THE UNIVERSITY OF CHICAGO

A CYCLOISOMERIZATION STRATEGY FOR THE *DE NOVO* SYNTHESIS OF STEROIDAL ALKALOIDS

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Dedicated to My Family

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LIST OF ABBREVIATIONS

AIBN = azobisisobutyronitrile

Ac = acetyl

AcOH = acetic acid

ATP = adenosine triphosphate

9-BBN = 9-borabicyclo(3.3.1)nonane

Bn = benzyl

Boc = *tert*-butyloxycarbonyl

Bs = benzenesulfonyl

Bu = butyl

Bz = benzoyl

c = concentration

CAN = ceric ammonium nitrate

Cbz = benzyloxycarbonyl

CDI = 1,1'-carbonyldiimidazole

Cp = cyclopentadienyl

Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl

cod = 1,5-cyclooctadiene

COSY = correlation spectroscopy

m-CPBA = *meta*-chloroperoxybenzoic acid

CSA = camphorsulfonic acid

DCE = 1,2-dichloroethane

DEG = diethylene glycol

DFT = density-functional theory

DIAD = diisopropyl azodicarboxylate

DIBAL-H = diisobutylaluminum hydride

(4-)DMAP = 4-dimethylaminodpyridine

DMF = dimethylformamide

DMP = Dess-Martin periodinane

DMPU = 1,3-Dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone

DMSO = dimethyl sulfoxide

DPPA = diphenylphosphoryl azide

2,6-DTBP = 2,6-di-*tert*-butylpyridine

dr = diastereomeric ratio

ee = enantiomeric excess

eq. = equivalents

ESI = electrospray ionization

Et = ethyl

h = hours

hν = light

HMDS = bis(trimethylsilyl)amine

HMPA = hexamethylphosphoramide

HRMS = high resolution mass spectrometry

HSQC = heteronuclear single-quantum correlation spectroscopy

Hz = Hertz

IR = infrared

LDA = lithium diisopropylamide

Me = methyl

MeCN = acetonitrile

MOM = methoxymethyl

Ms = methanesulfonyl

MVK = methyl vinyl ketone

NBS = *N*-bromosuccinimide

NCS = *N*-chlorosuccinimide

NMO = *N*-methylmorpholine *N*-oxide

NMR = nuclear magnetic resonance

NOE = nuclear Overhauser effect

Oct = octanoate

Ph = phenyl

PhH = benzene

PhMe = toluene

Piv = pivaloyl

PMB = *para*-methoxybenzyl

PPTS = pyridinium *para*-toluenesulfonate

Pr = propyl

pyr = pyridine

R_f = retention factor

sp. = species

TBAF = tetra-*n*-butylammonium fluoride

TBDPS = *tert*-butyldiphenylsilyl

TBS = *tert*-butyldimethylsilyl

TES = triethylsilyl

Tf = trifluoromethanesulfonyl

THF = tetrahydrofuran

THP = tetrahydropyranyl

TIPS = triisopropylsilyl

TLC = thin-layer chromatography

TMDSO = 1,1,3,3-tetramethyldisiloxane

TMP = 2,2,6,6-tetramethylpiperidine

TMS = trimethylsilyl

TPAP = tetrapropylammonium perruthenate

Tr = trityl

Troc = 2,2,2-trichloroethoxycarbonyl

TS = transition state

Ts = *para*-toluenesulfonyl

p-TsOH = *para*-toluenesulfonic acid

ACKNOWLEDGEMENTS

I must first express my sincerest sense of gratitude to Prof. Viresh Rawal, for providing the opportunity to join his group and entrusting me with these exciting projects. While I was initially drawn to him by all the intriguing ideas for research avenues he shared with me during our first meeting, in retrospect I really could not have selected a better person to advise me during my graduate studies. During the challenging phases of this work, he always showed patience and encouragement; it was through his overwhelming support that I was able to find the courage within myself to overcome all obstacles I faced. But apart from the guidance given on work that is described herein, Prof. Rawal has also been a tremendous mentor and teacher to me. Throughout my journey here at the University of Chicago he has gone out of his way to give me numerous opportunities that have allowed me to grow and develop experience and expertise beyond the bench. His infectious curiosity has and will continue to be a source of inspiration to me. Moreover, I am grateful for his kindness and generosity – he always found time to listen and provide guidance whenever I sought out his advice, was quick to offer keen insights and creative suggestions into chemical problems using his deep understanding of structure/reactivity, and personally funded countless coffee excursions and lunches for the group. There are many more reasons why I will look back on the time in his group with great fondness and pride.

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[1] Taenzler, F. J. *J. Schizo. Chem.* **2022**, *1*, 1.

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Last but not least, none of this would have been possible without my incredibly supportive and caring family. From a young age, my parents, Brian and Julie Cassaidy, instilled the importance of a strong education to me and have always encouraged me to pursue my passions. Every step of the way they have ensured that I have the tools to be successful and their love and support has been absolute through this long and sometimes arduous journey. I also would like to thank my brother and sister, Ben and Lauren, my grandparents, Roger and Jeanne Maharry, and my mother-in-law, Robyn Ticey, for their additional inspiration and support.

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ABSTRACT

A strategy that leverages a [2+2+2] cycloisomerization to open *de novo* access to the Veratrum family of alkaloids has been developed and deployed to achieve the total synthesis of steroidal alkaloids. The highly convergent approach described herein includes (i) the enantioselective synthesis of a diyne fragment containing the steroidal A/B rings, (ii) the asymmetric synthesis of a propargyl-substituted piperidinone (F ring) unit, (iii) the high-yielding union of the above fragments, and (iv) the intramolecular [2+2+2] cycloisomerization reaction of the resulting carbon framework to construct in a single step the remaining three rings (C/D/E) of the hexacyclic cevanine skeleton. From a common cevanine-type intermediate, two concise approaches toward other members of this important family of steroidal alkaloids have been devised, both of which rely on skeletal reorganization.

Chapter 1

Introduction: Total Synthesis of *Veratrum* Alkaloids

1.1. *Veratrum* Alkaloids

1.1A: Structure, Isolation, and Biological Activity

Steroid alkaloids derived from the *Veratrum* genus of liliaceous plants have long been known to possess broad and diverse biological activities that are relevant to human health.[1] More than 100 members of this large family of intricate alkaloids have been isolated to date, all of which share a common C-*nor*-D-*homo* [6-6-5-6] steroid skeleton as opposed to the classic [6-6-6-5] steroid framework. These alkaloids can be further divided into three different structural subtypes based on the connectivity to the distal piperidine (F) ring (Figure 1.1).[2] The cevanine-type alkaloids consist of an entirely fused hexacyclic scaffold, wherein rings E and F comprise a basic nitrogen-containing quinolizidine unit. Members of this group are adorned with varying levels of oxygenation, as exemplified by heilonine (**1.1**) and germine (**1.2**). Despite being the largest subclass of the *Veratrum* family—more than 70 members in total have been isolated to date—only one of them has yielded to chemical synthesis (*vide infra*). As opposed to their cevanine counterparts, the veratramine- and jervine-types are more investigated in terms of their

[1] (a) Roberts, M. F.; Wink, M. *Alkaloids — Biochemistry, Ecology, and Medicinal Applications*; Springer: New York, 1998. (b) Jiang, Q.- W.; Chen, M.-W.; Cheng, K.-J.; Yu, P.-Z.; Wei, X.; Shi, Z. *Med. Res. Rev.* **2016**, *36*, 119−143. (c) Dey, P.; Kundu, A.; Chakraborty, H. J.; Kar, B.; Choi, W. S.; Lee, B. M.; Bhakta, T.; Atanasov, A. G.; Kim, H. S. *Int. J. Cancer* **2019**, *145*, 1731−1744.

[2] For reviews of *Veratrum* alkaloids, see: (a) Greenhill, J. V.; Grayshan, P. *The Cevane Group of Veratrum Alkaloids. Alkaloids*; Academic Press: 1992; Vol. *41*, pp 177−252. (b) Heretsch, P.; Giannis, A. *The Veratrum and Solanum Alkaloids. Alkaloids*; Elsevier: 2015; Vol. *74*, pp 201−232.

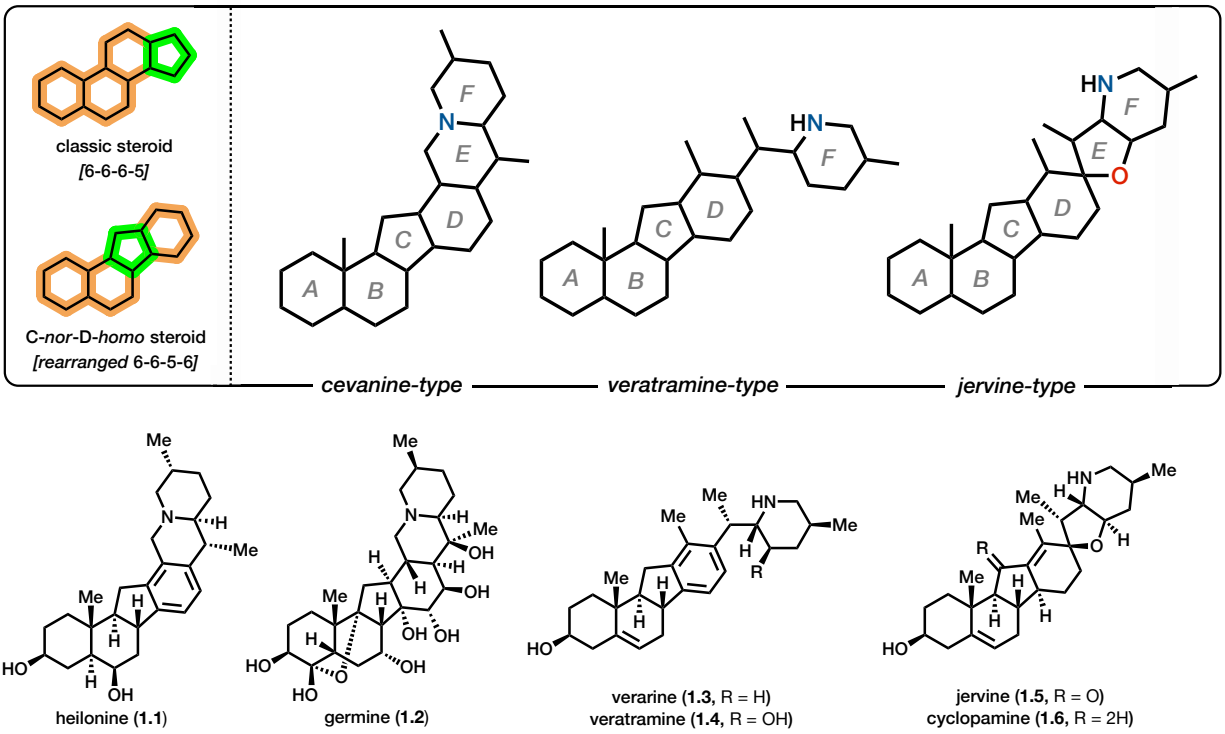

Figure 1.1. Structural characteristics of the *Veratrum* alkaloids and representative members.

synthesis and therapeutic potential. These members can be characterized by either the absence of an E ring or its inclusion as a spirofuran motif (cf. namesake compounds **1.4** and **1.5**, respectively).

The therapeutic potential of plants from the genus *Veratrum* has been recognized and exploited for a very long time. In fact, some of these toxic plants have been used as since medieval times in the treatment of fevers, for purposes of witchcraft, and as poisons, sedatives, emetics, and cardiotonics.[3] Indeed, the rhizome and root material of the plants has been utilized in traditional Chinese medicine for centuries and used by certain Native American tribes in North

[3] Brown, E.; Ragault, M. *Tetrahedron* **1979**, *35*, 911–927, and references therein.

America.[4] Phytochemical investigations during the nineteenth and twentieth centuries led to the discovery and structural elucidation of the causative agents of the promising bioactivities.

The first report of the isolation of *Veratrum* alkaloids came in 1819 from German chemist Carl Friedrich Wilhelm Meißner, where the term "alkaloid" was first coined to describe a dirty-white colored solid—now known to be a mixture of *Veratrum* alkaloids—obtained from the seeds of *Schoenocaulon officiale*.[5] Concurrent investigations by French chemists Caventou and Pelletier into the extracts of *S. officiale* seeds resulted in the isolation of a substance which was given the name veratrine, now known to consist of the highly neurotoxic compounds cevadine and veratridine.[6] Subsequent advances in separation techniques into the early twentieth century saw a rapid increase in new members along with an increased phytochemical understanding. However, these once-promising therapeutics had gradually fallen out of favor due to difficulties in administering safe and effective dosing.[7] In addition to growing concerns over undesirable side effects owing to the narrow therapeutic index, obtention of a reliable supply was often a problem due to fickle growing demands of the wild plants. However, the *Veratrum* alkaloids would soon come back into the spotlight for staggeringly lurid effects in pregnant mammals and their offspring.

In the 1950s, sheep ranchers in Idaho began to observe an alarming increase in cyclopic lambs. An ensuing US Department of Agriculture study uncovered a relationship between the grazing habits of the pregnant ewes with afflicted offspring. It was found that when certain herds would venture up to graze in the high-alpine meadows where the California false hellebore (or

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[4] (a) Li, H.-J.; Jiang, Y.; Li, P. *Nat. Prod. Rep.* **2006**, *23*, 735–752. (b) Chandler, C. M.; McDougal, O. M. *Phytochem. Rev.* **2014**, *13*, 671–694.
[5] Meißner, W. *Schweigger's J. Chem. Phys.* **1819**, *25*, 377–381.
[6] Pelletier, P.; Caventou, J. *Ann. Chim. Phys.* **1820**, *14*, 69–83.
[7] Meilman, E.; Krayer, O. *Circulation* **1950**, *1*, 204–213.

corn lily, *Veratrum californium*) prospers, the malignant birth defects would take hold. Eventually several steroidal alkaloids were isolated and one of them – of unknown structure at the time – effected the same birth defects in high potency and was thus named cyclopamine (**1.6**).[8] Careful stereoscopic analysis and chemical degradation studies of related jervine (**1.5**) revealed the nature of its highly sensitive structure: π orbitals interacting with adjacent spiro-furan C–O σ* renders it unstable to acid. The isolation and structural elucidation efforts paved the way for landmark biological studies by Beachy and coworkers, thus uncovering the mechanism of action to occur through antagonism of surface membrane receptor protein Smoothened (Smo) and downstream inhibition of the sonic hedgehog signaling pathway (Shh).[9] Aberrant activation of this developmental pathway has been linked to growth of certain human tumors, thus cyclopamine has undergone an interesting evolution from teratogenic culprit to indispensable lead for hedgehog-signaling inhibitors as novel anticancer therapies.[10]

1.1B: Biosynthesis

In addition to the three C-*nor*-D-*homo* steroid types of alkaloids described in the previous section, the *Veratrum* sp. also contain two types which possess the classical [6-6-6-5] steroid framework: solanidine and verazine alkaloids (sometimes collectively referred to as *Solanum* alkaloids). While it is surmised that the structurally similar *Solanum* and *Veratrum* alkaloids

[8] (a) Keeler, R. F. *Phytochemistry* **1968**, *7*, 303–306. (b) Keeler, R. F. *J. Agric. Food Chem.* **1969**, *17*, 473–482.
[9] (a) Cooper, M. K.; Porter, J. A.; Young, K. E.; Beachy, P. A. *Science* **1998**, *280*, 1603–1607. (b) Chen, J. K.; Taipale, J.; Cooper, M. K.; Beachy, P. A. *Genes Dev.* **2002**, *16*, 2743–2748.
[10] (a) Taipale, J.; Chen, J. K.; Cooper, M. K.; Wang, B.; Mann, R. K.; Milenkovic, L.; Scott, M. P.; Beachy, P. A. *Nature* **2000**, *406*, 1005–1009. (b) Rubin, L. L.; de Sauvage, F. J. *Nat. Rev. Drug Disc.* **2006**, *5*, 1026–1033. (c) Scales, S. J.; de Sauvage, F. J. *Trends Pharmacol. Sci.* **2009**, *30*, 303–312. (d) Lee, S. T.; Welch, K. D.; Panter, K. E.; Gardner, D. R.; Garrossian, M.; Chang, C.-W. T. *J. Agric. Food Chem.* **2014**, *62*, 7355−7362.

arise from the same biosynthetic pathway, the total biosynthesis of many congeners remains only partially elucidated (Scheme 1.1). Moreover, the biosynthesis of steroidal alkaloids is closely related to that of sapogenins (e.g., hecogenin, diosgenin), with both occurring together in plants.[11] Kaneko elegantly discovered the biosynthetic origins and identified cholesterol as the common precursor using radiolabeled carbon isotopes.[12] A series of oxidations along the cholesterol side chain sets the stage for piperidine (F-ring) formation via nitrogen installation and cyclization. As many *Veratrum* alkaloids are stereoisomeric about the EF rings, one can imagine an initial oxidation at either of the diastereotopic methyl groups on the side chain could be a plausible origin for stereodivergence in the biosynthetic pathway. Using ^{15}N-labelled amino acids, Kaneko also demonstrated that L-arginine is the most likely source of nitrogen in the biosynthesis (Scheme 1.1; Part A).[13] It has also been demonstrated that substitution of the C26 hydroxyl group by the amino group occurs directly instead of proceeding through an intermediate 26-oxo species.[14] Formation of the E-ring is achieved by C16 oxidation and ensuing ATP-driven phosphorylation; ensuing cyclization onto the piperidine furnishes solanidine (Part B).[15] Site-specific oxidations at either C18 or C12 represent a point of bifurcation in the biosynthesis: the former giving rise to the cevanine skeleton and the latter to veratramine- and jervine-types.

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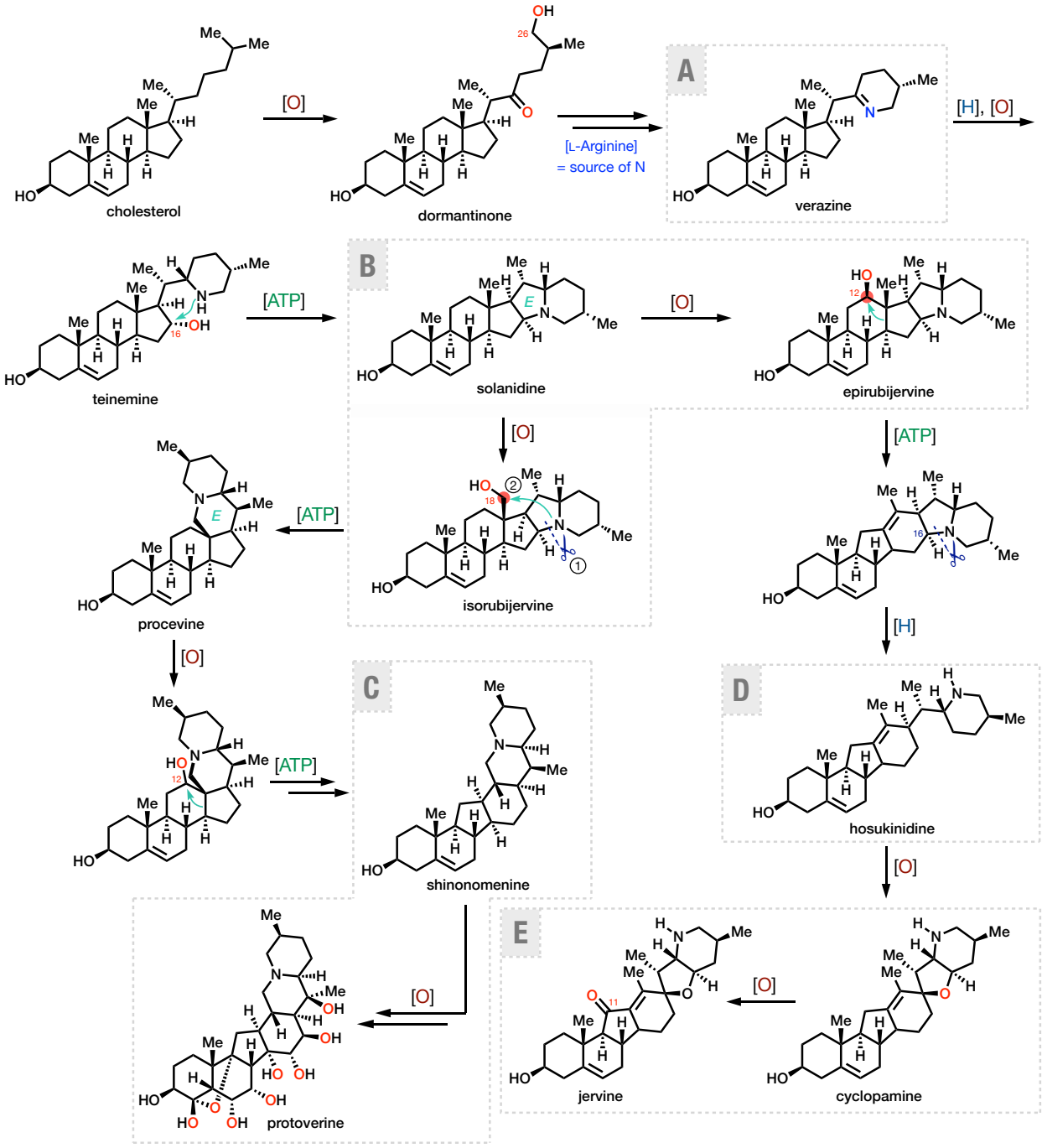
[11] Ripperger, K.; Schreiber, K. In *The Alkaloids*; Mankse, R. F. H.; Rodrigo, R. G. A., Eds., Academic Press: New York, 1981; Vol. 19, pp 81–192.
[12] Kaneko, K.; Mitsuhashi, H.; Hirayama, K.; Yoshida, N. *Phytochemistry* **1970**, *9*, 2489–2495.
[13] Kaneko, K.; Tanaka, M. W.; Mitsuhashi, H. *Phytochemistry* **1976**, *15*, 1391–1393.
[14] Ronchetti, F.; Russo, G.; Ferrara, G.; Vecchio, G. *Phytochemistry* **1975**, *14*, 2423–2425.
[15] Kaneko, K.; Watanabe, M.; Taira, S.; Mitsuhashi, H. *Phytochemistry* **1972**, *11*, 3199–3202.



Scheme 1.1. Biosynthetic pathways to the *Veratrum* alkaloid subfamilies.

The pathway to cevanine alkaloids commences with successive reductive opening of the E-ring of isorubijervine and ATP-driven cyclization to give isolated intermediate procevine.[16] This skeletal rearrangement process may also proceed through initial quaternization to an ammonium salt prior to reductive cleavage of the C(16)–N bond – a sequence of events that is supported by chemical synthetic studies.[17] Either hypothetical scheme leads to procevine, where an oxidation at C12 and leaving-group activation of the intermediate secondary alcohol as a phosphate sets up a Wagner-Meerwein rearrangement to afford the cevanine skeleton. Further unspecified oxidation along the "bottom" edge of the scaffold gives rise to the many highly oxygenated cevanine congeners (Part C; *cf.* shinonomenine → protoverine).

The alternative oxidation at C12 of solanidine opens access to the C-*nor*-D-*homo* core of the veratramine- and jervine-type alkaloids via a Wagner-Meerwein rearrangement. Indeed, such a biosynthetic hypothesis is supported by chemical rearrangements described in the 1950s and an identical biomimetic strategy that was successfully employed in the chemical synthesis of cyclopamine, both of which will be discussed in Section 1.1C and 1.1E, respectively. Reductive cleavage of the C(16)–N bond would furnish the veratramine-type skeleton (Part D) and further oxidation to introduce the spirofuran motif leads to the jervine-type skeleton. Cyclopamine was also found to be the biosynthetic precursor to its C11 oxidation product jervine, but it is not a progenitor to veratramine (Part E).[18] Since the pioneering studies by Kaneko in the 1970s into the biosyntheses of steroidal alkaloids, there has been virtually no studies into the biosynthetic machinery of these pathways using modern biochemical methods. Chemical synthesis has

[16] Kaneko, K.; Kawamura, N.; Mitsuhashi, H.; Ohsaki, K. *Chem. Pharm. Bull.* **1979**, *27*, 2534–2536.
[17] Pelletier, S. W.; Jacobs, W. A. *J. Am. Chem. Soc.* **1953**, *75*, 4442–4446.
[18] Kaneko, K.; Mitsuhashi, H.; Hirayama, K.; Ohmori, S. *Phytochemistry* **1970**, *9*, 2497–2501.

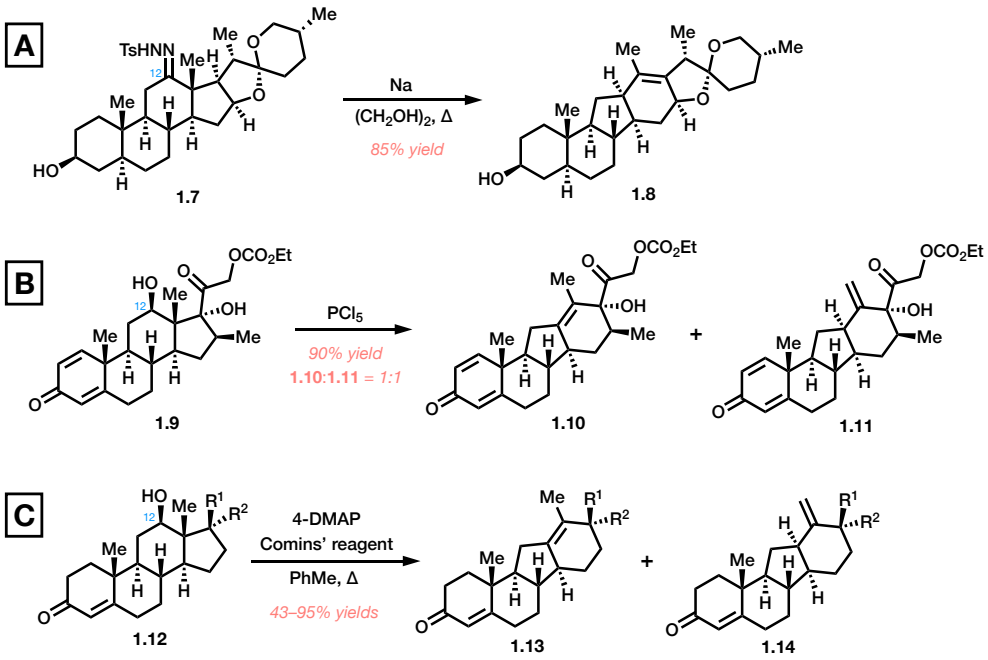
historically played a role in the understanding and can continue to stimulate a renewed interest into the biogenesis of this family of natural products.

1.1C: Previous Synthetic Approaches toward the C-nor-D-homo Core

Whereas preparation classical steroid structure has been the subject of intense efforts over the past century, the C-*nor*-D-*homo* counterparts have received much less attention. The unique structure of these rearranged steroids presents substantial challenges to the practicing synthetic chemist. Despite this fact, there have been several elegant strategies employed for the construction of the rearranged steroidal skeleton that is found in the *Veratrum* alkaloids. The seminal strategies relied on a biomimetic approach, wherein a "classical" [6-6-6-5] steroid serves as a precursor to a Wagner-Meerwein rearrangement. In contrast, robust ring-by-ring approaches have been successfully utilized to access the ABCD steroid framework of the *Veratrum* alkaloids. Many of these synthetic campaigns relied heavily on the use of classical annulation reactions (e.g., Robinson annulation). Other creative strategies have also emerged that elegantly and efficiently construct the homosteroid framework through a masterfully employed "key" transformation, in some cases forming several rings in a single step.

The first application of a biomimetic approach was reported by Merck in the 1950s, as alluded to in the previous section. The research group at Merck found that thermolysis of hecogenin derivative **1.7**, which contains a tosylhydrazone at C12, afforded C-*nor*-D-*homo* steroid **1.8** in high yield (Scheme 1.2A).[19] It was proposed that the reaction mechanism entails

[19] (a) Hirschmann, R.; Snoddy, Jr., C. S.; Hiskey, C. F.; Wendler, N. L. *J. Am. Chem. Soc.* **1954**, *76*, 4013–4025. (b) Hirschmann, R.; Snoddy, Jr., C. S.; Wendler, N. L. *J. Am. Chem. Soc.* **1952**, *74*, 2692–2694. (c) Hiskey, C. F.; Hirschmann, R.; Wendler, N. L. *J. Am. Chem. Soc.* **1953**, *75*, 5135–5136.

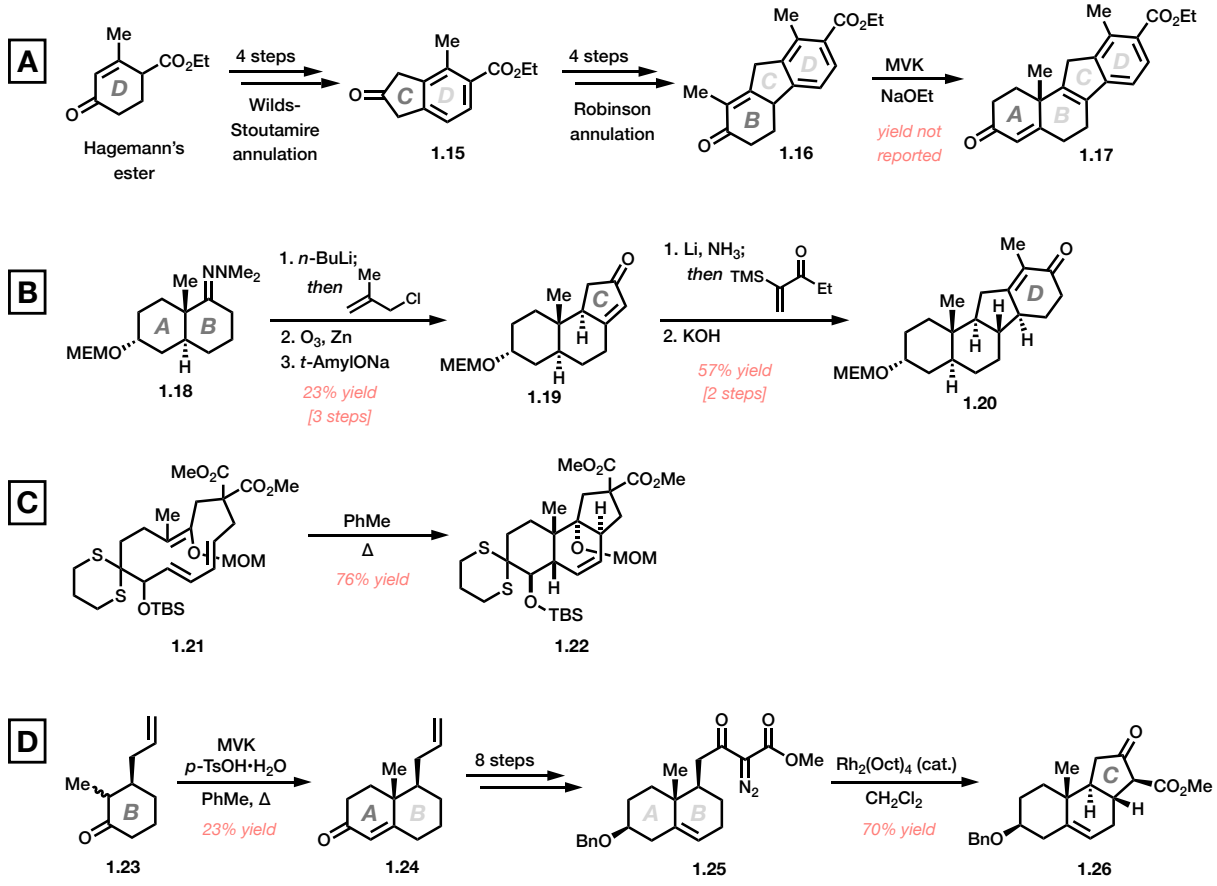


Scheme 1.2. Biomimetic approaches to C-*nor*-D-*homo* steroids.

concerted migration of the C–C bond and removal of H17 led to the high selectivity. The same group also discovered the same rearrangement via the mesylate, however a mixture of endo- and exocyclic olefins resulted. Since these remarkable achievements, several other groups have modified the general strategy involving the installation of a leaving moiety at C12 to trigger a biomimetic rearrangement. Schering-Plough reported a similar approach relying on *in situ* activation and dehydrative elimination of a 12β-hydroxyl (in **1.9**), which led to the formation of rearranged endo (**1.10**) and exo (**1.1**) olefins (Scheme 1.2B).[20] Another convenient modification was reported by Giannis and coworkers and involves a relatively mild combination of reagents (DMAP, Comins' reagent) to induce the Wagner-Meerwein rearrangement and allowed the authors to demonstrate their methodology on a series of derivatives containing more sensitive functionality (Scheme 1.2C).[21] The broad scope that was evaluated exhibited generally good endo selectivity, leading to the formation of **1.13** as the major isomer in most cases.

[20] Fu, X.; Chan, T.-M.; Tann, C.-H.; Thiruvengadam, T. K. *Steroids* **2002**, *67*, 549–554.
[21] Heretsch, P.; Rabe, S.; Giannis, A. *J. Am. Chem. Soc.* **2010**, *132*, 9968−9969.

The ring-by-ring approach to C-*nor*-D-*homo* steroids is inherently more linear but has greatly benefited from the robust application of classical transformations to access targets with preinstalled functional handles for further elaboration. The first totally synthetic entry into the C-*nor*-D-*homo* steroid structure was achieved by W. S. Johnson and coworkers in 1967.[22] Their approach commenced with Hagemann's ester and a Wilds-Stoutamire annulation (i.e., alkylation with ethyl β-ethoxy-γ-bromocrotonate, hydrolysis, and Knoevenagel-type condensation) to introduce the C-ring. Further elaboration gave 2-indanone **1.15**, which served as a suitable precursor for two sequential Robinson annulations (Scheme 1.3A). The first Robinson annulation



Scheme 1.3. Ring-by-ring approaches to C-*nor*-D-*homo* steroids.

[22] Johnson, W. S.; Cox, J. M.; Graham, D. W.; Whitlock, Jr., H. W. *J. Am. Chem. Soc.* **1967**, *89*, 4524-4526.

entailed the employment of ethyl vinyl ketone in a four-step protocol to provide BCD enone **1.16**. A second Robinson annulation furnished the remaining A ring and gave compound **1.17**, whereupon further elaboration resulted in the first synthesis of veratramine (see Section 1.1E). Brown and Leberton also devised a similar approach, but complementary sequence of ring formation, starting from a Wieland-Miescher ketone derivative containing resident A and B rings (Scheme 1.3B).[23] Thus, alkylation of **1.18** and a subsequent ozonolysis followed by aldol cyclization/dehydration formed the C ring of **1.19**, which was subjected to a tandem sequence involving a stereoselective conjugate reduction and Robinson annulation to give **1.20** in good yield.

Several other ring-by-ring approaches have been demonstrated in the construction of the ABC tricyclic core substructure. One particularly noteworthy and elegant example was reported by Deslongchamps, employing a transannular Diels-Alder reaction of a 13-membered macrocyclic triene (**1.21** → **1.22**; Scheme 1.3C).[24] Notably, this strategy allowed access to 9α-hydroxyl which could be poised to form the conspicuous hemiketal of several highly oxygenated cevanine-type congeners (cf. germine). Another more recent approach to the 6-6-5 tricycle from the Taber laboratory utilized a Robinson annulation of optically active cyclohexanone **1.23** (Scheme 1.3D).[25] The resultant octalone **1.24** was elaborated to α-diazo β-keto ester **1.25**, which underwent a Rh-mediated cyclization to smoothly afford tricycle **1.26** as a single diastereomer.

In addition to the aforementioned strategies, a few more miscellaneous and highly creative strategies deserve to be noted. A radical cascade sequence, reported by Pattenden and

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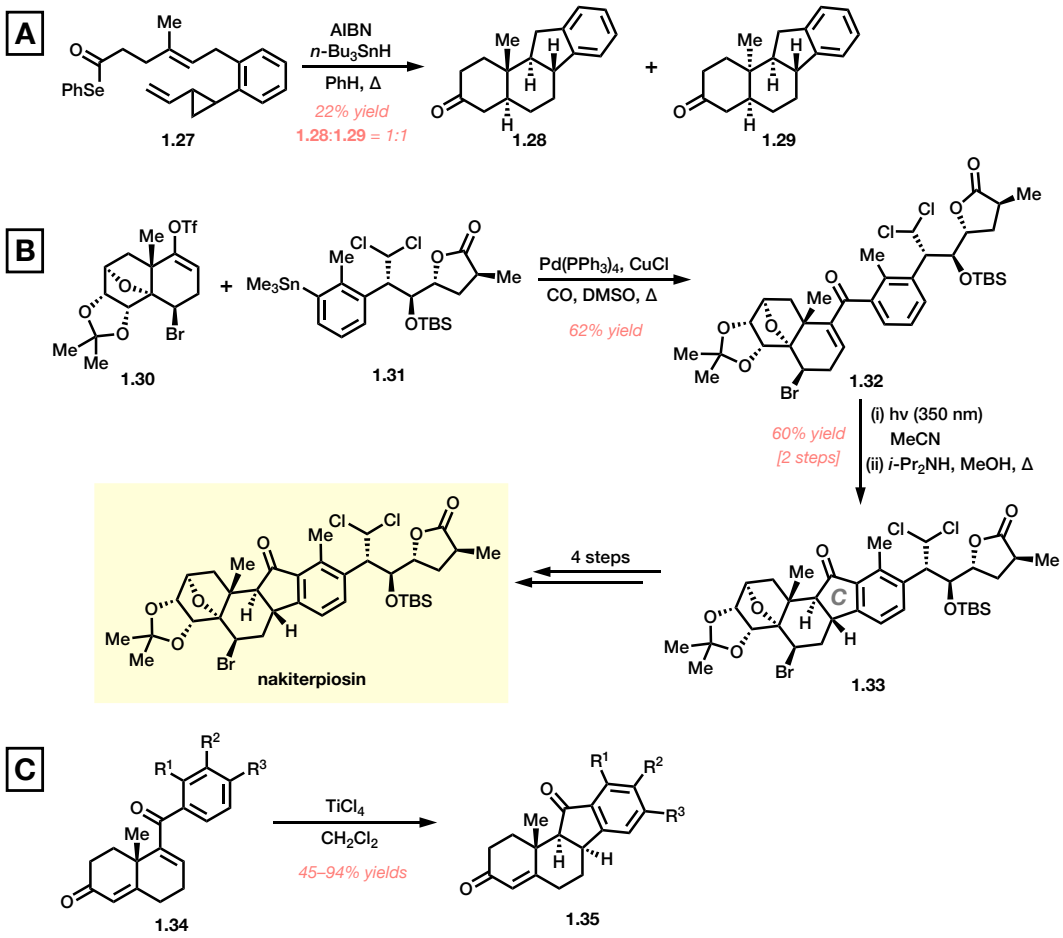
[23] (a) Brown, E.; Lebreton, J. *Tetrahedron Lett*. **1986**, *27*, 2595−2598. (b) Brown, E.; Lebreton, J. *Tetrahedron* **1987**, *43*, 5827−5840.
[24] Quimpère, M.; Ruest, L.; Deslongchamps, P. *Can. J. Chem.* **1992**, *70*, 2335−2349.
[25] Taber, D. F.; Berry, J. F. *J. Org. Chem*. **2013**, *78*, 8437−8441.



Scheme 1.4. Miscellaneous approaches to C-*nor*-D-*homo* steroids.

coworkers, utilizing acyl radical precursor **1.27** first underwent a 13-endo-trig macrocyclization onto the pendant vinyl cyclopropane substituent when treated with Bu_3SnH—AIBN (Scheme 1.4A).[26] Transannulation of the resulting benzyl radical in a 5-exo-trig fashion, followed by a final 6-exo-trig transannulation furnished C-*nor*-D-*homo* steroids **1.28** and **1.29**. The venerable Nazarov cyclization and variations thereof has been used to great advantage to synthesize substituted cyclopentenones in complex settings. In their landmark synthesis of nakiterpiosin, Chen and coworkers prepared cyclization precursor **1.32** through a carbonylative Stille coupling between vinyl triflate **1.30** and arylstannane **1.31** (Scheme 1.4B).[27] Photoirradiation of an

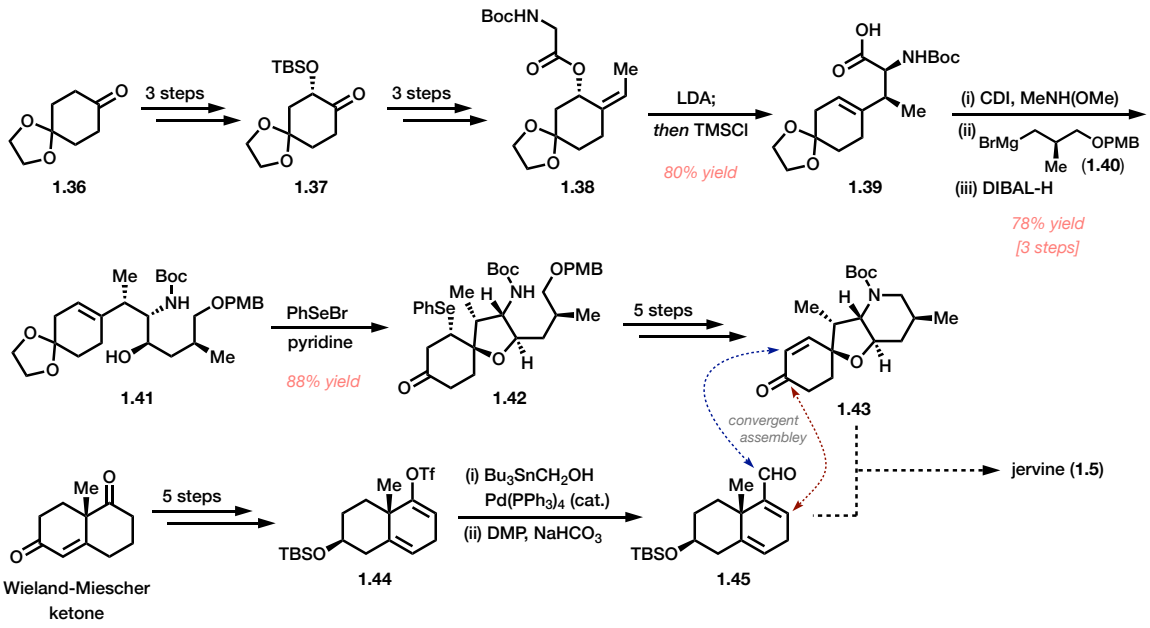
[26] Pattenden, G.; Stoker, D. A.; Winne, J. M. *Tetrahedron* **2009**, *65*, 5767−5775.
[27] Gao, S.; Wang, Q.; Chen, C. *J. Am. Chem. Soc.* **2009**, *131*, 1410−1412.

acetonitrile solution containing **1.32** promoted the formation of the C-ring by way of a Nazarov cyclization, then an ensuing epimerization step afforded **1.33** as a single diastereomer. Four additional steps completed the total synthesis of nakiterpiosin. The same strategy was later used by Giannis and coworkers, where the authors demonstrated a Lewis acid-mediated Nazarov cyclization strategy to transform a series of simpler derivatives of type-**1.34** to C-*nor*-D-*homo* steroids **1.35** containing a polysubstituted aromatized D ring (Scheme 1.4C).[28] All of the strategies described in this section paved the way for the total synthesis of the *Veratrum* family of alkaloids, which is described in Section 1.1E.

1.1D: Previous Synthetic Approaches toward the Veratrum Alkaloids

In addition to the C-*nor*-D-*homo* steroid skeleton, some of the other structural challenges posed by the *Veratrum* alkaloids have been addressed by the development of creative and enabling approaches. Very recently, the Johnson group concurrently reported two potential solutions to the spirofuran DEF ring system. One of those strategies commenced with an enantioselective α-aminoxylation of ketone **1.36** to provide α-siloxyketone **1.37** in three steps (Scheme 1.5)[29]. This intermediate was efficiently elaborated to **1.38**, then an Ireland-Claisen rearrangement was used to deliver **1.39** with excellent stereocontrol over the vicinal stereogenic centers. The authors next investigated a (3 + 3) piperidine (F ring) construction using a dipolar synthon (**1.40**), finding that the addition of the Grignard reagent to Weinreb amide of **1.39** and a subsequent chelation-controlled reduction stereoselectively furnished **1.41**. The spirofuran (E ring) was formed through a selenoetherification and closure of the F ring was accomplished in

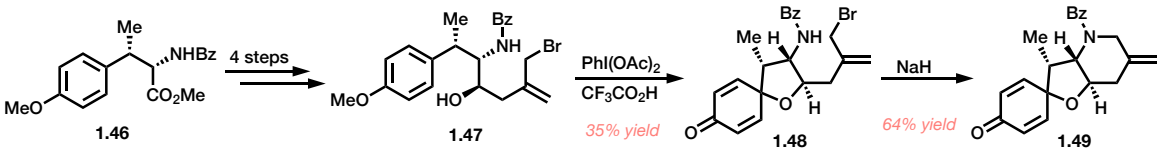
[28] Krieger, J.; Smeilus, T.; Schackow, O.; Giannis, A. *Chem. - Eur. J.* **2017**, *23*, 5000−5004.
[29] Zavesky, B. P.; De Jesus Cruz, P.; Johnson, J. S. *Org. Lett*. **2020**, *22*, 3537−3541.



Scheme 1.5. Synthesis of DEF (**1.43**) and AB (**1.45**) fragments by Johnson and coworkers.

several additional steps to give a fully functionalized DEF fragment **1.43**. A complementary steroidal AB ring fragment (**1.45**) for a potential *de novo* synthesis of jervine was also prepared seven steps from Wieland-Miescher ketone. If the two fragments were conjoined as shown in Scheme 1.5, then a *de novo* total synthesis of a jervine could be accomplished from this highly convergent strategy.

The same group also disclosed an oxidative dearomatization-based approach to furnish the DEF-ring core (Scheme 1.6).[30] Hence, **1.46** was prepared and the corresponding Weinreb amide underwent the addition of a Grignard reagent and a similar substrate-controlled 1,2-reduction, as previously mentioned, to provide **1.47**. This material underwent an oxidative

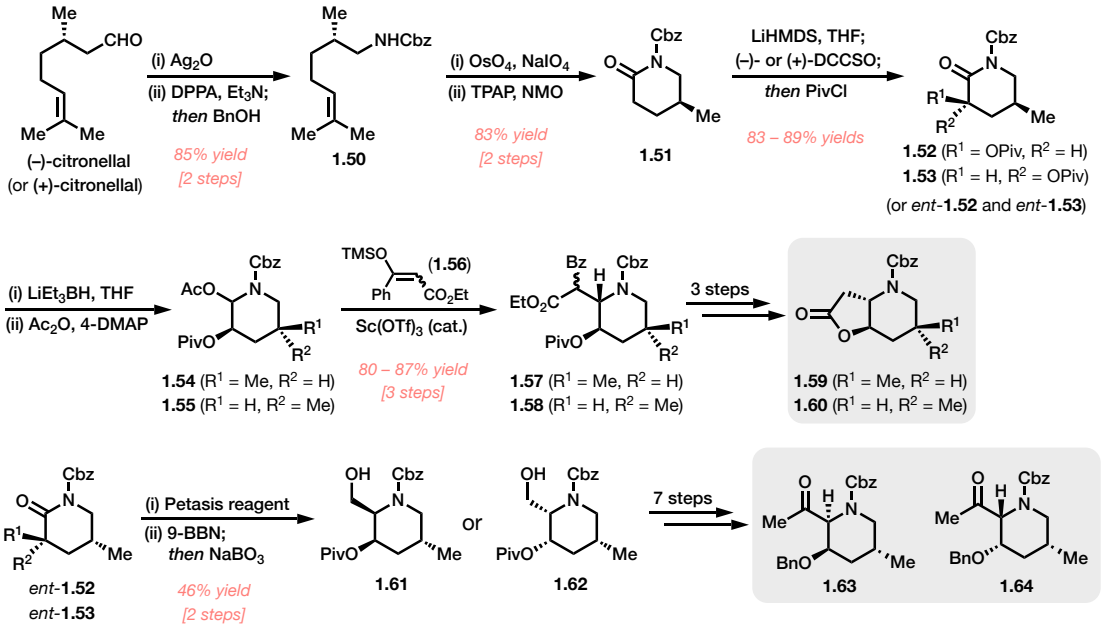


Scheme 1.6. Alternative synthesis of a DEF fragment (**1.49**) by Johnson and coworkers.

[30] Horwitz, M. A.; Robins, J. G.; Johnson, J. S. *J. Org. Chem.* **2020**, *85*, 6808−6814

dearomative cyclization (→ **1.48)**, followed by a base-mediated *N*-alkylation to bidirectionally close to E and F rings, respectively, and provide **1.49** with a fully installed DEF stereotriad.

Giannis and coworkers have also disclosed an enantiospecific and diastereodivergent approach to all possible stereoisomers of the piperidine F ring (Scheme 1.7).[31] The authors reported that either the (+)- or (–)-enantiomer of commercially available citronellal can be elaborated to protected amine **1.50** using a Curtius rearrangement, then an oxidative lactamization protocol affords piperidinone **1.51**. A reagent-controlled α-hydroxylation of a lactam enolate was then performed, where either enantiomer of 8,8-dichlorocamphoryl-sulfonyl oxaziridine (DCCSO) selectively delivers either **1.52** or **1.53** after a same-pot protection.



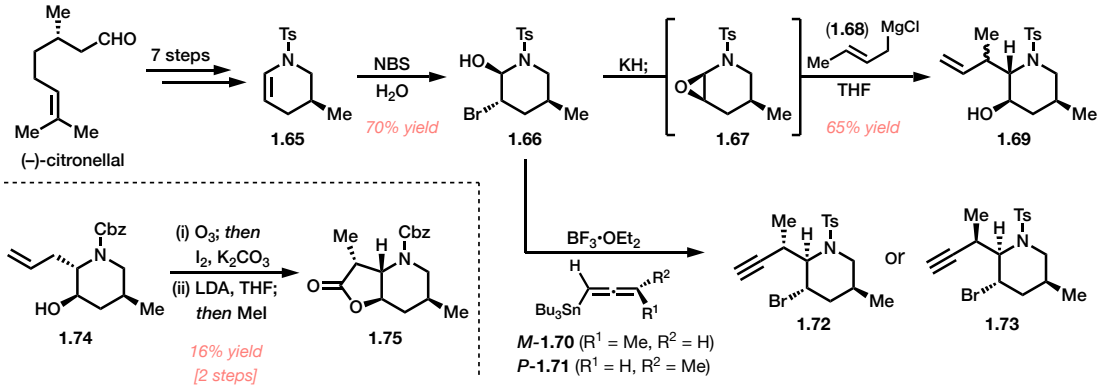
Scheme 1.7. Synthesis of stereoisomeric piperidine building blocks by Giannis and coworkers.

Chemoselective reduction and acetylation afforded **1.54** (or **1.55**), where subsequent Lewis-acid catalyzed substitution with TMS enol ether **1.56** gave **1.57** (or **1.58**) and further elaboration to **1.59** (or **1.60**) was also achieved. A diastereomeric set of derivatives (**1.63** and **1.64**) was also

[31] Heretsch, P.; Rabe, S.; Giannis, A. *Org. Lett.* **2009**, *11*, 5410−5412

prepared in a seven-step sequence from **1.61** (or **1.62**), which was accessed using *ent*-**1.52**/**53** via a Petasis methylenation and hydroboration–oxidation.

Taber and DeMatteo later published an improved route to a similar set of piperidine chirons which contain the ring-adjacent methyl group-bearing stereocenter (Scheme 1.8).[32] As before, enantiospecific preparation of piperidine **1.65** was achieved using (–)-citronellal, then this intermediate was treated with *N*-bromosuccinimide and the resulting bromohydrin (**1.66**) was converted in epoxide **1.67** *in situ*, followed by addition of Grignard reagent **1.68** to provide

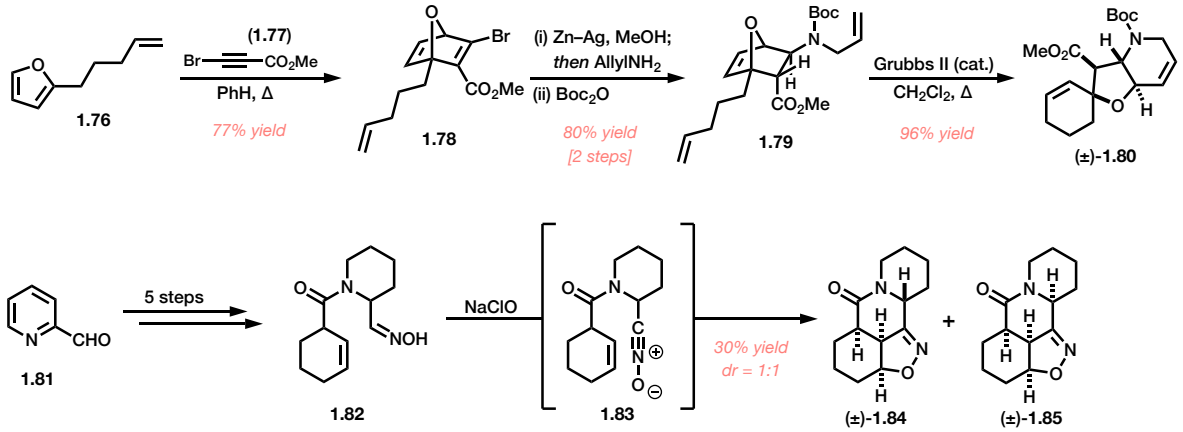


Scheme 1.8. Synthesis of piperidine building blocks by Taber and DeMatteo.

1.69 (as a 1:1 mixture of diastereomers). Giannis' intermediate **1.74** could be accessed in six steps using an analogous sequence to the one described above, whereupon α-methylation of the thus formed lactone gives **1.75** as a single diastereomer. Alternatively, bromohydrin **1.66** can undergo reagent-controlled Marshall-type propargylation with enantiomeric allenylstannanes *M*-**1.70** or *P*-**1.71** to stereoselectively afford **1.72** or **1.73**, respectively.

Some other concise synthetic approaches based on efficient ring-forming transformations have also been identified (Scheme 1.9). Wright and coworkers reported a tandem metathesis reaction of oxabicylo[2.2.1]heptene **1.79**, which was expediently prepared from **1.78** (accessed

[32] Taber, D. F.; DeMatteo, P. W. *J. Org. Chem*. **2012**, *77*, 4235−4241.

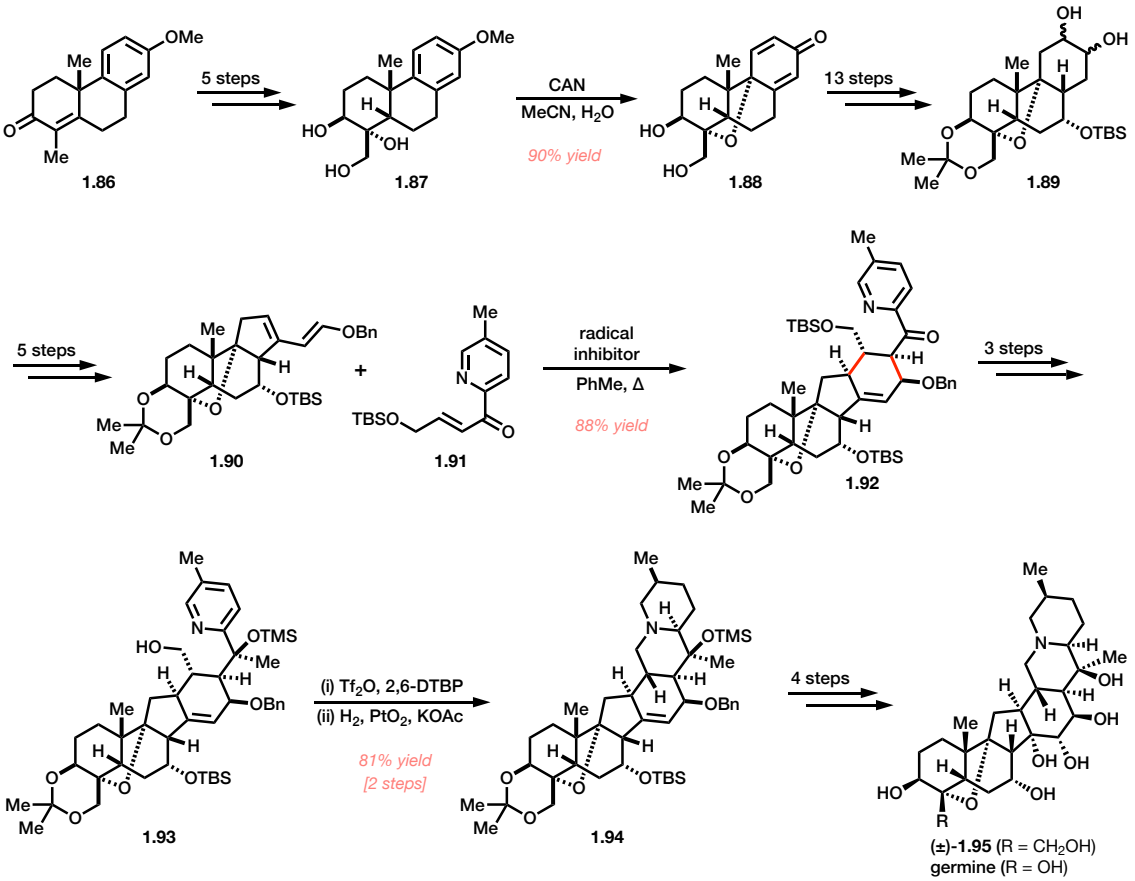


Scheme 1.9. Synthesis of spirocyclic DEF fragment (±)-**1.80** by Wright and coworkers (top) and cevanine DEF substructures by Yarnold and coworkers (bottom).

via a Diels-Alder reaction between **1.76** and **1.77**).[33] Upon exposure to second-generation Grubbs catalyst, the strained endocyclic alkene of **1.79** underwent ring-opening metathesis and two-consecutive ring-closing metathesis reactions with the pendant α-olefins to furnish (±)-**1.80**. One other approach utilized a 1,3-dipolar cycloaddition of nitrile oxide **1.83** to deliver EFG tricycles (±)-**1.84** and (±)-**1.85** of the cevanine-type.[34] While the key cycloaddition step was not diastereoselective, the modular assembly of oxime **1.82** may permit a more thorough evaluation for potential substrate-controlled selectivity.

In 2017, several few months before the work described in the remaining chapters started, the late great Gilbert Stork disclosed a remarkable total synthesis of (±)-4-methylenegermine ((±)-**1.95**; Scheme 1.10).[35] The total synthesis commenced from readily available tricycle **1.86**, which was elaborated to **1.87** to be subjected to an oxidative dearomatization and furnish dienone **1.88**. Further functionalization and protecting group manipulation gave an isomeric

[33] Oblak, E. Z.; G-Dayanandan, N.; Wright, D. L. *Org. Lett.* **2011**, *13*, 2433−2435.
[34] Jones, K.; Newton, R. F.; Yarnold, C. J. *Tetrahedron* **1996**, *52*, 4133−4140.
[35] Stork, G.; Yamashita, A.; Hanson, R. M.; Phan, L.; Phillips, E.; Dubé, D.; Bos, P. H.; Clark, A. J.; Gough, M.; Greenlee, M. L.; Jiang, Y.; Jones, K.; Kitamura, M.; Leonard, J.; Liu, T.; Parsons, P. J.; Venkatesan, A. M. *Org. Lett*. **2017**, *19*, 5150−5153.



Scheme 1.10. Synthesis of (±)-4-methylenegermine (**1.95**) by Stork and coworkers.

mixture of diols (**1.89**), which underwent ring contraction using oxidative cleavage—aldol cyclization and homologation of a resultant enal (not shown) to deliver diene **1.90**. A refluxing toluene solution of the thus obtained diene and dienophile **1.91** in the presence of a radical inhibitor, 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide, afforded endo Dies-Alder adduct **1.92**. The remarkably high stereoselectivity, also studied computationally in collaboration with the Houk group, was attributed to favorable secondary orbital interactions in endo transition state and approach of the dienophile from the face that avoids destabilizing O···O lone pair repulsion (i.e., top face, as shown in Scheme 1.10) between the dienophile carbonyl and OTBS groups in the endo-TS structure.[36] Subsequent elaboration to intermediate **1.93** set the stage of for a final

[36] Xue, X.-S.; Levandowski, B. J.; He, C. Q.; Houk, K. N. *Org. Lett.* **2018**, *20*, 6108–6111.

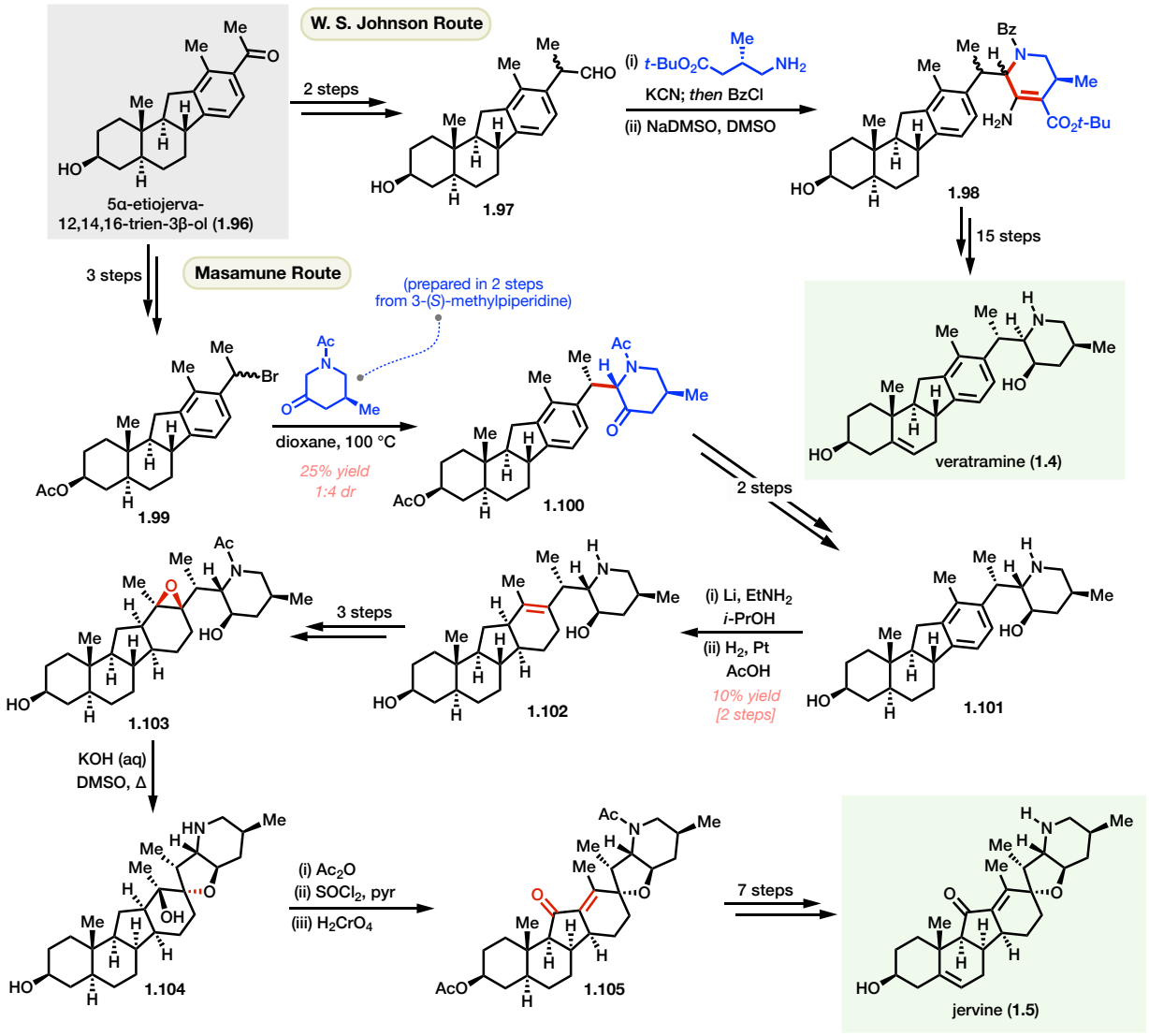
cyclization to give a pyridinium salt, which was hydrogenated from the more accessible α-face to stereoselectively deliver the quinolizidine substructure of **1.94**. A final dihydroxylation and removal of all protecting groups afforded (±)-**1.95**: racemic germine having an additional methylene group at C4. Stork sadly passed away before excision of the extraneous $–CH_2–$ could be realized, however this monumental achievement stands alone on the basis of masterful synthetic design by one of the greatest of all time.

1.1E: Previous Syntheses of Veratrum Alkaloids

The earlier synthetic studies into the *Veratrum* alkaloids culminated in concurrent syntheses of veratramine and jervine by the research groups of Johnson and Masamune, respectively (Scheme 1.11). Both strategies featured the assembly of the piperidine moiety onto a common C-*nor*-D-*homo* steroid starting framework. The starting material that was employed by both groups, 5α-etiojerva-12,14,16-trien-3β-ol, could be accessed via a known degradation of hecogenin or prepared synthetically and in optically pure form via ring-by-ring approach from Hagemann's ester and chiral resolution (see Section 1.1C). In addition to showcasing the power of a convergent strategy, these landmark achievements set a benchmark for the *Veratrum* alkaloids that even organic chemists equipped with more modern synthetic toolkits will strive to reach (*vide infra*).

In the Johnson route, homologation of the aryl ketone to an epimeric mixture of aldehydes (**1.97**) was achieved using a tandem Corey-Chaykovsky reaction–Meinwald rearrangement.[37] A Strecker reaction between **1.97** and L-*t*-butyl 3-methyl-4-aminobutyrate,

[37] Johnson, W. S.; DeJongh, H. A. P.; Coverdale, C. E.; Scott, J. W.; Burckhardt, U. *J. Am. Chem. Soc*. **1967**, *89*, 4523− 4524.



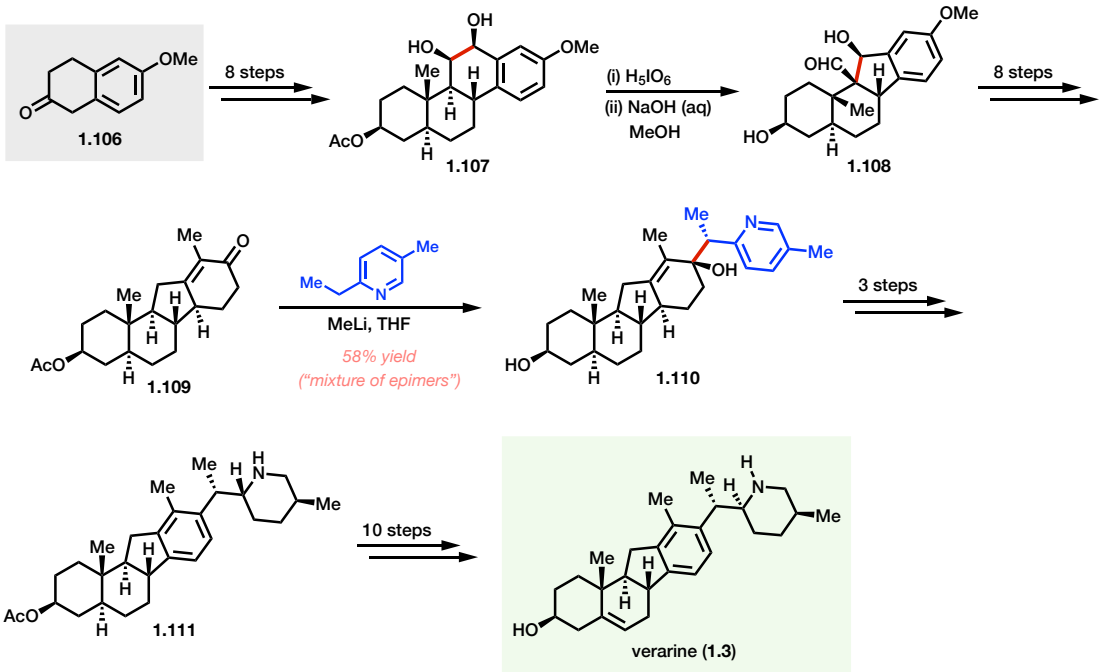
Scheme 1.11. Total syntheses of veratramine (**1.4**) and jervine (**1.5**) by the respective groups of Johnson and Masamune.

followed by benzoylation and Dieckmann-type condensation afforded enamino ester **1.98**. Subsequent protecting group and oxidation state manipulations afforded veratramine (**1.4**) in 15 additional steps.

The Masamune route commenced with the alkylation of **1.99**, prepared in 3 steps from 5α-etiojerva-12,14,16-trien-3β-ol, with a 3-piperidone derivative that could be expediently

accessed from 3-(*S*)-methylpiperidine.[38] The low yield which is attributed to the poor diastereoselectivity could be partially remediated by equilibration, separation of the diastereomers, and repeating epimerization. Birch reduction of the ketone and saponification gave **1.101**; further reduction of the aromatic ring under Benkeser conditions and hydrogenation afforded **1.102**. Epoxidation of the tetrasubstituted olefin furnished epoxide **1.103**, which underwent intramolecular cyclization to **1.104** upon refluxing an alkali solution in DMSO. Selective acetylation, followed by elimination of the tertiary alcohol, and allylic oxidation afforded **1.105**, which was further elaborated to jervine (**1.5**).

Ensuing synthetic efforts by the Kutney group also resulted in a successful foray into the *Veratrum* family (Scheme 1.12). Their total synthesis of verarine also features a convergent coupling of the heterocyclic motif onto a homosteroid framework, however an unsaturated



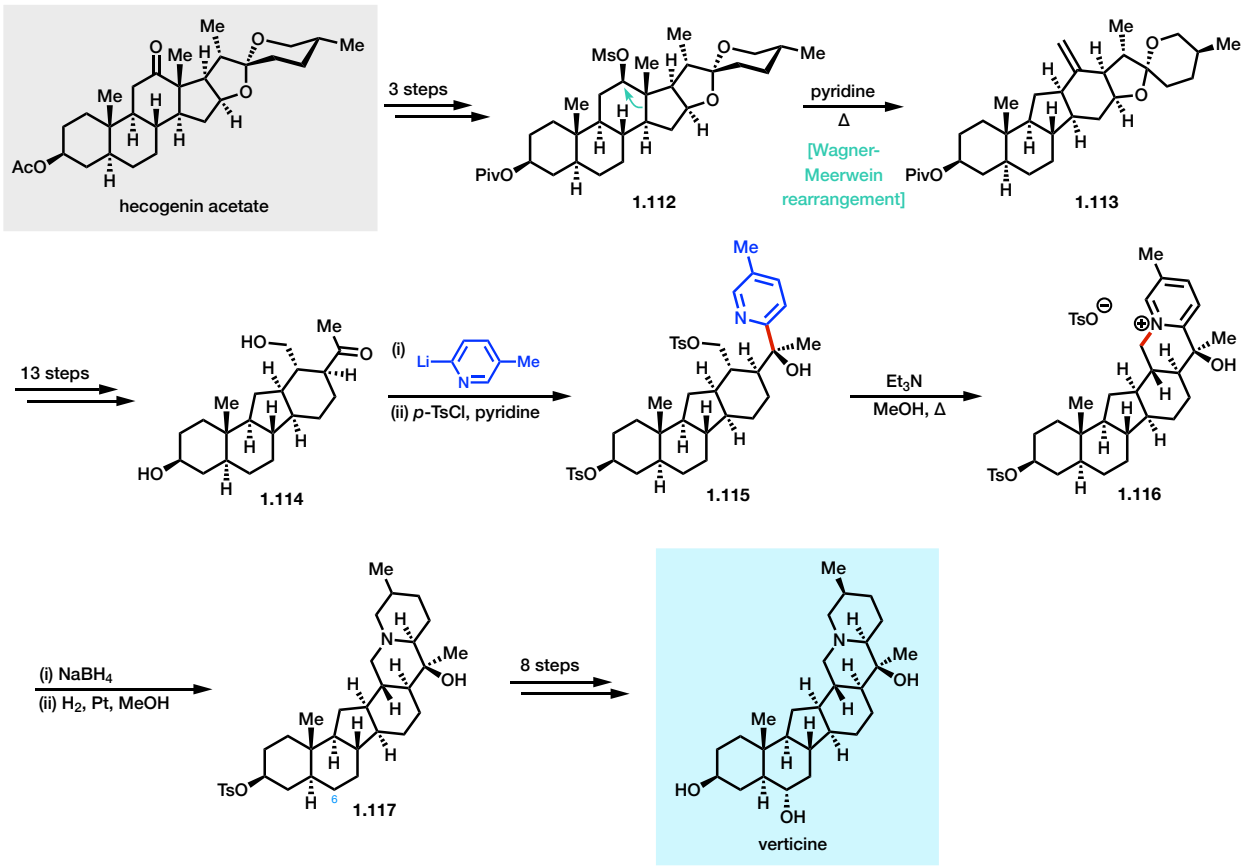
Scheme 1.12. Total synthesis of verarine (**1.3**) by Kutney and coworkers.

[38] Masamune, T.; Takasugi, M.; Murai, A.; Kobayashi, K. *J. Am. Chem. Soc*. **1967**, *89*, 4521−4523.

pyridine chiron was employed in contrast to the saturated counterparts in the Johnson and Masamune syntheses.[39] Starting from 6-methoxy-2-tetralone (**1.106**), a series of Robinson annulations efficiently constructed tetracyclic diol **1.107** in eight steps. In order to obtain the C-*nor*-D-*homo* skeleton, the C ring was contracted via oxidative cleavage of the diol and aldol cyclization of the resulting dialdehyde to furnish **1.108**. Further elaboration to **1.109** was achieved in eight steps by way of Birch reduction and removal of superfluous hydroxyl and aldehyde functional groups. The coupling steroid fragment (**1.109**) with the lithio derivative of 2-ethyl-5-methylpyridine afforded **1.110** as a mixture of epimers in 58% yield. The desired epimer was isolated and the D ring was rearomatized. Selective hydrogenation of the pyridine moiety unveiled the latent piperidine ring and provided **1.111**, then a final 10-step sequence involving protecting group and oxidation state manipulations afforded verarine (**1.3**).

Kutney later reported the synthesis of verticine, the first and only synthesis of the expansive cevanine-type subfamily that has been reported prior to publication of the work described herein (Scheme 1.13).[40] Starting from hecogenin acetate, mesylate **1.112** was prepared and underwent a Wagner-Meerwein upon refluxing in anhydrous pyridine to give C-*nor*-D-*homo* steroid **1.113** bearing an exocyclic olefin. A 13-step sequence involving olefin hydroboration and a deconstruction of the ketal portion was employed to give methyl ketone **1.114**. Taking precedent from Schreiber and Adam in their synthesis of *Solanum* alkaloids, the subsequent pivotal step involves the coupling of a pyridyl anion with a steroidal ketone.[41] As such, treatment

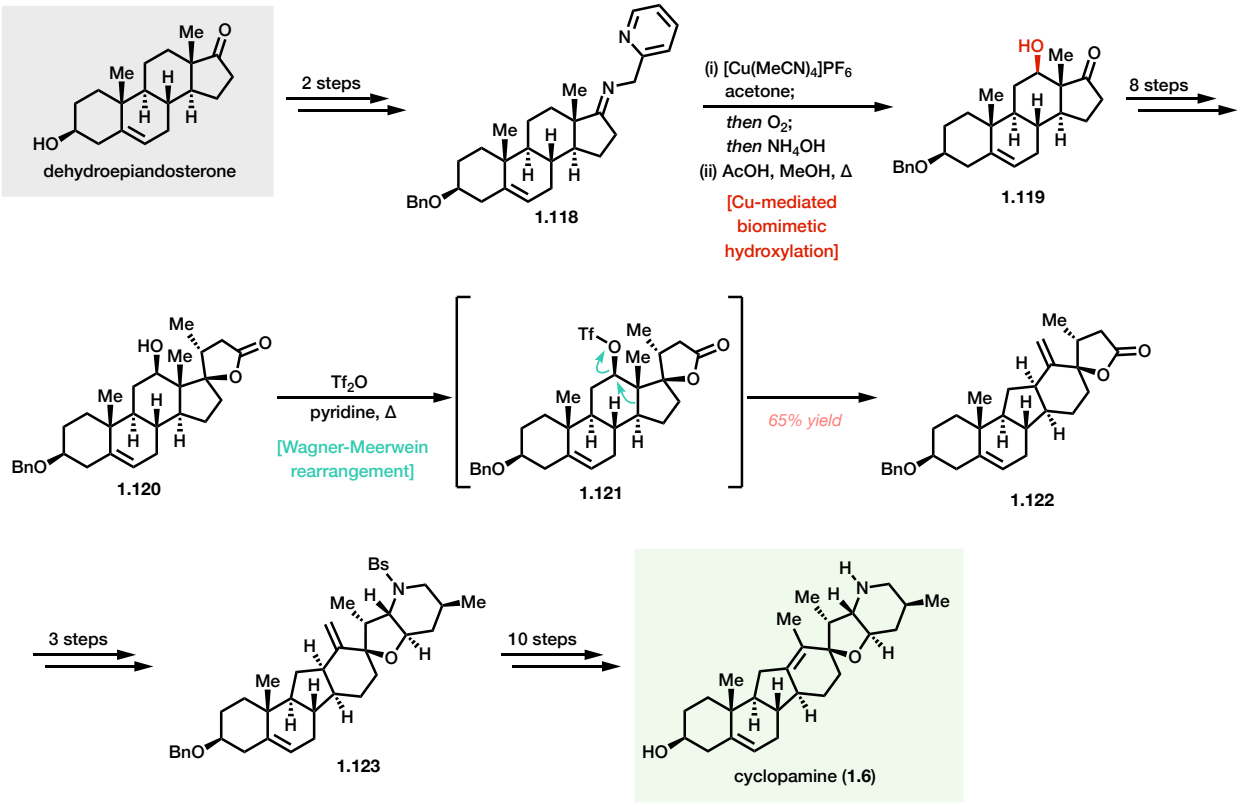
[39] Kutney, J. P.; Cable, J.; Gladstone, W. A. F.; Hanssen, H. W.; Torupka, E. J.; Warnock, W. D. C. *J. Am. Chem. Soc.* **1968**, *90*, 5332−5334.
[40] (a) Kutney, J. P.; Fortes, C. C.; Honda, T.; Murakami, Y.; Preston, A.; Ueda, Y. *J. Am. Chem. Soc.* **1977**, *99*, 964−966. (b) Kutney, J. P.; Brookes, R. W.; Fortes, C. C.; Murakami, Y.; Preston, A.; Ueda, Y. *J. Am. Chem. Soc.* **1977**, *99*, 963−964.
[41] Schreiber, K.; Adam, G. *Tetrahedron* **1964**, *20*, 1707–1718.



Scheme 1.13. Total synthesis of verticine by Kutney and coworkers.

of **1.114** with 2-lithio-5-methyl pyridine (readily generated from 2-bromo-5-methylpyridine and *n*-BuLi at –40 °C) afforded an epimeric mixture of tertiary alcohols. The major component was isolated, characterized, and determined to possess the desired configuration, then converted to its tosylate derivative **1.115**. When heated in refluxing triethylamine, the primary tosylate undergoes intramolecular displacement to give pyridinium salt **1.116**, then exhaustive reduction to the piperidine ring is achieved using sodium borohydride, followed by hydrogenation. The resulting cevanine-type skeleton of **1.117** is finally elaborated to verticine through late-stage introduction of the C6 hydroxyl group. Overall, the breakthrough synthesis of a cevanine alkaloid required 30 steps from hecogenin acetate to reach the final target.

The only other member to succumb to synthesis in the past 40 years was reported in 2009, when Giannis published a semisynthetic strategy to cyclopamine (Scheme 1.14).[42] The synthesis commenced with *O*-benzylation of dehydroepiandosterone and condensation with 2-picolylamine to afford **1.118**. Key to the success of the overall strategy was efficient installation of the 12β-hydroxy group, which was achieved using a Cu-mediated biomimetic hydroxylation



Scheme 1.14. Synthesis of cyclopamine (**1.6**) by Giannis and coworkers.

to furnish **1.119**. This elegant regio- and diastereoselective hydroxylation was developed by Schönecker and coworkers for the C–H activation of related steroids.[43] The D ring ketone was then used to construct 17α-spirolactone **1.120**. The key Wagner-Meerwein-type rearrangement

[42] Giannis, A.; Heretsch, P.; Sarli, V.; Stößel, A. *Angew. Chem. Int. Ed*. **2009**, *48*, 7911−7914.
[43] (a) Schönecker, B.; Zheldakova, T.; Liu, Y.; Kötteritzsch, M.; Günther, W.; Görls, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 3240–3244. (b) Schönecker, B.; Zheldakova, T.; Lange, C.; Günther, W.; Görls, H.; Bohl, M. *Chem. - Eur. J.* **2004**, *10*, 6029–6042.

then proceeded upon treatment with trifluoromethanesulfonic anhydride in pyridine to give a mixture of endo- (not shown) and exocyclic olefins (**1.122**) in excellent combined yield. The major isomer was carried forward through the installation of the piperidine ring. This task was achieved via a ten-step sequence consisting of α-azidation of a lactone enolate, Horner-Wadsworth-Emmons reaction/intramolecular Michael addition of a lactol, and intramolecular Mitsonobu reaction for ring closure. Cyclopamine was accessed in three additional steps from **1.123**, following olefin isomerization and removal of protecting groups.

Limitations found in the prior art is apparent by the lengthy step counts and low overall yield, despite the use of complex, pre-functionalized starting precursors. It was hence envisioned that a complementary *de novo* approach to the *Veratrum* family may offer a viable alternative. The remainder of this chapter discusses the inspiration for the strategy that would culminate in the successful realization of a *de novo* synthesis of these steroidal alkaloids.

1.2. Retrosynthetic Analysis: [2 + 2 + 2] Alkyne Cyclotrimerization Strategy

1.2A: [2 + 2 + 2] Cycloaddition Reaction

Synthetic transformations that form carbon-carbon bonds are held in the highest esteem for any practicing organic chemist. Beyond this fundamentally coveted asset, the most venerable reactions also create new rings to rapidly build molecular complexity. Hence, the [2 + 2 + 2] cycloisomerization of alkynes is a highly appealing transformation in its ability to accomplish both of these tasks simultaneously, as three new C–C bonds and one or more rings can be formed

in a single synthetic step.[44] Additional attractive features of significance to the contemporary synthetic chemist include the perfect atom economy and high functional group tolerance.[45]

The initial discovery of the thermal cyclotrimerization of acetylene to yield benzene, albeit in low yield and as part of a complex mixture containing higher order oligomers, was reported back in 1866 by Bertholet.[46] While the reaction is highly exothermic ($\Delta G = -142$ kcal/mol), very high temperature near to or in excess of 400 °C are required in order to overcome the unfavorable entropic and kinetic considerations. As a result, nearly a century elapsed until research in the field became active again. In 1948, Reppe and Schweckendiek reported the first transition metal-catalyzed [2 + 2 + 2] cycloaddition using a Ni(0) complex at 60 °C to achieve acetylene trimerization.[47] It was subsequently found that a large number of catalysts based on over a dozen early- to late-transition metals are capable of effecting this transformation. As will be discussed in the following section, however, only a small number of catalysts are practically useful.

In the basic reaction scheme, three separate two-carbon units of unsaturation (typically an alkyne) react in the presence of a transition metal catalyst to form a (poly)substituted benzene product (Figure 1.2). The scope extends to the formation of various heterocyclic systems and even cyclohexadiene derivatives by substituting an alkyne for the appropriate unsaturated

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[44] For reviews on the [2 + 2 + 2] cyclotrimerization of alkynes, see: (a) Tanaka, K. *Transition-Metal-Mediated Aromatic Ring Construction*; John Wiley & Sons: Hoboken, NJ, 2013. (b) Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds., Pergamon: Oxford, 1991; Vol. 9, pp 1129–1162. (c) Saito, S.; Yamamoto, Y. *Chem. Rev*. **2000**, *100*, 2901−2916. (d) Agenet, N.; Buisine, O.; Slowinski, F.; Gandon, V.; Aubert, C.; Malacria, M. *Org. React*. **2007**, *68*, 1−302. (e) Broere, D. L. J.; Ruijter, E. *Synthesis* **2012**, *44*, 2639− 2672.
[45] Trost, B. M. *Science* **1991**, *254*, 1471–1477.
[46] (a) Berthelot, M. *C R. Hebd. Seances Acad. Sci.* **1866**, *62*, 905. (b) Berthelot, M. *Justus Liebigs Ann. Chem*. **1866**, *139*, 272–282.
[47] Reppe, W.; Schweckendiek, W. J. *Justus Liebigs Ann. Chem.* **1948**, *560*, 104−116.

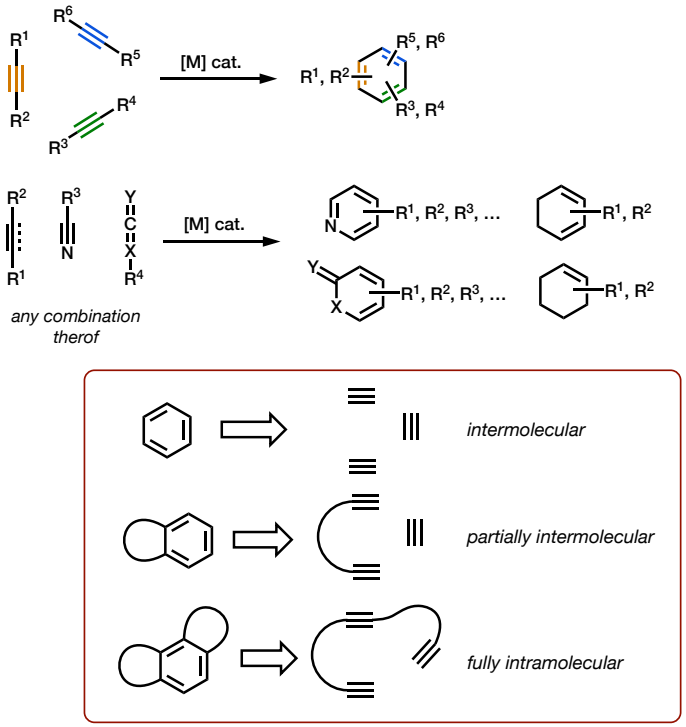

Figure 1.2. Overview of the [2 + 2 + 2] cycloisomerization.

precursor (e.g., nitrile and alkene, respectively). Of course, every powerful method has its limitations, and the [2 + 2 + 2] cycloisomerization is no exception. Among its limitations, the [2 + 2 + 2] cycloisomerization displays poor regiocontrol and a lack of chemoselectivity with unsymmetrical starting materials. However, tethering one or all the alkyne substrates together allows the reaction to proceed very efficiently, thus mediating the assembly of several new rings in a single step. Hence, the intramolecular [2 + 2 + 2] cycloisomerization has been applied in numerous complex settings to construct polycyclic natural products elegantly and efficiently.

The mechanism of this reaction has been studied in detail, primarily through the use of modern computational methods, and has been the subject of several reviews.[48] Given the wide

[48] (a) Roglans, A.; Pla-Quintana, A.; Solà, M. *Chem. Rev.* **2021**, *121*, 1894–1979. (b) Varela, J. A.; Saá, C. *J. Organomet. Chem.* **2009**, *694*, 143–149. (c) Calhorda, M. J.; Costa, P. J.; Kirchner, K. A. *Inorg. Chim. Acta* **2011**, *374*, 24−35.

variety of homogeneous and heterogeneous catalysts that can promote this transformation, as well as the diverse substrate scope beyond acetylenic functionality, several mechanistic pathways have been proposed and some particular mechanistic intricacies do, in fact, appear to be highly dependent on the specific metal catalyst used. The commonly accepted catalytic cycle for [2 + 2 + 2] cycloadditions of three alkynes and a transition metal complex (**A**) first involves reversible ligand dissociation to generate coordinatively unsaturated active catalyst **A'** (Figure 1.3). Sequential coordination of alkynes $\mathbf{B^1}$ (→ **C**) and $\mathbf{B^2}$ (→ **D**) precedes a rate-determining oxidative coupling to generate metallacyclopentadiene **E**. Such **E**-type intermediates (M = Co, Rh, Ni, Ir, Zr, etc.) have previously been isolated and well-characterized by X-ray crystallography.[49] Coordination of $\mathbf{B^3}$ affords intermediate **F**, whereupon insertion of the ligated alkyne gives a metallacycloheptatriene **G** and reductive elimination affords the substituted arene product **I**.[50]

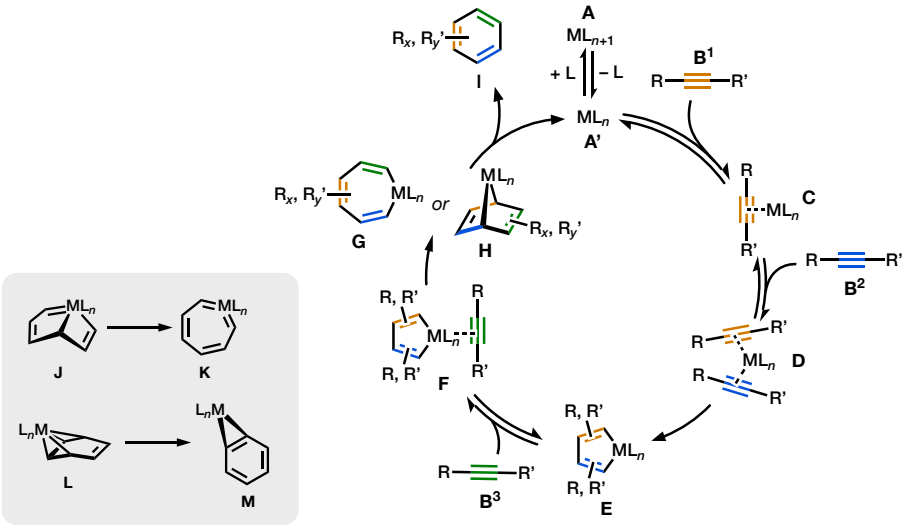

Figure 1.3. Mechanism of the transition metal-catalyzed [2 + 2 + 2] cycloisomerization.

[49] (a) Predieri, G.; Tiripicchio, A.; Tiripicchio Camellini, M.; Costa, M.; Sappa, E. *J. Organomet. Chem*. **1992**, *423*, 129−139. (b) Müller, E. *Synthesis* **1974**, 761−774.
[50] Schore, N. E. *Chem. Rev*. **1988**, *88*, 1081−1119.

Given the fact that the reductive elimination is symmetry forbidden (**G** → **I**) when one takes into account orbital symmetry considerations, alternative pathways have been proposed which may involve a more kinetically feasible reductive elimination.[51] One possibility, a [4 + 2]-type process, has been experimentally studied and computed to be a competitive pathway via a 7-metallanorbornadiene **H**, which can undergo reductive elimination to afford the product and regenerate active catalyst **A'**.[52] However, this still may be an imperfect representation of the mechanism, as reductive elimination leading to the product arene is also symmetry forbidden.[37] Other possible intermediates have been proposed, such as metallabicyclo[3.2.0]heptatriene **J** (M = Ru), which rearranges to metallacycloheptatetraene **K**.[53] The mechanism was also explored by Solá and coworkers using DFT calculations (B3LYP/cc-pVDZ-PP method), which indicate that an intramolecular [4 + 2] cycloaddition of **F** proceeds with a low barrier to generate an η^4-coordinated complex **L** (M = Rh), whereupon ring slippage leads to **M**.[54]

The substantial variety of mechanistic possibilities has been shown to stem from the wide range of transition metal catalysts, as well as the varying steric and electronic properties of each of the three unsaturated units that enter the catalytic cycle and particular reaction conditions. While this presents challenges to a detailed understanding of the entire reaction mechanism, it also plays a part in the enormous synthetic potential for this transformation. There is no doubt

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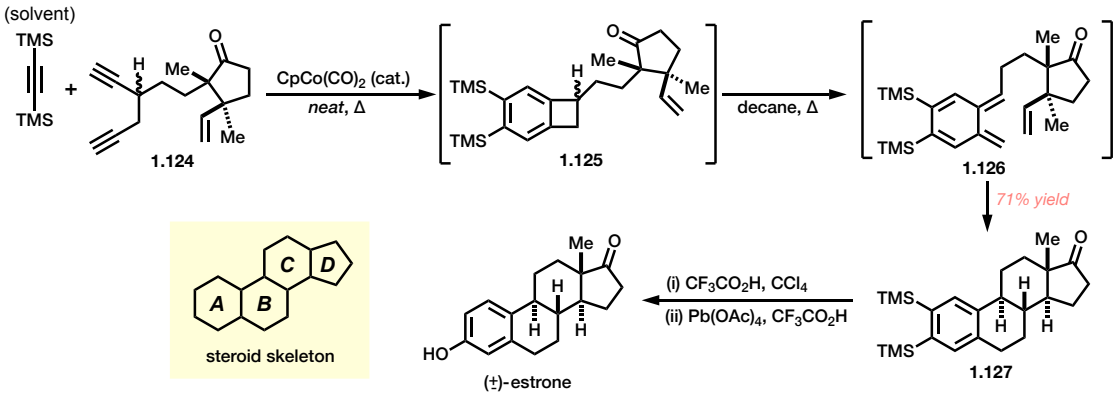
[51] Hardesty, J. H.; Koerner, J. B.; Albright, T. A.; Lee, G.-Y. *J. Am. Chem. Soc.* **1999**, *121*, 6055−6067.
[52] Bruck, M. A.; Copenhaver, A. S.; Wigley, D. E. *J. Am. Chem. Soc.* **1987**, *109*, 6125–6127.
[53] Kirchner, K.; Calhorda, M. J.; Schmid, R.; Veiros, L. F. *J. Am. Chem. Soc.* **2003**, *125*, 11721–11729.
[54] (a) Dachs, A.; Osuna, S.; Roglans, A.; Solà, M. *Organometallics* **2010**, *29*, 562–569. (b) Artigas, A.; Lledó, A.; Pla-Quintana, A.; Roglans, A. ;Solà, M. *Chem. - Eur. J.* **2017**, *23*, 15067−15072.

further analysis of the mechanistic aspects in detail will confer the necessary understanding to exploit the [2 + 2 + 2] cycloaddition to its full potential.

1.2B: [2 + 2 + 2] Cyclotrimerization of Alkynes in Total Synthesis of Natural Products

Polysubstituted (hetero)aromatic compounds are ubiquitous in natural products. Ideally, the [2 + 2 + 2] cycloisomerization could be employed to access any number of these targets in an efficient and economical manner. However, due to the limitations arising from regiochemical considerations (*vide supra*) the most powerful application of this transform in the synthesis of complex molecules is somewhat restricted. An ideal synthon is a polysubstituted (esp., 1,2,3,4-tetrasubstitution) benzene ring embedded in an alicyclic framework. The methodological development, especially owing to the identification of increasing variety of suitable transition metal catalysts, for the [2 + 2 + 2] cycloisomerization reaction has led to some interesting and elegant applications in natural product synthesis.

One of the earliest applications was Vollhardt's classic synthesis of estrone (Scheme 1.15).[55] The Vollhardt group had been pioneering the use of $CpCo(CO)_2$ as a particularly effective catalyst for the cyclotrimerization of alkynes and, later on, for pyridine synthesis by

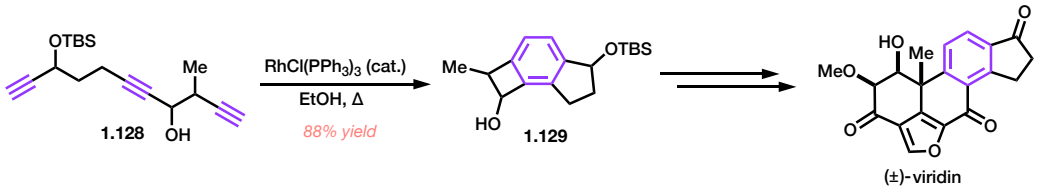


Scheme 1.15. Total synthesis of (±)-estrone by Vollhardt and coworkers.

[55] Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1980**, *102*, 5253–5261.

replacing one alkyne with a nitrile.[56] In their estrone synthesis, a refluxing solution of diyne **1.124** in trimethylsilylacetylene in the presence of $CpCo(CO)_2$ afforded an intermediate benzocyclobutane (**1.125**) via a partially intermolecular [2 + 2 + 2] cycloaddition. This intermediate underwent 4π-conrotatory electrocyclic ring opening upon further heating in a decane solution to generate transient *o*-quinodimethane **1.126** that participates in a [4 + 2] cycloaddition with the pendant vinyl-substituted cyclopentanone. This remarkable tandem process created the ABC rings to furnish the steroid skeleton in good yield and perfect atom economy. A site-selective protodesilylation and the ensuing oxidative cleavage of the remaining aryl carbon-silicon bond completed the total synthesis of (±)-estrone. The innovative efforts of Vollhardt and coworkers has also culminated in several additional elegant applications of the [2 + 2 + 2] cycloisomerization for efficient construction of a classical steroid framework.[57]

Stevenson and coworkers also reported the use of $RhCl(PPh_3)_3$ for the efficient construction of the illudalene sesquiterpenes.[58] Later, the Sorensen group would utilize a [2 + 2 + 2] cycloaddition to a tricyclic intermediate (**1.129**) in their synthesis of (±)-viridin.[59] When the authors subjected triyne **1.128** to the conditions used by Stevenson (3 mol% $RhCl(PPh_3)_3$, EtOH,



Scheme 1.16. Total synthesis of (±)-viridin by Sorensen and coworkers.

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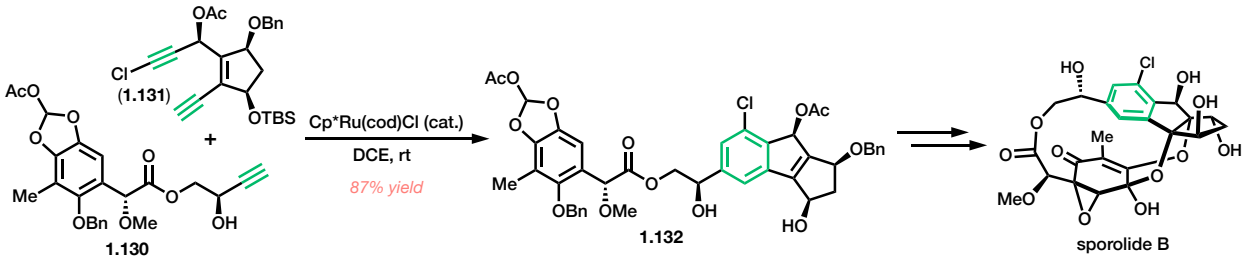
[56] Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539−556.
[57] (a) Vollhardt, K. P. C. *Pure Appl. Chem.* **1985**, *57*, 1819–1826. (b) Lecker, S. H.; Nguyen, N. H.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 856–858. (c) Sternberg, E. D.; Vollhardt, K. P. C. *J. Org. Chem*. **1982**, *47*, 3447–3450. (d) Sternberg, E. D.; Vollhardt, K. P. C. *J. Org. Chem*. **1984**, *49*, 1574–1583.
[58] (a) Neeson, S. J.; Stevenson, P. J. *Tetrahedron Lett.* **1988**, *29*, 813–814. (b) Neeson, S. J.; Stevenson, P. J. *Tetrahedron* **1989**, *45*, 6239–6248.
[59] Anderson, E. A.; Alexanian, E. J.; Sorensen, E. J. *Angew. Chem. Int. Ed*. **2004**, *43*, 1998−2001.

80 °C), they isolated tetrasubstituted aryl cyclobutenol **1.129** in 88% yield (Scheme 1.16). The aromatic ring thus formed eventually became the C ring of the furanosteroidal antibiotic viridin. In 2009, the Nicolaou group reported an incredible partially intermolecular [2 + 2 + 2] cycloaddition in their total synthesis of sporolide B (Scheme 1.17).[60] Two enantiomerically pure fragments were prepared – chlorodiyne **1.131** and terminal alkyne **1.130** – and combined in the presence of Yamamoto's catalyst (Cp*Ru(cod)Cl) to furnish the 1,2,3,5-tetrasubstituted arene

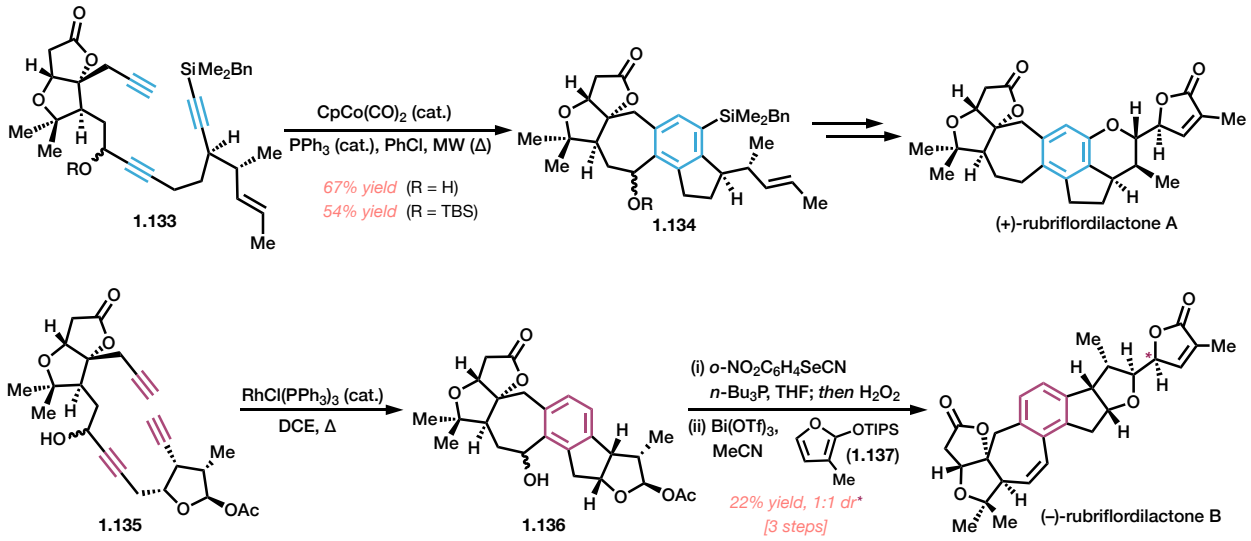


Scheme 1.17. Total synthesis of sporolide B by Nicolaou and coworkers.

product (**1.132**) in high yield and as a single regioisomer.[61] The regiochemical outcome of the reaction was attributed to the steric bulk of the chlorine substituent along with the coordinating ability of the propargylic hydroxyl group to lead to sole formation of the desired *meta*-chloro isomer.

The Anderson group has also taken advantage of the intramolecular trimerization of alkynes in several elegant approaches to the rubriflordilactones, arene-containing members of the large, structurally daunting family of *Schisandra* nortriterpenoids. In their total synthesis of (+)-rubriflordilactone A, the authors deployed $CpCo(CO)_2$ to induce the [2 + 2 + 2] cycloaddition of triyne **1.133** and furnish pentasubstituted arene **1.134** (Scheme 1.18).[62] In the recently published

[60] Nicolaou, K. C.; Tang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 3449−3453.
[61] (a) Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. J. Am. Chem. Soc. 2003, 125, 12143−12160. (b) Yamamoto, Y.; Ogawa, R.; Itoh, K. *Chem. Commun*. **2000**, 549–550.
[62] Goh, S. S.; Chaubet, G.; Gockel, B.; Cordonnier, M.-C. A.; Baars, H.; Phillips, A. W.; Anderson, E. A. *Angew. Chem. Int. Ed.* **2015**, *54*, 12618−12621.

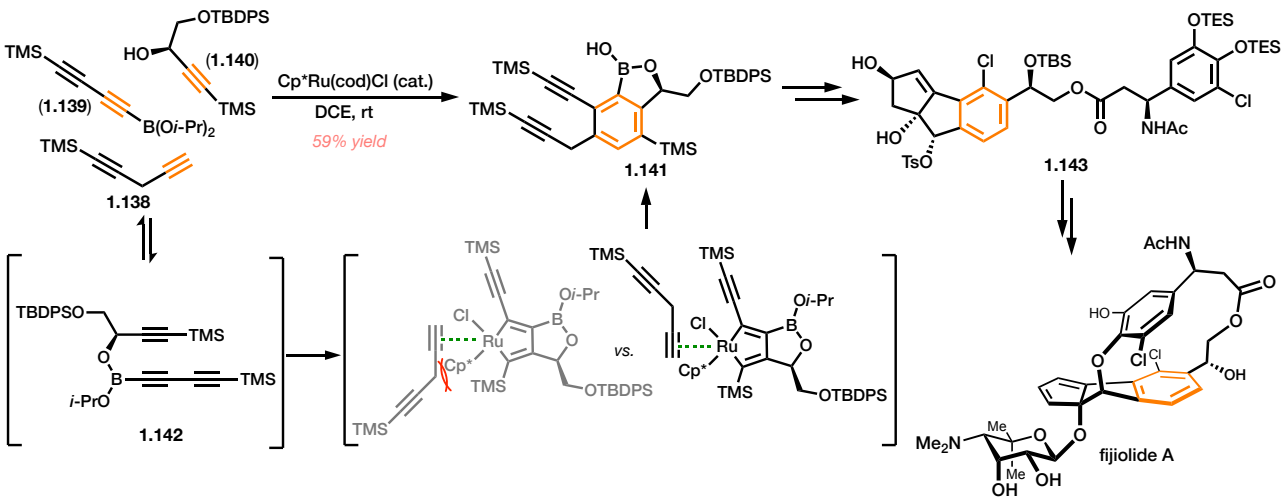


Scheme 1.18. Total syntheses of (+)-rubriflordilactone A and (–)-rubriflordilactone B by Anderson and coworkers.

total synthesis of the slightly more complex (–)-rubriflordilactone B, triyne **1.135** underwent cycloisomerization in the presence of $RhCl(PPh_3)_3$ in refluxing DCE to deliver **1.136**.[63] This material was subjected to dehydration of the benzylic alcohol using Grieco's method, then butenolide installation was achieved using Bi(III)-promoted addition of a furan derivative to give (–)-rubriflordilactone B, albeit in low yield and stereoselectivity for the three-step sequence.

In 2015, Cramer and Heinz reported the total synthesis of fijiolide A, a unique and complex glycosylated paracyclophane. The precursor to the key paracyclophane formation was efficiently assembled through the use of a fully intermolecular [2 + 2 + 2] cycloaddition (Scheme 1.19).[64] This is a rare example of a highly regioselective intermolecular [2 + 2 + 2] cycloaddition and the author's judicious choice of substituents were key to the successful heterotrimerization. The boronic ester substituent of 1,3-diyne **1.139** serves as a dynamic temporary tether that leads

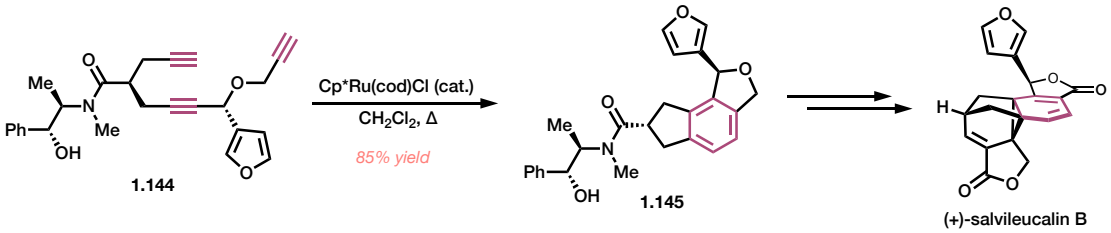
[63] Mohammad, M.; Chintalapudi, V.; Carney, J. M.; Mansfield, S. J.; Sanderson, P.; Christensen, K. E.; Anderson, E. A. *Angew. Chem. Int. Ed.* **2019**, *58*, 18177−18181.
[64] Heinz, C.; Cramer, N. *J. Am. Chem. Soc.* **2015**, *137*, 11278−11281.



Scheme 1.19. Total synthesis of fijiolide A by Cramer and Heinz.

to boronate ester **1.142** when exposed to propargyl alcohol **1.140**. As a result of the in situ tethering, ruthenacyclopentadiene formation can be templated prior to coordination of the third alkyne. The coordination of **1.138** and subsequent insertion proceeds with perfect selectivity, placing the unsubstituted alkyne terminus away from the bulky trimethylsilyl substituent of the ruthenacyclopentadiene to afford **1.141** as a single regioisomer in acceptable yield. The boronic acid handle of the product can be oxidized (CuCl, NCS) in an ensuing step to install the requisite chlorine substituent that is found in the natural product.

One final example of an intramolecular [2 + 2 + 2] cycloisomerization was utilized by Reisman and coworkers in a total synthesis of (+)-salvileucalin B (Scheme 1.20).[65] Triyne **1.144** was expediently assembled and treated with catalytic Cp*Ru(cod)Cl in refluxing CH_2Cl_2 to



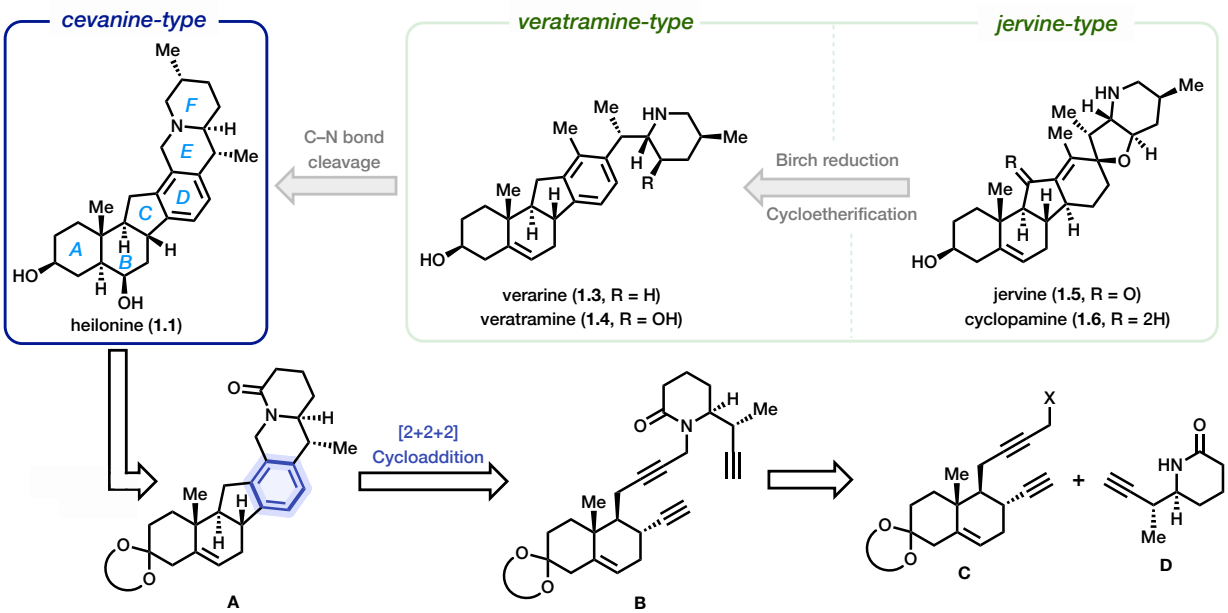
Scheme 1.20. Total synthesis of (+)-salvileucalin B by Reisman and coworkers.

[65] Levin, S.; Nani, R. R.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 774−776.

furnish tetrasubstituted arene **1.145** in excellent yield. The product was further elaborated to (+)-salvileucalin B by means of a key intramolecular Cu-catalyzed arene cyclopropanation to furnish the unusual norcaradiene core. All of these reports mentioned in this section demonstrate the power of a [2 + 2 + 2] strategy for the efficient construction of polysubstituted aromatic rings. Moreover, opportunities to rapidly build molecular complexity can be harnessed if it is used to stage an ensuing dearomative functionalization

1.3. Design of a Convergent Strategy Toward the *Veratrum* Alkaloids

It was envisioned that a [2 + 2 + 2] cycloaddition could lead to an efficient construction of the C-*nor*-D-*homo* skeleton and could be especially well suited to provide access to *Veratrum* alkaloids that contain an aromatic D ring. Consequently, a retrosynthetic analysis of heilonine (**1.1**) was devised (Scheme 1.21). It was anticipated that hexacyclic subtarget **A** could be simplified to triyne **B**. At this stage, two fragments of similar complexity could be conjoined through a simple *N*-alkylation of piperidinone **D** and propargyl electrophile **C**. In the forward



Scheme 1.21. Retrosynthetic analysis of the *Veratrum* alkaloids.

sense, hexacyclic intermediate **A** could be elaborated to heilonine upon lactam methylation and several redox adjustments: trans A/B decalin with β-hydroxyl groups at C3 and C6, lactam reduction to amine.

With this core blueprint in mind, several additional points warranted consideration. The first of these entails the efficient preparation of the di- and mono-alkyne containing fragments, which had to be prepared in optically pure form. Second, the lack of precedent surrounding [2 + 2 + 2] cycloadditions with a high degree of propargylic substitution and the presence of Lewis basic functionality forced us to examine the optimal conditions for our highly functionalized late-stage material. Lastly, it was anticipated that a total synthesis of other members in the *Veratrum* family could be achieved if the cevanine-type framework could be converted into the veratramine- and jervine-types. This would first entail selective C–N bond cleavage, followed by a Birch reduction (or alternative dearomatization method) and spirofuran forming intramolecular etherification. In order to complete a comprehensive assessment of this overall strategy, a model study was conducted to first probe the feasibility of our designed intramolecular [2 + 2 + 2] cycloaddition. The encouraging results of this initial study, as well as potential solutions to synthetic challenges posed by these targets will be presented in the following chapter.

Chapter 2

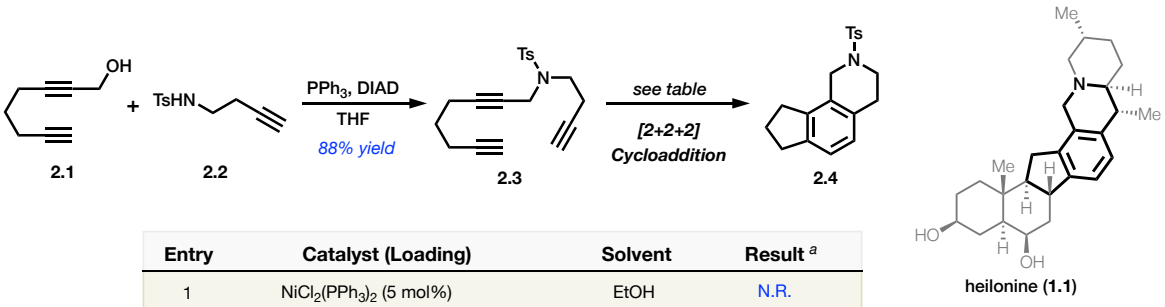
Initial Synthetic Efforts

2.1. [2 + 2 + 2] Model Studies

2.1A: Design of a Model System to Demonstrate the Cycloisomerization Strategy

In order to examine the [2 + 2 + 2] cycloisomerization strategy for the *Veratrum* alkaloids, the key proposed step was first studied in a simplified model system. Since there are relatively few examples of intramolecular [2 + 2 + 2] cyclotrimerizations of alkynes which contain a nitrogen atom in the linker region, it was decided to first identify a catalytic system that would be potentially compatible with Lewis basic functionality. A triyne substrate (**2.3**), which contains a sulfonamide in one of the linker domains, was expediently prepared via a Mitsonobu reaction between known propargyl alcohol **2.1** and sulfonamide **2.2** (Scheme 2.1). Next, a range of transition metal catalysts that have been reported to promote [2 + 2 + 2] alkyne trimerizations were surveyed. No conversion of the starting material was observed using either a Ni(II) complex or an Ir(I) dimer, whereas a Rh(I) dimer and first-generation Grubbs catalyst afforded **2.4** in low yield with most of the triyne (**2.3**) unreacted after 24 h (Entries 1–4).[1] Further screening revealed that $RhCl(PPh_3)_3$ could be used to deliver the product in modest isolated yield only after several hours (Entry 7). Increasing the catalyst loading led to a further increase in yield and dichloromethane was identified as the optimal solvent from this preliminary screen (Entries 8–11).

[1] (a) Bhatarah, P.; Smith, E. H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2163–2168. (b) Witulski, B.; Stengel, T.; Fernández-Hernández, J. M. *Chem. Commun.* **2000**, 1965–1966. (c) Kezuka, S.; Tanaka, S.; Ohe, T.; Nakaya, Y.; Takeuchi, R. *J. Org. Chem.* **2006**, *71*, 543–552.

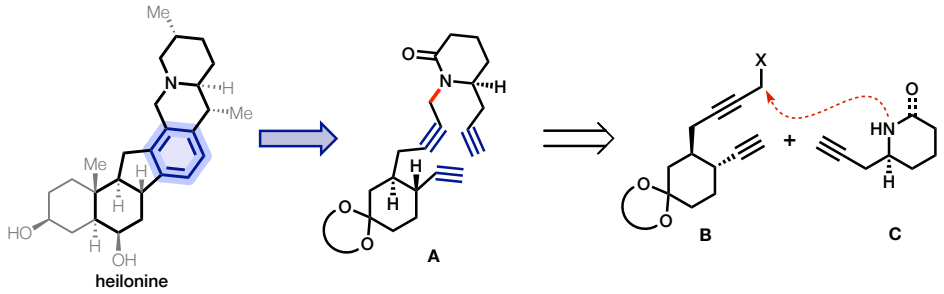


Entry	Catalyst (Loading)	Solvent	Result [a]
1	$NiCl_2(PPh_3)_2$ (5 mol%)	EtOH	N.R.
2	$[Ir(cod)Cl]_2$ (5 mol%)	PhMe	N.R.
3	$[Rh(cod)Cl]_2$ (5 mol%)	EtOH	9%
4	Grubbs I (5 mol%)	CH_2Cl_2	12%
5	$RuCl(\eta^5\text{-}C_9H_7)(PPh_3)_2$ (5 mol%)	PhMe	13%
6	$RhCl(PPh_3)_3$ (5 mol%)	EtOH	12%
7	$RhCl(PPh_3)_3$ (5 mol%)	CH_2Cl_2	37%[b]
8	$RhCl(PPh_3)_3$ (20 mol%)	CH_2Cl_2	84%[b]
9	$RhCl(PPh_3)_3$ (20 mol%)	THF	52%
10	$RhCl(PPh_3)_3$ (20 mol%)	PhMe	41%[b]
11[c]	$RhCl(PPh_3)_3$ (20 mol%)	PhMe	69%[b]

[0.1 mmol-scale]; Conditions: Reaction at 25 °C for 24 h or until TLC indicated full consumption of **2.3.** [a] NMR yield (unless stated otherwise). [b] Isolated yield. [c] At 120 °C

Scheme 2.1. [2 + 2 + 2] Cycloisomerization model study to generate tricycle **2.4**.

It was next envisaged that a pentacyclic (BCDEF) model system would not only offer a good showcase for the overall strategy, but also provide opportunities to scout different routes for key building blocks that may be needed later on. Thus, heilonine – our ultimate target – was simplified to [2 + 2 + 2] precursor triyne **A** (Scheme 2.2). If successful, this transformation would concomitantly form the skeletal CDE rings containing most of the requisite functionality and stereochemistry as found in the natural product. As mentioned in the previous section, triyne

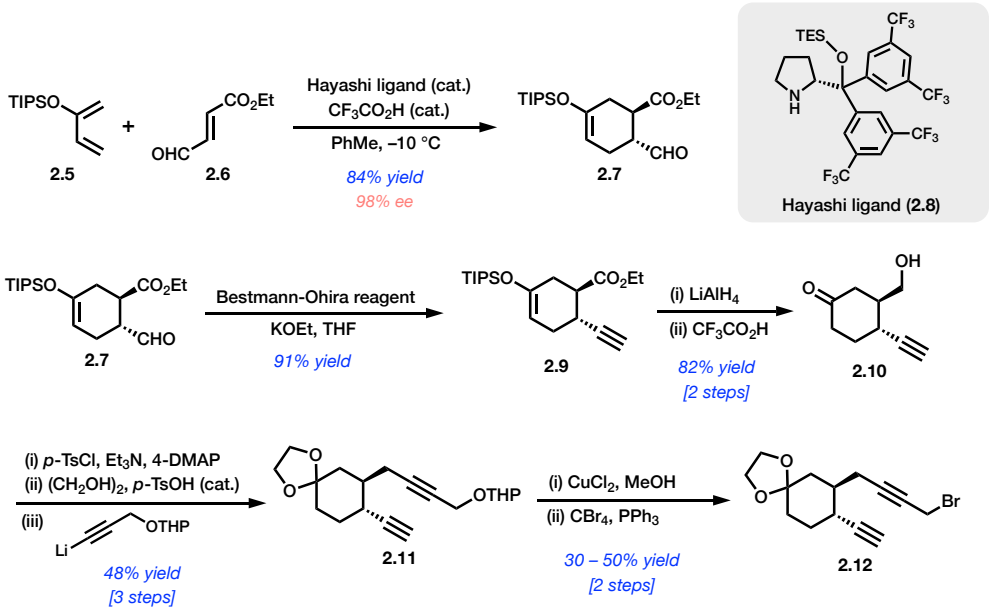


Scheme 2.2. Retrosynthetic analysis for the proposed model study.

A could be traced back to a diyne electrophile **B** and (pro)nucleophilic piperidine/-one **C** to be conjoined through a simple alkylation.

2.1B: Enantioselective Synthesis of the Diyne Fragment

The route to complementary diyne **B** commenced with the preparation of known, chiral building block **2.7** (Scheme 2.3). The efficient assembly of **2.7** involves an asymmetric Diels-Alder reaction between 2-siloxydiene **2.5** and commercially available dienophile **2.6**. Yang and coworkers initially reported a highly enantioselective, organocatalyzed Diels-Alder occurred through the use of a diarylprolinol-derived ligand (**2.8**) that was developed by Hayashi.[2,3] With access to **2.7**, attention was then focused on Gilbert-Seyferth homologation of the aldehyde to install the first alkyne.



Scheme 2.3. Synthesis of propargyl bromide **2.12**.

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[2] (a) You, L.; Liang, X.-T.; Xu, L.-M.; Wang, Y.-F.; Zhang, J.-J.; Su, Q.; Li, Y.-H.; Zhang, B.; Yang, S.-L.; Chen, J.-H.; Yang, Z. *J. Am. Chem. Soc.* **2015**, *137*, 10120−10123. (b) Zhang, J.-J.; You, L.; Wang, Y.-F.; Li, Y.-H.; Liang, X.-T.; Zhang, B.; Yang, S.-L.; Su, Q.; Chen, J.-H.; Yang, Z. *Chem. - Asian J.* **2016**, *11*, 1414−1424.

[3] Gotoh, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 2859−2862.

The standard protocol for the homologation of an aldehyde to alkyne using the Bestmann-Ohira reagent was attempted on **2.7** and resulted in a 1:1 mixture of diastereomers of the product alkyne.[4] Therefore, attempts were made to modify the procedure in order to suppress the extensive epimerization that occurred otherwise. It was found that when the Bestmann-Ohira reagent was added to an ethereal solution of an alkoxide base at low temperature prior to addition of the substrate aldehyde, the product could be isolated as a single diastereomer.[5] This protocol presumably generates the (diazomethyl)phosphonate anion (i.e., the active homologating species) rapidly in situ, thus obviating epimerization that occurred over the longer reaction times when using the standard procedure. Furthermore, careful control of the following reagent stoichiometry was determined to be essential in order to ensure reproducibility: (i) large excess of Bestmann-Ohira reagent relative to **2.7** due to instability and gradual decomposition of intermediate diazo anion and (ii) a slight excess of Bestmann-Ohira reagent relative to the alkoxide base. Potassium ethoxide was identified as the optimal base owing to its increased solubility over Na and Li alkoxides, as well as the degenerate transesterification with the ethyl ester in **2.7**. With all of these factors considered, the reaction could be reproduced on scale to afford alkyne **2.8** in 91% yield.

The ethyl ester was next reduced to the corresponding primary alcohol using $LiAlH_4$, then smooth hydrolysis of the silyl enol ether was achieved following treatment with trifluoroacetic acid to furnish keto alcohol **2.10** in 82% yield over both steps. Nucleophilic

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[4] (a) Ohira, S. *Synth. Commun*. **1989**, *19*, 561−564. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521−522.

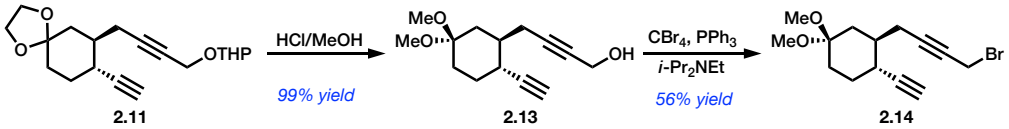
[5] (a) Nicolaou, K. C.; Fylaktakidou, K. C.; Monenschein, H.; Li, Y.; Weyershausen, B.; Mitchell, H. J.; Wei, H.; Guntupalli, P.; Hepworth, D.; Sugita, K. *J. Am. Chem. Soc*. **2003**, *125*, 15433−15442. (b) Zanato, C.; Pignataro, L.; Ambrosi, A.; Hao, Z.; Trigili, C.; Díaz, J. F.; Barasoain, I.; Gennari, C. *Eur. J. Org. Chem.* **2011**, 2643−2661.

displacement of a suitable leaving group with an acetylide was used to install the second alkyne. First, tosylation of the primary alcohol (*p*-TsCl, Et_3N, 4-DMAP) and protection of the ketone (ethylene glycol, *p*-TsOH·H_2O, Dean-Stark) was performed. Treatment of the resultant intermediate with the lithio derivative of propargyl tetrahydropyranyl (THP) ether in THF and heating the resultant solution to reflux for 18 h afforded diyne **2.11** in 48% yield over the three steps. These conditions proved to be unique in permitting clean conversion to the desired product.[6] Several other reaction parameters were examined, such as different leaving groups (X = Br, I) and propynyloxy acetylides, as well as the influence of dipolar aprotic additives (e.g., HMPA, DMPU) at a lower reaction temperature. While product diyne could be isolated in some cases, the major pathway observed was E2 elimination.

In efforts to move forward in the sequence towards a propargyl bromide, subsequent deprotection of the THP acetal proved challenging in the presence of the 1,3-dioxolane. Ultimately, it was discovered that treatment of a methanolic solution of **2.11** with $CuCl_2$ permitted selective removal of the THP acetal on a small scale. However, the selectivity was diminished on a 275 mg-scale and the fully deprotected product was isolated in ca. 1:1 ratio with the desired product. This problem would be revisited again on the actual system (see Section 3.4) and a better solution would be identified. The resulting propargyl alcohol was converted to bromide using Appel-like conditions to afford **2.12**.

In order to address the poor scalability of the THP deprotection, a different protocol was investigated that would still permit access to the key fragment. Interestingly, treatment of diyne **2.11** with a solution of HCl in methanol led to clean conversion to a transketalization product **2.13** in good yield (Scheme 2.4). This result is in stark contrast with the deprotection of a more

[6] Buck, M.; Chong, J. M. *Tetrahedron Lett*. **2001**, 42, 5825–5827.



Scheme 2.4. Transketalization sequence to propargyl bromide **2.14**.

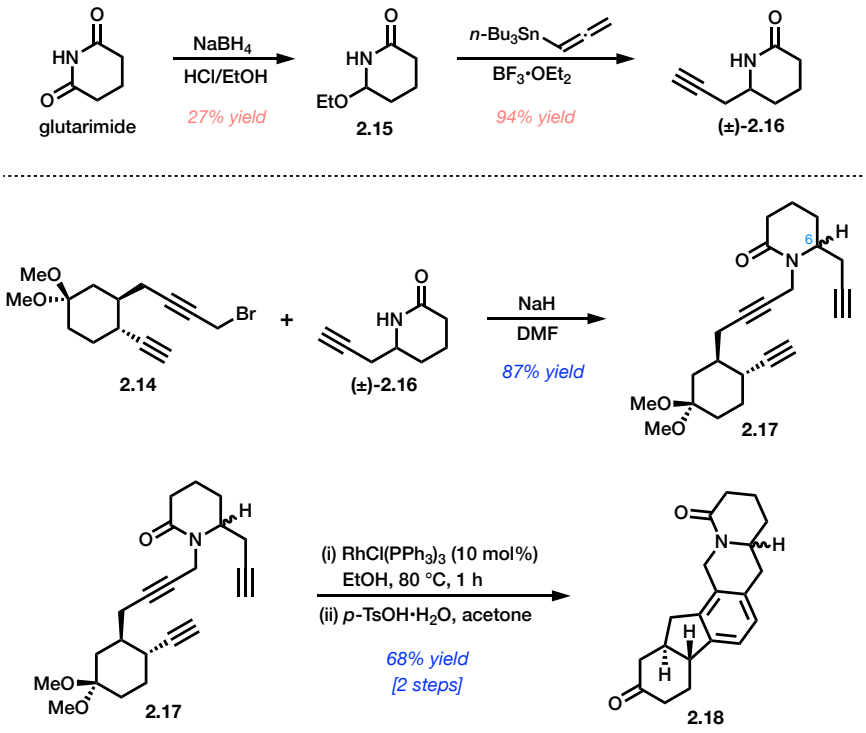
advanced intermediate (see Section 3.4), where smooth conversion of a neopentyl glycol acetal to an enone was achieved under the same conditions. Appel reaction on **2.13** afforded propargyl bromide **2.14**, however, it was found that amine base was necessary under the Appel conditions to prevent deprotection of the sensitive dimethyl ketal. With reliable access to enantiomerically enriched diyne fragment, our attention was next turned towards appending a piperidinone building block and examining the feasibility of the core to our strategy.

2.1C: Model [2 + 2 + 2] Cycloisomerization to Generate Pentacycle

Having secured access to the diyne fragment, an appropriate design for the piperidine motif was then considered to complete the model study. Since there are limited options to access enantiomerically enriched propargyl substituted piperidines, it was elected to use a known, racemic piperidinone **2.16** (Scheme 2.5).[7] Thus, reduction of commercially available glutarimide was achieved using $NaBH_4$ in EtOH to give the corresponding 6-ethoxy-piperidinone (**2.15**). Exposure of this material to a Lewis acid generates a highly reactive *N*-acyliminium species, which is trapped by allenylstannane to afford (±)-**2.16** along with a small amount of allenic isomer.

The *N*-alkylation of racemic piperdinone **2.16** with propargyl bromide **2.14** proceeded very efficiently using sodium hydride as a base in DMF (Scheme 2.5). Significantly, only one equivalent of each fragment could be used for the coupling and a high yield of **2.17** was still

[7] Karstens, W. F. J.; Rutjes, F. P. J. T.; Hiemstra, H. *Tetrahedron Lett.* **1997**, *38*, 6275–6278.



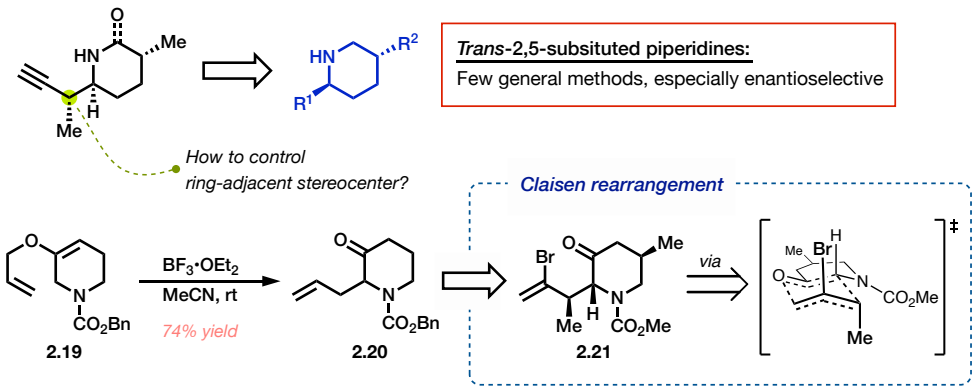
Scheme 2.5. Preparation of known piperidinone (±)-**2.16** and synthesis of model pentacycle **2.18**.

obtained. The consequential mixture of C6 epimers could not be separated prior to testing the key [2 + 2 + 2] cycloaddition, so **2.17** was carried forward as a 1:1 mixture of diastereomers. Gratifyingly, when an ethanolic solution of triyne **2.17** was heated to reflux in the presence of catalytic $RhCl(PPh_3)_3$ quantitative conversion was observed. However, the reaction profile was quite messy and four new product spots were isolated. Characterization of each product by NMR spectroscopy revealed that all had undergone the [2 + 2 + 2] cycloaddition to generate the aromatic ring and closer analysis indicated that extensive transketalization had occurred under the reaction conditions. In addition to the expected dimethyl ketal, diethyl and mixed (i.e., methyl ethyl) ketal were also observed, as well as a small amount of the corresponding ketone. To facilitate characterization, the mixture was combined and carried forward through a deprotection step (*p*-TsOH·H_2O, acetone) to afford **2.18** in an excellent yield over both steps.

Although the C6 diastereomers could still not be separated at this stage, we set off to identify an asymmetric preparation of the piperidinone building block with a strong sense of confidence in the core of our strategy.

2.2. Attempted Strategies to Prepare Functionalized Piperidine Building Blocks

The paucity of methods, especially enantioselective, to prepare *trans*-2,5-subsituted piperidines presented a challenge to develop a novel approach to our particular propargyl substituted target.[8] In addition to absolute stereocontrol about the ring, relative stereocontrol over the ring adjacent stereocenter was expected to pose an additional challenge. To tackle this problem, we were intrigued by the predictability of the Claisen rearrangement in generating complex stereochemical motifs and devised a novel strategy for installing a propargyl unit (Scheme 2.6). One key precedent for this proposed transformation was reported by Takeuchi and coworkers, where allyl enol ether **2.19** was prepared and underwent Claisen rearrangement to



Scheme 2.6. Opportunities and precedent for piperidine fragment synthesis.

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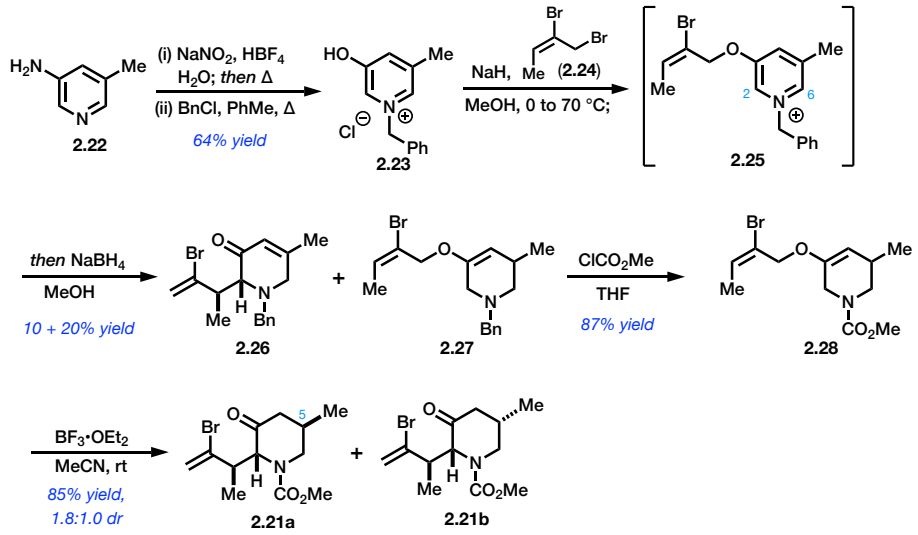
[8] Wanner, B.; Kreituss, I.; Gutierrez, O.; Kozlowski, M. C.; Bode, J. W. *J. Am. Chem. Soc*. **2015**, *137*, 11491−11497, and references therein, *viz*., Ref. 7. For selected reviews on the synthesis of piperidines, see: (a) Sandmeier, T.; Carreira, E. M. Modern Catalytic Enantioselective Approaches to Piperidines. In *Synthetic Approaches to Nonaromatic Nitrogen Heterocycles*; Faísca Phillips, A. M. M. M., Ed.; Wiley: Hoboken, 2021; pp 249–271. (b) Nebe, M. M.; Opatz, T. In *Advances in Heterocyclic Chemistry*; Scriven, E., Ramsden, C. A., Eds., Academic Press: 2017; Vol. 122, pp 191–244.

2.20 upon exposure to a strong Lewis acid.[9] This unexpected outcome was shown to involve isomerization of the double bond prior to the isomerization to give the desired product in 74% yield as a single regioisomer. The authors also demonstrated that thermal conditions (130 °C in *p*-cymene) afforded exclusively the alternative (expected) regioisomer.

We set out to prepare a more functionalized derivative of **2.21** to test the feasibility of this proposed transformation in the context of the piperidine fragment of the *Veratrum* alkaloids (Scheme 2.7). As such, commercially available **2.22** was subjected to diazotization/hydroxylation, followed by *N*-benzylation to afford pyridinium salt **2.23**. This material was then stirred with (*E*)-1,2-dibromobut-2-ene (**2.24**), which was prepared in 3 steps from 2-butyn-1-ol, in the presence of sodium hydride to effect *O*-alkylation. The intermediate



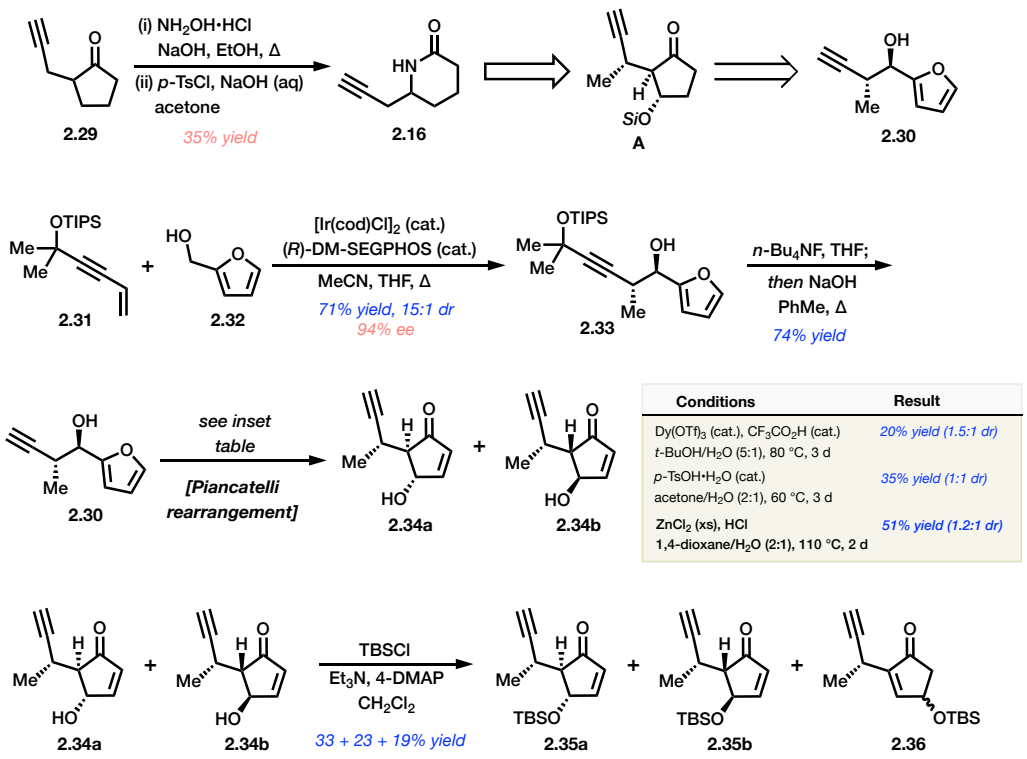
Scheme 2.7. Synthetic investigations into the proposed Claisen rearrangement.

2.25 underwent reduction with sodium borohydride in the same pot to afford the expected allyl enol ether **2.26** in 20% yield, along with 10% yield of unexpected enone product **2.27**. The latter presumably arises from initial hydride delivery at C6, followed by spontaneous Claisen rearrangement under the reaction conditions. The benzyl group of **2.26** was exchanged for

[9] Takeuchi, Y.; Hattori, M.; Abe, H.; Harayama, T. *Synthesis* **1999**, 1814–1818.

methyl carbamate, then **2.28** underwent a high-yielding Claisen rearrangement to give a separable 1.8:1.0 mixture of C5 epimers (**2.21a**/**b**). Preliminary investigations into dehydrobromination to convert alkenyl bromide to alkyne were promising, however the lack of facial selectivity during the [3,3]-rearrangement prompted us to consider alternative routes.

One of these potential solutions involved the use of a Beckmann rearrangement of a substituted cyclopentanone to construct the piperidinone. A closely related precedent involving cyclopentanone **2.29** yielded piperidinone **2.16** under classical Beckmann rearrangement conditions as a single regioisomer, albeit in a modest yield (Scheme 2.8).[10] It was surmised that a Beckmann rearrangement of a suitably decorated cyclopentanone **A** would permit access to the



Scheme 2.8. Precedent for the proposed Beckmann rearrangement and attempted synthesis of the requisite cyclopentanone substrate.

[10] Gilbert, N.; Ricard, S.; Bergeron, J.; Lambolez, P.; Daoust, B. *Eur. J. Org. Chem.* **2020**, *17*, 2517–2529.

piperidinone building block for the *Veratrum* alkaloids. The *trans* relationship between hydroxyl and propargyl groups could be secured via a Piancatelli rearrangement, allowing us to utilize a known enantioselective propargylation methodology to access homopropargylic alcohol **2.33**. The sequence commenced with a diastereo- and enantioselective iridium-catalyzed transfer hydrogenative coupling between enyne **2.31** and furfuryl alcohol (**2.32**), which was reported by Krische and coworkers to afford **2.33** in good yield and with excellent enantioselectivity.[11] The subsequent deprotection to afford terminal alkyne **2.30** was achieved upon exposure to *n*-Bu_4NF and NaOH at elevated temperature. Unfortunately, the pivotal Piancatelli rearrangement afforded inseparable 4-hydroxycyclopentenones **2.34a**/**b** with poor stereoselectivity. This result is not surprising considering the reaction mechanism, where an intermediate pentadienyl cation undergoes 4π-conrotatory electrocyclic ring closure. While torquoselective Nazarov cyclizations have been reported, there exists virtually no precedent to guide us in controlling the direction of substituent rotation in our case.[12]

Consequently, we attempted to move forward in the sequence and protect the somewhat unstable 4-hydroxycyclopentenones as their corresponding silyl ethers. This seemingly straightforward process produced TBS ethers **2.35a/b** in modest yield but led to a substantial amount of a regioisomeric side product **2.36**. Mechanistically, this product could arise via a synchronous enolate-induced [1,5]-sigmatropic siloxy shift to give the rearranged cyclopentenone **2.36**, which is a process that was previously studied by Szántay and coworkers.[13] While mechanistically intriguing, this deleterious pathway along with the lack of

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[11] Geary, L. M.; Woo, S. K.; Leung, J. C.; Krische, M. J. *Angew. Chem. Int. Ed.* **2012**, *51*, 2972–2976.
[12] Denmark, S. E.; Wallace, M. A.; Walker, Jr., C. B. *J. Org. Chem.* **1990**, *55*, 5543–5545.
[13] Novák, L.; Szántay, Cs.; Meisel, T.; Aszódi, J.; Szabó, É.; Fekete, J. *Tetrahedron* **1985**, *41*, 435–450.

torquoselectivity in the Piancatelli rearrangement forced us to abandon this low-yielding route in favor of more robust and direct approaches.

One final strategy that was briefly considered to furnish the requisite propargyl-substituted piperidinone was based on the known reactivity between allenylmetal reagents and certain classes electrophiles to install a propargyl group, in some cases with very high stereoselectivity. Despite the broad scope for addition of allenylmetal reagents to aldehydes and imines, there are very few examples of dearomative propargylations of activated heterocycles.[14] In 1987, Yamaguchi reported the reaction of allenyltin reagents and *N*-alkoxycarbonyl-isoquinolinium and -quinolinium salts (Scheme 2.9).[15] It was found that when quinoline (**2.37**) was treated with an allenyltin reagent in the presence of chloroformate esters, a reaction occurred exclusively at the α-position to afford compounds of type **2.38** in generally good yields. The authors, however, did not report or comment on the reactivity of reagents that are substituted at the nucleophilic terminus of the allenic system. Yamaguchi and other groups have also found allylstannanes react well with pyridinium salts.[16] A particularly striking example (**2.41** → **2.42**) was used by Magnus and coworkers in their total synthesis of norsecurinine.[17] The site selectivity in both of these examples is both intriguing and highly relevant to our system, wherein the nucleophile adds solely at the C2 position adjacent to an acetoxy substituent.

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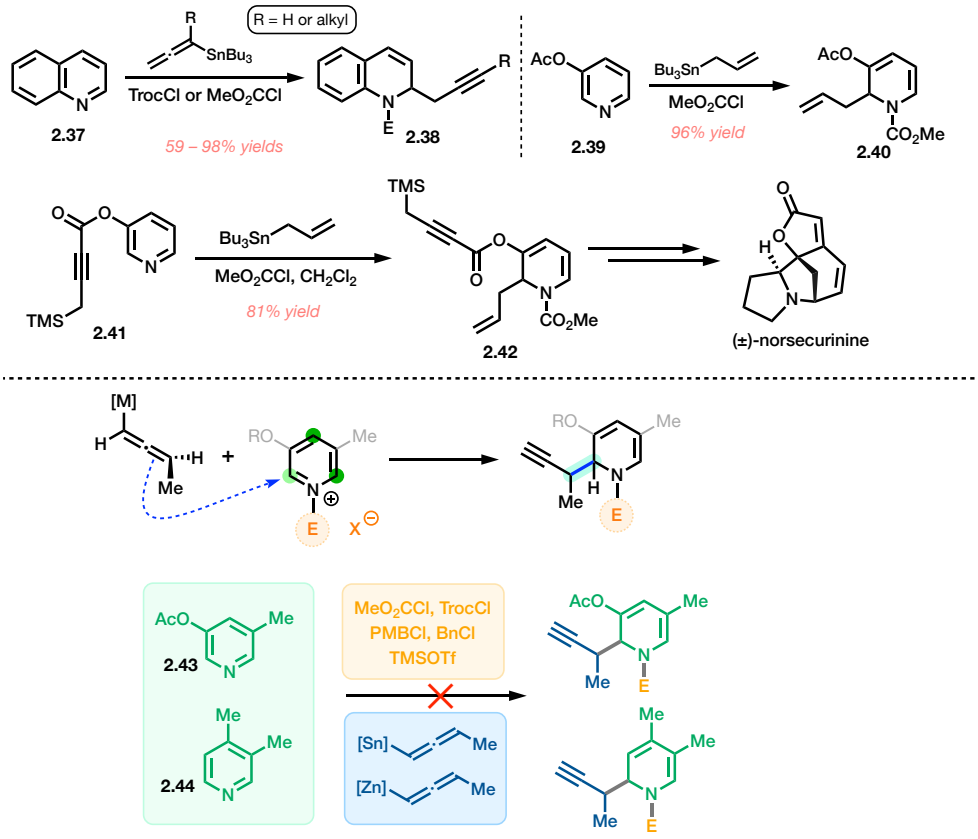
[14] Marshall, J. A.; Gung, B. W.; Grachan, M. L. In *Modern Allene Chemistry*; Krause, N.; Hashmi, A. S. K., Eds., Wiley-VCH: Weinheim, 2004; pp 493–592.
[15] Yamaguchi, R.; Moriyasu, M.; Takase, I.; Kawanisi, M.; Kozima, S. *Chem. Lett.* **1987**, *16*, 1519–1522.
[16] (a) Yamaguchi, R.; Moriyasu, M.; Yoshioka, M.; Kawanisi, M. *J. Org. Chem*. **1985**, *50*, 287–288. (b) Yamaguchi, R.; Moriyasu, M.; Yoshioka, M.; Kawanisi, M. *J. Org. Chem*. **1988**, *53*, 3507–3512.
[17] Magnus, P.; Ródriguez-López, J.; Mulholland, K.; Matthews, I. *Tetrahedron* **1993**, *49*, 8059–8072.



Scheme 2.9. Precedent for dearomative propargylation and unsuccessful attempts on a pyridine model.

The steric and electronic demands of two readily available pyridines (**2.43** and **2.44**) was surveyed in order to see if an allenylmetal species would react to give the propargylation products via addition to the 2-position. Different allenylmetal nucleophiles were prepared according to known procedures and were combined with the pyridine starting material in the presence of different electrophilic promoters. Unfortunately, the desired reactivity was never observed under all of the conditions that were screened. In most cases there was either simply no reaction or a very messy reaction profile. This shortcoming, along with the other failures to achieve an enantioselective synthesis of our piperidine building blocks that were discussed in this section, seem to concur with the notion that the asymmetric preparation of this saturated heterocycle does not have a general solution. In the next chapter (Section 3.3), a successful

solution to this problem in the context of the total synthesis of (+)-heilonine will be presented and discussed.

Concluding Remarks

In summary, model studies have been performed to demonstrate the feasibility for the [2 + 2 + 2] cycloaddition as an efficient means to construct polycyclic frameworks in the context of the *Veratrum* alkaloids. Initial synthetic routes have been devised and demonstrated to access the triyne precursor for the cycloisomerization in a simplified context. The remaining chapters will showcase some of the insights and observations from these early studies en route to the total synthesis of the *Veratrum* alkaloids. Unfortunately, none of strategies to prepare the piperidine motif were successful. The results obtained are further testament to the challenges of stereoselective piperidine construction.

Chapter 3

Enantioselective Total Synthesis of (+)-Heilonine

3.1. Heilonine Background

The isolation of heilonine (**1.1**) was reported in 1989 from *Fritillaria ussuriensis* Maxim, collected in the Heilongjiang province in northern China, from which its name was derived.[1] The complex hexacyclic structure of the natural product along with its nine stereogenic centers was elucidated by NMR spectroscopy and X-ray crystallographic analysis. Several other steroidal alkaloids were also isolated and elucidated in addition to heilonine, two of which possess a novel seven ring skeleton that will be discussed further in Section 5.1 (Figure 3.1). Heilonine is

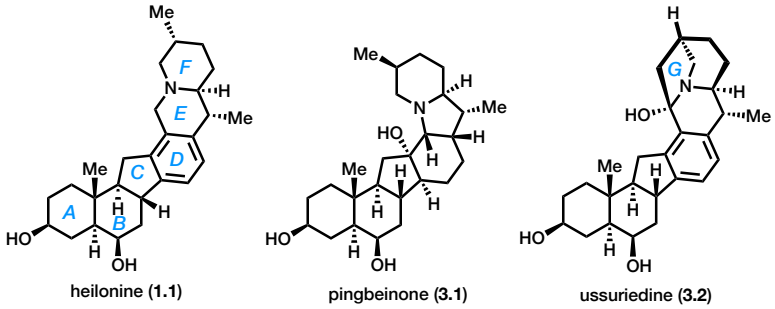


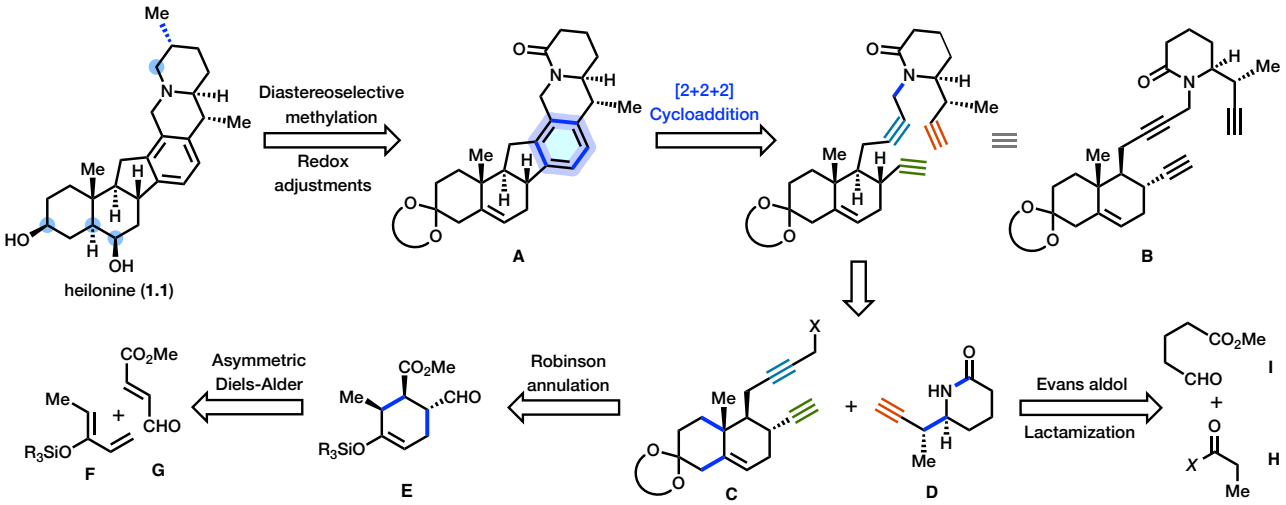
Figure 3.1. Steroidal alkaloids isolated from *Fritillaria ussuriensis*.

believed to be a constituent in the important Chinese herbal drug "Bei-mu", which has traditionally been used as a sedative, antitussive, and expectorant. To the best of our knowledge, this work represents the first synthetic studies aimed at these particular targets in the more than three decades since their isolation.

[1] Kitamura, Y.; Nishizawa, M.; Kaneko, K.; Shiro, M.; Chen, Y.-P.; Hsu, H.-Y. *Tetrahedron* **1989**, *45*, 7281−7286.

3.2. Retrosynthetic Analysis

In our retrosynthetic plan toward heilonine, hexacycle **A** was envisioned to be a key intermediate that could arise from an intramolecular [2 + 2 + 2] cycloisomerization of triyne **B** (Scheme 3.1). This powerful simplifying transform leads to a plausible point of divergence, as **B** could be traced back to two fragments of similar complexity: bicyclic diyne **C** and propargyl-substituted piperidinone **D**. The stereochemistry of **D** would be set during an asymmetric Evans

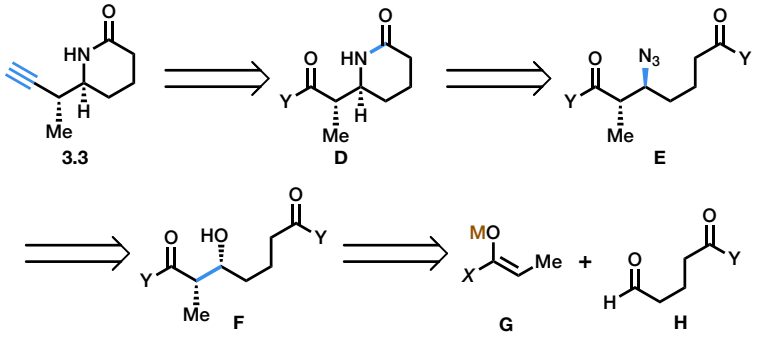


Scheme 3.1. Retrosynthetic analysis of heilonine (**1.1**).

aldol reaction between a propionyl unit (**H**) and aldehyde **I**. Stereoinvertive azidation of the resultant syn-aldol adduct followed by Staudinger-type reductive cyclization would form the piperidinone ring (see Section 3.3 for an in-depth retrosynthetic discussion). The preparation of fragment **C** was anticipated to be achieved by a Robinson annulation to construct the A ring. Functional group interconversions and nucleophilic displacement with an acetylide to introduce the propargyl unit led us to intermediate **E**, which was expected to arise from an enantioselective Diels−Alder reaction between **F** and **G**. With convergent access to the hexacyclic scaffold of **A**, it was anticipated that a diastereoselective methylation and several late-stage redox adjustments would round off the total synthesis of heilonine (**1.1**).

3.3. Successful Route to the Enantioenriched Piperidinone Fragment

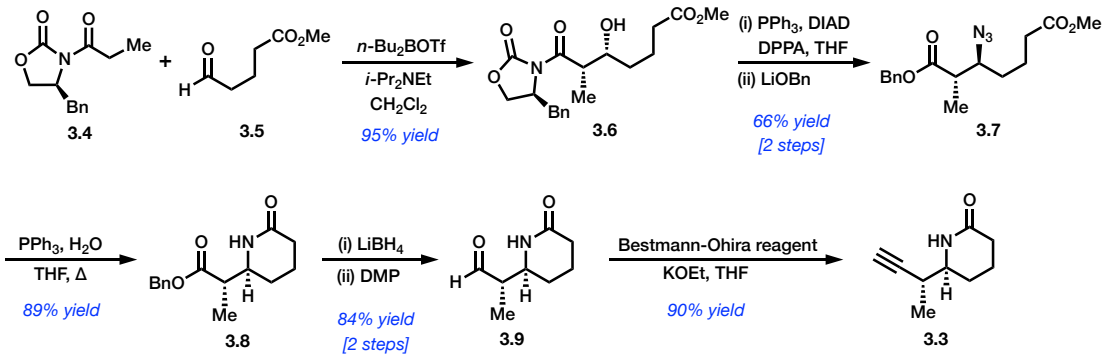
The study began with an initial focus on the preparation of the piperidine/-one fragment **C**. While multiple routes were considered and the subject of preliminary investigations (see Section 2.2), a robust seven-step sequence was designed and executed to afford our desired piperidinone building block. The retrosynthetic disassembly first entails installation of the alkyne, which could be introduced via homologation of a corresponding carboxylic acid derivative (**D**) (Scheme 3.2). The piperidinone ring could be broken at this stage, giving a linear azido ester **E** that would be subjected to a reductive lactamization in the forward sense. Intermediate **E** could be accessed in straightforward fashion from β- hydroxy ketone **F**, which itself is the syn-aldol adduct of *Z*-enolate **G** and aldehyde **H**. Given the stringent requirement for optically pure material, either an asymmetric catalytic or stereoselective aldol reaction employing a chiral auxiliary would represent an ideal starting point.



Scheme 3.2. Retrosynthetic analysis of piperidinone fragment **3.3**.

The synthesis commenced with the reliable Evans' acyl oxazolidinone method to cleanly access the *syn* product (Scheme 3.3).[2] Thus, exposure of known aldehyde **3.5** (prepared in two steps from δ-valerolactone) to a solution of the boron enolate derived from commercially available *N*-propionyl oxazolidinone **3.4** and *n*-Bu_2BOTf afforded the desired *syn* adduct **3.6** in

[2] (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129. (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099−3111.



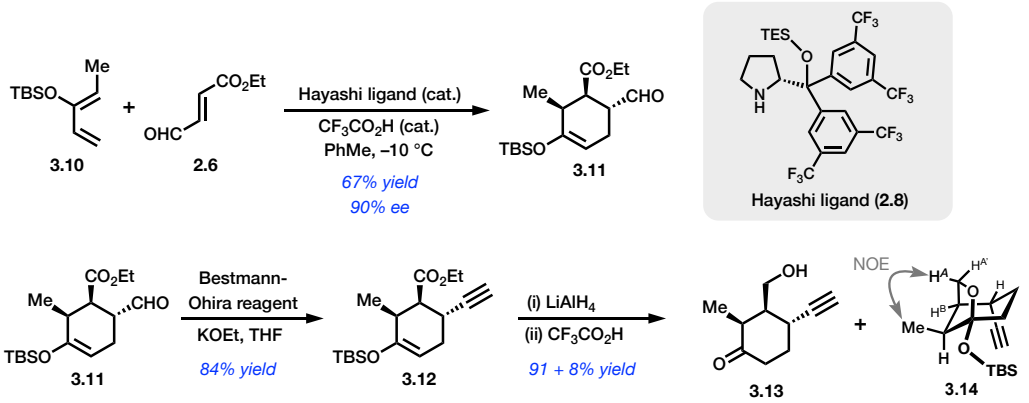
Scheme 3.3. Synthesis of piperidinone fragment **3.3**.

95% yield and as a single diastereomer. A Mitsonobu reaction (PPh_3, DIAD, DPPA) was used to install an azide, with the requisite stereochemistry arising from the stereoinvertive S_N2-type mechanism. The removal of the chiral auxiliary was achieved upon treatment with lithium benzylate to afford methyl benzyl diester **3.7** in 66% yield over two steps, as well as a small amount of a bisbenzyl diester (not shown) which was telescoped forward to the next step. Staudinger reduction of the azide resulted in spontaneous lactamization under the reaction conditions to cleanly afford piperidinone **3.8** in 89% yield. Of note, removal of the chiral auxiliary prior to the reductive cyclization was found to be necessary due to an exclusive competing cyclization onto the imide moiety. Once the piperidinone ring had been formed, the benzyl ester was reduced using $LiBH_4$ to give the corresponding primary alcohol as a highly polar, water soluble crystalline solid. This material underwent smooth oxidation to aldehyde **3.9** using Dess-Martin periodinane. A carefully optimized workup and isolation procedure was developed in order to deal with issues relating to poor solubility in organic solvents and an extreme propensity towards epimerization and hydrate formation. Once **3.9** was in hand, ensuing conversion to the alkyne using the Bestmann-Ohira reagent was anticipated to be straightforward. However, extensive epimerization occurred when the standard conditions (K_2CO_3, MeOH) were employed. Fortunately, the modified protocol where the diazo anion is

formed *in situ* prior to addition of aldehyde (see Section 2.1B and Experimental for more details) afforded the requisite fragment **3.3** with little to no evidence of epimerization.

3.4. Preparation of Bicyclic Diyne Fragment

Along the same lines as for the preparation of our model system diyne, preparation of propargylic bromide **3.25** began with known siloxydiene **3.10** and commercially available dienophile **2.6** through the use of an organocatalytic, enantioselective Diels–Alder reaction employing diarylprolinol-derived catalyst **2.8** (Scheme 3.4). Developed by Yang and co-workers for the preparation of a similar starting material en route to their landmark total synthesis of (+)-propindilactone G, this transformation is reported to be highly efficacious, atom-economic, and



Scheme 3.4. Preparation of keto alcohol **3.13**.

scalable, so it presented a convenient starting point for building the A/B ring fragment **3.25**.[3] Since the reaction worked well in our hands for the model system (see Section 2.1B), it was decided to also investigate whether it would also give suitable yield and selectivity for siloxydiene **3.10** to confer access to more densely substituted cyclohexanones. Indeed, the Diels–Alder reaction proceeded well and afforded exo cycloadduct **3.11** in 67% yield and 90%

[3] You, L.; Liang, X.-T.; Xu, L.-M.; Wang, Y.-F.; Zhang, J.-J.; Su, Q.; Li, Y.-H.; Zhang, B.; Yang, S.-L.; Chen, J.-H.; Yang, Z. *J. Am. Chem. Soc.* **2015**, *137*, 10120–10123.

ee on a decagram scale. The structure assigned to **3.11** was consistent with ^{1}H NMR coupling constants and NOE analysis of a downstream intermediate. While unconventional, formation of the exo adduct has been shown to be favored over the endo isomer in cycloadditions of related siloxy dienes possessing a methyl group at C1 with acyclic strongly electron-deficient dienophiles having a substituent at the β-carbon.[4] The rationale for the preferred exo pathway in such systems, which is supported by experimental and computational evidence, has been attributed to destabilizing steric interactions in the transition state that arise from increased substitution at the shorter of the forming C–C σ bonds. A twist-asynchronous model was used to explain the exo selectivity, which is ultimately a consequence of the concerted asynchronous mechanisms of unsymmetrical dienes and dienophiles in Diels–Alder reactions.[5]

Aldehyde **3.11** underwent the modified Gilbert−Seyferth homologation to provide alkyne **3.12** in 84% yield through the use of the Bestmann-Ohira reagent. A scalable protocol was developed using the key observations from the model study, moreover, slow addition of the reagents and substrate under careful temperature control were critical to ensure reproducibility on scale. Next, the ethyl ester of **3.12** was reduced using $LiAlH_4$ to afford a primary alcohol in high yield. Exposure of this intermediate to trifluoroacetic acid resulted in rapid hydrolysis of the silyl enol ether to afford keto alcohol **3.13**. However, variable quantities of a nonpolar side product were also formed, which was characterized by NMR spectroscopy (^{1}H and NOE) and identified to be bridging bicyclic ketal **3.14**. The formation of this side product presumably arises

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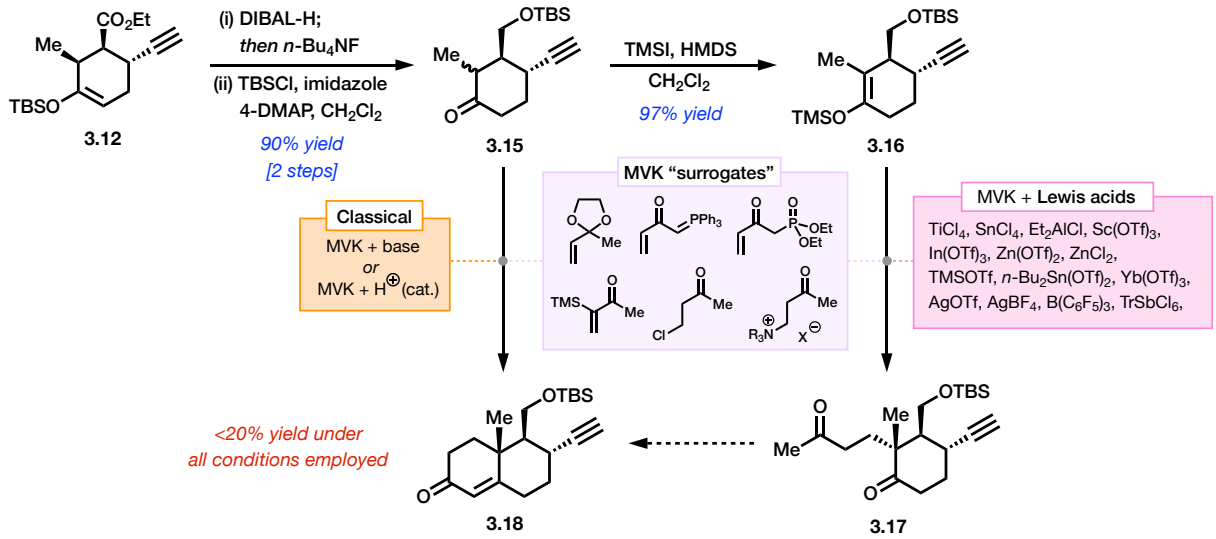
[4] For an in-depth experimental and computational study, see: (a) Lam, Y.-H.; Cheong, P. H.-Y.; Blasco Mata, J. M.; Stanway, S. J.; Gouverneur, V.; Houk, K. N. *J. Am. Chem. Soc*. **2009**, *131*, 1947−1957. For a systematic study and relevant examples, see: (b) Ho, G.-M.; Huang, C.-J.; Li, E. Y.-T.; Hsu, S.-K.; Wu, T.; Zulueta, M. M. L.; Wu, K. B.; Hung, S.-C. *Sci. Rep*. **2016**, *6*, 35147. (c) Zhou, J.-H.; Jiang, B.; Meng, F.-F.; Xu, Y.-H.; Loh, T.-P. *Org. Lett*. **2015**, *17*, 4432−4435. (d) Ho, G.-M.; Zulueta, M. M. L.; Hung, S.-C. *Nat. Commun.* **2017**, *8*, 679.

[5] Houk, K. N.; Gonzalez, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81–90.

from intramolecular trapping of a transient (silyl)oxocarbenium species. The NOE data also secures the relative stereoconfiguration and provides additional evidence of an exo-selective Diels-Alder reaction. Since the variable yields for this side product likely stems from different quantities of trace moisture in the solvent mixture, water-saturated dichloromethane was used in order to deliver the desired product in reproducibly high yield.

An alternative, shorter sequence involving one-pot ester reduction—silyl enol ether hydrolysis (DIBAL-H; then *n*-Bu_4NF) and silylation of the primary alcohol (TBSCl, imidazole, 4-DMAP) afforded **3.15** as an inconsequential mixture of diastereomers in 90% yield over two steps (Scheme 3.5). The inseparable mixture of diastereomers was treated with TMSI and HMDS



Scheme 3.5. Preparation of thermodynamic silyl enol ether **3.16** and initial exploration of the Robinson annulation.

to provide the thermodynamic silyl enol ether **3.16** in excellent yield and regioselectivity. Notably, other conditions for the soft enolization ($TMSI/Et_3N$, $TMSCl/NaI/Et_3N$, $TMSOTf/Et_3N$) gave noticeable amounts of the undesired kinetic isomer.

The Robinson annulation was next explored as the means to introduce the steroidal A ring. However, subjection of ketone **3.15** to methyl vinyl ketone (MVK) in the presence of hydroxide or alkoxide bases resulted in very messy reaction mixtures with no observable product formation. Limitations to the classical Robinson annulation have been recorded many times in the literature, where the major issue is often attributed to polymerization of the Michael acceptor by strongly basic enolates.[6] In the 1970s, Heathcock and McMurry developed and acid-catalyzed procedure as an effective method for promoting both the Michael and aldol stages of the Robinson annulation sequence.[7] However, refluxing a toluene solution of **3.15** in the presence of various organic acids (*p*-TsOH, PPTS, CSA) only delivered our product in low yield and purity due to extensive side product formation. With these classical protocols failing to provide sufficient quantities of **3.18** to move forward in the proposed synthetic sequence, several of the different methodological improvements that have been described for the Robinson annulation were explored.[8]

Due to the propensity for highly reactive α,β-unsaturated ketones, such as MVK, to cause undesirable side reactions, many different less-reactive surrogates have been used to achiever cleaner reactions and better yields. Some of these reported surrogates (e.g., Mannich bases, 4-chloro-2-butanone) operate by the slow and progressive release of free enone to keep the concentration as low as possible.[9] Anion-stabilizing and shielding reagents, such as α-silyl enones (Stork-Ganem method), have also been successfully used to deliver Robinson annulation

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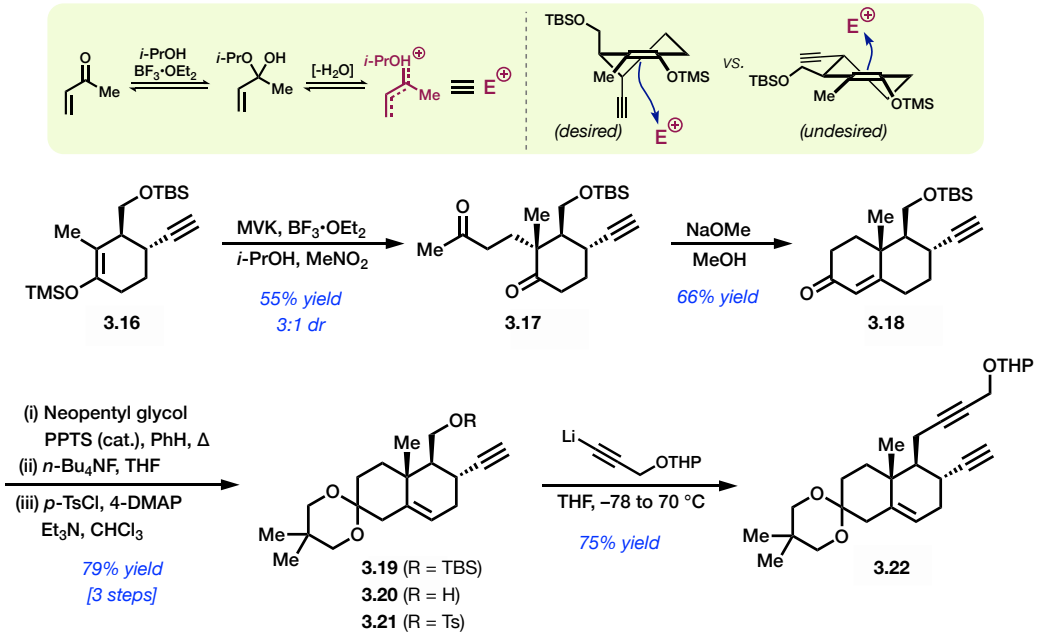
[6] Jung, M. E. *Tetrahedron* **1976**, *32*, 3–31.
[7] Heathcock, C. H.; Ellis, J. E.; McMurry, J. E.; Coppolino, A. *Tetrahedron Lett.* **1971**, *52*, 4995–4996.
[8] Gallier, F.; Martel, A.; Dujardin, G. *Angew. Chem. Int. Ed*. **2017**, *56*, 12424–12458.
[9] (a) Du Feu, E. C.; McQuillin, F. J.; Robinson, R. *J. Chem. Soc.* **1937**, 53–60. (b) Zoretic, P. A.; Branchaud, B.; Maestrone, T. *Tetrahedron Lett*. **1975**, *8*, 527–528.

products in modest to good yields.[10] Fuchs also reported a clever tactic to achieve Robinson annulation products via Mukaiyama-Michael reactions of a phosphonate enone and subsequent intramolecular Horner-Wadsworth-Emmons reaction.[11] All of these reagents, as well as two novel ones designed for this study (*viz*. MVK ethylene glycol ketal and triphenylphosphonium ylide vinyl ketone), were prepared and subjected to their standard protocols using either ketone **3.15** or TMS enol ether **3.16**. Disappointingly, either poor conversions or messy reactions were observed in all cases, with the Mannich base offering the best result at around 20% yield of **3.18**.

The Mukaiyama-Michael reaction, which is typically promoted by Lewis acids, can also offer an alternative solution to the MVK polymerization problem.[12] A variety of Lewis acids in conjunction with MVK were attempted, but most of the stronger Lewis acids (e.g., $TiCl_4$, $SnCl_4$, Et_2AlCl) resulted in hydrolysis back to **3.15** and others led to slow conversion to product (**3.17**) that was unable to compete with the gradual hydrolysis of the fragile enolsilane. Ultimately, we identified and utilized a three-step Robinson annulation protocol to furnish octalone **3.18** (Scheme 3.6). As such, once **3.15** was smoothly converted to its thermodynamic silyl enol ether, **3.16** underwent a Mukaiyama−Michael reaction using conditions reported by Duhamel (MVK, $BF_3{\cdot}OEt_2$, *i*-PrOH) and subsequent aldol closure/dehydration (NaOMe, MeOH) to provide **3.18**.[13] In accordance with a previous report, an additional quantity of $BF_3{\cdot}OEt_2$ that is added after several hours of stirring at –78 °C increases the conversion to the 1,5-diketone product

[10] Stork, G.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 6152–6153.
[11] Kuo, F.; Fuchs, P. L. *Synth. Commun.* **1986**, *16*, 1745–1759.
[12] (a) Heathcock, C. H.; Norman, M. H.; Uehling, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2797–2799. (b) Sato, T.; Wakahara, Y.; Otera, J.; Nozaki, H. *Tetrahedron* **1991**, *47*, 9773–9782. (c) Ishihara, K. Hananki, N.; Yamamoto, H. *Synlett* **1993**, 577–579.
[13] (a) Duhamel, P.; Dujardin, G.; Hennequin, L.; Poirier, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 387−396. (b) Duhamel, P.; Hennequin, L.; Poirer, G. M.; Tavel, G.; Vottero, C. *Tetrahedron* **1986**, *42*, 4777–4786.



Scheme 3.6. Successful Robinson annulation and synthesis of diyne **3.22**.

(**3.17**).[14] The mechanism of this reaction is believed to proceed through a transiently-formed, stabilized carbocation (Scheme 3.6; shown in maroon), which is in equilibrium with its hemiacetal vinylogue (not shown). The authors had previously synthesized hemiacetal vinylogues of MVK and demonstrated them to be very robust MVK surrogates under mildly acidic conditions to afford 1,5-diketone products. Undesirable side pathways entailing oligomerization are ostensibly prevented since the intermediate alkyl enol ether is not as nucleophilic as the starting TMS enol ether.

An inseparable 3:1 mixture of diastereomers was formed during the Mukaiyama−Michael reaction; however, only the major (desired) stereoisomer underwent subsequent aldol cyclization/dehydration, permitting clean isolation of **3.18** following column chromatography. The rationale for the observed diastereomeric mixture can be explained by the half chair

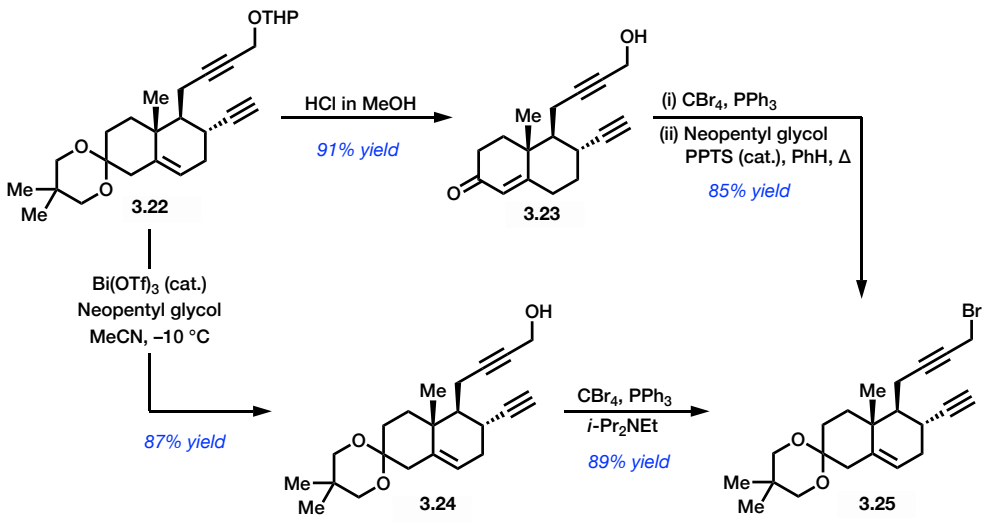
[14] Liffert, R. Total syntheses of eremophilane sesquiterpenoids based on biogenetic hypotheses. PhD Dissertation, University of Zurich, Zürich, Switzerland, 2018.

conformations of the starting enol ether. Due to $A^{1,2}$ strain between the methyl and CH_2OTBS groups, the conformation leading to the desired outcome where those groups become *cis* in the product is be favored.[12a, 15] However, the imperfect diastereoselectivity could be explained by the alkyne substituent blocking the incoming electrophile, thereby leading to some of the undesired epimer where the trans-diaxial approach in the alternate conformer experiences less steric hindrance. Although the isolated yield for this annulation sequence was moderate, due to competing silyl enol ether hydrolysis back to **3.15** during the Mukaiyama-Michael step, this material could be smoothly recycled to afford a 61% yield of **3.18** (over three steps) after three sequences of recycling hydrolyzed material.

Octalone **3.18** was transformed to tosylate **3.21** in 79% yield over an efficient three step sequence: ketalization with concomitant olefin isomerization, silyl deprotection, and sulfonylation (Scheme 3.6). Treatment of **3.21** with the lithio derivative of propargyl tetrahydropyranyl (THP) ether in THF and heating the resultant solution at reflux for 18 h afforded the desired diyne **3.22** in 75% yield. As observed in the model system, attempts to perform this reaction at lower temperature with or without the use of polar aprotic additives (e.g., DMPU, HMPA) gave inferior results.

In the interest of moving forward to the requisite propargyl bromide fragment, treatment of **3.22** with methanolic HCl furnished fully deprotected enone **3.23** in excellent yield (Scheme 3.7). The enone thus formed was then subjected to Appel bromination of the propargyl alcohol and re-ketalization delivered **3.25**. With an authentic sample of the long-sought propargyl bromide fragment, attention was focused back to investigate the chemoselective deprotection of the THP acetal in order to find a scalable, reproducible protocol that leaves the neopentyl glycol

[15] Johnson, F. *Chem. Rev.* **1968**, *68*, 375–413.

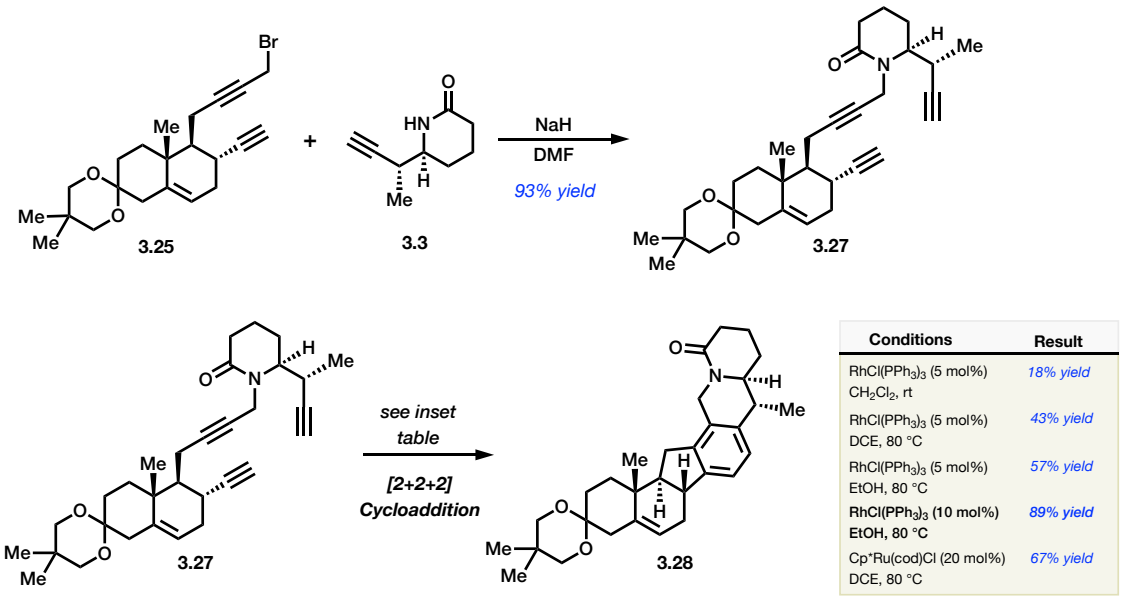


Scheme 3.7. Preparation of propargyl bromide **3.25**.

ketal intact. As before, copper (II) chloride gave inconsistent results, and the reaction yields were never able to be fully stabilized on larger scales. All protic acids usually led to rapid hydrolysis to the enone, thus we turned towards milder Lewis acids that could be carried out in the absence of residual moisture. Finally, bismuth (III) trifluoromethanesulfonate emerged as great candidate to achieve the selective deprotection of the THP acetal. It was found that optimal conditions were 5 mol% of $Bi(OTf)_3$ and 5 equivalents of neopentyl glycol in anhydrous acetonitrile at –10 °C, which provided **3.24** in 87% yield. The added neopentyl glycol was necessary to achieve full conversion and served its role as a means to transfer the THP group from the propargyl alcohol without the possibility of disrupting the C3 ketal. A final Appel-type bromination gave the requisite propargyl bromide fragment **3.25** in 89% yield.

3.5. Fragment Union and Synthesis End-Game

The two chiral fragments were conjoined by alkylation of piperidinone **3.3** (NaH, DMF) with propargyl bromide **3.25** to provide triyne **3.27** in excellent yield (Scheme 3.8). Significantly, only 1 equivalent of each fragment was necessary in this highly efficient reaction.

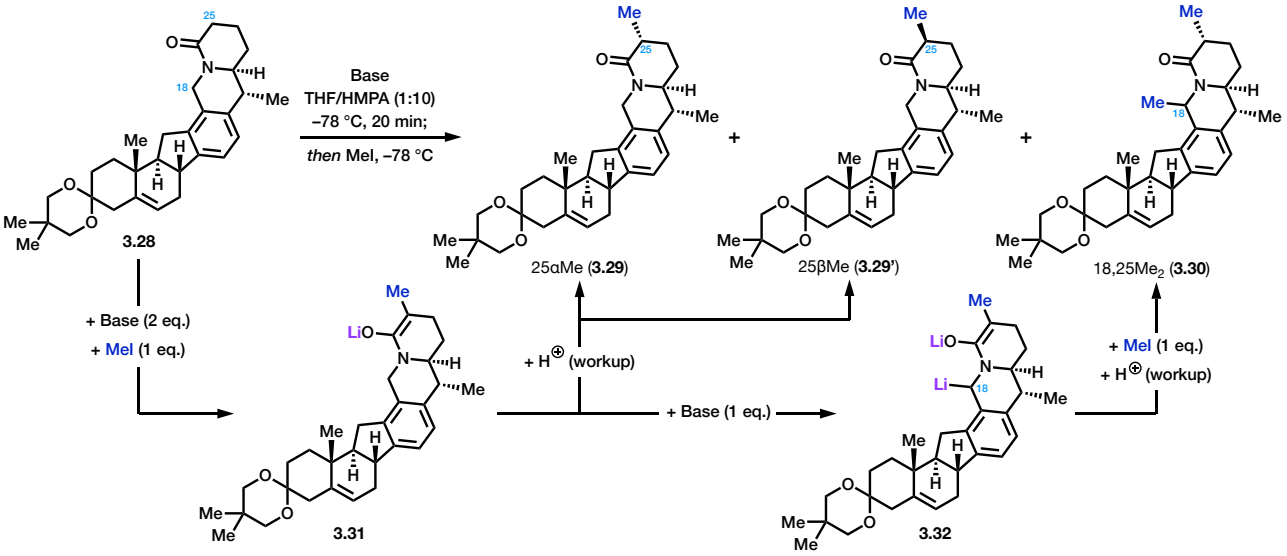


Scheme 3.8. Fragment union and optimization of the key [2 + 2 + 2] cycloisomerization.

The critical [2 + 2 + 2] cycloisomerization required some optimization to provide synthetically useful yields. Ultimately, we found that $RhCl(PPh_3)_3$ in refluxing ethanol smoothly effected the alkyne trimerization, affording the desired cevanine framework of **3.28** in 89% yield. In accordance with a previous report, it was found that a polar solvent was crucial to achieve a high yield of the cycloisomerized product. This transformation can also be performed using conditions developed by Yamamoto (Cp*Ru(cod)Cl, DCE), but it required higher catalyst loadings in order to obtain useful yields. With a robust set of conditions leading to hexacyclic intermediate **3.28**, all that remained was installation of the C27 methyl group and some redox adjustments.

We found the lactam methylation to be quite challenging, and many standard conditions failed to provide any conversion to the methylated product (Scheme 3.9).[16] It was not until strongly basic conditions (*n*-BuLi, *t*-BuLi) were employed that any methylation was observed,

[16] (a) Abels, F.; Lindemann, C.; Schneider, C. *Chem. - Eur. J.* **2014**, *20*, 1964−2979. (b) Lindemann, C.; Schneider, C. *Synthesis* **2016**, *48*, 828−844.



Base[a]	Yield (αMe:βMe)	Yield (18,25Me$_2$) [e]
LDA	0% (N/A)	—
LiHMDS	trace (N/A)	—
n-BuLi	31% (2:1)	nd
t-BuLi	50% (2:1)	nd
LiTMP	70% (2:1)	10–15%
LiTMP [b]	72% (7:1)	10–15%
LiTMP [b,c]	41% (7:1)	45%
LiTMP [d]	15% (nd)	—

[a] 3 eq. used (unless stated otherwise)
[b] Quenched at –78 °C with MeOH
[c] 4 eq. used
[d] 2 eq. used
[e] Isolated in 4:1 dr for all cases

Scheme 3.9. Installation of the C25 methyl substituent.

delivering **3.29** in moderate yield and as a ca. 2:1 mixture of C25 epimers. Upon further investigation, we found lithium 2,2,6,6-tetramethylpiperidine (LiTMP) in the presence of hexamethylphosphoramide (HMPA) as a co-solvent led to an extremely rapid trapping of the intermediate enolate by methyl iodide. After a thorough optimization of the reaction conditions, it was found that 3 equiv of LiTMP were necessary to achieve complete enolization (as indicated by full conversion of **3.28** upon ensuing treatment with MeI). Furthermore, quenching of the reaction mixture with methanol at −78 °C gave the desired diastereomer in high selectivity (dr = 7:1) and permitted clean isolation of **3.29** in 63% yield, while a side product containing an additional methyl group (**3.30**) was also recovered (10−15% yields). Precise control of reagent stoichiometry was deemed crucial, as a significant amount of this dimethylated side product (40−

45% yields) was formed when too large of an excess of base was used. An analysis of the 2-D NMR of the side-product indicates that the additional methyl group is incorporated at the benzylic carbon (C18), giving an inseparable 4:1 mixture of diastereomers of undetermined relative stereochemistry. The formation of this byproduct necessitates the intermediacy of the C-18-lithio species (**3.32**), presumably through benzylic lithiation of the initially formed enolate.[17] Intermediate **3.29**, which now possesses the entire carbon skeleton of the natural product, only needed to be taken through several redox adjustments in order to complete the total synthesis.

Several tactics were initially explored for the most difficult of those redox adjustments: installation of C6 axial hydroxy group (Scheme 3.10). Some of the prior syntheses described in Section 1.1E were faced with this same problem and many of the solutions that were ultimately reported to be enabling required lengthy step counts (>6 steps) to reach the final target. The $\Delta^{5,6}$ olefin of **3.28** was epoxidized with *m*-CPBA to furnish **3.33** in good yield, but as an inseparable 1.3:1 mixture of diastereomers. The stereoselectivity of olefin oxidations usually proceeds from the α-face (the so called "rule of α-attack") since the angular methyl group effectively shields the top face.[18] The considerable amount of the thus formed β-epoxide may arise due to influence of the neopentyl glycol ketal.[19] Unfortunately, attempts at regioselective reductive opening of the epoxides to give **3.34** were not successful.[20]

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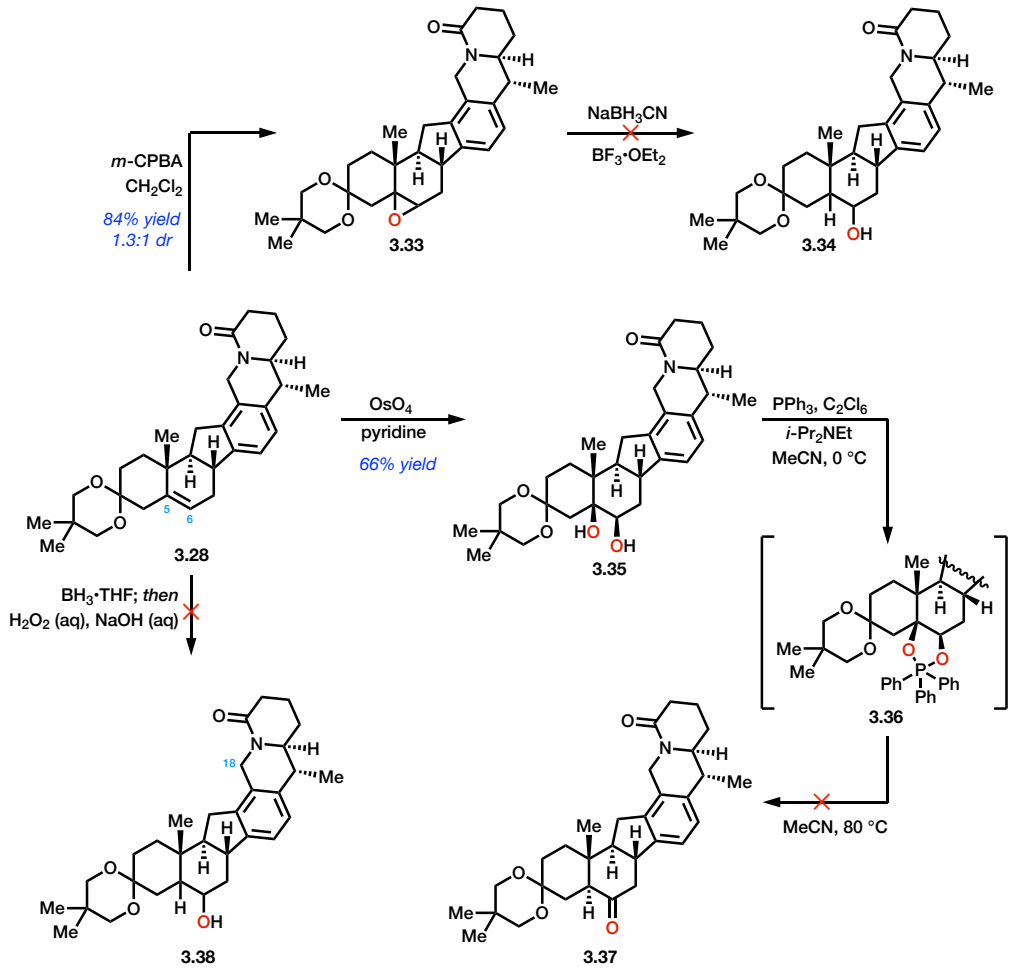
[17] For a recent review of benzylic lithiation, see: (a) Wong, J. Y. F.; Barker, G. *Tetrahedron* **2020**, *76*, 131704−131717. For relevant literature examples, see: (b) Li, X.; Leonori, D.; Sheikh, N. S.; Coldham, I. *Chem. - Eur. J.* **2013**, *19*, 7724−7730. (c) (c) Li, X.; Coldham, I. *J. Am. Chem. Soc.* **2014**, *136*, 1551−1554. (d) Talk, R. A.; Duperray, A.; Li, X.; Coldham, I. *Org. Biomol. Chem.* **2016**, *14*, 4908−4917.

[18] Kirk, D. N.; Hartshorn, M. P. *Steroid Reaction Mechanisms*; Elsevier: Amsterdam, London, and New York, 1968.

[19] Bernstein, S.; Allen, W. S.; Linden, C. E.; Clemente, J. *J. Am. Chem. Soc*. **1955**, *77*, 6612–6613.

[20] Hutchins, R. O.; Taffer, I. M.; Burgoyne, W. *J. Org. Chem.* **1981**, *46*, 5214–5215.



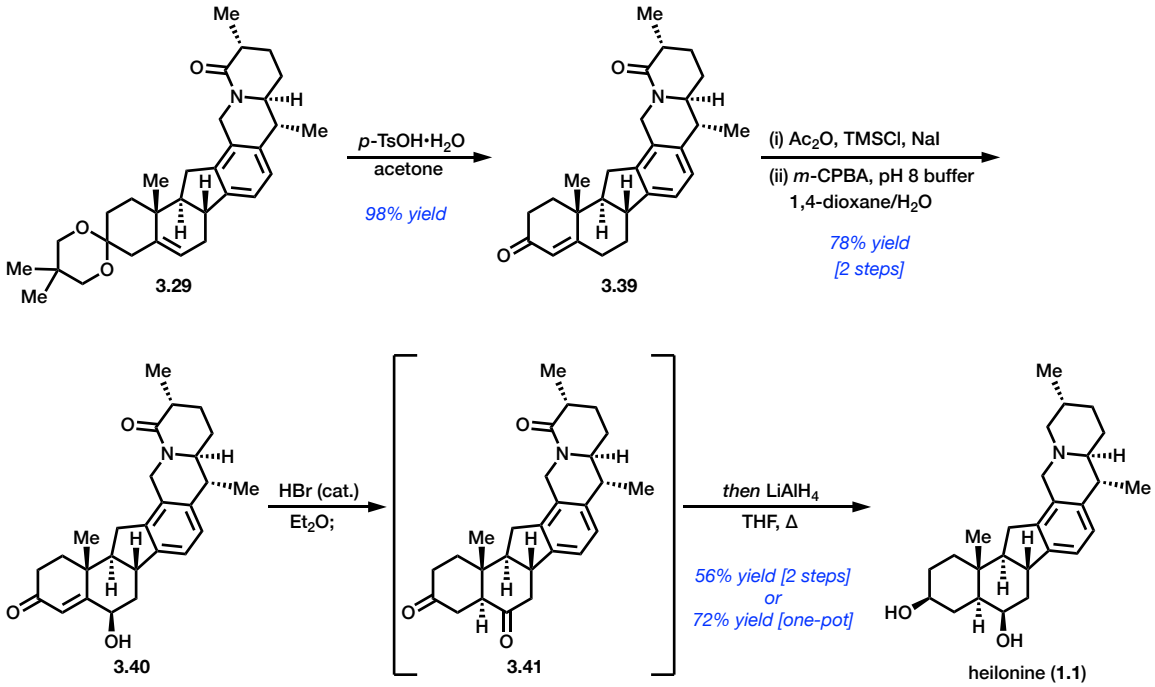
Scheme 3.10. Unsuccessful attempts to install the C6 hydroxyl group.

A dihydroxylation using osmium tetroxide gave even better selectivity, furnished β-diol **3.35** in 66% isolated yield.[21] It was then proposed that a phosphorane-mediated, pinacol-type rearrangement may lead to *trans*-decalin **3.37** featuring a C6 ketone.[22] When diol **3.35** was treated with triphenylphosphine and hexachloroethane the intermediate cyclic phosphorane (**3.36**) appeared to form according to TLC analysis, however heating to reflux led to nonspecific decomposition and the desired product was not observed.

[21] Bernstein, S.; Littell, R. *J. Org. Chem.* **1961**, *26*, 3610–3613.
[22] (a) DeCamp, A. E.; Mills, S. G.; Kawaguchi, A. T.; Desmond, R.; Reamer, R. A.; DiMichele, L.; Volante, R. P. *J. Org. Chem*. **1991**, *56*, 3564–3571. (b) Defaut, B.; Parsons, T. B.; Spencer, N.; Male, L.; Kariuki, B. M.; Grainger, R. S. *Org. Biomol. Chem*. **2012**, *10*, 4926–4932.

We also tried to functionalize the $\Delta^{5,6}$ olefin of **3.28** through standard hydroboration–oxidation, which would lead directly to **3.38**. Surprisingly, the olefin was unreactive under all of the conditions that were attempted. When conversion of the starting material was observed, analysis of the crude ^{1}H NMR seemed to reveal that lactam was reduced due to the upfield shift of the C18 methylene signals. Difficult hydroborations have also been noted by others in similar contexts.[23]

Despite these setbacks in functionalizing the $\Delta^{5,6}$ olefin toward the C6 β-hydroxyl, we eventually found a path forward. Intermediate **3.29** was treated with *p*-toluenesulfonic acid in acetone to afford enone **3.39** in near quantitative yield (Scheme 3.11). This material was transformed (Ac_2O, TMSCl, NaI) to a dienol acetate (not shown)[24] the oxidation of which with



Scheme 3.11. Completion of the total synthesis of heilonine (**1.1**).

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[23] (a) Rasmusson, G. H.; Reynolds, G. F.; Steinberg, N. G.; Walton, E.; Patel, G. F.; Liang, T.; Cascieri, M. A.; Cheung, A. H.; Brooks, J. R.; Berman, C. *J. Med. Chem.* **1986**, *29*, 2298–2315. (b) Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746–1757.
[24] Chowdhury, P. K.; Sharma, R. P.; Barua, J. N. *Tetrahedron Lett.* **1983**, *24*, 3383−3384.

m-chloroperoxybenzoic acid furnished γ-hydroxyenone **3.40** in 78% yield over two steps.[25] Treatment of **3.40** with catalytic hydrobromic acid promoted its clean isomerization to a γ-diketone **3.41**.[26] While the mechanism has not been studied in depth, the exclusive formation of the *trans*-fused product suggests that a stereospecific 1,2-hydride shift may occur upon protonation of the enone.

The resulting 1,4-diketone (**3.41**) was next subjected to global reduction through the action of $LiAlH_4$, which accomplished the diastereoselective reduction of both ketones and the total reduction of the lactam functionality to afford (+)-heilonine (**1.1.**). The reduction of the C3 and C6 ketones was selectively achieved α-delivery of the hydride and no detectable formation of other isomers was observed. For the purpose of full characterization, this material was converted to its diacetate, which was found to be spectroscopically identical to the diacetate derivative of naturally isolated heilonine. Given the very clean reaction profile for the acid-catalyzed isomerization, we attempted the global reduction by sequential addition of $LiAlH_4$ in the same pot once TLC analysis indicated complete conversion to **3.40**. This protocol afforded heilonine (**1.1**) in an improved 72% yield over that obtained for the two-step proceeding via isolated intermediate. In summary, the total synthesis of (+)-heilonine was achieved in 21 steps from ethyl vinyl ketone and a 1.9% overall yield.

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[25] (a) Kirk, D. N.; Wiles, J. M. *J. Chem. Soc. D* **1970**, 518. (b) Kirk, D. N.; Wiles, J. M. *J. Chem. Soc. D* **1970**, 1015–1016.

[26] (a) Wijnberg, J. B. P. A.; Jongedijk, G.; De Groot, A. *J. Org. Chem*. **1985**, *50*, 2650−2654. (b) Wijnberg, J. B. P. A.; Vader, J.; De Groot, A. *J. Org. Chem*. **1983**, *48*, 4380−4387.

Concluding Remarks

In summary, we have achieved the first total synthesis of heilonine, representing the first *de novo* synthesis of a cevanine-type alkaloid.[27] The key to the success of our strategy was the utilization of an intramolecular [2 + 2 + 2] cycloisomerization to forge the central aromatic D ring, along with C and E rings concomitantly. Other indispensable features to our strategy include an organocatalytic enantioselective Diels−Alder reaction, a challenging late-stage diastereoselective methylation of a heptacyclic intermediate, and a one-pot acid-catalyzed isomerization−global reduction. The modularity and convergent nature of the approach described herein will grant expedient access to unnatural analogs and facilitate evaluation of the biological activity of related members of the cevanine family. Efforts are currently underway in our laboratory to modify this strategy to allow access to the other subclasses of *Veratrum* alkaloids.

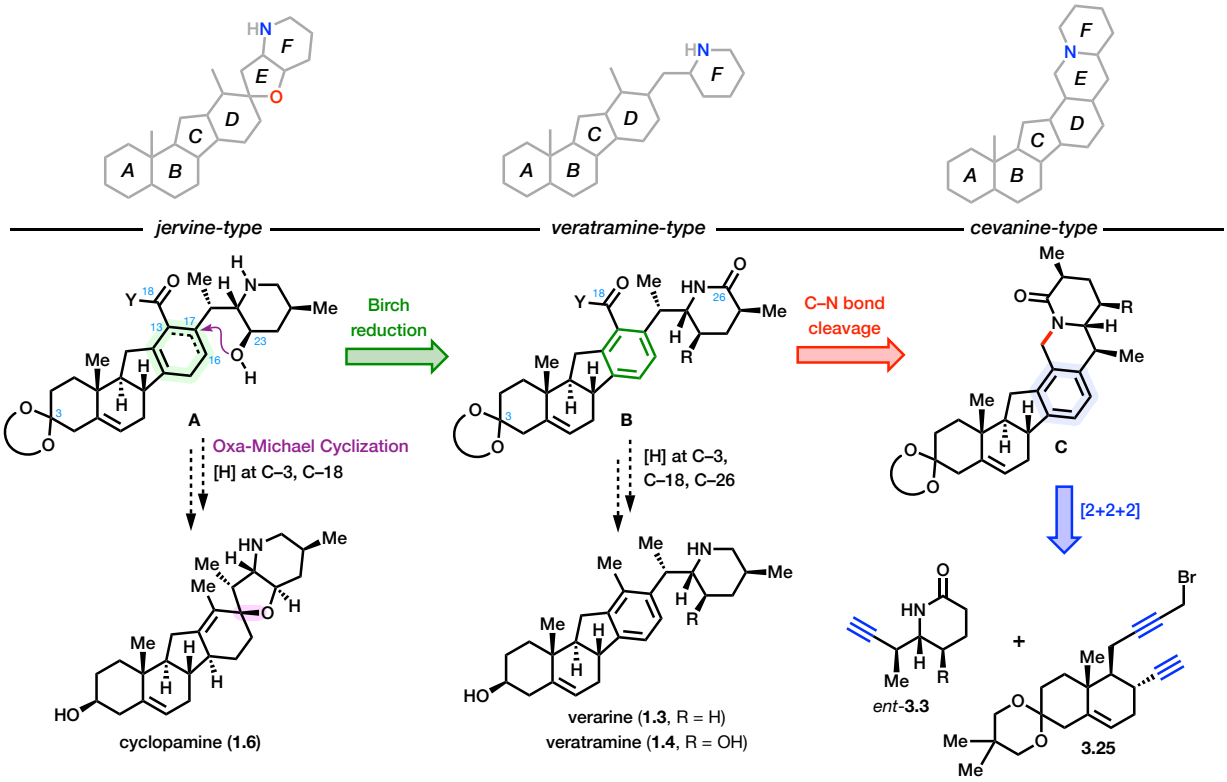
[27] Cassaidy, K. J.; Rawal, V. H. *J. Am. Chem. Soc.* **2021**, *143*, 16394–16400.

Chapter 4

Progress Toward a Collective Synthesis of the *Veratrum* Family

4.1. Discussion of Retrosynthetic Strategy

The success of our concise and convergent strategy to access the cevanine subgroup of *Veratrum* alkaloids yielded further investigations into a potential collective synthesis. In order to realize such a scenario, we would need an efficient means to convert the cevanine framework to respective veratramine and jervine. The overall retrosynthetic strategy is depicted in Scheme 4.1. It was surmised that a Birch reduction (or alternative dearomatization process) could afford an appropriate precursor to the jervine-type skeleton. The spiro furan ring could be forged following

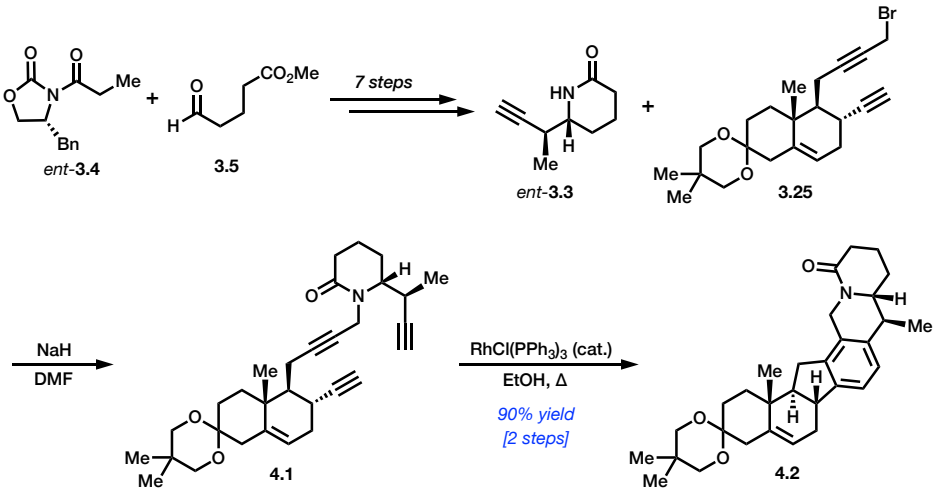


Scheme 4.1. Retrosynthetic plan for a collective synthesis of the *Veratrum* family.

alkene isomerization to an α,β-unsaturated ester and ensuing oxa-Michael reaction. Reductions at C3 and C18 would then afford cyclopamine. A veratramine-type intermediate **B** (Y = OH) was anticipated to be a suitable substrate for the critical Birch reduction. In turn, such an intermediate could also be elaborated to verarine and veratramine upon a series of reductions at C3, C18, and C26.

In the forward sense, a site-selective cleavage of the C–N bond of a cevanine intermediate **C** would provide straightforward entry to the veratramine skeleton. However, the rigid skeleton imposes constraints that severely restricts the tactics that may be used to achieve this transformation (*vide infra*). If successful, then **C** could be conveniently prepared using the same strategy that was used for heilonine. One important contrast, however, is the opposite absolute configuration about the E and F rings found in these veratramine and jervine targets. The modularity of our [2 + 2 + 2] cycloaddition strategy is expected to perfectly address this issue, as the piperidinone fragment could be prepared using the opposite enantiomer of Evans' acyl oxazolidinone to secure the requisite *ent*-**3.3** to be coupled with original diyne fragment **3.25**.

As such, *ent*-**3.3** was prepared using the same seven-step sequence shown in Section 3.3. The alkylation with propargyl bromide **3.25** afforded triyne **4.1** in high yield (Scheme 4.2). Using



Scheme 4.2. Synthesis of hexacycle **4.2**.

the previously optimized conditions of the [2 + 2 +2] cycloisomerization, hexacycle **4.2** was furnished in 89% yield.

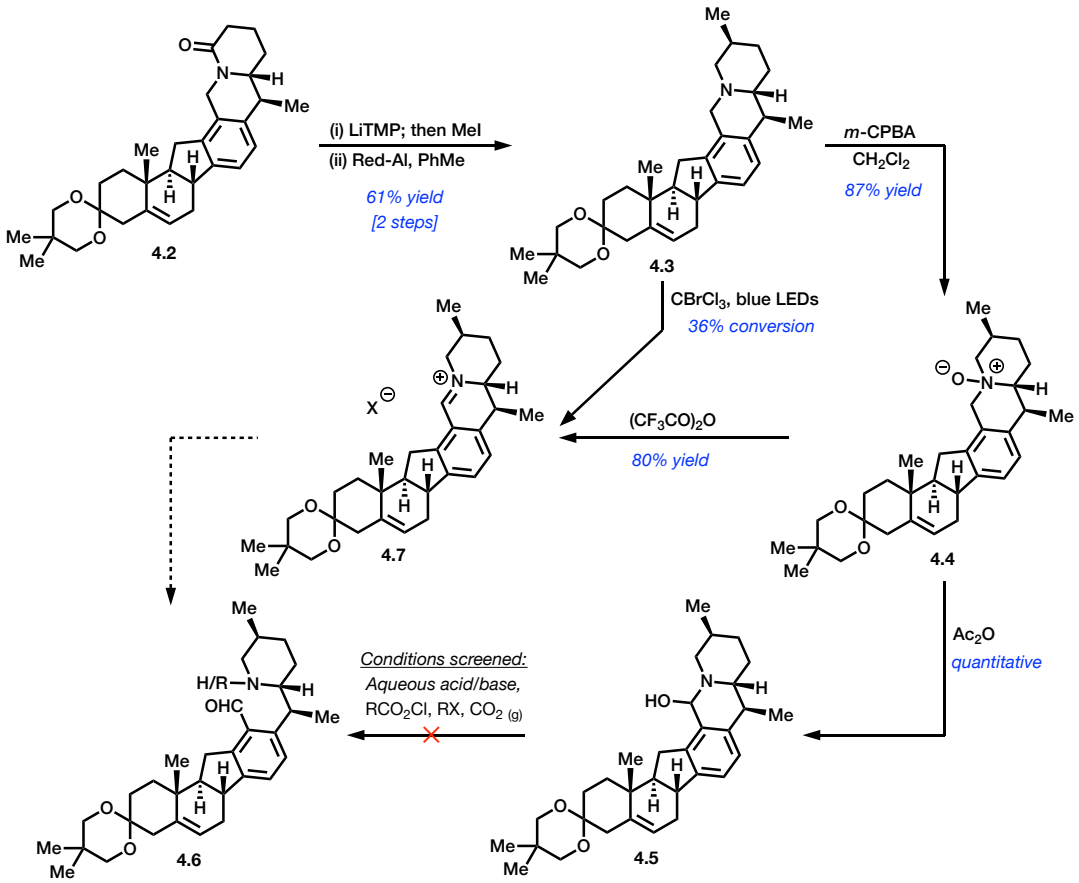
4.2. Initial Attempts C–N Bond Cleavage

Selective cleavage of C–N bonds in complex molecules has been a subject of intense investigation over recent years. Given the importance and abundance of heterocyclic systems which contain C(sp^3)–N bonds and the potential to access diversified chemical space at a late-stage, many different research groups have contributed elegant solutions.[1] The high bond dissociation energy and stability of unactivated C–N bonds, such as those found in tertiary amines, are some of the reasons why this area will likely continue to be a great challenge to the modern synthetic chemist. In our current context, the fused polycyclic framework presents an additional challenge as selective cleavage of the benzylic C–N bond would not benefit from stereoelectronic stabilization by the adjacent π-system. We considered several different reactivity modes to help address these challenges, including reductive, oxidative, photoredox catalysis, and transition-metal catalysis. The results of some of these approaches will be discussed in the remainder of this section.

One of the tactics we attempted to employ for the benzylic C–N bond cleavage was the Polonovski-Potier reaction. Since the seminal discovery by the Polonovski brothers that a tertiary amine *N*-oxide undergoes a rearrangement in which one of the alkyl groups attached to nitrogen is cleaved, this reaction has seen elegant applications to achieve structural diversification in

[1] (a) Roque, J. B.; Kuroda, Y.; Göttemann, L. T.; Sarpong, R. *Nature* **2018**, *564*, 244–248. (b) Zhang, J.; Chang, S. *J. Am. Chem. Soc.* **2020**, *142*, 12585–12590. (c) Su, J.; Ma, X.; Ou, Z.; Song, Q. *ACS Cent. Sci.* **2020**, *6*, 1819−1826. (d) Jurczyk, J.; Lux, M. C.; Adpressa, D.; Kim, S. F.; Lam, Y.; Yeung, C. S.; Sarpong, R. *Science* **2021**, *373*, 1004–1012. (e) Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. *Nature* **2021**, *593*, 223–227.

complex molecule synthesis.[2,3] In our current context, hexacyclic intermediate **4.2** was first elaborated to tertiary amine **4.3** using the carefully optimized methylation conditions and an ensuing reduction was achieved in excellent yield using sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) (Scheme 4.3). This material could be cleanly oxidized to the corresponding *N*-oxide (**4.4**) with *m*-CPBA. Treatment of **4.4** with acetic anhydride (Polonovski conditions) led to quantitative conversion to a new compound, which was characterized as lactamol **4.5**. This compound arises from the expected reaction mechanism, where **4.4** is first converted to *O*-



Scheme 4.3. Exploration of C–N bond cleavage using a Polonovski-Potier rearrangement.

[2] (a) Polonovski, M.; Polonovski, M. *Bull. Soc. Chim.* **1927**, 1190–1208. (b) Polonovski, M. *Bull. Soc. Chim. Belg.* **1930**, *39*, 1–39.
[3] (a) Langlois, N.; Guéritte, F.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1976**, *98*, 7017–7024. (b) Raucher, S.; Bray, B. L.; Lawrence, R. F. *J. Am. Chem. Soc.* **1987**, *109*, 442–446. (c) Morita, H.; Kobayashi, J. *J. Org. Chem.* **2002**, *67*, 5378–5381.

acylimonium salt, which undergoes E2-type elimination to an iminium salt that is in equilibrium with an α-acyloxy amine; however, the product exists exclusively as the cyclic hemiaminal as opposed to the ring-opened aldehyde and secondary amine. Various attempts to open the lactamol were all met with failure, as the desired aldehyde **4.6** was never observed.

Alternatively, the Potier modification of the Polonovski reaction was attempted on *N*-oxide **4.4**, where exposure to trifluoroacetic anhydride cleanly afforded metastable benzylic iminium species **4.7**.[4] Moreover, this intermediate could also be accessed from tertiary amine **4.3** upon treatment with bromotrichloromethane in the presence of visible light, albeit in modest yield.[5] As the iminium salt could be carefully isolated upon simple evaporation of solvent and the volatile reagent by-products, an extensive search was performed for conditions that would promote cleavage the C–N bond. Oppolzer and coworkers encountered a similar problem in their elegant synthesis of lycorenine-type Amaryllidaceae alkaloid (±)-clivonine and carefully studied a biomimetic ring-switch.[6] The authors reported that a benzylic iminium salt was first smoothly converted to the corresponding lactamol upon treatment of a DMSO-d_6/D_2O solution of the iminium with Cs_2CO_3, then addition of methyl iodide gave the corresponding *N*-methyl aldehyde. The initial part of the protocol translated well to our substrate, as it was found that Cs_2CO_3 proved to be unique in affording lactamol **4.5** (other inorganic bases gave no conversion) (Scheme 4.4). However, it was again found that lactamol **4.5** was highly resistant to undergo ring-opening in the presence of alkylating reagents.

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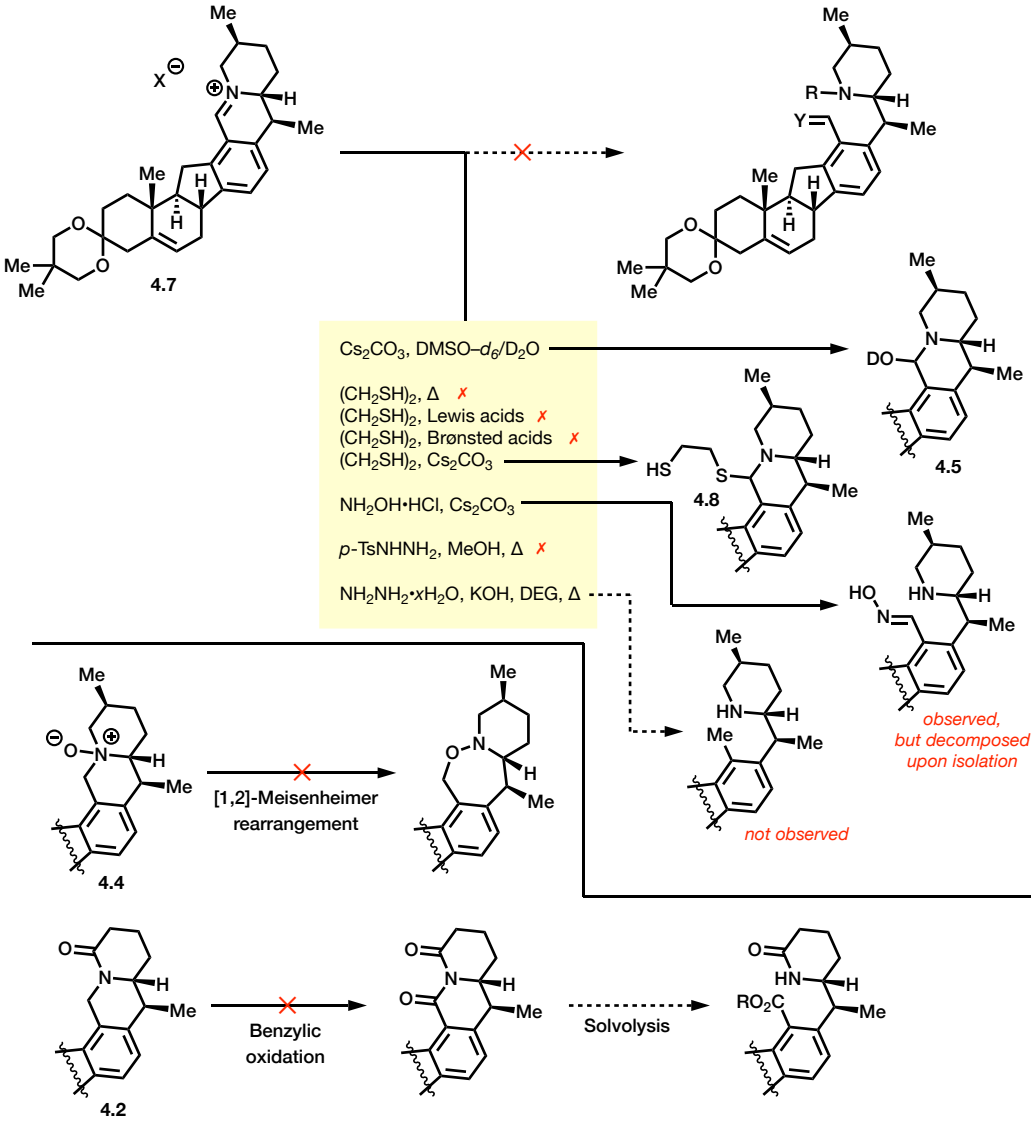
[4] Cave, A.; Kan-Fan, C.; Potier, P.; Le Men, J. *Tetrahedron* **1967**, *23*, 4681–4689.
[5] Franz, J. F.; Kraus, W. B.; Zeitler, K. *Chem. Commun*. **2015**, *51*, 8280–8283.
[6] Giró Mañas, C.; Paddock, V. L.; Bochet, C. G.; Spivey, A. C.; White, A. J. P.; Mann, I.; Oppolzer, W. *J. Am. Chem. Soc.* **2010**, *132*, 5176–5178.

We next turned our attention to other nucleophiles that could add to the iminium and reasoned that a 1,3-dithiolane would serve as an ideal group to introduce, as reductive desulfurization would afford the aromatic methyl group (Scheme 4.4). Under the typical conditions for 1,3-dithiolane protection from aldehydes (Brønsted and Lewis acids), no conversion of the iminium was observed. However, basic conditions (Cs_2CO_3) promoted addition of the thiolate to yield a thioaminal (**4.8**). Attempts to convert the iminium to oxime or hydrazone were met with failure, with the former being observed by ^{1}H NMR but decomposed



Scheme 4.4. Attempts to cleave C–N bond via benzylic iminium salt **4.7**.

upon isolation. Preliminary efforts at a one-pot ring-opening–Wolff-Kishner reduction only afforded complex mixtures and the desired product was not detected.

Several earlier intermediates were also subjected to different modes of reactivity that may afford products that would be less resistant to undergo ring-opening. One tactic that was briefly explored was a [1,2]-Meisenheimer rearrangement, which would give a 1,2-oxazepane where the weak N–O bond would be more easily cleaved. A solution of *N*-oxide **4.4** was heated in a sealed tube, but the projected [1,2]-Meisenheimer rearrangement did not occur and starting material was cleanly recovered. Also, it was surmised that if lactam **4.2** could be successfully oxidized to furnish an imide, then solvolysis should proceed through the more electrophilic E ring carbonyl. Unfortunately, several attempts to perform this oxidation were not successful on lactam **4.2**.

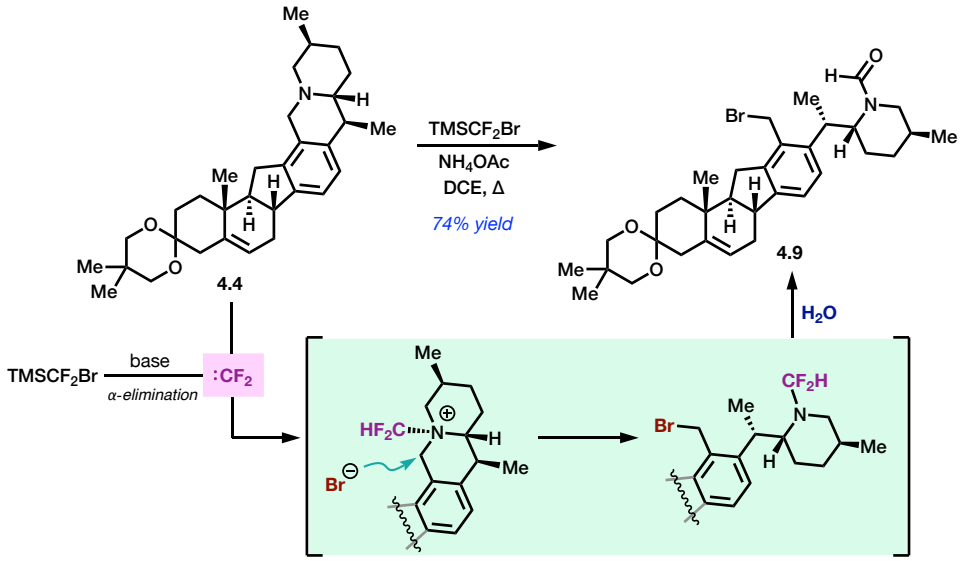
4.3. Total Synthesis of Verarine via a Novel Ring-Opening Functionalization

The isolation of verarine (**1.3**) was first reported in 1966 from *Veratrum album subsp. lobelianum*.[7] The structure of this alkaloid was assigned by Tomko and Bauer on the basis of chemical and spectroscopic investigations, while the relative and absolute stereochemistry was assigned by Masamune shortly thereafter.[8,9] Masamune would later report the conversion of veratramine to verarine through a five-step sequence, providing further confirmation of the structure and configuration. As discussed in the first chapter, this 23-desoxy-analog of veratramine was the subject of a remarkable total synthesis by Kutney and coworkers (see

[7] Tomko, J.; Vassová, A. *Chem. Zvesti* **1964**, *18*, 266–272.
[8] Tomko, J.; Bauer, S. *Collection Czechoslov. Chem. Commun.* **1964**, *25*, 2570–2574.
[9] Masamune, T.; Yamazaki, I.; Takasugi, M. *Bull. Chem. Soc. Jpn* **1966**, *39*, 1090.

Section 1.1E). Similar to cyclopamine, prominent inhibition (IC_{50} = 0.63 ± 0.02 μM) of the Hedgehog (Hh) signaling pathway has been recently reported in cells incubated with verarine.[10]

Despite the failures to break the C–N bond that were discussed in the previous section, a path towards the veratramine-type alkaloids was achieved through the application of a novel ring-opening functionalization. Seo and coworkers recently reported a general method for the ring-opening of pyrrolidines, piperidines, and other unstrained azacycles via a von Braun-type process that is enabled by difluorocarbene transfer.[11] It was found that when subjected to the reaction conditions ($TMSCF_2Br$, NH_4OAc, DCE, 80 °C), the tertiary amine-containing hexacycle **4.4** underwent successful ring-opening functionalization to provide **4.9** in 74% yield (Scheme 4.5). According to the authors mechanism and that of the related von Braun reaction, difluorocarbene is first generated *in situ* by α-elimination of $TMSCF_2Br$[12] and the resulting highly electrophilic species reacts with the tertiary amines to form a quaternary ammonium salt.

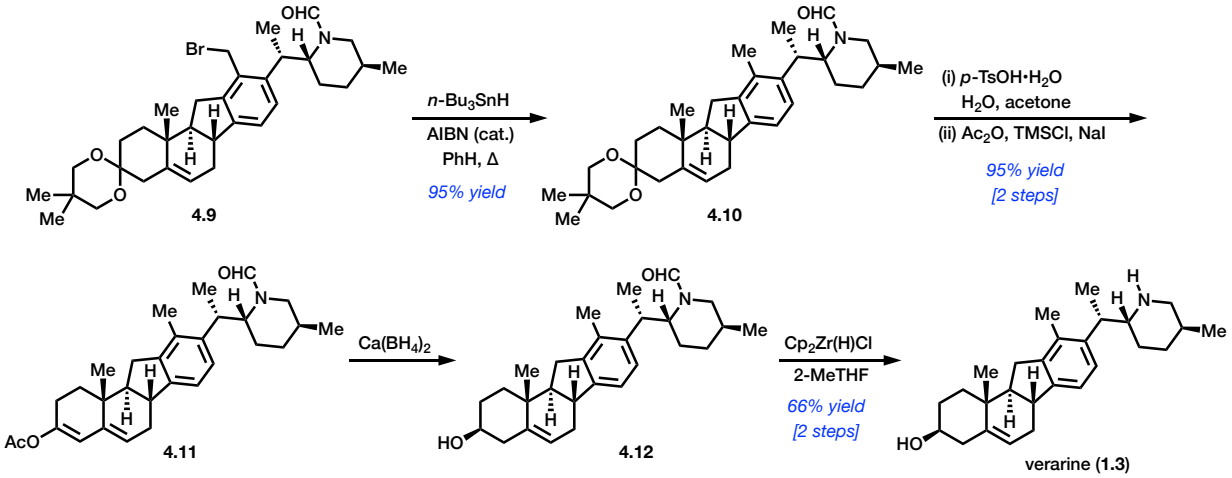


Scheme 4.5. Ring-opening functionalization of amine **4.4**.

[10] Gao, L.; Chen, F.; Li, X.; Xu, S.; Huang, W.; Ye, Y. *Bioorganic Med. Chem. Lett.* **2016**, *26*, 4735–4738.
[11] Kim, Y.; Heo, K.; Kim, D.; Chang, S.; Seo, S. *Nat. Commun.* **2020**, *11*, 4761.
[12] Li, L.; Wang, F.; Ni, C.; Hu, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 12390–12394.

Compelling evidence for this intermediate was found, as it could be cleanly isolated and characterized when the reaction was performed at ambient temperature. The ring-opening by the bromide counteranion proceeds only at elevated temperature and with complete regioselectivity for the more electrophilic and sterically accessible benzylic position. The *N*-formyl moiety is lastly unveiled through *in situ* hydrolysis of the unstable *N*-CF_2H group.[13] This highly practical and efficient strategy not only furnishes the veratramine-type skeleton but protects the piperidine nitrogen during the ensuing synthetic sequence with a readily removable group.

To complete the synthesis, the benzylic bromide was first subjected to radical debromination using Bu_3SnH/AIBN to afford **4.10** in excellent yield (Scheme 4.6). Ketal



Scheme 4.6. Completion of the total synthesis of verarine (**1.3**).

deprotection and treatment of the resultant enone with Ac_2O and TMSI (generated *in situ* from TMSCl and NaI) yielded dienol acetate **4.11**. Reduction of the dienol acetate with $Ca(BH_4)_2$ proceeded stereoselectively to install the C3 β-hydroxyl group with retention of $\Delta^{5,6}$-unsaturation (**4.12**).[14] Finally, reductive deformylation using CpZr(H)Cl (Schwartz's reagent) completed the

[13] Ma, X.; Deng, S.; Song, Q. *Org. Chem. Front.* **2018**, *5*, 3505–3509.
[14] (a) Moon, S.-S.; Stuhmiller, L. M.; McMorris, T. C. *J. Org. Chem*. **1989**, *54*, 26–28. (b) Moon, S.-S.; Stuhmiller, L. M.; Chadha, R. K.; McMorris, T. C. *Tetrahedron* **1990**, *46*, 2287–2306.

total synthesis of verarine (**1.3**). The spectroscopic data (^{1}H and ^{13}C NMR) were identical to reported spectra and optical rotation data was also consistent to the isolation data.

Concluding Remarks and Future Directions

Substantial progress has been made toward the collective synthesis of the entire family of the *Veratrum* alkaloids having demonstrated the feasibility of accessing veratramine-type congeners through cleavage of a cevane C–N bond. To complete the study, we propose utilizing a Birch reduction to dearomatize the aromatic ring of the veratramine-type alkaloids, to set the stage for a cycloetherification process that would forge the D/E oxaspiro[4.5]decene motif. Preliminary investigations into the Birch reduction have been conducted. However, subjection of either cevane- or veratramine-type intermediates (**4.3** and **4.10**, respectively) to the standard conditions for Birch or Benkeser reduction yielded no conversion. A thorough literature search revealed a startling scarcity of examples of Birch reduction on polyalkyl substituted benzenes. This effect appears to be related the unfavorable kinetics associated with the protonation of the initial radical anion.[15] It has been proposed that several, bulky alkyl substituents lessen the effective stabilization of the initially formed ion pair by solvation while also providing steric hindrance to approach of the alcohol.[16] In spite of these unencouraging results, it is envisioned that the new ring-opening functionalization protocol could afford substrates bearing a carboxylic acid that would significantly influence the outcome of the Birch reduction.

Along these lines, a route towards jervine-type congeners that would culminate in the first *de novo* synthesis of cyclopamine has been devised (Scheme 4.7). Such a route would

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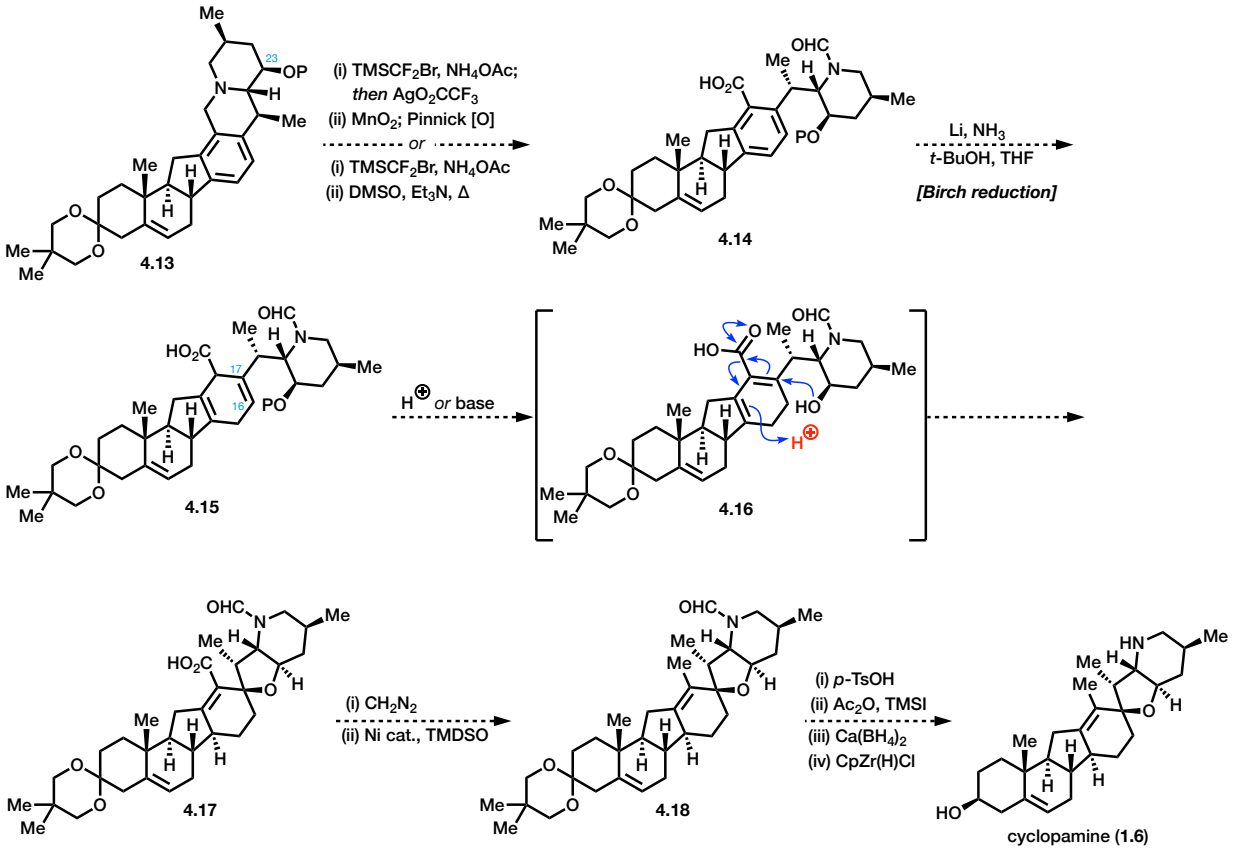
[15] Mander, L. N. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds., Pergamon: Oxford, 1991; Vol. 8, pp 489–521.
[16] Krapcho, A. P.; Bothner-By, A. A. *J. Am. Chem. Soc.* **1959**, *81*, 3658–3666.



Scheme 4.7. Proposed route to jervine-type alkaloids and cyclopamine.

necessitate a means to introduce the C23 hydroxyl group, which would ideally be installed during the preparation of the piperidinone fragment and protected for subsequent manipulation. Seo and coworkers very recently published results that demonstrate an increased scope of nucleophiles for the ring-opening functionalization of tertiary amines via an anion exchange process.[17] As such, the use of silver (I) trifluoroacetate during the ring-opening should afford a benzylic alcohol, which could be oxidized to the corresponding carboxylic acid (**4.14**). Alternatively, the original produce producing a benzyl bromide could be used, where a Kornblum oxidation would also lead to **4.14**. The Birch reduction should then proceed smoothly and with complete regioselectivity for 1,4-cyclohexadiene derivative shown (**4.15**). The $\Delta^{16,17}$-

[17] Lim, H.; Seong, S.; Kim, Y.; Seo, S.; Han, S. *J. Am. Chem. Soc.* **2021**, *143*, 19966–19974.

olefin of this intermediate may then undergo isomerization to the more stable tetrasubstituted and conjugated diene **4.16**, whereupon *in situ* deprotection would reveal the hydroxyl group and undergo an intramolecular cyclization to afford **4.17**. With the jervine-type framework of **4.17** in hand, all that would remain to complete the synthesis of cyclopamine would be several redox and protecting group manipulations. First, the alkenyl carboxylic acid would be converting to the corresponding methyl ester and subjected to an exhaustive reduction to furnish the methyl group.[18] Finally, the same four-step sequence to introduce the C3 alcohol and deprotect the *N*-formyl group from our verarine synthesis would be used to complete the total synthesis of cyclopamine.

[18] Cook, A.; Prakash, S.; Zhang, Y.-L.; Newman, S. G. *J. Am. Chem. Soc.* **2020**, *142*, 8109–8115.

Chapter 5

Synthetic Studies Toward Heptacyclic *Veratrum* Alkaloids

5.1. Ussurienine Background

In 1988, Kaneko and coworkers reported the isolation of ussurienine (**5.1**), a novel cevanine alkaloid from *Fritillaria ussuriensis* (Figure 5.1).[1] The heptacyclic structure was assigned on the basis of extensive 2-D NMR spectroscopy and confirmed by X-ray crystallographic analysis. As opposed to other cevanine alkaloids, ussurienine does not have a methyl group at C25, but rather a methylene that bridges to the benzylic C18 position to form an additional (G) ring. The EF rings must adopt a *cis*-quinolizidine structure, where the lone pair on nitrogen is uncapable of undergoing pyramidal inversion and is therefore cis to the α-configured

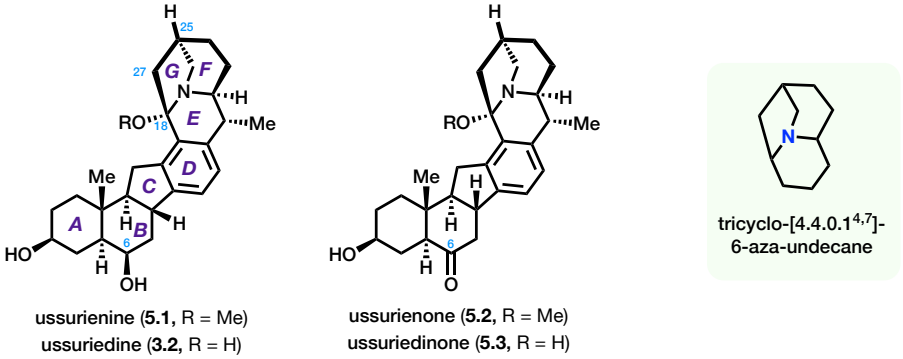


Figure 5.1. Structures of the heptacyclic alkaloids from *Fritillaria ussuriensis*.

hydrogen at C22. The unique EFG ring motif (tricyclo-[4.4.0.1^{4,7}]-6-aza-undecane), despite its structural rigidity, is surprisingly unstrained. Kaneko later published a full paper that disclosed ussurienine (**5.1**) and a newly isolated 6-keto derivative, ussurienone (**5.2**), were actually artifacts derived from the corresponding genuine alkaloids ussuriedine (**3.2**) and ussuriedinone (**5.3**),

[1] Kitamura, Y.; Nishizawa, M.; Kaneko, K. *Tetrahedron Lett.* **1988**, *29*, 1959–1962.

respectively.[2] The artifacts were shown to be produced upon acid hydrolysis in methanol during the isolation procedure.

To the best of our knowledge, the intricate tricyclo-[4.4.0.1^{4,7}]-6-aza-undecane remains unprecedented to this day in the alkaloid literature. While the biosynthesis of the cevanine alkaloids in general are relatively well understood (see Section 1.1B), C18 and C27 are quite distant and not activated sites.[3] Thus, these daunting targets are highly appealing not only from a structural perspective, but a means to explore synthetic strategies that may shed light on a plausible biogenesis. Ussuriedine and ussuriedinone were also shown to be characteristic alkaloids of *Fritillaria ussuriensis*, which is a major component in the Chinese medicinal herb "Bei-mu". A synthetic campaign would deliver structural analogs to permit a more thorough evaluation of the biological activity of cevanine-type alkaloids.

5.2. Retrosynthetic Analysis

In order to address the structural challenges as well as investigate a possible biosynthetic pathway, we have devised a synthetic strategy towards ussurienine that would be traced back to a common, cevanine-type intermediate in our heilonine synthesis. We envisioned that the C–C bond between C18 and C27 could arise from a [1,2]-Stevens rearrangement of an intermediate azetidinium ylide (Scheme 5.1).[4] This highly strained zwitterionic intermediate could be generated from **A** under thermal conditions, followed by treatment with strong base to

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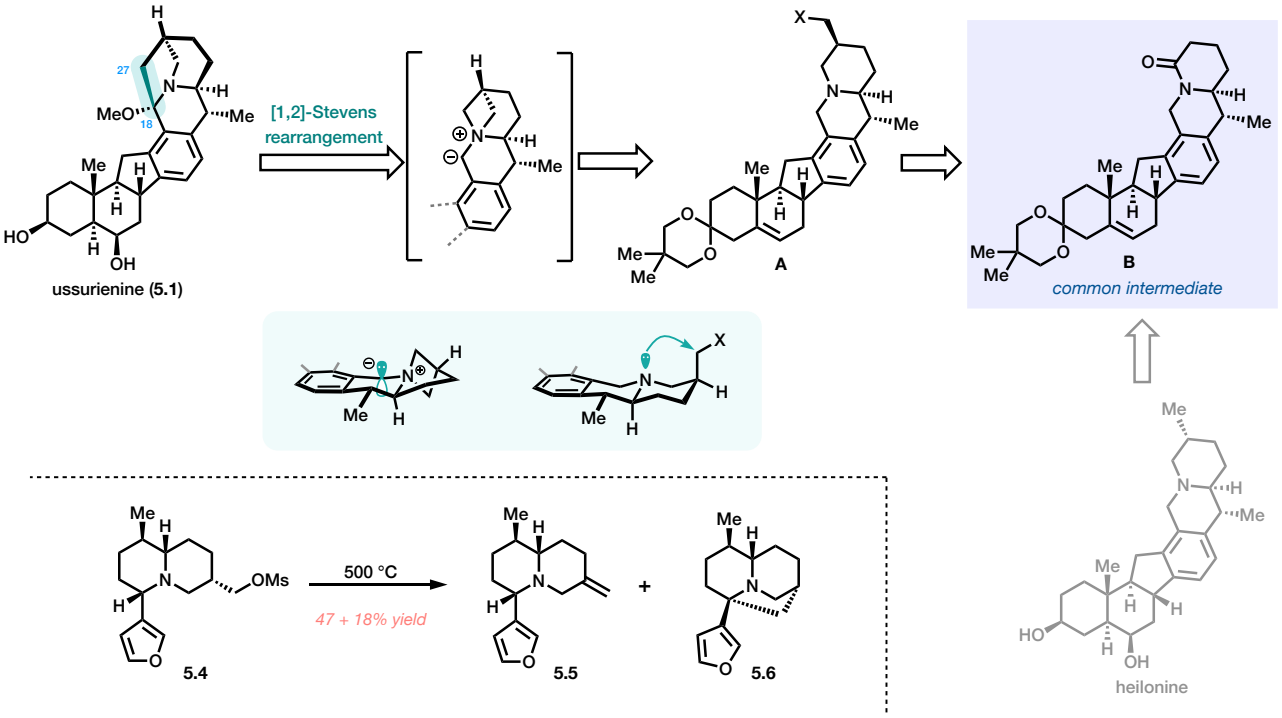
[2] Kitamura, Y.; Nishizawa, M.; Kaneko, K. *Tetrahedron* **1989**, *45*, 5755–5766.
[3] Gross, D.; Schütte, H. R.; Schreiber, K. In *Biochemistry of Alkaloids*; Mothes, K.; Schütte, H. R.; Luckner, M., Eds., VCH: Deerfield Beach, FL, 1985; pp 354–384.
[4] For seminal references, see: (a) Stevens, T. S.; Creighton, E. M.; Gordon, A. B.; MacNicol, M. *J. Chem. Soc.* **1928**, 3193–3197. (b) Stevens, T. S. *J. Chem. Soc.* **1930**, 2107–2119. For reviews on the [1,2]-Stevens rearrangement, see: (c) Pine, S. H. *Org. React.* **1970**, *18*, 403–464. (d) Vanecko, J. A.; Wan, H.; West, F. G. *Tetrahedron* **2006**, *62*, 1043–1062.



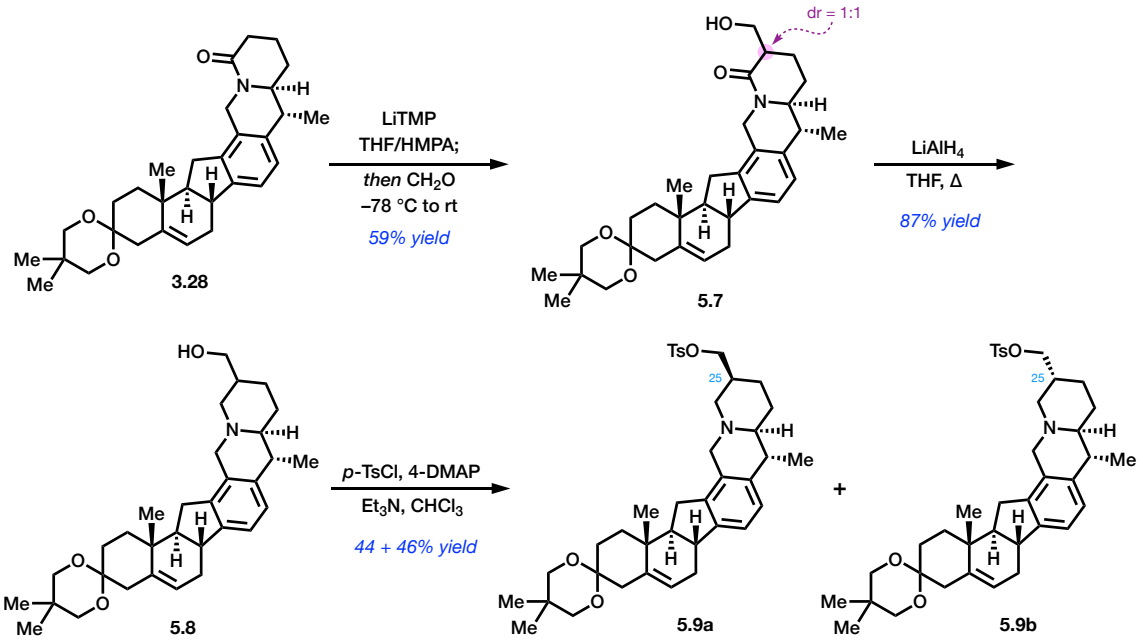
Scheme 5.1. Retrosynthetic analysis of ussurienine (**5.1**) and relevant precedent for key step.

deprotonate the benzylic position of the resultant quaternary ammonium salt. The reactivity of azetidinium ylides has been previously explored in the context of ring expansions, as well as for epoxidation and cyclopropanation. Maurer and Ohloff reported the pyrolysis of quinolizidine **5.4** afforded the expected elimination product (**5.5**), as well as a minor product that was assigned as bridging methylene constitutional isomer **5.6** (Scheme 5.1).[5] The relevance of this important precedent to our problem at hand is two-fold; (i) it indicates that formation of the azetidinium salt is possible under thermal conditions and (ii) that the [1,2]-Stevens rearrangement can be harnessed to construct bridging azatricycles. We sought to develop an analogous process that would proceed under milder conditions in the presence of potentially sensitive functionality. Thus, key intermediate **A** was conveniently traced back to the same [2 + 2 + 2]-cycloadduct (**B**) that was used for the total synthesis of heilonine.

[5] Maurer, B.; Ohloff, G. *Helv. Chim. Acta* **1976**, *59*, 1169–1185.

5.3: Preparation of Azetidinium Intermediate and [1,2]-Stevens Rearrangement

The synthetic sequence from **B** commenced with a hydroxymethylation of the lactam with formaldehyde (Scheme 5.2). Generation of the enolate proceeded as before using the optimized conditions (LiTMP, THF/HMPA), however no reaction was observed upon exposure to paraformaldehyde or several other X–CH_2–Y-type electrophiles that were screened. Using a protocol reported by Schlosser, an ethereal solution of monomeric formaldehyde was prepared by the depolymerization of paraformaldehyde using *p*-toluenesulfonic anhydride and



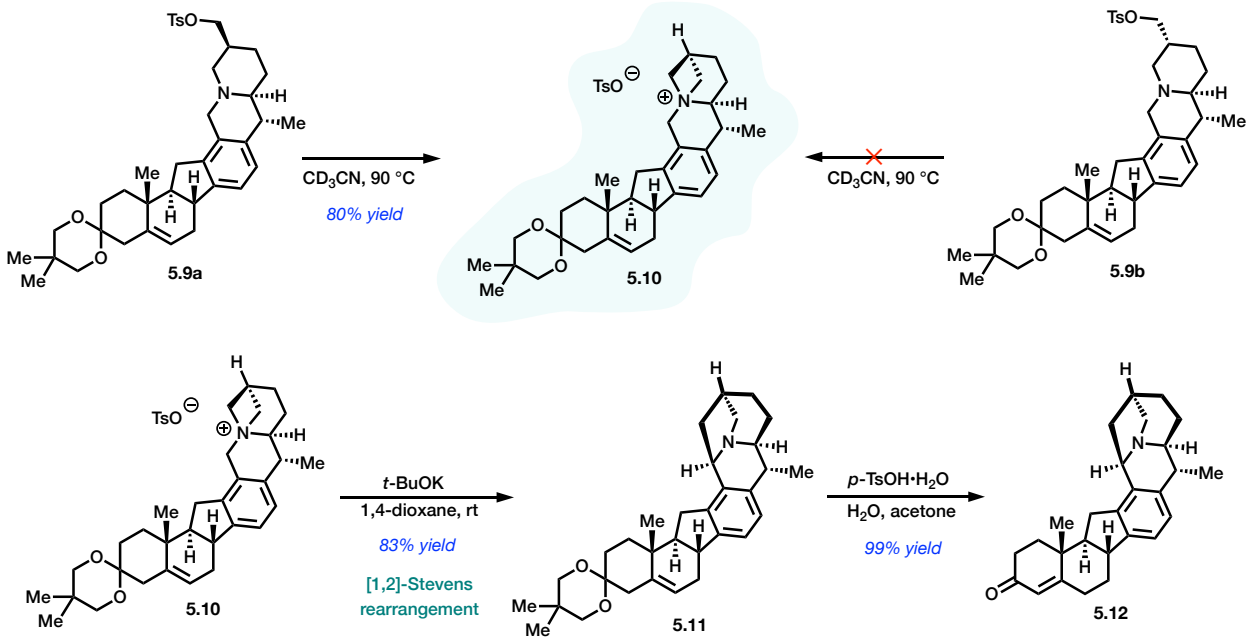
Scheme 5.2. Preparation of tosylates **5.9a** and **5.9b**.

codistillation with THF.[6] The resultant solution was added to the enolate of **3.28**, whereupon conversion to **5.7**, as a 1:1 mixture of C25 epimers, was observed upon warming to ambient temperature. Similar to the lactam methylation in the heilonine synthesis, varying amounts of a dialkylated product were observed. However, in contrast to the unexpected benzylic alkylation that was formed previously, the additional hydroxymethyl group was appended at C25. To

[6] Schlosser, M.; Jenny, T.; Guggisberg, Y. *Synlett* **1990**, 704.

ensure reproducibility, the reaction was performed batchwise on scale of less than 50 mg so that only a diminished 15% yield of this side product were obtained.

The inseparable mixture of diastereomers underwent reduction of the lactam ($LiAlH_4$, THF, 60 °C) and tosylation of the primary alcohol (*p*-TsCl, 4-DMAP, Et_3N) to generate **5.9a** and **5.9b**, which could then be separated by preparative thin-layer chromatography. The epimeric tosylates were then dissolved in acetonitrile-d_3 and the resultant solutions were heated to 90 °C (Scheme 5.3). One of them (**5.9a**) afforded a new, highly polar material, which was assigned as the key azetidinium salt intermediate (**5.10**). Meanwhile, the other epimer was found to be completely unreactive and did not lead to any formation of **5.10**. These observations are not entirely surprising, as the axially oriented (tosyloxy)methyl substituent would be able to achieve suitable conformation for intramolecular displacement by the β-disposed nitrogen lone pair. Interestingly, prolonged heating of the solution containing **5.9a** returned a diastereomeric mixture of **5.9a/b** and resulted in a somewhat diminished conversion to **5.10**. Based on this



Scheme 5.3. Azetidinium salt formation and key [1,2]-Stevens rearrangement.

observation as well as molecular models, it was surmised that **5.9b** may be able to assume a reactive conformation to undergo intramolecular displacement. However, heating a solution of **5.9b** to higher temperatures in different solvents led to either solvolytic decomposition or nonspecific decomposition, presumably occurring through an intermolecular displacement pathway. Thus, the optimal conditions for formation of **5.10** involved heating a solution **5.9a** in refluxing MeCN-d_3 for 18 h, followed by evaporation of the solvent and triturative workup/purification to cleanly deliver the azetidinium salt in 80% yield.

With the critical azetidinium salt intermediate in hand, attempts were then made to demonstrate the key [1,2]-Stevens rearrangement (Scheme 5.3). Using conditions identified by Takayama and used later by Hanessian for related Stevens rearrangements of 'azocinium' salts, it was found that **5.10** underwent clean conversion to a single, mobile spot on TLC following treatment with potassium *tert*-butoxide at ambient temperature.[7] Spectroscopic analysis (NMR and HRMS) of the product indicated a structure that is consistent with the outcome of the proposed [1,2]-Stevens rearrangement. A subsequent ketal deprotection could also be smoothly achieved to afford enone **5.12**. The synthesis currently rests at this stage; however, a potential route forward will be discussed in the following section.

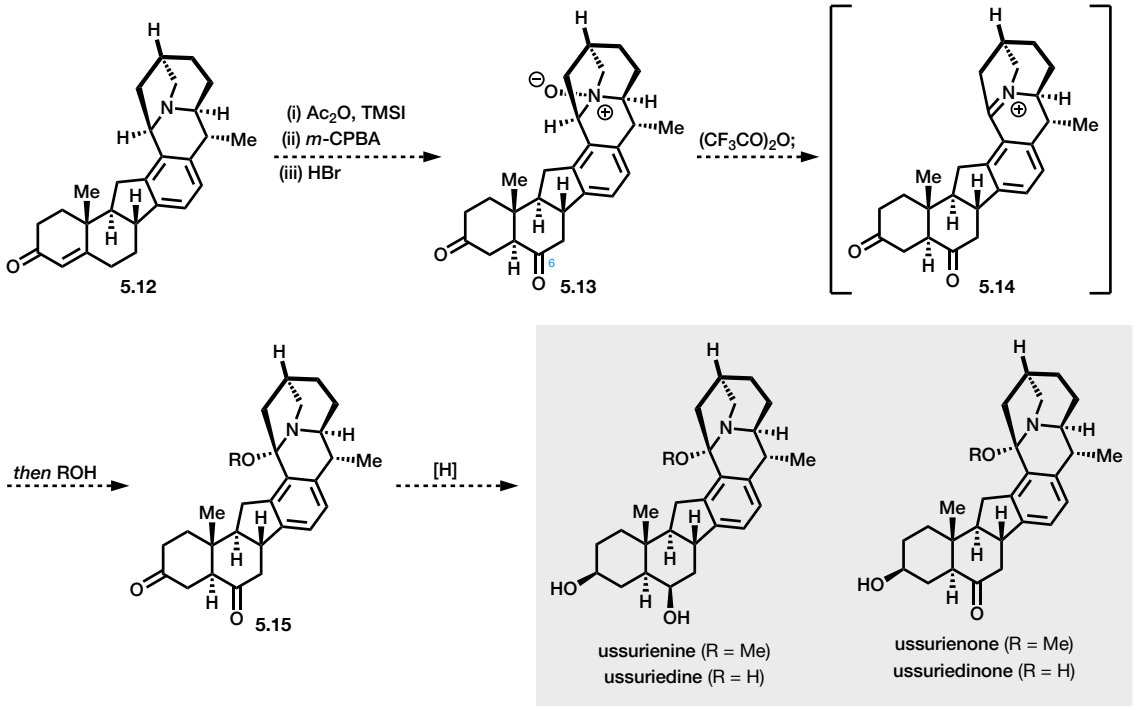
Concluding Remarks and Future Directions

While the available data suggests the proposed [1,2]-Stevens rearrangement occurred as expected, a more definite proof of structure is still required. So far, no crystals suitable for X-ray

[7] (a) Nomoto, T.; Takayama, H. *J. Chem. Soc. Chem. Commun.* **1982**, 1113–1114. (b) Takayama, H.; Nomoto, T.; Suzuki, T.; Takamoto, M.; Okamoto, T. *Heterocycles* **1978**, *9*, 1545–1548. (c) Hanessian, S.; Mauduit, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 3810–3813.

crystallographic analysis have been obtained of either **5.11**, **5.12**, or various derivatives thereof that have been prepared. A potential route forward to the natural products is described below.

Enone **5.12** could first be converted to the 6-keto derivative **5.13** bearing the requisite *trans*-AB ring fusion using the same sequence that was used for the heilonine end-game (Scheme 5.4). The oxidation of the intermediate dienol acetate would be carried out with an additional equivalent of *m*-CPBA to oxidize the tertiary amine to the corresponding *N*-oxide. Following



Scheme 5.4. Proposed synthetic end-game for ussurienine and related congeners.

acid-catalyzed isomerization, the resulting γ-diketone **5.13** would be subjected to Polonovski-Potier reaction of the tertiary *N*-oxide to give a highly strained anti-Bredt iminium species (i.e., **5.14**).[8] This highly reactive intermediate would be trapped upon the addition of water or methanol from the less hindered α-face to afford **5.15**. The proposed selectivity for the

[8] (a) Suzuki, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **2001**, *42*, 3013–3015. (b) Hoshi, M.; Kaneko, O.; Nakajima, M.; Arai, S.; Nishida, A. *Org. Lett.* **2014**, *16*, 768–771. (c) Yamazaki, N.; Suzuki, H.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 8280–8281.

Polonovski-Potier reaction could be rationalized as proceeding via *syn* elimination involving the hydrogen at C18 that is activated by the aromatic substituent.[9] A final global reduction of both C3 and C6 ketones would afford ussurienine and ussuriedine. A site selective reduction of the more sterically accessible C3 ketone could also be employed to deliver ussurienone and ussuriedinone.

[9] Grierson, D. S.; Husson, H.-P. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds., Pergamon: Oxford, 1991; Vol. 6, pp 909–947.

Chapter 6

Experimental Procedures and Characterization Data

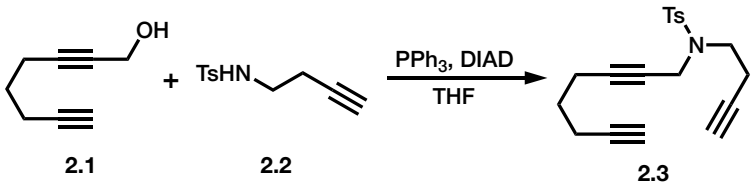
6.1. General Information

All reactions were performed in oven-dried (>12 h at 150 °C) and/or flame-dried glassware equipped with a Teflon-coated magnetic stir bar under an atmosphere of nitrogen which had been pre-dried by passage through a Drierite column ($CaSO_4 \geq 98\%$ + $CoCl_2$ <2%) unless otherwise specified. Reaction solvents dichloromethane (CH_2Cl_2; unstabilized HPLC grade), tetrahydrofuran (THF; HPLC grade), toluene (PhMe; ACS grade), and diethyl ether (Et_2O; ACS grade, stabilized with BHT) were dried by passage through an activated alumina column purification system (Innovative Technology Inc. Pure-Solv^{TM}). Anhydrous methanol (MeOH), ethanol (EtOH), 2-propanol (*i*-PrOH), and benzene (PhH) were purchased from Sigma-Aldrich and used as received. Anhydrous acetonitrile (MeCN) and *N*,*N*-dimethylformamide (DMF) was purchased from ACROS Organics and used as received. Commercially obtained reagents were used as received, unless stated otherwise. Ambient temperature refers to 20 – 24 °C. Higher than ambient temperature was maintained using pre-heated oil baths. Lower temperatures were maintained using a cooling bath of acetone/dry ice (–78 °C), water/ice (0 °C), or NESLAB CB-80 Cryobath for all other temperatures in between. All reaction temperatures refer to external bath temperatures monitored using a thermometer, unless otherwise stated.

Thin-layer chromatography (TLC) was performed using EMD Millipore silica gel 60 Å plates and visualization was achieved with either UV fluorescence quenching (254 nm), potassium permanganate stain ($KMnO_4$) with heat, or Seebach's stain ($Ce(SO_4)_2$ in

phosphomolybdic acid) with heat. Flash column chromatography was performed on SiliCycle SiliaFlash P60 (40-63 μm particle size) using ACS grade solvents purchased from Fisher Scientific. Nuclear magnetic resonance (NMR) data were acquired on either a 400 MHz Bruker Avance-III-HD nanobay spectrometer equipped with a BBFO SmartProbe and 60-sample SampleCase autosampler or a 500 MHz Bruker Avance-III-HD spectrometer equipped with a BBFO SmartProbe, using Topspin 3.6.2. ^{1}H NMR spectra were calibrated from internal standard (TMS: δ 0.0 ppm) or solvent (CD_3OD: δ 3.31 ppm; CD_3CN: δ 1.94 ppm; DMSO-d_6: δ 2.50 ppm) resonance and ^{13}C NMR spectra from solvent ($CDCl_3$: δ 77.16 ppm, CD_3OD: δ 49.00 ppm) resonance. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent resonance and coupling constants (*J*) are reported in hertz (Hz). NMR peak pattern abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, pent = pentet, sept = septet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, tt = triplet of triplets, qd = quarter of doublets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, tdd = triplet of doublet of doublets, m = multiplet, br = broad (i.e., signal is broadened), app = apparent (i.e., signal appears as). Most ^{1}H and ^{13}C are corroborated by 2-D experiments (e.g., COSY, HSQC). High-resolution mass spectral (HRMS) analysis was measured on Agilent Technologies 6224 TOF LC/MS using electrospray ionization (ESI) at the University of Chicago Mass Spectroscopy Core Facility. Optical rotations were measured on a Jasco DIP-1000 polarimeter using a 100 mm-path-length cell, *c* = g/100 mL. Infrared (IR) spectra were recorded on a Thermo Scientific Nicolet iS50 FT-IR spectrometer and are reported as a frequency of absorption (cm^{-1}). Chiral high-performance liquid chromatography (HPLC) analysis was performed using an Agilent analytical chromatography system with a commercial Chiralcel® column (OD-H) equipped with a guard.

6.2. Experimental Procedures and Characterization Data for Chapter 2



Triyne 2.3. To a solution of **2.1**[1] (0.250 g, 2.05 mmol, 1 equiv) and **2.2**[2] (0.503 g, 2.25 mmol, 1.1 equiv) in THF (20 mL) was added triphenylphosphine (0.590 g, 2.25 mmol, 1.05 equiv) at ambient temperature. The resultant solution was cooled to 0 °C, then treated dropwise with diisopropyl azodicarboxylate (0.44 mL, 2.25 mmol, 1.1 equiv). The resulting clear and yellow solution was brought to ambient temperature and stirred for 20 h. Concentration of the reaction mixture afforded a crude yellow oil, which was purified via flash column chromatography (5:1 hexanes:EtOAc → 3:1 hexanes:EtOAc) to provide triyne **2.3** (0.591 g, 88% yield) as a pale-yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 4.17 (t, *J* = 2.1 Hz, 2H), 3.36 (t, *J* = 7.4 Hz, 2H), 2.54 – 2.49 (td, *J* = 7.4, 2.7 Hz, 2H), 2.43 (s, 3H), 2.14 – 2.06 (m, 4H), 2.01 (t, *J* = 2.6 Hz, 1H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.53 – 1.46 (pent, *J* = 7.1 Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 143.4, 135.9, 129.3, 126.7, 84.7, 81.8, 80.9, 71.8, 71.3, 70.3, 45.4, 37.8, 28.1, 21.6, 18.9, 18.6, 18.1. R_f = 0.56 (2:1 hexanes:EtOAc; visualized with UV and/or $KMnO_4$ stain).

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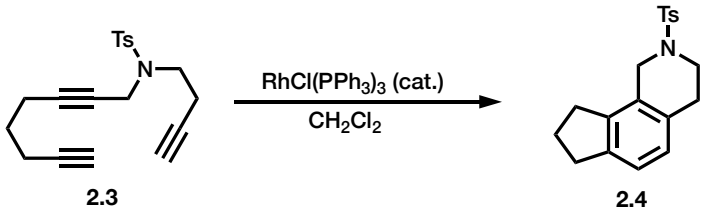
[1] Known compound; prepared from 1,6-heptadiyne in one step as described in the following reference: *J. Am. Chem. Soc.* **2010**, *132*, 11039–11041.

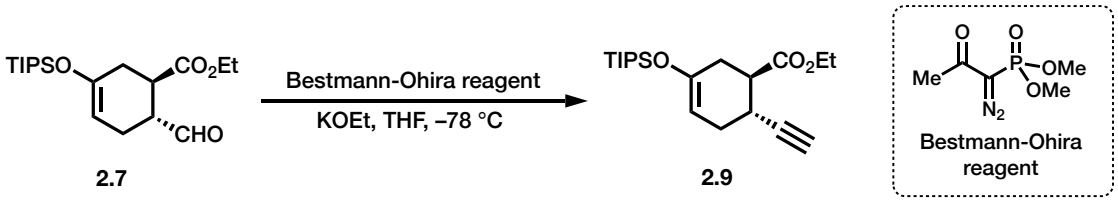
[2] Known compound; prepared from *p*-toluenesulfonamide in three steps as described in the following reference: *Org. Lett.* **2014**, *16*, 4352–4355.



2.3 2.4

Tricycle 2.4. A solution of triyne **2.3** (33 mg, 0.100 mmol, 1 equiv) in CH_2Cl_2 (1.5 mL) was sparged with Ar for 20 min, then treated with a single portion of $RhCl(PPh_3)_3$ (19 mg, 0.020 mmol, 20 mol%) at ambient temperature. The resultant mixture was stirred at ambient temperature for 2 h, then filtered through a layer of silica gel (washing with CH_2Cl_2). Concentration of the filtrate provided a crude brown oil, which was purified via flash column chromatography (6:1 hexanes:EtOAc) to afford tricycle **2.4** (28 mg, 84% yield) as an amorphous white solid.

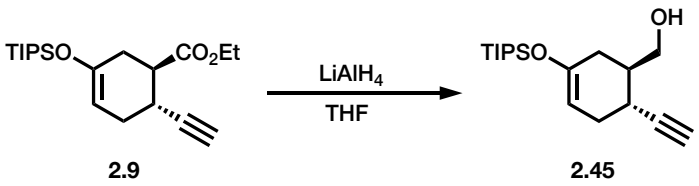
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 4.13 (s, 2H), 3.36 – 3.30 (t, *J* = 5.8 Hz, 2H), 2.94 – 2.89 (t, *J* = 5.8 Hz, 2H), 2.88 – 2.83 (t, *J* = 7.5 Hz, 2H), 2.73 – 2.68 (t, *J* = 7.5 Hz, 2H), 2.42 (s, 3H), 2.11 – 2.03 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 143.7, 142.4, 140.9, 140.9, 130.6, 129.8, 127.8, 127.7, 127.0, 122.7, 46.0, 43.8, 32.6, 30.5, 29.1, 25.1, 21.6. R_f = 0.29 (7:1 hexanes:EtOAc; visualized with UV and/or $KMnO_4$ stain).



Alkyne 2.9. To a pre-cooled solution of potassium ethoxide (1.67 g, 19.9 mmol, 3.2 equiv) in THF (100 mL) was slowly added a solution of Bestmann-Ohira reagent[3] (4.29 g, 22.4 mmol, 2.6 equiv) in THF (25 mL) at –78 °C. After complete addition, the resultant opaque, bright yellow mixture was stirred at –78 °C for 25 min. A solution of TIPS enol ether **2.7**[4] (2.20 g, 6.21 mmol, 1.0 equiv) in THF (8.0 mL) was then rapidly dispensed into the reaction mixture at –78 °C and the resultant mixture was vigorously stirred for 30 min before the cold bath was removed. The mixture was allowed to slowly warm to 0 °C, then quenched with saturated aqueous NH_4Cl solution (170 mL) and diluted with hexanes (200 mL). The resultant mixture was extracted with 5:1 hexanes:Et_2O (3 x 150 mL) and organic extracts were then combined, washed with brine (1 x 100 mL), and dried over $MgSO_4$. Concentration of the dried extracts afforded alkyne **2.9** (1.97 g, 91% yield) as a light-yellow oil, which was carried forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.80 (m, 1H), 4.26 – 4.15 (m, 2H), 2.81 – 2.74 (m, 1H), 2.74 – 2.67 (m, 1H), 2.45 – 2.28 (m, 3H), 2.25 – 2.15 (m, 1H), 2.07 (d, J = 2.2 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.19 – 1.04 (m, 21H). R_f = 0.48 (hexanes:EtOAc = 10:1; visualized with $KMnO_4$ stain).

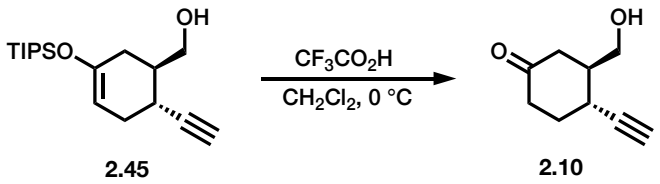
[3] Bestmann-Ohira reagent was prepared according to the following reference: *Synthesis* **2006**, 4266−4268.
[4] Known compound; prepared in reported 98% *ee*, see the following reference: *J. Am. Chem. Soc.* **2015**, *137*, 10120−10123.



2.9 2.45

Primary alcohol 2.45. To a pre-cooled solution of alkyne **2.9** (1.96 g, 5.60 mmol, 1.0 equiv) in THF (50 mL) was added lithium aluminum hydride solution (2.0 M in THF; 4.2 mL, 8.40 mmol, 1.5 equiv) dropwise at 0 °C. The resultant mixture was allowed to warm to ambient temperature and stirred for 2 h. Following complete consumption of starting material as indicated by TLC, the reaction mixture was cooled to 0 °C and diluted with Et_2O (60 mL). The reaction was carefully quenched by sequential addition of H_2O (0.30 mL), 2 M NaOH aqueous solution (0.30 mL), and H_2O (0.90 mL), then stirred vigorously for 15 min upon warming to ambient temperature. Anhydrous $MgSO_4$ was then added and the mixture was stirred for an additional 15 min. The mixture was next passed through a layer of Celite, washing the filter cake thoroughly with Et_2O (ca. 120 mL). Concentration of the filtrate provided primary alcohol **2.45** (1.62 g, 94% yield) as a clear, colorless oil. The crude concentrate was typically clean enough to be carried forward without purification, however flash column chromatography (10:1 hexanes:EtOAc) was used to obtain spectroscopically pure material.

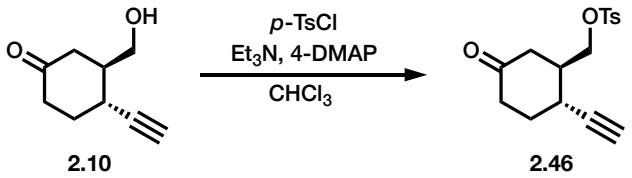
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.80 (m, 1H), 3.80 – 3.75 (m, 2H), 2.42 – 2.33 (m, 2H), 2.26 – 2.14 (m, 2H), 2.17 (d, J = 2.2 Hz, 1H), 2.09 – 1.99 (m, 1H), 1.95 – 1.86 (tt, J = 10.2, 5.1 Hz, 1H), 1.82 (t, J = 6.1 Hz, 1H), 1.19 – 1.04 (m, 21H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 149.8, 101.1, 86.7, 70.6, 65.9, 41.1, 32.3, 30.6, 28.4, 18.1, 12.8. **HRMS:** (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{32}O_2Si$: 309.2250, found: 309.2254. $\boldsymbol{R_f}$ = 0.46 (4:1 hexanes:EtOAc; visualized with $KMnO_4$ stain).



2.45 2.10

Ketone 2.10. To a pre-cooled solution of primary alcohol **2.45** (1.43 g, 4.63 mmol, 1 equiv) in CH_2Cl_2 (100 mL) was added trifluoroacetic acid (0.71 mL, 9.26 mmol, 2 equiv) dropwise at 0 °C. The initially opaque solution became clear and colorless and the resultant mixture was stirred at 0 °C for 30 min. Upon complete consumption of starting material as indicated by TLC, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (20 mL) at 0 °C. Upon warming to ambient temperature, the mixture was extracted with $CHCl_3$ (8 x 40 mL) and the organic extracts were combined and dried over Na_2SO_4. The dried extracts were concentrated *in vacuo* and the resultant crude residue was purified via flash column chromatography (100:0 hexanes:EtOAc → 1:1 hexanes:EtOAc) to afford ketone **2.10** (0.613 g, 87% yield) as a clear, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (dd, *J* = 10.8, 4.3 Hz, 1H), 3.67 (dd, *J* = 10.8, 4.3 Hz, 1H), 2.79 – 2.70 (m, 1H), 2.56 – 2.44 (m, 2H), 2.42 – 2.27 (m, 3H), 2.21 (d, *J* = 2.4 Hz, 1H), 2.09-2.00 (m, 1H), 1.94 (br s, 1H), 1.93 – 1.82 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 210.3, 85.0, 71.1, 64.6, 44.8, 42.8, 39.9, 30.9, 29.4. **HRMS:** (ESI): m/z $[M+H]^+$ calcd for $C_9H_{12}O_2$: 153.0915, found: 153.0907. R_f = 0.30 (1:1 hexanes:EtOAc; visualized with $KMnO_4$ stain).

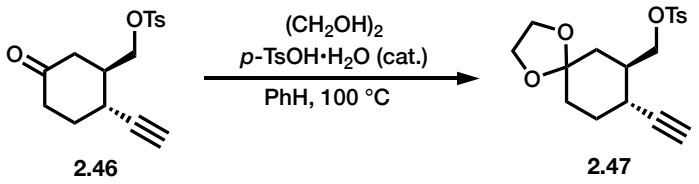


2.10 2.46

Tosylate 2.46. To a pre-cooled solution of ketone **2.10** (0.530 g, 3.48 mmol, 1 equiv) in $CHCl_3$ (50 mL) was added *p*-toluenesulfonyl chloride (1.98 g, 10.4 mmol, 3 equiv), triethylamine (4.9 mL, 34.8 mmol, 10 equiv), and 4-dimethylaminopyridine (0.850 g, 6.96 mmol, 2 equiv) sequentially at 0 °C. The resultant mixture was brought to ambient temperature and stirred for 20 h. Upon complete consumption of starting material as indicated by TLC, the reaction mixture was treated with 1:1 saturated aqueous $NaHCO_3$: H_2O solution (80 mL) and stirred vigorously for 30 min to hydrolyze unreacted *p*-TsCl. The mixture was then extracted with $CHCl_3$ (5 x 60 mL) and the organic extracts were combined and dried over Na_2SO_4. Concentration of the dried extracts provided a crude yellow oil, which was purified via flash column chromatography (10:10:1.2 hexanes:CH_2Cl_2:EtOAc) to afford tosylate **2.46** (0.915 g, 86% yield) as white, crystalline solid.

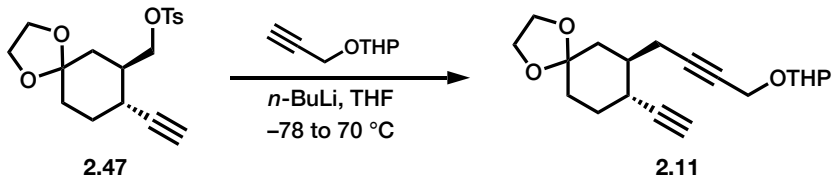
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.26 (dd, *J* = 9.9, 4.5 Hz, 1H), 4.05 (dd, *J* = 9.9, 3.7 Hz, 1H), 2.73 – 2.64 (m, *J* = 10.5, 3.5, 2.4 Hz, 1H), 2.46 (s, 3H), 2.47 – 2.40 (m, 2H), 2.35 – 2.23 (m, 3H), 2.15 – 2.07 (m, 1H), 2.08 (d, *J* = 2.4 Hz, 1H), 1.88 – 1.73 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 208.2, 145.2, 132.6, 130.1, 128.2, 83.4, 71.7, 71.1, 42.4, 42.1, 39.8, 30.7, 29.2, 21.8. **HRMS:** (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{18}O_4S$: 307.1004, found: 307.1006. R_f = 0.61 (1:1 hexanes:EtOAc; visualized with UV and $KMnO_4$ stain).



2.46 2.47

Ketal 2.47. To a solution of tosylate **2.46** (0.915 g, 2.99 mmol, 1.0 equiv) in anhydrous benzene (50 mL) was added ethylene glycol (0.84 mL, 15.0 mmol, 5.0 equiv) and *p*-toluenesulfonic acid monohydrate (11 mg, 0.060 mmol, 2 mol%) at ambient temperature. Upon assembly of a Dean-Stark apparatus, the mixture was then heated to reflux under an atm of N_2. The reaction mixture was stirred at reflux for 20 h, then brought back to ambient temperature and diluted with 1:1 hexanes:EtOAc (50 mL), treated with saturated aqueous $NaHCO_3$ solution (50 mL), and extracted with 1:1 hexanes:EtOAc (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and subsequent concentration afforded a ketal **2.47** (1.01 g, 96% yield) as a white, highly crystalline solid which was carried forward without further purification. Spectroscopically pure material was obtained via flash column chromatography (15:5:1 hexanes:CH_2Cl_2:acetone). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.83 – 7.76 (m, 2H), 7.34 (d, J = 8.1 Hz, 2H), 4.22 – 4.09 (m, 2H), 3.97 – 3.85 (m, 4H), 2.45 (s, 3H), 2.23 – 2.11 (m, 1H), 2.07 – 1.88 (m, 3H), 1.82 – 1.59 (m, 3H), 1.53 – 1.40 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 144.8, 132.9, 129.9, 128.2, 107.9, 84.8, 72.4, 70.6, 64.6, 64.5, 39.8, 36.8, 33.9, 29.7, 29.5, 21.8. **HRMS:** (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{18}O_4S$: 351.1266, found: 351.1263. $\boldsymbol{R_f}$ = 0.46 (1:2 hexanes:Et_2O; visualized with UV and $KMnO_4$ stain).

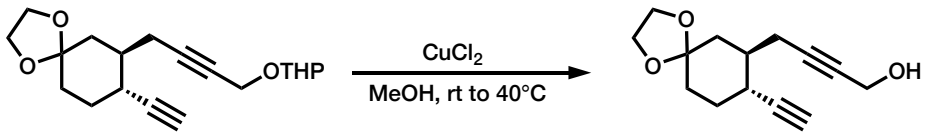


2.47 2.11

Diyne 2.11. To a solution of tetrahydro-2-(2-propynyloxy)-2*H*-pyran (0.53 mL, 3.77 mmol, 2.5 equiv) in dry THF (11 mL) was added *n*-butyllithium solution (1.60 M solution in hexanes; 2.2 mL, 3.52 mmol, 2.35 equiv) dropwise at –78 °C. The mixture was then allowed to warm to ambient temperature and the pale-yellow solution containing the lithium acetylide was stirred at room temperature for 2 h. Upon re-cooling to –78 °C, the reaction mixture was treated dropwise with a solution of ketal **2.47** (0.525 g, 1.50 mmol, 1 equiv) in dry THF (4.8 mL). Following complete addition, the cooling bath was removed and the mixture was allowed to warm to ambient temperature and stirred for an additional 30 min before warming to 70 °C in a pre-heated oil bath. The reaction mixture was stirred at this temperature for 18 h, then cooled to ambient temperature and diluted with 1:1 hexanes:Et_2O (20 mL), quenched with a saturated aqueous $NaHCO_3$ solution (20 mL), and extracted with 1:1 hexanes:EtOAc (3 x 50 mL). The combined organic extracts washed with brine (1 x 100 mL) and dried over Na_2SO_4. Concentration of the dried extracts provided a crude yellow oil which was purified via flash column chromatography (15:1 → 6:1 hexanes:EtOAc) to afford diyne **2.11** (0.275 g, 58% yield) as a clear, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.81 (t, *J* = 3.5 Hz, 1H), 4.32 – 4.20 (m, 2H), 3.98 – 3.91 (m, 4H), 3.85 (ddd, *J* = 11.4, 8.8, 3.2 Hz, 1H), 3.53 (ddt, *J* = 10.1, 5.7, 3.0 Hz, 1H), 2.60 – 2.41 (m, 2H), 2.21 – 2.11 (m, 1H), 2.10 (d, *J* = 2.3 Hz, 1H), 2.05 – 1.96 (m, 1H), 1.93 – 1.79 (m, 3H), 1.79 – 1.69 (m, 3H), 1.68 – 1.44 (m, 6H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 108.5, 96.8, 86.1, 83.7, 78.1, 70.1, 64.5, 64.5, 62.2, 54.8, 39.1, 39.0, 34.1, 32.8, 30.5, 29.8, 25.5, 23.9, 19.3.

HRMS: (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{26}O_4$: 319.1909, found: 319.1903. R_f = 0.53 (2:1 hexanes:EtOAc; visualized with $KMnO_4$ stain).



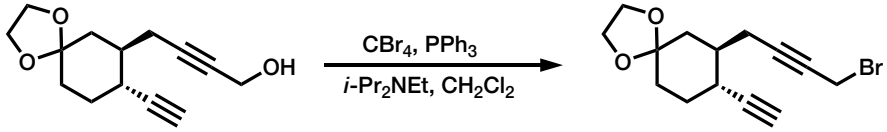
2.11 2.48

Propargyl alcohol 2.48. To a solution of diyne **2.11** (21 mg, 0.066 mmol, 1 equiv) in anhydrous MeOH (1.2 mL) was added copper (II) chloride (8.9 mg, 0.066 mmol, 1.0 equiv.) at room temperature. The resultant pale green solution was stirred at ambient temperature for 2 h. The mixture was then heated to 40 °C and stirred at the same temperature for an additional 3 h. Upon complete consumption of starting material, as indicated by TLC, the reaction mixture was cooled back to ambient temperature and quenched with saturated aqueous $NaHCO_3$ solution (2 mL). The teal blue mixture was then extracted with 1:1 hexanes:EtOAc (3 x 6 mL). The organic extracts were subsequently combined and washed with brine (1 x 10 mL) and dried over Na_2SO_4. Concentration of the dried extracts provided a crude clear oil, which was purified via flash column chromatography (8:1 → 2:1 hexanes:EtOAc) to afford propargyl alcohol **2.48** (12 mg, 77% yield)[5] as a clear, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.26 (app s, 2H), 3.98 – 3.91 (m, 4H), 2.59 – 2.44 (m, 2H), 2.21 – 2.12 (m, 1H), 2.11 (d, *J* = 2.3 Hz, 1H), 2.05 – 1.97 (m, 1H), 1.91 – 1.80 (m, 2H), 1.79 – 1.67 (m, 2H), 1.64 – 1.56 (m, 1H), 1.55 – 1.44 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 108.5, 86.1, 83.5, 80.6, 70.1, 64.5, 64.5, 51.6, 39.2, 38.9, 34.1, 32.8, 29.8, 23.8. **HRMS:** (ESI): m/z $[M+H]^+$

[5] Note: The reaction yield varied upon scale-up — A 0.864 mmol-scale reaction gave propargyl alcohol **2.48** (94 mg, 46% yield), along with recovered diyne **2.11** (0.135 g, 49% yield).

calcd for $C_{14}H_{18}O_3$: 235.1334, found: 235.1332. $\boldsymbol{R_f}$ = 0.45 (1:1 hexanes:EtOAc; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).



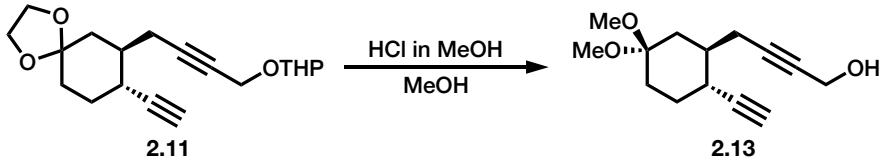
2.48 **2.12**

Propargyl bromide 2.12. To a solution of propargyl alcohol **2.48** (23 mg, 0.098 mmol, 1 equiv) in dry CH_2Cl_2 (10 mL) was added *N*,*N*-diisopropylethylamine (0.17 mL, 0.980 mmol, 10 equiv), triphenylphosphine (0.129 g, 0.490 mmol, 5 equiv), and tetrabromomethane (0.162 g, 0.490 mmol, 5 equiv) sequentially at ambient temperature. The resultant yellowish-orange mixture was stirred at ambient temperature for 1 h. Upon complete consumption of starting material as indicated by TLC, the reaction mixture was diluted with CH_2Cl_2 (10 mL) treated with saturated aqueous $NaHCO_3$ solution (8 mL). The biphasic mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL), then the organic extracts were combined and dried over Na_2SO_4. Concentration of the dried extracts[6] provided a crude, orangish-red oil that was carefully purified via flash column chromatography[7] (20:10:1 hexanes:CH_2Cl_2:Et_2O) to afford propargyl bromide **2.12** (19 mg, 65% yield) as clear, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.00 – 3.93 (m, 4H), 3.94 – 3.90 (m, 2H), 2.62 – 2.44 (m, 2H), 2.20 – 2.11 (m, 1H), 2.11 (d, *J* = 2.3 Hz, 1H), 2.06 – 1.97 (m, 1H), 1.92 – 1.81 (m, 2H), 1.79 –

[6] Bath temperature was maintained below 25 °C, as product decomposition was observed at higher temperatures.
[7] Note: This material had a tendency to decompose on the column. Best results were obtained by dissolving the crude residue in 2:1 hexanes:CH_2Cl_2 (2 mL) and loading directly onto a 12 mm wide x 80 mm tall column of silica gel that had been pre-packed with hexanes.

1.67 (m, 2H), 1.56 – 1.43 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 108.4, 86.0, 85.4, 77.5, 70.2, 64.5, 64.5, 39.1, 39.0, 34.1, 32.8, 29.8, 24.0, 15.6. **HRMS:** (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{17}BrO_2$: 296.0412, found: 296.0411. R_f = 0.63 (2:1 hexanes:EtOAc; visualized with $KMnO_4$ stain).

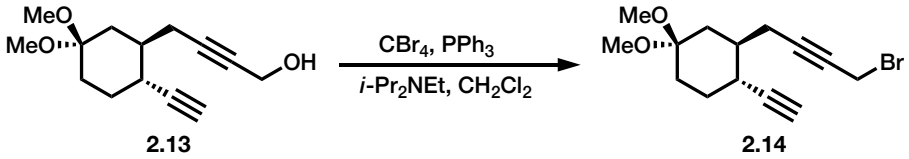


2.11 **2.13**

Dimethyl ketal 2.13. To a pre-cooled solution of diyne **2.11** (0.145 g, 0.455 mmol, 1 equiv) in anhydrous MeOH (8.0 mL) was added a solution of hydrogen chloride (~1.25 M in MeOH; 5.0 mL) dropwise at 0 °C. The resultant solution was brought to ambient temperature and stirred for 2 h. Upon complete consumption of starting material as carefully monitored by TLC, the reaction mixture was re-cooled to 0 °C and neutralized with a saturated aqueous $NaHCO_3$ solution (6 mL). The resultant mixture was extracted with $CHCl_3$ (5 x 10 mL) and the organic extracts were combined and dried over Na_2SO_4. Concentration of the dried extracts afforded a crude oil, which was purified via flash column chromatography (2:1 hexanes:EtOAc) to afford dimethyl ketal **2.13** (0.107 g, 99% yield) as a clear and colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.25 (s, 2H), 3.22 (s, 3H), 3.16 (s, 3H), 2.60 – 2.51 (ddt, *J* = 16.8, 4.1, 2.2 Hz, 1H), 2.48 – 2.40 (ddt, *J* = 16.8, 7.2, 2.2 Hz, 1H), 2.22 – 2.15 (dt, *J* = 13.6, 3.3 Hz, 1H), 2.15 – 2.09 (m, 1H), 2.12 (d, *J* = 2.2 Hz, 1H), 2.08 – 1.98 (m, 2H), 1.98 – 1.90 (dq, *J* = 13.4, 3.6 Hz, 1H), 1.79 – 1.67 (dddt, *J* = 12.2, 10.9, 7.3, 3.6 Hz, 1H), 1.67 – 1.54 (tdd, *J* = 13.6, 12.3, 3.7 Hz, 1H) 1.34 – 1.21 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 99.8, 86.3, 83.6, 80.6, 70.1, 51.5, 47.8, 47.6, 37.9, 36.9, 33.3, 31.6, 29.0, 23.7. **HRMS:** (ESI): m/z $[M+H]^+$-$[H_2O]$ calcd

for $C_{14}H_{20}O_3$: 219.1384, found: 219.1376. R_f = 0.51 (1:1 hexanes:EtOAc; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).

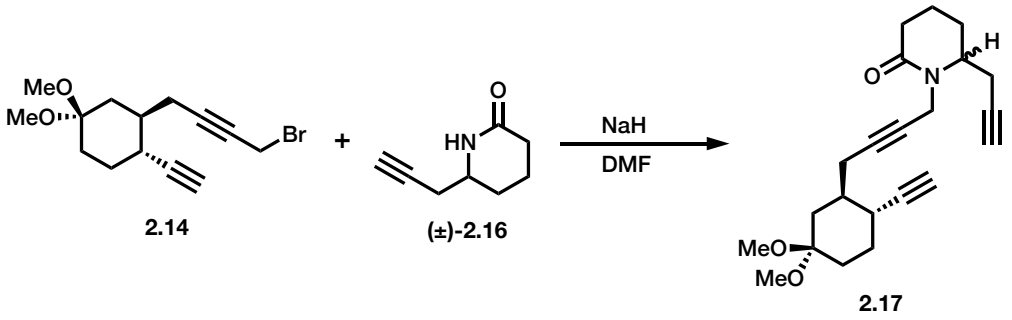


2.13 2.14

Propargyl bromide 2.14. To a solution of dimethyl ketal **2.13** (0.107 g, 0.453 mmol, 1 equiv) in dry CH_2Cl_2 (8 mL) was added *N*,*N*-diisopropylethylamine (0.24 mL, 1.36 mmol, 3 equiv) at ambient temperature. The resultant clear solution was cooled to 0 °C and treated with a single portion of tetrabromomethane (0.180 g, 0.544 mmol, 1.2 equiv). The resultant clear, pale-yellow solution was stirred for 5 min at 0 °C, then treated portionwise with triphenylphosphine (0.178 g, 0.680 mmol, 1.5 equiv). The reaction mixture subsequently brought to ambient temperature and stirred for an additional 2 h. Upon complete consumption of the starting material as indicated by TLC, the mixture was diluted with CH_2Cl_2 (15 mL), treated with a saturated aqueous $NaHCO_3$ solution (10 mL), and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were combined and dried over Na_2SO_4. Concentration of the dried extracts provided a crude yellow oil, which was purified via flash column chromatography (30:20:0 → 30:20:1 hexanes:CH_2Cl_2:acetone) to afford propargyl bromide **2.14** (0.078 g, 56% yield) as clear, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.92 (t, *J* = 2.3 Hz, 2H), 3.22 (s, 3H), 3.16 (s, 3H), 2.65 – 2.55 (m, 1H), 2.44 (ddt, *J* = 16.9, 7.5, 2.5 Hz, 1H), 2.20 (dt, *J* = 13.6, 3.3 Hz, 1H), 2.15 – 2.00 (m, 3H), 1.94 (dq, *J* = 13.5, 3.7 Hz, 1H), 1.80 – 1.68 (m, 1H), 1.67 – 1.55 (m, 1H), 1.34 – 1.18 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 99.7, 86.1, 85.5, 77.4, 70.2, 47.8, 47.6, 38.1, 36.9, 33.4,

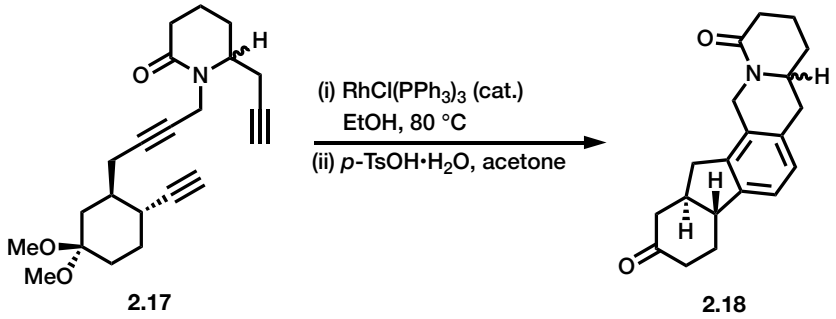
31.7, 29.0, 23.9, 15.6. **HRMS:** (ESI): m/z $[M+H]^+$-$[H_2O]$ calcd for $C_{14}H_{19}BrO_2$: 281.0540, found: 281.0531. R_f = 0.51 (4:1 hexanes:EtOAc; visualized with $KMnO_4$ stain).



Triyne 2.17. To a solution of propargyl bromide **2.14** (0.078 g, 0.260 mmol, 1 equiv) and alkyne **(±)-2.16** (0.037 g, 0.270 mmol, 1.05 equiv) in anhydrous DMF (2.5 mL) was added NaH (60% dispersion in mineral oil; 0.016 g, 0.405 mmol, 1.5 equiv) in a single portion at 0 °C. The resultant mixture was allowed to warm to ambient temperature and stirred for 22 h. The mixture was then diluted with Et_2O (5 mL) and quenched with a saturated aqueous $NaHCO_3$ solution (3 mL). Extracted with EtOAc (3 x 10 mL), then combined organic extracts, washed with brine (1 x 20 mL), and dried over Na_2SO_4. Concentration of the dried extracts provided a crude yellow oil, which was purified via flash column chromatography (4:1:1 → 3:1:1 → 2:1:1 hexanes:CH_2Cl_2:acetone) to afford triyne **2.17** (0.081 g, 87% yield) as an inseparable 1:1 mixture of diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$, *denotes corresponding diastereomer signals**):** δ 4.86 – 4.81 (dt, *J* = 9.3, 2.2 Hz, 0.5H*), 4.81 – 4.76 (dt, *J* = 9.3, 2.2 Hz, 0.5H*), 3.91 – 3.84 (m, 1H**), 3.85 – 3.76 (m, 1H**), 3.21 (s, 3H), 3.15 (s, 3H), 2.68 – 2.60 (dq, *J* = 16.9, 2.8 Hz, 1H), 2.57 – 2.47 (m, 2H), 2.44 – 2.33 (m, 3H), 2.20 – 2.00 (m, 6H), 1.99 – 1.84 (m, 3H), 1.80 – 1.68 (m, 2H), 1.66 – 1.54 (m, 1H), 1.33 – 1.17 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$,** *denotes corresponding

diastereomer signals**):** δ 170.1, 99.7, 86.2, 81.9, 80.1, 76.7*, 76.7*, 71.4, 70.1, 54.5**, 54.4**, 47.8***, 47.6***, 38.0, 37.0, 34.0****, 34.0****, 33.4, 32.3, 31.7, 29.0, 27.1, 23.7, 23.2, 17.7. **HRMS:** (ESI): m/z $[M+H]^+$-$[H_2O]$ calcd for $C_{22}H_{29}NO_3$: 338.2119, found: 338.2114. $\boldsymbol{R_f}$ = 0.45 (1:4 hexanes:EtOAc; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).

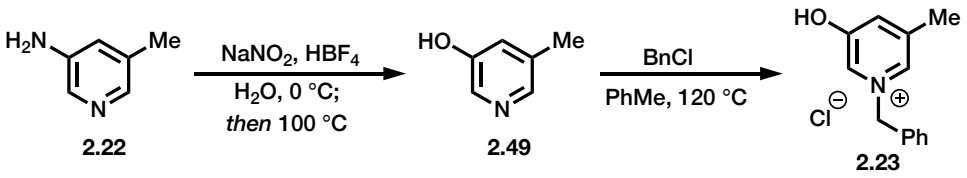


Pentacycle 2.18. To a solution of triyne **2.17** (0.063 g, 0.177 mmol, 1 equiv) in dry, degassed EtOH[8] (3.5 mL) was added $RhCl(PPh_3)_3$ (16.4 mg, 0.018 mmol, 10 mol%) at ambient temperature under an atmosphere of Ar. The initially heterogeneous mixture was heated to 80 °C, whereupon a clear, red amber solution resulted and was stirred at this temperature for 30 min. Upon consumption of the starting material as indicated by TLC, the mixture was brought back to ambient temperature. Concentration of the reaction mixture afforded a crude residue, which was purified via flash column chromatography (4:1:1 → 3:1:1 hexanes:Et_2O:acetone). All product-containing fractions (F_{pdt}; where $R_f = 0.20 \leq F_{pdt} \leq 0.45$ in 1:1:1 hexanes:Et_2O:acetone) were combined and concentrated in vacuo. The resulting residue was taken up in acetone (5.0 mL), then distilled water was added (50 μL) and the resulting solution was cooled to 0 °C. The cooled solution was next treated with *p*-toluenesulfonic acid monohydrate (3.3 mg, 0.017 mmol,

[8] Solvent was degassed by sparging with argon (ca. 3 L) for 30 min.

ca. 0.1 equiv) and stirred at 0 °C for 3 h. The reaction mixture was then allowed to warm to ambient temperature and stirred for an additional 15 h, then neutralized with a saturated aqueous $NaHCO_3$ solution (1 mL) and diluted with H_2O (10 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL) and the organic extracts were combined, washed with brine (1 x 20 mL), and dried over Na_2SO_4. Concentration of the dried extracts afforded a crude residue, which was purified via flash column chromatography (100% EtOAc → 1:1:1 hexanes:Et_2O:acetone) to afford pentacycle **2.18** (0.037 g, 68% yield) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$, *denotes corresponding diastereomer signals**):** δ 7.02 (d, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 7.6 Hz, 1H), 5.27 (d, *J* = 17.9 Hz, 0.5H*), 5.16 (d, *J* = 17.9 Hz, 0.5H*), 4.22 (d, *J* = 17.9 Hz, 0.5H**), 4.10 (d, *J* = 17.9 Hz, 0.5H**), 3.67 – 3.57 (m, 1H), 3.01 – 2.85 (m, 3H), 2.86 – 2.76 (td, *J* = 15.7, 3.4 Hz, 1H), 2.77 – 2.70 (m, 1H), 2.65 – 2.52 (m, 3H), 2.52 – 2.40 (m, 4H), 2.18 – 2.04 (m, 2H), 1.97 – 1.88 (m, 1H), 1.84 – 1.64 (m, 3H). **^{13}C NMR (101 MHz, $CDCl_3$,** *denotes corresponding diastereomer signals**):** δ 210.5*, 210.4*, 170.0, 143.1, 140.9**, 140.8**, 132.2***, 132.1***, 129.2, 126.6****, 126.5****, 120.2*****, 120.1*****, 53.7*, 53.6*, 48.8**, 48.7, 48.6**, 46.8, 43.4***, 43.3***, 40.9, 37.1****, 37.0****, 34.9, 32.9, 29.5*****, 29.4*****, 27.3, 18.8. **COSY/HSQC:** see **Figure A.26** / **Figure A.27**. **HRMS:** (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{23}NO_2$: 310.1807, found: 310.1802. $\boldsymbol{R_f}$ **=** 0.41 (1:1:2 hexanes:CH_2Cl_2:acetone; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).



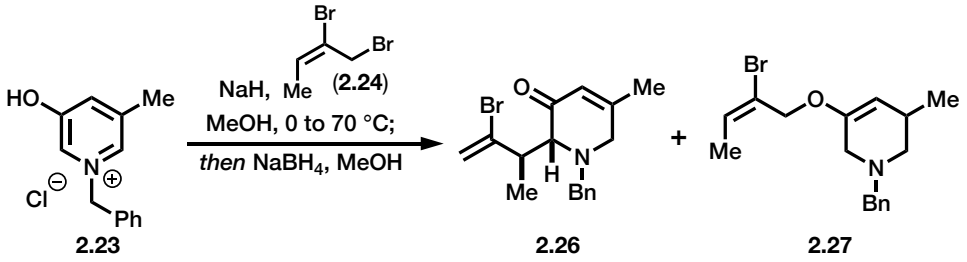
3-Hydroxy-5-methylpyridine (2.49).[9] To a solution of 3-amino-5-methylpyridine (**2.22**; 1.08 g, 10.0 mmol, 1 equiv) in H_2O (5.0 mL) was added tetrafluoroboric acid solution (50 wt.% in H_2O; 5.0 mL). The resultant solution was cooled to 0 °C, then treated dropwise with a solution of sodium nitrite (0.759 g, 11.0 mmol, 1.1 equiv) in H_2O (5.0 mL) and stirred at 0 °C for 1 h. Additional H_2O (5.0 mL) was then added and the reaction mixture was heated to 100 °C (**CAUTION**: Many diazonium salts have been reported to be explosive, it is thus recommended to use a blast shield to mitigate safety risk) and stirred at that same temperature for 24 h. Upon consumption of starting material as indicated by TLC, the reaction mixture was brought back to ambient temperature, then neutralized with saturated aqueous $NaHCO_3$ solution (20 mL) and diluted with EtOAc (20 mL). The resultant biphasic mixture was separated and the aqueous layer extracted with EtOAc (3 x 20 mL). The organic extracts were combined and washed with brine (1 x 50 mL), then dried over Na_2SO_4. Concentration of the dried extracts afforded a dark orange residue, which was purified via flash column chromatography (2:1 hexanes:acetone → 1:1 hexanes:acetone) to afford **2.49** (0.699 g, 64% yield) as a light yellow solid. Spectral data was consistent with published literature spectra.[10]

Benzyl pyridinium salt 2.23. To a suspension of **2.49** (0.639 g, 5.86 mmol, 1 equiv) in PhMe (4.5 mL) was added benzyl chloride (0.68 mL, 5.91 mmol, 1.01 equiv) at ambient temperature. The resultant mixture was heated to 120 °C and stirred at that same temperature for 1 h. Upon

[9] Known compound; this procedure was adapted from the following reference for the preparation of a related compound, see: *J. Am. Chem. Soc.* **2016**, *138*, 10730–10733.
[10] See the following reference for published spectra: *Chem. Commun.* **2017**, *53*, 6417–6420.

consumption of starting material as indicated by TLC, the reaction mixture was brought back to ambient temperature whereupon a sticky, tan precipitate was deposited on the walls of the flask. The solvent was carefully decanted and precipitate washed with Et_2O and collected via vacuum filtration to afford benzyl pyridinium salt **2.23** (1.36 g, 99% yield) as a tan solid.

^{1}H NMR (400 MHz, CD_3OD): δ 8.47 (s, 1H), 8.37 (s, 1H), 7.76 (s, 1H), 7.53 – 7.45 (m, 2H), 7.45 – 7.37 (m, 3H), 5.70 (s, 2H), 2.45 (s, 3H). **^{13}C NMR (101 MHz, CD_3OD):** δ 158.8, 142.0, 136.8, 134.9, 133.3, 131.2, 130.9, 130.6, 130.0, 65.5, 18.5.



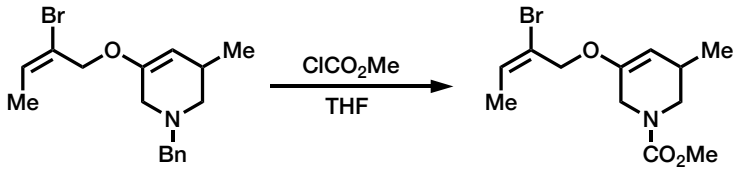
Dihydropyridin-3-one 2.26 and **1,2,3,6-Tetrahydropyridine 2.27.** To a solution of benzyl pyridinium salt **2.23** (1.36 g, 5.77 mmol, 1 equiv) in anhydrous MeOH (20 mL) was added (*E*)-1,2-dibromobut-2-ene (**2.24**)[11] (1.36 g, 6.35 mmol, 1.1 equiv) and the resultant solution was cooled to 0 °C, then treated with sodium hydride (60% dispersion in mineral oil; 0.254 g, 5.77 mmol, 1.1 equiv) portionwise at 0 °C. The resultant mixture was brought to ambient temperature, then the flask was equipped with reflux condenser and the reaction was heated further to 70 °C and stirred at that same temperature for 4 h. The reaction mixture was then brought back to ambient temperature and cooled further to 0 °C, then treated with sodium borohydride (0.218 g,

[11] Known compound; prepared from commercially available 2-butyn-1-ol in the following three steps: (i) hydrostannation (*Tetrahedron Lett.* **1991**, *32*, 1695–1698), (ii) bromodestannylation (*J. Am. Chem. Soc.* **2006**, *128*, 14825–14827), and (iii) Appel bromination (*Org. Lett.* **2012**, *14*, 1568–1571).

5.77 mmol, 1 equiv) portionwise at 0 °C. Following complete addition, the reaction mixture was subsequently warmed to ambient temperature and stirred for 2 h. The reaction mixture was carefully quenched with a 2 M HCl aqueous solution, then re-basified using a saturated aqueous $KHCO_3$ solution and further treated with 2 M NaOH aqueous solution until the mixture was approximately pH 12. The resultant mixture was extracted with 5:1 hexanes:EtOAc (3 x 50 mL) and the combined organic extracts were washed with brine (1 x 100 mL) and dried over Na_2SO_4. Concentration of the dried extracts afforded a crude residue, which was purified via flash column chromatography (25:1 → 10:1 → 4:1 hexanes:EtOAc) to afford dihydropyridine-3-one **2.26** (0.183 g, 10% yield) and 1,2,3,6-tetrahydropyridine **2.27** (0.279 g, 20% yield).

2.26: **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.38 – 7.23 (m, 5H), 5.90 (s, 1H), 5.69 (d, *J* = 1.4 Hz, 1H), 5.50 (d, *J* = 1.4 Hz, 1H), 3.80 (d, *J* = 13.6 Hz, 1H), 3.75 (d, *J* = 13.6 Hz, 1H), 3.56 (d, *J* = 19.7 Hz, 1H), 3.18 (d, *J* = 10.7 Hz, 1H), 3.04 (d, *J* = 19.7 Hz, 1H), 2.80 – 2.71 (dq, *J* = 10.7 Hz, 6.6 Hz, 1H), 1.84 (s, 3H), 1.08 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 197.7, 157.2, 140.0, 138.8, 129.0, 128.5, 127.4, 124.0, 116.8, 70.3, 58.8, 49.33, 43.5, 21.2, 17.3. $\boldsymbol{R_f}$ **=** 0.39 (5:1 hexanes:EtOAc; visualized with UV and/or $KMnO_4$ stain).

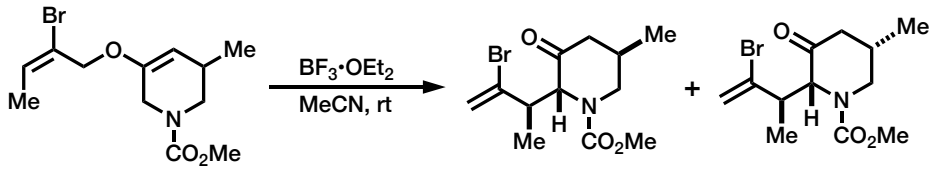
2.27: **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.38 – 7.22 (m, 5H), 6.17 (q, *J* = 7.3 Hz, 1H), 4.54 (s, 1H), 4.43 (d, *J* = 11.8 Hz, 1H), 4.39 (d, *J* = 11.8 Hz, 1H), 3.58 (s, 2H), 3.07 (d, *J* = 15.0 Hz, 1H), 2.86 (d, *J* = 15.0 Hz, 1H), 2.75 (dd, *J* = 11.0, 5.1 Hz, 1H), 2.52 – 2.45 (br s, 1H), 1.94 (dd, *J* = 11.0, 8.3 Hz, 1H), 1.71 (d, *J* = 7.3 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 152.1, 138.3, 132.3, 129.3, 128.4, 127.2, 119.3, 99.7, 66.6, 62.5, 58.1, 54.0, 29.4, 20.3, 15.5. $\boldsymbol{R_f}$ **=** 0.44 (5:1 hexanes:EtOAc; visualized with $KMnO_4$ stain).



2.27 2.28

Carbamate 2.28. To a pre-cooled solution of **2.27** (0.206 g, 0.613 mmol, 1 equiv) in THF (10 mL) was added methyl chloroformate (0.14 mL, 1.84 mmol, 3 equiv) dropwise at 0 °C. The resultant solution was allowed to warm to ambient temperature and stirred for 10 h. Upon consumption of starting material as indicated by TLC, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (5 mL) and diluted with H_2O (20 mL). The resultant mixture was extracted with 1:1 hexanes:EtOAc (3 x 20 mL), then the combined organic extracts were washed with brine (1 x 50 mL) and dried over Na_2SO_4. Concentration of the dried extracts provided a crude residue, which was purified via flash column chromatography (3:1 hexanes:Et_2O) to cleanly afford carbamate **2.28** (0.163 g, 87% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.11 (q, *J* = 6.6 Hz, 1H), 4.62 (br s, 1H), 4.36 (s, 2H), 4.12 – 3.96 (m, 1H), 3.85 – 3.73 (m, 2H), 3.72 (s, 3H), 2.91 – 2.80 (m, 1H), 2.48 – 2.37 (br s, 1 H), 1.80 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.1 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$);** *denotes corresponding rotamer signals**):** δ 156.2, 150.9*, 150.5*, 132.4, 118.9, 100.5**, 100.2**, 66.8, 52.8, 48.1***, 47.7***, 44.3, 28.9****, 28.5****, 19.5, 15.5. R_f = 0.37 (6:1 hexanes:EtOAc; visualized with $KMnO_4$ stain).

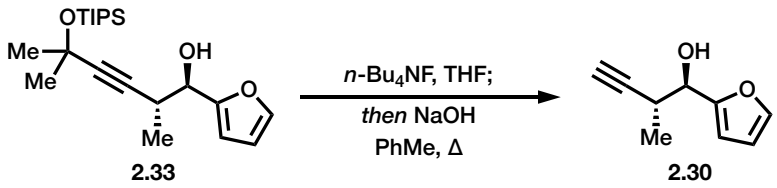


2.28 **2.21a** **2.21b**

3-Piperidones 2.21a and 2.21b. To a solution of carbamate **2.28** (0.070 g, 0.232 mmol, 1 equiv) in anhydrous MeCN (4.0 mL) was added boron trifluoride diethyl etherate (30 µL, 0.243 mmol, 1.05 equiv) dropwise at ambient temperature, then the resultant solution was stirred at ambient temperature for 5 h. Upon consumption of starting material as indicated by TLC, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (5 mL). The resultant mixture extracted with CH_2Cl_2 (3 x 10 mL), then the organic extracts were combined and dried over Na_2SO_4. Concentration of the dried extracts afforded a crude diastereomeric mixture of **2.21a**/**2.21b** (ca. 1.8:1.0), which were separated and purified via flash column chromatography (5:1 hexanes:EtOAc) to afford **2.21a** (0.039 g, 55% yield) and **2.21b** (0.021 g, 30% yield).

2.21a: ^{1}H NMR (500 MHz, $CDCl_3$, *denotes corresponding rotamer signals**):** δ 5.64 (app s, 1H), 5.46 (app s, 1H), 4.72 (d, J = 9.9 Hz, 0.4H*), 4.54 (d, J = 10.5 Hz, 0.6H*), 4.32 (app d, J = 13.8 Hz, 0.6H**), 4.14 (m, 0.4H**), 3.73 (s, 3H), 2.95 – 2.87 (m, 1H), 2.80 – 2.71 (m, 0.4H***), 2.72 – 2.64 (dd, J = 12.9, 11.6 Hz, 0.6H***), 2.54 – 2.45 (m, 1H), 2.19 – 2.06 (m, 2H), 1.16 (d, J = 6.3 Hz, 1H****), 1.13 (d, J = 6.6 Hz, 2H****), 1.03 (d, J = 4.8 Hz, 3H). $\boldsymbol{R_f}$ = 0.32 (2:1 hexanes:EtOAc; visualized with $KMnO_4$ stain).

2.21b: ^{1}H NMR (500 MHz, $CDCl_3$, *denotes corresponding rotamer signals**):** δ 5.63 (app s, 1H), 5.46 (app s, 1H), 4.81 – 4.65 (m, 0.4H*), 4.65 – 4.43 (m, 0.6H*), 4.18 – 3.94 (m, 0.6H**), 3.84 – 3.74 (m, 0.4H**) 3.74 (s, 3H), 3.39 (app d, J = 12.4 Hz, 0.4H***) 3.32 (app d, J = 12.6 Hz, 0.6H***), 2.99 – 2.87 (m, 1H), 2.61 (dd, J = 15.3, 4.9 Hz, 1H), 2.37 (br s, 1H), 1.15 (3H), 1.03 (d, J = 5.9 Hz, 3H). $\boldsymbol{R_f}$ = 0.38 (2:1 hexanes:EtOAc; visualized with $KMnO_4$ stain).



Alkyne 2.30. To a solution of **2.33**[12] (0.226 g, 0.621 mmol, 1 equiv) in THF (4.5 mL) was added tetrabutylammonium fluoride solution (1.0 M in THF; 0.93 mL, 0.930 mmol, 1.5 equiv) slowly at ambient temperature. The resultant solution was stirred at ambient temperature for 24 h, then the mixture was diluted with EtOAc (6 mL) and treated with a saturated aqueous $NaHCO_3$ solution (4 mL) and H_2O (6 mL). The resultant biphasic mixture was separated, then the aqueous layer was further extracted with 1:1 hexanes:EtOAc (3 x 5 mL). The organic extracts were combined and washed with brine (1 x 20 mL) and dried over Na_2SO_4. Concentration of the dried extracts afforded a clear residue, which was re-dissolved in PhMe (3.5 mL) and treated with sodium hydroxide (powdered; 0.074 g, 1.86 mmol, 3 equiv). The resultant mixture was heated to reflux and stirred for 1.5 h. Upon consumption of starting material as indicated by TLC, the reaction mixture was brought back to ambient temperature and concentrated in vacuo to afford a crude brown oil, which was purified via flash column chromatography[13] (6:1 hexanes:EtOAc) to provide alkyne **2.30** (0.069 g, 74% yield) as a clear and colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (dd, J = 1.6, 0.9 Hz, 1H), 6.37 – 6.33 (m, 2H), 4.55 (t, J = 6.1 Hz, 1H), 3.04 (pent d, J = 6.9, 2.4 Hz, 1H), 2.43 (d, J = 5.9 Hz, 1H), 2.20 (d, J = 2.4 Hz, 1H), 1.18 (d, J = 7.0 Hz, 3H). $\boldsymbol{R_f}$ = 0.44 (2:1 hexanes:EtOAc; visualized with UV and/or $KMnO_4$ stain).

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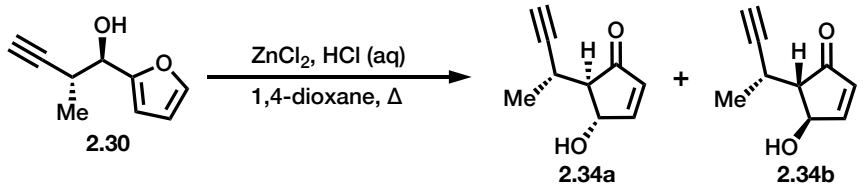
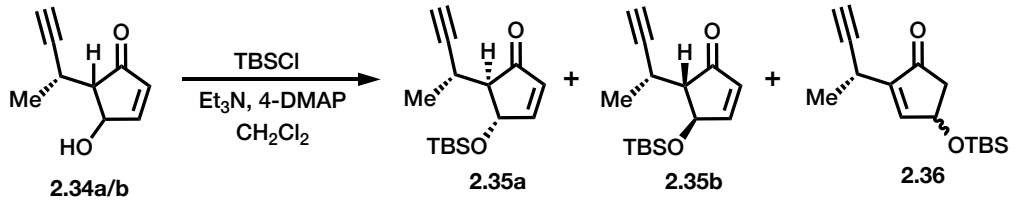
[12] Known compound; prepared in reported 94% *ee*, see the following reference: *Angew. Chem. Int. Ed.* **2012**, *51*, 2972–2976.

[13] Note: The crude concentrate was directly loaded onto the column, however, it was essential to first add a thick (ca. 1–2 cm) layer of sand onto the top of the column bed to ensure that residual NaOH does not interact with the silica.



4-Hydroxycyclopentenones 2.34a/b. To a solution of alkyne **2.30** (11.3 mg, 0.075 mmol, 1 equiv) in 1,4-dioxane (0.9 mL) was added a solution of $ZnCl_2$ (41 mg, 0.300 mmol, 4 equiv) in H_2O (0.5 mL) at ambient temperature, then a 0.5 M HCl aqueous solution was added until the reaction mixture was approximately pH 5.5. The resultant mixture was heated to reflux and stirred at that same temperature for 48 h. Upon near complete consumption of starting material as indicated by TLC, the reaction mixture was brought back to ambient temperature and quenched with a saturated aqueous $NaHCO_3$ solution (5 mL). The mixture was extracted with EtOAc (3 x 8 mL) and the organic extracts were combined, washed with brine (1 x 20 mL), then dried over Na_2SO_4. Concentration of the dried extracts provided 4-hydroxycyclopentenones **2.34a** and **2.34b** (5.8 mg, 51% yield) as an inseparable 1.2:1.0 mixture of diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$): *(Major diastereomer)* δ 7.56 – 7.53 (dd, *J* = 5.8, 2.2 Hz, 1H), 6.25–6.22 (1H), 5.07 – 5.04 (m, 1H), 3.20 – 3.08 (m, 1H), 2.27 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.03 (d, *J* = 2.4 Hz, 1H), 1.45 (d, *J* = 7.1 Hz, 3H). *(Minor diastereomer)* δ 7.59 – 7.56 (dd, *J* = 5.8, 2.2 Hz, 1H), 6.24 – 6.21 (1H), 5.02 – 4.99 (m, 1H), 3.20 – 3.08 (m, 1H), 2.54 (dd, *J* = 4.1, 2.7 Hz, 1H), 2.16 (d, *J* = 2.5 Hz, 1H), 1.13 (d, *J* = 7.1 Hz, 3H). $\boldsymbol{R_f}$ **=** 0.36 (1:1 hexanes:EtOAc; visualized with UV and/or $KMnO_4$ stain).



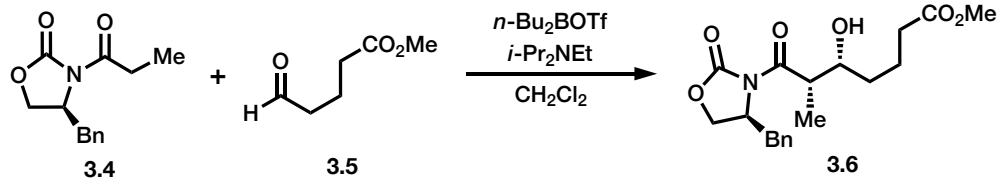
4-Silyloxycyclopenten-2-ones 2.35a/b and **2.36.** To a pre-cooled solution of **2.34a/b** (1.4:1.0 mixture of diastereomers; 8.0 mg, 0.533 mmol, 1 equiv) in CH_2Cl_2 (0.60 mL) was added Et_3N (11 μL, 0.800 mmol, 1.5 equiv) and 4-dimethylaminopyridine (1.3 mg, 0.011 mmol, 0.2 equiv) at 0 °C, followed by dropwise treatment with a solution of *tert*-butyldimethylsilyl chloride (8.8 mg, 0.586 mmol, 1.1 equiv) in CH_2Cl_2 (0.10 mL). The resultant solution was brought to ambient temperature and stirred for 24 h. Upon consumption of starting material as indicated by TLC, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed sequentially with H_2O (1 x 5 mL), 1 M citric acid aqueous solution (1 x 4 mL), saturated aqueous $NaHCO_3$ solution (1 x 5 mL), and brine (1 x 5 mL). The organic extracts were then dried over Na_2SO_4, whereupon ensuing concentration of the dried extracts provided a clear and colorless residue. Purification via preparative thin-layer chromatography (5:1 hexanes:EtOAc) afforded **2.35a/b** (7.9 mg, 56% yield) and **2.36** (2.7 mg, 19% yield), as 1.4:1.0 and 1:1 mixtures of diastereomers, respectively.

2.35a/b: ^{1}H NMR (400 MHz, $CDCl_3$): *(Major diastereomer)* δ 7.42 (dd, *J* = 5.8, 2.2 Hz, 1H), 6.16 (dd, *J* = 5.8, 1.0 Hz, 1H), 4.87 (m, 1H), 3.08 – 3.01 (m, 1H), 2.40 (dd, *J* = 3.7, 2.4 Hz, 1H), 2.03 (d, *J* = 2.5 Hz, 1H), 1.27 (d, *J* = 7.1 Hz, 3H), 0.91 (s, 9H), 0.18 (6H). *(Minor diastereomer)* δ 7.44 (dd, *J* = 5.8, 2.2 Hz, 1H), 6.20 (dd, *J* = 5.8, 1.2 Hz, 1H), 5.04 (m, 1H), 3.23 – 3.16 (m, 1H), 2.29 (dd, *J* = 3.5, 2.5 Hz, 1H), 1.98 (d, *J* = 2.4 Hz, 1H), 1.37 (d, *J* = 7.3 Hz, 1H), 0.91 (s, 9H), 0.17 (6H). **COSY:** see Figure A.41.

2.36: ^{1}H NMR (400 MHz, $CDCl_3$, *denotes corresponding diastereomer signals**):** δ 7.35 – 7.32 (m, 1H), 4.94 – 4.89 (m, 1H), 3.52 – 3.43 (m, 1H) , 2.82 (d, *J* = 5.9 Hz, 0.5H*), 2.77 (d, *J* = 5.9

Hz, 0.5H*), 2.36 (dd, *J* = 3.5, 2.2 Hz, 0.5 H**), 2.31 (dd, *J* = 3.4, 2.2 Hz, 0.5 H**), 2.21 (d, *J* = 2.5 Hz, 0.5H***), 2.20 (d, *J* = 2.5 Hz, 0.5H***), 1.37 (d, *J* = 7.1 Hz, 1.5H****), 1.34 (d, *J* = 7.1 Hz, 1.5H****), 0.92 (9H), 0.13 (6H). **COSY:** see Figure A.43.

6.3. Experimental Procedures and Characterization Data for Chapter 3



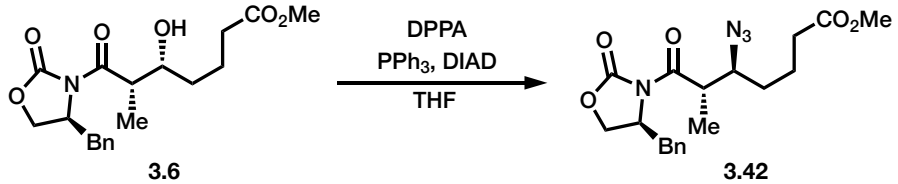
Alcohol 3.6. To a pre-cooled solution of (*S*)-(+)-4-Benzyl-3-propionyl-2-oxazolidinone (**3.4**) (5.77 g, 24.7 mmol, 1 equiv) in dry CH_2Cl_2 (120 mL) was added dropwise at −78 °C a solution of freshly distilled di-*n*-butylboron trifluoromethanesulfonate[14] (6.8 mL, 27.0 mmol, 1.1 equiv) in dry CH_2Cl_2 (13 mL). The resultant mixture was then slowly treated with freshly distilled *N*,*N*-diisopropylethylamine (6.0 mL, 34.4 mmol, 1.4 equiv) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min, subsequently brought to 0 °C and stirred at this same temperature for 3 h, before re-cooling to −78 °C. A separate solution containing aldehyde **3.5**[15] (3.54 g, 27.2 mmol, 1.1 equiv) in dry CH_2Cl_2 (30 mL) was cooled to −78 °C, then added dropwise to the reaction mixture via cannula transfer over 15 min. The resultant mixture was allowed to warm to ambient temperature and stirred for 20 h. Upon consumption of starting material as indicated by TLC, the reaction mixture was cooled to 0 °C, diluted with MeOH (120 mL) and 1.0 M aqueous

[14] Prepared from tri-*n*-butylborane (1 equiv) and trifluoromethanesulfonic acid (1 equiv) according to the following procedures: (a) *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174−178. (b) *J. Am. Chem. Soc.* **1981**, *103*, 3099−3111.

[15] Known compound: prepared from δ-valerolactone in two steps as described in the following reference: *Angew. Chem. Int. Ed.* **2017**, *56*, 15921–15925.

K_2HPO_4 — H_3PO_4 solution (pH 7; 30 mL), and finally slowly treated with a 1:1 MeOH/30% aqueous H_2O_2 solution (60 mL). The resultant mixture was vigorously stirred at 0 °C for 2 h. The mixture was subsequently extracted with CH_2Cl_2 (4 x 150 mL) and the organic extracts were combined and dried over Na_2SO_4. Concentration of the dried extracts provided a crude orange oil, which was purified via flash column chromatography (3:2 hexanes:EtOAc) to afford alcohol **3.6** (8.57 g, 95% yield) as a pale-yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (m, 2H), 7.28 (m, 1H), 7.21 (m, 2H), 4.71 (m, 1H), 4.28 – 4.17 (m, 2H), 3.97 (m, 1H), 3.75 (qd, *J* = 7.0, 2.7 Hz, 1H), 3.67 (s, 3H), 3.25 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.93 (br s, 1H), 2.79 (dd, *J* = 13.4, 9.5 Hz, 1H), 2.42 – 2.31 (m, 2H), 1.90 – 1.80 (m, 1H), 1.75 – 1.65 (m, 1H), 1.63 – 1.52 (m, 1H), 1.50 – 1.41 (m, 1H), 1.26 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 177.5, 174.1, 153.2, 135.1, 129.6, 129.1, 127.6, 71.2, 66.3, 55.2, 51.7, 42.4, 37.9, 33.9, 33.3, 21.5, 10.7. **HRMS:** (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{25}NO_6$: 364.1760, found: 364.1771. **$[\alpha]_D^{23.6}$** = +44.2 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 3512 (br), 2949 (m), 1772 (s), 1731 (s), 1692 (m), 1454 (w), 1383 (m), 1350 (m), 1207 (s), 1108 (m), 971 (m), 762 (w), 750 (w), 702 (s). ***R*$_f$** = 0.44 (1:1 hexanes:EtOAc; visualized with UV and $KMnO_4$ stain).



Azide 3.42. To a solution of triphenylphosphine (4.96 g, 18.9 mmol, 1.5 equiv) in dry THF (120 mL) was added diisopropyl azodicarboxylate (3.7 mL, 18.9 mmol, 1.5 equiv) dropwise at 0 °C.

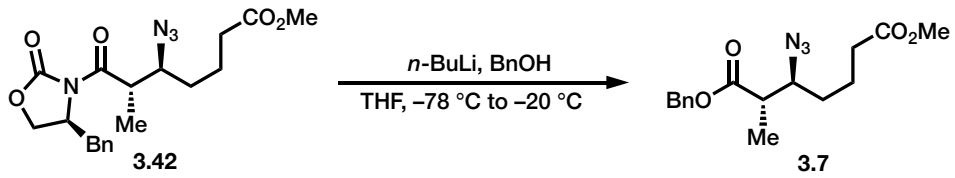
The resultant mixture was stirred at 0 °C for 15 min, whereupon a solution of alcohol **3.6** (4.58 g, 12.5 mmol, 1 equiv) in dry THF (100 mL) was added slowly over 15 min at 0 °C. This mixture was stirred at 0 °C for 20 min, followed by subsequent treatment with diphenylphosphoryl azide (4.1 mL, 19.0 mmol, 1.5 equiv) dropwise, then stirred at 0 °C for an additional 30 min. The resultant turbid beige mixture was then allowed to warm to ambient temperature and stirred for 10 h, slowly changing to a clear, pale-yellow solution. Upon consumption of starting material as indicated by TLC, the reaction mixture was treated with a saturated aqueous $NaHCO_3$ solution (200 mL) and extracted with 1:1 hexanes:EtOAc (3 x 200 mL). The organic extracts were combined, washed with brine (1 x 250 mL), and dried over Na_2SO_4. Concentration of the dried extracts[16] provided a crude yellow oil, which was purified via flash column chromatography (4:1:0 hexanes:CH_2Cl_2:EtOAc → 4:1:0.2 hexanes:CH_2Cl_2:EtOAc → 4:1:0.5 hexanes:CH_2Cl_2:EtOAc → 4:1:1 hexanes:CH_2Cl_2:EtOAc) to afford azide **3.42** (4.13 g, 85% yield) as a clear, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.27 (m, 3H), 7.22 (m, 2H), 4.74 (m, 1H), 4.27 (dd, *J* = 8.9, 7.9 Hz, 1H), 4.20 (dd, *J* = 9.1, 2.6 Hz, 1H), 3.92 – 3.83 (m, 1H), 3.78 – 3.70 (td, *J* = 9.1, 2.8 Hz, 1H), 3.69 (s, 3H), 3.26 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.80 (dd, *J* = 13.4, 9.5 Hz, 1H), 2.38 (m, 2H), 1.94 – 1.82 (m, 1H), 1.79 – 1.67 (m, 2H), 1.56 – 1.48 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 174.7, 173.6, 153.1, 135.2, 129.6, 129.1, 127.6, 66.4, 64.3, 55.4, 51.8, 42.1, 38.0, 33.7, 30.6, 21.1, 14.7. **HRMS:** (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{24}N_4O_5$: 389.1825, found: 389.1824. **$[\alpha]_D^{24.8}$ =** +72.0 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 2951

[16] Bath temperature was maintained at or below 30 – 35 °C, as extensive product decomposition was observed at higher temperatures.

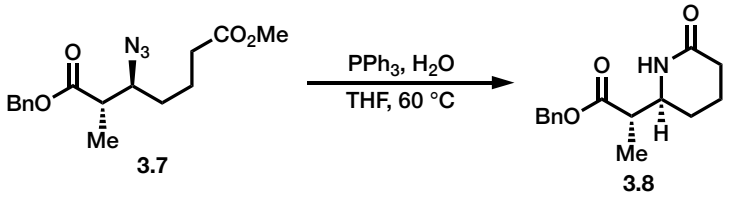
(m), 2099 (s), 1775 (s), 1733 (s), 1693 (s), 1454 (w), 1386 (m), 1349 (w), 1209 (s), 1110 (m), 972 (m), 762 (m), 749 (m), 703 (s). R_f = 0.54 (2:1 hexanes:EtOAc; visualized with $KMnO_4$).



Benzyl ester 3.7. To pre-cooled a solution of freshly distilled benzyl alcohol (2.0 mL, 19.2 mmol, 2.0 equiv) in dry THF (30 mL) was added *n*-butyllithium solution (1.60 M in hexanes; 10.5 mL, 16.8 mmol, *ca.* 1.8 equiv) dropwise at −78 °C. The resultant mixture was stirred at −78 °C for 15 min, then allowed to warm to 0 °C, stirred at this same temperature for 10 min, and subsequently re-cooled to −40 °C. A solution of azide **3.42** (3.70 g, 9.50 mmol, 1 equiv) in dry THF (50 mL) was added dropwise over 15 min at −40 °C to the solution containing LiOBn. The resultant yellow solution was stirred at −40 °C for 30 min, then allowed to slowly warm to −20 °C and stirred at this same temperature for an additional 3 h. Upon consumption of starting material as indicated by TLC, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (50 mL) at −20 °C and allowed to warm to ambient temperature. The mixture was extracted with 1:1 hexanes:EtOAc (3 x 150 mL) and the organic extracts were combined, washed with brine (1 x 200 mL), and dried over Na_2SO_4. Concentration of the dried extracts provided a crude yellow oil, which was purified via flash column chromatography (8:1 hexanes:EtOAc) to afford benzyl ester **3.7** (2.38 g, 78% yield) as a clear, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.30 (m, 5H), 5.19 (d, J = 12.3 Hz, 1H), 5.14 (d, J = 12.3 Hz, 1H), 3.67 (s, 3H), 3.60 (m, 1H), 2.72 – 2.63 (pent, J = 7.3 Hz, 1H), 2.40 – 2.26 (m, 2H), 1.88 – 1.75 (m, 1H), 1.74 – 1.44 (m, 3H), 1.19 (d, J = 7.1 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ

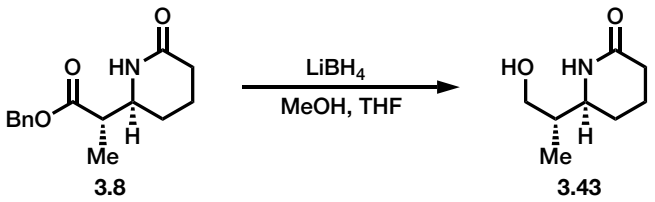
173.8, 173.6, 135.8, 128.8, 128.5, 128.4, 66.8, 64.4, 51.8, 44.2, 33.6, 30.6, 21.4, 13.7. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{16}H_{21}N_3O_4$: 320.1610, found: 320.1598. $[\alpha]_D^{20.7}$ = +5.7 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 2951 (m), 2098 (s), 1731 (s), 1455 (m), 1436 (w), 1249 (s), 1167 (s), 1074 (w), 1028 (w), 911 (w), 752 (s), 698 (s). R_f = 0.45 (4:1 hexanes:EtOAc; visualized with $KMnO_4$ stain).



Lactam 3.8. To a solution of azide **3.7** (2.38 g, 7.45 mmol, 1 equiv) in THF (220 mL) was added distilled water (1.35 mL, 75 mmol, 10 equiv) and triphenylphosphine (2.34 g, 8.94 mmol, 1.2 equiv) at ambient temperature. The resultant mixture was heated to 60 °C and stirred at that same temperature for 24 h. Upon consumption of starting material, as indicated by TLC, the mixture was cooled to ambient temperature and concentrated in vacuo to afford a crude yellow solid, which was purified via flash column chromatography (1:1:0.5 hexanes:CH_2Cl_2:acetone → 1:1:1 hexanes:CH_2Cl_2:acetone) to afford lactam **3.8** (1.73 g, 89% yield) as an off-white solid. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.41 – 7.32 (m, 5H), 6.07 (br s, 1H), 5.17 (d, *J* = 12.3 Hz, 1H), 5.13 (d, *J* = 12.3 Hz, 1H), 3.63 (m, 1H), 2.59 – 2.51 (pent, *J* = 7.3 Hz, 1H), 2.43 – 2.35 (m, 1H), 2.30 – 2.21 (m, 1H), 1.96 – 1.84 (m, 2H), 1.75 – 1.64 (m, 1H), 1.50 – 1.40 (m, 1H), 1.20 (d, *J* = 7.3 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 174.1, 172.2, 135.6, 128.8, 128.6, 128.4, 66.9, 54.5, 45.5, 31.5, 25.2, 19.4, 13.5. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{19}NO_3$: 262.1443, found: 262.1453. $[\alpha]_D^{22.9}$ = +5.5 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 2947 (m), 1728 (s),

1656 (s), 1454 (m), 1405 (w), 1349 (m), 1309 (w), 1150 (s), 1065 (m), 958 (m), 735 (s), 697 (s).

R_f = 0.50 (1:1 $CHCl_3$:acetone; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).

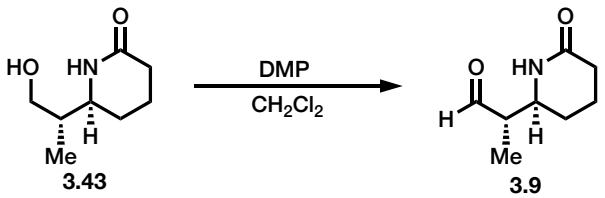


3.8 3.43

Alcohol 3.43. To a pre-cooled solution of benzyl ester **3.8** (1.60 g, 6.12 mmol, 1 equiv) in dry THF (60 mL) was added lithium borohydride (0.675 g, 31.0 mmol, 5 equiv) in a single portion at 0 °C, followed by anhydrous methanol (1.50 mL, 37.1 mmol, 6 equiv) dropwise at the same temperature. The resultant, cloudy white mixture was allowed to warm to ambient temperature and stirred for 24 h. Upon consumption of starting material as indicated by TLC, the mixture was diluted with Et_2O (50 mL) and slowly treated with distilled water (20 mL). The resultant biphasic mixture was separated, and the aqueous layer extracted with Et_2O (2 x 40 mL). The *aqueous* extracts were concentrated in vacuo to afford a whitish residue, which was subsequently azeotroped with benzene (3 x 5 mL) to remove remaining traces of water. The resulting white solid was resuspended in MeOH (10 mL) and filtered through a layer of Celite, washing the filter cake thoroughly with ice-cold MeOH (50 mL). Concentration of the filtrate provided a crude, off-white solid, which was purified via flash column chromatography (6% MeOH in CH_2Cl_2) to afford alcohol **3.43** (0.908 g, 94% yield) as a white, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (br s, 1H), 5.13 (br s, 1H), 3.81 (dd, *J* = 10.7, 3.6 Hz, 1H), 3.53 (t, *J* = 9.8 Hz, 1H), 3.34 – 3.25 (td, *J* = 9.8, 3.6 Hz, 1H), 2.42 – 2.31 (m, 1H), 2.30 – 2.19 (m, 1H), 1.98 – 1.85 (m, 2H), 1.79 – 1.60 (m, 2H), 1.39 – 1.28 (m, 1H), 0.83 (d, *J* = 6.9 Hz). **^{13}C**

NMR (125 MHz, $CDCl_3$): δ 172.8, 67.9, 58.8, 40.1, 31.0, 26.6, 20.0, 13.3. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_8H_{15}NO_2$: 158.1181, found: 158.1188. **$[\alpha]_D^{22.8}$** = −44.3 (*c* = 1.0, MeOH). **IR (thin film) ν_{max} (cm^{-1}):** 3275 (s), 2956 (m), 1625 (s), 1474 (m), 1408 (s), 1349 (m), 1329 (m), 1309 (m), 1168 (w), 1031 (s), 982 (w), 670 (s). ***R_f*** = 0.36 (10% MeOH in CH_2Cl_2; visualized with $KMnO_4$ stain).

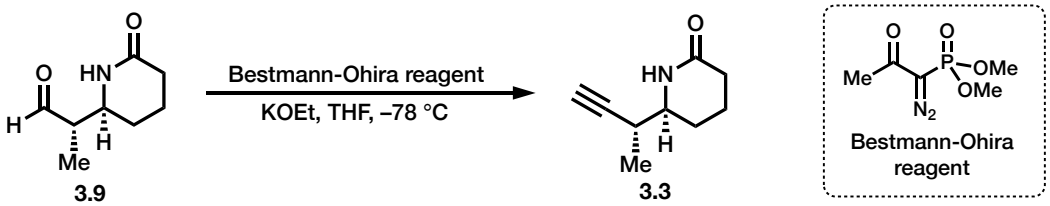


Aldehyde 3.9. To a solution of alcohol **3.43** (0.311 g, 1.98 mmol, 1 equiv) in CH_2Cl_2 (70 mL) was added Dess-Martin periodinane (1.09 g, 2.57 mmol, 1.3 equiv) in a single portion at ambient temperature. The resultant cloudy white mixture was stirred at ambient temperature for 3 h. Upon consumption of the starting material as indicated by TLC, the reaction mixture was treated with solid $NaHCO_3$ (0.490 g), diluted with 1:1 hexanes:Et_2O (150 mL), then filtered through a layer of Celite while washing the filter cake thoroughly with Et_2O (ca. 100 mL). Concentration of the filtrate afforded a crude off-white solid, which was purified via flash column chromatography (4:1 $CHCl_3$:acetone) to afford aldehyde **3.9**[17] (0.303 g, 98% yield) as an amorphous, white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.68 (s, 1H), 6.68 (br s, 1H), 3.78 – 3.70 (m, 1H), 2.60 – 2.50 (pent, *J* = 7.5 Hz, 1H), 2.45 – 2.35 (m, 1H), 2.32 – 2.21 (m, 1H), 1.96 – 1.84 (m, 2H), 1.79 –

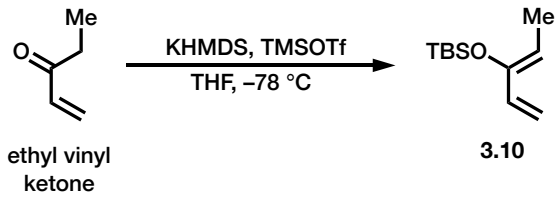
[17] This material was found to be sparingly soluble in most organic solvents and extremely prone to epimerization. Upon exposure to protic solvents, a diastereomeric mixture of hemiacetals is readily formed.

1.66 (m, 1H), 1.52 – 1.40 (m, 1H), 1.18 (d, J = 7.5 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 203.0, 172.5, 52.8, 51.5, 31.5, 25.2, 19.6, 9.7. **HRMS:** (ESI) m/z $[M+H]^+$ calcd for $C_8H_{13}NO_2$: 156.1024, found: 156.1026. **IR (thin film) ν_{max} (cm^{-1}):** 3213 (br), 2980 (m), 2873 (m), 1719 (s), 1659 (s), 1481 (w), 1402 (m), 1353 (s), 1319 (m), 1200 (w), 1173 (m), 1063 (w), 983 (s), 955 (w), 790 (m), 678 (w). **$[\alpha]_D^{24.7}$** = −36.7 (c = 1.0, MeOH). ***R*$_f$** = 0.33 (1:2 $CHCl_3$:acetone; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).



Alkyne 3.3. To a pre-cooled solution of potassium ethoxide (0.431 g, 5.12 mmol, 3.3 equiv) in THF (40 mL) was added dropwise over 10 min a solution of Bestmann-Ohira reagent[3] (1.19 g, 6.20 mmol, 4 equiv) in THF (8.0 mL) at −78 °C. After complete addition, the resultant opaque, bright yellow mixture was stirred at −78 °C for 20 min. Aldehyde **3.9** (0.240 g, 1.55 mmol, 1 equiv) was then added to the reaction mixture in a single portion at −78 °C and the resultant mixture was vigorously stirred for 10 min before allowing the solution to warm to −50 °C. The reaction mixture was then stirred at −50 °C for 1.5 h before allowing to warm to 0 °C, then quenched with saturated aqueous NH_4Cl solution (50 mL) and further diluted with H_2O (50 mL). The mixture was extracted with EtOAc (6 x 30 mL). The organic extracts were combined and washed with brine (1 x 100 mL), then dried over Na_2SO_4. Concentration of the dried organic extracts provided a crude yellow residue, which was purified via flash column chromatography (100% EtOAc) to afford alkyne **3.3** (0.211 g, 90% yield) as a white, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.27 (s, 1H), 3.26 (m, 1H), 2.48 – 2.38 (m, 2H), 2.33 – 2.23 (m, 1H), 2.19 (d, *J* = 2.3 Hz, 1H), 1.98 – 1.91 (m, 1H), 1.75 – 1.57 (m, 2H), 1.42 – 1.32 (m, 1H), 1.22 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 172.2, 84.7, 71.7, 56.9, 32.7, 31.4, 26.3, 19.8, 16.6. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_9H_{13}NO$: 152.1075, found: 152.1076. **IR (thin film) ν_{max} (cm^{-1}):** 3221 (s), 2949 (m), 2876 (m), 2128 (w), 1648 (s), 1451 (m), 1405 (m), 1349 (m), 1335 (m), 1296 (w), 1169 (m), 1070 (m), 976 (w), 952 (w), 670 (s). **$[\alpha]_D^{23.9}$** = +34.5 (*c* = 1.0, $CHCl_3$). ***R*$_f$** = 0.45 (1:1 $CHCl_3$:acetone; visualized with $KMnO_4$ stain).

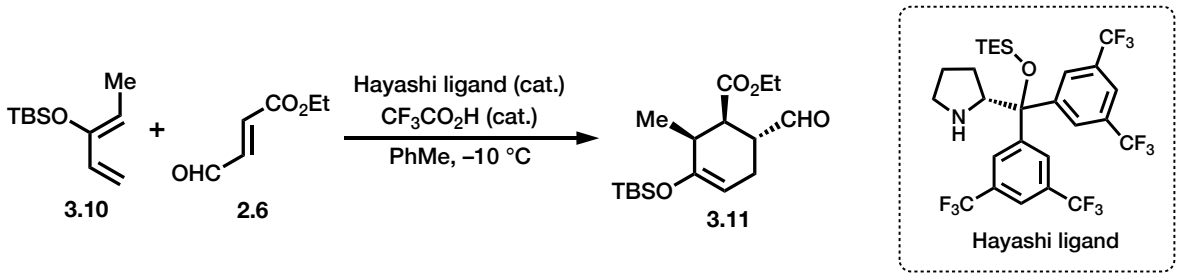


Siloxydiene 3.10.[18] To a pre-cooled solution of ethyl vinyl ketone (11.0 g, 131 mmol, 1.0 equiv) in THF (750 mL) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (30 mL, 131 mmol, 1.0 equiv) slowly at −78 °C. The resultant solution was treated with a 1.0 M solution of KHMDS in THF (160 mL, 160 mmol, ca. 1.2 equiv), which was added via cannula dropwise over 30 min at –78 °C. Following complete addition, the pale-yellow mixture was stirred at −78 °C for 45 min, then the cold bath was removed and reaction mixture was stirred for an additional 1 h upon warming to ambient temperature. The mixture was cooled to 0 °C and quenched with a saturated aqueous $NaHCO_3$ solution (300 mL), then concentrated in vacuo until the total volume was approximately 500 mL. The residual mixture was extracted with 10:1 hexanes:Et_2O (3 x 300

[18] Known compound; this procedure was adapted from the following reference: *J. Am. Chem. Soc.* **2010**, *132*, 10127−10135.

mL), then the combined organic extracts were washed with brine (1 x 400 mL) and dried over Na_2SO_4. Concentration of the dried extracts provided a crude yellow oil, which was purified via flash column chromatography (100% petroleum ether) to afford siloxydiene **3.10** (18.6 g, 72% yield; >50:1 *Z*:*E*) as a clear, colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.16 (dd, *J* = 17.1, 10.8 Hz, 1H), 5.27 (d, *J* = 17.1 Hz, 1H), 4.94 (d, *J* = 10.8 Hz, 1H), 4.87 (q, *J* = 7.0 Hz, 1H), 1.64 (d, *J* = 7.0 Hz, 3H), 1.01 (s, 9H), 0.12 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 149.6, 135.7, 111.8, 110.2, 26.1, 18.6, 11.9, -3.5. **IR (thin film) ν_{max} (cm^{-1}):** 3102 (w), 3024 (w), 2957 (s), 2930 (s), 2859 (s), 1648 (m), 1607 (m), 1474 (m), 1465 (w), 1385 (m), 1364 (w), 1340 (s), 1290 (m), 1255 (s), 1203 (m), 1082 (m), 1050 (s), 1015 (w), 1006 (w), 983 (w), 939 (m), 897 (m), 839 (s), 803 (m), 779 (s), 740 (w), 695 (m). ***R_f*** = 0.46 (100% hexanes; visualized with UV and $KMnO_4$ stain).



TBS enol ether 3.11. A solution of ethyl trans-4-oxo-2-butenoate[19] (**2.6**; 8.6 mL, 71.3 mmol, 1.0 equiv.) in PhMe (4.0 mL) was treated dropwise with solution of Hayashi ligand (4.56 g, 7.13 mmol, 10 mol%) in PhMe (11 mL) at ambient temperature. To the pale-yellow solution was

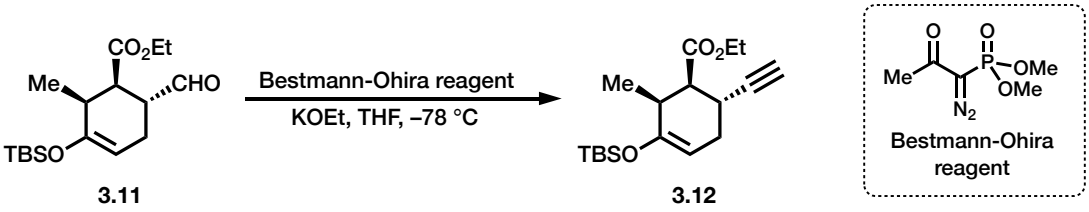
[19] This material (commercially available, Alfa Aesar) had a tendency to decompose upon storing for several months in a refrigerator. The purity was always checked via ^{1}H NMR prior to use and, if necessary, purified via flash column chromatography, see: *Org. Synth.* **2018**, *95*, 142−156.

added a solution of trifluoroacetic acid (1.10 mL, 14.3 mmol, 20 mol%) in PhMe (30 mL) and the mixture was cooled to −10 °C. The clear, yellow solution was next treated with siloxydiene **3.10** (16.9 g, 85.2 mmol, 1.2 equiv) dropwise over 15 min at −10 °C. The resultant solution was stirred at −10 ˚C for 16 h, then diluted with hexanes (80 mL) and neutralized with a saturated aqueous $NaHCO_3$ solution (40 mL) at −10 °C. The mixture was brought to ambient temperature and extracted with 5:1 hexanes:Et_2O (3 x 50 mL), then the combined organic extracts were washed with brine (1 x 100 mL) and dried over Na_2SO_4. Concentration of the dried extracts[20] afforded a crude, yellow residue that was purified via flash column chromatography (100:0 hexanes:EtOAc → 13:1 hexanes:EtOAc) to afford TBS enol ether **3.11** (15.6 g, 67% yield) as a pale-yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.81 (d, *J* = 1.8 Hz, 1H), 4.75 (dd, *J* = 5.3, 2.4 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.01 (dd, *J* = 11.8, 5.6 Hz, 1H), 2.92 (tdd, *J* = 11.6, 5.7, 1.8 Hz, 1H), 2.54 (app pent, *J* = 6.6 Hz, 1H), 2.30 (dt, *J* = 16.7, 5.5 Hz, 1H), 1.98 (app ddt, *J* = 16.7, 11.4, 2.0 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.93 (s, 9H), 0.15 (6H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 203.1, 172.9, 153.6, 99.3, 60.9, 45.3, 42.6, 35.2, 25.8, 24.0, 18.1, 15.0, 14.4, -4.2, -4.5. **HRMS:** (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{30}O_4Si$: 327.1991, found: 327.1994. **$[\alpha]_D^{21.9}$ =** −105.4 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 2956 (m), 2929 (m), 2856 (m), 1727 (s), 1669 (s), 1472 (m), 1463 (m), 1377 (m), 1302 (m), 1278 (m), 1251 (m), 1196 (s), 1097 (w), 1027 (m), 838 (s), 778 (s), 665 (w). R_f = 0.32 (10:1 hexanes:EtOAc; visualized with $KMnO_4$ stain). **HPLC:** t_{major} = 21.5 min, t_{minor} = 21.9 min (90% *ee*). (Chiralcel® OD-H column, see method details below; Detection wavelength = 210 nm).

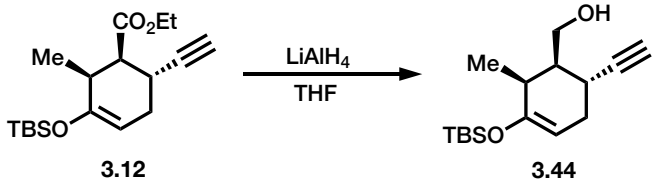
[20] Bath temperature was maintained below 30 °C, as product decomposition was observed at higher temperatures.

Time (min)	% Hexanes	% i-PrOH	Flow Rate (mL/min)
0	99.8	0.2	0.500
3.0	99.7	0.3	0.500
5.0	99.5	0.5	0.500
8.0	99.2	0.8	0.500
15	99.0	1.0	0.500



Alkyne 3.12. To a flame-dried 1-L, three-necked round-bottomed flask charged with a 4 cm Teflon-coated magnetic oval stir bar and equipped with an inert gas inlet (Ar), thermometer, and rubber septum was added potassium ethoxide (6.95 g, 82.6 mmol, 3.2 equiv) and THF (500 mL). The resultant mixture was cooled to −78 °C (internal temperature per thermometer) and treated with solution of Bestmann-Ohira reagent[3] (17.8 g, 92.9 mmol, 3.6 equiv) in THF (120 mL) via cannula transfer at a rate such that the internal reaction temperature did not exceed −74 °C. After complete addition, the empty flask and cannula were rinsed with THF (3 x 3 mL) and the resultant opaque, bright yellow reaction mixture was stirred at −78 °C for 25 min. A solution of TBS enol ether **3.11** (8.42 g, 25.8 mmol, 1 equiv) in THF (70 mL) was then added to the reaction mixture via cannula transfer at a rate such that the internal reaction temperature did not exceed −72 °C. After complete addition, the empty flask and cannula were rinsed with THF (3 x 3 mL) and the resultant yellowish-orange reaction mixture was stirred at −78 °C for 1 h. The cold bath was next removed and, upon warming to −5 °C (internal temperature), the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (300 mL) and diluted with hexanes (400 mL).

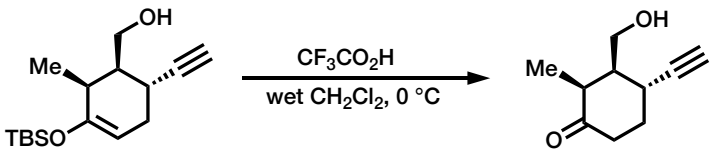
The biphasic mixture was separated and the aqueous extracts were washed with 5:1 hexanes:Et_2O (2 x 450 mL). All organic extracts were combined, washed with brine (1 x 500 mL), and dried over Na_2SO_4. Concentration of the dried extracts provided a crude yellow residue, which was purified via flash column chromatography (20:1 hexanes:Et_2O) to afford alkyne **3.12** (6.98 g, 84% yield) as a clear, light-yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.69 (dd, *J* = 5.1, 2.1 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 2.83 (dd, *J* = 11.7, 5.3 Hz, 1H), 2.77 (m, 1H), 2.48 – 2.37 (m, 2H), 2.18 (ddt, *J* = 17.0, 10.6 Hz, 1H), 2.03 (d, 2.1 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.00 (d, *J* = 7.0 Hz), 0.92 (s, 9H), 0.14 (6H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 172.4, 152.8, 100.1, 86.8, 69.0, 60.5, 49.9, 35.5, 30.3, 25.8, 23.3, 18.1, 14.8, 14.4, -4.3, -4.5. **HRMS:** (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{30}O_3Si$: 323.2042, found: 323.2046. **$[\alpha]_D^{23.2}$ =** −102.7 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 3312 (s), 2956 (m), 2929 (m), 2856 (m), 2111 (w), 1739 (s), 1670 (s), 1472 (m), 1463 (m), 1374 (m), 1253 (s), 1196 (s), 1152 (s), 1032 (m), 1005 (m), 910 (s), 838 (s), 799 (m), 778 (s), 671 (m), 634 (s). ***R*$_f$ =** 0.46 (10:1 hexanes:EtOAc; visualized with $KMnO_4$ stain).



3.12 **3.44**

Primary Alcohol 3.44. To a pre-cooled solution of alkyne **3.12** (6.81 g, 21.1 mmol, 1.0 equiv) in THF (200 mL) was added lithium aluminum hydride solution (2.0 M in THF; 13.5 mL, 27.0 mmol, 1.3 equiv) dropwise at 0 °C. The resultant mixture was allowed to warm to ambient temperature and stirred for 2 h. Following complete consumption of starting material as indicated

by TLC, the reaction mixture was re-cooled to 0 °C and diluted with Et_2O (200 mL). The reaction was carefully quenched by sequential addition of H_2O (1.0 mL), 2 M NaOH aqueous solution (1.0 mL), and H_2O (3.0 mL) and vigorously stirred for 15 min upon warming to ambient temperature. Anhydrous $MgSO_4$ was then added and the mixture was stirred for an additional 15 min. The mixture was next passed through a layer of Celite, washing the filter cake thoroughly with Et_2O (ca. 400 mL). Concentration of the filtrate provided primary alcohol **3.44** (5.62 g, 95% yield) as a clear, colorless oil which solidified to white crystals upon refrigeration. The crude concentrate was typically clean enough to be carried forward without purification, however flash column chromatography (8:1 hexanes:EtOAc) was used to obtain spectroscopically pure material. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.69 (dd, *J* = 5.1, 2.4 Hz, 1H), 3.96 (dd, *J* =11.3, 6.3 Hz , 1H), 3.65 (dd, *J* = 11.3, 6.9 Hz, 1H), 2.51 – 2.42 (tdd, *J* = 10.8, 5.3, 2.3 Hz, 1H), 2.40 – 2.28 (m, 2H), 2.24 – 2.17 (m, 1H), 2.16 (d, *J* = 2.4 Hz, 1H), 2.05 – 1.94 (m, 2H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.92 (s, 9H), 0.13 (6H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 154.4, 100.5, 87.1, 70.6, 64.1, 44.3, 35.7, 31.3, 25.8, 24.4, 18.1, 13.1, -4.3, -4.5. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{16}H_{28}O_2Si$: 281.1937, found: 281.1942. **$[\alpha]_D^{22.6}$ =** −98.7 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 3310 (br), 2956 (s), 2929 (s), 2896 (m), 2857 (m), 2110 (w), 1668 (s), 1472 (m), 1463 (m), 1361 (w), 1254 (s), 1196 (s), 1168 (m), 1075 (m), 903 (s), 836 (s), 778 (s), 631 (m). ***R_f* =** 0.42 (4:1 hexanes:EtOAc; visualized with $KMnO_4$ stain).

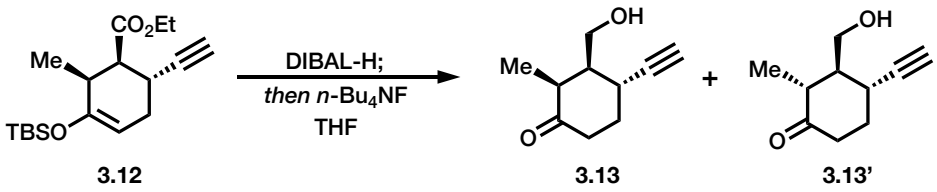


3.44 3.13

Ketone 3.13. To a pre-cooled solution of primary alcohol **3.44** (5.59 g, 19.9 mmol, 1 equiv) in H_2O-saturated CH_2Cl_2[21] (100 mL) was added trifluoroacetic acid (3.0 mL, 39.2 mmol, *ca.* 2 equiv) dropwise at 0 °C. The resultant mixture was stirred at 0 °C for 20 min and, following complete consumption of starting material by as indicated TLC, neutralized with a saturated aqueous $NaHCO_3$ solution (150 mL) at 0 °C. The biphasic mixture was stirred vigorously for 10 min as it was allowed to warm to ambient temperature, then the mixture was extracted with CH_2Cl_2 (6 x 80 mL) and the combined organic extracts were dried over Na_2SO_4. The dried extracts were concentrated in vacuo and the resultant crude residue was purified via flash column chromatography (6:2:1 hexanes:CH_2Cl_2:acetone) to afford ketone **3.13** (3.07 g, 95% yield) as a clear, viscous waxy oil which solidified upon refrigeration.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.74 (app dt, *J* = 11.2, 4.4 Hz, 1H), 3.55 (m, 1H), 3.11 (m, 2H), 2.66 (m, 1H), 2.39 – 2.32 (m, 2H), 2.25 – 2.17 (m, 1H), 2.20 (d, *J* = 2.4 Hz, 1H), 2.01 (m, 1H), 1.33 (t, 4.7 Hz, 1H), 1.09 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 212.7, 86.3, 70.4, 61.1, 49.1, 43.1, 37.8, 28.1, 28.0, 11.7. **HRMS:** (ESI) *m/z* $[M+H]^+$ calcd for $C_{10}H_{14}O_2$: 167.1072, found: 167.1069. **$[\alpha]_D^{24.3}$ =** +12.4 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 3400 (br), 3285 (s), 2936 (m), 2111 (w), 1699 (s), 1452 (m), 1424 (m), 1379 (w), 1322 (m), 1286 (w), 1218 (m), 1141 (w), 1113 (m), 1049 (s), 960 (s), 640 (s). ***R*$_f$ =** 0.47 (1:1 hexanes:EtOAc; visualized with $KMnO_4$ stain).

[21] Using a separatory funnel, the CH_2Cl_2 had been shaken vigorously with ca. 10 mL of distilled water for 30 sec, then separated from the aqueous layer and used directly.

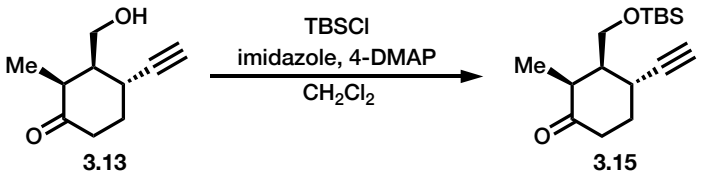


3.12 3.13 3.13'

Ketone 3.13/3.13'. To a pre-cooled solution of alkyne **3.12** (1.32 g, 4.09 mmol, 1.0 equiv) in THF (50 mL) was added diisobutylaluminum hydride solution (1.0 M in PhMe; 13.5 mL, 13.5 mmol, 3.3 equiv) dropwise at −78 °C. The resultant clear and colorless solution was stirred at −78 °C for 1 h, then brought to ambient temperature and stirred for an additional 2 h. The reaction mixture was cooled to 0 °C and treated slowly with methanol (0.65 mL; to quench unreacted DIBAL-H), followed by slow addition of tetrabutylammonium fluoride solution (1.0 M in THF; 12.0 mL, 12.0 mmol, ca. 3 equiv). The resultant pale-yellow solution was next allowed to warm to ambient temperature and stirred for 3 h. The reaction mixture was then treated with a saturated aqueous $NaHCO_3$ solution (25 mL) and saturated aqueous potassium sodium tartrate solution (100 mL) and extracted with 1:1 hexanes:EtOAc (4 x 80 mL). The organic extracts were combined and washed with brine (1 x 150 mL), then dried over Na_2SO_4. Concentration of the dried extracts afforded a crude colorless oil, which was purified via flash column chromatography (6:2:1 hexanes:CH_2Cl_2:acetone) to afford ketone **3.13** and **3.13'** (0.659 g, 97% yield) as a 1.0:2.3 mixture of inseparable C–2 epimers.

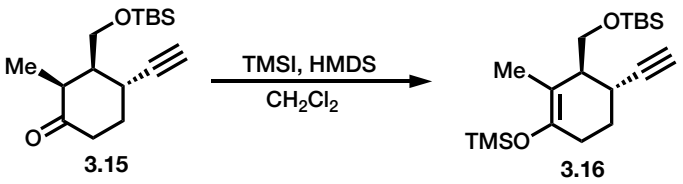
^{1}H NMR (400 MHz, $CDCl_3$): (*Major diastereomer* — **3.13'**) δ 4.16 (dd, *J* = 11.3, 1.9 Hz, 1H), 3.81 (dd, *J* = 11.3, 2.8 Hz, 1H), 2.98 – 2.88 (tt, *J* = 11.5, 2.7 Hz, 1H), 2.64 – 2.55 (m, 1H), 2.48 – 2.32 (m, 3H), 2.19 (d, *J* = 2.4 Hz, 1H), 2.06 – 1.93 (m, 1H), 1.91 – 1.77 (m, 1H), 1.55 – 1.47 (tt, *J* = 11.4, 2.4 Hz, 1H), 1.11 (d, *J* = 6.5 Hz, 3H). (*Minor diastereomer*) see ketone **3.13**.

^{13}C NMR (101 MHz, $CDCl_3$): (*Major diastereomer* — **3.13'**) δ 212.1, 85.4, 70.8, 61.2, 51.2, 44.3, 40.5, 32.2, 30.1, 11.5. (*Minor diastereomer*) see ketone **3.13**.



TBS ether 3.15. To a pre-cooled solution of ketone **3.13** (3.00 g, 18.5 mmol, 1.0 equiv) in CH_2Cl_2 (200 mL) was added imidazole (1.89 g, 27.8 mmol, 1.5 equiv), 4-dimethylaminopyridine (0.226 g, 1.85 mmol, 0.1 equiv), and *tert*-butyldimethylsilyl chloride (3.07 g, 20.4 mmol, 1.1 equiv) sequentially and in single, separate portions at 0 °C. The resultant opaque mixture was stirred at 0 °C for 4 h, then allowed to warm to ambient temperature and stirred for an additional 20 h. The mixture was quenched with a saturated aqueous $NaHCO_3$ solution (150 mL) and extracted with CH_2Cl_2 (3 x 150 mL). The combined organic extracts were dried over Na_2SO_4, concentrated in vacuo, and the residue purified via flash column chromatography (15:1 hexanes:Et_2O) to afford TBS ether **3.15** (4.80 g, 93% yield) as clear, viscous oil which froze into a white, waxy solid upon refrigeration.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.64 (dd, *J* = 10.6, 4.4 Hz, 1H), 3.47 (dd, *J* = 10.6, 8.2 Hz, 1H), 3.11 – 3.01 (m, 2H), 2.70 – 2.59 (m, 1H), 2.36 – 2.27 (m, 2H), 2.24 – 2.14 (m, 1H), 2.17 (d, *J* = 2.5 Hz, 1H), 2.01 – 1.93 (m, 1H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.02 (6H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 211.8, 86.8, 70.1, 61.4, 49.0, 42.8, 37.8, 28.5, 27.7, 25.9, 18.3, 11.7, -5.5, -5.5. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{16}H_{28}O_2Si$: 281.1937, found: 281.1940. **$[\alpha]_D^{22.6}$ =** +0.4 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 3310 (m), 2952 (m), 2928 (s), 2884 (m), 2856 (m), 2111 (w), 1712 (s), 1471 (m), 1463 (m), 1389 (w), 1361 (w), 1252 (s), 1092 (s), 1005 (w), 988 (w), 897 (m), 834 (s), 775 (s), 634 (s). R_f = 0.35 (10:1 hexanes:Et_2O; visualized with $KMnO_4$ stain).



TMS enol ether 3.16. To a pre-cooled solution of TBS ether **3.15**[22] (5.26 g, 18.8 mmol, 1.0 equiv) in CH_2Cl_2 (60 mL) was added freshly distilled hexamethyldisilazane (5.2 mL, 24.8 mmol, 1.3 equiv) at 0 °C. The resultant solution was stirred for 0.5 min, then treated with iodotrimethylsilane (3.1 mL, 22.5 mmol, 1.2 equiv) dropwise over 10 min at 0 °C. The thick, orange mixture was stirred for 20 min, then allowed to slowly warm to ambient temperature. Upon stirring at ambient temperature for 2 h, additional hexamethyldisilazane (1.4 mL, 6.2 mmol, 0.33 equiv) was added and stirring was continued for an additional 2 h. Upon consumption of starting material as indicated by TLC, the mixture was diluted with petroleum ether (250 mL) and the resultant cloudy, white mixture filtered through a layer of Florisil® (washing with ca. 200 mL of 10:1 petroleum ether:Et_2O). Concentration of the filtrate in vacuo afforded TMS enol ether **3.16** (6.44 g, 97% yield; 97:3 thermodynamic: kinetic) as a clear, colorless oil.[23,24]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.77 (dd, *J* = 10.3, 3.2 Hz, 1H), 3.48 (dd, *J* = 10.3, 7.6 Hz, 1H), 2.85 (m, 1H), 2.25 (m, 2H), 2.02 – 1.93 (m, 1H), 1.96 (d, *J* = 2.2 Hz, 1H), 1.87 (m, 1H), 1.74 – 1.66 (m, 1H), 1.60 (s, 3H), 0.89 (s, 9H), 0.17 (s, 9H), 0.05 (6H). **^{13}C NMR (101 MHz, $CDCl_3$):**

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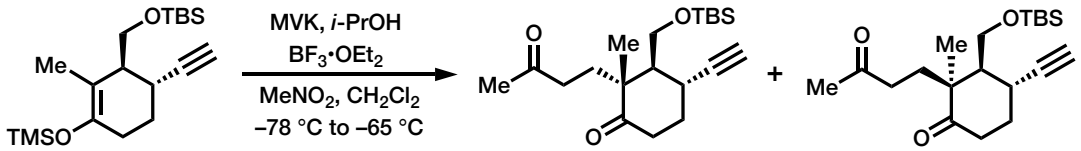
[22] Azeotroped with benzene (3 x 10 mL) prior to the reaction.
[23] A white solid precipitate occasionally remained following initial filtration and subsequent concentration. In this case, the residue was resuspended in pentane and re-filtered through a layer of Florisil® in order to remove this impurity. The crude concentrate was clean enough to be carried forward without purification; moreover, attempts to purify the product by column chromatography often resulted in considerable hydrolysis to return starting TBS ether **3.15** as a 1:1 mixture of diastereomers.
[24] Bath temperature was maintained at or below 20 °C, as product decomposition was observed at higher temperatures.

δ 145.1, 110.4, 88.1, 67.7, 62.8, 48.1, 27.9, 26.1, 24.8, 18.4, 14.9, 0.8, -5.2, -5.3. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{36}O_2Si_2$: 353.2332, found: 353.2326. $[\alpha]_D^{22.0}$ = +17.5 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 3310 (s), 2980 (s), 2929 (m), 2883 (m), 2113 (w), 1682 (m), 1472 (m), 1381 (s), 1252 (s), 1161 (m), 1092 (m), 939 (m), 841 (s), 775 (w), 739 (s), 703 (m), 630 (w). R_f = 0.65 (20:1 hexanes:Et_2O; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).



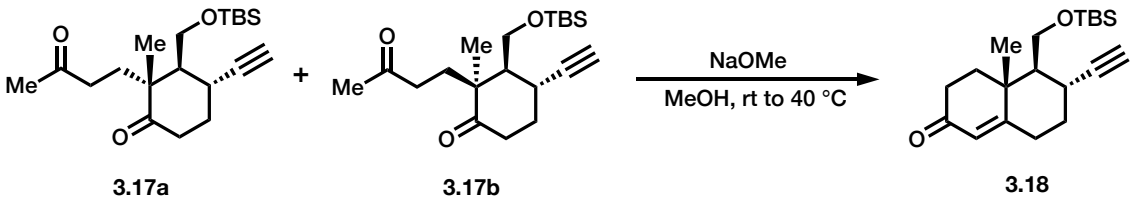
3.16 **3.17a** **3.17b**

1,5-Diketone 3.17a/b. A solution of TMS enol ether **3.16** (6.42 g, 18.2 mmol, 1.0 equiv) in dry CH_2Cl_2 (120 mL) was cooled to −78 °C. Nitromethane (3.0 mL, 54.6 mmol, 3.0 equiv), methyl vinyl ketone (3.1 mL, 36.4 mmol, 2.0 equiv), and 2-propanol (4.2 mL, 54.6 mmol, 3.0 equiv) were added sequentially and all dropwise at −78 °C. The resultant mixture was stirred for 5 min before $BF_3{\cdot}OEt_2$ (3.4 mL, 27.3 mmol, 1.5 equiv) was added dropwise at −78 °C via syringe pump over a period of 2 h. The reaction mixture was then stirred at −78 °C for 4 h. At this point, additional $BF_3{\cdot}OEt_2$ (1.8 mL, 14.6 mmol, 0.8 equiv) was added dropwise over 20 min. The reaction mixture was then brought to −65 °C and stirred for an additional 20 hours at this same temperature. Upon consumption of starting material as indicated by TLC, the reaction mixture was allowed to warm slowly to 0 °C and quenched with saturated aqueous $NaHCO_3$ solution (100 mL). The mixture was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organics were washed with brine (1 x 250 mL) and dried over Na_2SO_4. Concentration of the dried extracts provided a crude oil, which was purified via flash column chromatography (25:1 hexanes:EtOAc

→ 6:1 hexanes:EtOAc)[25] to afford 1,5-diketone **3.17a** and **3.17b** (3:1 dr; 3.51 g, 55% yield [86% brsm]) as a clear, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): (*Major diastereomer* — **3.17a**) δ 3.96 (dd, *J* = 10.7, 4.5 Hz, 1H), 3.84 (dd, *J* = 10.7, 2.1 Hz, 1H), 3.06 – 2.98 (m, 1H), 2.58 – 2.41 (m, 2H), 2.39 – 2.27 (m, 3H), 2.15 (s, 3H), 2.13 (d, *J* = 2.3 Hz, 1H), 2.12 – 2.02 (m, 1H), 1.87 – 1.74 (m, 3H), 1.16 (s, 3H), 0.89 (s, 9H), 0.07 (6H). (*Minor diastereomer* — **3.17b**) δ 4.07 (dd, *J* = 10.8, 4.3 Hz, 1H), 3.91 (dd, *J* = 10.8, 1.3 Hz, 1H), 3.19 – 3.09 (m, 1H), 2.58 – 2.41 (m, 1H), 2.39 – 2.27 (m, 3H), 2.12 – 2.02 (m, 1H), 2.10 (d, *J* = 2.4 Hz, 1H), 2.09 (s, 3H), 2.02 – 1.92 (m, 2H), 1.76 – 1.71 (m, 1H), 1.55 – 1.49 (m, 1H), 1.13 (s, 3H), 0.92 (s, 9H), 0.09 (6H). **^{13}C NMR (101 MHz, $CDCl_3$):** (*Major diastereomer* — **3.17a**) δ 213.4, 208.7, 86.5, 70.3, 61.6, 50.8, 48.5, 39.1, 37.1, 31.1, 30.1, 29.9, 26.7, 26.0, 22.0, 18.3, -5.6. (*Minor diastereomer* — **3.17b**) δ 213.5, 207.7, 86.1, 70.2, 61.5, 53.9, 51.5, 38.5, 37.7, 32.2, 30.1, 28.1, 26.4, 26.0, 20.3, 18.3, -5.5. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{20}H_{34}O_3Si$: 351.2355, found: 351.2359. **IR (thin film) ν_{max} (cm^{-1}):** 2953 (m), 2928 (s), 2883 (m), 2855 (m), 2112 (w), 1707 (s), 1471 (m), 1427 (w), 1360 (m), 1252 (s), 1165 (m), 1110 (s), 1069 (w), 1005 (m), 956 (m), 879 (w), 836 (s), 807 (w), 777 (s), 667 (m), 634 (m). $\boldsymbol{R_f}$ = 0.31 (5:1 hexanes:EtOAc; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).

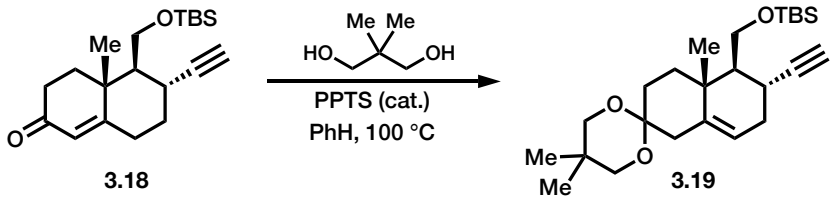
[25] This particular gradient was used to recover the less-polar TBS ether **3.15** (1.58 g, 31% yield).



Octalone 3.18. To a solution of 1,5-diketone **3.17a**/**b**, a 3:1 mixture of diastereomers obtained from the previous step, (3.12 g, 8.90 mmol, 1.0 equiv) in MeOH (100 mL) was added sodium methoxide (0.627 g, 11.6 mmol, 1.3 equiv) in a single portion. The resultant mixture was stirred at ambient temperature for 5 h, then an additional portion of sodium methoxide (0.144 g, 2.67 mmol, 0.3 equiv) was added. The yellow solution was then heated to 40 °C and stirred at the same temperature for 3 h. Upon consumption of starting material as indicated by TLC, the reaction mixture was brought back to ambient temperature, diluted with Et_2O (80 mL), and quenched with saturated aqueous $NaHCO_3$ solution (50 mL). The mixture was extracted first with 1:1 hexanes:Et_2O (2 x 100 mL), then with EtOAc (1 x 100 mL). The combined organic extracts were washed with brine (1 x 200 mL) and dried over Na_2SO_4. Concentration of the dried extracts provided a crude yellow oil, which was purified via flash column chromatography (9:1 hexanes:EtOAc) to afford octalone **3.18** (1.94 g, 66% yield) as a white, waxy solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.72 (s, 1H), 4.06 – 4.00 (dd, *J* = 10.9, 4.6 Hz, 1H), 4.00 – 3.94 (dd, *J* = 10.9, 1.4 Hz, 1H), 2.88 – 2.79 (m, 1H), 2.52 – 2.32 (m, 3H), 2.30 – 2.15 (m, 3H), 2.09 (d, *J* = 2.3 Hz, 1H), 1.88 – 1.77 (td, *J* = 13.7, 4.8 Hz, 1H), 1.66 – 1.53 (m, 1H), 1.40 – 1.33 (ddd, *J* = 11.6, 4.6, 1.4 Hz, 1H), 1.28 (s, 3H), 0.91 (s, 9H), 0.08 (6H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 199.3, 169.4, 124.1, 86.6, 69.9, 60.5, 53.3, 39.1, 36.7, 33.9, 33.1, 32.3, 27.4, 26.0, 19.7, 18.3, -5.5, -5.6. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{20}H_{32}O_2Si$: 333.2250, found: 333.2246. **$[\alpha]_D^{23.2}$ =** +77.4 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 2927 (s), 2883 (m), 2855 (m), 2113 (w), 1672 (s), 1619 (m), 1471 (m), 1348 (m), 1252 (s), 1234 (m), 1193 (w), 1115 (s), 1094 (s), 1063 (m),

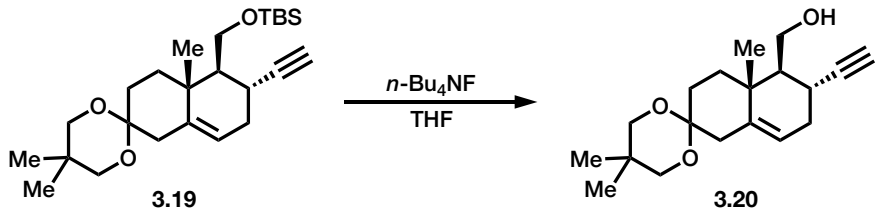
1005 (s), 964 (m), 952 (w), 882 (w), 835 (s), 809 (w), 775 (s), 666 (m), 630 (s), 560 (m). R_f = 0.35 (5:1 hexanes:EtOAc; visualized with UV, $KMnO_4$ stain, and/or $Ce(SO_4)_2$ in phosphomolybdic acid stain).



Neopentyl glycol ketal 3.19. To a solution of octalone **3.18** (1.93 g, 5.80 mmol, 1.0 equiv) in anhydrous benzene (120 mL) was added 2,2-dimethylpropane-1,3-diol (3.02 g, 29.0 mmol, 5 equiv) and pyridinium *p*-toluenesulfonate (0.292 g, 1.16 mmol, 0.2 equiv) at ambient temperature. A Dean-Stark apparatus was then assembled, then the entire reaction setup was put under an atmosphere of argon and heated to reflux. The initially clear and colorless reaction mixture was stirred at reflux for 20 h, then the resultant pale-yellow mixture was brought back to ambient temperature, diluted with 1:1 hexanes:EtOAc (100 mL) and quenched with saturated aqueous $NaHCO_3$ solution (100 mL). The mixture was extracted with 1:1 hexanes:EtOAc (3 x 100 mL), then the organic extracts were combined and washed with brine (1 x 200 mL) and dried over Na_2SO_4. Concentration of the dried extracts provided a crude oil, which was purified via flash column chromatography (40:1 hexanes:EtOAc → 4:1 hexanes:EtOAc)[26] to afford neopentyl glycol **3.19** (1.53 g, 63% yield [74% brsm]) as a white solid.

[26] This particular gradient was used to also isolate the more-polar primary alcohol **3.20** (0.424 g, 24% yield) and a small amount of unreacted octalone **3.18** (0.212 g, 11% yield).

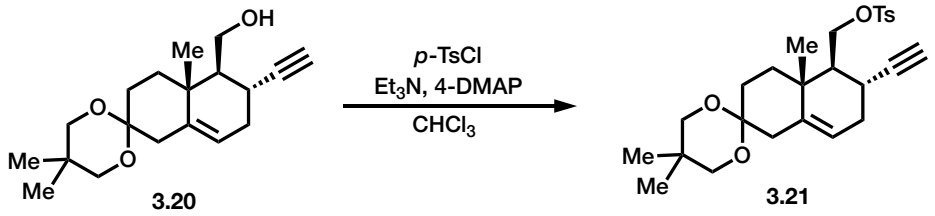
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.31 (m, 1H), 4.04 – 3.98 (dd, *J* = 10.6, 2.1 Hz, 1H), 3.98 – 3.91 (dd, *J* = 10.6, 5.6 Hz, 1H), 3.56 (d, *J* = 11.4 Hz, 1H), 3.50 (d, *J* = 11.4 Hz, 1H), 3.46 (s, 1H), 3.44 (s, 1H), 2.68 – 2.59 (tdd, *J* = 11.3, 5.4, 2.3 Hz, 1H), 2.59 – 2.53 (dd, *J* = 14.0, 3.1 Hz, 1H), 2.40 – 2.17 (m, 4H), 2.05 (d, *J* = 2.3 Hz, 1H), 1.99 – 1.91 (dt, *J* = 13.2, 3.5 Hz, 1H), 1.64 – 1.54 (td, *J* = 14.0, 4.0 Hz, 1H), 1.49 – 1.42 (qd, *J* = 5.8, 2.1 Hz, 1H), 1.34 – 1.23 (m, 1H), 1.10 (s, 3H), 0.99 (s, 3H), 0.92 (s, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 140.0, 120.8, 98.4, 87.86, 70.4, 70.0, 69.6, 61.3, 50.6, 39.6, 37.9, 35.8, 33.3, 30.3, 27.8, 26.1, 25.0, 22.9, 22.8, 19.7, 18.3, -5.4, -5.5. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{25}H_{42}O_3Si$: 419.2981, found: 419.2982. **$[\alpha]_D^{21.2}$ =** −41.7 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 2952 (s), 2927 (m), 2855 (m), 2113 (w), 1471 (s), 1393 (m), 1362 (m), 1252 (s), 1211 (w), 1105 (s), 1036 (m), 1006 (m), 985 (w), 966 (w), 938 (w), 873 (w), 858 (w), 836 (s), 811 (w), 775 (m), 666 (w), 629 (m). ***R*$_f$ =** 0.43 (10:1 hexanes:EtOAc; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).



Primary alcohol 3.20. To a solution of neopentyl glycol **3.19** (1.53 g, 3.65 mmol, 1.0 equiv) in THF (25 mL) was added tetrabutylammonium fluoride solution (1.0 M in THF; 7.3 mL, 7.30 mmol, 2.0 equiv) slowly at ambient temperature. The resultant pale burgundy solution was stirred at ambient temperature for 20 h. Upon consumption of starting material as indicated by TLC, the mixture was diluted with 1:1 hexanes:EtOAc (50 mL) and quenched with saturated

aqueous $NaHCO_3$ solution (50 mL). The layers were partitioned and the aqueous extracted with 1:1 hexanes:EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (1 x 100 mL) and dried over Na_2SO_4. Concentration of the dried extracts provided a crude, off-white solid, which was purified via flash column chromatography (15:5:2 hexanes:CH_2Cl_2:acetone) to afford primary alcohol **3.20** (1.03 g, 93% yield) as a white solid.

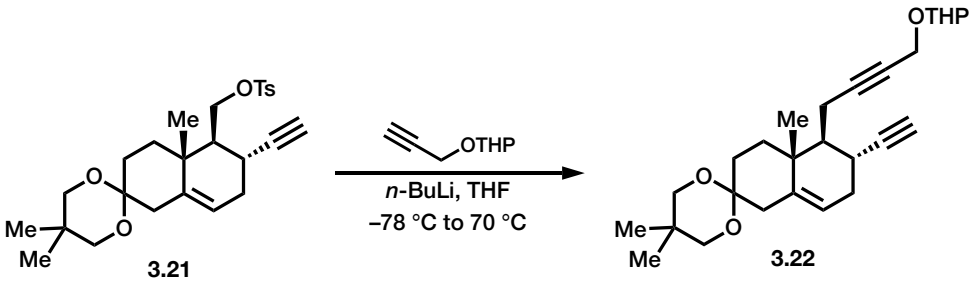
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.35 (m, 1H), 3.93 – 3.85 (m, 1H), 3.85 – 3.78 (m, 1H), 3.58 (d, J = 11.3 Hz, 1H), 3.48 (d, J = 11.3 Hz, 1H), 3.45 (s, 2H), 2.69 – 2.59 (tdd, J = 11.2, 5.4, 2.5 Hz, 1H), 2.58 – 2.49 (m, 2H), 2.38 – 2.19 (m, 4H), 2.23 (d, J = 2.4 Hz), 1.87 (dt, J = 13.0, 3.5 Hz, 1H), 1.60 – 1.50 (m, 2H), 1.43 – 1.33 (td, J = 13.6, 3.7 Hz, 1H), 1.01 (s, 3H), 0.99 (s, 3H) 0.91 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 139.6, 120.9, 98.2, 87.9, 70.9, 70.4, 70.0, 63.0, 52.6, 39.8, 37.7, 34.5, 33.1, 30.2, 27.2, 26.5, 22.9, 22.7, 18.5. **HRMS:** (ESI) m/z $[M+H]^+$ calcd for $C_{19}H_{28}O_3$: 305.2116, found: 305.2119. **$[\alpha]_D^{23.0}$** = −37.3 (c = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 3461 (br), 3301 (s), 2951 (s), 2866 (m), 2110 (w), 1671 (w), 1471 (m), 1394 (m), 1363 (s), 1269 (m), 1097 (s), 1058 (w), 1030 (s), 975 (m), 948 (w), 907 (w), 801 (w), 735 (s), 702 (m), 630 (s). R_f = 0.64 (1:1 hexanes:EtOAc; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).



Tosylate 3.21. To a pre-cooled solution of primary alcohol **3.20** (0.729 g, 2.39 mmol, 1 equiv) in $CHCl_3$ (35 mL) was added *p*-toluenesulfonyl chloride (1.37 g, 7.17 mmol, 3 equiv),

triethylamine (3.3 mL, 23.7 mmol, ca. 10 equiv), and 4-dimethylaminopyridine (0.584 g, 4.78 mmol, 2 equiv) sequentially at 0 °C. The resultant mixture was brought to ambient temperature and stirred for 24 h. Upon consumption of starting material as indicated by TLC, the reaction mixture was treated with 1:1 saturated aqueous $NaHCO_3$: H_2O solution (50 mL) and stirred vigorously for 30 min to hydrolyze unreacted *p*-TsCl. The mixture was then extracted with $CHCl_3$ (5 x 40 mL) and the combined organic extracts were dried over Na_2SO_4. Concentration of the dried extracts provided a crude yellow oil, which was purified via flash column chromatography (20:2:1 hexanes:EtOAc:CH_2Cl_2 → 20:3:2 hexanes:EtOAc:CH_2Cl_2) to afford tosylate **3.21** (1.05 g, 96% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 5.31 (m, 1H), 4.48 (dd, *J* = 10.1, 2.3 Hz, 1H), 4.28 (dd, *J* = 10.1, 5.7 Hz, 1H), 3.57 (d, *J* = 11.2 Hz, 1H), 3.47 (d, *J* = 11.2 Hz, 1H), 3.42 (s, 2H), 2.64 – 2.56 (tdd, *J* = 11.4, 5.5, 2.3 Hz, 1H), 2.56 – 2.50 (dd, *J* = 14.2, 3.1 Hz, 1H), 2.45 (s, 3H), 2.39 – 2.13 (m, 4H), 1.86 (d, *J* = 2.3 Hz, 1H), 1.83 – 1.76 (dt, *J* = 13.0, 3.5 Hz, 1H), 1.68 – 1.62 (ddd, *J* = 11.6, 5.7, 2.4 Hz, 1H), 1.59 – 1.49 (td, *J* = 14.1, 3.8 Hz, 1H), 1.34 – 1.24 (td, *J* = 13.6, 3.8 Hz, 1H), 1.05 (s, 3H), 1.00 (s, 3H), 0.90 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 144.8, 139.2, 133.0, 130.0, 128.4, 120.9, 98.0, 85.4, 70.8, 70.4, 70.1, 69.0, 48.6, 39.9, 37.7, 35.4, 33.0, 30.2, 27.2, 25.1, 22.9, 22.7, 21.8, 19.3. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{26}H_{34}O_5S$: 459.2205, found: 459.2205. **$[\alpha]_D^{22.1}$ =** −59.6 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 3276 (s), 2952 (s), 2867 (m), 1598 (m), 1467 (m), 1361 (s), 1269 (w), 1189 (m), 1176 (s), 1104 (s), 1022 (m), 941 (m), 857 (m), 814 (m), 711 (w), 664 (s), 555 (s). ***R*$_f$ =** 0.45 (3:1 hexanes:EtOAc; visualized with UV and $Ce(SO_4)_2$ in phosphomolybdic acid stain).

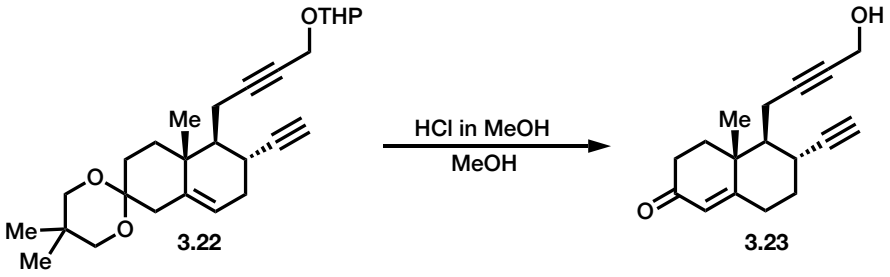


Diyne 3.22. To a solution of tetrahydro-2-(2-propynyloxy)-2*H*-pyran (0.80 mL, 5.66 mmol, 2.5 equiv) in dry THF (16 mL) was added *n*-butyllithium solution (1.60 M in hexanes; 3.3 mL, 5.28 mmol, 2.4 equiv) dropwise at −78 °C. The cold bath was removed and the mixture was allowed to warm to ambient temperature, then the pale-yellow solution was stirred at room temperature for 2 h. After re-cooling to −78 °C, the reaction mixture was treated dropwise with a solution of tosylate **3.21**[27] (1.01 g, 2.21 mmol, 1 equiv) in dry THF (7.5 mL). Following complete addition, the cooling bath was removed and the mixture was allowed to warm to ambient temperature and stirred for an additional 30 min before heating to 70 °C in a pre-heated oil bath. The reaction mixture was stirred at this temperature for 18 h, then cooled to ambient temperature, quenched with a saturated aqueous $NaHCO_3$ solution (40 mL), and extracted with 1:1 hexanes:EtOAc (3 x 40 mL). The combined organic extracts were washed with brine (1 x 100 mL), dried over Na_2SO_4, then concentrated in vacuo. The resulting crude product, a light-brown oil, was purified via flash column chromatography (18:1 hexanes:EtOAc → 9:1 hexanes:EtOAc) to afford diyne **3.22** (0.708 g, 75% yield) as a white, amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.33 (m, 1H), 4.85 (m, 1H), 4.24 (m, 2H), 3.89 – 3.80 (m, 1H), 3.57 (d, *J* = 11.2 Hz, 1H), 3.47 (d, *J* = 11.2 Hz, 1H), 3.56 – 3.48 (m, 1H), 3.45 (s, 1H), 3.44 (s, 1H), 2.72 – 2.52 (m, 4H), 2.40 – 2.17 (m, 4H), 2.11 (d, *J* = 2.2 Hz, 1H), 2.00 – 1.92 (dt, *J* = 13.1, 3.1 Hz, 1H), 1.88 – 1.78 (m, 1H), 1.78 – 1.68 (m, 1H), 1.68 – 1.46 (m, 6H), 1.38 – 1.27 (td, *J* =

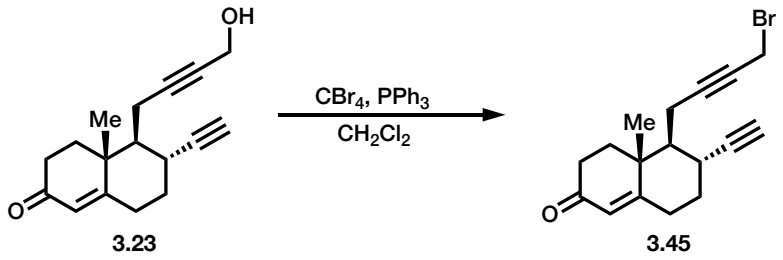
[27] Azeotroped with benzene (3 x 3 mL) prior to use.

13.7, 3.7 Hz, 1H), 1.10 (s, 3H), 1.00 (s, 3H), 0.91 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 139.5, 120.9, 98.2, 96.5, 87.1, 86.4, 77.3, 70.4, 70.0, 62.3, 62.2, 54.7, 48.0, 39.9, 38.6, 35.3, 33.2, 30.5, 30.2, 27.6, 27.5, 25.6, 22.9, 22.7, 19.4, 18.9, 18.3. **HRMS:** (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{38}O_4$: 427.2848, found: 427.2847. **$[\alpha]_D^{22.1}$** = −45.0 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 3303 (s), 2948 (s), 2867 (m), 2113 (w), 1673 (w), 1453 (m), 1394 (m), 1362 (m), 1266 (m), 1200 (m), 1077 (s), 1104 (w), 1020 (s), 968 (m), 902 (m), 869 (m), 811 (m), 735 (s), 702 (w), 633 (m). R_f = 0.46 (4:1 hexanes:EtOAc; visualized with $KMnO_4$ stain).



Propargyl alcohol 3.23. To a solution of diyne **3.22** (0.558 g, 1.31 mmol, 1 equiv) in MeOH (25 mL) was added a solution of hydrogen chloride (ca. 1.25 M in MeOH; 24 mL, 30 mmol, ca. 20 equiv) dropwise at 0 °C. The resultant mixture was stirred at 0 °C for 10 min, then allowed to reach ambient temperature and stirred for an additional 2 h. The reaction mixture was subsequently neutralized with a saturated aqueous $NaHCO_3$ solution (30 mL), diluted with H_2O (30 mL), and extracted with $CHCl_3$ (5 x 60 mL). The organic extracts were combined and dried over Na_2SO_4. Concentration of the dried extracts provided a crude pale-yellow oil, which was purified via flash column chromatography (10:1 CH_2Cl_2:acetone) afforded propargyl alcohol **3.23** (0.306 g, 91% yield) as an off-white, waxy oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74 (br d, *J* = 1.6 Hz, 1H), 4.29 – 4.24 (dt, *J* = 6.1 , 2.2 Hz, 2H), 2.85 – 2.77 (tdd, *J* = 12.0, 3.7, 2.3 Hz, 1H), 2.78 – 2.70 (m, 1H), 2.68 – 2.59 (m, 1H), 2.51 – 2.35 (m, 3H), 2.32 – 2.16 (m, 3H), 2.14 (d, *J* = 2.3 Hz, 1H), 1.91 – 1.80 (td, *J* = 13.3, 5.6 Hz, 1H), 1.68 – 1.52 (m, 3H), 1.30 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 199.0, 168.1, 124.6, 86.0, 85.0, 80.5, 70.5, 51.6, 50.3, 39.8, 36.1, 33.8, 33.0, 32.2, 30.3, 18.4, 18.0. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{20}O_2$: 257.1541, found: 257.1537. **$[\alpha]_D^{25.3}$ =** +92.5 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 3406 (br), 3284 (s), 2937 (s), 2865 (m), 2232 (w), 1660 (s), 1618 (m), 1430 (m), 1351 (m), 1274 (w), 1232 (m), 1187 (w), 1140 (w), 1020 (s), 948 (m), 868 (w), 647 (s). R_f = 0.55 (1:2 hexanes:EtOAc; visualized with UV, $KMnO_4$ stain, and/or $Ce(SO_4)_2$ in phosphomolybdic acid stain).

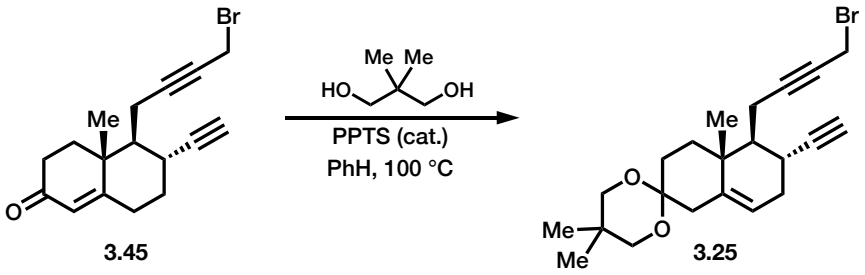


3.23 3.45

Propargyl bromide 3.45. To a solution of propargyl alcohol **3.23** (0.240 g, 0.936 mmol, 1.0 equiv) in dry CH_2Cl_2 (12 mL) was added tetrabromomethane (0.372 g, 1.12 mmol, 1.2 equiv) in a single portion at 0 °C. The resultant clear, pale-yellow solution was stirred for 10 min at 0 °C, then treated dropwise with a solution of triphenylphosphine (0.368 g, 1.40 mmol, 1.5 equiv) in dry CH_2Cl_2 (8.0 mL). The reaction mixture subsequently brought to ambient temperature and stirred for an additional 2 h. Upon complete consumption of the starting material as indicated by TLC, the mixture was diluted with CH_2Cl_2 (20 mL), treated with a saturated aqueous $NaHCO_3$

solution (30 mL), and extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were combined and dried over Na_2SO_4. Concentration of the dried extracts[28] provided a crude yellow oil, which was purified via flash column chromatography (40:10:1 CH_2Cl_2:hexanes:Et_2O) to afford propargyl bromide **3.45** (0.288 g, 96% yield) as an off-white, waxy oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74 (s, 1H), 3.94 (app s, 2H), 2.85 – 2.71 (m, 2H), 2.70 – 2.61 (m, 1H), 2.51 – 2.35 (m, 3H), 2.32 – 2.16 (m, 3H), 2.16 (d, *J* = 2.3 Hz, 1H), 1.91 – 1.80 (td, *J* = 13.4, 5.4 Hz, 1H), 1.69 – 1.53 (m, 2H), 1.30 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 198.8, 167.9, 124.6, 86.8, 85.8, 77.3, 70.6, 50.4, 39.7, 36.1, 33.8, 33.0, 32.1, 30.2, 18.4, 18.2, 15.8. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{19}BrO$: 319.0697, found: 319.0698. **$[\alpha]_D^{21.3}$** = +89.2 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 3287 (s), 2938 (s), 2231 (m), 2112 (w), 1664 (s), 1618 (m), 1425 (m), 1381 (w), 1345 (m), 1271 (w), 1214 (s), 1084 (w), 989 (w), 948 (m), 866 (m), 644 (s), 604 (s), 563 (w). ***R*$_f$** = 0.40 (2:1 hexanes:EtOAc; visualized with UV, $KMnO_4$ stain, and/or $Ce(SO_4)_2$ in phosphomolybdic acid stain).

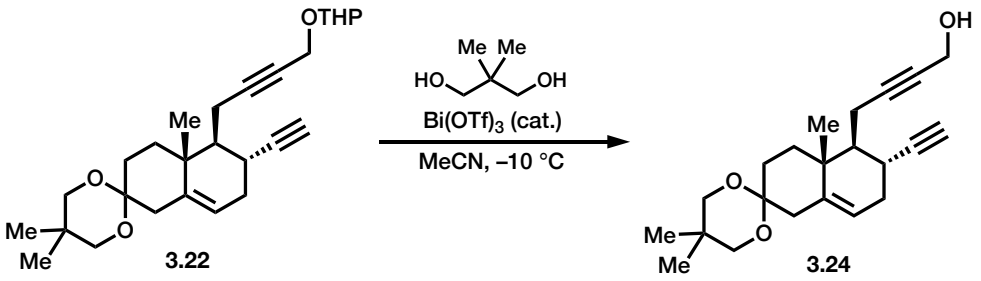


Ketalized propargyl bromide 3.25. To a solution of propargyl bromide **3.45** (0.240 g, 0.751 mmol, 1.0 equiv) in anhydrous benzene (30 mL) was added 2,2-dimethylpropane-1,3-diol (0.392

[28] Bath temperature was maintained at or below 25 °C, as product decomposition was observed at higher temperatures.

g, 3.76 mmol, 5 equiv) and pyridinium *p*-toluenesulfonate (0.038 g, 0.150 mmol, 0.2 equiv) at ambient temperature. A Dean-Stark apparatus was then assembled, and the entire reaction setup was put under an atmosphere of argon and heated to reflux. The initially clear and colorless reaction mixture was stirred at reflux for 20 h, then the resultant pale-yellow mixture was brought back to ambient temperature, diluted with 1:1 hexanes:EtOAc (40 mL), and neutralized with a solution of saturated aqueous $NaHCO_3$ (5 mL) and diluted further with H_2O (50 mL). The mixture was extracted with 1:1 hexanes:EtOAc (3 x 30 mL), then the organic extracts were combined and washed with brine (1 x 80 mL) and dried over Na_2SO_4. Concentration of the dried extracts provided a crude oil, which was purified via flash column chromatography (12:1 hexanes:EtOAc) to afford ketalized propargyl bromide **3.25** (0.271 g, 89% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.33 (m, 1H), 3.93 (app s, 2H), 3.58 (d, *J* = 11.2 Hz, 1H), 3.49 (d, *J* = 11.2 Hz, 1H), 3.45 (s, 2H), 2.72 – 2.59 (m, 3H), 2.59 – 2.54 (dd, *J* = 14.1, 3.2 Hz, 1H), 2.40 – 2.20 (m, 4H), 2.14 (d, *J* = 2.3 Hz, 1H), 1.96 – 1.90 (dt, *J* = 13.1, 3.5 Hz, 1H), 1.68 – 1.61 (ddd, *J* = 11.6, 6.5, 3.7 Hz, 1H), 1.61 – 1.52 (td, *J* = 14.1, 3.8 Hz, 1H), 1.38 – 1.28 (td, *J* = 13.7, 3.7 Hz, 1H), 1.10 (s, 3H), 1.00 (s, 3H), 0.91 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 139.4, 121.0, 98.2, 88.3, 87.0, 76.5, 70.6, 70.4, 70.0, 48.1, 39.9, 38.5, 35.3, 33.1, 30.2, 27.5, 27.4, 22.9, 22.7, 18.9, 18.5, 16.3. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{22}H_{29}BrO_2$: 405.1429, found: 405.1412. **$[\alpha]_D^{21.3}$ =** −46.8 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 3297 (s), 2923 (s), 2853 (s), 2359 (m), 2161 (w), 1552 (m), 1461 (m), 1393 (w), 1364 (w), 1259 (w), 1210 (w). 1106 (s), 1025 (s), 967 (m), 907 (w), 814 (w), 748 (m), 668 (s). ***R*$_f$ =** 0.43 (6:1 hexanes:EtOAc; visualized with $KMnO_4$ stain).

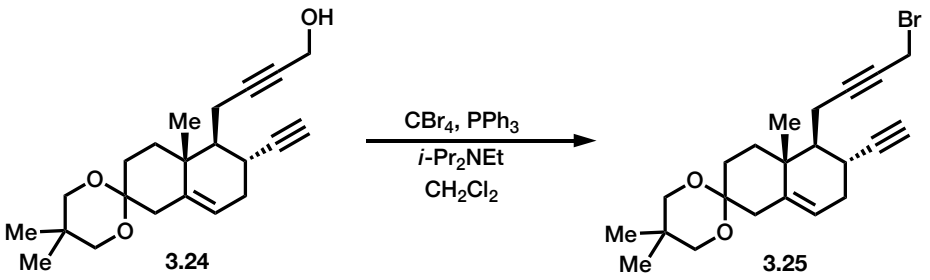


Ketalized propargyl alcohol 3.24. To a pre-cooled solution of diyne **3.22** (0.565 g, 1.32 mmol, 1 equiv) and 2,2-dimethylpropane-1,3-diol (0.690 g, 6.62 mmol, 5 equiv) in anhydrous MeCN (16 mL) was added bismuth(III) trifluoromethanesulfonate (0.043 g, 0.066 mmol, 5 mol%) in a single portion at −10 °C. The resultant clear and colorless solution was stirred at −10 °C for 2 h, then quenched with a saturated aqueous $NaHCO_3$ solution (10 mL) and subsequently extracted with 1:1 hexanes:EtOAc (3 x 25 mL). The combined organic extracts were washed with brine (1 x 40 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting crude product, a pale-yellow oil, was purified via flash column chromatography (100% $CHCl_3$ → 20:1 $CHCl_3$:acetone)[29] to afford ketalized propargyl alcohol **3.24** (0.394 g, 87% yield [100% brsm]) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.33 (m, 1H), 4.24 (s, 2H), 3.57 (d, *J* = 11.4 Hz, 1H), 3.49 (d, *J* = 11.4 Hz, 1H), 3.45 (s, 1H), 3.44 (s, 1H), 2.69 – 2.54 (m, 4H), 2.41 – 2.20 (m, 4H), 2.13 (d, *J* = 2.3 Hz, 1H), 1.97 – 1.91 (dt, *J* = 13.1, 3.5 Hz, 1H), 1.69 – 1.60 (m, 2H), 1.61 – 1.52 (td, *J* = 14.1, 3.9 Hz, 1H), 1.39 – 1.30 (td, *J* = 13.8, 3.8 Hz, 1H), 1.10 (s, 3H), 1.00 (s, 3H), 0.92 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 139.4, 121.0, 98.2, 87.2, 86.5, 79.7, 70.5, 70.4, 70.0, 51.7, 48.0, 39.8, 38.6, 35.3, 33.2, 30.2, 27.6, 27.5, 22.9, 22.7, 18.9, 18.3. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{22}H_{30}O_3$: 343.2273, found: 343.2275. **$[\alpha]_D^{20.2}$ =** −56.7 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 3301 (br), 2953 (s), 2868 (m), 2359 (m), 2341 (m), 2113 (w), 1455 (w), 1427 (w), 1395

[29] This particular gradient was used to recover unreacted diyne **3.22** (75 mg, 13% yield).

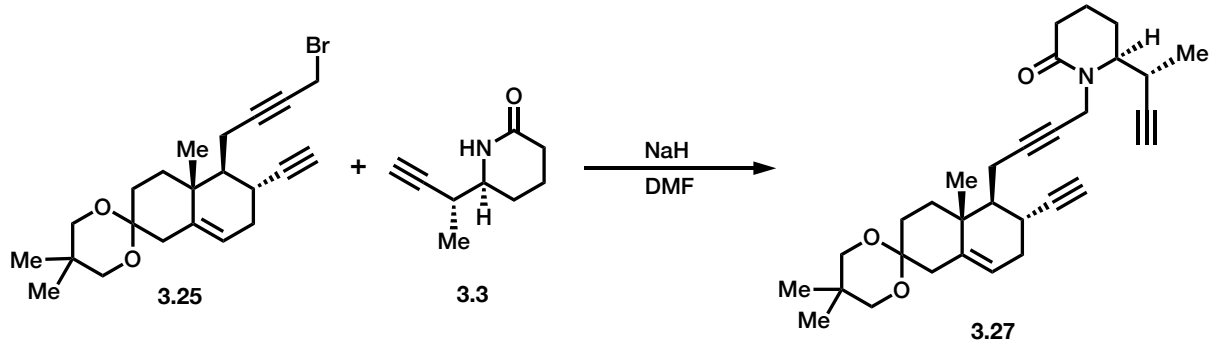
(w), 1364 (m), 1310 (w), 1265 (s), 1140 (w), 1104 (s), 1022 (w), 968 (m), 847 (w), 805 (w), 736 (s), 703 (m), 640 (w). R_f = 0.38 (2:1 hexanes:EtOAc; visualized with $KMnO_4$ stain).



Ketalized propargyl bromide 3.25. To a solution of ketalized propargyl alcohol **3.24** (0.362 g, 1.06 mmol, 1 equiv) in dry CH_2Cl_2 (25 mL) was added diisopropylethylamine (0.45 mL, 3.17 mmol, 3 equiv) at ambient temperature. The resultant clear solution was cooled to 0 °C and treated with a single portion of tetrabromomethane (0.422 g, 1.27 mmol, 1.2 equiv). The resultant clear, pale-yellow solution was stirred for 5 min at 0 °C, then treated portionwise with triphenylphosphine (0.417 g, 1.59 mmol, 1.5 equiv). The reaction mixture subsequently brought to ambient temperature and stirred for an additional 2 h. Upon complete consumption of the starting material as indicated by TLC, the mixture was diluted with CH_2Cl_2 (25 mL), treated with a saturated aqueous $NaHCO_3$ solution (20 mL), and extracted with CH_2Cl_2 (3 x 20 mL). The organic extracts were combined and dried over Na_2SO_4. Concentration of the dried extracts[30] provided a crude yellow oil, which was purified via flash column chromatography (12:1 hexanes:EtOAc) to afford propargyl bromide **3.25** (0.382 g, 89% yield) as an off-white, waxy oil.

[30] Bath temperature was maintained at or below 25 °C, as product decomposition was observed at higher temperatures.

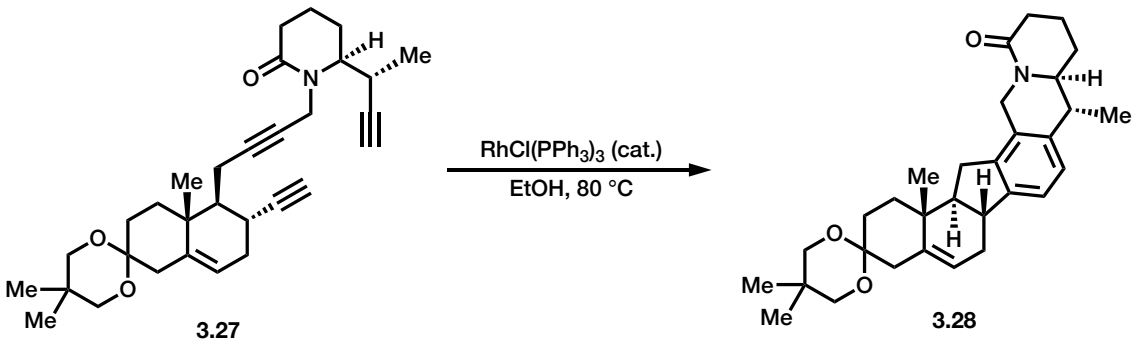
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.33 (m, 1H), 3.93 (t, *J* = 2.3 Hz, 2H), 3.58 (d, *J* = 11.2 Hz, 1H), 3.49 (d, *J* = 11.2 Hz, 1H), 3.45 (s, 2H), 2.72 – 2.59 (m, 3H), 2.59 – 2.54 (dd, *J* = 14.1, 3.2 Hz, 1H), 2.40 – 2.20 (m, 4H), 2.14 (d, *J* = 2.3 Hz, 1H), 1.96 – 1.90 (dt, *J* = 13.1, 3.5 Hz, 1H), 1.68 – 1.61 (ddd, *J* = 11.6, 6.5, 3.7 Hz, 1H), 1.61 – 1.52 (td, *J* = 14.1, 3.8 Hz, 1H), 1.38 – 1.28 (td, *J* = 13.7, 3.7 Hz, 1H), 1.10 (s, 3H), 1.00 (s, 3H), 0.91 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 139.4, 120.9, 98.1, 88.3, 86.9, 76.4, 70.6, 70.4, 70.0, 48.1, 39.8, 38.5, 35.3, 33.1, 30.2, 27.5, 27.4, 22.9, 22.7, 18.9, 18.5, 16.2.



Triyne 3.27. To a solution of propargyl bromide **3.25** (0.262 g, 0.646 mmol, 1 equiv) and alkyne **3.3** (0.098 g, 0.650 mmol, 1 equiv) in anhydrous DMF (6.0 mL) was added sodium hydride (60% dispersion in mineral oil; 0.039 g, 0.990 mmol, 1.5 equiv) in a single portion at 0 °C. The resultant mixture was allowed to warm to ambient temperature and stirred for 18 h. The mixture was then diluted with Et_2O (15 mL) and quenched with a saturated aqueous $NaHCO_3$ solution (10 mL). Following further dilution with water (50 mL), the mixture was extracted with EtOAc (3 x 40 mL), then the organic extracts were combined, washed with brine (1 x 100 mL), and dried over Na_2SO_4. Concentration of the dried extracts provided a crude yellow oil, which was

purified via flash column chromatography (35:10:6.0 hexanes:CH_2Cl_2:acetone) to afford triyne **3.27** (0.286 g, 93% yield) as a foamy, white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.33 (m, 1H), 5.01 (dt, *J* = 17.5, 2.2 Hz, 1H), 4.01 – 3.94 (dt, *J* = 7.5, 5.6 Hz, 1H), 3.63 (app d, *J* = 17.5 Hz, 1H), 3.58 (d, *J* = 11.3 Hz, 1H), 3.49 (d, *J* = 11.3 Hz, 1H), 3.44 (s, 2H), 3.11 – 3.02 (m, 1H), 2.73 – 2.62 (m, 1H), 2.62 – 2.56 (m, 2H), 2.56 – 2.50 (m, 1H), 2.50 – 2.41 (dtd, *J* = 17.5, 5.6, 1.4 Hz, 1H), 2.41 – 2.18 (m, 5H), 2.15 – 2.06 (m, 1H), 2.13 (d, *J* = 2.4 Hz, 1H), 2.11 (d, *J* = 2.5 Hz, 1H), 1.93 – 1.84 (m, 2H), 1.84 – 1.57 (m, 3H), 1.57 – 1.51 (dd, *J* = 14.0, 3.9 Hz, 1H), 1.36 – 1.26 (td, *J* = 13.7, 3.8 Hz, 1H), 1.12 (d, *J* = 7.1 Hz, 3H), 1.10 (s, 3H), 1.00 (s, 3H), 0.91 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 171.0, 139.4, 121.0, 98.2, 87.2, 85.8, 84.5, 75.7, 70.8, 70.4, 70.4, 70.0, 57.7, 47.9, 39.9, 38.5, 35.3, 33.8, 33.1, 32.6, 30.2, 28.2, 27.5, 27.4, 24.3, 22.9, 22.7, 19.0, 18.7, 18.2, 15.1. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{31}H_{41}NO_3$: 476.3164, found: 476.3166. **$[\alpha]_D^{23.7}$** = −43.9 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 3291 (s), 2950 (s), 2867 (m), 2112 (w), 1640 (s), 1452 (m), 1415 (w), 1394 (w), 1336 (m), 1308 (w), 1243 (m), 1200 (w), 1161 (w), 1140 (w), 1105 (s), 1026 (m), 967 (m), 906 (w), 805 (m), 735 (s), 700 (m), 637 (m). R_f = 0.47 (1:1 hexanes:EtOAc; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).

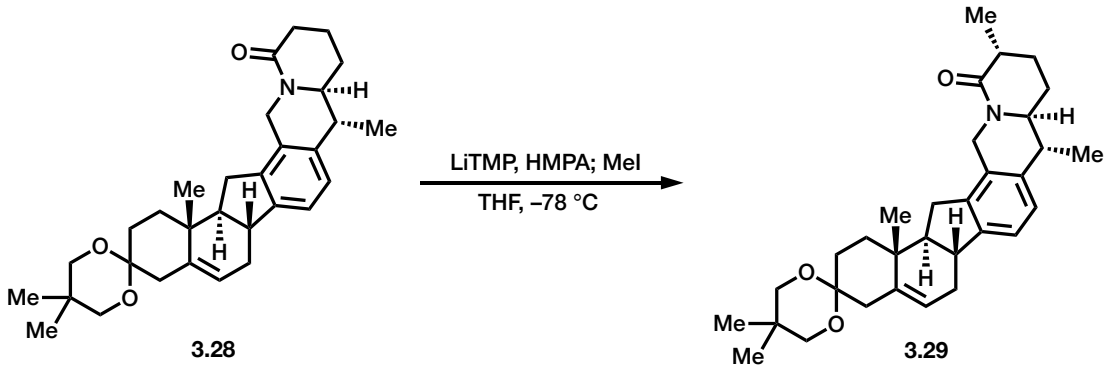


Hexacycle 3.28. To a solution of triyne **3.27** (0.286 g, 0.601 mmol, 1 equiv) in dry, degassed EtOH[31] (12 mL) was added $RhCl(PPh_3)_3$ (56 mg, 0.060 mmol, 10 mol%) at ambient temperature under an atmosphere of Ar. The initially heterogeneous mixture was heated to 80 °C, whereupon a clear, red amber solution resulted and was stirred at this temperature for 30 min. Upon consumption of the starting material as indicated by TLC, the mixture was brought back to ambient temperature. Concentration of the reaction mixture afforded a crude residue, which was redissolved in benzene (5 mL) and diluted with cyclohexane (40 mL) to precipitate impurities. The mixture was then filtered through a layer of Celite (washing with ca. 60 mL of 10:1 cyclohexane: benzene) and the filtrate concentrated in vacuo. The resultant light-orange solid was purified via flash column chromatography (3:1:1 hexanes:acetone:Et_2O) to afford hexacycle **3.28** (0.252 g, 89% yield) as a light-yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 5.49 (m, 1H), 5.22 (d, *J* = 17.2 Hz, 1H), 4.17 (d, *J* = 17.2 Hz, 1H), 3.63 (d, *J* = 11.5 Hz, 1H), 3.50 (d, *J* = 11.5 Hz, 1H), 3.47 (s, 2H), 3.31 – 3.22 (m, 1H), 3.03 – 2.91 (td, *J* = 11.5, 5.4 Hz, 1H), 2.91 – 2.81 (m, 1H), 2.72 (dd, *J* = 15.1, 7.5 Hz, 1H), 2.68 – 2.54 (m, 3H), 2.54 – 2.29 (m, 4H), 2.23 – 2.04 (m, 2H), 1.99 – 1.86 (m, 2H), 1.84 – 1.57 (m, 4H), 1.48 – 1.37 (m, 1H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.14 (s, 3H), 1.04 (s, 3H), 0.90 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 169.7, 144.7, 141.6,

[31] Solvent was degassed by sparging with argon (ca. 4 L) for 30 min.

140.5, 136.6, 129.1, 124.4, 122.4, 121.1, 98.7, 70.4, 70.1, 59.7, 56.9, 43.4, 41.0, 40.4, 38.4, 37.6, 35.9, 32.7, 30.4, 30.3, 29.3, 27.2, 27.0, 23.0, 22.7, 19.1, 18.7, 17.1. **COSY/HSQC:** see Figure A.97 / Figure A.98. **HRMS:** (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{41}NO_3$: 476.3164, found: 476.3163. **$[\alpha]_D^{21.3}$** = +64.2 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 2923 (s), 2853 (s), 1763 (m), 1621 (s), 1462 (s), 1361 (m), 1302 (w), 1260 (s), 1169 (w), 1105 (s), 1029 (m), 978 (w), 807 (s), 748 (s), 668 (w). ***R_f*** = 0.26 (1:4 hexanes:EtOAc; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).



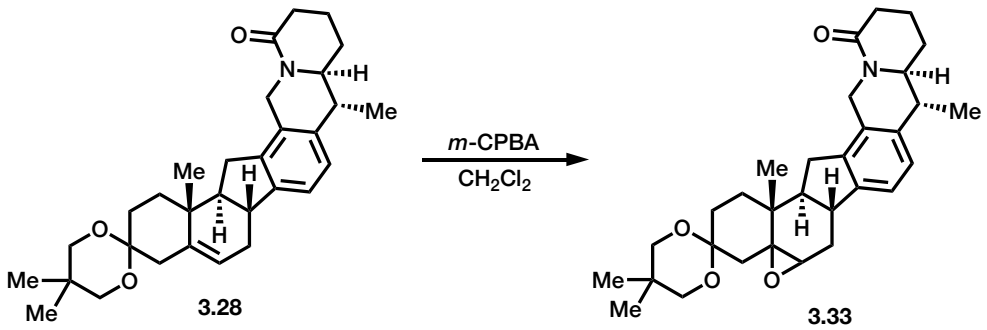
α-Methyl lactam 3.29.[32] To a pre-cooled solution of freshly distilled 2,2,6,6,-tetramethylpiperidine (1.20 mL, 7.05 mmol) in THF (3.0 mL) was added dropwise *n*-butyllithium solution (1.53 M in hexanes; 4.50 mL, 6.89 mmol) at 0 °C. The resultant pale-yellow solution was stirred at 0 °C for 30 min to afford a 0.81 M solution of LiTMP. A separate round-bottom flask was charged with hexacycle **3.28** (40 mg, 0.084 mmol, 1 equiv) and THF (4.0 mL), then cooled to −78 °C under an atmosphere of Ar. The resultant solution was first treated with freshly distilled hexamethylphosphoramide (0.35 mL) at −78 °C, followed by

[32] In order to ensure reproducibility, this reaction was run batchwise on scales of 50 mg or less. Larger reaction scales occasionally led to slightly diminished yields owing to increased formation of a benzylic (C18) methylated side product **3.30**.

dropwise addition of the 0.81 M LiTMP solution (0.32 mL, 0.259 mmol, ca. 3 equiv). The orangish brown mixture was stirred at −78 °C for 20 min, then iodomethane (0.04 mL, 0.643 mmol, ca. 8 equiv) was slowly added. The resultant pale-yellow solution was stirred for 1 min, then rapidly quenched with MeOH (0.06 mL) at −78 °C. The mixture was then brought to 0 °C, treated with a 1:1 H_2O:saturated aqueous $NaHCO_3$ solution (3 mL), and subsequently diluted with EtOAc (10 mL). The biphasic mixture was separated and aqueous layer subsequently extracted with EtOAc (3 x 15 mL). All organic extracts were then combined, washed with brine (1 x 30 mL), and dried over Na_2SO_4. Concentration of the dried extracts provided a crude colorless residue, which was purified via flash column chromatography (3:1 hexanes:EtOAc) to afford α-methyl lactam **3.29** (7:1 dr; 26 mg, 63% yield of single isolated diastereomer) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 5.49 (m, 1H), 5.10 (d, *J* = 17.5 Hz, 1H), 4.23 (d, *J* = 17.5 Hz, 1H), 3.63 (d, *J* = 11.4 Hz, 1H), 3.50 (d, *J* = 11.4 Hz, 1H), 3.47 (s, 2H), 3.26 – 3.16 (dt, *J* = 9.3, 5.6 Hz, 1H), 3.03 – 2.92 (td, *J* = 11.7, 5.2 Hz, 1H), 2.84 – 2.69 (m, 2H), 2.68 – 2.52 (m, 3H), 2.48 – 2.25 (m, 4H), 2.15 – 2.05 (m, 1H), 2.05 – 1.97 (m, 1H), 1.97 – 1.87 (td, *J* = 11.9, 7.5 Hz, 1H), 1.73 – 1.56 (m, 3H), 1.55 – 1.37 (m, 2H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.28 (d, *J* = 7.1 Hz, 3H), 1.14 (s, 3H), 1.04 (s, 3H), 0.90 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 173.2, 144.7, 141.6, 140.5, 136.6, 129.2, 123.8, 122.4, 121.0, 98.7, 70.4, 70.0, 60.2, 56.9, 43.6, 41.0, 40.4, 39.3, 37.5, 36.8, 35.9, 30.4, 30.2, 29.1, 27.7, 27.1, 26.9, 23.0, 22.7, 19.1, 17.9, 16.2. **COSY/HSQC:** see Figure A.101 / Figure A.102. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{32}H_{43}NO_3$: 490.3321, found: 490.3325. **$[\alpha]_D^{22.2}$ =** +72.0 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 2954 (m), 2924 (s), 2855 (s), 1641 (s), 1558 (m), 1458 (s), 1393 (w), 1361 (m),

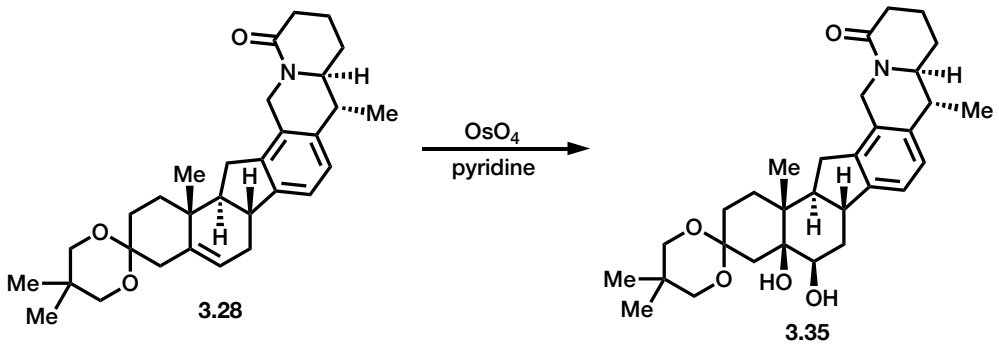
1260 (s), 1211 (w), 1105 (s), 1030 (m), 977 (m), 807 (s), 749 (m), 668 (w). $\boldsymbol{R_f}$ = 0.49 (1:1 hexanes:EtOAc; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).



Epoxide 3.33. To a solution of hexacycle **3.28** (2.2 mg, 4.6 µmol, 1 equiv) in CH_2Cl_2 (0.50 mL) was added a solution of *m*-chloroperoxybenzoic acid (80% w/w; 2.2 mg, 10 µmol, ca. 1.5 equiv) in CH_2Cl_2 (0.10 mL) dropwise at ambient temperature. The resultant solution was stirred at ambient temperature for 4 h, then quenched with a saturated aqueous $NaHCO_3$ solution (1 mL) and diluted with H_2O (5 mL). The mixture was extracted with $CHCl_3$ (3 x 5 mL), then organic extracts were combined and washed with saturated aqueous $NaHCO_3$ solution (1 x 10 mL) and dried over Na_2SO_4. Concentration of the dried extracts afforded a crude residue, which was purified via preparative TLC (93.5:6.5 $CHCl_3$:acetone) to afford epoxide **3.33** (1.9 mg, 84% yield) as a 1.3:1 mixture of β/α epimers.

NMR: Due to the diastereomeric mixture and high volume of overlapping peaks the full NMR spectra was not assigned (see Figure A.103 for spectral data). Diagnostic signals for β- and α-epoxide, respectively, are as follows: **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.21 (m, 1.3H) and δ 2.78

(dd, J = 13.1, 6.8 Hz, 1H).[33] $\boldsymbol{R_f}$ = 0.46 (1:1 hexanes:EtOAc; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).

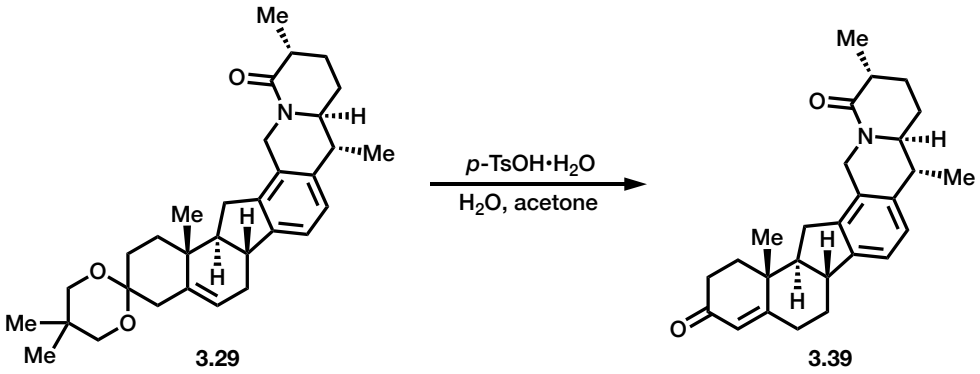


Diol 3.35. To a solution of hexacycle **3.28** (2.5 mg, 5.3 µmol, 1 equiv) in benzene (0.40 mL) was added pyridine (15 µL) and osmium tetroxide (1.5 mg, 6 µmol, ca. 1.1 equiv). The resultant solution was stirred for 2 d, then an additional portion of osmium tetroxide (ca. 0.4 equiv) was added at ambient temperature and the reaction mixture was stirred at ambient temperature for an additional 2 d. Upon consumption of the starting material as indicated by TLC, the reaction mixture was treated with solid Na_2SO_3 (16 mg), solid $KHCO_3$ (16 mg), H_2O (0.15 mL), and MeOH (0.15 mL). The resultant mixture was stirred for an additional 4 h, then filtered through a layer of Celite, which was washed thoroughly with $CHCl_3$ (10 mL). The filtrate was washed with H_2O (1 x 5 mL), then the organic layer was collected and the aqueous was extracted with $CHCl_3$ (3 x 5 mL). All of the organic extracts were combined and washed with brine (1 x 10 mL), then dried over Na_2SO_4. Concentration of the dried extracts delivered a crude residue, which was

[33] The stereochemistry of β/α steroidal epoxides (at C–5 and C–6) is routinely assigned based on the ^{1}H NMR chemical shift at C–6, where δ = 3.25 – 3.05 ppm corresponds to the β-epoxide and δ = 2.95 – 2.75 ppm corresponds to the α-epoxide, see: (a) *Chem. - Eur. J.* **2000**, *6*, 3517 – 3521. (b) *J. Am. Chem. Soc.* **1962**, *84*, 3206 – 3207.

purified via preparative thin-layer chromatography (1:5 hexanes:EtOAc) to afford diol **3.35** (1.8 mg, 66% yield).

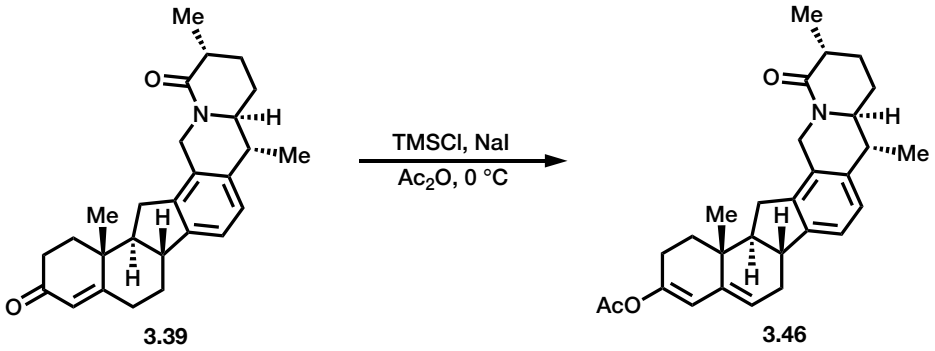
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, *J* = 7.8 Hz, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 5.15 (d, *J* = 17.2 Hz, 1H), 4.20 (d, *J* = 17.2 Hz, 1H), 4.12 (s, 1H), 3.73 (s, 2H), 3.65 – 3.56 (m, 2H), 3.50 – 3.31 (m, 3H), 3.27 – 3.19 (m, 1H), 3.13 – 3.00 (m, 1H), 2.89 – 2.80 (m, 1H), 2.65 – 2.58 (dd, *J* = 14.8, 7.0 Hz, 1H), 2.56 – 2.50 (m, 1H), 2.50 – 2.40 (m, 3H), 2.40 – 2.31 (m, 2H), 2.26 – 2.13 (m, 2H), 2.04 – 1.85 (m, 3H), 1.82 – 1.71 (m, 3H), 1.71 – 1.55 (m, 2H), 1.45 – 1.38 (m, 1H), 1.34 (d, *J* = 6.9 Hz, 3H), 1.21 (s, 3H), 1.09 (s, 3H), 0.84 (s, 3H). **HRMS:** (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{45}NO_5$: 524.3376, found: 524.3385. $\boldsymbol{R_f}$ = 0.27 (1:1:1 hexanes:Et_2O:acetone; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).



Enone 3.39. To pre-cooled solution of α-methylated lactam **3.29** (36 mg, 0.074 mmol, 1 equiv) in acetone (1.5 mL) was added distilled water (50 µL), followed by *p*-toluenesulfonic acid monohydrate (35 mg, 0.184 mmol, 2.5 equiv) in a single portion at 0 °C. The resultant yellow solution was stirred at 0 °C for 3 h, then brought to ambient temperature and stirred for an additional 12 h. Following consumption of starting material as indicated by TLC, the clear and colorless reaction mixture was neutralized with a saturated aqueous $NaHCO_3$ solution (1 mL)

and diluted with EtOAc (8 mL). The resultant biphasic mixture was separated and the aqueous layer extracted with EtOAc (3 x 10 mL). The organic extracts were combined, washed with brine (1 x 20 mL), and dried over Na_2SO_4. Concentration of the dried extracts provided enone **3.39** (29 mg, 98% yield) as a white solid. The crude concentrate was typically clean enough to be carried forward without further purification, however flash column chromatography (12:1 $CHCl_3$:acetone) was used to obtain spectroscopically pure material.

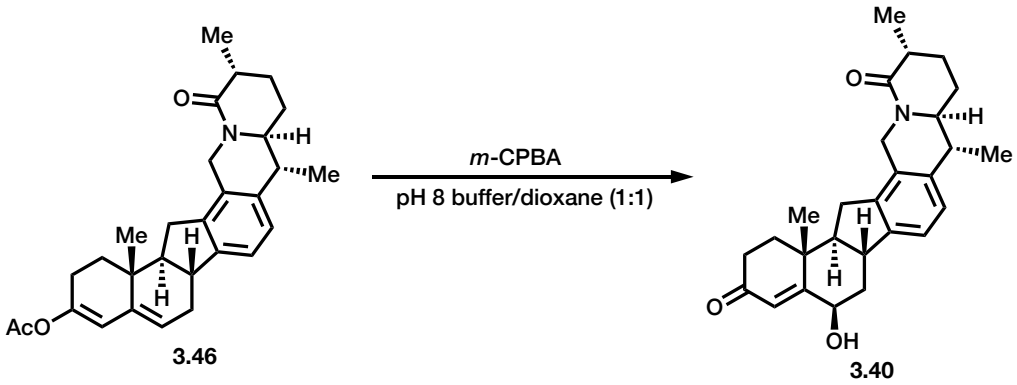
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, *J* = 7.8 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 5.83 (s, 1H), 5.13 (d, *J* = 17.5 Hz, 1H), 4.20 (d, *J* = 17.5 Hz, 1H), 3.25 – 3.17 (dt, *J* = 9.3, 5.5 Hz, 1H), 3.12 – 3.02 (app t, *J* = 11.7 Hz, 1H), 2.85 – 2.75 (m, 1H), 2.75 – 2.67 (dd, *J* = 14.8, 7.0 Hz, 1H), 2.67 – 2.53 (m, 3H), 2.53 – 2.36 (m, 4H), 2.35 – 2.26 (m, 1H), 2.07 – 1.97 (m, 2H), 1.92 – 1.82 (td, *J* = 14.3, 4.5 Hz, 1H), 1.83 – 1.74 (td, *J* = 12.0, 7.1 Hz, 1H), 1.73 – 1.63 (m, 1H), 1.55 – 1.44 (m, 2H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.30 (s, 3H), 1.28 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 199.5, 173.2, 169.7, 143.5, 139.7, 137.0, 129.5, 125.4, 124.1, 120.6, 60.2, 59.9, 43.5, 43.4, 39.3, 38.6, 36.8, 36.2, 33.9, 33.3, 29.7, 28.8, 27.6, 27.0, 17.9, 17.0, 16.4. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{27}H_{33}NO_2$: 404.2589, found: 404.2586. **$[\alpha]_D^{21.4}$ =** +197.9 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 2927 (s), 2858 (s), 1666 (s), 1638 (s), 1461 (m), 1432 (m), 1377 (w), 1345 (w), 1326 (w), 1260 (m), 1227 (m), 1210 (m), 1107 (w), 951 (w), 867 (w), 821 (m), 781 (w), 734 (s), 700 (w). R_f = 0.39 (8:1 $CHCl_3$:acetone; visualized with UV and/or $Ce(SO_4)_2$ in phosphomolybdic acid stain).



Dienol acetate 3.46. To a pre-cooled solution of enone **3.39** (29 mg, 0.072 mmol, 1 equiv) in acetic anhydride (0.90 mL) was added dropwise chlorotrimethylsilane (37 μL, 0.288 mmol, 4 equiv), followed by addition of sodium iodide (43 mg, 0.288 mmol, 4 equiv) in a single portion at 0 °C. The resultant opaque yellow mixture was stirred at 0 °C for 4 h, then concentrated to dryness under a stream of dry N_2 and further via high vacuum. The yellow-orange residue was re-dissolved in a solution of 1:1 Et_2O:hexanes (10 mL) and washed successively with a 2% aqueous $Na_2S_2O_3$ solution (1 x 8 mL), saturated aqueous $NaHCO_3$ solution (1 x 8 mL), distilled water (1 x 10 mL), and brine (1 x 10 mL). The organic extracts were then dried over Na_2SO_4 and concentrated to afford dienol acetate **3.46** (32 mg, 100% yield) as light-yellow solid. The crude concentrate was typically clean enough to be carried forward without further purification, however flash column chromatography (30:1 $CHCl_3$:acetone) was used to obtain spectroscopically pure material.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 5.81 (s, 1H), 5.53 (s, 1H), 5.13 (d, *J* = 17.5 Hz, 1H), 4.23 (d, *J* = 17.5 Hz, 1H), 3.26 – 3.18 (td, *J* = 9.2, 5.5 Hz, 1H), 3.18 – 3.09 (td, *J* = 11.6, 5.6 Hz, 1H), 2.85 – 2.70 (m, 3H), 2.66 – 2.56 (m, 1H), 2.57 – 2.47 (m, 1H), 2.45 – 2.36 (m, 1H), 2.34 – 2.26 (m, 1H), 2.23 – 2.09 (m, 2H), 2.16 (s, 3H), 2.07 – 1.98 (m, 1H), 1.95 – 1.87 (td, *J* = 11.8, 7.2 Hz, 1H), 1.86 – 1.79 (dd, *J* = 12.6, 5.4 Hz, 1H), 1.72 – 1.59 (m, 1H), 1.59 – 1.44 (m, 2H), 1.35 (d, *J* = 6.7 Hz, 3H), 1.28 (d, *J* = 7.1 Hz, 3H), 1.14 (s,

3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 173.2, 169.5, 147.7, 144.8, 140.7, 140.2, 136.7, 129.3, 124.1, 123.9, 120.8, 116.9, 60.2, 55.5, 43.5, 40.6, 39.3, 36.8, 35.5, 35.0, 30.5, 29.2, 27.7, 27.0, 24.8, 21.3, 18.9, 17.9, 16.3. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{29}H_{35}NO_3$: 446.2695, found: 446.2697. **$[\alpha]_D^{20.3}$** = +6.3 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 2329 (s), 2853 (m), 1755 (s), 1639 (s), 1434 (m), 1365 (m), 1216 (s), 1195 (s), 1112 (m), 1015 (w), 934 (w), 810 (m), 735 (m). ***R*$_f$** = 0.70 (8:1 $CHCl_3$:acetone; visualized with UV and/or $Ce(SO_4)_2$ in phosphomolybdic acid stain).



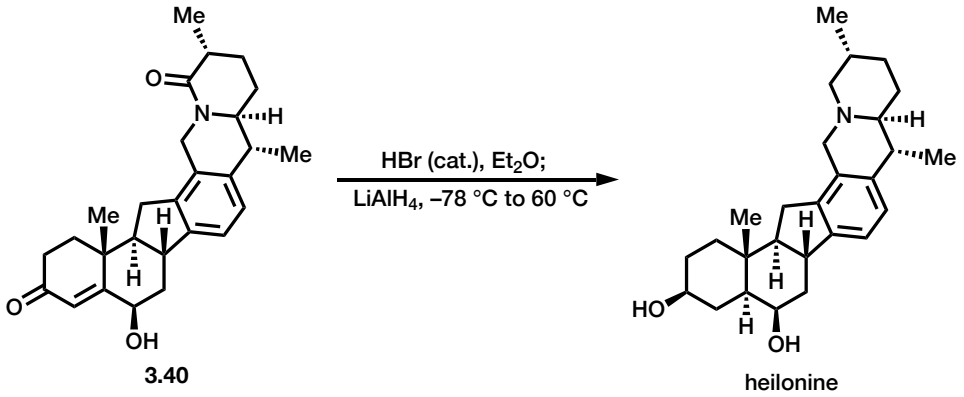
γ-Hydroxy enone 3.40. A solution of dienol acetate **3.46** (30 mg, 0.067 mmol, 1 equiv) in 1:1 1,4-dioxane: pH 8 buffer[34] (0.6 mL) was cooled to 0 °C and treated dropwise with a solution of *meta*-chloroperoxybenzoic acid (80% w/w; 18 mg, 0.081 mmol, 1.2 equiv) in 1:1 1,4-dioxane: pH 8 buffer (1.1 mL) over a period of 1 h. Following complete addition, the resultant mixture was brought to ambient temperature and stirred for 19 h. Upon consumption of the starting material as indicated by TLC, the reaction mixture was treated with solid $Na_2S_2O_3$ (15 mg) and

[34] Prepared according to a modified protocol, as follows: To a solution of 0.1 M aqueous KH_2PO_4 was added a sufficient quantity of 0.1 M aqueous Na_2HPO_4 until the pH was approximately 8. For additional detail, see the following reference: *J. Org. Chem.* **1979**, *44*, 1351−1352.

solid $NaHCO_3$ (30 mg). The mixture was then stirred vigorously for 15 min and diluted with H_2O (6 mL) and $CHCl_3$ (8 mL). The biphasic mixture was separated, aqueous layer repeatedly extracted with $CHCl_3$ (6 x 6 mL), and the organic extracts were combined and dried over Na_2SO_4. Concentration of the dried extracts provided a crude tan solid, which was purified via flash column chromatography (4:1 $CHCl_3$:acetone) to afford γ-hydroxy enone **3.40** (22 mg, 78% yield) as an off-white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (d, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 5.91 (s, 1H), 5.12 (d, *J* = 17.4 Hz, 1H), 4.54 (app s, 1H), 4.21 (d, *J* = 17.4 Hz, 1H), 3.54 (m, 1H), 3.21 (td, *J* = 9.2, 5.7 Hz, 1H), 2.84 – 2.76 (m, 1H), 2.75 – 2.69 (dd, *J* = 14.8, 7.1 Hz, 1H), 2.68 – 2.57 (m, 3H), 2.48 – 2.42 (m, 1H), 2.42 – 2.36 (m, 1H), 2.34 – 2.26 (m, 1H), 2.20 (br s, 1H), 2.06 – 1.95 (m, 2H), 1.93 – 1.84 (m, 1H), 1.83 – 1.75 (td, *J* = 11.8, 7.1 Hz, 1H), 1.74 – 1.63 (m, 2H), 1.54 – 1.45 (m, 1H), 1.49 (s, 3H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.28 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 200.4, 173.3, 167.6, 143.7, 139.8, 137.0, 129.4, 127.7, 124.2, 120.7, 77.4, 74.2, 60.2, 59.9, 43.5, 39.3, 38.3, 38.2, 37.6, 36.8, 34.2, 28.9, 27.6, 26.9, 18.9, 17.9, 16.4.

HRMS: (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{27}H_{33}NO_3$: 420.2538, found: 420.2536. **$[\alpha]_D^{21.4}$ =** +136.8 (*c* = 1.0, $CHCl_3$). **IR (thin film) ν_{max} (cm^{-1}):** 3381 (br), 2929 (s), 2869 (m), 1674 (s), 1618 (s), 1464 (m), 1442 (s), 1378 (w), 1326 (w), 1261 (m), 1226 (m), 1210 (w), 1180 (w), 1100 (w), 1050 (m), 1010 (m), 954 (w), 931 (w), 877 (w), 829 (w), 810 (w), 733 (s), 700 (m), 641 (w). R_f = 0.31 (3:1 $CHCl_3$:acetone; visualized with UV and/or $Ce(SO_4)_2$ in phosphomolybdic acid stain).



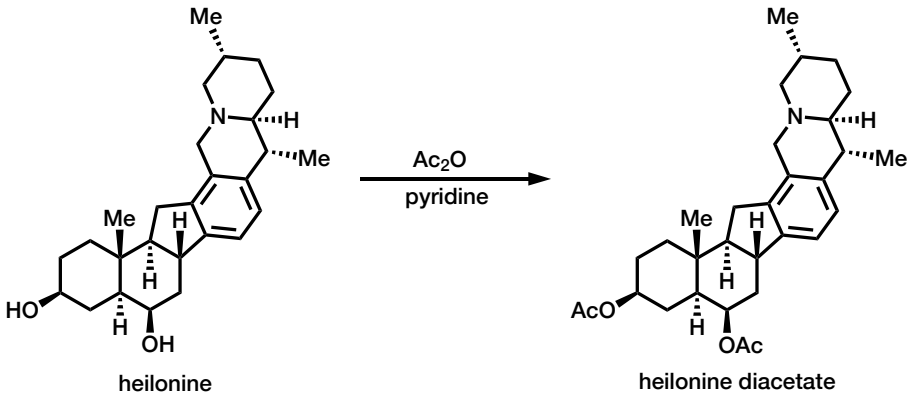
Heilonine. To a solution of γ-hydroxy enone **3.40** (8.7 mg, 0.021 mmol, 1 equiv) in Et_2O (1.2 mL) was added hydrobromic acid (48 wt.% in H_2O; 0.4 mg, 2.1 μmol, ca. 0.1 equiv) at ambient temperature. The resultant mixture was stirred at ambient temperature for 6 h. Upon complete consumption of starting material as indicated by TLC,[35] the reaction mixture was cooled to −78 °C and treated with lithium aluminum hydride solution (1.05 M in THF; 0.06 mL, 0.063 mmol, 3 equiv) dropwise at −78 °C. The resultant mixture was stirred at −78 °C for 0.5 h, then brought to ambient temperature. The opaque mixture was stirred for 1 h, then treated with additional lithium aluminum hydride solution (1.05 M in THF; 0.08 mL, 0.084 mmol, 4 equiv) dropwise at ambient temperature. The resultant mixture was heated to 60 °C, whereupon the solution became beige and clear, and was stirred at the same temperature for 18 h. The reaction mixture was brought to ambient temperature, then cooled further to 0 °C and diluted with Et_2O (1.5 mL). The reaction was carefully quenched by sequential addition of H_2O (20 μL), 2 M NaOH aqueous solution (20 μL), additional H_2O (50 μL), and vigorously stirred for 15 min upon warming to ambient temperature. Anhydrous $MgSO_4$ was then added and the mixture was stirred for an additional 15 min. The mixture was filtered through a layer of Celite, which was subsequently washed

[35] The data for γ-diketone (**3.41**) is as follows: R_f = 0.60 (3:1 $CHCl_3$:acetone; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid and/or $KMnO_4$ stain); see Figure A.111 for spectral data of an unpurified sample.

thoroughly with Et_2O (ca. 25 mL). Concentration of the filtrate provided a crude whitish residue, which was purified via preparative thin-layer chromatography (88:11:1 $CHCl_3$: MeOH: aq. NH_4OH) to afford heilonine (6.1 mg, 72% yield) as a white solid.[36]

^{1}H NMR (500 MHz, CD_3OD): δ 7.06 (d, *J* = 7.9 Hz, 1H), 6.96 (d, *J* = 7.9 Hz, 1H), 3.93 (m, 1H), 3.72 (d, *J* = 15.0 Hz, 1H), 3.64 – 3.56 (m, 1H), 3.28 (d, *J* = 15.0 Hz, 1H), 3.24 – 3.16 (m, 1H), 3.06 – 2.99 (m, 1H), 2.75 – 2.67 (m, 1H), 2.61 – 2.55 (dd, *J* = 14.5, 6.8 Hz, 1H), 2.51 – 2.44 (m, 1H), 2.43 – 2.38 (dt, *J* = 13.1, 3.1 Hz, 1H), 2.21 – 2.15 (dq, *J* = 13.5, 3.0 Hz, 1H), 1.92 – 1.75 (m, 5H), 1.75 – 1.64 (m, 2H), 1.63 – 1.53 (m, 3H), 1.53 – 1.46 (m, 1H), 1.37 – 1.30 (m, 1H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.24 – 1.18 (m, 2H), 1.16 (s, 3H), 1.10 – 1.01 (m, 1H), 0.94 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR (101 MHz, CD_3OD):** δ 145.4, 140.6, 137.4, 130.1, 126.2, 121.5, 73.4, 72.7, 67.2, 64.9, 62.8, 57.0, 49.9, 40.1, 40.0, 40.0, 38.43, 36.8, 35.7, 33.9, 32.6, 31.9, 31.7, 29.6, 20.4, 19.8, 15.9. **COSY/HSQC:** see Figure A.114 / Figure A.115. **HRMS:** (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{39}NO_2$: 410.3059, found: 410.3055. **$[\alpha]_D^{23.8}$ =** +64.3 (*c* = 1.0, CH_3OH). **IR (thin film) ν_{max} (cm^{-1}):** 3382 (br), 2924 (m), 1652 (w), 1558 (w), 1456 (m), 1275 (s), 1261 (s), 1032 (w), 764 (s), 750 (s), 668 (m). ***R_f* =** 0.34 (13% MeOH in $CHCl_3$; visualized with $KMnO_4$ stain).

[36] In accordance with the isolation paper (see footnote 37 for reference) heilonine was found to have only modest solubility at best in organic solvents. Spectral characterization of the natural product itself was not reported by the isolation team. We found CD_3OD to be a suitable NMR solvent, whereas $CDCl_3$ led to significant peak broadening despite apparent solubilization (see Figures A.112 and A.116, respectively, for ^{1}H NMR spectra). Solutions containing the natural product appeared to be surprisingly hygroscopic, a property that can be appreciated by the relatively large HDO peak in the NMR spectrum.



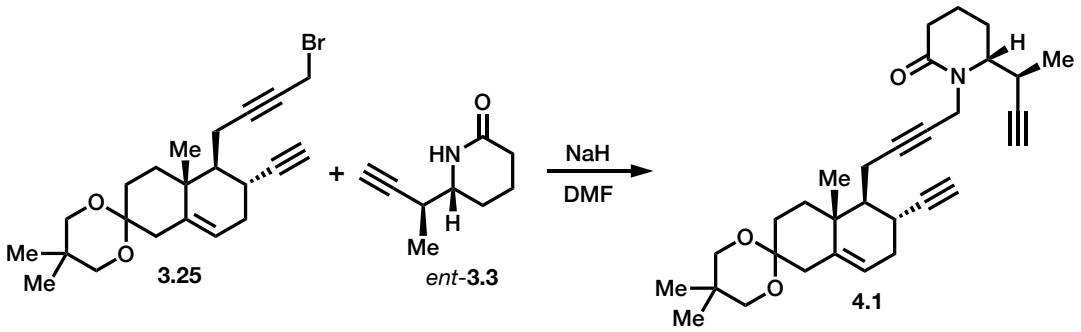
heilonine | heilonine diacetate

Heilonine diacetate. To a solution of heilonine (13.4 mg, 0.033 mmol, 1 equiv) in acetic anhydride (1.2 mL) was added pyridine (1.2 mL) at ambient temperature. The resultant mixture was heated to 60 °C and stirred for 6 h, then brought back to ambient temperature and stirred for an additional 18 h. Upon consumption of the starting material as indicated by TLC, the mixture was concentrated under a stream of dry N_2 and dried further under high vacuum (2 h at 1 mm Hg) to afford a crude off-white solid, which was purified via preparative thin-layer chromatography (95.5: 5.0: 0.5 $CHCl_3$: MeOH: aq. NH_4OH) to afford heilonine diacetate (12.4 mg, 77% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.06 (d, J = 7.8 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 5.11 (m, 1H), 4.78 (m, 1H), 3.71 (d, *J* = 14.6, 1H), 3.24 (d, *J* = 14.6, 1H), 3.09 (td, *J* = 12.3, 2.7 Hz, 1H), 3.02 (br s, 1H), 2.72 (br s, 1H), 2.62 – 2.55 (dd, *J* = 14.4, 6.8 Hz, 1H), 2.50 – 2.43 (m, 2H), 2.16 – 2.09 (m, 1H), 2.07 (s, 3H), 2.04 (s, 3H), 1.92 – 1.77 (m, 4H), 1.77 – 1.71 (m, 1H), 1.70 – 1.61 (m, 4H), 1.61 – 1.53 (td, *J* = 13.6, 3.1 Hz, 1H), 1.46 – 1.39 (td, J = 12.9, 2.4 Hz, 1H), 1.37 – 1.30 (m, 1H), 1.27 (d, J = 6.9 Hz, 3H), 1.26 – 1.20 (m, 1H), 1.15 (s, 3H), 1.05 – 0.97 (m, 1H), 0.92 (d, *J* = 5.4 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 170.6, 170.6, 142.9, 139.1, 137.2, 130.1, 125.4, 120.3, 74.2, 73.6, 65.8, 64.5, 60.7, 56.4, 47.3, 39.2, 39.2, 38.6, 35.9, 34.3, 33.2, 32.1, 30.9, 30.5, 28.8, 27.2, 21.5, 21.5, 19.8, 19.8, 15.1. **COSY/HSQC:** see Figure A.119 / Figure A.120. **HRMS:** (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{43}NO_4$: 494.3270, found: 494.3255. **$[\alpha]_D^{21.1}$** = +29.8 (*c*

= 1.05); lit.: +34 (*c* = 1.05).[37] **IR (thin film) ν_{max} (cm^{-1}):** 2929 (s), 2853 (m), 1734 (s), 1458 (m), 1375 (m), 1240 (m), 1139 (w), 1098 (w), 1077 (w), 1025 (s), 956 (w), 829 (w), 809 (w), 750 (w), 606 (w). R_f = 0.46 (9% MeOH in $CHCl_3$; visualized with $KMnO_4$ and/or $Ce(SO_4)_2$ in phosphomolybdic acid stain).

6.4. Experimental Procedures and Characterization Data for Chapter 4

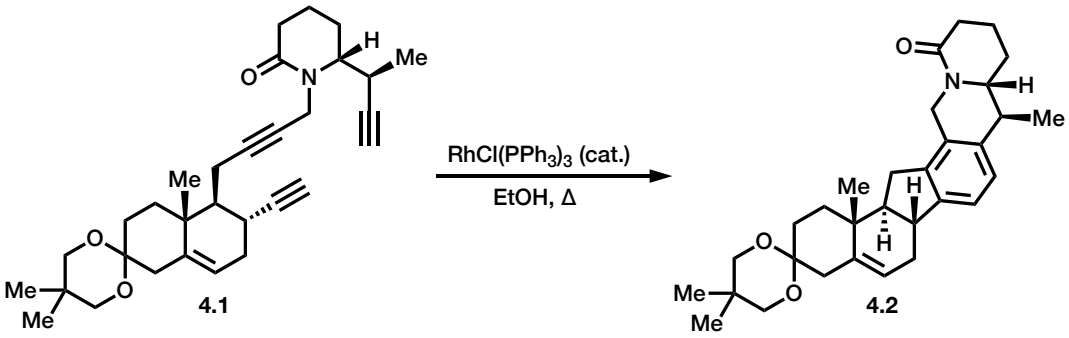


Triyne 4.1. To a solution of propargyl bromide **3.25** (0.253 g, 0.625 mmol, 1 equiv) and alkyne *ent*-**3.3** (0.095 g, 0.625 mmol, 1 equiv) in anhydrous DMF (5.8 mL) was added sodium hydride (60% dispersion in mineral oil; 37.5 mg, 0.937 mmol, 1.5 equiv) in a single portion at 0 °C. The resultant mixture was allowed to warm to ambient temperature and stirred for 18 h. The mixture was then diluted with Et_2O (10 mL) and quenched with a saturated aqueous $NaHCO_3$ solution (5 mL). Following further dilution with water (10 mL), the mixture was extracted with EtOAc (3 x 25 mL), then the organic extracts were combined, washed with brine (1 x 60 mL), and dried over Na_2SO_4. Concentration of the dried extracts provided a crude yellow oil, which was purified via flash column chromatography (35:10:6.0 hexanes:CH_2Cl_2:acetone) to afford triyne **4.1** as a

[37] For isolation data, including optical rotation, see the following reference: *Tetrahedron* **1989**, *45*, 7281−7286.

foamy, white solid. This unstable material was then immediately carried forward and subjected to the next step.

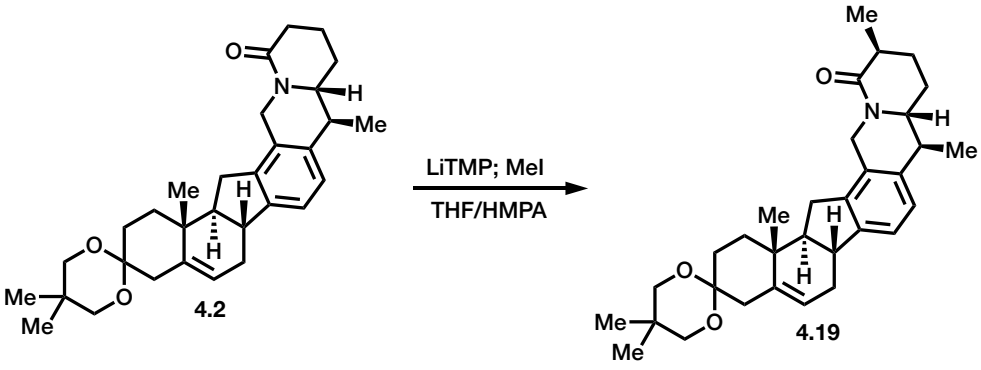
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.32 (m, 1H), 4.93 (dt, *J* = 17.5 Hz, 2.3 Hz, 1H), 3.96 – 3.89 (m, 1H), 3.69 (dt, *J* = 17.5, 1.6 Hz, 1H), 3.58 (d, *J* = 11.3 Hz, 1H), 3.49 (d, *J* = 11.3 Hz, 1H), 3.44 (s, 2H), 3.13 – 3.05 (qdt, *J* = 7.1, 4.7, 2.4 Hz, 1H), 2.69 – 2.51 (m, 4H), 2.50 – 2.41 (dtd, *J* = 17.5, 5.5, 1.6 Hz, 1H), 2.40 – 2.18 (m, 5H), 2.13 (d, *J* = 2.3 Hz, 1H), 2.11 (d, *J* = 2.5 Hz, 1H), 2.12 – 2.06 (m, 1H), 1.93 – 1.84 (m, 2H), 1.84 – 1.57 (m, 3H), 1.56 – 1.48 (m, 1H), 1.36 – 1.28 (m, 1H), 1.13 (d, *J* = 7.1 Hz, 3H), 1.10 (s, 3H), 1.00 (s, 3H), 0.91 (s, 3H). **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{31}H_{41}NO_3$: 476.3164, found: 476.3168. R_f = 0.47 (1:1 hexanes:EtOAc; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).



Hexacycle 4.2. To a solution of triyne **4.1** (from previous step, ca. 0.62 mmol) in dry, degassed EtOH (20 mL) was added $RhCl(PPh_3)_3$ (58 mg, 0.062 mmol, 10 mol%) at ambient temperature under an atmosphere of Ar. The initially heterogeneous mixture was heated to 80 °C, whereupon a clear, red amber solution resulted and was stirred at this temperature for 30 min. Upon consumption of the starting material as indicated by TLC, the mixture was brought back to ambient temperature. Concentration of the reaction mixture afforded a crude residue, which was

purified via flash column chromatography (3:1:1 hexanes:acetone:Et_2O) to afford hexacycle **4.2** (0.268 g, 90% yield over 2 steps) as a light-yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 5.49 (m, 1H), 5.36 (d, *J* = 17.2 Hz, 1H), 4.04 (d, *J* = 17.2 Hz, 1H), 3.63 (d, *J* = 11.3 Hz, 1H), 3.50 (d, *J* = 11.3 Hz, 1H), 3.48 (s, 2H), 3.31 – 3.23 (m, 1H), 3.03 – 2.93 (td, *J* = 11.5, 5.4 Hz, 1H), 2.91 – 2.81 (m, 2H), 2.64 (dd, *J* = 14.3, 2.8 Hz, 1H), 2.62 – 2.31 (m, 7H), 2.22 – 2.04 (m, 2H), 1.99 – 1.86 (m, 2H), 1.85 – 1.56 (m, 4H), 1.49 – 1.39 (m, 1H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.14 (s, 3H), 1.04 (s, 3H), 0.90 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 169.7, 144.8, 141.6, 140.4, 136.8, 129.1, 124.5, 122.4, 121.0, 98.7, 70.4, 70.0, 59.7, 57.3, 43.2, 41.2, 40.5, 38.4, 37.5, 35.9, 32.8, 30.4, 30.3, 29.1, 27.2, 26.9, 23.0, 22.7, 19.1, 18.7, 17.3. **COSY/HSQC:** see Figure A.124 / Figure A.125. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{31}H_{41}NO_3$: 476.3164; found 476.3165. R_f = 0.26 (1:4 hexanes:EtOAc; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).

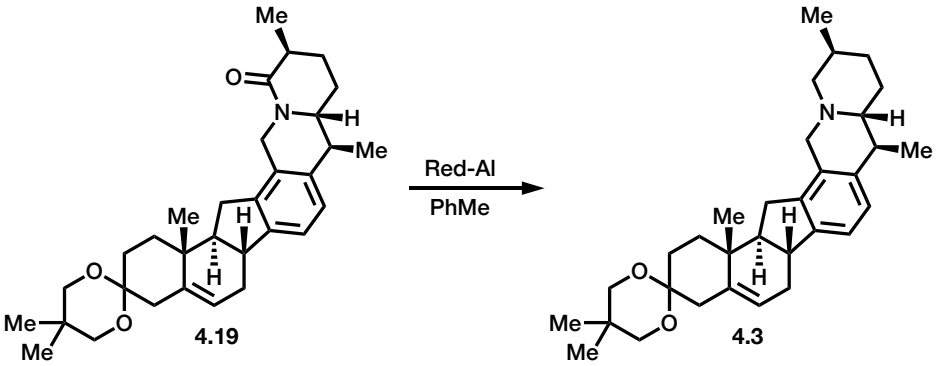


α-Methyl lactam 4.19. To a pre-cooled solution of freshly distilled 2,2,6,6,-tetramethylpiperidine (0.76 mL, 4.45 mmol) in THF (3.4 mL) was added dropwise *n*-butyllithium solution (1.56 M in hexanes; 2.8 mL, 4.34 mmol) at 0 °C. The resultant pale-yellow solution was stirred at 0 °C for 30 min to afford a 0.62 M solution of LiTMP. A separate round-

bottom flask was charged with hexacycle **4.2** (45 mg, 0.095 mmol, 1 equiv) and THF (4.8 mL), then cooled to −78 °C under an atmosphere of Ar. The resultant solution was first treated with freshly distilled hexamethylphosphoramide (0.39 mL) at −78 °C, followed by dropwise addition of the 0.62 M LiTMP solution (0.49 mL, 0.303 mmol, ca. 3.2 equiv). The orangish brown mixture was stirred at −78 °C for 20 min, then iodomethane (50 µL, 0.757 mmol, ca. 8 equiv) was slowly added. The resultant pale-yellow solution was stirred for 1 min, then rapidly quenched with MeOH (0.07 mL) at −78 °C. The mixture was then brought to 0 °C, treated with a 1:1 saturated aqueous $NaHCO_3$: H_2O solution (4 mL), and subsequently diluted with EtOAc (10 mL). The biphasic mixture was separated and aqueous layer subsequently extracted with EtOAc (3 x 15 mL). All organic extracts were then combined, washed with brine (1 x 25 mL), and dried over Na_2SO_4. Concentration of the dried extracts provided a crude colorless residue, which was purified via flash column chromatography (3:1 hexanes:EtOAc) to afford α-methyl lactam **4.19** (7:1 dr; 29 mg, 62% yield of single isolated diastereomer) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, *J* = 7.8 Hz, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 5.49 (m, 1H), 5.26 (d, *J* = 17.6 Hz, 1H), 4.09 (d, *J* = 17.6 Hz, 1H), 3.63 (d, *J* = 11.3 Hz, 1H), 3.50 (d, *J* = 11.3 Hz, 1H), 3.47 (s, 2H), 3.26 – 3.17 (td, *J* = 9.1, 5.3 Hz, 1H), 3.03 – 2.92 (td, *J* = 11.6, 5.2 Hz, 1H), 2.87 – 2.73 (m, 2H), 2.68 – 2.48 (m, 3H), 2.45 – 2.25 (m, 4H), 2.15 – 1.98 (m, 2H), 1.98 – 1.89 (td, *J* = 11.9, 7.4 Hz, 1H), 1.73 – 1.56 (m, 3H), 1.54 – 1.39 (m, 2H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.28 (d, *J* = 7.1 Hz, 3H), 1.14 (s, 3H), 1.04 (s, 3H), 0.90 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 173.1, 144.8, 141.6, 140.4, 136.7, 129.1, 124.0, 122.4, 120.9, 98.7, 70.4, 70.0, 60.3, 57.2, 43.4, 41.1, 40.4, 39.3, 37.5, 36.8, 35.8, 30.4, 30.2, 29.0, 27.7, 27.1, 26.9, 23.0, 22.7, 19.1, 17.9, 16.5. **COSY/HSQC:** see Figure A.128 / Figure A.129. **HRMS:** (ESI) *m/z* $[M+H]^+$ calcd for

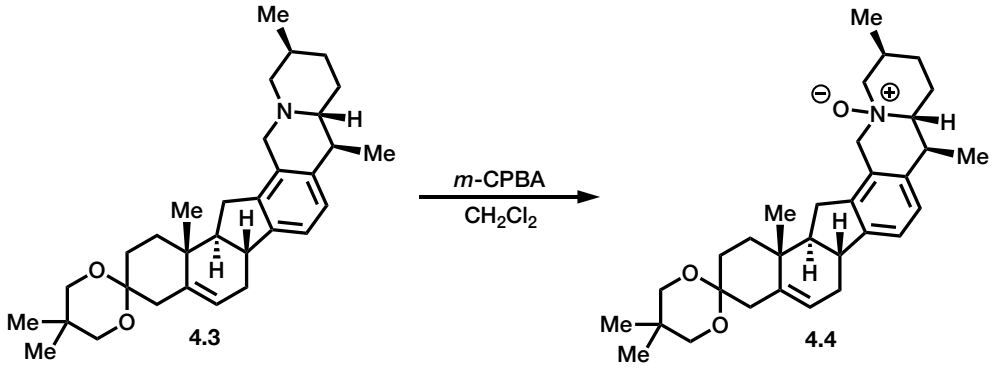
$C_{32}H_{45}NO_2$: 490.3321, found: 490.3308. **$[\alpha]_D^{20.6}$** = -166.8 (*c* = 1.0, $CHCl_3$). ***R_f*** = 0.46 (1:1 hexanes:EtOAc; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).



Amine 4.3. To a pre-cooled solution of α-methyl lactam **4.19** (42 mg, 0.086 mmol, 1 equiv) in PhMe (2.5 mL) was added Red-Al® sodium bis(2-methoxyethoxy)aluminum hydride solution (≥60 wt. % in PhMe; 0.18 mL, 0.516 mmol, 6 equiv) dropwise at 0 °C. The resultant solution was brought to ambient temperature and stirred for 4 h. Upon consumption of the starting material as indicated by TLC, the reaction mixture was quenched by dropwise treatment with 1 M aqueous NaOH solution (ca. 0.8 mL or until effervescence ceased). Following further dilution with a saturated aqueous Rochelle's salt solution (3 mL) and H_2O (5 mL), the resultant mixture was extracted with $CHCl_3$ (3 x 10 mL), then the organic extracts were combined, washed with brine (1 x 20 mL), and dried over Na_2SO_4. Concentration of the dried extracts provided amine **4.3** (41 mg, 99% yield) as waxy white solid, which was carried forward without purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 5.48 (m, 1H), 3.79 (d, *J* = 15.0 Hz, 1H), 3.62 – 3.42 (m, 4H), 3.12 (d, *J* = 15.0 Hz, 1H), 3.05 – 2.92 (m, 2H), 2.74 – 2.64 (m, 3H), 2.61 – 2.52 (dtd, *J* = 16.6, 5.3, 2.4 Hz, 1H), 2.51 – 2.42 (dd, *J* = 14.8, 11.7 Hz, 1H), 2.40 – 2.32 (dq, *J* = 14.4, 2.3 Hz, 1H), 2.32 – 2.23 (m, 1H), 2.15 – 2.01 (m, 2H), 1.94 –

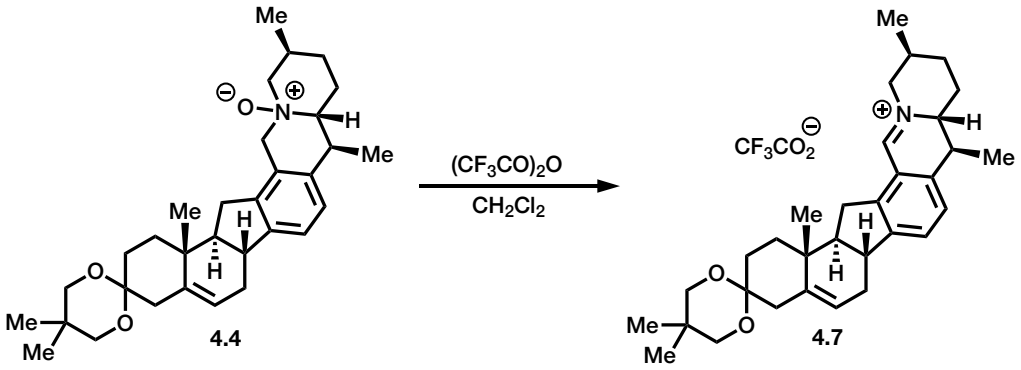
1.84 (td, J = 11.9, 7.3 Hz, 1H), 1.84 – 1.72 (m, 4H), 1.69 – 1.58 (m, 2H), 1.50 – 1.39 (m, 1H), 1.37 – 1.25 (m, 2H), 1.28 (d, J = 6.8 Hz, 3H), 1.13 (s, 3H), 1.01 (s, 3H), 0.93 (s, 3H), 0.91 (d, J = 5.5 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 143.6, 141.4, 139.4, 137.3, 130.3, 125.3, 122.7, 120.8, 98.7, 70.4, 70.1, 66.0, 64.6, 57.3, 56.3, 41.2, 39.8, 39.3, 37.5, 36.0, 33.3, 32.3, 31.1, 30.5, 30.3, 28.8, 27.7, 22.9, 22.8, 20.1, 19.9, 19.1. **COSY/HSQC:** see Figure A.132 / Figure A.133. **HRMS:** (ESI) m/z $[M+H]^+$ calcd for $C_{32}H_{45}NO_2$: 476.3528, found: 476.3533. **$[\alpha]_D^{20.8}$** = -57.3 (c = 1.0, $CHCl_3$). ***R_f*** = 0.33 (4:1:1 hexanes:acetone:Et_2O; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).



Amine *N*-oxide 4.4. To a pre-cooled solution of amine **4.3** (16 mg, 0.034 mmol, 1 equiv) in CH_2Cl_2 (1.4 mL) was added *m*-CPBA (80% w/w; 8.0 mg, 0.037 mmol, 1.1 equiv) at 0 °C. The resultant mixture was stirred at 0 °C for 1 h, then quenched with dimethyl sulfide (1 drop). Concentration of the reaction mixture afforded a crude residue, which was purified via preparative thin-layer chromatography (87:11:2 MeOH: $CHCl_3$: aq. NH_4OH) to provide pure amine *N*-oxide **4.4** (11.6 mg, 70% yield) as a light yellow solid.

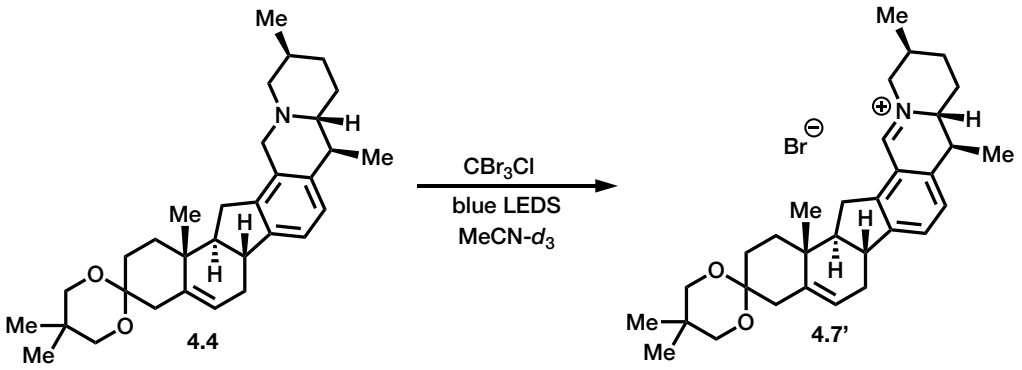
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, J = 7.8 Hz, 1H), 7.06 (d, J = 7.8 Hz, 1H), 5.49 (m, 1H), 4.46 (d, J = 14.4 Hz, 1H), 4.28 (d, J = 14.4 Hz, 1H), 3.61 (d, J = 11.4 Hz, 1H), 3.59 – 3.52 (m,

1H), 3.51 (d, J = 11.4 Hz, 1H), 3.47 (s, 2H), 3.26 – 3.17 (m, 1H), 3.01 – 2.91 (td, J = 11.4, 5.3 Hz, 1H), 2.91 – 2.78 (m, 1H), 2.77 – 2.70 (dd, J = 14.7, 7.2 Hz, 1H), 2.70 – 2.63 (dd, J = 14.2, 2.8 Hz, 1H), 2.61 – 2.52 (dtd, J = 16.7, 5.4, 2.4 Hz, 1H), 2.47 – 2.38 (m, 1H), 2.39 – 2.33 (m, 1H), 2.34 – 2.26 (m, 1H), 2.17 – 1.85 (m, 6H), 1.81 – 1.55 (m, 4H), 1.47 – 1.39 (m, 1H), 1.34 (d, J = 6.9 Hz, 3H), 1.12 (s, 3H), 1.02 (s, 3H), 0.96 (d, J = 6.5 Hz, 3H), 0.92 (s, 3H). **HRMS:** (ESI) m/z $[M+H]^+$ calcd for $C_{32}H_{45}NO_3$: 492.3477, found: 492.3484. $\boldsymbol{R_f}$ = 0.67 (13% MeOH in $CHCl_3$; visualized with $KMnO_4$ stain).



Iminium salt 4.7. To a pre-cooled solution of amine *N*-oxide **4.4** (8 mg, 16.3 μmol, 1 equiv) in CH_2Cl_2 (1.2 mL) was added trifluoroacetic anhydride (23 μL, 0.163 mmol, 10 equiv) dropwise at 0 °C. The resultant solution was stirred at 0 °C for 1.5 h, then it was brought to ambient temperature and stirred for an additional 1.5 h. Concentration of the reaction mixture under a stream of dry N_2 afforded iminium salt **4.7** (7.6 mg, 80% yield), which was used without further purification.

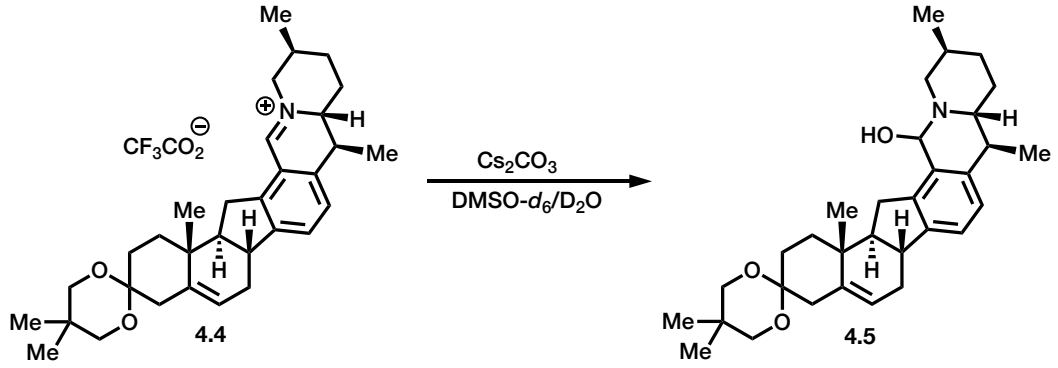
NMR: Due to presence of some impurities, the NMR was not fully assigned (see Figure A.135 / Figure A.136 for spectral data). Diagnostic signal: iminium methine, s at δ 9.46.



Iminium salt 4.7'. To a solution of amine **4.4** (4 mg, 8.4 μmol, 1 equiv) in 4:1 MeCN-d_3/CCl_4 (0.8 mL) was added bromotrichloromethane (2.5 mg, 12.6 μmol, 1.5 equiv). The reaction mixture was placed under an Ar atmosphere and stirred under blue LED irradiation, then the reaction progress was checked by ^{1}H NMR analysis of an aliquot after 4 h.[38]

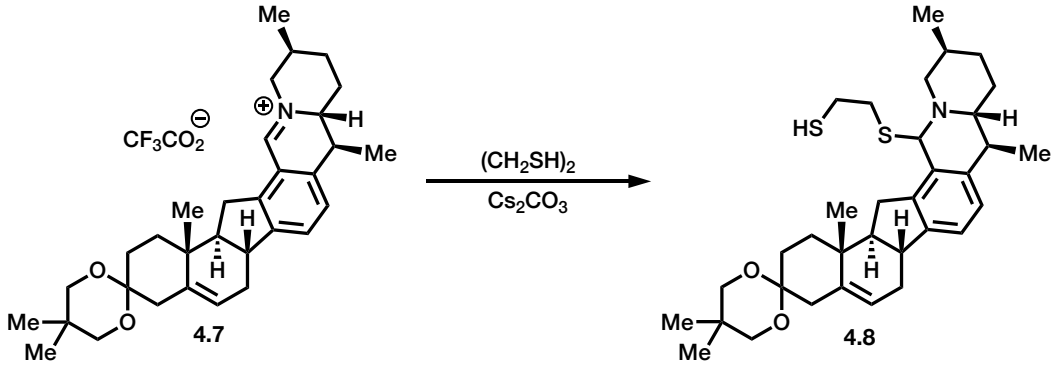
NMR: 36% conversion to iminium salt **4.**7', as determined by integration of the iminium salt **4.7'** methine, s at δ 8.89 ppm relative to alkenyl H at C–6.

[38] Longer reaction times did not increase conversion to the desired product, but rather were found to lead to gradual decomposition.



Hemiaminal 4.5. To a solution of crude iminium salt **4.4**[39] (ca. 11 μmol) in 10:1 DMSO-d_6/D_2O (0.8 mL) was added cesium carbonate (13 mg; 40 μmol; ca. 4 equiv) at ambient temperature. The resultant mixture was stirred at ambient temperature for 1 h, then the reaction progress was checked by ^{1}H NMR analysis of an aliquot.

NMR: Quantitative conversion to hemiaminal **4.5** (see Figure A.137 for spectral data), as evidenced by iminium salt **4.7** methine, s at δ 9.24 ppm → hemiaminal **4.5** methine, s at δ 5.02 ppm.

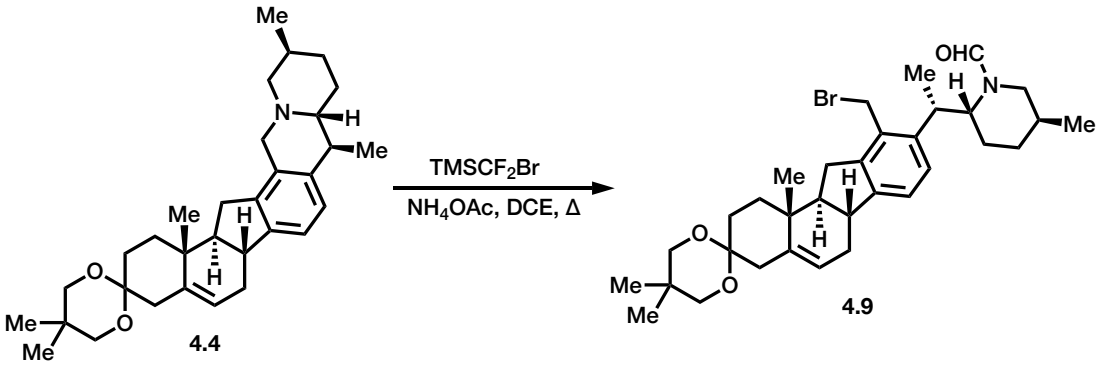


Thioaminal 4.8. To a solution of crude iminium salt **4.7** (ca. 5 μmol) in MeCN-d_3 was added 1,2-ethanedithiol (5 μL, 60 μmol, ca. 12 equiv) and cesium carbonate (6.5 mg, 20 μmol, ca. 4

[39] The starting material was contaminated with 3-chlorobenzoic acid from the amine oxidation, as the product (i.e., **4.4**) was carried forward without further purification.

equiv) at ambient temperature. The resultant mixture was stirred at ambient temperature for 0.5 h, then the reaction progress was checked by ^{1}H NMR analysis of an aliquot.

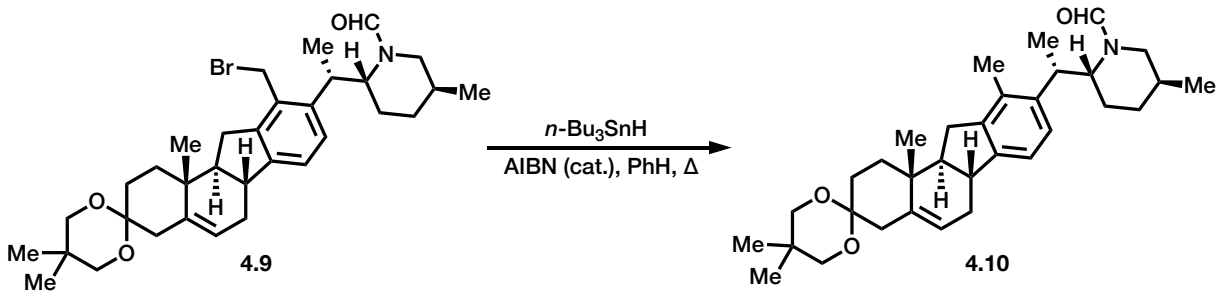
NMR: Quantitative conversion to thioaminal **4.8** (see Figure A.138 for spectral data), as evidenced by iminium salt **4.7** methine, s at δ 8.74 ppm → thioaminal **4.8** methine, s at δ 5.21 ppm.



Benzyl bromide 4.9. Dissolved amine **4.4** (40 mg, 0.084 mmol, 1 equiv) in DCE (1.9 mL) and added ammonium acetate (26 mg, 0.336 mmol, 4 equiv) at ambient temperature. Added (bromodifluoromethyl)trimethylsilane (50 μL, 0.336 mmol, 4 equiv) dropwise at ambient temperature, then heated the resultant solution to 80 °C. The pale-yellow solution was stirred at 80 °C for 8 h, then the resulting turbid white mixture was cooled to ambient temperature. Filtered the reaction mixture through a layer of Celite, washing the filter cake thoroughly with CH_2Cl_2 (ca. 20 mL). Concentration of the filtrate provided a crude yellow oil, which was purified via flash column chromatography (3:1:1 hexanes:Et_2O:acetone) to afford benzyl bromide **4.9** (36 mg, 74% yield) as a colorless, waxy solid.

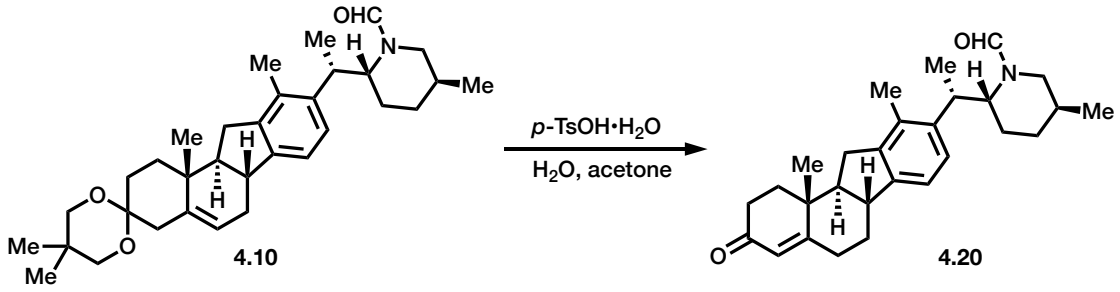
NMR: Due to the rotamerism of this compound, its NMR was not assigned (see Figure A.139 / Figure A.140 for spectral data). **COSY/HSQC:** see Figure A.141 / Figure A.142. **HRMS:** (ESI)

m/*z* $[M+H]^+$ calcd for $C_{33}H_{46}BrNO_3$: 584.2739, found: 584.2739. R_f = 0.48 (2:1:1 hexanes:acetone:Et_2O; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).



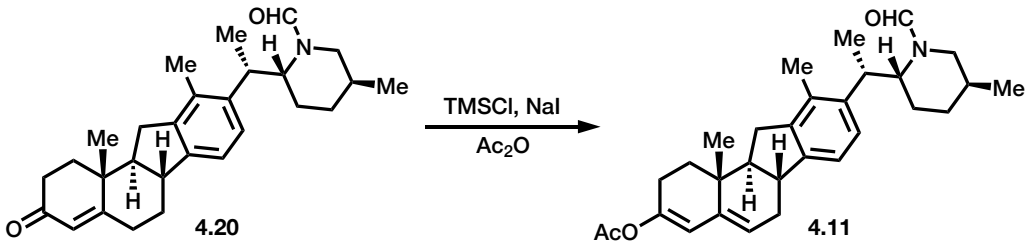
Toluene 4.10. To 2-dram vial containing a solution of benzyl bromide **4.9** (19 mg, 0.032 mmol, 1 equiv) and 2,2'-azobis(2-methylpropionitrile) (0.4 mg, 2.44 μmol, ca. 0.1 equiv) in degassed benzene (1.5 mL) was added tributyltin hydride (10 μL, 0.036 mmol, 1.1 equiv) at ambient temperature. The reaction vial was sealed, then resultant solution was heated to 90 °C and stirred at that same temperature for 4 h. Upon consumption of the starting material as indicated by TLC, the mixture was brought back to ambient temperature and concentrated under reduced pressure. The resultant crude oily residue was purified via preparative thin-layer chromatography (8:1 $CHCl_3$:acetone) to afford toluene **4.10** (16.4 mg, 95% yield).

NMR: Due to the rotamerism of this compound, its NMR was not assigned (see Figure A.143 / Figure A.144 for spectral data). **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{33}H_{47}NO_3$: 506.3634, found: 506.3634. R_f = 0.51 (2:1:1 hexanes:acetone:Et_2O; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).



Enone 4.20. To pre-cooled solution of toluene **4.10** (19 mg, 0.038 mmol, 1 equiv) in acetone (0.80 mL) was added distilled water (25 μL), followed by *p*-toluenesulfonic acid monohydrate (18 mg, 0.095 mmol, 2.5 equiv) in a single portion at 0 °C. The resultant yellow solution was stirred at 0 °C for 3 h, then brought to ambient temperature and stirred for an additional 16 h. Following consumption of starting material as indicated by TLC, the clear and colorless reaction mixture was neutralized with a saturated aqueous $NaHCO_3$ solution (5 mL) and diluted with EtOAc (6 mL). The resultant biphasic mixture was separated and the aqueous layer extracted with EtOAc (3 x 6 mL). The organic extracts were combined, washed with brine (1 x 25 mL), and dried over Na_2SO_4. Concentration of the dried extracts provided enone **4.20** (15.3 mg, 97% yield) as a white solid. The crude concentrate was typically clean enough to be carried forward without further purification, however preparative thin-layer chromatography (33:50:17 hexanes:Et_2O:CH_2Cl_2; developed 3 times) was used to obtain spectroscopically pure material. **^{1}H NMR (400 MHz, $CDCl_3$;** *denotes corresponding rotamer signals**):** δ 7.69 (s, 0.5H*), 7.67 (s, 0.5H*), 7.16 (d, *J* = 7.8 Hz, 0.5H), 7.00 – 6.94 (m, 1.5H), 5.82 (s, 1H), 4.76 – 4.69 (m, 0.5H), 3.71 – 3.47 (m, 2.5H), 3.18 – 2.97 (m, 2H), 2.81 – 2.67 (m, 1.5H), 2.65 – 2.49 (m, 3H), 2.49 – 2.36 (m, 2.5H), 2.31 (s, 1.5H), 2.22 (s, 1.5H), 2.10 – 1.82 (m, 5.5H), 1.82 – 1.57 (m, 2.5H), 1.52 – 1.38 (m, 2H), 1.30 (s, 1.5H), 1.29 (s, 1.5H), 1.22 (d, *J* = 6.8 Hz, 1.5H), 1.18 (d, *J* = 6.8 Hz, 1.5H), 0.97 (d, *J* = 6.9 Hz, 1.5H), 0.96 (d, *J* = 6.9 Hz, 1.5H). **^{13}C NMR (101 MHz, $CDCl_3$;** *denotes corresponding rotamer signals**):** δ 199.5*, 199.5*, 170.2**, 170.1**, 162.0, 161.8,

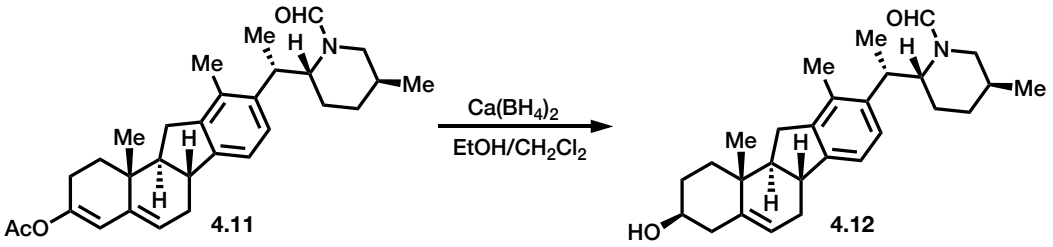
143.2, 142.8, 142.6, 141.7, 140.5, 140.2, 131.7, 131.1, 125.6, 125.3, 124.1, 120.2, 119.9, 60.8, 59.7, 59.7, 51.9, 48.5, 43.9, 43.8, 43.1, 38.7, 36.3, 34.0, 33.3, 33.3, 33.0, 30.2, 30.2, 29.7, 28.0, 27.8, 27.5, 25.7, 23.7, 20.6, 20.3, 20.3, 17.2, 17.0, 17.0, 16.7, 15.7, 15.5. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{28}H_{37}NO_2$: 420.2902, found: 420.2901. $\boldsymbol{R_f}$ = 0.40 (2:1:1 hexanes:acetone:Et_2O; visualized with UV and/or $Ce(SO_4)_2$ in phosphomolybdic acid stain).



Dienol acetate 4.11. To a pre-cooled solution of enone **4.20** (8.2 mg, 0.020 mmol, 1 equiv) in acetic anhydride (0.60 mL) was added dropwise chlorotrimethylsilane (10 µL, 0.079 mmol, 4 equiv), followed by the addition of sodium iodide (11.7 mg, 0.078 mmol, 4 equiv) in a single portion at 0 °C. The resultant opaque yellow mixture was stirred at 0 °C for 3 h, then concentrated to dryness under a stream of dry N_2 and further via high vacuum. The yellow-orange residue was re-dissolved in a solution of 1:1 hexanes:Et_2O (10 mL) and washed successively with a 2% aqueous $Na_2S_2O_3$ solution (1 x 4 mL), saturated aqueous $NaHCO_3$ solution (1 x 4 mL), distilled water (1 x 5 mL), and brine (1 x 5 mL). The organic extracts were then dried over Na_2SO_4 and concentrated to afford dienol acetate **4.11** (8.8 mg, 98% yield) as a clear, waxy solid.

^{1}H NMR (500 MHz, $CDCl_3$); *denotes corresponding rotamer signals**):** δ 7.70 (s, 1H), 7.14 (d, *J* = 7.8 Hz, 0.5H), 6.99 – 6.93 (m, 1.5H), 5.81 (s, 1H), 5.53 (m, 1H), 4.75 – 4.69 (m, 0.5H), 3.68 – 2.48 (m, 2.5H), 3.17 – 3.05 (m, 2H), 2.82 – 2.69 (m, 2.5H), 2.62 – 2.49 (m, 2H), 2.32 (s, 1.5H),

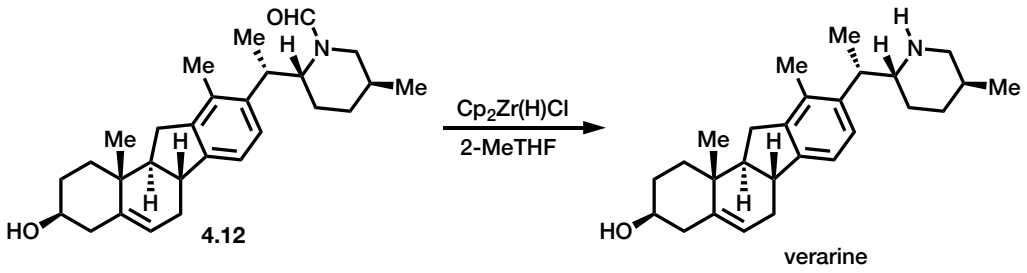
2.23 (s, 1.5H), 2.23 – 2.18 (m, 0.5H), 2.18 – 2.01 (m, 2H), 2.15 (s, 3H), 2.01 – 1.96 (m, 1H), 1.96 – 1.81 (m, 3H), 1.81 – 1.75 (m, 0.5H), 1.75 – 1.67 (m, 0.5H), 1.66 – 1.50 (m, 1H), 1.45 – 1.38 (m, 1H), 1.23 (d, J = 6.8 Hz, 1.5H), 1.19 (d, J = 6.8 Hz, 1.5H), 1.13 (s, 3H), 0.96 (d, J = 6.9 Hz, 1.5H), 0.95 (d, J = 6.9 Hz, 1.5H). **^{13}C NMR (125 MHz, $CDCl_3$;** *denotes corresponding rotamer signals**):** δ 169.6*, 169.5*, 162.1**, 161.8**, 147.6***, 147.5***, 144.4, 144.0, 143.1, 142.2, 140.6, 140.5, 140.1, 139.9, 131.5, 130.9, 125.4, 124.6, 124.4, 124.0, 120.4, 120.0, 117.1****, 117.0****, 60.8, 55.3*****, 55.2*****, 51.9, 48.5, 43.1, 41.0, 40.9, 35.5, 35.1, 35.1, 33.5, 33.0, 30.6, 30.6, 30.5, 30.5, 29.9, 28.1, 27.8, 27.6, 25.7, 24.8, 24.8, 23.8, 22.8, 21.3, 20.6, 20.3, 20.3, 18.9, 18.9, 17.2, 16.7, 15.7, 15.5. **HRMS:** (ESI) m/z $[M+H]^+$ calcd for $C_{30}H_{39}NO_3$: 462.3008, found: 462.3006. $\boldsymbol{R_f}$ = 0.47 (1:1 hexanes:EtOAc; visualized with UV and/or $Ce(SO_4)_2$ in phosphomolybdic acid stain).



Alcohol 4.12. To a pre-cooled solution of dienol acetate **4.11** (8.8 mg, 0.019 mmol, 1 equiv) in 5:1 EtOH/CH_2Cl_2 (0.90 mL) was added calcium borohydride solution (ca. 0.2 M in EtOH; 0.29 mL, 0.057 mmol, ca. 3 equiv) dropwise at –15 °C. The resultant mixture was stirred at –15 °C for 3 h, then brought to ambient temperature and stirred for an additional 5 h. Upon consumption of starting material as indicated by TLC, the reaction was quenched via slow and careful addition of glacial acetic acid (20 µL), then further diluted with H_2O (4 mL) and $CHCl_3$ (4 mL). The biphasic mixture was separated, then the aqueous layer was repeatedly extracted with $CHCl_3$ (3 x

4 mL). The organic extracts were subsequently combined and dried over Na_2SO_4. Concentration of the dried extracts provided alcohol **4.12** (8.0 mg, 96% yield) as an off-white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (s, 1H), 7.13 (d, *J* = 7.8 Hz, 0.5H), 6.97 – 6.91 (m, 1.5H), 5.48 (m, 1H), 4.74 – 4.68 (m, 0.5H), 3.68 – 3.47 (m, 3.5H), 3.14 (dd, *J* = 13.5, 3.7 Hz, 0.5H), 3.09 (dd, *J* = 13.3, 3.9 Hz, 0.5H), 2.98 – 2.87 (m, 1H), 2.80 – 2.70 (m, 1H), 2.63 – 2.50 (m, 2H), 2.44 – 2.38 (m, 1H), 2.31 (s, 1.5H), 2.31 – 2.23 (m, 1H), 2.22 (s, 1.5H), 2.10 – 1.96 (m, 3H), 1.96 – 1.75 (m, 5.5H), 1.75 – 1.67 (m, 1H), 1.66 – 1.55 (m, 1.5H), 1.45 – 1.38 (m, 1H), 1.22 (d, *J* = 6.8 Hz, 1.5H), 1.19 (d, *J* = 6.8 Hz, 1.5H), 1.14 (s, 1.5H), 1.13 (s, 1.5H), 0.96 (d, *J* = 6.9 Hz, 1.5H), 0.95 (d, *J* = 6.9 Hz, 1.5H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 162.1, 161.8, 144.3, 143.9, 143.4, 142.6, 142.5, 142.5, 140.0, 139.8, 131.4, 130.9, 125.4, 123.9, 122.3, 122.1, 120.6, 120.2, 72.0, 71.97, 60.76, 57.16, 57.14, 51.92, 48.45, 43.10, 42.05, 41.34, 41.31, 38.18, 37.05, 37.03, 33.43, 32.98, 32.95, 31.47, 31.45, 31.07, 30.61, 30.58, 30.46, 30.44, 30.38, 29.84, 28.03, 27.80, 27.60, 25.65, 23.77, 20.60, 20.33, 20.26, 19.43, 19.42, 17.19, 16.69, 15.71, 15.52. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{28}H_{39}NO_2$: 422.3059, found: 422.3056. R_f = 0.32 (1:1 hexanes:EtOAc; visualized with $KMnO_4$ stain).



Verarine. To a solution of alcohol **4.12** (10.5 mg, 0.025 mmol, 1 equiv) in dry 2-MeTHF (0.6 mL) was added bis(cyclopentadienyl)zirconium(IV) chloride hydride (9.7 mg, 0.038 mmol, 1.5

equiv) at ambient temperature, then the resultant solution was stirred at ambient temperature for 1 h. Upon consumption of starting material as indicated by TLC, the reaction mixture was diluted with EtOAc (6 mL) and poured into a separatory funnel containing saturated aqueous $NaHCO_3$ solution (5 mL). The biphasic mixture was separated, then the aqueous layer was repeatedly extracted with EtOAc (3 x 6 mL). The organic extracts were combined and washed with brine (1 x 20 mL), then dried over Na_2SO_4. Concentration of the dried extracts provided a crude colorless residue, which was purified via preparative thin-layer chromatography (87:12:1 $CHCl_3$: MeOH: aq. NH_4OH) to afford verarine (6.8 mg, 69% yield) as a white solid.

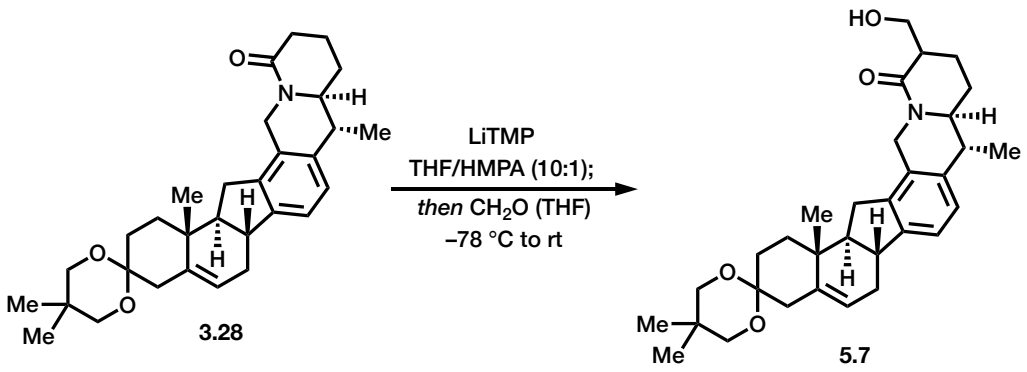
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.04 (d, *J* = 7.7 Hz, 1H), 6.99 (d, *J* = 7.7 Hz, 1H), 5.49 (m, 1H), 3.62 – 3.54 (tt, *J* = 11.3, 4.5 Hz, 1H), 3.06 (br s, 1H), 3.01 – 2.92 (m, 2H), 2.79 (dd, *J* = 14.8, 7.3 Hz, 1H), 2.67 – 2.54 (m, 3H), 2.44 – 2.38 (m, 1H), 2.31 – 2.24 (m, 1H), 2.29 (s, 3H), 2.16 (t, *J* = 11.3 Hz, 1H), 2.07 – 1.99 (m, 1H), 1.97 – 1.77 (m, 6H), 1.76 – 1.65 (m, 1H), 1.66 – 1.55 (m, 1H), 1.40 – 1.21 (m, 3H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.14 (s, 3H), 1.05 – 0.95 (qd, *J* = 12.8, 3.9 Hz, 1H), 0.83 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 144.1, 143.3, 142.7, 141.0, 132.9, 123.8, 122.1, 120.4, 72.0, 62.3, 57.1, 54.6, 42.1, 41.4, 39.7, 38.2, 37.1, 33.7, 31.5, 31.0, 30.7, 30.5, 29.9, 19.5, 19.4, 18.4, 15.9. **COSY/HSQC:** see Figure A.153 / Figure A.154.

HRMS: (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{27}H_{39}NO$: 394.3110 found, 394.3109.

$[\alpha]_D^{21.2}$ = -43.7 (*c* = 0.52, $CHCl_3$); lit.: -53.3 (*c* = 1.3852, $CHCl_3$).[40] ***R_f* =** 0.28 (12% MeOH in $CHCl_3$; visualized with $KMnO_4$ stain).

[40] For isolation data, including optical rotation, see the following reference: *Collection Czechoslov. Chem. Commun.* **1964**, *25*, 2570–2574.

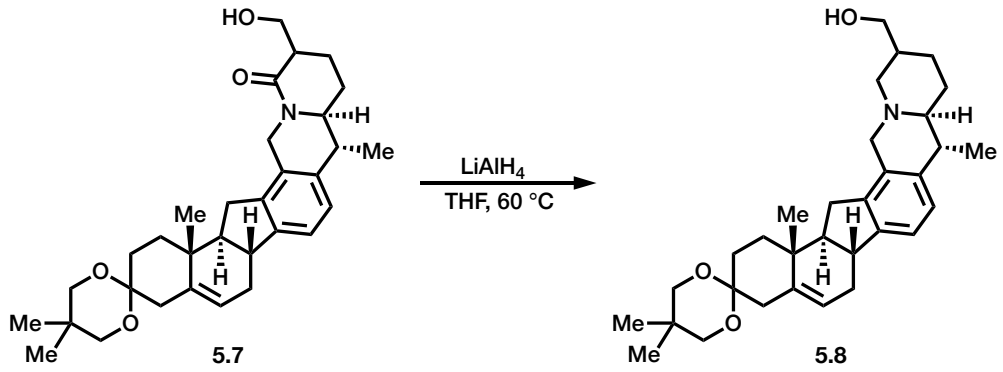
6.5. Experimental Procedures and Characterization Data for Chapter 5



α-Hydroxymethyl lactam 5.7. To a pre-cooled solution of freshly distilled 2,2,6,6,-tetramethylpiperidine (0.96 mL, 5.66 mmol) in THF (2.0 mL) was added dropwise *n*-butyllithium solution (1.57 M in hexanes; 3.5 mL, 5.53 mmol) at 0 °C. The resultant pale-yellow solution was stirred at 0 °C for 30 min to afford a 0.85 M solution of LiTMP. A separate round-bottom flask was charged with hexacycle **3.28** (40 mg, 0.084 mmol, 1 equiv) and THF (3.5 mL), then cooled to −78 °C under an atmosphere of Ar. The resultant solution was first treated with freshly distilled hexamethylphosphoramide (0.31 mL) at −78 °C, followed by dropwise addition of the 0.85 M LiTMP solution (0.25 mL, 0.213 mmol, ca. 2.5 equiv). The orangish brown mixture was stirred at −78 °C for 20 min, then treated dropwise with a monomeric formaldehyde solution (ca. 0.7 M in THF; 0.60 mL; 0.42 mmol; ca. 5 equiv). The resultant solution was stirred at –78 °C for 30 min, then the cold bath was removed. The reaction mixture was slowly brought to ambient temperature, then quenched with a saturated aqueous NH_4Cl solution (4 mL). The resultant mixture was extracted with EtOAc (4 x 10 mL), then the organic extracts were combined, washed with brine (1 x 30 mL), and dried over Na_2SO_4. Concentration of the dried extracts afforded a crude residue, which was purified via flash column chromatography (3:1:1 →

2:1:1 hexanes:Et_2O:acetone) to afford α-hydroxymethyl lactam **5.7** (1:1 dr; 25 mg, 59% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$; *denotes corresponding diastereomer signals**):** δ 7.13 (d, *J* = 7.7 Hz, 1H), 7.06 (d, *J* = 7.7 Hz, 0.5H*), 7.05 (d, *J* = 7.7 Hz, 0.5H*), 5.49 (m, 1H), 5.31 (d, *J* = 16.5 Hz, 0.5H**), 5.04 (d, *J* = 17.7 Hz, 0.5H**), 4.31 – 4.20 (m, 1H), 4.30 (d, *J* = 17.7 Hz, 0.5H***), 4.10 (d, *J* = 16.5 Hz, 0.5H***), 3.82 – 3.64 (m, 2H), 3.63 (d, *J* = 11.4 Hz, 1H), 3.51 (d, *J* = 11.4 Hz, 1H), 3.47 (s, 2H), 3.38 – 3.31 (td, *J* = 9.8, 4.4 Hz, 0.5H****), 3.24 – 3.16 (td, *J* = 10.0, 5.3 Hz, 0.5H****), 3.04 – 2.91 (m, 1.5H), 2.79 – 2.46 (m, 6H), 2.44 – 2.28 (m, 2.5H), 2.15 – 2.03 (m, 2H), 1.98 – 1.84 (m, 1.5H), 1.82 – 1.73 (m, 0.5H), 1.72 – 1.55 (m, 3H), 1.54 – 1.39 (m, 1H), 1.36 (d, *J* = 6.8 Hz, 1.5H*****), 1.33 (d, *J* = 6.8 Hz, 1.5H*****), 1.14 (s, 3H), 1.03 (s, 3H), 0.90 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 173.4, 172.5, 145.0, 144.7, 141.6, 140.5, 140.4, 136.7, 136.2, 129.2, 128.3, 125.3, 123.6, 122.4, 121.4, 121.2, 98.7, 70.4, 70.0, 64.9, 64.7, 59.8, 59.2, 57.0, 56.9, 43.4, 43.2, 43.1, 43.0, 41.1, 41.0, 40.3, 40.3, 39.9, 37.5, 37.5, 36.7, 35.9, 35.9, 30.4, 30.2, 29.2, 29.2, 28.1, 27.1, 24.3, 23.0, 22.7, 22.6, 20.1, 19.1, 18.2, 15.9. **COSY/HSQC:** see Figure A.157 / Figure A.158. **HRMS:** (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{43}NO_4$: 506.3270, found: 506.3276. R_f = 0.45 (1:1:1 hexanes:Et_2O:acetone; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).



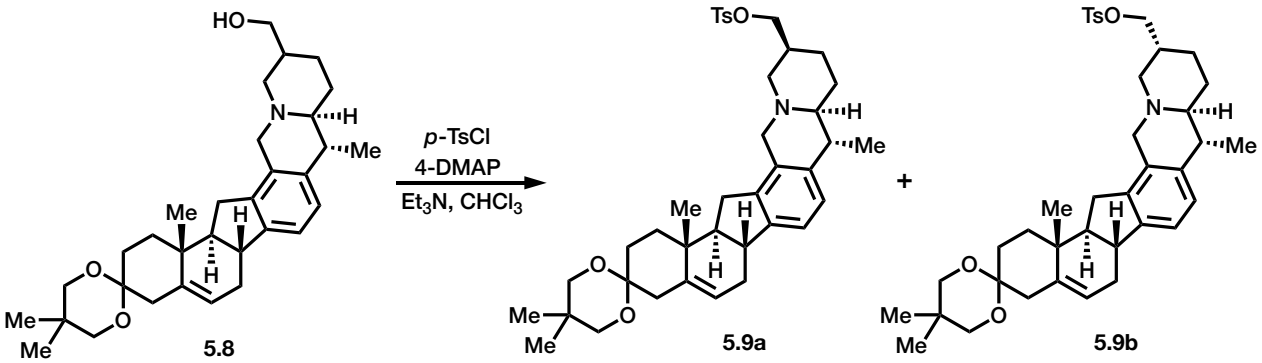
Primary alcohol 5.8. To a pre-cooled solution of α-hydroxymethyl lactam **5.7** (1:1 mixture of C–25 epimers; 48 mg, 0.095 mmol, 1 equiv) in THF (2.8 mL) was added lithium aluminum hydride solution (2.0 M in THF; 0.34 mL, 0.665 mmol, 7 equiv) dropwise at 0 °C. The resultant solution was stirred at 0 °C for 30 min, then brought to ambient temperature and stirred at that same temperature for an additional 30 min. The reaction mixture was then heated to 60 °C and stirred at that same temperature for 18 h. Upon consumption of starting material as indicated by TLC, the reaction mixture was brought to ambient temperature, then cooled further to 0 °C and diluted with Et_2O (3 mL). The reaction mixture was carefully quenched by sequential addition of H_2O (30 μL), 2 M NaOH aqueous solution (30 μL), additional H_2O (80 μL), and vigorously stirred for 15 min upon warming to ambient temperature. Anhydrous $MgSO_4$ was then added and the mixture was stirred for an additional 15 min. The mixture was filtered through a layer of Celite, which was subsequently washed thoroughly with Et_2O (ca. 30 mL). Concentration of the filtrate provided primary alcohol **5.8** (1:1 dr; 41 mg, 87% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$); *denotes corresponding diastereomer signals**):** δ 7.08 (d, *J* = 7.6 Hz, 0.5H*), 7.06 (d, *J* = 7.6 Hz, 0.5H*), 7.00 (d, *J* = 7.6 Hz, 0.5H**), 6.98 (d, *J* = 7.6 Hz, 0.5H**), 5.48 (m, 1H), 3.89 (dd, *J* = 10.6, 5.2 Hz, 0.5H***), 3.81 (dd, *J* = 10.9, 4.6 Hz, 0.5H***), 3.72 (d, *J* = 15.1 Hz, 0.5H****), 3.70 (d, *J* = 15.1 Hz, 0.5H****), 3.65 – 3.42 (m, 5.5H), 3.26 (d, *J* = 15.1 Hz, 0.5H*****), 3.24 (d, *J* = 15.1 Hz, 0.5H*****), 3.21 – 3.16 (m,

0.5H), 3.11 – 3.04 (m, 0.5H), 2.99 – 2.87 (m, 1H), 2.76 – 2.62 (m, 2H), 2.62 – 2.49 (m, 2.5H), 2.45 – 2.24 (m, 3H), 2.20 – 2.03 (m, 2H), 2.02 – 1.76 (m, 5H), 1.73 – 1.57 (m, 3H), 1.49 – 1.38 (m, 1H), 1.35 – 1.19 (m, 1H), 1.28 (d, J = 6.8 Hz, 1.5H*), 1.27 (d, J = 6.8 Hz, 1.5H*), 1.13 (s, 1.5H**), 1.12 (s, 1.5H**), 1.02 (s, 3H), 0.92 (s, 1.5H***), 0.91 (s, 1.5H***).

^{13}C NMR (101 MHz, $CDCl_3$); *denotes corresponding diastereomer signals**):** δ 143.6*, 143.5*, 141.4, 139.4**, 139.4**, 136.9, 130.1***, 129.8***, 125.3****, 125.2****, 122.6, 122.6, 121.0*****, 120.9*****, 98.7, 70.4*, 70.0*, 67.1, 66.5, 66.1, 65.6, 62.8, 59.7, 58.2, 56.9, 56.5, 40.9**, 40.9**, 40.0***, 39.9***, 39.2****, 39.1****, 38.4, 37.5*****, 37.5*****, 36.0, 34.9, 31.5, 30.5, 30.3, 30.1, 29.8, 28.9, 28.9, 28.5, 27.5, 27.5, 27.4, 27.1, 22.9, 22.8, 19.8, 19.5, 19.1.

COSY/HSQC: see Figure A.161 / Figure A.162. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{32}H_{45}NO_3$: 492.3477, found: 492.3478. $\boldsymbol{R_f}$ = 0.41 (1:1:1 hexanes:Et_2O:acetone; visualized with $KMnO_4$ stain).



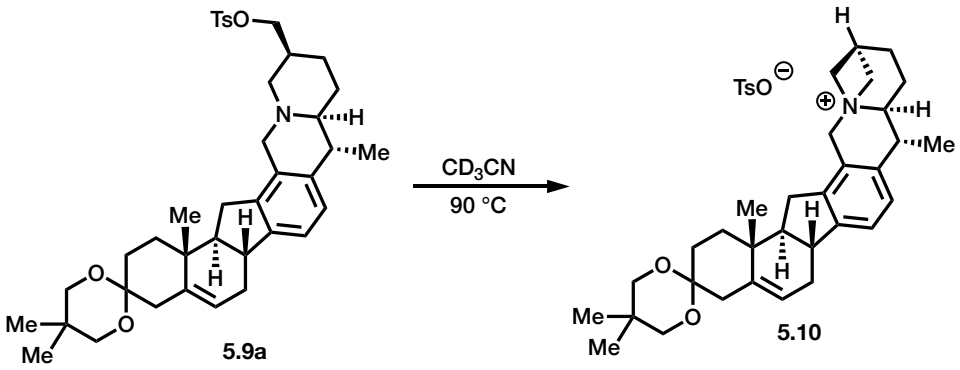
Tosylates 5.9a/5.9b. To a pre-cooled solution of primary alcohol **5.8** (40 mg, 0.081 mmol, 1 equiv) in $CHCl_3$ (4.8 mL) was added *p*-toluenesulfonyl chloride (46 mg, 0.243 mmol, 3 equiv), triethylamine (0.11 mL, 0.810 mmol, ca. 10 equiv), and 4-dimethylaminopyridine (20 mg, 0.162 mmol, 2 equiv) sequentially at 0 °C. The resultant mixture was brought to ambient temperature

and stirred for 5 h. Upon consumption of starting material as indicated by TLC, the reaction mixture was treated with 1:1 saturated aqueous $NaHCO_3$: H_2O solution (6 mL) and stirred vigorously for 30 min to hydrolyze unreacted *p*-TsCl. The mixture was then extracted with $CHCl_3$ (3 x 10 mL) and the combined organic extracts dried over Na_2SO_4. Concentration of the dried extracts provided a crude yellow oil, which was purified via flash column chromatography (8:1 → 4:1 $CHCl_3$:EtOAc) to afford tosylate **5.9a** (23 mg, 44% yield) and tosylate **5.9b** (24 mg, 46% yield).

5.9a: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.05 (d, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 5.48 (m, 1H), 4.26 – 4.11 (m, 2H), 3.61 (d, *J* = 11.3 Hz, 1H), 3.57 – 3.49 (m, 1H), 3.52 (d, *J* = 11.3 Hz, 1H), 3.47 (s, 2H), 3.33 – 3.19 (br m, 1H), 2.98 – 2.88 (td, *J* = 11.5, 5.3 Hz, 1H), 2.83 (d, *J* = 11.1 Hz, 1H), 2.67 (dd, *J* = 14.3, 2.3 Hz, 1H), 2.64 – 2.51 (m, 4H), 2.42 – 2.26 (m, 3H), 2.38 (s, 3H), 2.20 – 2.05 (m, 2H), 1.97 – 1.84 (m, 3H), 1.81 – 1.71 (m, 1H), 1.70 – 1.51 (m, 3H), 1.48 – 1.38 (m, 1H), 1.35 – 1.27 (m, 1H), 1.22 (d, *J* = 6.8 Hz, 3H), 1.14 (s, 3H), 1.02 (s, 3H), 0.91 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 144.7, 143.7, 141.5, 139.5, 136.6, 133.2, 129.9, 128.1, 125.3, 122.6, 121.1, 98.7, 77.4, 71.8, 70.4, 70.1, 65.1, 56.8, 56.2, 40.9, 40.0, 37.5, 35.9, 33.7, 30.5, 30.3, 29.8 28.9, 27.4, 26.7, 24.2, 23.0, 22.8, 21.7, 19.4, 19.1. **COSY/HSQC:** see Figure A.165 / Figure A.166. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{39}H_{51}NO_5S$: 646.3566, found: 646.3574. $\boldsymbol{R_f}$ **=** 0.43 (2:1 $CHCl_3$:EtOAc; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).

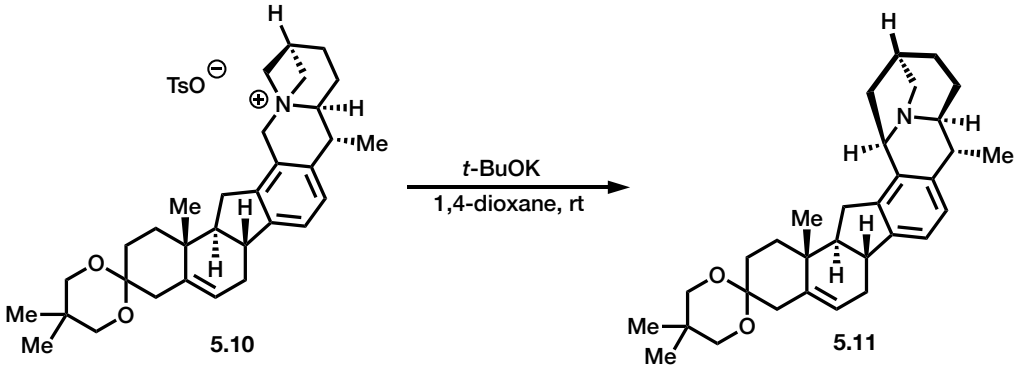
5.9b: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.05 (d, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 5.48 (m, 1H), 3.97 – 3.91 (dd, *J* = 9.6, 5.4 Hz, 1H), 3.91 – 3.85 (dd, *J* = 9.6, 7.1 Hz, 1H), 3.69 (*J* = 14.9 Hz, 1H), 3.61 (d, *J* = 11.3 Hz, 1H), 3.52 (d, *J* = 11.3 Hz, 1H), 3.47 (s, 2H), 3.24 (d, *J* = 14.9 Hz, 1H), 3.14 – 3.07 (m, 1H), 2.97 – 2.87 (td, *J* =

11.5, 5.3 Hz, 1H), 2.73 – 2.63 (m, 2H), 2.63 – 2.51 (m, 3H), 2.46 (s, 3H), 2.41 – 2.34 (m, 1H), 2.34 – 2.26 (m, 1H), 2.18 – 2.02 (m, 3H), 1.96 – 1.84 (m, 2H), 1.85 – 1.72 (m, 2H), 1.70 – 1.57 (m, 2H), 1.49 – 1.39 (m, 1H), 1.35 – 1.27 (m, 1H), 1.26 (d, J = 6.8 Hz, 3H), 1.13 (s, 3H), 1.11–1.04 (dd, J = 12.6, 3.2 Hz, 1H), 1.02 (s, 3H), 0.91 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 144.9, 143.6, 141.4, 139.4, 136.6, 133.2, 130.0, 128.1, 125.3, 122.6, 121.1, 98.7, 73.0, 70.4, 70.0, 65.7, 58.8, 56.9, 56.2, 40.9, 40.1, 39.1, 37.5, 35.9, 35.8, 31.1, 30.5, 30.3, 29.8, 28.9, 27.3, 27.1, 23.0, 22.8, 21.8, 19.7, 19.1. **COSY/HSQC:** see Figure 169 / Figure 170. **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{39}H_{51}NO_5S$: 646.3566, found: 646.3571. $\boldsymbol{R_f}$ = 0.63 (2:1 $CHCl_3$:EtOAc; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).



Azetidinium salt 5.10. A solution of tosylate **5.9a** (7.4 mg, 0.0115 mmol, 1 equiv) in dry, degassed acetonitrile-d_3 (1.4 mL) was heated to 90 °C under an atm of Ar and stirred at that same temperature for 18 h. The resultant solution was brought back to ambient temperature, then concentrated under reduced pressure. The remaining residue was azeotroped with benzene (3 x 2 mL), then triturated with anhydrous Et_2O (3 x 1.5 mL; collecting supernatant is a separate vessel). The resulting white solid was dried under high vacuum for 30 min to afford azetidinium salt **5.10** (5.9 mg, 80% yield).

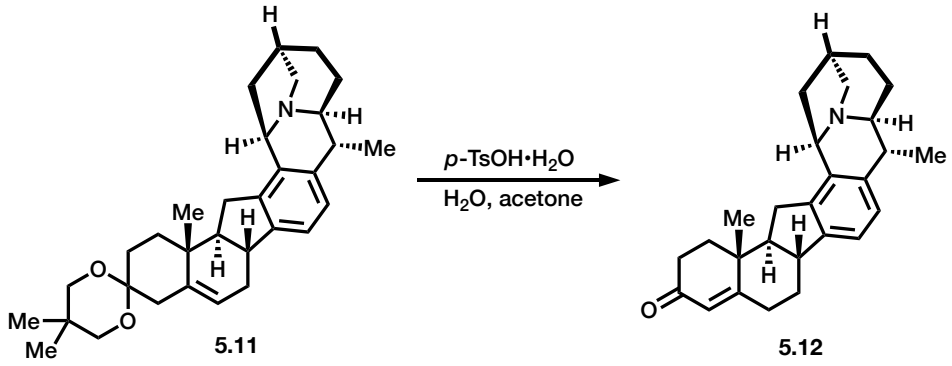
^{1}H NMR (500 MHz, CD_3CN): δ 7.56 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.17 (d, *J* = 7.9 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 5.45 (m, 1H), 4.45 (d, *J* = 15.3 Hz, 1H), 4.39 – 4.35 (dd, *J* = 9.0, 5.3 Hz, 1H), 4.29 (d, *J* = 15.3 Hz, 1H), 4.01 – 3.96 (m, 1H), 3.94 – 3.88 (dd, *J* = 8.4, 7.1 Hz, 1H), 3.73 – 3.67 (m, 1H), 3.52 (s, 2H), 3.51 – 3.46 (dd, *J* = 8.5, 7.1 Hz, 1H), 3.44 – 3.36 (m, 2H), 3.32 – 3.24 (m, 1H), 2.99 – 2.91 (td, *J* = 11.5, 5.4 Hz, 1H), 2.80 – 2.69 (m, 2H), 2.69 – 2.51 (m, 4H), 2.32 (s, 3H), 2.30 – 2.24 (m, 1H), 2.23 – 2.15 (m, 2H), 2.15 – 2.09 (m, 1H), 2.09 – 2.01 (m, 1H), 1.98 – 1.90 (m, 1H), 1.85 – 1.76 (td, *J* = 11.8, 7.9 Hz, 1H), 1.67 – 1.56 (m, 2H), 1.44 – 1.36 (m, 1H), 1.35 (d, *J* = 6.8 Hz, 3H), 1.14 (s, 3H), 0.93 (s, 3H), 0.90 (s, 3H). R_f = 0.00 (1:1:1 hexanes:Et_2O:acetone; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).



Amine 5.11. To a solution of azetidinium salt **5.10** (5.9 mg, 0.0091 mmol, 1 equiv) in dry 1,4-dioxane (0.8 mL) was added potassium *tert*-butoxide (3.1 mg, 0.0275 mmol, 3 equiv) in a single portion at ambient temperature. The resultant pale yellow reaction mixture was stirred at ambient temperature for 1 h, then diluted with H_2O (3 mL) and the mixture was extracted with $CHCl_3$ (3 x 4 mL). The organic extracts were combined, washed with brine (1 x 5 mL), and dried over Na_2SO_4. Concentration of the dried extracts afforded a crude yellow residue, which was purified

via preparative thin-layer chromatography (89:10:1 $CHCl_3$: MeOH: aq. NH_4OH) to provide amine **5.11** (3.6 mg, 83% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$):[41] δ 7.00 (d, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 5.50 (m, 1H), 3.61 (d, *J* = 11.3 Hz, 1H), 3.52 (d, *J* = 11.3 Hz, 1H), 3.48 (s, 2H), 3.04 – 2.93 (td, *J* = 12.1, 5.5 Hz, 1H), 2.71 – 2.45 (m, 3H), 2.45 – 2.26 (m, 2H), 2.16 – 2.03 (m, 2H), 2.01 – 1.91 (td, *J* = 11.9, 7.2 Hz, 1H), 1.80 – 1.57 (m, 6H), 1.52 – 1.33 (m, 5H), 1.25 (d, *J* = 6.8 Hz, 3H), 1.16 (s, 3H), 1.03 (s, 3H), 0.92 (s, 3H). **HRMS:** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{32}H_{43}NO_2$: 474.3372, found: 474.3370. R_f = 0.29 (10% MeOH in $CHCl_3$; visualized with $Ce(SO_4)_2$ in phosphomolybdic acid stain).



Enone 5.12. To pre-cooled solution of amine **5.11** (7.4 mg, 0.016 mmol, 1 equiv) in acetone (0.50 mL) was added distilled water (5 μL), followed by *p*-toluenesulfonic acid monohydrate (7.5 mg, 0.039 mmol, 2.5 equiv) in a single portion at 0 °C. The resultant yellow solution was stirred at 0 °C for 3 h, then brought to ambient temperature and stirred for an additional 12 h.

[41] Some signals are omitted due to poor peak shape and peak broadening, as well as discrepancies in the chemical shift values between different purified samples that had been prepared (see Figure A.173).

Following consumption of starting material as indicated by TLC, the clear and colorless reaction mixture was neutralized with a saturated aqueous $NaHCO_3$ solution (0.5 mL), then diluted with H_2O (5 mL) and $CHCl_3$ (5 mL). The resultant biphasic mixture was separated and the aqueous layer extracted with $CHCl_3$ (6 x 5 mL). The organic extracts were combined and dried over Na_2SO_4. Concentration of the dried extracts provided enone **5.12** (6.0 mg, 99% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (d, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 7.6 Hz, 1H), 5.84 (s, 1H), 4.37 – 4.26 (m, 1H), 3.21 – 3.13 (m, 1H), 3.13 – 3.04 (td, *J* = 12.1, 3.0 Hz, 1H), 3.00 – 2.94 (app d, *J* = 11.3 Hz, 1H), 2.69 – 2.53 (m, 3H), 2.53 – 2.35 (m, 6H), 2.35 – 2.12 (m, 3H), 2.09 – 2.03 (m, 1H), 2.03 – 1.96 (m, 1H), 1.95 – 1.86 (td, *J* = 14.1, 4.5 Hz, 1H), 1.86 – 1.80 (m, 1H), 1.80 – 1.71 (td, *J* = 12.6, 5.6 Hz, 1H), 1.64 – 1.35 (m, 3H), 1.38 (d, *J* = 7.1 Hz, 3H), 1.31 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 199.4, 169.8, 139.9, 127.6, 125.4, 120.7, 61.1, 60.4, 60.1, 58.4, 43.6, 40.0, 38.6, 37.9, 36.3, 34.0, 33.9, 33.3, 32.1, 30.4, 29.7, 29.6, 29.5, 25.2, 22.8, 22.7, 17.1. **COSY:** see Figure A.176. R_f = 0.54 (86:13:1 $CHCl_3$: MeOH: aq NH_4OH; visualized with UV and/or $KMnO_4$ stain).

Appendix

Selected ^{1}H and ^{13}C NMR Spectra

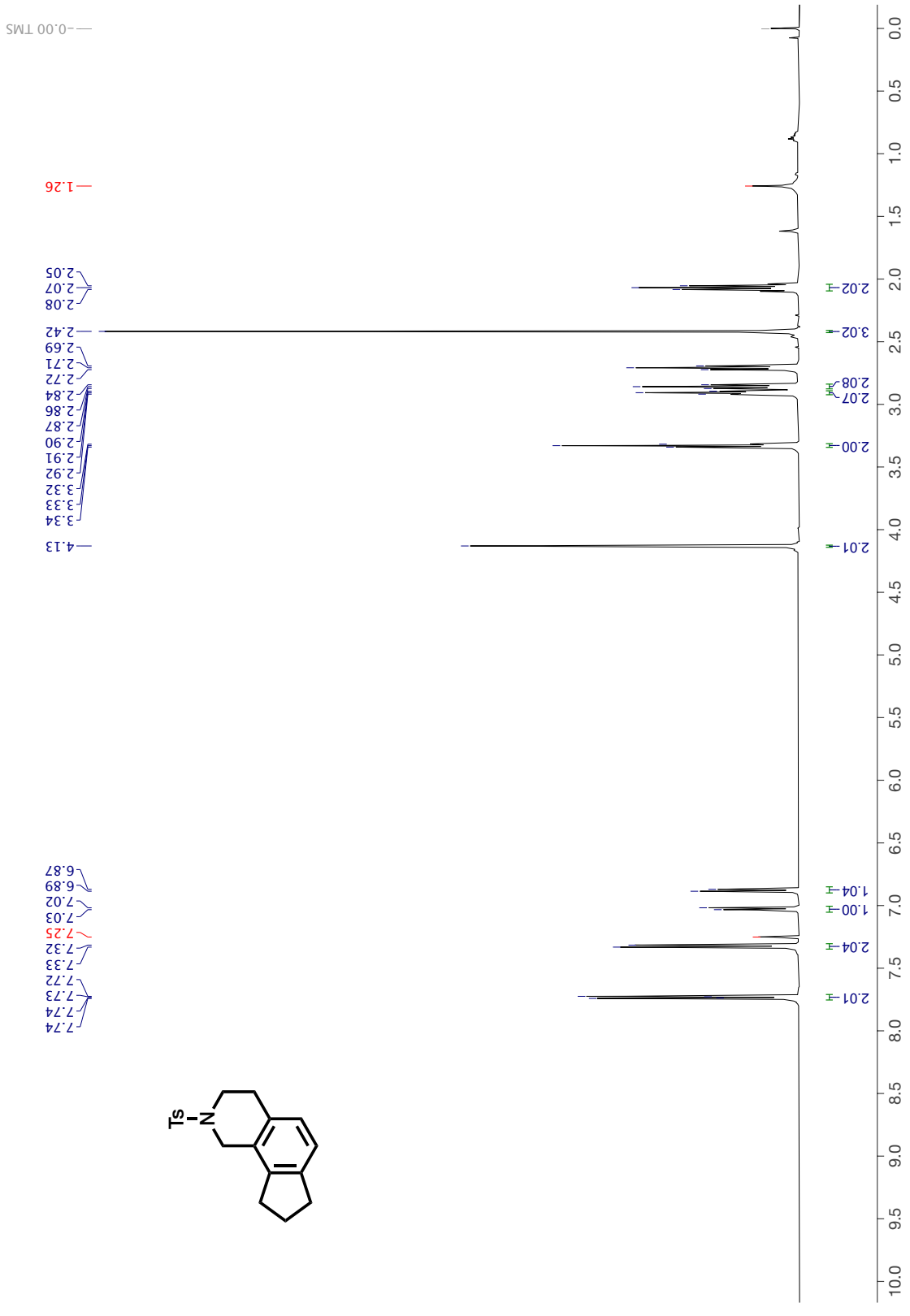


Figure A.1. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **2.4**.

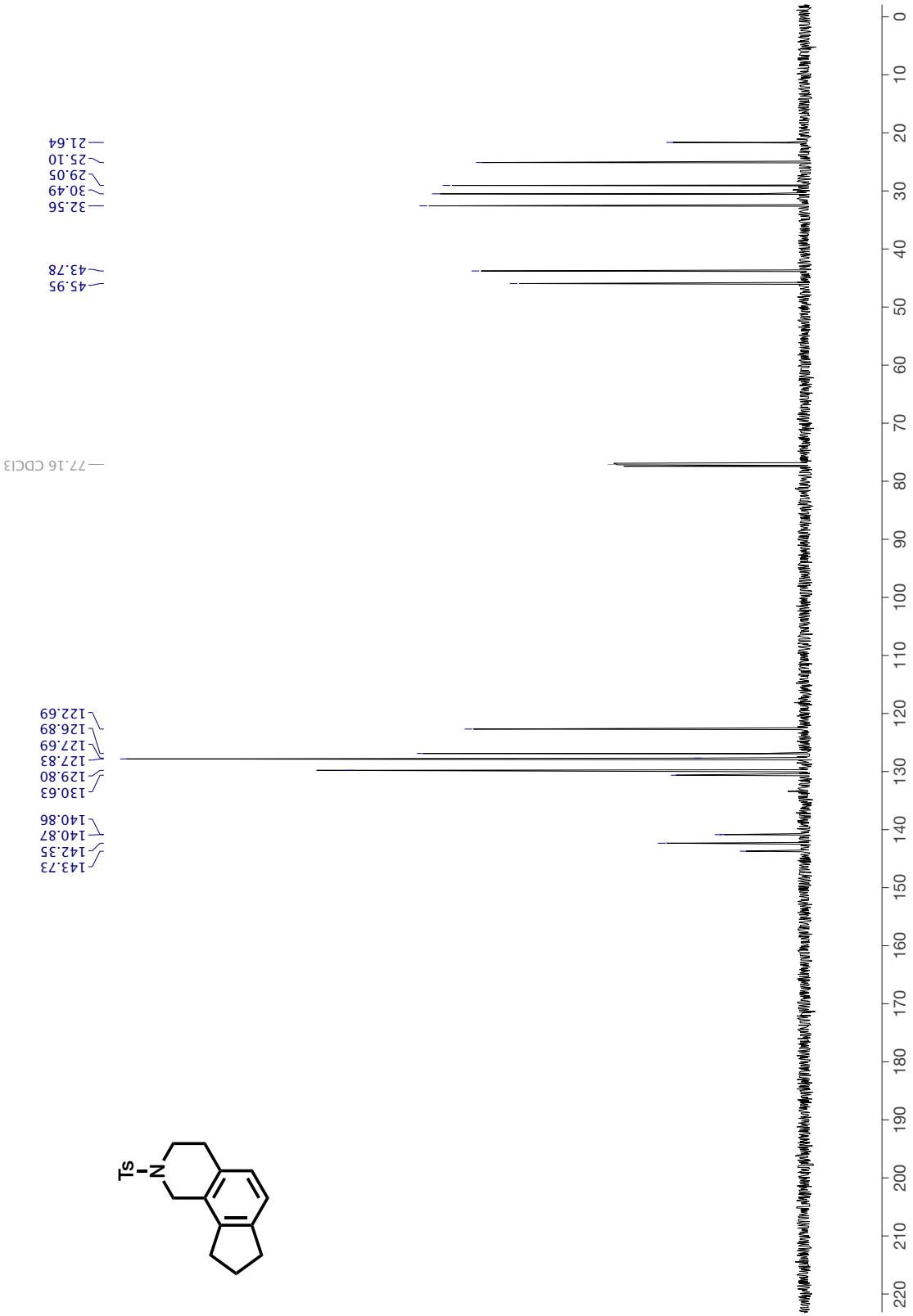


Figure A.2. ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of **2.4**.

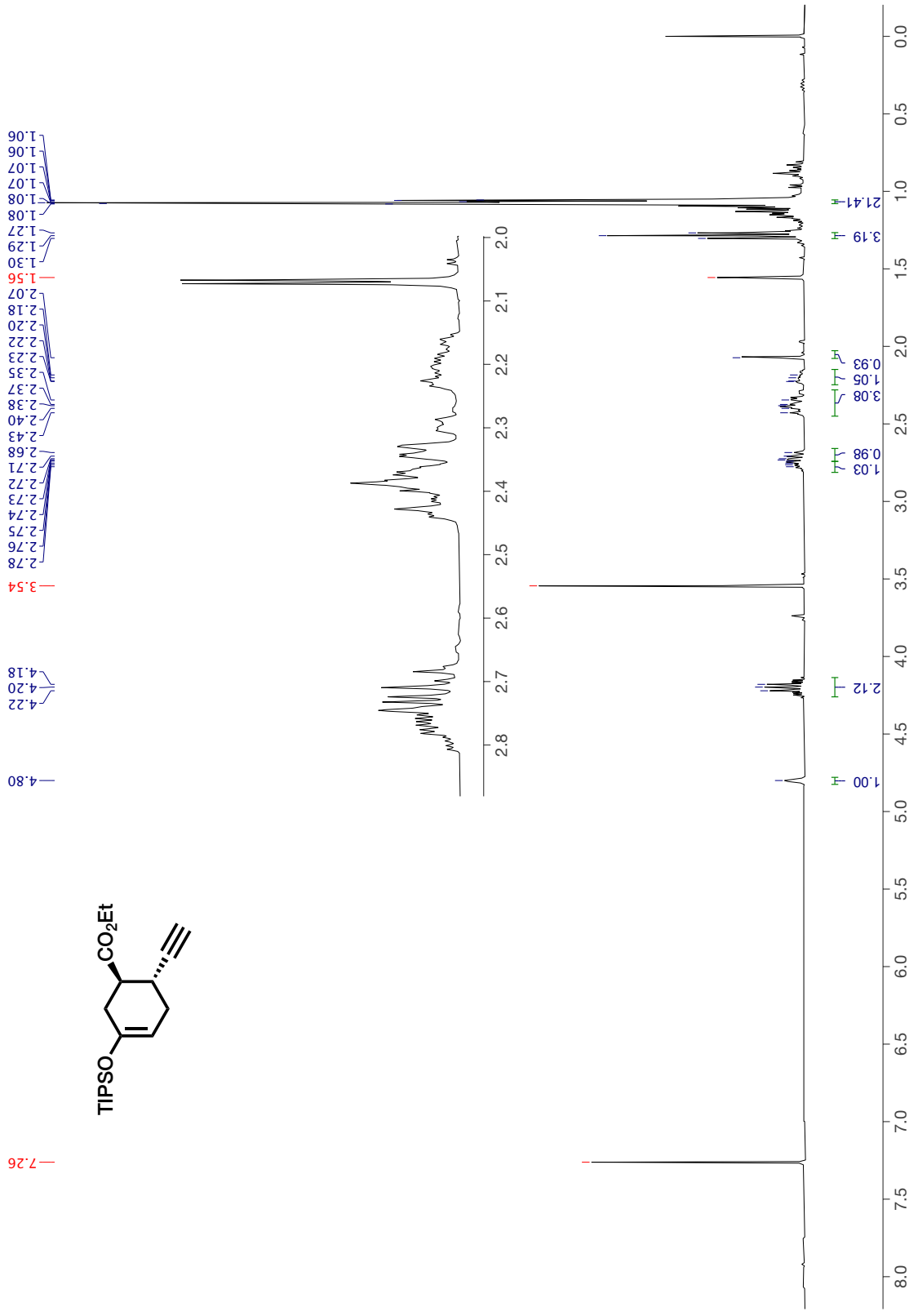


Figure A.3. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2.9**.

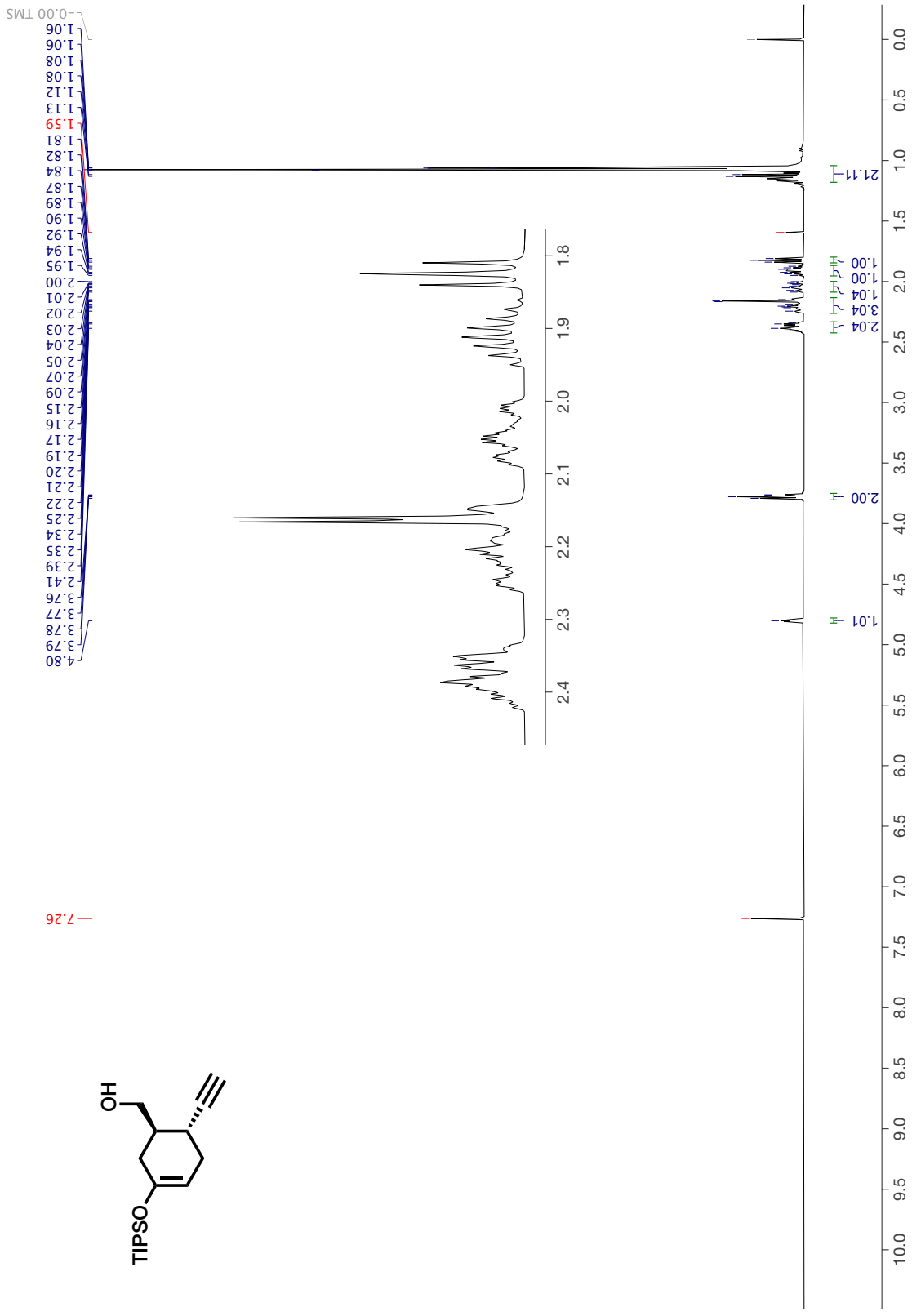


Figure A.4. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2.45**.

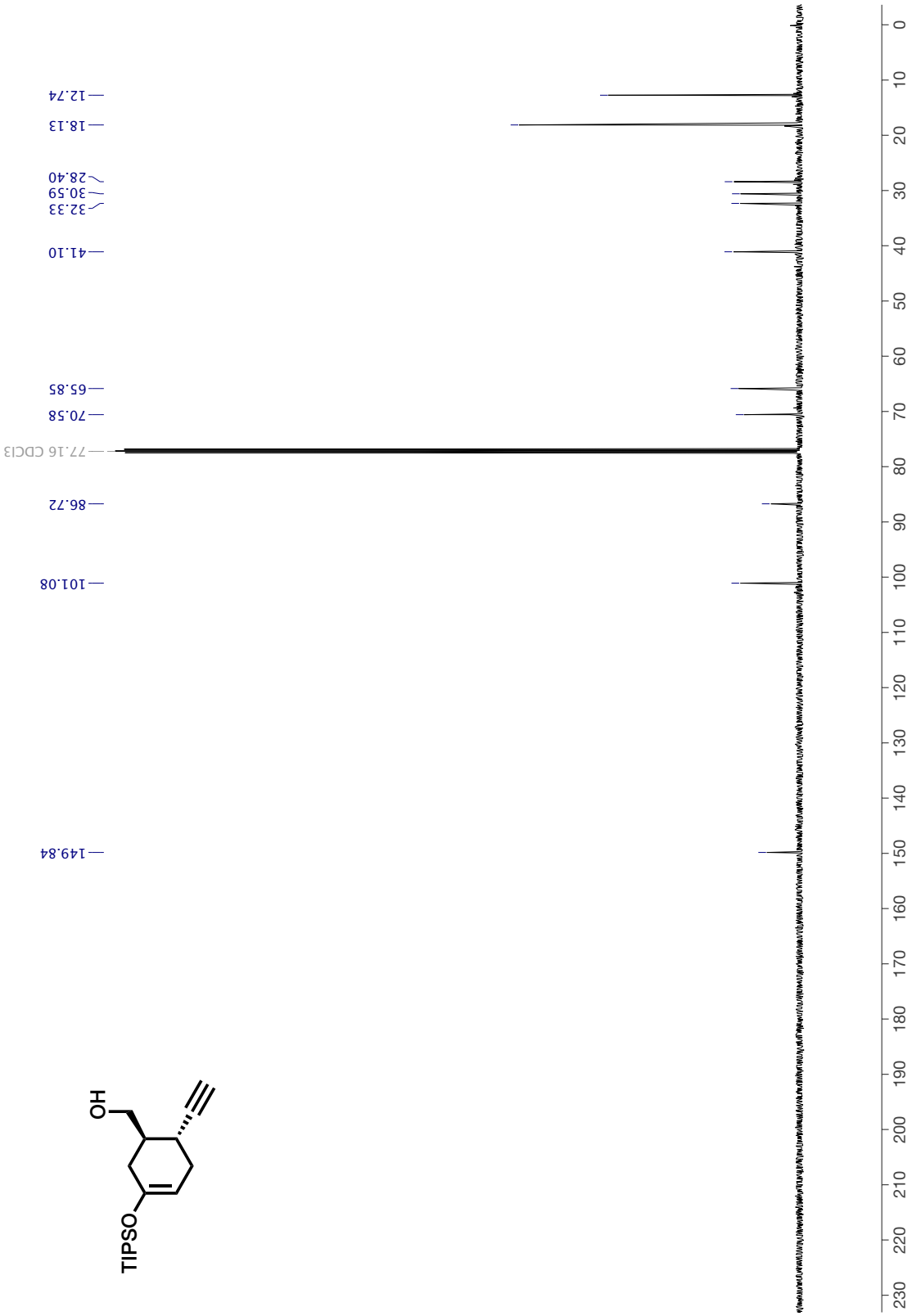


Figure A.5. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **2.45**.

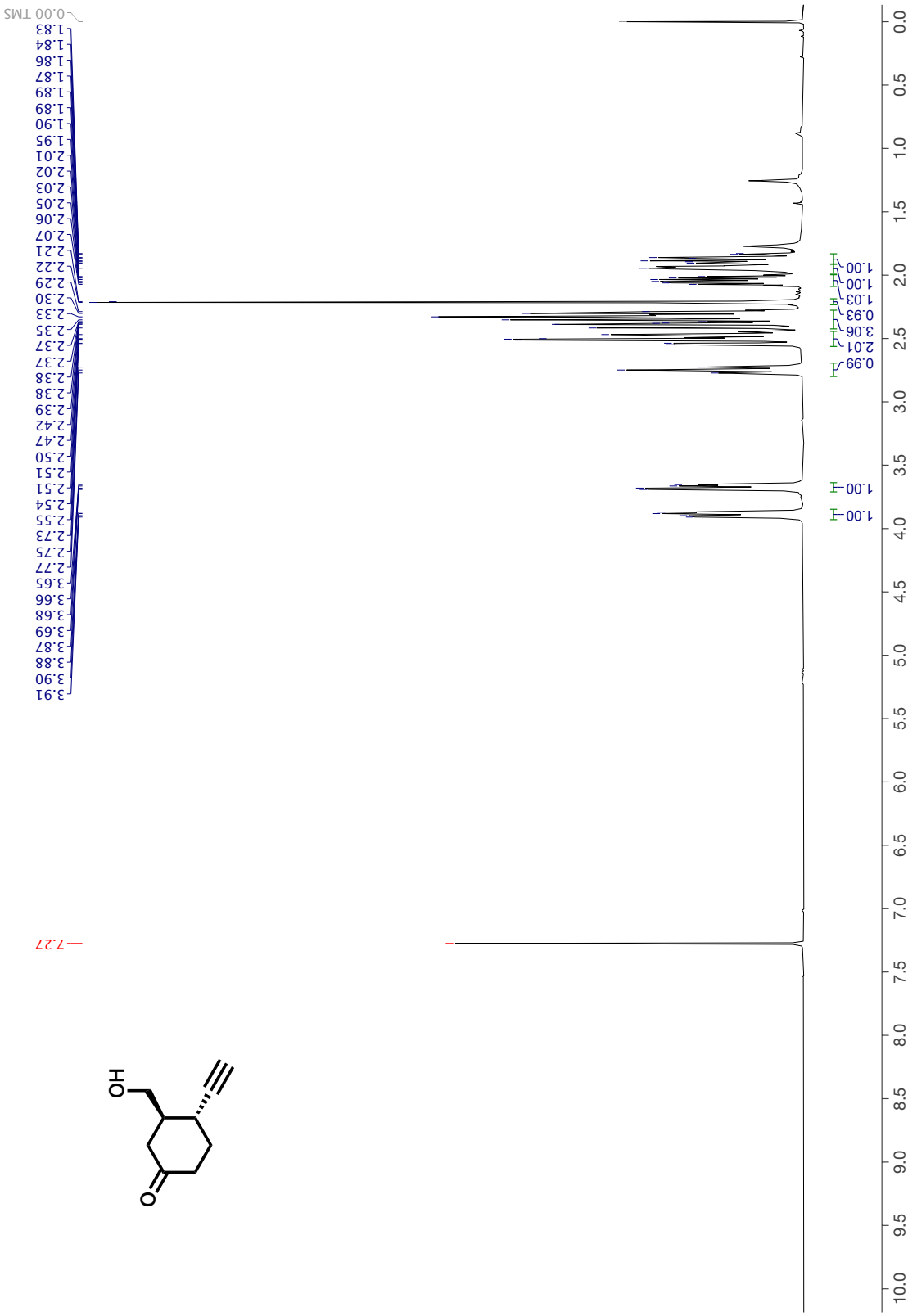


Figure A.6. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2.10**.

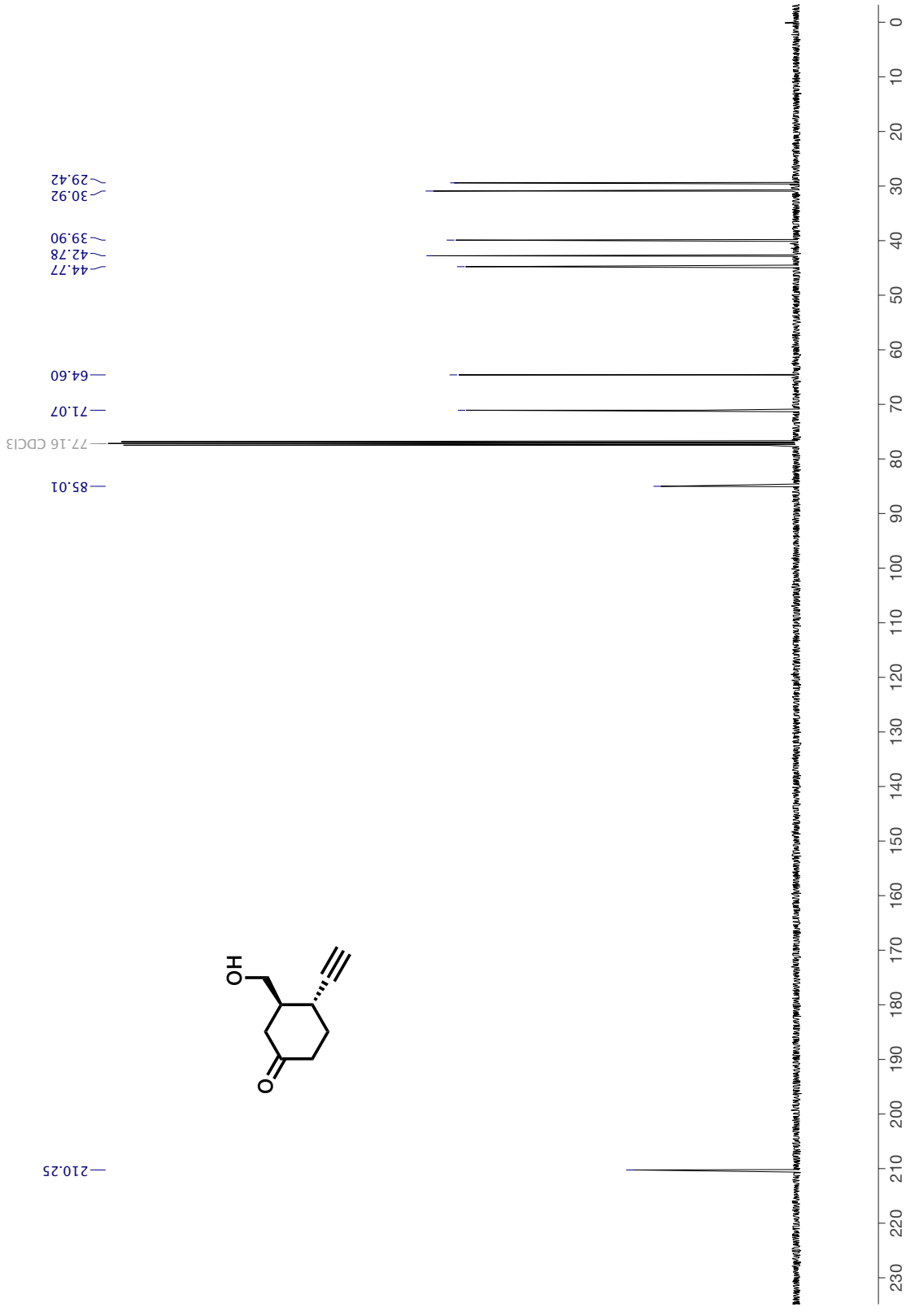


Figure A.7. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **2.10**.

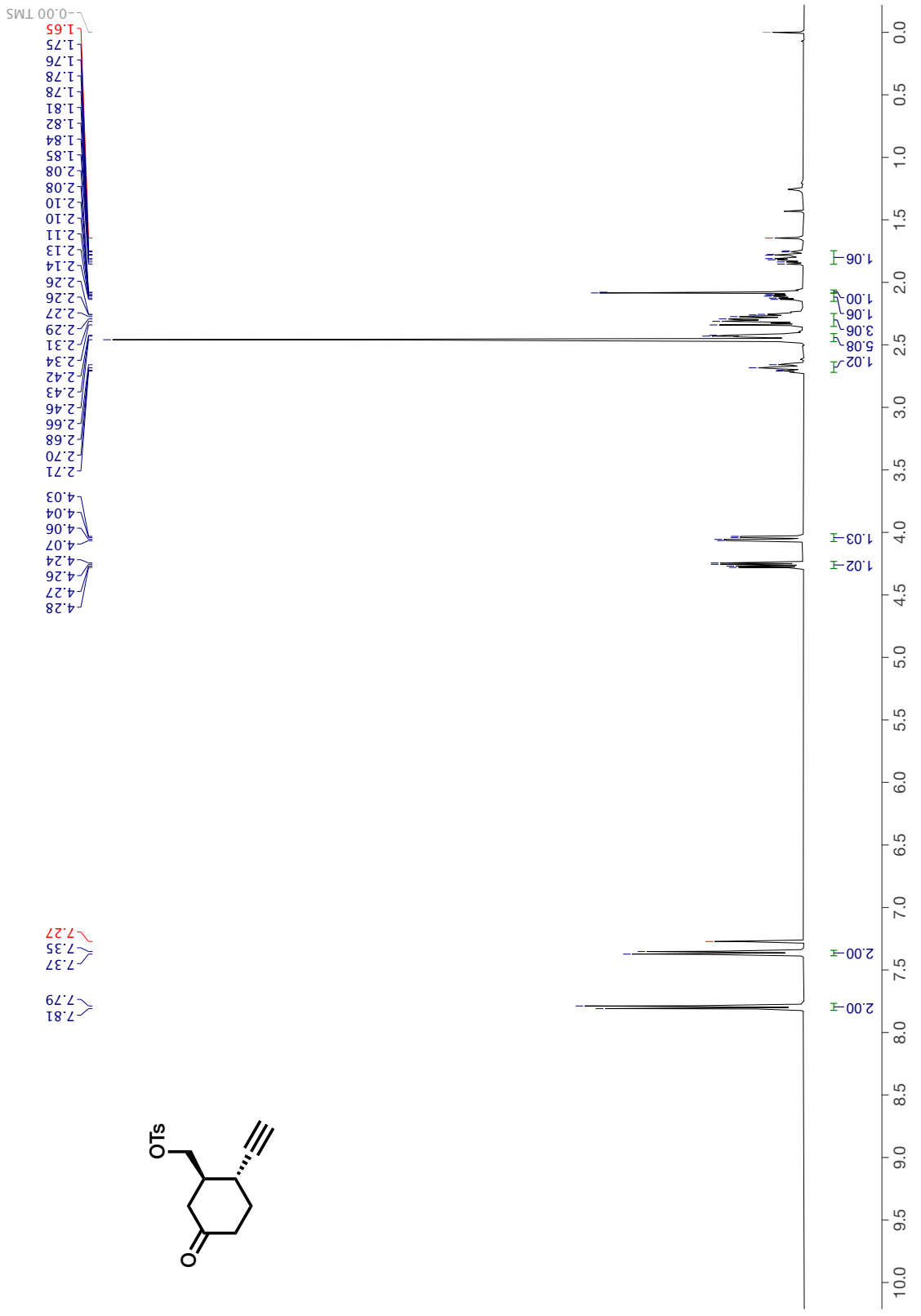


Figure A.8. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2.46**.

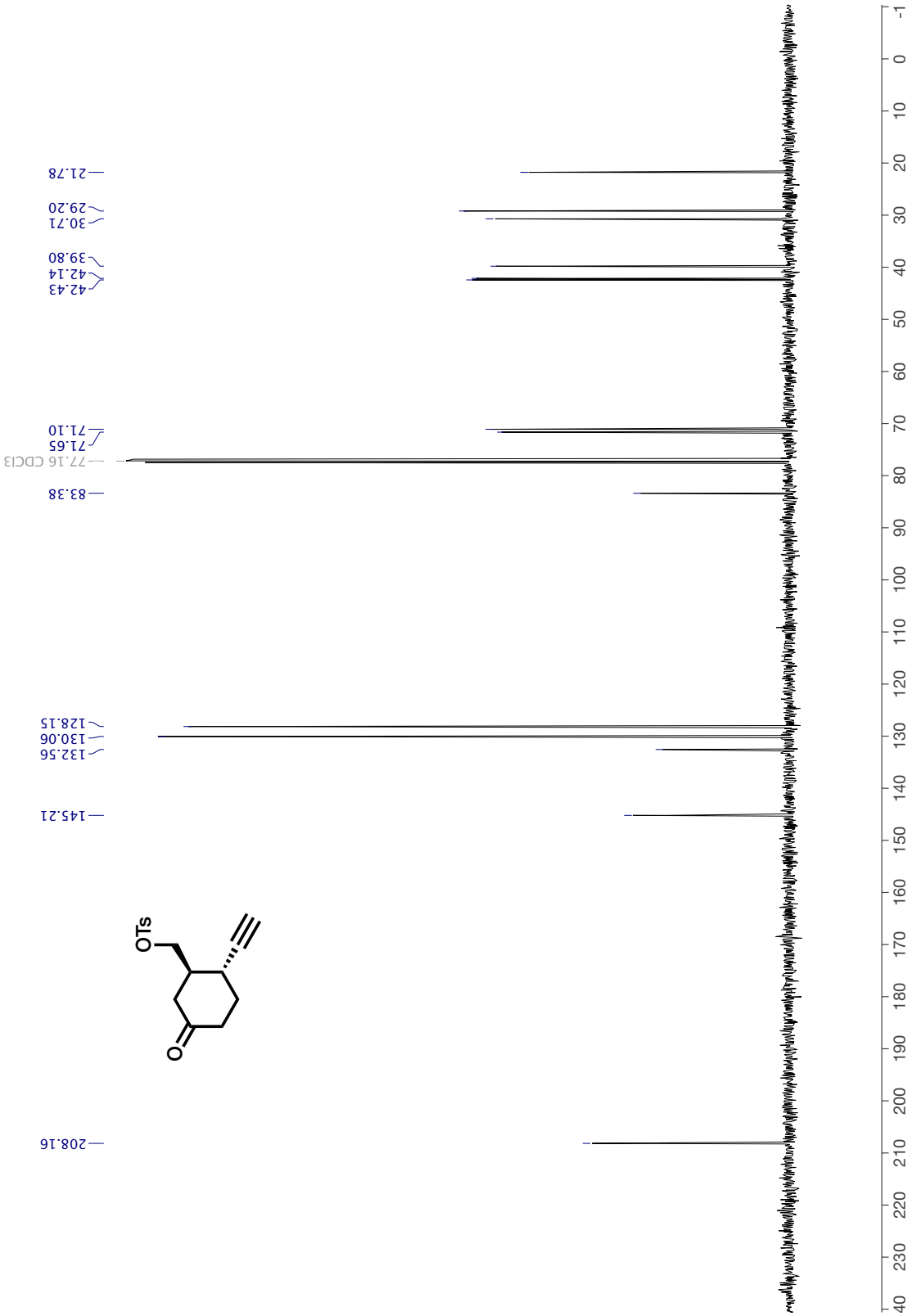


Figure A.9. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **2.46**.

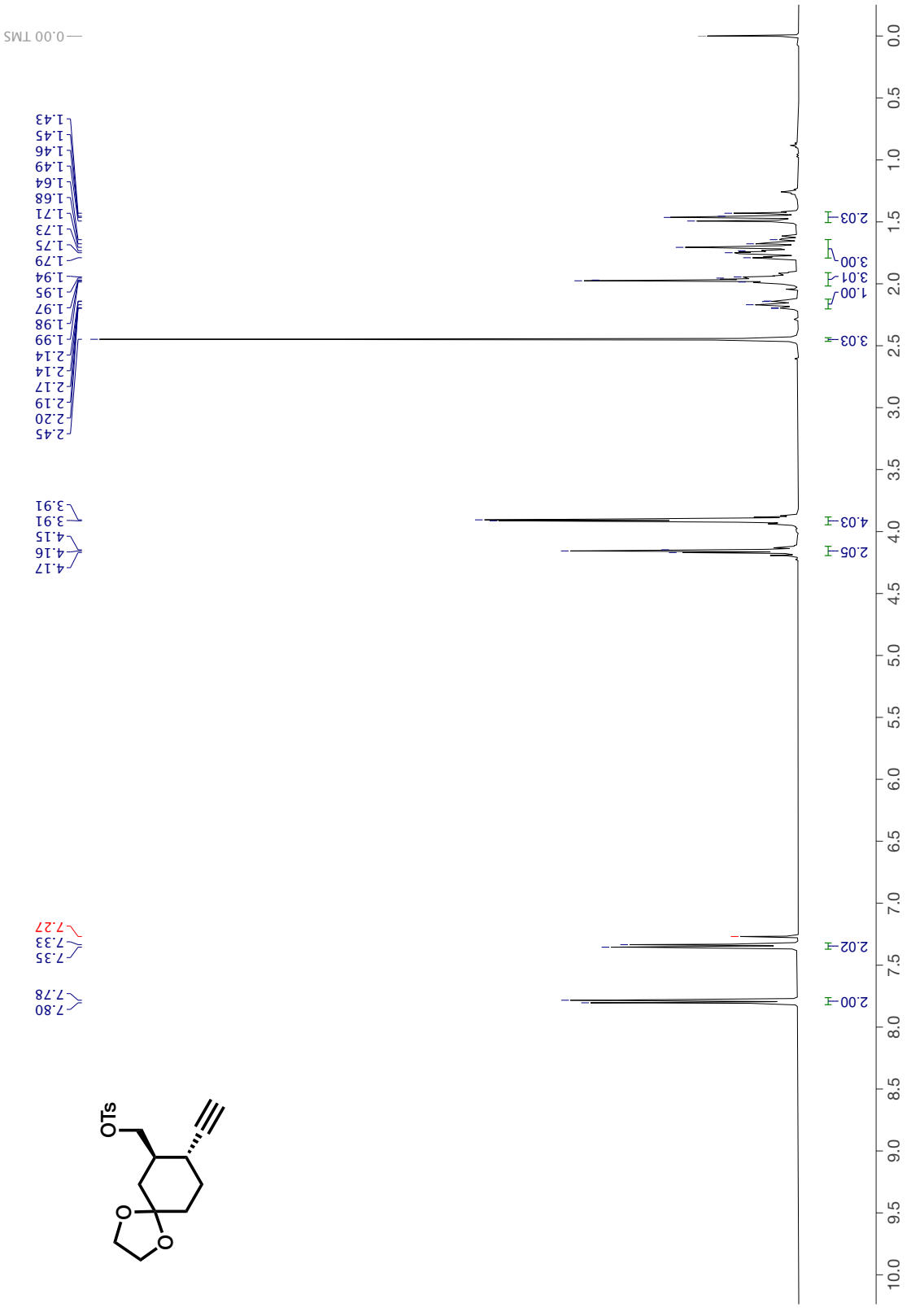


Figure A.10. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2.47**.

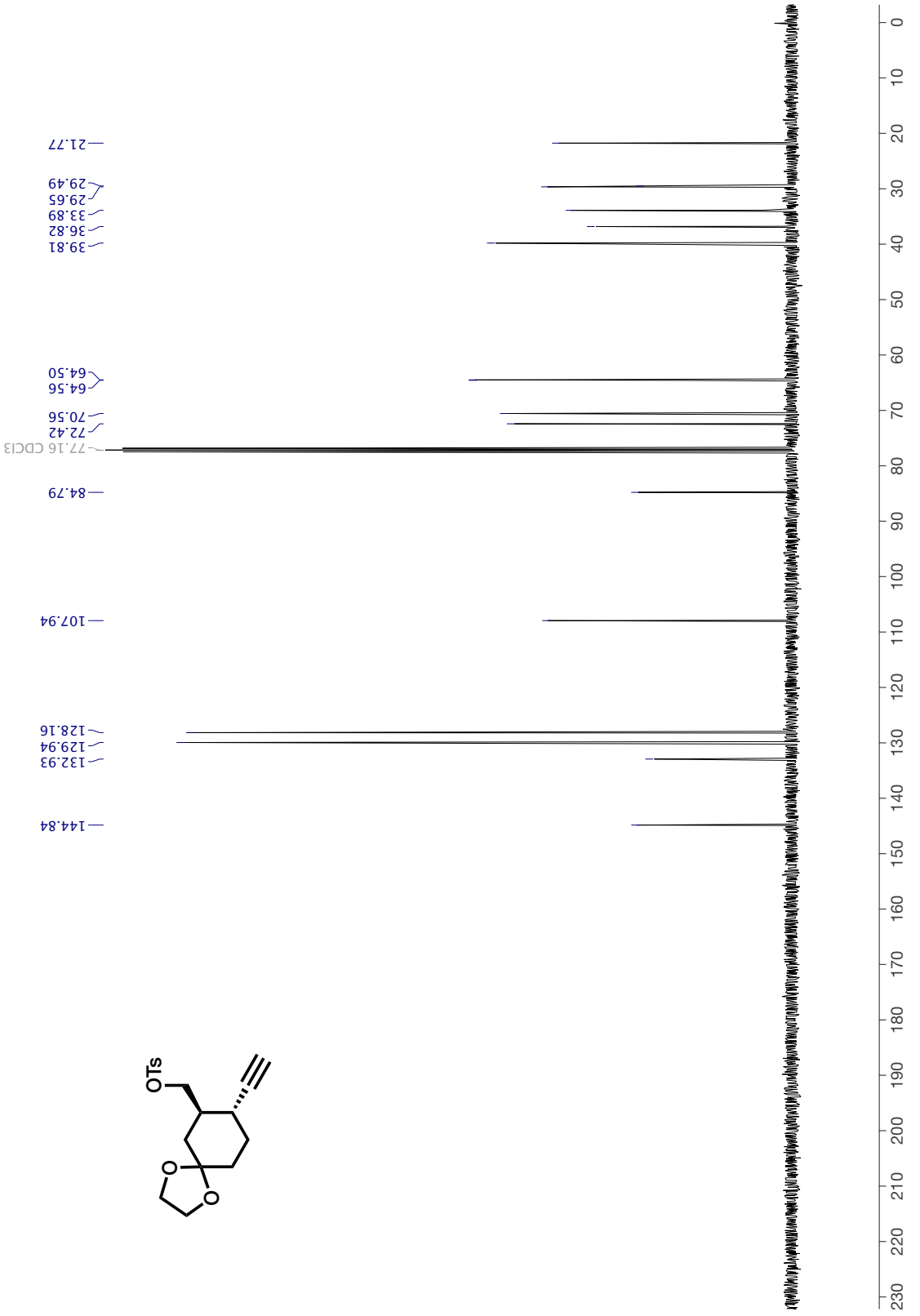


Figure A.11. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **2.47**.

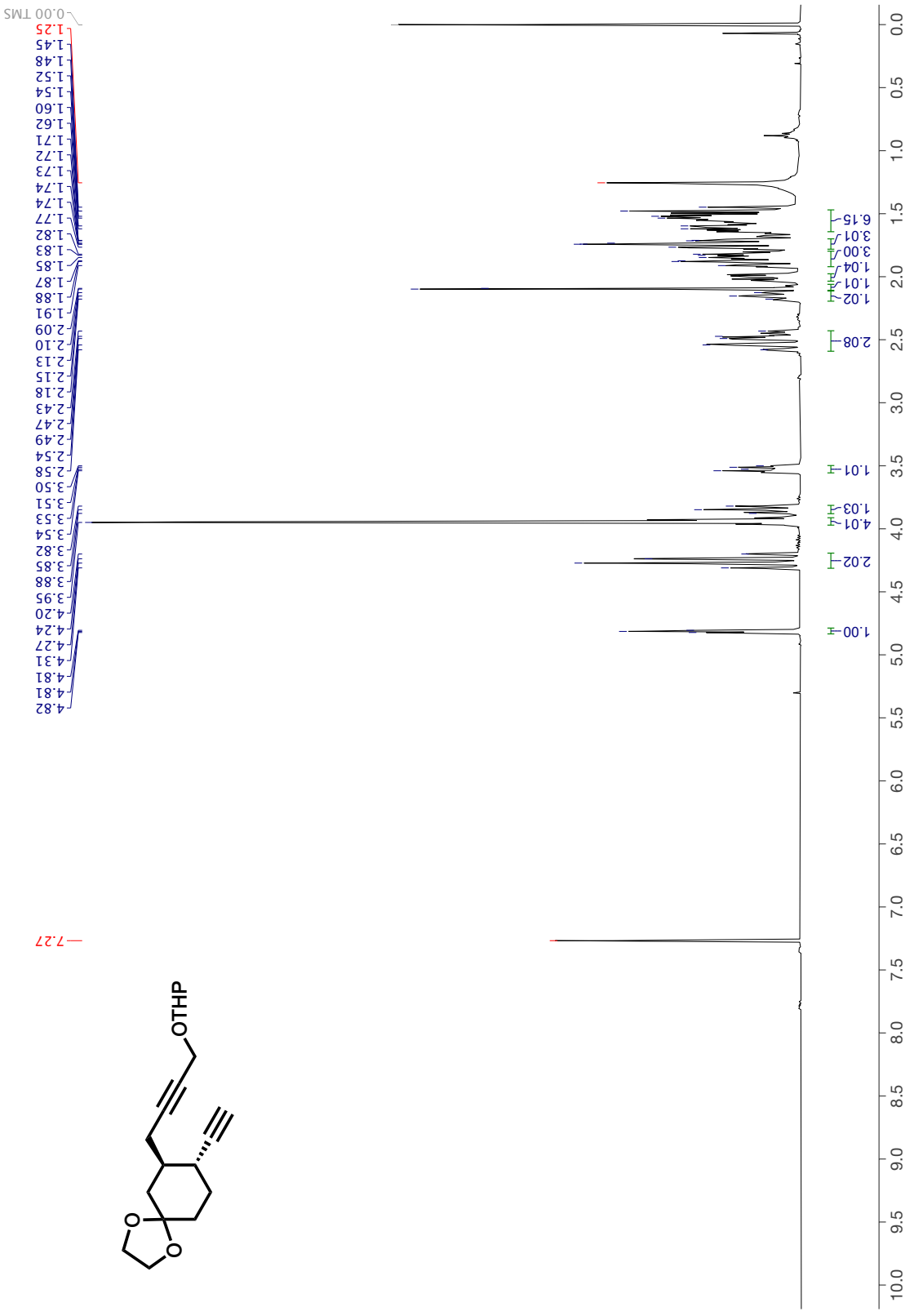


Figure A.12. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2.11**.

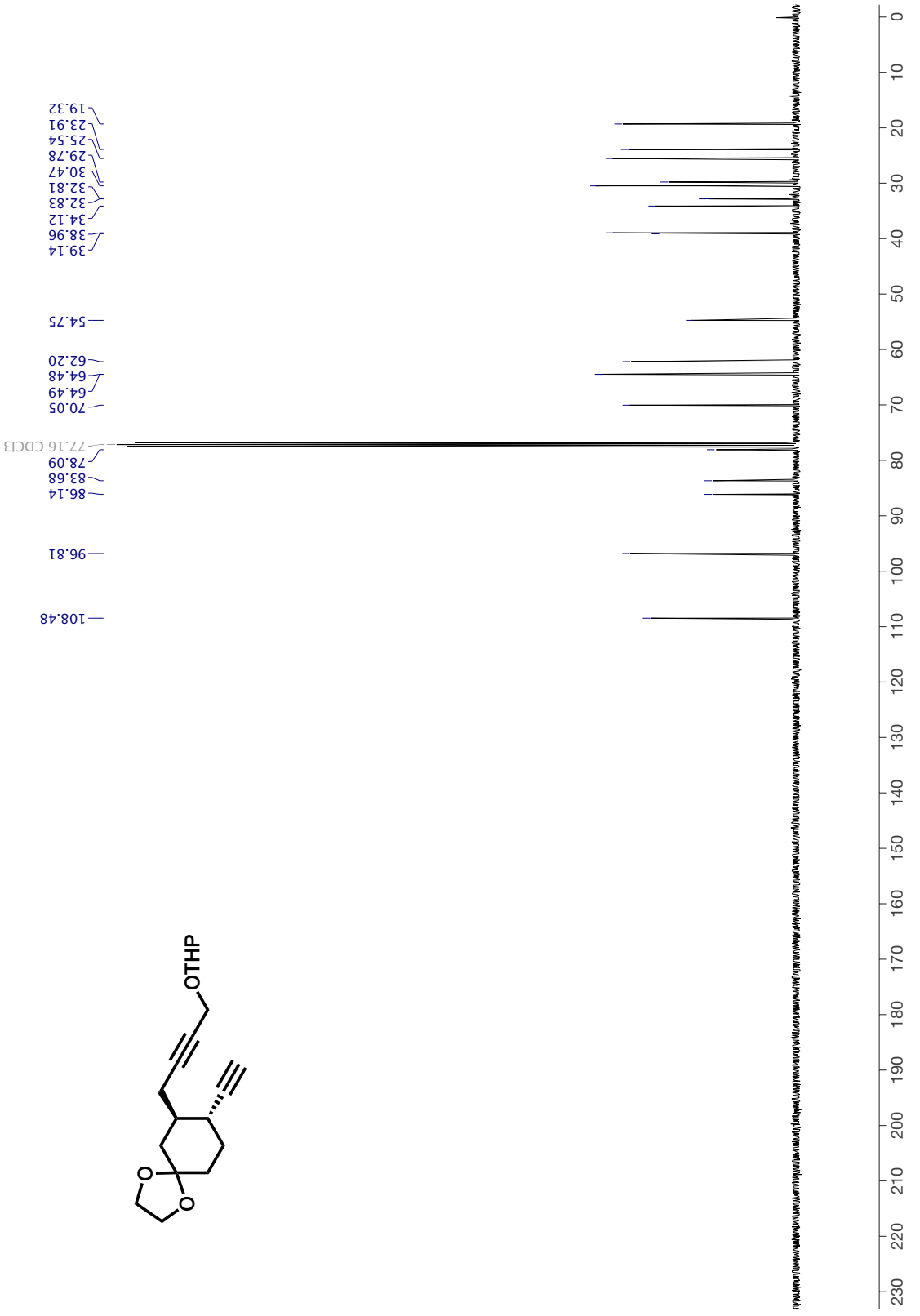


Figure A.13. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **2.11**.

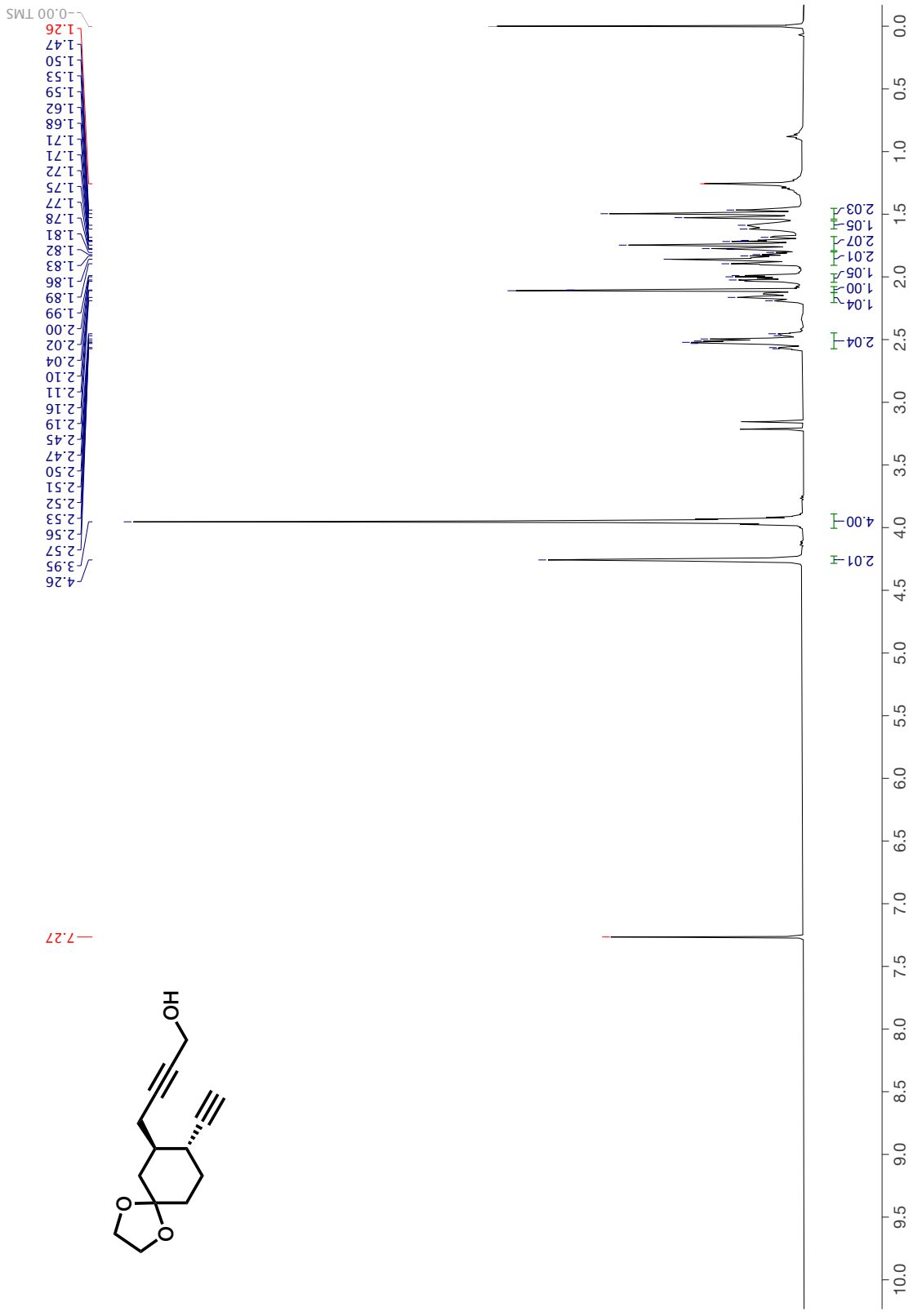


Figure A.14. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2.48**.

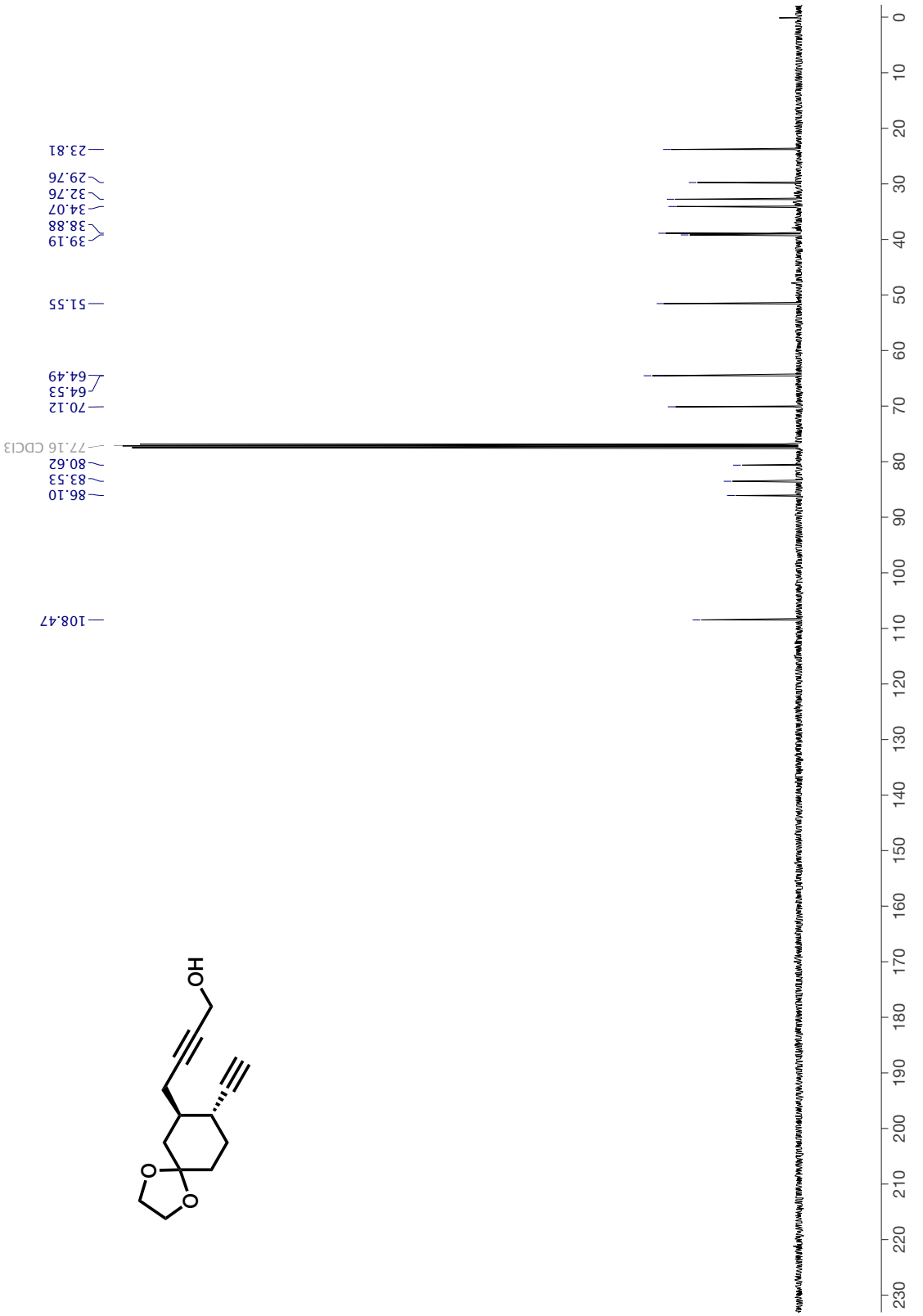


Figure A.15. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **2.48**.

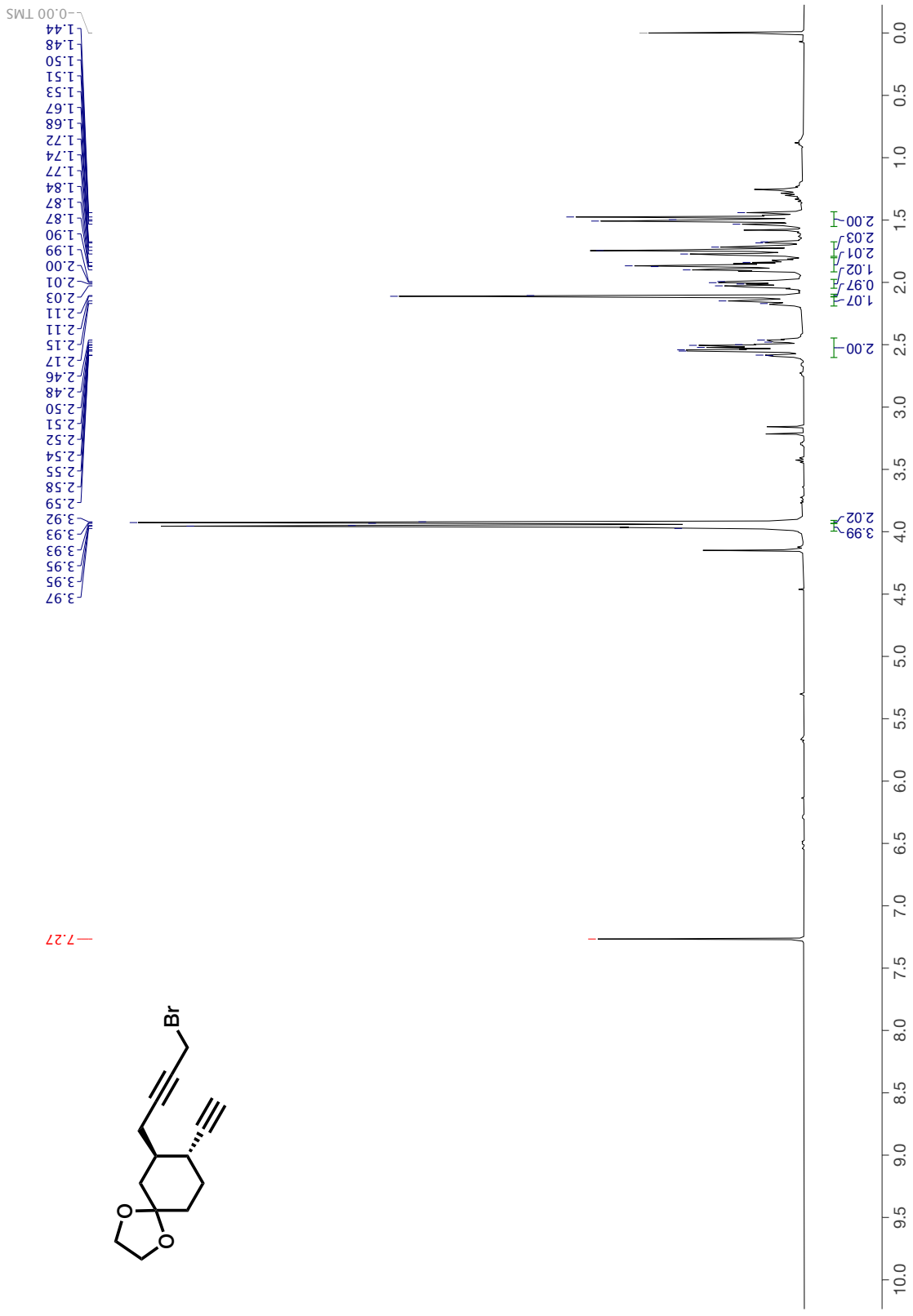


Figure A.16. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2.12**.

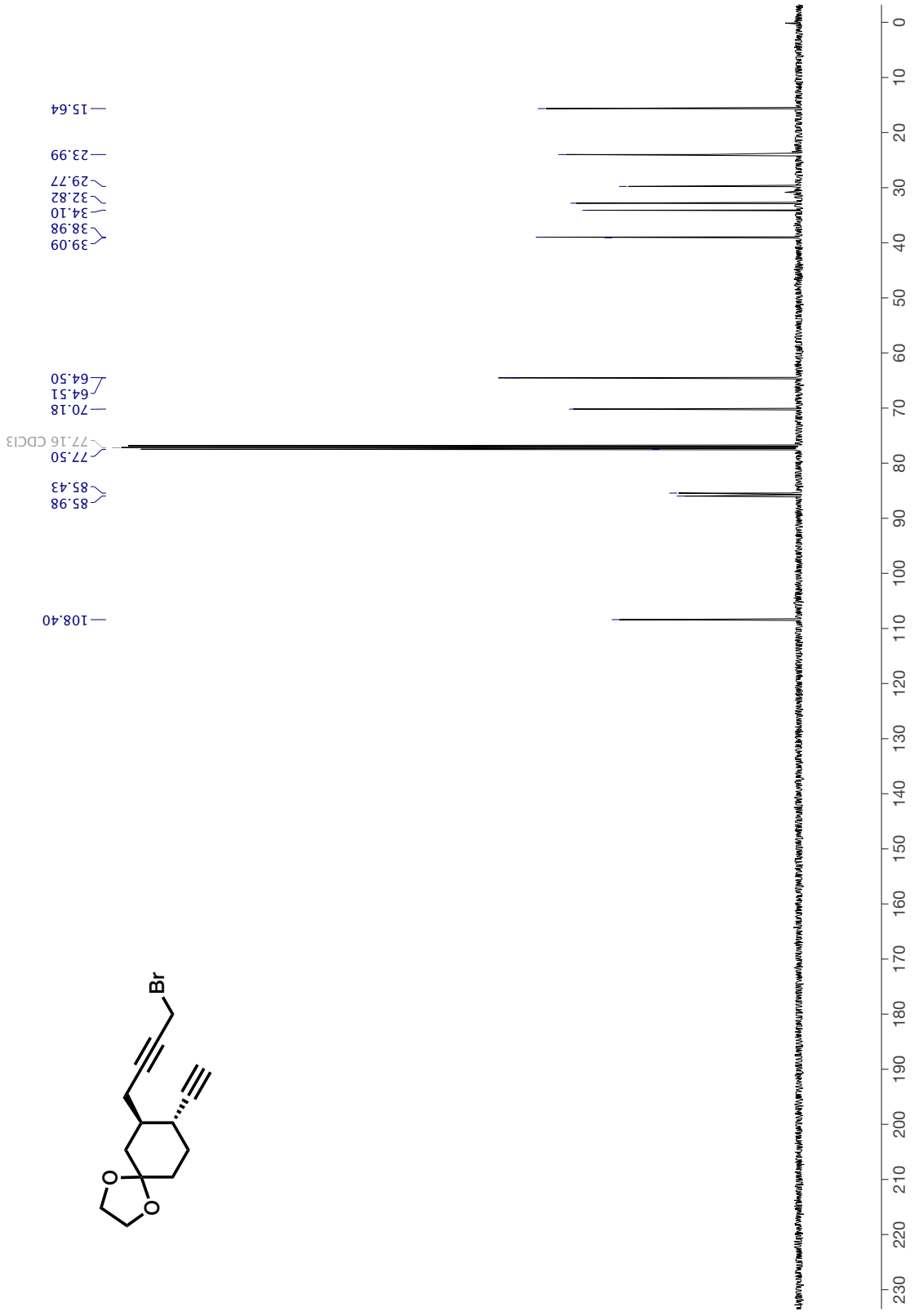


Figure A.17. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **2.12**.

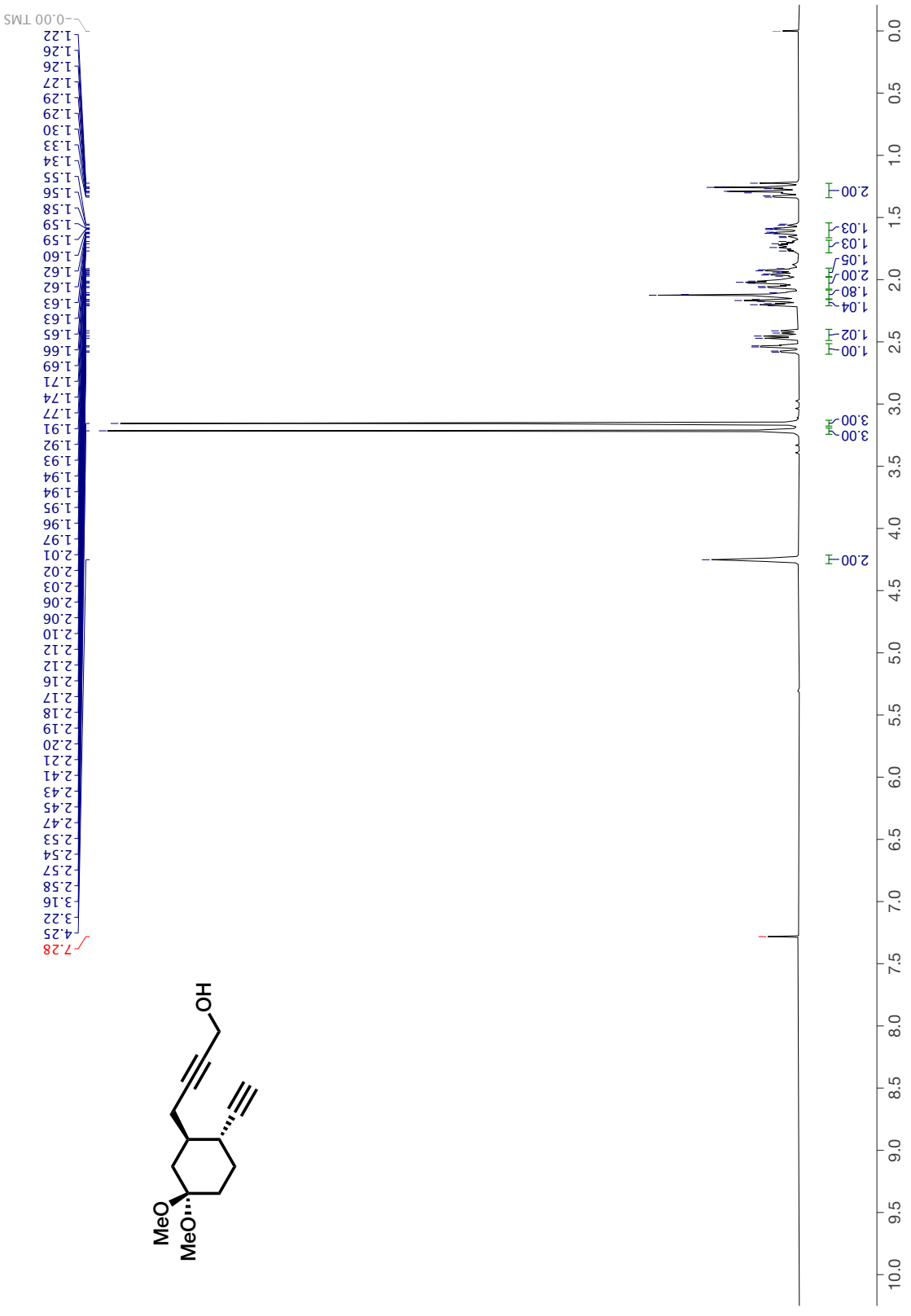


Figure A.18. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2.13**.

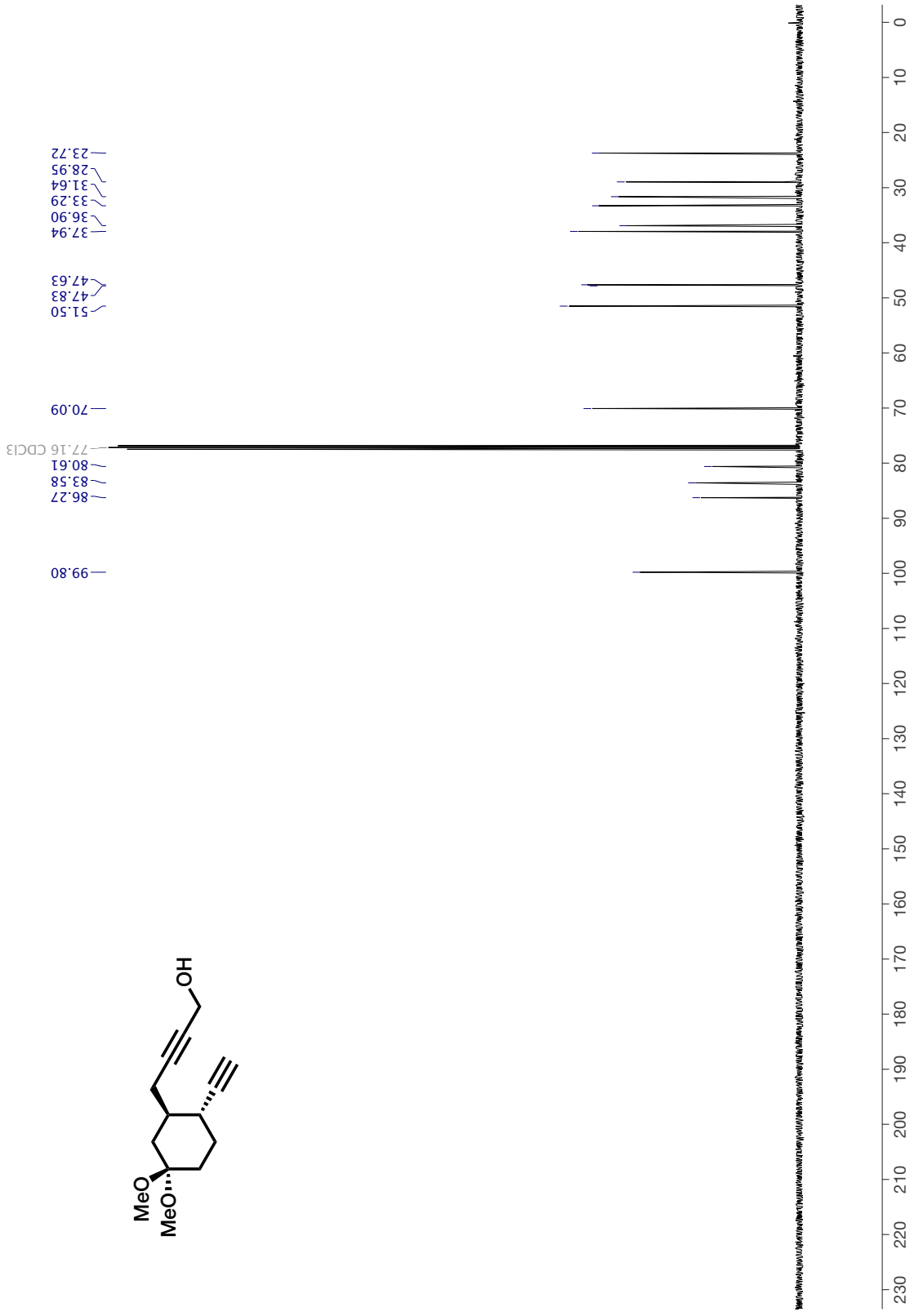


Figure A.19. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **2.13**.

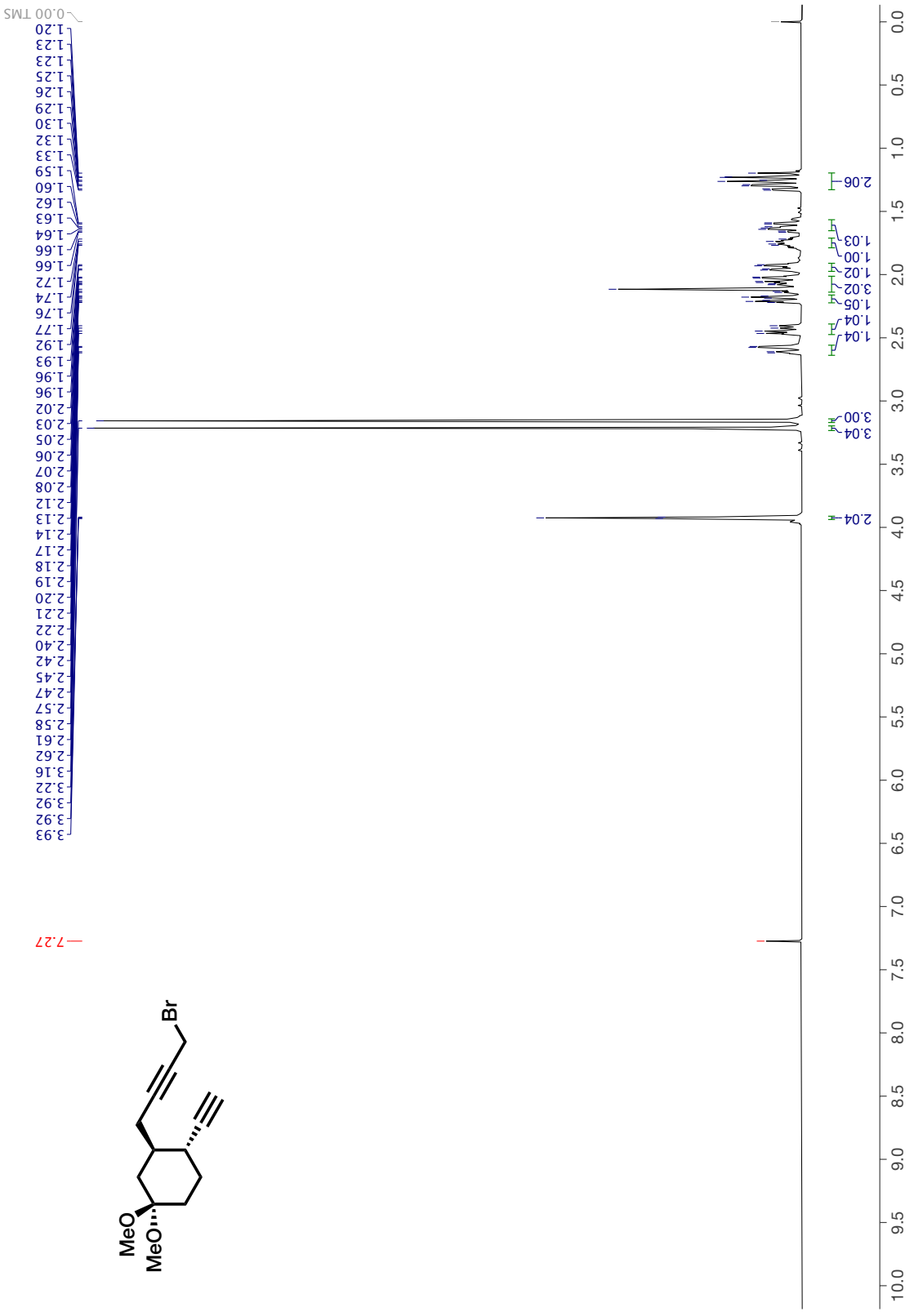


Figure A.20. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2.14**.

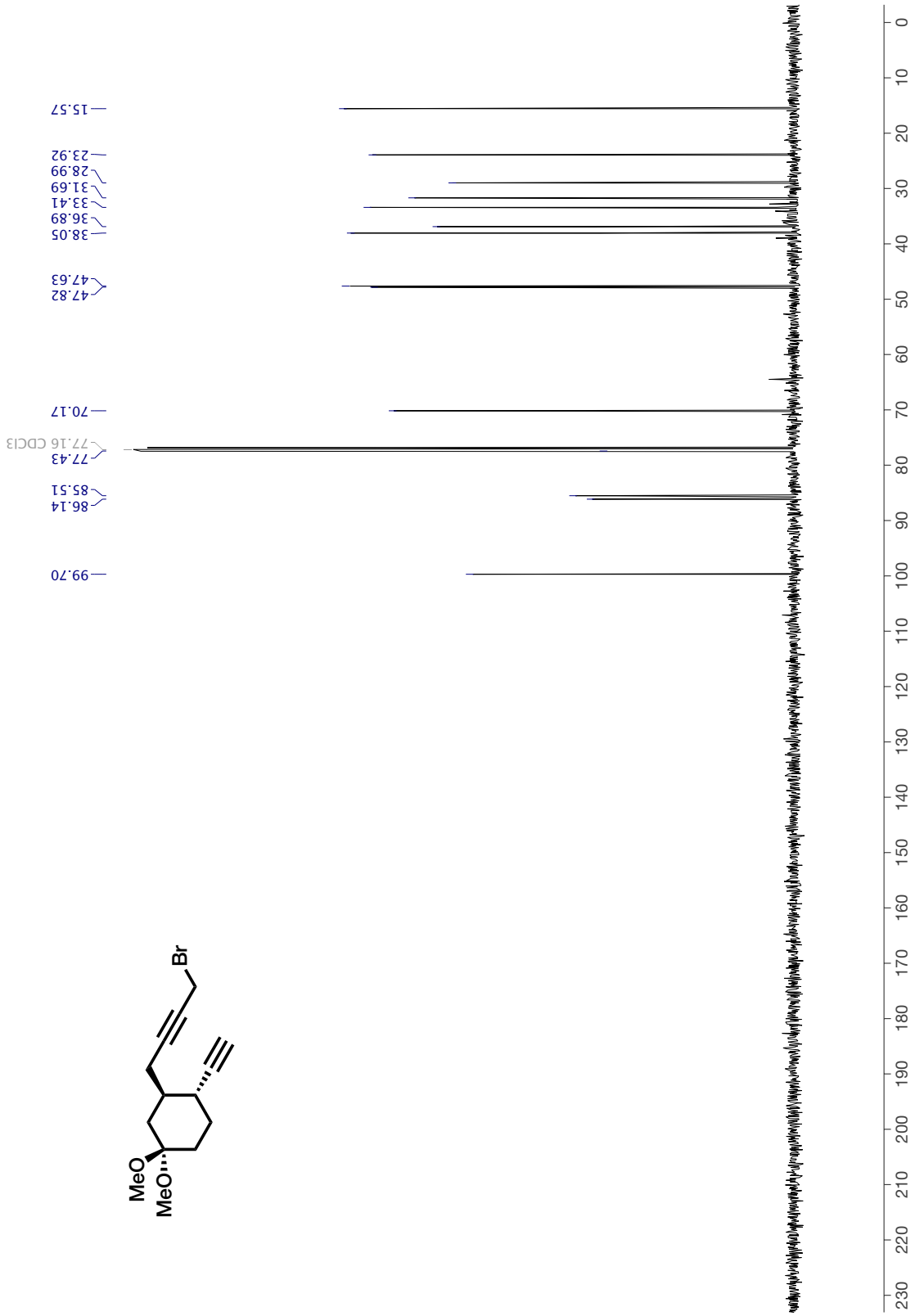


Figure A.21. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **2.14**.

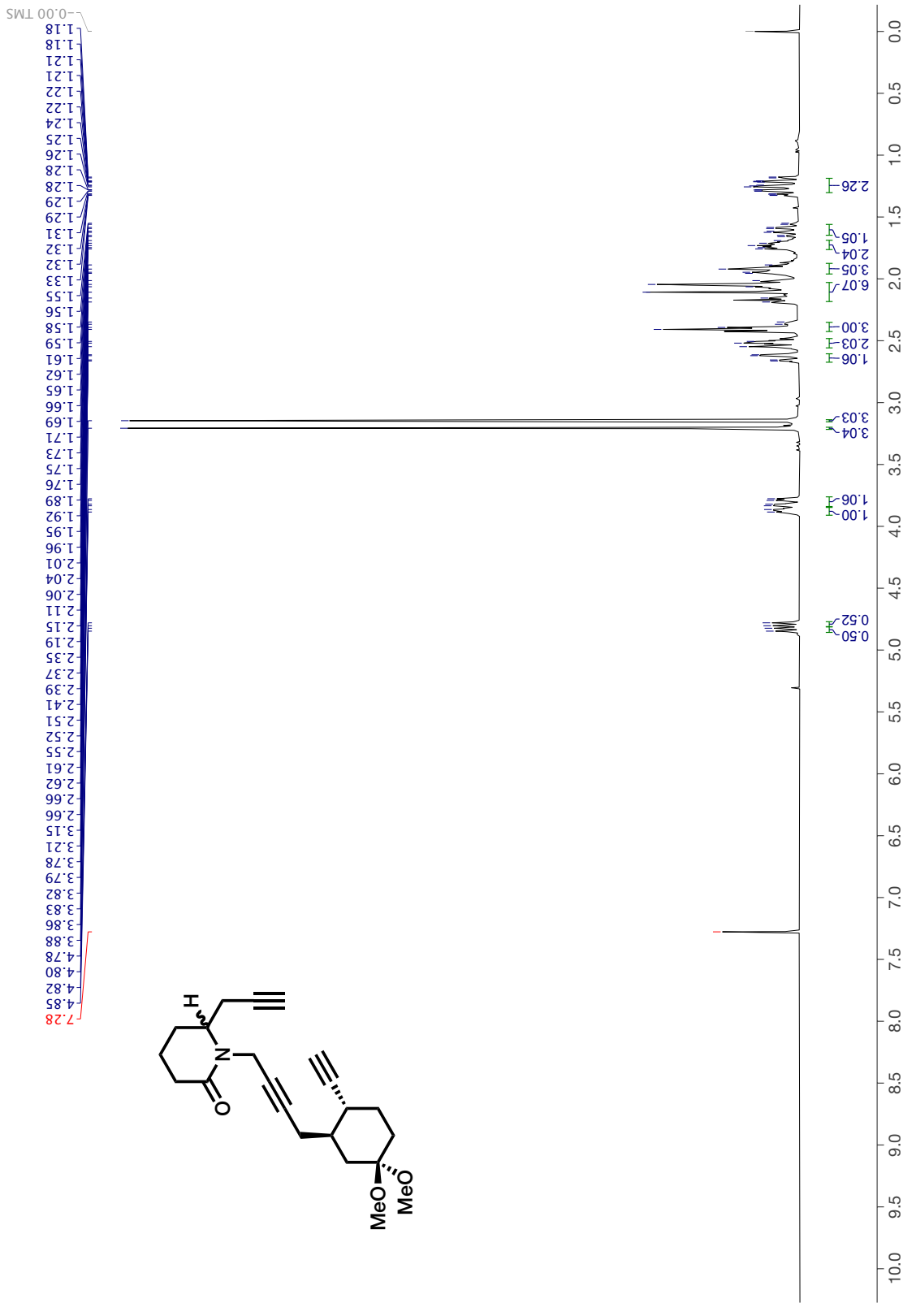


Figure A.22. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2.17**.

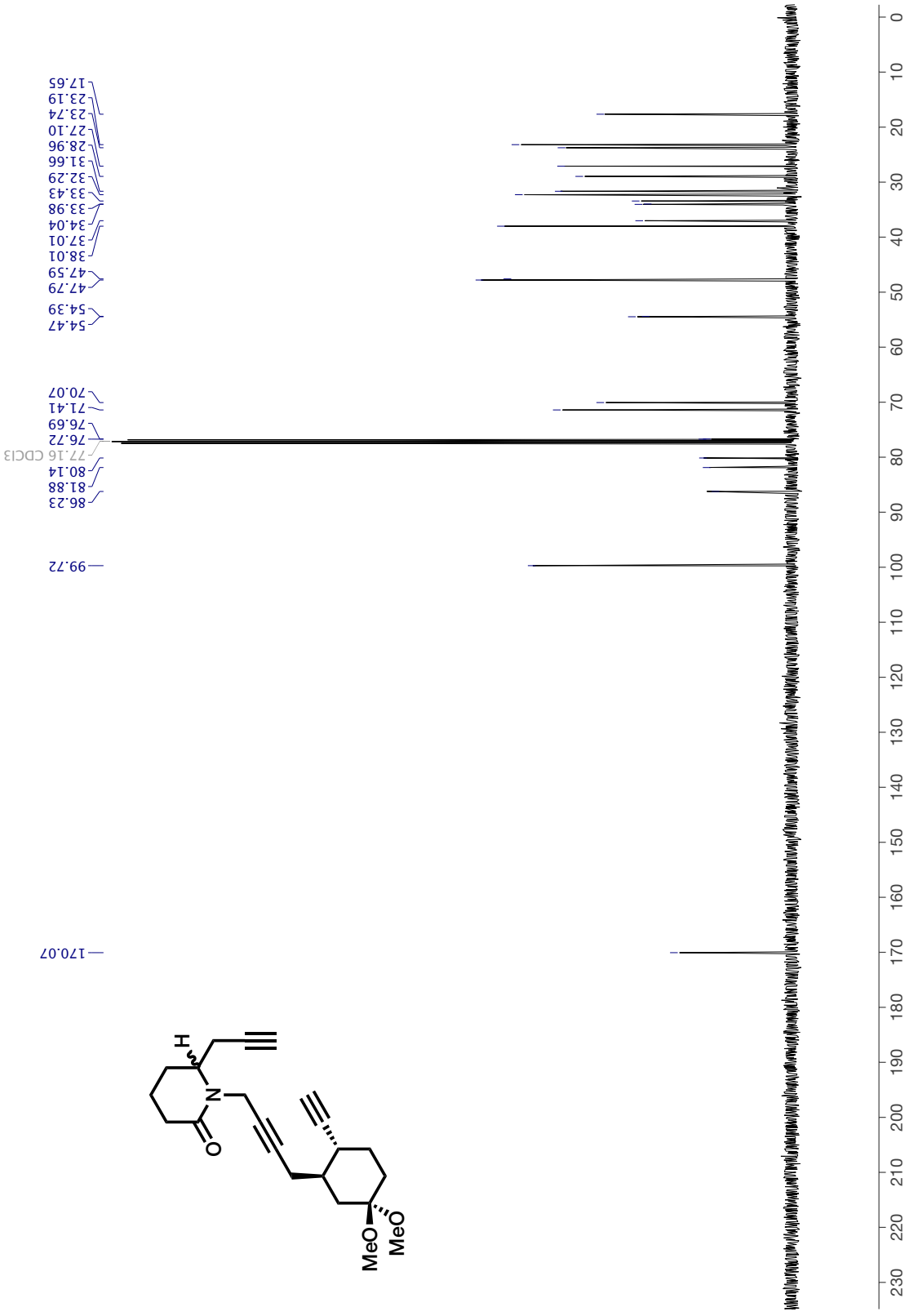


Figure A.23. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **2.17**.

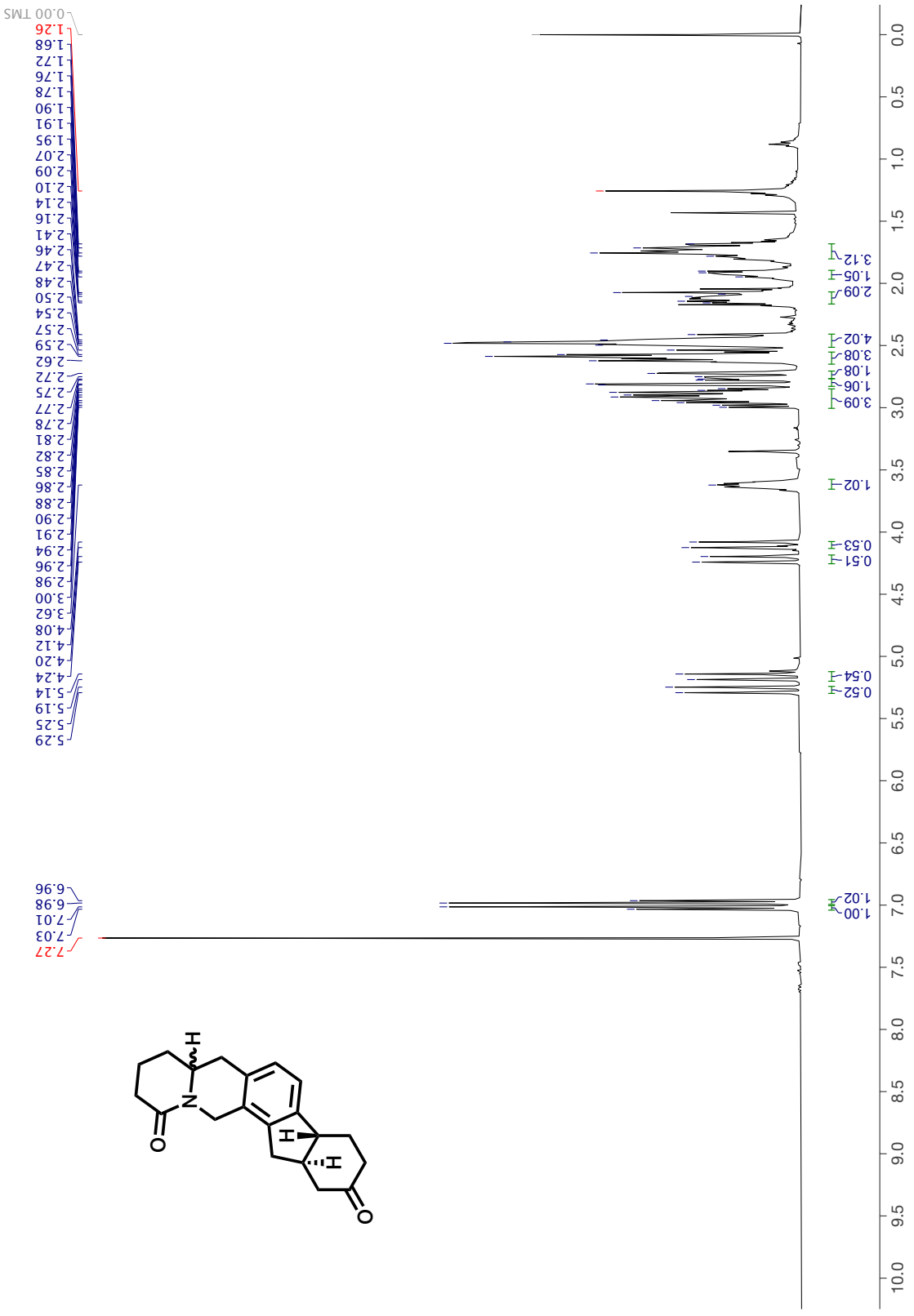


Figure A.24. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2.18**.

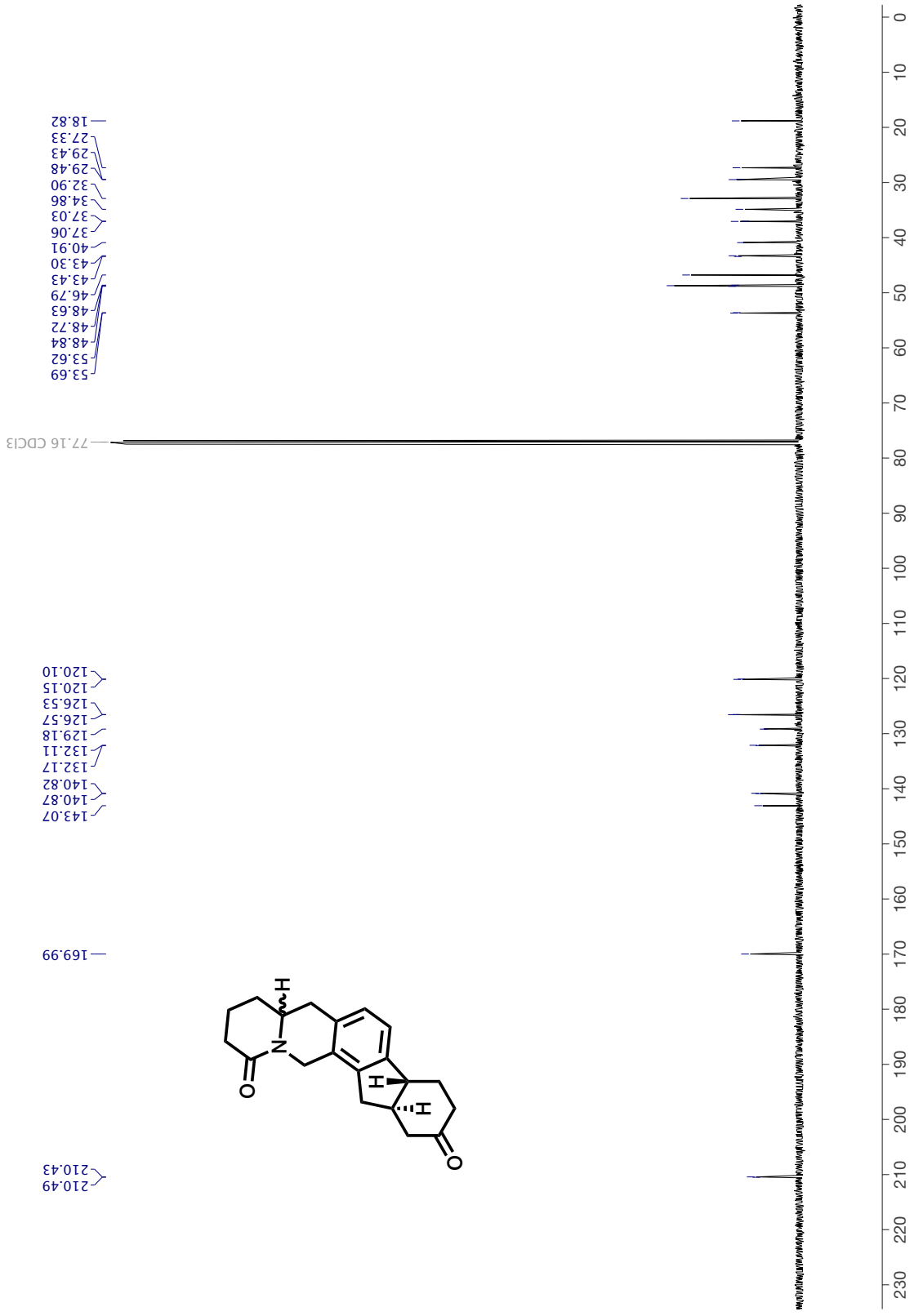


Figure A.25. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **2.18**.

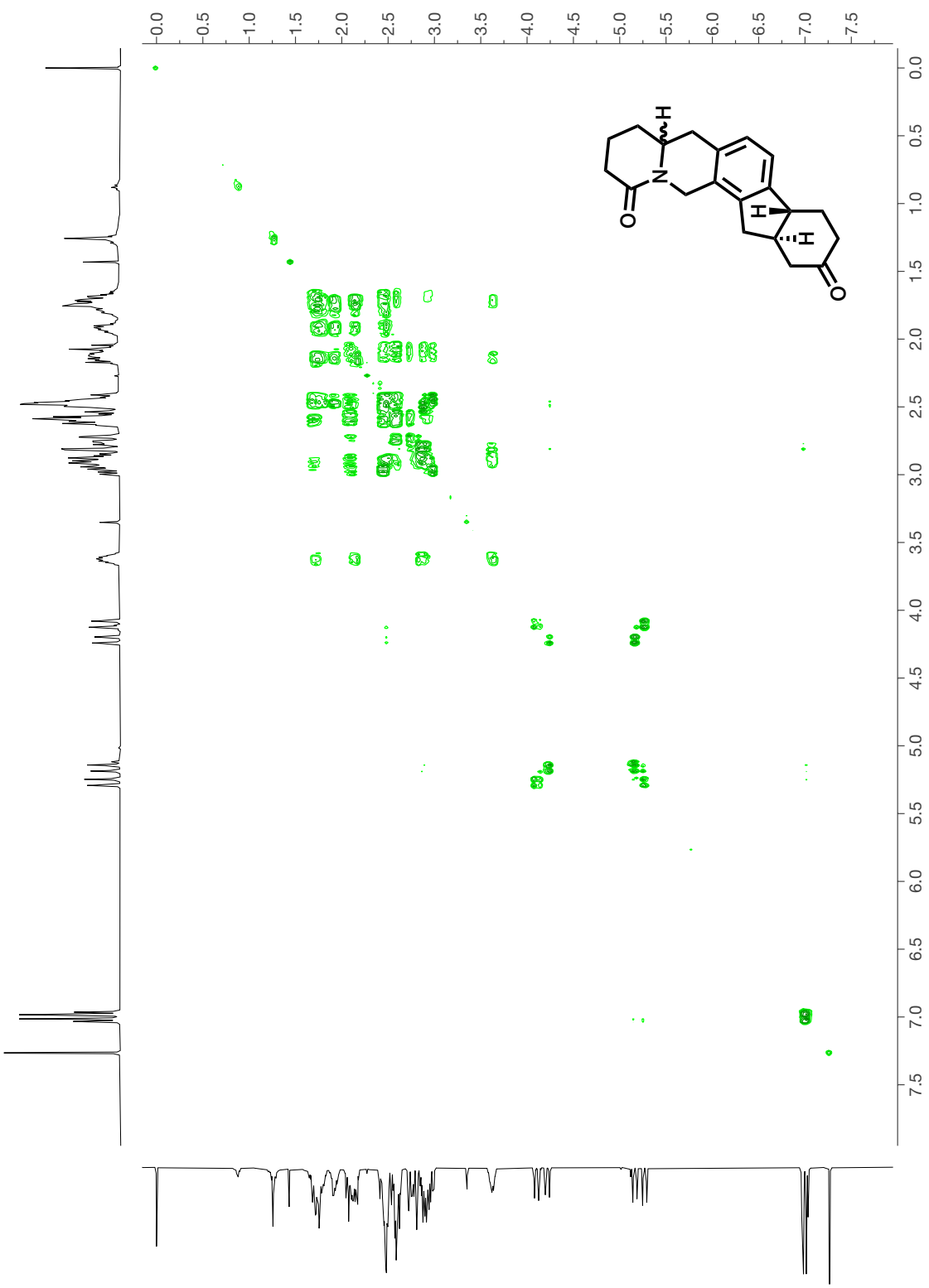


Figure A.26. ^{1}H–^{1}H COSY spectrum (400 MHz, $CDCl_3$) of **2.18**.

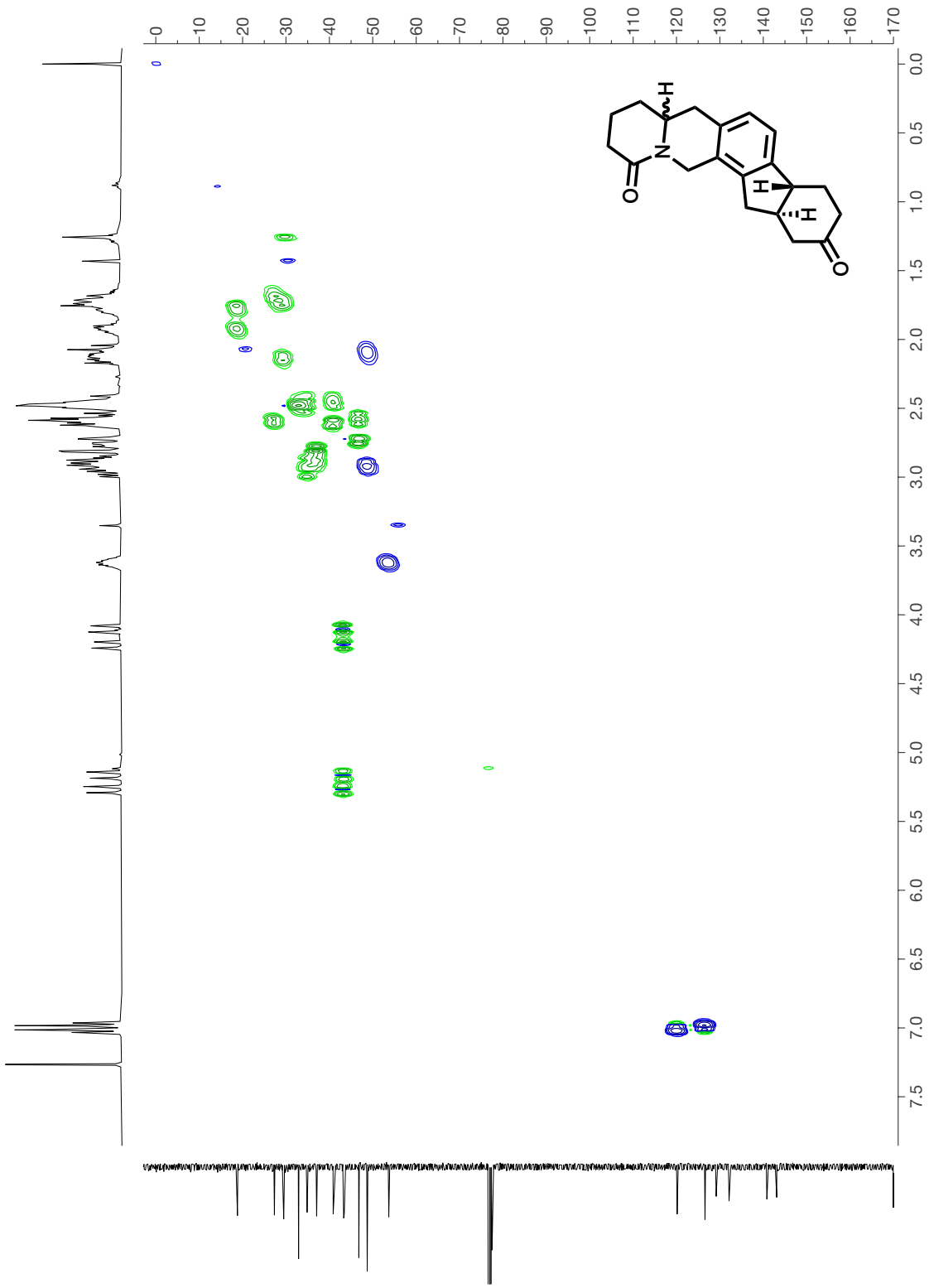


Figure A.27. $^{1}H–^{13}C$ HSQC spectrum (400 MHz, 101 MHz, $CDCl_3$) of **2.18**.

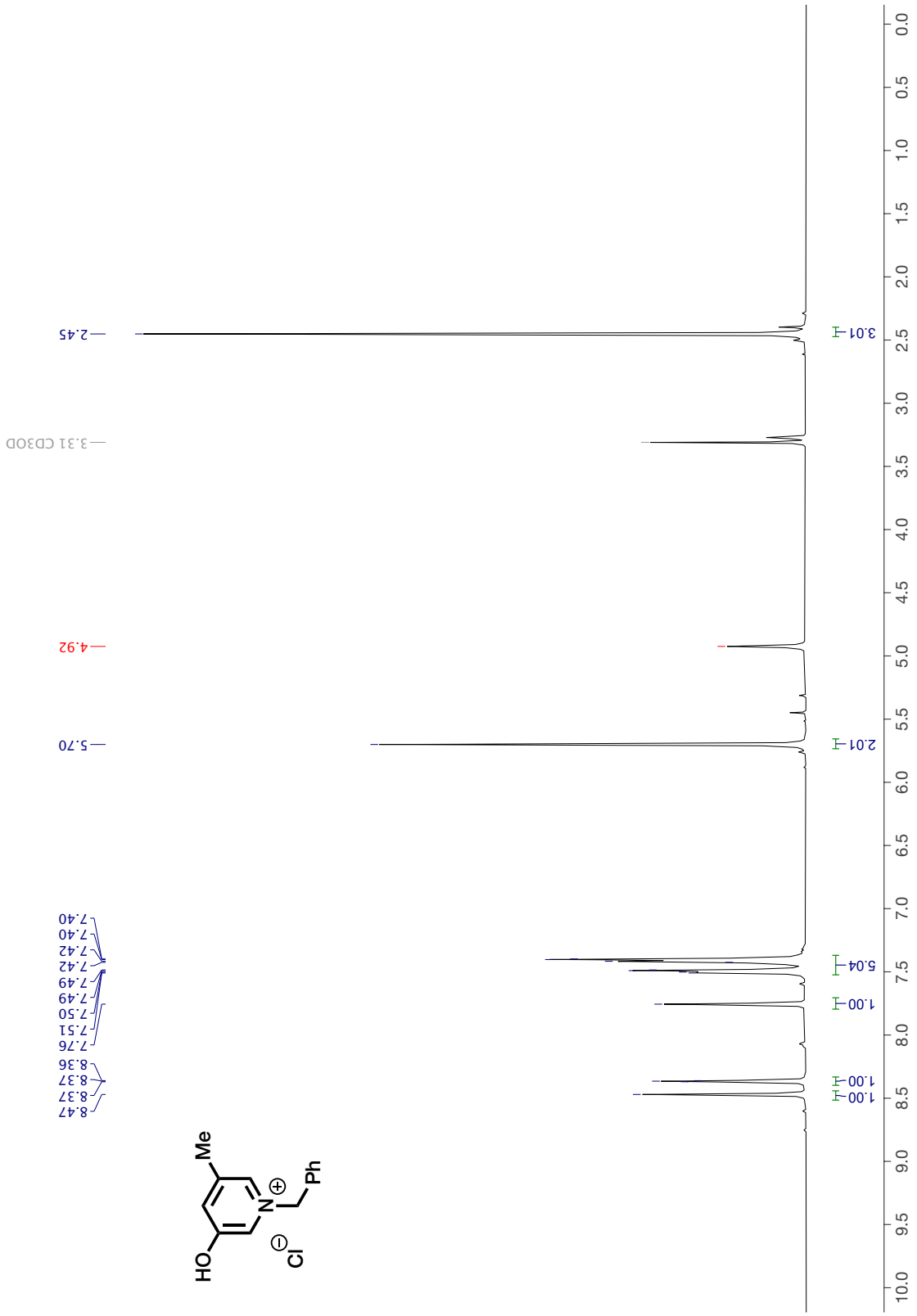


Figure A.28. ^{1}H NMR spectrum (400 MHz, CD_3OD) of **2.23**.

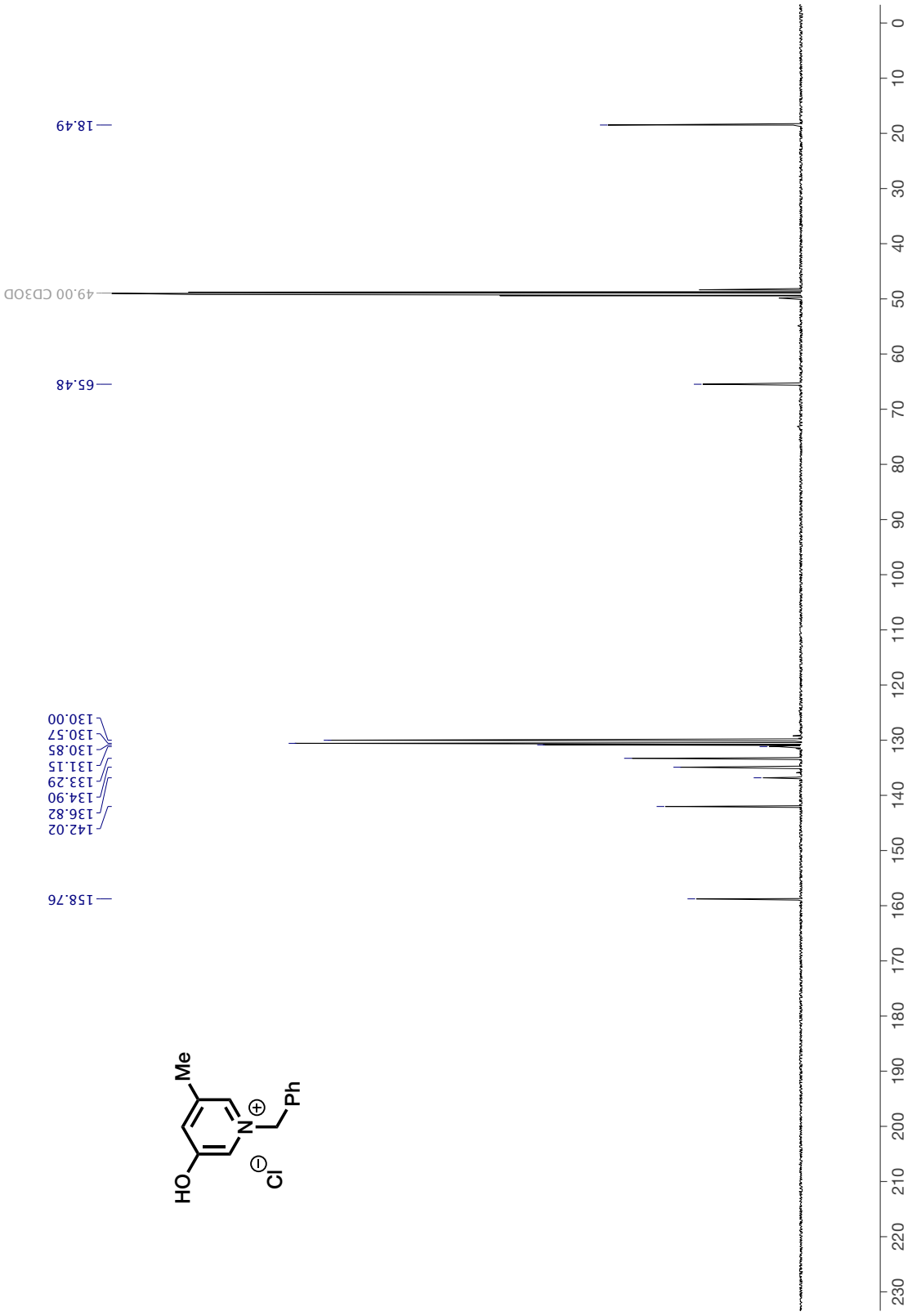


Figure X. ^{1}H NMR spectrum (101 MHz, CD_3OD) of **2.23**.

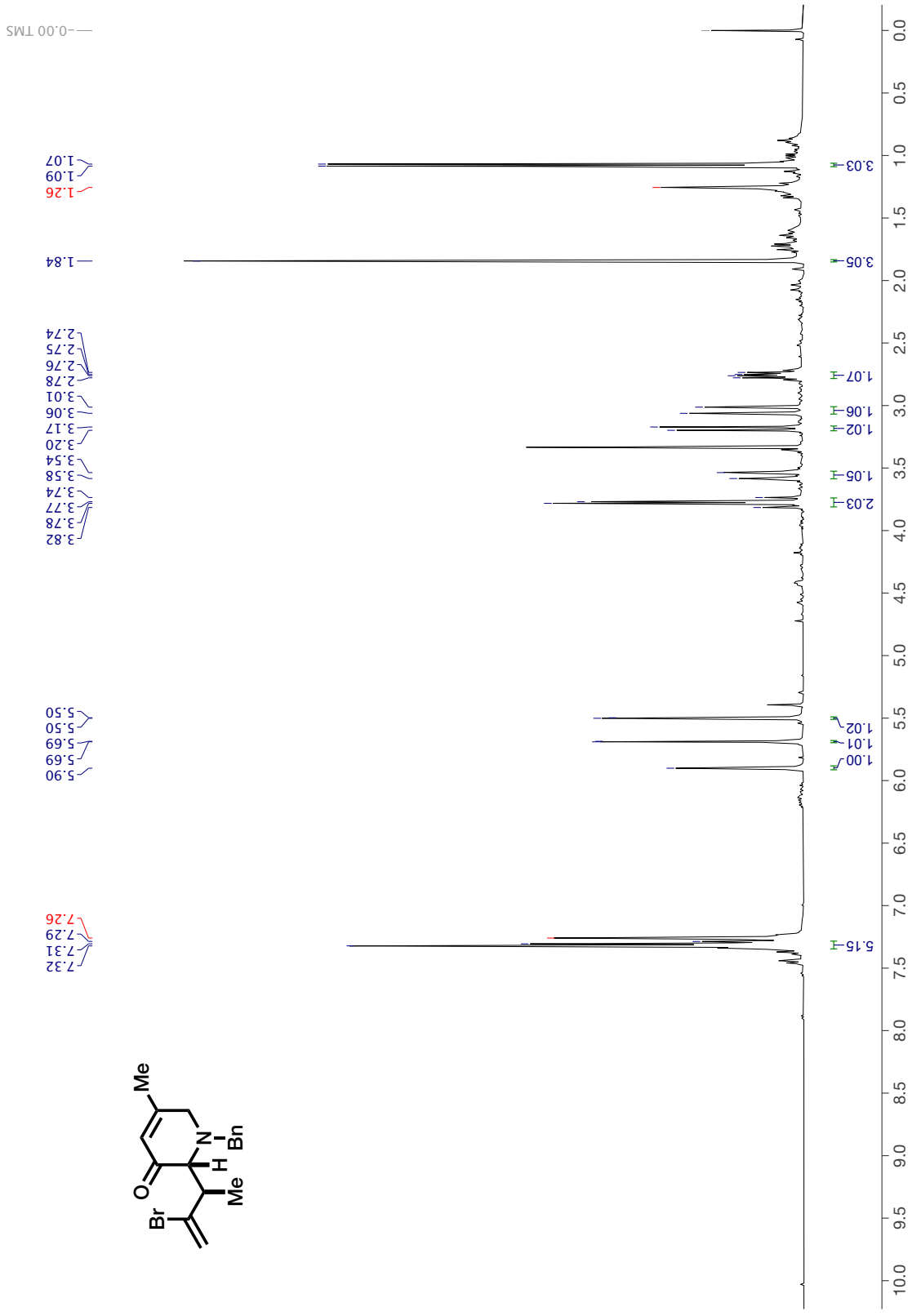


Figure A.30. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2.26**.

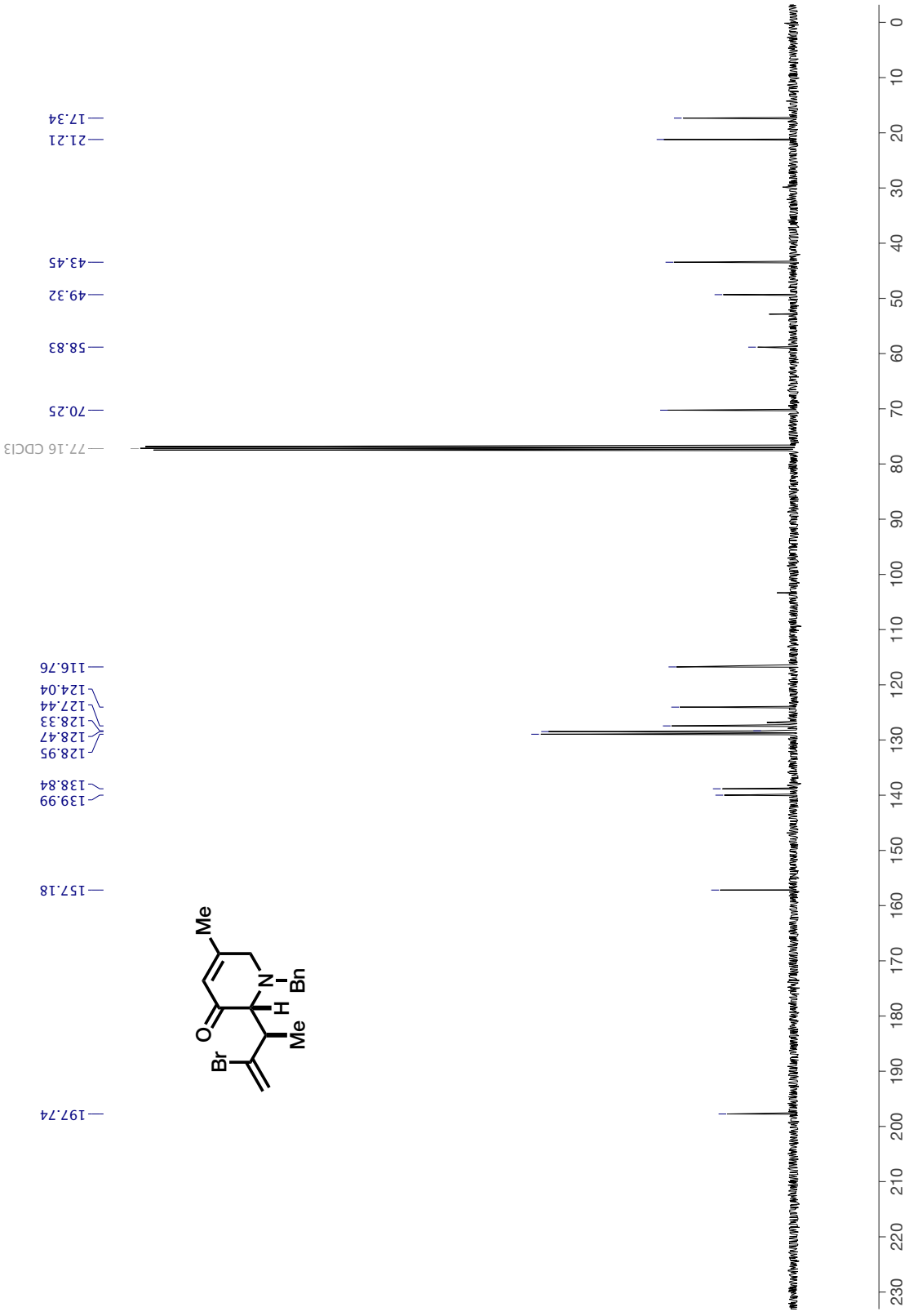


Figure A.31. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **2.26**.

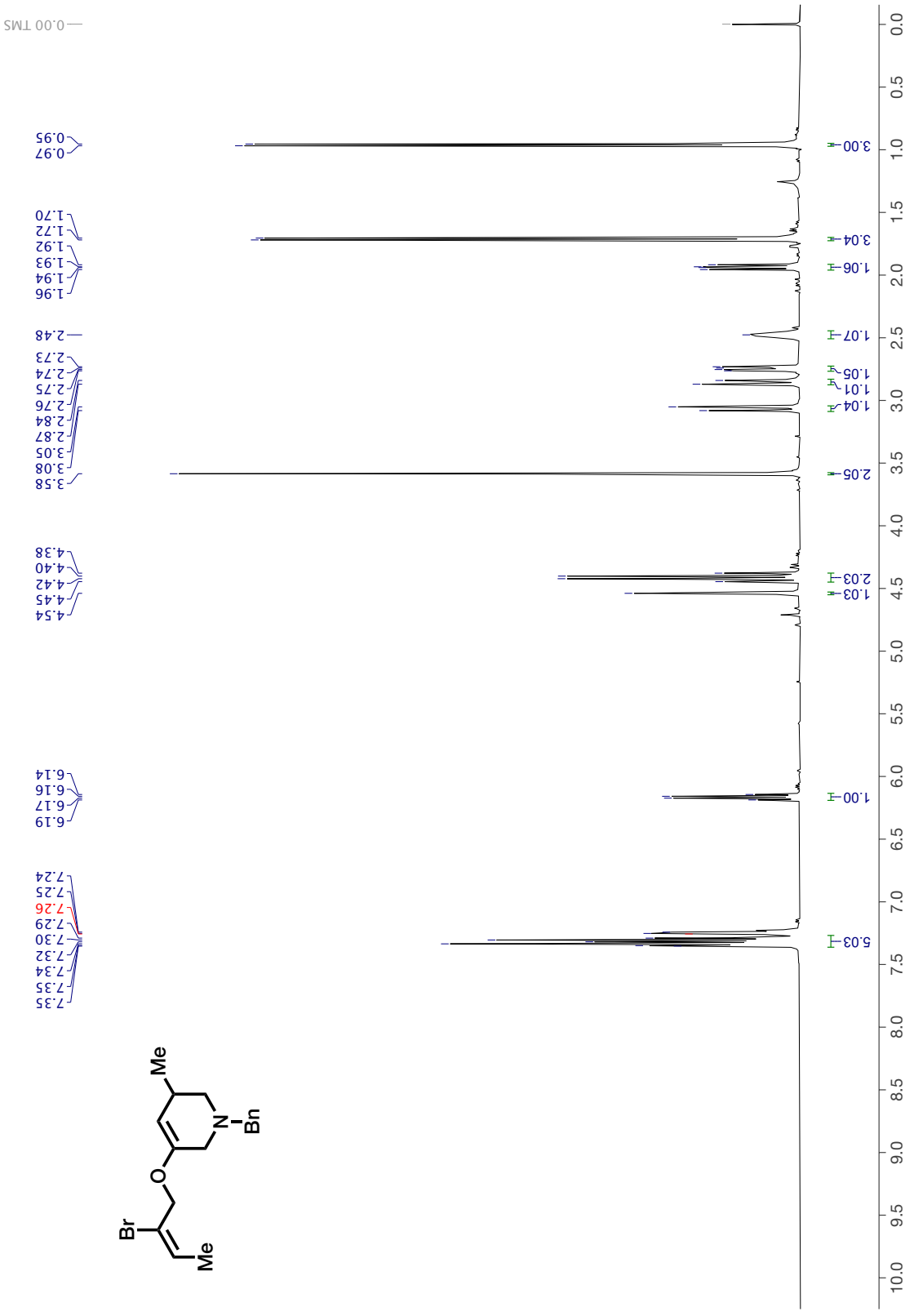


Figure A.32. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **2.27**.

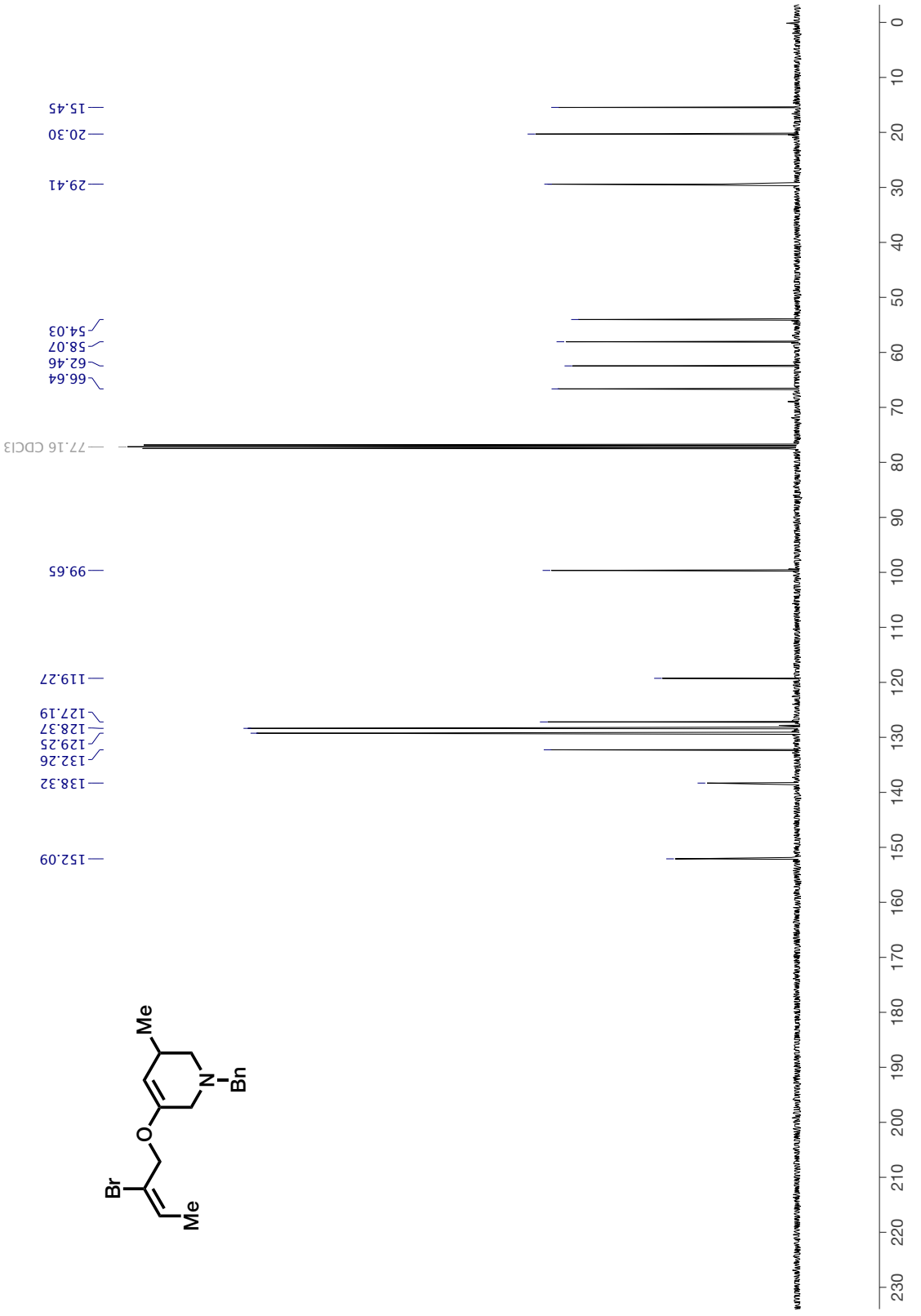


Figure A.33. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **2.27**.

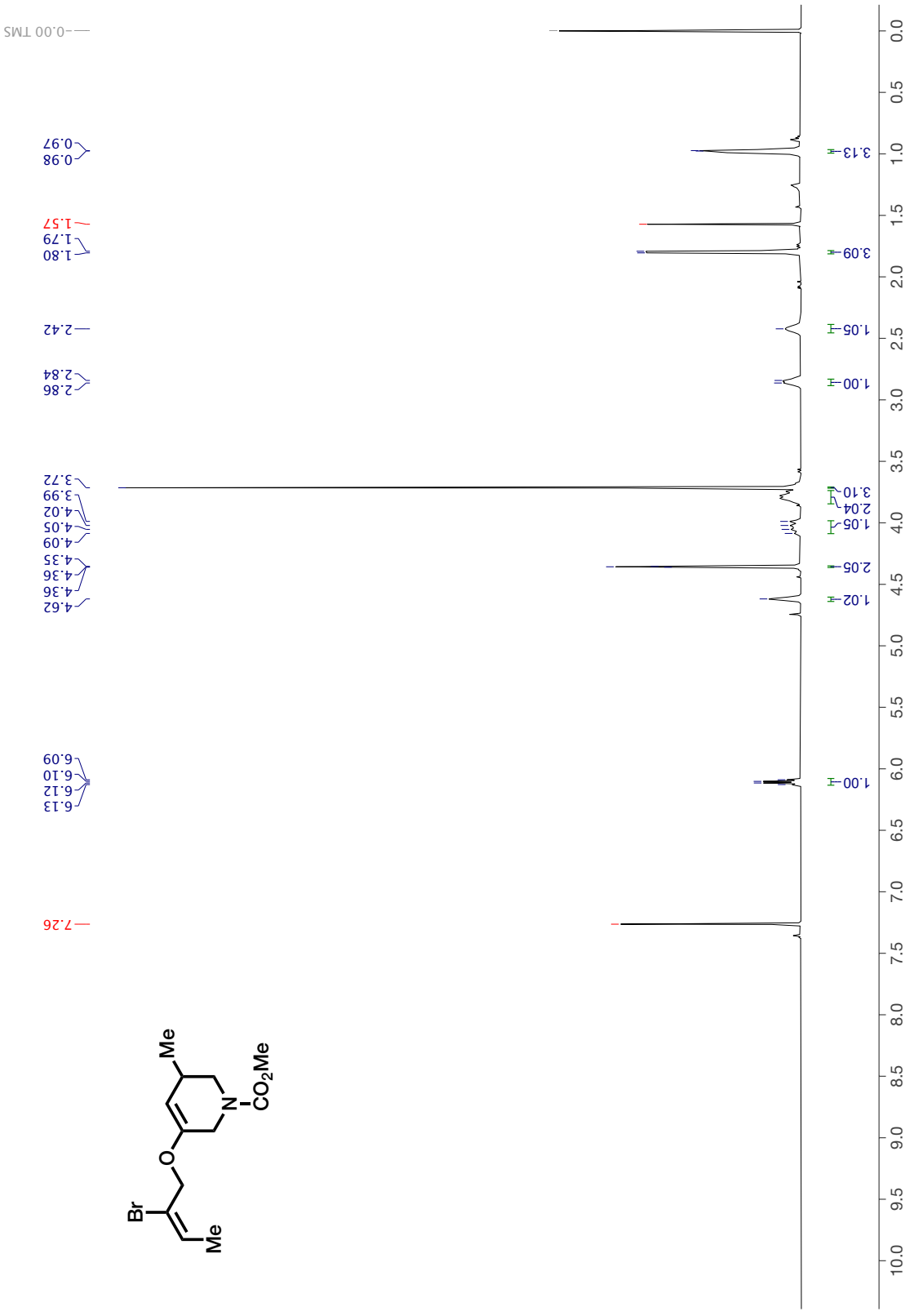


Figure A.34. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **2.28**.

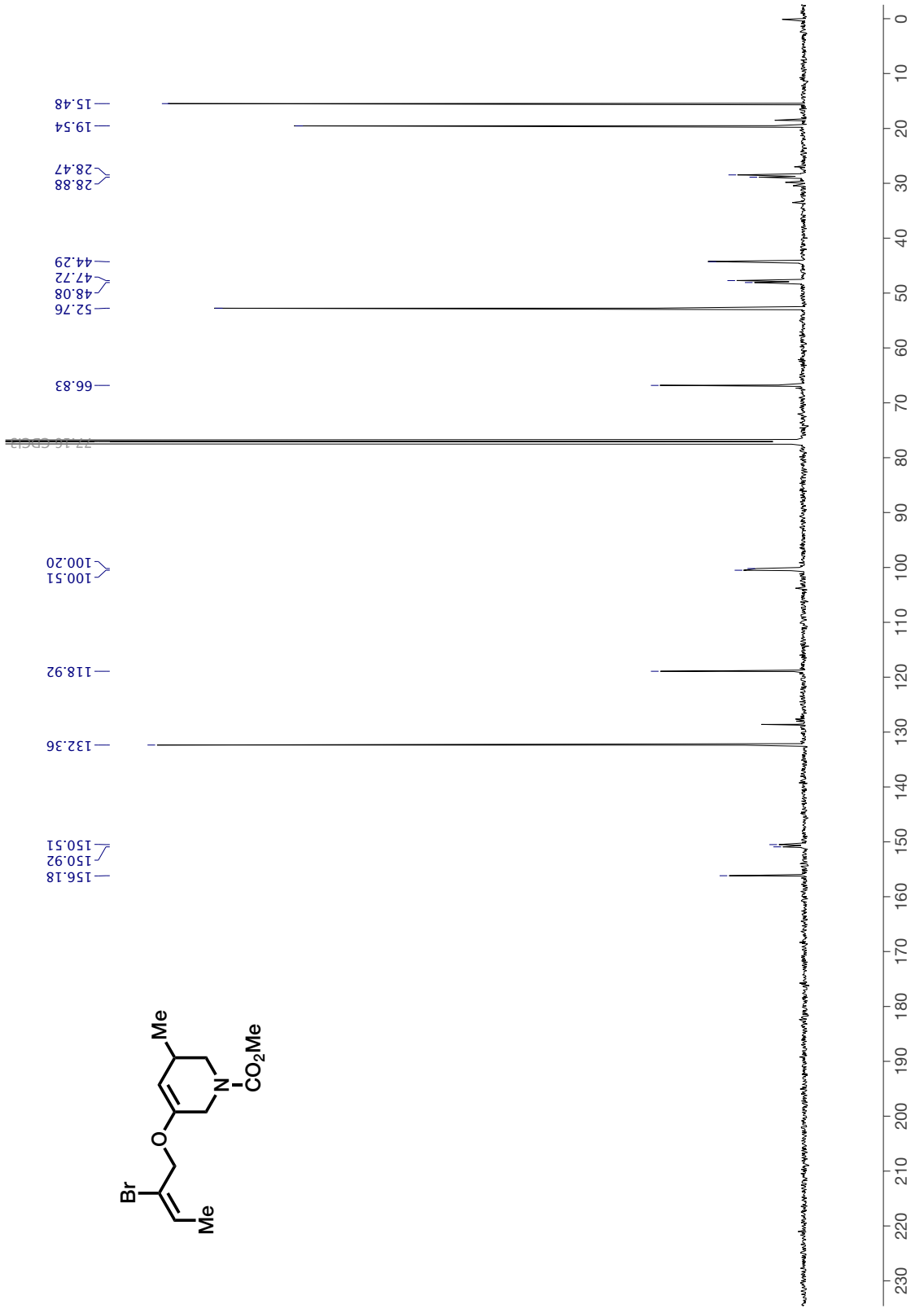


Figure A.35. ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of **2.28**.

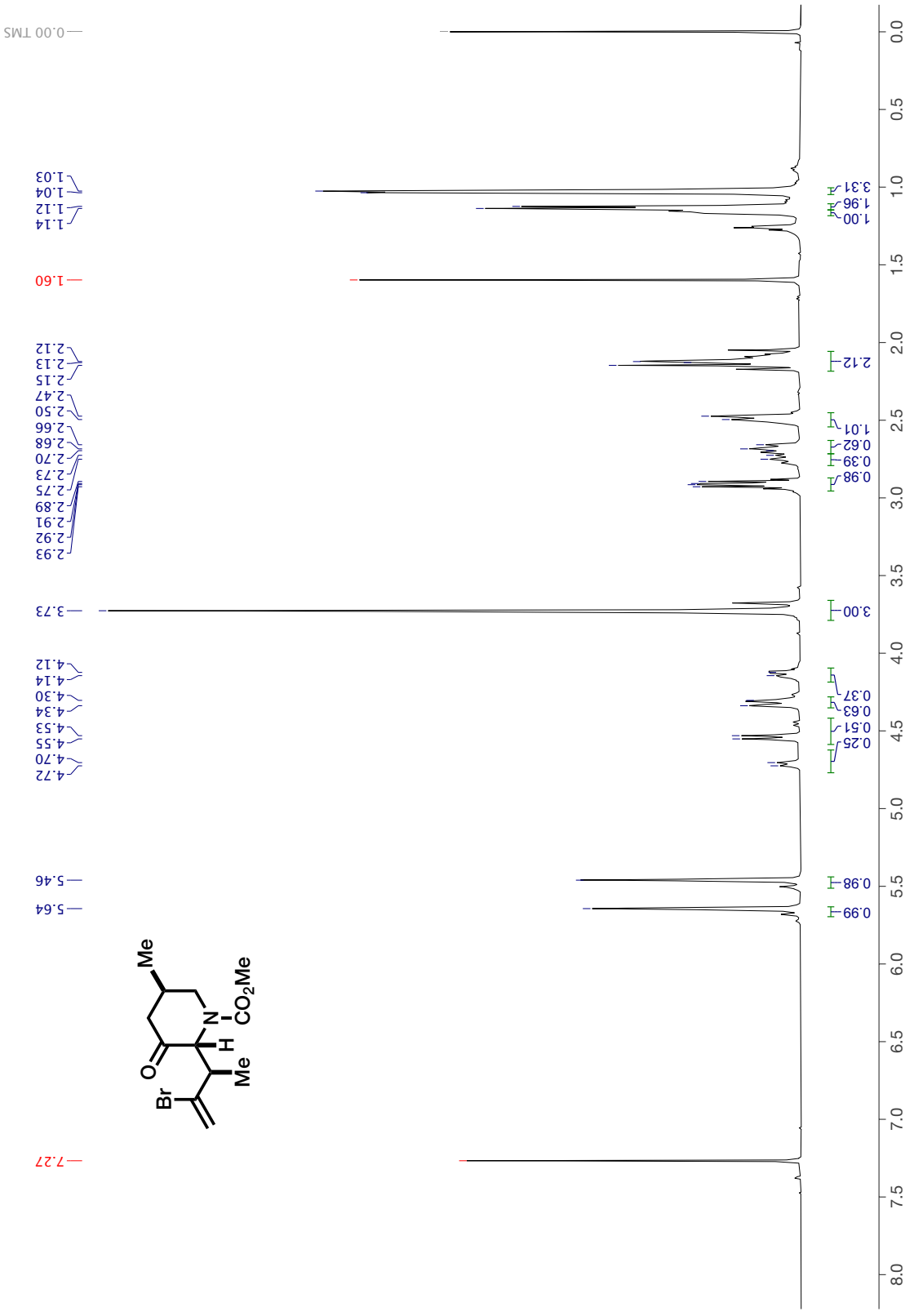


Figure A.36. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **2.21a**.

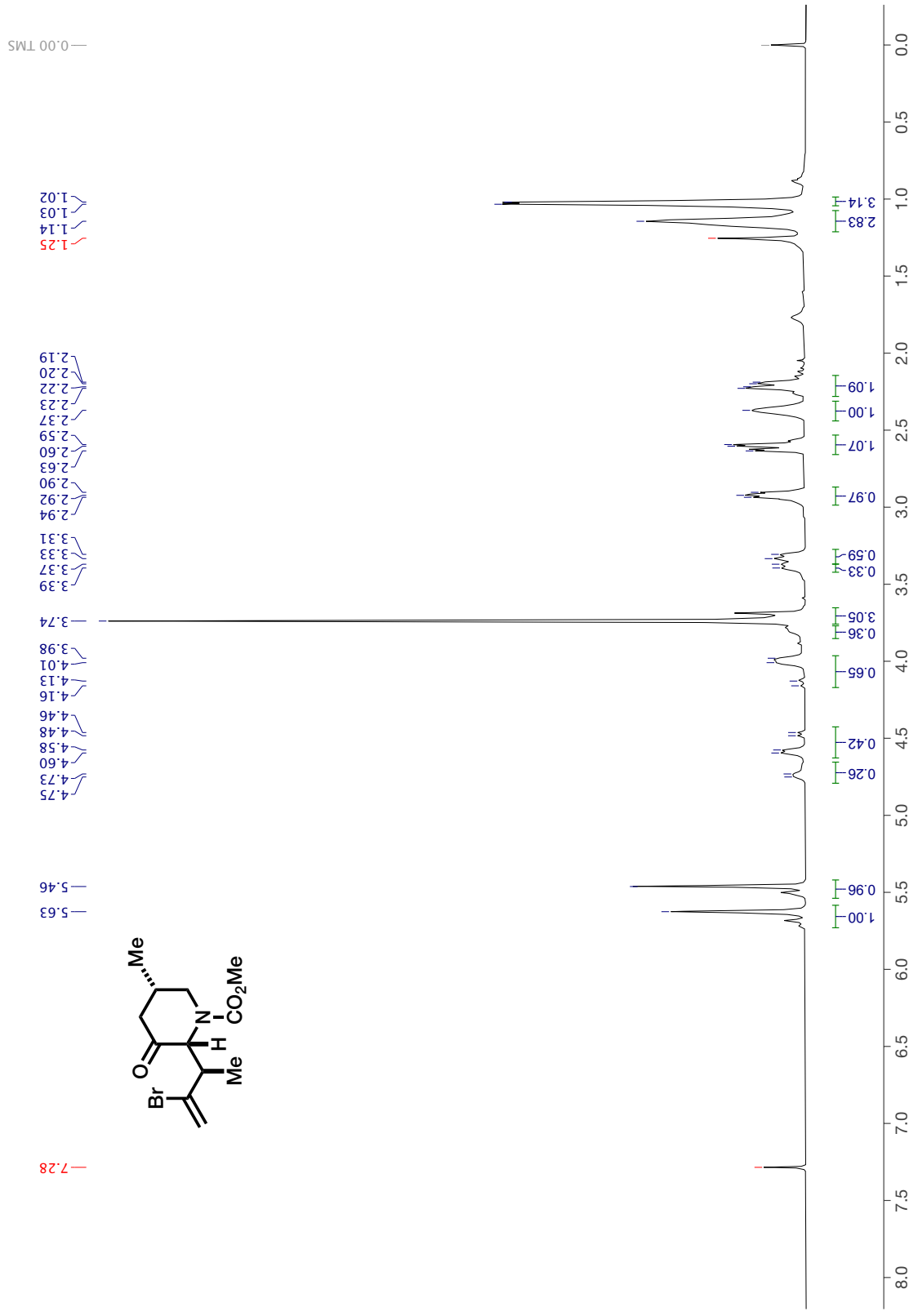


Figure A.37. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **2.21b**.

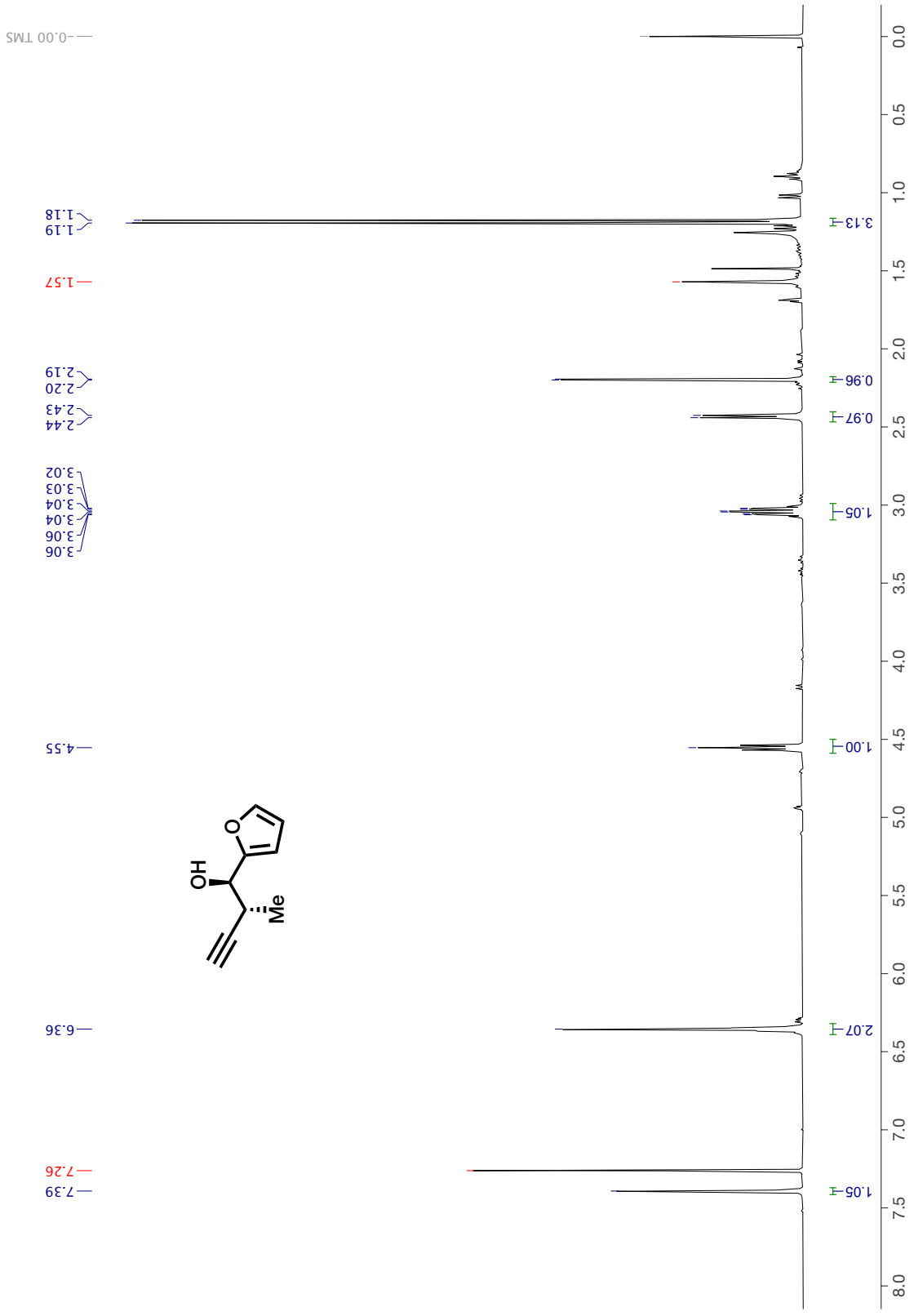


Figure A.38. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2.30**.

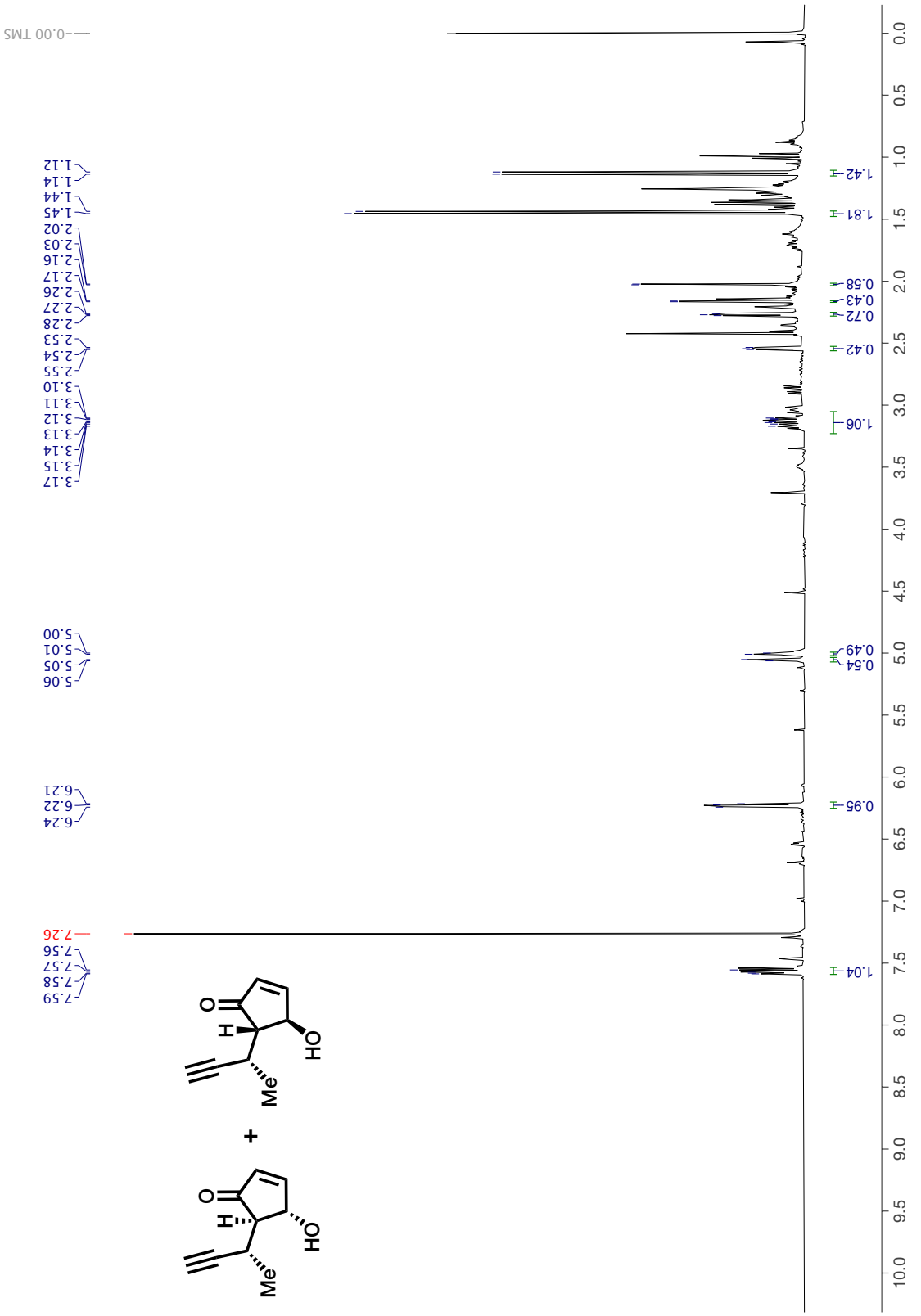


Figure A.39. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2.34a/b**.

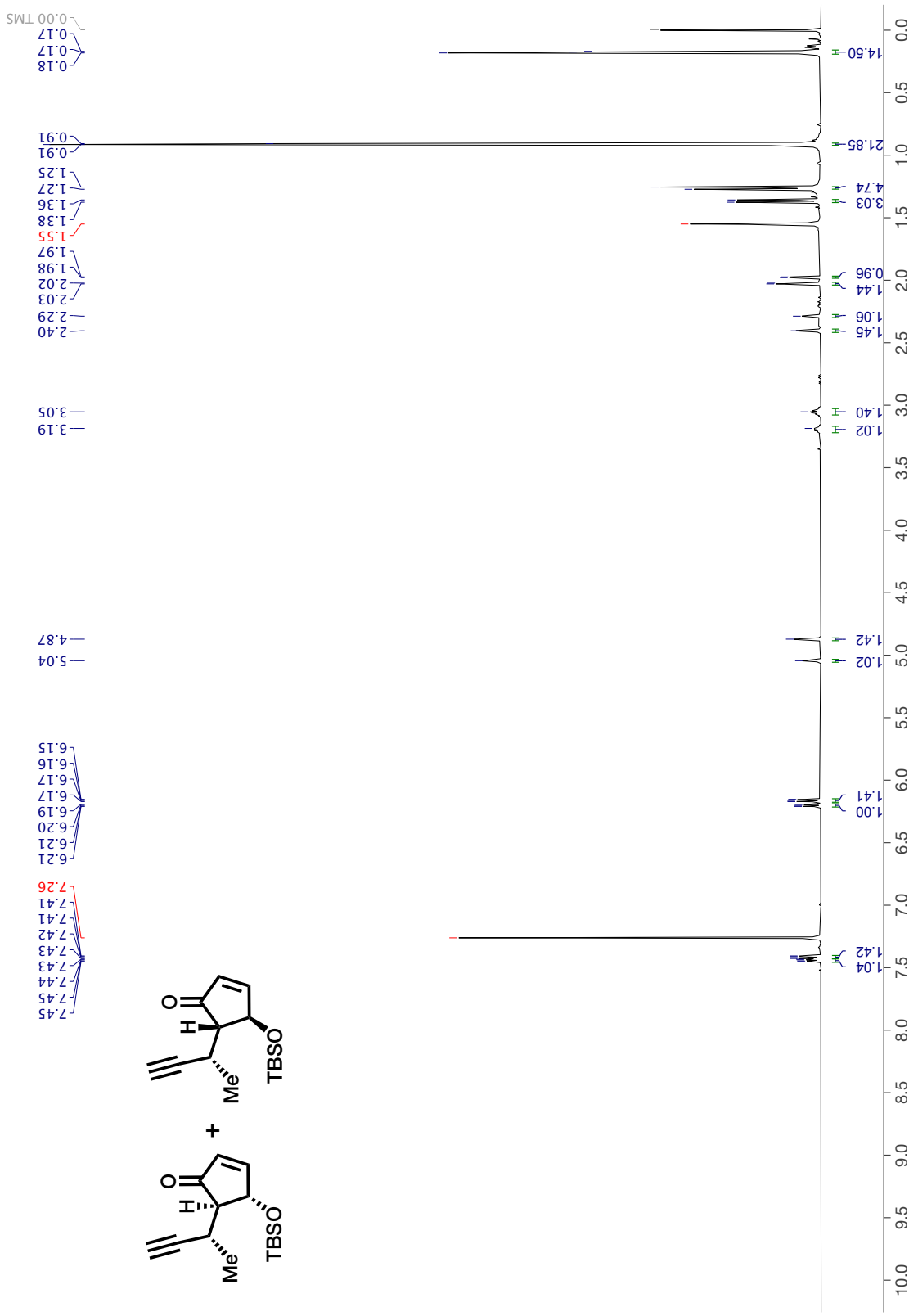


Figure A.40. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2.35a/b**.

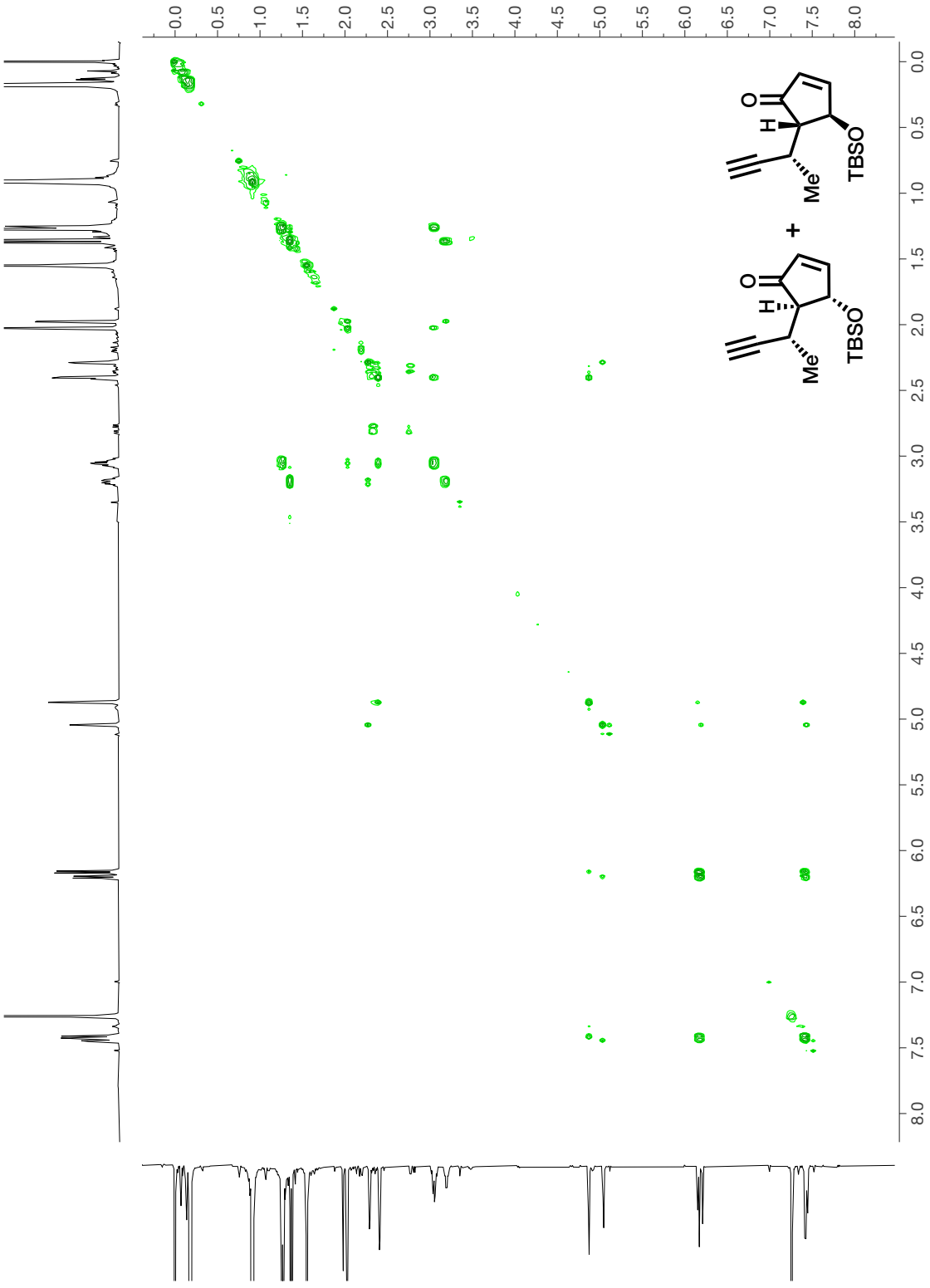


Figure A.41. ^{1}H–^{1}H COSY spectrum (400 MHz, $CDCl_3$) of **2.35a/b**.

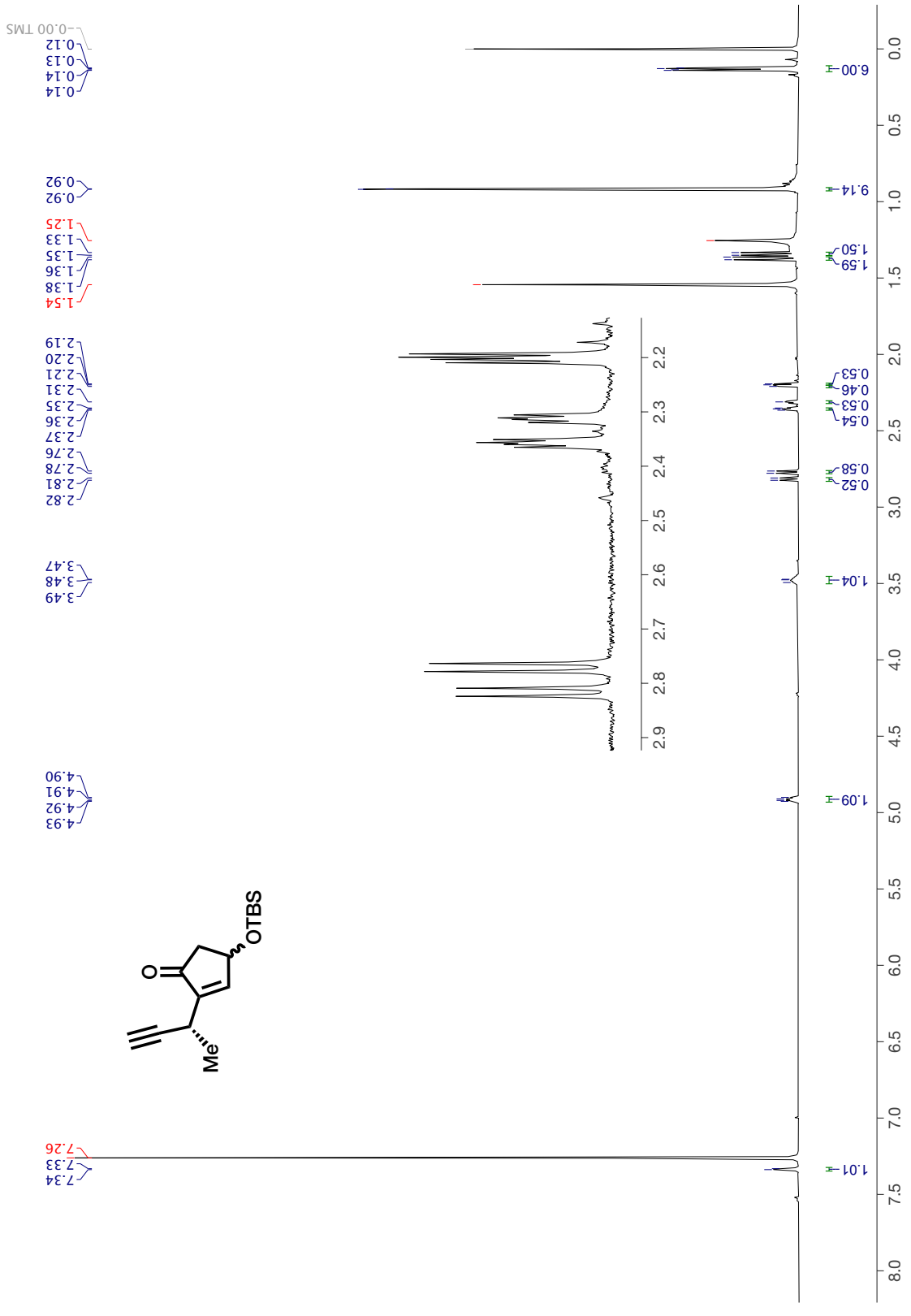


Figure A.42. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2.36**.

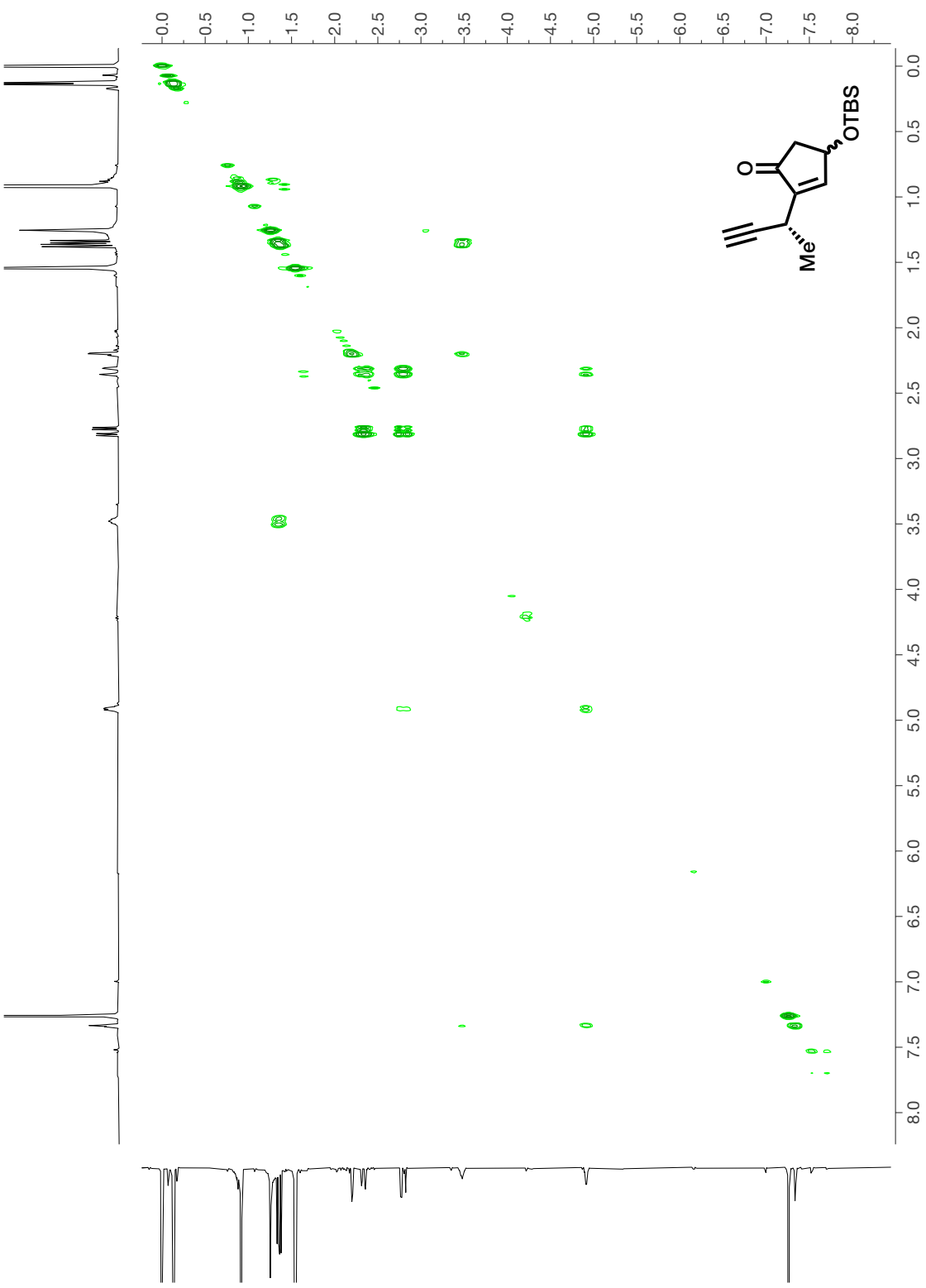


Figure A.43. ^{1}H–^{1}H COSY spectrum (400 MHz, $CDCl_3$) of **2.36**.

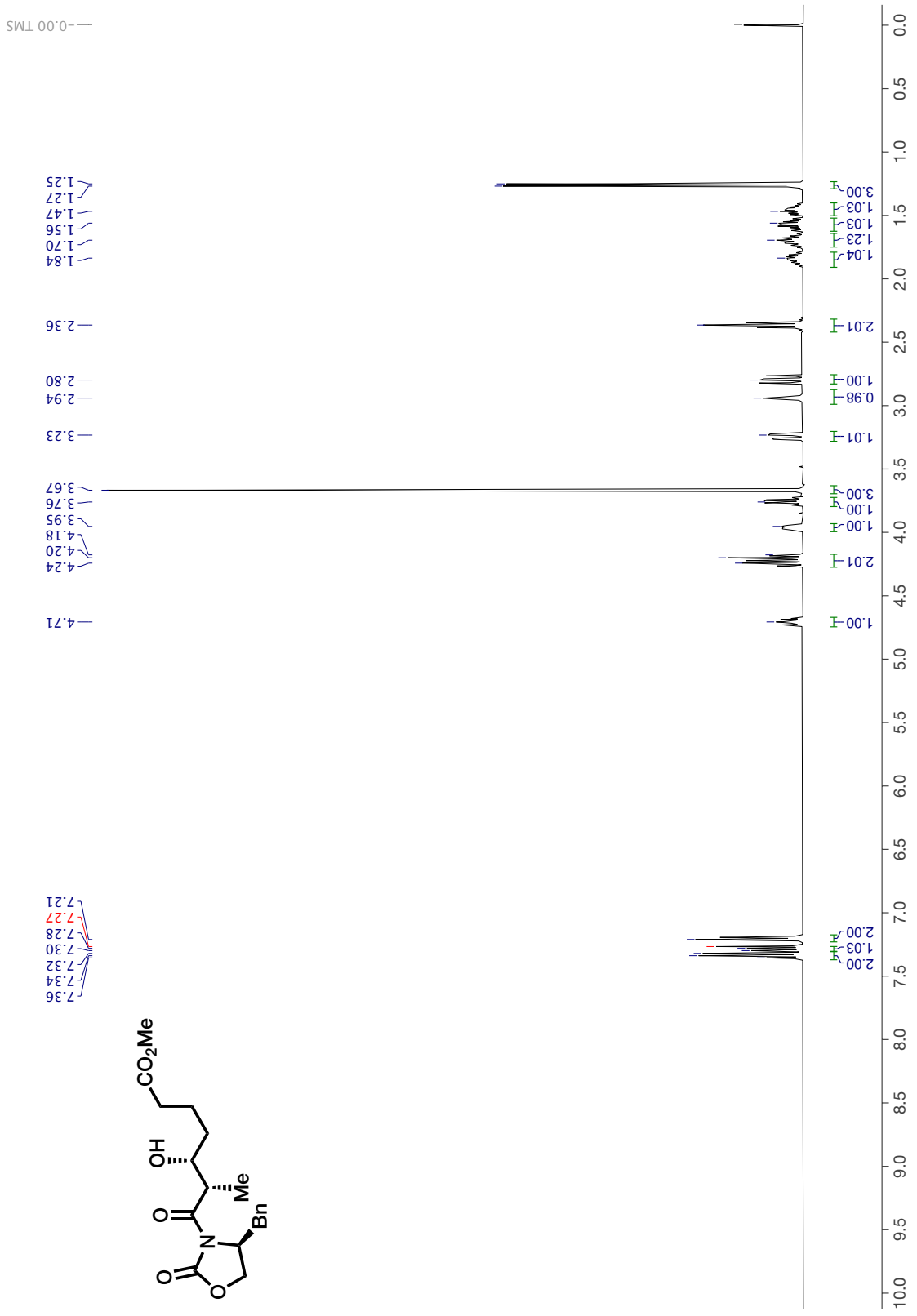


Figure A.44. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **3.6**.

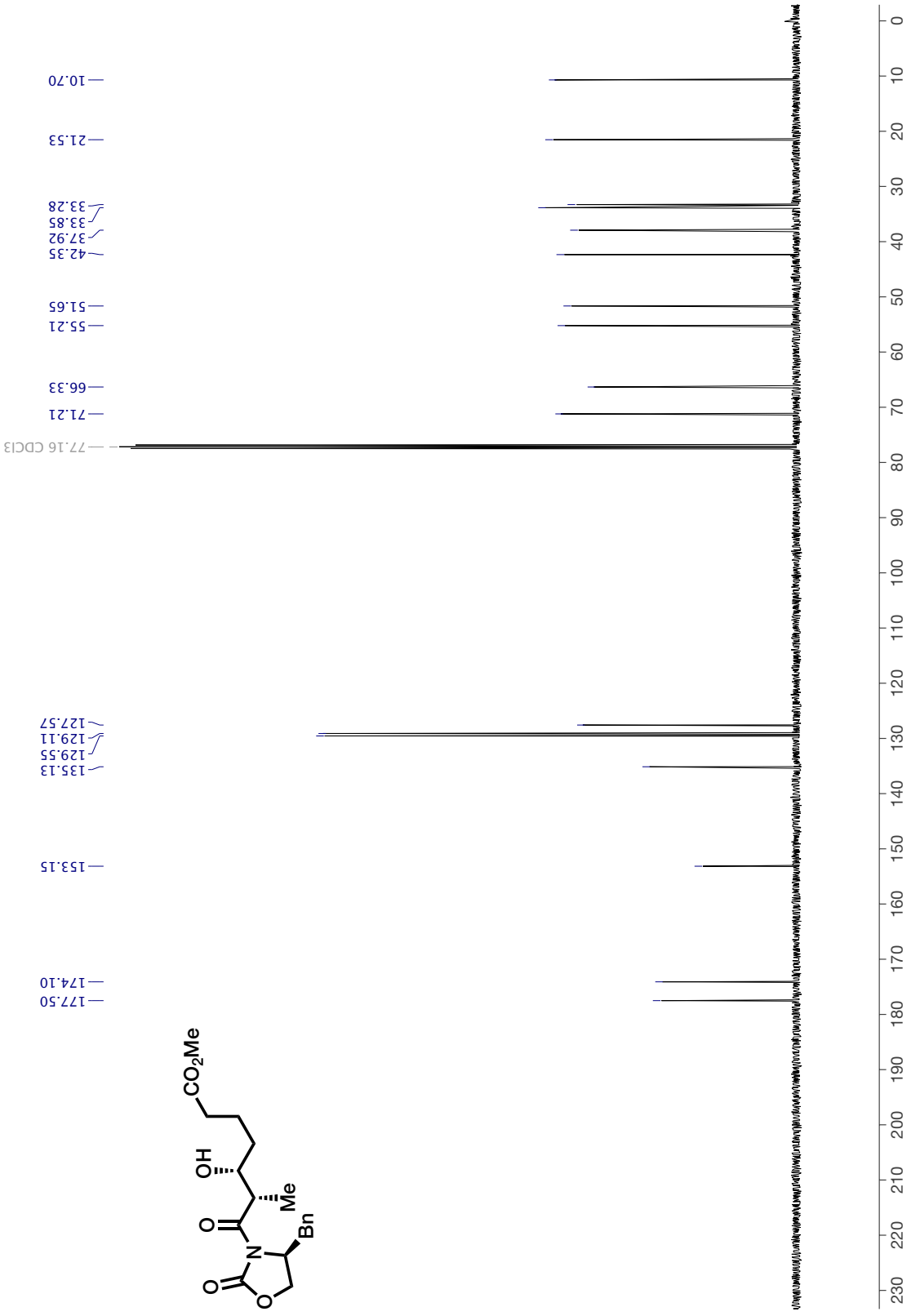


Figure A.45. ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of **3.6**.

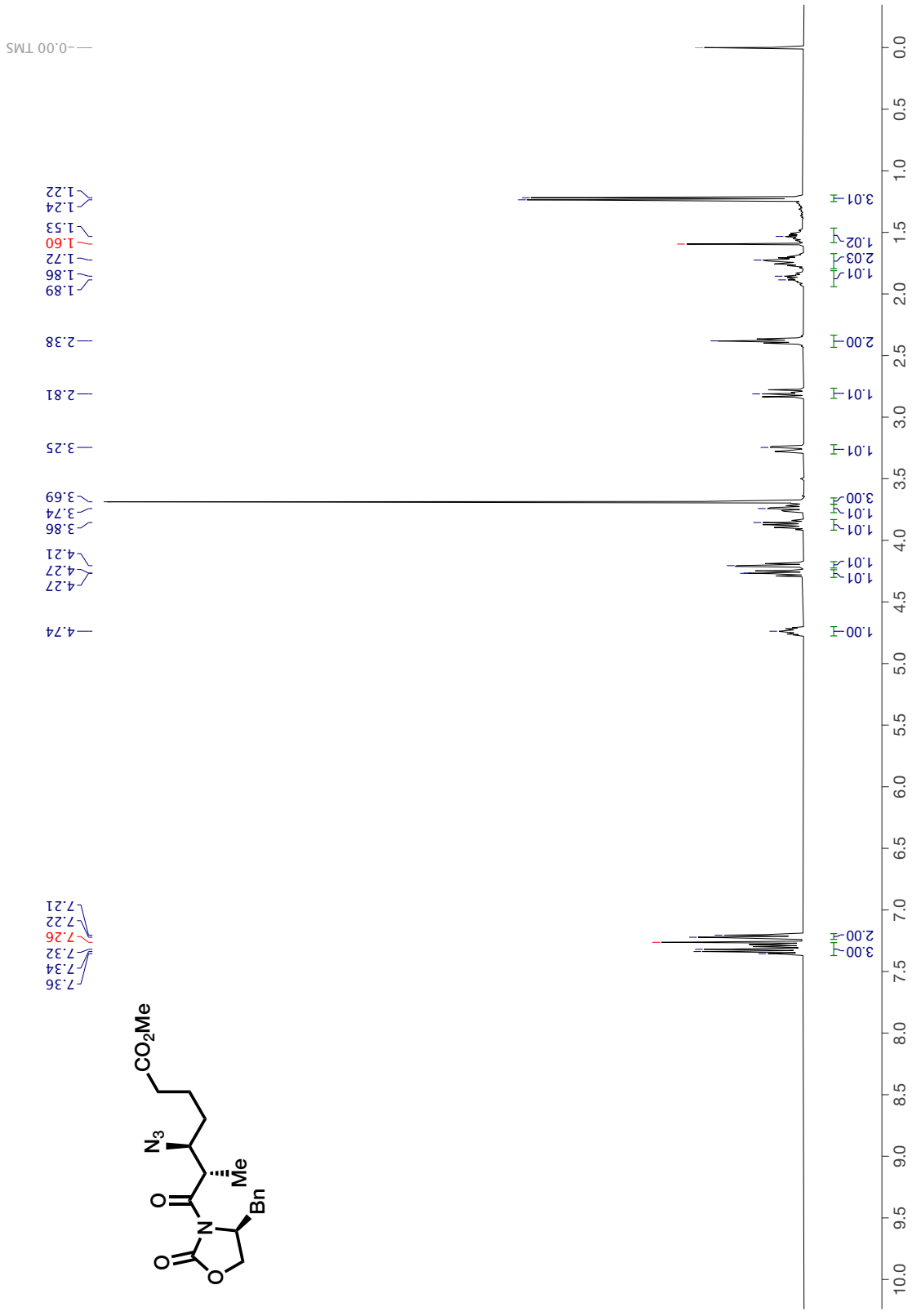


Figure A.46. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.42**.

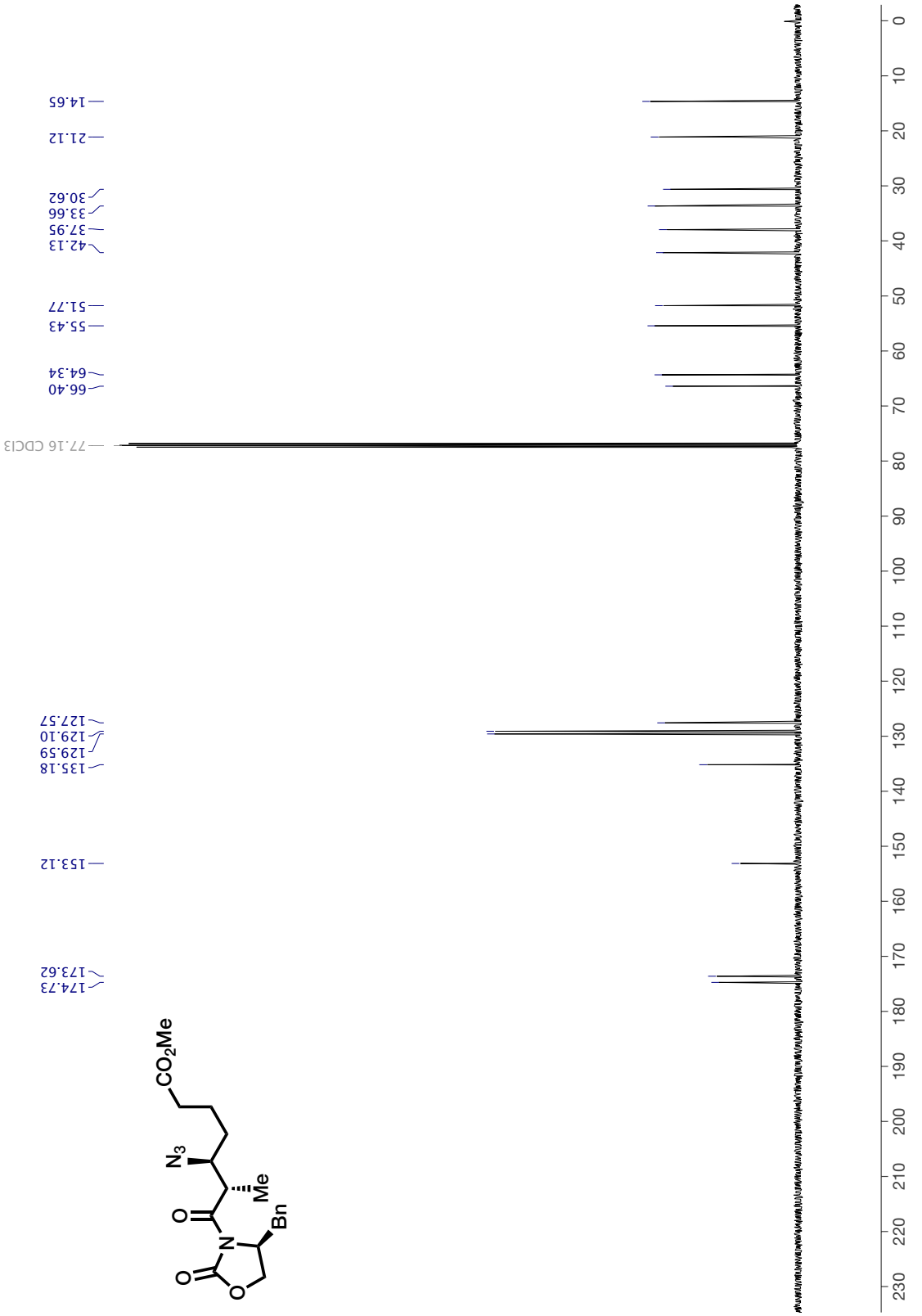


Figure A.47. ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of **3.42**.

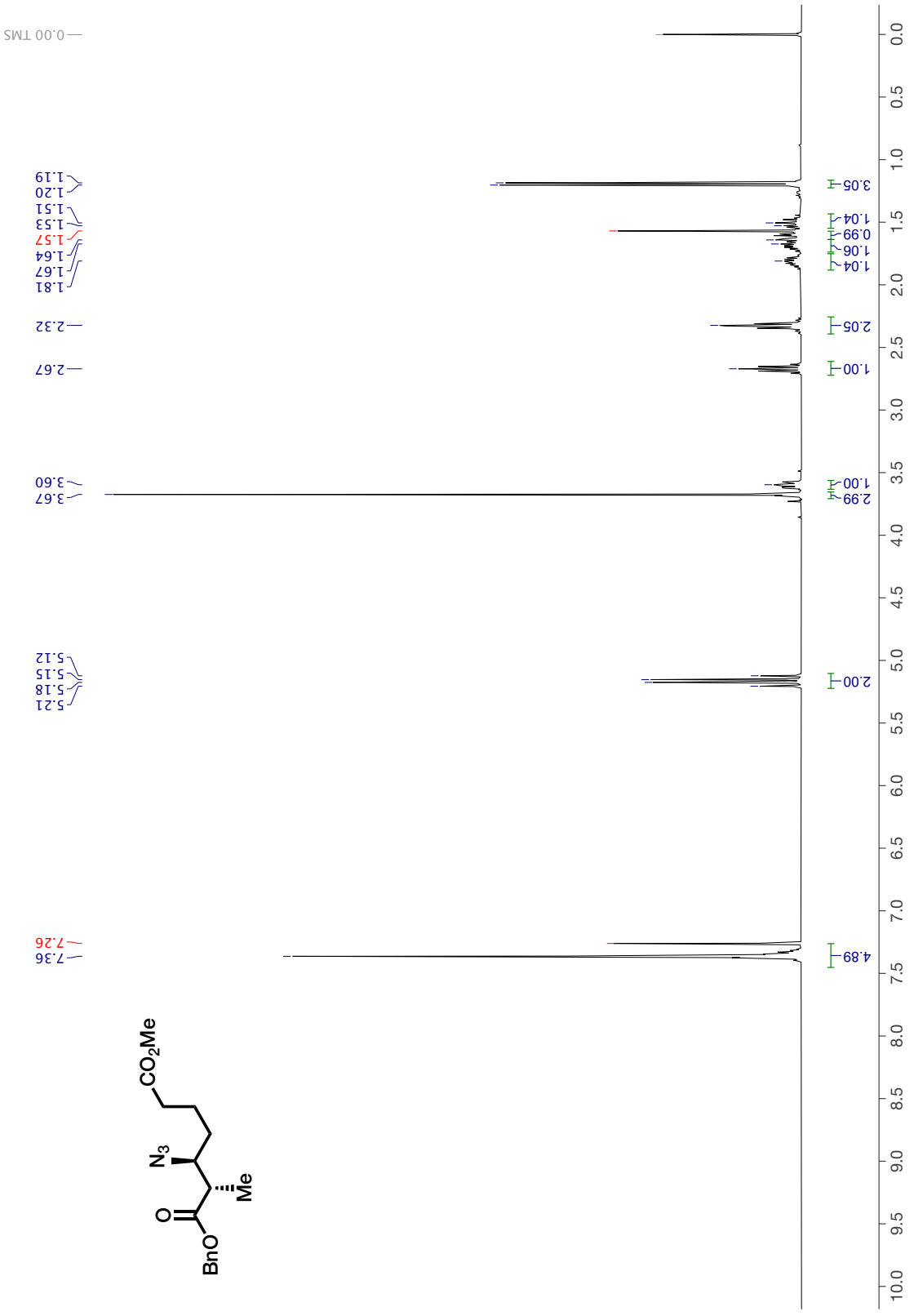


Figure A.48. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.7**.

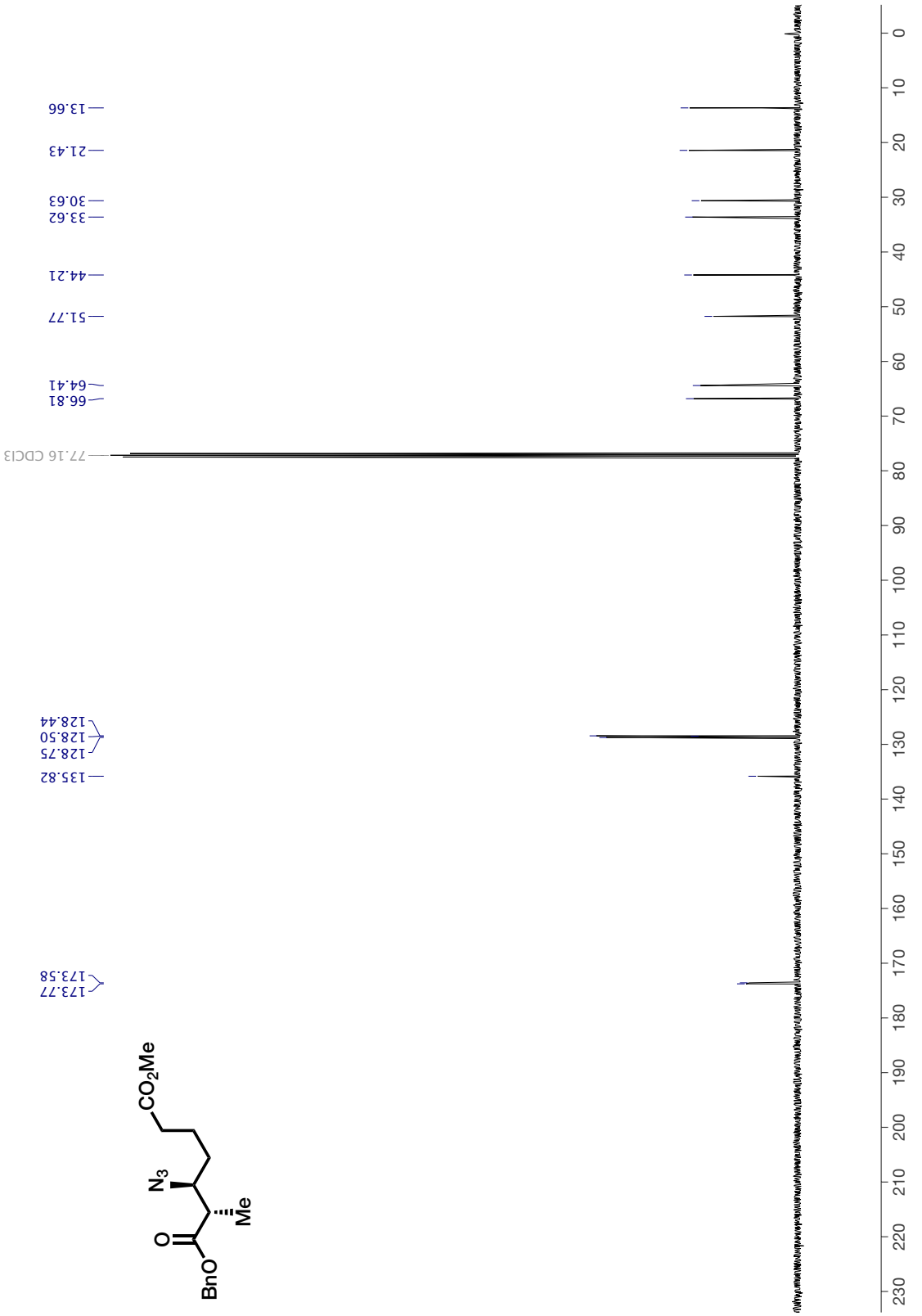


Figure A.49. ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of **3.7**.

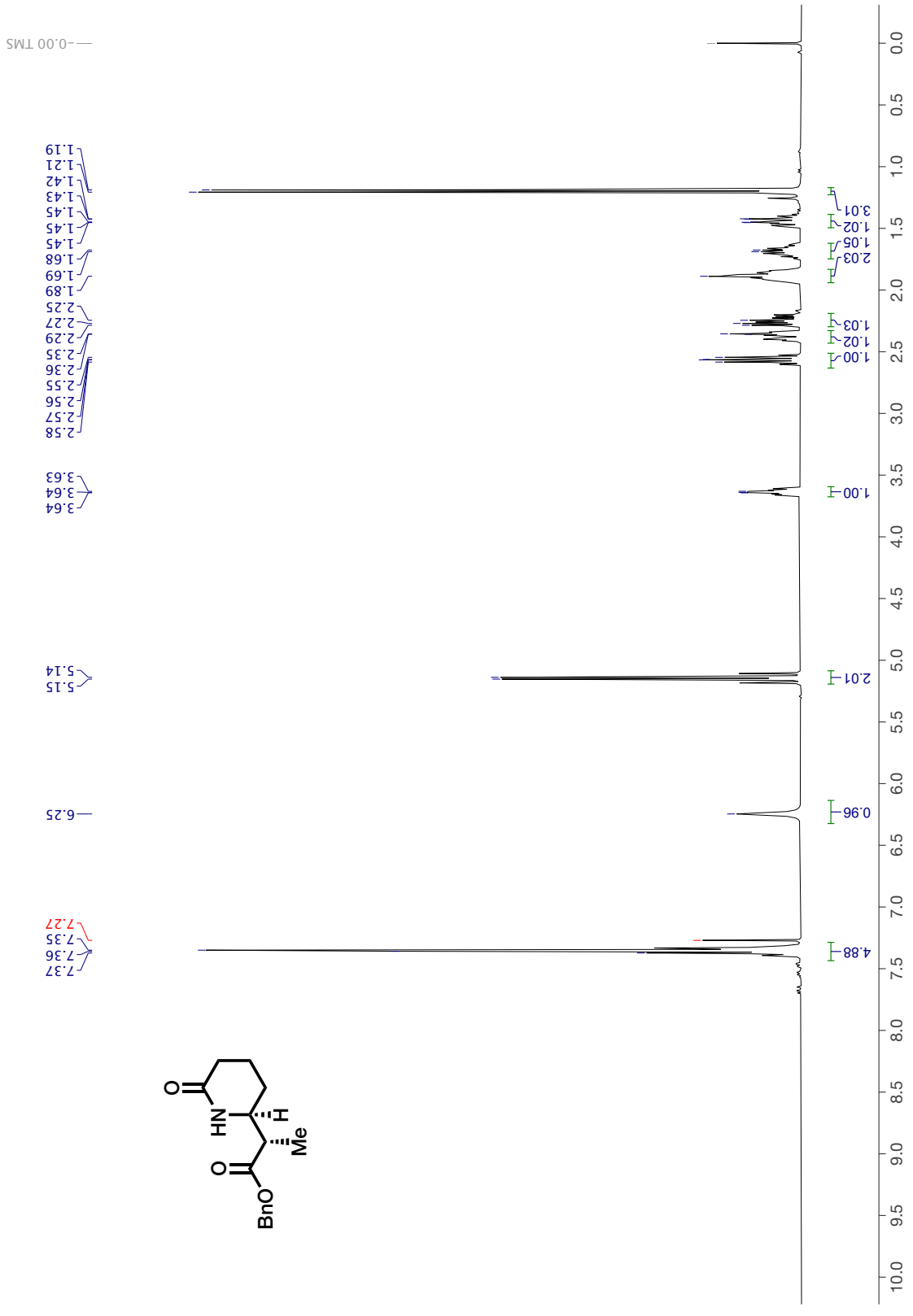


Figure A.50. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.8**.

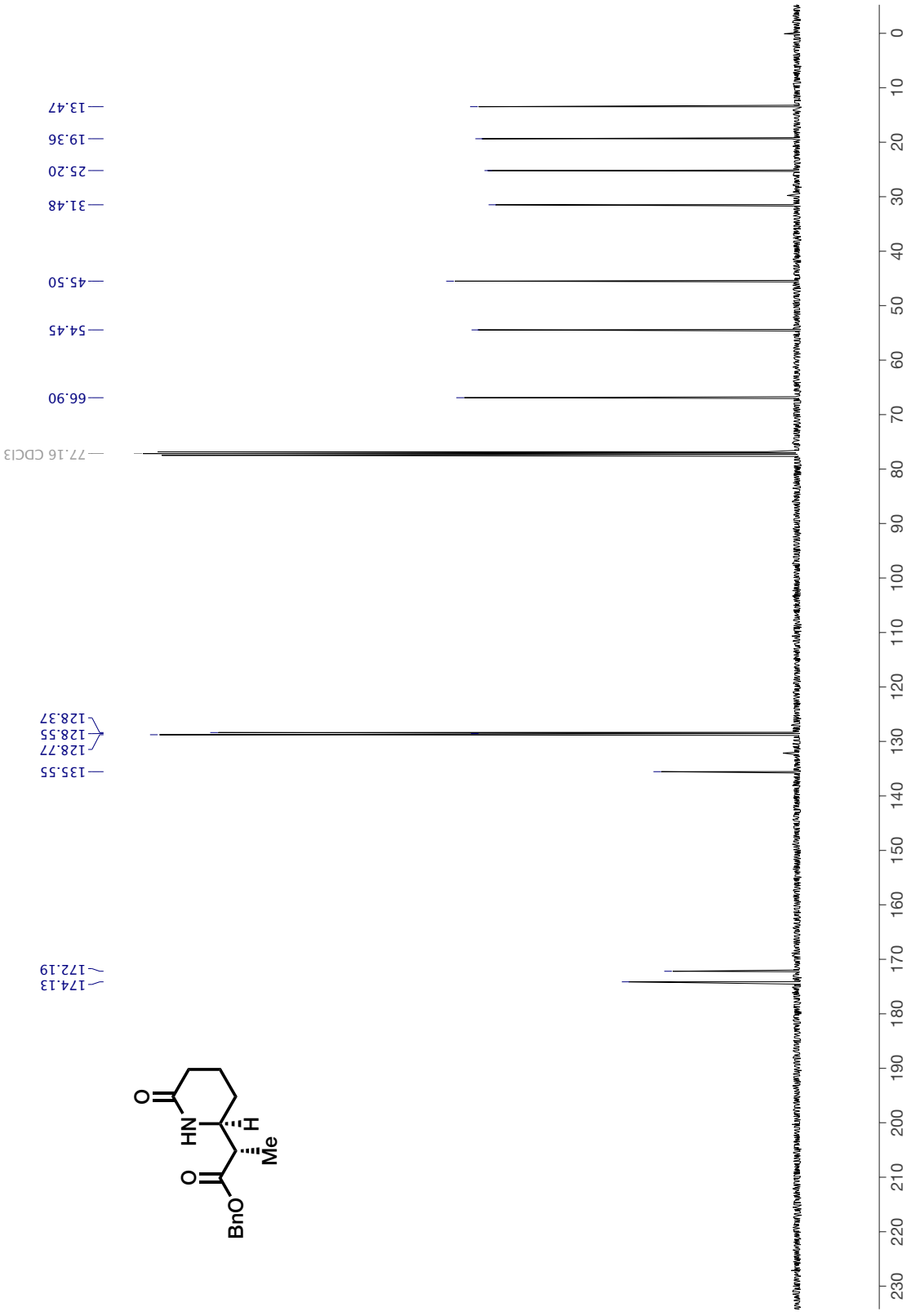


Figure A.51. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.8**.

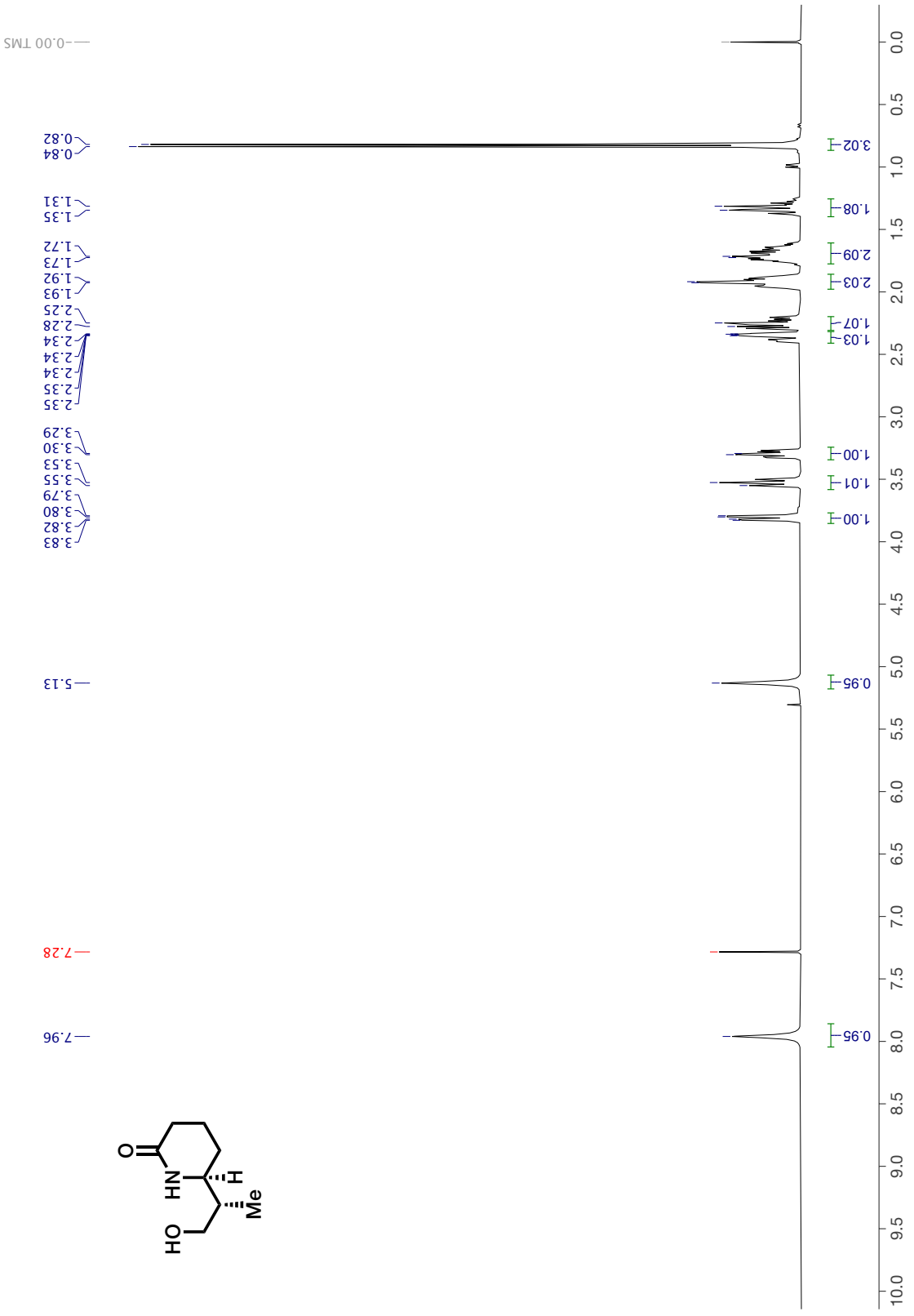


Figure A.52. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.43**.

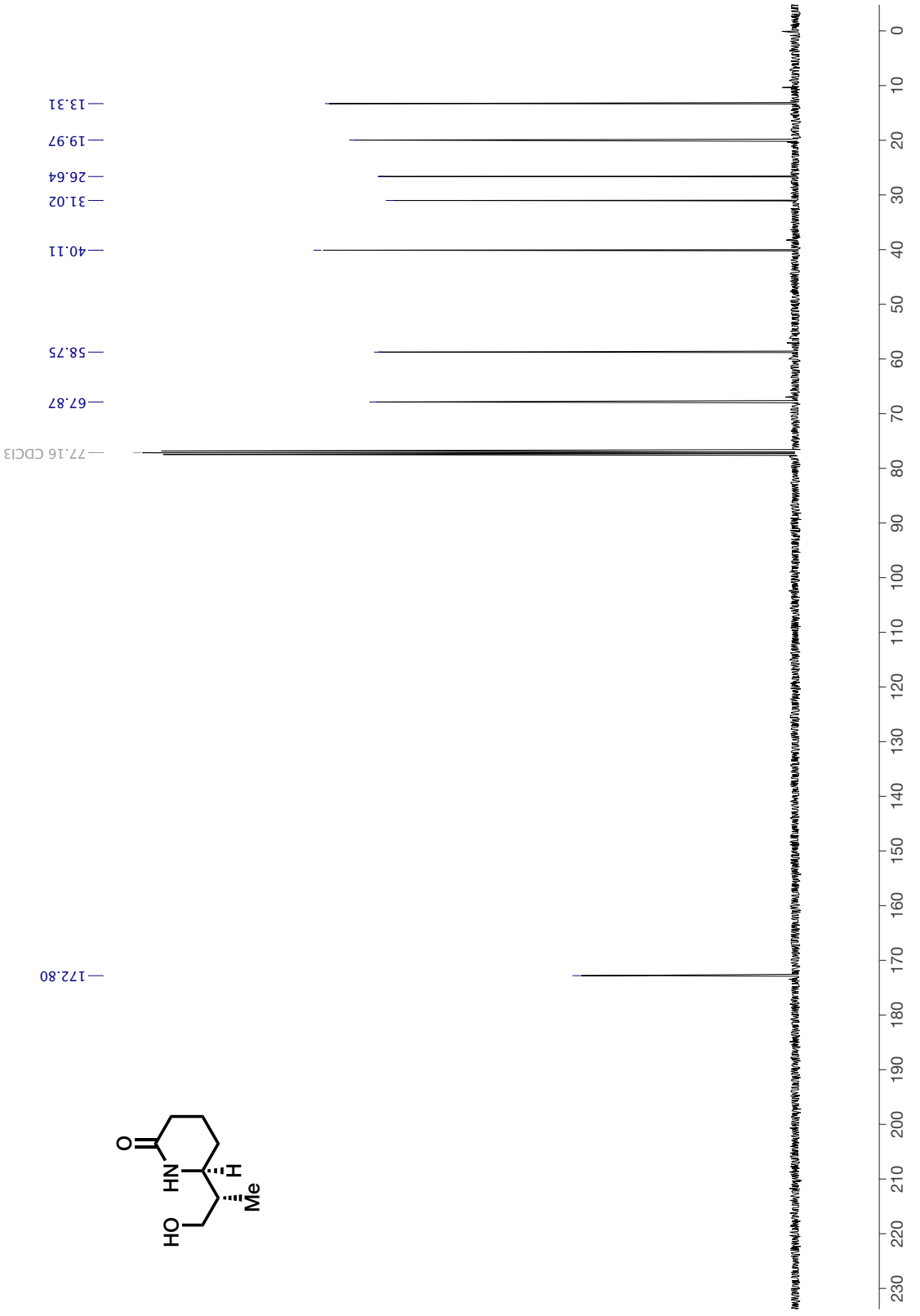


Figure A.53. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.43**.

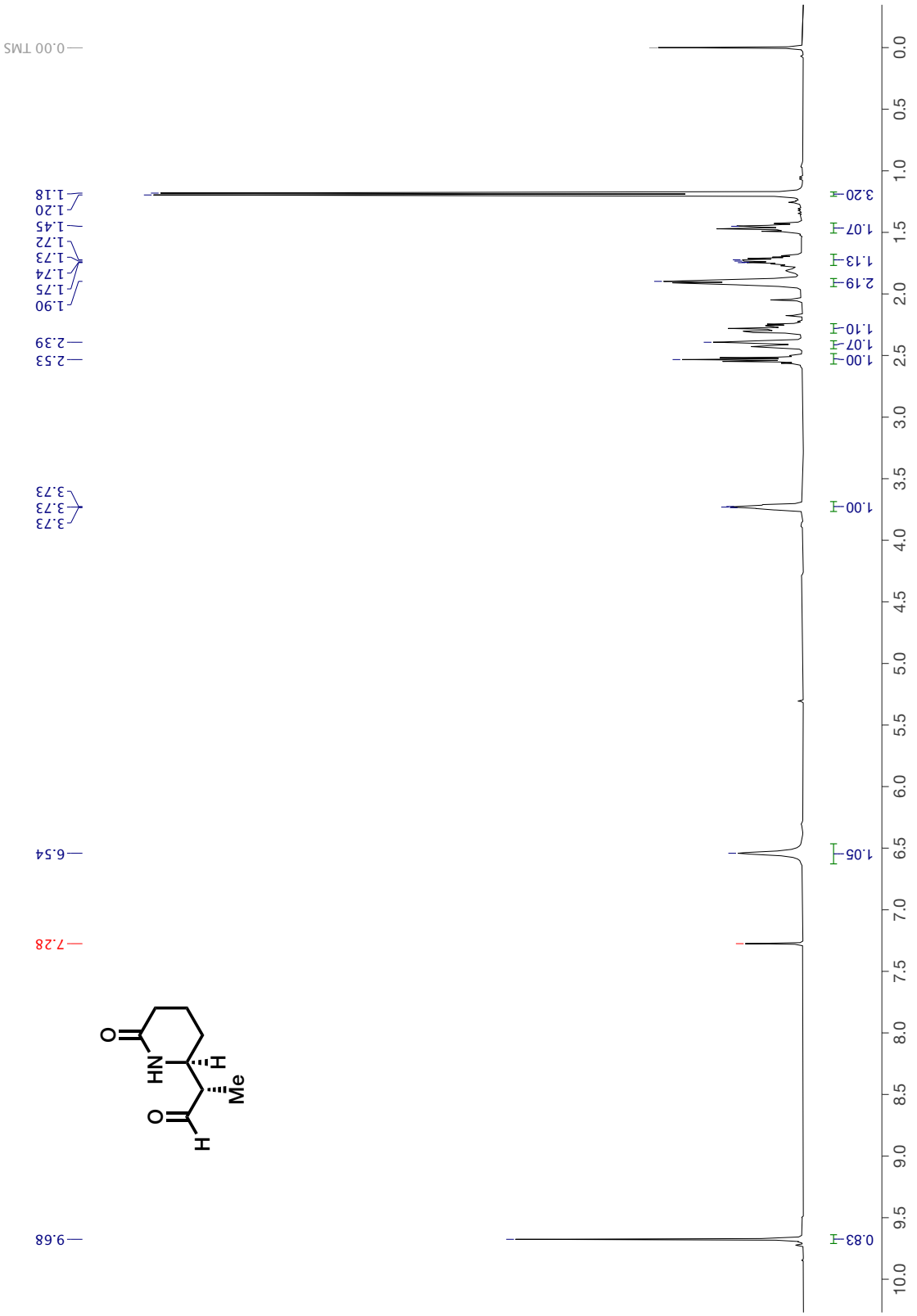


Figure A.54. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **3.9**.

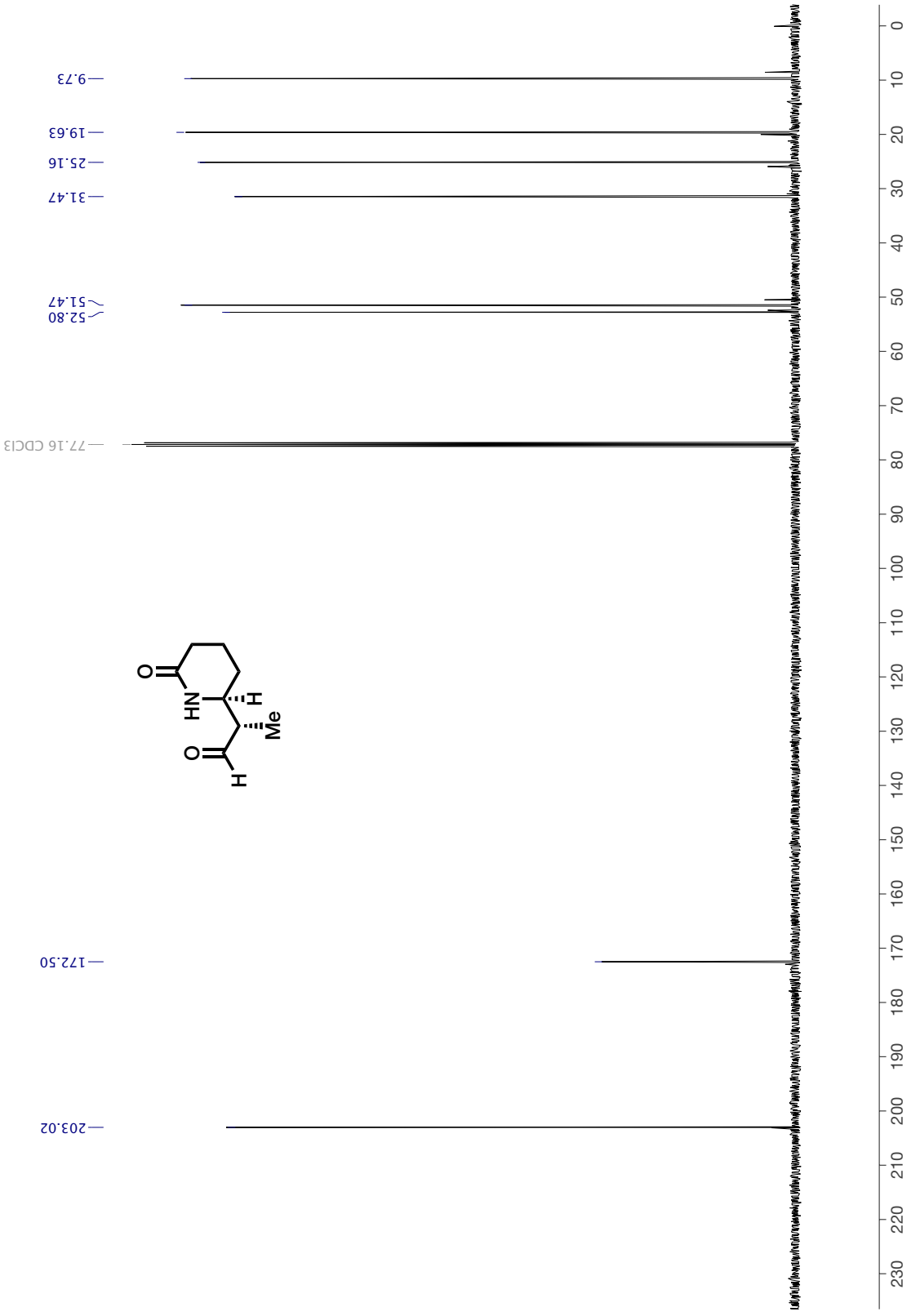


Figure A.55. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.9**.

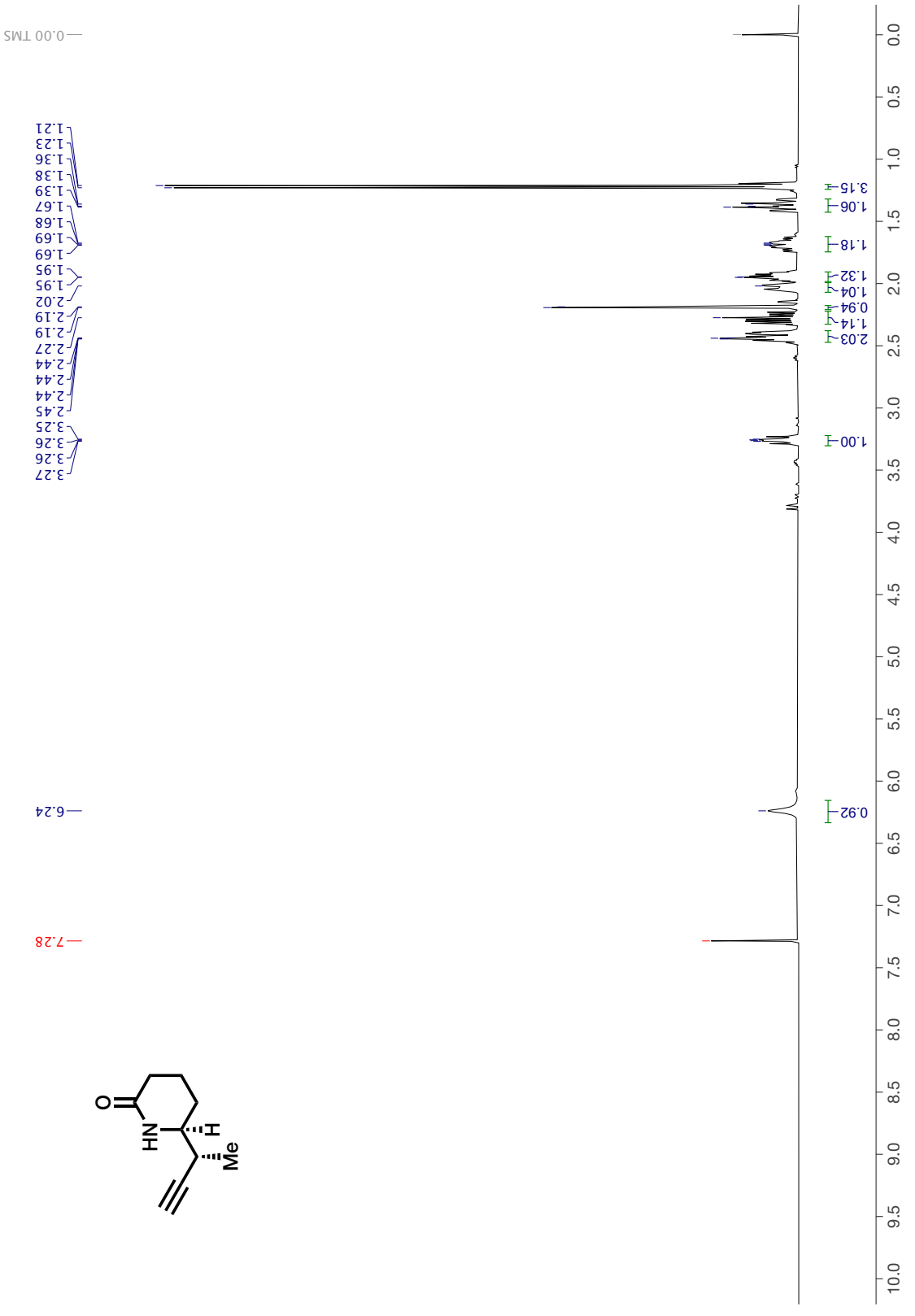


Figure A.56. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.3**.

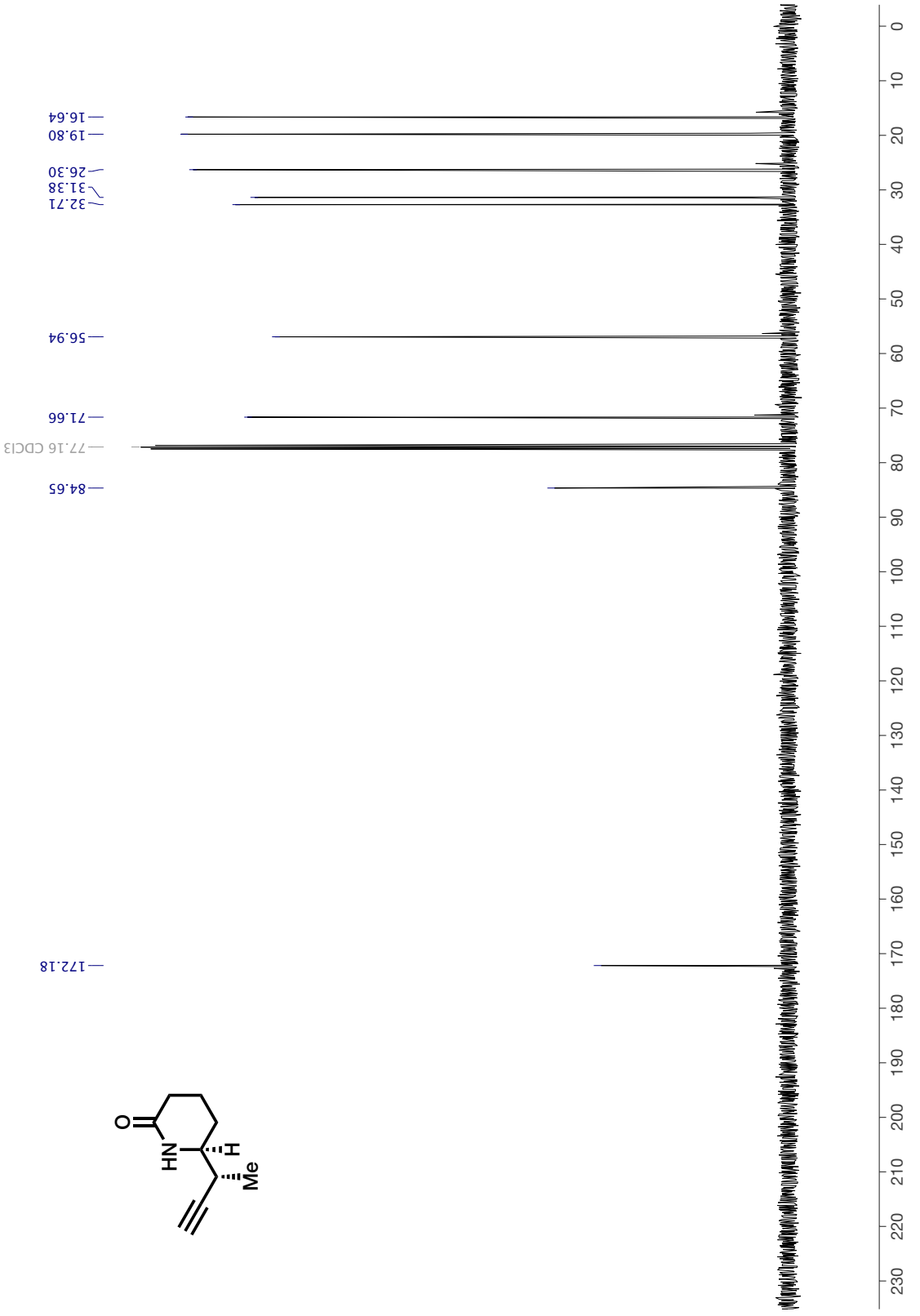


Figure A.57. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.3**.

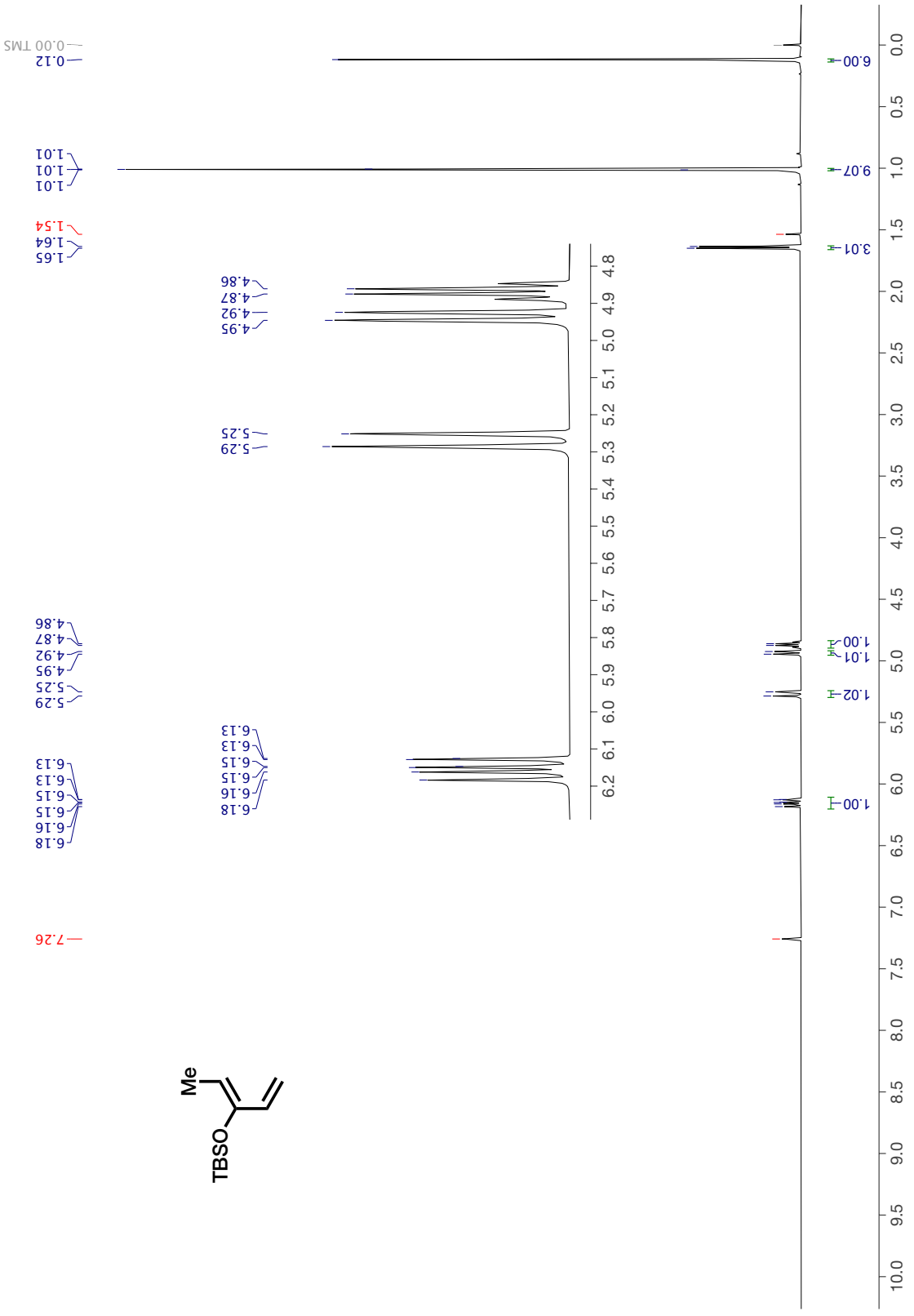


Figure A.58. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **3.10**.

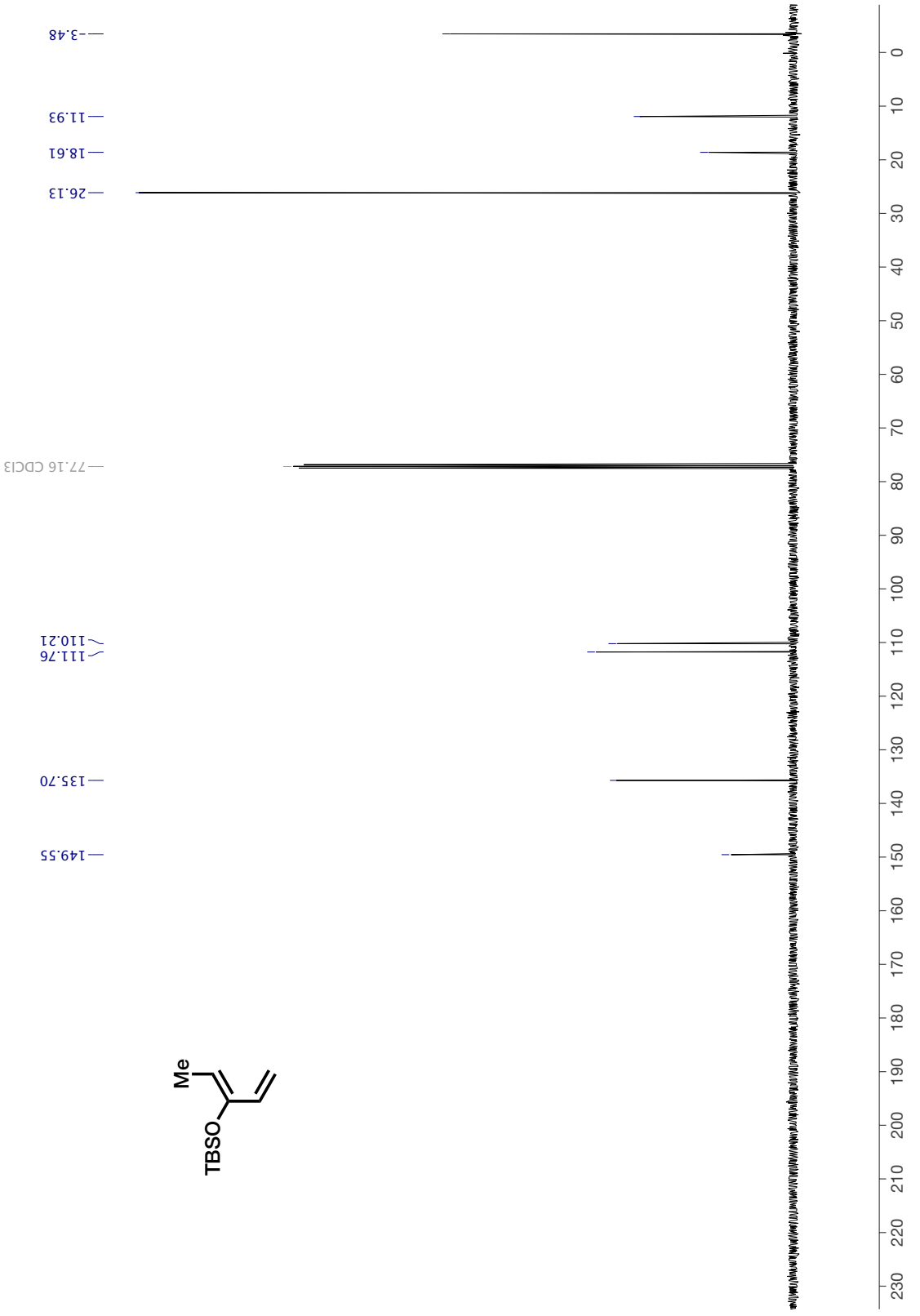


Figure A.59. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.10**.

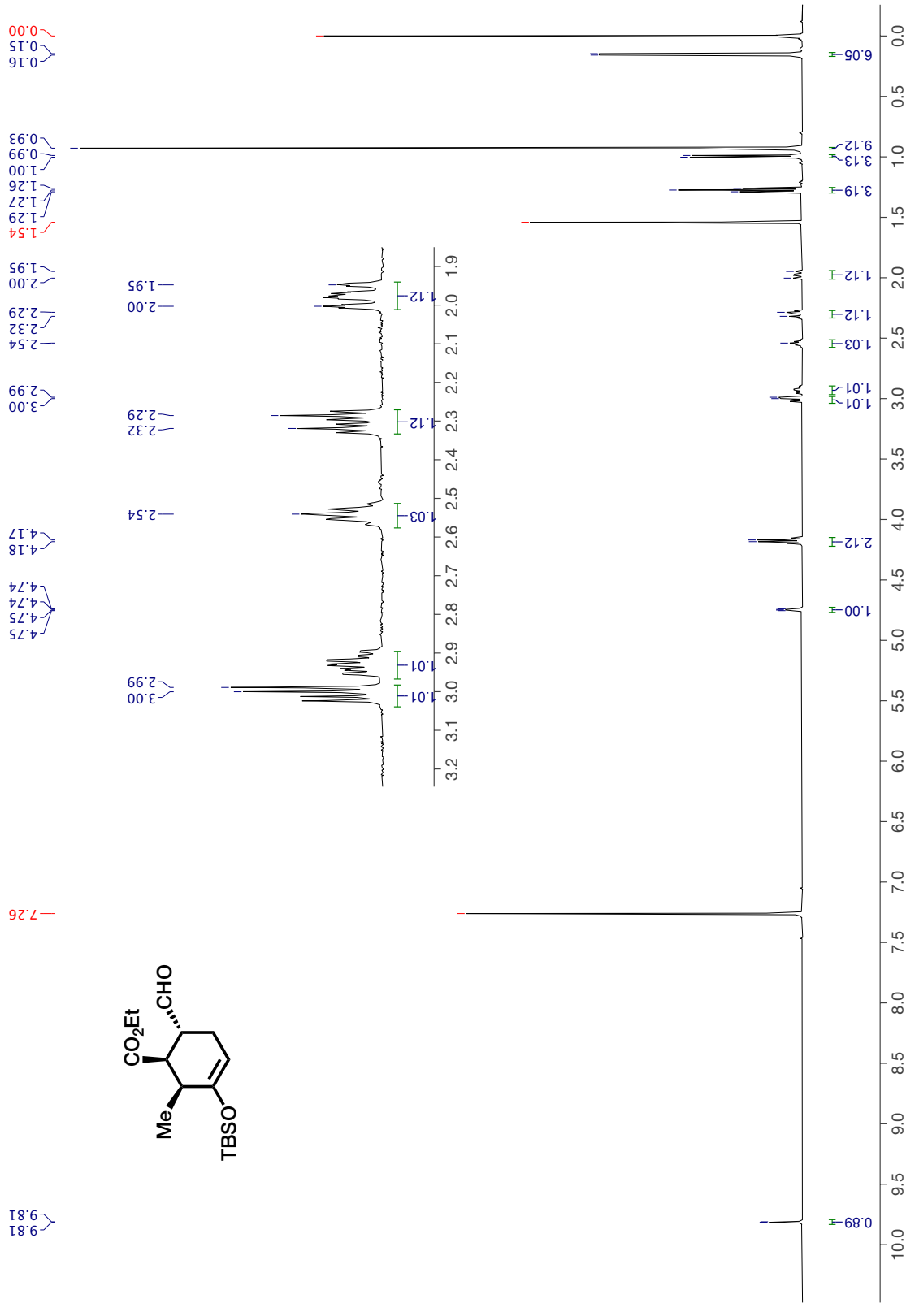


Figure A.60. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **3.11**.

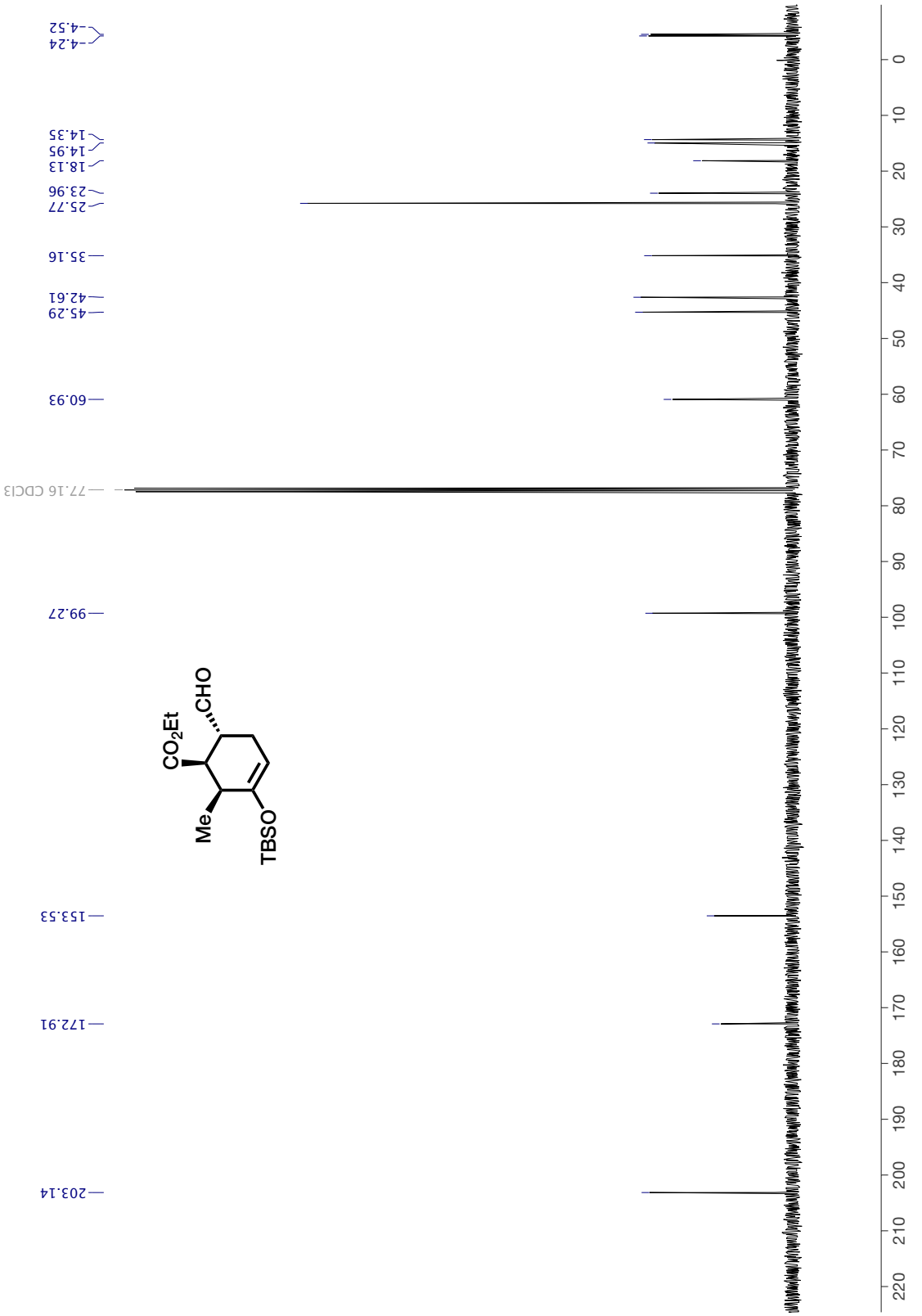


Figure A.61. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.11**.

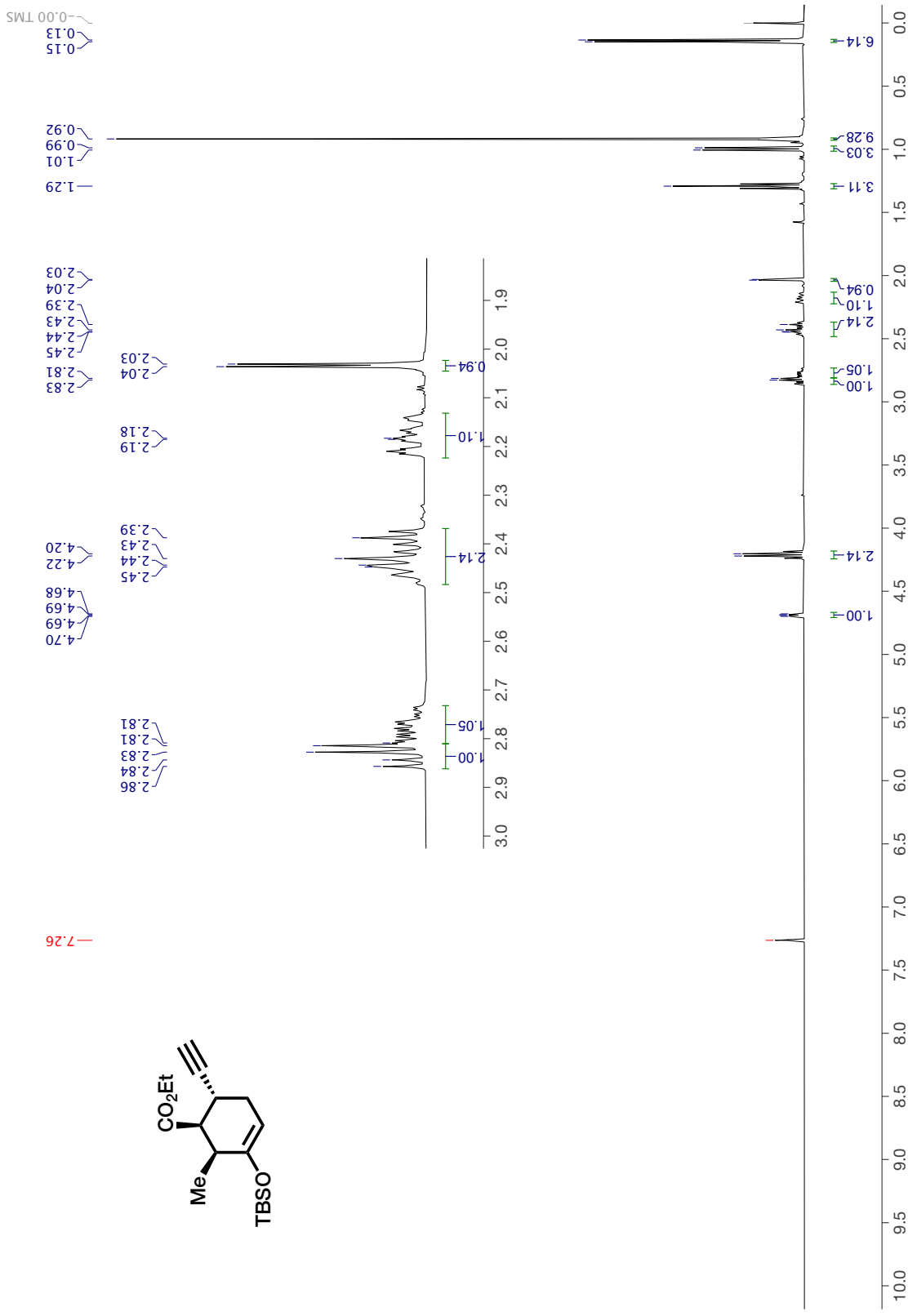


Figure A.62. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.12**.

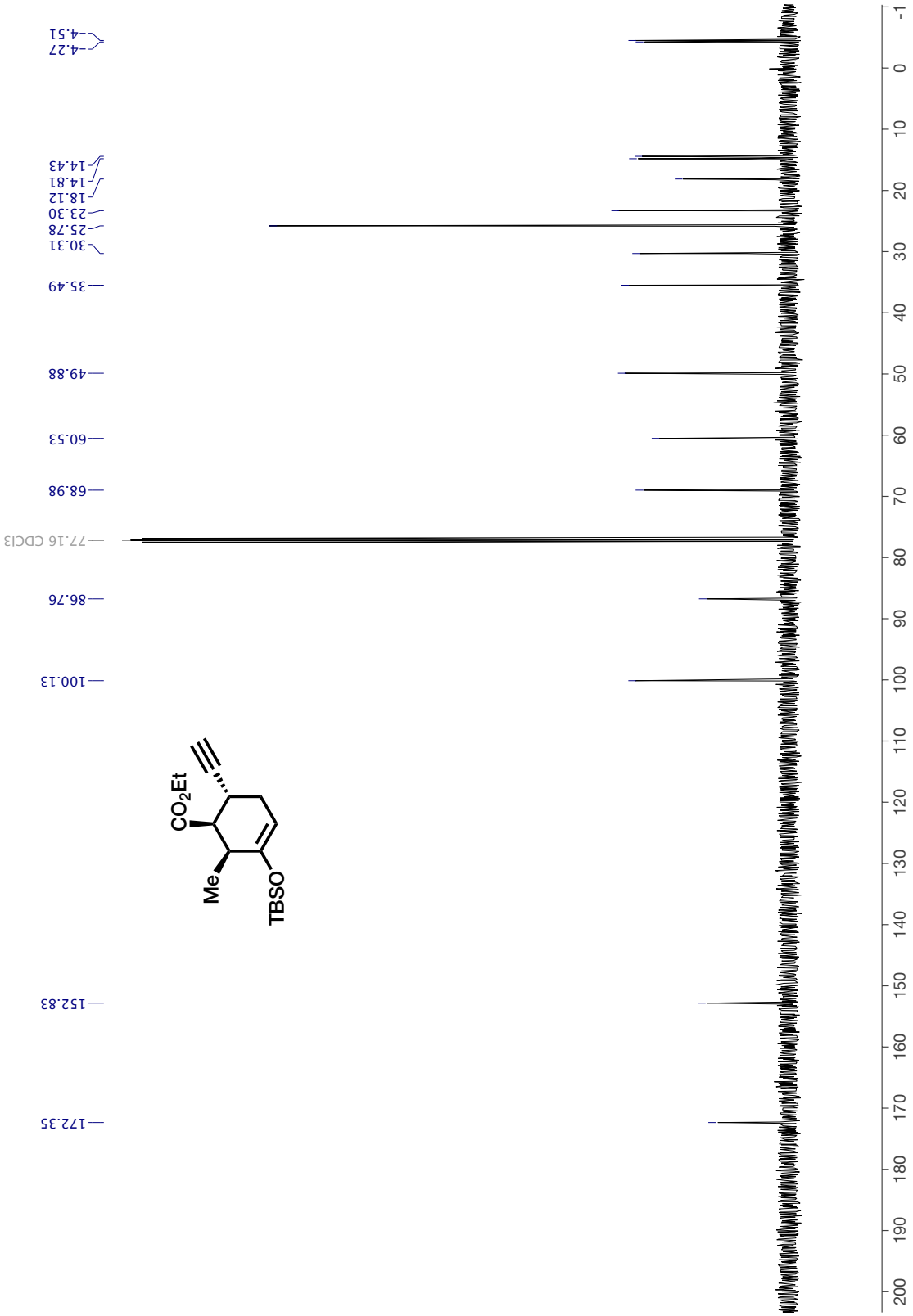


Figure A.63. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.12**.

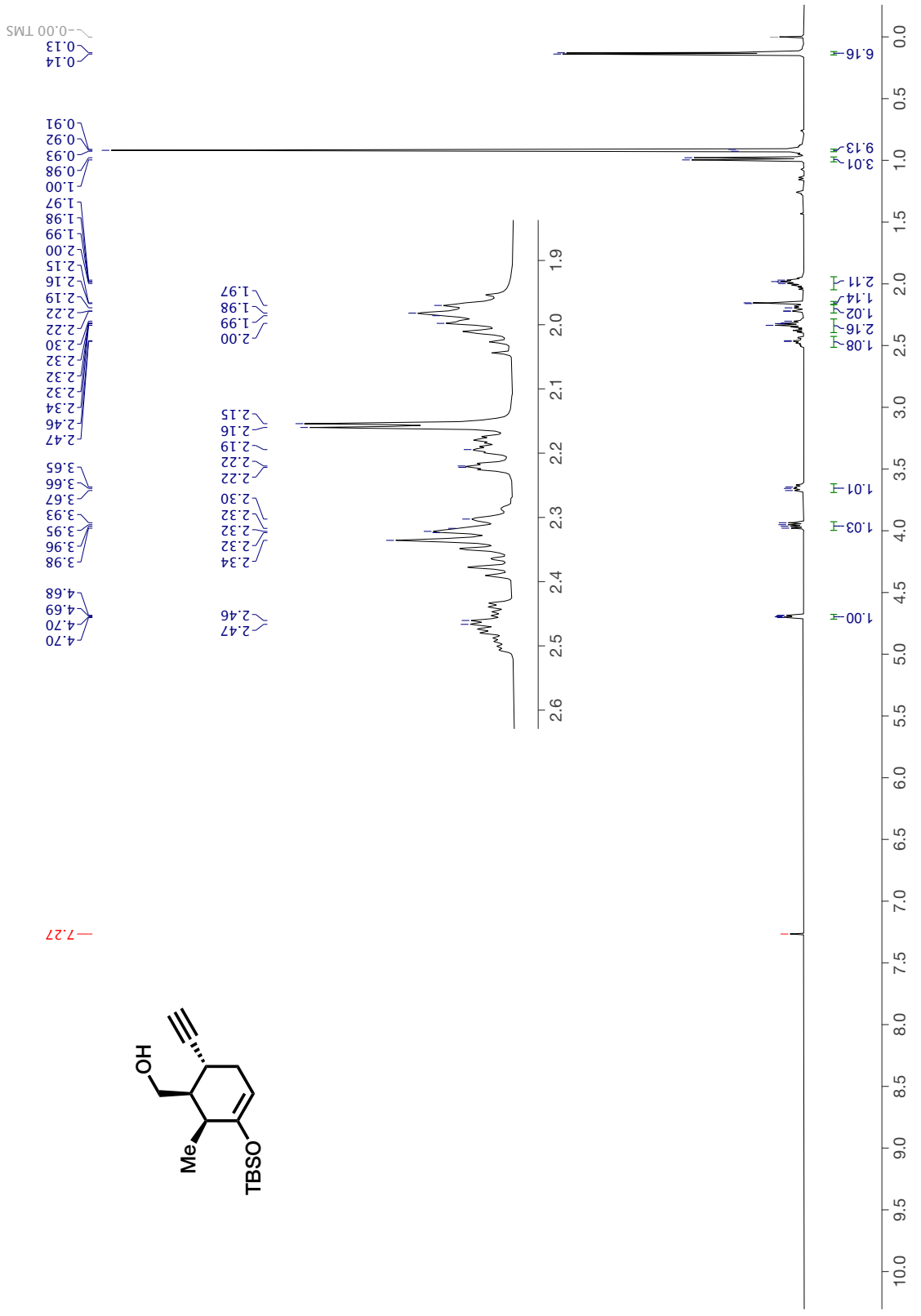


Figure A.64. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.44**.

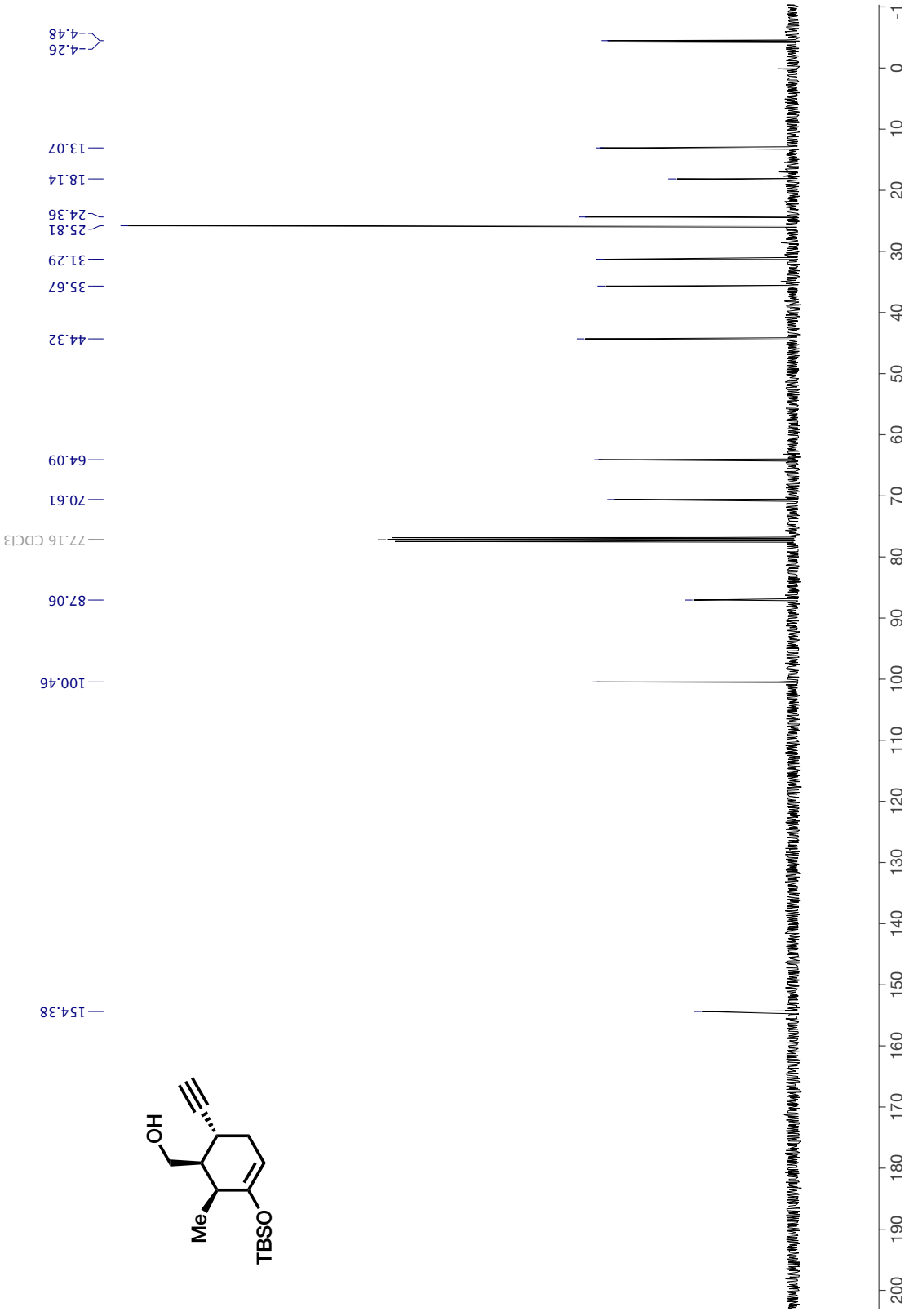


Figure A.65. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.44**.

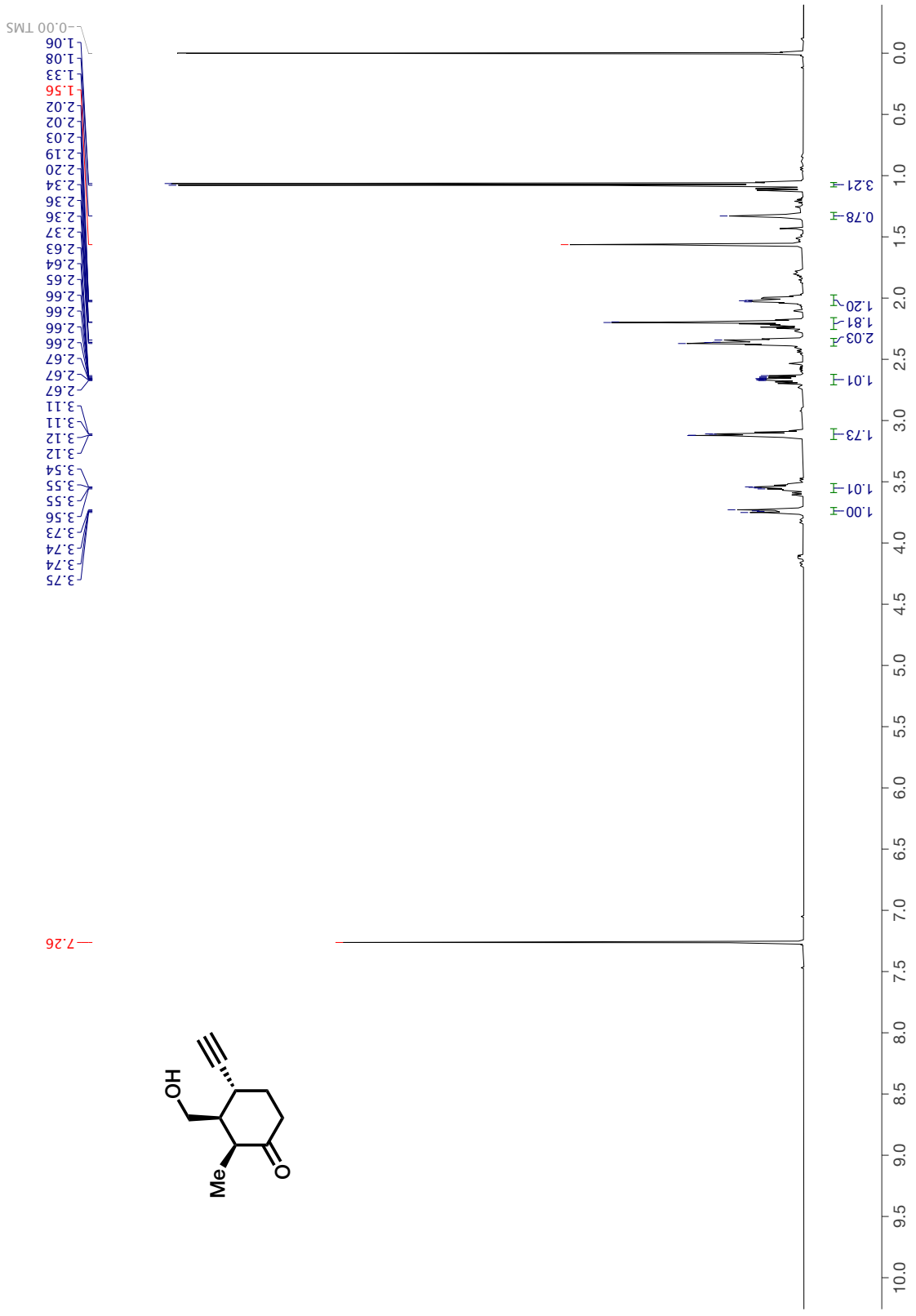


Figure A.66. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **3.13**.

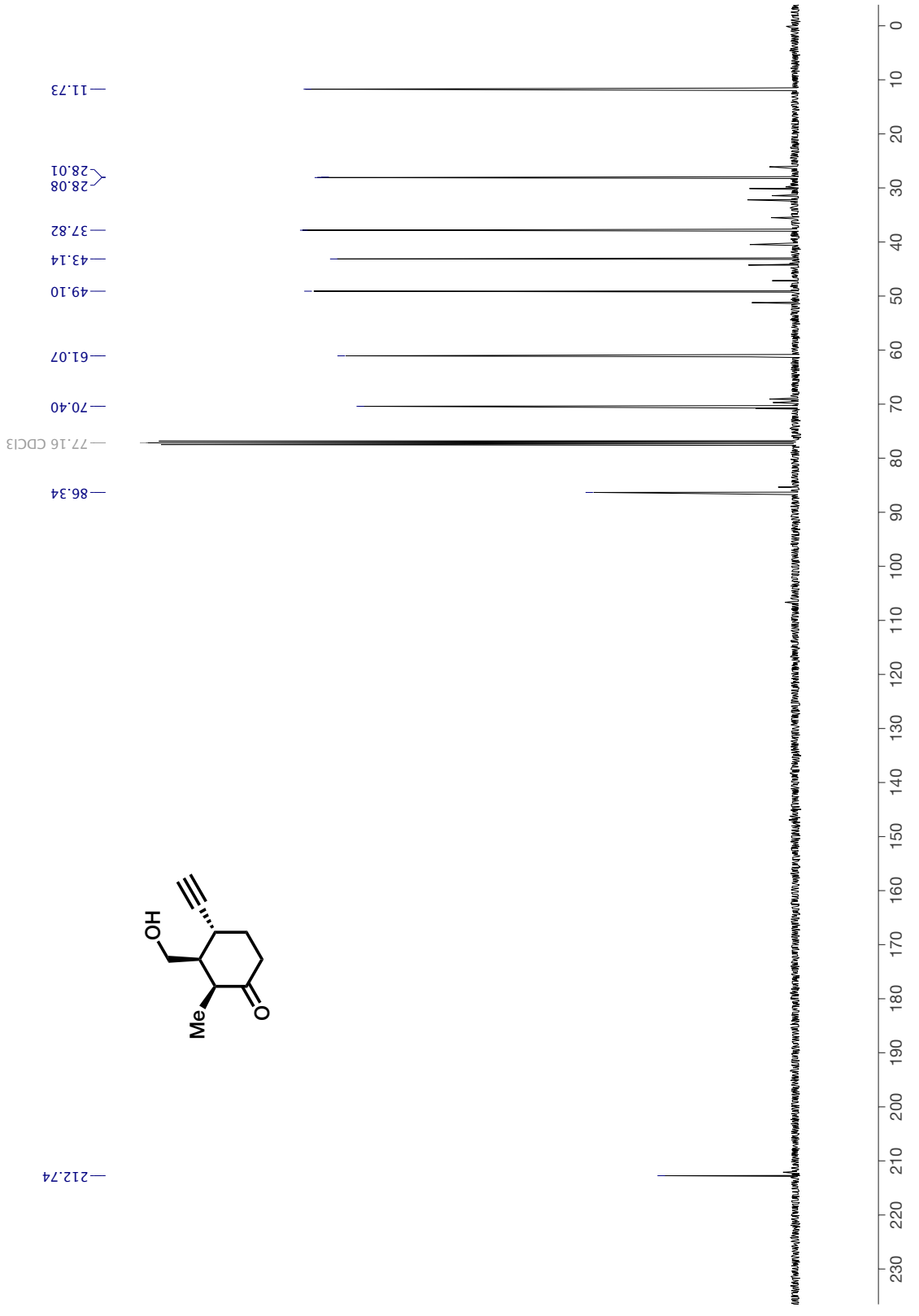


Figure A.67. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.13**.

Figure A.68. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **3.14**.

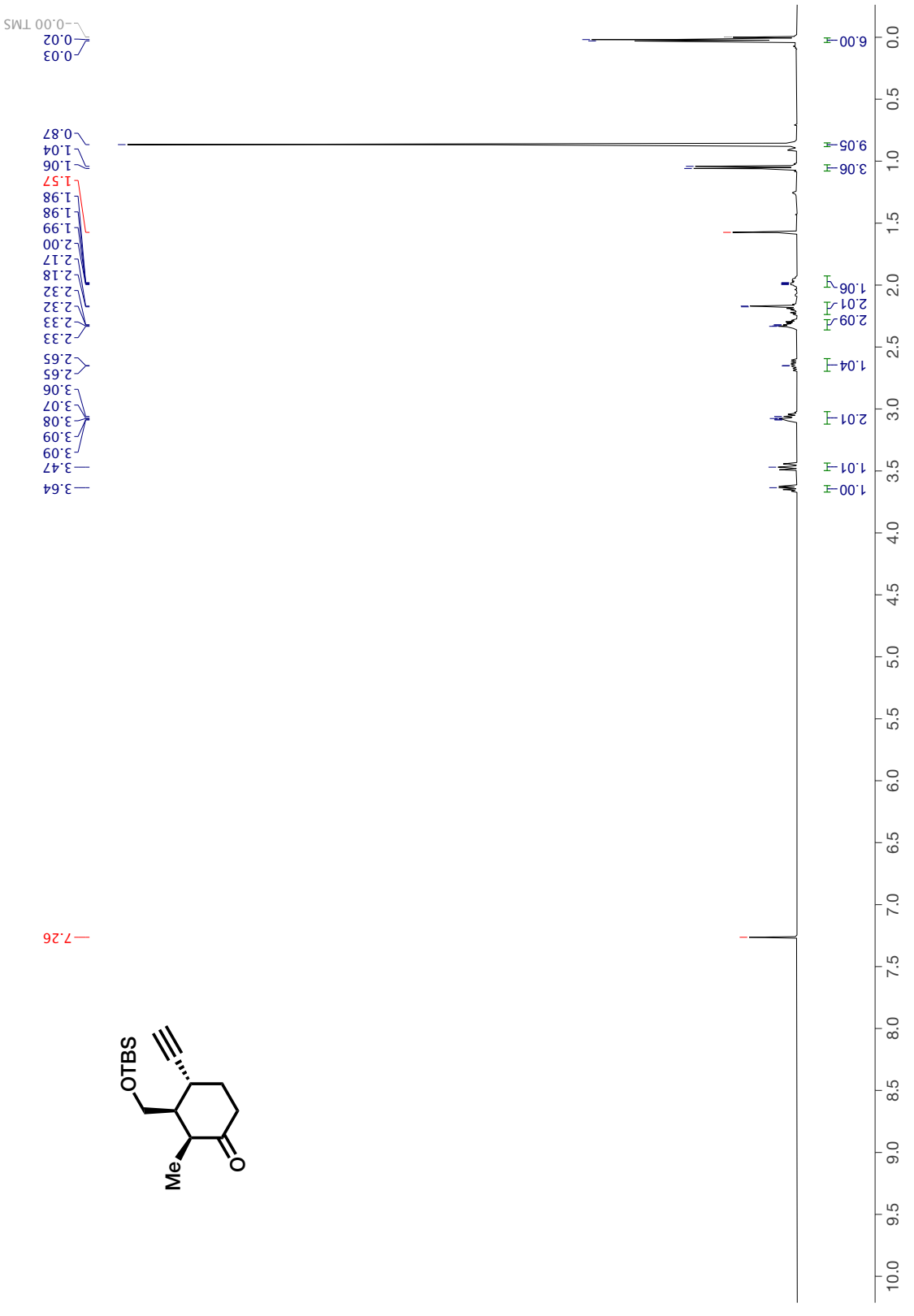


Figure A.69. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.15**.

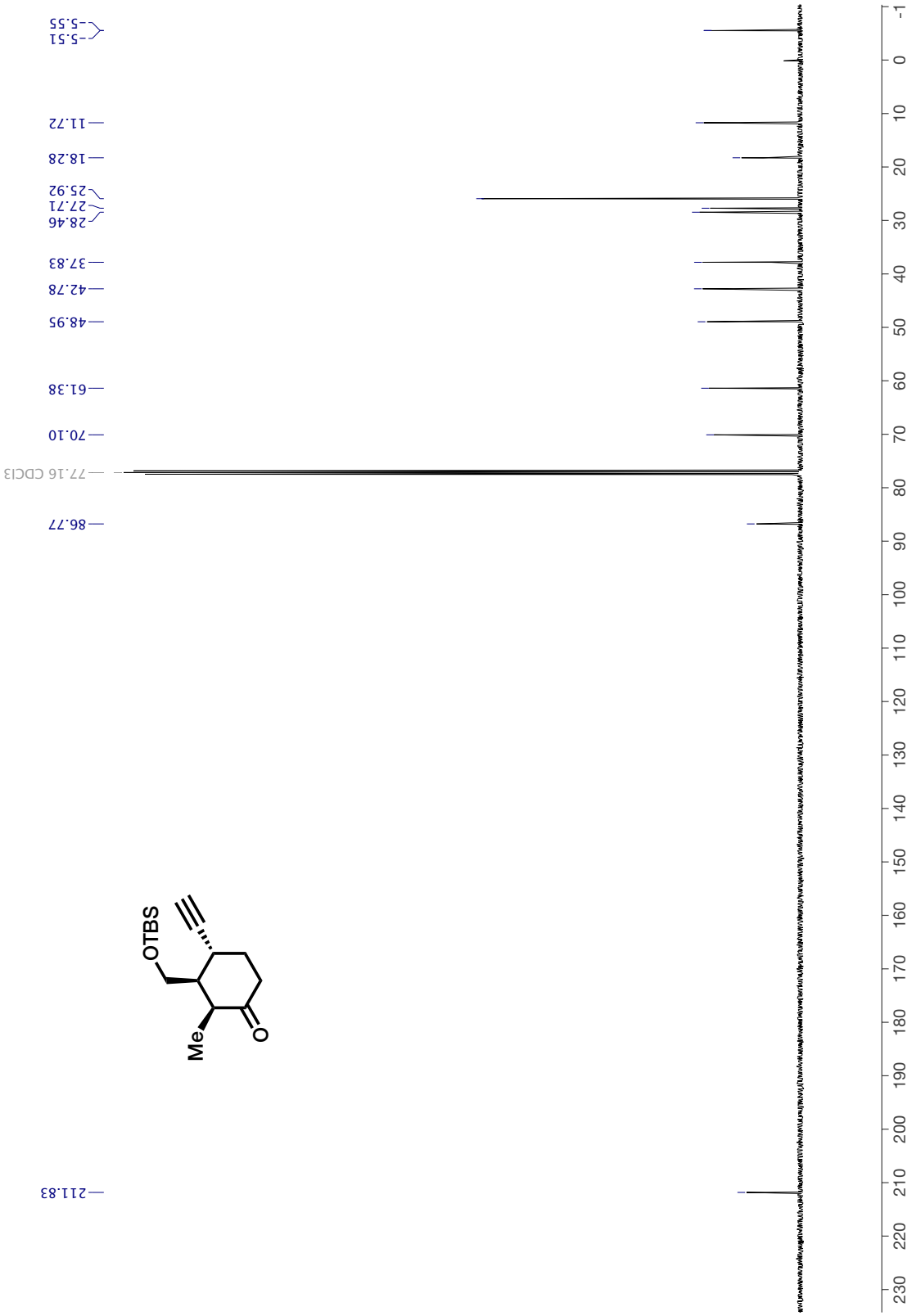


Figure A.70. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.15**.

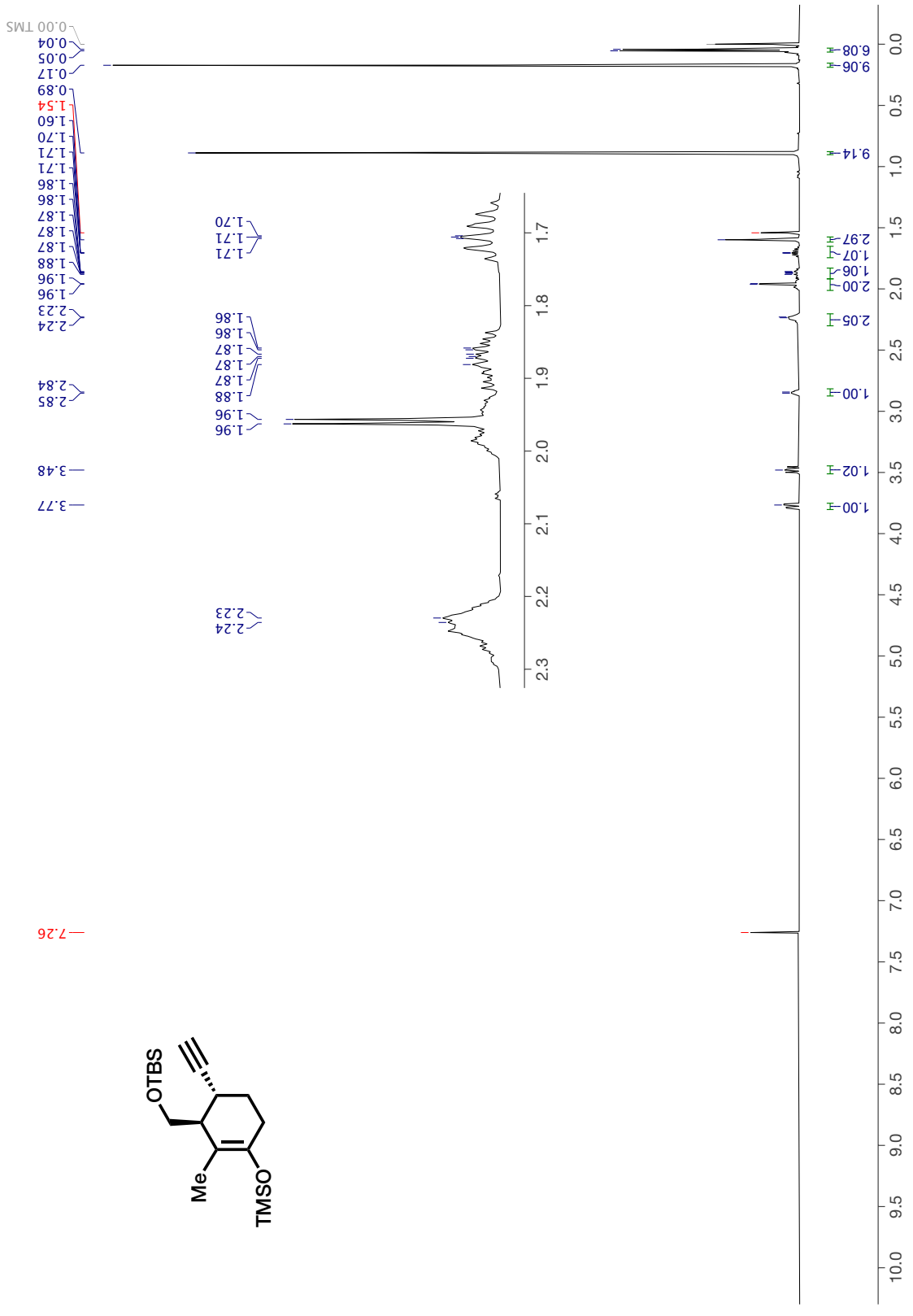


Figure A.71. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.16**.

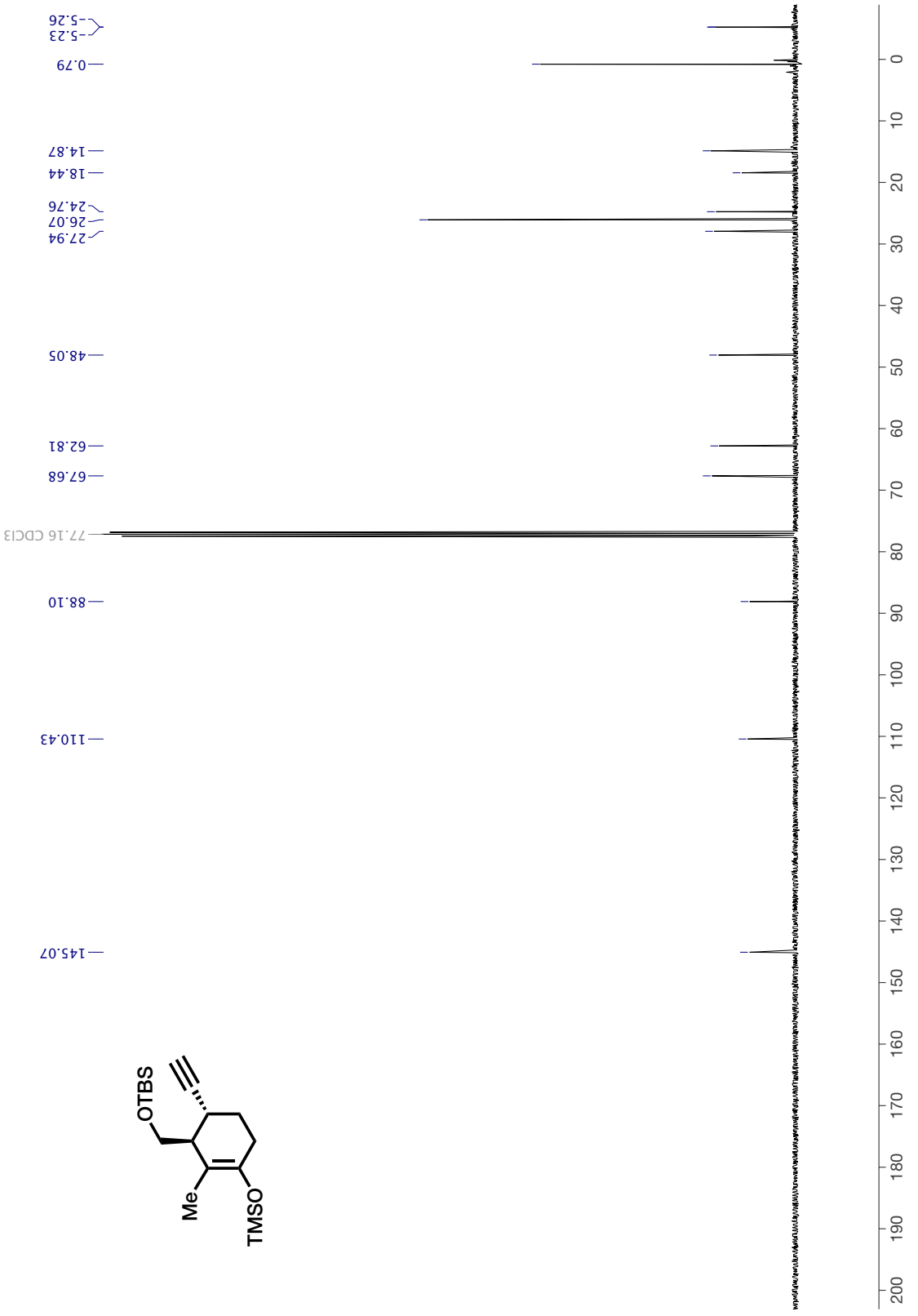


Figure A.72. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.16**.

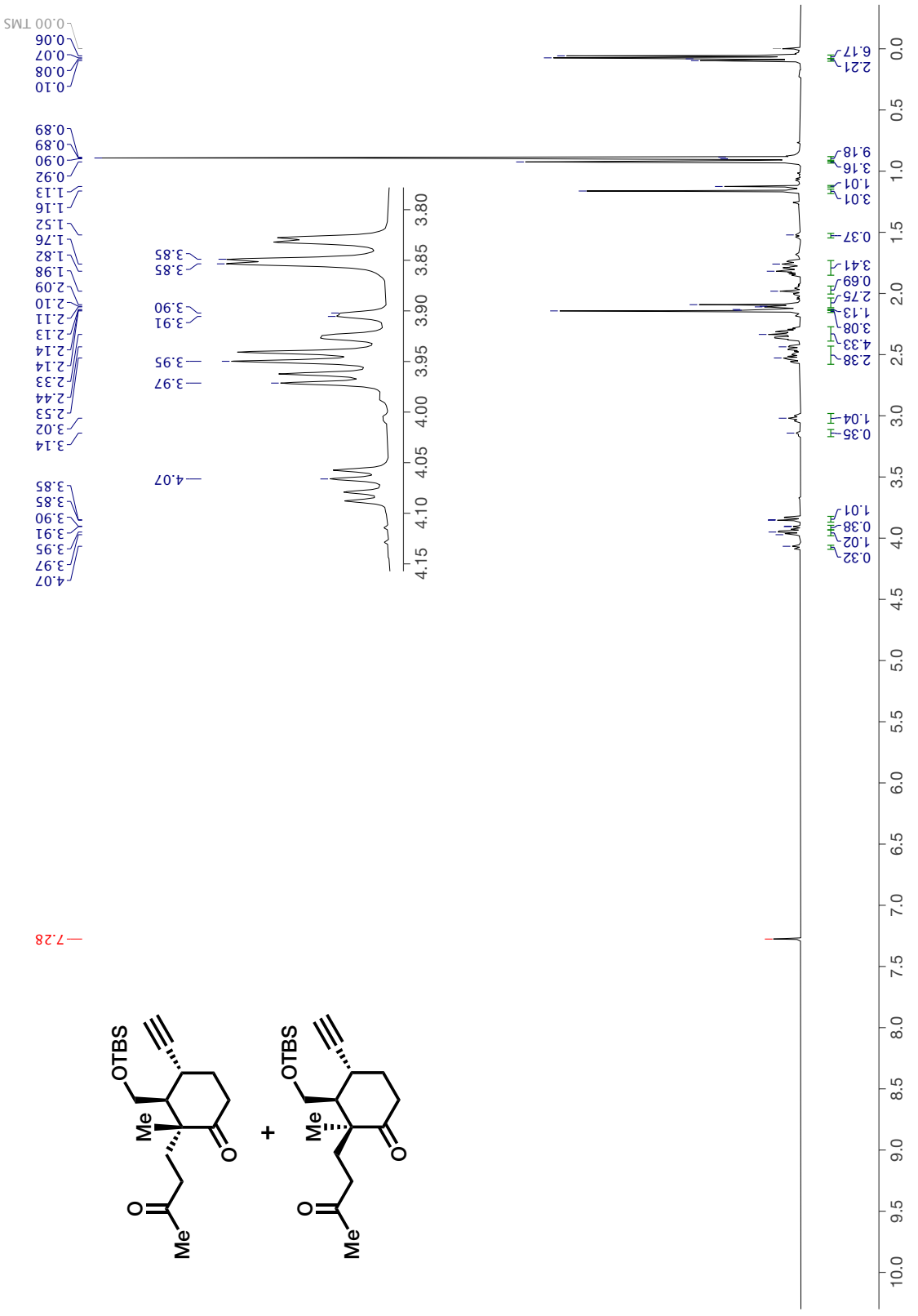


Figure A.73. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.17a**/**b**.

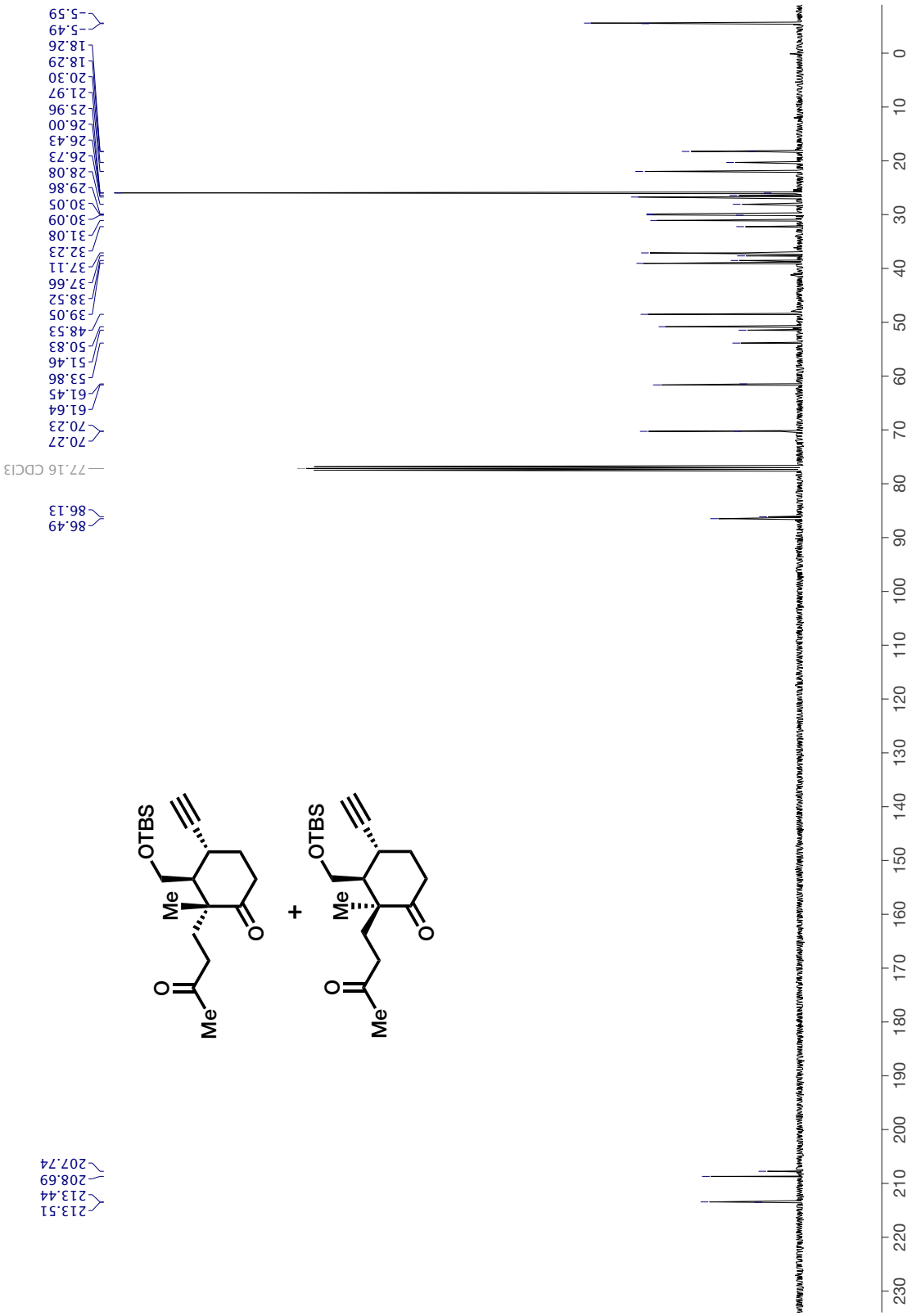


Figure A.74. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.17a**/**b**.

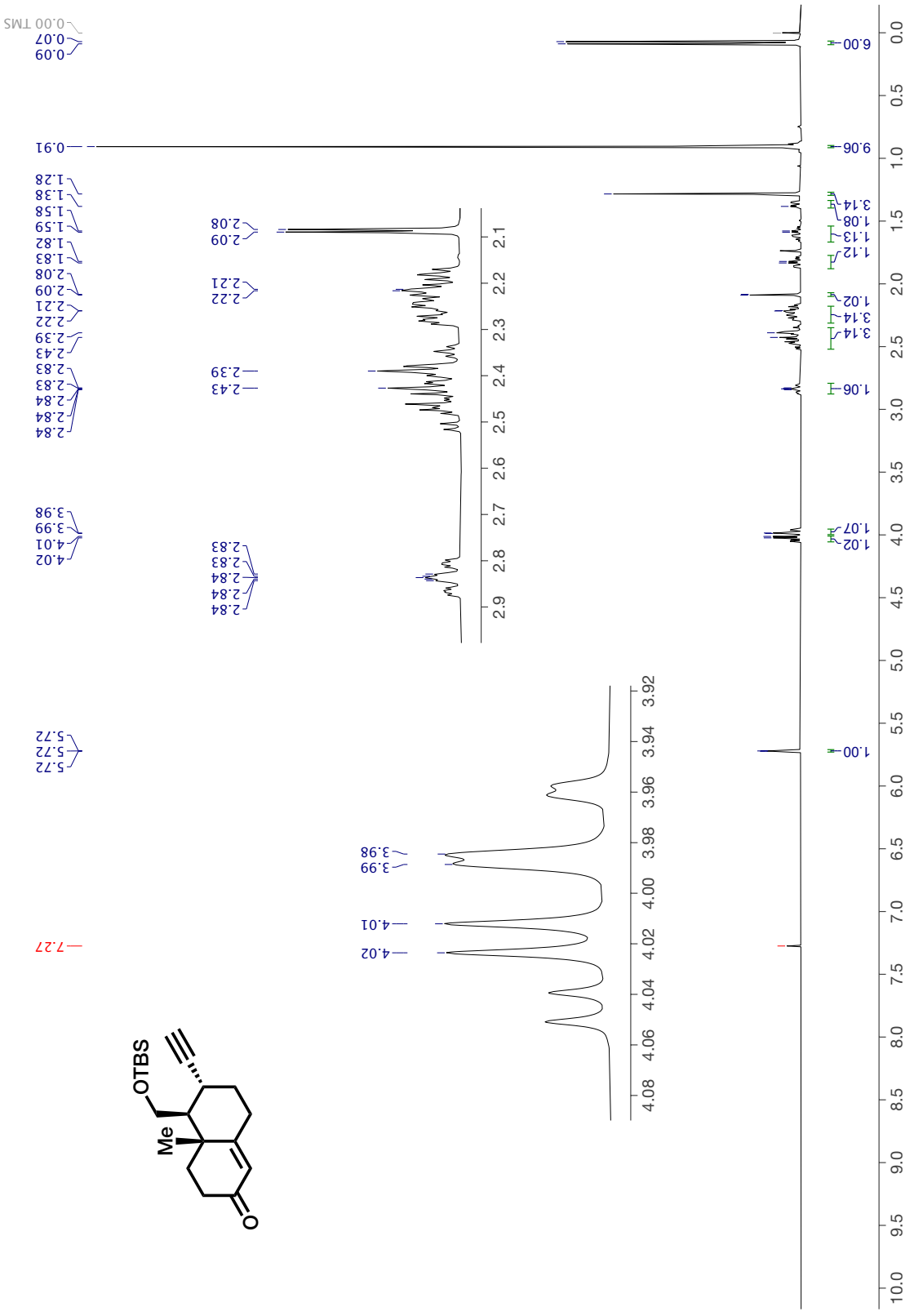


Figure A.75. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.18**.

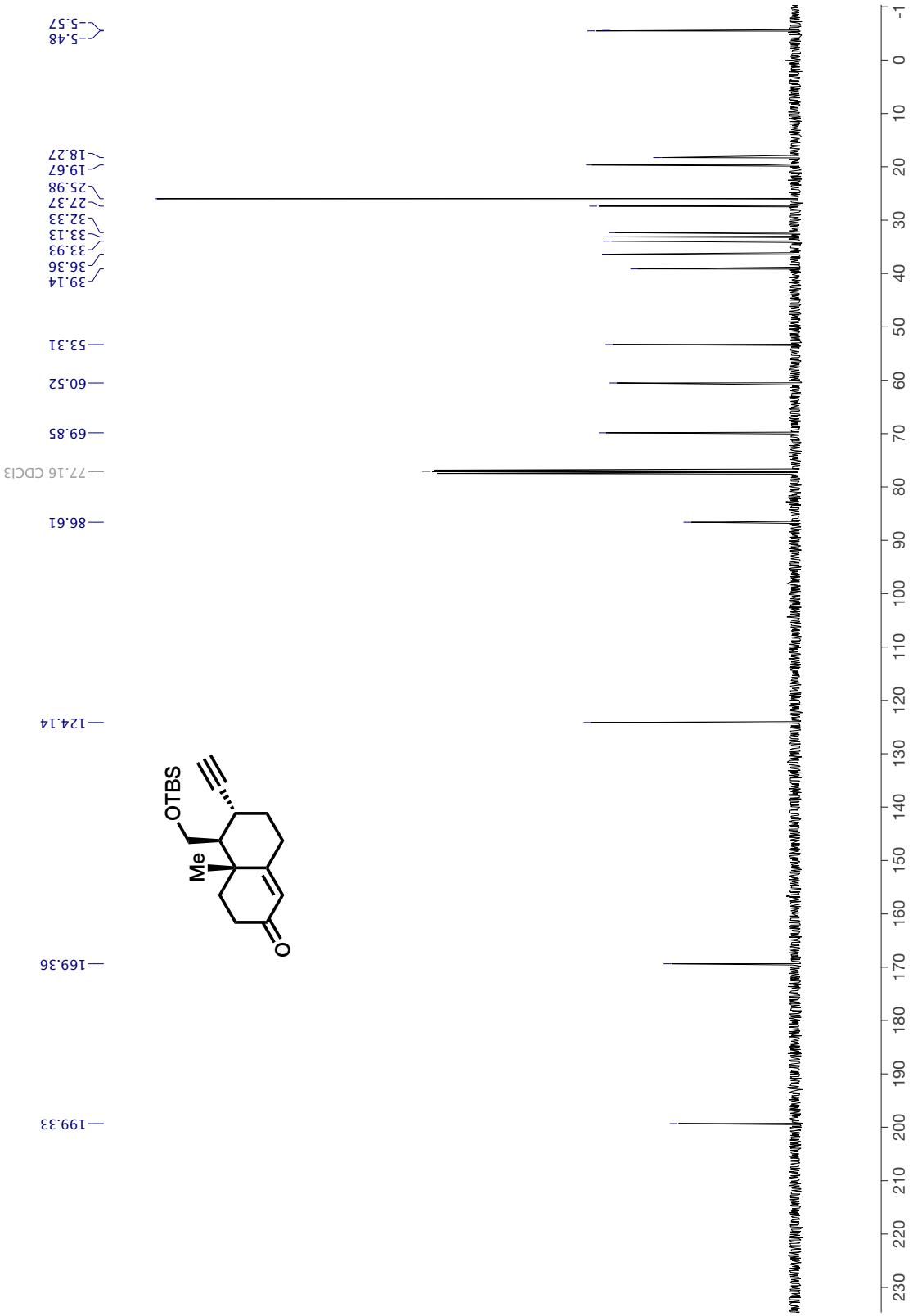


Figure A.76. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.18**.

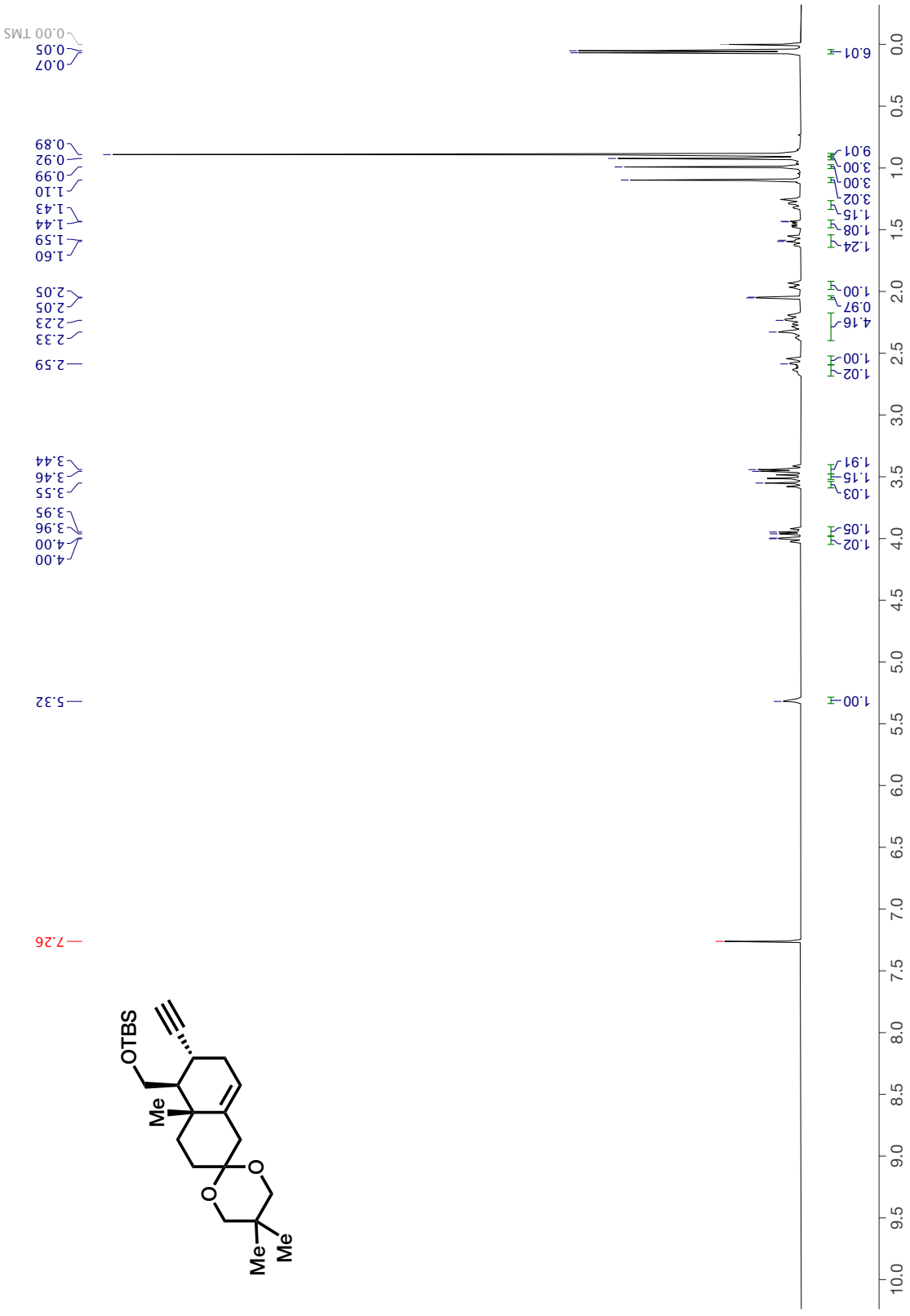


Figure A.77. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.19**.

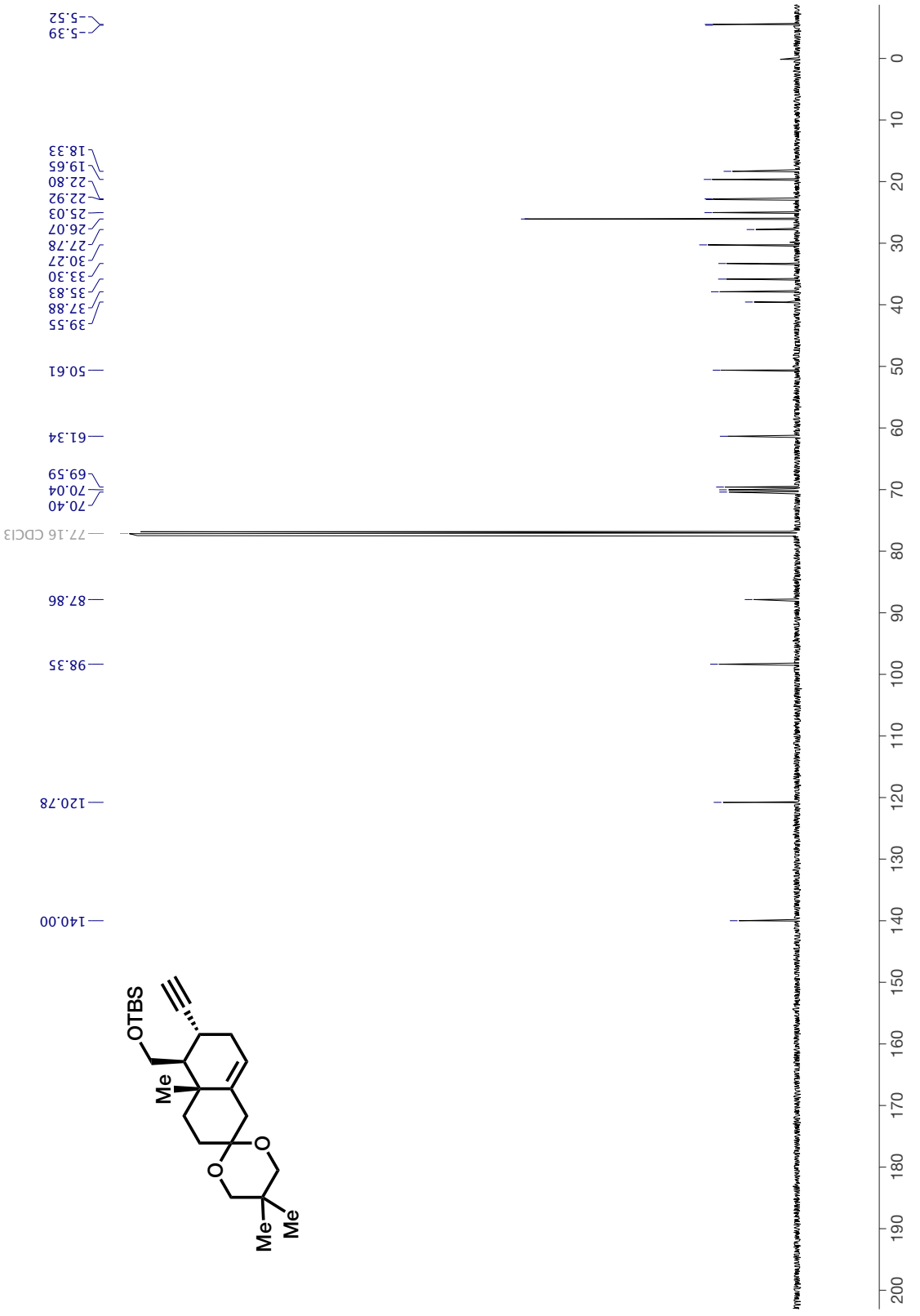


Figure A.78. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.19**.

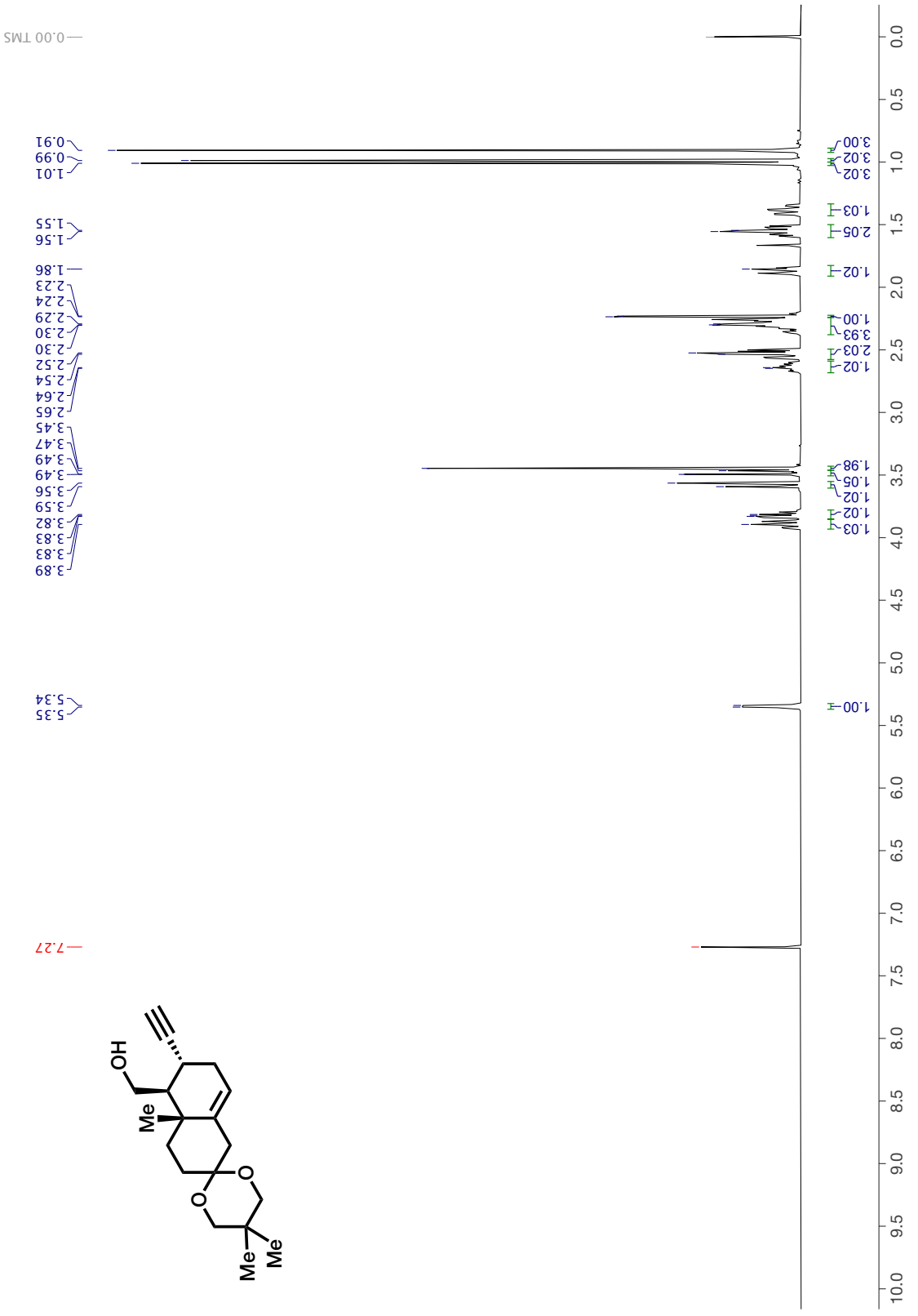


Figure A.79. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.20**.

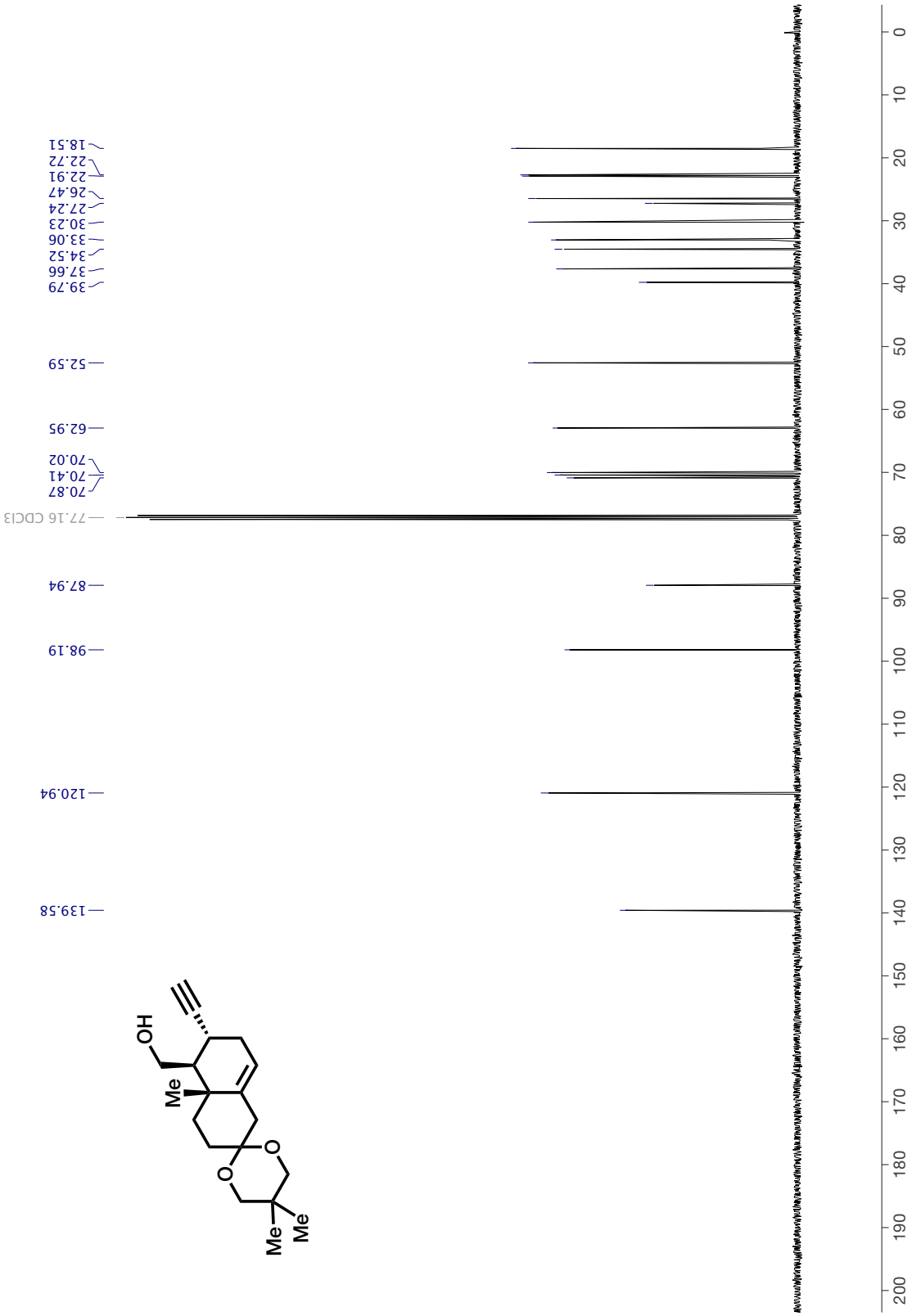


Figure A.80. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.20**.

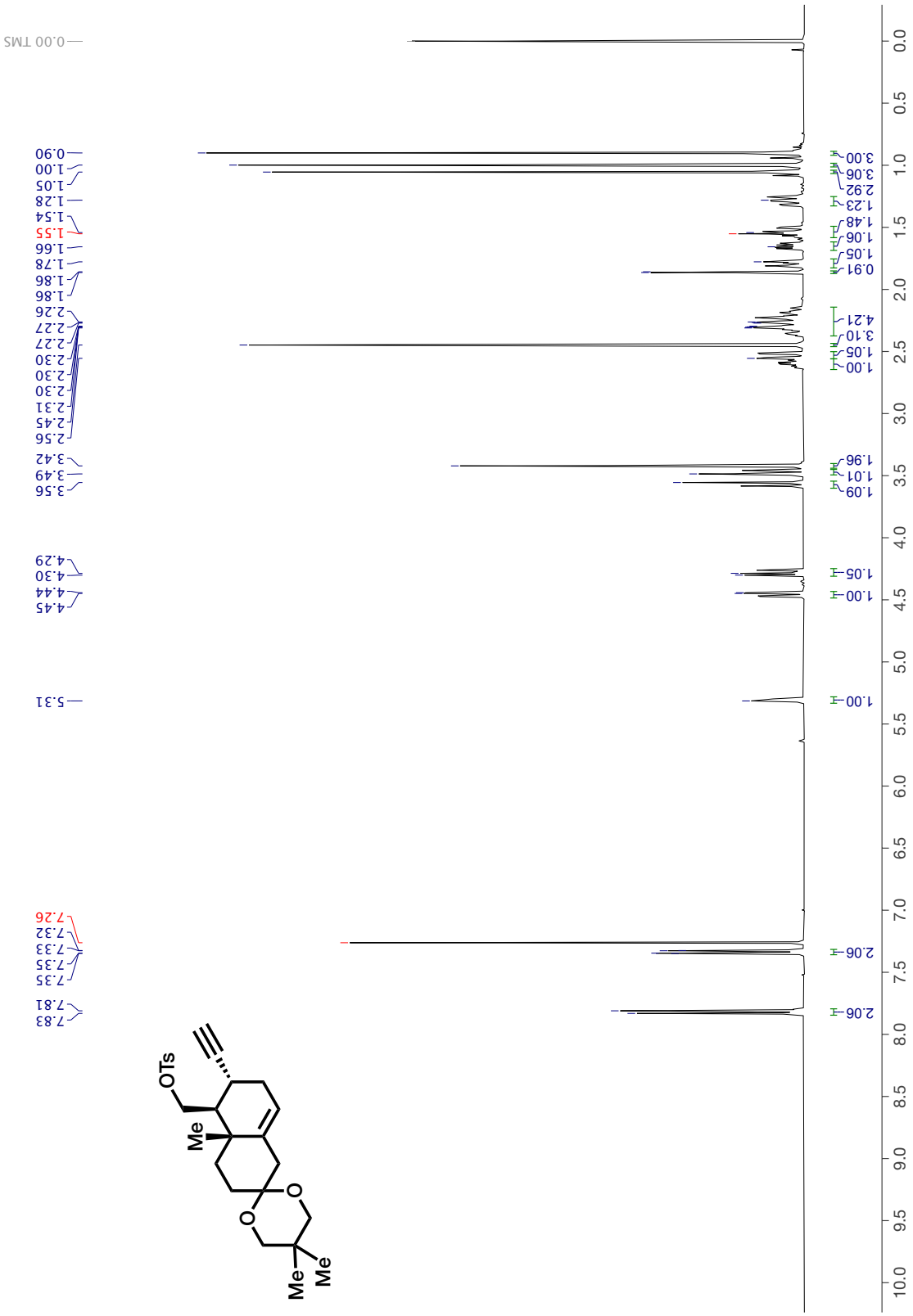


Figure A.81. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.21**.

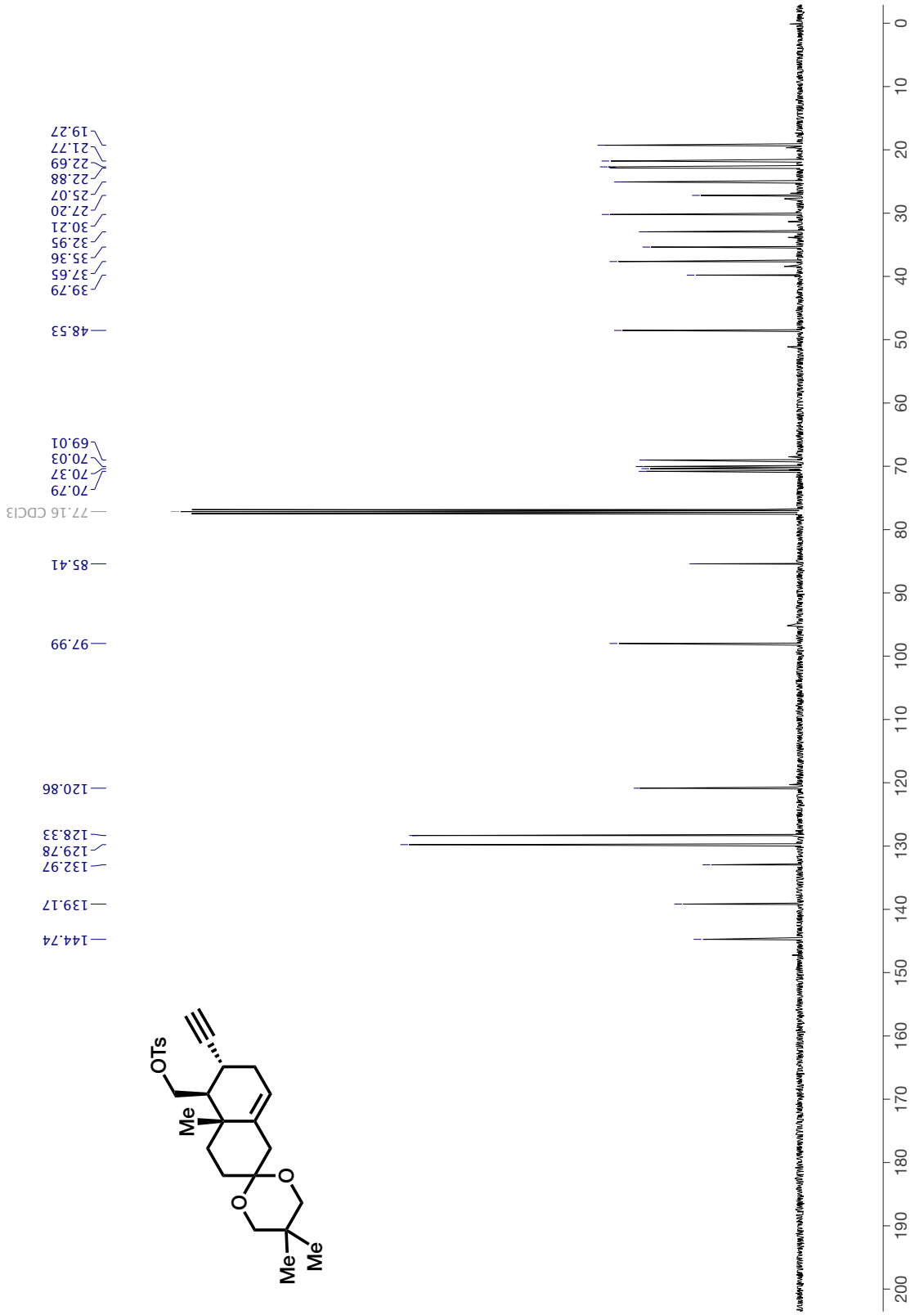


Figure A.82. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.21**.

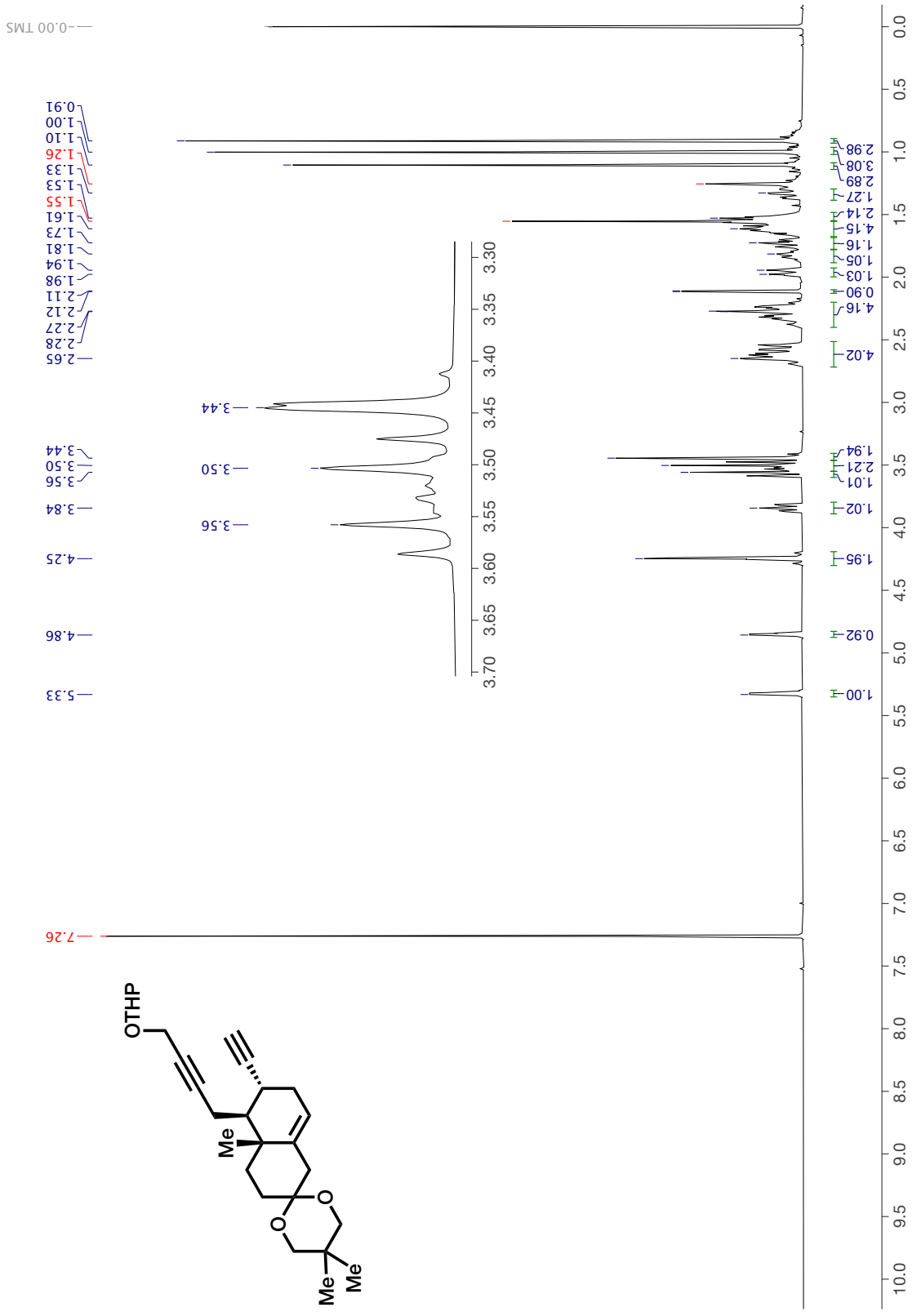


Figure A.83. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.22**.

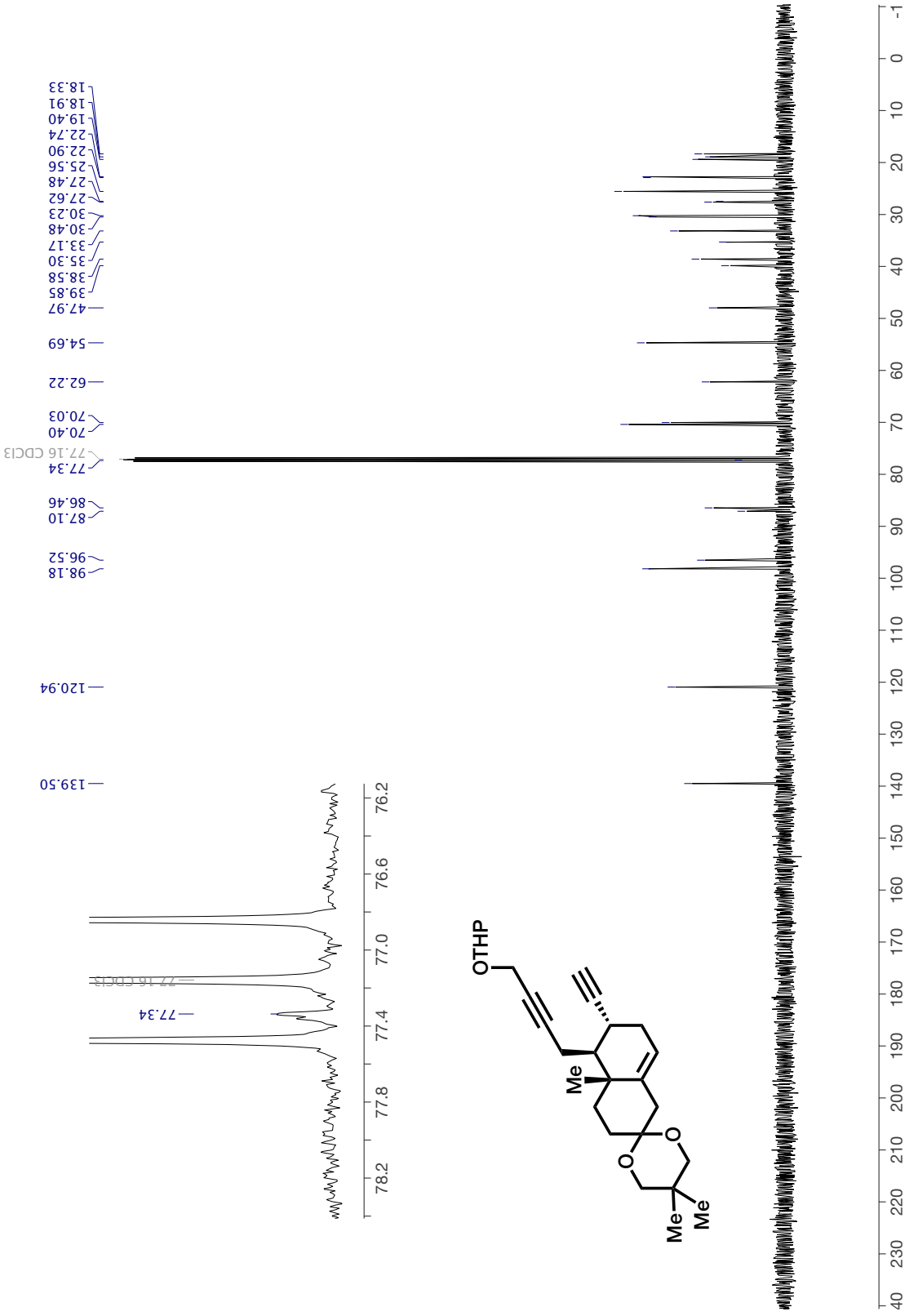


Figure A.84. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.22**.

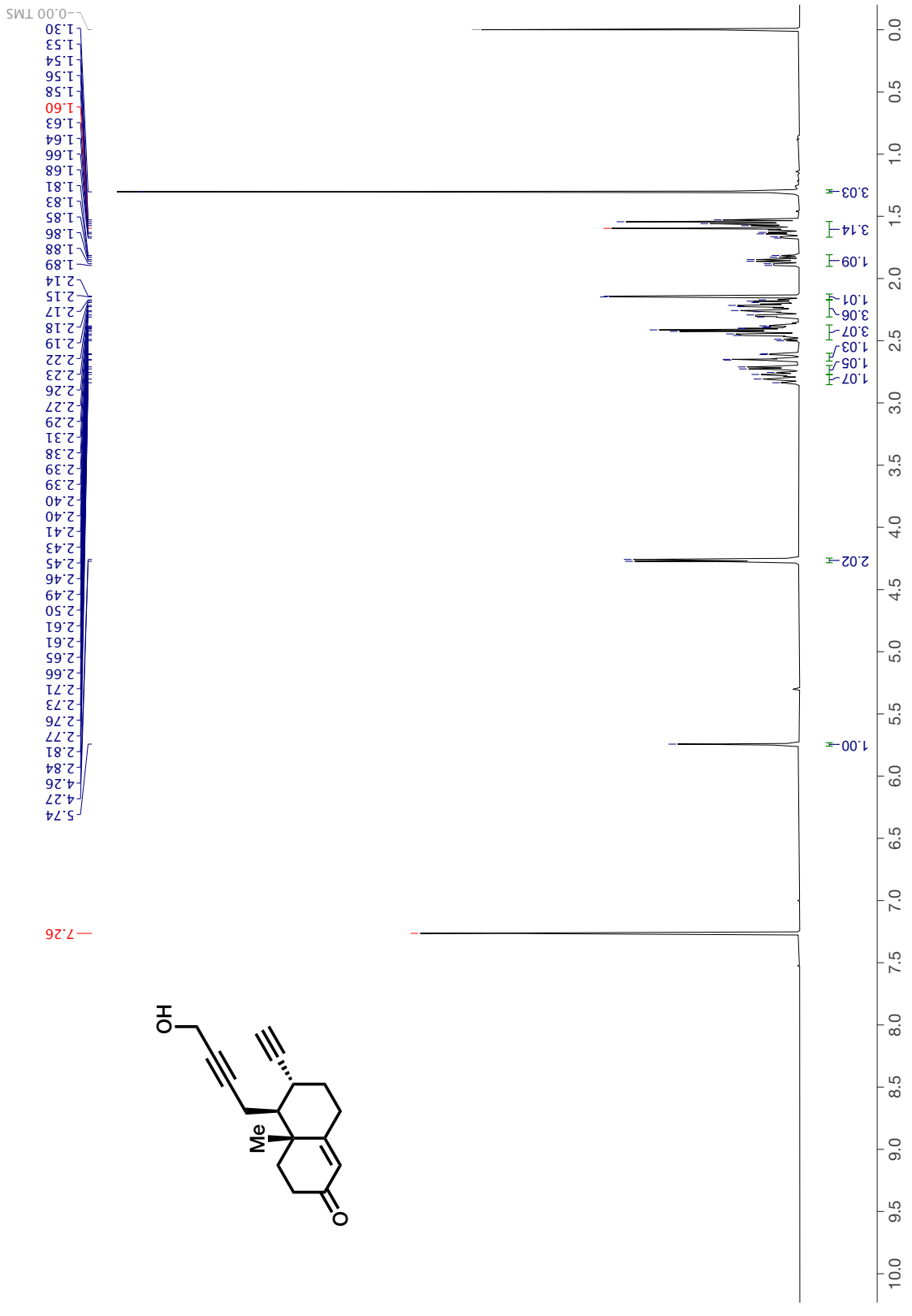


Figure A.85. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.23**.

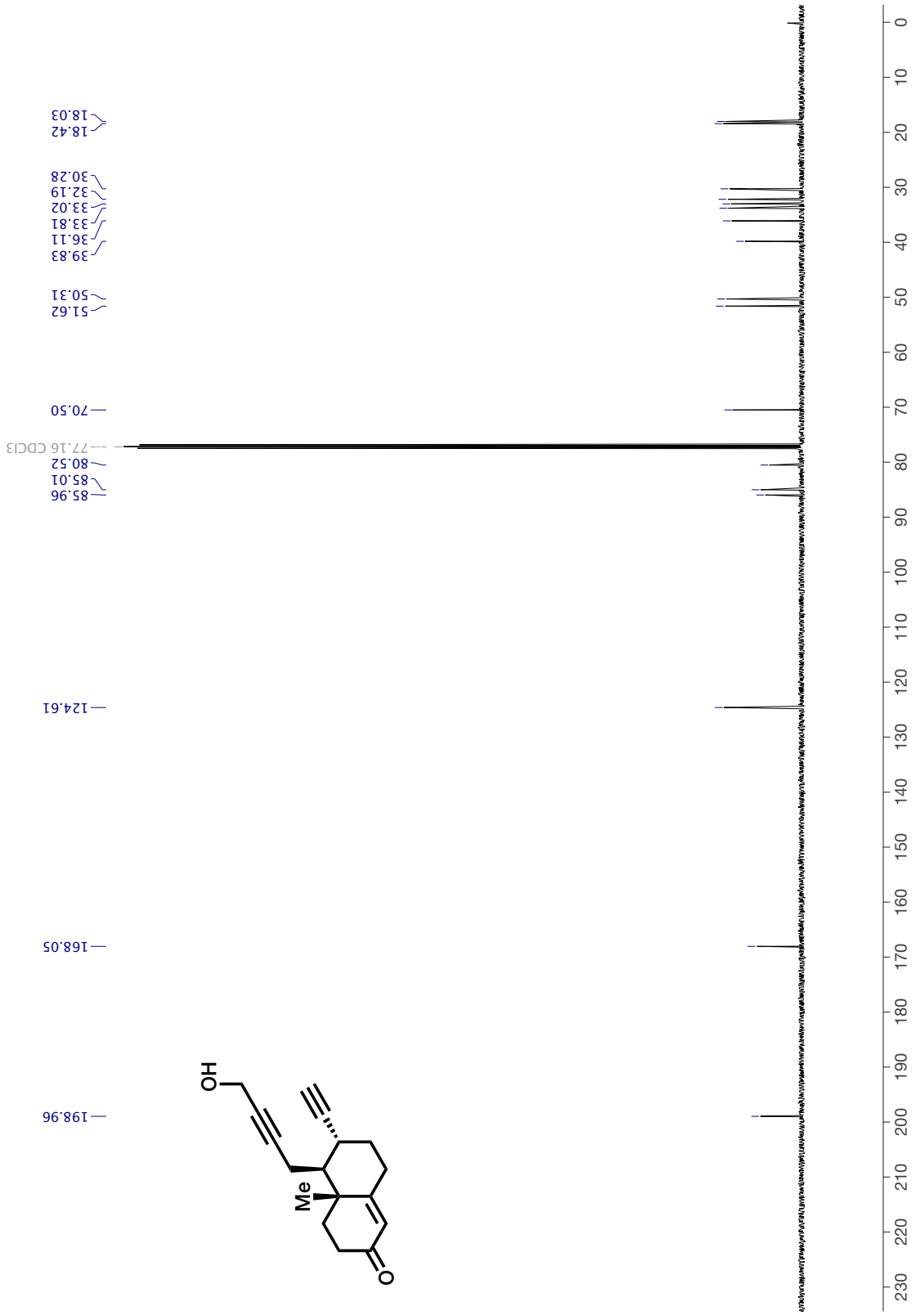


Figure A.86. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.23**.

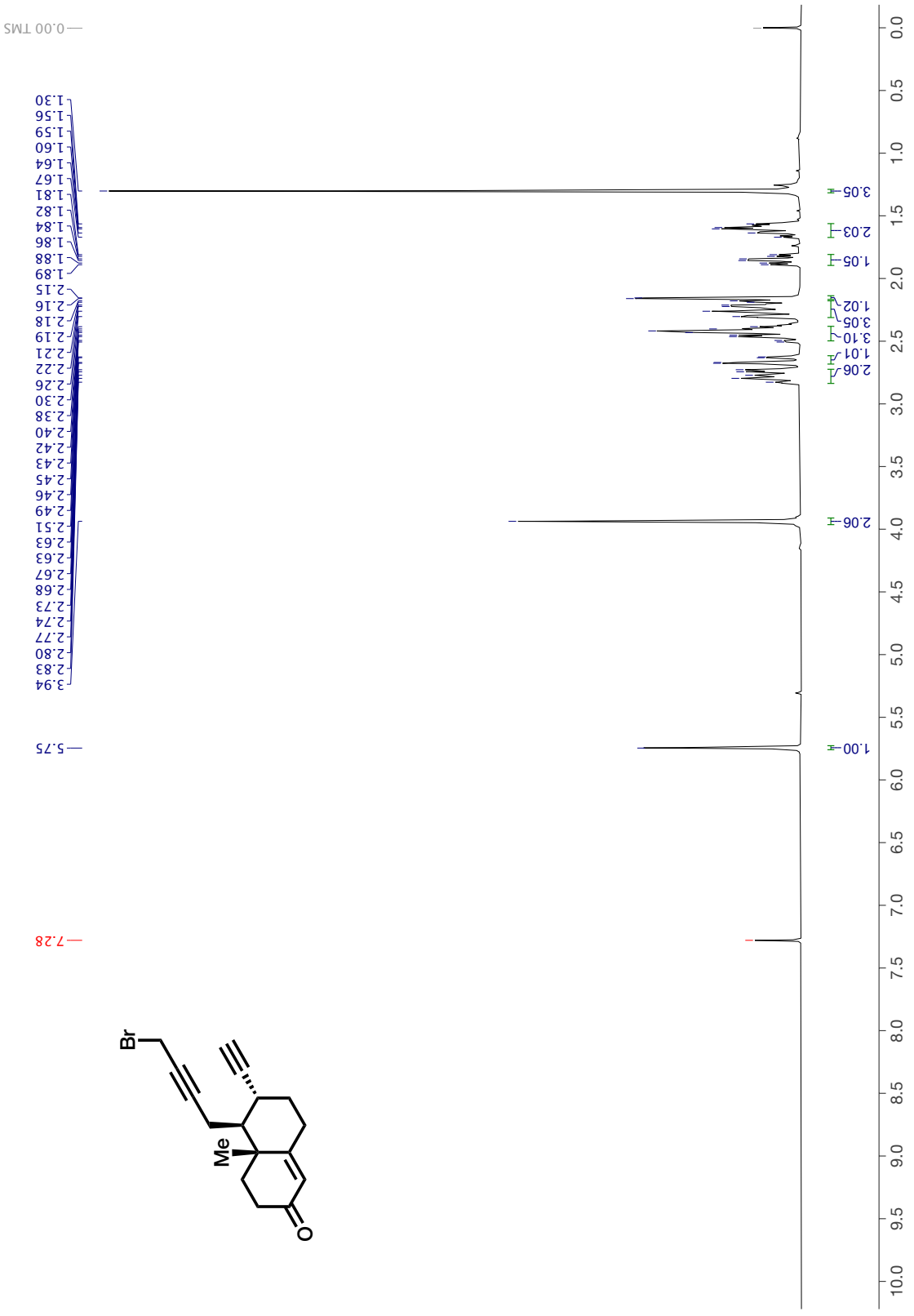


Figure A.87. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.45**.

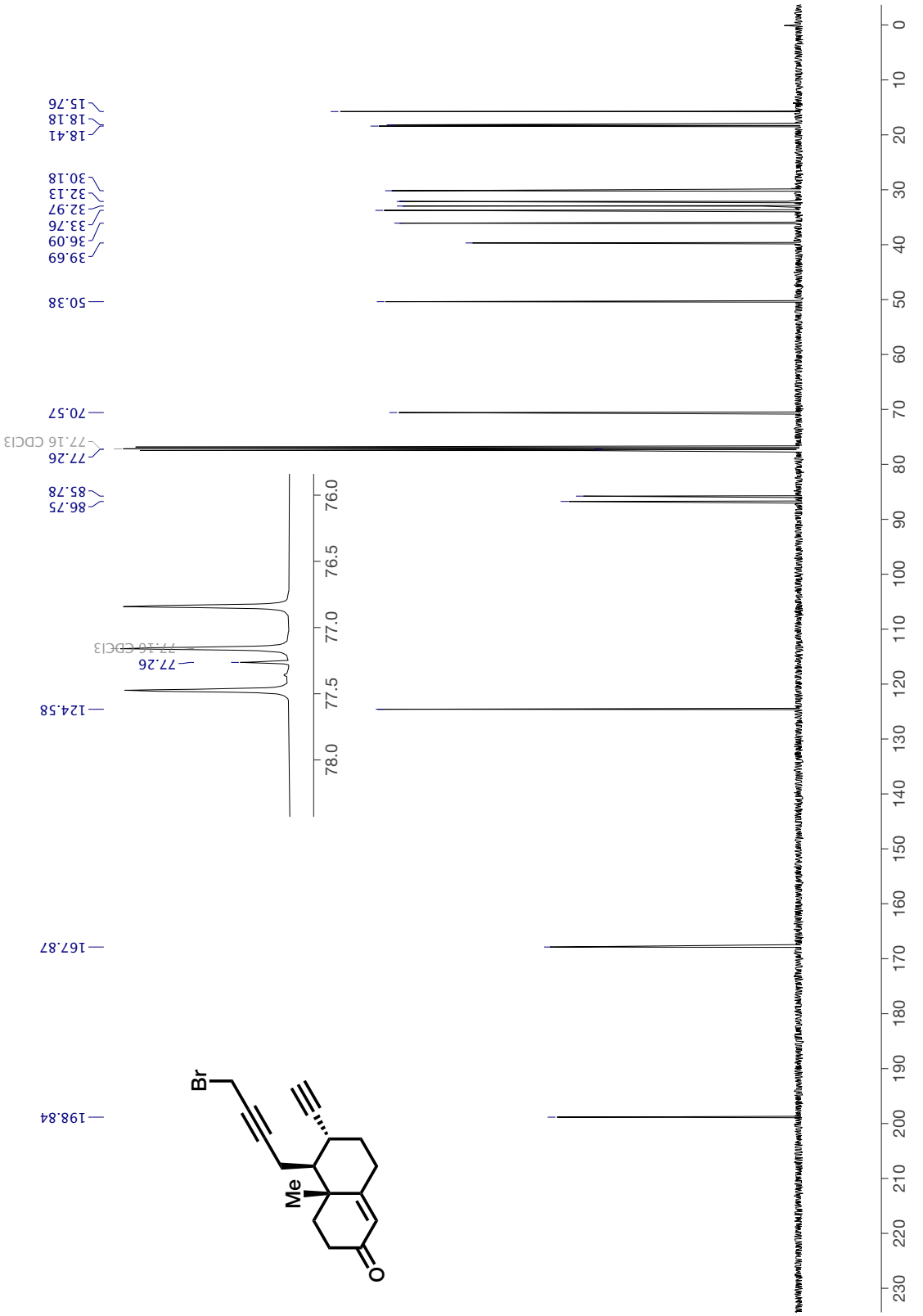


Figure A.88. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.45**.

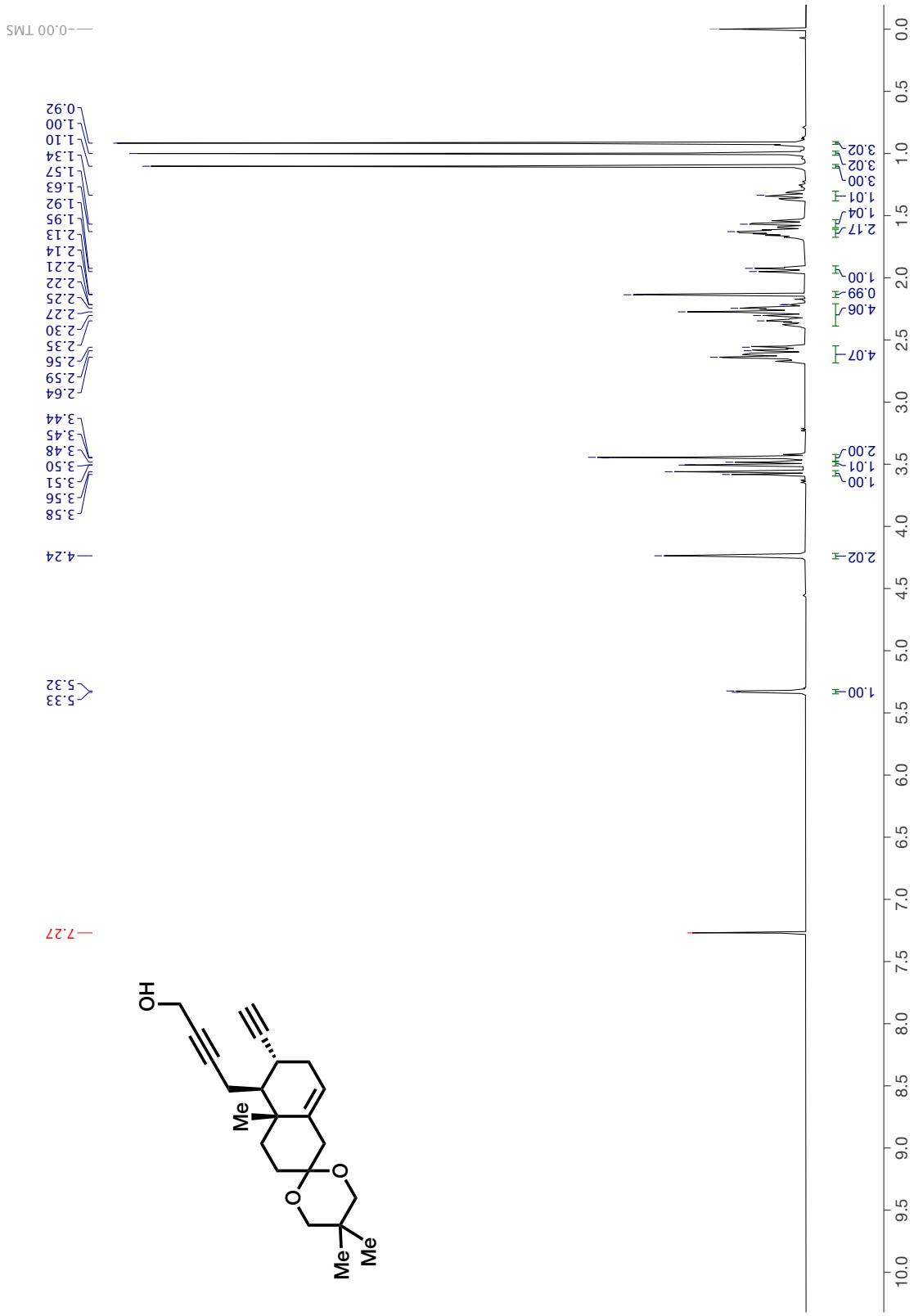


Figure A.89. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **3.24**.

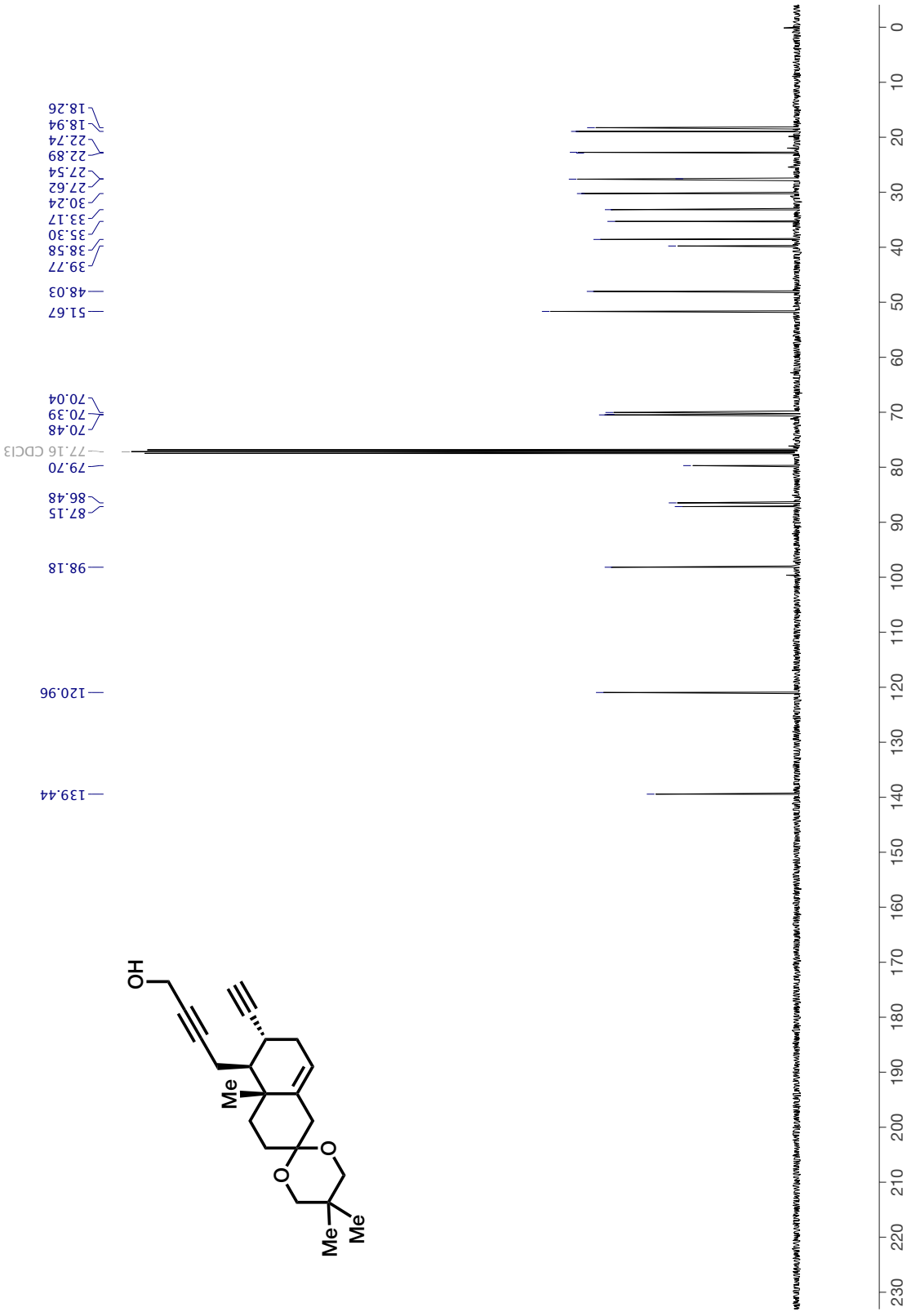


Figure A.90. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.24**.

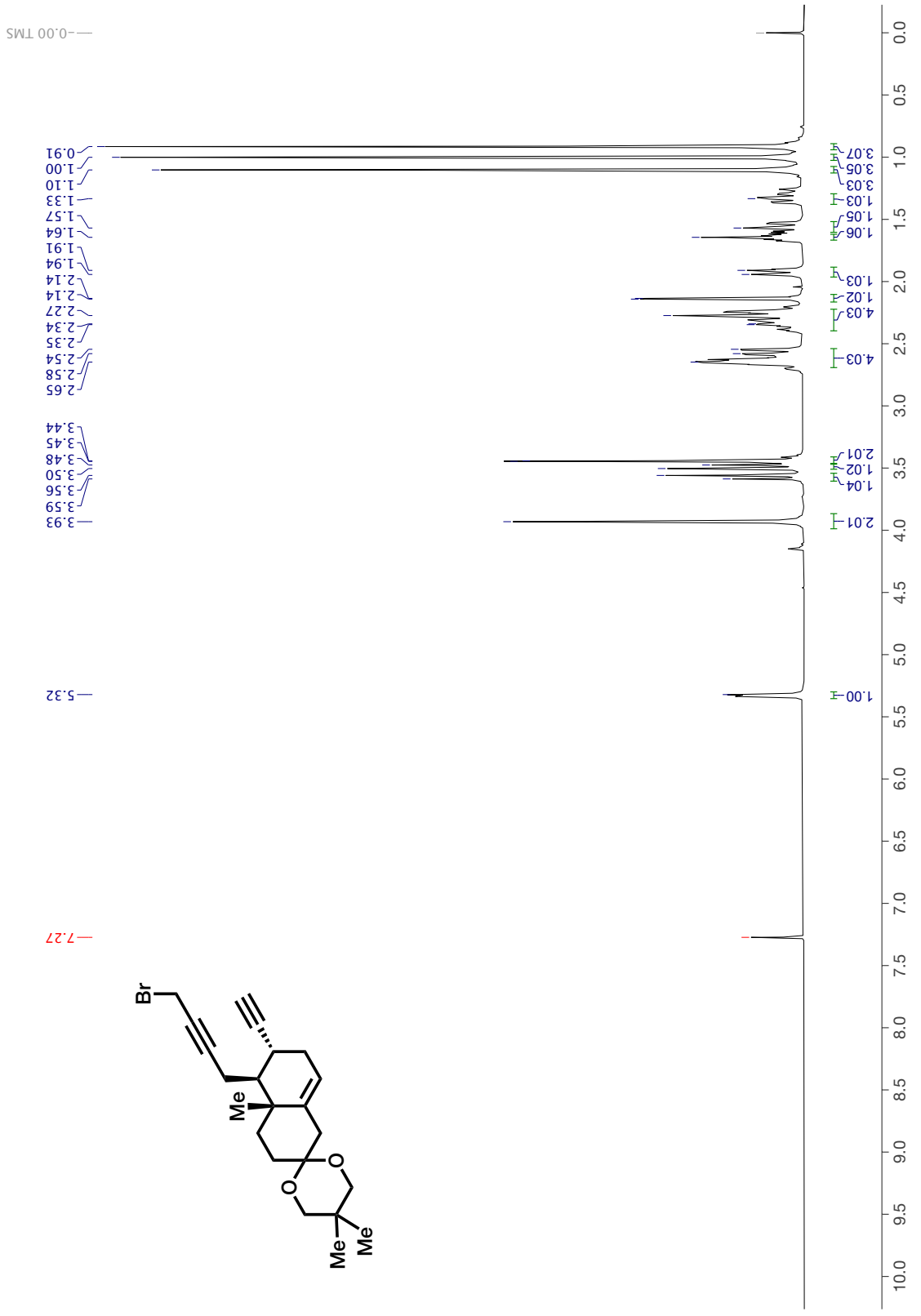


Figure A.91. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **3.25**.

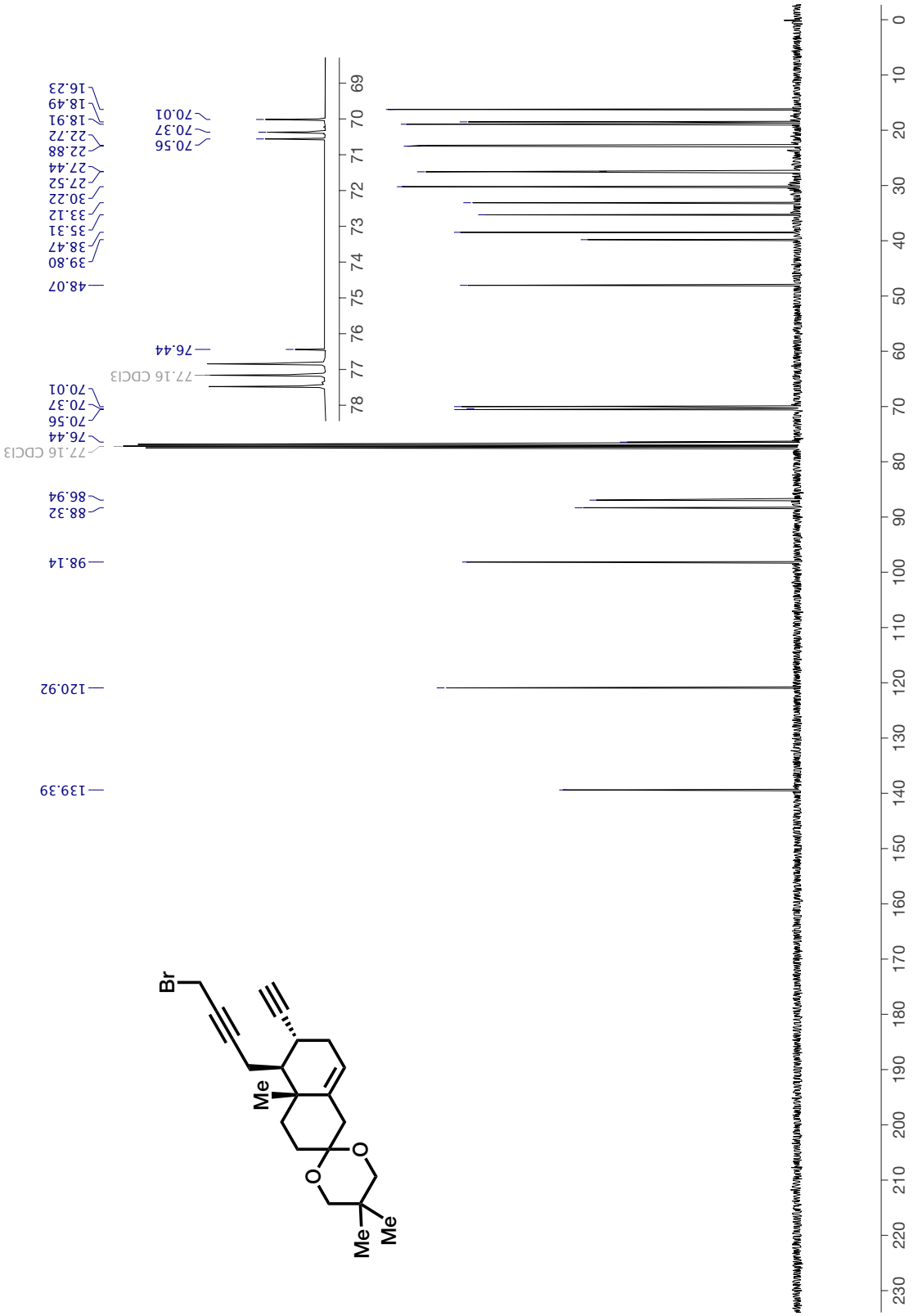


Figure A.92. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.25**.

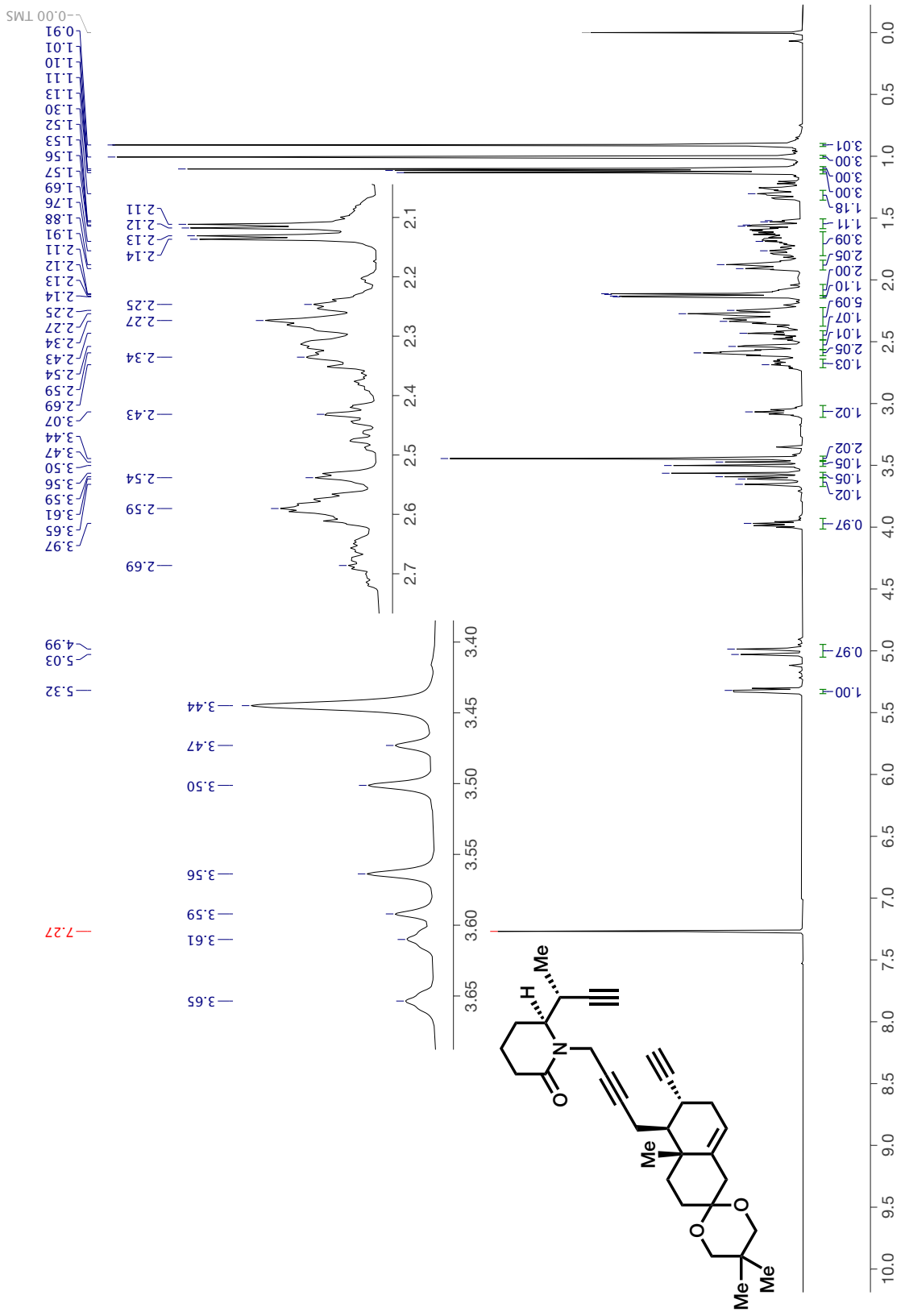


Figure A.93. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.27**.

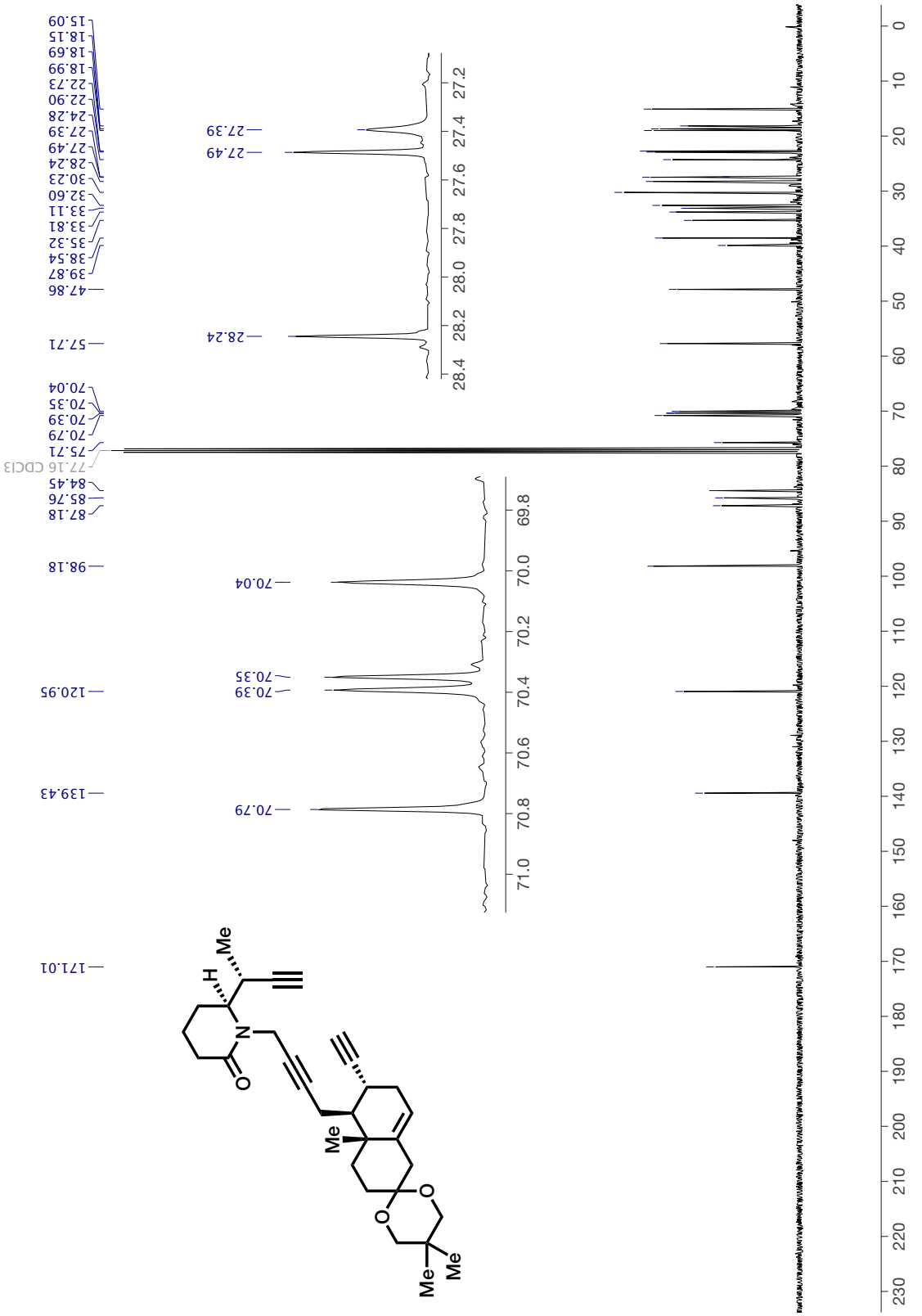


Figure A.94. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.27**.

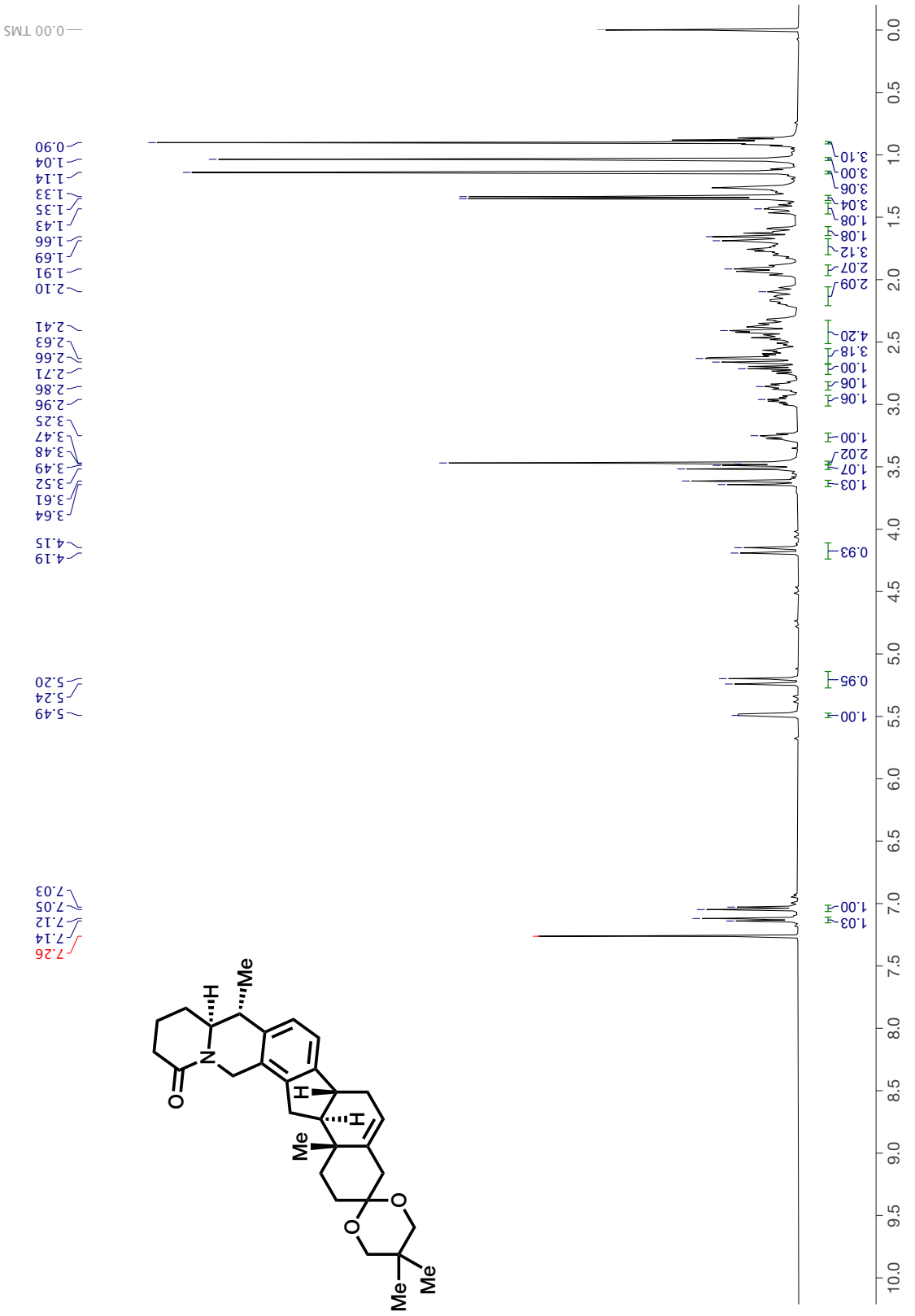


Figure A.95. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.28**.

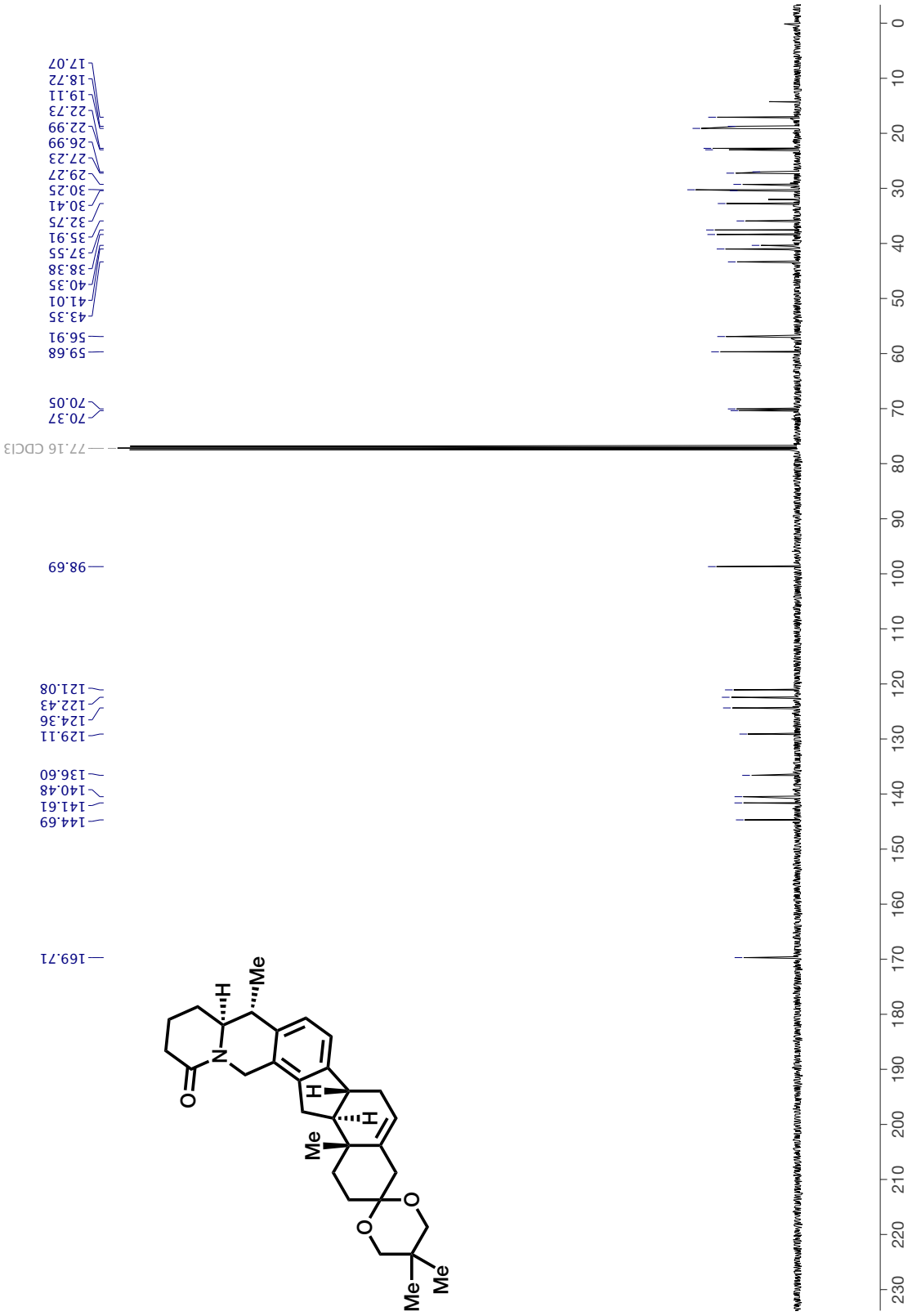


Figure A.96. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.28**.

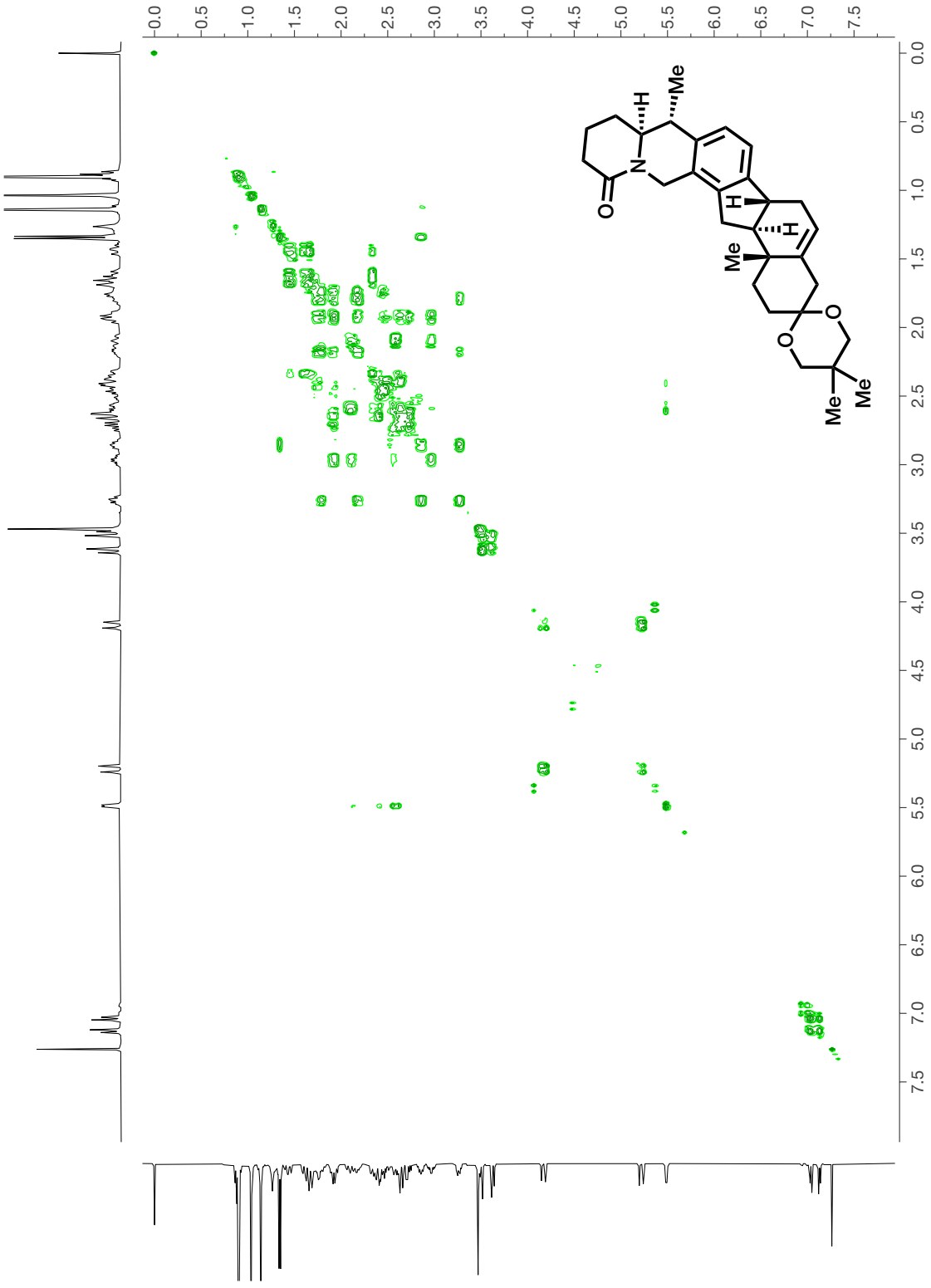


Figure A.97. ^{1}H–^{1}H COSY spectrum (400 MHz, $CDCl_3$) of **3.28**.

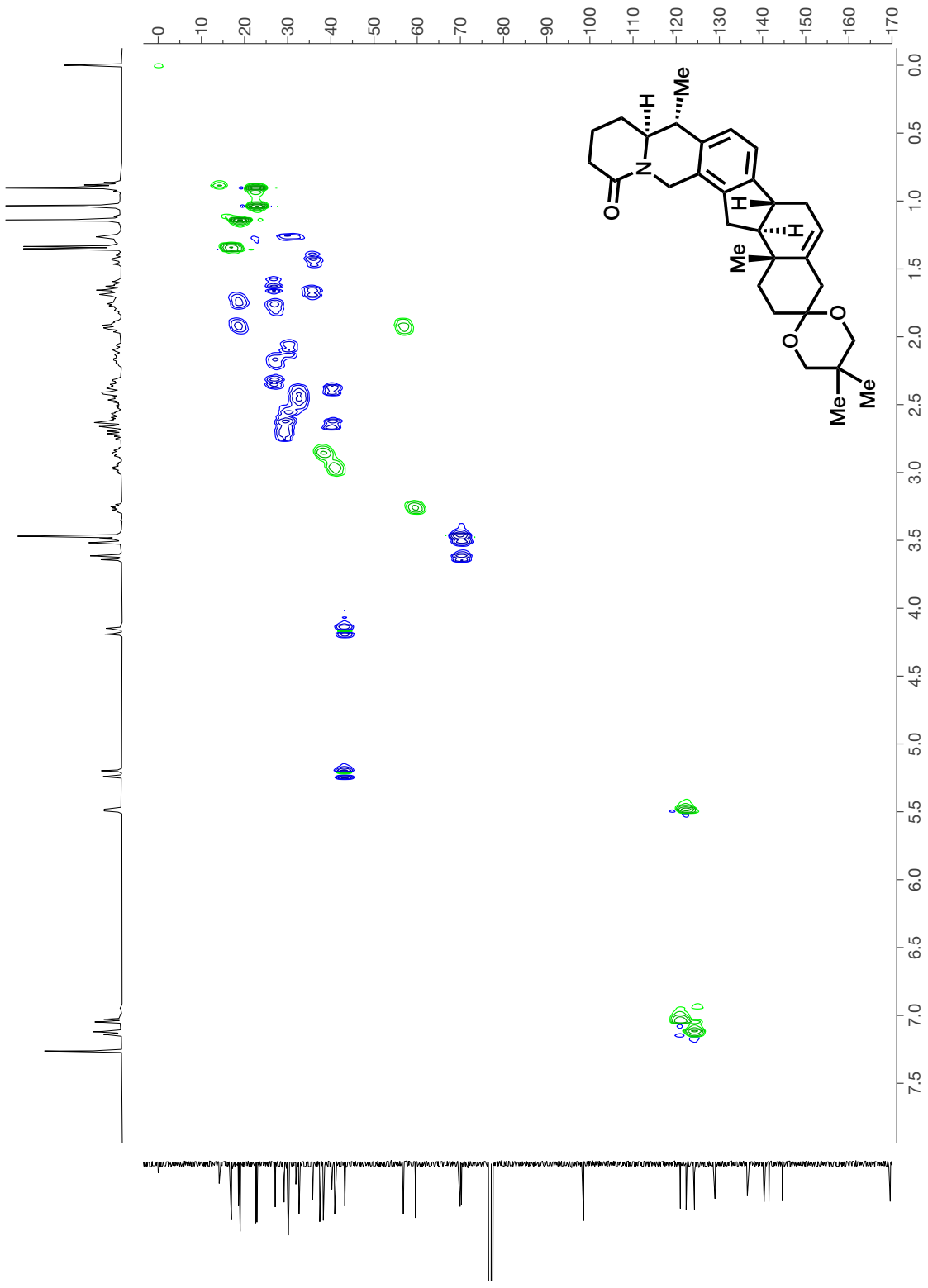


Figure A.98. $^{1}H–^{13}C$ HSQC spectrum (400 MHz, 101 MHz, $CDCl_3$) of **3.28**.

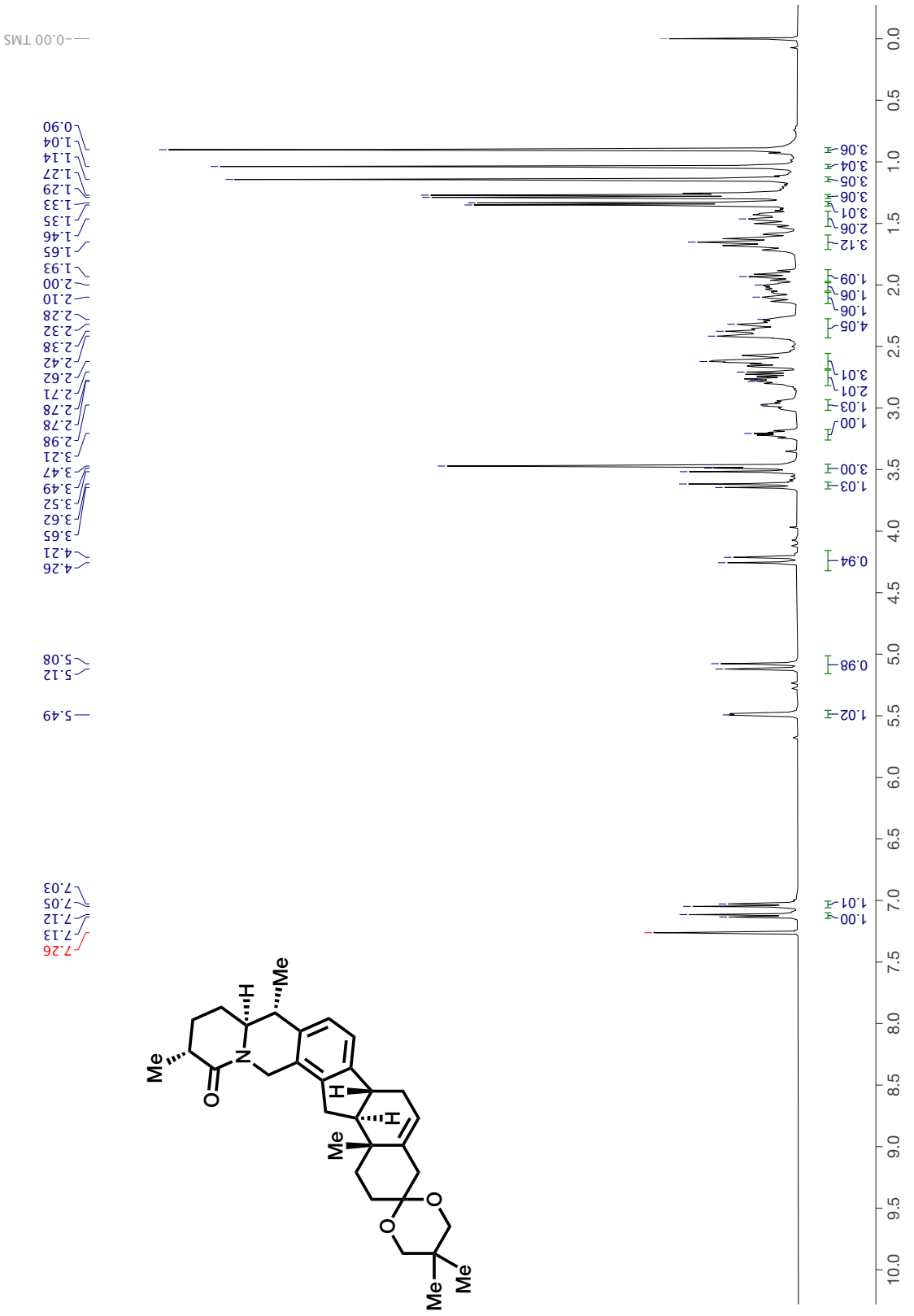


Figure A.99. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.29**.

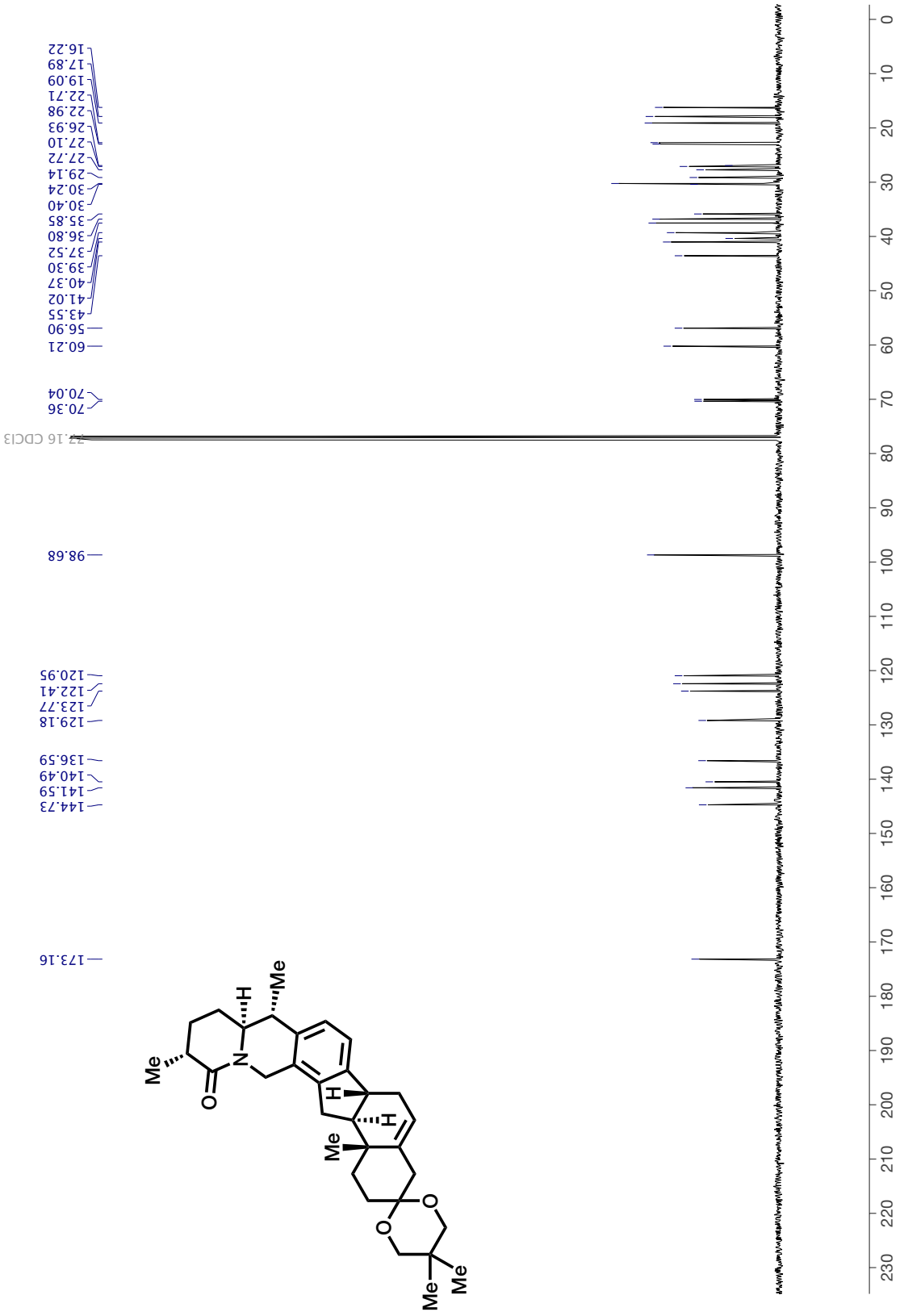


Figure A.100. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.29**.

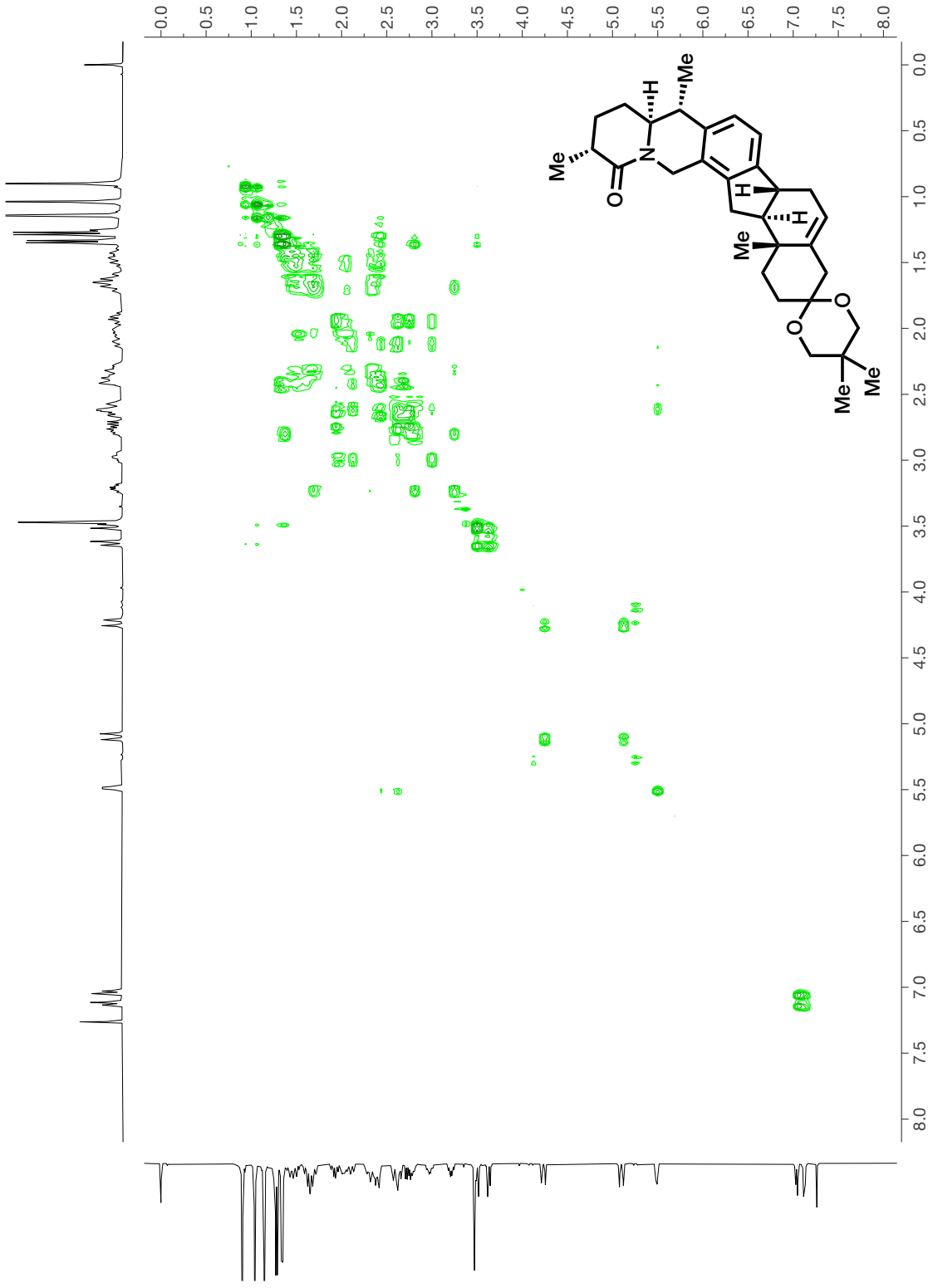


Figure A.101. ^{1}H–^{1}H COSY spectrum (400 MHz, $CDCl_3$) of **3.29**.

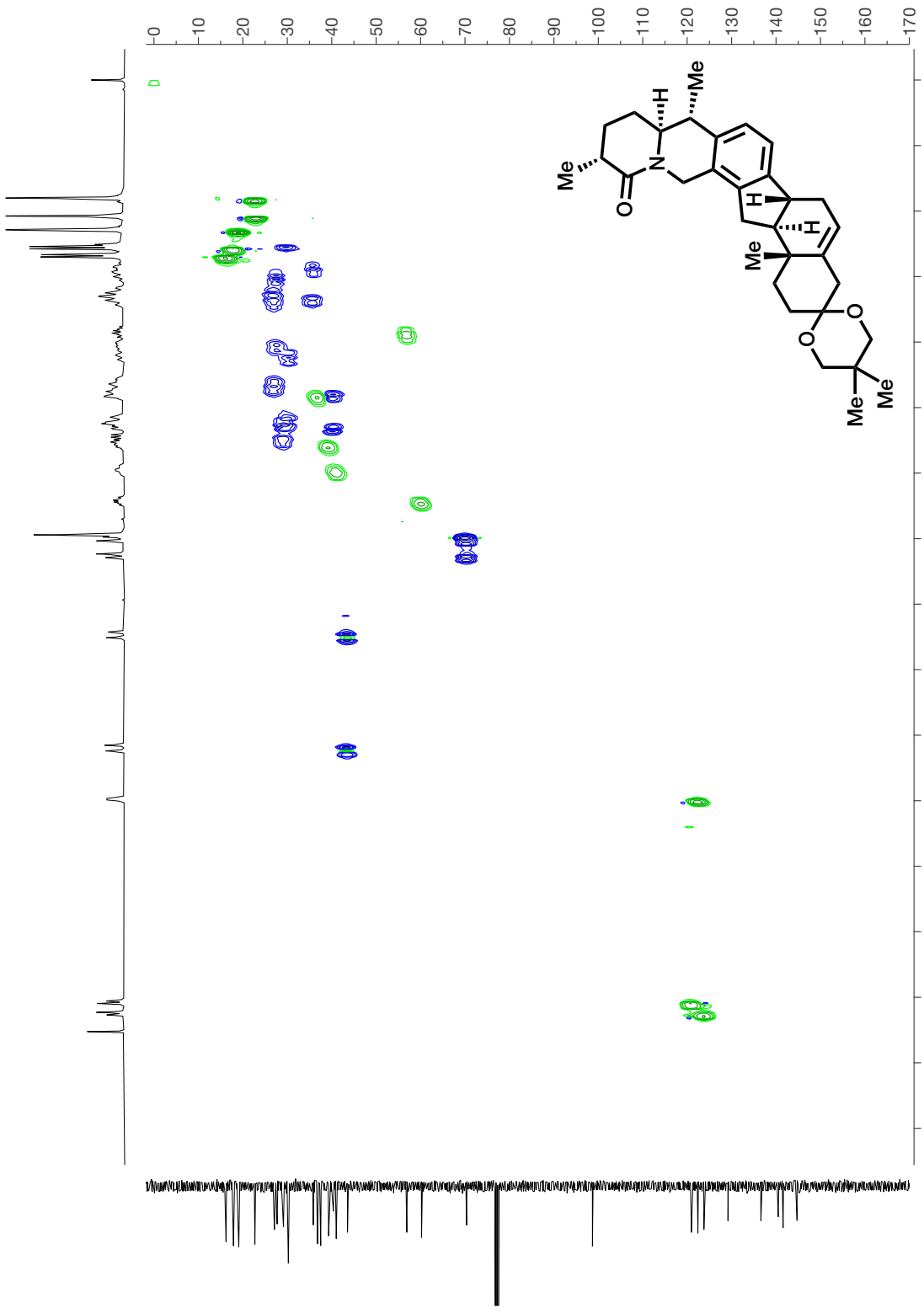


Figure A.102. $^{1}H–^{13}C$ HSQC spectrum (400 MHz, 101 MHz, $CDCl_3$) of **3.29**.

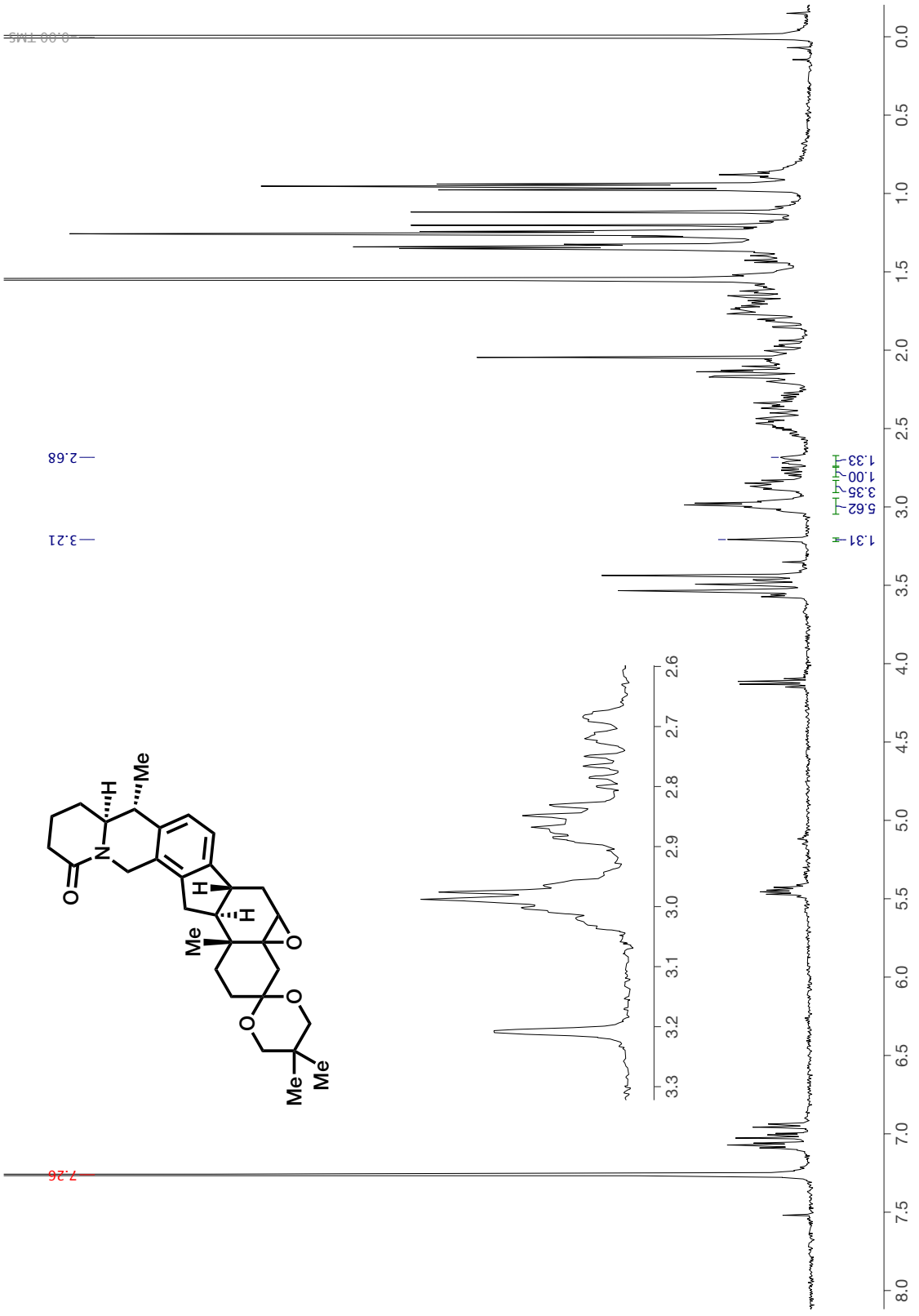


Figure A.103. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.33**.

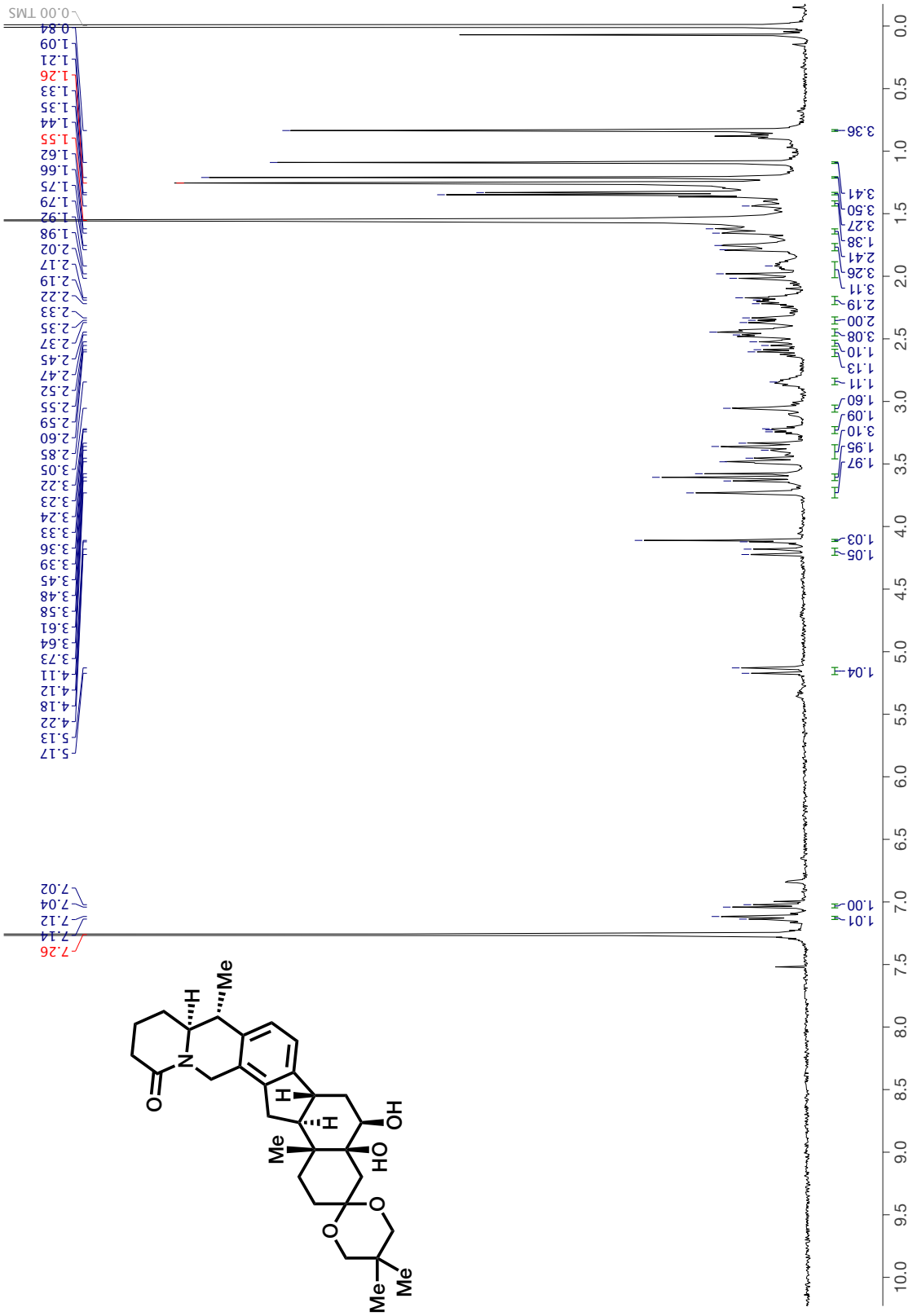


Figure A.104. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.35**.

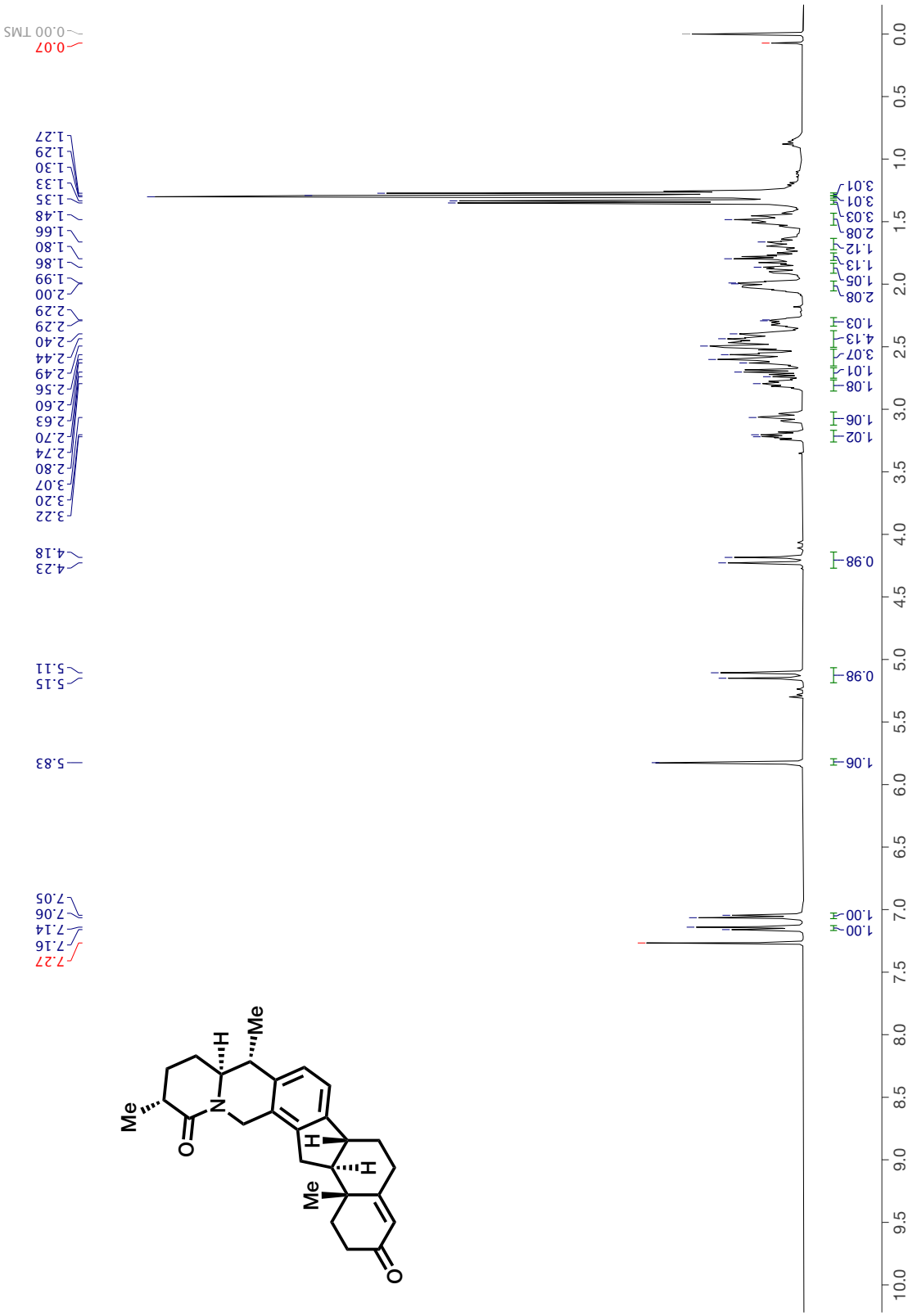


Figure A.105. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.39**.

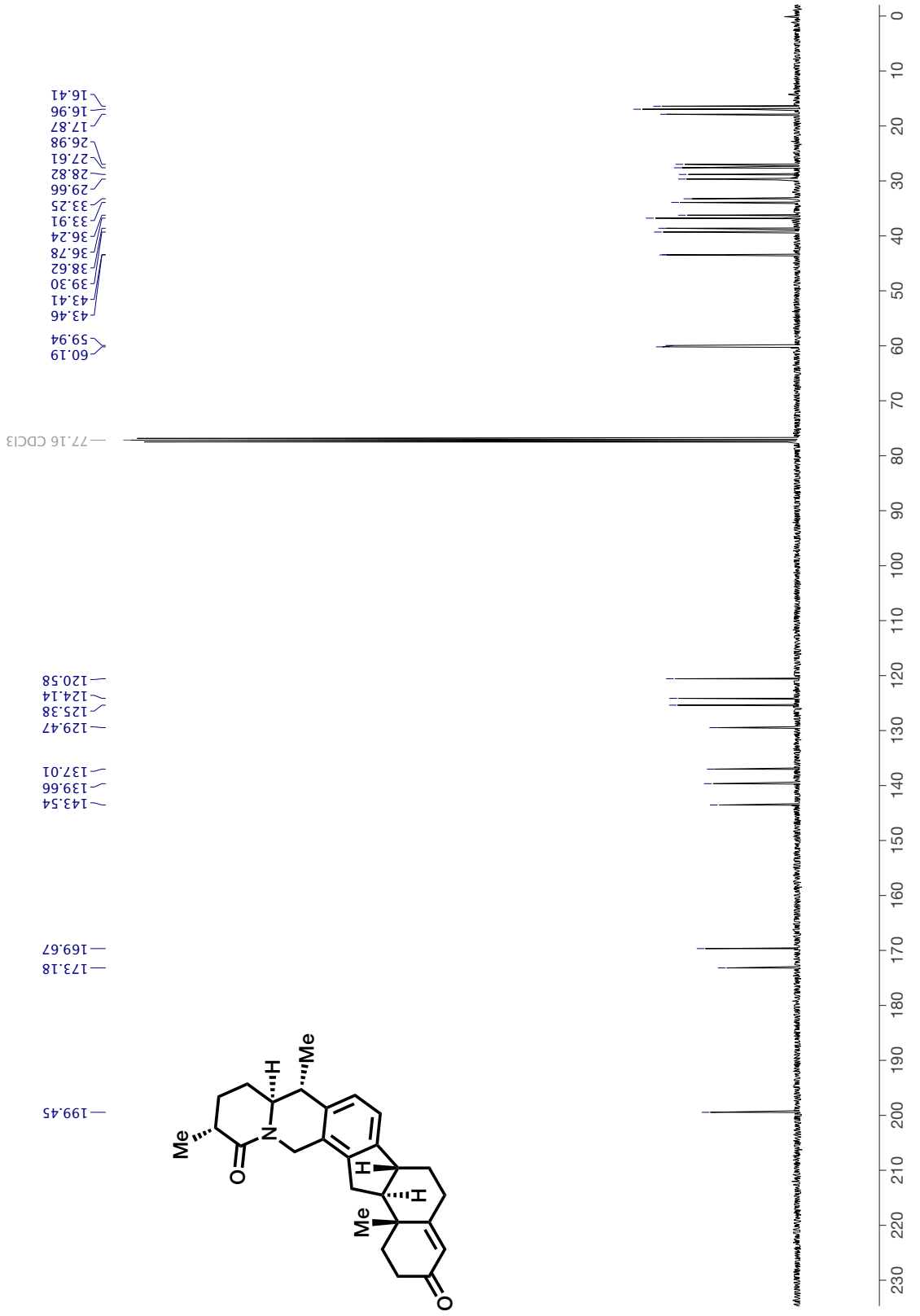


Figure A.106. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.39**.

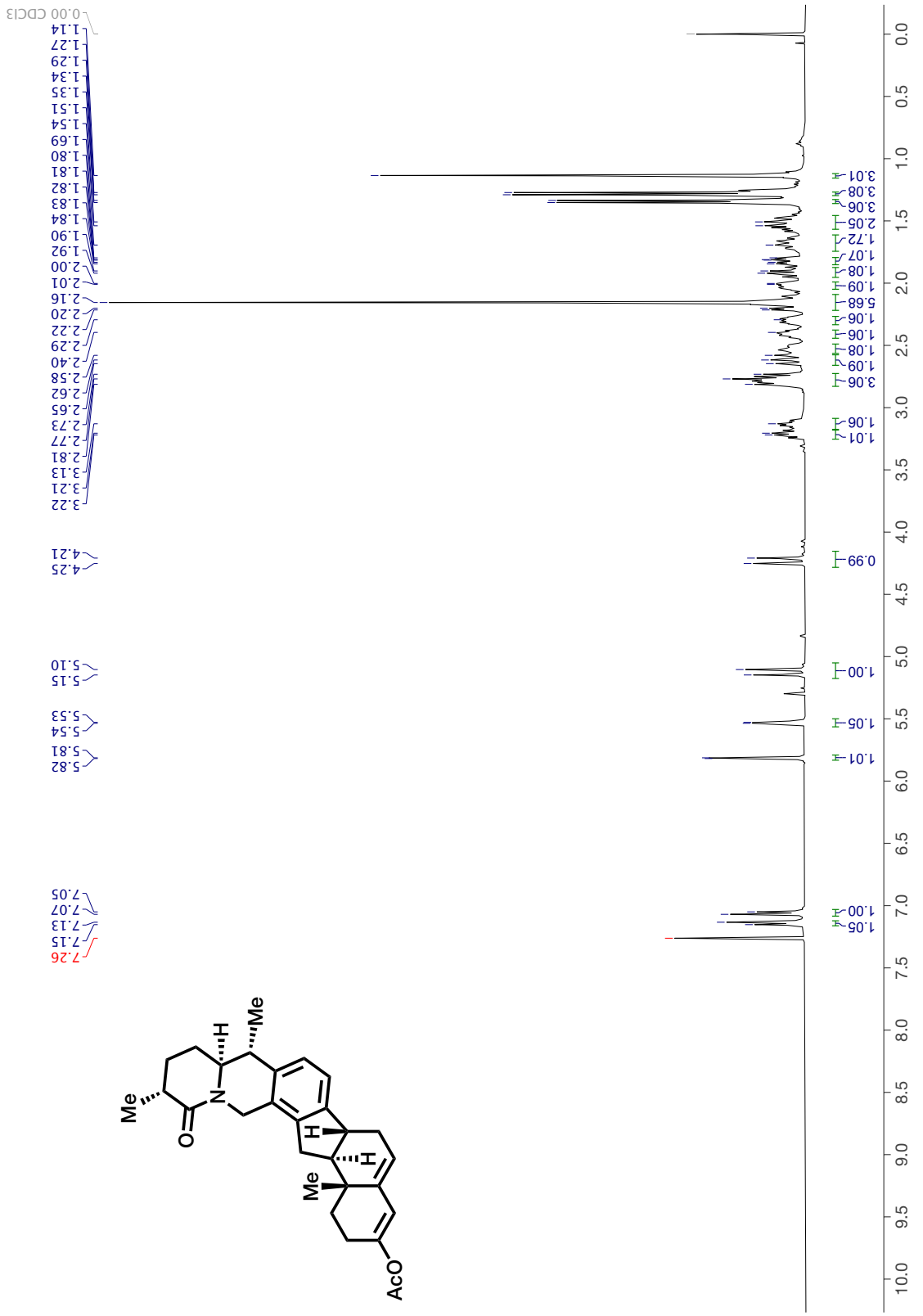


Figure A.107. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3.46**.

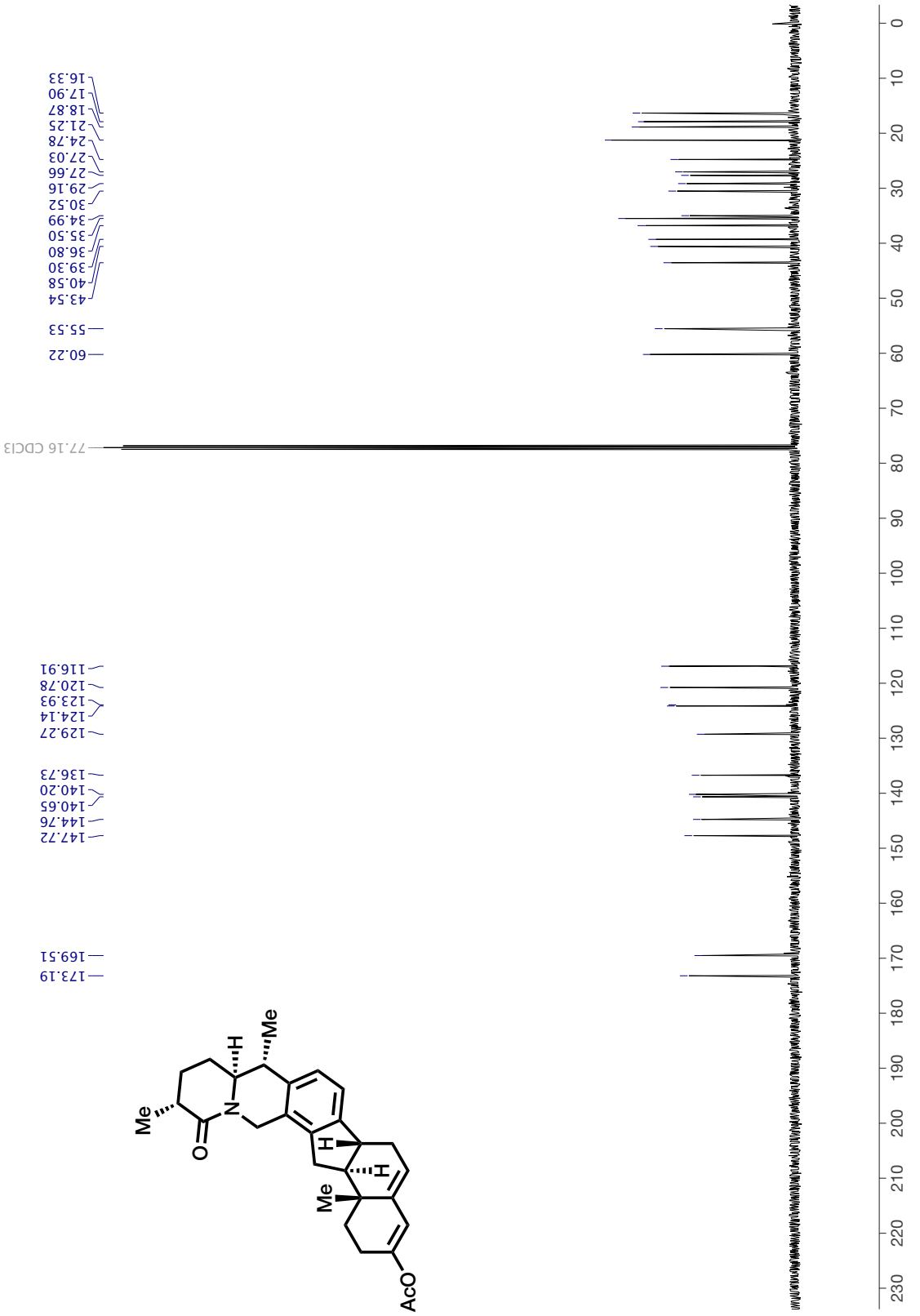


Figure A.108. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.46**.

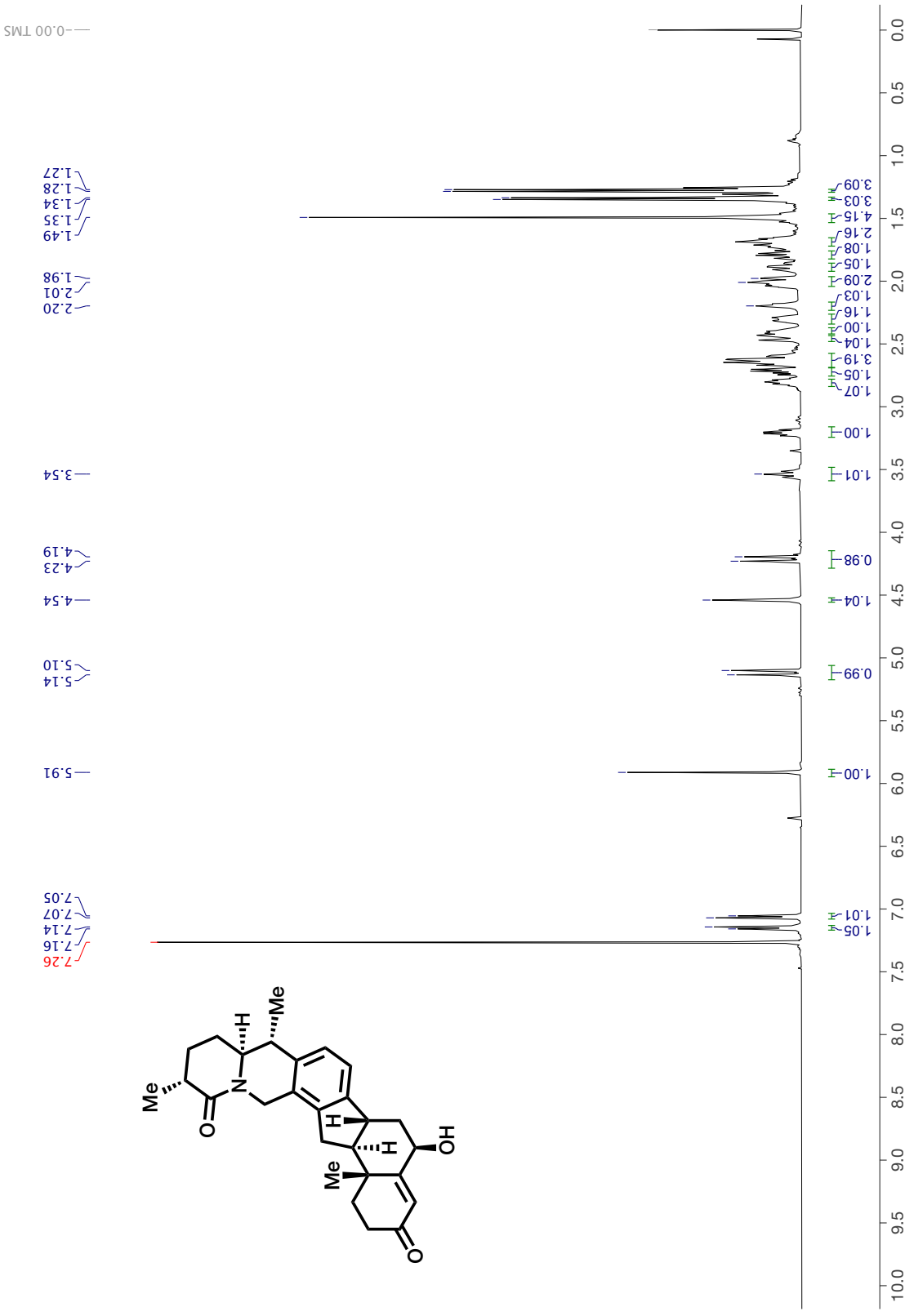


Figure A.109. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **3.40**.

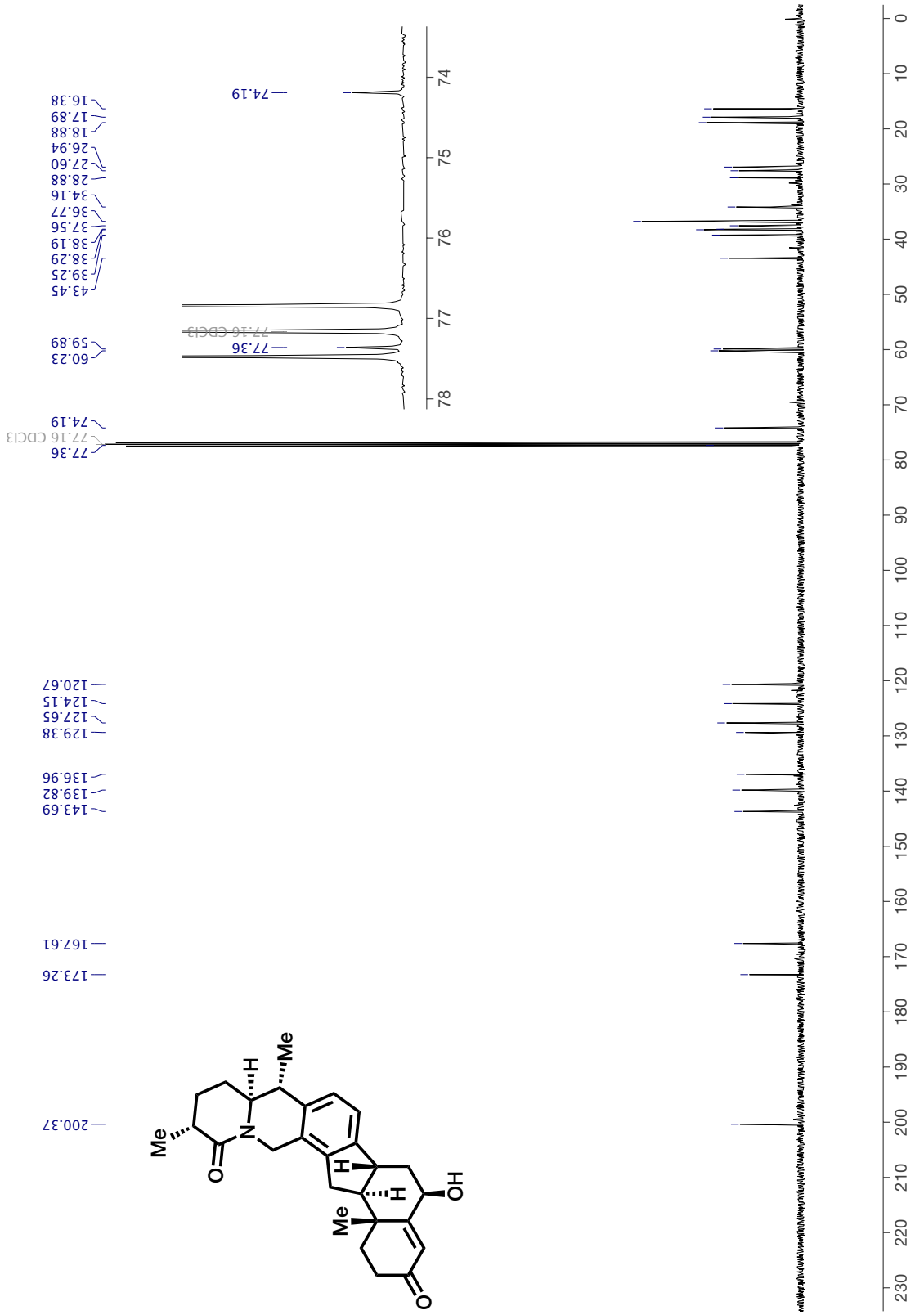


Figure A.110. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **3.40**.

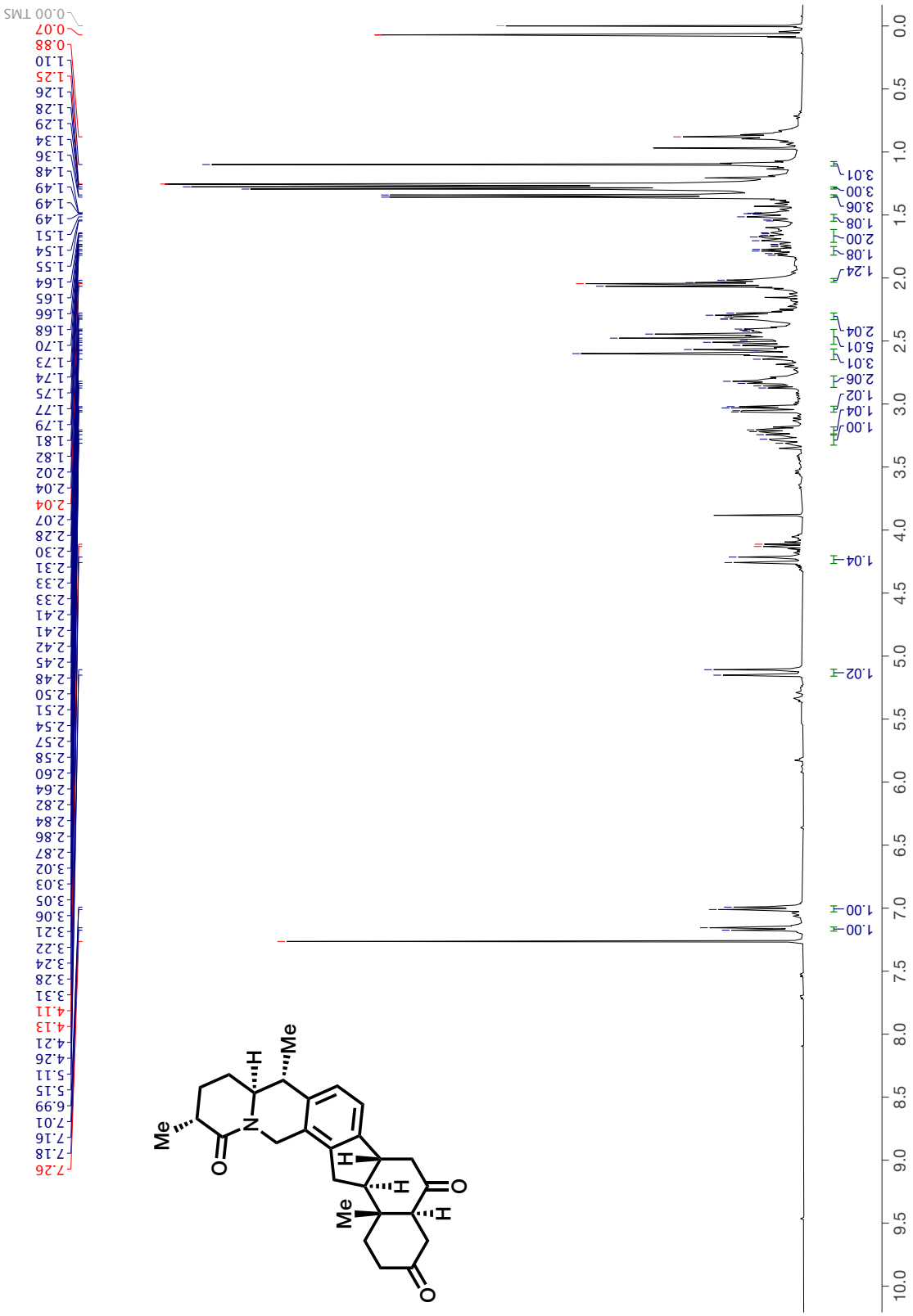


Figure A.111. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of unpurified **3.41**.

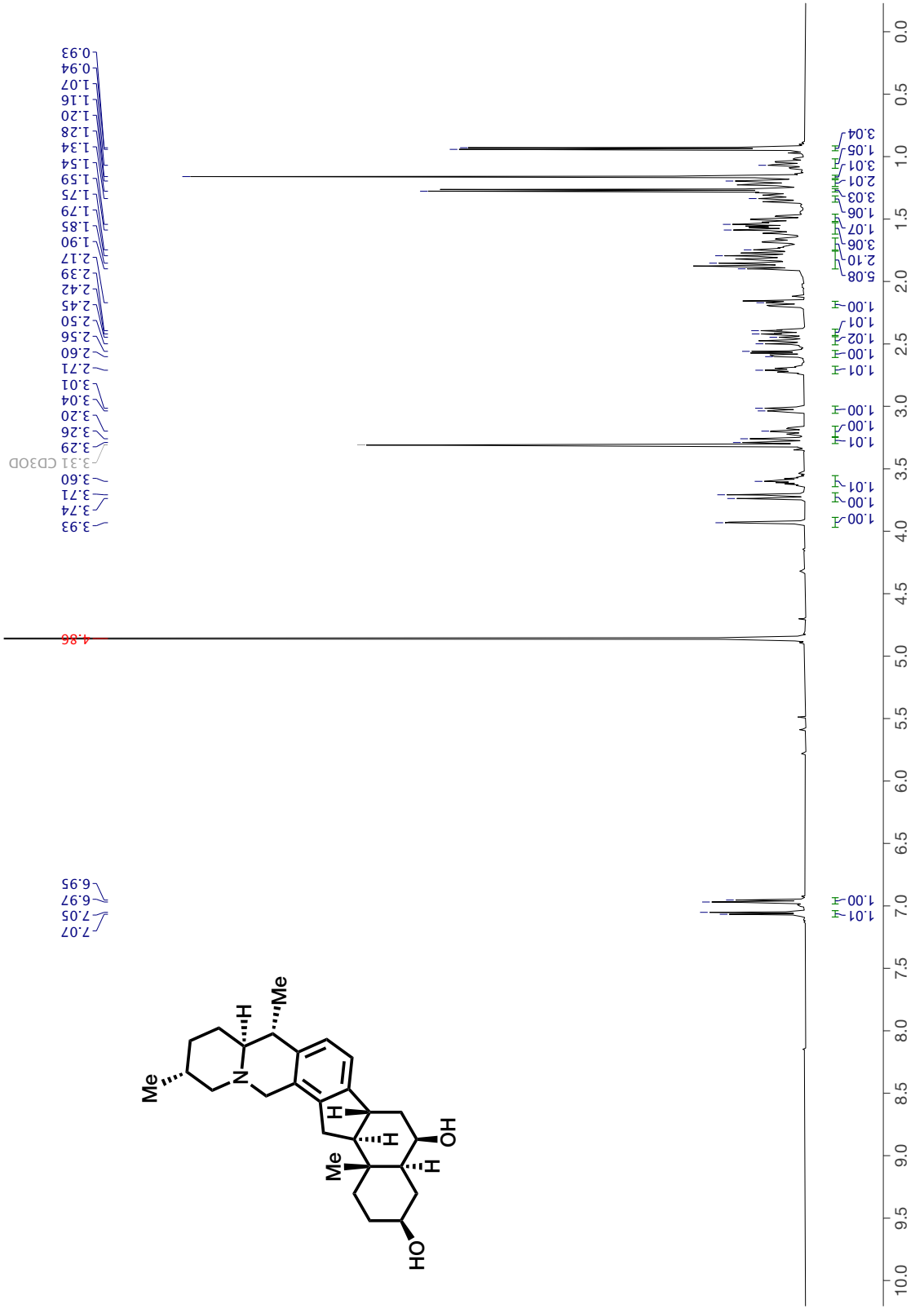


Figure A.112. ^{1}H NMR spectrum (500 MHz, CD_3OD) of **heilonine**.

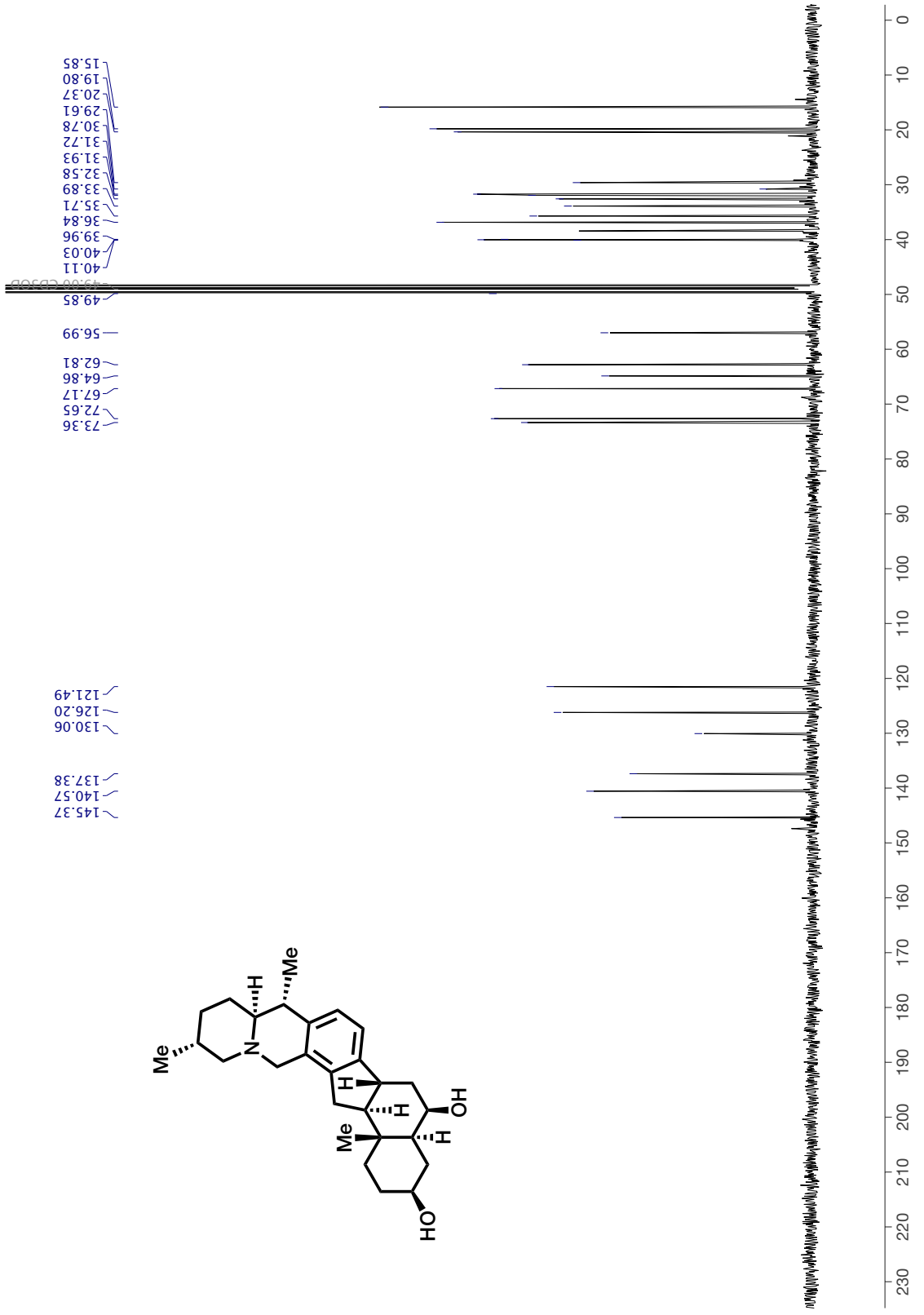


Figure A.113. ^{13}C NMR spectrum (101 MHz, CD_3OD) of **heilonine**.

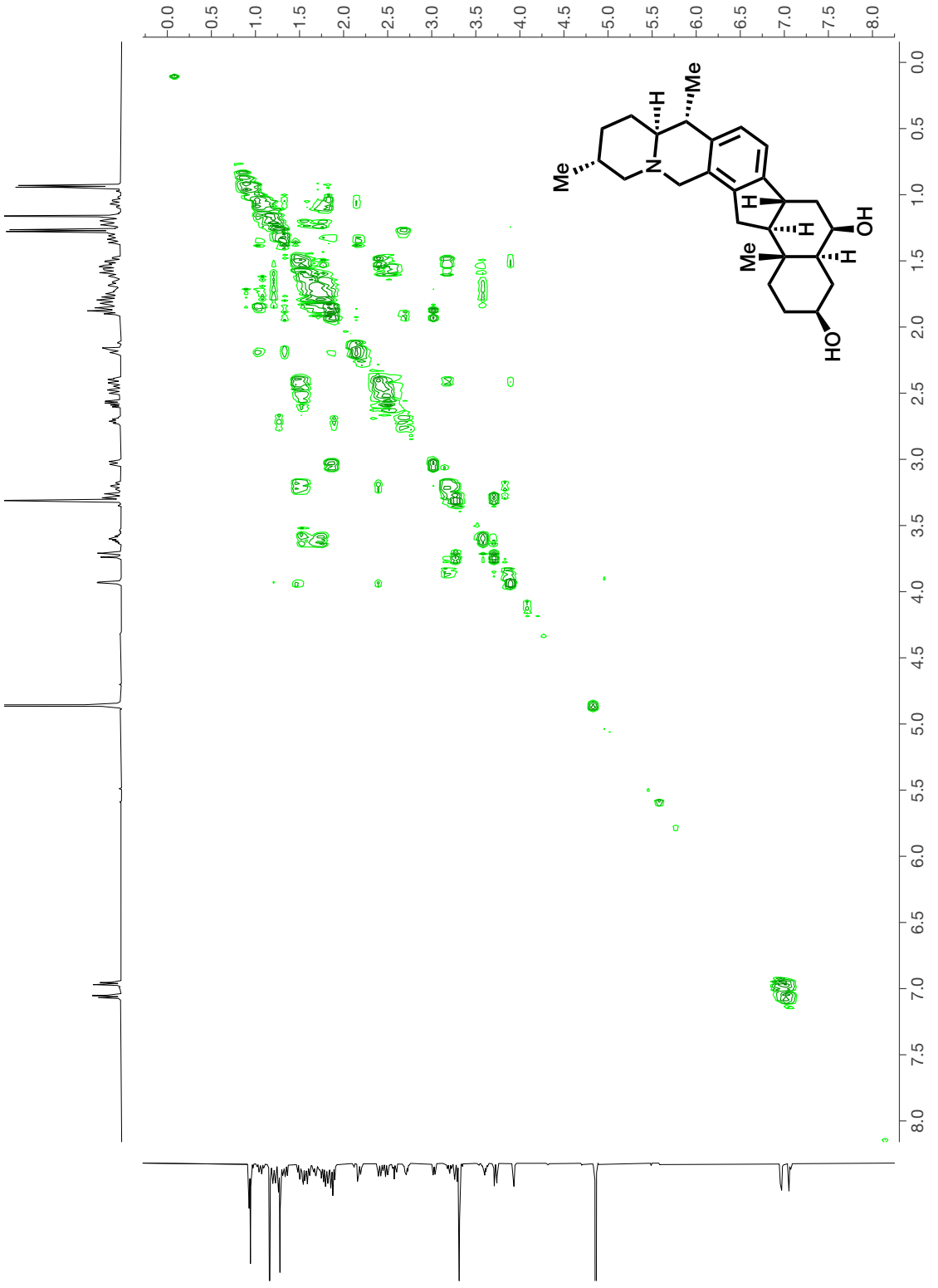


Figure A.114. ^{1}H–^{1}H COSY spectrum (400 MHz, CD_3OD) of **heilonine**.

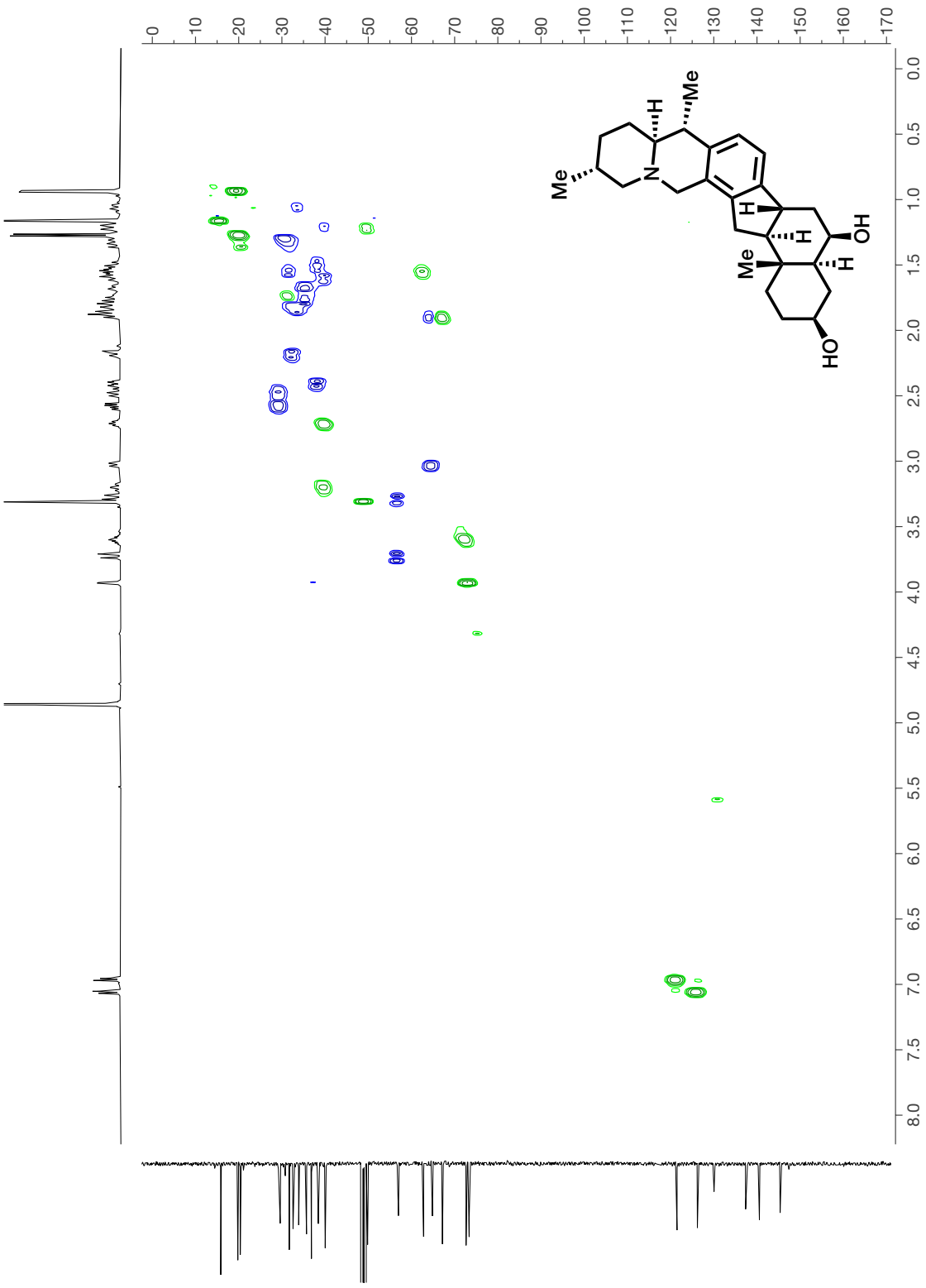


Figure A.115. ^{1}H–^{13}C HSQC spectrum (400 MHz, 101 MHz, CD_3OD) of **heilonine**.

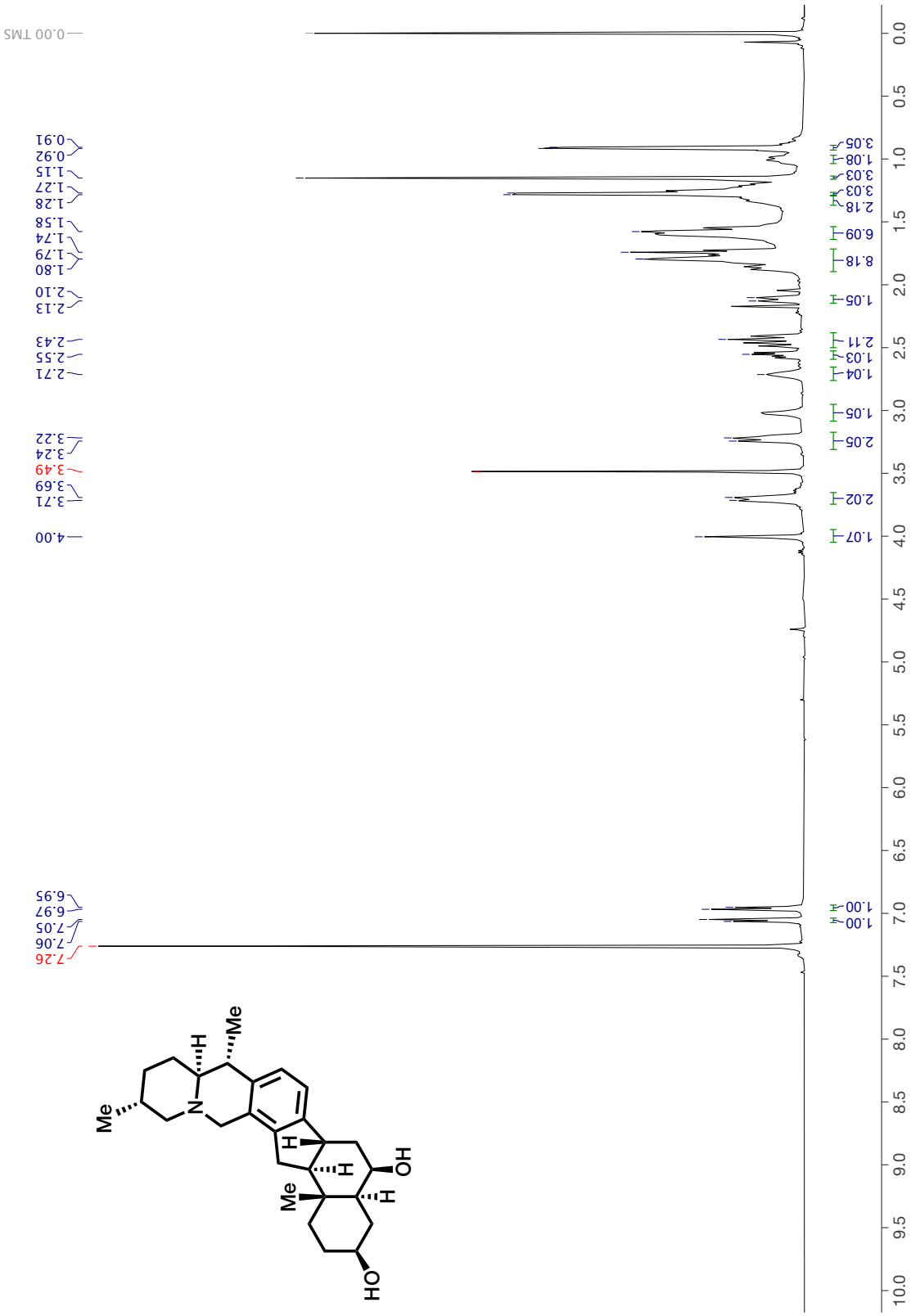


Figure A.116. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **heilonine**.

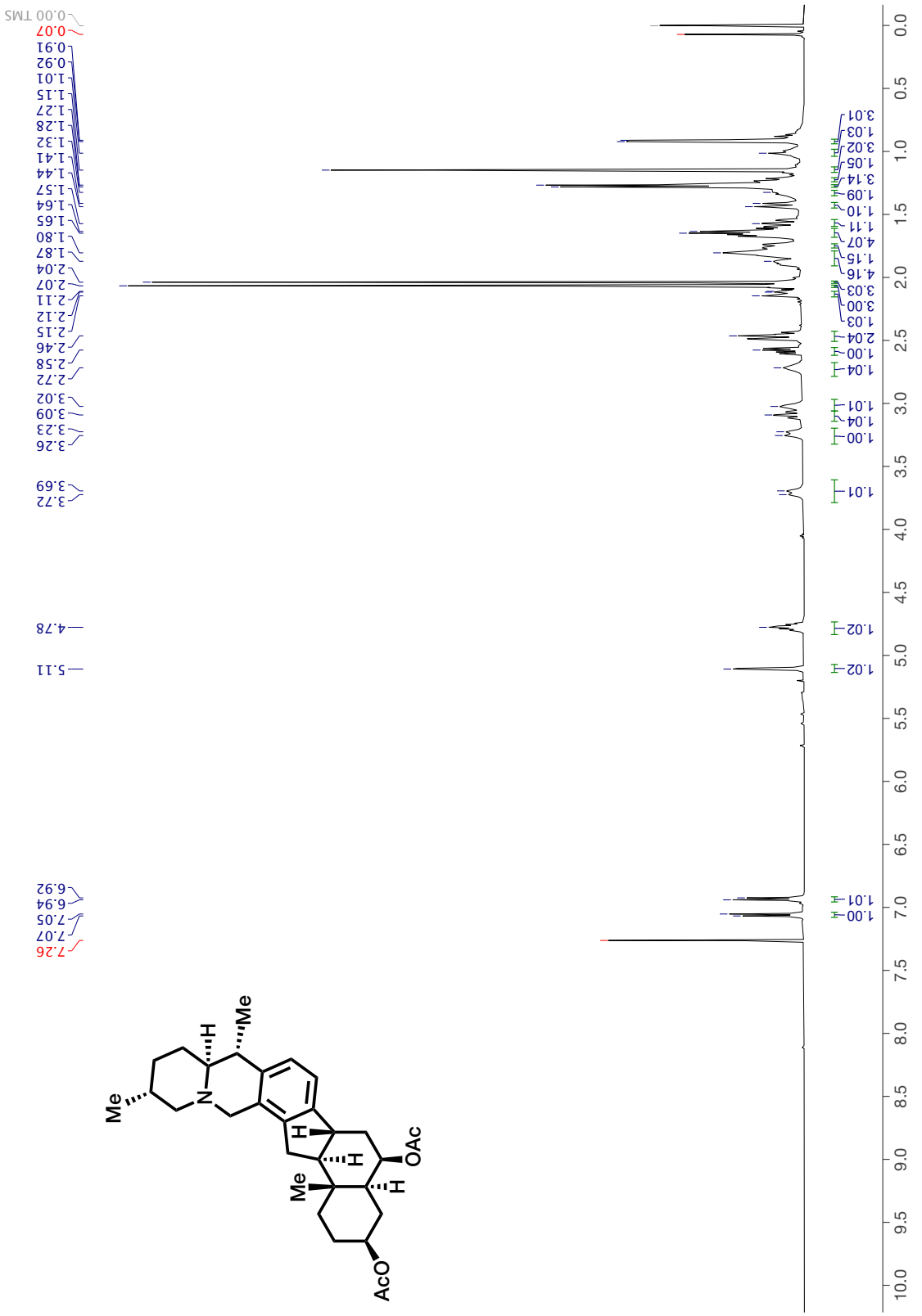


Figure A.117. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **heilonine diacetate**.

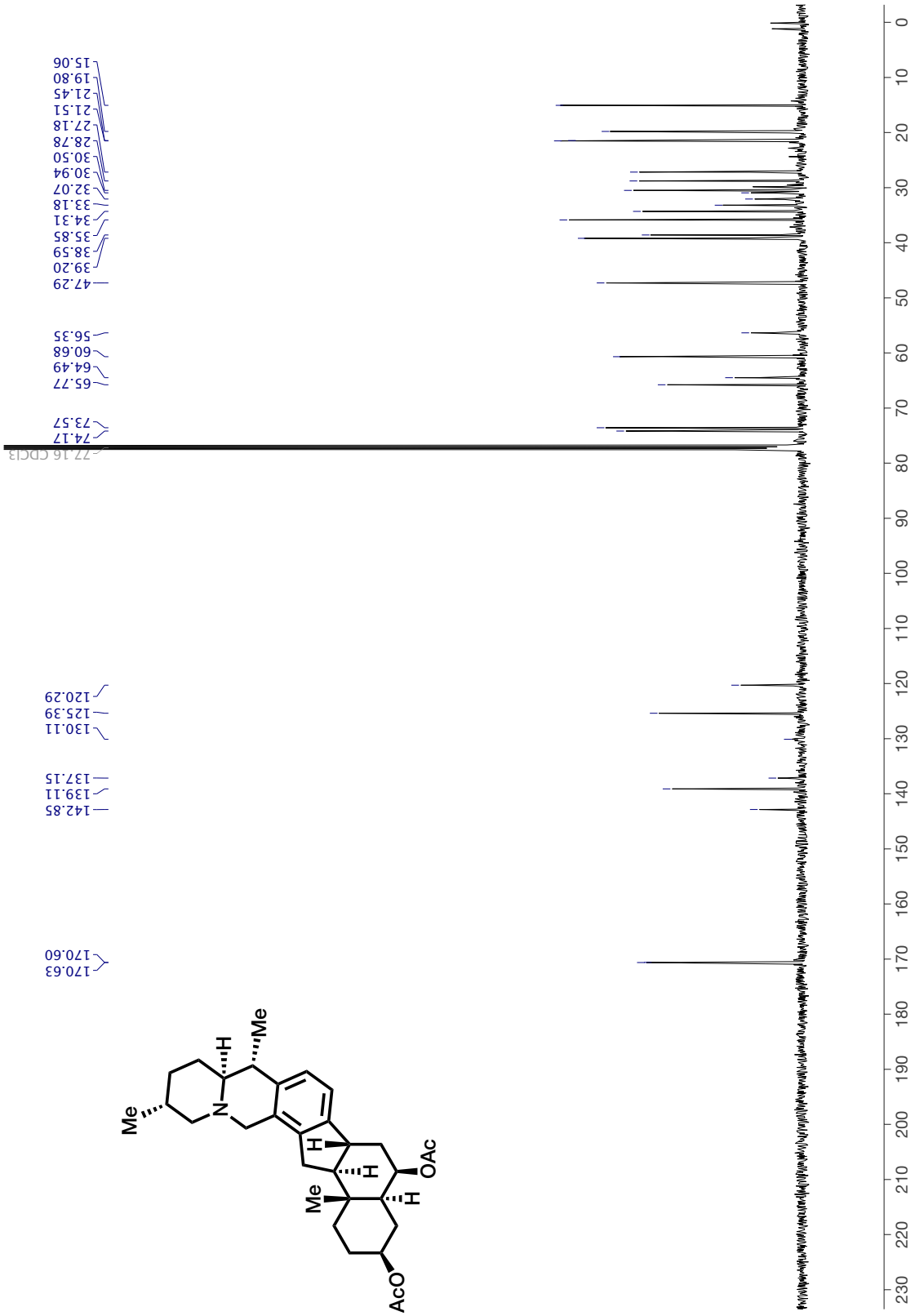


Figure A.118. ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of **heilonine diacetate**.

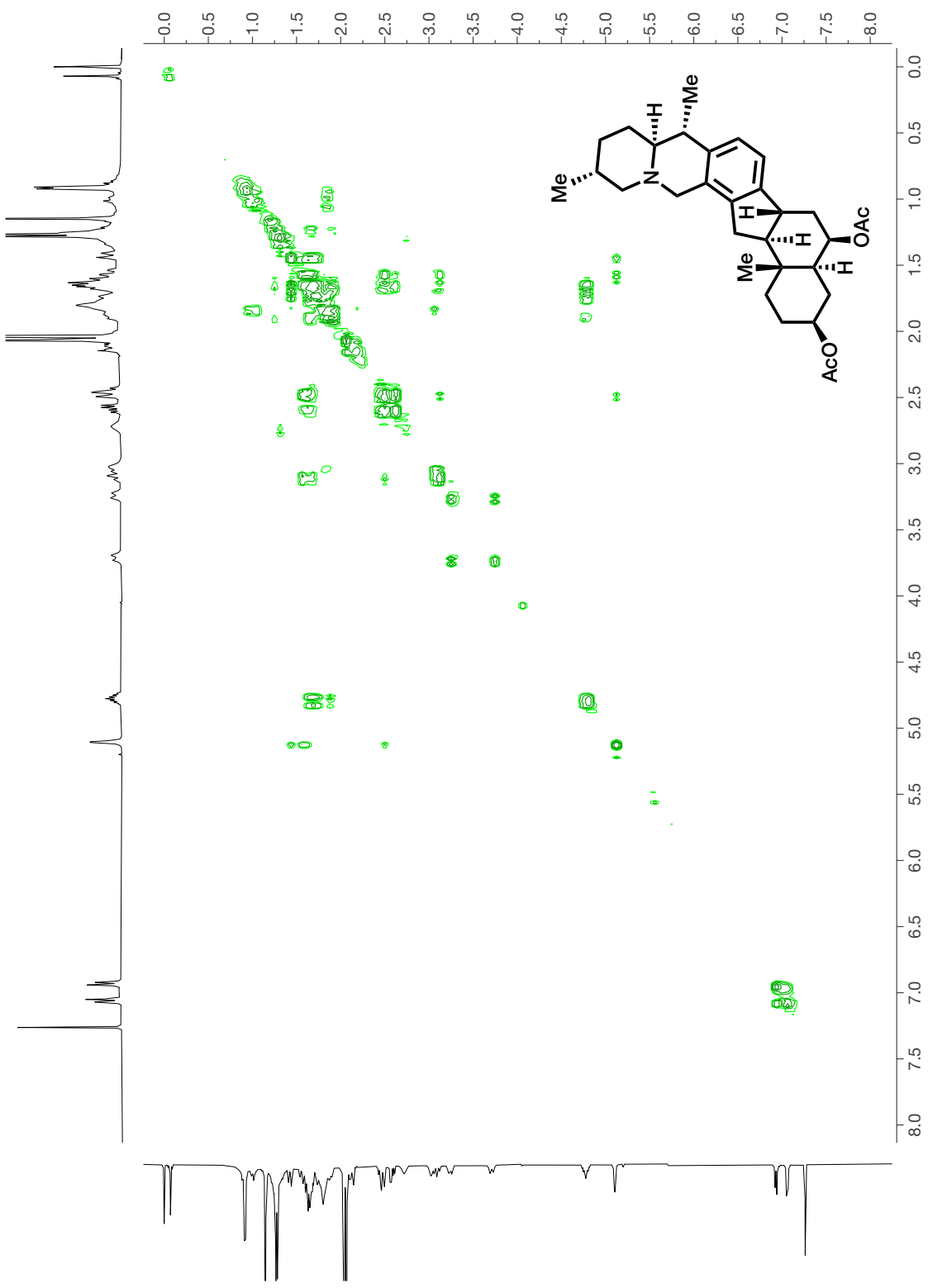


Figure A.119. ^{1}H–^{1}H COSY spectrum (400 MHz, $CDCl_3$) of **heilonine diacetate**.

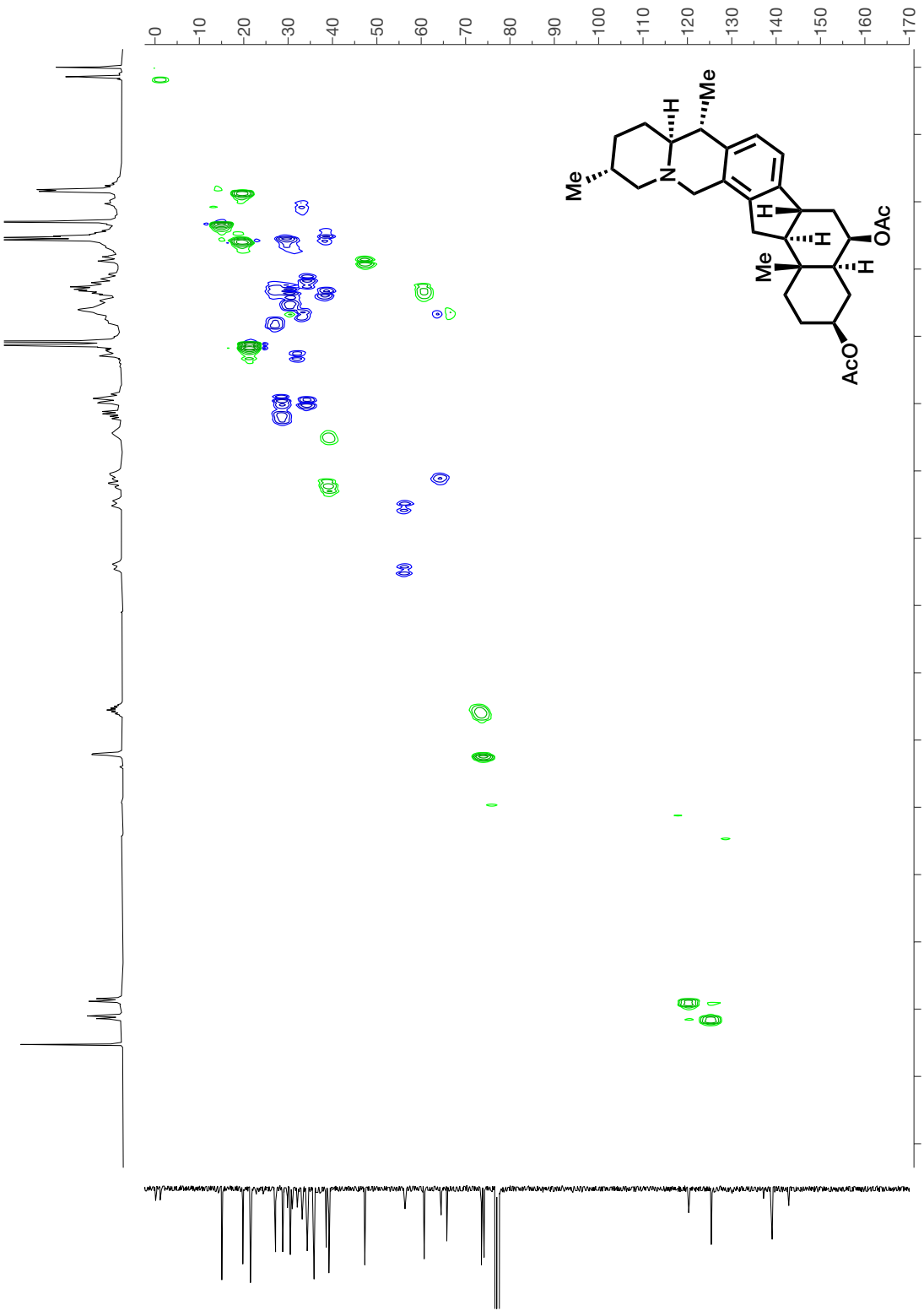


Figure A.120. $^{1}H–^{13}C$ HSQC spectrum (400 MHz, 101 MHz, $CDCl_3$) of **heilonine diacetate**.

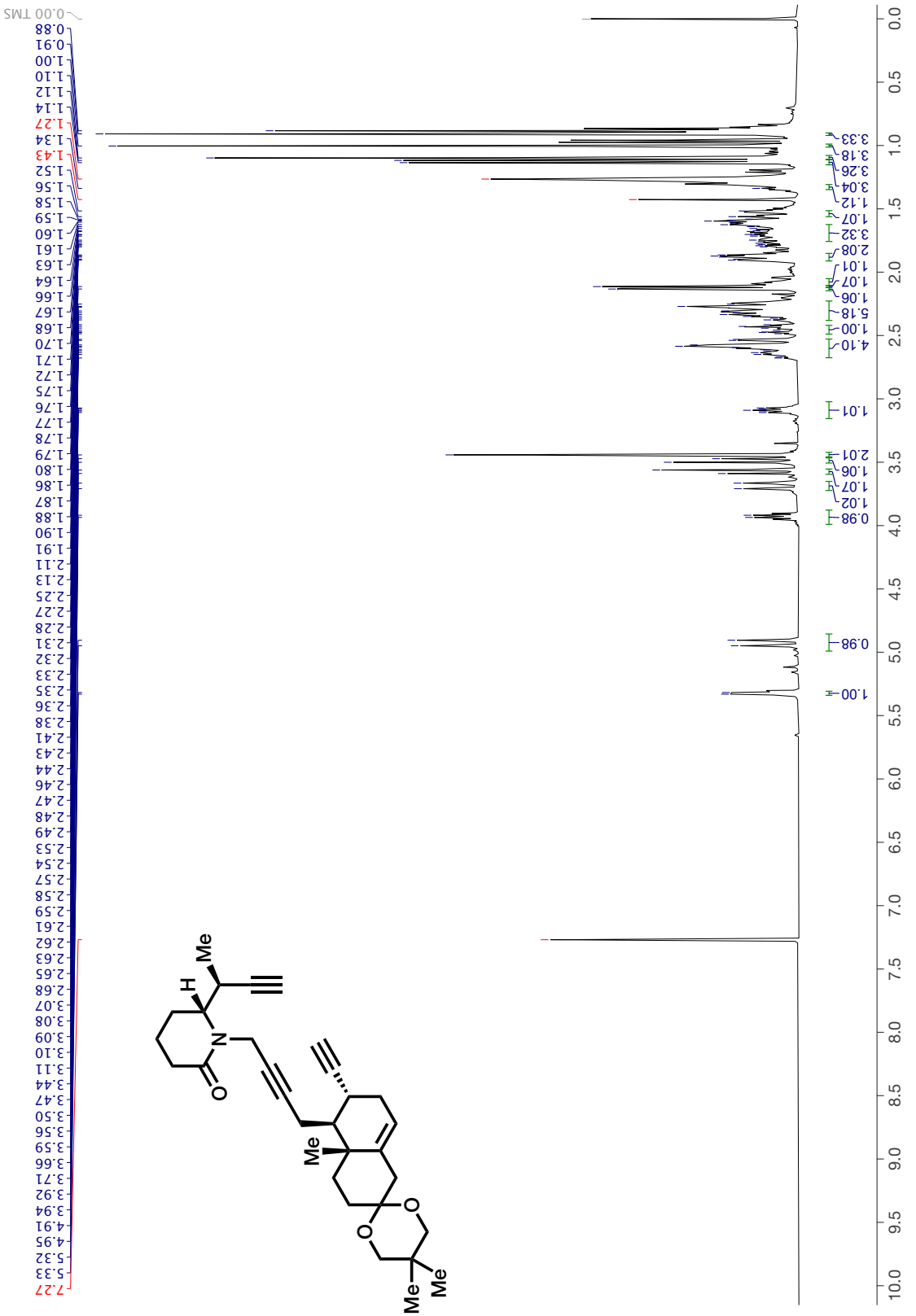


Figure A.121. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4.1**.

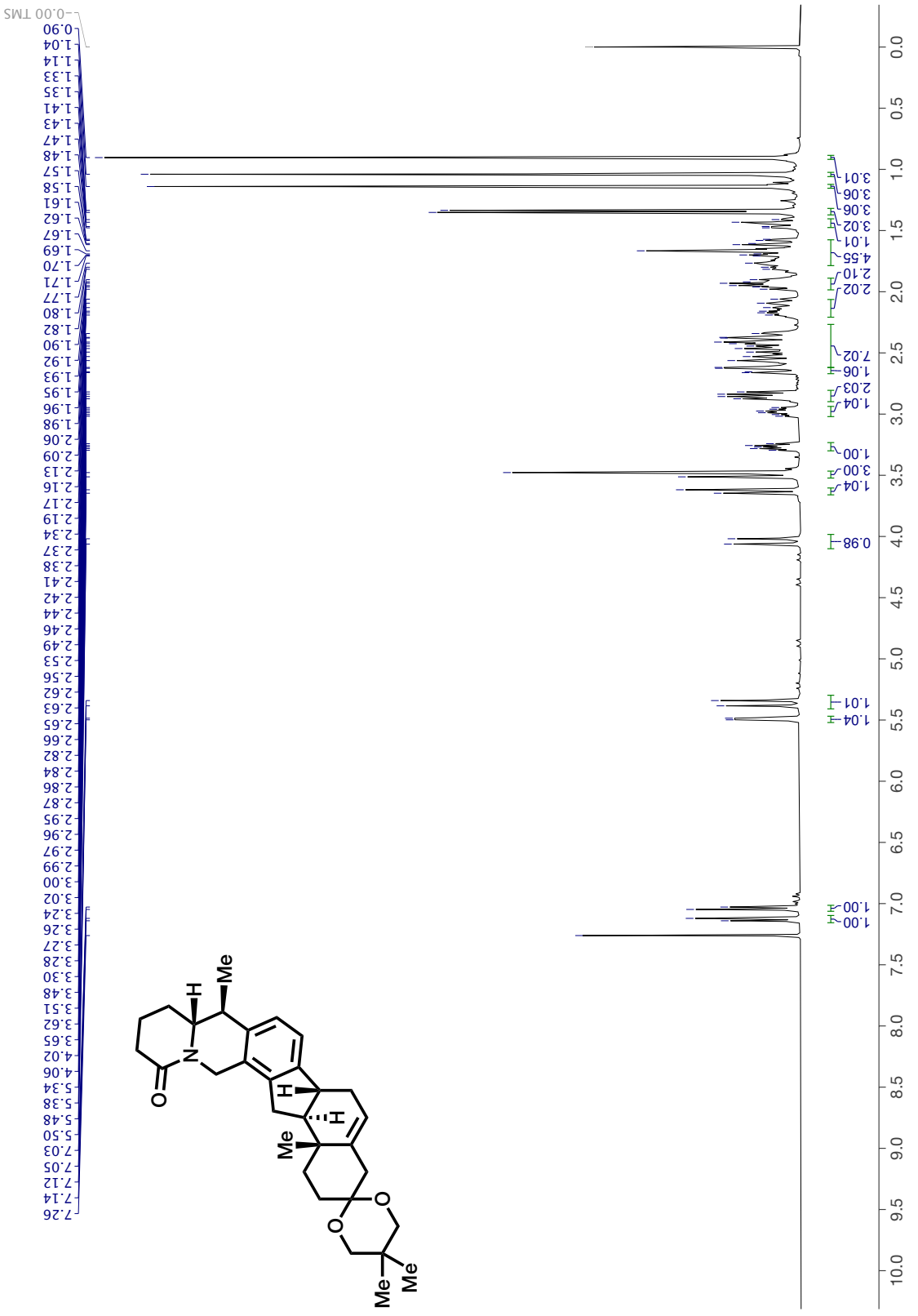


Figure A.122. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4.2**.

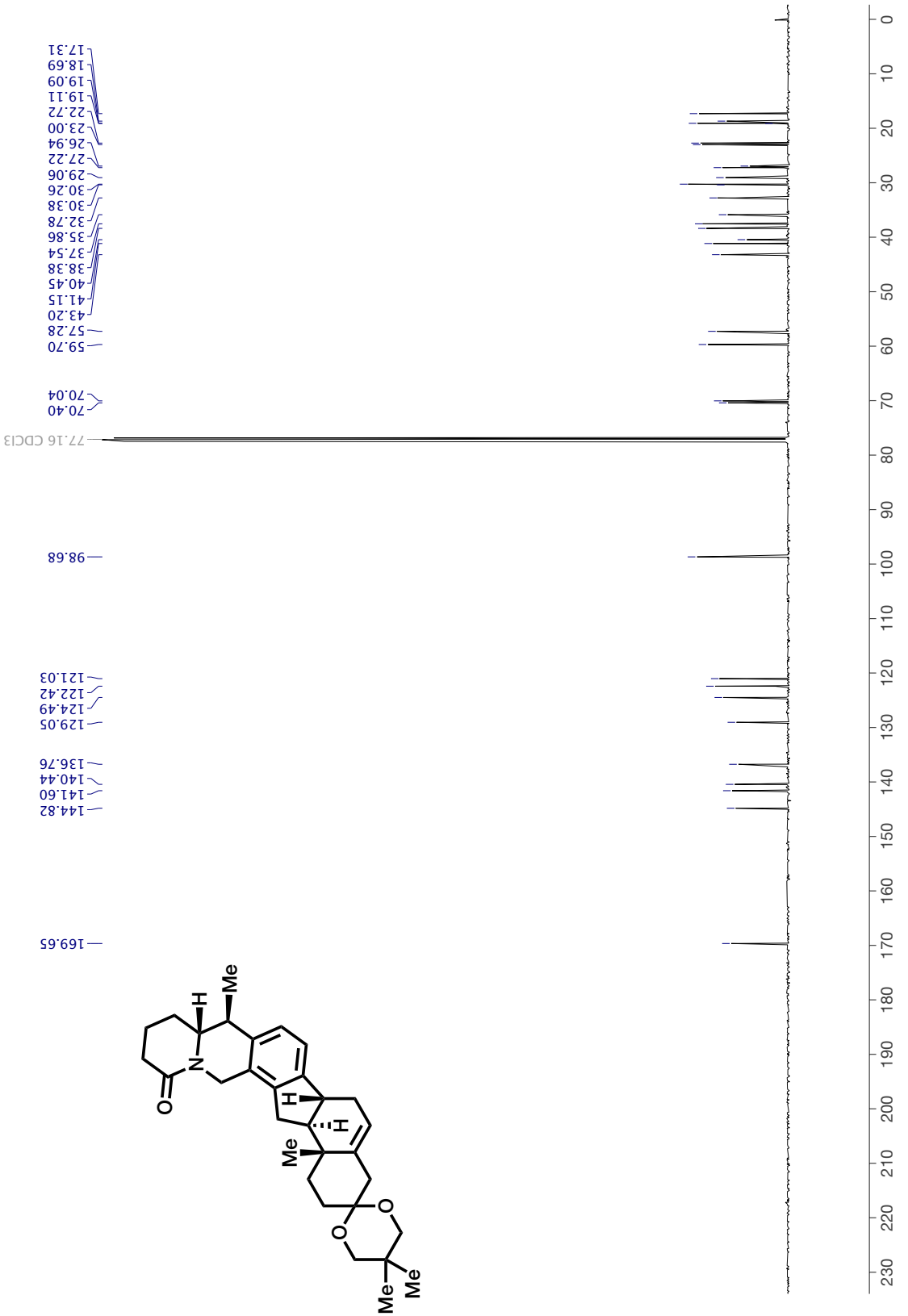


Figure A.123. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **4.2**.

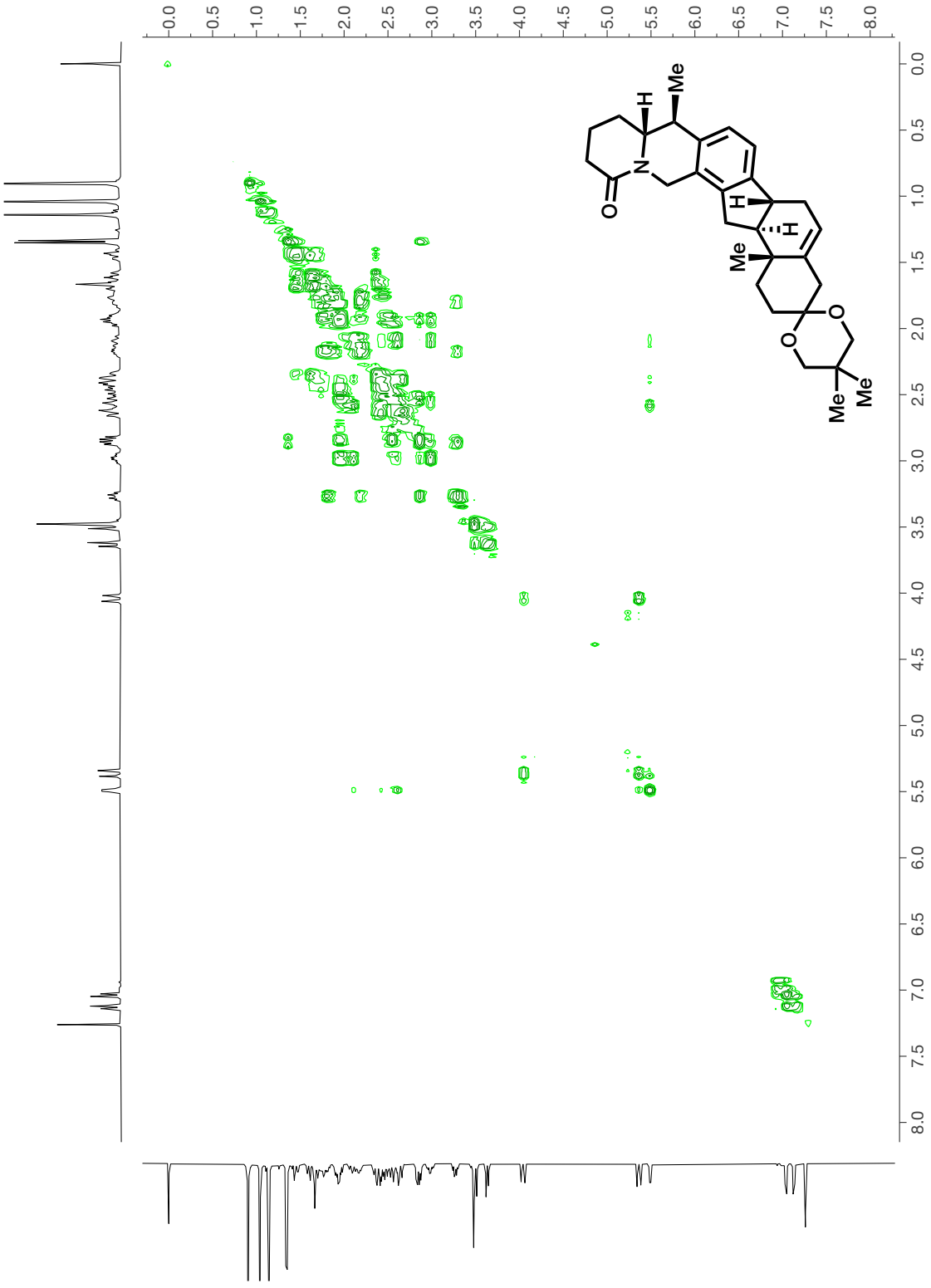


Figure A.124. ^{1}H–^{1}H COSY spectrum (400 MHz, $CDCl_3$) of **4.2**.

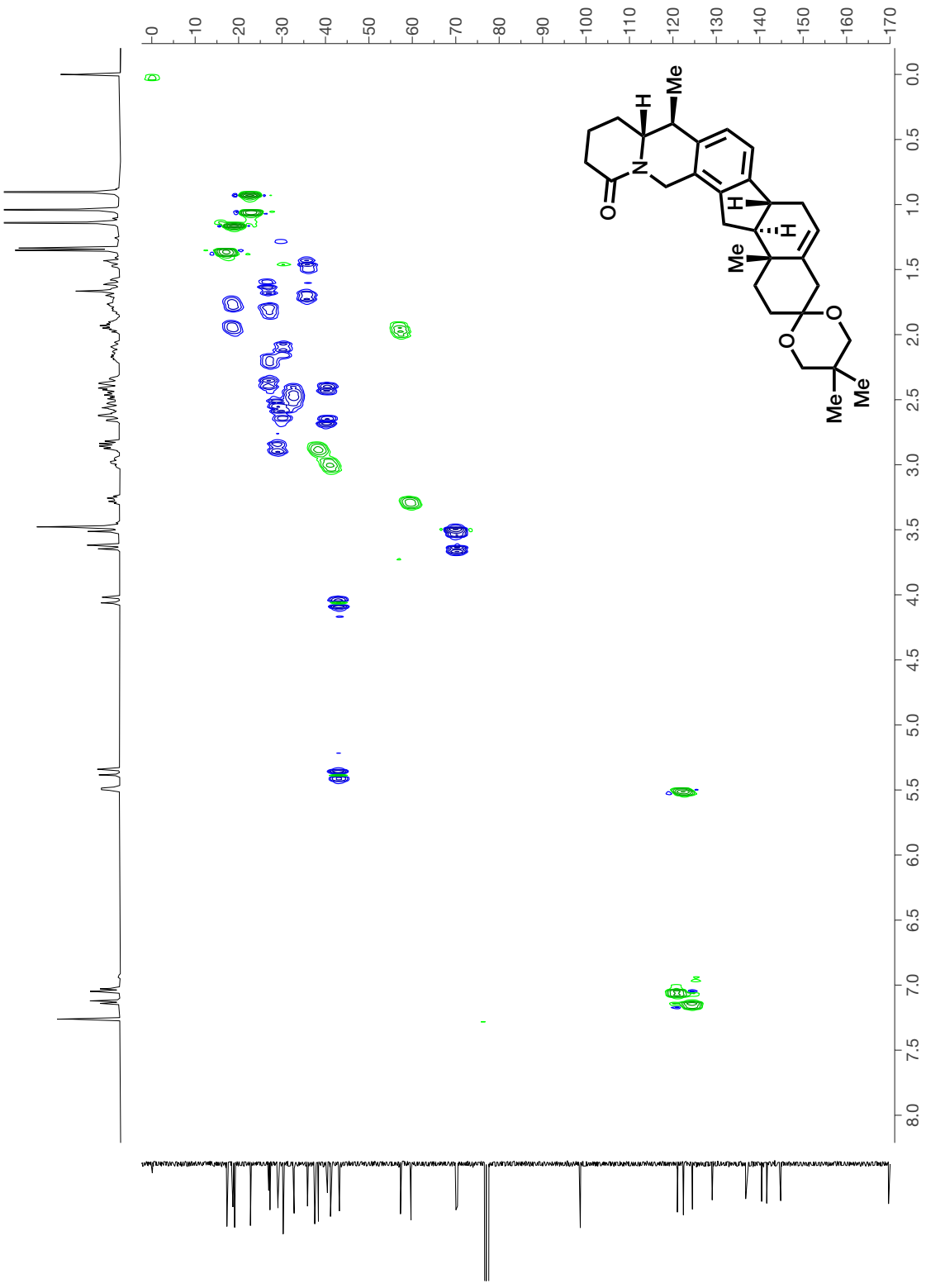


Figure A.125. ^{1}H–^{13}C HSQC spectrum (400 MHz, 101 MHz, $CDCl_3$) of **4.2**.

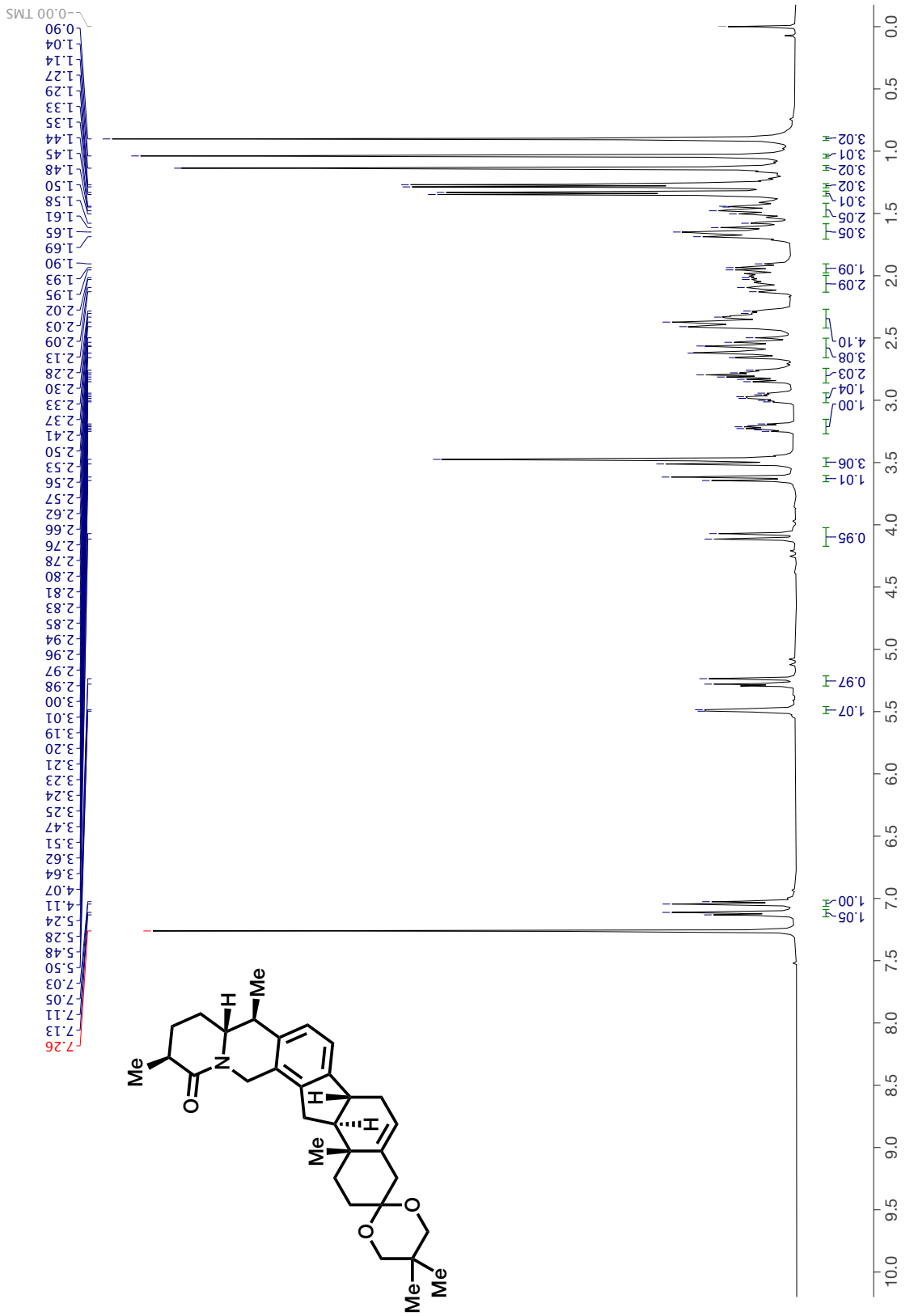


Figure A.126. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4.19**.

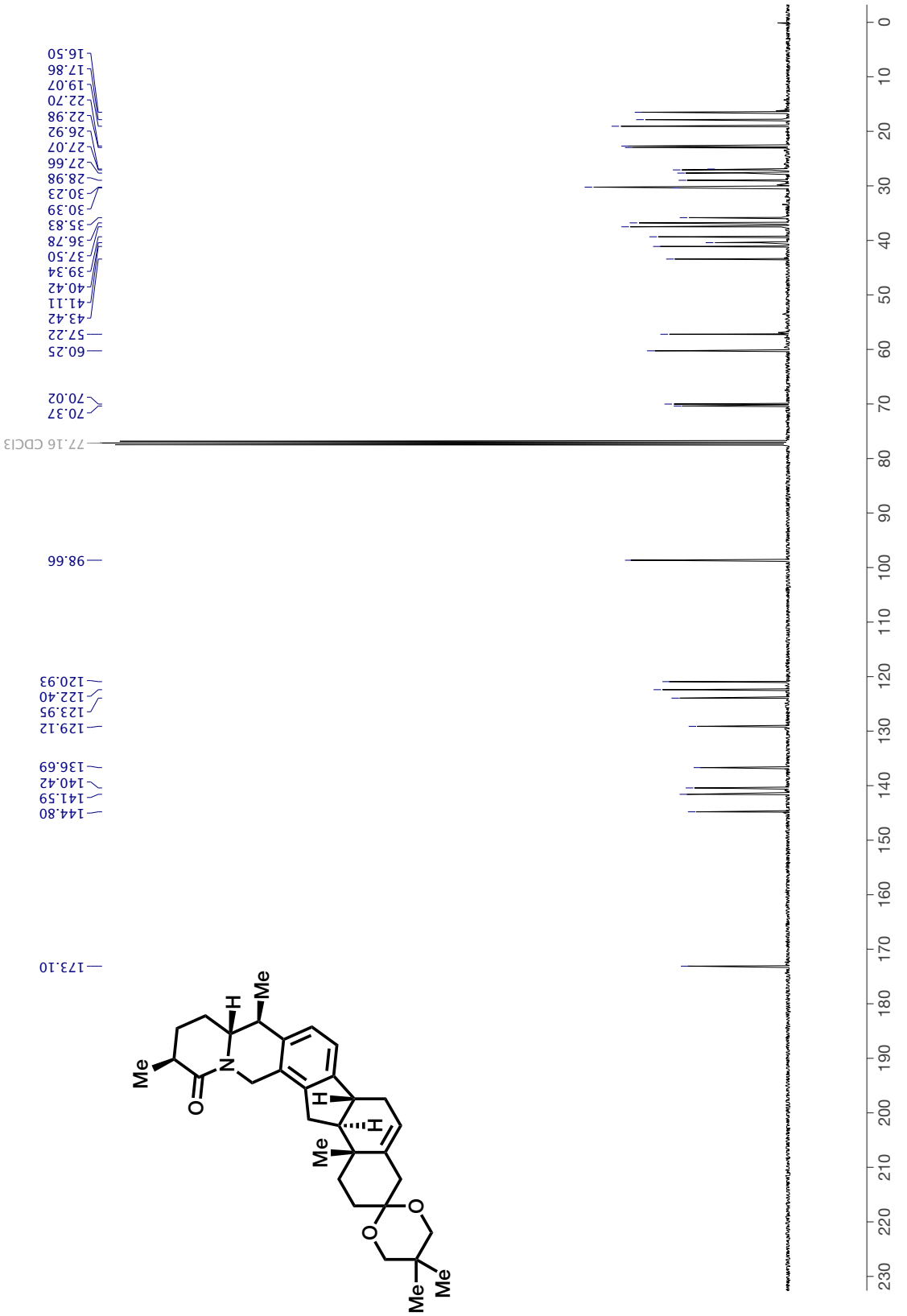


Figure A.127. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **4.19**.

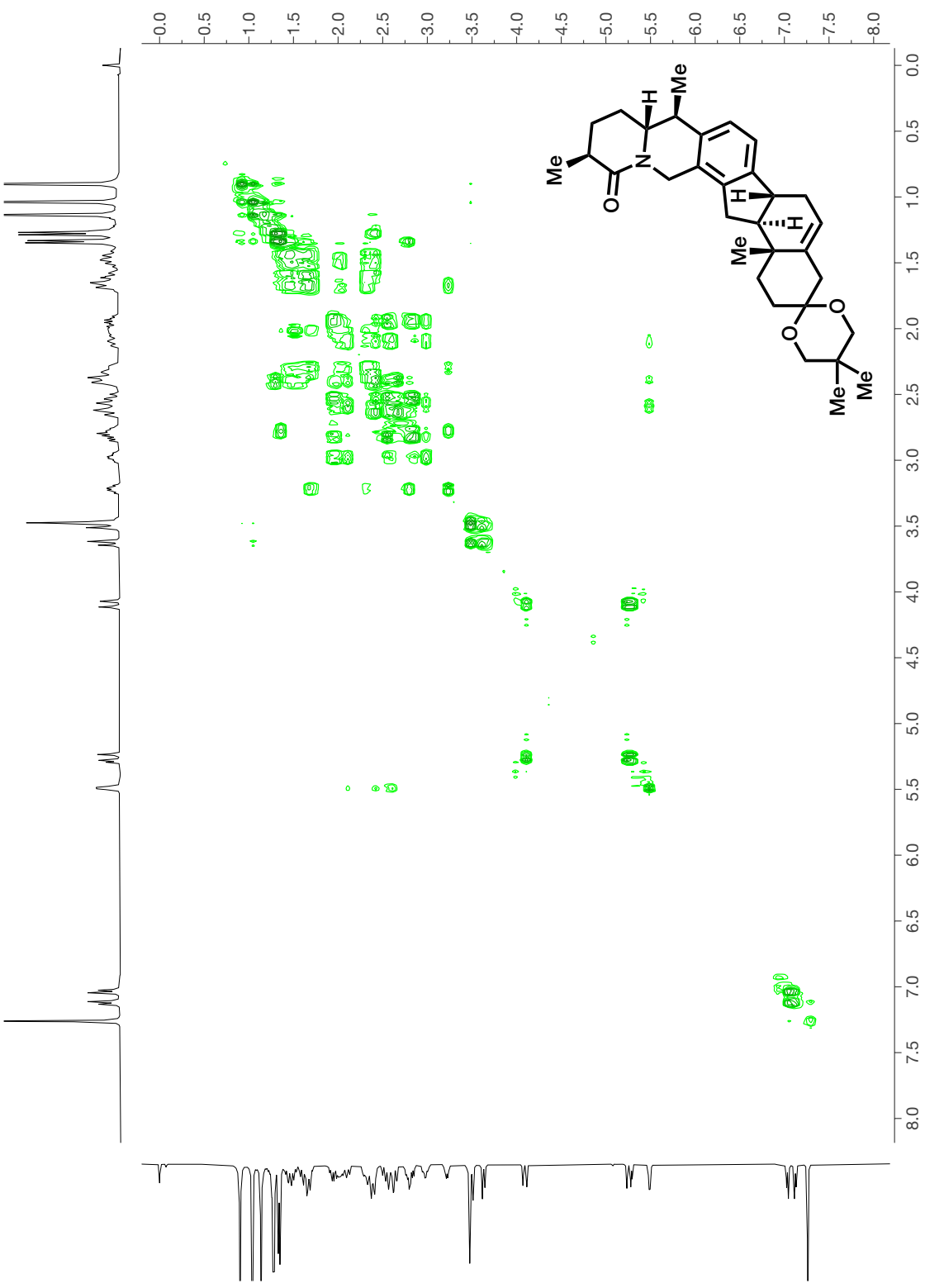


Figure A.128. ^{1}H–^{1}H COSY spectrum (400 MHz, $CDCl_3$) of **4.19**.

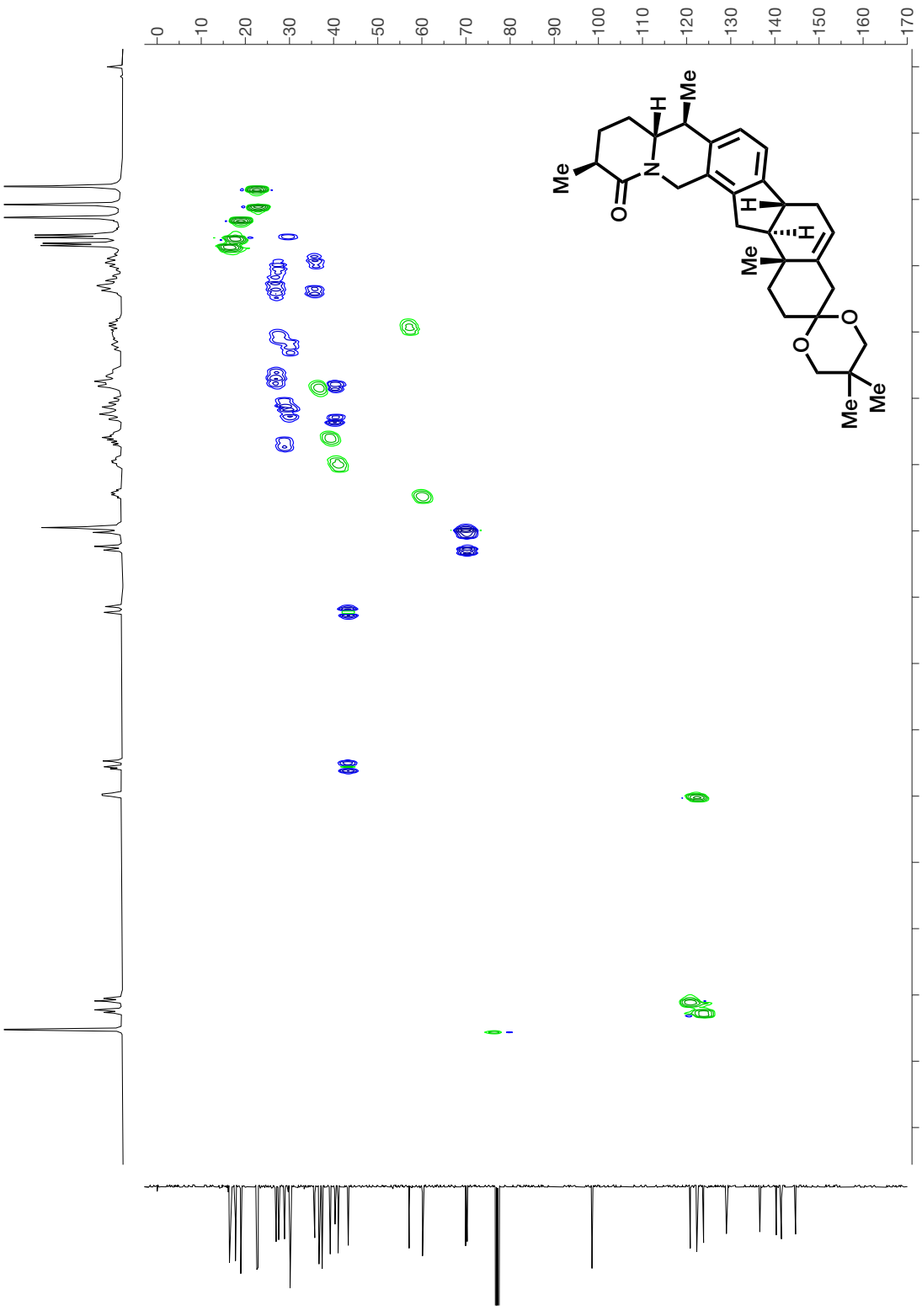


Figure A.129. $^{1}H–^{13}C$ HSQC spectrum (400 MHz, 101 MHz, $CDCl_3$) of **4.19**.

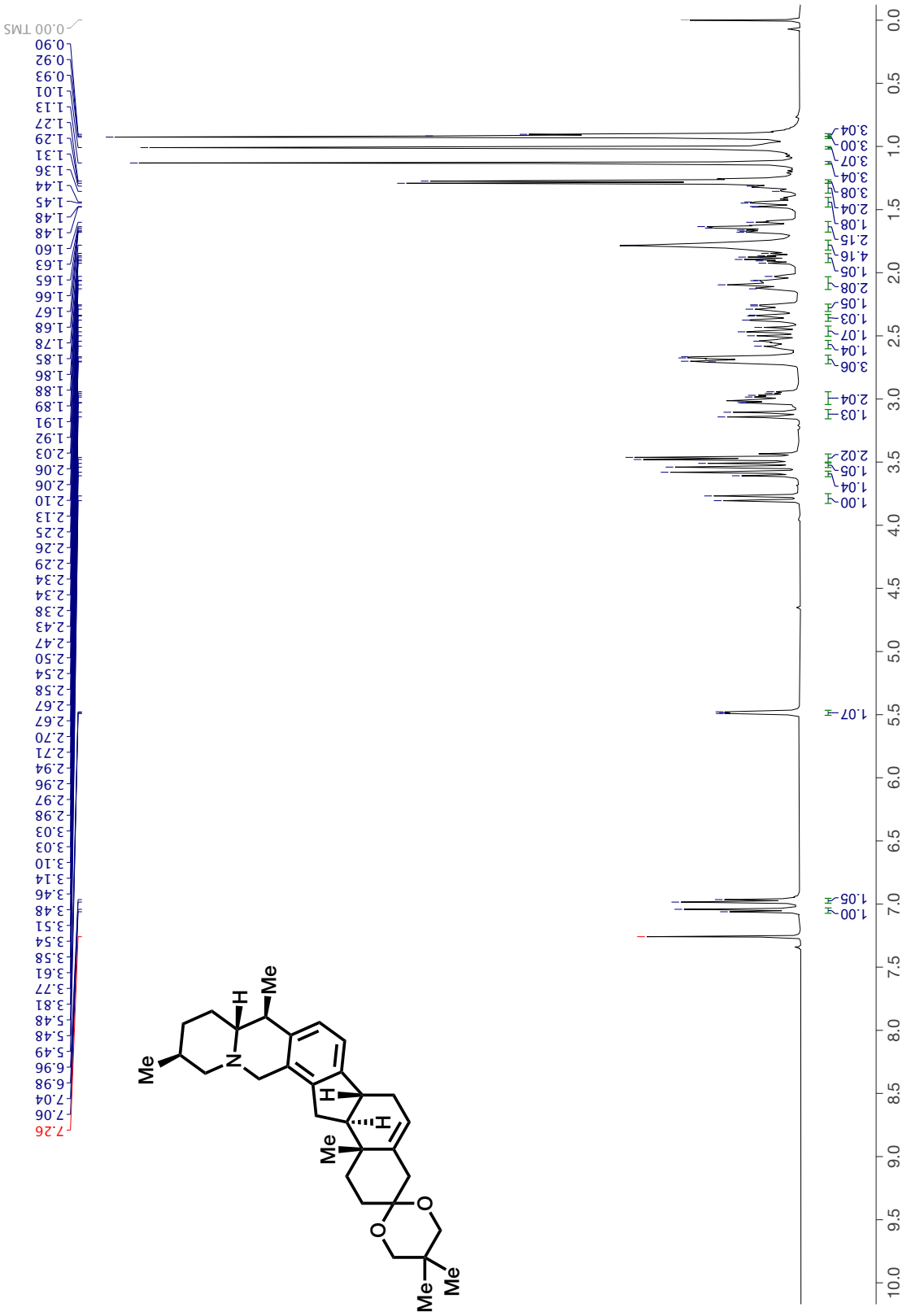


Figure A.130. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4.3**.

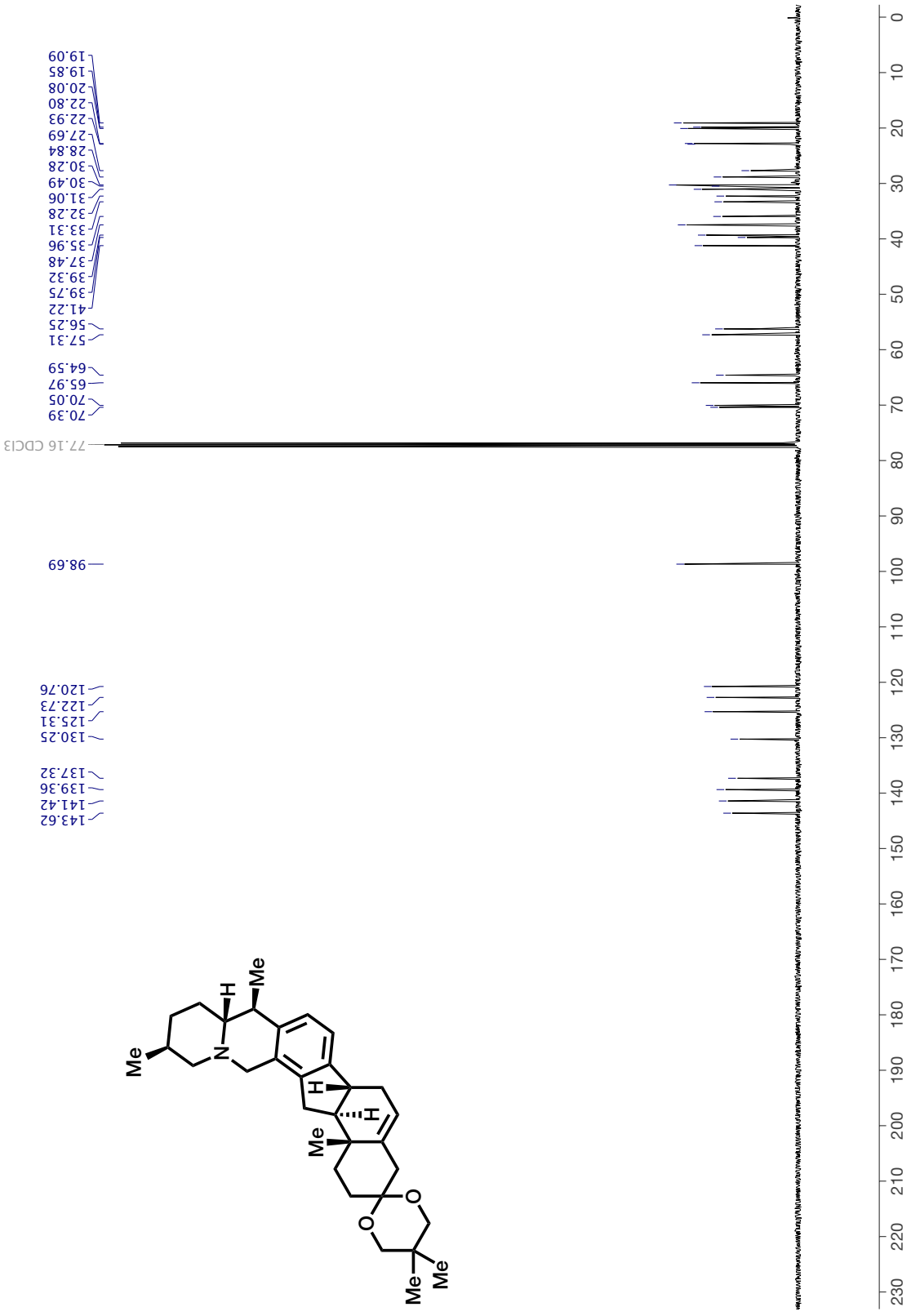


Figure A.131. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **4.3**.

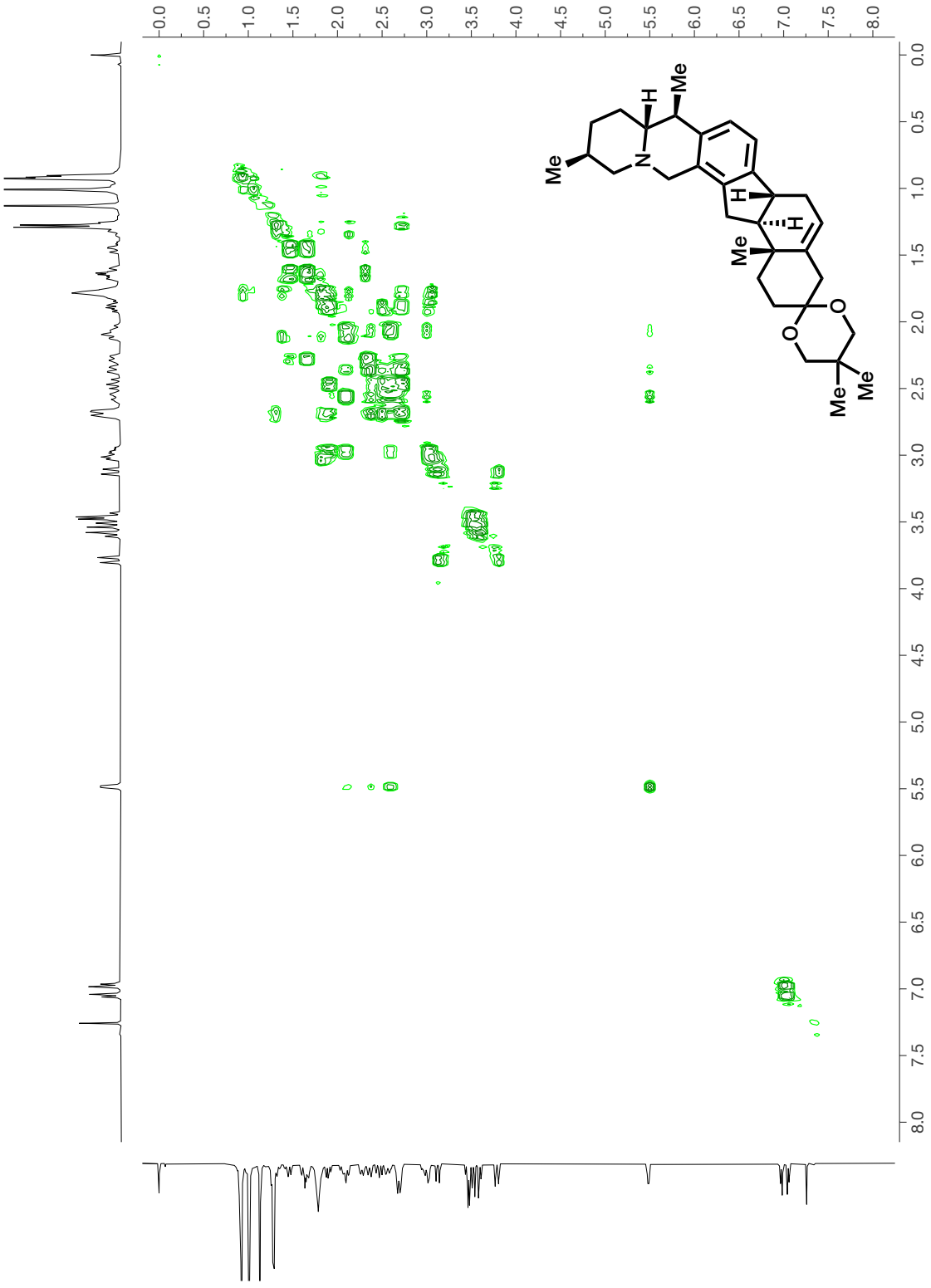


Figure A.132. ^{1}H–^{1}H COSY spectrum (400 MHz, $CDCl_3$) of **4.3**.

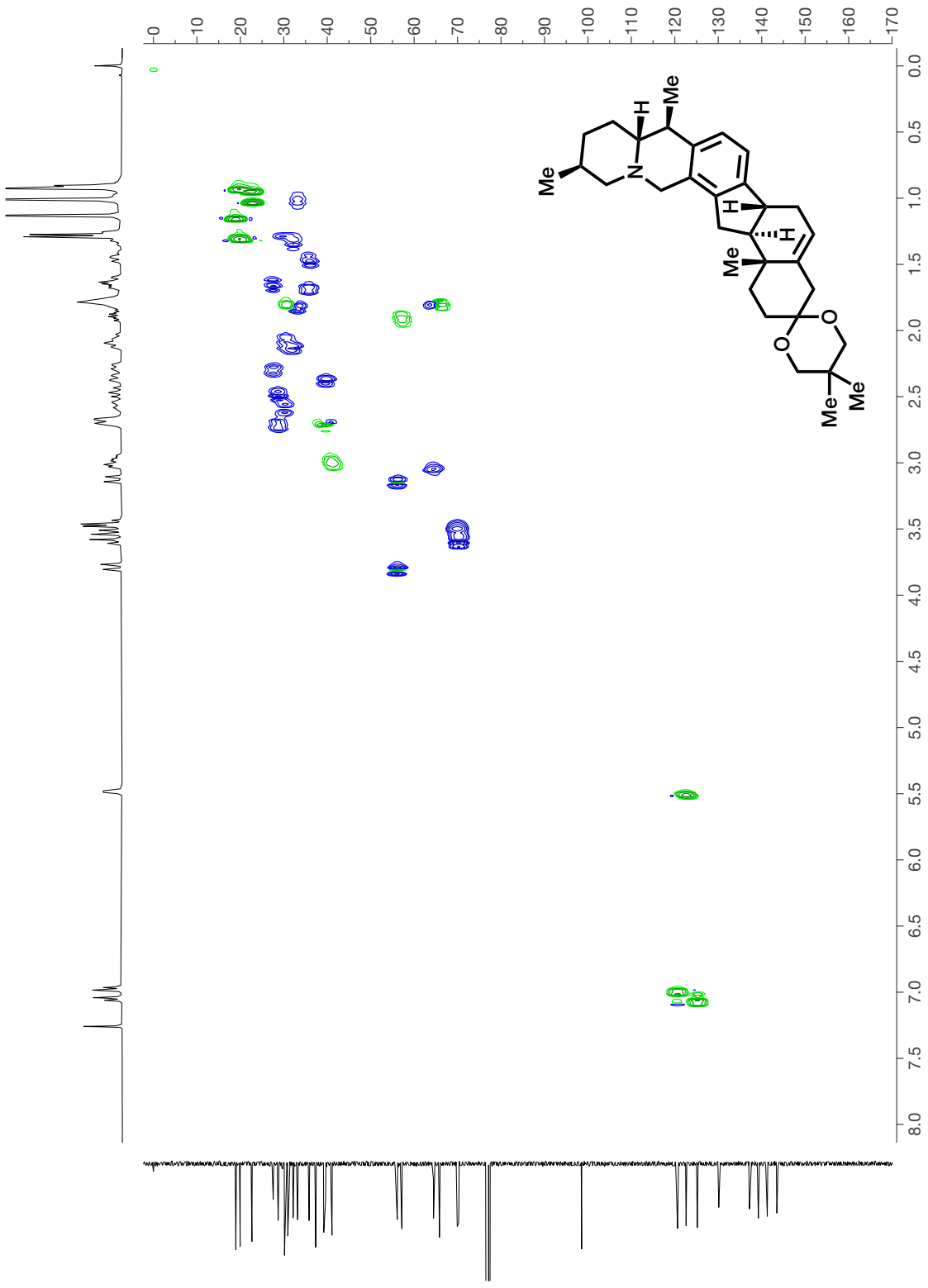


Figure A.133. ^{1}H–^{13}C HSQC spectrum (400 MHz, 101 MHz, $CDCl_3$) of **4.3**.

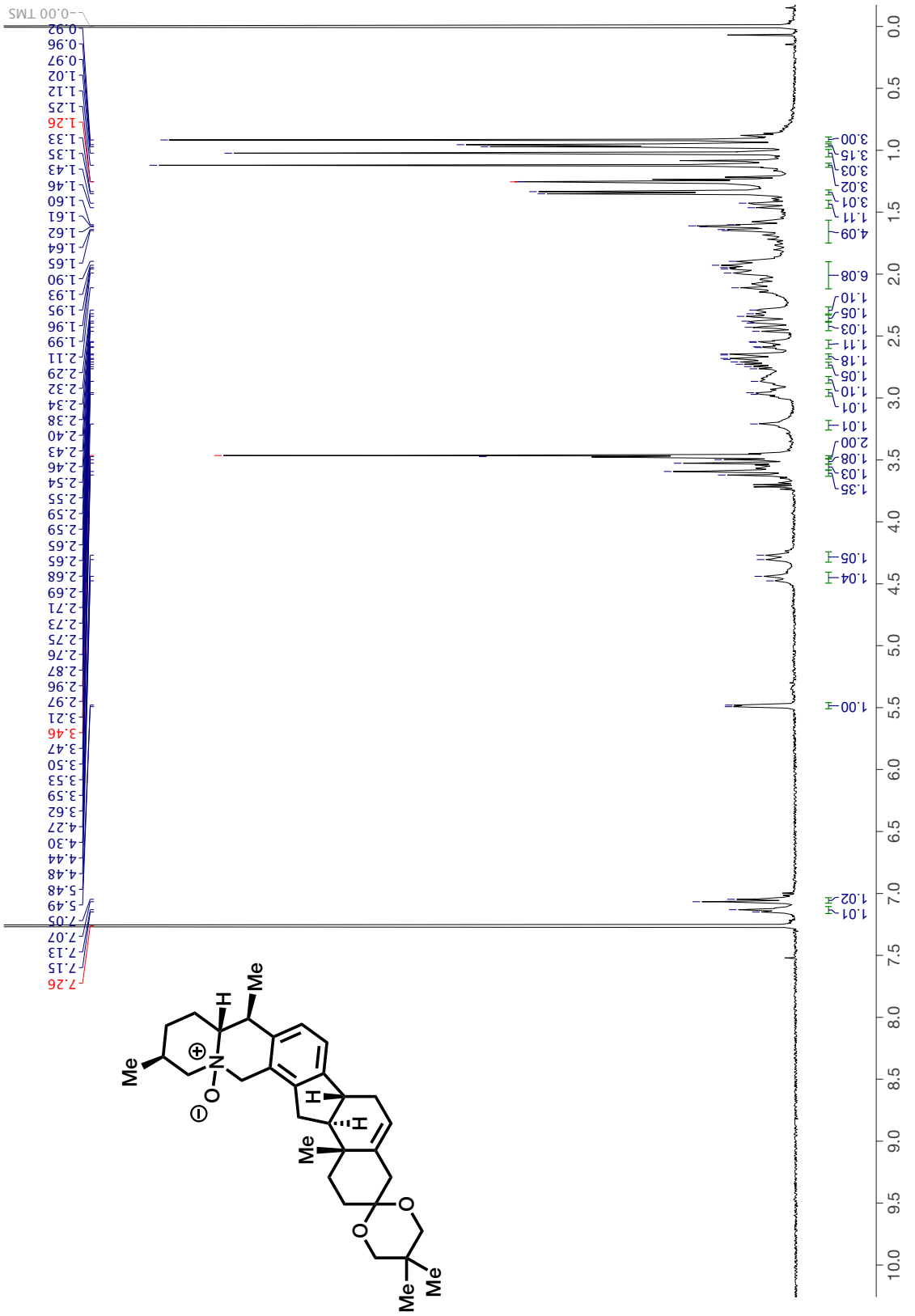


Figure A.134. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4.4**.

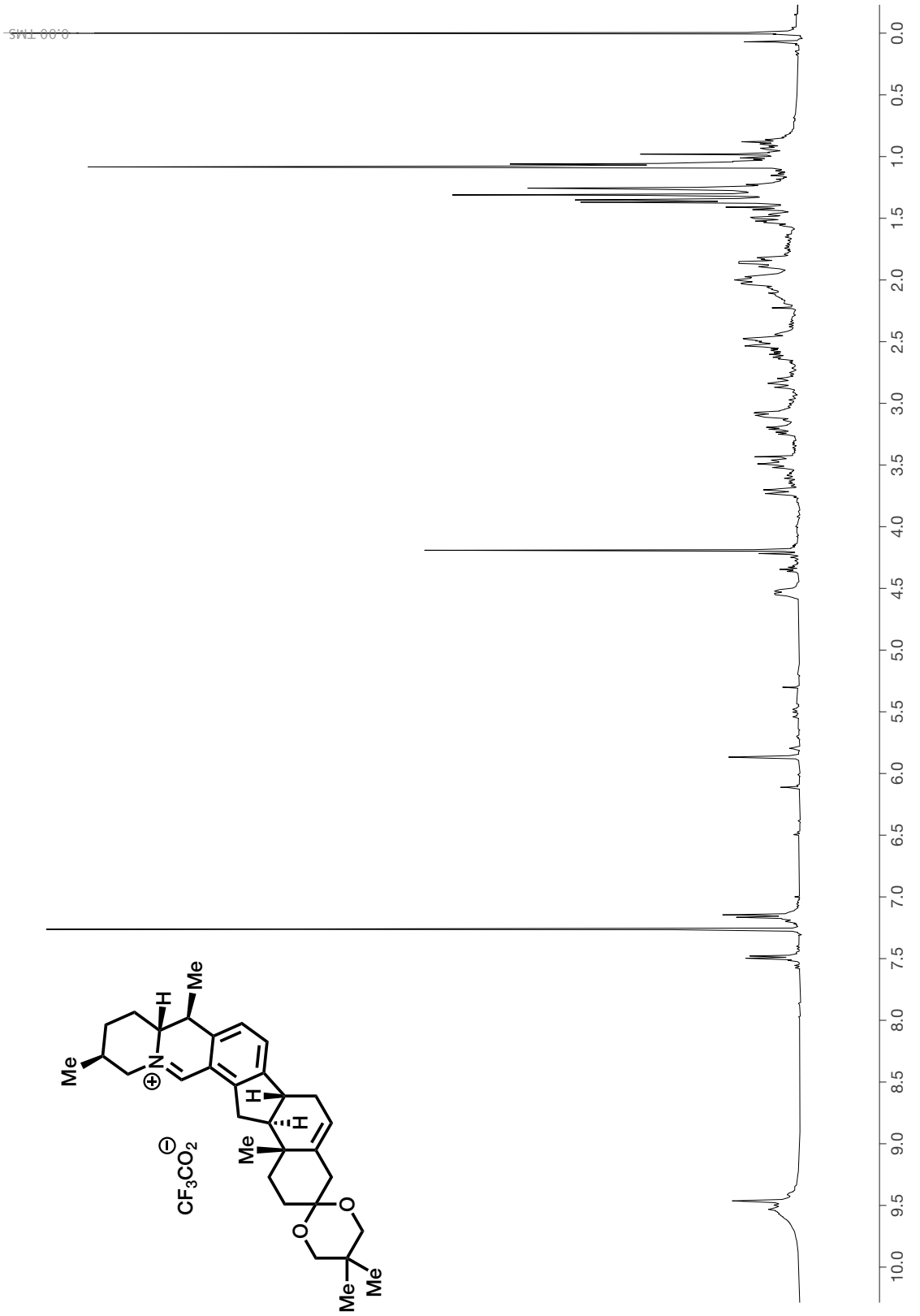


Figure A.135. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of unpurified **4.7**.

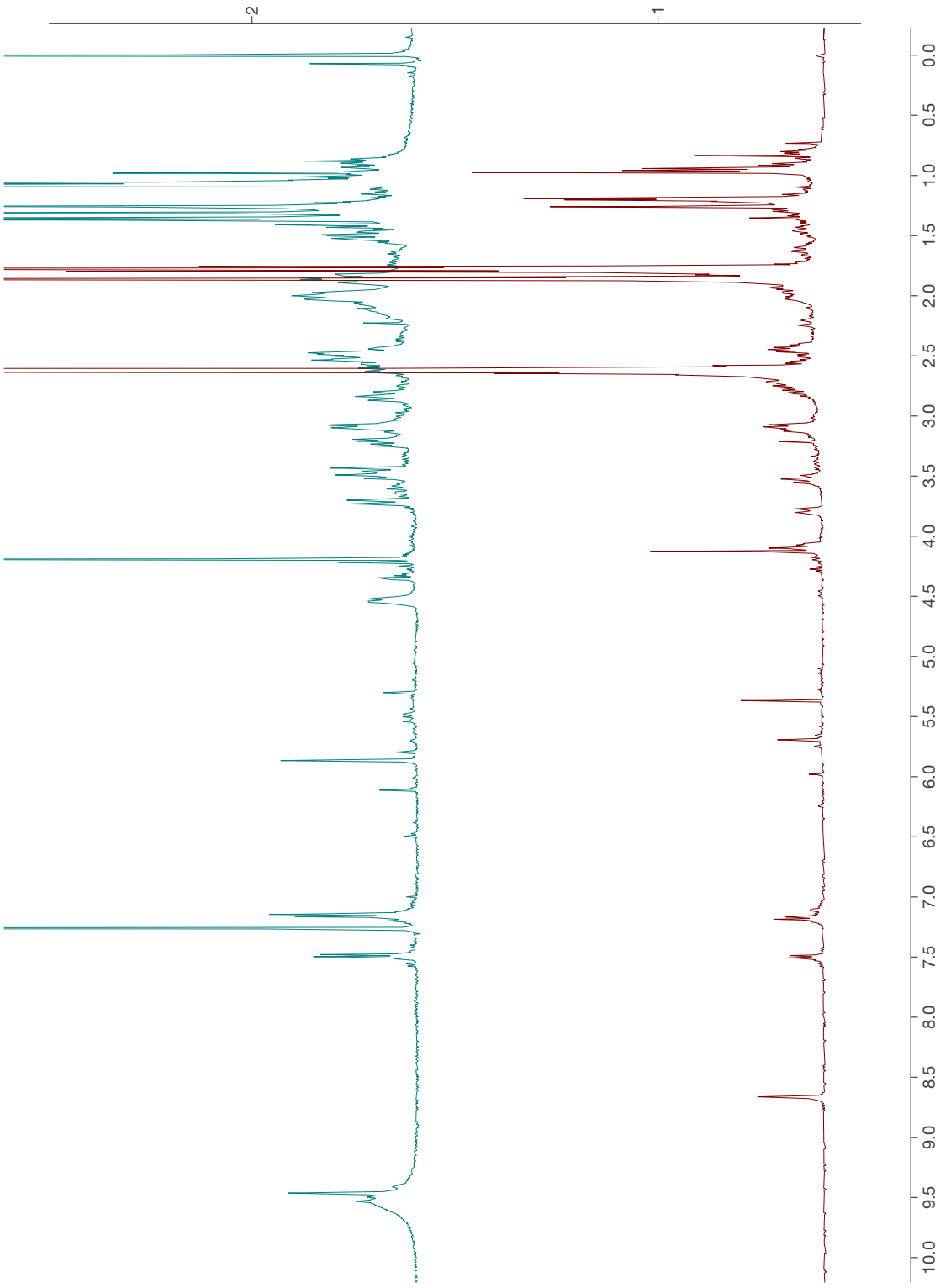


Figure A.136. Stacked ^{1}H NMR spectra (400 MHz, $CDCl_3$ = top, CD_3CN = bottom) of **4.7**.

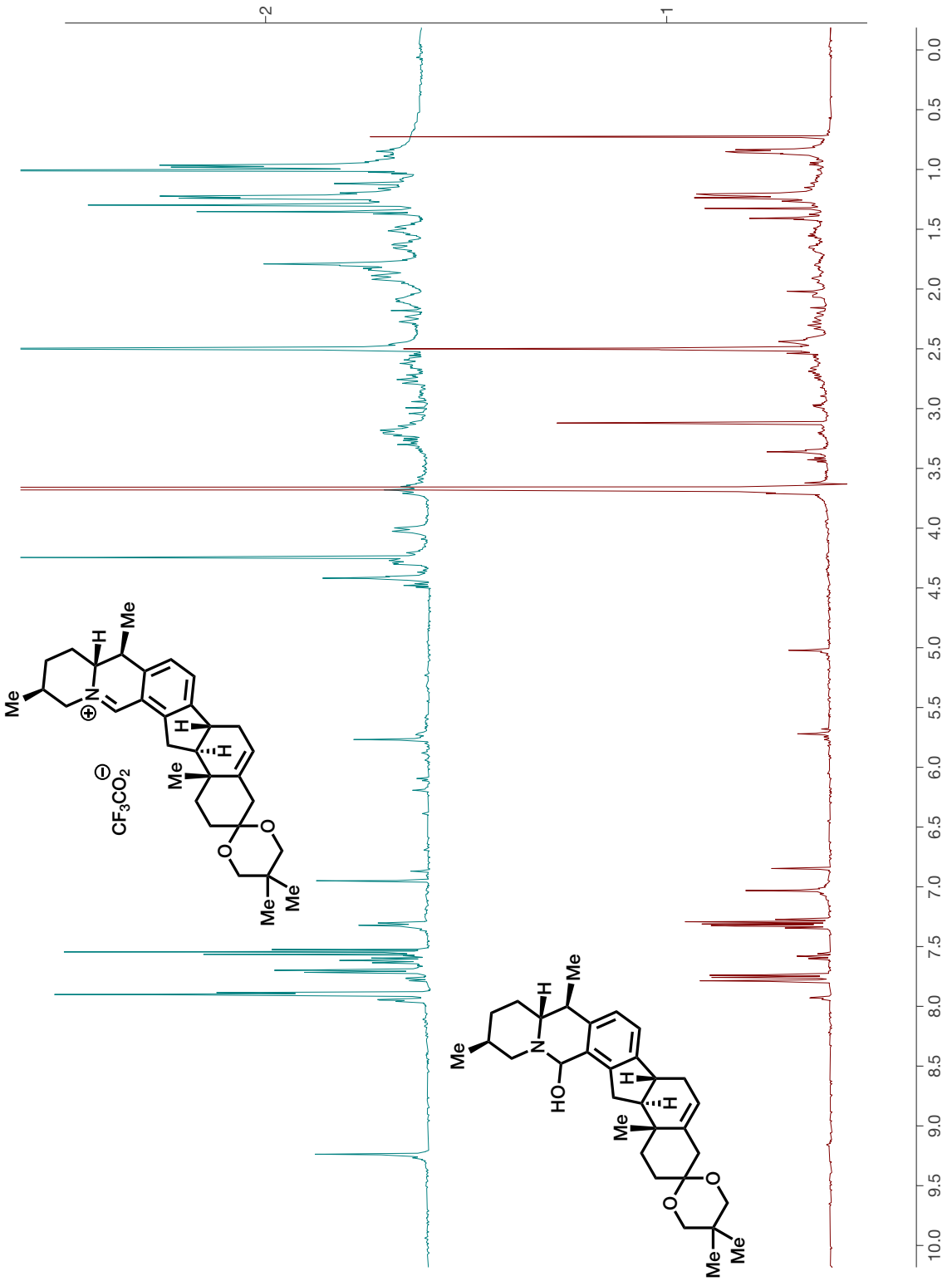


Figure A.137. Stacked ^{1}H NMR spectra (400 MHz, DMSO-d_6) of **4.7** (top) and **4.5** (bottom).

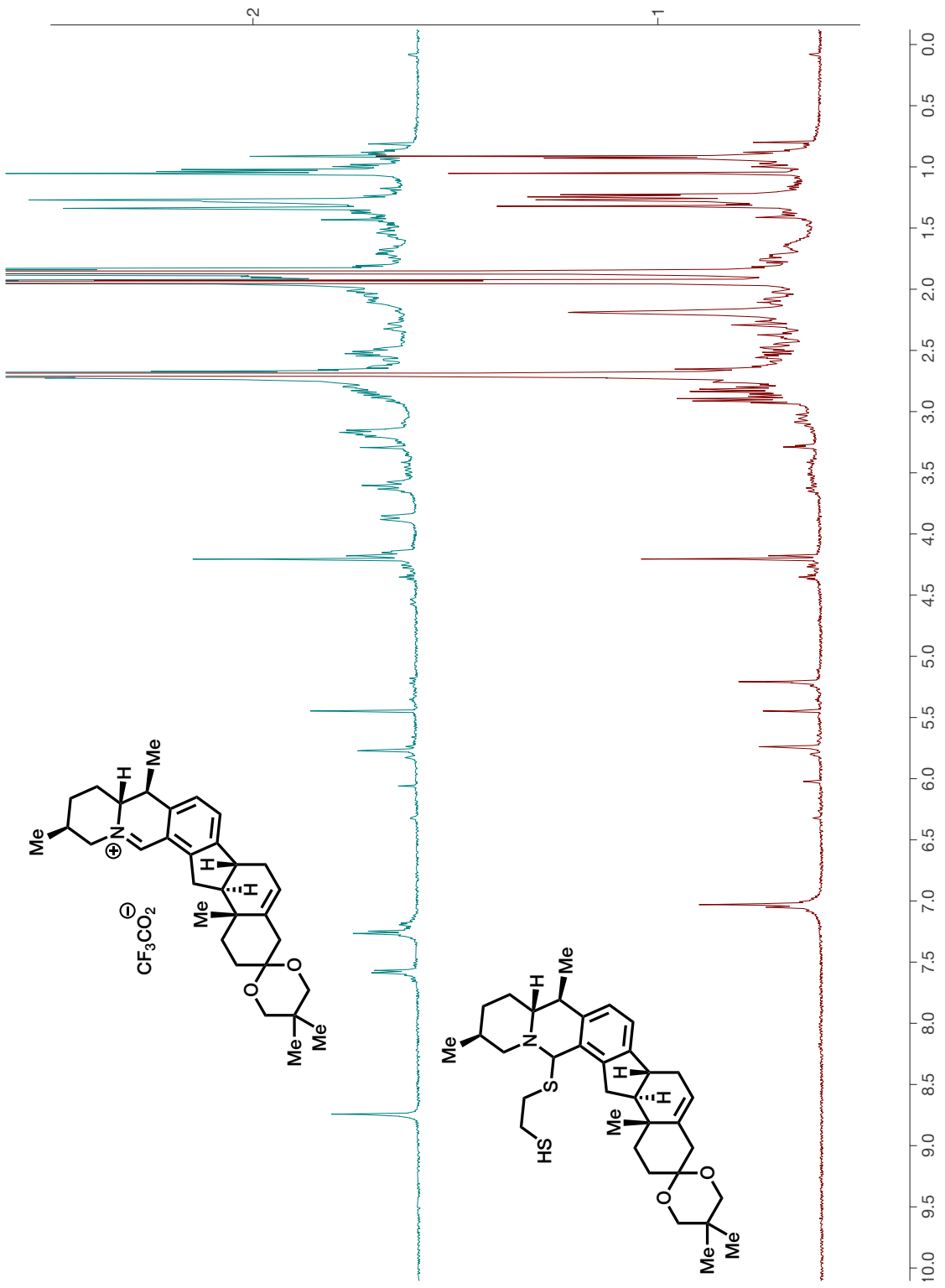


Figure A.138. Stacked ^{1}H NMR spectra (400 MHz, CD_3CN) of **4.7** (top) and **4.8** (bottom).

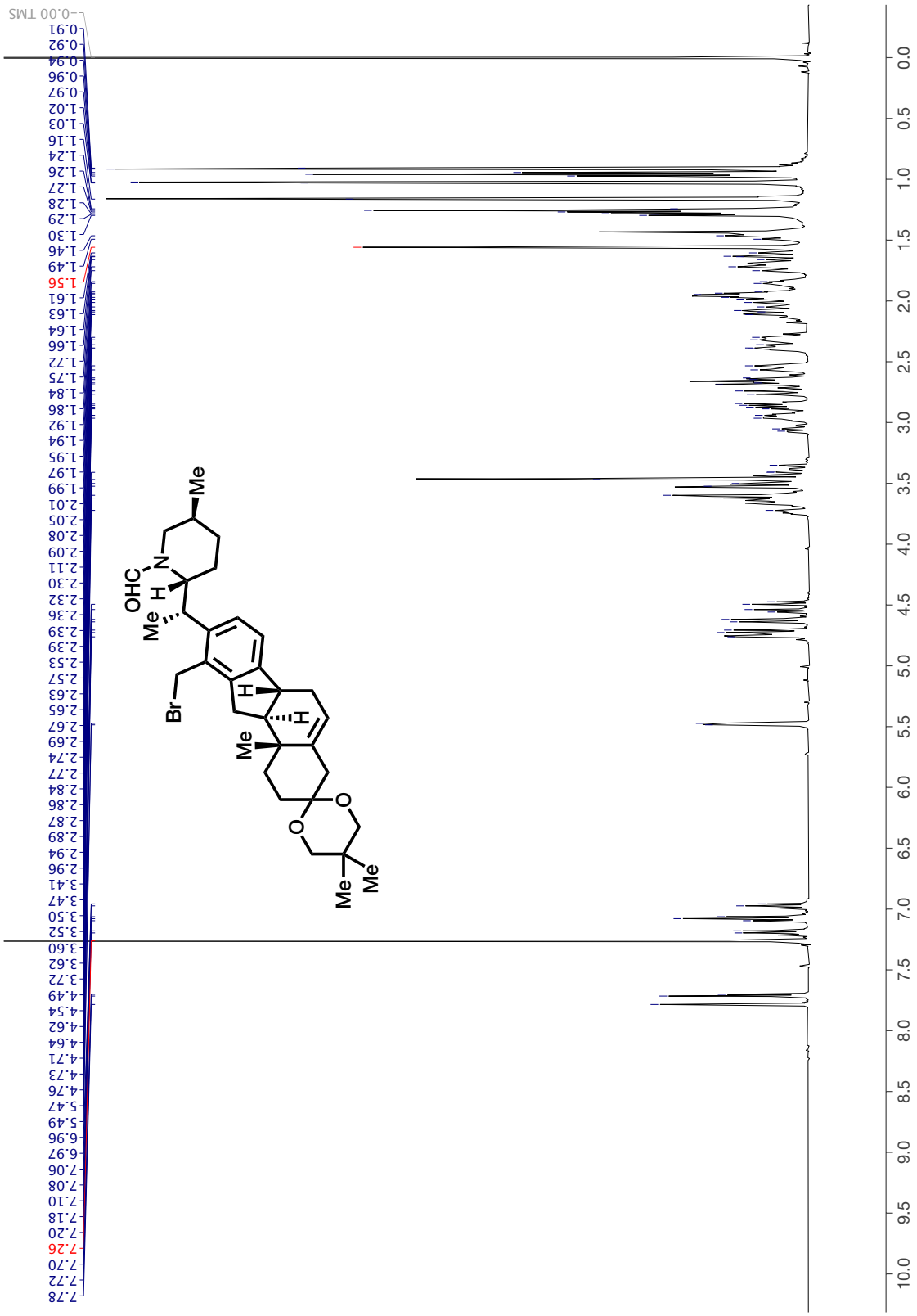


Figure A.139. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **4.9**.

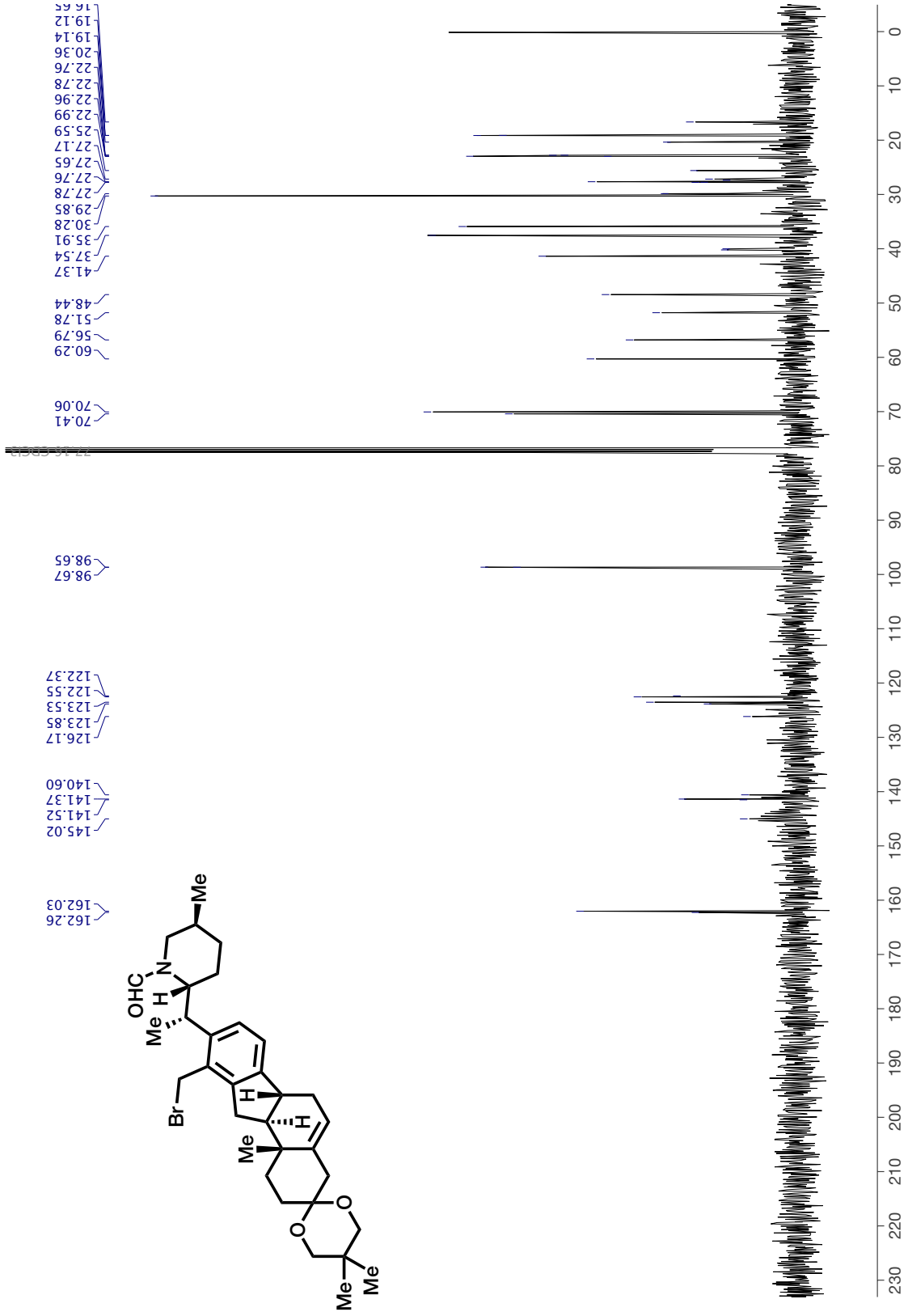


Figure A.140. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **4.9**.

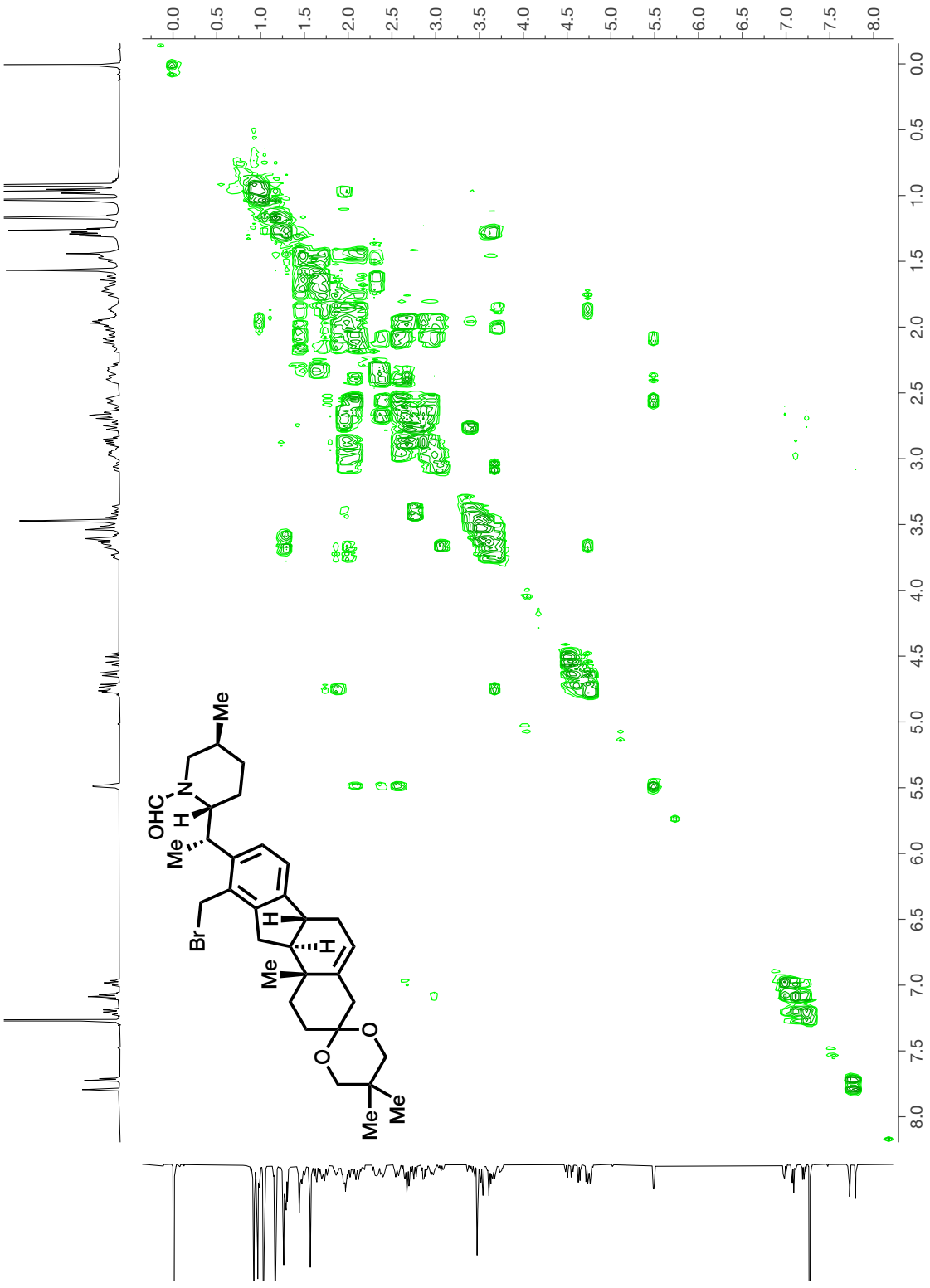


Figure A.141. ^{1}H–^{1}H COSY spectrum (400 MHz, $CDCl_3$) of **4.9**.

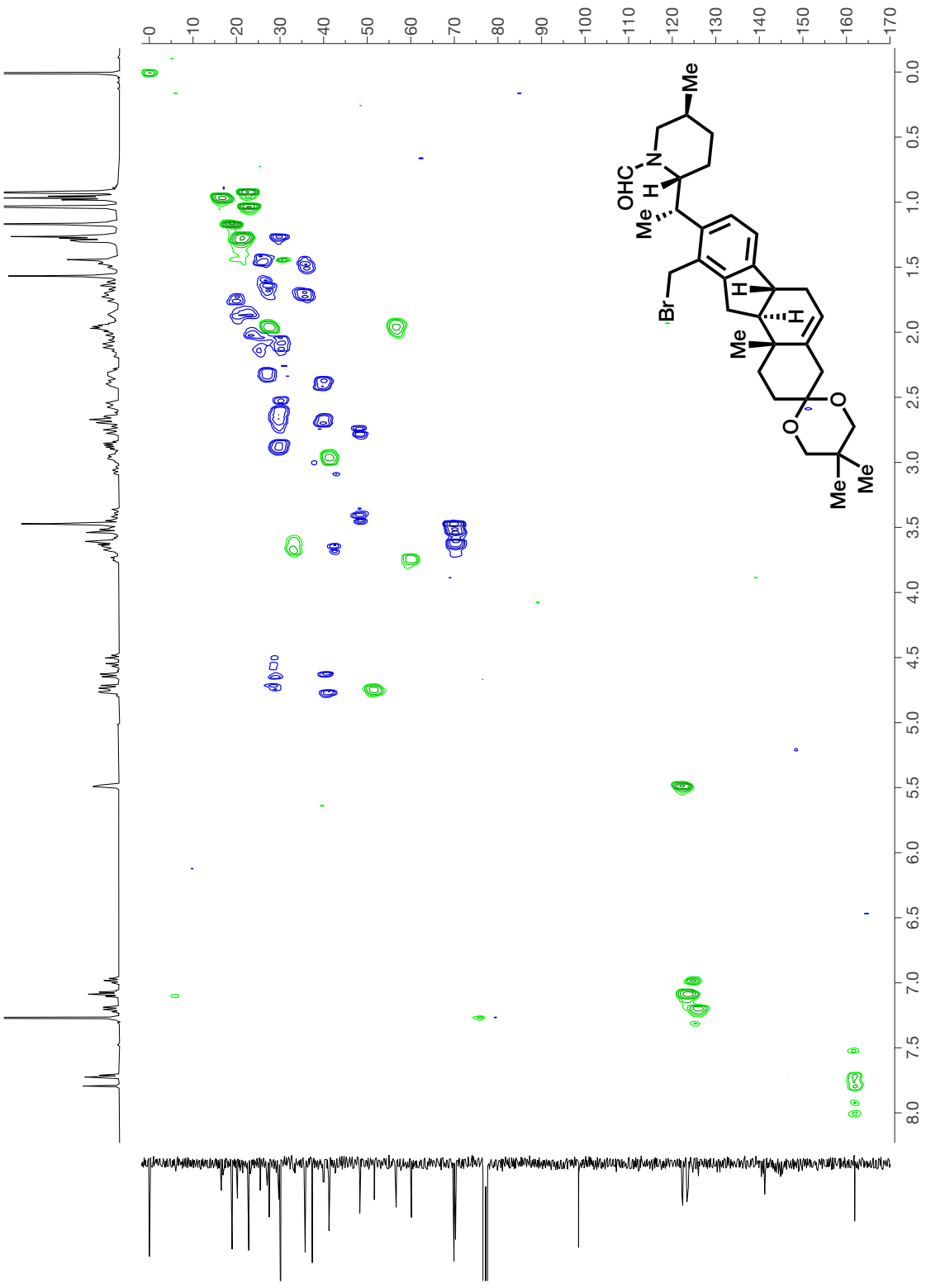


Figure A.142. ^{1}H–^{13}C HSQC spectrum (400 MHz, 101 MHz, $CDCl_3$) of **4.9**.

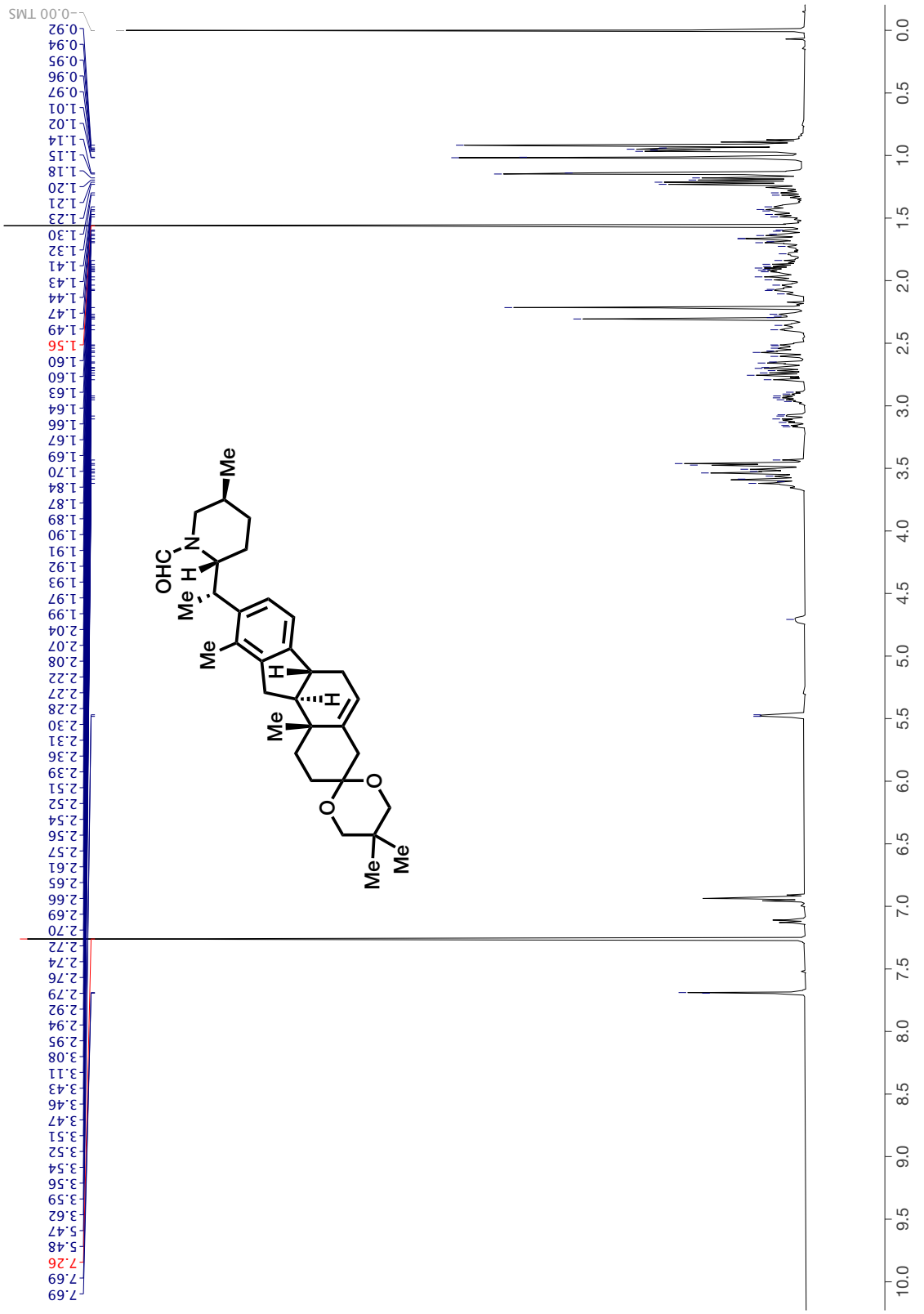


Figure A.143. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **4.10**.

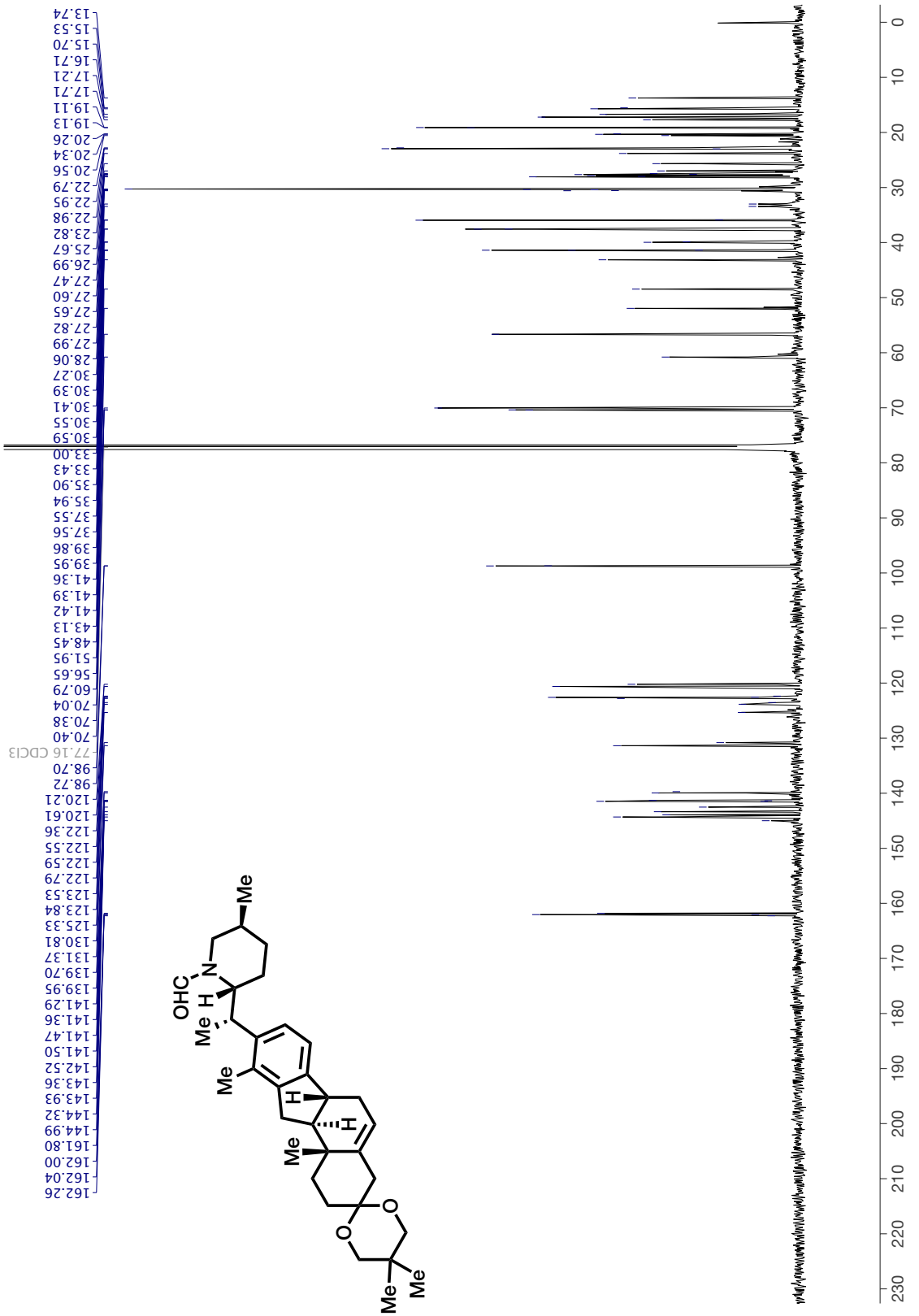


Figure A.144. ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of **4.10**.

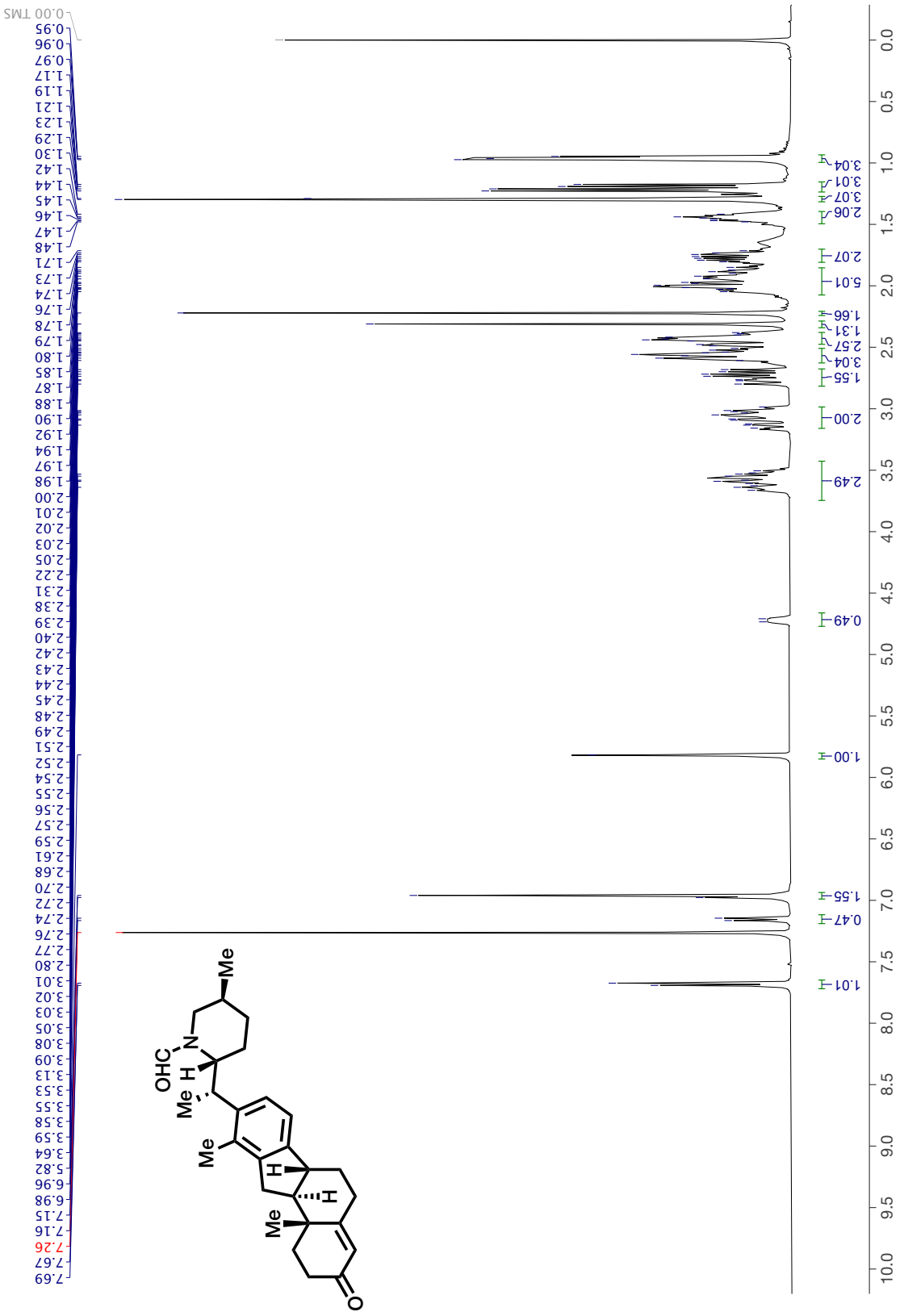


Figure A.145. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4.20**.

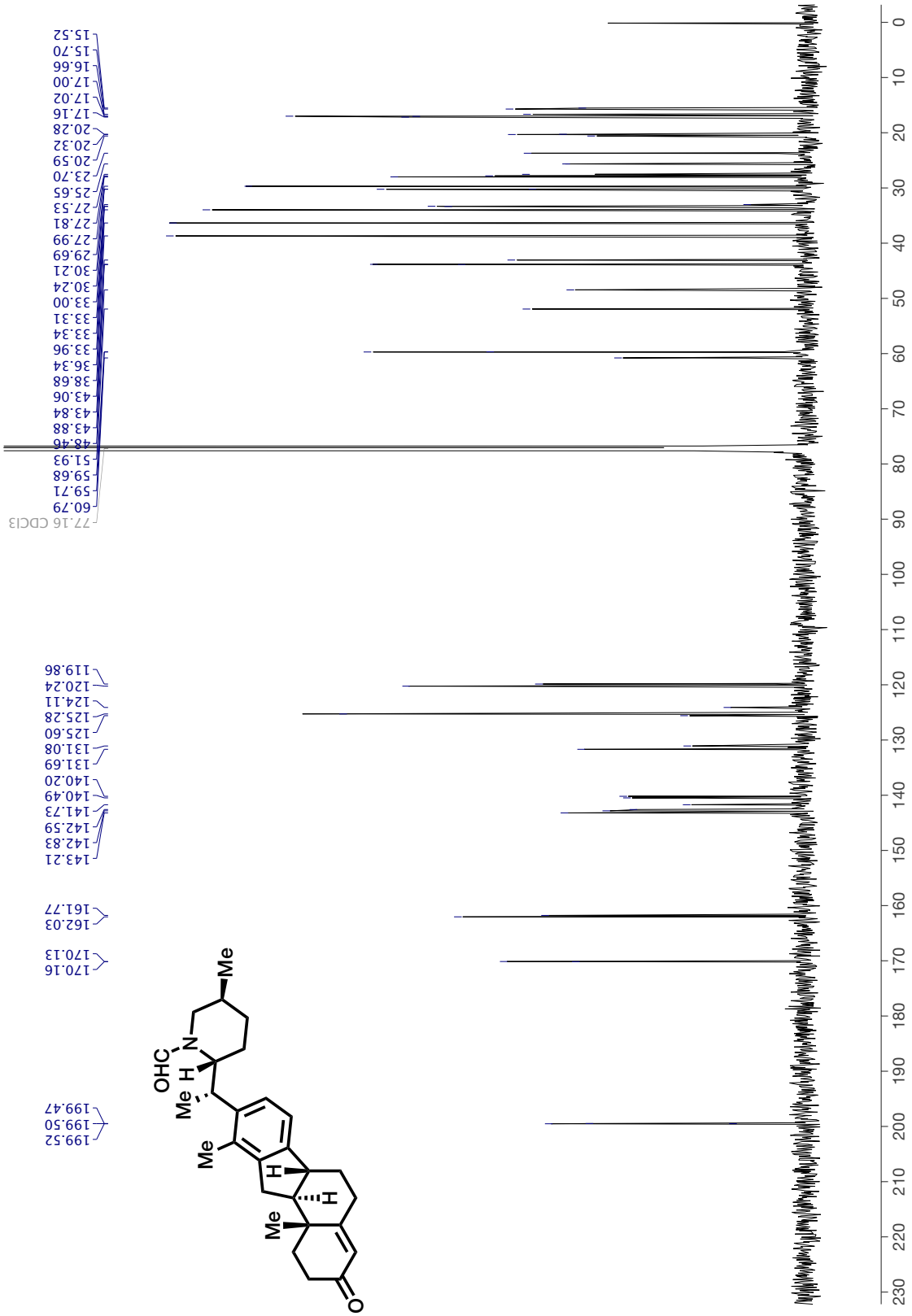


Figure A.146. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **4.11**.

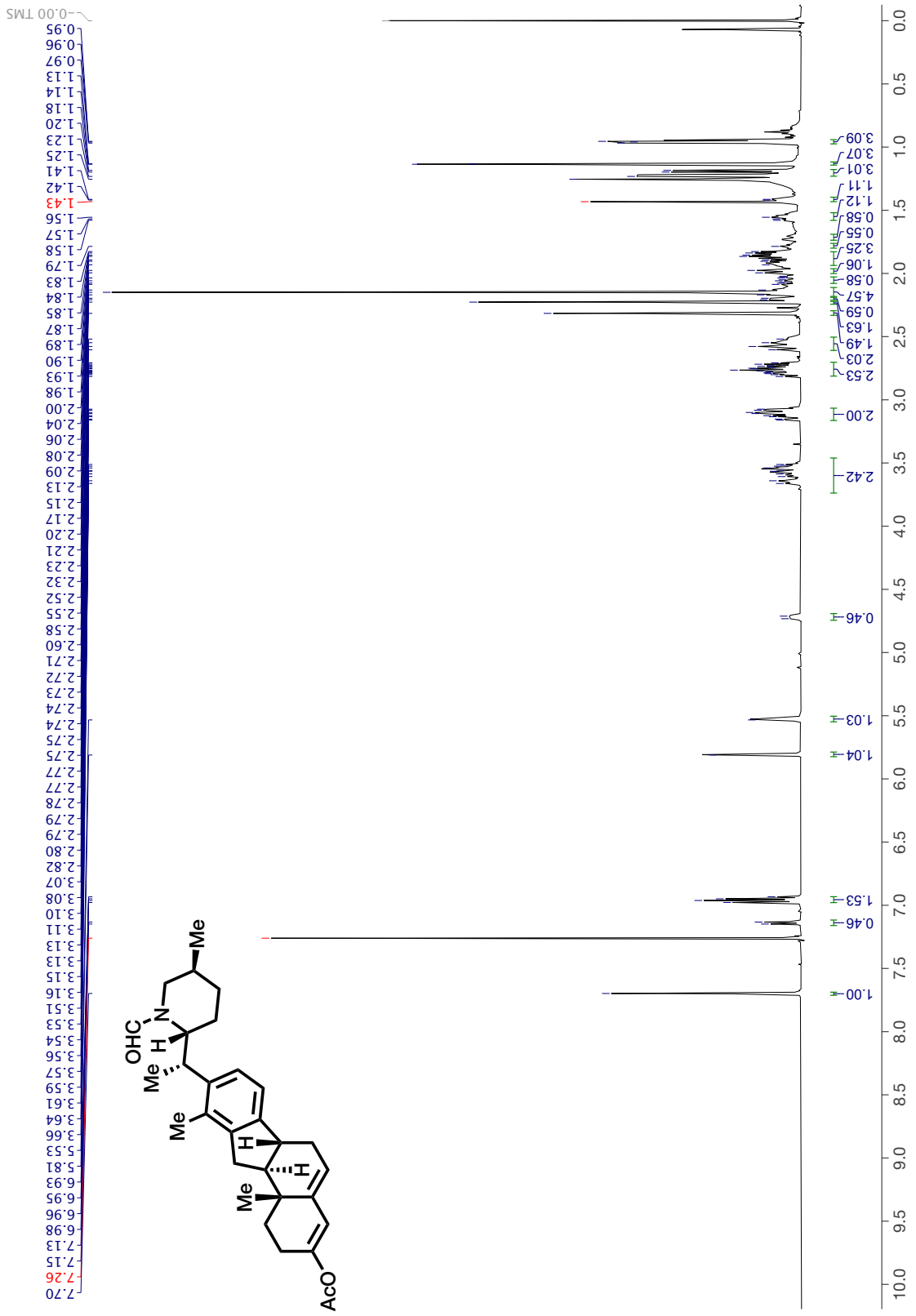


Figure A.147. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **4.11**.

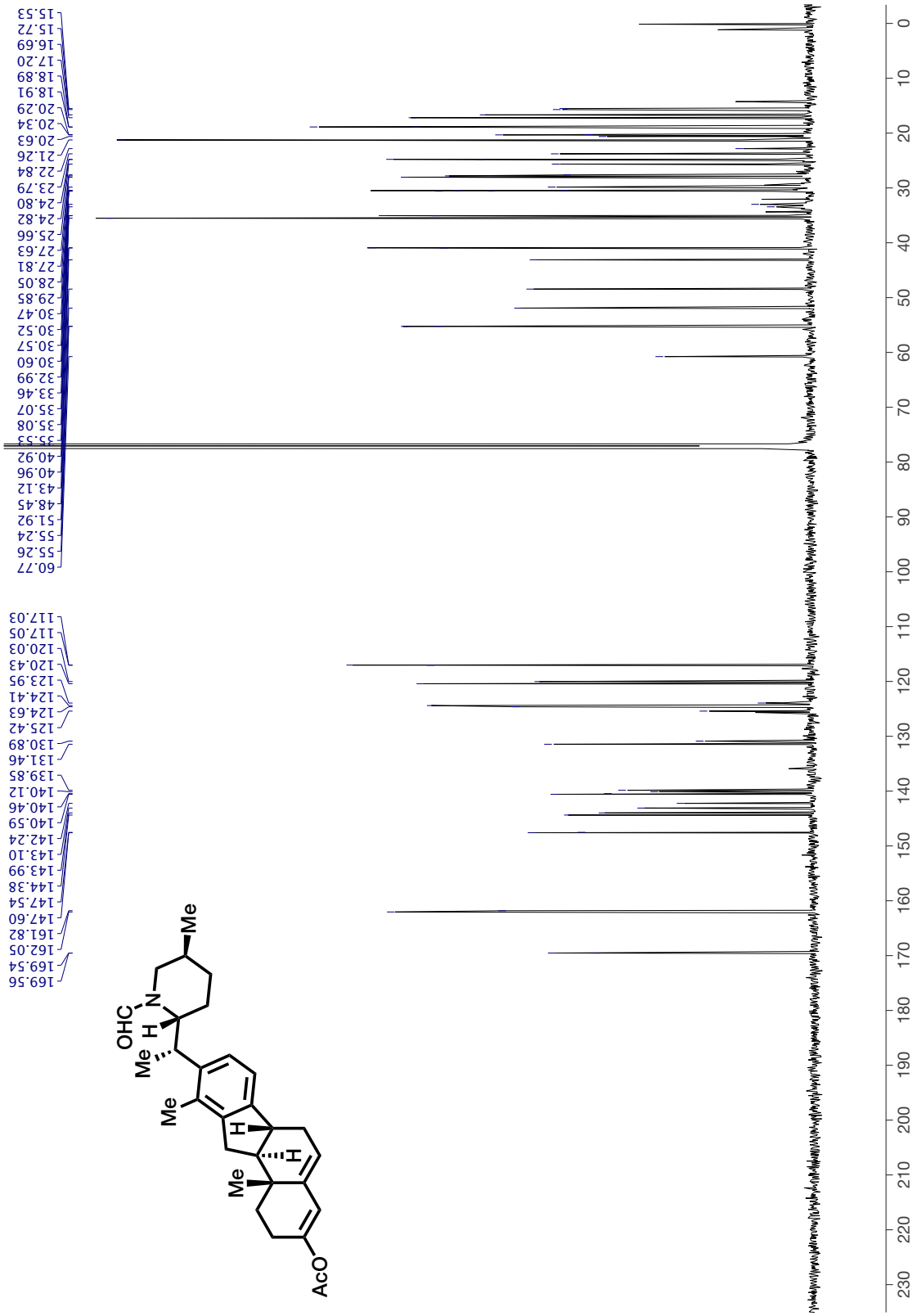


Figure A.148. ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of **4.11**.

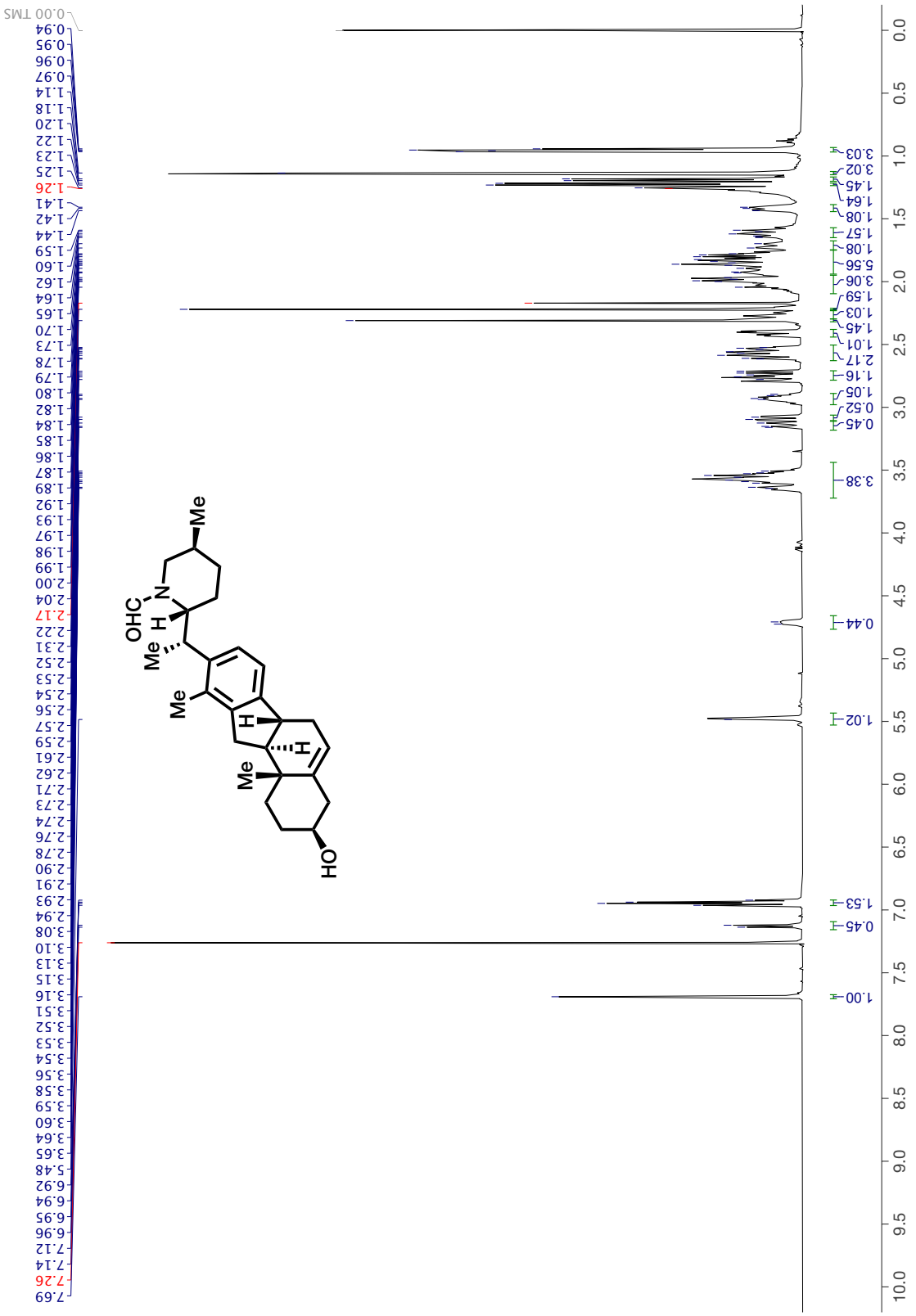


Figure A.149. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **4.12**.

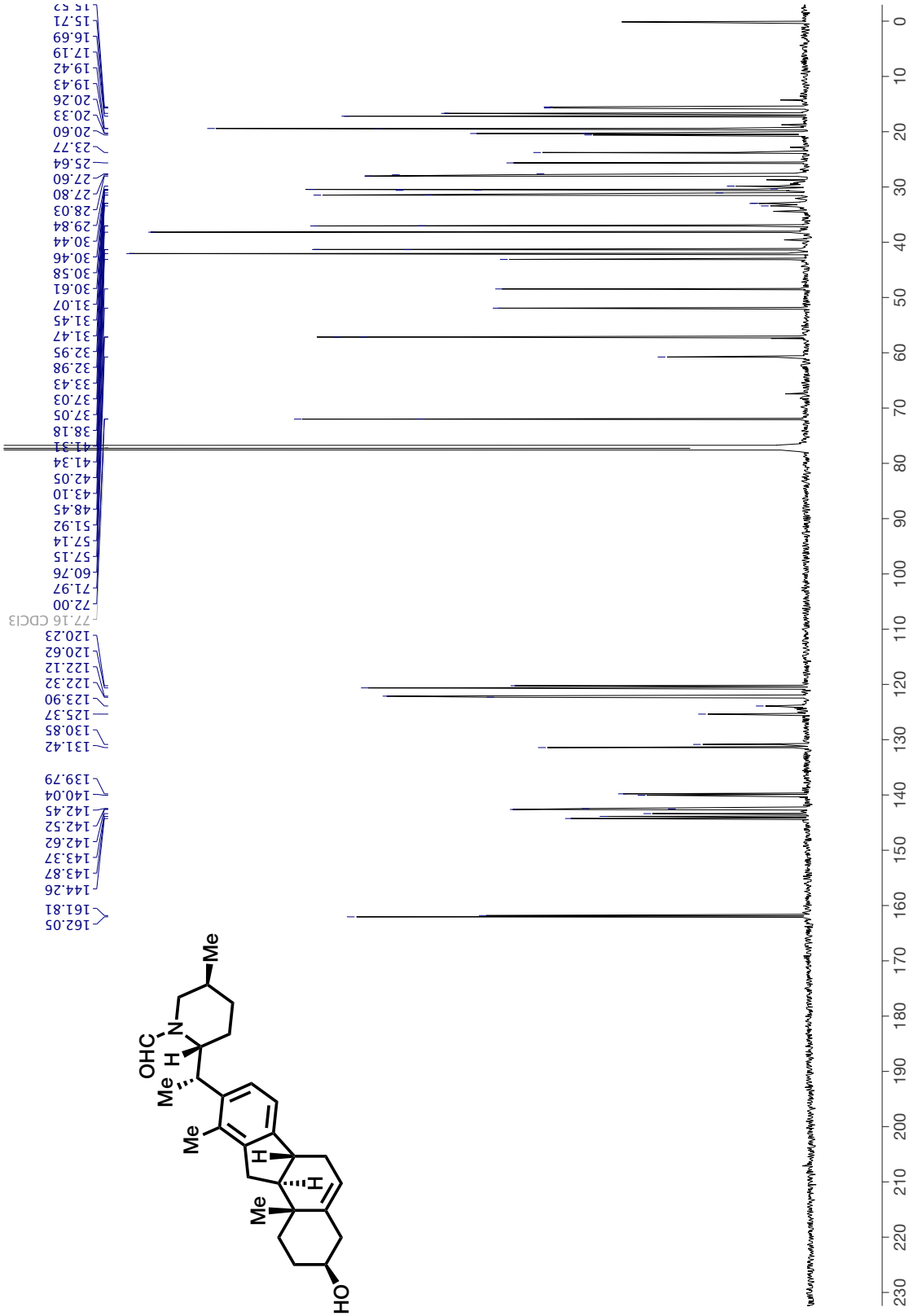


Figure A.150. ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of **4.12**.

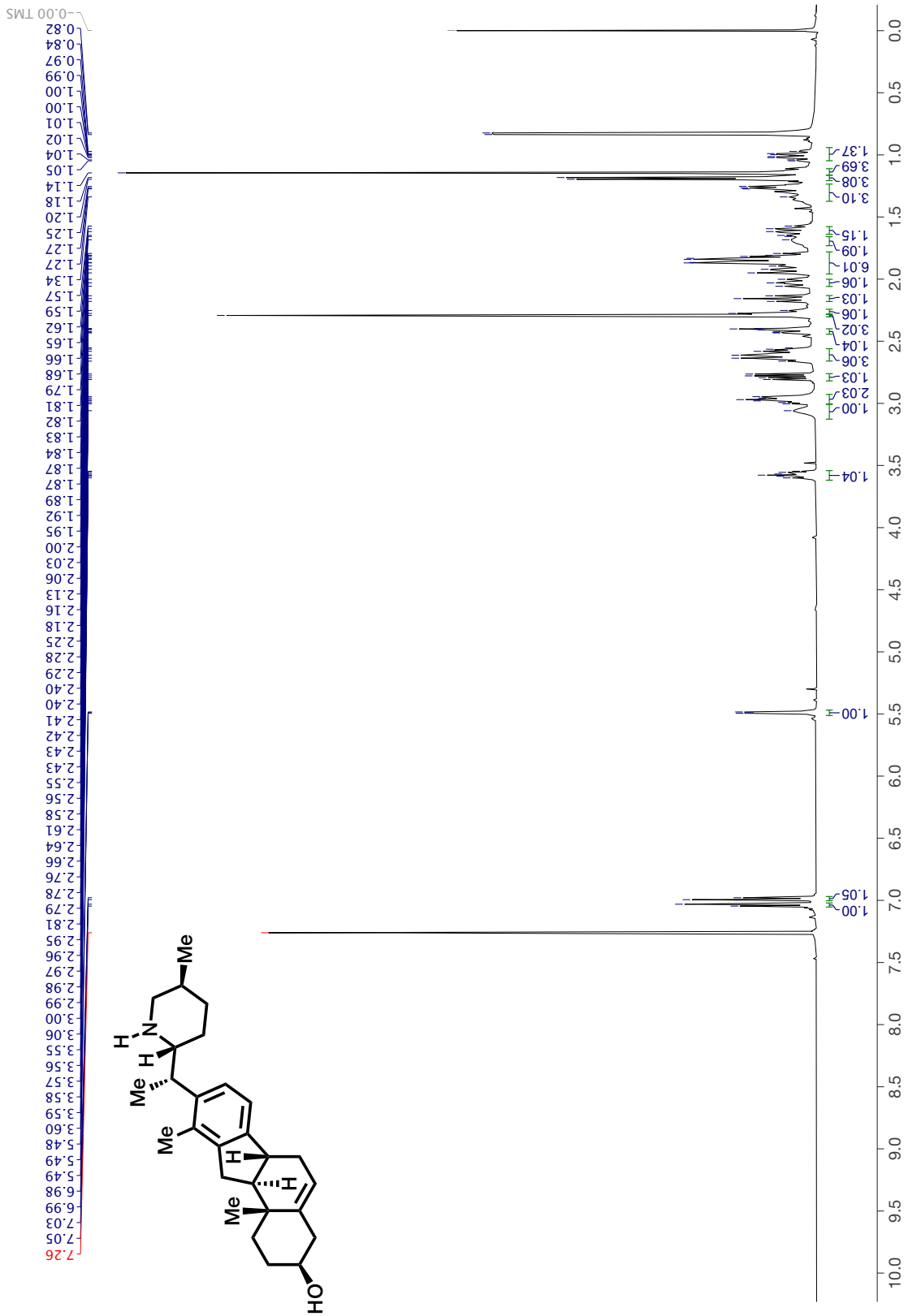


Figure A.151. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **verarine**.

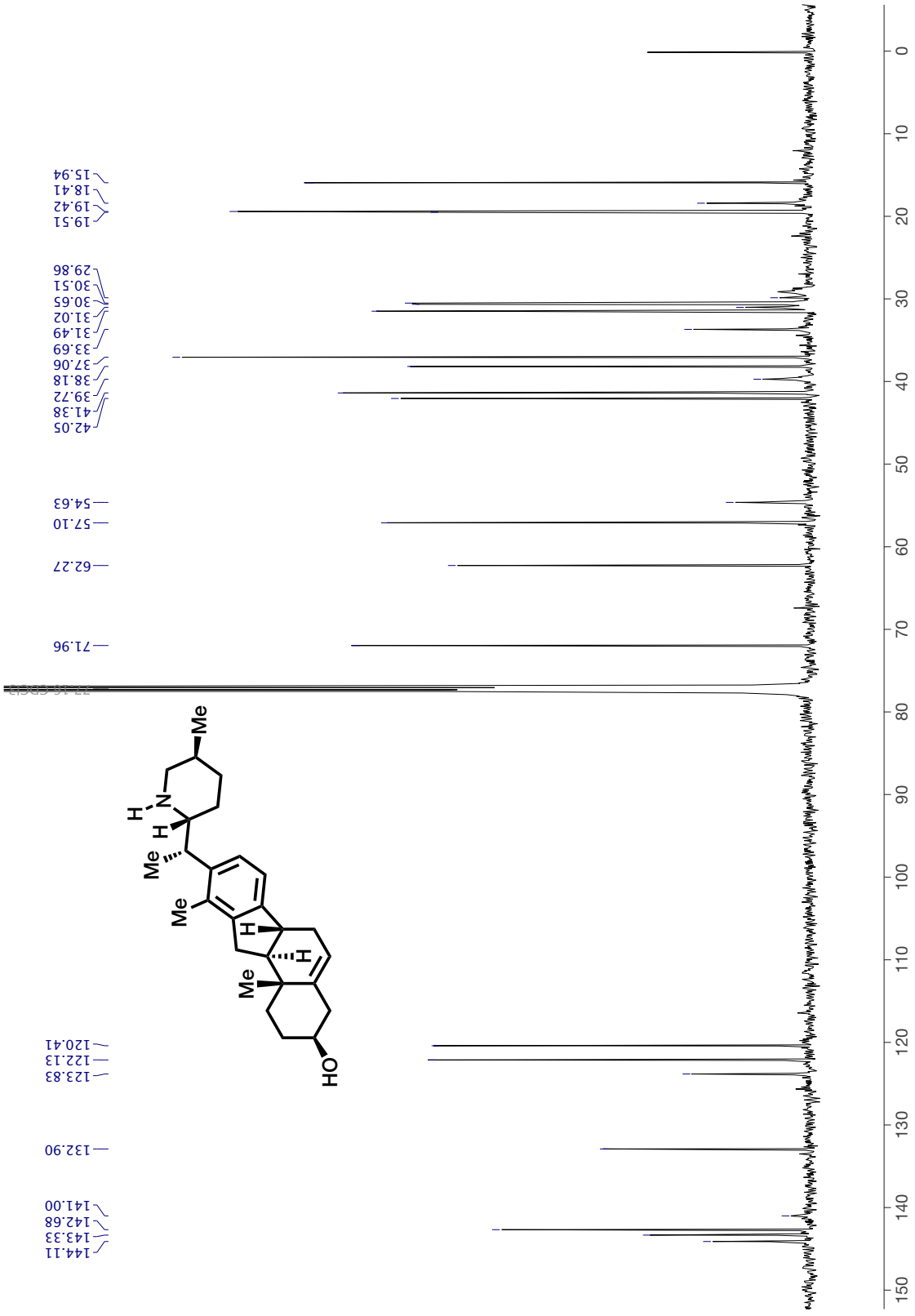


Figure A.152. ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of **verarine**.

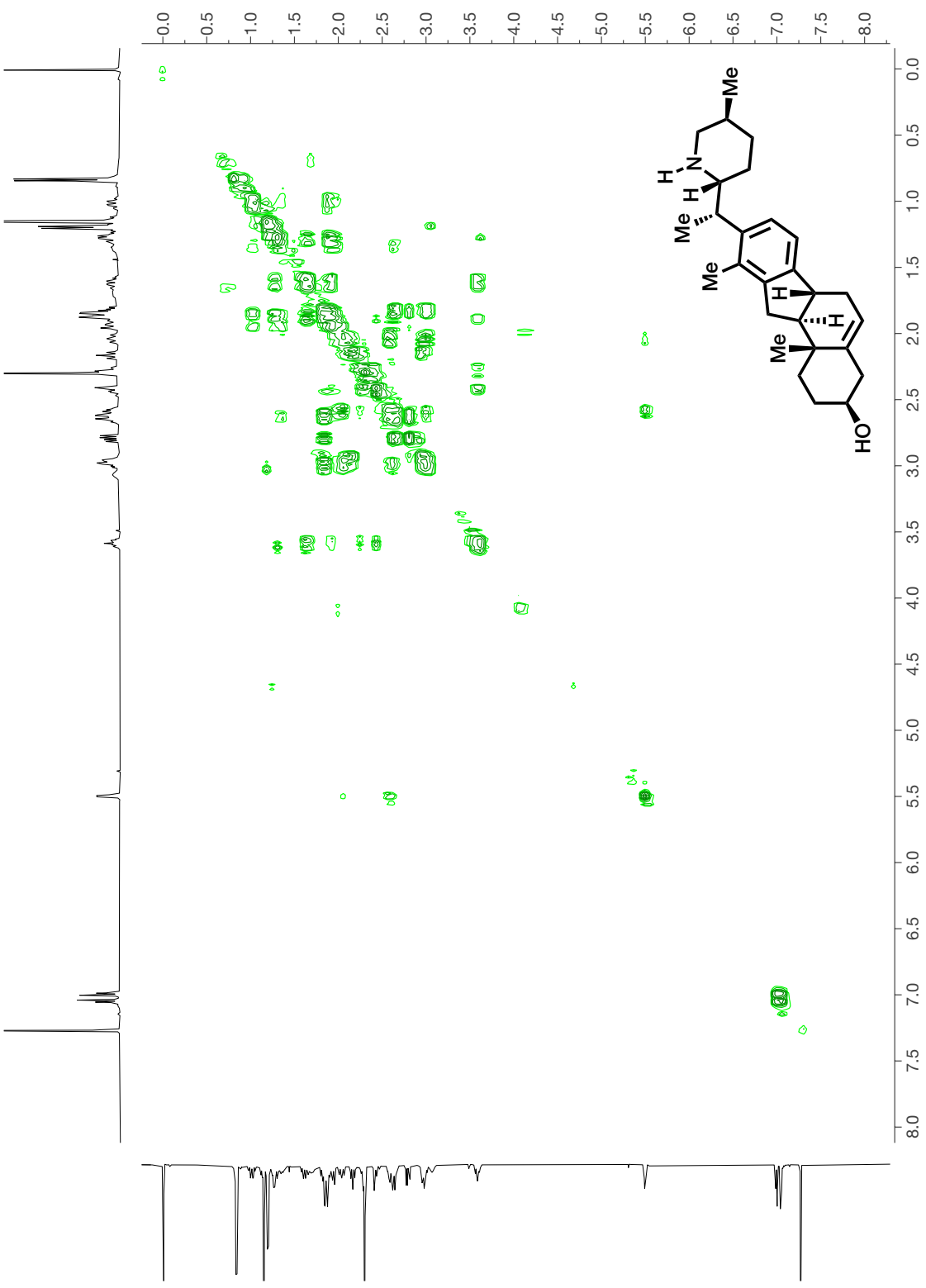


Figure A.153. ^{1}H–^{1}H COSY spectrum (400 MHz, $CDCl_3$) of **verarine**.

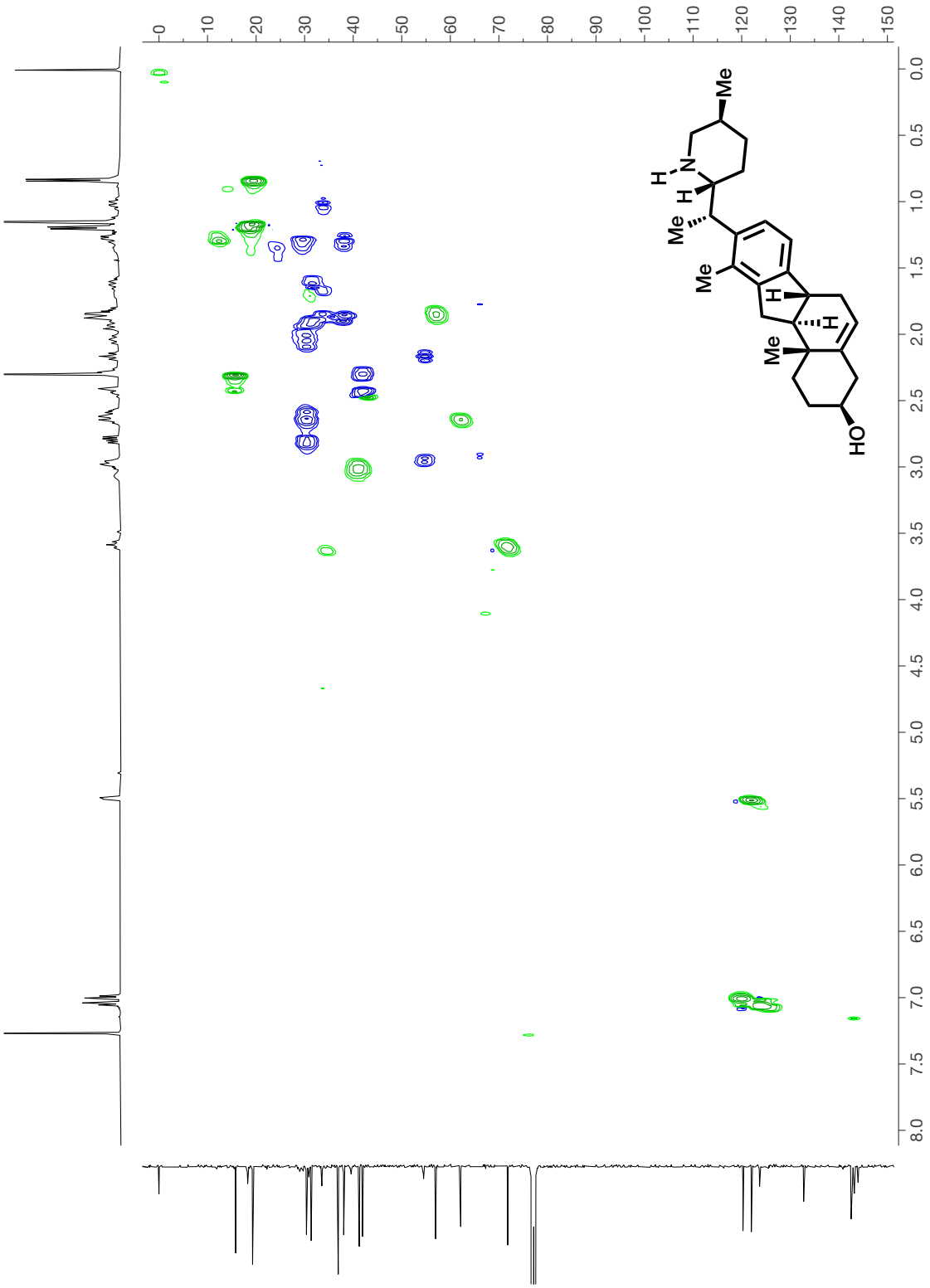


Figure A.154. ^{1}H–^{13}C HSQC spectrum (400 MHz, 101 MHz, $CDCl_3$) of **verarine**.

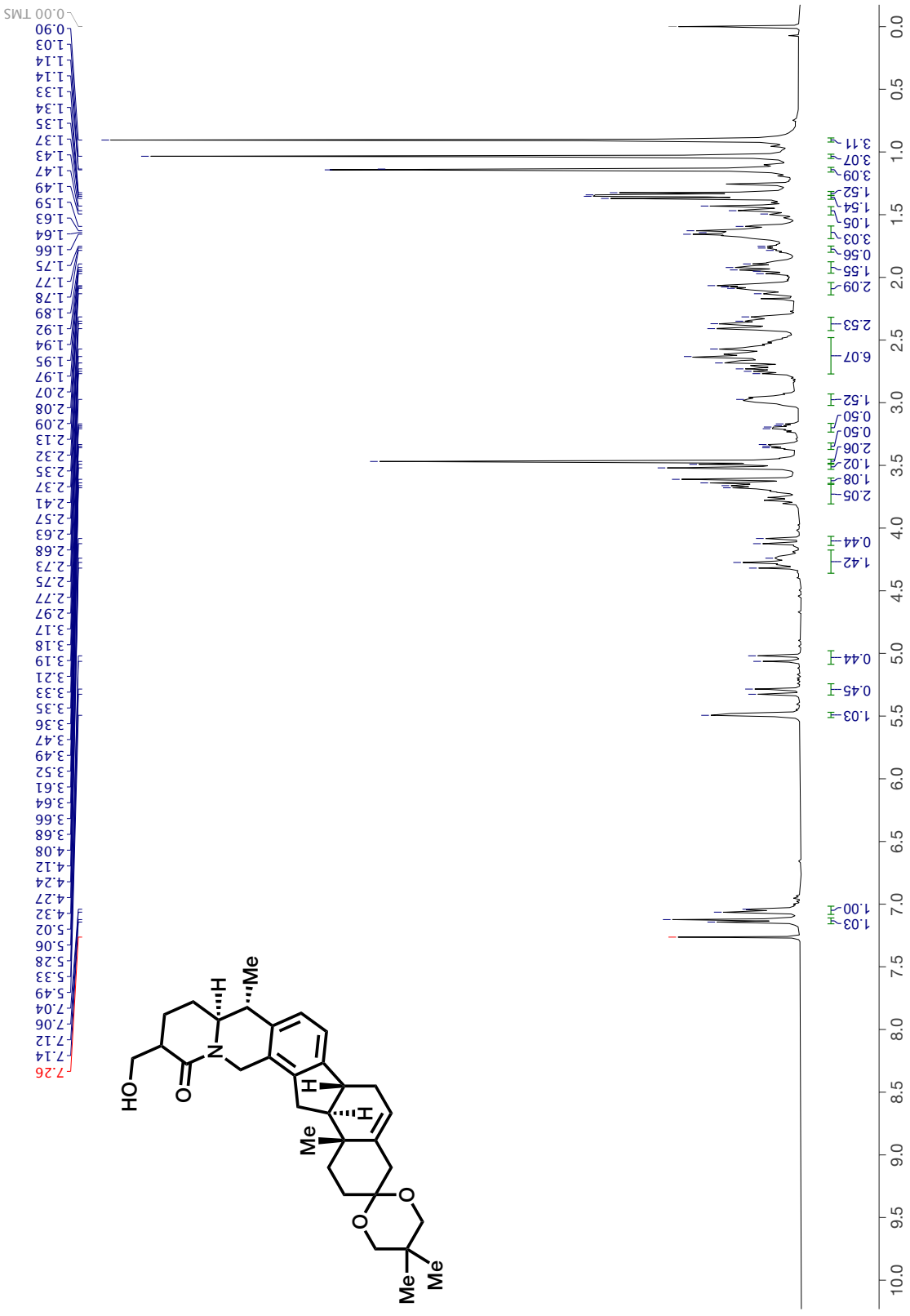


Figure A.155. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5.7**.

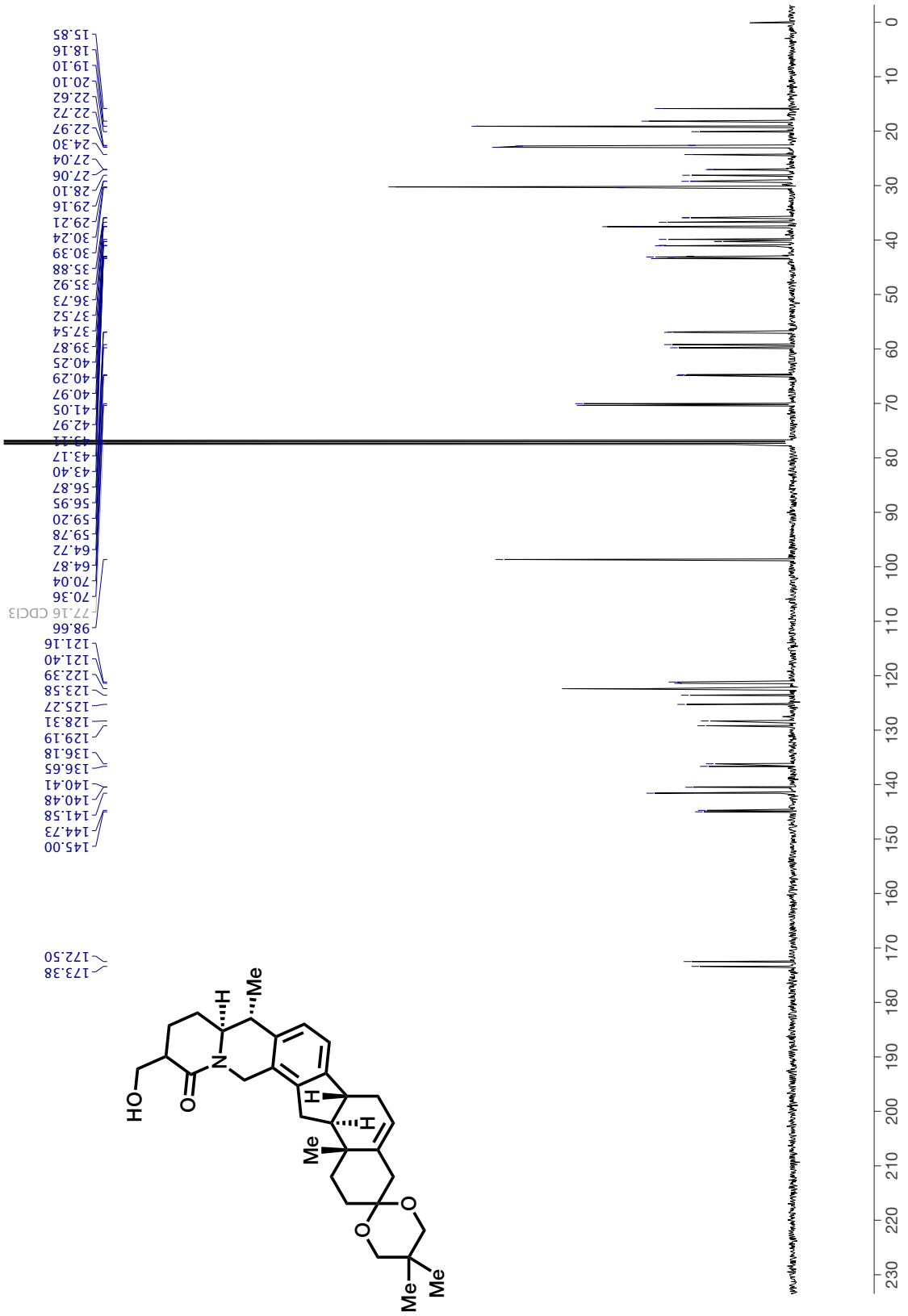


Figure A.156. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **5.7**.

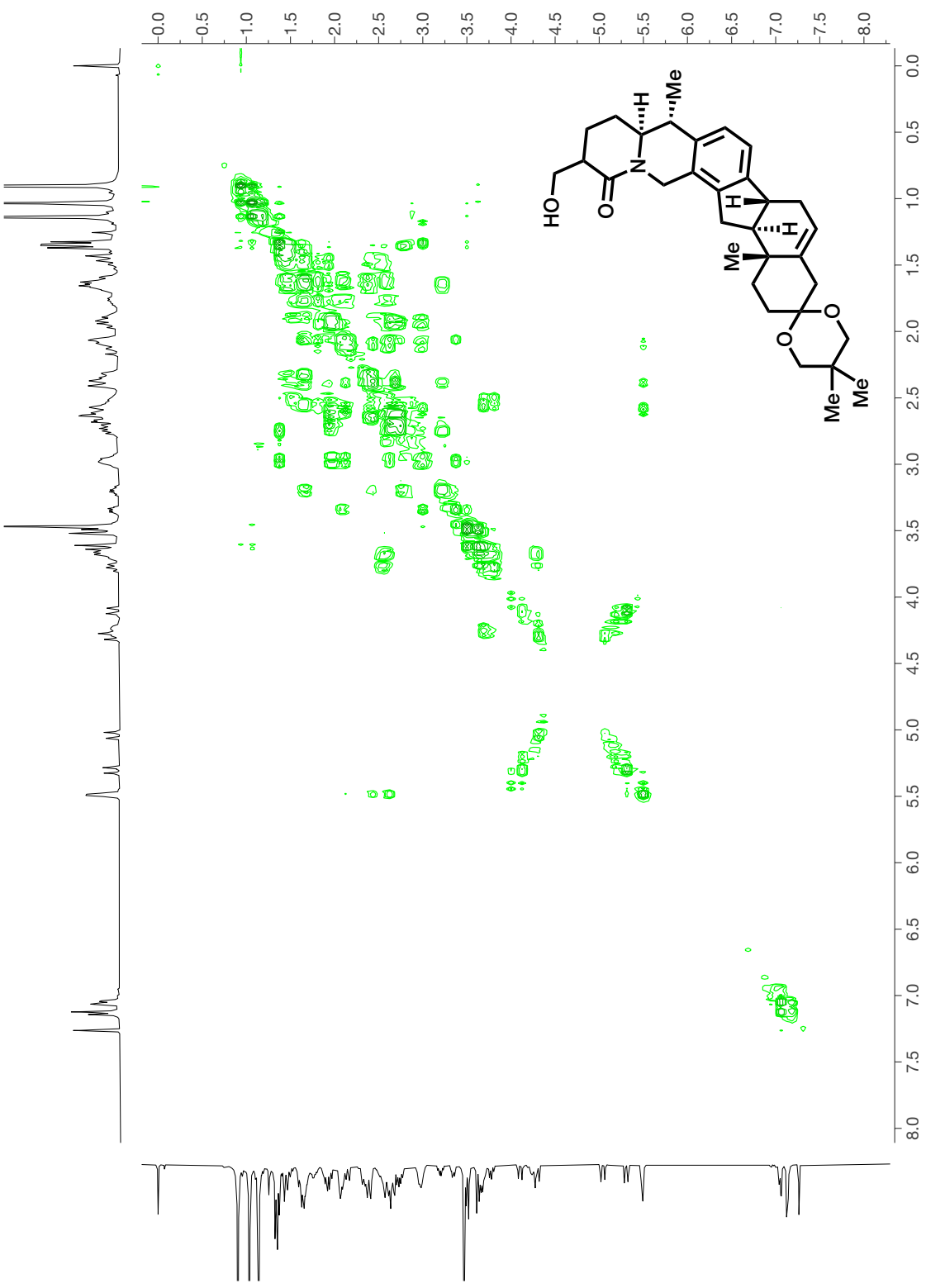


Figure A.157. ^{1}H–^{1}H COSY spectrum (400 MHz, $CDCl_3$) of **5.7**.

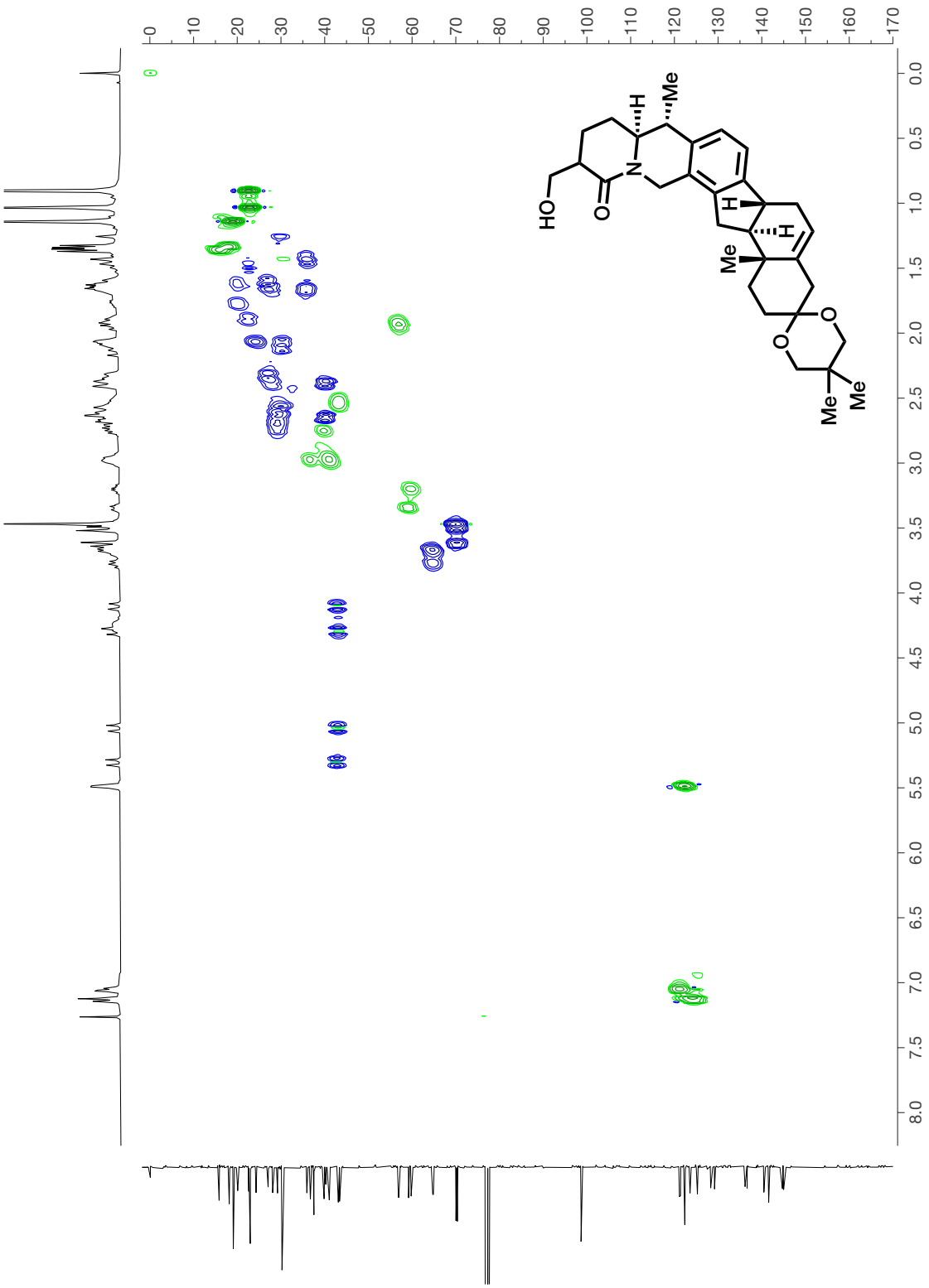


Figure A.158. ^{1}H–^{13}C HSQC spectrum (400 MHz, 101 MHz, $CDCl_3$) of **5.7**.

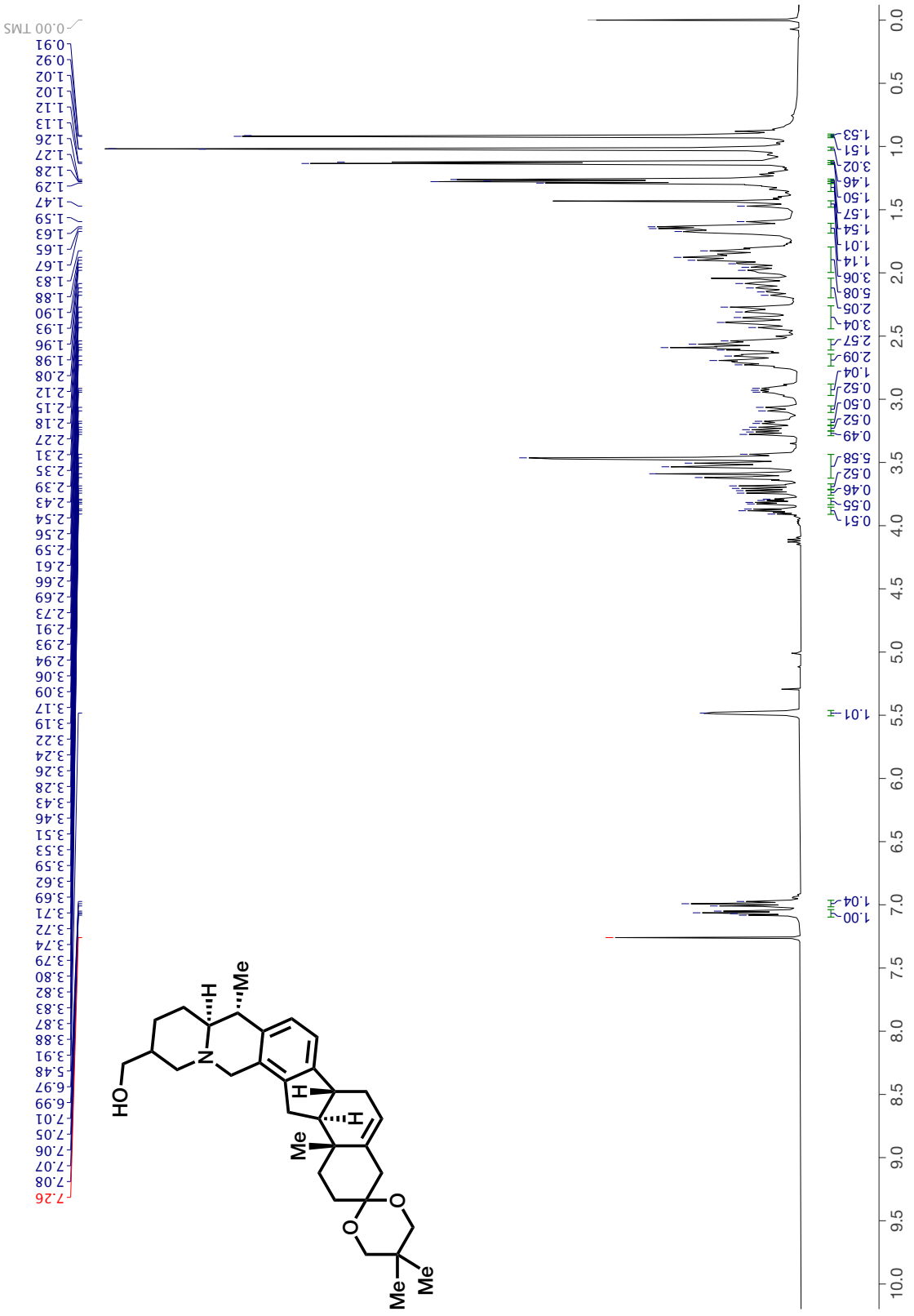


Figure A.159. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5.8**.

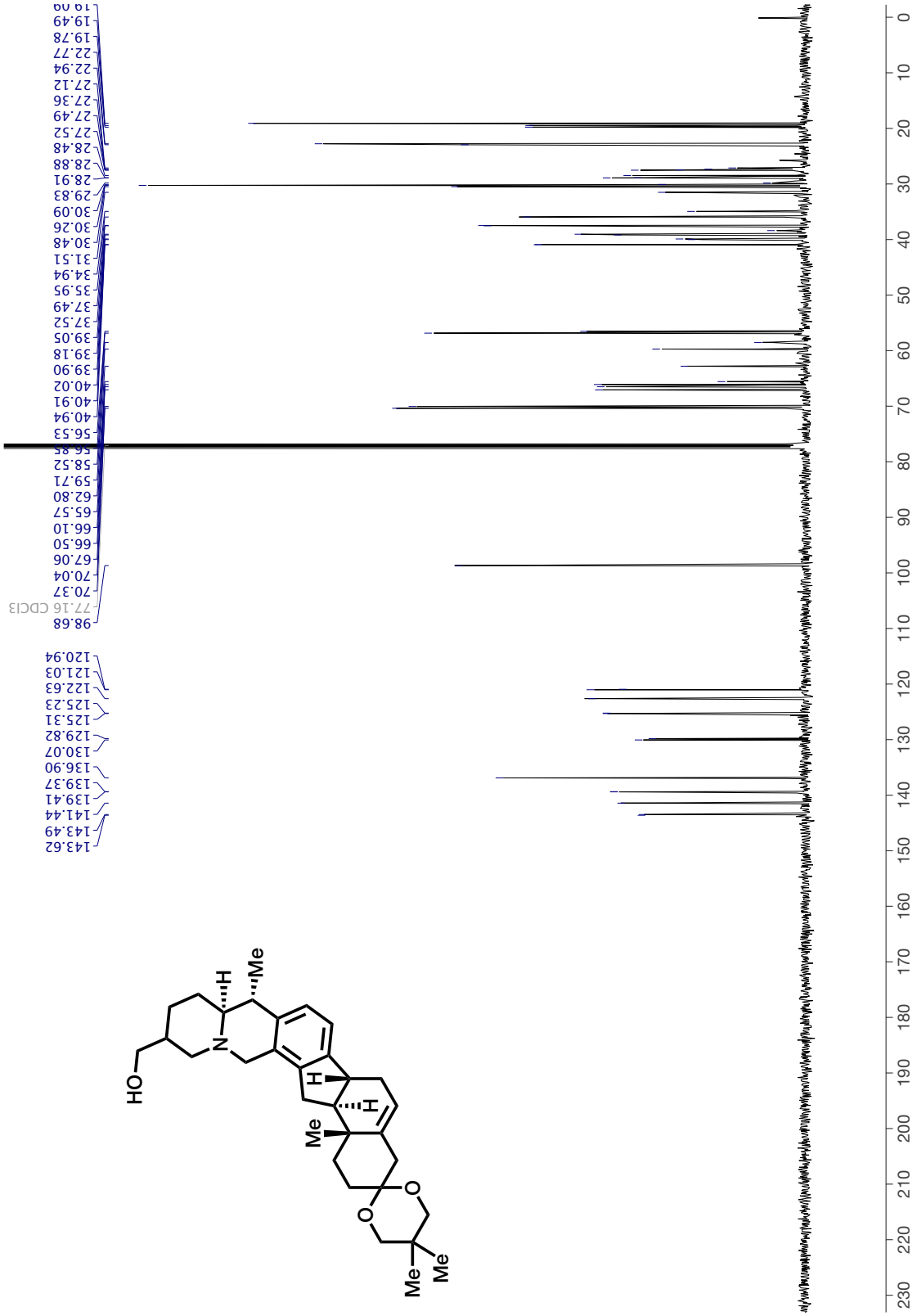


Figure A.160. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **5.8**.

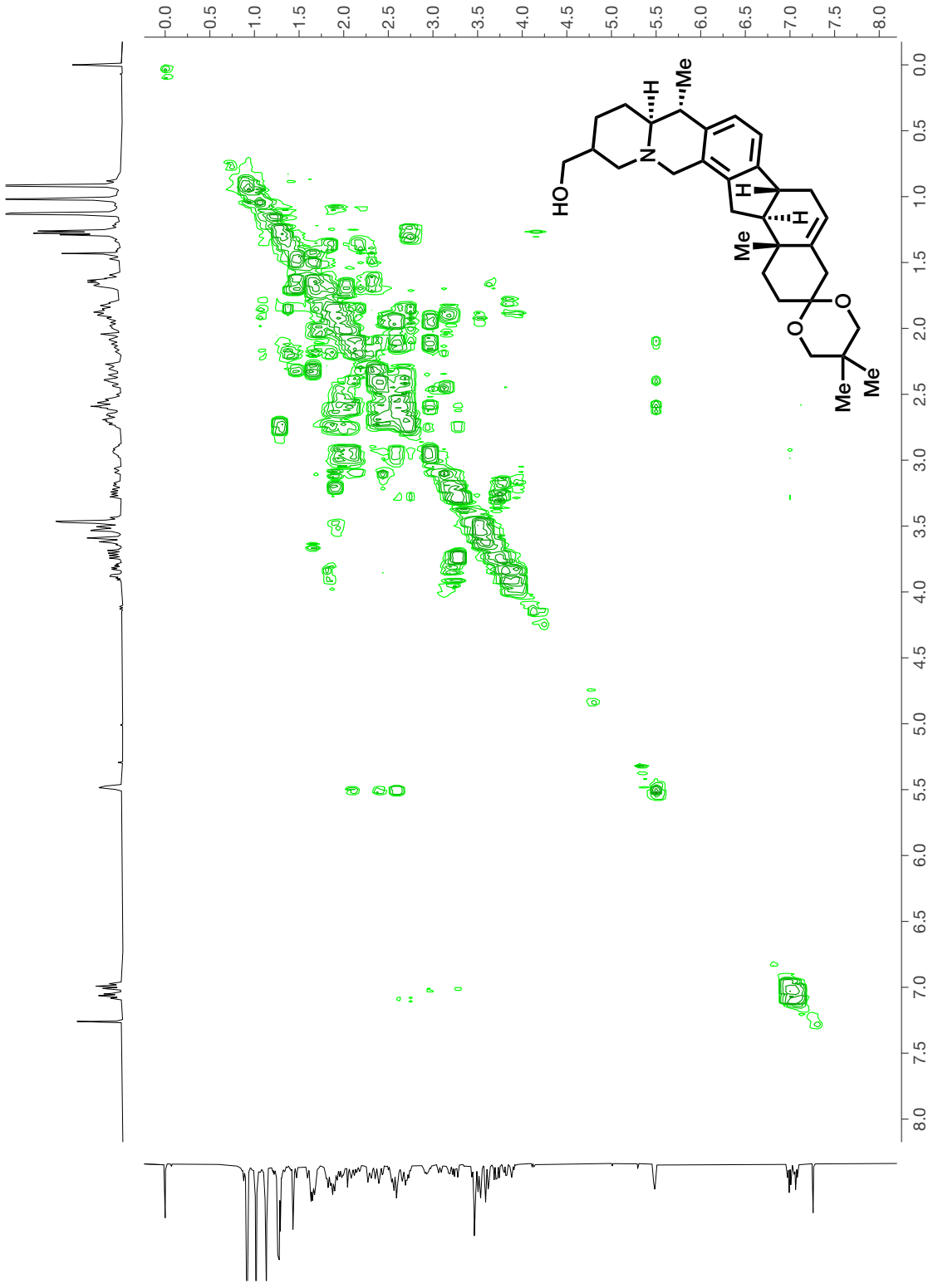


Figure A.161. ^{1}H–^{1}H COSY spectrum (400 MHz, $CDCl_3$) of **5.8**.

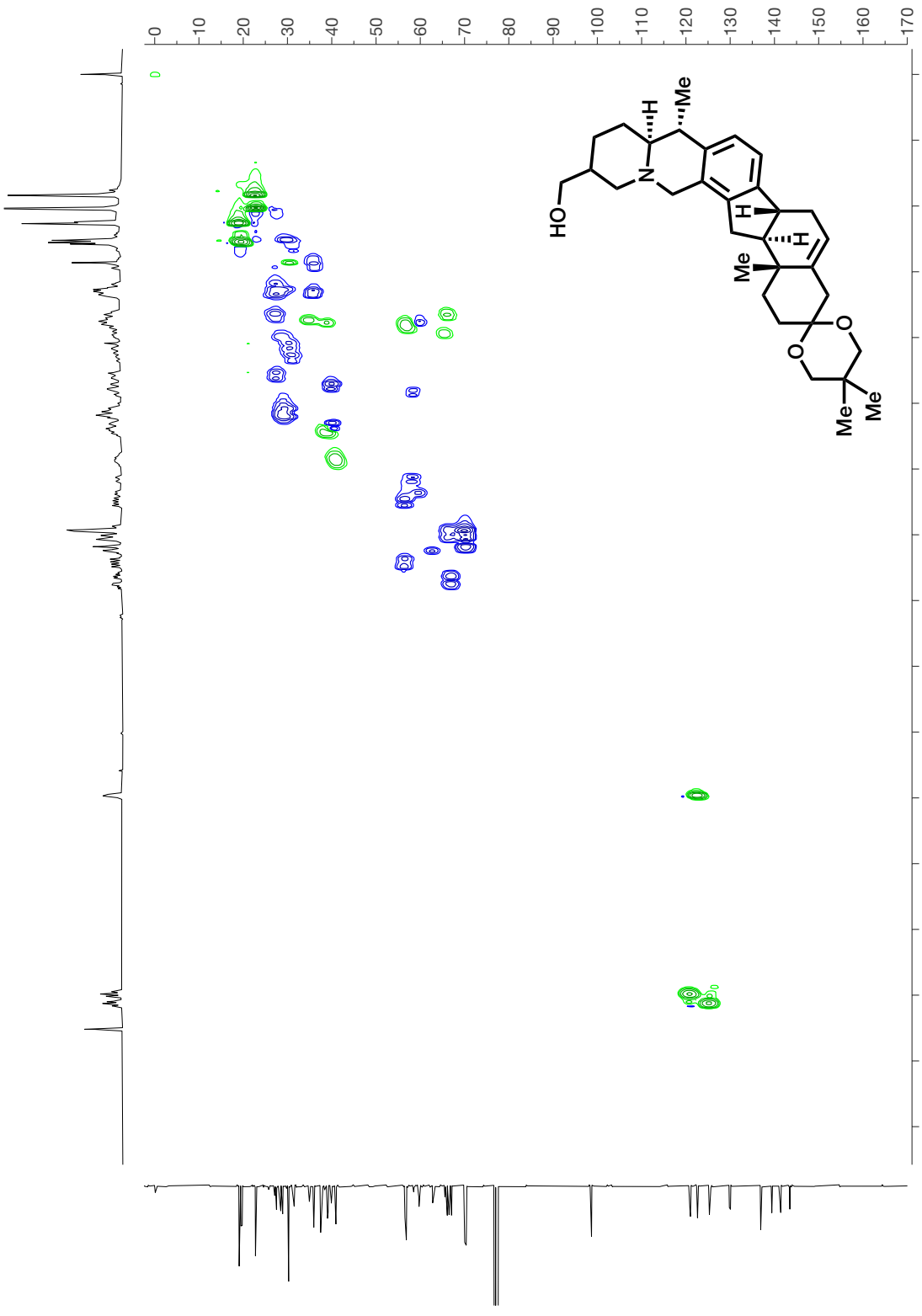


Figure A.162. ^{1}H–^{13}C HSQC spectrum (400 MHz, 101 MHz, $CDCl_3$) of **5.8**.

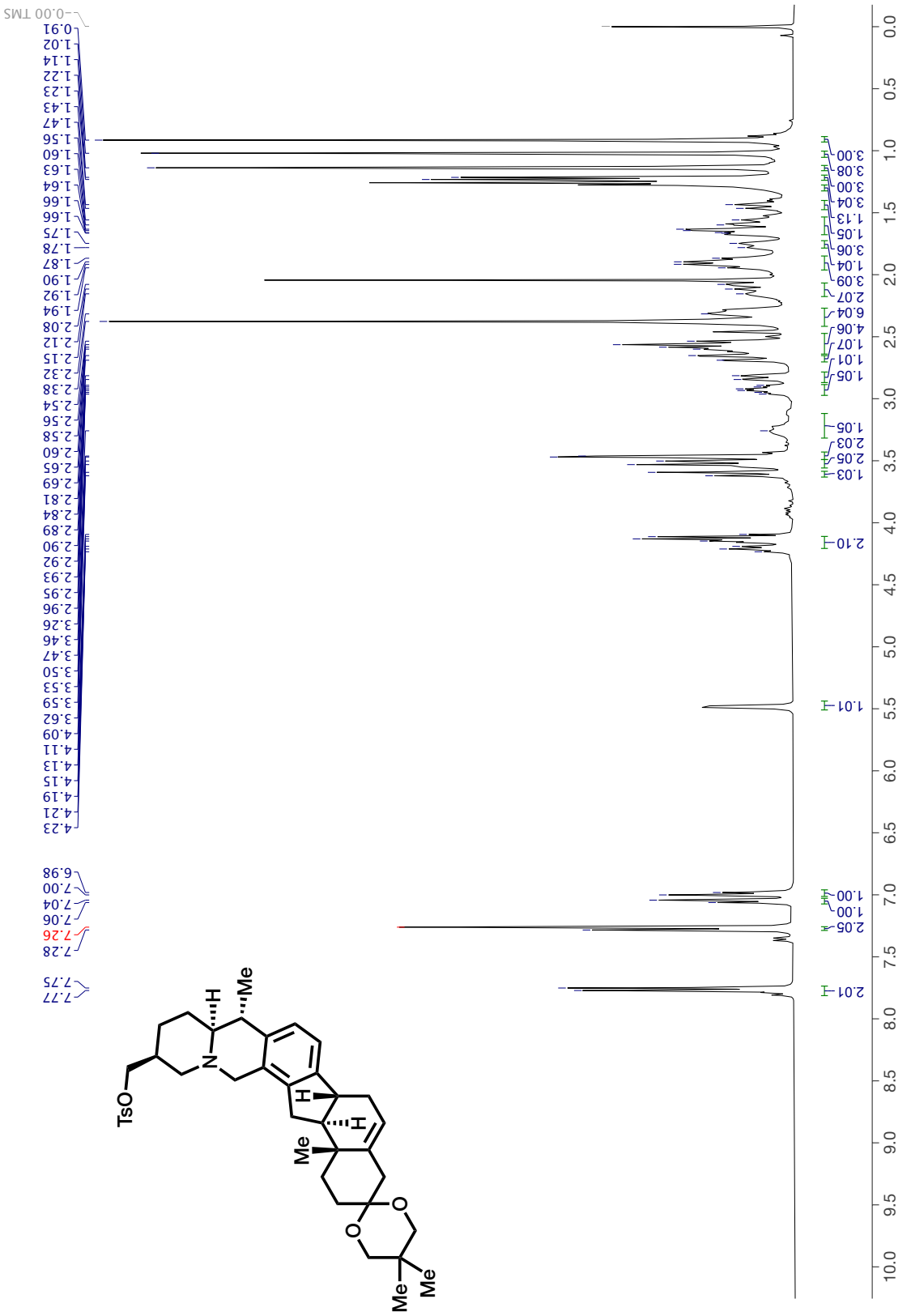


Figure A.163. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5.9a**.

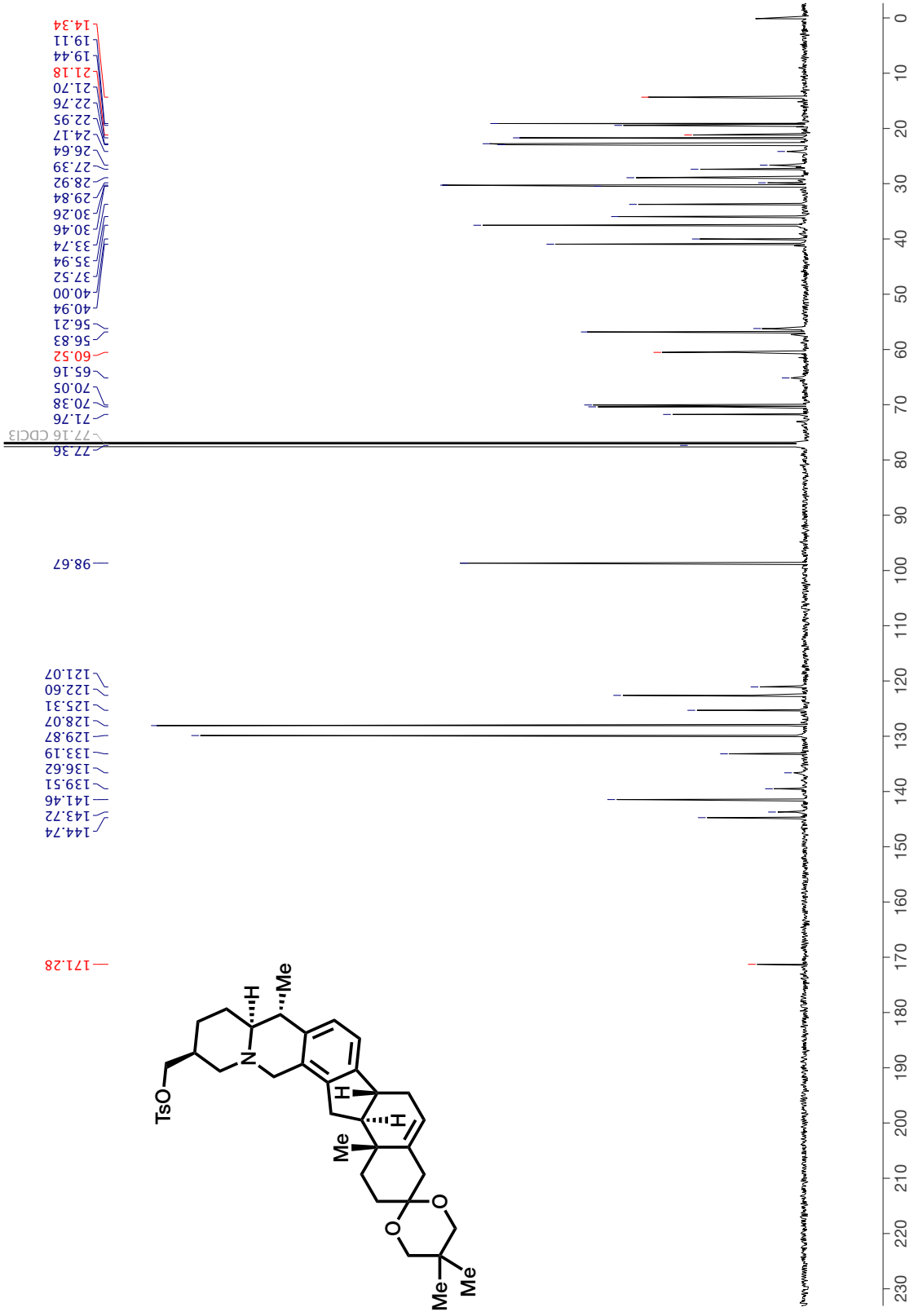


Figure A.164. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **5.9a**.

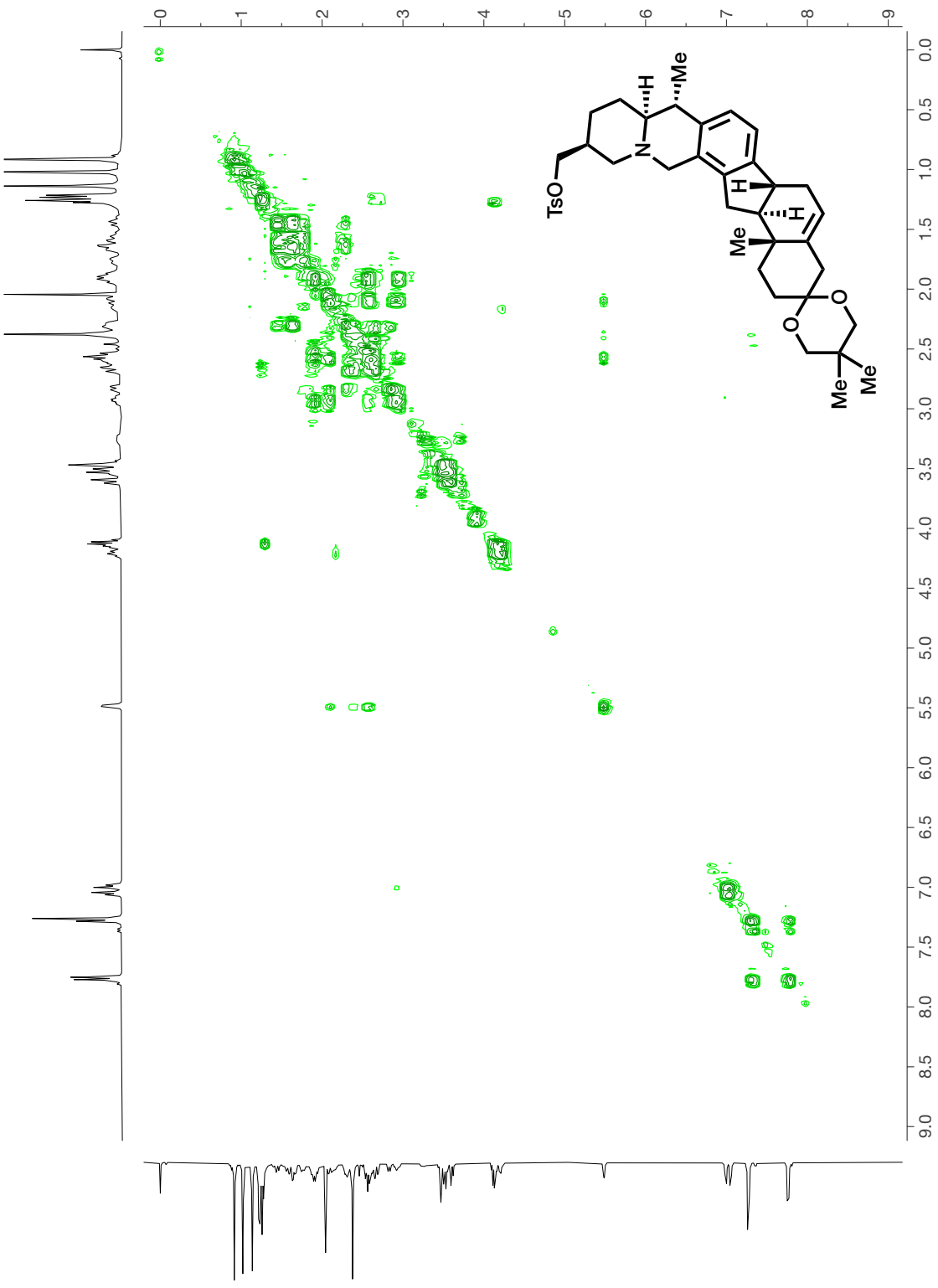


Figure A.165. ^{1}H–^{1}H COSY spectrum (400 MHz, $CDCl_3$) of **5.9a**.

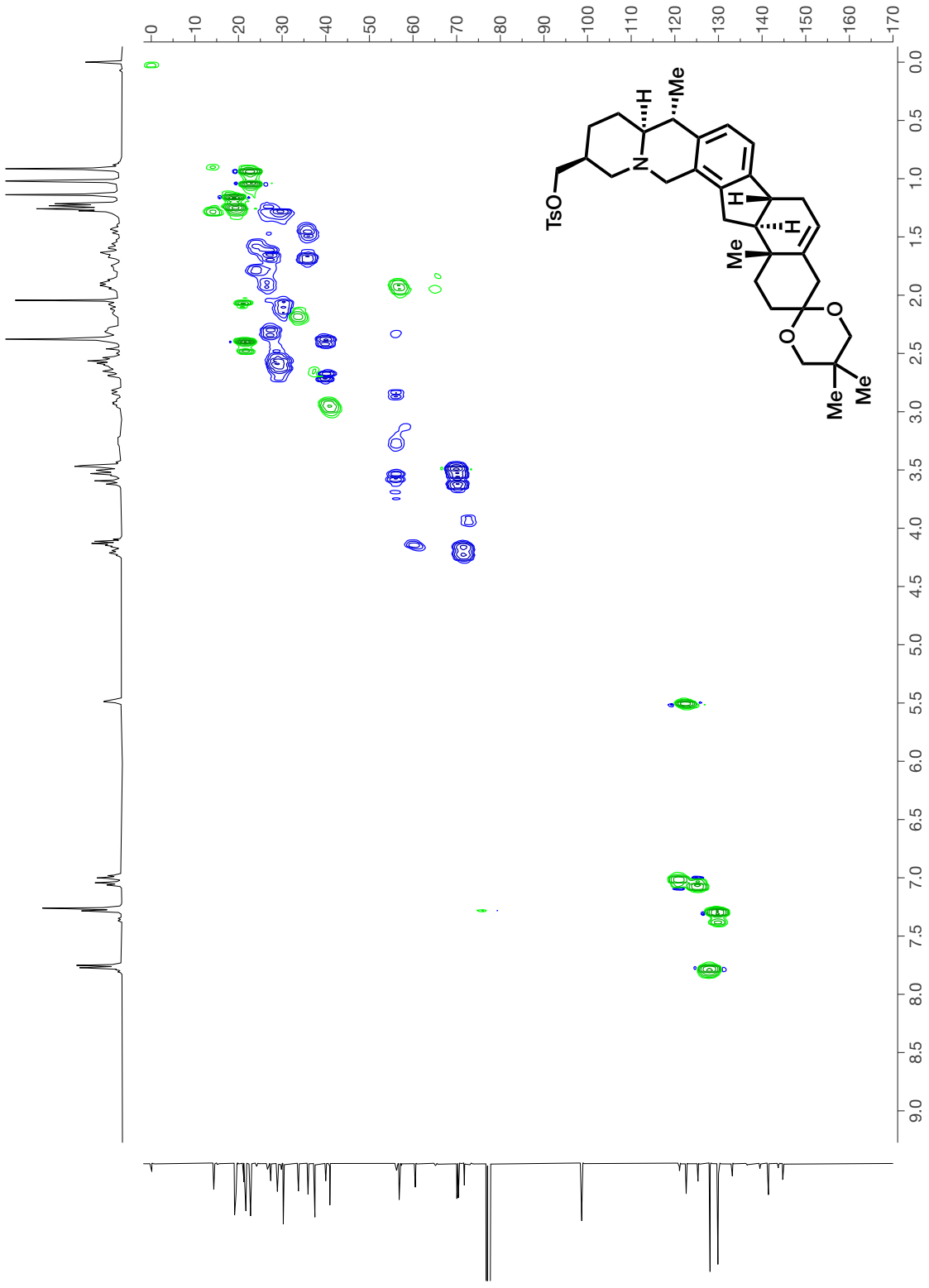


Figure A.166. $^{1}H–^{13}C$ HSQC spectrum (400 MHz, 101 MHz, $CDCl_3$) of **5.9a**.

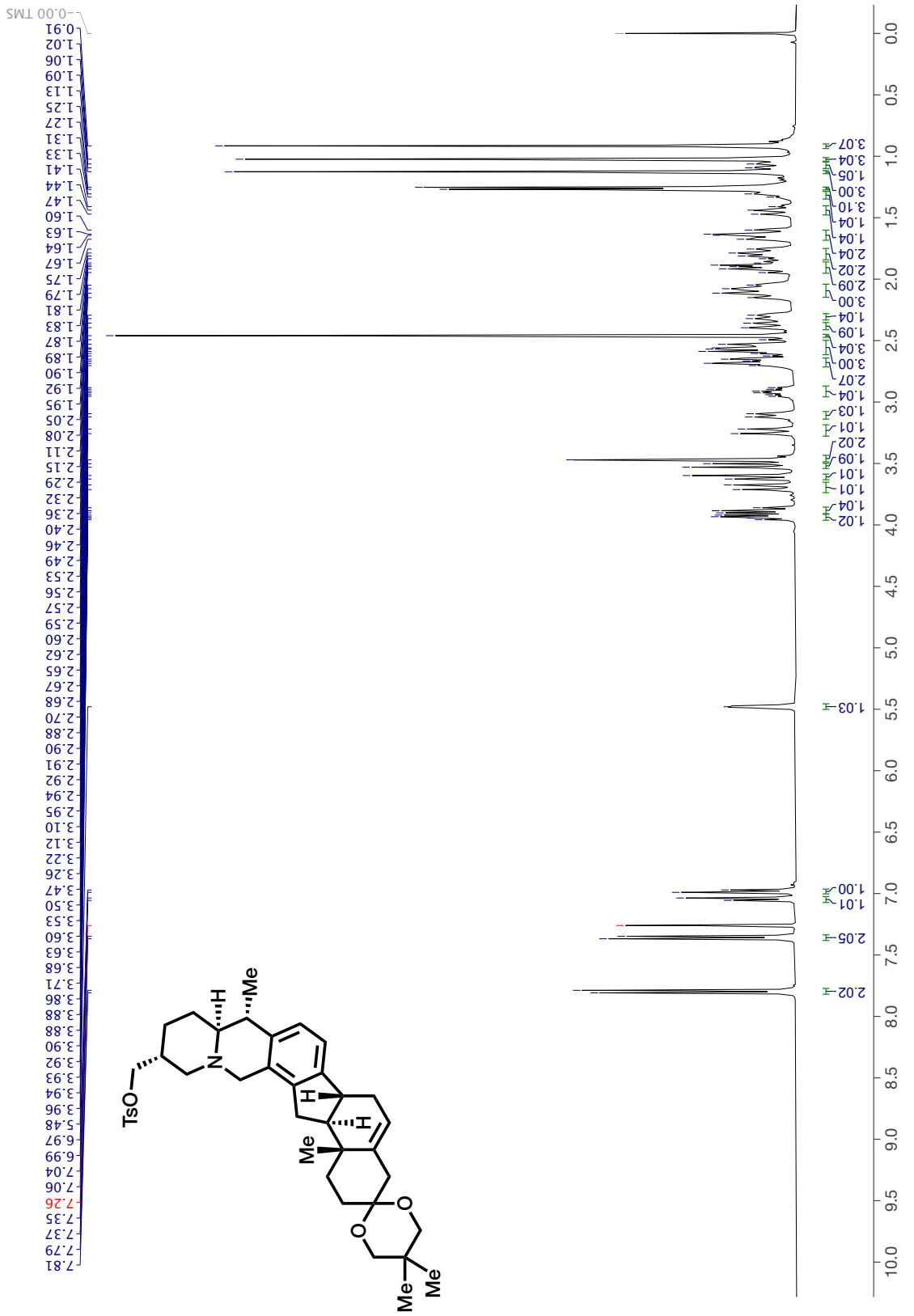


Figure A.167. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5.9b**.

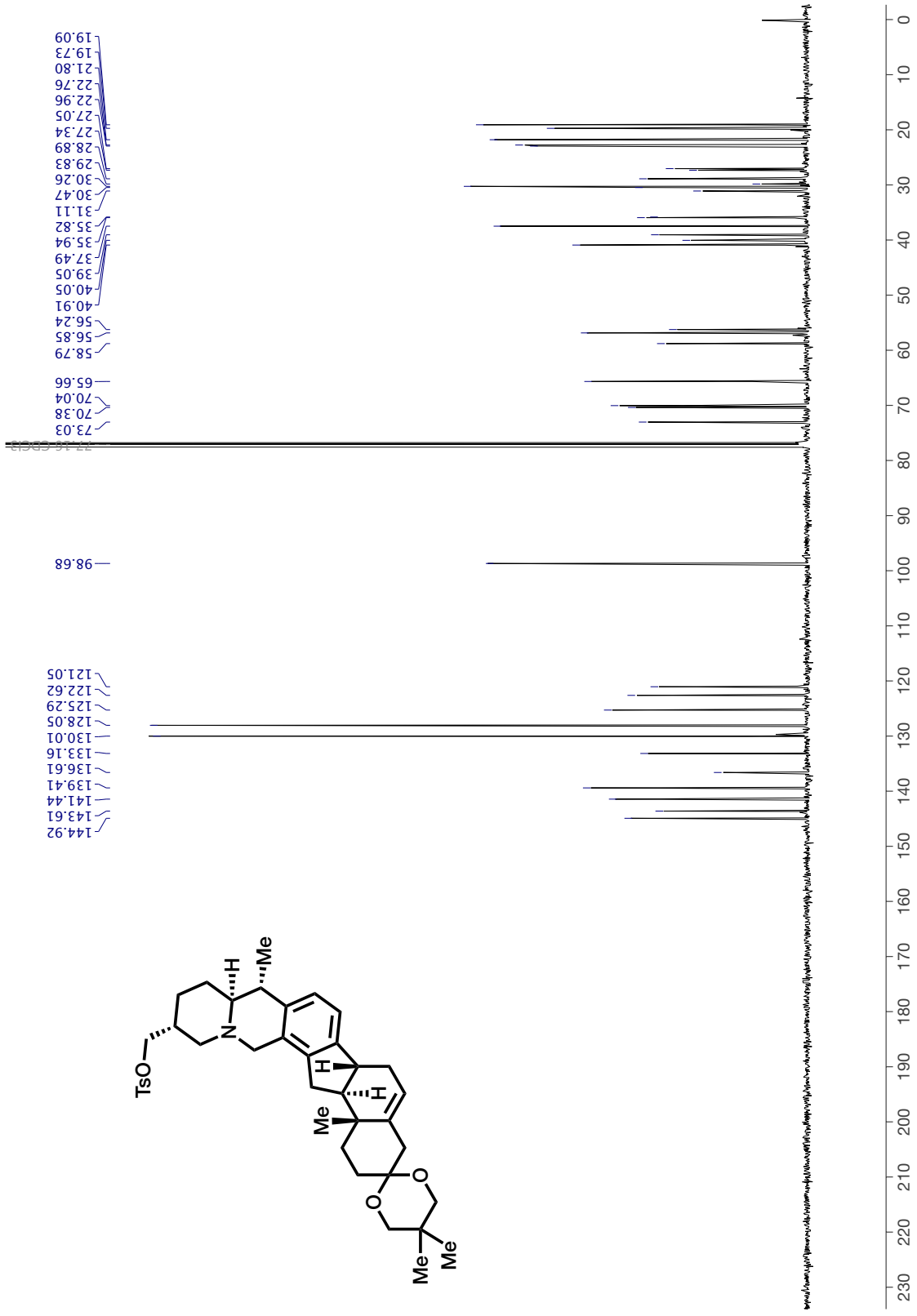


Figure A.168. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **5.9b**.

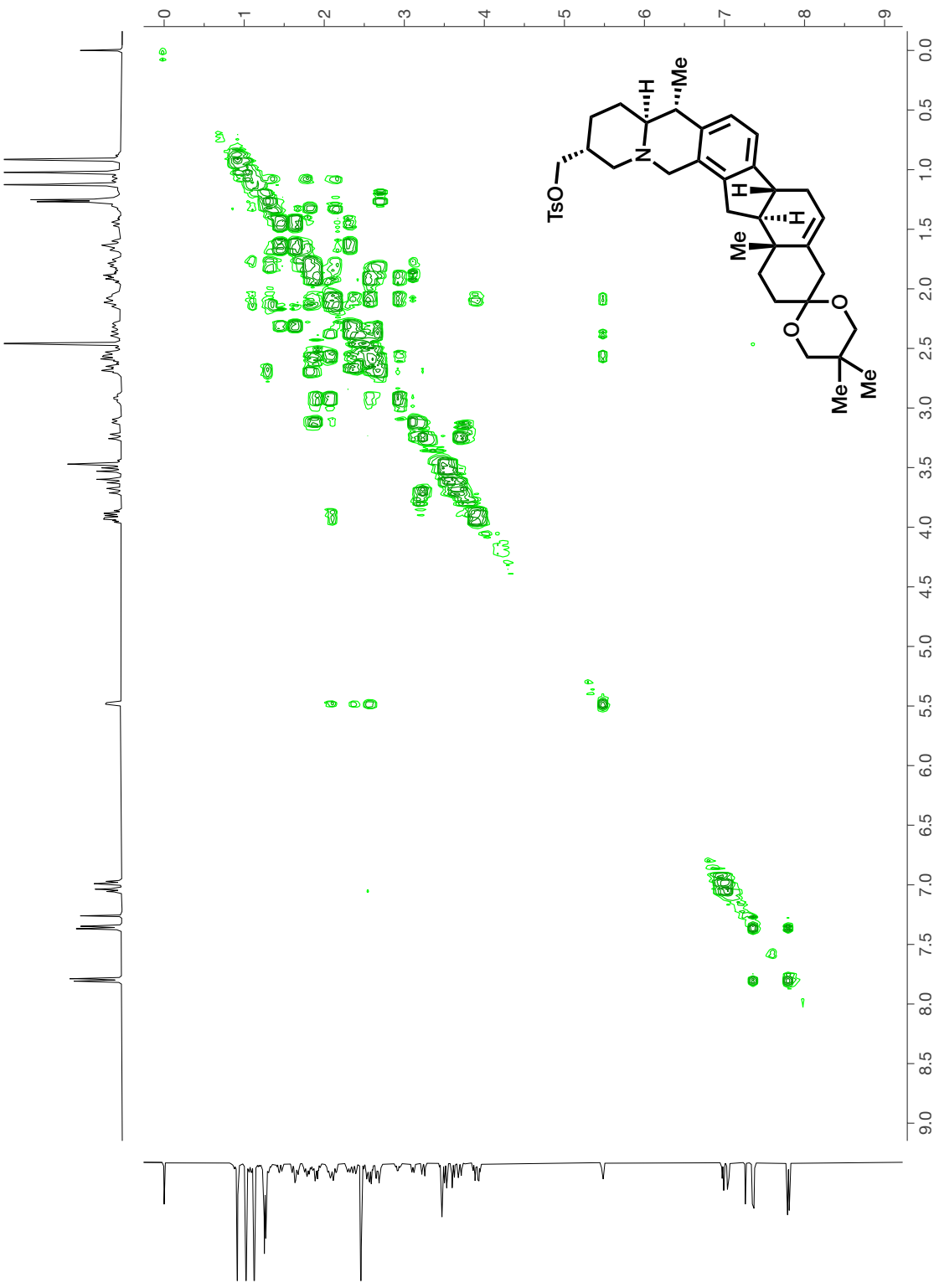


Figure A.169. ^{1}H–^{1}H COSY spectrum (400 MHz, $CDCl_3$) of **5.9b**.

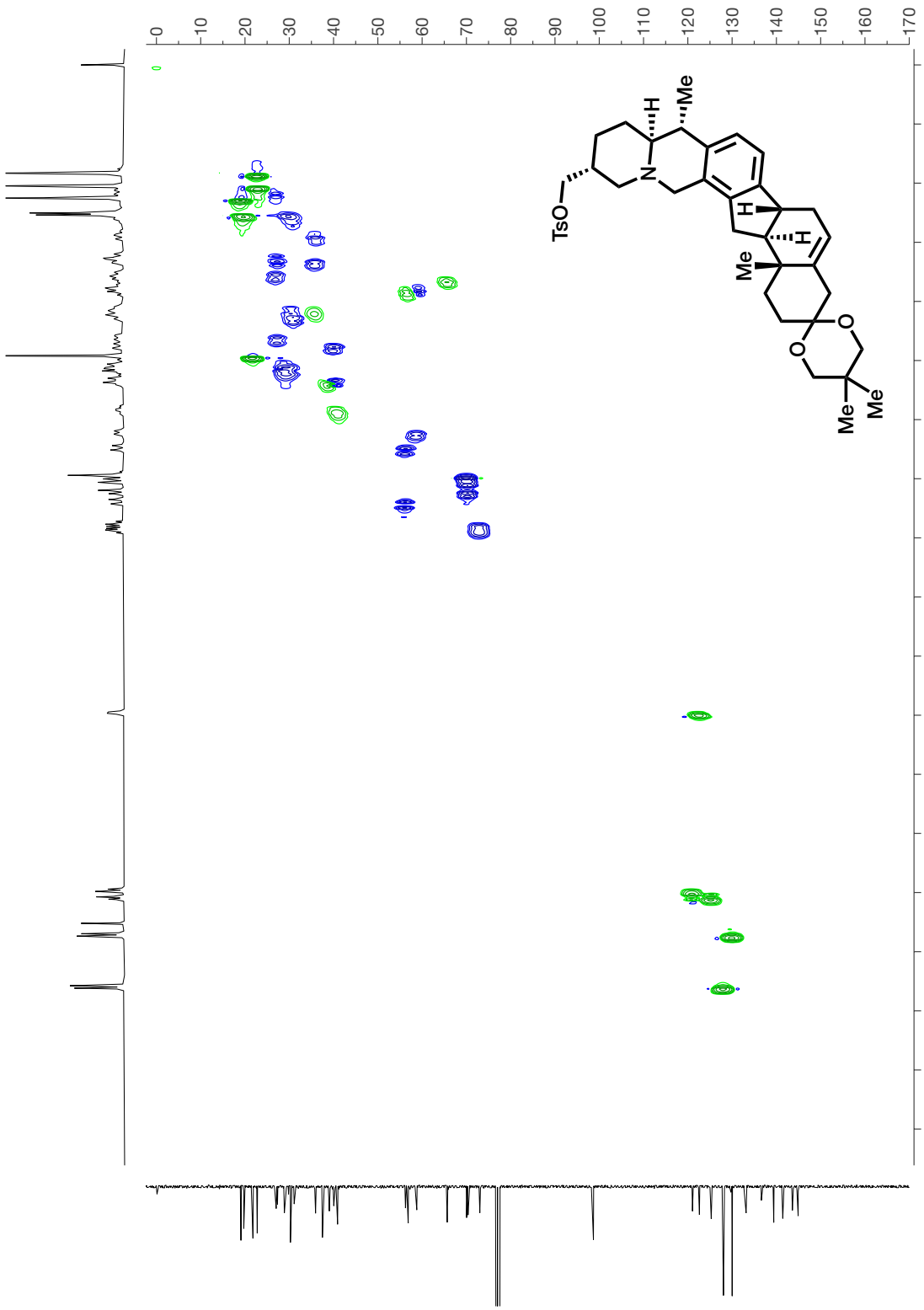


Figure A.170. $^{1}H–^{13}C$ HSQC spectrum (400 MHz, 101 MHz, $CDCl_3$) of **5.9b**.

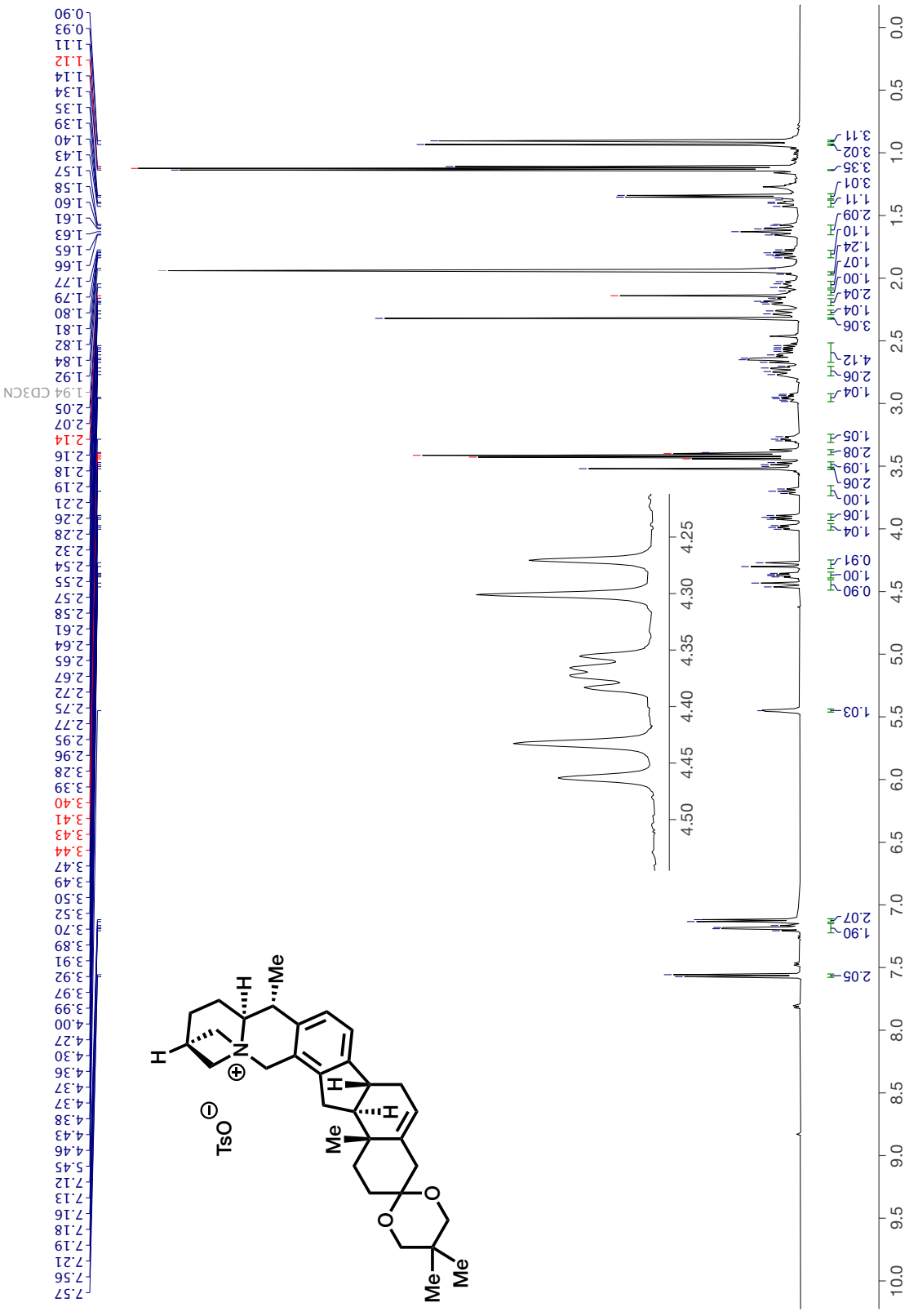


Figure A.171. ^{1}H NMR spectrum (500 MHz, CD_3CN) of **5.10**.

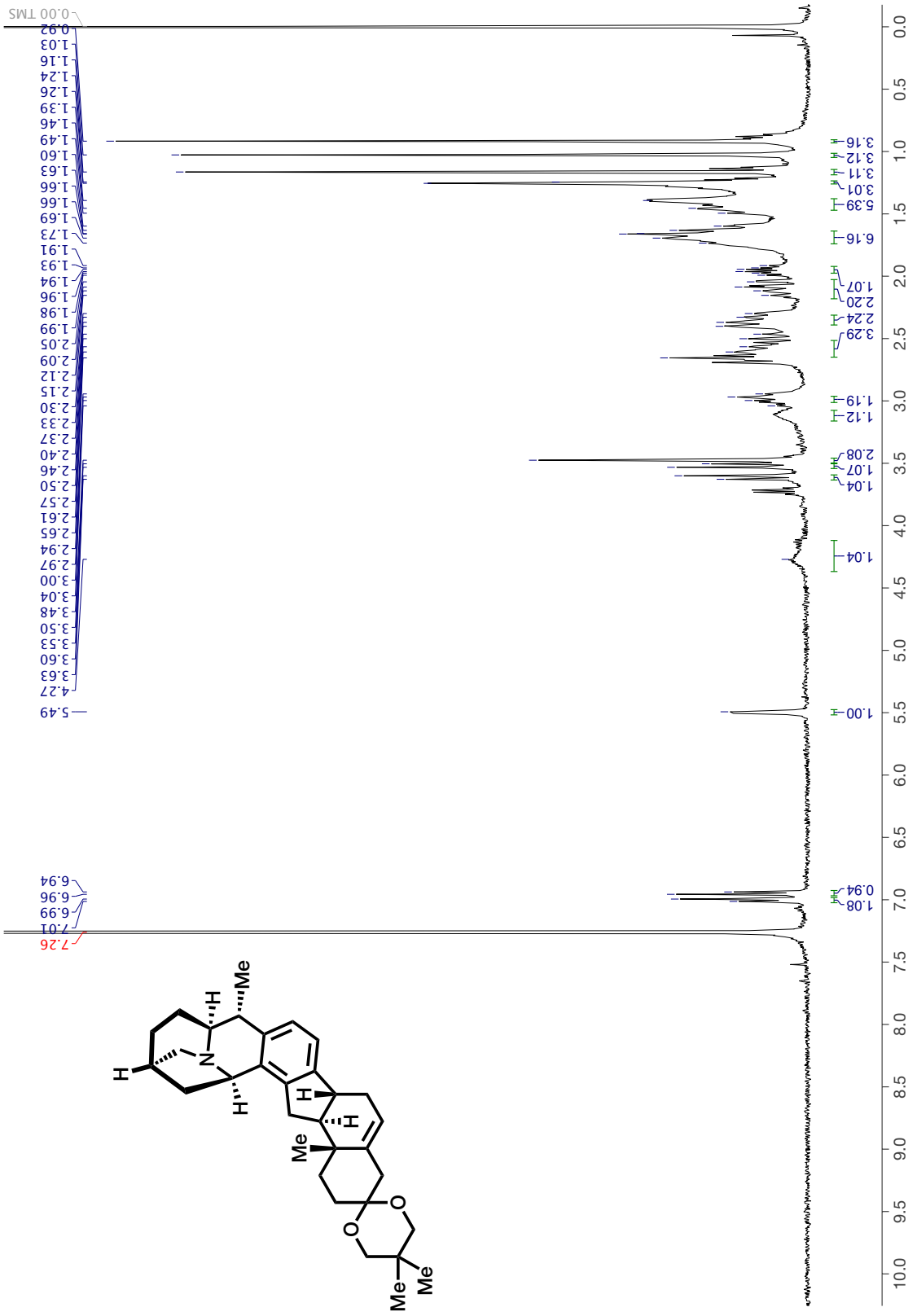


Figure A.172. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5.11**.

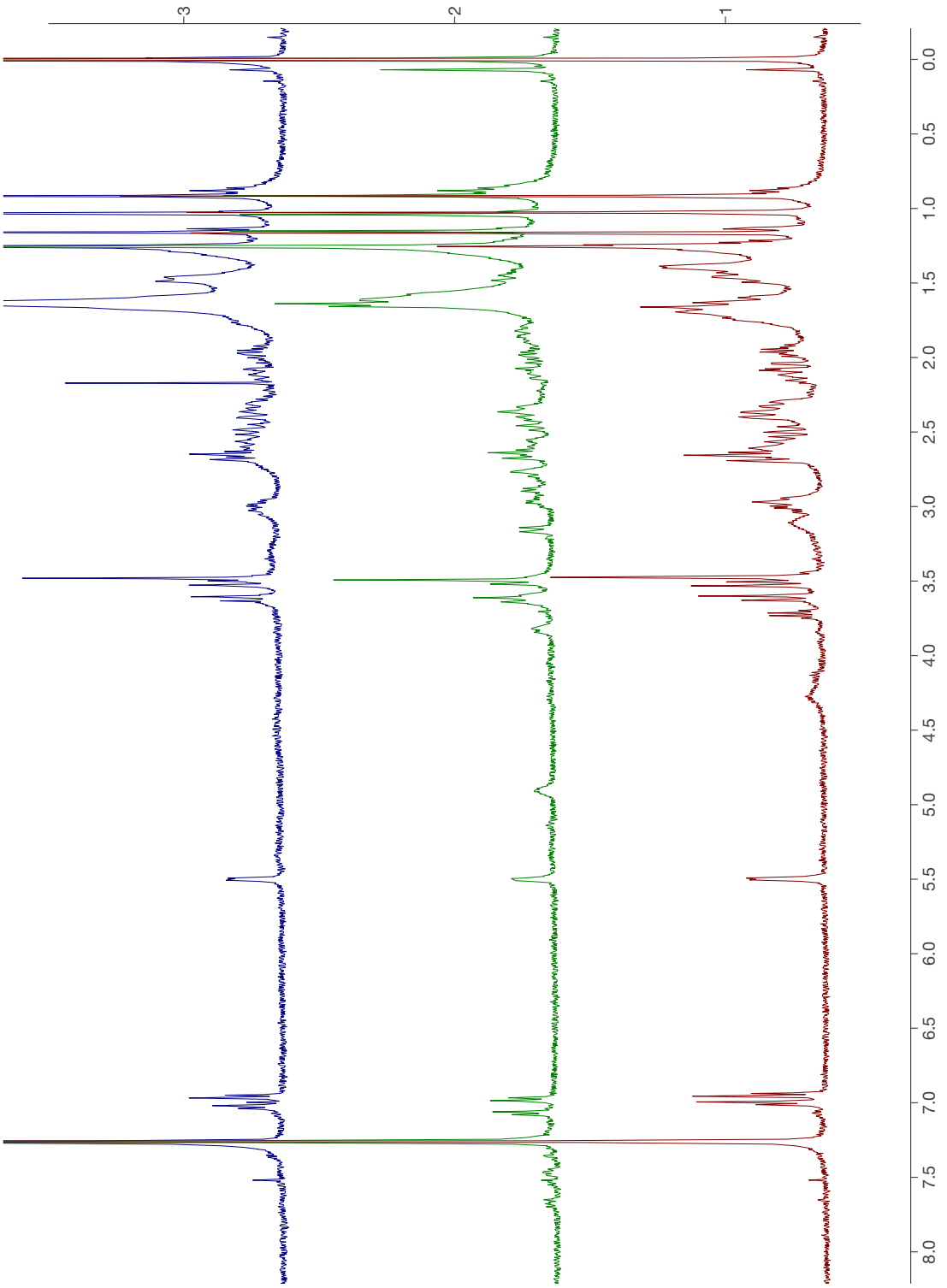


Figure A.173. Stacked ^{1}H NMR spectra (400 MHz, $CDCl_3$) of three independently purified samples of **5.11**.

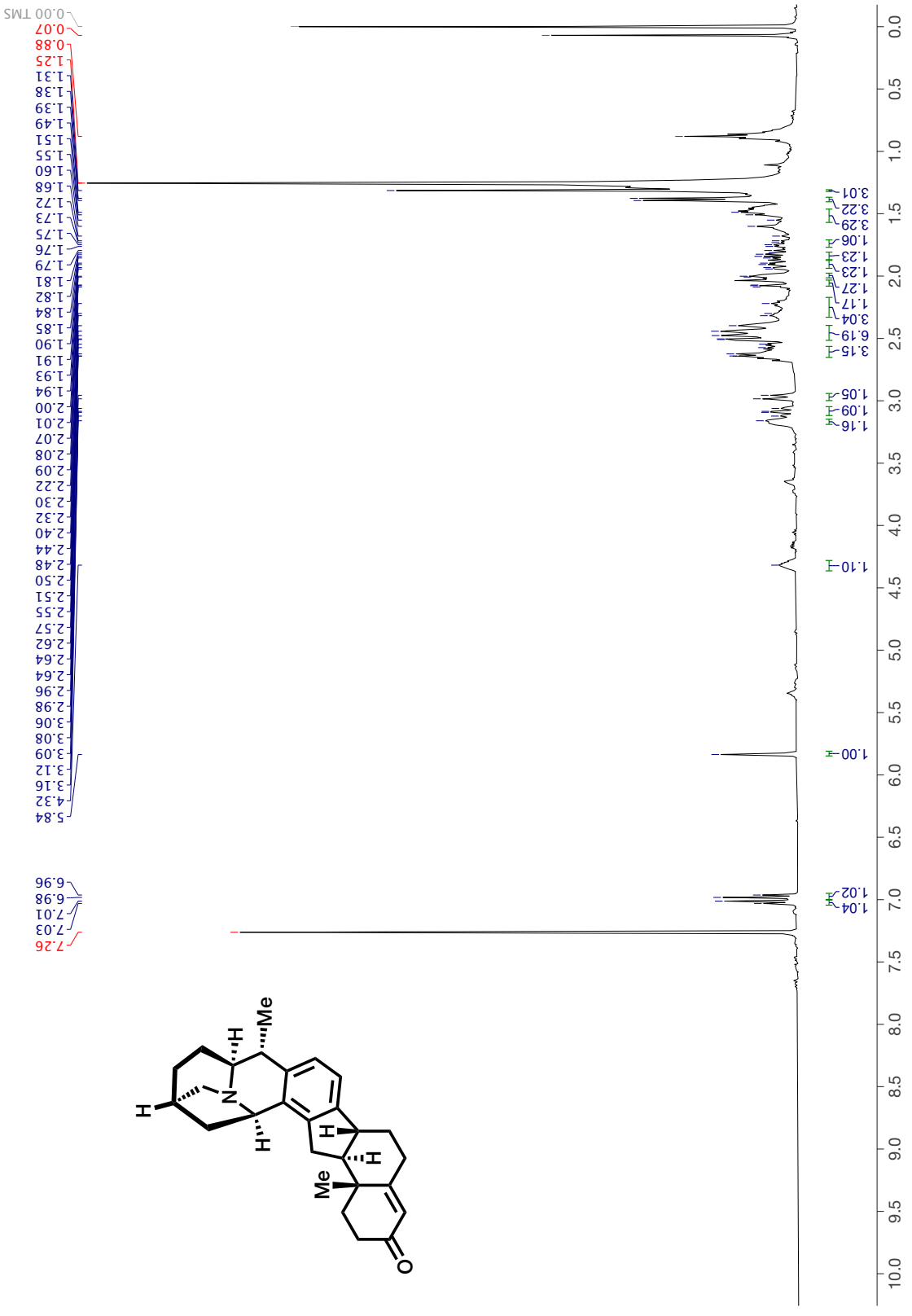


Figure A.174. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5.12**.

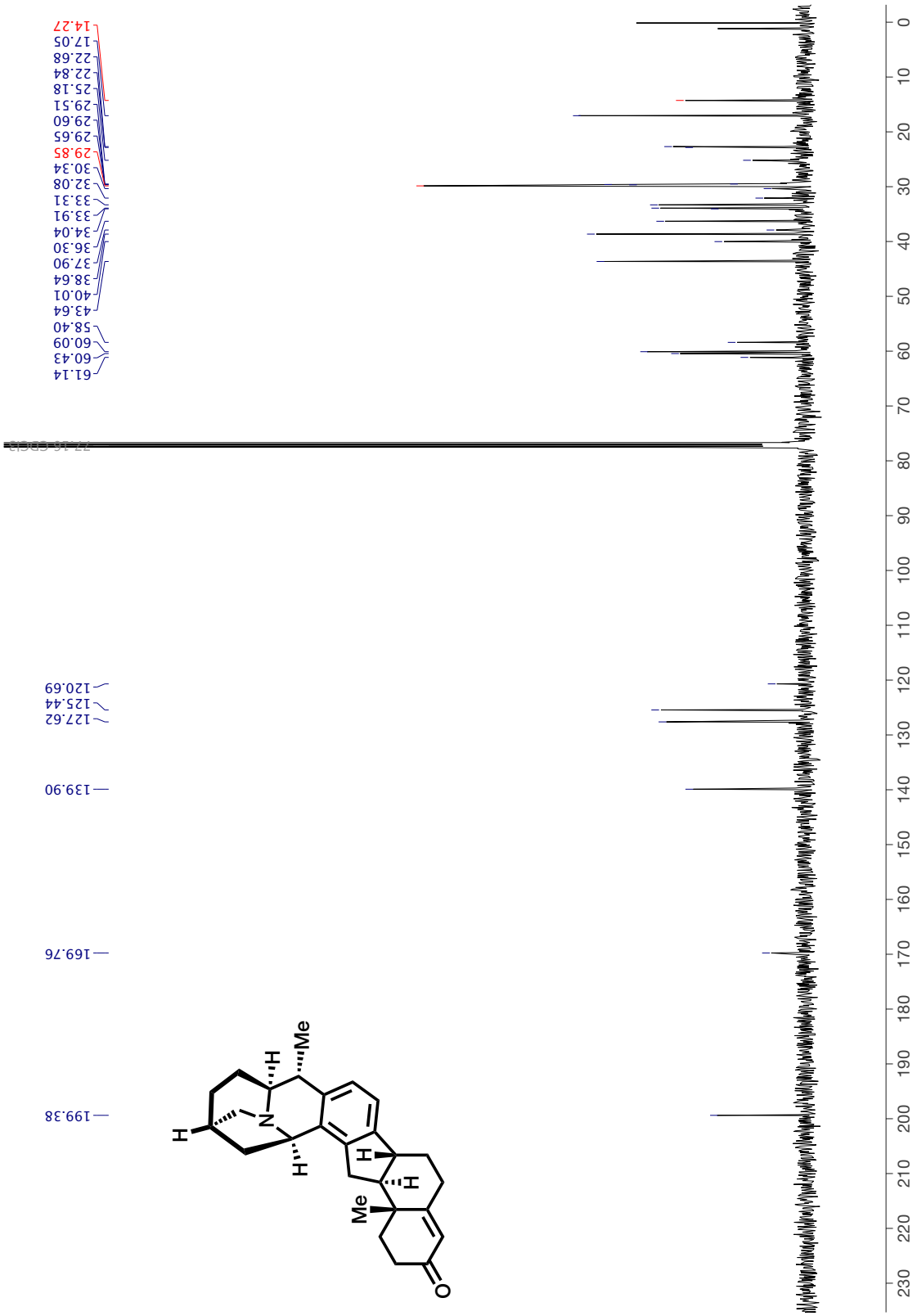


Figure A.175. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **5.12**.

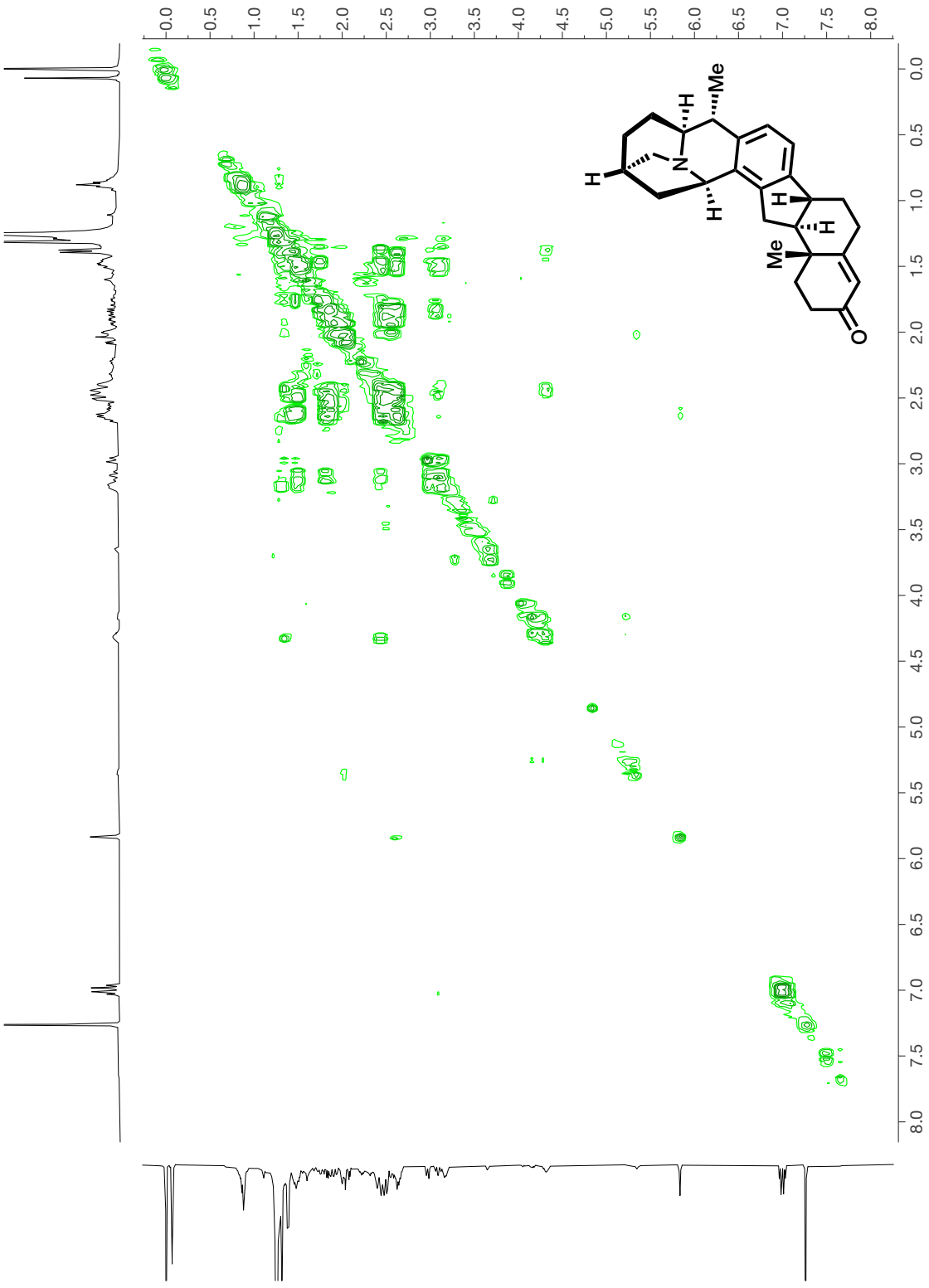


Figure A.176. ^{1}H–^{1}H COSY spectrum (400 MHz, $CDCl_3$) of **5.12**.