A Scalable, Enantioselective Total Synthesis of Two Anticancer Marine-derived Natural Products: Portimine A and B.

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As members of the committee appointed to evaluate the thesis of **Junchen Tang** we have read his thesis and found it to be acceptable without revision in partial fulfillment of The Scripps Research Institute's requirements for granting of the doctoral degree. Therefore, we the undersigned are satisfied that **Junchen Tang** has met the requirements for the Doctorate of Philosophy Degree with respect to the written thesis, thesis presentation, and examination by this Committee.

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Abstract

Marine-derived cyclic imine toxins, a family of intricate natural product, have stimulated broad interest due to their appealing chemical architectures and fascinating bioactivities. Of these, portimine A and B, possess promising anti-cancer therapeutic potential. Nevertheless, chemical solution to large quantities of portimines is currently unfeasible and the molecular mechanism behind their potent activity is unknown.

This thesis detailed the first successful total synthesis and follow-up structural diversification of portimine A and B to address the aforementioned question. In Chapter 1, representative examples of cyclic imine total syntheses were summarized. In the first section of Chapter 2, the isolation background and the preliminary study of bioactivities of portimine A and B were briefly described. Seven distinct approaches to synthesize portimines explored by multiple research groups were discussed in the following sections to highlight the challenge of synthesizing these two structurally formidable molecules.

Chapters 3 and 4 detailed the retrosynthesis used in this work and efforts to construct the macrocycle and transannular ketal system of natural products. Here, an unprecedented strategy utilizing the innate geometry of the spirocyclic moiety of portimines to control the C-16 stereochemistry was outlined. Subsequent key macrocyclization, regarded as the main subject of the total synthesis, was accomplished by ring-closing alkyne metathesis (RCAM). Moreover, the innate reactivity of a macrocycle was leveraged to install both the correct oxygenation pattern as well as the stereochemistry. To construct the unique

transannular polyketal system in portimines, certain intermediates served to “self-protect” key functional groups and enable the final sequence by strategically timed ring-chain tautomerization events.

In Chapter 5 and 6, the completion of the first synthesis, as well as the chemical diversification of portimines were detailed. In this work, two oxygen atoms at C-5 and C-13 were installed in a single step, marking the endpoint of an “oxidase phase”. The total synthesis of portimine B led to a structural revision of its originally assigned structure, and the scalable solution to portimine A led to fully assess its bioactivity and therapeutical potential. The target identification, validation, and mechanism-of-action (MOA) study of portimine A in live cells via tandem mass tags (TMT)-based proteomics (which was beyond this thesis) was achieved by synthesizing corresponding photo-clickable probes.

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List of Abbreviations

Å Angstrom

Ac_2O acetic anhydride

AcOH acetic acid

Alloc allyloxycarbonyl

aq. aqueous

Bn benzyl

Boc *tert*-butoxycarbonyl

n-Bu *n*-butyl

t-Bu *tert*-butyl

Bz benzoyl

cap caprolactamate

cat. catalytic

C_6D_6 benzene-d^6

$CDCl_3$ chloroform-*d*

CD_3CN acetonitrile-d^3

conv. Conversion

Cp cyclopentadienyl

Cp* pentamethylcyclopentadienyl

m-CPBA *m*-chloroperoxybenzoic acid

CSA (1*S*)-(+)-10-camphorsulfonic acid

°C Celsius degree

DABCO 1,4-diazabicyclo[2.2. 2]octane

d(s) day(s)

DCE 1,2-dichloroethane

DCM dichloromethane

decomp. decomposition

DIBAL diisobutylaluminium hydride

DMAP 4-dimethylaminopyridine

DMB 3,4-dimethoxylbenzyl

DMDO 3,3-dimethyldioxirane

DMF dimethylformamide

DMI 1,3-dimethyl-2-imidazolidinone

DMP Dess-Martin periodane

DMSO dimethylsulfoxide

dppf 1,1'-bis(diphenylphosphino)ferrocene

dr diastereomeric ratio

E1cb elimination unimolecular conjugate base

ee enantiomeric excess

EtOAc ethyl acetate

ESI electrospray ionization

Et ethyl

FG functional group

h(s) hour(s)

HMBC heteronuclear multiple bond correlation

HRMS high-resolution mass spectrometry

HSQC heteronuclear single quantum coherence

i.p. intraperitoneal injection

kcal kilocalorie

kg kilogram

KHMDS potassium bis(trimethylsilyl)amide

LAH lithium aluminium hydride

LDA lithium diisopropylamide

LiHMDS lithium bis(trimethylsilyl)amide

M molar

Me methyl

MeCN acetonitrile

mg milligram

mM millimolar

μM micromolar

mmol millimole

mol mole

MOM methoxylmethyl ether

NaHMDS sodium bis(trimethylsilyl)amide

NBS *N*- bromosuccinimide

NCS *N*-chlorosuccinimide

NIS *N*-iodosuccinimide

nM nanomolar

NMO *N*-methylmorpholine

NMR nuclear magnetic resonance

NOE nuclear Overhauser effect

[O] oxidant or oxidation

Ph phenyl

PIDA (diacetoxyiodo)benzene

Piv pivalyl

PMB *p*-methoxylbenzyl

PPh_3 triphenylphosphine

ppm parts per million

PTLC preparative thin layer chromatography

PTSA *p*-toluenesulfonic acid

i-Pr isopropyl

Py pyridine

quant. quantitative

R group/chemical entity

rt room temperature

TASF trissulfonium difluorotrimethylsilicate

TBAC tetrabutylammonium chloride

TBAF tetrabutylammonium fluoride

TBHP *tert*-butyl hydroperoxide

TBS *tert*-butyldimethylsilyl

TCCA trichloroisocyanuric acid

temp. temperature

TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl

TES triethylsilyl

Tf trifluoromethanesulfonyl

TFA trifluoroacetic acid

TFAA trifluoroacetic anhydride

THF tetrahydrofuran

TIPS triisopropylsilyl

TLC thin layer chromatography

TMS trimethylsilyl

TPAP tetrapropylammonium perruthenate

TPPO triphenylphosphine oxide

Troc 2,2,2-Trichloroethoxycarbonyl

X halogen

XPhos dicyclohexyl[2′,4′,6′-tris(propan-2-yl)[1,1′-biphenyl]-2-yl]phosphane

Chapter 1: Classical strategies used in cyclic imine toxins syntheses.

Section 1.1 Case study 1: pinnatoxin A.

(+)-Pinnatoxin A was first characterized by Uemura and co-workers in 1995 from the shellfish *Pinna muricata* (*1*, *2*). The plausible biogenesis of its unique carbon framework includes a key intramolecular Diels-Alder cycloaddition of an open-chain polyketide triggered by the newly-formed Schiff base to establish its 6,7-spirocyclic imine motif (Figure 1.1). As we shall see later, the cyclohexene fragment in cyclic imine toxins also indicates a potential [4+2] type disconnection for their chemical syntheses.

In 1998, the Kishi group reported the first enantioselective total synthesis of (-)-pinnatoxin A (enantiomer of the naturally existing one), which successfully applied the aforementioned biosynthetic hypothesis as the key step to construct its 27-membered macrocycle at the end of synthesis (*3*). The retrosynthesis and key transformations were outlined in Figure 1.1, where diene **1** was envisioned as the cycloaddition precursor of (-)-pinnatoxin A. Stereochemical control on such an intricate molecule is formidable due to its flexible conformation. Thus, **1** should be synthesized from the coupling of several fragments possessing established stereochemistry. To this end, two sequential Nozaki-Hiyama-Kishi couplings could happen at C-32 and C-6 to install the side chains and stereocenters in **1**, arriving at ketone **2** as a key intermediate. Ketone **2** could be accessed from bis-spiroketal **3** via nucleophilic addition to install the C-6 – C-9 side chain, and dithiane chemistry to install the C-25 – C-32 moiety. Acid-catalyzed ketalization of **4** (11 steps from simple building blocks such as ethylene epoxide, allylMgBr, **5**, and **6**) followed by silylation delivered **3** as the exclusive product. The detailed condition and precursor

used in the key cycloaddition step were highlighted in the blue box (Figure 1.1), where the concentrations and solvents for cycloaddition were screened to optimize the ratio of desired adduct **8** among all possible eight isomers. It is worth mentioning that the imine formation step presented here required unexpectedly high temperature (200 °C) and low pressure (1-2 torr), which is consistent with the reported hydrolytic lability of pinnatoxin A (*1*). In conclusion, Kishi and co-workers reported the first enantioselective total synthesis of pinnatoxin A, which produced 1.0 mg of (-)-pinnatoxin from simple building blocks via overall 73 chemical translations (LLS: 38 from commercial material) (*4*), featuring a pre-installation of all functionalities before skeletal formation, as well as late-stage biomimetic intramolecular cycloaddition and imine cyclization.

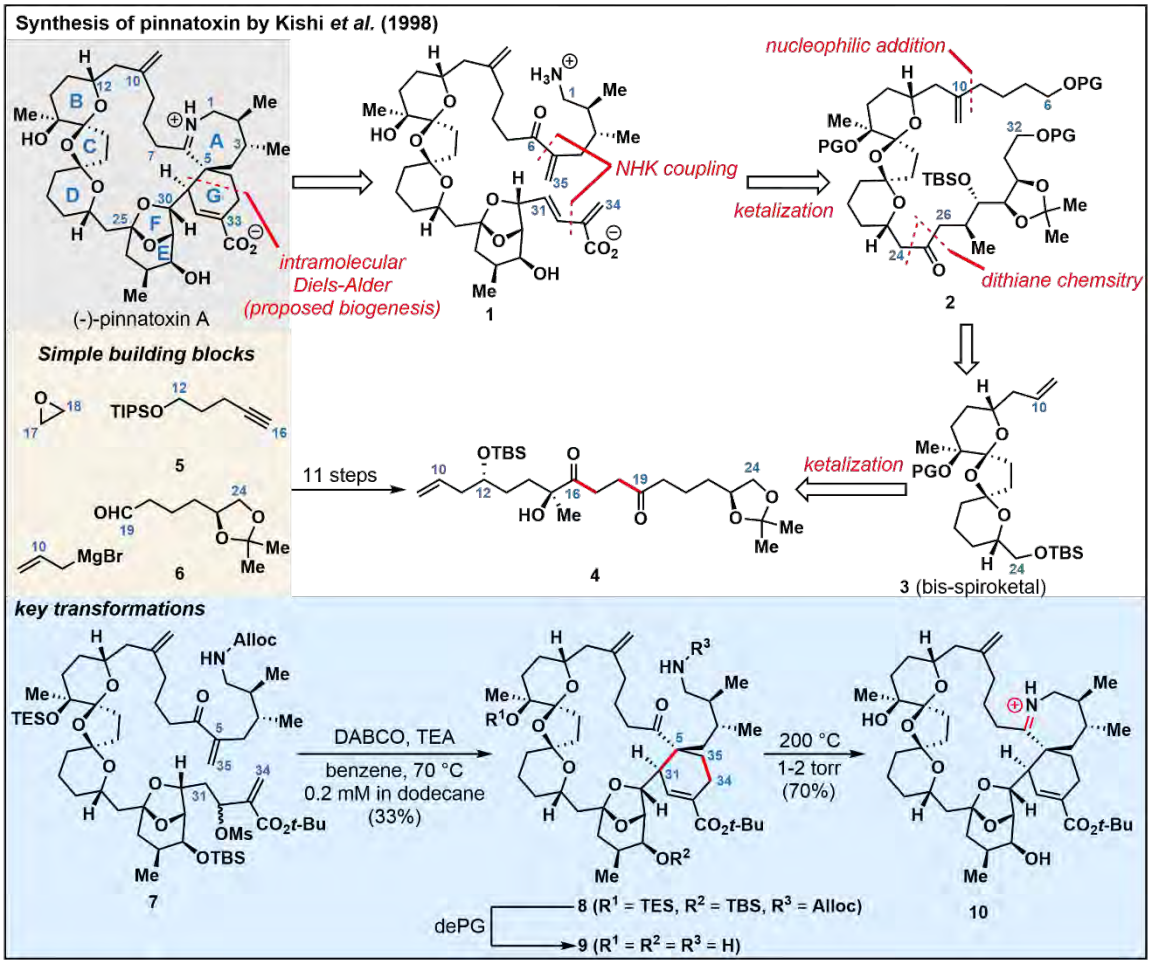


Figure 1.1 Synthesis of pinnatoxin by Kishi group (1998).

A sizable amount of (+)-pinnatoxin A (40 mg) was synthesized by Zakarian *et al.* in 2008 (*5*), featuring a different macrocyclization strategy prioritizing the assembly of the quaternary stereocenter C-5 at the core of the spirocyclic imine (Figure 1.2). Retrosynthetically, the 27-membered carbocyclic backbone of (+)-pinnatoxin A can be disconnected to two major fragments possessing comparable chemical complexities, bis-spiroketal **11** and cyclohexene **12**, via ring-closing alkene metathesis (RCM) and nucleophilic addition. Indeed, **11** was synthesized by an acid-triggered spiroketalization

using the same logic pioneered by Kishi's total synthesis (*1*). In terms of **12**, they noticed that the cyclohexene moiety can be accessed by applying intramolecular aldol condensation to open-form molecule **13**. Intuitively, the construction of the C-5 chirality would be the major subject in this synthesis. To achieve this, **14** was treated with Koga-type chiral lithium amide **15** (*6*) to undergo a stereospecific silyl ketene formation at -78 °C, delivering **16** as the plausible intermediate. Upon warming to ambient temperature, **16** would undergo a stereoselective [3,3]-sigmatropic shift to install the C-5–C-31 bond, affording **17** in 94% yield. Arrival at **17** was a milestone since all requisite core C–C bonds were in place to arrive at **13**. Subsequent reduction and deprotection (dePG) afforded **13** as the precursor for cyclohexene formation. To summarize, this total synthesis features a highly convergent strategy enabled by a well-designed Ireland-Claisen rearrangement. Moreover, this total synthesis also benefitted from the high-yielding chemical transformations throughout the whole sequence, which enabled scalable preparations of most intermediates.

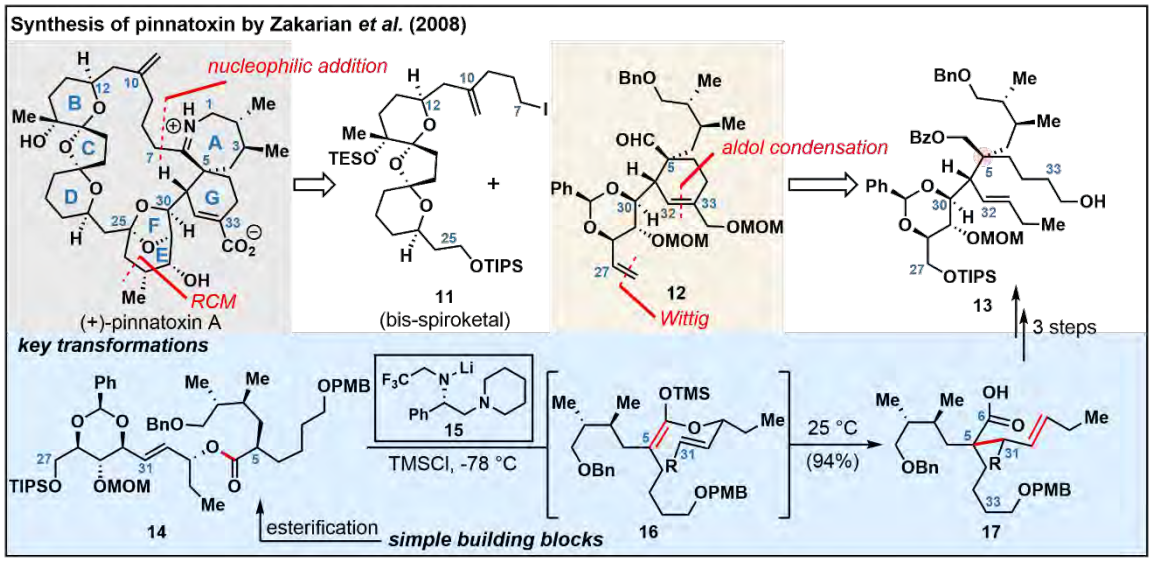


Figure 1.2 Synthesis of pinnatoxin by Zakarian group (2008).

Although the total syntheses done by the Kishi group (1998) and the Zakarian group (2008) are presented herein to represent the logic used in the chemical synthesis of pinnatoxin A, one of the most complex cyclic imine toxins identified to date. This molecule has long been viewed as a challenging target of total synthesis and pursued by many other labs during 1998–2008. Here, the synthetic studies mainly focus on fragments done by the Murai group in (*7*, *8*), formal synthesis achieved by the Inoue-Hirama group in 2004 (*9*), and total synthesis accomplished by the Nakamura group (*10*) are outlined in Figure 1.3.

In the first example, Murai and co-workers developed a highly stereoselective one-step ketalization of tetraketone **18** to form BCDEF pentacyclic system in pinnatoxin A (fragment A, **19**) (*7*). This interesting finding still remains to be the only example to assemble the polyketal system in pinnatoxin A in a single step. On the other hand, the spirocyclic moiety (**20**) in pinnatoxin itself was targeted by the Murai group and described in 2002 (*8*), where they successfully controlled both the enantio- and *exo* selectivity in the Diels-Alder cycloaddition between dienophile **21** and diene **22**.

In 2004, the Inoue-Hirama group reported a formal synthesis of pinnatoxin A targeting Kishi's late-stage keto-amine intermediate **10** (*9*, Figure 1.3). The key C–C bond to disconnect was between C-8 and C-9 and reconstructed via RCM, while fragment **24** containing C-26 was joined to **23** using dithiane coupling. To construct the crucial C5–C-31 bond in **24**, a stereoselective epoxide ring-opening triggered by deprotonation of **26** at C-5 was applied, delivering **25** in 72% yield. Subsequent allylation and functional manipulations were executed, arriving at eastern fragment **24**. As the second successful

total synthesis of pinnatoxin A, the authors showed herein the feasibility of a highly convergent strategy joining two fully functionalized fragments and aiming at an abiotic macrocyclization.

Shortly after the Zakarian group disclosed their total synthesis, Nakamura *et al*. reported the third total synthesis of pinnatoxin A (*10*), featuring a key cycloisomerization to set up the 27-membered macrocycle. This crucial step was outlined in Figure 1.3 where enyne **28** was heated with $[CpRu(MeCN)_3]PF_6$ to activate the alkyne at C-10, followed by the formation of the C-9–C-10 bond, delivering **27** as the exclusive product. Arrival at **27** was regarded as the "end-point" of the total synthesis since only simple redox manipulations remained. On the other hand, the G ring in pinnatoxin A was synthesized by a diastereoselective intermolecular Diels-Alder reaction between pentacyclic **29** and lactone **30**.

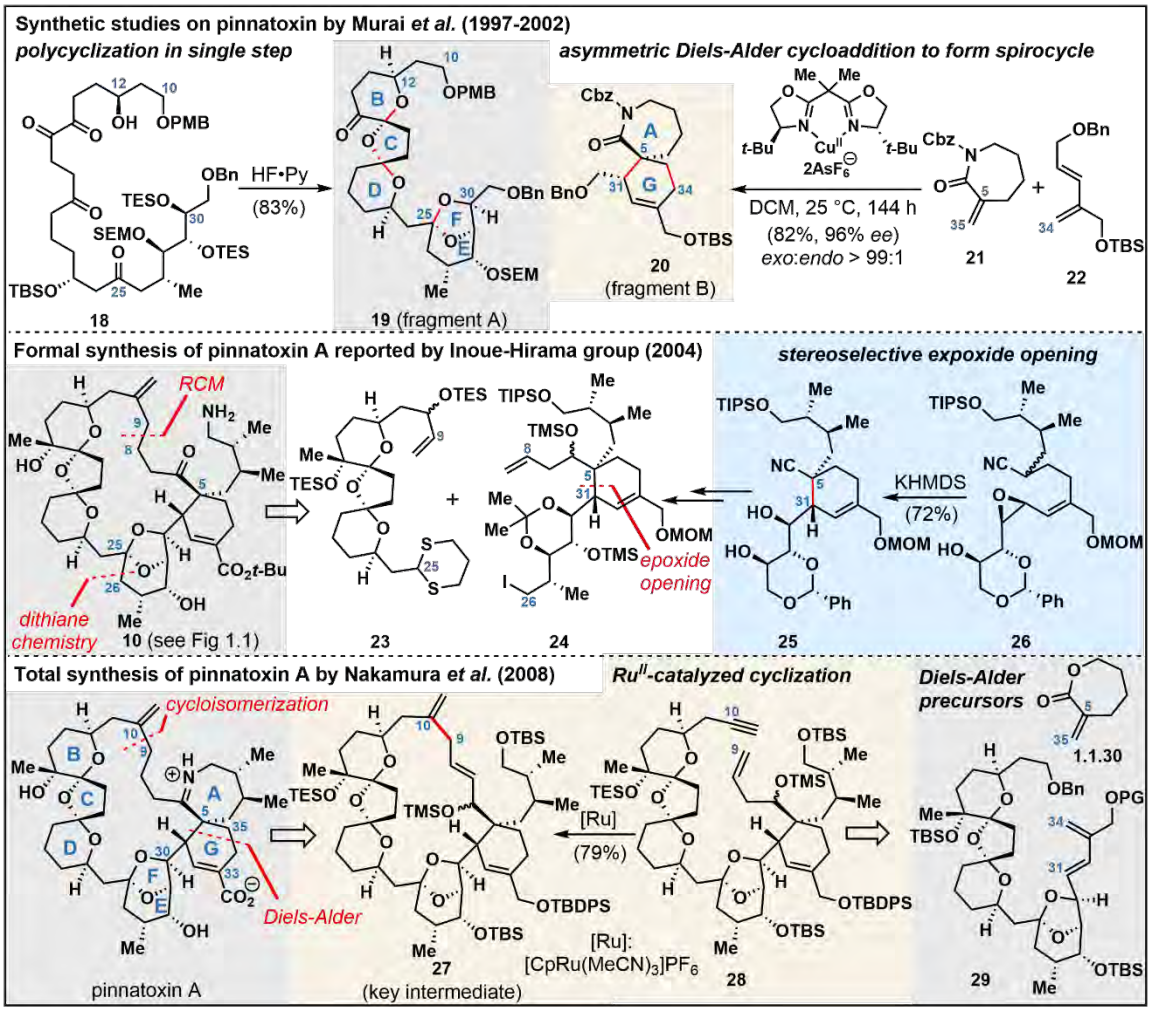


Figure 1.3 Other strategies used in total syntheses of pinnatoxin A.

Section 1.2 Case study 2: gymnodimine.

In this section, the total synthesis of gymnodimine will be discussed since this spirocyclic imine, similar to pinnatoxin A, is the subject of multiple strategies and has been explored by multiple groups (Kishi, White, Zakarian, Romo, *11–15*), of that only the Romo lab (*14*, *15*) accomplished the entire total synthesis. The uncompleted approaches were summarized in Figure 1.4.

In the first case, a biomimetic intramolecular [2+4] strategy explored by Kishi lab in

2005 was presented (*11*), where they successfully arrived at a hydrolysis-resistant imine **30** by an assembly of simple building blocks and subsequent global deprotection. Treating this linear molecule in pH 6.5 buffer at extremely low concentration delivered a 1:1 mixture of Diels-Alder adducts with good stereocontrol at C-22. It is also worth mentioning that the undesired diastereomer was demonstrated more hydrolytically unstable relative to its C-7 epimer and isolated as keto-amine form. This work confirmed the feasibility of utilizing a biomimetic intramolecular Diels-Alder cycloaddition highlighted in the synthesis of pinnatoxin A to construct the spirocyclic imine motif in gymnodimine.

One year after Kishi group published their biomimetic strategy, the White lab disclosed their progress on the synthesis of gymnodimine (*12*), which was illustrated in Figure 1.4. In contrast to Kishi's intramolecular Diels-Alder strategy, they established the cyclohexene containing the quaternary C-22 in a single step via an intermolecular Diels-Alder cycloaddition between **31** and a highly reactive dienophile derived from Meldrum's acid (*16*). Moderate selectivity could be achieved (1.2:1) and spirocycle **32** was isolated in 46% yield. To construct the 16-membered macrocycle in gymnodimine, they executed an sp^2-sp^3 Suzuki coupling between borane **33** and a fully-functionalized fragment (the western part of gymnodimine, synthesis was not depicted here), followed by an alkynylation on C-8, to give a methyl-capped alkyne **34**. Unfortunately, efforts to manipulate the functionalities to arrive at the macrocyclization precursor **35** were not successful presumably due to the relatively hindered surrounding of the alkyne.

In 2007, the Zakarian group detailed the synthesis of the eastern fragment of

gymnodimine utilizing the Ireland-Claisen rearrangement strategy used in their pinnatoxin A synthesis (*13*). Similarly, the C–C bond between quaternary carbon C-22 and C-7 was disconnected, and the C5/C6 double bond was envisioned as a result of the self-aldol condensation of **36**. In terms of the forward synthesis, the stereo-defined silyl ketene acetal **38** would then undergo a [3,3]-sigmatropic rearrangement to arrive at **37**. Subsequent redox and functional manipulations delivered aldehyde **36** as expected, which then underwent a cyclization in the presence of piperidine and PTSA, constructing the eastern part of the natural product. This study validated the strategy using Ireland-Claisen rearrangement to access the spirocyclic segment of gymnodimine.

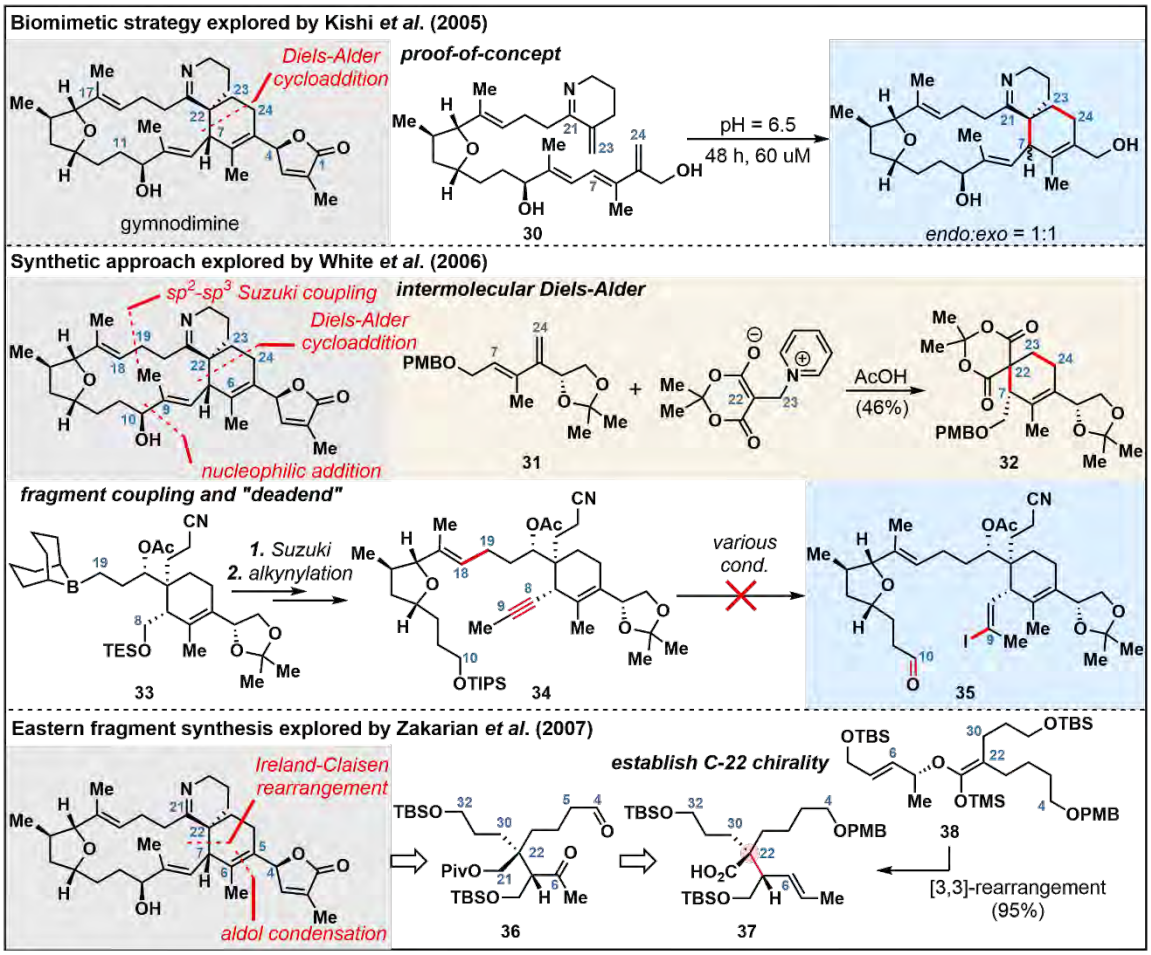


Figure 1.4 Uncompleted synthetic approaches toward gymnodimine.

The only successful total synthesis of gymnodimine to date was published by Romo group (*14*, *15*) and outlined in Figure 1.5. The initial strategy explored by the Romo group was similar to the strategy published by White *et al*. utilizing an intermolecular Diels-Alder cycloaddition followed by an NHK-type macrocyclization to establish the skeleton of natural product. This idea led to nearly equally distributing the functionalities embedded in gymnodimine to two fragments, tetrahydrofuran **39** and spirocycle **40**. To synthesize **40**, an elegant asymmetric Diels-Alder catalyzed by a chiral Cu-BOX complex (*8*) took place between lactam **41** and diene **42**, with both excellent *exo* and enantioselectivity. To form

the bond between C-20 and C-21, alkyllithium **43** was generated via multiple chemical transformations from **39**, followed by treatment with electrophilic **40**, delivering ketone **44** possessing all skeletal carbon atoms of the macrocycle in 92 % yield. Problems that remained included functional manipulations such as oxidation and formal hydroiodination (4 steps in total), arriving at the macrocyclization precursor **45**. Disappointedly, **45** failed to undergo the desired intramolecular cyclization under various conditions. Other harsher conditions such as Li–X exchange had also been tested and unfortunately, led to the recovery of the deiodinated starting material.

De facto, they found that chloride **49,** formed from the combination of fragments **47** and **48** via NHK coupling, could undergo a Finkelstein reaction to give the other precursor of macrocyclization, iodide **50**. Delightfully, the “bottom first” strategy (in contrast to the “top first” strategy used above) indeed construct the challenging macrocycle via a Barbier-type nucleophilic addition. Surprisingly, the abnormally high temperature (25 °C) was crucial since little to no macrocycle was observed under low temperatures.

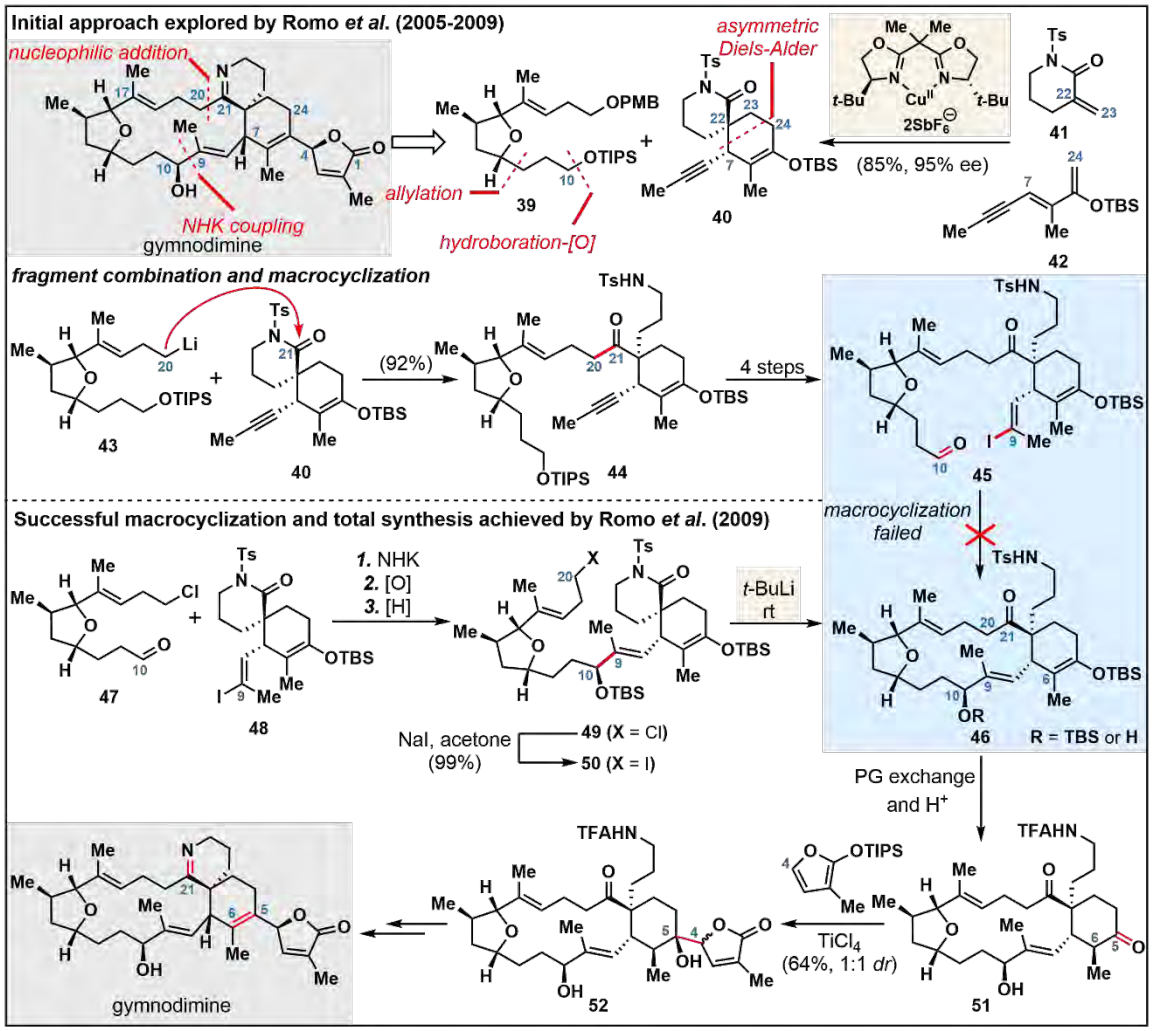


Figure 1.5 Total synthesis of gymnodimine by Romo lab (2011).

Section 1.3 Summary: General strategy used in total syntheses of cyclic imine toxins.

As we have just seen from the synthetic works focusing on complex marine-derived cyclic imine toxins pinnatoxin A and gymnodimine, most of them utilized highly convergent strategies disconnecting the parent molecules into several nearly fully functionalized fragments. To pursue a concise synthesis based on this retrosynthesis logic, quick access to polyketide-type fragments from simple commercial building blocks is required (Figure 1.6). In other words, the ideality (*17*) of the classical total syntheses of

cyclic imine toxin represented by the above examples, will be inevitably limited by the efficiency of mimicking the polyketide synthases (PKSs).

In the case of pinnatoxin A, which is featured by its formidably functionalized pentacyclic ketal system (ring BCDEF) embedded in a 27-membered macrocycle. In stark contrast, the largest cyclic ketal is only 6-membered, indicating a potentially stable product of spontaneous spiroketalization without the assistance of the natural product's backbone. On the other hand, the 6,7-spirocyclic imine of pinnatoxin A is unstable and thereby absent from stereocontrol throughout the synthesis. The LLS of each existing synthesis was outlined, all of which require >38 steps to arrive at this natural product, reflecting the fact that tremendous efforts are required to reach the heavily oxygenated polyketide fragments such as **53**, **55**, and **56**, probably due to little to no rigidity can be utilized for stereochemical control throughout the synthesis. Notably, all completed syntheses preinstalled the BCD tricyclic system prior to macrocyclization, consistent with the rationale that the polycyclic ketal system can exist without stabilization by the macrocycle. Although the BCD system can serve as a "self-protecting" group for redox-sensitive groups such as ketone and hydroxyl groups in **54** and **55** at the late stage of the syntheses, enantio- and diastereoselective synthesis for this moiety is quite challenging and requires redundant non-strategic transformations.

From a higher level, the biomimetic strategy mimicking PKSs used in the synthesis of pinnatoxin A failed to significantly simplify this project since all strategies required arduous transformations to control the stereochemistry without the help of a rigid system.

Despite that, the efficiency of the whole route can still be overcome by impressively high yield for each step, represented by the work from the Zakarian group (*5*). On the other hand, a strategy based on potentially diastereoselective oxidation and ketalization to generate BCDEF cyclic system after macrocyclization is counterintuitive and unnecessary given that such type of ketalization is spontaneous.

The logic used in the approaches to gymnodimine, a cyclic imine toxin also possessing a much smaller THF ring relative to its macrocycle (16-membered), is no exception and illustrated in Figure 1.6. As we can see, both biomimetic (*11*) and abiotic (*14*, *15*) syntheses require to synthesize their corresponding fully-functionalized polyketide fragment, **57** and **60**, and no strategic redox manipulation will happen after the construction of the macrocycle. In Romo's total synthesis, 30 steps (LLS) were required to arrive at the natural product, 13 of which were used to construct the polyketide western fragment.

The logic of using fully-functionalized polyketide fragments as the precursors for macrocyclization was quite reasonable and successful in the cases of pinnatoxin A and gymnodimine. Their much larger macrocyclic skeleton relative to the cyclic ketal system naturally leads to strategies preinstalling the oxygen atoms prior to skeleton formation. However, these strategies may suffer from redundant redox and functional transformations and compromise the efficiency of the synthesis.

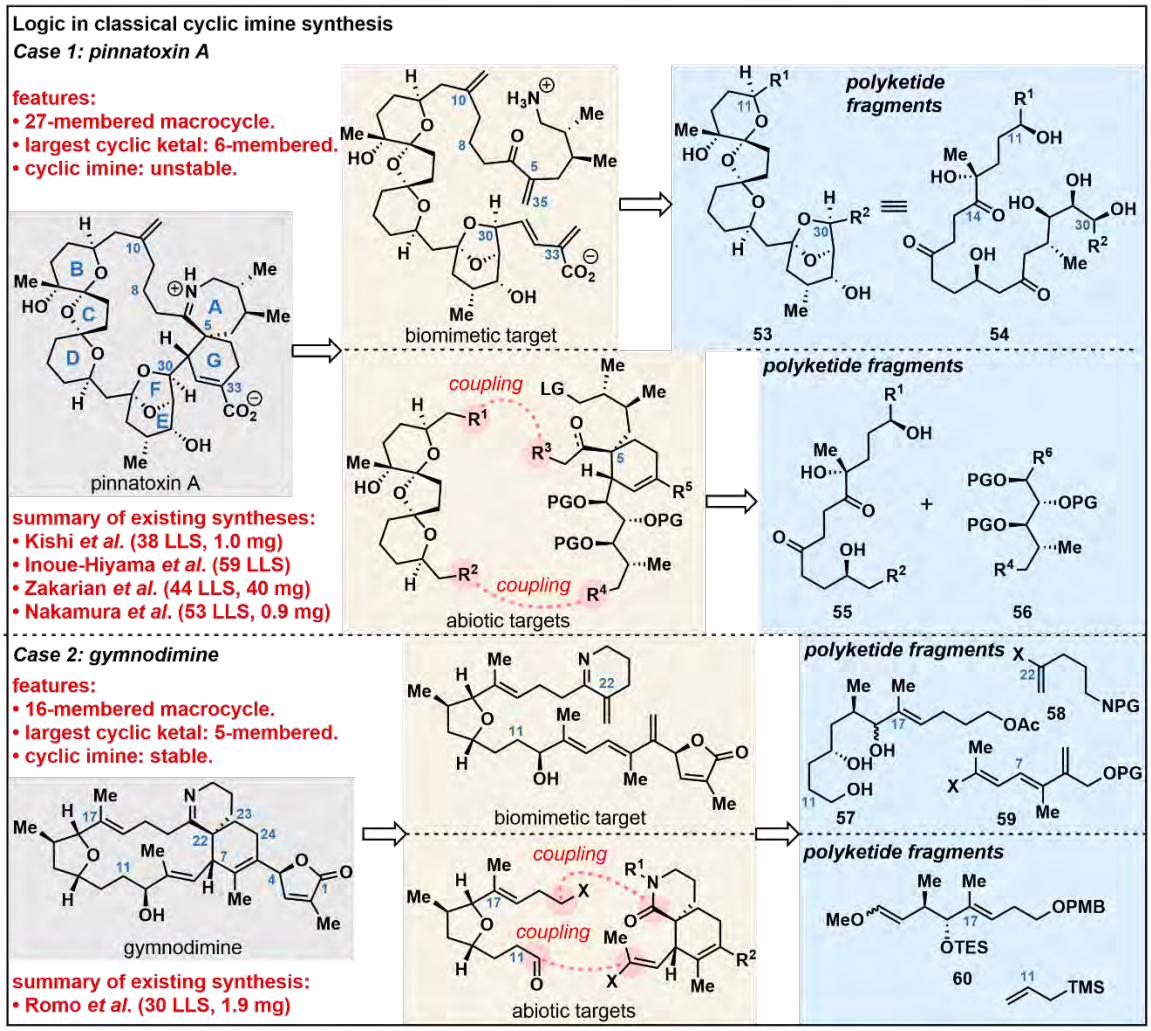


Figure 1.6 Logic used in the syntheses of pinnatoxin A and gymnodimine.

Reference

(1) Uemura, D.; Chou, T.; Haino, T.; Nagatsu, A.; Fukuzawa, S.; Zheng, S. Z.; Chen, H. S. Pinnatoxin A - a Toxic Amphoteric Macrocycle from the Okinawan Bivalve Pinna-Muricata. *J. Am. Chem. Soc.* **1995**, *117*, 1155–1156.

(2) Chou, T.; Kamo, O.; Uemura, D. Relative stereochemistry of pinnatoxin A, a potent shellfish poison from Pinna muricata. *Tetrahedron Lett.* **1996**, *37*, 4023–4026.

(3) McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.;

Kishi, Y. Total synthesis of pinnatoxin A. *J. Am. Chem. Soc.* **1998**, *120*, 7647–7648.

(4) Beaumont, S.; Ilardi, E. A.; Tappin, N. D. C.; Zakarian, A. Marine Toxins with Spiroimine Rings: Total Synthesis of Pinnatoxin A. *Eur. J. Org. Chem.* **2010**, *2010*, 5743–5765.

(5) Stivala, C. E.; Zakarian, A. Total synthesis of (+)-pinnatoxin A. *J. Am. Chem. Soc.* **2008**, *130*, 3774–3776.

(6) Qin, Y.; Stivala, C. E.; Zakarian, A. Acyclic Stereocontrol in the Ireland-Claisen Rearrangement of Alpha-Branched Esters. *Angew. Chem. Int. Ed.* **2007**, *46*, 7466–7469.

(7) Ishihara, J.; Tojo, S.; Kamikawa, A.; Murai, A. One-step assembling reaction to the pentacyclic acetal of pinnatoxins. *Chem. Commun.* **2001**, 1392–1393.

(8) Ishihara, J.; Horie, M.; Shimada, Y.; Tojo, S.; Murai, A. Asymmetric construction of the azaspiro[5.6]dodec-9-ene system in marine natural toxins. *Synlett* **2002**, 403–406.

(9) Sakamoto, S.; Sakazaki, H.; Hagiwara, K.; Kamada, K.; Ishii, K.; Noda, T.; Inoue, M.; Hirama, M. A formal total synthesis of (+)-pinnatoxin A. *Angew. Chem. Int. Ed.* **2004**, *43*, 6505–6510.

(10) Nakamura, S.; Kikitchi, F.; Hashimoto, S. Total synthesis of pinnatoxin A. *Angew. Chem. Int. Ed.* **2008**, *47*, 7091–7094.

(11) Johannes, J. W.; Wenglowsky, S.; Kishi, Y. Biomimetic macrocycle-forming Diels-Alder reaction of an iminium dienophile: Synthetic studies directed toward gymnodimine. *Org. Lett.* **2005**, *7*, 3997–4000.

(12) White, J. D.; Quaranta, L.; Wang, G. Q. Studies on the synthesis of (-)-

gymnodimine. Subunit synthesis and coupling. *J. Org. Chem.* **2007**, *75*, 1717–1728.

(13) Qin, Y. C.; Stivala, C. E.; Zakarian, A. Acyclic stereocontrol in the Ireland-Claisen rearrangement of alpha-branched esters. *Angew. Chem. Int. Ed.* **2007**, *46*, 7466–7469.

(14) Kong, K.; Romo, D.; Lee, C. Enantioselective Total Synthesis (-)-Gymnodimine Employing a of the Marine Toxin Barbier-Type Macrocyclization. *Angew. Chem. Int. Ed.* **2009**, *48*, 7402–7405.

(15) Kong, K.; Moussa, Z.; Lee, C.; Romo, D. Total Synthesis of the Spirocyclic Imine Marine Toxin (-)-Gymnodimine and an Unnatural C4-Epimer. *J. Am. Chem. Soc.* **2011**, *133*, 19844–19856.

(16) Zia-Ebrahimi, M.; Huffman, G. W. Synthesis and utility of a novel methylene Meldrum's acid precursor. *Synthesis* **1996**, 215–218.

(17) Peters, D. S.; Pitts, C. R.; McClymont, K. S.; Stratton, T. P.; Bi, C.; Baran, P. S. Ideality in Context: Motivations for Total Synthesis. *Acc. Chem. Res.* **2021**, *54*, 605–617.

Chapter 2: Portimine A and B, isolation background and synthetic approaches.

Section 2.1 Isolation and characterization of portimine A and B.

In 2013, a new spirocyclic imine toxin was identified from a pinnatoxin-producing benthic dinoflagellate *Vulcanodinium rugosum* (*1*, Figure 2.1), which was named portimine (later portimine A) after *Portodinium honu*, the preliminary name of this species. 12.5 mg portimine A was isolated from a 60-liter culture of cells as a white amorphous powder. The formula of portimine A was determined by HRMS as $C_{23}H_{21}NO_6$, and NMR data unambiguously showed an unprecedented 6,5-spirocyclic imine embedded in a highly oxidized all-carbon macrocyclic core. Unfortunately, they failed to obtain the single crystal to determine its absolute configuration. It is also worth mentioning that portimine A possesses an uncommon C-5 hydroxyl group adjacent to imine relative to other cyclic imine toxins. Consistent with pinnatoxins and gymnodimine, the collision-induced fragmentation mass spectrum for the $[M+H]^+$ ion can be rationalized by a process initialed by a retro Diels-Alder ring-opening, indicating its biogenesis from **61**. From a preliminary study, they also found that portimine A exhibits strong potency against two mammalian cell lines, P388 and Vero, with EC_{50} values of 2.7 nM and 3.0 nM, respectively. Surprisingly, the acute toxicity of portimine A (1570 μg/kg, i.p.) is significantly lower than other cyclic imine toxins (*1*), which suggests a promising therapeutic index. Finally, the absolute configuration of portimine A was determined by X-ray in 2019 when it was co-isolated with another new cyclic imine toxin kabirimine from *V. rugosum* (*2*).

A metabolomic analysis of cultures of *V. rugosum* demonstrated the production of an oxidized analog of portimine A, named portimine B (*3*), and was depicted in Figure 1.1.

The formula of this compound was determined by high-resolution electrospray ionization mass spectrometry (HRESIMS) as $C_{23}H_{21}NO_6$, indicating an additional oxygen atom while retaining the same degree of unsaturation. Furthermore, the 1D and 2D NMR data of this compound revealed a ketone at C-5, while the rest of the molecule showed no dramatic difference to portimine A. Based on this, the authors concluded that portimine B presents an open-form THF ring compared to portimine A, while counterintuitively still retains a transannular 8-membered cyclic hemiacetal. The uncommon structure of portimine B made it an attractive target for chemical synthesis. However, the "appealing" structure was revised and the formula of portimine B was corrected to $C_{23}H_{19}NO_5$ through the synthetic work described in Section 5.2.

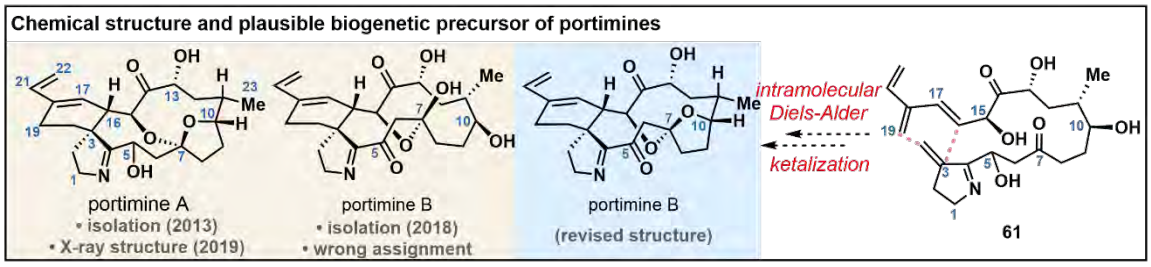


Figure 2.1 Portimine A and B and their hypothetical biogenetic precursor.

Portimines have attracted broad attention from both synthetic and biological chemists due to their unusual bioactivity and intriguing chemical architecture. As of now, no successful total synthesis of either portimine A or B has been disclosed except for the total synthesis presented in this thesis. The synthetic studies toward portimines will be discussed in the following sections.

Section 2.2 Synthesis of the cyclohexene segment of portimine by Fujiwara group.

Stimulated by the promising therapeutic index of portimine A, the Fujiwara group aimed to obtain sufficient quantities of it via chemical synthesis (*4*), and their synthetic study was outlined in Figure 2.2. In this work, they first intended to synthesize the cyclohexene segment **62**, which contains three continuous stereocenters (C-3, C-16, C-15) and a conjugate diene. The exocyclic diene could be accessed from ketone, leading to key intermediate **63**. Key disconnections applied to **63** included a conjugate addition to C-16 to install C-14 and C-15, an ethylenation taking place at C-18, as well as an aldol reaction constructing the C-2-C-3 bond to establish the C-3 quaternary center. The oxidation state and stereochemistry at C-15 could be installed by a diastereoselective dihydroxylation, arriving at several simple building blocks shown in the grey box (Figure 2.2).

The forward route targeting **62** started with a facile Cu-mediated conjugate addition happening to enone 64, delivering a 1:1 mixture of **65** and **66**. The choice of the *i*-Bu group was critical since switching to either a less bulky methyl ester or a highly bulkier *t*-butyl ester would lead to unsatisfying outcomes (low yield, undesired diastereoselectivity, etc.). Subsequently, olefin **66** was dihydroxylated under Upjohn's condition to give a 1:2 mixture of lactone **67** and diol **68**, the latter was confirmed as the desired product. With all stereocenters set up, a sequence of tedious functional and PG manipulations (9 steps overall) were still required to arrive at **62**, and the whole sequence called for 18 steps to synthesize the cyclohexene segment of portimines! On the other hand, despite reasonable retrosynthetic analysis, poor stereoselectivities observed in key steps including conjugate

addition and dihydroxylation were disappointing, leading to the question of whether the desired stereo outcome can be obtained by diastereoselective conjugate addition. As we shall see in Section 3.2, an overwhelmingly desired stereochemical outcome at C-16 can be obtained and controlled by C-3 when applying a rigid spirocycle as the substrate.

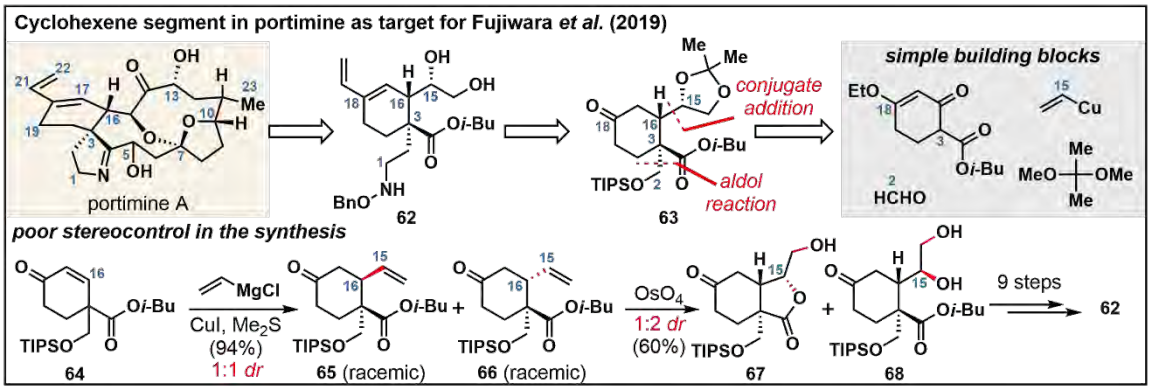


Figure 2.2 Synthesis of the cyclohexene segment of portimine by Fujiwara group.

Section 2.3 Synthetic approach toward potimines by Brimble group.

Perhaps a biomimetic synthesis of portimines is charming partially encouraged by Kishi's pioneering legendary work on the total synthesis of pinnatoxin A. As we can see in Brimble group's pursuit of this molecule (*5*–*8*, Figure 2.3), a retrosynthesis based on biogenesis was used, targeting tetraene **61**. Key C–C bond formations to assemble **61** included an alkyne addition to generate the C-14–C15 bond, and C-5 and C-6 would be joined by an aldol reaction. In their model study published in 2020 (*5*), a diastereoselective aldol reaction catalyzed by chiral took place between silyl enol ether **70** and an α-keto aldehyde, delivered aldol product **69** in an acceptable yield (32%). This study confirmed the feasibility to append the bottom side chain to C-5 via classical aldol condensation.

Meanwhile, Brimble *et al.* reported their progress in using Diels-Alder cycloaddition to construct the spirocyclic imine motif of portimines (*6*, *7*, and Figure 2.3). Despite cycloadduct **73** being isolated in a pleasing yield, the diastereoselectivity was undesired. Subsequently, they explored cyclization via Au-catalyzed alkyne amination. Applying Seyferth–Gilbert homologation to **73** delivered terminal alkyne **74**, which was deprotected and underwent a spirocyclization in the presence of [Au(PPh_3)Cl] to give spirocycle **75**.

In 2021, the Brimble group reported their most recent progress in the asymmetric synthesis of portimines (*8*), where they targeted polyketide **76** and aimed to access it via two fragment couplings happening at C-12/C-13 and C-10/C-11, using S_N2 and Evans aldol reaction, respectively. Arrival at **77** was a great success since all requisite carbons in **76** are presented, all that remained was to install the oxygen atoms at C14/C15. To this end, an unusual condensation between propargylic alcohol **77** and ninhydrin in the presence of silver(I) ion was executed, affording enol ether **78**, followed by epoxidation with DMDO under low temperature to give **79**. Subsequent hydrolysis and deprotection gave ketalization precursor **80** in a moderate yield. Unfortunately, various conditions were screened for this key step yet no **81** or any other cyclized compounds were identified, suggesting the formation of the unique ketal system in portimines is not facile, at least, with the use of a linear polyketide precursor.

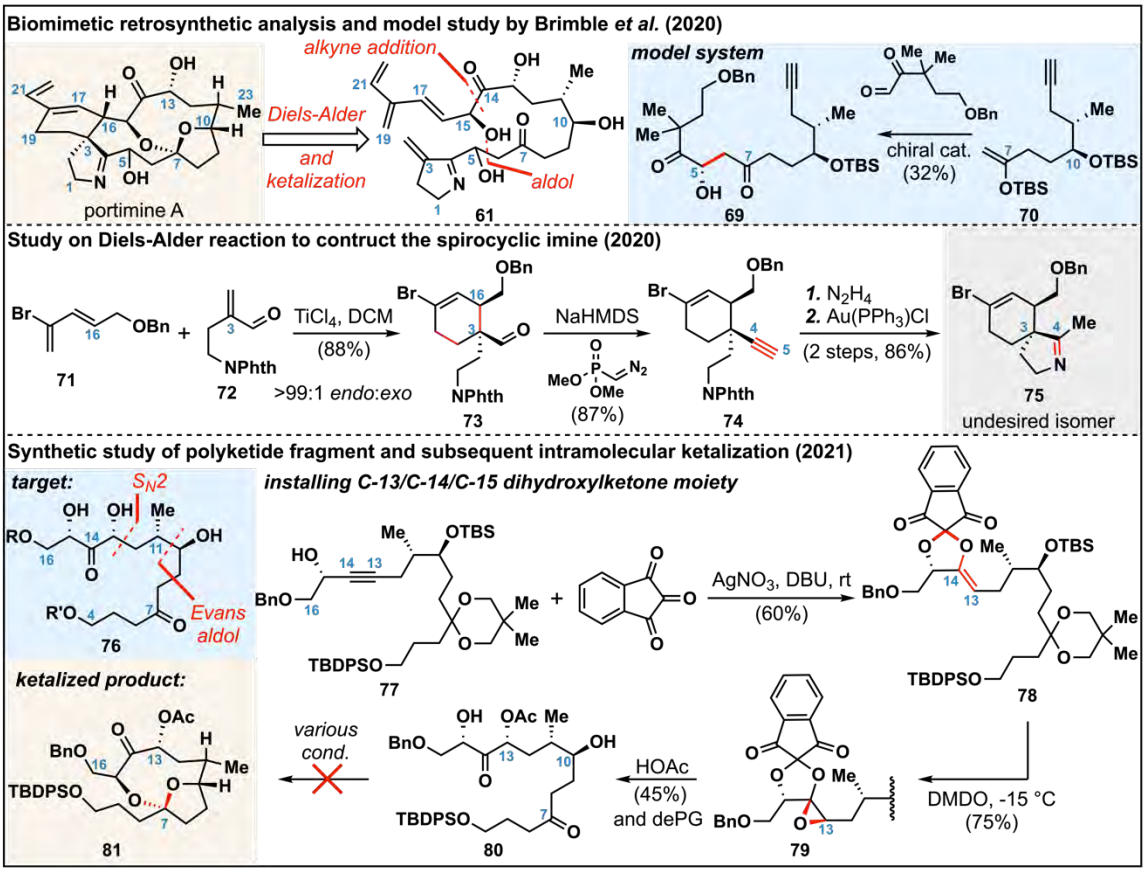


Figure 2.3 Synthetic studies toward portimines by Brimble group.

Section 2.4 Synthetic approach toward potimines by Harran group.

Very recently, the Harran group at UCLA reported their synthetic approach towards portimines, which was outlined in Figure 2.4 (*9*, *10*). Compared to Brimble's model study, the Harran group launched a more ambitious biomimetic synthesis aiming at preinstalling all functionalities to the polyketide chain prior to macrocyclization. In their retrosynthesis, they proposed that the α-position of imine can be oxidized by late-stage oxidation. Therefore, a Diels-Alder precursor **82** lacking the C-5 hydroxyl group (Figure 2.4) was pursued. The cyclic imine moiety of **82** can be reasonably accessed by a Staudinger reaction of the corresponding azide-ketone **83**. To build this linear polyketide, they mapped

out a Kulinkovich reaction to install the C-5-C-6, followed by a cyclopropanol homologation to append the C-1 – C-4 sidechain to C-5. In terms of the right fragment of **83**, the C-10–C-11 bond, as well as the C–C bond between C-13 and C-14, were formed by two sequential enantioselective organocatalytic transformations. Finally, the triene motif would derive from olefination taking place at C-16.

The forward synthesis as outlined in Figure 2.4, commenced with an asymmetric Michael addition between 2-trimethylsiloxyfuran and commercial crotonaldehyde, generating two adjacent stereocenters at C-11 and C-10. Subsequent hydrogenation of the butanolide would deliver lactone **84**, which was then submitted to an asymmetric cross-aldol catalyzed by a TBS-protected D-thymine acting in concert with co-catalytic methylcyanoglyoxalate oxime, affording **85**, a polyketide compound bearing 4 key stereocenters, in 75% yield on a 20-gram scale. It is also worth mentioning that this transformation was carried out in an aqueous solution. To append the olefinic fragment required for Diels-Alder to this polyketide chain, a sequence including redox and PG manipulation was executed, arriving at aldehyde **86** as one of the coupling partners for Wittig olefination in an acceptable overall yield. Subsequent Wittig reaction took place between C-16 and C-17, followed by a Kulinkovich reaction to give cyclopropanol **88** as the product. This cyclopropanol, acting as a homoenolate surrogate (*11*), was successfully converted to 1,4-dicarbonyl compound **83** under Pd-catalyzed cross-coupling in the presence of an acid chloride. Harboring all requisite carbons in natural portimines, compound **83** was deprotected, followed by a Staudinger reaction to liberate the free amine

at C-1, to undergo dehydration to form cyclic imine **82**. Expectedly but disappointedly, **82** was quite unstable and spontaneously underwent an intramolecular Diels-Alder under pH 6 buffer to arrive at **89** as the only detectable macrocylized product, in pretty low yield (~10%), yet the cyclization taking place between the less-hindered terminal diene and the unsaturated imine. The formation of **89** was considered as a "dead-end" for the total synthesis since the connection of the carbon skeleton was incorrect and hard to reconstruct. This result might indicate that the transannular ketal system is crucial for the intramolecular Diels-Alder via templatizing the intermediates.

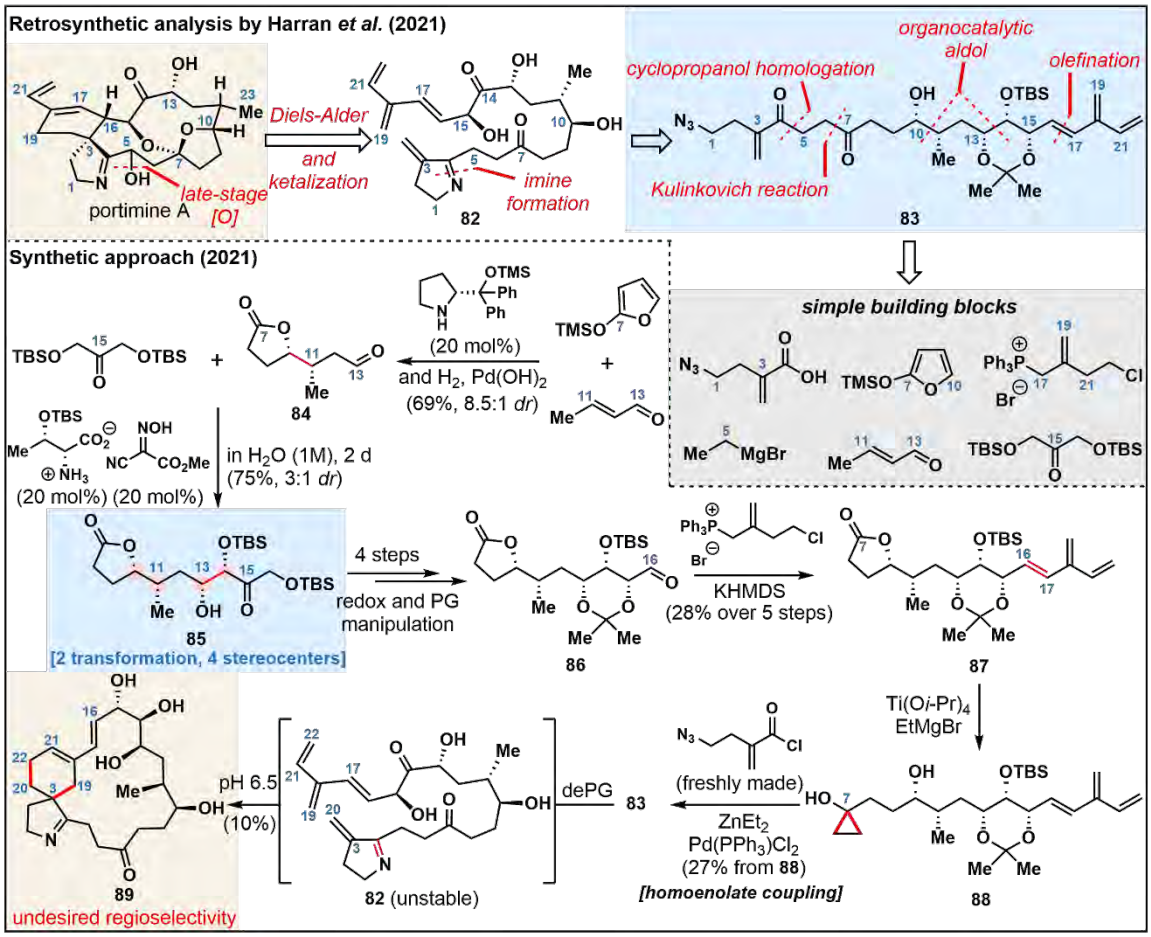


Figure 2.4 Synthetic studies toward portimines by Harran group.

Section 2.5 Synthetic approach toward potimines by Zakarian group.

A synthetic study towards portimines based on abiotic macrocyclization was disclosed in the thesis of Joshua Joseph Gladfelder from the Zakarian group (*12*) in 2022. In this work, the hydroxyl group at C-5 was also forgone until the establishment of the macrocycle. Thus, key intermediate **90** was targeted and accessed by intramolecular ketalization of a fully functionalized macrocycle. To construct the challenging macrocycle, a Stetter reaction was chosen, appending C-6 to C-7 under mild umpolung conditions thereby without touching the rest of the molecule, targeting **91**. The side chain possessing two stereocenters at C-10 and C-11 was installed to **92** via a Weinreb reaction, where the resulting undesired redox states on C-13/C-14 would be reconstructed by redox manipulations. The building blocks required for **92** were shown in the grey box (Figure 2.5).

The synthesis commenced with the protection of L-ribose to form an acetonide and subsequent degradation, to give **93**, which was olefinated to give *cis*-alkene **94**. After a sequence of redox and PG manipulations, the resulting allylic alcohol **95** was condensed with a chiral secondary carboxylic acid **96**, smoothly delivering ester **97** in satisfying yield. The key transformation to establish the chiral center at C-3 was initiated by stereospecific deprotonation via chiral lithium amide **15**, followed by an aforementioned Ireland-Claisen rearrangement to arrive at **98** in fascinating yield and good stereoselectivity (98%, 7:1 *dr*). Delightfully, subsequent alkene-alkyne metathesis under an ethylene atmosphere delivered cyclohexene **100** in 86% yield. With the western fragment of portimines in hand, efforts to

couple the eastern side chain commenced with a series of non-strategic manipulations to arrive at Weinreb amide **92**, which was attacked by the freshly-made alkyl lithium **101** bearing stereocenters at C-10 and C-11. The coupled product **102** was isolated in 74% yield, followed by a reduction of C-13, and the reactivity of generated alcohol was masked by a TBS group to give **103** as the final product in 69% overall yield. Five chemical transformations were implemented to install the vinyl group as well as oxidize C-7, delivering the cyclization precursor **104** as the product. Indeed, the key macrocyclization took place when heating **104** with NHC catalyst for 7 hours, and an excellent yield (50%) could be achieved. This result was encouraging enough and optimizations were currently carried out to improve the yield as well as the consistency to afford a sufficient amount of **105** for ketalization.

In conclusion, learning the lessons from the synthetic approaches reported by Brimble *et al*. and Harran *et al*., this synthesis aimed at ketalization with the establishment of the macrocycle. Navigated by this logic, they successfully set up most oxidation states and accomplished the key macrocyclization via the abiotic NHC chemistry.

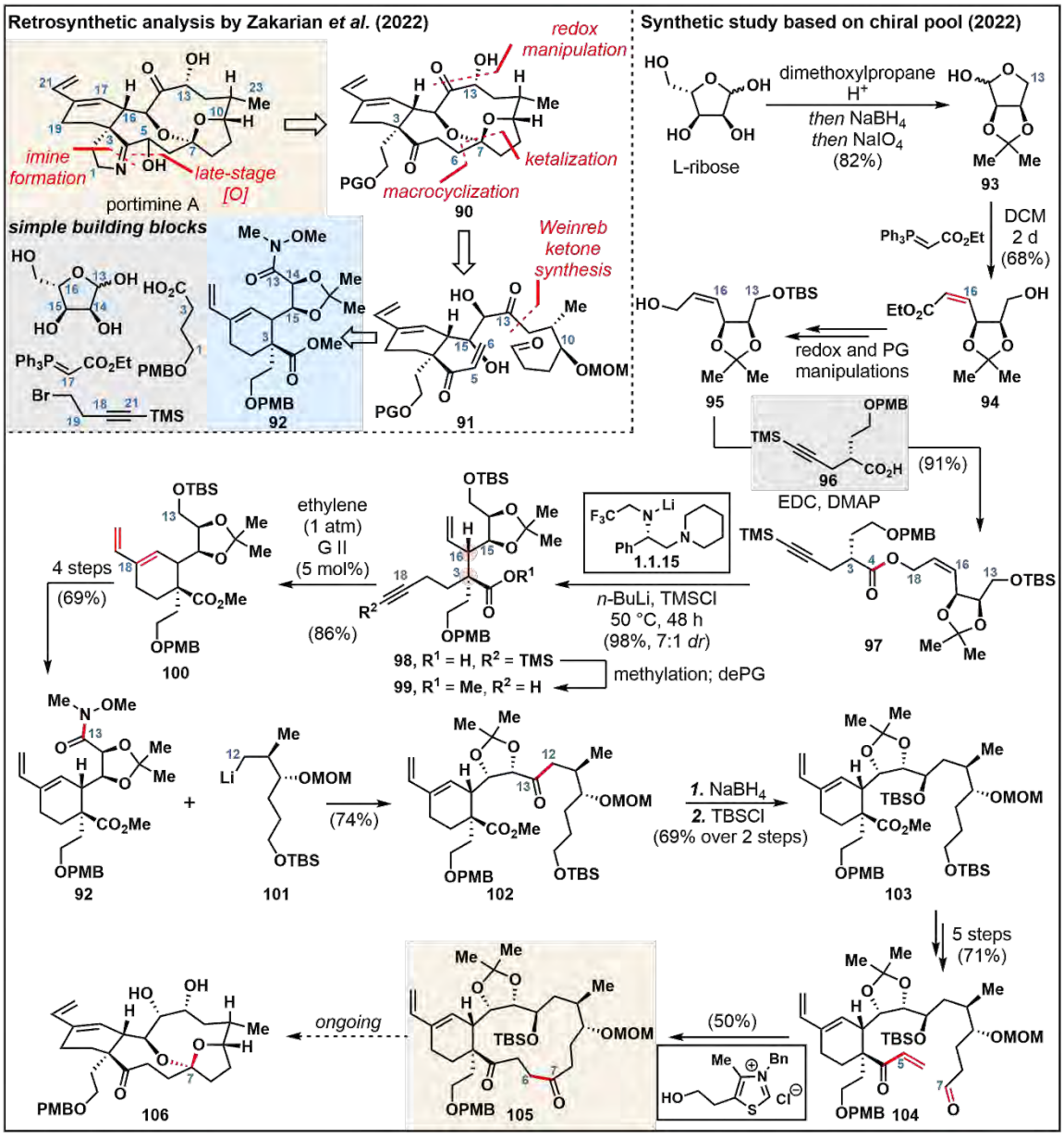


Figure 2.5 Synthetic approach toward potimines by Zakarian lab.

Section 2.6 Synthetic progress toward potimines by our lab (till 2020)

This marathonic project started in our lab from 2016 and was mainly driven by Yi Yang See *et al*. (*13*). Their first-generation retrosynthesis as outlined in Figure 2.6, where a macrocyclic core **107** was targeted and two oxidations would happen at C-5 and C-13 at

the late stage to install all functionalities embedded in portimines' skeleton. To install the exocyclic vinyl group at C-18, a chlorocyclohexene moiety was chosen, which was compatible with various chemical transformations therefore stable enough to carry on throughout the whole synthesis. To construct the 14-membered macrocycle, the eastern fragment **109** would be appended to the spirocyclic western fragment **108** via a nucleophilic addition at C-14, followed by a macrocyclization event taking place between C-4 and C-5.

The first-generation approach was optimized in 2019 by me and commenced with an alkylation at C-3 of a radical anion generated by Birch reduction of methyl benzoate, affording bromide **110** in high yield. Subsequent spirocyclization took place under microwave in the presence of $PMBNH_2$, delivering skipped diene **111** as a beige solid. To oxidize C-18, a highly efficient allylic oxidation catalyzed by rhodium (II) was executed to afford a symmetric dienone **112** in 95% yield. The next bond to make was between C-15 and C-16, and ideally, would desymmetrize **112** to generate a chiral quaternary center at C-3 meanwhile control the stereocenters at C-15 and C-16. Satisfyingly, a chiral silyl ketene acetal reported by Ley *et al.* (*14*) derived from 2,3-butanedione was discovered as an amenable desymmetrizing reagent for this transformation. Indeed, two isolable products, **113** and **114** were characterized, both possessing a perfect stereo control at C-15 and an acceptable desymmetrizing ratio at C-3 (ca. 2:1). After a careful purification by chromatography, desired Michael adduct **113** could be isolated in 37% yield. Subsequently, under the treatment of NaHMDS at low temperature followed by adding Mcmurry's

reagent, vinyl triflate **115** was isolated in 42-50% yield on a gram-scale. To convert the susceptible triflate group to a chlorine atom, a Ru (II)-catalyzed chlorination developed by Shirakawa-Hayashi group (*15*) was applied, delivering **116** as the product in 67% yield. In Yi Yang's attempts to fragment union using **117** (the PMB analog of **116**) as substrate, the chiral auxiliary was first cleaved by methanolic in situ-generated HCl to give **118**. The liberated hydroxyl group was then remasked by a TBS group to arrive at the western fragment **119**, followed by a coupling accomplished by selective nucleophilic addition of alkyl lithium **125** to C-14. To synthesize the iodide precursor of **125**, an eight-step sequence was applied, starting from Baeyer-Villigar oxidation to give **121**. The resulting lactone was methanolized, protected by a PMB group, and selectively reduced, giving aldehyde **118** in a moderate yield over three steps. To install the continuous stereochemistry at C-10/C-11, an asymmetric Brown crotylation was implemented, using [B] stoichiometrically, successfully affording **123** as the solely isolable product. Next, an acid-catalyzed methanolysis took place to take off the acetonide, triggering an intramolecular ketalization to form a THF ring, finally arriving at **124** as a 1:1 mixture of diastereoisomers at C-7. The remaining to do were concerting the terminal alkene to alkyl lithium **125** via a three-step sequence including hydroboration/oxidation, Appeal reaction, and Li–X exchange. Satisfyingly, high chemo selectivity could be obtained under -78 °C, delivering ketone **126** as the major product. This result was extremely encouraging since all requisite carbon atoms were successfully installed and ready for the skeleton-formation event happening between C-4 and C-5. Intuitively, the attempts to **127** should largely benefit from the pre-

formation of the transannular ketal system, not only the potential acceleration by the resulting conformation but also getting rid of the characterization issues raised by the annoying mixture of diastereomers. Unfortunately, but consistent with the findings of Brimble *et al.* (*5*–*8*) and Harran *et al*. (*9*, *10*), no ketalization among C-15, C-10, and C-7 was detected using **126**. On the other hand, efforts to make C-5 nucleophilic (via preparation of corresponding alkyl lithium, magnesium, stannane, borane, zinc, etc.) to attack C-4, were not successful presumably due to the heavily oxygenated skeleton of the intermediates.

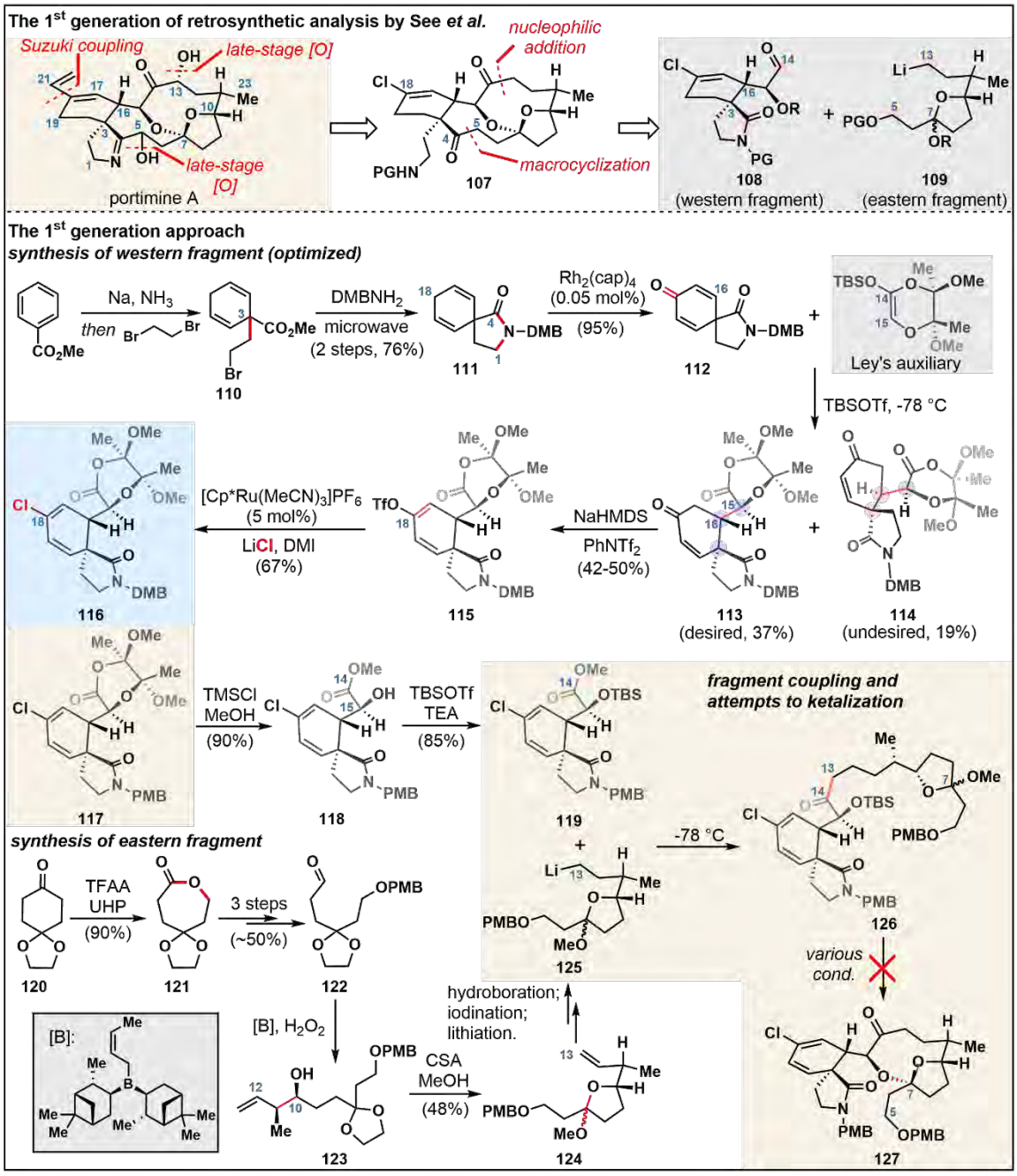


Figure 2.6 Retrosynthesis by See *et al.* and the 1st generation strategy.

Lessons learned from the 1st generation strategy were to construct the macrocycle prior to ketalization. However, precursors such as **126** could hardly undergo a ring formation at C-4 due to steric effect, not to mention that the lactam lacked enough electrophilicity.

Toward this end, a second-generation strategy appending the eastern fragment to C-4 prior to macrocyclization taking place between C-13 and C-14 was designed and described in Figure 2.7. As a result, the macrocyclic core **107** would be synthesized from fragment coupling and subsequent cyclization between spirocycle **128** and THF **129**.

The synthesis of the western fragment could start from an intermediate **116** used in the first-generation route. To increase the reactivity of C-4, a thiolation mediated by Lawessen's powerful reagent selectively occurred to C-4, converting the lactam moiety to a thiolactam presented in **130**. Exposing **130** to acidified methanol cleaved Ley's auxiliary smoothly, followed by a chemoselective, diimide-mediated hydrogenation of the double bond at C-19/C-20 with the use of sulfonyl hydrazine, delivering **132** in 37% overall yield with perfect regioselectivity. Masking the hydroxyl group at C-15 by a TMS group afforded **133** as the precursor of fragment coupling.

An alternative western fragment **137**, without a PG at the nitrogen atom, can be accessed by **116** via a series of transformations. Treating **116** with the acidified methanol gave free alcohol **134** in high yield (85%). Subsequently, several functional manipulations took place, including protecting the C-15 hydroxyl group with a TBS group, followed by the aforementioned diimide reduction to deliver **135** in good yield (61%) over two steps. To convert **135** to its imidoyl thioether analog **137**, the free lactam was liberated under DDQ, affording **136** in 72% yield. Thiolation of this lactam was accomplished by Lawessen's reagent to give the corresponding thiolactam, which was methylated by MeI in the presence of K_2CO_3 to arrive at **137**.

Attention was then turned to installing the eastern fragment to C-4 via nucleophilic addition. In order to activate **133** at C-4 position, methyl triflate (MeOTf) was used to methylate the thiolactam, generating a stable thioiminium salt as the intermediate. Based on the assumption by Yi Yang and his co-workers., selective C–C formation would take place at C-4 due to its highly cationic nature. Unfortunately, nucleophilic sp^3 or sp^2 carbon failed to selectively react with the thio-iminium at C-4 as expected. Despite that, the perfect chemoselectivity was achieved when adding lithium acetylide **139** into a suspension of **138** under low temperature, followed by reducing the newly-formed iminium intermediate by $NaBH_4$, affording cross-coupled product **140** as a mixture of four isomers (*16*). Treating **140** with $CDCl_3$ in the presence of acetic acid would trigger a Meyer-Schuster rearrangement to arrive at a single product **141**, eliminating the two uncontrolled stereocenters. Indeed, this fascinating transformation was discovered by Yi Yang and his co-workers.

Attempts to construct the macrocycle based on **142** (the PMB analog of **141**) were extensively explored by Yi Yang *et al.* Encouragingly, a vinyl group could be installed to C-14 via Grignard reaction, while the resulting diene showed little to no conversion under various RCM conditions, and no cyclized product can be detected. Other macrocyclization strategies, such as Barbier-type cyclization, reductive Heck coupling, and nitrile oxide-alkene [3+2] cycloaddition strategies were not investigated due to the failure of these precursors to synthesize. For instance, standard chemical transformations to hydrolyze, reduce, or thiolate the methyl ester in **142** were not successful, and harsher conditions will

destory the sensitive enone moiety. These results, again, highlighted the difficulty to execute functional manipulations on such a highly functionalized molecule.

The potential of using **137** as a coupling partner was explored by me at the beginning of 2020. As we have just seen, using **133** as coupling partner failed to deliver any iminated products due to the restricted reactivity of the thio-iminium salt. In other words, even though macrocyclization of **142** was successful, maneuver including tautomerization of the keto-amine to hydroxyl imine was required to set up the desired oxidation states at C-4 and C-5. This tautomerization, based on enolization of C-5 carbonyl, was regarded facile in Yi Yang's thesis considering the fast D/H scrambling rate observed in many cyclic imine toxins. However, as we shall see later in Section 5.2, the enolization of that position is nearly impossible on potimines' skeleton. Therefore, **137** was thought promising since a spirocyclic imine possessing the desired geometry at C-4 could be set up via an aza-Fukuyama-type coupling (*17*). To assess the feasibility, **144**, a model system of **137**, was synthesized and submitted to Fukuyama's condition in the presence of a Reformatsky reagent, delivering the desired imine **145** in an acceptable yield (31%). Surprisingly, no cross-coupled product was observed while applying this condition to the real system. To address this problem, a harsher condition was examined, where **144** was complexed by BF_3 etherate, followed by treatment with homopropargylic lithium at -78 °C, affording corresponding imine **146** in a slightly higher yield (40%). This condition was then tested on **137**, but unsatisfyingly, little to no reaction was observed under low temperatures, and ester at C-14 started reacting with nucleophiles upon heating.

In conclusion, due to the presence of sensitive functional groups, installing the eastern fragment to either **137** or **138** was unfeasible. Specifically, we would have to activate a lactam carbonyl (C-4) adjacent to a quaternary center (C-3) to compete with the terminal ester (C-14). Although milder conditions such as Pd-catalyzed cross-coupling to form the C–C bond was feasible on model molecule, no cross-coupled product was observed in real system, presumably due to the unexpected steric effect brought by the α-hydroxyl ester motif (C-14 and C-15). Furthermore, the extremely low throughput and long sequence required for synthesizing **137** and **138** added to the difficulty. For example, to desymmetrize dienone **112**, 63% of the material was lost, and to convert the C-18 carbonyl to chloride, approximately 65% of the material was lost, not to mention the tedious non-strategic manipulations to make thiolactam. To address these problems, a new strategy was invoked and will be discussed in the next section, mainly focusing on the quick and efficient assembly of eastern and western fragments, to test the macrocyclization as soon as possible.

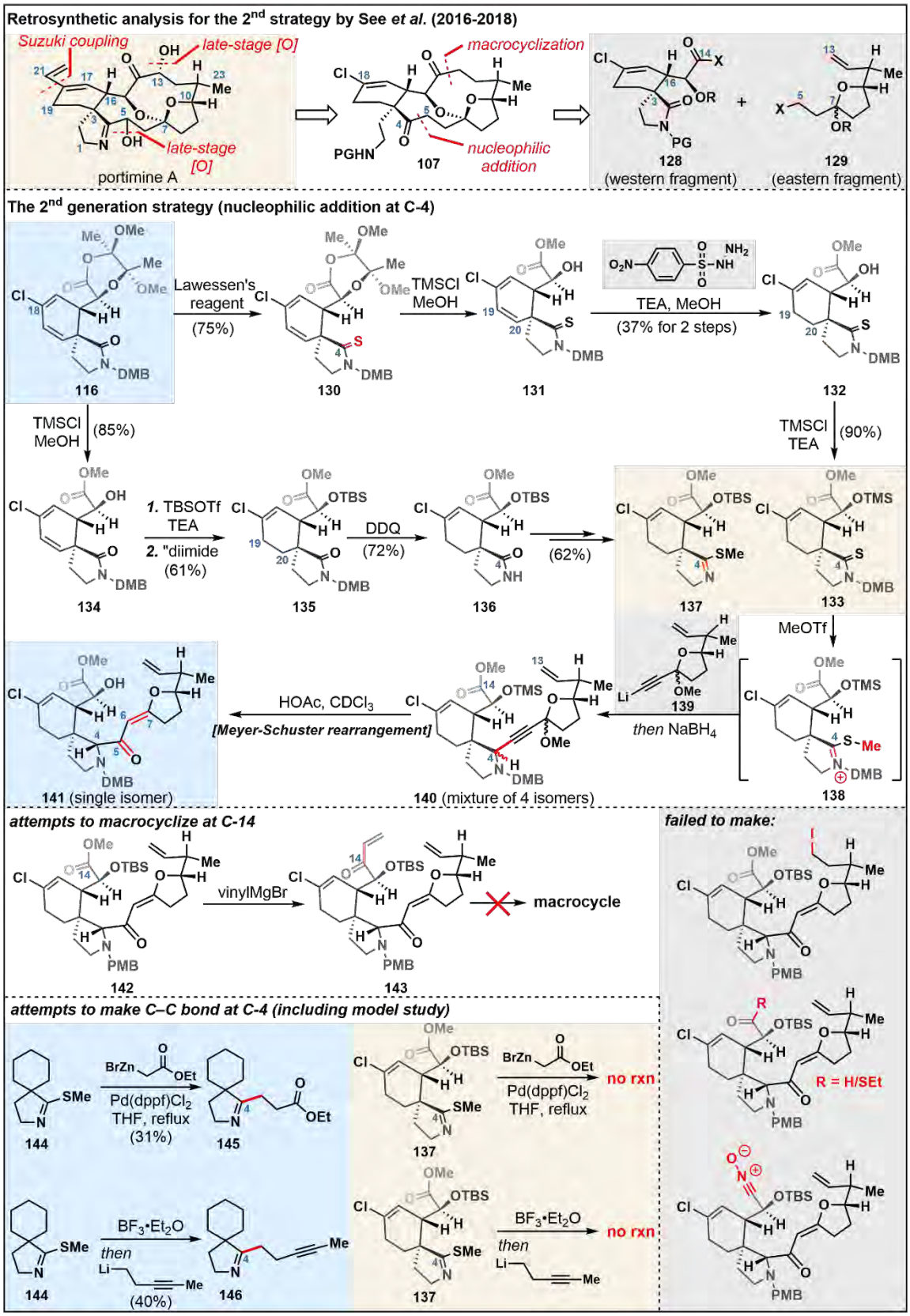


Figure 2.7 The 2nd generation strategy.

Reference

(1) Selwood, A. I.; Wilkins, A. L.; Munday, R.; Shi, F.; Rhodes, L. L.; Holland, P. T. Portimine: a bioactive metabolite from the benthic dinoflagellate *Vulcanodinium rugosum*. *Tetrahedron Lett.* **2013**, *54*, 4705−4707.

(2) Hermawan, I.; Higa, M.; Hutabarat, P. U. B.; Fujiwara, T.; Akiyama, K.; Kanamoto, A.; Haruyama, T.; Kobayashi, N.; Higashi, M.; Suda, S. Kabirimine, a New Cyclic Imine from an Okinawan Dinoflagellate. *Mar. Drugs* **2019**, *17*, 353.

(3) Fribley, A. M.; Xi, Y.; Makris, C.; Alves-de-Souza, C.; York, R.; Tomas, C.; Wright, J. L. C.; Strangman, W. K. Identification of Portimine B, a New Cell Permeable Spiroimine That Induces Apoptosis in Oral Squamous Cell Carcinoma. *ACS Med. Chem. Lett.* **2019**, *10*, 175−179.

(4) Saito, T.; Fujiwara, K.; Kondo, Y.; Akiba, U.; Suzuki, T. Synthesis of the cyclohexene segment of portimine. *Tetrahedron Lett.* **2019**, *60*, 386−389.

(5) Aitken, H. R. M.; Brimble, M. A.; Furkert, D. P. A Catalytic Asymmetric Ene Reaction for Direct Preparation of α-Hydroxy 1,4-Diketones as Intermediates in Natural Product Synthesis. *Synlett*. **2020**, *31*, 687−690.

(6) Freeman, J. L.; Li, F. F.; Furkert, D. P.; Brimble, M. A. Synthetic Studies Towards Spirocyclic Imine Marine Toxins Using N-Acyl Iminium Ions as Dienophiles in Diels-Alder Reactions. *Synlett* **2020**, *31*, 657−671.

(7) Choi, H.; Shirley, H. J.; Aitken, H. R. M.; Schulte, T.; Sohnel, T.; Hume, P. A.; Brimble, M. A.; Furkert, D. P. Intermolecular Diels-Alder Cycloaddition/Cross-Coupling Sequences of 2-Bromo-1,3-butadienes. *Org. Lett.* **2020**, *22*, 1022−1027.

(8) Ding, X. B.; Aitken, H. R. M.; Pearl, E. S.; Furkert, D. P.; Brimble, M. A. Synthesis of the C4-C16 Polyketide Fragment of Portimines A and B. *J. Org. Chem.* **2021**, *86*, 12840−12850.

(9) Li, L.; El Khoury, A.; Clement, B. O.; Wu, C.; Harran, P. G. Asymmetric Organocatalysis Enables Rapid Assembly of Portimine Precursor Chains. *Org. Lett.* **2022**, *24*, 2607−2612.

(10) Li, L. Chain Assembly Tactics for Efficient Syntheses of Callyspongiolide and Portimine. Ph.D. Dissertation, University of California, Los Angeles, CO, 2021.

(11) Parida, B. B.; Das, P. P.; Niocel, M.; Cha, J. K. C-acylation of cyclopropanols: preparation of functionalized 1,4-diketones.*Org. Lett.* **2013**, *15*, 1780−1783.

(12) Gladfelder, J. J. The Direct Asymmetric Alkylation of 2-Alkyl Pyridines and the Total Synthesis of Portimine A. Ph.D. Dissertation, University of California, Santa Barbara, CO, 2022.

(13) See, Y. Y. Synthesis of Highly Oxidized Bioactive Natural Products. Ph.D. Dissertation, The Scripps Research Institute, La Jolla, CO, 2018.

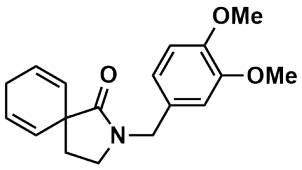
(14) Ley, S. V.; Dixon, D. J.; Guy, R. T.; Rodriguez, F.; Sheppard, T. D. Michael, Michael-aldol and Michael-Michael reactions of enolate equivalents of butane-2,3-diacetal protected glycolic acid derivatives. *Org. Biomol. Chem.* **2005**, *3*, 4095−4107.

(15) Imazaki, Y.; Shirakawa, E.; Ueno, R.; Hayashi, T. Ruthenium-Catalyzed Transformation of Aryl and Alkenyl Triflates to Halides. *J. Am. Chem. Soc.* **2012**, *13*, 14760−14763.

(16) Murai, T.; Toshio, R.; Mutoh, Y. Sequential addition reaction of lithium acetylides and Grignard reagents to thioiminium salts from thiolactams leading to 2,2-disubstituted cyclic amines. *Tetrahedron* **2006**, *62*, 6312−6320.

(17) Koshiba, T.; Miyazaki, T.; Tokuyama, H.; Fukuyama, T. Palladium-Catalyzed Coupling of N-Heteroaryl Sulfides with Organozinc Reagents. *Heterocycles* **2009**, *77*, 233−239.

Experimental

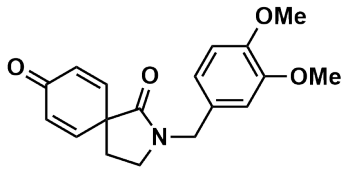


Compound **111**. A flame-dried 3-neck flask charged a mixture of methyl benzoate (13.6 g, 100 mmol) and *t*-BuOH (7.5 g, 101 mmol) was added chilled to -78 °C. Subsequently, liquid NH_3 (ca. 60 ml) was added (via condensation of NH_3 (g) by Dewar condenser) dropwise. The solution was then added sodium metal (2.5 g, 109 mmol) portionwise, and the dark blue mixture was allowed to stir at the same temperature for 1 h.

Meanwhile, a solution of 1,2-dibromoethane (30 ml, 65.1 g, 347 mmol) in THF (30 ml) was prepared under argon and cooled to -78 °C. The solution was then added to the Birch reaction mixture via cannular. The mixture was stirred for 30 min and slowly warmed

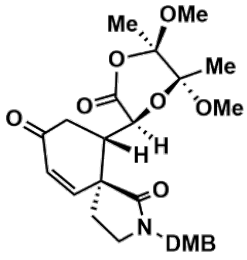
to -33 °C (by removing the dry ice bath) and stirred for another 30 min. Up completion (checked by TLC, 10% Et_2O in hexanes), the mixture was opened to air and added sat. aq. NH_4Cl (100 ml). The mixture was stirred vigorously overnight at room temperature to evaporate the residual ammonia. Upon completion, H_2O (100 ml) was added and the mixture was extracted by EtOAc (3x 100 ml). The combined organic layer was dried over $MgSO_4$ and concentrated. Pure product (22.5 g, 91.8 mmol, 92%) was obtained from chromatography (pure hexanes to 5% EtOAc in hexanes) and used for next step.

The bromide obtained above (1.8 g, 7.3 mmol) was mixed with $DMBNH_2$ (3.7 g, 22.1 mmol) in a 25 ml-microwave vial and purged by argon. The mixture was prestirred in reactor for 20 s and held at 165 °C under microwave for 1 min. The reaction was taken out and diluted by EtOAc (20 ml) and washed by HCl (3x 10 ml, 1 M in H_2O). The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by chromatography (20% EtOAc in hexanes) to yield spirocycle **111** (1.72 g, 5.7 mmol, 78%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.33 – 7.26 (m, 1H), 7.14 (d, *J* = 8.9 Hz, 1H), 6.53 – 6.37 (m, 2H), 5.93 (dd, *J* = 8.3, 5.0 Hz, 2H), 5.69 – 5.49 (m, 2H), 4.45 (s, 2H), 3.80 (s, 6H), 3.26 – 3.19 (m, 2H), 2.84 (d, *J* = 22.9 Hz, 1H), 2.66 (d, *J* = 22.9 Hz, 1H), 1.97 (t, *J* = 6.9 Hz, 1H).



Compound **112**. To a solution of diene **111** (20.0 g, 66.8 mmol) in DCE (400 ml) was added K_2CO_3 (20 g), TBHP (70 ml, 5-6 M in decane), and $Rh_2(cap)_4$ (24 mg, 0.037 mmol) at 0 °C, and stirred for 30 min. Subsequently, the ice bath was removed and the reaction mixture was allowed to warm to room temperature gradually. Upon completion (indicated by TLC, 50% EtOAc in hexanes), the mixture was quenched by sat. aq. $Na_2S_2O_3$ and extracted by DCM (3x 300 ml). The combined mixture was dried over $MgSO_4$ and concentrated. The crude product was added DCM (200 ml) and TEA (20 ml) to convert byproduct (peroxide ether) to desired product (indicated by TLC). Upon completion, the mixture was concentrated again and purified by chromatography (20% EtOAc to 60% EtOAc in hexanes) to yield dienone **112** (20.5 g, 65.5 mmol, 98%).

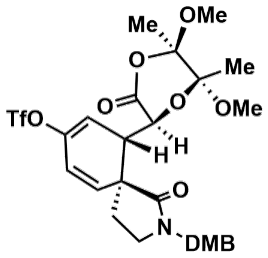
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.15 (m, 1H), 6.79 (d, *J* = 10.0 Hz, 2H), 6.53 – 6.46 (m, 2H), 6.43 (d, *J* = 10.0 Hz, 2H), 4.50 (s, 2H), 3.84 (s, 3H), 3.84 (s, 3H), 3.43 (t, *J* = 6.8 Hz, 2H), 2.28 (t, *J* = 6.8 Hz, 2H).



Compound **113**. To a solution of dienone **112** (10.3 g, 32.9 mmol) and Ley's auxiliary (15.0 g, 49.3 mmol) in DCM (600 ml) was added TBSOTf (11.2 ml, 12.9 g, 48.9 mmol)

dropwise at -78 °C. The mixture was allowed to stir at the same temperature for 2.5 h, and checked by TLC (product should be silyl enol ether). Upon completion, the mixture was quenched by TEA (100 ml, 6% in MeOH) and warmed to room temperature gradually. Subsequently, TBAF (50 ml, 1 M in THF) was added to this mixture and stirred vigorously overnight, and the formation of the enone was monitored by TLC (5% *i*-PrOH in Et_2O). The mixture was then added H_2O (500 ml) and extracted by DCM (3x 500 ml). The organic layer was dried over $MgSO_4$ and concentrated. Crude product was purified by chromatography (1% *i*-PrOH to 5% *i*-PrOH in Et_2O) to afford pure **113** (6.1 g, 12.2 mmol, 37%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.0 Hz, 1H), 6.58 (d, *J* = 10.1 Hz, 1H), 6.50 – 6.44 (m, 2H), 6.04 (d, *J* = 10.1 Hz, 1H), 4.60 (d, *J* = 14.3 Hz, 1H), 4.32 (d, *J* = 14.2 Hz, 1H), 4.12 (d, *J* = 3.1 Hz, 1H), 3.83 (s, 3H), 3.83 (s, 3H), 3.81 (d, *J* = 3.1 Hz, 1H), 3.43 (s, 3H), 3.33 – 3.25 (m, 3H), 3.23 (s, 3H), 2.56 (dt, *J* = 14.2, 7.5 Hz, 1H), 2.42 (dd, *J* = 16.5, 8.4 Hz, 1H), 2.04 (dt, *J* = 12.9, 6.2 Hz, 1H), 1.48 (s, 3H), 1.33 (s, 3H).

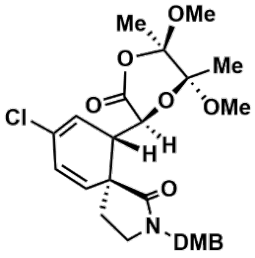


Compound **115**. To a solution of enone **113** (1.56 g, 3.1 mmol) in toluene/THF (35 ml, 6:1 v/v) was added NaHMDS (15.6 ml, 0.6 M in toluene, 9.4 mmol) dropwise at -78 °C. The resulting mixture was stirred for 1.5 h, and $PhNTf_2$ (2.78 g, 7.8 mmol) was added

protionwise. The reaction was stirred for 1 h, and warmed to the ambient temperature for 15 min. Upon completion, sat. aq. $NaHCO_3$ (30 ml) was added to quench the reaction, followed by extraction with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated. Pure triflate **115** (1.01 g, 1.59 mmol, 51%) was obtained by chromatography (10% EtOAc to 50% EtOAc in hexanes).

TLC: R_f = 0.35 (50% EtOAc in hexanes, UV active, $KMnO_4$ staining)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 7.7 Hz, 1H), 6.48 – 6.36 (m, 2H), 5.91 (ddd, *J* = 3.8, 2.2, 0.6 Hz, 1H), 5.86 (dd, *J* = 10.1, 2.1 Hz, 1H), 5.73 (d, *J* = 10.0 Hz, 1H), 4.62 (d, *J* = 14.3 Hz, 1H), 4.21 (d, *J* = 14.3 Hz, 1H), 4.18 (d, *J* = 5.3 Hz, 1H), 3.79 (d, *J* = 0.6 Hz, 6H), 3.78 – 3.74 (m, 1H), 3.43 (s, 3H), 3.26 (s, 3H), 3.23 – 3.11 (m, 2H), 2.45 (dt, *J* = 13.2, 8.2 Hz, 1H), 1.95 – 1.87 (m, 1H), 1.47 (s, 3H), 1.33 (s, 3H).

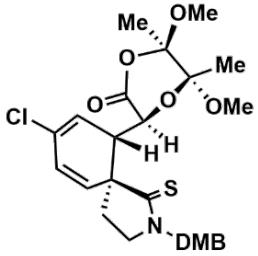


Compound **116**. To a solution of triflate **115** (2.3 g, 3.6 mmol) and $[Cp^*Ru(MeCN)_3]PF_6$ (72 mg, 0.14 mmol) in DMI (12 ml) was added LiCl (200 mg, 4.7 mmol) in one portion. The resulting mixture was heated to 60 °C overnight. Upon completion (indicated by TLC, 8% EtOAc in DCM), the mixture was diluted by brine (10 ml) and extracted by EtOAc (3x 10 ml). The combined organic layer was dried over $MgSO_4$ and concentrated. Pure vinyl

chloride **116** (1.2 g, 2.4 mmol, 67%) was obtained by flash chromatography (50% EtOAc in hexanes).

TLC: R_f = 0.35 (50% EtOAc in hexanes, UV active, $KMnO_4$ staining)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 7.9 Hz, 1H), 6.48 – 6.38 (m, 2H), 5.98 (dd, *J* = 3.8, 1.7 Hz, 1H), 5.84 (dd, *J* = 9.8, 1.7 Hz, 1H), 5.62 (d, *J* = 9.8 Hz, 1H), 4.62 (d, *J* = 14.3 Hz, 1H), 4.21 (d, *J* = 14.3 Hz, 1H), 4.16 (d, *J* = 5.7 Hz, 1H), 3.80 (s, 6H), 3.64 (dd, *J* = 5.7, 3.7 Hz, 1H), 3.46 (s, 3H), 3.25 (s, 3H), 3.23 – 3.13 (m, 2H), 2.47 (dt, *J* = 13.2, 8.2 Hz, 1H), 1.91 (ddd, *J* = 13.0, 7.3, 3.2 Hz, 1H), 1.47 (s, 3H), 1.34 (s, 3H).

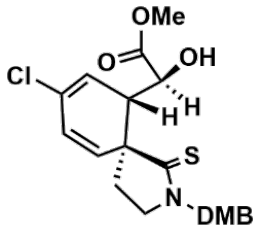


Compound **130**. To a solution of lactam **116** (355 mg, 0.68 mmol) in toluene (25 ml) was added Lawessen's reagent (ca. 700 mg, recrystallized) in one portion. The resulting mixture was heated to reflux and stirred vigorously for 1 h. Upon completion (indicated by TLC, 60% EtOAc in hexanes), the mixture was cooled to 0 °C and filtered through a silica plug. The filtrate was concentrated and purified by flash chromatography (40% EtOAc in hexanes) to afford thiolactam **130** (274 mg, 0.51 mmol, 75%).

TLC: R_f = 0.55 (50% EtOAc in hexanes, extremely UV active, $KMnO_4$ staining)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.3 Hz, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 6.43 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.85 – 5.84 (m, 1H), 5.81 (dd, *J* = 9.8, 1.8 Hz, 1H), 5.69 (d, *J* = 9.8

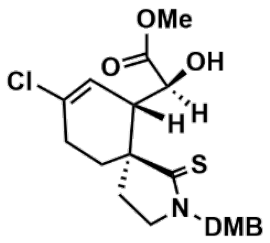
Hz, 1H), 5.06 (d, *J* = 14.2 Hz, 1H), 4.80 (d, *J* = 14.2 Hz, 1H), 4.26 (t, *J* = 3.3 Hz, 1H), 4.00 (d, *J* = 3.3 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.50 (d, *J* = 7.3 Hz, 2H), 3.48 (s, 3H), 3.21 (s, 3H), 2.86 (dt, *J* = 13.4, 7.6 Hz, 1H), 1.92 (dt, *J* = 13.3, 6.5 Hz, 1H), 1.47 (s, 3H), 1.36 (s, 3H).



Compound **131**. To a solution of compound **130** (1.4 g, 2.8 mmol) in MeOH (10 ml) was added TMSCl (2.0 ml) at 0 °C. The resulting mixture was stirred at the same temperature for 1 h. Upon completion, the reaction mixture was poured to a solution of TEA (5 ml) in H_2O (30 ml), followed by extraction with DCM (3x 10 ml). The organic layer was dried over $MgSO_4$ and concentrated. Pure **131** (713 mg, 1.8 mmol, 64%) was obtained by chromatography (20% EtOAc to 30% EtOAc in hexanes).

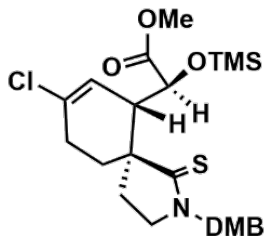
TLC: R_f = 0.48 (30% EtOAc in hexanes, extremely UV active, $KMnO_4$ staining)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 1H), 6.53 – 6.40 (m, 2H), 5.90 – 5.80 (m, 1H), 5.77 – 5.70 (m, 1H), 5.56 (dd, *J* = 9.9, 1.3 Hz, 1H), 5.08 (d, *J* = 14.3 Hz, 1H), 4.91 (d, *J* = 14.3 Hz, 1H), 4.34 (dd, *J* = 10.5, 2.4 Hz, 1H), 4.16 (t, *J* = 10.7 Hz, 1 H), 3.83 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.79 – 3.74 (m, 1H), 3.58 – 3.49 (m, 2H), 2.42 (dt, *J* = 12.7, 9.2 Hz, 1H), 1.97 – 1.88 (m, 1H).



Compound **132**. To a solution of diene **131** (700 mg, 1.7 mmol) in MeOH (2.5 ml) was added *p*-nosyl hydrazine (1.2 g, 5.5 mmol) and TEA (0.95 ml, 0.69 g, 6.8 mmol) at room temperature. The mixture was then heated to 70 °C and stirred for 1 h. The second portion of *p*-nosyl hydrazine (1.2 g, 5.5 mmol) and TEA (0.95 ml, 0.69 g, 6.8 mmol) was added, and the mixture was allowed to stir at the same temperature for another hour. Upon completion (judged by TLC), the mixture was cooled to room temperature, and added sat. aq. NH_4Cl (3 ml). The mixture was then extracted by DCM (3x 5 ml) and dried over $MgSO_4$. After concentration, the crude product was purified by chromatography (pure hexanes to 20% EtOAc in hexanes) to afford **132** (440 mg, 1.1 mmol, 65%) as product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 7.8, 0.9 Hz, 1H), 6.57 – 6.40 (m, 2H), 5.71 (q, *J* = 1.9 Hz, 1H), 5.05 – 5.00 (m, 1H), 4.93 – 4.85 (m, 1H), 3.99 – 3.90 (m, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.86 – 3.81 (m, 1H), 3.82 (s, 3H), 3.80 – 3.74 (m, 1H), 3.64 – 3.56 (m, 1H), 3.55 – 3.45 (m, 1H), 2.88 (d, *J* = 11.2 Hz, 1 H), 2.45 – 2.35 (m, 2H), 2.22 – 2.07 (m, 2H), 1.92 – 1.77 (m, 1H).

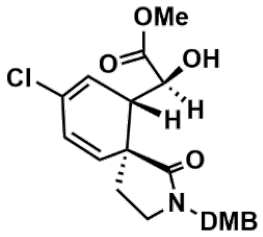


Compound **133**. To a solution of compound **132** (440 mg, 1.0 mmol) in DCM (2.0 ml) was added TMSCl (0.22 ml, 217 mg, 2.0 mmol) and TEA (0.3 ml, 250 mg, 2.5 mmol) at room temperature. The resulting mixture was stirred for 30 min, and added DMAP (5 mg) in one portion. After 1 h, the reaction was quenched by sat aq. $NaHCO_3$ (1 ml) and extracted by DCM (3x 2 ml). The organic layer was dried over $MgSO_4$ and concentrated. Pure TMS-ether **133** (460 mg, 0.90 mmol, 90%) was obtained from flash chromatography (10% EtOAc in hexanes).

TLC: R_f = 0.55 (10% EtOAc in hexanes, UV active, $KMnO_4$ staining)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.1 Hz, 1H), 6.51 – 6.37 (m, 2H), 5.70 (d, *J* = 1.8 Hz, 1H), 5.29 (d, *J* = 14.5 Hz, 1H), 4.40 (d, *J* = 14.5 Hz, 1H), 4.20 (d, *J* = 3.5 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.77 – 3.68 (m, 1H), 3.66 (s, 3H), 3.53 – 3.46 (m, 1H), 3.40 (ddd, *J* = 11.2, 9.4, 4.0 Hz, 1H), 2.45 (ddd, *J* = 12.8, 8.7, 4.0 Hz, 1H), 2.36 (szz, 3H), 1.64 – 1.56 (m, 1H), 1.47 – 1.41 (m, 1H), 0.10 (s, 9H).

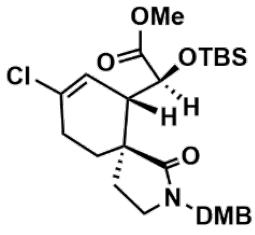
^{13}C NMR (151 MHz, $CDCl_3$) δ 204.6, 172.4, 160.9, 158.9, 131.7, 131.1, 126.1, 116.0, 104.4, 98.6, 73.9, 56.4, 55.6, 52.3, 51.8, 48.0, 46.2, 37.8, 30.1, 26.3, -0.1.



Compound **134**. To a solution of compound **116** (2.1 g, 4.0 mmol) in MeOH (8.0 ml) was added TMSCl (3.2 ml) at 0 °C. The mixture was then allowed to stir for 1 h. Upon completion (monitored by TLC, 50% EtOAc in hexanes), the reaction was quenched by sat. aq. $NaHCO_3$ (20 ml), and extracted by DCM (3x 10 ml). The combined organic phase was dried over $MgSO_4$ and concentrated. Pure **134** (1.35 g, 3.2 mmol, 80%) was obtained by chromatography (20% EtOAc to 50% EtOAc in hexanes).

TLC: R_f = 0.29 (50% EtOAc in hexanes, UV active, $KMnO_4$ staining)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.13 (m, 1H), 6.54 – 6.40 (m, 2H), 5.99 – 5.89 (m, 1H), 5.79 – 5.71 (m, 2H), 4.61 – 4.52 (m, 1H), 4.45 – 4.36 (m, 1H), 4.27 – 4.15 (m, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.63 – 3.51 (m, 1H), 3.29 – 3.14 (m, 2H), 2.70 (d, *J* = 10.5 Hz, 1H), 2.37 (dt, *J* = 12.5, 8.8 Hz, 1H), 1.84 – 1.72 (m, 1H).



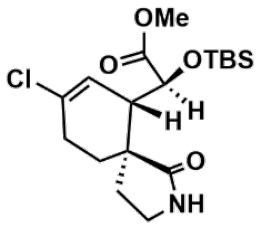
Compound **135**. To a solution of compound **134** (100 mg, 0.24 mmol) in DCM (1.0 ml) was added TEA (0.1 ml) and TBSOTf (0.05 ml) at room temperature. The resulting mixture was stirred at the same temperature for 30 min, and quenched by H_2O (1 ml). Subsequently, the mixture was extracted by DCM (3x 2 ml) and dried over $MgSO_4$. After concentration,

the crude material was purified by chromatography (pure hexanes to 10% EtOAc in hexanes) to give the corresponding silyl ether (120 mg, 0.22 mmol, 92%).

The silyl ether obtained above was dissolved in MeOH (0.6 ml), and added *p*-nosyl hydrazine (121 mg, 0.56 mmol). The mixture was stirred for 2 min, and TEA (0.08 ml) was added. The resulting mixture was heated to reflux and stirred for 1 h. Subsequently, the second portion of *p*-nosyl hydrazine (121 mg, 0.56 mmol) and TEA (0.08 ml) was added. After 1 h, the starting material was fully conversed and the reaction mixture was quenched by H_2O (2 ml) and diluted by Et_2O (2 ml). The mixture was then extracted by Et_2O (3x 2 ml) and dried over $MgSO_4$. After concentration, pure **135** (79 mg, 0.15 mmol, 66%) was obtained by chromatography (10% EtOAc to 20% EtOAc in hexanes).

TLC: R_f = 0.25 (25% EtOAc in hexanes, UV active, $KMnO_4$ staining)

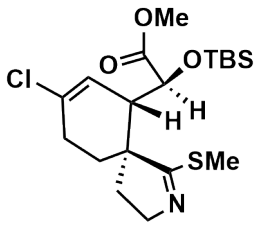
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.9 Hz, 1H), 6.43 (dq, *J* = 5.3, 2.4 Hz, 2H), 5.68 (d, *J* = 2.1 Hz, 1H), 4.69 (d, *J* = 14.6 Hz, 1H), 4.27 (d, *J* = 3.6 Hz, 1H), 4.01 (d, *J* = 14.6 Hz, 1H), 3.79 (s, 3H), 3.79 (s, 3H), 3.68 (s, 3H), 3.28 (td, *J* = 9.2, 4.9 Hz, 1H), 3.22 (t, *J* = 3.0 Hz, 1H), 3.06 (td, *J* = 8.9, 5.8 Hz, 1H), 2.52 (ddd, *J* = 14.0, 8.8, 5.8 Hz, 1H), 2.42 – 2.26 (m, 2H), 1.94 (ddd, *J* = 13.6, 10.4, 6.8 Hz, 1H), 1.61 (dd, *J* = 8.4, 4.8 Hz, 1H), 1.55 – 1.50 (m, 1H), 0.90 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).



Compound **136**. To a solution of DMB-lactam **135** (90 mg, 0.17 mmol) in DCE (0.5 ml) was added DDQ (77 mg, 0.34 mmol) in one portion under argon. The mixture was then added H_2O (0.05 ml) and heated to 90 °C. After 2 h, the reaction was quenched by sat. aq. $NaHCO_3$ (1 ml) and extracted by DCM (3x 2 ml). The organic layer was dried over $MgSO_4$ and concentrated. Pure **136** (50 mg, 0.13 mmol, 76%) was obtained by chromatography (pure Et_2O to 20% EtOAc in Et_2O).

TLC: R_f = 0.10 (60% EtOAc in hexanes, UV active, $KMnO_4$ staining)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (q, *J* = 1.9 Hz, 1H), 5.43 (s, 1H), 4.27 (d, *J* = 4.3 Hz, 1H), 3.70 (s, 3H), 3.46 – 3.38 (m, 1H), 3.27 (td, *J* = 8.6, 6.1 Hz, 1H), 3.15 (tt, *J* = 3.9, 2.4 Hz, 1H), 2.65 (ddd, *J* = 14.4, 8.8, 6.2 Hz, 1H), 2.47 – 2.29 (m, 2H), 1.98 – 1.87 (m, 1H), 1.81 (ddd, *J* = 13.0, 8.2, 4.6 Hz, 1H), 1.67 (ddd, *J* = 13.5, 5.4, 2.9 Hz, 1H), 0.90 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H).

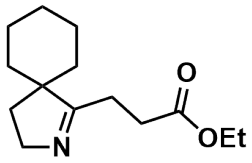


Compound **137**. To a solution of free lactam **136** (39 mg, 0.10 mmol) in toluene (0.5 ml) was added Lawessen's reagent (40 mg, 0.10 mmol, recrystallized) in one portion under argon. The resulting mixture was then allowed to reflux overnight. Upon completion (checked by TLC, 15% EtOAc in DCM), the mixture was filtered through a Celite® plug and concentrated under reduced pressure. The corresponding thiolactam (41 mg, 0.10 mmol, quantitative) was obtained by chromatography (pure DCM to 10% EtOAc in DCM).

The pure thiolactam obtained above was dissolved in acetone (0.5 ml), and added K_2CO_3 (28 mg, 0.20 mmol) and MeI (5 drops) at room temperature. The resulting mixture was stirred overnight. To quench the reaction, Et_2O (1.5 ml) and sat. aq. $NaHCO_3$ (1 ml) was added and the mixture was extracted with EtOAc (3x 2ml). The combined organic layer was dried over $MgSO_4$ and concentrated. Pure **137** (26 mg, 0.062 mmol, 62%) was obtained by PTLC (pure DCM).

TLC: R_f = 0.39 (pure DCM, UV active, $KMnO_4$ staining)

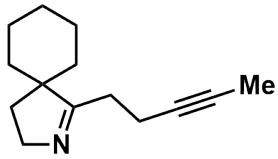
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (dt, *J* = 3.1, 1.7 Hz, 1H), 4.18 (d, *J* = 4.2 Hz, 1H), 3.89 (ddd, *J* = 15.1, 8.4, 5.4 Hz, 1H), 3.78 (ddd, *J* = 15.1, 8.2, 5.7 Hz, 1H), 3.68 (s, 3H), 3.05 (dq, *J* = 4.2, 2.9 Hz, 1H), 2.39 (s, 3H), 2.39 – 2.35 (m, 3H), 2.26 – 2.13 (m, 1H), 1.95 (dt, *J* = 13.2, 7.9 Hz, 1H), 1.77 – 1.62 (m, 2H), 0.88 (s, 8H), 0.03 (s, 3H), 0.03 (s, 3H).



Compound **145**. To a suspension of zinc (1.3 g, 20 mmol) in THF (12 ml) was treated with 1,2-dibromoethane (0.1 ml) in one portion to activate the metal. The mixture was then heated to 65 °C and stirred for 5 min. The solution was then cooled to room temperature, and added TMSCl (0.1 ml), followed by vigorous stirring for 15 min. Upon completion, neat 3-iodoethylacetate (2.28 g, 10 mmol) was added dropwise. The mixture was then allowed to stirred for 18 h, and the concentration of the prepared zinc reagent was determined by titration (I_2 with LiCl) as 0.48 M.

Subsequently, compound **144** (18.3 mmol, 0.1 mmol) was dissolved in toluene (0.5 ml), and added the freshly prepared zinc reagent (0.9 ml, 0.43 mmol) dropwise at room temperature. The mixture was then heated to 90 °C and stirred overnight. After the full conversion of **144** (checked by TLC, 50% EtOAc in hexanes), the reaction was added sat. aq. NH_3 (2 ml) and extracted by EtOAc (3x 2 ml). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Pure **145** (7.5 mg, 0.032 mmol, 31%) was obtained from PTLC (50% EtOAc in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (q, *J* = 7.1 Hz, 2H), 3.72 – 3.63 (m, 2H), 2.70 (t, *J* = 7.2 Hz, 2H), 2.54 – 2.44 (m, 2H), 1.81 (t, *J* = 7.1 Hz, 2H), 1.75 – 1.64 (m, 3H), 1.52 – 1.45 (m, 2H), 1.37 – 1.29 (m, 3H), 1.26 – 1.25 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).



Compound **146**. To a solution of 3-pentynyl iodide (40 mg, 0.21 mmol) in Et_2O (1.0 ml) was added *t*-BuLi (0.23 ml, 1.7 M in pentane, 0.39 mmol) dropwise at -78 °C. The Li-X exchange took place and was allowed to stir for 1.5 h.

Meanwhile, imidoyl sulfide **144** (18.5 mg, 0.10 mmol) was dissolved in Et_2O (0.5 ml) and cooled to -78 °C, followed by treating with BF_3 etherate (14.2 mg, 0.10 mmol). The resulting mixture was stirred for 1 h. Subsequently, the freshly prepared alkyl lithium was added to the imine-BF_3 complex dropwise. The mixture was then stirred for 30 min. Upon completion, the mixture was quenched by sat. aq. $NaHCO_3$ (1 ml) and extracted by DCM (3x 2 ml). The organic layer was dried over $MgSO_4$ and concentrated to give the crude product. Imine **146** (8.1 mg, 0.040 mmol, 40%) was obtained by chromatography (40% EtOAc in hexanes).

TLC: R_f = 0.35 (40% EtOAc in hexanes, $KMnO_4$ staining)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (tt, *J* = 7.2, 2.1 Hz, 2H), 2.47 (ddt, *J* = 8.2, 5.6, 2.3 Hz, 2H), 2.39 (ddq, *J* = 9.2, 4.8, 1.9 Hz, 2H), 1.88 – 1.83 (m, 1H), 1.80 (t, *J* = 7.2 Hz, 2H), 1.76 (t, *J* = 2.5 Hz, 3H), 1.73 – 1.62 (m, 3H), 1.47 – 1.43 (m, 2H), 1.38 – 1.26 (m, 4H).

Chapter 3: Retrosynthesis of portimines and efforts to macrocyclization

Section 3.1 Retrosynthetic analysis in this work

Shortly after I started rerouting this project in March 2020, the COVID-19 pandemic swept the whole country and the lab was lock down. It was unprecedently discouraging since everyone would have to stay at home and work remotely, and doing bench work was prohibited. However, to drive this project and try to survive this formidable molecule, I carefully revisited the data I already had and proposed an entirely new strategy to construct the skeleton as well as the stereocenters in this natural product, several modifications were made and will be discussed in the following sections. This plan ultimately led to the first asymmetric total synthesis of portimine A and B.

The details of the original retrosynthesis are outlined in Figure 3.1. Similar to Yi Yang's strategy, two late-stage oxidations and a Suzuki coupling would take place with the establishment of the macrocycle, targeting **147** as the key intermediate. To determine the key C–C bond to be disconnected on the macrocycle, **147** was displayed as its "hydrated" form **148**, thus C-7 is a ketone now. Inspired by the fact that a carbonyl can be viewed as a "hydrated alkyne", key intermediate **149** was targeted. Therefore, alkyne on C-7/C-8 offered an intuitive site for disconnection that could be reformed by ring-closing alkyne metathesis (RCAM) from a linear dialkynated compound **150**. To arrive at **150**, an alkyl NHK (*1*) was planned to append iodide **151** to aldehyde **152**, the latter could be synthesized from a conjugate addition occurring to chiral cyclohexenone **153** at C-16. To install the stereochemistry at C-15, a strategy using the aforementioned chiral Ley's auxiliary was proposed (Figure 3.1).

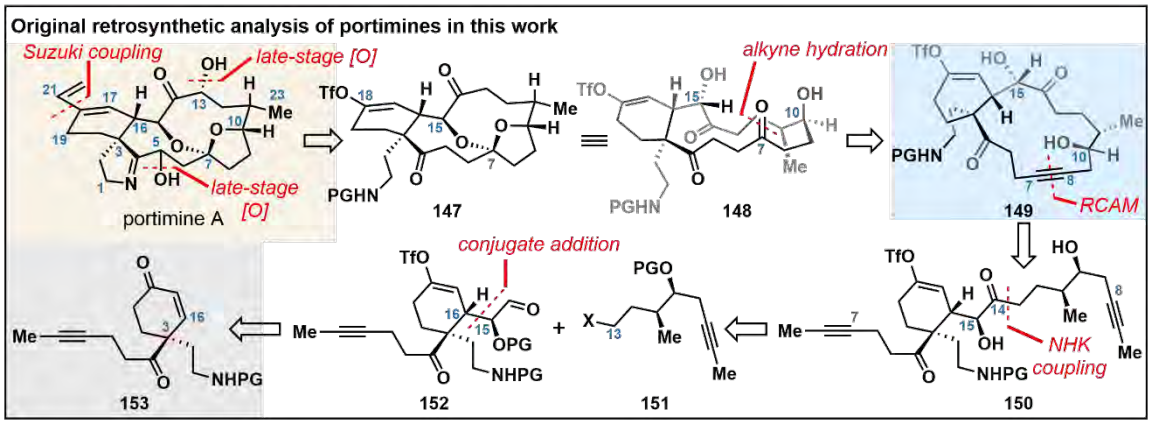


Figure 3.1 Original retrosynthetic analysis of portimine A and B in this work (March 2020).

Section 3.2 Discovery of a spirocycle-controlled conjugate addition

Establishing the chirality at C-3 was regarded as the threshold of the total synthesis, to achieve this, a retrosynthetic analysis based on an asymmetric Diels-Alder was forged and outlined in Figure 3.2. In order to append the alkynated side chain to C-4 without touching the rest of the molecule, C-4 would be oxidized to a highly reactive aldehyde and the primary amine at C-1 should be fully masked by two PGs, suggesting **155** as the key intermediate. In terms of the asymmetric Diels-Alder cycloaddition, an elegant method developed by Rawal *et al.* (*2*) was applied, a quantitative yield, as well as excellent enantioselectivity, can be achieved by mixing acrolein **157** with Rawal's diene **158** in the presence of an impressive cobalt-based catalyst, which can be easily prepared from $Co(OAc)_2$ and salen ligand.

Technical issues were found when trying to scale-up the synthesis of Rawal's diene, brought by the fact that the condensation between the recrystallized **160** and 3-

oxobutyraldehyde dimethylacetal was low-yielding and extremely hard to purify. Therefore, attention was turned to synthesize **161** from carbamation of a conjugate enamine **162**. De facto, **162** could be used as a crude form after its formation from a cross-Michael reaction in methanol. Upon treatment with *n*-BuLi, the generated anion was subsequently quenched by adding methyl chloroformate at -78 °C, delivering **161** in a satisfying yield. To install the TBS group, a silylation taking place in ether was carried out (ether was critical since other solvents such as DCM would lead to a complex mixture), affording Rawal's as a pale-yellow solid, which was directly used for Diels-Alder cycloaddition.

Synthesis of the western fragment commenced with a reductive amination of *p*-anisaldehyde by a commercial amine **163**, followed by a Boc-amide formation, arriving at a fully-protected amine **164** in 85% yield after a single purification. Hydrolysis of the dimethyl acetal under aqueous acetic acid gave aldehyde **165** in a high yield, which was then submitted to an organocatalytic methylenation, to give acrolein **166** in 94% yield. Subsequent asymmetric Diels-Alder using only 1.0 mol% cobalt catalyst smoothly delivered cycloadduct **167** in 92% yield, with perfect enantioselectivity (>95% ee, determined by Mosher's acid). Attempts to dismantle the carbamate auxiliary as well as the TBS group via E1cb were not successful due to the instability of the aldehyde under basic/acidic conditions. To this end, C-4 would have to be reduced to an alcohol by $NaBH_4$, followed by desilylation and E1cb to give compound **168** as the single product in 99% yield. To install the sidechain, C-4 was oxidized back to the aldehyde form and attacked by a freshly made Grignard reagent, to give secondary alcohol, which was used as a crude

form. Subsequent oxidation at C-4 was carried out under DMP, affording **170** as the final product in 85% yield after a single purification.

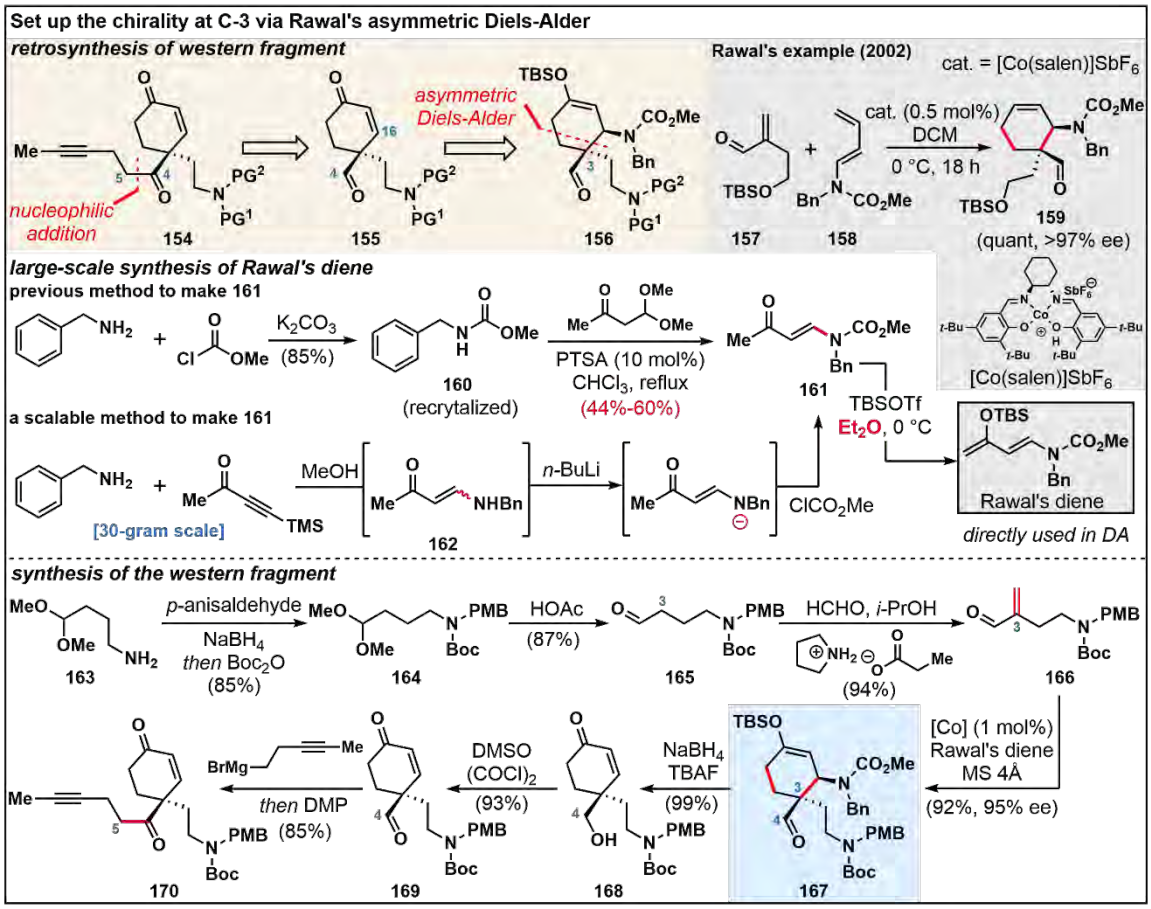


Figure 3.2 An asymmetric Diels-Alder cyclization to establish C-3 chirality.

With this key intermediate **170** in place, the aforementioned strategy utilizing Ley's chiral auxiliary to install C-14/C-15 motif was assessed and the results were outlined in Figure 3.3. Unfortunately, only 1,2-adduct **171** was occasionally observed in screened conditions. To understand this, cyclohexenone, as well as its analog possessing a quaternary center at γ position, were submitted to the conditions for Michael addition. Consistently, cyclohexenone exclusively underwent the 1,4-addition under the Mukaiyama

Michael condition, whereas its dimethyl analog was demonstrated to undergo a 1,2-addition as the major pathway. To our satisfaction, the copper-mediated conjugate addition was found feasible to make a C–C bond at C-15, appending a vinyl group to **170** meanwhile generating an enolate at C-17/C-18, which was triflated by Comins' reagent, to give a **172** as a 7:1 mixture of diastereomers, in 81% yield. To determine the diastereo outcome of this step, **172** was deprotected in a two-step sequence, affording spirocyclic imine **173**. Unfortunately, the NOE correlations in **173** revealed it as the undesired isomer, calling for a modified conjugate addition to revert the innate diastereoselectivity on **170** via chiral ligands or substrates with different geometry.

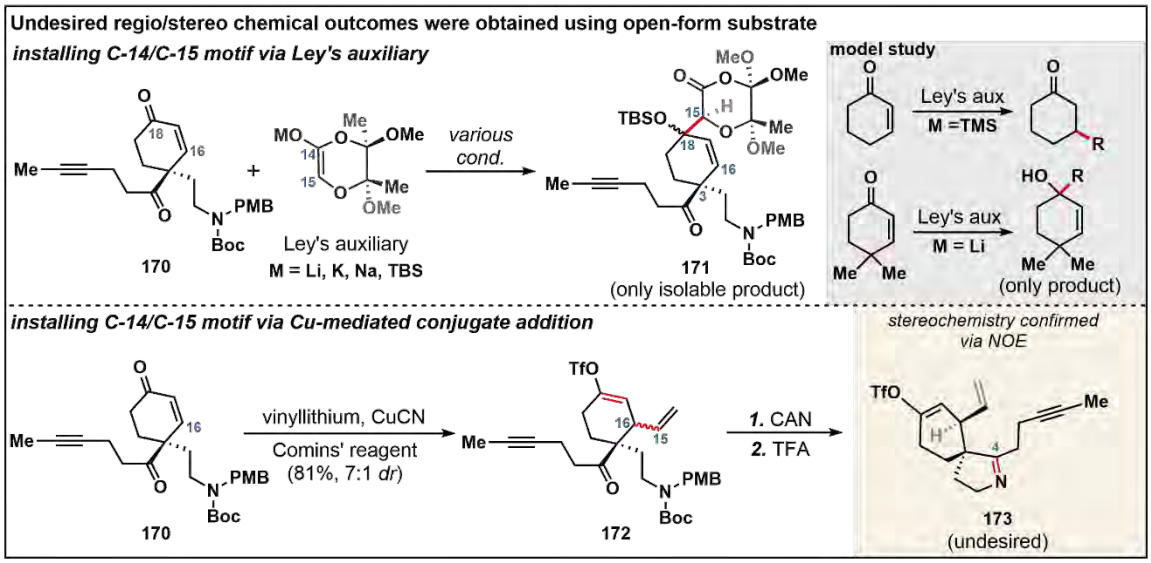


Figure 3.3 Attempts to install C-14/C-15 motif to cyclohexenone 170.

Although it is quite counterintuitive and risky to install the spirocyclic imine motif in portimine A and B at the early stage of the synthesis, attention was turned to this rigidified system since a potential stereochemical control at C-16 was presented, originating from the

blockade of the top face by the alkynyl side chain (Figure 3.4). Attempts to access **174** from **170** were not facile, since Boc deprotection of **170** will not lead to the expected spiro cyclization due to a competitive 5-*exo* aza-Michael addition between PMB-amine and C-16. On the other hand, deprotection of PMB under oxidants (DDQ, CAN, $K_2S_2O_8$, etc.) led to a decomposition. As a result, a single-step full deprotection of the masked amine was required, thereby targeting bis-Boc imide **180**. To access **180**, Boc carbamate **175** was first deprotonated by NaHMDS, followed by quenching with Boc anhydride to give the fully protected amine. The crude mixture was then dissolved in a mixture of acetone and water, treated with PTSA at room temperature, and stirred for 36 h, to afford aldehyde **176** in 90% yield via a single purification. Heating a mixture of formaldehyde, pyrrolidine, propionic acid, and **176** in isopropanol delivered crude **177**, which was used directly for the Diel-Alder reaction. The same condition mentioned above was applied for this transformation, affording cycloadduct **178** in 88% yield and 94% *ee*, which was submitted to $NaBH_4$ and TBAF to undergo an E1cb process, to give **179** in a quantitative yield. Subsequently, C-4 was smoothly oxidized to an aldehyde, followed by a nucleophilic addition and oxidation, to generate **180** in a moderate yield (50%-60%). The relatively lower yield could be explained by the susceptibility of the bis-Boc imide to nucleophiles. Treating **180** with TFA in DCM dismantled both Boc groups in a couple of hours, followed by neutralization, delivering **174** as the major product. Interestingly, a stronger base, as well as a prolonged work-up time, was crucial to get a higher yield (see the work-up method in the grey box in Figure 3.4).

With **174** in hand, copper-mediated conjugate addition was executed under a stronger condition using *n*-Bu_3P as a ligand (*3*, Figure 3.4). Satisfyingly and encouragingly, **183** was isolated as a single product after quenching the enolate **181** with water, and NOE correlation analysis confirmed its configuration as the desired one. As expected, adding Comins' reagent to the THF solution of **181** delivered triflate **182** in 81% yield.

Conclusively, a strategy utilizing the innate geometry of the cyclic imine motif in portimines for stereo control at C-16 was demonstrated here, which paved the way for the subsequent fragment union and macrocyclization.

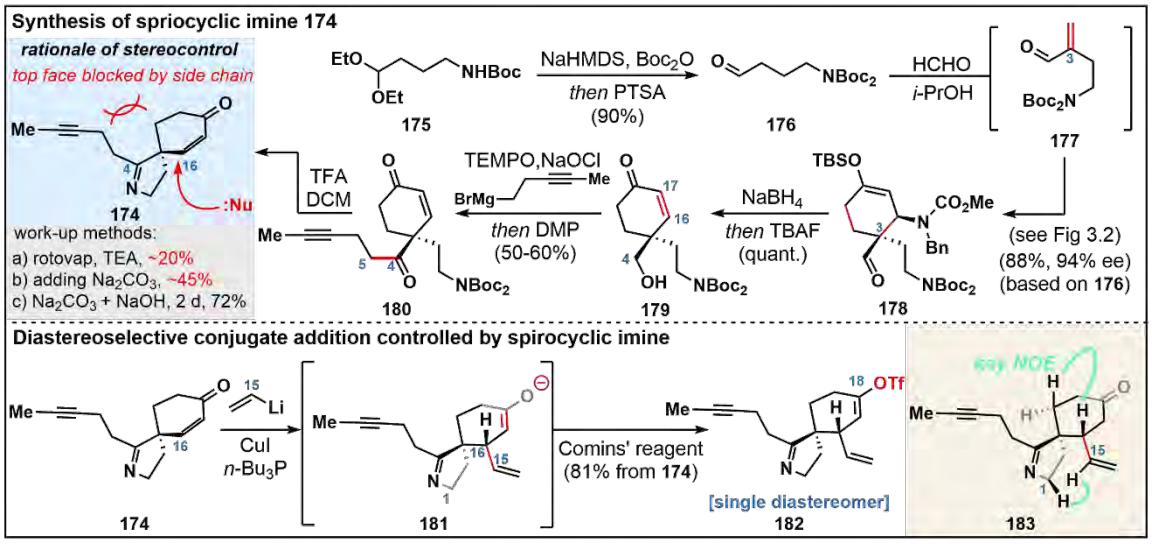


Figure 3.4 Cyclic imine 174 controlled the stereochemical outcome in conjugate addition.

Section 3.3 Attempts to fragment coupling and synthesis of the eastern fragment.

Based on the retrosynthesis shown in Figure 3.1, the method to affix the eastern fragment C-16 onto the spirocyclic imine was based on an alkyl NHK, therefore targeting aldehyde **184**. To this end, **182** was dihydroxylated under osmium-catalyzed/mediated

conditions to give **185** as the major product, along with a small amount of **186**. It is worth mentioning that I failed to determine the stereochemistry of **185** and **186** via NOE due to ambiguity. Nonetheless, the fact that the *dr* could be improved by DHQ-based catalysts and deteriorated by DHQD-based catalysts suggested a desired stereochemical outcome in this transformation. Unfortunately, partially due to the redox sensitivity of the spirocyclic imine, low yields, as well as purification issues were encountered in most conditions (see the grey box in Figure 3.1). For instance, a narrow temperature window and an inconsistent pH dependence were observed, and better result was obtained when using osmate salt instead of OsO_4. Subsequent protection of the generated diol at C-14 and C-15 by two TES groups delivered **187** in a good yield, which could be converted to the corresponding diene **188** under Stille coupling.

All that remained was oxidizing C-14 to aldehyde, which seemed facile since selective oxidation of bis-TES-protected 1,2-diol is well-documented (*4*). Even if the direct oxidation failed, selective deprotection of primary TES ether/TBS ether under milder conditions could circumvent this issue. Surprisingly, **187** was found quite unstable and would immediately decompose under various conditions such as Swern oxidation, TEMPO/TCCA, Cr(VI)-based oxidation, DMP, Ru(IV)-based oxidation, etc. Selective deprotection of TES/TBS had been explored, giving mono-TES/TBS-protected products. But unfortunately, these compounds still underwent decomposition in the presence of oxidants.

The failure to arrive at NHK precursor **184** forced me to come up with a new strategy

aiming at oxidizing C-14/C-15 after macrocyclization, requiring a fragment coupling between **174** and eastern fragment **189** via the aforementioned Cu-mediated conjugate addition, following which a key RCAM took place to construct the macrocycle. The dihydroxylation of C-14 and C-15 would now occur in macrocycle **190**, followed by deprotection, arriving at triol **191** as the product. It was proposed that the construction of the unique ketal system in portimines will be triggered by activating the C-7/C-8 triple bond by an alkynylphilic catalyst such as gold (I) and platinum (II) complex, delivering **192** as the final product (Figure 3.5).

The eastern fragment was featured by its two adjacent stereocenters at C-10 and C-11. This moiety used to be constructed by asymmetric crotylation in Yi Yang's work (Figure 2.6) from a different substrate. Unfortunately, a similar strategy using asymmetric propargylation was perilous due to limited reports as well as known competitive pathways including allenylation (*5*). Perhaps the easiest way to install chiral centers is to buy them. Therefore, an efficient synthesis of eastern fragment **201** was developed, utilizing a six-step chiral pool strategy from commercial (+)-solketal, to deliver **189** in 28% overall yield. This route was outlined in Figure 3.5 and started with an HWE olefination of the freshly prepared **193**, affording acrylate **194** in 59% yield. Subsequently, a reported diastereoselective conjugate addition (*6*) took place at C-11, leading to **195** with the establishment of the C-10/C-11 stereochemistry. To install the alkyne moiety to C-14, this carbon was first reduced to an alcohol by LAH, followed by an Appeal iodination to give iodide **196**. The crude product obtained could directly undergo an S_N2 reaction in the

presence of a lithium acetylide, arriving at **197** as the final product in 75% yield after a single purification. In order to liberate the diol in **197**, the acetonide was dismantled under concentrated HCl. The crude diol would undergo formal dehydration in the presence of tosyl-imidazole and NaH, delivering epoxide **198** smoothly in 87% yield. In order to append the methyl-capped alkyne moiety to C-9, BF_3 etherate was used to activate the epoxide, followed by an addition of propynyllithium under -78 °C. The resulting mixture was then warmed to ambient temperature and added TBAF, liberating the terminal alkyne, to give **200** as the product. The solvents were then removed, and the free hydroxyl group at C-10 was masked by a TBS group, affording **200** in 92% yield after a single purification. Treating the dialkyne **200** with Schwartz's reagent led to a selective hydrozirconation on the terminal alkyne, which was followed by iodination, arriving at the eastern fragment **201** in an excellent yield.

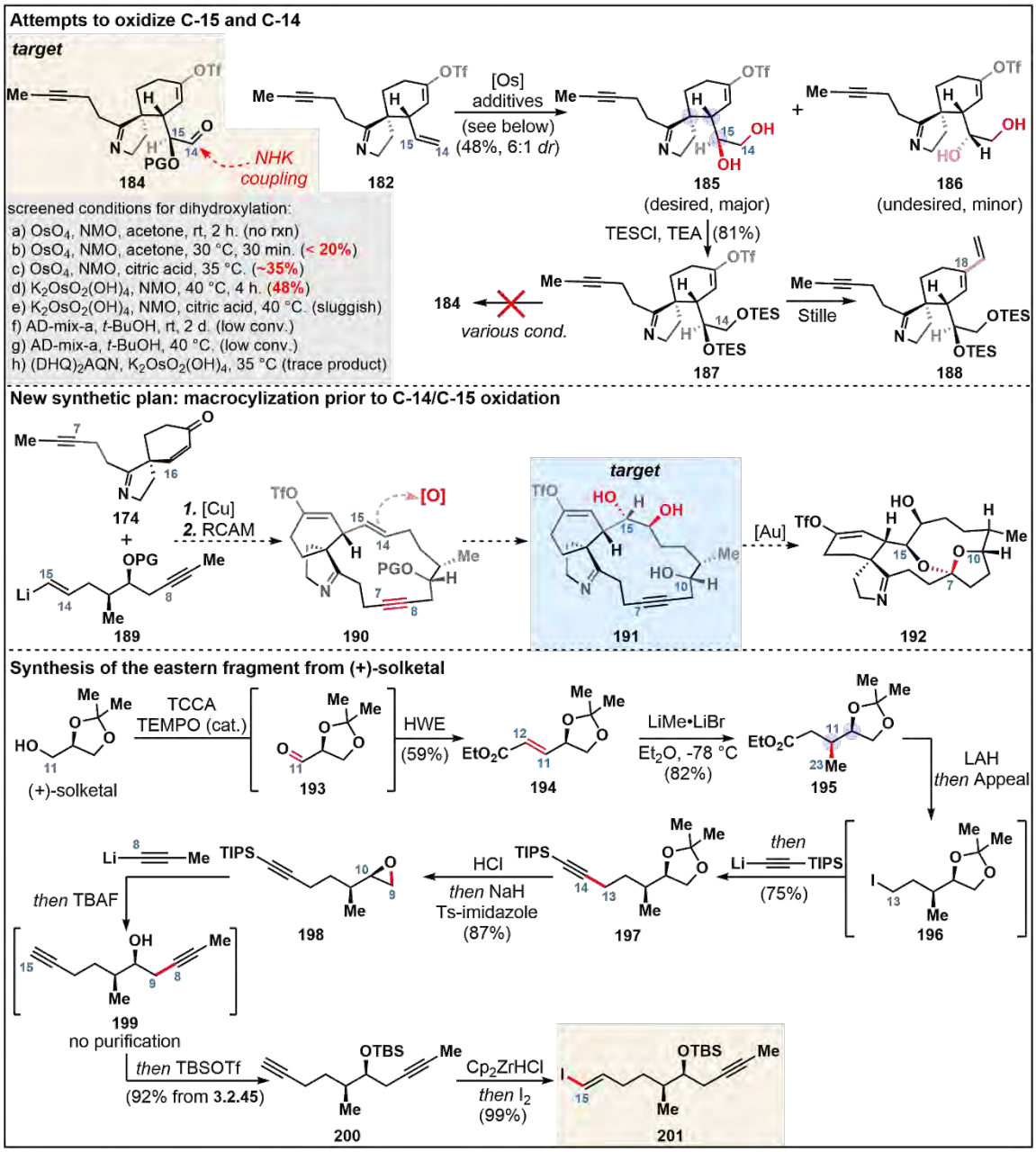


Figure 3.5 Attempts to oxidize C-14/C-15 and synthesis of the eastern fragment.

Section 3.4 Endpoint of the "cyclase phase" — fragment coupling and macrocyclization.

With both fragments in hand, I sought to couple them via the aforementioned Cu-mediated conjugate addition. Surprisingly, the *n*-Pu_3P/CuI system working for simple vinyl

lithium failed to afford any 1,4-adduct on **201** (see screened conditions in Figure 3.5). Fortunately, a special, highly reactive copper (I) acetylide reported by Corey *et al*. (*7*) was capable to deliver **203** in an acceptable yield, yet the majority of the western fragment stayed unreacted. Switching *n*-BuLi to *t*-BuLi significantly increased the reactivity, presumably due to the elimination of deleterious generated alkyl iodide, giving **203** in 70% yield. Switching to other phosphorous-based ligands, such as phosphorous amide or trimethylphosphine led to unsatisfying results. Arrival at **203** was encouraging since all requisite skeletal carbons were in place to arrive at the macrocycle.

Attention was then turned to constructing the 14-membered macrocycle in portimines' skeleton through RCAM, a maneuver that might be derailed by the imine, olefin, or vinyl triflate. Fürstner's extremely efficient, canopy-shaped catalyst, [Mo] (*8*, *9*) was chosen at this point owning to its outstanding reactivity and demonstrated functional compatibility. Satisfyingly, an amazing yield (62%) can be obtained by heating **203** with 15 mol % of the catalyst in toluene. The relatively higher loading, as well as a strict pre-activation of molecular sieves, were essential to reach the yield (Figure 3.5). As expected, the TBS in **204** could be smoothly removed in the presence of PTSA, giving free alcohol **205** in 83% yield. The formation of **204** and **205** was a milestone since it could be viewed as the endpoint of the "cyclase phase" in the total synthesis of portimines, and the installation of five oxygen atoms at C-5, C-7, C-13, C-14, and C-15, would commence afterward.

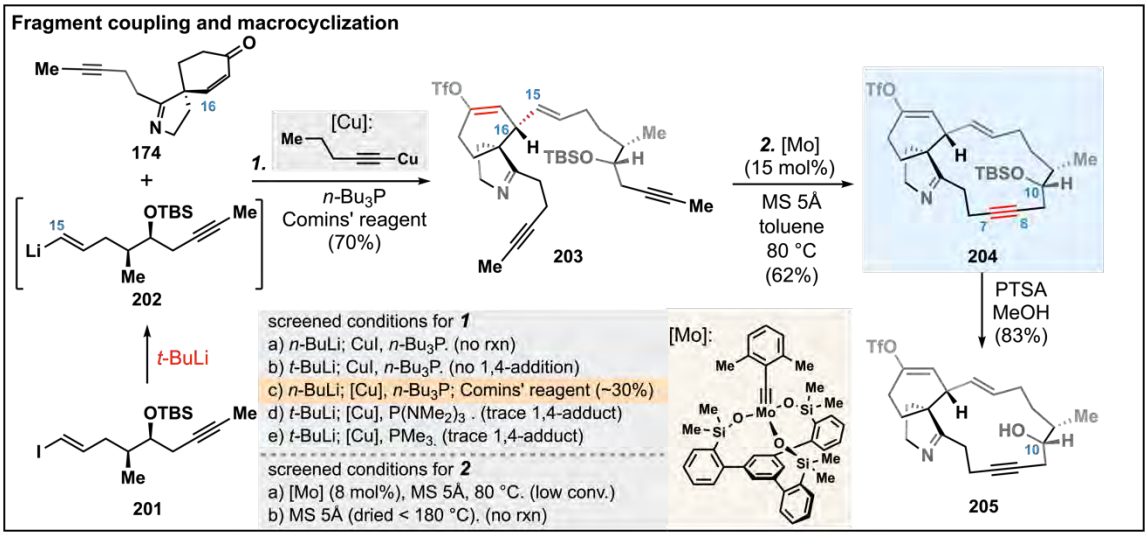


Figure 3.6 Fragment coupling and macrocyclization.

Reference

(1) Takai, K.; Nitta, K.; Fujimura, O.; Utimoto, K. Preparation of Alkylchromium Reagents by Reduction of Alkyl-Halides with Chromium (II) Chloride under Cobalt Catalysis. *J. Org. Chem.* **1989**, *54*, 4732−4734.

(2) Huang, Y.; Iwama, T.; Rawal, V. H. Design and development of highly effective lewis acid catalysts for enantioselective Diels-Alder reactions. *J. Am. Chem. Soc.* **2002**, *124*, 5950−5951.

(3) House, H. O.; Respess, W. L.; Whitesides, G. M. The Chemistry of Carbanions. XII. The Role of Copper in the Conjugate Addition of Organometallic Reagents. *J. Org. Chem.* **1966**, *31*, 3128–3141.

(4) Rodriguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J. J. Selective oxidation of primary silyl ethers and its application to the synthesis of natural products. *Tetrahedron Lett.* **1999**, *40*, 5161−5164.

(5) Xu, D.; Li, Z.; Ma, S. Efficient preparation of highly optically active (S)-(-)-2,3-allenols and (R)-(+)-2,3-allenyl acetates by a clean Novozym-435-catalyzed enzymatic separation of racemic 2,3-allenols. *Chem. Eur. J.* **2002**, *8*, 5012−5018.

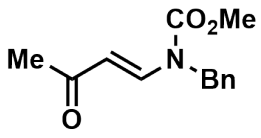
(6) Leonard, J.; Ryan, G.; Swain, P. A. Stereoselective conjugate addition to organolithium reagents to enoates derived from glyceraldehyde acetonide. *Synlett*. **1990**, *10*, 613–614.

(7) Corey, E. J.; Beames, D. J. Mixed Cuprate Reagents of Type R1R2CuLi Which Allow Selective Group Transfer. *J. Am. Chem. Soc.* **1972**, *94*, 7210−7211.

(8) Hillenbrand, J.; Leutzsch, M.; Yiannakas, E.; Gordon, C. P.; Wille, C.; Nothling, N.; Coperet, C.; Fürstner, A. "Canopy Catalysts" for Alkyne Metathesis: Molybdenum Alkylidyne Complexes with a Tripodal Ligand Framework. *J. Am. Chem. Soc.* **2020**, *142*, 11279−11294.

(9) Haack, A.; Hillenbrand, J.; Leutzsch, M.; van Fastel, M.; Neese, F.; Fürstner, A. Productive Alkyne Metathesis with “Canopy Catalysts” Mandates Pseudorotation. *J. Am. Chem. Soc.* **2021**, *143*, 5643–5648.

Experimental



Compound **161**. To a solution of $BnNH_2$ (30.6 g, 286 mmol) in MeOH (200 mL) at 0 °C was added 4-(trimetylsilyl)-3-butyn-2-one (21.6 mL, 143 mmol) dropwise. After stirring

for 1.0 h at rt, the solvent was removed in vacuo. The crude product was suspended in EtOAc (200 ml) and rinsed by aq. sat. NaH_2PO_4 (200 ml) to remove benzylamine. The organic layer was separated and the aqueous phase was extracted with EtOAc(3x 200 ml). The combined organic layer was dried over $MgSO_4$, and concentrated under reduced pressure to give the crude enamine, which was directly used for next step.

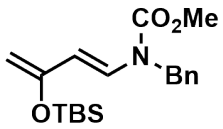
The crude enamine obtained above was dissolved in THF (10 ml/g), and and *n*-BuLi (2.5 M, 60 ml, 150 mmol) was added at 0 °C under argon over 30 min. After 10 min, $ClCO_2Me$ (11.6 ml, 14.2 g, 150 mmol) was added slowly, and the solution was stirred for 2 h. Upon completion, the mixture was poured into H_2O (500 ml). The mixture was extracted with EtOAc (3x 200 ml), and dried over $MgSO_4$. **161** (27.9 g, 120 mmol, 84%) can be obtained by chromatography (0-40% EtOAc in hexanes).

TLC: R_f = 0.28 (30% EtOAc in hexanes, UV active, $KMnO_4$ staining)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 14.4 Hz, 1H), 7.36 – 7.03 (m, 5H), 5.50 (d, *J* = 14.4 Hz, 1H), 4.76 (s, 2H), 3.84 (s, 3H), 2.13 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 197.3, 154.6, 142.0, 135.4, 129.0 (2C), 127.3 (2C), 126.6, 110.0, 54.6, 48.4, 27.7.

HRMS (ESI-TOF): calc'd for $C_{13}H_{15}NO_3$ $[M+H]^+$: 234.1125, found: 234.1126



Rawal's diene. The pure compound **161** (52 g, 223 mmol) was dissolved in Et_2O (650 ml) under argon. To this solution, TEA (45.5 g, 450 mmol) was added in one portion at -78 °C.

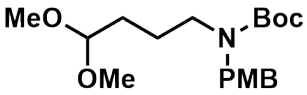
TBSOTf (59.5 g, 225 mmol) was dropped into this solution slowly. A cloudy mixture was generated during addition. After stirring at -78 °C for 30 min, the flask was gradually warmed to 0 °C for another 30 min. The reaction was quenched by a mixture of hexanes (200 ml) and sat. aq. $NaHCO_3$ (500 ml), followed by extraction with hexanes (3x 400 ml). The organic phase was dried over $MgSO_4$, and concentrated to give Rawal's diene (purity was determined by NMR, used directly for next step).

TLC: R_f = 0.43 (hexanes+1% TEA, UV active, $KMnO_4$ staining)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.42 (m, 1H), 7.32 (t, *J* = 7.3 Hz, 2H), 7.27 – 7.13 (m, 3H), 5.36 (d, *J* = 14.1 Hz, 2H), 4.80 (s, 2H), 4.13 (s, 1H), 4.07 (s, 1H), 3.83 (s, 3H), 1.00 (s, 9H), 0.18 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.1, 154.5, 136.9, 128.8 (2C), 127.3 (2C), 126.7, 126.3, 108.4, 93.0, 53.8, 48.2, 25.9 (3C), 18.4, -4.5 (2C).

HRMS (ESI-TOF): calc'd for $C_{19}H_{29}NO_3Si$ $[M+H]^+$: 348.1990, found: 348.1986



Compound **164**. To a solution of *p*-anisaldehyde (42.0 g, 308 mmol) in DCM (200 mL) was added $MgSO_4$ (50 g) and 4-aminobutyraldehyde dimethyl acetal (41 g, 308 mmol) dropwise (open flask). The resulting mixture was allowed to stir at ambient temperature for 2 h.

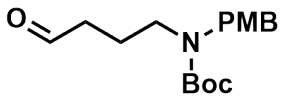
The formation of the imine was monitored by NMR. Upon completion, the solvents were removed via rotovap, and the residue was dissolved in MeOH (300 ml). Subsequently,

$NaBH_4$ (12.6 g, 333 mmol) was added portionwise, and the resulting mixture was allowed to stir at room temperature for 30 min. The progress of the imine reduction could be monitored by NMR. After the completion, the reaction was quenched by H_2O (300 ml) and extracted with DCM (3x 200 ml). The organic phase was dried over $MgSO_4$, and concentrated to give the crude amine.

The crude PMB-amine was then dissolved in a mixture of DCM (200 ml) and H_2O (100 ml), followed by adding NaOH (8.4 g, 210 mmol) at room temperature. Boc_2O (65 g, 297 mmol) was added to this mixture with vigorous stirring. The reaction was then allowed stirred overnight at the same temperature, and quenched by adding sat. aq. NH_4Cl (200 ml) and DCM (100 ml). The mixture was extracted by DCM (3x 150 ml), and the combined organic phase was dried over $MgSO_4$ and concentrated. Pure **164** (87 g, 245 mmol, 79%) was obtained by flash chromatography (10% EtOAc in hexanes).

TLC: R_f = 0.42 (20% EtOAc in hexanes, slightly UV active)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (s, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.42 – 4.25 (m, 3H), 3.80 (s, 3H), 3.29 (s, 6H), 3.23 – 3.07 (m, 2H), 1.60 – 1.51 (m, 4H), 1.50 – 1.40 (m, 9H).

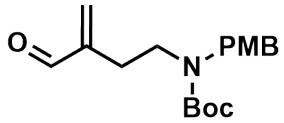


Compound **165**. To a solution of dimethyl acetal **164** (87 g, 245 mmol) in acetone/H_2O (1 L, 4:1 v/v) was added PTSA (10 g, 52 mmol) at room temperature in one portion. The mixture was then heat to reflux for 2 h, and cooled down. The reaction was quenched by sat. aq. $NaHCO_3$ (300 ml), and extracted by DCM (3x 300 ml). The combined organic

phase was dried over $MgSO_4$ and concentrated. Pure **165** (65.5 g, 213 mmol, 87%) was obtained by flash chromatography (20% EtOAc in hexanes).

TLC: R_f = 0.33 (20% EtOAc in hexanes, slightly UV active, $KMnO_4$ staining)

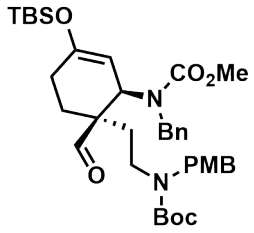
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.16 (s, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.41 – 4.30 (m, 2H), 3.82 – 3.76 (m, 3H), 3.25 – 3.09 (m, 2H), 2.40 (s, 2H), 1.80 (s, 2H), 1.47 (s, 9H).



Compound **166**. To a solution of aldehyde **165** (100 mg, 0.33 mmol) in *i*-PrOH (0.3 ml) was added formaldehyde (37 wt% in H_2O, 0.026 ml), pyrrolidine (1 drop), and propionic acid (1 drop) at room temperature. The mixture was allowed to stir at 50 °C for 3 h. Upon completion, the mixture was diluted with H_2O (1 ml), and extracted with DCM (3x 1 ml). The combined organic phase was dried over $MgSO_4$ and concentrated. Pure **166** (82 mg, 0.26 mmol, 79%) was obtained by flash chromatography (15% EtOAc in hexanes).

TLC: R_f = 0.38 (20% EtOAc in hexanes, UV active, $KMnO_4$ staining)

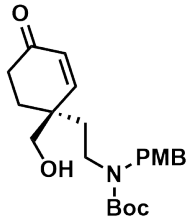
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.18 (s, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.32 – 6.14 (m, 1H), 5.99 (s, 1H), 4.40 – 4.28 (m, 2H), 3.80 (s, 3H), 3.33 – 3.15 (m, 2H), 2.52 – 2.40 (m, 2H), 1.47 (s, 9H).



Compound **167**. To a solution of acrolein **166** (3.0 g, 9.40 mmol) in DCM (30 ml) was added [Co(salen)]SbF_6 (156 mg, 0.19 mmol), MS 4Å (2.5 g). The mixture was then cooled to 0 °C, and stirred vigorously. After 10 min, Rawal's diene (4 g, 11.5 mmol) was added to this dark green mixture portionwise. The reaction mixture was allowed to stir at the same temperature overnight. Upon completion, the mixture was filtered through a pad of Celite, and the resulting clear solution was concentrated. Pure **167** (5.9 g, 8.85 mmol, 94%) was obtained by chromatography (5% EtOAc to 15% EtOAc in hexanes).

TLC: R_f = 0.40 (20% EtOAc in hexanes, UV active, $KMnO_4$ staining)

^{1}H NMR contains rotamers.

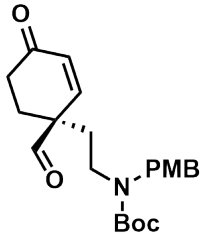


Compound **168**. To a solution of DA-adduct **167** (5.5 g, 8.25 mmol) in MeOH (10 ml) was added $NaBH_4$ (400 mg, 10. 6 mmol) in one portion. The resulting mixture was stirred vigorously at room temperature for 1 h, and checked by TLC (20% EtOAc in hexanes). Upon completion, TBAF (1 M in THF, 20 ml) was added to the solution via syringe. The desilylation took place and completed in 12 h. The reaction was quenched by adding sat. aq. NH_4Cl (10 ml) and extracted by DCM (3x 10 ml). The combined organic phase was

dried over $MgSO_4$ and concentrated. Pure **168** (82 mg, 0.26 mmol, 79%) was obtained by chromatography (10% to 40% EtOAc in hexanes).

TLC: R_f = 0.44 (40% EtOAc in hexanes, UV active, $KMnO_4$ staining)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.1 Hz, 2H), 6.86 (d, *J* = 8.1 Hz, 2H), 6.74 (s, 1H), 5.95 (d, *J* = 10.3 Hz, 1H), 4.35 (s, 2H), 3.80 (s, 3H), 3.62 (s, 1H), 3.51 (d, *J* = 11.2 Hz, 1H), 3.27 – 3.09 (m, 2H), 3.01 – 2.91 (m, 1H), 2.48 – 2.40 (m, 1H), 2.40 – 2.31 (m, 1H), 1.87 – 1.63 (m, 4H), 1.48 (s, 9H).

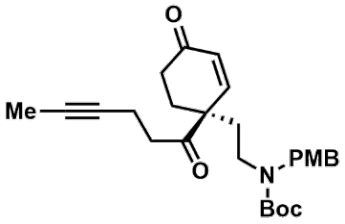


Compound **169**. To a solution of alcohol **168** (2.9 g, 7.45 mmol) in DCM (20 ml) was added DMP (3.16 g, 7.45 mmol) at room temperature, followed by adding solid $NaHCO_3$ (5 g). The resulting mixture was stirred vigorously at the same time for 1 h. Upon completion, the mixture was quenched by adding H_2O (10 ml) and sat. aq. $Na_2S_2O_3$ (10 ml). The resulting mixture was stirred at room temperature for 1 h, giving a clear biphasic mixture. Subsequently, the mixture was extracted by DCM (3x 10 ml) and dried over $MgSO_4$. After concentration, pure **169** (2.67 g, 6.90 mmol, 93%) was obtained by flash chromatography (20% EtOAc in hexanes).

TLC: R_f = 0.57 (30% EtOAc in hexanes, UV active, $KMnO_4$ staining)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.47 (s, 1H), 7.14 (s, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.82 – 6.64 (m, 1H), 6.11 (d, *J* = 10.3 Hz, 1H), 4.40 – 4.19 (m, 2H), 3.80 (s, 3H), 3.31 – 2.97 (m,

2H), 2.43 (dd, *J* = 8.9, 5.5 Hz, 2H), 2.29 – 2.17 (m, 1H), 1.92 (s, 3H), 1.48 (s, 9H).



Compound **170**. To a suspension of LiCl (651 mg, 15.3 mmol) and magnesium (411 mg, 17.1 mmol) in THF (12 ml) was added 3-pentynyl bromide (2.06 g, 14 mmol) in THF (2 ml) dropwise under argon. After initiation with a piece of I_2, the resulting mixture was heated to reflux for 2 h, and cooled down to ambient temperature. The freshly prepared Grignard reagent was obtained as 0.44 M (titrated with I_2)

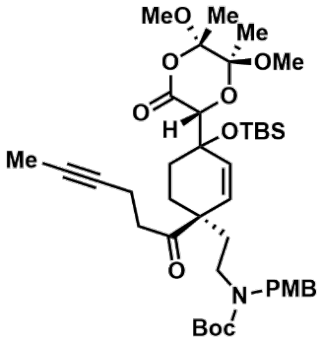
Meanwhile, a solution of aldehyde **169** (2.7 g, 6.97 mmol) in THF (20 ml) was prepared and cooled to -78 °C. The aforementioned Grignard reagent (17 ml) was added to the solution under argon dropwise, and the reaction mixture was allowed to stir at the same temperature for 2 h. Upon completion, sat. aq. NH_4Cl (20 ml) was added to quench the reaction, and the flask was allowed to warm to room temperature gradually. The mixture was then extracted by EtOAc (3x 20 ml), dried over $MgSO_4$, and concentrated. After removal of the solvents, crude product was obtained and directly used for the next step.

The crude alcohol obtained was dissolved in DCM (10 ml) and added solid $NaHCO_3$ (3 g). Subsequently, DMP (3.39 g, 8.0 mmol) was added protionwise to this suspension. The reaction was allowed to stir at room temperature for 1 h, and quenched by a mixture of H_2O (5 ml) and sat. aq. $Na_2S_2O_3$ (10 ml). The resulting mixture was stirred vigorously for 1 h, and diluted with H_2O (10 ml), followed by extraction with DCM (3x 20 ml). The

organic phase was dried over $MgSO_4$ and concentrated. Pure **170** (2.3 g, 0.51 mmol, 73%) was obtained by chromatography (5% to 15% EtOAc in hexanes).

TLC: R_f = 0.40 (20% EtOAc in hexanes, UV active, $KMnO_4$ staining)

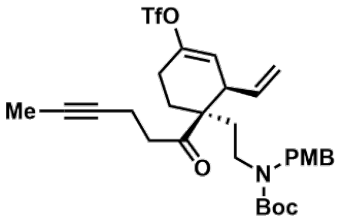
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (s, 2H), 7.00 (s, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.05 (d, *J* = 10.3 Hz, 1H), 4.32 (d, *J* = 14.5 Hz, 1H), 4.25 – 4.20 (m, 1H), 3.80 (s, 3H), 3.30 – 2.89 (m, 2H), 2.62 (d, *J* = 27.5 Hz, 2H), 2.42 – 2.30 (m, 4H), 1.97 – 1.73 (m, 4H), 1.71 (t, *J* = 2.5 Hz, 3H), 1.47 (s, 9H).



Compound **171**. To a solution of enone **170** (22 mg, 0.049 mmol) in DCM (0.5 ml) was added Ley's auxiliary TBS ketene acetal (30 mg, 0.099 mmol) in one portion under argon. The resulting mixture cooled to -78 °C, subsequently, TBSOTf (0.05 ml, 0.22 mmol) was added to this mixture at the same time. The reaction was allowed to stir for 1 h, and quenched by adding TBAF at room temperature. The mixture was then added H_2O (1 ml) and extracted with DCM (3x 2 ml). The organic phase was dried over $MgSO_4$ and concentrated. Compound **171** (15 mg, 0.020 mmol, 41%) was isolated by PTLC (25% EtOAc in hexanes).

TLC: R_f = 0.46 (20% EtOAc in hexanes, slightly UV active, $KMnO_4$ staining)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (s, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.90 (d, *J* = 9.4 Hz, 1H), 5.78 (s, 1H), 4.30 (s, 1H), 3.98 (s, 1H), 3.79 (s, 3H), 3.36 (s, 3H), 3.22 (s, 3H), 3.03 – 2.78 (m, 1H), 2.71 – 2.50 (m, 1H), 2.37 – 2.18 (m, 2H), 2.12 (ddd, *J* = 13.8, 7.6, 3.2 Hz, 1H), 2.04 (s, 6H), 1.72 (t, *J* = 2.5 Hz, 3H), 1.71 – 1.61 (m, 4H), 1.51 – 1.39 (m, 9H), 0.82 (s, 9H), 0.11 – -0.04 (m, 6H).



Compound **172**. A suspension of CuCN (57.8 mg, 0.65 mmol) in THF (0.5 ml) was treated with MeLi (0.9 ml, 1.6 M in ether, 1.44 mmol) at 0 °C under argon. Subsequently, the ice bath was removed, and the mixture was allowed to stir at ambient temperature for 10 min.

Meanwhile, a solution of tributyl(vinyl)tin (0.38 ml, 456 mg, 1.44 mmol) in THF (0.5 ml) was added dropwise to the freshly cupurate solution at room temperature. The transmetalation step was allowed to process at room temperature for 1.5 hr.

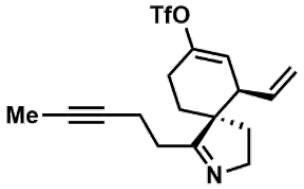
Upon completion, the solution containing vinyl cupurate was cooled to -78 °C, and a solution of enone **170** (200 mg, 0.44 mmol) in THF (1 ml) was added dropwise. The reaction mixture was allowed to stir at the same temperature for 1.5 h, followed by an addition of Comins' reagent (251 mg, 0.64 mmol) at -45 °C. The triflation took place and was completed in 12 h. The mixture was then quenched by H_2O (5 ml) and extracted by EtOAc (3x 10 ml). The combined organic layer was dried over $MgSO_4$ and concentrated. Compound **172** (220 mg, 0.36 mmol, 82%) was isolated by chromatography (hexanes to

15% EtOAc in hexanes).

TLC: R_f = 0.67 (20% EtOAc in hexanes, slightly UV active, $KMnO_4$ staining)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19 – 7.05 (m, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.57 (s, 1H), 5.50 (t, *J* = 8.5 Hz, 1H), 5.16 – 5.12 (m, 1H), 5.09 (d, *J* = 17.0 Hz, 1H), 4.46 – 4.08 (m, 2H), 3.79 (s, 3H), 2.97 (s, 2H), 2.58 (d, *J* = 30.9 Hz, 0H), 2.43 – 2.11 (m, 4H), 2.04 – 1.95 (m, 1H), 1.94 – 1.78 (m, 2H), 1.73 (t, *J* = 2.6 Hz, 3H), 1.68 – 1.58 (m, 1H), 1.53 – 1.40 (m, 9H).

^{13}C NMR contains rotamers.



Compound **173**. To a solution of compound **172** (20 mg, 0.033 mmol) in MeCN/H_2O (1 ml, 4:1 v/v) was added crystalline CAN (18 mg, 0.033 mmol) in one portion at 0 °C. The mixture was then stirred at the same temperature for 20 min and checked by TLC (30% EtOAc in hexanes). Upon completion, H_2O (1 ml) was added to dilute the mixture, and the resulting mixture was extracted with EtOAc (3x 1 ml). The combined organic layer was dried over $MgSO_4$ and concentrated. The crude product was used directly for the next step.

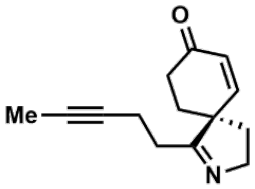
The crude Boc carbamate obtained above was dissolved in $CDCl_3$ (0.2 ml) and added TFA (0.05 ml) dropwise at room temperature. Subsequently, the mixture was stirred for 30 min. Upon completion, the mixture was quenched by adding NaOH (4 M). The mixture was then extracted by DCM (3x 1 ml) and dried over $MgSO_4$. After concentration, **173** (5.7

mg, 0.015 mmol, 45%) was obtained by PTLC (40% EtOAc in hexanes).

TLC: R_f = 0.40 (40% EtOAc in hexanes, UV active, $KMnO_4$ staining)

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.76 (ddd, *J* = 17.1, 10.2, 8.0 Hz, 1H), 5.64 (dt, *J* = 5.4, 1.4 Hz, 1H), 5.27 (dd, *J* = 10.0, 1.2 Hz, 1H), 5.14 (d, *J* = 17.0 Hz, 1H), 3.92 (dd, *J* = 15.5, 8.7 Hz, 1H), 3.85 – 3.76 (m, 1H), 2.95 (t, *J* = 6.7 Hz, 1H), 2.55 (q, *J* = 11.7 Hz, 2H), 2.51 – 2.41 (m, 3H), 2.38 – 2.29 (m, 1H), 2.16 (ddd, *J* = 13.2, 9.9, 6.9 Hz, 1H), 2.03 (ddd, *J* = 12.6, 7.1, 1.9 Hz, 1H), 1.84 – 1.78 (m, 1H), 1.76 (t, *J* = 2.4 Hz, 3H), 1.62 – 1.57 (m, 1H).

^{1}H-^{1}H-NOESY was available.



Compound **174**. To a solution of compound **180** (8.8 g, 20.3 mmol) in DCM (62.8 ml) was added TFA (31.4 ml) at rt. The resulting red solution was stirred for 1.5 h at the same temperature. The reaction mixture was added carefully (via dropping funnel) to a mixture of Na_2CO_3 (64 g, in 120 ml H_2O) and 4 M NaOH (24 ml), then stirred vigorously for 36 h. The mixture was extracted with Et_2O (for the first time, 100 ml) and DCM (5x 50 ml). The organic layer was dried over $MgSO_4$, and was concentrated under reduced pressure. The crude product was purified by chromatography (Et_2O to 5% MeOH +1% TEA in Et_2O) to yield compound **174** (3.14 g, 14.6 mmol, 72%).

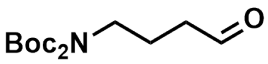
TLC: R_f = 0.37 (pure EtOAc, highly UV active, $KMnO_4$ staining)

$[\alpha]^{25}_D$: -155.8 (*c* = 0.5, $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.62 (dd, *J* = 10.1, 1.6 Hz, 1H), 6.05 (d, *J* = 10.1 Hz, 1H), 3.96 (dddt, *J* = 16.0, 8.6, 3.8, 1.9 Hz, 1H), 3.81 (dtt, *J* = 15.6, 7.6, 2.4 Hz, 1H), 2.58 – 2.48 (m, 4H), 2.48 – 2.34 (m, 2H), 2.20 – 2.09 (m, 2H), 1.96 (dddd, *J* = 13.0, 8.7, 7.7, 1.0 Hz, 1H), 1.86 (dtd, *J* = 13.5, 4.9, 1.7 Hz, 1H), 1.75 (t, *J* = 2.5 Hz, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 198.3, 178.0, 152.0, 129.7, 78.4, 76.2, 58.3, 55.7, 35.4, 35.2, 30.1, 29.3, 16.0, 3.7.

HRMS (ESI-TOF): calc'd for $C_{14}H_{17}NO$ $[M+H]^+$: 216.1388, found: 216.1382



Compound **176**. To a solution of 4-aminobutyraldehyde diethyl acetal (32.2 g, 200 mmol) in DCM (200 mL), was added Boc_2O (43.8 g, 201 mmol) dropwise at rt. The reaction was monitored by TLC (stain: 1% ninhydrin in ethanol). Upon completion, the solvent was removed under reduced pressure, and the residue was dissolved in THF (200 mL) at 0 ºC under argon. To this solution, NaHMDS (0.6 M in toluene, 400 ml, 240 mmol) was added dropwise with vigorous stirring. The resulting solution was kept stirring at the same temperature, followed by a slow addition of Boc_2O (43.8 g, 201 mmol). After completion, sat. aq. NH_4Cl (500 ml) was added and stirred overnight. The organic layer was separated, while the aqueous layer was extracted with Et_2O (3x 300 ml). The combined organic layer was dried over $MgSO_4$, followed by concentration to give the crude Boc-imide as product.

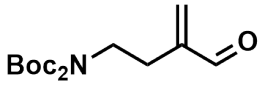
The crude carbamate obtained above was dissolved in acetone/H_2O (4:1, 500 ml). PTSA monohydrate (14.0 g, 73.6 mmol) was added and stirred at rt for 16 h. The mixture

was neutralized with sat. aq. $NaHCO_3$ (500 ml) and extracted with Et_2O (3x 300 ml). The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by chromatography (5% EtOAc in hexanes to 15% EtOAc in hexanes) to afford **176** (51.7 g, 90%) as colorless oil.

TLC: R_f = 0.41 (25% EtOAc in hexanes, $KMnO_4$ staining)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.74 (t, *J* = 2.2 Hz, 1H), 3.58 (t, *J* = 7.2 Hz, 2H), 2.43 (t, *J* = 7.2 Hz, 2 H), 1.86 (quin, *J* = 7.2 Hz, 2H), 1.47 (s, 18H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 201.6, 152.7 (2C), 82.6 (2C), 45.5, 41.1, 28.1(6C), 21.6.

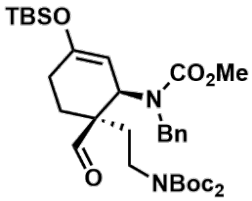


Compound **177**.

TLC: 0.45 (25% EtOAc in hexanes, UV active, $KMnO_4$ staining)

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.51 (s, 1H), 6.24 (s, 1H), 6.00 (s, 1H), 3.68 (t, *J* = 7.1 Hz, 2H), 2.52 (t, *J* = 7.1 Hz, 2H), 1.48 (s, 16H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 194.0, 152.5 (2C), 147.3, 135.2, 82.5 (2C), 44.8, 28.2 (6C), 27.9.



Compound **178**. To a mixture of aqueous formaldehyde solution (13 ml, 37% formaldehyde in water) and **176** (46.8 g, 162.9 mmol) in *i*-PrOH (95 mL) were added propionic acid (1.20 g, 16.2 mmol, 0.1 eq.) and pyrrolidine (1.15 g, 16.2 mmol, 0.1 equiv.). The reaction mixture

was stirred at 55 °C for 1.0 h. Upon completion, sat. aq. $NaHCO_3$ (20 ml) and brine (100 ml) was added, and the mixture was extracted with Et_2O (3x 100 ml). The combined organic layer was dried over $MgSO_4$, and concentrated in vacuo to remove all volatiles. The crude acrolein (**177**) obtained was directly used for Diels-Alder cycloaddition.

177 was dissolved in DCM (200 mL), followed by adding MS4Å (25 g, dried in oven overnight, 110 °C) and Rawal's diene (70.5 g, 10.7 mmol, 1.2 equiv.) under argon. After stirring the mixture at 0 °C for 15 min, [Co(salen)]SbF_6 (984 mg, 1.63 mmol, 0.01 equiv.) was added in one portion. The reaction mixture was stirred at 0 °C and allowed to warm up to rt overnight. Upon completion, silica gel (ca. 150 g) was added. After concentration in vacuo, the crude was purified with chromatography (dry loading, 0-20% EtOAc in hexanes) to afford **178** (92.7 g, 143.3 mmol, 88%).

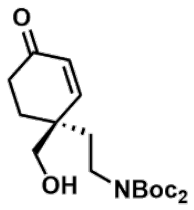
TLC: R_f = 0.35 (20% EtOAc in hexanes, UV active, $KMnO_4$ staining)

$[\alpha]^{25}_D$: -55.4 (c = 1.0, $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 9.89-9.59 (m, 1H), 7.28 – 7.24 (m, 2H), 7.21 – 7.14 (m, 1H), 7.14 – 6.98 (m, 2H), 5.12 – 4.75 (m, 1H), 4.59 (d, J = 5.7 Hz, 1H), 4.52 (d, J = 16.4 Hz, 1H), 4.37 (d, J = 16.4 Hz, 1H), 3.79 – 3.47 (m, 4H), 3.40 – 3.30 (m, 1H), 2.23 – 2.02 (m, 3H), 2.01 – 1.83 (m, 2H), 1.63 – 1.56 (m, 1H), 1.51 (s, 18H), 0.83 (s, 9H), -0.04 (s, 3H), -0.13 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 204.8, 158.2, 155.7, 152.2, 152.1, 139.5, 128.3 (2C),126.7, 126.2, 126.1, 99.4, 82.8, 57.4, 53.0, 48.1, 42.2, 30.9, 29.8, 28.3 (6C), 25.8, 25.6 (3C), 22.8, 20.3, 18.0, -4.7 (2C).

HRMS (ESI-TOF): calc'd for $C_{34}H_{54}N_2O_8Si$ $[M+H]^+$: 647.3728, found: 647.3736



Compound **179**. To a solution of compound **178** (81.4 g, 126 mmol) in a mixture of MeOH (400 ml) and DCM (100 ml) was added $NaBH_4$ (4.7 g, 124 mmol) portionwise at 0 °C. The reaction was kept stirring for 1 h, and was quenched by sat. aq. NH_4Cl (300 ml). The mixture was extracted with DCM (3x 400 ml) and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure to afford the crude product, which was directly used for next step.

The crude product was dissolved in THF (500 ml), and added TBAF (130 ml, 1.0 M in THF). The reaction mixture was stirred for 30 min, and quenched by sat. aq. NH_4Cl (200 ml). The mixture was extracted with DCM (3x 300 ml) and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure. The crude product was purified by chromatography (30% EtOAc in hexanes to 80% EtOAc in hexanes) to yield compound **179** (46 g, 126 mmol, quantitative yield).

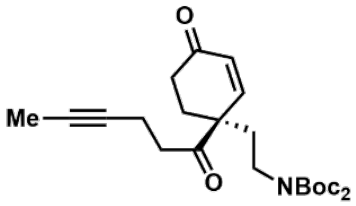
TLC: R_f = 0.25 (30% EtOAc in hexanes, UV active, $KMnO_4$ staining)

$[\alpha]^{25}_D$: +37.8 (*c* = 1.0, $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.82 (d, *J* = 10.2 Hz, 1H), 6.01 (d, *J* = 10.2 Hz, 1H), 3.71 – 3.61 (m, 3H), 3.56 (d, *J* = 11.6 Hz, 1H), 2.93 (t, *J* = 6.4 Hz, 1H), 2.55 – 2.38 (m, 2H), 1.95 – 1.76 (m, 4H), 1.51 (s, 18H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 199.3, 154.3, 152.8 (2C), 129.5, 83.2 (2C), 66.8, 42.0, 40.3, 33.9, 33.1, 28.4, 28.2 (6C).

HRMS (ESI-TOF): calc'd for $C_{19}H_{31}NO_6$ $[M\text{-}Boc+2H]^+$: 270.1705, found: 270.1704



Compound **180**. To a solution of **179** (16.1 g, 43.6 mmol) in DCM (60 ml) was added $NaHCO_3$ (15 g) and water (50 ml). The resulting mixture was added KBr (539 mg, 4.5 mmol) and TEMPO (68 mg, 0.44 mmol) at rt (open air). The reaction was cooled to 0 °C, and a solution of NaOCl (6 wt%, 105 ml) was added slowly at the same temperature. The reaction mixture turned red immediately, and the ice bath was removed. The reaction mixture was quenched by sat. aq. $Na_2S_2O_3$ (100 ml), and extracted with DCM (3x 200 ml). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The product (ca. 16 g) was used directly to next step without purification.

To a suspension of Mg powder (3.1 g,129 mmol) and LiCl (6.0 g, 141 mmol) in THF (29 ml), DIBAL-H (1.3 ml, 1.0 M in toluene) was dropwise subsequently under argon at 0 °C.

Meanwhile, a solution of 3-pentynyl bromide (19.0 g, 129 mmol, in 72.8 ml THF) was prepared at rt. A small portion of this stock solution (8.7 ml) was added to the above suspension at 0 °C to initiate the Grignard reaction. After 15 min, the rest of the stock solution was added slowly. The residual bromide was rinsed by THF (3x 10 ml). The

reaction mixture was stirred vigorously at 0 °C for 30 min and warmed up to rt for an extra 30 min. The Grignard reagent was obtained as 0.54 M (theo. 0.95 M) indicated by titration with I_2 in THF.

To a solution of the freshly-made aldehyde (16 g, 43.6 mmol, in 320 ml THF) at -78 °C was added the freshly-prepared Grignard reagent (110 ml, 59.4 mmol) dropwise in 1 h (under argon). The reaction mixture was kept stirring at the same temperature for an extra hour, and AcOH (10 ml) was added to quench the reaction. The resulting solution was warmed up to rt gradually, followed by adding brine (250 ml) and sat. aq. $NaHCO_3$ (50 ml) The mixture was extracted with EtOAc (4x 400 ml) and dried over $MgSO_4$. The obtained organic phase was concentrated under reduced pressure to obtain the crude product, which was used in next step without purification.

The crude product obtained from Grignard addition was dissolved in DCM (100 ml, open air), and cooled to 0 °C. Solid $NaHCO_3$ (10 g) was added to the solution, followed by adding Dess-Martin periodinane (19.0 g, 44.8 mmol). The reaction mixture was warmed to rt. After 1 h, the reaction mixture was diluted with DCM (ca. 50 ml), and was quenched by sat. aq. $Na_2S_2O_3$ (90 ml) and sat. aq. $NaHCO_3$ (150 ml). The resulting mixture was kept stirring for 45 min. The mixture was extracted with DCM (3x 100 ml) and dried over $MgSO_4$. The organic phase was concentrated under reduced pressure. The crude product was purified by chromatography (5% EtOAc in hexanes to 20% EtOAc in hexanes) to yield compound **180** (11.3 g, 26.1 mmol, 60%).

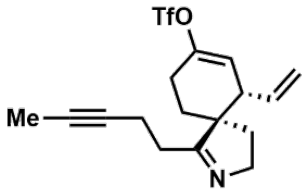
TLC: R_f = 0.60 (30% EtOAc in hexanes, UV active, $KMnO_4$ staining)

$[\alpha]^{25}_{D}$: -32.2 (*c* = 1.0, $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.01 (d, *J* = 10.3 Hz, 1H), 6.09 (d, *J* = 10.3 Hz, 1H), 3.60 – 3.45 (m, 2H), 2.81 – 2.68 (m, 2H), 2.54 – 2.35 (m, 5H), 2.06 – 1.93 (m, 3H), 1.72, (s, 3H), 1.50 (s, 18H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 207.5, 198.3, 152.4 (2C), 150.1, 130.6, 83.0 (2C), 77.6, 76.6, 52.4, 42.1, 38.8, 36.5, 34.8, 29.8, 28.3 (6C), 13.6, 3.6.

HRMS (ESI-TOF): calc'd for $C_{24}H_{35}NO_6$ $[M+Na]^+$: 456.2362, found: 456.2350



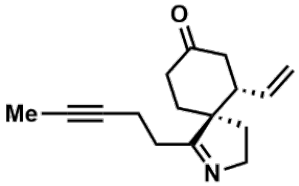
Compound **182**. To a suspension of copper iodide (836 mg, 4.39 mmol) in THF (15 ml) was added *n*-Bu_3P (1.97 ml, 7.83 mmol) dropwise under argon at room temperature, and then cooled to -78 °C. Subsequently, vinyllithium (5.5 ml, 0.8 M, 4.4 mmol, prepared from PhLi and tetravinylstannane) was added to this solution dropwise, and stirred at the same temperature for 30 min. A solution of compound **174** (630 mg, 2.93 mmol) in THF (2 ml) was added to the freshly prepared organocopper reagent slowly at -78°C. The mixture was allowed to stir at the same temperature for 1 h, and monitored by TLC (30% EtOAc in DCM). Upon completion, Comins' reagent (1.80 g, 4.58 mmol) was added in one portion, and the mixture was warmed to ambient temperature gradually by removing the dry ice bath. The reaction was quenched by H_2O (10 ml), followed by extraction by EtOAc (3x 20 ml). The combined organic layer was dried over $MgSO_4$, and concentrated under reduced

pressure. Pure compound **182** (761 mg, 2.03 mmol, 69%) was obtained by chromatography (10% EtOAc to 40% EtOAc in hexanes).

TLC: R_f = 0.42 (50% EtOAc in hexanes, $KMnO_4$ staining)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.73 (d, *J* = 2.6 Hz, 1H), 5.63 (ddd, *J* = 17.3, 10.4, 7.1 Hz, 1H), 5.16 (dt, *J* = 10.4, 1.0 Hz, 1H), 5.10 (dt, *J* = 17.2, 1.2 Hz, 1H), 3.93 – 3.76 (m, 1H), 3.58 (dt, *J* = 15.9, 8.0 Hz, 1H), 3.20 (s, 1H), 2.60 – 2.51 (m, 2H), 2.43 (s, 4H), 2.09 – 1.98 (m, 1H), 1.93 (ddd, *J* = 12.4, 8.4, 3.3 Hz, 1H), 1.76 (t, *J* = 2.5 Hz, 3H), 1.68 – 1.54 (m, 2H).

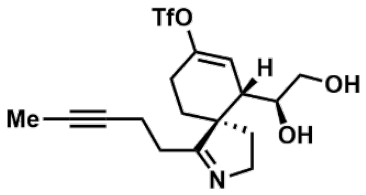
^{13}C-NMR (126 MHz, $CDCl_3$) δ 177.8, 149.2, 134.8, 119.5, 118.1, 78.8, 76.1, 58.7, 56.5, 43.9, 31.5, 29.9, 28.9, 25.5, 15.9, 3.7. (CF_3 is missing in the carbon NMR).



Compound **183**.

TLC: R_f = 0.55 (40% EtOAc in DCM, $KMnO_4$ staining)

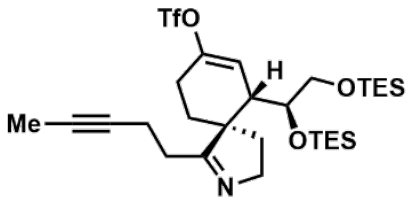
^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.59 (ddd, *J* = 17.0, 10.5, 6.4 Hz, 1H), 5.10 (dt, *J* = 10.5, 1.2, 1.2 Hz, 1H), 5.04 (dt, *J* = 17.1, 1.3, 1.3 Hz, 1H), 3.91 (dddd, *J* = 15.7, 8.4, 4.2, 1.7 Hz, 1H), 3.82 – 3.72 (m, 1H), 2.76 – 2.68 (m, 1H), 2.59 – 2.53 (m, 2H), 2.49 – 2.44 (m, 2H), 2.42 (ddd, *J* = 9.8, 6.6, 3.8 Hz, 3H), 2.38 – 2.31 (m, 1H), 2.12 (ddd, *J* = 13.7, 9.1, 5.1 Hz, 1H), 2.01 (td, *J* = 13.5, 13.5, 4.9 Hz, 1H), 1.88 (ddd, *J* = 13.0, 9.2, 6.0 Hz, 1H), 1.79 – 1.72 (m, 4H).



Compound **185**. To a solution of compound **182** (29 mg, 0.077 mmol) in acetone/H_2O (0.5ml, 4:1 v/v) was added $K_2OsO_2(OH)_4$ (1.0 mg, 0.0027 mmol) and NMO (0.06 ml, 50 wt% in H_2O) at 40 °C. The reaction mixture was then stirred for 4 h, and quenched by sat. aq. $NaHSO_3$ (0.2 ml) at room temperature. The resulting biphasic mixture was extracted with DCM (3x 2 ml). The combined organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. Pure compound **185** (15 mg, 0.036 mmol, 48%) was obtained by chromatography (pure EtOAc to 1% TEA in EtOAc).

TLC: R_f = 0.35 (pure EtOAc, $KMnO_4$ staining)

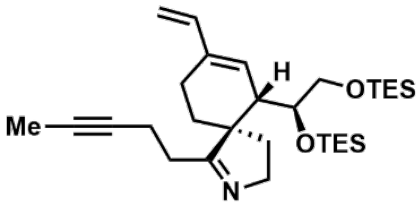
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.6 (s, 1H), 3.8 – 3.7 (m, 2H), 3.7 – 3.6 (m, 2H), 3.5 (dd, *J* = 11.5, 5.1 Hz, 1H), 3.0 (br s, 2H), 2.9 (dd, *J* = 7.9, 3.6 Hz, 1H), 2.6 – 2.4 (m, 4H), 2.3 – 2.2 (m, 1H), 2.0 (dt, *J* = 13.8, 7.3 Hz, 1H), 1.9 (td, *J* = 12.3, 6.8 Hz, 1H), 1.8 – 1.7 (m, 5H), 1.7 – 1.6 (m, 1H).



Compound **187**. Diol **185** (50.1 mg, 0.12 mmol) and imidazole (25 mg, 0.37 mmol) was dissolved in DCM (0.5 ml) under argon at room temperature. To this solution, TESCl (0.06 ml, 55 mg, 0.37 mmol) was added dropwise. The resulting solution was stirred at the

ambient temperature for 1 h, and quenched by adding H_2O (1 ml). The mixture was then extracted by DCM (3x 1 ml) and dried over $MgSO_4$. After concentration, pure **187** (63 mg, 0.10 mmol, 93%) was obtained by chromatography (pure hexanes to 30% EtOAc in hexanes).

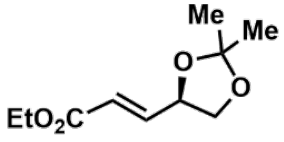
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (s, 1H), 3.86 – 3.69 (m, 2H), 3.65 – 3.54 (m, 3H), 2.93 (s, 1H), 2.61 (dd, *J* = 16.8, 7.7 Hz, 1H), 2.54 – 2.42 (m, 3H), 2.42 – 2.35 (m, 1H), 2.31 (dd, *J* = 16.5, 8.3 Hz, 1H), 1.98 (dt, *J* = 12.9, 8.2 Hz, 1H), 1.83 (td, *J* = 12.0, 6.3 Hz, 1H), 1.76 (t, *J* = 2.5 Hz, 3H), 1.65 (ddd, *J* = 12.6, 7.9, 4.3 Hz, 1H), 1.57 – 1.49 (m, 1H),1.00 – 0.85 (m, 18H), 0.66 – 0.50 (m, 12H).



Compound **188**. To a solution of triflate **187** (120 mg, 0.19 mmol) in THF (1.0 ml) was added $Pd(PPh_3)_4$ (11 mg, 0.009 mmol), LiCl (25 mg, 0.6 mmol), and tributyl(vinyl)tin (71 mg, 0.22 mmol) under argon at room temperature. The resulting mixture was allowed to stir at 80 °C for 1 h. Upon completion, the mixture was quenched by adding K_2CO_3 (30 mg) and H_2O (1 ml) to remove the generated stannane chloride. After vigorous stirring for 1 h, the mixture was extracted with DCM (3x 2 ml). The combined organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. Pure compound **188** (45 mg, 0.087 mmol, 46%) was obtained by chromatography (pure EtOAc).

TLC: R_f = 0.40 (pure EtOAc, UV active, $KMnO_4$ staining)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.11 (d, *J* = 17.4 Hz, 1H), 4.97 (d, *J* = 10.7 Hz, 1H), 3.85 – 3.66 (m, 2H), 3.65 – 3.51 (m, 3H), 2.81 (s, 1H), 2.71 – 2.59 (m, 1H), 2.53 (s, 2H), 2.39 – 2.24 (m, 2H), 2.23 – 2.09 (m, 1H), 1.94 (dt, *J* = 13.0, 8.1 Hz, 1H), 1.76 (t, *J* = 2.5 Hz, 3H), 1.75 – 1.67 (m, 1H), 1.67 – 1.59 (m, 3H), 0.99 – 0.93 (m, 18H), 0.64 – 0.51 (m, 12H).



Compound **194**. To a solution of (*S*)-solketal (50.0 g, 378 mmol) in EtOAc (500 ml) was added NaOAc (37 g, 451 mmol) and 4-NHAc-TEMPO (0.81 g, 3.8 mmol) under argon. TCCA (35 g, 151 mmol) was added by portions at 0 °C. The mixture was stirring at the same temperature for 1.5 h, then filtered through a Büchner funnel. The residue was rinsed with EtOAc, and the resulting filtrate was added water (190 ml), K_2CO_3 (157 g, 1.14 mol), and triethyl phosphonoacetate (81.5 ml, 92.1 g, 411 mmol) at 0 °C. The reaction mixture was stirred overnight at rt, and a mixture of Et_2O (200 ml) and water (100 ml) was added. The organic layer was separated and the aqueous phase was extracted with Et_2O (3x 200 ml). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure (100 mbar, 25 °C). The residue was purified by chromatography (20% Et_2O in pentane) to yield compound **194** (44.8 g, 224 mmol, 59%).

TLC: R_f = 0.40 (10% EtOAc in hexanes, UV active, $KMnO_4$ staining)

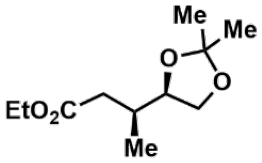
$[\alpha]^{25}_D$: -36.4 (*c* = 1.0, $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.88 (dd, *J* = 15.6, 5.6 Hz, 1H), 6.10 (dd, *J* = 15.6, 1.4 Hz,

1H), 4.66 (tdd, *J* = 7.0, 5.6, 1.4 Hz, 1H), 4.26 – 4.14 (m, 3H), 3.68 (dd, *J* = 8.3, 7.0 Hz, 1H), 1.48 – 1.43 (m, 3H), 1.41 (d, *J* = 0.8 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 166.3, 144.8, 122.7, 110.4, 75.1, 69.0, 60.8, 26.6, 25.9, 14.4.

HRMS (ESI-TOF): calc'd for $C_{10}H_{16}O_4$ $[M+Na]^+$: 223.0941, found: 223.0942



Compound **195**. To a solution of compound **194** (21.0 g, 104 mmol) in Et_2O (550 ml) was added MeLi·LiBr (1.6 M in Et_2O, 71.5 ml, 157 mmol) dropwise via syringe pump (or dropping funnel) under -78 °C over 2.5 h. Upon completion, the solution was quenched by MeOH (10 ml) and sat. aq. $NaHCO_3$ (200 ml) at -78 °C, then warmed to rt slowly. The resulting mixture was extracted with Et_2O (3x 200 ml) and dried over $MgSO_4$. The solvents were removed under reduced pressure, and the crude product was purified by chromatography (0% to 20% EtOAc in hexanes) to obtain compound **195** (18.5 g, 85.5 mmol, 82%).

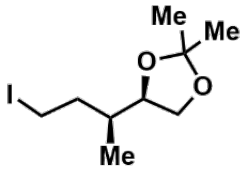
TLC: R_f = 0.47 (20% EtOAc in hexanes)

$[\alpha]^{25}_D$: -9.60 (*c* = 1.0, $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 4.14 (q, *J* = 7.2 Hz, 2H), 4.05 – 3.96 (m, 2H), 3.66 – 3.61 (m, 1H), 2.40 (dd, *J* = 14.9, 5.0 Hz, 1H), 2.24 – 2.17 (m, 1H), 2.13 (dd, *J* = 14.9, 8.8 Hz, 1H), 1.25 (s, 3H), 1.22 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.00 (d, *J* = 6.8, 3H).

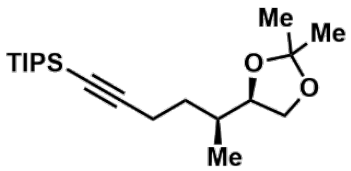
^{13}C-NMR (150 MHz, $CDCl_3$) δ 172.8, 109.1, 79.0, 67.0, 60.6, 37.8, 33.2, 26.6, 25.4, 15.6, 14.4.

HRMS (ESI-TOF): calc'd for $C_{11}H_{20}O_4$ $[M+Na]^+$: 239.1259, found: 239.1254



Compound **196**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 – 3.91 (m, 2H), 3.65 (td, *J* = 6.2, 3.2 Hz, 1H), 3.31 (ddt, *J* = 9.0, 5.0, 2.0 Hz, 1H), 3.16 (tdd, *J* = 9.9, 8.0, 2.2 Hz, 1H), 1.92 (dddd, *J* = 13.5, 11.2, 7.5, 2.9 Hz, 1H), 1.81 – 1.72 (m, 1H), 1.74 – 1.60 (m, 1H), 1.41 (s, 3H), 1.34 (s, 3H), 0.95 (d, *J* = 6.4 Hz, 3H).



Compound **197**. To a solution of compound **195** (10.4 g, 48.1 mmol) in THF (90 ml) was added LAH (1.83 mg, 48.2 mmol) by portions at 0 °C. The ice bath was removed, then the reaction mixture was allowed to stir at rt for 2 h. Upon completion, EtOAc (100 ml) was added slowly, then water (2 ml) was added to quench the remaining LAH. After stirring for 30 min, sat. aq. Rochelle's salt (200 mL) was added to this mixture and stirred overnight. After separating the organic layer, the aqueous phase was extracted with EtOAc (3x 100 ml). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude alcohol.

The alcohol obtained from above was dissolved in DCM (50 ml) under argon, imidazole (4.25 g, 62.5 mmol) and PPh_3 (15.1 g, 57.7 mmol) was added. To this mixture, I_2 (14.0 g, 55.3 mmol) was added slowly. The red color faded since all I_2 was consumed. Upon completion (indicated by TLC), methanol was added to quench the excess iodine, followed by blowing air over the solution to quench the excess PPh_3 (normally takes 30 min). The volatiles were then removed by reduced pressure, and pentane (150 ml) was added and stirred vigorously (sonication if necessary). After 1 h, the solids were removed by filtration through a Büchner funnel, and the residue was washed with pentane (2x 150 ml). Subsequently, the filtrate was collected and the pentane was removed under reduced pressure to give the crude iodide **196** (contained ~6% TPPO).

In another flame-dried round bottom flask, TIPS acetylene (9.65 g, 52.9 mmol) was dissolved in THF (86 ml), and *n*-BuLi (2.5 M in hexanes, 19.2 ml, 48.1 mmol) was added dropwise under argon. The mixture was then stirred at 0 °C for 30 min, and cooled to -78 °C. DMPU (12 ml) was added to this solution in one portion. Subsequently, a solution of the freshly prepared **196** (in 20 ml THF) was added dropwise to the freshly prepared lithium acetylide. The mixture was stirred at rt overnight, and quenched with water. The aqueous phase was extracted with Et_2O (3x 100 ml) and combined. The combined organic phase was rinsed with water (3x 100 ml) to remove the residual DMPU, and dried over $MgSO_4$. After removal of the solvents, the residue was purified with chromatography (hexanes to 5% EtOAc in hexanes) to give **197** (12.2 g, 36.1 mmol, 75%).

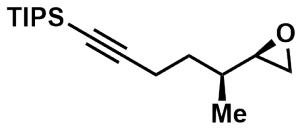
TLC: R_f = 0.21 (30% DCM in hexanes, $KMnO_4$ staining)

$[\alpha]^{25}_{D}$: -16.5 (*c* = 1.0, $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 4.02 (dd, *J* = 7.6, 6.3 Hz, 1H), 3.92 (q, *J* = 6.3 Hz, 1H), 3.64 (t, *J* = 7.6 Hz, 1H), 2.35 (ddd, *J* = 17.0, 7.5, 5.7 Hz, 1H), 2.27 (ddd, *J* = 17.0, 8.2, 7.3 Hz, 1H), 1.87 – 1.75 (m, 1H), 1.61 – 1.54 (m, 1H), 1.39 (s, 3H), 1.35 (s, 3H), 1.36 – 1.29 (m, 1H), 1.10 – 1.00 (m, 21H), 0.99 (d, *J* = 6.6 Hz, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 108.9, 108.6, 80.8, 79.9, 67.9, 35.6, 32.2, 26.7, 25.7, 18.8 (6C), 17.8, 15.0, 11.5 (3C).

HRMS (ESI-TOF): calc'd for $C_{20}H_{38}O_2Si$ $[M+H]^+$: 339.2719, found: 339.2711



Compound **198**. A solution of compound **28** (18.5 g, 54.5 mmol) in a mixture of HCl (3 M, 50 ml) and THF (100 ml) was heated at 75 °C for 12 h. The mixture was then cooled down to rt, and sat. aq. $NaHCO_3$ (100 ml) was slowly added to neutralize the HCl. The mixture was extracted with Et_2O (3x 100 ml) and the organic phase was dried over $MgSO_4$. The crude was obtained from concentrating under reduced pressure and used directly.

NaH (5.4 g, 60 wt% in mineral oil, 135 mmol) was suspended in THF (100 ml) under argon atmosphere. This mixture was then cooled to 0 °C. To this solution, the crude product obtained above (dissolved in 20 ml THF) was added dropwise. Upon completion, ice bath was removed to allow the mixture to warm up. The mixture was then stirred under rt for 1.5 h, and Ts-imidazole (14.4 g, 65 mmol) was added by portion. The resulting mixture was stirred vigorously at the same temperature for 45 min. Upon completion, H_2O (100

mL) was added in and the mixture was stirred for 15 min. The organic layer was separated and the aqueous phase was extracted with Et_2O (3x 100 ml). The combined organic phase was dried over $MgSO_4$ and concentrated. The crude product was purified by chromatography (hexanes to 30% DCM in hexanes) to yield epoxide **29** (13.3 g, 47.4 mmol, 87%).

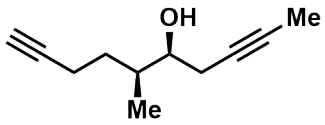
TLC: R_f = 0.33 (40% DCM in hexanes, $KMnO_4$ staining)

$[\alpha]^{25}_D$: +13.3 (*c* = 1.0, $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.77 (dd, *J* = 5.0, 3.2 Hz, 1H), 2.70 (dt, *J* = 6.8, 3.2 Hz, 1H), 2.59 (dd, *J* = 5.0, 3.2 Hz, 1H), 2.39 – 2.26 (m, 2H), 1.64 (tt, *J* = 11.3, 4.7 Hz, 1H), 1.56 – 1.47 (m, 2H), 1.13 – 0.96 (m, 24H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 108.4, 80.9, 56.7, 47.1, 35.3, 32.8, 18.8 (6C), 17.9, 16.9, 11.4 (3C).

HRMS (ESI-TOF): calc'd for $C_{17}H_{32}OSi$ $[M+H]^+$: 281.2301, found: 281.2296

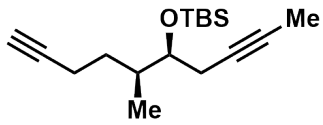


Compound **199**.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.70 – 3.58 (m, 1H), 2.35 – 2.30 (m, 2H), 2.31 – 2.25 (m, 1H), 2.24 – 2.16 (m, 1H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.90 (d, *J* = 4.3 Hz, 1H), 1.80 (t, *J* = 2.5 Hz, 3H), 1.79 – 1.75 (m, 1H), 1.71 (dtd, *J* = 13.2, 7.7, 5.6 Hz, 1H), 1.46 – 1.35 (m, 1H), 0.92 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 84.5, 78.5, 75.8, 73.1, 68.6, 36.5, 32.0, 25.3, 16.4, 13.5,

3.7.



Compound **200**. A solution of *n*-BuLi (73.0 ml, 182 mmol in hexanes) in THF (300 ml) was cooled to -78 °C under argon. To this solution, a balloon of propyne was added via needle, and the solution began to absorb the gas. Upon completion (the solution turned cloudy), the balloon was removed. The generated mixture was allowed to stir at -78 °C for 30 min.

To this freshly prepared propynyllithium, a solution of compound **198** (17.0 g, 60.6 mmol) in THF (30 ml) was added slowly at the same temperature. BF_3 etherate (22.0 ml, 178 mmol) was added subsequently, and the reaction mixture was allowed to stir at -78 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (100 mL) and diluted with Et_2O (50 mL), then stirred for 1 h. The mixture was extracted with EtOAc (3x 150 ml) and the organic layer was dried over $MgSO_4$. The solvents were removed in vacuo and the crude product was directly used for next transformation.

The crude product obtained from above was added TBAF (100 ml, 1.0 M in THF, 100 mmol) under argon. The resulting mixture was stirred at 45 °C overnight. Upon completion, sat. aq. NH_4Cl (80 mL) and EtOAc (50 mL) was added. The mixture was extracted with EtOAc (3x 100 ml) and dried over $MgSO_4$. After removing solvents under reduced pressure, the crude was dissolved in DCM (120 ml), then added TEA (18.2 g, 25.1 ml, 180 mmol). To this solution, TBSOTf (31.7 g, 27.6 ml, 120 mmol) was slowly added under rt. The

mixture was stirred at the same temperature for 30 min, then heated to reflux for 1 h. Upon completion, sat. aq. $NaHCO_3$ (120 mL) was added and the mixture was extracted with DCM (3x 100 ml). The combined organic layer was dried over $MgSO_4$ and concentrated. The crude was purified by chromatography (0-5% EtOAc in hexanes) to yield compound **200** (15.5 g, 55.7 mmol, 92%).

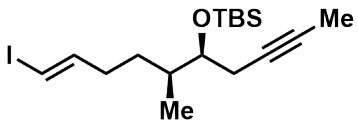
TLC: R_f = 0.50 (5% EtOAc in hexanes, $KMnO_4$ staining)

$[\alpha]^{25}_D$: -10.5 (*c* = 1.0, $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 3.71 (td, *J* = 6.7, 2.8 Hz, 1H), 2.30 – 2.22 (m, 2H), 2.18 (dtd, *J* = 16.9, 7.8, 2.6 Hz, 1H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.92 – 1.85 (m, 1H), 1.77 (t, *J* = 2.6 Hz, 3H), 1.67 (dtd, *J* = 13.3, 7.9, 5.3 Hz, 1H), 1.38 (dtd, *J* = 13.3, 8.4, 6.0 Hz, 1H), 0.88 (s, 9H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.08 (s, 3H), 0.06 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 84.8, 77.2, 76.8, 74.5, 68.3, 36.4, 32.3, 26.0 (3C), 25.0, 18.3, 16.7, 13.0, 3.70, -4.1, -4.6.

HRMS (ESI-TOF): calc'd for $C_{17}H_{30}OSi$ $[M+H]^+$: 279.2139, found: 279.2142



Compound **201**. To a solution of Cp_2ZrCl_2 (13.6 g, 46.5 mmol) in THF (100 ml) was added DIBAL-H (38.6 ml, 38.6 mmol, 1.0 M in hexanes) dropwise at 0 °C. A white precipitation was formed. The mixture was allowed to stir for 1 h, and a solution of compound **30** (8.58 g, 30.8 mmol) in THF (10 ml) was added slowly. The reaction mixture (cloudy) was warmed up to rt slowly, and kept stirring overnight. A solution of I_2 (12.0 g, 47.2 mmol) in

THF (20 ml) was added at 0 °C, the resulting dark solution was stirred for 1 h at the same temperature. The reaction was quenched with sat. aq. $Na_2S_2O_3$ (150 mL), and filtered to remove undissolved impurities (if needed). The obtained mixture was extracted with Et_2O (3x 100 ml), and the organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product. Pure compound **13** (12.4 g, 30.4 mmol, 99%) was obtained by chromatography (2% EtOAc in hexanes).

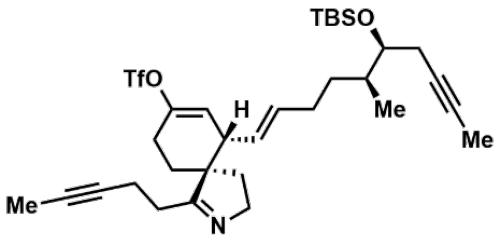
TLC: R_f = 0.44 (3% EtOAc in hexanes, UV active, $KMnO_4$ staining)

$[\alpha]^{25}_D$: -13.6 (*c* = 1.0, $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.51 (dt, *J* = 14.3, 7.2 Hz, 1H), 5.99 (dd, *J* = 14.3, 1.5 Hz, 1H), 3.68 (td, *J* = 6.8, 2.8 Hz, 1H), 2.29 – 2.18 (m, 2H), 2.17 – 1.99 (m, 2H), 1.78 (t, *J* = 2.6 Hz, 3H), 1.77 – 1.70 (m, 1H), 1.55 – 1.46 (m, 1H), 1.28 – 1.18 (m, 1H), 0.88 (s, 9H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.07 (s, 3H), 0.04 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 146.8, 77.3, 76.7, 74.6, 74.4, 36.4, 34.1, 32.0, 26.0 (3C), 25.0, 18.3, 13.3, 3.8, -4.1, -4.5.

HRMS (ESI-TOF): calc'd for $C_{17}H_{31}IOSi$ $[M+H]^+$: 407.1267, found: 407.1260



Compound **203**.

Lithium-halogen exchange

To a solution of compound **13** (7.42 g, 18.3 mmol, in 46 ml Et_2O) at -78 °C, *t*-BuLi

(23.8 ml, 1.6 M in pentane, 38.1 mmol) was added dropwise. A bright yellow solution was formed immediately, followed by a formation of precipitation. The reaction was kept stirring under -78 °C for at least 2.5 h to give the solution of vinyllithium.

Preparation of [Cu]

To a 1L round-bottom flask charged CuI (38.0 g, 200 mmol), an aqueous ammonia solution (28-30 %, 500 ml) was added under argon. A blue solution was generated (indicating the oxidation of Cu (I)) and the dissolution of CuI took place. To reduce the amount of Cu (II) as much as possible, solid hydroxylammonium chloride was added (ca. 7 g) portionwise until the color of the solution did not fade.

Subsequently, ethanol (300 ml) was added to the solution, followed by the addition of 1-pentyne (14 ml, 142 mmol) in one portion. The solution turned dark quickly and was stirred vigorously overnight. The yellow slurry was collected by a Büchner funnel, followed by washing with water, methanol, and finally ether. After drying in vacuo for 24 h, [Cu] was obtained as a light, yellow powder (12.1 g, 93 mmol, 47% based on CuI, 65% based on 1-pentyne).

Copper (I)-phosphine complex preparation

Meanwhile, [Cu] (2.86 g, 21.5 mmol) was suspended in THF (16 ml) under argon. To this suspension, *n*-Bu_3P (10.9 ml, 8.82 g, 43.6 mmol) was added dropwise. The dissolution of the yellow participates took place was and completed in 15-30 min.

Transmetallation and conjugate addition

To the generated vinyllithium solution at -78 °C, the prepared Cu (I)-phosphine

complex was added dropwise in 5 min. After addition, the orange mixture was stirred for 1 h at -78 °C.

A solution of compound **12** (3.14 g, 14.6 mmol, in 10 ml THF) was added to the above solution dropwise at -78 °C. The resulting mixture was kept stirring at the same temperature for 40 min. Then a solution of Comins' reagent (8.59 g, 21.9 mmol, in 20 ml THF) was added and the resulting solution was warmed to 0 °C. The reaction mixture was stirred at 0 °C for 1 h, and quenched by 5% aq. NH_3 (100 ml), Na_2CO_3 (10 g), and blew with air for 1 h. The resulting mixture was stirred vigorously for 45 min, and extracted with Et_2O (3x 150 ml). The organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting residue was purified by gradient chromatography (20% Et_2O in hexanes to 40% Et_2O + 1% TEA in hexanes) to yield compound **7** (6.41 g, 10.2 mmol, 70%).

TLC: R_f = 0.58 (50% Et_2O in hexanes, $KMnO_4$ staining)

$[\alpha]^{25}_D$: -53.1 (c = 1.0, $CHCl_3$)

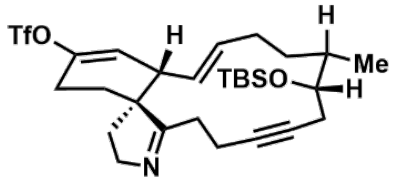
^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.68 (d, J = 2.0 Hz, 1H), 5.46 (dt, J = 14.3, 6.8 Hz, 1H), 5.21 (ddt, J = 14.3, 7.44, 1.49 Hz, 1H), 3.85 – 3.77 (m, 1H), 3.67 (td, J = 6.96, 2.80 Hz, 1H), 3.52 (tdd, J = 10.3, 8.3, 4.1 Hz, 1H), 3.17 – 3.06 (m, 1H), 2.56 – 2.51 (m, 2H), 2.50 – 2.34 (m, 4H), 2.28 – 2.18 (m, 2H), 2.10 – 1.93 (m, 3H), 1.93 – 1.86 (m, 1H), 1.71 – 1.65 (m, 1H), 1.81 – 1.73 (m, 6H), 1.65 – 1.53 (m, 2H), 1.46 – 1.39 (m, 1H), 1.21 – 1.12 (m, 1H), 0.88 (s, 9H), 0.81 (d, J = 6.8 Hz, 3H), 0.07 (s, 3H), 0.04 (s, 3H)

^{13}C-NMR (150 MHz, $CDCl_3$) δ 177.8, 148.9, 134.4, 126.3, 120.6, 118.7 (q, $J_{C\text{-}F}$ = 316 Hz),

78.9, 77.1, 76.9, 75.9, 74.7, 58.7, 56.7, 43.1, 37.0, 33.1, 31.5, 30.9, 30.0, 29.0, 26.0 (3C), 25.5, 25.1, 18.3, 15.9, 13.2, 3.7 (2C), -4.0, -4.5

^{1}H-COSY, ^{1}H-^{13}C-HSQC, ^{1}H-^{13}C-HMBC, NOESY spectra are available

HRMS (ESI-TOF): calc'd for $C_{32}H_{48}F_3NO_4SSi$ $[M+H]^+$: 628.3104, found: 628.3093



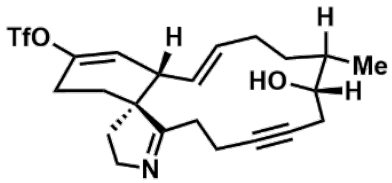
Compound **204**. A 250 ml round bottom flask charged imine **203** (54 mg, 0.086 mmol) was added MS 5Å (250 mg, 500 wt % to SM, dried at >200 °C under high vacuum overnight) and [Mo] (8.0 mg, 0.011 mmol) in glovebox. Then the flask was taken out from glovebox, and toluene (4.0 ml) was added under argon. The mixture was pre-stirred for 5 min, and heated to 80 °C. After 2 h, TLC (50% Et_2O in hexanes) indicated the full conversion. The reaction mixture was allowed to filter over a Celite® plug to remove the molecular sieves, and rinsed with DCM. The filtrate was concentrated under reduced pressure. Compound **204** (38 mg, 0.066 mmol, 77%) was obtained by chromatography (10% to 50% Et_2O in hexanes).

TLC: R_f = 0.48 (50% Et_2O in hexanes, $KMnO_4$ staining)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69 – 5.58 (m, 2H), 5.23 (dd, *J* = 15.4, 7.9 Hz, 1H), 3.98 – 3.84 (m, 1H), 3.76 – 3.62 (m, 1H), 3.58 (ddd, *J* = 9.0, 4.4, 2.8 Hz, 1H), 3.20 (d, *J* = 7.9 Hz, 1H), 2.74 (ddt, *J* = 14.3, 9.1, 2.9 Hz, 1H), 2.52 – 2.20 (m, 8H), 2.14 – 1.88 (m, 5H), 1.70 – 1.64 (m, 1H), 1.64 – 1.57 (m, 1H), 1.43 – 1.34 (m, 1H), 0.86 (s, 9H), 0.80 (d, *J* =

6.7 Hz, 3H), 0.02 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 176.6, 148.3, 133.5, 126.9, 121.4, 72.8, 58.8, 56.4, 44.3, 33.2, 31.9, 31.8, 29.8, 28.0, 27.6, 25.8, 25.5, 18.1, 15.3, 14.8, 12.5, -4.1, -4.8.



Compound **205**. To a solution of macrocycle **204** (100 mg, 0.17 mmol) in MeOH (3.0 ml) was added PTSA (50 mg, 0.26 mmol) in one portion. The resulting mixture was stirred at 40 °C for 1 h. Upon completion, the mixture was quenched with sat. aq. $NaHCO_3$ (5 ml) and extracted with DCM (3x 3 ml). The combined organic layer was dried over $MgSO_4$ and concentrated. Pure **205** (72 mg, 0.16 mmol, 94%) was obtained by chromatography (30% EtOAc in hexanes to pure EtOAc).

TLC: R_f = 0.32 (pure EtOAc, $KMnO_4$ staining)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68 – 5.59 (m, 2H), 5.24 (dd, *J* = 15.3, 8.1 Hz, 1H), 3.92 – 3.82 (m, 1H), 3.61 (dtd, *J* = 16.1, 8.3, 5.2 Hz, 1H), 3.48 – 3.43 (m, 1H), 3.18 (sf, 1H), 2.79 – 2.69 (m, 1H), 2.60 – 2.50 (m, 1H), 2.48 – 2.23 (m, 6H), 2.17 – 2.00 (m, 2H), 1.99 – 1.86 (m, 3H), 1.67 – 1.61 (m, 1H), 1.61 – 1.55 (m, 1H), 1.44 (dddt, *J* = 11.9, 7.9, 6.0, 3.1 Hz, 1H), 1.27 – 1.16 (m, 1H), 0.89 (d, *J* = 7.4 Hz, 3H).

Chapter 4: Establishment of the transannular ketal system of portimines.

Section 4.1 Initial attempts at stereoselective oxidation of C-14/C-15.

As shown in Figure 3.5, the oxidation of C-14 and C-15 was planned to occur after the construction of the macrocycle. Therefore, compound **204** was submitted to various conditions for dihydroxylation and the results were outlined in Figure 4.1. Miserably, the macrocyclic system showed contrary stereoselectivity to its open form and delivered undesired diol **206** as the major product in most cases. The stereochemistry of this diol was unambiguously confirmed as undesired isomer via NOE analysis of its acetonide **209**. Despite that, a trace amount of desire diol **207** could be observed when exposing **204** to Sharpless's $(DHQ)_2AQN$ ligand, yet poor regioselectivity was observed due to the formation of **208**. Alternatively, the TBS ether at C-10 could be liberated upon treatment of PTSA, giving free alcohol **205**. In order to fix the stereochemical outcome, the free hydroxyl group at C-10 was thought to serve as a directing group for dihydroxylation under Donohoe's condition (*1*) using TMEDA and stochiometric OsO_4. Unfortunately, such conditions seemed too harsh and decomposed **205** rapidly even at -78 °C.

To overcome the stereochemical issue at C-15, a strategy based on a cascade electrophilic addition of olefin at C-14/C-15 was proposed and delineated in Figure 4.1. In detail, **205** would undergo alkyne hydration in the presence of water and gold-based catalyst, to afford the keto-alcohol **210**. The electron-deficient oxidants, depicted as X^+, would trigger a cascade reaction starting from an electrophilic addition to C-14/C-15 alkene, followed by a key transannular C–O bond formation by the carbonyl at C-7, and ended with a ketalization by hydroxyl group at C-10, arriving at the final product **211**

possessing the unique skeleton of portimines. Strikingly, upon activating the alkyne, the nitrogen of cyclic imine initiated a 5-*exo* cyclization, delivering pyrrole **212** as the exclusive product. Efforts to convert this aromatic compound back to imine failed in all cases, indicating it as a so-called "dead-end" in total synthesis. The lesson learned from this transformation (and will see more later) was that the functionalities on the macrocycle should be viewed as a whole considering the accessibility of each group dramatically enhanced by both close distance and confined conformation.

To prevent the imine from involving the alkyne activation, an electro-neutral enamide was prepared by TFAA and TEA, followed by removing the TBS at C-10, affording **213** as a single isomer. Activating the alkyne at C-7/C-8 under condition ***a*** or ***b*** (see Figure 4.1) would deliver **214** or **215** as a product, respectively. Intuitively, **214** would not survive olefin oxidations, thus it was convert to **215** to be oxidized under various conditions. Surprisingly, only *m*-CPBA could deliver a characterizable, yet quite unstable product **216** among the screen conditions, other oxidants, ranging from milder ones like I_2, to stronger such as DMDO, would give a messy mixture or decompose the starting material. Even if **216** could be isolated, it was quite unstable and decomposed in stock solution within a couple of days. Alternatively, the TFA group of **215** was cleaved under aqueous ammonia, giving **217** as the major yet unstable product. Exposing **217** to I_2 would initiate a pyrrole formation and an unusual tandem di-iodination, giving **218** as the final product.

In conclusion, I initially confirmed that the direct dihydroxylation failed to deliver the correct stereochemistry at C-15, thereby turning to a new strategy leveraging the innate

geometry of the macrocycle. This strategy aimed at setting up the oxidation state, as well as the stereochemical outcome at C-15 via a transannular electrophilic addition to C-14/C-15 alkene. However, all attempts to activate alkyne or alkene in the presence of a free imine were unsuccessful due to the inevitable, rapid pyrrole formation.

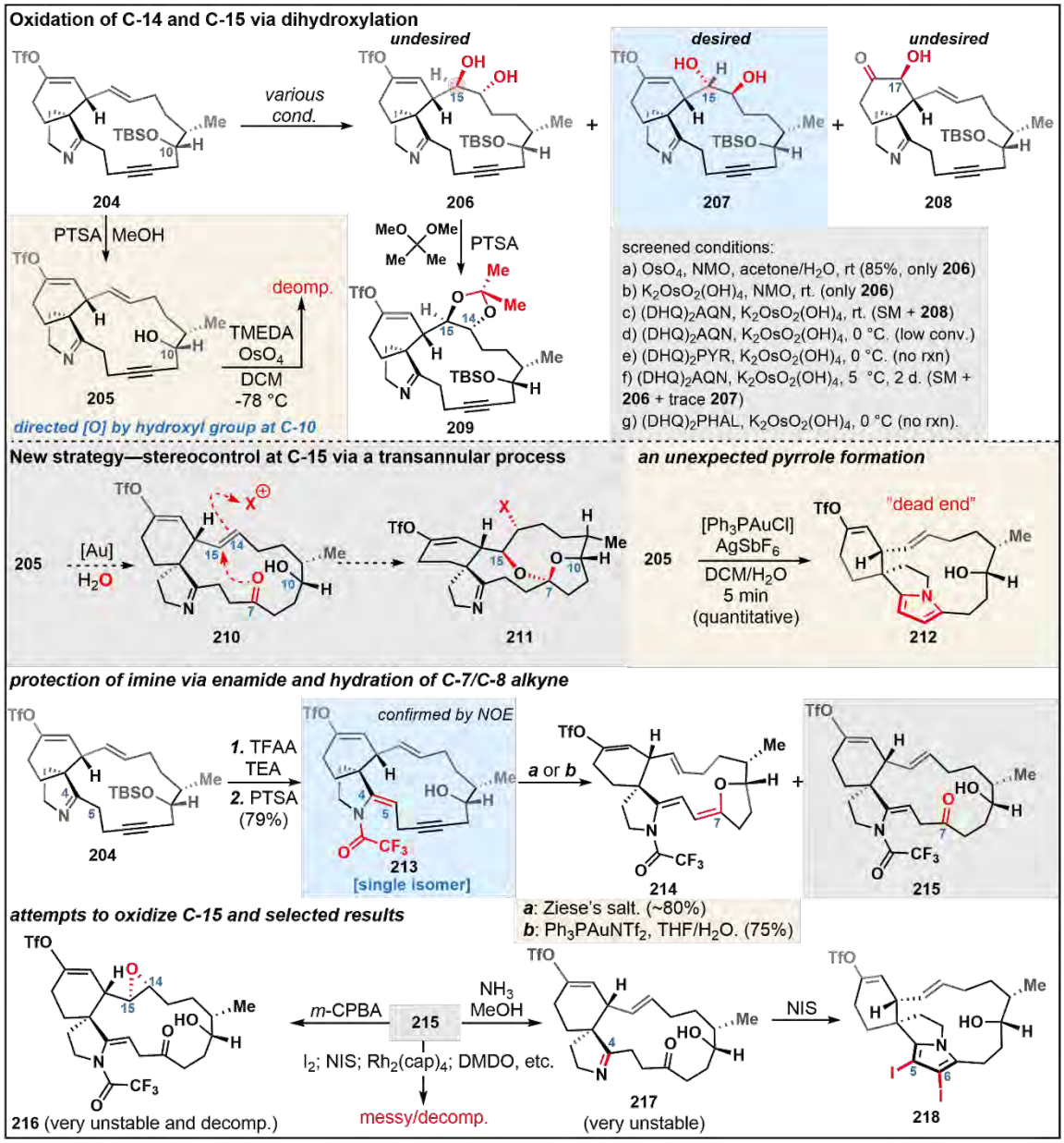


Figure 4.1 Attempts to oxidize C-14 and C-15.

Shortly after I realized that TFA-enamide was not stable enough to carry through, a more electron-rich PG, Troc group, was noticed since its enamide could be hydrolyzed under acidic conditions to give a highly stable keto-carbamate (*2*). This inactive, open-formed keto-carbamate, should not only tolerate most well-documented oxidants but also potentially release the ring strain of the macrocycle to accelerate the transannular C–O bond formation. For this purpose, **204** was heated with TrocCl and DMAP to give Troc enamide **219** in 63% yield, which was subsequently hydrolyzed by PTSA in MeOH, first delivering the TBS-cleaved product **220**, which further reacted with the acid, arriving at keto-carbamate **221** as the desired product.

With **221** in hand, an epoxidation mediated by *m*-CPBA smoothly occurred at C-14/C-15 olefin, followed by alkyne hydration triggered by XPhosAuNTf$_2$, delivering **222** as the single isomer. At this point, **222** was treated with various acids to initiate a transannular regioselective epoxide ring opening at C-15, aiming at the formation of **223**. Unsatisfyingly, a competitive 6-*exo* cyclization by the hydroxyl group at C-10 dominated in most cases, affording **224** as the single product. To prevent this pathway, the free alcohol at C-10 was first masked by an acetyl group, then submitted to acidic conditions. Astonishingly, **225** remained intact under milder conditions, while in the case of TFA, the formation of **226** was detected, which resulted from an undesired transannular cyclization by carbonyl at C-4.

Overall, the disappointing but reasonable results from the transannular strategy were summarized, where we can see the difficulty to control the chemo- and stereoselectivity on

such a compact, rigidified system. Nucleophilic groups embedded in the macrocyclic skeleton, such as the nitrogen at C-1, the ketone at C-4 and C-7, as well as the hydroxyl group at C-10, would engage the transannular process unexpectedly and result in undesired outcomes.

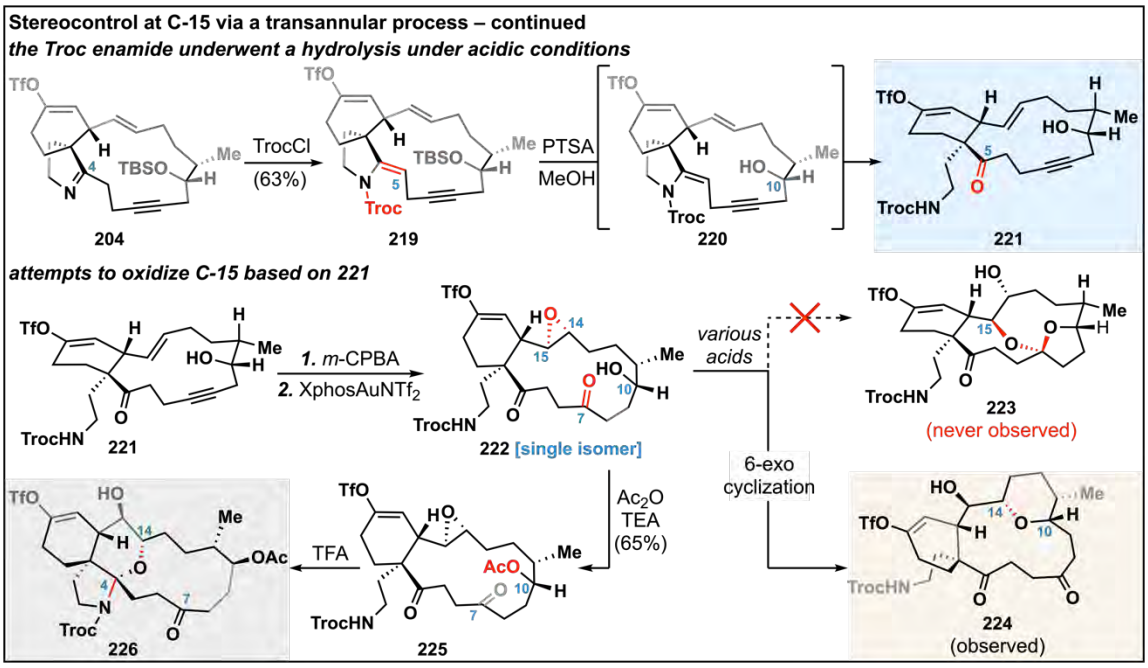


Figure 4.2 Attempts to control the stereochemistry at C-15 via transannular C–O bond formation.

Section 4.2 Attempts to oxidize C-5.

In this section, I would like to discuss some results from the oxidation of Troc-enamide **219**, which eventually inspired the key oxidation step (oxidizing C-13 and C-5 in a single step) presented in Section 5.5. The general idea to oxidize C-5 was based on the nucleophilic nature of the Troc enamide, which was supported by its facile hydrolysis in the presence of acids. Therefore, **219** might be oxidized to corresponding di-epoxide **227**,

which might undergo an acid-catalyzed ring-opening, followed by alkyne hydration under a gold-catalyst, arriving at key intermediate **228** (Figure 4.3). Compared to **222** presented in Section 4.1, the hydroxyl group at C-5 was preinstalled, mimicking the skeleton of portimines, which might accelerate the transannular ketalization and suppress the undesired pathway, to arrive at **229**.

Accordingly, a variety of oxidants were tested, among that DMDO and persulfate (*p*-$NsO)_2$ (*3*) showed clean conversion and characterizable results. In the case of using DMDO, **219** was heavily oxidized and afforded an α-carbonate nitrone **230** in one pot. Moreover, a striking selectivity was observed in this case since little to no oxidation at C-14/C-15 olefin was observed. A plausible mechanism was depicted in Figure 4.3, where **231** was postulated as the primary product and underwent an irreversible epoxide ring opening to afford the mesoionic compound **232**. The nucleophilic oxygen atom at C-5 might attack the Troc-iminium spontaneously via a 5-*exo* cyclization, to afford **233** as the key intermediate. Afterward, the free imine was liberated by Troc migration, which underwent a second oxidation by DMDO, arriving at nitrone **230**. Intuitively, oxidation and alkyne activation of such a sensitive α-oxidized nitrone were not successful, leading to messy results that failed to characterize.

Promisingly, when exposing **219** to (p-$NsO)_2$, a C-5 oxidized product **234** could be isolated in good yield, mainly presenting as a hemiaminal form. Treating **234** with Olah's reagent (HF in pyridine) delivered **235** as the major product. Unfortunately, efforts to hydrate the internal alkyne were unsuccessful on this highly functionalized molecule.

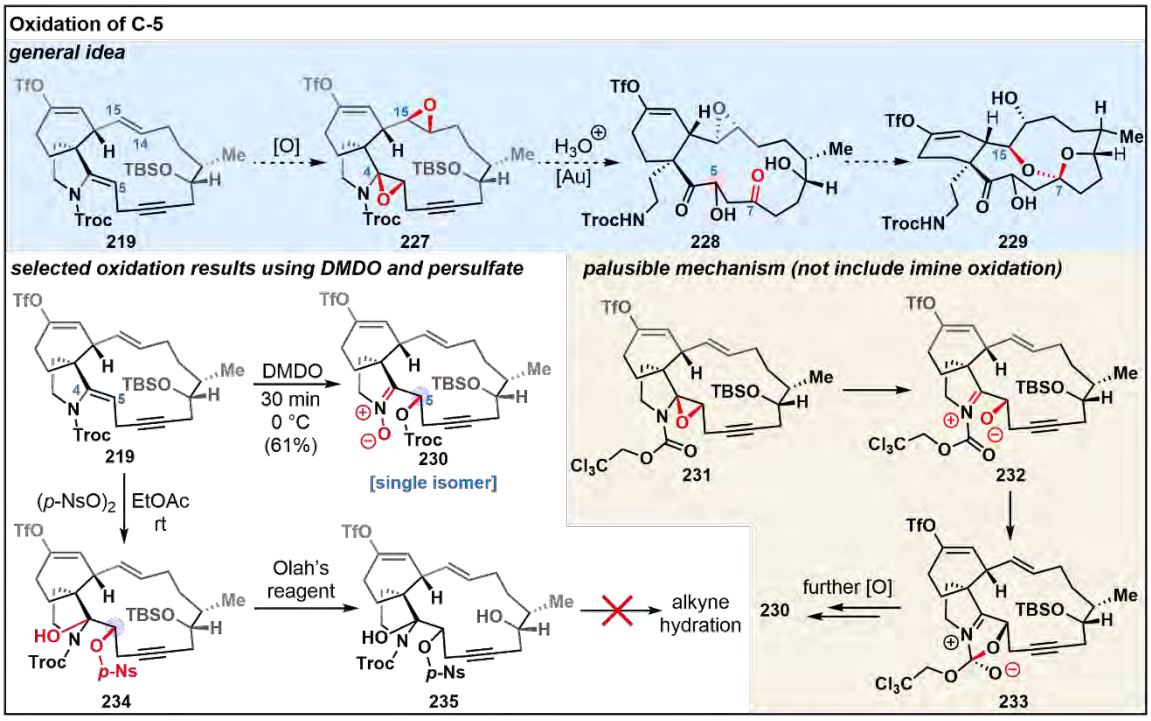


Figure 4.3 Oxidation of C-5.

Section 4.3 Discovery of a rigidified, inactive tricyclic system for late-stage redox manipulation.

When compound **221** was hydrated under $XPhosAuTf_2$ in the presence of water, the hydroxyl ketone **236** was isolated as expected. Characterization of this compound was carried out in neutral solvents such as deuterated benzene in case of seeing peaks from hemiacetals. Occasionally, I misused $CDCl_3$ to take the ^{13}C spectrum, giving a single compound with no carbonyl and much less polar than **236** on silica gel, later confirmed as a tricyclic compound **237** (Figure 4.4). The formation of **237** was not only serendipitous but also extremely attractive to us since this compound should be redox inactive, thereby serving as a platform for late-stage redox manipulations. Furthermore, as I just mentioned

in the past sections, the nitrogen at C-1, the carbonyl at C-5 and C-7, as well as the hydroxyl group at C-10, would engage the oxidation of C-14/C-15 olefin and lead to unexpected products. Therefore, we rationalized that the newly-formed tricyclic system organized potentially sensitive sites into their inactive states with a unique rigidified backbone to control downstream stereochemical issues.

Efforts to stereoselective oxidation at C-15 was then carried out and depicted in Figure 4.4. First, C-14/C-15 alkene was oxidized to an epoxide **238**, which possessed undesired stereochemistry at C-15. This result was not surprising since the rigid polycyclic system did not perturb the local steric environment of the olefin. With a sizable amount of **238** in hand, several conditions for acid-catalyzed epoxide ring-opening were executed and afforded a single product **224**, resulting from the 6-*exo* cyclization triggered by hydroxyl group at C-10, which was consistent with its opened form analog (see Figure 4.2). Attention was then turned to dihydroxylation, where **237** was exposed to OsO_4 and NMO (Upjohn's condition) to afford diol **239**. Although the stereochemical outcome at C-15 was undesired, regioselective oxidation at C-14 and following metal-assisted epimerization might solve this problem. To achieve this, a regioselective Swern oxidation happened to **239** at C-14, delivering α-hydroxyl ketone **240** as the major product in 73% isolated yield. Subsequently, **240** was submitted to various Lewis acids to epimerize C-15, however, the desired product **242** was never observed in all cases. Instead, a tautomerization was identified when trimethyl aluminum was used, affording **242** as the major product.

The lesson learned from above approaches was that the desired stereochemical

outcome at C-15 might only be generated by an intermolecular reduction utilizing the innate geometry of the macrocycle. Following this logic, diol **239** was oxidized to a highly reactive 1,2-diketone **243** under TFAA and DMSO at -78 °C, this oxidation could also be achieved by a single transformation from alkene **237** by the ruthenium-based catalyst (*4*) in the presence of TBHP in 53% yield (see Table 1 for more details). With diketone **243** in place, a new strategy based on regio- and stereoselective reduction of C-15 was proposed, starting from an enol ether formation at C-14 to give **244**, which could be reduced to **245**. Specifically, if **245** was a silyl enol ether, further oxidation at C-13 might be facile and benefit from using milder conditions such as Rubottom oxidation.

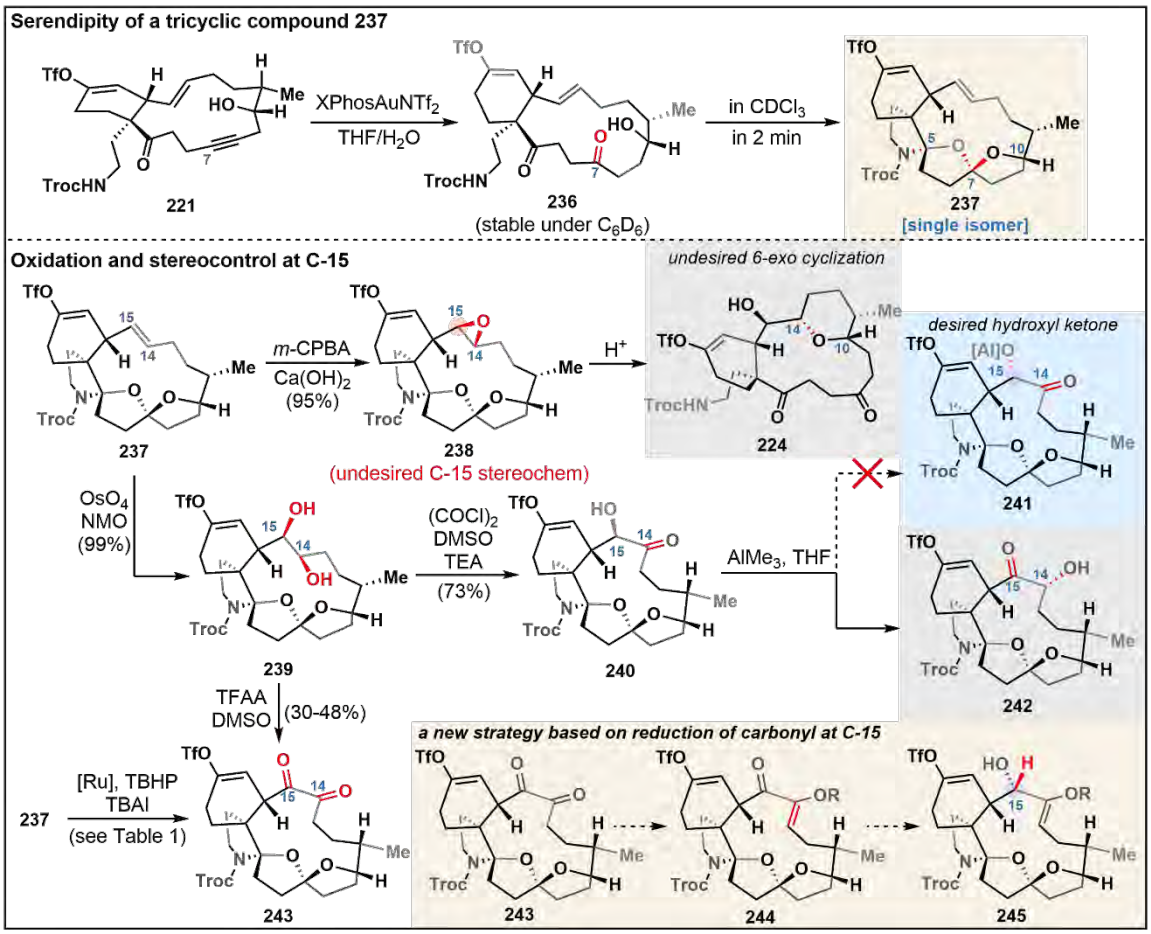


Figure 4.4 Formation and oxidation of tricyclic 237.

Table 1. Screened conditions for 1,2-diketone formation from compound 237.

entry	condition	result (based on **243**)
1	NMO, OsO_4, *then* DMSO, $(COCl)_2$ (>10 eq.), TEA	**240** as product (73%)
2	NMO, OsO_4, *then* DMSO, TFAA (10 eq.)	trace **243**
3	NMO, OsO_4, *then* DMSO, TFAA (>45 eq.)	20% + messy byproducts
4	NMO, OsO_4, *then* CrO_3, H_2SO_4	decomposed
5	NMO, OsO_4, *then* DMP, DCE, 60 °C	**240** + **242** + trace **243**
6	NMO, OsO_4, *then* DMP, Py, DCE, 40 °C	no **243** observed, messy
7	NMO, OsO_4, *then* IBX, DMSO, rt	no **243** observed, SM
8	$NaBrO_3$ (excess), $RuCl_3$ (10 mol%), buffer (pH = 8)	trace **243**
9	TBHP, $[Ru(cymene)Cl_2]_2$ (8 mol%), TBAI, MeCN/PhMe/H_2O	35-55%

10	TBHP, $RuCl_3$ (8 mol%), TBAI, MeCN/PhMe/H_2O	trace **243** + decomposed
11	TBHP, [$Ru(PPh_3)_3Cl_2$] (8 mol%), TBAI, MeCN/PhMe/H_2O	50–65%
12	TBHP, [$Ru(BINAP)Cl_2$] (8 mol%), TBAI, MeCN/PhMe/H_2O	50%
13	TBHP, [$Ru_3(CO)_{12}$] (8 mol%), TBAI, MeCN/PhMe/H_2O	35%
14	TBHP, [$Ru(DMSO)_4Cl_2$] (8 mol%), TBAI, MeCN/PhMe/H_2O	30%
15	TBHP, [$Ru(PPh_3)_3Cl_2$] (8 mol%), TBAI, $MeNO_2$/PhMe/H_2O	sluggish, messy
16	TBHP, [$Ru(PPh_3)_3Cl_2$] (8 mol%), TBAI, MeCN/PhMe (dry)	sluggish, low conv.
17	TBHP, [$Ru(PPh_3)_3Cl_2$] (8 mol%), TMAI, MeCN/PhMe/H_2O	no **243** observed, SM
18	TBHP, [$Ru(PPh_3)_3Cl_2$] (8 mol%), MeCN/PhMe/H_2O	no **243** observed, SM
19	*m*-CPBA, [$Ru(PPh_3)_3Cl_2$] (8 mol%), TBAI, MeCN/PhMe/H_2O	no **243** observed, SM
20	H_2O_2, [$Ru(PPh_3)_3Cl_2$] (8 mol%), TBAI, MeCN/PhMe/H_2O	no **243** observed, SM
21	$NaBrO_3$, [$Ru(PPh_3)_3Cl_2$] (8 mol%), TBAI, MeCN/PhMe/H_2O	no **243** observed, SM
22	$K_2S_2O_8$, [$Ru(PPh_3)_3Cl_2$] (8 mol%), TBAI, MeCN/PhMe/H_2O	no **243** observed, SM
23	cymene hydroperoxide, [$Ru(PPh_3)_3Cl_2$] (8 mol%), TBAI, MeCN/PhMe/H_2O	no **243** observed, SM
24	TBHP, [$Ru(PPh_3)_3Cl_2$] (8 mol%), TBAI, MeCN/PhMe/H_2O, $NaHCO_3$	sluggish, low conv.
25	TBHP, [$Ru(PPh_3)_3Cl_2$] (8 mol%), TBAI, MeCN/PhMe/H_2O, NaH_2PO_4	sluggish, low conv.

Section 4.4 Accomplishment of the desired stereochemical outcome at C-15 and regioselective oxidation at C-14.

With diketone **243** in hand, I focused on establishing the stereocenter at C-15 via the aforementioned method. Thus, **243** was first deprotonated by LiHMDS, followed by adding TBSOTf at -78 °C, delivering enone **246** in a good yield (Figure 4.5). The geometry

of **246** was confirmed by NOE, adopting a *Z*-alkene at C-13/C-14, where the carbonyl at C-15 points to the bottom of the macrocycle. This promising conformation should deliver the desired stereochemical outcome at C-15 upon being attacked by a hydride. Astonishingly, the carbonyl at C-15 seemed extremely inactive and kept intact under borohydrides, DIBAL-H, and even LAH at low temperatures. Heating **246** in the presence of $NaBH_4$ or $LiBH_4$ in MeOH delivered no product but recovered the starting material. Stronger reagents, such as Red-Al and alane (aluminum hydride, AlH_3), would lead to decomposition. In conclusion, **246** exhibited an extremely reduction-resistant ketone presumably due to its steric surrounding as well as higher electronic density, which prevented it from access by reductants. Despite the fact that the steric effect could be minimized by reductions based on single-electron transfer (SET), I was discouraged by the known lability of the Troc group to these reagents, thereby abandoning this strategy at this point.

Next, I was wondering if any stereoselectivity could be achieved via a stepwise reductive sequence. Thus, **243** was reduced by a bulky reductant L-selectride at -78 °C, delivering hydroxyl ketone **242** as the single product, which was also obtained from the tautomerization of **240** (see Section 4.3). Fortunately, reducing the C-15 carbonyl of **242** via $NaBH_4$ was feasible and led to a single diastereomer **248**, which was confirmed presenting the correct stereochemistry at C-15. The presence of C-14 hydroxyl group seemed crucial for the stereoselectivity since reducing **243** with $NaBH_4$ would afford a mixture of all 4 possible isomers.

The formation of **248** was indeed a milestone in my Ph.D. since it was the first time I successfully utilized the geometry of my substrate to solve the stereochemical issue at C-15. Therefore, all that remained before the reconstitution of the ketal system in portimines was the oxidation of C-14. Initially, I aimed to reorganize the tricyclic system prior to C-14 oxidation, presumably utilizing the innate geometry of the polycyclic system. In this hypothesis, **248** would undergo a ring-chain rearrangement in the presence of an acid, arriving at **223** as the final product. Subsequent oxidation would then take place at C-14, C-13, and C-5, to give the fully-functionalized portimines' core in several steps. Interestingly, a clean, apolar product **251** was observed and isolated in 90% yield upon treating **248** with TFA, possessing a carbonyl at C-14 confirmed by ^{13}C NMR, HSQC, and HMBC. This result was quite confusing since it was hard to identify which group could act as a "hydride acceptor". Eventually, based on the 1D and 2D NMR data, the spiro ketal system in **248** was confirmed to be reduced via a transannular borrowing-hydrogen process. Hypothetically, this remarkable transformation was triggered by generating an oxonium at C-7 (**249**), which was immediately reduced by the hydrogen atom at C-14 due to the close proximity brought by the macrocycle, converting C-14 to its ketone form. Moreover, the Troc-iminium also engaged and was attacked by the hydroxyl group at C-15 to form a 5,5,6-tricyclic system (Figure 4.5), affording **251** as the final product. This transannular process underlined the necessity of establishing the correct oxidation state at C-14 prior to skeleton reconstitution.

Efforts to regioselective oxidation of C-14 were carried out and summarized in Table

2. As we can see from the screening table, TBS silylation (entry 19) selectively took place at C-14, consistent with its 3D structure that the hydroxyl group at C-14 should be much more accessible than C-15. Confusingly, DMP oxidation at 0 °C (entry 1) exclusively occurred at C-15, highlighting the high uncertainty in the redox manipulation of this molecule. A series of oxidations based on activated DMSO were screened and the desired hydroxyl ketone **252** could be occasionally obtained as a minor product, yet the ratio was very inconsistent. Cr(VI)-based oxidants such as Jones' reagent and Collins reagent led to decomposition, while the use of silver-based oxidants such as Fetizon's reagent showed little to no reactivity. Delightfully, a classical TEMPO-catalyzed condition seemed to be reactive and highly regioselective. An amazing yield (over 93%) of **252** could be isolated as a single diastereomer.

With the correct oxidation state at C-14 and stereochemistry at C-15 in place, the key skeletal reconstitution can now commence establishing the unusual poly ketal system presented in portimine A and B, which will be described in the next section.

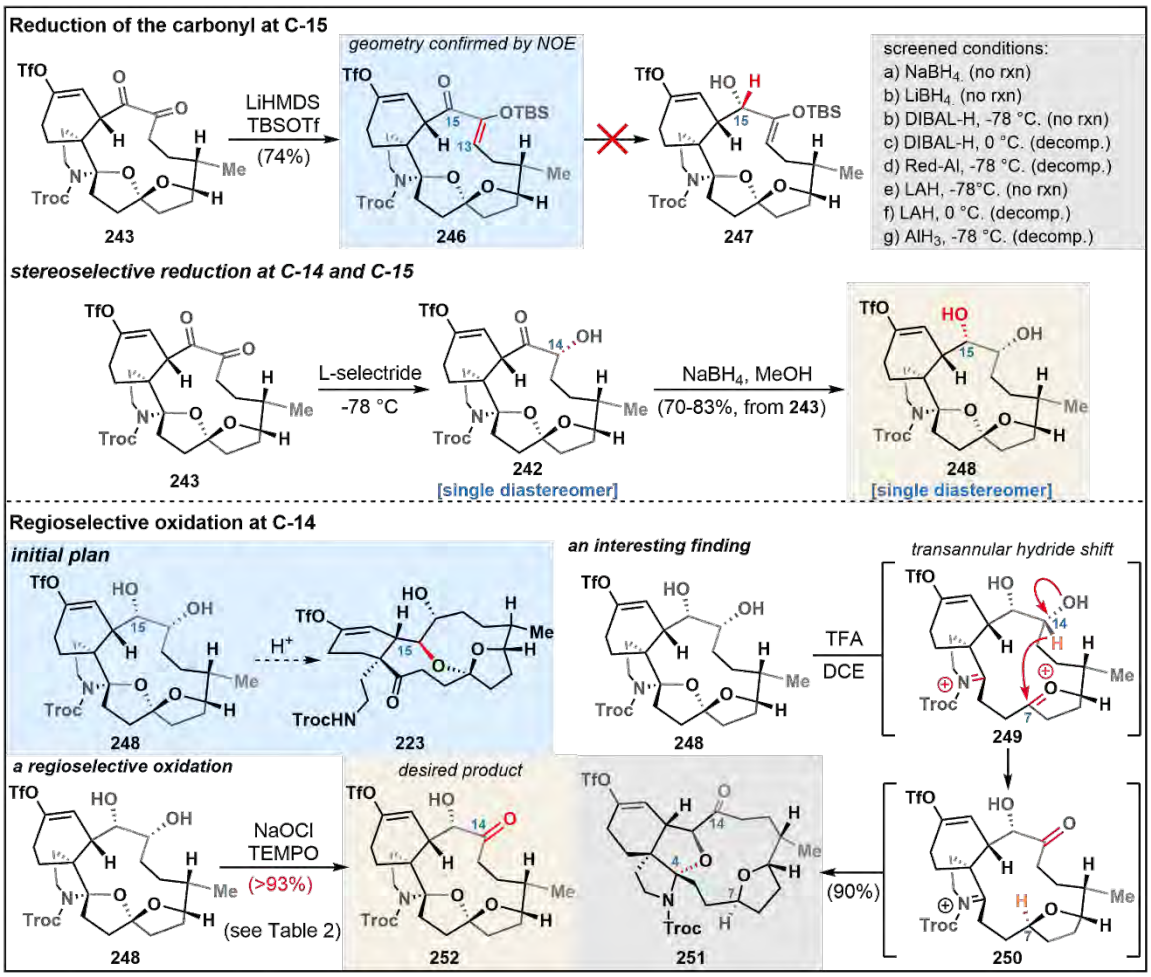


Figure 4.5 Stereoselective reduction of C-15 and regioselective oxidation of C-14.

Table 2. Screened conditions for selective C-14 oxidation from 248.

entry	condition	result
1	DMP, DCM, 0 °C	**242** only
2	DMP, DCM, rt	**242** + **243**
3	Collins reagent	messy
4	Jones' reagent	decomposed
5	PCC, DCM, 0 °C	messy
6	Fetizon's reagent, benzene, reflux	no reaction
7	DMSO, $(COCl)_2$, TEA, -78 °C to 0 °C	SM + **252** + **242** + **243** + **240**
8	DMSO, $(COCl)_2$, TEA, -78 °C	SM + **252**:**242** (1:1) + **243**
9	DMSO, $(COCl)_2$, DIPEA, -78 °C to rt	**242** + **243** + **252**
10	DMSO, DCC, Py, TFA, benzene, rt	no reaction

11	$Py{\cdot}SO_3$, DIPEA, DCM:DMSO = 1:1	no reaction
12	Ac_2O, DMSO, rt	**243** (major)
13	NCS, Me_2S, benzene	messy
14	DMSO, TFAA, TEA, -78 °C	**243** as major product
15	DMSO, TFAA, DIPEA, -78 °C	**242** + **252**
16	DMSO, TFAA, morpholine, -78 °C to -50 °C	**242** + **252**
17	DMSO, $(COCl)_2$, DIPEA, -78 °C to -50 °C	**242** + **252**
18	DMSO, $(COCl)_2$, morpholine, -78 °C to -50 °C	**242** (major) + **252**
19	TBSOTf, 2,6-lutidine, DCM	C-14 silylated only
20	DMDO, acetone, 0 °C	decomposed
21	NMO, TPAP, MS 4Å, DCM	**243** (major)
22	TEMPO, NaOCl (large excess), KBr, DCM, $NaHCO_3$	**252** (major) + **243**
23	TEMPO, NaOCl (ca. 2.0 eq.), KBr, DCM, $NaHCO_3$	**252** (93-99%)

Section 4.5 Reconstitution of the transannular ketal system of portimines.

Perhaps the “holy grail” of all synthetic works toward portimine A and B, constructing the unusual poly ketal system in portimines is extremely challenging and failed in all previous studies, even with the macrocyclic core in place (see Chapter 2). As I just mentioned in Chapter 3, polyketalization in the synthesis of portimines was highly demanding and required pre-installation of key functionalities. The formation of **252** was encouraging since C-4, C-7, C-10, C-14, and C-15 all presented as their final oxidation state and correct stereochemistry in portimine A and B, and this was an unprecedented achievement. Thus, to arrive at the natural products, **252** was believed to rearrange to protimines skeleton by unraveling its tricyclic system and liberating the aforementioned key functional groups.

My preliminary studies commenced with treating the key intermediate **252** with a variety of Lewis or Brønsted acids. Surprisingly, **252** was much more susceptible relative

to its C-15 epimer **240**, the latter remained intact even heating with 1 M $HClO_4$. Although several products could be isolated in the case of **252**, I failed to characterize their structures due to insufficient quantities. The successful skeletal reconstitution was carried out under deprotection of the Troc-carbamate, presumably resulting in an oxonium **253**, which then underwent a transannular C–O bond formation by the hydroxyl group at C-15, arriving at **255** as the single product. ^{13}C NMR indicated that **255** exhibited a portimines' skeleton presenting a transannular spirocyclic ketal system. Carbon atoms on the macrocyclic skeleton, for instance, C-3, C-4, C-6, C-7-C-12, and C-14-16, all displayed close chemical shifts to the corresponding carbons in natural products. Interestingly, pyrrole **254** resulting from nucleophilic attack by imine would be obtained as the major product when anhydrous AcOH was used. Consistently, an increasing amount of **254** was observed when removing AcOH from the reaction via rotovap. To minimize this undesired pathway, an aqueous solution of AcOH (containing 30 wt % H_2O) would be used, and the work-up would have to be carried out by dropping the reaction mixture into an aqueous solution of K_2CO_3.

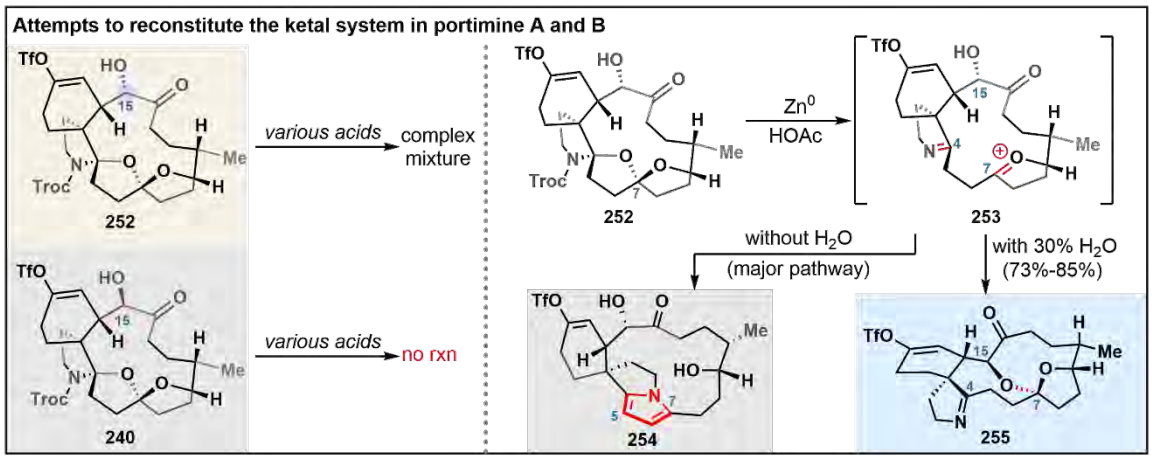


Figure 4.6 Free imine is crucial for ring-chain rearrangement.

Reference

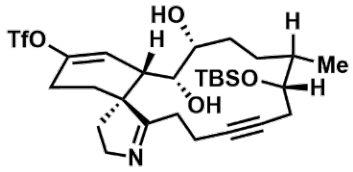
(1) Donohoe, T. J.; Blades, K.; Moore, P. R.; Waring, M. J.; Winter, J. J. G.; Helliwell, M.; Newcombe, N. J.; Stemp, G. Directed dihydroxylation of cyclic allylic alcohols and trichloroacetamides using OsO_4/TMEDA. *J. Org. Chem.* **2002**, *67*, 7946−7956.

(2) Wang, Z. W.; Krozsgaard-Larsen, N.; Daniels, B.; Furkert, D. P.; Brimble, M. A. Cyclic Enecarbamates as Precursors of alpha,beta-Unsaturated Iminium Ions: Reactivity and Synthesis of 6,6-Spirocyclic Ring Systems. *J. Org. Chem.* **2016**, *81*, 10366−10375.

(3) Hoffman, R. V. Preparation of 1-Arenesulfonyloxyalkyl Ketones. *Synthesis-Stuttgart* **1985**, *8*, 760−762.

(4) Chen, S.; Liu, Z.; Shi, E.; Chen, L.; Wei, W.; Li, H.; Cheng, Y.; Wan, X. Ruthenium-Catalyzed Oxidation of Alkenes at Room Temperature: A Practical and Concise Approach to α-Diketones. *Org. Lett.* **2011**, *13*, 2274–2277.

Experimental



Compound **206**. To a solution of olefin **204** (63 mg, 0.11 mmol) in acetone/H_2O (1 ml, 4:1 v/v) was added $K_2OsO_2(OH)_4$ (4 mg, 0.011 mmol) at 0 °C. The resulting mixture was stirred for 5 min (during when the pink solution turned darker and ended up with a brown solution), and added NMO (15 drops, 50 wt% in water, ca, 0.15 mmol). The reaction was kept stirred at 0 °C overnight and quenched by adding sat. aq. $NaHSO_3$ (0.1 ml) at the

ambient temperature, followed by stirring vigorously for 30 min. Subsequently, DCM (1 ml) was added to this mixture, and the aqueous layer was extracted with DCM (3x 1ml). The combined organic layer was dried over $MgSO_4$ and concentrated. Pure diol **206** (38 mg, 0.063 mmol, 57%) was obtained by chromatography (pure Et_2O to 10% MeOH in Et_2O).

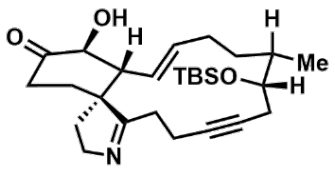
TLC: R_f = 0.25 (5% MeOH in Et_2O, $KMnO_4$ staining)

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.28 (d, *J* = 2.1 Hz, 1H), 4.00 – 3.90 (m, 1H), 3.80 (dtt, *J* = 16.0, 8.2, 2.9 Hz, 1H), 3.68 (ddd, *J* = 9.4, 4.8, 1.6 Hz, 1H), 3.46 (dt, *J* = 8.0, 3.9 Hz, 1H), 3.32 (s, 1H), 2.82 – 2.73 (m, 1H), 2.68 (s, 1H), 2.56 (ddd, *J* = 13.1, 8.2, 2.8 Hz, 1H), 2.52 – 2.30 (m, 5H), 2.26 (dddd, *J* = 21.8, 11.0, 5.0, 2.5 Hz, 3H), 2.00 (d, *J* = 6.2 Hz, 1H), 1.95 (td, *J* = 12.3, 6.1 Hz, 1H), 1.82 – 1.74 (m, 2H), 1.74 – 1.65 (m, 1H), 1.64 – 1.57 (m, 2H), 1.58 – 1.47 (m, 3H), 0.86 (s, 9H), 0.83 (d, *J* = 6.7 Hz, 3H), 0.02 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.2, 148.9, 119.0, 81.9, 76.5, 74.9, 74.768, 68.6, 59.2, 56.5, 45.5, 34.8, 33.5, 33.0, 31.8, 31.2, 30.3, 28.9, 28.4, 26.0, 25.8, 25.4, 22.8, 18.2, 14.5, 12.1, -4.1, -4.6.

(1 carbon *C*F_3 is missing in the carbon spectrum due to its splitting.)

^{1}H-^{1}H-NOESY was available.

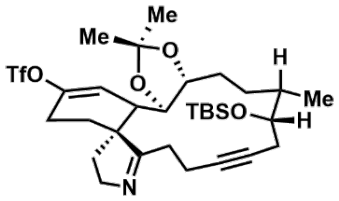


Compound **208**. To a solution of olefin **205** (15 mg, 0.026 mmol) in *t*-BuOH/H_2O (0.3 ml,

1:1 v/v) was added $K_2OsO_2(OH)_4$ (1 mg, 0.0052 mmol), $(DHQ)_2AQN$ (4.5 mg, 0.0052 mmol), and $MeSO_2NH_2$ (2 mg, 0.026 mmol). The resulting suspension was stirred at rom temperature for 10 min, followed by an addition of K_2CO_3 (10 mg) and $K_3[Fe(CN)_6]$ (26 mg, 0.078 mmol). The mixture was stirred vigorously at the same temperature overnight, giving a green solution. Upon completion, the mixture was diluted with H_2O (1 ml), and extracted with DCM. Compound **208** was isolated as a major product from the crude material by PTLC (5% MeOH in Et_2O).

TLC: R_f = 0.50 (5% MeOH in Et_2O, $KMnO_4$ staining)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68 (ddd, *J* = 14.3, 9.3, 4.3 Hz, 1H), 5.31 (dd, *J* = 14.6, 9.0 Hz, 1H), 4.00 (d, *J* = 11.0 Hz, 1H), 3.98 – 3.87 (m, 2H), 3.55 (dt, *J* = 8.1, 3.9 Hz, 1H), 2.76 – 2.66 (m, 1H), 2.65 – 2.52 (m, 2H), 2.46 (dd, *J* = 11.1, 8.4 Hz, 1H), 2.43 – 2.26 (m, 6H), 2.27 – 2.19 (m, 2H), 2.09 (tt, *J* = 9.4, 3.9 Hz, 1H), 2.03 – 1.90 (m, 3H), 1.78 – 1.72 (m, 1H), 1.47 – 1.39 (m, 1H), 0.86 (s, 9H), 0.82 (d, *J* = 6.7 Hz, 3H), 0.03 (s, 3H), 0.02 (s, 3H).



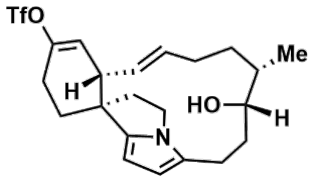
Compound **209**. To a solution of diol **206** (5 mg, 0.0082 mmol) in acetone (0.1 ml) was added 2,2-dimethxoylpropane (0.1 ml) in one portion at room temperature under argon. The resulting mixture was stirred for 5 min, and added PTSA (5 mg). The reaction was stirred for 1 h. Upon completion, sat. aq. $NaHCO_3$ (1 ml) was added to this solution to

quench the reaction. The mixture was then extracted by DCM (3x 1 ml) and dried over $MgSO_4$. After concentration, pure acetonide **209** (5.0 mg, 0.0077 mmol) was obtained by PTLC (35% EtOAc in hexanes).

TLC: R_f = 0.75 (50% EtOAc in hexanes, $KMnO_4$ staining)

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.74 (s, 1H), 3.95 (dd, *J* = 16.1, 9.6 Hz, 1H), 3.85 (dd, *J* = 9.2, 5.4 Hz, 1H), 3.77 – 3.70 (m, 1H), 3.61 (d, *J* = 9.1 Hz, 1H), 3.33 (dt, *J* = 7.9, 3.6 Hz, 1H), 2.80 (dd, *J* = 16.2, 12.4 Hz, 1H), 2.50 (ddt, *J* = 13.0, 9.4, 4.5 Hz, 2H), 2.46 – 2.39 (m, 3H), 2.38 – 2.25 (m, 2H), 2.20 – 2.08 (m, 2H), 1.98 (td, *J* = 12.2, 6.2 Hz, 1H), 1.67 – 1.53 (m, 4H), 1.51 – 1.44 (m, 1H), 1.35 (s, 3H), 1.28 (s, 3H), 1.12 (t, *J* = 13.2 Hz, 1H), 1.03 (qd, *J* = 11.4, 5.2 Hz, 1H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 176.4, 149.4, 117.1, 108.9, 81.7, 76.7, 75.8, 74.9, 74.8, 59.0, 56.2, 39.8, 33.1, 30.8, 28.8, 27.6, 27.3, 27.0, 26.7, 26.1, 25.7, 24.5, 18.3, 16.1, 14.5, -4.2, -4.4.



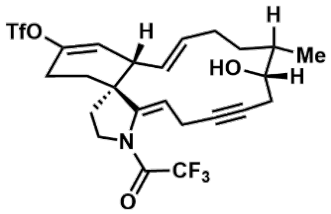
Compound **212**. To a solution of compound **205** (5 mg, 0.011 mmol) in DCM (0.15 ml) was added Ziese's salt (2.0 mg, 0.0052 mmol) in one portion at room temperature. The resulting pale-yellow solution was stirred at the same temperature for 10 min. Upon completion, the mixture was concentrated under reduced pressure. Pyrrole **212** (4.5 mg, 0.0099 mmol, 90%) was obtained by PTLC (25% EtOAc in hexanes).

TLC: R_f = 0.35 (25% EtOAc in hexanes, UV active, $KMnO_4$ staining)

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.90 (d, *J* = 3.3 Hz, 1H), 5.67 (d, *J* = 3.4 Hz, 1H), 5.63 (d, *J* = 2.1 Hz, 1H), 5.29 – 5.23 (m, 2H), 3.95 – 3.84 (m, 1H), 3.72 (td, *J* = 9.7, 7.4 Hz, 1H), 3.38 (ddd, *J* = 7.6, 5.2, 1.8 Hz, 1H), 3.07 (d, *J* = 6.0 Hz, 1H), 2.95 (ddd, *J* = 15.3, 8.2, 3.9 Hz, 1H), 2.57 – 2.39 (m, 4H), 2.37 – 2.14 (m, 4H), 2.02 – 1.80 (m, 6H), 1.77 (t, *J* = 2.6 Hz, 1H), 0.72 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 149.0, 135.1, 128.1, 127.0, 121.2, 109.7, 97.3, 50.1, 45.1, 44.8, 35.9, 34.8, 34.7, 33.2, 31.8, 30.2, 27.0, 26.1, 26.0, 22.5, 12.4.

^{1}H-^{1}H-COSY, ^{1}H-^{13}C-HSQC data are available.



Compound **213**. To a solution of compound **204** (25 mg, 0.044 mmol) in DCM (0.5 ml) was added TEA (0.05 ml, 36 mg, 0.36 mmol) at room temperature. The resulting solution was cooled to 0 °C, followed by adding TFAA (10 drops) at the same temperature. The reaction was allowed to stir at 0 °C for 30 min, and another 30 min at room temperature. Upon completion, the mixture was added H_2O (1 ml), followed by extraction with Et_2O (3x 1 ml). The combined organic layer was dried over $MgSO_4$ and concentrated. The crude TFA-enamide was used directly for next transformation.

Data of the TFA-enamide:

TLC: R_f = 0.88 (50% EtOAc in hexanes, UV active, $KMnO_4$ staining)

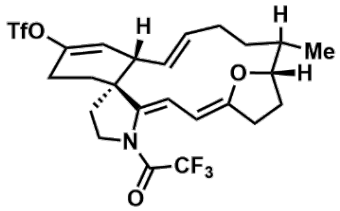
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.72 (ddd, *J* = 14.4, 9.1, 4.5 Hz, 1H), 5.63 (s, 1H), 5.29 (dd, *J* = 15.3, 8.6 Hz, 1H), 5.18 (t, *J* = 6.7 Hz, 1H), 3.96 (s, 1H), 3.68 – 3.58 (m, 1H), 3.54 – 3.47 (m, 1H), 3.19 (d, *J* = 8.6 Hz, 1H), 2.98 – 2.90 (m, 1H), 2.85 (dd, *J* = 18.6, 6.5 Hz, 1H), 2.51 – 2.35 (m, 2H), 2.22 (dd, *J* = 5.7, 3.1 Hz, 2H), 2.21 – 2.13 (m, 1H), 2.12 – 1.99 (m, 3H), 1.90 – 1.82 (m, 1H), 1.78 (dt, *J* = 13.2, 8.3 Hz, 1H), 1.73 (ddd, *J* = 13.8, 6.0, 1.7 Hz, 1H), 1.41 – 1.33 (m, 1H), 1.32 – 1.27 (m, 1H), 0.87 (s, 9H), 0.84 (d, *J* = 6.7 Hz, 3H), 0.02 (s, 3H), 0.02 (s, 3H).

^{1}H-^{1}H-NOESY data is available.

To a solution of the crude TFA-enamide in MeOH (1 ml) was treated with PTSA (10 mg) at 40 °C. The reaction mixture was allowed to stir at the same temperature for 1 h. Upon completion, sat. aq. $NaHCO_3$ (2 ml) was added to quench the acid, and the resulting mixture was extracted by DCM (3x 1 ml). The combined organic layer was dried over $MgSO_4$ and concentrated. Pure alcohol **213** (19 mg, 0.034 mmol, 85%) was obtained by PTLC (40% EtOAc in hexanes).

TLC: R_f = 0.45 (50% EtOAc in hexanes, UV active, $KMnO_4$ staining)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (ddd, *J* = 14.6, 10.0, 4.1 Hz, 1H), 5.62 (s, 1H), 5.29 (dd, *J* = 9.3, 8.2 Hz, 1H), 5.19 (t, *J* = 6.8 Hz, 1H), 3.96 (t, *J* = 9.9 Hz, 1H), 3.63 (q, *J* = 9.0 Hz, 1H), 3.37 (s, 1H), 3.17 (d, *J* = 9.3 Hz, 1H), 2.96 – 2.91 (m, 2H), 2.51 – 2.40 (m, 3H), 2.40 – 2.31 (m, 1H), 2.21 (q, *J* = 11.5 Hz, 1H), 2.13 – 2.07 (m, 1H), 2.07 – 1.99 (m, 1H), 1.99 – 1.92 (m, 1H), 1.88 (td, *J* = 12.5, 6.4 Hz, 1H), 1.82 – 1.76 (m, 1H), 1.76 – 1.70 (m, 1H), 1.42 – 1.36 (m, 1H), 0.99 (d, *J* = 6.6 Hz, 3H).



Compound **214**. ***Procedure 1*:** To a solution of compound **213** (4.0 mg, 0.0072 mmol) in Et_2O (0.2 ml) was added Ziese's salt (1 mg, 0.0026 mmol) in one portion at room temperature. The mixture was allowed to stir at the ambient temperature for 30 min, and quenched by sat. aq. $NaHCO_3$ (1 ml). The mixture was then extracted with Et_2O and dried over $MgSO_4$. After concentration, pure **214** (3.1 mg, 0.0056 mmol, 78%) was obtained by PTLC (20% Et_2O in hexanes).

***Procedure 2*:** To a solution of $Au(PPh_3)Cl$ (10 mg, 0.020 mmol) in DCM (1 ml) was added $AgSbF_6$ (6.8 mg, 0.020 mmol) in one portion under argon. A milky suspension generated and was stirred for 30 min. The mixture was then allowed to stand for 10 min.

To a solution of compound **213** (5.0 mg, 0.010 mmol) in DCM (0.1 ml) was added the freshly prepared gold (I) reagent (0.1 ml, supernatant) dropwise at 0 °C. The resulting mixture was stirred for 15 min, and concentrated. Pure **214** (2.5 mg, 0.005 mmol, 50%) was obtained by PTLC (20% Et_2O in hexanes).

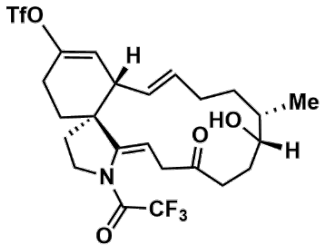
TLC: R_f = 0.39 (20% Et_2O in hexanes, UV active, $KMnO_4$ staining)

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.17 (d, *J* = 11.0 Hz, 1H), 6.03 (ddd, *J* = 15.0, 11.3, 3.6 Hz, 1H), 5.63 (d, *J* = 1.8 Hz, 1H), 5.17 (ddd, *J* = 14.9, 10.4, 1.7 Hz, 1H), 4.86 (dd, *J* = 11.0, 1.9 Hz, 1H), 4.44 (ddd, *J* = 10.2, 6.4, 4.1 Hz, 1H), 3.88 – 3.75 (m, 2H), 3.48 – 3.32 (m, 1H), 2.60 (s, 1H), 2.50 – 2.39 (m, 3H), 2.19 – 2.12 (m, 1H), 2.12 – 2.04 (m, 1H), 2.00 – 1.90

(m, 3H), 1.90 – 1.80 (m, 2H), 1.79 – 1.68 (m, 1H), 1.63 – 1.56 (m, 1H), 1.25 – 1.13 (m, 2H), 0.92 (d, *J* = 7.3 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 159.9, 147.2, 138.7, 131.3, 124.9, 123.0, 115.1, 95.0, 85.3, 45.8, 45.1, 44.8, 36.5, 32.0, 30.8, 30.6, 30.5, 26.1, 24.6, 24.4, 17.8.

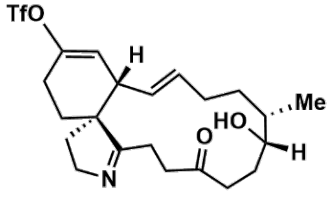
^{1}H-^{1}H-COSY, ^{1}H-^{1}H-NOESY, ^{1}H-^{13}C-HSQC, ^{1}H-^{13}C-HMBC are available.



Compound **215**. To a solution of alcohol **213** (40.1 mg, 0.072 mmol) in THF/H_2O (1 ml, 5:1 v/v) was added PPh_3AuNTf_2 (4.0 mg, 0.0054 mmol) in one portion. The mixture was then heated to 50 °C and stirred for 1.5 h. Upon completion (checked by TLC, 40% EtOAc in hexanes), the mixture was extracted with EtOAc (3x 1 ml). The organic layer was dried over $MgSO_4$ and concentrated. **215** (39 mg, 0.068 mmol, 94%) was obtained by chromatography (10% to 45% EtOAc in hexanes).

TLC: R_f = 0.40 (50% EtOAc in hexanes, UV active, $KMnO_4$ staining)

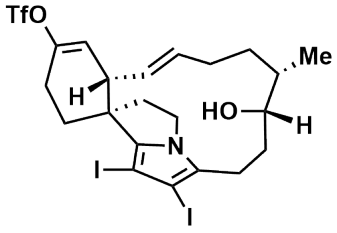
^{1}H NMR and ^{13}C NMR are not assigned due to mixture of ketals.



Compound **217**. To a solution of freshly prepared **215** (15 mg, 0.026 mmol) in MeOH (1 ml) was added NH_3 (0.1 ml, 37 wt% in H_2O) in one portion. The resulting mixture was

stirred for 1 h, and extracted with benzene. Crude **217** was obtained from concentration of the dried organic layer. Purification of this compound on silica gel is not feasible due to irreversible pyrrole formation.

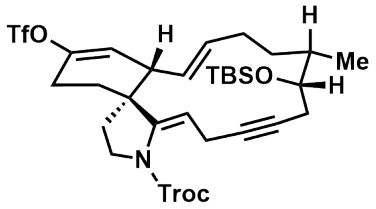
^{1}H NMR of the crude product is available.



Compound **218**. To a solution of freshly prepared imine **217** (ca. 4 mg, 0.0084 mmol) in MeCN/H_2O (0.3 ml, 9:1 v/v) was added NIS (3 mg, 0.013 mmol) at 0 °C. The mixture was stirred at the same temperature for 5 min, and quenched by sat. aq. $Na_2S_2O_3$ (0.5 ml). The mixture was extracted by DCM (3x 1 ml). The organic layer was dried over $MgSO_4$ and concentrated. Pure **218** was obtained as the major product by PTLC (20% EtOAc in hexanes).

TLC: R_f = 0.33 (20% EtOAc in hexanes, UV active, $KMnO_4$ staining)

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.66 (d, *J* = 2.5 Hz, 1H), 5.26 – 5.22 (m, 2H), 4.00 – 3.90 (m, 1H), 3.75 (td, *J* = 9.8, 7.9 Hz, 1H), 3.42 – 3.31 (m, 2H), 2.98 (ddd, *J* = 15.4, 8.0, 3.7 Hz, 1H), 2.74 (ddd, *J* = 13.5, 11.2, 6.5 Hz, 1H), 2.59 (ddd, *J* = 15.4, 9.3, 3.8 Hz, 1H), 2.56 – 2.41 (m, 3H), 2.21 (dt, *J* = 13.4, 9.7 Hz, 1H), 2.14 (ddd, *J* = 12.9, 8.9, 4.0 Hz, 1H), 2.02 – 1.89 (m, 2H), 1.80 – 1.71 (m, 2H), 1.44 – 1.29 (m, 2H), 0.78 (d, *J* = 5.9 Hz, 3H).

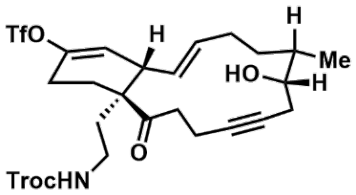


Compound **219**. To a solution of imine **204** (69 mg, 0.12 mmol) in DCM (3 ml) was added DMAP (75 mg, 0.61 mmol) and TrocCl (1.0 ml, large excess) at room temperature. The resulting mixture was heat to reflux, and stirred for 1 h. Upon completion, the reaction was quenched by adding to sat. aq. $NaHCO_3$ (5 ml) dropwise. Subsequently, the mixture was extracted by Et_2O (3x 5 ml) and dried over $MgSO_4$. After concentration, the crude product was purified by chromatography (5% EtOAc in hexanes) to yield Troc-enamide **219** (72 mg, 0.10 mmol, 83%).

TLC: R_f = 0.40 (5% EtOAc in hexanes, UV active, $KMnO_4$ staining)

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.71 – 5.61 (m, 2H), 5.39 (dd, *J* = 15.8, 7.7 Hz, 1H), 4.89 – 4.86 (m, 3H), 3.83 (dt, *J* = 11.0, 8.0 Hz, 1H), 3.63 (ddd, *J* = 8.1, 4.9, 2.9 Hz, 1H), 3.61 – 3.55 (m, 1H), 3.33 (s, 1H), 2.94 (ddt, *J* = 18.4, 9.6, 2.7 Hz, 1H), 2.90 – 2.81 (m, 1H), 2.52 – 2.41 (m, 1H), 2.41 – 2.35 (m, 1H), 2.30 – 2.21 (m, 2H), 2.21 – 2.14 (m, 1H), 2.12 – 1.99 (m, 2H), 1.85 (dt, *J* = 13.0, 8.6 Hz, 1H), 1.81 (dd, *J* = 8.1, 4.1 Hz, 1H), 1.79 – 1.69 (m, 2H), 1.51 (dt, *J* = 7.9, 4.2 Hz, 1H), 1.25 – 1.17 (m, 1H), 0.88 (s, 9H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H).

^{1}H-^{1}H-NOESY is available.



Compound **221**. To a solution of Troc-enamide **219** (340 mg, 0.45 mmol) in MeOH/H_2O (6 ml, 5:1 v/v) was added PTSA (85 mg, 0.45 mmol) in one portion. The resulting mixture was heated to 45 °C and stirred overnight. Upon completion, sat. aq. $NaHCO_3$ (5 ml) was added to the mixture to quench the excess acid. The resulting mixture was then extracted by DCM (3x 5 ml) and dried over $MgSO_4$. After concentration, pure **221** (236 mg, 0.36 mmol, 80%)

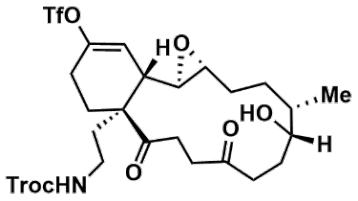
TLC: R_f = 0.45 (20% Et_2O in hexanes, $KMnO_4$ staining)

[α]$^{25}_D$: -41.4 (*c* = 0.5, $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.65 (ddd, *J* = 15.3, 9.7, 4.7 Hz, 1H), 5.60 (d, *J* = 2.3 Hz, 1H), 5.27 (dd, *J* = 15.3, 8.6 Hz, 1H), 5.17 (t, *J* = 5.8 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 3.56 – 3.50 (m, 1H), 3.45 (s, 1H), 3.34 – 3.27 (m, 1H), 3.26 – 3.20 (m, 1H), 2.80 (ddd, *J* = 18.8, 11.2, 3.0 Hz, 1H), 2.64 – 2.46 (m, 4H), 2.46 – 2.28 (m, 3H), 2.20 – 2.01 (m, 4H), 1.95 (dd, *J* = 14.0, 5.8 Hz, 1H), 1.85 (dq, *J* = 9.4, 6.6 Hz, 1H), 1.64 (ddd, *J* = 14.0, 9.4, 5.0 Hz, 1H), 1.50 – 1.39 (m, 2H), 1.23 – 1.15 (m, 1H), 0.93 (d, *J* = 6.6 Hz, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 209.9, 154.7, 147.6, 133.9, 126.5, 120.5, 118.6 (q, J_{C-F} = 320 Hz), 95.7, 81.5, 75.8, 74.7, 73.0, 52.0, 46.2, 37.7, 35.7, 33.0, 32.3, 28.3, 28.0, 27.2, 25.6, 24.9, 13.6, 13.1.

HRMS (ESI-TOF): calc'd for $C_{25}H_{31}Cl_3F_3NO_7S$ $[M+H]^+$: 652.0917, found: 652.0919



Compound **222**. To a solution of compound **221** (68 mg, 0.10 mmol) in $CHCl_3$ (1.0 ml) was heated to 40 °C and added *m*-CPBA (60 mg, 0.35 mmol) in one portion. The mixture was allowed to stir for 45 min, and added $Ca(OH)_2$ (30 mg) after completion. The mixture was then filtered through a silica gel plug and concentrated. Crude epoxide was obtained after concentration and used directly for next step.

To a solution of the crude epoxide in THF/H_2O (2 ml, 9:1 v/v) was added PPh_3AuNTf_2 (3.0 mg, 0.0041 mmol) in one portion at 50 °C. The mixture was stirred for 30 min and cooled down. Upon completion, sat. aq. $NaHCO_3$ (1 ml) was added and the resulting mixture was extracted by DCM (3x 1 ml). The combined layer was dried over $MgSO_4$ and concentrated to give the crude product, which was purified chromatography (10% EtOAc to 50% EtOAc in hexanes) to yield **222** (22 mg, 0.032 mmol, 32%).

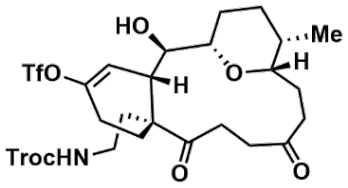
TLC: R_f = 0.33 (50% EtOAc in hexanes, $KMnO_4$ staining)

^{1}H NMR (600 MHz, C_6D_6) δ 5.85 (t, *J* = 2.1 Hz, 1H), 4.58 (d, *J* = 12.1 Hz, 1H), 4.44 (d, *J* = 12.1 Hz, 1H), 3.94 – 3.89 (m, 1H), 3.47 (td, *J* = 5.0, 2.7 Hz, 1H), 2.75 – 2.59 (m, 4H), 2.57 – 2.49 (m, 2H), 2.30 (dd, *J* = 8.7, 2.2 Hz, 1H), 2.14 – 1.99 (m, 2H), 1.97 – 1.88 (m, 5H), 1.84 (dd, *J* = 17.9, 5.3 Hz, 1H), 1.53 – 1.17 (m, 10H), 0.79 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, C_6D_6) δ 211.2, 154.3, 148.2, 118.2, 74.7, 71.4, 58.5, 56.0, 49.3, 44.8,

40.7, 37.3, 35.0, 34.4, 30.9, 29.4, 28.4, 27.3, 26.2, 24.6, 12.8.

^{1}H-^{13}C-HSQC, ^{1}H-^{13}C-HMBC, ^{1}H-^{1}H-NOESY are available.

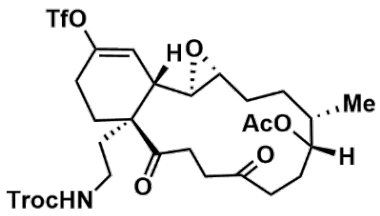


Compound **224**. To a solution of epoxide **222** (10 mg, 0.015 mmol) in benzene (0.1 ml) was added CSA (0.2 mg) in one portion at room temperature. After 1 h, TLC indicated the full conversion of the starting material. The mixture was then stirred at the ambient temperature for 1 h, and quenched by sat. aq. $NaHCO_3$ (1 ml). The mixture was then extracted by DCM (3x 1 ml) and dried over $MgSO_4$. After concentration, the crude product was purified by PTLC (30% EtOAc in hexanes) to afford **224** (ca. 3 mg).

TLC: R_f = 0.45 (50% EtOAc in hexanes, $KMnO_4$ staining)

^{1}H NMR (600 MHz, C_6D_6) δ 5.62 (d, *J* = 2.2 Hz, 1H), 4.64 (d, *J* = 12.1 Hz, 1H), 4.50 (d, *J* = 12.1 Hz, 1H), 4.35 (s, 1H), 3.53 – 3.44 (m, 1H), 3.24 – 3.18 (m, 2H), 2.99 (dd, *J* = 18.8, 9.8 Hz, 1H), 2.88 (dt, *J* = 9.9, 2.2 Hz, 2H), 2.83 – 2.76 (m, 1H), 2.71 – 2.66 (m, 1H), 2.64 (ddd, *J* = 11.5, 9.0, 2.6 Hz, 1H), 2.35 (dt, *J* = 12.6, 6.2 Hz, 1H), 2.30 – 2.11 (m, 3H), 2.04 (dd, *J* = 14.5, 7.8 Hz, 1H), 1.98 – 1.89 (m, 2H), 1.86 (dt, *J* = 13.6, 4.0 Hz, 1H), 1.73 – 1.37 (m, 9H), 0.70 (d, *J* = 7.0 Hz, 3H).

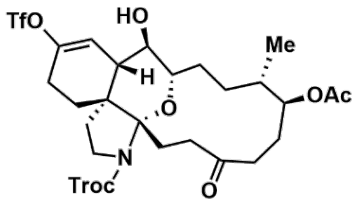
^{13}C NMR (151 MHz, C_6D_6) δ 212.9, 207.7, 158.9, 154.4, 148.1, 117.1, 79.1, 78.8, 74.6, 70.2, 51.5, 41.6, 37.4, 31.7, 30.4, 30.1, 28.5, 26.9, 26.6, 24.4, 23.1, 22.3, 14.4.



Compound **225**. To a solution of alcohol **222** (ca. 10 mg, 0.014 mmol) in DCM (1 ml) was added DMAP (5 mg, 0.041 mmol) and Ac_2O (1 drop). The resulting mixture was stirred at room temperature for 1 h, and quenched by adding H_2O (0.5 ml). The resulting mixture was extracted by DCM (3x 1.0 ml) and dried over $MgSO_4$. After concentration, pure **225** (9.3 mg, 0.012 mmol, 86%) was obtained from PTLC (30% EtOAc in hexanes).

TLC: R_f = 0.50 (30% EtOAc in hexanes, $KMnO_4$ staining)

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.81 (t, *J* = 2.0 Hz, 1H), 4.88 (t, *J* = 6.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.67 – 4.62 (m, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 3.29 – 3.17 (m, 3H), 3.16 – 3.04 (m, 1H), 2.60 – 2.46 (m, 5H), 2.45 – 2.33 (m, 2H), 2.26 – 2.15 (m, 6H), 2.07 (s, 3H), 1.88 – 1.77 (m, 1H), 1.75 – 1.51 (m, 4H), 1.47 – 1.38 (m, 1H), 1.35 (ddt, *J* = 14.2, 9.6, 4.7 Hz, 1H), 0.99 (d, *J* = 6.8 Hz, 3H).



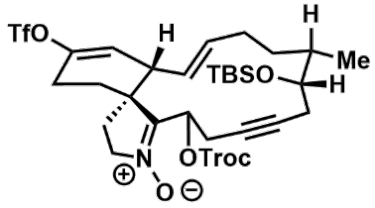
Compound **226**. To a solution of compound **225** (ca. 5 mg, 0.0069 mmol) in DCM (0.3 ml) was added TFA (1 drop) at room temperature. The mixture was then allowed to stir for 30 min, and concentrated. Pure **226** (2.2 mg) was isolated from PTLC (90% Et_2O in hexanes).

^{1}H NMR (600 MHz, C_6D_6) δ 5.88 (d, *J* = 1.8 Hz, 1H), 4.77 (d, *J* = 12.0 Hz, 1H), 4.73 –

4.69 (m, 1H), 4.36 (d, *J* = 12.2 Hz, 1H), 3.77 – 3.64 (m, 1H), 3.40 (t, *J* = 10.4 Hz, 1H), 3.24 (td, *J* = 10.7, 7.9 Hz, 1H), 3.02 – 2.84 (m, 2H), 2.77 (t, *J* = 9.8 Hz, 1H), 2.70 (t, *J* = 10.0 Hz, 1H), 2.62 – 2.56 (m, 1H), 2.24 – 2.13 (m, 2H), 2.09 (dt, *J* = 16.5, 6.7 Hz, 1H), 1.99 (dd, *J* = 14.0, 9.1 Hz, 1H), 1.94 – 1.85 (m, 2H), 1.84 – 1.76 (m, 1H), 1.74 – 1.68 (m, 2H), 1.67 (s, 3H), 1.60 – 1.45 (m, 2H), 1.42 – 1.14 (m, 6H), 0.80 – 0.77 (m, 3H).

^{13}C NMR (151 MHz, C_6D_6) δ 212.5, 169.6, 152.2, 148.6, 130.8, 118.5, 96.3, 94.5, 77.1, 74.8, 68.0, 65.4, 49.3, 43.7, 39.2, 38.7, 36.2, 32.4, 30.9, 30.2, 28.0, 27.9, 25.4, 20.5, 15.9.

^{1}H-^{13}C-HSQC, ^{1}H-^{13}C-HMBC, ^{1}H-^{1}H-NOESY are available.



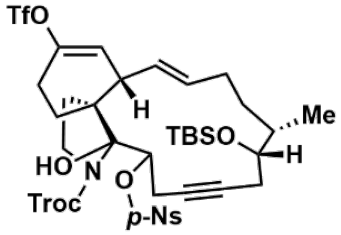
Compound **230**. To a solution of Troc-enamide **219** (32 mg, 0.042 mmol) in DCM (0.1 ml) was added freshly prepared DMDO (ca. 0.08 M, 1.5 ml) dropwise at 0 °C. The mixture was allowed to stir at the same temperature for 30 min. Upon completion, the volatiles were removed by rotovap, and the residue was purified by PTLC (15% Et_2O in hexanes) to yield nitrone **230** (20 mg, 0.026 mmol, 61%).

TLC: R_f = 0.48 (20% EtOAc in hexanes, slightly UV active, $KMnO_4$ staining)

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.67 (d, *J* = 2.0 Hz, 1H), 5.66 – 5.58 (m, 1H), 5.42 (dt, *J* = 10.4, 2.5 Hz, 1H), 5.23 (dd, *J* = 15.6, 6.9 Hz, 1H), 4.90 (d, *J* = 11.9 Hz, 1H), 4.76 (d, *J* = 11.8 Hz, 1H), 4.02 (ddd, *J* = 17.0, 9.4, 4.0 Hz, 1H), 3.88 – 3.77 (m, 1H), 3.58 (ddd, *J* = 8.0, 4.8, 3.1 Hz, 1H), 3.30 (s, 1H), 3.24 (ddt, *J* = 15.9, 10.7, 2.7 Hz, 1H), 2.63 (dd, *J* = 15.5, 2.7

Hz, 1H), 2.50 – 2.41 (m, 2H), 2.39 – 2.25 (m, 3H), 2.19 – 2.11 (m, 0H), 2.08 – 1.97 (m, 2H), 1.90 (ddt, *J* = 13.0, 11.2, 4.9 Hz, 2H), 1.85 – 1.74 (m, 2H), 1.48 – 1.39 (m, 1H), 1.18 (dddt, *J* = 13.4, 9.9, 6.8, 3.7 Hz, 1H), 0.87 (s, 9H), 0.82 (d, *J* = 6.7 Hz, 3H), 0.03 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.4, 153.6, 148.4, 133.4, 126.9, 120.9, 79.7, 76.0, 72.7, 71.8, 59.1, 56.3, 43.6, 32.4, 32.1, 30.1, 28.2, 26.0, 25.8, 22.8, 18.2, 13.4, -4.0, -4.7.

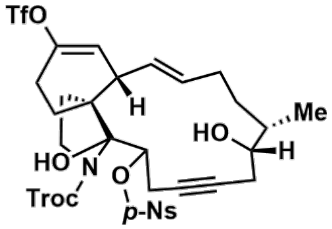


Compound **234**.To a solution of Troc-enamide **219** (2.3 mg, 0.0031 mmol) in EtOAc (0.1 ml) was added (*p*-NsO)$_2$ (1.5 mg, 0.0035 mmol), H_2O (3 drops), and $NaHCO_3$ (4 mg) at room temperature. The mixture was allowed to stir at the ambient temperature for 2 h. Upon completion, H_2O (1 ml) was added to quench the reaction. The resulting mixture was extracted by benzene (3x 1 ml) and dried over $MgSO_4$. After concentration, crude material was purified by PTLC (10% EtOAc in hexanes) to yield **234** (2.0 mg, 0.0021 mmol, 68%) as single product.

TLC: R_f = 0.41 (10% EtOAc in hexanes, UV active, $KMnO_4$ staining)

^{1}H NMR (500 MHz, C_6D_6) δ 7.80 (d, *J* = 8.5 Hz, 2H), 7.60 – 7.48 (m, 2H), 5.91 (d, *J* = 10.1 Hz, 1H), 5.74 (s, 1H), 5.68 – 5.58 (m, 1H), 5.19 (s, 1H), 5.15 – 5.04 (m, 1H), 4.59 – 4.50 (m, 1H), 4.39 (d, *J* = 12.0 Hz, 1H), 3.87 – 3.81 (m, 1H), 3.34 (d, *J* = 9.6 Hz, 1H), 3.10 (q, *J* = 10.0 Hz, 1H), 2.92 (t, *J* = 9.8 Hz, 1H), 2.33 (s, 2H), 2.29 – 2.18 (m, 3H), 2.14 – 1.98

(m, 2H), 1.94 – 1.74 (m, 3H), 1.36 – 1.19 (m, 4H), 1.14 (d, *J* = 6.8 Hz, 3H), 0.96 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H).



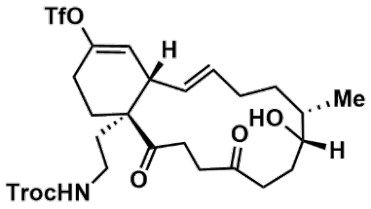
Compound **235**. To a solution of compound **234** (4.2 mg, 0.0043 mmol) in DCM (0.1 ml) was added Olah's reagent (1 drop) at room temperature. The mixture was then allowed to stir for 1 h, and directly purified by PTLC (35% EtOAc in hexanes) to yield free alcohol **235** (2.8 mg, 0.0034 mmol, 79%).

TLC: R_f = 0.19 (20% EtOAc in hexanes, UV active, $KMnO_4$ staining)

^{1}H NMR (500 MHz, C_6D_6) δ 7.80 (d, *J* = 8.8 Hz, 2H), 7.59 – 7.49 (m, 2H), 5.91 (d, *J* = 10.0 Hz, 1H), 5.85 (ddd, *J* = 14.5, 9.4, 4.4 Hz, 1H), 5.64 (s, 1H), 5.18 (s, 1H), 5.04 (dd, *J* = 15.4, 9.8 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.36 (d, *J* = 12.0 Hz, 1H), 3.37 (d, *J* = 9.9 Hz, 1H), 3.32 (s, 1H), 3.08 (q, *J* = 10.3 Hz, 1H), 2.90 (t, *J* = 9.4 Hz, 1H), 2.33 – 2.18 (m, 3H), 2.12 (dd, *J* = 13.1, 6.3 Hz, 2H), 2.08 – 1.97 (m, 2H), 1.97 – 1.88 (m, 1H), 1.89 – 1.73 (m, 3H), 1.69 – 1.57 (m, 1H), 1.36 – 1.21 (m, 4H), 1.16 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (151 MHz, C_6D_6) δ 153.4, 150.5, 147.3, 142.5, 136.4, 129.1, 128.6, 124.3, 124.0, 120.2, 95.9, 94.0, 85.5, 80.8, 78.1, 74.3, 73.6, 49.2, 44.2, 42.6, 35.7, 32.3, 30.2, 29.0, 28.1, 26.7, 24.4, 24.2, 22.6, 15.8.

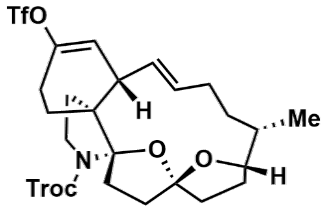
^{1}H-^{13}C-HSQC, ^{1}H-^{13}C-HMBC, ^{1}H-^{1}H-NOESY are available.



Compound **236**. To a solution of alkyne **221** (5.3 mg, 0.0081 mmol) in THF/H_2O (0.3 ml, 5:1 v/v) was added PPh_3AuNTf_2 (1.0 mg, 0.0014 mmol) in one portion. The mixture was allowed to stir at 40 °C for 1.5 h. Upon completion, the mixture was extracted by benzene (3x 1 ml) and dried over $MgSO_4$. After concentration, the crude material was purified by PTLC (30% EtOAc in hexanes) to give **236** (4.5 mg, 0.0067 mmol, 83%).

TLC: R_f = 0.31 (80% EtOAc in hexanes, $KMnO_4$ staining)

^{1}H NMR (500 MHz, C_6D_6) δ 5.46 (ddd, *J* = 15.0, 10.4, 4.5 Hz, 1H), 5.21 (s, 1H), 4.86 (dd, *J* = 15.1, 10.1 Hz, 1H), 4.56 (d, *J* = 12.1 Hz, 1H), 4.46 (d, *J* = 12.1 Hz, 1H), 4.00 (s, 1H), 3.27 (d, *J* = 9.3 Hz, 1H), 2.88 (ddd, *J* = 30.4, 15.1, 7.1 Hz, 3H), 2.76 – 2.62 (m, 2H), 2.59 – 2.48 (m, 1H), 2.25 – 2.10 (m, 2H), 2.06 – 1.95 (m, 3H), 1.93 – 1.80 (m, 4H), 1.62 – 1.41 (m, 7H), 1.01 (d, *J* = 6.7 Hz, 3H).

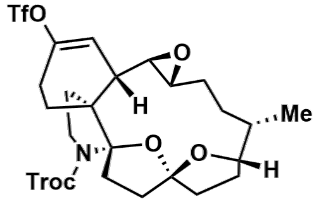


Compound **237**. Compound **236** was cyclized spontaneously in $CDCl_3$ to give **237**.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.85 (ddd, *J* = 15.2, 10.0, 5.3 Hz, 1H), 5.48 (d, *J* = 2.2 Hz, 1H), 5.19 (dd, *J* = 15.0, 9.6 Hz, 1H), 4.81 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 3.90 (td, *J* = 10.3, 5.3 Hz, 1H), 3.72 – 3.60 (m, 1H), 3.40 (td, *J* = 11.1, 7.1 Hz, 1H), 3.18

(d, *J* = 9.6 Hz, 1H), 2.96 (dt, *J* = 13.1, 10.3 Hz, 1H), 2.41 (d, *J* = 5.9 Hz, 1H), 2.33 – 2.18 (m, 4H), 2.16 – 1.98 (m, 4H), 1.99 – 1.81 (m, 3H), 1.68 (dd, *J* = 12.1, 7.4 Hz, 2H), 1.61 (d, *J* = 12.7 Hz, 4H), 0.86 (d, *J* = 7.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 146.7, 136.0, 127.1, 124.6, 118.4, 105.7, 85.6, 74.5, 48.9, 44.0, 42.3, 39.7, 36.5, 32.6, 32.5, 29.9, 29.0, 28.2, 25.1, 24.3, 22.9, 21.0.



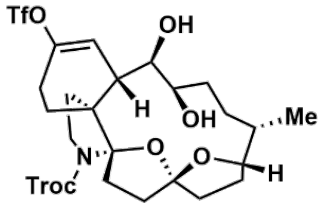
Compound **238**. To a solution of compound **237** (5 mg, 0.0077 mmol) in DCM (0.2 ml) was cooled to 0 °C and added *m*-CPBA (95% pure, 6 mg) in one portion at the same temperature. The reaction was allowed to stir at the same temperature for 15 min, and added $Ca(OH)_2$ (10 mg). The suspension was stirred for another 1 h, and filtered. The filtrate was concentrated and purified by PTLC (40% Et_2O in hexanes) to yield epoxide **238** (5 mg, 0.0075 mmol, 97%).

TLC: R_f = 0.70 (60% EtOAc in hexanes, $KMnO_4$ staining)

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.94 (s, 1H), 4.83 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.07 (ddd, *J* = 10.1, 6.4, 3.5 Hz, 1H), 3.68 (t, *J* = 10.3 Hz, 1H), 3.49 (td, *J* = 11.0, 7.2 Hz, 1H), 3.44 (dt, *J* = 9.6, 2.6 Hz, 1H), 2.86 – 2.77 (m, 1H), 2.57 (dd, *J* = 8.6, 2.1 Hz, 1H), 2.44 (dd, *J* = 13.6, 8.1 Hz, 2H), 2.34 – 2.27 (m, 1H), 2.27 – 2.20 (m, 1H), 2.14 (dp, *J* = 21.7, 8.0 Hz, 4H), 1.98 – 1.86 (m, 3H), 1.86 – 1.79 (m, 2H), 1.77 – 1.67 (m, 3H), 1.64 – 1.58 (m, 2H), 1.16 – 1.09 (m, 1H), 0.88 (d, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 152.2, 148.0, 120.8, 118.3, 104.5, 85.0, 74.5, 63.5, 60.3, 48.8, 43.8, 41.1, 40.0, 38.3, 35.4, 34.3, 30.1, 28.5, 28.3, 25.5, 24.8, 24.5, 23.7, 20.3.

^{1}H-^{13}C-HSQC, ^{1}H-^{13}C-HMBC, ^{1}H-^{1}H-NOESY are available.



Compound **239**. To a solution of tricycle **237** (ca. 4 mg, 0.0058 mmol) in acetone/H_2O (0.5 ml, 9:1 v/v) was added OsO_4 (1 drop, 5 wt% in H_2O) at room temperature. The resulting mixture was then added NMO (1 drop, 50 wt% in H_2O) and stirred for 30 min. Upon completion, the reaction was quenched by adding sat. aq. $NaHSO_3$ (0.1 ml) and diluted with brine (1 ml). The mixture was extracted by EtOAc (3x 1 ml) and dried over $MgSO_4$. After concentration, pure diol **239** (3.9 mg, 0.0057 mmol, 98%) was obtained from PTLC (45% EtOAc in hexanes).

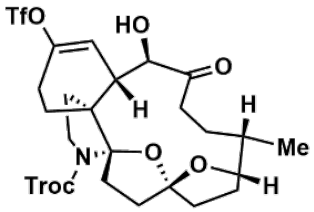
TLC: R_f = 0.40 (40% EtOAc in hexanes, $KMnO_4$ staining)

^{1}H NMR (600 MHz, C_6D_6) δ 6.36 (d, *J* = 2.8 Hz, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.60 (s, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 3.65 (dd, *J* = 10.6, 2.6 Hz, 1H), 3.59 (dt, *J* = 11.1, 4.5 Hz, 1H), 3.48 (t, *J* = 10.2 Hz, 1H), 3.20 (q, *J* = 11.2 Hz, 1H), 3.10 – 2.98 (m, 1H), 2.59 (s, 1H), 2.30 – 2.15 (m, 2H), 2.14 – 2.06 (m, 2H), 2.03 – 1.96 (m, 1H), 1.94 – 1.89 (m, 1H), 1.87 – 1.77 (m, 2H), 1.77 – 1.70 (m, 1H), 1.69 – 1.59 (m, 3H), 1.58 – 1.48 (m, 3H), 1.43 – 1.22 (m, 2H), 1.22 – 1.11 (m, 1H), 0.62 (d, *J* = 7.3 Hz, 3H).

^{13}C NMR (151 MHz, C_6D_6) δ 152.4, 149.4, 120.5, 118.1, 107.1, 85.7, 74.6, 73.4, 67.7,

48.9, 44.7, 43.3, 38.8, 37.3, 35.4, 34.6, 30.8, 29.7, 28.6, 26.1, 25.1, 24.6, 24.5, 19.5.

^{1}H-^{13}C-HSQC, ^{1}H-^{13}C-HMBC are available.

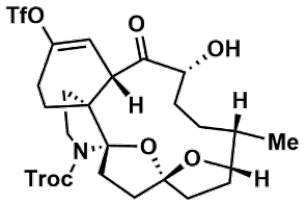


Compound **240**. To a solution of DMSO (1 drop) in DCM (0.1 ml) at -78 °C was added $(COCl)_2$ (2 drops). The resulting mixture was allowed to stir at the same temperature for 20 min. After activation, a solution of diol **239** (5.0 mg, 0.0073 mmol) in DCM (0.1 ml) was added slowly to the solution at -78 °C, and stirred at the same temperature for 1 h. Upon completion, TEA (3 drops) was added into the reaction mixture, and stirred for 30 min. The mixture was allowed to warm to -45 °C for another 30 min. To quench the mixture, sat. aq. NH_4Cl (0.5 ml) was added, followed by diluting with DCM (1 ml). The mixture was then extracted by DCM (3x 1 ml) and dried over $MgSO_4$. After concentration, pure **240** (4.5 mg, 0.0066 mmol, 90%) was obtained by PTLC (20% EtOAc in hexanes).

TLC: R_f = 0.34 (20% EtOAc in hexanes, $KMnO_4$ staining)

^{1}H NMR (600 MHz, C_6D_6) δ 5.37 (d, *J* = 6.2 Hz, 1H), 5.31 (d, *J* = 2.7 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 3.69 (d, *J* = 6.4 Hz, 1H), 3.66 – 3.55 (m, 2H), 3.48 – 3.36 (m, 1H), 3.16 (q, *J* = 9.9 Hz, 2H), 2.93 (s, 1H), 2.43 (q, *J* = 11.5 Hz, 1H), 2.30 – 2.20 (m, 2H), 2.15 (dq, *J* = 19.2, 10.2 Hz, 2H), 2.01 – 1.89 (m, 2H), 1.80 (ddd, *J* = 21.3, 14.4, 7.8 Hz, 3H), 1.69 (dq, *J* = 11.9, 7.0 Hz, 2H), 1.51 – 1.32 (m, 3H), 1.15 (tt, *J* = 10.7, 5.1 Hz, 2H), 0.49 (d, *J* = 7.1 Hz, 3H).

^{1}H-^{1}H-COSY, ^{1}H-^{1}H-NOESY are available.



Compound **242**. To a solution of compound **240** (3.0 mg, 0.0044 mmol) in THF (0.1 ml) was added $AlMe_3$ (1 drop, 1 M in THF) at room temperature. The resulting mixture was allowed to stir at the same temperature for 1 h. Upon completion, H_2O (0.5 ml) was added to this mixture, and the biphasic mixture was extracted by DCM (3x 1 ml). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Pure **242** (2.8 mg, 0.00041 mmol, 92%) was obtained by PTLC (20% EtOAc in hexanes).

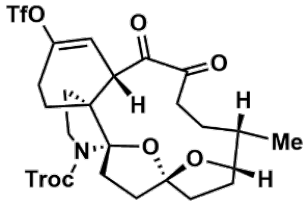
TLC: R_f = 0.28 (20% EtOAc in hexanes, $KMnO_4$ staining)

^{1}H NMR (600 MHz, C_6D_6) δ 5.52 (s, 1H), 5.36 (d, *J* = 2.4 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.60 (dt, *J* = 4.6, 2.5 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.15 (d, *J* = 10.2 Hz, 1H), 3.63 (dt, *J* = 11.2, 4.7 Hz, 1H), 3.31 (t, *J* = 10.2 Hz, 1H), 3.18 (t, *J* = 11.6 Hz, 1H), 2.95 (td, *J* = 11.1, 7.0 Hz, 1H), 2.75 – 2.59 (m, 1H), 2.19 (s, 1H), 2.12 – 1.96 (m, 4H), 1.84 (dt, *J* = 13.4, 10.6 Hz, 1H), 1.81 – 1.71 (m, 2H), 1.69 – 1.57 (m, 2H), 1.54 (dd, *J* = 13.5, 7.1 Hz, 1H), 1.48 – 1.41 (m, 1H), 1.33 (d, *J* = 11.8 Hz, 1H), 1.12 (td, *J* = 7.3, 3.7 Hz, 1H), 1.07 (ddt, *J* = 15.0, 7.8, 3.2 Hz, 1H), 0.96 (dd, *J* = 13.0, 5.0 Hz, 1H), 0.86 (ddd, *J* = 13.6, 5.3, 2.3 Hz, 1H), 0.55 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (151 MHz, C_6D_6) δ 212.7, 152.2, 149.7, 119.1 (q, $J_{C\text{-}F}$ = 320 Hz), 118.7, 117.9, 105.3, 96.4, 86.6, 78.2, 74.6, 50.6, 44.7, 40.4, 39.0, 37.3, 36.2, 31.7, 30.2, 29.1, 27.7, 25.9,

25.2, 24.7, 24.3, 19.6.

^{1}H-^{13}C-HSQC, ^{1}H-^{13}C-HMBC, ^{1}H-^{1}H-NOESY are available.



Compound **243**. To a solution of compound **221** (3.02 g, 4.62 mmol, azeotroped with benzene to remove residual H_2O) in DCM (30 ml) was added XPhosAuNTf$_2$ (30.2 mg, 0.032 mmol) under argon. The mixture was refluxed for 2 h. Upon completion (indicated by TLC, 20% Et_2O in DCM), it was cooled to rt, and TEA (0.05 ml) was added to quench the gold catalyst. Subsequently, the solvent was removed under reduced pressure to give crude **237**.

The resulting polycyclic compound was dissolved in MeCN/PhMe/H_2O (5:5:1, 112 ml), and TBAI (808 mg, 2.19 mmol) was added in one portion to give a clear solution. $Ru(PPh_3)_3Cl_2$ (191 mg, 0.2 mmol) was added to this solution subsequently. A gray-green mixture was generated. Subsequently, TBHP (5-6 M in decane, 10.9 ml) was added dropwise. The yellow green solution turned dark (ca. 15 min, prevent light by wrapping the flask in aluminum foil since the product is light-sensitive). The reaction was allowed to stir at rt for 1.5 h (open air, water bath to maintain a constant temperature). Upon completion, the reaction was diluted by Et_2O (50 ml), and quenched by a mixture of water (100 ml), $NaHSO_3$ (12 g) and NaCl (30 g). The resulting cloudy mixture was stirred for 1 h to give a good phase separation. After collecting the organic phase, the aqueous phase

was extracted with Et_2O (4x 100 ml). The combined organic phase was dried over $MgSO_4$, and concentrated under reduced pressure, The crude product was purified by chromatography (DCM to 5% Et_2O in DCM) to yield compound **243** (1.67 g, 2.44 mmol, 53%).

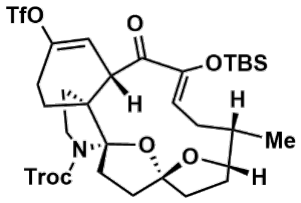
TLC: R_f = 0.45 (20% Et_2O in hexanes, yellow under light, $KMnO_4$ staining)

[α]$^{25}_D$: +40.4 (*c* = 1.0, MeOH)

^{1}H-NMR (600 MHz, CD_3CN) δ 5.57 (m, 1H), 4.82 (d, *J* = 12.3 Hz, 1H), 4.70 (d, *J* = 12.3 Hz, 1H), 4.48 (dt, *J* = 4.9, 2.5 Hz, 1H), 3.78 (ddd, *J* = 10.1, 6.1, 3.8 Hz, 1H), 3.68 – 3.53 (m, 1H), 3.47 (td, *J* = 11.1, 7.1 Hz, 1H), 3.15 – 3.06 (m, 1H), 2.77 (dt, *J* = 12.6, 10.0 Hz, 1H), 2.68 (dddd, *J* = 13.6, 11.5, 9.7, 1.8 Hz, 1H), 2.63 – 2.54 (m, 1H), 2.38 (ddt, *J* = 18.3, 5.3, 2.3 Hz, 1H), 2.32 – 2.20 (m, 3H), 2.02 (ddd, *J* = 13.6, 8.6, 3.0 Hz, 1H), 1.96 – 1.93 (m, 1H), 1.88 (dd, *J* = 13.2, 7.0 Hz, 1H), 1.81 – 1.73 (m, 1H), 1.72 – 1.64 (m, 3H), 1.63 – 1.53 (m, 2H), 0.83 (d, *J* = 7.2 Hz, 3H).

^{13}C-NMR (150 MHz, CD_3CN) δ 199.8, 199.0, 152.7, 150.6, 119.7 (q, $J_{C\text{-}F}$ = 320 Hz), 119.0, 117.9, 105.5, 96.9, 84.3, 75.0, 52.4, 45.2, 40.4, 37.6, 37.4, 37.0, 32.9, 29.1, 27.4, 25.4, 25.4, 24.1, 23.8, 18.9.

HRMS (ESI-TOF): calc'd for $C_{25}H_{29}Cl_3F_3NO_9S$ $[M+H]^+$: 682.0659, found: 682.0668

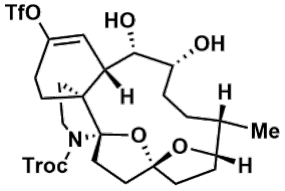


Compound **246**. To a solution of diketone **243** (1.5 mg, 0.0022 mmol) in THF (0.1 ml) was

added LiHMDS (3 drops, 1.0 M in THF) at -78 °C. The deprotonation was carried out under the same temperature, and stirred for 1 h. Subsequently, TBSOTf (1 drop) was added to this solution and the resulting mixture was stirred for another 1 h. Upon completion, H_2O (1 ml) was added to the reaction mixture at -78 °C and it was allowed to warm to room temperature gradually. Et_2O was used to extract the mixture (3x 1 ml). The combined organic layer was dried over $MgSO_4$ and concentrated. Silyl enol ether **246** (1.1 mg, 0.0015 mmol, 68%) was purified by PTLC (20% Et_2O in hexanes).

TLC: R_f = 0.53 (20% Et_2O in hexanes, UV active, $KMnO_4$ staining)

^{1}H NMR (600 MHz, C_6D_6) δ 6.43 – 6.36 (m, 1H), 5.34 (dd, *J* = 3.7, 2.1 Hz, 1H), 4.62 – 4.44 (m, 2H), 4.20 (td, *J* = 3.6, 1.6 Hz, 1H), 3.55 (d, *J* = 11.2 Hz, 1H), 3.34 (ddd, *J* = 10.9, 8.4, 4.5 Hz, 1H), 3.31 – 3.14 (m, 2H), 2.62 – 2.52 (m, 1H), 2.23 – 2.07 (m, 3H), 2.00 – 1.91 (m, 2H), 1.79 (d, *J* = 17.4 Hz, 2H), 1.69 (ddd, *J* = 12.8, 8.1, 5.9 Hz, 1H), 1.61 (ddt, *J* = 18.8, 12.3, 6.0 Hz, 1H), 1.35 – 1.22 (m, 4H), 1.07 (s, 9H), 0.67 (d, *J* = 7.1 Hz, 3H), 0.41 (d, *J* = 2.9 Hz, 6H).



Compound **248**. To a solution of compound **243** (2.43 g, 3.53 mmol) in THF (135 ml) was added L-selectride (1.0 M in THF, 6.7 ml) at -78 °C under argon. The yellow solution turned to colorless as completion (usually takes 30 min). The reaction was quenched according to the following procedure:

i. Adding MeOH (3.8 ml) to the mixture at -78 °C and stirred at this temperature for 5 min.

ii. The cooling bath was removed, and a mixture of water (50 ml), EtOAc (10 ml) and Na_2CO_3 (3.0 g) was added subsequently. The resulting mixture was allowed to stir for 5 min.

iii. A solution of H_2O_2 (50 wt % in H_2O, 2 ml) was added dropwise, and the mixture was stirred for 60 min at rt.

After work up, the mixture was extracted with EtOAc (3x 50 ml), and the combined organic layer was dried over $MgSO_4$. After concentrating under reduced pressure, the residue was dissolved in MeOH (100 ml) and cooled to 0 °C. $NaBH_4$ (large excess, around 500 mg) was added portionwise at this temperature. The reaction was stirred for 1 h. Upon completion (indicated by TLC), sat. aq. NH_4Cl (50 ml) and water (100 ml) was added, and the mixture was extracted with DCM (3x 150 ml). The combined organic phase was dried over $MgSO_4$ and concentrated, the crude product was purified by chromatography (5% EtOAc in DCM to 15% EtOAc in DCM) to yield compound **248** (2.03 g, 83%).

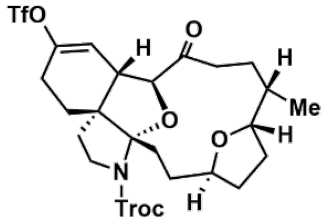
TLC: R_f = 0.23 (30% EtOAc in hexanes, $KMnO_4$ staining)

$[\alpha]^{25}_D$: +17.9 (*c* = 1.0, $CHCl_3$)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.86 (s, 1H), 4.81 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.06 (td, *J* = 8.9, 8.3, 4.0 Hz, 1H), 3.92 – 3.82 (m, 1H), 3,60 (t, *J* = 10.4 Hz, 1H), 3.56 – 3.10 (m, 3H), 3.03 – 2.81 (m, 1H), 2.57 – 2.22 (m, 5H), 2.11 – 1.74 (m, 10H), 1.73 – 1.52 (m, 4H), 0.86 (d, *J* = 7.2 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 152.3, 149.3, 124.0, 118.7 (q, J_{C-F} = 320 Hz), 116.2, 106.5, 96.0, 86.2, 81.4, 75.0, 74.6, 66.0, 49.7, 44.8, 38.0, 36.4, 35.8, 34.5, 29.9 (2C), 28.7, 26.6, 25.1, 24.1,18.1.

HRMS (ESI-TOF): calc'd for $C_{25}H_{33}Cl_3F_3NO_9S$ $[M\text{-}OH]^+$: 668.0866, found: 668.0869



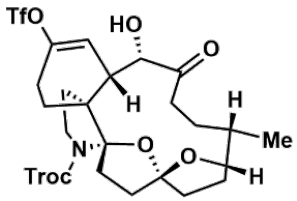
Compound **251**. To a solution of diol **248** (5.6 mg, 0.0084 mmol) in DCE (0.3 ml) was added TFA (3 drops) at room temperature. The mixture was then heated to 50 °C, and stirred at the same temperature for 30 min. Upon completion, the mixture was allowed to cool down, and the volatiles were removed by vacuum. Pure **251** (5.3 mg, 0.0080 mmol, 95%) was obtained by PTLC (25% EtOAc in hexanes).

TLC: R_f = 0.59 (30% EtOAc in hexanes, $KMnO_4$ staining)

^{1}H NMR (600 MHz, C_6D_6) δ 6.18 (q, *J* = 1.8 Hz, 1H), 4.63 (d, *J* = 10.7 Hz, 2H), 4.09 (s, 1H), 3.90 (ddt, *J* = 11.5, 7.3, 3.8 Hz, 1H), 3.72 – 3.60 (m, 2H), 3.52 (t, *J* = 14.9 Hz, 1H), 3.04 (dd, *J* = 10.6, 2.6 Hz, 1H), 2.99 (td, *J* = 11.5, 6.6 Hz, 1H), 2.72 (s, 1H), 2.25 (d, *J* = 19.0 Hz, 1H), 2.07 – 1.82 (m, 3H), 1.73 – 1.57 (m, 2H), 1.49 – 1.14 (m, 9H), 1.08 – 0.98 (m, 2H), 0.71 (d, *J* = 7.1 Hz, 3H).

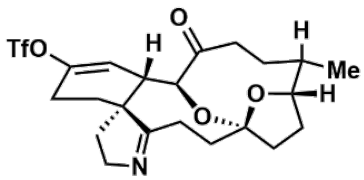
^{13}C NMR (151 MHz, C_6D_6) δ 208.7, 152.3, 149.2, 119.1 (q, J_{C-F} = 320 Hz , 118.9, 101.9, 96.3, 82.8, 81.3, 80.3, 75.1, 56.5, 46.0, 45.7, 34.7, 33.1, 32.4, 30.1, 28.1, 27.4, 26.6, 24.4, 15.0.

^{1}H-^{13}C-HSQC, ^{1}H-^{13}C-HMBC, ^{1}H-^{1}H-NOESY are available.



Compound **252**.

^{1}H NMR (600 MHz, C_6D_6) δ 5.51 (d, *J* = 4.4 Hz, 1H), 4.77 (d, *J* = 12.1 Hz, 1H), 4.39 (d, *J* = 12.1 Hz, 1H), 3.78 (dd, *J* = 14.5, 9.0 Hz, 2H), 3.66 (t, *J* = 2.8 Hz, 1H), 3.32 (s, 1H), 3.28 – 3.22 (m, 1H), 3.14 (q, *J* = 9.7 Hz, 1H), 3.02 – 2.90 (m, 1H), 2.82 – 2.74 (m, 1H), 2.53 – 2.47 (m, 1H), 2.23 – 2.12 (m, 1H), 2.10 – 2.04 (m, 2H), 2.00 (dd, *J* = 12.8, 7.1 Hz, 1H), 1.97 – 1.85 (m, 2H), 1.83 (d, *J* = 5.8 Hz, 2H), 1.68 – 1.59 (m, 1H), 1.50 – 1.38 (m, 3H), 1.32 (q, *J* = 7.4 Hz, 2H), 1.24 (dt, *J* = 14.0, 5.7 Hz, 1H), 1.19 – 1.12 (m, 1H), 0.54 (d, *J* = 7.0 Hz, 3H).



Compound **255**. To a solution of diol **248** (1.95 g, 2.84 mmol) in DCM (37 ml) was added TEMPO (55.5 mg, 0.059 mmol), KBr (1.3 g, 10.9 mmol) and sat. $NaHCO_3$ aq. (9.3 ml), then cooled to 0 °C. The mixture was then stirred for 5 min and a solution of NaOCl (6%, ca. 0.8 M, 5.1 ml) was added dropwise. The resulting red biphasic solution was stirred at the same temperature for 3.5 h, then quenched by adding sat. aq. $Na_2S_2O_3$ (10 ml). The yellow mixture turned colorless in a few seconds, followed by extraction with DCM for couple of times. The combined organic layer was dried over $MgSO_4$ and concentrated

under reduced pressure to give a white foam (C-14 oxidized product **252**).

The crude compound **252** obtained above was mixed with zinc powder (1.7 g, 26 mmol), then dissolved in a mixture of AcOH (70 ml) and H_2O (23 ml), heated at 70 °C under argon. The mixture was stirred for 3 h at the same temperature, then cooled down to 45 °C. After stirring at 45 °C for 2 h, the mixture was cooled down to rt, and dropped into a solution of K_2CO_3 (70 g in 100 ml H_2O). After quenching the acetic acid, the biphasic mixture was extracted with DCM (4x 50 ml), and dried over $MgSO_4$. After removal of the solvents, the crude product was purified with chromatography (EtOAc to 10% MeOH + 1% TEA in EtOAc) to give compound **255** (1.03 g, 2.10 mmol, 74%).

TLC: R_f = 0.23 (3% MeOH in EtOAc, $KMnO_4$ staining)

$[\alpha]^{25}_D$: -35.6 (c = 0.5, $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.09 (q, J = 1.7 Hz, 1H), 4.29 (dt, J = 10.3, 6.2 Hz, 1H), 4.04 (d, J = 12.0 Hz, 1H), 4.00 – 3.94 (m, 1H), 3.89 – 3.81 (m, 1H), 3.65 – 3.58 (dtt, J = 17.2, 6.9, 3.6 Hz, 1H), 2.74 – 2.56 (m, 3H), 2.55 – 2.43 (m, 4H), 2.38 – 2.28 (m, 1H), 2.19 – 2.07 (m, 2H), 2.00 – 1.80 (m, 4H), 1.79 – 1.68 (m, 3H), 1.49 (dt, J = 12.6, 6.3 Hz, 1H), 1.43 (dd, J = 14.6, 8.1 Hz, 1H), 0.83 (d, J = 7.1 Hz, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 206.5, 182.0, 148.4, 119.1, 118.6 (q, $J_{C\text{-}F}$ = 320 Hz), 110.7, 84.6, 75.9, 56.0, 53.6, 48.7, 40.4, 37.2, 36.5, 34.1, 28.6, 28.3, 27.0, 26.3, 24.8, 24.4, 17.7.

HRMS (ESI-TOF): calc'd for $C_{22}H_{28}F_3NO_6S$ $[M+H]^+$: 492.1668, found: 492.1663

Chapter 5: Late-stage oxidation and the scalable total synthesis of portimine A and B.

Section 5.1 Endpoint of the "oxidase phase" — oxidation of C-13 and C-5 in a single step.

With the core of portimines in hand, I aimed at developing an efficient method to install the two hydroxyl groups at C-5 and C-13. Intuitively, these two oxidations might be achieved in a single step via oxidizing enolized C-5 and C-13 generated from deprotonation by strong bases such as LiHMDS, LDA, KHMDS, and NaHMDS. The rationale of the stereochemical outcome was based on the geometry of the macrocycle and depicted in Figure 5.1 (blue box). As shown in Figure 5.1, imine **255** could be deprotonated to give a di-enolized product, where the geometry at C-13/C-14 was unambiguous. On the other hand, to rationalize the geometry of the double bond on C-4/C-5, the embedded 8-membered cyclic ether was highlighted in **256** and **257**. The *Z*-type enamine (in **256**) would lead to a *trans*-8-membered ring, which is extremely strained (*1*), **257** (or related species) should dominate after deprotonation. Subsequent oxidation of **257** might deliver **258** as the major product possessing two oxidation states at C-5 and C-13, where the undesired stereochemical outcome at C-5 could be reversed by downstream transformations.

The enolization of **255** was then executed by deprotonating with strong bases as aforementioned. Unfortunately, no reaction was observed at low temperatures, yet significant decomposition was observed upon warming the mixture. It was quite questionable whether the deprotonation took place since no product was formed even after quenching the mixture with highly reactive electrophiles such as TrocCl and TBSOTf.

Nevertheless, **255** was found to react with TBSOTf in the presence of TEA, affording its corresponding silyl enol ether **259**, in 85%% yield.

In Section 4.2, we have learned that the spirocyclic imine could be selectively oxidized to nitrone via DMDO. Thus, I was concerned whether this reactivity could be used to install the hydroxyl group at C-5 via a [3,3] sigmatropic rearrangement by analogy with the Boekelheide reaction. De facto, a similar transformation was documented (*2*) in the 1980s using acid chloride to form N-oxyenamine, followed by rearrangement and hydrolysis, affording α-oxidized ketone. Satisfyingly, **255** could be smoothly oxidized to **260** by DMDO, which was subsequently heated with Ac_2O and TEA, to trigger the expected Boekelheide-type reaction, arriving at **262** as a single diastereomer in 83% overall yield. Not surprisingly, the stereochemical outcome of **262** could be explained by the formation of **261**, presenting a preferential *E*-configuration on C-4/C-5.

The extremely encouraging results from C-5 oxidation and the TBS enol ether formation stimulated a more ambitious goal that the oxidation of C-5 and C-13 should take place in a single step. To achieve this, **259** was treated with DMDO to give a globally oxidized product **263**, subsequent Boekelheide-type rearrangement was carried out under Ac_2O and TEA, leading to diacetate **264** in 95% yield.

In conclusion, a single-step transformation to install the oxygen atoms at C-5 and C-13 was demonstrated. Although downstream stereochemical manipulations were required to set the correct stereochemistry at C-5, the formation of **264** should be viewed as a

milestone of the total synthesis and more remarkably, the endpoint of the “oxidase phase”, since all oxidations happening after skeleton formation were now completed.

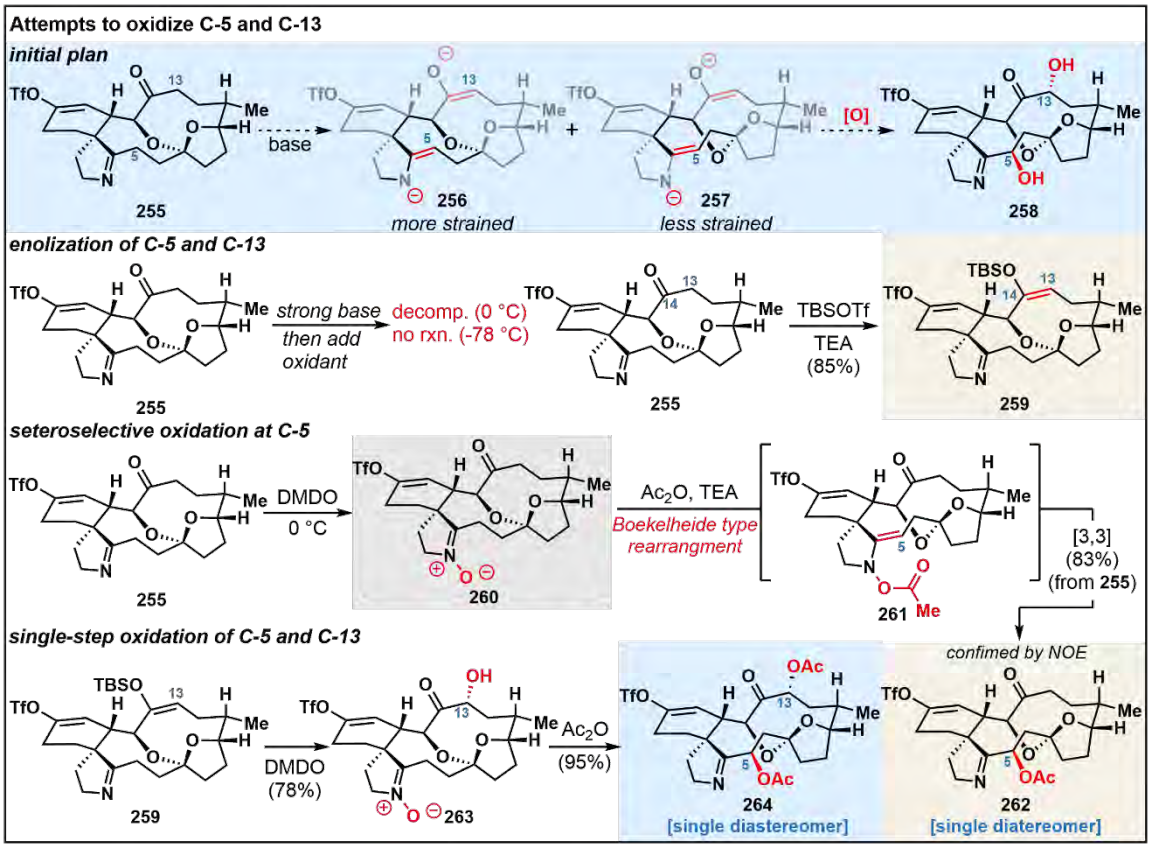


Figure 5.1 Late-stage oxidation of C-5 and C-13.

Section 5.2 Structural revision of portimine B and total synthesis of portimine A.

With diacetate **264** in place, all that remained to arrive at portimine B were oxidizing C-5 to its ketone form. Based on my preliminary study, treating compound **264** under basic conditions would deliver a mixture of all three possible hydrolyzed products **265**, **266**, and **267**, depending on the properties of bases, temperatures, reaction time, and solvents. For instance, LiOH in THF would afford **265** as the major product in 72% isolated yield, while using ethanolic KCN would give **266** as the major product. Unexpectedly, running

hydrolysis in aqueous ammonia could cleave both acetyl groups in **264**, arriving at the free diol **267**. Attempts to selectively oxidize C-5 on this compound to **268** failed, and an over-oxidized product **269** could be isolated in certain cases (DMP, TEMPO/NaOCl, etc.).

Next, a Suzuki coupling using Molander's salt was executed to append the exocyclic vinyl group, delivering diene **270** in 75% yield. Subsequent oxidation of C-5 would happen upon treatment with DMP, followed by hydrolysis, arriving at portimine B as a white amorphous powder. More importantly, the chemical transformations shown here decisively supported portimine B as a ring-closed tautomer expressed in portimine A (blue box) since no oxidation was observed at C-10. Consistently, High-resolution mass spectrometry (HRMS) further confirmed the formula of portimine B as $C_{23}H_{29}NO_5$ rather than $C_{23}H_{31}NO_6$ reported by prior work.

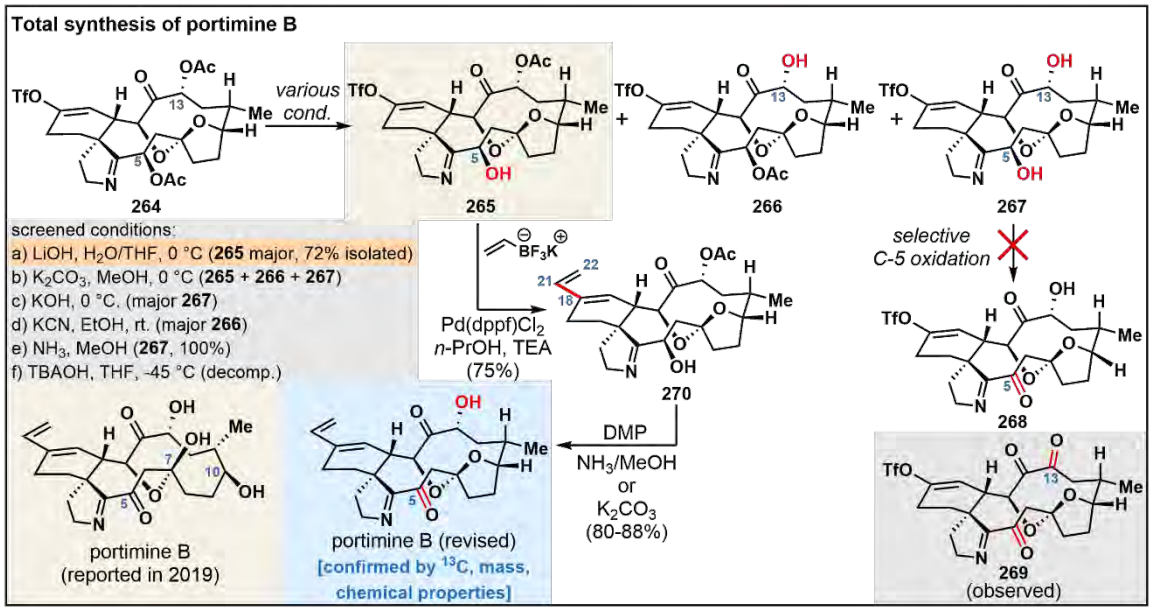


Figure 5.2 Discovery of a regioselective hydrolysis at C-5 to complete the total synthesis of portimine B.

The other natural product, portimine A, was initially thought to derive from the C-5 epimerization of **270** or analogs thereof. Unfortunately, no epimerized product was perceived during an extensive screening of reagents including Lewis acids, metal salts, Brønsted bases, etc. Interestingly, imine **270** could be fully recovered after treatment with $NaBH_3CN$ in AcOH. The unusual resistance of this imine to $NaBH_3CN$ inspired me to reduce the ketone at C-5 using the same reagent since all other functional groups were unlikely perturbed by it. Fortunately, portimine B was converted to portimine A in excellent yield upon treatment with $NaBH_3CN$ without the formation of amine or any other over-reduced products. Less reactive reductants, such as $NaBH(OAc)_3$, failed to deliver any product.

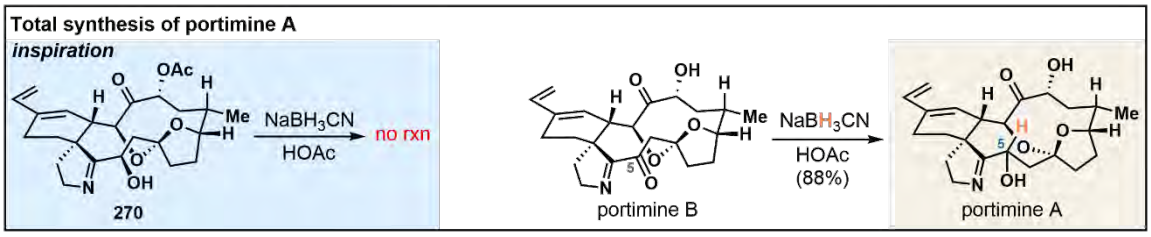


Figure 5.3 Conversion of portimine B to A.

Section 5.3 Summary

In conclusion, the scalable total synthesis (with modified and optimized steps) of portimine A and B presented herein benefitted from a strategy that is distinct from both biosynthesis and prior approaches. Driven by a desire to avoid an abundance of functional group manipulations, non-strategic redox fluctuations, and protecting groups, a plan was forged to forego the installation of oxygenation until a late stage. By analogy to two-phase

terpene synthesis this required the construction of a minimally decorated carbon skeleton followed by sequential oxidations. In this way, the innate reactivity of a macrocycle could be leveraged to install both the correct oxygenation pattern as well as the stereochemistry. Certain intermediates served to “self-protect” key functional groups and enable the final sequence by strategically timed ring-chain tautomerization events. Finally, an unusually stable vinyl triflate was carried through the majority of the synthesis, allowing for a thorough SAR study of this biologically active natural product, which will be presented in next chapter.

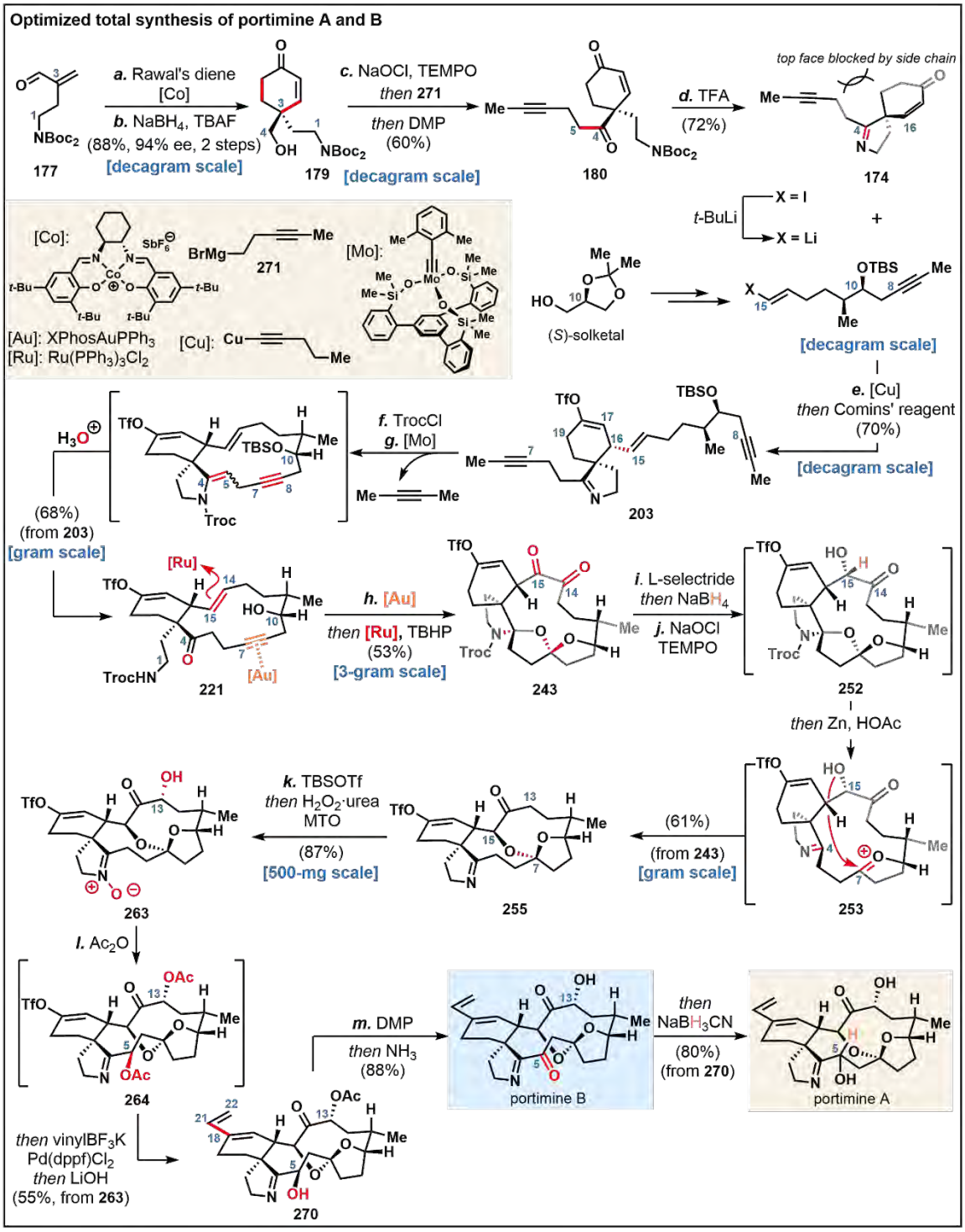


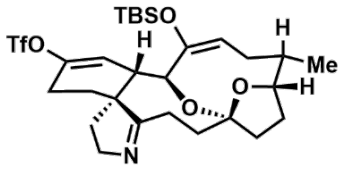
Figure 5.4 Optimized total synthesis of portimine A and B.

Reference

(1) Favini, G.; Buemi, G.; Raimondi, M. Molecular conformation of cyclenes. I. Cyclohexene, cycloheptene, *cis*- and *trans*-cyclooctene, *cis*- and *trans*-cyclononene. *J. Mol. Structure* **1968**, *2*, 137–148.

(2) Cummins, C. H.; Coates, R. M.α-Oxygenation of Aldehydes and Cyclic Ketones by Acylation-Rearrangement of Nitrones. *J. Org. Chem.* **1983**, *48*, 2070–2076.

Experimental



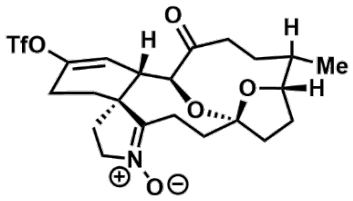
Compound **259**. To a solution of compound **255** (21.0 mg, 0.043 mmol) in refluxing DCM (0.35 ml) was added TEA (0.05 ml, 36.3 mg, 0.358 mmol) and TBSOTf (0.05 ml,57.5 mg,0.22 mmol). The reaction mixture was then allowed to stir for 45 min. Upon completion, the mixture was rinsed with sat. aq. $NaHCO_3$ (0.05 ml), followed by extraction with DCM (3x 1 ml). The organic phase was dried over MgSO4, filtered and concentrated. Pure **259** (23 mg, 0.038 mmol, 88 %) was obtained by PTLC (5% MeOH in EtOAc, neutralized by 1% TEA before loading).

TLC: R_f = 0.45 (5% MeOH in EtOAc, slightly UV active, $KMnO_4$ staining)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.54 (q, *J* = 1.7 Hz, 1H), 4.84 (ddd, *J* = 11.5, 5.4, 1.8 Hz, 1H), 4.63 (dt, *J* = 12.4, 1.6 Hz, 1H), 4.28 (dt, *J* = 9.1, 6.7 Hz, 1H), 3.83 (dd, *J* = 15.4, 9.1

Hz, 1H), 3.70 – 3.53 (m, 2H), 3.07 – 2.96 (m, 1H), 2.73 – 2.59 (m, 2H), 2.55 – 2.46 (m, 3H), 2.46 – 2.38 (m, 1H), 2.11 – 1.96 (m, 3H), 1.96 – 1.87 (m, 1H), 1.81 – 1.68 (m, 5H), 1.62 – 1.57 (m, 1H), 1.36 – 1.27 (m, 2H), 0.94 (s, 8H), 0.79 (d, J = 7.1 Hz, 3H), 0.28 (s, 3H), 0.23 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 182.37, 147.68, 144.97, 121.39, 118.60 (q, $J_{C\text{-}F}$ = 320 Hz), 112.62, 110.19, 83.88, 72.99, 56.01, 53.70, 46.02, 42.16, 36.76, 34.62, 33.10, 28.82, 28.58, 27.97, 26.98, 26.35, 26.02, 24.79, 18.44, 17.47, -4.00, -4.73.



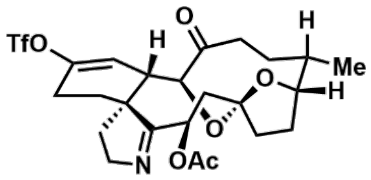
Compound **260**. To a solution of compound **255** (5.1 mg, 0.010 mmol) in DCM (0.1 ml) was added freshly-made DMDO (0.08 M solution in acetone, 0.5 ml) at 0 °C. The resulting solution was stirred at the same temperature for 30 min, and monitored by TLC (10% MeOH in EtOAc). Upon completion, the solvents were removed, and the residue was purified by PTLC (10% MeOH in EtOAc) to yield **260** as the product (3.8 mg, 0.0075 mmol, 75%).

TLC: R_f = 0.31 (10% MeOH in EtOAc, UV active, $KMnO_4$ staining)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.03 (s, 1H), 4.33 (dt, J = 11.6, 6.1 Hz, 1H), 4.09 (dd, J = 15.2, 9.3 Hz, 2H), 3.99 – 3.90 (m, 2H), 3.49 (s, 1H), 2.69 – 2.62 (m, 1H), 2.59 – 2.44 (m, 4H), 2.33 (q, J = 13.0 Hz, 1H), 2.28 – 2.22 (m, 1H), 2.15 – 2.02 (m, 3H), 2.02 – 1.90 (m,

3H), 1.90 – 1.79 (m, 2H), 1.76 (dt, *J* = 12.9, 7.1 Hz, 1H), 1.60 (td, *J* = 12.8, 7.5 Hz, 1H), 1.47 (dd, *J* = 14.9, 7.9 Hz, 1H), 0.84 (d, *J* = 7.1 Hz, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 205.84, 152.45, 147.90, 118.6 (q, J_{C-F} = 319 Hz), 117.82, 110.97, 85.46, 76.15, 59.64, 49.15, 40.47, 37.67, 37.04, 33.76, 29.87, 29.05, 25.70, 24.83, 24.40, 22.75, 18.42, 17.71.



Compound **262**. To a solution of compound **260** (3.0 mg, 0.006 mmol) in DCM (0.1 ml) was added Ac_2O (2 drops) and TEA (2 drops) at ambient temperature. The resulting mixture was then stirred for overnight. Upon completion, H_2O (1 ml) was added and the mixture was extracted with DCM (3x 1ml). The organic phase was dried over MgSO4, filtered and concentrated. Pure **262** (3.2 mg, 0.006 mmol, quantitative) was obtained by PTLC (5% MeOH in DCM)

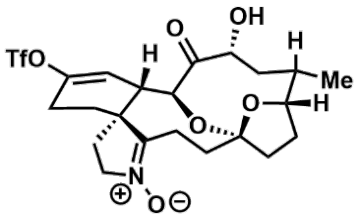
TLC: R_f = 0.35 (5% MeOH in EtOAc, $KMnO_4$ staining)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.79 (dd, *J* = 10.9, 8.1 Hz, 1H), 5.10 (t, *J* = 1.7 Hz, 1H), 4.29 (dt, *J* = 10.2, 6.2 Hz, 1H), 4.15 (d, *J* = 10.9 Hz, 1H), 4.06 (d, *J* = 12.0 Hz, 1H), 3.96 – 3.88 (m, 1H), 3.76 (ddd, *J* = 16.4, 10.3, 6.8 Hz, 1H), 2.68 – 2.58 (m, 2H), 2.49 (dddd, *J* = 23.0, 14.7, 11.1, 6.0 Hz, 3H), 2.37 – 2.26 (m, 2H), 2.24 – 2.14 (m, 1H), 2.14 – 2.09 (m, 1H), 2.07 (s, 3H), 2.07 – 2.04 (m, 1H), 1.99 – 1.90 (m, 2H), 1.87 (dd, *J* = 12.6, 6.7 Hz, 1H),

1.78 (dtd, J = 11.6, 6.9, 6.2, 2.7 Hz, 2H), 1.57 (td, J = 12.6, 7.7 Hz, 1H), 1.45 (dd, J = 14.9, 7.8 Hz, 1H), 0.84 (d, J = 7.1 Hz, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 206.1, 177.6, 169.4, 148.6, 118.8, 118.4 (q, $J_{C\text{-}F}$ = 320 Hz), 108.1, 84.6, 76.0, 72.1, 56.3, 53.7, 48.7, 40.4, 39.6, 37.1, 36.6, 29.4, 28.7, 26.4, 24.8, 24.6, 21.3, 17.7.

^{1}H-^{13}C-HSQC, NOESY spectra are available



Compound **263**. The crude **259** obtained from the silylation of **255** (550 mg) was dissolved in DCM (3 ml), and added DMDO solution (freshly prepared, ca. 0.08 M in acetone, 50 ml) at 0 °C dropwise. After stirring at 0 °C for 1 h, the solvent was removed in vacuo. The residual was redissolved in acetone/H_2O (v/v = 1:1, 20 ml) and added $NaHCO_3$ solid. Oxone® (550 mg) was added to this mixture, and the reaction was stirred at rt for 1 h. Upon completion, a mixture of brine (10 ml) and DCM (5 ml) was added. The aqueous phase was extracted with DCM (4x 10 ml), and the organic layer was dried and concentrated. The crude product was purified by chromatography (EtOAc to 10% MeOH in EtOAc) to give compound **20** (387.1 mg, 0.74 mmol, 73% based on **255**).

TLC: R_f = 0.30 (10% MeOH in EtOAc, UV active, $KMnO_4$ staining)

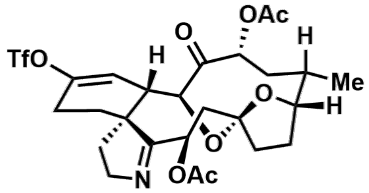
$[\alpha]^{25}_D$: +49.0 (c = 0.1, $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.23 (s, 1H), 4.78 (br s, 1H), 4.59 (d, J = 12.0 Hz, 1H),

4.25 (dt, *J* = 11.2, 6.0 Hz, 1H), 4.09 – 4.02 (m, 1H), 4.00 (dd, *J* = 11.3, 2.8 Hz, 1H), 3.95 – 3.86 (dt, *J* = 13.4, 6.4 Hz, 2H), 3.45 (td, *J* = 14.3, 7.3 Hz, 1H), 2.60 – 2.43 (m, 3H), 2.30 (dt, *J* = 14.1, 11.0 Hz, 1H), 2.26 – 2.18 (m, 2H), 2.14 – 2.04 (m, 2H), 2.04 – 1.92 (m, 2H), 1.92 – 1.84 (m, 2H), 1.82 (dd, *J* = 15.2, 7.2 Hz, 1H), 1.73 (dt, *J* = 12.7, 7.0 Hz, 1H), 1.59 (dt, *J* = 12.7, 6.3 Hz, 1H), 1.54 (dd, *J* = 14.1, 2.8 Hz, 1H), 0.88 (d, *J* = 6.9 Hz, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 204.2, 153.4, 147.8, 118.6 (q, J_{C-F} = 320 Hz), 118.0, 110.7, 84.9, 78.7, 70.9, 59.5, 49.3, 40.2, 37.7, 34.3, 33.9, 33.6, 29.0, 25.6, 24.4, 22.7, 18.4, 17.6.

HRMS (ESI-TOF): calc'd for: $C_{22}H_{28}F_3NO_8S$ $[M+H]^+$: 524.1561, found: 524.1561



Compound **264**. Nitrone **263** (339 mg, 0.65 mmol) was dissolved in DCM (6.0 ml), and TEA (0.9 ml, 660 mg, 6.5 mmol) was added. The mixture was then heated to 35 °C, and Ac_2O (0.34 ml, 365 mg, 3.58 mmol) was added dropwise. The mixture was stirred overnight (monitored with TLC using 5% MeOH in DCM). Upon completion, the reaction was quenched with sat. aq. $NaHCO_3$ (2.0 ml) at rt. The mixture was extracted with DCM (3x 10 ml), and the combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure to give crude **264** (purity determined by NMR).

TLC: R_f = 0.42 (5% MeOH in DCM, $KMnO_4$ staining)

$[\alpha]^{25}_D$: +5.30 (*c* = 1.0, $CHCl_3$)

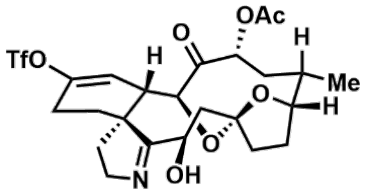
^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.78 (dd, *J* = 10.9, 8.0 Hz, 1H), 5.19 (dd, *J* = 11.1, 2.8 Hz,

1H), 5.05 (q, *J* = 1.7 Hz, 1H), 4.36 (d, *J* = 12.0 Hz, 1H), 4.25 (dt, *J* = 10.0, 6.0 Hz, 1H), 4.18 – 4.08 (m, 1H), 3.92 (dd, *J* = 16.2, 9.1 Hz, 1H), 3.77 (ddd, 16.2, 10.2, 6.9 Hz, 1H), 2.64 – 2.41 (m, 3H), 2.41 – 2.26 (m, 3H), 2.23-2.13 (m, 1H), 2.12 – 1.95 (m, 2H), 2.08 (s, 3H), 2.05 (s, 3H), 1.93-1.73 (m, 4H), 1.60 (td, *J* = 12.5, 7.6 Hz, 1H), 1.52 (dd, *J* = 13.2, 2.8 Hz, 1H), 0.88 (d, *J* = 6.5 Hz, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 199.8, 177.2, 169.3, 169.0, 148.8, 118.6 (q, J_{C-F} = 320 Hz), 117.8, 108.1, 84.0, 79.9, 73.0, 72.1, 56.4, 53.7, 40.4, 39.1, 36.7, 34.0, 31.6, 29.4, 28.7, 26.5, 24.5, 21.3, 20.9, 17.4.

^{1}H-^{13}C-HSQC, ^{1}H-^{13}C-HMBC spectra are available

HRMS (ESI-TOF): calc'd for $C_{26}H_{32}F_3NO_{10}S$ $[M+H]^+$: 608.1777, found: 608.1776



Compound **265**. The crude **264** obtained from **263** (339 mg) reacting with Ac_2O was dissolved in THF (8.1 ml) and H_2O (0.95 ml), and a solution of LiOH (1.4 M in H_2O, 1.0 ml) was added dropwise at 0 °C. The resulting solution was then stirred at 0 °C, and carefully monitored by TLC (5% MeOH in DCM). The reaction was quenched by a mixture of sat. aq. $NaHCO_3$ (10 ml) and DCM (10 ml), followed by extraction with DCM (3x 10 ml). The organic layer was combined and dried over $MgSO_4$. After removal of the solvents, the crude product was purified by chromatography (pure DCM to 5% MeOH in DCM) to afford compound **265** (226 mg, 0.41 mmol, 64% based on **263**).

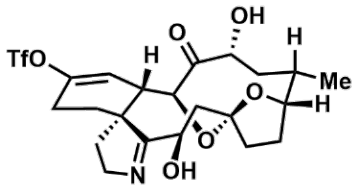
TLC: R_f = 0.25 (5% MeOH in DCM, $KMnO_4$ staining)

[α]$^{25}_{D}$: +14.0 (*c* = 0.1, $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.19 (dd, *J* = 11.4, 2.7 Hz, 1H), 5.06 (q, *J* = 1.7 Hz, 1H), 4.75 (dd, *J* = 11.1, 7.6 Hz, 1H), 4.34 (d, *J* = 12.2 Hz, 1H), 4.29 – 4.20 (m, 2H), 3.81 (dd, *J* = 15.7, 8.9 Hz, 1H), 3.61 (ddt, *J* = 16.2, 10.5, 5.8 Hz, 1H), 2.72 (dd, *J* = 14.9, 11.2 Hz, 1H), 2.57 – 2.25 (m, 5H), 2.19 (dd, *J* = 15.0, 7.6 Hz, 1H), 2.04 (s, 3H), 2.03 – 1.98 (m, 1H), 1.98 – 1.93 (m, 1H), 1.91 – 1.81 (m, 2H), 1.77 (dt, *J* = 12.1, 7.1 Hz, 1H), 1.70 – 1.67 (m, 1H), 1.58 (dd, *J* = 12.6, 7.7 Hz, 1H), 1.52 (dd, *J* = 13.6, 2.8 Hz, 1H), 0.88 (d, *J* = 6.9 Hz, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 199.6, 183.2, 169.1, 148.6,118.7 (q, $J_{C\text{-}F}$ = 319 Hz), 118.0, 108.4, 84.0, 80.0, 72.9, 70.3, 55.4, 53.5, 42.7, 38.9, 37.0, 34.0, 31.5, 29.5, 29.1, 26.5, 24.4, 21.0, 17.5.

HRMS (ESI-TOF): calc'd for $C_{24}H_{30}F_3NO_9S$ $[M+H]^+$: 566.1666, found: 566.1658

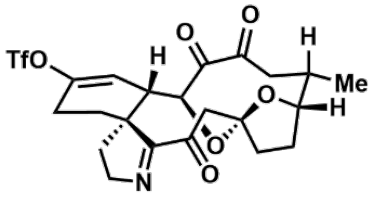


Compound **267**. Diol **267** was isolated as the byproduct from the hydrolysis of **264**.

TLC: R_f = 0.35 (10% MeOH in DCM, $KMnO_4$ staining)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.12 (d, *J* = 1.8 Hz, 1H), 4.77 (dd, *J* = 11.1, 7.7 Hz, 1H), 4.50 (d, *J* = 12.1 Hz, 1H), 4.28 – 4.19 (m, 2H), 4.10 (dd, *J* = 11.1, 2.7 Hz, 1H), 3.83 (dd, *J* = 15.9, 9.0 Hz, 1H), 3.65 (ddd, *J* = 16.3, 10.4, 6.8 Hz, 1H), 3.49 – 3.37 (m, 1H), 2.97 (s, 1H), 2.71 (dd, *J* = 14.8, 11.1 Hz, 1H), 2.57 – 2.46 (m, 2H), 2.46 – 2.35 (m, 1H), 2.35 – 2.23

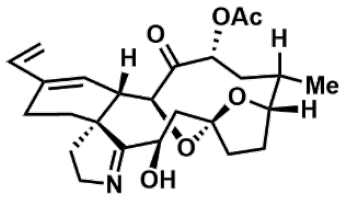
(m, 2H), 2.19 (dd, *J* = 14.9, 7.7 Hz, 1H), 2.02 (dd, *J* = 12.2, 7.0 Hz, 1H), 1.99 – 1.91 (m, 1H), 1.91 – 1.83 (m, 2H), 1.78 – 1.70 (m, 2H), 1.57 – 1.50 (m, 2H), 0.90 (d, *J* = 6.7 Hz, 3H).



Compound **269**. To a solution of diol **267** (1.0 mg, 0.002 mmol), $NaHCO_3$ (1 mg), KBr (1 mg) and TEMPO (0.05 mg, 0.0003 mmol) in DCM (0.1 ml) was added H_2O (1 drop) and NaOCl (ca. 0.8 M in H_2O, 2 drops) at 0 °C. The mixture was then stirred for 30 min, and quenched by sat. aq. $Na_2S_2O_3$ (0.1 ml) at room temperature. The mixture was then extracted by DCM (3x 1ml). The organic layer was combined and dried over $MgSO_4$. After removal of the solvents, the crude **269** was obtained and characterized.

TLC: R_f = 0.60 (6% MeOH in DCM, $KMnO_4$ staining)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.65 (d, *J* = 1.8 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.40 – 4.34 (m, 1H), 4.17 – 4.10 (m, 1H), 3.85 (ddd, *J* = 16.8, 9.7, 7.4 Hz, 1H), 3.63 (d, *J* = 12.1 Hz, 1H), 3.23 (d, *J* = 14.5 Hz, 1H), 2.99 (d, *J* = 14.5 Hz, 1H), 2.88 – 2.80 (m, 1H), 2.58 (dd, *J* = 14.3, 10.7 Hz, 3H), 2.23 – 2.19 (m, 1H), 2.05 – 1.95 (m, 3H), 1.93 – 1.87 (m, 2H), 1.87 – 1.82 (m, 1H), 1.01 (d, *J* = 7.0 Hz, 3H).



Compound **270**. To a solution of compound **265** (23 mg, 0.041 mmol), vinylBF_3K (35 mg, 0.26 mmol), and Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ (2.0 mg, 0.0024 mmol) in *n*-PrOH (0.5 ml) was added TEA (0.05 ml) at room temperature. The solution was then stirred vigorously at 90 °C for 1 h. Upon completion, the solvent was removed in vacuo, and the residue was redissolved in DCM (1 ml) and H_2O (1 ml) was added. The resulting biphasic mixture was extracted with DCM (3x 1 ml). The organic layer was combined and dried over $MgSO_4$. After removal of the solvents, pure **270** (14 mg, 0.032, 78%) was obtained by PTLC (5% *i*-PrOH in DCM).

TLC: R_f = 0.43 (40% acetone in hexanes, UV active, $KMnO_4$ staining)

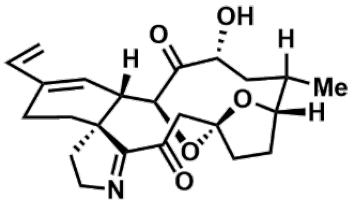
$[\alpha]^{25}_D$: +18.0 (*c* = 0.1, $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.18 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.24 – 5.19 (m, 1H), 5.10 (d, *J* = 17.5 Hz, 1H), 4.91 – 4.99 (m, 2H), 4.75 (dd, *J* = 11.2, 7.4 Hz, 1H), 4.31 (d, *J* = 12.1 Hz, 1H), 4.26 (dt, *J* = 10.7, 5.6 Hz, 1H), 4.16 (d, *J* = 12.1 Hz, 1H), 3.76 (dd, *J* = 16.2, 8.8 Hz, 1H), 3.61 (ddd, *J* = 16.2, 10.4, 6.8 Hz, 1H), 2.81 (dd, *J* = 14.8, 11.3 Hz, 1H), 2.42 – 2.22 (m, 5H), 2.19 – 2.14 (m, 1H), 2.07 (s, 3H), 2.03 (dd, *J* = 12.3, 7.0 Hz, 1H), 1.91 – 1.71 (m, 4H), 1.71 – 1.63 (m, 1H), 1.57 (td, *J* = 12.5, 7.6 Hz, 1H), 1.53 – 1.46 (m, 1H), 0.87 (d, *J* = 7.0 Hz, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 200.1, 184.0, 168.9, 139.0, 135.4, 127.7, 111.6, 108.2,

83.7, 80.1, 73.7, 70.8, 55.4, 54.2, 42.5, 39.8, 36.9, 34.0, 31.6, 29.6, 29.2, 24.3, 22.7, 21.1, 17.4.

HRMS (ESI-TOF): calc'd for $C_{25}H_{33}NO_6$ $[M+H]^+$: 444.2381, found: 444.2377



Portimine B. To a solution of compound **270** (16.7 mg, 0.038 mol) in DCM (0.3 ml) was added DMP (55.1 mg, 0.13 mmol) and $NaHCO_3$ powder (25 mg). The resulting mixture was allowed to stir at rt for 1 h. Upon completion, sat. aq. K_2CO_3 (0.2 ml) and sat. aq. $Na_2S_2O_3$ (0.2 ml) was added, followed by dilution with DCM (2 ml) and water (2 ml). The biphasic mixture was stirred vigorously for 30 min, and the organic layer was separated. The aqueous phase was extracted with DCM (3x 2 ml), and the combined DCM phase was dried over $MgSO_4$ and filter. After concentration, the residue was dissolved in MeOH (0.2 ml) and added aq. NH_3 (37%, 0.1 ml). The progress of hydrolysis can be monitored by TLC (5% MeOH in DCM). After completion, the mixture was added brine to facilitate phase separation. DCM was chosen to extract the solution (3x 2 ml), and the combined DCM layer was dried and concentrated. Portimine B (**2**) (13.3 mg, mmol, 88%) was obtained by chromatography (pure DCM to 5% MeOH in DCM).

TLC: R_f = 0.22 (3% MeOH in DCM, UV active, $KMnO_4$)

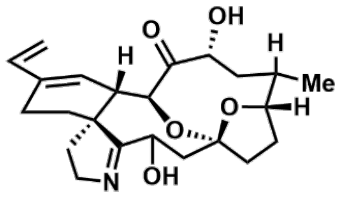
$[\alpha]^{25}_D$: +42.9 (c = 0.08, $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.21 (dd, J = 17.4, 10.8 Hz, 1H), 5.11 (d, J = 17.4 Hz, 1H),

5.07 (d, *J* = 2.0 Hz, 1H), 4.97 (d, *J* = 10.8 Hz, 1H), 4.62 (d, *J* = 12.2 Hz, 1H), 4.281 (dt, *J* = 10.1, 6.0 Hz, 1H), 4.15 (d, *J* = 11.3 Hz, 1H), 4.08 (dd, *J* = 16.2, 9.1 Hz, 1H), 3.83 (ddd, *J* = 16.6, 10.4, 6.7 Hz, 1H), 3.78 (d, *J* = 12.8 Hz, 1H), 3.43 (d, *J* = 17.5 Hz, 1H), 2.79 (d, *J* = 17.5 Hz, 1H), 2.50 (s, 1H), 2.42 – 2.24 (m, 4H), 2.12 (dd, *J* = 12.5, 7.1 Hz, 1H), 2.03 – 1.90 (m, 2H), 1.87 (dd, *J* = 12.5, 6.6 Hz, 1H), 1.78 (dt, *J* = 12.4, 6.4 Hz, 2H), 1.73 – 1.65 (m, 1H), 1.63 – 1.53 (m, 1H), 0.91 (d, *J* = 7.1 Hz, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 204.4, 200.9, 182.5, 138.6, 136.0, 126.7, 112.4, 107.1, 84.7, 78.9, 72.2, 58.1, 54.7, 53.0, 40.9, 38.2, 34.3, 34.1, 28.7, 28.6, 24.4, 22.6, 17.7.

HRMS (ESI-TOF): calc'd for $C_{23}H_{29}NO_5$ $[M+H]^+$: 400.2119, found: 400.2117



Portimine A. To a solution of crude portimine B (ca. 20 mg, 0.05 mmol) in MeOH (0.5 ml) was added $NaBH_3CN$ (10 mg, 0.16 mol) and AcOH (0.025 ml) at rt. The resulting mixture was stirred at the same temperature for 1.5 h, and quenched with sat. $NaHCO_3$ aq. The mixture was extracted with DCM (4x 1 ml), and the organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified with chromatography (DCM to 10% MeOH in DCM) to obtain compound **1** (19.2 mg, 0.048 mol, 95%).

TLC: R_f = 0.54 (10% MeOH in DCM, UV active, $KMnO_4$ staining)

$[\alpha]^{25}_D$: +5.8 (*c* = 1.0, $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.21 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.17 – 5.01 (m, 2H), 4.93

(d, *J* = 10.8 Hz, 1H), 4.71 (br s, 1H), 4.52 (s, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.18 (dt, *J* = 11.2, 5.6 Hz, 1H), 4.08 (dd, *J* = 11.2, 2.7 Hz, 1H), 3.86 (dd, *J* = 15.2, 8.8 Hz, 1H), 2.81 (dd, *J* = 15.9, 5.1 Hz, 1H), 2.43 – 2.19 (m, 4H), 2.09 (d, *J* = 15.8 Hz, 1H), 2.01 – 1.92 (m, 2H), 1.93 – 1.79 (m, 2H), 1.79 – 1.61 (m, 5H), 1.50 (dd, *J* = 13.7, 2.6 Hz, 1H), 0.88 (d, *J* = 6.9 Hz, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 204.6, 185.0, 138.8, 135.2, 127.8, 111.7, 109.1, 83.2, 79.3, 71.6, 65.6, 54.9, 52.7, 43.1, 40.6, 37.6, 34.3, 33.8, 29.6, 29.0, 24.6, 22.6, 17.6.

HRMS (ESI-TOF): calc'd for $C_{23}H_{31}NO_5$ $[M+H]^+$: 402.2275, found: 402.2265

Chapter 6: Chemical diversification and bioactivity evaluation of portimine A and B.

Section 6.1 Portimines can be diversified at multiple sites.

Multiple sites on portimines' skeleton could be diversified based on this synthetic work (Figure 6.1). For instance, the vinyl triflate of compound **265** allowed for flexible diversification of portimine A, B and C-5 epimer of portimine A (ePA, **272**, R = vinyl, R' = H), via traditional cross-coupling chemistry or OTf-X exchange (*1*).

In the first part of my diversification work, compound **265** was directly submitted to Suzuki conditions with numerous boronic acid nucleophiles. Satisfyingly, phenyl (**275**), 3-pyridyl (**276**), 4-pyridyl (**277**), and photo-clickable probe (**278**, **279**) could be accessed under similar conditions (for details, see Experimental), offering a small library of natural products (PA and PB) and C-5 epimer (ePA). The bioactivity of each analog was evaluated (collaborated with Parker and Lairson lab).

Moreover, the hydroxyl group at C-13 could be masked/modified from the stage of nitrone **263** and deprotected in the last step, leading to analogs such as 13-OMe-Ph-PA (**283**) and Cl-PA (**284**). Intuitively, protection of the hydroxyl group at C-13 prior to Boekelheide rearrangement would get rid of late-stage regioselective hydrolysis, as presented in Figure 5.2, providing easier procedure and higher material throughput. Indeed, methylation, silylation (TES), and carbonation (Boc) worked well on **263**, as shown in Figure 6.1. It is also worth mentioning that portimines' skeleton is susceptible to acidic conditions, therefore the Boc group was deprotected under basic condition (K_2CO_3/MeOH, reflux, see Experimental).

Interestingly, 13-deoxyportimine (**286**), and its related analogs (**285**, **287**), could be prepared by several chemical transformation starting from **262**.

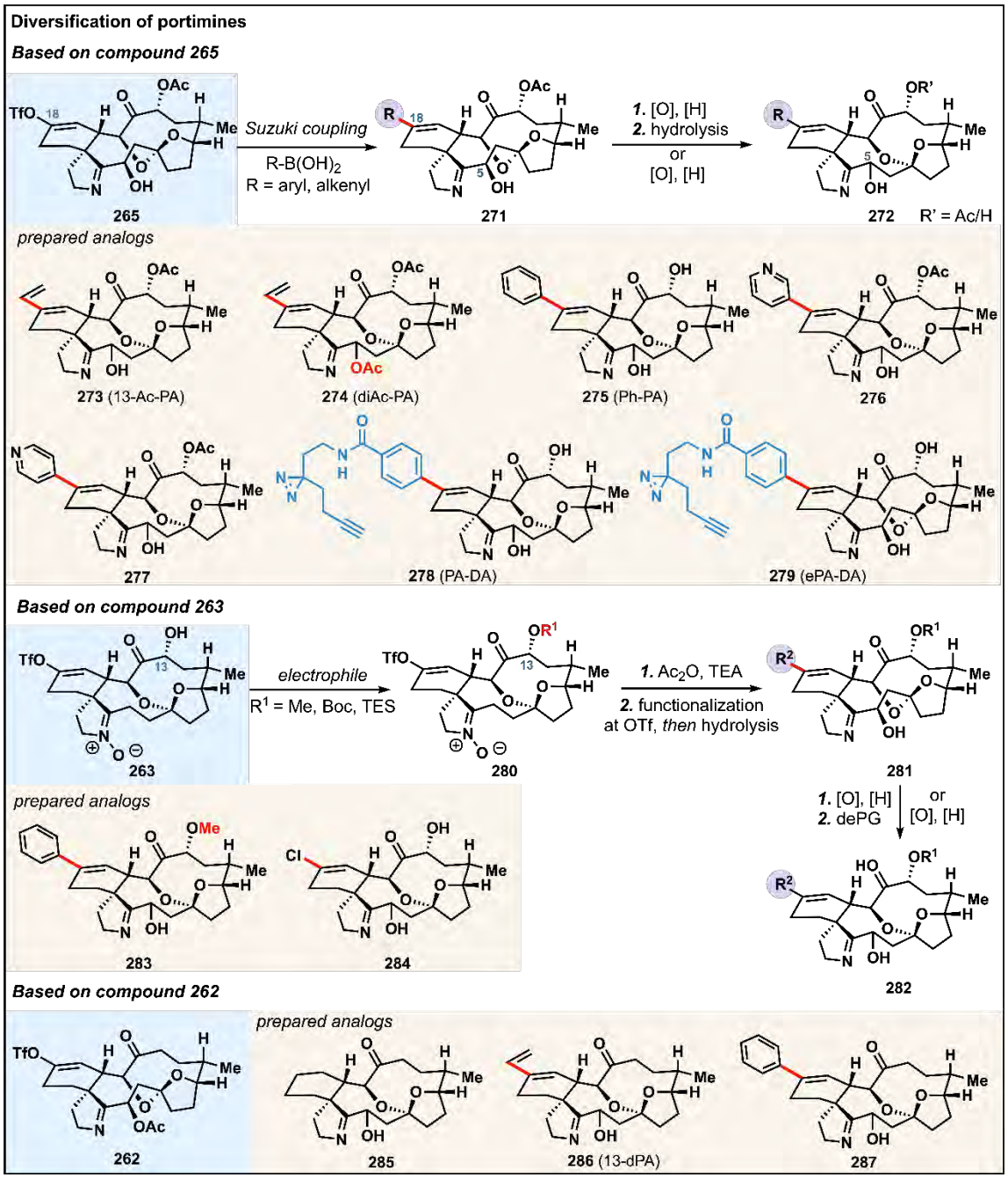


Figure 6.1 Diversification of portimines.

Section 6.2 Structural-activity relationship (SAR) study of portimine A.

As the first step to understand the MoA of PA, we sought to identify sites that could accommodate a “fully functionalized” retrieval tag to facilitate chemical proteomic target identification without interfering with the bioactivity of PA (*2*-*7*). With a series of natural product derivatives in hand (Figure 6.2), an evaluation of these compounds was carried out in Jurkat (human T lymphocyte) cells and confirmed that the fully-synthetic PB is significantly less potent than PA, both of which were consistent to previous report (Figure 6.3, *8*). Strikingly, ePA also exhibits a neglectable potency compared with PA (IC_{50} >1000 nM compared with 0.9 nM), underlining the stereochemistry at C-5 is crucial to PA’s bioactivity. Moreover, replacement of the exocyclic vinyl group at C-18 by a phenyl group did not perturb the observed potency, indicating the terminal vinyl group is not essential for the biological activity.

Taken together, the above data supported that the potency of PA is dependent on the stereochemistry at C-5, suggesting that ePA could be employed as an inactive control compound for further studies, and independent on the terminal group at C-18. Fortunately, the epimeric photoaffinity probes PA-DA and ePA-DA, retained identical activities to their parent analogs, suggesting that they could serve as target identification tools in chemical proteomics (Figure 6.3).

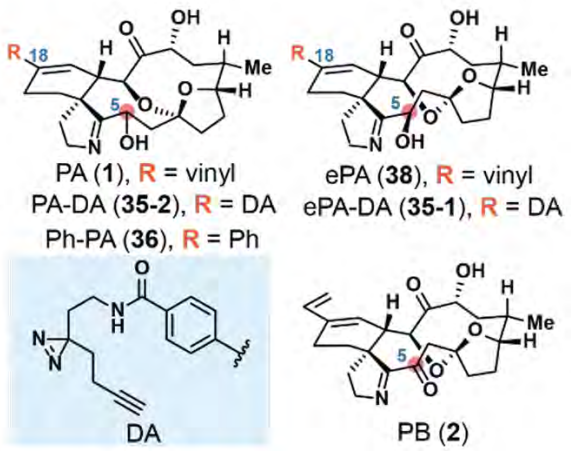


Figure 6.2 Chemical structure of portimine A and its selected derivatives.

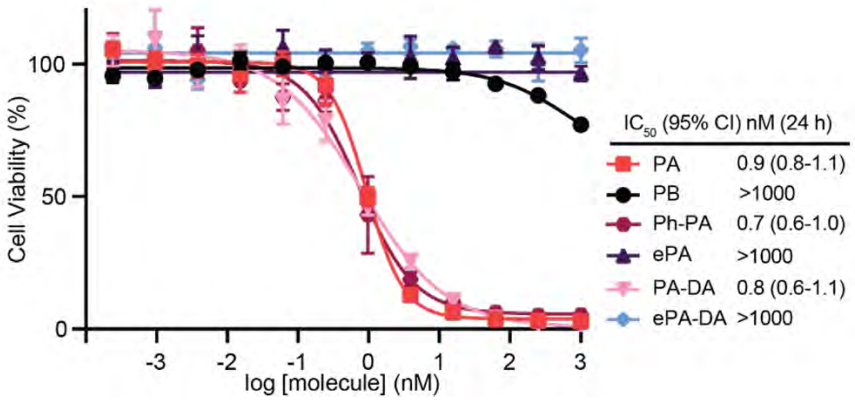


Figure 6.3 Effects of PA and its selected analogs on Jurkat cell viability at 24 h.

Distribution of credit

The ideas used in Chapter 6 were conceived by me, Weichao Li (Parker lab) under the supervision of Prof. Phil Baran, Prof. Christopher Parker, and Prof. Luke Lairson. The synthesis of each analog was completed, characterized and optimized by me. The evaluation of the biological activity was carried out, summarized, and depicted by Weichao Li.

Reference

(1) Imazaki, Y.; Shirakawa, E.; Ueno, R.; Hayashi, T. Ruthenium-Catalyzed Transformation of Aryl and Alkenyl Triflates to Halides. *J. Am. Chem. Soc.* **2012**, *13*, 14760−14763.

(2) Li, Z.; Hao, P.; Li, L.; Tan, Y. J.; Cheng, X.; Chen, G. Y. J.; Sze, S. K.; Shen, H-M.; Yao, S. Q. Design and Synthesis of Minimalist Terminal Alkyne-Containing Diazirine Photo Crosslinkers and Their Incorporation into Kinase Inhibitors for Cell- and Tissue-Based Proteome Profiling. *Angew. Chem. Int. Ed.* **2013**, *52*, 8551−8556.

(3) Parker, C. G.; Galmozzi, A.; Wang, Y.; Correia, B. E.; Sasaki, K.; Joslyn, C. M.; Kim, A. S.; Cavallaro, C. L.; Lawrence, R. M.; Johnson, S. R.; Narvaiza, I.; Saez, E.; Cravatt, B. F. Ligand and Target Discovery by Fragment-Based Screening in Human Cells. *Cell* **2017**, *168*, 527−541.e529.

(4) Wang, Y. J.; Dix, M. M.; Bianco, G.; Remsberg, J. R.; Lee, H. Y.; Kalocsay, M.; Gygi, S. P.; Forli, S.; Vite, G.; Lawrence, R. M.; Parker, C. G.; Cravatt, B. F. Expedited mapping of the ligandable proteome using fully functionalized enantiomeric probe pairs. *Nat. Chem.* **2019**, *11*, 1113−1123.

(5) Parker, C. G.; Pratt, M. R. Click Chemistry in Proteomic Investigations. *Cell* **2020**, *180*, 605−632.

(6) Parker, C. G.; Kuttruff, C. A.; Galmozzi, A.; Jorgensen, L.; Yeh, C. H.; Hermanson, D. J.; Wang, Y. J.; Artola, M.; McKerrall, S. J.; Josyln, C. M.; Norremark, B.; Dunstl, G.; Felding, J.; Saez, E.; Baran, P. S.; Cravatt, B. F. Chemical Proteomics Identifies SLC25A20

as a Functional Target of the Ingenol Class of Actinic Keratosis Drugs. *ACS Central Science* **2017**, *3*, 1276−1285.

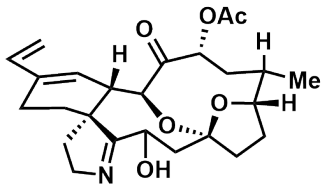
(7) Conway, L. P.; Li, W.; Parker, C. G. Chemoproteomic-enabled phenotypic screening. *Cell Chem. Bio.* **2021**, *28*, 371−393.

(8) Fribley, A. M.; Xi, Y.; Makris, C.; Alves-de-Souza, C.; York, R.; Tomas, C.; Wright, J. L. C.; Strangman, W. K. Identification of Portimine B, a New Cell Permeable Spiroimine That Induces Apoptosis in Oral Squamous Cell Carcinoma. *ACS Med. Chem. Lett.* **2019**, *10*, 175–179.

Experimental

General procedure for Suzuki coupling of compound 265 (aryl boronic acid as partner):

To a mixture of triflate **265** (1.0 eq.), $Pd(dppf)Cl_2$ or its DCM complex (0.05 eq.), $NaHCO_3$ (300 wt % to **265**), corresponding aryl boronic acid (5.0 eq.) under argon was added degassed DME/H_2O (4:1 v/v, 0.02 M). The resulting mixture was prestirred at rt for 5 min, and heated to 80 °C. Upon completion (usually took 1-2 h), the mixture was cooled to rt and diluted with H_2O. The mixture was extracted by DCM (3x) and dried over $MgSO_4$. After concentration under reduced pressure, pure product was obtained from PTLC.



Compound **273** (13-Ac-PA). **273** (6.3 mg, 0.014 mmol) was prepared from compound **270**

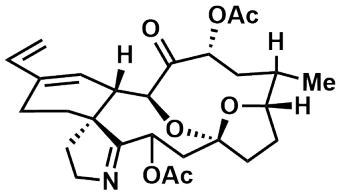
(9.0 mg, 0.020 mmol) by oxidation with DMP (excess, ca. 10 mg) and reduction with $NaBH_3CN$ (same as the synthesis of portimine A). Purified by PTLC (5% *i*-PrOH in DCM).

TLC: R_f = 0.58 (10% MeOH in DCM, UV active, $KMnO_4$ staining)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.16 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.21 – 5.16 (m, 1H), 5.10 (d, *J* = 17.5 Hz, 1H), 4.96 (d, *J* = 10.8 Hz, 1H), 4.90 (s, 1H), 4.52 (t, *J* = 4.2 Hz, 1H), 4.29 (d, *J* = 11.9 Hz, 1H), 4.20 (dt, *J* = 10.8, 5.4 Hz, 1H), 3.88 (dd, *J* = 15.3, 8.9 Hz, 1H), 3.75 (d, *J* = 12.4 Hz, 1H), 3.70 (ddd, *J* = 14.7, 7.1, 3.7 Hz, 1H), 2.81 (dd, *J* = 16.0, 5.1 Hz, 1H), 2.45 – 2.26 (m, 4H), 2.11 (dd, *J* = 16.1, 1.9 Hz, 1H), 2.06 (s, 3H), 1.99 (dd, *J* = 12.2, 7.1 Hz, 2H), 1.93 (dd, *J* = 12.5, 6.9 Hz, 1H), 1.88 – 1.63 (m, 5H), 1.49 (dd, *J* = 12.9, 2.8 Hz, 1H), 0.87 (d, *J* = 6.6 Hz, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 200.5, 185.8, 169.0, 138.8, 135.6, 127.3, 112.2, 109.4, 83.3, 80.2, 73.6, 65.7, 54.8, 52.8, 43.3, 40.7, 37.8, 34.1, 31.6, 29.5, 29.0, 24.7, 22.7, 21.3, 17.6.

HRMS (ESI-TOF): calc'd for $C_{25}H_{33}NO_6$ $[M+H]^+$: 444.2381, found: 444.2379



Compound **274** (di-Ac-PA). To a solution of portimine A (2.5 mg, 0.0062 mmol) in DCM (0.1 ml) was added TEA (1 drop) and Ac_2O (1 drop) under argon. The resulting mixture was then heated to reflux and reacted for 1 h. Upon completion, volatiles were removed

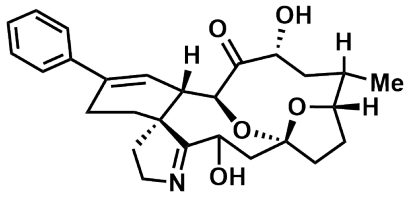
under vacuo, and the residue was purified by PTLC (3% MeOH in DCM) to give diacetate **274** (2.7 mg, 0.0056 mmol, 90%).

TLC: R_f = 0.60 (5% MeOH in DCM, UV active, $KMnO_4$ staining)

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.17 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.58 (dd, *J* = 6.6, 3.0 Hz, 1H), 5.20 (d, *J* = 8.8 Hz, 1H), 5.12 (d, *J* = 17.4 Hz, 1H), 4.97 (d, *J* = 10.8 Hz, 1H), 4.95 – 4.86 (m, 1H), 4.32 (d, *J* = 12.0 Hz, 1H), 4.22 (dt, *J* = 11.0, 5.9 Hz, 1H), 3.92 (dd, *J* = 15.4, 8.7 Hz, 1H), 3.78 – 3.64 (m, 2H), 3.00 (d, *J* = 15.3 Hz, 1H), 2.46 – 2.26 (m, 5H), 2.20 – 2.16 (m, 1H), 2.14 (s, 3H), 2.07 (s, 3H), 2.01 – 1.96 (m, 1H), 1.92 – 1.79 (m, 4H), 1.76 (dt, *J* = 12.7, 7.0 Hz, 1H), 1.64 (td, *J* = 12.9, 7.5 Hz, 1H), 1.50 (dd, *J* = 12.9, 2.7 Hz, 1H), 0.88 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.1, 169.1, 138.8, 127.1, 112.3, 109.0, 83.7, 67.9, 56.4, 54.0, 40.7, 37.5, 34.2, 31.8, 29.9, 28.7, 28.6, 24.7, 22.7, 21.3, 21.3, 17.5.

(Carbonyl at C-14 and imine at C-4 were missing)



Compound **275** (Ph-PA). Following the general procedure and the aforementioned redox manipulation to epimerize C-5, using phenyl boronic acid.

TLC: R_f = 0.46 (10% MeOH in DCM, UV active, $KMnO_4$ staining)

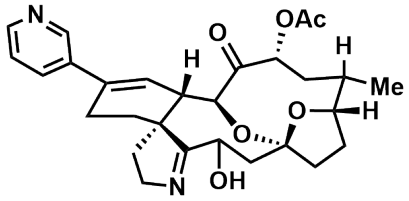
^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 5.47 (s, 1H), 4.53 (d, *J* = 12.1 Hz, 1H), 4.37 (s, 1H2), 4.21 (dt, *J* = 11.2,

6.0 Hz, 1H), 4.09 (dd, *J* = 11.2, 2.6 Hz, 1H), 3.84 (dd, *J* = 15.3, 9.0 Hz, 1H), 3.71 – 3.61 (m, 1H), 3.55 (d, *J* = 12.1 Hz, 1H), 2.78 (dd, *J* = 15.9, 5.1 Hz, 1H), 2.58 – 2.41 (m, 2H), 2.39 – 2.24 (m, 2H), 2.11 (d, *J* = 15.9 Hz, 1H), 2.01 – 1.93 (m, 2H), 1.93 – 1.81 (m, 2H), 1.76 – 1.70 (m, 1H), 1.71 – 1.63 (m, 3H), 1.55 (dd, *J* = 14.1, 2.7 Hz, 1H), 0.91 (d, *J* = 6.9 Hz, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 206.1, 140.4, 135.4, 128.5, 127.6, 125.2, 123.4, 109.2, 83.4, 79.6, 71.7, 65.7, 54.8, 52.1, 43.1, 40.5, 37.7, 34.5, 33.5, 29.9, 29.4, 29.1, 25.6, 24.8, 17.8.

(1 carbon (C=N) was missing in ^{13}C NMR)

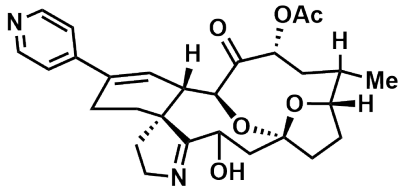
HRMS (ESI-TOF): calc'd for $C_{27}H_{33}NO_5$ $[M+H]^+$: 452.2432, found: 452.2435



Compound **276**. Following the general procedure and the aforementioned redox manipulation to epimerize C-5, using 3-pyridyl boronic acid.

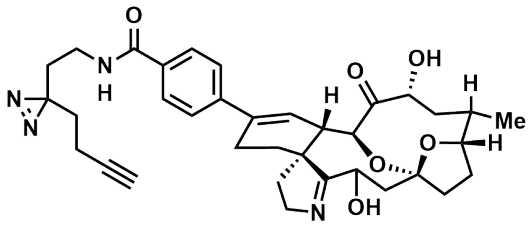
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.5 (dd, *J* = 2.4, 0.8 Hz, 1H), 8.5 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.6 (dt, *J* = 8.1, 2.0 Hz, 1H), 7.2 (ddd, *J* = 7.9, 4.7, 0.8 Hz, 1H), 5.3 (d, *J* = 2.0 Hz, 1H), 5.2 – 5.2 (m, 1H), 4.7 (d, *J* = 3.2 Hz, 1H), 4.5 (s, 1H), 4.4 (d, *J* = 12.0 Hz, 1H), 4.2 (dt, *J* = 11.0, 5.5 Hz, 1H), 3.9 (dd, *J* = 15.4, 8.8 Hz, 1H), 3.8 (d, *J* = 11.9 Hz, 1H), 3.8 – 3.7 (m, 1H), 2.8 (dd, *J* = 16.1, 5.1 Hz, 1H), 2.7 – 2.6 (m, 2H), 2.4 – 2.3 (m, 2H), 2.2 (dd, *J* = 16.1,

1.9 Hz, 1H), 2.1 (m, 1H), 2.1 (s, 3H), 2.0 (dt, *J* = 12.8, 6.3 Hz, 2H), 1.9 – 1.8 (m, 3H), 1.8 – 1.7 (m, 1H), 1.7 – 1.7 (m, 1H), 1.5 (dd, *J* = 12.9, 2.8 Hz, 1H), 0.9 – 0.8 (m, 3H).



Compound **277**. Following the general procedure and the aforementioned redox manipulation to epimerize C-5, using 4-pyridyl boronic acid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.5 (d, *J* = 6.2 Hz, 2H), 7.2 (d, *J* = 6.3 Hz, 2H), 5.5 (q, *J* = 2.0 Hz, 1H), 5.3 – 5.2 (m, 1H), 4.6 – 4.5 (m, 1H), 4.4 (d, *J* = 12.0 Hz, 1H), 4.3 (dt, *J* = 10.9, 5.8 Hz, 1H), 3.9 (dd, *J* = 15.4, 8.9 Hz, 1H), 3.9 (dd, *J* = 12.1, 3.0 Hz, 1H), 3.8 (tdd, *J* = 10.9, 6.8, 3.4 Hz, 1H), 2.9 (dd, *J* = 16.1, 5.1 Hz, 1H), 2.7 – 2.6 (m, 2H), 2.5 – 2.3 (m, 2H), 2.2 (dd, *J* = 16.2, 1.9 Hz, 1H), 2.1 (s, 3H), 2.1 – 2.0 (m, 4H), 1.9 – 1.9 (m, 1H), 1.9 – 1.8 (m, 1H), 1.8 – 1.7 (m, 2H), 1.6 (dd, *J* = 13.0, 2.9 Hz, 1H), 0.9 (d, *J* = 6.3 Hz, 3H).



Compound **278** (PA-DA). Following the general procedure and the aforementioned redox manipulation to epimerize C-5, using the corresponding boronic acid.

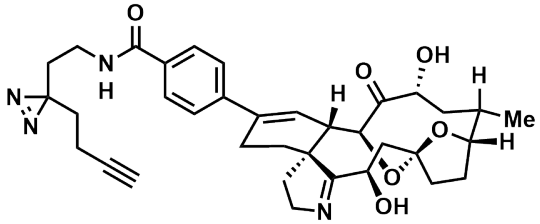
TLC: R_f = 0.23 (10% MeOH in DCM, UV active, $KMnO_4$ staining)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 6.31 (s, 1H), 5.54 (d, *J* = 2.2 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.43 (s, 1H), 4.21 (dt, *J* = 11.2,

5.9 Hz, 1H), 4.10 (dd, *J* = 11.3, 2.7 Hz, 1H), 3.90 – 3.83 (m, 1H), 3.72 – 3.62 (m, 2H), 3.30 (q, *J* = 6.4 Hz, 2H), 2.80 (dd, *J* = 15.9, 5.1 Hz, 1H), 2.54 (d, *J* = 7.8 Hz, 2H), 2.39 – 2.32 (m, 1H), 2.31 – 2.25 (m, 1H), 2.13 (d, *J* = 15.9 Hz, 1H), 2.07 – 1.96 (m, 5H), 1.92 (dd, *J* = 12.6, 6.7 Hz, 1H), 1.89 – 1.83 (m, 1H), 1.81 (t, *J* = 6.6 Hz, 2H), 1.75 (td, *J* = 12.3, 5.1 Hz, 2H), 1.72 – 1.63 (m, 3H), 1.61 – 1.51 (m, 2H), 0.90 (d, *J* = 6.9 Hz, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 205.5, 185.2, 167.3, 143.7, 135.0, 133.0 (2C), 127.1, 125.4, 109.2, 83.5, 82.9, 79.4, 71.6, 69.7, 65.7, 55.0, 52.1, 43.2, 40.8, 37.8, 35.1, 34.5, 33.8, 32.6, 32.3, 29.9, 29.5, 29.3, 27.2, 25.7, 24.8, 17.8. 13.4.

HRMS (ESI-TOF): calc'd for $C_{35}H_{42}N_4O_6$ $[M+H]^+$: 615.3177, found: 615.3193



Compound **279** (ePA-DA). Following the general procedure, using the corresponding boronic acid.

An alternative procedure:

To a solution of compound **265** (5.1 mg, 0.0091 mmol) and the corresponding boronic acid (6.6 mg, 0.018 mmol) in DME (0.2 ml) was added $Pd(PPh_3)_4$ (1.0 mg, 0.00091 mmol). The resulting yellow solution was added sat. aq. Na_2CO_3 (0.1 ml) while stirring, followed by heating to 100 °C. Upon completion (normally 4 h), water (0.5 ml) was added and the mixture was extracted with DCM (3x 1ml). The combined organic layer was dried over $MgSO_4$ and concentrated. Crude product was purified by PTLC (8% MeOH in DCM) to

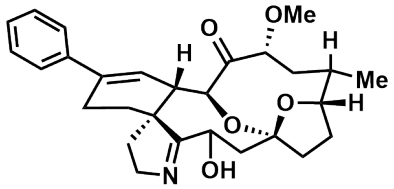
afford **279** (4.4 mg, 0.0072 mmol, 79%) as product.

TLC: R_f = 0.21 (10% MeOH in DCM, UV active, $KMnO_4$ staining)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.12 (br s, 1H), 5.63 (s, 1H), 4.74 (t, *J* = 9.3 Hz, 1H), 4.62 (d, *J* = 11.9 Hz, 1H), 4.31 (s, 1H), 4.14 – 4.03 (m, 1H), 3.92 (d, *J* = 12.0 Hz, 1H), 3.59 (q, *J* = 6.5 Hz, 1H), 3.54 – 3.45 (m, 1H), 3.42 – 3.30 (m, 1H), 2.96 (q, *J* = 9.1 Hz, 1H), 2.85 (t, *J* = 12.9 Hz, 1H), 2.43 – 2.29 (m, 2H), 2.29 – 2.20 (m, 2H), 2.18 – 2.09 (m, 1H), 2.05 – 1.87 (m, 6H), 1.86 – 1.70 (m, 4H), 1.68 (td, *J* = 7.2, 4.5 Hz, 2H), 1.65 – 1.55 (m, 3H), 1.54 – 1.44 (m, 1H), 0.95 (d, *J* = 6.5 Hz, 3H)

^{13}C-NMR (150 MHz, $CDCl_3$) δ 207.8, 185.1, 167.7, 142.3, 133.8, 132.9 (2C), 127.4, 124.7, 124.4, 108.1, 84.3, 82.9, 79.6, 71.5, 70.8, 69.6, 54.7, 53.8, 42.4, 40.3, 37.1, 34.9, 34.6, 33.0, 32.8, 32.3, 29.9, 29.7, 28.9, 27.2, 25.1, 24.4, 17.8, 13.5

HRMS (ESI-TOF): calc'd for $C_{35}H_{42}N_4O_6$ $[M+H]^+$: 615.3177, found: 615.3170

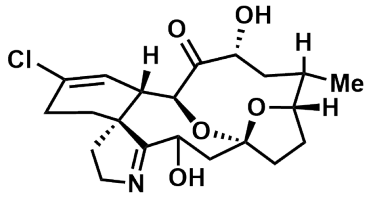


Compound **283**. To a solution of nitrone **263** (12.0 mg, 0.023 mmol) and MeI (4 drops, large excess) in DMF (0.5 ml) was added NaH (60 wt % in mineral oil, ca. 2 mg) in one portion at 0 °C under argon. The resulting mixture was stirred at the same temperature for 30 min. Upon completion (checked by TLC, 8% MeOH in DCM), the mixture was quenched by adding brine (0.5 ml) and extracted by EtOAc (3x 1 ml). The organic layer

was dried over $MgSO_4$ and concentrated in vacuo. Pure 13-OMe-**263** (12 mg, 0.022 mmol, 96%) was obtained by PTLC (8% MeOH in DCM).

Subsequently, 13-OMe-**263** underwent the Boekelheide rearrangement using the aforementioned procedure (see the preparation of **264**) with Ac_2O and TEA, and using the general Suzuki coupling procedure, followed by epimerization of C-5 to get compound **283**.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 4H), 7.23 (ddt, *J* = 8.4, 5.6, 2.1 Hz, 1H), 5.33 (q, *J* = 1.9 Hz, 1H), 4.55 (s, 1H), 4.43 (d, *J* = 12.0 Hz, 1H), 4.19 (dt, *J* = 11.4, 5.9 Hz, 1H), 3.89 (dd, *J* = 15.3, 8.7 Hz, 1H), 3.85 – 3.79 (m, 1H), 3.77 – 3.67 (m, 1H), 3.47 (dd, *J* = 11.2, 2.7 Hz, 1H), 3.35 (s, 3H), 2.87 (dd, *J* = 15.9, 5.2 Hz, 1H), 2.72 – 2.57 (m, 2H), 2.33 – 2.19 (m, 2H), 2.14 (dd, *J* = 16.0, 1.8 Hz, 1H), 2.07 – 1.95 (m, 3H), 1.91 – 1.79 (m, 3H), 1.73 (dt, *J* = 12.5, 7.3 Hz, 1H), 1.70 – 1.64 (m, 1H), 1.53 (dd, *J* = 13.8, 2.7 Hz, 1H), 0.89 (d, *J* = 6.8 Hz, 3H).



Compound **284** (Cl-PA). To a solution of nitrone **263** (20.0 mg, 0.038 mmol) and MeI (7 drops, large excess) in DMF (0.85 ml) was added NaH (60 wt % in mineral oil, ca. 2 mg) in one portion at 0 °C under argon. The resulting mixture was stirred at the same temperature for 1.5 h. Upon completion (checked by TLC, 8% MeOH in DCM), the mixture was quenched by adding brine (0.5 ml) and extracted by EtOAc (3x 1 ml). The

organic layer was dried over $MgSO_4$ and concentrated in vacuo. Pure 13-OBoc-**263** (22 mg, 0.035 mmol, 92%) was obtained by PTLC (8% MeOH in DCM).

Data of 13-OBoc-263:

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.00 (s, 1H), 4.99 – 4.95 (m, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 4.31 – 4.22 (m, 1H), 4.10 (dddd, *J* = 13.6, 10.7, 7.7, 3.2 Hz, 1H), 3.93 (t, *J* = 11.4 Hz, 2H), 3.58 – 3.45 (m, 1H), 2.65 – 2.47 (m, 3H), 2.42 – 2.24 (m, 3H), 2.15 – 2.06 (m, 2H), 2.05 – 1.93 (m, 2H), 1.93 – 1.80 (m, 3H), 1.75 (dd, *J* = 12.5, 6.7 Hz, 1H), 1.67 – 1.56 (m, 2H), 1.46 (s, 9H), 0.90 (d, *J* = 6.6 Hz, 3H).

Purified 13-OBoc-**263** (22 mg, 0.035 mmol) underwent the Boekelheide rearrangement using the aforementioned procedure (see the preparation of **264**) with Ac_2O and TEA, giving 13-OBoc-**264** as the product in quantitative yield.

Data of 13-OBoc-264:

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.78 (dd, *J* = 11.0, 8.0 Hz, 1H), 5.07 (d, *J* = 2.0 Hz, 1H), 5.03 – 4.94 (m, 1H), 4.38 (d, *J* = 12.1 Hz, 1H), 4.24 (dt, *J* = 10.7, 5.7 Hz, 1H), 4.12 (d, *J* = 11.8 Hz, 1H), 3.91 (dd, *J* = 16.2, 9.0 Hz, 1H), 3.76 (ddd, *J* = 16.6, 10.3, 6.9 Hz, 1H), 2.60 (dd, *J* = 14.8, 11.0 Hz, 1H), 2.57 – 2.52 (m, 1H), 2.51 – 2.44 (m, 1H), 2.38 – 2.29 (m, 3H), 2.22 – 2.14 (m, 1H), 2.08 (s, 3H), 1.98 (q, *J* = 10.4 Hz, 1H), 1.93 – 1.82 (m, 2H), 1.78 (dq, *J* = 12.5, 6.8 Hz, 2H), 1.60 (ddd, *J* = 13.0, 10.4, 5.5 Hz, 3H), 1.47 (s, 9H), 0.89 (d, *J* = 6.0 Hz, 3H).

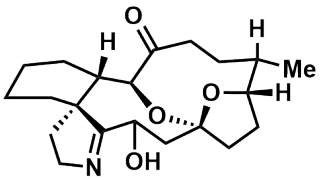
Purified 13-OBoc-**264** (20 mg, 0.035 mmol) was dissolved in DMI (0.5 ml) at rt under argon. To this solution, LiCl (ca. 10 mg, large excess) and $[Cp^*Ru(MeCN)_3]PF_6$ (1 mg,

0.0023 mmol) was added in one portion. The resulting brown solution was heated to 55 °C and stirred overnight. Upon completion (indicated by TLC, 40% Et_2O in DCM), the solvent was removed by a flow of air at 40 °C (may take 24 h). The residue was dissolved in MeOH/H_2O (4:1 v/v, 1.0 ml) and added K_2CO_3 (10 mg). Upon completion, H_2O (1 ml) was added and the mixture was extracted by DCM (3x 1 ml). The organic layer was dried over $MgSO_4$ and concentrated. The product was purified by PTLC (50% Et_2O in DCM) to yield Cl-13-OBoc-**265** (7 mg, 0.014 mmol, 40%) as the final product.

Cl-13-OBoc-**265** was epimerized following the aforementioned procedure (see the synthesis of portimine A). The Boc group was removed by heating the starting material in MeOH in the presence of K_2CO_3. Purified by PTLC (10% MeOH in DCM).

Data of Cl-PA (284):

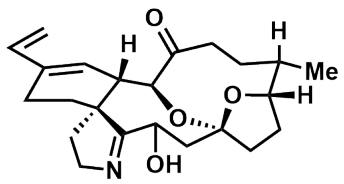
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.16 (d, *J* = 1.9 Hz, 1H), 4.47 (s, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.19 (dt, *J* = 11.2, 6.0 Hz, 1H), 4.08 (dd, *J* = 11.2, 2.7 Hz, 1H), 3.90 (dd, *J* = 15.4, 9.0 Hz, 1H), 3.75 (dd, *J* = 12.3, 2.9 Hz, 1H), 3.73 – 3.62 (m, 1H), 2.75 (dd, *J* = 16.0, 5.2 Hz, 1H), 2.54 – 2.41 (m, 2H), 2.36 – 2.17 (m, 3H), 2.10 (dd, *J* = 16.0, 1.9 Hz, 1H), 2.08 – 2.00 (m, 1H), 1.98 (dd, *J* = 12.8, 7.0 Hz, 2H), 1.88 – 1.79 (m, 2H), 1.75 – 1.69 (m, 2H), 1.69 – 1.57 (m, 1H), 1.51 (dd, *J* = 13.8, 2.8 Hz, 1H), 0.89 (d, *J* = 6.8 Hz, 3H).



Compound **285**. To a solution of compound **262** (5.5 mg, 0.01 mmol) in MeOH/H_2O (4:1 v/v, 0.3 ml) was added K_2CO_3 (4 mg) at rt. The resulting mixture was stirred for 1 h, and quenched by an addition of H_2O (1 ml). The mixture was then extracted by DCM (3x 1 ml). The combined organic layer was dried over $MgSO_4$ and concentrated under vacuo. The hydrolyzed product was purified by PTLC (7% MeOH in DCM).

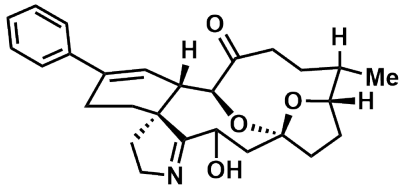
The product obtained above was epimerized by the aforementioned procedure (see the synthesis of portimine A). The purified triflate (3.0 mg, 0.006 mmol) was mixed with Pd/C (5%, 1 mg), and dissolved in MeOH (0.1 ml) under argon. The atmosphere was changed to H_2, and the mixture was stirred at rt for 24 h. Upon completion, the mixture was diluted with EtOAc (2 ml) and filter through Celite®. The resulting solution was concentrated under reduced pressure and purified by PTLC (10% MeOH in DCM) to yield **285** (1.2 mg, 0.0033 mmol, 55%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.54 (s, 1H), 4.21 (dt, *J* = 11.2, 6.2 Hz, 1H), 3.89 – 3.80 (m, 2H), 3.76 – 3.50 (m, 3H), 2.85 (dd, *J* = 15.8, 5.2 Hz, 1H), 2.77 – 2.70 (m, 1H), 2.63 – 2.52 (m, 1H), 2.41 (dd, *J* = 15.6, 7.9 Hz, 1H), 2.35 – 2.24 (m, 2H), 2.07 (dd, *J* = 13.5, 7.3 Hz, 3H), 1.96 (td, *J* = 13.6, 8.3 Hz, 2H), 1.90 – 1.80 (m, 1H), 1.71 (dt, *J* = 12.4, 7.2 Hz, 2H), 1.63 (td, *J* = 12.5, 7.2 Hz, 2H), 1.52 (d, *J* = 13.7 Hz, 1H), 1.46 (t, *J* = 13.2 Hz, 1H), 1.42 – 1.34 (m, 3H), 0.81 (d, *J* = 7.1 Hz, 3H).



Compound **286** (13-dPA). This compound was prepared from compound **262** via a sequence including Suzuki, hydrolysis and epimerization (as aforementioned).

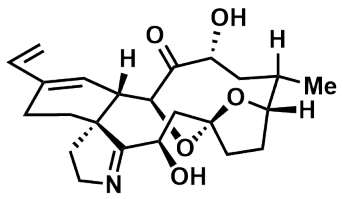
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.19 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.09 (d, *J* = 17.5 Hz, 1H), 4.99 (s, 1H), 4.95 (d, *J* = 10.7 Hz, 1H), 4.50 (s, 1H), 4.24 (dt, *J* = 11.0, 6.2 Hz, 1H), 4.01 (d, *J* = 11.9 Hz, 1H), 3.87 (dd, *J* = 15.2, 8.8 Hz, 1H), 3.76 (d, *J* = 12.1 Hz, 1H), 3.73 – 3.65 (m, 1H), 2.83 (dd, *J* = 16.0, 5.2 Hz, 1H), 2.69 – 2.61 (m, 1H), 2.53 (dd, *J* = 15.6, 7.7 Hz, 1H), 2.33 (dq, *J* = 20.2, 10.9 Hz, 3H), 2.16 – 2.07 (m, 2H), 2.01 – 1.93 (m, 2H), 1.93 – 1.85 (m, 2H), 1.74 (tt, *J* = 11.5, 9.3 Hz, 3H), 1.65 (td, *J* = 12.6, 7.7 Hz, 1H), 1.42 (dd, *J* = 15.1, 7.8 Hz, 1H), 0.83 (d, *J* = 7.2 Hz, 3H).



Compound **287**. This compound was prepared from compound **262** via a sequence including Suzuki, hydrolysis and epimerization (as aforementioned).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (s, 2H), 7.33 (s, 3H), 5.57 (s, 1H), 4.56 (d, *J* = 11.9 Hz, 1H), 4.31 – 4.26 (m, 1H), 4.23 (dt, *J* = 11.1, 5.8 Hz, 1H), 4.09 (d, *J* = 10.5 Hz, 1H), 3.82 (dd, *J* = 15.2, 9.1 Hz, 1H), 3.67 – 3.59 (m, 1H), 3.38 (d, *J* = 11.4 Hz, 1H), 2.76 (dd, *J* = 15.8, 5.0 Hz, 1H), 2.50 – 2.39 (m, 1H), 2.34 (q, *J* = 10.8 Hz, 3H), 2.11 (d, *J* = 15.9 Hz, 1H), 2.01 – 1.90 (m, 2H), 1.90 – 1.81 (m, 2H), 1.75 (dt, *J* = 12.3, 7.1 Hz, 1H), 1.68 (td, *J*

= 12.6, 7.5 Hz, 1H), 1.60 (d, *J* = 13.4 Hz, 1H), 1.54 (dd, *J* = 13.0, 6.9 Hz, 1H), 0.93 (d, *J* = 6.6 Hz, 3H).



5-*epi*-portimine A. Compound **270** (2.2 mg, 0.005 mmol) was dissolved in *n*-PrOH (0.1 ml), followed by addition of vinylBF_3K (1.5 mg, 0.011 mmol) and Pd(dppf)Cl_2 (0.4 mg, 0.0005 mmol) under argon. TEA (1 drop) was added to this solution. Subsequently, the reaction was heated to 80 °C for 1 h. Upon completion (monitored by TLC), the solvent was removed under vacuo, and the residue was dissolved in MeOH (0.1 ml). Aq. NH_3 (37%, 0.1 ml) was added to this solution. The resulting solution was stirred for 2 h, and concentrated. The residue was purified by PTLC (10% *i*-PrOH in DCM) to give ePA (1.8 mg, 0.004 mmol, ca. 80%) as single product.

TLC: R_f = 0.44 (10% MeOH in DCM, UV active, $KMnO_4$ staining)

$[\alpha]^{25}_D$: -8.0 (*c* = 0.1, $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.21 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.08 (d, *J* = 17.5 Hz, 1H), 5.04 (s, 1H), 4.93 (d, *J* = 10.8 Hz, 1H), 4.78 (dd, *J* = 11.1, 7.5 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.23 (dt, *J* = 10.4, 6.0 Hz, 1H), 4.14 (d, *J* = 12.0 Hz, 1H), 4.08 (dd, *J* = 11.2, 2.7 Hz, 1H), 3.75 (dd, *J* = 16.0, 8.8 Hz, 1H), 3.63 (ddd, *J* = 16.0, 10.3, 7.0 Hz, 1H), 2.80 (dd, *J* = 14.6, 11.1 Hz, 1H), 2.40 – 2.21 (m, 5H), 2.15 (dd, *J* = 14.0, 6.7 Hz, 1H), 2.01 (dd, *J* = 12.1, 7.1 Hz, 1H), 1.92 – 1.82 (m, 2H), 1.79 (dd, *J* = 12.5, 6.7 Hz, 1H), 1.76 – 1.66 (m,

2H), 1.58 – 1.49 (m, 2H), 0.88 (d, *J* = 6.0 Hz, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 204.7, 184.8, 139.1, 135.3, 128.2, 111.6, 108.2, 83.9, 79.3, 71.9, 70.7, 55.3, 54.5, 42.5, 40.1, 37.0, 34.6, 33.9, 29.8, 29.2, 24.5, 22.8, 17.7.

HRMS (ESI-TOF): calc'd for $C_{23}H_{31}NO_5$ $[M+H]^+$: 402.2275, found: 402.2266

Appendix 1: Curriculum vitae

Junchen Tang

PERSONAL INFORMATION

Mailing address: 9045 Judicial Dr. Apt. 1224, San Diego, CA, 92122
Email: jctang@scripps.edu
Tel: +1 8587294202

EDUCATION

2019-2023 Ph.D. Graduate Student in Chemistry
Advisor: Professor Phil S. Baran
The Scripps Research Institute, La Jolla, California

2015-2019 B.Sc. in Chemistry
Defense advisor: Professor Zhen Yang
College of Chemistry and Molecular Engineering, Peking University, Beijing, China

RESEARCH EXPERIENCE

2019-2023 Ph.D student, Scripps Research
Advisor: Professor Phil S. Baran
Work: Enantioselective total synthesis of portimine A and B

2017.7-2019.6 Research Assistant, College of Chemistry and Molecular Engineering, Peking University
Advisor: Professor Zhen Yang
Work: Synthetic Approach towards Phainanoid F Total Synthesis of (+)-haperforin *G*

2018.6-2018.8 Internship, Scripps Research
Advisor: Professor Phil S. Baran; Professor Floyd E. Romesberg, mentored by David S. Peters
Work: Synthetic work towards arylomycins, Synthetic work towards kibdelomycin

AWARDS

Gold Medal of Chinese Chemistry Olympics, *2015*
Tang Junyuan Fellowship, *2017*
2022-2023 Bristol Myers Squibb Graduate Fellowship in Synthetic Organic Chemistry, *2023*

PUBLICATIONS

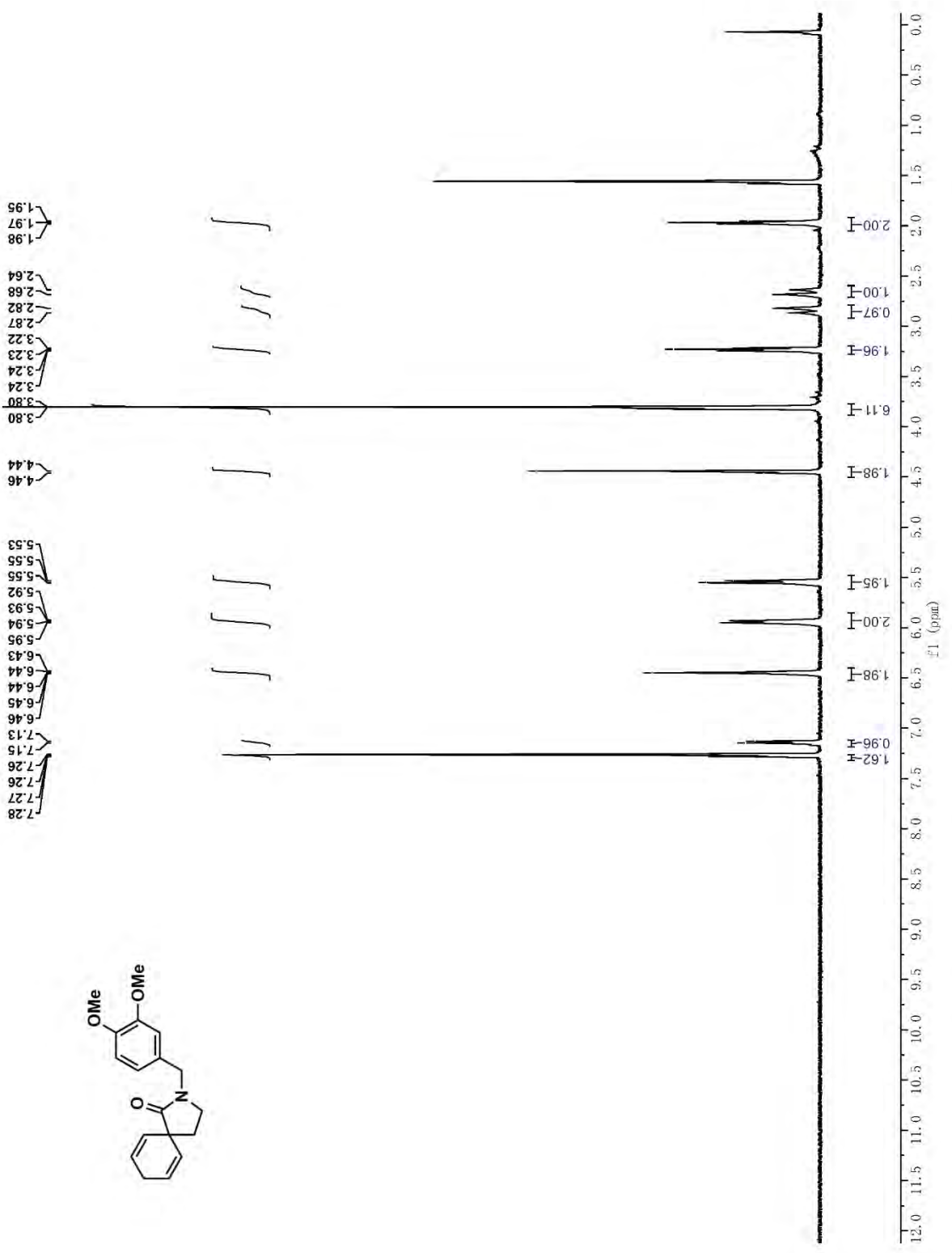
1. Wei Zhang, Zhenyu Zhang, **Jun-Chen Tang**, Jin-Teng Che, Hao-Yu Zhang, Jia-Hua Chen*, and Zhen Yang*. “Total Synthesis of (+)-Haperforin G” *J. Am. Chem. Soc*. **2020**, *142*, 19487-19492.

2. ,Zhenyu Zhang, Wei Zhang, **Jun-Chen Tang**, Jin-Teng Che, Zhongchao Zhang, Jia-Hua Chen*, and Zhen Yang*. “Total Synthesis of (+)-Haperforin G” *J. Org. Chem.* **2023**, *in press*.

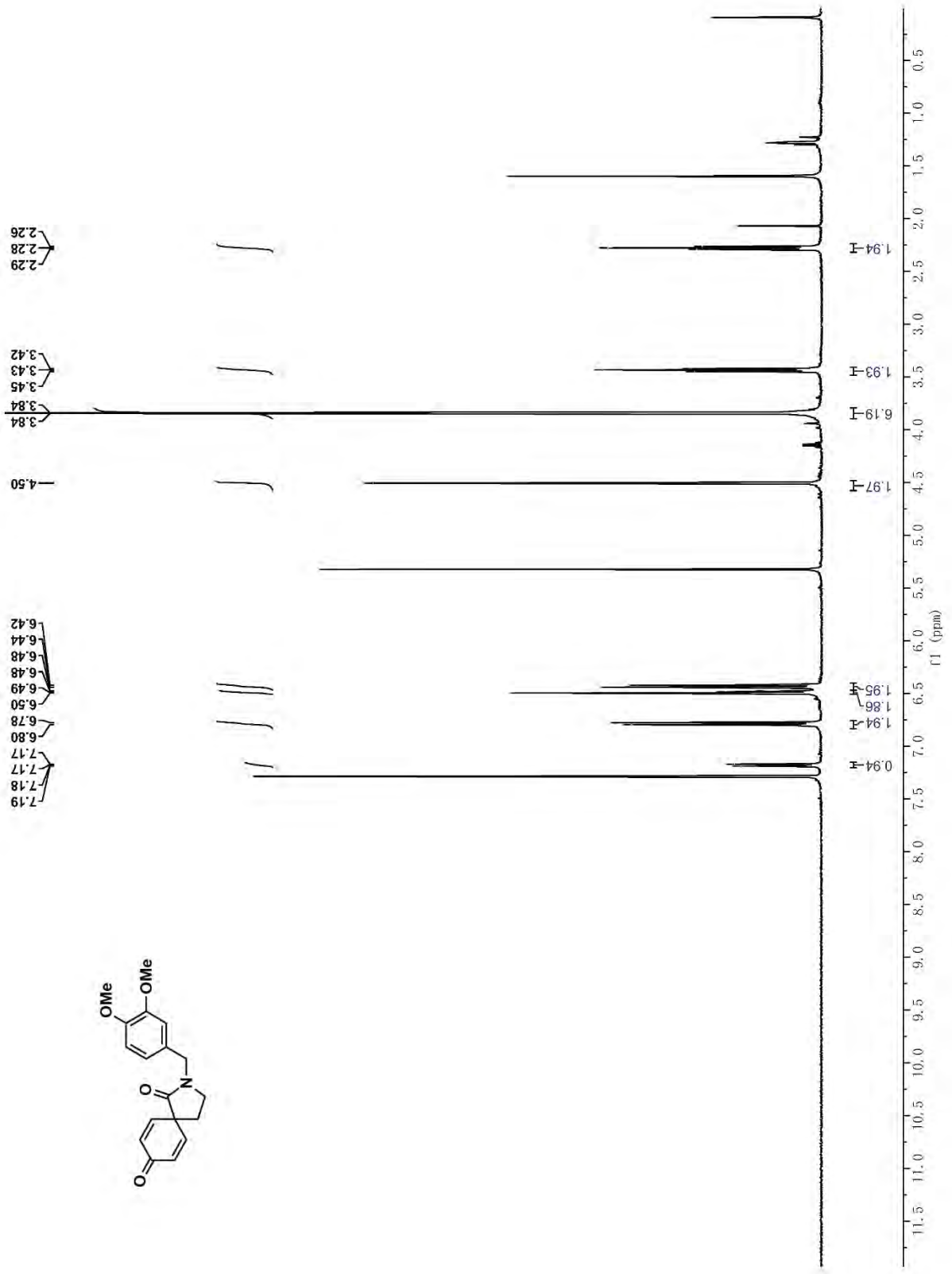
3. **Junchen Tang***, WeichaoLi*, Tzu-Yuan Chiu, Francisco Martínez-Peña, Zengwei Luo,Christine T. Chong, QijiaWei, Nathalia Gazaniga, Yi Yang See, Luke L. Lairson†, Christopher G. Parker†and Phil S. Baran†.“A Scalable Total Synthesis of Portimine A and B Reveals the Basis2of Their Potent and Selective Anti-cancer Activity” *Nature* **2023**, *under peer-review*.

Appendix 2: NMR Spectra

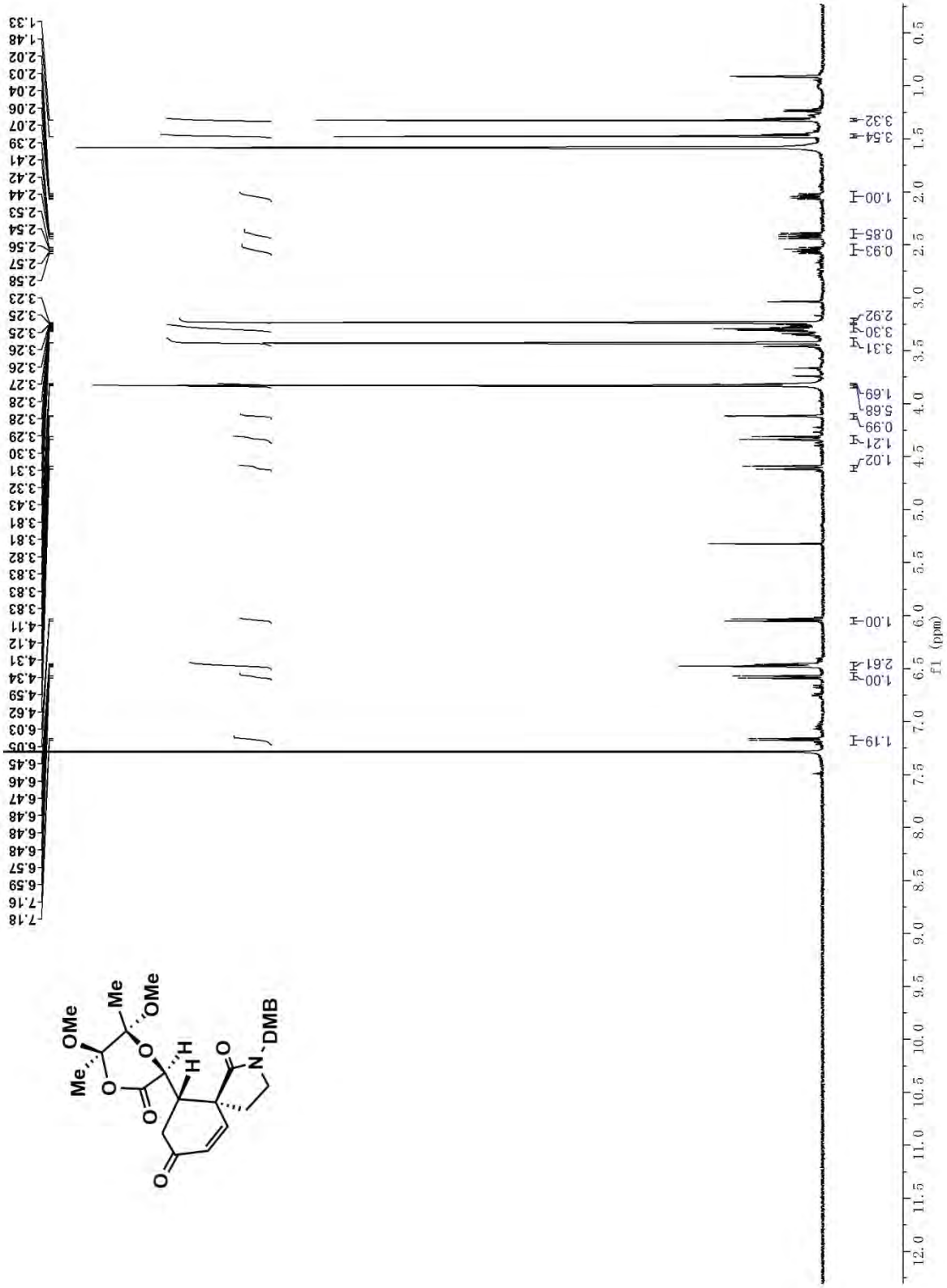
^{1}H NMR: Compound **111**



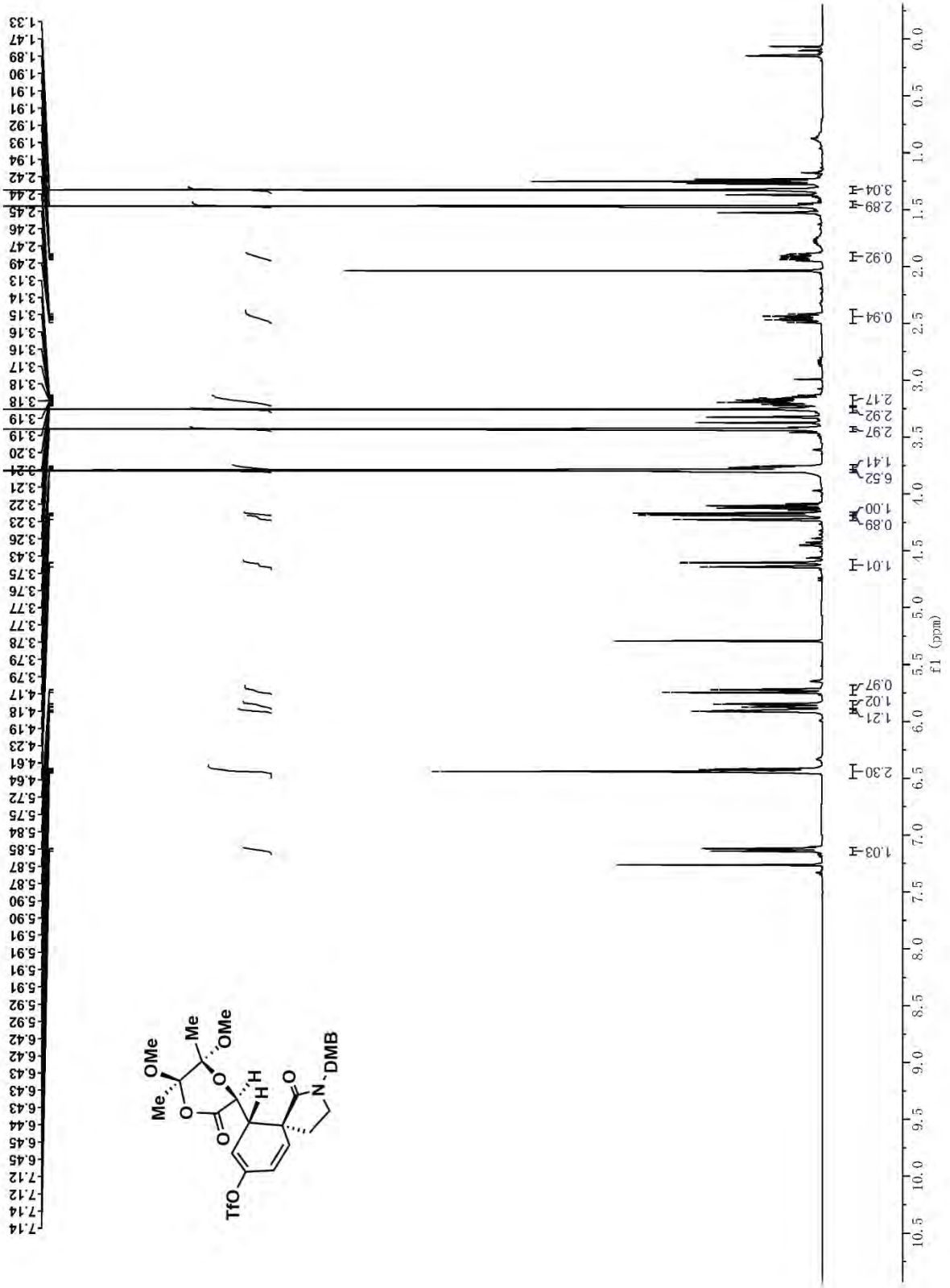
^{1}H NMR: Compound **112**



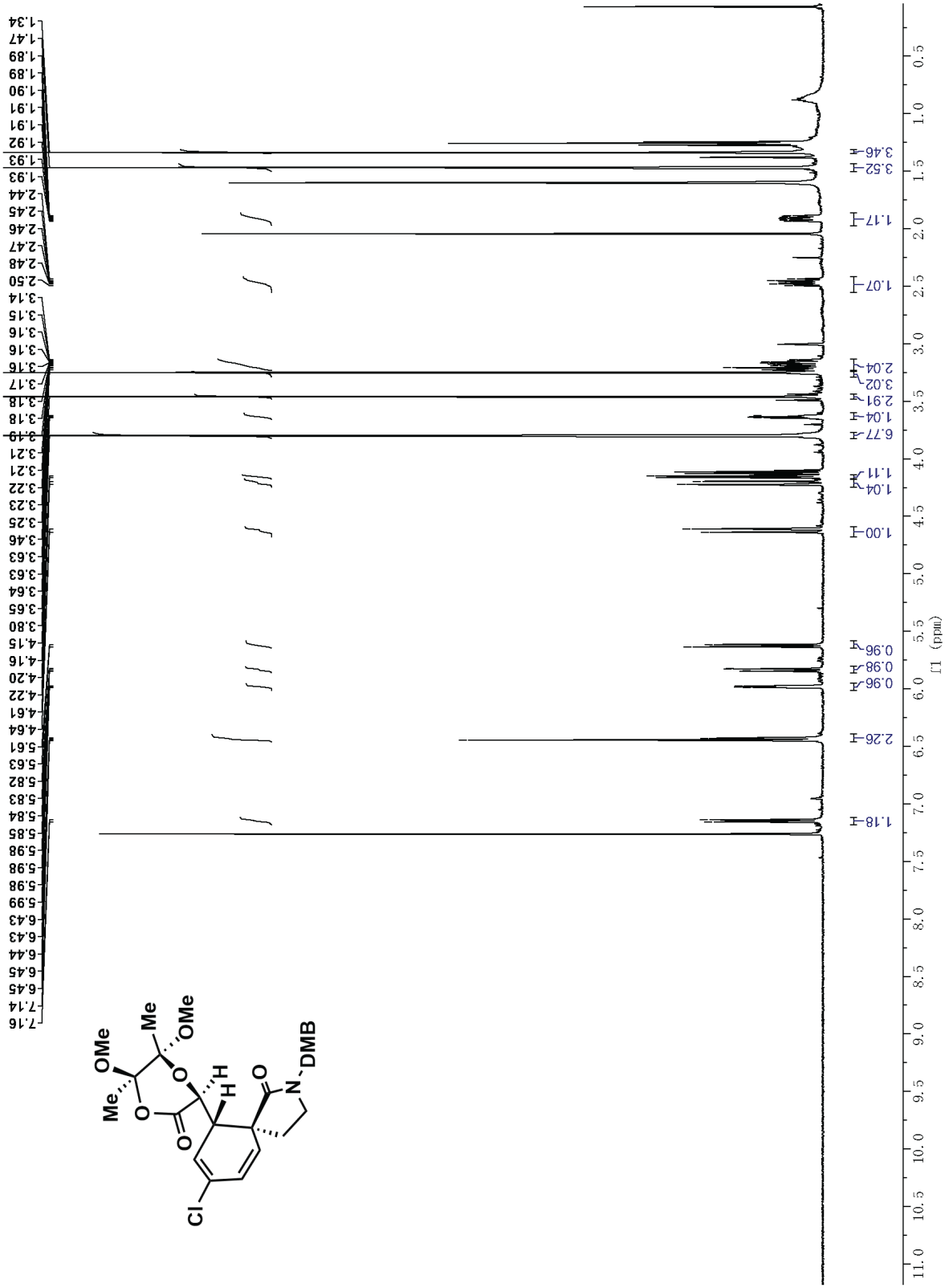
^{1}H NMR: Compound **113**



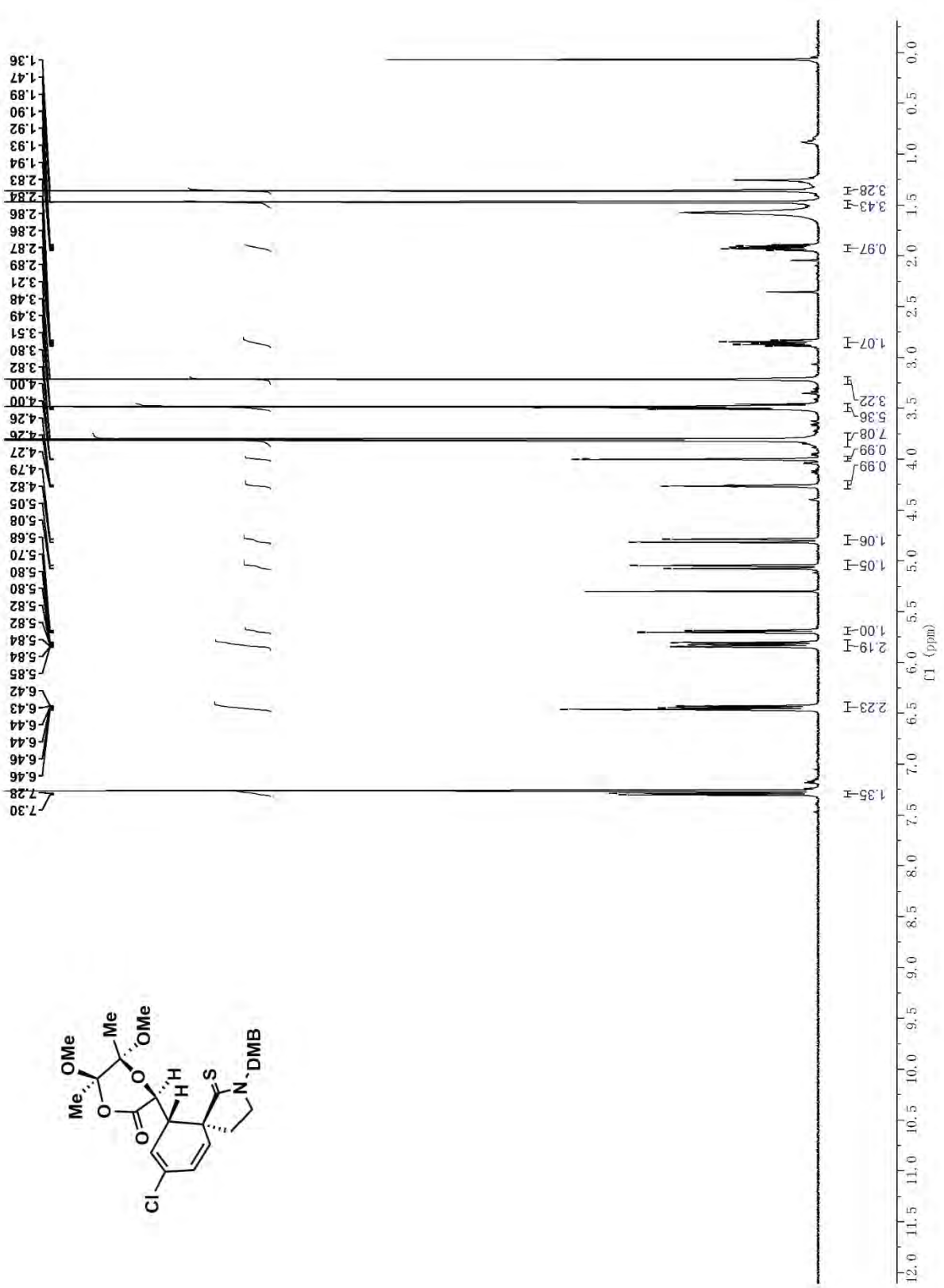
^{1}H NMR: Compound **115**



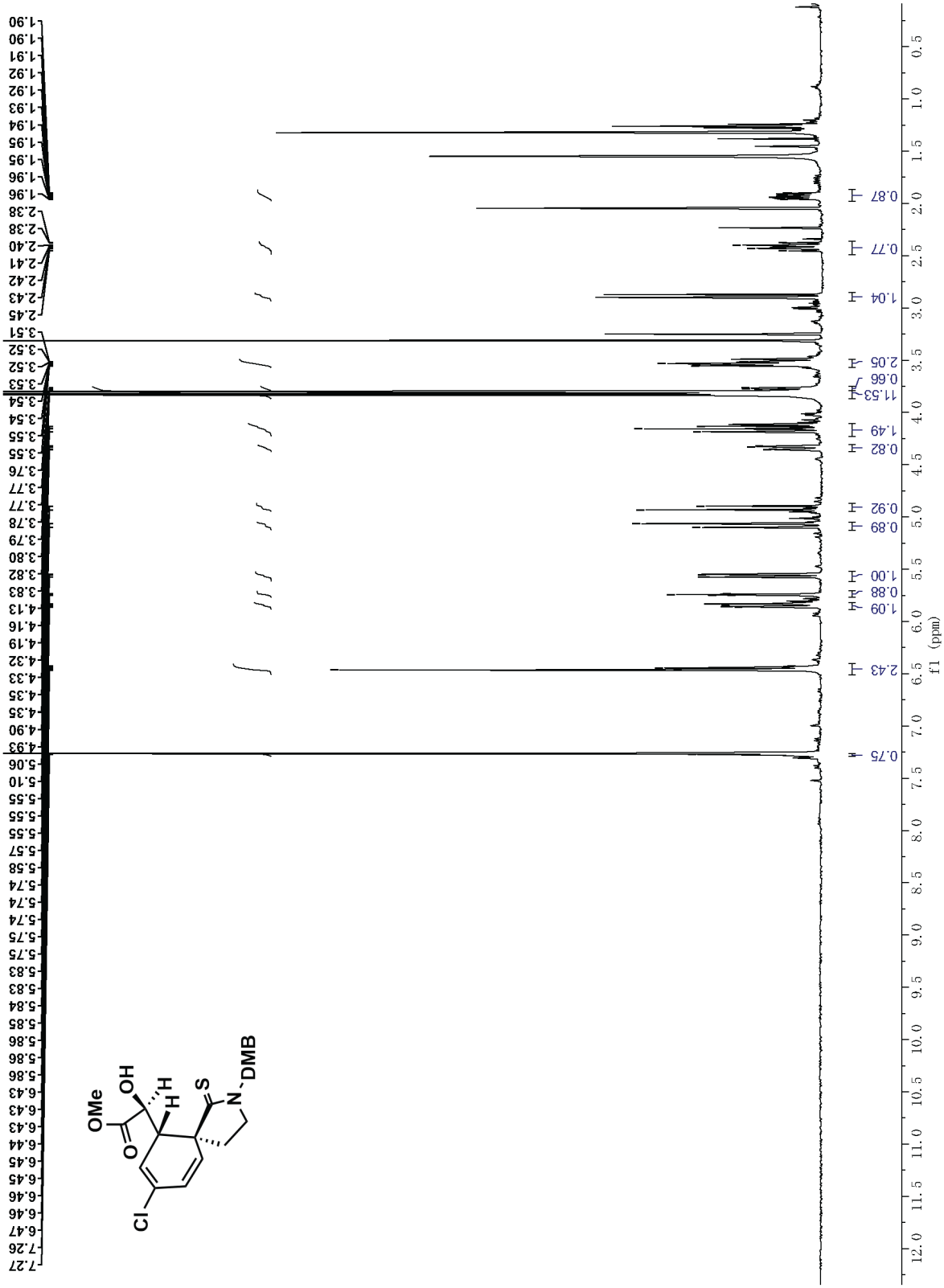
^{1}H NMR: Compound **116**



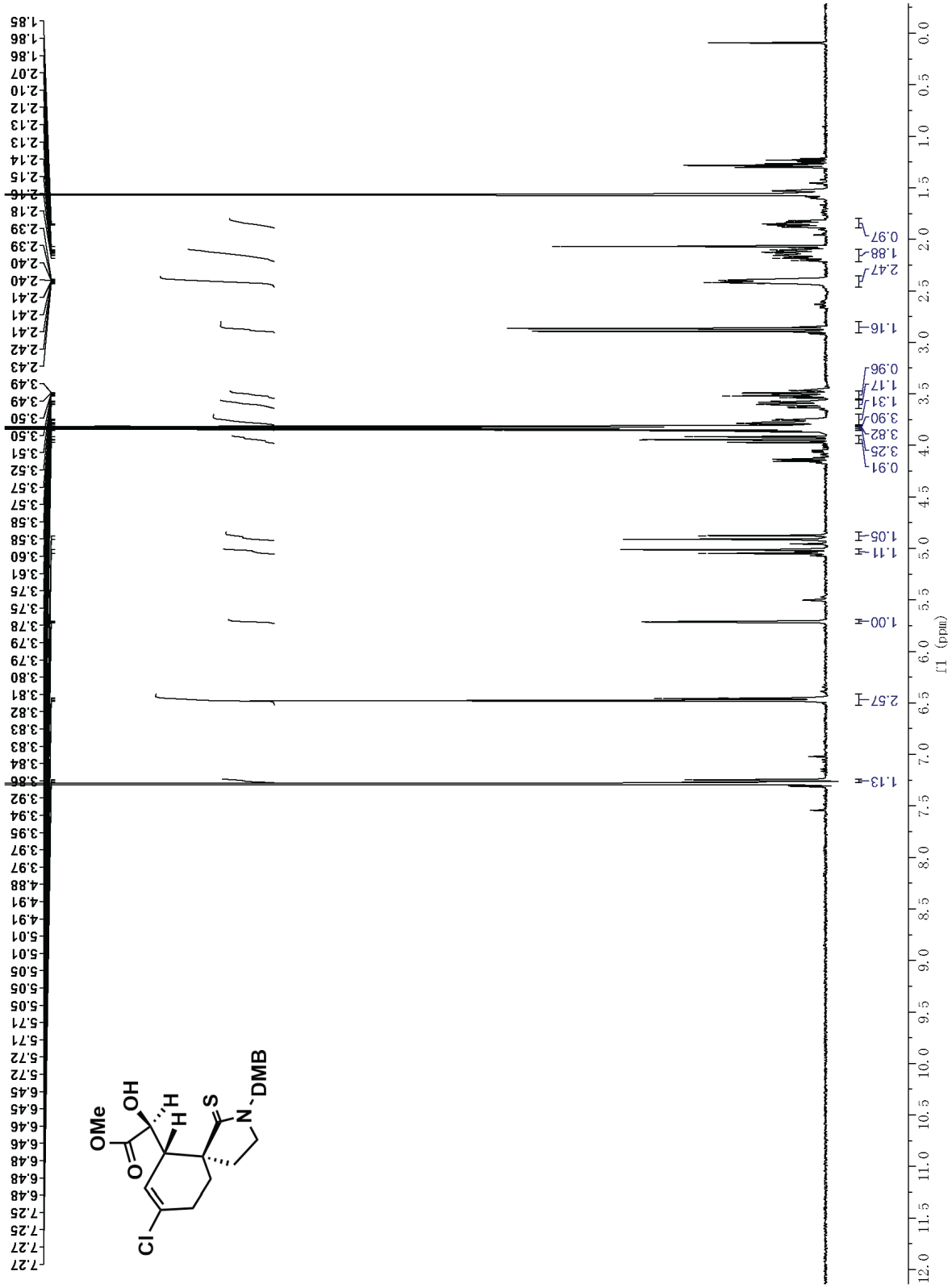
^{1}H NMR: Compound **130**



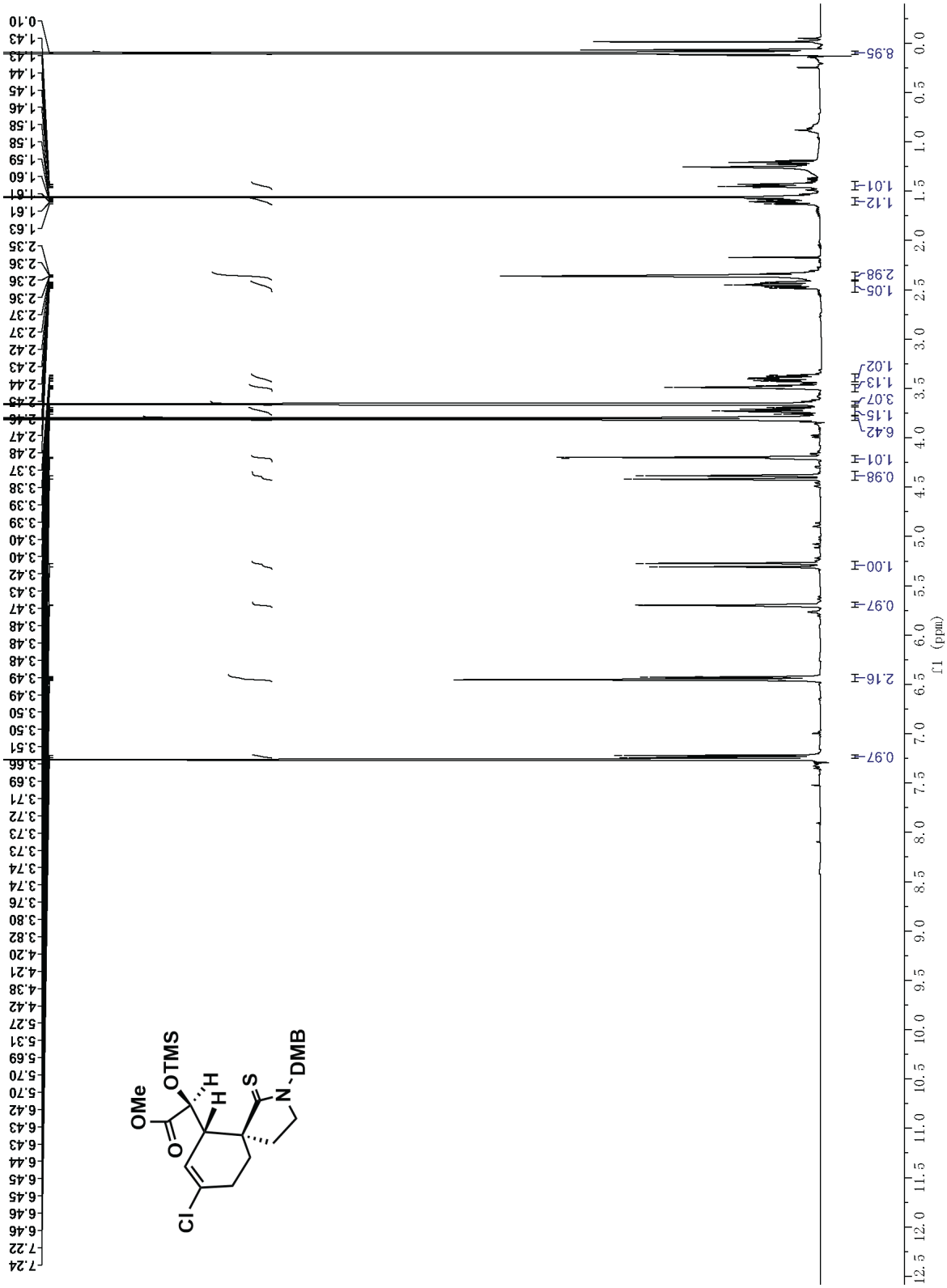
^{1}H NMR: Compound **131**



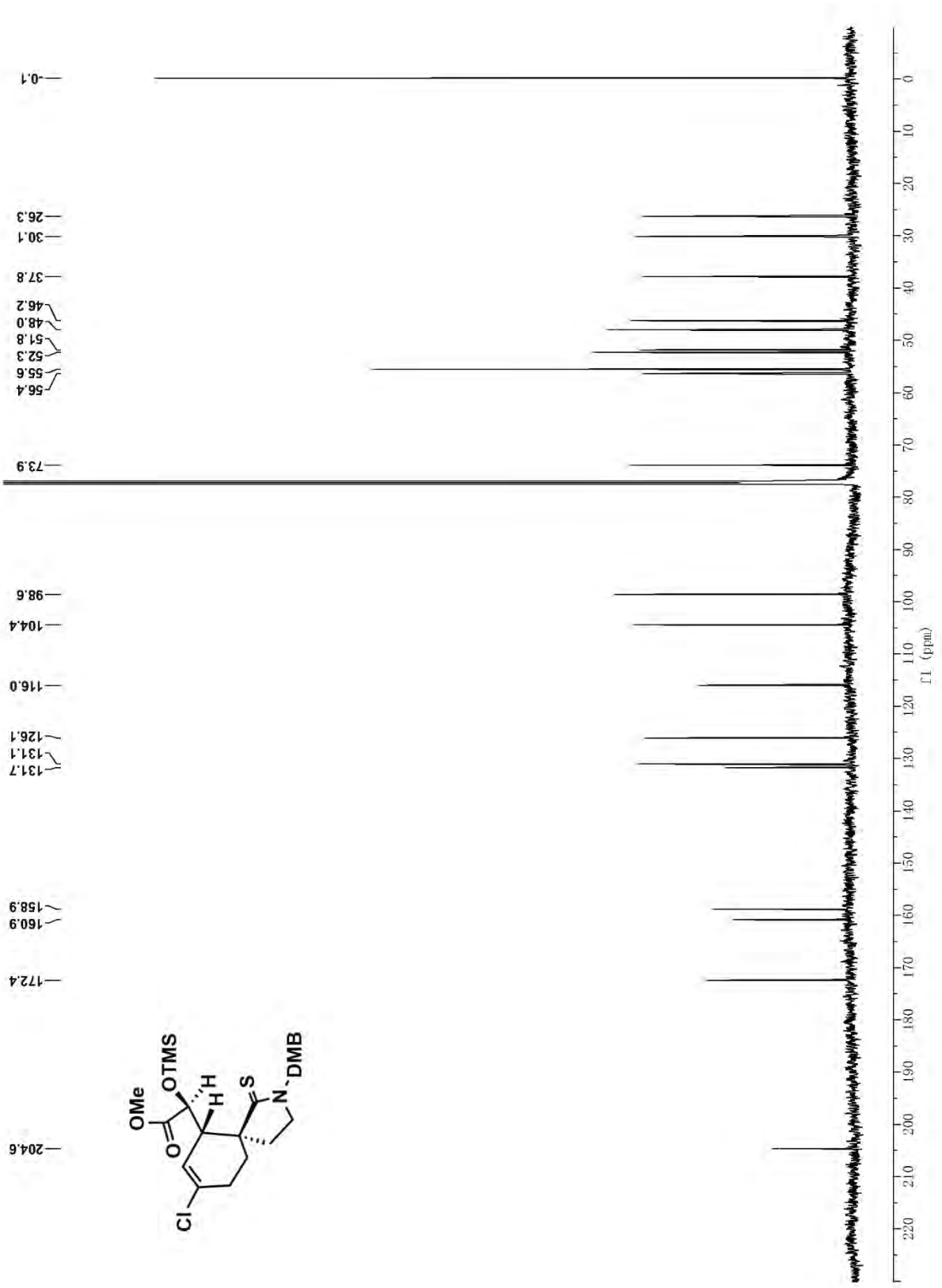
^{1}H NMR: Compound **132**



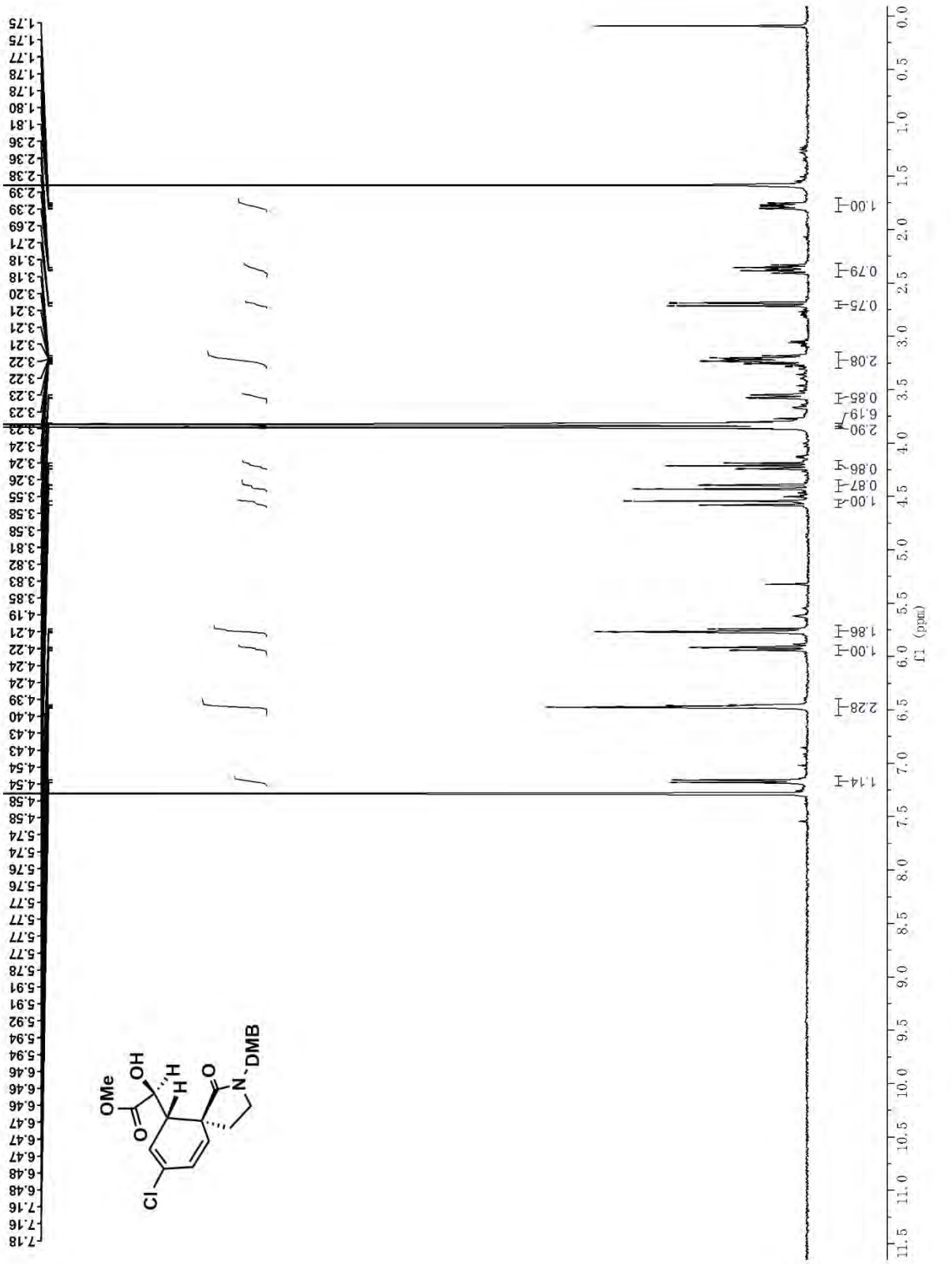
^{1}H NMR: Compound **133**



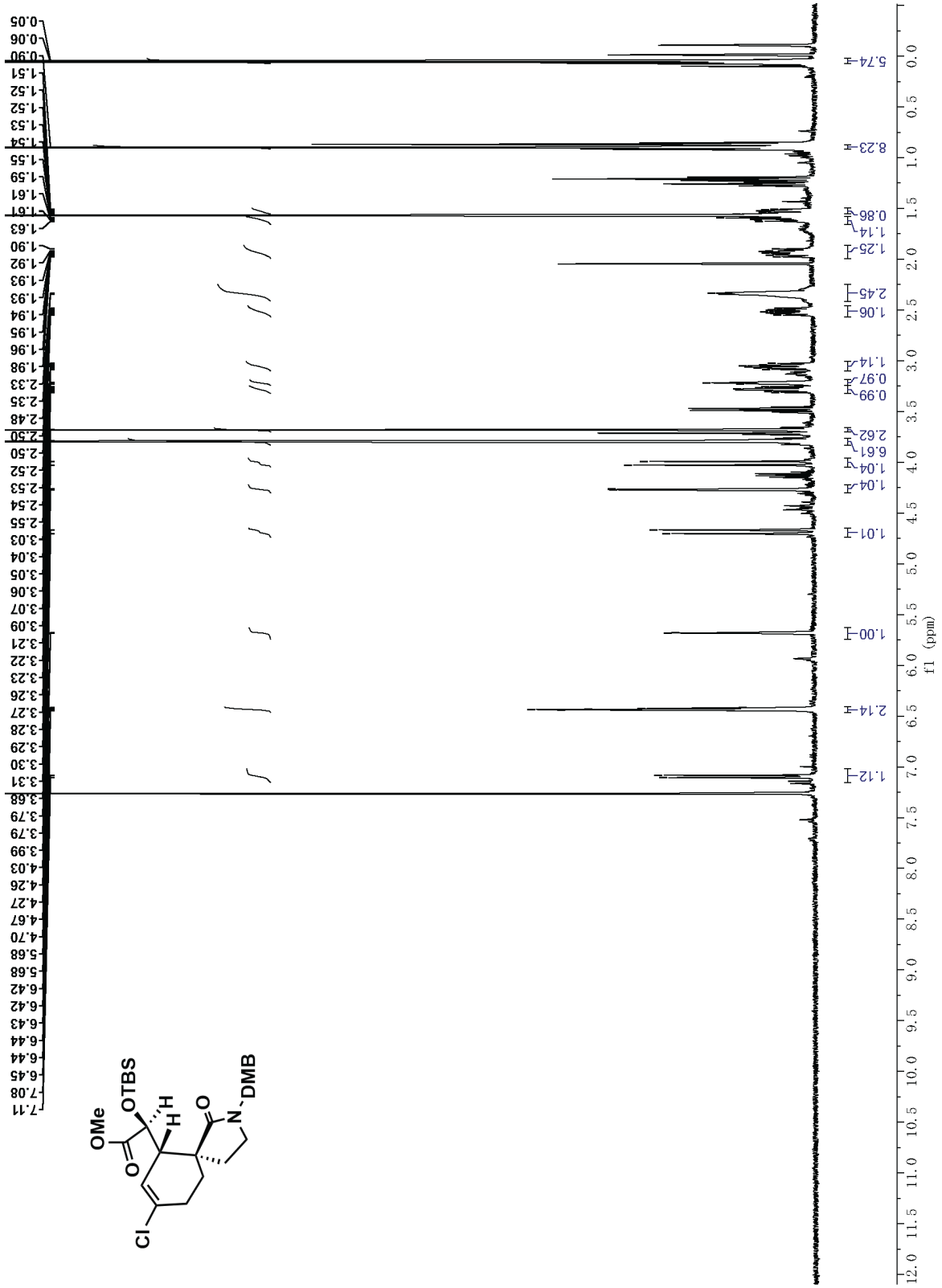
^{13}C NMR: Compound **133**



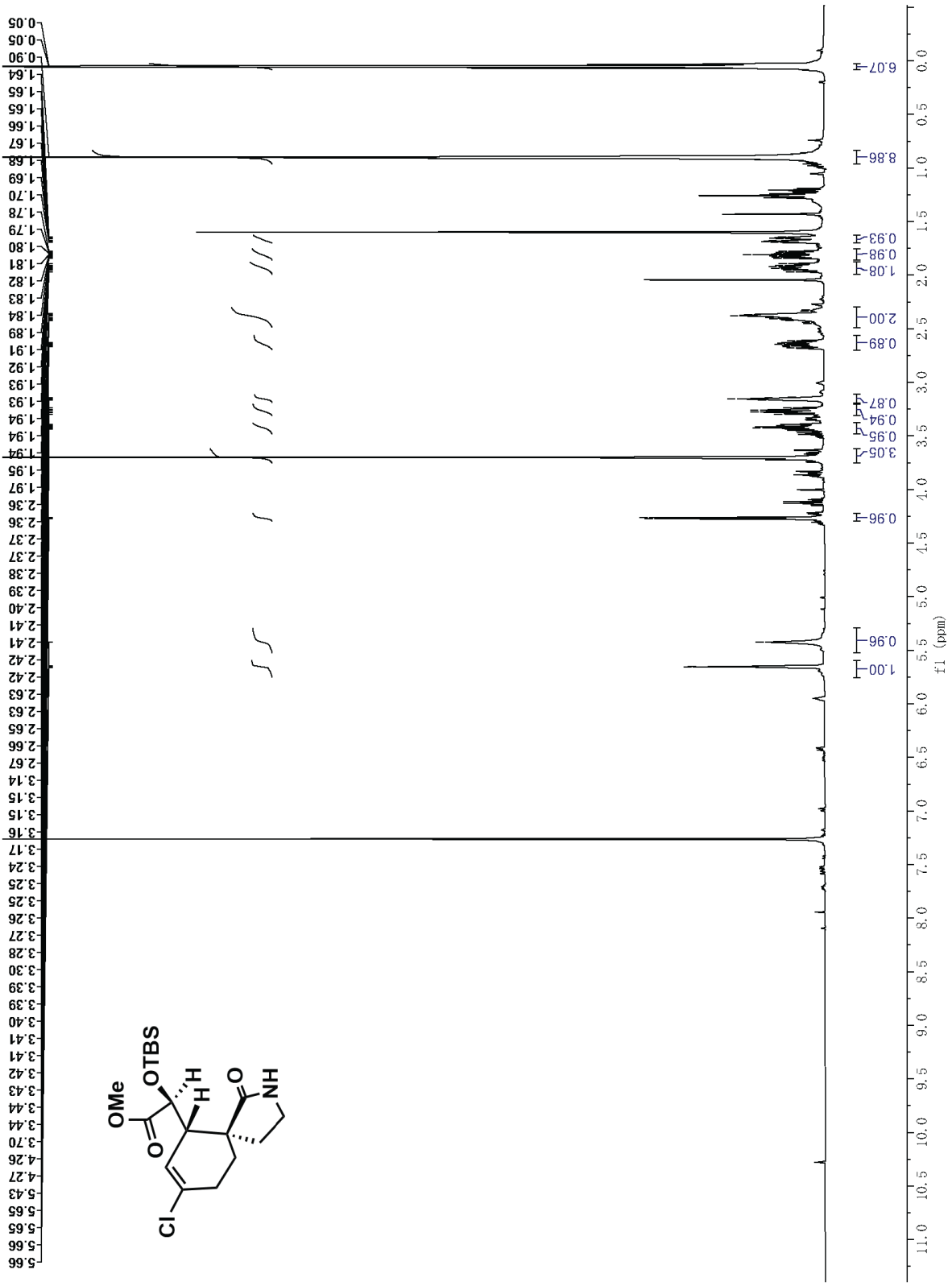
^{1}H NMR: Compound **134**



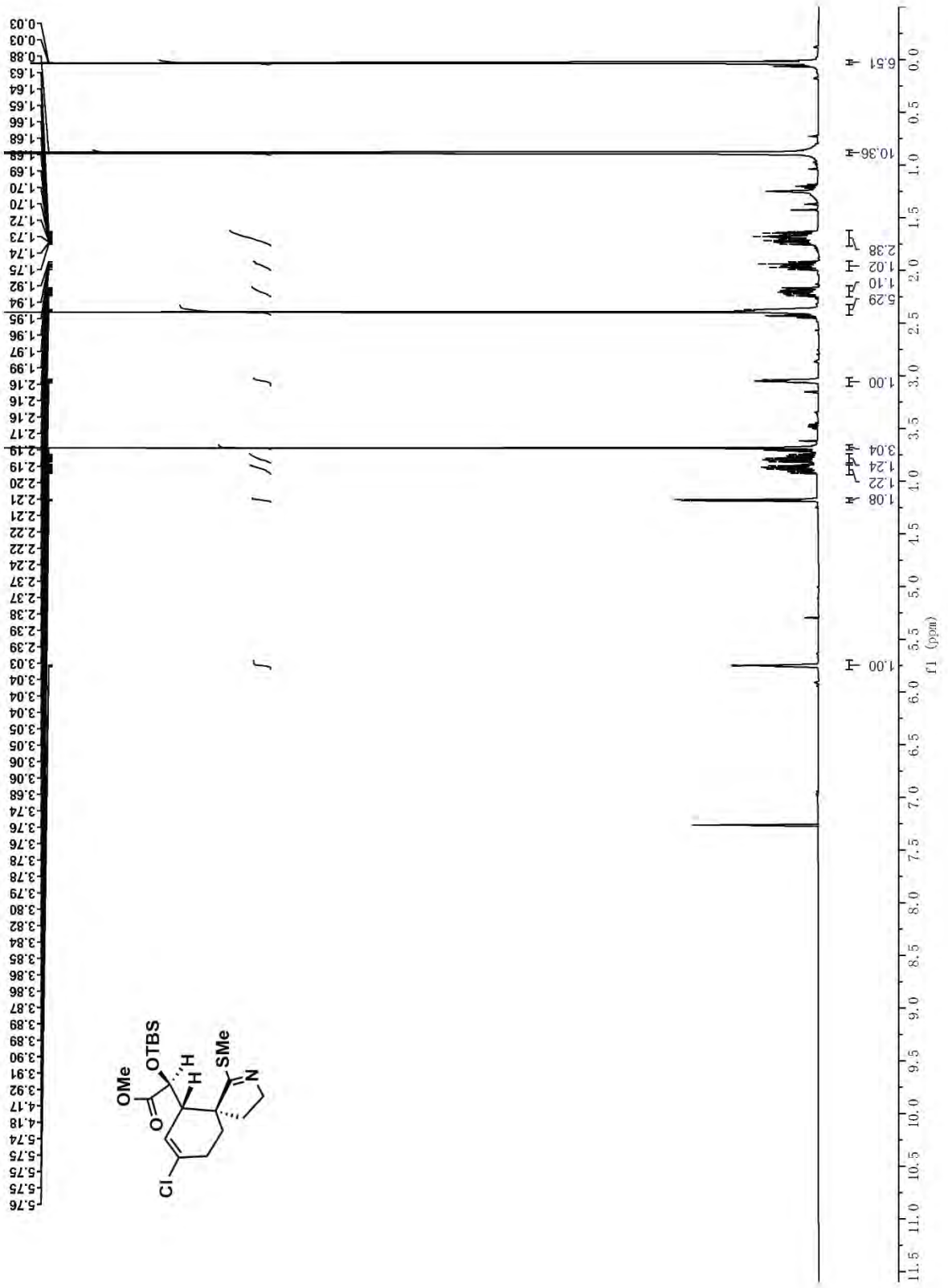
^{1}H NMR: Compound **135**



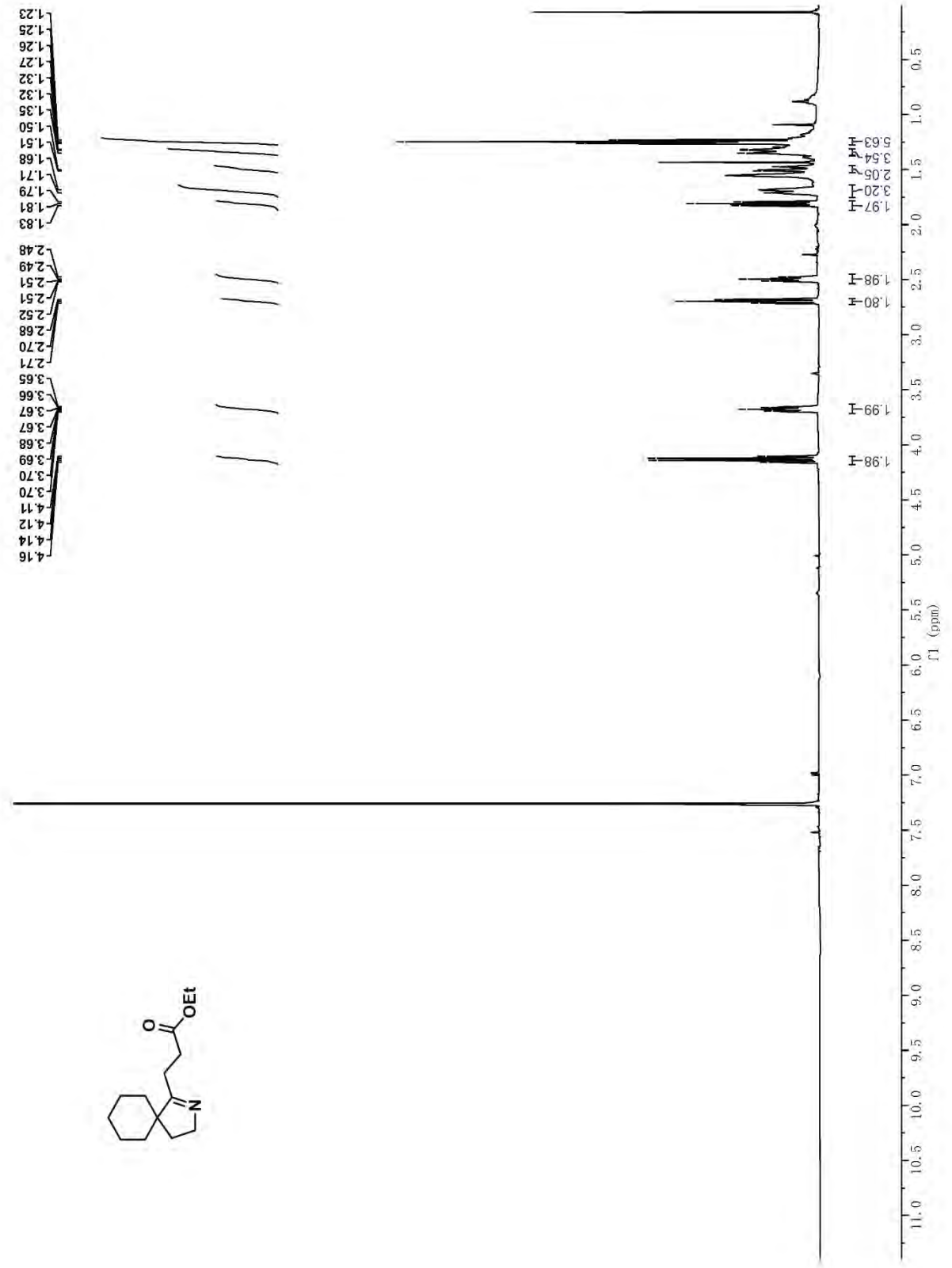
^{1}H NMR: Compound **136**



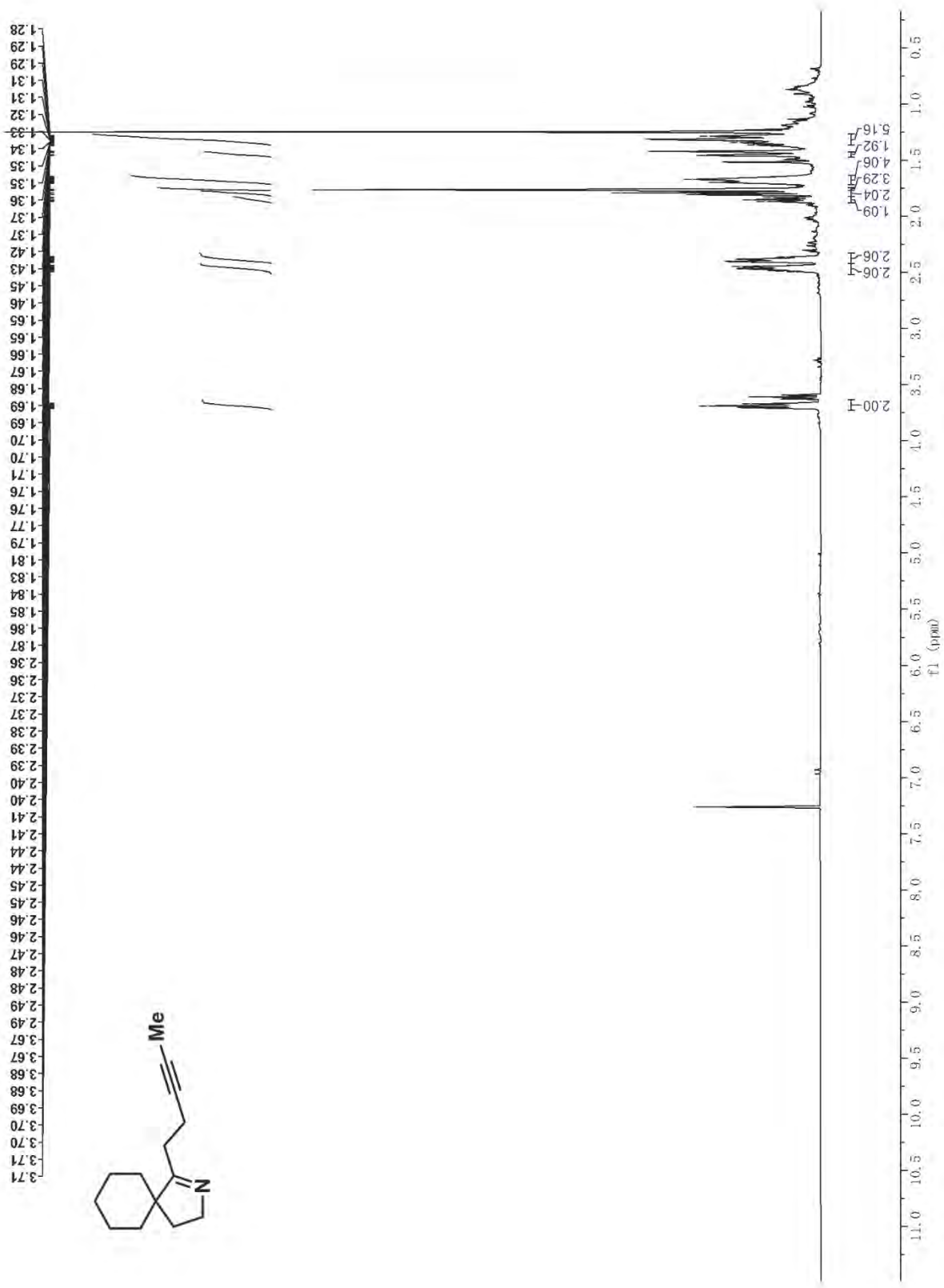
^{1}H NMR: Compound **137**



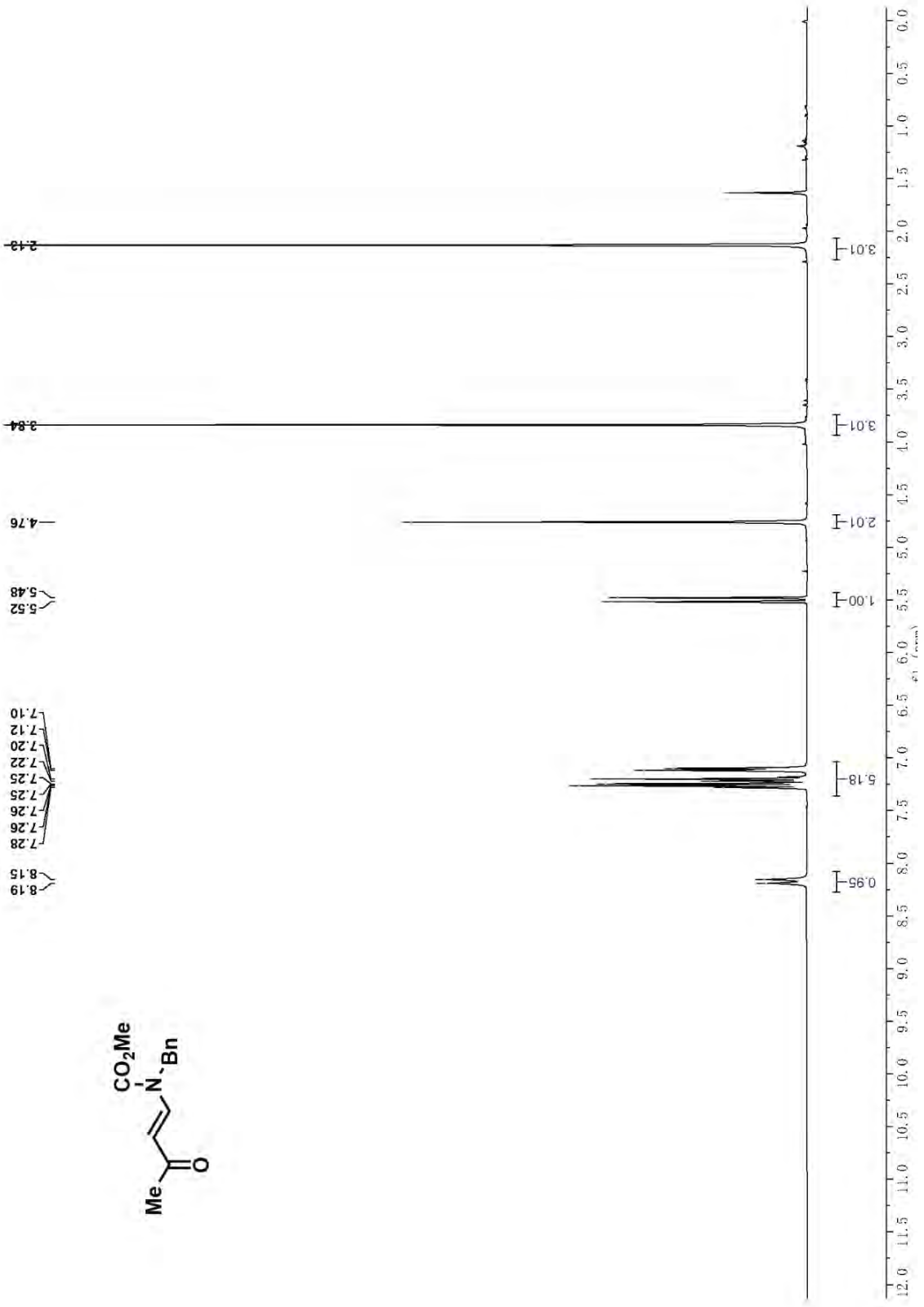
^{1}H NMR: Compound **145**



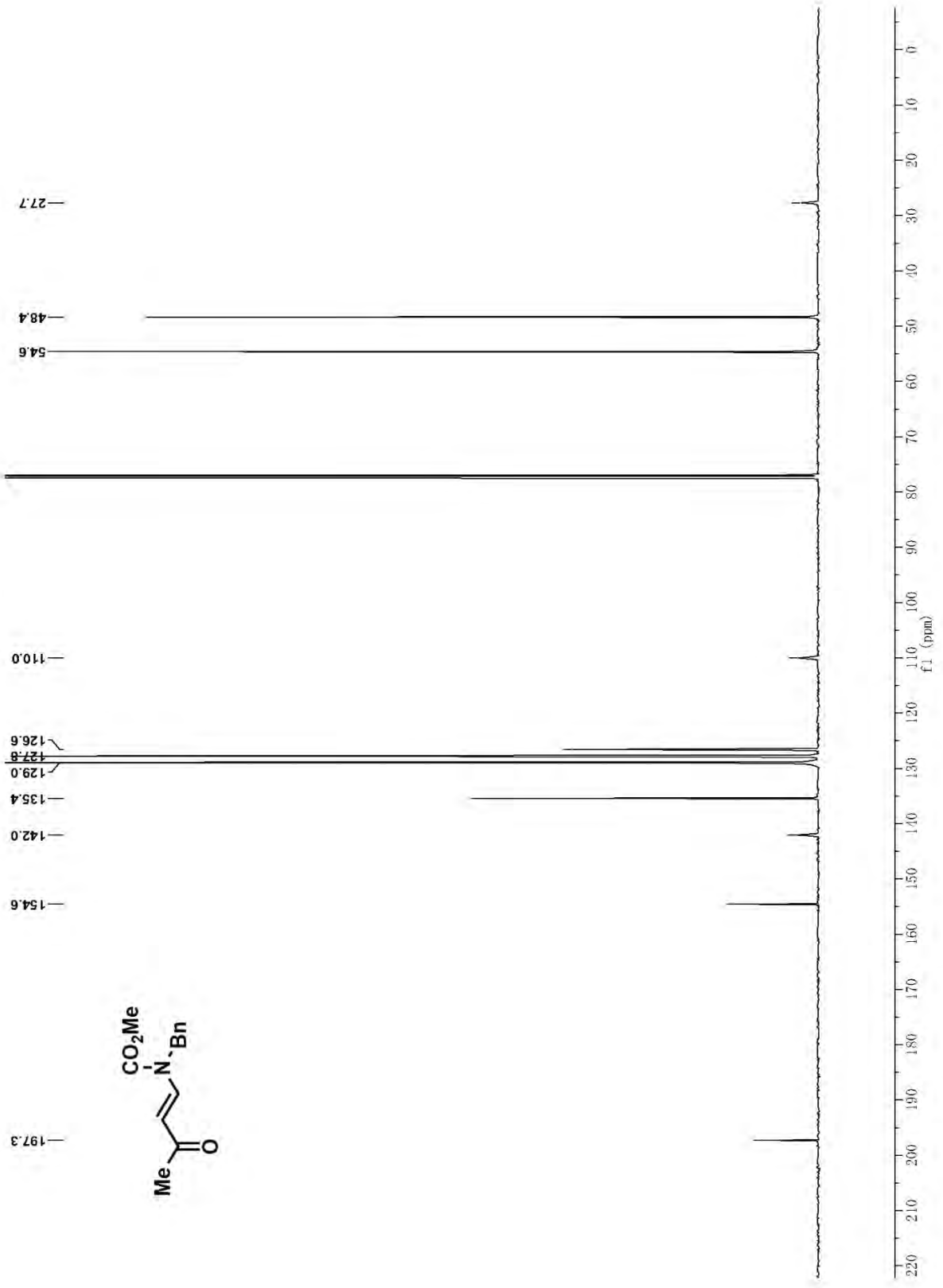
^{1}H NMR: Compound **146**



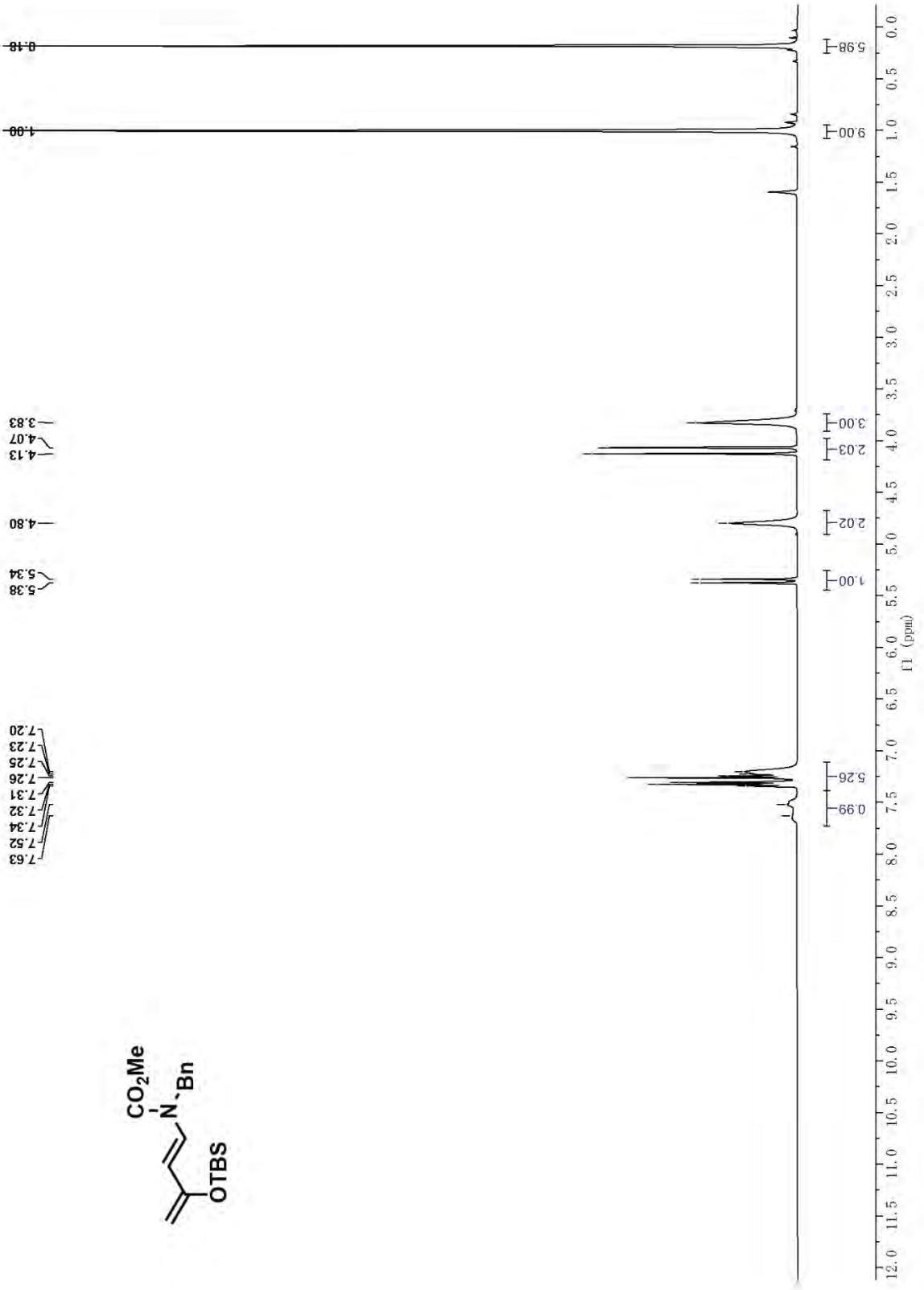
^{1}H NMR: Compound **161**



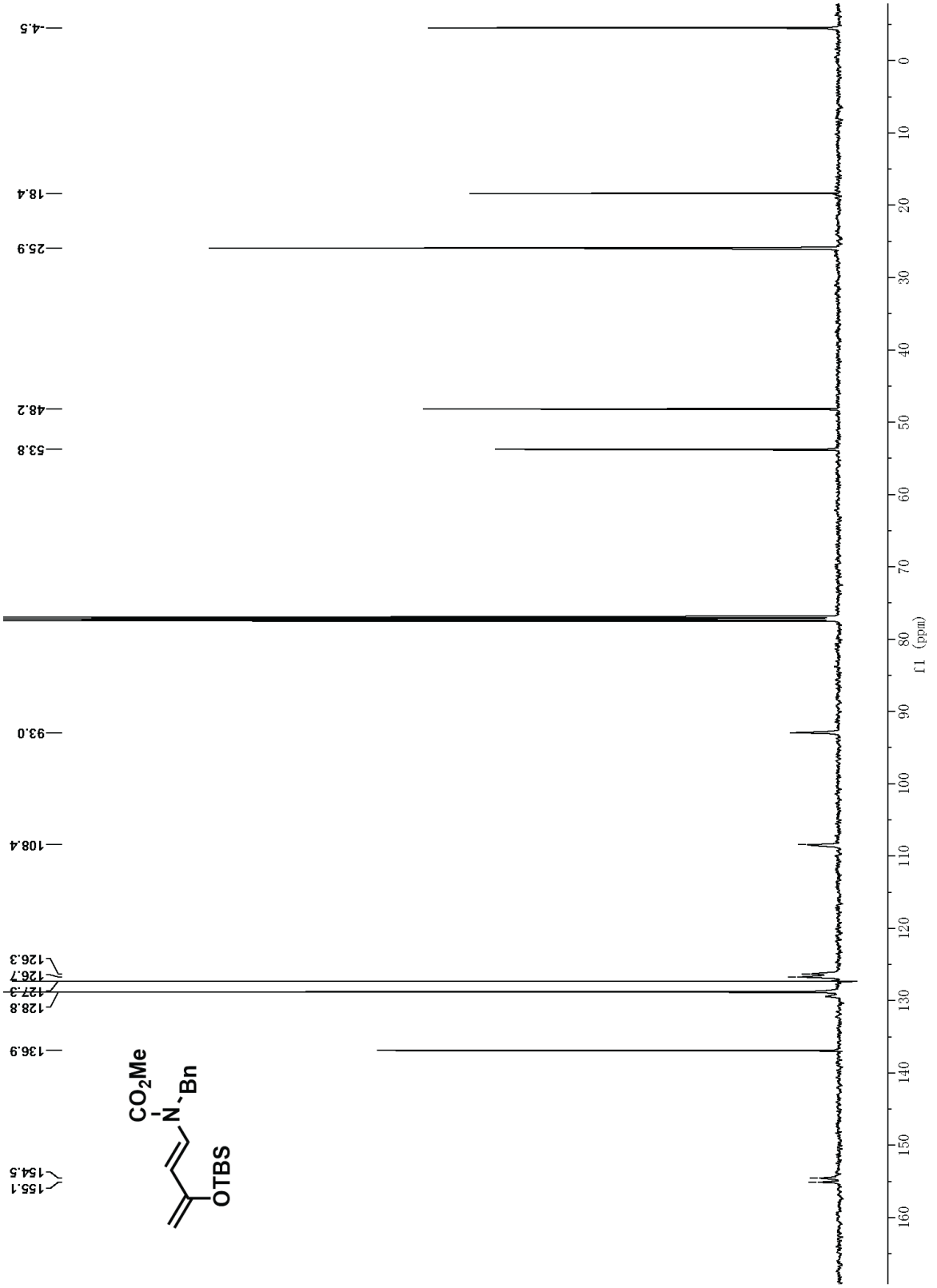
^{13}C NMR: Compound **161**



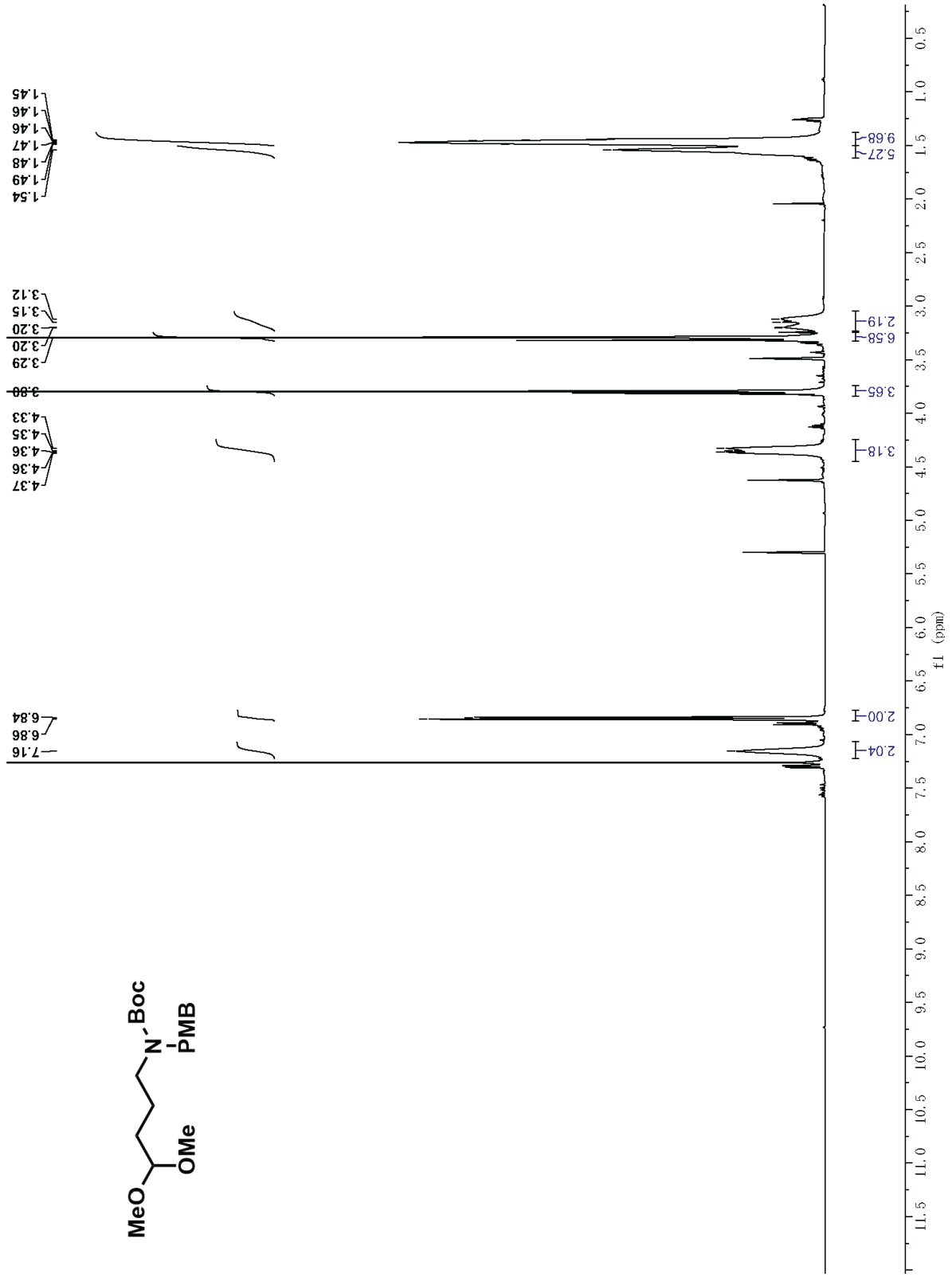
^{1}H NMR: Rawal's diene



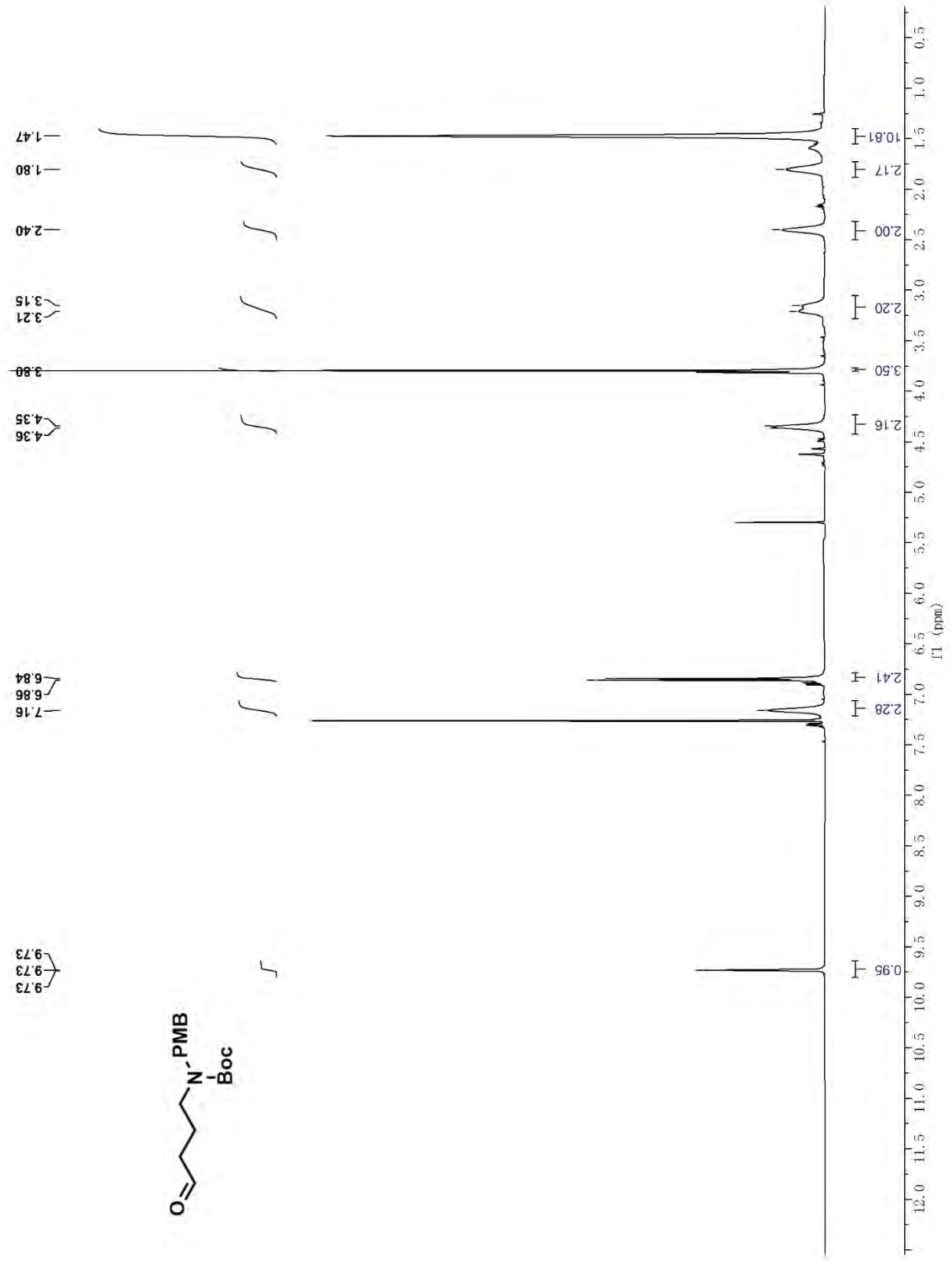
^{13}C NMR: Rawal's diene



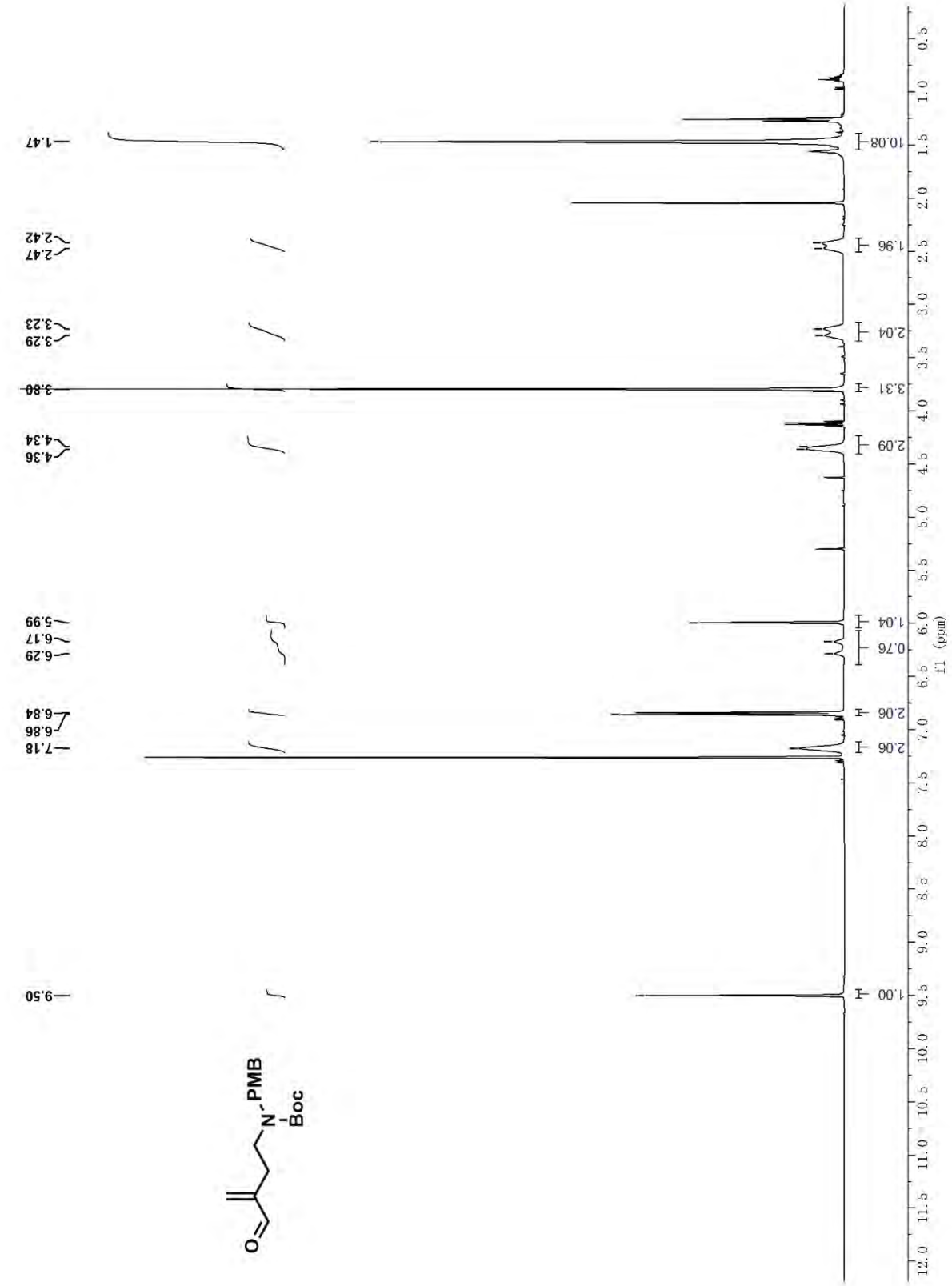
^{1}H NMR: Compound **164**



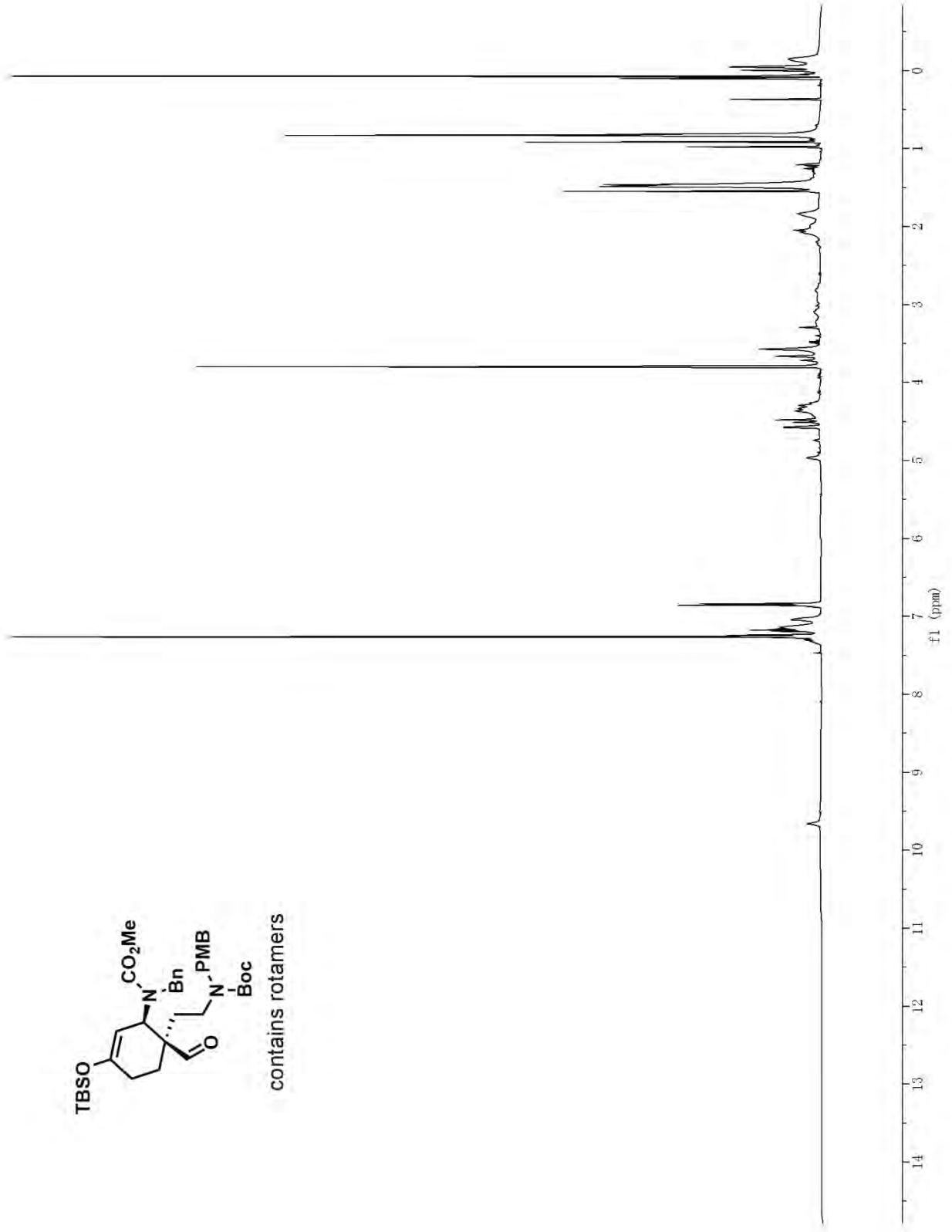
^{1}H NMR: Compound **165**



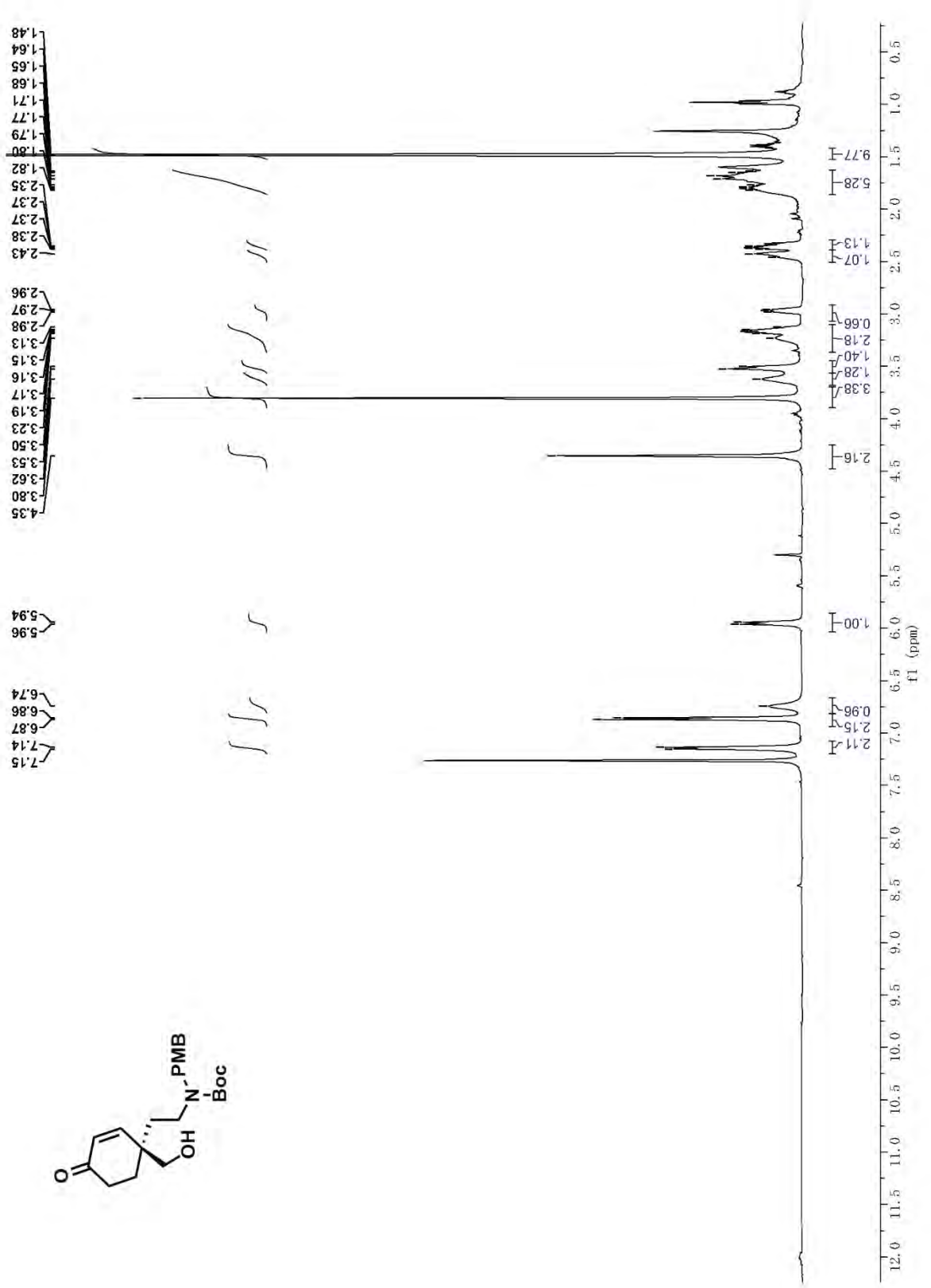
^{1}H NMR: Compound **166**



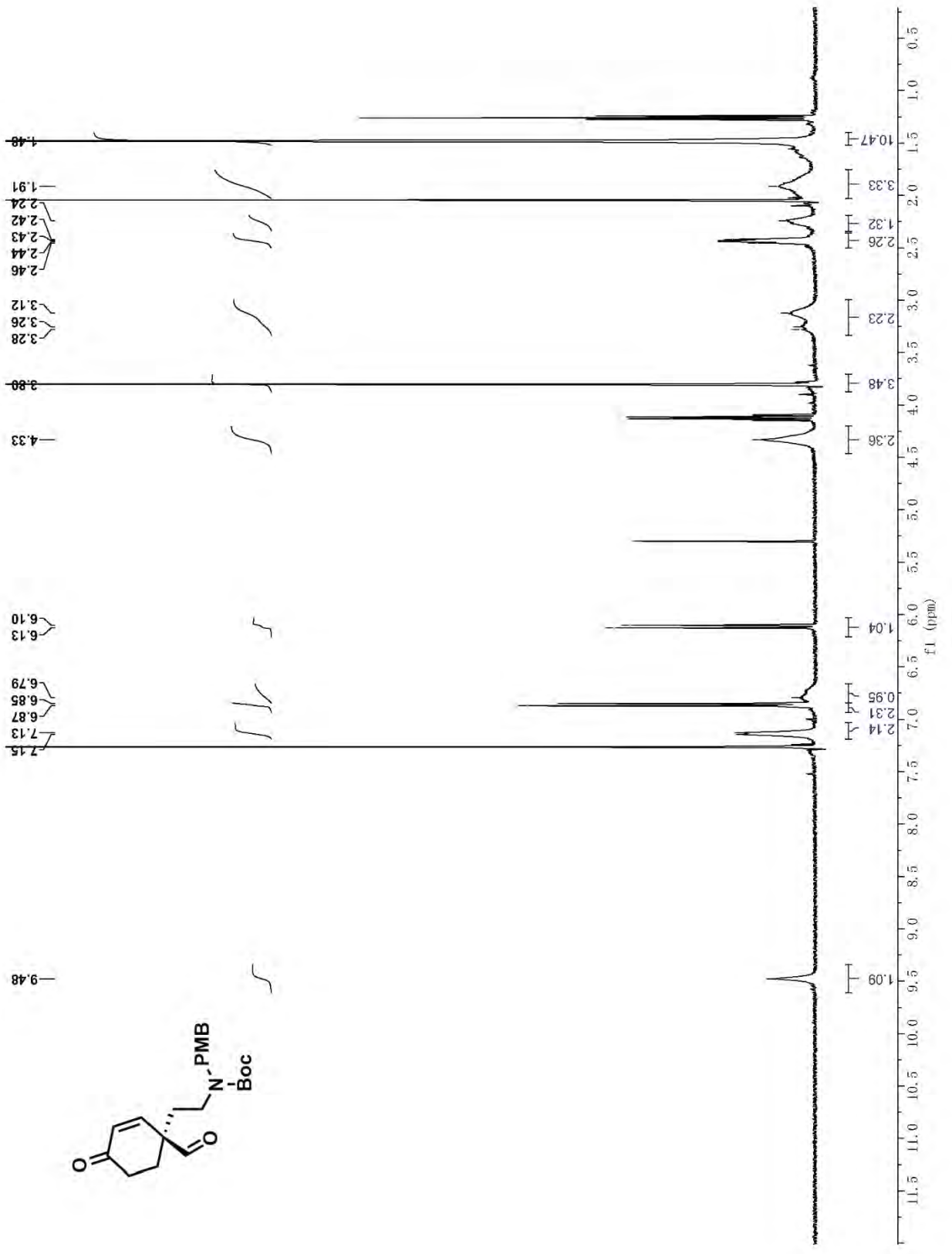
^{1}H NMR: Compound **167**



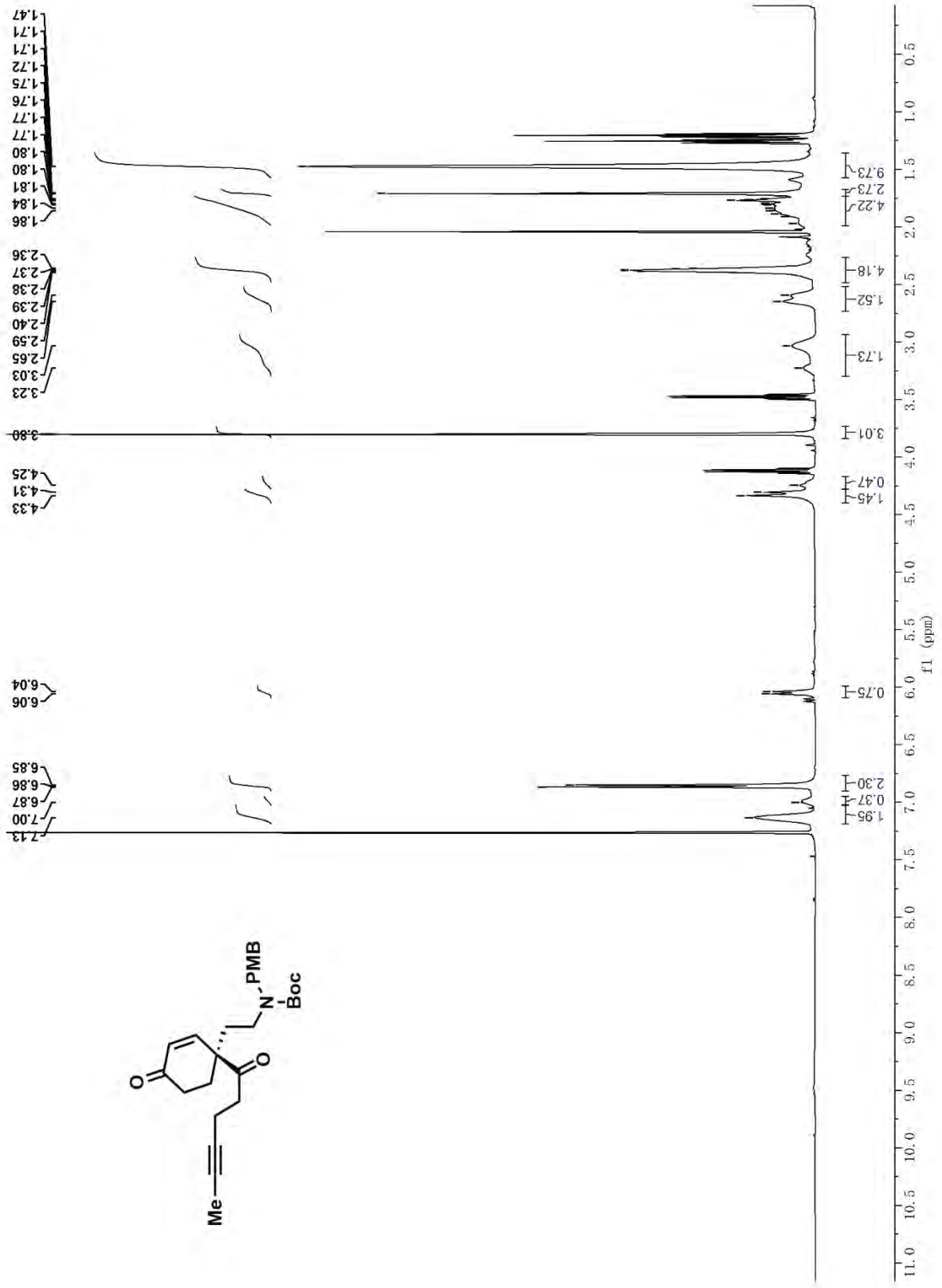
^{1}H NMR: Compound **168**



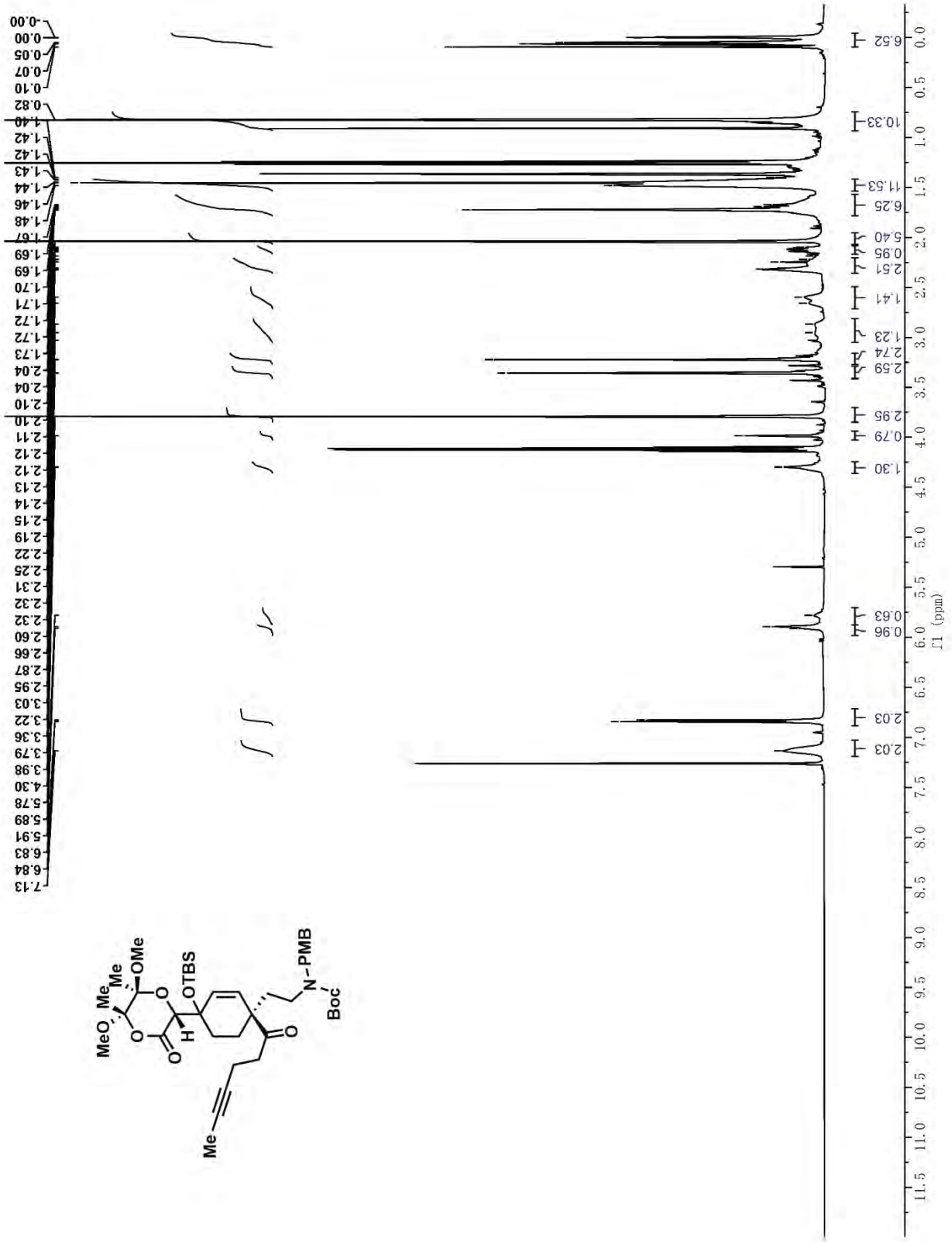
^{1}H NMR: Compound **169**



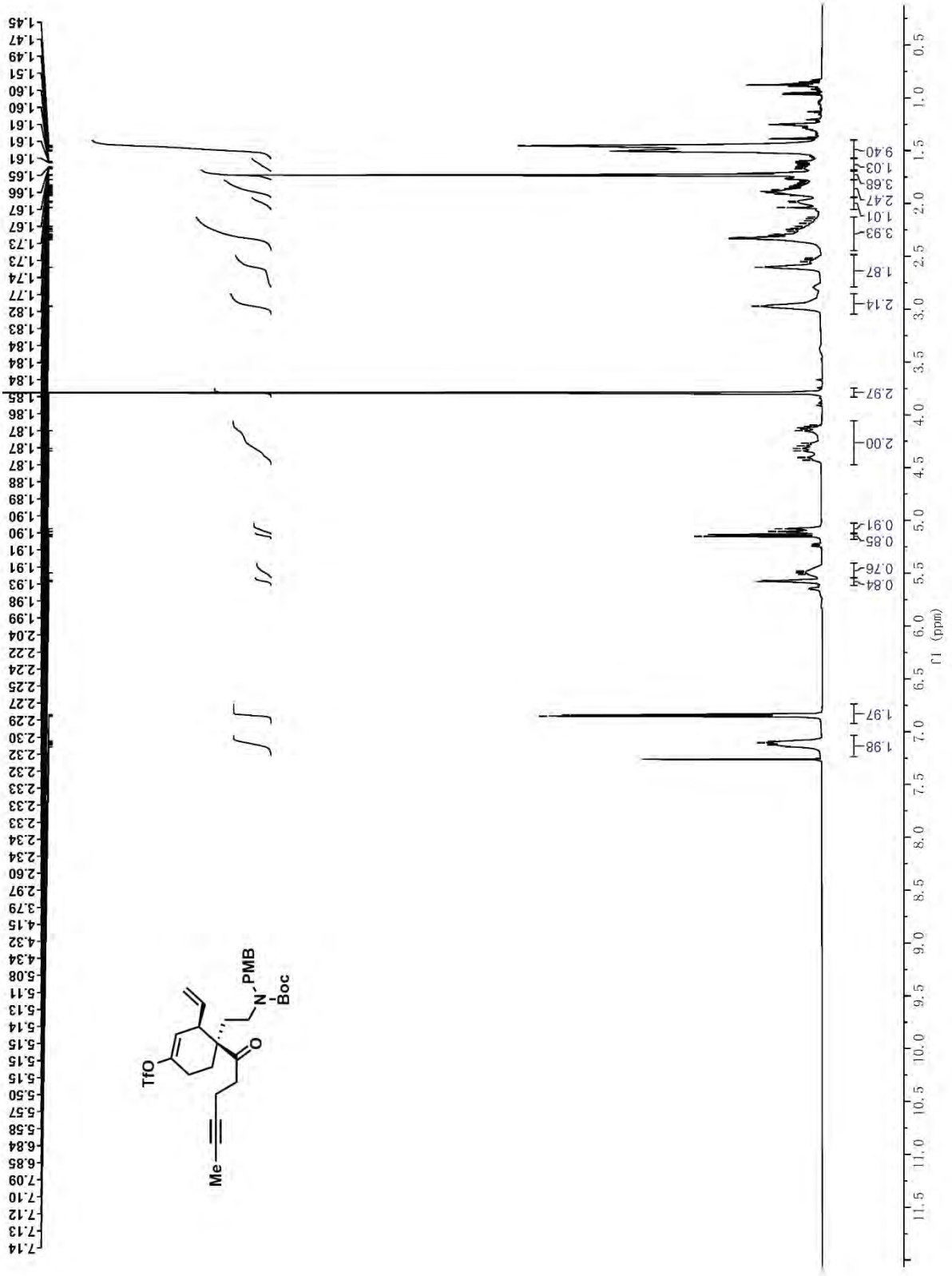
^{1}H NMR: Compound **170**



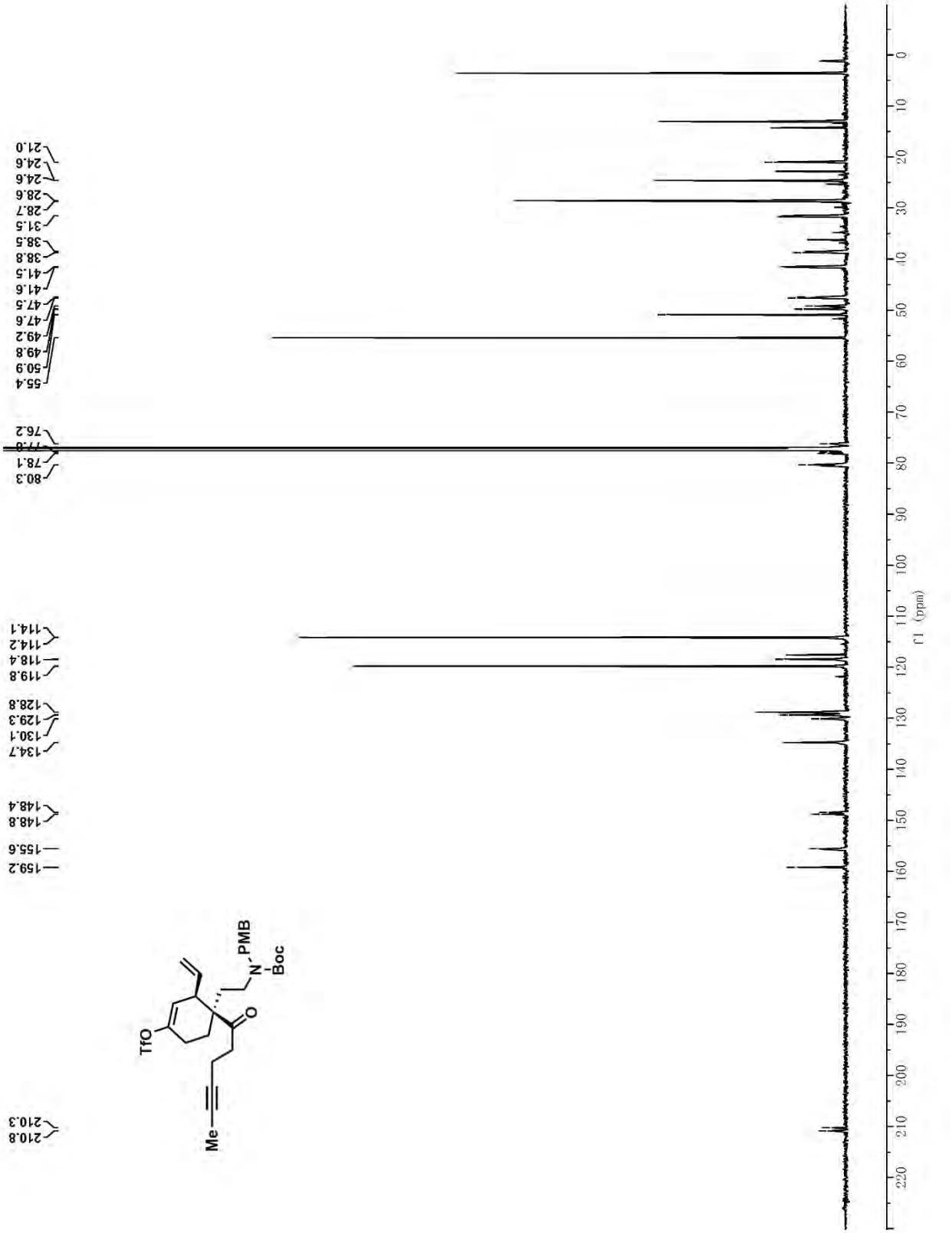
^{1}H NMR: Compound **171**



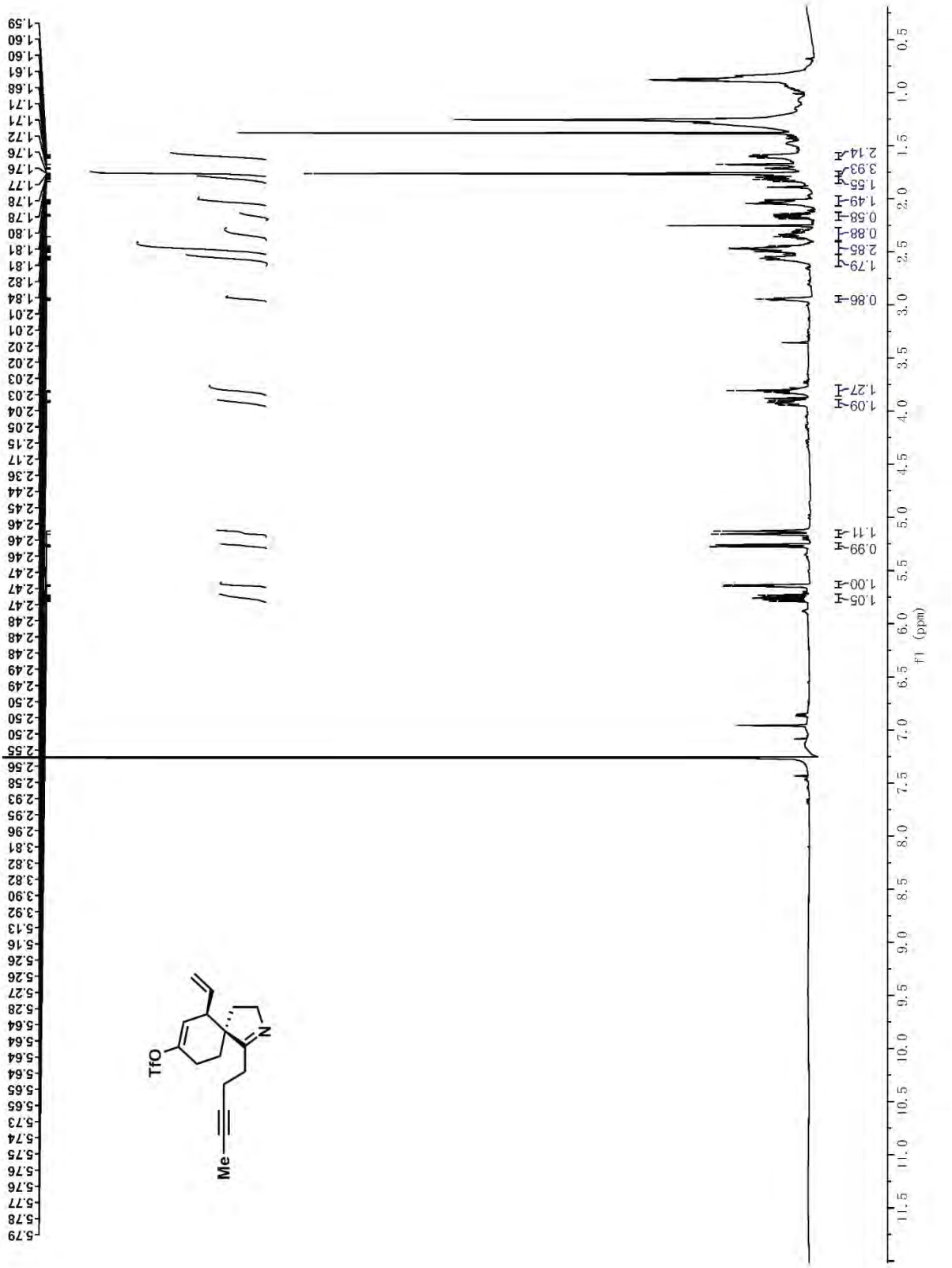
^{1}H NMR: Compound **172**



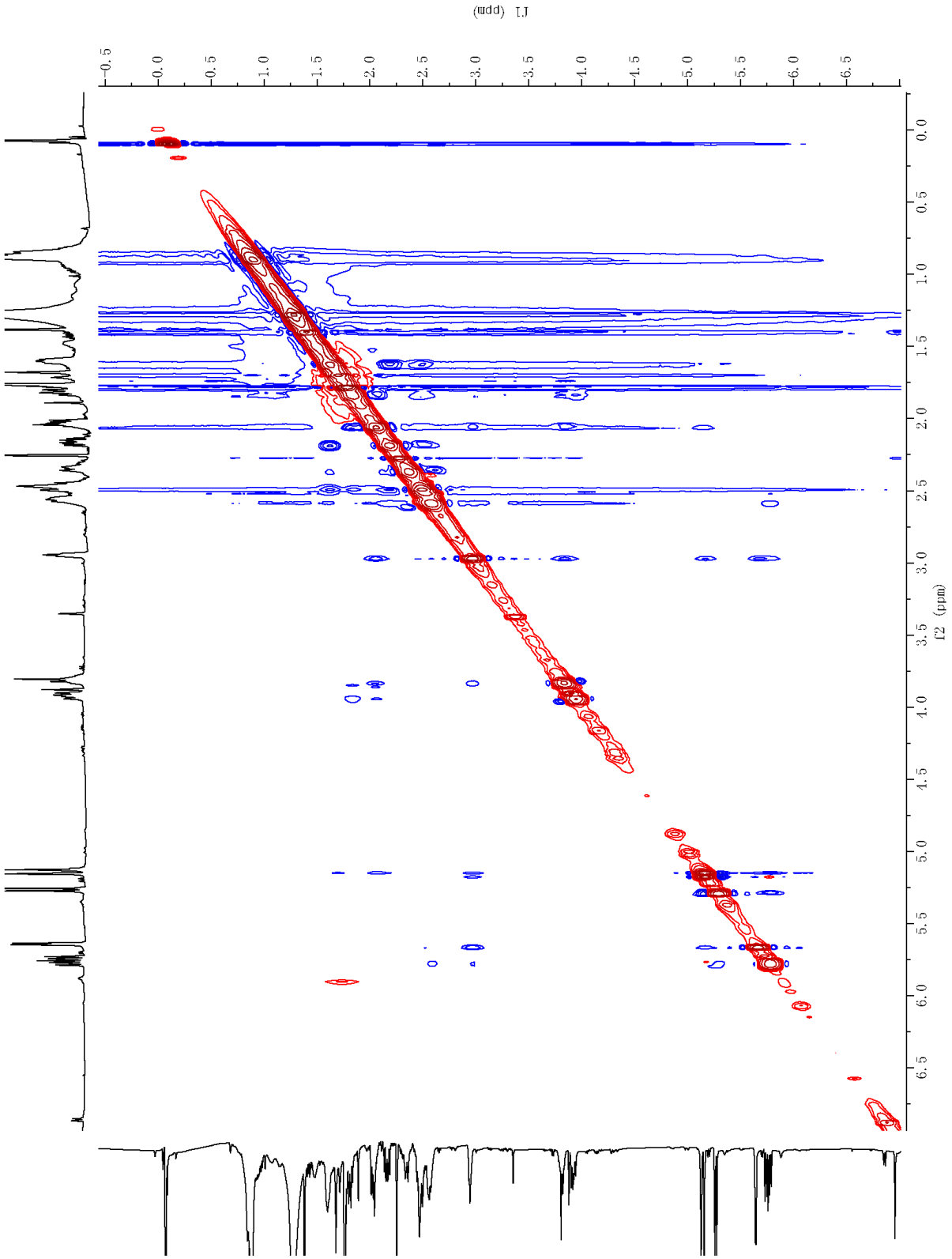
^{13}C NMR: Compound **172**



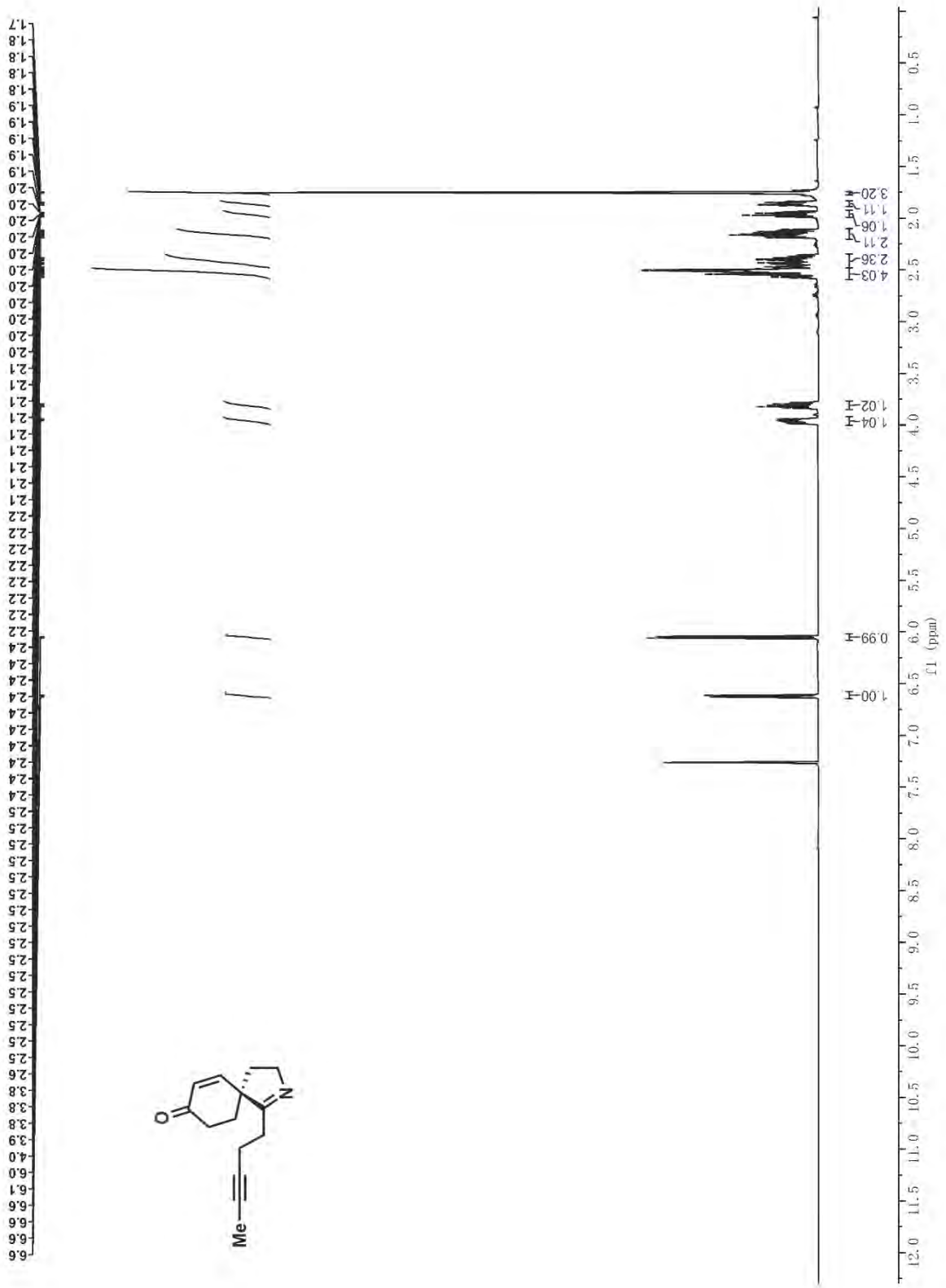
^{1}H NMR: Compound **173**



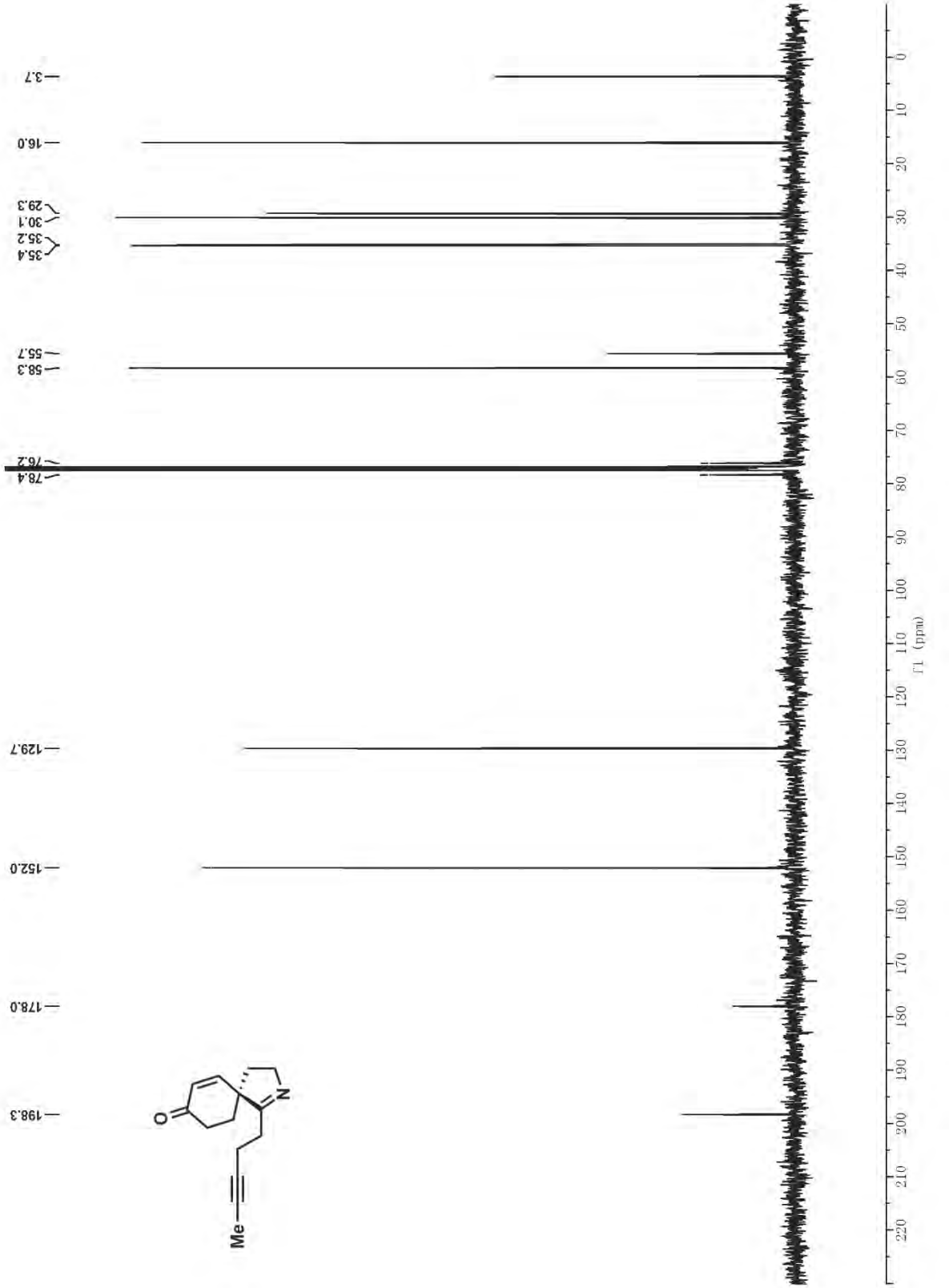
^{1}H-^{1}H-NOESY: Compound **173**



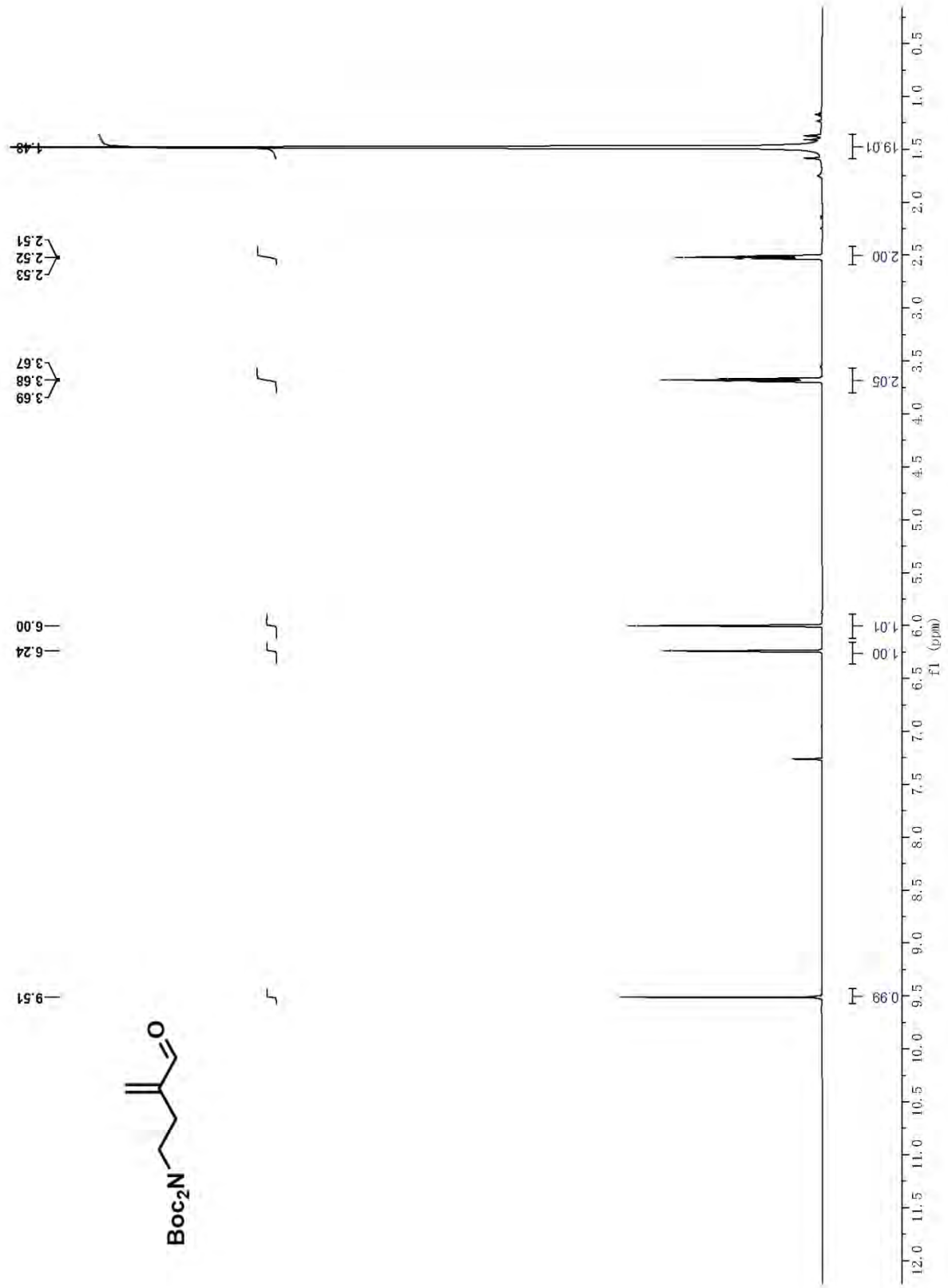
^{1}H NMR: Compound **174**



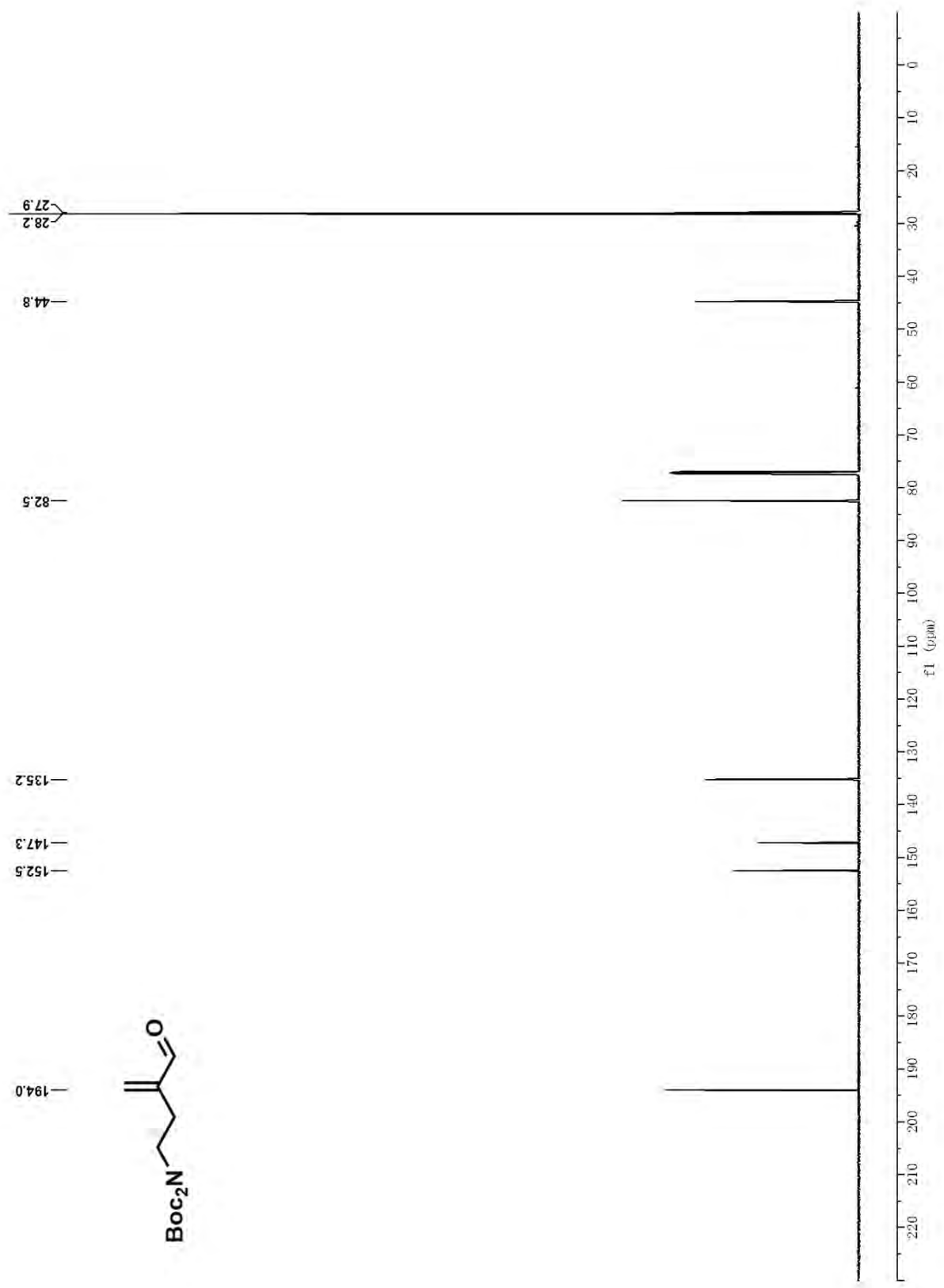
^{13}C NMR: Compound **174**



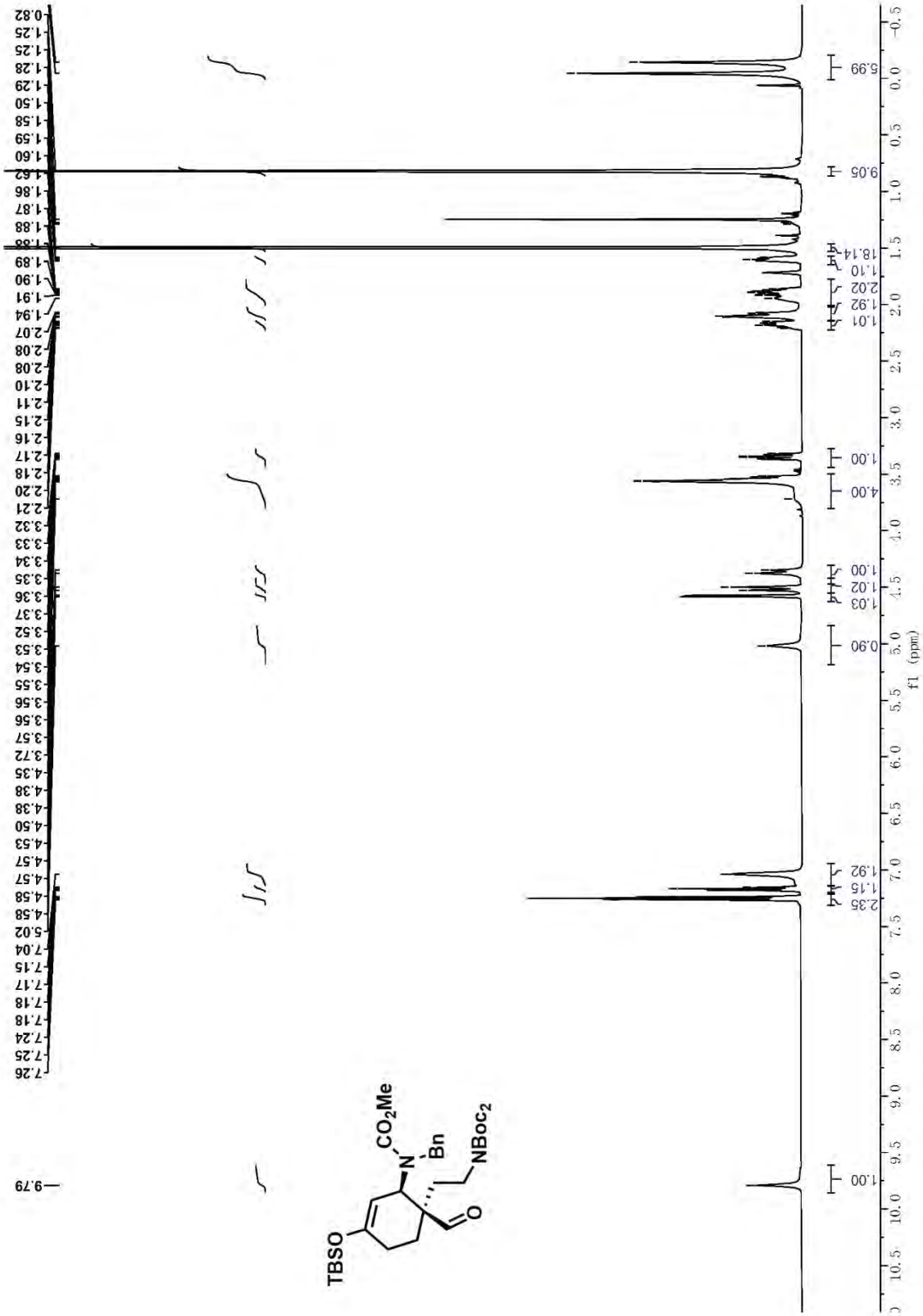
^{1}H NMR: Compound **177**



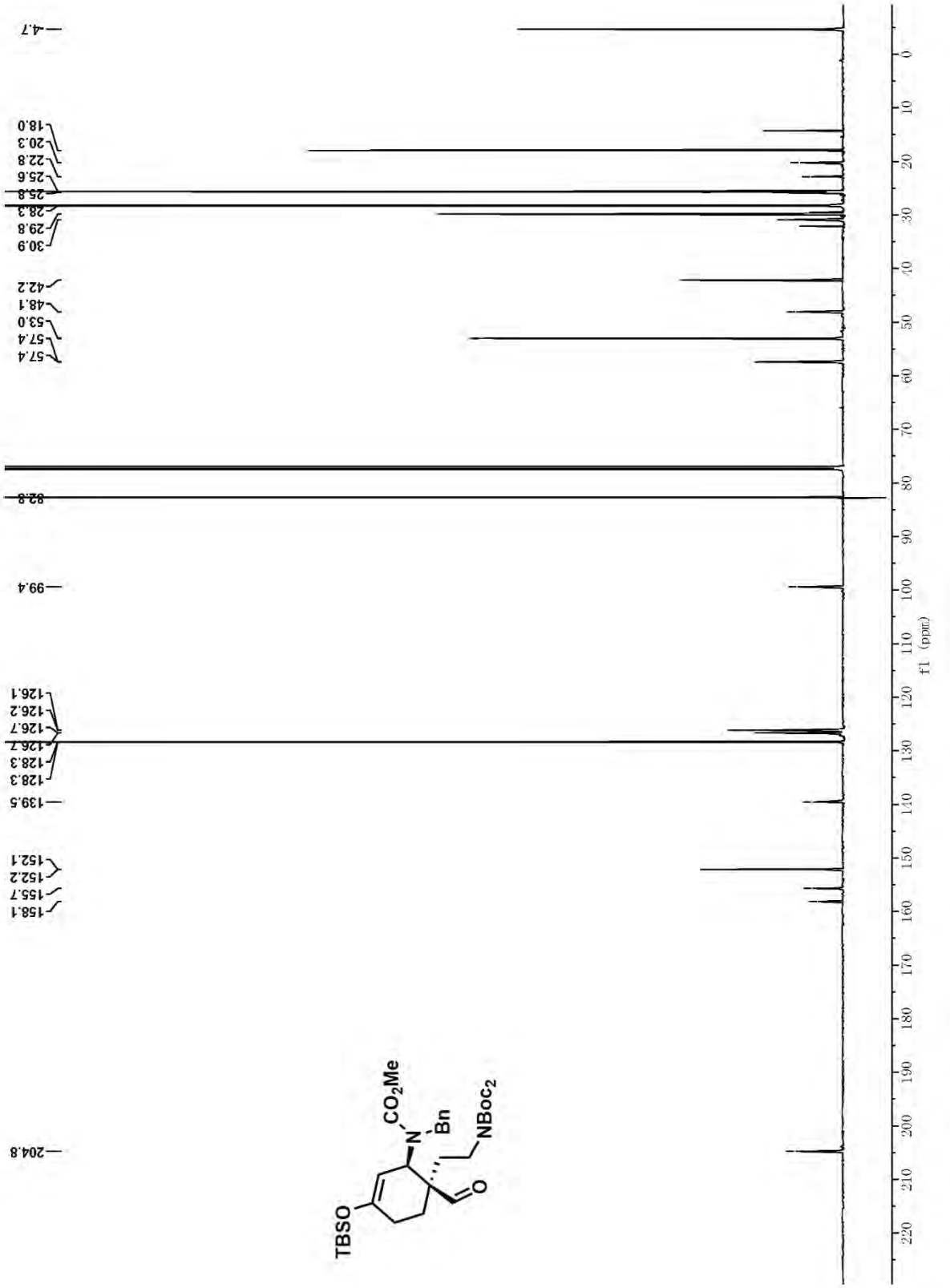
^{13}C NMR: Compound **177**



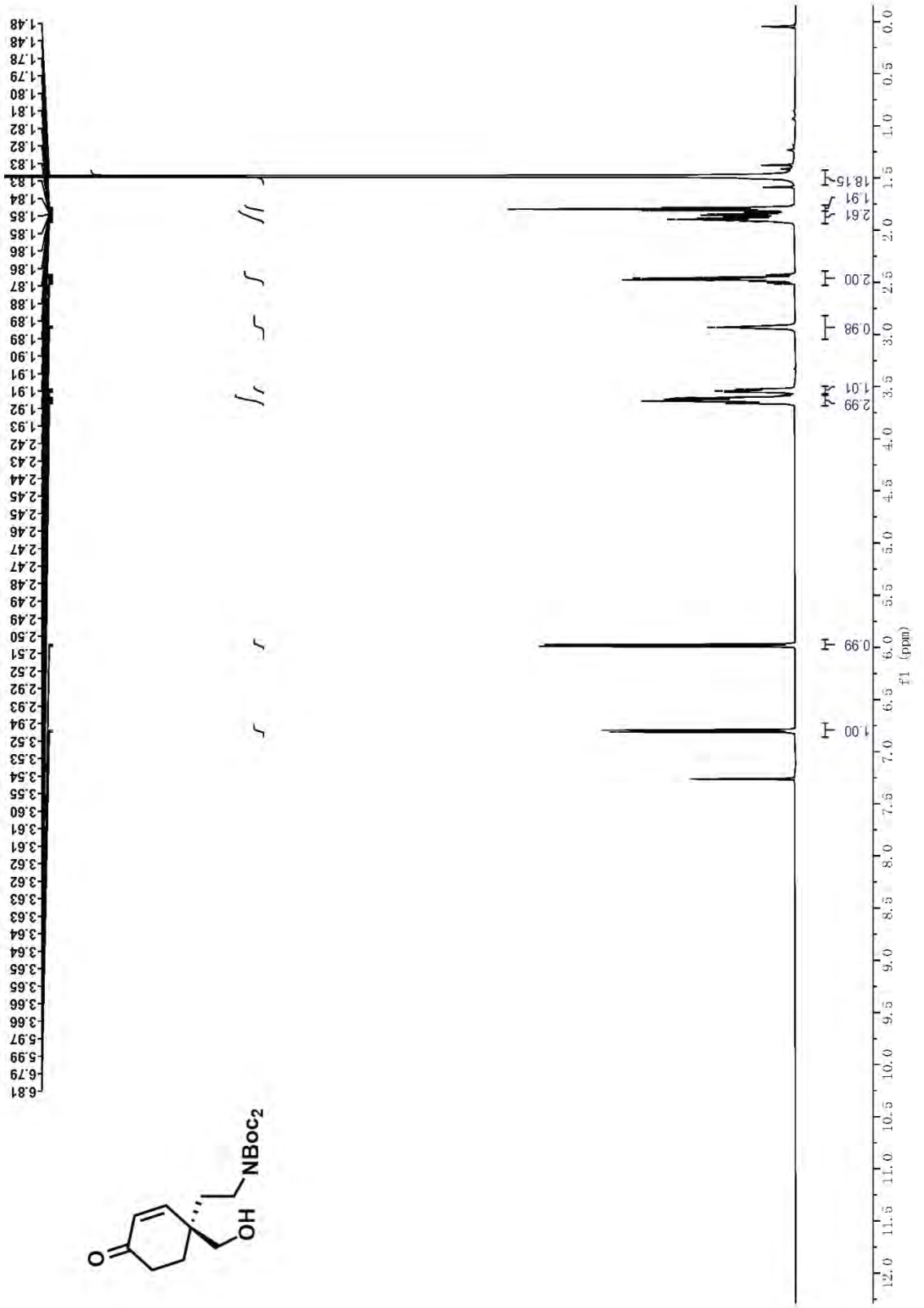
^{1}H NMR: Compound **178**



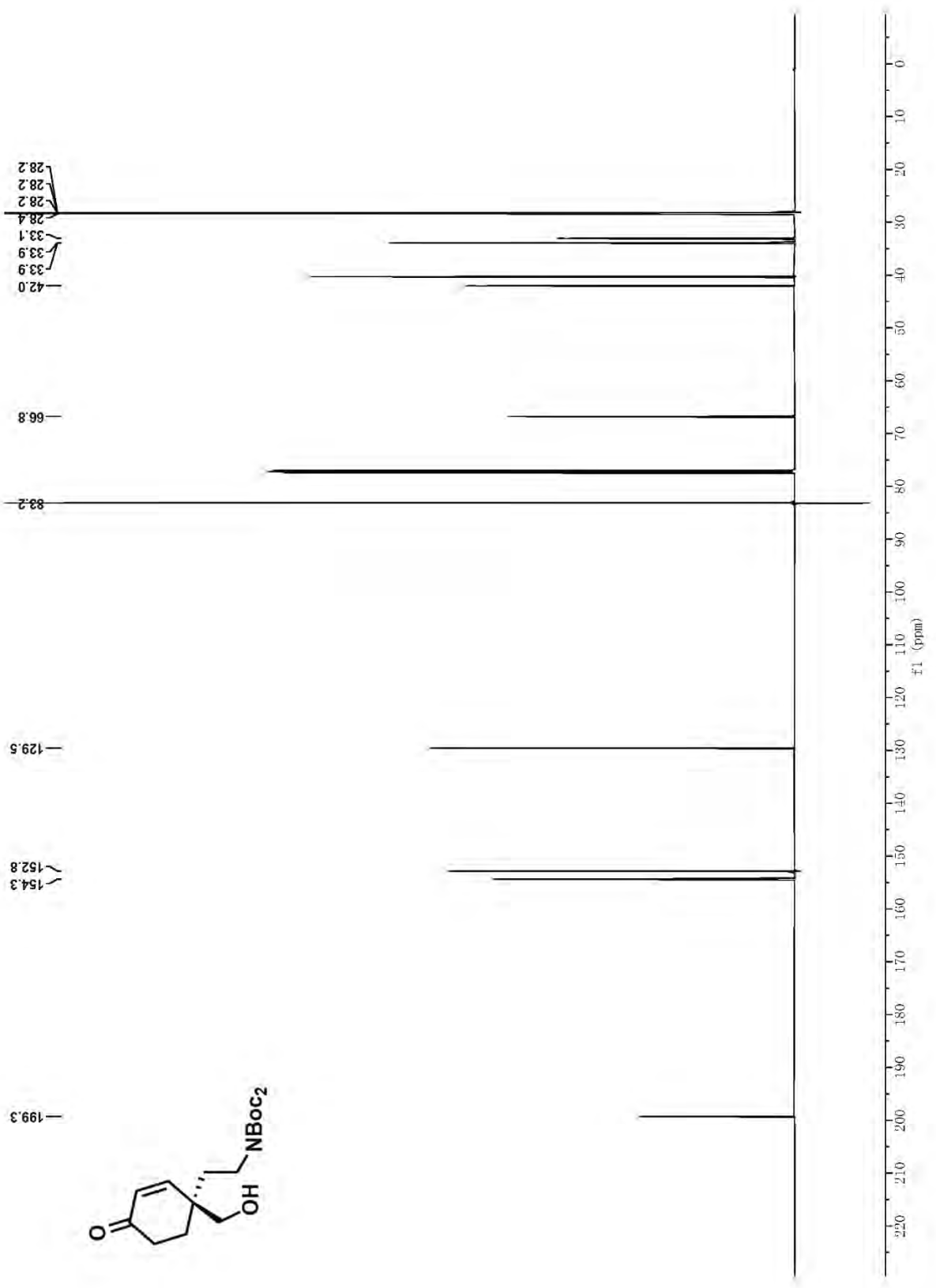
^{13}C NMR: Compound **178**



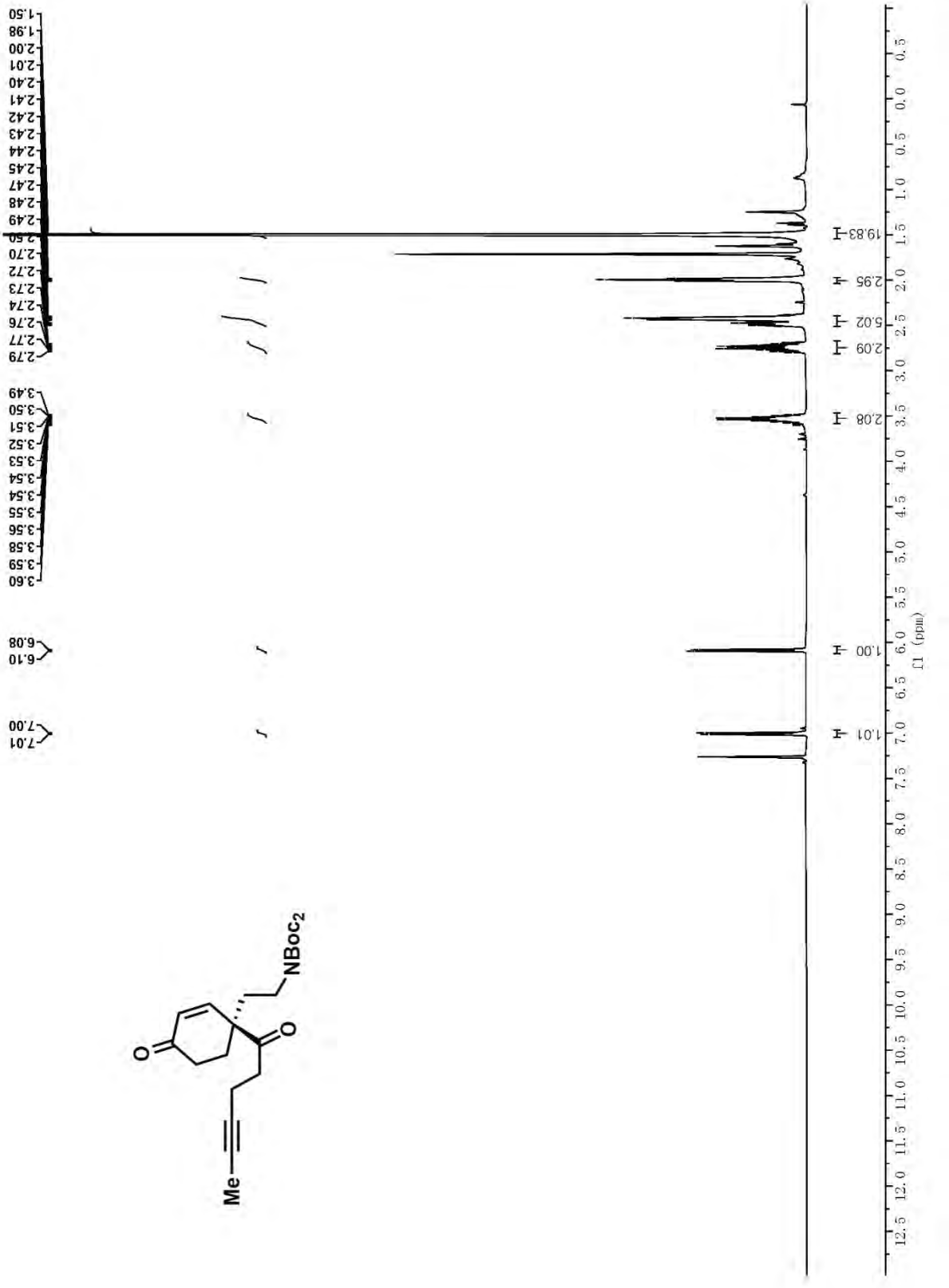
^{1}H NMR: Compound **179**



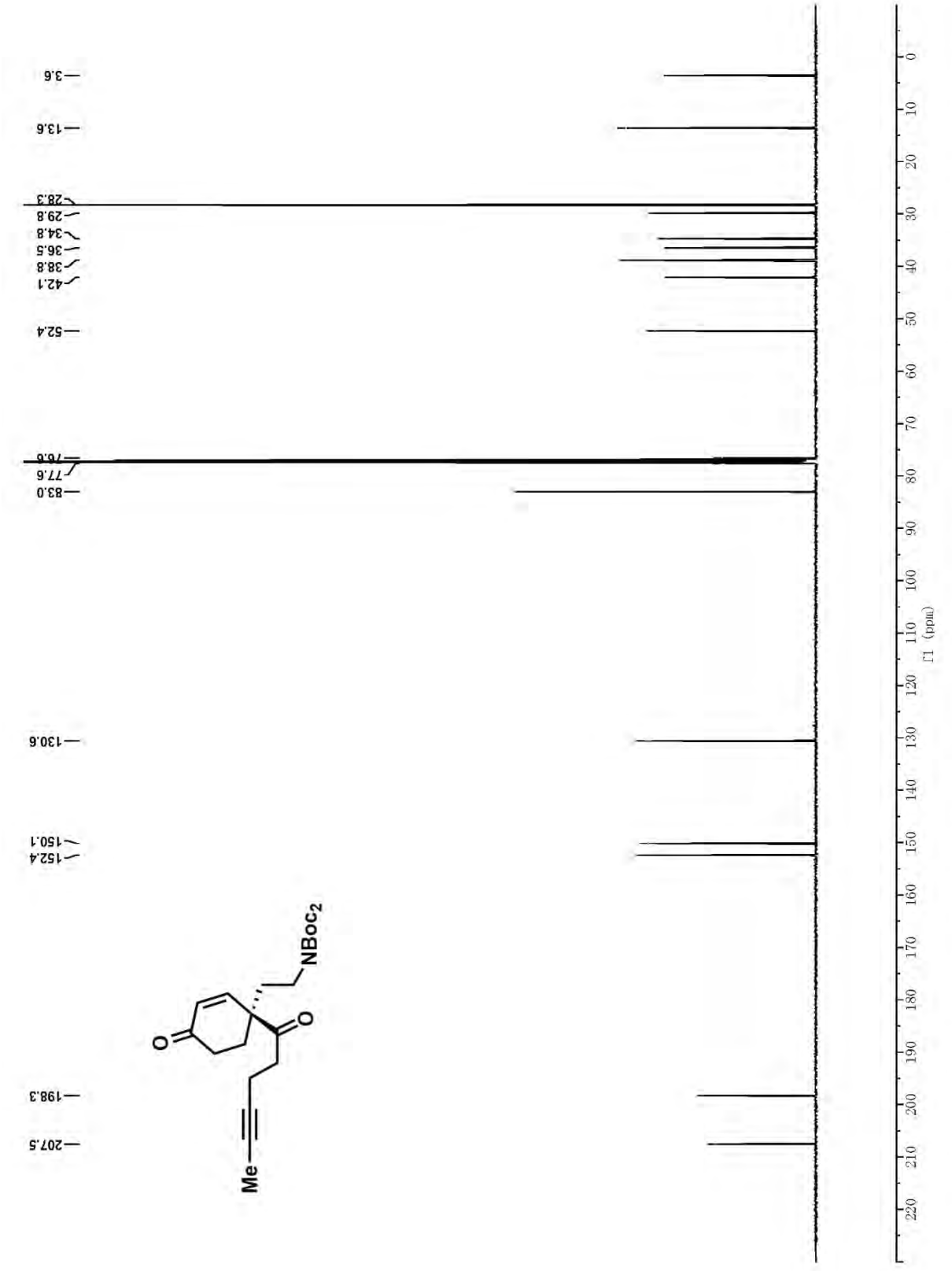
^{13}C NMR: Compound **179**



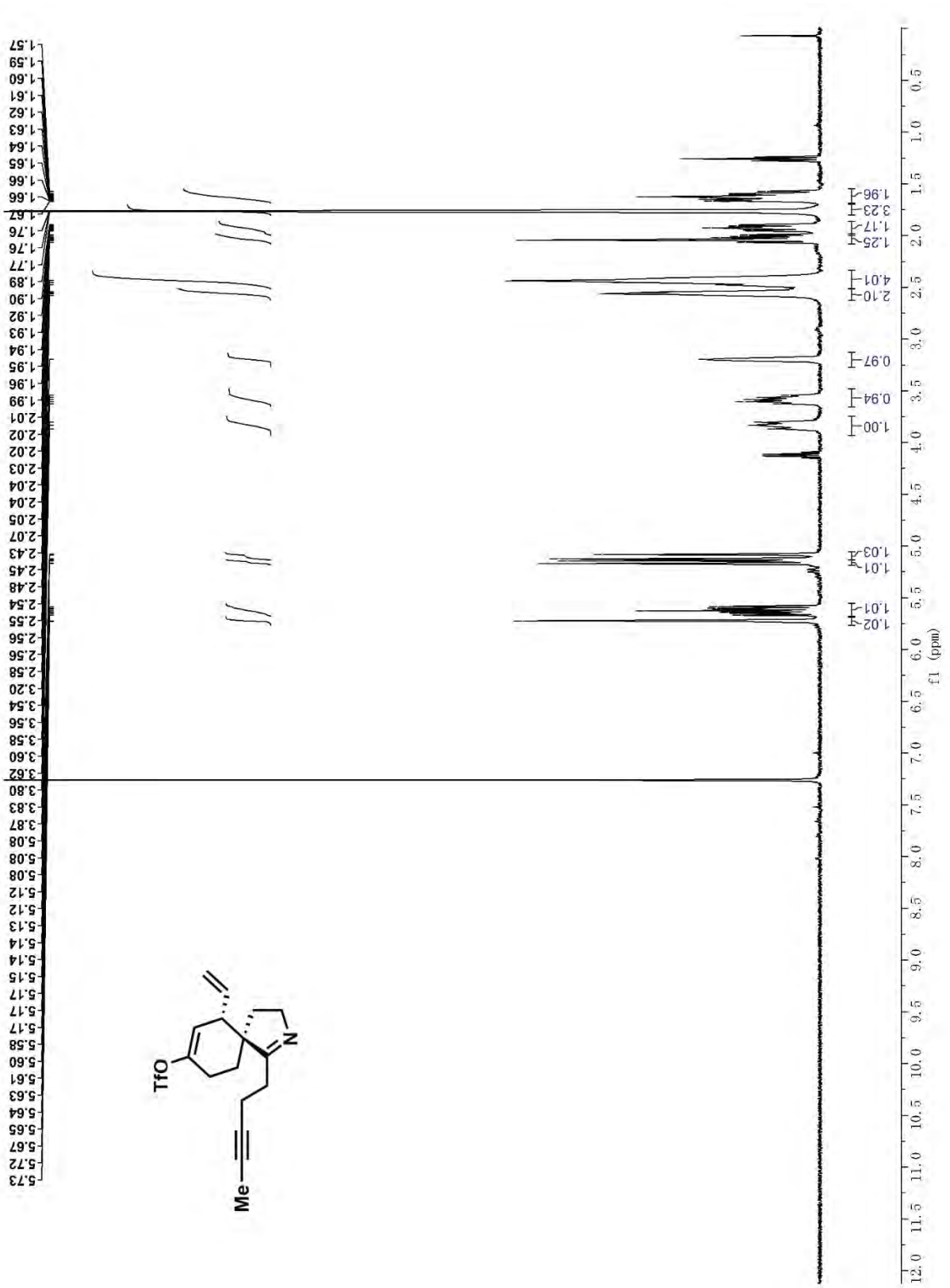
^{1}H NMR: Compound **180**



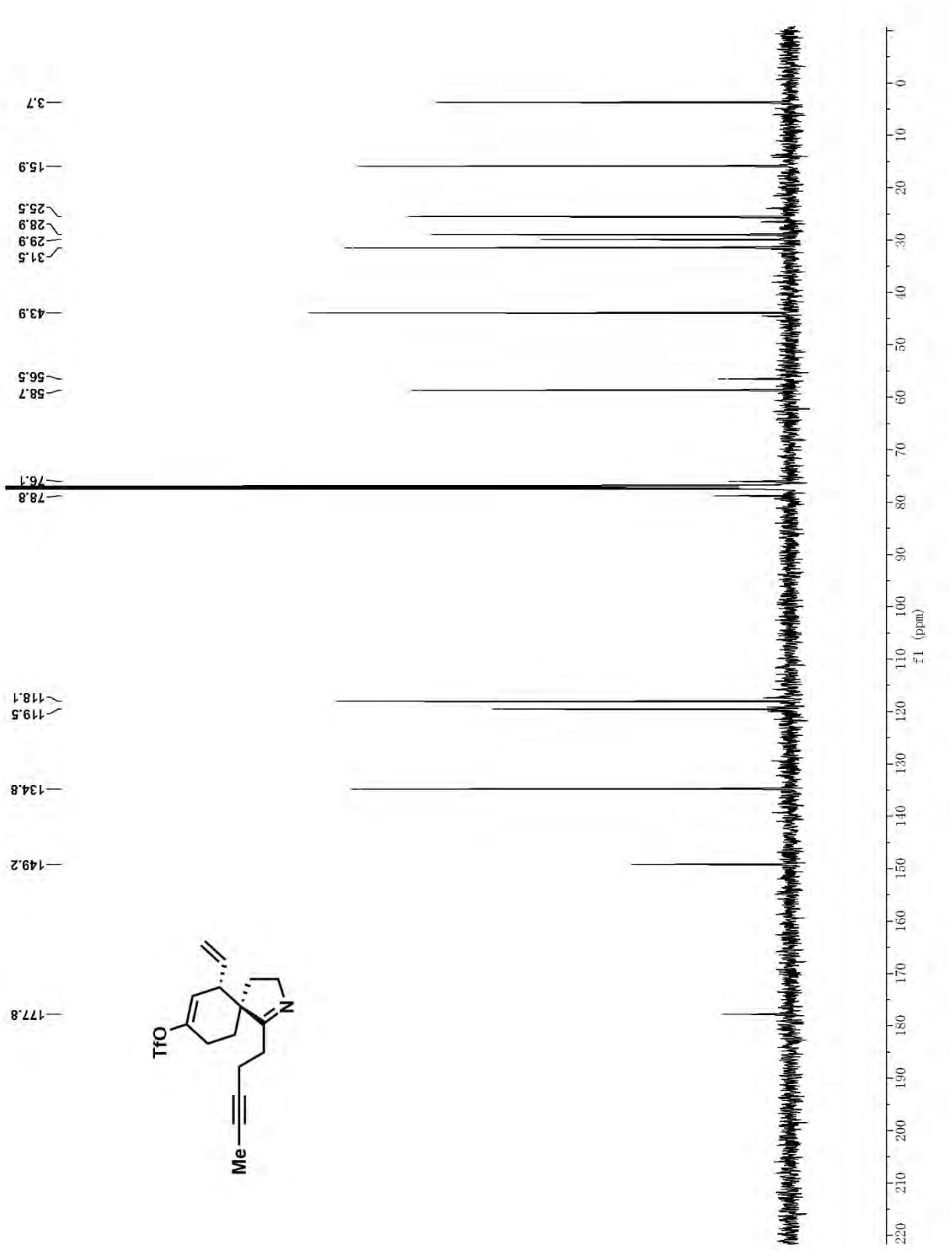
^{13}C NMR: Compound **180**



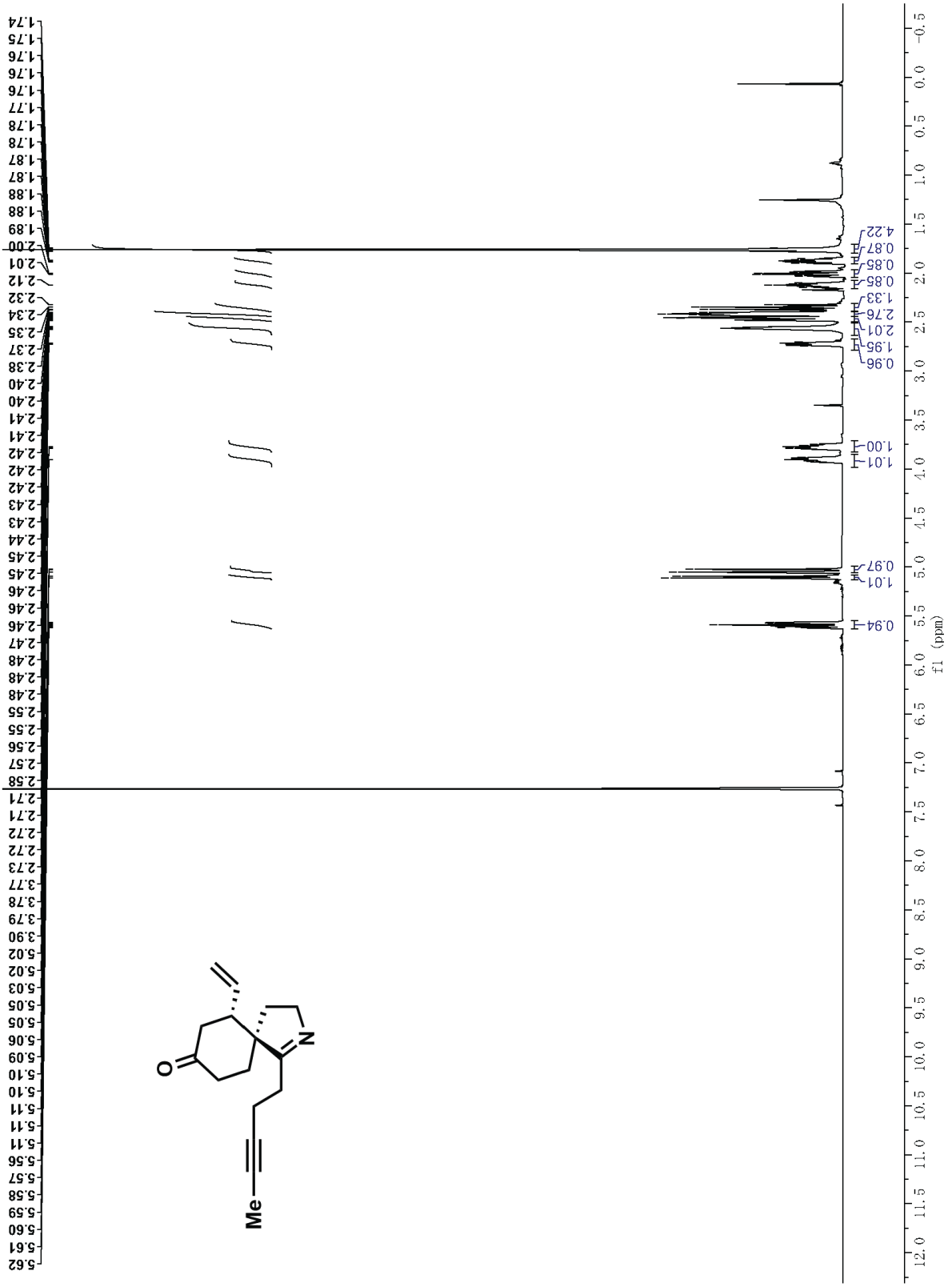
^{1}H NMR: Compound **182**



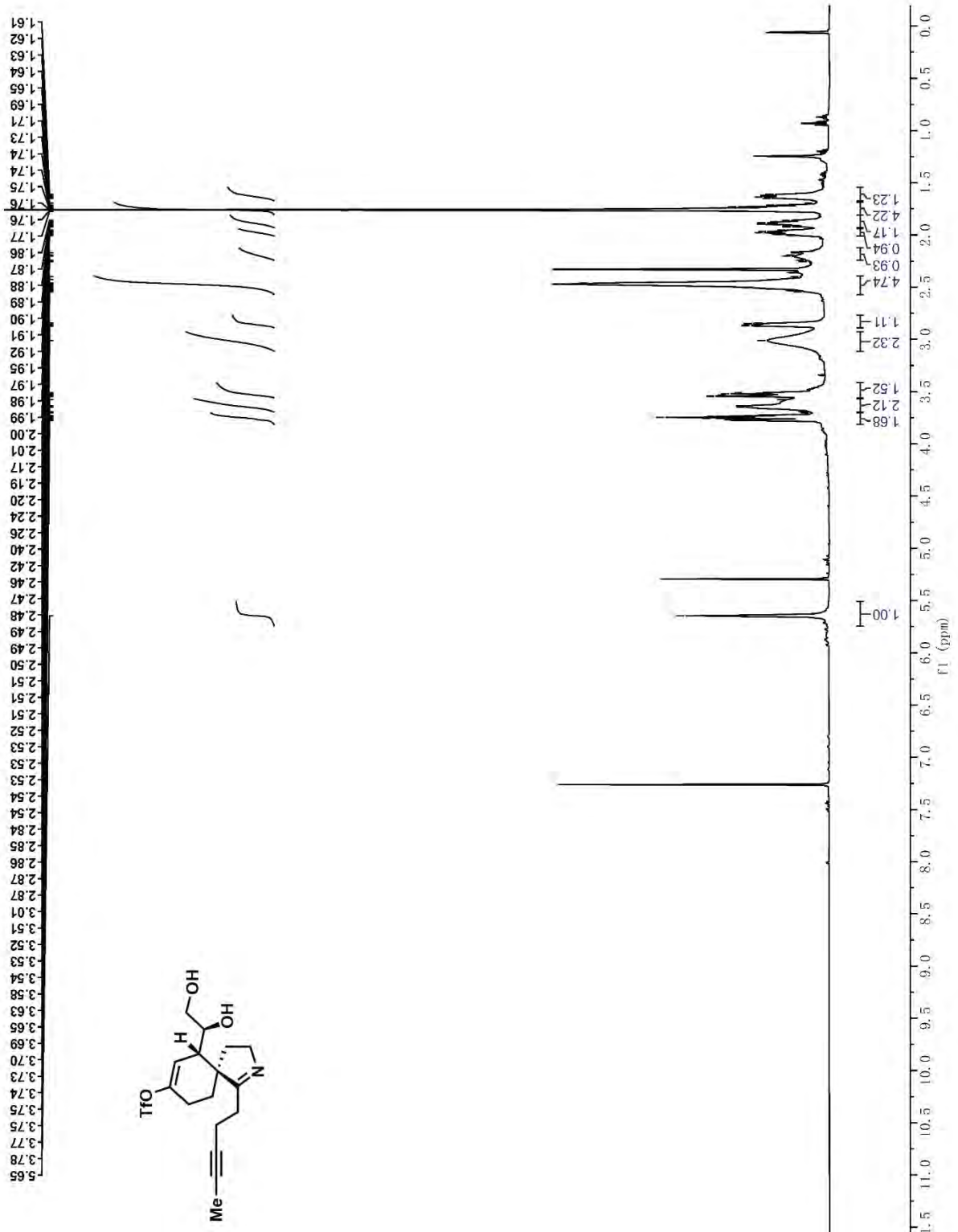
^{13}C NMR: Compound **182**



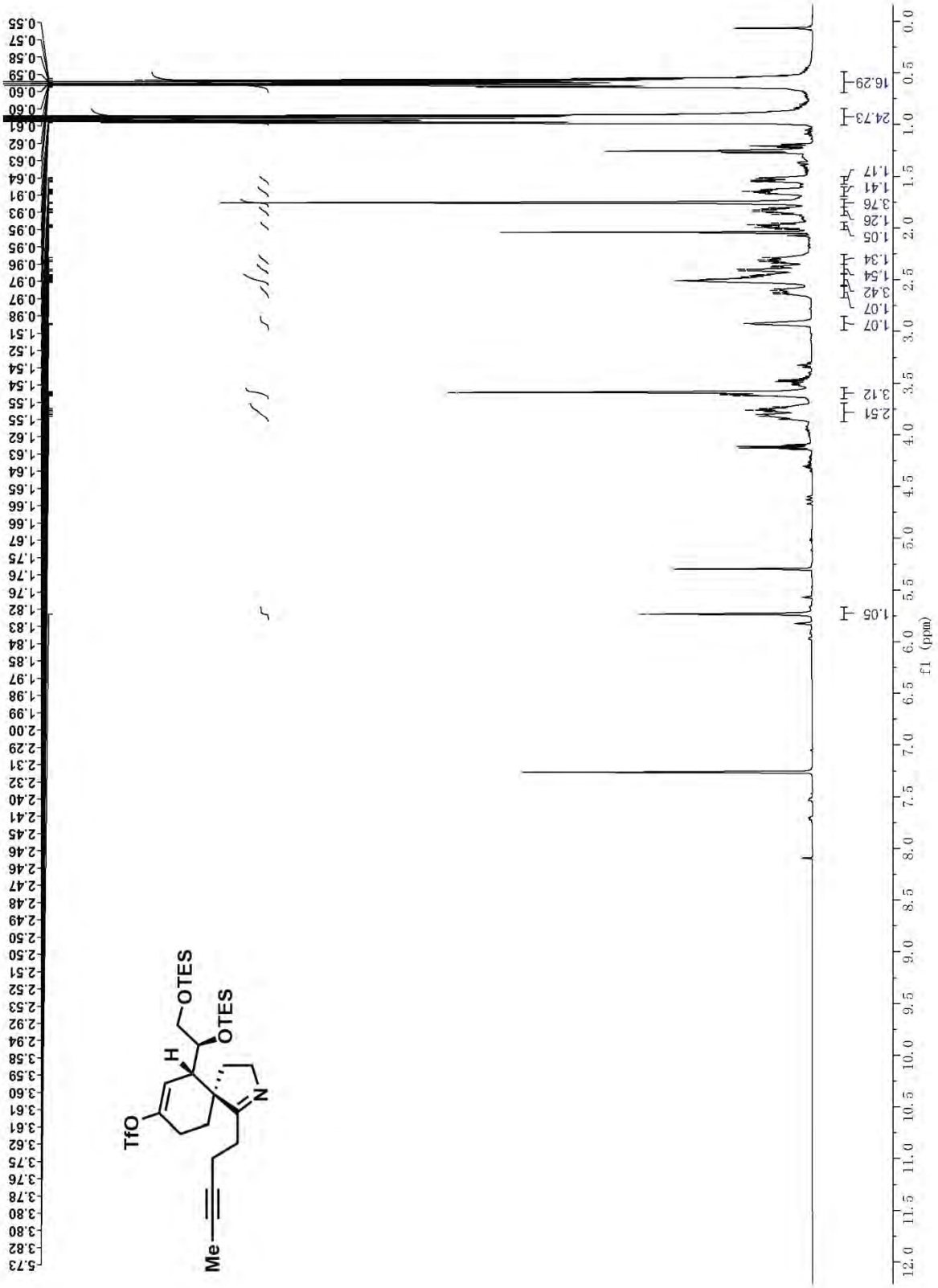
^{1}H NMR: Compound **183**



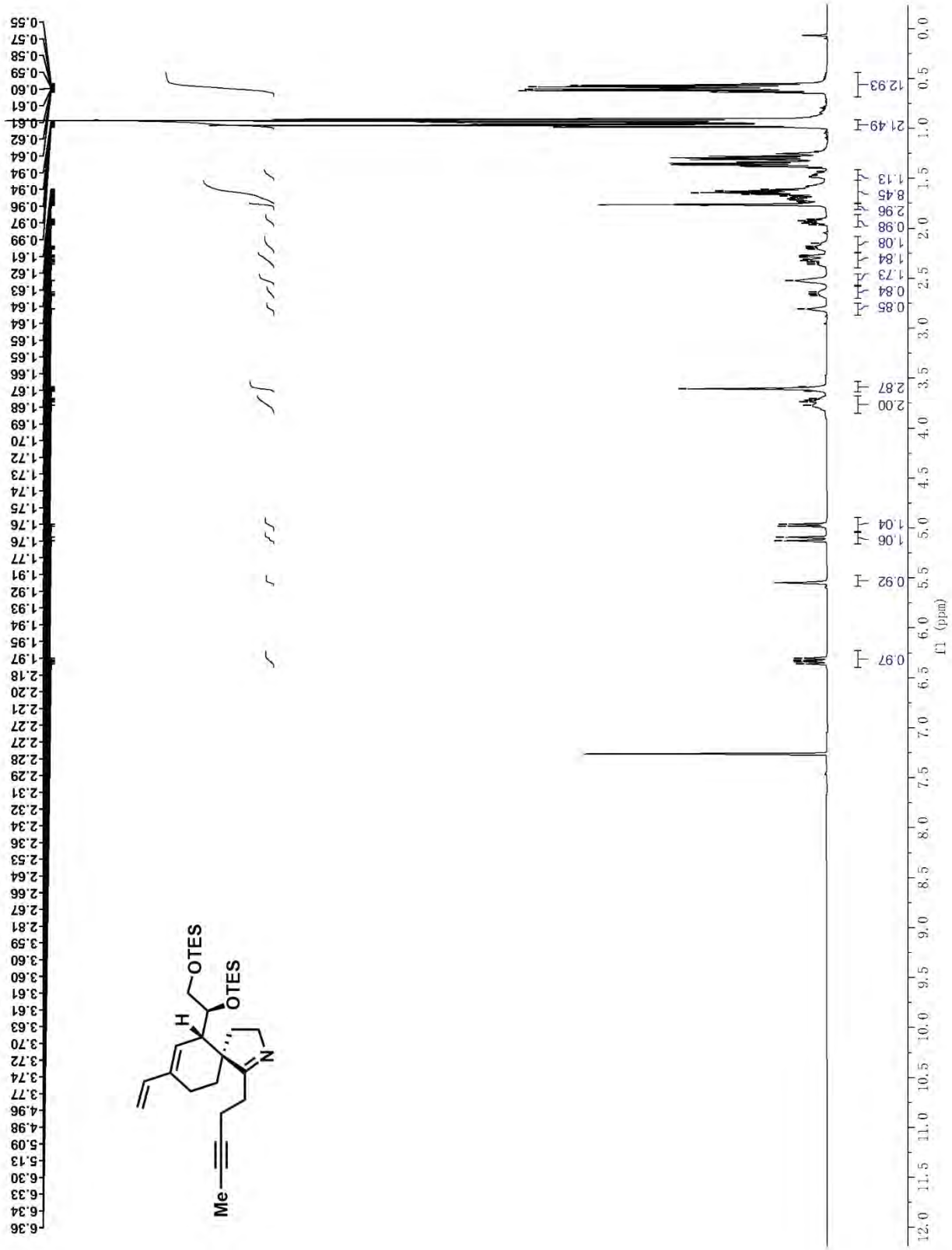
^{1}H NMR: Compound **185**



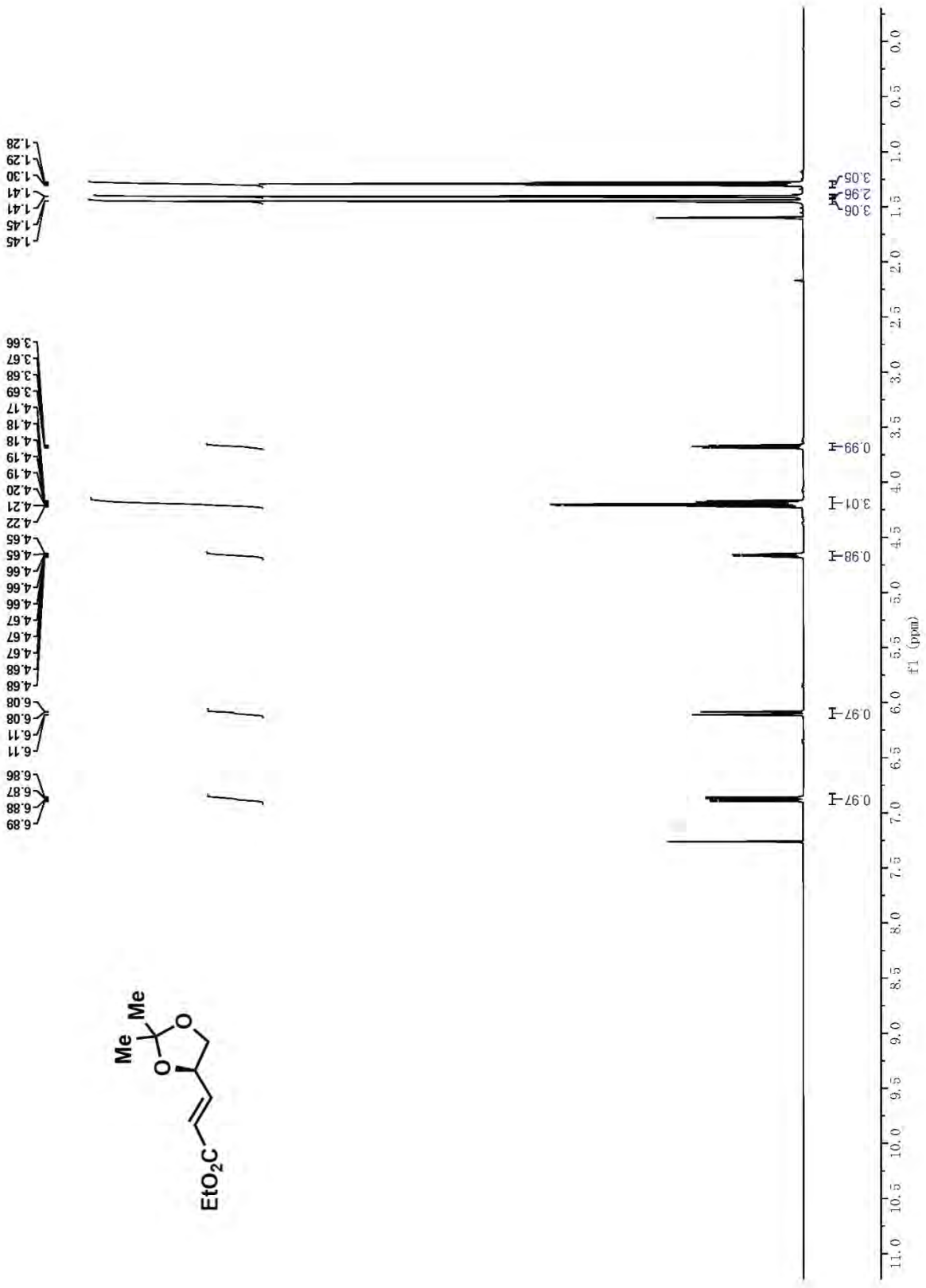
^{1}H NMR: Compound **187**



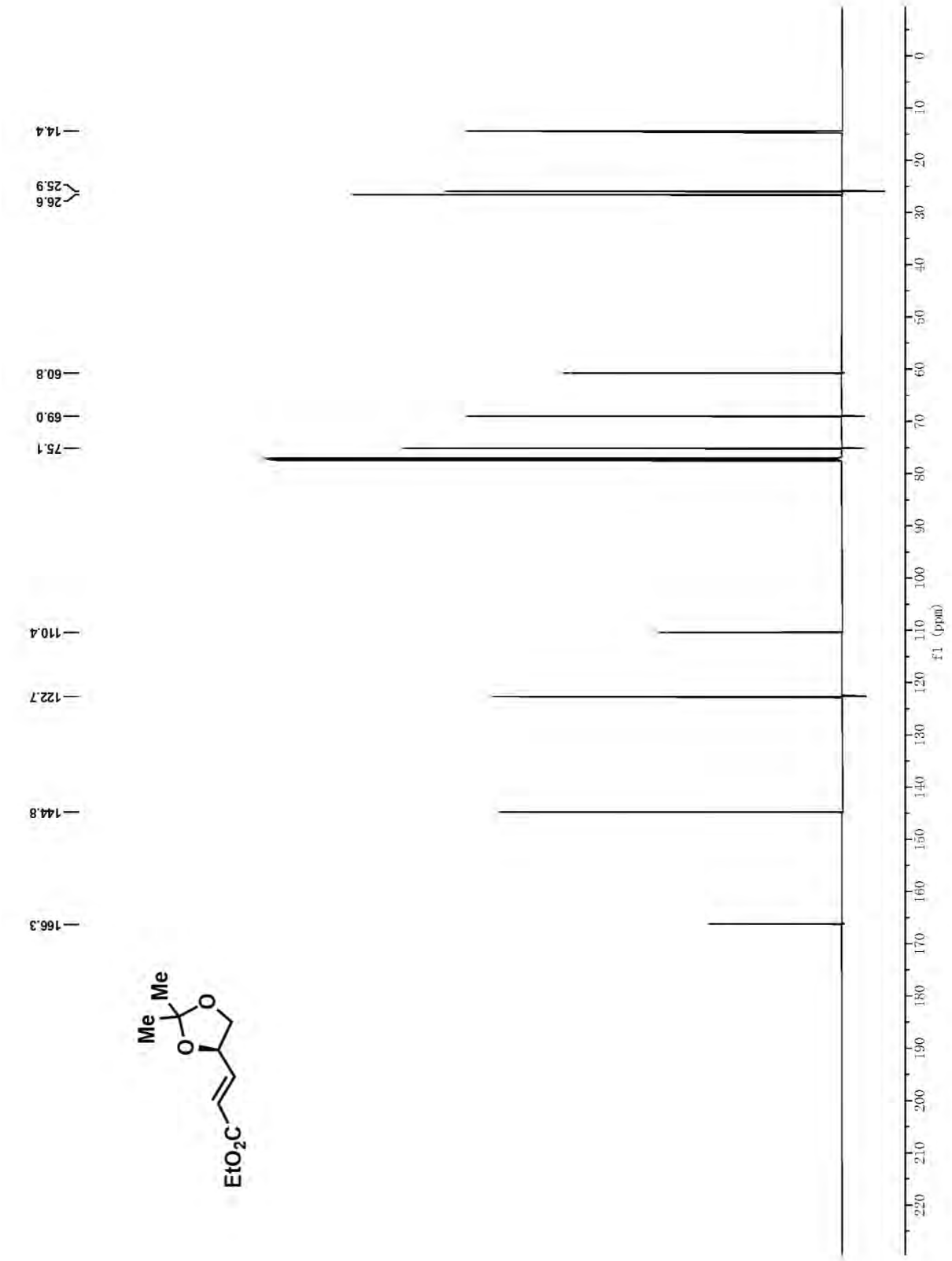
^{1}H NMR: Compound **188**



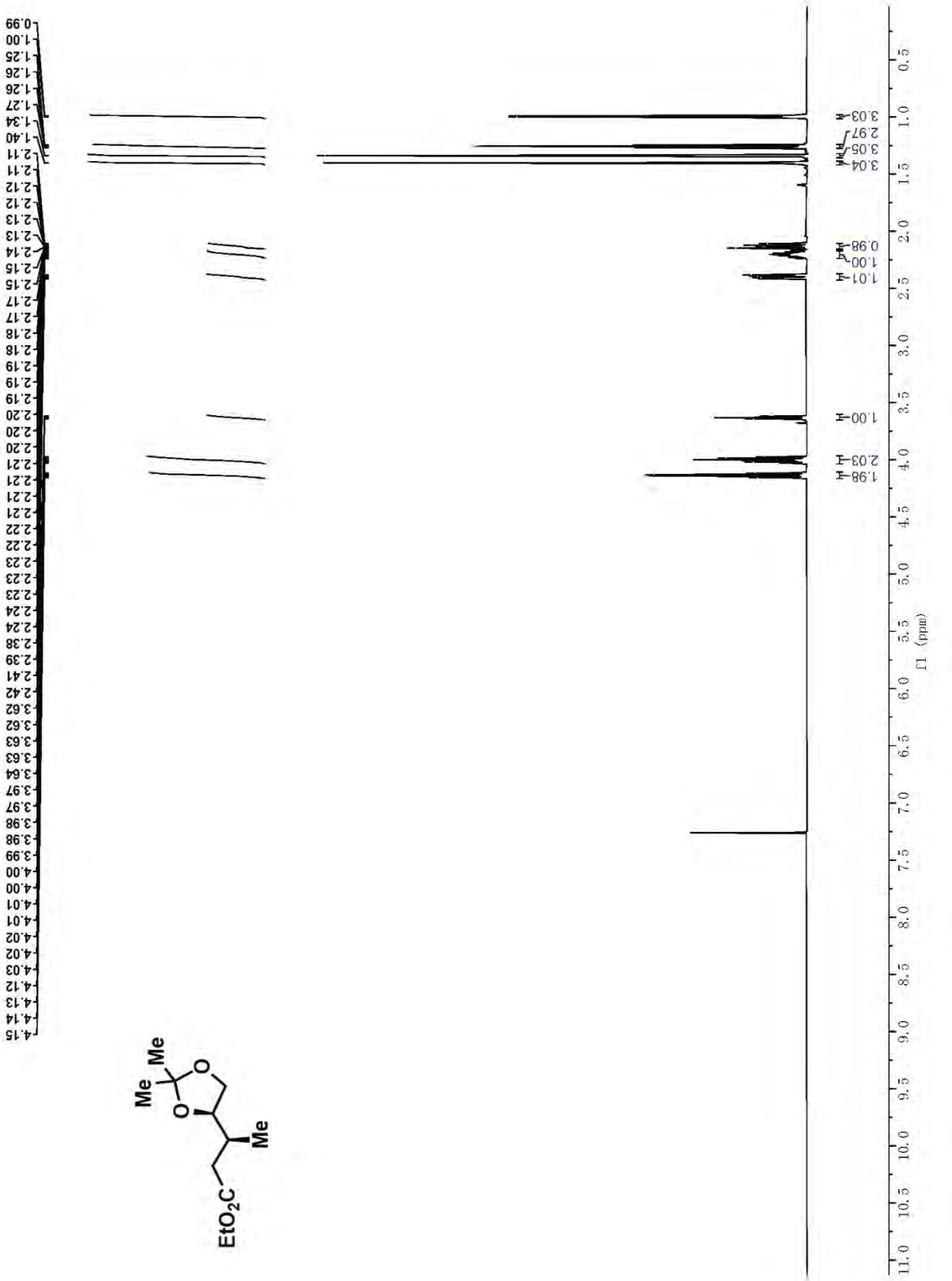
^{1}H NMR: Compound **194**



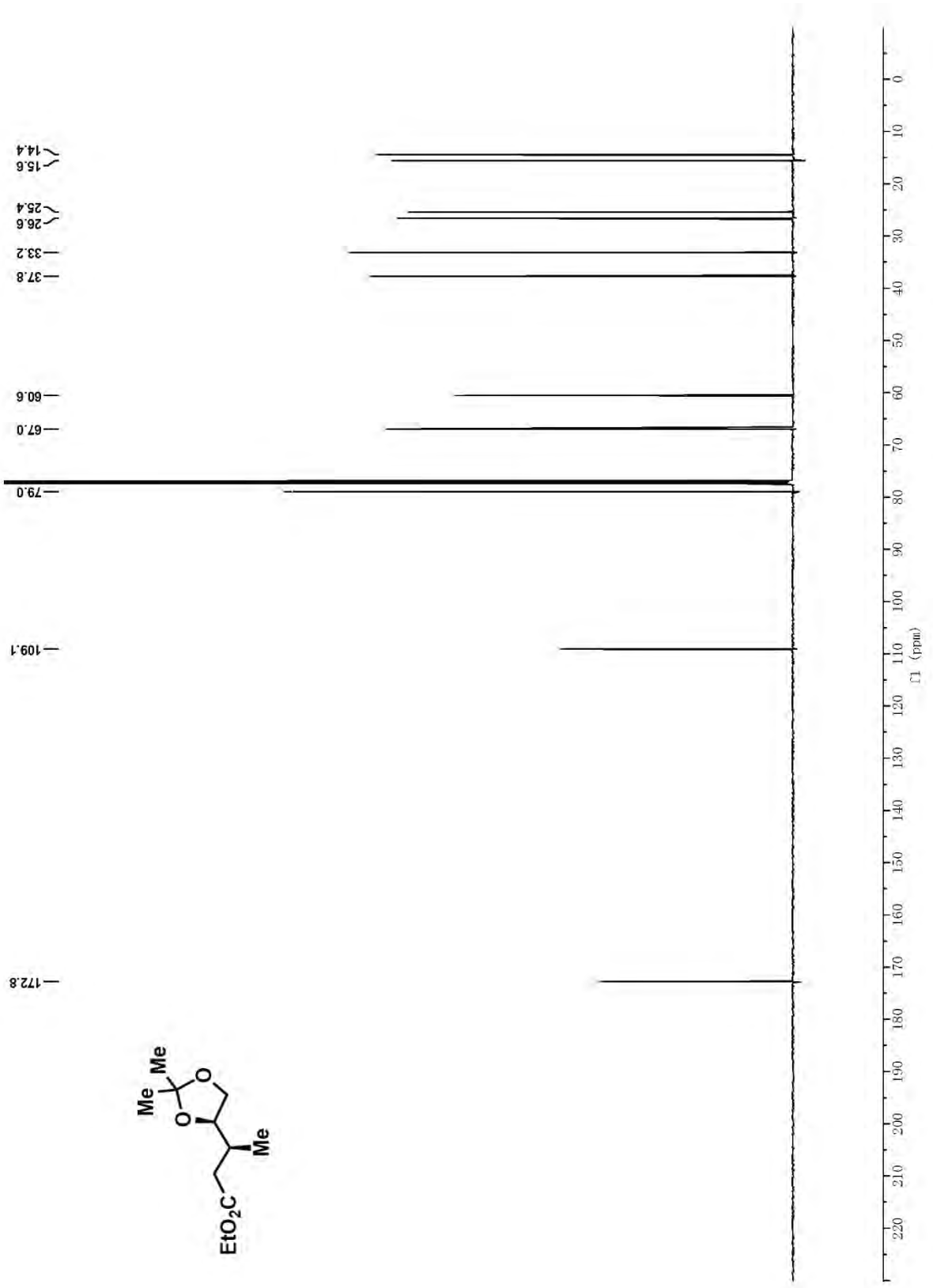
^{13}C NMR: Compound **194**



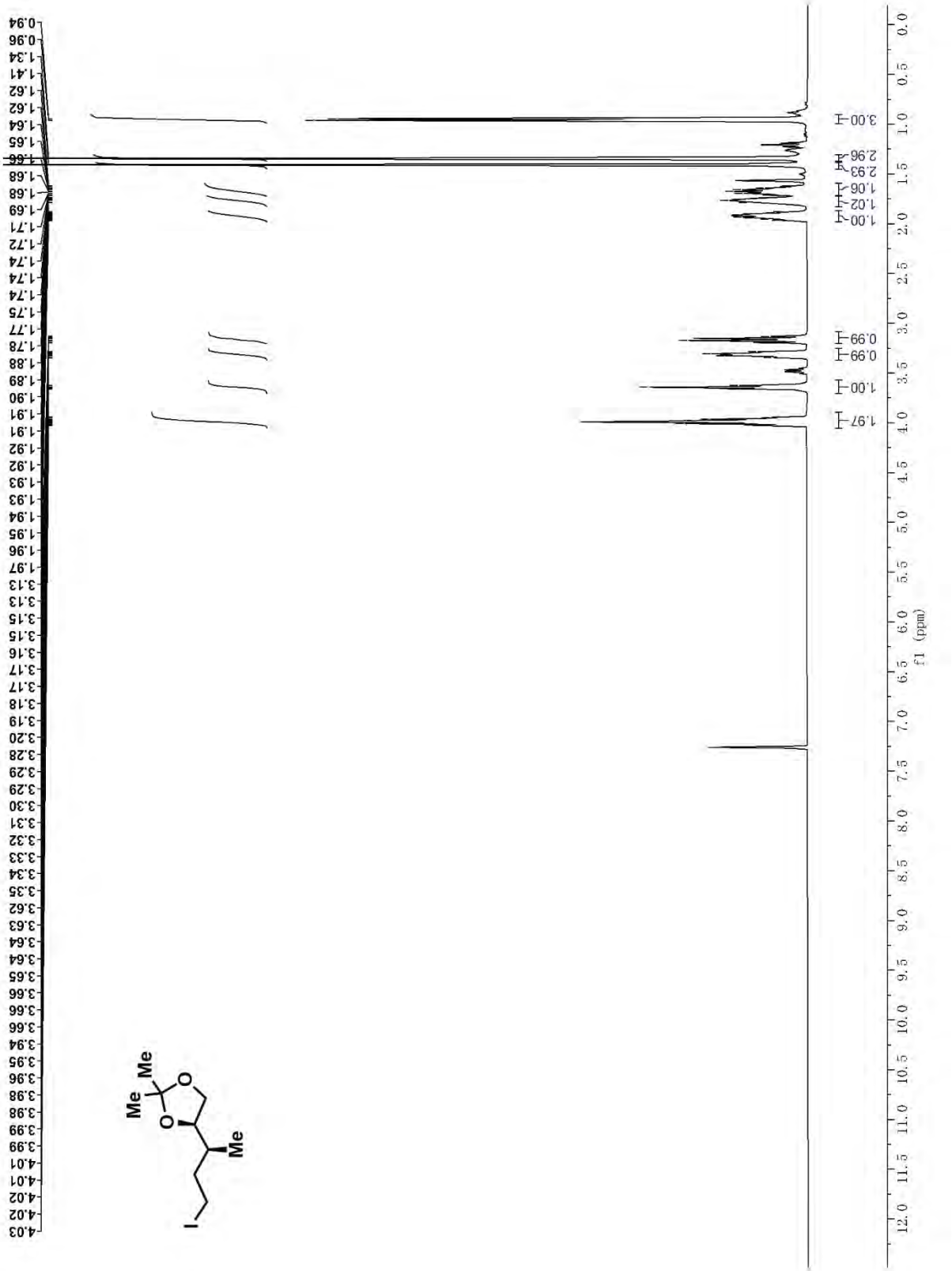
^{1}H NMR: Compound **195**



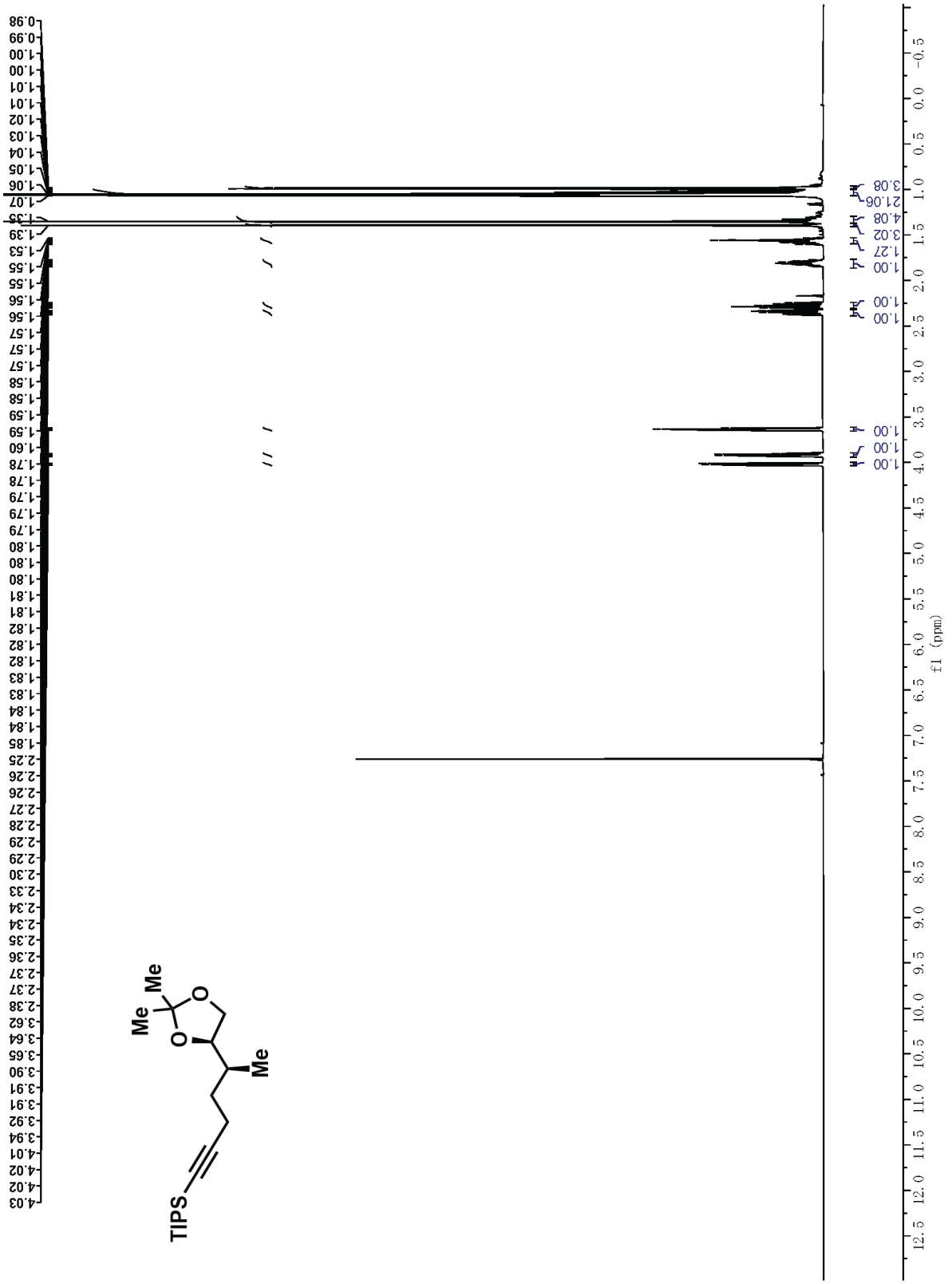
^{13}C NMR: Compound **195**



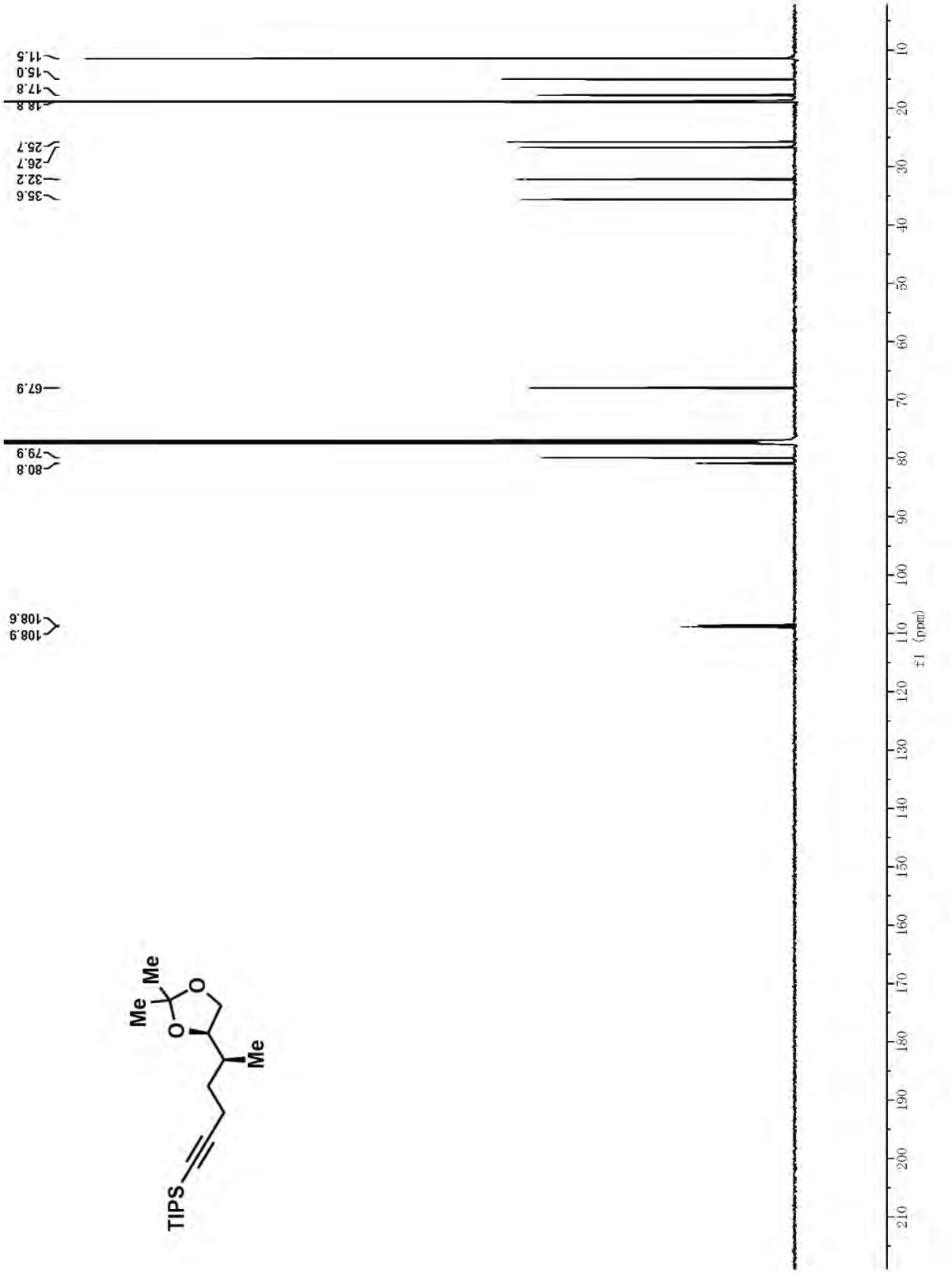
^{1}H NMR: Compound **196**



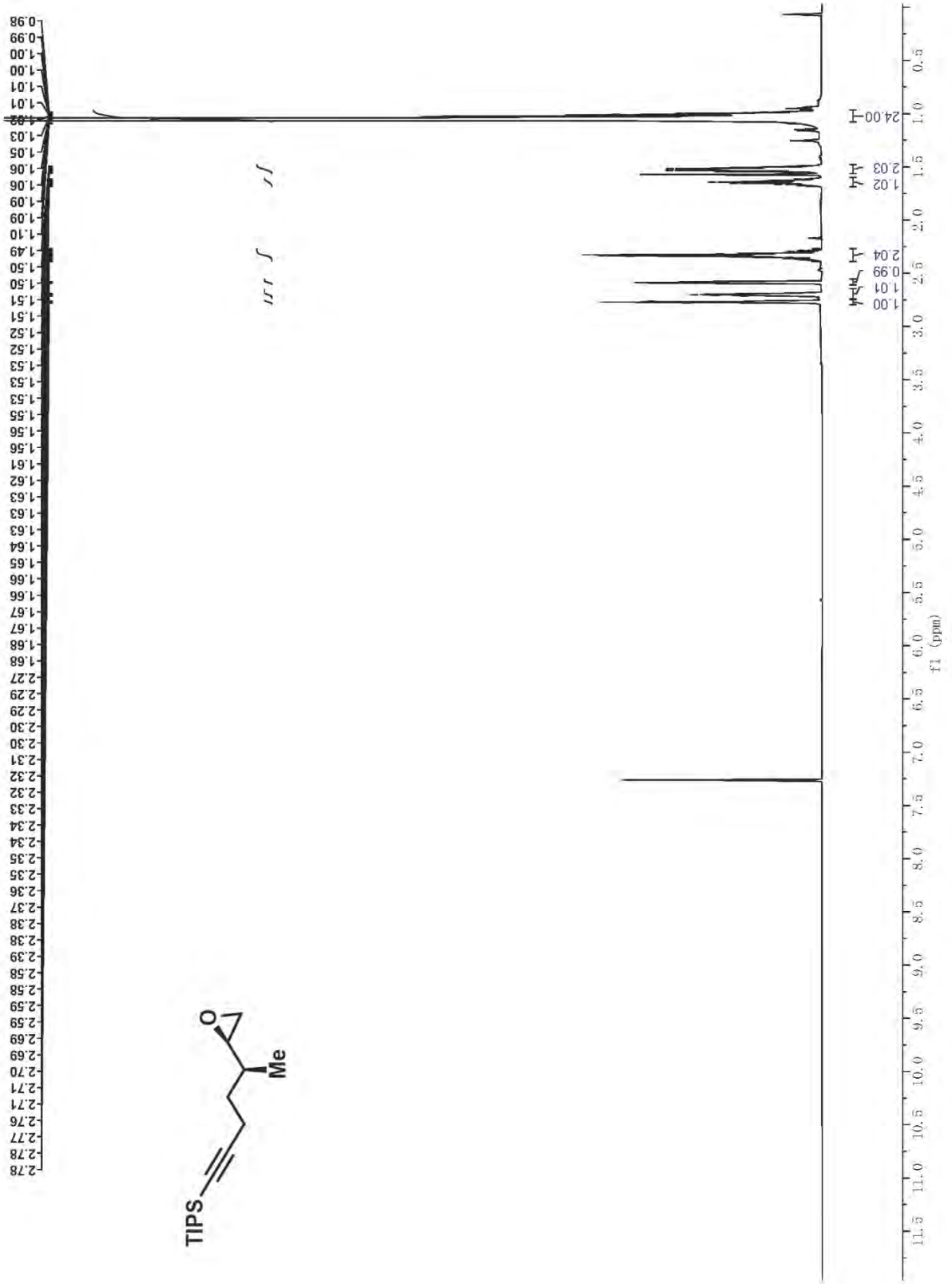
^{1}H NMR: Compound **197**



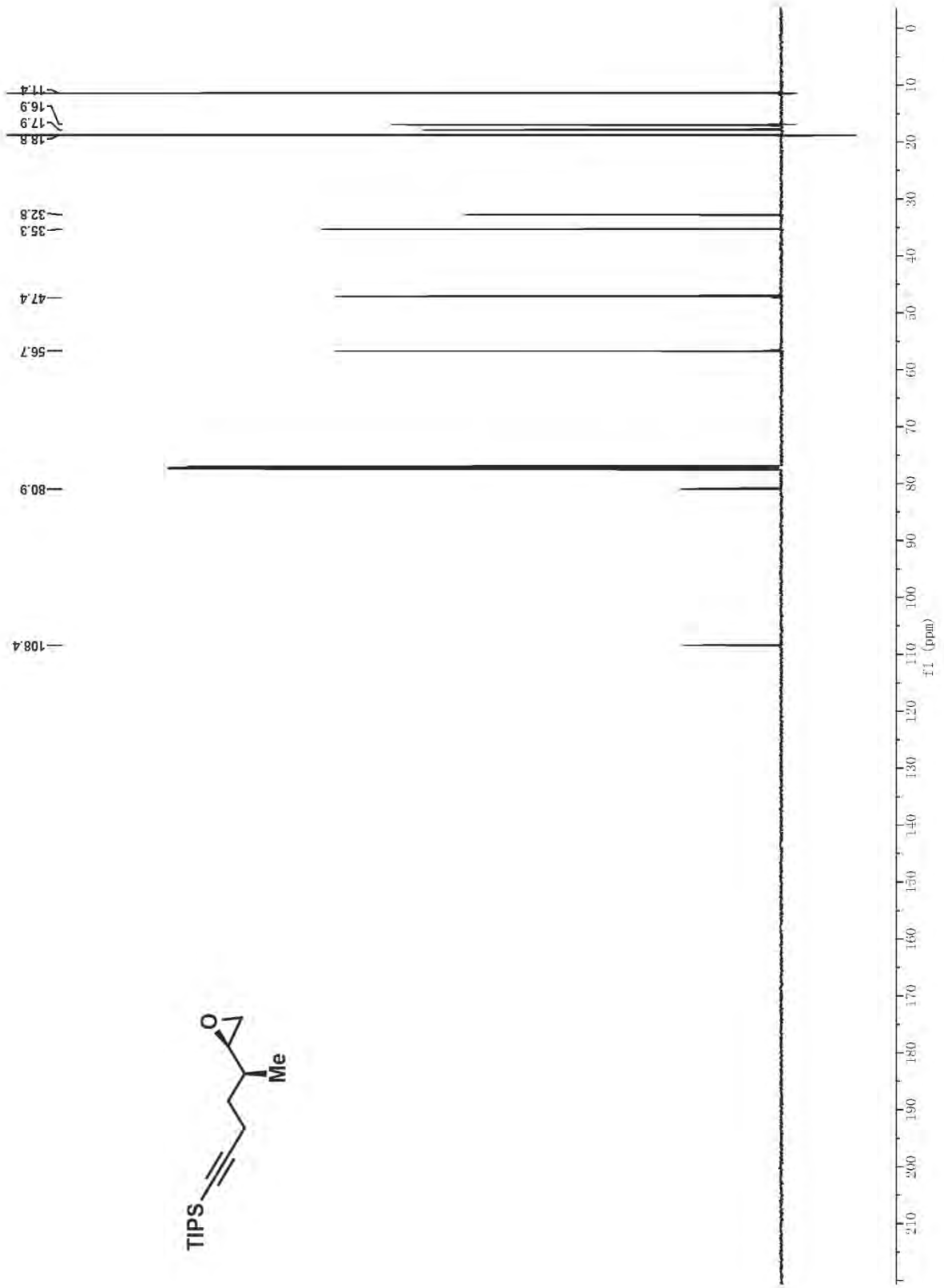
^{13}C NMR: Compound **197**



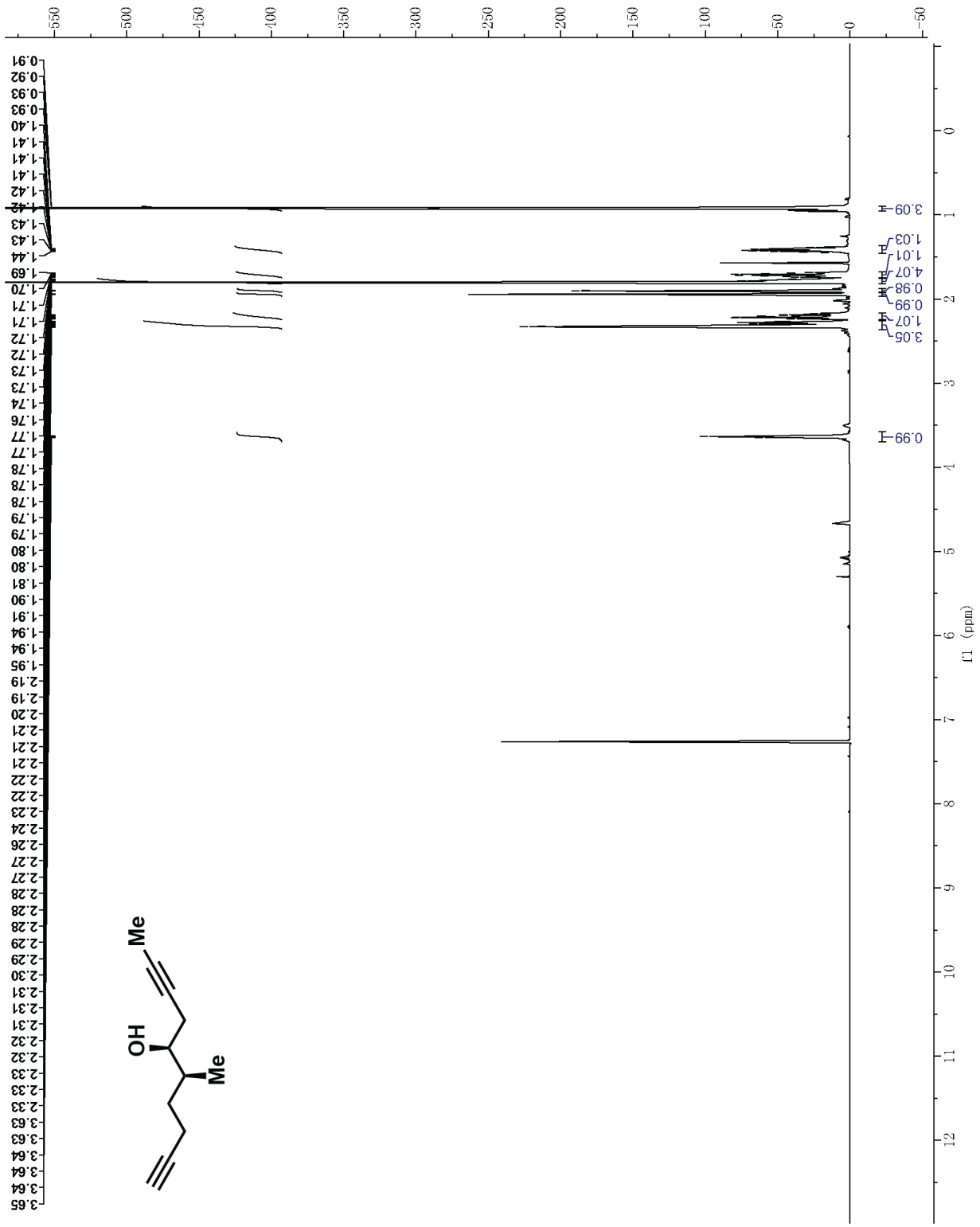
^{1}H NMR: Compound **198**



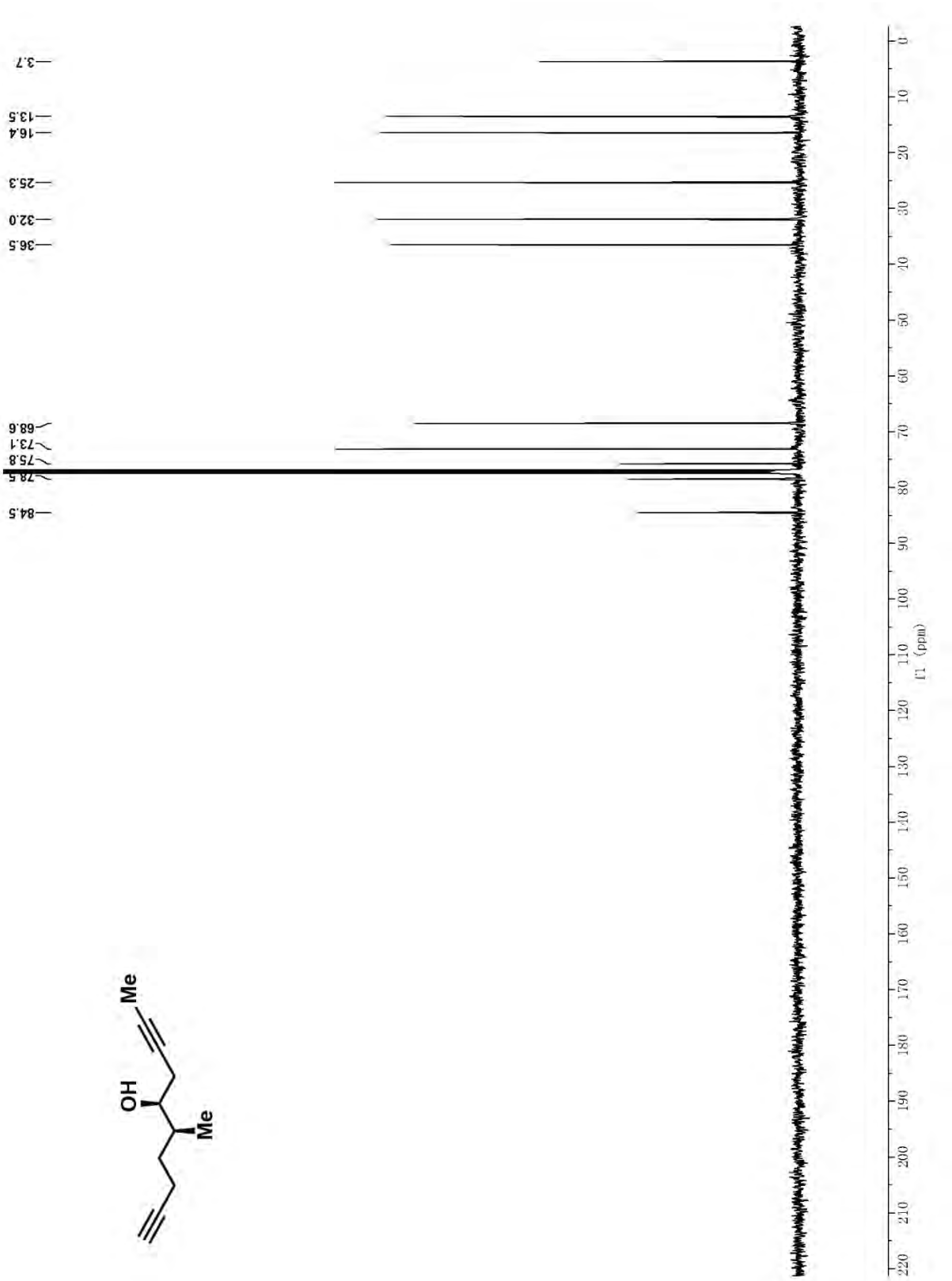
^{13}C NMR: Compound **198**



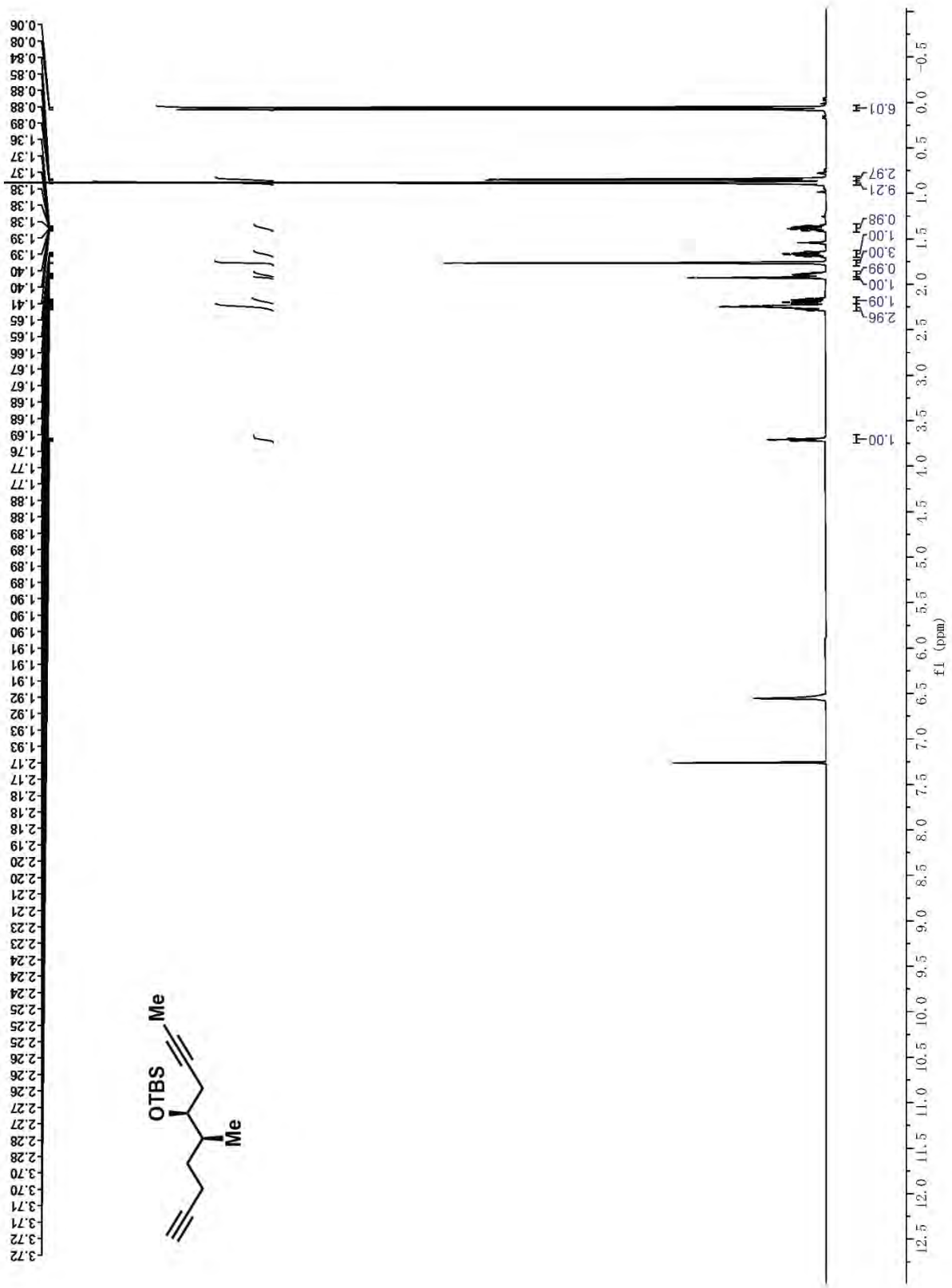
^{1}H NMR: Compound **199**



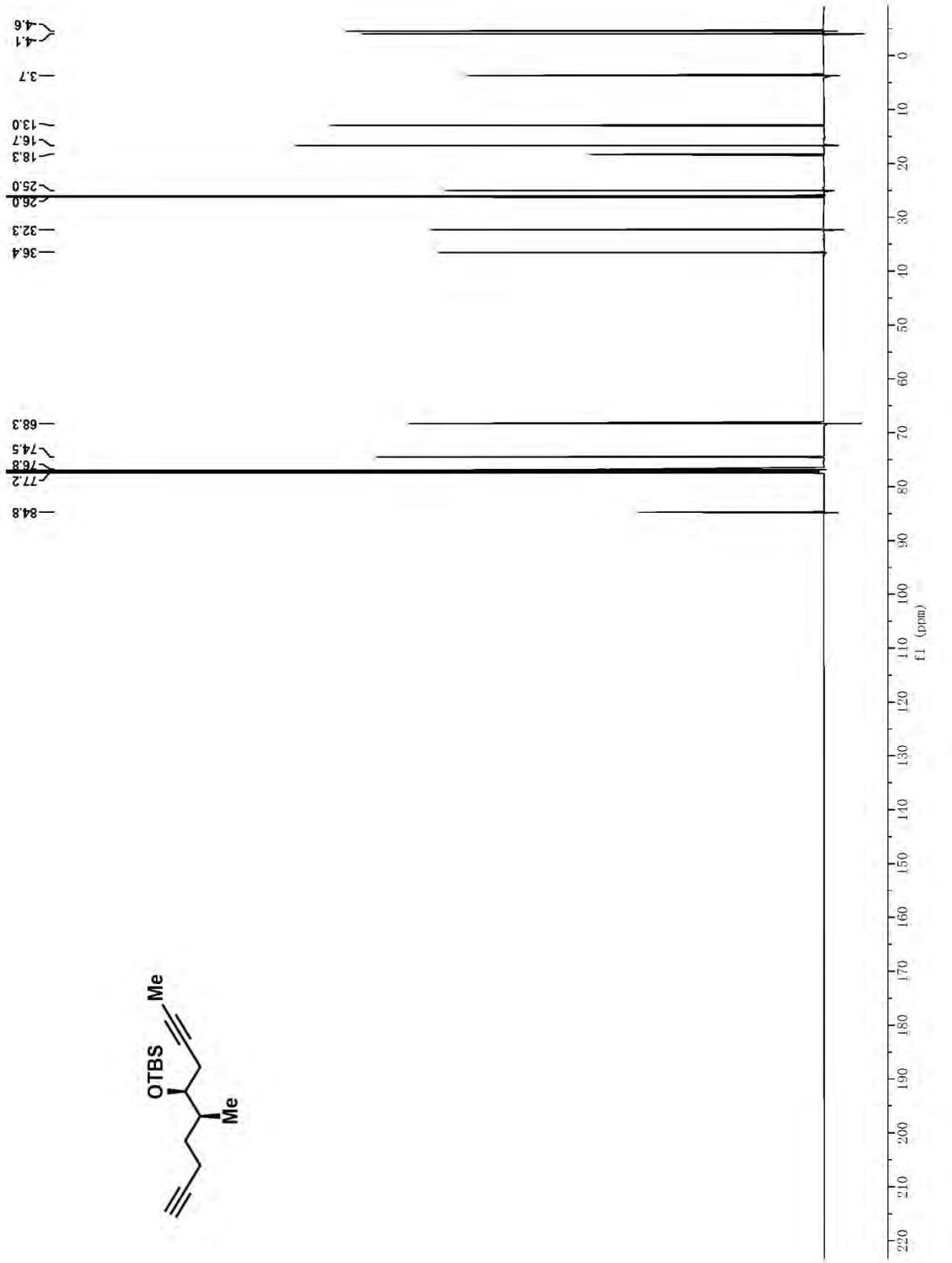
^{13}C NMR: Compound **199**



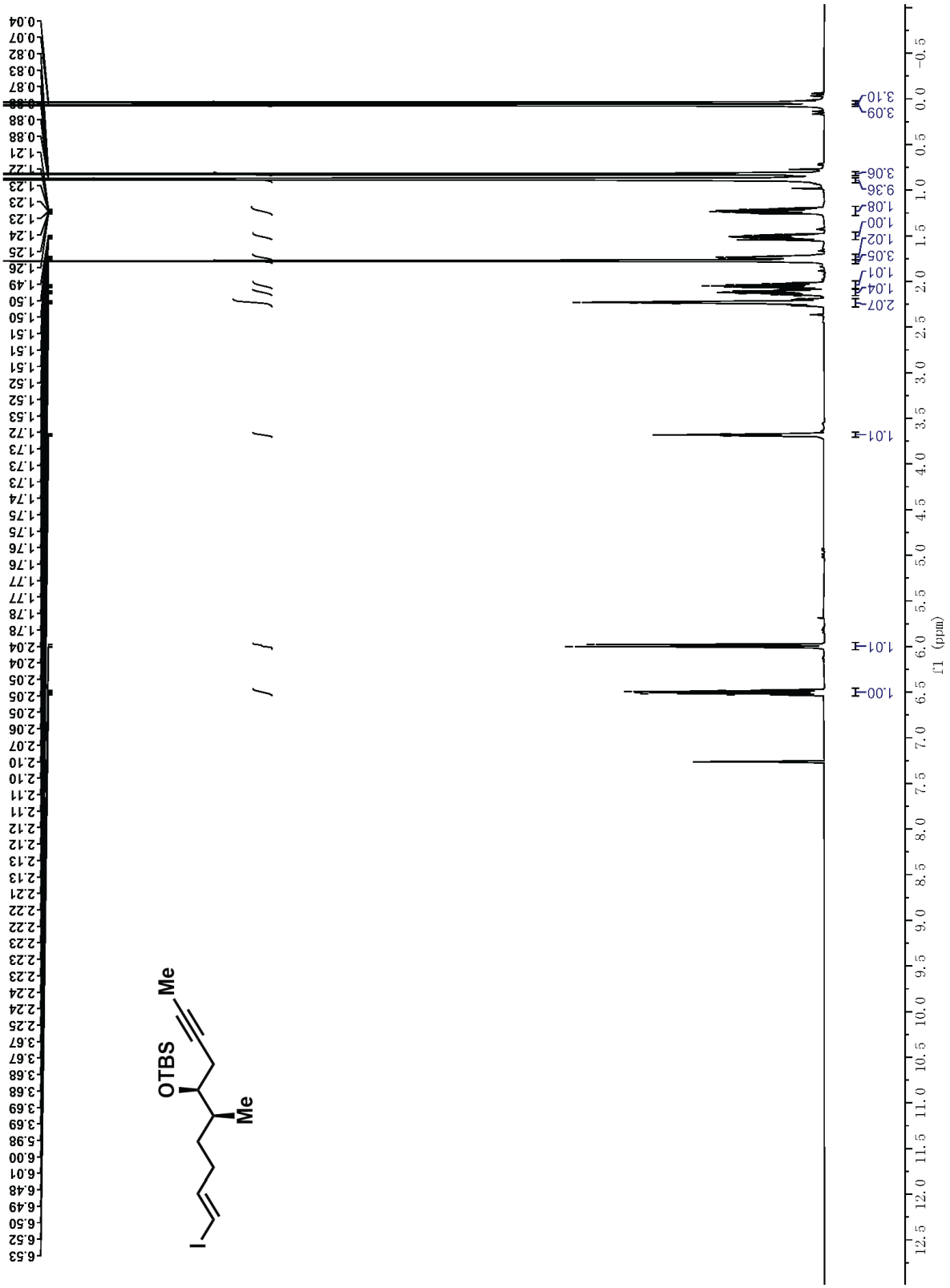
^{1}H NMR: Compound **200**



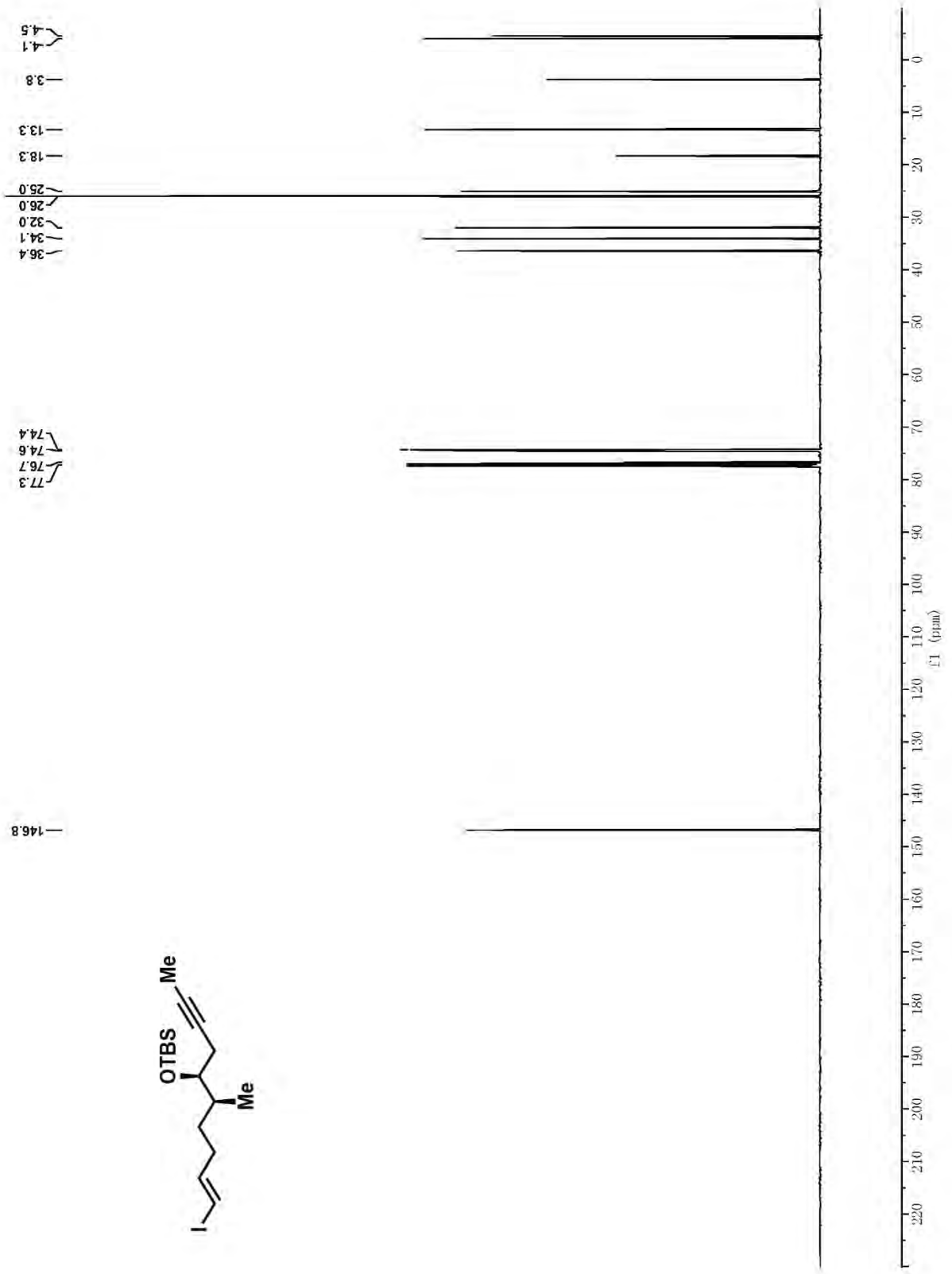
^{13}C NMR: Compound **200**



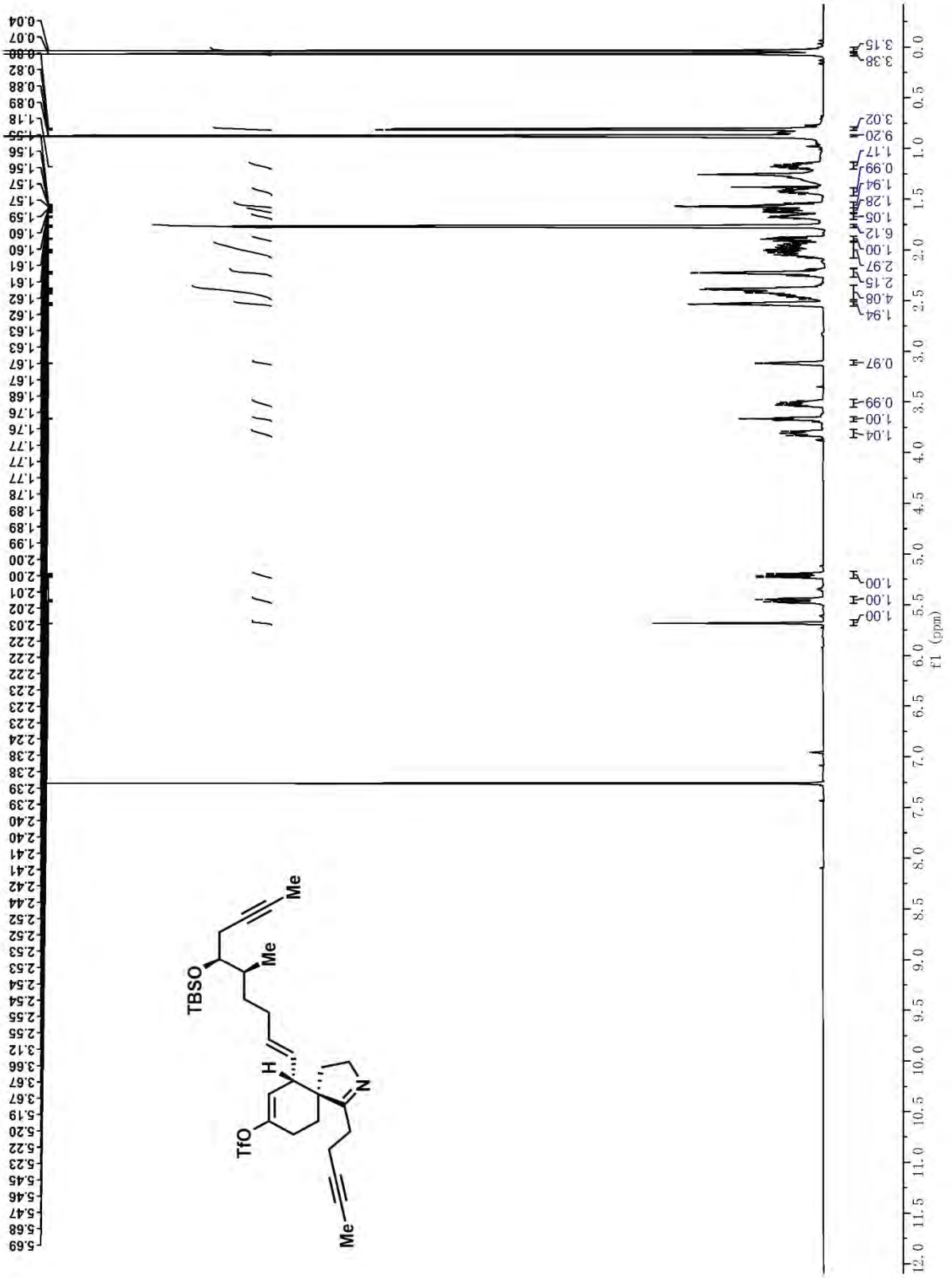
^{1}H NMR: Compound **201**



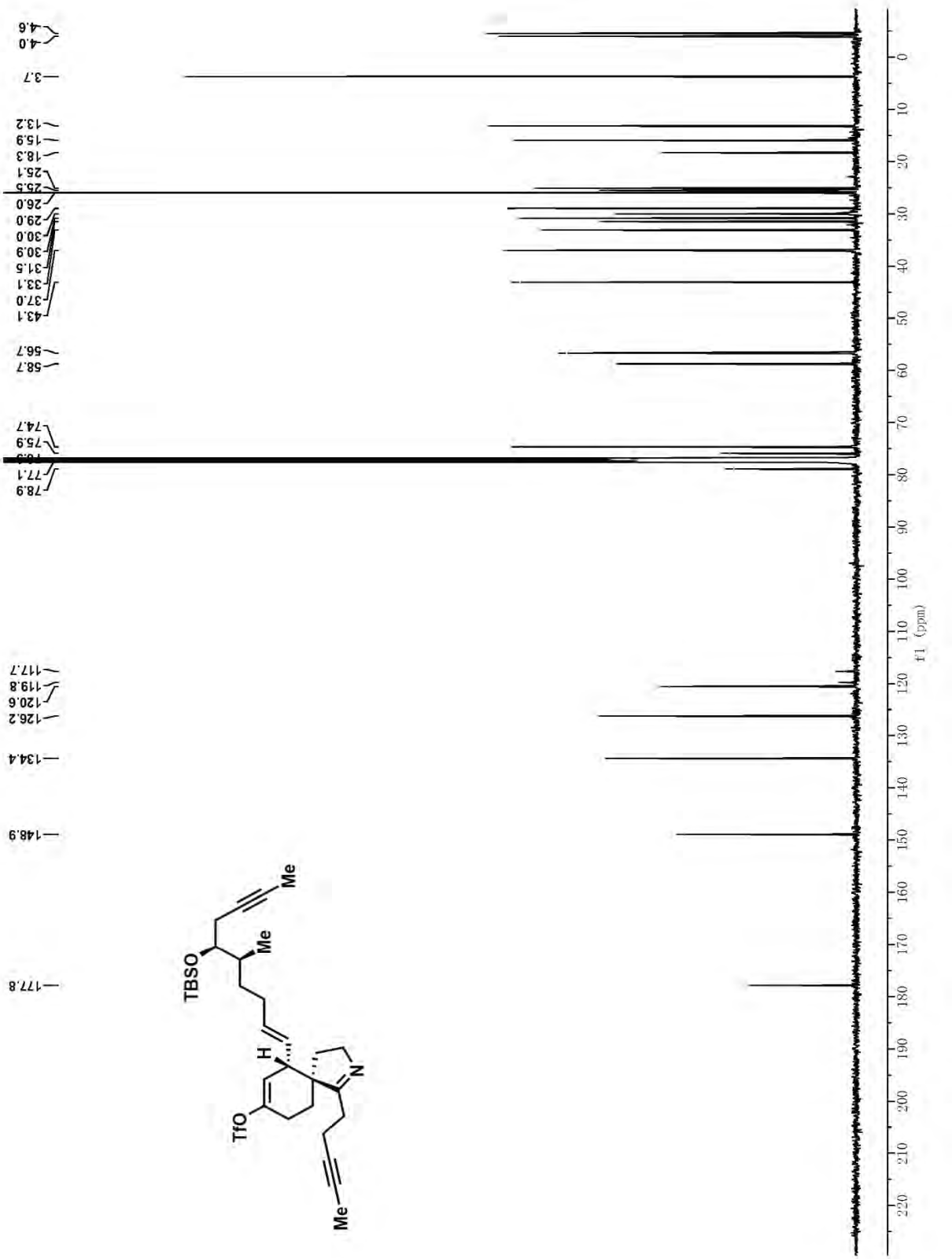
^{13}C NMR: Compound **201**



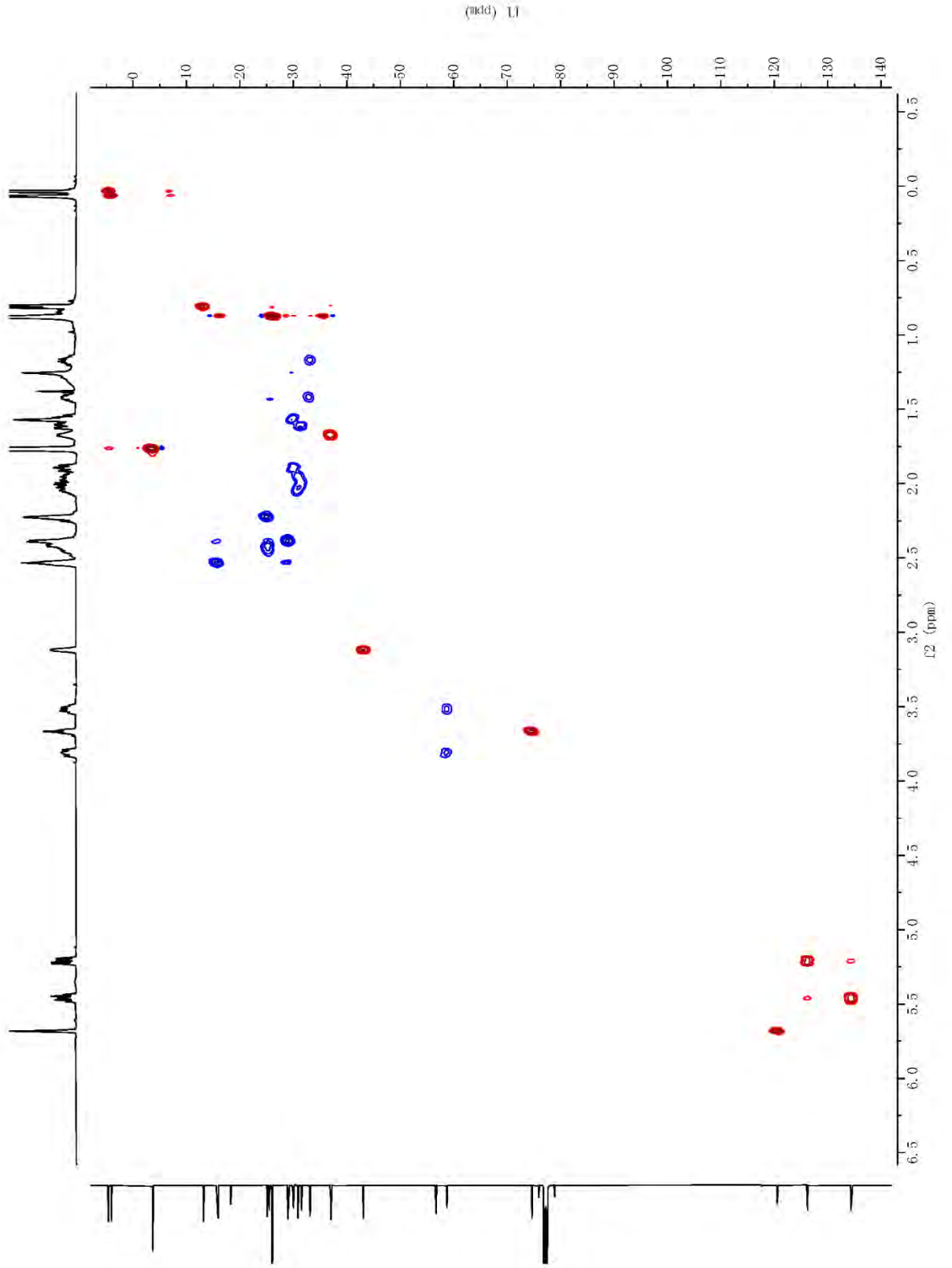
^{1}H NMR: Compound **203**



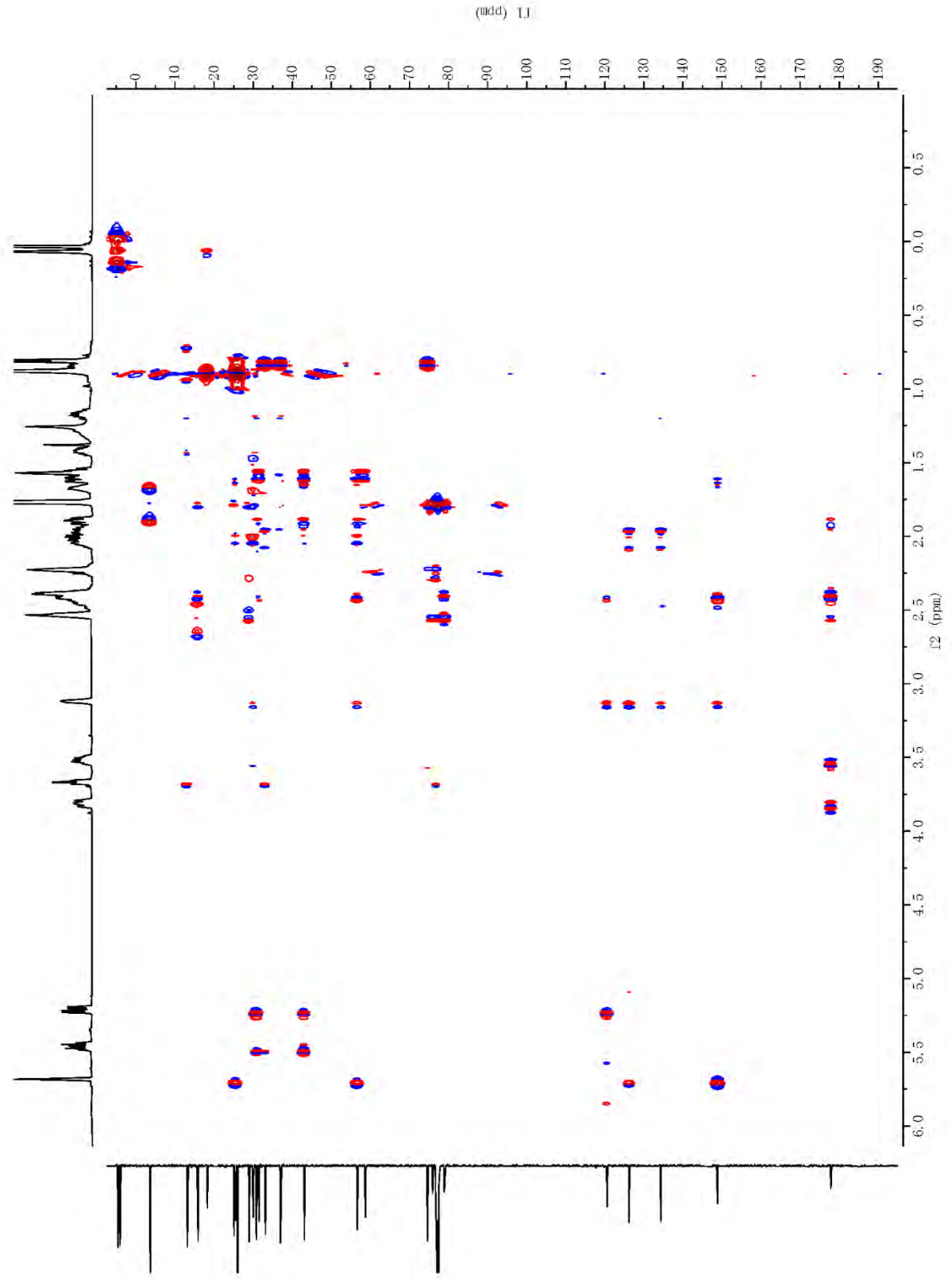
^{13}C NMR: Compound **203**



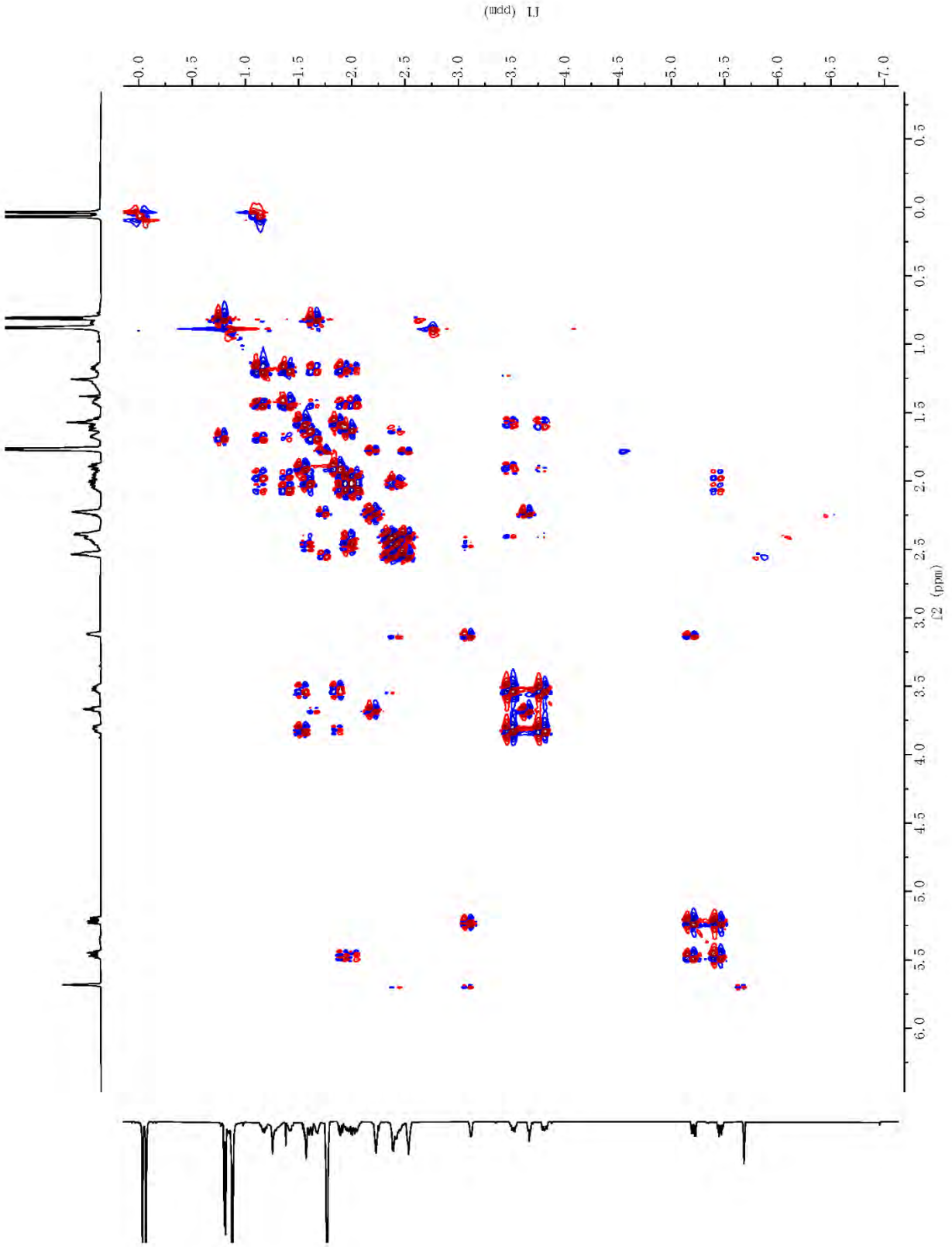
^{1}H-^{13}C-HSQC: Compound **203**



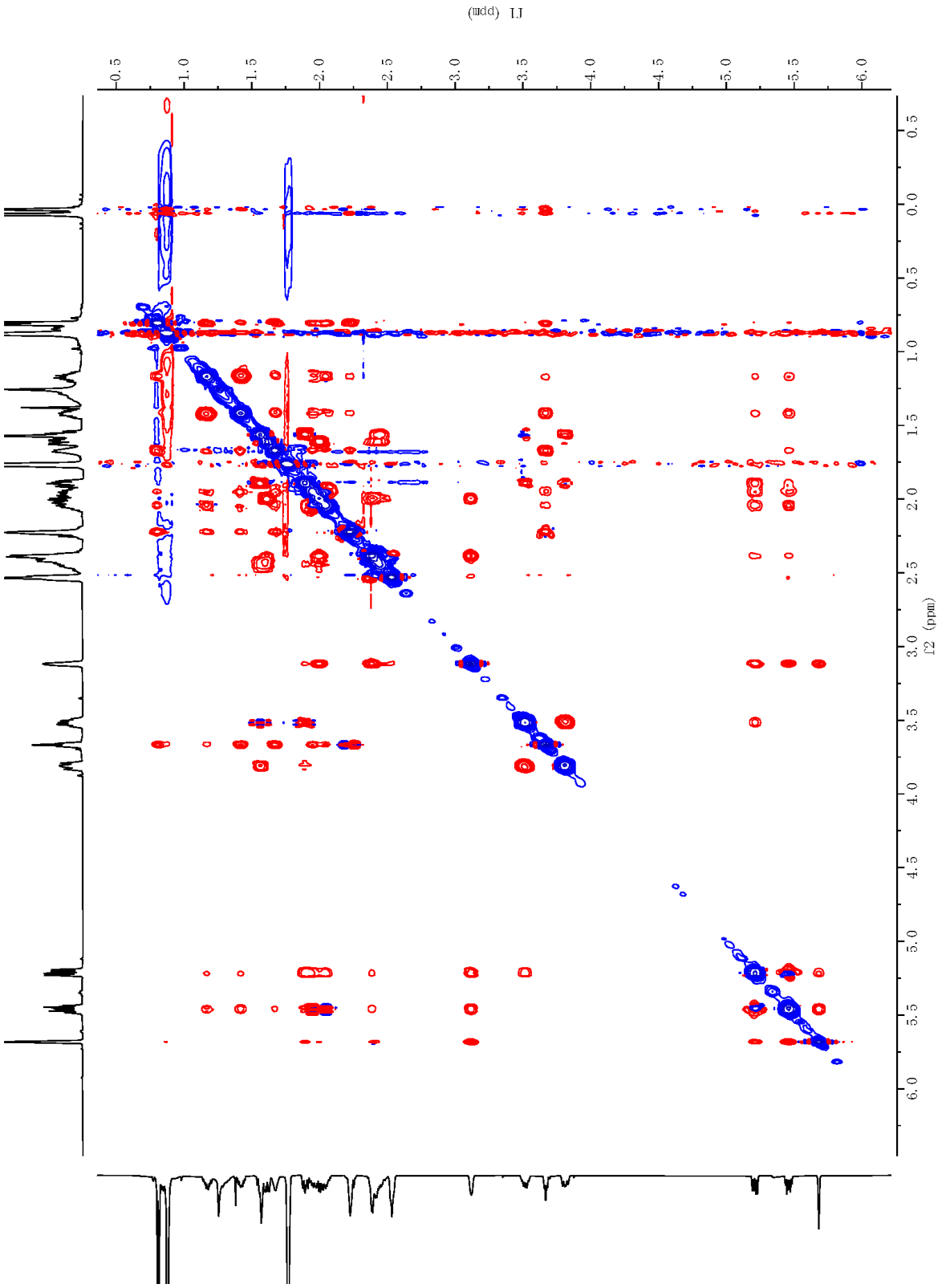
^{1}H-^{13}C-HMBC: Compound **203**



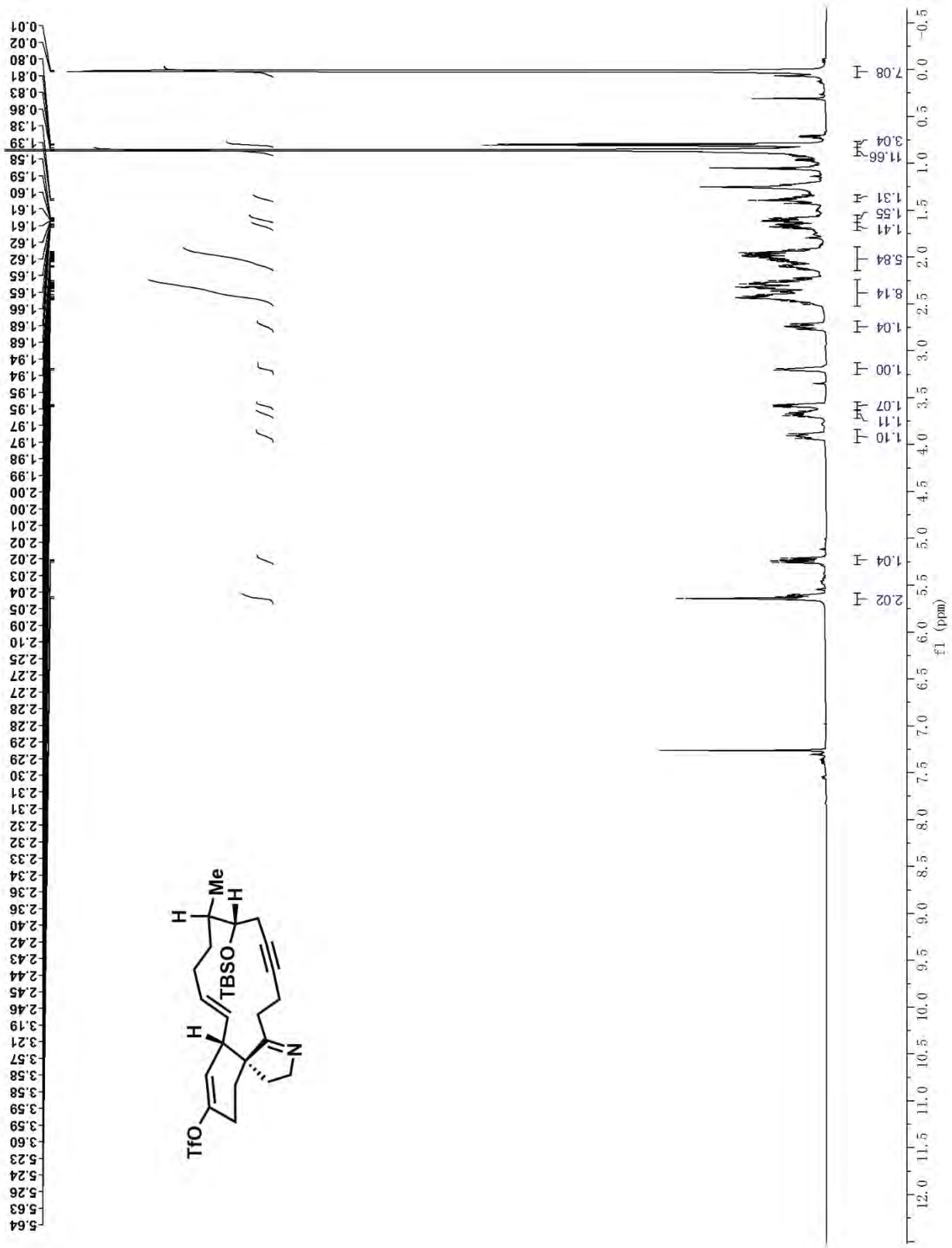
^{1}H-^{1}H-COSY: Compound **203**



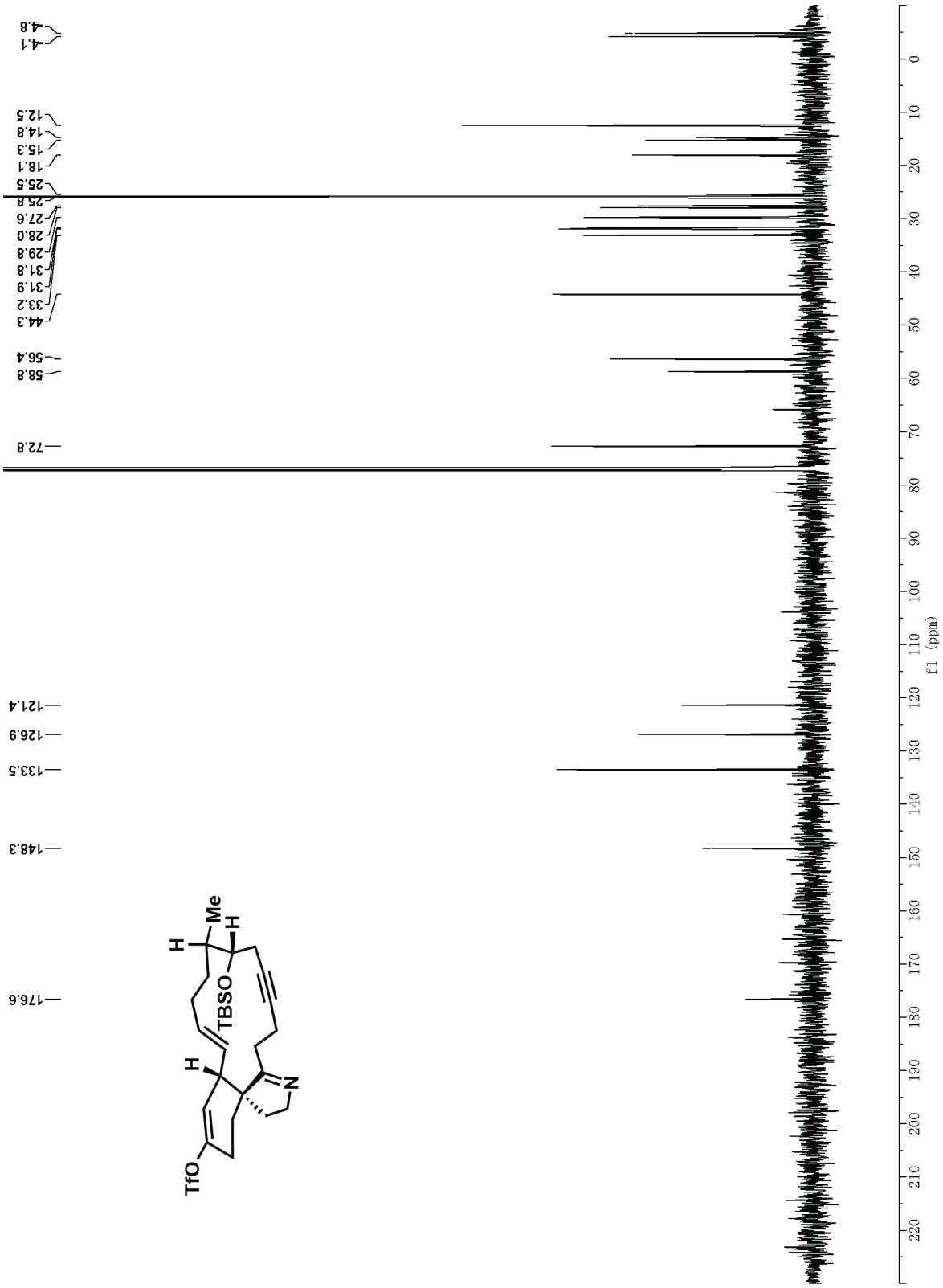
^{1}H-^{1}H-NOESY: Compound **203**



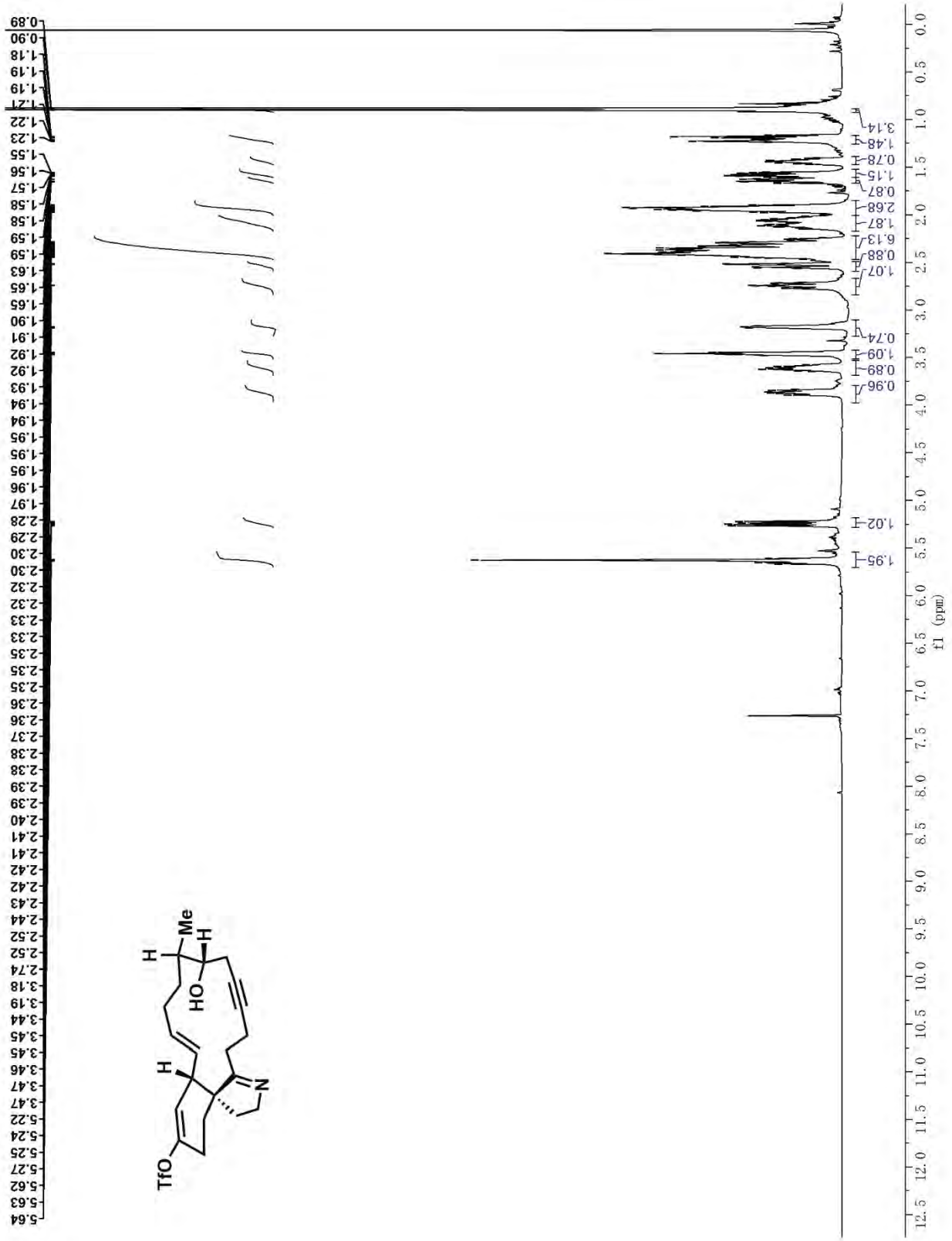
^{1}H NMR: Compound **204**



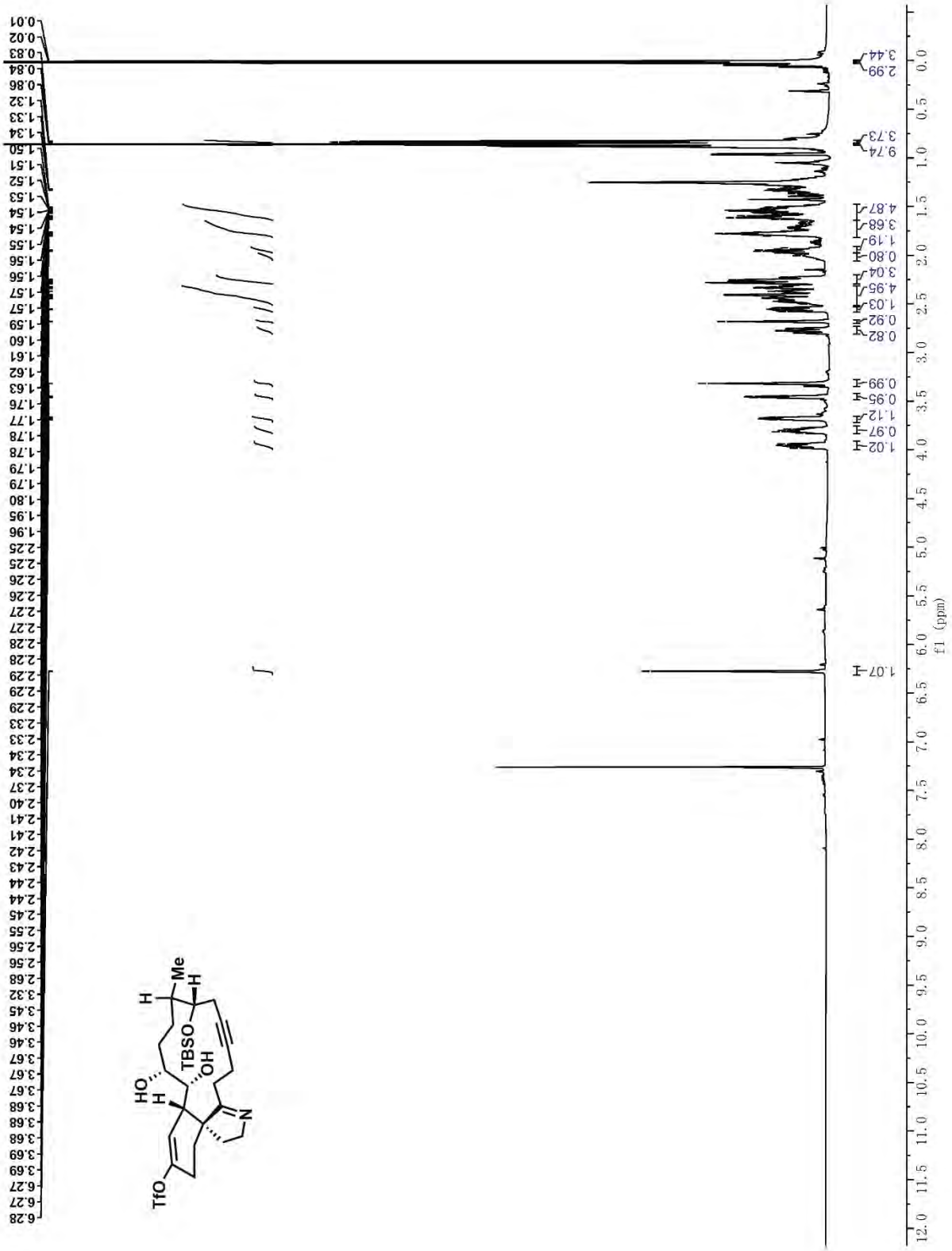
^{13}C NMR: Compound **204**



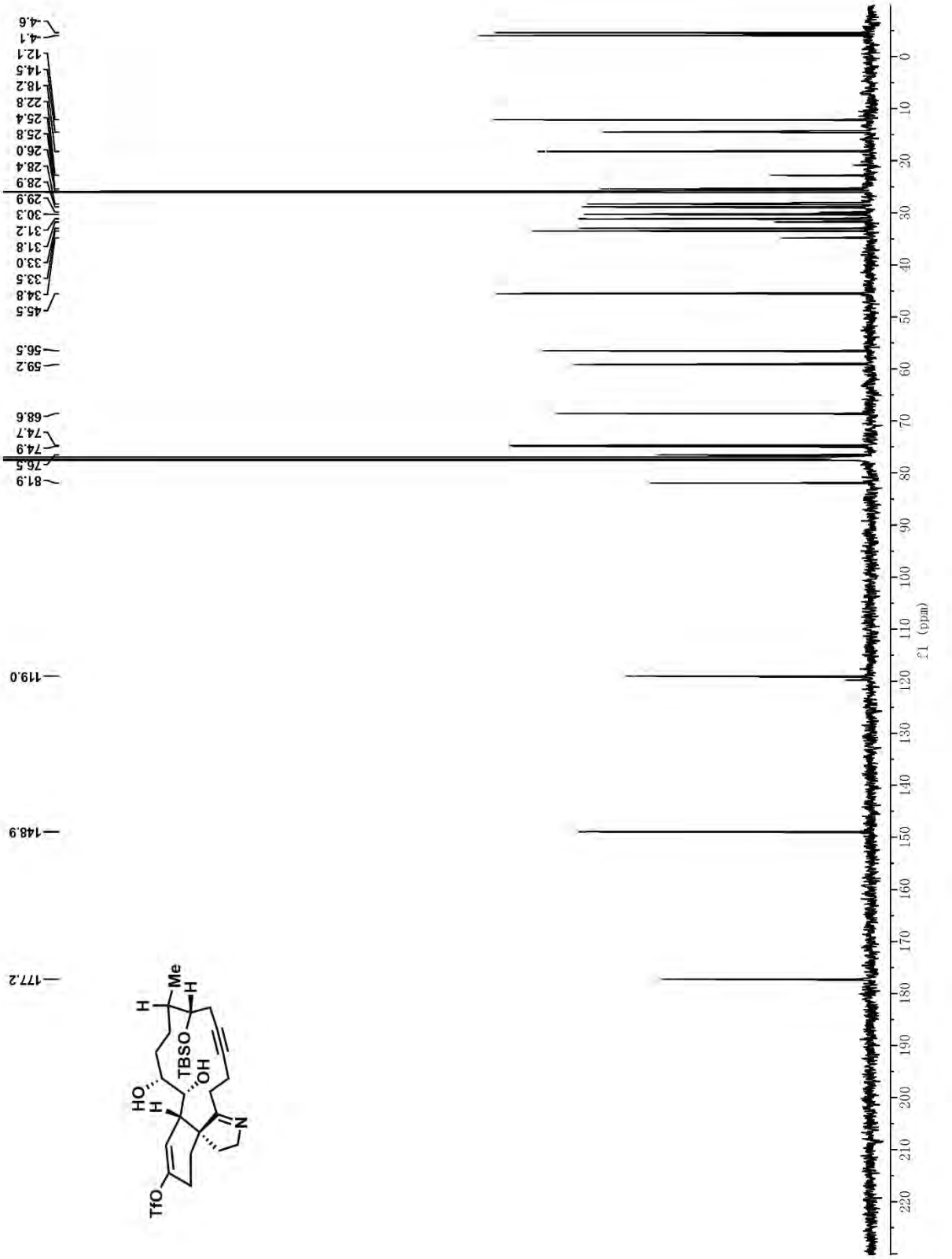
^{1}H NMR: Compound **205**



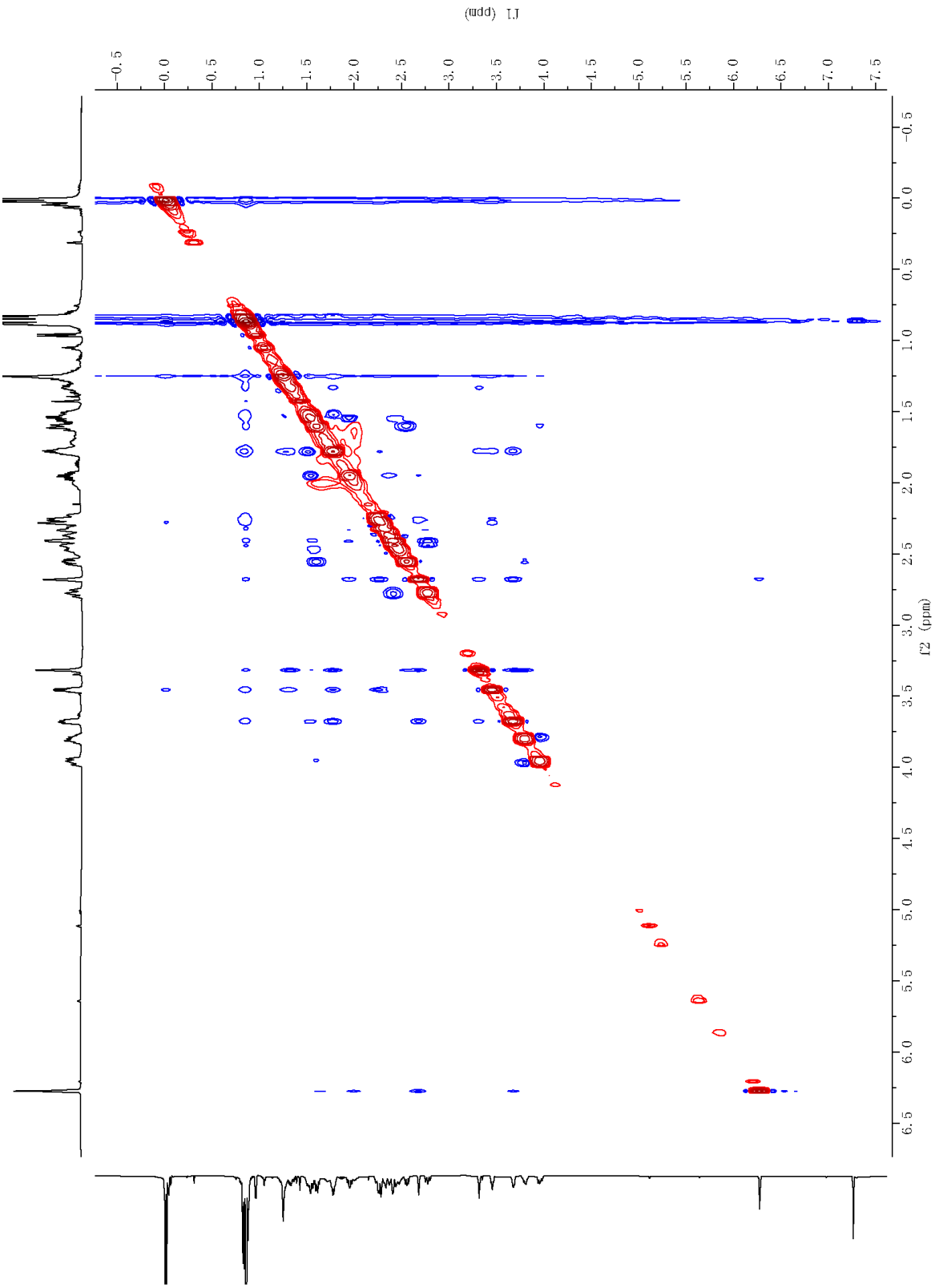
^{1}H NMR: Compound **206**



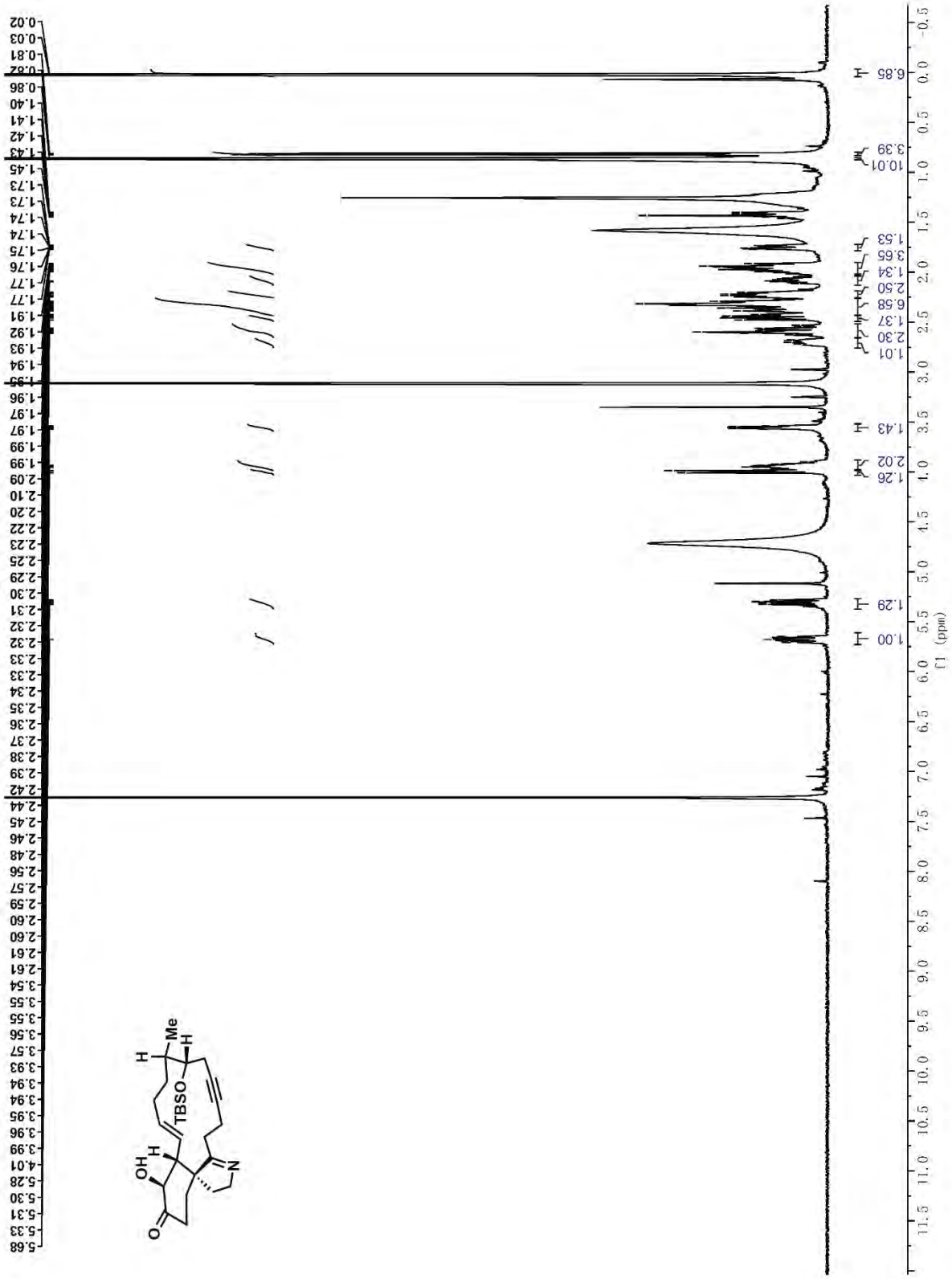
^{13}C NMR: Compound **206**



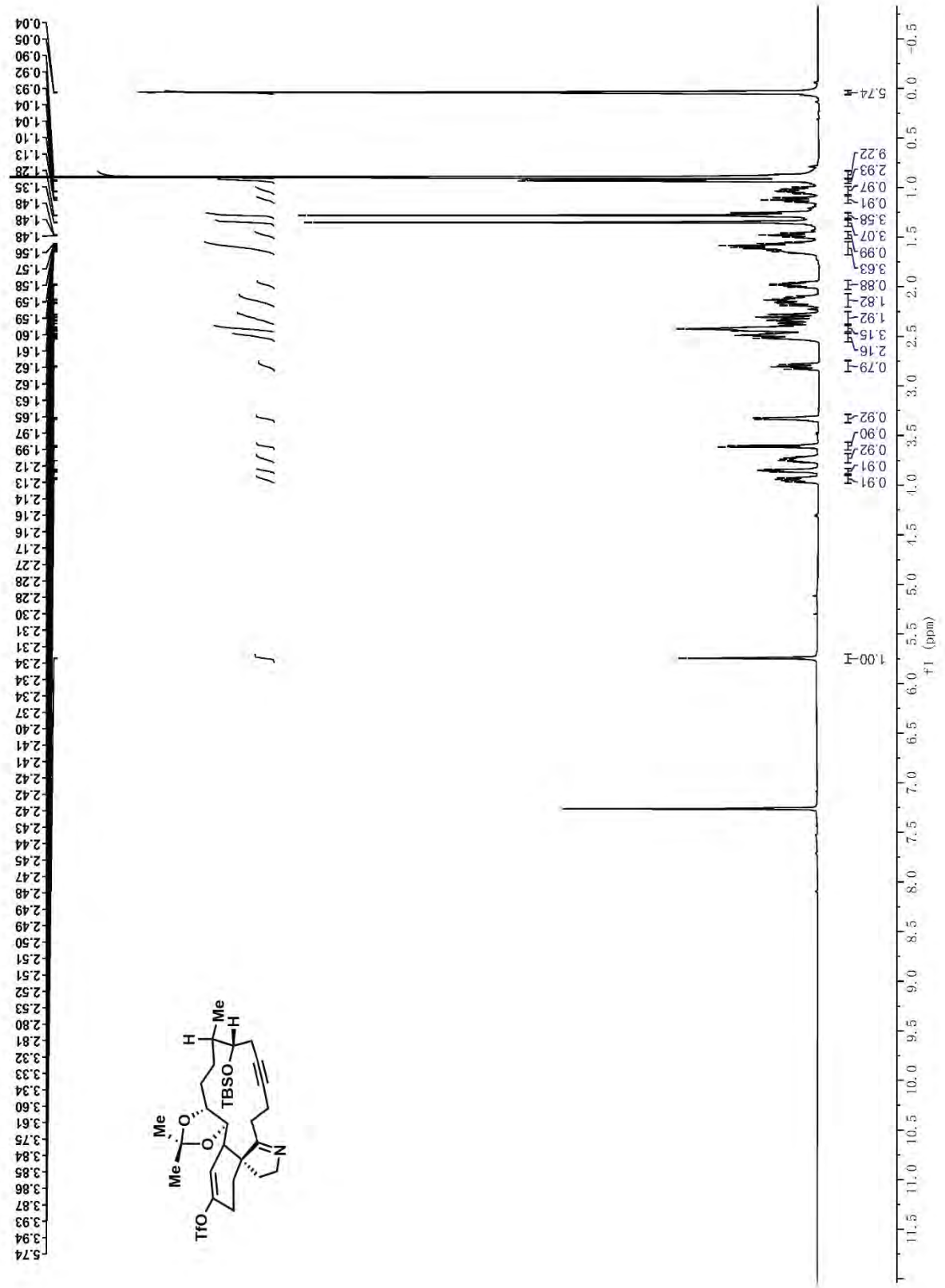
^{1}H-^{1}H-NOESY: Compound **206**



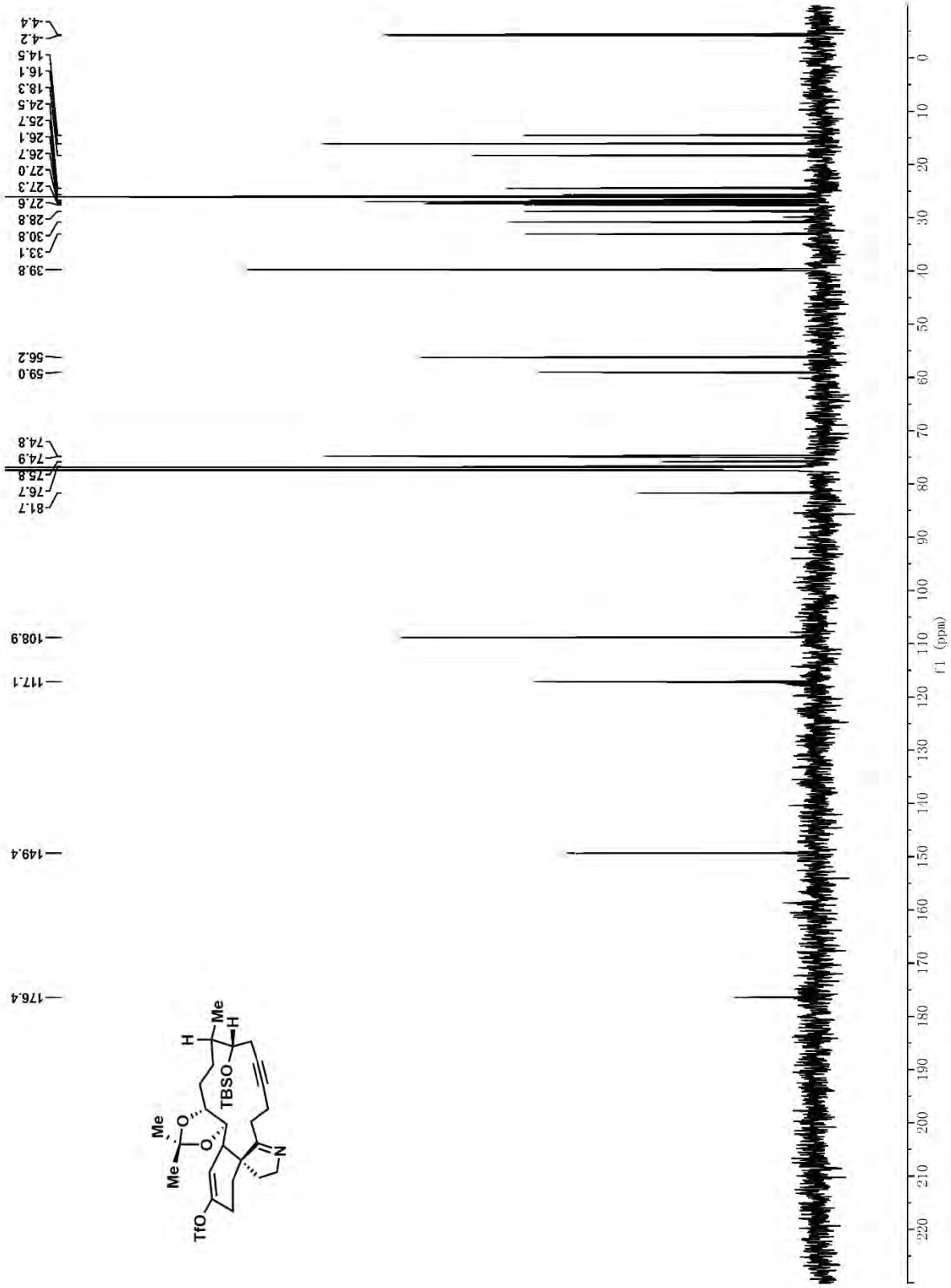
^{1}H NMR: Compound **208**



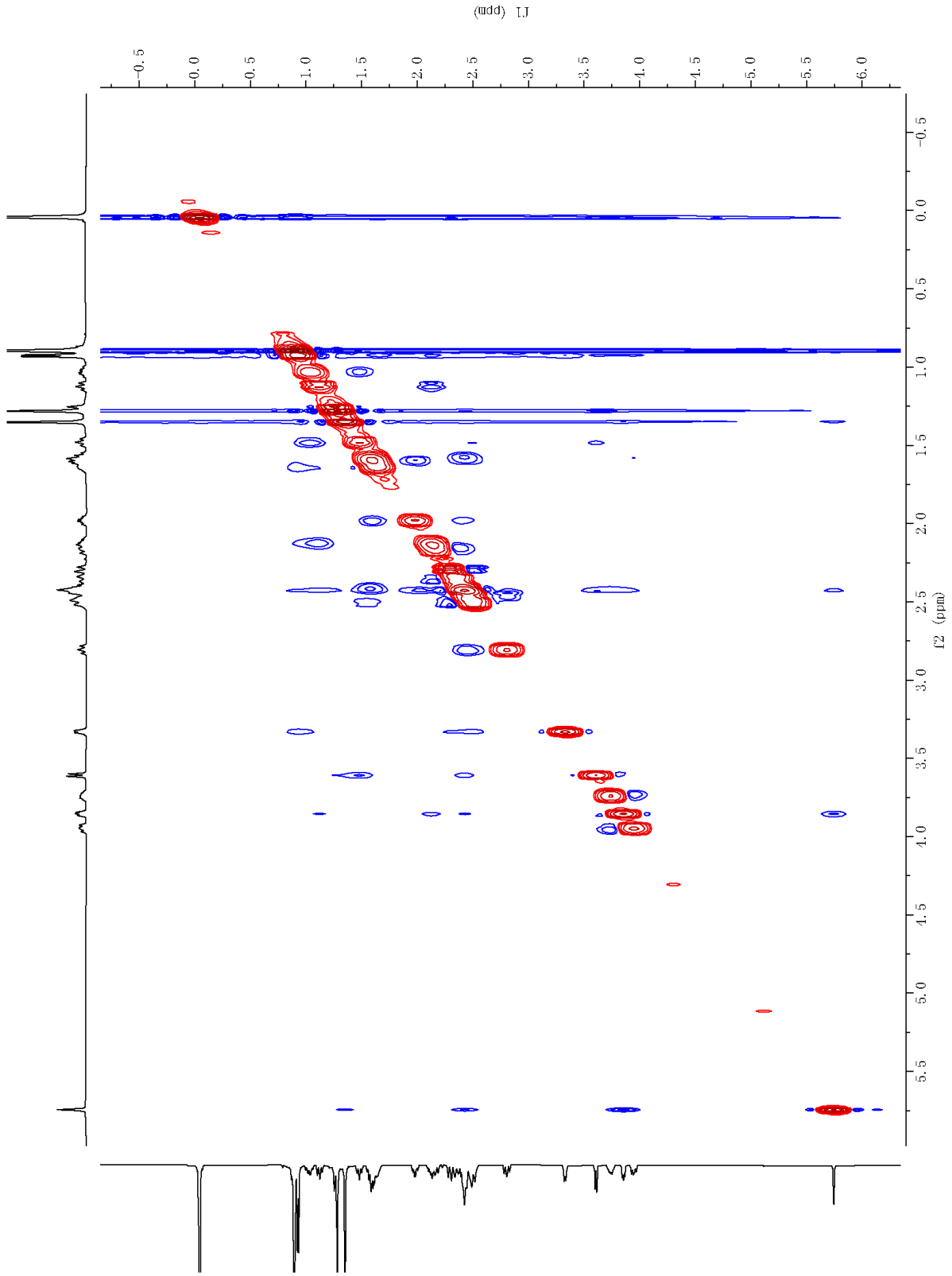
^{1}H NMR: Compound **209**



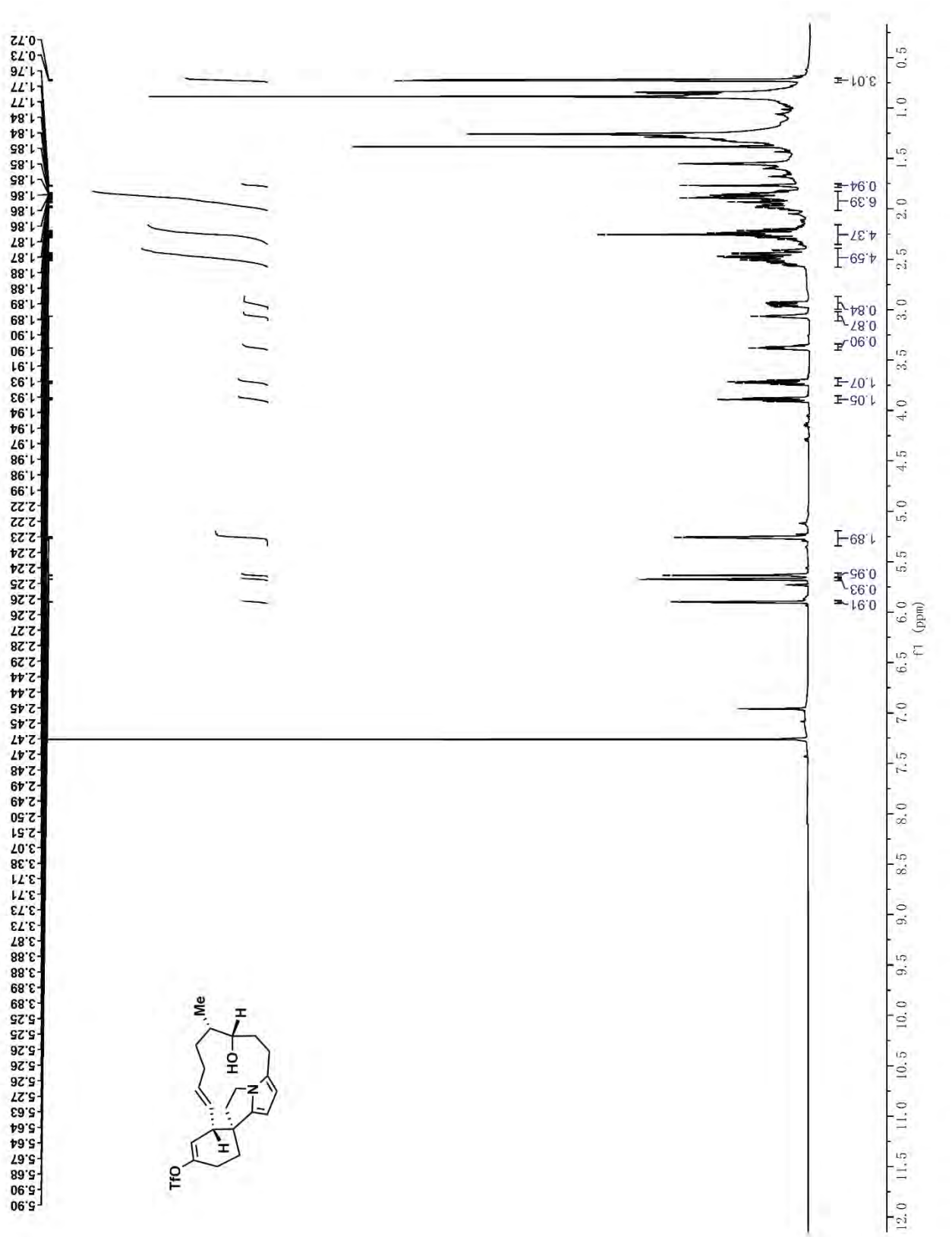
^{13}C NMR: Compound **209**



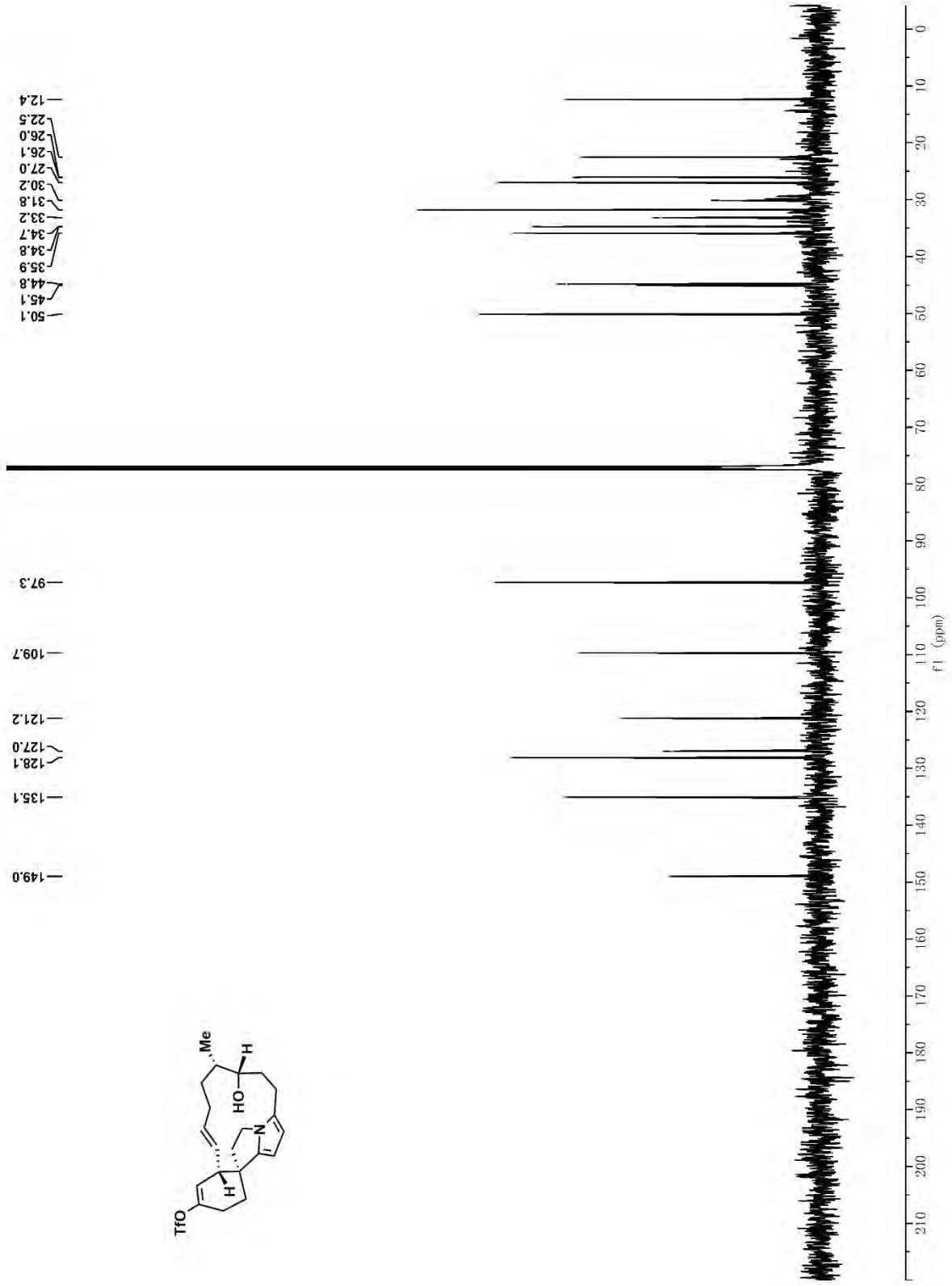
^{1}H-^{1}H-NOESY: Compound **209**



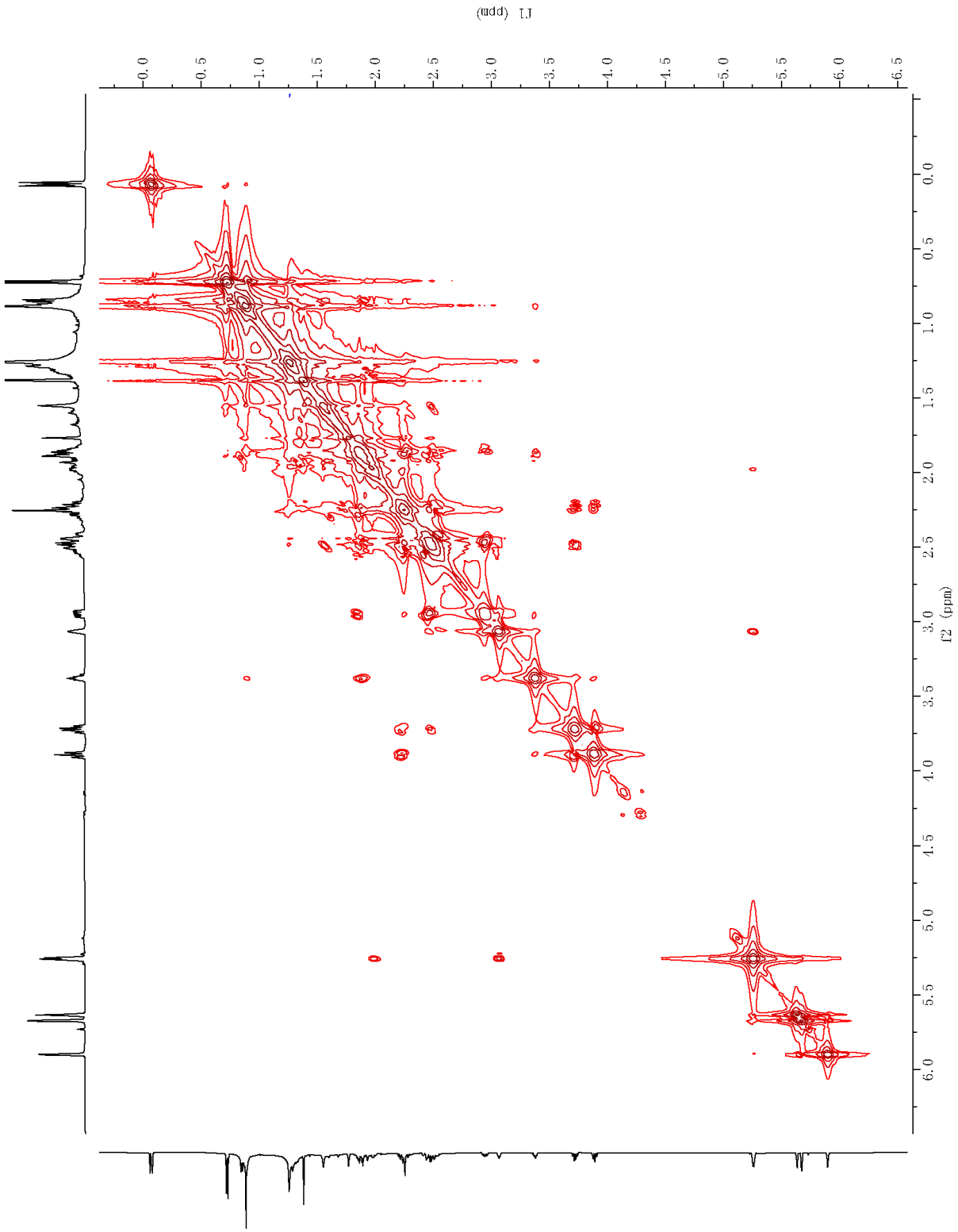
^{1}H NMR: Compound **212**



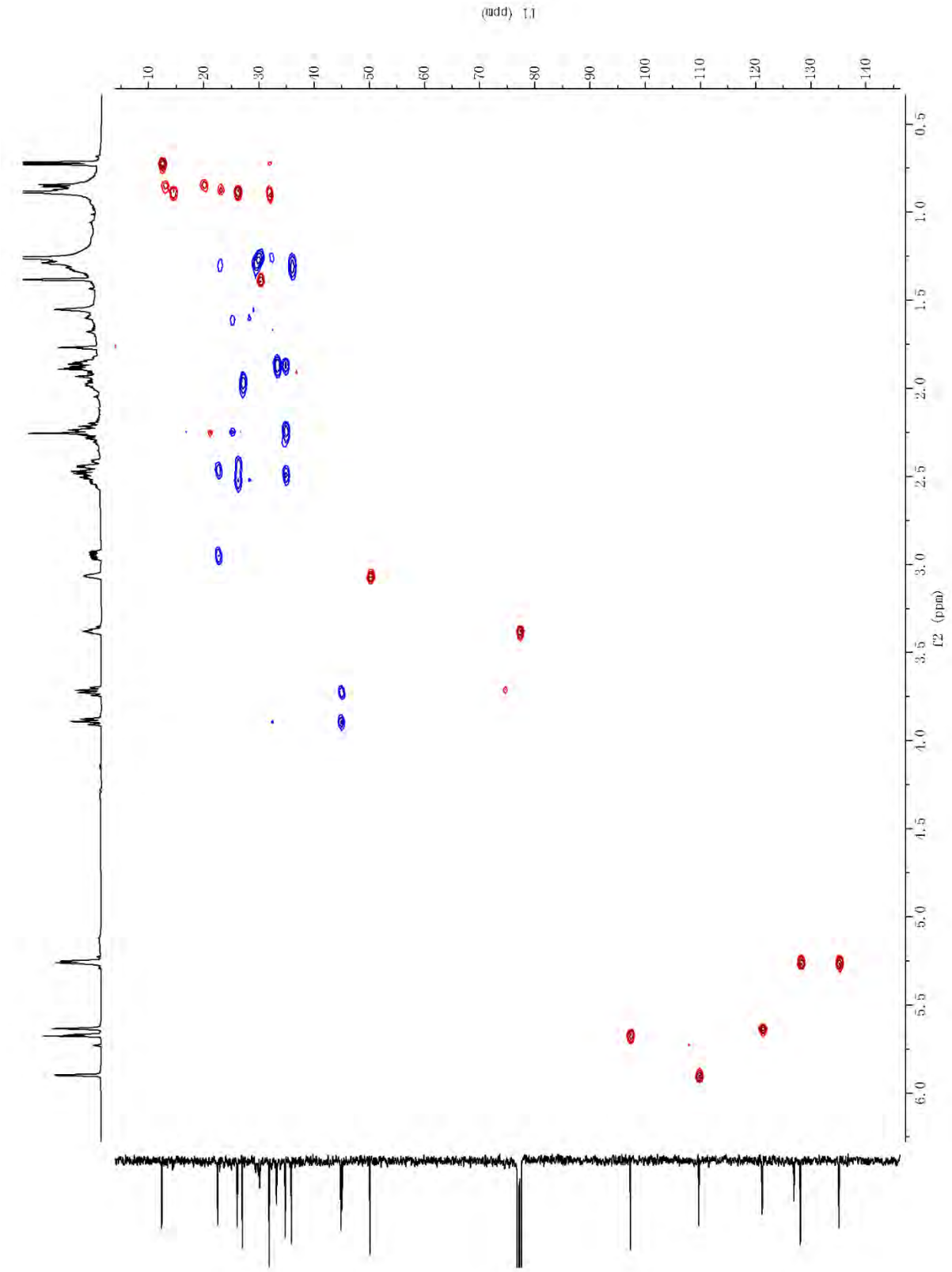
^{13}C NMR: Compound **212**



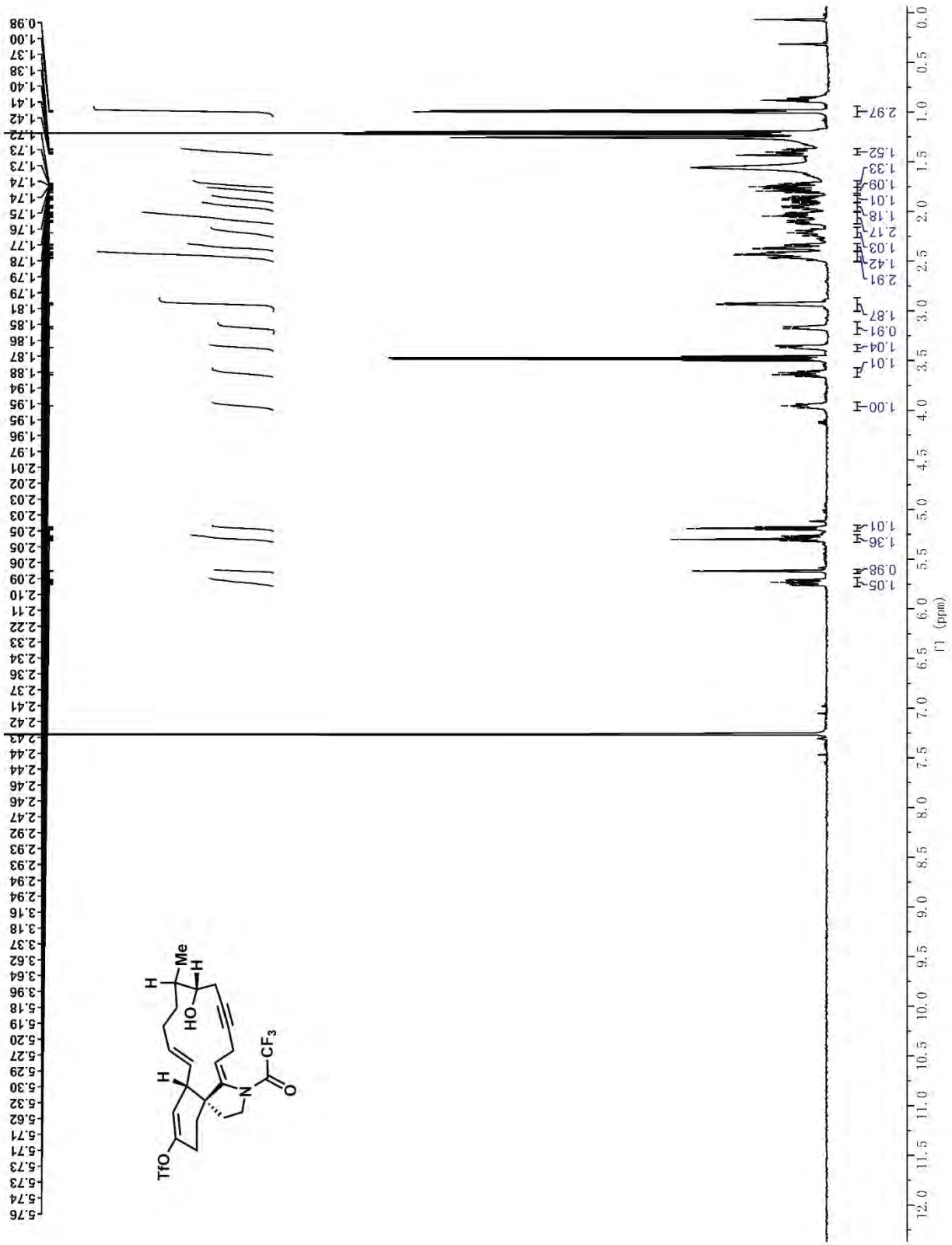
^{1}H-^{1}H-COSY: Compound **212**



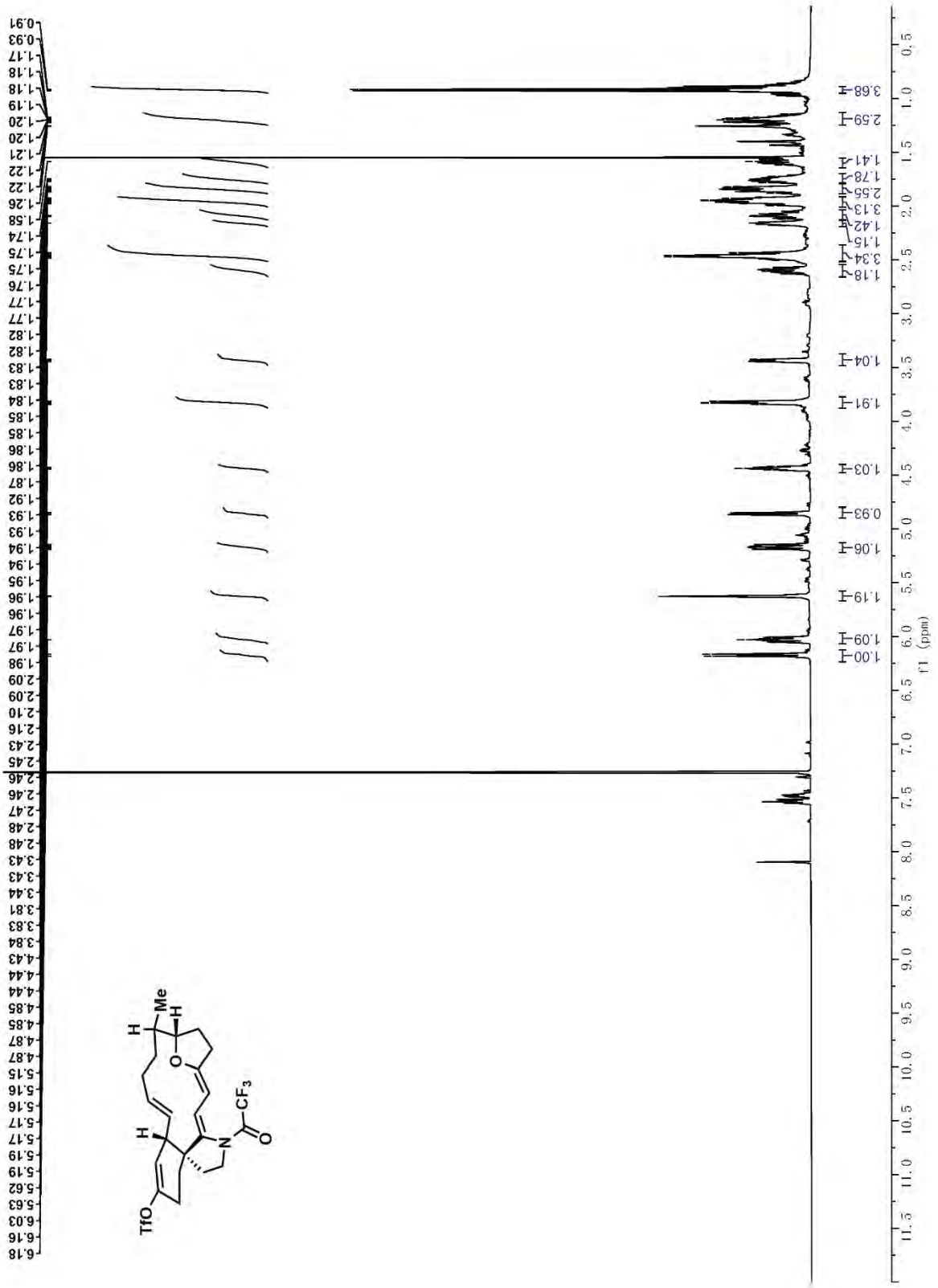
^{1}H-^{13}C-HSQC: Compound **212**



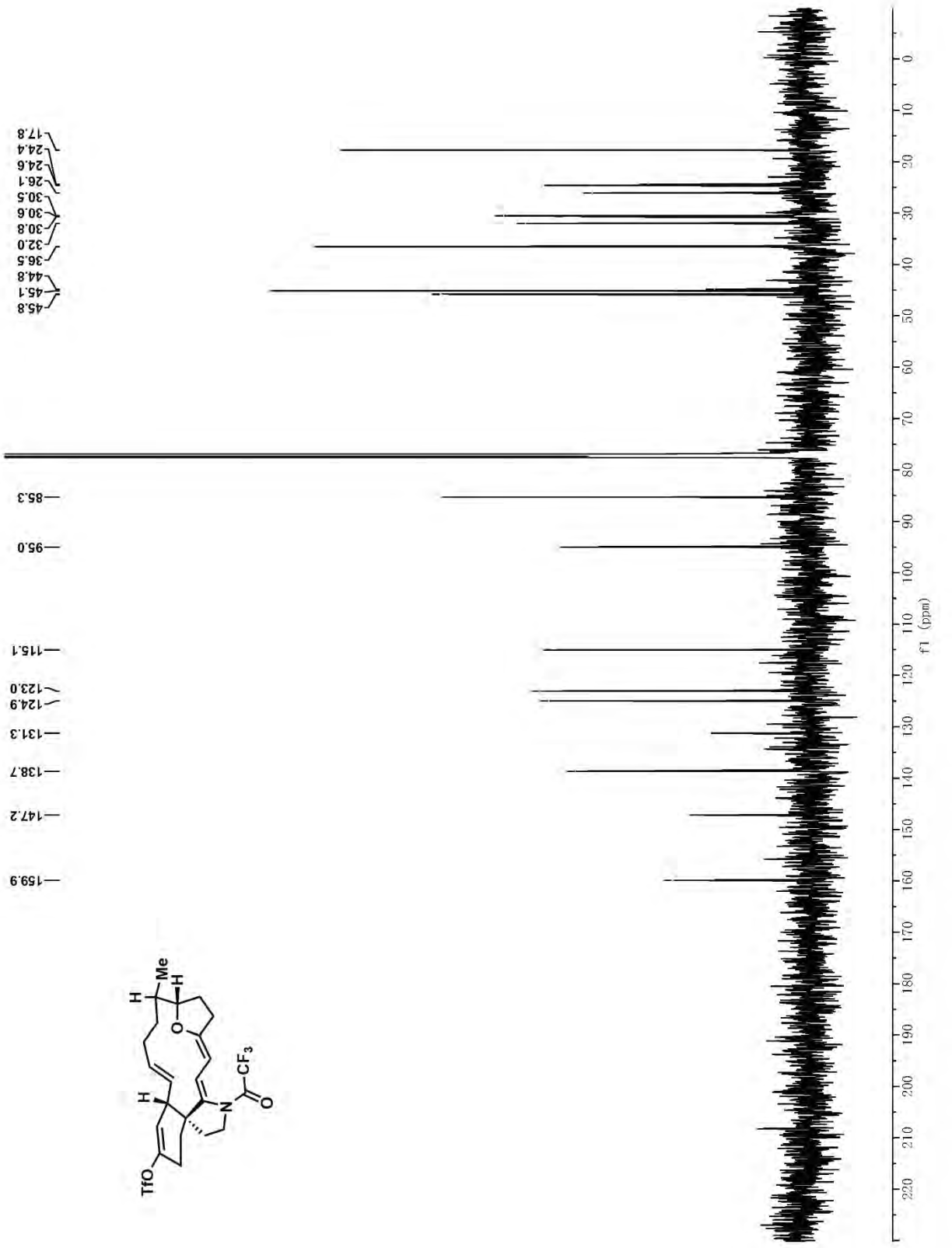
^{1}H NMR: Compound **213**



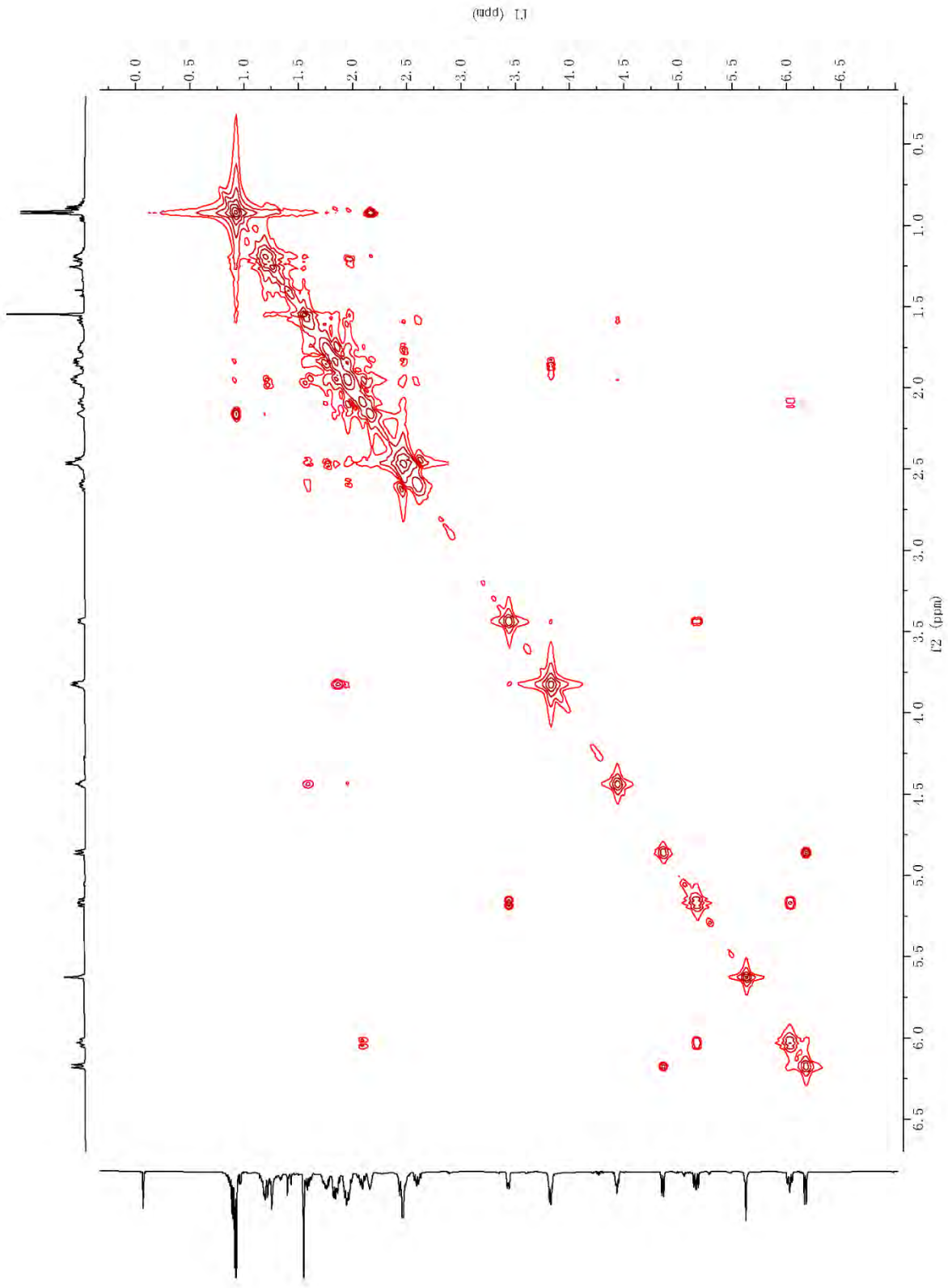
^{1}H NMR: Compound **214**



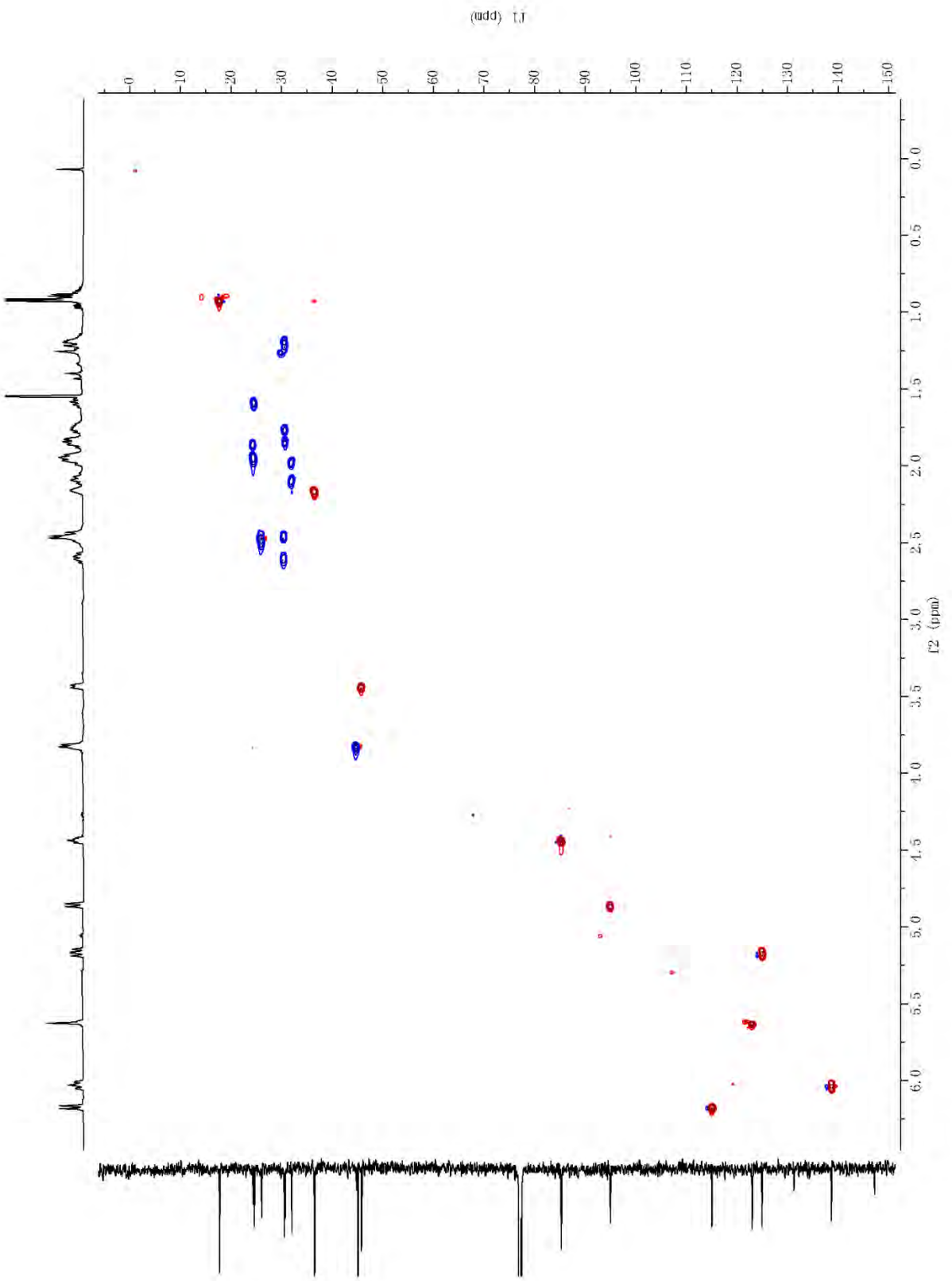
^{13}C NMR: Compound **214**



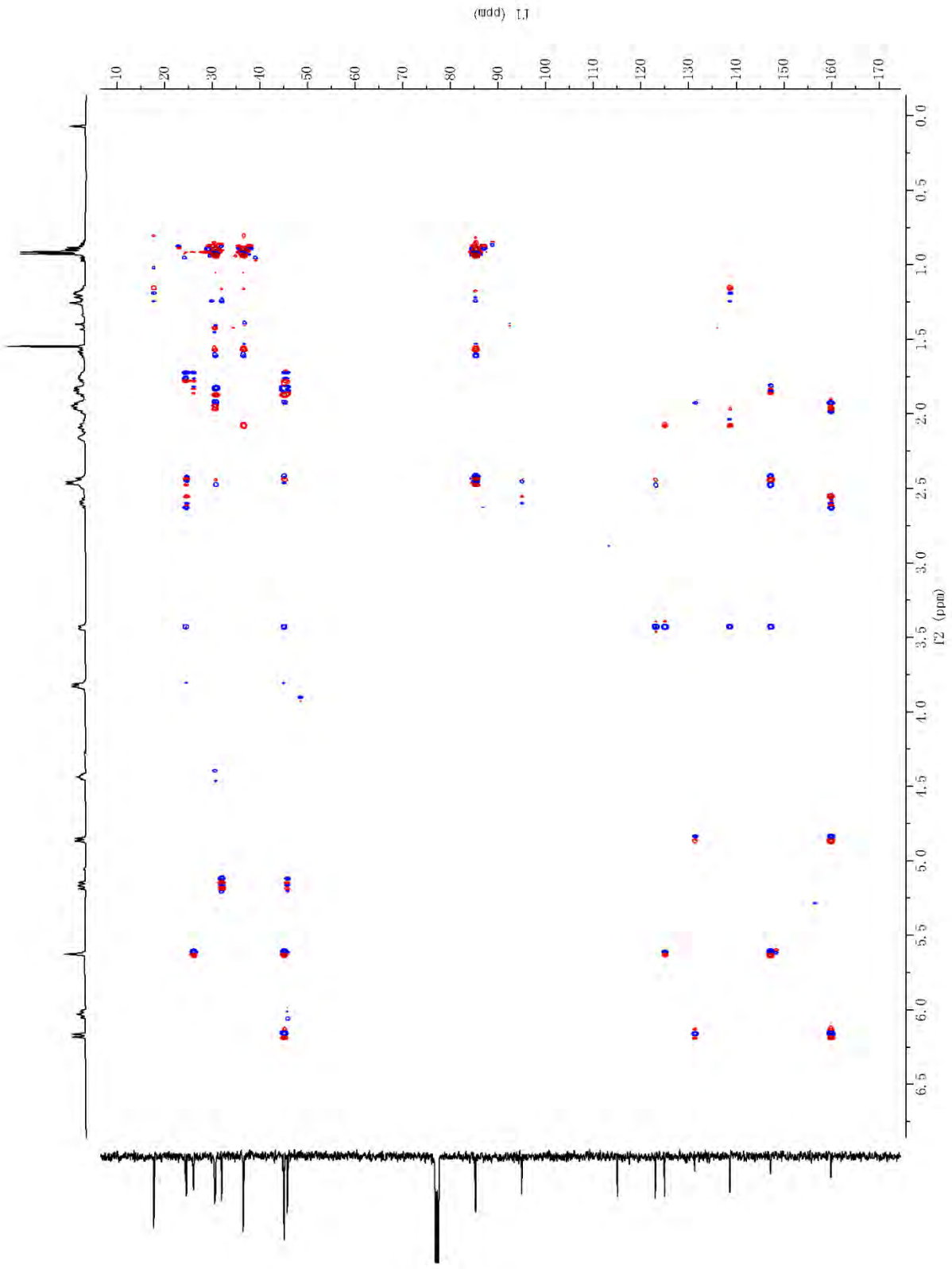
^{1}H-^{1}H-COSY: Compound **214**



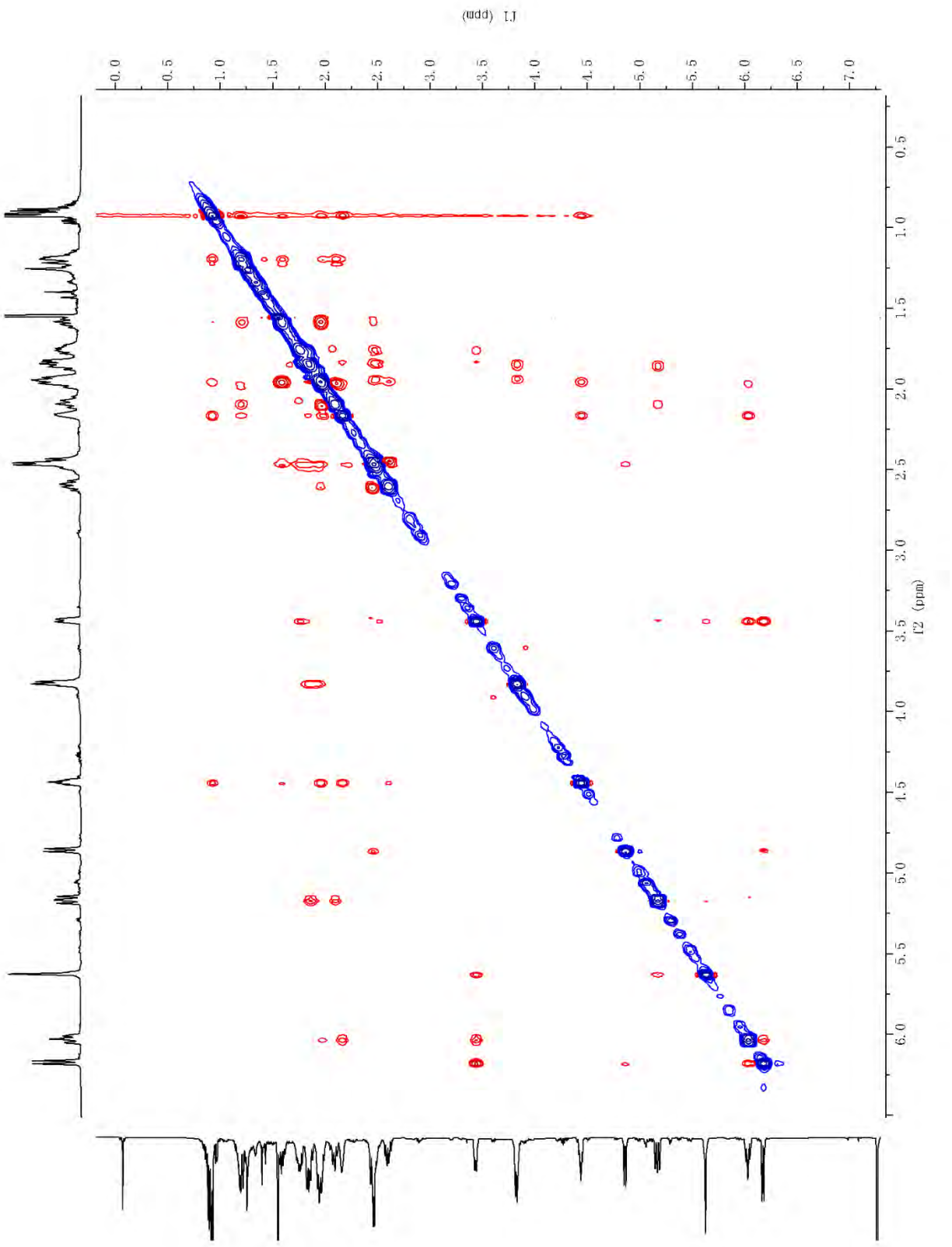
^{1}H-^{13}C-HSQC: Compound **214**



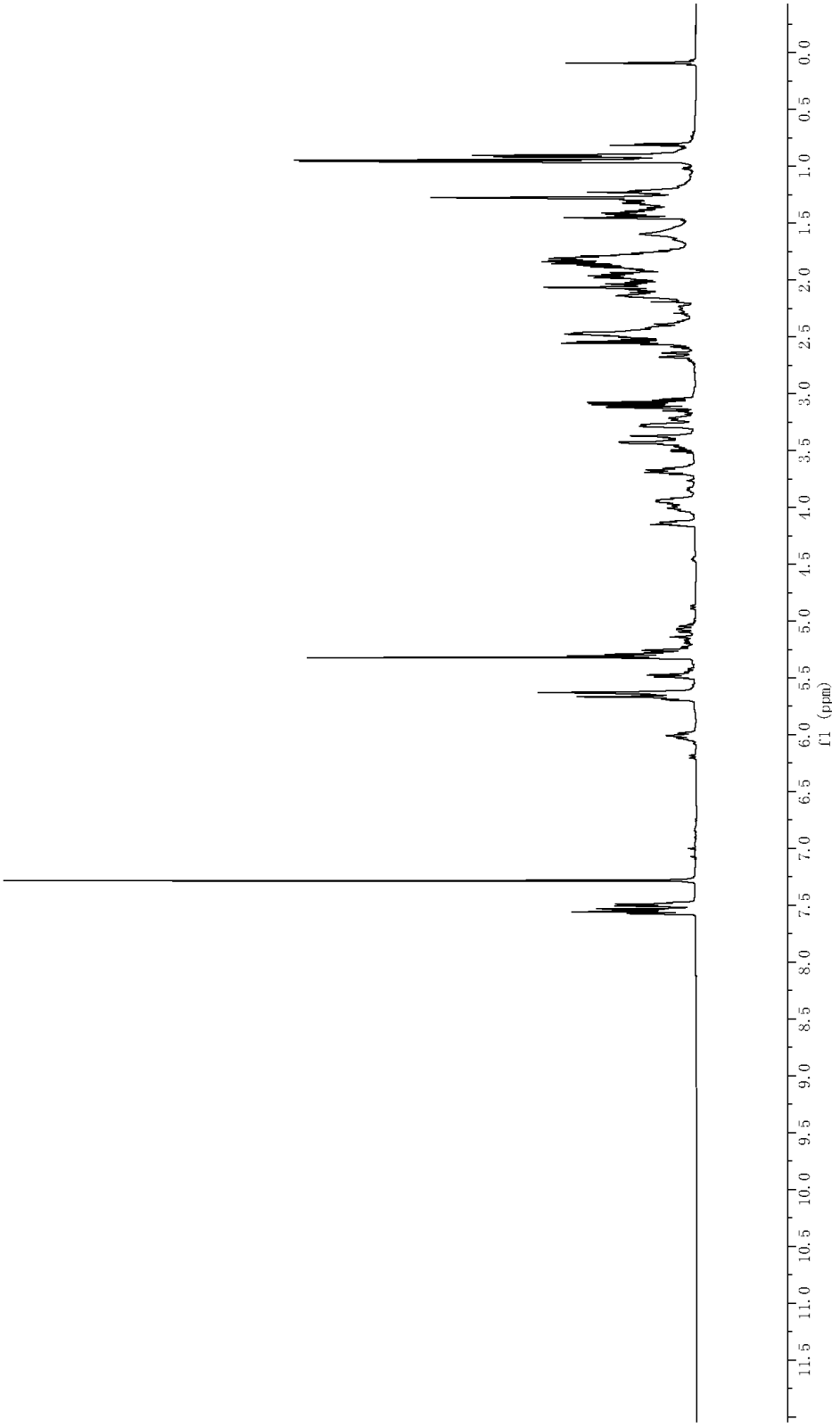
^{1}H-^{13}C-HMBC: Compound **214**



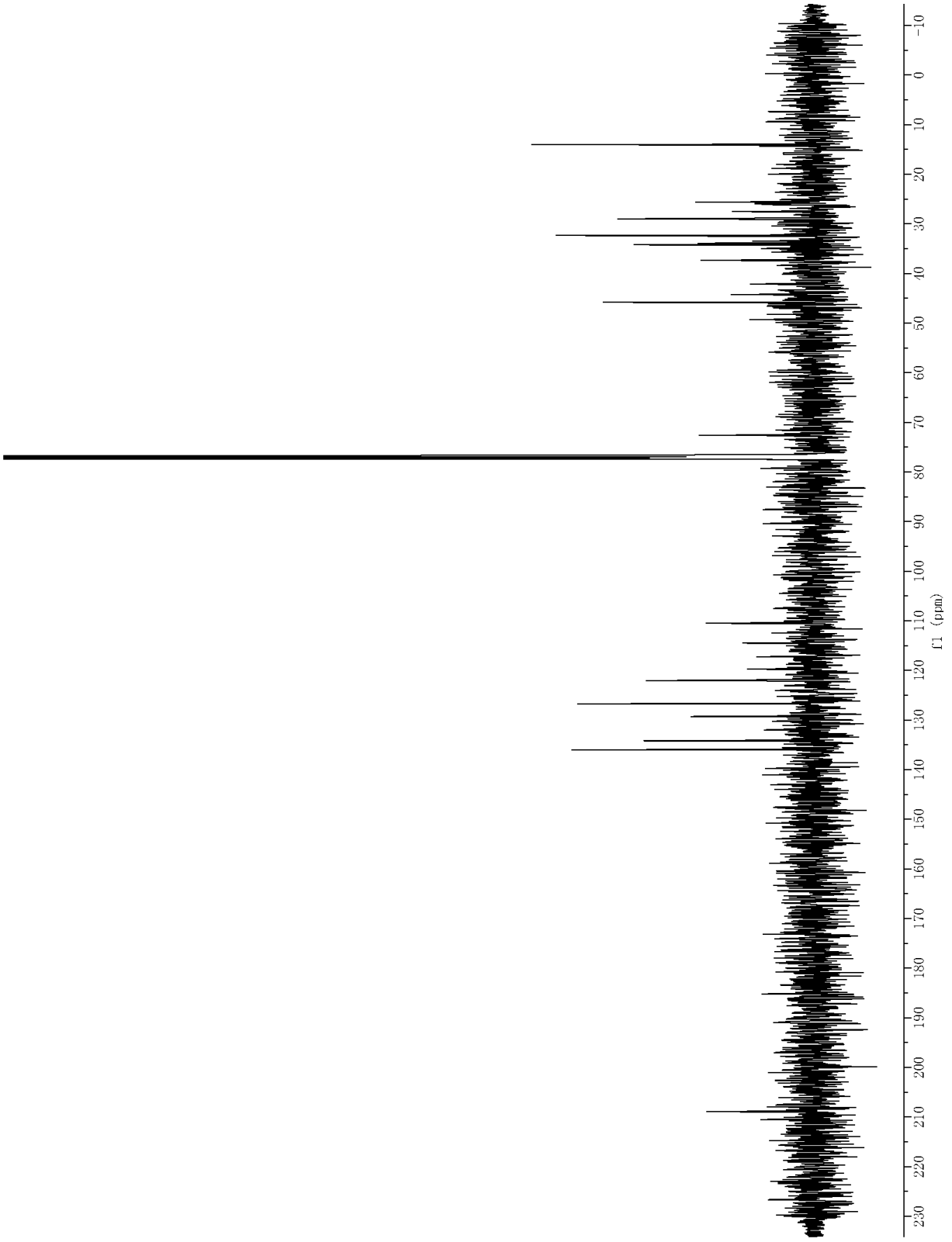
^{1}H-^{1}H-NOE: Compound **214**



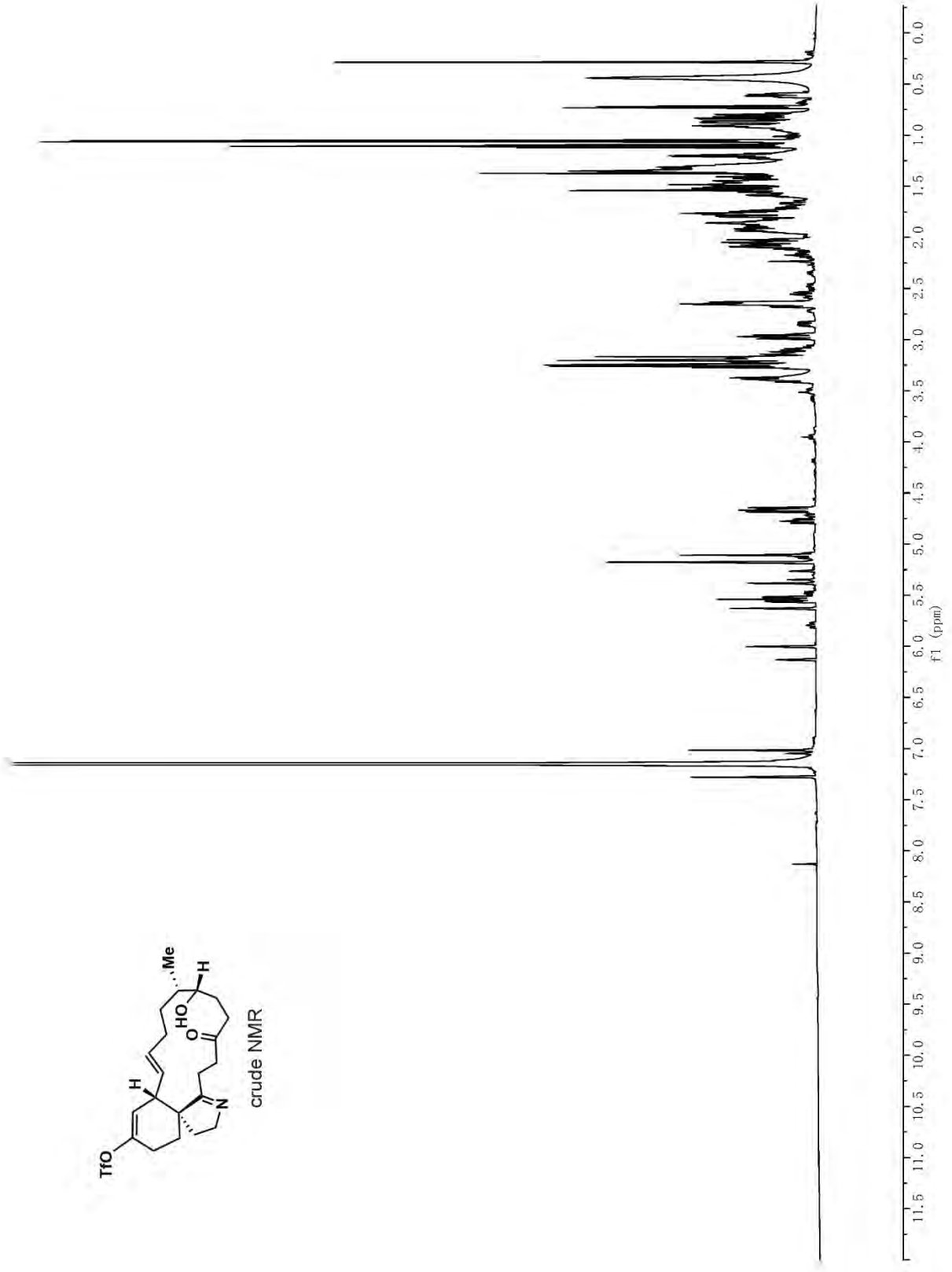
^{1}H NMR: Compound **215**



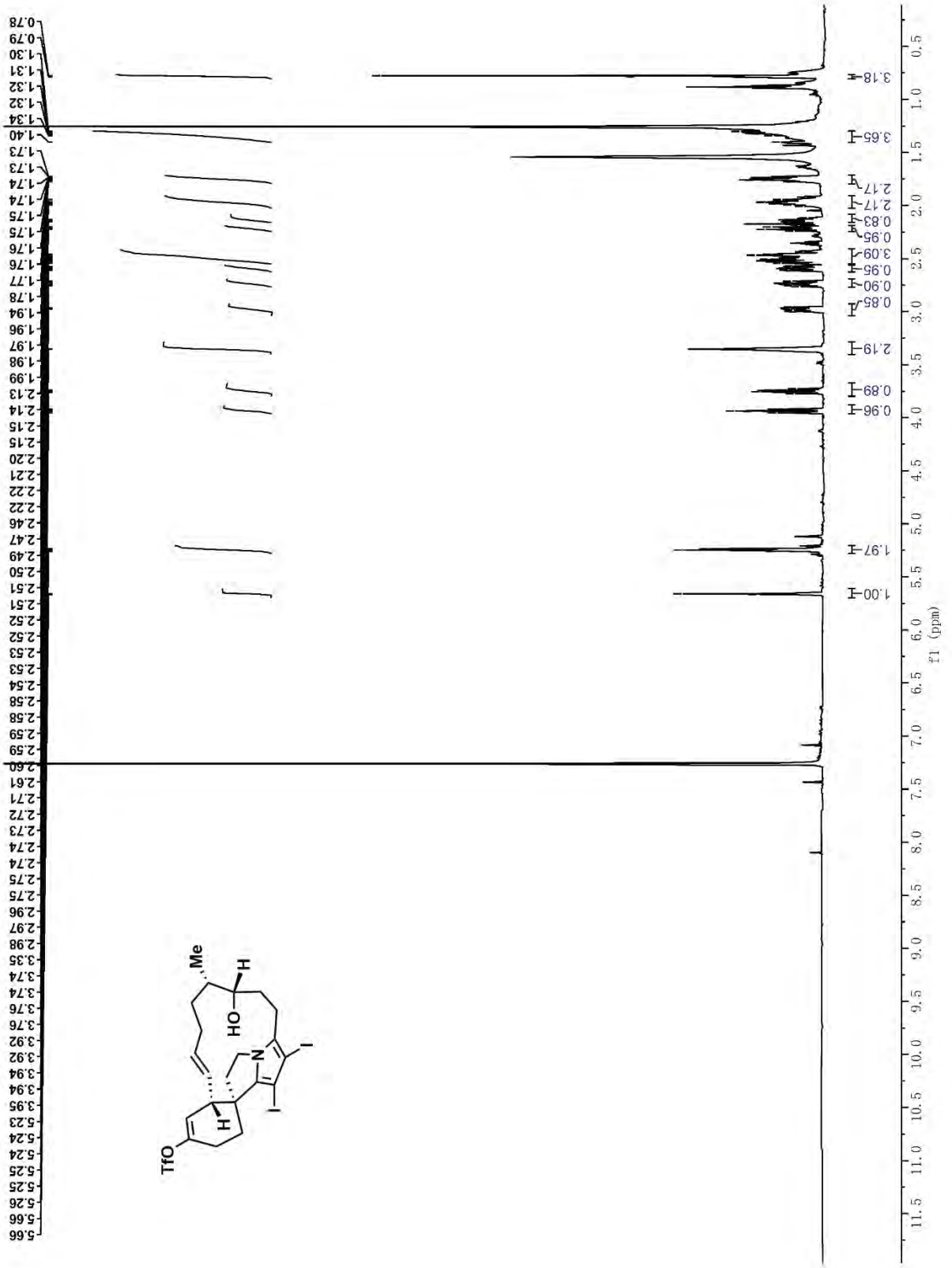
^{13}C NMR: Compound **215**



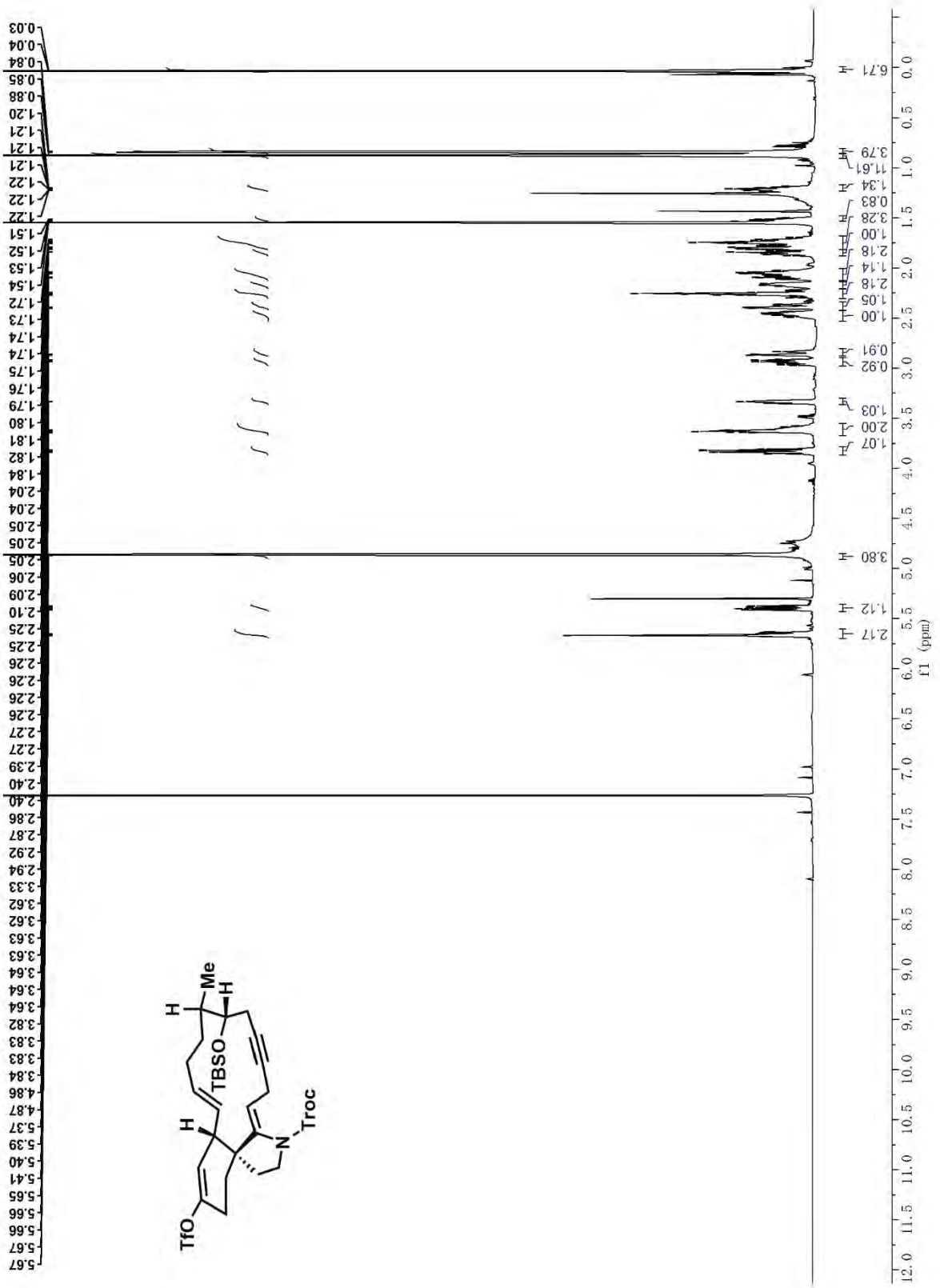
^{1}H NMR: Compound **217**



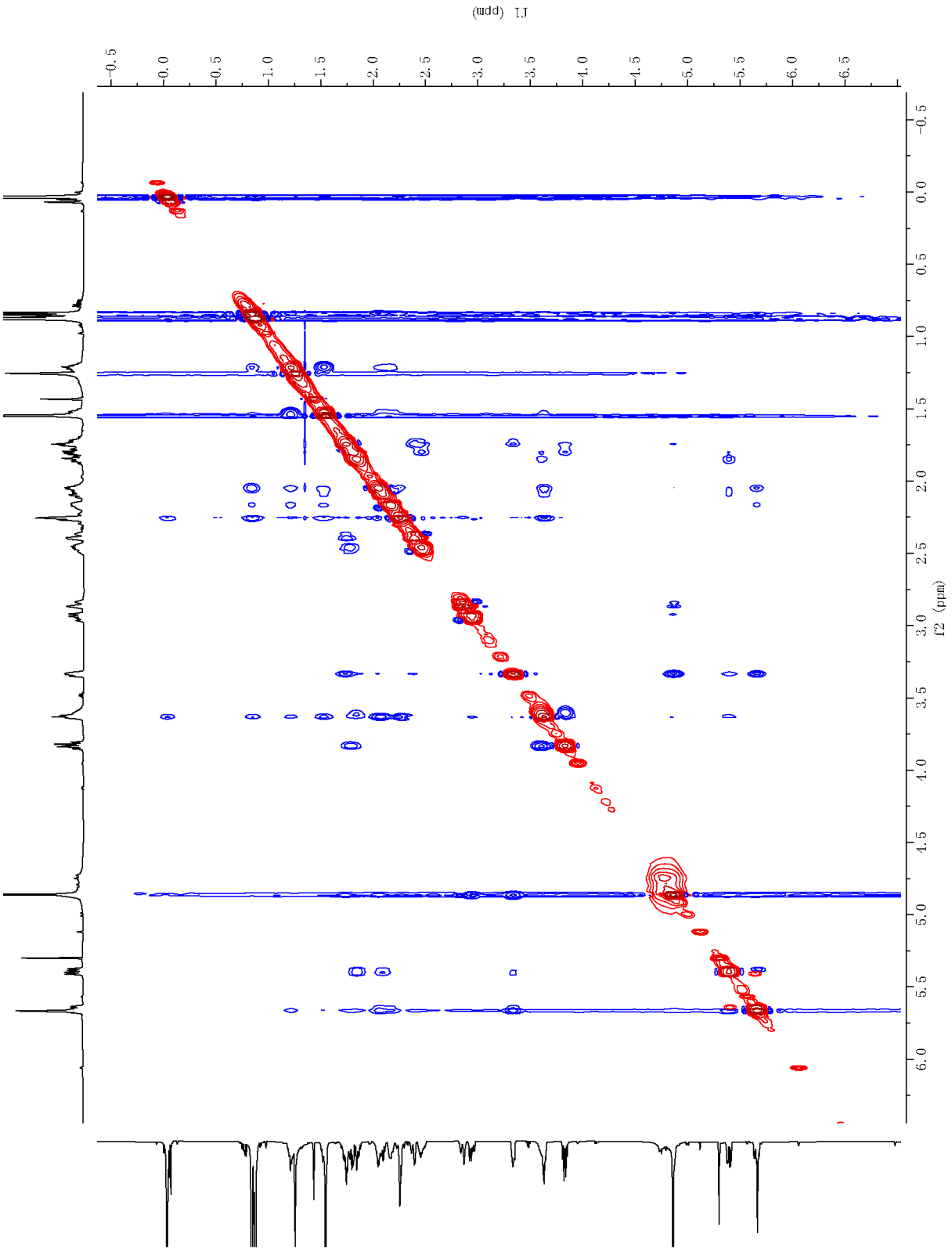
^{1}H NMR: Compound **218**



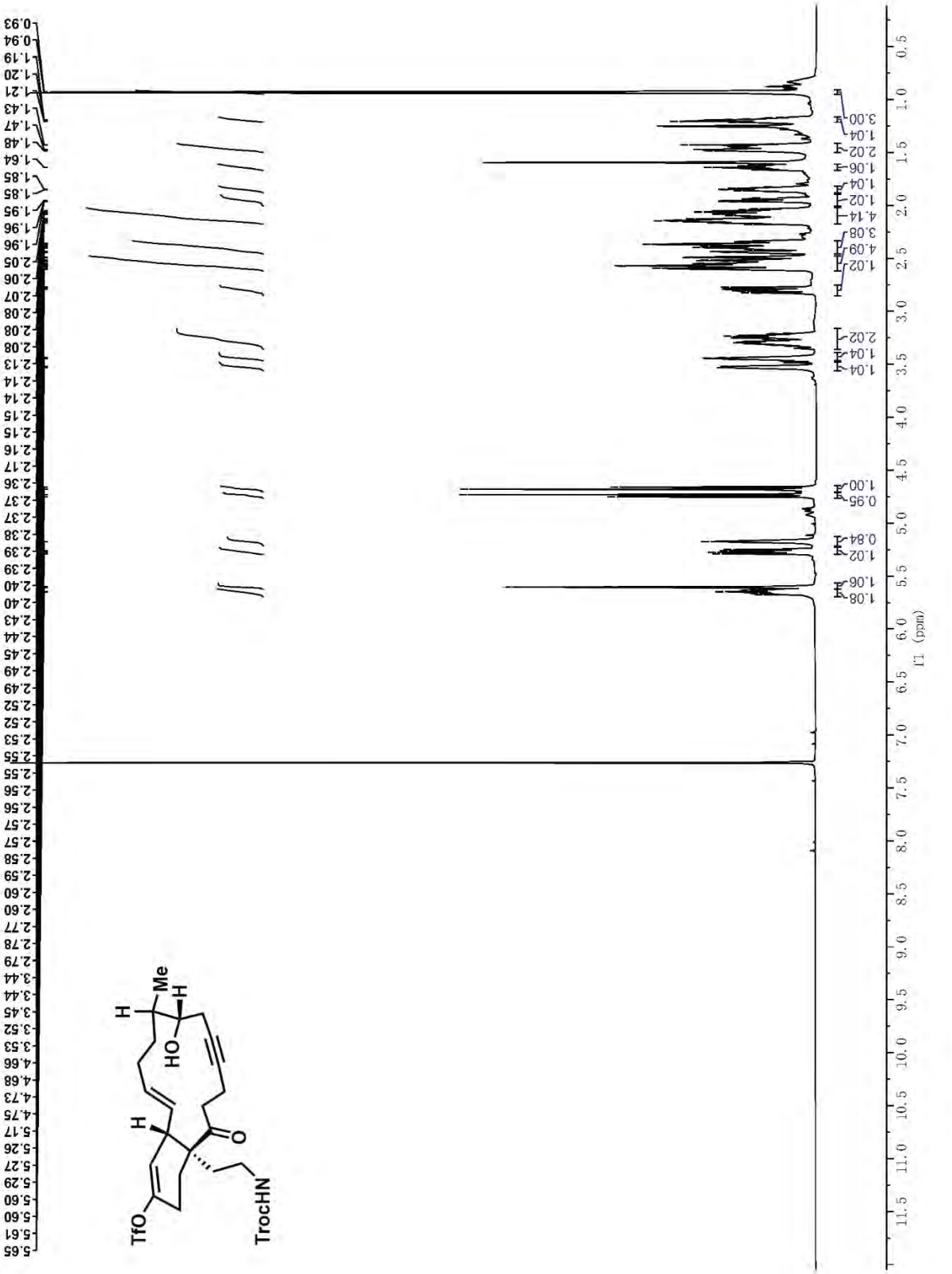
^{1}H NMR: Compound **219**



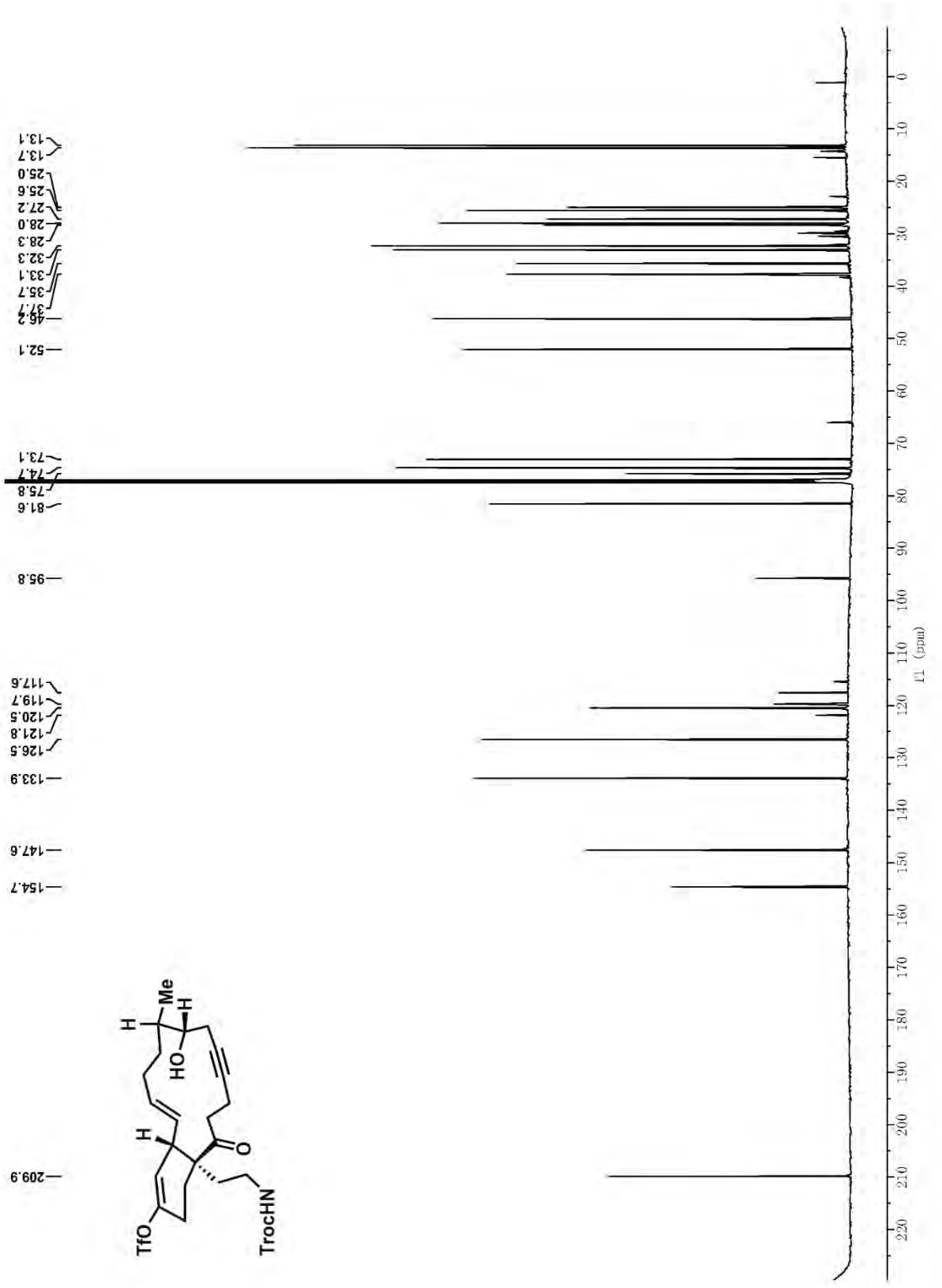
^{1}H-^{1}H-NOESY: Compound **219**



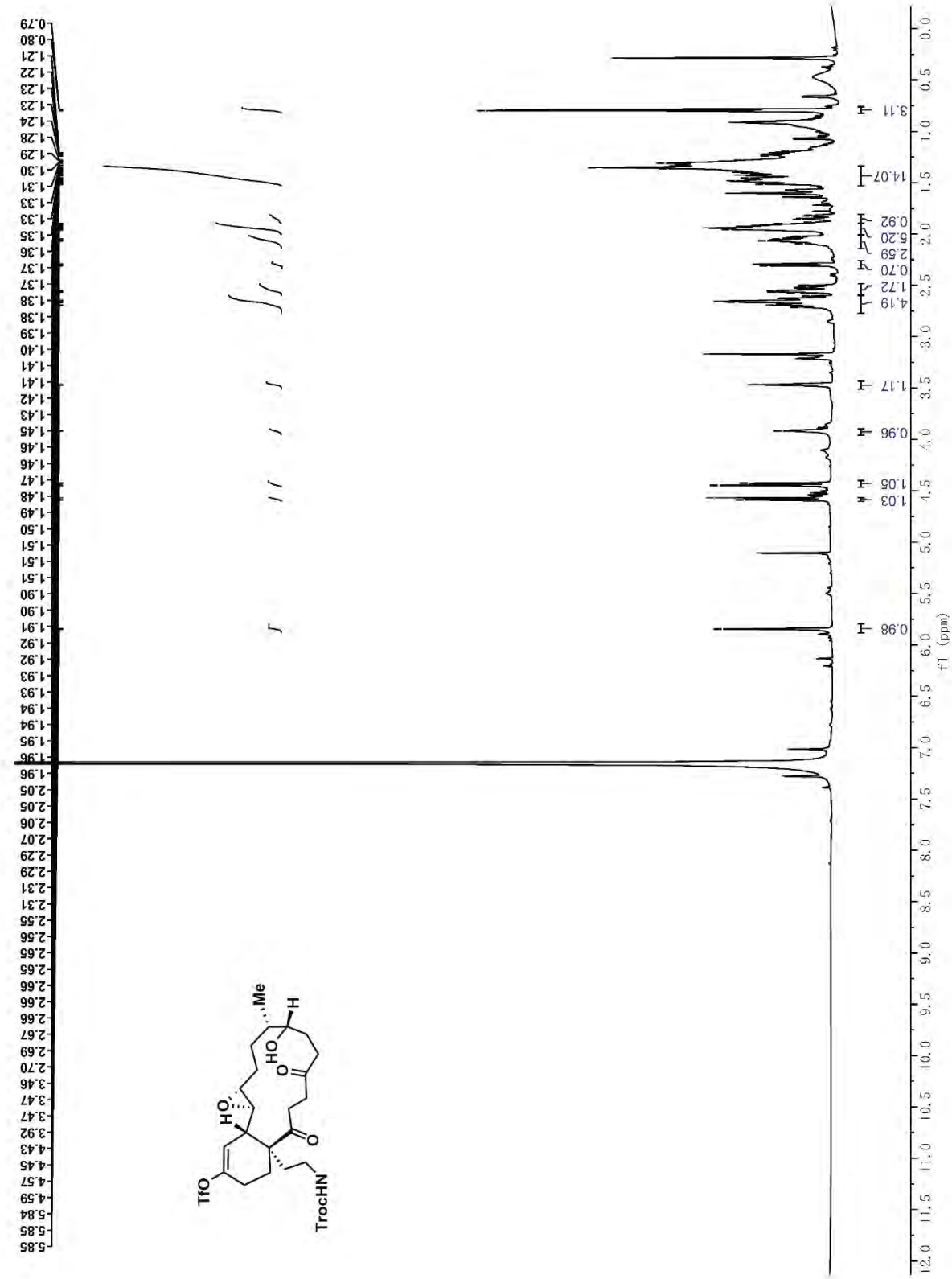
^{1}H NMR: Compound **221**



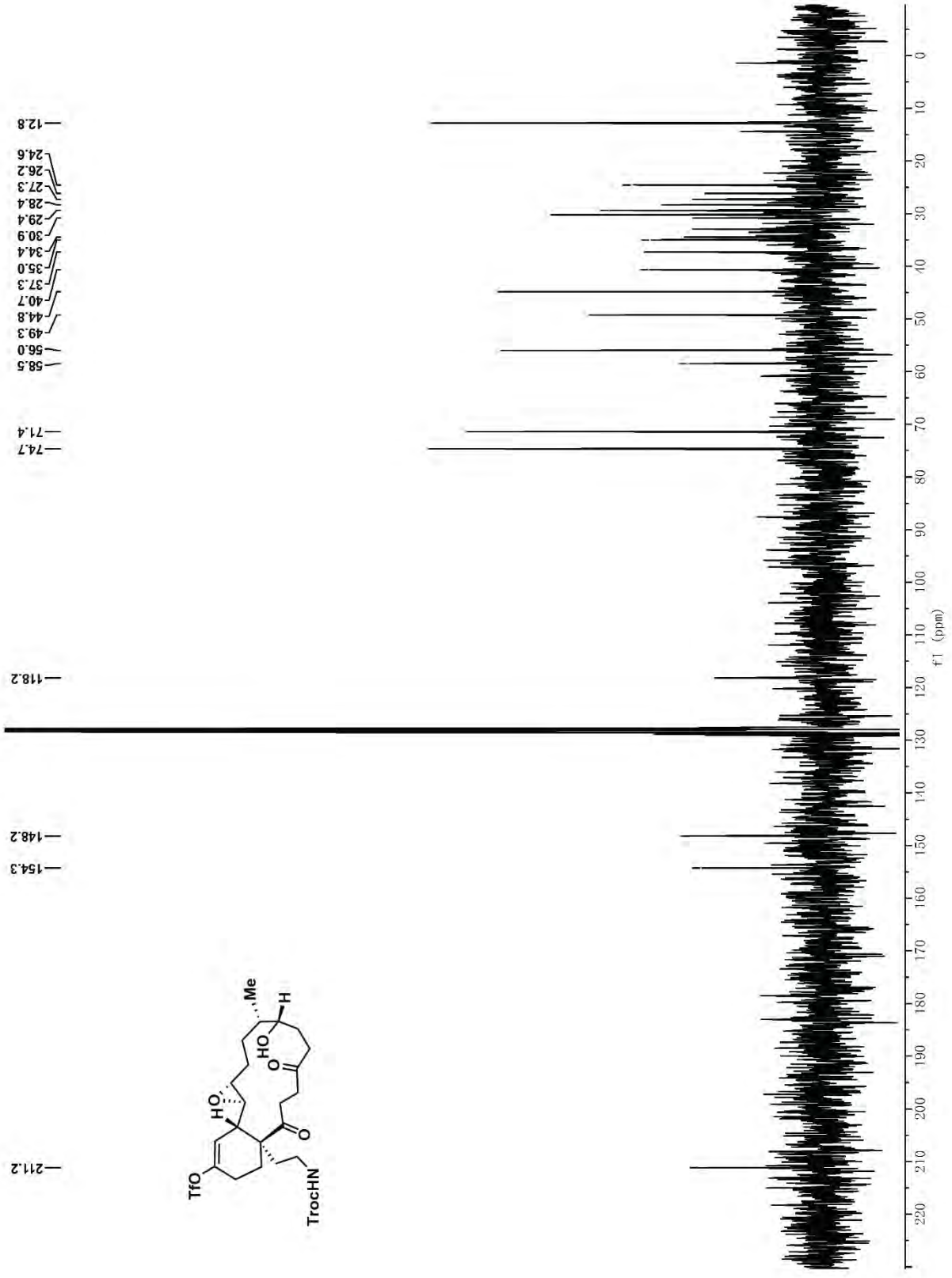
^{13}C NMR: Compound **221**



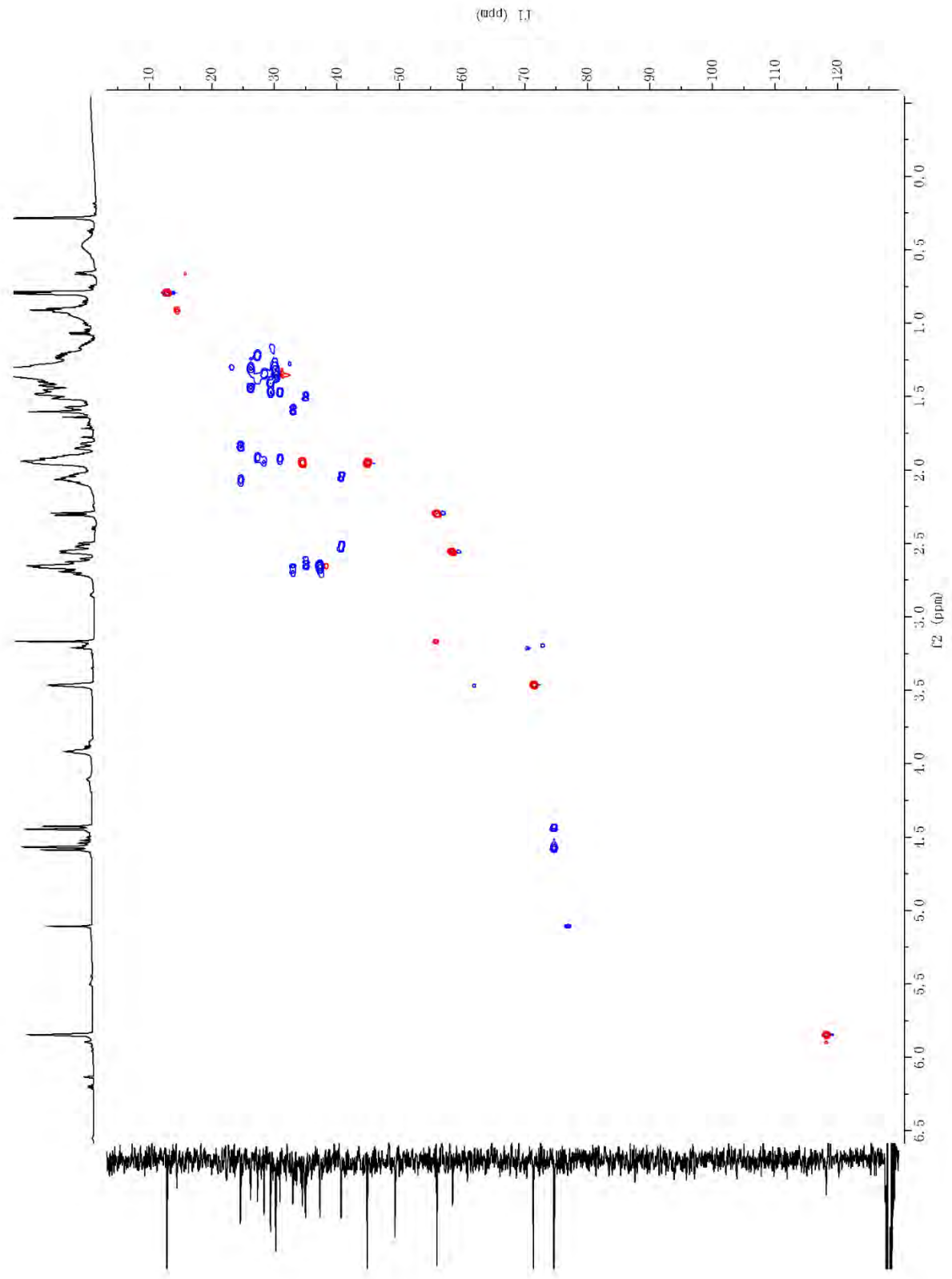
^{1}H NMR: Compound **222**



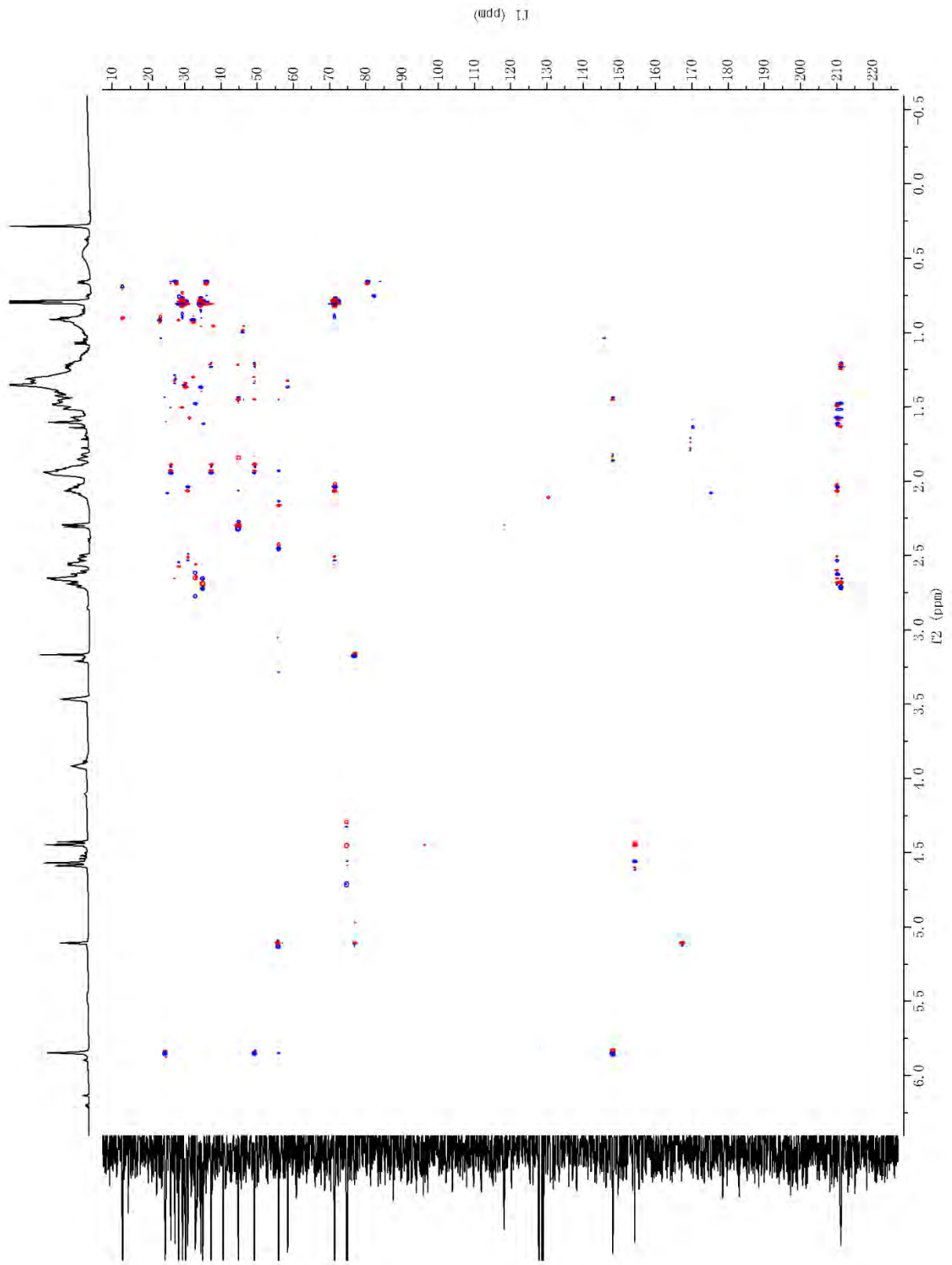
^{13}C NMR: Compound **222**



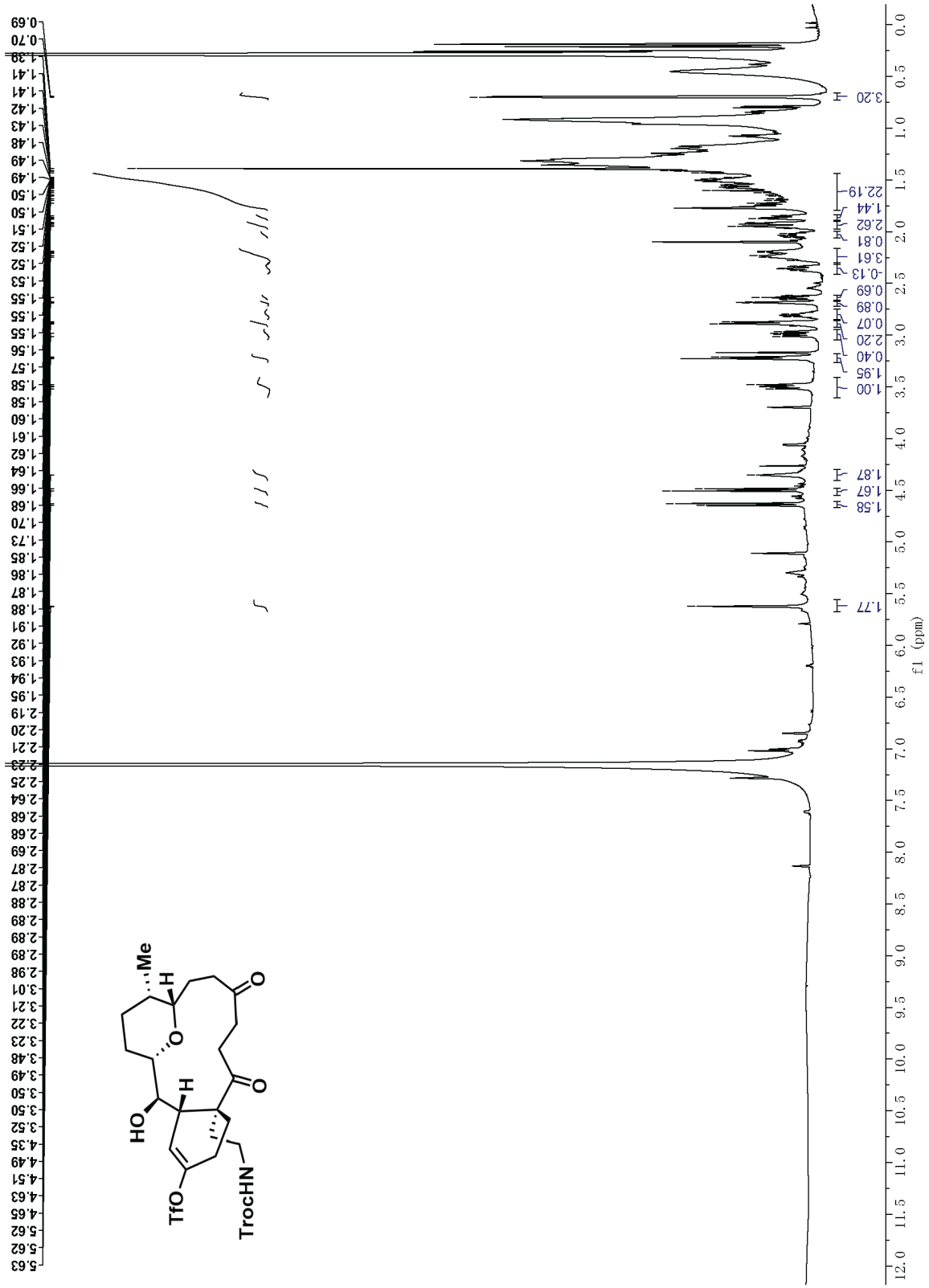
^{1}H-^{13}C-HSQC: Compound **222**



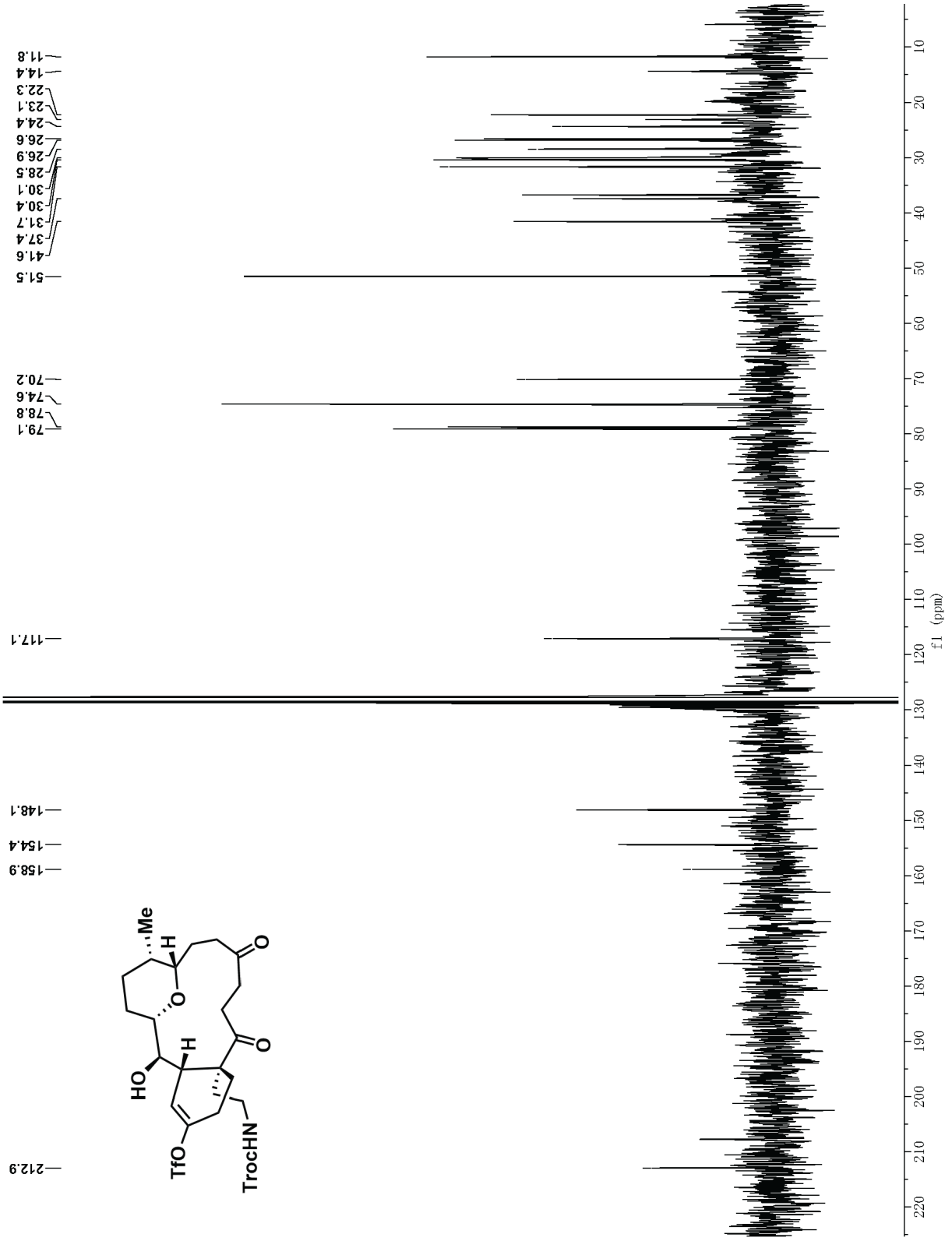
^{1}H-^{13}C-HSQC: Compound **222**



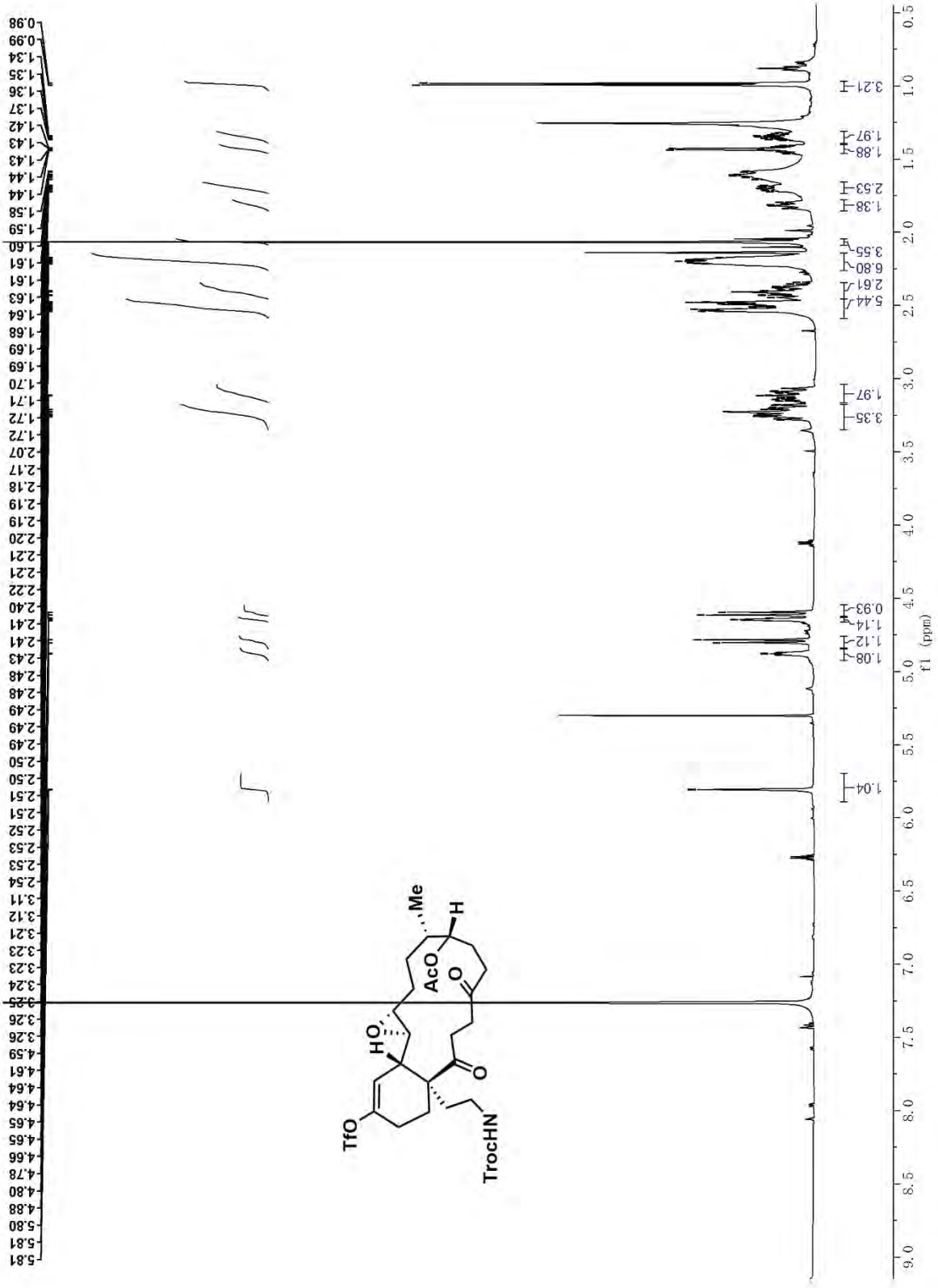
^{1}H NMR: Compound **224**



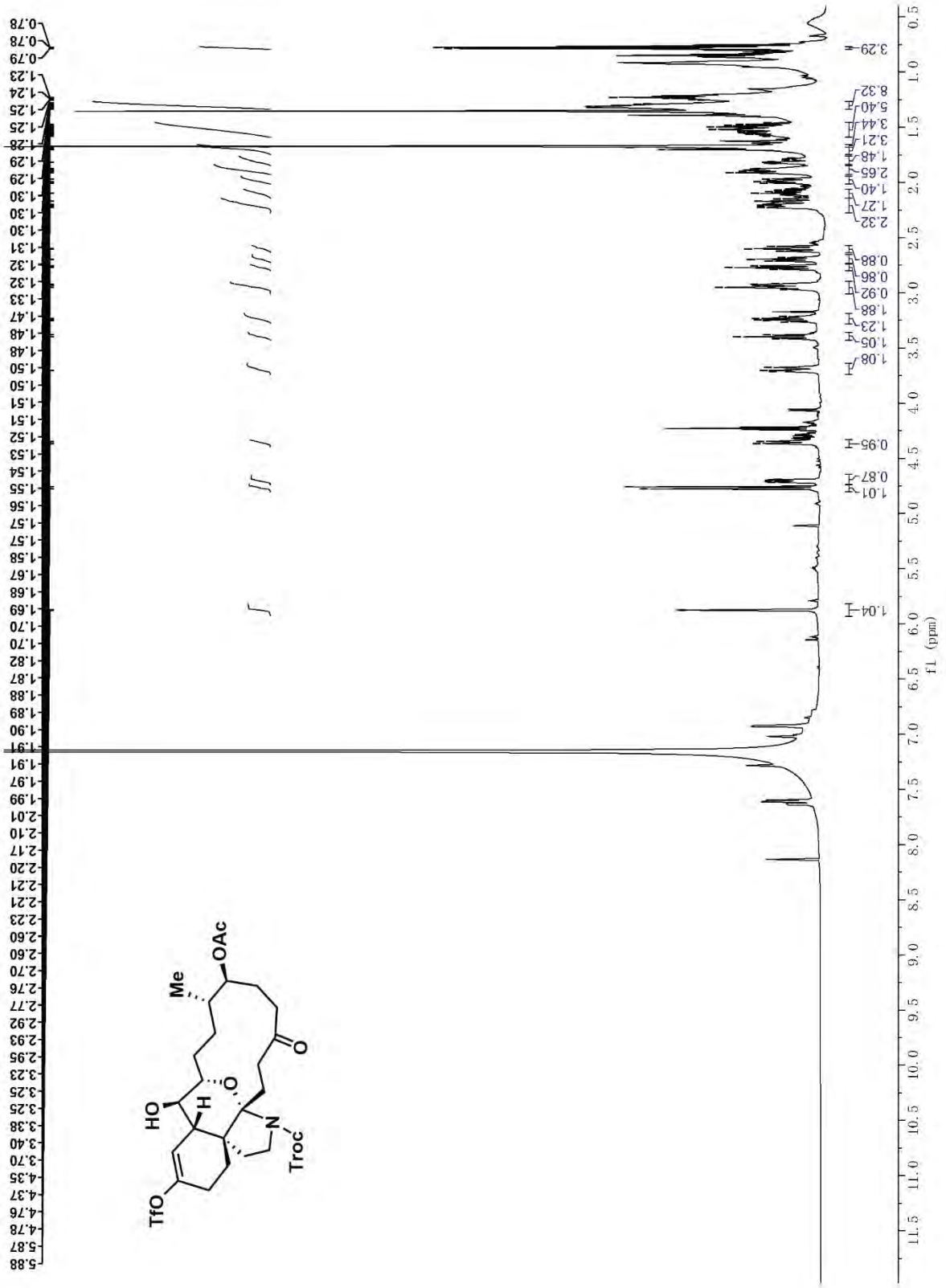
^{13}C NMR: Compound **224**



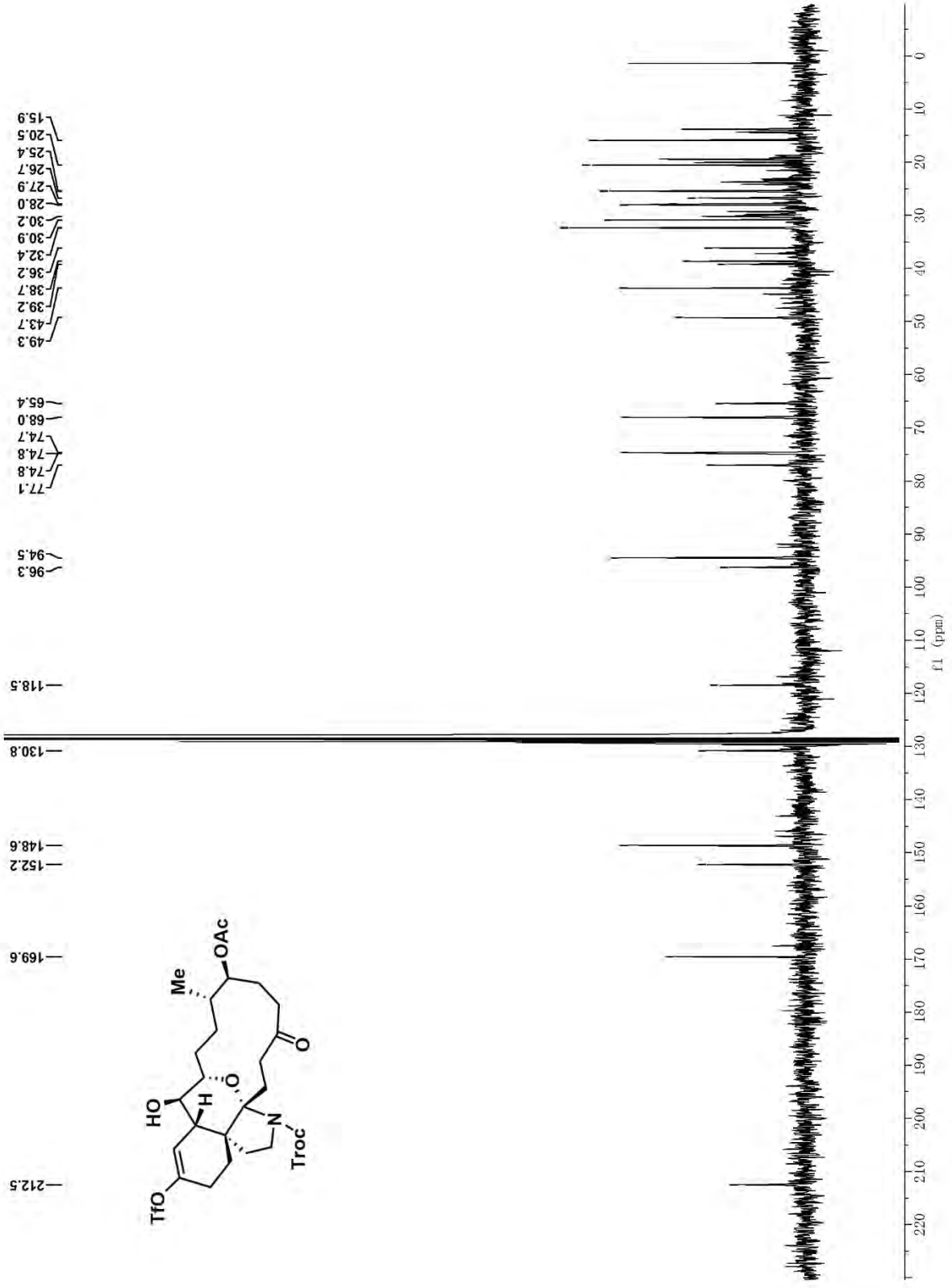
^{1}H NMR: Compound **225**



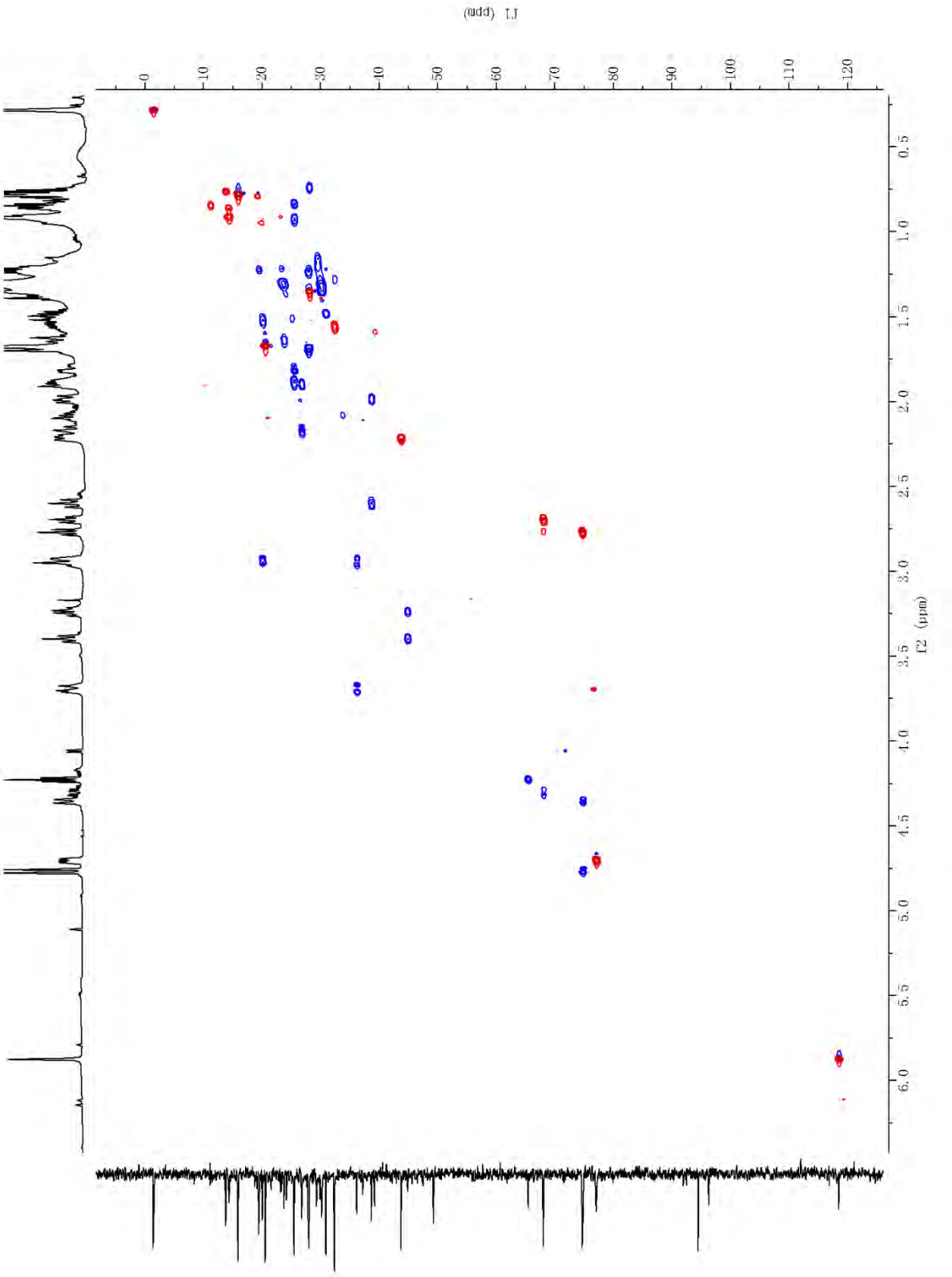
^{1}H NMR: Compound **226**



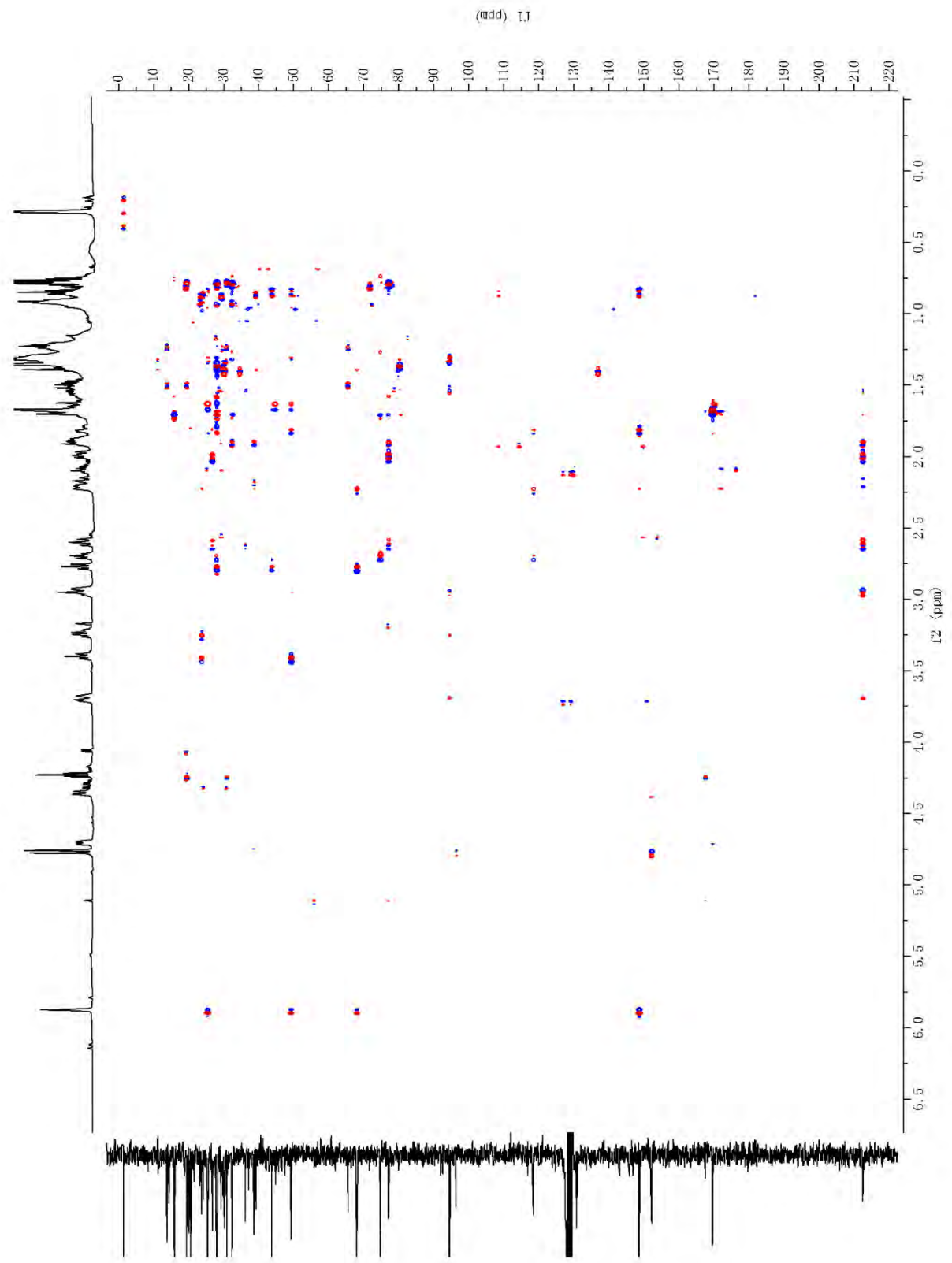
^{13}C NMR: Compound **226**



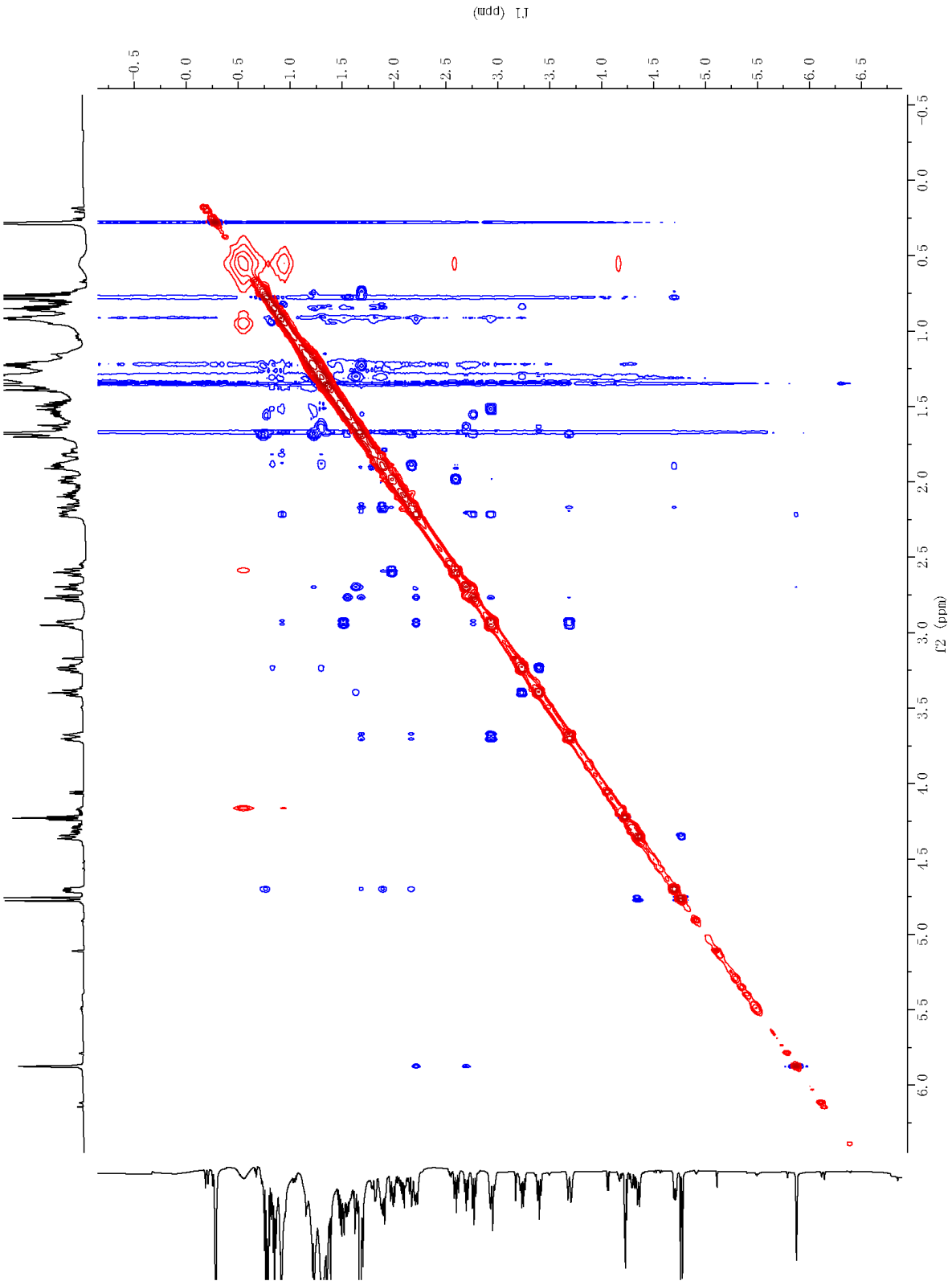
^{1}H-^{13}C-HSQC: Compound **226**



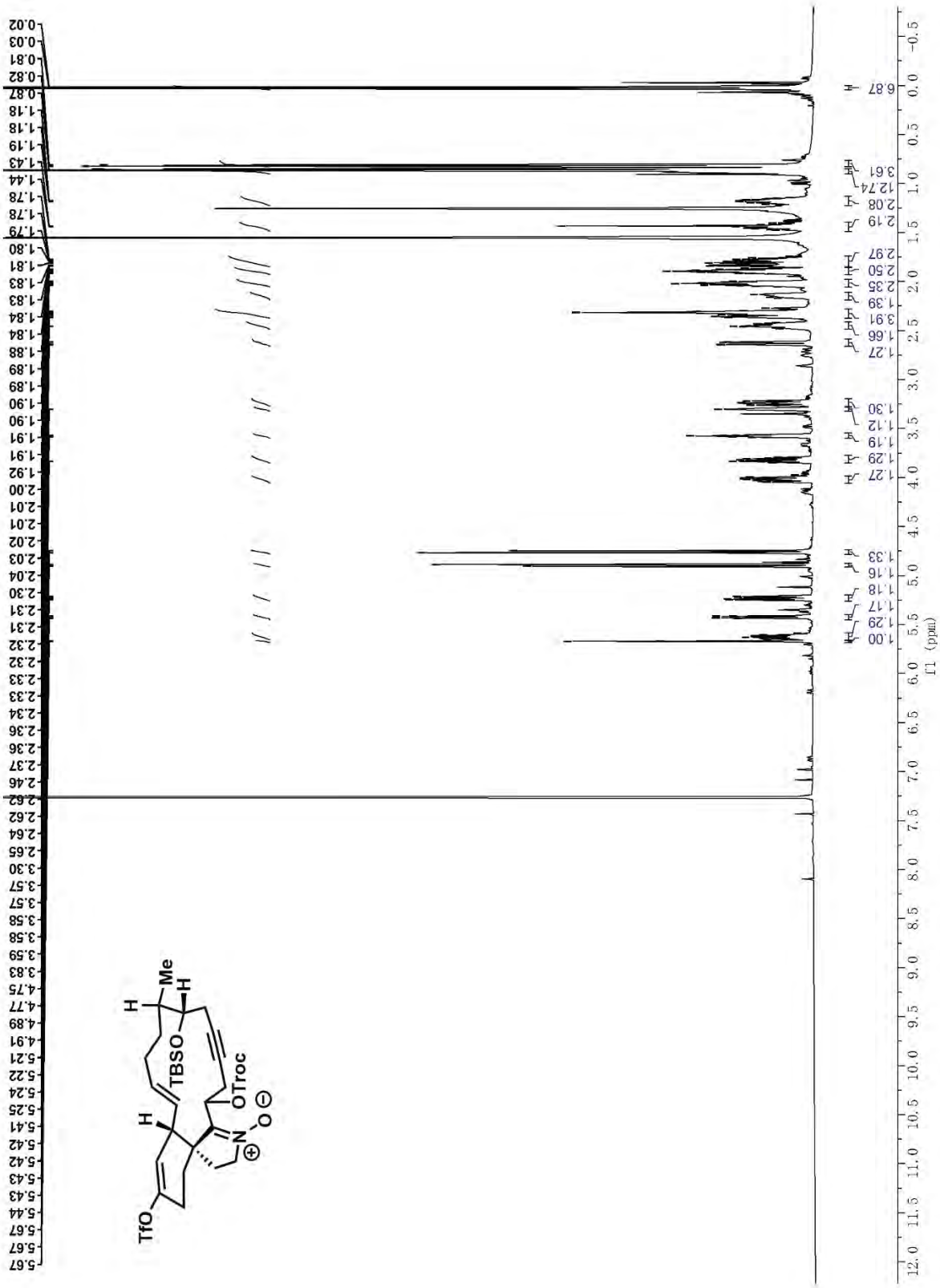
^{1}H-^{13}C-HMBC: Compound **226**



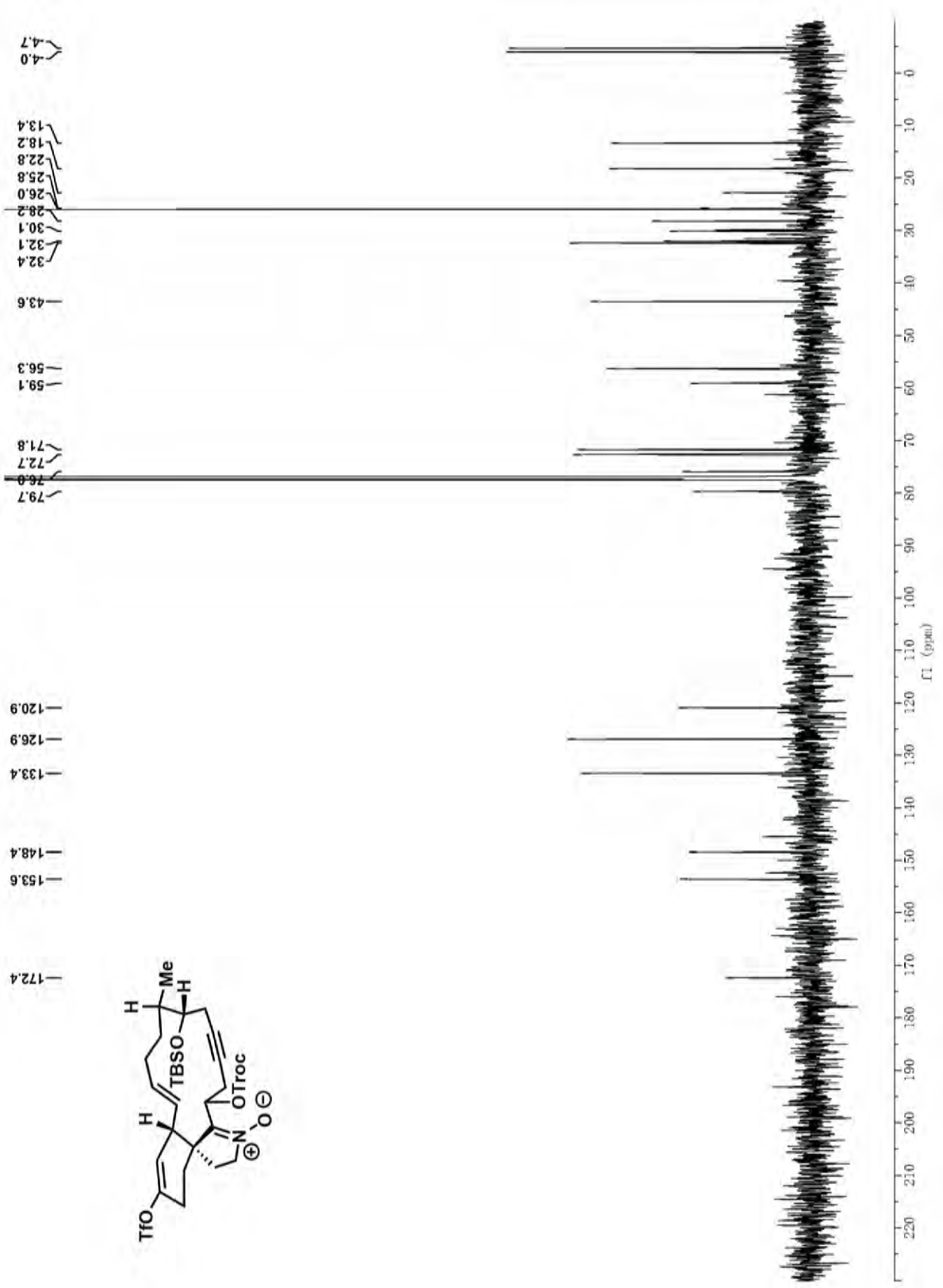
^{1}H-^{1}H-NOESY: Compound **226**



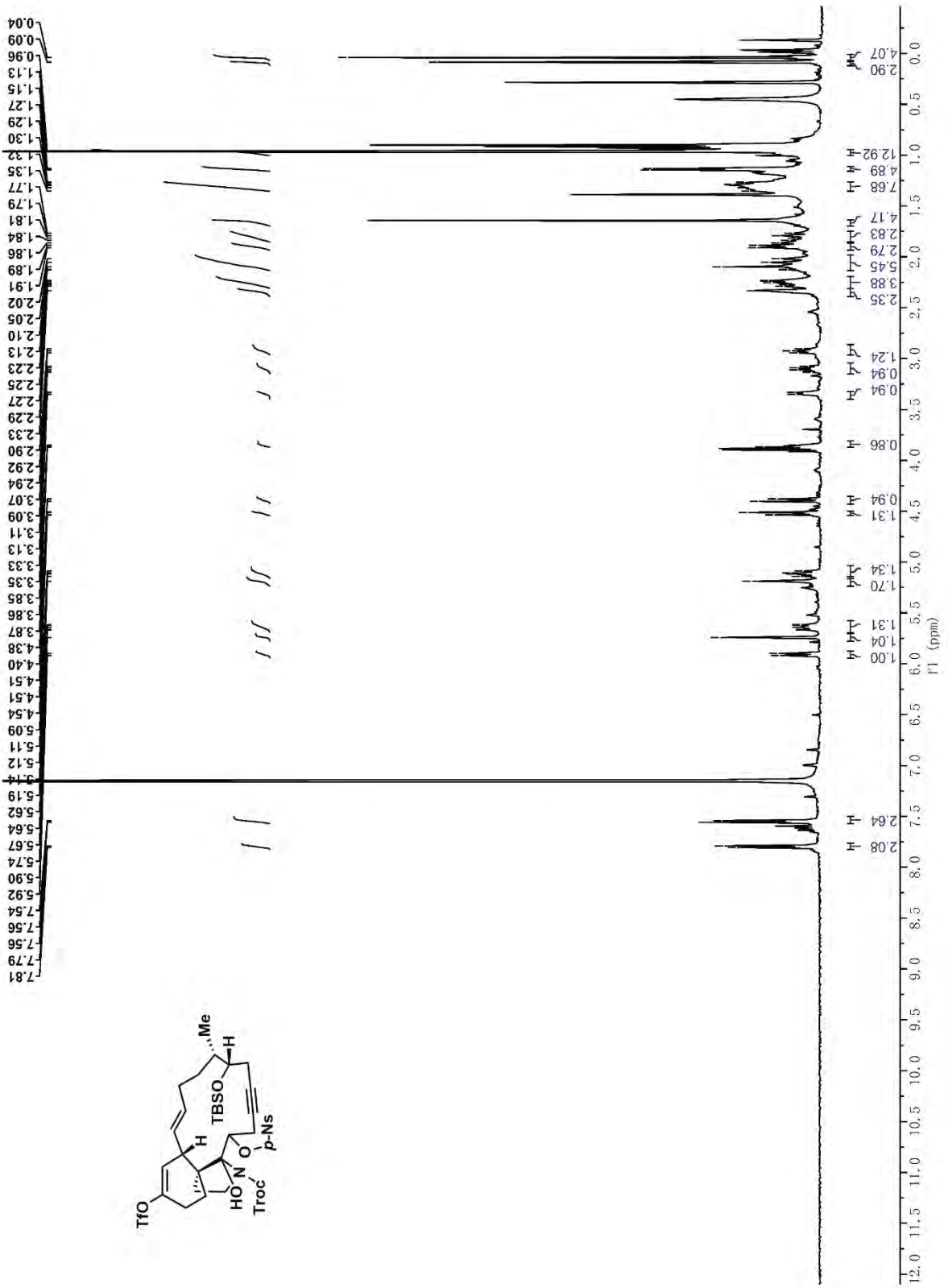
^{1}H NMR: Compound **230**



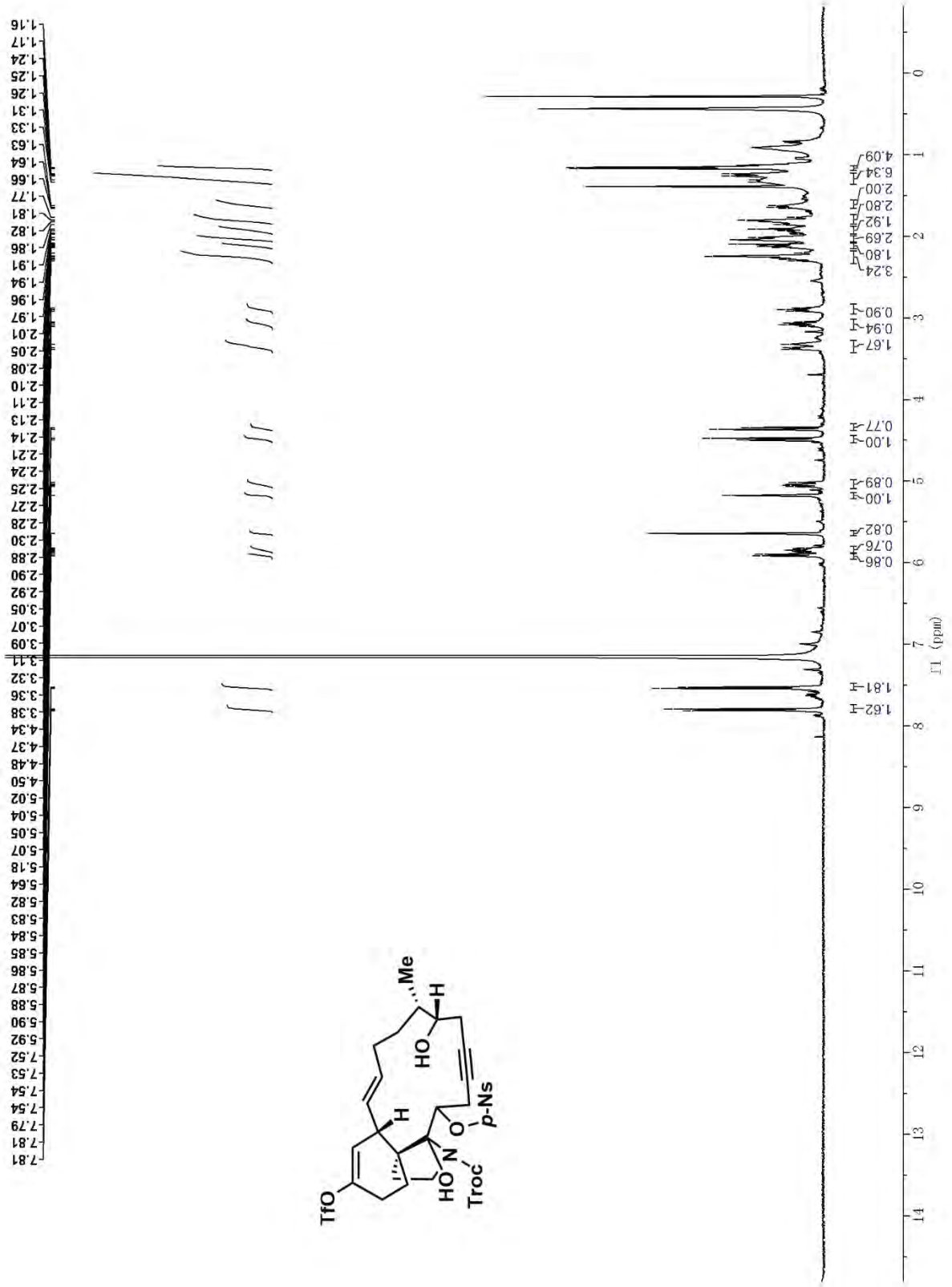
^{13}C NMR: Compound **230**



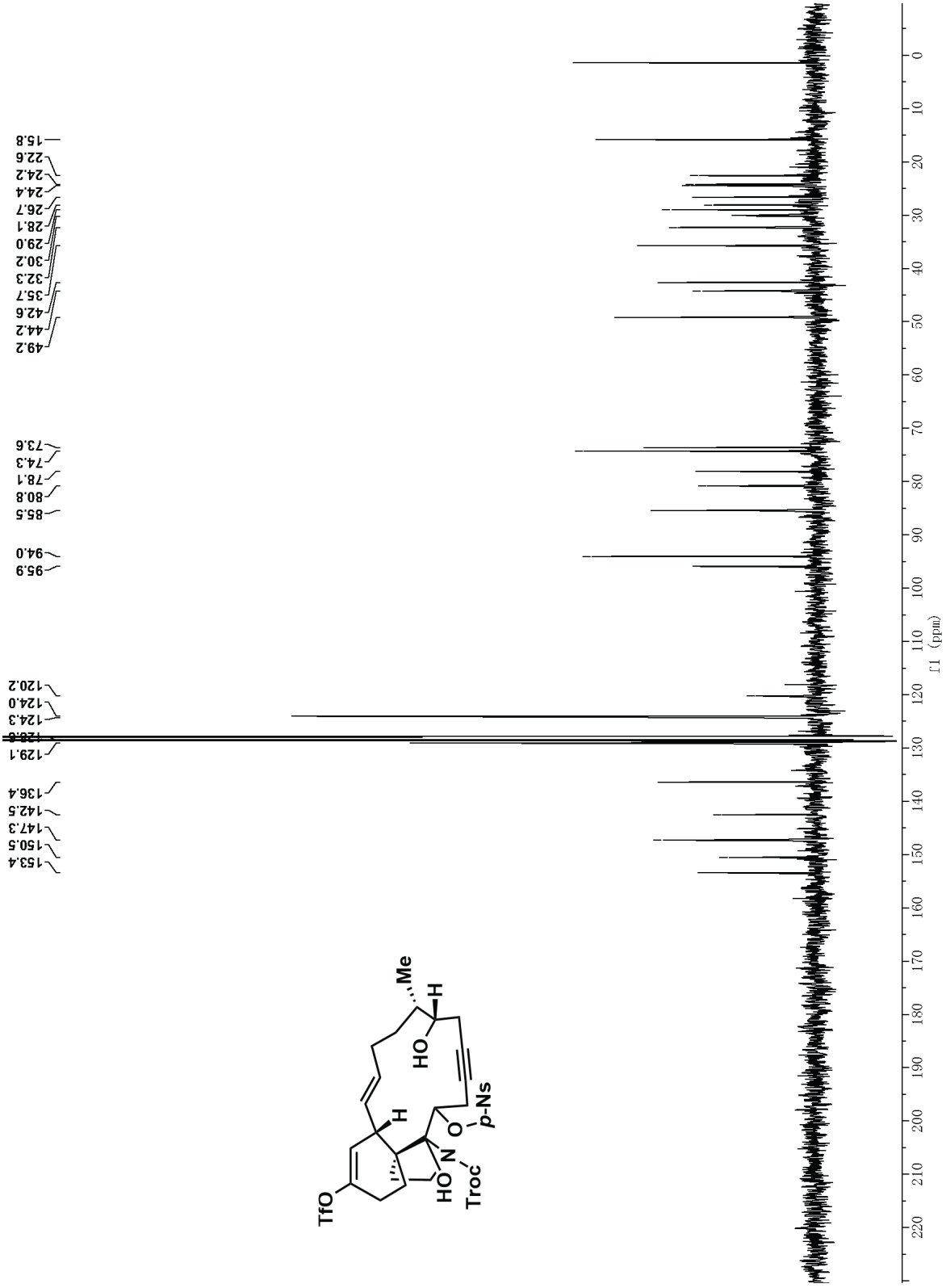
^{1}H NMR: Compound **234**



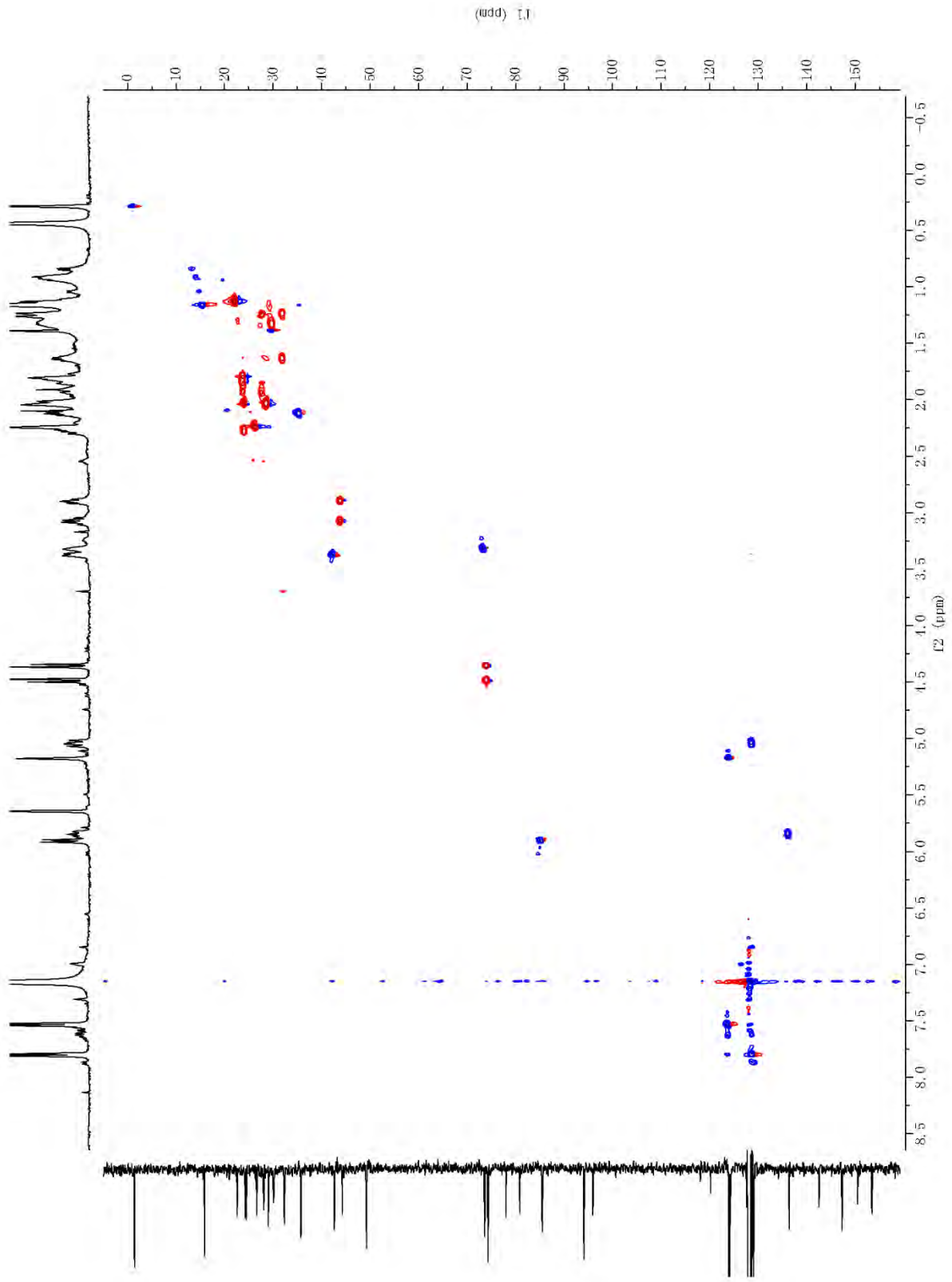
^{1}H NMR: Compound **235**



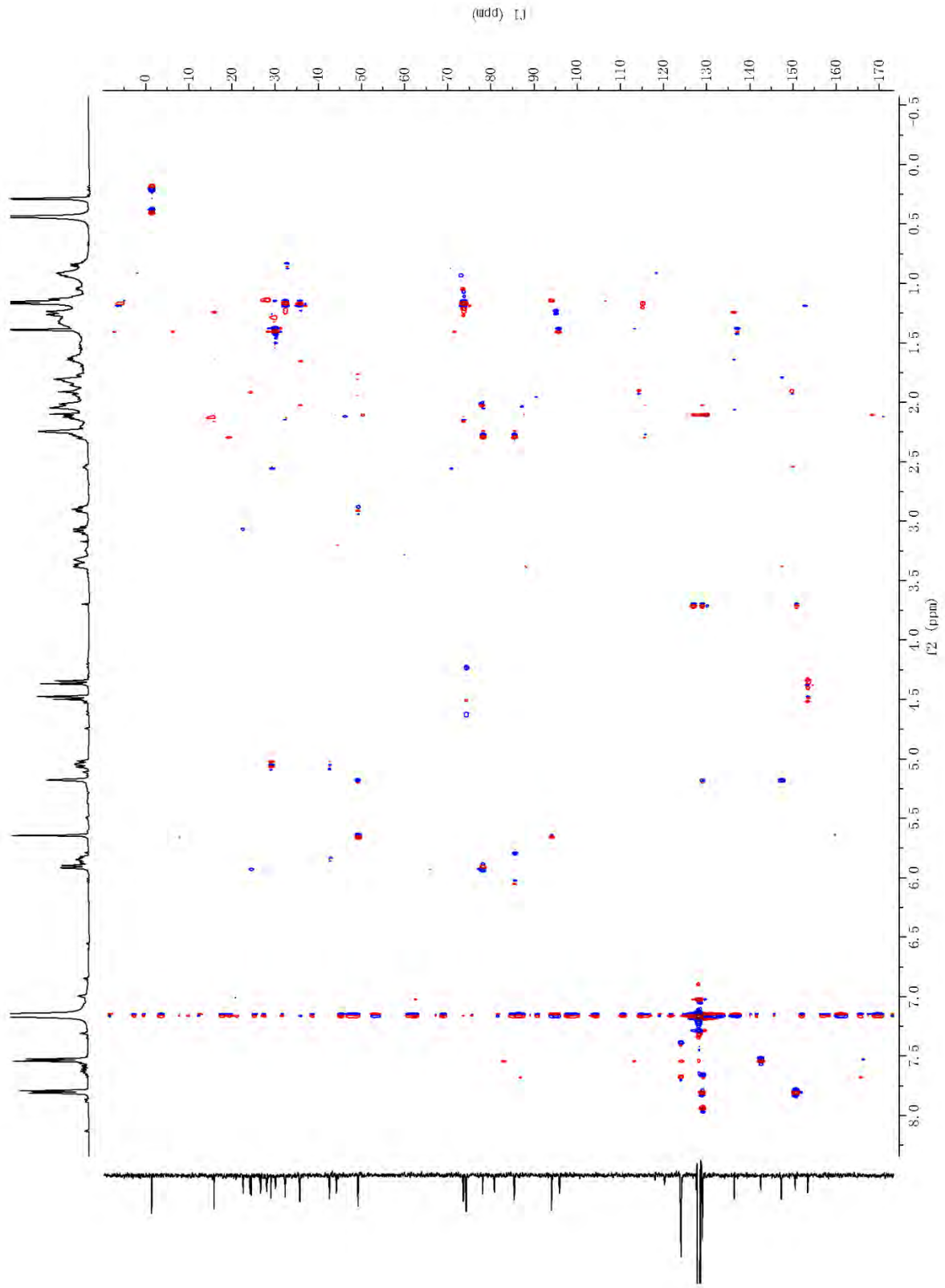
^{13}C NMR: Compound **235**



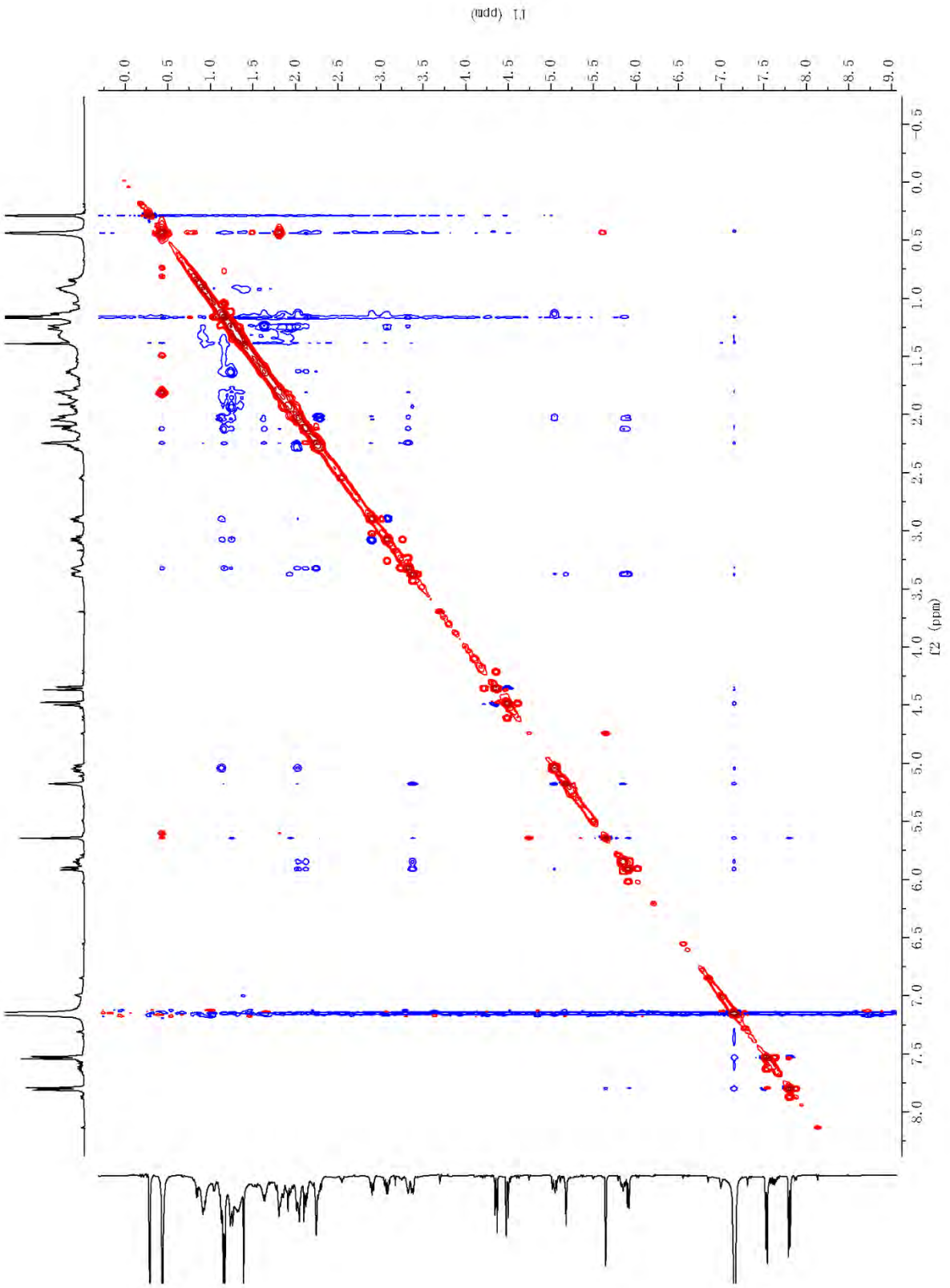
^{1}H-^{13}C-HSQC: Compound **235**



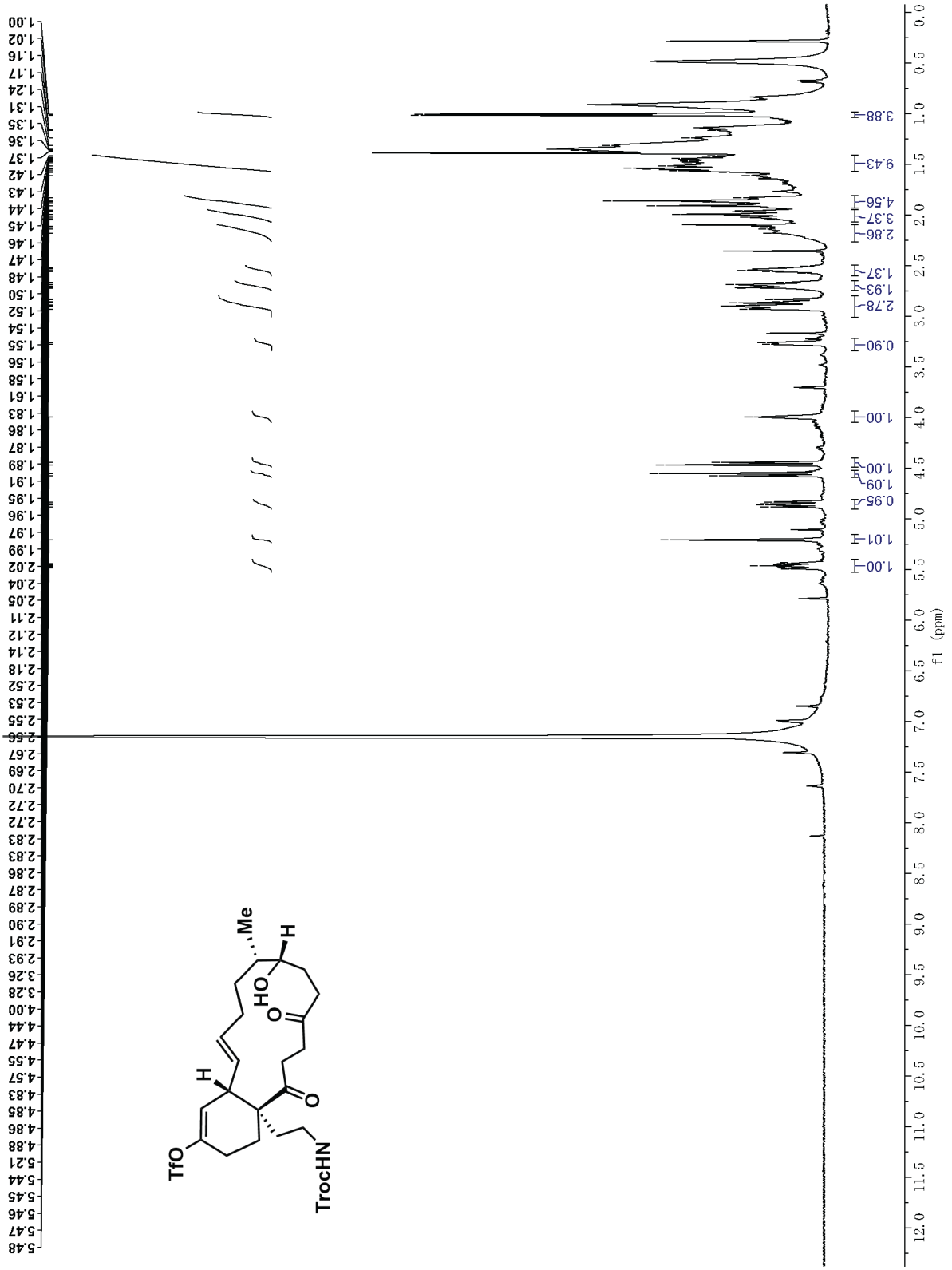
^{1}H-^{13}C-HMBC: Compound **235**



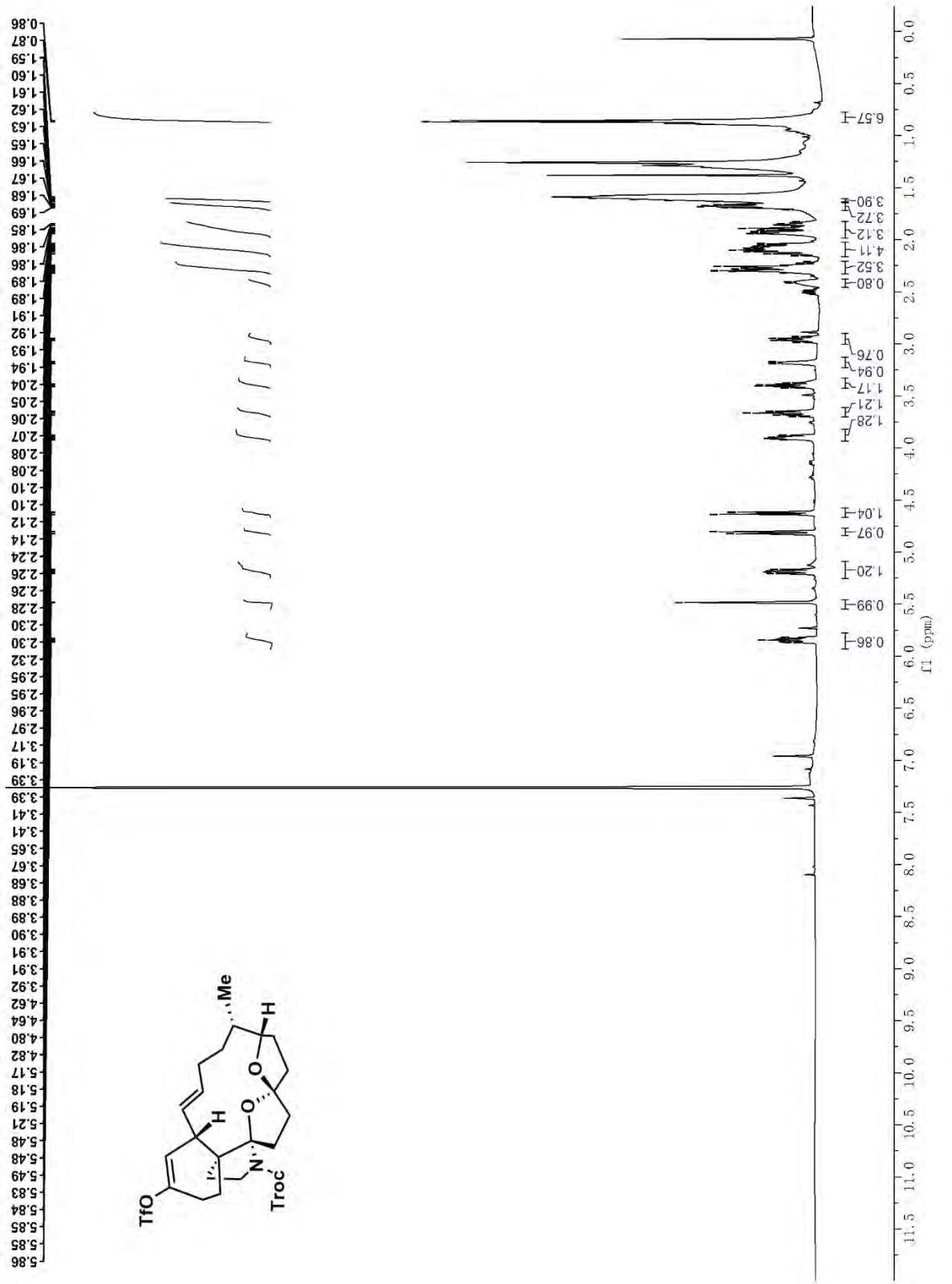
^{1}H-^{1}H-NOESY: Compound **235**



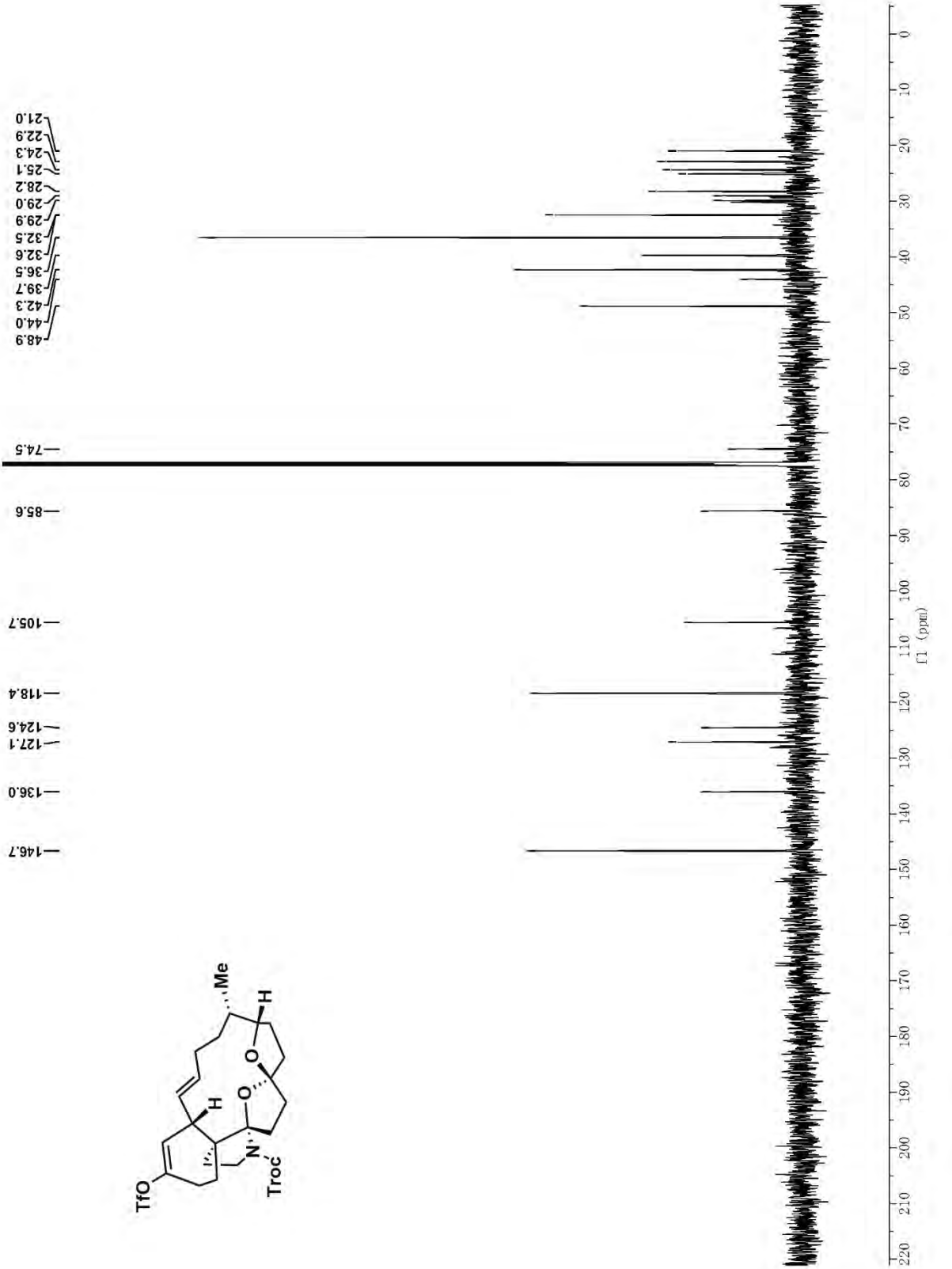
^{1}H NMR: Compound **236**



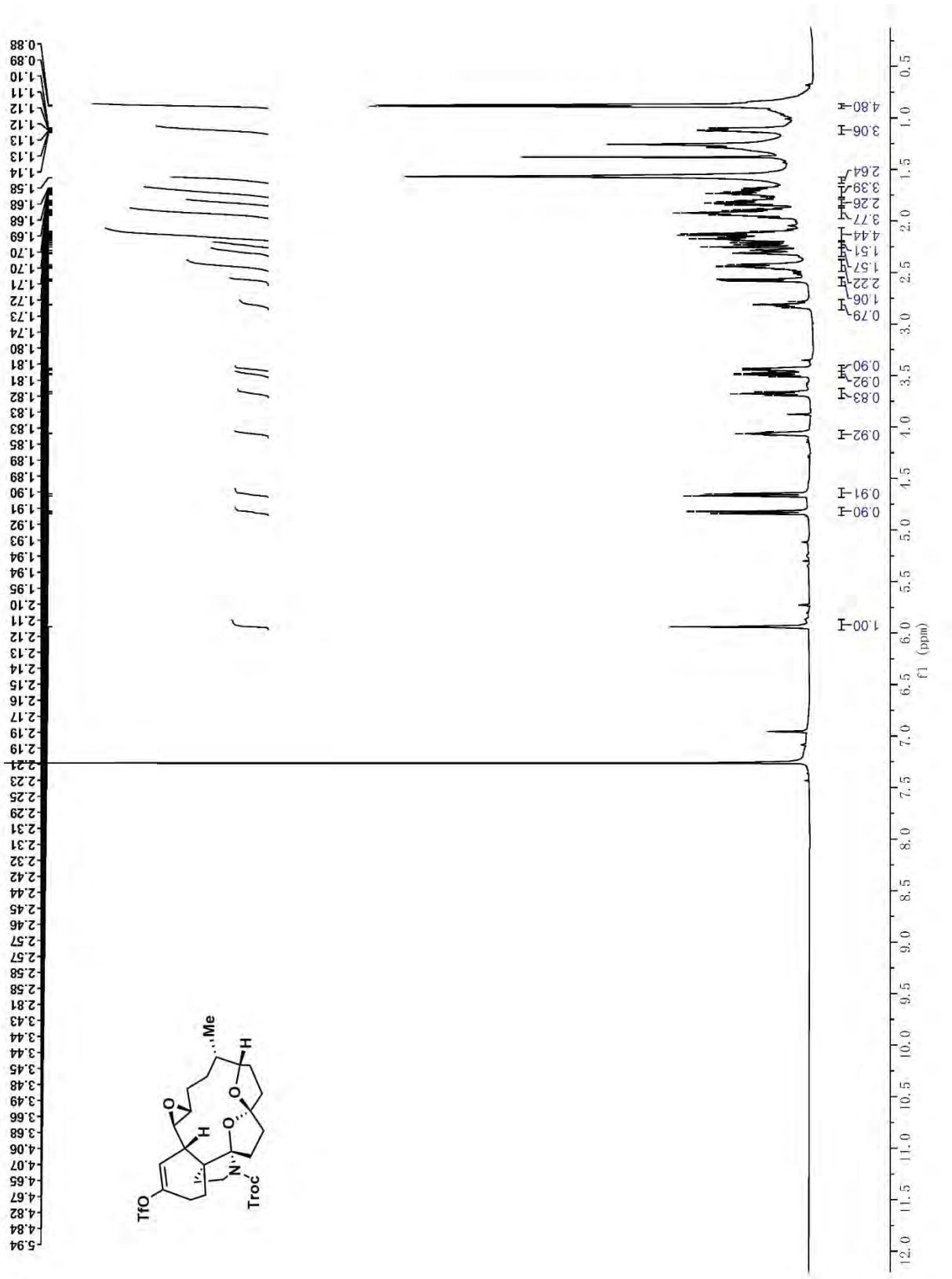
^{1}H NMR: Compound **237**



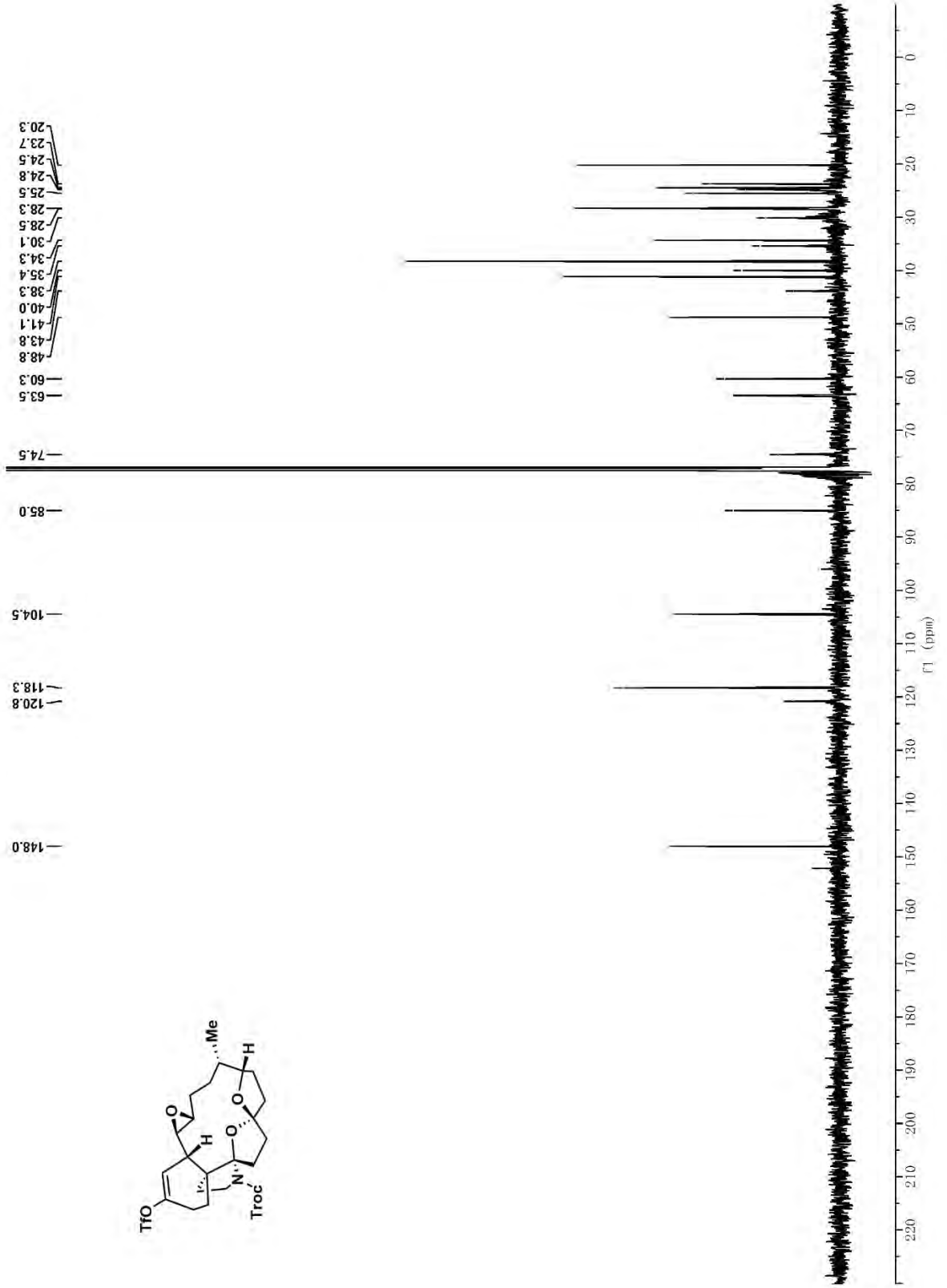
^{13}C NMR: Compound **237**



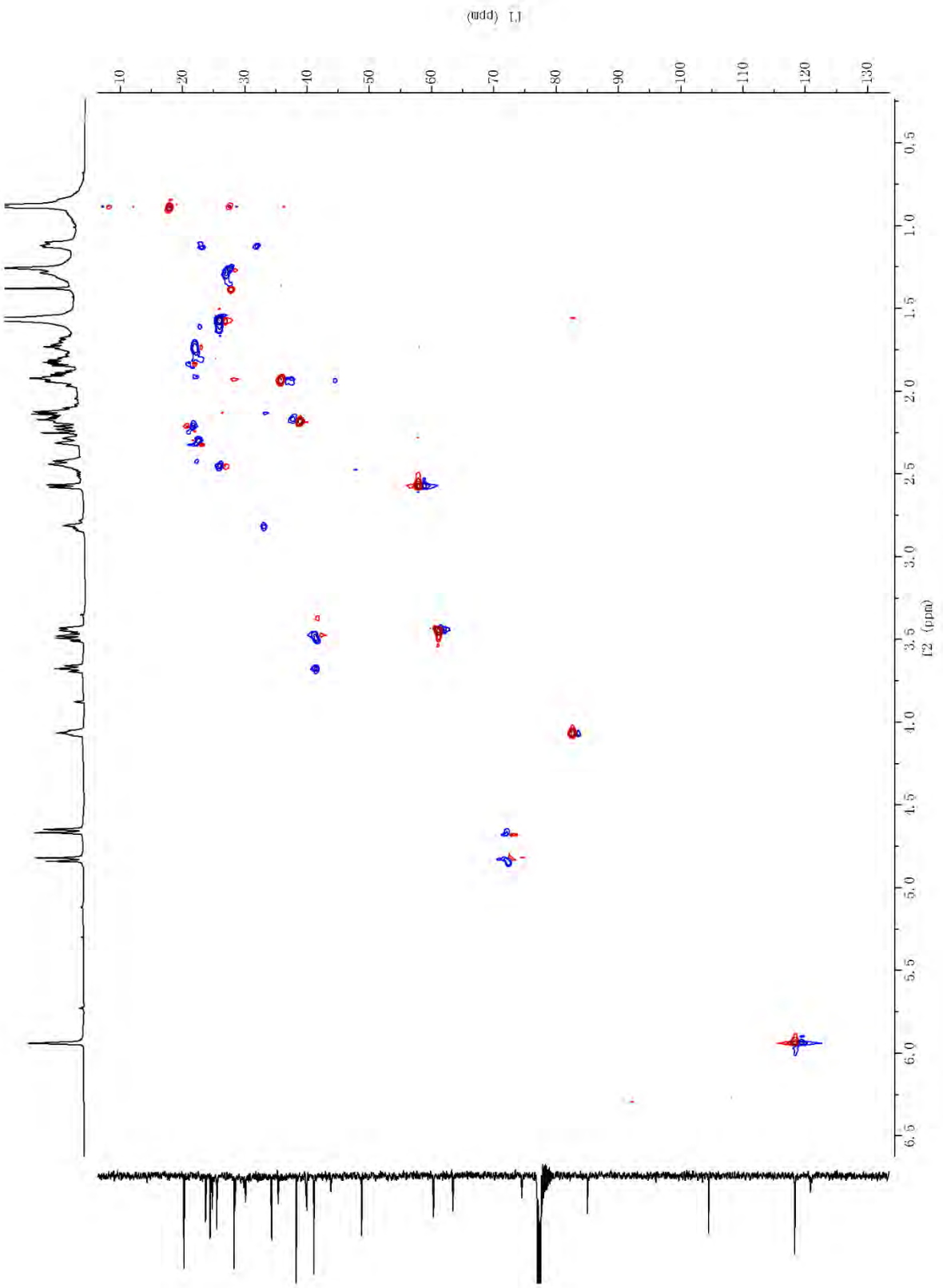
^{1}H NMR: Compound **238**



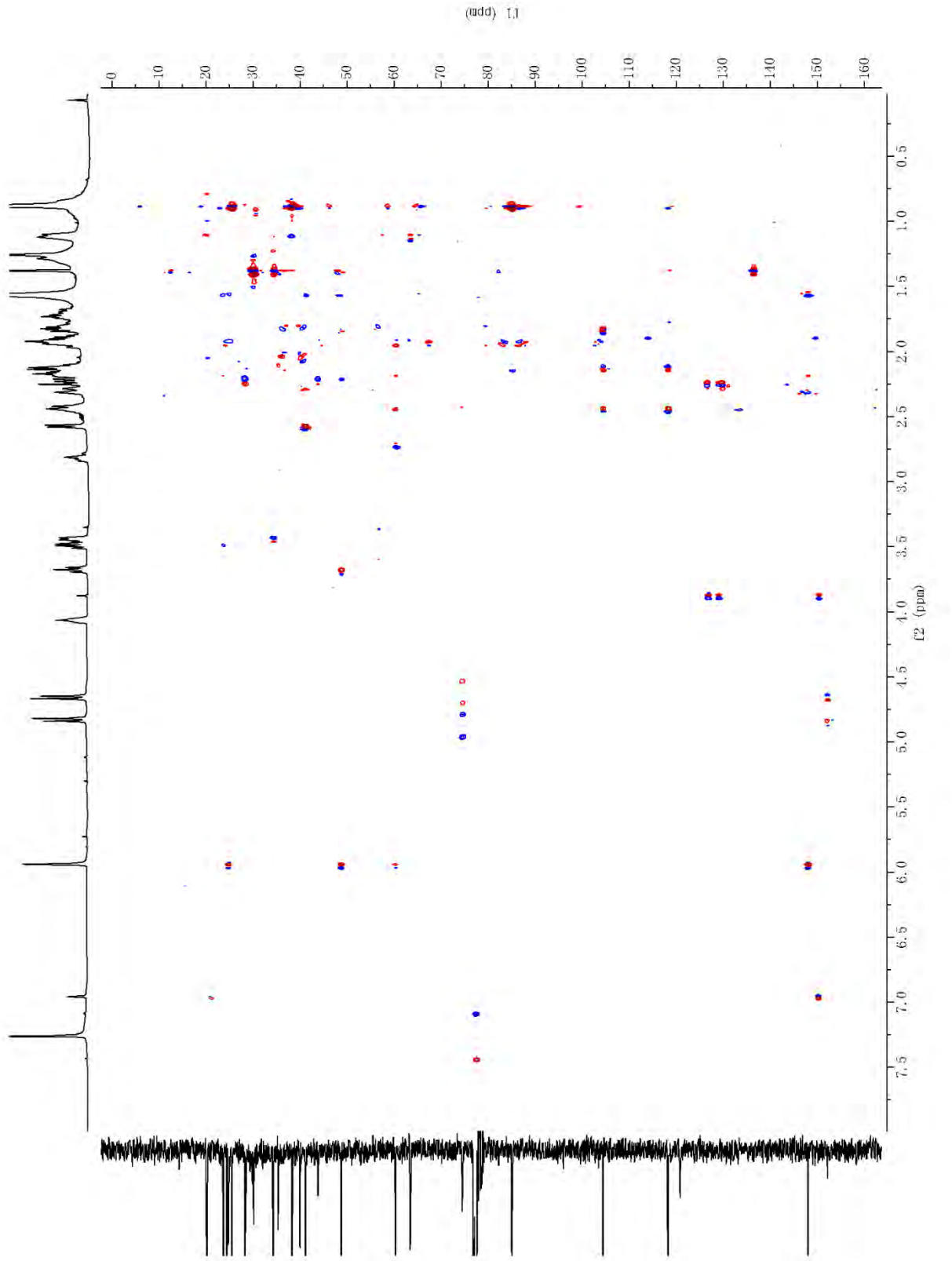
^{13}C NMR: Compound **238**



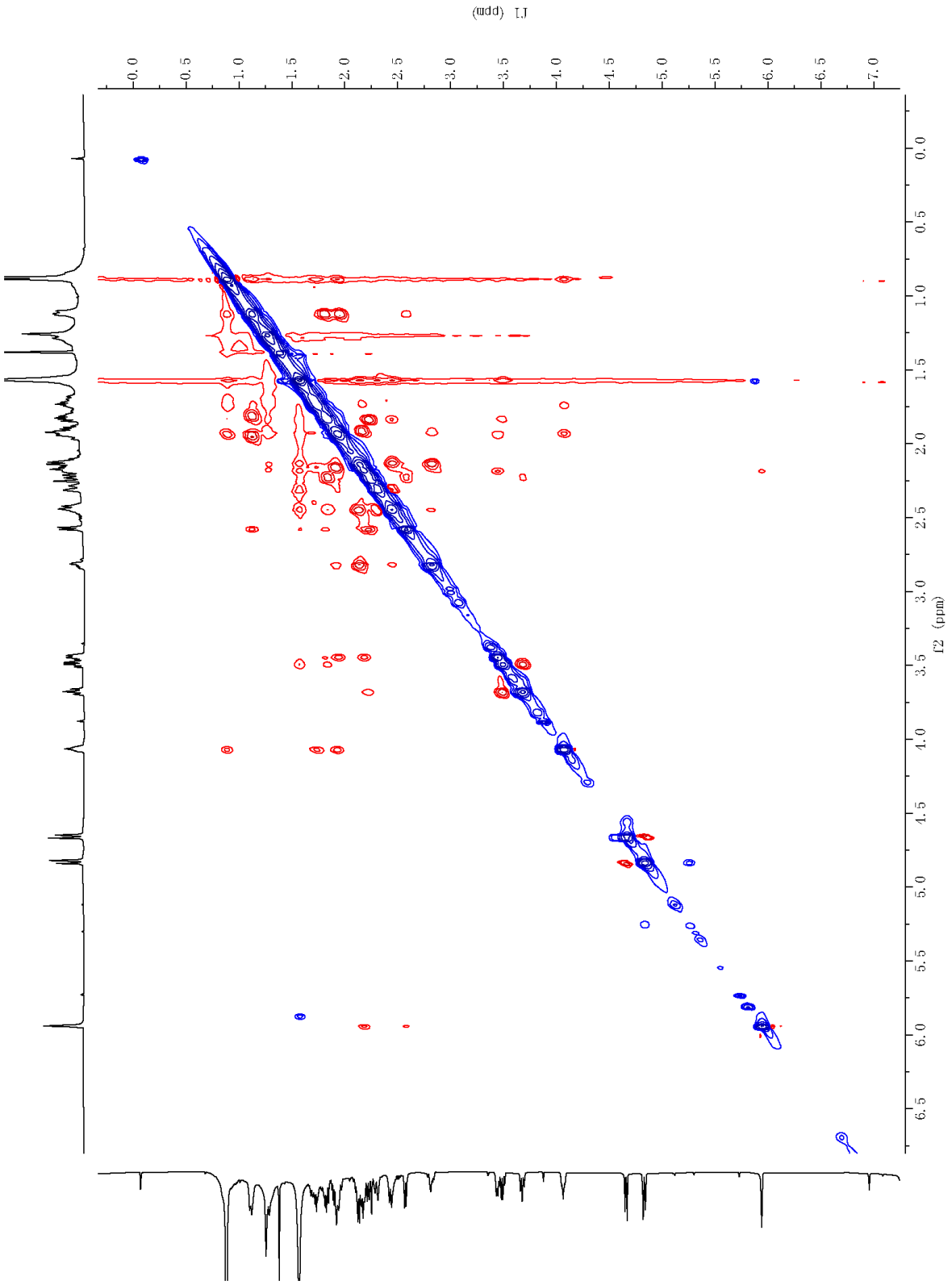
^{1}H-^{13}C-HSQC: Compound **238**



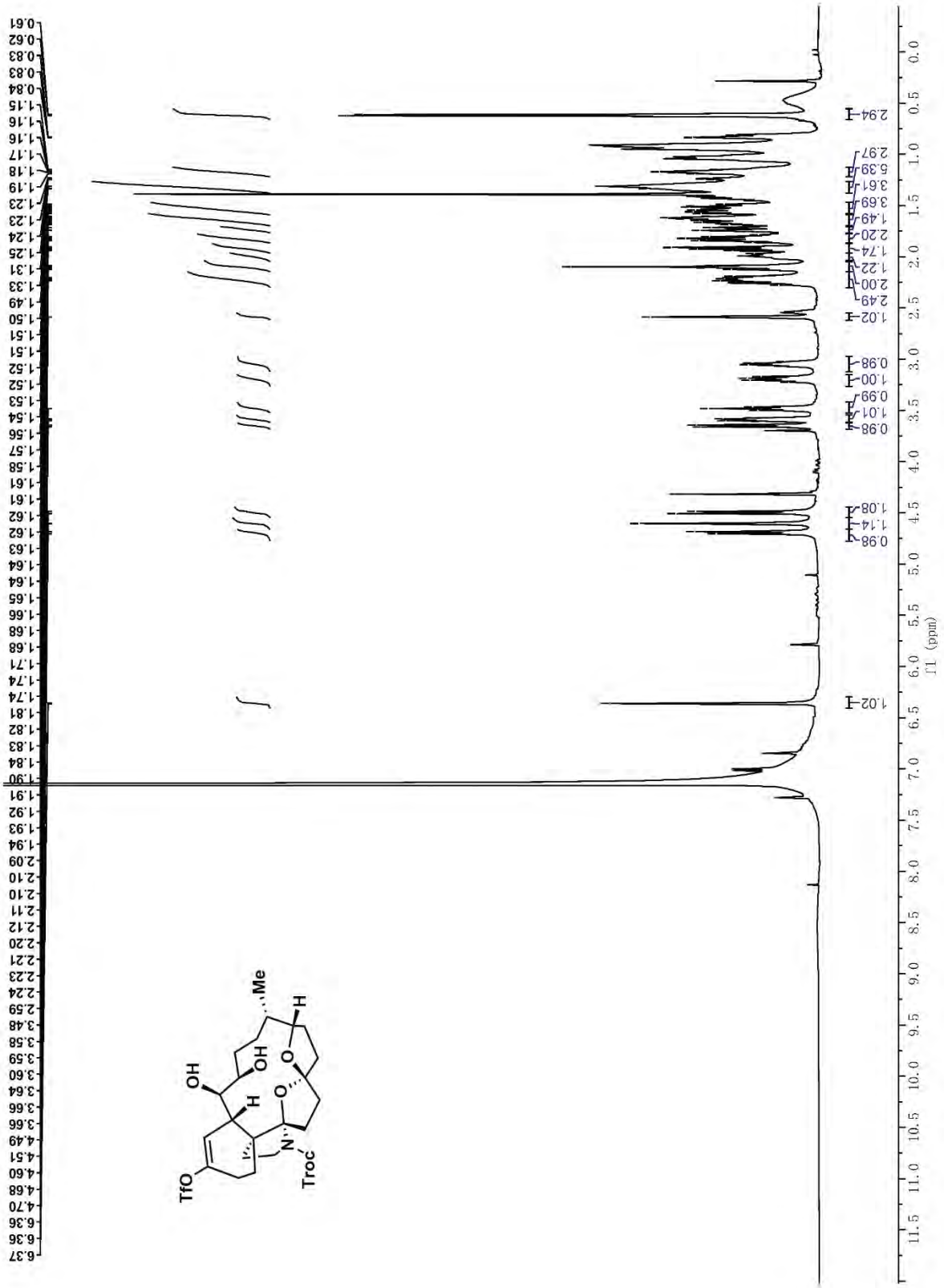
^{1}H-^{13}C-HMBC: Compound **238**



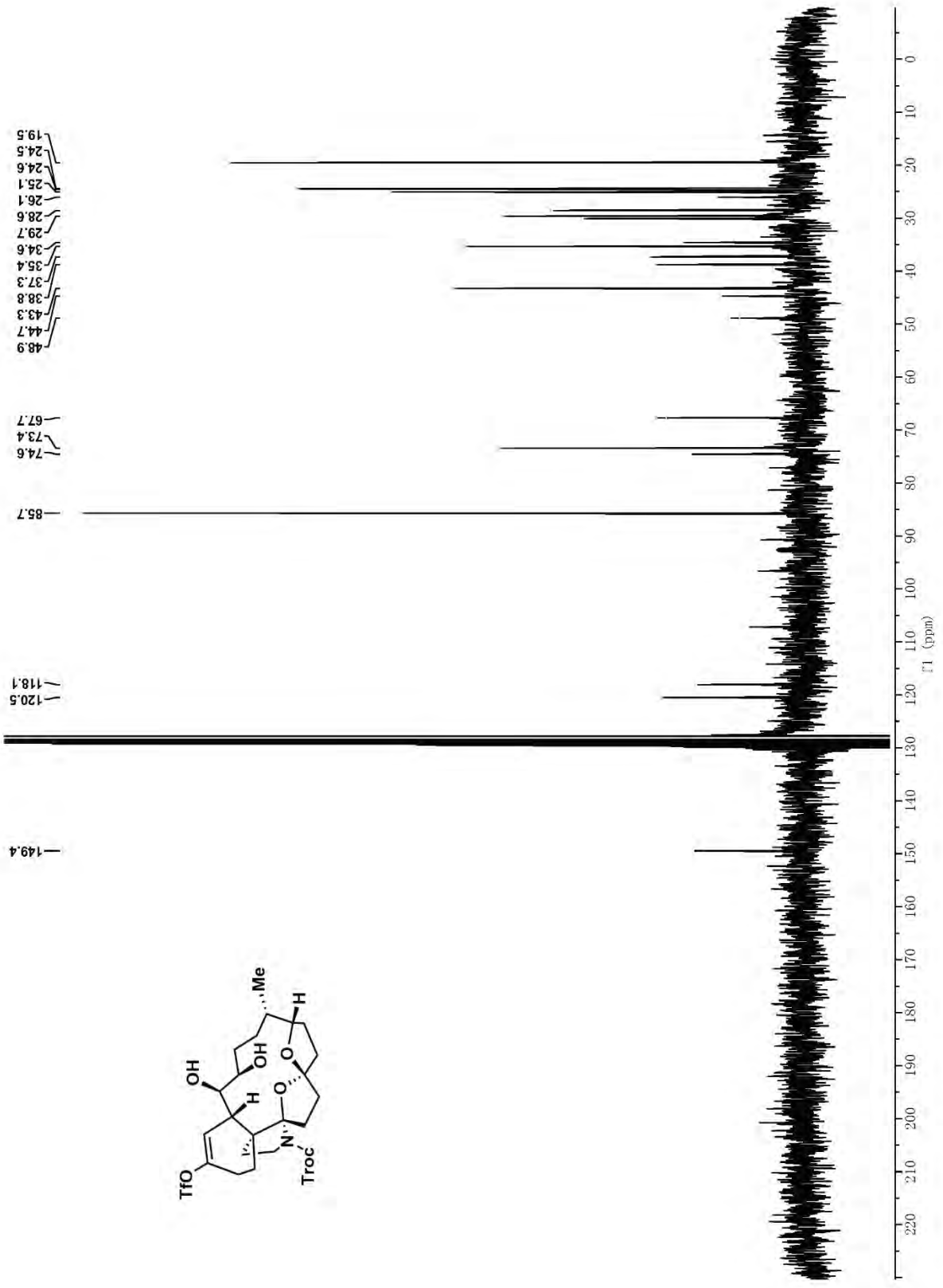
^{1}H-^{1}H-NOE: Compound **238**



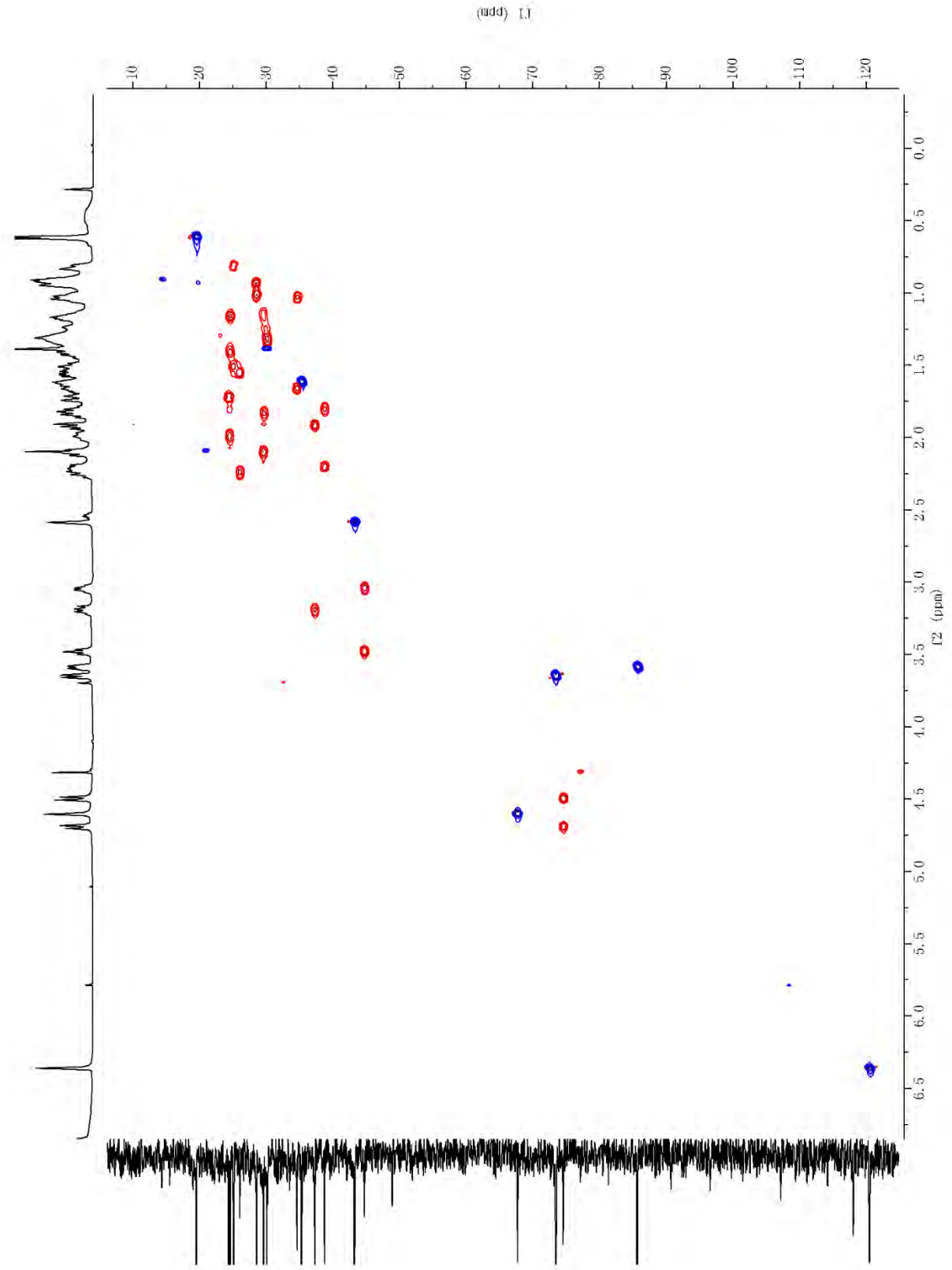
^{1}H NMR: Compound **239**



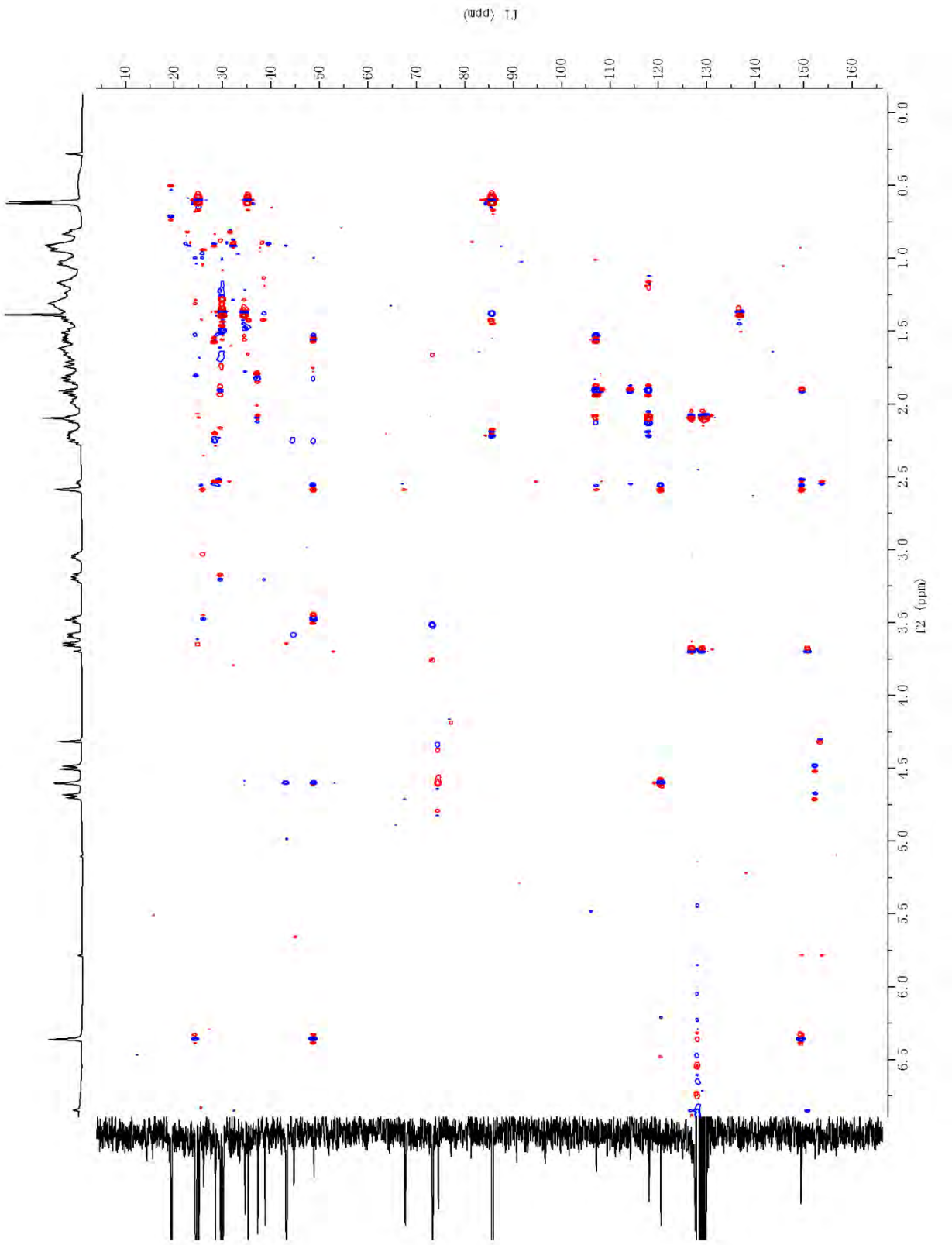
^{13}C NMR: Compound **239**



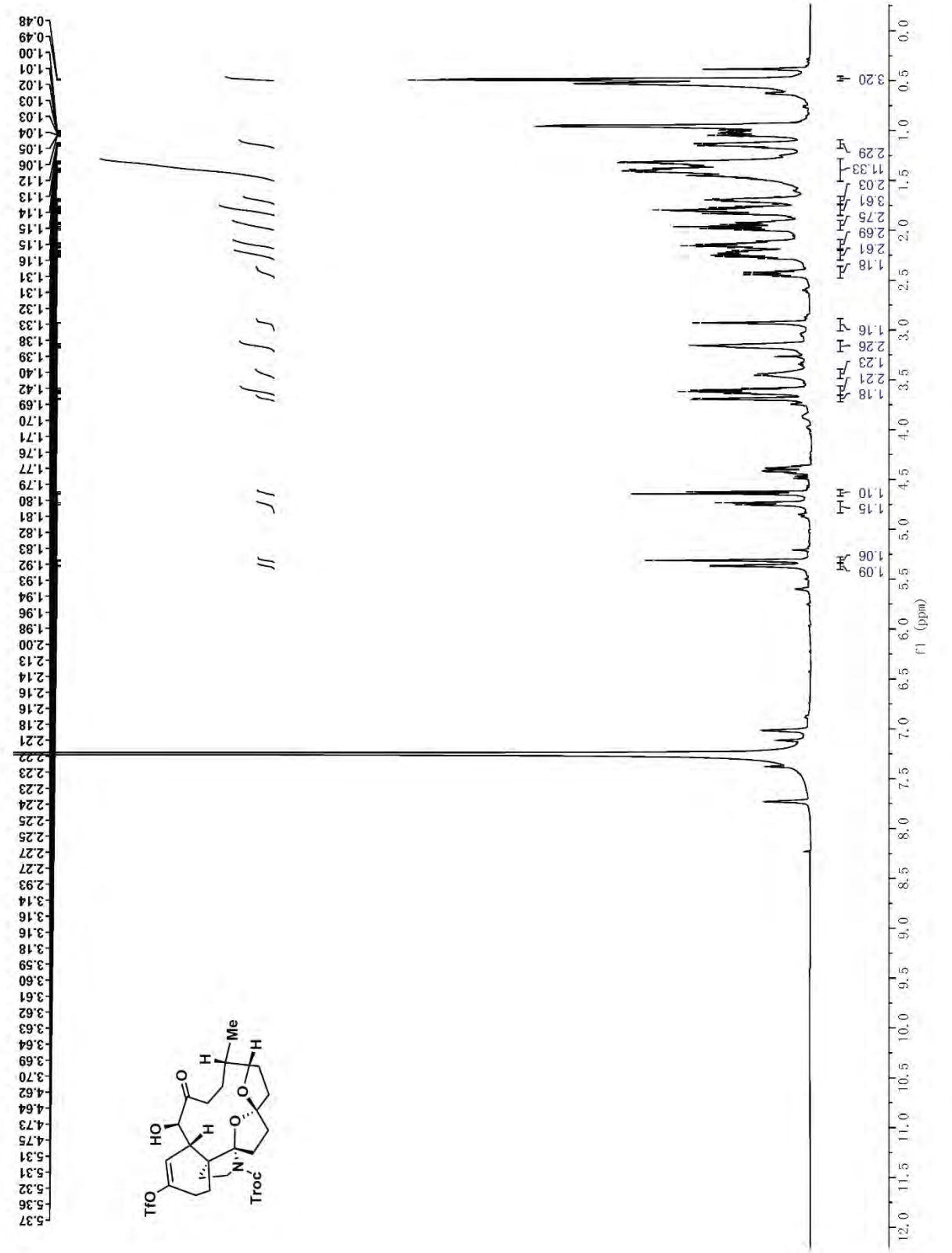
^{1}H-^{13}C-HSQC: Compound **239**



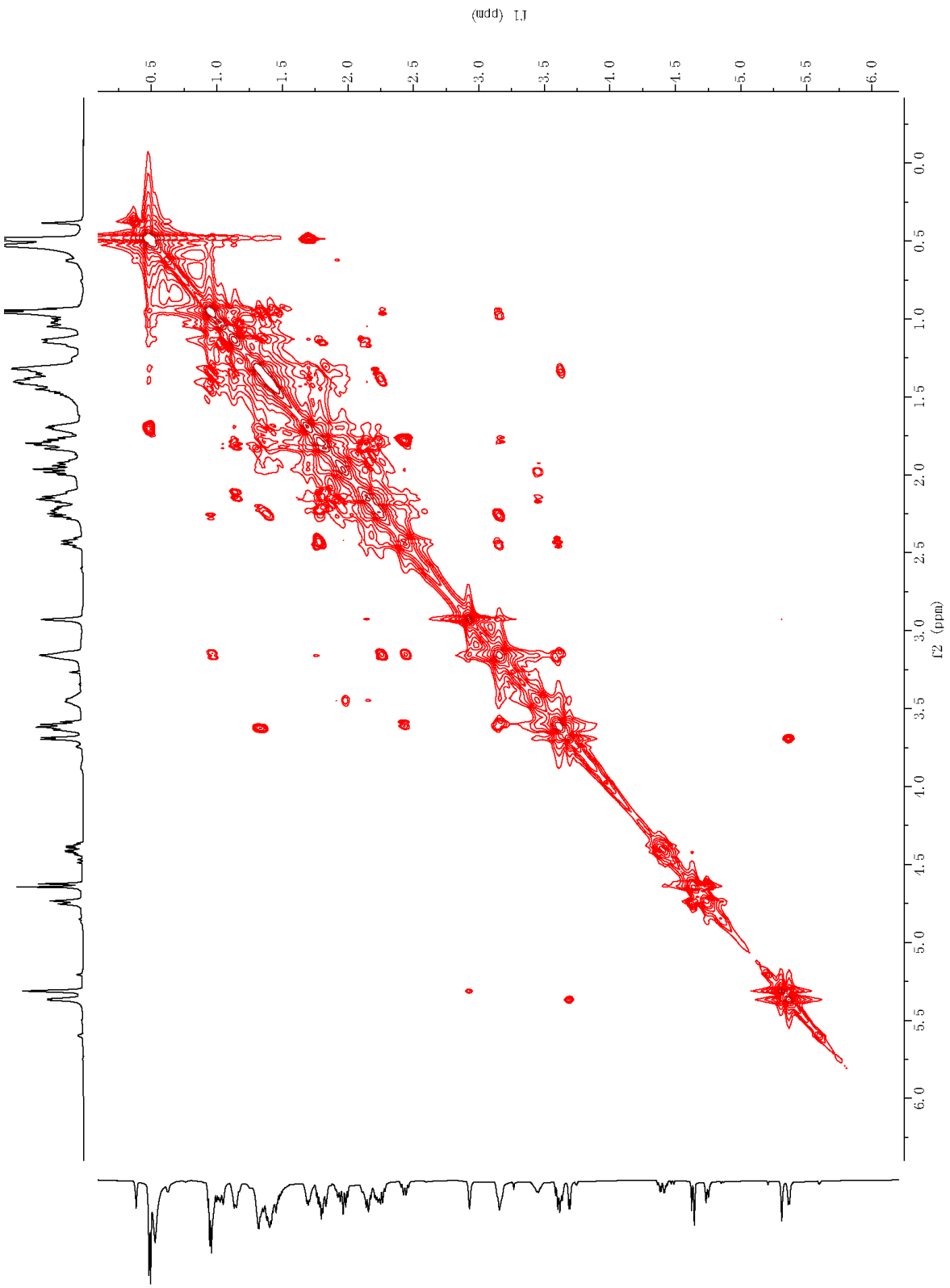
^{1}H-^{13}C-HMBC: Compound **239**



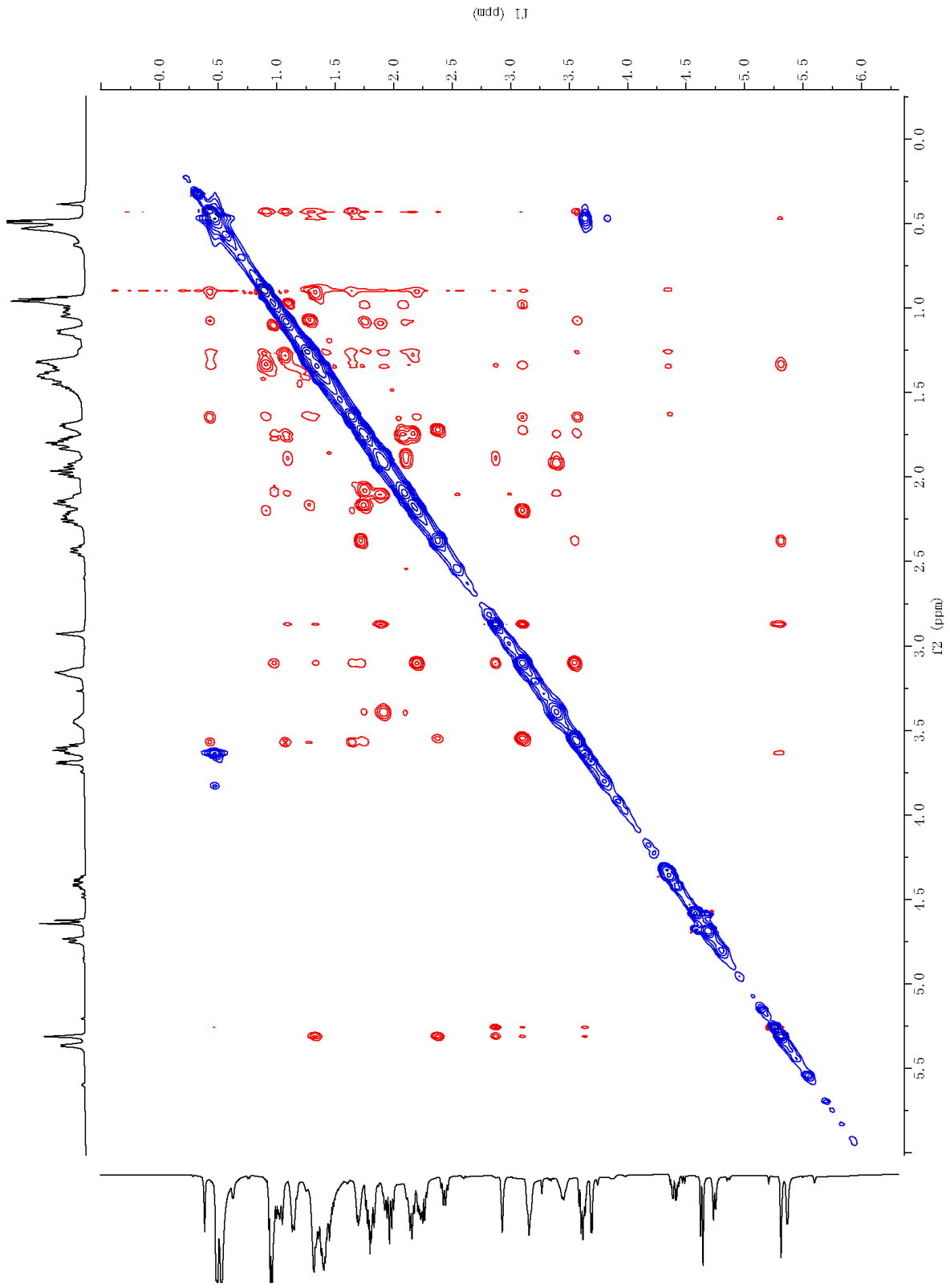
^{1}H NMR: Compound **240**



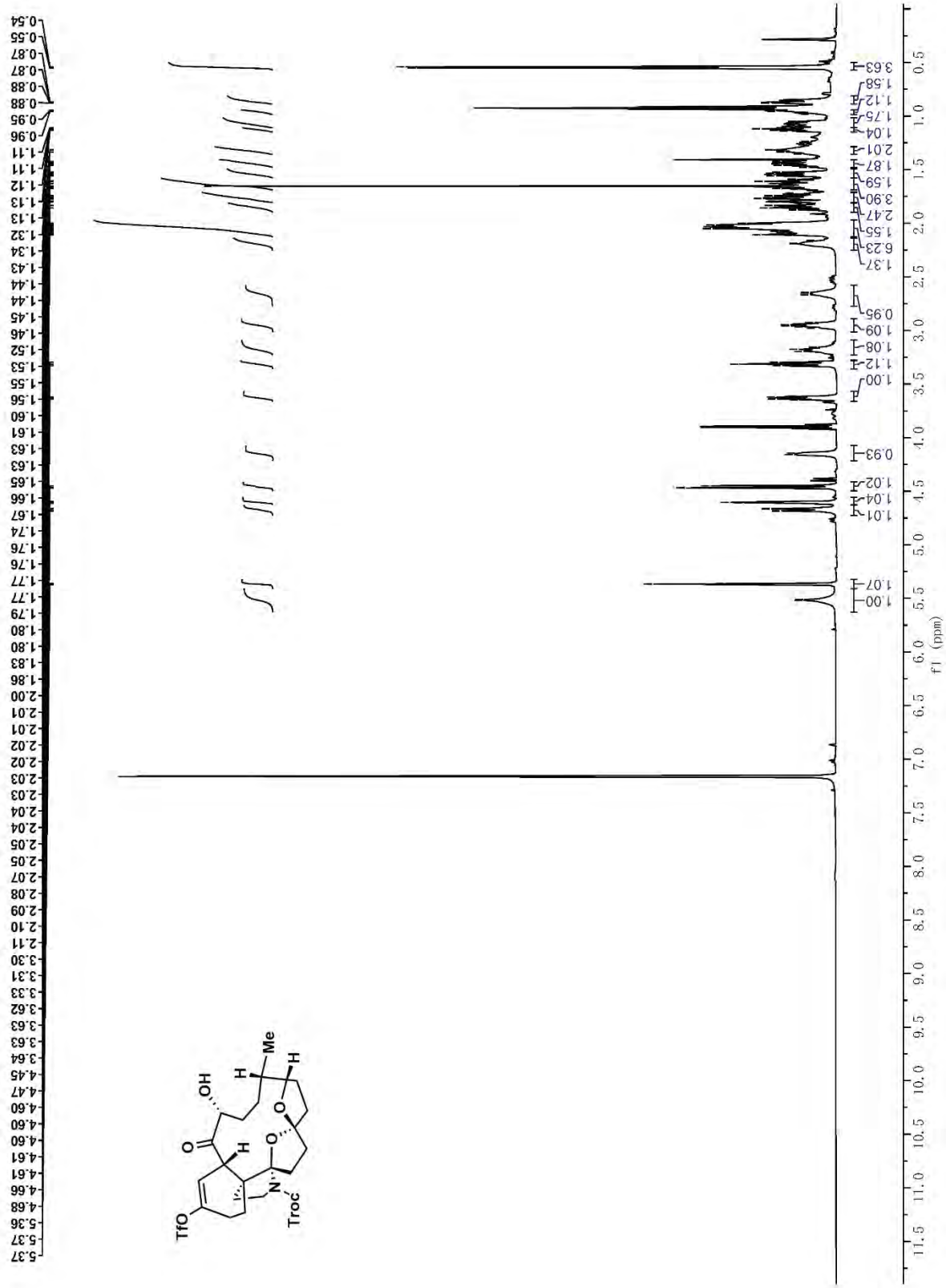
^{1}H-^{1}H-COSY: Compound **240**



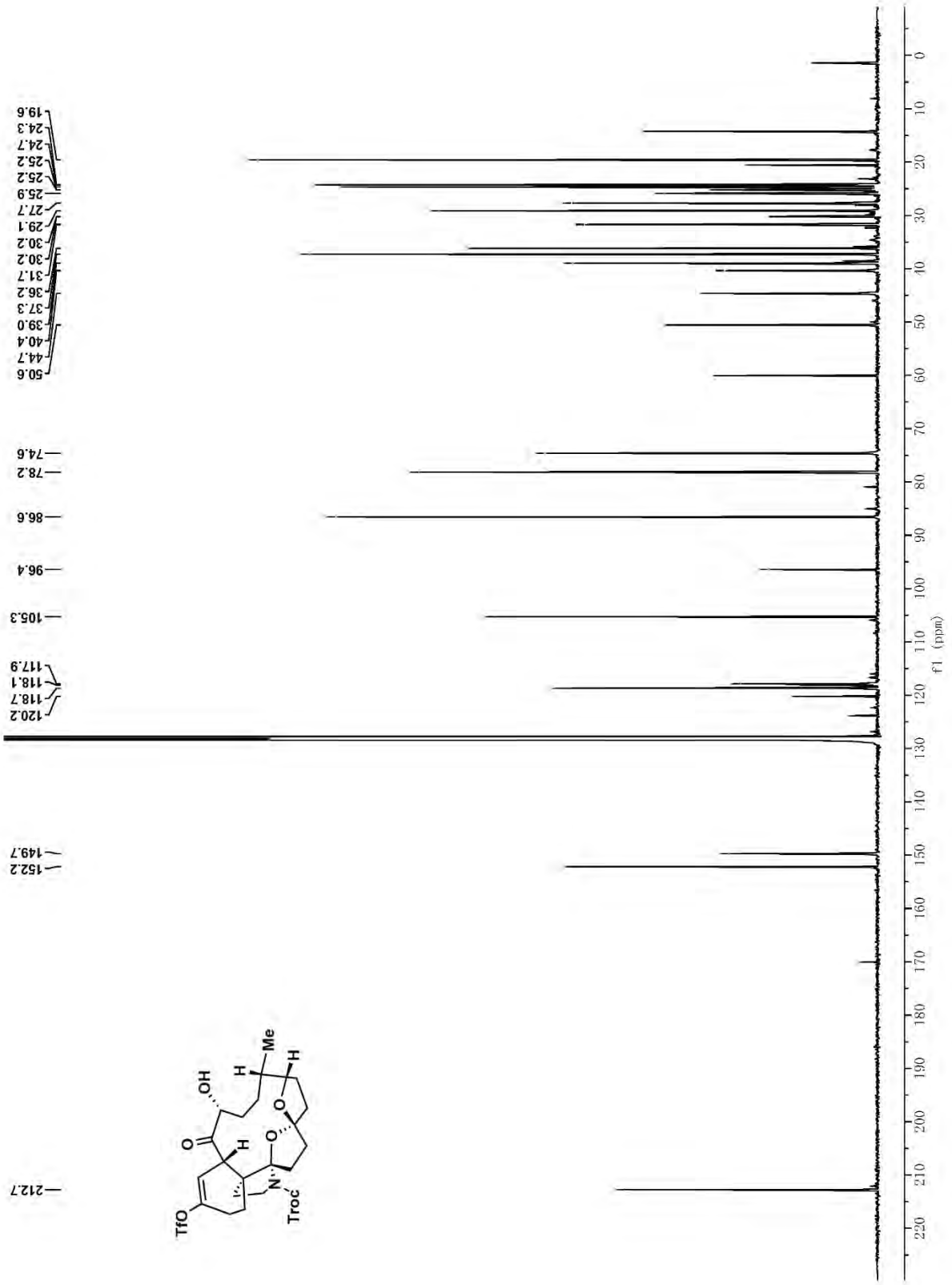
^{1}H-^{1}H-NOESY: Compound **240**



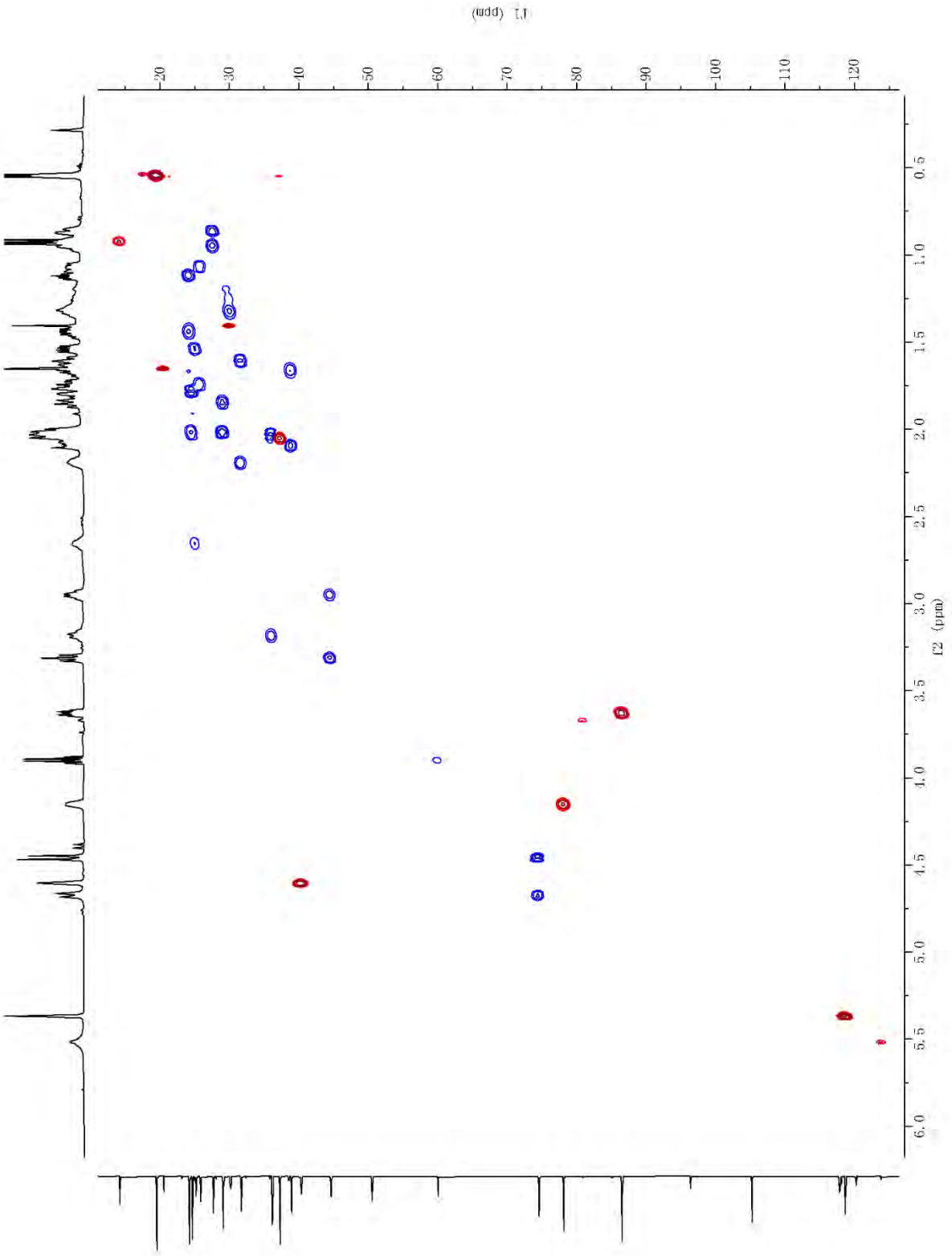
^{1}H NMR: Compound **242**



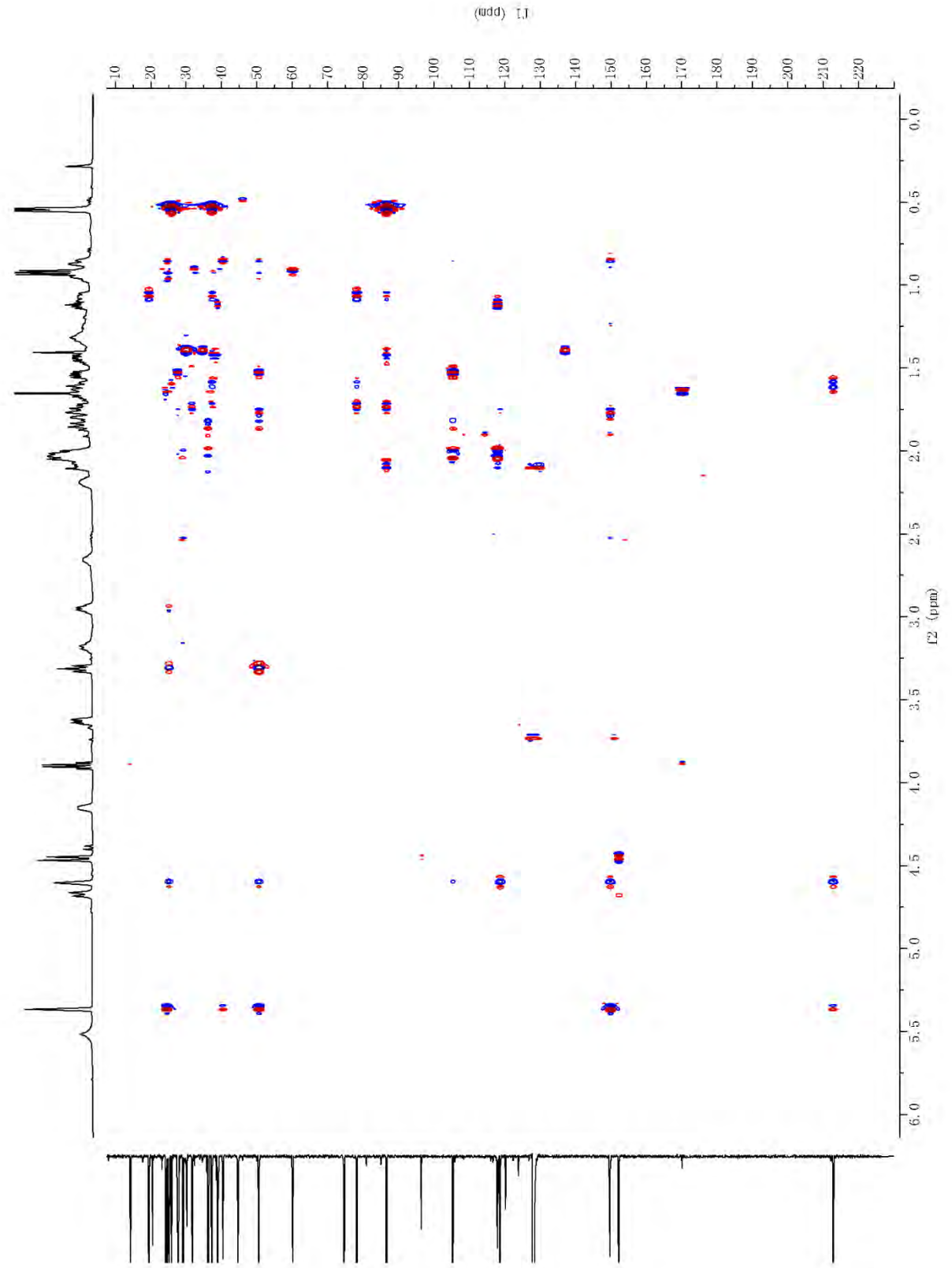
^{13}C NMR: Compound **242**



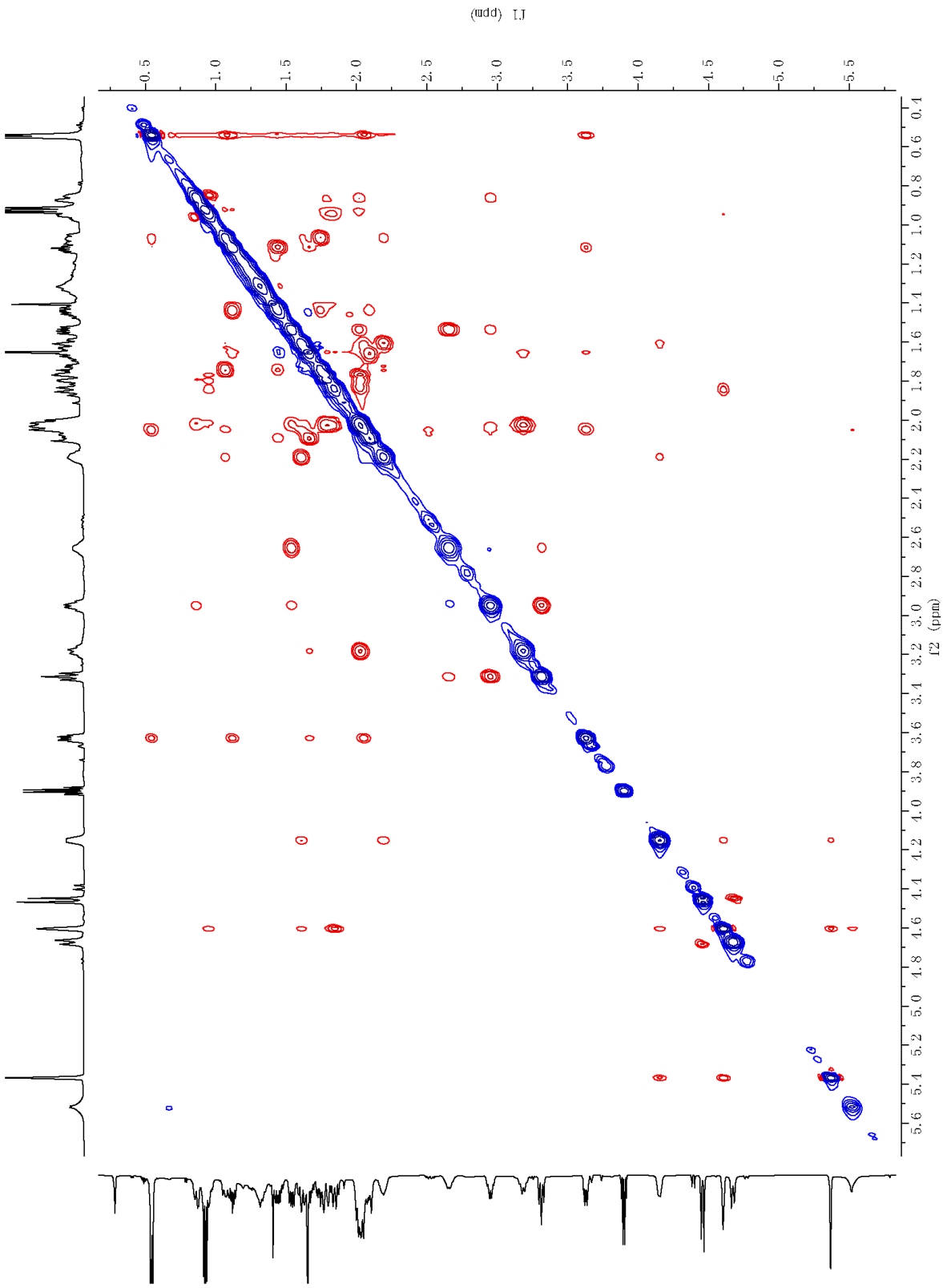
^{1}H-^{13}C-HSQC: Compound **242**



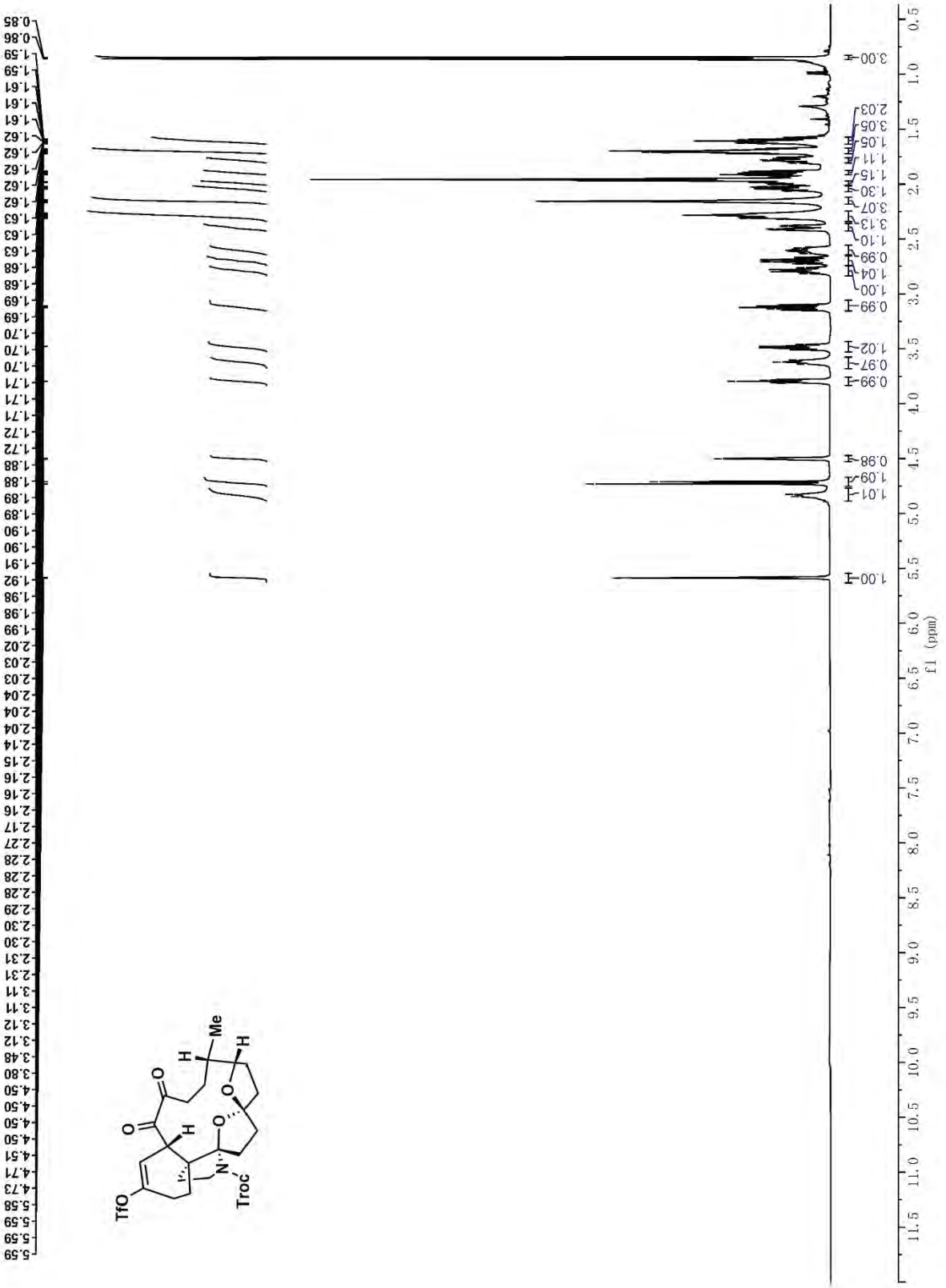
^{1}H-^{13}C-HMBC: Compound **242**



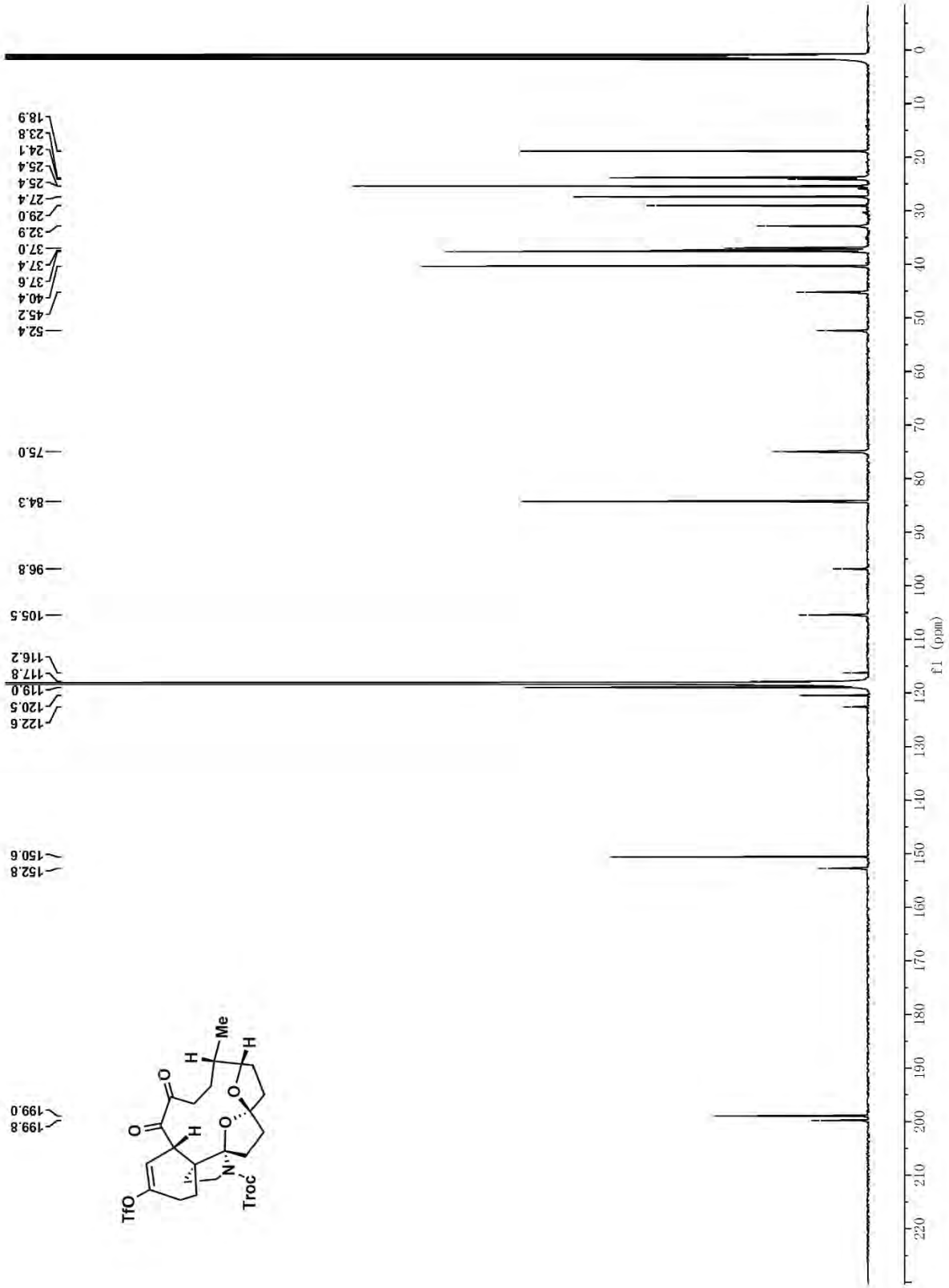
^{1}H-^{1}H-NOESY: Compound **242**



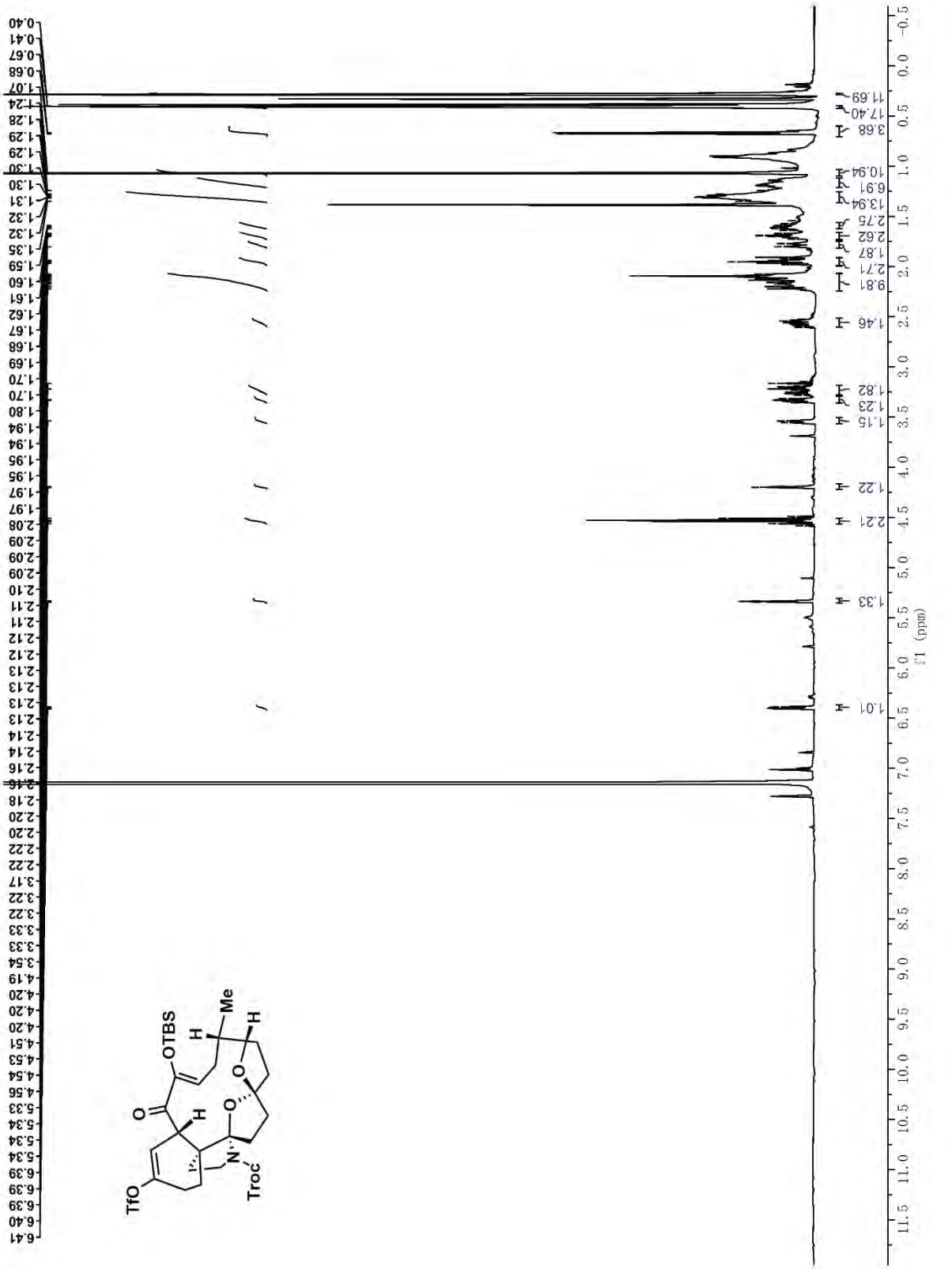
^{1}H NMR: Compound **243**



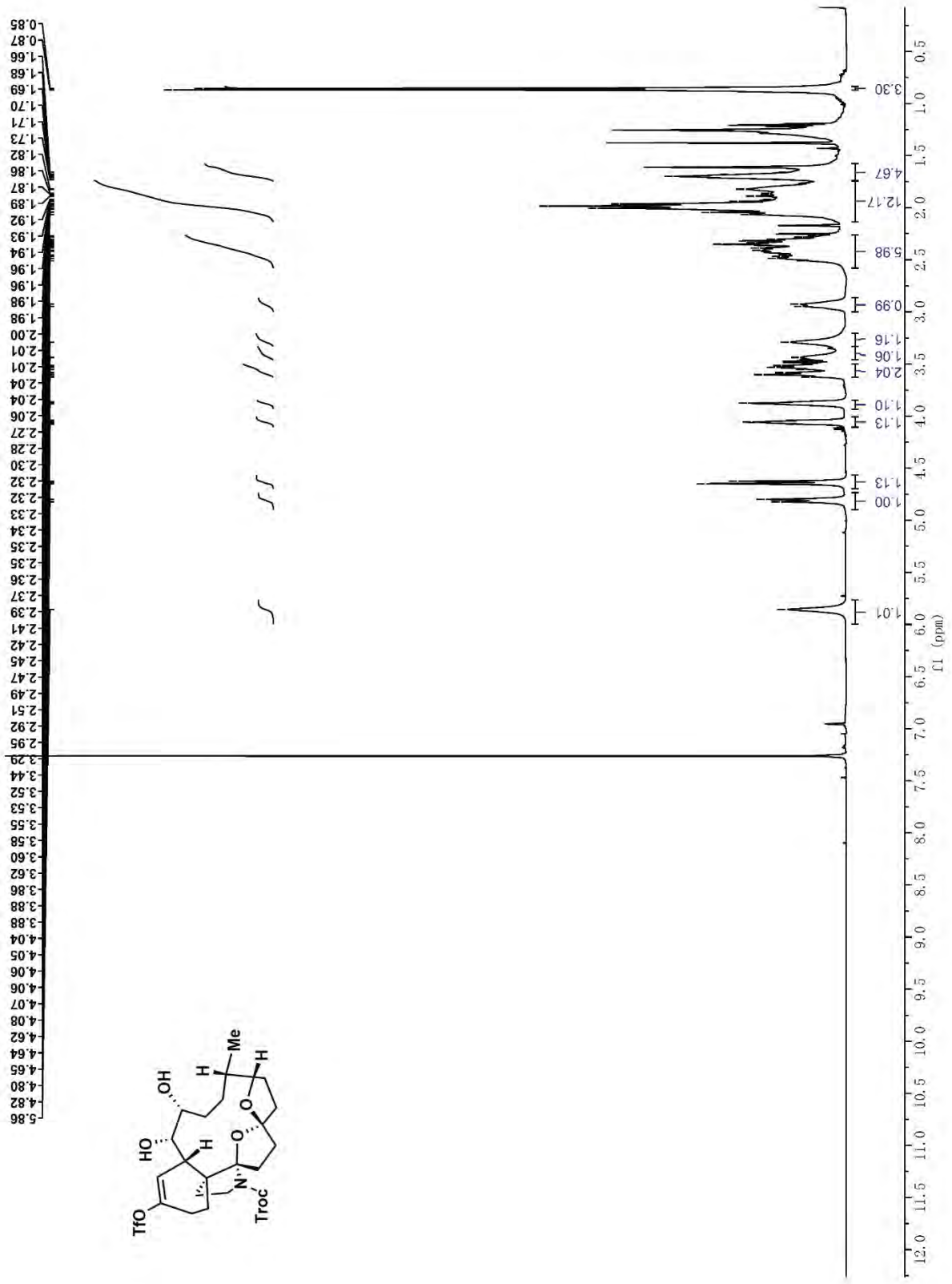
^{13}C NMR: Compound **243**



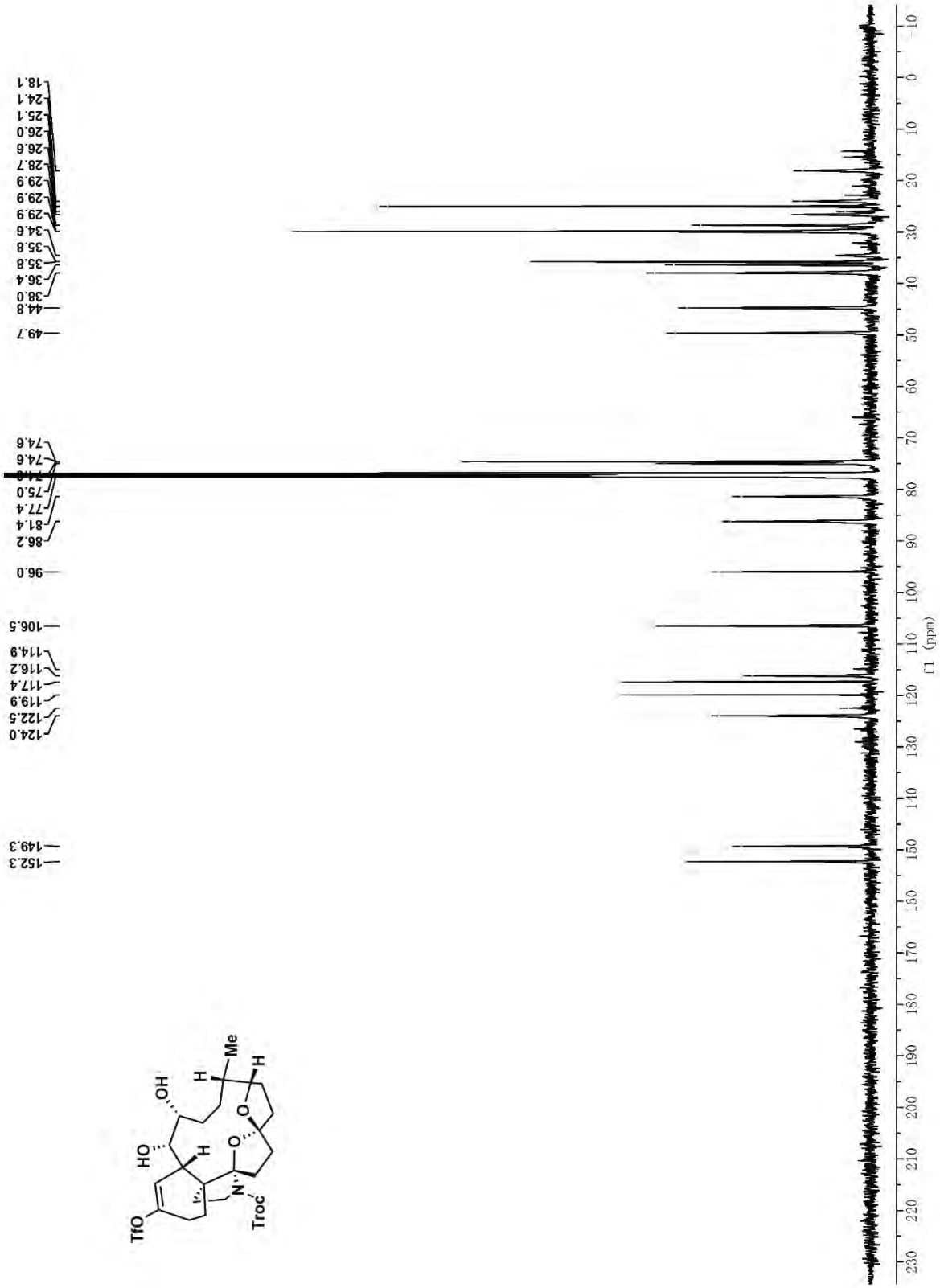
^{1}H NMR: Compound **246**



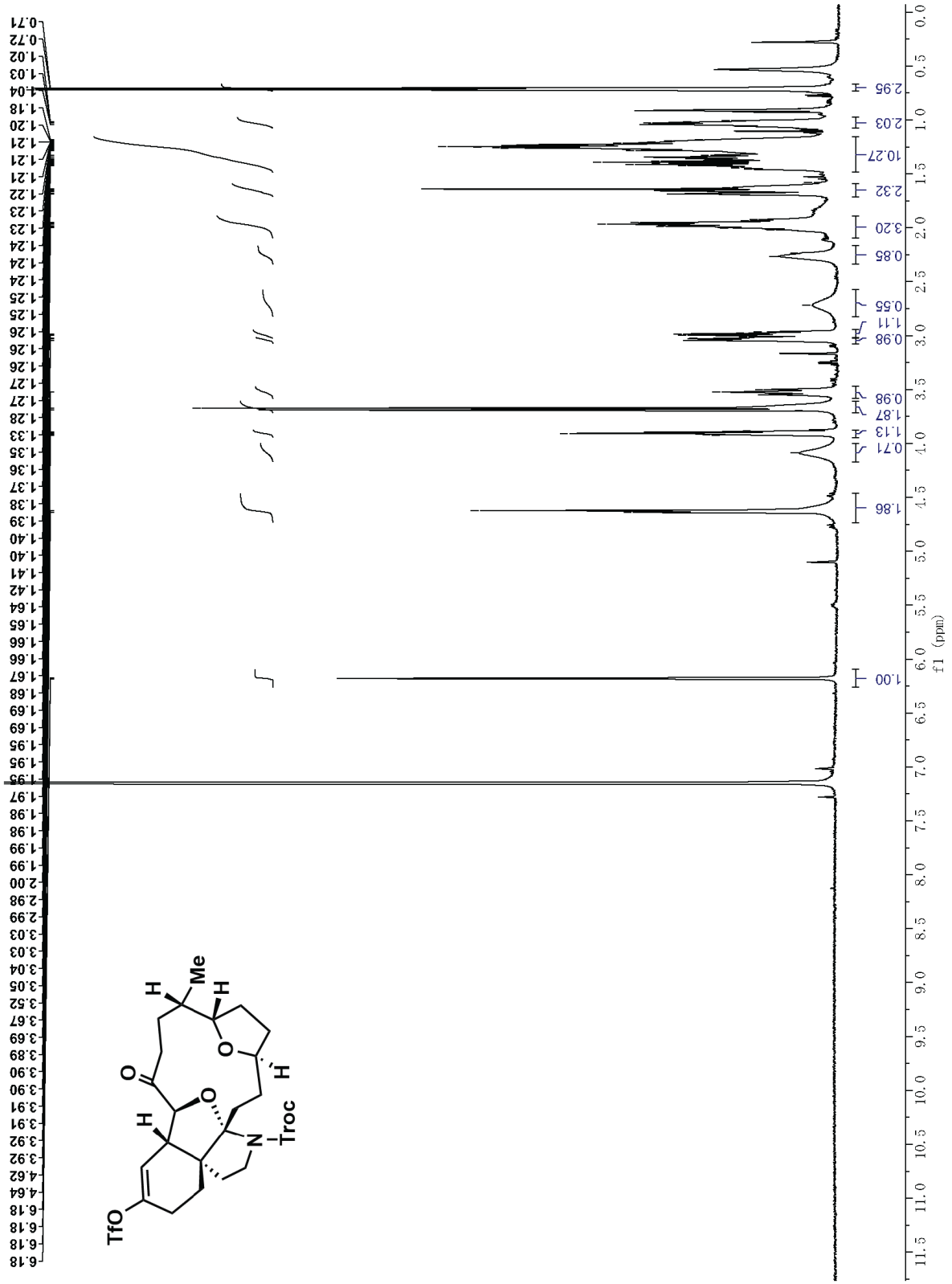
^{1}H NMR: Compound **248**



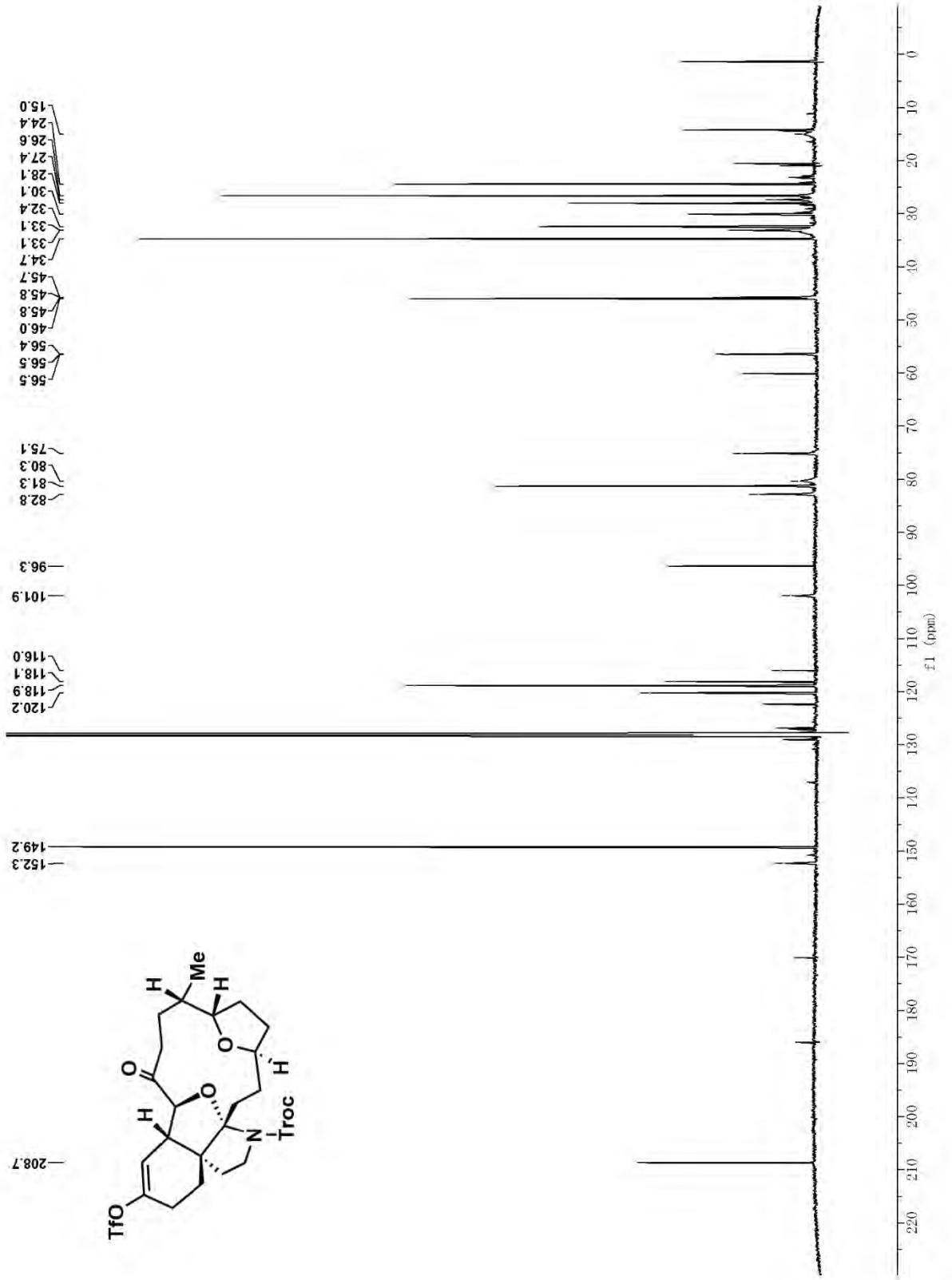
^{13}C NMR: Compound **248**



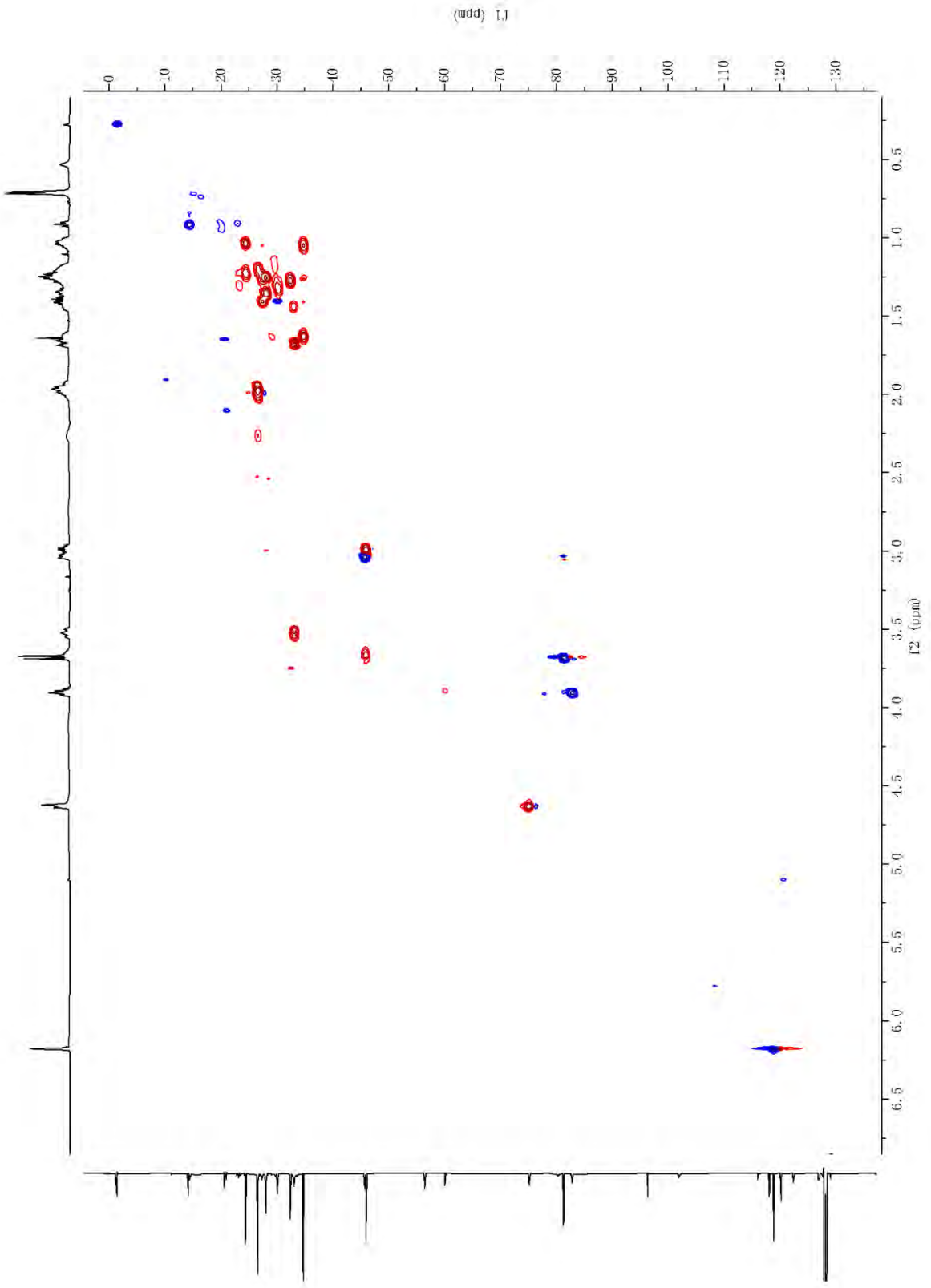
^{1}H NMR: Compound **251**



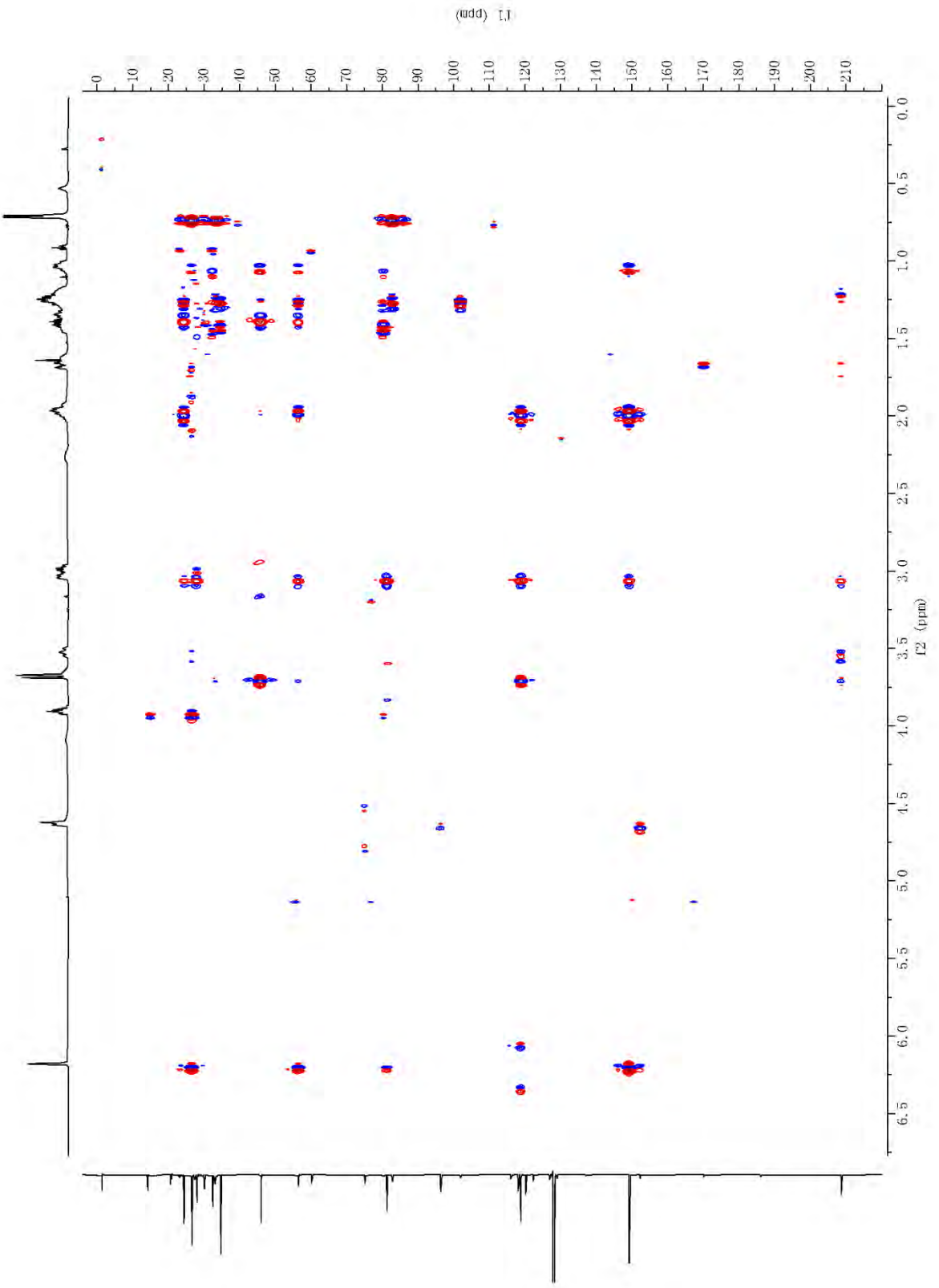
^{13}C NMR: Compound **251**



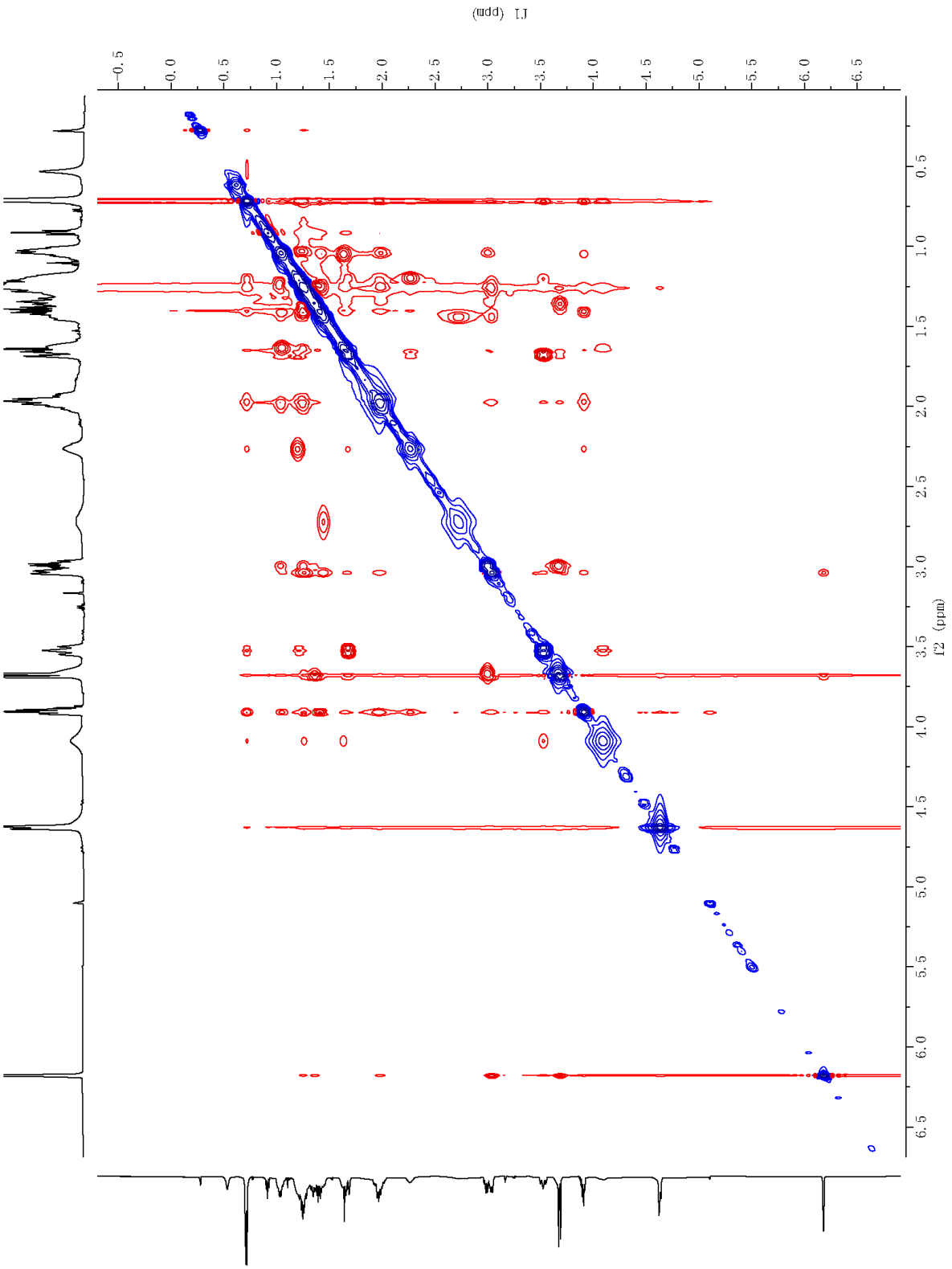
^{1}H-^{13}C-HSQC: Compound **251**



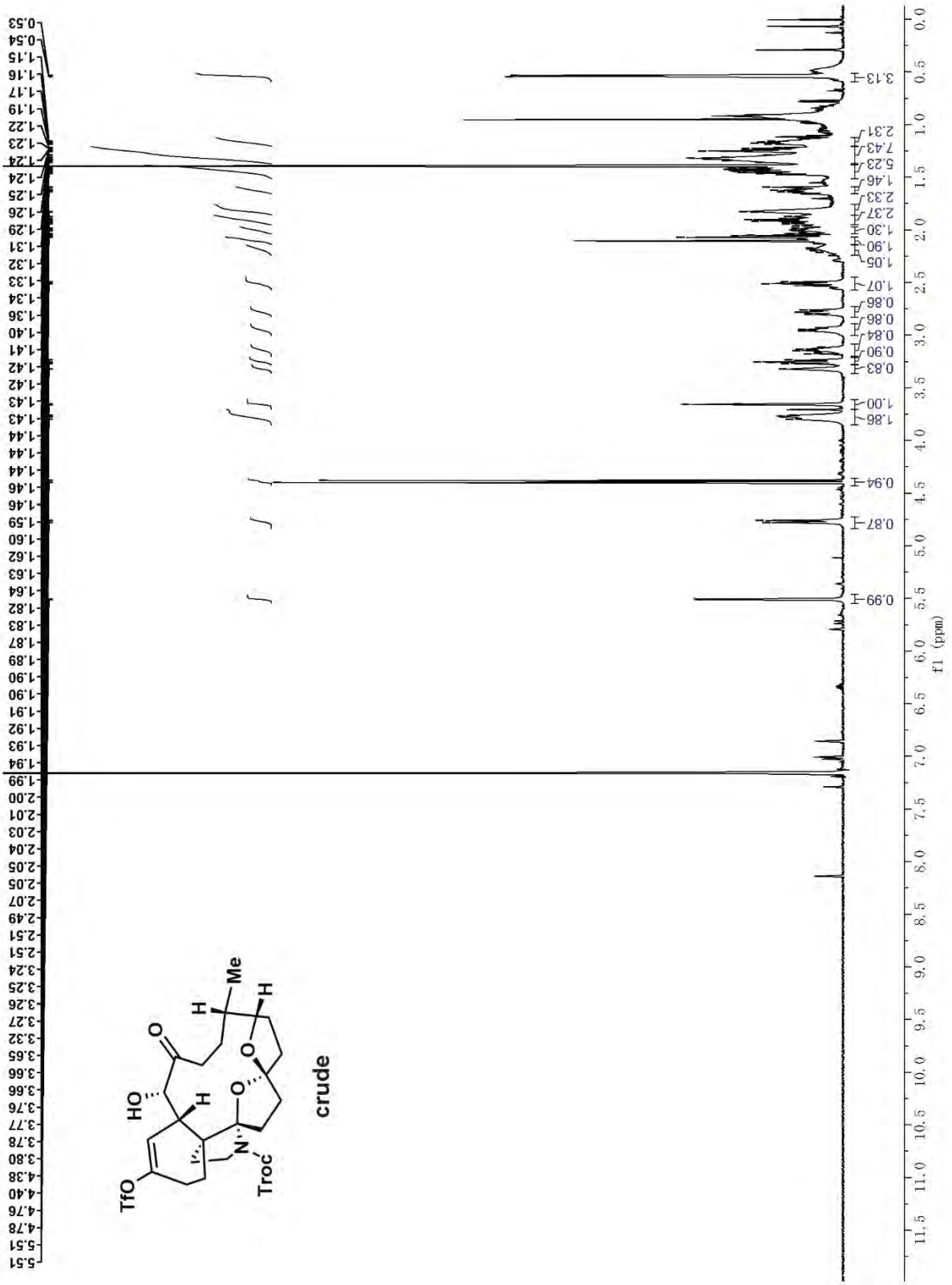
^{1}H-^{13}C-HMBC: Compound **251**



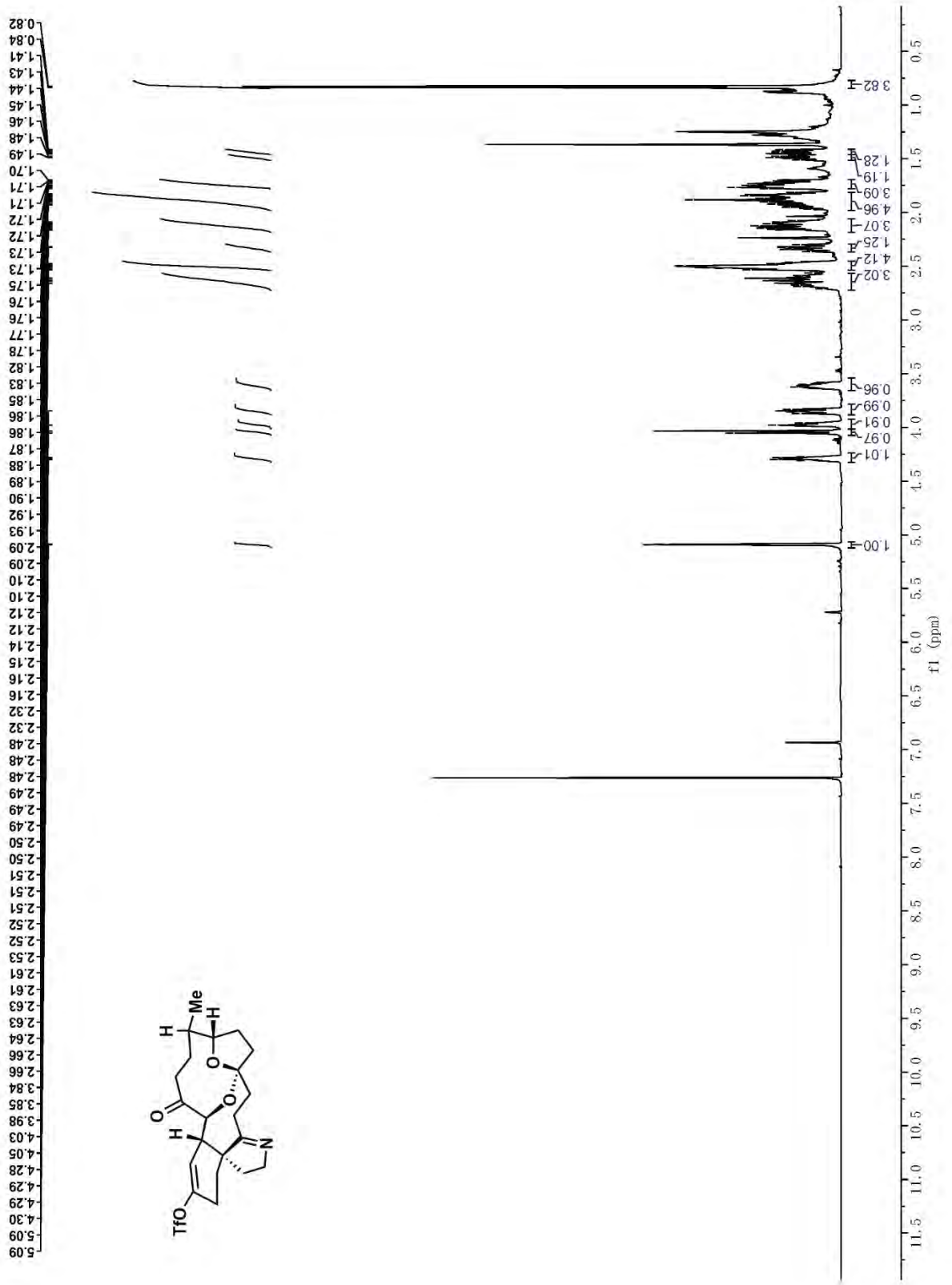
^{1}H-^{1}H-NOESY: Compound **251**



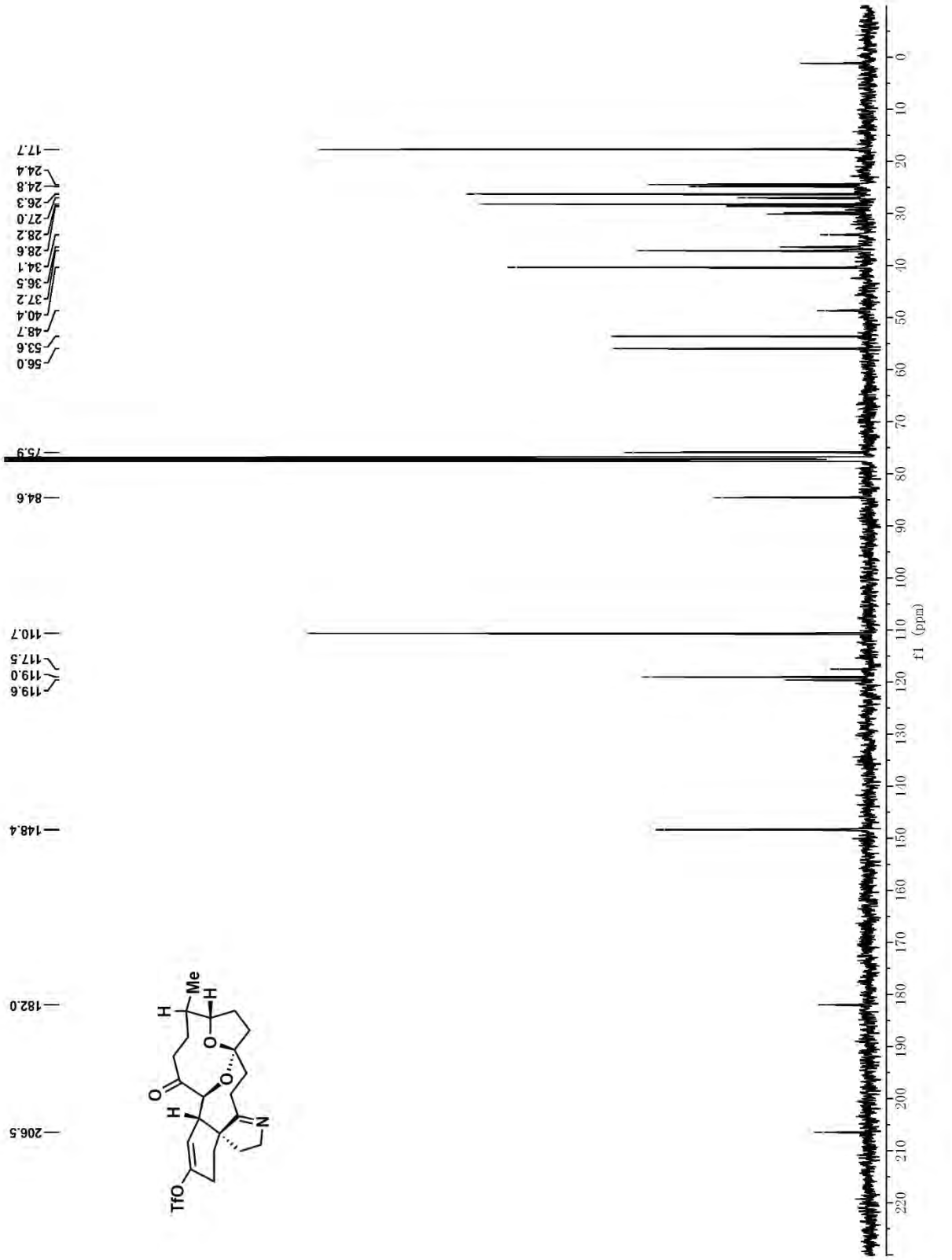
^{1}H NMR: Compound **252**



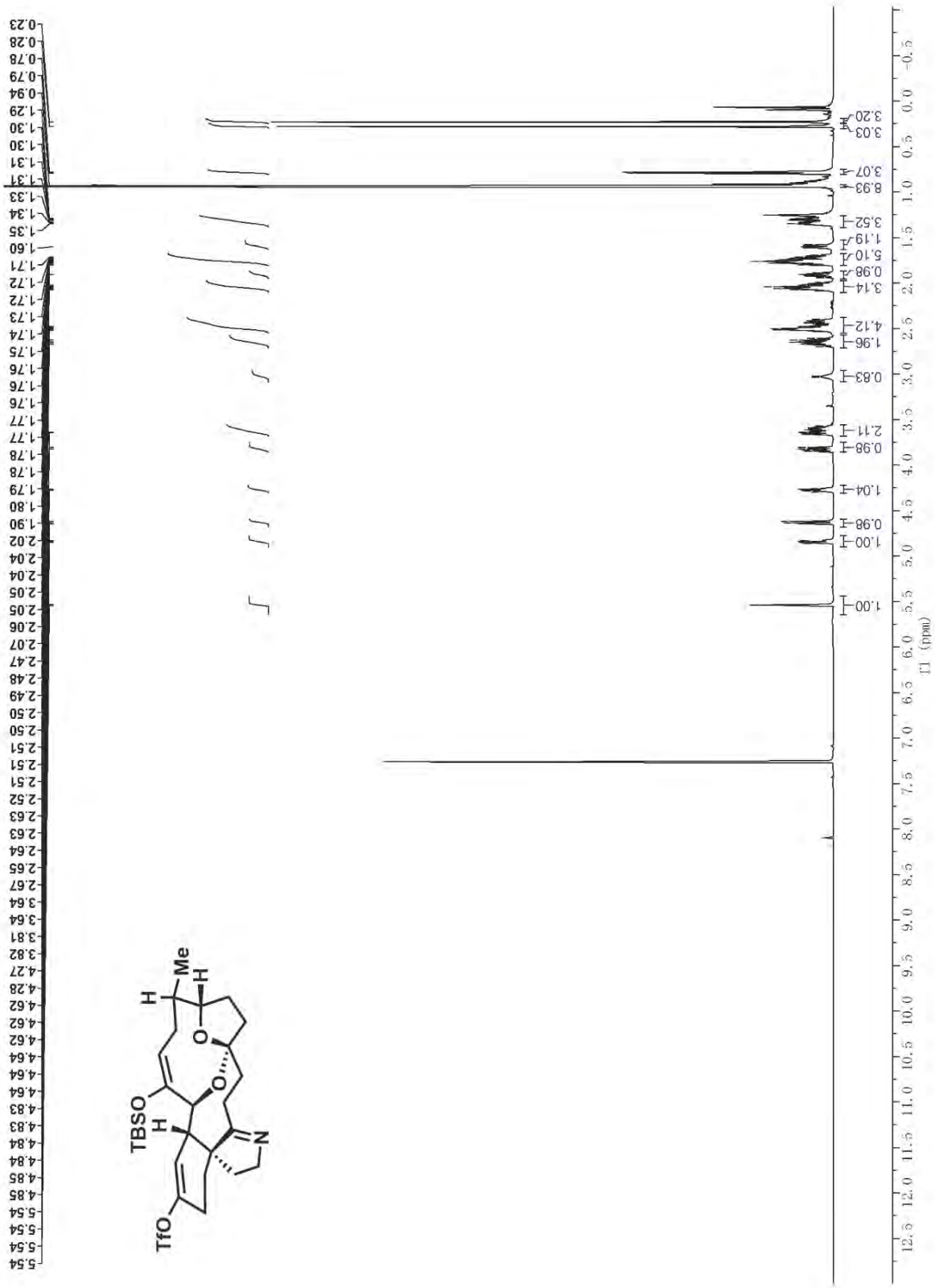
^{1}H NMR: Compound **255**



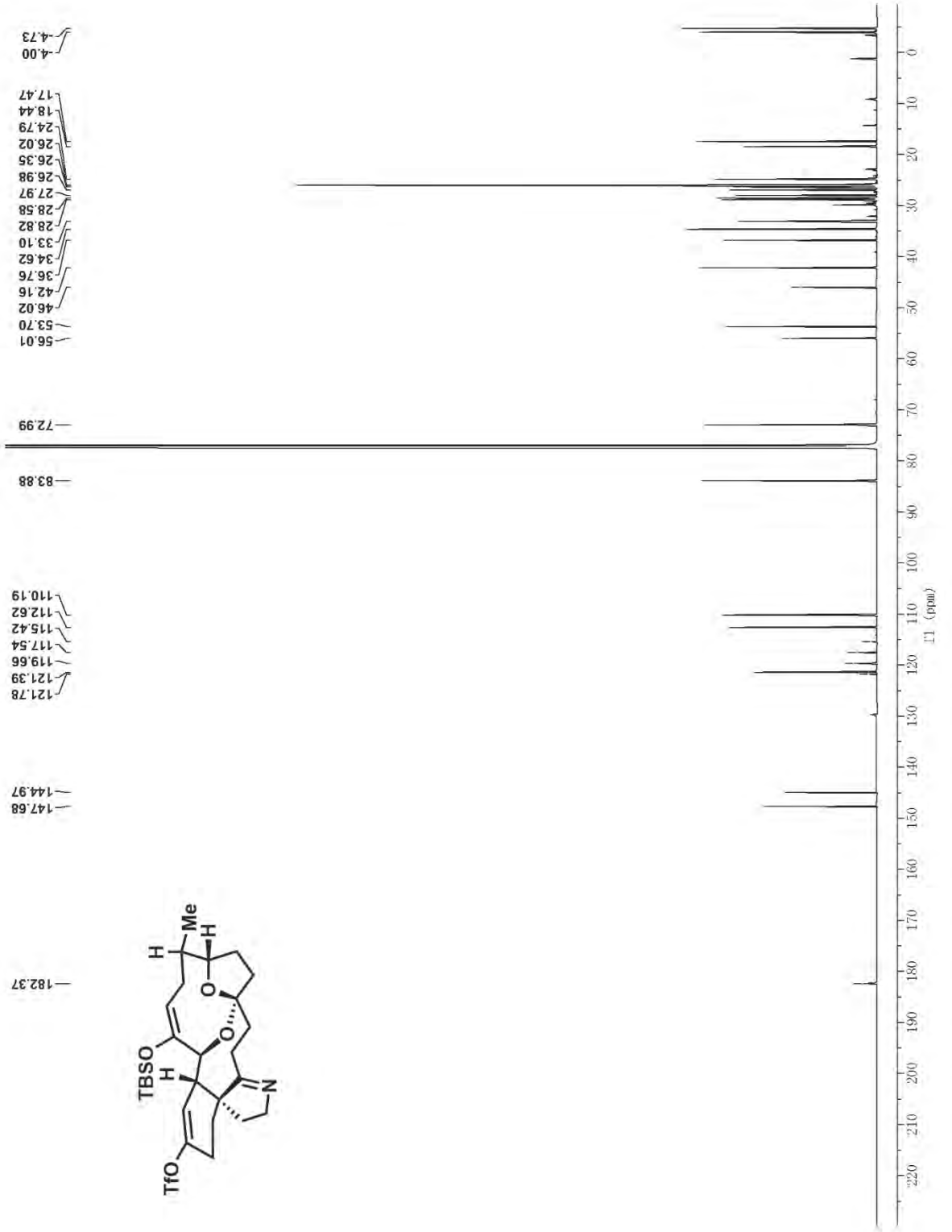
^{13}C NMR: Compound **255**



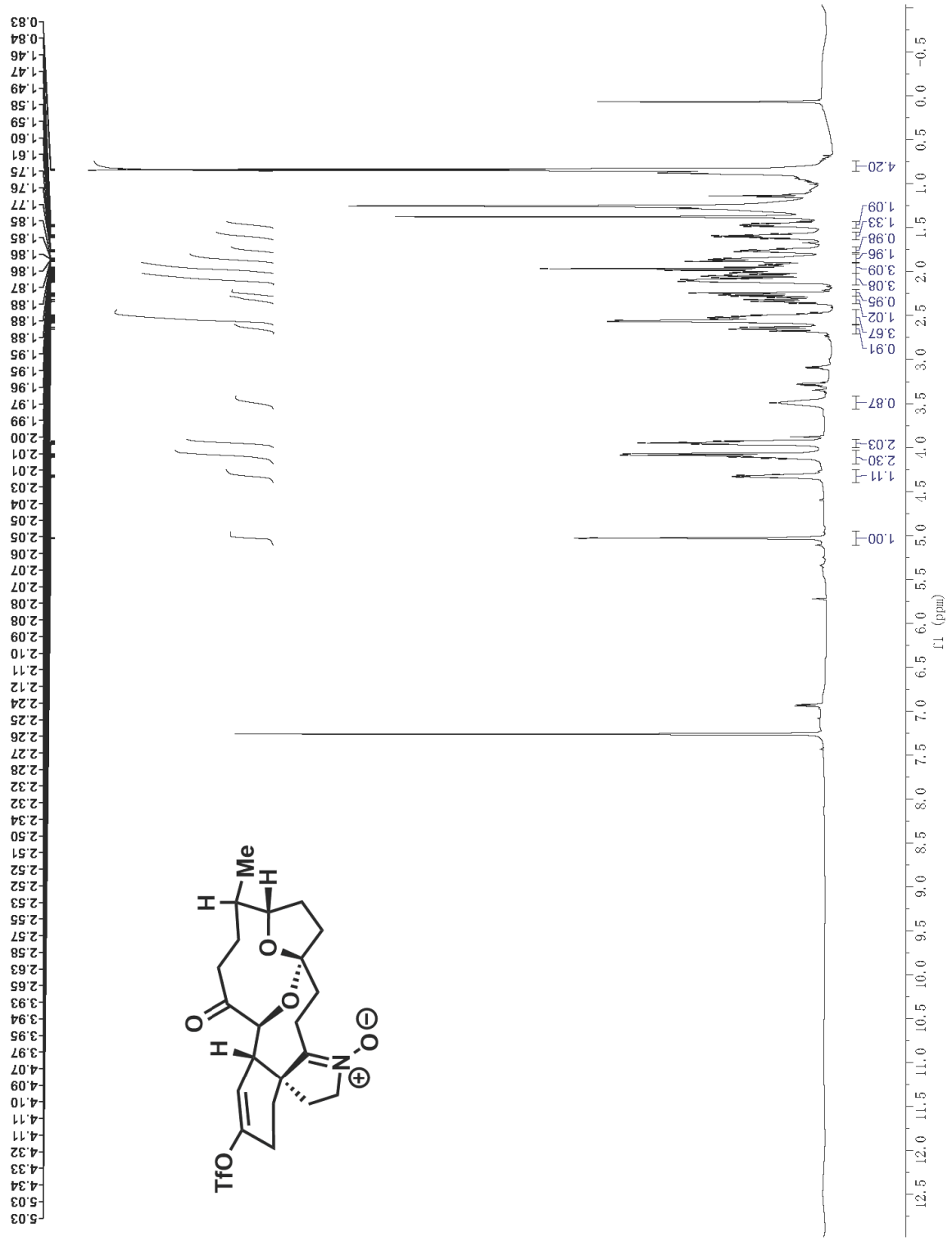
^{1}H NMR: Compound **259**



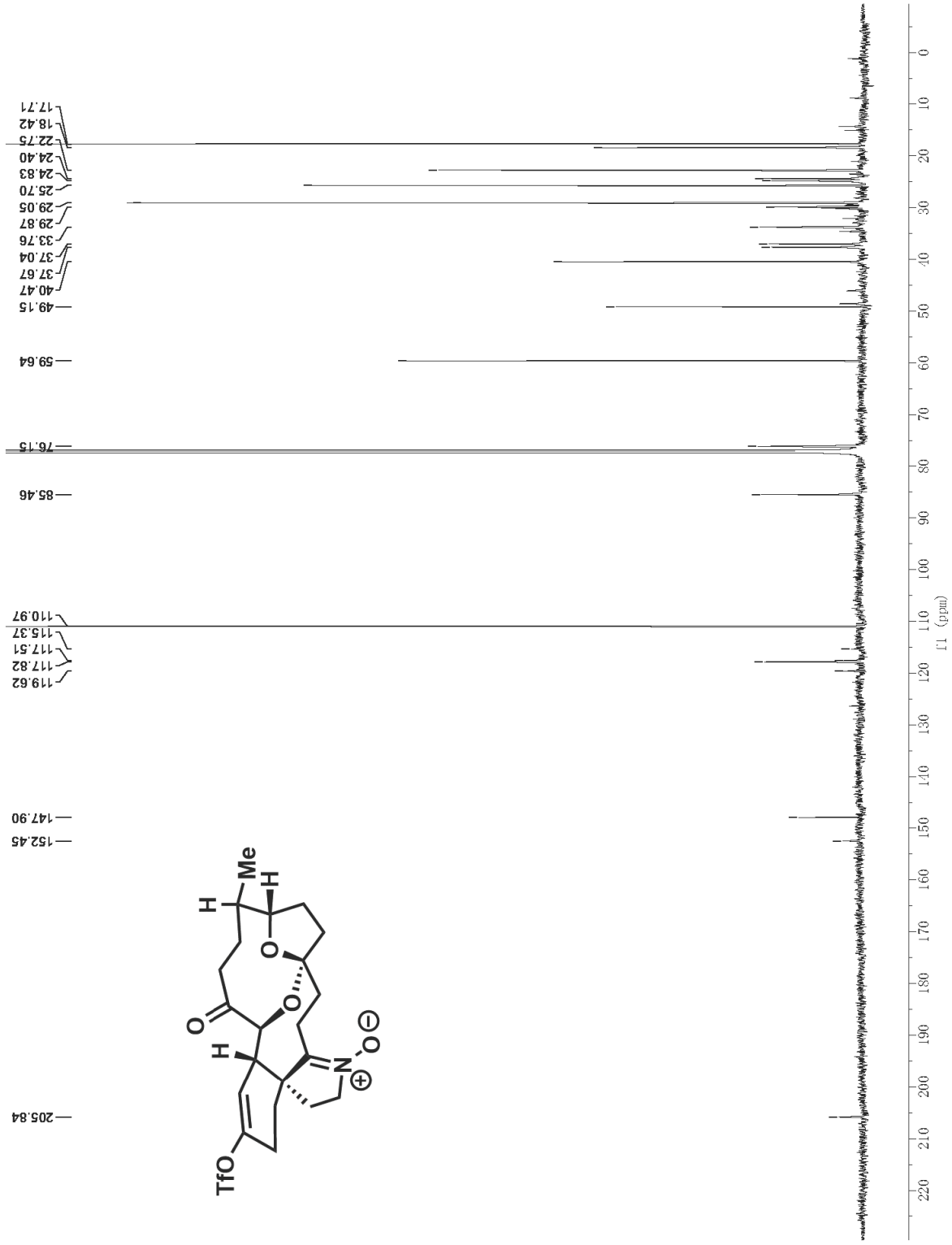
^{13}C NMR: Compound **259**



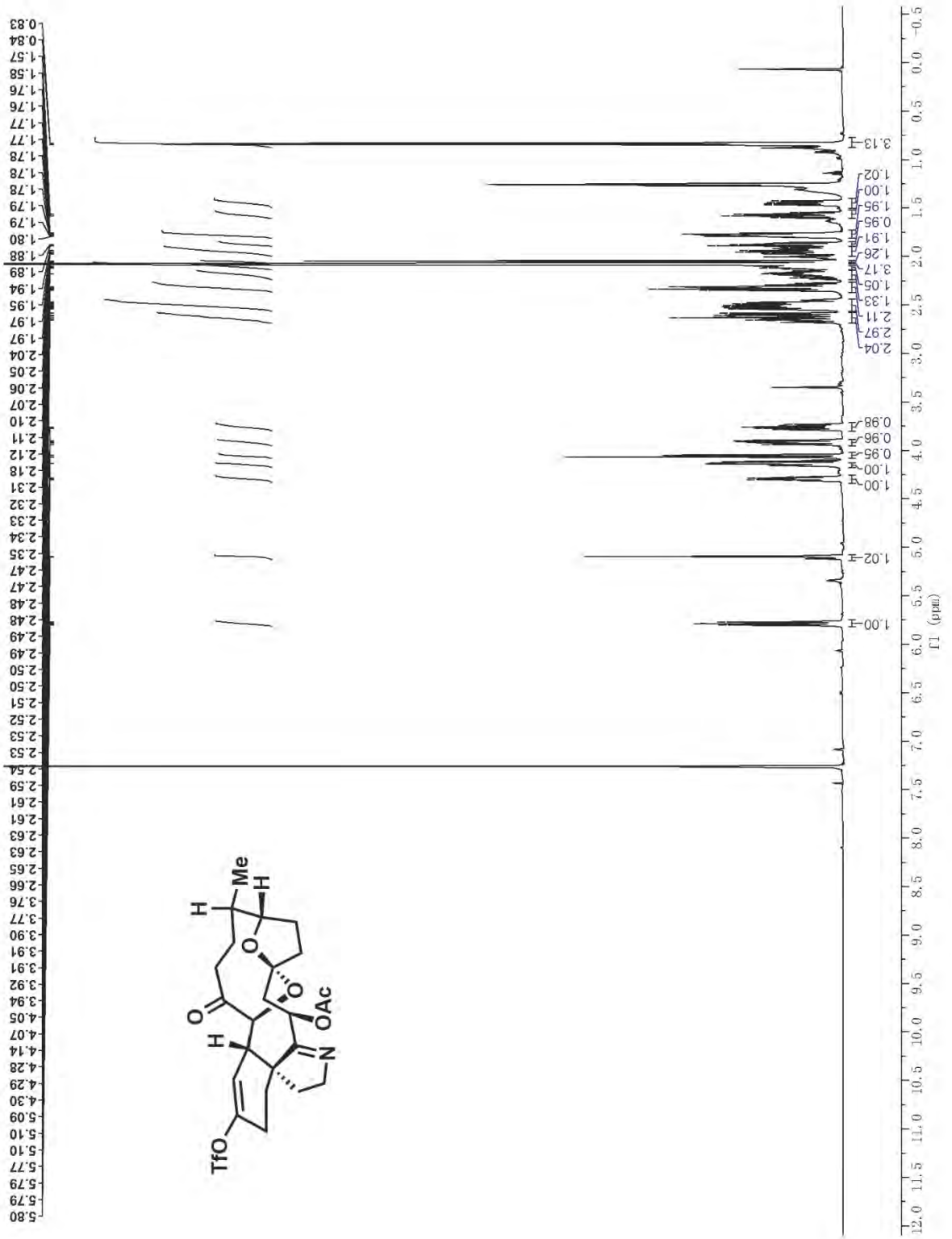
^{1}H NMR: Compound **260**



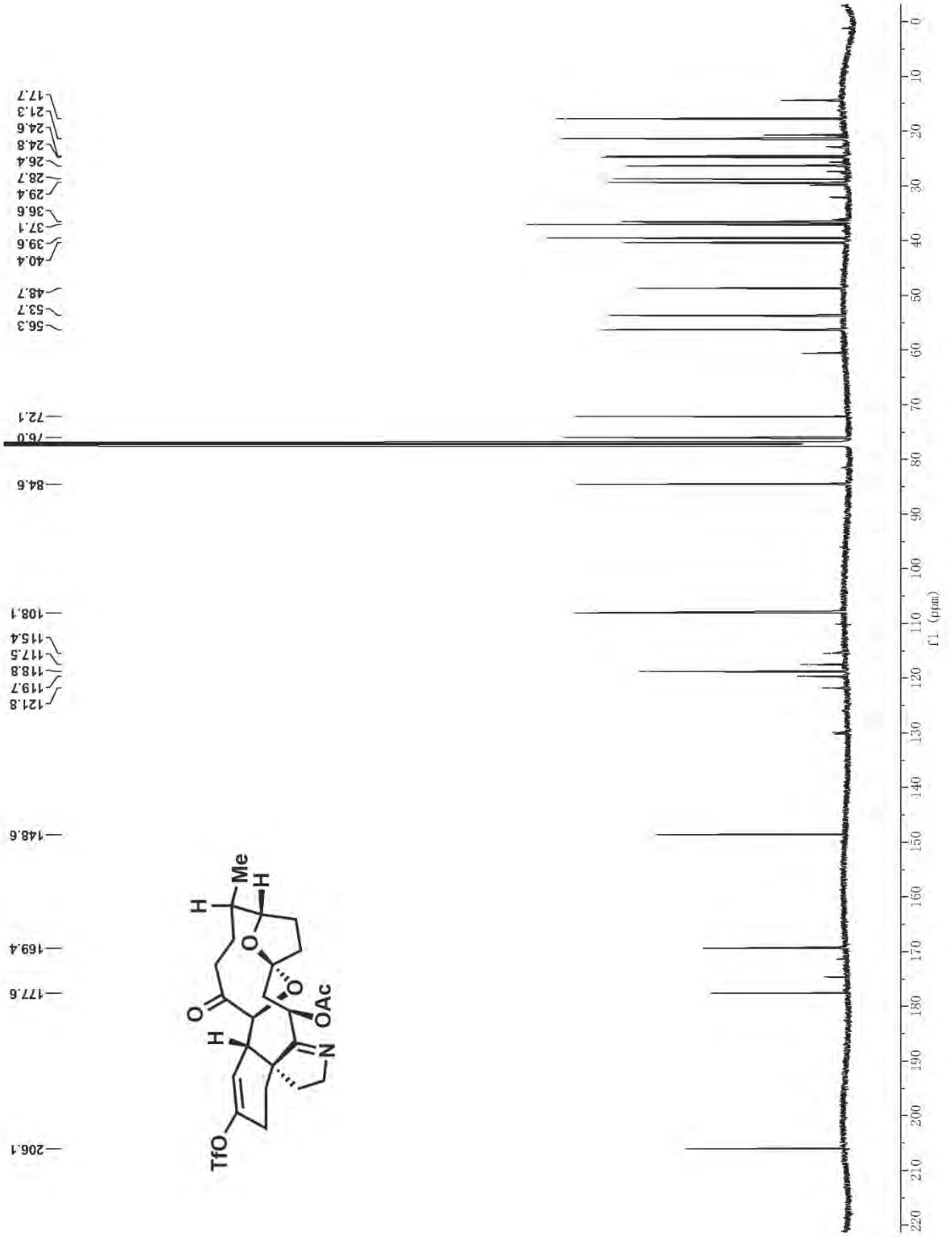
^{13}C NMR: Compound **260**



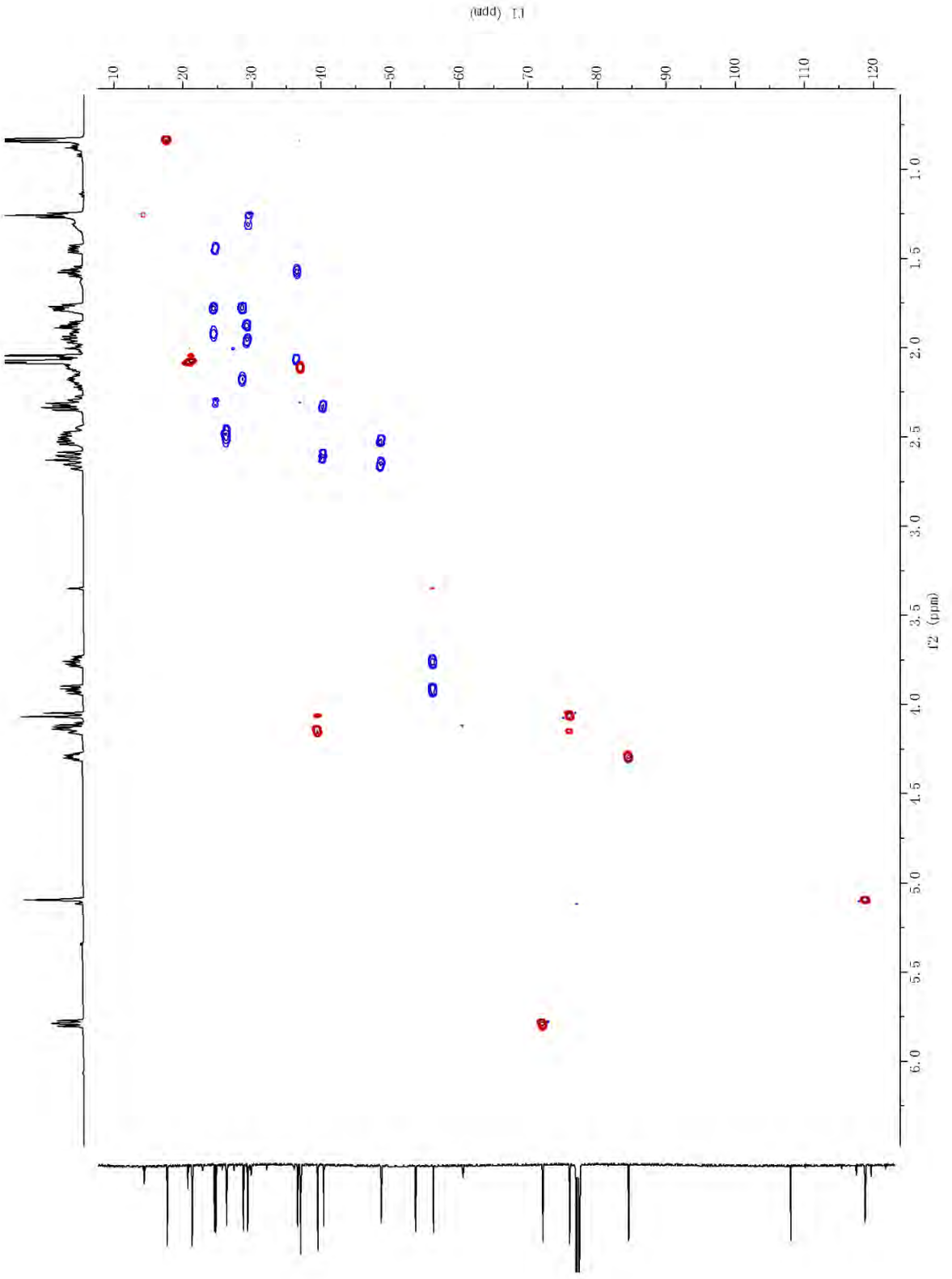
^{1}H NMR: Compound **262**



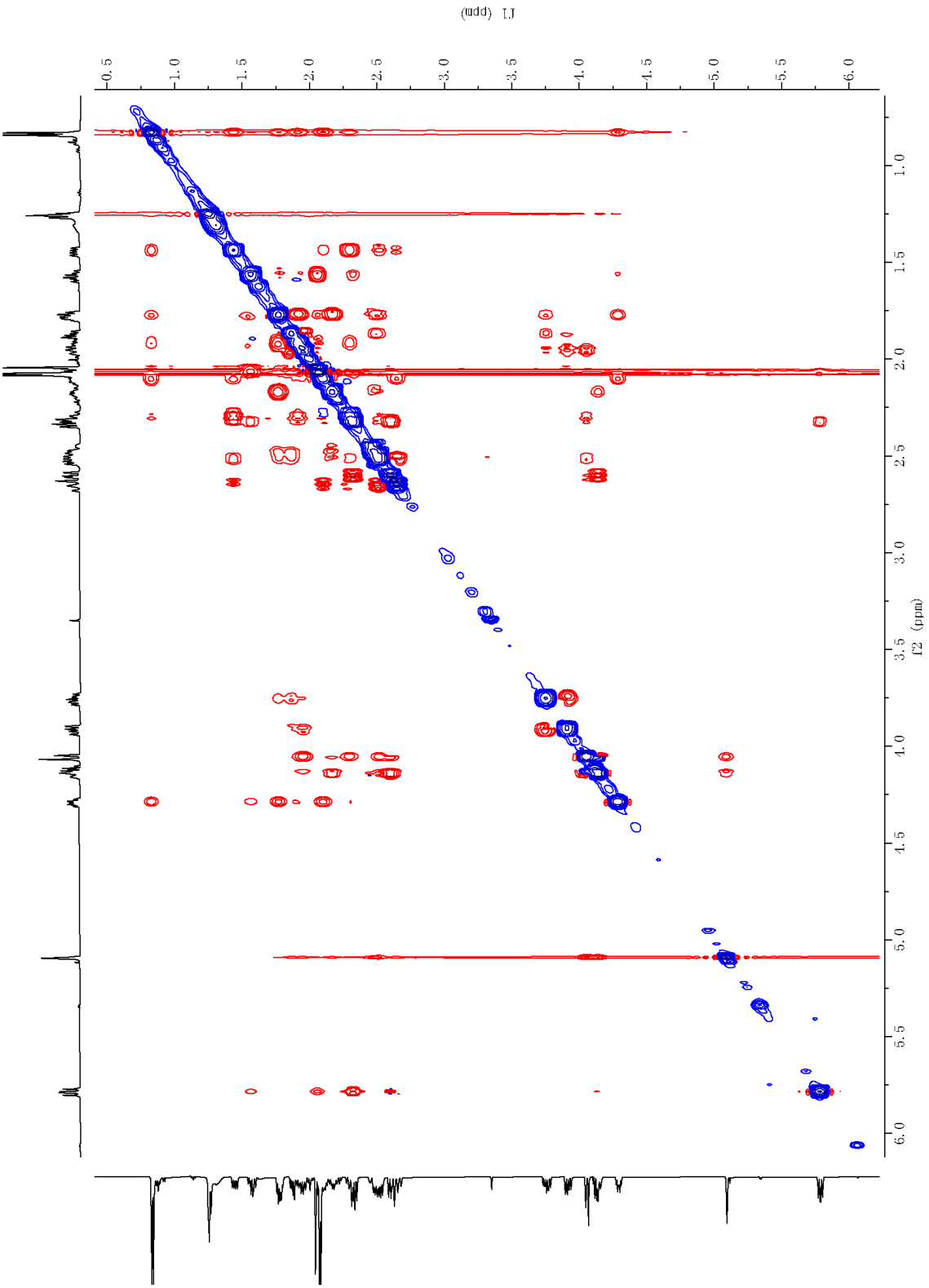
^{13}C NMR: Compound **262**



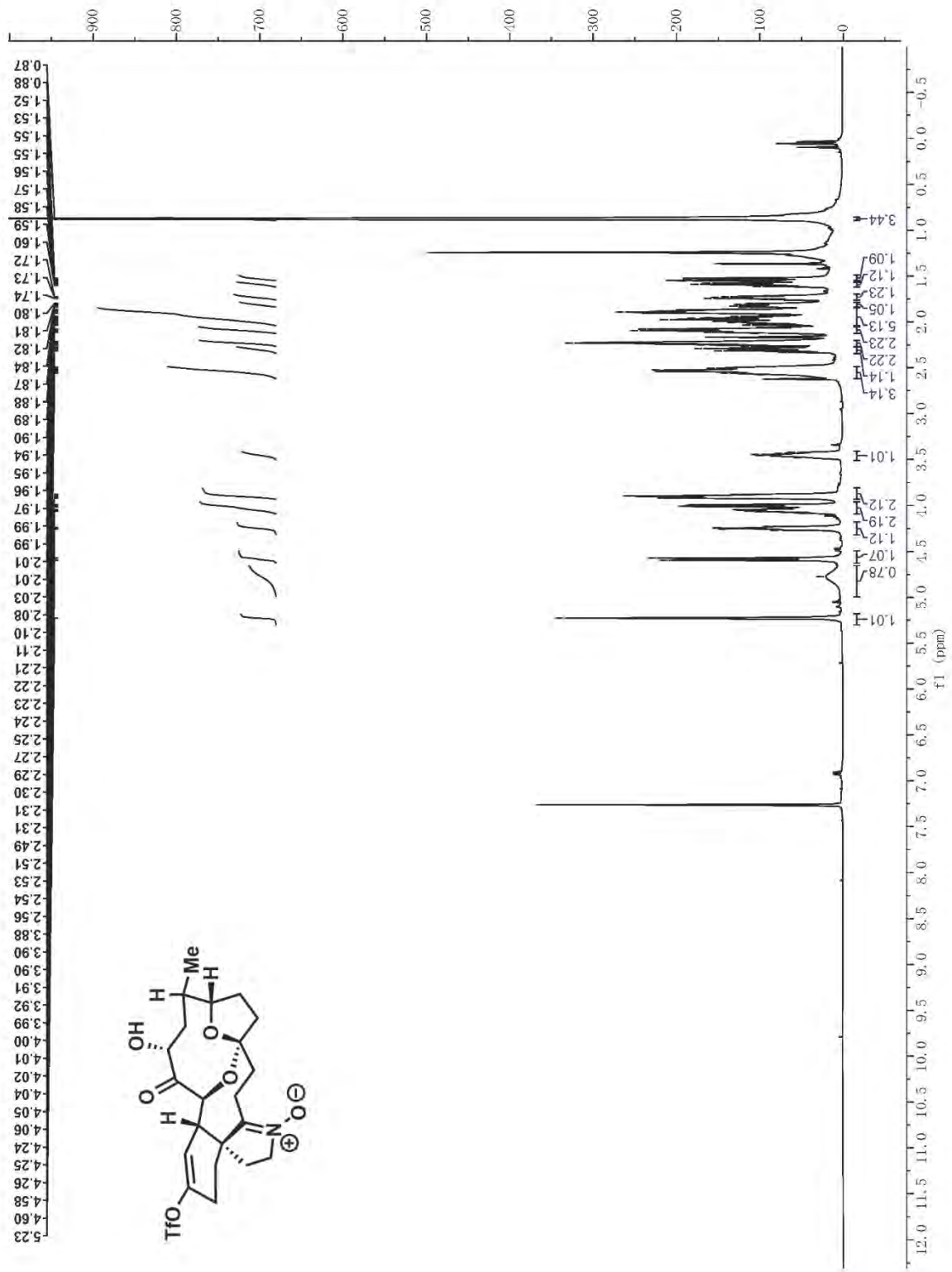
^{1}H-^{13}C HSQC: Compound **262**



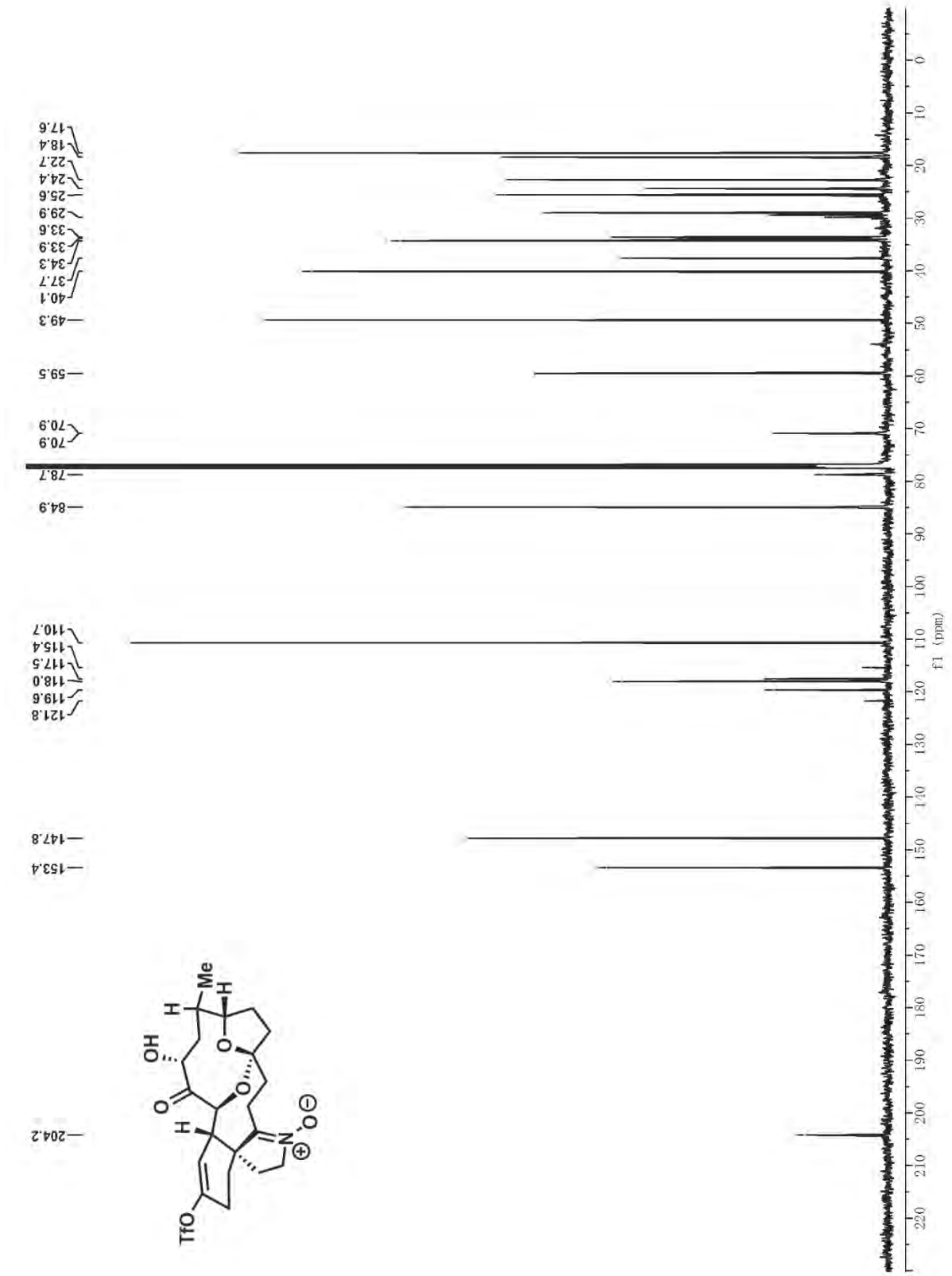
^{1}H-^{1}H NOESY: Compound **262**



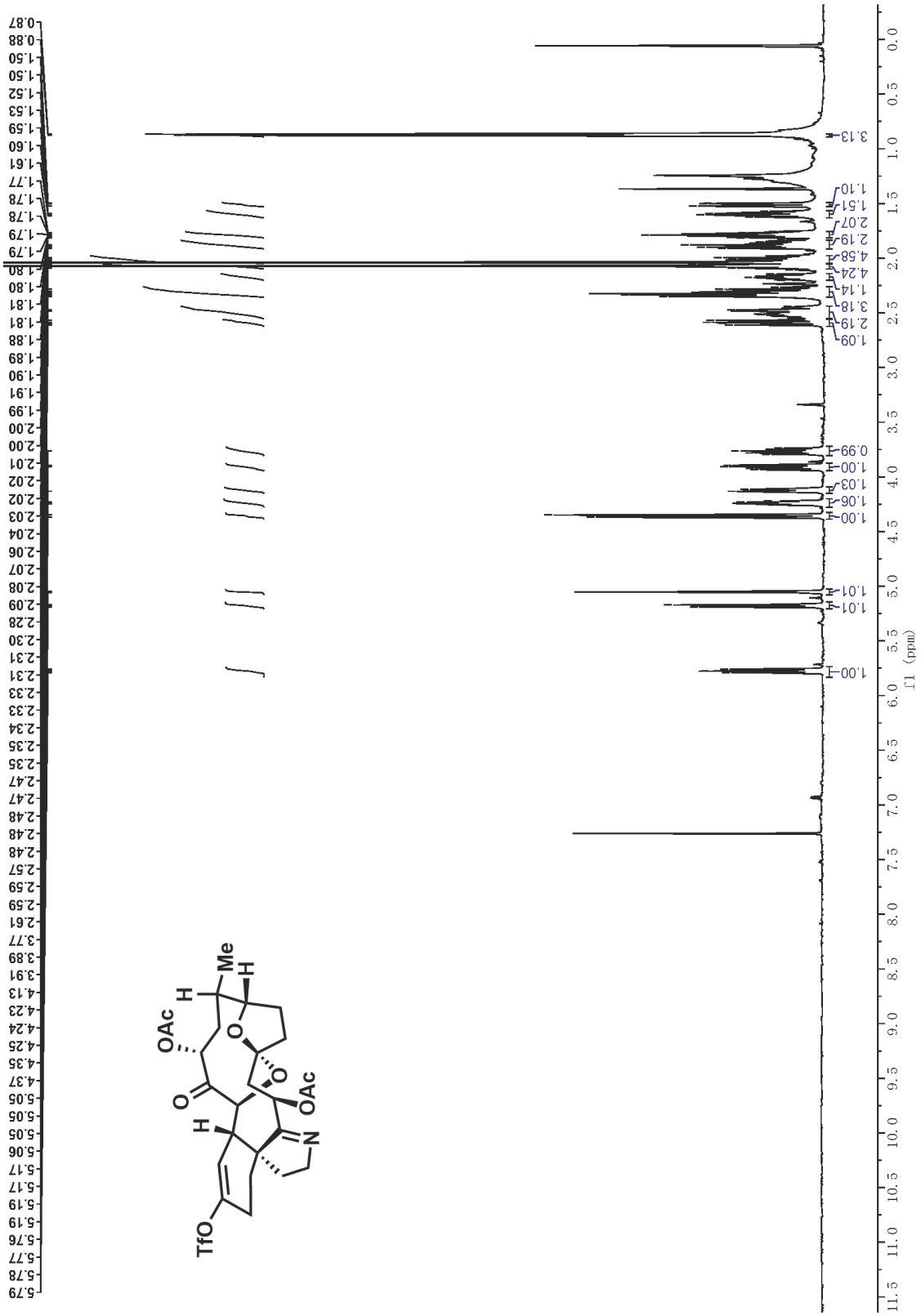
^{1}H NMR: Compound **263**



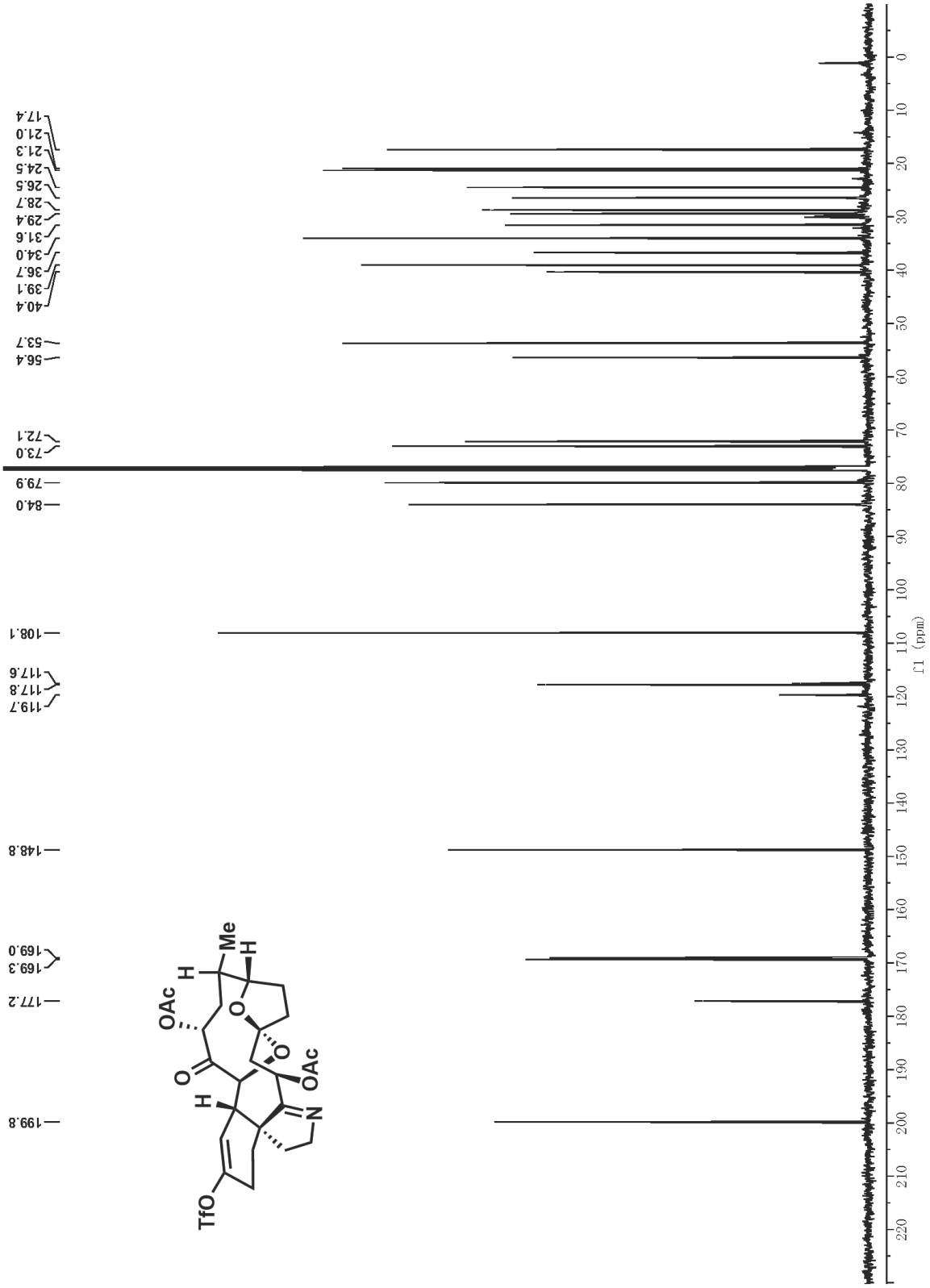
^{13}C NMR: Compound **263**



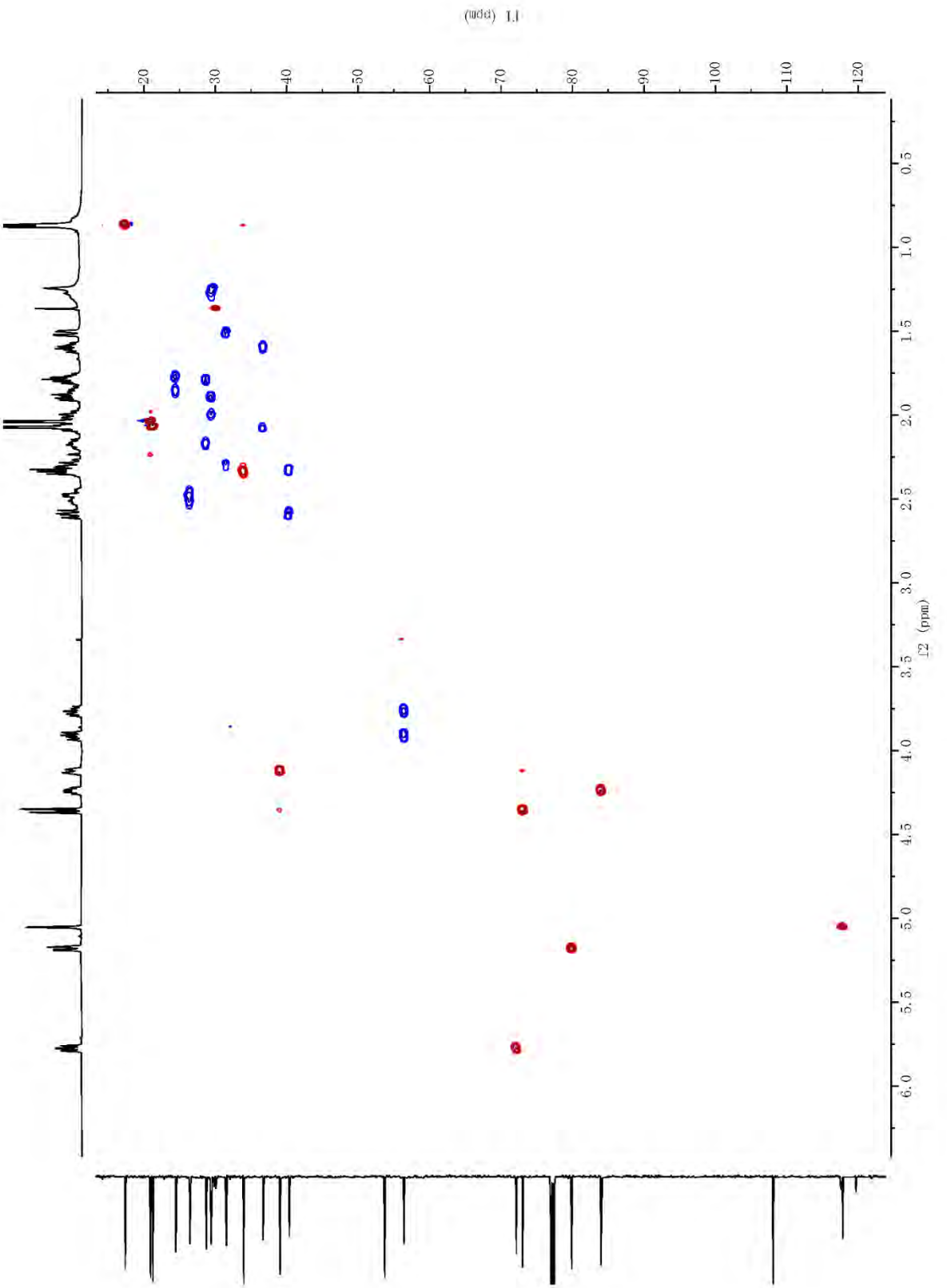
^{1}H NMR: Compound **264**



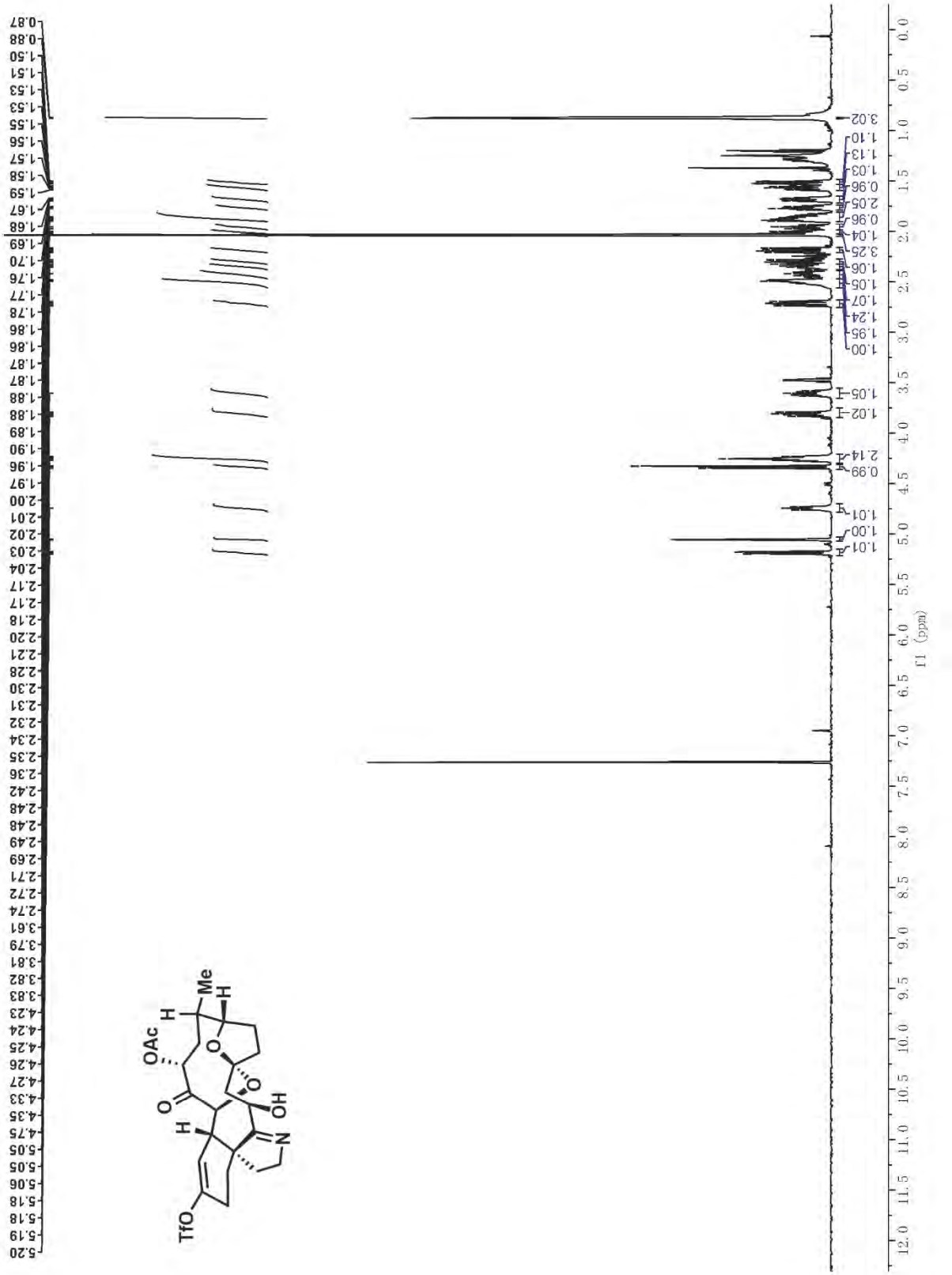
^{13}C NMR: Compound **264**



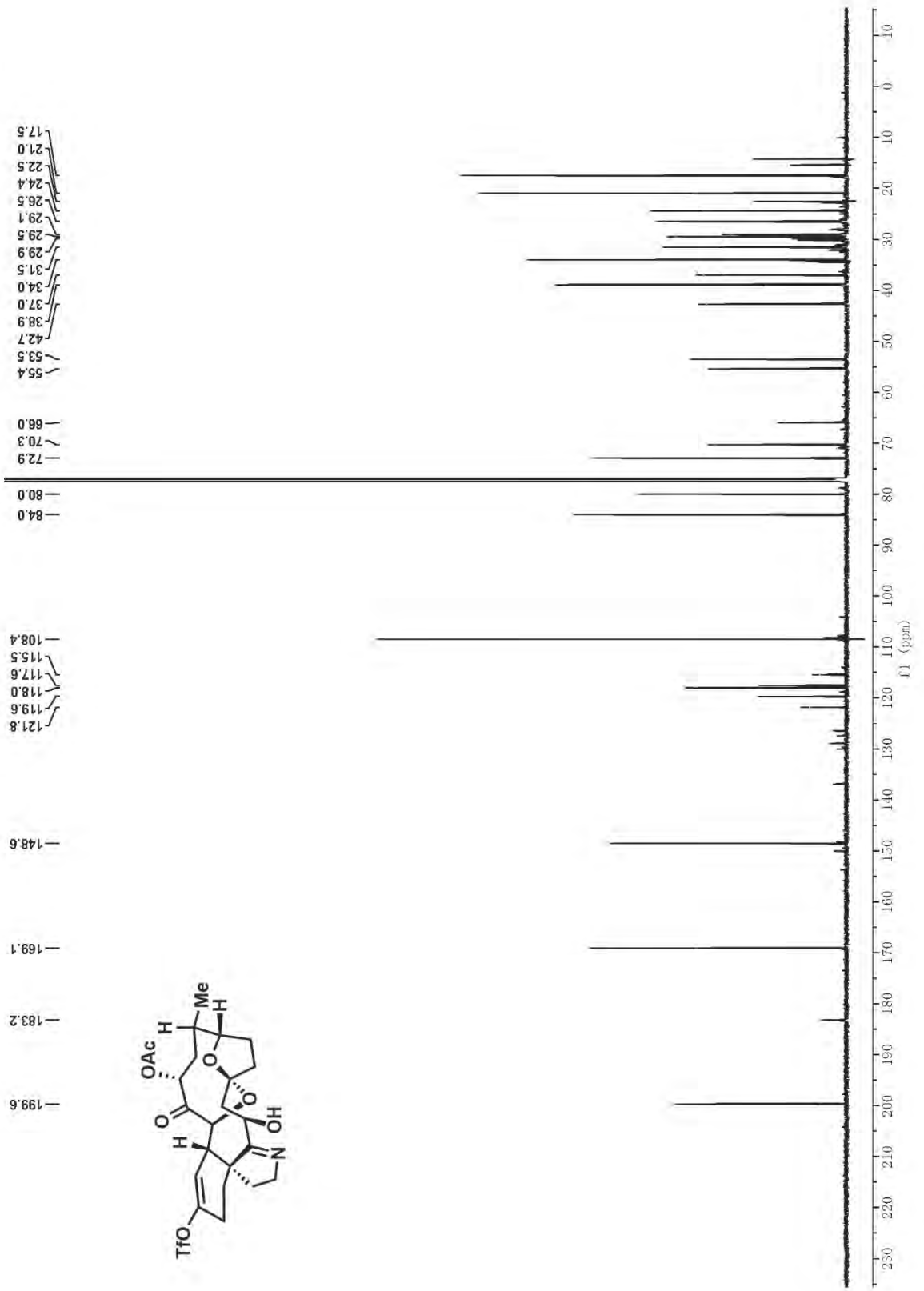
^{1}H-^{13}C HSQC: Compound **264**



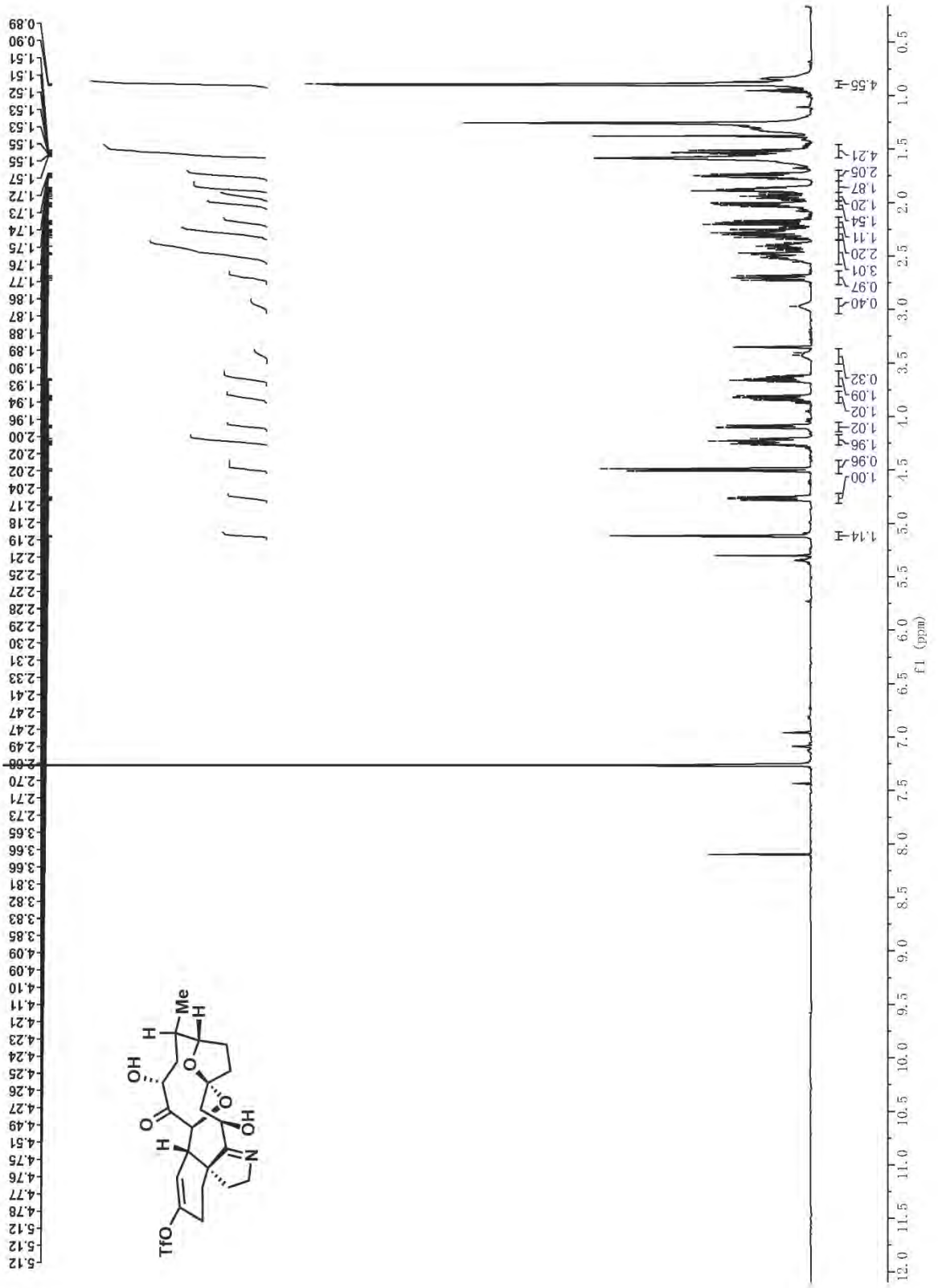
^{1}H NMR: Compound **265**



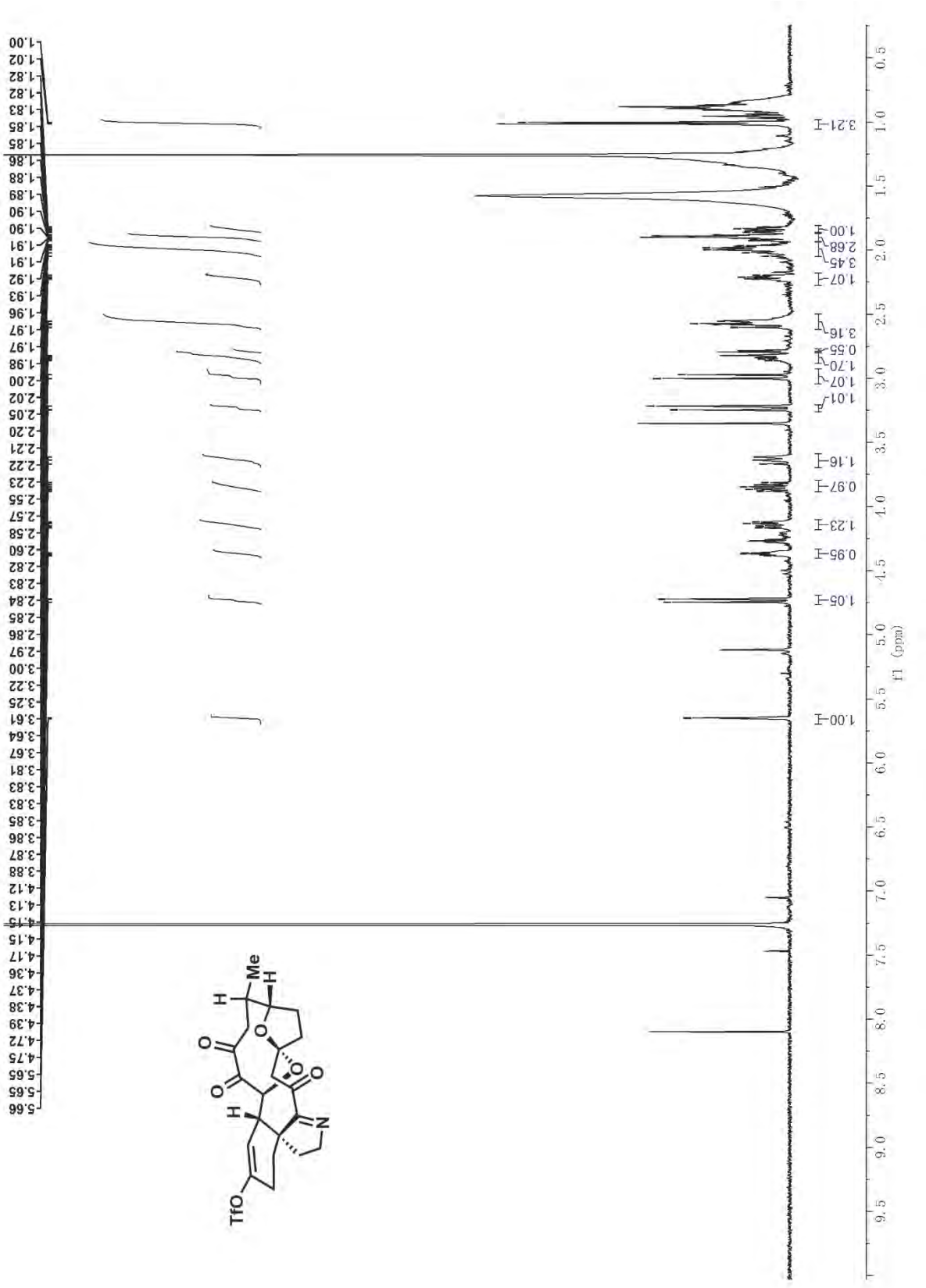
^{13}C NMR: Compound **265**



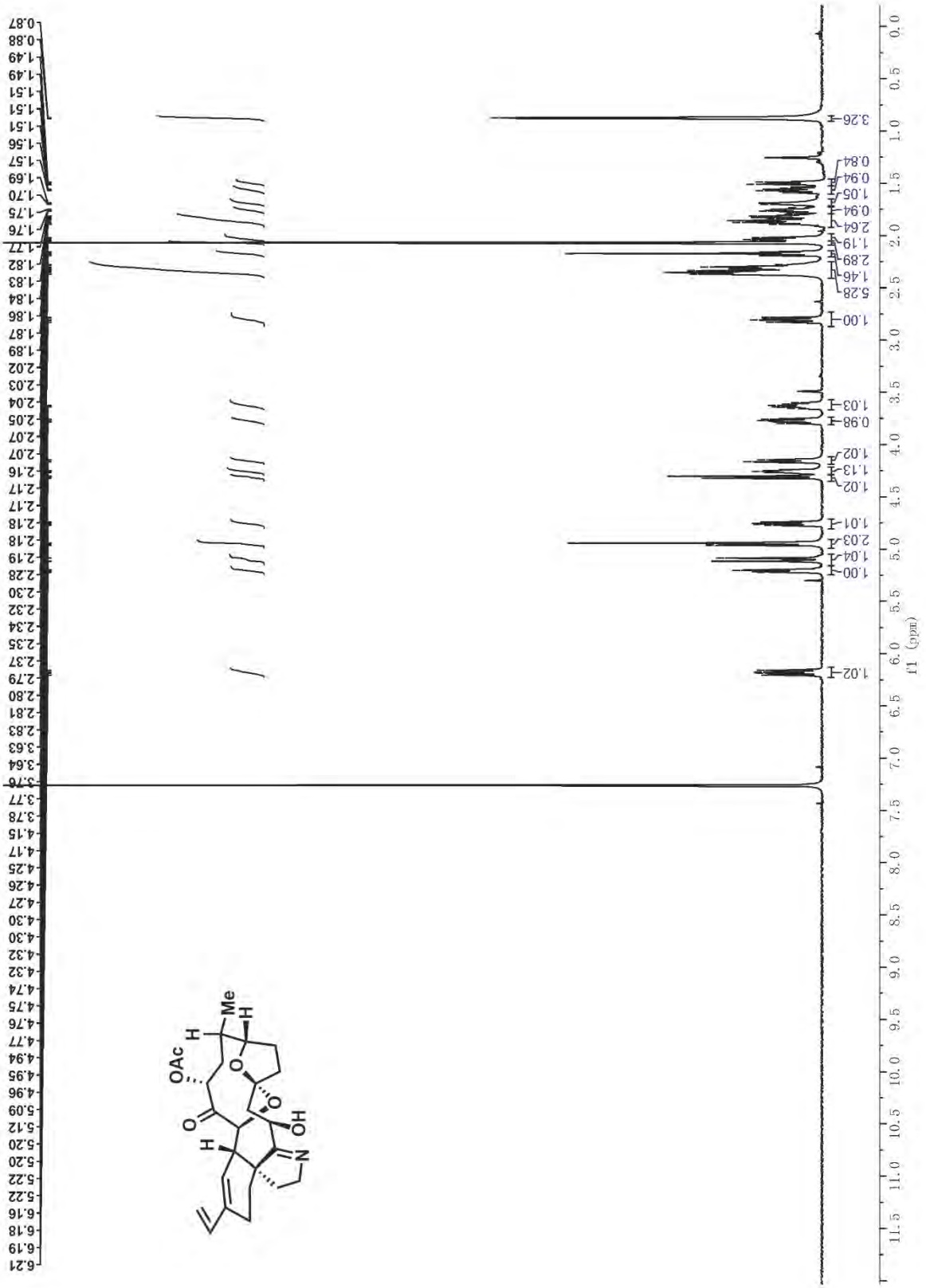
^{1}H NMR: Compound **267**



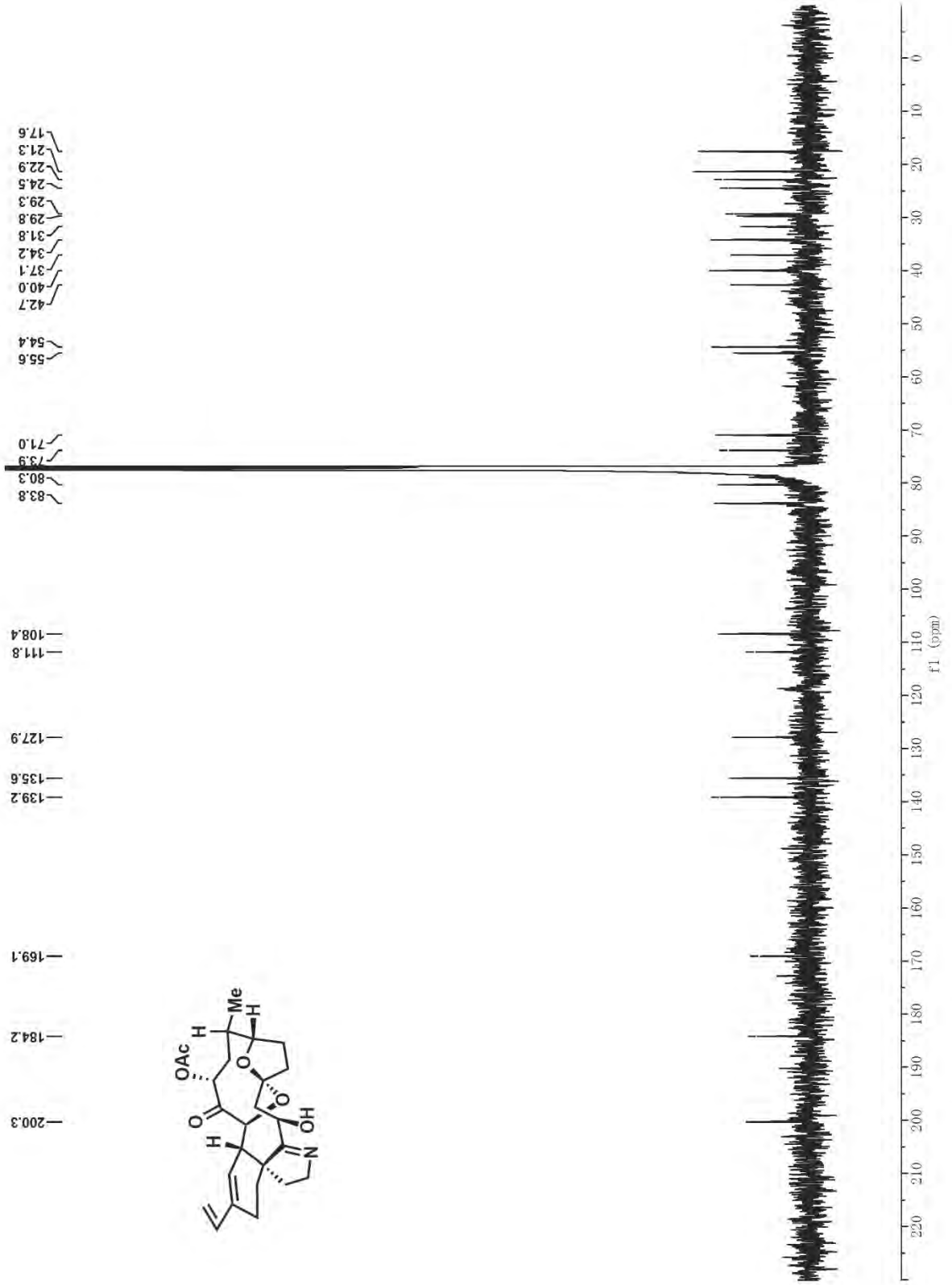
^{1}H NMR: Compound **269** (crude)



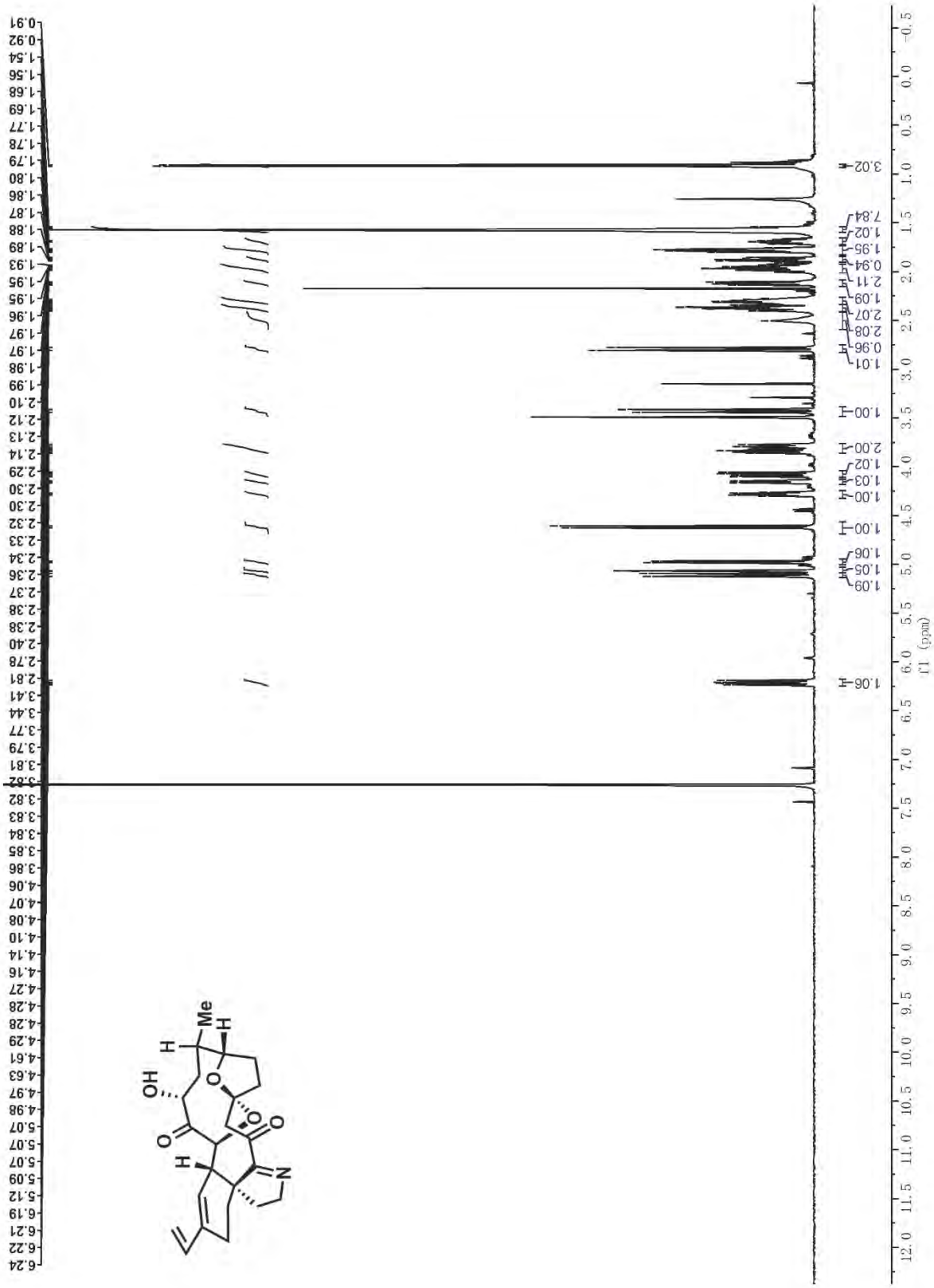
^{1}H NMR: Compound **270**



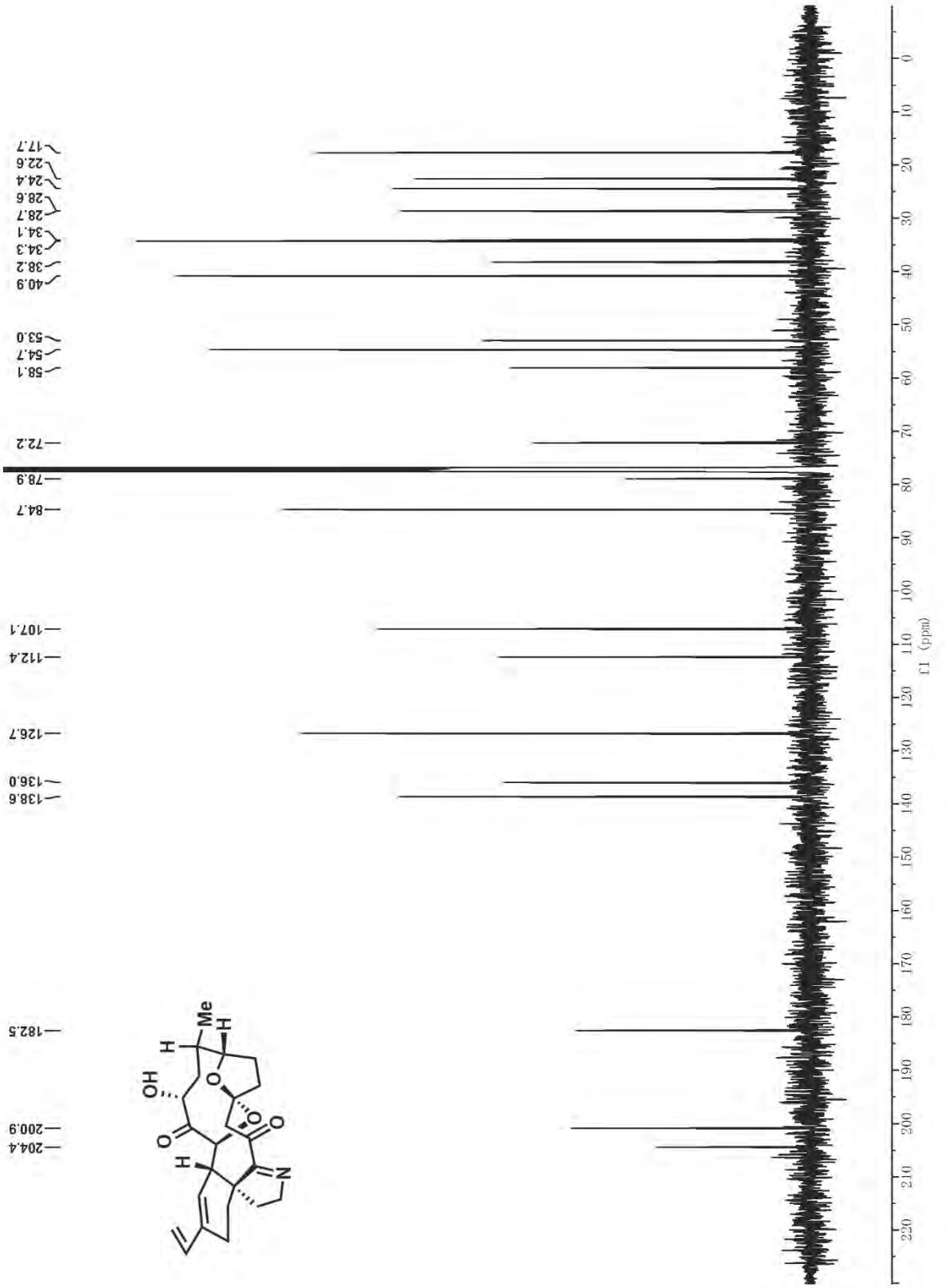
^{13}C NMR: Compound **270**



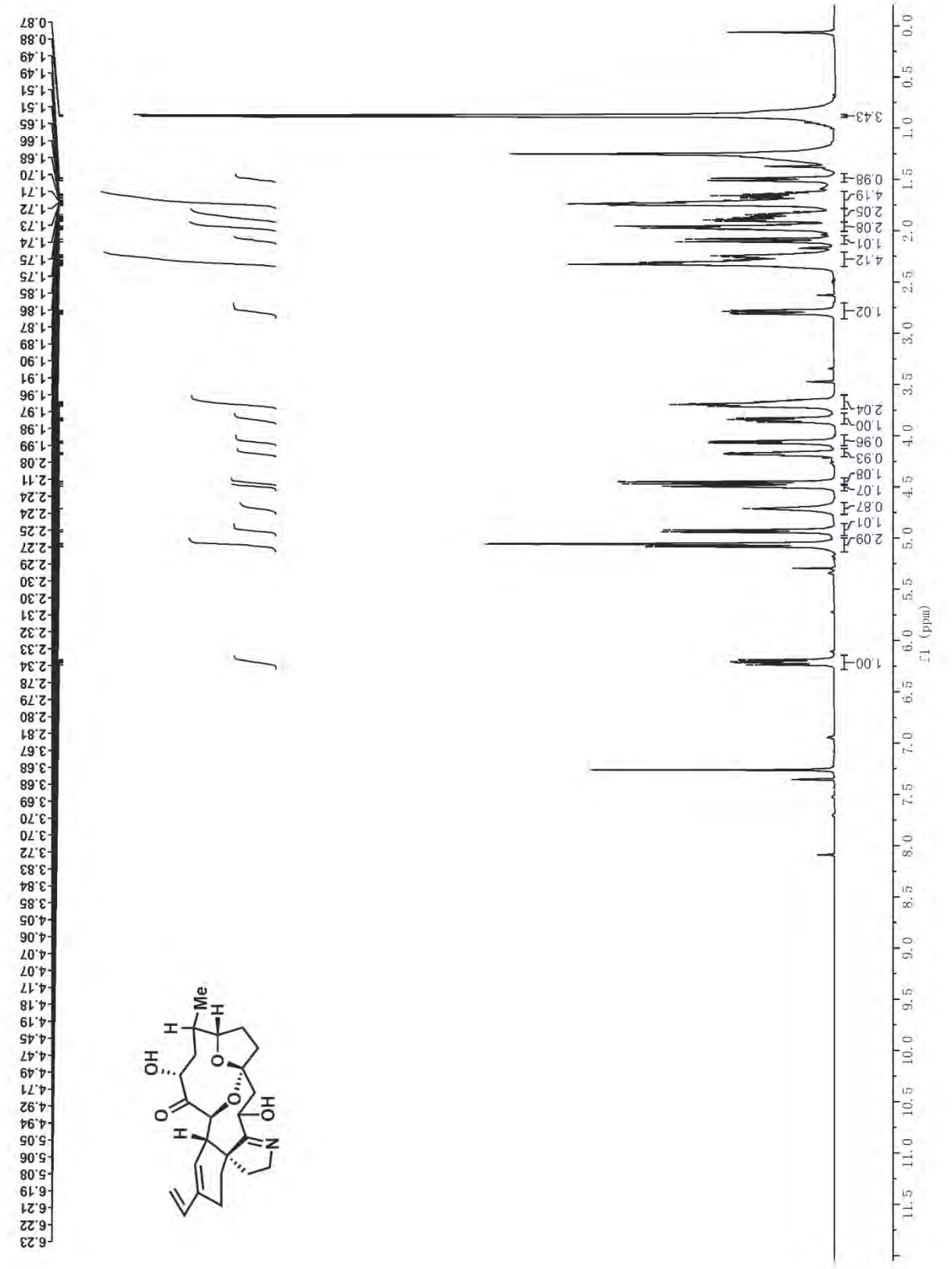
^{1}H NMR: **Portimine B**



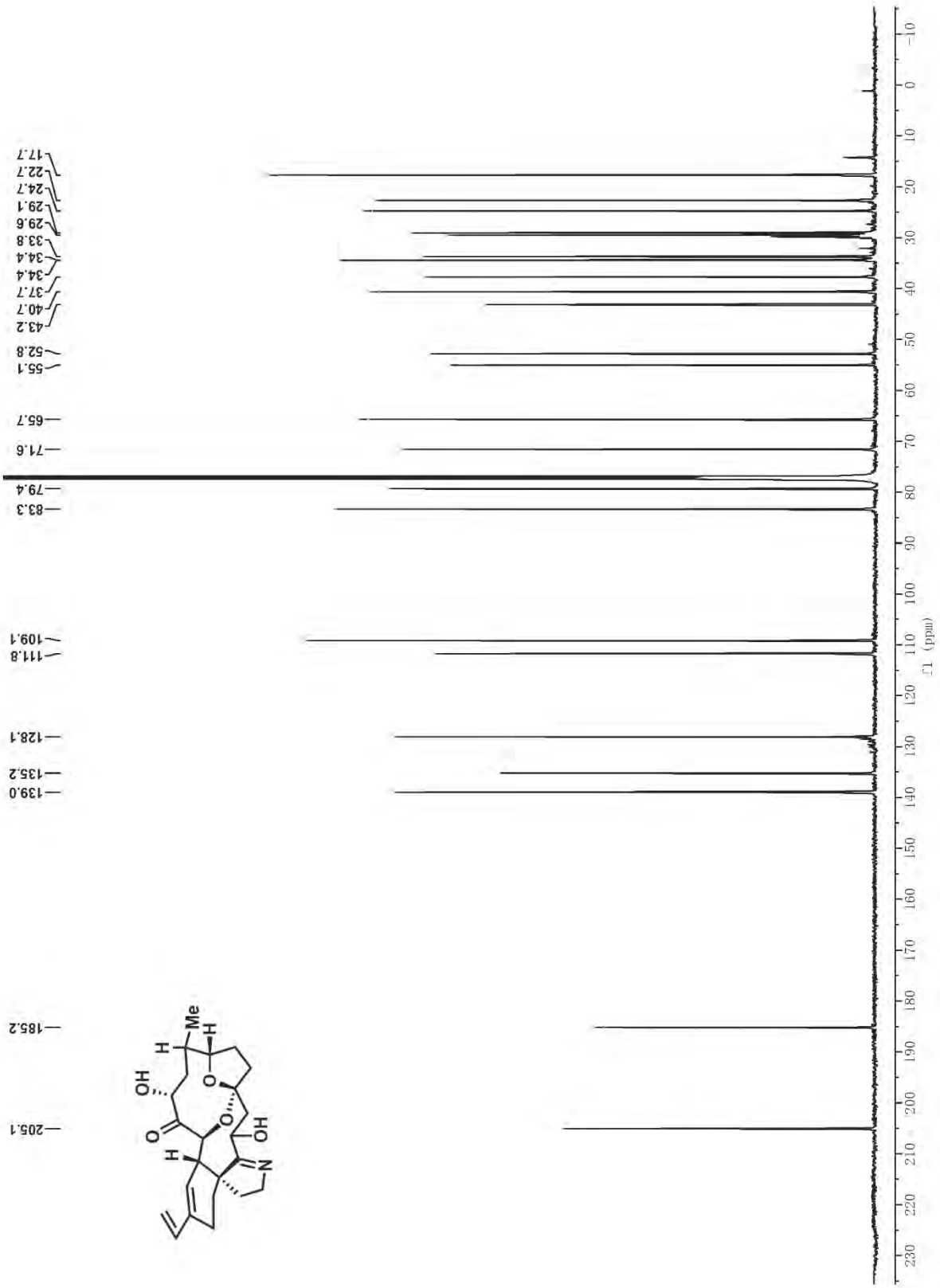
^{13}C NMR: **Portimine B**



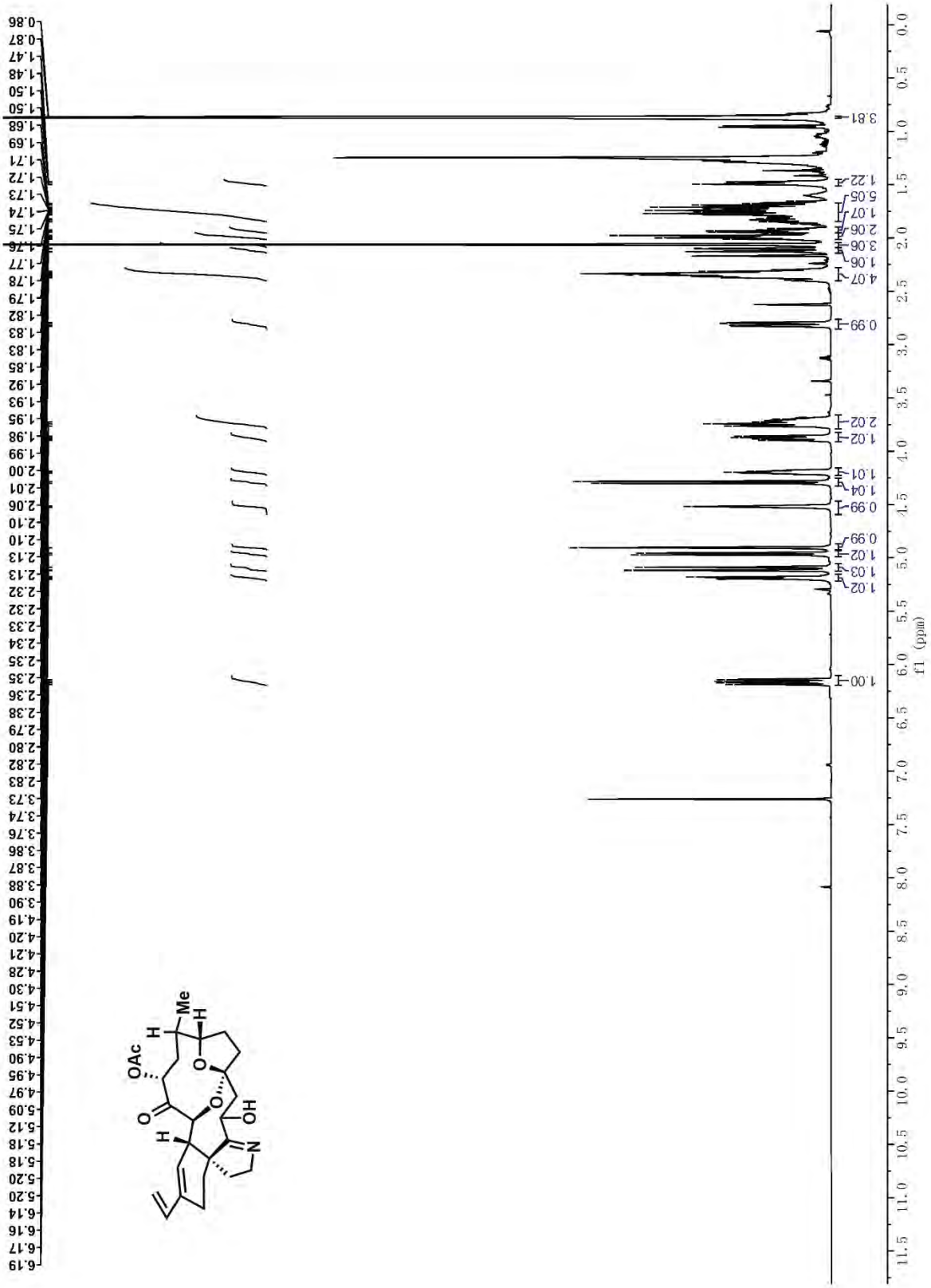
^{1}H NMR: **Portimine A**



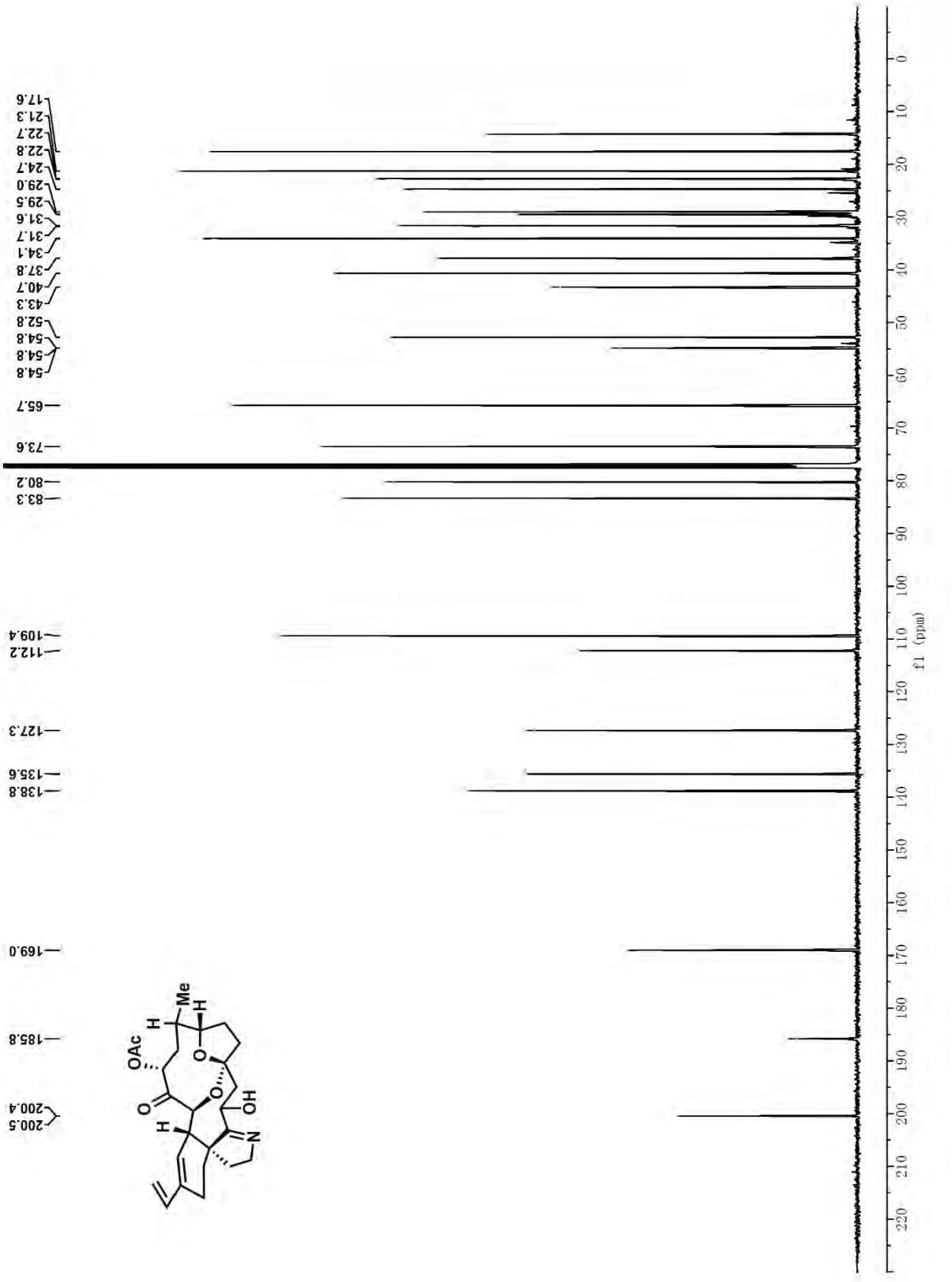
^{13}C NMR: **Portimine A**



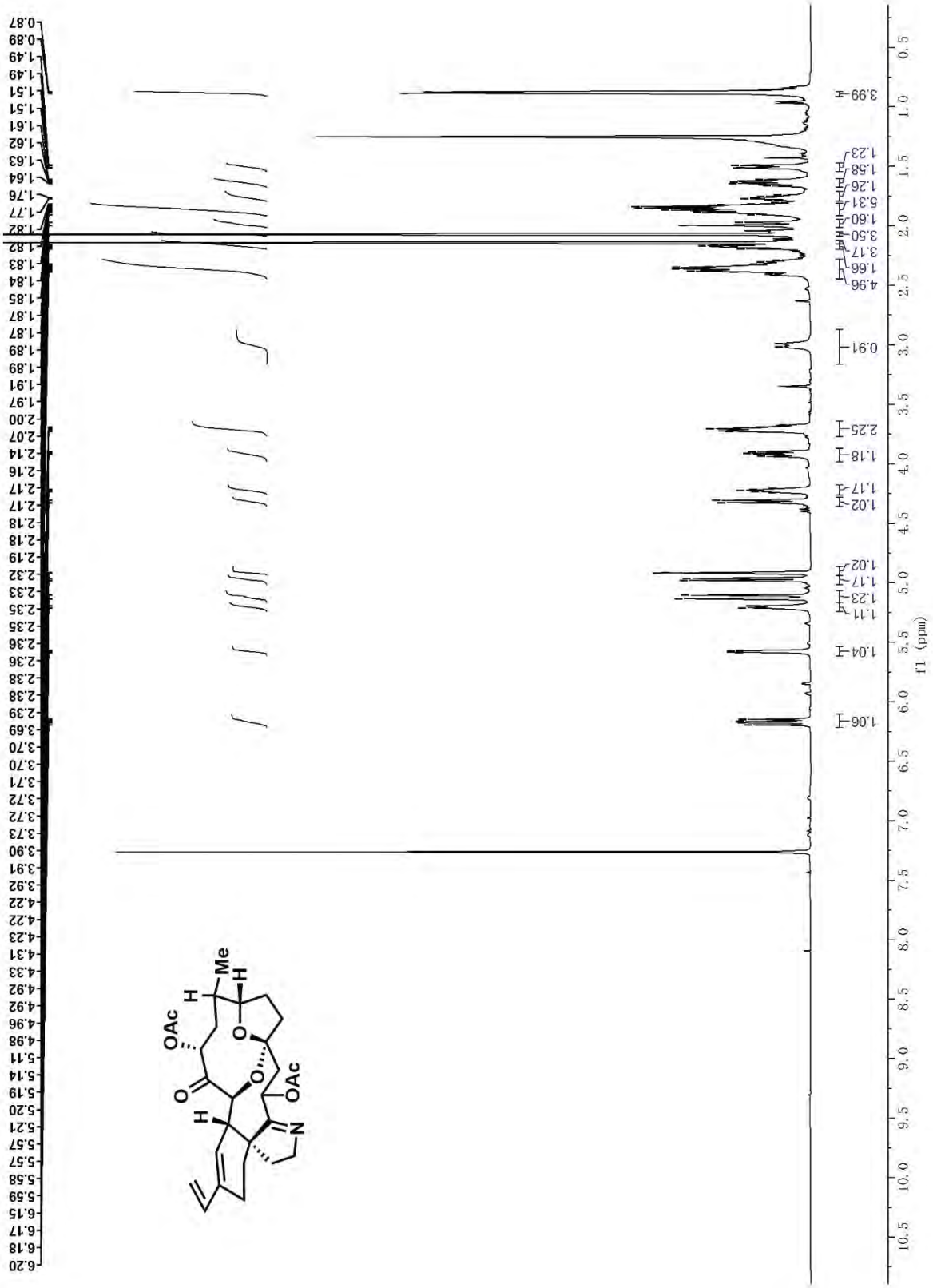
^{1}H NMR: Compound **273**



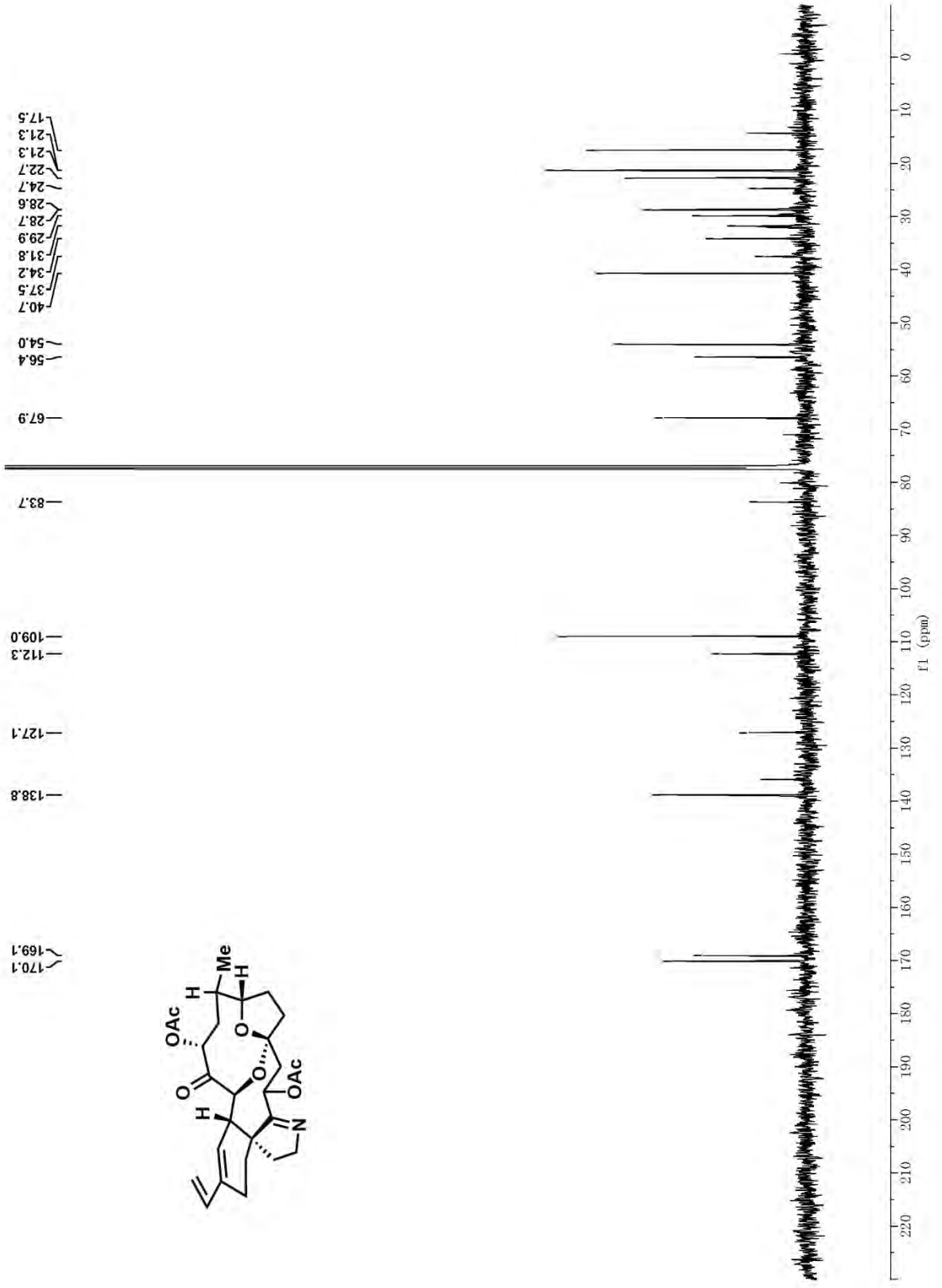
^{13}C NMR: Compound **273**



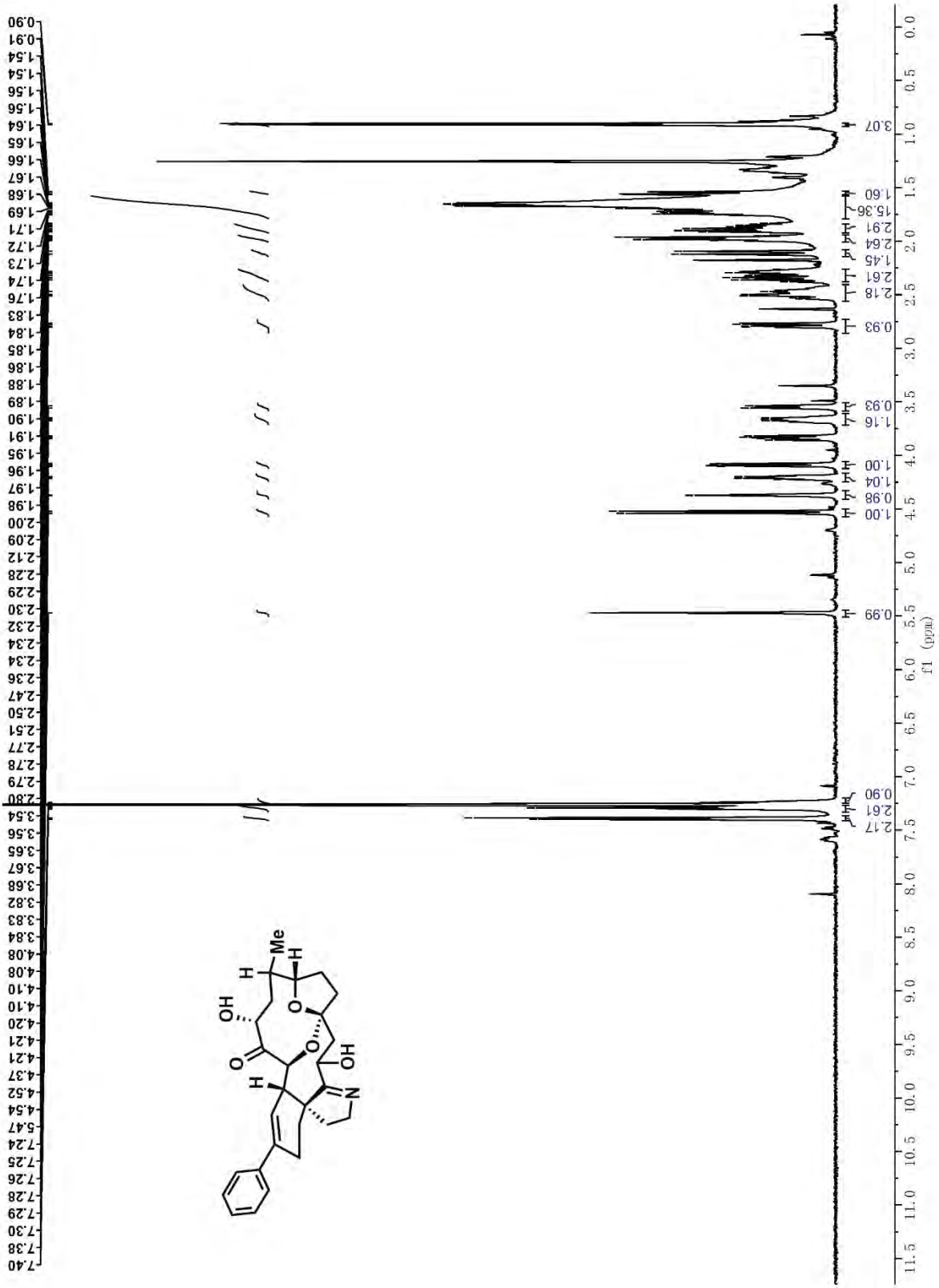
^{1}H NMR: Compound **274**



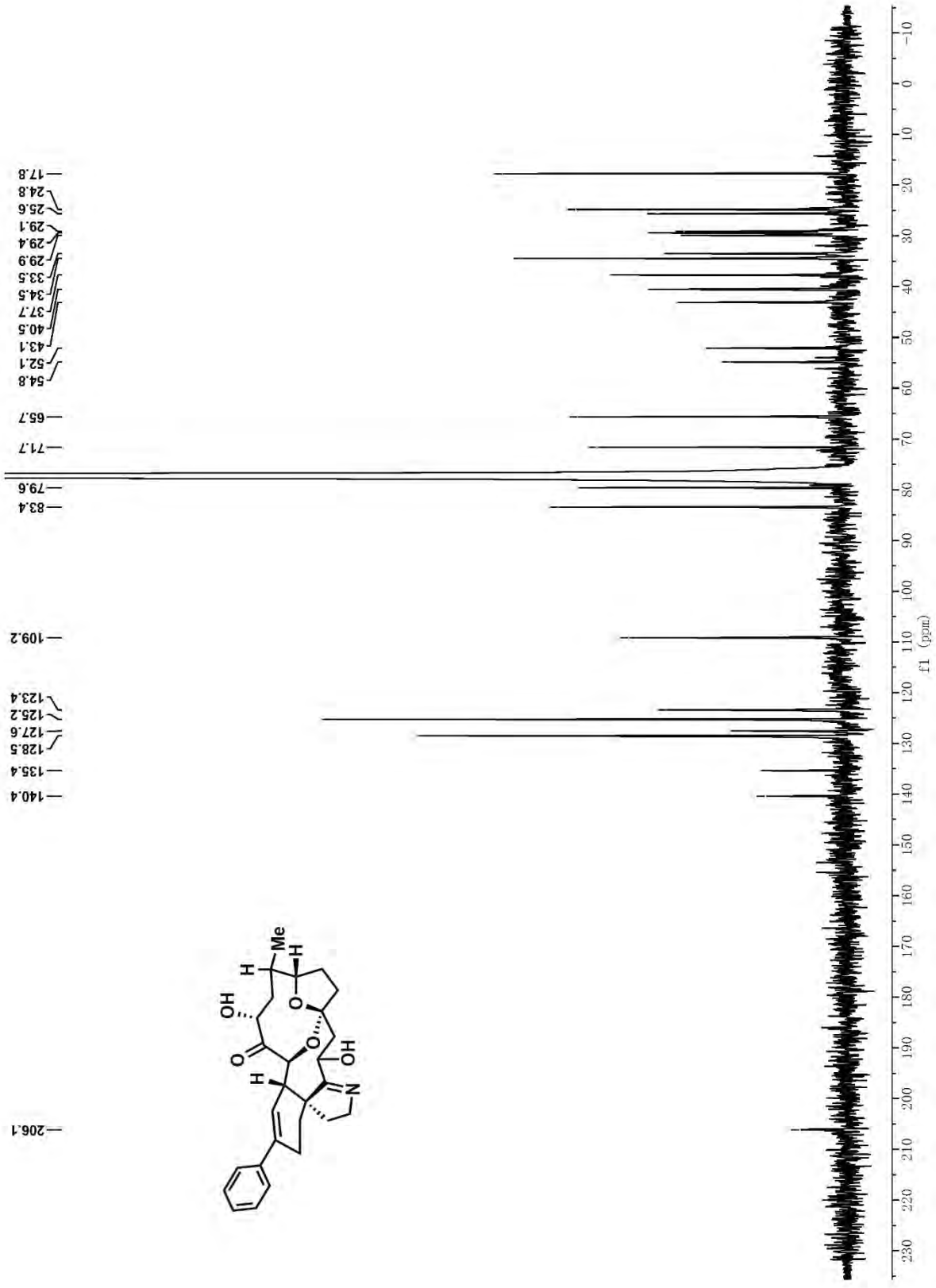
^{13}C NMR: Compound **274**



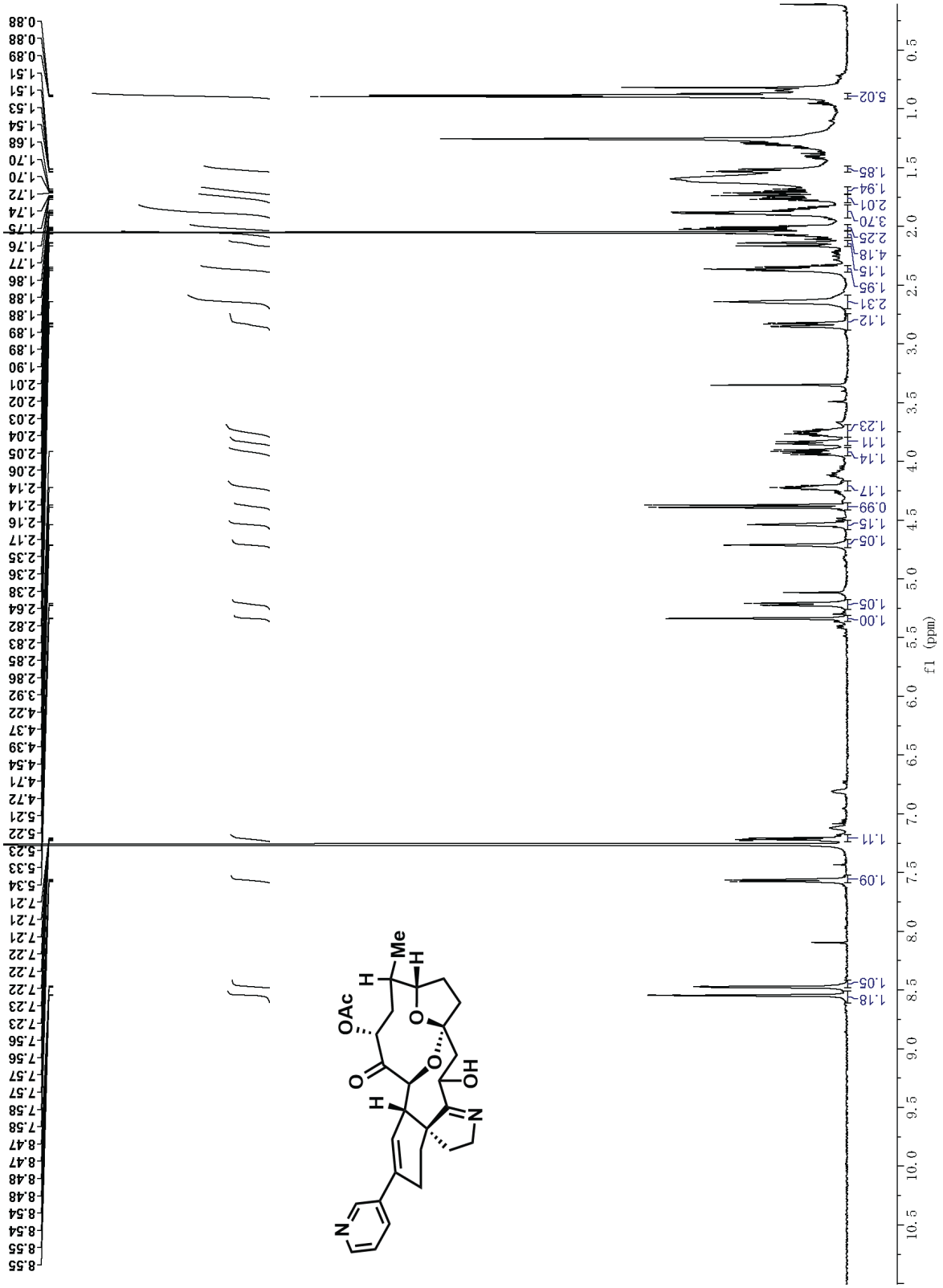
^{1}H NMR: Compound **275**



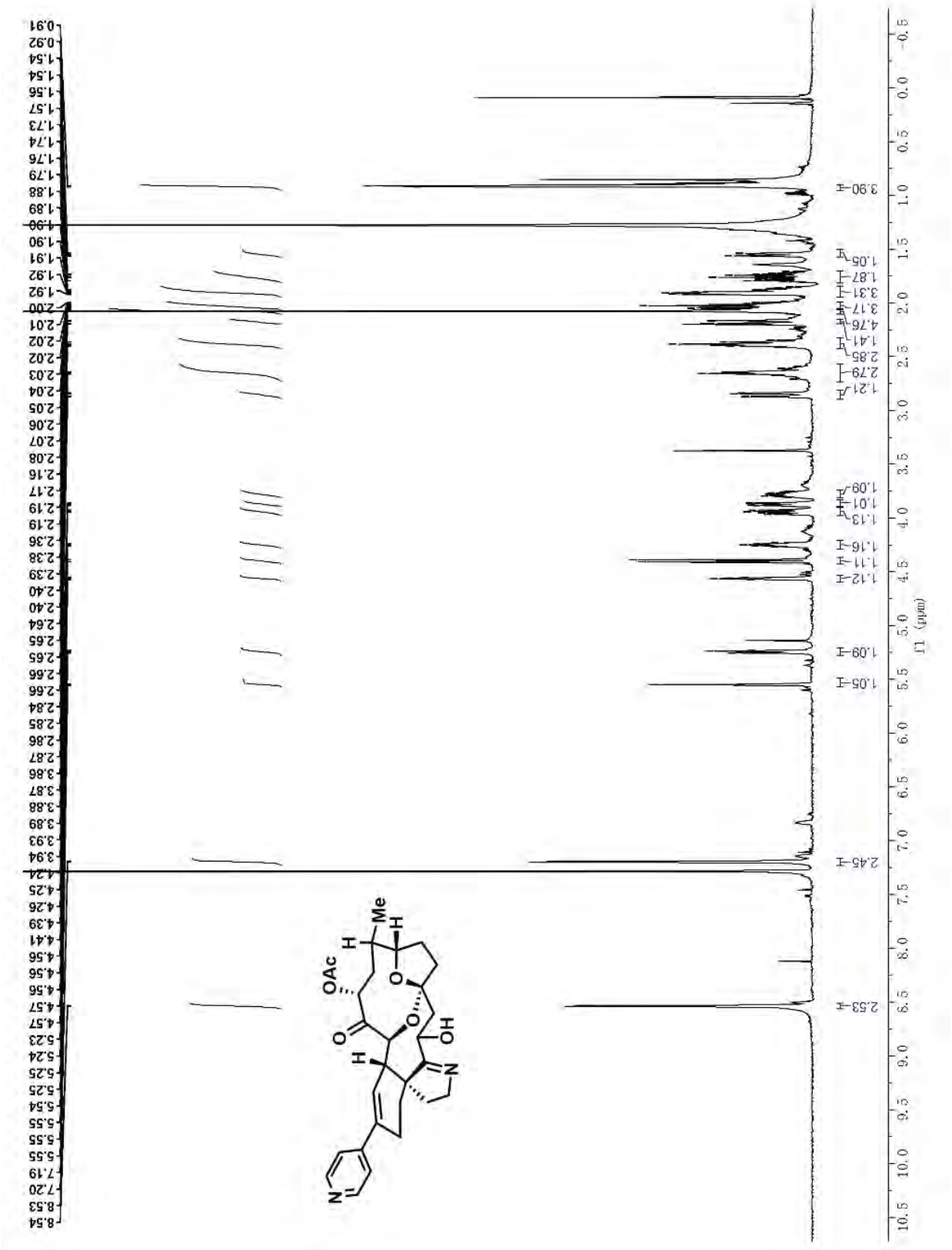
^{13}C NMR: Compound **275**



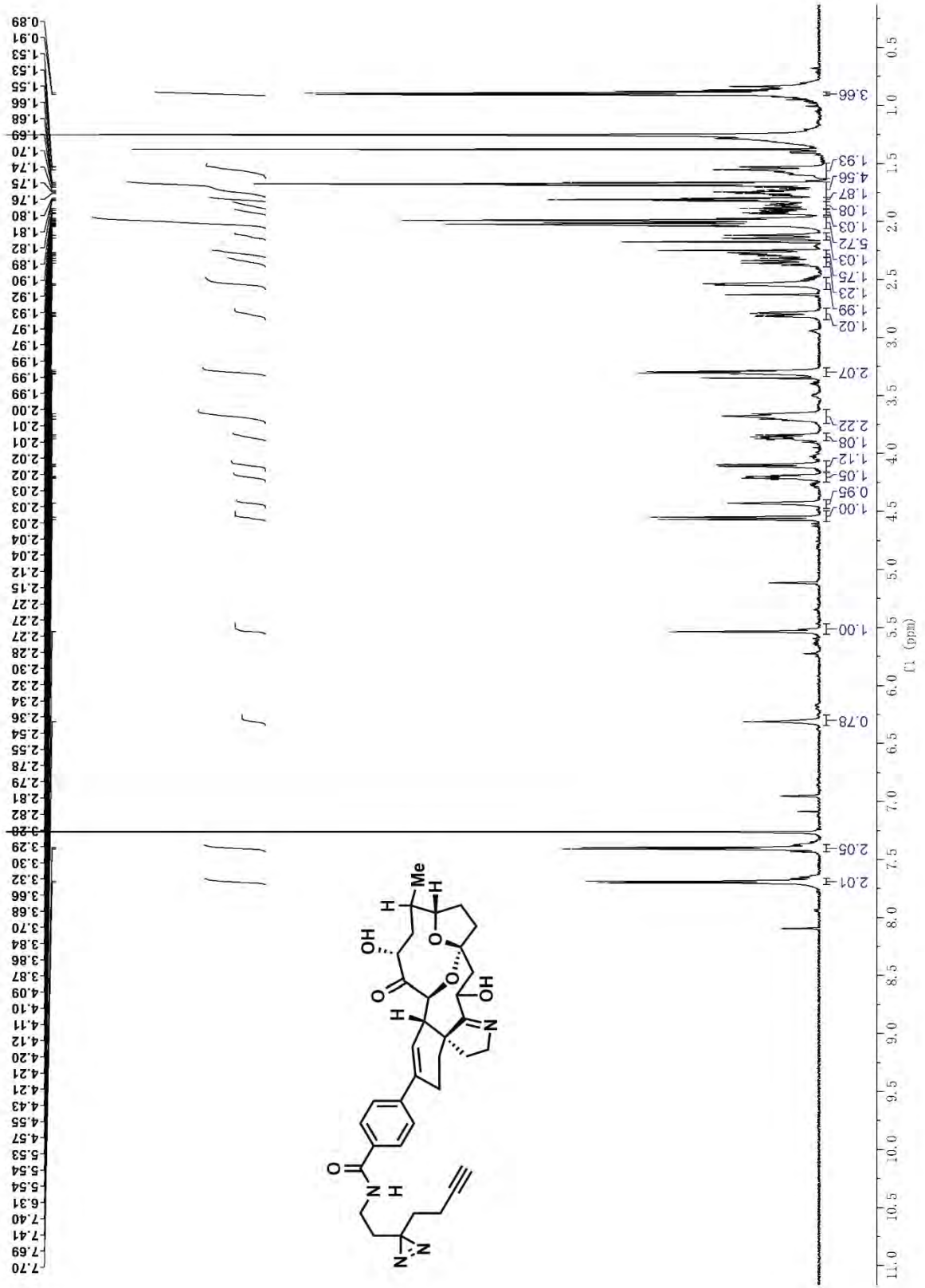
^{1}H NMR: Compound **276**



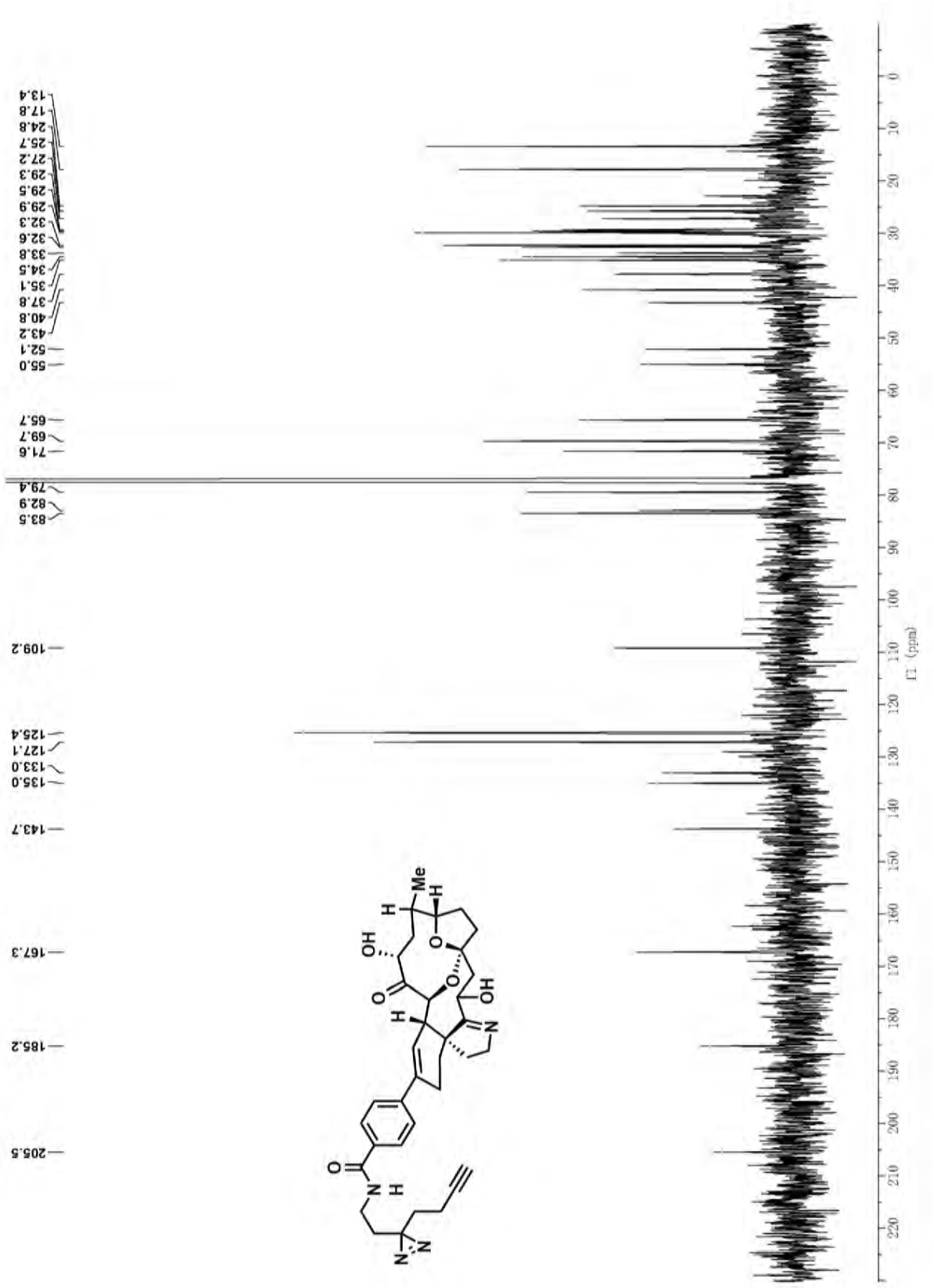
^{1}H NMR: Compound **277**



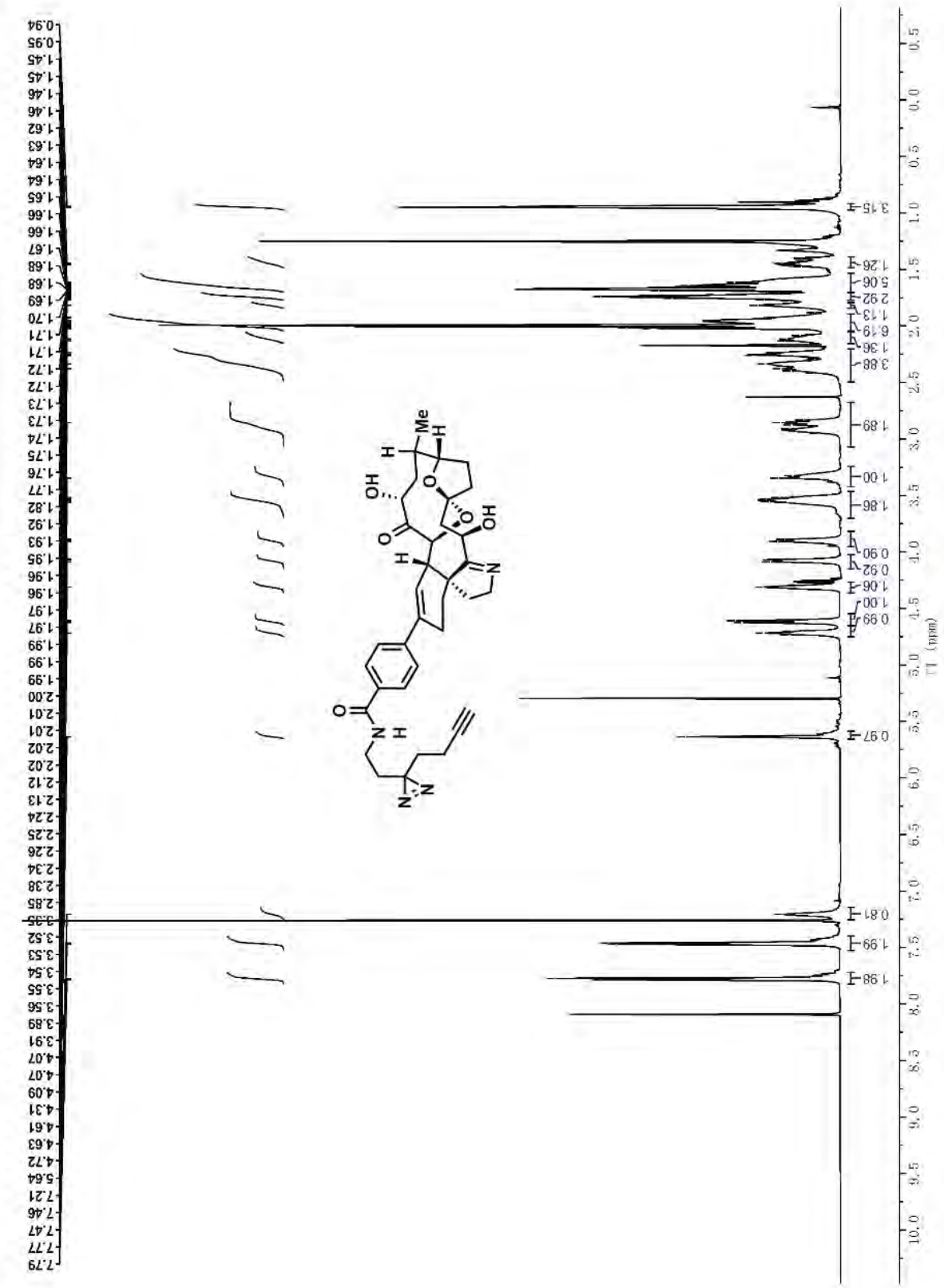
^{1}H NMR: Compound **278**



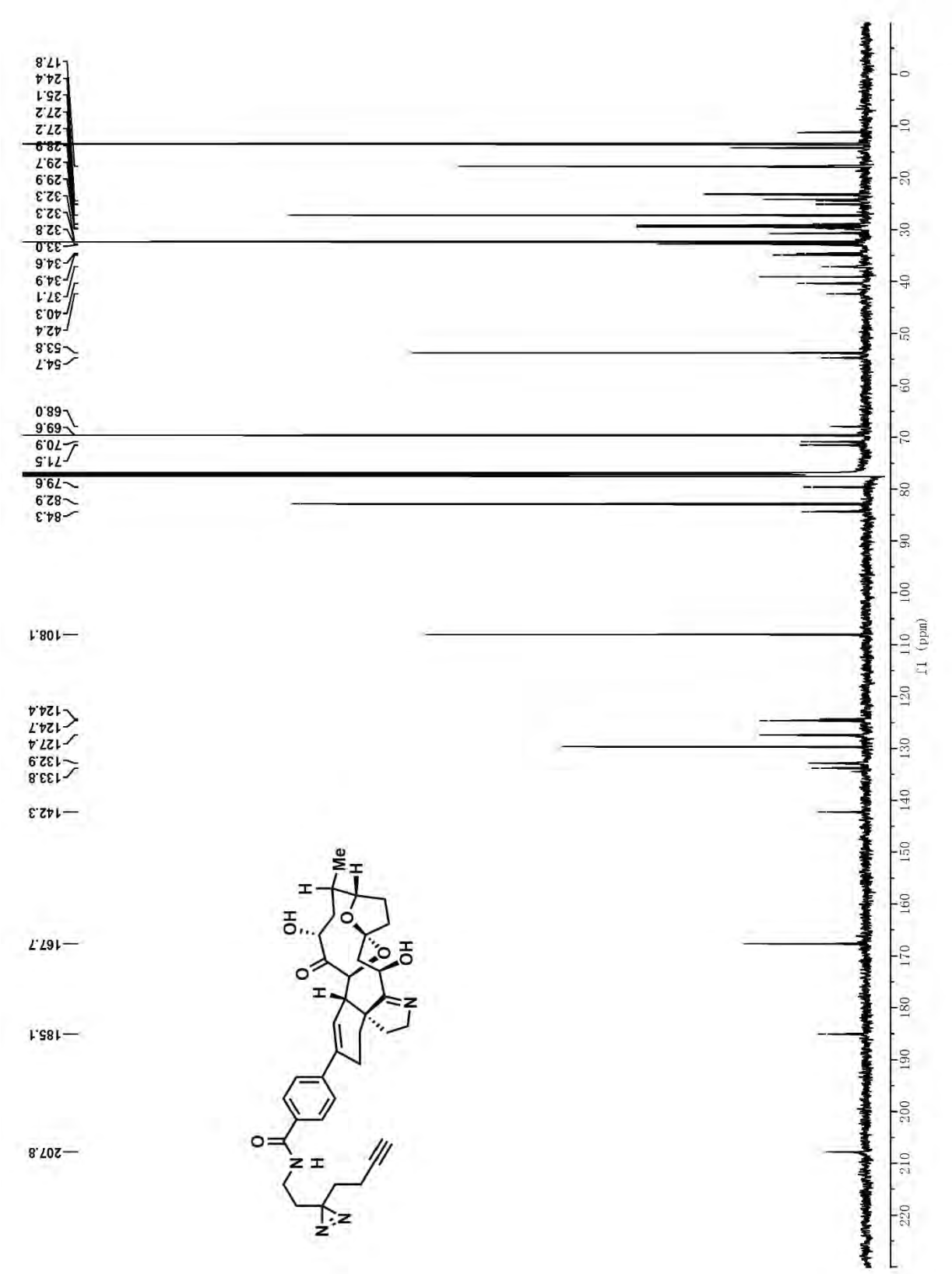
^{13}C NMR: Compound **278**



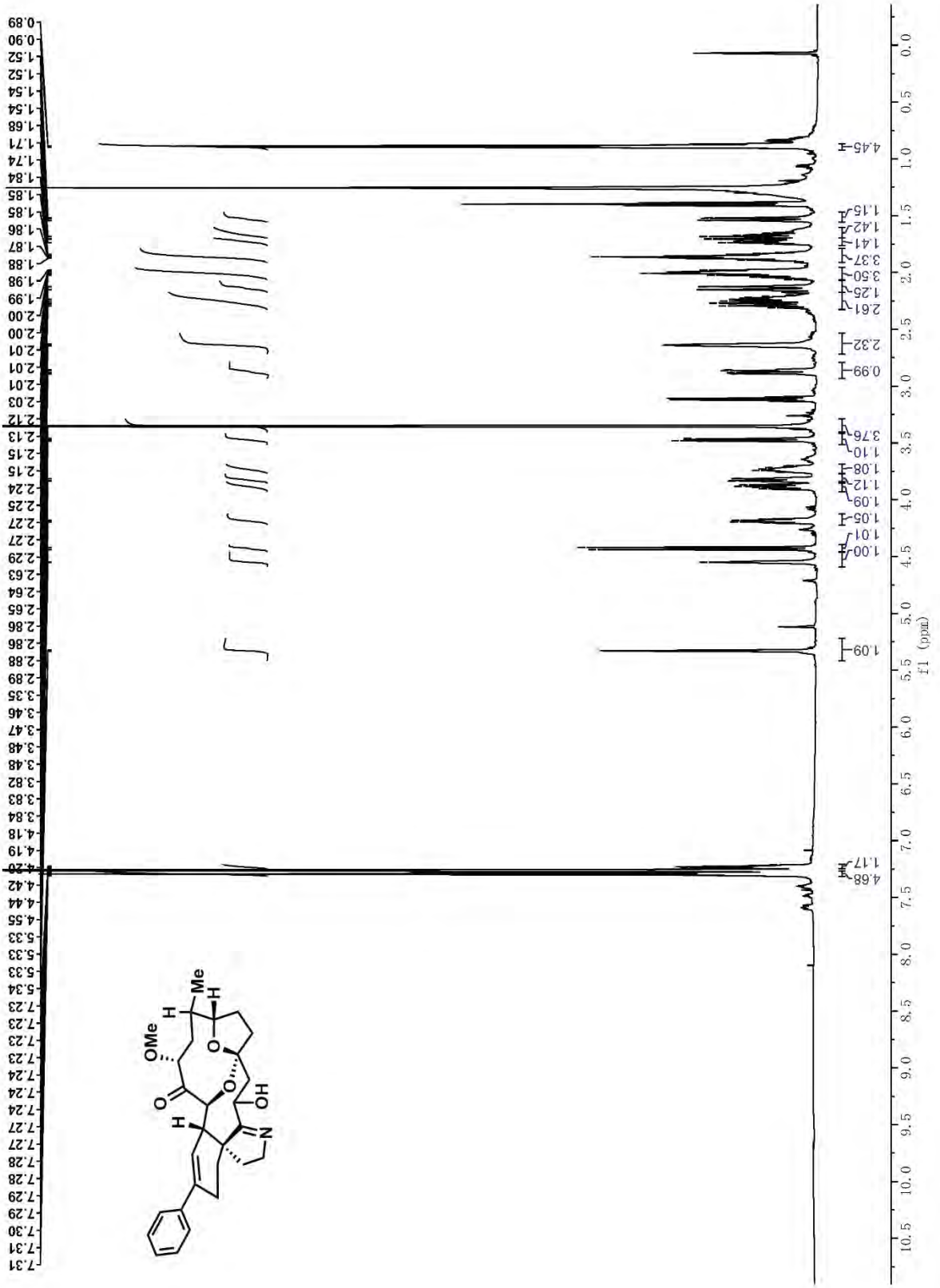
^{1}H NMR: Compound **279**



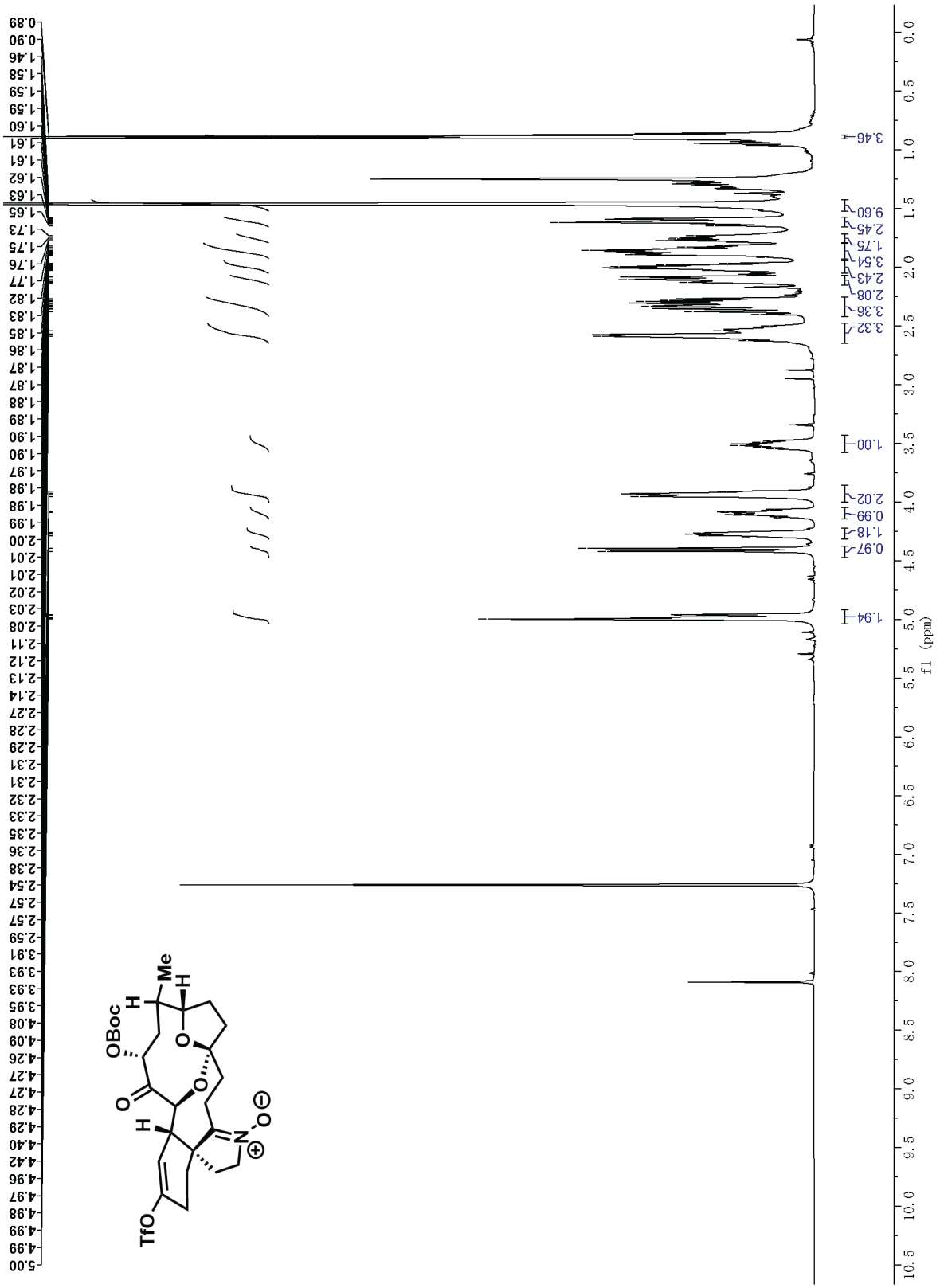
^{13}C NMR: Compound **279**



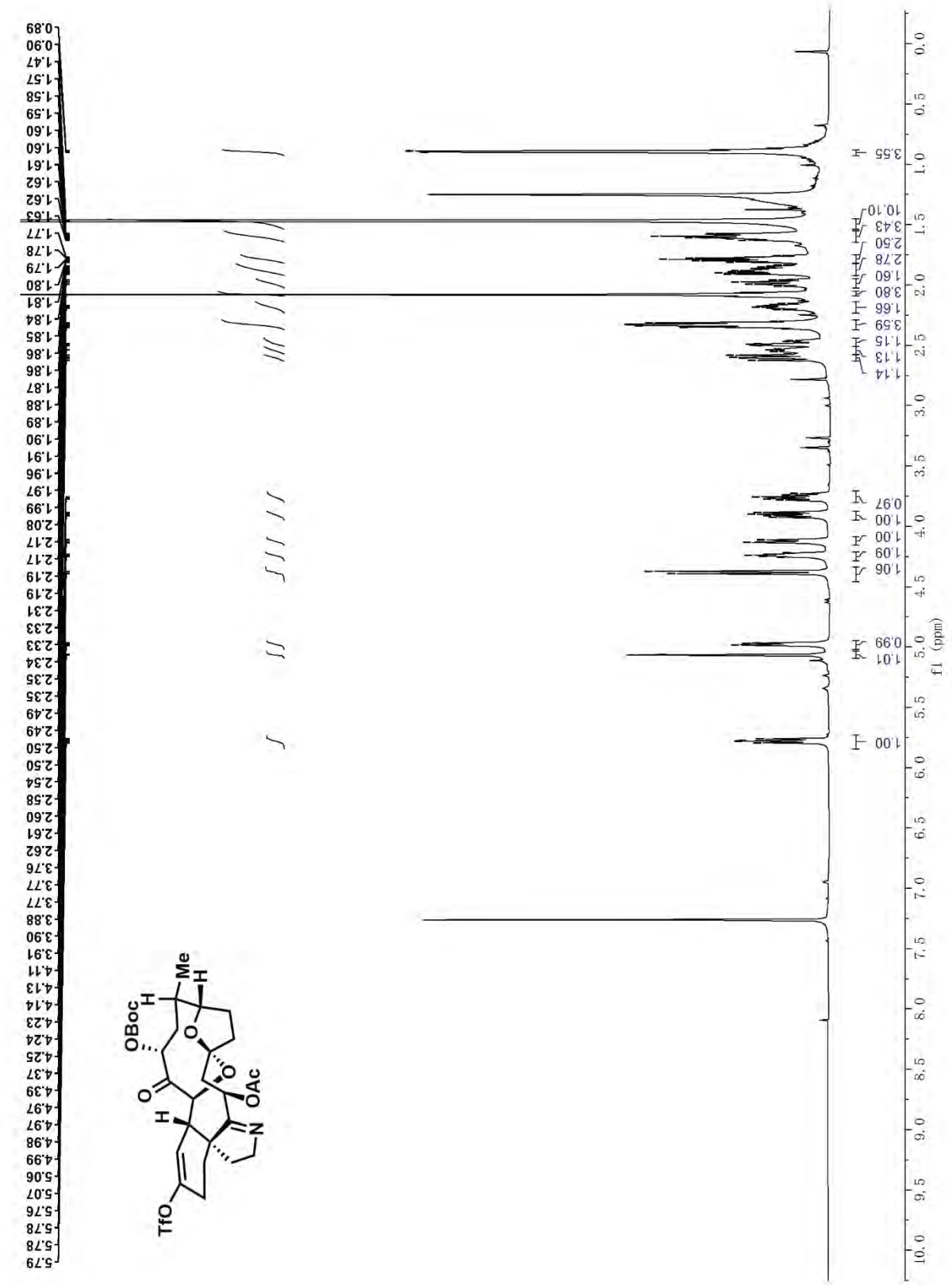
^{1}H NMR: Compound **283**



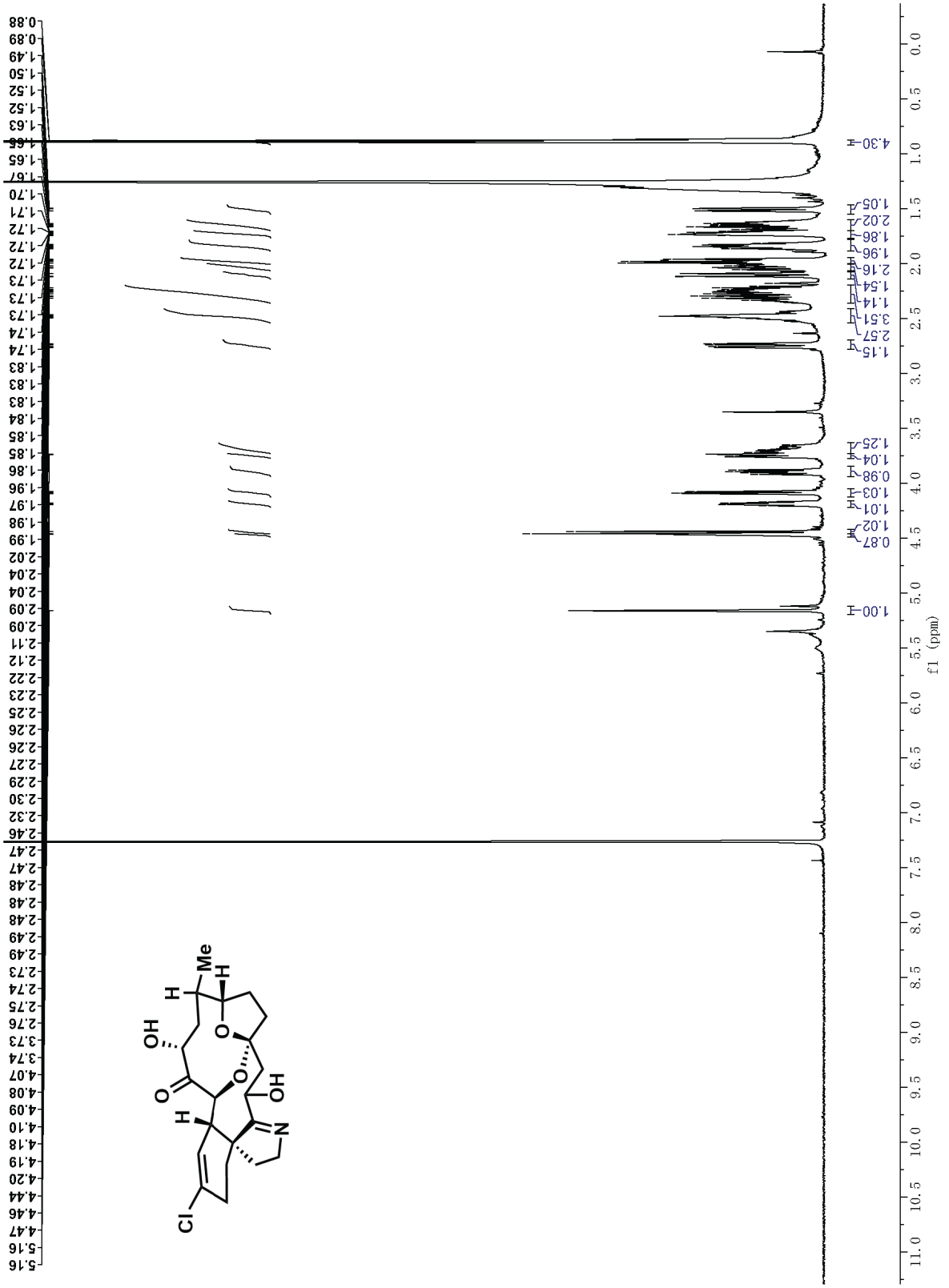
^{1}H NMR: 13-OBoc-**263**



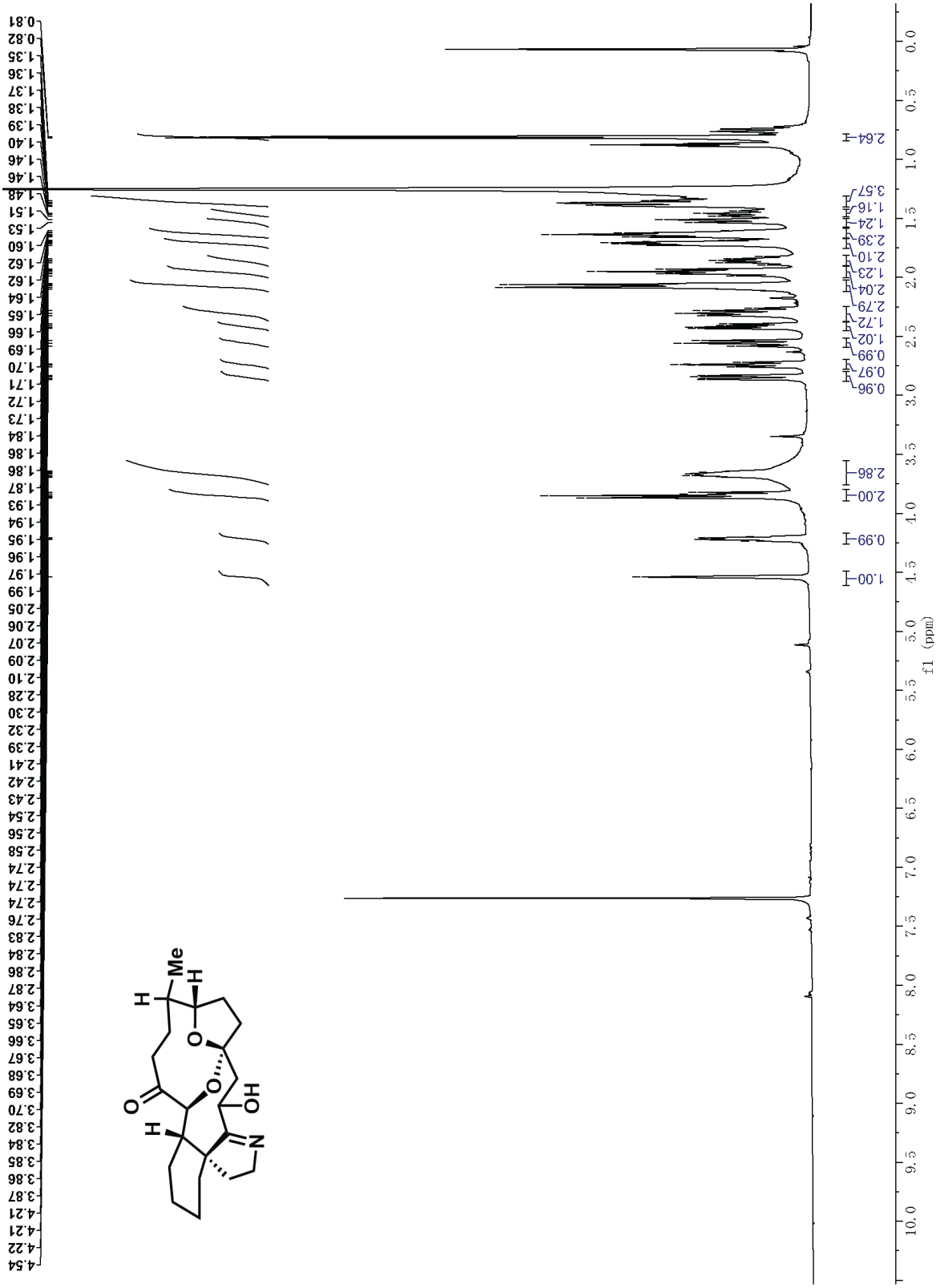
^{1}H NMR: 13-OBoc-**264**



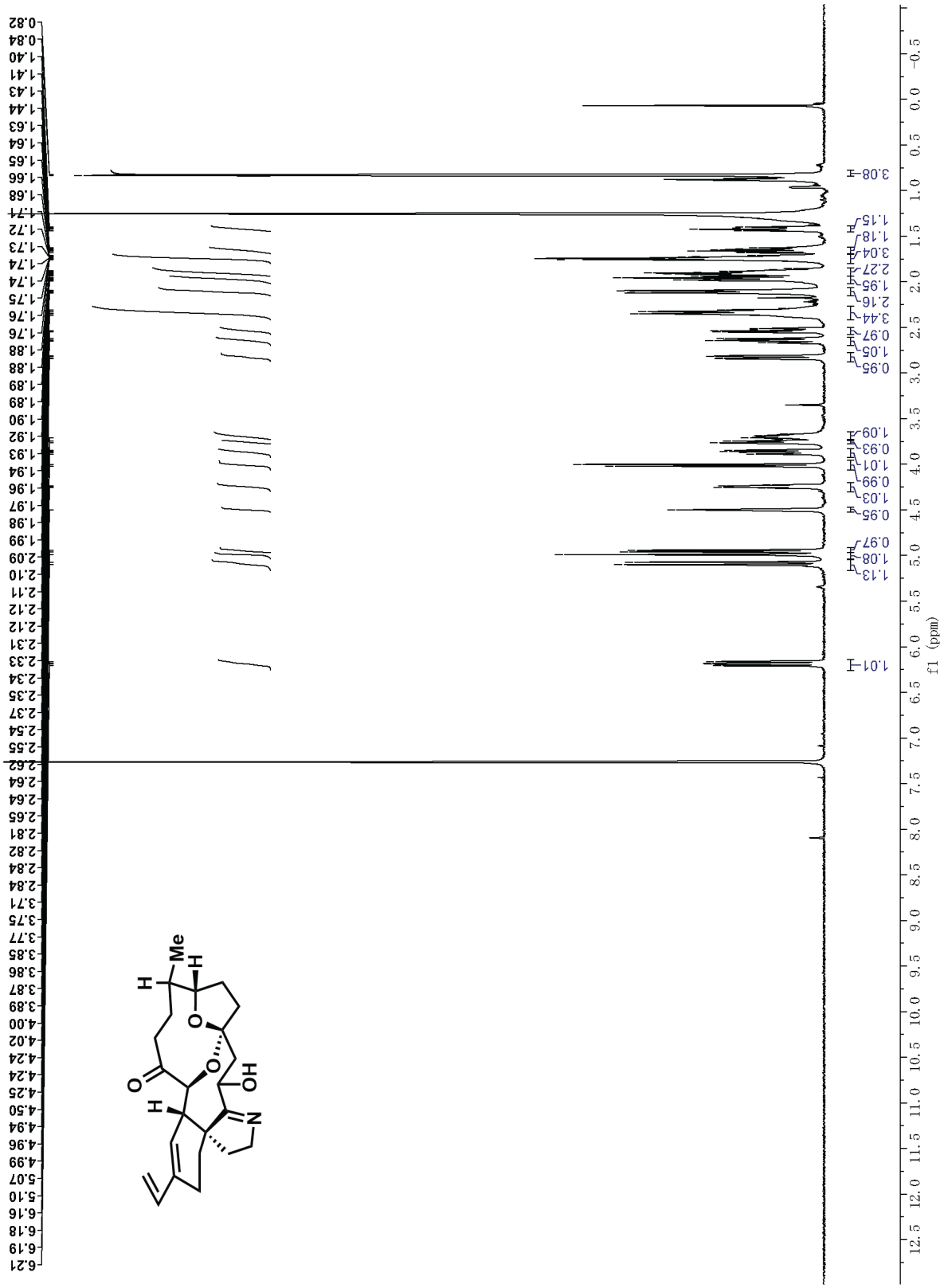
^{1}H NMR: Compound **284**



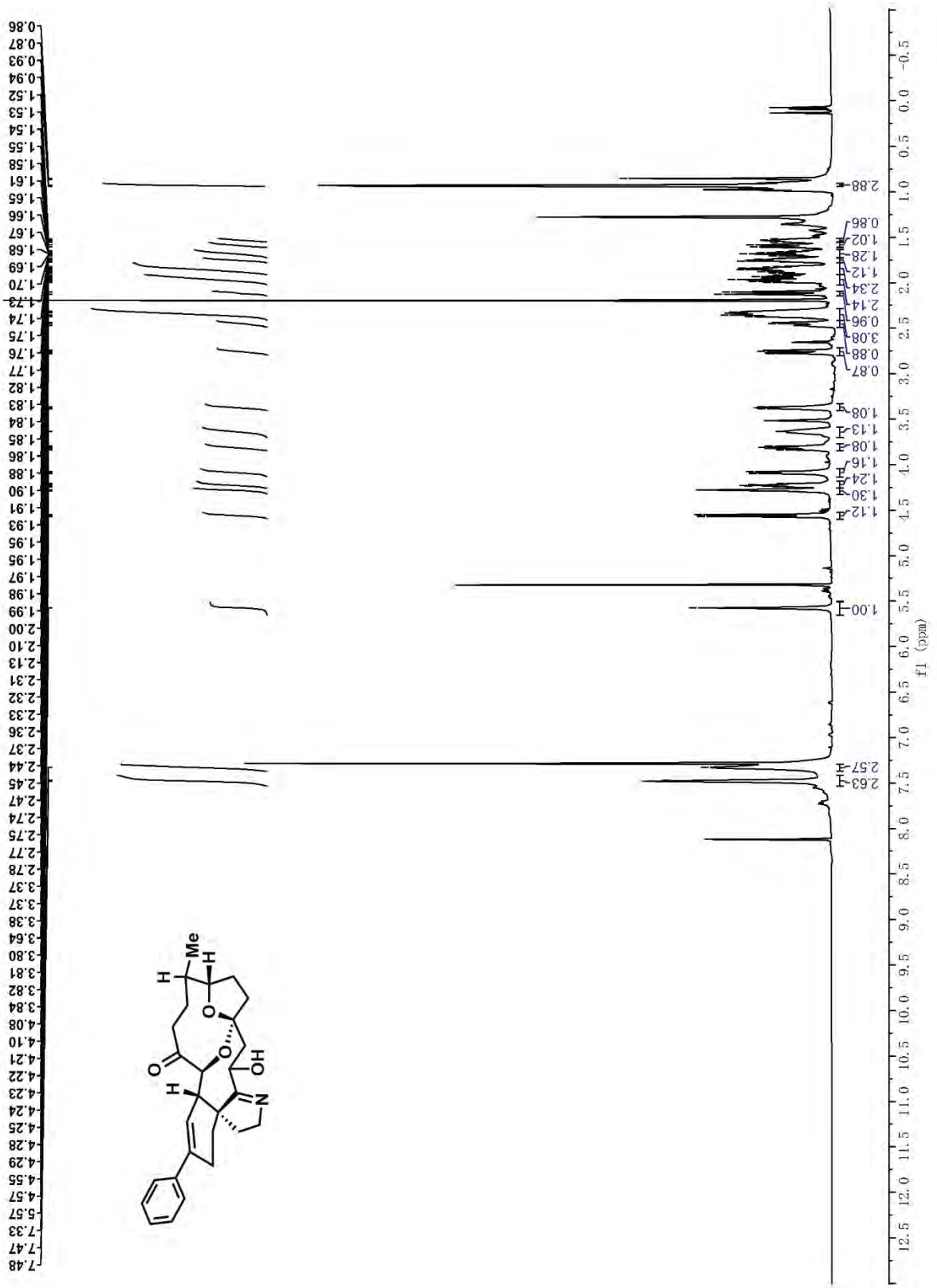
^{1}H NMR: Compound **285**



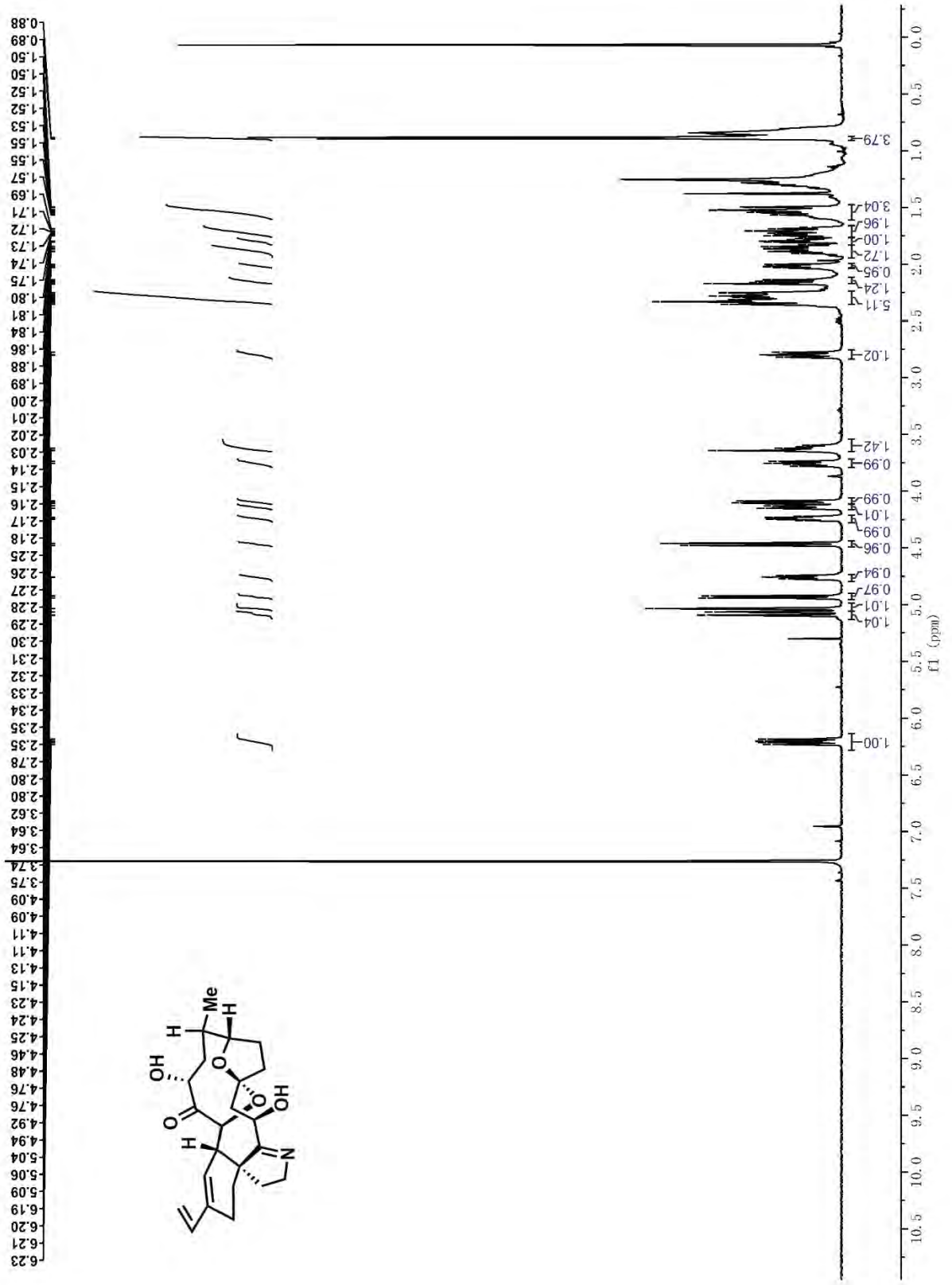
^{1}H NMR: Compound **286**



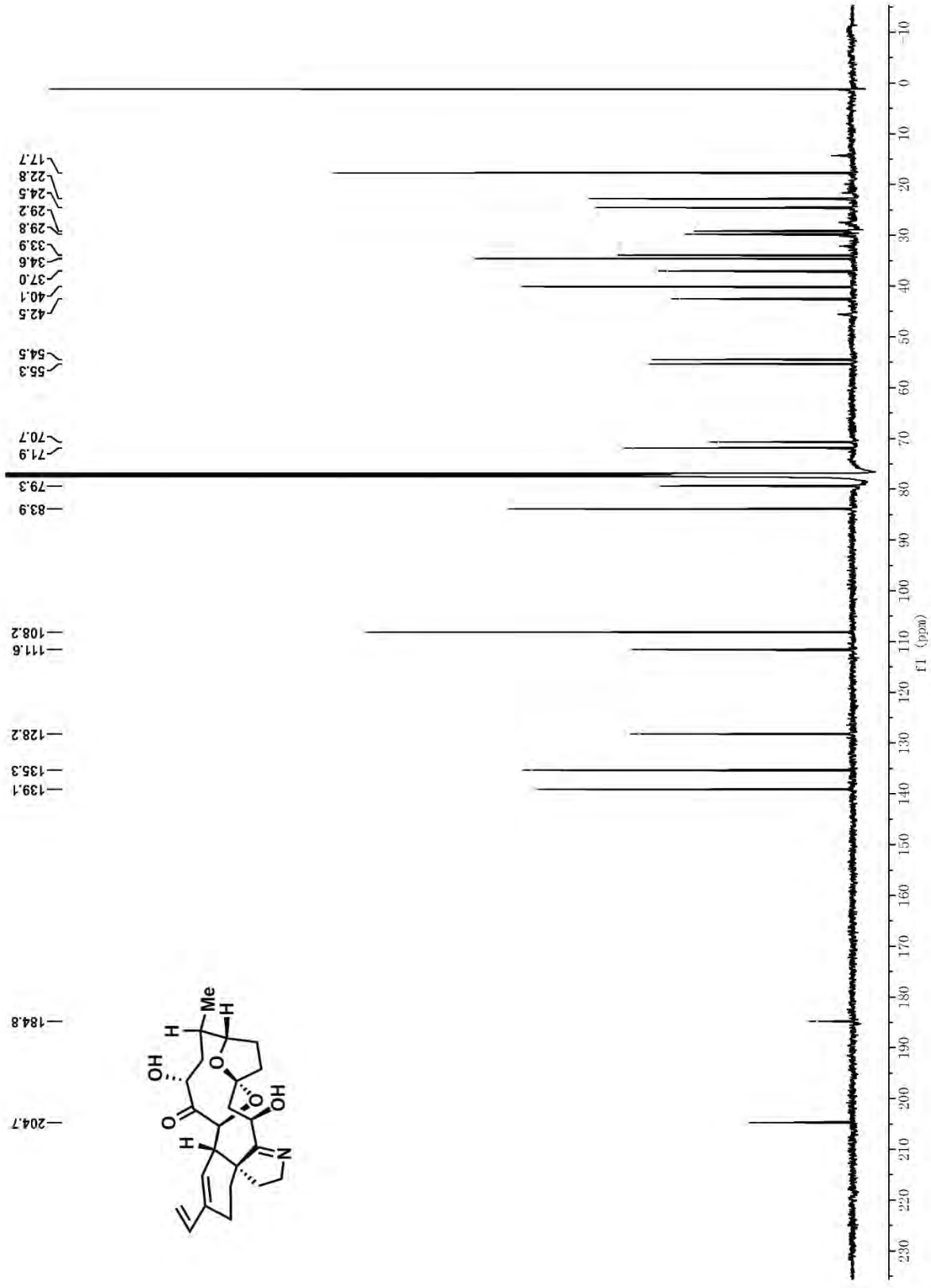
^{1}H NMR: Compound **287**



^{1}H NMR: **5-*epi*-portimine A**



^{13}C NMR: **5-*epi*-portimine A**



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