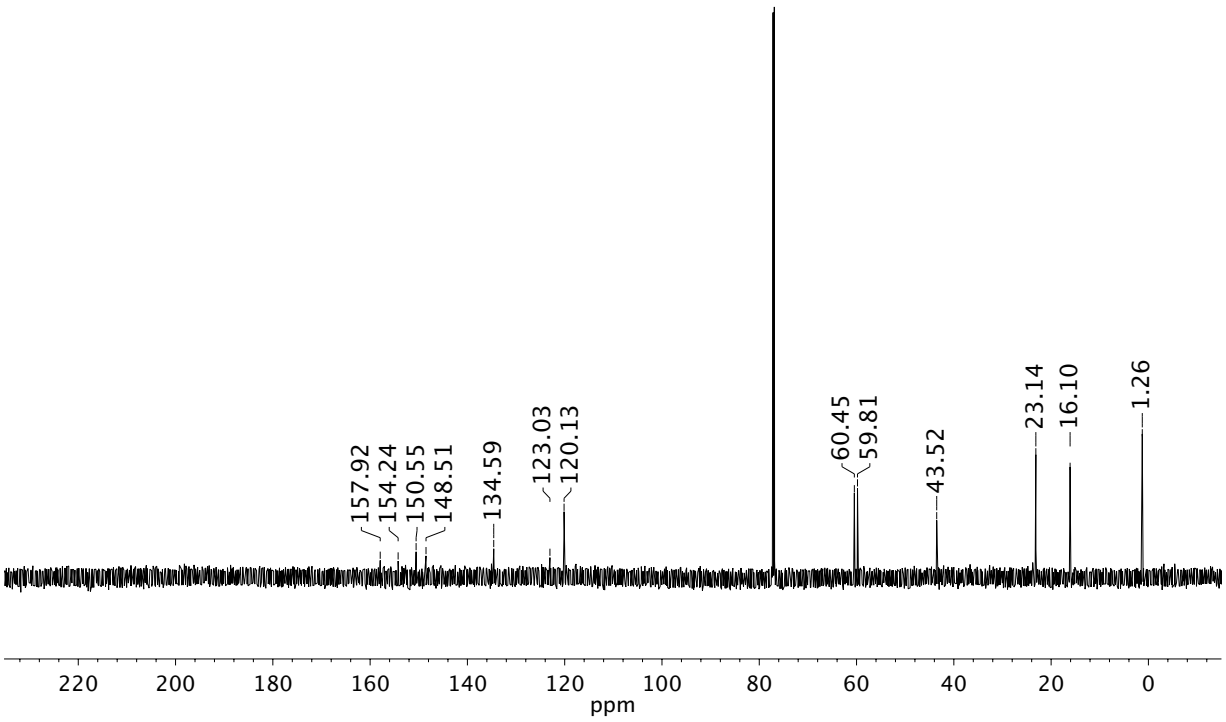
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S4**.



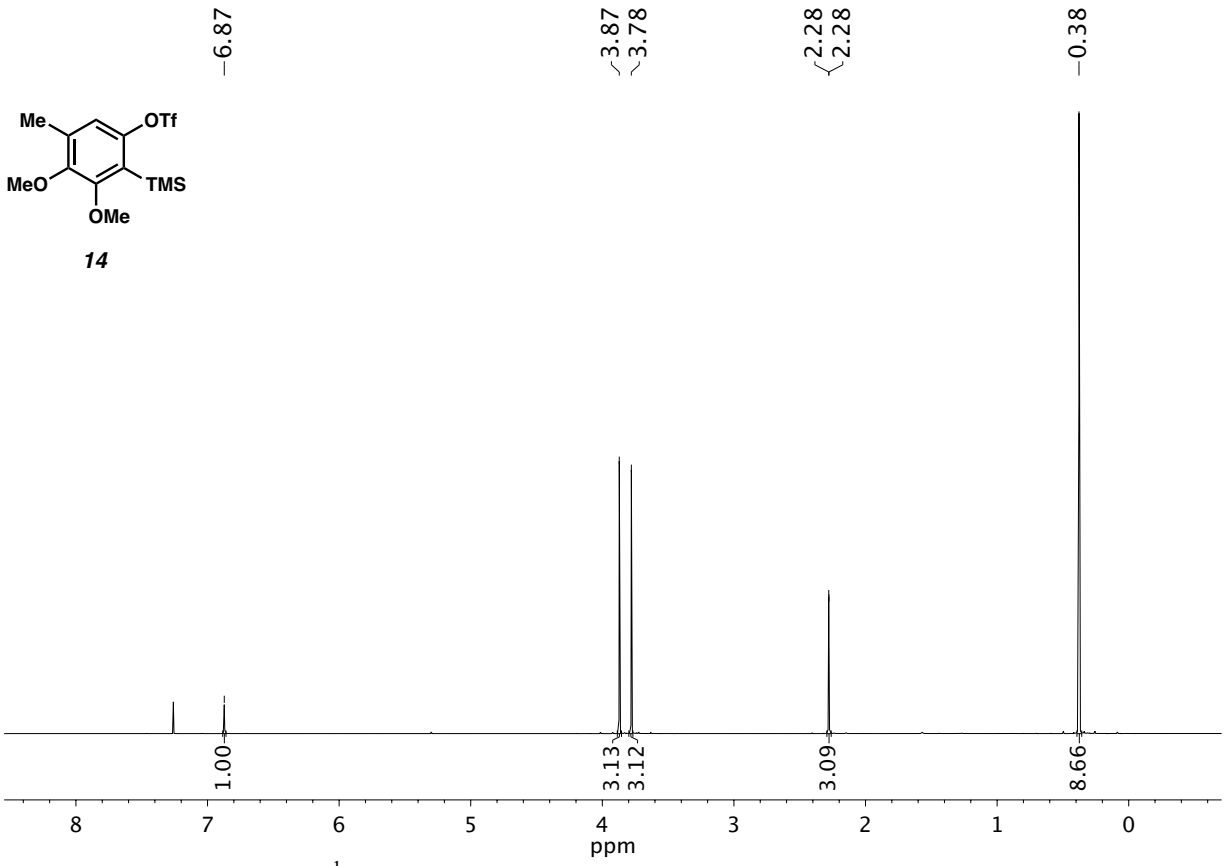
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S4**.



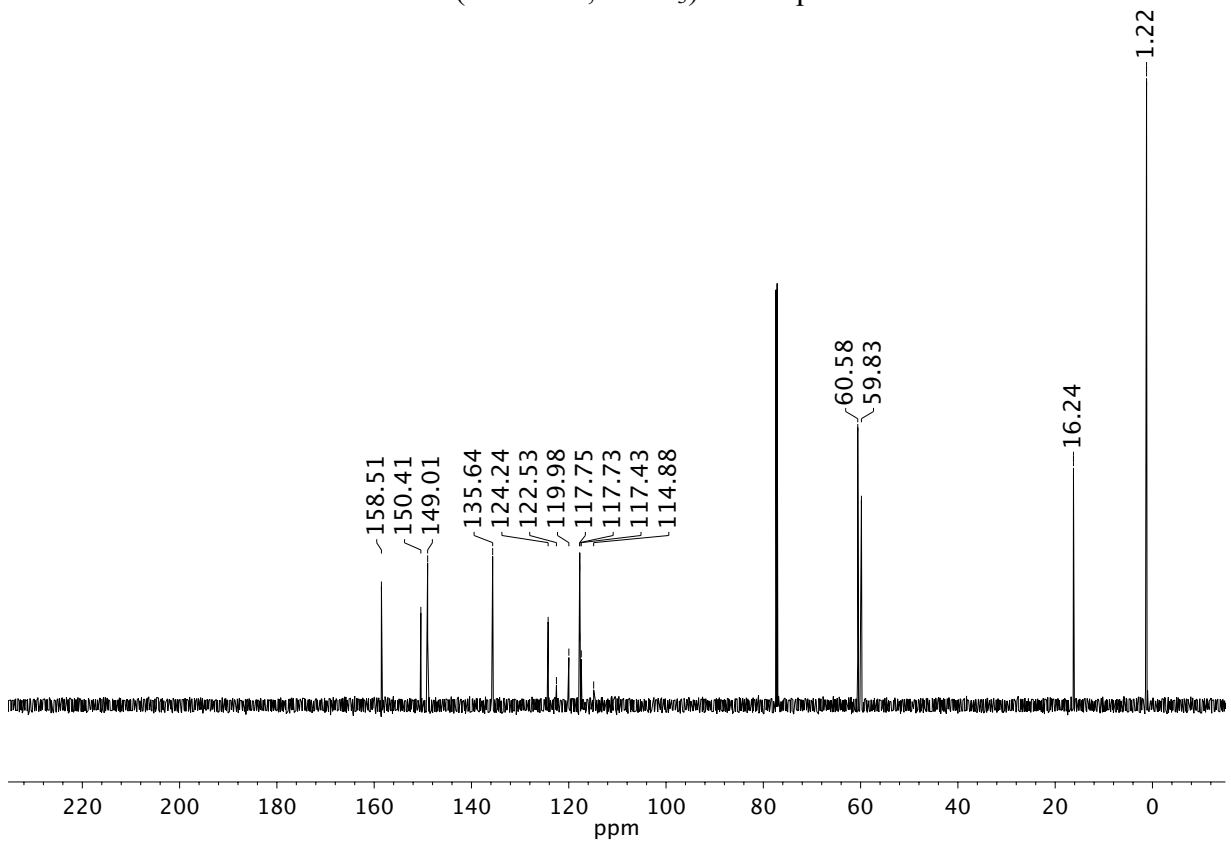
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S5**.



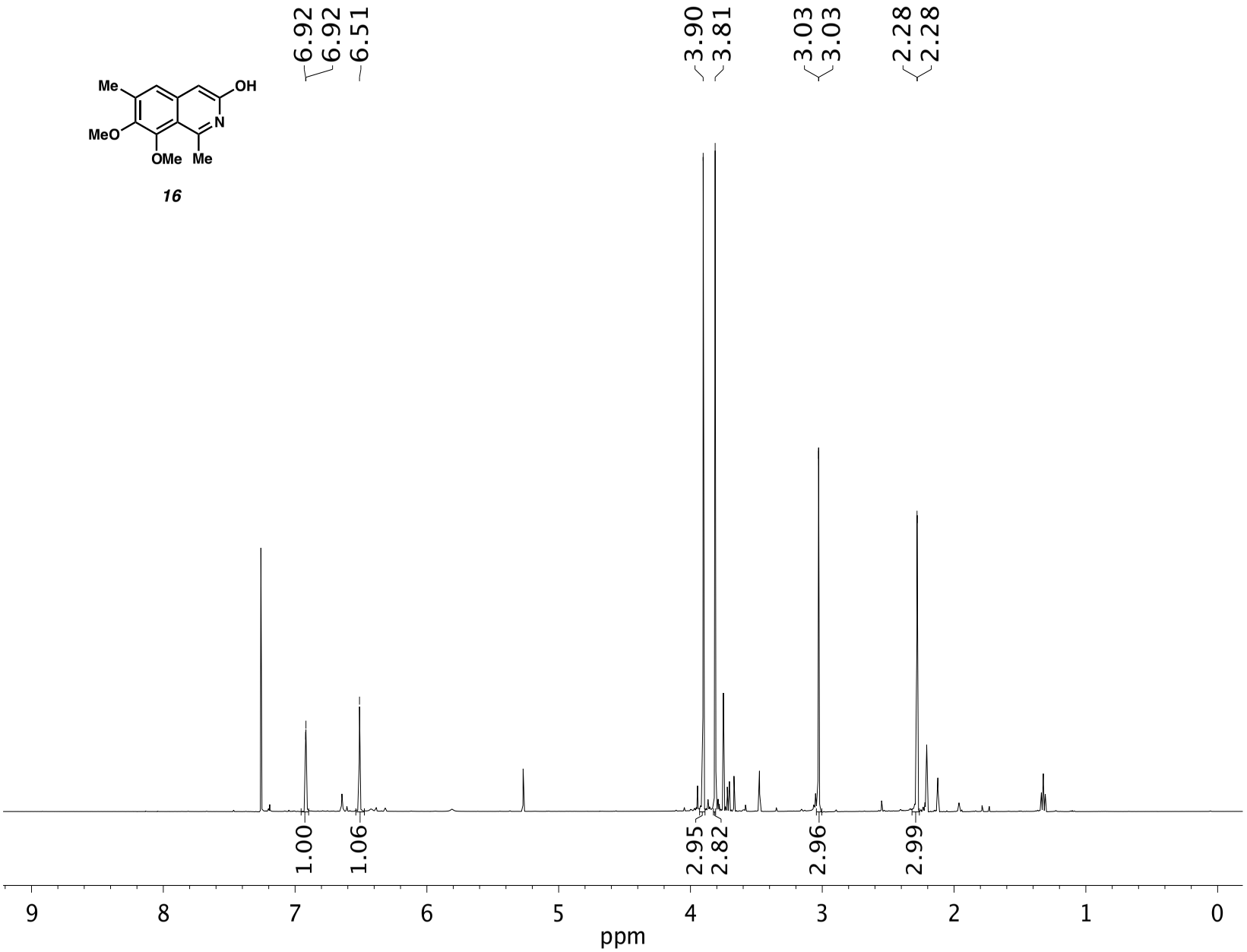
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S5**.



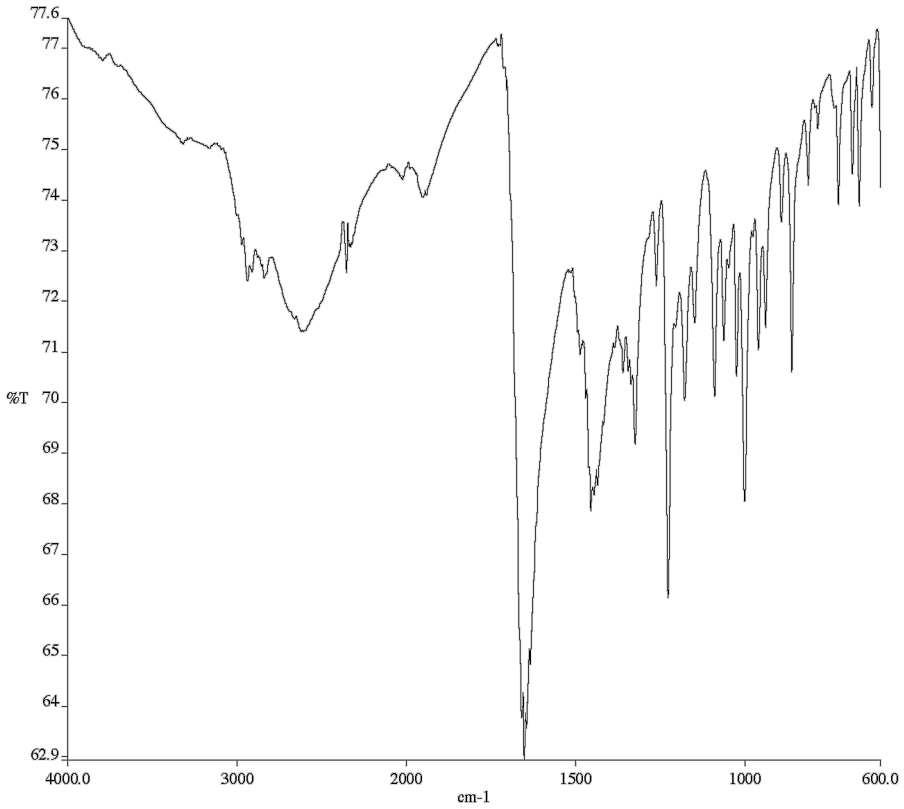
^{1}H NMR (400 MHz, $CDCl_3$) of compound **14**.



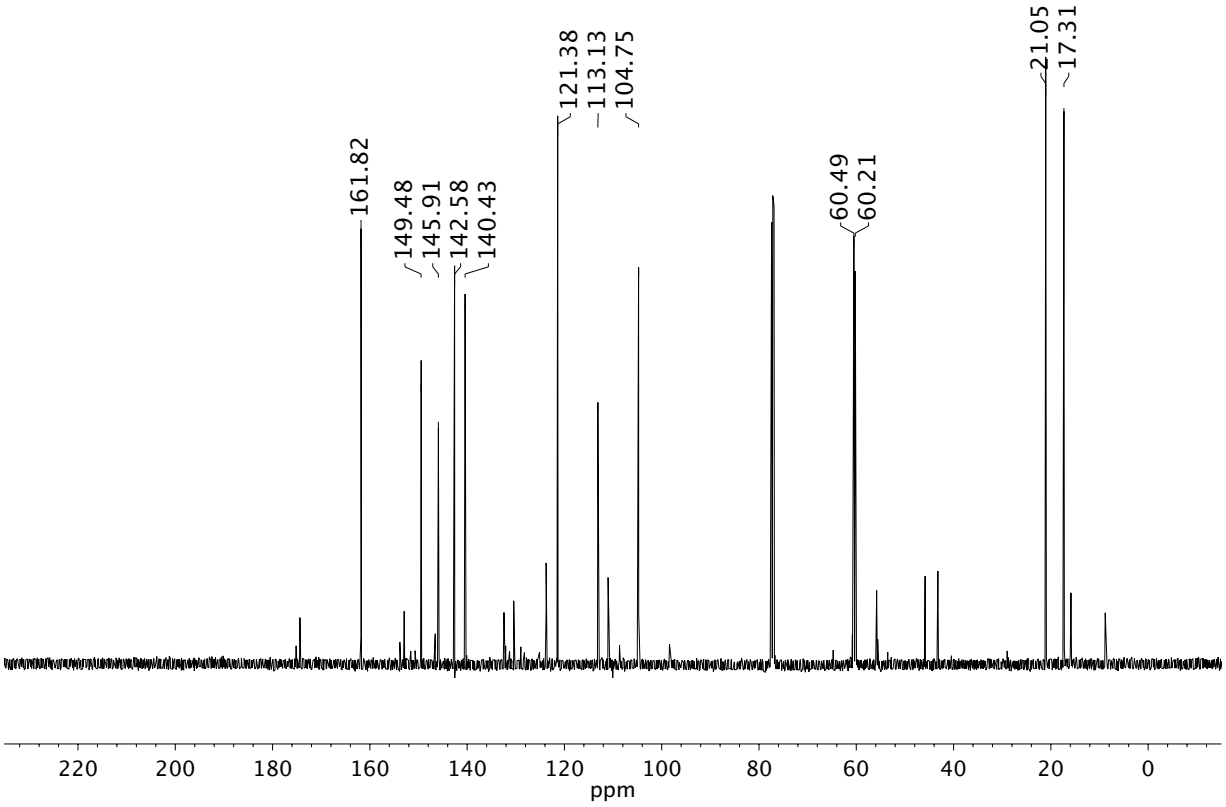
^{13}C NMR (101 MHz, $CDCl_3$) of compound **14**.



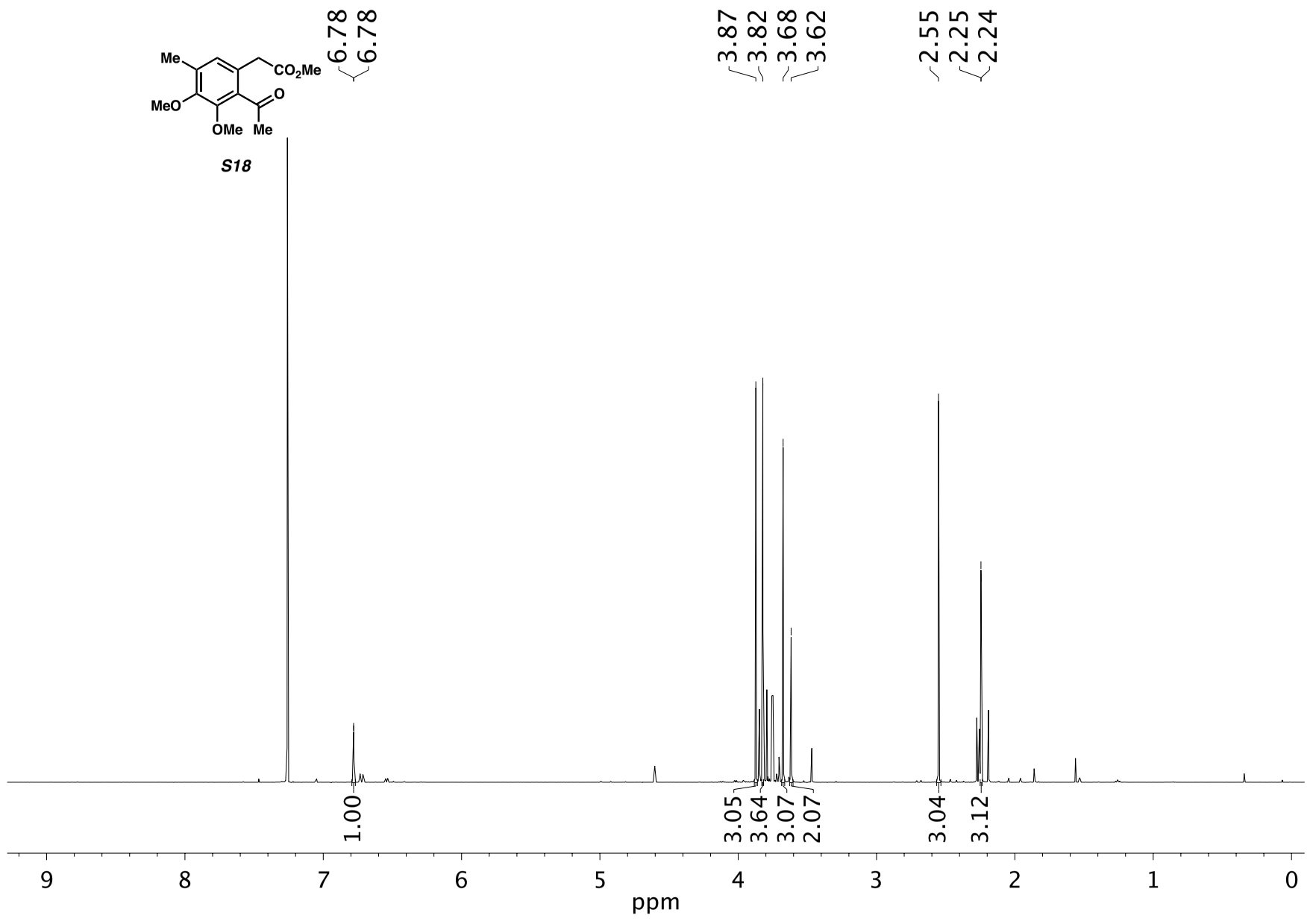
^{1}H NMR (400 MHz, $CDCl_3$) of compound **16**.



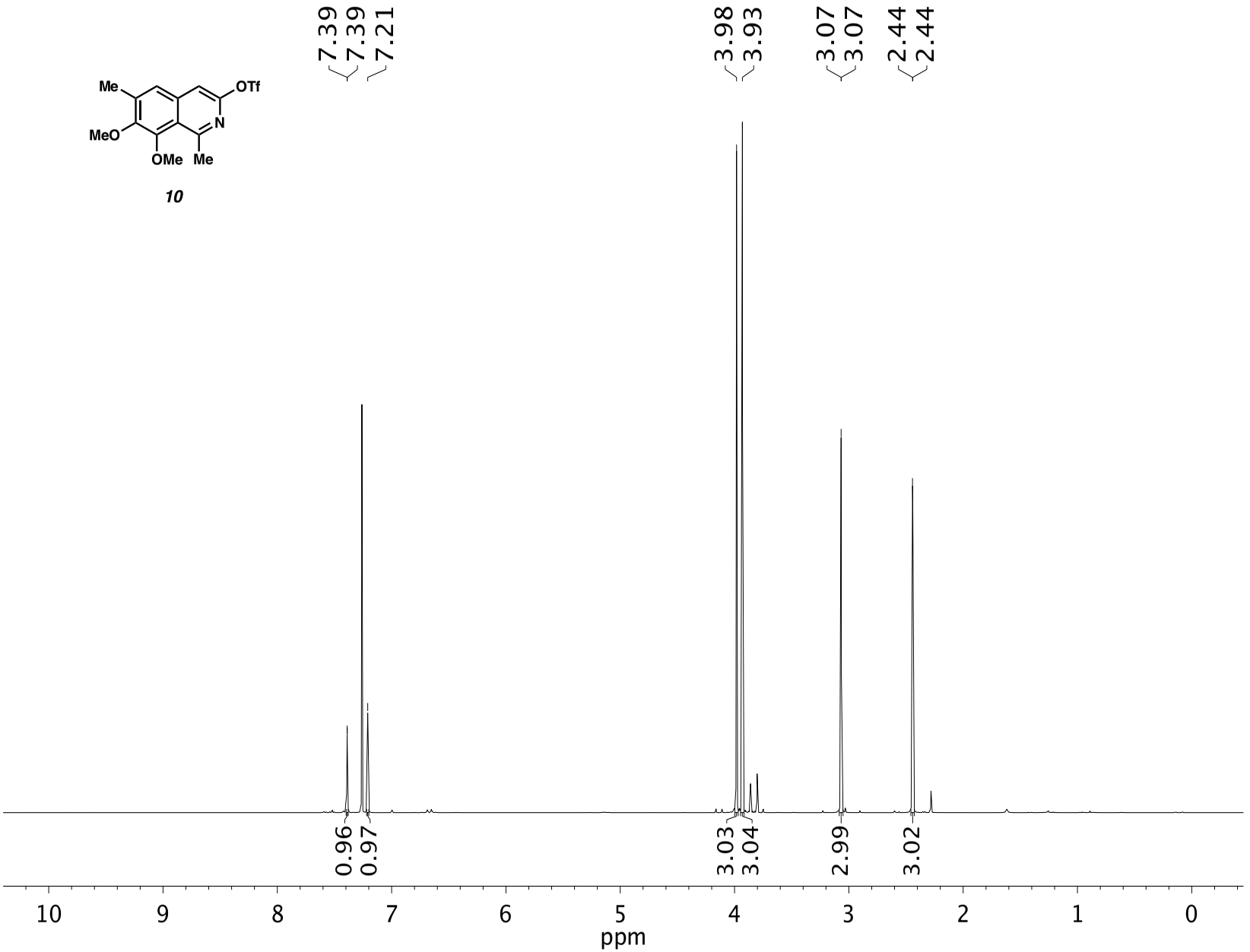
Infrared spectrum (Thin Film, NaCl) of compound **16**.



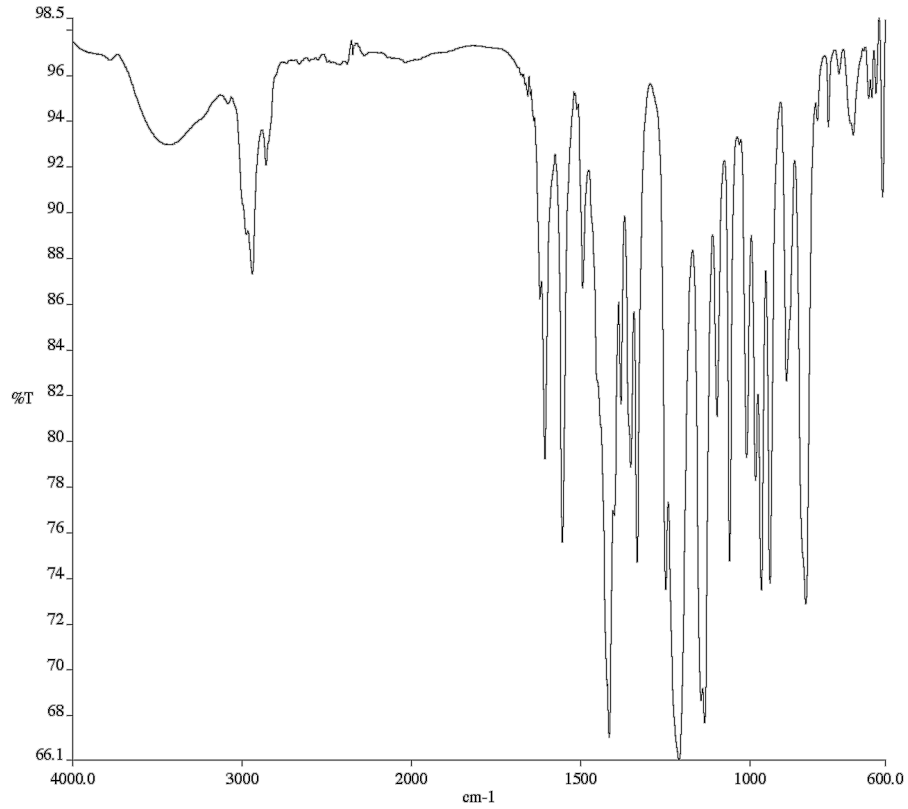
^{13}C NMR (101 MHz, $CDCl_3$) of compound **16**.



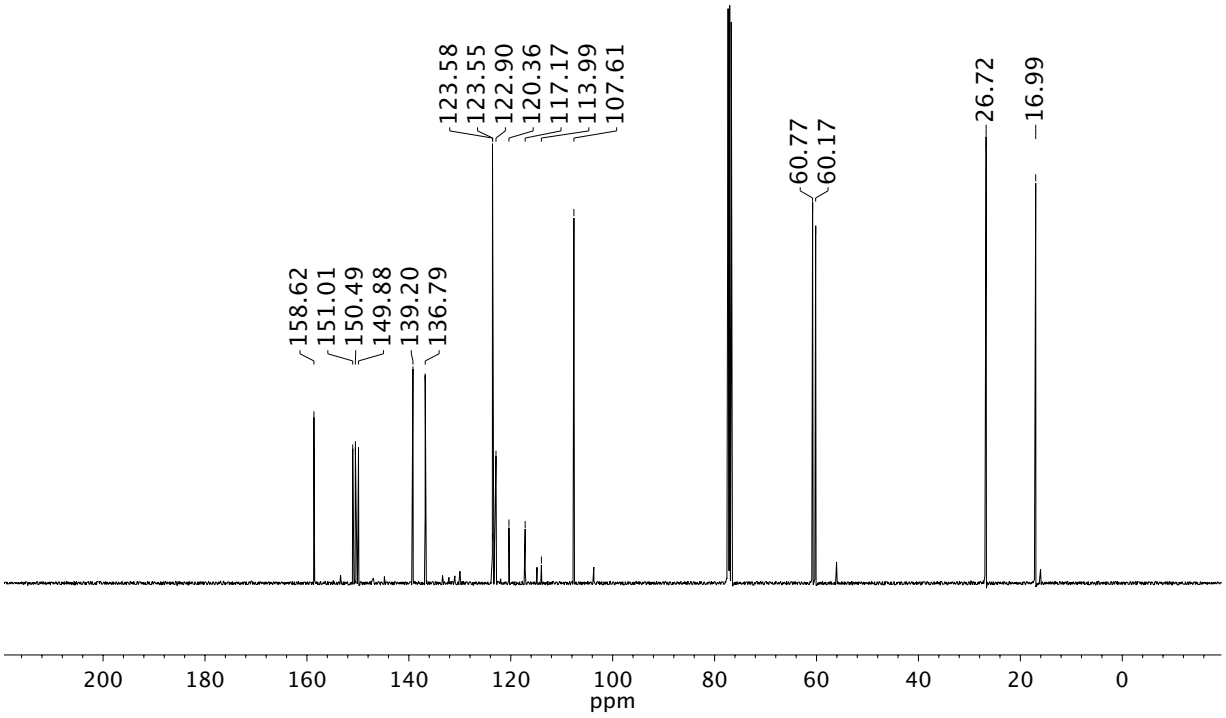
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S18**.



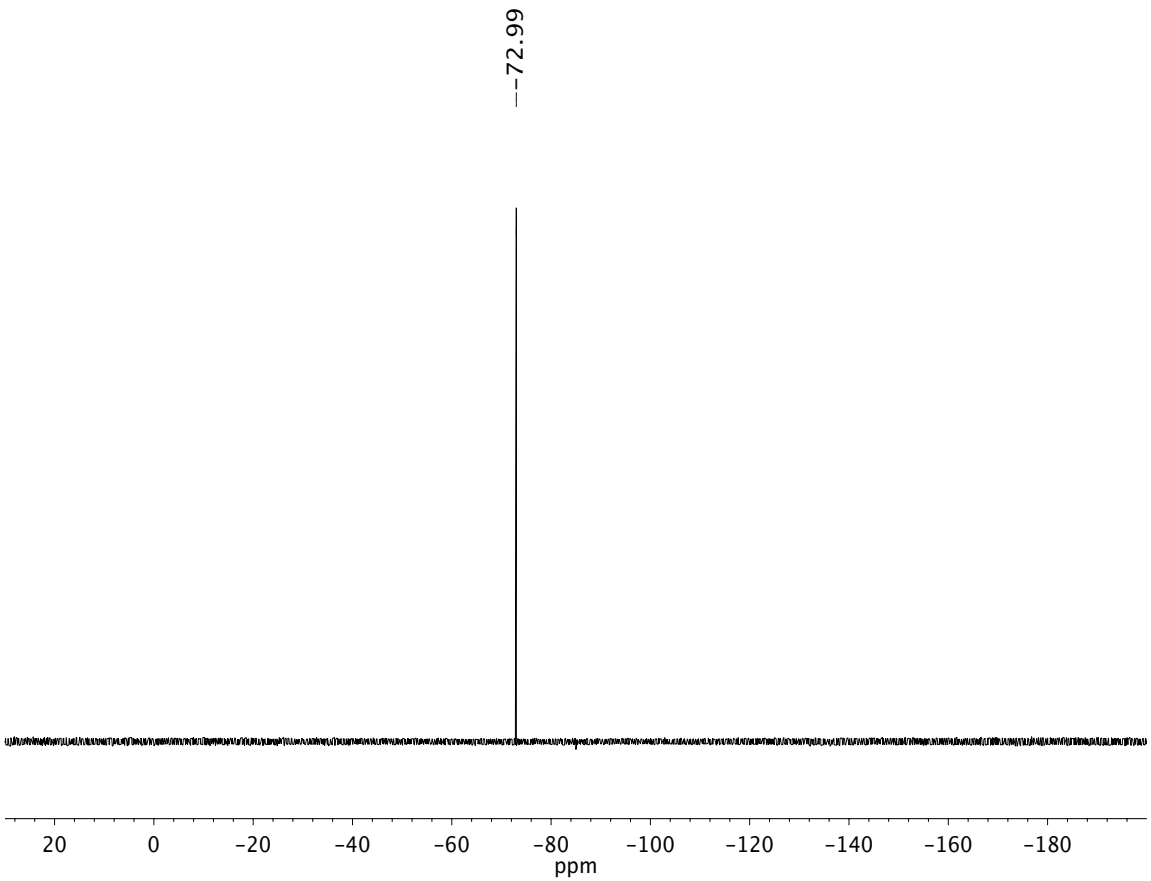
^{1}H NMR (400 MHz, $CDCl_3$) of compound **10**.



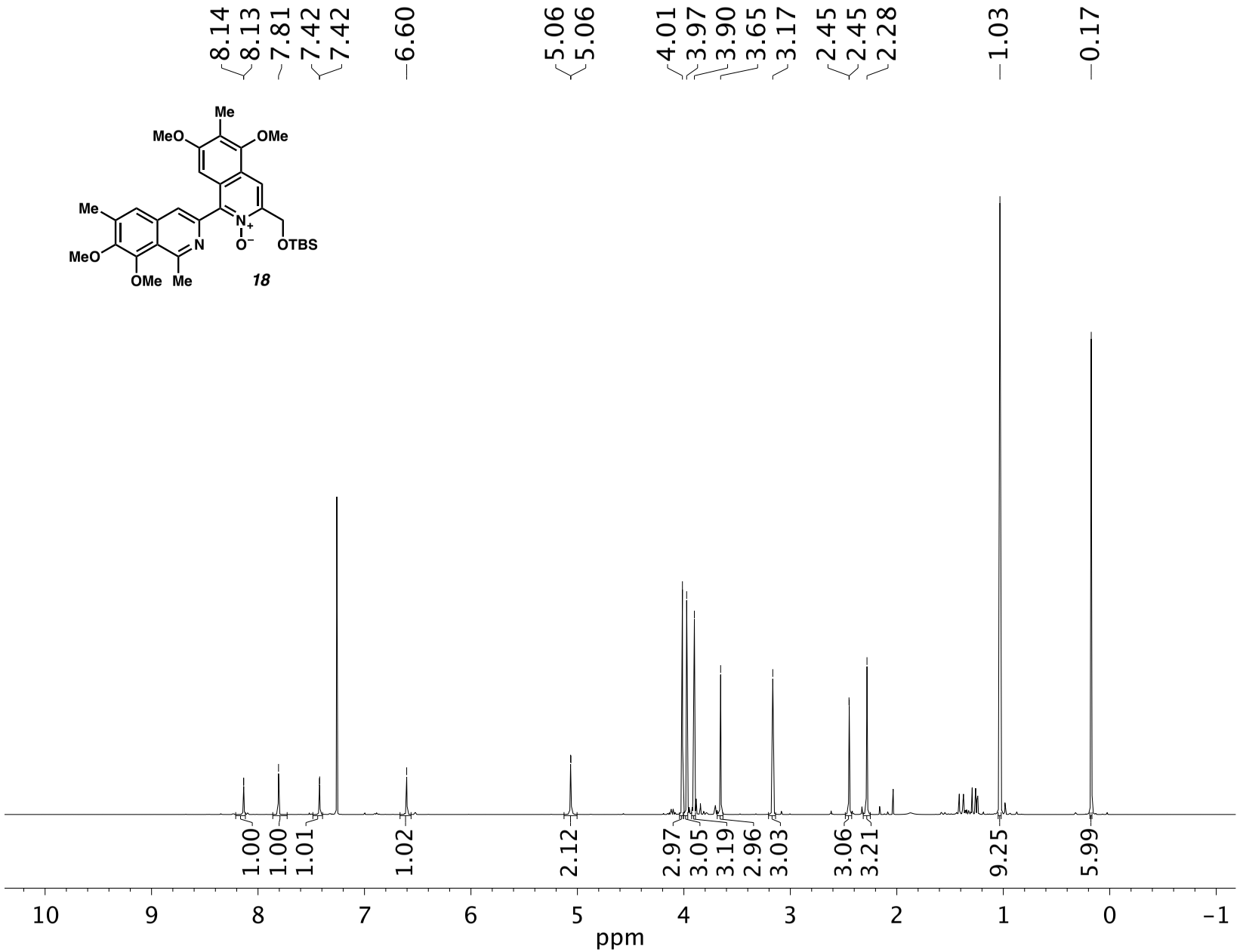
Infrared spectrum (Thin Film, NaCl) of compound **10**.



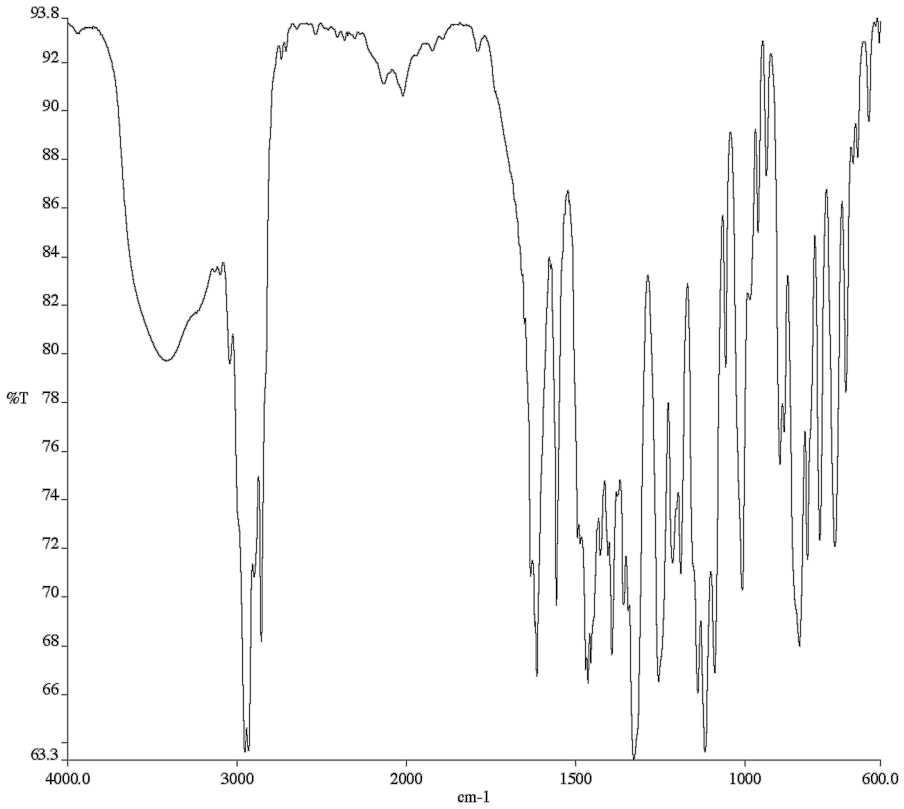
^{13}C NMR (101 MHz, $CDCl_3$) of compound **10**.



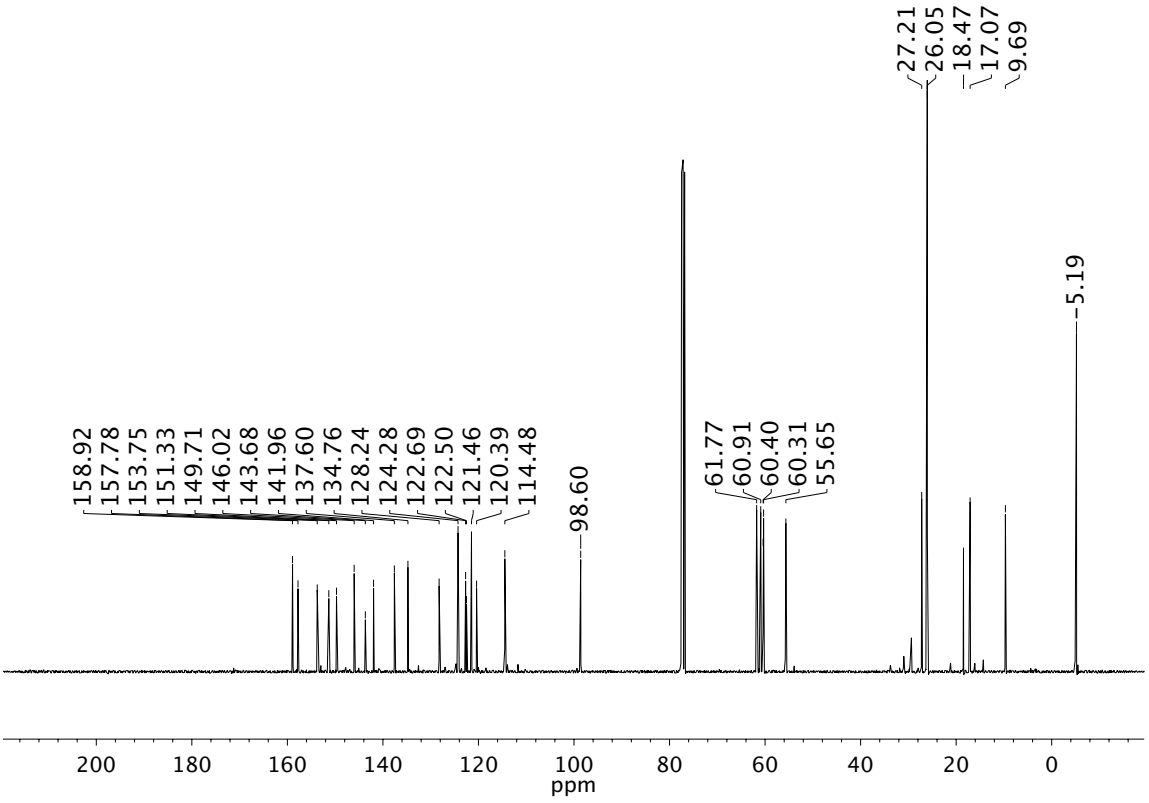
^{19}F NMR (282 MHz, $CDCl_3$) of compound **10**



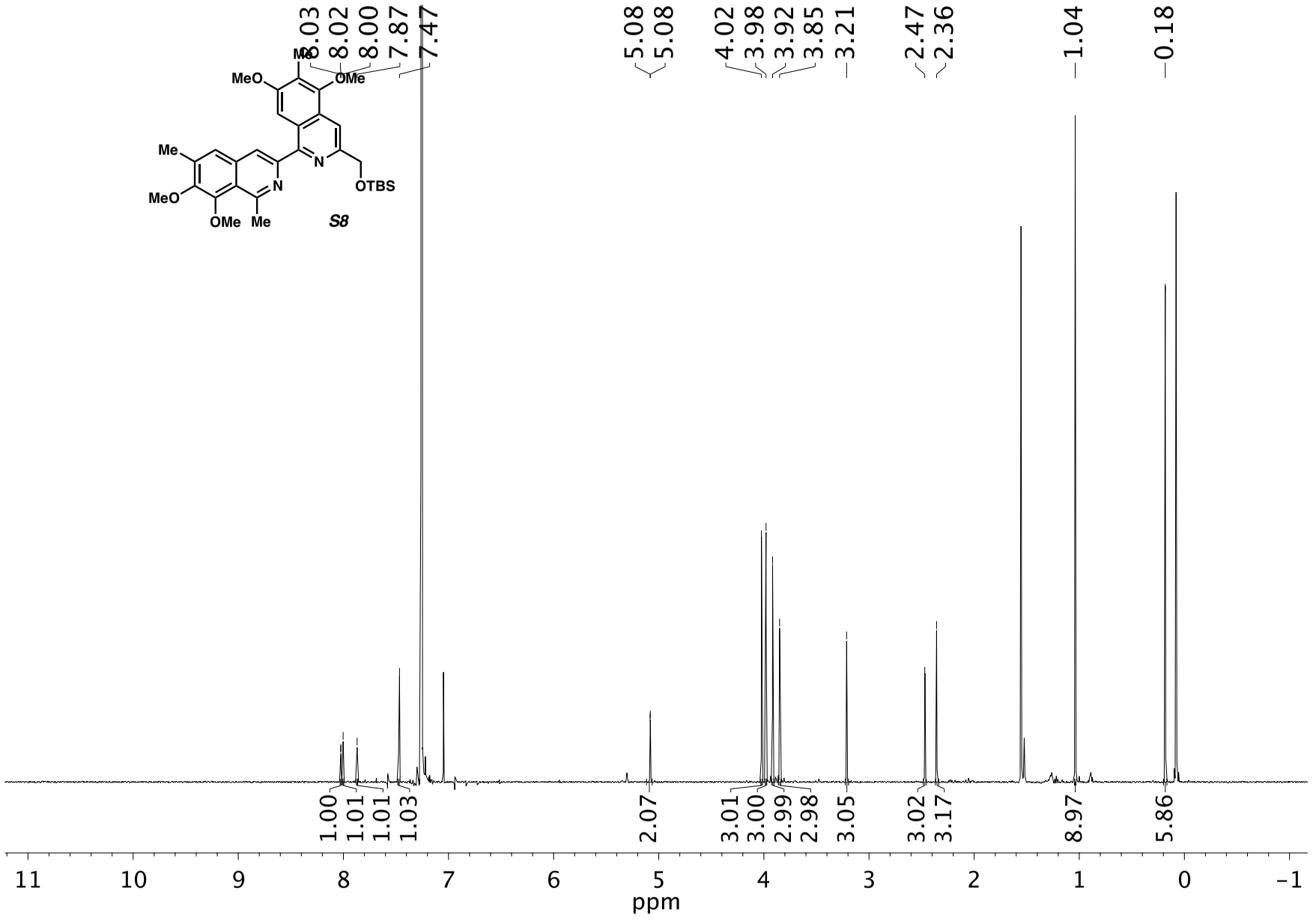
^{1}H NMR (400 MHz, $CDCl_3$) of compound **18**.



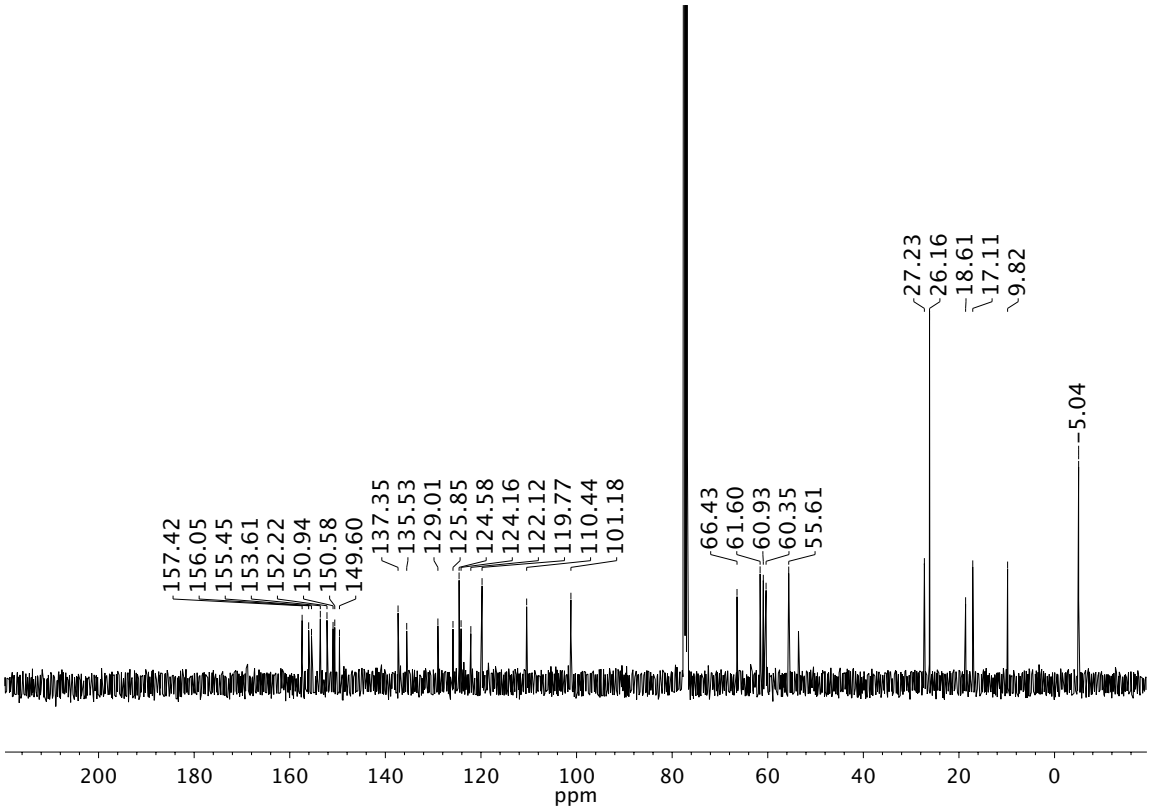
Infrared spectrum (Thin Film, NaCl) of compound **18**.



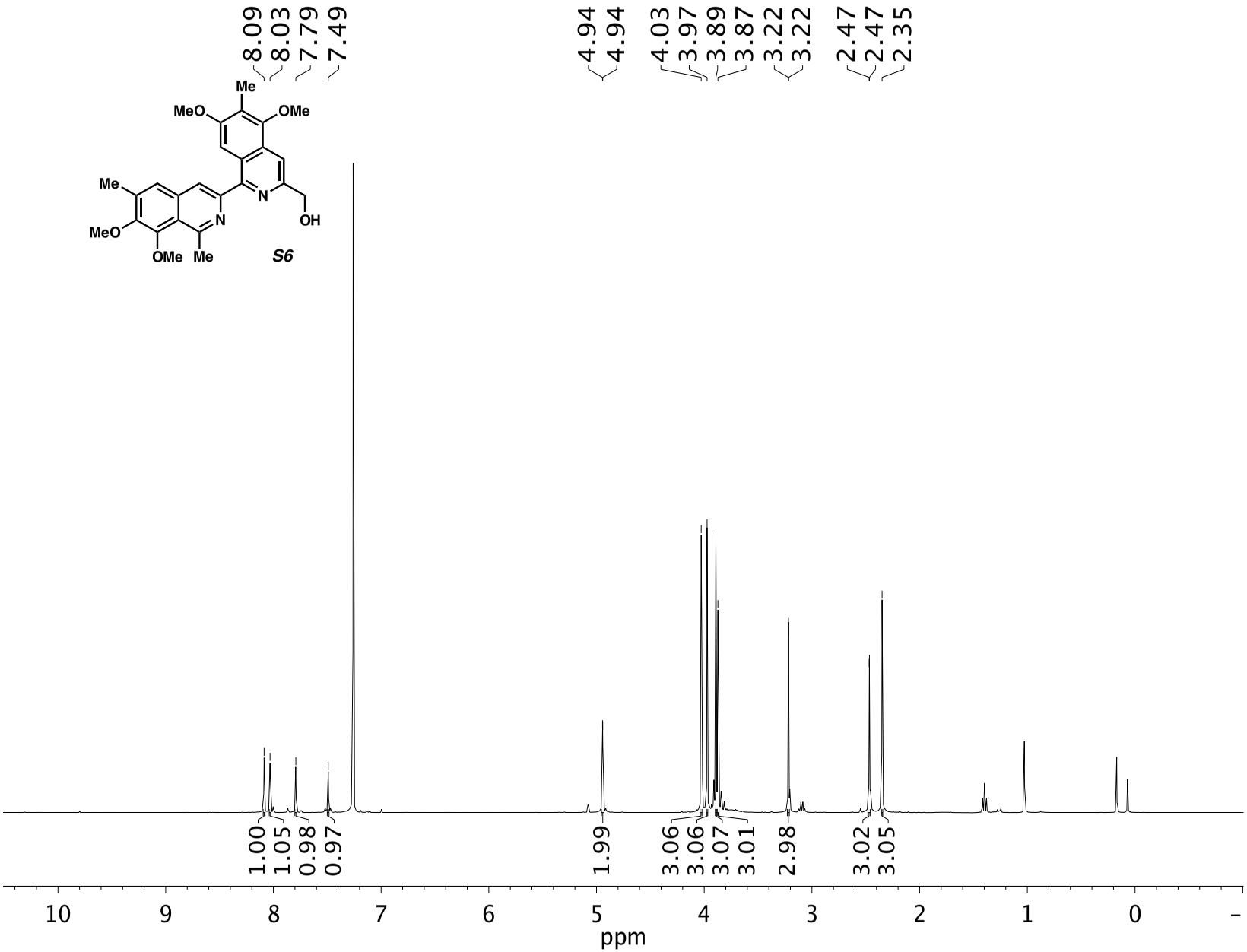
^{13}C NMR (101 MHz, $CDCl_3$) of compound **18**.



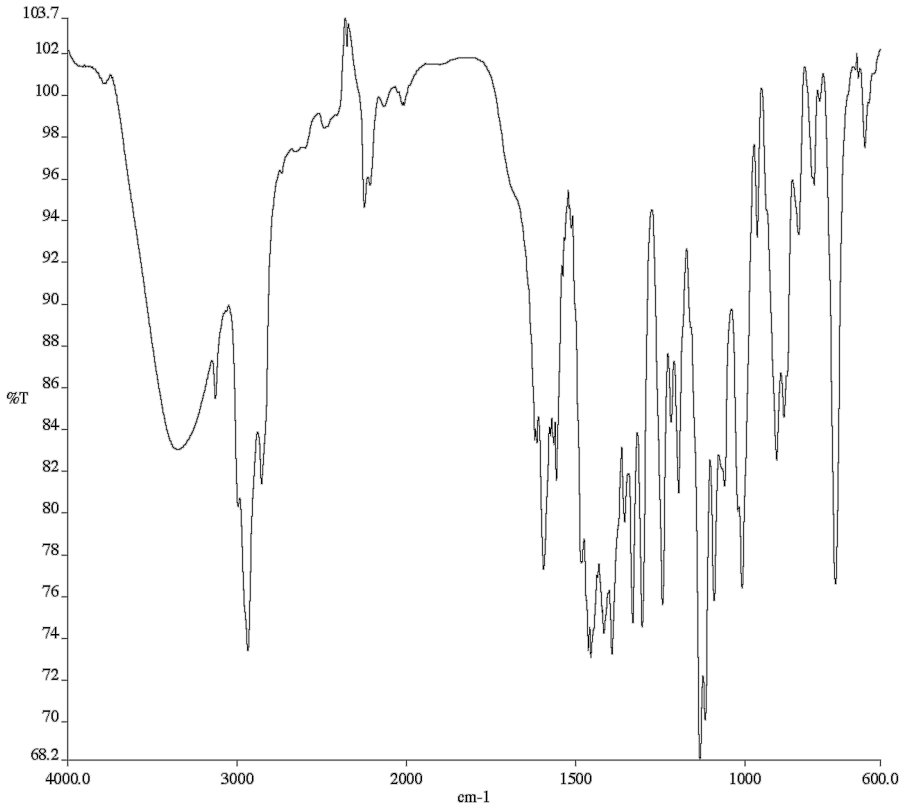
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S8**.



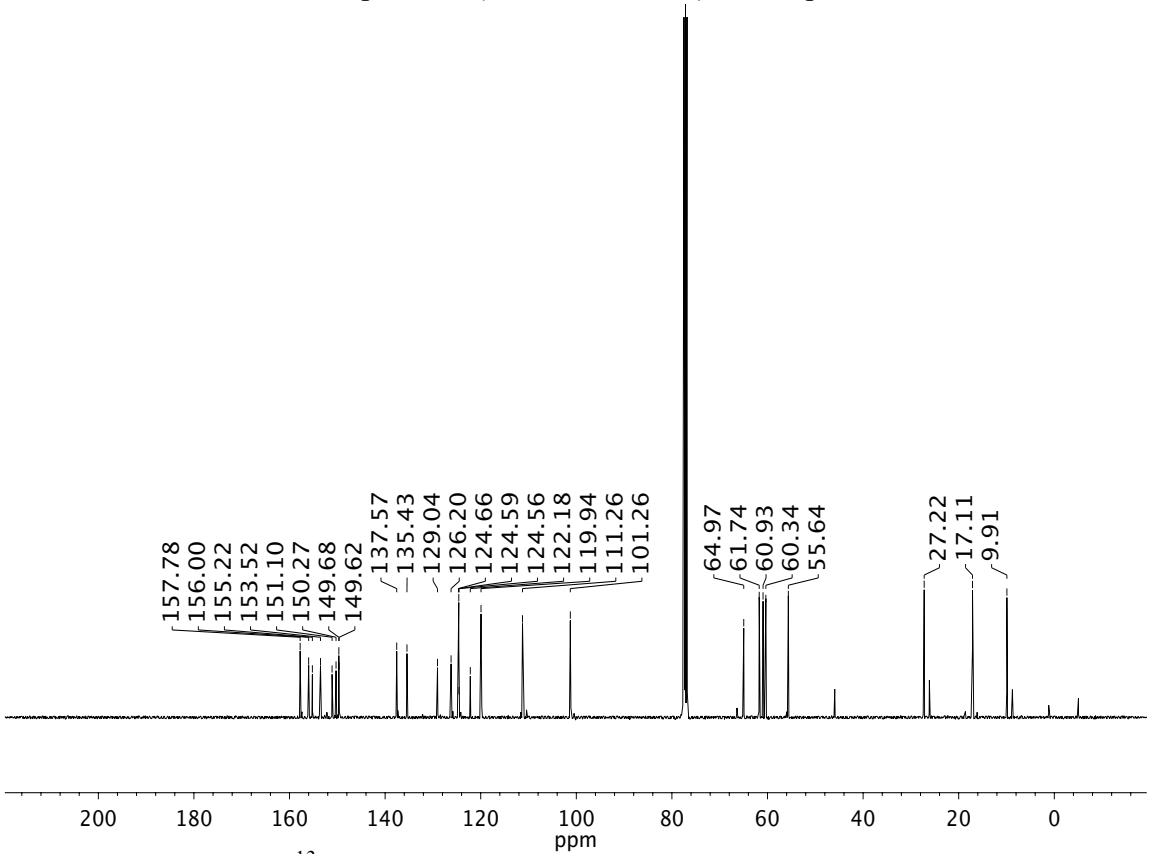
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S8**.



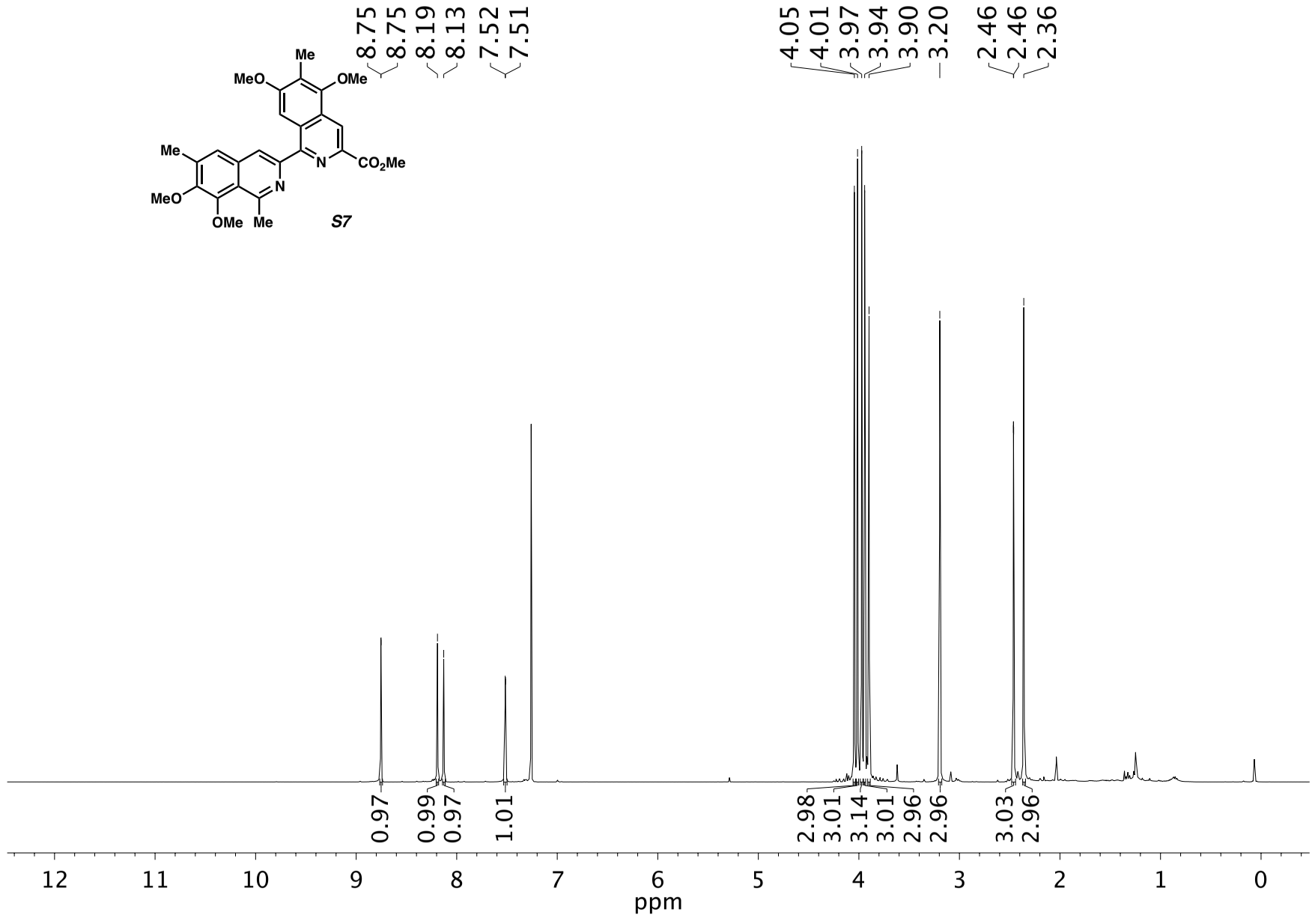
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S6**.



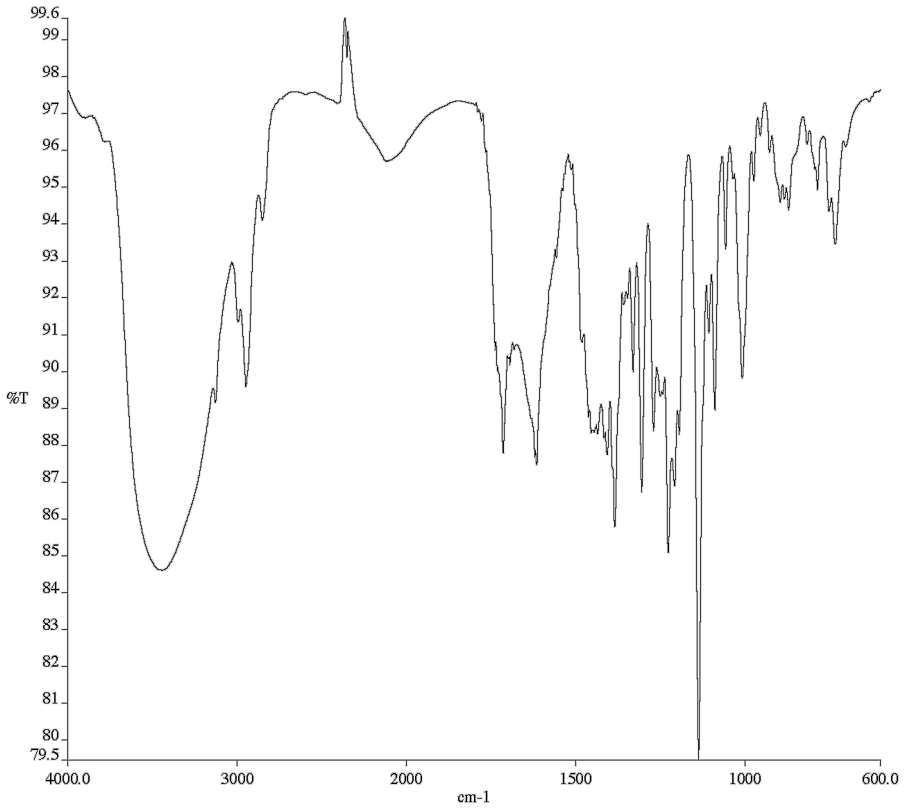
Infrared spectrum (Thin Film, NaCl) of compound **S6**.



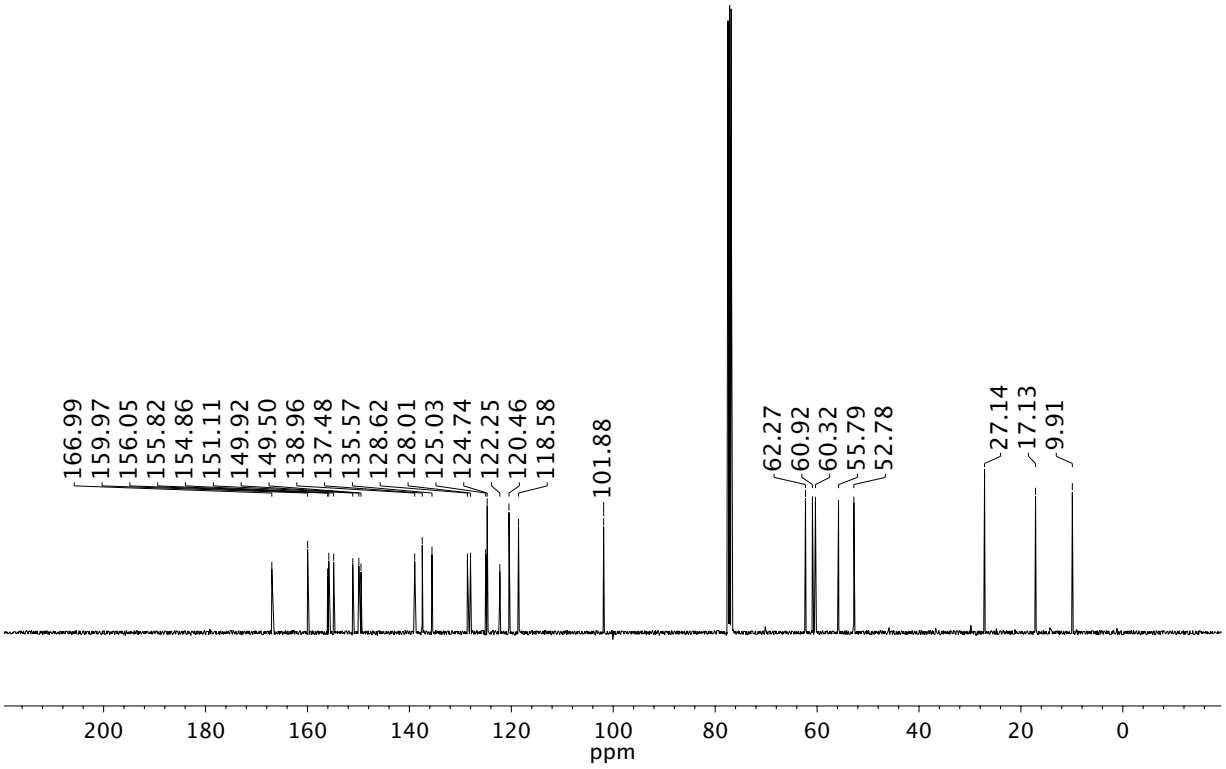
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S6**.



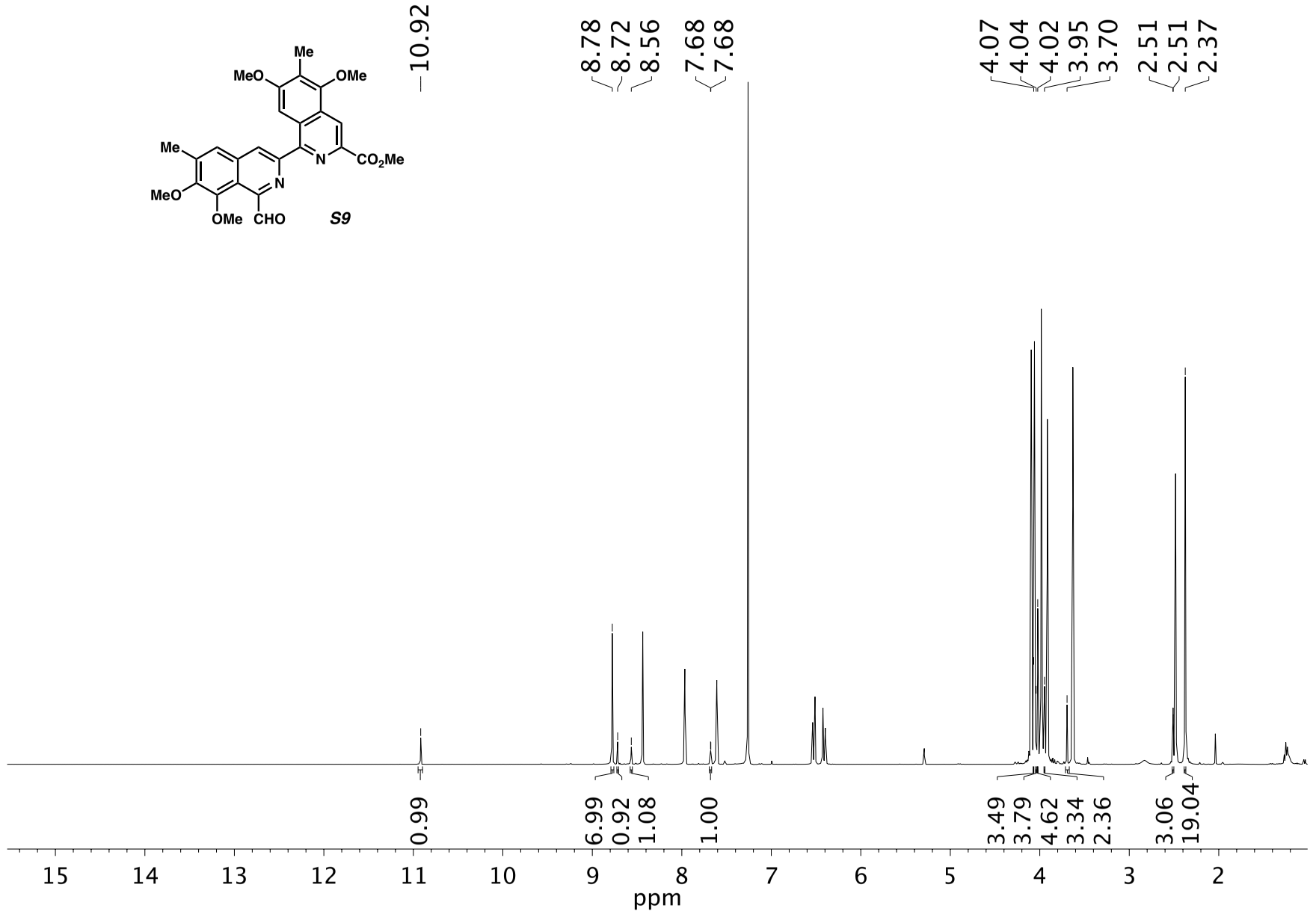
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S7**.



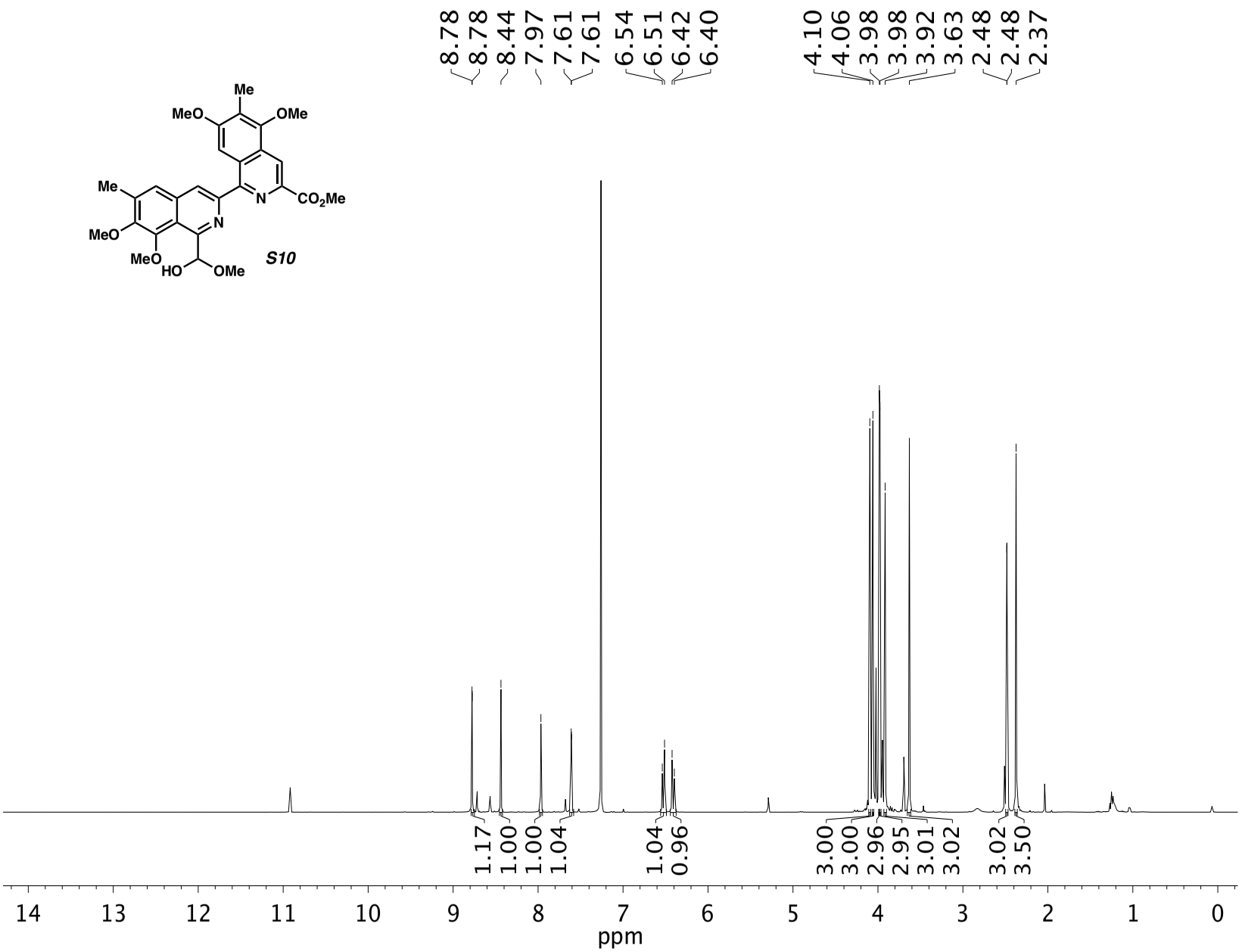
Infrared spectrum (Thin Film, NaCl) of compound **S7**.



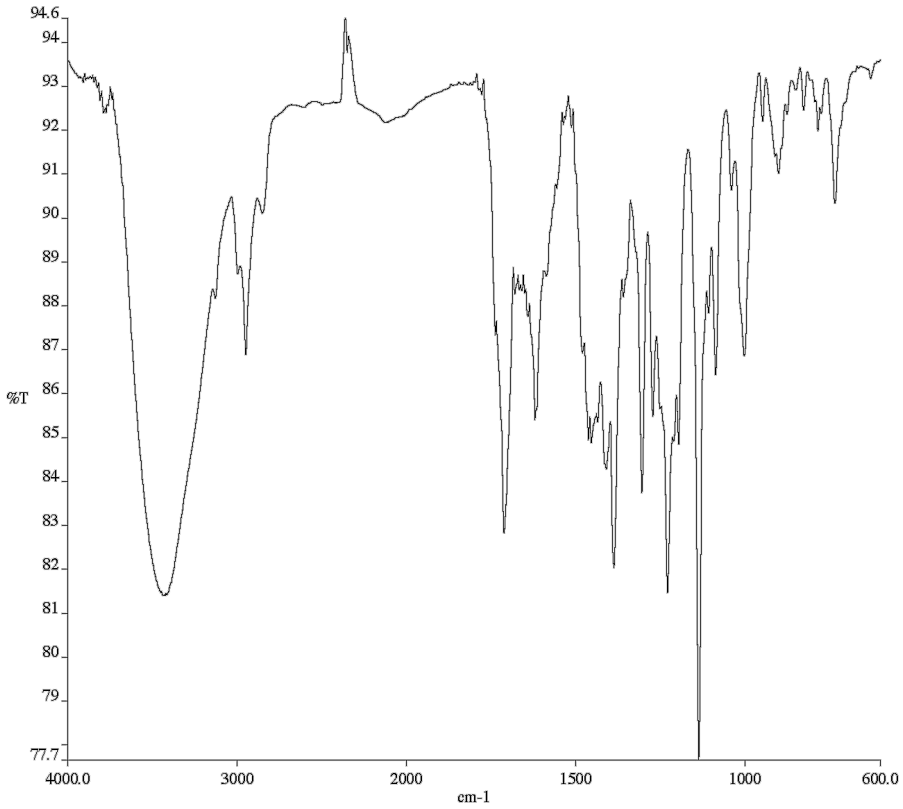
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S7**.



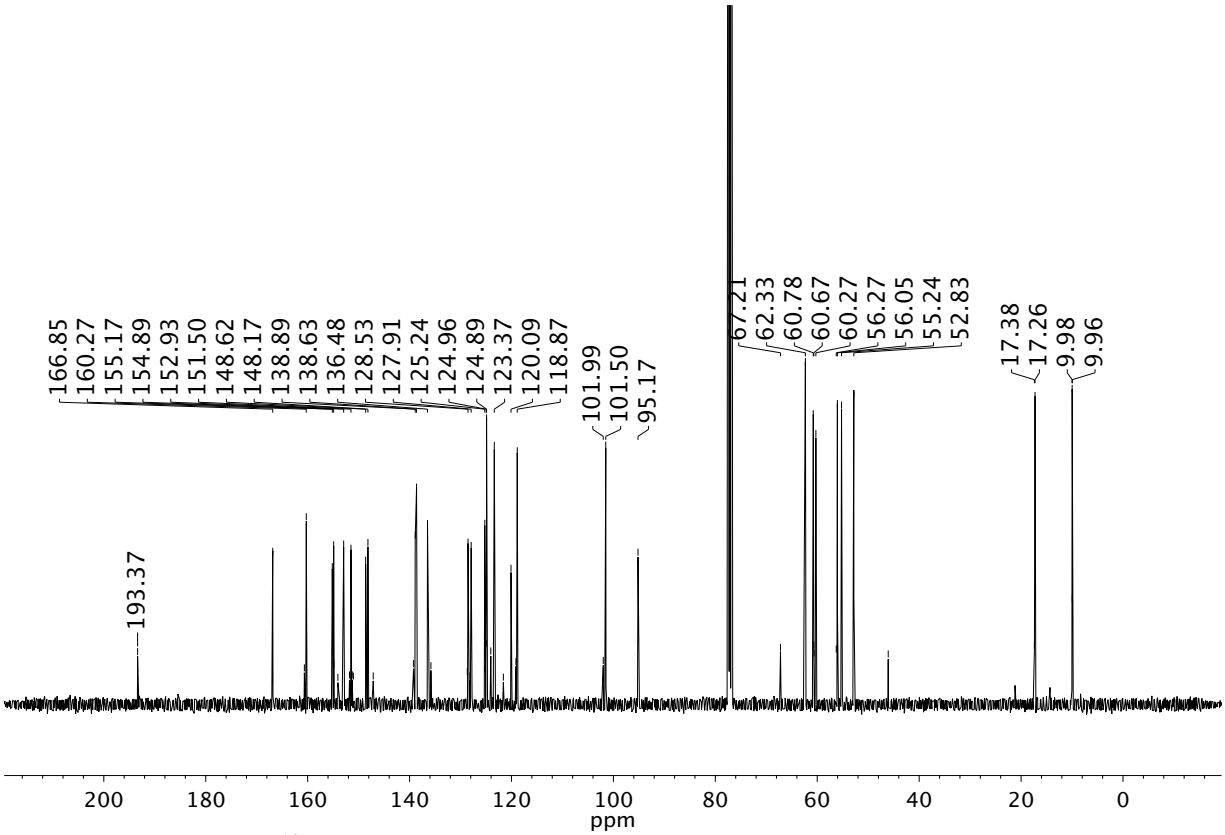
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S9**.



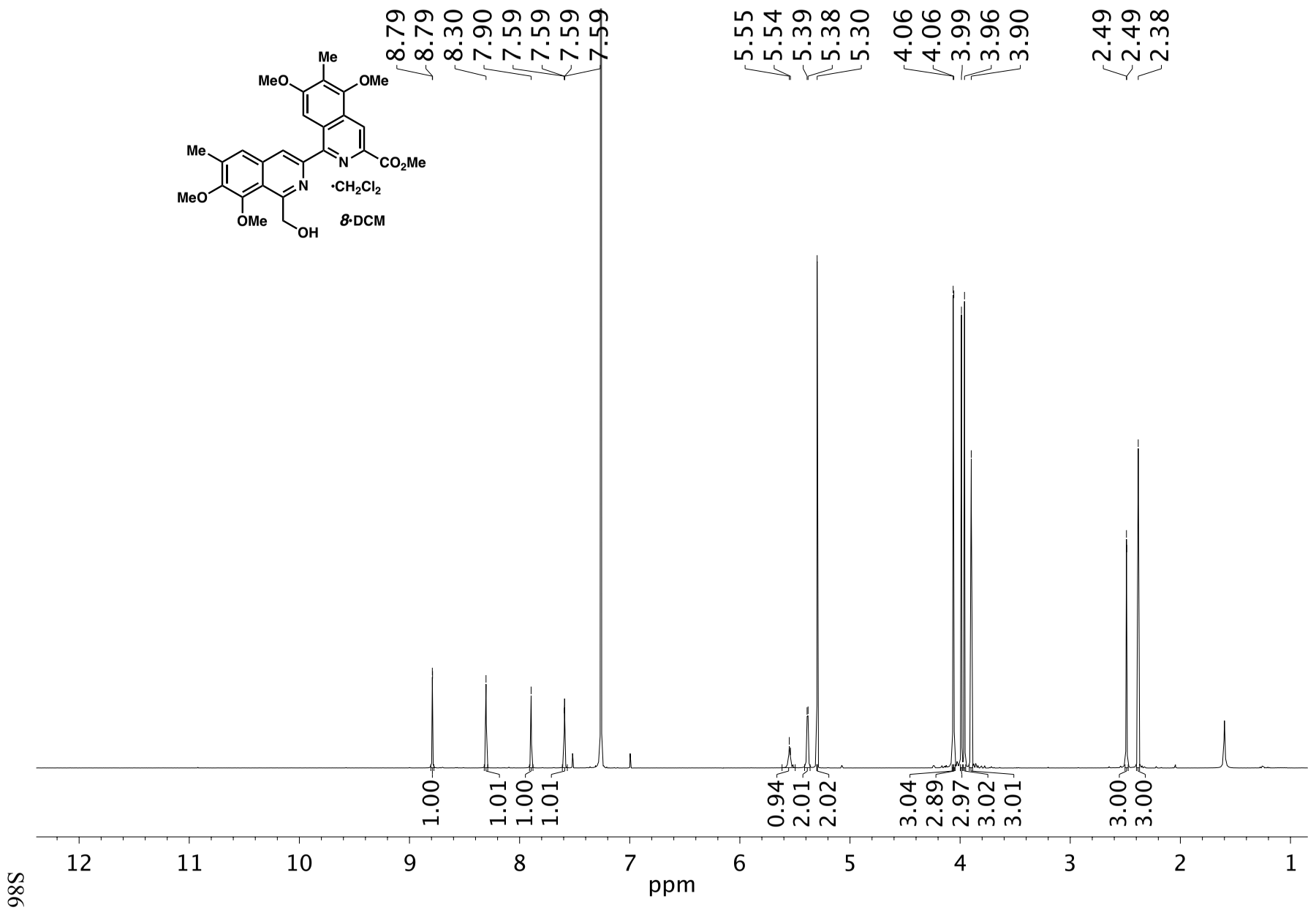
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S10**.



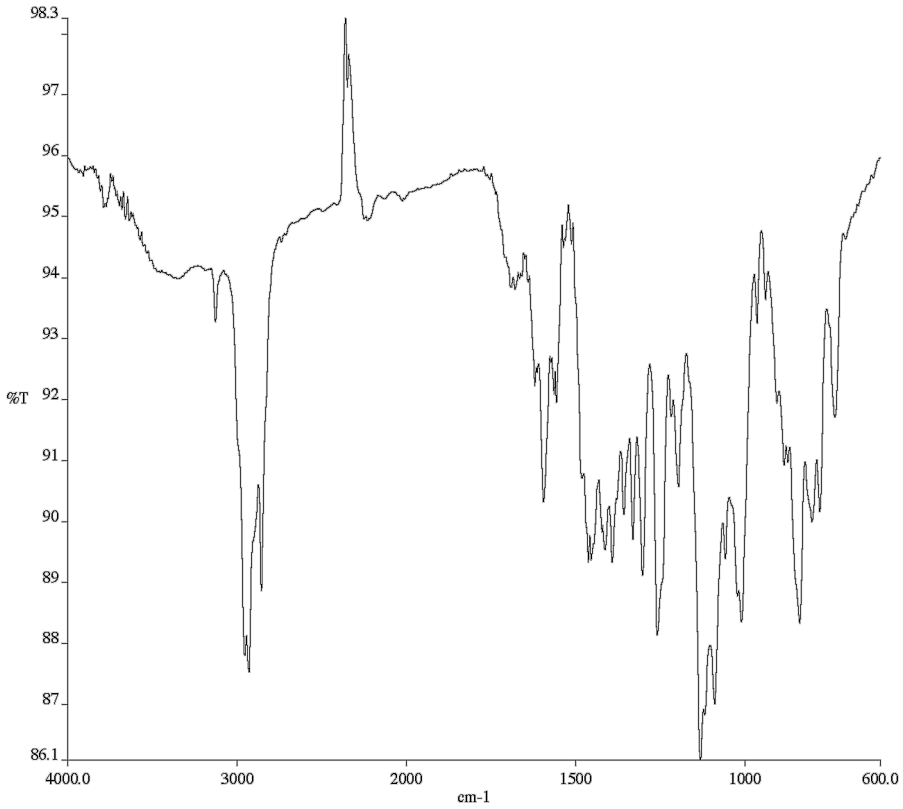
Infrared spectrum (Thin Film, NaCl) of compound **S9** and **S10**.



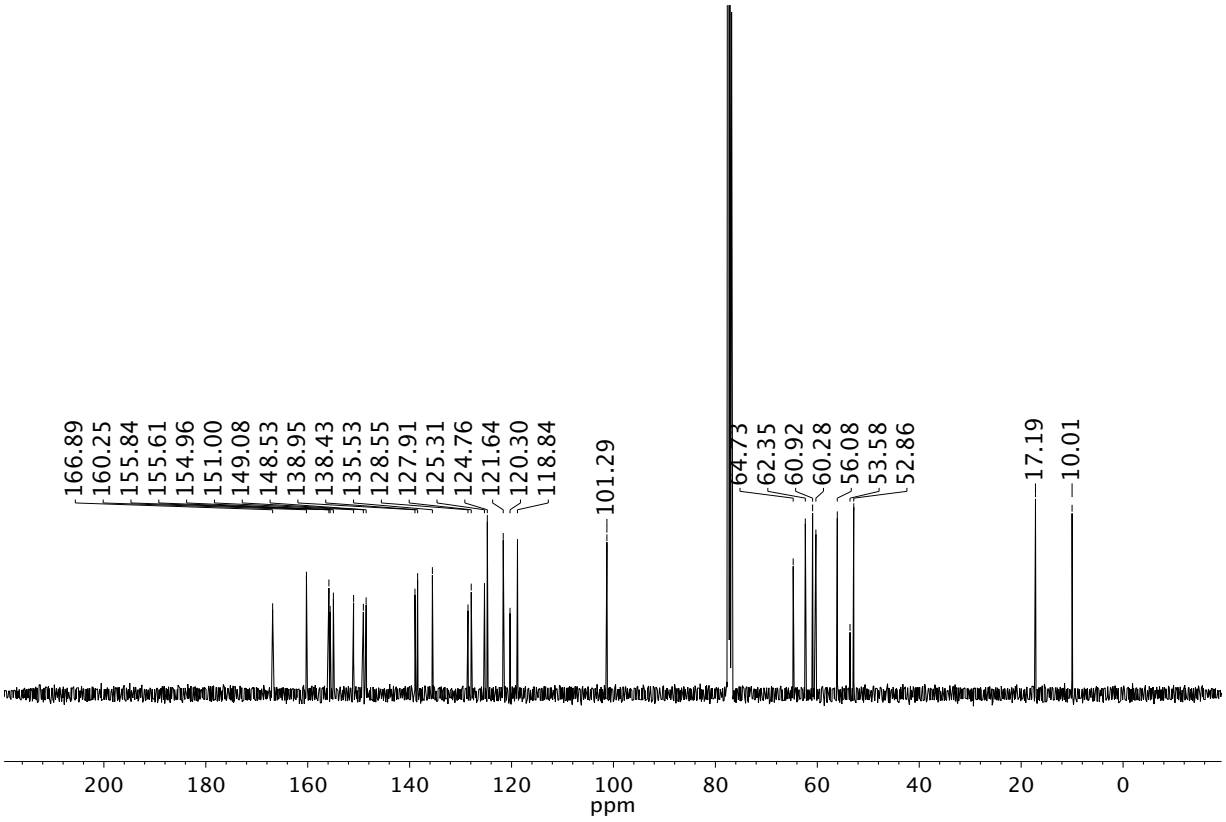
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S9** and **S10**.



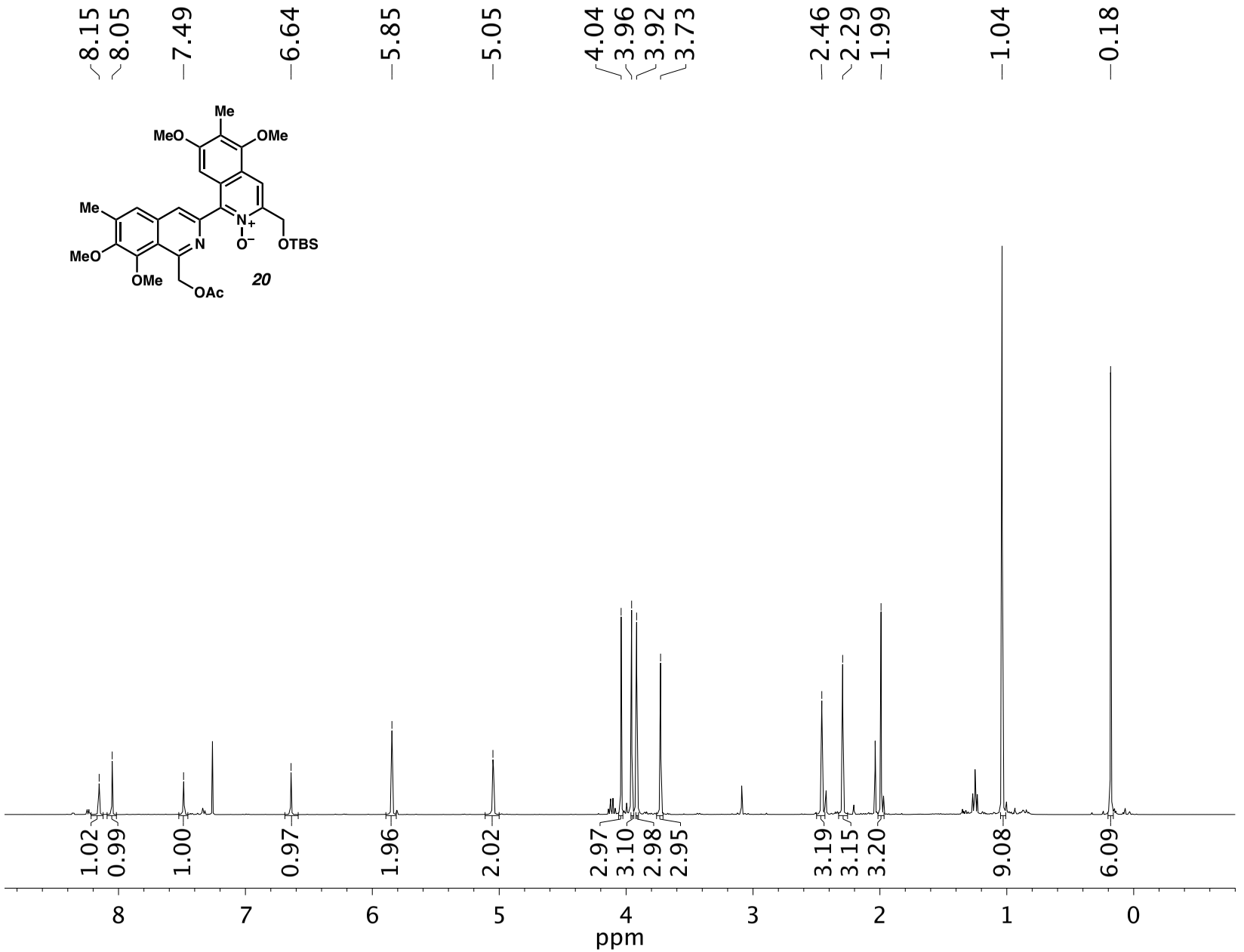
^{1}H NMR (400 MHz, $CDCl_3$) of compound **8•DCM**.



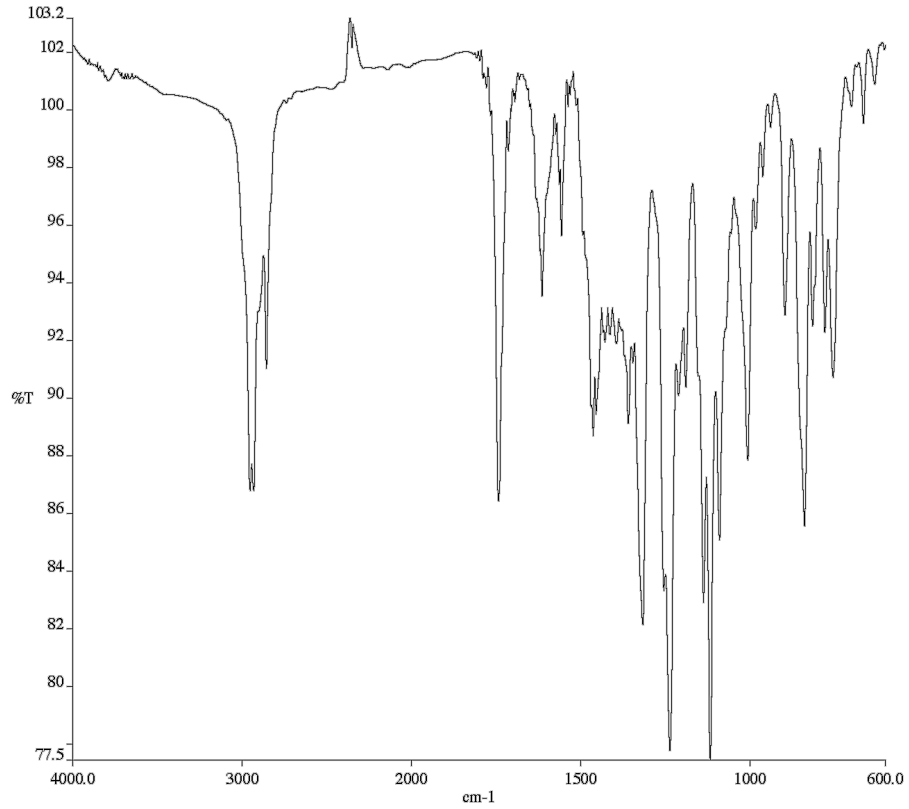
Infrared spectrum (Thin Film, NaCl) of compound **8•DCM**.



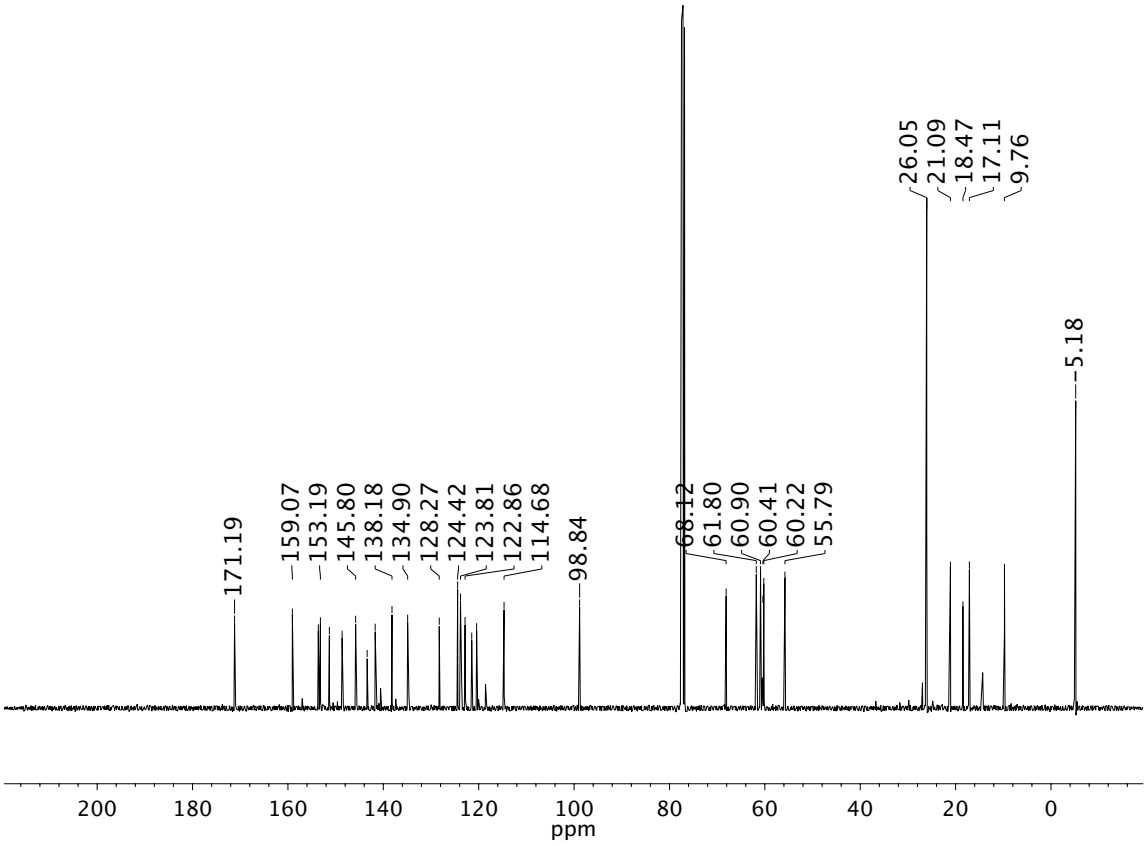
^{13}C NMR (101 MHz, $CDCl_3$) of compound **8•DCM**.



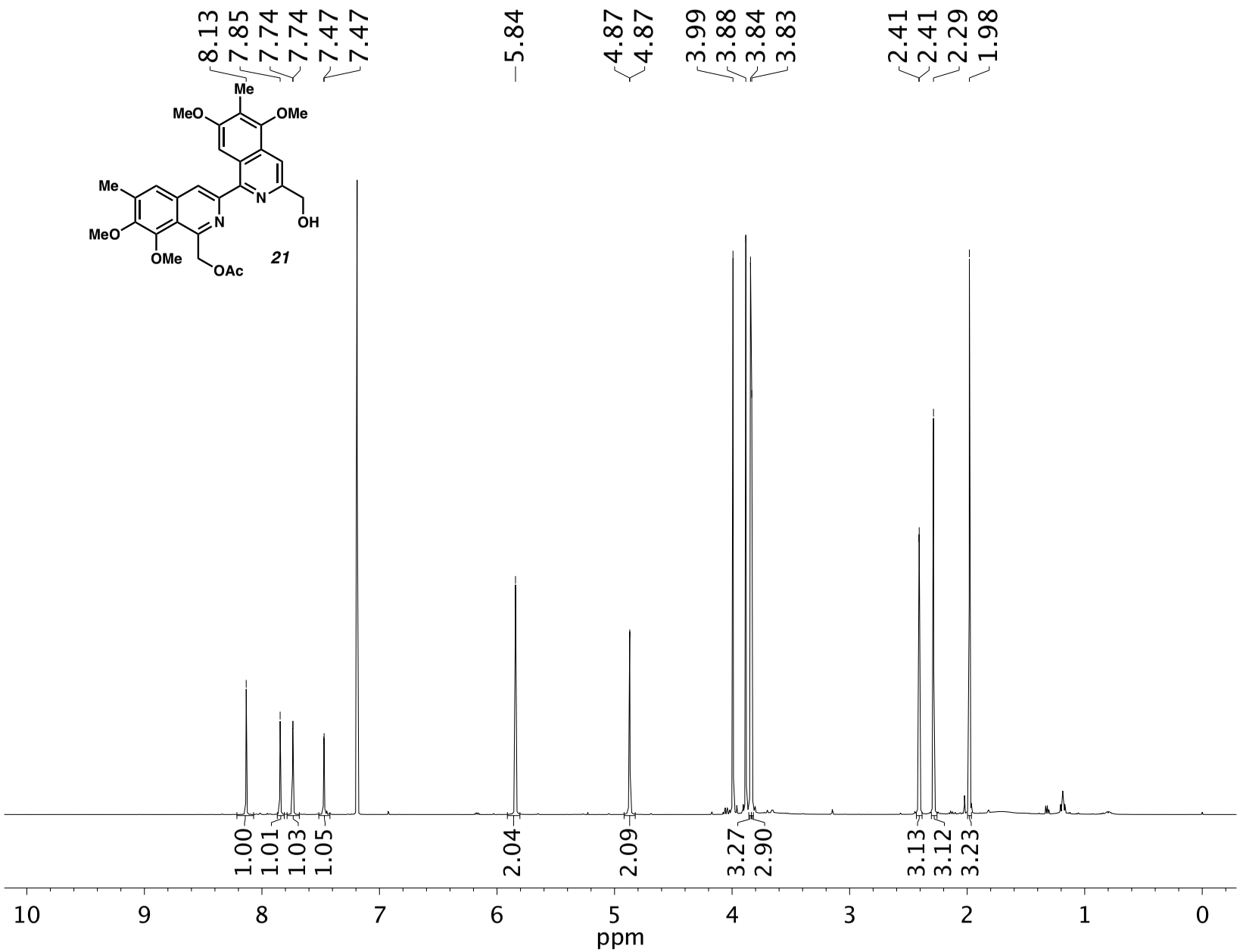
^{1}H NMR (400 MHz, $CDCl_3$) of compound **20.**



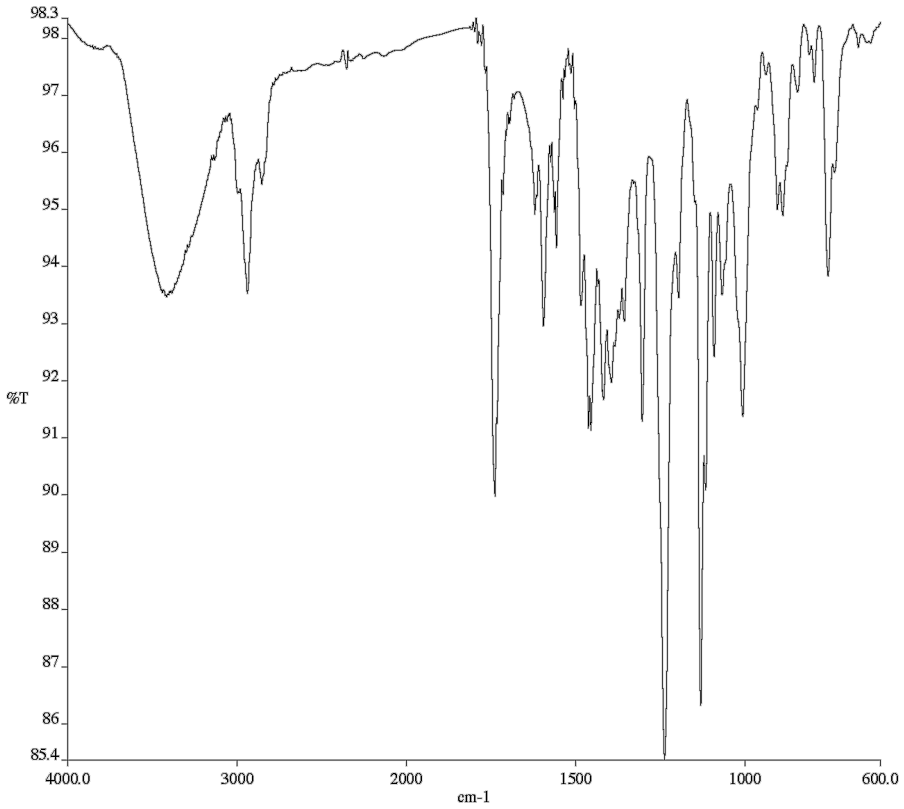
Infrared spectrum (Thin Film, NaCl) of compound **20**.



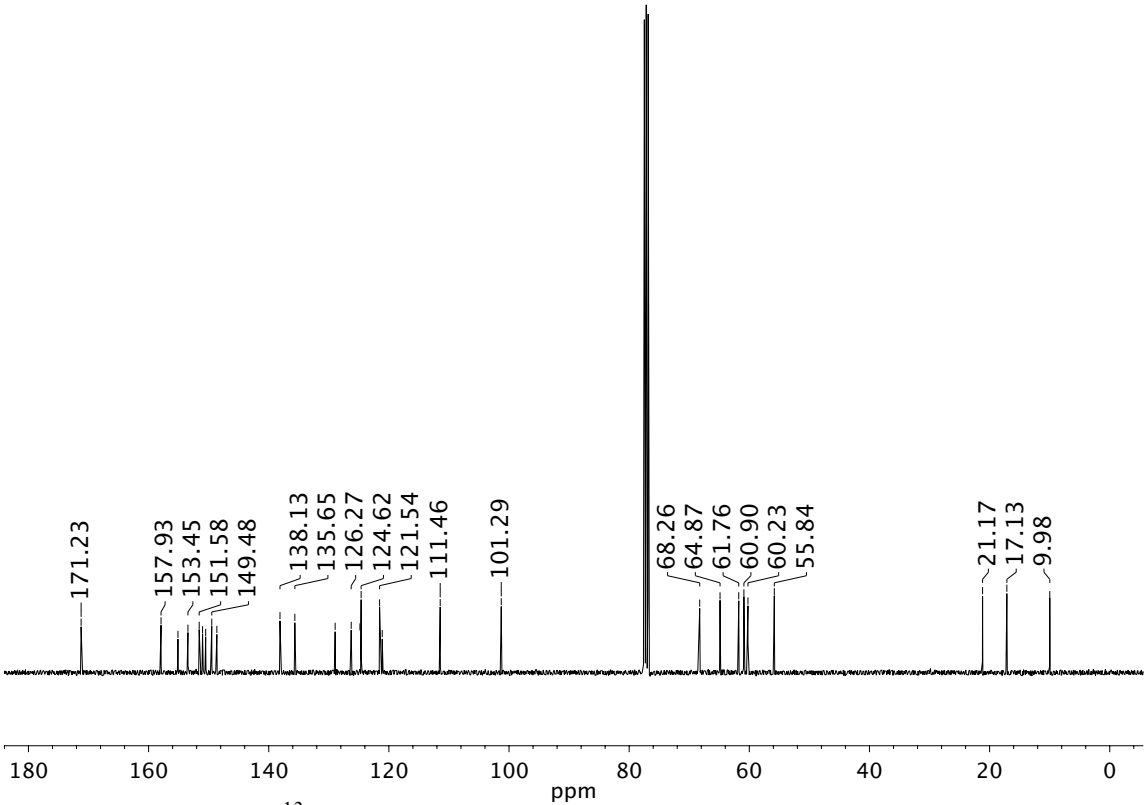
^{13}C NMR (101 MHz, $CDCl_3$) of compound **20**.



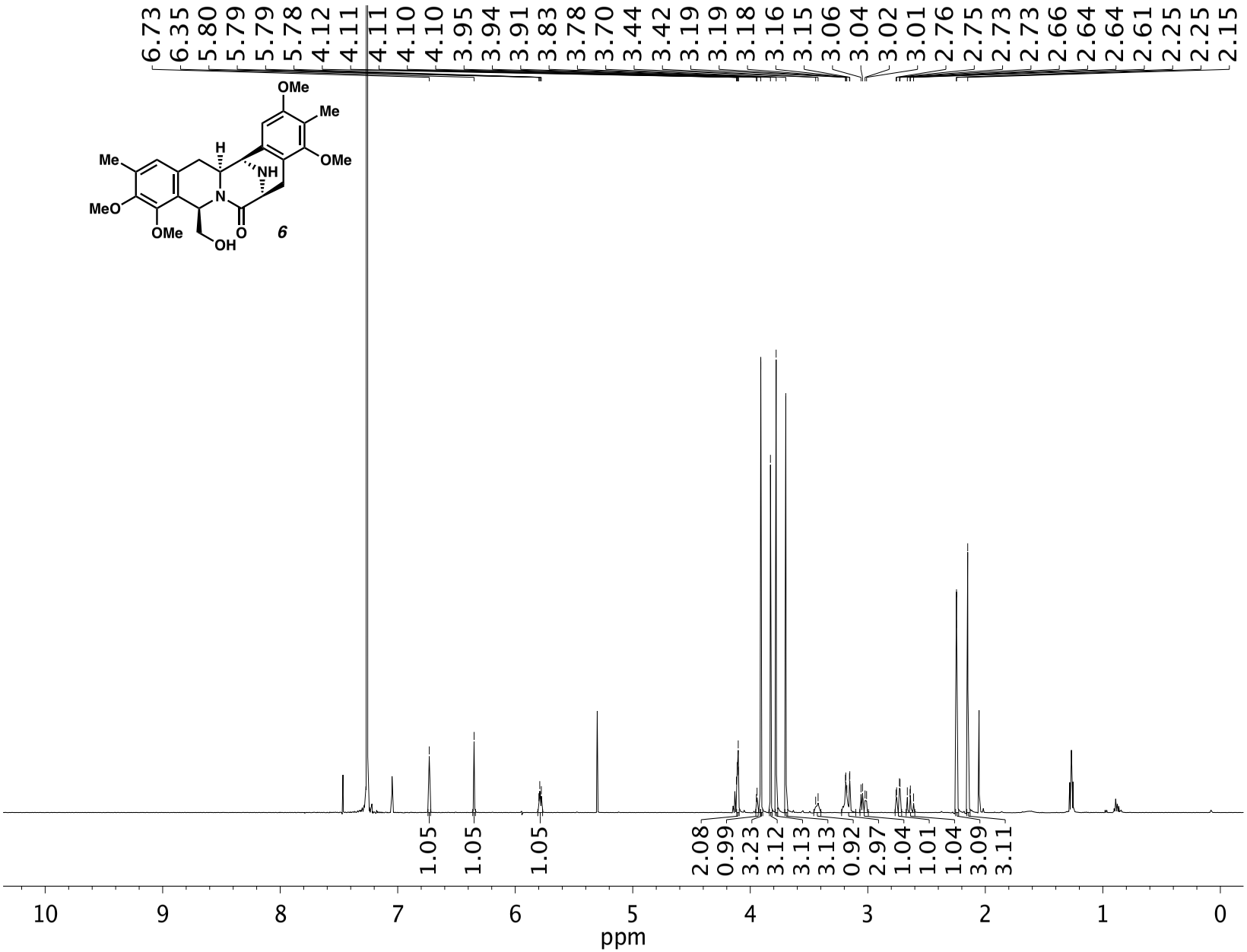
^{1}H NMR (400 MHz, $CDCl_3$) of compound **21**.



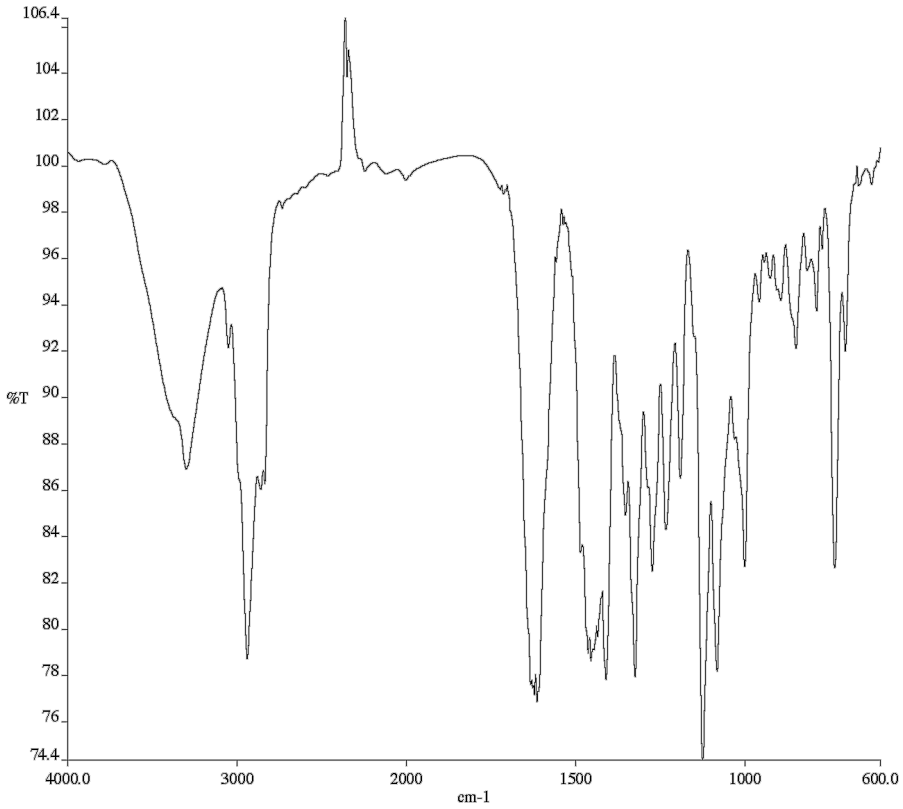
Infrared spectrum (Thin Film, NaCl) of compound **21**.



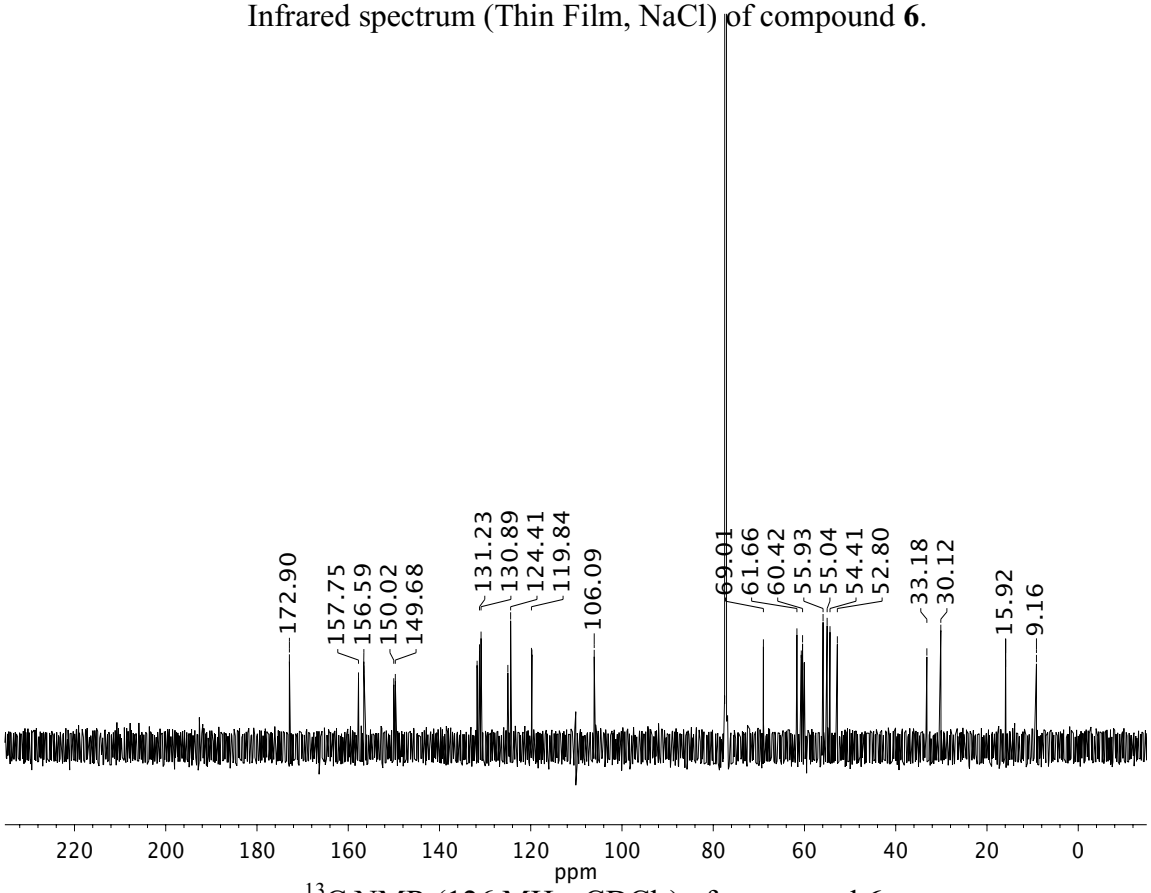
^{13}C NMR (101 MHz, $CDCl_3$) of compound **21**.



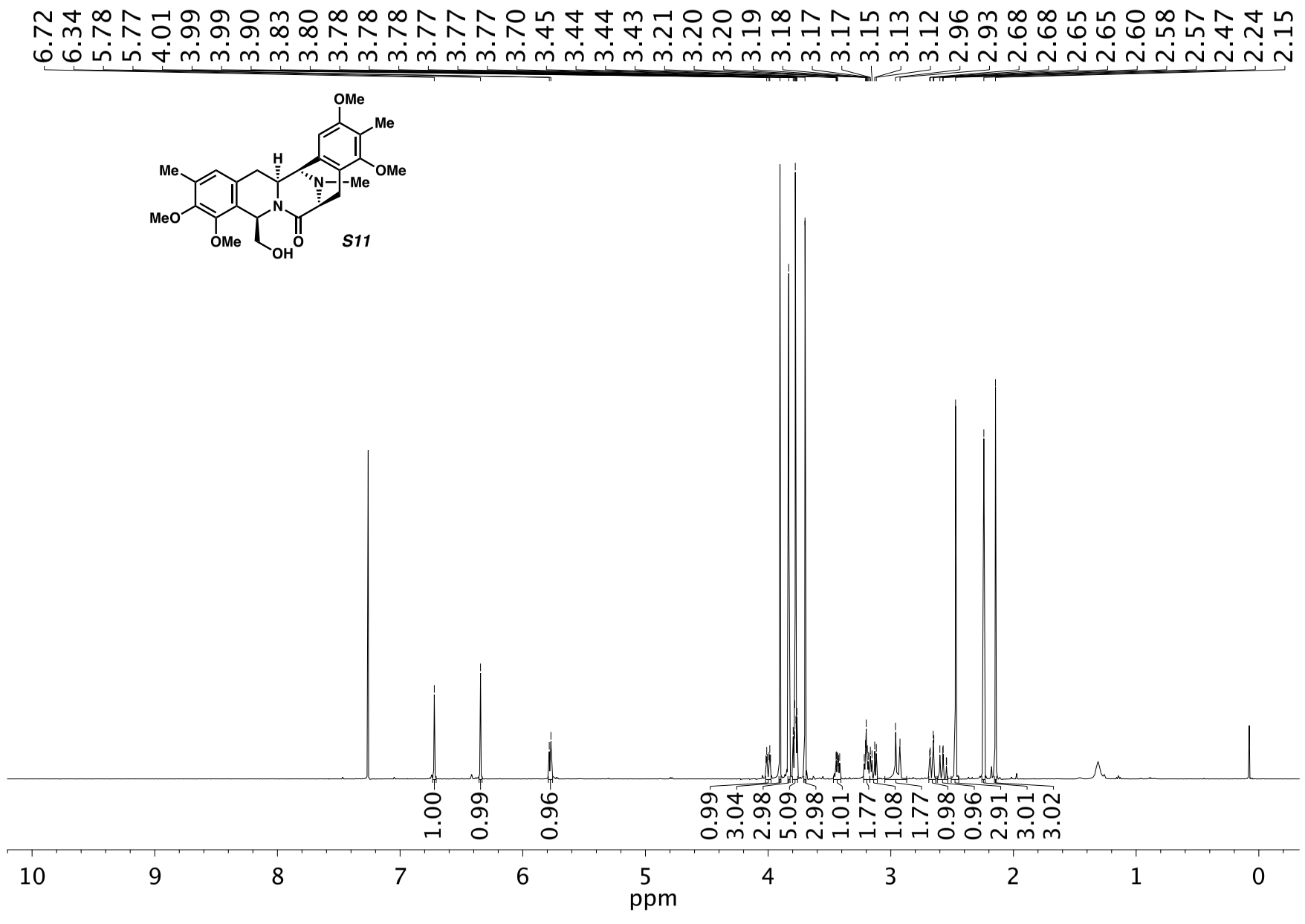
^{1}H NMR (500 MHz, $CDCl_3$) of compound **6**.



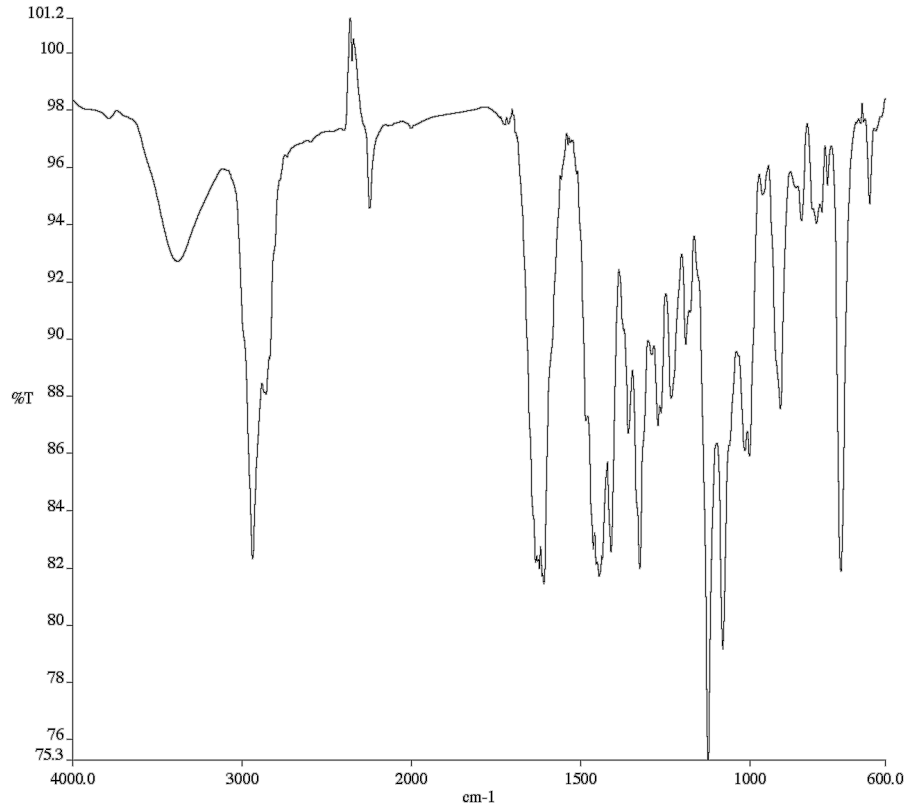
Infrared spectrum (Thin Film, NaCl) of compound **6**.



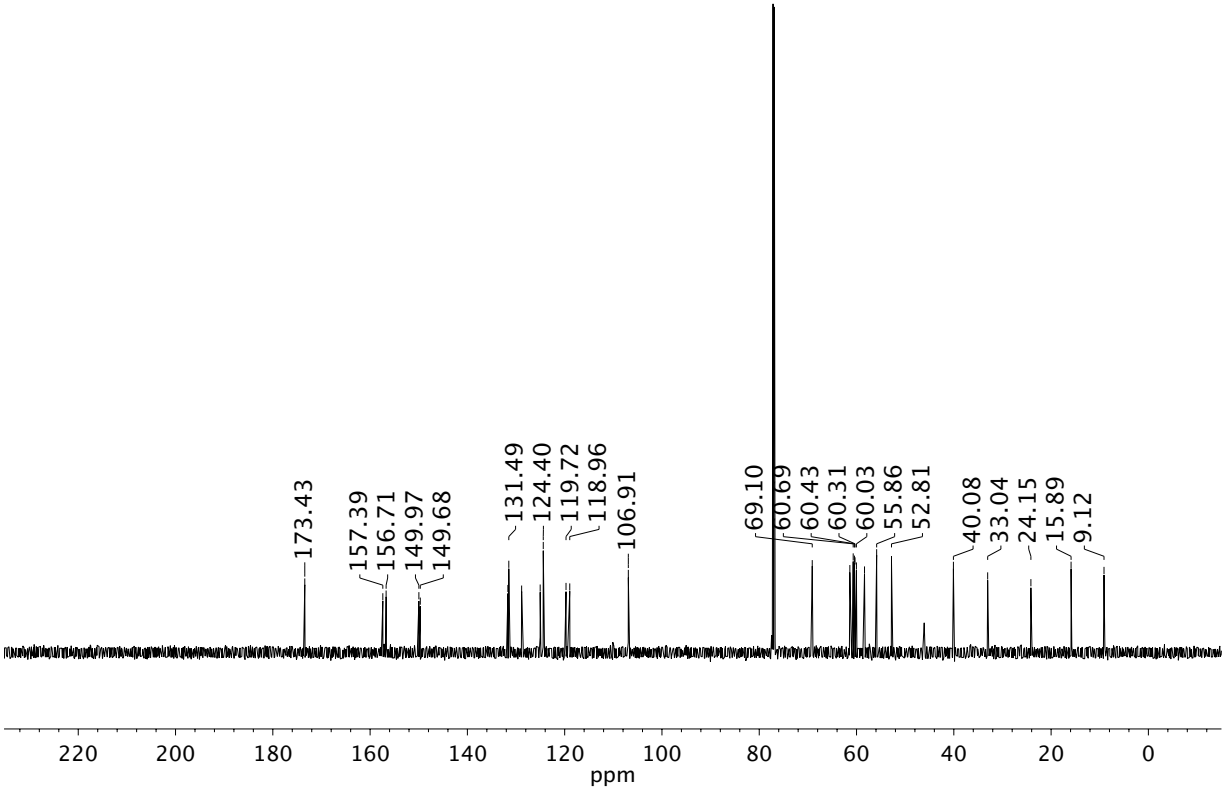
^{13}C NMR (126 MHz, $CDCl_3$) of compound **6**.



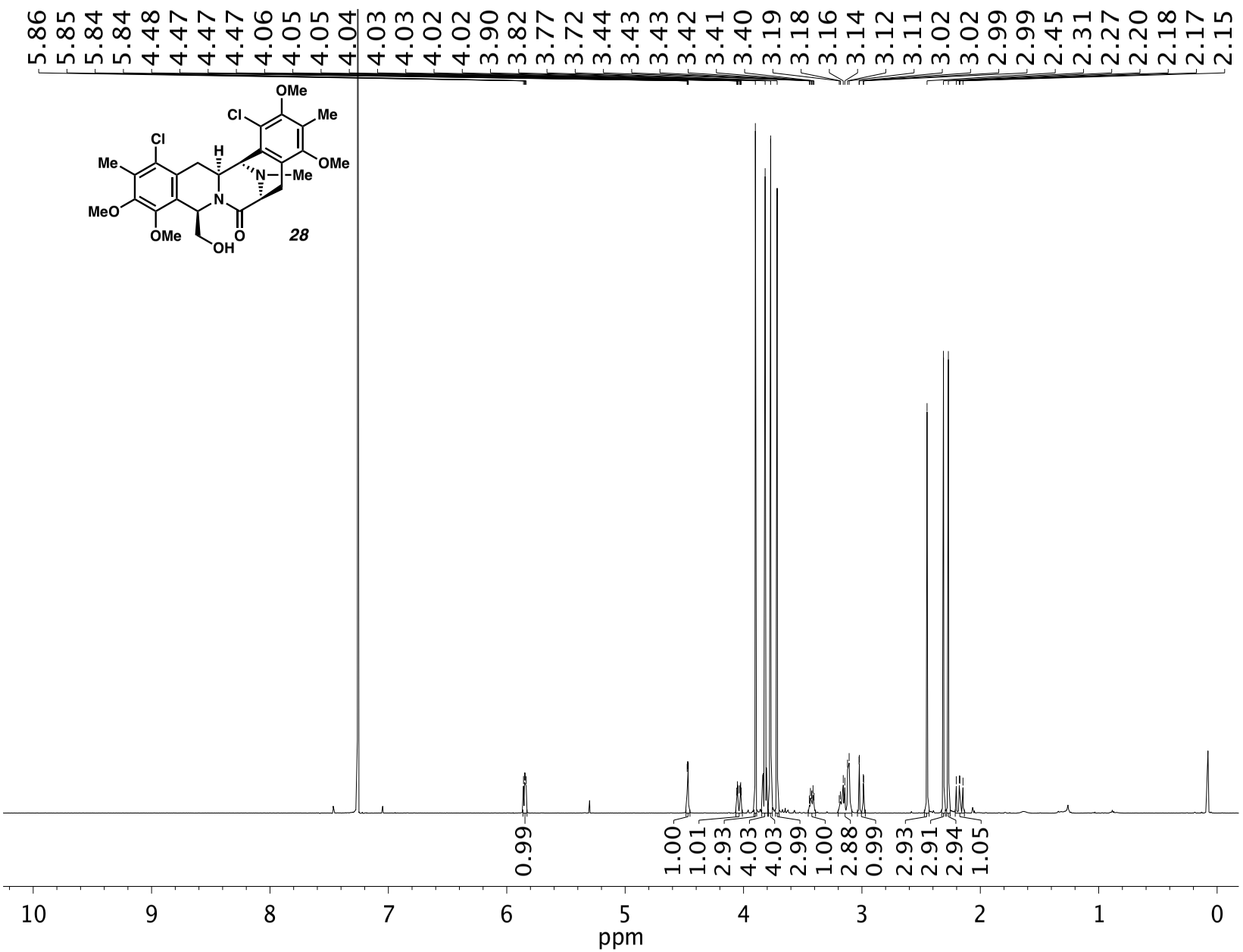
^{1}H NMR (500 MHz, $CDCl_3$) of compound **S11**.



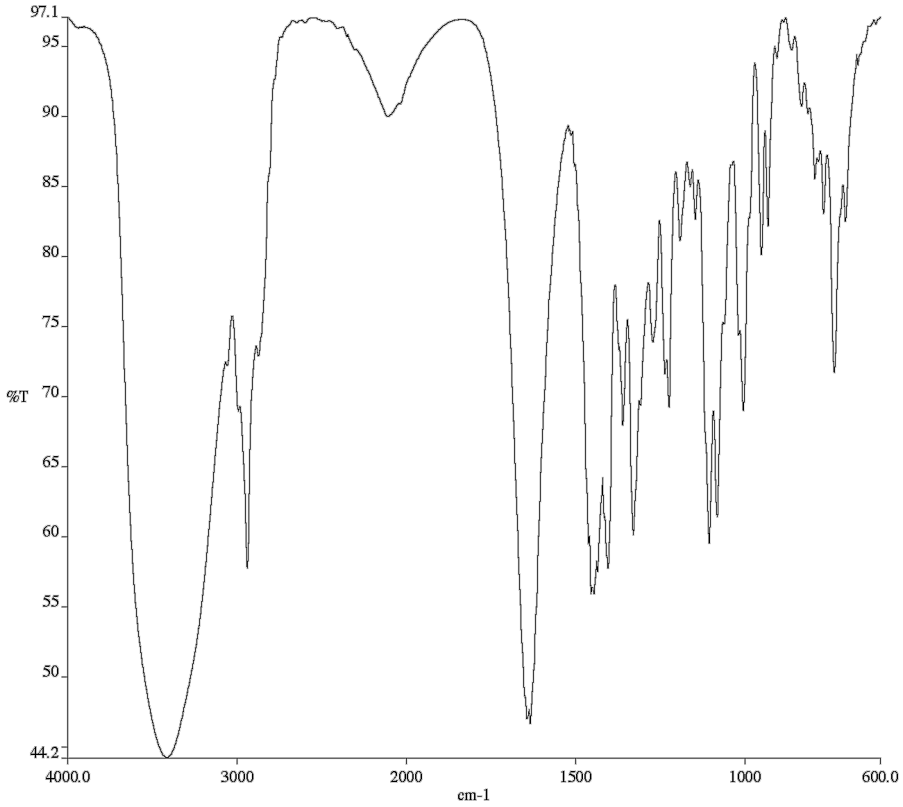
Infrared spectrum (Thin Film, NaCl) of compound **S11**.



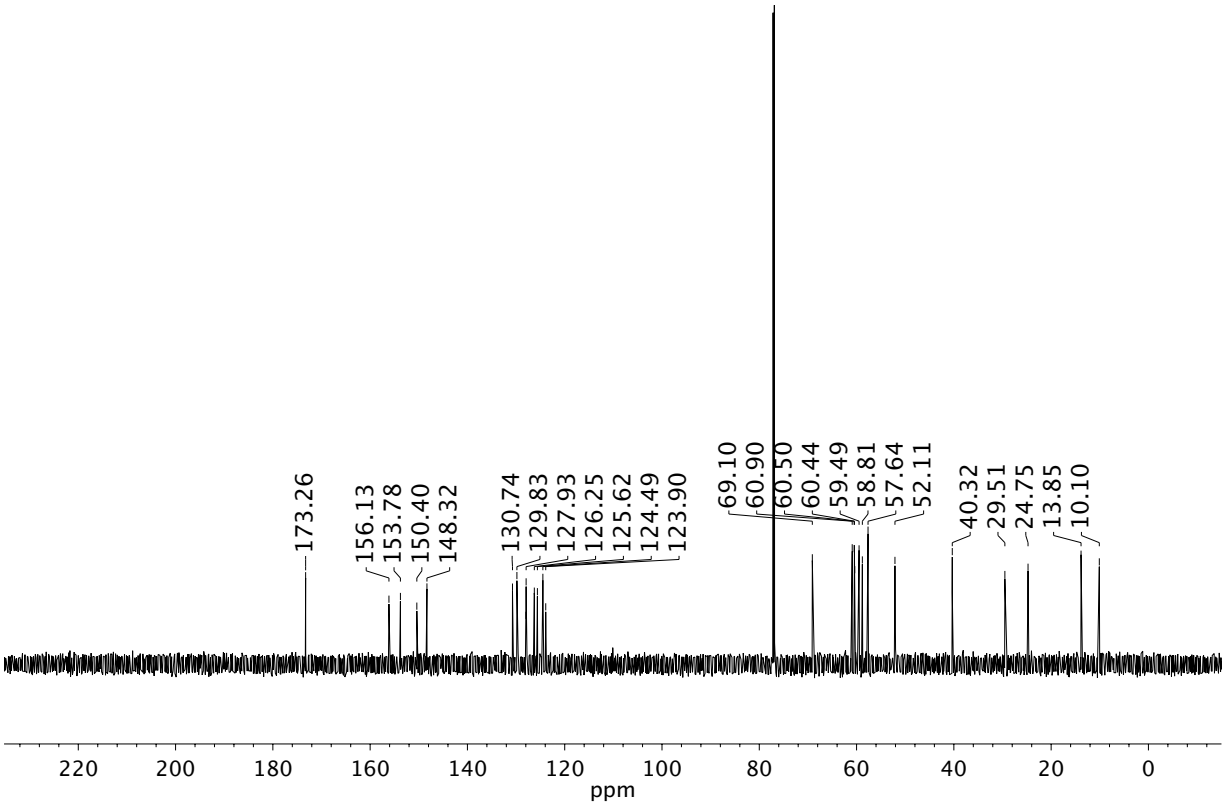
^{13}C NMR (126 MHz, $CDCl_3$) of compound **S11**.



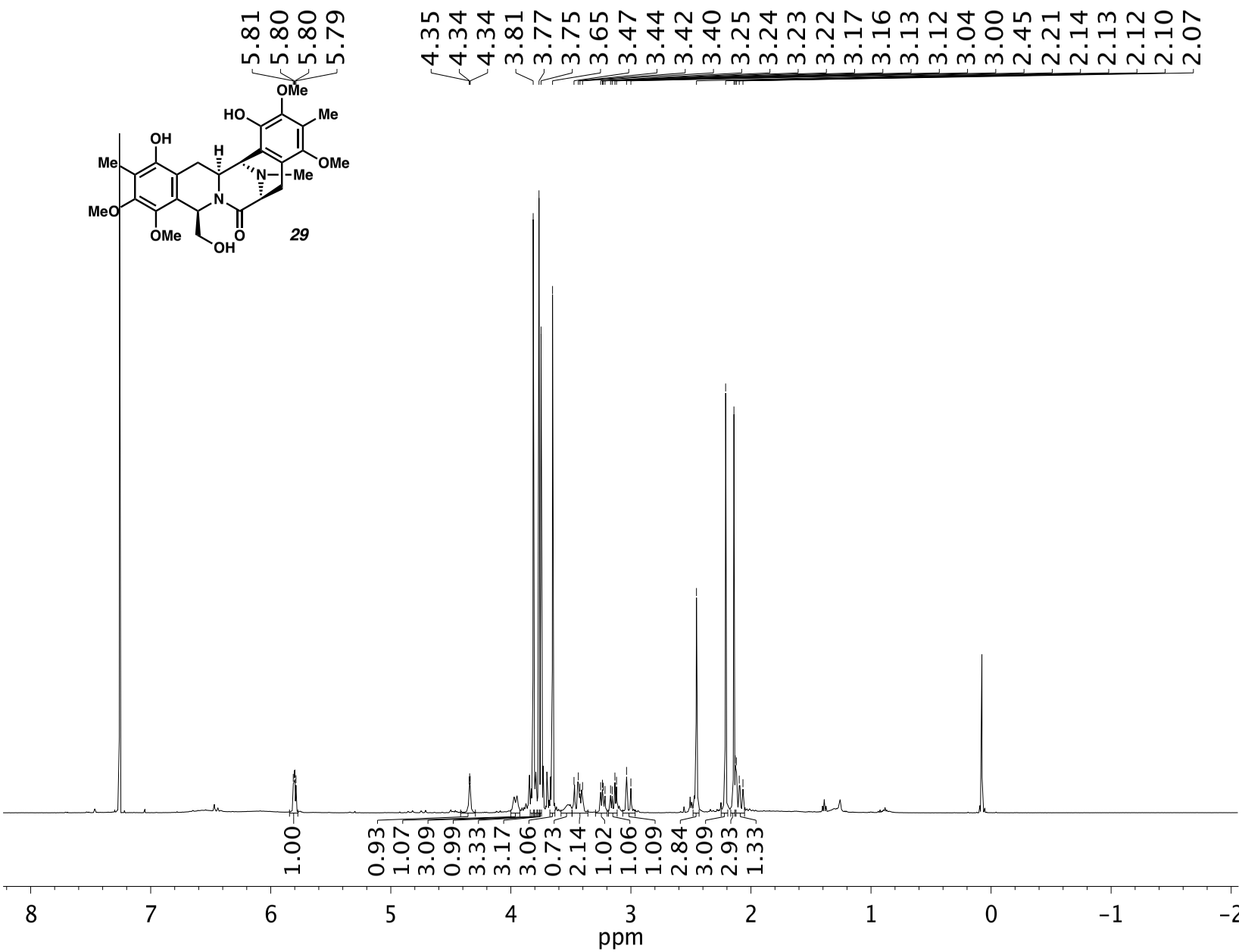
^{1}H NMR (500 MHz, $CDCl_3$) of compound **28**.



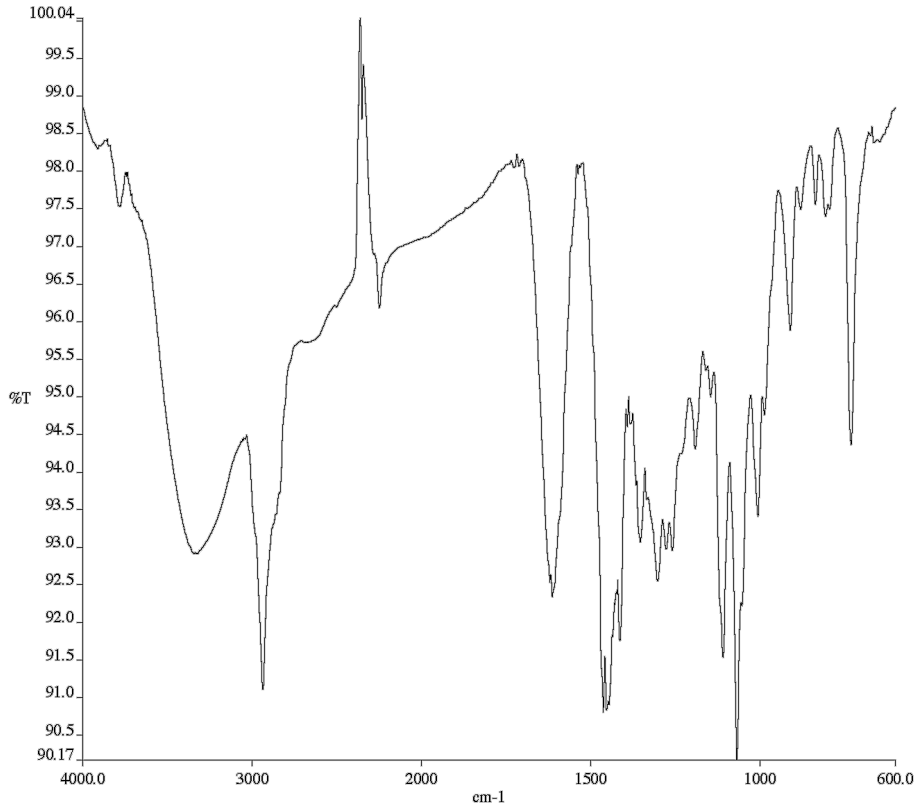
Infrared spectrum (Thin Film, NaCl) of compound **28**.



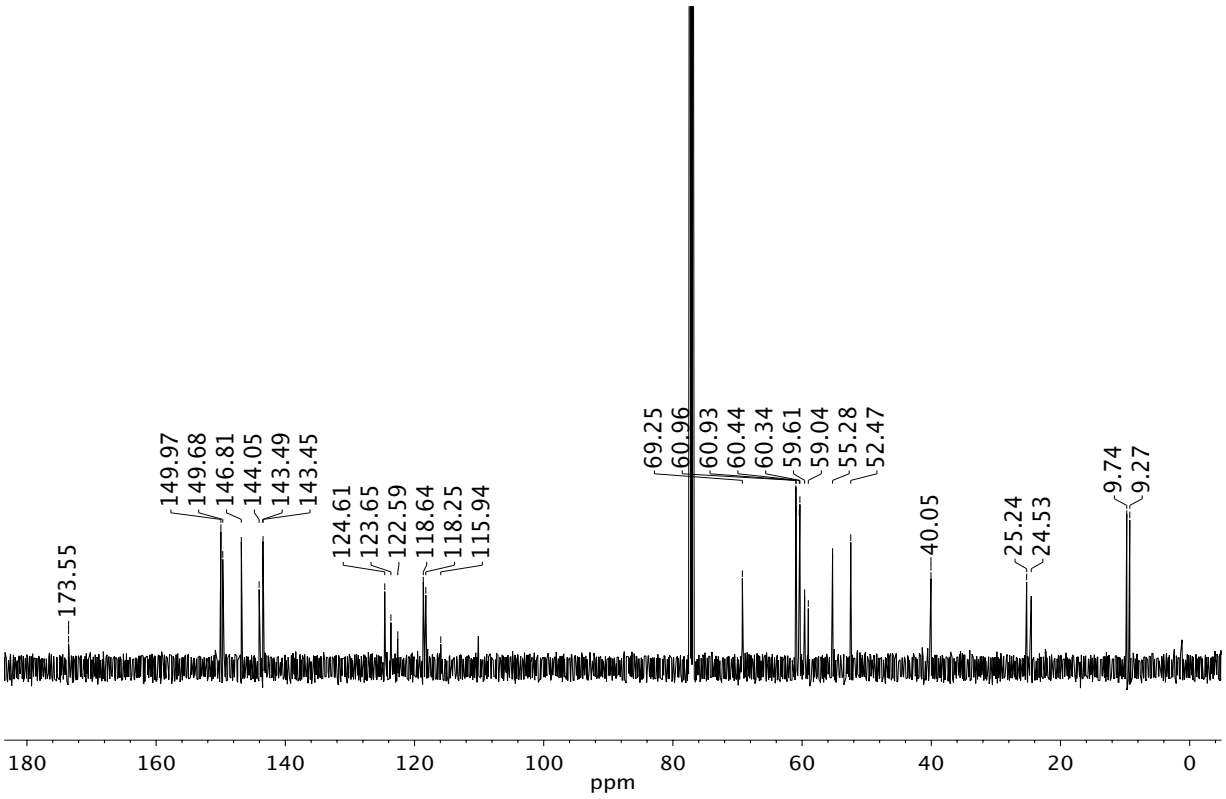
^{13}C NMR (126 MHz, $CDCl_3$) of compound **28**.



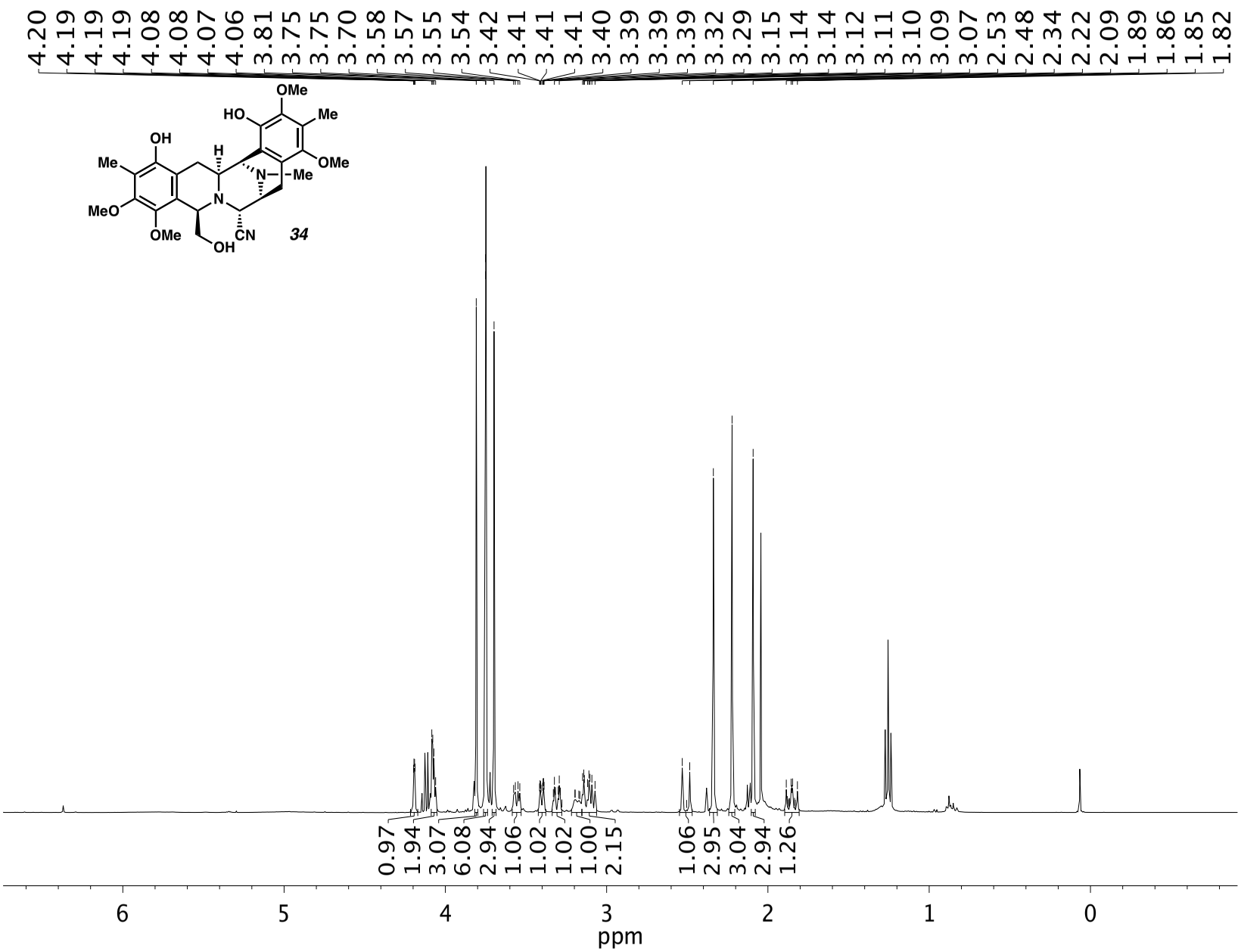
^{1}H NMR (500 MHz, $CDCl_3$) of compound **29**.



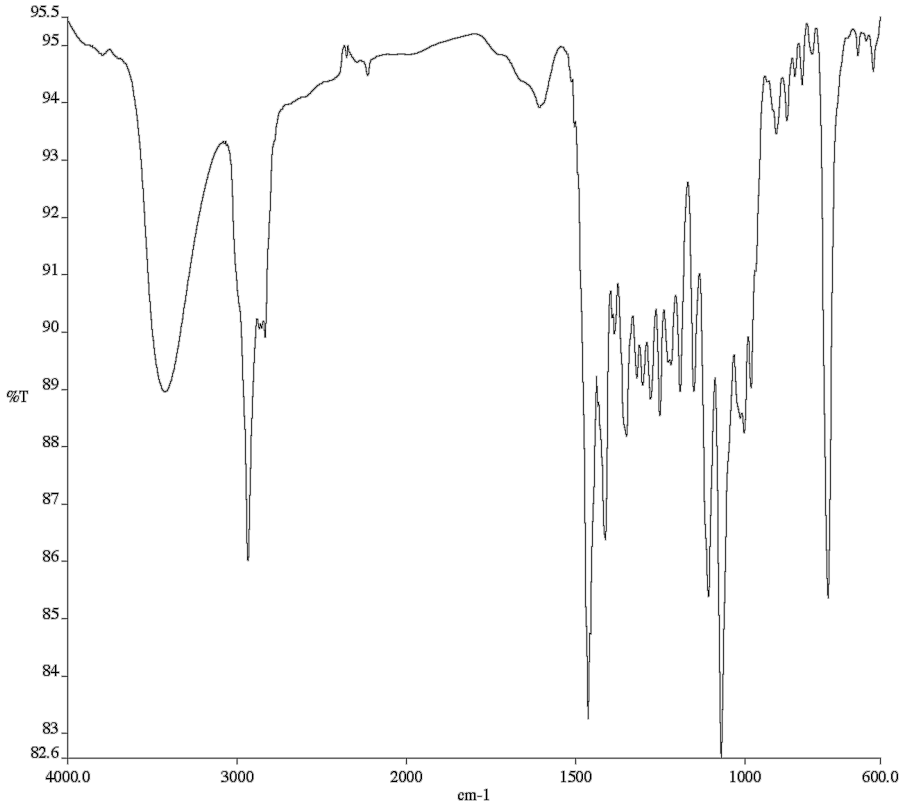
Infrared spectrum (Thin Film, NaCl) of compound **29**.



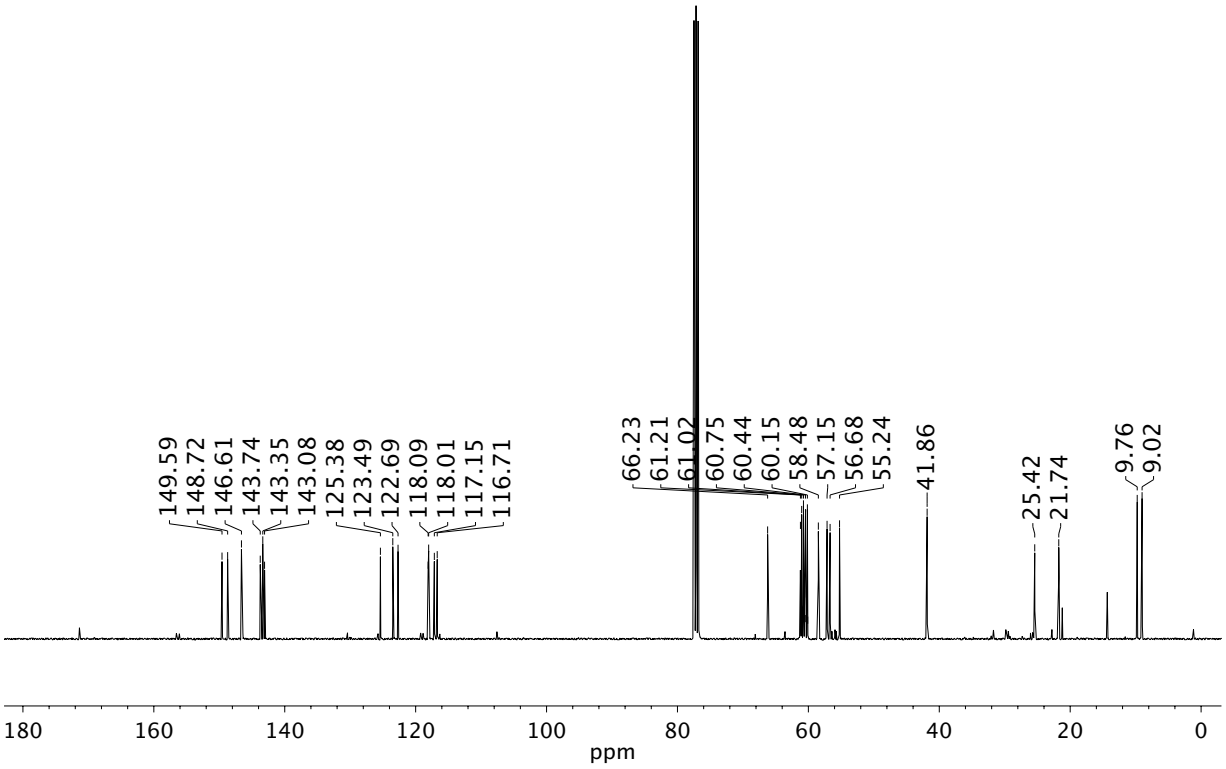
^{13}C NMR (126 MHz, $CDCl_3$) of compound **29**.



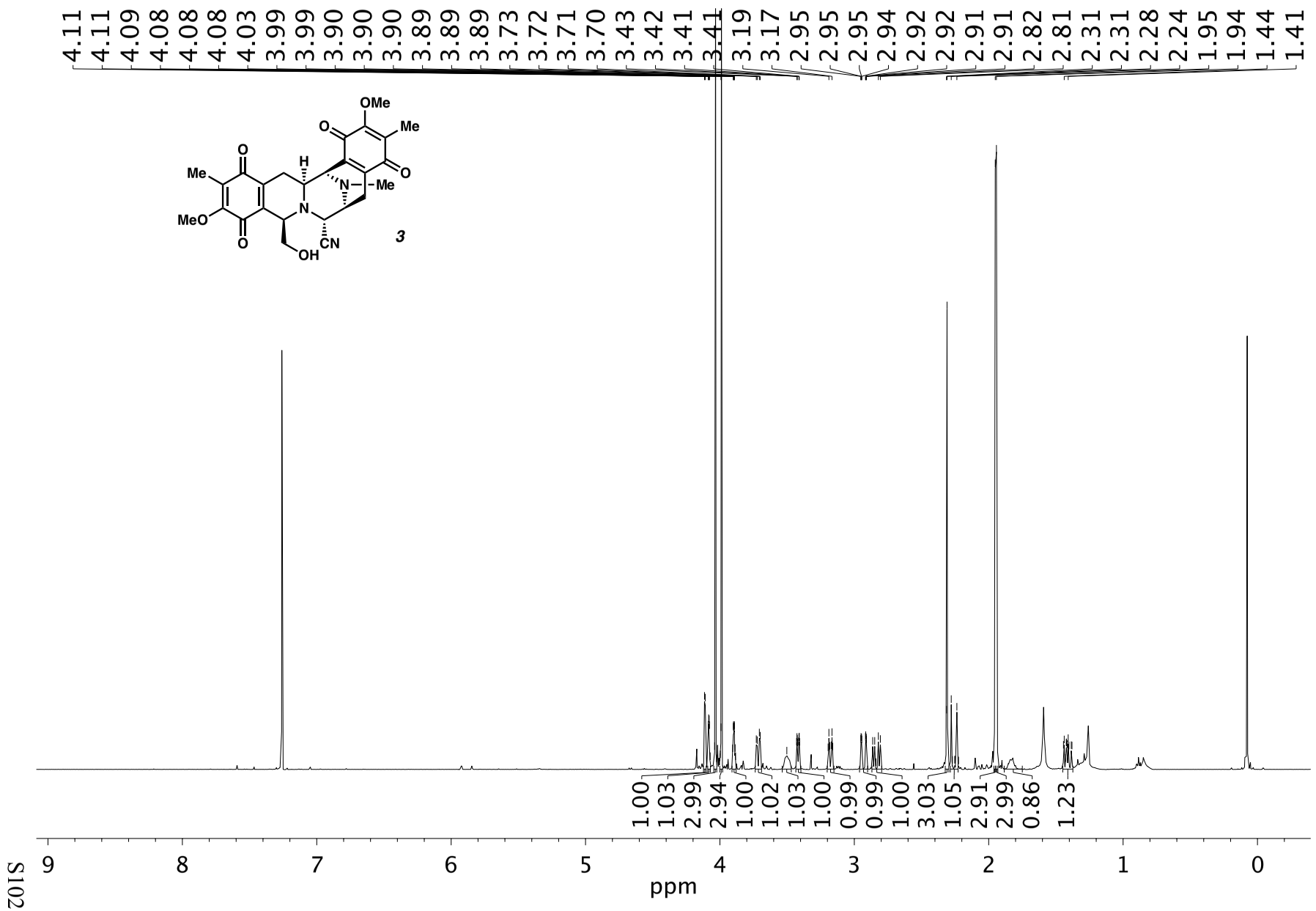
^{1}H NMR (400 MHz, $CDCl_3$) of compound **34**.



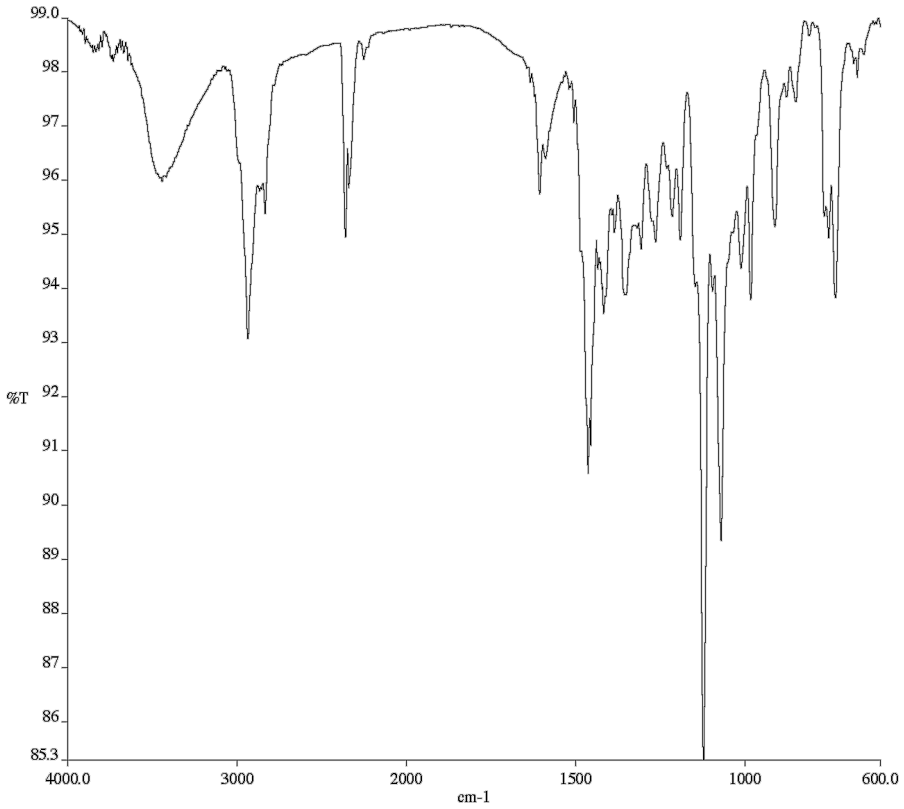
Infrared spectrum (Thin Film, NaCl) of compound **34**.



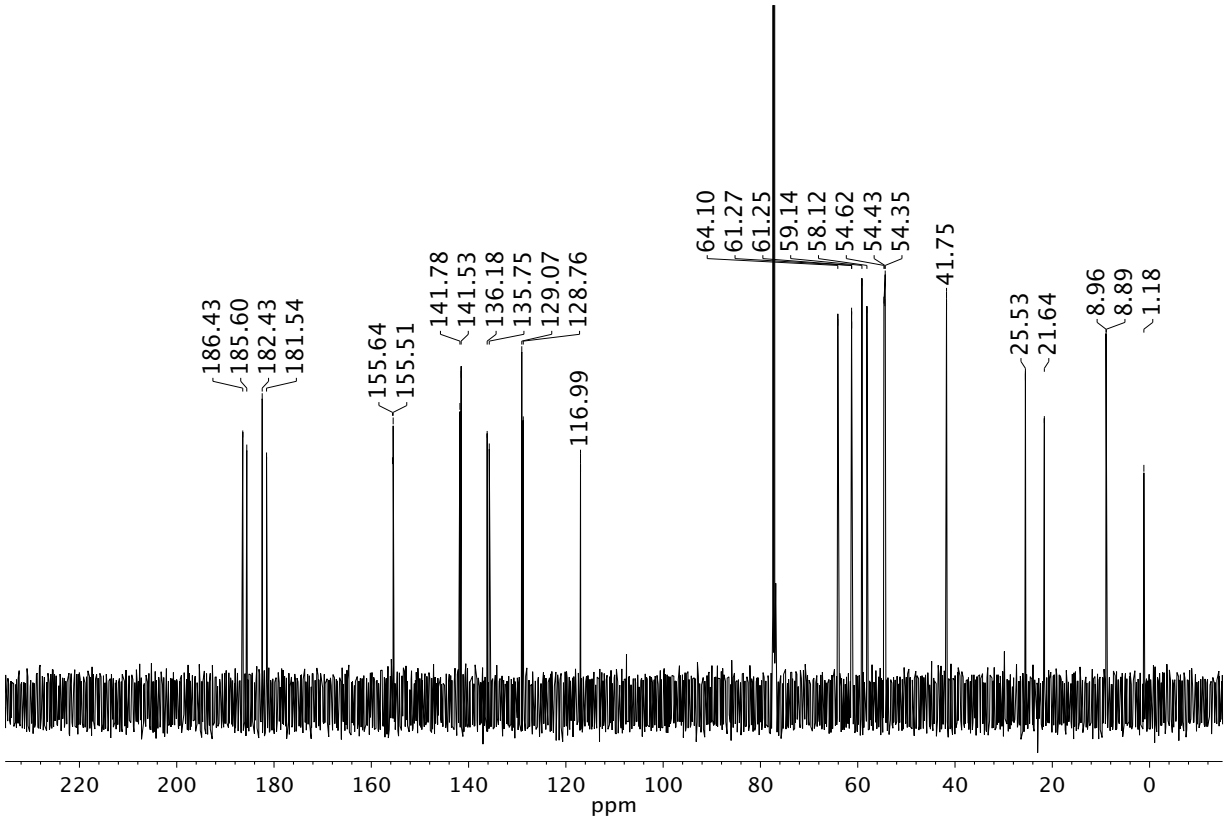
^{13}C NMR (101 MHz, $CDCl_3$) of compound **34**.



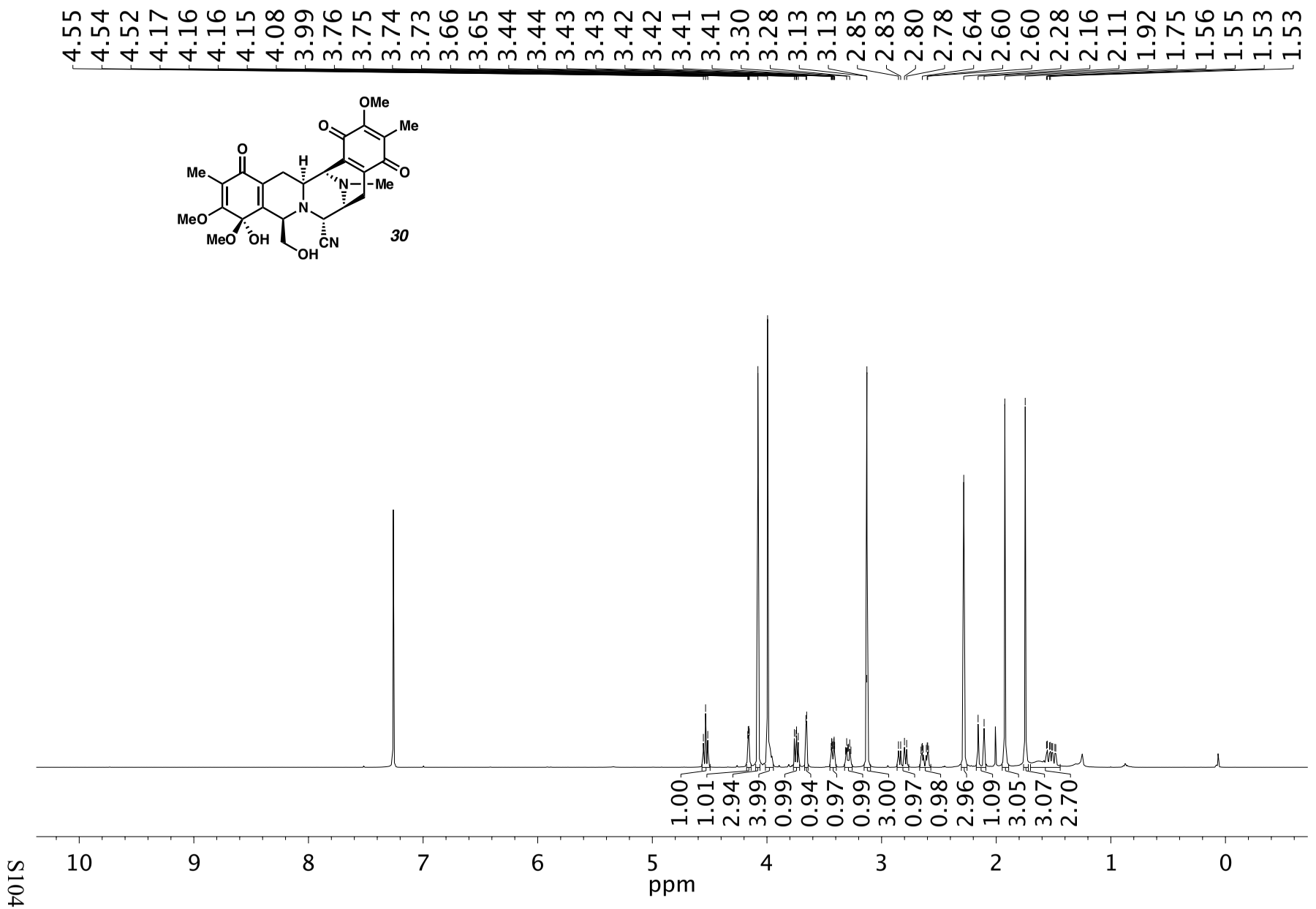
^{1}H NMR (400 MHz, $CDCl_3$) of compound **3**.



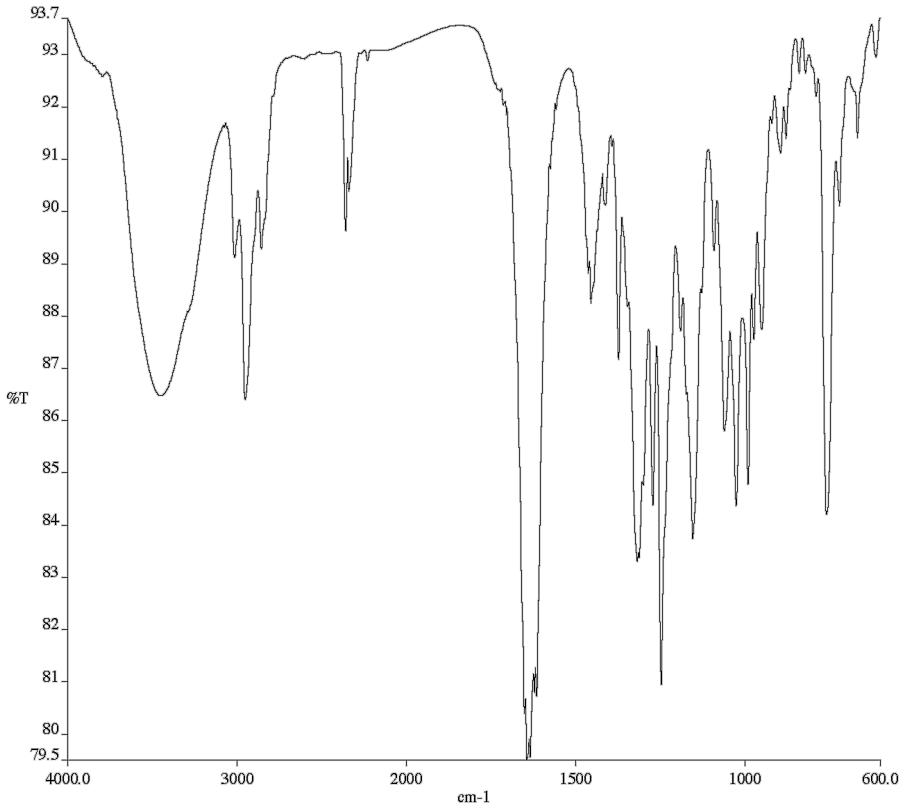
Infrared spectrum (Thin Film, NaCl) of compound **3**.



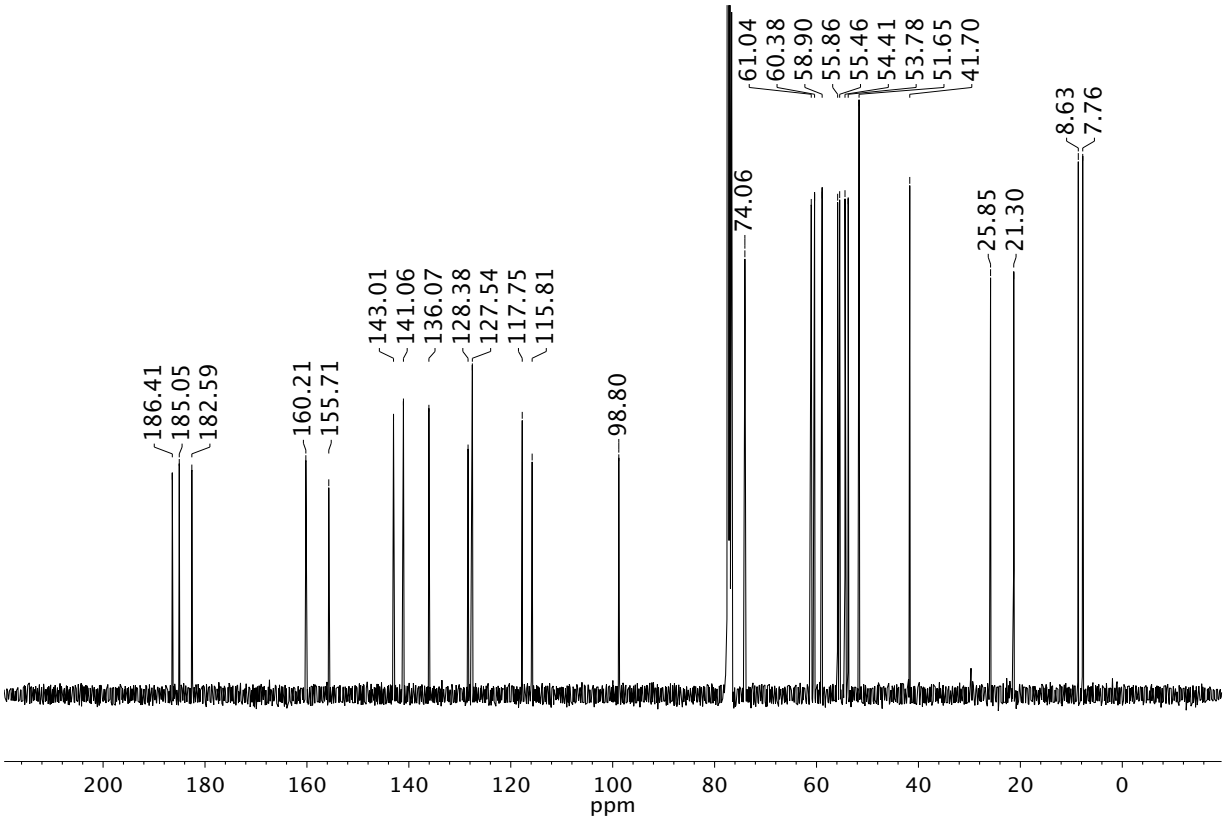
^{13}C NMR (101 MHz, $CDCl_3$) of compound **3**.



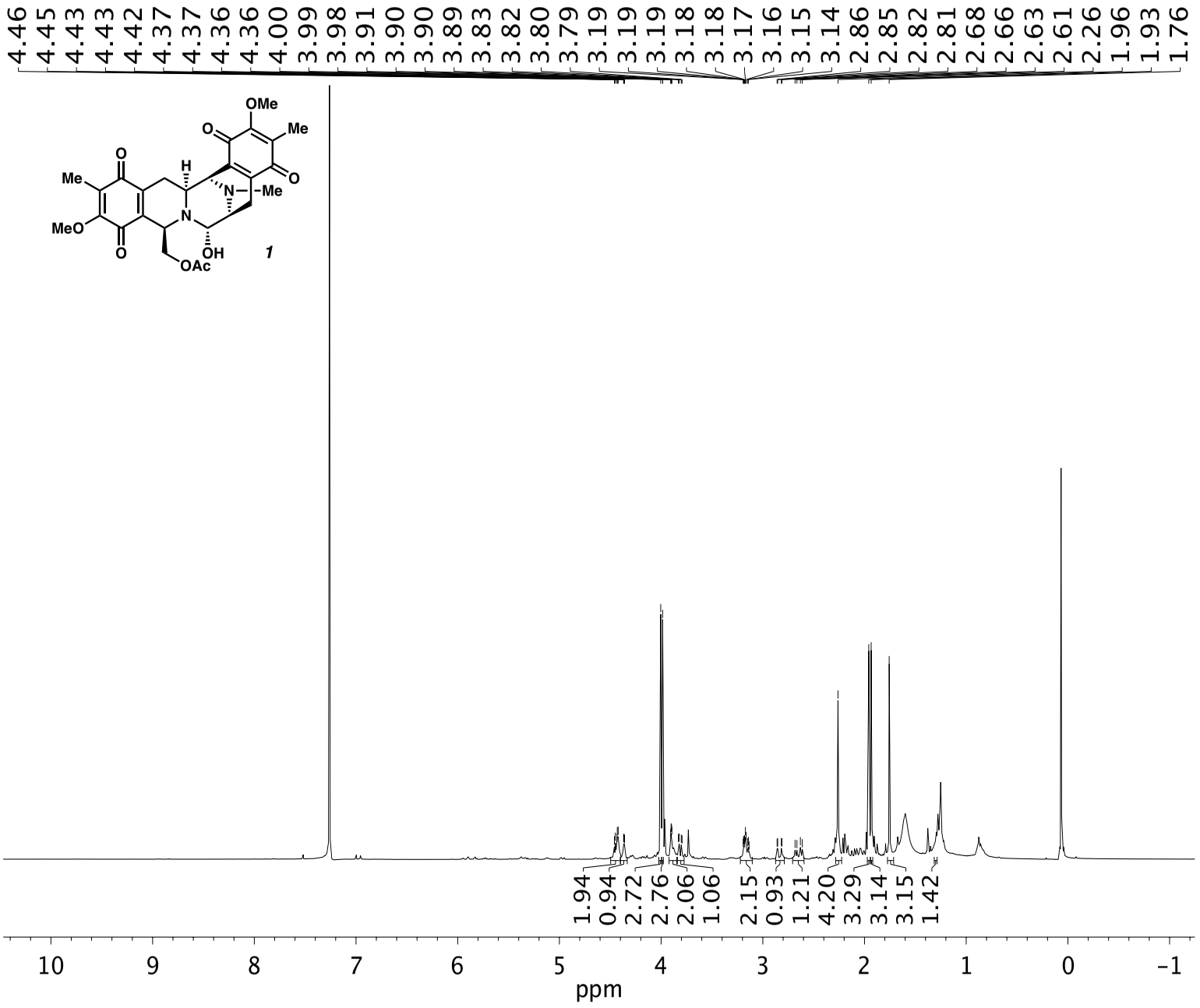
^{1}H NMR (400 MHz, $CDCl_3$) of compound **30**.



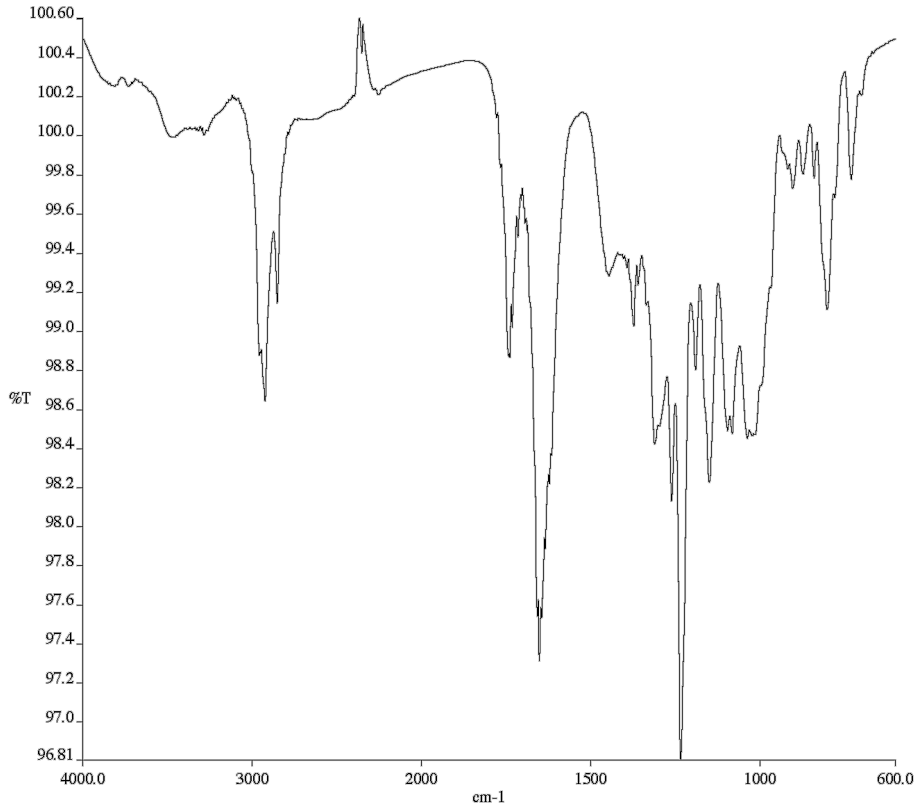
Infrared spectrum (Thin Film, NaCl) of compound **30**.



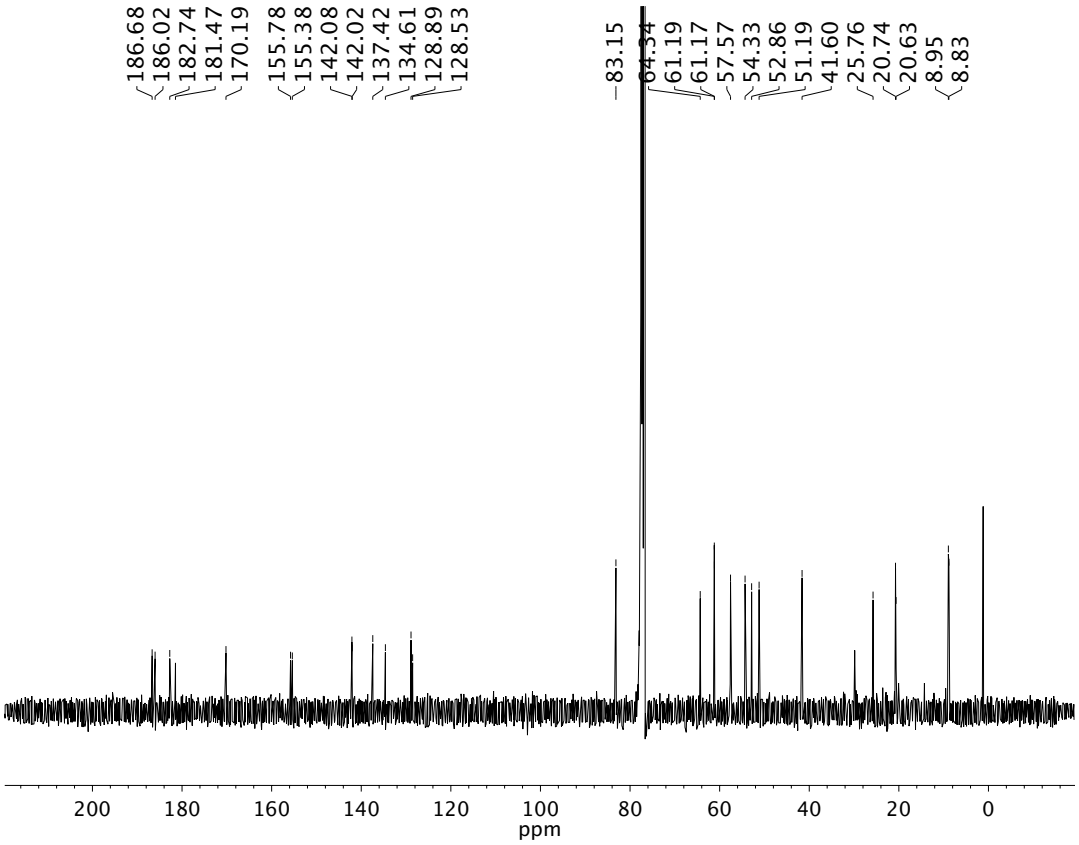
^{13}C NMR (101 MHz, $CDCl_3$) of compound **30**.



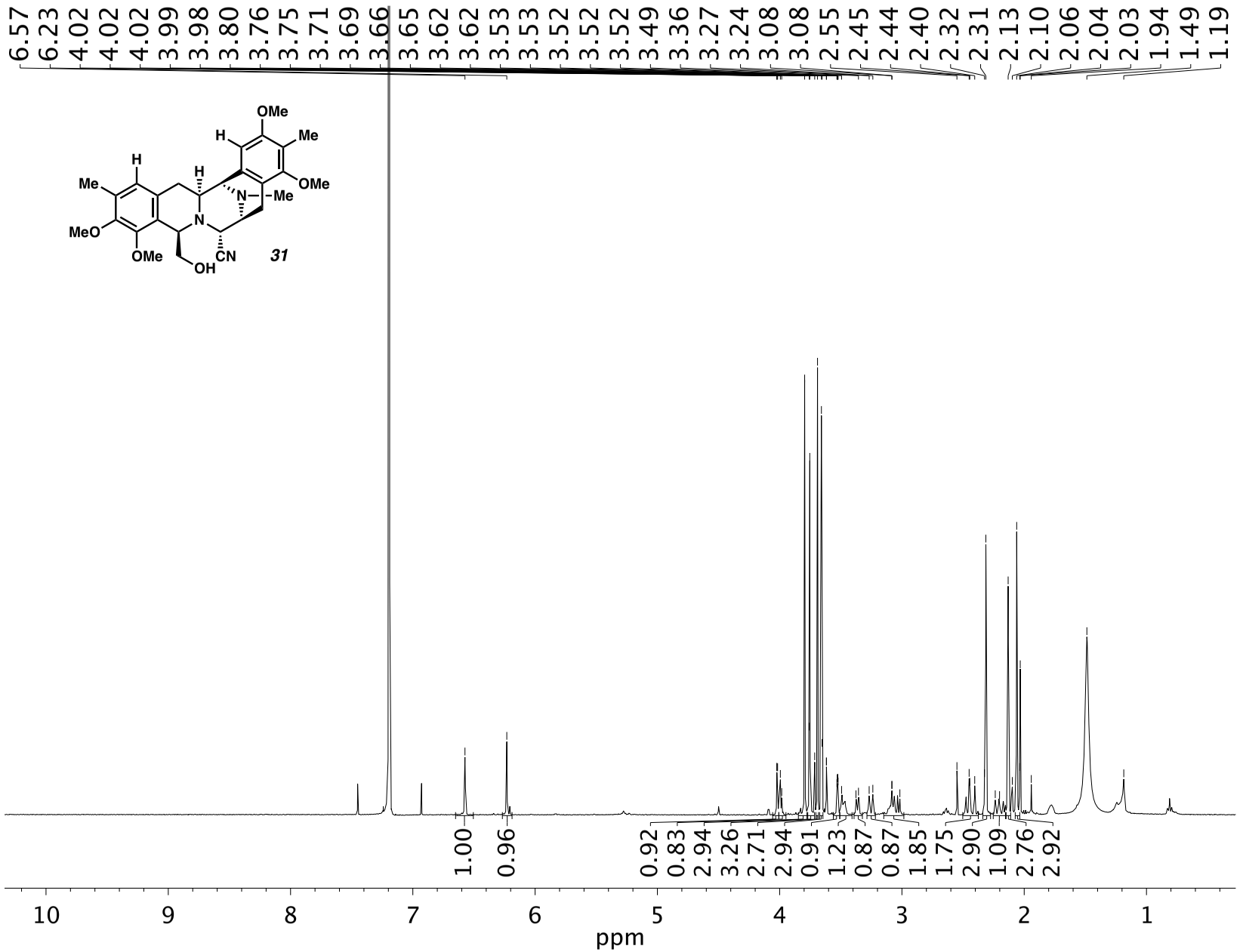
^{1}H NMR (400 MHz, $CDCl_3$) of compound **1**.



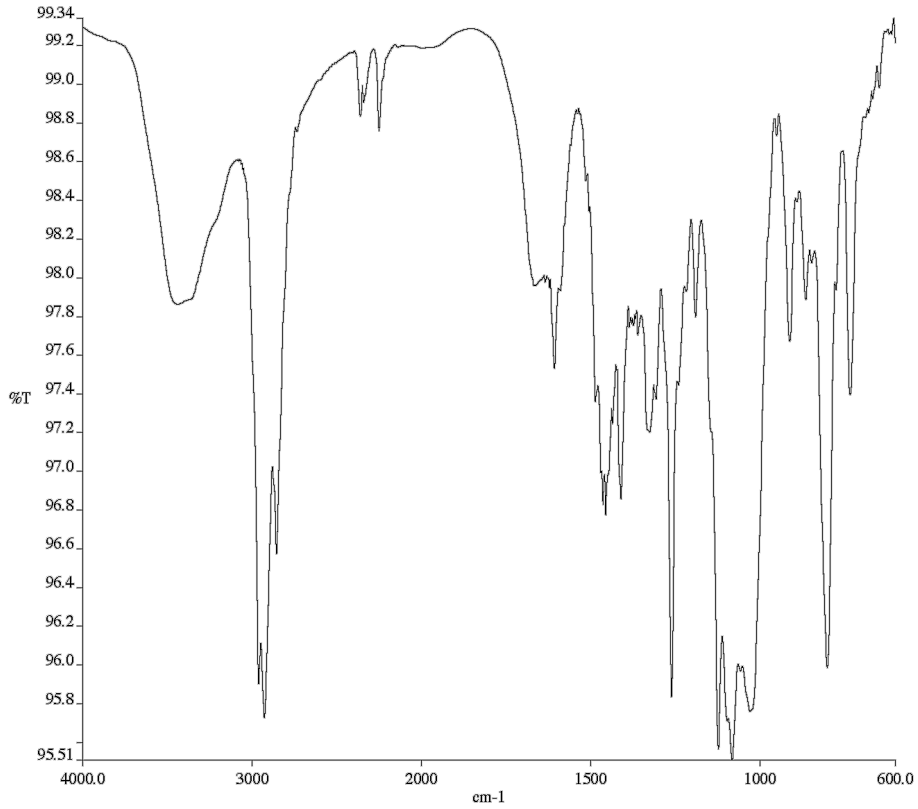
Infrared spectrum (Thin Film, NaCl) of compound **1**.



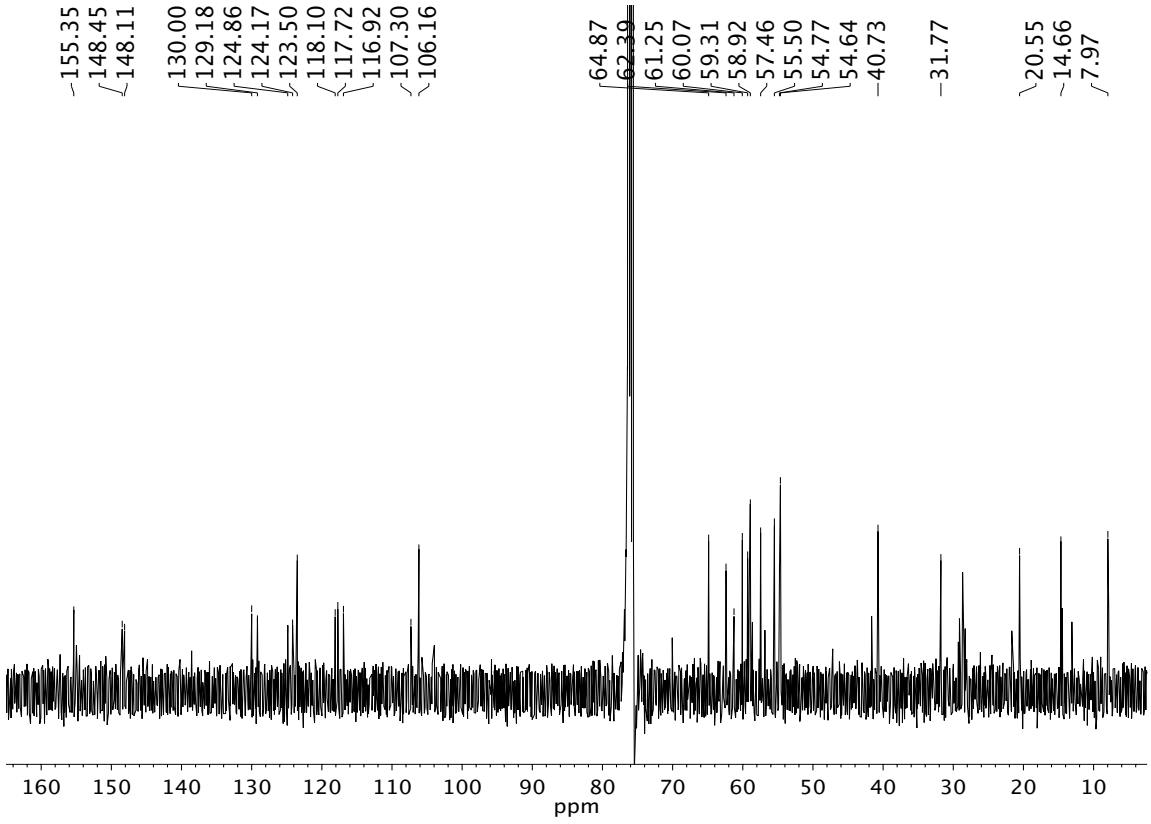
^{13}C NMR (101 MHz, $CDCl_3$) of compound **1**.



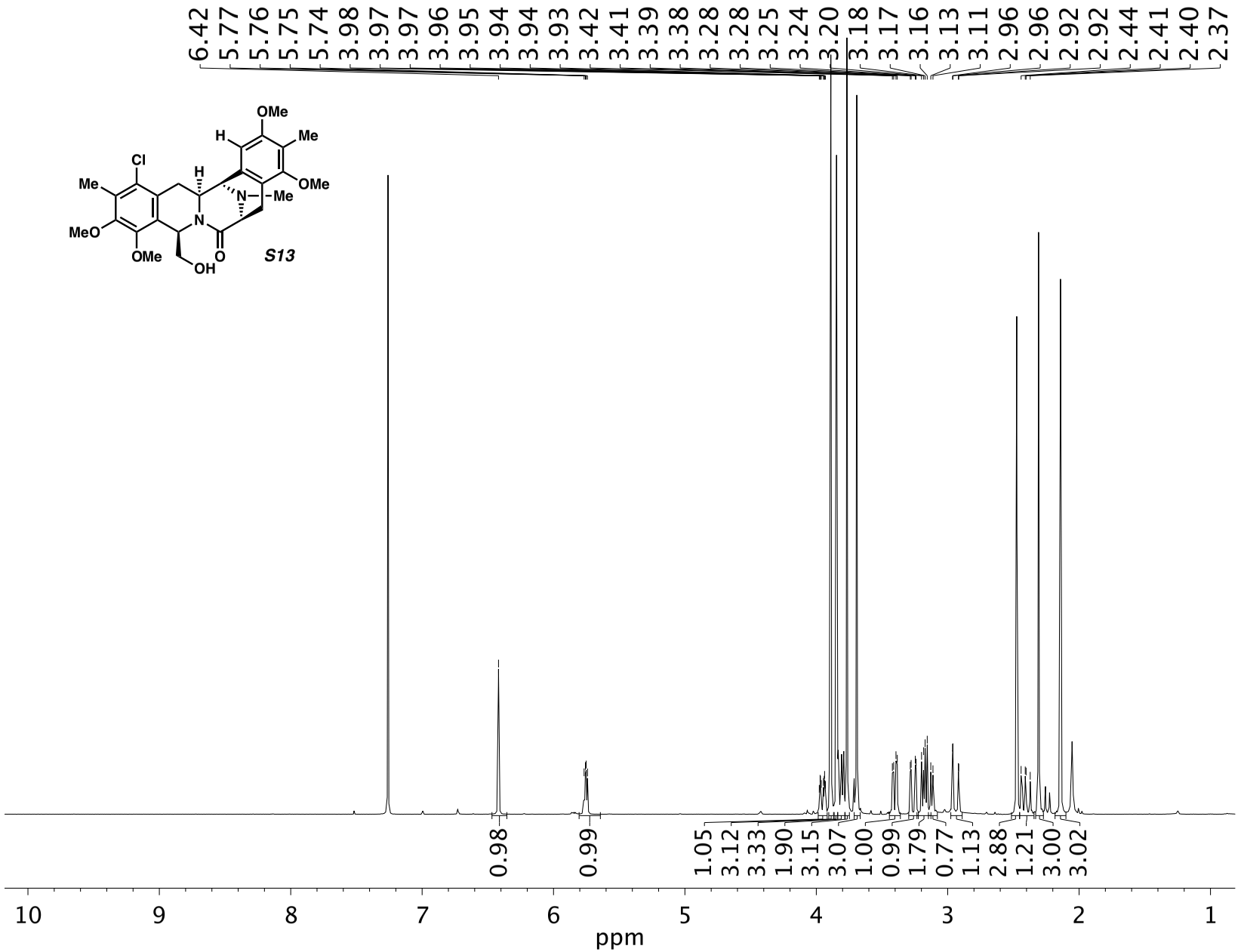
^{1}H NMR (400 MHz, $CDCl_3$) of compound **31**.



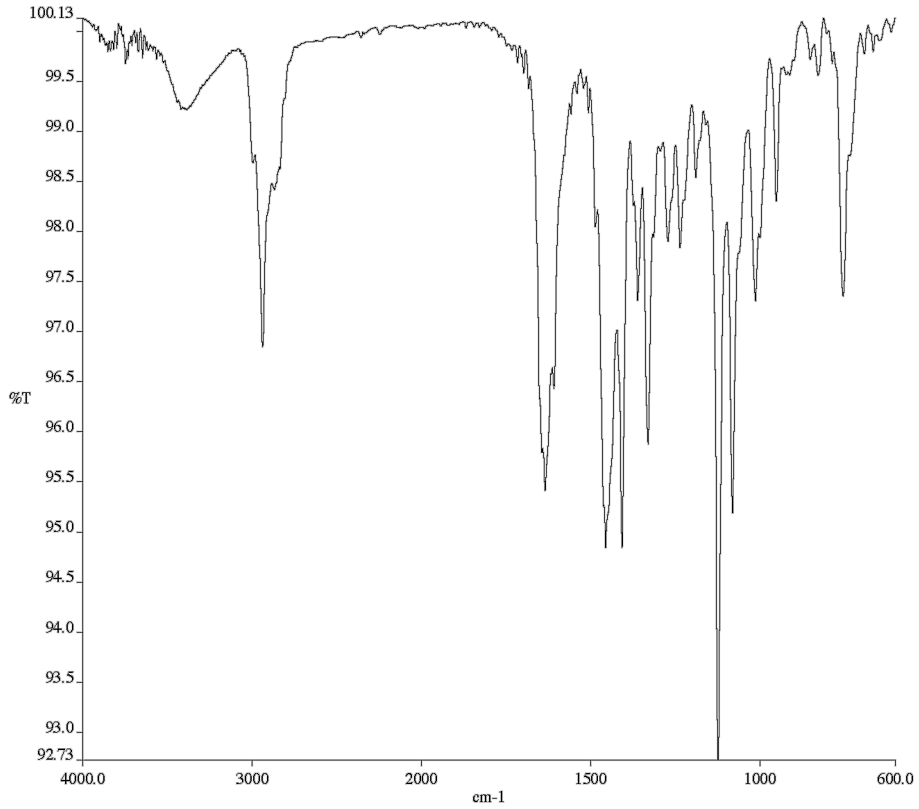
Infrared spectrum (Thin Film, NaCl) of compound **31**.



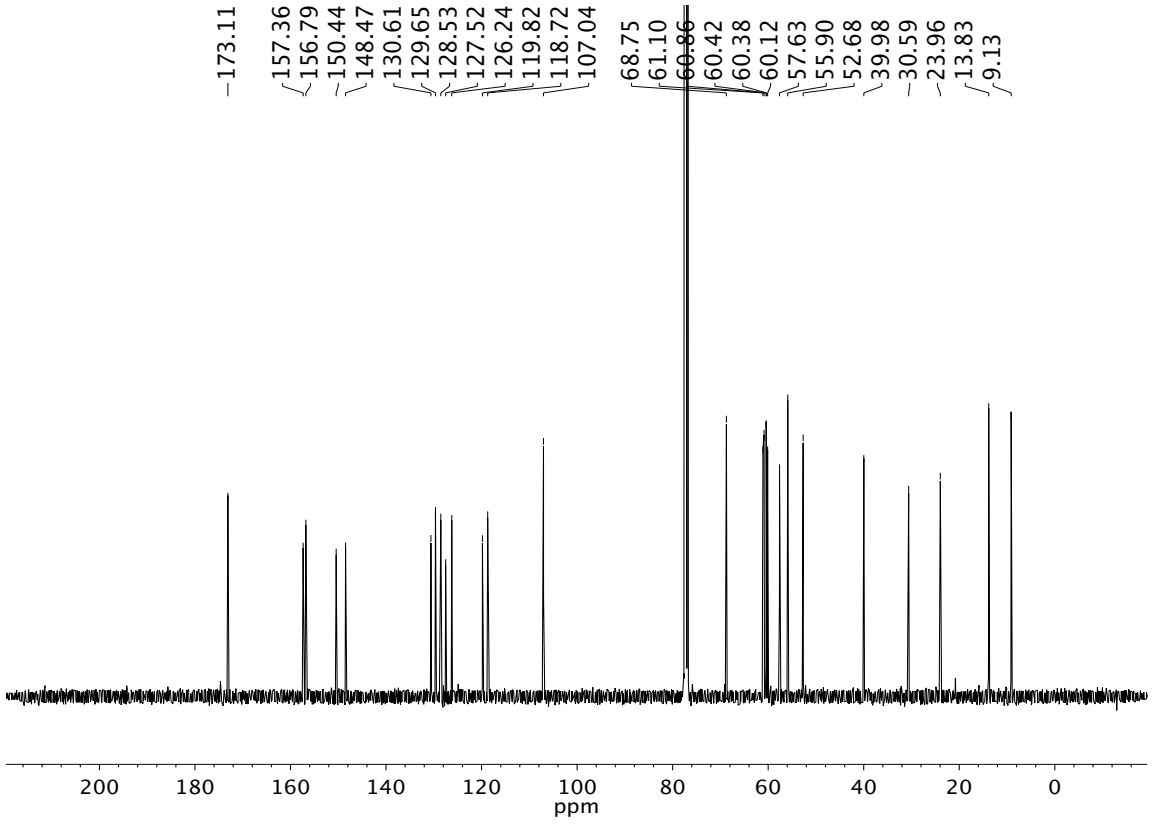
^{13}C NMR (101 MHz, $CDCl_3$) of compound **31**.



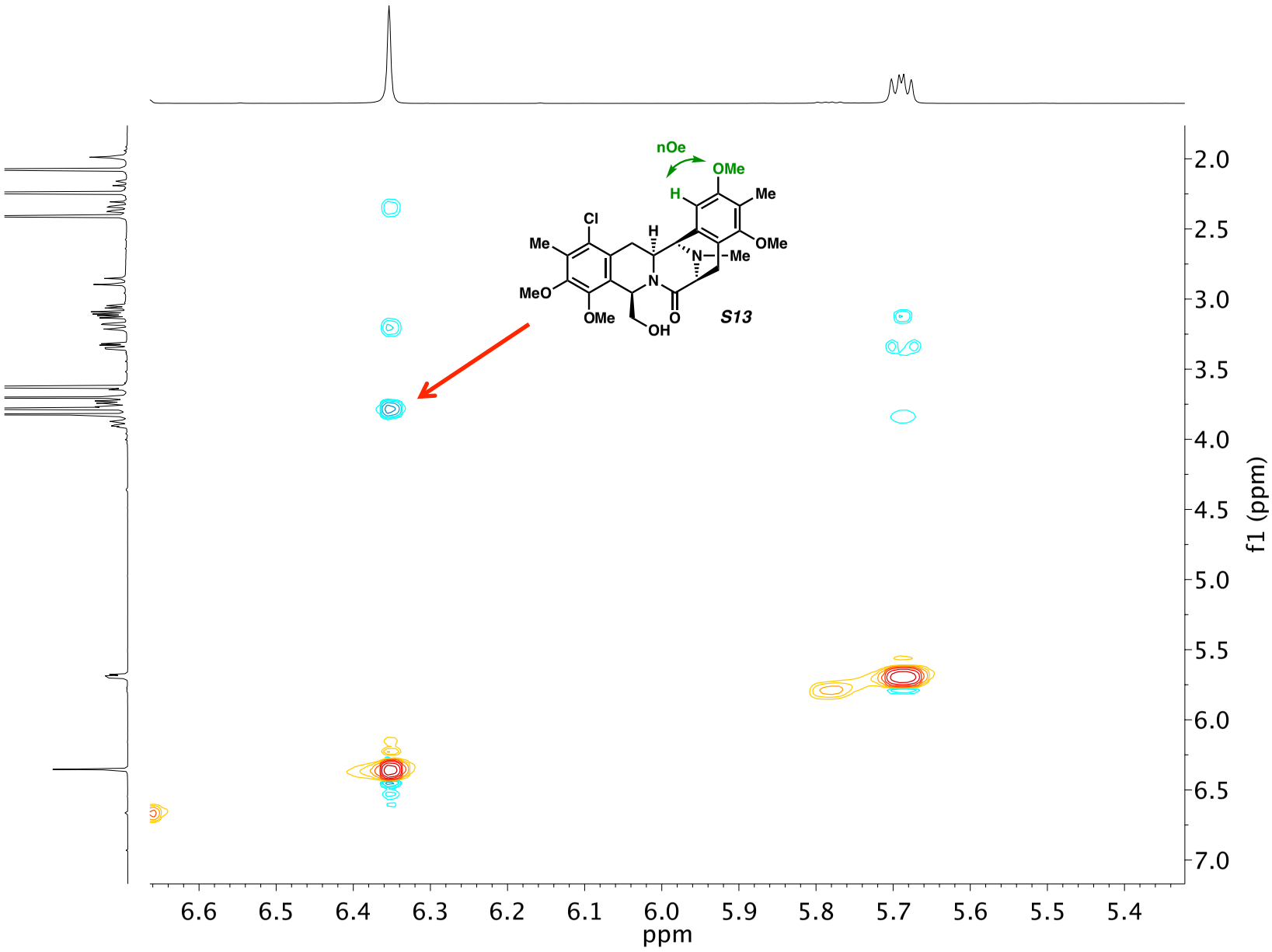
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S13**.



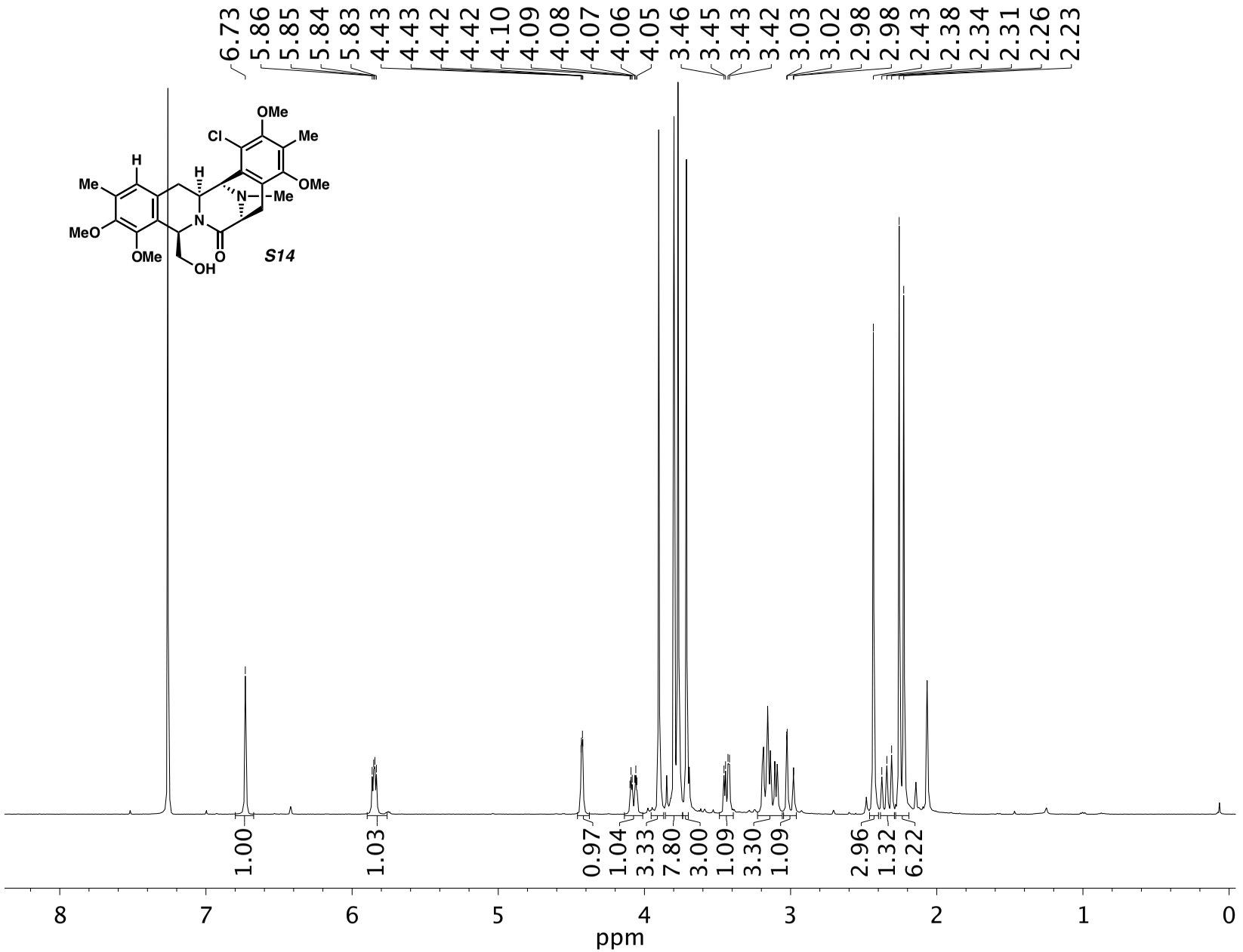
Infrared spectrum (Thin Film, NaCl) of compound **S13**.



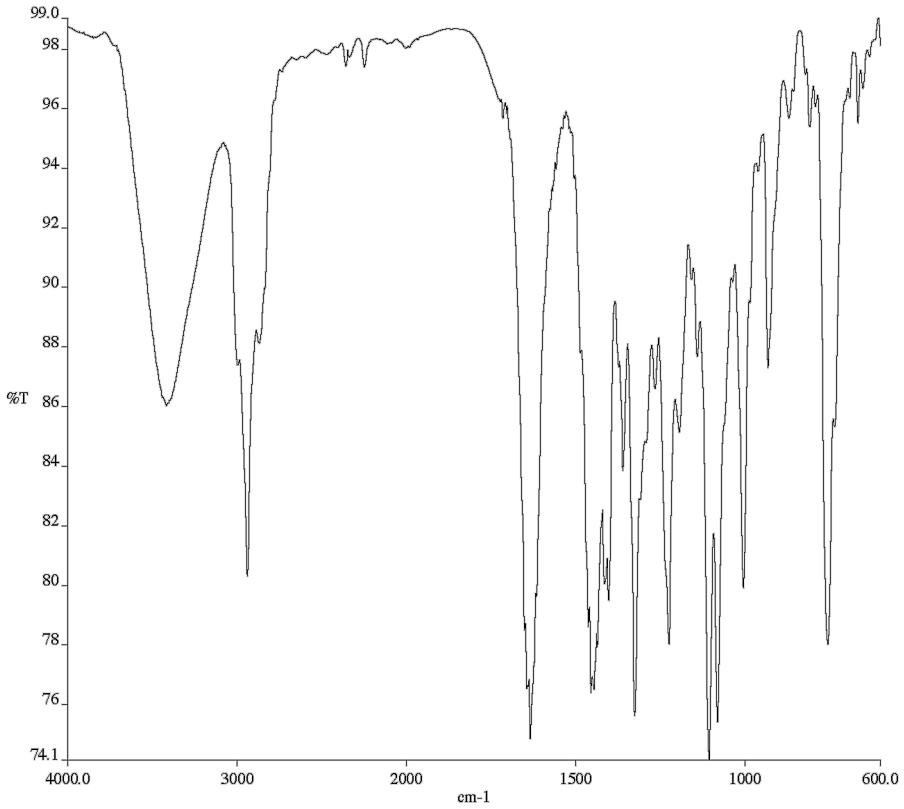
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S13**.



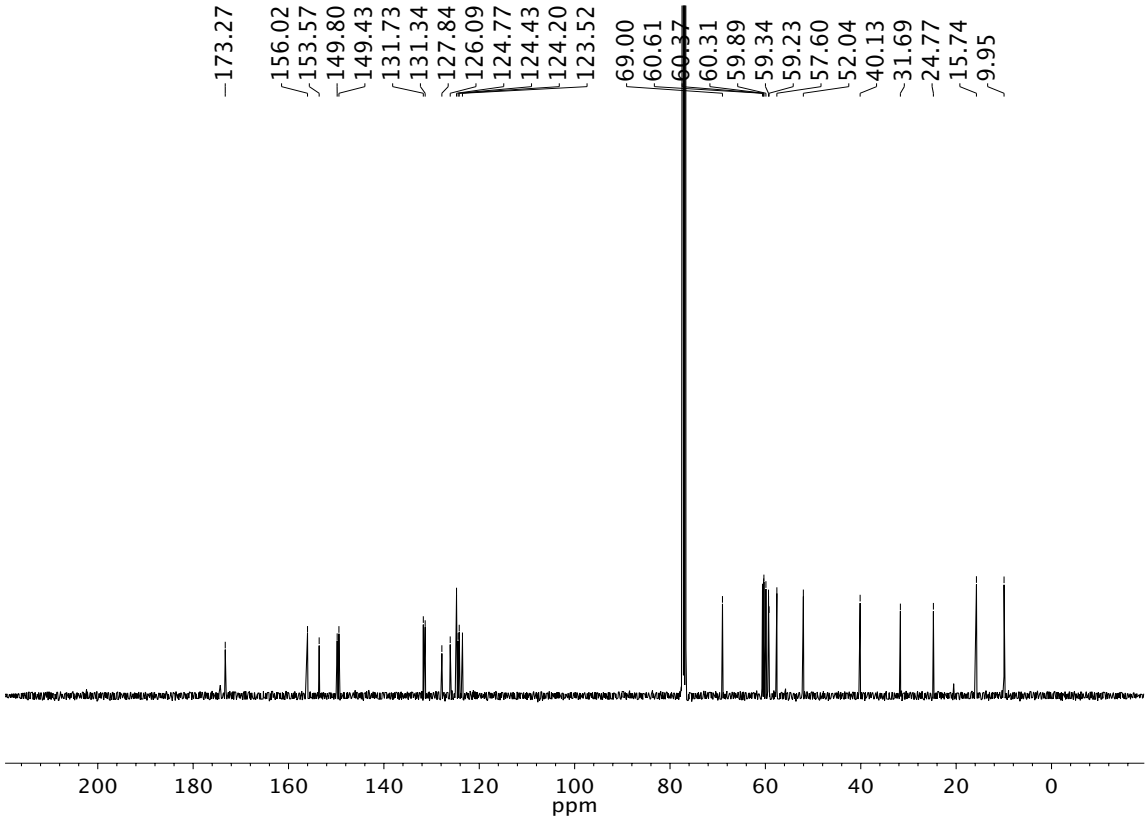
2D NOESY NMR of compound **S13**.



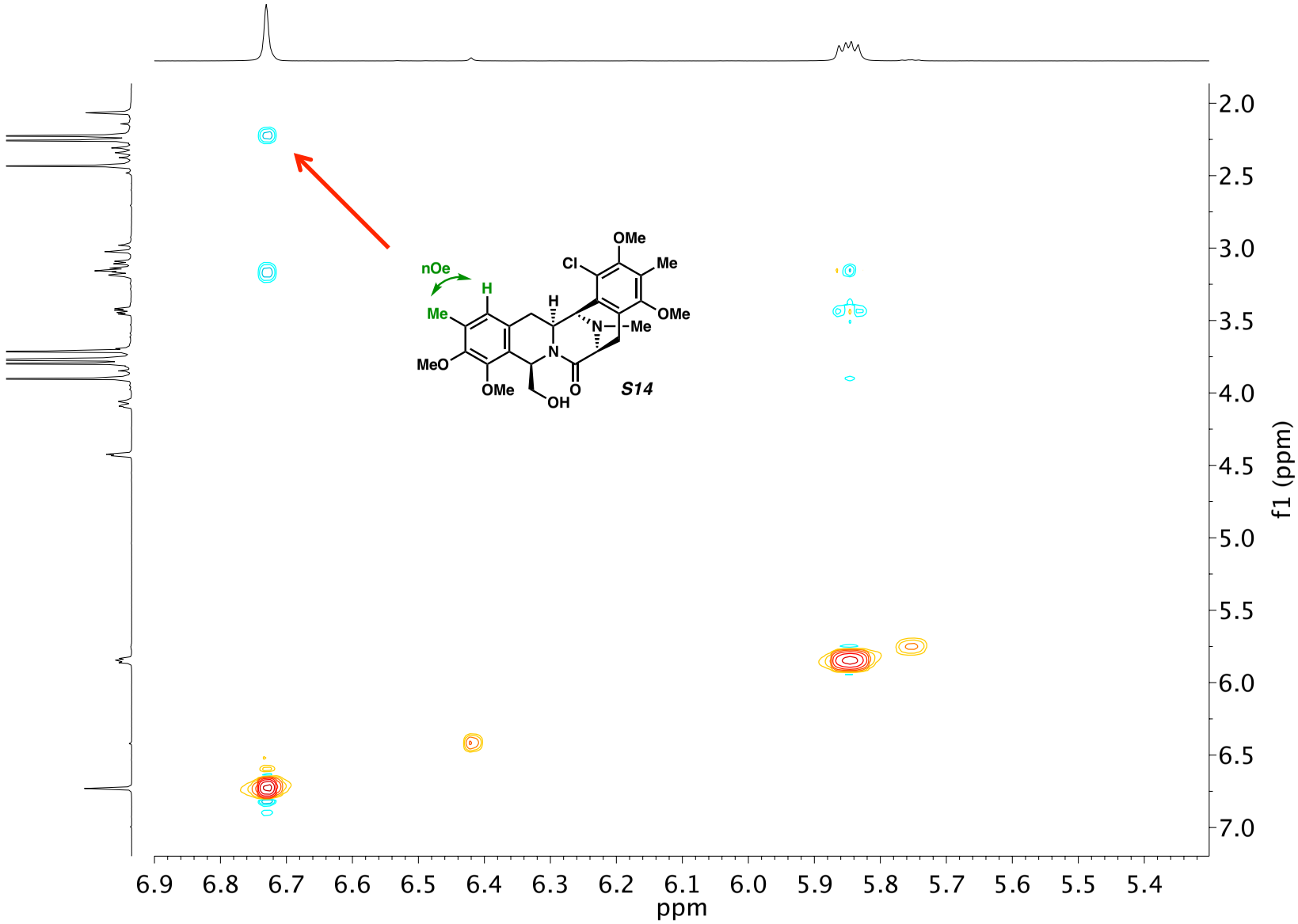
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S14**.



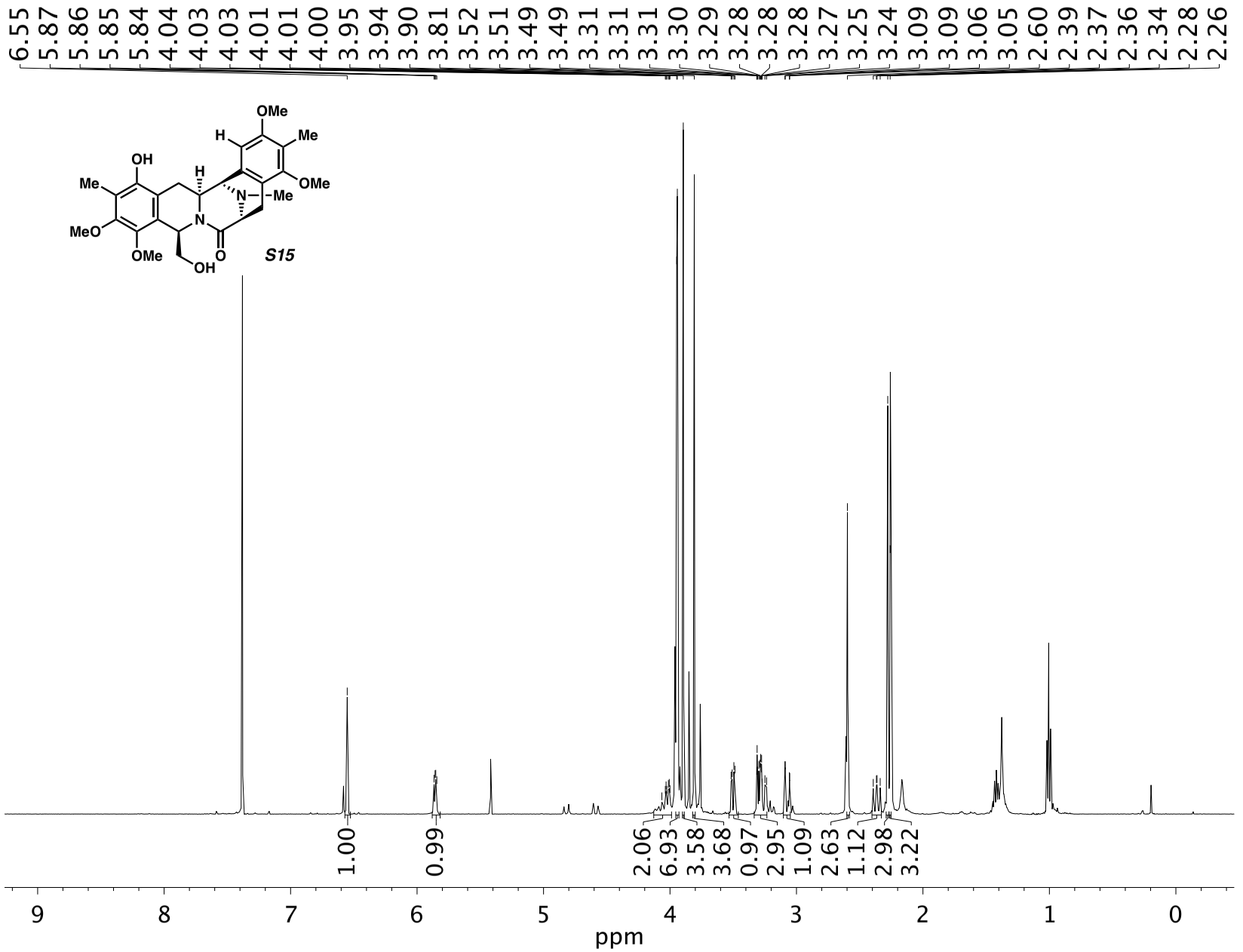
Infrared spectrum (Thin Film, NaCl) of compound **S14**.



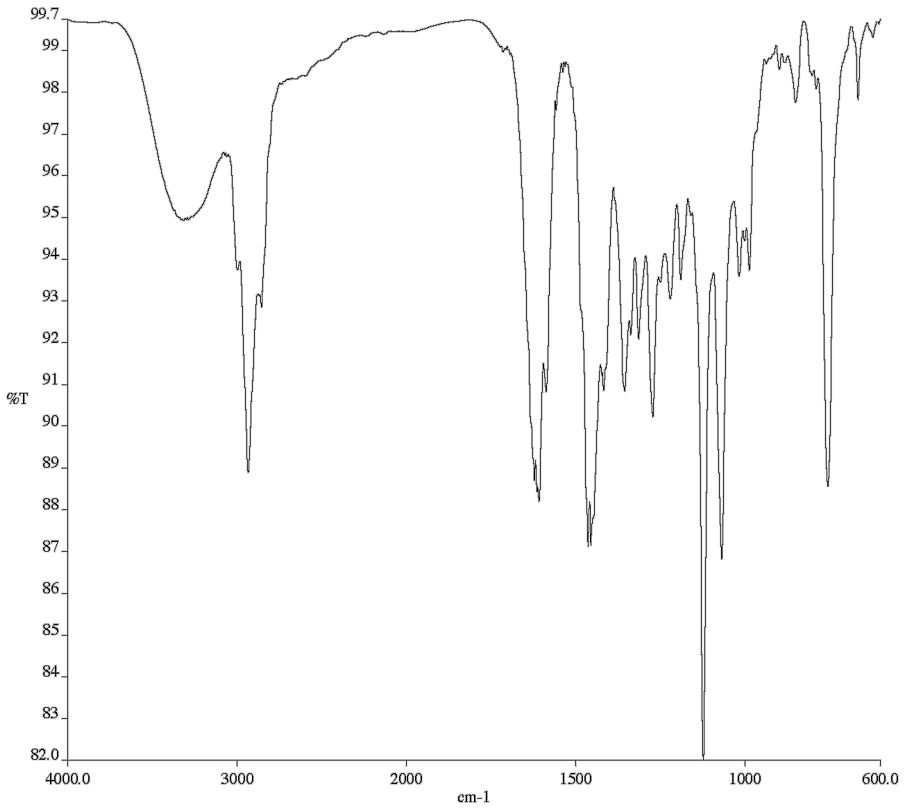
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S14**.



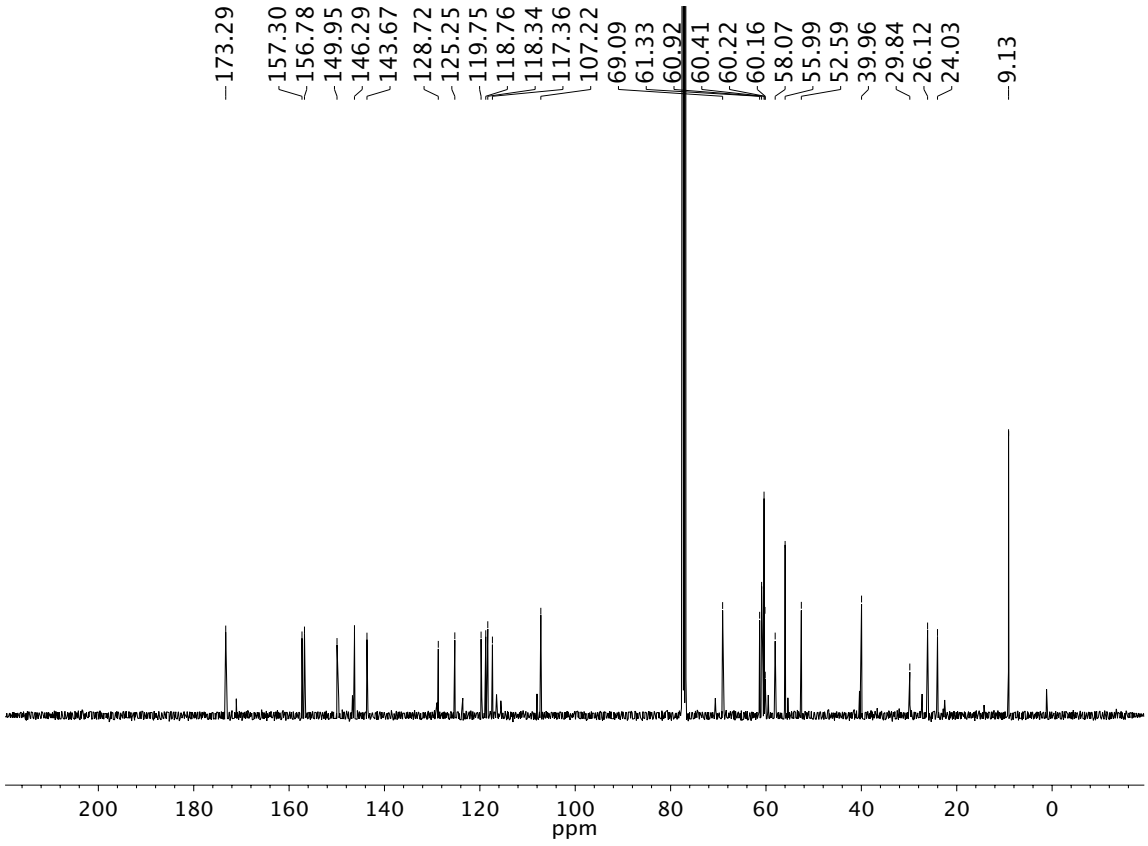
2D NOESY NMR of compound **S14**.



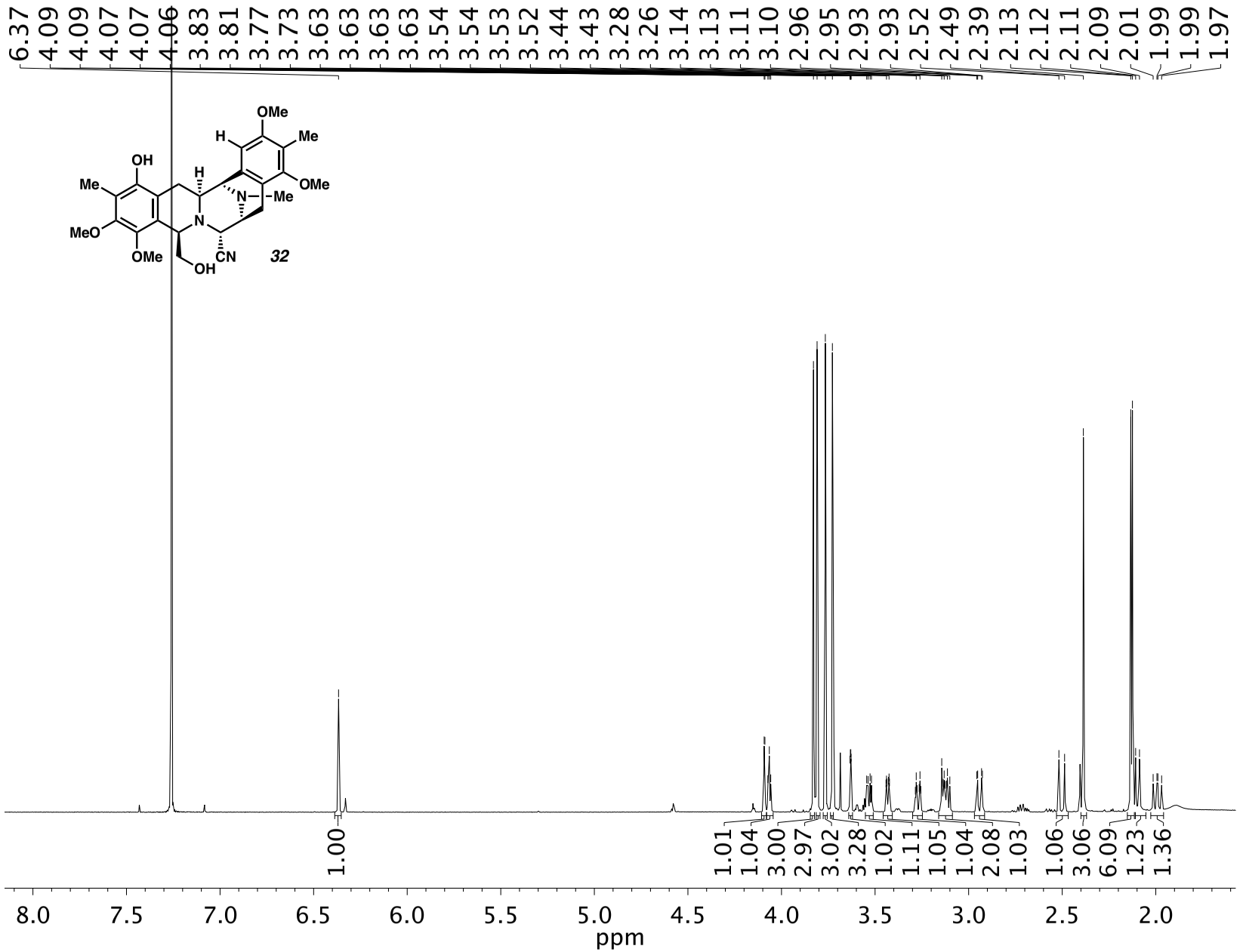
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S15**.



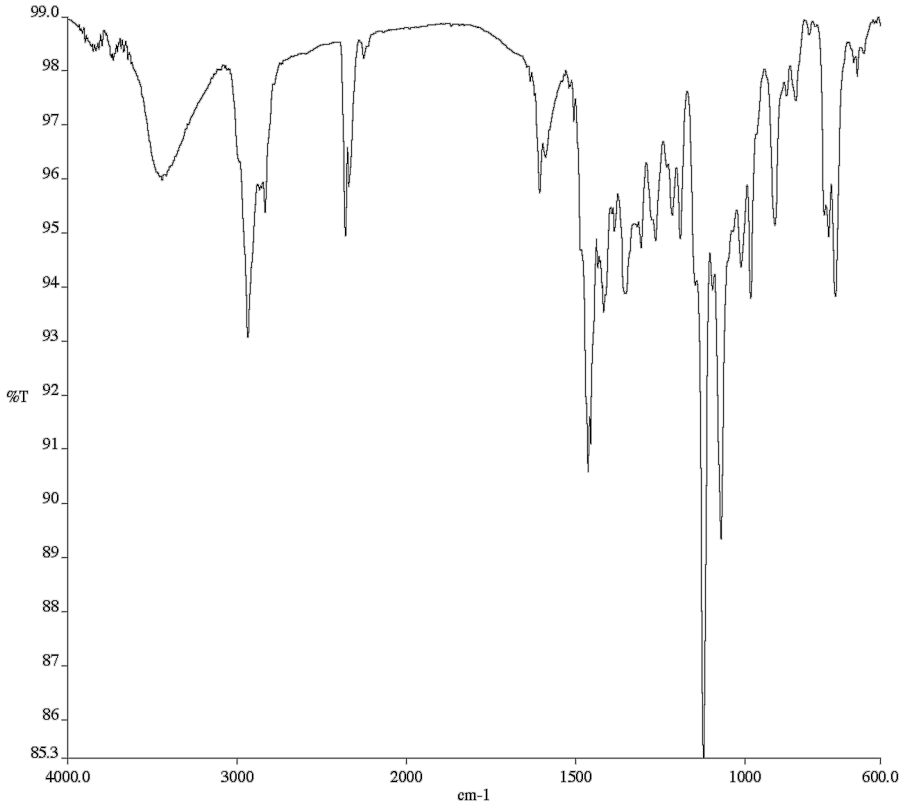
Infrared spectrum (Thin Film, NaCl) of compound **S15**.



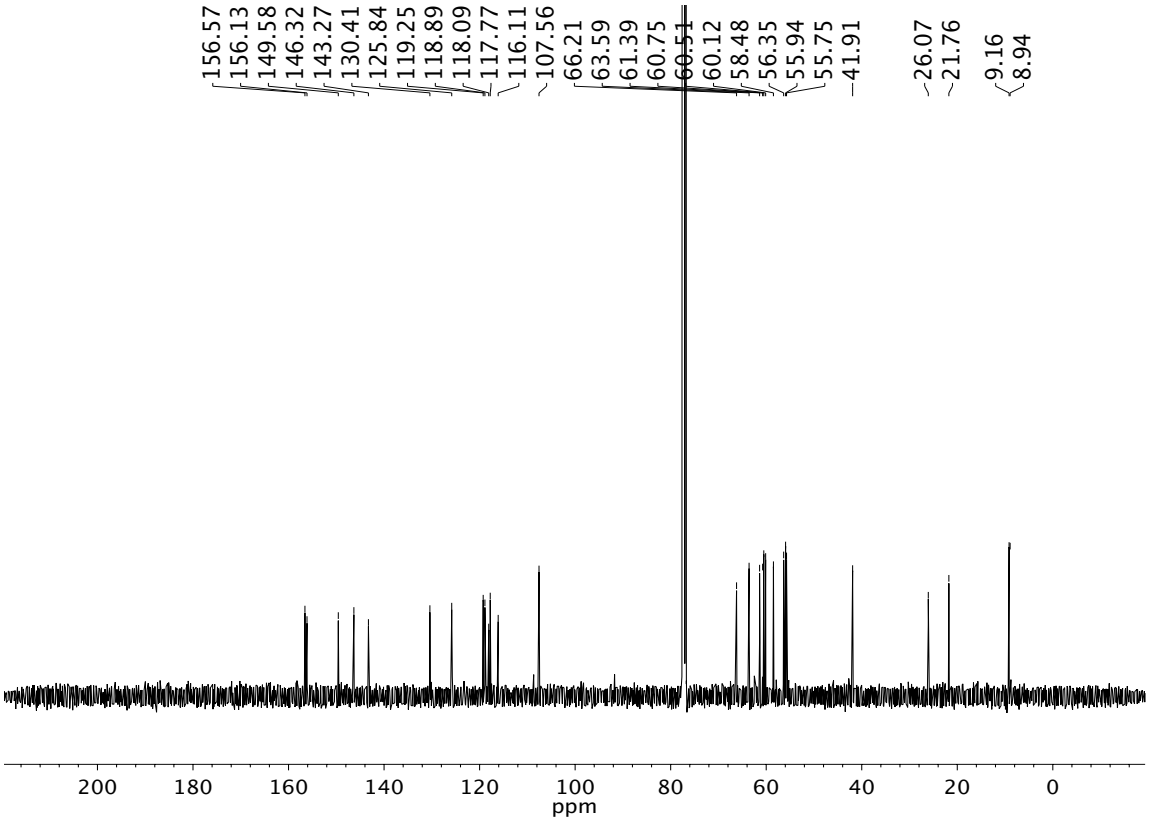
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S15**.



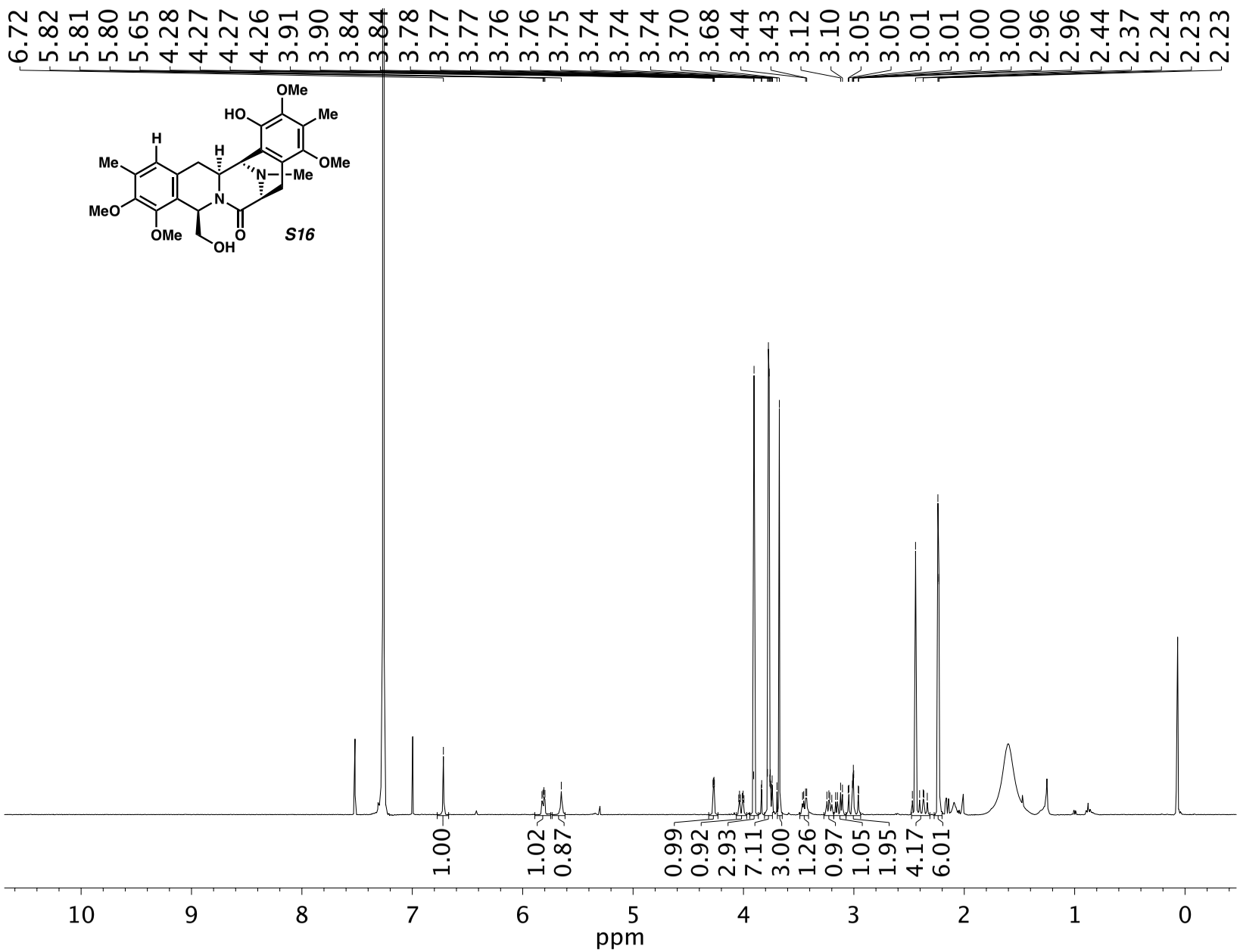
^{1}H NMR (400 MHz, $CDCl_3$) of compound **32**.



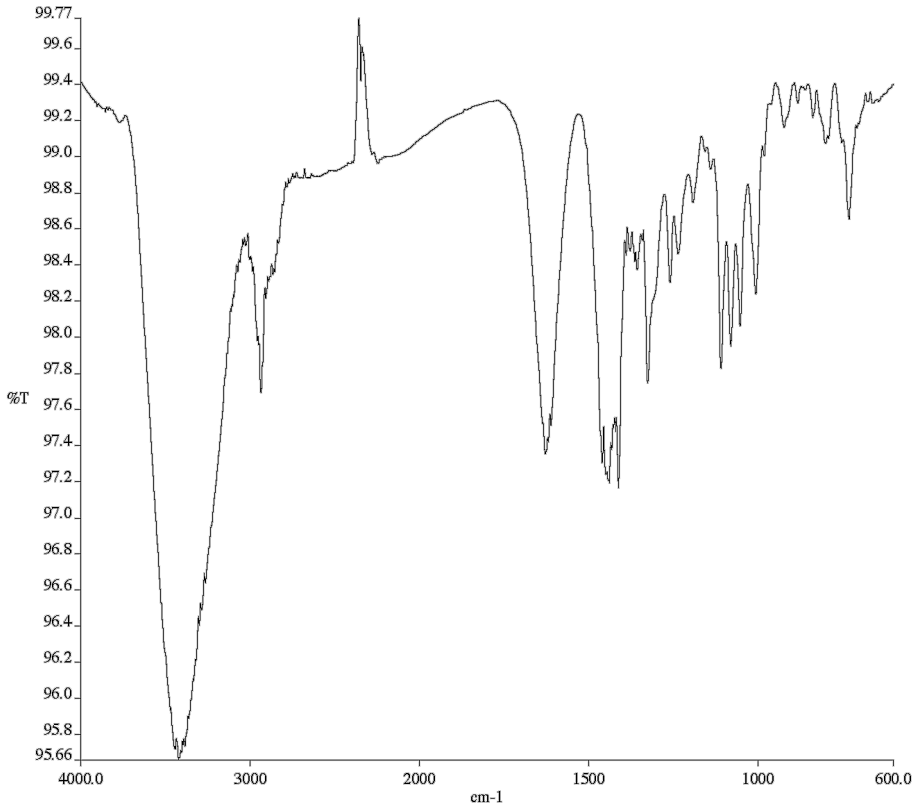
Infrared spectrum (Thin Film, NaCl) of compound **32**.



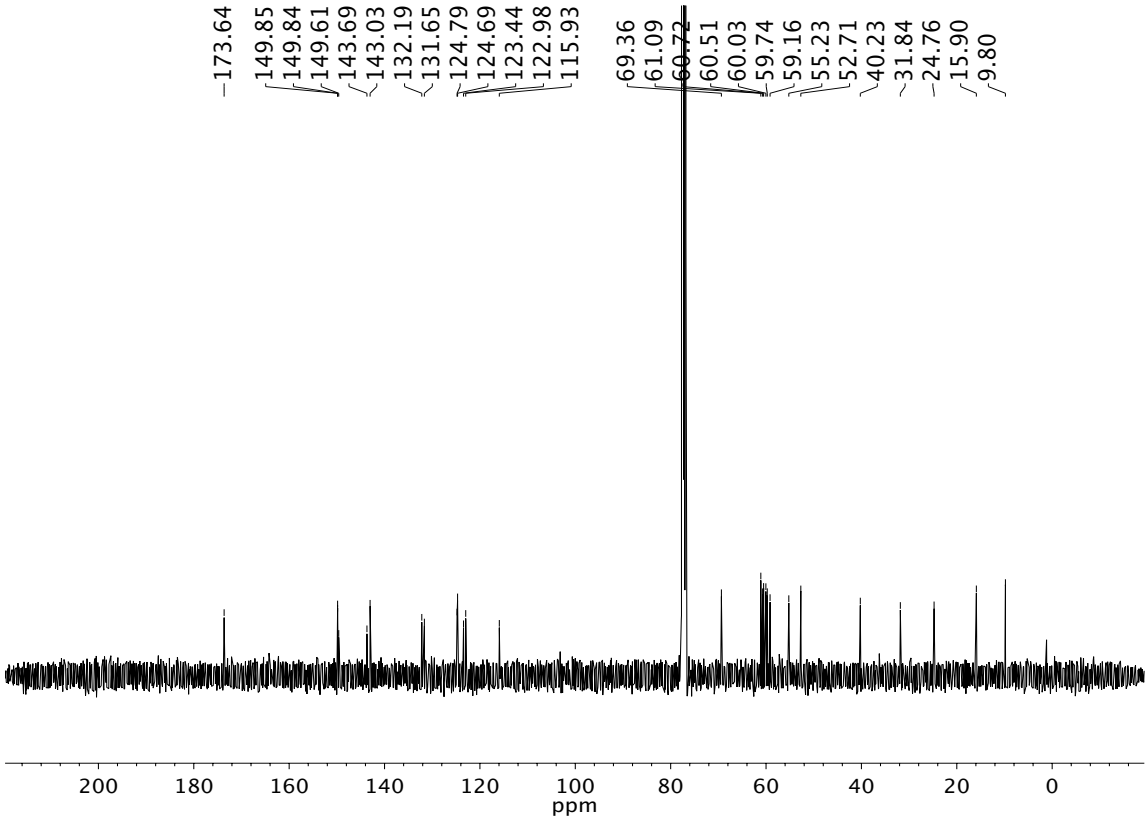
^{13}C NMR (101 MHz, $CDCl_3$) of compound **32**.



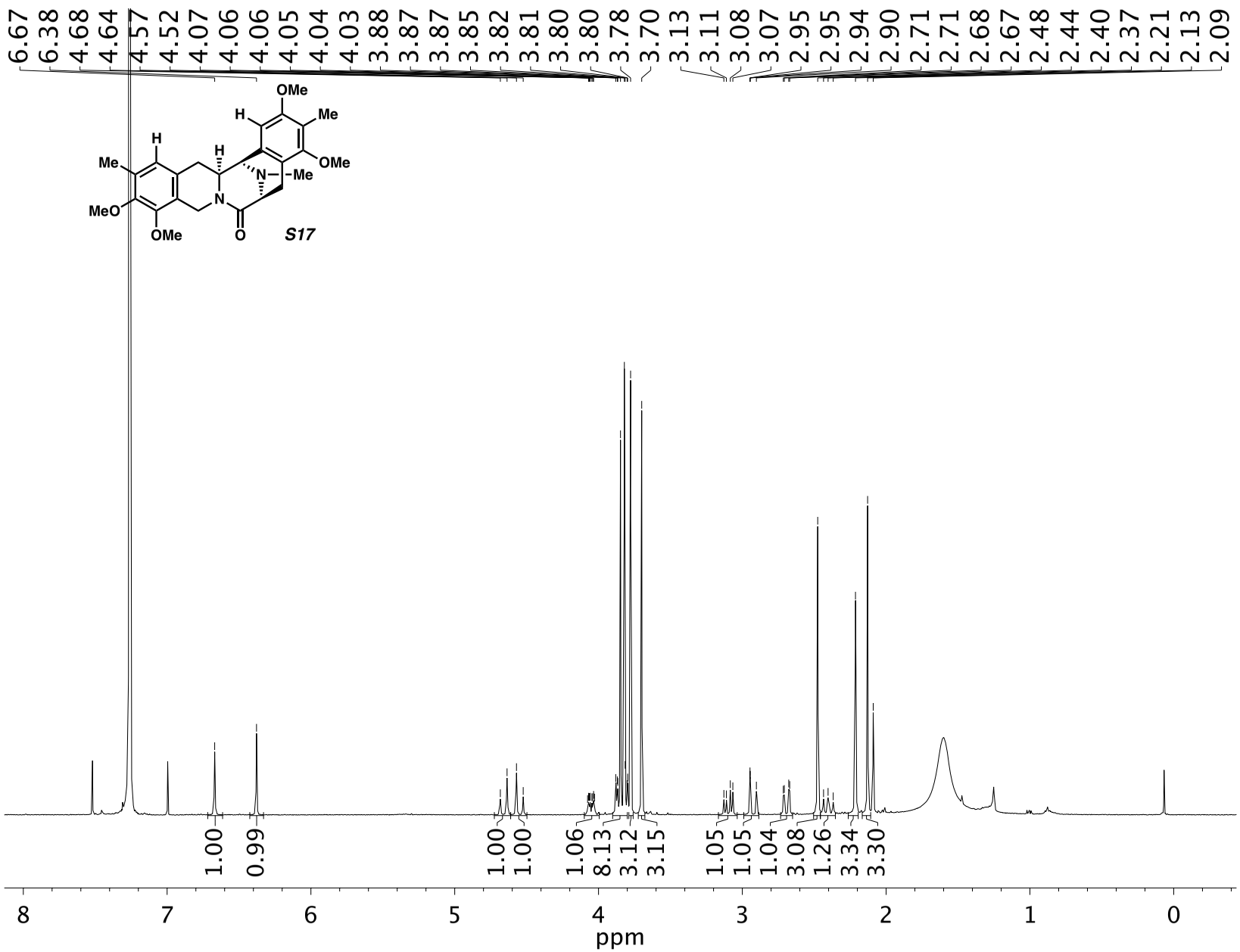
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S16**.



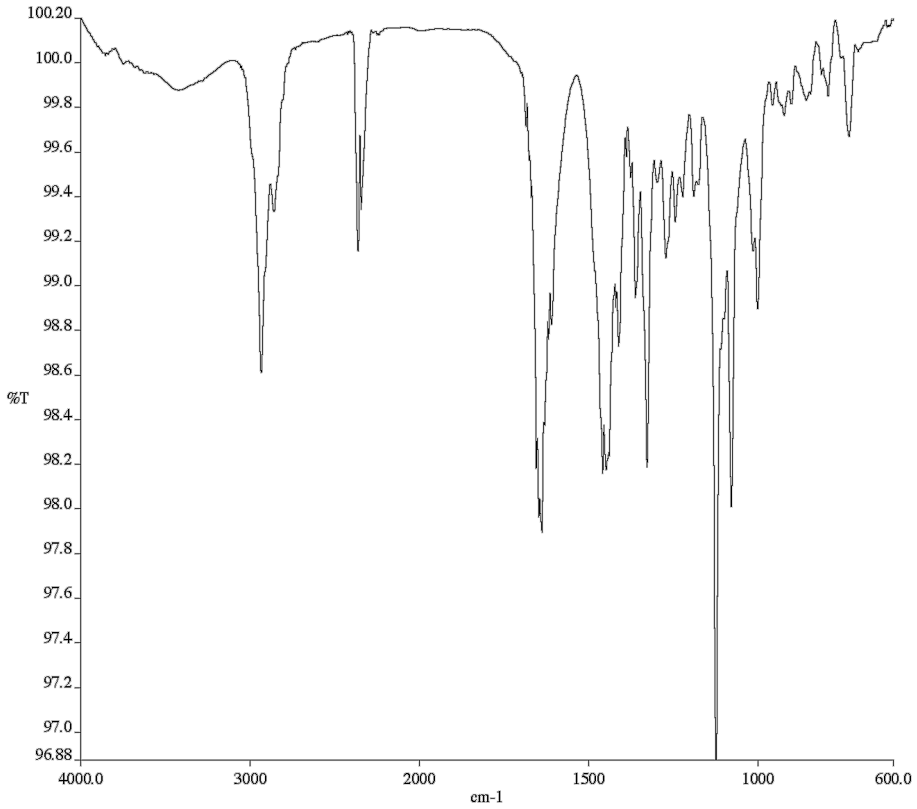
Infrared spectrum (Thin Film, NaCl) of compound **S16**.



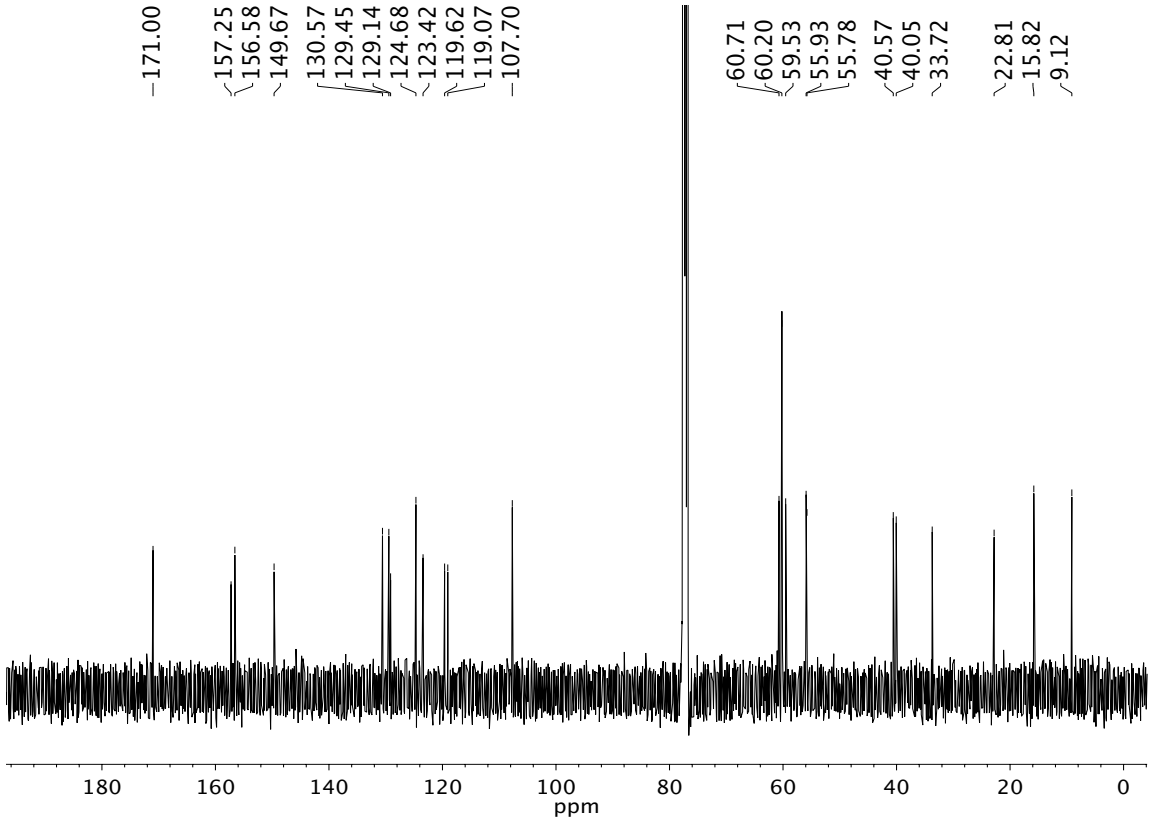
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S16**.



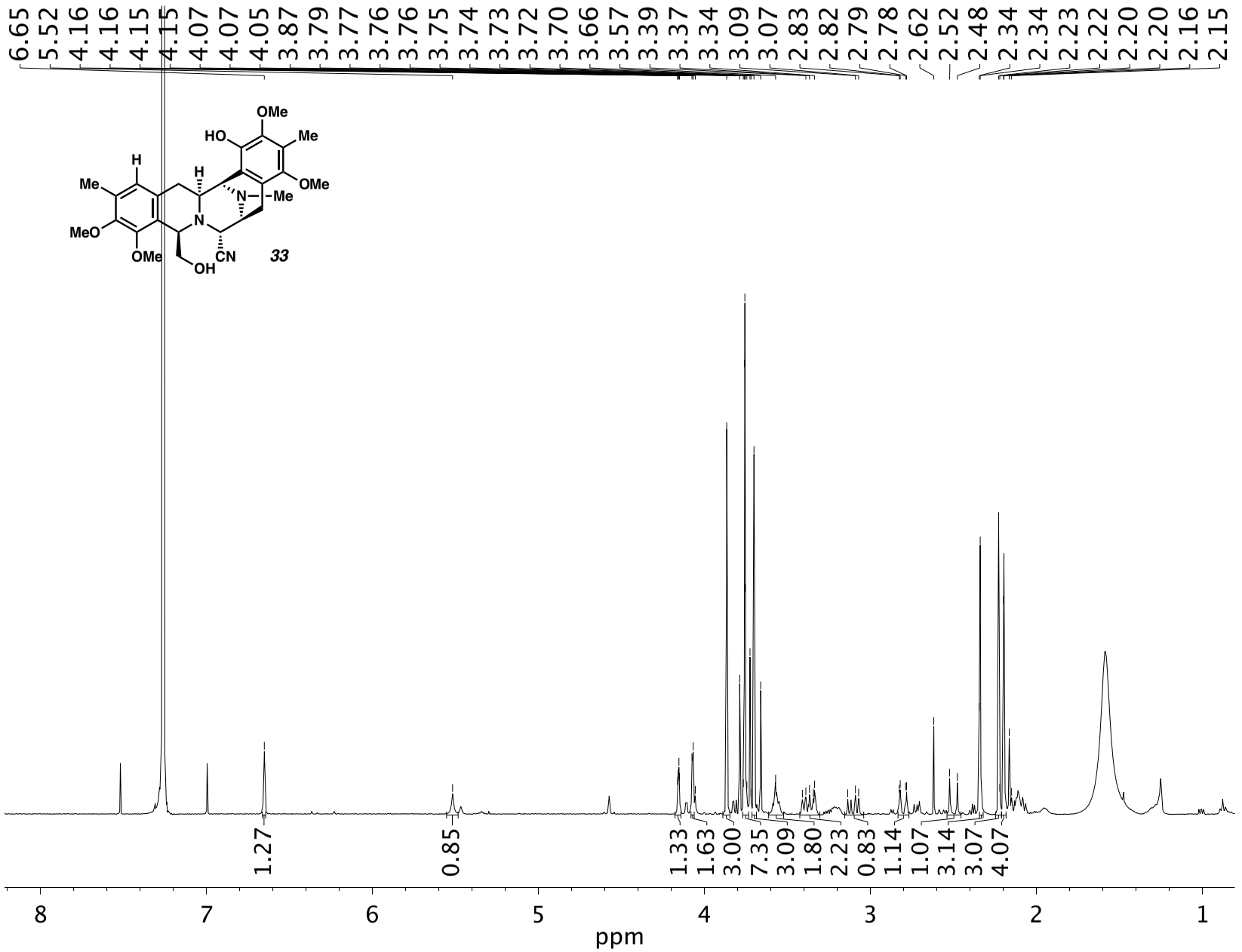
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S17**.



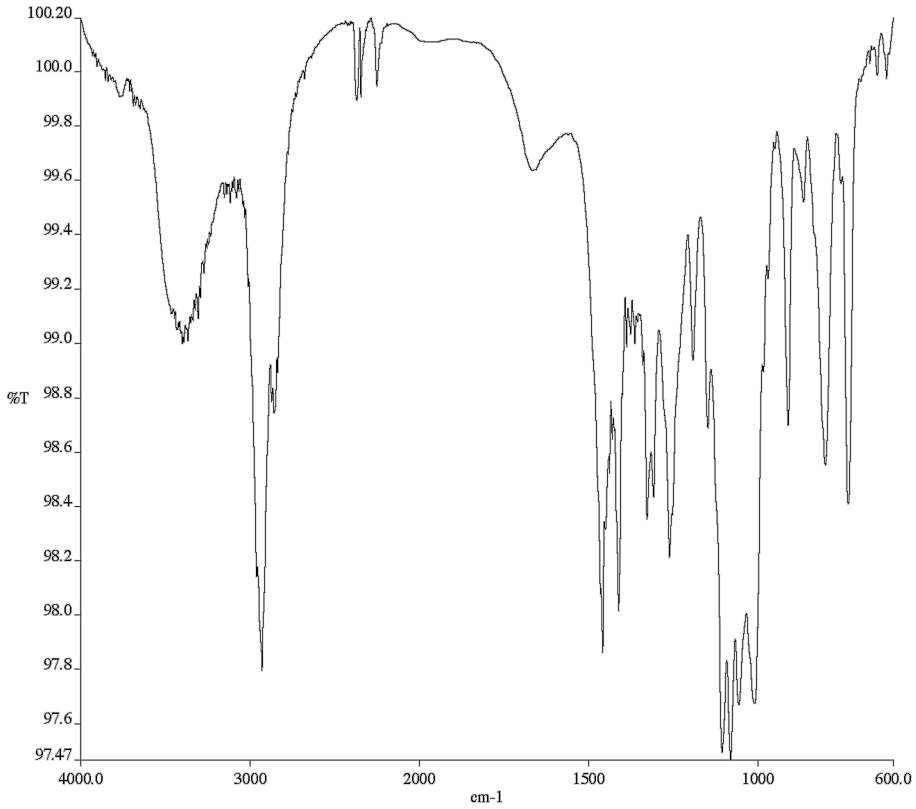
Infrared spectrum (Thin Film, NaCl) of compound **S17**.



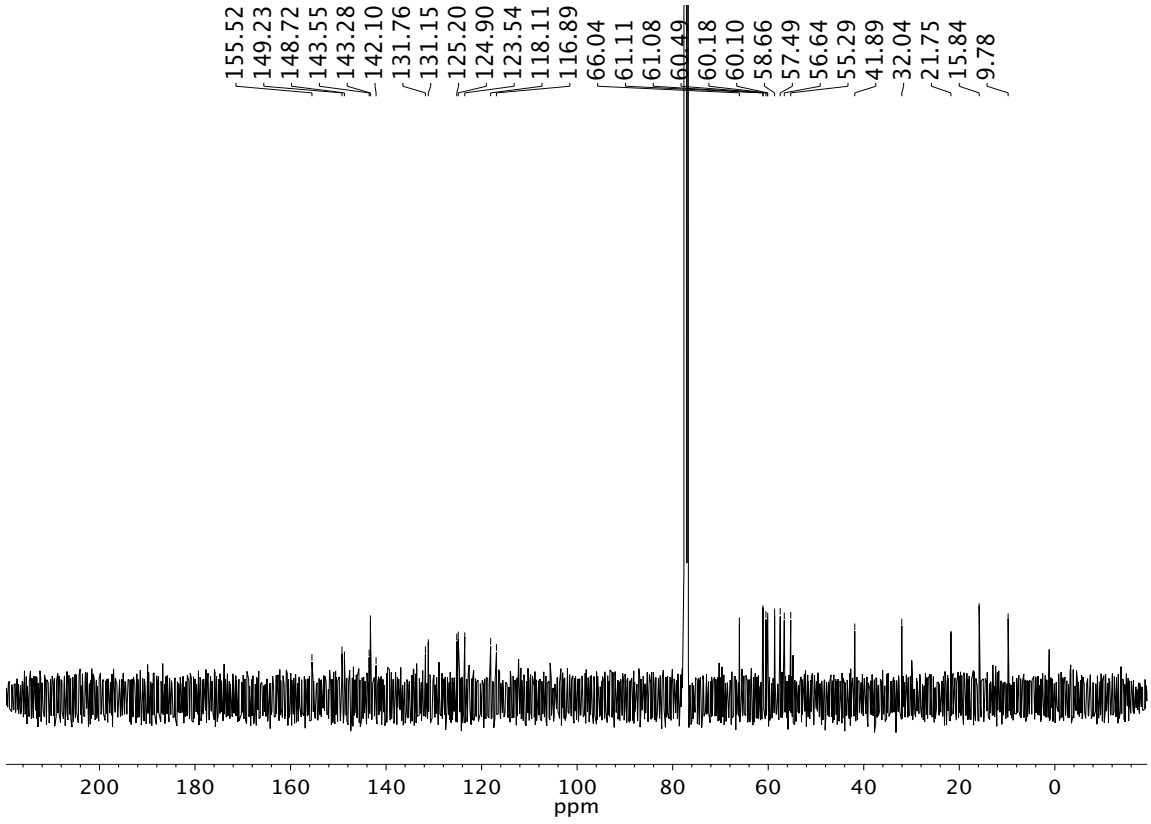
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S17**.



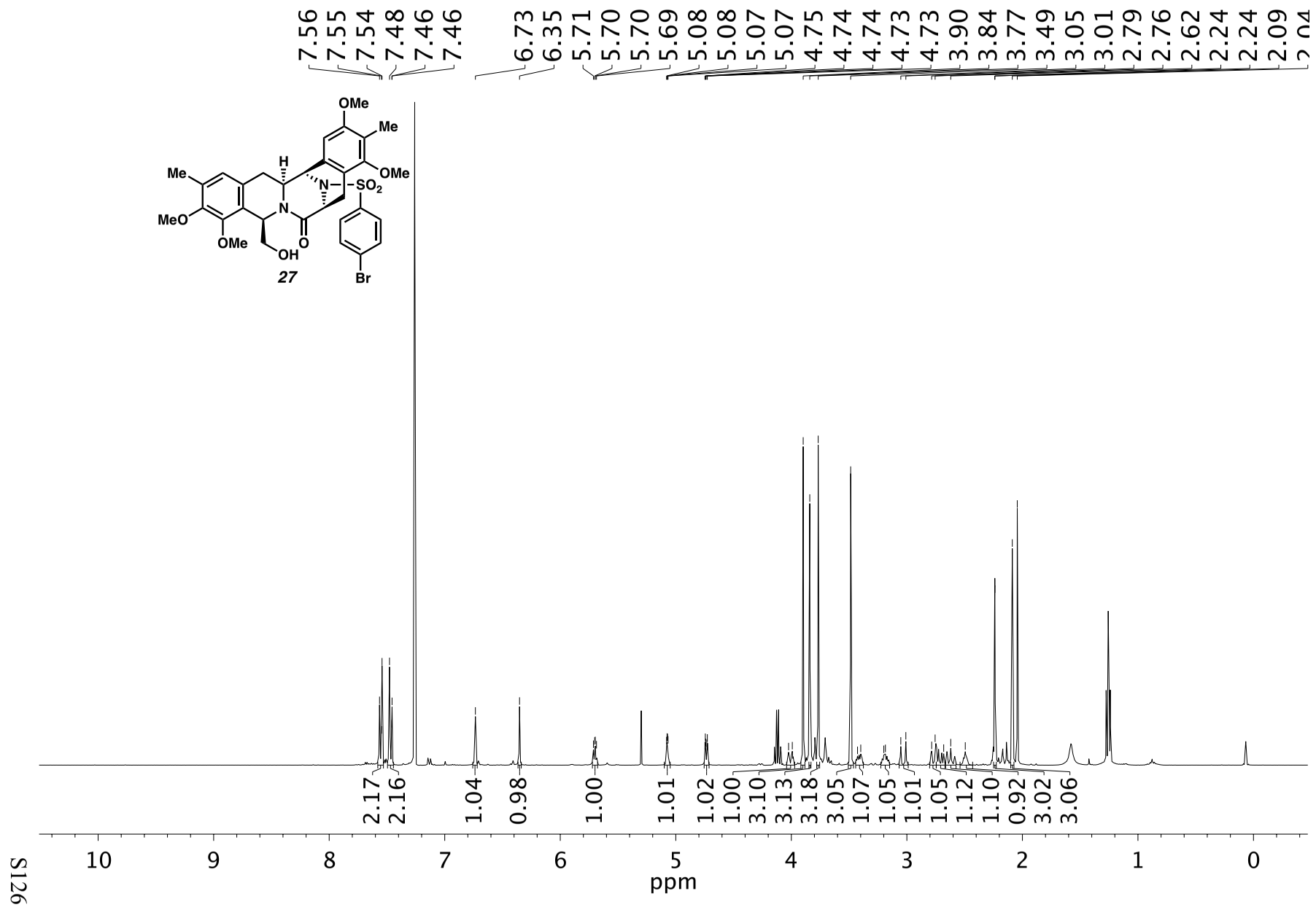
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S3**.



Infrared spectrum (Thin Film, NaCl) of compound **S33**.



^{13}C NMR (101 MHz, $CDCl_3$) of compound **S33**.



^{1}H NMR (400 MHz, $CDCl_3$) of compound **27**.

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36. The lower ee measured on isolated **6** as compared to isolated **22** can be rationalized by competitive (although minor), non-selective D-ring reduction leading to the same major diastereomer. See Supplementary Materials.

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