THE UNIVERSITY OF CHICAGO

ADVANCES IN PERICYCLIC REACTIONS:
I. NOVEL HIGHLY REACTIVE AMINODIENES FOR DIELS-ALDER REACTIONS
II. DEAROMATIVE INDOLO-CLAISEN REARRANGEMENTS
III. SYNTHETIC STUDIES TOWARDS HINCKDENTINE A AND MELONINE

A DISSERTATION SUBMITTED TO
THE FACULTY OF THE DIVISION OF THE PHYSICAL SCIENCES
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DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

BY
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To my family

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Ac	acetyl
acac	acetylacetonate
Boc	*tert*-butoxylcarbonyl
brsm	based on recovered starting material
Bs	benzenesulfonyl
Bu	*n*-butyl
CSA	(+)-camphorsulfonic acid
COSY	correlation spectroscopy
Cy	cyclohexyl
DA	Diels-Alder
DMP	Dess-Martin periodinane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DCE	dichloroethane
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMBn	dimethoxybenzyl
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess

Et	ethyl
h	hours
H-atom	hydrogen atom
HDA	hetero-Diels-Alder reaction
HRMS	high resolution mass spectrometry
Hz	Hertz
IBX	2-iodoxybenzoic acid
IR	infrared spectroscopy
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
lut	2,6-lutidine
m-CPBA	3-chloroperbenzoic acid
Me	methyl
MMPP	magnesium monoperoxyphthalate
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
ND	not determined
NFSI	*N*-fluorobenzenesulfonimide
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy

Ns	*p*-nitrobenzenesulfonyl
PCC	pyridinium chlorochromate
Ph	phenyl
phen	1,10-phenanthroline
PIDA	iodobenzene diacetate
PIFA	iodobenzene bis(trifluoroacetate)
Pr	*n*-propyl
Pyr	pyridine
R_f	retention factor
RT	room temperature
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TBAF	tetrabutylammonium fluoride
Ts	*p*-toluenesulfonyl
VT	variable temperature

Acknowledgements

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Chapter 1.

Introduction. Doubly-Activated Butadienes In The Diels-Alder Reaction

Section 1.1. Activated dienes for the Diels-Alder reaction. 1,3-disubstituted dienes

Among the many transformations reliably used for the synthesis of complex molecules, the Diels-Alder reaction is perhaps the most powerful, giving access to six-membered cyclic compounds in a regio- and stereocontrolled manner, with up to four chiral centers.[1] The power of the Diels-Alder reaction is evident from the pivotal strategic role it has played in the synthesis of numerous complex natural products.[2] Since the first reports by Diels and Alder[3], the synthetic potential of the Diels-Alder reaction has been greatly expanded by modification of both diene and dienophile components of the reaction[4]. From early synthetic studies, it was envisioned that the use of heteroatom-substituted dienes exerts significant effect on the reaction outcomes, governing the regio- and stereochemistry of the resulting cycloadduct, as well as increasing the overall

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[1] a) Whiting, A. *'Chapter 3, Asymmetric Diels-Alder reactions'* in Advanced Asymmetric Synthesis. State-of-the-art and future trends in feature technology. Springer Netherlands; **1996**; p. 126-145; b) Corey, E. J., Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, 37, 388; c) Evans, D., Johnson, J. '*Diels-Alder reactions*' in Comprehensive Asymmetric Catalysis I-III, Jacobsen, E. N., Pflatz, A.; Yamamoto, H., Eds. Springer-Verlag, Berlin Heidelberg, **1999**; p. 1177-1235. (d) Brocksom, T. J., Nakamura, J., Ferreira, M. L., Brocksom, U. *Journal of the Brazilian Chemical Society*. **2001,** *12*, 597. (e) Nicolaou, K. C., Snyder, S. A., Montagnon, T., Vassilikogiannakis, G. *Angew Chem Int Ed.* **2002,** *41***,** 1668; f) Maruoka, K.. '*Asymmetric Carbon–Carbon Bond-Forming Reactions: Asymmetric Cycloaddition Reactions*.' in Catalytic Asymmetric Synthesis, Ojima, I.,Ed., Wiley VCH: New York, **2005**.

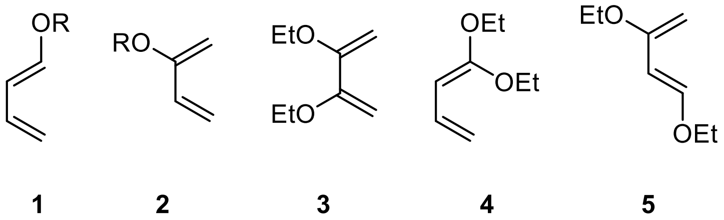
[2] Corey E. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1650.

[3] a) Diels, O.; Alder, K. *Justus Liebigs Annalen der Chemie* **1928**, *460*, 98; b) Diels, O.; Alder, K. *Berichte der deutschen chemischen Gesellschaft (A and B Series)* **1929**, *62*, 554; c) Diels, O.; Alder, K. *Berichte der deutschen chemischen Gesellschaft (A and B Series)* **1929**, *62* (8), 2087–2090.

[4] For some reviews, see: a) Kloetzel, M. C. *Org. React.* **1948**, 4, 1. (b) Holmes, H. C. *Org. React*. **1948**, 4, 60; c) Butz, L. W.; Rytina, A. W. *Org. React.* **1949**, 5, 136. (d) Onishenko, A. S. *Diene Synthesis*; Daniel Davy & Co.: New York, **1964**. (e) Oppolzer, W. In *Comprehensive Organic Synthesis*; Pergamon Press: New York, **1991**; Vol. 5

reaction rate and efficiency of the transformation.[5] Later, these empirical observations were further supported by multiple theoretical studies[6].

The first reports of heteroatom-substituted dienes involved 1- and 2- alkoxysubstituted butadienes (**1** and **2**, Scheme **1**)[7]. At nearly the same time the first report on the doubly-substituted 2,3-diethoxy-1,3-butadiene **3** appeared in the literature[8]. Shortly after these first reports, the preparation and the reactivity in Diels-Alder reaction of doubly-activated dienes **4**[9] and **5**[10] was reported. It is interesting to note, that despite even in the first reports of the latter dienes authors have emphasized, that they react readily with the regular dienophiles (benzoquinone, maleic anhydride), and a significant rate enhancement compared to unsubstituted analogs was observed, no further investigation of the use of these dienes have been reported, in part due to the complications associated with their preparations.



Scheme 1. First heteroatom-substituted dienes for the Diels-Alder reaction

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[5] a) Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753; b) Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reaction*; Wiley:New York, **1990**.

[6] For example, see: (a) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, **1970**; b) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: London, **1976**; c) Herndon, W. C. *Chem. Rev.* **1972**, 72, 157; d) Sauer, J.; Sustamnn, R. *Angew. Chem., Int. Ed. Engl.* **1980**, 19, 779; e) Houk, K. N.; Li, Y.; Evanseck, J. D. *Angew. Chem., Int. Ed. Engl.* **1992**, 31, 682; f) Houk, K. N.; Gonzalez, J.; Li, Y. *Acc. Chem. Res.* **1995**, 28, 81

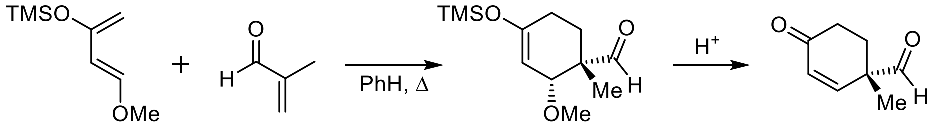
[7] a) Petrov, A. A. *Zh. Obshch. Khim.* **1941**, 11, 661; b) Fiesselmann, H. *Chem. Ber.* **1942**, 75, 881; c) Wichterle, O. *Collect. Czech. Chem. Commun.* **1938**, 10, 497; d) Flaig, W. *Liebigs Ann. Chem.* **1950**, 568,1

[8] Johnson, J. R.; Jobling, W. H.; Bodamer, G. W. *J. Am. Chem. Soc.* **1941**, *63*, 131.

[9] McElvain, S. M.; Morris, L. R. *J. Am. Chem. Soc.* **1952**, *74*, 2657.

[10] Shavrygina, O. A.; Makin, S. M. *Khim. Farm. Zh.* **1969**, 3, 17

A major breakthrough in the synthesis and use of activated dienes occurred after the development of efficient ways to convert carbonyl compounds into their corresponding silyl enol ethers[11]: In 1974 Danishefsky and Kitahara published the historic paper on the synthesis of a 'Useful Diene for the Diels-Alder Reaction'[12]. In this first short report the authors noted that 1-methoxy-3-trimethylsiloxy butadiene **6** reacts readily with activated dienophiles such as maleic anhydride, dimethyl acetylenedicarboxylate and benzoquinone to give rise to the corresponding cycloadducts, which upon acidic treatment readily hydrolyze to form cyclohexanones or phenols. One of the most interesting observations made by the authors was that the diene **6** reacts with methacrolein, a relatively unreactive dienophile, upon refluxing in benzene to provide cyclohexene **8**, which upon treatment with acid readily hydrolyzes to give 4,4-disubstituted cyclohexenone **9**, a valuable synthetic building block for the total synthesis of multiple natural products. (Scheme **2**).



6 **7** **8** **9**
72%

Scheme 2. Initial report of the Diels-Alder reaction of Danishefsky's diene

The newly developed diene very soon acquired enormous popularity due to its high reactivity towards a range of dienophiles, including heterodienophiles, and the ability to easily convert the cycloadducts of the reaction into substituted cyclohexenones, dihydropyranones and phenols[13]. Soon after the initial report on the synthesis and use of the 1-methoxy-3-trimethylsiloxy

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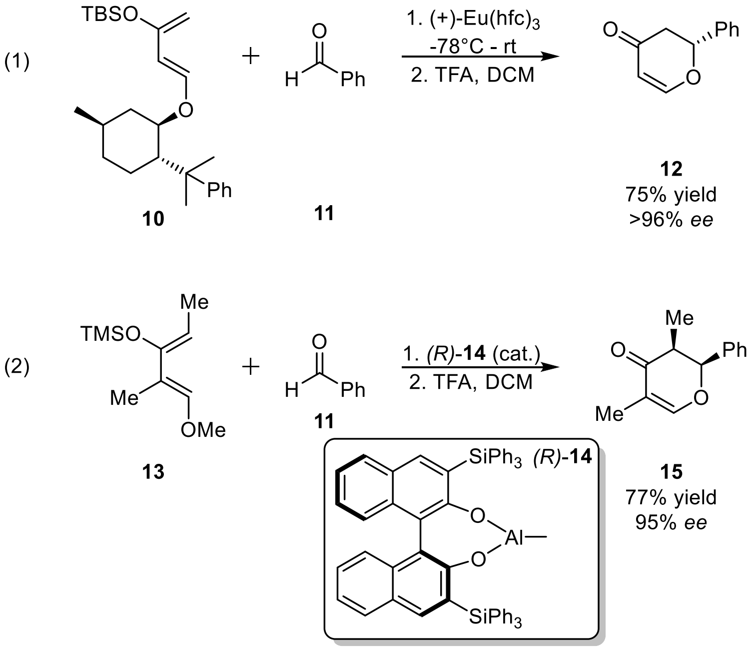
[11] a) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.***1969**, 34, 2324; b) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, 90, 4462.; c) Pierce, A. E. '*Silylation of Organic Compounds*' Pierce Chemical Co., Rockford, Illinois, **1968**

[12] Danishefsky, S.; Kitahara, *J. Am. Chem. Soc.* **1974**, *96*, 7807.

[13] For some reviews, see a) Danishefsky, S. *Acc. Chem. Res.* **1981**, 14, 400; b) Danishefsky, S. J. DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, 15; c) Danishefsky, S. *Chemtracts: Org. Chem.* **1989**, 2, 273

butadiene, Danishefsky reported the first example of a diastereoselective hetero-Diels-Alder (HDA) reaction of the enantiomerically pure analog of the Danishefsky diene **10** with aromatic aldehydes in the presence of a chiral lanthanide Lewis acid to access, after hydrolysis of the initially formed cycloadduct, chiral dihydropyranones with high levels of enantioselectivity (Scheme **3**, eq. 1).[14] Several years later Yamamoto published the first example of an asymmetric HDA reaction between diene **13** and aromatic aldehydes catalyzed by binaphtyl-based organoaluminium catalyst (*R)*-**14** (Scheme **3**, eq. 2)[15]. Following these reports, multiple examples of enantioselective Diels-Alder reactions of the Danishefky-type dienes have been published[16], further expanding the scope of application of this doubly-activated diene.



Scheme 3. Enantioselective Diels-Alder reactions with Danishefskys' diene

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[14] Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1986**, *108*, 7060.

[15] Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110,* 310.

[16] For the recent examples of the enantioselective DA reactions with Danishefskys' diene, see: a) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *9*, 1007; b) Hu, Y.; Xu, K.; Zhang, S.; Guo, F.; Zha, Z.; Wang, Z. *Org. Lett.* **2014**, *16*, 3564; c) Li, Y.; Hu, Y.; Zhang, S.; Sun, J.; Li, L.; Zha, Z.; Wang, Z. *J. Org. Chem.* **2016**, *81*, 2993; d) Taheri kal Koshvandi, A.; Heravi, M. M. *Tetrahedron: Asymmetry* **2017**, *28,* 1506 and references therein

Previously, in our group we developed 1-amino-3-siloxy-butadienes (e.g., **16,** Scheme **4**) as highly reactive dienes that undergo DA cycloaddition reactions under mild conditions with a broad range of dienophiles to afford upon hydrolysis various 4,4-disubstituted cyclohexenones.[17]. It was shown that these newly developed dienes are (a) considerably more reactive (*ca.* 3,000 times), (b) give excellent *endo*-selectivities with many dienophiles, and (c) give adducts containing an amino group, allowing further elaboration to the frameworks found in alkaloid natural products.[18] In our lab were also developed related carbamate dienes (e.g., **17**) and it was demonstrated that they undergo enantioselective DA reactions catalyzed by chiral salen complexes, giving rise to a range of chiral 4,4-disubstituted cyclohexenones in high yields and enantioselectivities (Scheme 4).[19] These methods have proven immensely useful and have played key roles in the syntheses of several natural products.[20] For instance, Cole have utilized this methodology to access the core building unit during the total synthesis of (-)-Phomactin A in an enantioselective fashion (Scheme **4**, eq.2).[21]

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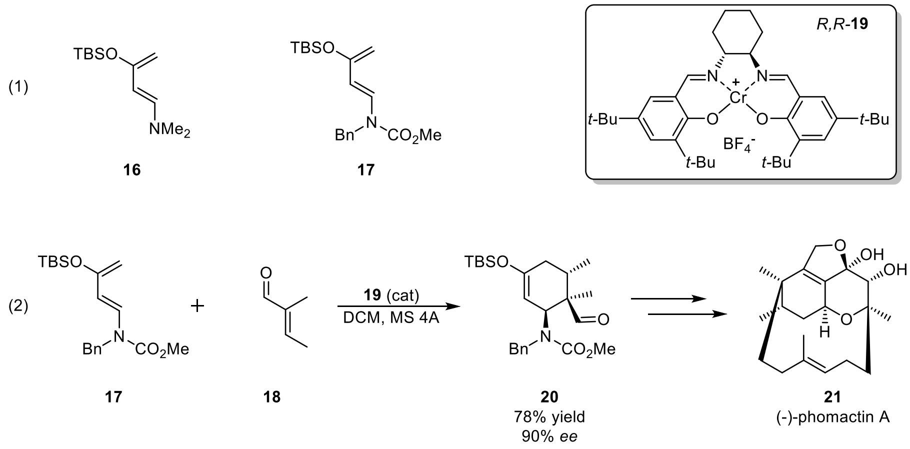
[17] a) Kozmin, S.A.; Rawal, V. H. *J. Org. Chem.* **1997**, 62, 5252; b) Kozmin, S. A.; Green, M. T.; Rawal, V.H. *J. Org. Chem.* **1999**, *64*, 8045; c) Kozmin, S. A.; Janey, J. M.; Rawal, V.H. *J. Org. Chem.* **1999,** *64*, 3039; d) Kozmin S. A.; Rawal, V. H *J. Am. Chem. Soc.* **1999,** *121*, 9562.

[18] a) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1998**, *120*, 13523 (b) Hayashida, J.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2008**, *47*, 4373

[19] a) Huang, Y.; Iwama, T.; Rawal, V.H *J. Am. Chem. Soc.* **2000,** *122*, 7843; b) Huang, Y.; Iwama, T.; Rawal, V. H. *Org. Lett.* **2002,** *4*, 1163; c) McGilvra, J. D.; Rawal, V. H. *Synlett*. **2004**, 2440; d) Ohfusa, T.; Nishida, A. *Tetrahedron*. **2011**, *67*, 1893

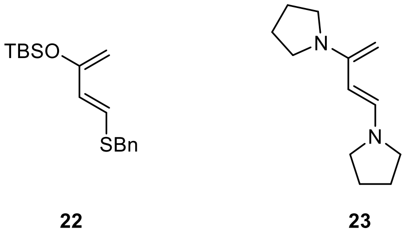
[20] a) Smith, A.B.; Basu, K.; Bosanac, T. *J. Am. Chem. Soc.* **2007**, *129*, 14872; b) Petronijevic, F.R.; Wipf, P. *J. Am. Chem. Soc.* **2011**, *133*, 7704; c) Mukai, K.; Urabe, D.; Kasuya, S.; Aoki, N.; Inoue, M .*Angew. Chem. Int. Ed.* **2013**, *52*, 5300; d) Nicolaou, K.C.; Tria, G.S.; Edmonds, D.J.; Kar, M. *J. Am. Chem. Soc.* **2009**, *131*, 15909.

[21] You, L.-F.; Hsung, R. P.; Bedermann, A. A; Kurdyumov, A. V.; Tang, Y.; Buchanan, G. S.; Cole, K. P *Adv Synth Catal*. **2008**, 350, 2885.



Scheme 4. 1-dialkylamino-1-siloxy-1,3-butadiene and its application in synthesis

Following the initial reports from our lab, Gravel has published studies on two analogs of the 1-dialkylamino-1-siloxy-1,3-butadiene – 1-benzylthio-3-(tert-butyldimethylsilyloxy)-1,3-butadiene **22**[22] and 1,3-dipyrrolidino-1,3-butadiene **23**.[23] The former diene **22**, based on the competition experiment, appeared to be 3 times less reactive than Danishefsky diene. However, 1,3-dipyrrolidino-1,3-butadiene **23** proved to be at least 20 times more reactive than the 1-dialkylamino-1-siloxy-1,3-butadiene, being one of the most active heteroatom-substituted butadienes known to date.



Scheme 5. Other examples of 1,3-diactivated butadienes

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[22] Holmes, J. M.; Albert, A. L.; Gravel, M. *J. Org. Chem.* **2009**, *74*, 6406.
[23] Zhou, S.; Sánchez-Larios, E.; Gravel, M. *J. Org. Chem.* **2012**, *77*, 3576.

Section 1.2. 1,1-Disubstituted Dienes And Brassards' Diene

Another class of doubly-activated dienes, which is also one of the oldest known classes, is 1,1-disubstituted dienes. As previously noted, the first report of 1,1-diethoxy-1,3-butadiene **4** is dated 1952. However, due to the difficulties associated with their preparation and stability, such type of reactive dienes have not found any use in the Diels-Alder reaction for more than 20 years, until Brassard published the first report on the efficient use of such type of ketene acetals for the rapid construction of anthraquinones (Scheme **6**, eq. 1)[24]. Following this initial report, several other research groups studied the synthesis and applications of ketene acetals in the context of natural product synthesis[25]. For example, Echavarren has reported the use of dioxolane-protected ketene acetal **26** for the synthesis of daunomycinone (Scheme **6**, eq. 2) [26]. Despite the decent amount of the research on the 1,1-dialkoxy-1,3-butadienes, the use of such dienes in synthesis is limited due to their low reactivity. Because of the severe steric issues associated with the presence of the *Z*-alkoxy substituent at the C1 position of the diene, these type of dienes have proven to be reactive only with very reactive dienophiles, such as benzoquinones, which limits their use only to the construction of anthraquinone-type structures. Sustmann *et. al.* extensively studied the Diels-Alder reactions of 1,1-disubstituted dienes and concluded that, apart from benzoquinones, all other active dienophiles react with this type of dienes through a stepwise mechanism, producing corresponding zwitterionic intermediates that take part in multiple side reactions[27].

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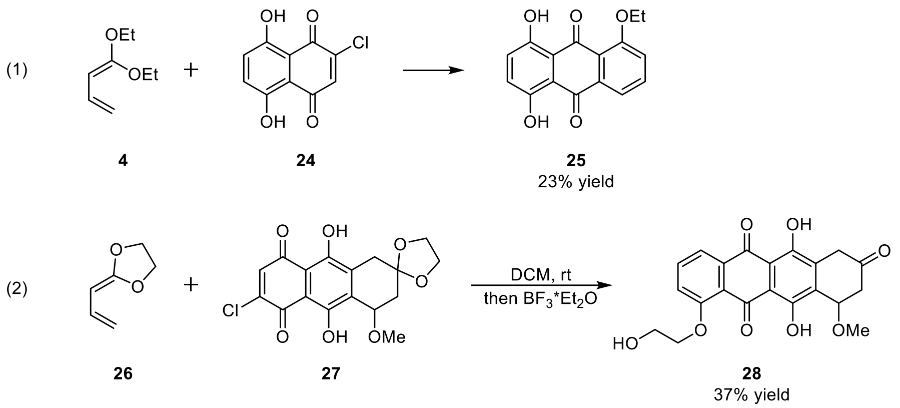
[24] Banville, J.; Grandmaison, J.-L.; Lang, G.; Brassard, P. *Can. J. Chem.* **1974***, 52*, 80.

[25] a) Ley, S. V.; Mitchell, W. L.; Radhakrishnan, T. V.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1981**, *0*, 1582; b) Lombardo, L. A *Tetrahedron Lett.* **1985**, *26*, 381; c) Ohno, M.; Mori, K.; Eguchi, S. *Tetrahedron Lett.* **1986**, *27*, 3381; d) Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Org. Chem.* **1987**, *52*, 1273; e) Aurell, M. J.; Gaviña, P.; Mestres, R. *Tetrahedron* **1994**, *50*, 2571; e) Kelly, T. R.; Fu, Y.; Sieglen, Jeffrey T.; De Silva, H. *Org. Lett.* **2000**, *2*, 2351

[26] Echavarren, A.; Prados, P.; Fariña, F. *Tetrahedron* **1984**, *40*, 4561.

[27] Sustmann, R.; Tappanchai, S.; Bandmann, H. *J. Am. Chem. Soc.* **1996**, *118*, 12555



Scheme 6. Diels-Alder reactions of 1,1-dialkoxy-1,3-butadienes

Two years after the initial report of the use of 1,1-dialkoxy-1,3-butadienes for anthraquinone synthesis, the group of Prof. Brassard, inspired by the publication from the Danishefsky group about the 1-methoxy-3-trimethylsiloxy-1,3-butadiene, reported a modification on their initial dialkoxybutadiene to include a third heteroatom substituent to give 1,3-dimethoxy-1-trimethylsiloxy-1,3-butadiene **29** (Scheme **7**). [28] The presence of an extra methoxy group at the C3 position of the diene rendered it significantly more reactive, allowing the diene to overcome the steric issues associated with the (Z)-methoxy group at the C1 position. This newly developed diene (generally known as Brassards' diene) due to the increased reactivity has found significantly broader use over its parent 1,1-dialkoxy-1,3-butadiene. Multiple applications of Brassards diene in the natural produce synthesis have been reported to date[29]. For instance, Danishefsky has demonstrated the efficient use of Brassard's diene for the construction of the spirocyclic fragment during the total synthesis of the Epigriseofulvin **31** (Scheme **7**).

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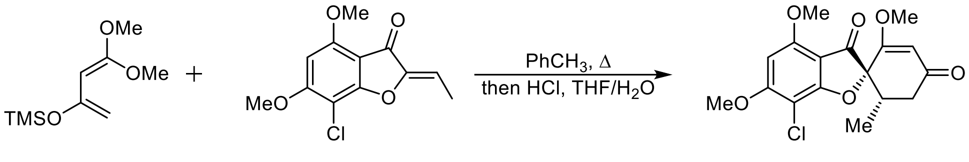
[28] a) Banville, J.; Brassard, P. *J. Chem. Soc., Perkin Trans. 1* **1976**, *0*, 1852; b) Savard, J.; Brassard, P. *Tetrahedron Lett.* **1979**, *20*, 4911.

[29] a) Roberge, G.; Brassard, P. *J. Chem. Soc., Perkin Trans. 1* **1978**, *0*, 1041–1046; b) Danishefsky, S.; Etheredge, S. J. *J. Org. Chem.* **1979**, *44*, 4716; c) Roberge, G.; Brassard, P. *Synthesis* **1979**, *1979*, 148; d) Danishefsky, S.; Walker, F. J. *J. Am. Chem. Soc.* **1979**, *101*, 7018.



Scheme 7. Use of the Brassard's diene in the total synthesis of Epigriseofulvin

Recently, Brassards' diene has received significant attention due to its ability to participate in the HDA reactions with aromatic aldehydes and imines. Since from the pioneering work by the group of Prof. Midland[30] on the diastereoselective cycloaddition of Brassard's diene with chiral aldehydes in the presence of a Eu (III) Lewis acid catalyst (Scheme **8**, eq. 1), multiple approaches on catalytic enantioselective HDA reactions have been reported to date[31]. For example, the group of Prof. Feng has recently reported an enantioselective HDA, catalyzed by chiral Zn (II) complex to produce spiro[cyclohexane-oxindolines] in good yields and with excellent enantioselectivities (Scheme **8**, eq. 2)[32].

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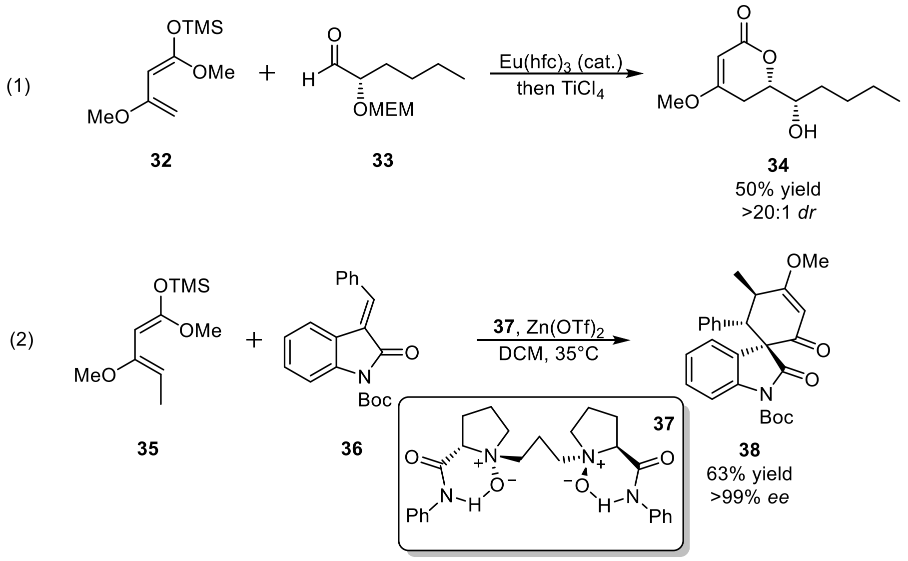
[30] a) Midland, M. M.; Graham, R. S. *J. Am. Chem. Soc.* **1984**, 106, 4294; b) Midland, M. M.; McLoughlin, J. I. *Tetrahedron Lett.* **1988**, 29, 4653; c) Midland, M. M.; Afonso, M. M. *J. Am. Chem. Soc.* **1989**, *111*, 4368.

[31] For the recent reviews, see: a) Sleet, C. E.; Tambar, U. K.; Maity, P. *Tetrahedron* **2017**, *73*, 4023; b) Sogani, N.; K. Bansal, R. *Current Catalysis* **2017**, *6*, 3; c) Špulák, M.; Ghavre, M.; Pour, M. *Tetrahedron Lett.* **2017**, *58*, 263.

[32] Zheng, J.; Lin, L.; Fu, K.; Zheng, H.; Liu, X.; Feng, X. *J. Org. Chem.* **2015**, *80*, 8836.



Scheme 8. Use of the Brassard's diene in HDA reactions

Section 1.3. Conclusive remarks

The development of activated dienes, such as Danishefsky-type and Brassard-type dienes, has significantly expanded the scope of application of the Diels-Alder reaction in the total synthesis of natural products. However, despite the big amount of research dedicated to the heteroatom-substituted activated 1,3-butadienes, the vast majority of the research was focused on the use of Danishefsky's diene and Brassards' diene. While these dienes provide direct access to key building blocks of many complex molecules, it produces only 4,4-disubstituted cyclohexenones, limiting the applications of these useful 4π components. Thus, we envisioned that the development of other activation patterns on dienes could expand the utilit of the Diels-Alder reaction in organic synthesis and provide a useful tool to construct the core fragments of multiple natural products. In this vein, we proceeded towards the development of activated 1,1-disubstituted 1,3-butadienes.

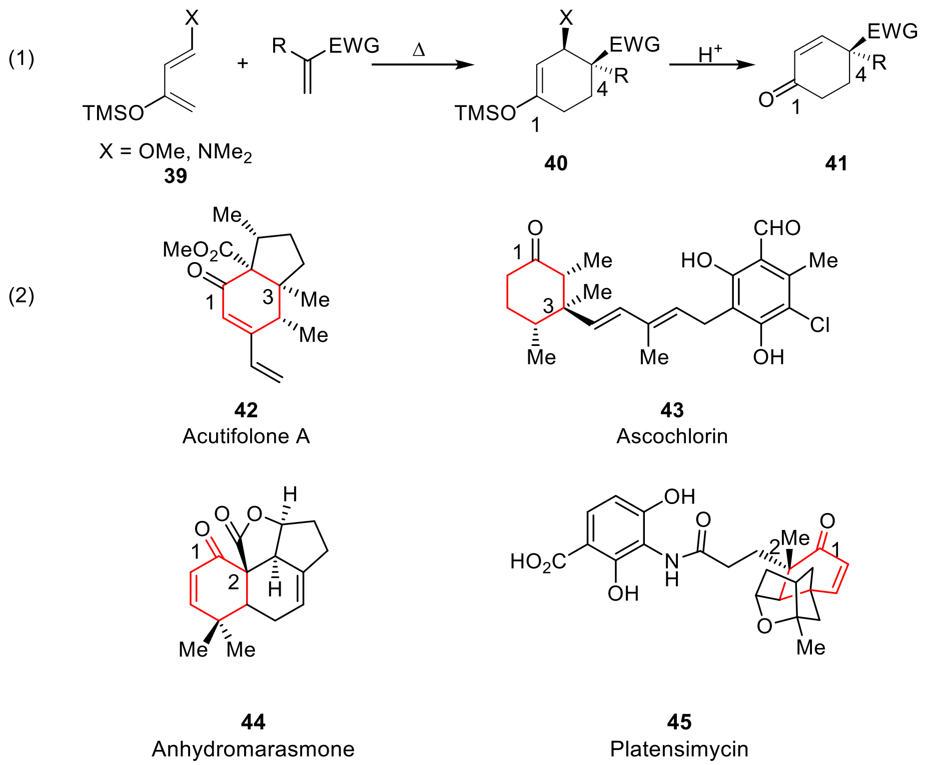
Chapter 2.

Diels-Alder Reactions Of 1-Amino-1-Oxo-1,3-Butadienes: Direct Synthesis Of 6-Substituted And 6,6'-Disubstituted 2-Cyclohexenones

Section 2.1. Introduction

2.1.1. Use of doubly-activated dienes to access substituted cyclohexanones

As was described in Chapter 1, the development of doubly-activated dienes, such as Danishefsky's and Rawal's dienes, significantly expanded the scope of the Diels-Alder reaction and its application in the total synthesis of natural products. Two major factors for this can be identified. First is the increased reactivity of these dienes, that comes along with an improved regio- and stereoselectivity in the reactions involving doubly-activated dienes compared to the regular unactivated dienes. Second is that the cyclohexenes **40**, produced during the Diels-Alder reaction between these dienes and proper dienophiles, can be hydrolyzed under acidic conditions to form 4,4-disubstituted cyclohexanones **41**, which present useful building blocks in the synthesis of many natural products. The latter factor presents the major advantage and the major limitation in the use of the doubly-activated dienes developed thus far. Since many natural products possess 3,3 - disubstituted cyclohexanones as the core building blocks, like Ascochlorin and Acutifolone A, and 2,2 – disubstituted cyclohexanones, such as Anhydromarasmone and Platensimycin (Scheme **9**), the use of doubly-activated dienes to construct these core fragments utilizing the Diels-Alder reaction is limited.



Scheme 9. Diels-Alder reaction as a route to access substituted cyclohexanones. 1) Use of activated dienes to access 4,4-disubstituted cyclohexanones; 2) Natural products, containing 3,3 - and 2,2 -disubstituted cyclohexanones

In the Rawal group we have a longstanding interest in the development of novel activated dienes for the Diels-Alder reaction and their utilization in natural product synthesis. We proposed that he challenge of synthesizing the 2,2 - and 3,3 -disubstituted cylclohexenones can be addressed by the development of new types of dienes, that upon reacting with the proper dienophiles will give rise, after the hydrolysis step, to the desired substituted cyclic structures. Accordingly, our group has recently synthesized and investigated a novel class of dienes, namely 1-amino-2-methoxybutadienes **46,**[33] which react with a variety of common dienophiles to produce cycloadducts **48**, that upon acidic work-up reveal the 3,3-disubstituted cyclohexane structures **49**

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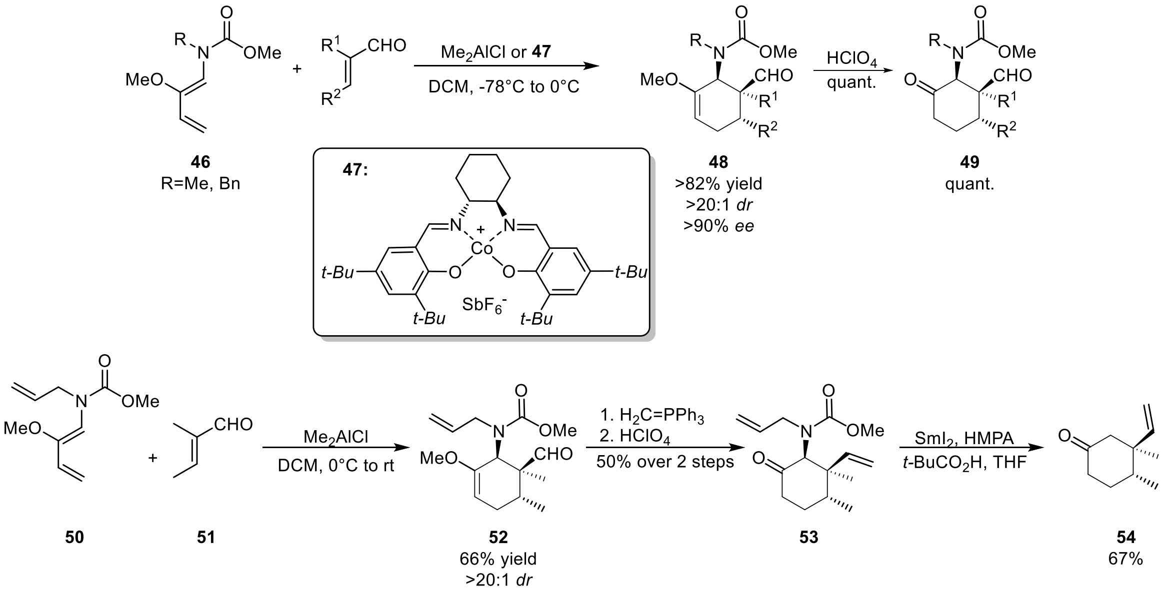
[33] Chu, H.; Wu, Y.-K.; Unni, A. K, Rawal, V. H., *unpublished work*

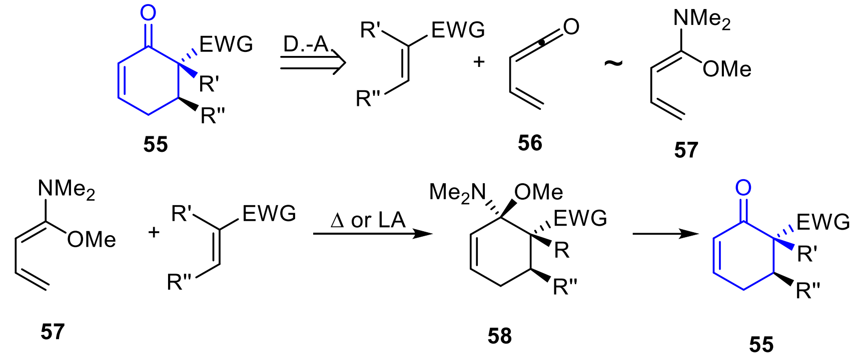
(Scheme **10)**. The strong electron-donating effect of the amino group on the C1 position of the diene efficiently served for two purposes - to increase the overall reactivity of the diene and to guide the regiochemical outcome of the reaction. Further studies revealed that utilizing the chiral Co-Salen based Lewis acid catalyst **47** allowed the formation of the corresponding cycloadducts with high enantiomeric excess. This new transformation was successfully applied to the synthesis of Ascochlorin core **54.**



Scheme 10. Utilizing 1-alkylamino-2-methoxybutadienes for the synthesis of 3,3-disubstituted cyclohexanones

In continuation of these studies, we pursued to develop a similar type of activated diene that could provide access to 2,2-disubstituted cyclohexanones, another common core motif found in many natural products. Retrosynthetically, such type of diene can be represented as a stable analog of a ketene diene **56**, which upon reaction with a proper dienophile would give rise to the cyclohexenone **55**. This new type of diene could be even more useful from the synthetic point of view than the 1-alkylamino-2-methoxybutadiene previously developed due to the formation of a

6,6 - disubstitued cyclohexenone as a final reaction product, which can further be functionalized on the enone fragment. With this in mind, we propose that 1-dialkylamino-1-alkoxybutadiene can become an analog of such type of diene: the Diels-Alder reaction of this diene with a dienophile should give rise to cyclohexene **58**, which upon acidic hydrolysis will reveal the desired cyclohexenone pattern. Moreover, the presence of two strong electron donating groups at the C1 position of the diene should make this type of diene highly reactive in the Diels-Alder reaction. Our previous successes with the asymmetric catalysis of the Diels-Alder reaction of doubly-activated dienes also gave us hope that we would be able to apply our previously developed approaches to the Diels-Alder reactions of this novel type of dienes, allowing access to the asymmetric synthesis of 6,6’-disubstitued cyclohexenones.



Scheme 11. Identifying a doubly-activated diene to access 6,6-disubstitued cyclohexenones

2.1.2. Previous approaches to 6,6’-disubstituted cyclohexenones

When we approached the idea of synthesizing the novel diene as a tool to efficiently construct 6,6’-disubstituted cyclohexenones, the first thing that struck our attention was the significant lack of general methods to construct disubstituted cyclohexenones, that are reported in the literature. All of the methods reported so far can be merged into four general categories: (1) electrophilic addition of halogen or selenide to a cyclohexanone enolate followed by elimination under basic or oxidative conditions; (2) aldol condensation; (3) direct enolate oxidation (which is essentially a modification of the first group of methods); and (4) Tsuji-Trost decarboxylative allylation.

The first group of methods, which involves installation of the leaving group through enolate chemistry, followed by elimination, is one of the oldest and most used groups of methods. To our knowledge, he first reports on the preparation of 2,2'-disubstituted cyclohexenone came from the group of Prof. Burger in 1950[34]. During their studies of different synthetic analogues of methadone, they synthesized 2,2-diphenylcyclohexenone by treatment of the corresponding saturated ketone with Br_2 in CCl_4, followed by refluxing of the resulting bromide in collidine (Scheme **12**, eq. 1). Similar methods to construct substituted cyclohexenones were later adopted in the total synthesis of terpenoid natural products. For example, the group of prof. Welch used this approach in the total synthesis of a monoterpenoid fungal metabolite,[35] and the group of Prof. Kametani applied this methodology toward the total synthesis of a steroid hormone.[36] A modification to this approach was introduced by Sharpless[37]: treatment of ketone enolates with phenylselenyl chloride gave rise to the α-phenylselenoketones, which upon exposure to mild oxidative conditions (H_2O_2 or CH_3CO_3H) gave rise to the corresponding enones. This milder methodology to produce conjugated enones was efficiently used by Hayashi in the total synthesis of Nagilactone F[38] (Scheme **12**, eq. 2).

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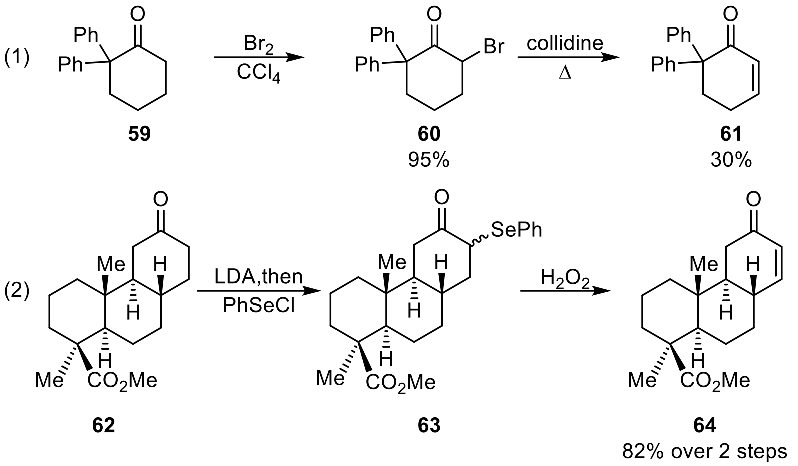
[34] Burger, A.; Bennet, W. B. *J. Am. Chem. Soc.* **1950**, *72*, 5414; b) Bennet, W. B.; Burger, A. *J. Am. Chem. Soc.* **1953**, *75*, 84.

[35] Welch, S. C.; Hagan, C. P.; White, D. H.; Fleming, W. P.; Trotter, J. W. *J. Am. Chem. Soc.* **1977**, *99*, 549.

[36] Kametani, T.; Suzuki, K.; Nemoto, H. *J. Org. Chem.* **1980**, *45*, 2204.

[37] Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137.

[38] Hayashi, Y.; Matsumoto, T.; Nishizawa, M.; Togami, M.; Hyono, T.; Nishikawa, N.; Uemura, M.; Sakan, T. *J. Org. Chem.* **1982**, *47*, 3428.



Scheme 12. Accessing cyclohexenones by addition-elimination strategy

The aldol condensation reaction presents a rare strategy to construct 2,2-disubstituted cyclohexenones due to the difficulties associated with the construction of the corresponding ketoaldehydes. Such a route to construct cyclohexenones is, to our knowledge, described only twice in the literature. First, Baldwin described that during the reduction of [2+2] photochemical cycloaddition product between 2,2,6-trimethyl-1,3-dioxolenone **65** and tetramethyl ethylene spontaneous formation of the ketoaldehyde **69** was observed, which under mild acidic conditions converted to the enone **70** (Scheme **13**). [39] The second example was reported by the group of Prof. Eilbracht who reported that Rh-catalyzed hydroformylation of ketoalkene **71** provides aldehyde **72**, which takes part in the subsequent intramolecular aldol condensation under the reaction conditions[40].

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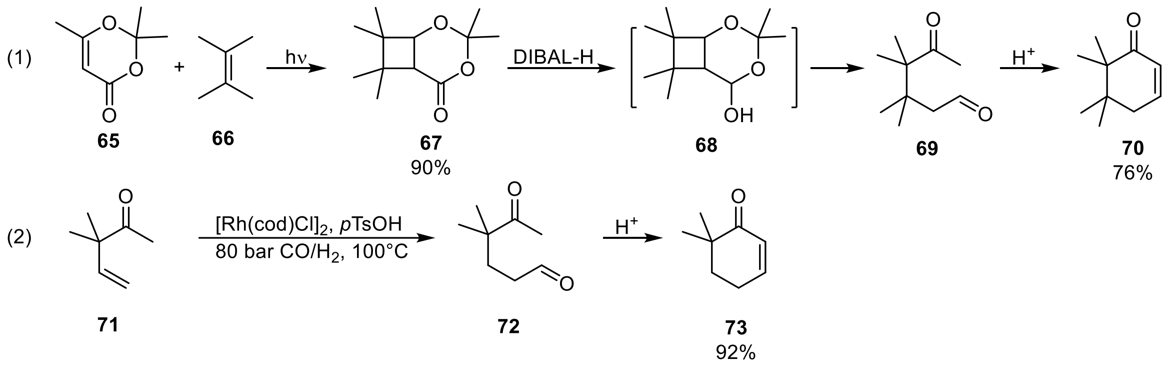
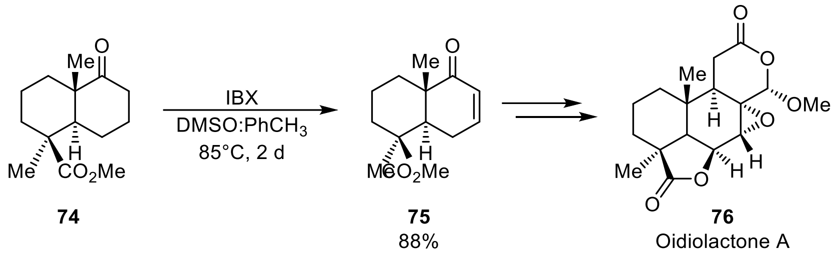
[39] Baldwin, S. W.; Wilkinson, J. M. *J. Am. Chem. Soc.* **1980**, *102*, 3634.

[40] Keränen, M. D.; Kot, K.; Hollmann, C.; Eilbracht, P. *Org. Biomol. Chem.* **2004**, *2* (22), 3379–3384.



Scheme 13. Accessing cyclohexenones through aldol condensation

Direct enolate oxidation strategy is similar to that of addition-elimination strategy. It was first introduced by Nicolaou who described that oxidation of the ketones with the excess of IBX in DMSO gives rise to the corresponding enones in high yield.[41] This reaction is believed to proceed through the formation of the iodonium enol, which through the single electron transfer mechanism oxidizes the α position of the ketone creating radical cation, which upon elimination yields desired enone. This reaction was efficiently applied by Hanessian *et. al.* during the total syntheses of the Oidiodendrolides (Scheme **14**). [42]



Scheme 14. Accessing cyclohexenones through IBX oxidation of ketones

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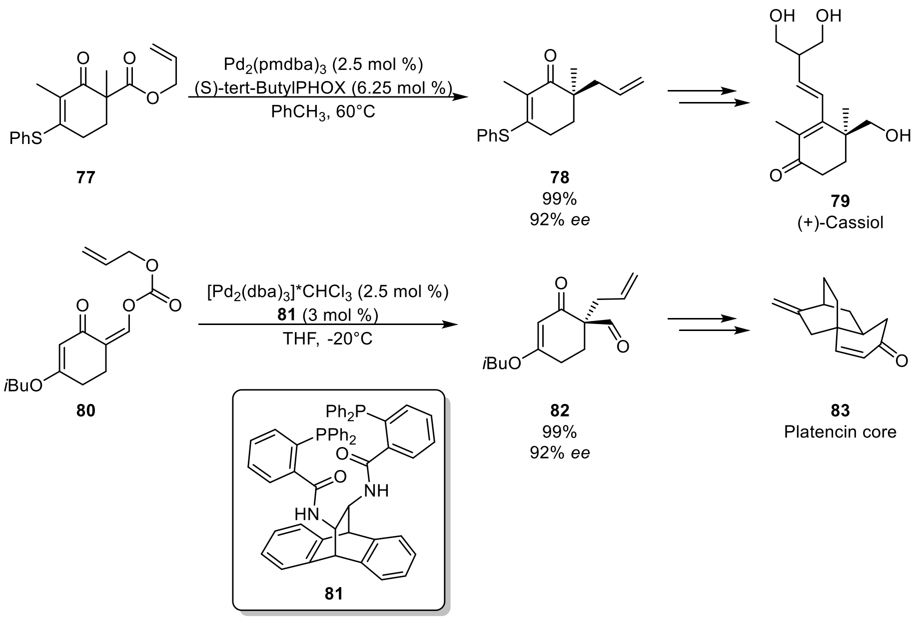
[41] Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245.

[42] Hanessian, S.; Boyer, N.; Reddy, G. J.; Deschênes-Simard, B. *Org. Lett.* **2009**, *11*, 4640.

The last group of methods to access 6,6-disubstituted cyclohexenones was relatively recently developed by the group of Prof. Stoltz. In their studies they have shown the efficient use of the asymmetric Tsuji-Trost allyl enol carbonate allylations to access disubstituted cyclohexanes and cyclohexenones in high yield and with high *ee*[43]. This approach was efficiently utilized to access the core structures of multiple natural products, including (+)-Cassiol[44] and Platencin[45] (Scheme **15**).



Scheme 15. Accessing cyclohexenones through the Tsuji decarboxylative allylation

Apart from the addition-elimination strategy, all other approaches towards the cyclohexenones suffer from the small substrate scope, and, in some cases, poor compatibility with

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[43] a)Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044; b) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924; c) Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novák, Z.; Krout, M. R.; et al. *Chem. – Eur. J.* **2011**, *17*, 14199. d) Bennett, N. B.; Duquette, D. C.; Kim, J.; Liu, Wen-Bo; Marziale, A. N.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Chem. – Eur. J.* **2013**, *19*, 4414.

[44] Petrova, K. V.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 293.

[45] Varseev, G. N.; Maier, M. E. *Angew. Chem. Int. Ed.* **2009**, *48*, 3685.

other functional groups in the molecule. Thus, we envisioned that a general one-step approach towards 6,6 - disubstituted cyclohexenones may be of synthetic value.

2.1.3. Previous studies on 1-dialkylamino-1-alkoxy-1,3-butadienes

In the previous chapter a short description of several rare examples of acyclic 1,1-dialkoxybutadienes and 1,1-diaminobutadiens have been presented. The significant limitation, that is associated with their limited use as a diene in the Diels-Alder reaction, is their surprisingly poor reactivity in the reaction with the common dienophiles (dimethyl fumarate, acrolein, etc.) that most likely arises from the significant steric hindrance, created by the cis-alkoxy or cis-dialkylamino substituent[46]. Moreover, based on the mechanistic study reported by the group of Prof. Sustmann[47], the calculated HOMO of the 1,1-dialkoxybutadienes is polarized more towards the C2 carbon of the diene rather than C4, that is present in the simple 1-methoxybutadiene. Based on this unfavorable polarization 1,1-dialkoxybutadienes should be less efficient dienes than their monosubstituted analogs.

Previously in our group we have shown, that by replacing the methoxy group in trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene to the dimehtylamino group we were able to acquire a significantly more reactive diene, that efficiently reacted even with sterically hindered and non-activated dienophiles to produce corresponding cycloadducts (Scheme **16**). Based on this experience we proposed that by utilizing the same strategy we can convert a poorly reactive 1,1-dialkoxybutadiene to the more reactive 1-dialkylamino-1-alkoxybutadiene, which can be used in the Diels-Alder reaction to give rise to corresponding cycloadducts, which upon hydrolysis will reveal the 6,6-disubstituted cyclohexenone core motive. Upon thorough literature search, we were

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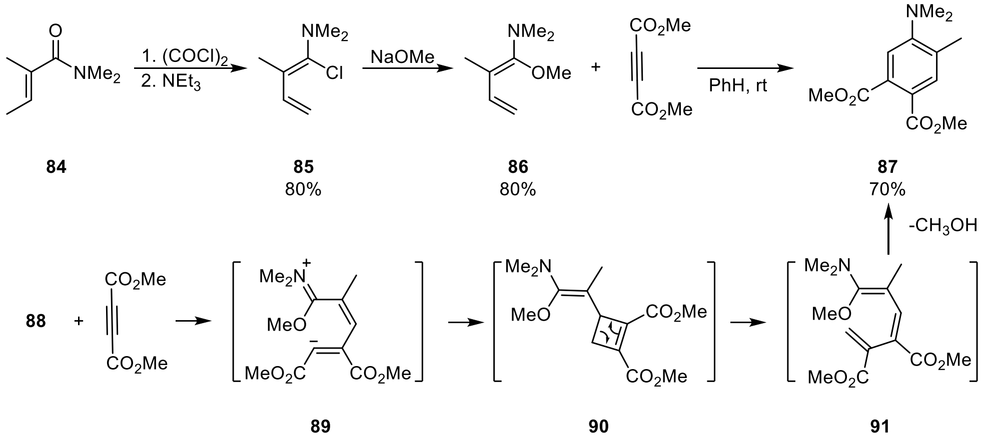
[46] For the mechanistical comparison of *cis*- vs. *trans*- substituted dienes see: Rücker, C.; Lang, D.; Sauer, J.; Friege, H.; Sustmann, R. *Chem. Ber.* **1980**, *113*, 1663.

[47] Sustmann, R.; Tappanchai, S.; Bandmann, H. *J. Am. Chem. Soc.* **1996**, *118*, 12555.

able to locate several examples of this type of dienes synthesized before. The first report on the 1-dialkylamino-1-alkoxy-1,3-butadienes was made by the group of Prof. Ghosez[48]. In their studies they were able to prepare 1-chloro-1-dimethylaminoisoprene **85** in 2 steps from N,N-dimethyltiglic amide (Scheme **16**). Resulting diene **85** showed high reactivity towards various nucleophilic reagents, including sodium methoxide, providing the desired doubly-activated diene in high yield as a mixture of *E* and *Z* isomers. However, attempts to involve the diene **86** in a cycloaddition reaction with dimethyl acetylenedicarboxylate led to an unexpected result: aromatic compound **87** was the only isolated product in the reaction mixture, which is incompatible with the Diels-Alder reaction pathway. Authors proposed, that the activated diene takes place in a vinylogous Michael addition, forming the zwitterionic intermediate **89**, which cyclizes to form cyclobutene intermediate **90**. Electrocyclic opening of the butadiene ring, followed by electrocyclization of the formed triene and loss of methanol furnishes the aromatic product **87.**



Scheme 16. First report of 1-dialkylamino-1-alkoxy-1,3-butadiene

Another report of the 1-dimethylamino-1-alkoxy-1,3-butadiene came from the group of Boyd[49]. They reported that treatment of N,N-dimethylcrotonamide **92** with benzoyl chloride in

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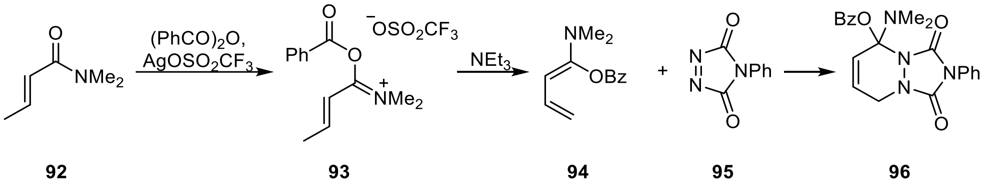
[48] Gillard, M.; T'Kint, C.; Sonveaux, E.; Ghosez, L *J. Am. Chem. Soc.* **1979**, *101*, 5837.
[49] Bottomley, W. E.; Boyd, G. V. *J. Chem. Soc., Chem. Commun.* **1980**, No. 16, 790.

presence of silver trifluoromethanesulfonate provided stable salt **93.** Deprotonation of **93** provided, as Boyd reported, ‘the unstable base’ that yielded the Diels-Alder adduct with N-phenyltriazolinedione **95**. However, no details were included in this paper, and no exploration of the Diels-Alder activity of such type of dienes was further reported by this group.



Scheme 17. First example of the Diels-Alder reaction of 1-dimethylamino-1-bezyloxy-1,3-butadiene

To our knowledge, those two papers present the only reports of the use of 1-dimethylamino-1-alkoxy-1,3-butadienes in the Diels-Alder reaction. However, significant amount of research has been devoted to the vinylogous Mukaiyama aldol reaction of similar type of dienes with various aldehydes and imines. Thus, the group of Prof. Kobayashi have reported the preparation of the chiral oxazolidinone-based butadiene by deprotonation of the corresponding amide **97** with NaHMDS, followed by trapping of the formed enolate with TBSCl[50]. Resulting diene reacts with aromatic and aliphatic aldehydes in the presence of 1 equivalent of $TiCl_4$ at -78°C to provide vinylogous aldol addition product **99** in high yield and with excellent diasteroselectivity (>20:1). (Scheme **18**, eq. 1).

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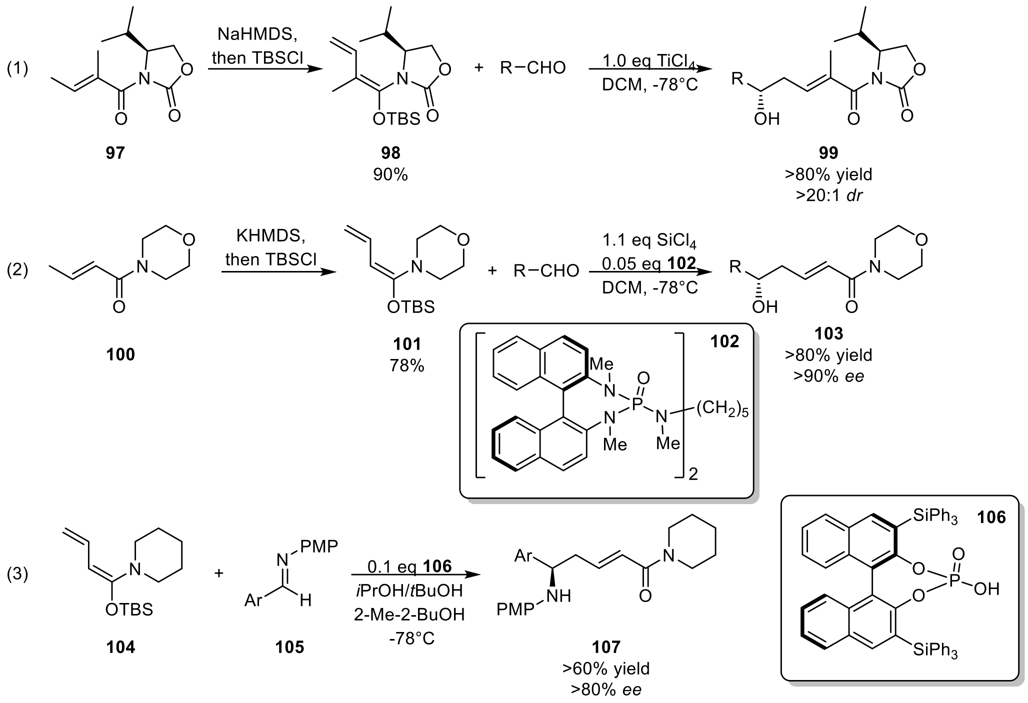
[50] Shirokawa, S.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 13604; b) Nakamura, T.; Shirokawa, S.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 677.



Scheme 18. Vinylogous Mukaiyama aldol reaction of 1-amino-1-oxo-1,3-butadienes

Later, the group of Prof. Denmark utilized the achiral 1-amino-1-oxo-1,3-butadienes, prepared by Kobayashi's procedure, for the enantioselective vinylogous aldol reaction, catalyzed by the silicon tetrachloride-chiral phosphoramide catalytic system[51] (Scheme **18**, eq. 2). Following these initial publications, the group of Prof. Schneider developed enantioselective phosphoric-acid catalyzed Mannich reaction of the same type of dienes with aromatic imines[52] (Scheme **18**, eq. 3). A year later, the group of Prof. Bolm have utilized chiral copper catalyst to promote the enantioselective vinylogous Mukaiyama aldol addition of the dienes, prepared by Denmark's group, to the α-ketoesters[53]. Finally, in 2014 an organocatalytic enantioselective vinylogous

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[51] Denmark, S. E.; Heemstra, J. R. *J. Am. Chem. Soc.* **2006**, *128*, 1038; b) Denmark, S. E.; Heemstra, J. R. *J. Org. Chem.* **2007**, *72*, 5668.

[52] a) Giera, D. S.; Sickert, M.; Schneider, C. *Org. Lett.* **2008**, *10*, 4259; b) Giera, D.; Sickert, M.; Schneider, C. *Synthesis* **2009**, *2009*, 3797.

[53] Frings, M.; Goedert, D.; Bolm, C. *Chem. Commun.* **2010**, *46*, 5497.

Mukaiyama aldol addition, catalyzed by diphenyl prolinol, was published by the group of Prof. Schneider[54].

The fact that none of the groups, who reported the vinylogous Mukaiyama aldol reaction of 1-amino-1-oxo-1,3-butadienes, never mentioned any traces of the Diels-Alder reaction product forming in the mixture aligns well with the theory proposed for 1,1 – dialkoxysubstituted dienes, that despite the diene is very electron reach due to the presence of two strong electron-donating groups, the steric hindrance for dialkylamino-substituted diene is bigger than for the alkoxy-substituted one. Thus, the adoption of the desired *s-cis* conformation, that is required for the diene to take part in the Diels-Alder reaction, becomes strongly energetically unfavorable, and the Mukaiyama aldol reaction pathway prevails for 1-amino-1-alkoxybutadienes. We proposed that if we were able to decrease the steric hindrance on this doubly-activated diene, the resulting compound should present a highly reactive diene and can become a stable and efficient equivalent for the ketene diene for the Diels-Alder reaction.

Section 2.2. Development Of Novel *N*-Methyl Oxazolidine Butadienes

2.2.1 Preparation of N - methyl oxazolidine butadiene

In order to reduce the steric hindrance of the *cis*-alkoxy group on the 1-amino-1-alkoxybutadienes, we proposed to "tie" the alkyl chain of the alkoxy group to the nitrogen by substituting the dialkylamino and alkoxy groups with the methyl oxazolidine (Scheme **19**, eq. 1). In theory, butadiene **111** should poses both alkoxy- and dialkylamino- substituenets that will make it very nucleophilic, and at the same time the oxazolidine ring should lock the conformation of the alkoxy substituent and minimize the allylic strain. Also, the oxazolidine fragment provides an opportunity to introduce the chirality in the diene structure by using amino acid-derived

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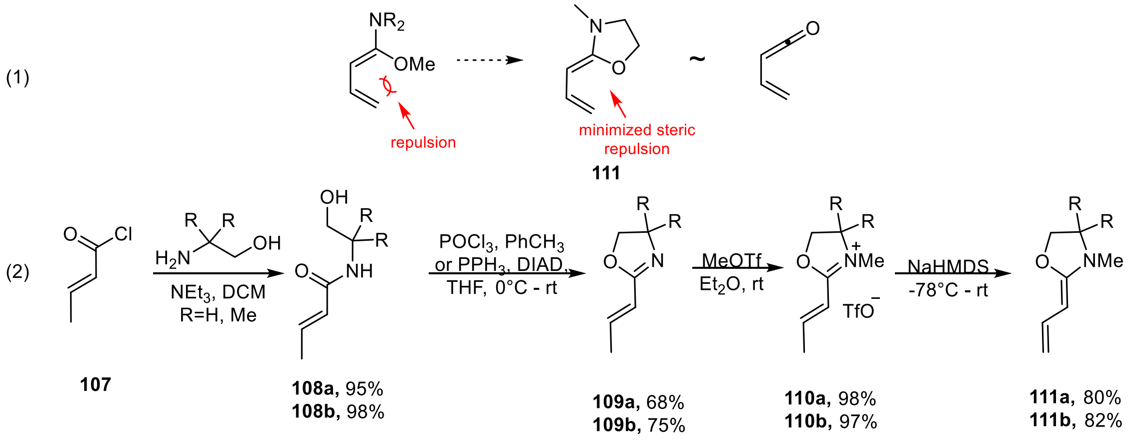
[54] Basu, S.; Gupta, V.; Nickel, J.; Schneider, C. *Org. Lett.* **2014**, *16*, 274.

oxazolidines that would allow to generate the corresponding cycloadducts in a diastereoselective manner. Hydrolysis of the resulting chiral hemiaminal would provide access to enantioenriched 6,6'-disubstituted cyclohexenones.



Scheme 19. Oxazolidinebutadiene – from the idea to synthesis

With this in mind, we proceeded towards the synthesis of oxazolidinebutadienes (Scheme **19**, eq. 2). Treating crotonyl chloride **107** with ethanol amine or 2-amino-2-methyl-1-propanol gave rise to amides **108a** and **108b** correspondingly. Treatment of the formed amides under Mitsunobu conditions[55] or with $POCl_3$ gave rise to the cyclized products **109**. Methylation of oxazolines **109** with methyl trifluoromethanesulfonate in diethyl ether gave rise to the corresponding oxazolium salts, white, crystalline compounds, which can be isolated by filtration and stored for a prolonged periods of time (up to 1 month) under N_2 at 4°C. Treatment of the slurry of the salt in THF with NaHMDS at -78°C, followed by slowly (over 2 h) warming up the reaction mixture to rt provided, after filtration of insoluble sodium salts and evaporation of the solvent under vacuum, essentially pure dienes **111** as a single *E*-isomer in 60-65% overall yield. **111** can be further purified by vacuum distillation to provide colorless oils that could be stored indefinitely

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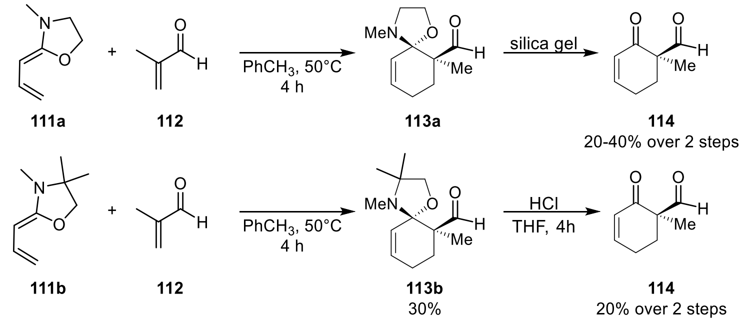
[55] Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380; b) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 6267.

at 4°C under N_2[56] The established route allowed us to prepare the desired dienes in multigram quantities (2-3 g batches) using cheap, commercially available reagents.

2.2.2 Reaction of oxazolidinebutadienes with common dienophiles

With the dienes in hand, we turned our attention to exploration of its performance in a Diels-Alder reaction. The initial Diels-Alder (DA) cycloaddition experiments were conducted utilizing methacrolein as dienophile (Scheme **20**). Upon heating the two reactants together in toluene at 60°C; complete disappearance of the dienes were observed, and formation of the 2 major products was envisioned by NMR. Based on the ^{1}H NMR we assigned one of them to be the desired cycloadduct **113**, whereas the other one is believed to be the Hetero Diels-Alder (HDA) –type product (it can also be produced in a stepwise fashion through the vinylogous Mukaiyama aldol addition-anionic ring closure reaction cascade). Cycloadduct **113a** proved to be unstable on silica gel, giving the product of hydrolysis **114** in 20-40% overall yield. Cycloadduct **113b**, however appeared to be more stable towards hydrolysis on silica gel, and we were able to isolate it by column purification, yet in a very small yield (30%). Treatment of **113b** with HCl furnished the desired cyclohexenone **114** in 20% total yield. Possible HDA cycloadduct decomposed upon exposure to silica gel or to aqueous work-up. All attempts to isolate it so far were fruitless.



Scheme 20. Reaction of oxazolidinebutadienes with methacrolein

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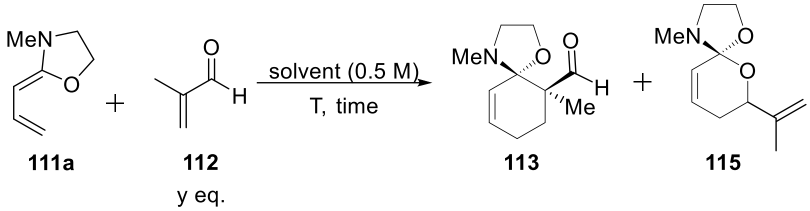
[56] Upon exposure to air dienes slowly hydrolyze, forming a complex mixture of products

Encouraged by this result, we performed the optimization of the cycloaddition conditions, using diene **111a** and methacrolein as model substrates (Table **1**).

Table 1. Optimization of the Diels-Alder reaction conditions



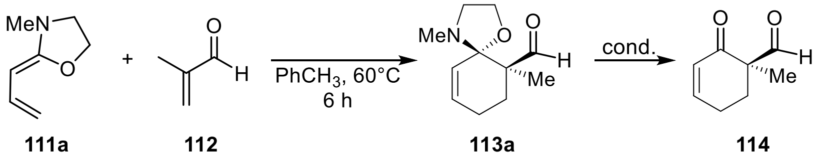
111a **112** y eq. **113** **115**

entry	solvent	time (h)	temp. (°C)	y (eq.)	conv. (%)	A/B
1	toluene	10	rt	1.2	100	3.3/1
2	hexanes	10	rt	1.2	100	4.0/1
3	DCM	10	rt	1.2	100	1/1.1
4	THF	10	rt	1.2	73	2.3/1
5	CH_3CN	10	rt	1.2	100	1/2
6	^{t}BuOH	10	rt	1.2	100	1/3.5
7	toluene	3	50	1.2	50	3.5/1
8	toluene	3	70	1.2	72	3.2/1
9	**benzene**	**6**	**50**	**1.5**	**100**	**4.0/1**
10	benzene	6	50	5.0	100	2/1

During optimization, we found that using less polar solvents (hexanes, toluene, benzene, entries 1, 2, 7, 8, 9) speeds up the reaction and increases the DA/HDA product ratio, whereas polar solvents (entries 3-6) decreases the reaction rate and increases the amount of undesired HDA product produced. In the ultimate case, when ^{t}BuOH was used as a solvent, a complete switch of selectivity towards the HDA reaction was observed (entry 6). Increasing the temperature speeds up the cycloaddition reactions but has only a minor effect on the HDA/DA product ratio. On the contrary, changing the amount of dienophile has a significant effect, giving the maximum amount of desired DA adduct with 1.5 eq of methacrolein. Increasing the amount of methacrolein to 5 eq significantly speeds up the reaction but leads to a drop in DA/HAD ratio. Eventually we found that using benzene as a solvent at 50°C and utilizing the 1.5 eq of dienophile were the optimal conditions for performing the reaction, to yield the maximum amount of the desired Diels-Alder cycloadduct.

Both cycloadducts **113a** and **113b** proved to be unstable towards moisture and tended to hydrolyze after prolonged exposure to air and on silica gel. Due to this reason, we decided to not try to isolate and purify them by column, but to hydrolyze them after the formation to get directly the desired cyclohexenone **114**. However, simple hydrolysis conditions that we utilized at first (1M HCl, THF, rt) provided **114** only in a low yield. After screening of different hydrolysis conditions (Table **2**), we were pleased to find out that treating the cycloadduct **113a** with aq. oxalic acid (3 eq.) in toluene-water mixture at 50°C within 1 hour afforded the desired cyclohexenone in 70% yield. Cycloadduct **113b** appeared to be harder to hydrolyze (the complete hydrolysis required 10 h at 50°C), and the yield of the desired product **114** was a bit lower (60% vs 70% for cycloadduct **113a**), so we decided to focus our research on the unsubstituted oxazolidinebutadiene **111a**.

Table 2. Optimization of the hydrolysis conditions

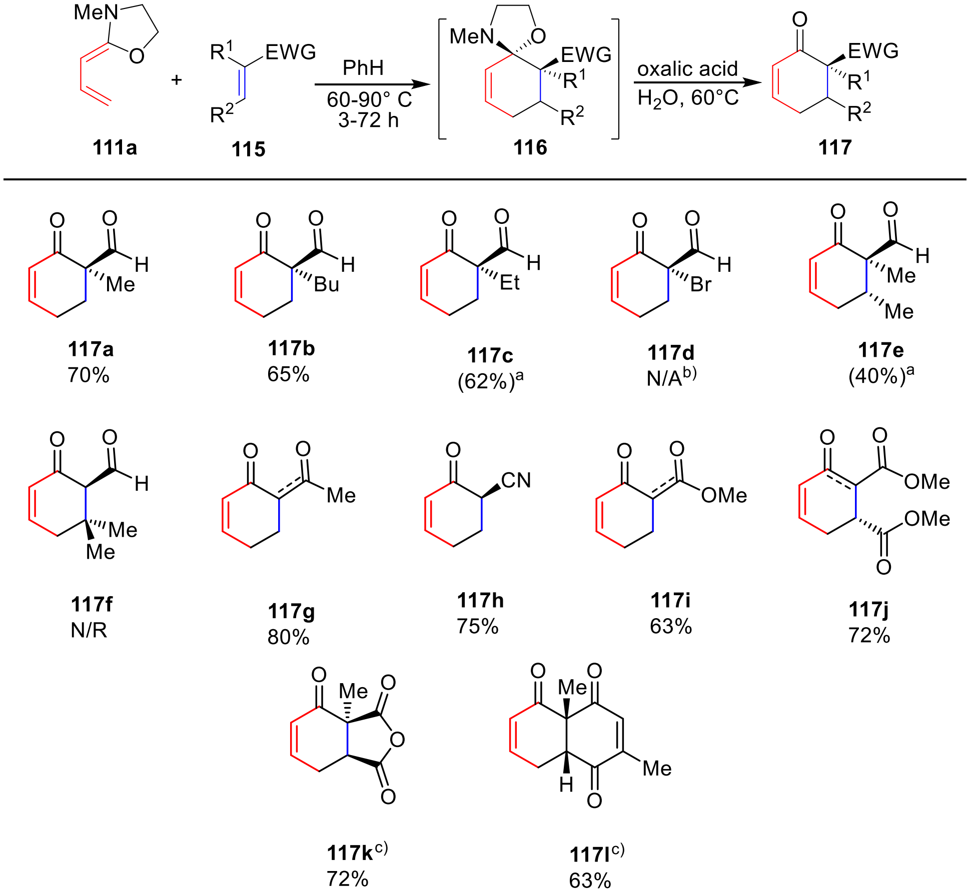


entry	conditions	yield,%
1	1M HCl, THF	40
2	AcCl (5 eq.), MeOH	20
3	TFA, $H_2O/PhCH_3$	N/A[a)]
4	70% AcOH, Δ	N/A[a)]
5	silica gel, DCM	30
6	PPTS	N/A[a)]
7	oxalic acid, $H_2O/PhCH_3$	70

a) only traces of **114** were seen in crude ^1H NMR

With optimized conditions in hand, we proceeded to explore the scope of dienophiles that can be used in the Diels-Alder reaction with our novel diene **111a** (Scheme **21**). Because of the low stability of the cycloadducts, all of them were hydrolyzed under optimized conditions without isolation to get the corresponding cyclohexenones. The novel doubly-activated diene **111a** readily reacted with 1-substituted acroleins, providing, after hydrolysis, 6,6 – disubstituted cyclohexenones **117a-b** in good yields. Ethyl acrolein **115c** successfully reacted with the diene to provide, after the acidic hydrolysis, cyclohexenone **117c**. However, upon purification on silica gel or neutral alumina compound **117c** rapidly polymerizes, resulting in an inseparable mixture of side products. 1-bromoacrolein **117e** appeared to be too reactive under the standard experimental conditions – upon adding a solution of dienophile **117d** to the solution of the diene **111a** in benzene the mixture instantly became dark, and a polymer-like precipitate was formed. NMR experiment showed full conversion of the dienophile with no trace of the desired cycloadduct present. All attempts to change the reaction conditions - switching the solvent or cooling down the reaction mixture to -78°C were fruitless, and we were not able to prevent the formation of polymeric products. We were delighted to see that less reactive tiglic aldehyde reacted with the oxazoline butadiene, providing after hydrolysis 5, 6, 6 – trisubstituted cyclohexenone **117e**, albeit, as in the case of ethyl acrolein addition product **117c**, rapid polymerization upon column purification occured. 3-methylcrotonaldehyde **117f** appeared to be completely unreactive under the standard reaction conditions. Increasing the temperature or the concentration of the reaction mixture did not lead to any Diels-Alder cycloadduct formation – instead only the formation of the Hetero Diels-Alder adduct was seen in the crude ^{1}H NMR. Regular dienophiles, such as methyl acrylate, methyl vinyl ketone and acrylonitrile reacted well with diene **111a**, providing, after hydrolysis, corresponding cycloadducts **117g-i** in good yields. Citraconic anhydride **115j** and 2, 6 -

dimethylbenzoquinone **115k** both appeared to be too reactive under regular conditions, providing a complex mixtures of oligomeric and polymeric products. Cooling the reaction to -40°C allowed to prevent polymerization and produce, after acidic hydrolysis, bicyclic adducts **117j-k** in high yields and as a perfect diastereoselectivity (along with the enol form).



a) NMR yield. Compound is unstable during purification; b) only polymer-like products were seen in NMR; c) reactions were performed in $PhCH_3$ at -40°C to 0°C

Scheme 21. Diels-Alder reaction of the diene **111a** with various dienophiles

Encouraged by the reactivity shown by diene **111a** in the Diels-Alder reactions with various dienophiles, we switched our attention to another type of active dienophiles – nitroalkenes. Nitroalkenes have been previously shown to be very efficient dienophiles, taking part in the Diels-Alder reaction with simple dienes like cyclopentadiene even at room temperature, due to the presence of the strong electron withdrawing nitro group.[57] We were delighted to find out that mixing a solution of oxazolidine butadiene **111a** with a solution of nitrostyrene at room temperature leads to the clean formation of the cycloadduct **119a**, reaching full conversion of starting diene within several minutes based on the ^{1}H NMR of the mixture. Hydrolysis of the resulting cycloadduct using previously utilized conditions (toluene, aq. oxalic acid) results in the clean formation of the nitrocyclohexenone **120a** in 75% yield. Excited by this result, we examined different nitroalkenes as dienophiles in the reaction with oxazolidinebutadiene **111a**. Both electron-withdrawing and electron-donating group substituted nitrostyrenes have all shown to be very reactive dienophiles, exhibiting full conversion to the corresponding cycloadducts **119b-c** within a minute. Hydrolysis of the resulting cycloadducts lead to cyclohexenones **120b-c** in high yieds. More sterically hindered nitroalkenes **118d** and **118e**, bearing α- and β- naphtyl groups respectively, proved to be as reactive as the parent nitrostyrene, furnishing, after hydrolysis, cyclohexenones **120d** and **120e** in 71% and 75% yield correspondingly. It is noteworthy that alkyl-substituted nitroalkenes **118g** and **118h** also took part in the Diels-Alder reaction with the oxazolidine butadiene **111a**. These reactions, however, required significantly longer time to reach completion (~10 h. at room temperature). To our great delight, (nitromethylene)cyclohexane **118h** reacted successfully with diene **111a**, providing after acidic hydrolisis the spiro bicyclic compound **120h** in 78% yield, thus demonstrating that our newly developed diene can help to access even the most complex spirocyclic structures in one step and with high yield.

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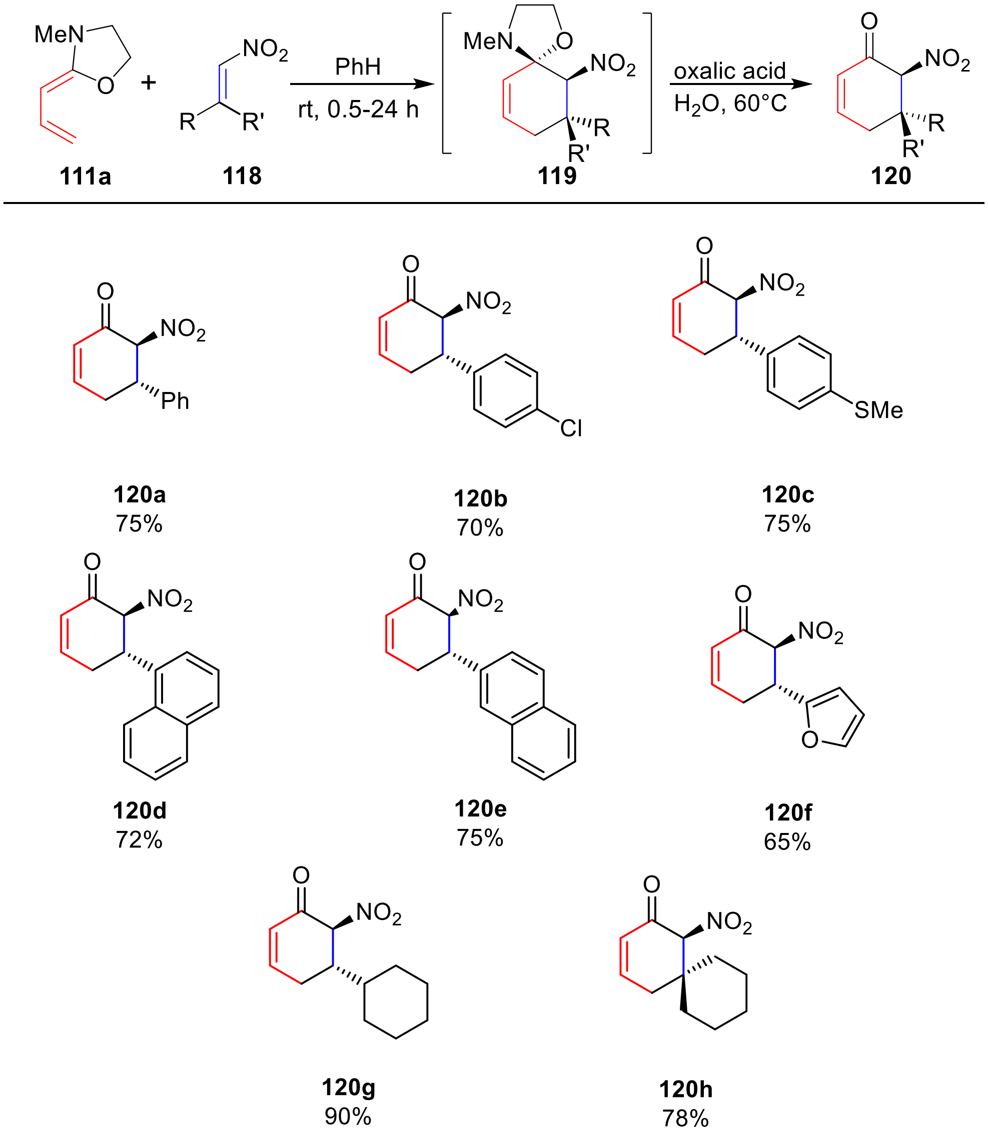
[57] a) Ono, N. *The Nitro Group in Organic Synthesis*; Feuer, H., Series Ed.; Wiley Series in Organic Nitro Chemistry; John Wiley & Sons, Inc.: New York, USA, 2001;b) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, **1990**; c) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B.M.; Fleming, I.; Paquette, L.A., Eds; Pergamon: Oxford, **1991**; Vol. 5, p.315.

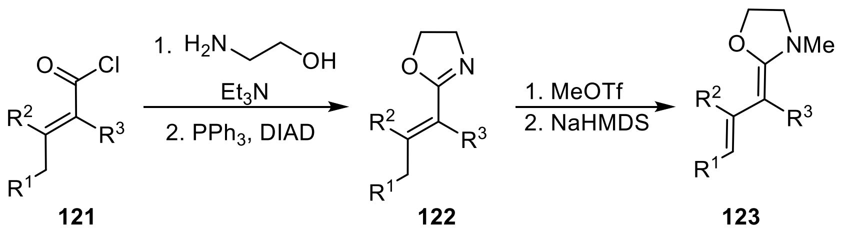


Scheme 22. Diels-Alder reaction of the diene **111a** with nitroalkenes

2.2.3. Synthesis and reactivity of substituted oxazolidinebutadienes

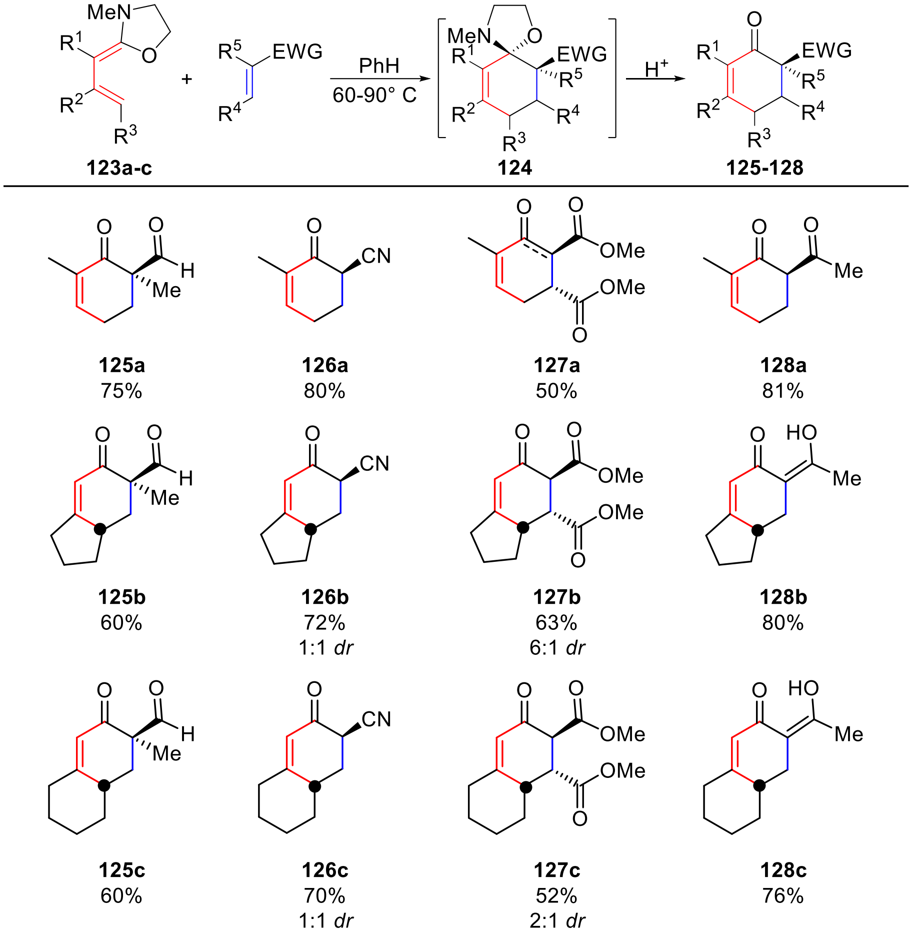
Encouraged by the good performance of the diene **111a** in the Diels-Alder reaction, we turned our attention to expanding the scope of oxazolidinebutadienes by synthesizing substituted analogues of diene **111a** that would allow us to access various polysubstituted cyclohexenones in a single step (Table **3**). The dienes were synthesized by our previously established 4-step procedure, starting with corresponding crotonyl chlorides. The resulting dienes present colorless liquids, which decompose quickly in the presence of air or moisture, but are stable for prolonged periods of time (up to 6 months) upon storage under N_2 at 4°C.

Table 3. Synthesis of substituted oxazolidinebutadienes



Entry	R1, R2	R^3	product	yield (%)	product	yield (%)
1	H, H	Me	**122a**	68	**123a**	70
2	$-(CH_2)_3-$	H	**122b**	75	**123b**	83
3	$-(CH_2)_4-$	H	**122c**	60	**123c**	80
4	OMe, H	H	**122d**	50	**123d**	82

With substituted dienes in hand, we examined their reactivity towards different dienophiles (Scheme **23**). Dienes **123a-c** reacted with methacrolein upon heating in toluene, providing the corresponding cycloadducts **125a-c** in good yields and excellent *dr* (>20:1 *endo:exo*) after hydrolysis. However, the reaction with diethyl fumarate and acrylonitrile gave rise to the cyclohexenones **126-127a-c** with only moderate yields and poor *dr*. Overall, all dienes but **123d** show good reactivity towards regular dienophiles, allowing for efficient access to polycyclic systems.



Scheme 23. Reaction of substituted oxazolidinebutadienes with various dienophiles

Diene **123d** showed completely different performance than the other dienes. The sole idea of diene **123d** was to provide access, after hydrolysis, to the substituted 1,3-cyclohexanediones, the core motif of the Hyperforins. However, all attempts to involve it in a Diels-Alder reaction with methacrolein or diethyl fumarate failed. The methoxy group on the C4 carbon of the diene proved to make a dramatic change in the electronics of the diene, changing the overall structure of the HOMO of the diene and preventing it from acting as a coupling partner in the Diels-Alder reaction. Instead, in the crude NMR several different products that looked like Mukaiyama aldol addition products to the C2 and C3 positions of the diene were seen. All attempts to isolate them or hydrolize the oxazolidine subunit and isolate the resulting carbonyl compound failed – upon exposure to silica gel or to acid these products completely polymerized.

2.2.4. Synthesis and reactivity of chiral oxazolidine butadienes; attempts to access enantioenriched cyclohexenones

The use of chiral auxiliaries in the Diels-Aldrer reaction has been widely explored over the past 70 years, starting from the pioneering work by Walborsky *et. al.*[58], who reported a Diels-Alder reaction between bis(menthyl) fumarate and 1,3-butadiene in the presence of $TiCl_4$. Since then, multiple variations of the Diels-Alder reaction, utilizing chiral dienophiles to enhance diastereoselectivity and to create, after the cleavage of auxiliary group, enantioenriched products have been reported[59]. On the other hand, the use of chiral auxiliaries on the diene portion has been less developed. Thus, the first examples of the use of saccharide-linked alkoxybutadienes, reported by David *et. al.* in 1979**[60]** were followed by Trost**[61]** and Danishefsky**[62]** groups, who reported the

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[58] Walborsky, H. M.; Barash, L.; Davis, T. C. *Tetrahedron* **1963**, *19*, 2333.

[59] For some reviews, see: (a) Taschner, M. J. *Asymmetric Diels-Alder Reactions*; Taschner, M. J., Ed.; JAI Press: Greenwich, **1989**; Vol. 1, pp. 1-101; (b) Mulzer, J.; Altenbach, H.-J.; Braun, M.; Krohn, K. Ressig, H.-U. *Organic Synthesis Highlights* ; VCH Verlagsgesellschaft: Weinheim, **1991**; pp 60-61;c) Oppolzer, W. *Angew. Chem. Int. Ed.* **2003**, *23,* 876; d) Oh, T.; Reilly, M. *Org. Prep. Proc. Int.* **1994**, *26*, 129; e) Coxon, J. A.; McDonald D. Q.; Steel, P. J. *Advances in Detailed Reaction Mechanisms*, Vol. 3. James M. Coxon, Ed., Jai Press: Greenwich, CT **1994**; f) Barluenga, J.; Su'arez-Sobrino, A.; L'opez, L. A. *Aldrichimica Acta* **1999**, *32*, 4-15; g) *Chiral Auxiliaries in Cycloadditions,* Rück-Braun, K.; Kunz, H. Wiley: New York, **1999**; h). Nicolaou K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int.Ed.* **2002**, *41*, 1668.

[60] (a) David, S.; Eustache, J.; Lubineau, A. *J. Chem. Soc., Perkin Trans.1,* **1974**, 2274. (b) David, S.; Lubineau, A.; Vatele, J.-M. *J. Chem. Soc., Chem. Commun.,* **1975**, 701. (c) David, S.; Lubineau, A.; Vatele, J.-M. *J. Chem. Soc., Perkin Trans. 1,* 1976, 1831. (d) David, S.; Lubineau, A.; Thieffry, A. *Tetrahedron,* **1978**, 34, 299. (e) David, S.; Eustache, J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2230. (f) David, S.; Eustache, J.; Lubineau, A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1795.

[61] a) Trost, B. A.; Godleski, S. A.; Genet, J. P. *J. Am. Chem. Soc.* **1978**, 100, 3930; b) Trost, B. M.; O'Krongly, D.; Belletire, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595.

[62] a) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, 105, 6968; b) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1986**, *108*, 7060.

use of Danishefsky – type dienes, substituted with (S)-*O*-methylmandelic acid and glucose residues correspondingly. Later, chiral amino-substituted butadienes, utilizing asymmetric pyrrolidine[63] and oxazolidine[64] units to induce chirality, have been shown to provide excellent diastereoselectivity, providing cyclohexenes in 96-99% *ee* after the cleavage of the auxiliaries. We envisioned that oxazoline butadines are well suited to attach the chiral auxiliaries as the oxazoline unit, that is present in our diene, can be easily made asymmetric by using a chiral aminoalcohol instead of aminoethanol. Thus, using a slightly modified route, we prepared a series of chiral dienes **129a-c** (Table **4**). Treatment of crotonyl chloride **107** with enantiopure aminoalcohols (prepared from corresponding natural aminoacids[65]), followed by a Mitsunobu reaction provided enantiopure oxazolines **129**, which were further transformed into chiral dienes **130a-c** through the methylation-deprotonation sequence.

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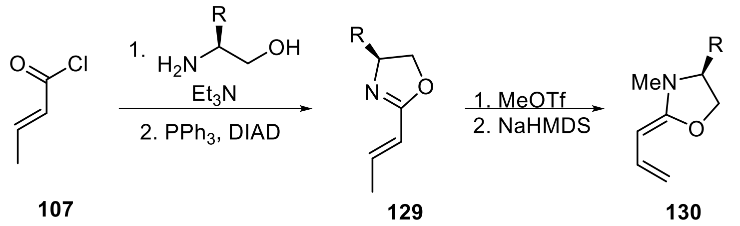
[63] a) Enders, D.; Meyer, O.; Raabe, G. *Synthesis* **1992**, 1242; b) Enders, D.; Meyer, O.; Runsink, J. *Synthesis* **1994**, 66; c) Barluenga, J.; Aznar, F.; Valdes, C.; Martin, A.; Garcia-Granda, S.; Martin, E. *J. Am. Chem. Soc.* **1993**, 115, 4403; d) Barluenga, J.; Aznar, F.; Ribas, C.; Valdes, C.; Fernandez, M.; Cabal, M.-P., Trujillo, J. *Chem.Eur. J.* **1996**, 2, 805; e) Barluenga, J.; Aznar, F.; Martin, A.; Vazquez, J. T. *J. Am. Chem. Soc.* **1995**, 117, 9419. (d) Barluenga, J.; Canteli, R. M.; Florez, J.; Garcia-Granda, S.; Gutierrez-Rodriguez, A.; Martin, E. *J. Am. Chem. Soc.* **1998**, 120, 2514.

[64] (a) Murphy, J. P.; Nieuwenhuyzen, M.; Reynolds, K.; Sarma, P. K. S.; Stevenson, P. J. *Tetrahedron Lett.* **1995**, 36, 9533; b) McAlonan, H.; Murphy, J. P. Nieuwen-huyzen, M.; Reynolds, K.; Sarma, P. K. S.; Stevenson, P. J.; Thompson, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1, 69; c) Janey, J. M.; Iwama, T.; Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **2000**,65, 9059; (d) Robiette, R.; Defacqz, N.; Stofferis, J.; Marchand-Brynaert, J. *Tetrahedron* **2003**, 59, 4167

[65] a) Kanth, J. V. B.; Periasamy, M. *J. Org. Chem.* **1991**, *56*, 5964; b) McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568.

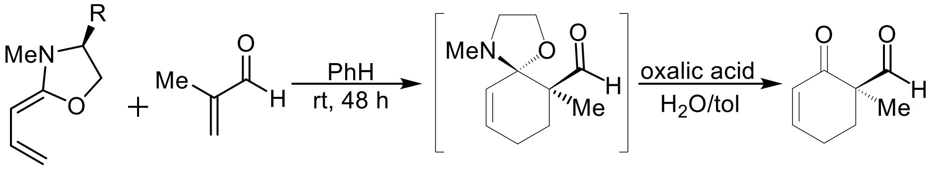
Table 4. Synthesis of chiral oxazolidinebutadienes



Entry	R	product	yield (%)	product	yield (%)
1	Ph	**129a**	83	**130a**	87
2	Bn	**129b**	52	**130b**	74
3	*i*-Pr	**129c**	68	**130c**	70
4	*t*-Bu	**129d**	60	**130d**	83

With the asymmetric dienes in hand, we examined their reactivity in the Diels-Alder reaction with methacrolein (Table **5**). Reactions with the asymmetric dienes proved to be slower than with the unsubstituted oxazolidine butadiene **111a**, reaching full conversion in 48 hours at ambient temperature. Despite our expectations, the diastereoselectivity of the product formation appeared to be quite low – in the best case, utilizing the *tert*-leucinol derived oxazolidine butadiene **130c**, we were able to achieve only 5:1 disatereoselectivity based on the ^{1}H NMR of the crude mixture. Cleavage of the resulting hemiaminal also proved to be tricky, resulting in the formation of the cyclohexenone **114** in only 30% yield, with multiple side products present in the mixture. As a result, the *ee* of the resulting product was not determined. Attempts to lower the temperature to 0°C or lower didn't prove to be beneficial for the diasteromeric ratio of the productsat significant cost to the reaction rate.

Table 5. Reaction of asymmetric dienes with methacrolein



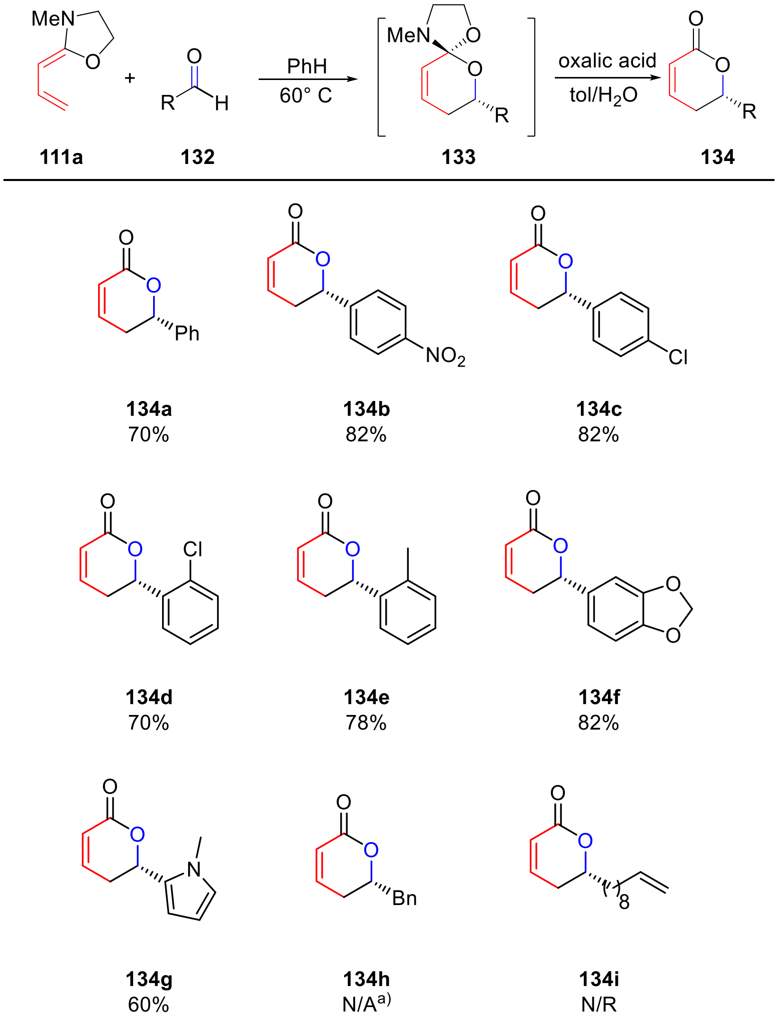
130 **112** **131** **114**

Entry	R	product	NMR yield (%)	**dr**
1	Ph	**131a**	85	4:3
2	Bn	**131b**	80	1:1
3	*i*-Pr	**131c**	75	5:1
4	*t*-Bu	**131d**	72	8:1

With this poor results in hand, we switched to a different approach – rather than using chiral oxazolidinione butadienes, employing instead chiral Lewis acids to catalyze the reaction of simple diene **111a** with the methacrolein. However, upon screening the regular Lewis acids ($ZnCl_2$, CuOTf, $TiCl_4$, Me_2AlCl, etc.) we found that all of them hydrolize the diene, causing its degradation and self-polymerization. Weaker Lewis acids ($Sc(OTf)_3$, $InCl_3$, LiCl in Et_2O) didn't catalyze the reaction at all, and the use of hydrogen-bonding catalysts (thioureas, squaramides) resulted in the hydrolysis of the diene. Use of TADDOL-based catalysts was semi-successful – addition of TADDOLs doubled the reaction rate, but at the same time the undesired Hetero Diels-Alder reaction pathway was catalyzed to an even greater extent, reducing the ratio of DA/HDA product in the crude mixture to 3/2. The best result with the use of chiral TADDOL catalysts was achieved when 1-naphtyl-based TADDOL was used – the desired cyclohexenone was produced with a 15% *ee* based on chiral HPLC trace that was completely non-useful for our purposes.

2.2.5. Hetero Diels-Alder reaction of oxazolidine butadiene

Heteroatom-substituted dienes are known to take part in the Hetero Diels-Alder (HDA) type reactions with various aldehydes and imines. As we have seen in our initial studies of the reactivity of oxazolinebutadiene it can react with methacroleins, giving rise to both Diels-Alder and Hetero Diels-Alder type cycloadducts. Encouraged by this, we examined the reaction of the diene **111a** with a simpler aldehyde – benzaldehyde (Scheme **24**). To our delight diene **111a** smoothly reacted with benzaldehyde in the standard experimental conditions (benzene, 60°C), giving rise to cycloadduct **133a**, which was observed by ^{1}H NMR. However, our attempts to isolate the cycloadduct by column chromatography or perform regular acidic hydrolysis (HCl, H_2O/THF) failed to provide any product. However, after a short screening of conditions we were delighted to find out that using aqueous oxalic acid was crucial for an efficient hydrolysis of **133a**, providing cyclic lacton product **134a** in 70% yield. Having the optimized conditions in hand, we turned to examining the reactivity of oxazoline butadiene **111a** towards other aldehydes. Because of the poor stability of the cycloadducts, they were subjected to the hydrolysis conditions without isolation from the reaction mixture. Aromatic aldehydes **132b-d**, bearing an electron-withdrawing group, proved to be more reactive than benzaldehyde, with the cycloaddition reaction reaching full conversion after 36 h at 60°C. Aldehydes **132e-f,** substituted with electron donating groups, proved to be significantly less reactive, reaching full conversion of the diene after 60 h at 60°C, providing after the hydrolysis 5,6-dihydro-2H-pyran-2-ones **134e-f** in 78% and 82% yield respectively. Heterocycle-substituted aldehyde **132g** reacted less smoothly with diene **111a,** with several other unidentified products, apart from the desired cycloadduct **134g**, appearing in the crude NMR spectra of the reaction mixture. This led to a significant decrease of the yield of corresponding 5,6-dihydro-2H-pyran-2-one after the hydrolysis. As we expected, oxazolidine butadiene **111a** didn't react with aliphatic aldehydes **133h-i**; no reaction was observed after the prolonged (>36 hours) heating of the mixture of diene **111a** and undecelynic aldehyde **132i**. Phenylacetic aldehyde **132h**, in turn, reacted rapidly, giving rise to a complicated mixture of oligomeric products.



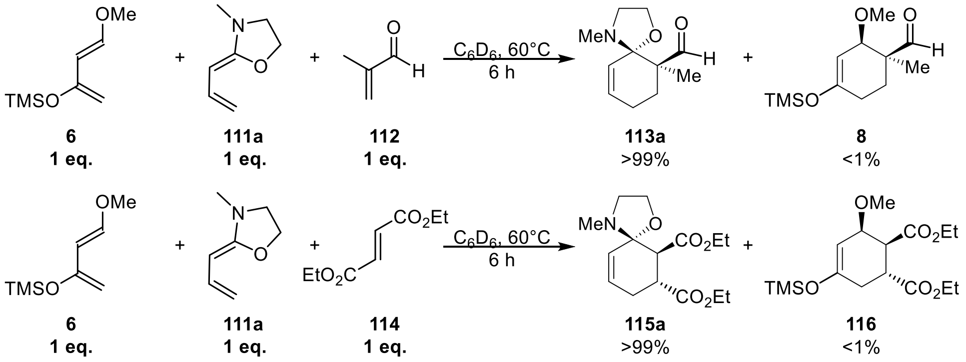
a) complex mixture of oligomeric products

Scheme 24. Hetero Diels-Alder reactions type reactions of diene **111a**

With aldehydes proving to be successful substrates, we looked into other types of common dienophiles, such as imines, nitroso compounds and azodicarboxylates. Alas, most aromatic imines and nitroso compouds proved to be unreactive under standard reaction conditions. Diisopropylazodicarboxylate reacted with oxalodine diene **111a** to produce what looked to be the cycloadduct based on ^{1}H NMR. However, all attempts to either isolate it by column chromatography or hydrolyze the hemiaminal moiety led to the decomposition of the resulting product.

*2.2.6 Kinetic studies of the Diels-Alder reactions of diene **111a***

In an effort to compare the reactivity of oxazolinebutadiene with previously known active dienes we performed a competition experiment between our newly developed diene and Danishefsky diene (Scheme **25**). It was shown that a mixture of equimolar amounts of Danishefsky diene and 1-amino-1-oxobutadiene with 1 eq. of methacrolein at room temperature gives rise to exclusive formation of cycloadduct **113a.** Similar results were obtained when we used another dienophile, diethyl fumarate: exclusive formation of cycloadduct **115a** was observed. These results indicate that 1-amino-1-oxobutadiene is approximately 100 times more reactive than Danishefskys' diene.



Scheme 25. Competition experiment

To get a better estimation of the reactivity of the novel diene, we performed a more thorough kinetic investigation of its reaction with diethyl fumarate (Figure **1**). Based on the kinetic reaction profile, the reaction is a 1st order in regard to both diene and diethyl fumarate. The reaction constant is estimated to be $3.07*10^{-3}$ $M^{-1}s^{-1}$ (at 70°C) compared to $2*10^{-2}$ $M^{-1}s^{-1}$ (at 65°C), measured previously for 1-dimethylamino-1-methoxybutadiene and $3{,}6*10^{-6}$ $M^{-1}s^{-1}$ (at 17°C) for Danishefskys' diene[66].

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[66] Kozmin, S. A.; Green, M. T.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 8045.

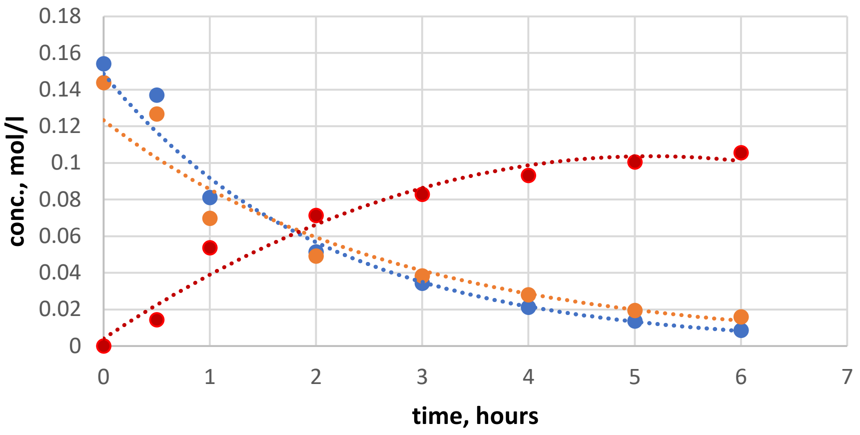

Figure 1. Kinetic studies of the reaction between oxazolidine butadiene **111a** with methacrolein

Section 2.3. Concluding Remarks

In conclusion, we developed and synthesized the new family of doubly activated dienes: oxazolidine butadienes. The use of the oxazolidine motive in the butadiene allowed us to prepare the diene that was doubly activated on the 1st position while not experiencing significant steric issues that were previously reported for 1,1-disubstituted 1,3-butadienes. Novel dienes efficiently took part in the Diels-Alder reaction with a vast variety of dienophiles, including acrolein derivatives, quinones, maleimides and nitroalkenes, to provide, after the hydrolysis of the oxazolidine moiety, 6-substituted cyclohexenones in high yield and with good diastereoselectivity. The novel dienes showed good reactivity in the Hetero Diels-Alder reaction with aromatic and aliphatic aldehydes, providing an easy access to dihydropyranone, a useful motif in natural product synthesis. Kinetic studies of the reaction between the simple oxazolidine 1,3-butadiene and methyl acrylate have revealed, that our newly developed diene is ~300 times more reactive than the known activated dienes, Danishefskys' diene and Brassards' diene. Currently we are planning to focus on the studies of enantioselective Diels-Alder reactions between our newly developed dienes and different dienophiles to access enantioenriched 6,6’-disubstittued cyclohexenones. We are planning to apply the newly developed methodology towards the synthesis of several natural products, including Acutifolone A and Platensimycin.

Chapter 3.

Meerwein-Eschenmoser-Claisen Rearrangement As A Route To Asymmetric 2,2 – Disubstituted Indoles

Section 3.1. Introduction

3.1.1. 2,2 – Disubstituted Indolines In Nature

Indole presents one of the most common structural fragments found in natural products. From the essential amino acid tryptophan to the neurotransmitter serotonin, from antitumor agent Discorhabdin A to vasoconstrictor ergotamine, the wide range of biological activities exhibited by indole-containing compounds has made the indole framework a privileged structural motif in drug design[67]. Moreover, the unique reactivity profiles and complex polycyclic and highly functionalized structures of many naturally occurring indole alkaloids have attracted the interest of the synthetic community, resulting in multiple synthetic studies towards their intriguing molecular frameworks[68].

Indoline-containing alkaloids represent a large subclass of indole-based natural products, which are characterized by a set of unique bioactivity profiles, including strong antitumor and antineoplastic activities. The most well-known examples of indoline natural products are the anticancer drugs Vinblastine (**117**) and Vincristine (**118**) (Scheme **26**), isolated from the

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[67] a) Natural Products Containing the Indole Nucleus. *Chemistry of Heterocyclic Compounds* **2008**; b) de Sa Alves, F. R.; Barreiro, E. J.; Manssour Fraga, C. A. *Mini Reviews in Medicinal Chemistry* **2009**, *9*, 782–793.

[68] Gribble, G. *Indole Ring Synthesis: From Natural Products to Drug Discovery*, John Wiley & Sons Ltd.: Chichester, West Sussex, 2016.

Catharanthus roseus plant[69]. Mitomycin C (**119**), isolated from *Streptomyces caespitosus*, represents another indoline-based compound that is widely used in the clinic as an antitumor drug and antibiotic[70]. A large number of indoline natural products belong to the kopsane family of alkaloids, which consists of more than 100[71] members. Most kopsane alkaloids show good antihypertensive[72], antitumor and antineoplastic properties[73]. Specifically, Paucidactine A (**121**) and Lundurine B (**122**) exhibit high potency against melanoma cell lines without any cytotoxicity against other cultured cell lines[74], and Aspidophylline A (**123**) was shown to be efficient in reversing drug-resistance in drug-resistant KB cells[75].

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[69] a) Johnson, I. S.; Armstrong, J. G.; Gorman, M.; Burnett, J. P. *Cancer Res* **1963**, *23*, 1390; b) Brade, W. P., Nagel, G. A., Seeber, S. Critical Review of Pharmacology, Toxicology, Pharmacokinetics of Vincristine, Vindesine, Vinblastine; International Vinca Alkaloid Symposium - Vindesine. *Proceedings. Contrib Oncol*. Basel, Karger **1981**, *6*, 95–123; c) van Der Heijden, R.; Jacobs, D. I.; Snoeijer, W.; Hallard, D.; Verpoorte, R. *Curr. Med. Chem.* **2004**, *11*, 607.

[70] Tomasz, M. *Chemistry & Biology* **1995**, *2*, 575–579.

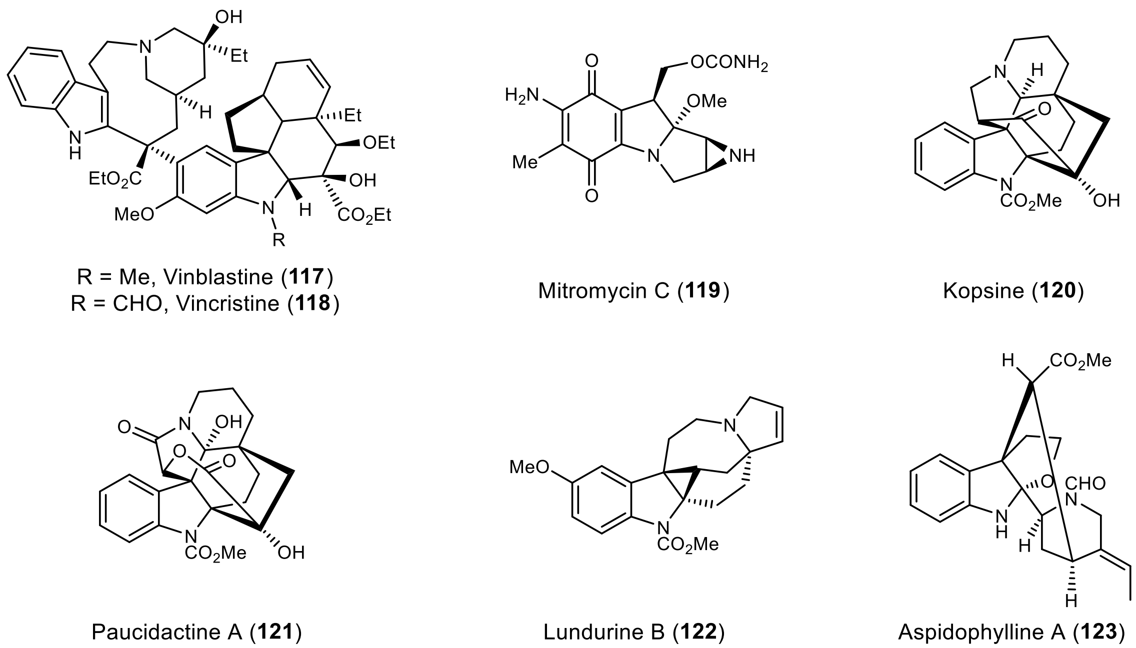
[71] Kam, T.-S. and Lim, K.-H. "Chapter 1 Alkaloids of Kopsia" *The Alkaloids: Chemistry and Biology* **2008**, 66: 1–111.

[72] Mok, S.-L., Yoganathan, K., Lim, T.-M., Kam, T.-S. *J. Nat. Prod.* **1998**, 61, 328

[73] a) Kam, T.-S., Yoganathan, K., Koyano, T., Komiyama, K. *Tetrahedron Lett.* 1996, 37, 5765; b) Lim, S.-H., Sim, K.-M., Abdullah, Z., Hiraku, O., Hayashi, M., Komiyama, K., Kam, T.-S. *J. Nat. Prod.* **2007**, 70, 1380.

[74] a) Kam, T.-S.; Yoganathan, K.; Koyano, T.; Komiyama, K. *Tetrahedron Lett.* **1996**, *37*, 5765; b) Kam, T.-S.; Lim, K.-H.; Yoganathan, K.; Hayashi, M.; Komiyama, K. *Tetrahedron* **2004**, *60*, 10739.

[75] Subramaniam, G.; Hiraku, O.; Hayashi, M.; Koyano, T.; Komiyama, K.; Kam, T.-S.. *J. Nat. Prod.* **2007**, *70*, 1783.



R = Me, Vinblastine (**117**)
R = CHO, Vincristine (**118**)

Mitromycin C (**119**)

Kopsine (**120**)

Paucidactine A (**121**)

Lundurine B (**122**)

Aspidophylline A (**123**)

Scheme 26. Indoline-based alkaloids.

Because of their interesting biological properties and intriguing complex skeleton framework, numerous total syntheses and synthetic studies towards kopsane alkaloids have been undertaken.[76] One of the key challenges in the synthesis of these compounds that was envisioned by many researchers, is the introduction of the C2 quaternary center. Multiple approaches to solve this problem have been demonstrated, including radical and metal-catalyzed dearomative cyclizations, nucleophilic substitution-iminium trapping cascades, [4+2] and [2+1] cycloaddition reactions and many others. The downside of most of these approaches is that they are substrate-dependent, and in many cases minor modifications in the structures of the compounds dramatically change the reaction outcome. Thus, development of a general approach to the 2,2-disubstituted indoline framework is attrractive.

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[76] For some examples, see: a) Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2086; b) Magnus, P.; Brown, P. *J. Chem. Soc., Chem. Commun.* **1985**, *0*, 184; c) Ogawa, M.; Kitagawa, Y.; Natsume, M. A *Tetrahedron Lett.* **1987**, *28*, 3985; d) Wenkert, E.; Pestchanker, M. J. A *J. Org. Chem.***1988**, *53*, 4875; e) Arai, S.; Nakajima, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 5569

3.1.2. Previous Synthetic Approaches To The 2,2 – Disubstituted Indoline Core Structure

One of the first approaches to the 2,2-disubstituted indoline framework in the context of natural product synthesis was demonstrated by the group of Prof. Langlois[77] (Scheme **27**, eq. 1). In their synthetic studies towards Venalstonine and Kopsinine they have shown that the 2,2-disubstituted fragment of this molecules can be prepared by Mannich-type reaction of iminium ion **125**. Similar strategies were later adopted by other groups. For example, the group of Prof. Natsume[78] in their synthesis of *rac*-Kopsinine utilized a cascade of indole C3 alkylation - iminium trapping to construct 2 of the 5 rings in Vindorosine. Since indole can react with a variety of electrophiles to form the desired iminium ion intermediate, which can then be trapped in both an inter- and intra-molecular fashion to give rise to 2-substituted indolines, this strategy has found broad usage in the total synthesis of indoline-contatining natural products. For instance, Ma *et. al.* have utilized this strategy to construct the core of Methyl *N*-decarbomethoxychanofruticosinate[79] (eq. 3). Thus, treatment of ketone **127** with an exess of LiHMDS, followed by the addition of iodine, triggered an oxidative coupling[80] to provide cyclized product **128**, which upon treatment with TMSCN gave rise to indoline **129**.

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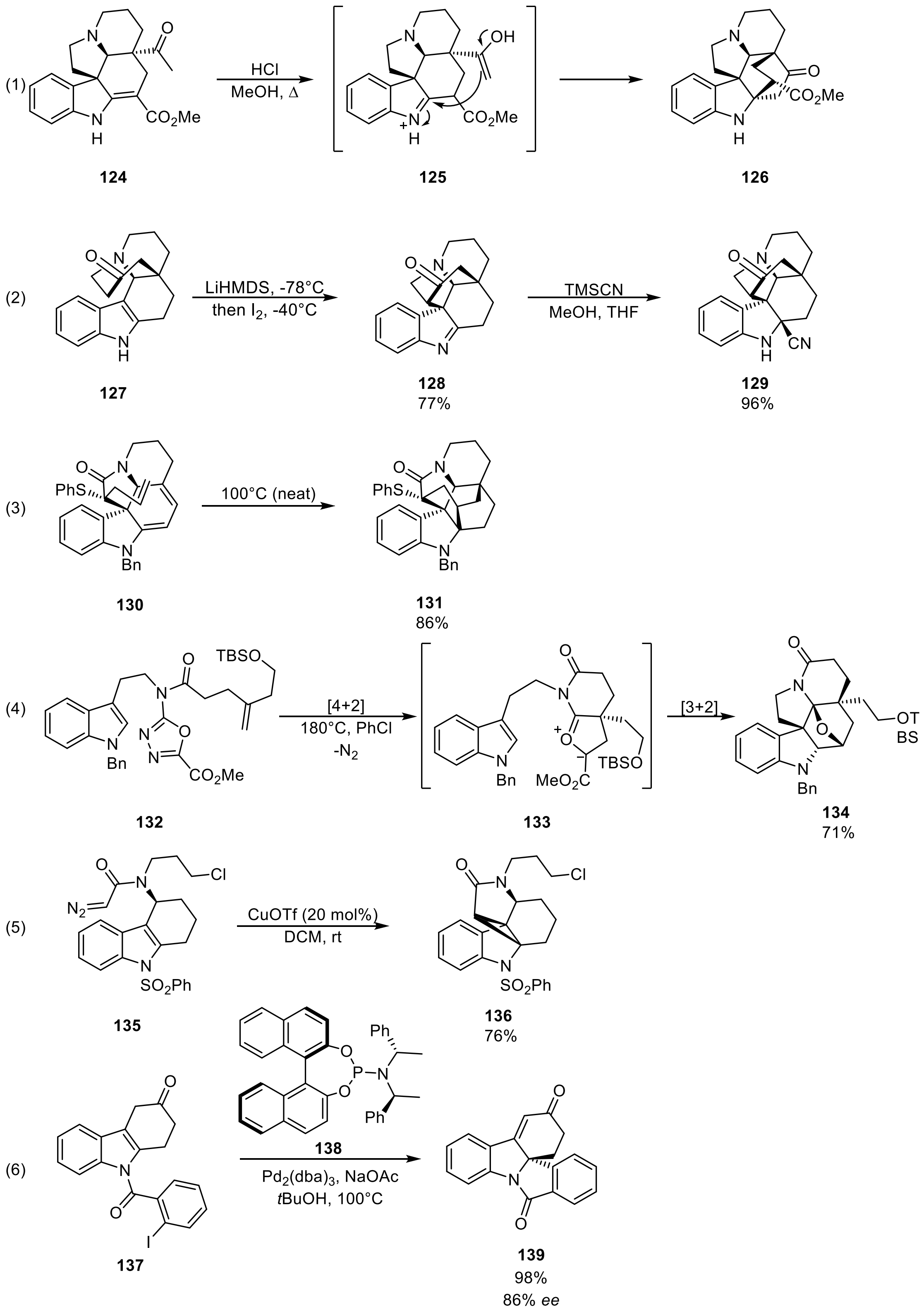
[77] Langlois, N.; Andriamialisoa, R. Z. *J. Org. Chem.* **1979**, *44*, 2468.
[78] Natsume, M.; Utsunomiya, I. *Chem. Pharm. Bull.* **1984**, *32*, 2477.
[79] Wei Yi, Zhao, D., Ma, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 12988.
[80] Watanabe, T., Umezawa, N., Kato, N., Higuchi, T. *Chem. Eur. J.* **2013**, *19*, 4255.



124 **125** **126**

127 **128** 77% **129** 96%

130 **131** 86%

132 **133** **134** 71%

135 **136** 76%

137 **138** **139** 98% 86% *ee*

Scheme 27. Previously reported routes to access 2-substituted indolines

A different powerful strategy to access 2,2-disubstituted indolines was developed independently by groups of Magnus[81] and Kuehne[82]. They utilized a Diels-Alder reaction of indoline diene **130** to construct the 6-membered ring fragment in total syntheses of Kopsanone and related alkaloids. Despite the harsh conditions involved (100°C, neat), the reaction proved to be tolerant to various substituents on the aliphatic portion of the molecule, which allowed its efficient use in total synthesis of several alkaloids of the kopsia family.

Another example of the efficient use of a cycloaddition reaction to construct the kopsinine core was presented by the group of Boger.[83] In their synthesis, they utilized a cascade of intramolecular [4+2] and [3+2] cycloaddition reactions to access the core pentacyclic fragment of Kopsinine, providing one of the most efficient and step-economical routes to *Aspidosperma* alkaloids reported to date.

Cyclopropanation, among other cycloaddition methods, has also recently found application in the synthesis of complex indoline-based alkaloids[84]. For instance, the group of Spino[85] reported an intramolecular copper-catalyzed cyclopropanation as a key step to access the 5-membered ring in Aspidofractinine (eq. 5).

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[81] a) Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.***1983**, *105*, 2086; b) Magnus, P.; Gallagher, T.; Brown, P.; Huffman, J. C. *J. Am. Chem. Soc.***1984**, *106*, 2105; c) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35; d) Magnus, P.; Brown, P. *J. Chem. Soc., Chem. Commun.* **1985**, *0*, 184; e) Magnus, P.; Matthews, I. R.; Schultz, J.; Waditschatka, R.; Huffman, J. C. *J. Org. Chem.***1988**, *53*, 5772; f)) Magnus, P.; Katoh, T.; Matthews, I. R.; Huffman, J. C. *J. Am. Chem. Soc.***1989**, *111*, 6707; j) Magnus, P.; Gazzard, L.; Hobson, L.; Payne, A. H.; Rainey, T. J.; Westlund, N.; Lynch, V. *Tetrahedron* **2002**, *58*, 3423.

[82] Kuehne, M. E.; Seaton, P. J. *J. Org. Chem.***1985**, *50*, 4790.

[83] Xie, J.; Wolfe, A. L.; Boger, D. L. *Org. Lett.* **2013**, *15*, 868.

[84] For the recent example see: Xu, H.; Li, Y.-P.; Cai, Y.; Wang, G.-P.; Zhu, S.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2017**, *139*, 7697 and references therein

[85] Gagnon, D.; Spino, C. *J. Org. Chem.* **2009**, *74*, 6035.

Lastly, a palladium-catalyzed dearomatization strategy have demonstrated moderate success in accessing 2,2-disubstituted indolines. The most recent example came from Fukuyama group[86], where they applied an enantioselective palladium-catalyzed dearomatization as a key step in the total synthesis of (+)-Hinckdentine. The significant downside of this approach is the necessity to have a carbonyl group at the β-postion to the indole for the reaction to take place, which limits the substrate scope of this transformation.

Despite multiple total syntheses of indoline alkaloids have been reported thus far, most of them present racemic syntheses of the corresponding alkaloids. The enantioselective installation of the stereocenter at the C2 carbon of the indoline remains a challenge. With the goal of identifying a general solution to this problem, we considered the use of sigmatropic rearrangements to transfer a substituent from the benzylic position of the indole to the C2 position. The process was expected to have a high activation energy, as it would disrupt the aromatic stabilization of the pyrrolo-portion of the indole unit. Ideally, if the process were effective, then it would also allow transfer of chirality from the benzylic to C2 position, an otherwise challenging transformation. As few such dearomatizing rearrangements involving the indole unit were found in the literature, we directed our preliminary studies to the feasibility and generality of such a process.

3.1.3. Claisen rearrangement in indoles

[3,3] Sigmatropic rearrangements are among the oldest and the most powerful transformations in organic chemistry. Discovered in 1912 by Rainer Ludwig Claisen, it has found multiple applications in total synthesis as a powerful tool, enabling access to the complex

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[86] Douki, K.; Ono, H.; Taniguchi, T.; Shimokawa, J.; Kitamura, M.; Fukuyama, T. *J. Am. Chem. Soc.* **2016**, *138*, 14578.

molecular frameworks[87]. Some of the key factors that make the Claisen rearrangement so attractive for the synthetic applications are its atom economy during the rearrangement process and its predictability with respect to the sterochemical outcome of the reaction due to a highly ordered transition state. The literature records many examples of the aromatic Claisen rearrangement, including those that disrupt aromaticity[88]. In light of this precedent and the fact that the pyrrolo-ring of indole has considerably less aromatic stabilization, the paucity of examples involving indole-based precursors is surprising. All of the reported examples can be divided into two groups – rearrangement of allyloxyindoles to provide 3-substituted 2-oxindoles and rearrangement of indole alcohols to provide 2-substituted indolines.

Among the most effective indole-based Claisen rearrangements are those of 2-alloxy indoles, which rearrange to 3-allyl substituted oxindoles. The formation of the thermodynamically more stable oxindole makes this type of rearrangement favorable, allowing for the reactions to proceed at low temperatures (as low as room temperature). Thus, the group of Prof. Sakamoto was the first to demonstrate that 2-oxoindole **141**, formed during the Horner–Wadsworth–Emmons olefination, spontaneously rearranges to 3-oxindole **142** at room temperature[89] (Scheme **28**). Later, group of Prof. Kobayashi has shown that cyclic 2-oxoindoles **143** can also take part in Claisen

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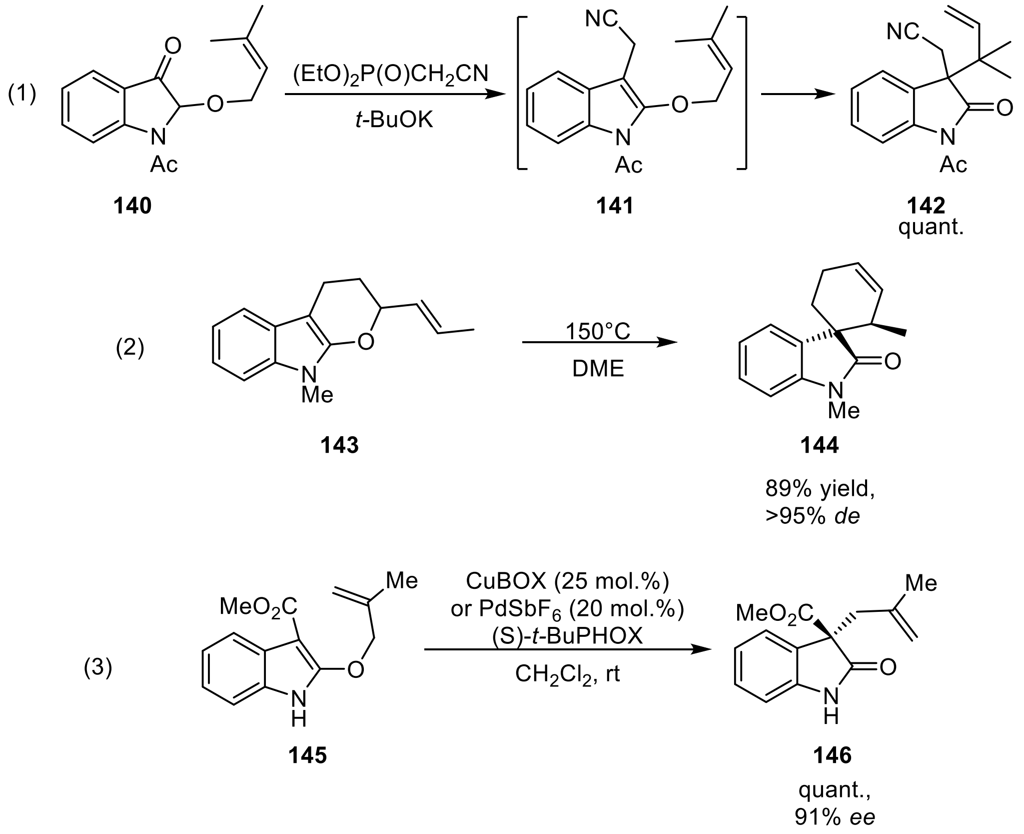
[87] *The Claisen Rearrangement: Methods and Applications;* Hiersemann, M., Nubbemeyer, U., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Darmstadt, 2007

[88] For recent reviews, see: a) Bennett, G. B. *Synthesis* **1977**, *1977*, 589; b) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205; c) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423; d) Wipf, P. 7.2 - Claisen Rearrangements. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; p. 827; e) Ganem, B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 936; f) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43; g) Martín Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939.

[89] a) Kawasaki, T.; Terashima, R.; Sakaguchi, K.; Sekiguchi, H.; Sakamoto, M. *Tetrahedron Lett.* **1996**, *37*, 7525; b) Kawasaki, T.; Ogawa, A.; Takashima, Y.; Sakamoto, M. *Tetrahedron Lett.* **2003**, *44*, 1591.

rearrangements to provide oxindoles **144** in high yield and with excellent diastereoselectivity[90]. In the latter case, rearrangement required harsh conditions (heating to 150°C over several hours) due to the significant steric strain in the substrate that prevents adoption of a chair-like transitions state and the lack of activating groups in the system. Recently, the group of Prof. Kozlowski has demonstrated the efficient use of a chiral Lewis acid catalyst to promote enantioselective Claisen rearrangements of oxoindoles **145**, providing the corresponding 2-oxindoles **146** in high yield and with high enantioselectivity[91].



Scheme 28. Formation of 2-oxindoles through Claisen rearrangement

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[90] a) Miyamoto, H.; Okawa, Y.; Nakazaki, A.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2274; b) Miyamoto, H.; Hirano, T.; Okawa, Y.; Nakazaki, A.; Kobayashi, S. *Tetrahedron* **2013**, *69*, 9481.

[91] a) Linton, E. C.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 16162; b) Cao, T.; Deitch, J.; Linton, E. C.; Kozlowski, M. C. *Angew. Chem., Int. Ed.* **2012**, *51*, 2448; c) Cao, T.; Linton, E. C.; Deitch, J.; Berritt, S.; Kozlowski, M. C. *J.Org. Chem.***2012**, *77*, 11034.

Examples that transfer a carbon substituent to the 2-position of indole are significantly more rare. Thus, in the late 1970s Raucher and coworkers demonstrated that 3-indoleglyoxylic acid derivatives **147** can take part in the Johnson-Claisen orthoester rearrangement, giving rise to 2-substituted indolines, which under the reaction conditions rearrange to provide 2-substituted indoles in high yield.[92] However, the reported reaction has several significant downsides. First, the reaction requires rather harsh conditions (heating of indole alcohol in neat triethylacetoformate in the presence of acid at 185° for 8 h). And second, the presence of the carboxyl group at the benzylic position has a crucial influence on the reaction outcome – in the absence of it the rearrangement does not procced to any extent. It is also noteworthy that Raucher concluded that while the Johnson-Claisen rearrangement of indoles allowed introduction of a C2 substituent, it did not allow the creation of a 2,2-disubstituted indoline. The rearrangement did not proceed when anything other than hydrogen was attached to the C2 position of the indole.

An interesting example of an asymmetric aza-Claisen rearrangement for the construction of 2-substituted indoles was recently disclosed by the group of prof. Tambar.[93] Treatment of unprotected *N*-benzyl-3-aminoindole **150** with a chiral phosphoric acid in toluene at 60°C gives rise to the corresponding 2-substituted indoles **153** in high yield and with high enantioselectivity. To the best of our knowledge, the sole example of a Claisen rearrangement of an indolic precursor to generate a 2,2-disubstituted indoline is within a report by Craig and coworkers on the microwave-assisted decarboxylative Claisen rearrangement.[94] Treatment of indole ester **154**,

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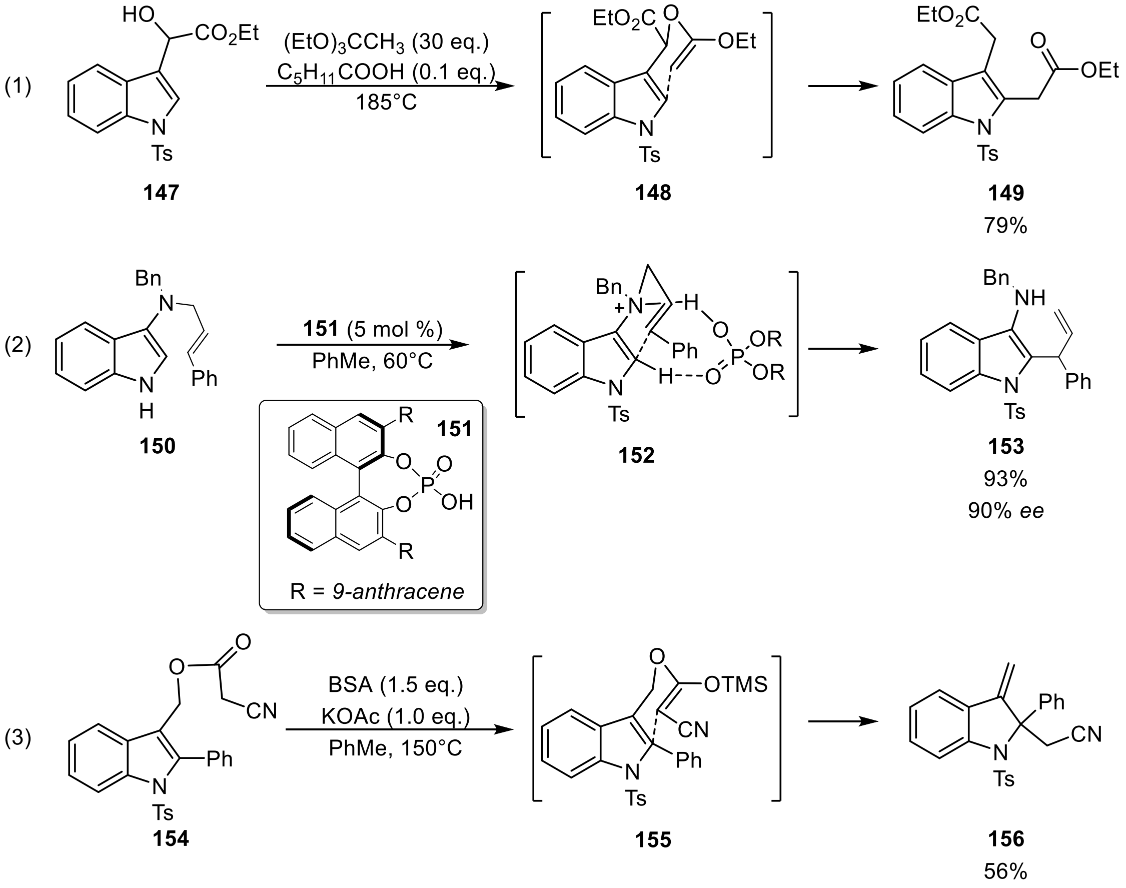
[92] a) Raucher, S.; Lui, A. S.-T. *J. Am. Chem. Soc.* **1978**, *100*, 4902; b) Raucher, S.; Hwang, K.-J.; Macdonald, J. E. *Tetrahedron Lett.* **1979**, *20*, 3057; c) Raucher, S.; Macdonald, J. E.; Lawrence, R. F. *Tetrahedron Lett.* **1980**, *21*, 4335; e) Raucher, S.; Macdonald, J. E.; Lawrence, R. F. *J. Am. Chem. Soc.* **1981**, *103*, 2419; f) Raucher, S.; Lawrence, R. F. *Tetrahedron* **1983**, *39*, 3731

[93] Maity, P.; Pemberton, R. P.; Tantillo, D. J.; Tambar, U. K. *J. Am. Chem. Soc.* **2013**, *135*, 16380

[94] Camp, J. E., Craig, D., Funai, K., and White, A. J. P. *Org. Biomol. Chem.* **2011,** 9, 7904

bearing a strong electron withdrawing group at the α-position of the ester, with *N*,*O*-bis(trimethylsilyl)acetamide in the presence of a weak base (KOAc) in toluene upon rapid microwave heating generates silyl enol ether **155**, which under the reaction conditions takes part in a decarboxylative Ireland-Claisen type rearrangement, giving rise to indolines **156** in moderate yields.



Scheme 29. Formation of 2-substituted indoles and indolines through Claisen rearrangement

Given our interest in the total synthesis of the indoline-based natural products listed above combined with the possibility of developing a fundamental transformation that may be of general value, we decided to carry out model studies to test the feasibility of the desired indole-based Claisen rearrangements.

Section 3.2. Development Of A General Route To Access 2,2 – Disubstituted Indolines Through Claisen Rearrangement

3.2.1 Initial screening of different variants of the Claisen reaction

To date, multiple variants of the Claisen rearrangement have been reported[95]. Despite the amount of experimental information on different variants of this powerful rearrangement, a general model for predicting which type of Claisen rearrangement will work best with different allylic alcohol substrates is still lacking. Thus, we aimed our attention towards screening different Claisen rearrangements to identify the best conditions for the indole dearomative rearrangement. As a model substrate, we choose simple indole alcohol **157** (Scheme **30**). Previous reports from the groups of Raucher and Craig indicated that dearomative Ireland-Claisen and Johnson-Claisen rearrangements in indoles require specialized substrates to proceed. Yet, very little or no information was reported on the outcome of this rearrangements with more simplified indole substrate. Thus, we started our screen of different Claisen rearrangement variants with the Irealnd-Claisen protocol[96] (eq. 1): conversion of alcohol **157** to the ester **158**, followed by deprotonation with LDA and trapping of the formed enolate with TBSCl provided desired silyl enol **159**. However, all attempts to engage compound **159** in a thermal Ireland-Claisen rearrangement failed; no reaction was observed upon heating the reaction in toluene up to 140°C. Exposure of ester **158** to the anion-accelerated Ireland-Claisen rearrangement conditions (eq. 2) also didn’t succeed – heating the enolate **160** to room temperature didn’t lead to the formation of any detectable amount

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[95] *The Claisen Rearrangement*; Hiersemann, M., Nubbemeyer, U., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA, 2007.

[96] a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94,* 5897; b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98,* 2868.

of the desired product, and prolonged heating of the enolate led to its complete decomposition. Heating the alcohol **157** with trimethylacetoformate in chlorobenzene to trigger the Johnson-Claisen reaction[97] led only to the formation of a small amounts of ether **162** (eq. 3). Utilizing Ficini-Claisen procedure[98] by treating the indole alcohol with aminoalkyne **164** in the presence of gold catalyst or catalytic amounts of triflic acid led to the exclusive formation of a formal [1,3] rearrangement product **166** (eq. 4). Attempts to perform Belus-Claisen rearrangement[99], treating the protected gramine **167** with the *in situ* generated dichloroketene (line 5) led to a complex mixture of products, with the major product being chloroindole **169**. After an extensive screening, we were able to identify that only the Meerwein-Eschenmoser-Claisen procedure[100] provides the desired rearrangement product in a nearly quantitative yield (line 6). It can be proposed that such a significant change from nearly 0% yield for other Claisen methods to nearly 100% yield for the Eschenmoser-Claisen method can be explained by the combination of mild reaction conditions, required to produce the diene intermediate **170** (no acid/base/strong nucleophile is required, thus the possibility of the side reactions is minimized) and the presence of the strong electron-donating group $–NMe_2$ on the C5 position of the diene intermediate **170**, that has previously been shown to significantly lower the activation barrier for the Claisen rearrangement in more simple substrates.

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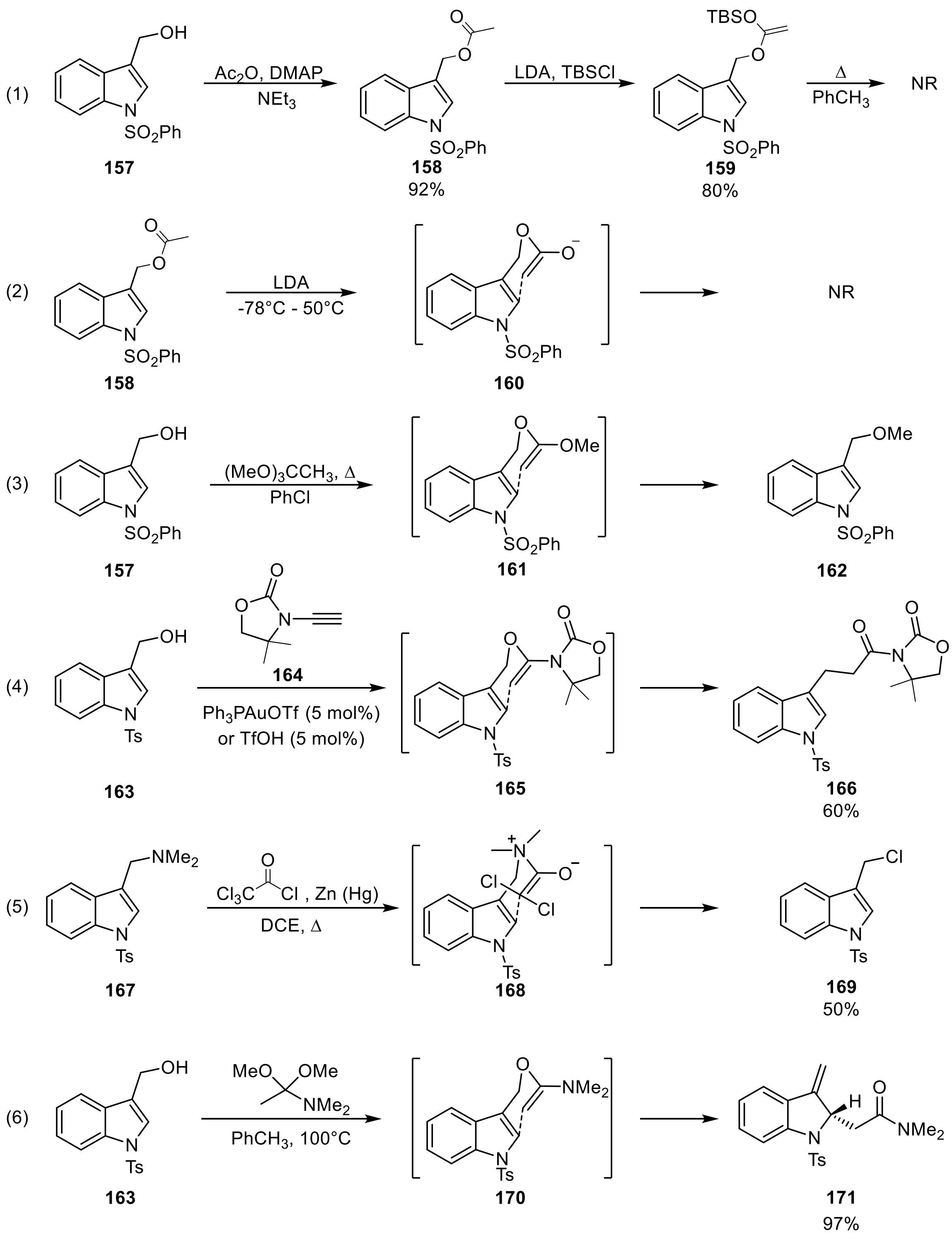
[97] Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

[98] a) Ficini, J.; Barbara, C. *Tetrahedron Lett.***1966**, *7*, 6425; b) Ficini, J.; Lumbroso-Bader, N.; Pouliquen, J. *Tetrahedron Lett.***1968**, *9*, 4139.

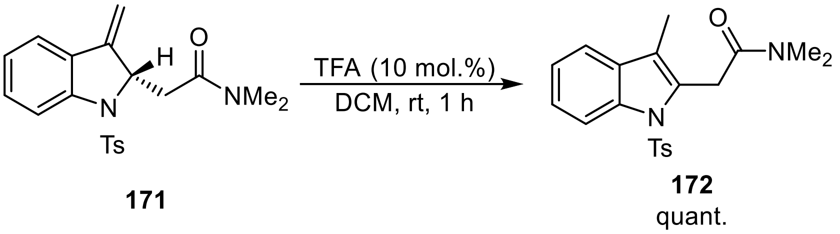
[99] a) Malherbe, R.; Belluš, D. *Helv. Chim. Acta.* **1978**, *61*, 3096; b) Malherbe, R.; Rist, G.; Bellus, D. *J. Org. Chem.* **1983**, *48*, 860

[100] a) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta.* **1964**, *47*, 2425; b) Felix, D.; Gschwend-Steen, K.; Wick, A. E.; Eschenmoser, A. *Helv. Chim. Acta.* **1969**, *52*, 1030.



Scheme 30. Screening of different variants of Claisen rearrangement

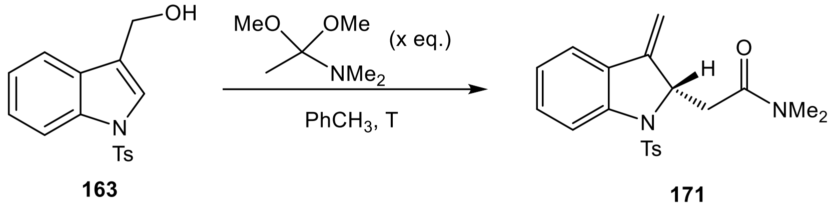
To provide extra support to our structural assignment of the rearrangement product, we submitted indoline **171** to acidic conditions in order to facilitate the double bond migration. Indeed, treatment of **171** with a catalytic amount of trifluoroacetic acid in dichloromethane at room temperature provided its full conversion to the known indole **172** within 1 hour in quantitative yield (Scheme **31**).



Scheme 31. Double bond migration

Encouraged by this result, we aimed towards optimizing the reaction conditions (Table **6**). In agreement with the previously reported studies on the Meerwein-Eschenmoser-Claisen rearrangement, the limiting step of the reaction for simple indole alcohol proved to be the formation of intermediate **170.** To facilitate this process, the methanol that is formed as a byproduct is required to be distilled out of the reaction mixture. Thus, reaction requires elevated temperatures (above 80°C) to proceed (entries **3-6**); below 60°C reaction completely shuts down (entries **1-2**). As an alternative to conventional heating, microwave radiation can be efficiently used to accelerate the reaction. Thus, heating a mixture of indole alcohol **163** and dimethylacetamide dimethyl acetal in toluene a microwave reactor (400 W, 110°C) led to 97% conversion of the alcohol to the desired indoline after only 15 minutes (entry **7**). Reducing the amount of dimethylacetamide dimethyl acetal significantly slows down the reaction; upon utilizing equimolar amount of acetal and alcohol reaction reached only 10% conversion at 80°C after 1 h (entry **9**), whereas with the use of 3 equivalents of acetal reaction reaches 60% conversion in the same amount of time (entry **3**).

Table 6. Optimization of the reaction conditions



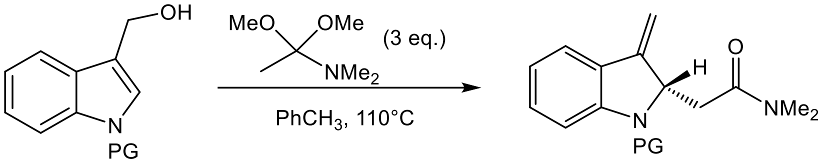
163 **171**

Entry	X (eq.)	T, °C	conv., %
1	3	40	0
2	3	60	2
3	3	80	60
4	3	90	72
5	3	100	85
6	3	110	95
7	3	110[a)]	97
8	2	80	31
9	1.5	80	25
10	1	80	10

a) microwave reactor, 15 min.

Finally, the nature of the protecting group on the indole plays a crucial role in the reaction outcome (Table **7**). Switching to electron-donating protecting groups (methyl and benzyl, entries **2** and **3**) completely shuts down the rearrangement and leads to multiple unidentified side products. Use of the *Boc* protecting group gave the desired product in 95% yield (entry **4**). Finally, the Cbz protecting group proved to be unstable under the reaction conditions, giving rise to the unprotected indole alcohol as the major product of the reaction (entry **5**).

Table 7. Influence of the protecting group on the indole on the reaction outcome

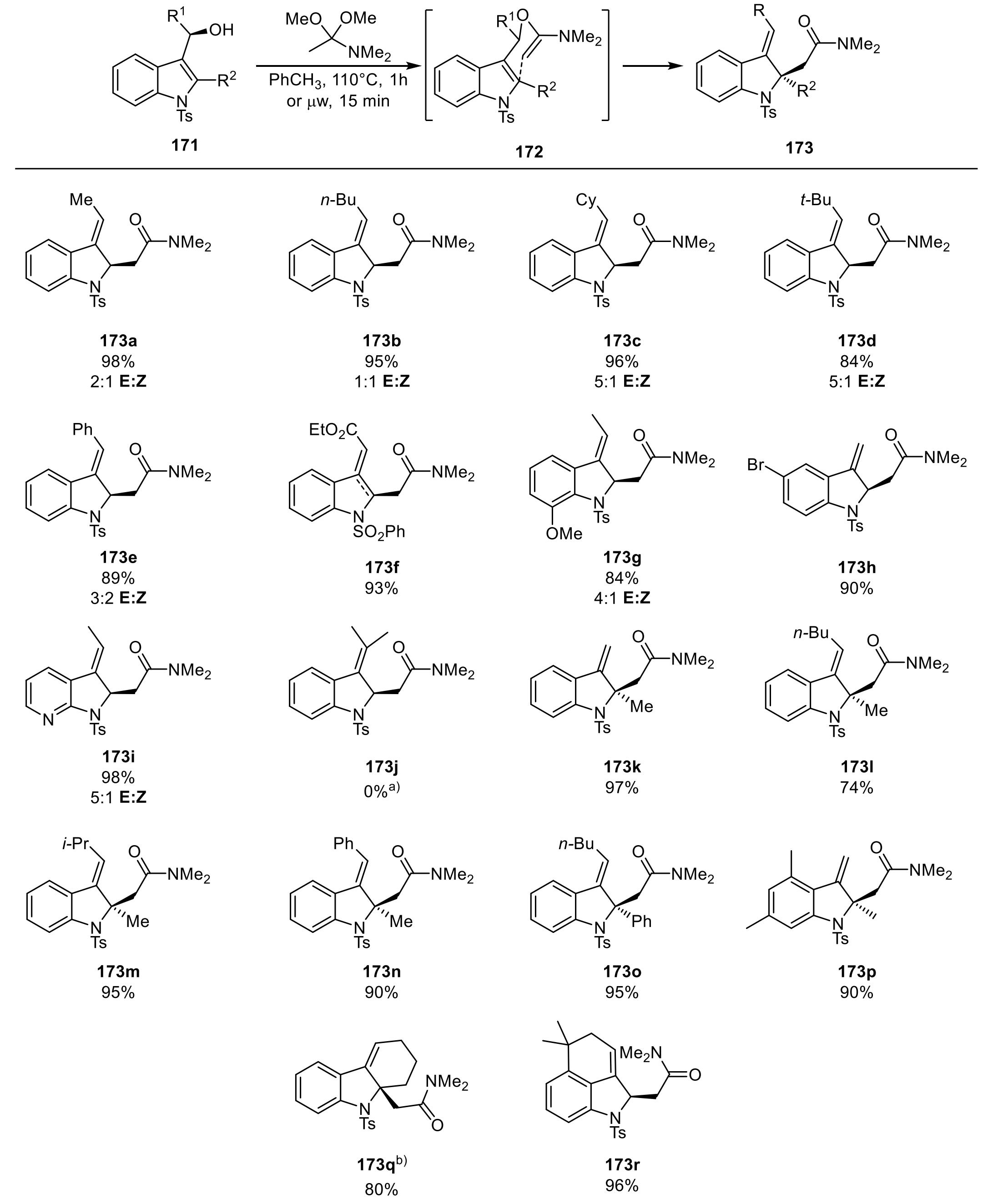


Entry	PG	Substrate	Product	Yield, %
1	Ts	**163**	**171**	97
2	Me	**172**	**173**	NR
3	Bn	**174**	**175**	NR
4	Boc	**176**	**177**	92
5	Cbz	**178**	**179**	NA[a]

a) cleavage of Cbz was observed, along with other products

3.2.2 Substrate scope of the Eschenmoser-Claisen rearrangement of indole alcohols

With optimized conditions in hand, we turned our attention to examining the scope of this transformation (Scheme **32**). Thus, the reaction proved to be tolerable to both alkyl and aryl substituents on the benzylic position of the alcohols, including bulky cyclohexyl and *tert*-butyl substituents, providing corresponding indolines **173a-e** in high yield as a mixture of double bond isomers. 3-indoleglyoxilic ester **173f**, which was previously reported by Raucher as a successful substrate for the Johnson-Claisen rearrangement, efficiently reacted under our optimized conditions, providing the corresponding product in a very high yield as a single diastereomer (isolated along with ~20% of the corresponding 2-substituted indole). Substitution on the benzene ring of the indole alcohol and use of other indole-based heterocycles has nearly no influence on the reaction efficiency, giving rise to substituted indolines **173g-i** in high yield. Exposure of the disubstituted indole alcohols to the reaction conditions resulted only in the formation of the dehydrated product, with no trace of the desired indoline **173j**. To our delight, 2-substituted indoles, which were proposed to be completely unreactive under Johnson-Claisen conditions, successfully took part in the rearrangement under Eschenmoser-Claisen conditions, providing 2, 2–disubstituted indolines **173k-p** in high yield. It is especially noteworthy that in case of 2-substituted indoles, bearing a substituent at the benzylic position, corresponding indolines were produced as an exclusive Z - isomer, indicating that the reaction proceeds through a highly-ordered transition state, with a strong preference for the benzylic substituent to adopt the pseudo-equatorial arrangement. Fused indole alcohols also took part in the Meerwein-Eschenmoser-Claisen rearrangement to give the indolines **173q-r**, albeit required harsher conditions for the reaction to reach completion. Under standard reaction conditions ($PhCH_3$, 110°C) the yield of the desired indoline was significantly diminished (30% after 8 h), and the alcohol dehydration product proved to be the major side product in the reaction mixture (60%). Using microwave radiation as a source of heat and heating the reaction rapidly to 140°C allowed to minimize the side product formation, providing the desired fused indolines in up to 85% yield. Overall, the rearrangement proved to be applicable to a wide variety of indole-based alcohols, providing an easy and efficient access to corresponding indolines in high yield and with good to excellent diastereoselectivity.



a) only dehydration product isolated; b) μω, 140°C, 3 h

Scheme 32. Substrate scope of the Eschenmoser-Claisen rearrangement of indole alcohols

3.2.3 Chirality transfer in the Eschenmoser-Claisen rearrangement as a route to access enantioenriched 2,2 – disubstituted indolines

Having proved that the Eschenmoser-Claisen rearrangement can be used to install a quarternary center on the C2 of the indoline, we decided to make the next logical step in our studies – attempt to create this center in a stereo-controlled manner. The Meerwein-Eschenmoser-Claisen rearrangement, which proceeds through a highly ordered chair transition state, is known to be capable of efficiently transferring chiral information from a chiral alcohol to a newly formed quarternary carbon[101].We decided to check, if the use of enantioenriched indole alcohols would allow us to generate 2,2-disubstituted indolines with the desired stereochemistry.

Starting from the ketones **174**, asymmetric reduction utilizing the Corey-Bakshi-Shibata (CBS)[102] protocol resulted in the formation of chiral alcohols **175** with high *er* (up to 97:3) (Scheme **33**). Treating them with dimethylacetamide dimethylacetal under standard reaction conditions resulted in the formation of the corresponding indolines **176** with the complete transfer of chirality, as was indicated by the chiral HPLC traces. The absolute configurations of the formed alcohols (**S**) and indolines (**R**) were assigned based on the models of chiral reduction and Claisen rearrangement transition states.

Using the opposite enantiomer for the Corey-Bakshi-Shibata reduction, the (S)-(−)-2-Methyl-CBS-oxazaborolidine, gave rise to an excess of the opposite enantiomer of the alcohol,

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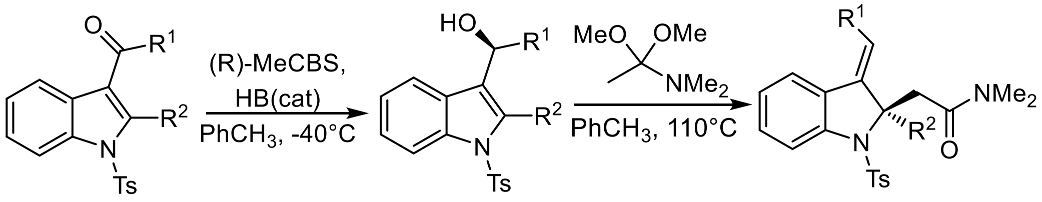
[101] For the recent examples see: a) Heathcock, C. H.; Finkelstein, B. L. *J. Chem. Soc., Chem. Commun.* **1983**, *0*, 919; b) Masaki, Y.; Arasaki, H.; Itoh, A. *Tetrahedron Lett.* **1999**, *40*, 4829; c) Williams, D. R.; Brugel, T. A. *Org. Lett.* **2000**, *2*, 1023; d) Frederick, M. O.; Hsung, R. P.; Lambeth, R. H.; Mulder, J. A.; Tracey, M. R. *Org. Lett.* **2003**, *5*, 2663; e) Mulzer Johann. *Journal für Praktische Chemie/Chemiker-Zeitung* **2004**, *336*, 287.

[102] Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925; b) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551; c) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861; d) Corey E. J.; Helal C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

175b, which upon subjection to the rearrangement conditions gave rise to the opposite enantiomer of the indoline **176b**, which showcased that our newly developed indolo-Claisen rearrangement can provide an easy access to the indolines bearing a quarterny center at the C2 carbon in a high yield and with the desired configuration.



174 **175** **176**

R^1	R^2	alcohol	yield	er	product	yield	er
n-Bu	Me	**175a**	90	95:5	**176a**	97	95:5
n-Bu	Me	**175b**$^{a)}$	90	5:95$^{a)}$	**176b**	97	5:95$^{a)}$
i-Pr	Me	**175c**	87	95:5	**176c**	80	95:5
t-Bu	Me	**175d**	90	92:8	**176d**	50	92:8
Ph	Me	**175e**	92	93:7	**176e**	95	93:7

a) (S)-MeCBS was used as a catalyst

Scheme 33. Chirality transfer during the Eschenmoser-Claisen rearrangement

Section 3.2. Concluding Remarks

In conclusion, we were able to identify that only Meerwein-Eschenmoser-Claisen rearrangement can be successfully applied to the indole alcohols to provide access to 2-substituted indoles and 2,2 - disubstituted indolines. The newly developed rearrangement proved to have a broad substrate scope, and can be efficiently applied to the indole alcohols, bearing a variety of sterically bulky, electron withdrawing and electron donating groups, giving rise to corresponding indolines in high yield. A combination of Corey-Bakshi-Shibata reduction methodology and our newly developed indolic Claisen rearrangement provided a simple and convenient procedure to access chiral 2,2 - disubstituted indolines with the desired configuration of the quaternary center at the C2 position of the indoline. This novel methodology has a high synthetic potential in the total synthesis of the indoline-containing alkaloids.

Chapter 4.

Total Synthesis Of Hinckdentine A

Section 4.1. Introduction. Previous Approaches Towards Total Synthesis Of Hinckdentine A

To demonstrate the utility of the previously designed Meerwein-Eschenmoser-Claisen rearrangement, we have elected to apply this transformation to the total synthesis of Hinckdentine A (**177**) (Scheme **34**), a unique polybrominated indoline-based alkaloid isolated in 1987 from the marine bryozoan *Hincksinoflustra denticulate*[103]. Its unique structure presents several challenges, such as the highly brominated indolo[1,2-*c*]quinazoline core and the 7-membered lactam unit that is fused to the indoline moiety through two contiguous stereogenic centers. Although the biological activity of Hinckdentine has not been reported, possibly due to the small amount isolated from the natural source, related indolo[1,2-*c*]quinazolines are known to possess good antimicrobial and antifungal activity[104]. The challenge posed by hinckdentine has attracted the attention of synthetic chemists, culminating in two synthetic studies, one racemic and one assymetric total synthesis of this alkaloid reported to date.

The first synthetic approach[105] to the Hinckdentine A skeleton was published by Cava *et. al.*[106]. In their synthetic plan, they proposed to first synthesize the indolo[1,2-c]quinazoline core

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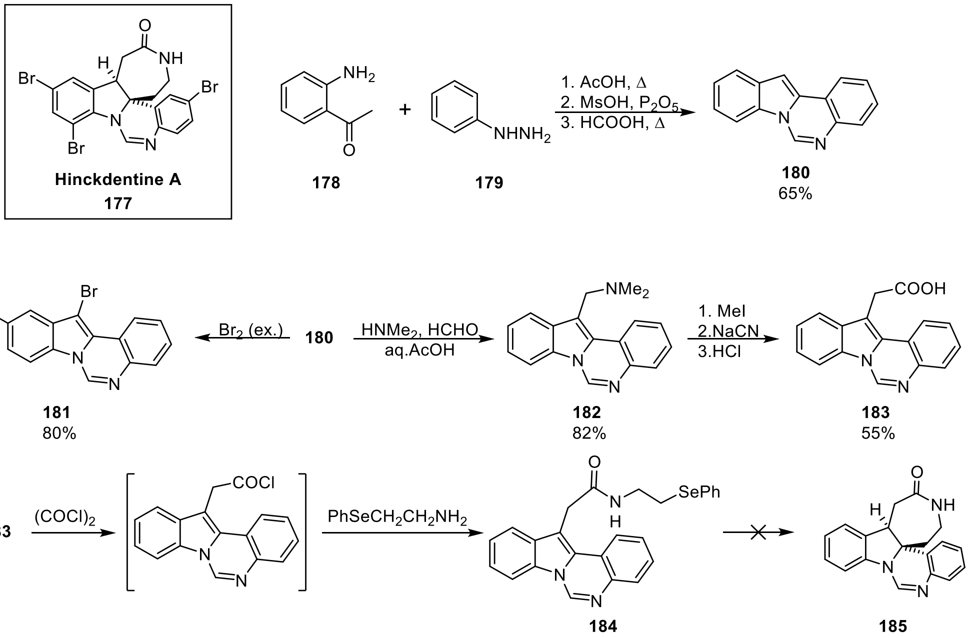
[103] Blackman, A. J.; Hambley, T. W.; Picker, K.; Taylor, W. C.; Thirasasana, N. *Tet. Lett.* **1987**, *28*, 5561.

[104] Rohini, R.; Shanker, K.; Reddy, P. M.; Sekhar, V. C.; Ravinder, V. *Archiv der Pharmazie* **2009**, *342*, 533.

[105] The first synthetic study was published by Joule et. al.: A. Joule, J.; Barnwell, N.; L. Beddoes, R.; B. Mitchell, M. *Heterocycles* **1994**, *37*, 175.

[106] Billimoria, A. D.; Cava, M. P. *J. Org. Chem.* **1994**, *59*, 6777.

of Hinckdentine, and then further functionalize it, installing the lactam ring and providing the desired bromination pattern. Thus, Fisher indole cyclization of the phenylhydrazone of 2-aminoacetphenone, followed by treatment with formic acid, provided indolo[1,2-c]quinazoline **180** in high yield. However, functionalization of the formed heterocycle proved to be tricky. Whereas Vilsmeier-Haack formylation and Michael addition to compound **180** proceeded smoothly to the C3 position of the indole portion of the indolo[1,2-c]quinazoline, all attempts to involve **180** in Friedel-Crafts acylation resulted in complete recovery of starting material, possibly due to acylation of the imidine nitrogen. Accessing the desired polybromination pattern also appeared to be a non-trivial task, as treatment of compound **180** with excess bromine resulted in the formation of undesired dibrominated compound **181**. In an attempt to construct the 7-membered lactam ring through a radical cyclization, authors prepared phenylselenide **184**, starting from amine **182** in 5 steps. However, all attempts to perform the cyclization under a variety of conditions failed to produce the desired product.



Scheme 34. Cava's approach towards Hinckdentine A

A thorough synthetic study towards Hinckdentine A, resulting in the total synthesis of 8-Desbromohinckdentine A, was published by Liu and McWhorter[107]. They utilized a different approach from the one proposed by Cava – the key step of their synthesis was the construction of the quaternary center at the C2 position of the indoline, followed by the construction of the lactam unit. Formation of the quinazoline ring and polybromination were left for a later stage of the synthesis. Thus, the previously described 2-(2-bromophenyl)-indole **186**, which can be easily accessed by the Fisher indole synthesis, was converted in 4 steps to 3H-indol-3-one **187** (Scheme **35**). Treatment of **187** with allylmagnesium bromide, followed by heating in the presence of formic acid triggered a pinacol-like rearrangement, giving rise to the indolone **188**, which bears the desired quarternary center at C2. However, the subsequent installation of the 7-membered lactam proved to be challenging. Initial attempts to build a cyclohexanone ring, which then can be subjected to the Beckmann rearrangement conditions, provided only traces of the desired lactam, (3% overall yield starting from indolone **188**). Thus, an alternative approach was pursued, wherein conversion of alkene **188** to dimethoxybenzyl (DMBn) protected acetamide **189** was followed by aldol reaction and subsequent alkene reduction to access the desired amide **190.** Buchwald-Hartwig amination, total deprotection and quinazoline ring formation finished construction of the Hinckdentine core. However, attempts to perform the late stage bromination resulted in selective formation of Desbromohinckdentine A. Attempts to further brominate compound **192** under harsher bromination conditions (Br_2/fuming sulfuric acid) resulted in the formation of a complex mixture of tribrominated products, along with decomposition products.

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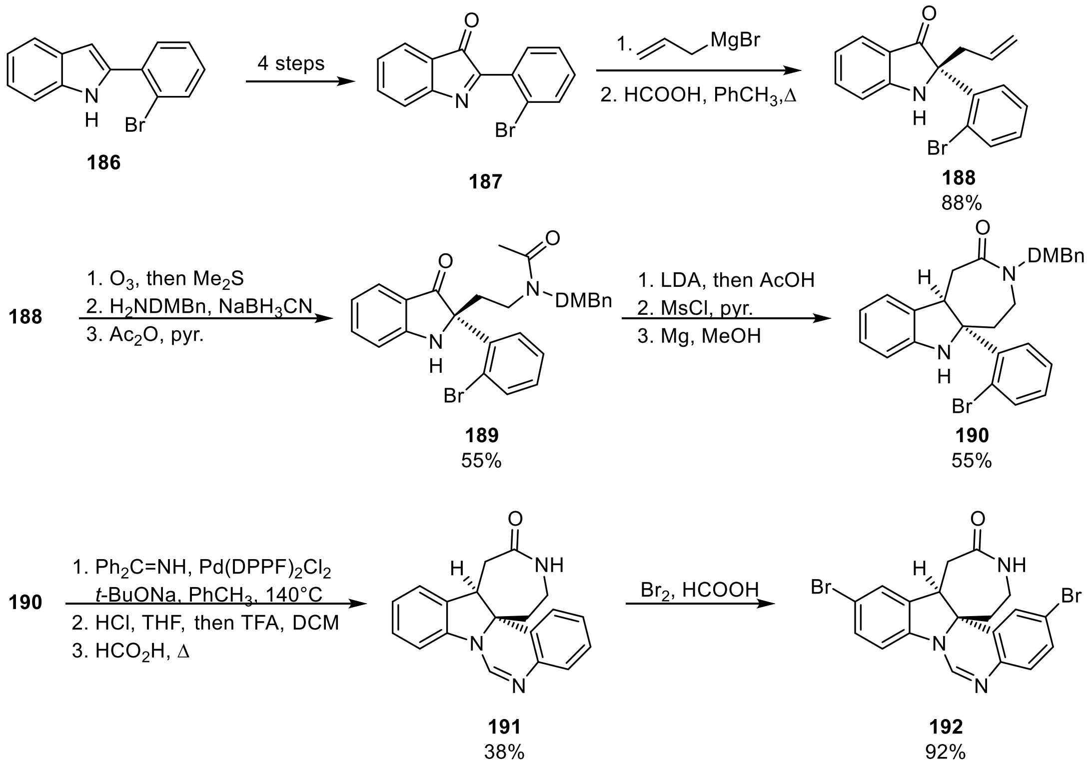
[107] Liu, Y.; McWhorter, W. W. *J. Am. Chem. Soc.* **2003**, *125*, 4240.



Scheme 35. McWhorter's synthetic studies towards Hinckdentine A

The first total synthesis of Hinckdentitne A was published by Kawasaki and co-workers in 2009 (Scheme **36**).[108] Their strategy towards construction of this elusive alkaloid resembled the strategy previously applied by McWhorter. Construction of the C2 quaternary center of the indoline by means of a nucleophilic addition to a 3-oxoindole was envisioned as the key step of the sequence; formation of the pyrimidine ring, followed by seven-membered lactam formation and bromination should have furnished the desired alkaloid. Thus, starting from 2-hydroxyindolineone **193**, which can be readily accessed from 2-(2-nitirophenyl)indole in 2 steps, treatment of it with (trimethylsiloxy)ethylene in the presence of equimolar amounts of camphorsulfonic acid provided 2,2-disubstituted indolin-3-one **194** in 56% yield. Reduction of epy aldehyde, followed by protecting group manipulations, nitro group reduction and treatment with

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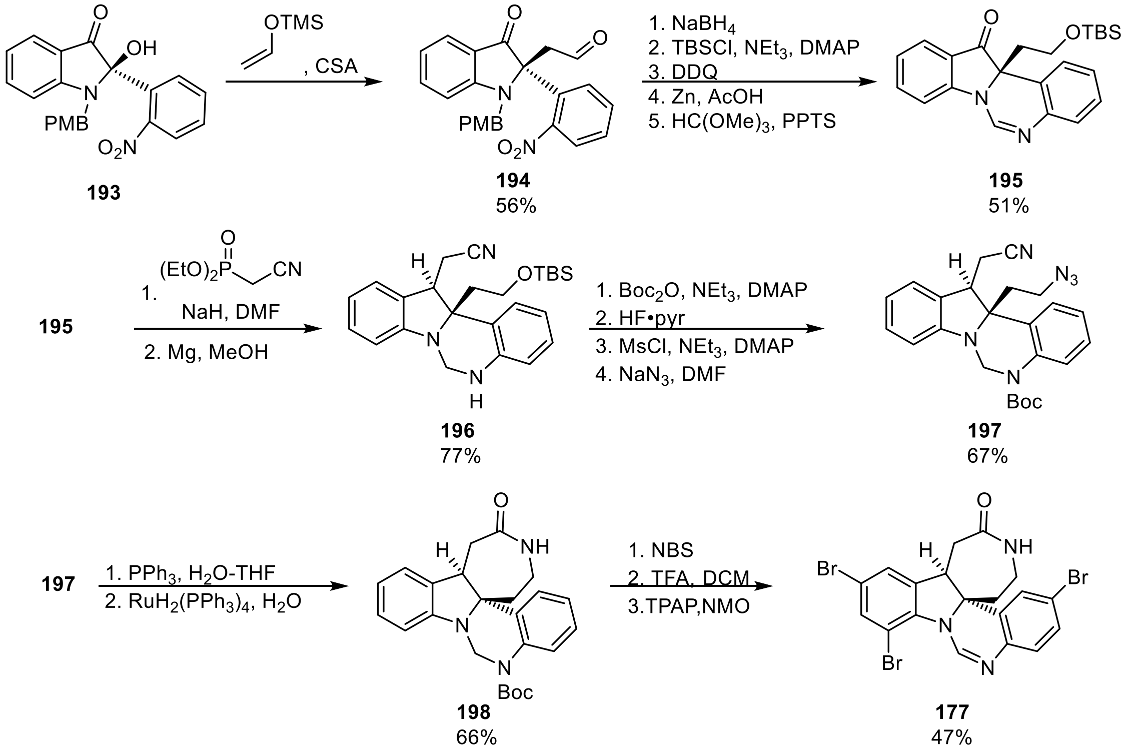
[108] Higuchi, K.; Sato, Y.; Tsuchimochi, M.; Sugiura, K.; Hatori, M.; Kawasaki, T. *Org. Lett.* **2009**, *11*, 197.

trimethylorthoformate in the presence of PPTS gave rise to dihydropyrimidine **195**. At this stage, authors focused on the formation of lactam unit, which proved to be a tricky task. Horner-Wadsworth-Emmons olefination of **195**, followed by quinazoline ring reduction, provided amine **196**, which upon protecting group manipulation and treatment with sodium azide gave rise to azide **197**. Reduction of azide **197** utilizing the Staudinger protocol and subsequent ruthenium-catalyzed amidation of the nitrile furnished the desired 7-membered lactam **198**. It is noteworthy that the formed Boc-protected tetrahydroquinazoline **198** proved to be significantly more reactive towards electrophilic bromination than dihydroquinazoline **191**, previously reported by McWhorter. Thus, treatment of **198** with NBS in a single step provided the desired tribromination of both aromatic rings. Cleavage of the Boc protecting group, followed by re-oxidation of the tetrahydroquinazoline unit provided Hinckdentine A in 19 steps with a 4% total yield.



Scheme 36. Total synthesis of Hinckdentine A by Kawasaki *et al.*

Finally, the group of prof. Fukuyama has recently demonstrated an elegant approach towards an enantioselective synthesis of (+)-Hinckdentine A (Scheme **37**). As their predecessors, they proposed that the construction of the 2,2-disubstituted indoline core presents the major challenge in this molecule. Thus, it was envisioned that it should be executed during an earlier stage of the synthesis. As an efficient route to the core of Hinckdentine, they proposed utilizing a palladium-catalyzed asymmetric dearomative Heck-type cyclization[109]. Thus, treatment of ketone **199** with $Pd_2(dba)_3$ in the presence of Feringa's phsophoramidate ligand **200** gives rise to enone **201** in 98% yield and with 86% *ee*. Attempts to involve **201** in a Beckmann rearrangement to access directly the 7-membered lactam unit led only to a complex mixture of products. As such, a stepwise approach was employed. Thus, introduction of an oxime to the α-postion of the ketone, followed by treatment with $SOCl_2$ triggered the Beckmann fragmentation, giving rise to nitrile **202**. Thorough reduction of the alkene and nitrile functionalities, followed by treatment with base furnished the desired lactam in 5 steps and with 50% yield (starting from enone **201**). At this point, the residual tasks were to install the aniline moiety, perform the tribromination and form the dihydroquinozaline ring. To achieve these tasks, the tertiary amide moiety in **203** was selectively reduced with $NaBH_4$ in THF-MeOH. The resulting primary alcohol and indole were, the alcohol was oxidized with Jones reagent to afford corresponding aldehyde, which was trapped with hydroxylamine to afford aldoxime **204**. Utilizing modified Rawal's modification of Kim's procedure, **204** was converted to the corresponding isothiocyante, which upon treatment with

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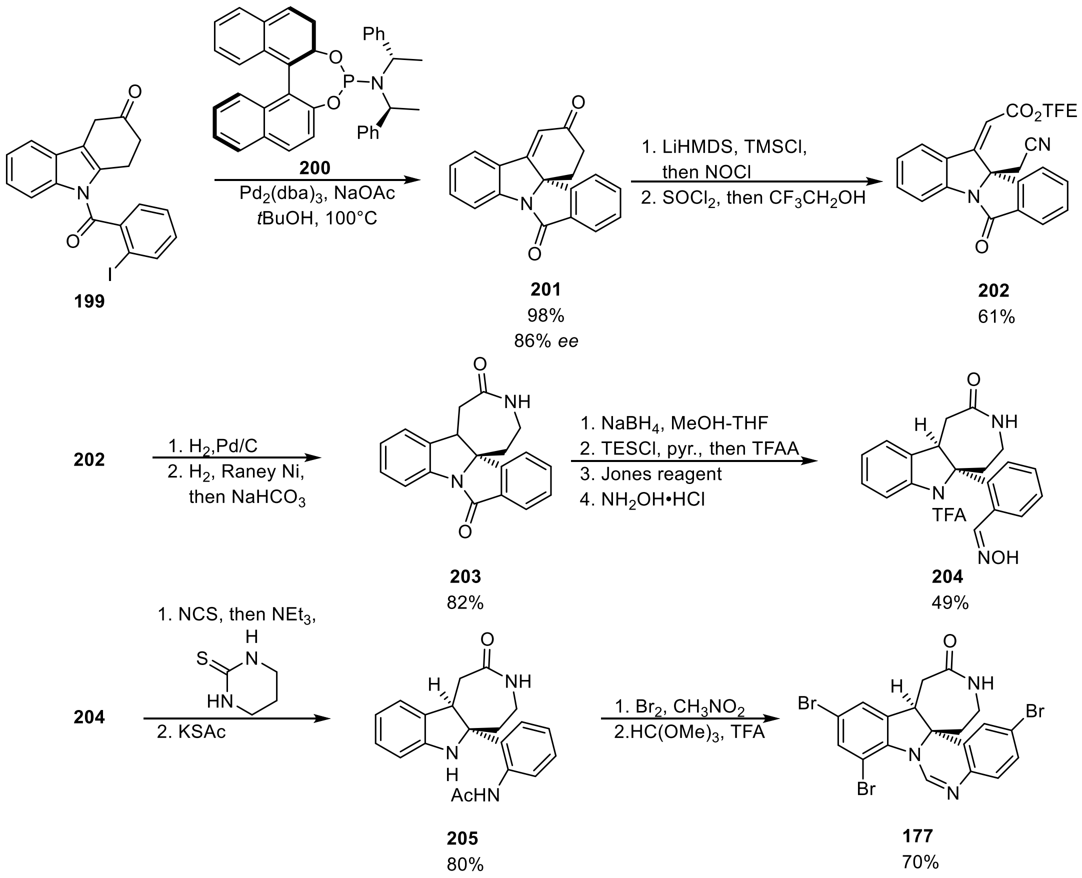
[109] For previous examples of Pd-catalyzed dearomative Heck-type cyclizations see: a) Brown, S.; Clarkson, S.; Grigg, R.; Thomas, W. A.; Sridharan, V.; Wilson, D. M. *Tetrahedron* **2001**, *57*, 1347; b) Zhao, L.; Li, Z.; Chang, L.; Xu, J.; Yao, H.; Wu, X. *Org. Lett.* **2012**, *14*, 2066; c) Petrone, D. A.; Yen, A.; Zeidan, N.; Lautens, M. *Org. Lett.* **2015**, *17*, 4838; d) Shen, C.; Liu, R.-R.; Fan, R.-J.; Li, Y.-L.; Xu, T.-F.; Gao, J.-R.; Jia, Y.-X. *J. Am. Chem. Soc.* **2015**, *137*, 4936; e) Petrone, D. A.; Kondo M.; Zeidan N.; Lautens M. *Chem.- Eur. J.* **2016**, *22*, 5684.

KSAc, followed by basic work-up, provided acetamide **205** in 50% yield over 2 steps. Bromination of **205** with Br_2 in nitromethane, followed by treatment with trimethylorthoformate in the presence of TFA completed the total synthesis of (+)-Hinckdentine A, providing the desired natural product in 14 steps and with a total of 8.8% yield starting from **199.**



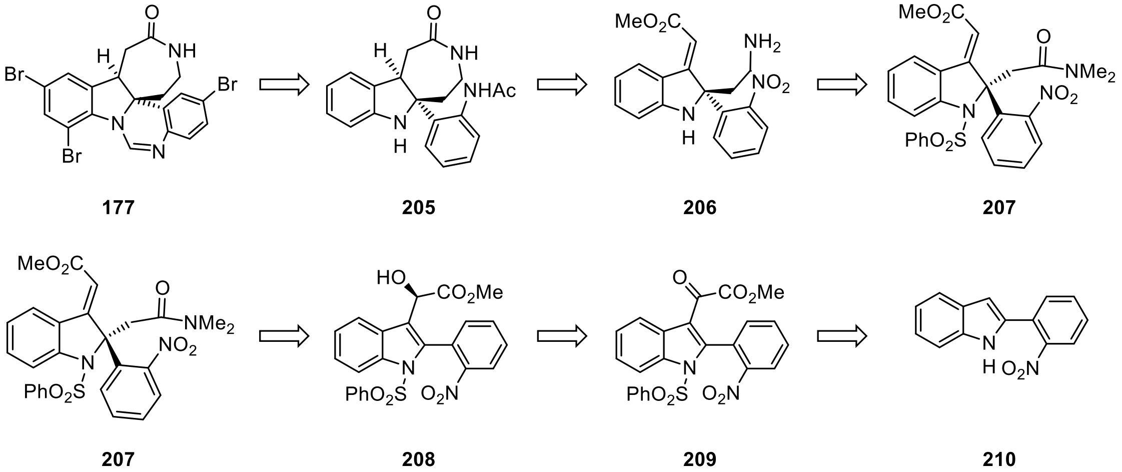
Scheme 37. Enantioselective total synthesis of Hinckdentine A by Fukuyama *et al.*

From the examples of total synthesis of Hinckdentine A completed so far, we learned that one of the key challenges associated with accessing the core structure of the molecule is the installation of the quaternary carbon at the C2 position of the indoline. We envisioned that our newly discovered indolic Claisen rearrangement could provide an elegant solution to this problem.

Section 4.2. Synthetic studies towards Hinckdentine A

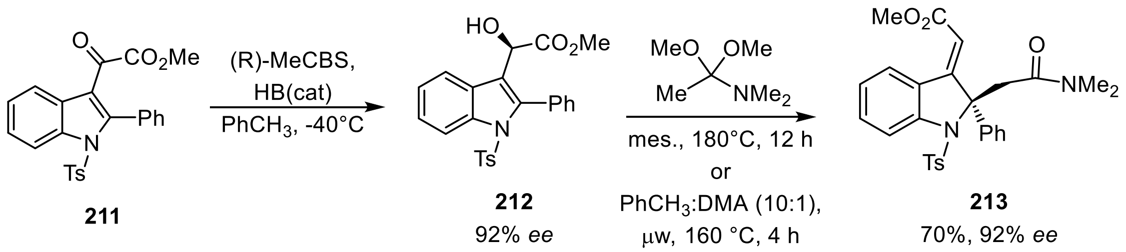
4.2.1 Proposed retrosynthesis and preliminary studies

When we approached the retrosynthesis of Hinckdentine A, we proposed that we can simplify the structure to the acetmaide **205**, previously reported by the group of Fukuyama (Scheme **38**). **205**, in turn, can be traced back to the amine **206** through a sequence of reductions and macrolactamization. Amine **206** can be prepared from amide **207** by selective reduction with Schwartz's reagent and reductive amination. Amide **207** is a product of the Meerwein-Eschnmoser-Claisen rearrangement of indole alcohol **208**, which can be prepared in enantioenriched fashion by the Corey-Bakshi-Shibata reduction of corresponding indole glyoxalate **209**. Finally, **209** can be traced back to known indole **210**.



Scheme 38. Retrosynthetic analysis of Hinckdentine A

As a model study, we prepared indole alcohol **212** in an enantioenriched manner by utilizing the CBS reduction protocol (Scheme **39**). Initial attempts to involve **212** in the Meerwein-Eschenmoser-Claisen rearrangement were not successful. Upon heating a mixture of alcohol **212** and dimethylacetamide dimethylacetal in toluene nearly no conversion of starting material was observed. Switching to a higher boiling solvent (mesitylene) and increasing the reaction temperature to 180°C proved beneficial, giving rise to the desired rearrangement product in high yield (70%) and with a complete transfer of chirality. Alternatively, microwave irradiation of the reaction mixture can be utilized to increase the reaction rate, decreasing the reaction time to 4 h. However, a significant increase in the formation of decomposition products was observed, which may be in part due to the increased polarity of the solvent media. To reach higher temperatures in the microwave reactor, the presence of polar solvent (dimethylacetamide) was required. Previously, we observed that the reaction profile is sensitive to the presence of polar solvents, which potentially can facilitate the formation of a carbocation at the benzylic position of the indole at elevated temperatures, leading to side product formation.



Scheme 39. Model substrate study toward Hinckdentine A

4.2.2 Primary synthetic efforts towards total synthesis of Hinckdentine A

Encouraged by the successful results of the model study, we directed our efforts towards the synthesis of Hinckdentitne A starting from readily available indole **210**[110]. Friedel-Crafts acylation, followed by protection of the indole nitrogen provided us with glyoxylate **214** (Scheme **40**). To our surprise, treatment of **214** with sodium borohydride to access the racemic alcohol sample resulted in the selective formation of the diol **215**. However, utilizing the conditions

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[110] Bourderioux, A.; Kassis, P.; Mérour, J.-Y.; Routier, S. *Tetrahedron* **2008**, *64*, 11012.

reported by Soai and Ookawa[111], we were able to achieve selective reduction of the ketone to provide desired alcohol **216**. It is interesting to note that alcohol **216** is formed as a 6:1 mixture of atropisomers at room temperature (configuration not determined), which are characterized by two distinct sets of peaks in the ^{1}H NMR spectrum. The equilibration between the atropismers was found to occur upon heating above 70° C.

With the alcohol in hand, we turned our attention towards identifying optimal conditions for the Meerwein-Eschenmoser-Claisen rearrangement. However, multiple attempts to perform the newly established indolic Claisen rearrangement did not succeed. Heating the alcohol **216** with dimethylacetamide dimethyl acetal in refluxing toluene under standard reaction conditions resulted only in equilibration between atropoisomers, with no trace of the desired indoline product observed. Prolonged heating gave rise to the formation of unidentified side products. Although switching the solvent to chlorobenzene and increasing the reaction temperature after a prolonged period of time (10 h) resulted in complete conversion of the starting alcohol, only an inseparable mixture of side products with no trace of indoline **217** was observed. Microwave irradiation of a solution of **216** and dimethylacetamide dimethyl acetal in a 10:1 toluene:dimethylacetamide mixture at 140°C for 4 h in a sealed microwave cuvette gave rise to multiple undesired products, with methyl *p*-toluenesulfonate being the only isolated product. The only minor success we saw was upon heating indole **216** with a large excess of dimethylacetamide dimethyl acetal (9 equivalents) in toluene in a sealed tube for 4 hours in the presence of activated 5Å molecular sieves to absorb the formed methanol. By using these reaction conditions, we were able to isolate desired product **217** in 10% yield. Prolonged heating, elevated temperatures (up to 180°C) and attempts to utilize microwave irradiation as a heating source did not lead to any improvements in the yield of

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[111] Soai, K.; Ookawa, A. *J. Org. Chem.* **1986**, *51*, 4000.

the reaction. We propose, that the difficulty in engaging **216** in a productive manner can be rationalized based on a combination of steric and electronic factors. First, the large size of the nitro group prevents free rotation of the aromatic ring around the C2-aryl single bond, thus making it difficult for the compound to achieve the chair-like transition state that is required for the Claisen rearrangement to take place. Second, previous studies of the electronic effects of substituents on the rate of Claisen rearrangements have demonstrated that the presence of an electron-withdrawing substituent at the 5 position of an allyl vinyl ether system increases the energy of the transition state, leading to the significant deceleration of the reaction[112]. Thus, the 2-nitrophenyl group as a strong electron-withdrawing group may significantly raise the energy of the transition state of the rearrangement, which in combination with steric hindrance could make the transition state difficult to access.

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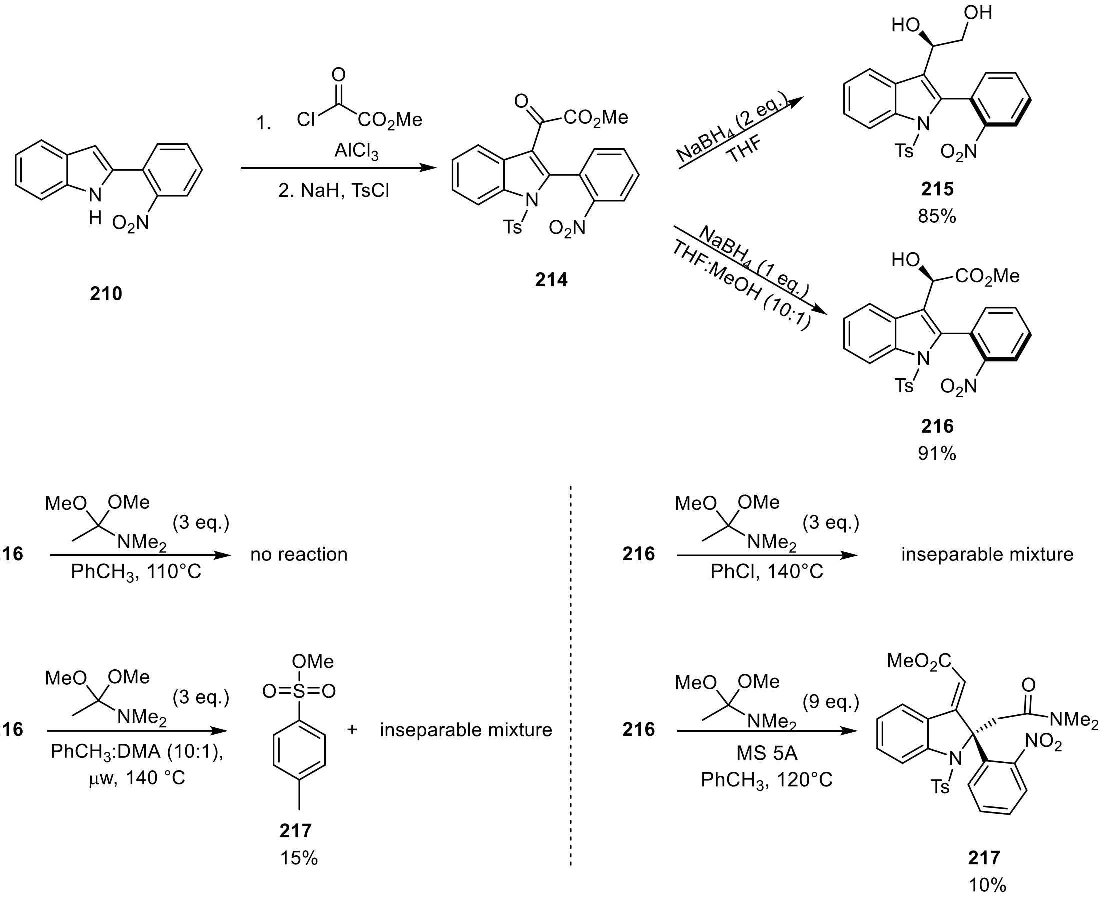
[112] a) Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6983; b) Burrows, C.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6984.



Scheme 40. Primary synthetic attempts towards the core structure of Hinckdentine A

4.2.3. Alternative strategy towards Hinckdentine A – late stage amination

Due to the difficulty of advancing 2-(2-nitrophenyl)indole, we turned our attention to alternative approaches to the synthesis of the core structure of Hinckdentine A. Since the nitro group presented serious steric and electronic issues, we decided to utilize 2-(2-bromophenyl)indole as an alternative starting point for our synthesis (Scheme **41**). We envisioned that a presence of bromine atom should not make significant influence on the electronics of the system during the rearrangement step, while providing significantly less steric bulk compared to the nitro group[113]. Following [3,3]-sigmatropic rearrangement indoline **219** would be advanced in a manner similar

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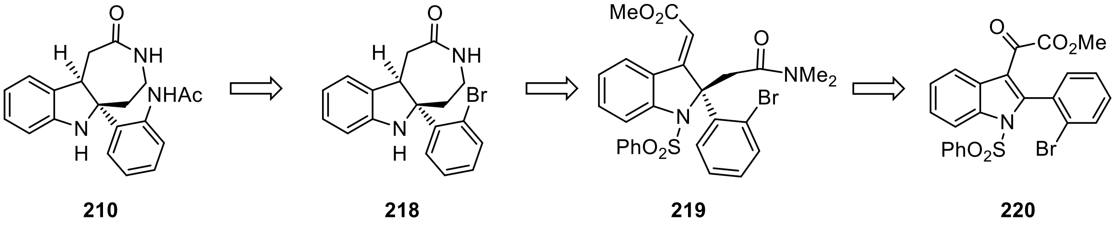
[113] As a point of comparison the A value for Br is 0.476, for NO_2 it is 1.05, see: Jensen, F. R.; Bushweller, C. H.; Beck, B. H. *J. Am. Chem. Soc.* **1969**, *91*, 344.

for nitro-indoline **217**. At a late stage of the synthesis Buchwald-Hartwig type amination[114] could give rise to desire acetamide **210**.



Scheme 41. Proposed alternative approach to amide **210**

Proceeding from 2-(2-bromophenyl)indole[115] we accessed alcohol **222** by a manner analogous that for **216**. Notably **222** did not exist as a mixture of atropisomers on the NMR timescale. To our delight, upon subjection of **222** to the standard reaction conditions ($PhCH_3$, 110°C), conversion to desired indoline **219** was observed, albeit in a very slow manner and with multiple side products formed. Upon changing the reaction conditions to heating the solution of indole and dimethylacetamide dimethyl acetal in 9:1 toluene:dimethylacetamide mixture in a sealed cuvette in the microwave reactor for 4 h at 160°C we were able to isolate desired indoline **219** in 40% yield on a 0.1 mmol scale. However, all attempts to reproduce this result on a larger scale failed. Hydrogenation of the enoate in **219** followed by chemoselective reduction of the tertiary amide in the presence of an ester using the Schwartz reagent[116] provided aldehyde **223** in 80% yield over 2 steps. Reductive amination of the aldehyde with ammonium acetate in the presence of sodium cyanoborohydride gave rise to the amine **224**, albeit in low 32% yield.

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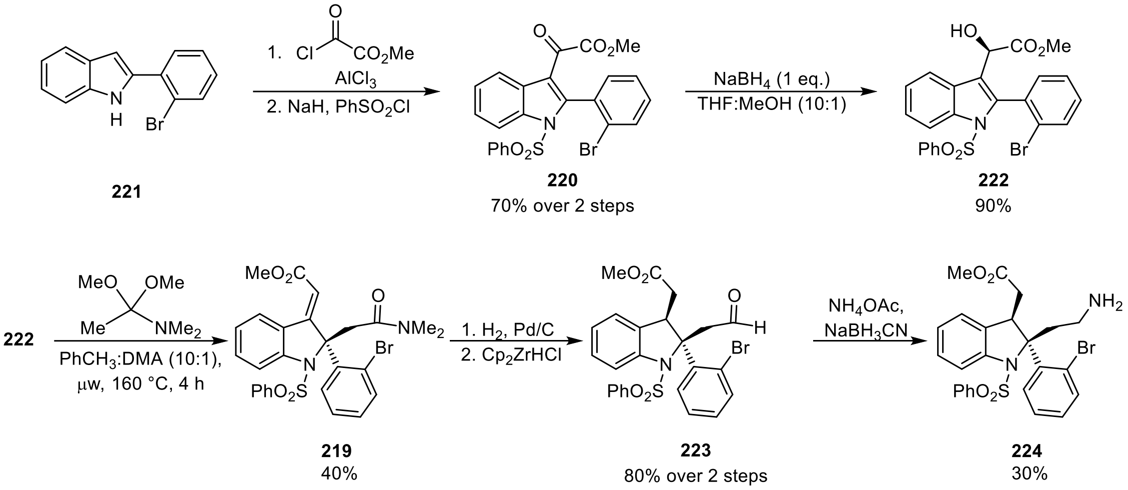
[114] a) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901; b) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969; c) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852; d) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805; e) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534.

[115] Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org. Lett.* **2003**, *5*, 3843.

[116] Zhao, Y.; Snieckus, V. *Org. Lett.* **2014**, *16*, 390.

Unfortunately, low material throughput at this point forced us to develop a more practical solution to Hinckdentine A.



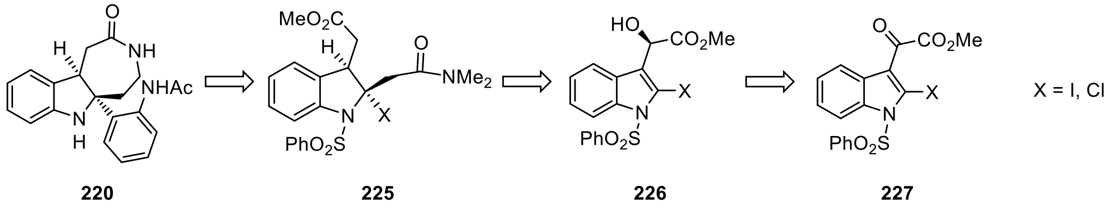
Scheme 42. Alternative approach to amide **210** utilizing 2-(2-bromophenyl)indole

Despite primary results of utilizing the 2-(2-bromophenyl)indole in the synthetic sequence looked very promising (*e.g.*, the absence of atropoisomers at room temperature as indicated by ^{1}H NMR, formation of the desired indoline **219** upon exposure to the Eschenmoser-Claisen rearrangement conditions), the scale-up of the key rearrangement step utilizing this substrate proved to be challenging, and results of the large scale reactions were not consistent. Due to these observations, we decided to pursue alternative ways to approach the desired core of Hinckdentine.

4.2.3. Alternative strategies towards Hinckdentine A – late stage Pd-coupling

Since the presence of a 2-substituted phenyl group at the C2 position of the indole proved to be an obstacle for the indolic Claisen rearrangement, potentially due to a combination of steric and electronic factors, we looked to alternative substrates containing less sterically demanding C2 substituents that would still allow for the key rearrangement step to take place. With this idea in mind, we considered whether the 2-haloindoles may be competent substrates for our rearrangement

(Scheme **43**). If successful, the C2 halide-bearing carbon was envisioned to be functionalized utilizing the chemistry developed by the groups of Fu[117] or Aggarwal[118].



Scheme 43. Proposed alternative approach to acetamide **220** utilizing 2-haloindoles

With this plan in hand, we proceeded to the synthesis of alcohols **226a** and **226b** (Scheme **44**). Starting with the known benzenesulfonyl-protected 2-haloindoles **228a** and **228b**[119], Friedel-Crafts acylation with methyl chlorooxoacetate provided ketoesters **227a** and **227b**. To our surprise, treatment of **227a** with $NaBH_4$ under previously utilized Soai conditions resulted in a complete reduction of iodide to produce the alcohol **229** in 90% yield. Having observed this high instability of the iodide moiety at the C2 position of the indole, we proposed that even if we find a mild way to produce the alcohol **226a**, the chance that it will be able to participate in the Eschenmoser-Claisen rearrangement without the loss of iodide moiety was too small to pursue. Thus, we shifted efforts towards chloroalcohol **226b**. To our delight, reduction of ketoester **227b** with $NaBH_4$ produced the desired alcohol **226b** with a very high yield (95%). However, all attempts to involve **226b** in the indolic Claisen rearrangement failed. Heating of **226b** with dimethylacetamide dimethyl acetal in toluene or in toluene-dimethylacetamide mixture resulted in the formation of complex mixtures of products, containing only trace amounts of desired indoline **225b**. Based on LCMS studies, most of the side products in these mixtures did not contain chlorine, which led us

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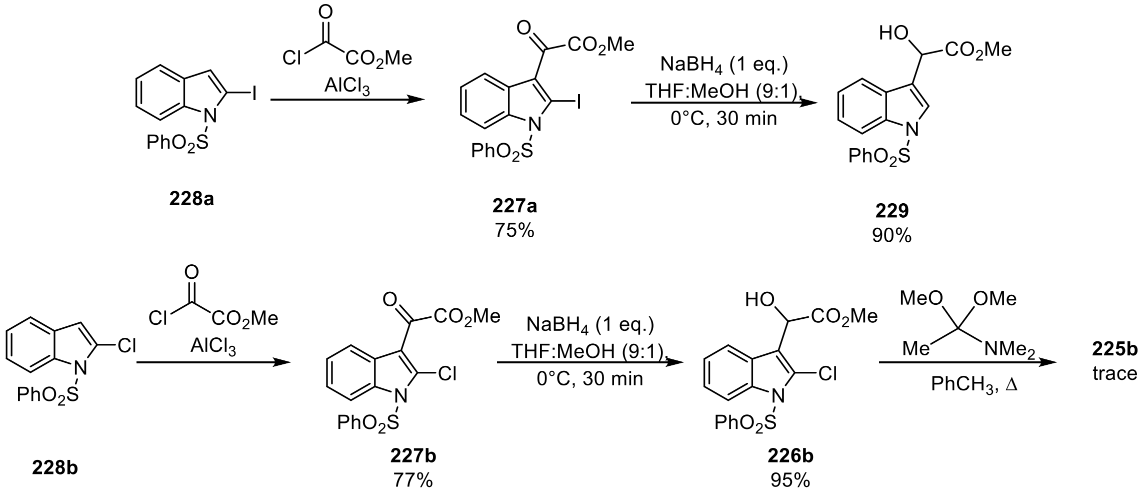
[117] Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 624.

[118] Leonori, D.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2015**, *54*, 1082.

[119] Ketcha, D. M.; Lieurance, B. A.; Homan, D. F. J.; Gribble, G. W. *J. Org. Chem.* **1989**, *54*, 4350.

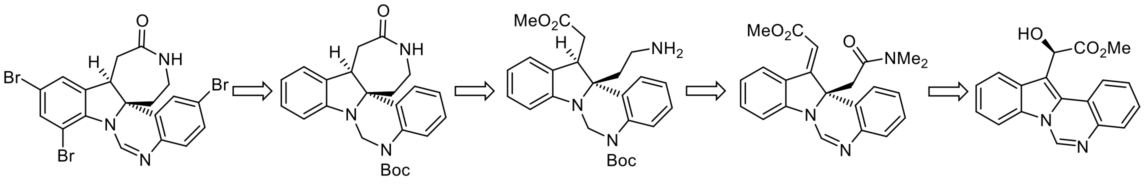
to propose, that instead of an Eschenmoser-Claisen rearrangement a Michael-type addition at the C2-carbon of the indole might be taking place, which is followed by multiple degradation pathways.



Scheme 44. Alternative approach to amide **220** utilizing 2-haloindoles

4.2.4. Alternative strategies – early construction of quinazoline core. A promising avenue toward Hinckdentine A

Discouraged by the failure of the haloindole strategy, we looked for a different strategy that would allow us to efficiently utilize the Eschenmoser-Claisen rearrangement. On the hypothesis that the failure of 2-nitrophenyl and 2-bromophenyl indoles to undergo sigmatropic rearrangement is partly due to the steric interactions, created by 2-substituted phenyl ring that prevented the system from adopting the necessary chair-like transition state, we envisioned that preventing the phenyl group from free rotation around C2 bond by binding it in a form of quinazoline prior to Indolic Claisen rearrangement can decrease the steric strain during the transition state of the rearrangement. Additionally, early construction of indolo[1,2-*c*]quinazoline core can decresase the amount of steps in the total synthesis of Hinckdentine and make it more efficient. With this in mind, we propose another alternative retrosynthetic approach (Scheme **45**), wherein Hinckdentine A is traced back to indoline **198**, as reported by Kawasaki. **198** was envisioned to arise form amine **230**, obtained by a sequence of hydrogenation and amine protection, starting from amide **231**. Amide **231** is the product of the Eschenmoser-Claisen rearrangement of alcohol **232**, which can be traced to a known indolo[1,2-*c*]quinazoline.

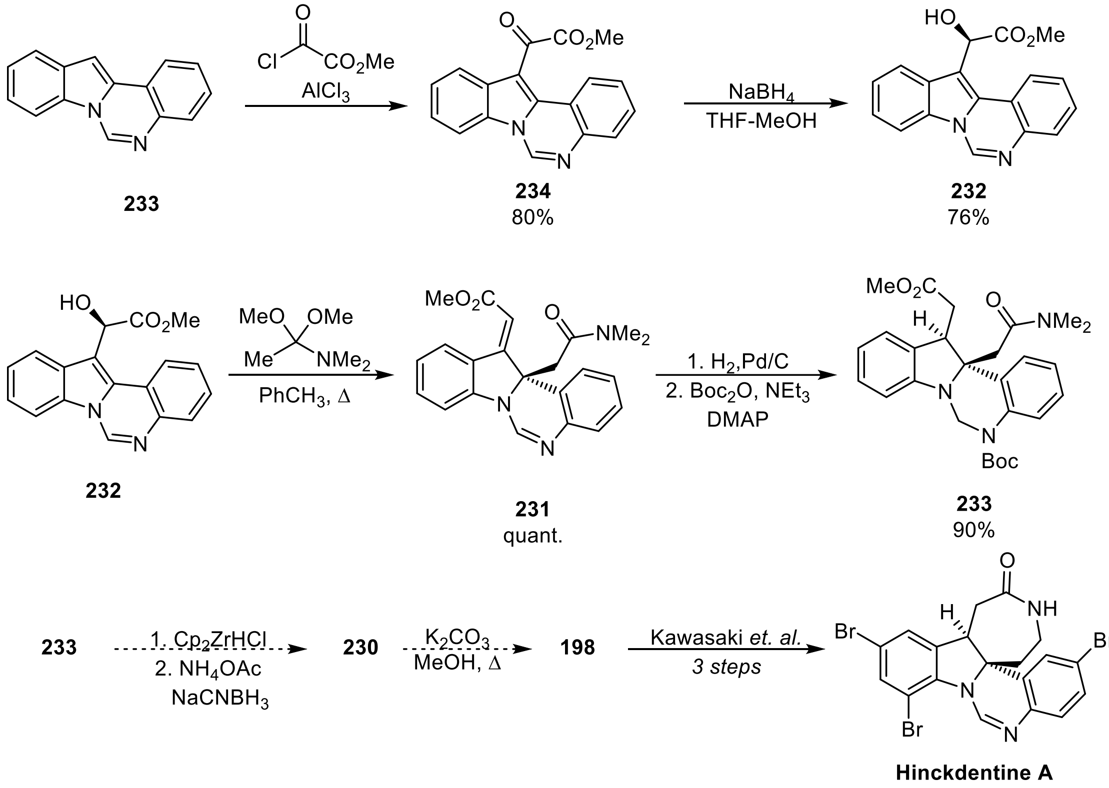


177 **198** **230** **231** **232**

Scheme 45. Proposed alternative approach to acetamide **220** from indolo[1,2-*c*]quinazoline

With this strategy in mind, we went forward with the synthesis of Hinckdentine A (Scheme **46**). Starting with commercially available indolo[1,2-*c*]quinazoline **233** (for our synthesis we prepared **233** by a 3-step procedure, as described by Cava *et. al.*), Friedel-Crafts acylation with methyl chlorooxoacetate provided ketoester **234** in 80% yield. It's interesting to note that in the synthetic studies towards Hinckdentine A, reported by the group of Cava, researchers noted that treatment of indolo[1,2-*c*]quinazoline **233** with the strong acylating agent oxalyl chloride in the absence of Lewis acid catalyst resulted in the complete regeneration of starting material, and only Vilsmeier-Haack formylation allowed the authors to access the desired substitution at C3 of the indole portion of compound **233**. Treatment of ketoester **234** with $NaBH_4$ provided alcohol **232.** Attempts to utilize a Corey-Bakshi-Shibata asymmetric reduction protocol have been fruitless to date, perhaps due to the Lewis basicity of the quinazolidine nitrogen. To our great delight, heating of alcohol **232** with dimethylacetamide dimethyl acetal in toluene at 120°C over 4 hours resulted in complete conversion of starting alcohol, providing key amide **231** in quantitative yield. Hydrogenation of **231** over Pd on carbon followed by Boc protection of the secondary amine provided amine **233** as a single diastereomers (the configuration was established based on the NOESY correlations).

Chemoselective reduction of the tertiary amide with Schwartz reagent followed by reductive amination and macrolactamization would then furnish the amide **198**, previously described by Kawasaki *et. al.* in their total synthesis of Hinckdentine A. Based on their report, bromination of **198** with bromine, followed by N-Boc group deprotection and oxidation will furnish the desired Hinckdentine A.



Scheme 46. Potential route to a formal synthesis of Hinckdentine A

Section 4.3. Concluding Remarks

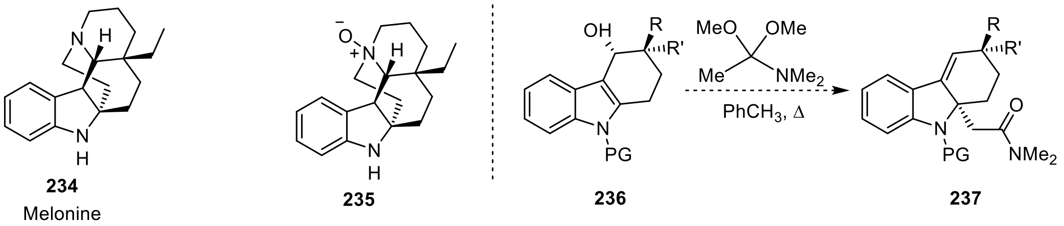
In conclusion, the successful application of our newly developed indolic Claisen rearrangement may permit a formal synthesis of *rac*-Hinckdentine A in 11 steps from a commercially available indolo[1,2-*c*]quinazoline. Future studies will investigate the asymmetric reduction of ketone **234** so as to provide access to enantioenriched Hinckdentine A.

Chapter 5.

Synthetic Studies Towards Melonine

Section 5.1. Introduction.

As another synthetic target for the demonstration of our newly developed Meerwein-Eschenmoser-Claisen rearrangement we chose the pentacyclic alkaloid Melonine (**234**) (Scheme **47**), isolated in 1982, along with its oxidized form **235**, from *Melodinus celastroides* Baill.[120], an endemic plant from New Caledonia.



Scheme 47. Melonine. Proposed key transformation.

Over the past 40 years, the plants of the *Melodinus* genus, which is a part of the large Apocynaceae family, have been under the intense focus of natural product isolation chemists due to their extensive use in traditional folk medicine as a treatment of meningitis in children, rheumatic heart diseases, and diuresis, as well as its use a decongestive against migraine and sinusitis. These efforts resulted in the isolation of more than 263 unique compounds, most of which belong to the kopsinine, tabersonine, aspidospermidine and eburnamine families of natural products[121]. Among others, Melonine possesses a unique alkaloid framework, potentially

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[120] Baassou, S.; Mehri, H. M.; Rabaron, A.; Plat, M. *Tetrahedron Lett.* **1983**, *24*, 761.

[121] Jiang, J.-H.; Zhang, W.-D.; Chen, Y.-G. *Tropical Journal of Pharmaceutical Research* **2015**, *14*, 2325

originated from the aspidospermane series of alkaloids. Despite there being no studies of its biological activity reported to date, which in part may be due to the small amount of substance isolated from the natural source, related aspidospermidine alkaloids possess antitumor and anti-inflammatory effects, and have been shown to reverse chloroquine resistance during *in vitro* studies with several malaria protozoa species[122]. The unique rigid pentacyclic indoline skeleton of Melonine, possessing 4 contiguous stereogenic centers, has drawn our attention from the synthetic point of view. We envisioned that our newly developed indolic Claisen rearrangement could provide an efficient tool to install the stereocenter on the C2 position of indoline, leading to useful intermediate **237**, which can be transformed into melonine in several synthetic steps. Since no total synthesis of melonine or similar compounds have been reported to date, we decided to proceed with the synthesis of this unique alkaloid.

Section 5.2. Synthetic studies towards Melonine.

5.2.1 Proposed retrosynthesis and preliminary studies

Our initial retrosynthetic analysis of Melonine is outlined in Scheme **48**. We proposed that we can access the penatcyclic skeleton of the alkaloid by intramolecular anionic[123] or transition-metal catalyzed[124] anti-Markovnikov hydroamination, starting from amine **238. 238** can be

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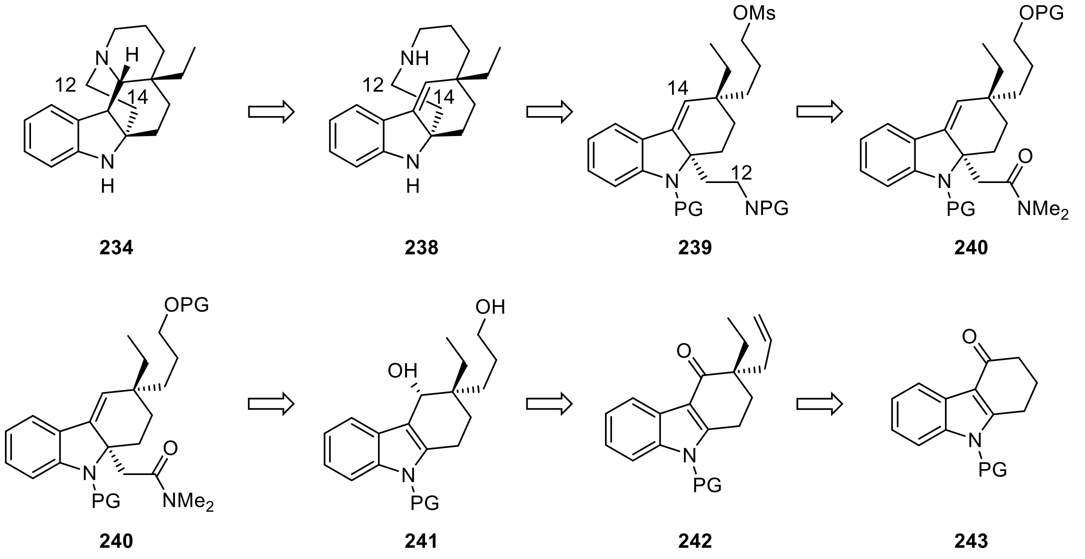
[122] Rasoanaivo, P.; Martin, M.-T.; Guittet, E.; Frappier, F. New Contributions to the Structure Elucidation and Pharmacology of Strychnos Alkaloids. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Bioactive Natural Products; Elsevier, Amsterdam, 2002; Vol. 26, pp 1029–1072.

[123] a) Dauphin, G.; Jamilloux, B.; Kergomard, A.; Planat, D. *Tetrahedron* **1977**, *33*, 1129; b) Vasilevsky, S. F.; Mikhailovskaya, T. F.; Mamatyuk, V. I.; Salnikov, G. E.; Bogdanchikov, G. A.; Manoharan, M.; Alabugin, I. V. *J. Org. Chem.* **2009**, *74*, 8106; c) Kleine, T.; Bergander, K.; Fröhlich, R.; Wibbeling, B.; Würthwein, E.-U. *J. Org. Chem.* **2011**, *76*, 1979.

[124] a) Takemiya, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 6042; b) Nguyen, T. M.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2013**, *135*, 9588.

accessed through the macrocyclization reaction from amine **239**, which can be traced back to the amide **240**. Amide **240** presents a product of the Meerwein-Eschenmoser-Claisen rearrangement of alcohol **241**, which can be derived from ketone **242** by a sequence of alkene hydroboration-oxidation and ketone reduction. **242** can be prepared from commercially available carbazolone **243** in a chiral fashion by a known route[125].



Scheme 48. Retrosynthetic analysis of Melonine

As a test if our indolic Claisen rearrangement can be applied to the chiral carbazolone-derived alcohols to construct corresponding 2,2-disubstituted indolines in a chiral fashion with the desired configuration of chiral center, we prepared model substrate **245** in enantioenriched fashion by employing the Corey-Bakshi-Shibata protocol (Scheme **49**). To our delight, after some screening of the reaction conditions, we identified that heating alcohol **245** with 6 equivalents of

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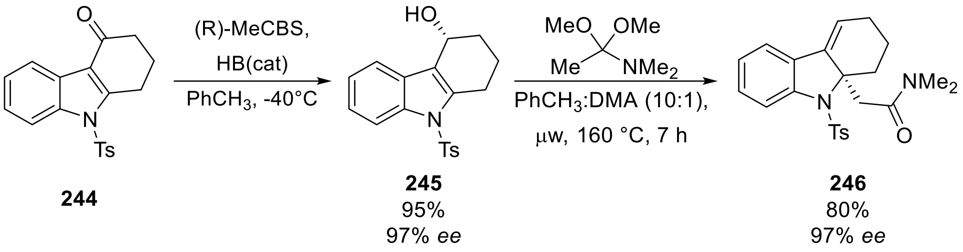
[125] Similar carbazolones were prepared by groups of Lupton and She: a) Gartshore Christopher J.; Lupton David W. *Angew. Chem., Int. Ed.* **2013**, *52*, 4113; b) Gartshore, C. J.; Lupton, D. W. *Aust. J. Chem.* **2013**, *66*, 882.; c) Li Zeqian; Zhang Shaoxiong; Wu Shoutao; Shen Xiaolei; Zou Liwei; Wang Fengqun; Li Xiang; Peng Fangzhi; Zhang Hongbin; Shao Zhihui. *Angew. Chem., Int. Ed.* **2013**, *52*, 4117; d) Zhang, S.-X.; Shen, X.-L.; Li, Z.-Q.; Zou, L.-W.; Wang, F.-Q.; Zhang, H.-B.; Shao, Z.-H. *J. Org. Chem.* **2013**, *78*, 11444; e) Jing, P.; Yang, Z.; Zhao, C.; Zheng, H.; Fang, B.; Xie, X.; She, X. *Chem.—Eur. J.* **2012**, *18*, 6729.

dimethylacetamide dimethylacetal in a mixture of 10:1 toluene:dimethylacetamide in a microwave reactor at 160°C over 7 hours gave rise to the desired indoline **246** in high yield and with complete chirality transfer.



Scheme 49. Model substrate study

5.2.2 Primary attempts towards synthesis of Melonine

With the encouraging results from model substrate studies in hand, we proceeded towards the total synthesis of melonine. Starting from commercially available carbazolone **247**, indole protection, followed by deprotonation of the α-position of the ketone and treatment of it with allyl chloroforamte, and alkylation of the resulting β-ketoester with ethyl iodide produced compound **248**. As was previously reported by the groups of Lupton and She, by utilizing the enantioselective Tsuji-Trost allylation, developed by the Stoltz group, [126] we were able to access the desired ketone **249** in 92% yield and with 95:5 *er* based on the chiral HPLC. To our great delight, this short reaction sequence was easy to scale up, and we were able to produce the ketone **249** on a multigram scale in a single run. Having ketone **249** in hand, we went forward to convert it to the diol **253**, which, after the selective protection of the primary alcohol, was then exposed to Eschenmoser-Claisen rearrangement conditions. We proposed that we can access the diol **253** starting from

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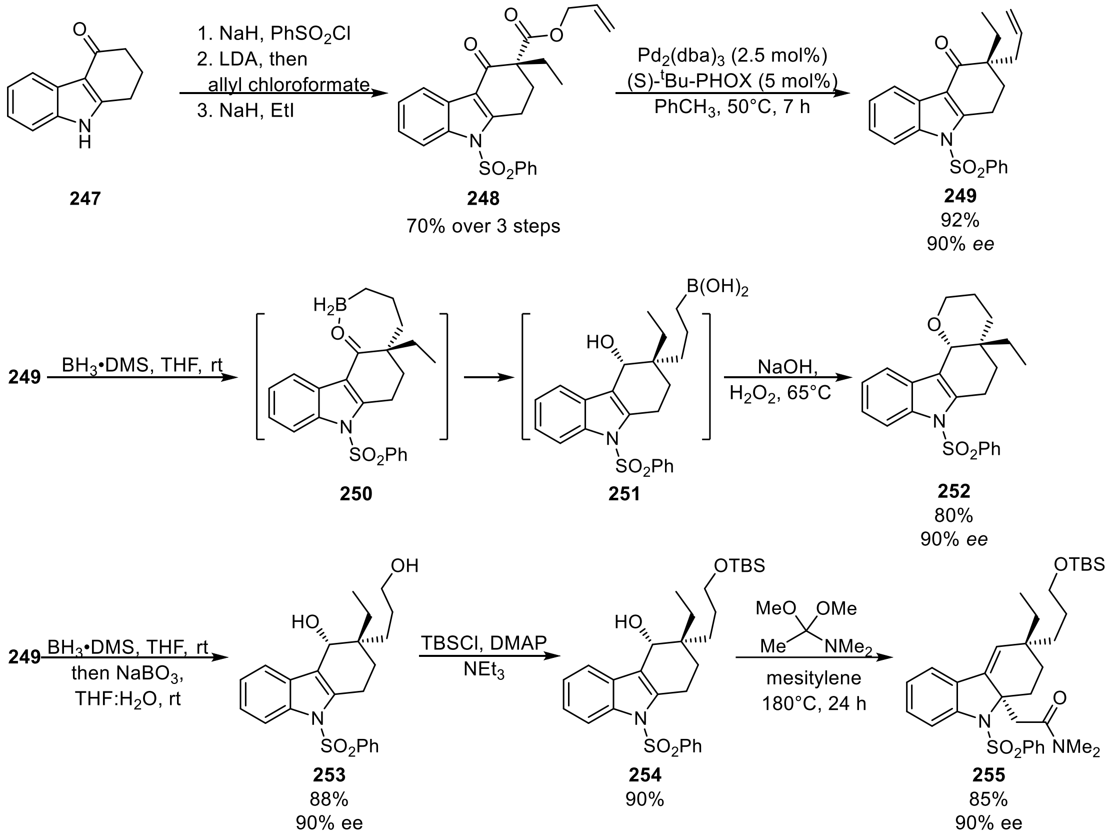
[126] a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044; b) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz B. M *Angew. Chem., Int. Ed.* **2005**, *44*, 6924; c) Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard, W. A. *J. Am. Chem. Soc.* **2007**, *129*, 11876.

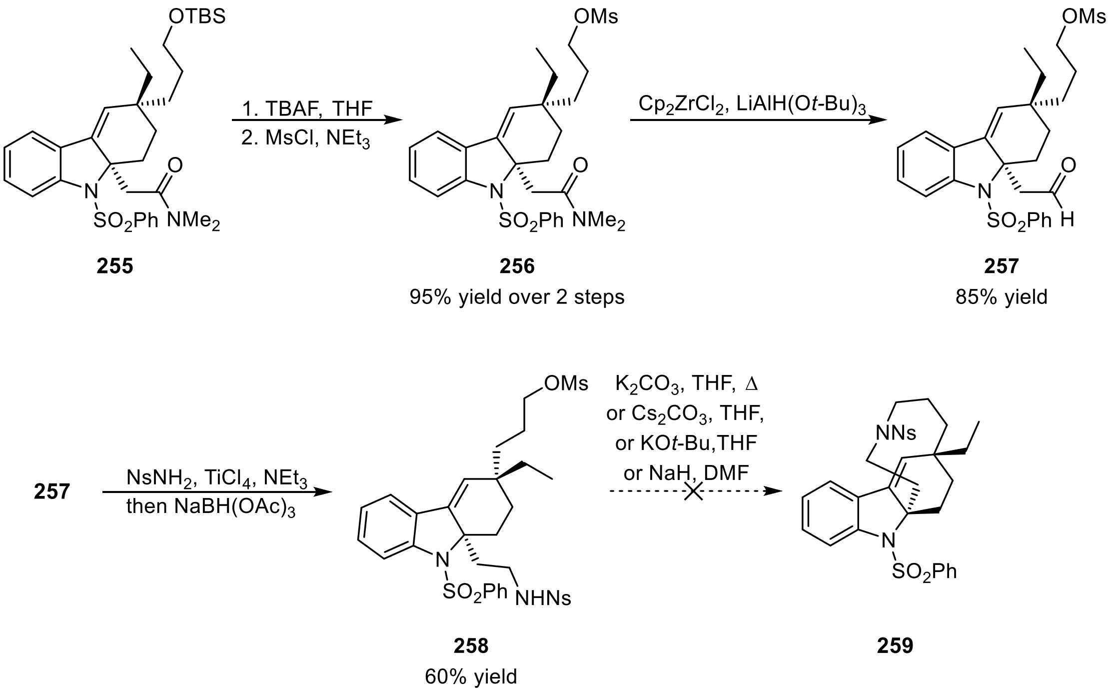
alkene **249** by a sequence of double bond oxidation – hydroboration, followed by diastereoselective reduction of ketone with a bulky reducing agent. However, when we tried to hydroborate the terminal double bond under mild conditions to prevent the reduction of the ketone to occur, we were faced with an unexpected complication: the alkene proved to be resistant to regular selective hydroboration conditions (9-BBN, rt to reflux; HB(cat), $HBCy_2$ (5 mol%); HB(cat), $RhPPh_3Cl$(10 mol%)), with no hydroboration observed under these conditions even after prolonged periods of time (up to 48 h). However, to our great surprise, upon treatment of alkene **249** with 1 equivalent of borane-tetrahydrofuran complex at 0°C, within 1 hour we observed full conversion of **249** to alcohol **251**. Based on the ^1H NMR of the reaction mixture, the resulting alcohol was the only product formed; moreover, it was formed as a single diastereomer. The exclusive diastereoselectivity of the reduction can be explained by the formation of a seven-membered borocyclic intermediate **250**, where the β-face of the ketone is blocked from the attack. Thus, the hydride from another molecule of borane gets selectively delivered from the α-face of the molecule, providing corresponding alcohol **251** as a single diastereomer. However, regular oxidative treatment of the borane **251** with hydrogen peroxide in the presence of NaOH gave rise to cyclic ether **252** as the only isolated product. Configuration of **252** was confirmed by NOESY studies. We proposed that under listed conditions formation of the desired alcohol **251** takes place, which upon heating forms a benzylic carbocation that gets attacked by the primary alcohol to form the cyclic ether. Utilizing of the milder oxidative conditions ($NaBO_3$, H_2O, rt) prevented the side product formation, giving rise to the desired diol in 88% yield as a single diastereomer (configuration was confirmed by NOESY). Protection of the primary alcohol, followed by treatment with dimethylacetamide dimethyl acetal in mesitylene at 180°C over 24 h gave rise to the desired amide **255** in 85% yield with complete transfer of chirality. Higher reaction temperature, compared to the standard reaction conditions, was required to overcome the steric hindrance of the substrate. Attempts to run the reaction in a mesitylene:dimethylacetamide (10:1) solvent mixture in a microwave reactor resulted in a significantly lower yield due to unidentified side products formation, potentially arising from the dehydration of the alcohol and formation of benzylic carbocation, followed by different rearrangement and degradation pathways.



Scheme 50. Synthesis of the 2,2-disubstituted indoline **255.**

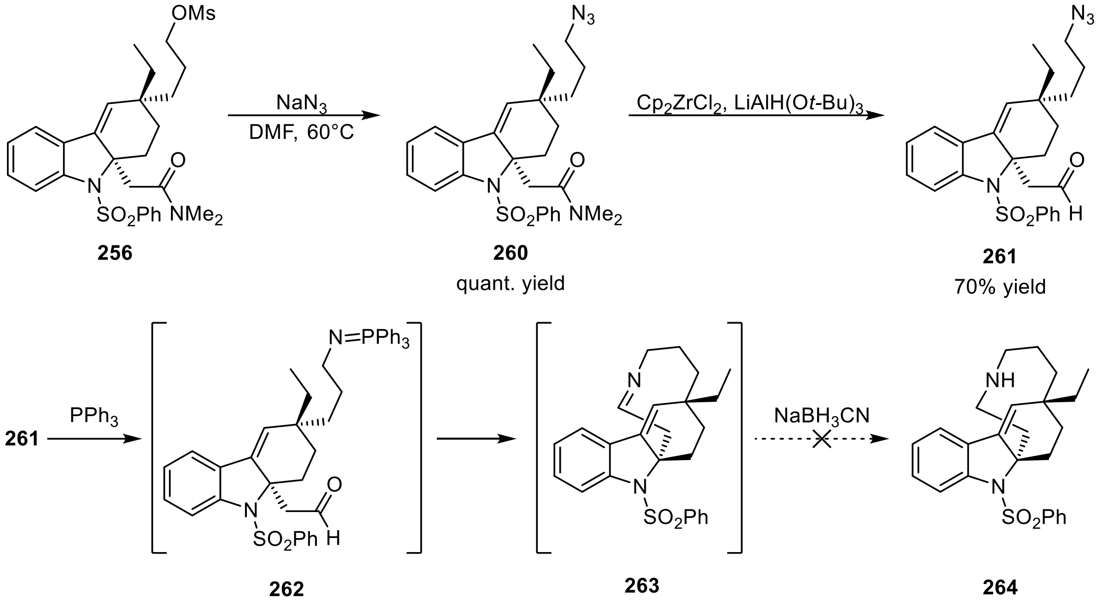
With the key amide **255** in hand, we proceeded further to the construction of the 10-membered cyclic amine fragment (Scheme **51**). Deprotection of the alcohol by treatment with TBAF, followed by mesylation provided intermediate **256**. Treatment of **256** with the in situ generated Schwartz reagent, followed by reductive amination with *p*-nitrobenzenesulfonamide gave rise to the amine **258**. However, all efforts to construct the 10-membered ring by intramolecular nucleophilic amination of compound **258** failed – upon treatment of a highly dilute

(0.001 M) solution of **258** with various bases (K_2CO_3, Cs_2CO_3, KO*t*-Bu, *etc.*) no reaction occurred, even after prolonged heating. Treatment with NaH in DMF led to a slow elimination of mesylate, giving rise to corresponding alkene, with no trace of the desired cyclic product.



Scheme 51. Attempts to synthesize the macrocyclic fragment by nucleophilic amination**.**

Having experienced difficulties with the nucleophilic amination strategy to construct the desired 10-membered ring, we decided to utilize an alternative approach to close this ring fragment (Scheme **52**). We decided to try a cascade of Staudinger amination – aza-Wittig olefination to approach the key macrocyclic fragment. Thus, treating the mesylate **256** with NaN_3 provided azide **260** in quantitative yield. Reduction of **260** with Schwartz reagent provided aldehyde **261**, which was treated with PPh_3 or PMe_3 to trigger the Staudinger - aza-Wittig cascade. However, even under high dilution conditions, only side products, among which multiple oligomerized products, were observed. No traces of the desired amine **264** were observed by NMR or LCMS.



Scheme 52. Attempts to synthesize the macrocyclic fragment through Staudinger-Wittig cascade.

5.2.3 Alternative approach towards synthesis of Melonine

Having trouble with the construction of the 10-membered macrocyclic fragment, we aimed for a different approach to synthesize the last two rings of Melonine (Scheme **53**). We proposed that instead of the tricky construction of the C12-N bond, followed by the late stage construction of the C14-N bond, we can construct the C14-N bond first, creating a 6-membered ring through Brown amination[127], followed by nucleophilic closure of the last 6-membered ring.

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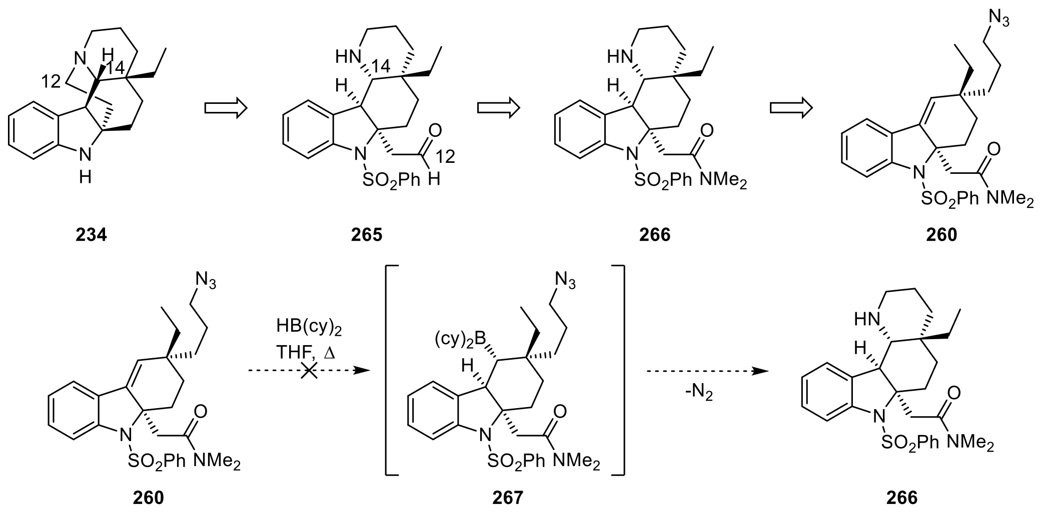
[127] a) Brown, H. C.; Heydkamp, W. R.; Breuer, E.; Murphy, W. S. *J. Am. Chem. Soc.* **1964**, *86*, 3565; b) Matteson, D. S.; Kim, G. Y. *Org. Lett.* **2002**, *4*, 2153.

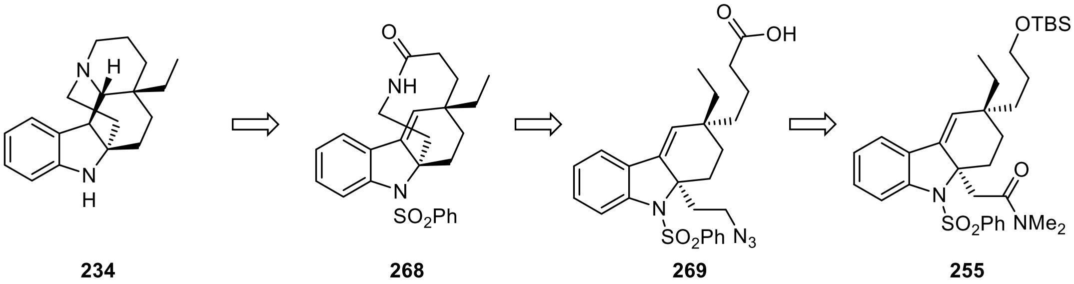


Scheme 53. Alternative retrosynthetic strategy towards Melonine.

However, we were never able to bring this alternative plan to work. The double bond in compound **260** proved to be too sterically hindered to be hydroborated under a variety of conditions (9-BBN; HB(cat) with $Rh(PPh_3)_3Cl$; $HB(cy)_2$; BH_3•THF, etc.) (Scheme **53**). In most conditions the compound was recovered intact after 48 h of heating. In case when $HB(cy)_2$ was used, very slow reduction of the azide to an amine upon refluxing in THF was observed. With BH_3•THF reduction of azide was quite facile at room temperature, leading to the complete conversion of **260** to the corresponding primary amine, with no traces of the cyclized product.

5.2.4 Latest efforts towards the total synthesis of Melonine

After experiencing no success in functionalizing the double bond and creating small, 6-membered rings one by one, we returned to our studies on macrocyclizaion efforts. Since regular nucleophilic amination and Staudinger-aza-Wittig strategies never worked in our hands, we envisioned that we can have more success with the macrolactamization strategy (Scheme **54**). We proposed that we can form the macrocycle by Staudinger-Vilarrasa reaction[128] from the carboxylic acid **269**, which in can be traced back to the amide **255**.



Scheme 54. Alternative retrosynthetic strategy towards Melonine utilizing macrolactamization

Going forward with the synthesis, treatment of amide **255** with lithium triethylborohydride[129] furnished alcohol **270**, which was converted to the azide **271** in 2 steps with a total of 80% yield (Scheme **55**). Deprotection of the primary alcohol, followed by oxidation, provided carboxylic acid **269**, which upon exposure to the conditions reported by Vilarrasa *et. al.* provided desired macrolactam **269** only in a very small (>15%) yield, along with other products. Reduction of the amide with lithium aluminum hydride furnished the desired amine **264**, albeit in small (3 mg) quantities. First attempts to finish the construction of the polycyclic framework of the Melonine by treatment with catalytic amount of *sec*-BuLi at -78°C to 0°C returned only the recovered starting material. As a future prospect, we're planning on trying multiple methods to construct the final ring juncture, including anioinic cyclization, radical cyclization and transition metal-catalyzed C-N bond formation

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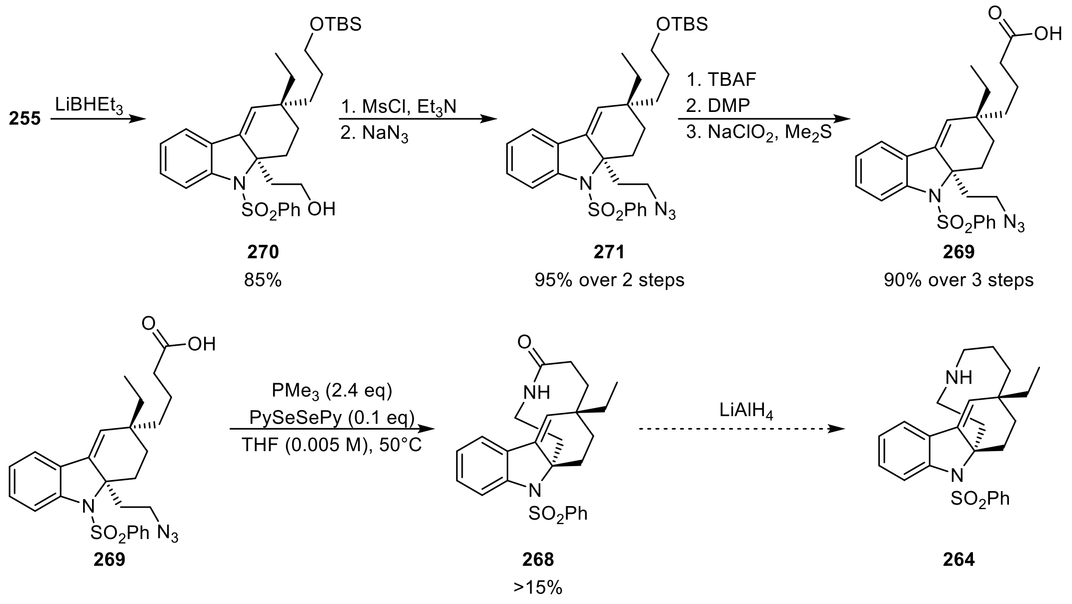
[128] Burés, J.; Martín, M.; Urpí, F.; Vilarrasa, J. *J. Org. Chem.* **2009**, *74*, 2203.
[129] Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1.



Scheme 55. Attempts to complete the total synthesis of Melonine

5.3. Concluding Remarks

As a result, we were able to synthesize the complex tetracyclic framework of the natural product Melonine in 14 steps from the commercially available carbazolone, utilizing our newly developed Indolic Claisen rearrangement. At the present moment we were not able to succeed in the key ring-closing step to finish the total synthesis of melonine. Presently we are working on exploring more methods to complete the final C-N bond formation, including radical, anioinic and transition-metal catalyzed bond forming reactions. Execution of this final synthetic step will allow us to finish the total synthesis of Melonine and compare it with the previously reported sample, derived from the natural sources.

Chapter 6.

Experimental section

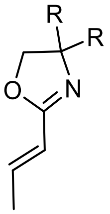
6.1. General information

Unless stated otherwise, reactions were performed under a N_2 atmosphere using flame- or oven-dried glassware and stir bars. Ambient temperature refers to 22-26 °C. Higher than ambient temperatures were maintained using pre-heated oil baths. Lower temperatures were maintained using the following Dewar baths: acetone/$CO_{2(s)}$ (−78 °C), MeCN/$CO_{2(s)}$ (−40 °C) and water/ice (0 °C) baths. Dichloromethane, tetrahydrofuran, and toluene (all of Optima® grade) and dimethylformamide (Certified ACS grade) were purchased from Fisher Scientific and dried by passage through an activated alumina column solvent purification system (Innovative Technology Inc. Pure Solv^{TM}). Benzene (anhydrous, 99.5%) was purchased from Sigma Millipore and used as received. Commercially obtained reagents were used as received, unless stated otherwise NaHMDS (1M in THF), *n*-Butyllithium, *sec*- Butyllithium were purchased from Sigma-Aldrich and titrated using menthol/2,2′-bipyridine

Reactions and compounds were visualized on EMD Millipore silica gel 60 Å F254 plates by UV fluorescence quenching (254 nm), I_2/SiO_2, PMA, or Seebach's stain. Flash column chromatography was performed on SiliCycle SiliaFlash P60 (40-63 μm particle size) using ACS or HPLC grade solvents purchased from Fisher Scientific. ^{1}H and ^{13}C NMR spectra were measured on Bruker DRX-500, DMX-500 and DMX-400 spectrometers (at 500 MHz and 125 MHz or at 400 MHz and 100 MHz respectively) at 294-300 K. ^{1}H spectra were calibrated from internal standard TMS (δ 0.0) or solvent resonance ($CHCl_3$: 7.26, C_6D_6: 7.16, CD_2Cl_2: δ 5.32, CD_3CN: δ 1.94). ^{13}C spectra were calibrated from solvent resonance ($CDCl_3$: δ 77.00, C_6D_6: δ 128.06, CD_3CN: δ 118.26). NMR data are reported as: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), and integration). ^{13}C chemical shifts arising from ^{37}Cl/^{35}Cl isotope effects are indicated in parentheses. High-resolution mass spectral analysis was measured on an Agilent Technologies 6224 TOF LC/MS (electrospray ionization). IR spectra were measured on Nicolet 6700 FTIR spectrometer and are reported as frequency of absorption (cm^{-1})

6.2. Experimental procedures and characterization data for chapter 2

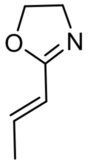
General procedure for the synthesis of oxazolines



109a, R = H
109b, R = Me

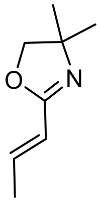
A 50 mL recovery flask equipped with a Teflon-coated magnetic stir bar was charged with DCM (20 ml) and crotonoyl chloride (1.9 ml, 20 mmol). Resulting solution was cooled to 0°C by means of ice water bath, and the solution of ethanolamine (2.6 ml, 44 mmol) (for **109a**) or 2-amino-2-methyl-1-propanol (4.2 ml, 44 mmol) (for **109b**) in DCM (5 ml) was added dropwise other 20 min (Note: the reaction is highly exothermic, and significant pressure can build if the addition is too rapid). Resulting slurry was warmed to room temperature and stirred at ambient temperature. After 1 hour the slurry was filtered through celite, the filtrate was washed with $NaHCO_3$ (aq.) (2x30 ml), organic phase was separated, dried over Na_2SO_4 and concentrated under reduced pressure to provide crude amides **108a** and **108b**, essentially pure based on ^{1}H NMR.

The crude amide was dissolved in THF (4 ml), PPh_3 (6.0 g, 21 mmol) was added to the resulting solution, and the resulting mixture was cooled to 0°C by means of ice water bath. Diisopropyl azodicarboxylate (4.1 ml, 21 mmol) was dropwise added to the mixture, the resulting dark-red solution was stirred at 0°C for 15°min, the ice water bath was removed, and the mixture was stirred at ambient temperature over 1 hour. The resulting mixture was diluted with Et_2O (30 ml) and kept at -20°C over 8 h, during which significant amounts of white precipitate of triphenylphosphine oxide formed. Resulting slurry was filtered through the celite, the filter cake was washed with 1:1 Hexanes:Et_2O mixture, the solvent was evaporated under the reduced pressure. Resulting slurry was redissolved in 1:1 Hexanes:Et_2O (30 ml), filtered through celite, and the solvent was evaporated under the reduced pressure. Residue was distilled under reduced pressure in short path distillation apparatus to provide the desired oxazolines **109** as colorless oils.



109a

Colorless oil, m=1.44 g (65% yield). B. p. , ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.59 (dq, *J* = 15.8, 7.0 Hz, 1H), 6.01 (d, *J* = 15.8 Hz, 1H), 4.26 (dd, *J* = 14.0, 4.9 Hz, 2H), 3.90 (dd, *J* = 14.0, 4.9 Hz, 2H), 1.87 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.8, 119.0, 66.9, 54.6, 18.2; IR (Neat film): 3412, 1674, 1644, 1613, 1482, 1444, 1378, 1368, 1000 cm^{-1}; HRMS (ES) calcd for $C_6H_{10}NO$ $[M+H]^+$: 112.0762, found 112.0803

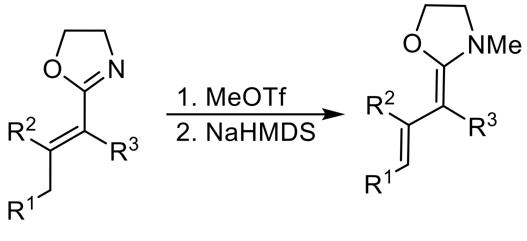


109b

Colorless oil, m=2.04 g (74% yield). B. p. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.57 (dd, *J* = 7.0, 1.0 Hz, 1H), 5.95 (d, *J* = 15.5 Hz, 1H), 3.95 (s, 2H), 1.87 (d, 3H, *J* = 7.0 Hz), 1.29 (s, 6H). ^{13}C

NMR (125 MHz, $CDCl_3$): δ 161.3, 138.6, 119.3, 78.6, 66.9, 28.3, 18.2; IR (Neat film): 3072, 1665, 1464, 1449, 1266, 1161, 1142, 1033, 1001 cm^{-1}; HRMS (ES) calcd for $C_8H_{14}NO$ $[M+H]^+$: 140.1075, found 140.1068.

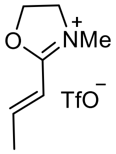
General procedure for the synthesis of oxazolinebutadienes (General procedure A)



109a-b
122a-e

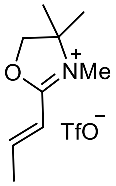
111a-b
122a-e

A 50 mL recovery flask equipped with a Teflon-coated magnetic stir bar was charged with Et_2O (10 ml) and corresponding oxazoline (10 mmol). Resulting solution was cooled to -40°C, and MeOTf (1.2 ml, 11 mmol) was added dropwise other 20 min. Resulting slurry was warmed to room temperature and stirred at ambient temperature for 1 h, during which the white crystalline precipitate formed. After 1 hour the solvent was decanted, and the crystals were dried under reduced pressure to provide corresponding triflate salts, which proved to be essentially pure by ^1H NMR. Resulting salts were re-dissloved in THF (15 ml), the solution was cooled to -78°C, and the solution of NaHMDS in THF was added dropwise to the resulting mixture. The mixture was stirred at -78°C for 1 concentrated under reduced pressure. . Resulting slurry was filtered through the celite, the filter cake was washed with 1:1 Hexanes:Et_2O mixture, the solvent was evaporated under the reduced pressure. The procedure was repeated 3 times. After the third concentration the residual yellowish oi is the desired diene **111** or **122**, essentially pure based on the ^1H NMR. The dienes can be further purified by distillation under reduced pressure to give rise to colorless oils, readily hydrolysable upon exposure to moisture.



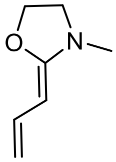
110a

White crystalline solid, m=2.69 g (98% yield). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.41 (dq, *J* = 14.0, 7.0 Hz, 1H), 6.34 (d, *J* = 14.0 Hz, 1H), 5.00 (t, *J* = 9.8 Hz, 2H), 4.38 (t, *J* = 9.8 Hz, 2H), 3.46 (s, 3H), 2.14 (dd, *J* = 7.0, 1.5 Hz, 4H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 157.1, 110.3, 70.5, 52.5, 33.9, 19.8; HRMS (ES) calcd for $C_7H_{12}NO^+$ [M]$^+$: 126.0913, found 126.0910



110b

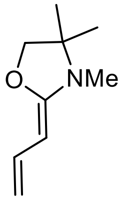
White crystalline solid, m=2.94 g (97% yield). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.47 (d, *J* = 15.4 Hz, 1H), 6.42 (d, *J* = 15.4 Hz, 1H), 4.71 (s, 2H), 3.36 (s, 3H), 1.60 (s, 11H); ^{13}C NMR (125 MHz, CDCl$_3$): δ. 157.9, 111.4, 81.2, 28.8, 23.9, 20.0.; HRMS (ES) calcd for $C_7H_{12}NO^+$ [M]$^+$: 154.1226, found 154.1205



111a

Colorless oil, m=1.00 g (80% yield). B. p. ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.59 (dt, *J* = 17.0, 10.6 Hz, 1H), 4.71 (dd, *J* = 17.0, 2.3 Hz, 1H), 4.43 (dd, *J* = 10.4, 2.3 Hz, 1H), 4.27 – 4.26 (m, 1H), 4.26 – 4.19 (m, 2H), 3.31 (t, *J* = 9.0 Hz, 2H), 2.71 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$):

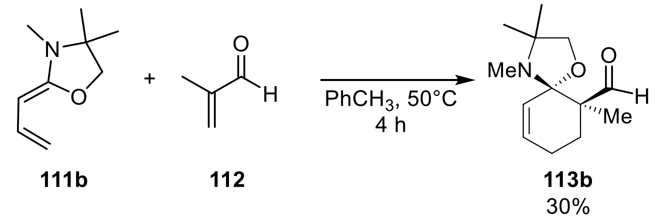
δ 132.1, 102.6, 74.2, 65.3, 50.8, 33.3.; IR (Neat film): 3423, 1635, 1489, 1408, 1266, 1162, 1051 cm^{-1}; HRMS (ES) calcd for $C_7H_{12}NO$ $[M+H]^+$: 126.0919, found 126.0916



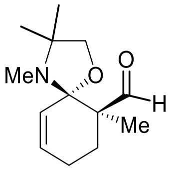
111b

Colorless oil, m=1.26 g (82% yield). B. p. ^1H NMR (500 MHz, $CDCl_3$): δ 6.61 (ddd, *J* = 17.0, 10.5, 2.5 Hz, 1H), 4.69 (dd, *J* = 17.0, 2.5 Hz, 1H), 4.40 (dd, *J* = 10.9, 2.5 Hz, 1H), 4.18 (d, *J* = 10.9 Hz, 1H), 3.91 (s, 2H), 2.51 (s, 3H), 1.16 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 132.3, 102.0, 77.4, 74.1, 26.7, 21.8.; HRMS (ES) calcd for $C_9H_{16}NO$ $[M+H]^+$: 154.1232, found 154.1206

Diels-Alder reaction between diene 111b and methacrolein



To a flame-dried 1 dram vial, equipped by a magnetic stir bar and charged with Ar, were added dry benzene (1 ml), followed by methacrolein (25 μl, 0.3 mmol) and diene **111b** (30 mg, 0.2 mmol). Resulting solution was heated to 60°C for 8 hours until the full conversion of diene (monitored by ^1H NMR), at which point the mixture was concentrated under the reduced pressure and the residue was purified by column chromatography (SiO_2, 10-50% EtOAc/hexanes) to afford 13 mg of cyclohexenone **113b** as a colorless oil.

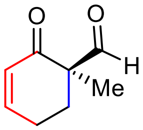


113b

Colorless oil, m=13 mg (30% yield). ^{1}H NMR (500 MHz, CDCl$_3$): δ 9.73 (s, 1H), 6.16 – 5.85 (m, 1H), 5.55 – 5.14 (m, 1H), 3.78 (d, *J* = 7.8 Hz, 1H), 3.64 (dd, *J* = 7.8, 0.7 Hz, 1H), 2.23 (s, 3H), 2.13 (tt, *J* = 12.7, 8.2 Hz, 3H), 1.68 – 1.51 (m, 2H), 1.12 (s, 3H), 1.09 (s, 3H), 1.07 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 204.63, 131.57, 128.15, 77.98, 26.68, 24.81, 22.05, 21.11, 16.77.; HRMS (ES) calcd for $C_{13}H_{22}NO_2$ [M+H]$^+$: 224.1650, found 224.1660

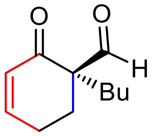
General procedure for the Diels-Alder reaction between oxazolidine butadienes and dienophiles (General procedure B)

To a flame-dried 1 dram vial, equipped by a magnetic stir bar and charged with Ar, were added dry benzene (1 ml), followed by corresponding dienophile (0.3 mmol) and diene (0.2 mmol). Resulting solution was heated to 60°C until full conversion of the diene (monitored by ^{1}H NMR, typically for 8-16 hours), at which point the mixture was diluted with water (1 ml), and oxalic acid (135 mg, 7.5 eq) was added to the mixture. Resulting heterogeneous mixture was stirred extensively at 60°C over 6 h, cooled to room temperature and diluted with EtOAc (2 ml). The organic layer was decanted, aqueous layer was washed with EtOAc (2x2 ml), combined organic layers were washed with NaHCO$_3$ (aq.), dried over Na$_2$SO$_4$ and concentrated under the reduced pressure. The residue was purified by column chromatography (SiO$_2$, 10-50% EtOAc/hexanes) to afford corresponding cylohexenones.



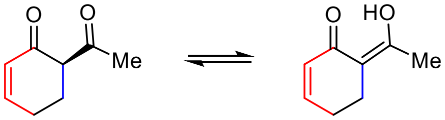
117a

Prepared by general procedure **B**. Colorless oil, m=19 mg (70% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.62 (s, 1H), 7.01 (dt, *J* = 10.1, 4.3 Hz, 1H), 6.27 – 5.94 (m, 1H), 2.62 – 2.46 (m, 1H), 2.44 – 2.24 (m, 2H), 1.96 – 1.73 (m, 1H), 1.32 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$): δ 200.41, 150.58, 128.90, 37.16, 29.69, 28.99, 22.93, 17.90; HRMS (ES) calcd for $C_8H_{11}O_2$ $[M+H]^+$: 139.0759, found 139.0732



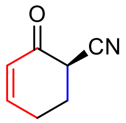
117b

Prepared by general procedure **B**. Colorless oil, m=23 mg (65% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.65 (s, 1H), 7.02 – 6.95 (m, 1H), 6.02 (d, *J* = 10.1 Hz, 1H), 2.57 – 2.45 (m, 1H), 2.44 – 2.33 (m, 1H), 2.33 – 2.26 (m, 1H), 2.01 – 1.92 (m, 1H), 1.87 – 1.79 (m, 2H), 1.40 – 1.07 (m, 6H), 0.89 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ. 201.30, 150.62, 129.14, 31.55, 29.18, 25.95, 25.42, 24.97, 23.04, 22.87, 13.77.; HRMS (ES) calcd for $C_{11}H_{17}O_2$ $[M+H]^+$: 181.1228, found 181.1215



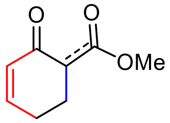
117g

Prepared by general procedure **B**. Colorless oil, m=22 mg (80% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.36 (br s, 1H), 5.85 – 5.75 (m, 1H), 5.22 – 5.20 (m, 1H), 5.18 (dd, *J* = 4.3, 3.3 Hz, 1H), 3.05 (dd, *J* = 15.6, 7.7 Hz, 1H), 2.51 (t, *J* = 7.4 Hz, 2H), 2.15 (s, 3H), 2.04 (dt, *J* = 14.7, 7.2 Hz, 1H), 1.86 (dq, *J* = 14.8, 7.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ. 208.05, 179.14, 134.78, 118.32, 48.94, 40.50, 30.71, 29.96, 25.35.; HRMS (ES) calcd for $C_8H_{10}O_2$ $[M]^+$: 138.0681, found 138.0668



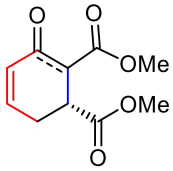
117h

Prepared by general procedure **B**. Colorless oil, m=18 mg (75% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09 (dddd, *J* = 10.2, 4.8, 3.2, 0.9 Hz, 1H), 6.15 (dt, *J* = 10.5, 2.0 Hz, 1H), 3.56 (dd, *J* = 11.1, 4.4 Hz, 1H), 2.67 – 2.56 (m, 1H), 2.48 (qdd, *J* = 9.3, 6.8, 3.8 Hz, 2H), 2.41 – 2.30 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ. 187.95, 151.00, 128.07, 39.61, 26.89, 24.36.; HRMS (ES) calcd for C_7H_7NO $[M]^+$: 121.0528, found 121.0515



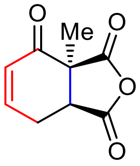
117i

Prepared by general procedure **B**. Colorless oil, m=19 mg (63% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 – 6.97 (m, 1H), 6.08 (dt, *J* = 10.2, 2.0 Hz, 1H), 3.76 (s, 3H), 3.48 – 3.39 (m, 1H), 2.46 – 2.33 (m, 3H), 2.28 – 2.07 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ. 193.91, 170.45, 150.81, 129.09, 53.32, 52.35, 25.60, 24.33; HRMS (ES) calcd for $C_8H_9O_3$ $[M]^+$: 153.0551, found 153.0568



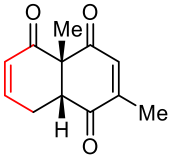
117j
72%

Prepared by general procedure **B**. Colorless oil, m=30 mg (72% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97 (ddd, *J* = 10.1, 5.4, 2.9 Hz, 1H), 6.12 (ddd, *J* = 10.1, 2.7, 1.5 Hz, 1H), 3.81 (s, 3H), 3.77 (d, *J* = 9.8 Hz, 2H), 3.73 (s, 3H), 3.71 (d, *J* = 2.5 Hz, 2H), 3.51 (ddd, *J* = 11.4, 10.1, 5.3 Hz, 1H), 2.85 (dtd, *J* = 19.1, 5.3, 1.5 Hz, 1H), 2.58 (ddt, *J* = 19.2, 10.1, 2.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ. 192.16, 172.47, 169.59, 149.35, 147.68, 129.14, 128.51, 55.10, 53.75, 52.74, 52.60, 52.57, 52.38, 42.14, 41.24, 27.68, 25.73; HRMS (ES) calcd for $C_{10}H_{12}O_5$ $[M]^+$: 212.0685, found 212.0692



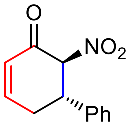
117k

Prepared by general procedure **B**. Yellowish solid, m=27 mg (72% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.91 (ddd, *J* = 10.1, 4.8, 3.4 Hz, 1H), 6.10 – 6.06 (m, 1H), 2.93 – 2.86 (m, 1H), 2.64 (d, *J* = 14.3 Hz, 1H), 2.39 (d, *J* = 16.3 Hz, 1H), 1.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ. 197.01, 194.43, 162.50, 153.24, 147.07, 132.71, 131.82, 130.41, 129.64, 46.71, 44.39, 43.10, 40.52, 35.31, 24.60, 24.37; HRMS (ES) calcd for $C_9H_8O_4$ $[M]^+$: 180.0422, found 180.0420



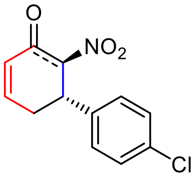
117l

Prepared by general procedure **B**. Yellowish solid, m=25 mg (63% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.89 (ddd, *J* = 10.1, 6.3, 2.3 Hz, 1H), 6.82 (dd, *J* = 3.0, 1.5 Hz, 1H), 6.23 (ddd, *J* = 10.1, 3.0, 0.9 Hz, 1H), 2.71 (ddd, *J* = 19.0, 6.3, 0.9 Hz, 1H), 2.49 (dd, *J* = 19.0, 2.4 Hz, 1H), 2.04 (d, *J* = 1.5 Hz, 1H), 1.33 – 1.29 (m, 3H), 1.25 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ. 193.61, 145.87, 145.27, 128.13, 114.17, 53.85, 29.71, 27.78, 24.31, 16.18; HRMS (ES) calcd for $C_{12}H_{12}O_3$ $[M]^+$: 204.0786, found 204.0770



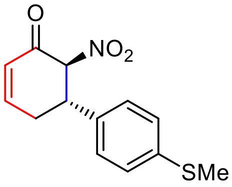
120a

Prepared by general procedure **B**. Yellowish solid, m=32 mg (75% yield). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.36 (tt, *J* = 8.1, 1.8 Hz, 2H), 7.33 – 7.27 (m, 3H), 7.19 – 7.12 (m, 1H), 6.28 (ddd, *J* = 10.1, 2.8, 1.0 Hz, 1H), 5.64 (d, *J* = 13.5 Hz, 1H), 4.03 (ddd, *J* = 13.5, 11.2, 5.3 Hz, 1H), 2.86 (dtd, *J* = 19.5, 5.6, 1.1 Hz, 1H), 2.81 – 2.77 (m, 1H). ^{13}C NMR (125 MHz, CDCl$_3$): δ.150.23, 129.27, 128.48, 127.88, 127.07, 94.46, 45.54, 33.56; HRMS (ES) calcd for $C_{12}H_{11}NO_3$ [M]$^+$: 217.0738, found 217.0705



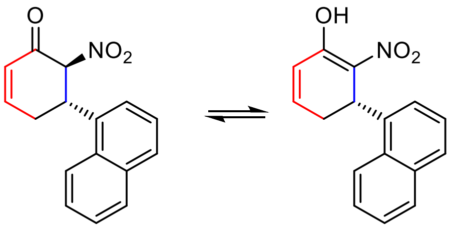
120b

Prepared by general procedure **B**. Yellowish solid, m=35 mg (70% yield). Isolated as a 2:1 keto-enol mixture. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.33 (d, *J* = 8.5 Hz, 2H), 7.19 – 7.02 (m, 2H), 5.72 (dd, *J* = 6.6, 3.9 Hz, 2H), 4.62 (dd, *J* = 18.2, 10.4 Hz, 2H), 3.18 – 3.02 (m, 2H). ^{13}C NMR (125 MHz, CDCl$_3$): δ. 175.43, 131.58, 129.36, 129.11, 128.91, 125.25, 79.22, 46.14, 37.09; HRMS (ES) calcd for $C_{12}H_{11}ClNO_3$ [M]$^+$: 252.0427, found 252.0440



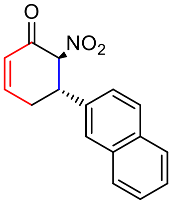
120c

Prepared by general procedure **B**, using 4-methylthio-beta-nitrostyrene as dienophile. Brownish solid, m=42 mg (80% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 – 7.19 (m, 2H), 7.15 (dd, *J* = 11.0, 5.1 Hz, 2H), 5.80 – 5.69 (m, 1H), 4.61 (ddd, *J* = 15.7, 9.6, 7.8 Hz, 2H), 3.12 (d, *J* = 6.0 Hz, 2H), 2.47 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ. 175.29, 131.89, 127.98, 127.10, 124.94, 79.41, 46.30, 37.19, 15.91, 15.71; HRMS (ES) calcd for $C_{13}H_{14}NO_3S$ $[M]^+$: 264.0694, found 264.0680



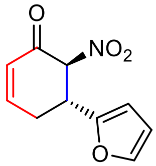
120d

Prepared by general procedure **B**. Brownish solid, m=39 mg (72% yield). Exists in chloroform as a keto-enol mixture, mostly enol form. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 – 8.10 (m, 1H), 7.90 (dd, *J* = 7.5, 4.0 Hz, 2H), 7.81 (dd, *J* = 8.1, 4.5 Hz, 1H), 7.60 (ddd, *J* = 8.4, 5.7, 1.4 Hz, 1H), 7.53 (tdd, *J* = 17.9, 8.6, 7.0 Hz, 2H), 7.48 – 7.41 (m, 1H), 7.35 (dd, *J* = 15.0, 7.2 Hz, 1H), 5.97 – 5.70 (m, 2H), 4.83 – 4.73 (m, 2H), 3.14 (d, *J* = 6.7 Hz, 1H), 2.99 – 2.78 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ. 176.33, 146.61, 134.17, 133.85, 133.43, 131.82, 130.83, 130.64, 129.44, 129.28, 128.77, 128.64, 128.60, 127.11, 126.94, 126.19, 126.11, 125.48, 125.42, 125.33, 124.70, 124.54, 123.60, 122.44, 122.02, 121.95, 78.90, 41.83, 37.75, 37.36, 35.09, 32.76, 29.71; HRMS (ES) calcd for $C_{16}H_{13}NO_3$ $[M+H]^+$: 268.0973, found 268.0960



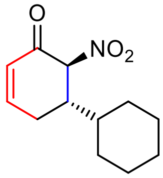
120e

Prepared by general procedure **B**. Yellowish solid, m=40 mg (75% yield). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.96 – 7.74 (m, 3H), 7.74 – 7.62 (m, 1H), 7.57 – 7.42 (m, 2H), 7.42 – 7.30 (m, 1H), 5.84 (ddd, *J* = 18.9, 7.2, 1.1 Hz, 2H), 4.79 – 4.73 (m, 2H), 3.15 (d, *J* = 6.5 Hz, 2H). ^{13}C NMR (125 MHz, CDCl$_3$): δ. 176.15, 132.01, 129.06, 127.81, 127.72, 126.58, 126.51, 126.33, 125.21, 125.08, 124.97, 79.43, 46.93, 37.28.; HRMS (ES) calcd for $C_{16}H_{13}NO_3$ [M]$^+$: 268.0973, found 268.0950



120f

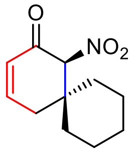
Prepared by general procedure **B**. Yellowish solid, m=27 mg (65% yield). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.36 (t, J = 7.9 Hz, 1H), 6.35 – 6.28 (m, 1H), 6.18 – 6.12 (m, 1H), 5.93 – 5.73 (m, 1H), 4.88 – 4.71 (m, 1H), 4.66 – 4.49 (m, 1H), 3.26 (dt, J = 13.8, 6.9 Hz, 1H), 3.16 (t, J = 8.8 Hz, 1H). ^{13}C NMR (125 MHz, CDCl$_3$): δ. ^{13}C NMR (101 MHz, CDCl$_3$) δ 146.21, 142.57, 142.51, 129.06, 127.63, 126.53, 125.90, 123.54, 110.54, 107.89, 107.34, 106.94, 84.22, 40.91, 37.05, 36.75, 36.41, 34.43, 33.50, 32.31, 26.38.; HRMS (ES) calcd for $C_{10}H_{10}NO_4$ [M+H]$^+$: 208.0609, found 208.0635



120g

Prepared by general procedure **B**. Yellowish solid, m=40 mg (90% yield). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.13 (ddd, *J* = 9.7, 6.0, 2.3 Hz, 1H), 6.17 (dd, *J* = 10.0, 1.9 Hz, 1H), 5.31 (d, *J* = 13.2 Hz, 1H), 2.88 – 2.78 (m, 1H), 2.59 (dt, *J* = 19.3, 5.4 Hz, 1H), 2.37 (ddt, *J* = 19.3, 11.1, 2.6

Hz, 1H), 1.84 – 1.75 (m, 3H), 1.70 (d, *J* = 12.2 Hz, 3H), 1.60 – 1.53 (m, 1H), 1.39 (ddd, *J* = 11.9, 7.4, 3.0 Hz, 2H), 1.34 – 1.04 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ. 151.17, 127.56, 92.88, 44.04, 38.21, 30.63, 26.83, 26.45, 26.28, 26.21, 25.72.; HRMS (ES) calcd for $C_{12}H_{17}NO_3$ $[M+H]^+$: 224.1286, found 224.1260



120h

Prepared by general procedure **B**. Yellowish solid, m=32 mg (78% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.07 (ddd, *J* = 10.2, 5.4, 3.1 Hz, 1H), 6.27 – 6.15 (m, 1H), 5.03 (s, 1H), 2.68 (dt, *J* = 19.6, 2.8 Hz, 1H), 2.42 (dd, *J* = 19.6, 4.6 Hz, 1H), 1.64 (ddd, *J* = 13.8, 8.6, 3.4 Hz, 2H), 1.61 – 1.39 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): δ. 150.44, 127.04, 40.24, 33.35, 32.81, 25.44, 21.11, 20.84; HRMS (ES) calcd for $C_{11}H_{16}NO_3$ $[M+H]^+$: 210.1130, found 210.1168

General procedure for the synthesis of substituted oxazolines (General procedure C)

A 50 mL recovery flask equipped with a Teflon-coated magnetic stir bar was charged with DCM (20 ml) and corresponding acid chloride (1.9 ml, 20 mmol)[130]. Resulting solution was cooled to 0°C by means of ice water bath, and the solution of ethanolamine (2.6 ml, 44 mmol) in DCM (5 ml) was added dropwise other 20 min (Note: the reaction is highly exothermic, and significant pressure can build if the addition is too rapid). Resulting slurry was warmed to room temperature and stirred at ambient temperature. After 1 hour the slurry was filtered through celite, the filtrate

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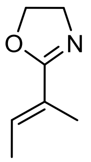
[130] For the synthesis of chlorides, see: a) Snider, B. B.; Che, Q. *Org. Lett.* **2004**, *6*, 2877; b) Kong, W.-J.; Liu, Y.-J.; Xu, H.; Chen, Y.-Q.; Dai, H.-X.; Yu, J.-Q.. *J. Am. Chem. Soc.* **2016**, *138*, 2146; c) Cowie, T. Y.; Veguillas, M.; Rae, R. L.; Rougé, M.; Żurek, J. M.; Prentice, A. W.; Paterson, M. J.; Bebbington, M. W. P. *J. Org. Chem.* **2017**, *82*, 6656.

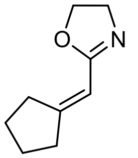
was washed with $NaHCO_3$ (aq.) (2x30 ml), organic phase was separated, dried over Na_2SO_4 and concentrated under reduced pressure to provide crude amides, essentially pure based on ^1H NMR.

The crude amide was dissolved in THF (4 ml), PPh_3 (6.0 g, 21 mmol) was added to the resulting solution, and the resulting mixture was cooled to 0°C by means of ice water bath. Diisopropyl azodicarboxylate (4.1 ml, 21 mmol) was dropwise added to the mixture, the resulting dark-red solution was stirred at 0°C for 15°min, the ice water bath was removed, and the mixture was stirred at ambient temperature over 1 hour. The resulting mixture was diluted with Et_2O (30 ml) and kept at -20°C over 8 h, during which significant amounts of white precipitate of triphenylphosphine oxide formed. Resulting slurry was filtered through the celite, the filter cake was washed with 1:1 Hexanes:Et_2O mixture, the solvent was evaporated under the reduced pressure. Resulting slurry was redissolved in 1:1 Hexanes:Et_2O (30 ml), filtered through celite, and the solvent was evaporated under the reduced pressure. Residue was distilled under reduced pressure in short path distillation apparatus to provide the desired oxazolines **122** as colorless oils.



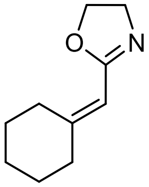
122a

Prepared by general procedure **C**. Colorless oil, b.p. 52°C/5 mm Hg, m=1.65 g (66% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 6.51 (q, *J* = 6.8 Hz, 1H), 4.27 (t, *J* = 9.4 Hz, 2H), 3.93 (t, *J* = 9.4 Hz, 2H), 1.93 (s, 3H), 1.78 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ. 166.34, 132.50, 125.07, 67.11, 54.78, 14.08, 12.97; HRMS (ES) calcd for $C_7H_{12}NO$ $[M+H]^+$: 126.0919, found 126.0902



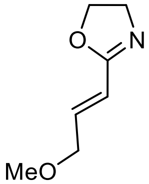
122b

Prepared by general procedure **C**. Colorless oil, b.p. 80°C/0.2 mm Hg, m=2.26 g (75% yield). Compound exists as 1:1 mixture of rotomers. ^{1}H NMR (500 MHz, CDCl$_3$): δ 5.90 – 5.87 (m, 1H), 5.57 – 5.53 (m, 1H), 4.24 (td, *J* = 9.4, 4.9 Hz, 5H), 3.95 – 3.81 (m, 5H), 3.10 (d, *J* = 0.9 Hz, 3H), 2.68 (t, *J* = 7.1 Hz, 2H), 2.44 (t, *J* = 7.0 Hz, 2H), 2.37 – 2.29 (m, 5H), 1.99 – 1.83 (m, 3H), 1.81 – 1.65 (m, 4H), 1.65 – 1.55 (m, 2H). ^{13}C NMR (125 MHz, CDCl$_3$): δ. 166.49, 164.72, 137.64, 127.52, 108.10, 67.34, 66.66, 54.44, 54.41, 35.72, 34.96, 32.46, 32.43, 30.31, 26.54, 25.70, 23.31; HRMS (ES) calcd for $C_9H_{14}NO$ $[M+H]^+$: 152.1075, found 152.1060



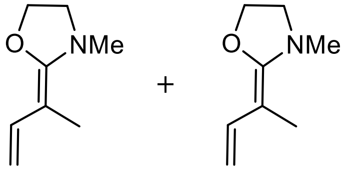
122c

Prepared by general procedure **C**. Colorless oil, b.p. 112°C/0.2 mm Hg, m=1.98 g (60% yield). ^{1}H NMR (500 MHz, CDCl$_3$): δ 5.66 (s, 1H), 4.23 (t, *J* = 9.5 Hz, 2H), 3.90 (t, *J* = 9.5 Hz, 2H), 2.77 – 2.63 (m, 2H), 2.27 – 2.13 (m, 2H), 1.67 – 1.52 (m, 6H). ^{13}C NMR (125 MHz, CDCl$_3$): δ. 140.83, 121.64, 65.57, 50.63, 34.35, 34.19, 32.95, 28.66, 27.13; HRMS (ES) calcd for $C_{10}H_{16}NO$ $[M+H]^+$: 166.1231, found 166.1254



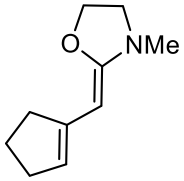
122d

Prepared by general procedure **C**. Colorless oil, b.p. 95°C/5 mm Hg, m=1.41 g (50% yield). ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.62 – 6.54 (m, 1H), 6.23 (t, *J* = 8.9 Hz, 1H), 4.29 (dd, *J* = 14.0, 4.9 Hz, 2H), 4.07 (ddd, *J* = 4.9, 1.7, 0.7 Hz, 2H), 3.94 (t, *J* = 9.5 Hz, 2H), 3.40 – 3.31 (m, 3H). ^{13}C NMR (125 MHz, CDCl$_3$): δ. 163.53, 138.71, 118.38, 71.56, 67.09, 58.41, 54.80.; HRMS (ES) calcd for $C_7H_{12}NO_2$ [M+H]$^+$: 142.0868, found 142.0860



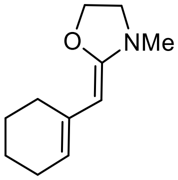
123a

Prepared by general procedure **A**. Diastereomers have close boiling points, fraction collected contained 1:1 Z:E mixture. Colorless oil, b.p. 120°C/0.1 mm Hg, m=0.97 g (73% yield). ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.89 (dd, *J* = 17.3, 10.8 Hz, 1H), 6.76 (dd, *J* = 17.0, 10.7 Hz, 1H), 4.82 – 4.51 (m, 1H), 4.09 (td, *J* = 6.9, 3.5 Hz, 1H), 3.42 – 3.14 (m, 1H), 2.92 (d, *J* = 7.5 Hz, 1H), 1.76 (d, *J* = 16.5 Hz, 2H). ^{13}C NMR (125 MHz, CDCl$_3$): δ. 134.98, 103.23, 102.17, 64.39, 60.62, 53.76, 37.21, 11.27.; HRMS (ES) calcd for $C_8H_{14}NO$ [M+H]$^+$: 140.1075, found 140.1077



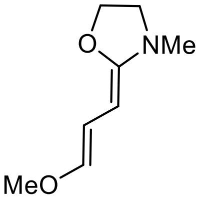
123b

Prepared by general procedure **C**. Colorless oil, b.p. 130°C/0.1 mm Hg, m=1.37 g (83% yield). ^{1}H NMR (500 MHz, CDCl$_3$): δ 5.41 (dd, *J* = 2.5, 1.9 Hz, 1H), 4.23 (t, *J* = 6.9 Hz, 2H), 4.07 (s, 1H), 3.25 (t, *J* = 6.9 Hz, 2H), 2.68 (s, 3H), 2.51 (td, *J* = 7.7, 2.0 Hz, 2H), 2.37 (td, *J* = 7.4, 2.3 Hz, 2H), 1.91 – 1.75 (m, 2H). ^{13}C NMR (125 MHz, CDCl$_3$): δ. 172.74, 133.70, 118.23, 117.51, 65.53, 50.84, 36.06, 34.07, 32.72, 23.65; HRMS (ES) calcd for $C_{10}H_{16}NO$ $[M+H]^+$: 166.1232, found 166.1220



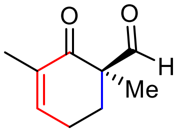
123c

Prepared by general procedure **C**. Colorless oil, b.p. 146°C/0.1 mm Hg, m=1.43 g (80% yield). ^{1}H NMR (500 MHz, C_6D_6): δ 5.99 – 5.80 (m, 1H), 4.13 (s, 1H), 3.53 (t, *J* = 6.8 Hz, 2H), 2.67 (ddd, *J* = 8.2, 4.1, 2.0 Hz, 2H), 2.41 – 2.31 (m, 2H), 2.20 (s, 3H), 1.83 – 1.73 (m, 2H), 1.66 (dtd, *J* = 9.2, 6.1, 2.8 Hz, 2H) ^{13}C NMR (125 MHz, C_6D_6): δ. 117.27, 78.56, 65.46, 50.92, 34.47, 30.19, 29.09, 26.77, 24.44, 23.74; HRMS (ES) calcd for $C_{11}H_{18}NO$ $[M+H]^+$: 180.1388, found 180.1370



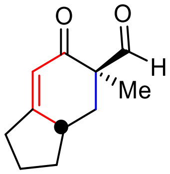
123d

Prepared by general procedure **C**. Colorless oil, b.p. 108°C/0.1 mm Hg, m=1.27 g (82% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.60 (d, *J* = 6.1 Hz, 1H), 5.28 (dd, *J* = 11.1, 6.1 Hz, 1H), 4.40 – 4.26 (m, 1H), 4.19 (t, *J* = 6.8 Hz, 2H), 3.61 (s, 3H), 3.26 (t, *J* = 6.8 Hz, 2H), 2.69 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.89, 102.76, 66.84, 65.33, 59.49, 51.33, 33.86; HRMS (ES) calcd for $C_8H_{14}NO_2$ $[M+H]^+$: 156.1024, found 156.1019



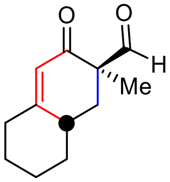
125a

Prepared by general procedure **B** from methacrolein and diene **122a**. Colorless oil, m=22 mg (75% yield). ^{1}H NMR (500 MHz, CDCl$_3$): δ 9.63 (s, 1H), 6.97 – 6.64 (m, 1H), 2.63 – 2.18 (m, 4H), 1.99 – 1.65 (m, 5H), 1.30 (s, 4H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 200.93, 145.58, 134.96, 57.34, 29.40, 22.63, 17.98, 16.12; HRMS (ES) calcd for $C_9H_{13}O_2$ [M+H]$^+$: 153.0915, found 153.0924



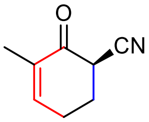
125b

Prepared by general procedure **B** from methacrolein and diene **122b**. Colorless oil, m=21 mg (60% yield). ^{1}H NMR (500 MHz, CDCl$_3$): δ. 9.83 (s, 1H), 5.93 – 5.91 (m, 1H), 2.75 – 2.61 (m, 2H), 2.51 – 2.41 (m, 2H), 2.31 – 2.19 (m, 3H), 2.12 – 2.04 (m, 2H), 1.93 – 1.87 (m, 2H), 1.72 – 1.67 (m, 2H), 1.11 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 202.32, 202.12, 174.35, 174.25, 121.95, 121.07, 43.51, 41.11, 38.07, 32.90, 31.61, 23.72, 15.55; HRMS (ES) calcd for $C_{11}H_{15}O_2$ [M+H]$^+$: 179.1072, found 179.1045



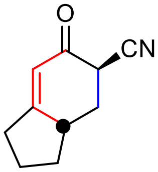
125c

Prepared by general procedure **B** from methacrolein and diene **122c**. Colorless oil, m=23 mg (60% yield). ^{1}H NMR (500 MHz, CDCl$_3$): δ 9.81 (s, 1H), 5.80 (s, 1H), 2.54 – 2.39 (m, *J* = 15.5 Hz, 3H), 2.29 – 2.17 (m, 1H), 2.07 – 1.99 (m, 1H), 1.98 – 1.78 (m, 3H), 1.62 – 1.41 (m, 3H), 1.28 (s, 3H), 1.26 – 1.17 (m, 1H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 202.15, 167.02, 122.91, 55.45, 35.10, 34.97, 34.70, 34.35, 26.62, 25.46, 17.86.; HRMS (ES) calcd for $C_{12}H_{17}O_2$ [M+H]$^+$: 193.1228, found 193.1215



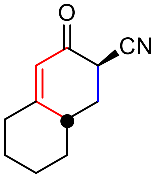
126a

Prepared by general procedure **B** from acrylonitrile and diene **122a**. Colorless oil, m=21 mg (80% yield). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.14 – 6.66 (m, 1H), 3.56 (dd, *J* = 11.0, 4.6 Hz, 1H), 2.55 (ddd, *J* = 7.3, 6.8, 1.8 Hz, 1H), 2.50 – 2.46 (m, 1H), 2.45 – 2.40 (m, 1H), 2.38 – 2.29 (m, 1H), 1.84 (d, *J* = 1.5 Hz, 3H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 145.88, 134.86, 116.72, 39.80, 27.40, 24.42, 16.10. HRMS (ES) calcd for $C_8H_{10}NO$ [M+H]$^+$: 136.0762, found 136.0780



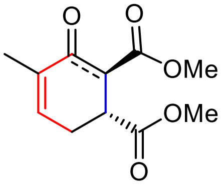
126b

Prepared by general procedure **B** from acrylonitrile and diene **122b**. Colorless oil, m=23 mg (72% yield). ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.03 (d, *J* = 1.9 Hz, 1H), 3.54 (dd, *J* = 14.1, 4.2 Hz, 1H), 2.73 – 2.64 (m, 2H), 2.58 (dd, *J* = 19.5, 10.1 Hz, 2H), 2.22 – 2.14 (m, 2H), 2.14 – 2.00 (m, 2H), 1.91 – 1.71 (m, 2H), 1.42 – 1.30 (m, 2H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 188.19, 176.21, 120.76, 120.45, 117.13, 42.40, 39.91, 33.56, 32.44, 32.05, 23.58. HRMS (ES) calcd for $C_{10}H_{12}NO$ [M+H]$^+$: 162.0853, found 162.0901



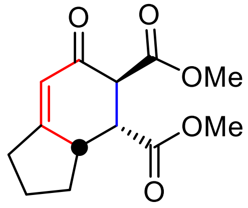
126c
1:1 *dr*

Prepared by general procedure **B** from acrylonitrile and diene **122c**. Colorless oil, m=24 mg (75% yield). ^{1}H NMR (500 MHz, CDCl$_3$): δ 5.91 (dd, *J* = 3.9, 2.0 Hz, 1H), 3.48 (ddd, *J* = 11.5, 10.5, 4.6 Hz, 1H), 2.53 – 2.34 (m, 3H), 2.31 – 2.16 (m, 1H), 2.08 – 1.83 (m, 4H), 1.66 – 1.17 (m, 4H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 122.72, 121.81, 116.80, 39.36, 37.42, 37.00, 36.00, 35.91, 35.22, 34.25, 33.79, 33.17, 32.22, 27.31, 26.34, 25.38, 25.09.. HRMS (ES) calcd for $C_{11}H_{14}NO$ [M+H]$^+$: 176.1075, found 176.1071



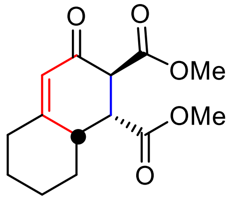
127a

Prepared by general procedure **B** from dimethyl fumarate and diene **122a**. Colorless oil, m=22 mg (50% yield). ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.72 (ddd, *J* = 5.6, 2.9, 1.4 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 1H), 3.72 (s, 3H), 3.72 – 3.68 (m, 1H), 3.49 (ddd, *J* = 11.7, 10.5, 5.3 Hz, 1H), 2.87 – 2.77 (m, 1H), 2.61 – 2.45 (m, 1H), 1.81 (dt, *J* = 2.7, 1.4 Hz, 4H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 192.73, 172.60, 169.91, 142.39, 135.52, 55.27, 53.79, 52.45, 52.43, 42.60, 41.68, 27.69, 25.83, 16.03, 15.77. HRMS (ES) calcd for $C_{11}H_{14}O_5$ [M+H]$^+$: 226.0841, found 226.0852



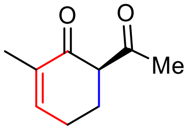
127b
6:1 *dr*

Prepared by general procedure **B** from dimethyl fumarate and diene **122b**. Colorless oil, m=31 mg (63% yield). ^{1}H NMR (500 MHz, CDCl$_3$): δ 5.99 (d, *J* = 2.1 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.18 (dd, *J* = 12.9, 11.2 Hz, 1H), 2.81 – 2.66 (m, 2H), 2.61 – 2.48 (m, 1H), 2.36 (t, *J* = 7.5 Hz, 1H), 2.26 – 2.14 (m, 1H), 2.03 – 1.86 (m, 2H), 1.78 – 1.65 (m, 2H), 1.48 (ddd, *J* = 24.2, 12.1, 7.2 Hz, 1H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 192.21, 172.65, 172.52, 170.06, 121.73, 55.54, 52.44, 52.24, 49.09, 44.59, 31.86, 31.65, 23.15. HRMS (ES) calcd for $C_{13}H_{17}O_5$ $[M+H]^+$: 253.1076, found 253.1076



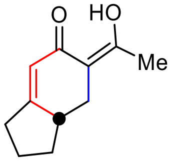
127c
52%
2:1 *dr*

Prepared by general procedure **B** from dimethyl fumarate and diene **122c**. Colorless oil, m=27 mg (52% yield). ^{1}H NMR (500 MHz, CDCl$_3$): δ 5.90 (s, 1H), 3.78 (s, 3H), 3.74 – 3.72 (m, 4H), 3.69 (d, *J* = 2.5 Hz, 1H), 3.13 (dd, *J* = 13.2, 9.9 Hz, 1H), 2.98 (s, 1H), 2.62 (ddd, *J* = 13.5, 9.3, 7.9 Hz, 1H), 2.57 – 2.45 (m, 2H), 2.27 – 2.12 (m, 2H), 2.05 (d, *J* = 21.8 Hz, 3H), 1.89 (dddd, *J* = 13.9, 9.0, 5.3, 2.6 Hz, 3H), 1.70 – 1.53 (m, 3H), 1.51 – 1.37 (m, 3H), 1.35 – 1.21 (m, 2H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 192.05, 173.05, 169.76, 164.81, 123.33, 55.13, 52.46, 52.41, 48.59, 40.14, 35.40, 33.13, 28.33, 26.33, 25.30, 25.14, 22.69, 21.92. HRMS (ES) calcd for $C_{14}H_{19}O_5$ $[M+H]^+$: 267.1232, found 267.1245



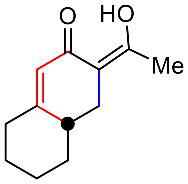
128a

Prepared by general procedure **B** from methyl vinyl ketone and diene **122a**. Yellowish oil, m=24 mg (81% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 6.00 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.18 (dd, *J* = 14.0, 8.9 Hz, 1H), 2.52 – 2.42 (m, 2H), 2.20 – 2.12 (m, 3H), 2.08 – 1.93 (m, 2H), 1.31 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.13, 114.97, 38.98, 31.94, 30.02, 23.95, 21.00. HRMS (ES) calcd for $C_9H_{13}O_2$ $[M+H]^+$: 153.0915, found 153.0903



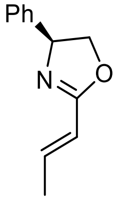
128b

Prepared by general procedure **B** from methyl vinyl ketone and diene **122b**. Yellowish oil, m=28 mg (80% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 5.94 – 5.81 (m, 1H), 2.49 (m, 2H), 2.34 (m, *J* = 5.4 Hz, 3H), 2.20 – 2.05 (m, 2H), 1.89 – 1.70 (m, 2H), 1.59 (dd, *J* = 7.9, 4.2 Hz, 2H), 1.33 (s, 3H), 1.23 (d, *J* = 3.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 122.40, 83.11, 81.00, 55.28, 47.70, 41.90, 31.34, 28.32, 23.49, 22.73, 17.67. HRMS (ES) calcd for $C_{11}H_{15}O_2$ $[M+H]^+$: 179.1072, found 179.1090



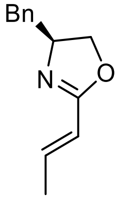
128c

Prepared by general procedure **B** from methyl vinyl ketone and diene **122b**. Yellowish oil, m=29 mg (76% yield). ^{1}H NMR (500 MHz, CDCl$_3$): δ 9.83 (d, *J* = 1.6 Hz, 1H), 5.82 (s, 1H), 2.49 (dd, *J* = 19.4, 18.0 Hz, 2H), 2.30 – 2.22 (m, 1H), 2.05 (d, *J* = 13.0 Hz, 1H), 1.96 (dd, *J* = 12.3, 10.4 Hz, 1H), 1.93 – 1.87 (m, 1H), 1.87 – 1.79 (m, 1H), 1.57 – 1.44 (m, 2H), 1.30 (dd, *J* = 3.2, 1.7 Hz, 2H), 1.28 – 1.19 (m, 1H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 202.45, 122.92, 55.61, 35.09, 35.00, 34.71, 34.37, 26.62, 25.46, 17.86. HRMS (ES) calcd for $C_{12}H_{17}O_2$ [M+H]$^+$: 193.1228, found 193.1240



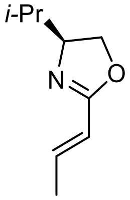
129a

Prepared by general procedure for the synthesis of oxazolines, utilizing (R)-(−)-2-Phenylglycinol as amino alcohol Purified by column chromatography (10-30% Hexanes:EtOAc). Colorless oil, m=3.1 g (83% yield). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.46 – 7.25 (m, 5H), 6.70 (dd, *J* = 15.8, 6.9 Hz, 1H), 6.11 (dd, *J* = 15.8, 1.7 Hz, 1H), 5.31 – 5.15 (m, 1H), 4.63 (dd, *J* = 10.0, 8.4 Hz, 1H), 4.11 (t, *J* = 8.2 Hz, 1H), 3.48 (q, *J* = 7.0 Hz, 1H), 2.05 – 1.84 (m, 3H).



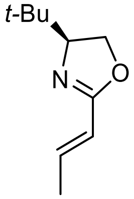
129b

Prepared by general procedure for the synthesis of oxazolines, utilizing L-phenylalaniol as amino alcohol Purified by distillation. Colorless oil, m=2.1 g (52% yield), b. p. 128°C/1.2 Torr. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.31 – 7.28 (m, *J* = 7.1 Hz, 2H), 7.23 – 7.20 (m, *J* = 8.0 Hz, 3H), 6.59 (dq, *J* = 13.9, 6.9 Hz, 1H), 6.01 (dd, *J* = 15.8, 1.6 Hz, 1H), 4.98 (dt, *J* = 12.5, 6.2 Hz, 1H), 4.49 – 4.35 (m, 1H), 4.19 (t, *J* = 8.8 Hz, 1H), 4.00 – 3.89 (m, 1H), 3.14 (dd, *J* = 13.8, 5.3 Hz, 1H), 2.65 (dd, *J* = 13.7, 8.8 Hz, 1H), 1.87 (dd, *J* = 6.8, 1.3 Hz, 3H).



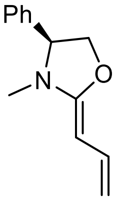
129c

Prepared by general procedure for the synthesis of oxazolines, utilizing iso-leucinol as amino alcohol Purified by distillation. Colorless oil, m=2.1 g (68% yield), b. p. 70°C/1.3 Torr. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.57 (dq, *J* = 15.7, 6.8 Hz, 1H), 6.01 (ddd, *J* = 15.7, 3.3, 1.6 Hz, 1H), 4.32 – 4.20 (m, 1H), 3.98 – 3.90 (m, 2H), 1.86 (dd, *J* = 6.9, 1.7 Hz, 3H), 1.27 – 1.24 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H).



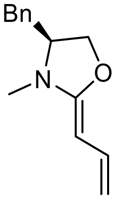
129d

Prepared by general procedure for the synthesis of oxazolines, utilizing tert-leucinol as amino alcohol Purified by distillation. Colorless oil, m=2.0 g (67% yield), b. p. 71°C/1.4 Torr. Prepared as a 1:1 mixture of E/Z isomers. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09 – 6.90 (m, 1H), 6.56 (dq, *J* = 15.5, 6.9 Hz, 1H), 6.06 (ddq, *J* = 32.1, 15.7, 1.7 Hz, 2H), 4.26 – 4.11 (m, 2H), 4.08 – 4.01 (m, 1H), 3.90 (dd, *J* = 9.7, 8.2 Hz, 1H), 1.93 – 1.81 (m, 6H), 0.97 (s, 9H), 0.90 (s, 9H).



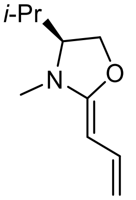
130a

Prepared by general procedure **A** from **129a**. Purified by distillation. Colorless oil, m=1.7 g (87% yield), b. p. 125°C/0.25 Torr. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.43 – 7.28 (m, 5H), 6.65 (dt, *J* = 17.0, 10.6 Hz, 1H), 4.77 (dd, *J* = 17.0, 2.2 Hz, 1H), 4.58 – 4.46 (m, 1H), 4.34 (dd, *J* = 13.3, 6.9 Hz, 1H), 3.98 (t, *J* = 8.2 Hz, 1H), 2.51 (s, 3H).



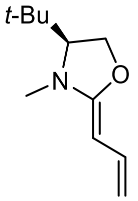
130b

Prepared by general procedure **A** from **129b**. Purified by distillation. Colorless oil, m=1.6 g (87% yield), b. p. 126°C/0.1 Torr. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.36 – 7.29 (m, 3H), 7.17 – 7.14 (m, 2H), 6.66 – 6.53 (m, 1H), 4.71 (dd, *J* = 17.0, 2.0 Hz, 1H), 4.43 (ddd, *J* = 10.4, 2.3, 0.5 Hz, 1H), 4.24 (d, *J* = 10.9 Hz, 1H), 4.10 (dd, *J* = 8.3, 6.9 Hz, 1H), 3.92 (dd, *J* = 8.3, 6.3 Hz, 1H), 3.06 (dd, *J* = 13.5, 4.7 Hz, 1H), 2.70 (s, 3H), 2.61 (dd, *J* = 13.5, 9.2 Hz, 1H).



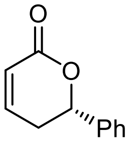
130c

Prepared by general procedure **A** from **129c**. Purified by distillation. Colorless oil, m=1.1 g (70% yield), b. p. 102°C/0.1 Torr. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.21 (dt, *J* = 17.1, 10.6 Hz, 2H), 5.10 (dd, *J* = 17.0, 2.4 Hz, 1H), 4.83 (dd, *J* = 10.4, 2.4 Hz, 1H), 4.44 (d, *J* = 10.8 Hz, 1H), 3.62 – 3.48 (m, 2H), 2.61 (ddd, *J* = 7.7, 6.3, 4.0 Hz, 1H), 2.17 (s, 3H), 1.46 – 1.27 (m, 1H), 0.52 (d, *J* = 6.9 Hz, 3H), 0.40 (d, *J* = 7.0 Hz, 3H).



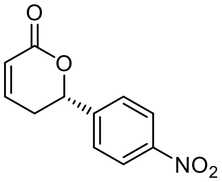
130d

Prepared by general procedure **A** from **129d**. Purified by distillation. Colorless oil, m=1.5 g (83% yield), b. p. 114°C/0.1 Torr. ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.66 – 6.53 (m, 1H), 4.67 (dd, *J* = 17.0, 2.3 Hz, 1H), 4.38 (dd, *J* = 10.4, 2.3 Hz, 1H), 4.20 (d, *J* = 10.9 Hz, 1H), 4.17 – 4.07 (m, 2H), 3.10 (dd, *J* = 7.4, 4.0 Hz, 1H), 2.87 (s, 3H), 0.90 (s, 9H).



134a

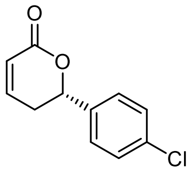
Prepared by general procedure **B**. Purified by column (Hexanes : EtOAc, 10-30% EtOAc). Yellowish solid, m=24 mg (70% yield). ^{1}H NMR (500 MHz, CDCl$_3$): 7.47 – 7.32 (m, 4H), 6.98 (ddd, *J* = 9.6, 5.6, 2.8 Hz, 1H), 6.22 – 6.09 (m, 1H), 5.46 (dd, *J* = 11.3, 4.6 Hz, 1H), 2.76 – 2.49 (m, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 144.69, 138.50, 128.67, 128.61, 126.03, 121.80, 79.21, 31.67. HRMS (ES) calcd for $C_{11}H_{11}O_2$ [M+H]$^+$: 175.0759, found 175.0740



134b
82%

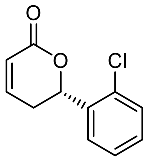
Prepared by general procedure **B**. Purified by column (Hexanes : EtOAc, 10-30% EtOAc). Yellowish solid, m=35 mg (82% yield). ^{1}H NMR (500 MHz, CDCl$_3$): 8.29 (d, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 8.9 Hz, 2H), 7.02 (ddd, *J* = 9.6, 5.9, 2.5 Hz, 1H), 6.28 – 6.11 (m, 1H), 5.60

(dd, *J* = 11.8, 4.3 Hz, 1H), 2.82 – 2.53 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.38, 144.23, 126.73, 123.99, 121.87, 77.80, 31.54. HRMS (ES) calcd for $C_{11}H_{10}NO_4$ $[M+H]^+$: 220.0609, found 220.0618



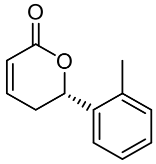
134c

Prepared by general procedure **B**. Purified by column (Hexanes : EtOAc, 10-50% EtOAc). Yellowish solid, m=34 mg (82% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.34 (dd, *J* = 26.0, 17.8 Hz, 4H), 5.76 (d, *J* = 10.6 Hz, 1H), 5.22 (d, *J* = 12.1 Hz, 1H), 4.44 (s, 1H), 2.83 (dd, *J* = 57.6, 22.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.73, 131.46, 128.97, 128.91, 128.78, 127.28, 127.24, 64.02, 62.76, 40.92. HRMS (ES) calcd for $C_{11}H_{10}ClO_2$ $[M+H]^+$: 209.0369, found 209.0360



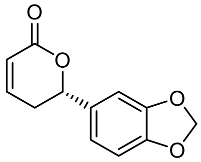
134d

Prepared by general procedure **B**. Purified by column (Hexanes : EtOAc, 10-40% EtOAc). Yellowish solid, m=29 mg (70% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.56 (dd, *J* = 23.7, 7.7 Hz, 1H), 7.47 – 7.32 (m, 3H), 6.16 (d, *J* = 10.7 Hz, 1H), 5.63 (d, *J* = 11.4 Hz, 1H), 4.50 (s, 1H), 2.92 (d, *J* = 18.3 Hz, 1H), 2.82 (d, *J* = 17.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.06, 129.71, 129.38, 127.39, 127.29, 74.16, 62.91, 38.62, 37.06. HRMS (ES) calcd for $C_{11}H_{10}ClO_2$ $[M+H]^+$: 209.0369, found 209.0360



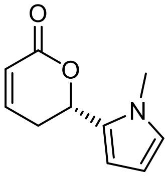
134e

Prepared by general procedure **B**. Purified by column (Hexanes : EtOAc, 10-30% EtOAc). White solid, m=25 mg (67% yield). ^{1}H NMR (500 MHz, CDCl$_3$): 7.29 (d, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 8.3 Hz, 2H), 7.02 – 6.90 (m, 1H), 6.15 (ddd, *J* = 9.8, 2.5, 1.1 Hz, 1H), 5.43 (dd, *J* = 11.2, 4.8 Hz, 1H), 2.68 – 2.60 (m, 2H), 2.38 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 145.38, 144.23, 126.73, 123.99, 121.87, 77.80, 31.54. HRMS (ES) calcd for $C_{12}H_{13}O_2$ $[M+H]^+$: 189.0916, found 189.0965



134f

Prepared by general procedure **B**. Purified by column (Hexanes : EtOAc, 10-30% EtOAc). White solid, m=37 mg (82% yield). ^{1}H NMR (500 MHz, CDCl$_3$): 7.09 – 6.92 (m, 1H), 6.92 – 6.77 (m, 2H), 6.13 (ddd, *J* = 9.8, 2.6, 0.9 Hz, 1H), 5.98 (d, *J* = 1.5 Hz, 2H), 5.36 (dd, *J* = 11.8, 4.3 Hz, 1H), 4.30 (dd, *J* = 12.0, 4.3 Hz, 1H), 4.16 (dd, *J* = 12.0, 5.9 Hz, 1H), 2.77 – 2.43 (m, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 145.38, 144.23, 126.73, 123.99, 121.87, 77.80, 31.54. HRMS (ES) calcd for $C_{12}H_{11}O_4$ $[M+H]^+$: 219.0657, found 219.0642



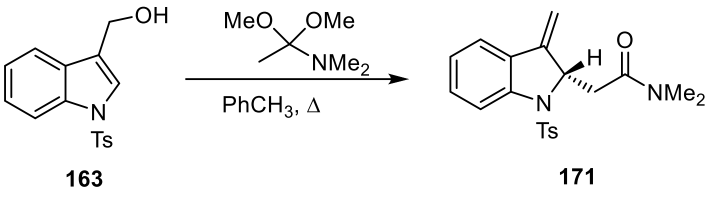
134g

Prepared by general procedure **B**. Purified by column (Hexanes : EtOAc, 10-40% EtOAc). Yellowish solid, m=21 mg (60% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.07 (dd, *J* = 4.0, 1.8 Hz, 1H), 6.84 (t, *J* = 2.0 Hz, 2H), 6.15 (dd, *J* = 4.0, 2.5 Hz, 2H), 3.93 (S, 3H), 3.10 – 2.98 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.29, 132.04, 130.62, 121.20, 119.72, 117.28, 108.31, 42.70, 36.98, 14.79. HRMS (ES) calcd for $C_{10}H_{12}NO_2$ $[M+H]^+$: 178.0868, found 178.0872

6.3. Experimental procedures and characterization data for chapter 3

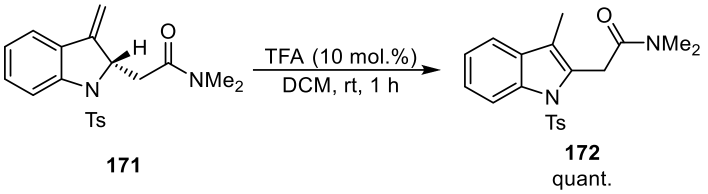
General information.

All Meerwein-Eschenmoser-Claisen reactions were performed under Ar in an oven-dried glassware, utilizing freshly distilled dimethylacetamide dimethyl acetal (purchased from Oakwood, distilled over Ca). Indole alcohols **171a-e** and **171l-n** were prepared by addition of the corresponding Grignard reagent to indole carboxaldehydes by a known procedure. Indole alcohols **171f-i** and **171k-r** were prepared by reduction of the corresponding known carbonyl compounds with $NaBH_4$. All spectra matched previously reported.



A 15 mL recovery flask equipped with a reflux condenser and a Teflon-coated magnetic stir bar was charged with alcohol **163** (150 mg, 0.5 mmol), toluene (4 ml) and dimethylacetamide dimethyl acetal (220 μl, 1.5 mmol). Resulting solution was heated under reflux over 1 h, when TLC analysis indicated complete conversion of the starting material. Resulting dark solution was concentrated under reduced pressure, and the residue was purified by flash chromatography (hexanes:EtOAc, 10-50% EtOAc) to provide amide **171** as a yellowish oil (179 mg, 97% yield).

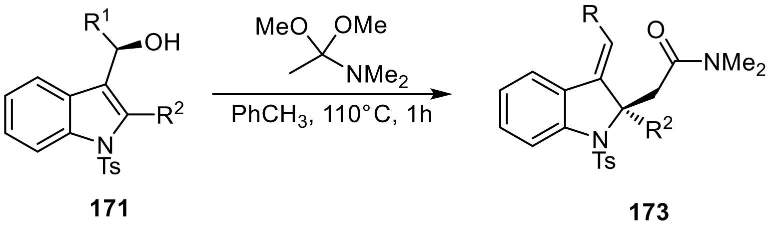
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.29 (ddd, *J* = 8.6, 2.6, 0.9 Hz, 2H), 7.16 (dd, *J* = 8.0, 0.6 Hz, 2H), 7.05 (ddd, *J* = 8.3, 1.5, 0.7 Hz, 1H), 5.33 (d, *J* = 2.4 Hz, 1H), 5.26 – 5.18 (m, 1H), 5.14 (d, *J* = 2.0 Hz, 1H), 3.24 (dd, *J* = 15.9, 3.3 Hz, 1H), 3.01 (s, 3H), 2.99 (s, 3H), 2.77 (dd, *J* = 15.9, 8.9 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 169.67, 145.18, 144.12, 143.20, 129.89, 129.62, 129.51, 127.30, 124.42, 120.89, 116.52, 104.41, 62.89, 41.93, 37.23, 35.39, 21.44. HRMS (ES) calcd for $C_{20}H_{23}N_2O_3S$ $[M+H]^+$: 371.1429, found 371.1415



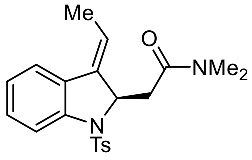
A 10 mL recovery flask equipped with a Teflon-coated magnetic stir bar was charged with amide **171** (80 mg, 0.2 mmol), DCM (3 ml) and TFA (2 μl, ~1 drop). Resulting solution was stirred for 1 h at ambient temperature, when TLC analysis indicated complete conversion of the starting material. Resulting solution was concentrated under reduced pressure, and the residue was purified by flash chromatography (hexanes:EtOAc, 5-30% EtOAc) to provide amide **172** as a yellowish oil (79 mg, 99% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 – 7.84 (m, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.42 – 7.38 (m, 1H), 7.20 (dd, *J* = 6.2, 2.6 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 4.11 (s, 2H), 3.17 (s, 3H), 3.00 (s, 3H), 2.30 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 169.05, 144.35, 135.96, 131.03, 130.78, 129.51, 127.02, 124.14, 123.06, 119.28, 118.65, 114.38, 37.50, 35.78, 31.27, 21.49, 8.97. HRMS (ES) calcd for $C_{20}H_{23}N_2O_3S$ $[M+H]^+$: 371.1429, found 371.1429

General procedure for the Meerwein-Eschenmoser-Claisen rearrangement

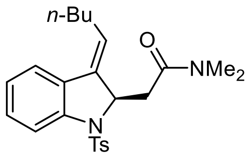


A 15 mL recovery flask equipped with a reflux condenser and a Teflon-coated magnetic stir bar was charged with indole alcohol **171** (0.5 mmol), toluene (4 ml) and dimethylacetamide dimethyl acetal (220 μl, 1.5 mmol). Resulting solution was heated under reflux for 1 h (in some cases up to 4 h, where indicated), when TLC analysis indicated complete conversion of the starting material. Resulting brown solution was concentrated under reduced pressure, and the residue was purified by flash chromatography (hexanes:EtOAc, 10-50% EtOAc) to provide amide **173** as a yellowish oil.



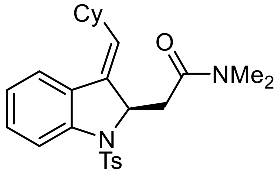
173a
98%
2:1 **E:Z**

Yellow foam, 188 mg (98% yield), isolated as a 2:1 E:Z mixture of isomers. ^{1}H NMR (500 MHz, $CDCl_3$, major diastereomer): δ 7.78 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.42 (dd, *J* = 18.8, 7.6 Hz, 1H), 7.25 – 7.20 (m, 2H), 7.18 – 7.12 (m, 3H), 7.05 (dtd, *J* = 11.3, 7.6, 0.8 Hz, 2H), 5.72 (qd, *J* = 7.4, 1.7 Hz, 1H), 5.13 (ddt, *J* = 8.4, 3.5, 1.7 Hz, 1H), 3.12 (dt, *J* = 14.7, 3.7 Hz, 1H), 2.99 (s, 3H), 2.98 (s, 4H), 2.71 (dd, *J* = 15.7, 8.5 Hz, 1H), 2.32 (s, 3H), 1.83 (dd, *J* = 7.4, 1.6 Hz, 3H); minor diastereomer: 7.71 (dd, *J* = 6.0, 2.7 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.22 – 7.18 (m, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 7.03 (dd, *J* = 7.6, 0.7 Hz, 1H), 5.78 (tt, *J* = 6.8, 3.4 Hz, 1H), 5.25 (d, *J* = 1.3 Hz, 1H), 3.09 (s, 3H), 3.03 – 3.01 (m, 1H), 2.98 – 2.97 (m, 3H), 2.63 (dd, *J* = 14.5, 4.5 Hz, 1H), 2.31 (s, 3H), 1.77 – 1.72 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 169.85, 169.62, 143.91, 143.86, 143.55, 141.96, 137.53, 136.85, 134.04, 131.08, 129.95, 129.80, 129.51, 129.42, 128.67, 128.60, 127.23, 127.09, 126.75, 124.89, 124.83, 124.34, 119.91, 119.73, 117.27, 116.59, 116.41, 63.47, 62.24, 42.46, 40.14, 38.03, 37.33, 35.61, 35.42, 21.44, 14.39, 14.18. HRMS (ES) calcd for $C_{21}H_{25}N_2O_3S$ $[M+H]^+$: 385.1586, found 385.1572



173b
95%
3:1 **E:Z**

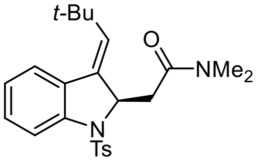
Yellowish foam, 202 mg (95% yield), isolated as a 1:1 E:Z mixture of isomers. ^{1}H NMR (500 MHz, CDCl$_3$, mixture of diastereomers): δ 7.80 (dd, *J* = 27.3, 8.1 Hz, 1H), 7.70 (dd, *J* = 18.2, 8.1 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.30 – 7.19 (m, 1H), 7.19 – 6.98 (m, 1H), 5.77 – 5.62 (m, 1H), 5.61 – 5.50 (m, 1H), 5.17 (d, *J* = 4.4 Hz, 1H), 5.14 – 4.99 (m, 1H), 3.09 (s, 1H), 3.07 – 3.02 (m, 1H), 3.01 – 2.93 (m, 1H), 2.68 (dd, *J* = 15.3, 8.3 Hz, 1H), 2.57 (dd, *J* = 14.4, 4.3 Hz, 1H), 2.30 (d, *J* = 9.5 Hz, 1H), 2.24 (dd, *J* = 14.5, 7.2 Hz, 1H), 2.10 (q, *J* = 6.7 Hz, 1H), 1.39 – 1.10 (m, 1H), 0.84 (q, *J* = 7.1 Hz, 1H). ^{13}C NMR (125 MHz, CDCl$_3$) 169.77, 169.53, 143.83, 143.79, 143.67, 142.09, 136.63, 135.64, 134.15, 131.26, 129.99, 129.45, 129.40, 128.69, 128.63, 127.37, 127.34, 127.25, 127.12, 126.71, 126.46, 124.95, 124.76, 124.55, 122.41, 120.04, 117.59, 117.13, 63.95, 62.47, 42.17, 40.54, 38.07, 37.45, 35.60, 35.42, 31.47, 31.35, 28.50, 27.87, 22.13, 22.09, 21.40, 13.92, 13.80.. HRMS (ES) calcd for C$_{24}$H$_{21}$N$_2$O$_3$S [M+H]$^+$: 427.2055, found 427.2054



173c
96%
5:1 **E:Z**

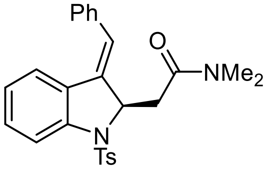
Yellowish foam, 216 mg (96% yield), isolated as a 5:1 E:Z mixture of isomers. ^{1}H NMR (500 MHz, CDCl$_3$, mixture of diastereomers): δ 7.76 (d, *J* = 8.1 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.36 (d, *J* = 7.5 Hz, 1H), 7.29 – 7.20 (m, 2H), 7.15 – 7.01 (m, 4H), 5.38 (dd, *J* = 9.3, 1.4 Hz, 1H), 5.06

(ddd, *J* = 8.1, 4.5, 1.4 Hz, 1H), 3.04 (dd, *J* = 14.9, 4.6 Hz, 1H), 2.98 (s, 6H), 2.66 (dd, *J* = 14.9, 8.3 Hz, 1H), 2.48 (d, *J* = 9.6 Hz, 1H), 2.31 (d, *J* = 3.4 Hz, 4H), 2.20 – 2.11 (m, 5H), 1.74 – 1.61 (m, 5H), 1.43 (dd, *J* = 9.4, 3.7 Hz, 1H), 1.37 – 0.85 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$) 169.61, 143.77, 133.86, 131.92, 129.57, 129.36, 129.29, 128.63, 127.19, 127.08, 124.70, 124.49, 117.37, 64.18, 41.88, 37.55, 36.58, 35.36, 32.33, 32.31, 25.75, 25.54, 25.52, 21.32. HRMS (ES) calcd for $C_{26}H_{33}N_2O_3S$ [M+H]$^+$: 453.2212, found 453.2206



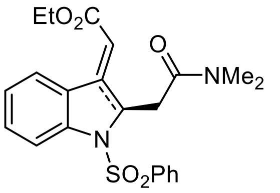
173d
84%
5:1 **E:Z**

Yellowish foam, 179 mg (96% yield), isolated as a 5:1 E:Z mixture of isomers. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers): δ 7.72 (d, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.26 – 7.20 (m, 2H), 7.17 – 7.07 (m, 3H), 5.59 (d, *J* = 1.7 Hz, 1H), 5.39 (dt, *J* = 9.7, 2.3 Hz, 1H), 3.09 (s, 2H), 3.00 (s, 2H), 2.97 (d, *J* = 2.5 Hz, 1H), 2.89 (dd, *J* = 13.7, 9.7 Hz, 1H), 2.45 (dd, *J* = 13.7, 2.4 Hz, 1H), 2.31 (s, 2H), 1.08 (s, 7H). ^{13}C NMR (125 MHz, $CDCl_3$) 169.61, 143.80, 140.70, 137.41, 133.90, 133.10, 132.74, 129.34, 128.73, 128.65, 127.38, 127.28, 127.26, 125.58, 124.73, 120.03, 119.00, 118.85, 66.81, 62.74, 41.63, 40.49, 38.40, 37.86, 35.59, 35.51, 33.98, 31.67, 30.37, 29.77, 21.39. HRMS (ES) calcd for $C_{24}H_{31}N_2O_3S$ [M+H]$^+$: 427.2055, found 427.2048



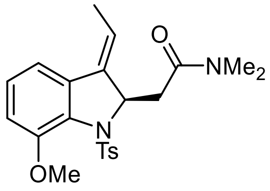
173e
89%
3:2 **E:Z**

Yellowish foam, 198 mg (89% yield), isolated as a 3:2 E:Z mixture of isomers. ^{1}H NMR (500 MHz, CDCl$_3$, mixture of diastereomers): 7.80 (t, *J* = 6.5 Hz, 1H), 7.77 (dd, *J* = 16.0, 7.9 Hz, 2H), 7.60 (t, *J* = 9.6 Hz, 3H), 7.53 (t, *J* = 9.5 Hz, 2H), 7.47 (t, *J* = 12.3 Hz, 2H), 7.44 – 7.33 (m, 4H), 7.32 – 7.23 (m, 6H), 7.20 (ddd, *J* = 11.8, 8.0, 6.2 Hz, 5H), 7.13 (dd, *J* = 10.3, 3.9 Hz, 3H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 7.8 Hz, 1H), 6.79 (dd, *J* = 11.1, 3.8 Hz, 1H), 6.69 (d, *J* = 2.0 Hz, 1H), 6.63 (s, 1H), 5.67 (dt, *J* = 8.0, 2.4 Hz, 1H), 5.29 (dtd, *J* = 5.7, 3.8, 1.9 Hz, 1H), 3.03 (d, *J* = 0.7 Hz, 6H), 3.00 (s, 4H), 2.95 (s, 3H), 2.93 – 2.87 (m, 1H), 2.86 – 2.80 (m, 1H), 2.60 (dd, *J* = 14.6, 2.7 Hz, 1H), 2.36 – 2.30 (m, 4H), 2.26 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) 169.68, 169.58, 144.33, 144.09, 144.01, 142.19, 138.15, 137.42, 136.63, 135.11, 133.73, 132.17, 129.63, 129.53, 129.47, 128.78, 128.74, 128.57, 128.46, 128.33, 128.18, 127.50, 127.41, 127.26, 127.17, 126.74, 125.12, 124.21, 124.12, 123.67, 120.11, 119.83, 117.71, 117.20, 64.08, 63.37, 42.27, 37.97, 37.88, 37.41, 35.60, 35.49, 21.41, 21.38. HRMS (ES) calcd for C$_{26}$H$_{27}$N$_2$O$_3$S [M+H]$^+$: 447.1742, found 447.1739



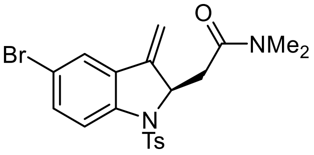
173f
93%

White foam, 199 mg (93% yield), isolated as a single diastereomer. ^{1}H NMR (500 MHz, CDCl$_3$): 7.80 (dd, *J* = 8.6, 0.9 Hz, 1H), 7.70 – 7.63 (m, 2H), 7.52 – 7.45 (m, 1H), 7.46 – 7.32 (m, 5H), 7.11 (td, *J* = 7.7, 1.0 Hz, 1H), 6.05 (d, *J* = 2.3 Hz, 1H), 5.61 (td, *J* = 4.9, 2.4 Hz, 1H), 4.27 – 4.08 (m, 3H), 3.35 (dd, *J* = 15.3, 5.0 Hz, 1H), 3.24 (dd, *J* = 15.3, 4.9 Hz, 1H), 3.14 (s, 3H), 2.81 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) 168.80, 133.32, 132.37, 130.20, 129.03, 127.13, 125.01, 121.55, 116.99, 107.66, 63.43, 60.23, 38.53, 37.89, 35.45, 14.25. HRMS (ES) calcd for $C_{22}H_{25}N_2O_5S$ $[M+H]^+$: 429.1484, found 429.1491.



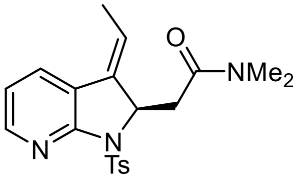
173g
84%
4:1 **E:Z**

Yellowish foam, 173 mg (84% yield), isolated as a 4:1 E:Z mixture of diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.2 Hz, 2H), 7.17 – 7.10 (m, 3H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 5.56 (q, *J* = 7.3 Hz, 1H), 5.19 (dd, *J* = 7.5, 6.3 Hz, 1H), 3.89 (s, 3H), 2.89 (s, 1H), 2.88 (s, 3H), 2.81 (dt, *J* = 14.9, 5.0 Hz, 1H), 2.47 (dd, *J* = 14.9, 8.2 Hz, 1H), 2.34 (s, 3H), 1.67 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 169.53, 152.92, 143.42, 137.00, 135.17, 134.80, 132.57, 128.86, 128.12, 127.93, 127.69, 127.55, 121.39, 117.39, 112.95, 112.67, 66.85, 56.13, 40.32, 37.48, 35.38, 21.44, 13.86. HRMS (ES) calcd for $C_{22}H_{27}N_2O_4S$ $[M+H]^+$: 415.1692, found 415.1689.



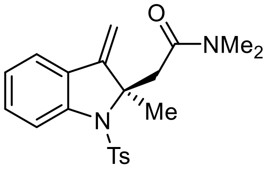
173h
90%

White foam, 201 mg (90% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.6 Hz, 1H), 7.62 – 7.58 (m, 1H), 7.40 (d, *J* = 2.0 Hz, 1H), 7.37 (dd, *J* = 8.6, 2.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 5.33 (d, *J* = 2.7 Hz, 1H), 5.18 (dt, *J* = 8.3, 2.7 Hz, 2H), 3.21 (dd, *J* = 16.0, 2.9 Hz, 1H), 3.01 (s, 3H), 2.99 (s, 3H), 2.79 (dd, *J* = 16.1, 9.1 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 169.46, 144.49, 144.02, 142.35, 132.63, 131.70, 129.82, 127.33, 123.99, 117.96, 117.56, 105.98, 63.19, 41.83, 37.25, 35.45, 21.52. HRMS (ES) calcd for $C_{20}H_{22}BrN_2O_3S$ $[M+H]^+$: 449.0535, found 449.0525.



173i
98%
5:1 **E:Z**

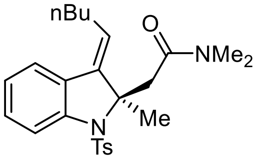
White foam, 189 mg (98% yield), isolated as a 5:1 Z:E mixture of diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 4.8 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 7.4 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 2H), 6.90 (dd, *J* = 7.6, 5.1 Hz, 1H), 5.99 – 5.90 (m, 1H), 5.38 (d, *J* = 6.5 Hz, 1H), 3.27 (dd, *J* = 15.9, 2.6 Hz, 1H), 3.02 (s, 3H), 2.98 (s, 3H), 2.81 (dd, *J* = 15.8, 8.7 Hz, 1H), 2.35 (s, 3H), 1.92 – 1.88 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 169.61, 156.86, 147.83, 147.44, 144.12, 135.72, 134.51, 132.39, 129.42, 127.88, 127.61, 122.73, 119.03, 118.99, 118.62, 62.07, 42.55, 37.32, 35.47, 21.54, 14.46.. HRMS (ES) calcd for $C_{20}H_{24}N_3O_3S$ $[M+H]^+$: 386.1538, found 386.1526.



173k
97%

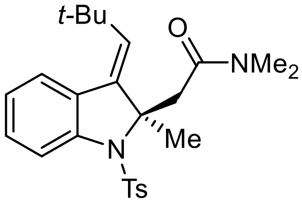
Yellowish foam, 186 mg (97% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 – 7.76 (m, 2H), 7.55 – 7.50 (m, 1H), 7.48 – 7.43 (m, 1H), 7.21 (dd, *J* = 9.6, 1.7 Hz, 3H), 7.00 (td, *J* = 7.5, 0.9 Hz, 1H), 5.43 (d, *J* = 1.1 Hz, 1H), 4.83 (d, *J* = 1.0 Hz, 1H), 3.60 (d, *J* = 16.0 Hz, 1H), 2.97 (s, 3H), 2.86 (d, *J* = 16.0 Hz, 1H), 2.73 (s, 3H), 2.36 (s, *J* = 7.5 Hz, 3H), 1.74 (s, 3H).

HRMS (ES) calcd for $C_{20}H_{24}N_3O_3S$ $[M+H]^+$: 386.1538, found 386.1526.



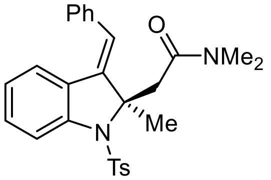
173l
74%

White foam, 162 mg (74% yield). ^1H NMR (500 MHz, $CDCl_3$) 7.80 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 7.16 (t, *J* = 8.0 Hz, 1H), 6.99 (t, *J* = 7.6 Hz, 1H), 5.31 (t, *J* = 6.9 Hz, 1H), 3.43 (d, *J* = 15.3 Hz, 1H), 2.92 (s, 3H), 2.89 (d, *J* = 15.3 Hz, 1H), 2.76 (s, 3H), 2.43 (dd, *J* = 14.6, 7.1 Hz, 2H), 2.35 (s, 3H), 1.79 (d, *J* = 11.9 Hz, 3H), 1.53 – 1.45 (m, 2H), 1.42 – 1.30 (m, 3H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 169.61, 156.86, 147.83, 147.44, 144.12, 135.72, 134.51, 132.39, 129.42, 127.88, 127.61, 122.73, 119.03, 118.99, 118.62, 62.07, 42.55, 37.32, 35.47, 21.54, 14.46. HRMS (ES) calcd for $C_{25}H_{33}N_2O_3S$ $[M+H]^+$: 441.2212, found 441.2209.



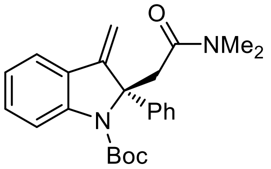
173m
90%

Yellowish foam, 198 mg (90% yield). ^1H NMR (500 MHz, $CDCl_3$) 7.82 (d, *J* = 8.5 Hz, 2H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.17 – 7.12 (m, 1H), 7.03 – 6.96 (m, 1H), 5.34 (s, 1H), 3.45 (d, *J* = 15.2 Hz, 1H), 2.93 (s, 3H), 2.88 (d, *J* = 15.2 Hz, 1H), 2.79 (s, 3H), 2.37 (s, 3H), 1.79 (s, 3H), 1.26 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) 168.68, 143.81, 143.45, 132.57, 129.54, 128.60, 127.45, 126.88, 122.19, 114.03, 73.88, 43.78, 37.97, 35.41, 31.48, 30.05, 21.45. HRMS (ES) calcd for $C_{25}H_{33}N_2O_3S$ $[M+H]^+$: 441.2212, found 441.2209


173n

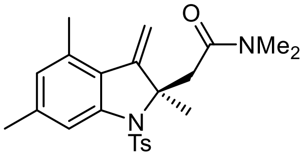
95%

Yellowish foam, 218 mg (95% yield). ^1H NMR (500 MHz, $CDCl_3$) 7.83 (d, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.37 – 7.33 (m, 3H), 7.28 – 7.18 (m, 2H), 7.14 – 7.02 (m, 2H), 6.73 – 6.61 (m, 1H), 6.30 (s, 1H), 3.69 (d, *J* = 15.9 Hz, 1H), 2.98 (s, 3H), 2.91 (d, *J* = 15.9 Hz, 1H), 2.77 (s, 3H), 2.37 (s, 3H), 1.87 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 168.41, 143.92, 143.78, 143.54, 137.19, 129.51, 129.49, 128.54, 127.20, 126.84, 126.77, 124.10, 122.17, 118.93, 113.82, 73.00, 43.88, 37.71, 35.35, 21.43. HRMS (ES) calcd for $C_{27}H_{29}N_2O_3S$ $[M+H]^+$: 461.1899, found 461.1890


173o

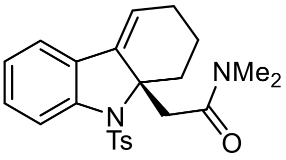
90%

White foam, 186 mg (95% yield). ^1H NMR (500 MHz, $CDCl_3$) 8.24 (t, *J* = 9.6 Hz, 1H), 7.58 (d, *J* = 6.0 Hz, 1H), 7.45 – 7.28 (m, 11H), 5.45 (d, *J* = 0.9 Hz, 1H), 2.98 – 2.90 (m, 1H), 2.90 – 2.85 (m, 4H), 2.83 – 2.65 (m, 6H), 2.54 – 2.29 (m, 3H), 1.31 – 1.11 (m, 9H).


173p

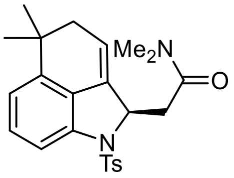
90%

White foam, 185 mg (90% yield). ^{1}H NMR (500 MHz, CDCl$_3$) 7.78 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 4.1 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 2H), 6.61 (s, 1H), 5.35 (s, 1H), 4.85 (s, 1H), 3.56 (d, *J* = 15.9 Hz, 1H), 2.94 (s, 3H), 2.83 (d, *J* = 15.9 Hz, 1H), 2.72 (s, 3H), 2.39 (s, 3H), 2.34 (s, 3H), 2.26 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) 168.51, 152.03, 143.86, 143.39, 139.31, 134.85, 129.45, 126.72, 126.71, 122.85, 112.20, 102.73, 72.47, 43.57, 37.63, 35.27, 29.01, 21.85, 21.52, 21.43. HRMS (ES) calcd for $C_{27}H_{28}N_2O_3S$ [M+H]$^+$: 461.1878, found 461.1880



173q
80%

Yellowish foam, 164 mg (80% yield). ^{1}H NMR (500 MHz, CDCl$_3$) 7.83 (d, *J* = 8.2 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.35 (t, *J* = 8.3 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 3H), 7.03 (t, *J* = 7.5 Hz, 1H), 5.89 (t, *J* = 3.9 Hz, 1H), 3.11 (s, 1H), 3.03 (d, *J* = 4.1 Hz, 1H), 2.99 (d, *J* = 4.6 Hz, 1H), 2.81 – 2.79 (m, 1H), 2.75 (s, 3H), 2.35 (s, 3H), 2.31 (m, 1H), 2.24 (d, *J* = 4.5 Hz, 1H), 2.20 – 2.17 (m, 1H), 2.14 (d, *J* = 4.2 Hz, 1H), 1.99 – 1.95 (m, 1H), 1.90 (s, 1H), 1.52 (dd, *J* = 8.9, 3.2 Hz, 1H). ^{13}C NMR (125 MHz, CDCl$_3$) 169.10, 143.40, 141.60, 139.45, 139.40, 129.71, 129.62, 128.77, 126.20, 124.01, 120.40, 119.45, 114.72, 71.68, 40.96, 38.82, 35.44, 29.37, 23.19, 21.49, 18.14. HRMS (ES) calcd for $C_{23}H_{27}N_2O_3S$ [M+H]$^+$: 411.1742, found 411.1740.

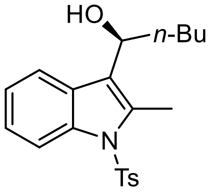


173r
96%

Yellowish foam, 203 mg (96% yield). ^{1}H NMR (500 MHz, $CDCl_3$) 7.63 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.17 (dd, *J* = 7.5, 5.7 Hz, 3H), 6.92 (d, *J* = 7.6 Hz, 1H), 5.59 (d, *J* = 1.6 Hz, 1H), 5.14 (d, *J* = 9.7 Hz, 1H), 3.35 (dd, *J* = 16.0, 2.8 Hz, 1H), 3.01 (s, 3H), 3.00 (s, 3H), 2.73 (dd, *J* = 16.0, 9.9 Hz, 1H), 2.34 (s, 3H), 2.24 – 2.03 (m, 2H), 1.13 (d, *J* = 5.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) 169.95, 143.97, 141.70, 139.92, 135.73, 129.70, 129.65, 127.38, 126.81, 118.89, 116.62, 113.30, 62.91, 41.31, 40.36, 37.22, 35.32, 33.24, 28.78, 28.06, 21.51. HRMS (ES) calcd for $C_{24}H_{29}N_2O_3S$ $[M+H]^+$: 425.1899, found 425.1895.

General procedure for the Corey-Bakshi-Shibata reduction of the ketones 174a-e

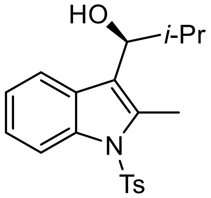
A 25 mL recovery flask equipped with a Teflon-coated magnetic stir bar was charged with toluene (10 ml), **174a-e** (1 mmol) and solution of (R)-MeCBS (1M in toluene, 100 μl, 0.1 mmol) (or solution of (S)-MeCBS for **175b**). Resulting solution was cooled to -40°C by means of dry ice-acetonitrile bath, and the solution of catecholborane (1 M in THF, 2.0 ml, 2 mmol) was added dropwise other 10 min. Resulting solution was stirred at -40°C until TLC analysis indicated the complete conversion of the starting material. Resulting solution was warmed to room temperature, diluted with 1M NaOH (aq.) (20 ml), organic layer was separated and washed with several portions of 1M NaOH (aq.) until the aqueous phase turns colorless (3-4 times by 20 ml aq. NaOH). Organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to provide crude **212** as dark oil. Purification by flash chromatography (hexanes:EtOAc, 10-30% EtOAc) provided alcohols **175a-e** as yellow foams. Racemic samples of the alcohols were prepared by reduction with $NaBH_4$.



175a

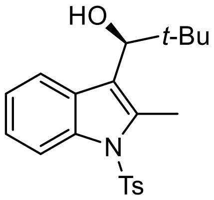
Yellowish foam, 333 mg (90% yield). ^{1}H NMR matches with previously reported. Enantiomeric ratio: 95:5, Rt$_1$ = 16.2, Rt$_2$ = 19.8, Chiralcel AD-H, 10% IPA/Hexanes, 1 mL/min

Enantiomeric ratio for **175b** : 5:95



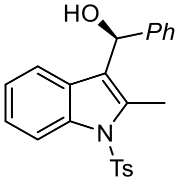
175c

Yellowish foam, 310 mg (87% yield). ^{1}H NMR (500 MHz, CDCl$_3$) 8.26 – 8.15 (m, 1H), 7.82 – 7.66 (m, 1H), 7.59 (dd, *J* = 22.5, 8.3 Hz, 1H), 7.24 – 7.04 (m, 1H), 4.49 (dd, *J* = 9.0, 2.0 Hz, 1H), 2.56 (s, 1H), 2.33 (s, *J* = 17.4 Hz, 1H), 2.24 – 2.14 (m, 1H), 1.12 (d, *J* = 6.5 Hz, 1H), 0.59 (d, *J* = 6.8 Hz, 1H). ^{13}C NMR (125 MHz, CDCl$_3$) 144.71, 136.71, 136.22, 133.44, 129.82, 128.58, 126.29, 123.99, 123.23, 121.85, 120.56, 114.71, 74.19, 34.18, 21.54, 19.49, 19.11, 13.32. HRMS (ES) calcd for $C_{20}H_{24}NO_3S$ [M+H]$^+$: 358.1477, found 358.1470. Enantiomeric ratio: 95:5, Rt$_1$ = 26.9, Rt$_2$ = 36.3, Chiralcel AS-H, 5% IPA/Hexanes, 1 mL/min



175d

Yellowish foam, 333 mg (90% yield). Enantiomeric ratio: 95:5, Rt_1 = 18.5, Rt_2 = 23.8, Chiralcel AS-H, 6% IPA/Hexanes, 1 mL/min

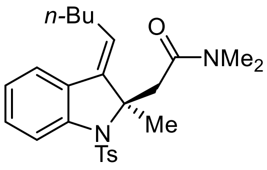


175e

Yellowish foam, 360 mg (92% yield). Enantiomeric ratio: 93:7, Rt_1 = 30.7, Rt_2 = 39.4, Chiralcel OD-H, 10% IPA/Hexanes, 1 mL/min

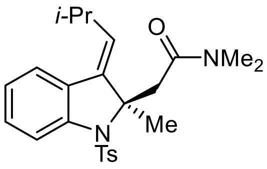
General information on the rearrangements utilizing enantioenriched substrates

Reactions, utilizing enantioenriched substrates, were run under same reaction conditions as with the regular substrates on 0.5 mmol scale.



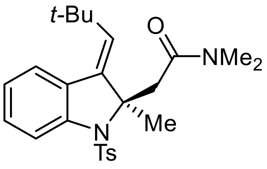
176a-b

Yellowish foam, 214 mg (97% yield). Enantiomeric ratio: 95:5, Rt_1 = 14.5, Rt_2 = 17.9, Chiralcel OD-H, 10% IPA/Hexanes, 1 mL/min



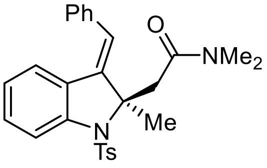
176c

Yellowish foam, 170 mg (80% yield). Enantiomeric ratio: 95:5, Rt_1 = 35.0, Rt_2 = 46.8, Chiralcel OD-H, 5% IPA/Hexanes, 1 mL/min



176d

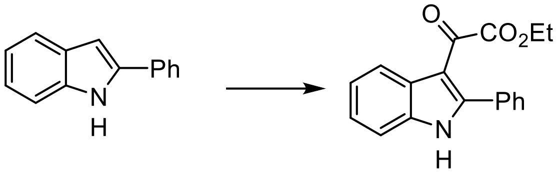
Yellowish foam, 110 mg (50% yield). Enantiomeric ratio: 96:4, Rt_1 = 18.6, Rt_2 = 23.8, Chiralcel OD-H, 9% IPA/Hexanes, 1 mL/min



176e

Yellowish foam, 211 mg (92% yield). Enantiomeric ratio: 93:7, Rt_1 = 23.2, Rt_2 = 39.7, Chiralcel AD-H, 10% IPA/Hexanes, 1 mL/min

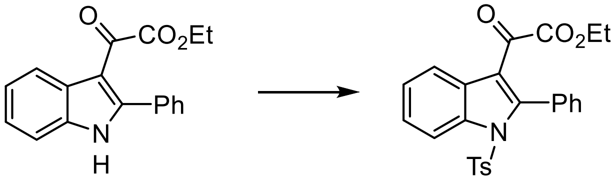
6.4. Experimental procedures and characterization data for chapter 4



211a **211b**

A 50 mL recovery flask equipped with a Teflon-coated magnetic stir bar was charged with Et_2O (15 ml) and oxalyl chloride (1.0 ml, 12.5 mmol). Resulting solution was cooled to 0°C by means of ice water bath, and the solution of 2-phenylindole (966 mg, 5 mmol) in Et_2O (5 ml) was added dropwise other 10 min. Resulting solution was warmed to room temperature and stirred at ambient temperature for 3 hours, when TLC analysis indicated complete conversion of the starting material. Resulting solution was cooled down to 0°C and carefully quenched with anhydrous ethanol (1.2 ml, 20 mmol). Resulting mixture was stirred at ambient temperature for 3 h, concentrated under the reduced pressure, diluted with EtOAc and washed successively with H_2O, sat. $NaHCO_3$ (aq.) and brine. Combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to provide crude **211b** as a yellowish solid. Purification by flash chromatography (hexanes:EtOAc, 5-30% EtOAc) provided ester **211b** as a yellow solid (1.0 g, 70% yield).

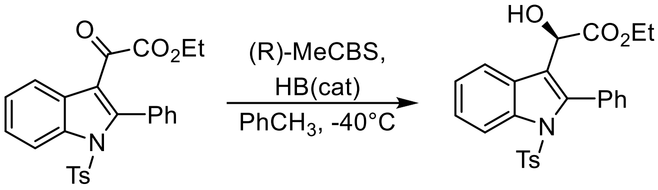
^{1}H NMR (500 MHz, $CDCl_3$): 8.35 (br. s, 1H), 7.72 – 7.66 (m, 1H), 7.63 (ddd, *J* = 7.9, 1.9, 0.8 Hz, 1H), 7.51 – 7.38 (m, 3H), 7.33 (dt, *J* = 9.1, 4.3 Hz, 1H), 7.20 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.15 – 7.05 (m, 1H), 6.83 (dd, *J* = 2.2, 0.9 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H).. ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.87, 132.41, 129.28, 129.01, 127.70, 125.53, 125.15, 122.35, 120.65, 120.26, 110.85, 100.00, 63.10, 13.91. HRMS (ES) calcd for $C_{18}H_{16}NO_3$ $[M+H]^+$: 294.1130, found 294.1145



211b **211**

A 50 mL recovery flask equipped with a Teflon-coated magnetic stir bar was charged with THF (10 ml) and NaH (60% dispersion in oil, 88 mg, 2.2 mmol). Resulting slurry was cooled to 0°C by means of ice water bath, and the solution of methyl 2-oxo-2-(2-phenyl-1H-indol-3-yl)acetate (558 mg, 2 mmol) in THF (3 ml) was added dropwise other 10 min. Resulting slurry was warmed to room temperature and stirred at ambient temperature for 30 min, after that time *p*-toluenesulfonyl chloride was added in one portion. Resulting solution was stirred at room temperature for 1 hour, when TLC analysis indicated complete conversion of the starting material. Resulting solution was carefully quenched with sat. NH_4Cl (aq.), extracted with EtOAc, organic phase was separated, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to provide crude **211**as yellowish solid. Purification by flash chromatography (hexanes:EtOAc, 5-20% EtOAc) provided ester **211** as a yellow solid (823 mg, 95% yield).

^1H NMR (500 MHz, $CDCl_3$): δ 8.39 (d, *J* = 8.3 Hz, 1H), 8.27 (d, *J* = 7.8 Hz, 1H), 7.50 (dd, *J* = 15.0, 7.6 Hz, 2H), 7.47 – 7.38 (m, 3H), 7.30 (dd, *J* = 10.3, 8.5 Hz, 4H), 7.11 (d, *J* = 8.1 Hz, 2H), 3.52 (q, *J* = 7.1 Hz, 2H), 2.34 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.34, 163.22, 147.65, 145.75, 136.56, 135.14, 132.54, 130.37, 129.68, 128.32, 127.44, 127.11, 127.01, 126.39, 125.55, 122.05, 115.34, 61.74, 21.61, 13.53. HRMS (ES) calcd for $C_{24}H_{20}NO_5S$ $[M+H]^+$: 434.1062, found 434.1050



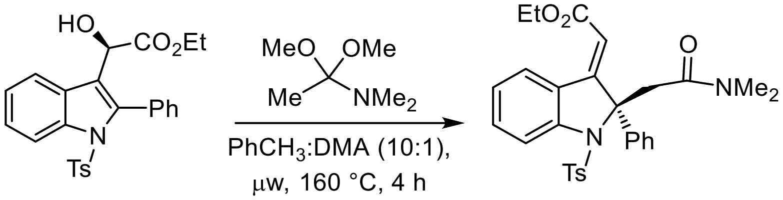
211

212
92% *ee*

A 25 mL recovery flask equipped with a Teflon-coated magnetic stir bar was charged with toluene (7 ml), **211** (447 mg, 1 mmol) and solution of (R)-MeCBS (1M in toluene, 100 μl, 0.1 mmol). Resulting solution was cooled to -40°C by means of dry ice-acetonitrile bath, and the solution of catecholborane (1 M in THF, 2.0 ml, 2 mmol) was added dropwise other 10 min. Resulting solution was stirred at -40°C until TLC analysis indicated the complete conversion of the starting material. Resulting solution was warmed to room temperature, diluted with 1M NaOH (aq.) (15 ml), organic layer was separated and washed with several portions of 1M NaOH (aq.) until the aqueous phase turns colorless (3-4 times by 15 ml aq. NaOH). Organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to provide crude **212** as dark oil. Purification by flash chromatography (hexanes:EtOAc, 10-30% EtOAc) provided alcohol **212** as a yellow semi-solid (359 mg, 80% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (d, *J* = 8.5 Hz, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 24.3, 7.7 Hz, 4H), 7.38 (ddd, *J* = 8.5, 7.3, 1.3 Hz, 2H), 7.34 – 7.29 (m, 2H), 7.27 (dd, *J* = 11.5, 4.4 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 2H), 4.96 (s, 1H), 4.09 (qd, *J* = 10.7, 7.1 Hz, 2H), 2.30 (s, 3H), 1.05 (t, *J* = 7.1 Hz, 3H).

Enantiomeric ratio: 96:4, Rt_1 = 37.7, Rt_2 = 41.9, Chiralcel AD-H, 10% IPA/Hexanes, 1 mL/min



212
92% *ee*

213
70%, 92% *ee*

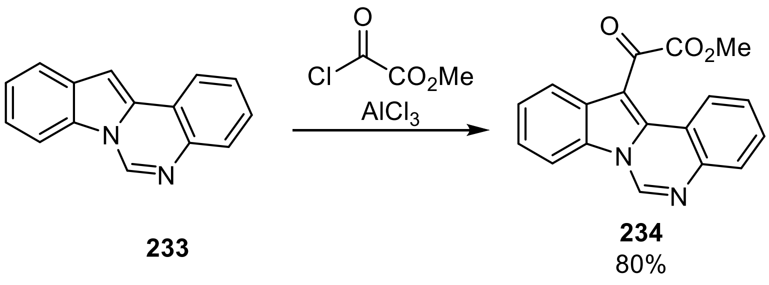
A 5 ml microwave cuvette, equipped with a Teflon-coated magnetic stir bar was charged with toluene (2.0 ml), dimethyl acetamide (0.2 ml) and dimethylacetamide dimethyl acetal (175 μl, 1.2 mmol). Resulting solution was purged with Ar for 20 min, **212** (90 mg, 0.2 mmol) was added under the Ar, and the cuvette was sealed with a Teflon-lined cap. The cuvette was irradiated in a microwave reactor (400 W) at 160°C for 4h, cooled down to ambient temperature, the contents of the cuvette were transferred into a 25 ml recovery flask, the insides of the cuvette were rinsed with EtOAc, and resulting solution was evaporated under the reduced pressure. Residual black oil was purified by flash chromatography (30% hexanes:EtOAc, then DCM:EtOAc, 0-20% EtOAc) to provide **213** as yellowish oil, 73 mg (70% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.07 (d, *J* = 7.1 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.49 – 7.41 (m, 1H), 7.23 – 7.05 (m, 9H), 6.98 (d, *J* = 8.0 Hz, 2H), 5.26 (s, 1H), 4.52 (d, *J* = 15.9 Hz, 1H), 4.19 – 3.97 (m, 2H), 3.30 (d, *J* = 15.9 Hz, 1H), 3.14 (d, *J* = 12.1 Hz, 3H), 2.78 (d, *J* = 16.6 Hz, 3H), 2.29 (d, *J* = 10.9 Hz, 3H), 1.29 – 1.06 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.42, 165.99, 161.74, 147.38, 143.43, 142.24, 137.69, 132.69, 129.29, 129.08, 128.33, 128.13, 126.70, 126.63, 126.21, 122.92, 112.75, 110.48, 76.14, 60.12, 42.00, 37.75, 35.62, 21.44, 14.22.

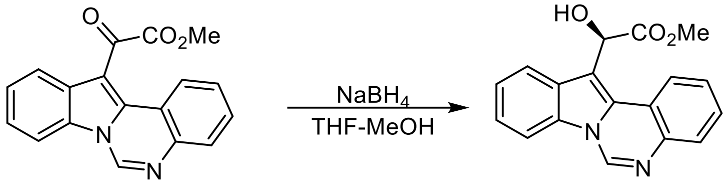
HRMS (ES) calcd for $C_{29}H_{31}N_2O_5S$ $[M+H]^+$: 519.1953, found 519.1954

Enantiomeric ratio: 96:4, Rt_1 = 21.1, Rt_2 = 26.2, Chiralcel AD-H, 10% IPA/Hexanes, 1 mL/min



A 50 mL recovery flask equipped with a Teflon-coated magnetic stir bar was charged with DCM (20 ml) and $AlCl_3$ (5.32 g, 40 mmol). Resulting slurry was cooled to 0°C by means of ice water bath, and methyl chlorooxoacetate (3.7 ml, 40 mmol) was dropwise added to the mixture. Resulting slurry was stirred for 30 min at room temperature, during which partial dissolution of solid was seen. Resulting slurry was cooled to 0°C, and the solution of indoloquinazoline **223** (4.3 g, 20 mmol) in DCM (10 ml) was added dropwise other 10 min. Resulting deep purple slurry was warmed to room temperature and stirred at ambient temperature for 2 hours, when TLC analysis indicated complete conversion of the starting material. Resulting slurry was carefully poured other crushed ice, diluted with DCM (30 ml), layers were separated, organic layer was washed successively with water (3x15 ml) and brine, dried over Na_2SO_4 and concentrated under reduced pressure to provide crude **234** as a yellowish solid. Recrystallization from methanol provided ester **234** as a yellow solid (4.8 g, 80% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.35 (d, *J* = 7.9 Hz, 1H), 9.26 (s, 1H), 8.04 (d, *J* = 7.3 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.87 (dd, *J* = 10.5, 8.3 Hz, 1H), 7.82 (t, *J* = 7.6 Hz, 1H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.60 – 7.51 (m, 1H), 4.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 181.80, 166.06, 154.08, 142.38, 138.84, 135.79, 132.38, 130.26, 128.67, 128.38, 128.08, 126.40, 124.33, 120.24, 112.65, 110.21, 53.04. HRMS (ES) calcd for $C_{18}H_{13}N_2O_3$ $[M+H]^+$: 305.0926, found 305.0928

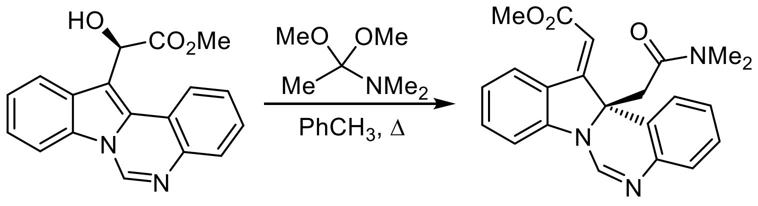


234

232
76%

A 25 mL recovery flask equipped with a Teflon-coated magnetic stir bar was charged with ketoester **234** (608 mg, 2 mmol), THF (10 ml) and MeOH (2 ml). Resulting solution was cooled to 0°C by means of ice water bath, and $NaBH_4$ (76 mg, 2 mmol) was added to the mixture in a single portion. Resulting solution was stirred for 30 min at 0°C, warmed to ambient temperature and stirred at this for another 30 min. Resulting solution was concentrated under reduced pressure, residue was partitioned between water (15 ml) and EtOAc (15 ml), organic layer was separated, aqueous layer was washed with EtOAc (2x10 ml). Combined organic layers were washed with H_2O, brine, dried over Na_2SO_4 and evaporated under the reduced pressure to provide crude **232** as a white solid. Recrystallization from methanol provided alcohol **232** as a white solid (464 mg, 76% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.09 (s, 1H), 8.40 (d, *J* = 8.0 Hz, 1H), 8.01 (s, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.70 – 7.58 (m, 1H), 7.50 (d, *J* = 4.0 Hz, 2H), 6.25 (s, 1H), 3.78 (s, 3H), 3.58 – 3.54 (m, 1H). ^{13}C NMR (125 MHz, DMSO-D6) 173.35, 140.59, 139.16, 129.81, 128.80, 128.72, 128.61, 128.23, 127.91, 126.37, 124.32, 123.12, 120.99, 120.20, 111.61, 109.04, 65.66, 52.40. HRMS (ES) calcd for $C_{18}H_{15}N_2O_3$ $[M+H]^+$: 307.1082, found 307.1079

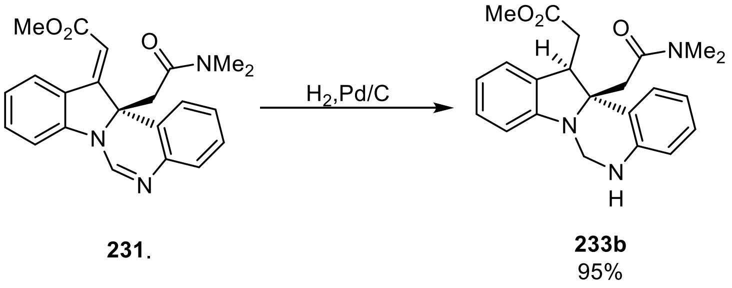


232

231
quant.

A 15 mL recovery flask equipped with a reflux condenser and a Teflon-coated magnetic stir bar was charged with alcohol **232** (306 mg, 1 mmol), toluene (3 ml) and dimethylacetamide dimethyl acetal (440 ml, 3 mmol). Resulting solution was heated under reflux over 4 h, when TLC analysis indicated complete conversion of the starting material. Resulting dark solution was concentrated under reduced pressure, and the residue was purified by flash chromatography (DCM:MeOH, 0-10% MeOH) to provide amide **231** as a yellowish oil (370 mg, 99% yield).

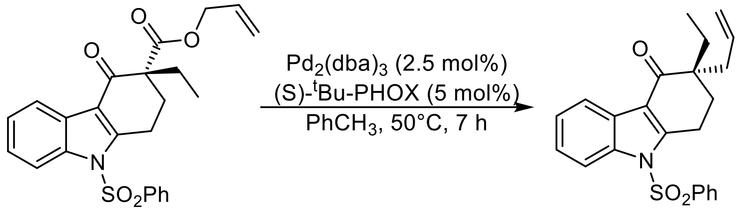
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.95 (d, *J* = 7.8 Hz, 1H), 7.51 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.41 – 7.31 (m, 4H), 7.30 – 7.21 (m, 1H), 7.11 – 7.00 (m, 3H), 6.18 (s, 1H), 3.85 (s, 3H), 3.06 (d, *J* = 16.2 Hz, 1H), 2.79 (s, 3H), 2.76 (s, 3H), 2.66 (d, *J* = 16.3 Hz, 1H).. ^{13}C NMR (125 MHz, $CDCl_3$) 166.93, 166.07, 153.99, 146.70, 142.46, 140.93, 132.95, 129.68, 128.81, 126.02, 125.02, 122.87, 122.09, 111.97, 109.21, 66.75, 51.66, 44.02, 37.41, 35.43.. HRMS (ES) calcd for $C_{22}H_{22}N_3O_3$ $[M+H]^+$: 376.1661, found 376.1658



A Parr apparatus hydrogenation flask was charged with a solution of amide **231** (180 mg, 0.5 mmol) in EtOAc (10 ml) and Pd/C (10 wt.% Pd, 53 mg, 0.05 mmol). The flask was evacuated, filled with hydrogen (75 psi), and the resulting slurry was shook in a Parr hydrogenation apparatus over 24 h, when TLC analysis indicated the complete conversion of the starting material. At this point the pressure was released and the flask was purged with N_2. The reaction mixture was filtered through a pad of celite, filter cake was washed with EtOAc (3x10 ml), filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography (DCM:EtOAc, 0-50% EtOAc) to provide amide **233b** as a yellowish oil (180 mg, 95% yield).

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.30 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.06 (t, *J* = 7.1 Hz, 3H), 6.90 (td, *J* = 8.1, 1.4 Hz, 1H), 6.69 (dt, *J* = 14.9, 5.3 Hz, 2H), 6.65 – 6.59 (m, 1H), 6.35 (dd, *J* = 8.0, 1.0 Hz, 1H), 4.83 (d, *J* = 13.2 Hz, 1H), 4.71 (d, *J* = 13.2 Hz, 1H), 4.19 (dd, *J* = 11.3, 3.8 Hz, 1H), 3.80 (dd, *J* = 14.7, 3.8 Hz, 1H), 3.68 (s, 3H), 3.28 (d, *J* = 14.0 Hz, 1H), 2.84 (s, 3H), 2.82 – 2.74 (m, 2H), 2.48 (s, 43). ^{13}C NMR (125 MHz, CDCl$_3$) 172.91, 169.81, 148.11, 141.83, 133.05, 128.08, 127.79, 127.56, 125.40, 124.80, 120.30, 118.01, 115.79, 109.59, 69.86, 51.95, 51.42, 46.77, 38.94, 37.46, 37.38, 35.59. HRMS (ES) calcd for $C_{22}H_{26}N_3O_3$ $[M+H]^+$: 380.1974, found 380.1971

6.5. Experimental procedures and characterization data for chapter 5



248

249
92%
90% *ee*

A 100 mL Schlenk flask equipped with a Teflon-coated magnetic stir bar was charged with degassed toluene (35ml), Pd$_2$(dba)$_3$ (160 mg, 0.175 mmol) and (S)-*t*-Bu-PHOX (136 mg, 0.35 mmol)[131][132]. Resulting purple solution was purged with Ar for 20 min under extensive stirring, after which a solution of ketoester **248**[133] (3.06 g, 7 mmol) in degassed toluene (10 ml) was added to the mixture. The Schlenk flask was sealed with a Teflon stopper, and the solution was heated to 60°C for 4h, when the TLC analysis indicated complete conversion of the starting material. Resulting solution was transferred to a 100 ml recovery flask, the Schlenk flask was rinsed with EtOAc (2x5 ml). Combined mixture was evaporated under the reduced pressure, and the brownish residue was directly loaded on column. Purification by flash chromatography (Hexanes:EtOAc, 2-20% EtOAc) provided ketone **249** as a yellowish semisolid (2.53 g, 92% yield). Determination of the enantiomeric purity of the sample proved to be tricky at this stage – the purity of the sample was measured at a later stage of the synthesis.

^{1}H NMR (500 MHz, CDCl$_3$): δ 8.39 – 8.29 (m, 1H), 8.25 – 8.14 (m, 1H), 7.97 – 7.85 (m, 2H), 7.72 – 7.59 (m, 1H), 7.52 (dd, *J* = 15.3, 7.6 Hz, 2H), 7.48 – 7.35 (m, 2H), 5.94 – 5.74 (m, 1H), 5.10 (d, *J* = 4.7 Hz, 1H), 5.08 (s, 1H), 3.40 – 3.34 (m, 2H), 2.54 – 2.48 (m, 1H), 2.31 (dd, *J*

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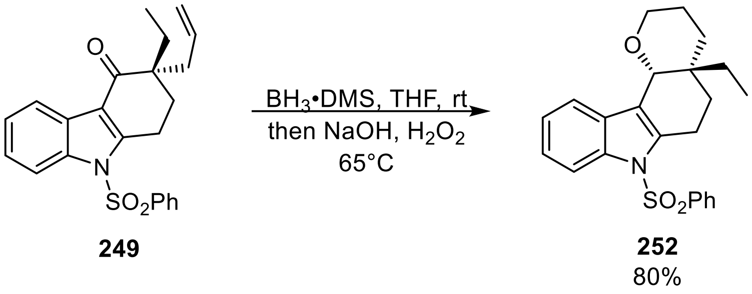
[131] The ligand was prepared according to : PREPARATION OF (S)-Tert-ButylPHOX. *Organic Syntheses* **2009**, *86*, 181.

[132] For the racemic synthesis, dppe (5 mol.%) was used as a ligand

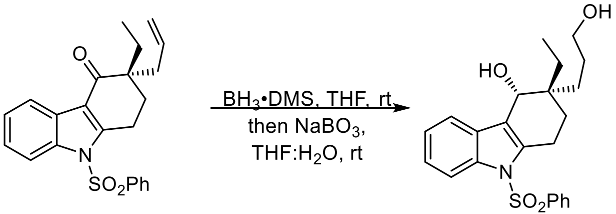
[133] Compound **248** was previously synthesized by the group of Lupton *et.al.*: Gartshore Christopher J.; Lupton David W. *Angew. Chem., Int. Ed.* **2013**, *52*, 4113

= 13.9, 7.7 Hz, 1H), 1.73 (dq, *J* = 14.9, 7.4 Hz, 1H), 1.63 (dq, *J* = 14.5, 7.4 Hz, 1H), 0.91 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.62, 149.18, 138.55, 136.27, 134.41, 134.17, 129.62, 129.59, 129.55, 126.48, 126.46, 126.27, 125.29, 125.22, 124.91, 124.88, 122.00, 117.99, 116.83, 113.81, 113.75, 47.99, 38.63, 31.05, 27.05, 21.59, 8.36. HRMS (ES) calcd for $C_{23}H_{24}NO_3S$ $[M+H]^+$: 394.1477, found 394.1468



A 25 mL recovery flask equipped with a reflux condenser and a Teflon-coated magnetic stir bar was charged with the solution of ketone **249** (195 mg, 0.5 mmol) in THF (5 ml). The flask was cooled to 0°C by means of ice water bath, and BH_3*DMS (48 μl, 0.5 mmol) was dropwise added to the solution. Resulting mixture was stirred at 0°C for 30 min, warmed to room temperature and stirred for additional 60 min, when NMR of an aliquot indicated the complete disappearance of the alkene (TLC analysis proved to be complicated due to the presence of boronic acid residues). Resulting solution was diluted with 1M NaOH (aq.) (7.5 ml) and 30% H_2O_2 (160 ml, 1.5 mmol), and the resulting byphasic mixture was stirred extensively upon heating to 65°C over 60 min. Resulting mixture was cooled to room temperature, transferred to separatory funnel, extracted with EtOAc (3x12 ml). Combined organic extracts were washed with water, brine, dried over Na_2SO_4 and evaporated under the reduced pressure to provide crude **252.** Purification by flash chromatography (Hexanes:EtOAc, 10-40% EtOAc) provided ether **252** as a yellowish oil (158 mg, 80% yield) as a single diastereomer as indicated by ^{1}H NMR.

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.13 (d, *J* = 7.9 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.19 (t, *J* = 15.5 Hz, 2H), 4.27 (s, 1H), 3.78 (s, 1H), 3.54 (t, *J* = 10.6 Hz, 1H), 3.06 (d, *J* = 17.4 Hz, 1H), 2.91 (dt, *J* = 29.3, 16.2 Hz, 1H), 2.72 – 2.50 (m, 1H), 2.22 (s, 1H), 1.76 (dd, *J* = 42.3, 27.8 Hz, 1H), 1.50 – 1.41 (m, 1H), 1.39 – 1.23 (m, 1H), 1.13 (d, *J* = 29.6 Hz, 1H), 0.85 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 136.98, 133.62, 129.41, 129.25, 128.39, 126.34, 124.11, 123.53, 114.16, 74.99, 33.96, 28.32, 21.89, 7.45. HRMS (ES) calcd for $C_{23}H_{26}NO_3S$ $[M+H]^+$: 396.1633, found 396.1630

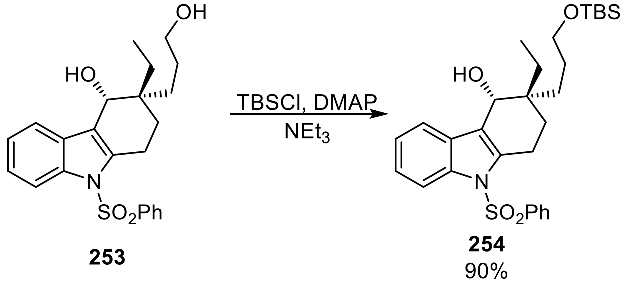


249

253
88%

A 50 mL recovery flask equipped with a Teflon-coated magnetic stir bar was charged with the solution of ketone **249** (1.95 g, 5 mmol) in THF (25 ml). The flask was cooled to 0°C by means of ice water bath, and BH_3*DMS (480 μl, 5 mmol) was dropwise added to the solution. Resulting mixture was stirred at 0°C for 30 min, warmed to room temperature and stirred for additional 60 min, when NMR of an aliquot indicated the complete disappearance of the alkene (TLC analysis proved to be complicated due to the presence of boronic acid residues). Resulting solution was diluted with H_2O (15 ml), and $NaBO_3$*H_2O (998 mg, 10 mmol) was added to the solution. Resulting byphasic mixture was stirred extensively at room temperature over 3 hours, transferred to separatory funnel and extracted with EtOAc (3x20 ml). Combined organic extracts were washed with water, brine, dried over Na_2SO_4 and evaporated under the reduced pressure to provide crude **253.** Purification by flash chromatography (Hexanes:EtOAc, 10-40% EtOAc) provided diol **253** as a yellowish semi-solid (1.81 g, 88% yield) as a single diastereomer as indicated by ^{1}H NMR.

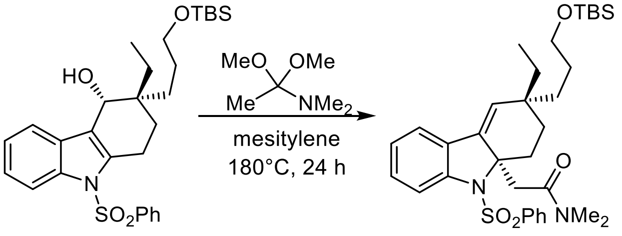
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.1 Hz, 1H), 7.79 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 7.0 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 2H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.33 – 7.28 (m, 1H), 4.54 (s, 1H), 3.71 (ddd, *J* = 12.3, 8.7, 4.7 Hz, 1H), 3.13 – 2.98 (m, 1H), 2.91 – 2.71 (m, 1H), 1.78 – 1.61 (m, 4H), 1.53 – 1.43 (m, 1H), 1.13 (td, *J* = 14.8, 7.1 Hz, 2H), 0.91 – 0.75 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.03, 136.83, 136.72, 133.78, 129.45, 129.34, 126.34, 124.37, 123.65, 119.28, 118.51, 114.38, 67.71, 63.46, 39.26, 28.34, 26.98, 25.63, 23.16, 21.86, 8.06. HRMS (ES) calcd for $C_{23}H_{27}NO_4S$ $[M+H-H_2O]^+$: 396.1627, found 396.1628



A 50 mL recovery flask equipped with a Teflon-coated magnetic stir bar was charged with the solution of diol **253** (1.21 g, 3 mmol) in DCM (20 ml), DMAP (37 mg, 0.3 mmol) and NEt_3 (0.6 ml, 4.5 mmol). The flask was cooled to 0°C by means of ice water bath, and TBSCl (475 mg, 5.25 mmol) was added to the solution in a single portion. Resulting mixture was stirred at 0°C for 60 min, warmed to room temperature and stirred for additional 2 hours, when TLC analysis indicated the complete consumption of the starting material. Resulting solution was quenched with sat. NH_4Cl (aq.) (15 ml), the mixture was transferred to separatory funnel, layers were separated and aqueous layer was extracted with DCM (3x20 ml). Combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated under the reduced pressure to provide crude **254.** Purification by flash chromatography (Hexanes:EtOAc, 5-20% EtOAc) provided ether **254** as a yellowish solid (1.41 g, 90% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.1 Hz, 1H), 7.75 (dd, *J* = 8.4, 0.9 Hz, 2H), 7.58 (d, *J* = 7.3 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.31 – 7.20 (m, 3H), 4.53 (s, 1H), 3.54 – 3.36 (m, 2H), 3.05 (ddd, *J* = 18.5, 5.5, 3.1 Hz, 1H), 2.91 – 2.73 (m, 1H), 1.72 (ddd, *J* = 16.1, 10.6, 5.7 Hz, 1H), 1.69 – 1.56 (m, 3H), 1.54 – 1.44 (m, 2H), 1.38 (ddd, *J* = 21.5, 14.1, 6.6 Hz, 2H), 1.29 – 1.14 (m, 1H), 1.05 (d, *J* = 4.2 Hz, 1H), 0.92 (dd, *J* = 12.6, 5.0 Hz, 3H), 0.85 (s, 9H), 0.04 – -0.02 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.09, 136.74, 136.62, 133.65, 129.37, 129.24, 126.25, 124.27, 123.57, 119.64, 118.60, 114.33, 67.88, 63.63, 38.87, 27.45, 27.06, 26.69, 25.97, 25.89, 25.10, 21.90, 18.26, 7.25, -5.33, -5.34. HRMS (ES) calcd for $C_{29}H_{41}NO_4SSi$ $[M+H-H_2O]^+$: 510.2482, found 510.2486

Enantiomeric ratio: 95:5, Rt_1 = 8.4, Rt_2 = 11.5, Chiralcel AD-H, 10% IPA/Hexanes, 1 mL/min



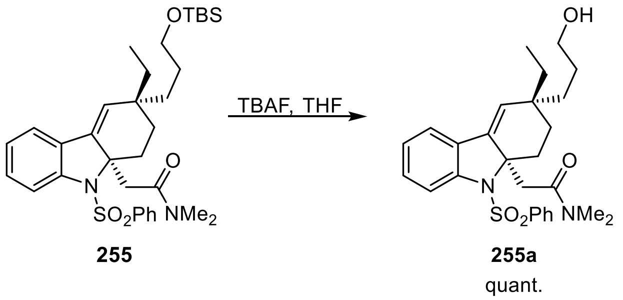
254

255
85%
90% ee

A 25 mL pressure-resistant Schlenk flask equipped with a Teflon-coated magnetic stir bar was charged with freshly distilled degassed mesitylene (8 ml), dimethylacetamide dimethyl acetal (877 ml, 6 mmol) and **254** (1.05 g, 2 mmo, after which a l). Resulting solution was purged with Ar for 20 min under extensive stirring, the Schlenk flask was sealed with a Teflon stopper, and the solution was heated to 180°C for 24h, when the TLC analysis indicated complete conversion of the starting material. Resulting solution was cooled to room temperature, transferred to a 100 ml recovery flask, the Schlenk flask was rinsed with EtOAc (2x5 ml). Combined mixture was evaporated under the reduced pressure, and the brownish residue was directly loaded on column.

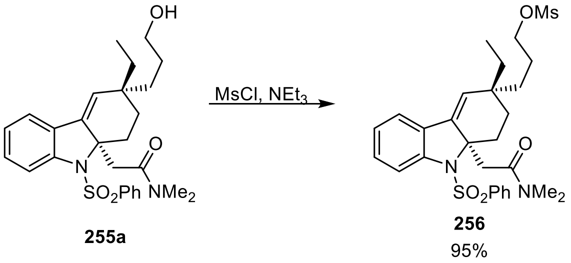
Purification by flash chromatography (Hexanes:EtOAc, 10-30% EtOAc, then DCM:EtOAc, 0-20% EtOAc) provided amide **255** as a yellowish oil (1.01 g, 85% yield).

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.88 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.38 (dd, *J* = 10.4, 5.1 Hz, 3H), 7.26 (dd, *J* = 14.0, 5.1 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 5.61 (s, 1H), 3.38 (t, *J* = 4.8 Hz, 2H), 3.12 (s, *J* = 10.9 Hz, 3H), 2.94 – 2.86 (m, 2H), 2.83 (s, 4H), 2.77 (d, *J* = 13.1 Hz, 1H), 1.93 (t, *J* = 12.7 Hz, 1H), 1.63 (t, *J* = 13.8 Hz, 3H), 1.43 (q, *J* = 7.1 Hz, 3H), 1.28 – 1.09 (m, 5H), 0.90 (t, *J* = 7.4 Hz, 4H), 0.87 (d, *J* = 2.0 Hz, 10H), 0.02 – -0.03 (m, 6H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.62, 149.18, 138.55, 136.27, 134.41, 134.17, 129.62, 129.59, 129.55, 126.48, 126.46, 126.27, 125.29, 125.22, 124.91, 124.88, 122.00, 117.99, 116.83, 113.81, 113.75, 47.99, 38.63, 31.05, 27.05, 21.59, 8.36. HRMS (ES) calcd for $C_{33}H_{49}N_2O_4SSi$ [M+H]$^+$: 597.3182, found 597.3175



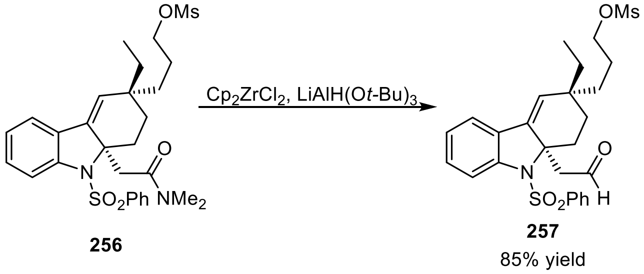
To a 25 mL recovery flask equipped with a Teflon-coated magnetic stir bar was added the solution of amide **255** (298 mg, 0.5 mmol) in THF (10 ml), followed by the solution of TBAF (1M in THF, 0.5 ml, 0.5 mmol). Resulting mixture was stirred at room temperature for 1 hour, when TLC analysis indicated complete conversion of the starting material. Resulting solution was diluted with sat. NH_4Cl (aq.) (10 ml) and transferred to separatory funnel, layers were separated and the aqueous layer was extracted with EtOAc (3x12 ml). Combined organic extracts were washed with water, brine, dried over Na_2SO_4 and evaporated under the reduced pressure to provide crude **255a.** Purification by flash chromatography (DCM:EtOAc, 0-15% EtOAc) provided alcohol **255a** as a yellowish oil (241 mg, quant. yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 – 7.85 (m, 1H), 7.73 – 7.62 (m, 2H), 7.51 – 7.44 (m, 1H), 7.41 – 7.34 (m, 3H), 7.24 (dd, *J* = 7.2, 1.0 Hz, 1H), 7.09 (td, *J* = 7.5, 0.9 Hz, 1H), 5.58 (s, 1H), 3.38 (dd, *J* = 14.7, 8.7 Hz, 2H), 3.10 (d, *J* = 5.4 Hz, 3H), 2.89 (dd, *J* = 8.0, 4.2 Hz, 1H), 2.88 – 2.84 (m, 1H), 2.81 (s, 4H), 2.72 (d, *J* = 13.3 Hz, 1H), 1.98 – 1.86 (m, 1H), 1.67 – 1.54 (m, 3H), 1.41 (q, *J* = 7.4 Hz, 2H), 1.29 – 1.03 (m, 6H), 0.88 (t, *J* = 7.5 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.87, 142.67, 142.07, 139.33, 132.48, 129.79, 129.10, 129.02, 127.93, 126.06, 124.52, 120.86, 115.68, 71.89, 63.38, 40.71, 38.80, 38.03, 37.18, 35.45, 33.93, 29.18, 27.80, 27.38, 8.63. HRMS (ES) calcd for $C_{27}H_{35}N_2O_4S$ $[M+H]^+$: 483.2318, found 483.2310



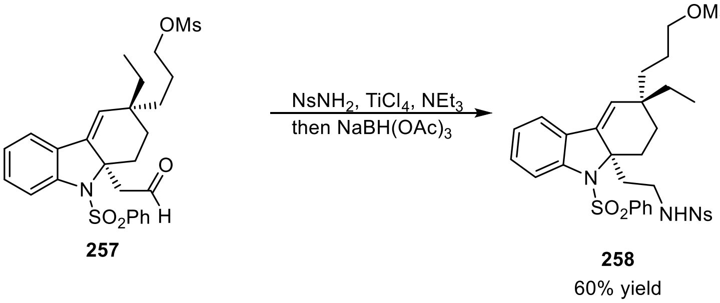
To a 25 mL recovery flask equipped with a Teflon-coated magnetic stir bar was added the solution of amide **255a** (241 mg, 0.5 mmol) in DCM (10 ml), followed by NEt_3 (139 μl, 1.0 mmol). Resulting mixture was cooled to 0°C and MsCl (43 μl, 0.55 mmol) was dropwise added to the mixture. The resulting solution was allowed to warm to room temperature and stirred at ambient temperature for 2 hour, when TLC analysis indicated complete conversion of the starting material. Resulting solution was diluted with sat. NH_4Cl (aq.) (10 ml) and transferred to separatory funnel, layers were separated and the aqueous layer was extracted with DCM (3x12 ml). Combined organic extracts were washed with water, brine, dried over Na_2SO_4 and evaporated under the reduced pressure to provide crude **256.** Purification by flash chromatography (Hexanes:EtOAc, 0-40% EtOAc) provided amide **256** as a yellowish oil (266 mg, 95% yield).

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.92 – 7.81 (m, 1H), 7.70 – 7.63 (m, 2H), 7.54 – 7.47 (m, 1H), 7.41 – 7.33 (m, 3H), 7.30 – 7.22 (m, 1H), 7.11 (td, *J* = 7.5, 0.9 Hz, 1H), 5.55 (s, 1H), 4.00 – 3.91 (m, 2H), 3.09 (s, *J* = 5.6 Hz, 3H), 2.93 (s, *J* = 3.7 Hz, 2H), 2.91 (ddd, *J* = 8.7, 4.9, 2.5 Hz, 1H), 2.81 (s, 4H), 2.74 (dd, *J* = 16.9, 8.7 Hz, 1H), 2.02 – 1.87 (m, 1H), 1.59 (dq, *J* = 15.3, 3.8 Hz, 2H), 1.41 (q, *J* = 7.4 Hz, 2H), 1.34 – 1.24 (m, 3H), 1.20 – 1.11 (m, 1H), 0.89 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 168.77, 163.29, 142.14, 139.98, 132.78, 129.56, 129.32, 129.11, 126.98, 125.99, 124.58, 124.01, 120.92, 118.37, 115.73, 71.73, 70.20, 40.70, 38.80, 37.92, 37.28, 36.83, 35.45, 33.93, 31.53, 29.71, 29.04, 27.38, 24.43, 8.60. HRMS (ES) calcd for $C_{28}H_{37}N_2O_6S_2$ [M+H]$^+$: 561.2093, found 561.2074



To a 25 mL recovery flask equipped with a Teflon-coated magnetic stir bar was added the solution of amide **256** (266 mg, 0.5 mmol) in THF (10 ml), followed by Cp_2ZrCl_2 (161 mg, 0.55 mmol). Resulting mixture was cooled to 0°C and solution of LiAlH(O*t*-Bu)$_3$ (1M in THF, 550 μl, 0.55 mmol) was dropwise added to the mixture. The resulting solution was stirred at 0°C for 1 hour, when TLC analysis indicated complete conversion of the starting material. Resulting solution was diluted with 1M HCl (10 ml) and transferred to separatory funnel, layers were separated and the aqueous layer was extracted with EtOAc (3x12 ml). Combined organic extracts were washed with water, brine, dried over Na_2SO_4 and evaporated under the reduced pressure to provide crude **257.** Purification by flash chromatography (Hexanes:EtOAc, 0-40% EtOAc) provided amide **257** as a yellowish oil (220 mg, 85% yield).

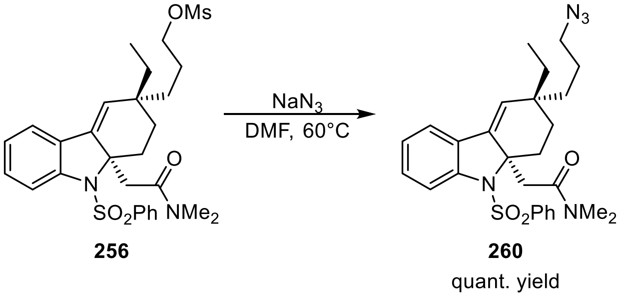
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (t, *J* = 3.0 Hz, 1H), 7.79 (t, *J* = 8.2 Hz, 2H), 7.69 (dd, *J* = 12.7, 7.4 Hz, 2H), 7.60 – 7.51 (m, 2H), 7.45 (dd, *J* = 15.7, 7.8 Hz, 2H), 7.35 (d, *J* = 7.6 Hz, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 5.65 – 5.52 (m, 1H), 4.04 (t, *J* = 6.3 Hz, 2H), 3.50 – 3.35 (m, 2H), 3.06 – 3.02 (m, 1H), 2.95 (s, 3H), 2.85 – 2.72 (m, 2H), 1.77 (ddd, *J* = 29.7, 13.7, 3.8 Hz, 2H), 1.66 – 1.55 (m, 5H), 1.43 (dd, *J* = 14.8, 7.3 Hz, 3H), 1.36 – 1.25 (m, 4H), 1.19 (t, *J* = 7.0 Hz, 1H), 0.90 (t, *J* = 7.4 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.32, 142.26, 141.94, 138.81, 133.09, 129.86, 129.24, 127.13, 126.41, 124.40, 120.72, 115.24, 70.38, 70.02, 52.74, 37.86, 37.34, 36.47, 33.63, 29.72, 28.82, 26.76, 24.44, 8.60. HRMS (ES) calcd for $C_{26}H_{32}NO_6S_2$ $[M+H]^+$: 518.1671, found 518.1655



To a 15 mL recovery flask equipped with a Teflon-coated magnetic stir bar was added the solution of aldehyde **257** (52 mg, 0.1 mmol) in DCM (2 ml), followed by *p*-nitrobenzenesulfonamide (21 mg, 0.1 mmol) and NEt_3 (45 μl, 0.3 mmol). Resulting mixture was cooled to -10°C and the solution of $TiCl_4$ (1M in DCM, 83 μl, 0.08 mmol) was dropwise added to the mixture (upon addition of $TiCl_4$ rapid color change from light-orange to dark brown was observed). The resulting solution was stirred at 0°C for 8 hour, when TLC analysis indicated complete conversion of the starting material. Resulting solution was warmed to room temperature, filtered through celite, filter cake was washed with DCM (3x1 ml). Filtrate was concentrated to

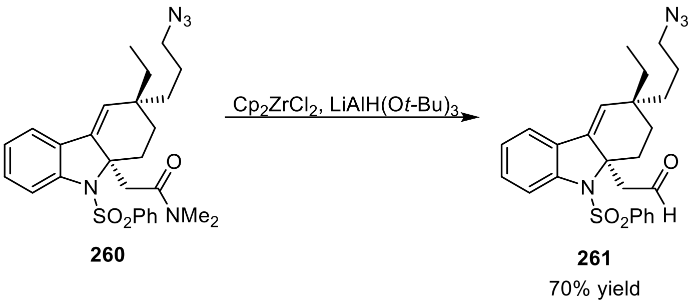
~1 ml, and $Na(OAc)_3BH$ (70 mg, 0.3 mmol) was added in one portion. Resulting slurry was stirred extensively for 12 h, quenched with sat. $NaHCO_3$ (aq.), transferred to separatory funnel, layers were separated and the aqueous layer was extracted with DCM (3x5 ml). Combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated under the reduced pressure to provide crude **258.** Purification by flash chromatography (Hexanes:EtOAc, 0-40% EtOAc) provided amine **258** as a yellowish solid (43 mg, 60% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 – 8.30 (m, 1H), 7.96 – 7.90 (m, 1H), 7.79 – 7.74 (m, 1H), 7.55 (dd, *J* = 7.8, 5.7 Hz, 1H), 7.46 (dd, *J* = 19.6, 11.4 Hz, 2H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 7.06 (dd, *J* = 11.8, 4.3 Hz, 1H), 5.28 (ddd, *J* = 10.2, 5.9, 4.3 Hz, 1H), 4.92 – 4.85 (m, 1H), 4.31 (dt, *J* = 8.1, 3.4 Hz, 1H), 4.18 (ddd, *J* = 12.0, 5.9, 2.5 Hz, 2H), 3.07 (s, 3H), 2.38 – 2.33 (m, 2H), 1.70 – 1.61 (m, 3H), 1.53 (d, *J* = 5.6 Hz, 2H), 0.90 (dd, *J* = 7.6, 6.3 Hz, 3H).



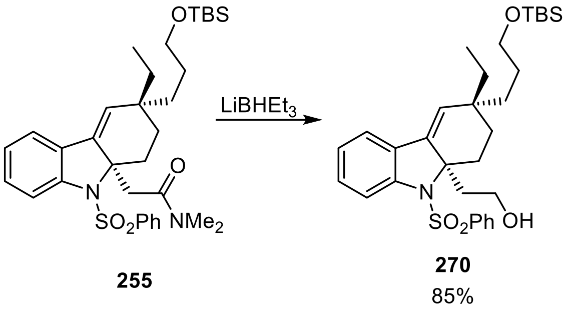
To a 25 mL recovery flask equipped with a Teflon-coated magnetic stir bar was added the solution of amide **256** (112 mg, 0.2 mmol) in DMF (5 ml), followed by NaN_3 (39 mg, 0.6 mmol). The resulting solution was stirred at 60°C for 10 hour, when TLC analysis indicated complete conversion of the starting material. Resulting solution was diluted with water (15 ml) and transferred to separatory funnel, layers were separated and the aqueous layer was extracted with EtOAc (3x12 ml). Combined organic extracts were washed with water, brine, dried over Na_2SO_4 and evaporated under the reduced pressure to provide crude **260.** Purification by flash chromatography (Hexanes:EtOAc, 0-40% EtOAc) provided amide **260** as a yellowish oil (100 mg, quant. yield).

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.88 (dd, *J* = 8.5, 7.9 Hz, 1H), 7.70 – 7.61 (m, 2H), 7.51 – 7.44 (m, 1H), 7.37 (tt, *J* = 9.1, 1.6 Hz, 3H), 7.26 – 7.22 (m, 1H), 7.10 (td, *J* = 7.5, 0.9 Hz, 1H), 5.55 (d, *J* = 9.3 Hz, 1H), 3.13 – 3.07 (m, 3H), 3.02 (dq, *J* = 18.5, 6.0 Hz, 2H), 2.81 (s, 4H), 2.74 – 2.66 (m, 1H), 2.01 – 1.89 (m, 1H), 1.64 – 1.52 (m, 2H), 1.45 – 1.35 (m, 3H), 1.27 – 1.05 (m, 6H), 0.87 (dt, *J* = 14.3, 5.1 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ ^{13}C NMR (101 MHz, CDCl$_3$) δ 168.80, 142.63, 142.12, 139.68, 132.69, 132.56, 129.67, 129.22, 129.02, 128.91, 128.13, 128.07, 127.36, 126.00, 124.56, 120.89, 115.70, 71.79, 51.97, 40.72, 38.79, 38.17, 38.10, 35.44, 33.91, 29.09, 27.37, 24.12, 8.60. HRMS (ES) calcd for $C_{27}H_{34}N_5O_3S$ [M+H]$^+$: 508.2382, found 508.2375



To a 15 mL recovery flask equipped with a Teflon-coated magnetic stir bar was added the solution of amide **260** (50 mg, 0.1 mmol) in THF (5 ml), followed by Cp$_2$ZrCl$_2$ (35 mg, 0.12 mmol). The resulting solution was cooled to 0°C, and the solution of LiAlH(O*t*-Bu)$_3$ (1M in THF, 0.12 ml, 0.12 mmol) was added dropwise over 10 min. Resulting mixture was stirred at room temperature for 30 min, when TLC analysis indicated complete conversion of the starting material. Resulting solution was quenched with 1M HCl (5 ml) and transferred to separatory funnel, layers were separated and the aqueous layer was extracted with EtOAc (3x10 ml). Combined organic extracts were washed with water, brine, dried over Na$_2$SO$_4$ and evaporated under the reduced pressure to provide crude **261.** Compound **261** proved to be unstable on the silica gel, thus, it was used in further transformations without purification (32 mg, 70% yield).

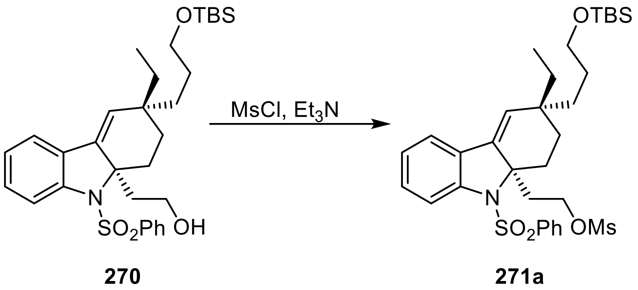
^{1}H NMR (500 MHz, CDCl$_3$) δ 9.72 (t, *J* = 3.0 Hz, 1H), 7.85 – 7.76 (m, 1H), 7.70 (t, *J* = 9.0 Hz, 1H), 7.56 – 7.45 (m, 1H), 7.44 – 7.33 (m, 1H), 7.10 – 6.98 (m, 1H), 5.61 (s, 1H), 3.81 (s, 1H), 3.35 – 3.28 (m, 1H), 3.10 (dt, *J* = 12.2, 5.5 Hz, 1H), 3.06 – 3.00 (m, 2H), 2.71 (t, *J* = 5.2 Hz, 2H), 1.84 – 1.64 (m, 2H), 1.48 – 1.40 (m, 2H), 0.89 (t, *J* = 7.5 Hz, 3H).



To a 15 mL recovery flask equipped with a Teflon-coated magnetic stir bar was added the solution of amide **260** (298 mg, 0.5 mmol) in THF (5 ml). The flask was cooled to -78°C, and the solution of superhydride (1M in THF, 1.5 ml, 1.5 mmol) was dropwise added over 15 min. Resulting solution was slowly warmed to 0°C and stirred at this temperature for 1 h, when TLC analysis indicated complete conversion of the starting material. Resulting solution was quenched with 1M HCl (5 ml) and transferred to separatory funnel, layers were separated and the aqueous layer was extracted with EtOAc (3x10 ml). Combined organic extracts were washed with water, brine, dried over Na_2SO_4 and evaporated under the reduced pressure to provide crude **270.** Purification by column chromatography (DCM:EtOAc, 0-20% EtOAc) provided **270** as colorless oil (236 mg, 85% yield).

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.79 (d, *J* = 7.4 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 6.9 Hz, 1H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.02 (t, *J* = 7.3 Hz, 1H), 5.59 (s, 1H), 3.76 (s, 1H), 3.63 (s, 1H), 3.43 (t, *J* = 5.4 Hz, 2H), 2.73 (d, *J* = 9.5

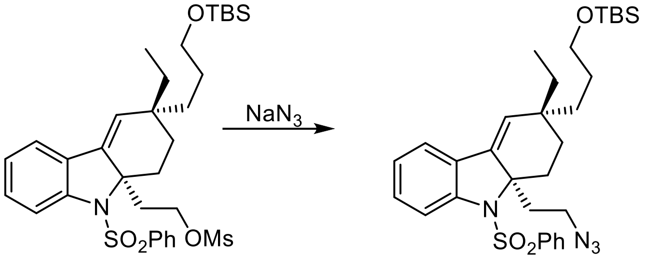
Hz, 1H), 2.39 – 2.29 (m, 1H), 2.07 – 1.97 (m, 1H), 1.76 (t, *J* = 12.1 Hz, 2H), 1.62 (d, *J* = 6.5 Hz, 1H), 1.42 (q, *J* = 7.4 Hz, 2H), 1.25 (t, *J* = 9.5 Hz, 4H), 0.88 (t, *J* = 7.5 Hz, 3H), 0.85 (s, 9H), -0.01 (s, *J* = 0.9 Hz, 6H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 142.44, 141.89, 139.43, 132.65, 129.11, 129.04, 128.90, 128.02, 127.45, 126.44, 123.79, 120.19, 114.72, 72.49, 63.54, 59.22, 42.20, 37.90, 36.90, 33.90, 30.08, 29.37, 27.84, 25.95, 8.66, -5.29. HRMS (ES) calcd for $C_{31}H_{46}NO_4SSi$ [M+H]$^+$: 556.2917, found 556.2910



To a 25 mL recovery flask equipped with a Teflon-coated magnetic stir bar was added the solution of amide **255a** (166 mg, 0.3 mmol) in DCM (10 ml), followed by NEt$_3$ (139 µl, 1.0 mmol). Resulting mixture was cooled to 0°C and MsCl (28 µl, 0.36 mmol) was dropwise added to the mixture. The resulting solution was allowed to warm to room temperature and stirred at ambient temperature for 2 hour, when TLC analysis indicated complete conversion of the starting material. Resulting solution was diluted with sat. NH$_4$Cl (aq.) (10 ml) and transferred to separatory funnel, layers were separated and the aqueous layer was extracted with DCM (3x12 ml). Combined organic extracts were washed with water, brine, dried over Na$_2$SO$_4$ and evaporated under the reduced pressure to provide crude **271a.** Purification by flash chromatography (DCM:EtOAc, 0-30% EtOAc) provided amide **271a** as a yellowish oil (180 mg, 95% yield)

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.80 (t, *J* = 15.0 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.51 (dd, *J* = 18.4, 10.9 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 7.5 Hz, 1H), 7.26 – 7.18 (m, 2H), 7.04 (dd, *J* = 18.1, 10.7 Hz, 1H), 7.04 (dd, *J* = 18.1, 10.7 Hz, 1H), 5.62 (s, *J* = 9.4 Hz, 1H), 4.42 – 4.30

(m, 1H), 4.30 – 4.20 (m, 1H), 3.47 (s, 2H), 2.87 – 2.75 (m, 3H), 2.74 – 2.68 (m, 1H), 2.53 (dd, *J* = 14.4, 6.9 Hz, 1H), 2.29 – 2.16 (m, 2H), 1.75 (t, *J* = 10.9 Hz, 2H), 1.67 – 1.59 (m, 1H), 1.44 (dd, *J* = 14.8, 7.3 Hz, 3H), 1.35 – 1.19 (m, 6H), 0.89 (dd, *J* = 16.3, 9.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.70, 138.91, 132.84, 129.31, 129.15, 127.75, 126.45, 124.15, 120.46, 114.90, 108.06, 71.31, 66.75, 63.34, 38.99, 38.06, 37.14, 36.79, 33.91, 29.83, 29.05, 27.76, 8.73. HRMS (ES) calcd for $C_{32}H_{48}NO_6S2Si$ $[M+H]^+$: 634.2692, found 634.2690

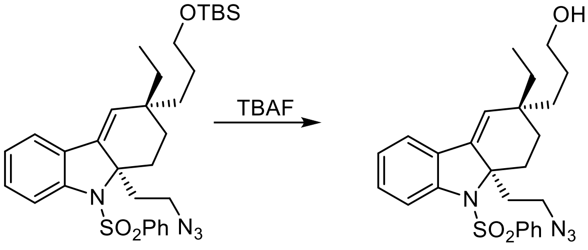


271a **271**

To a 25 mL recovery flask equipped with a Teflon-coated magnetic stir bar was added the solution of amide **256** (180 mg, 0.3 mmol) in DMF (5 ml), followed by NaN_3 (39 mg, 0.6 mmol). The resulting solution was stirred at 60°C for 10 hour, when TLC analysis indicated complete conversion of the starting material. Resulting solution was diluted with water (15 ml) and transferred to separatory funnel, layers were separated and the aqueous layer was extracted with EtOAc (3x12 ml). Combined organic extracts were washed with water, brine, dried over Na_2SO_4 and evaporated under the reduced pressure to provide crude **271.** Purification by flash chromatography (Hexanes:EtOAc, 0-60% EtOAc) provided amide **271** as a yellowish oil (165 mg, quant. yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 14.6 Hz, 2H), 7.82 (d, *J* = 7.6 Hz, 2H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.53 (dd, *J* = 13.2, 6.2 Hz, 2H), 7.44 (dd, *J* = 14.6, 7.0 Hz, 3H), 7.34 (d, *J* = 7.3 Hz, 1H), 7.22 (d, *J* = 7.1 Hz, 1H), 7.03 (dd, *J* = 14.6, 7.3 Hz, 1H), 5.63 (s, 1H), 3.45 (d, *J* = 5.2 Hz, 2H), 3.40 – 3.24 (m, 1H), 3.24 – 3.12 (m, 1H), 2.79 – 2.65 (m, 1H), 2.48 – 2.39 (m, 1H), 2.05

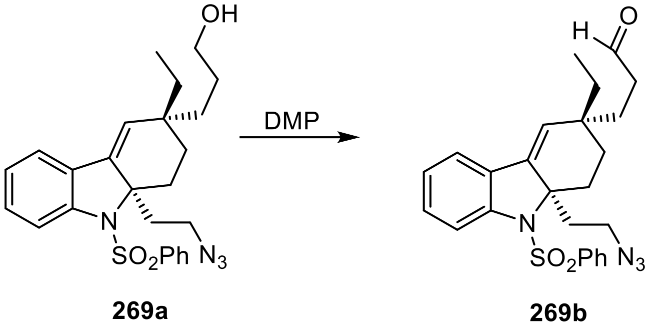
– 1.95 (m, 2H), 1.50 – 1.40 (m, 2H), 0.94 – 0.87 (m, 4H), 0.88 – 0.81 (m, 9H), -0.00 (s, *J* = 4.3 Hz, 6H).



271 **269a**

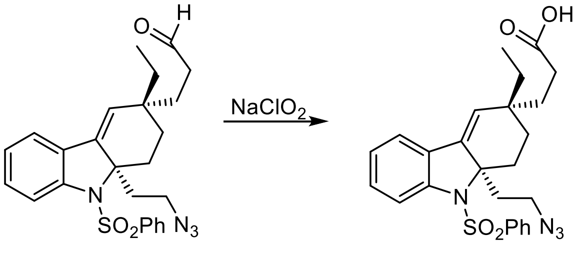
To a 15 mL recovery flask equipped with a Teflon-coated magnetic stir bar was added the solution of amide **271** (116 mg, 0.2 mmol) in THF (10 ml), followed by the solution of TBAF (1M in THF, 0.2 ml, 0.2 mmol). Resulting mixture was stirred at room temperature for 1 hour, when TLC analysis indicated complete conversion of the starting material. Resulting solution was diluted with sat. NH_4Cl (aq.) (10 ml) and transferred to separatory funnel, layers were separated and the aqueous layer was extracted with EtOAc (3x12 ml). Combined organic extracts were washed with water, brine, dried over Na_2SO_4 and evaporated under the reduced pressure to provide crude **269a.** Purification by flash chromatography (DCM:EtOAc, 0-15% EtOAc) provided alcohol **269a** as a yellowish oil (93 mg, quant. yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 – 7.73 (m, 2H), 7.64 (t, *J* = 9.1 Hz, 1H), 7.60 – 7.47 (m, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.33 (dd, *J* = 7.5, 0.7 Hz, 1H), 7.24 – 7.16 (m, 1H), 7.13 – 7.00 (m, 1H), 5.58 (d, *J* = 25.3 Hz, 1H), 3.48 (t, *J* = 5.8 Hz, 2H), 3.35 (ddd, *J* = 12.2, 10.0, 5.5 Hz, 1H), 3.30 – 3.11 (m, 1H), 2.75 – 2.59 (m, 1H), 2.42 – 2.30 (m, 1H), 2.07 – 1.94 (m, 1H), 1.77 (ddd, *J* = 12.8, 11.8, 2.4 Hz, 2H), 1.63 (dd, *J* = 10.1, 1.9 Hz, 1H), 1.46 – 1.36 (m, 2H), 1.33 – 1.20 (m, 2H), 0.95 – 0.78 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.38, 141.80, 139.02, 132.77, 129.29, 129.11, 128.86, 127.42, 126.47, 123.92, 120.14, 114.65, 71.69, 63.37, 47.21, 38.98, 38.03, 37.11, 34.04, 30.07, 29.23, 27.78, 8.72. HRMS (ES) calcd for $C_{25}H_{31}N_4O_3S$ $[M+H]^+$: 467.2117, found 467.2120



To a 15 mL recovery flask equipped with a Teflon-coated magnetic stir bar was added the solution of alcohol **269a** (93 mg, 0.2 mmol) in DCM (10 ml), followed by Dess-Martin periodinane (93 mg, 0.22 mmol). Resulting mixture was stirred at room temperature for 8 hour, when TLC analysis indicated complete conversion of the starting material. Resulting solution was diluted with sat. NH_4Cl (aq.) (10 ml) and transferred to separatory funnel, layers were separated and the aqueous layer was extracted with EtOAc (3x12 ml). Combined organic extracts were washed with water, brine, dried over Na_2SO_4 and evaporated under the reduced pressure to provide crude **269a.** Purification by flash chromatography (DCM:EtOAc, 0-15% EtOAc) provided alcohol **269a** as a yellowish oil (93 mg, quant. yield)..

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (t, *J* = 1.5 Hz, 1H), 7.86 – 7.76 (m, 2H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.60 – 7.50 (m, 1H), 7.44 (ddd, *J* = 12.3, 8.6, 5.6 Hz, 2H), 7.38 – 7.28 (m, 1H), 7.25 – 7.22 (m, 1H), 7.05 (td, *J* = 7.5, 0.9 Hz, 1H), 5.54 (d, *J* = 0.8 Hz, 1H), 3.36 (ddd, *J* = 12.3, 9.8, 5.6 Hz, 1H), 3.28 – 3.17 (m, 1H), 2.78 – 2.66 (m, 1H), 2.37 (ddd, *J* = 11.4, 9.8, 6.5 Hz, 1H), 2.25 – 2.10 (m, 2H), 2.09 – 1.98 (m, 1H), 1.84 – 1.73 (m, 2H), 1.44 (q, *J* = 7.4 Hz, 2H), 0.98 – 0.88 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.68, 142.43, 133.32, 132.95, 129.60, 129.20, 126.46, 126.06, 124.03, 120.23, 114.74, 71.48, 47.16, 39.49, 38.95, 37.68, 33.98, 32.67, 29.87, 28.98, 8.72. HRMS (ES) calcd for $C_{25}H_{31}N_4O_3S$ $[M+H]^+$: 467.2117, found 467.2120



269b **269**

To a 25 mL recovery flask equipped with a Teflon-coated magnetic stir bar was added the solution of aldehyde **269b** (93 mg, 0.2 mmol) in THF (5 ml), followed by Me_2S (50 μL, 0.6 mmol) and aqueous solution of NaH_2PO_4 (500 mg, 4.0 mmol in 5 ml of H_2O). Resulting slurry was cooled to 0°C, a solution of $NaClO_2$ (30 mg, 0.24 mmol) in H_2O was dropwise added to the flask , and the resulting mixture was extensively stirred at room temperature for 1 hour, when TLC analysis indicated complete conversion of the starting material. Resulting solution was diluted with H_2O (10 ml) and transferred to separatory funnel, layers were separated and the aqueous layer was extracted with EtOAc (3x12 ml). Combined organic extracts were washed with water, brine, dried over Na_2SO_4 and evaporated under the reduced pressure to provide crude **269.** Purification by flash chromatography (DCM:EtOAc, 0-15% EtOAc) provided acid **269** as a yellowish oil (96 mg, quant. yield)

^{1}H NMR (500 MHz, $CDCl_3$) 7.86 – 7.74 (m, 2H), 7.67 (dd, *J* = 26.8, 7.7 Hz, 1H), 7.54 (dddd, *J* = 10.9, 6.6, 3.0, 1.8 Hz, 1H), 7.48 – 7.39 (m, 2H), 7.39 – 7.30 (m, 1H), 7.21 (ddd, *J* = 9.4, 8.3, 4.2 Hz, 1H), 7.01 (ddd, *J* = 19.3, 13.0, 4.6 Hz, 1H), 5.56 (s, 1H), 3.36 (ddd, *J* = 12.3, 9.8, 5.5 Hz, 1H), 3.25 – 3.13 (m, 1H), 2.76 – 2.66 (m, 1H), 2.42 – 2.30 (m, 1H), 2.03 (dddd, *J* = 15.6, 14.1, 6.7, 3.8 Hz, 3H), 1.82 – 1.68 (m, 2H), 1.64 – 1.54 (m, 3H), 1.49 – 1.37 (m, 3H), 0.91 (dd, *J* = 14.8, 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.03, 149.23, 142.43, 141.53, 140.05, 132.99, 129.53, 129.19, 128.45, 126.41, 125.95, 123.91, 120.21, 114.58, 71.46, 47.16, 39.03, 37.84, 35.65, 34.16, 30.12, 29.41, 28.94, 8.71. HRMS (ES) calcd for $C_{25}H_{31}N_4O_3S$ $[M+H]^+$: 467.2117, found 467.2120

Appendix.

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

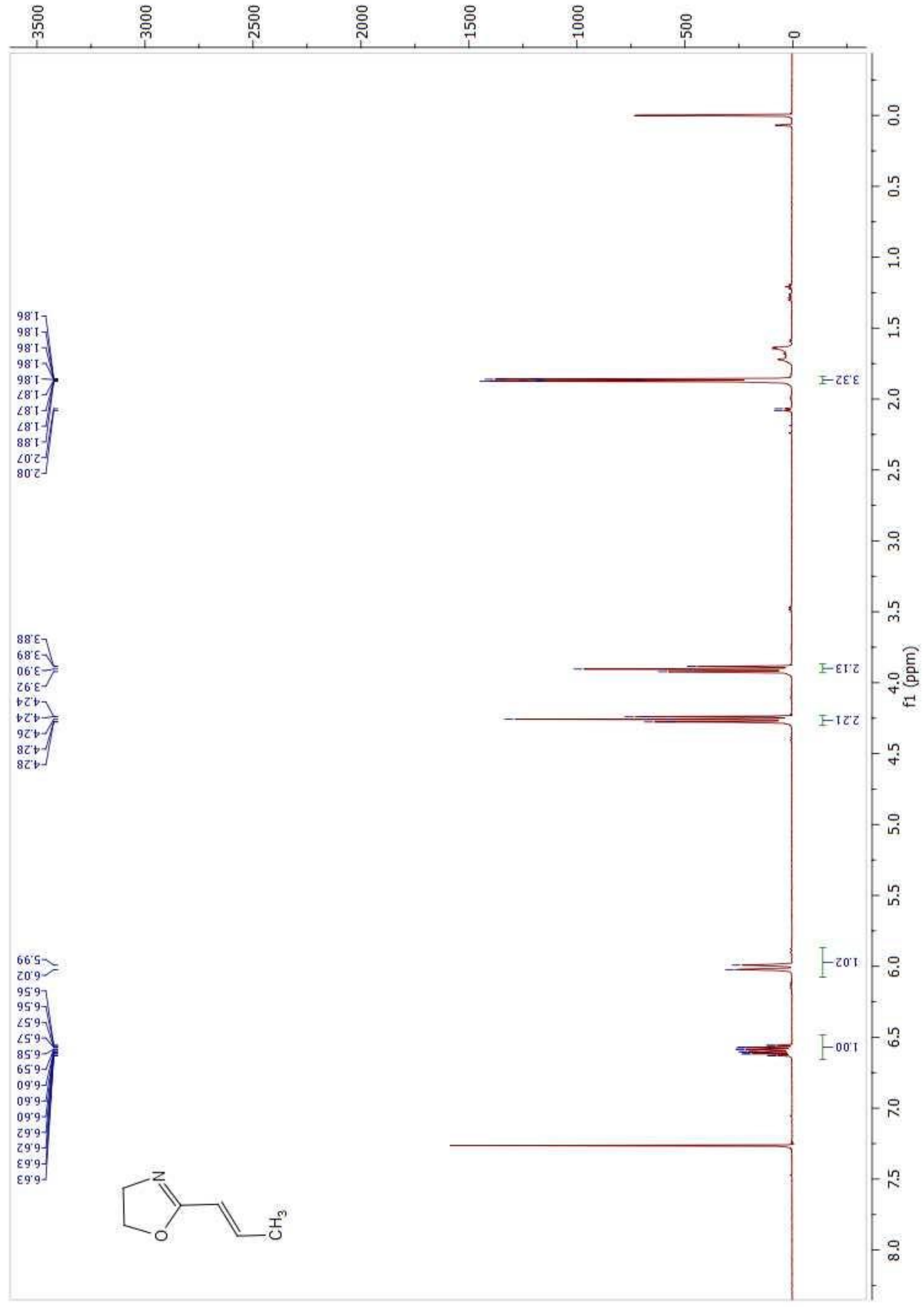


Figure 2. ^{1}H NMR spectrum of **109a** (500 MHz, $CDCl_3$).

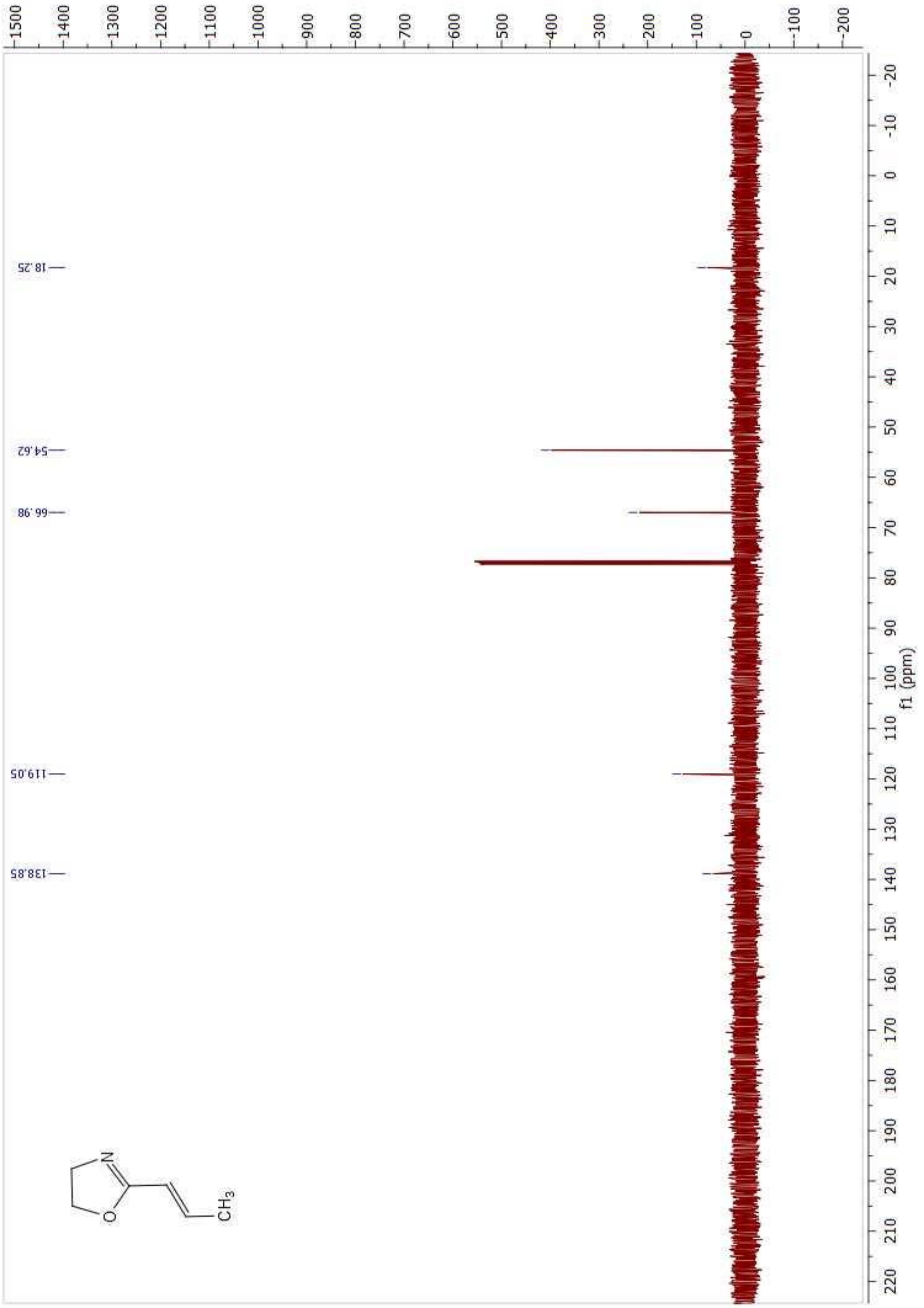


Figure 3. ^{13}C NMR spectrum of **109a** (125 MHz, $CDCl_3$).

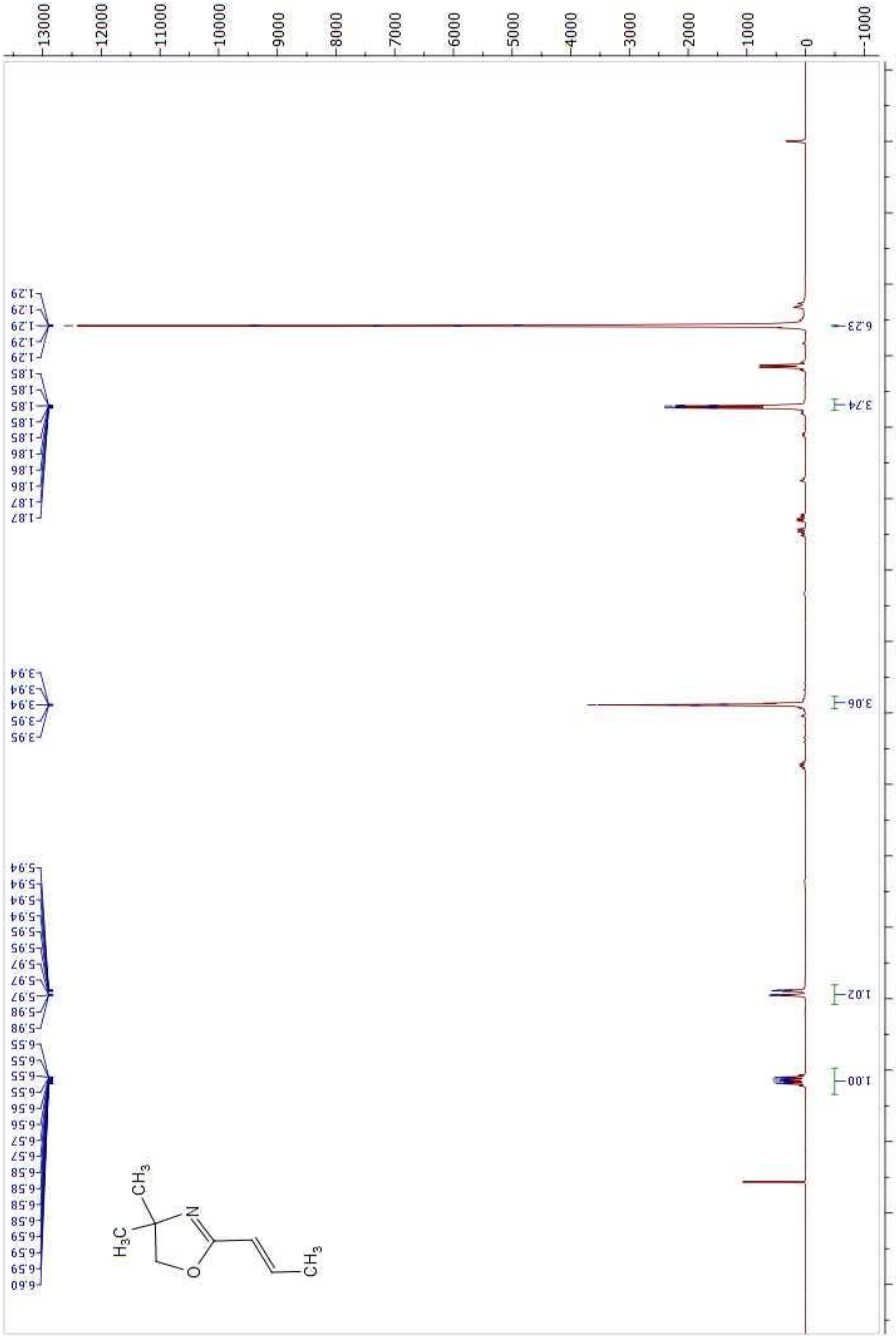


Figure 4. ^{1}H NMR spectrum of **109b** (500 MHz, $CDCl_3$).

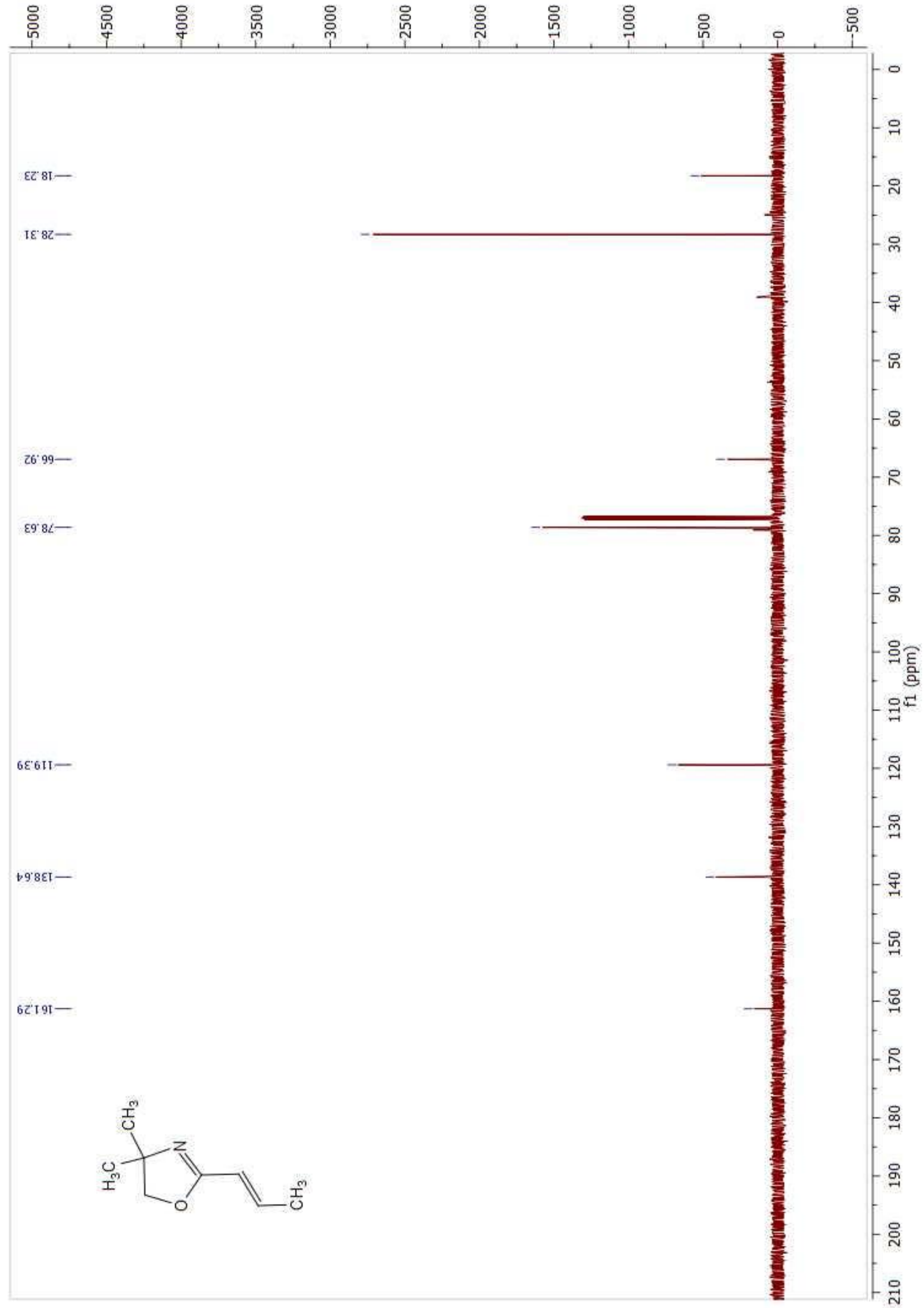


Figure 5. ^{13}C NMR spectrum of **109b** (125 MHz, $CDCl_3$).

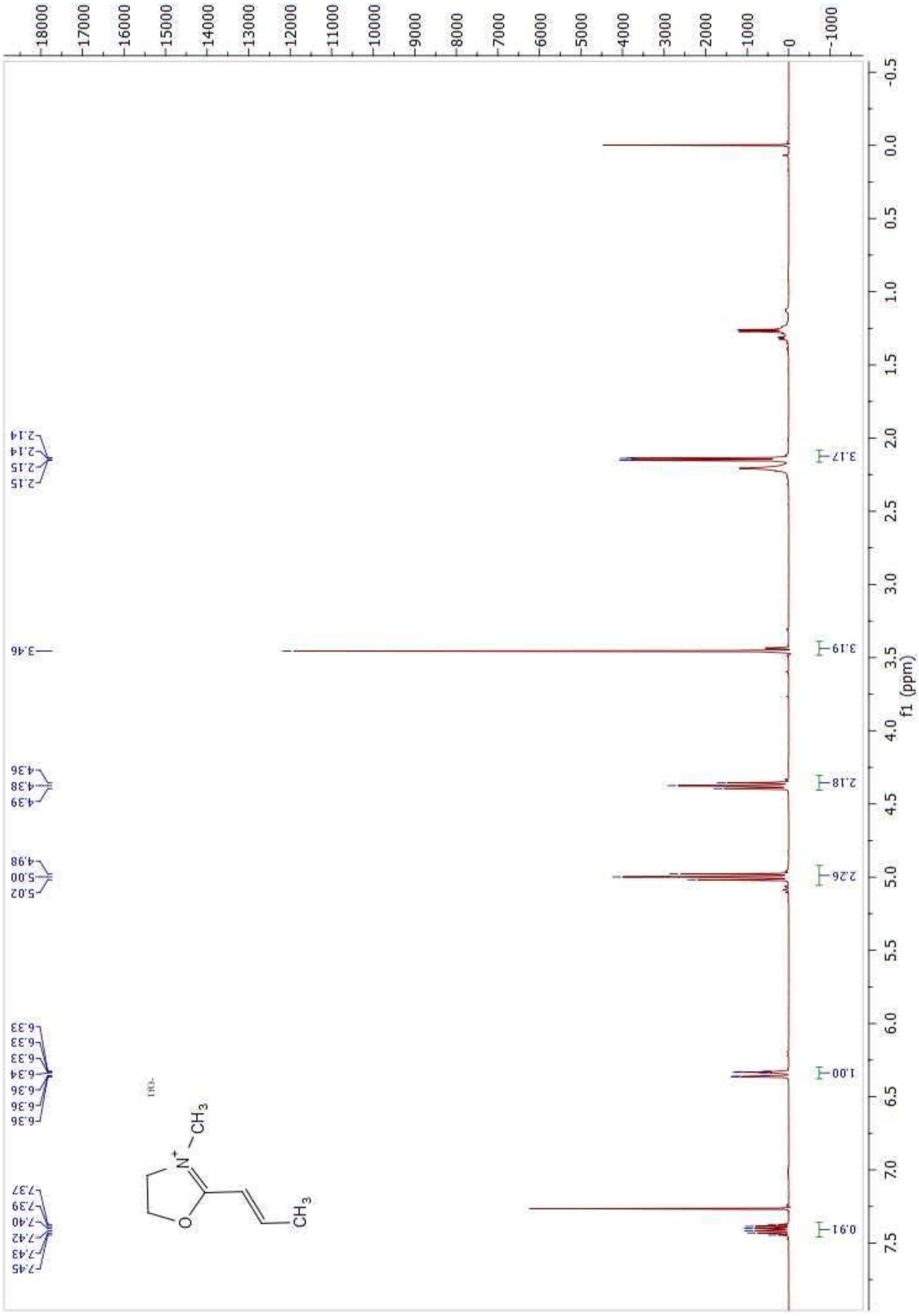


Figure 6. ^{1}H NMR spectrum of **110a** (500 MHz, $CDCl_3$).

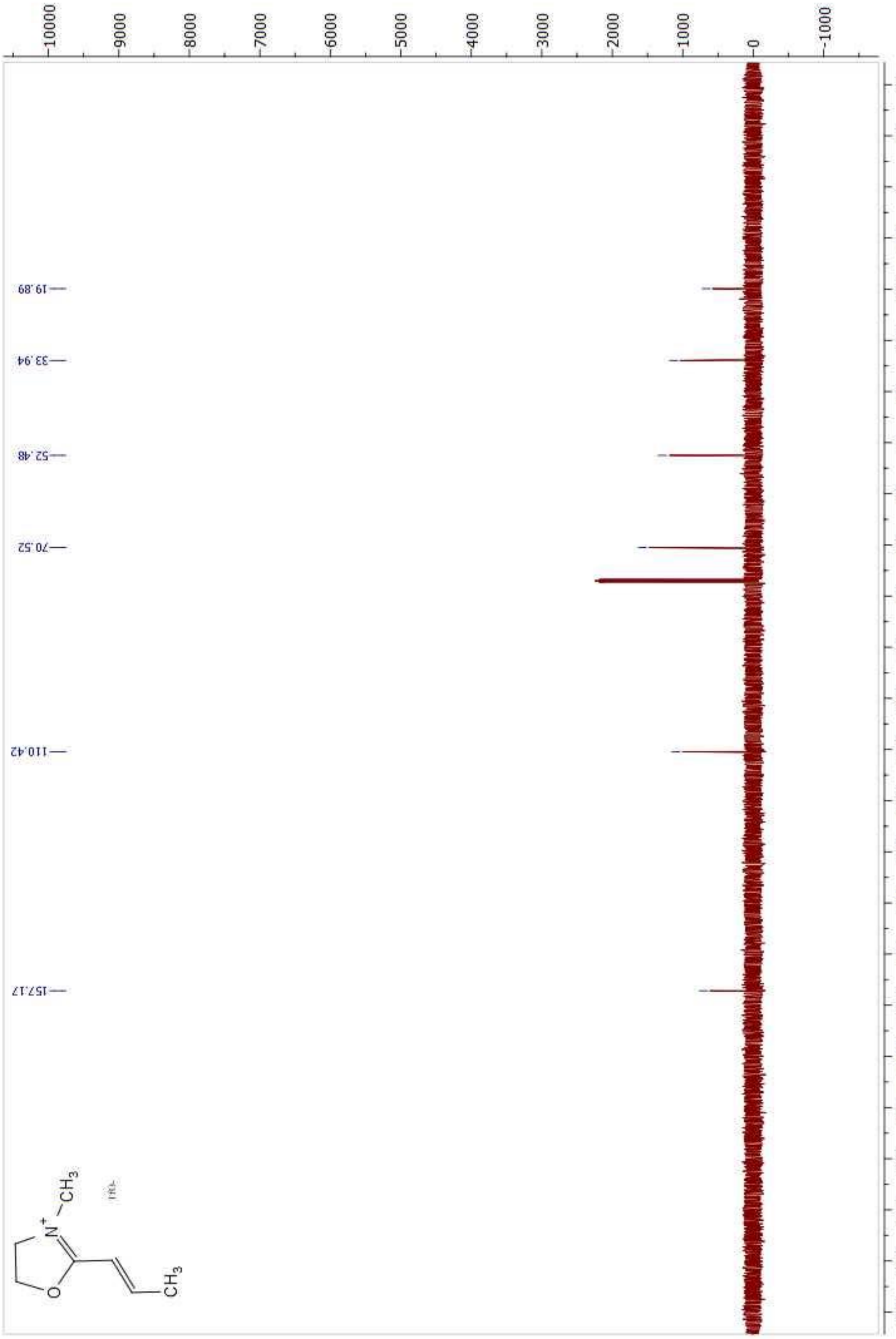


Figure 7. ^{13}C NMR spectrum of **110a** (125 MHz, $CDCl_3$).

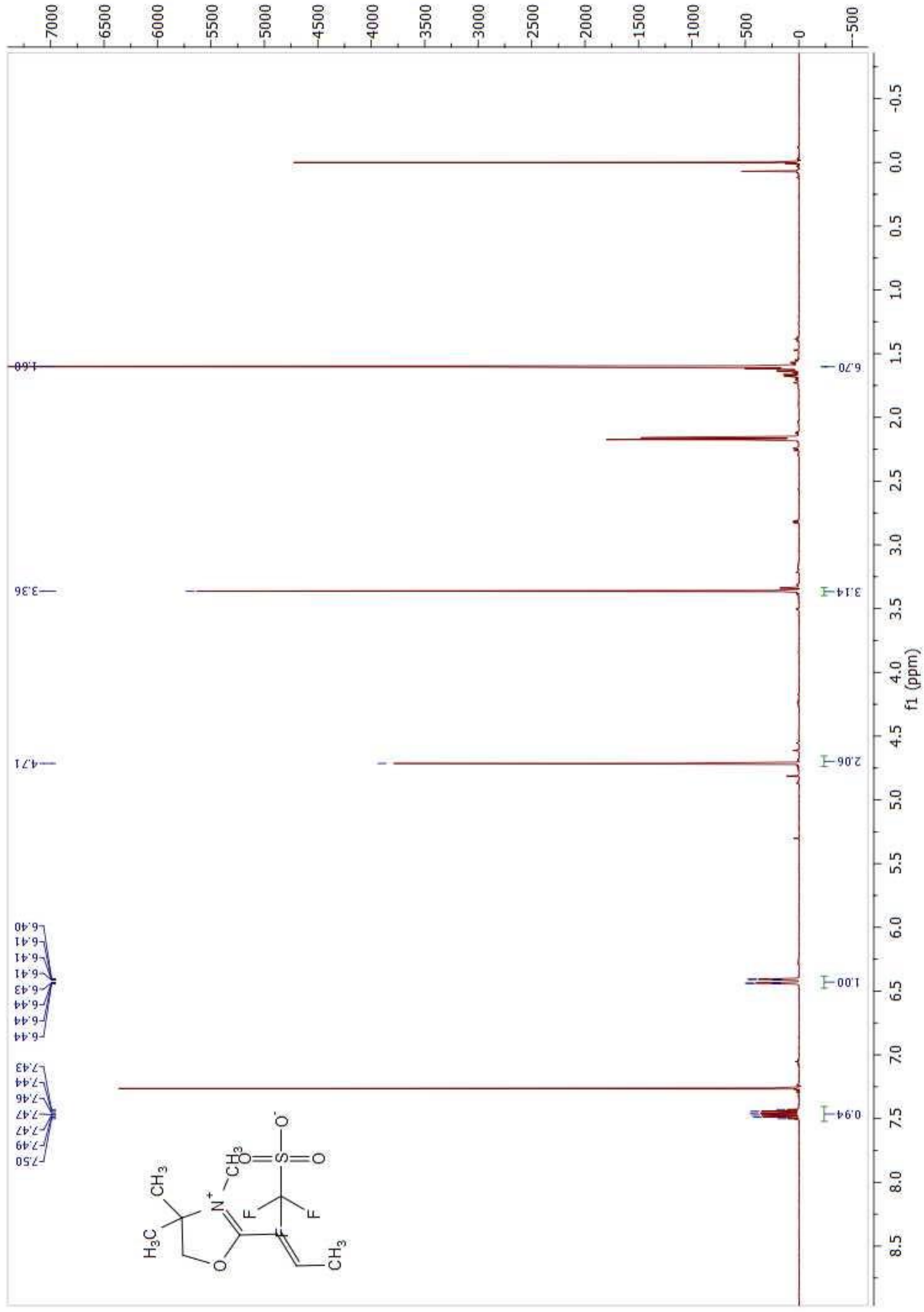


Figure 8. ^{1}H NMR spectrum of **110b** (500 MHz, $CDCl_3$).

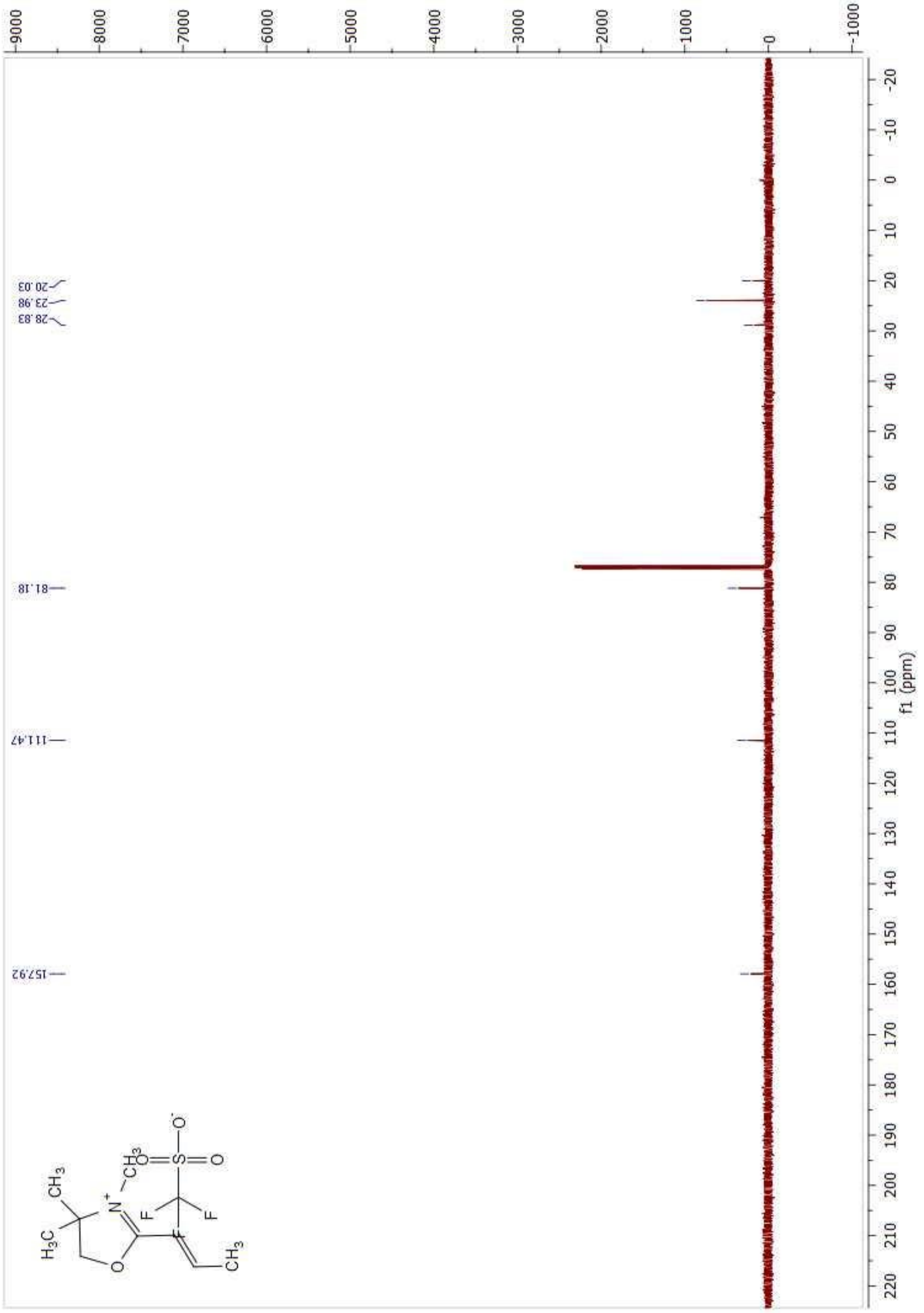


Figure 9. ^{13}C NMR spectrum of **110b** (125 MHz, $CDCl_3$).

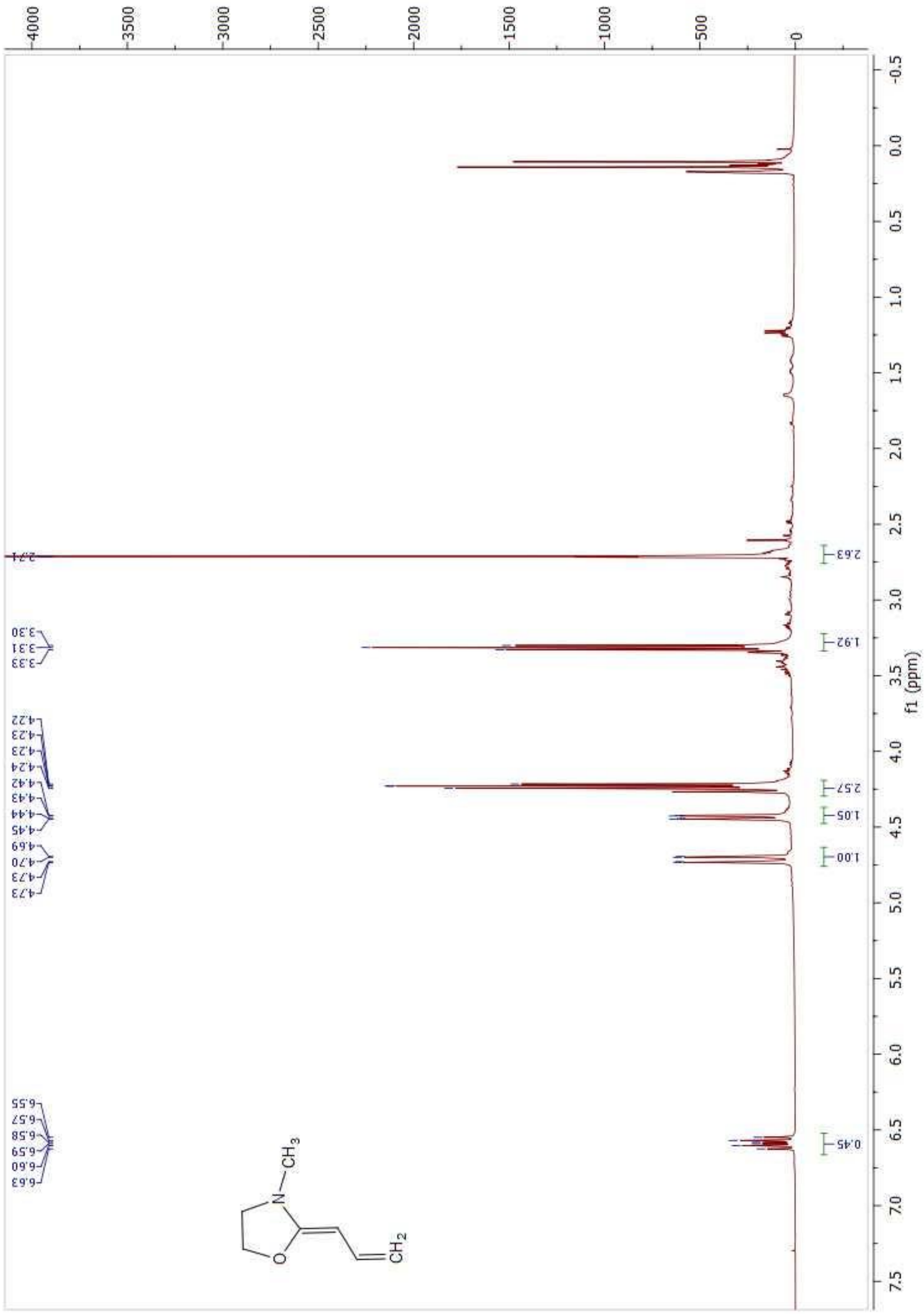


Figure 10. ^{1}H NMR spectrum of **111a** (500 MHz, $CDCl_3$).

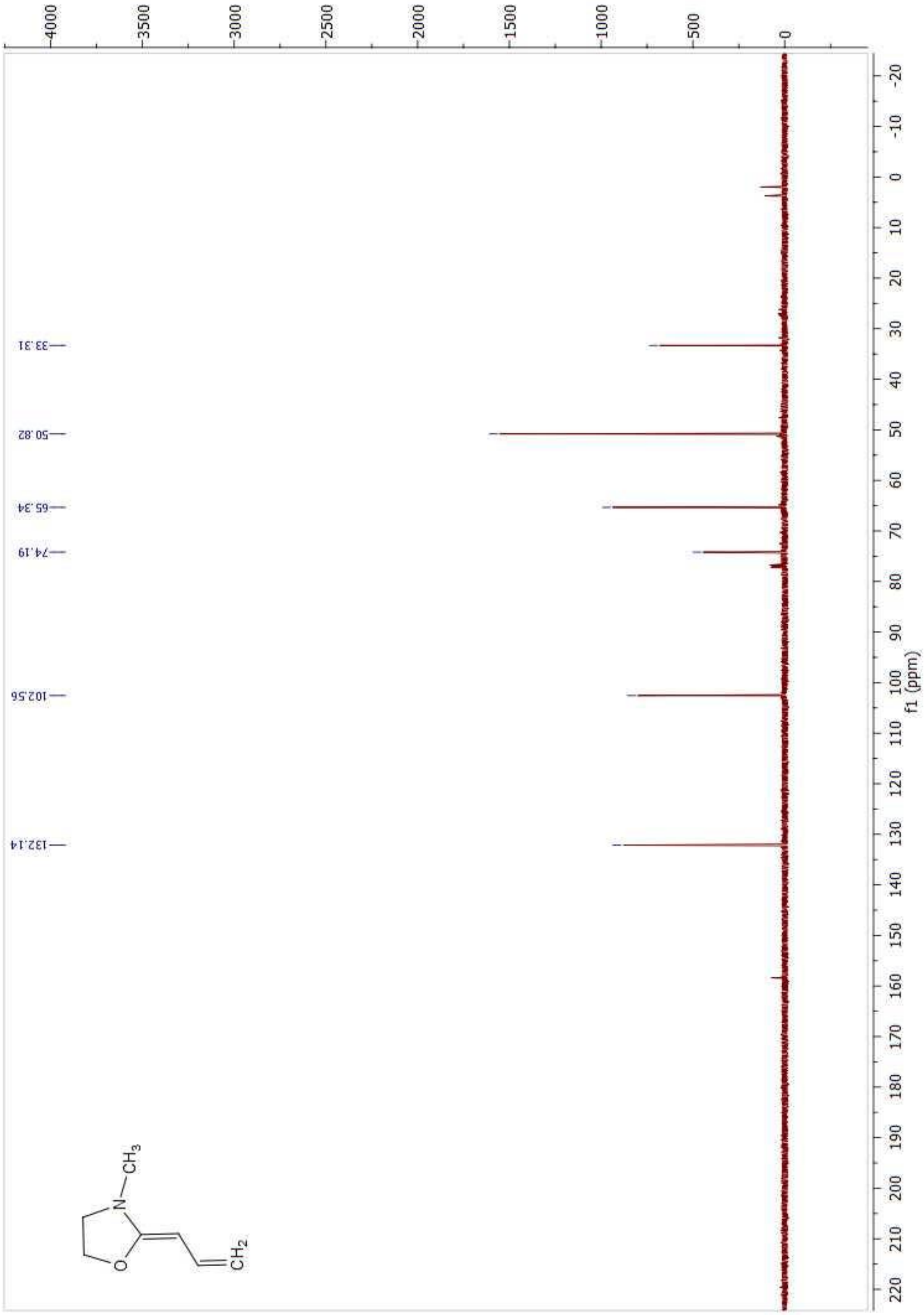


Figure 11. ^{13}C NMR spectrum of **111a** (125 MHz, $CDCl_3$).

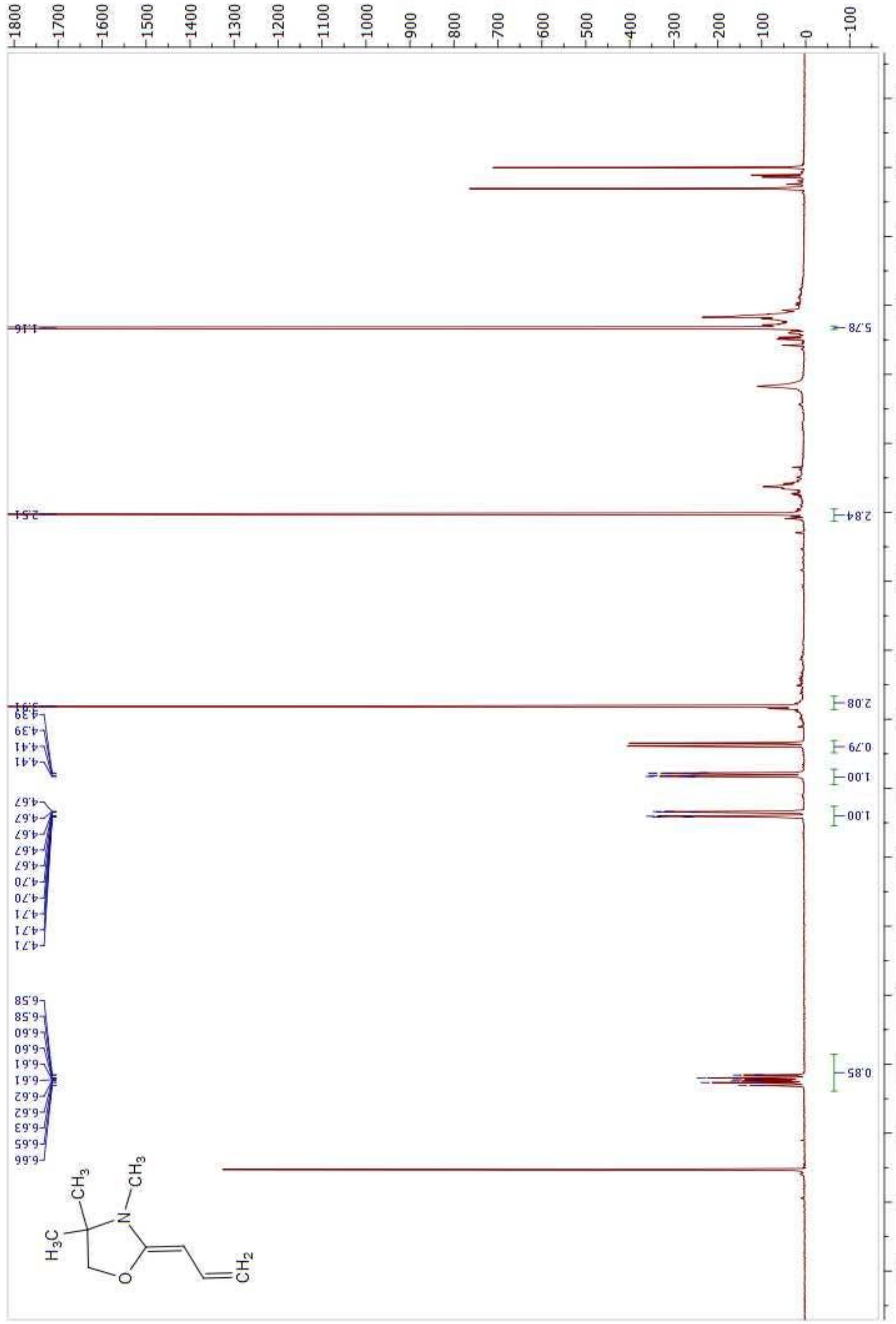


Figure 12. ^{1}H NMR spectrum of **111b** (500 MHz, $CDCl_3$).

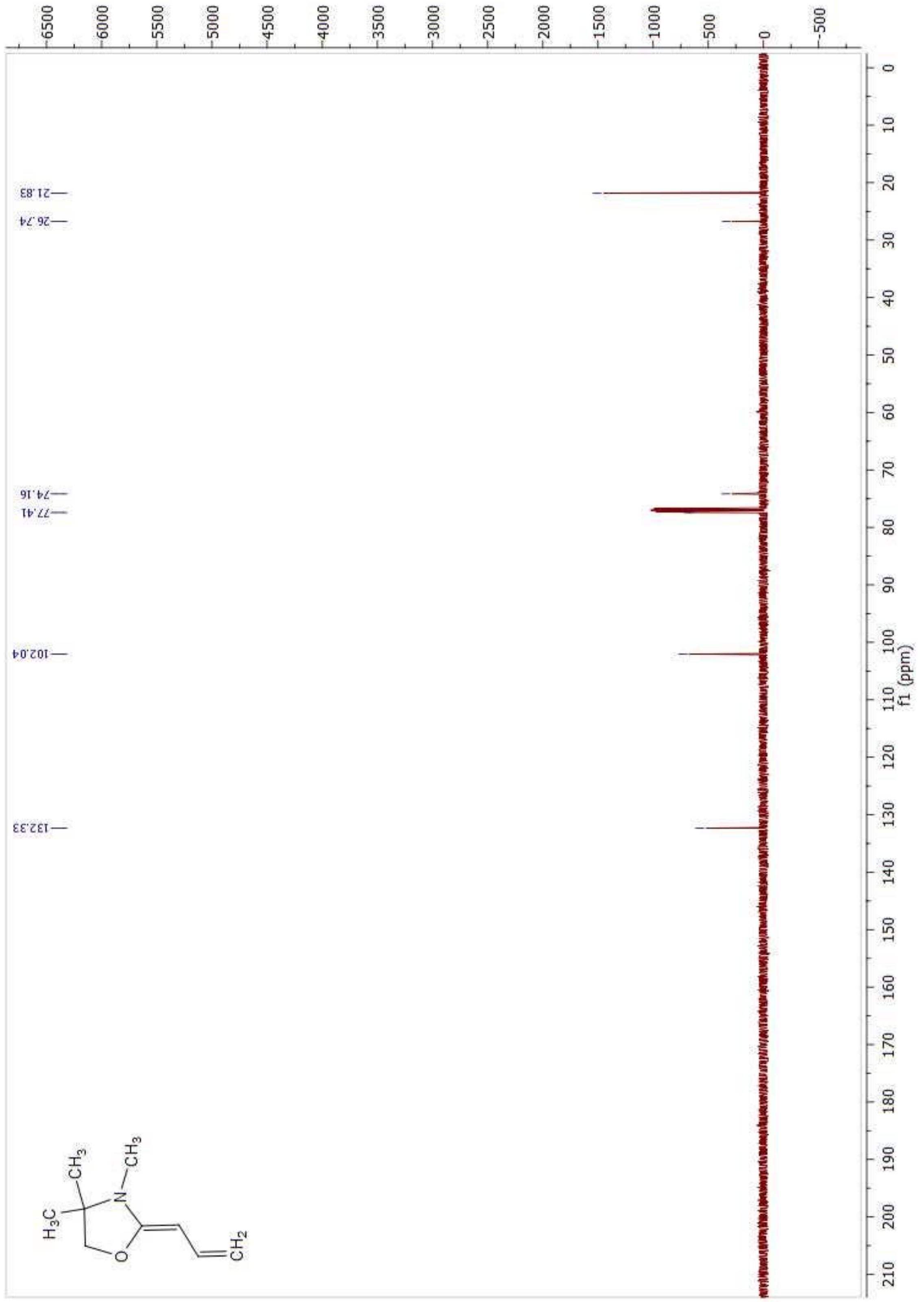


Figure 13. ^{13}C NMR spectrum of **111b** (125 MHz, $CDCl_3$).

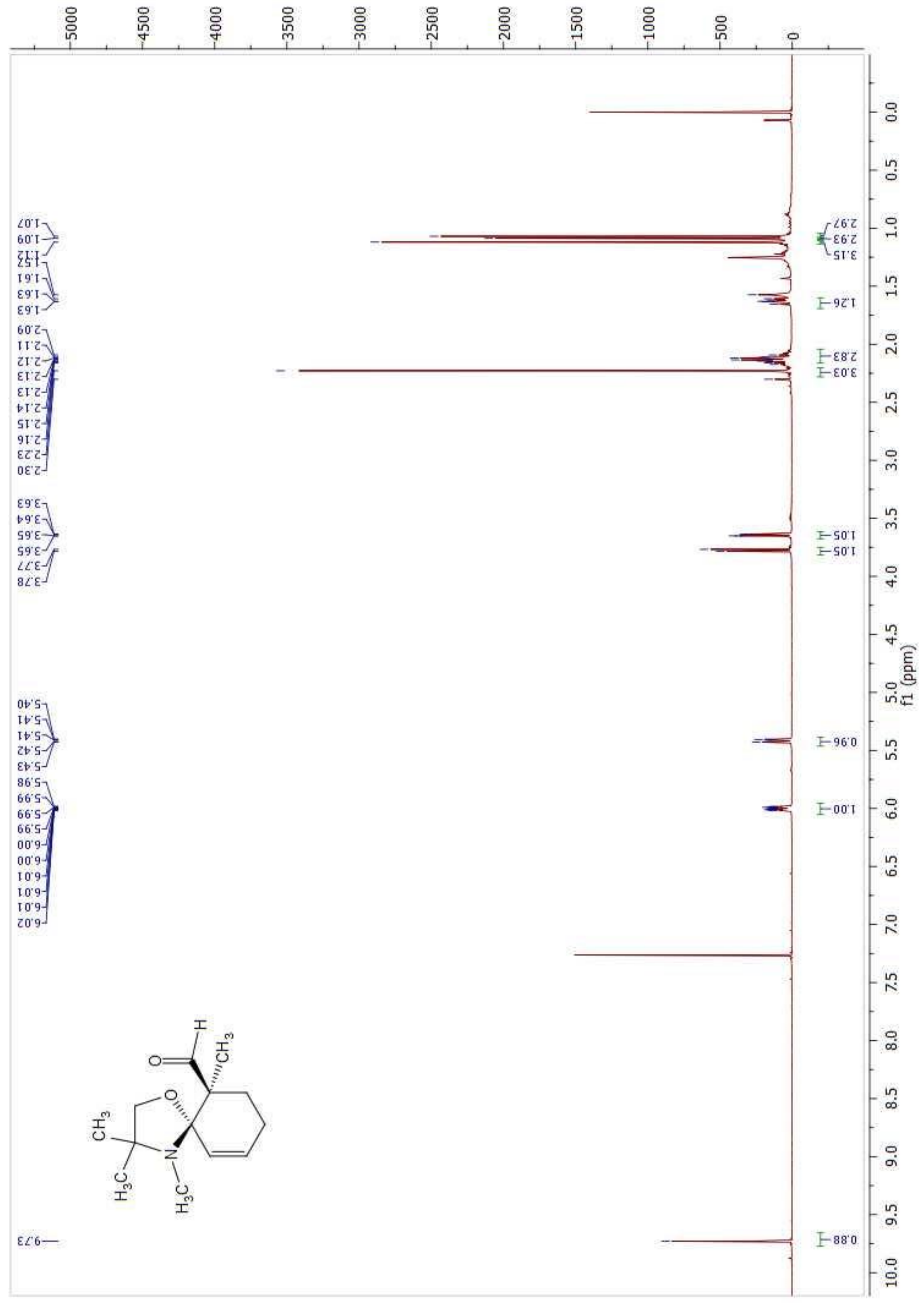


Figure 14. ^{1}H NMR spectrum of **113b** (500 MHz, $CDCl_3$).

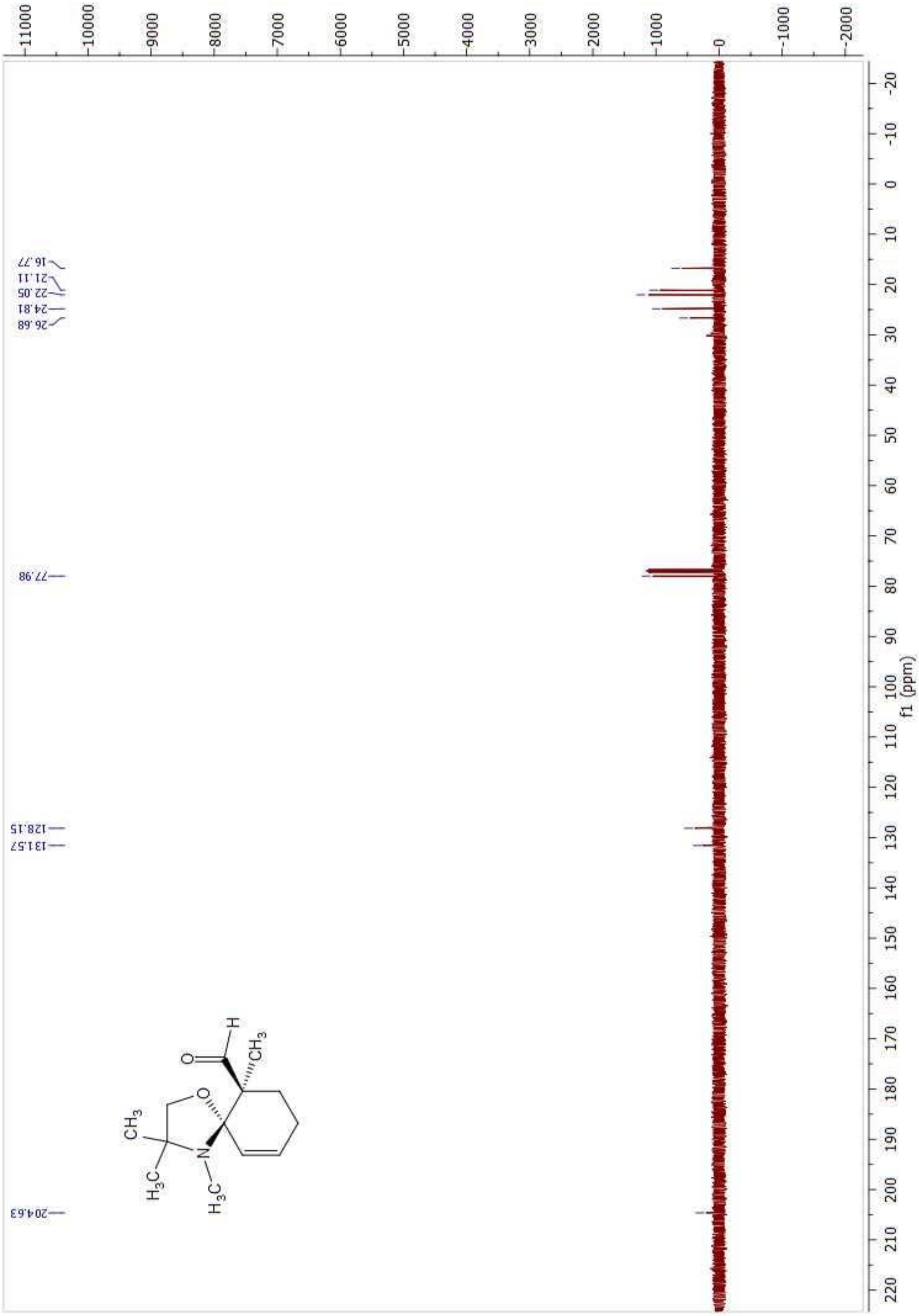


Figure 15. ^{13}C NMR spectrum of **113b** (125 MHz, $CDCl_3$).

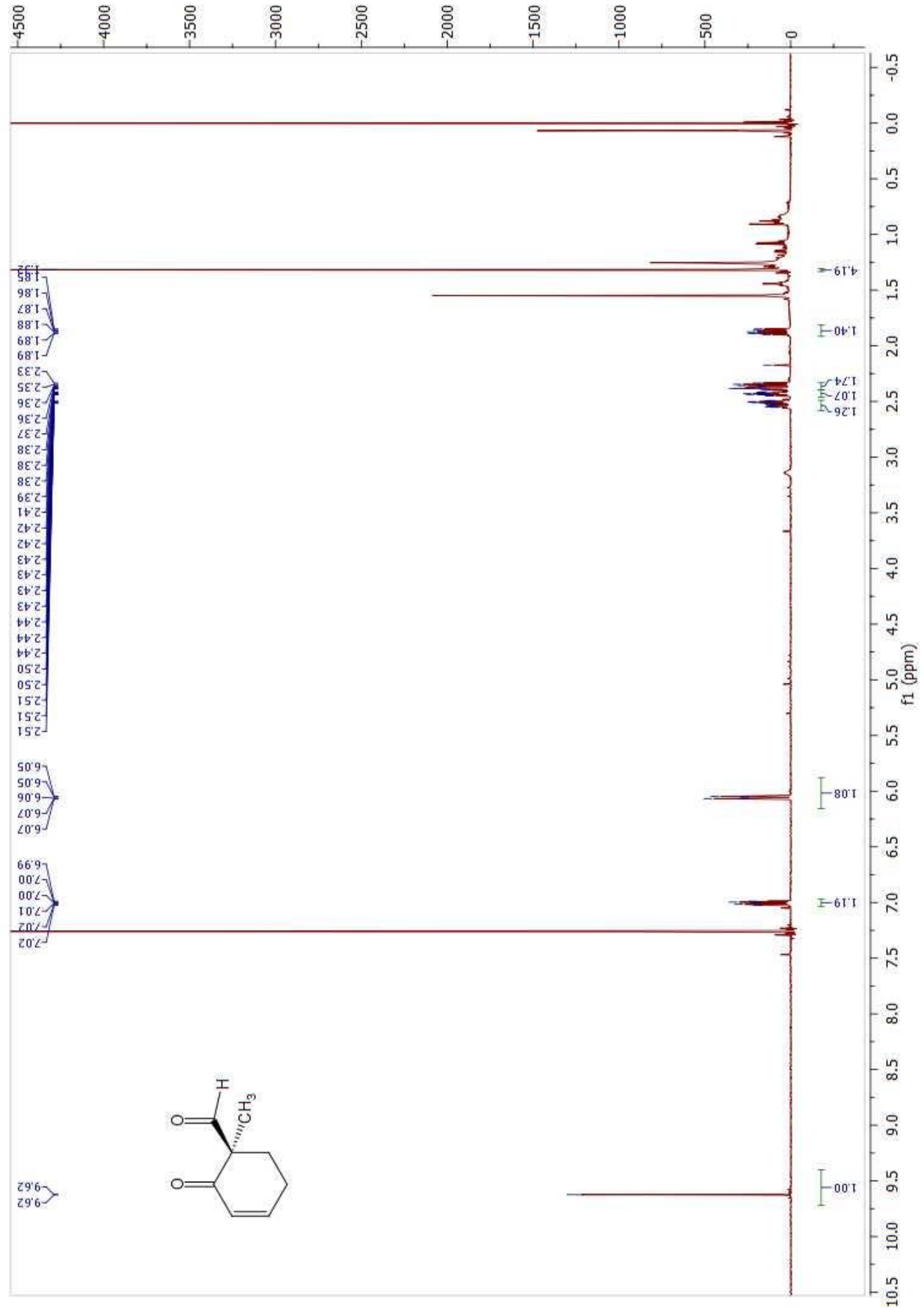


Figure 16. ^{1}H NMR spectrum of **117a** (500 MHz, $CDCl_3$).

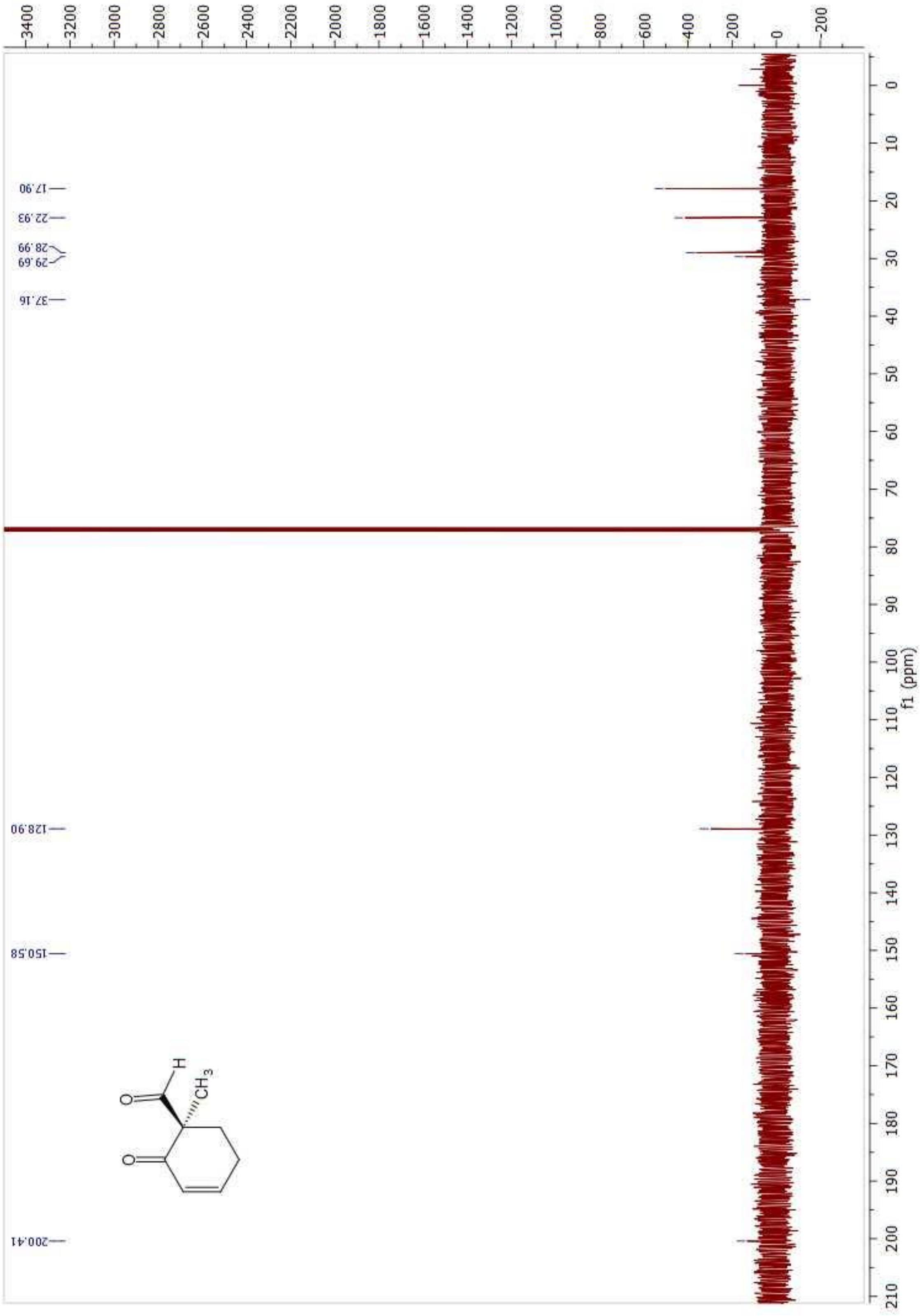


Figure 17. ^{13}C NMR spectrum of **117a** (125 MHz, $CDCl_3$).

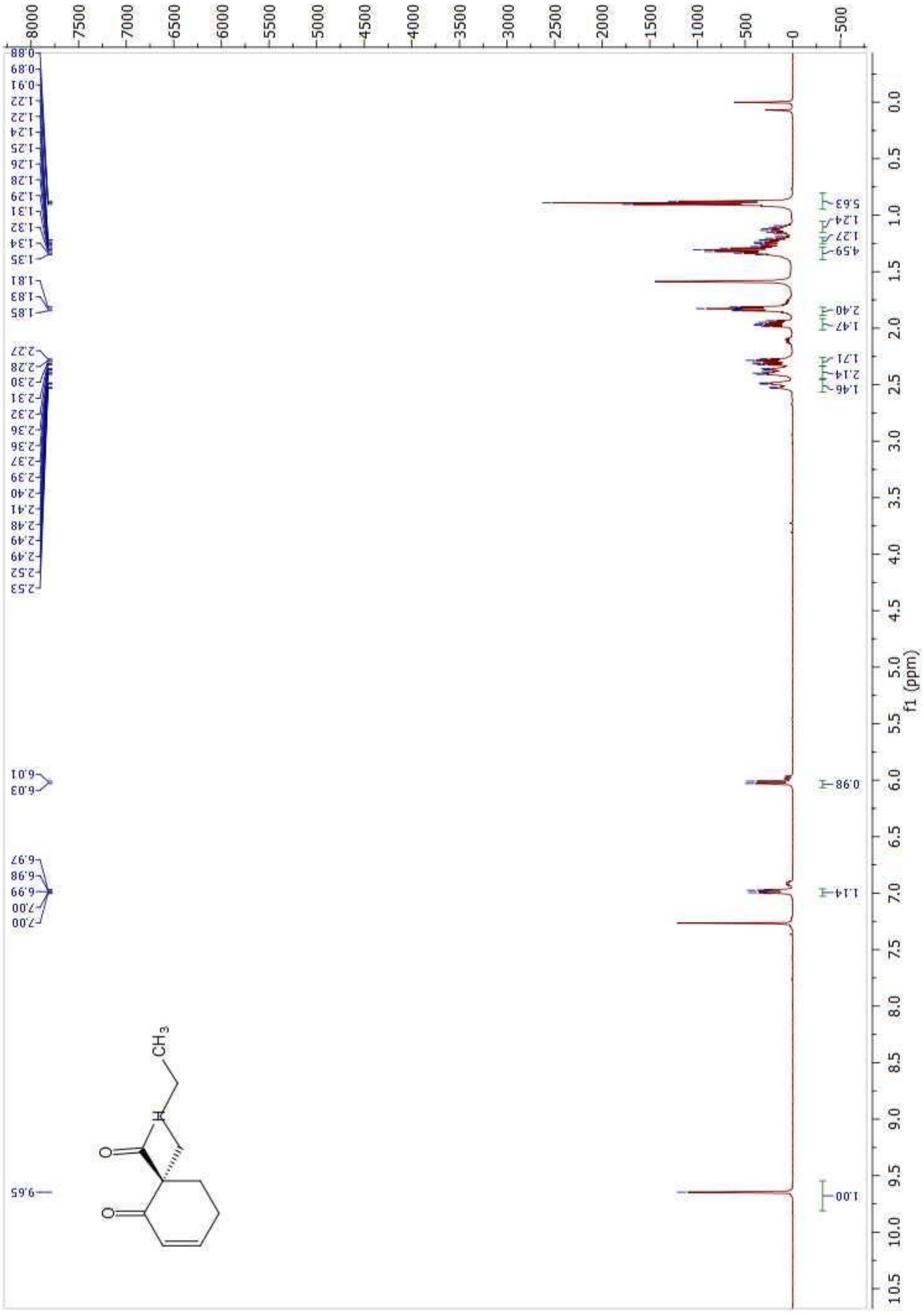


Figure 18. ^{1}H NMR spectrum of **117b** (500 MHz, $CDCl_3$).

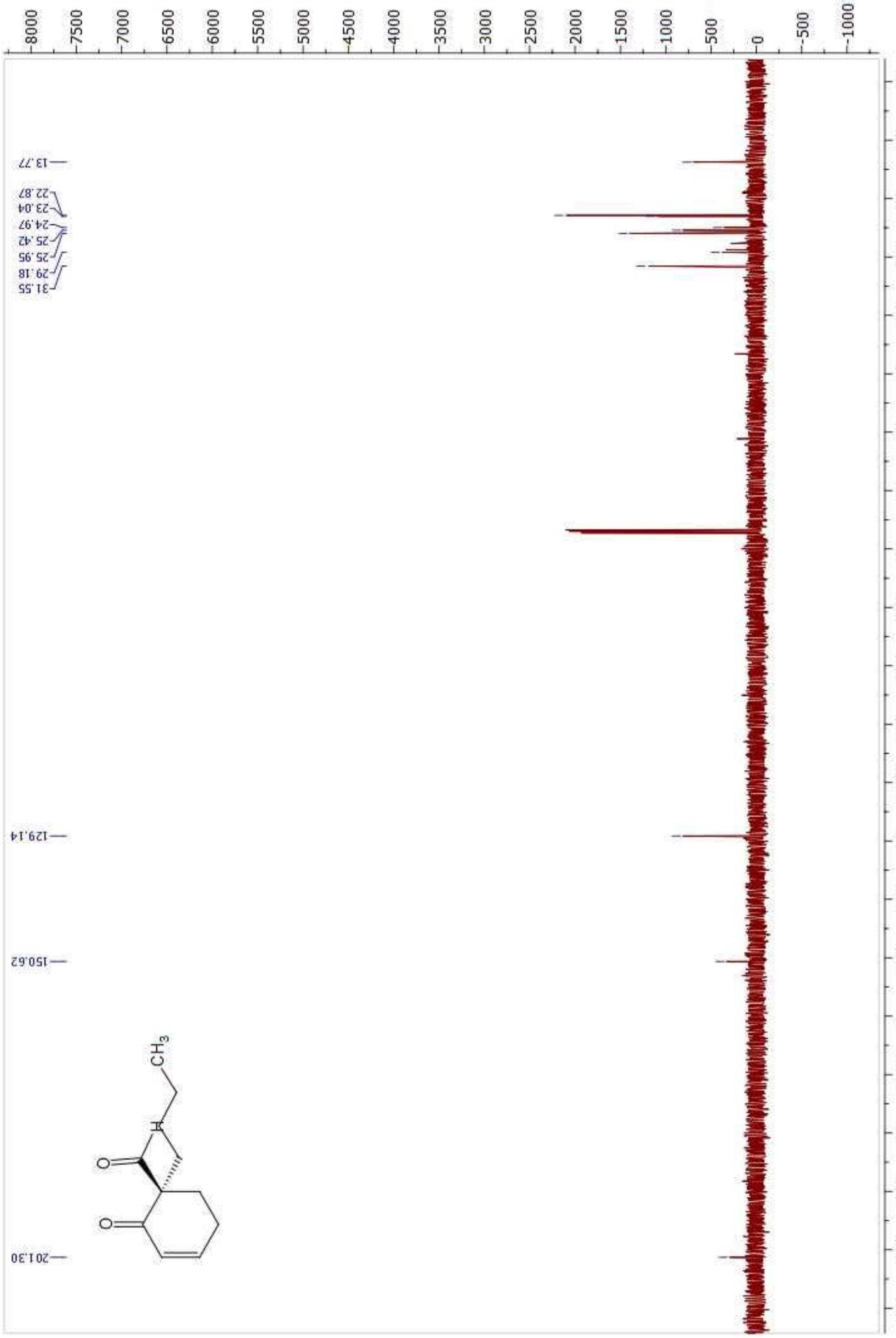


Figure 19. ^{13}C NMR spectrum of **117b** (125 MHz, $CDCl_3$).

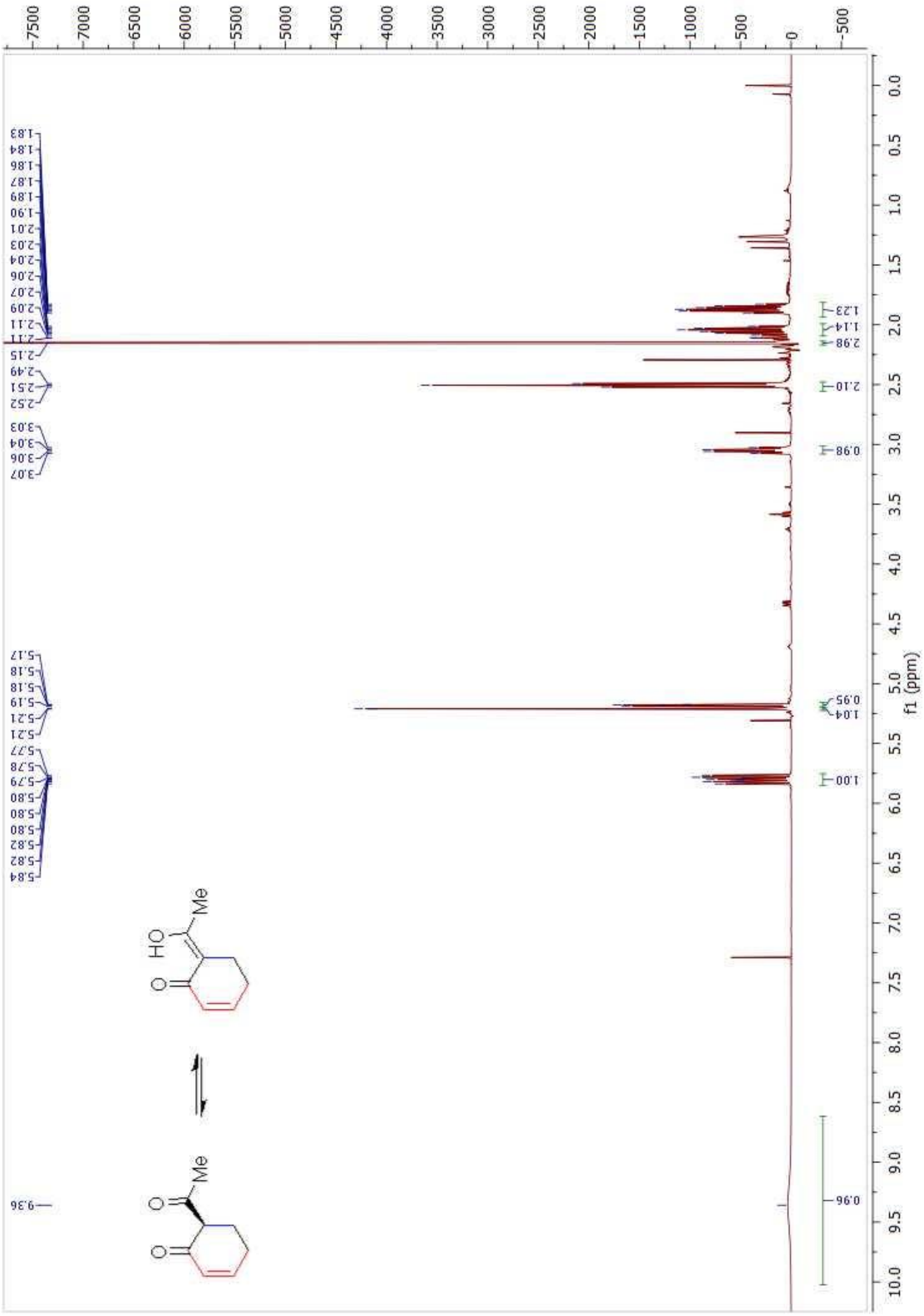


Figure 20. ^{1}H NMR spectrum of **117g** (500 MHz, $CDCl_3$).

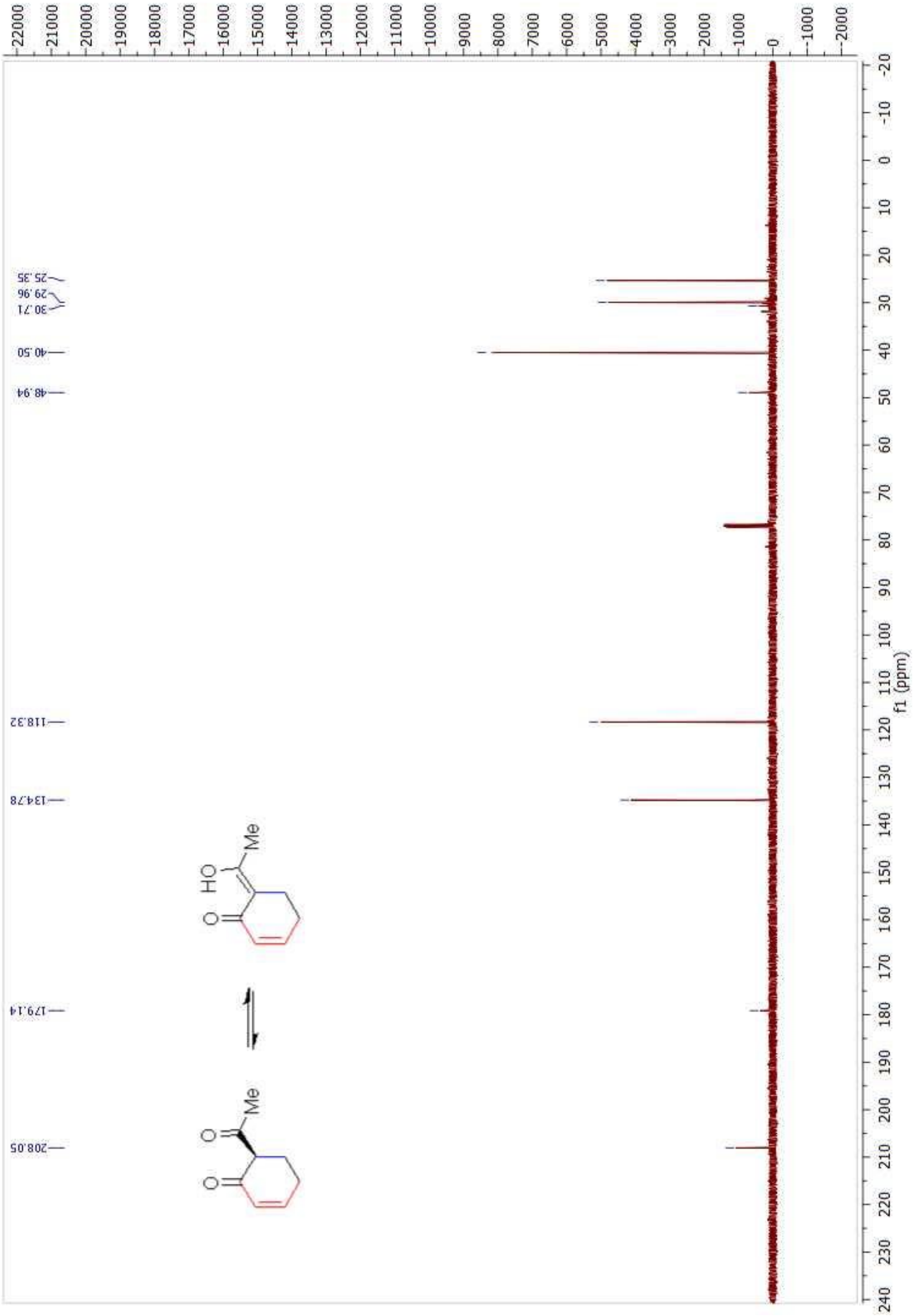


Figure 21. ^{13}C NMR spectrum of **117g** (125 MHz, $CDCl_3$).

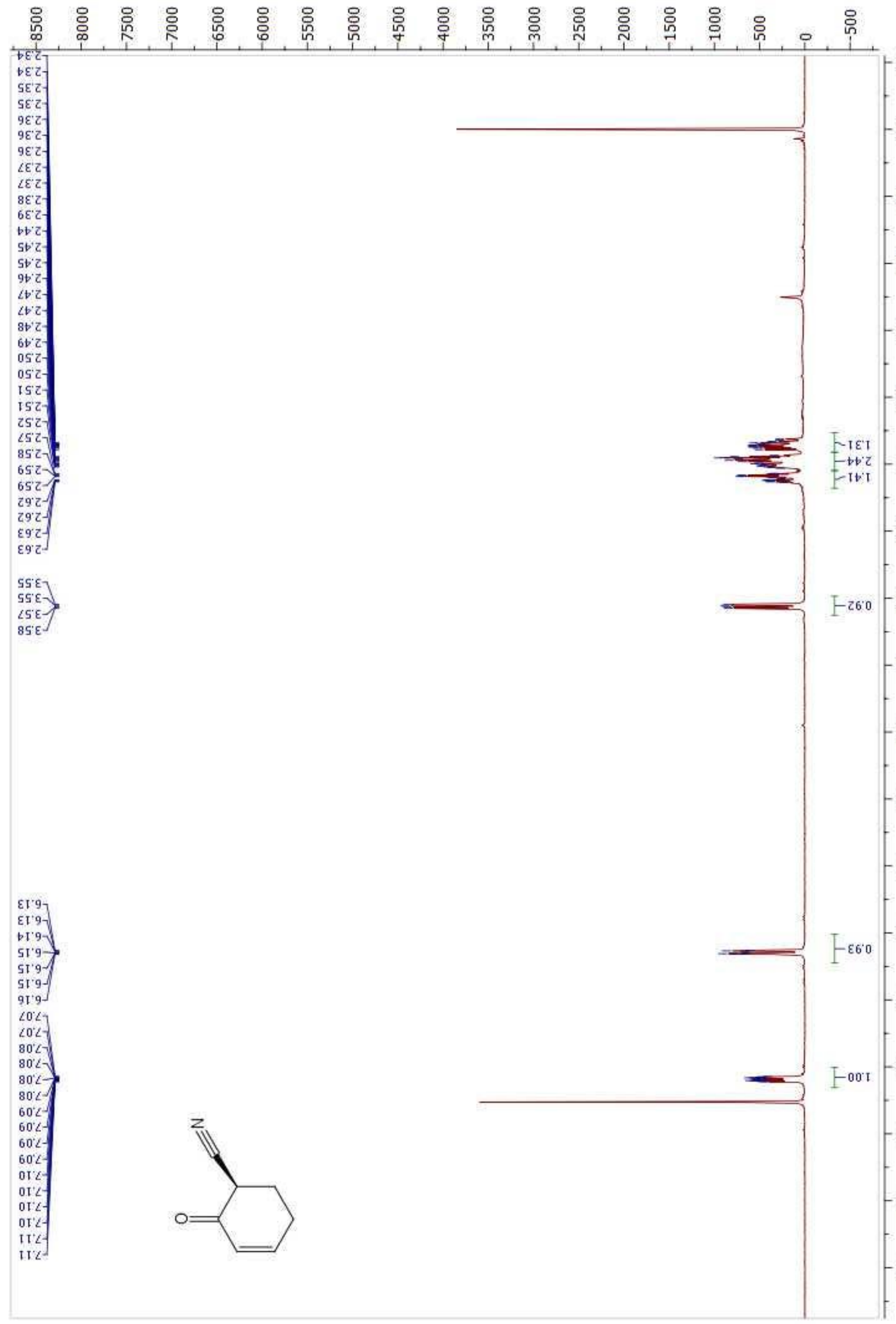


Figure 22. ^{1}H NMR spectrum of **117h** (500 MHz, $CDCl_3$).

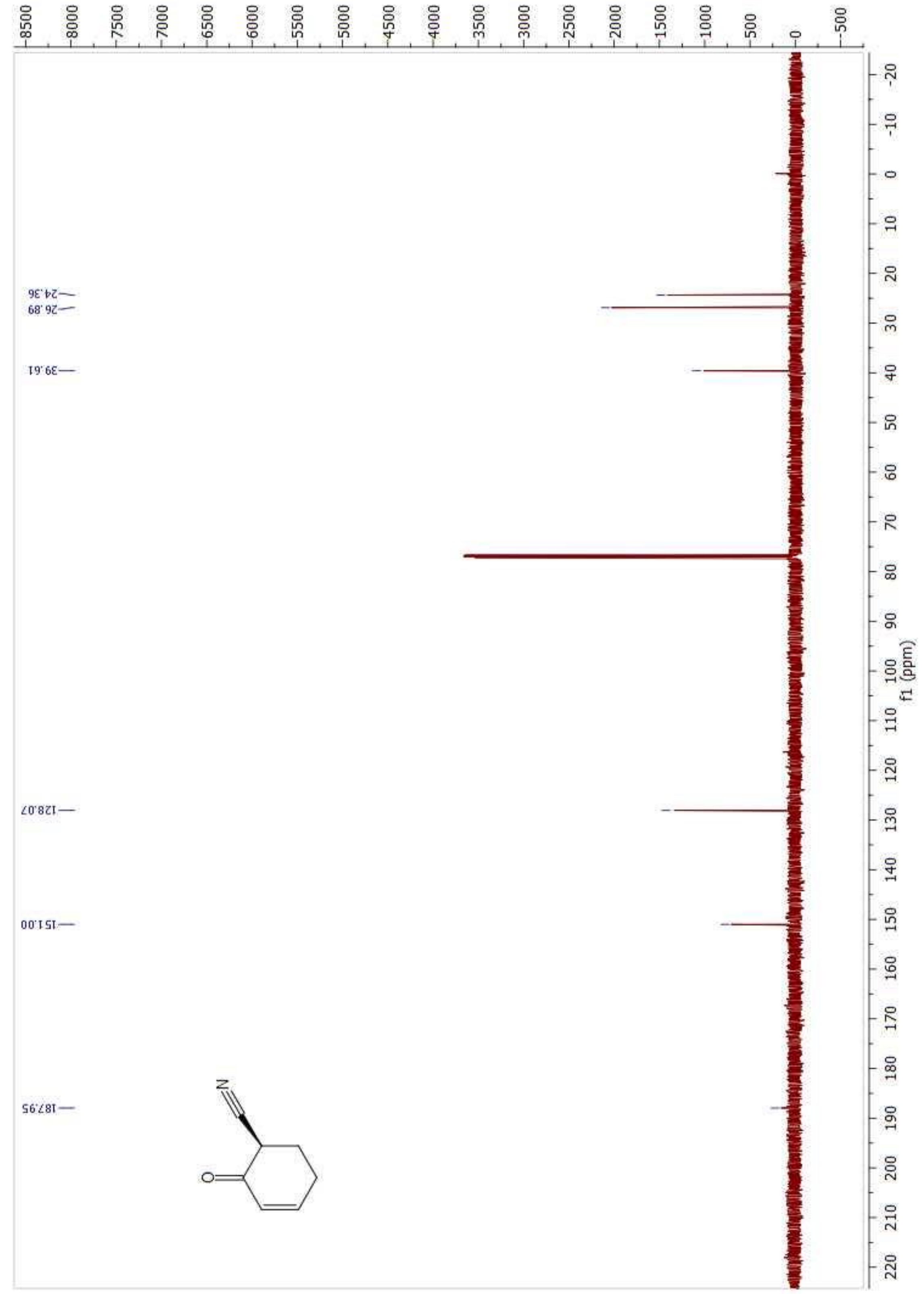


Figure 23. ^{13}C NMR spectrum of **117h** (125 MHz, $CDCl_3$).

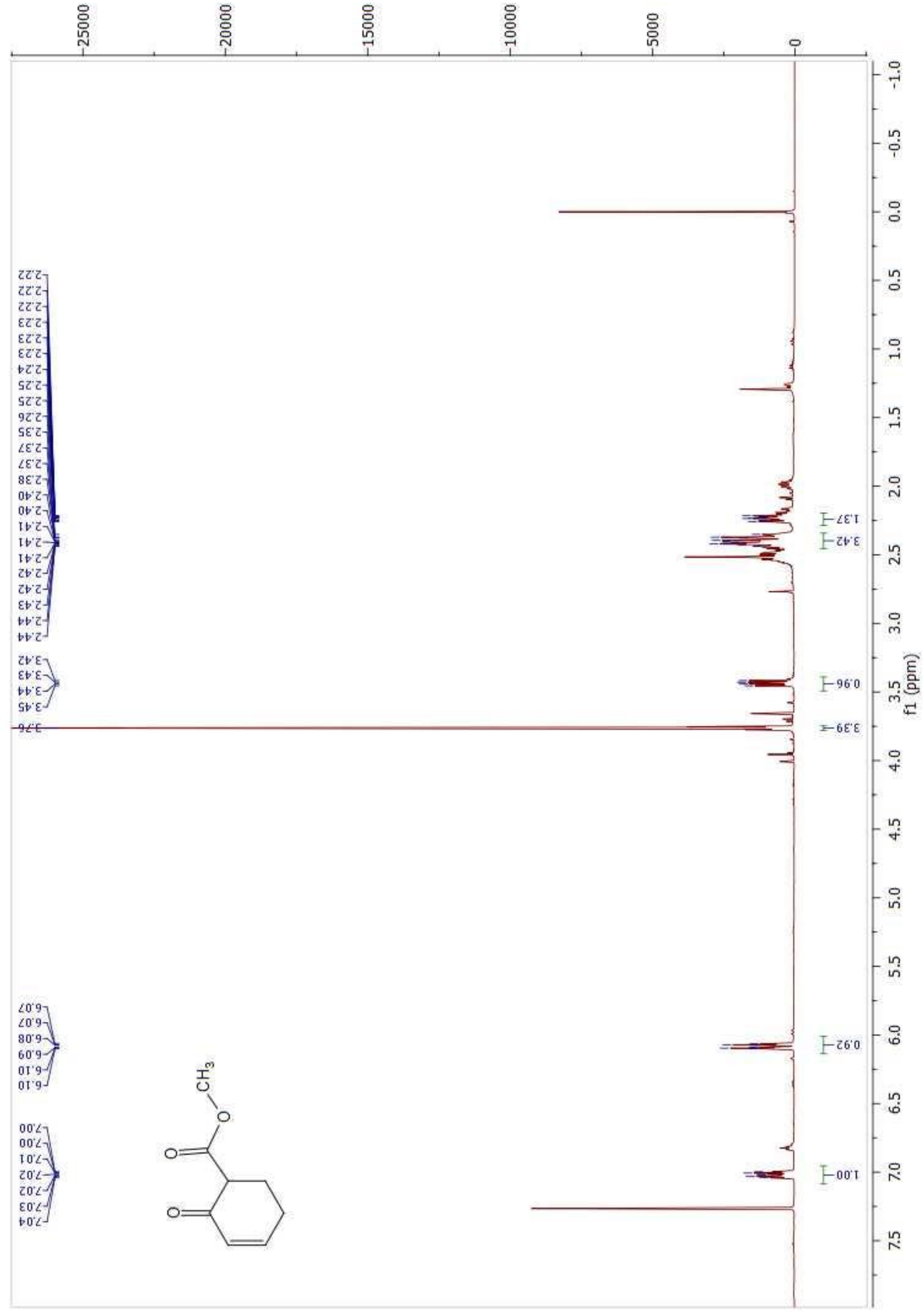


Figure 24. ^{1}H NMR spectrum of **117i** (500 MHz, $CDCl_3$).

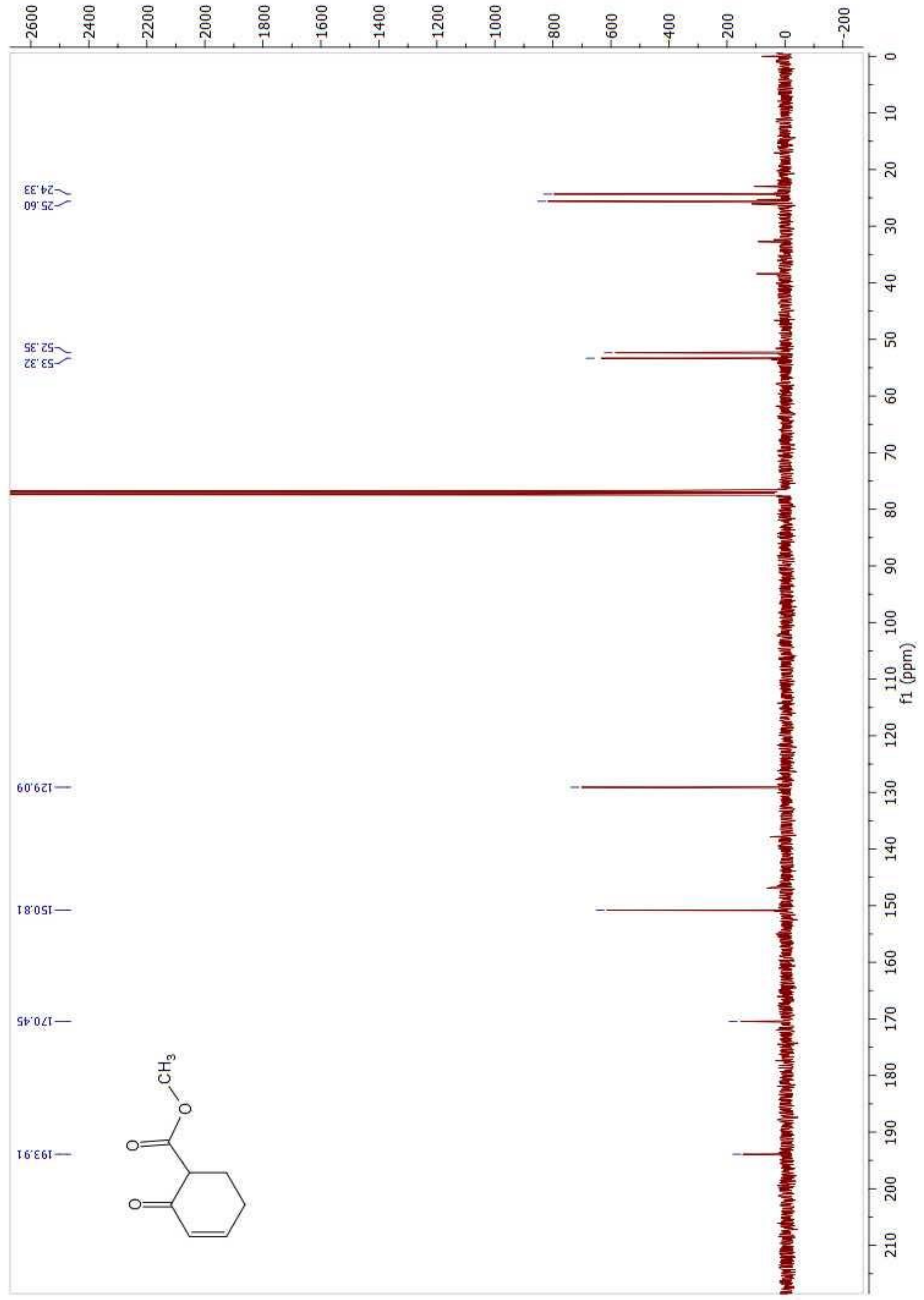


Figure 25. ^{13}C NMR spectrum of **117i** (125 MHz, $CDCl_3$).

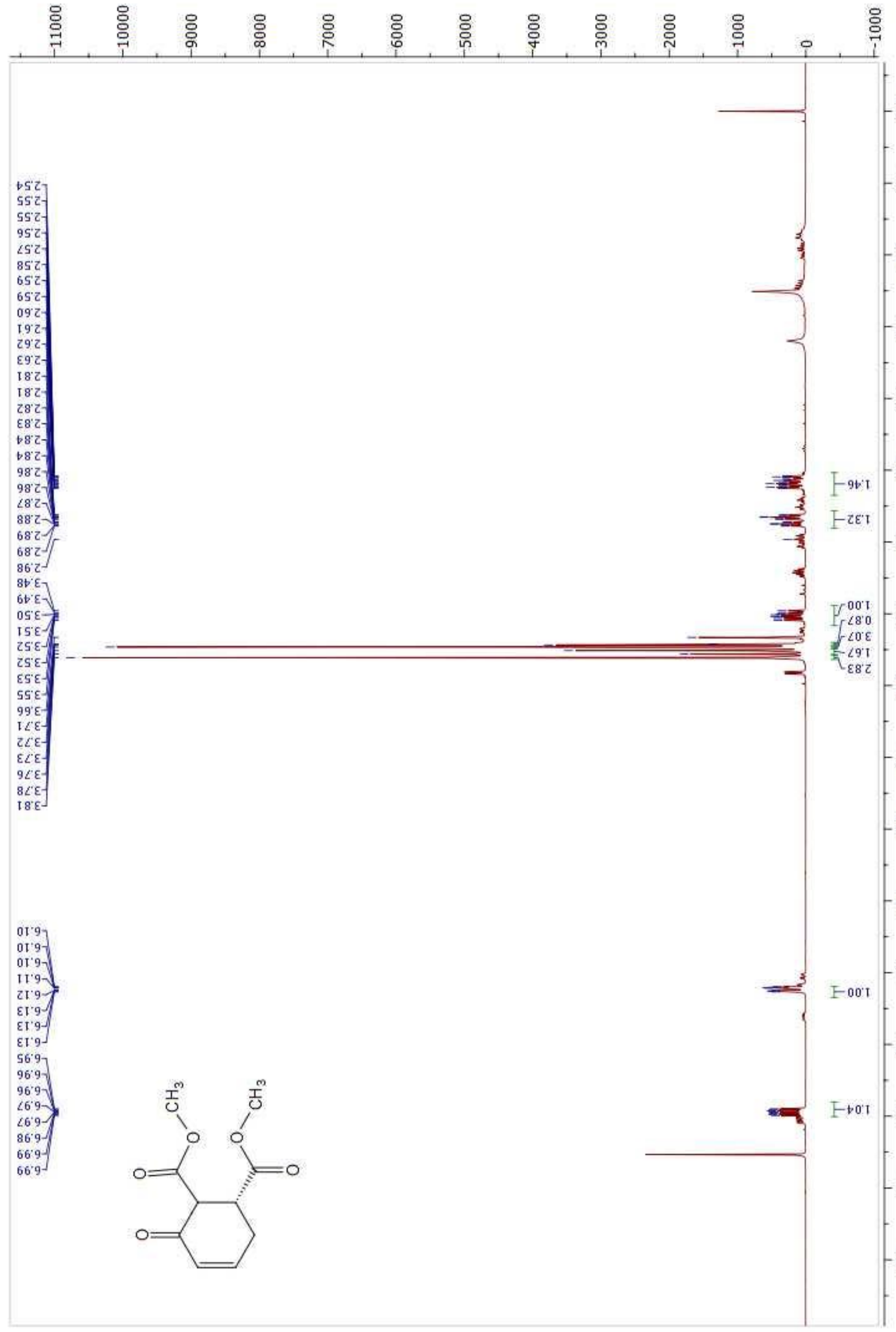


Figure 26. ^{1}H NMR spectrum of **117j** (500 MHz, $CDCl_3$).

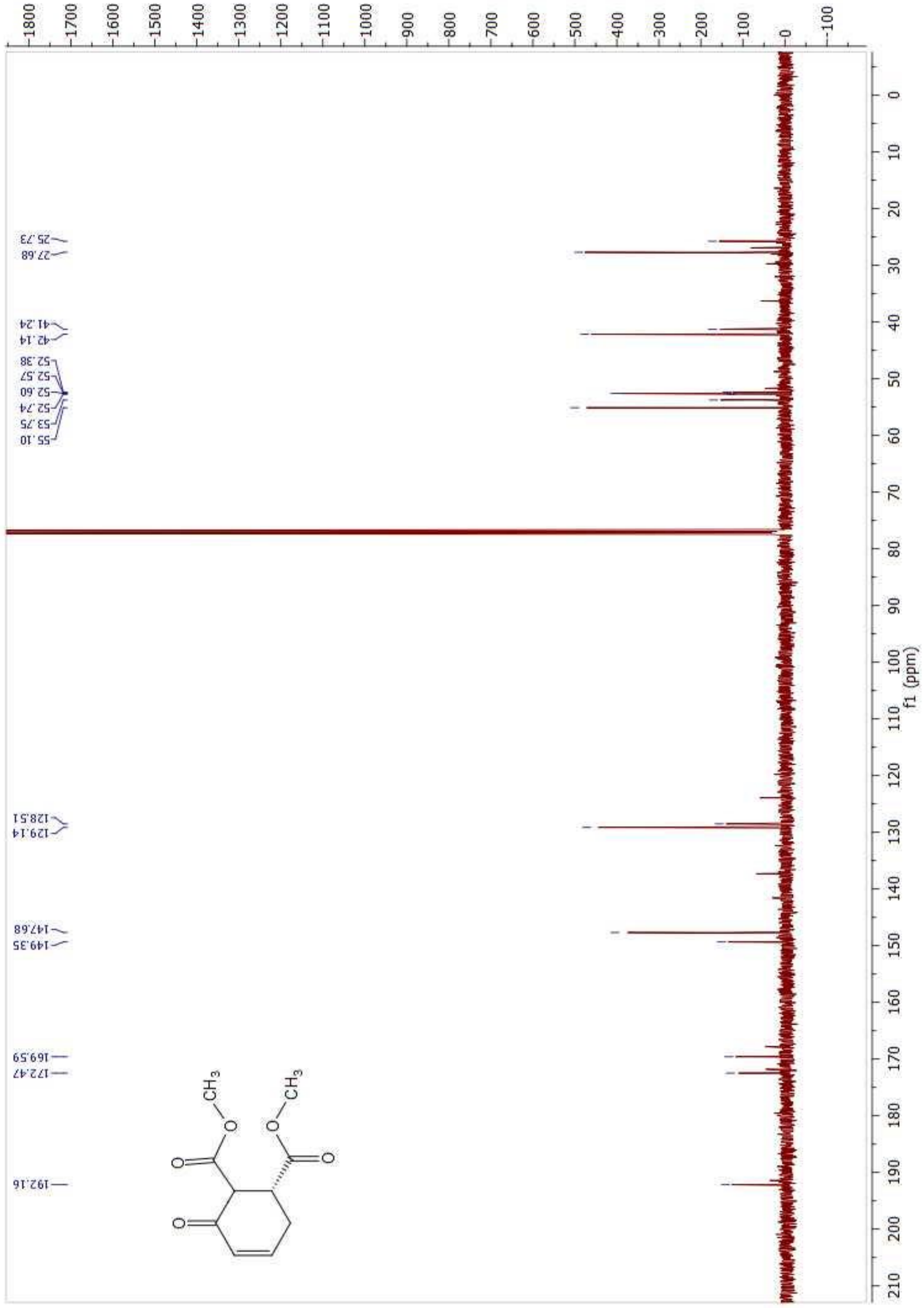


Figure 27. ^{13}C NMR spectrum of **117j** (125 MHz, $CDCl_3$).

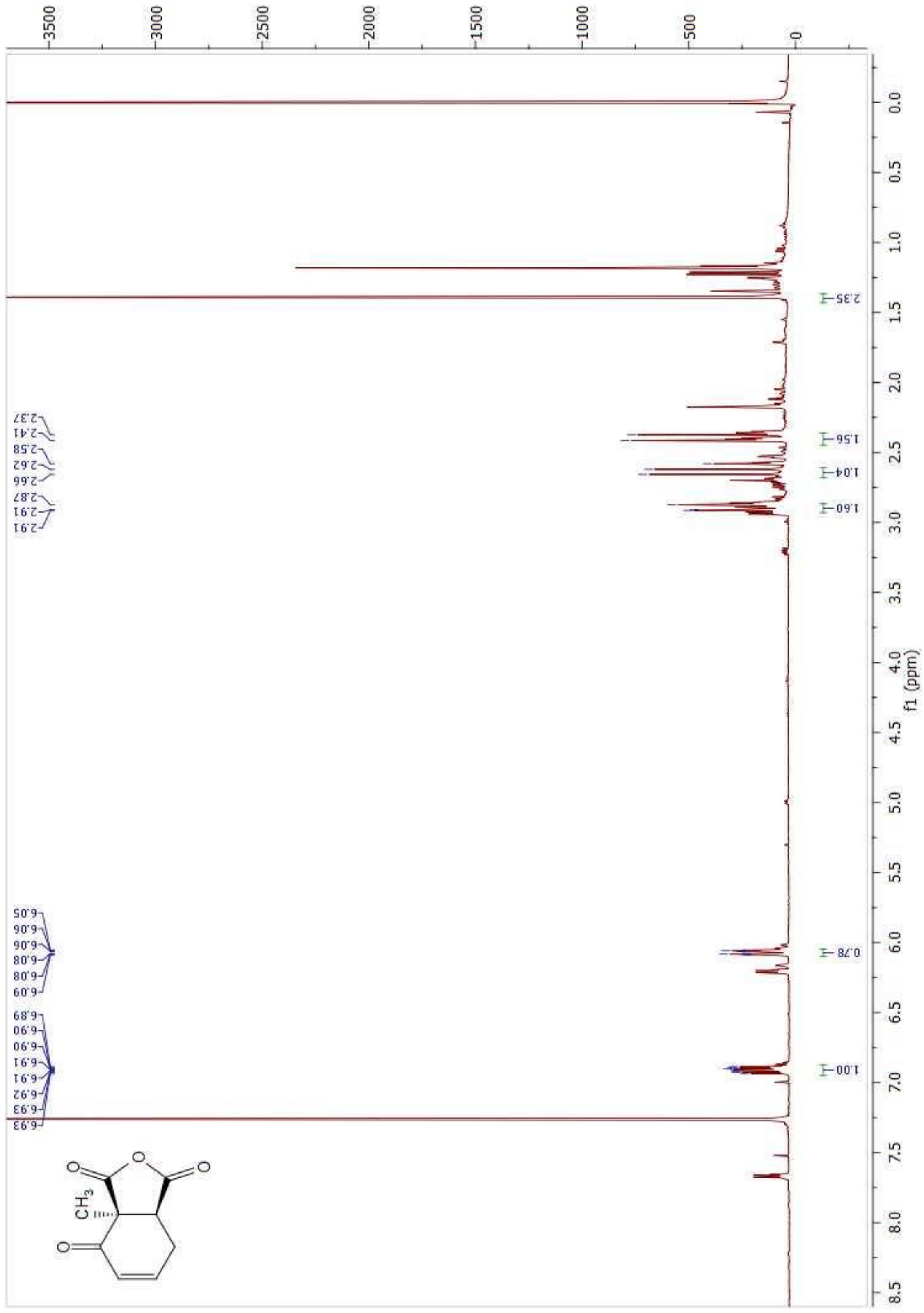


Figure 28. ^{1}H NMR spectrum of **117k** (500 MHz, $CDCl_3$).

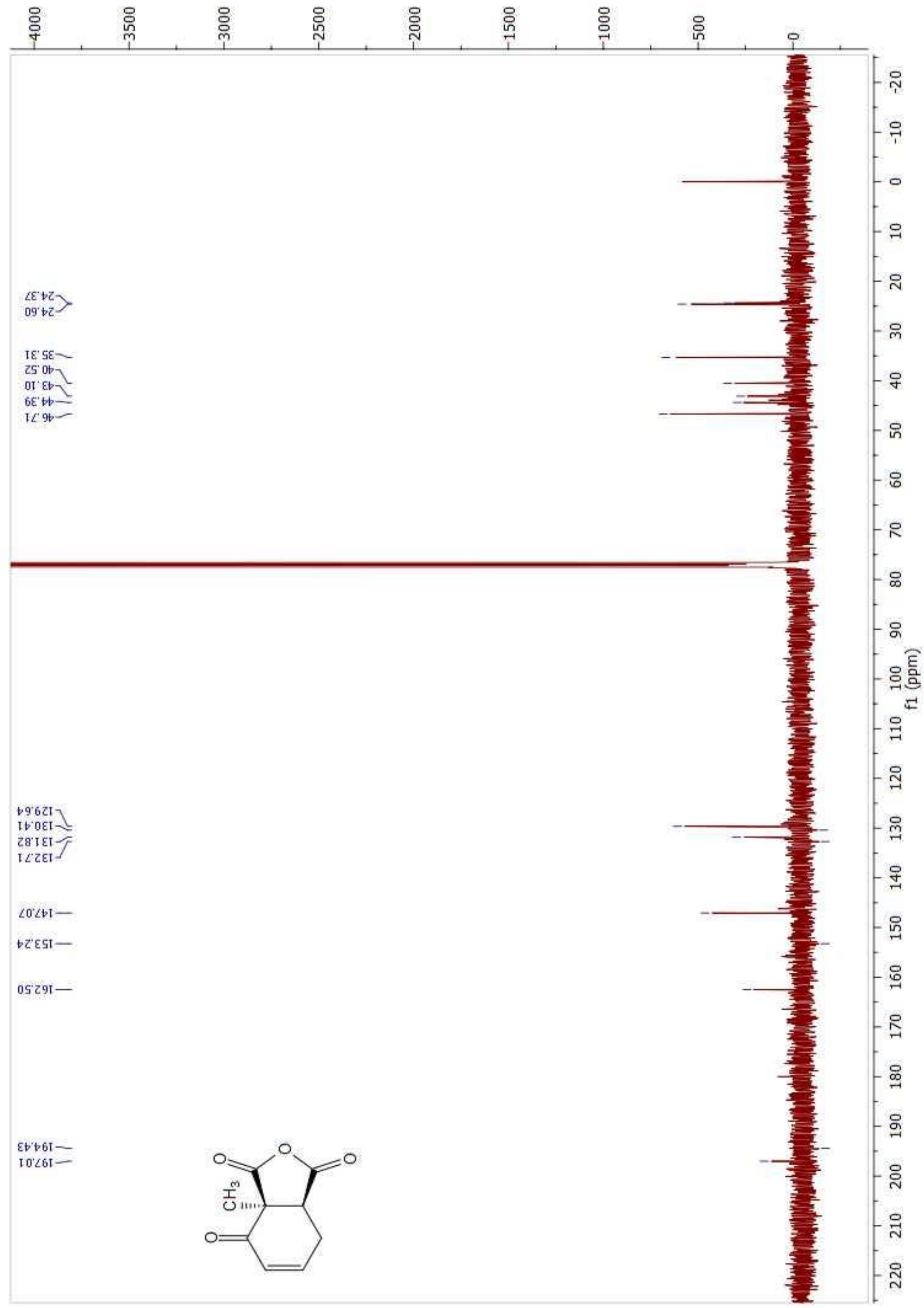


Figure 29. ^{13}C NMR spectrum of **117k** (125 MHz, $CDCl_3$).

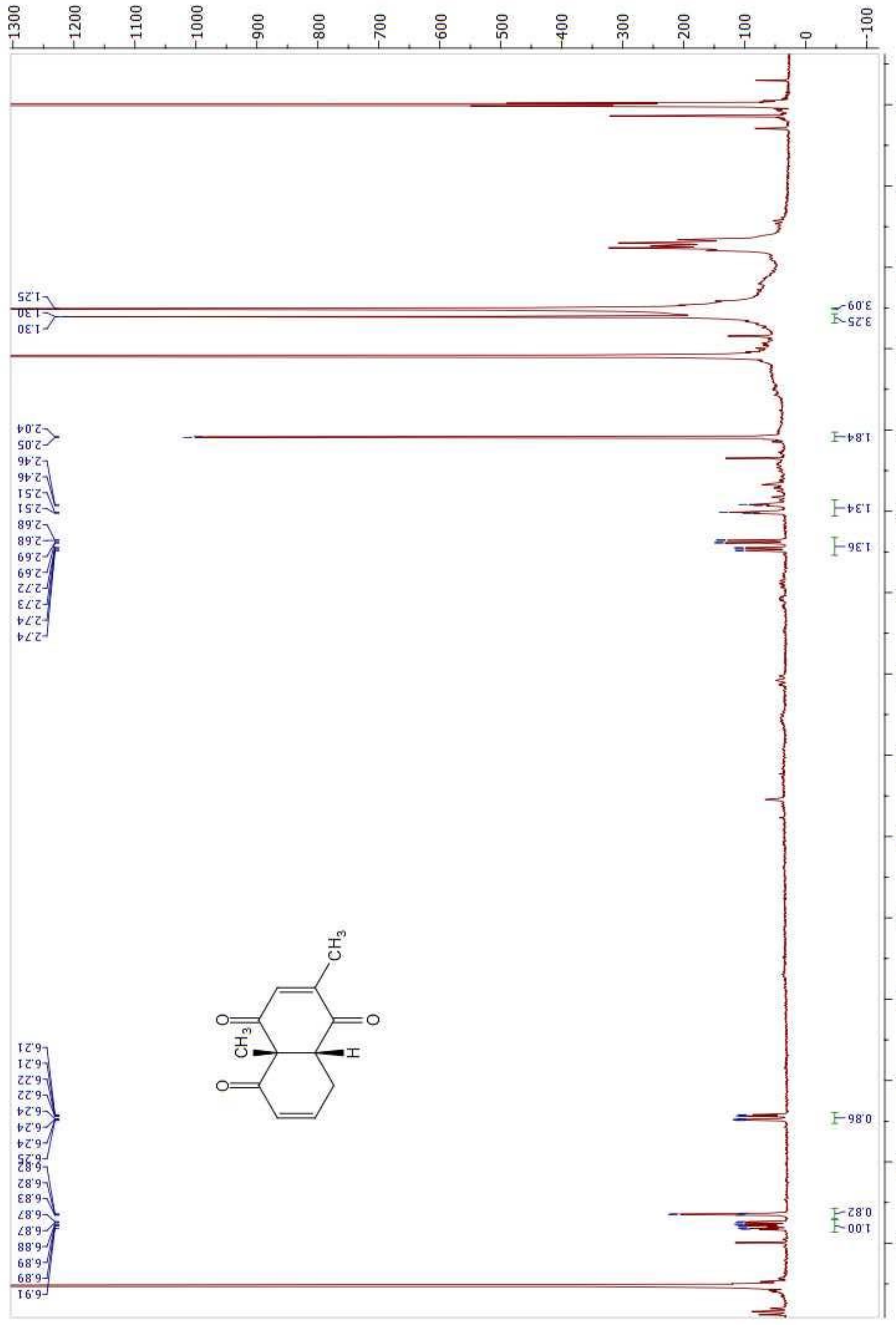


Figure 30. ^{1}H NMR spectrum of **117l** (500 MHz, $CDCl_3$).

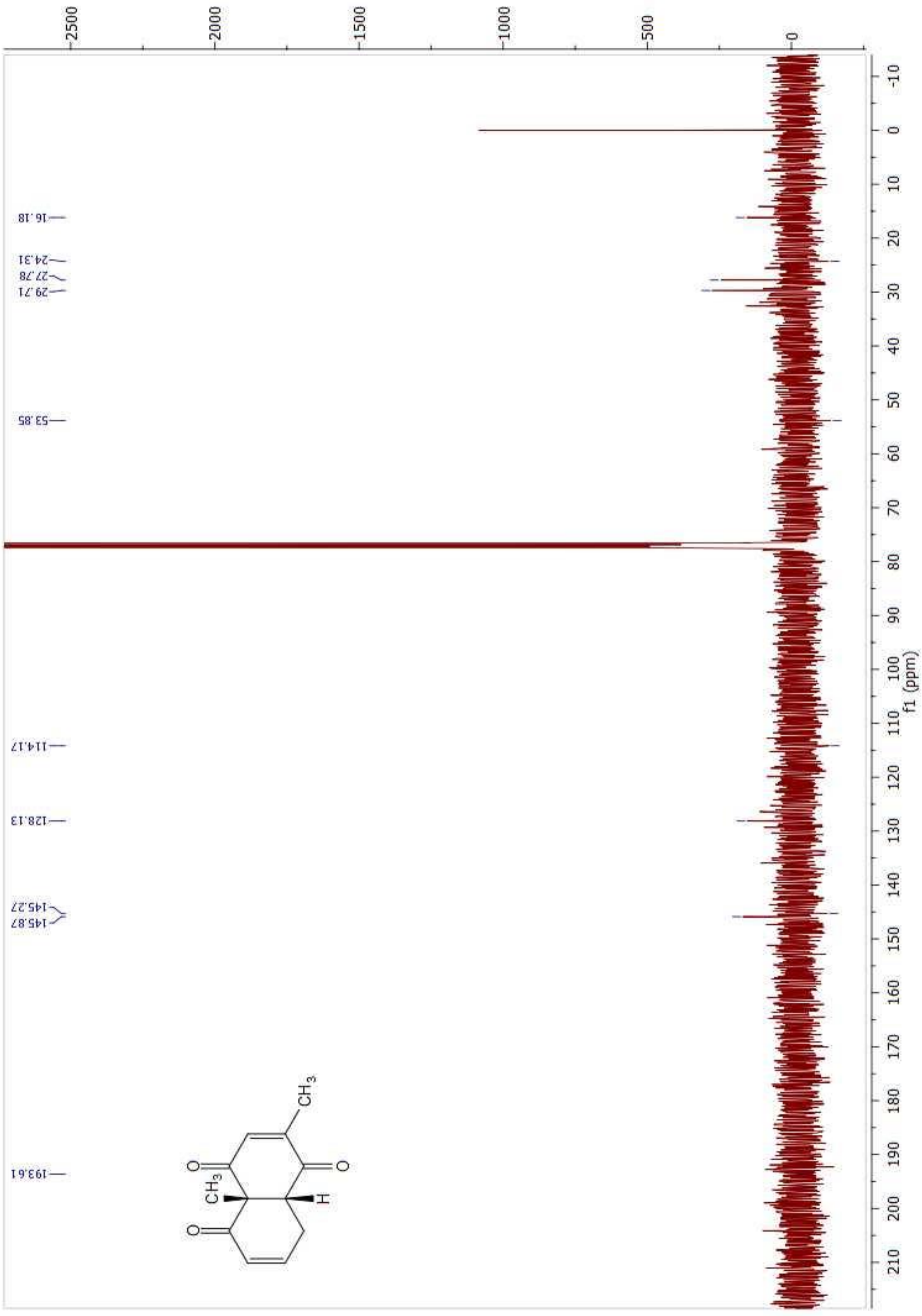


Figure 31. ^{13}C NMR spectrum of **117l** (125 MHz, $CDCl_3$).

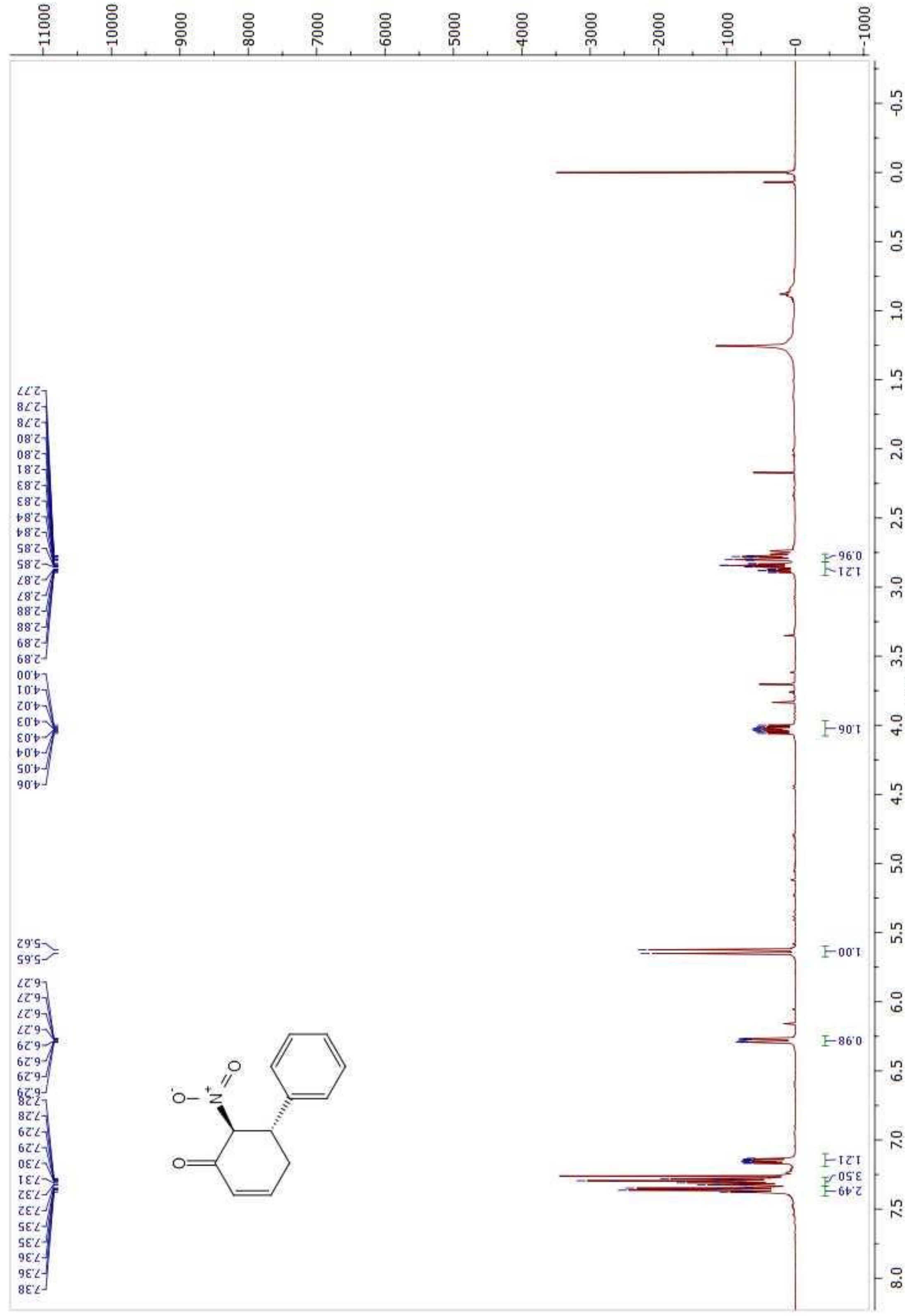


Figure 32. ^{1}H NMR spectrum of **120a** (500 MHz, $CDCl_3$).

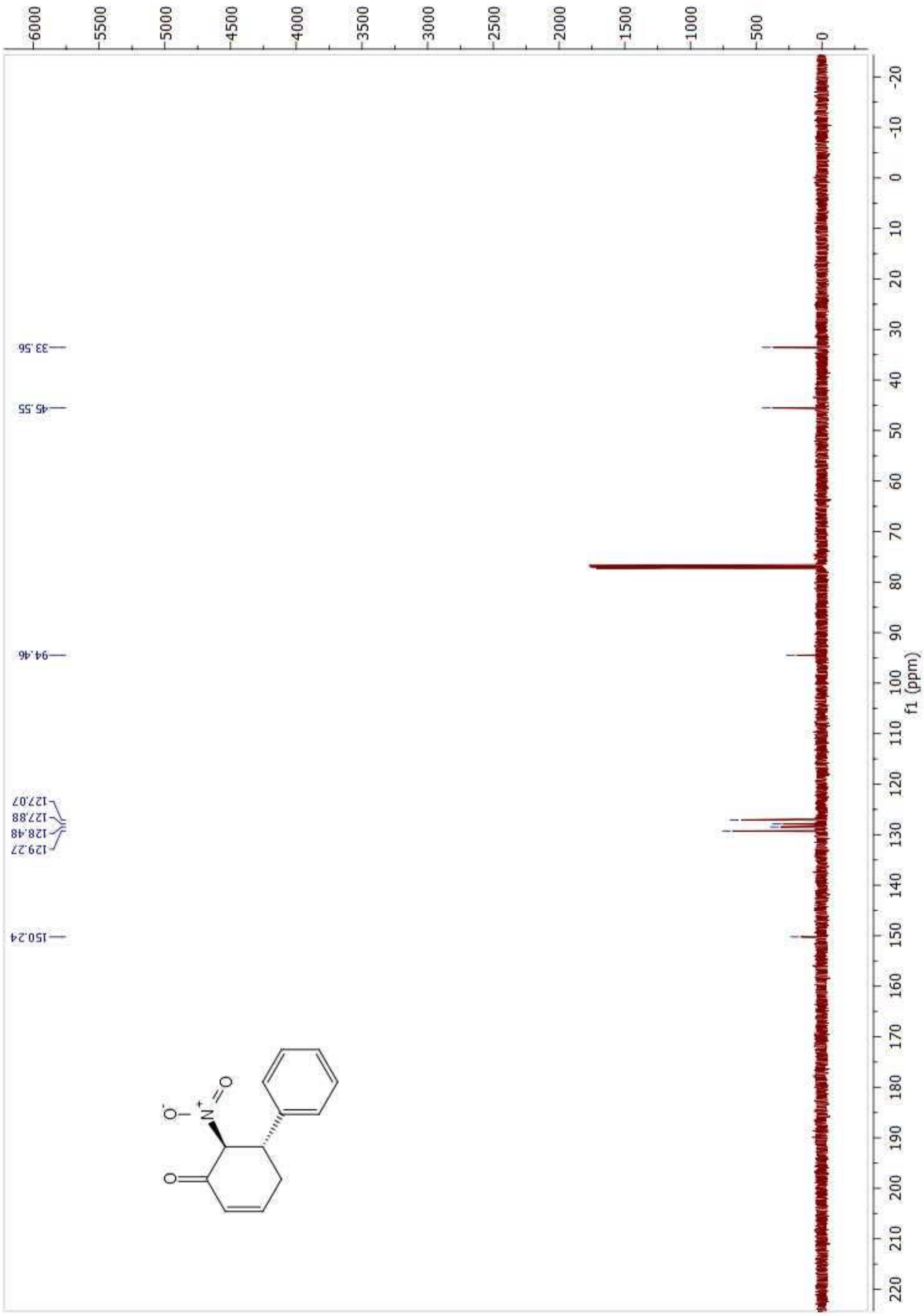


Figure 33. ^{13}C NMR spectrum of **120a** (125 MHz, $CDCl_3$).

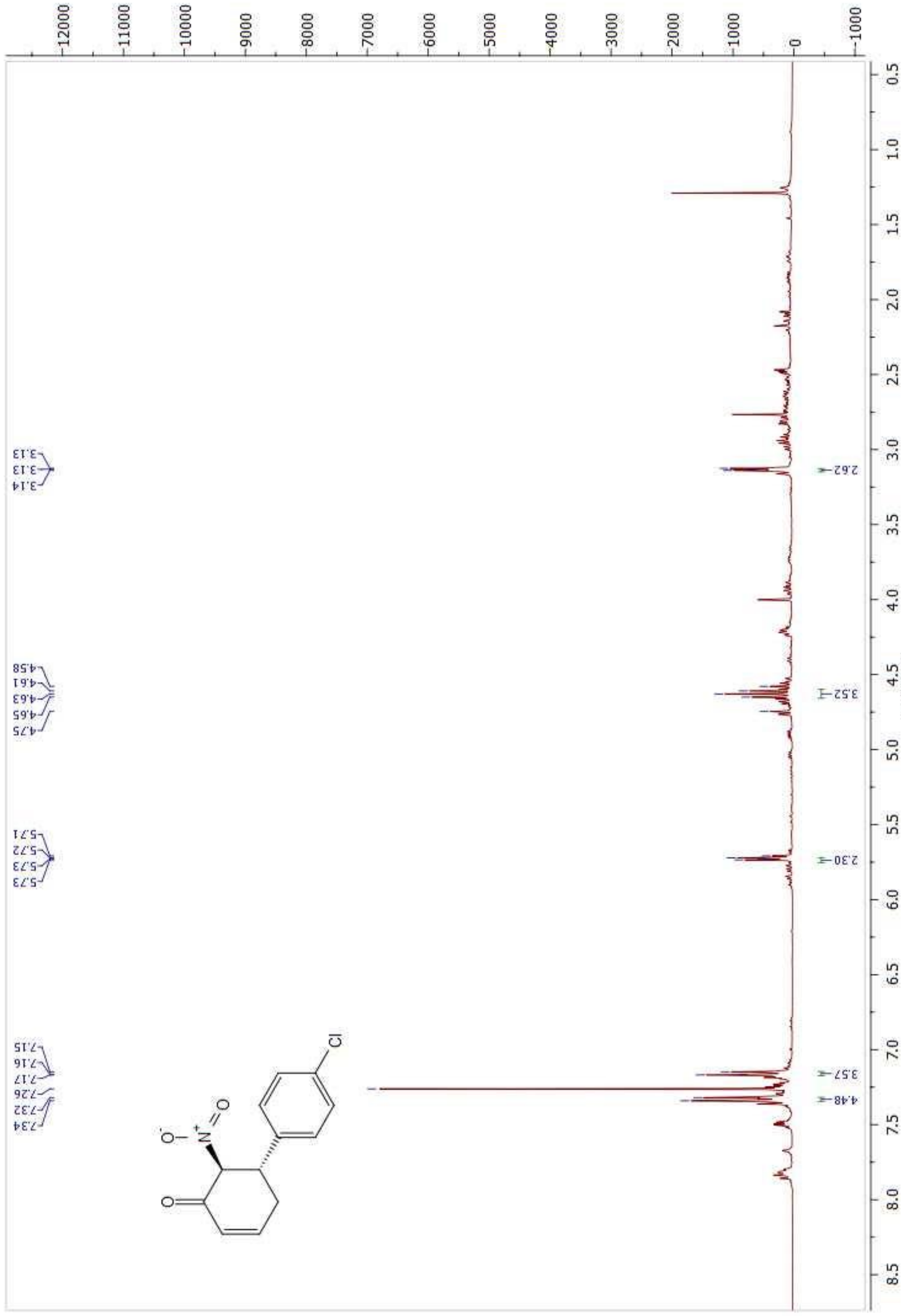


Figure 34. ^{1}H NMR spectrum of **120b** (500 MHz, $CDCl_3$).

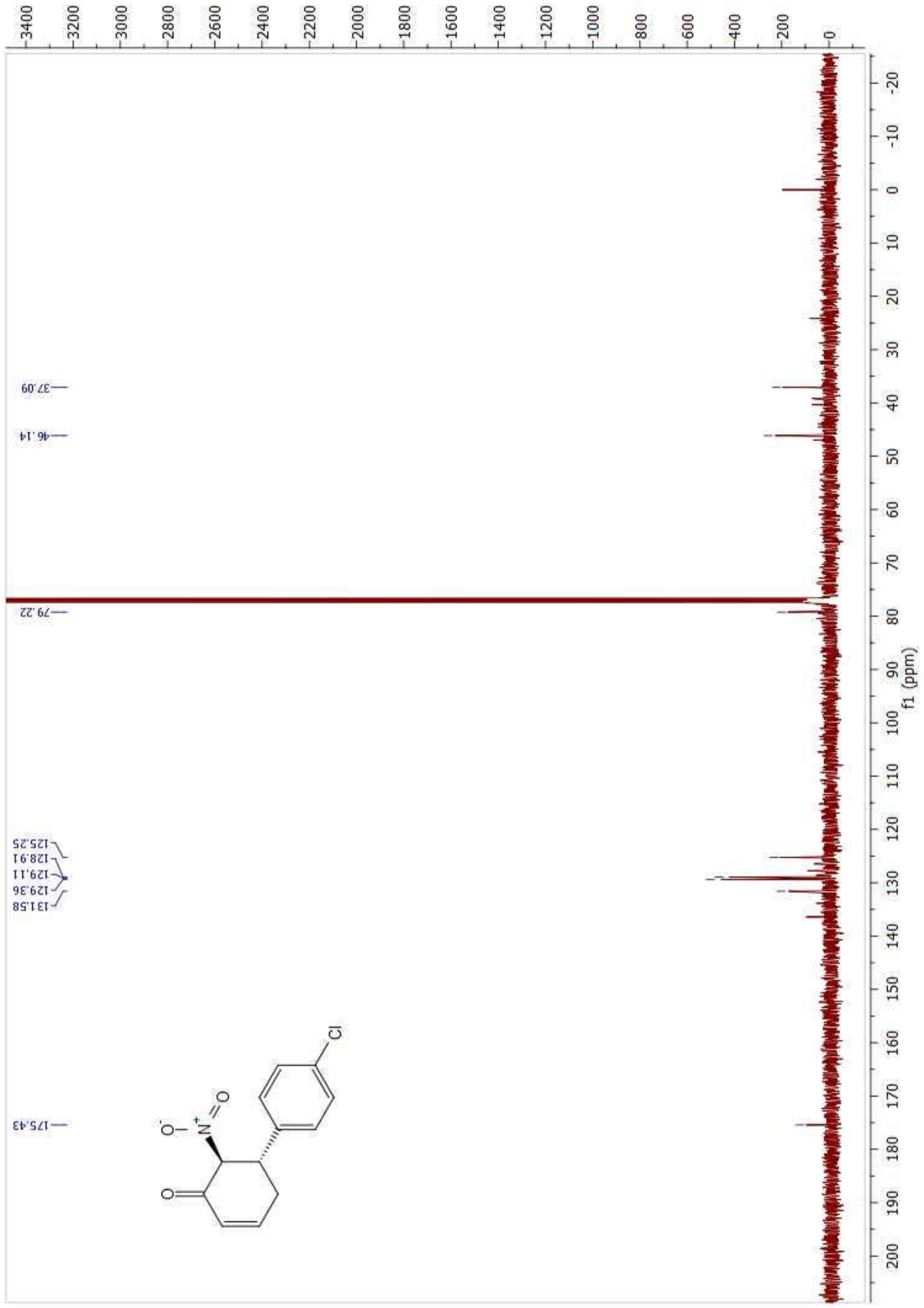


Figure 35. ^{13}C NMR spectrum of **120b** (125 MHz, $CDCl_3$).

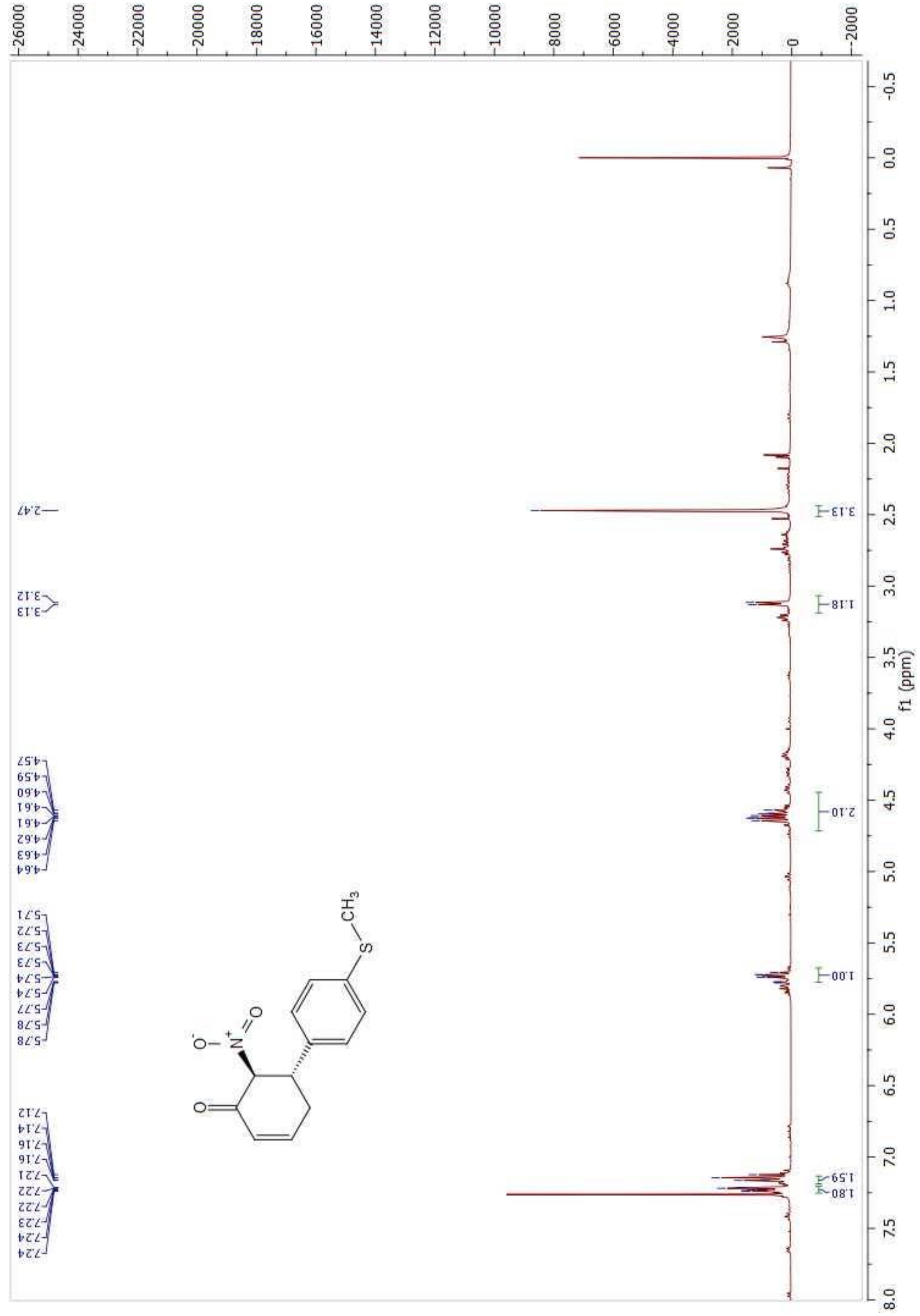


Figure 36. ^{1}H NMR spectrum of **120c** (500 MHz, $CDCl_3$).

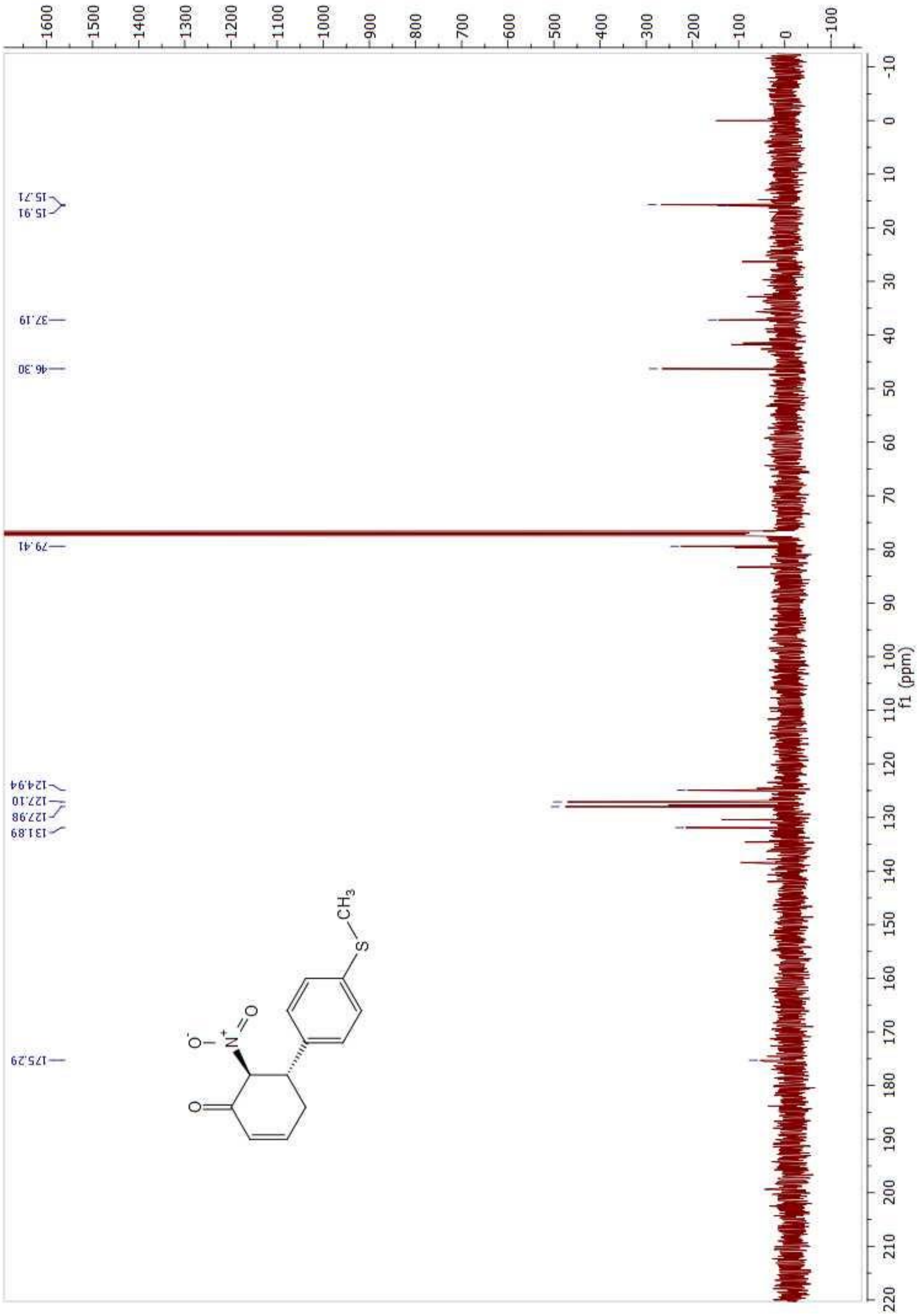


Figure 37. ^{13}C NMR spectrum of **120c** (125 MHz, $CDCl_3$).

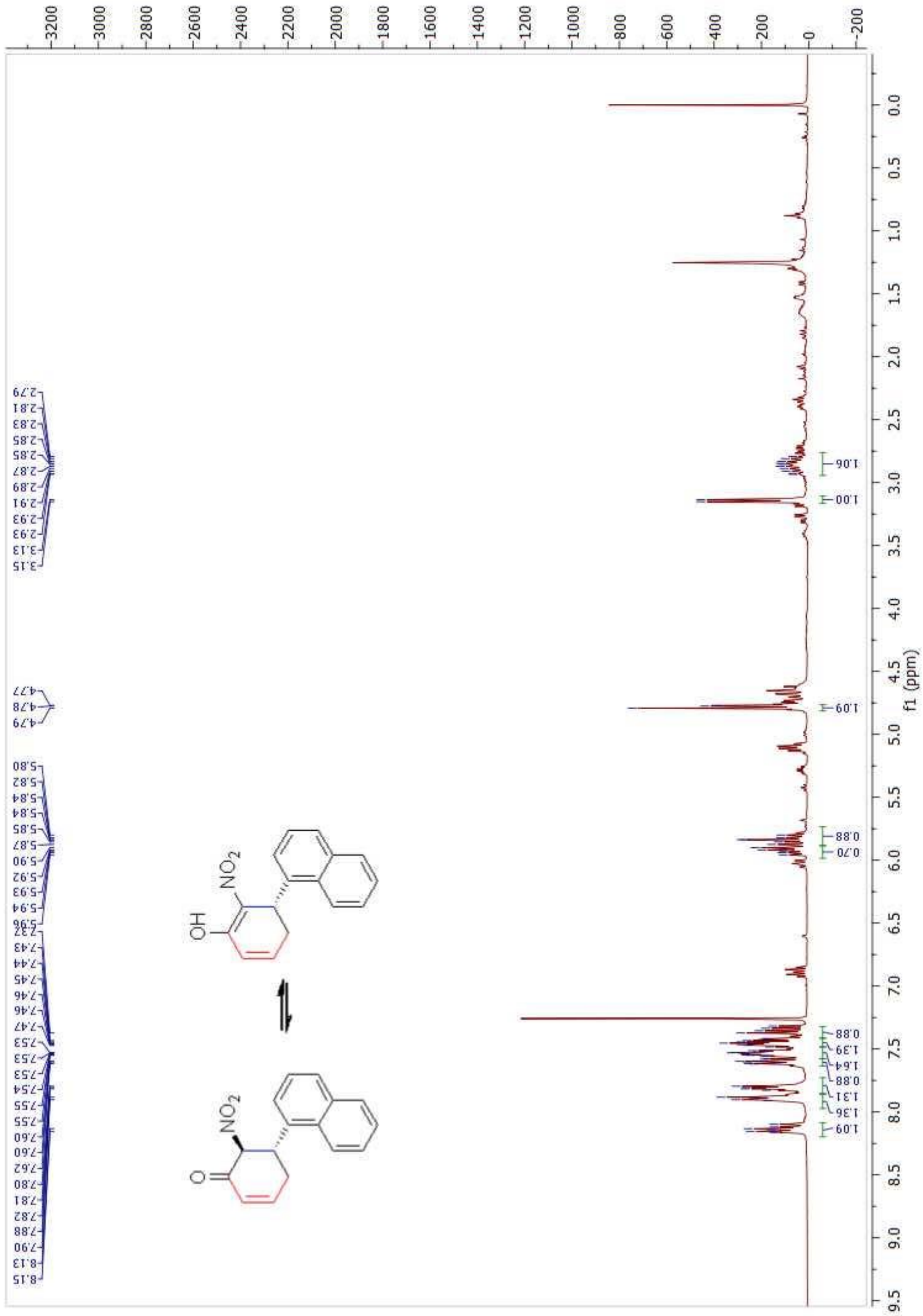


Figure 38. ^{1}H NMR spectrum of **120d** (500 MHz, $CDCl_3$).

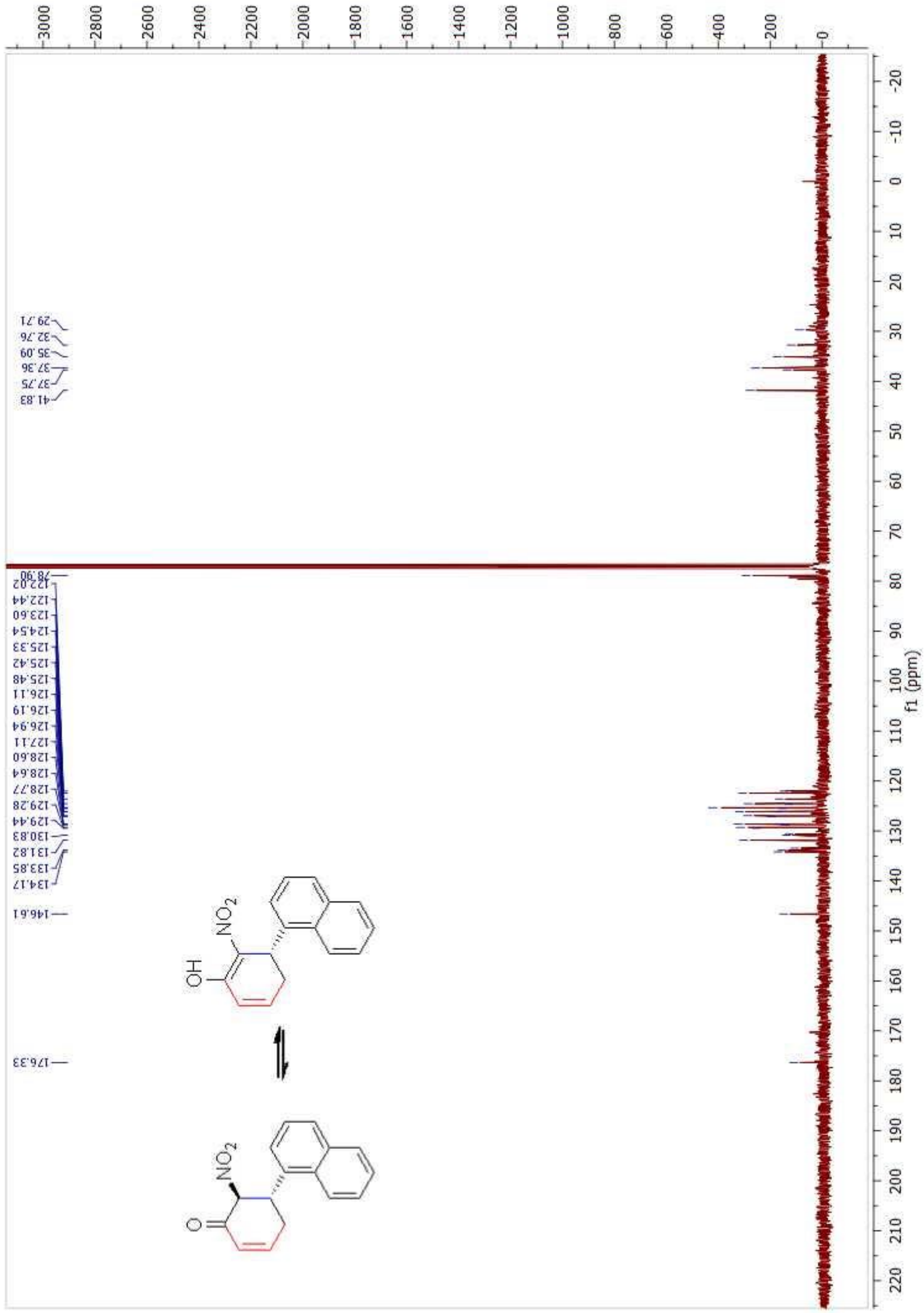


Figure 39. ^{13}C NMR spectrum of **120d** (125 MHz, $CDCl_3$).

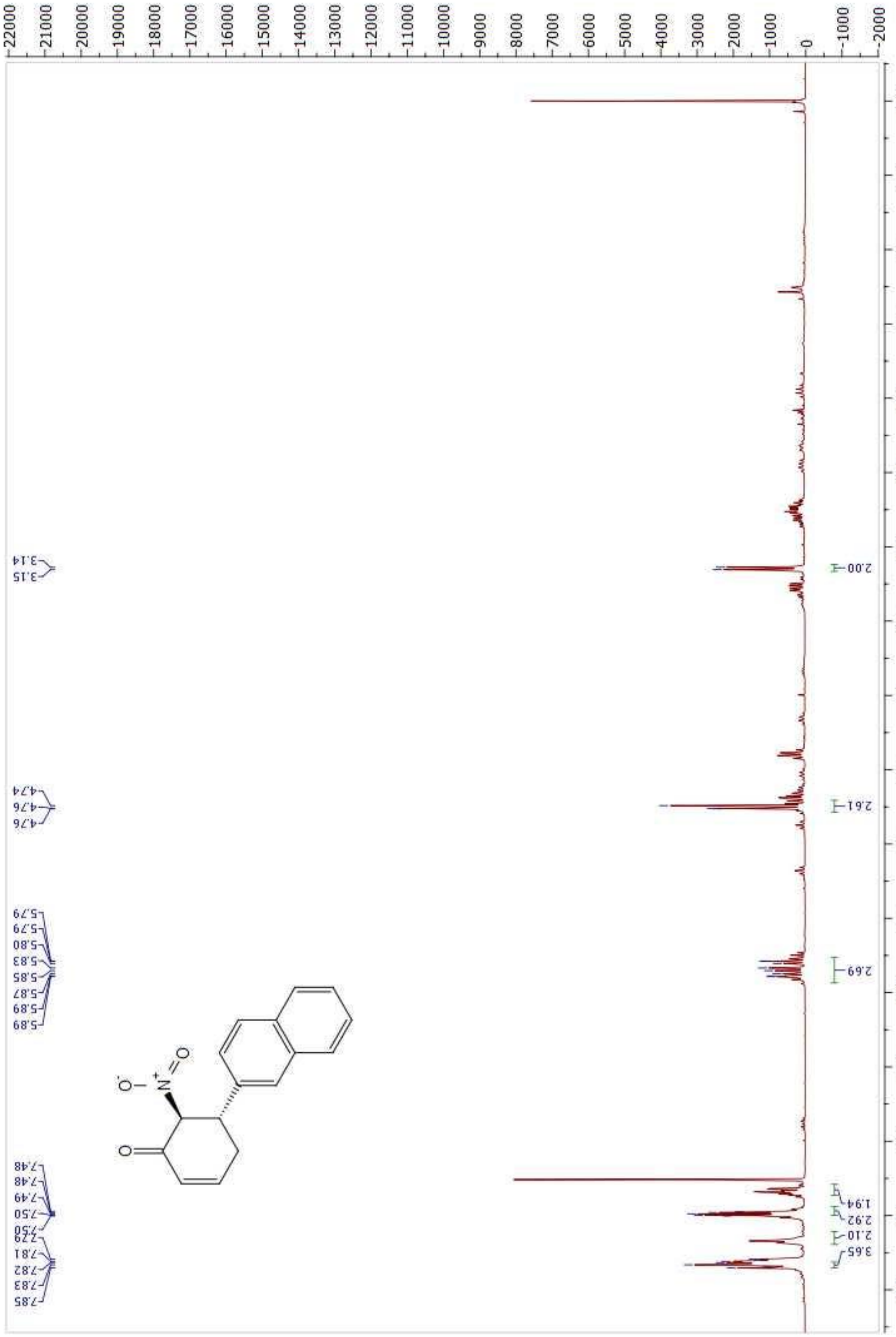


Figure 40. ^{1}H NMR spectrum of **120e** (500 MHz, $CDCl_3$).

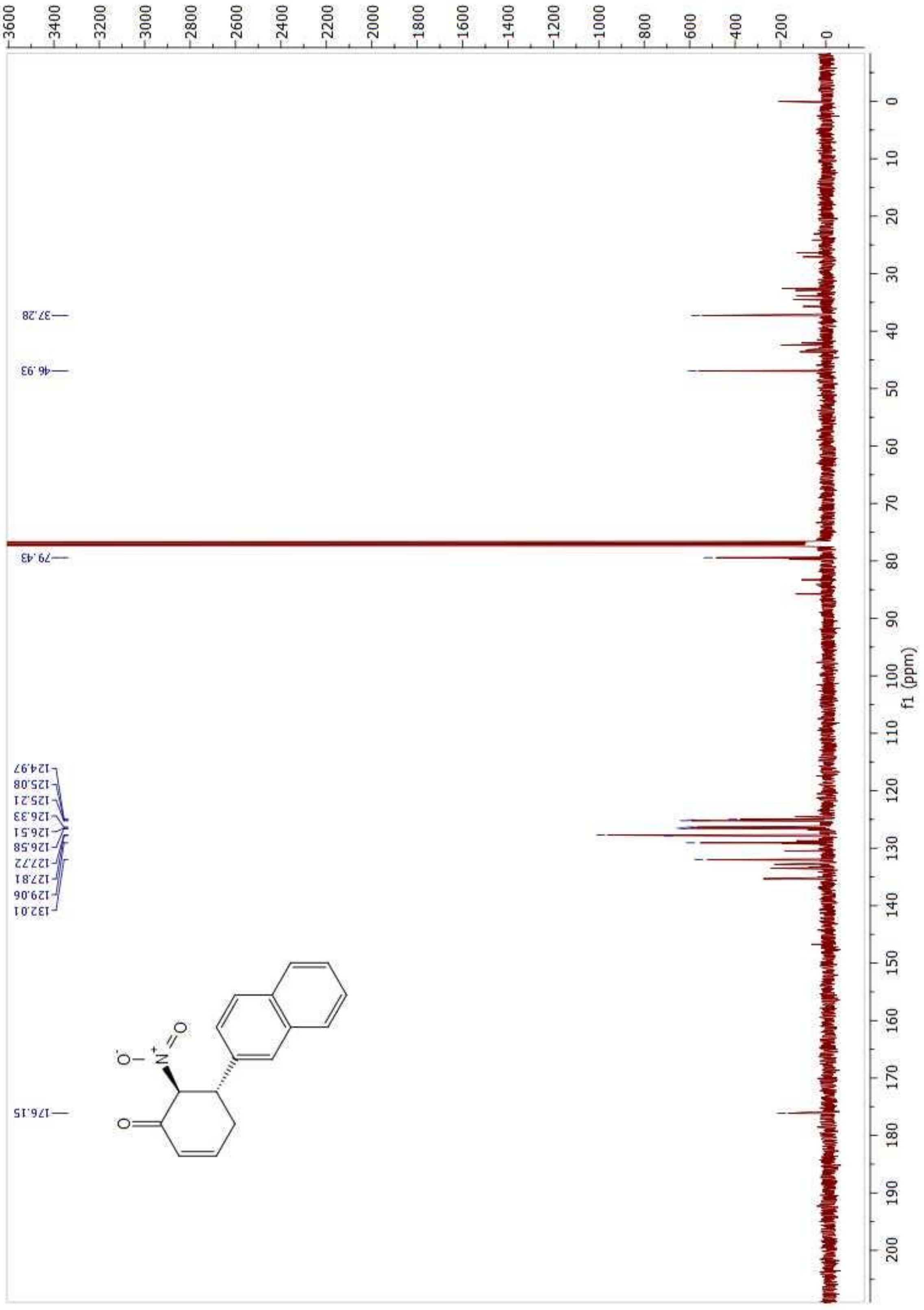


Figure 41. ^{13}C NMR spectrum of **120e** (125 MHz, $CDCl_3$).

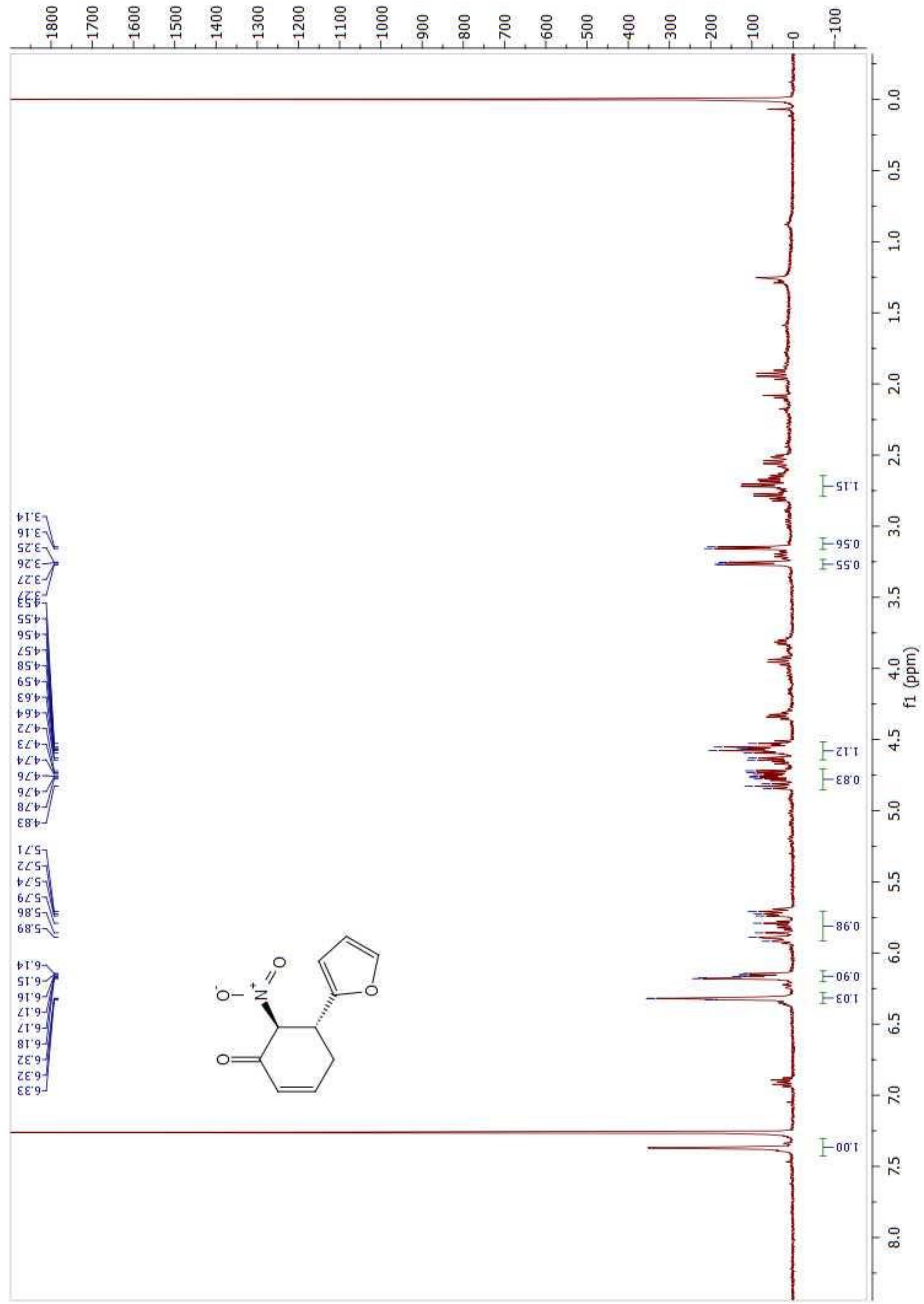


Figure 42. ^{1}H NMR spectrum of **120f** (500 MHz, $CDCl_3$).

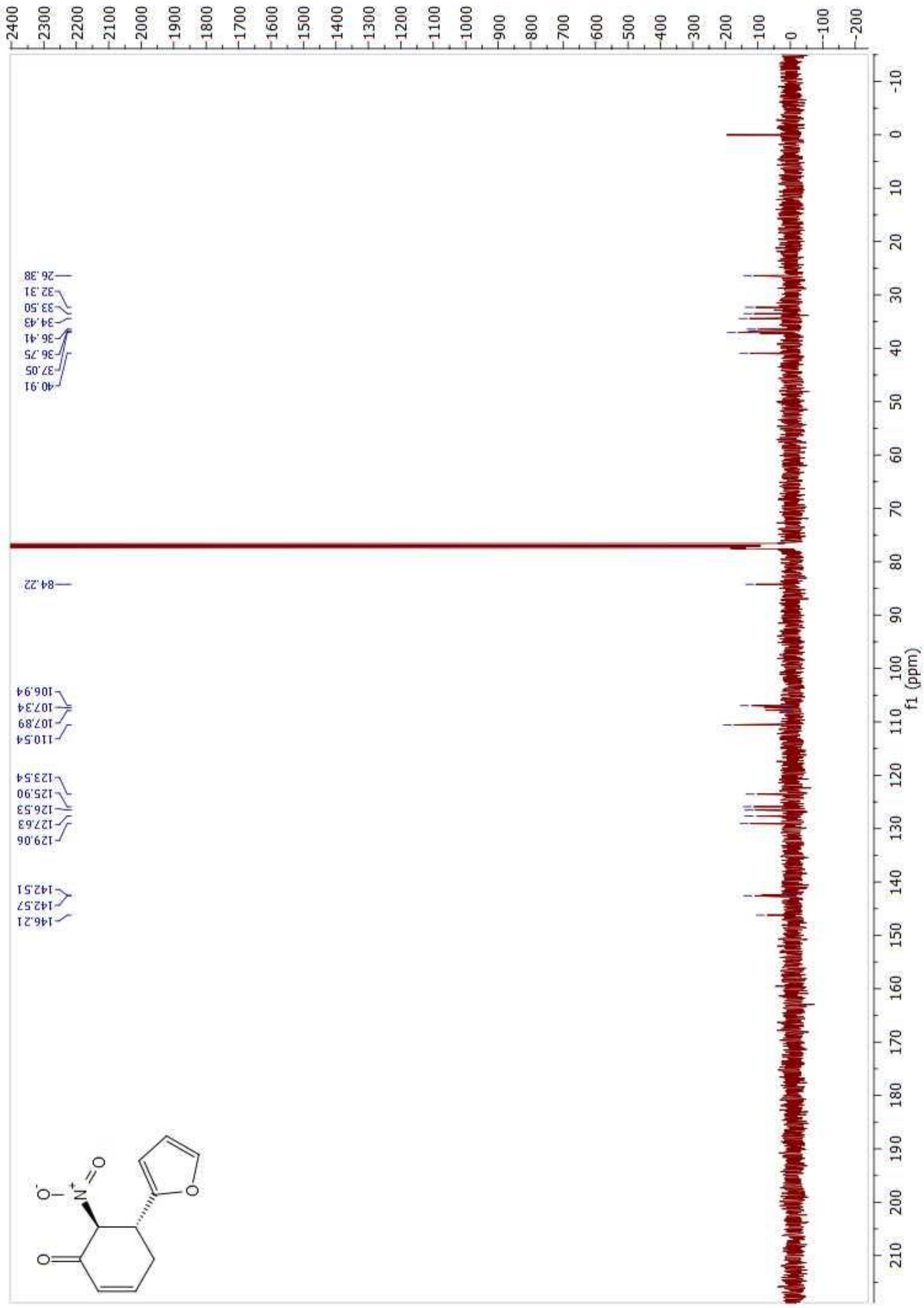


Figure 43. ^{13}C NMR spectrum of **120f** (125 MHz, $CDCl_3$).

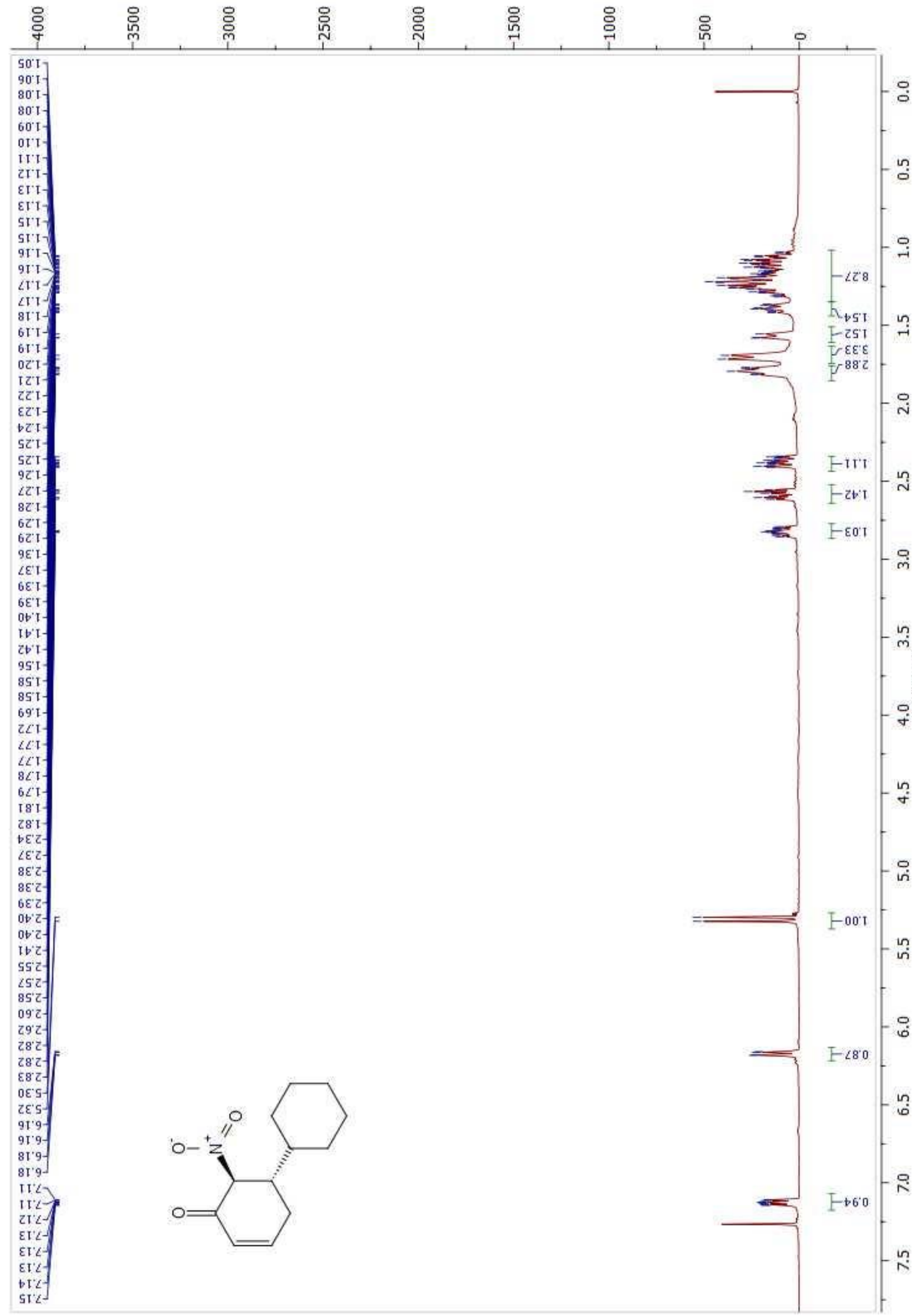


Figure 44. ^{1}H NMR spectrum of **120g** (500 MHz, CDCl$_3$).

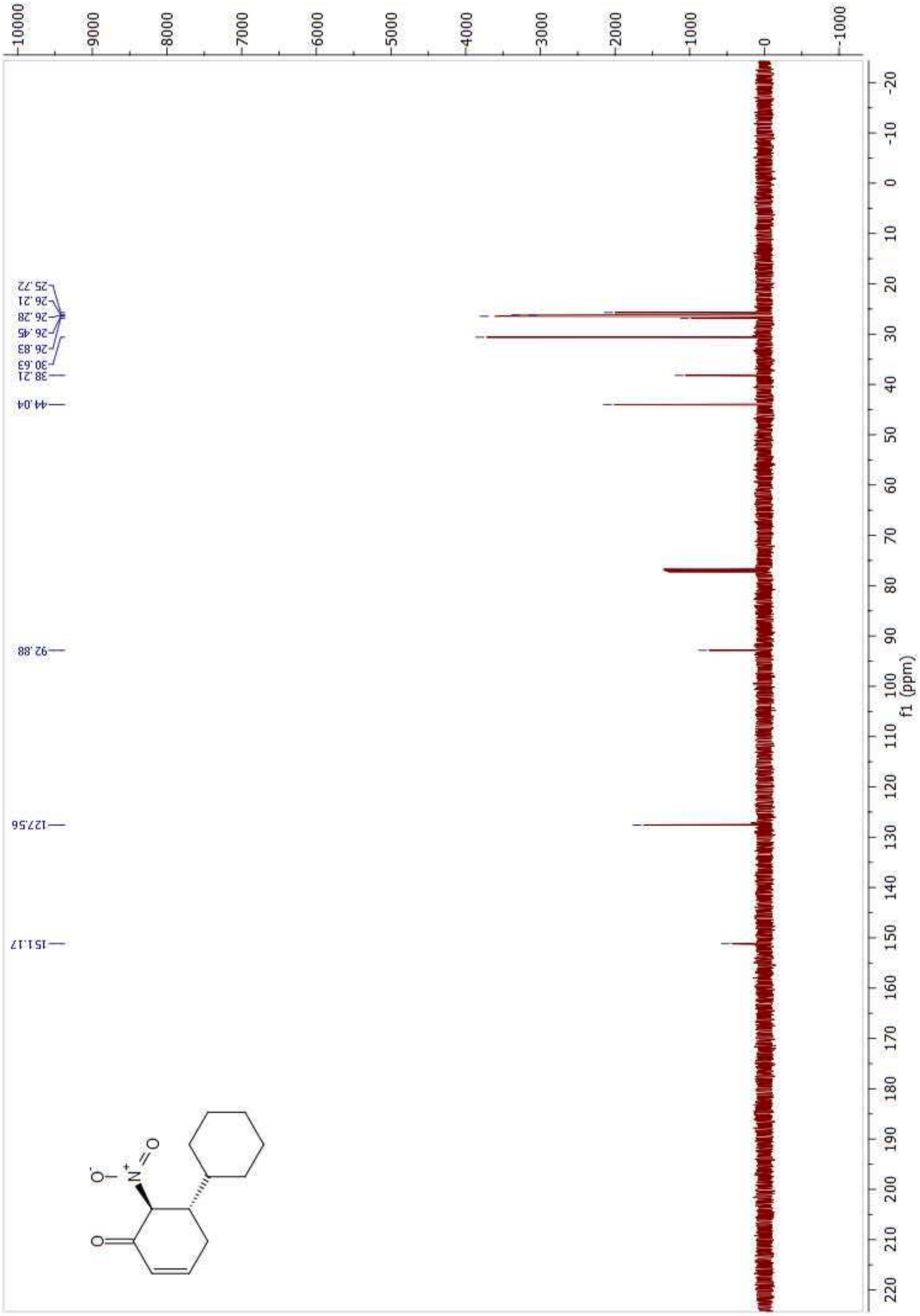


Figure 45. ^{13}C NMR spectrum of **120g** (125 MHz, CDCl$_3$).

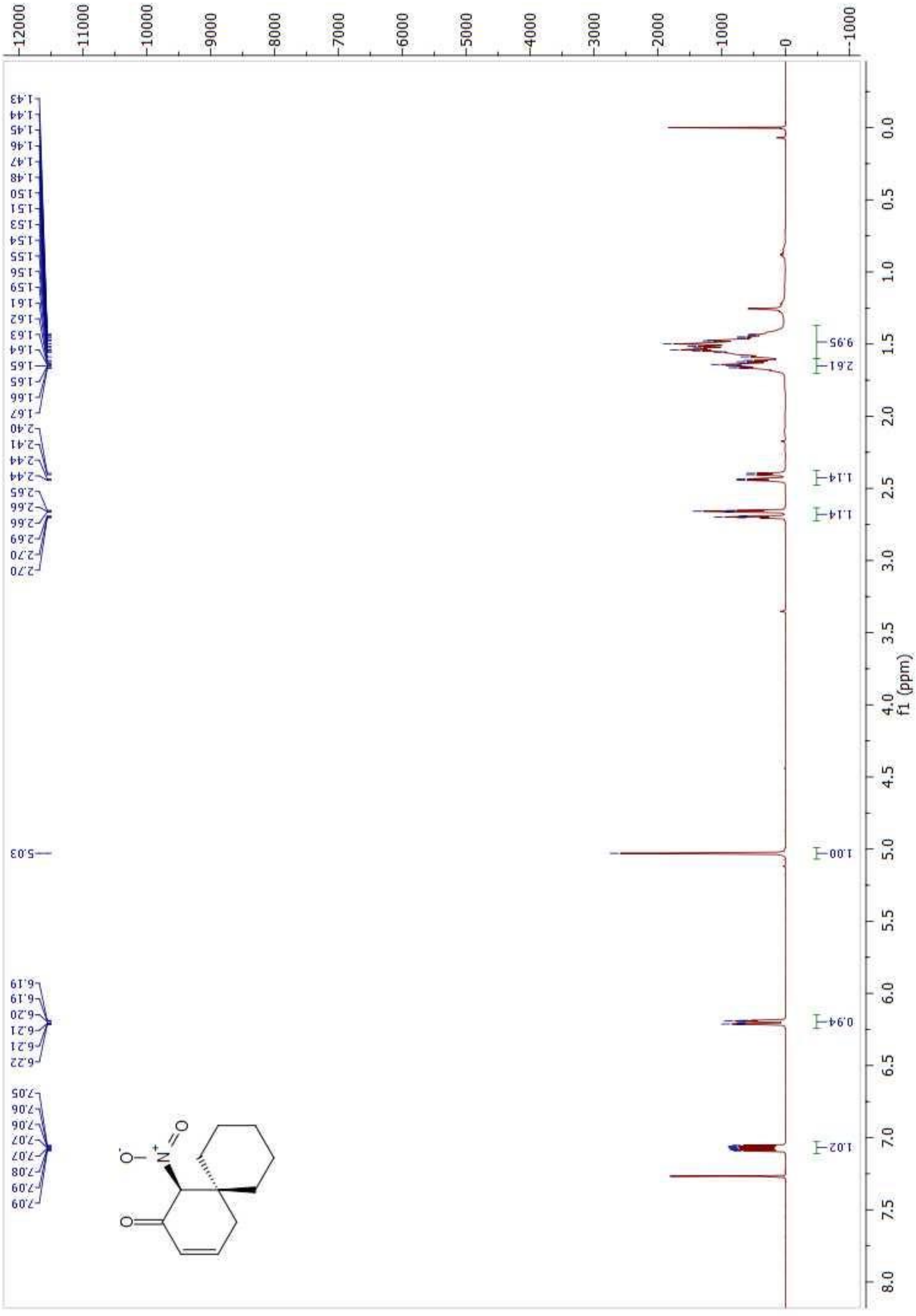


Figure 46. ^{1}H NMR spectrum of **120h** (500 MHz, $CDCl_3$).

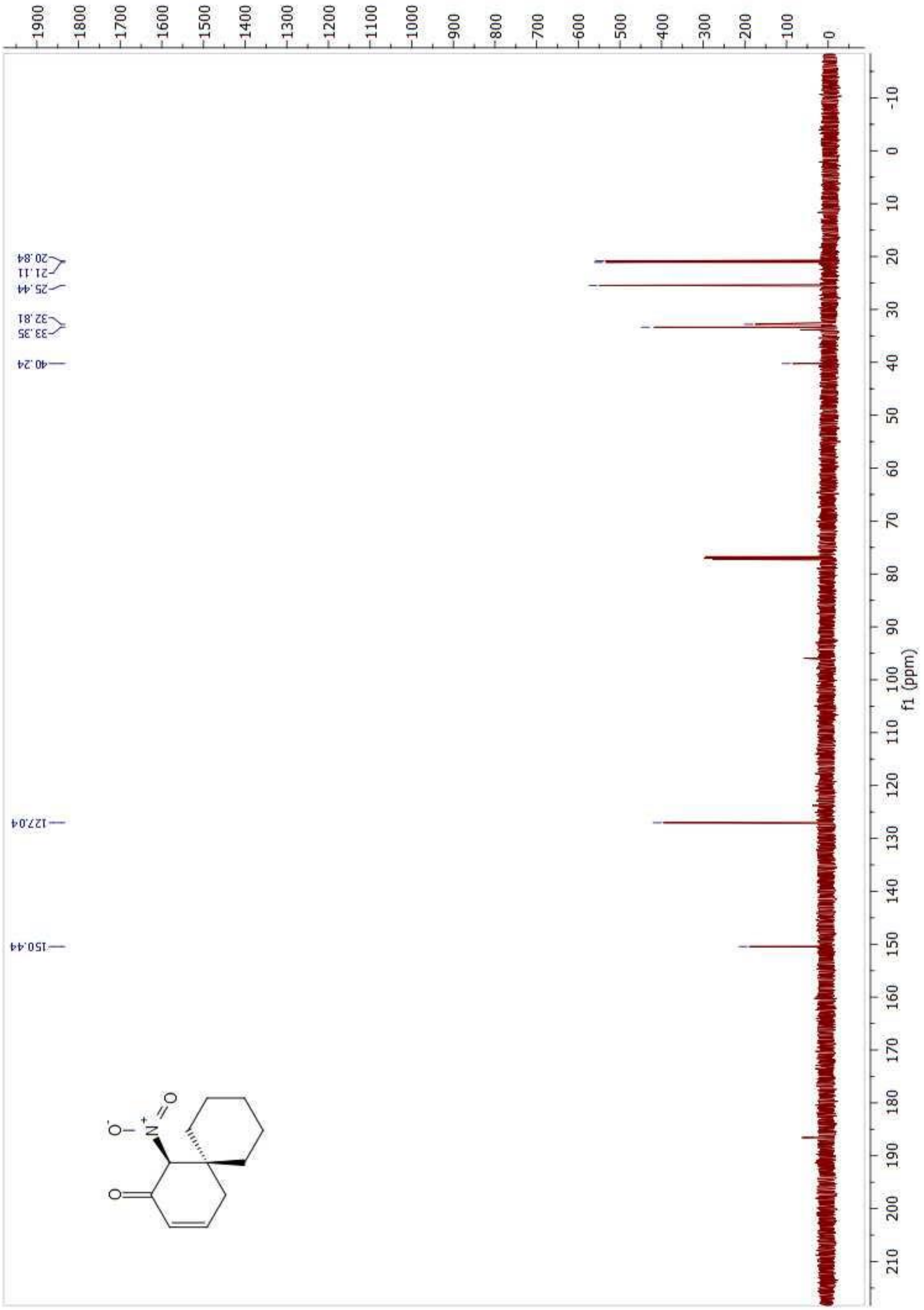


Figure 47. ^{13}C NMR spectrum of **120h** (125 MHz, $CDCl_3$).

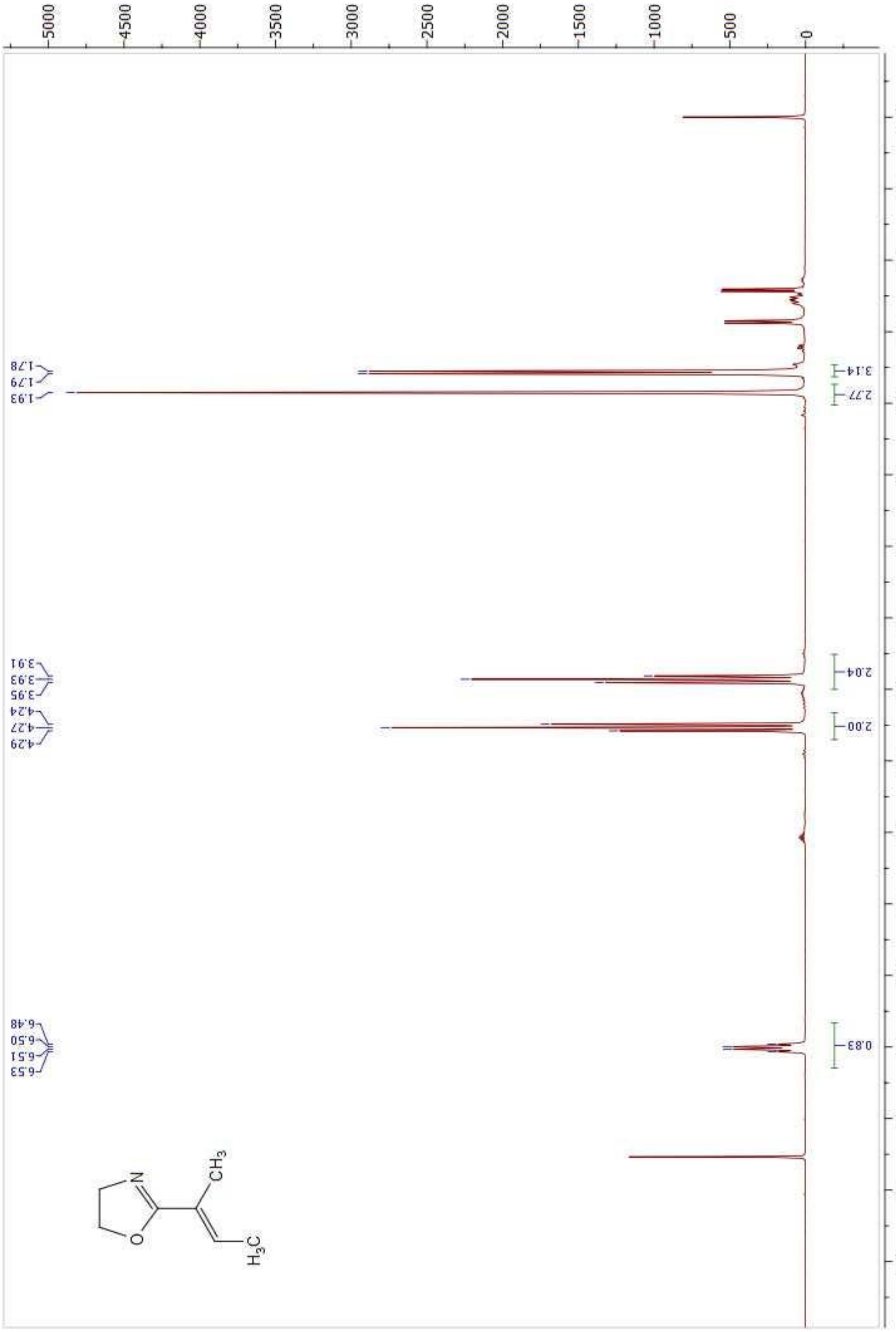


Figure 48. ^{1}H NMR spectrum of **122a** (500 MHz, $CDCl_3$).

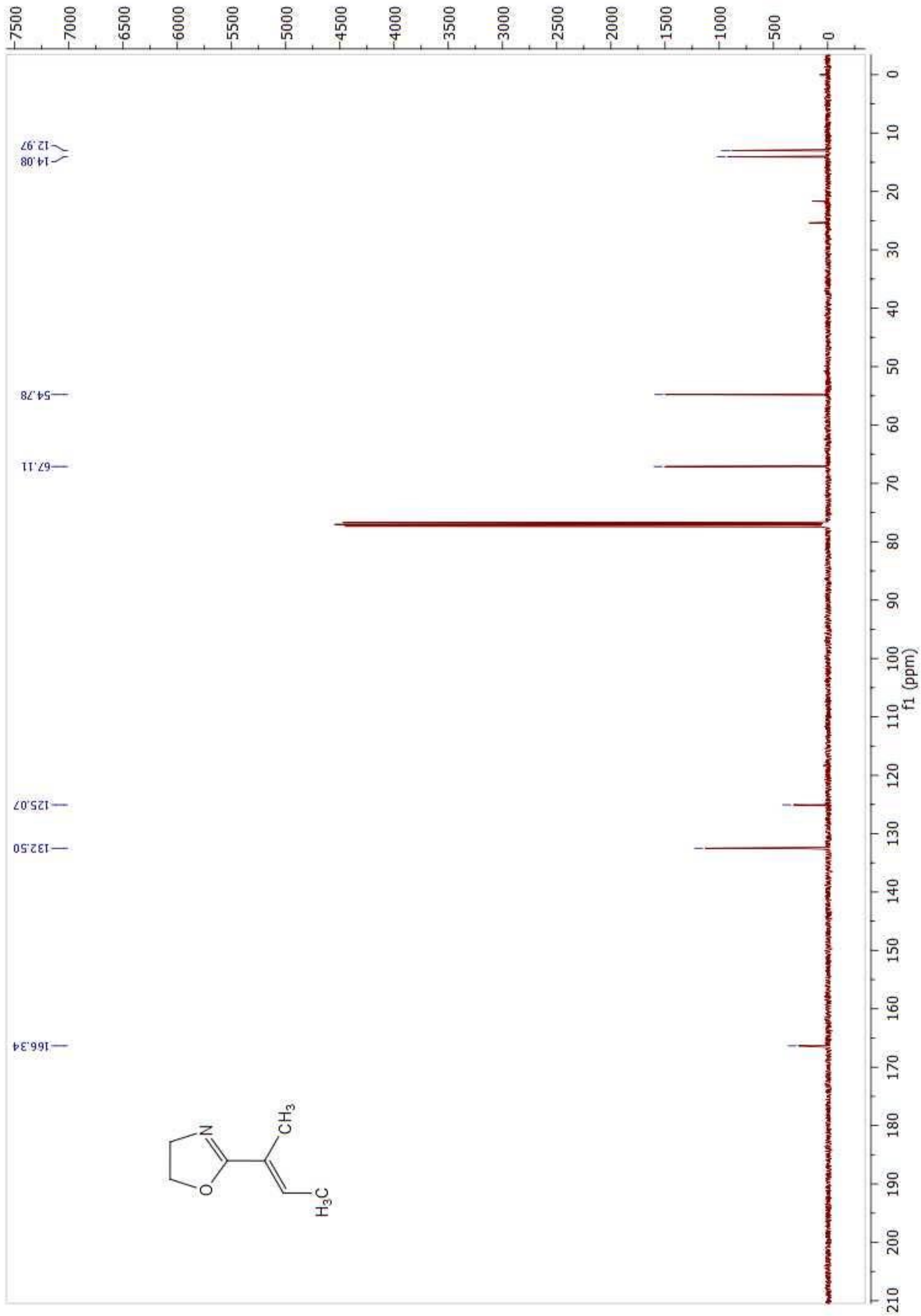


Figure 49. ^{13}C NMR spectrum of **122a** (125 MHz, $CDCl_3$).

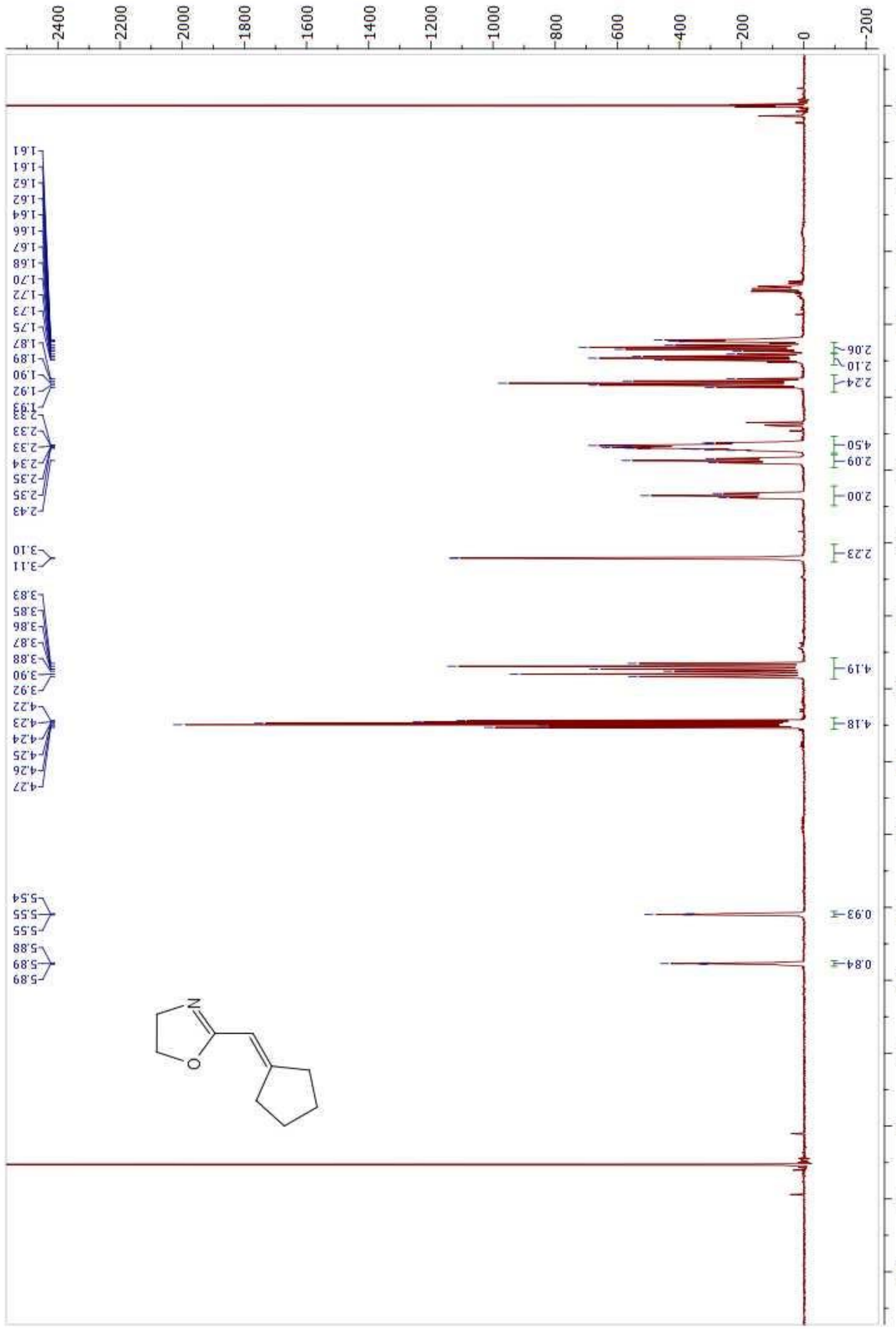


Figure 50. ^{1}H NMR spectrum of **122b** (500 MHz, $CDCl_3$).

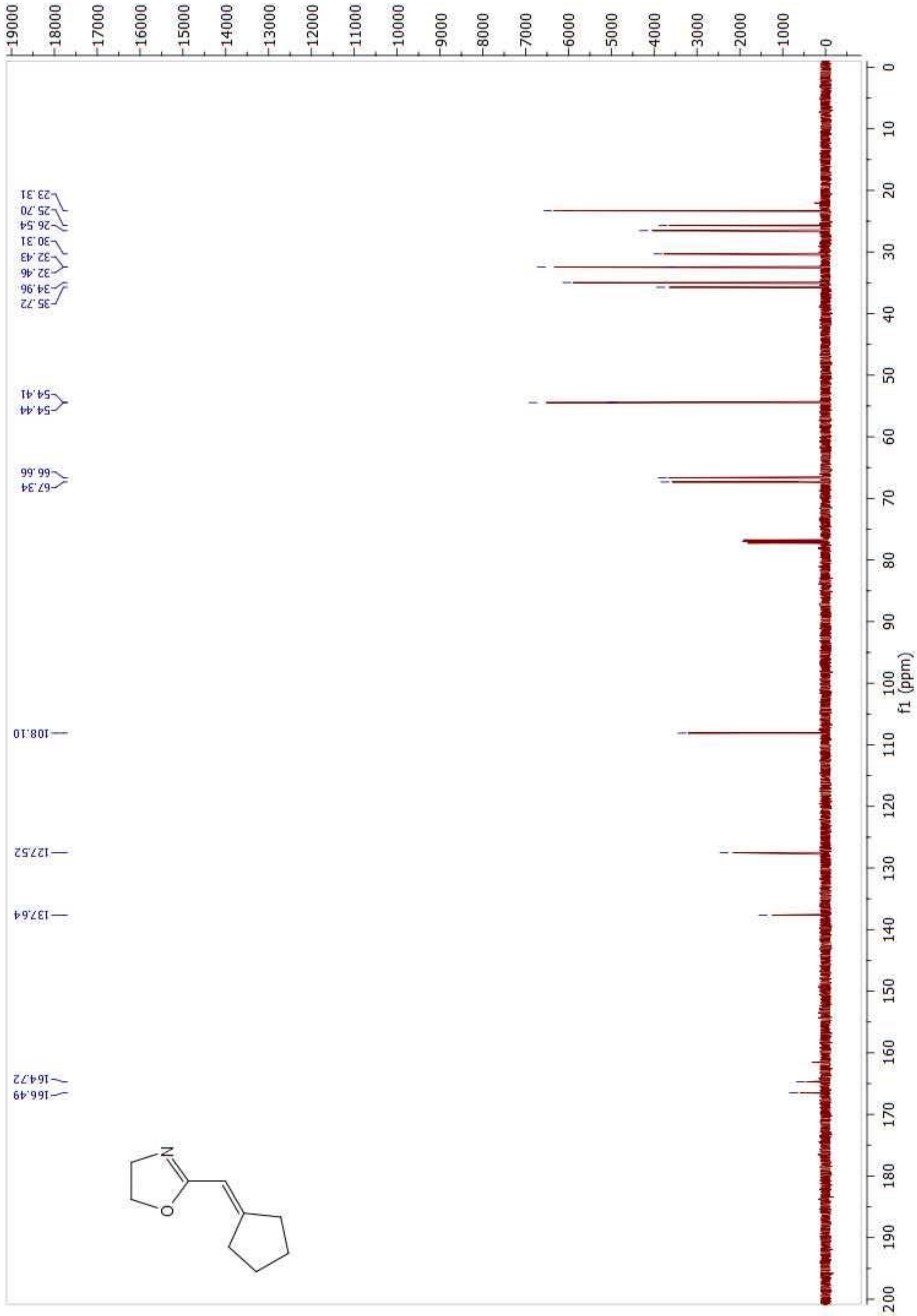


Figure 51. ^{13}C NMR spectrum of **122b** (125 MHz, $CDCl_3$).

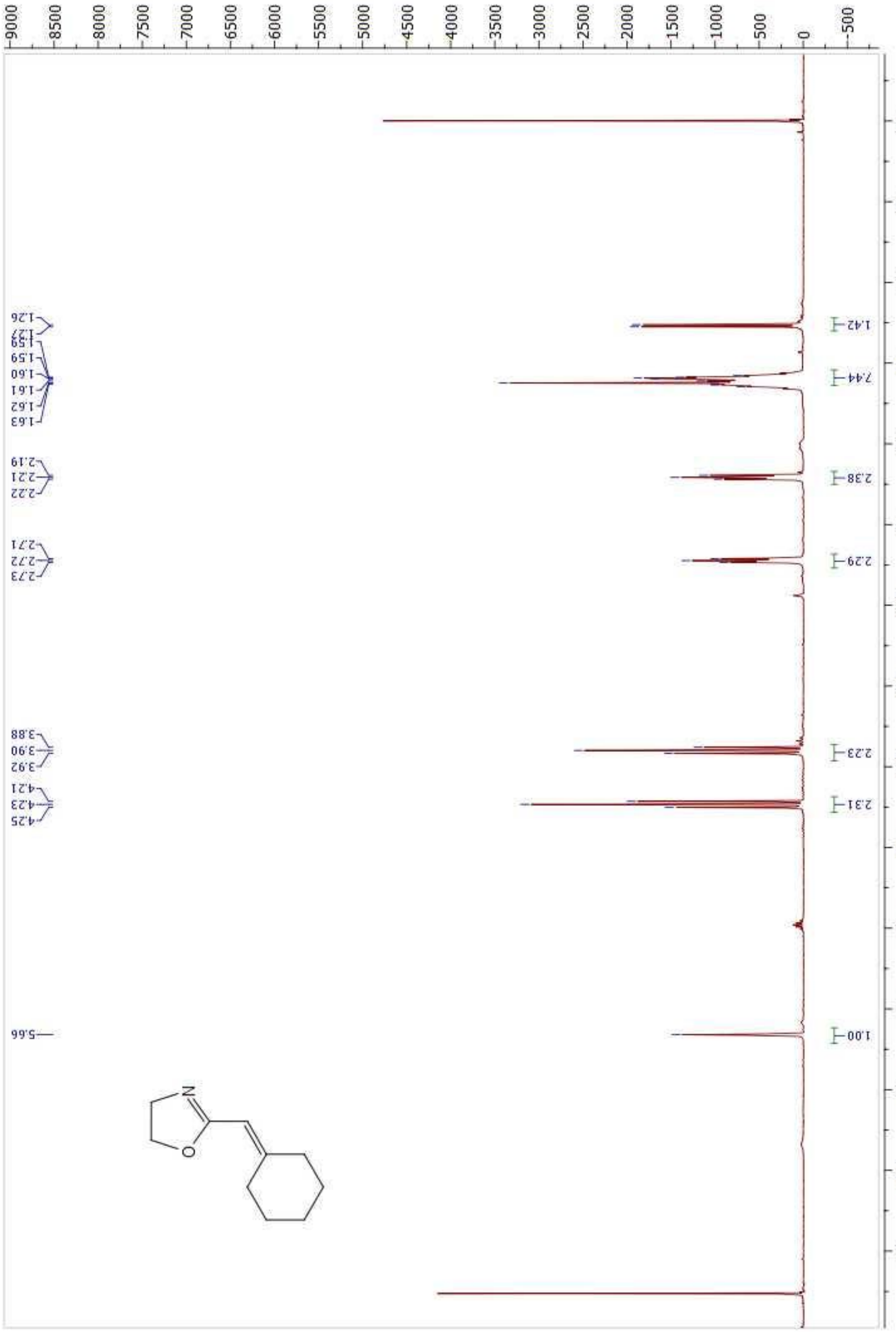


Figure 52. ^{1}H NMR spectrum of **122c** (500 MHz, $CDCl_3$).

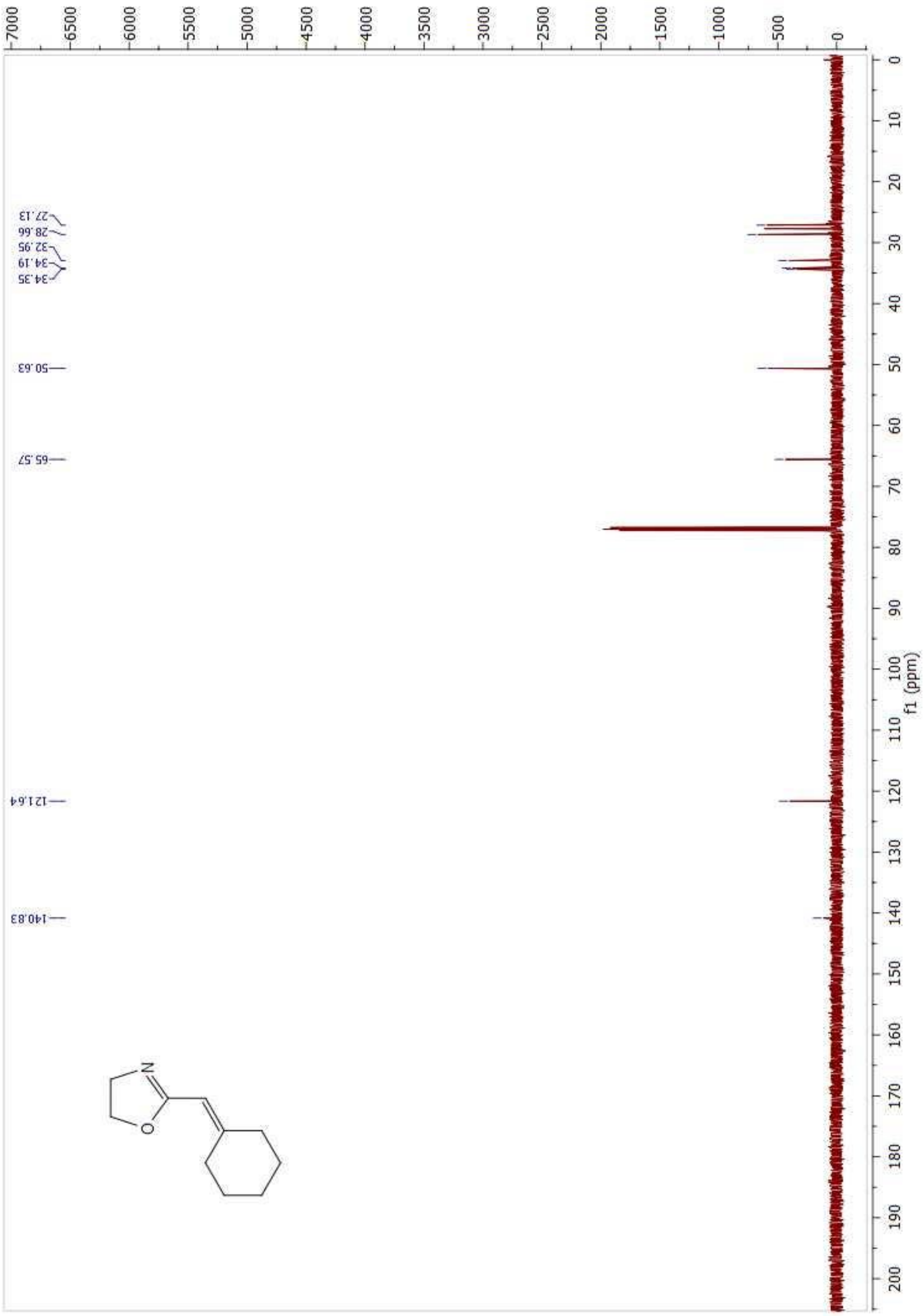


Figure 53. ^{13}C NMR spectrum of **122c** (125 MHz, $CDCl_3$).

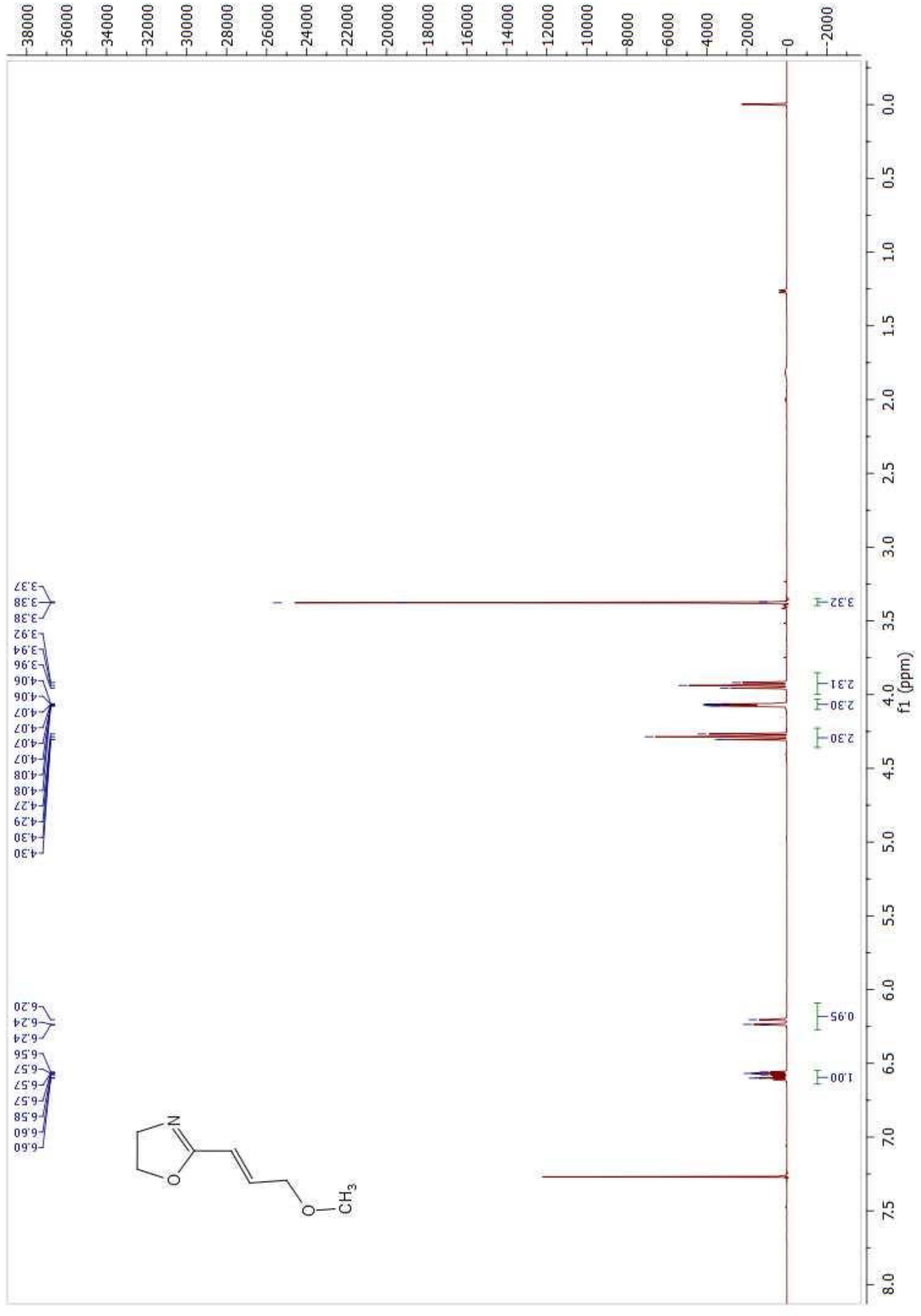


Figure 54. ^{1}H NMR spectrum of **122d** (500 MHz, CDCl$_3$).

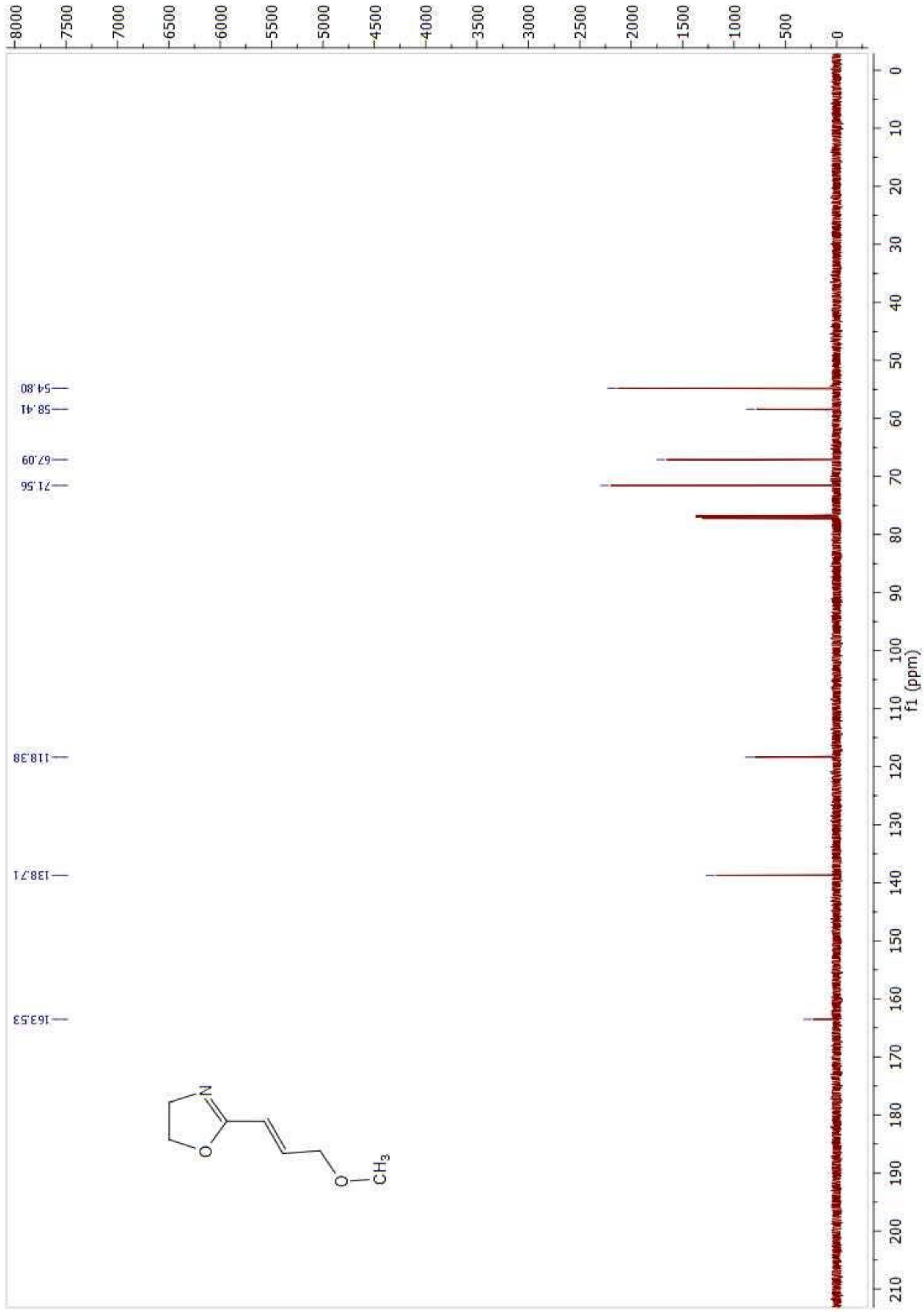


Figure 55. ^{13}C NMR spectrum of **122d** (125 MHz, $CDCl_3$).

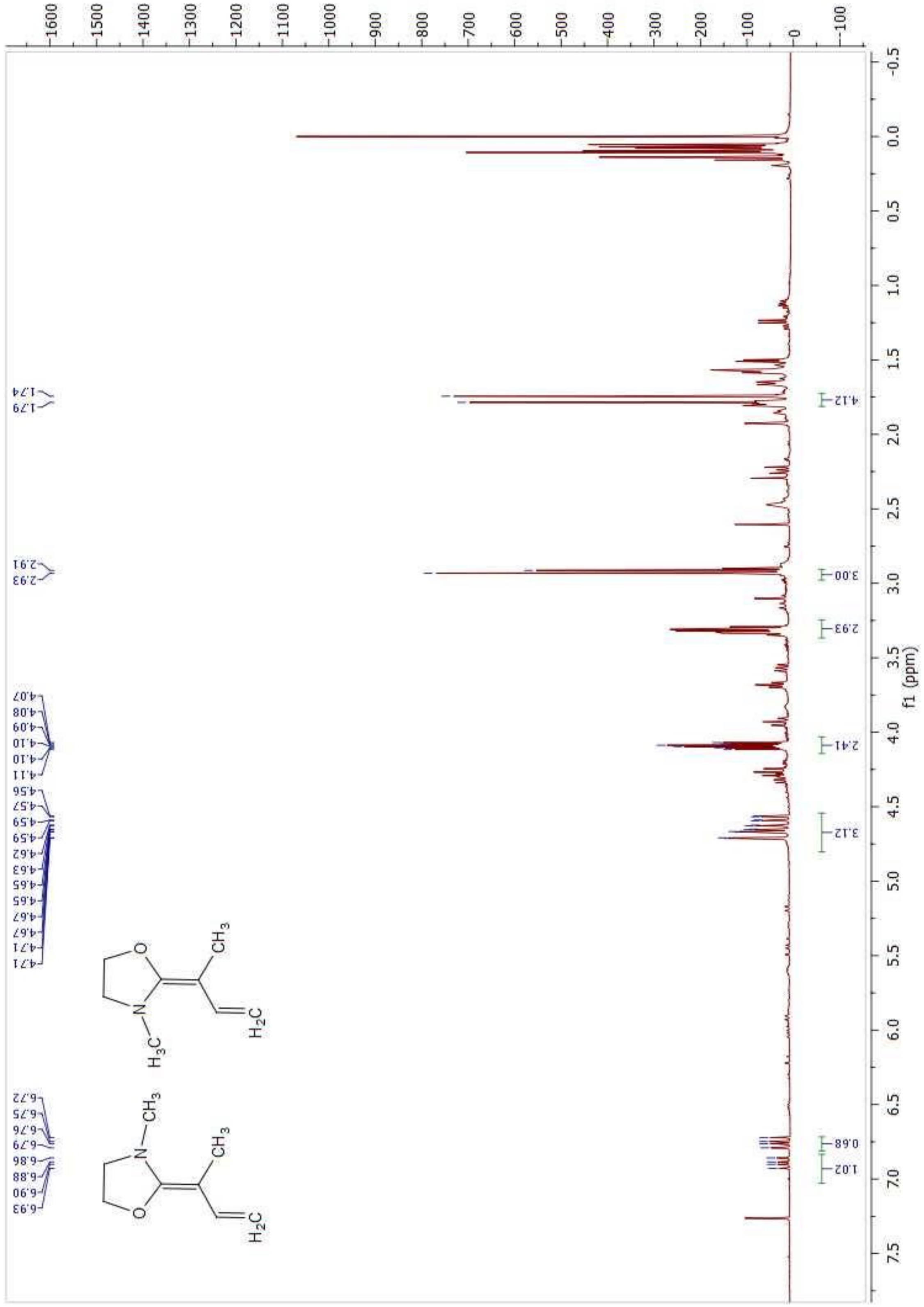


Figure 56. ^{1}H NMR spectrum of **123a** (500 MHz, $CDCl_3$).

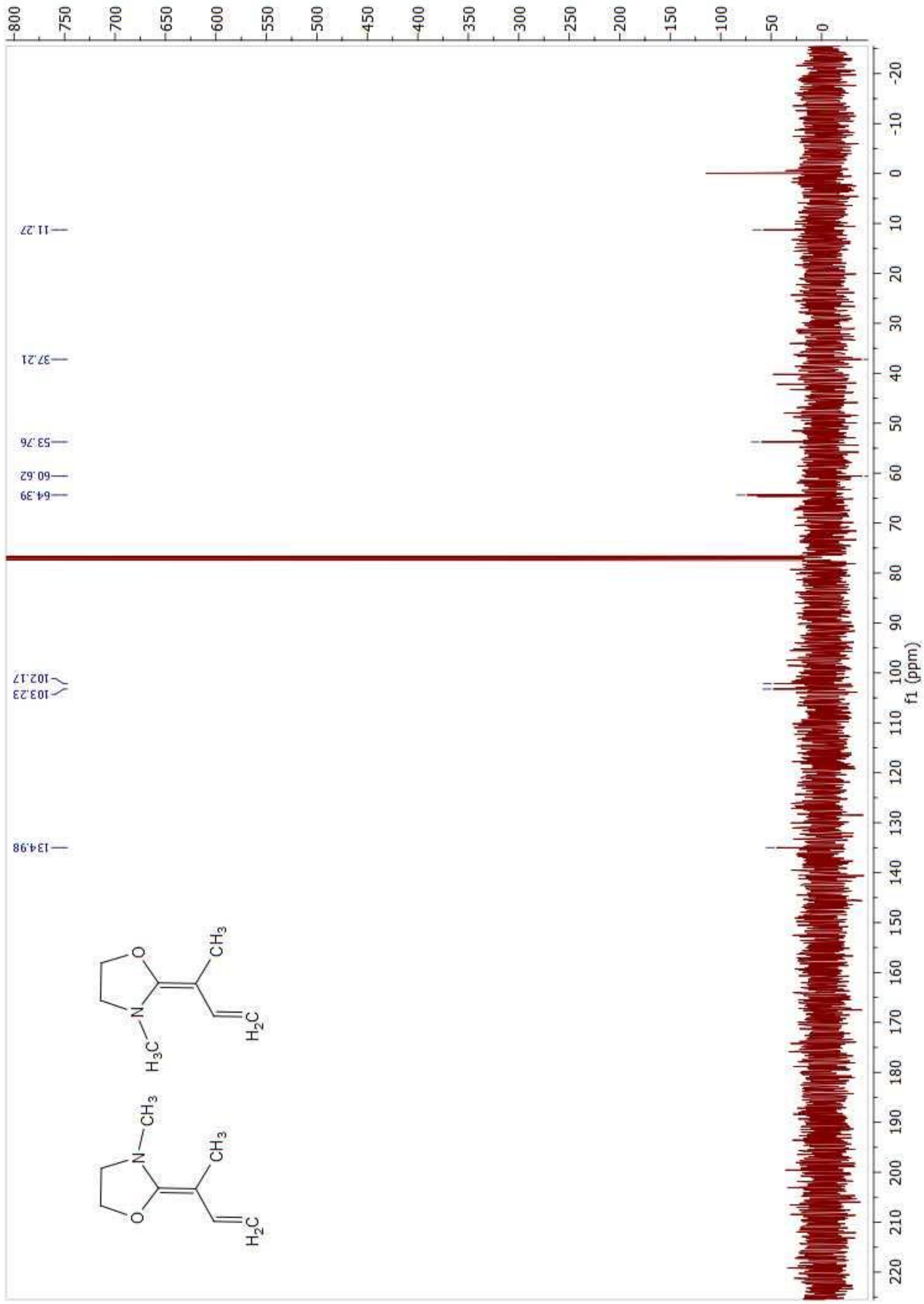


Figure 57. ^{13}C NMR spectrum of **123b** (125 MHz, $CDCl_3$).

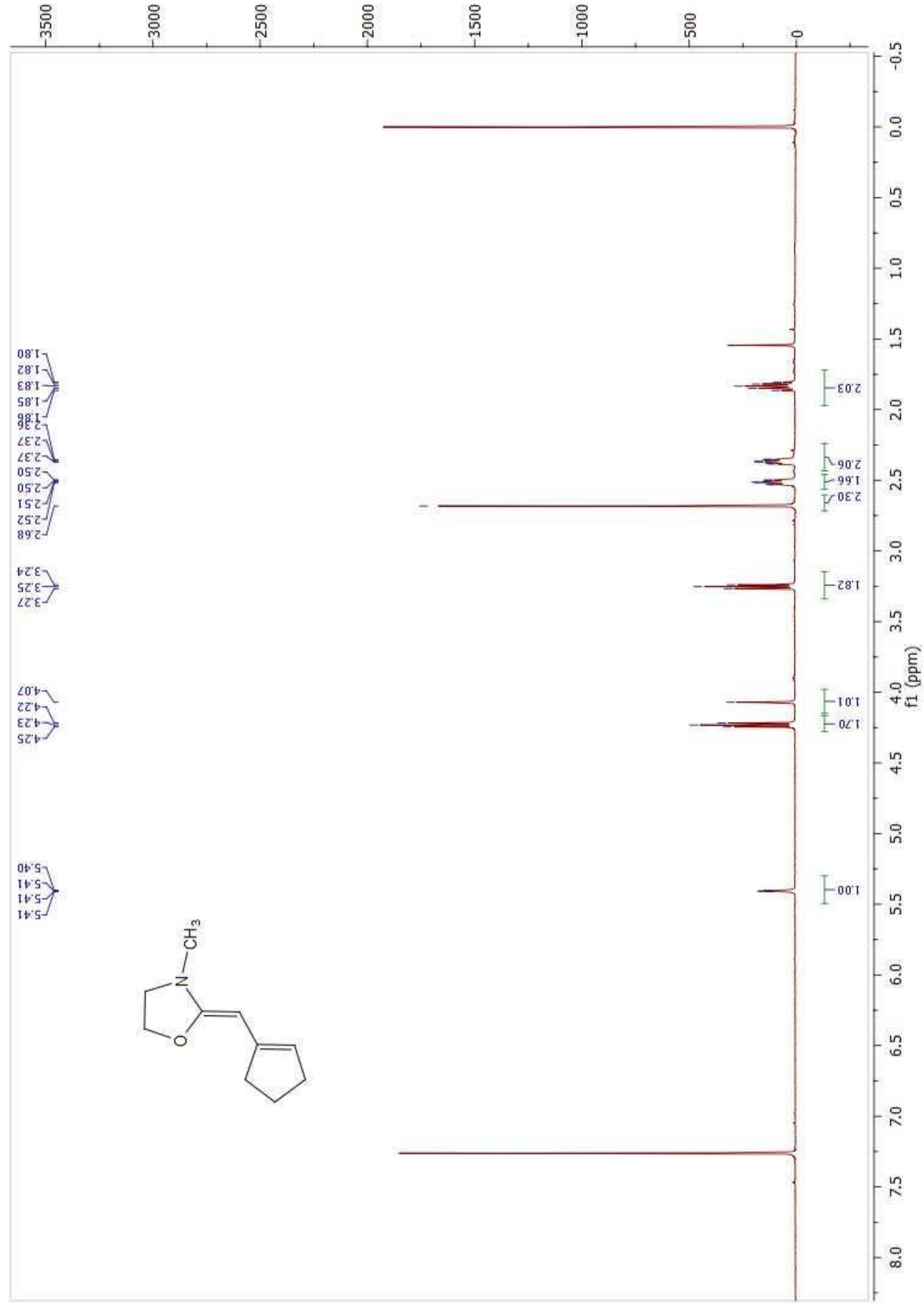


Figure 58. ^{1}H NMR spectrum of **123b** (500 MHz, $CDCl_3$).

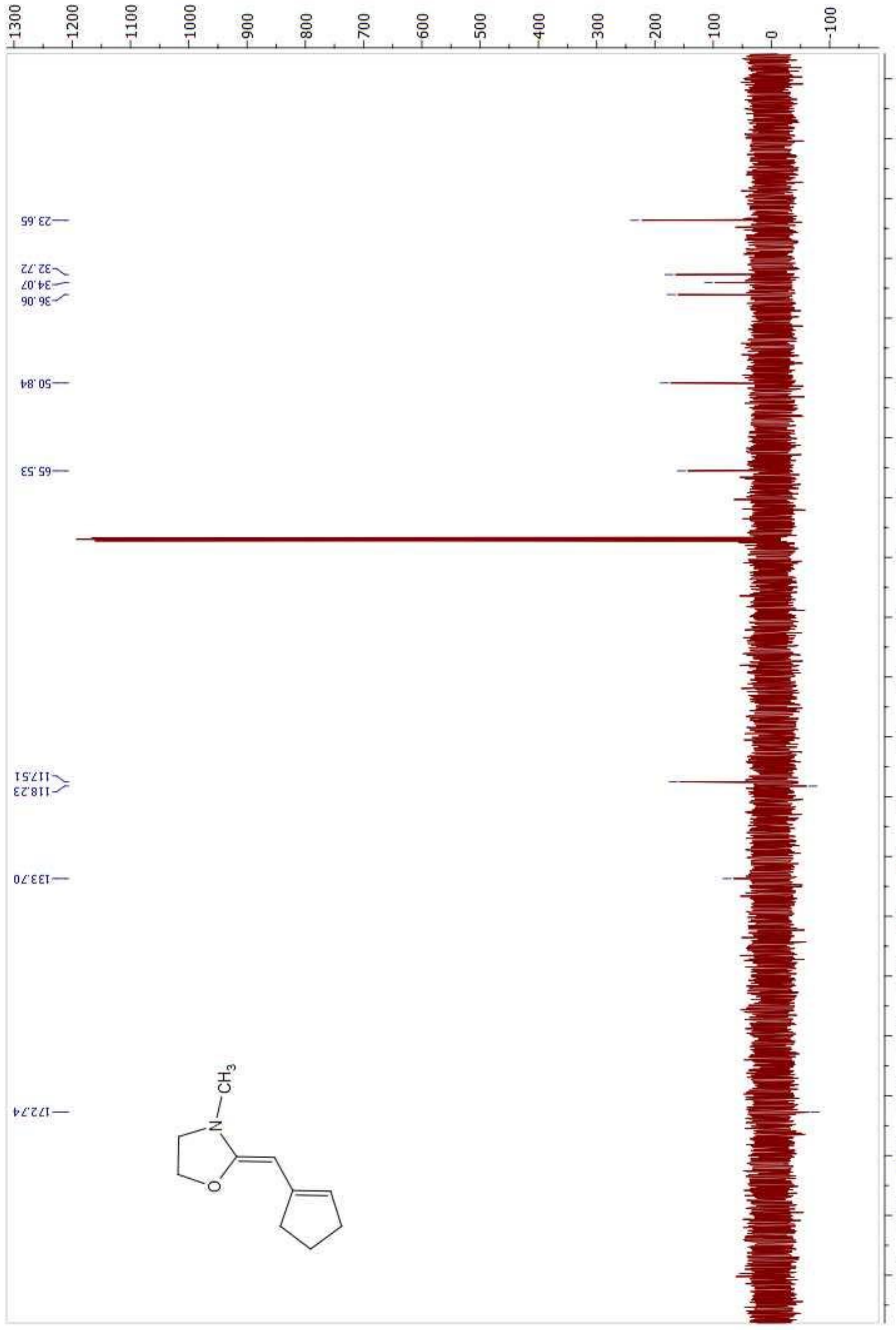


Figure 59. ^{13}C NMR spectrum of **123b** (125 MHz, $CDCl_3$).

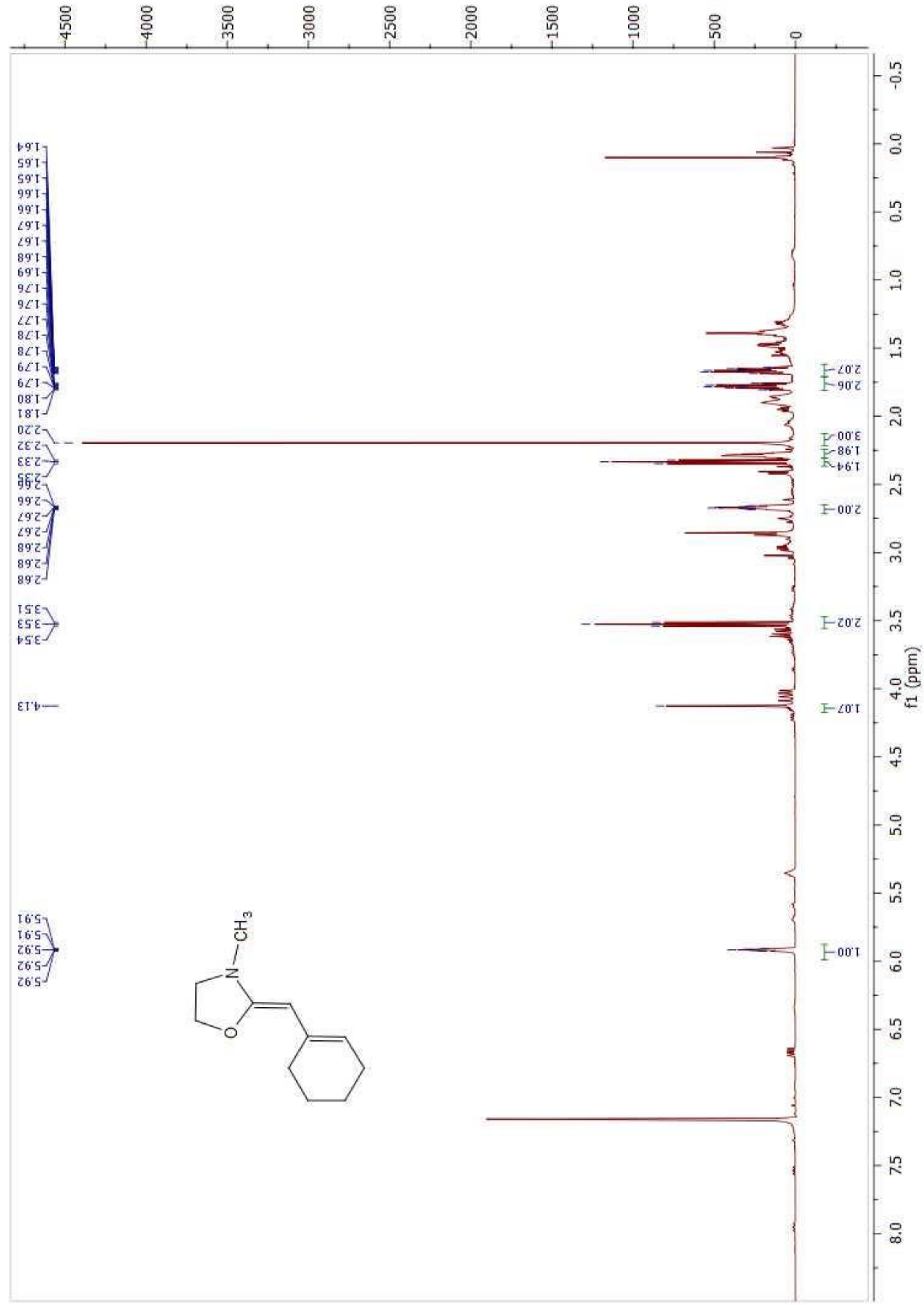


Figure 60. ^{1}H NMR spectrum of **123c** (500 MHz, C_6D_6).

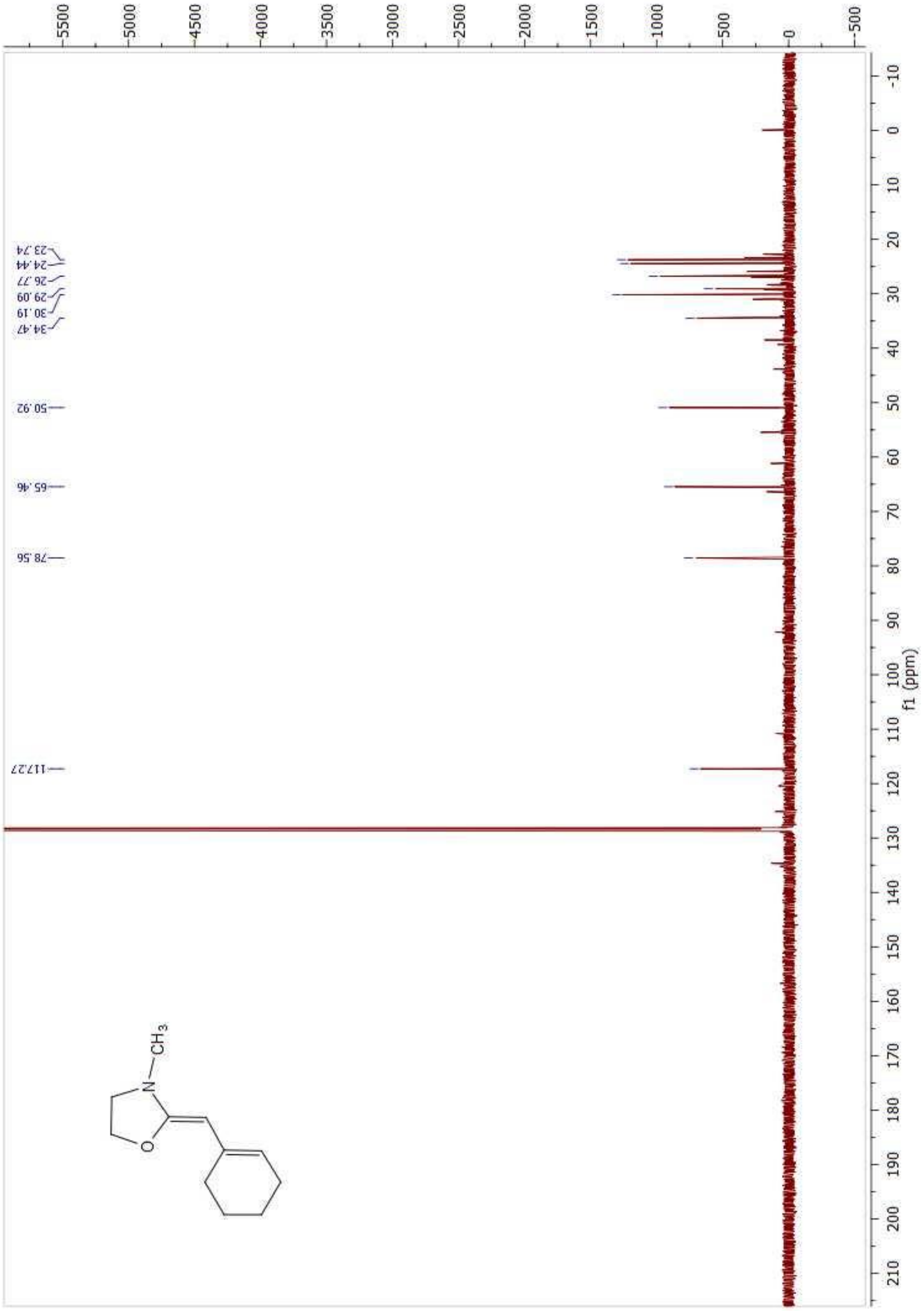


Figure 61. ^{13}C NMR spectrum of **123c** (125 MHz, C_6D_6).

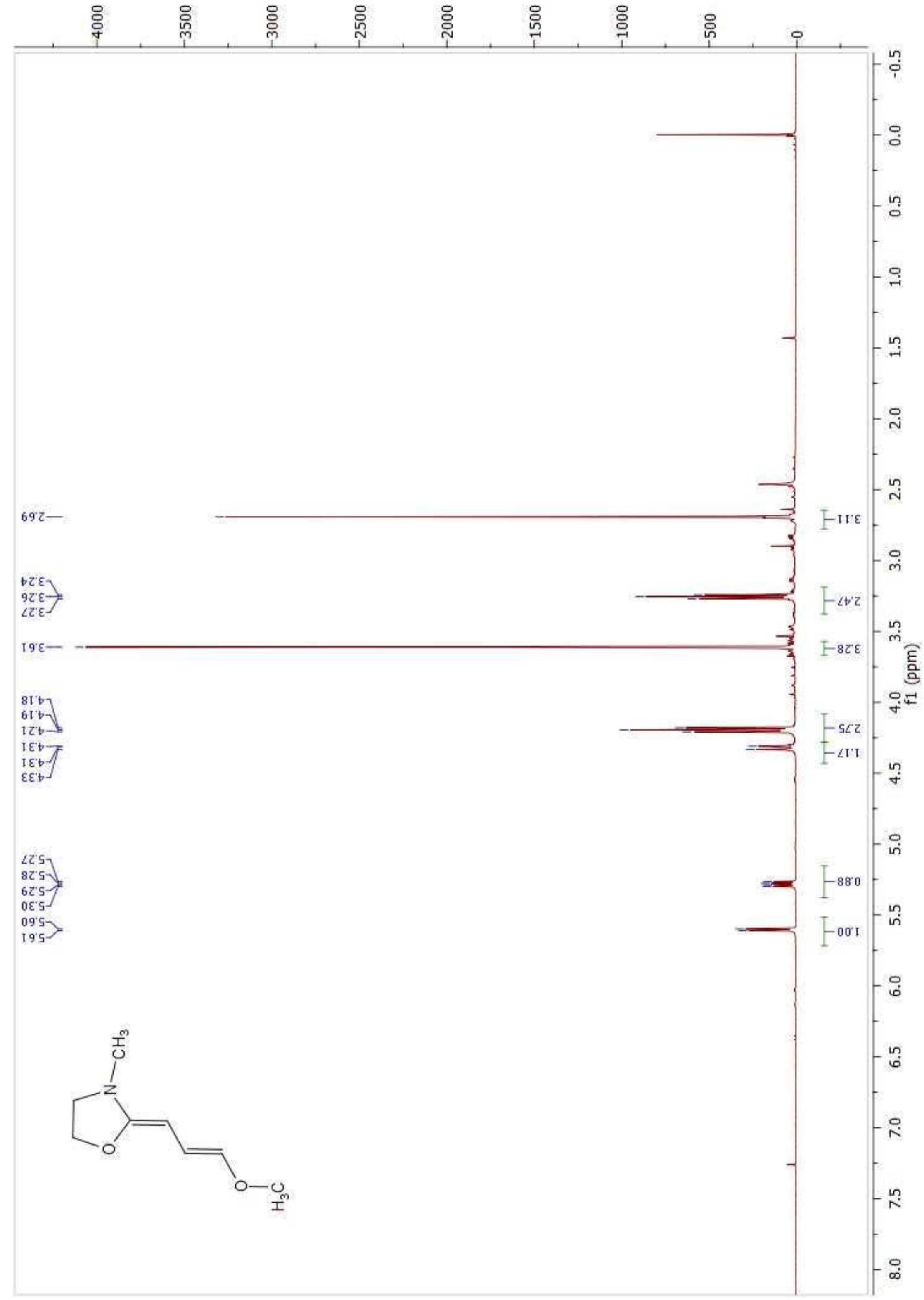


Figure 62. ^{1}H NMR spectrum of **123d** (500 MHz, $CDCl_3$).

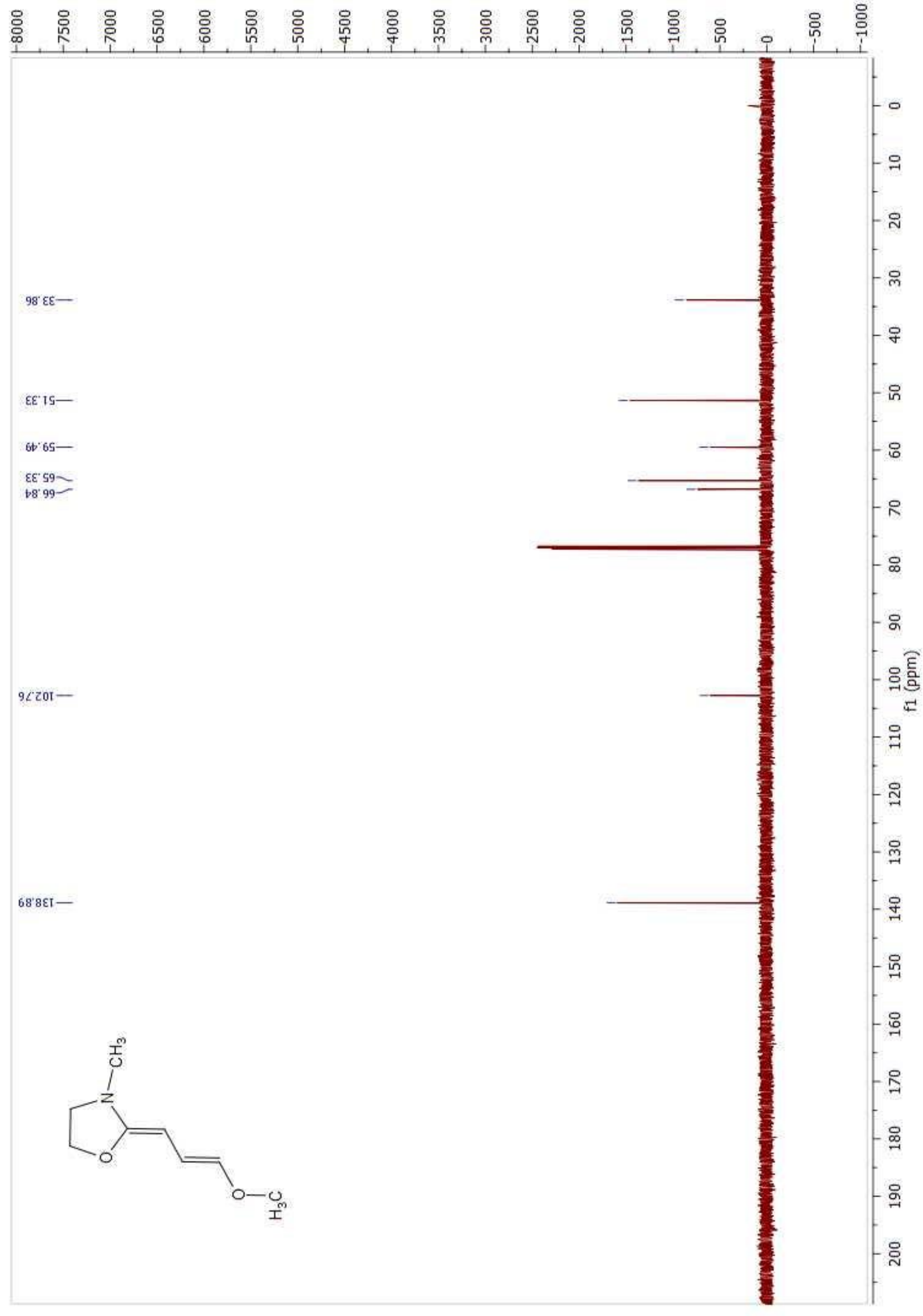


Figure 63. ^{13}C NMR spectrum of **123d** (125 MHz, $CDCl_3$).

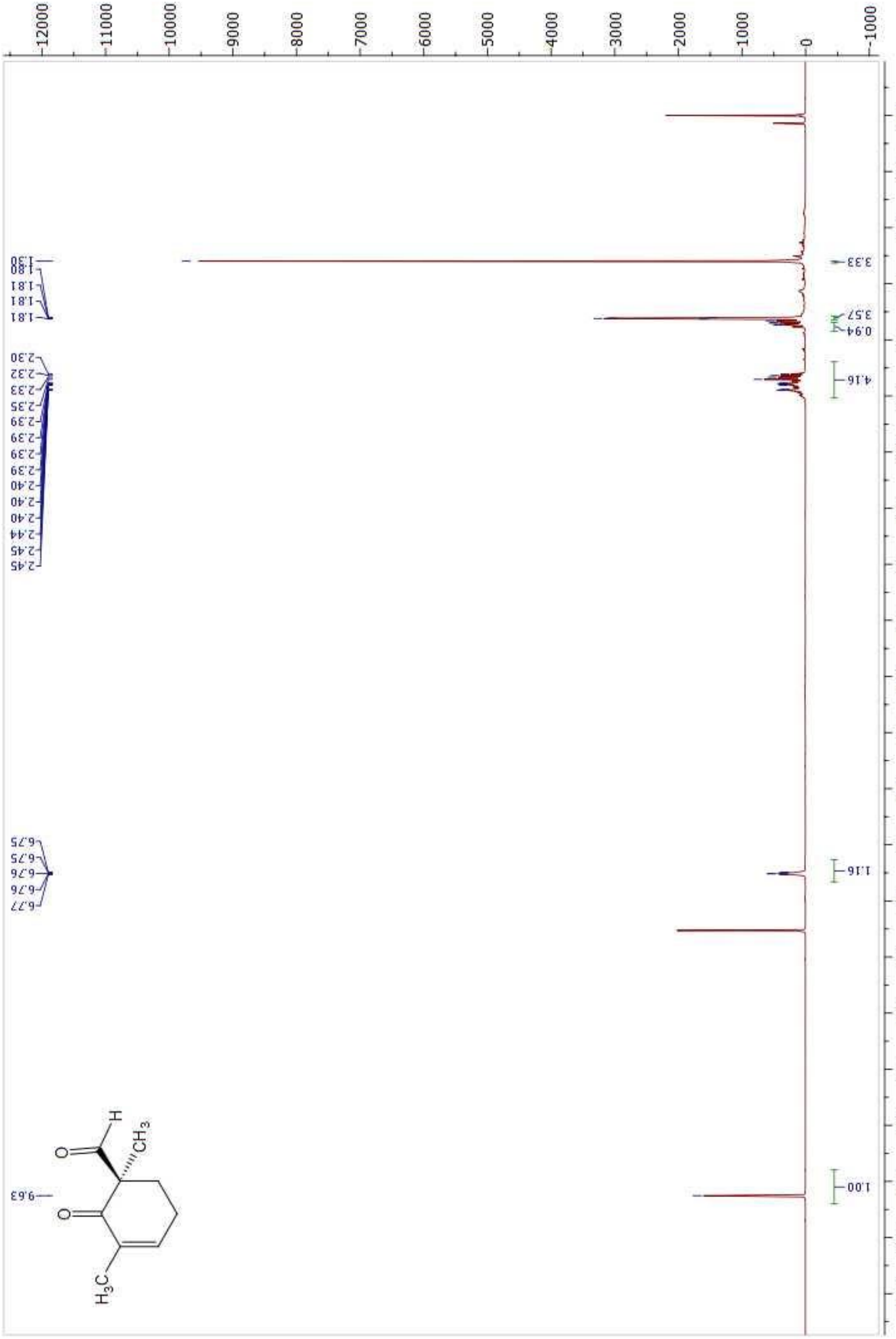


Figure 64. ^{1}H NMR spectrum of **125a** (500 MHz, $CDCl_3$).

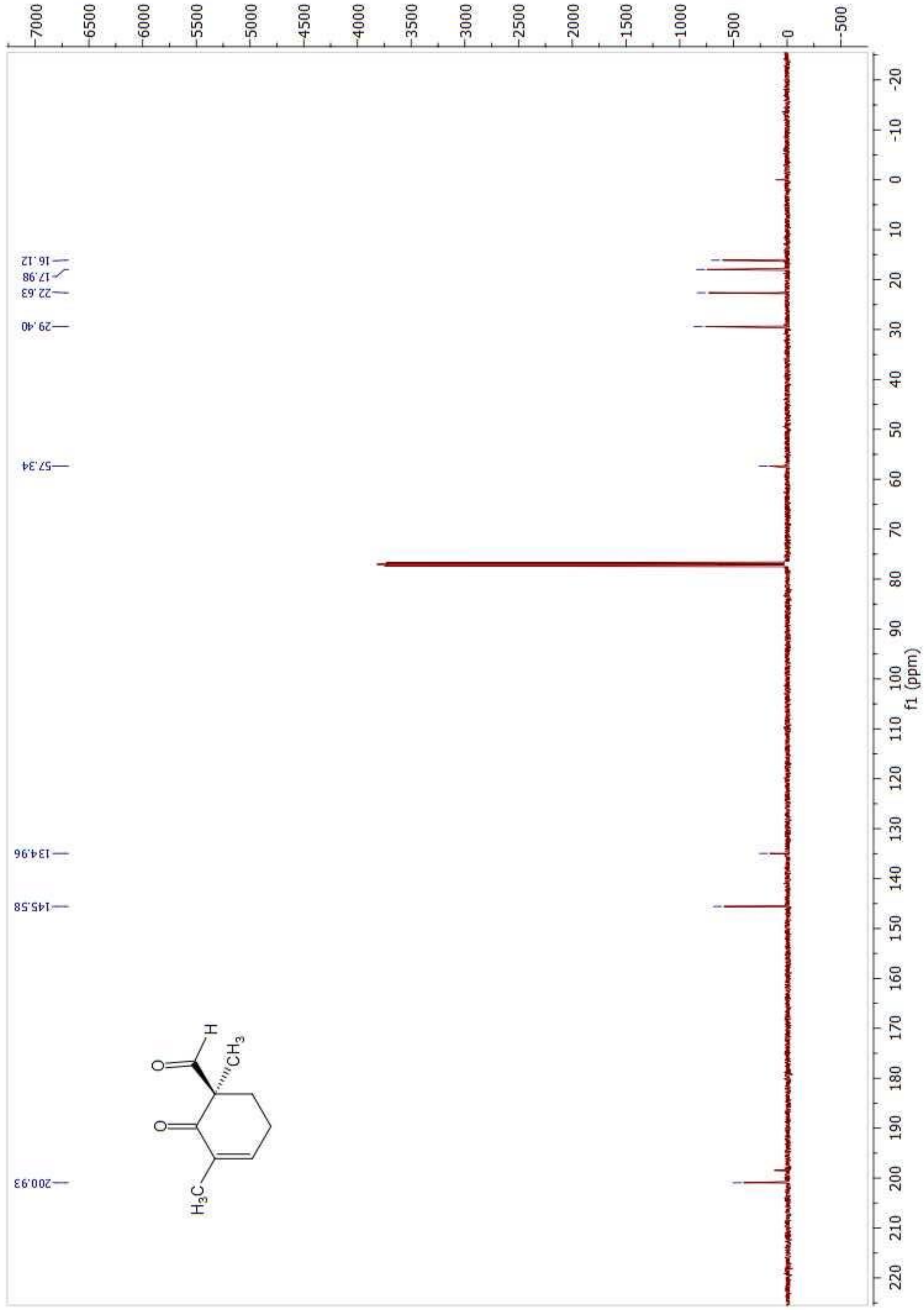


Figure 65. ^{13}C NMR spectrum of **125a** (125 MHz, $CDCl_3$).

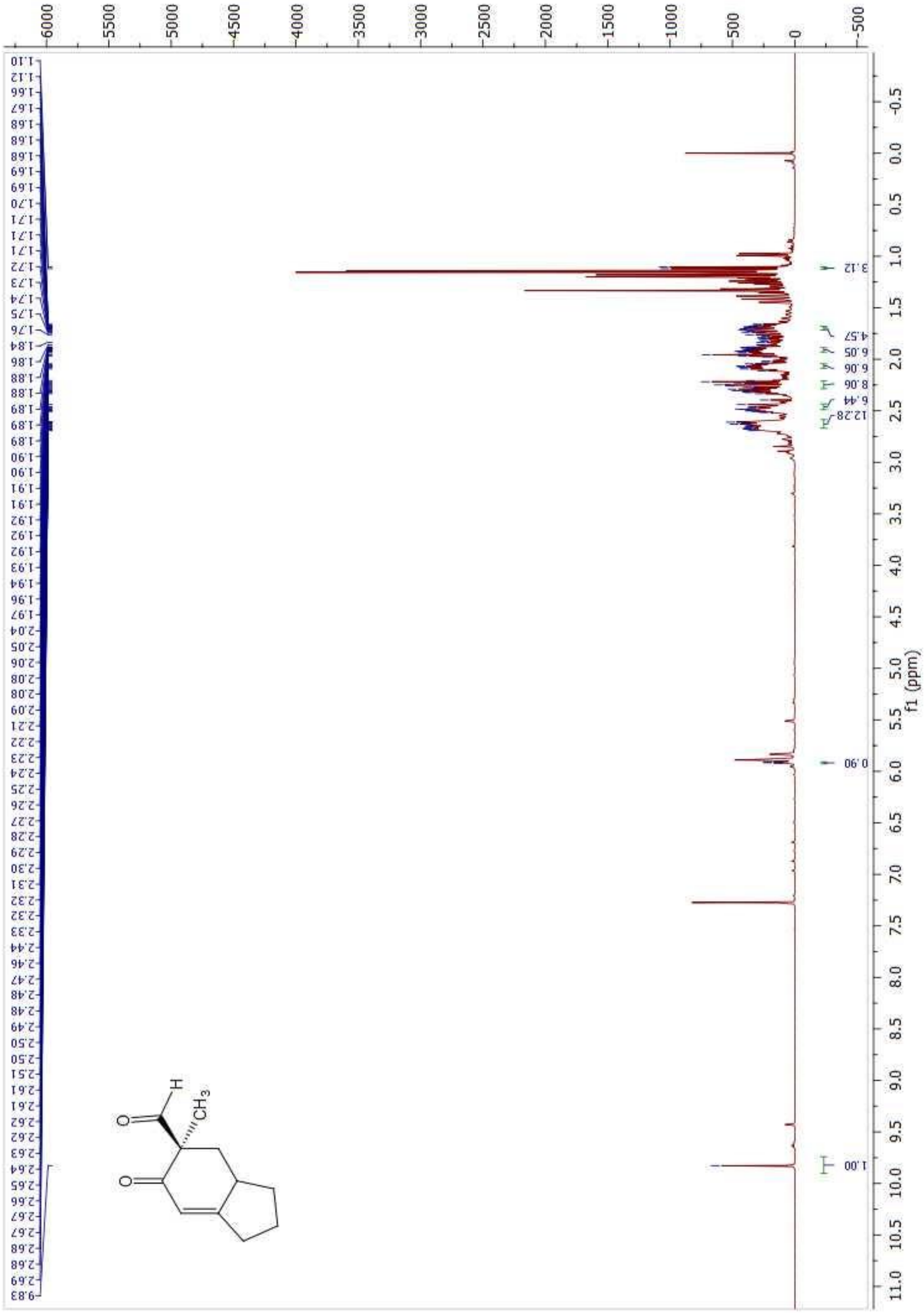


Figure 66. ^{1}H NMR spectrum of **125b** (500 MHz, $CDCl_3$).

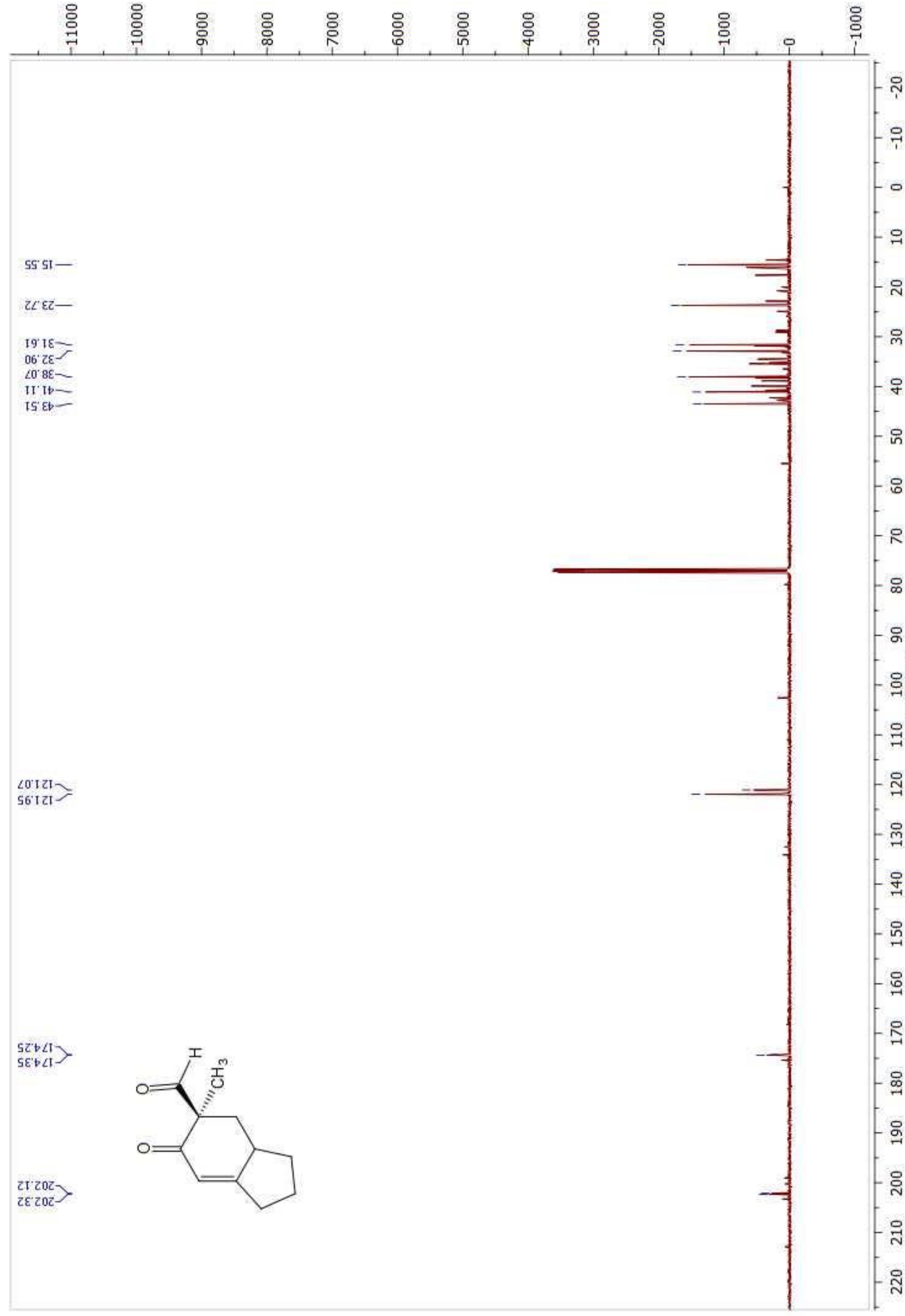


Figure 67. ^{13}C NMR spectrum of **125b** (125 MHz, CDCl$_3$).

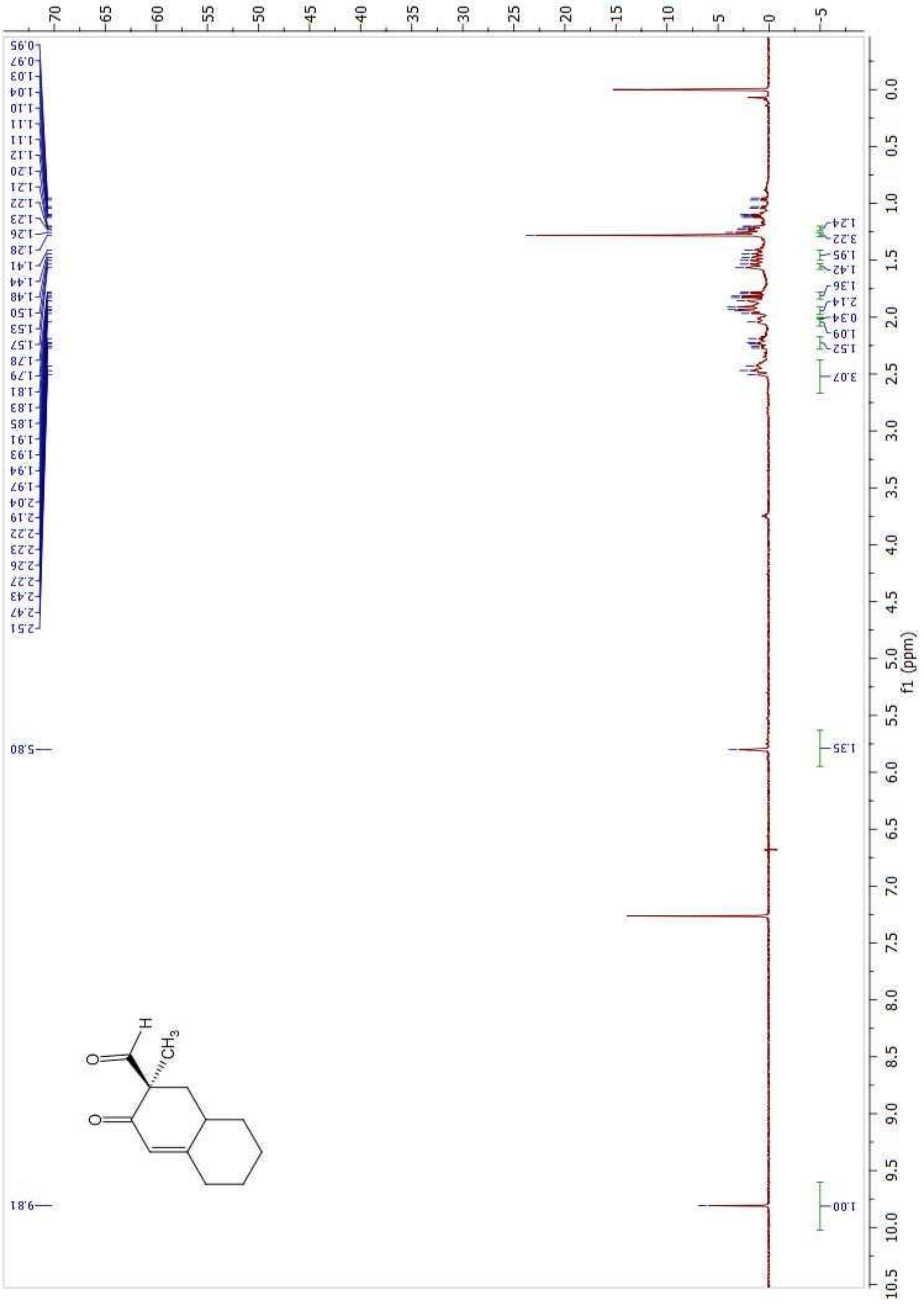


Figure 68. ^{1}H NMR spectrum of **125c** (500 MHz, $CDCl_3$).

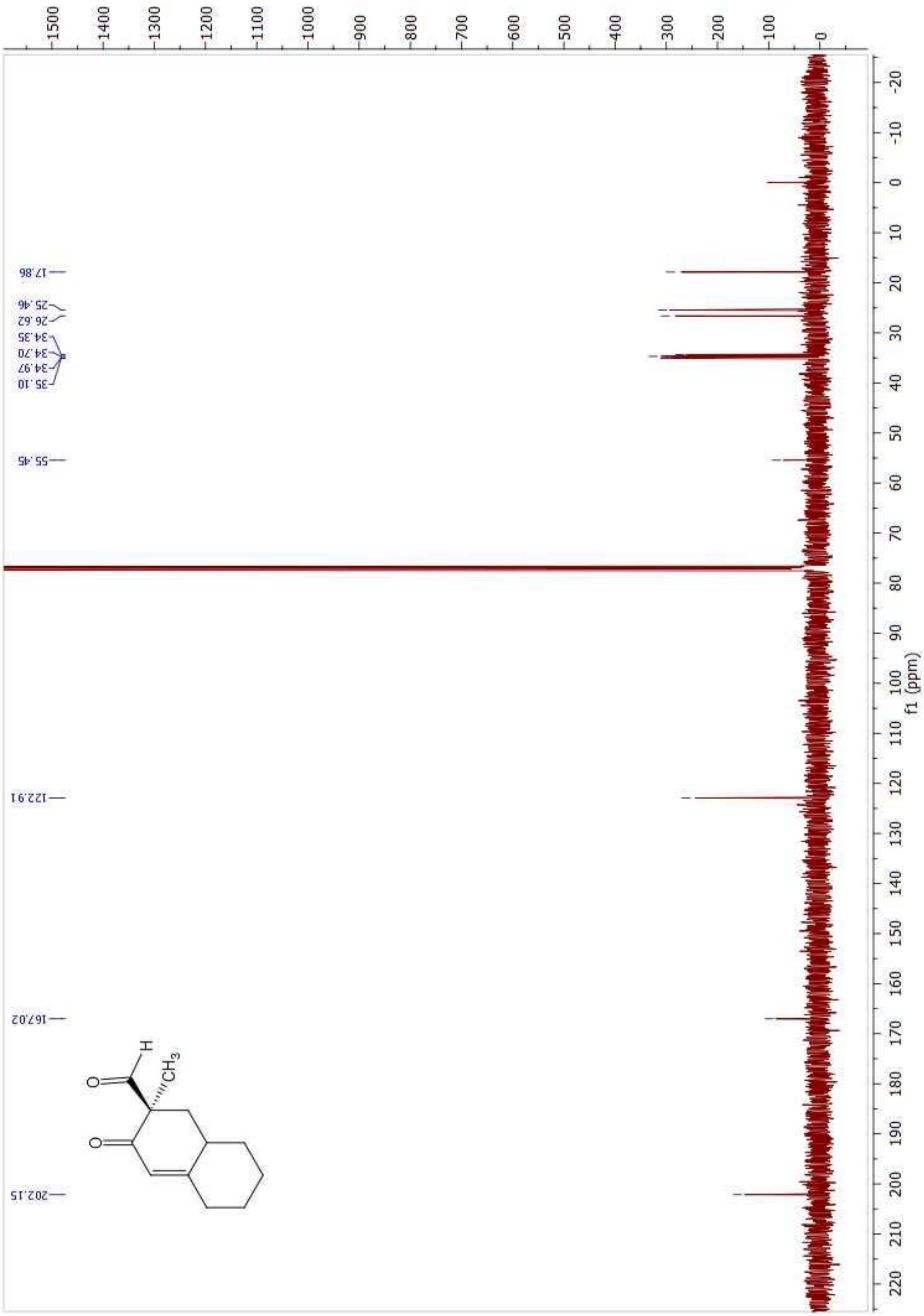


Figure 69. ^{13}C NMR spectrum of **125c** (125 MHz, $CDCl_3$).

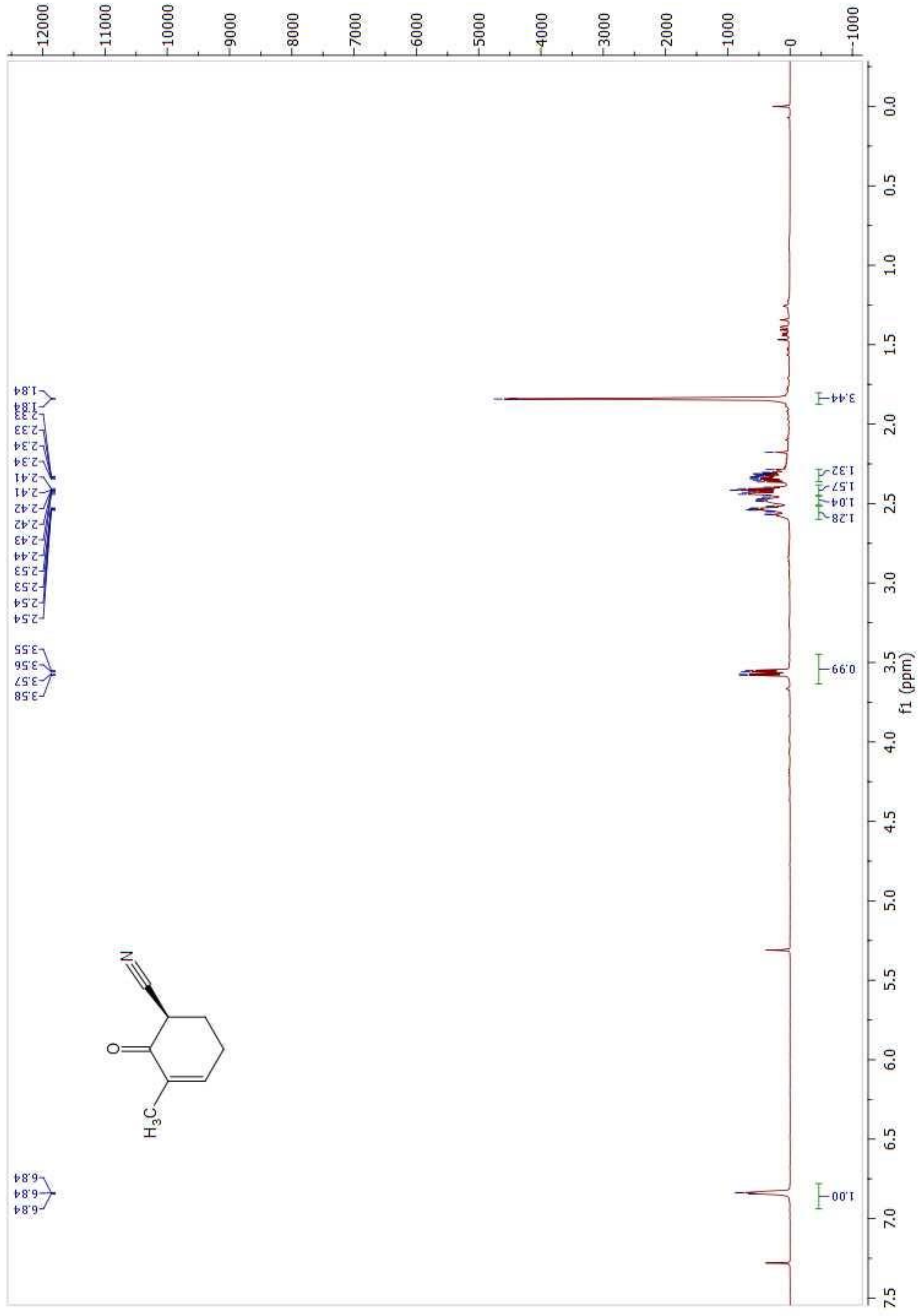


Figure 70. ^{1}H NMR spectrum of **126a** (500 MHz, $CDCl_3$).

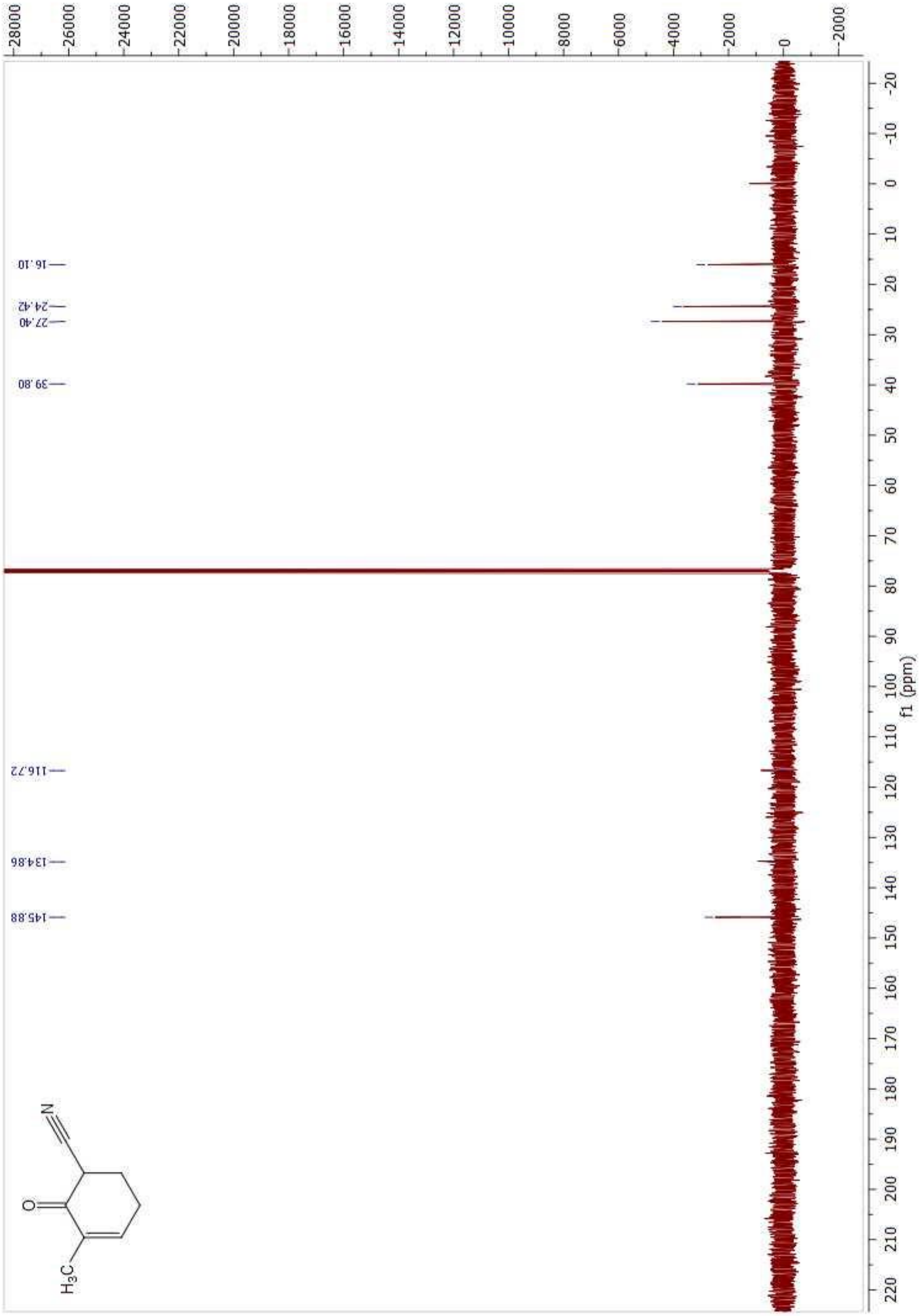


Figure 71. ^{13}C NMR spectrum of **126a** (125 MHz, $CDCl_3$).

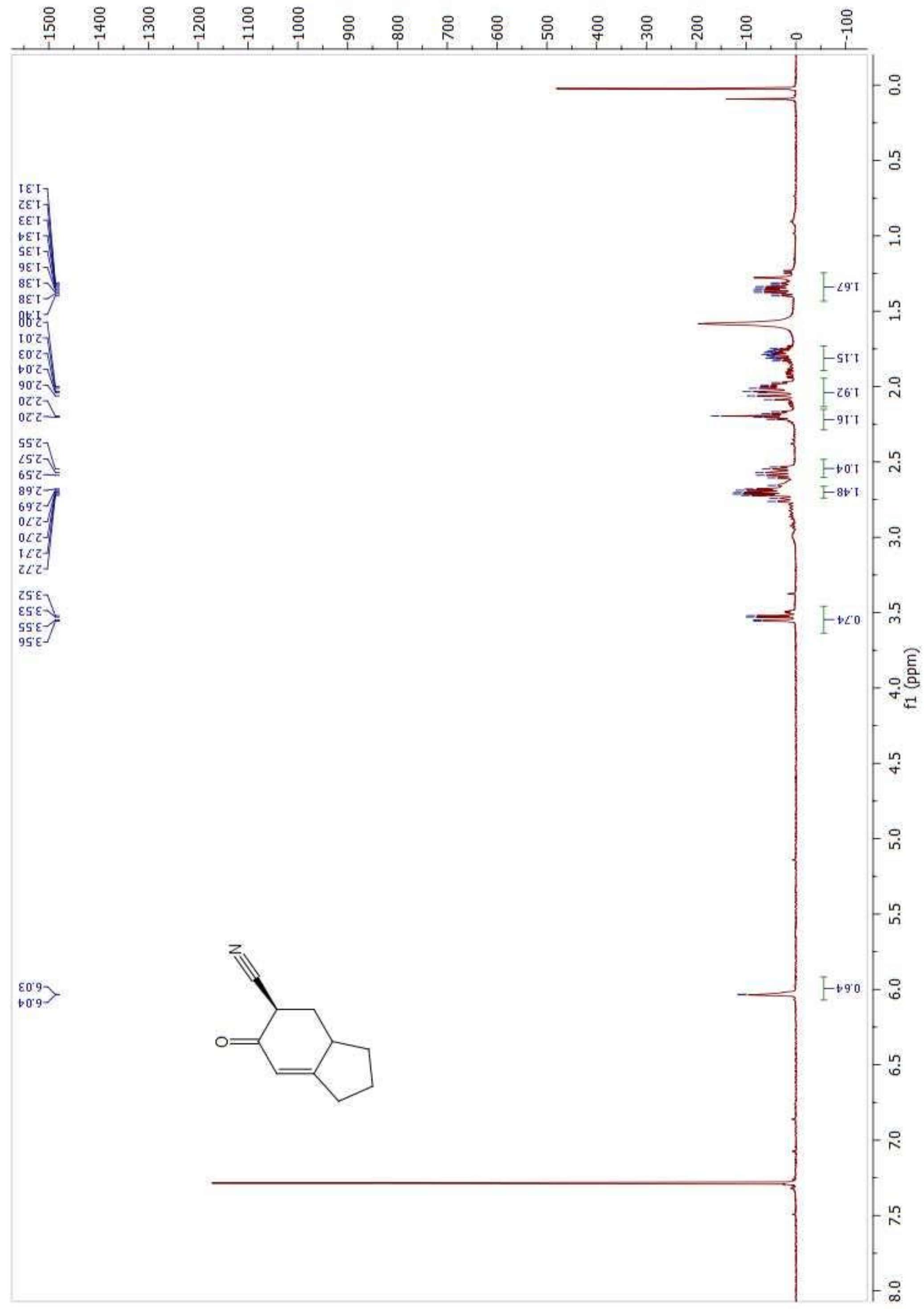


Figure 72. ^{1}H NMR spectrum of **126b** (500 MHz, $CDCl_3$).

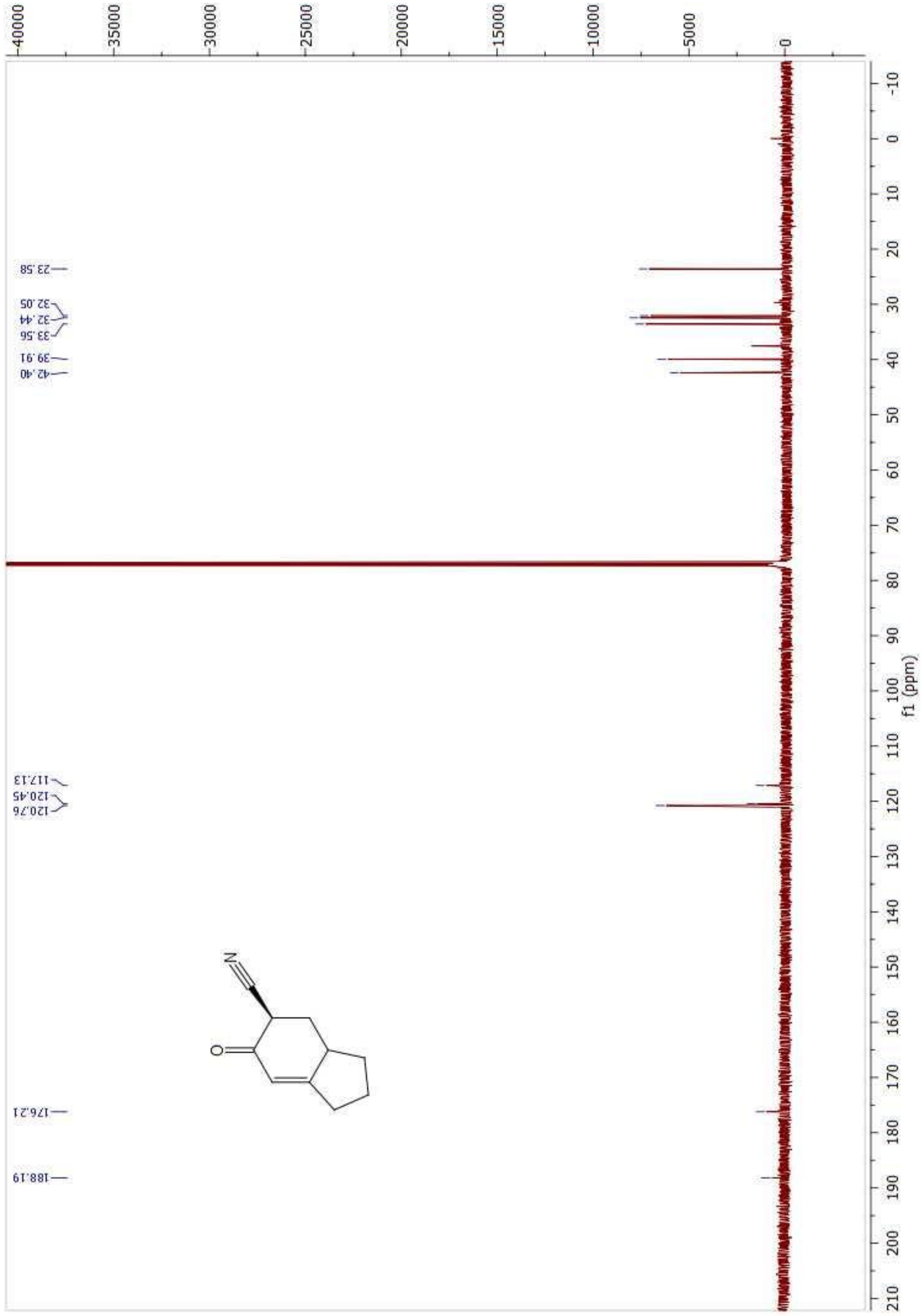


Figure 73. ^{13}C NMR spectrum of **126b** (125 MHz, $CDCl_3$).

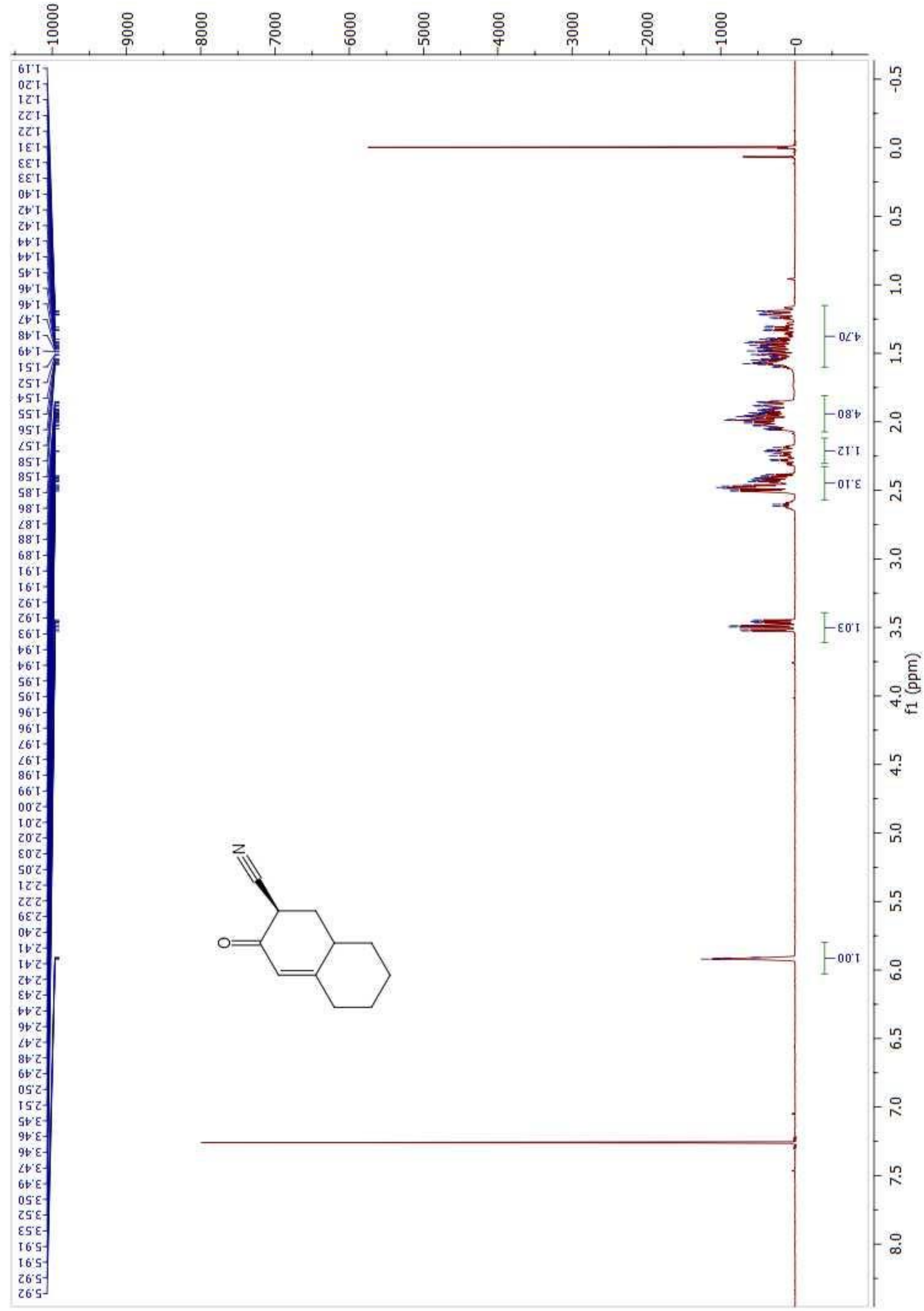


Figure 74. ^{1}H NMR spectrum of **126c** (500 MHz, $CDCl_3$).

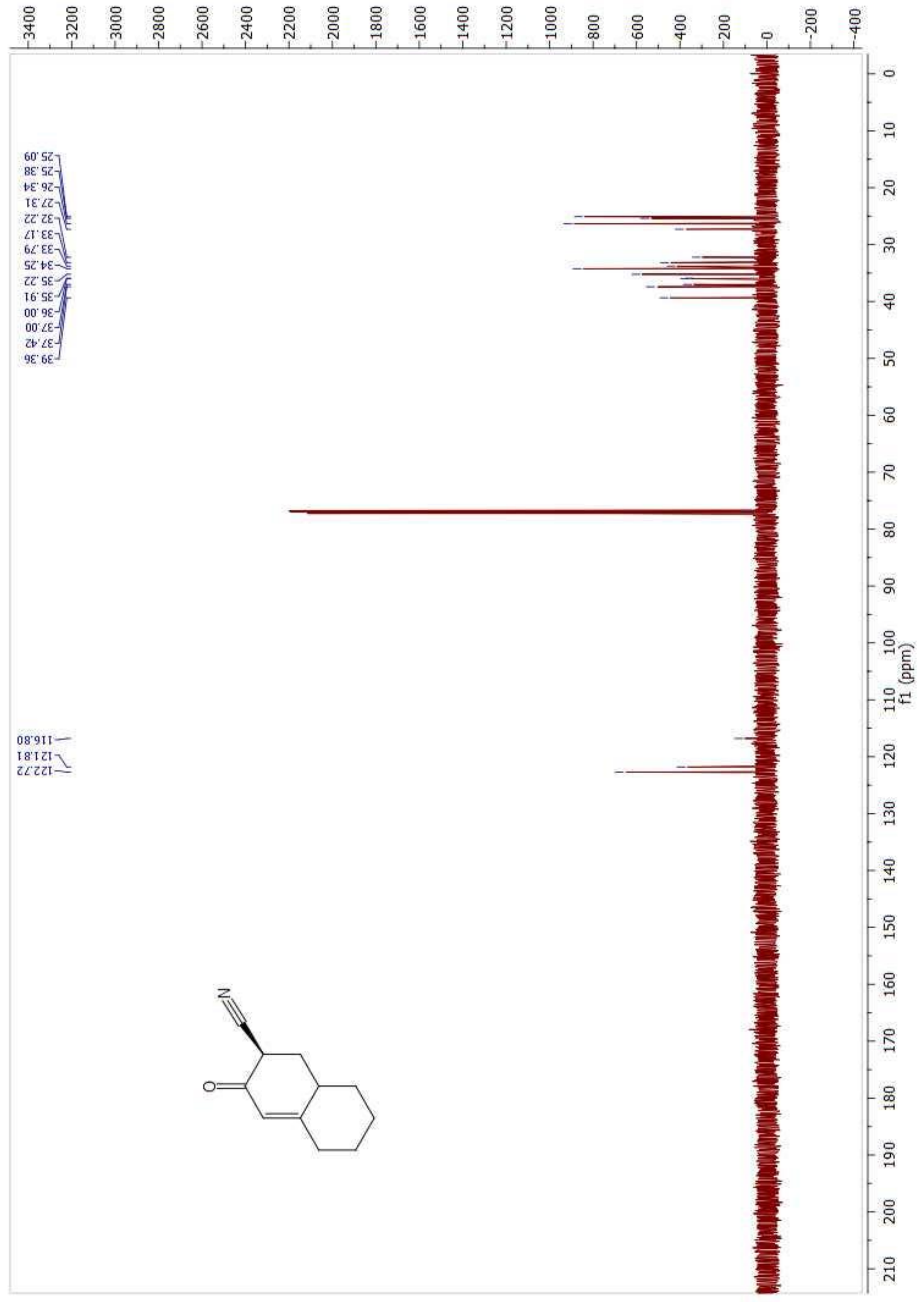


Figure 75. ^{13}C NMR spectrum of **126c** (125 MHz, CDCl$_3$).

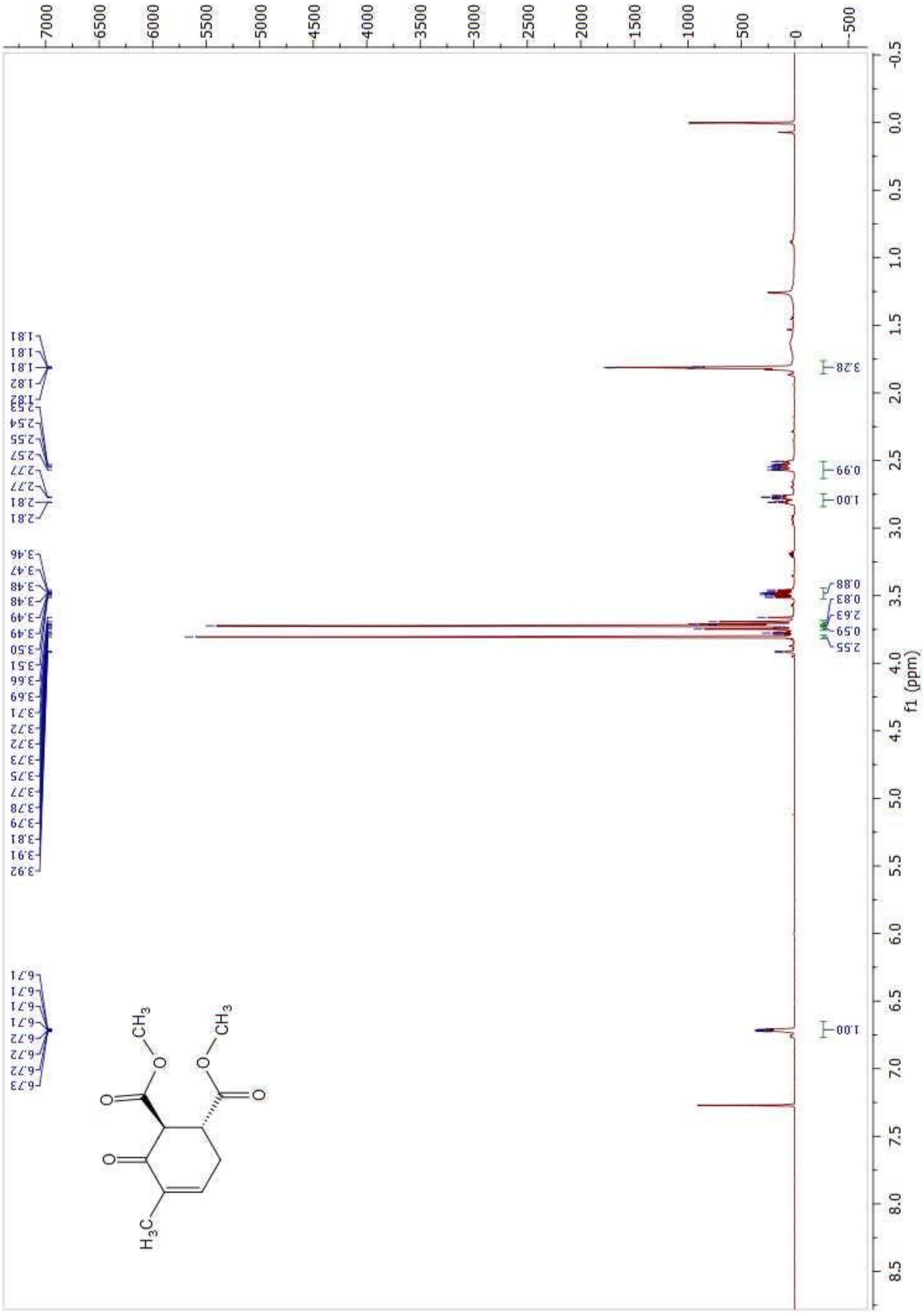


Figure 76. ^{1}H NMR spectrum of **127a** (500 MHz, $CDCl_3$).

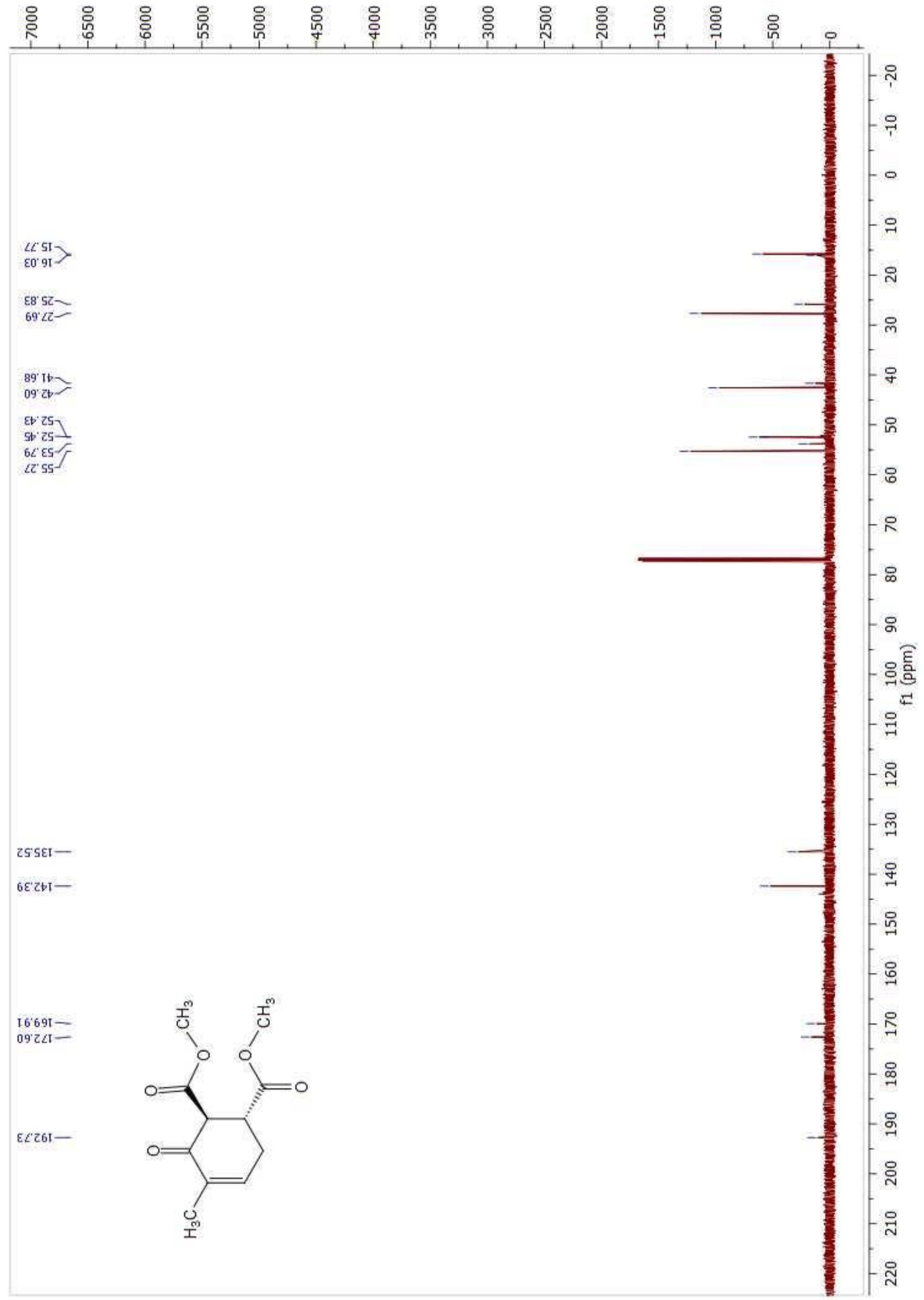


Figure 77. ^{13}C NMR spectrum of **127a** (125 MHz, $CDCl_3$).

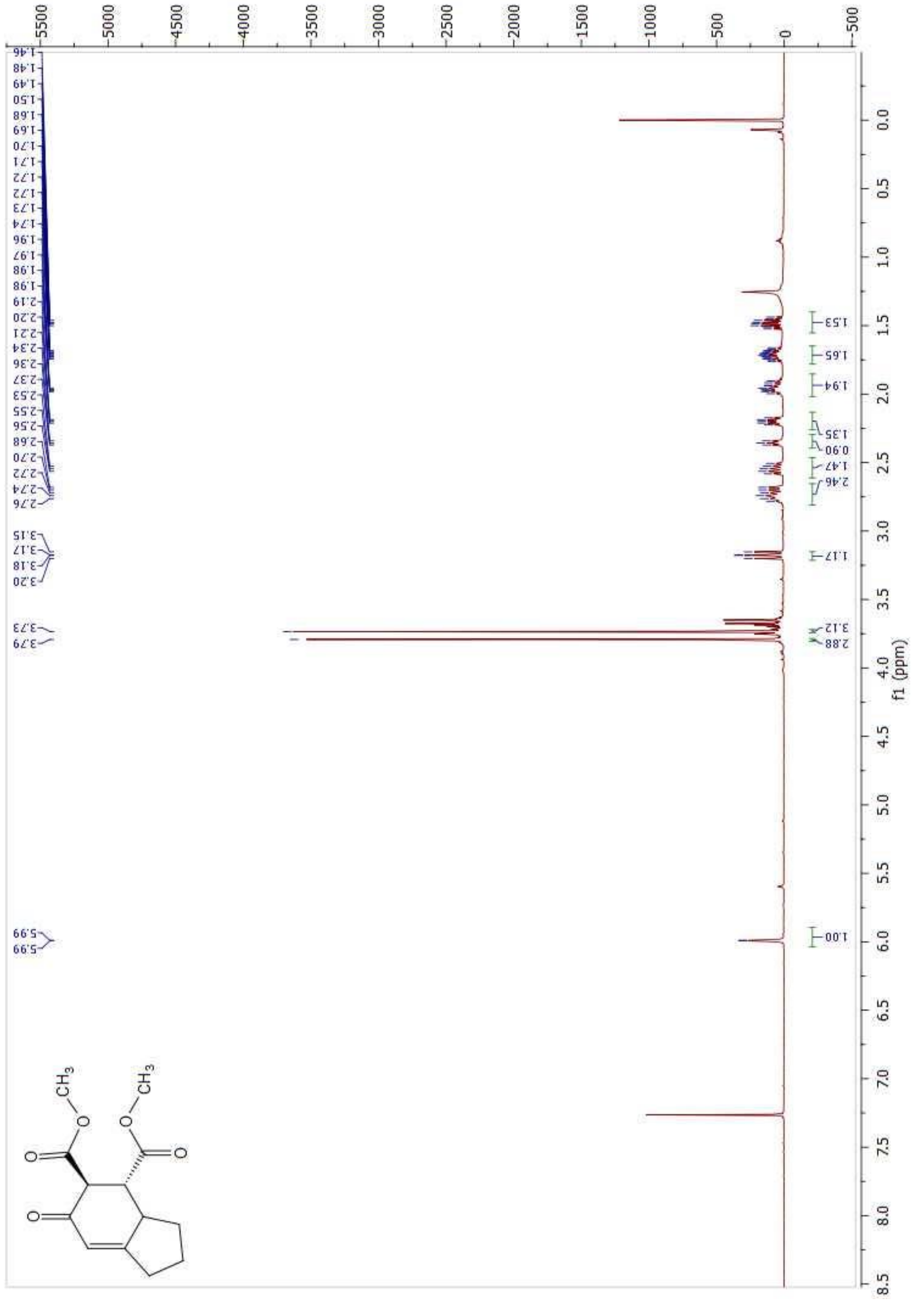


Figure 78. ^{1}H NMR spectrum of **127b** (500 MHz, CDCl$_3$).

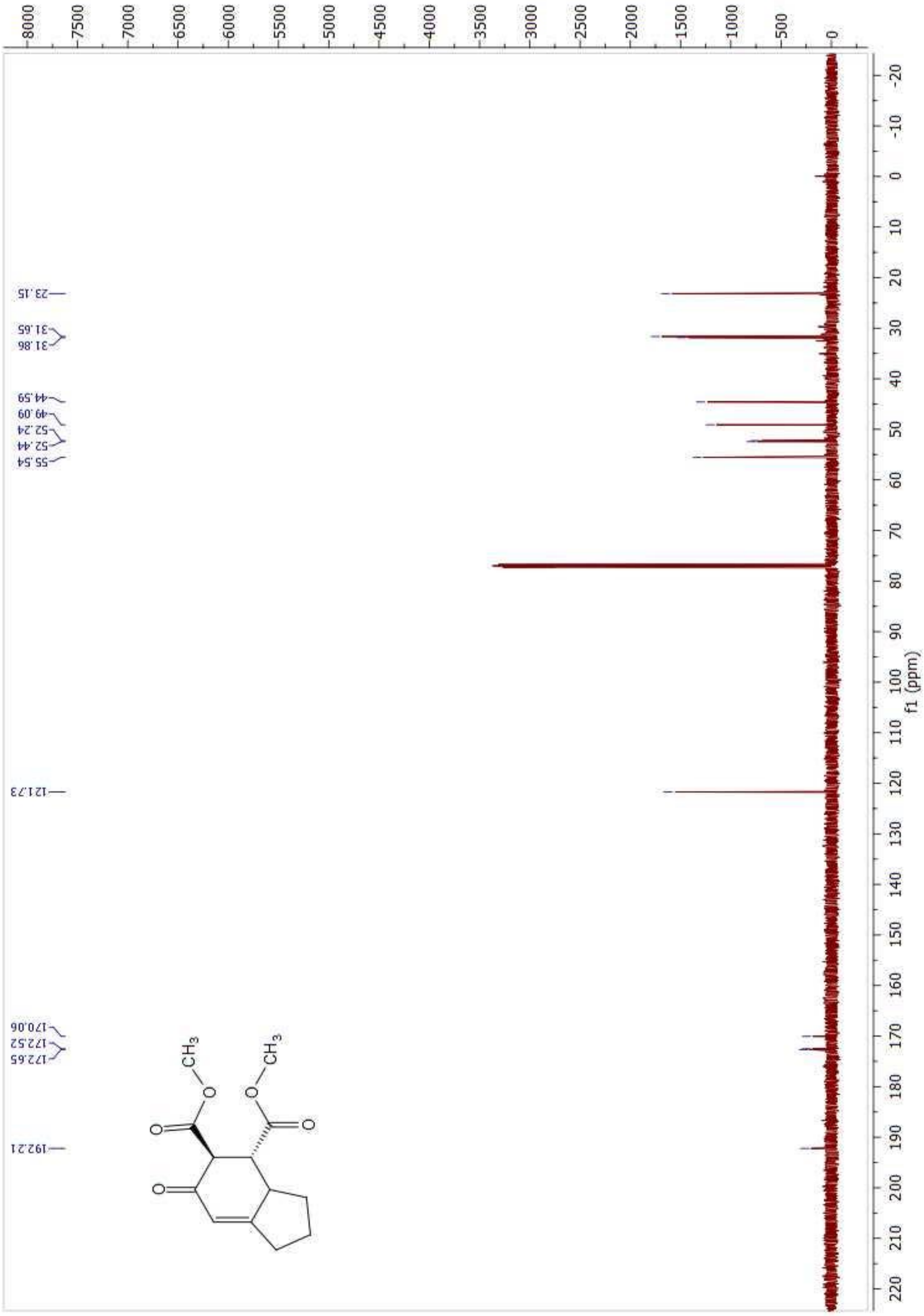


Figure 79. ^{13}C NMR spectrum of **127b** (125 MHz, $CDCl_3$).

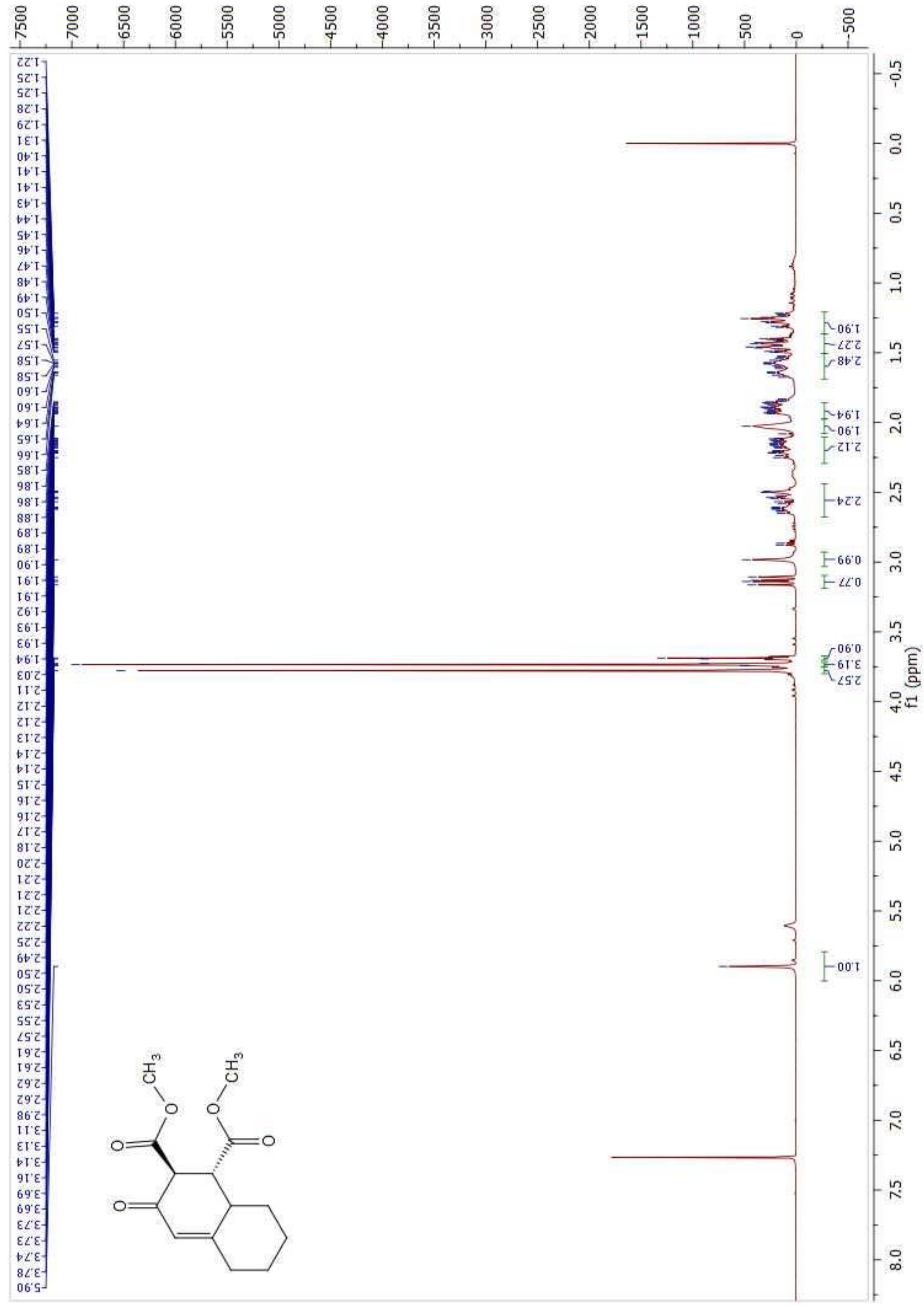


Figure 80. ^{1}H NMR spectrum of **127c** (500 MHz, $CDCl_3$).

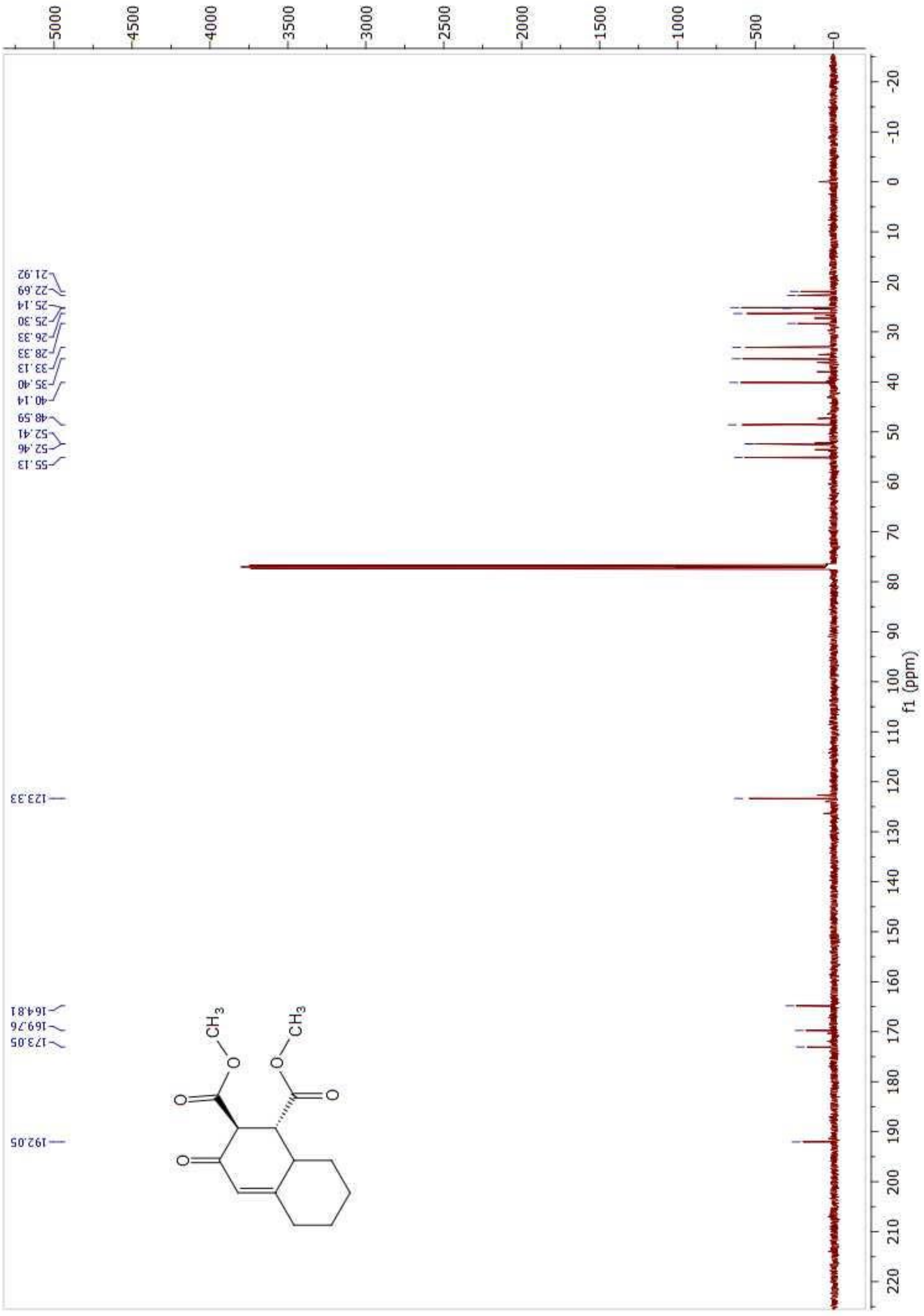


Figure 81. ^{13}C NMR spectrum of **127c** (125 MHz, $CDCl_3$).

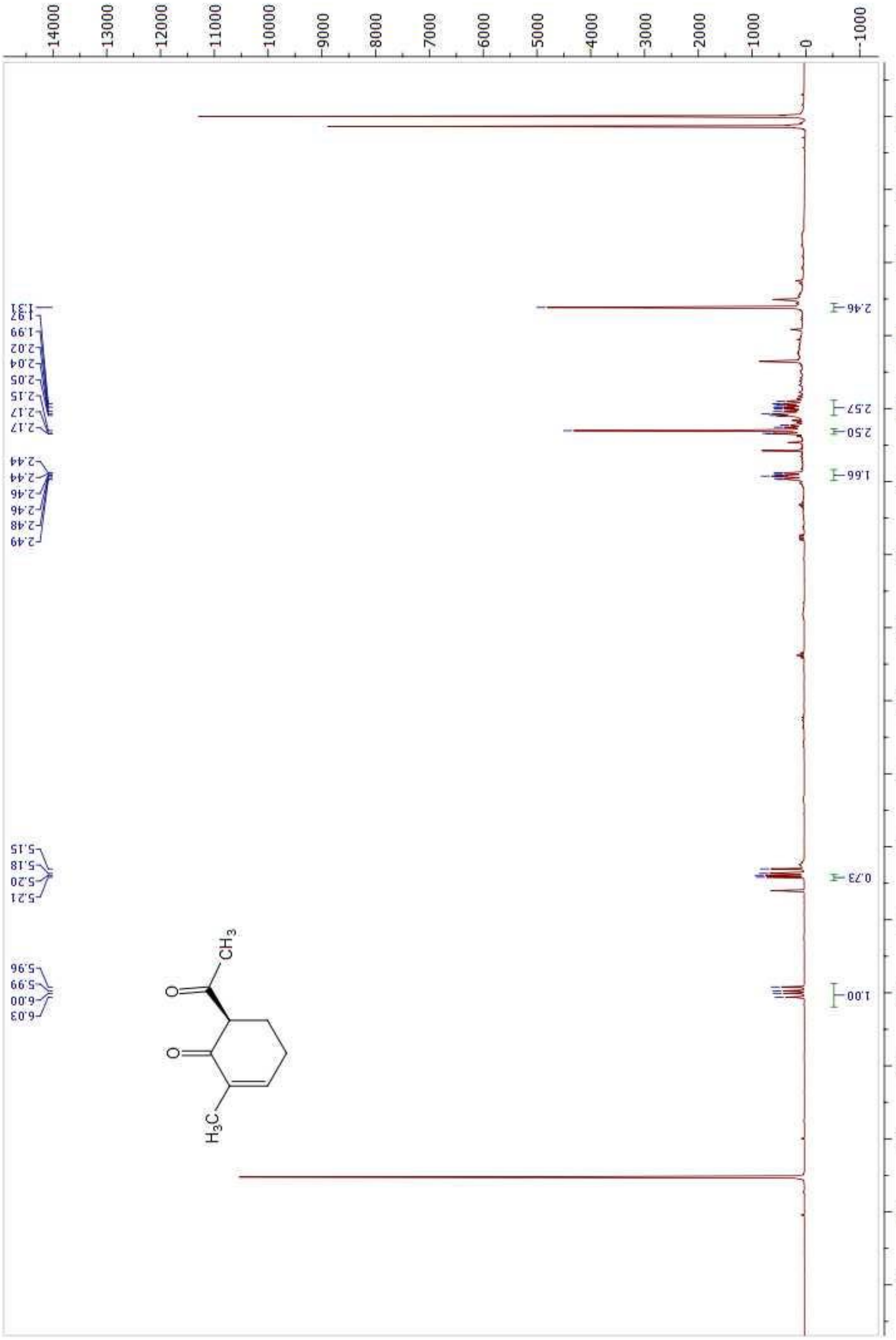


Figure 82. ^{1}H NMR spectrum of **128a** (500 MHz, $CDCl_3$).

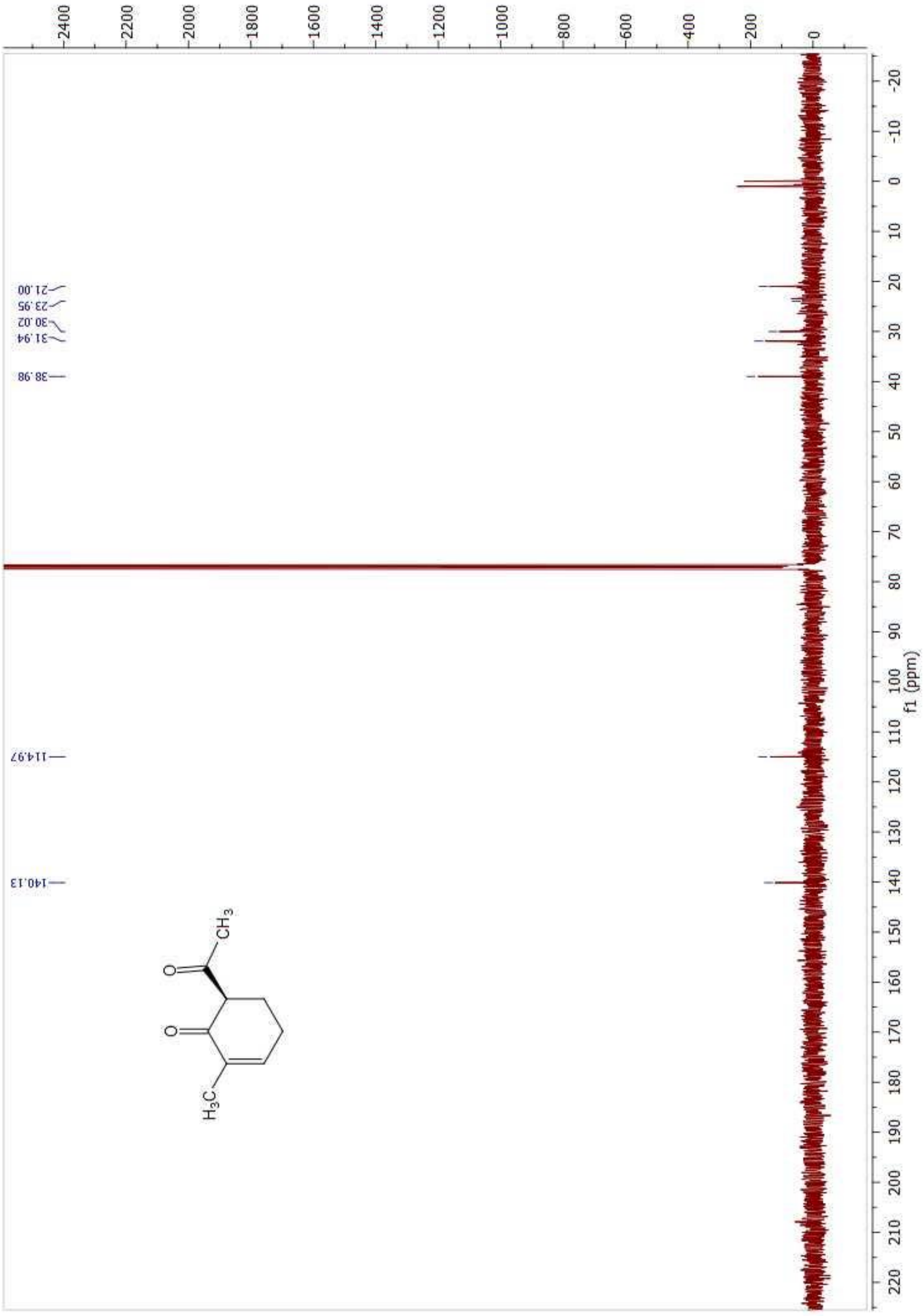


Figure 83. ^{13}C NMR spectrum of **128a** (125 MHz, $CDCl_3$).

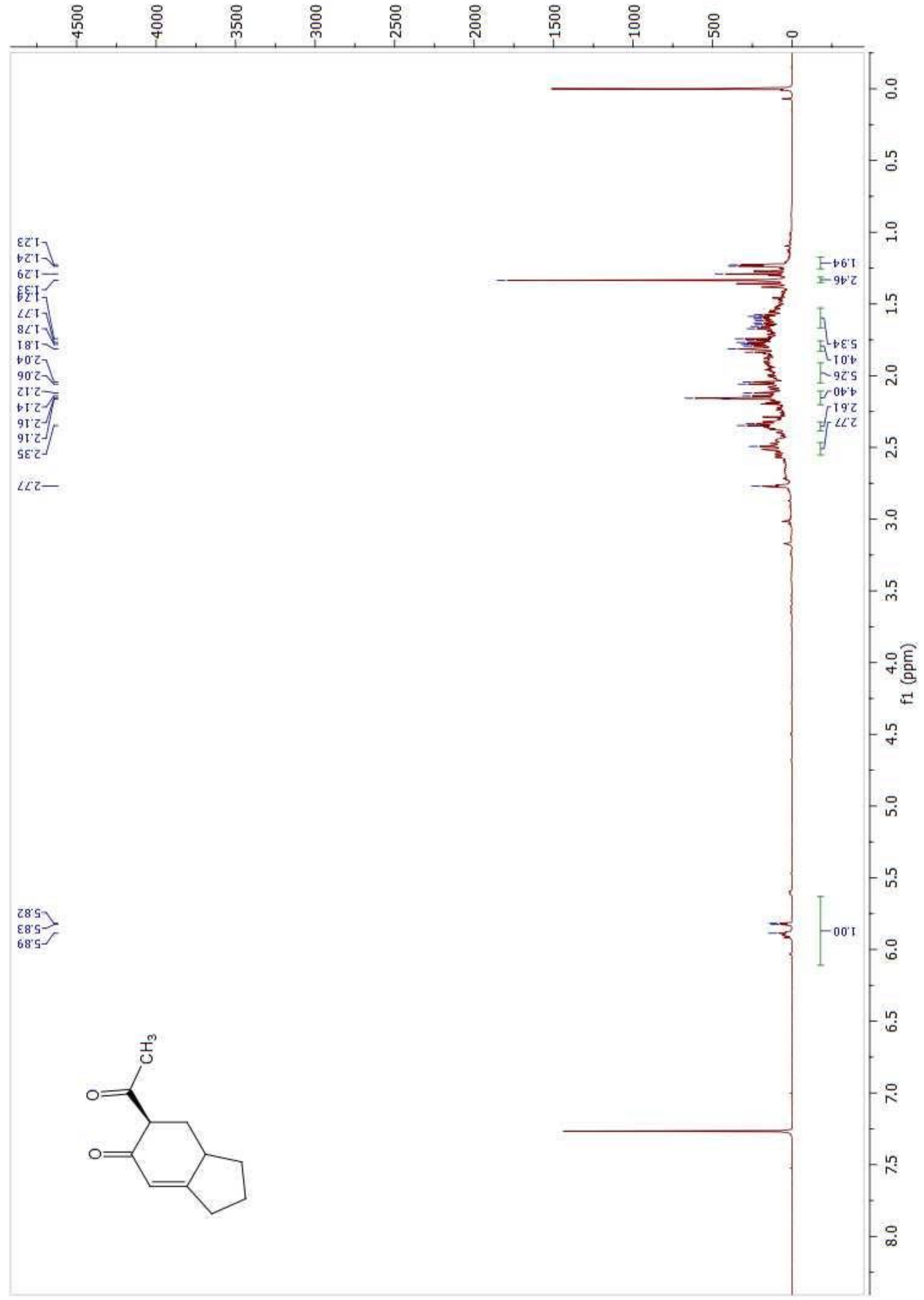


Figure 84. ^{1}H NMR spectrum of **128b** (500 MHz, $CDCl_3$).

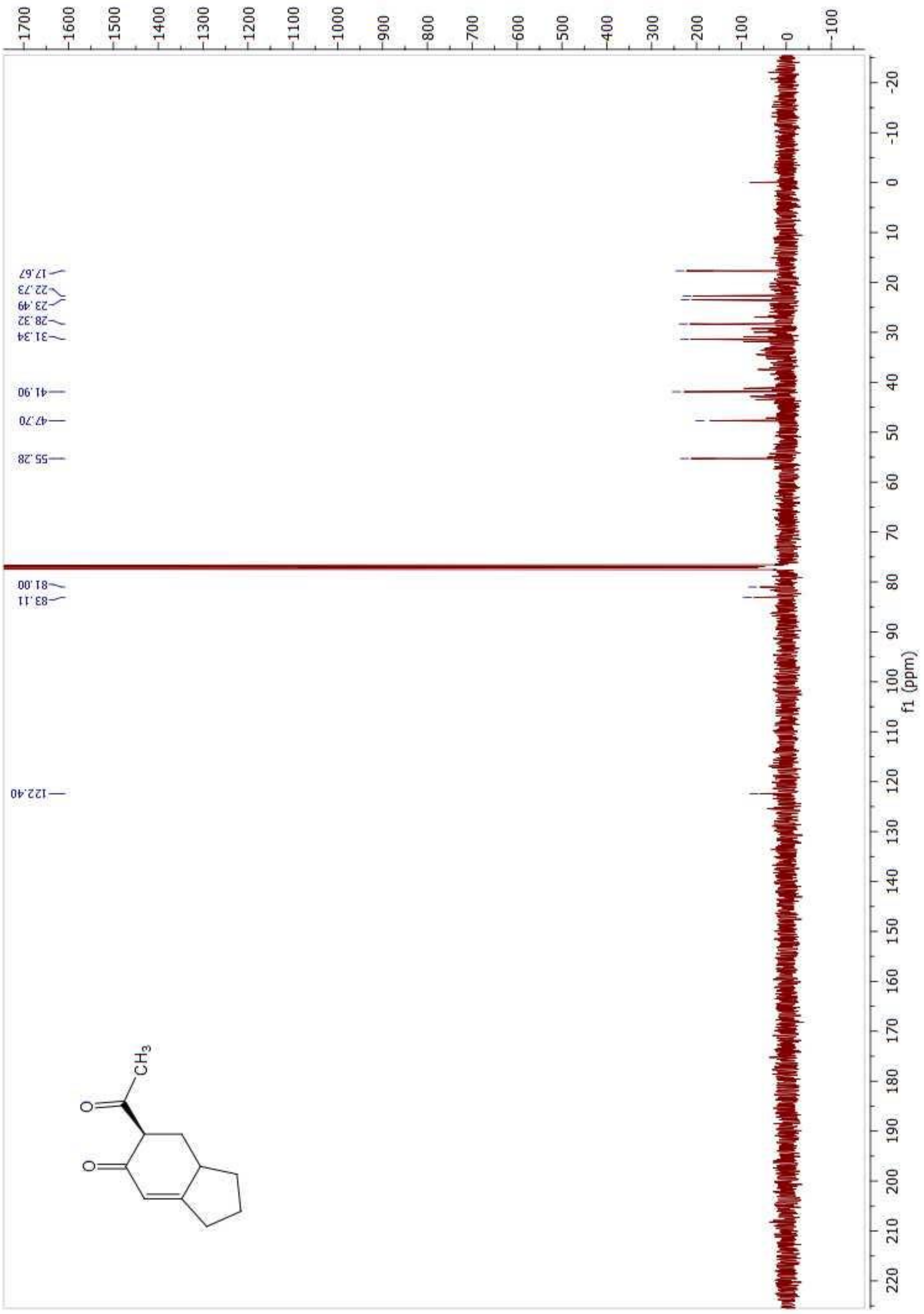


Figure 85. ^{13}C NMR spectrum of **128b** (125 MHz, CDCl$_3$).

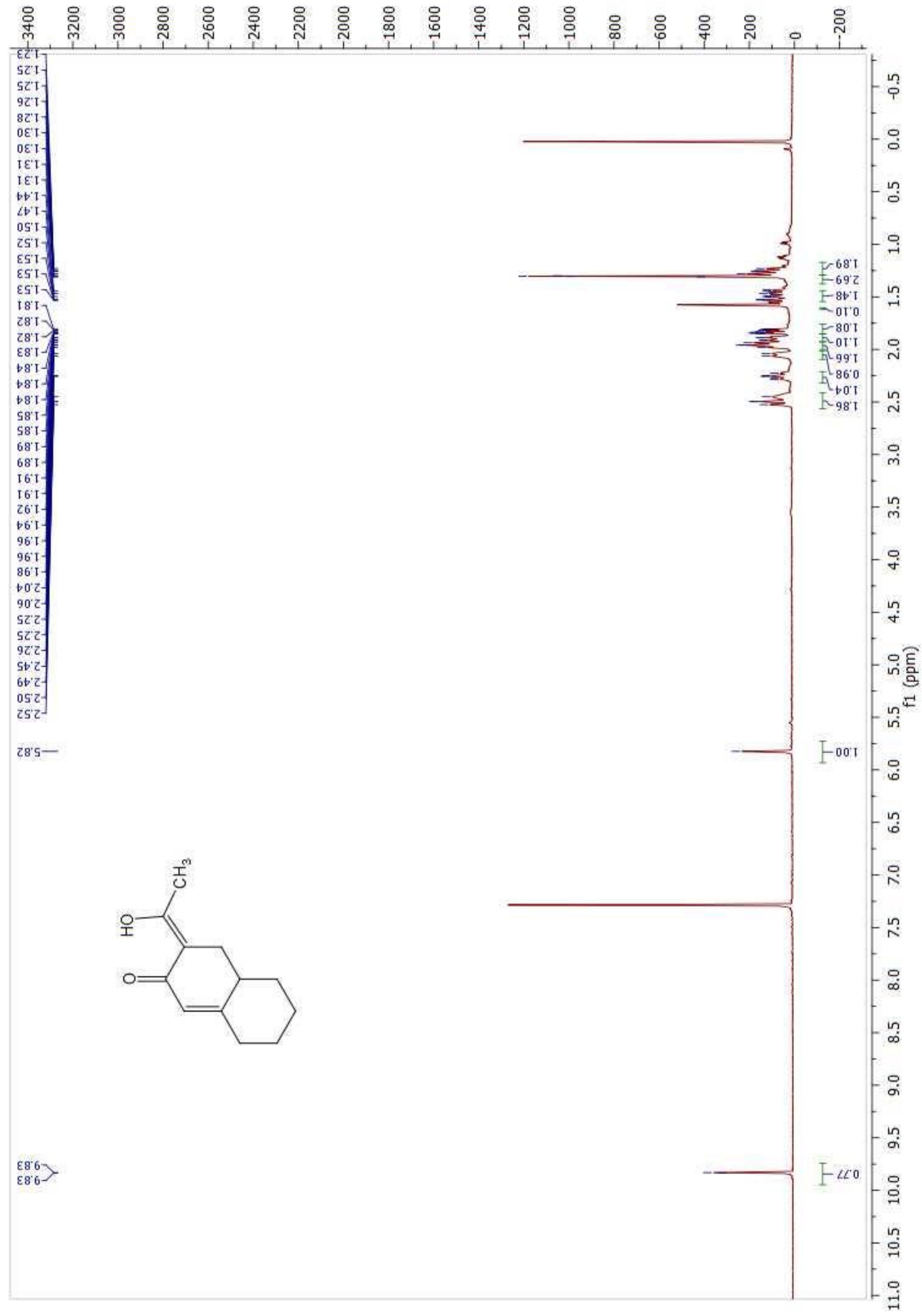


Figure 86. ^{1}H NMR spectrum of **128c** (500 MHz, $CDCl_3$).

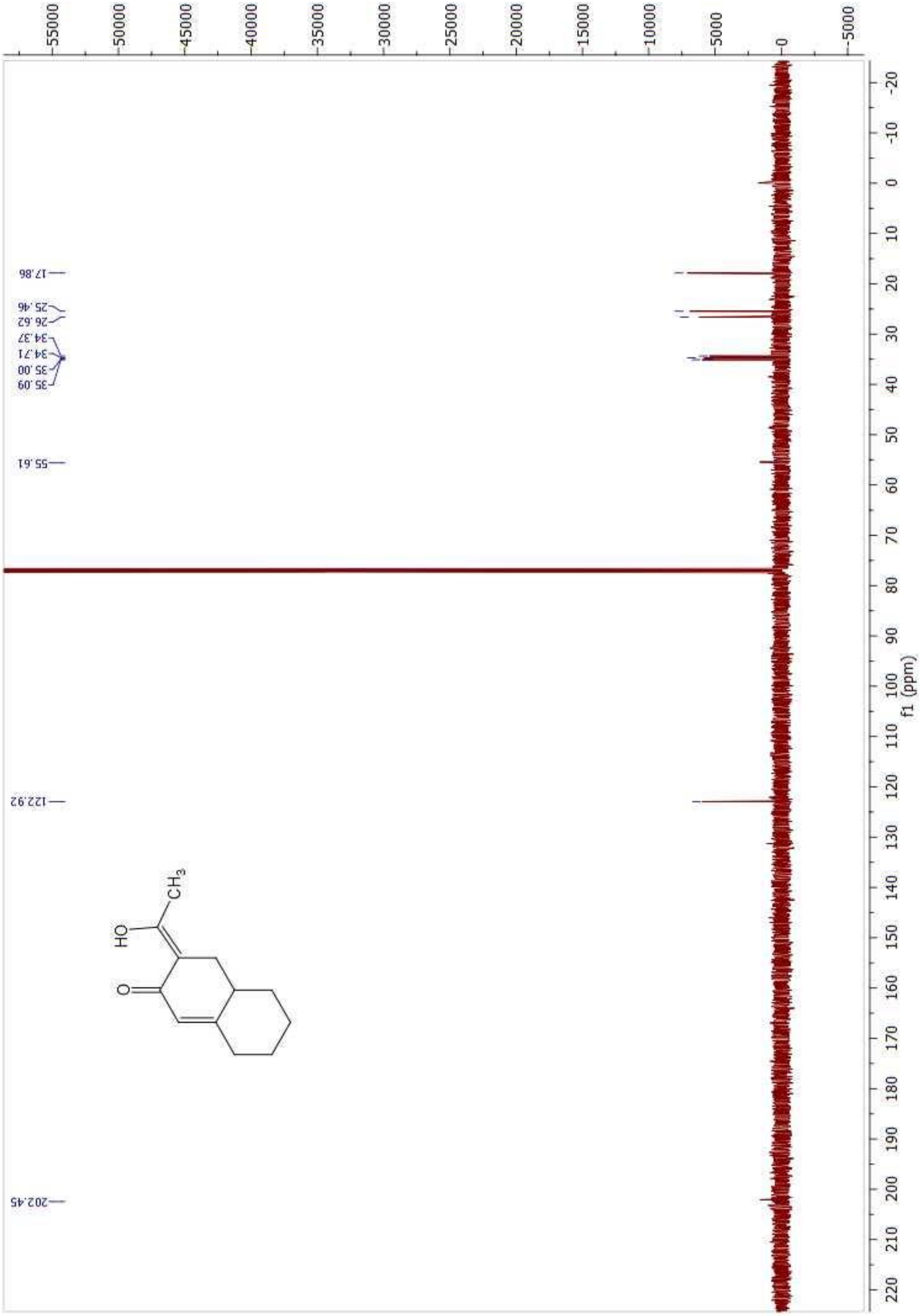


Figure 87. ^{13}C NMR spectrum of **128c** (125 MHz, $CDCl_3$).

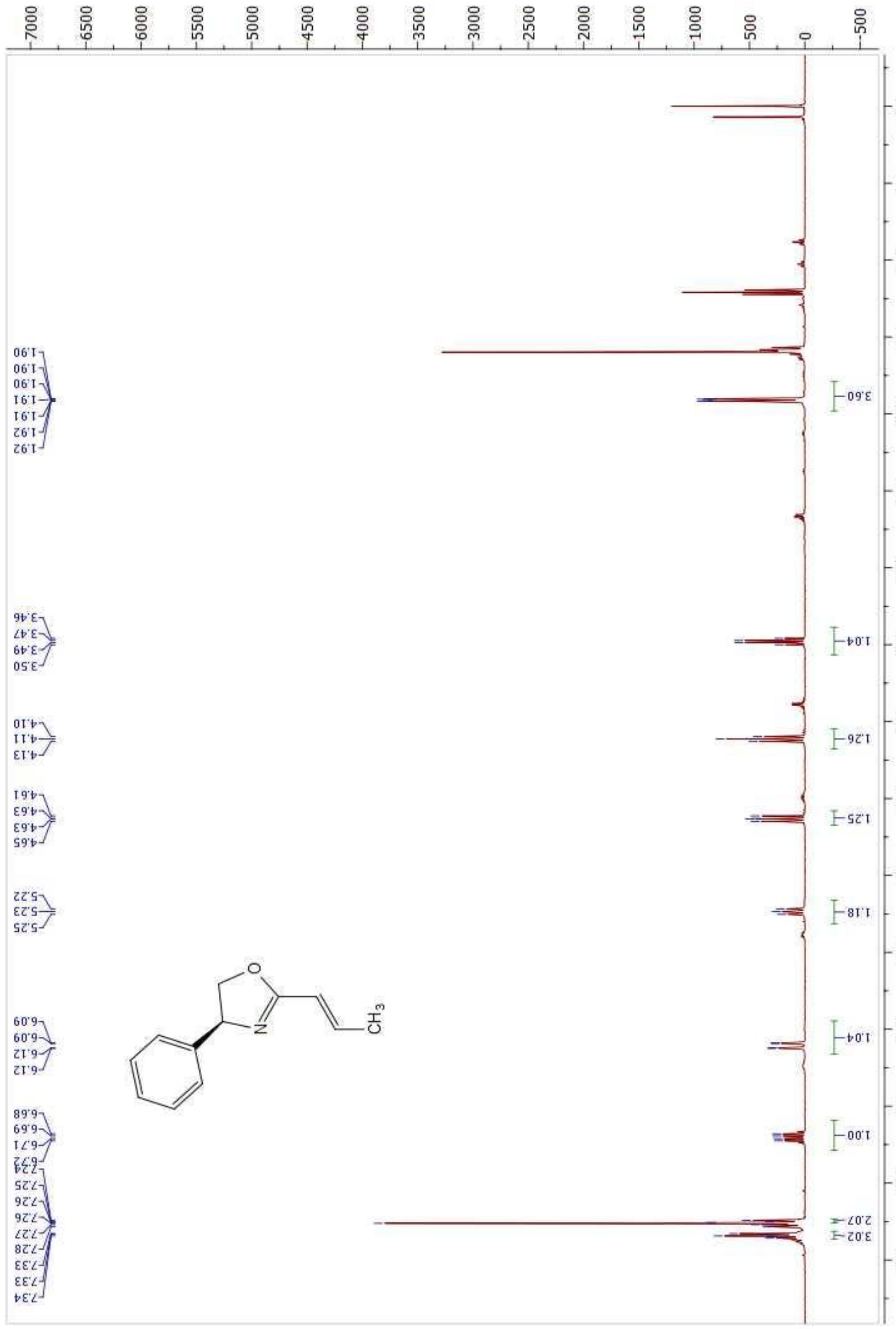


Figure 88. ^{1}H NMR spectrum of **129a** (500 MHz, CDCl$_3$).

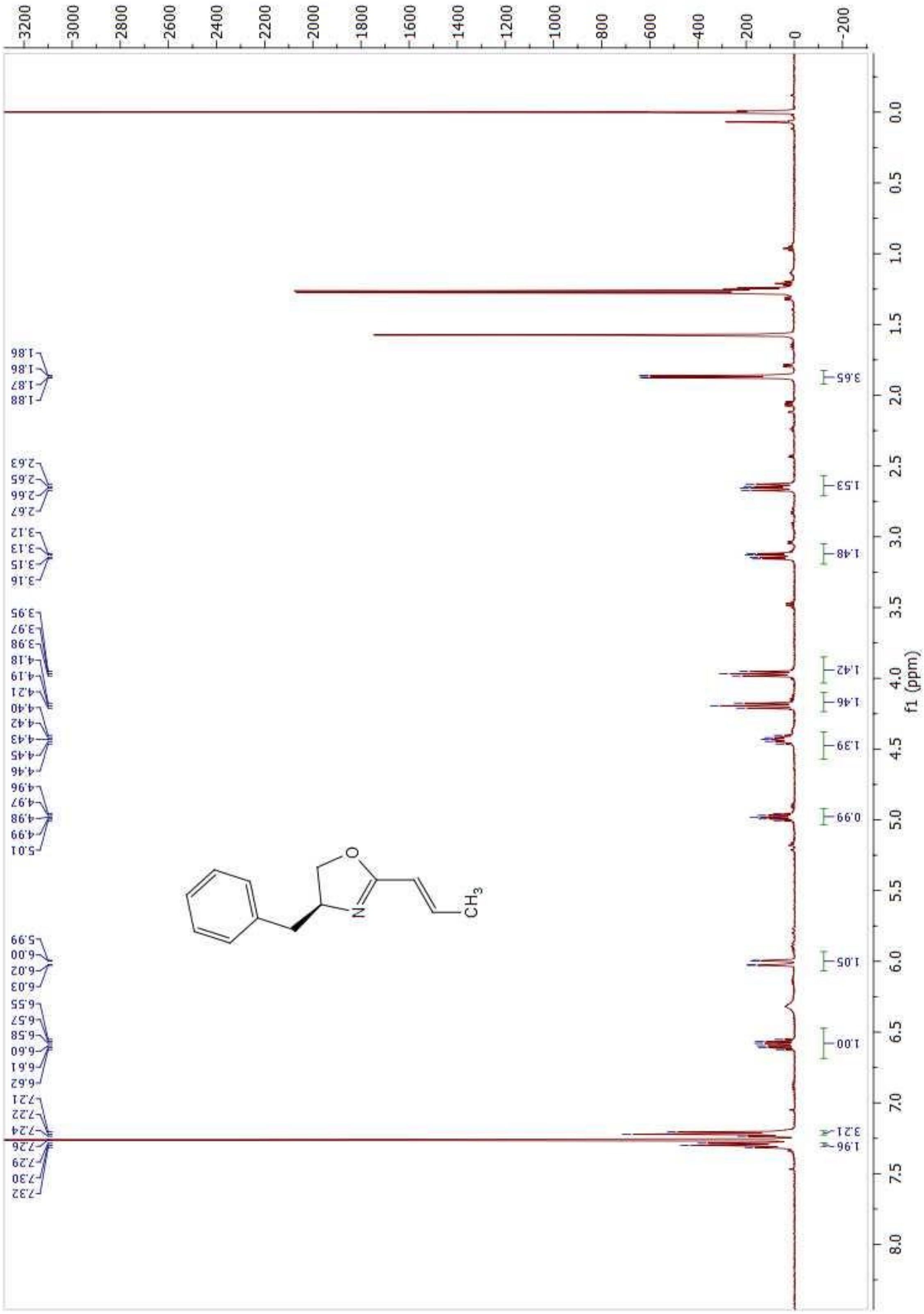


Figure 89. ^{1}H NMR spectrum of **129b** (500 MHz, $CDCl_3$).

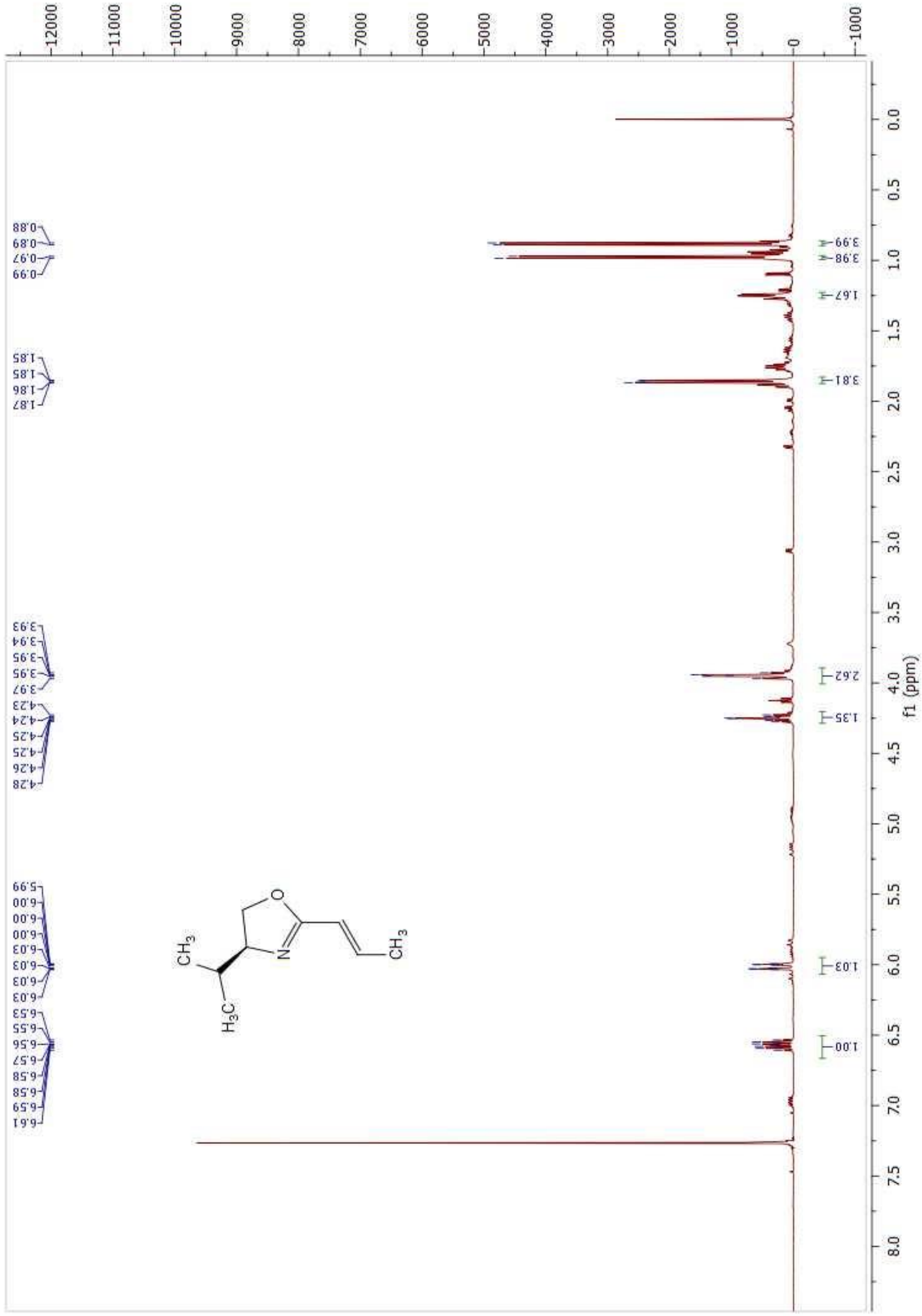


Figure 90. ^{1}H NMR spectrum of **129c** (500 MHz, $CDCl_3$).

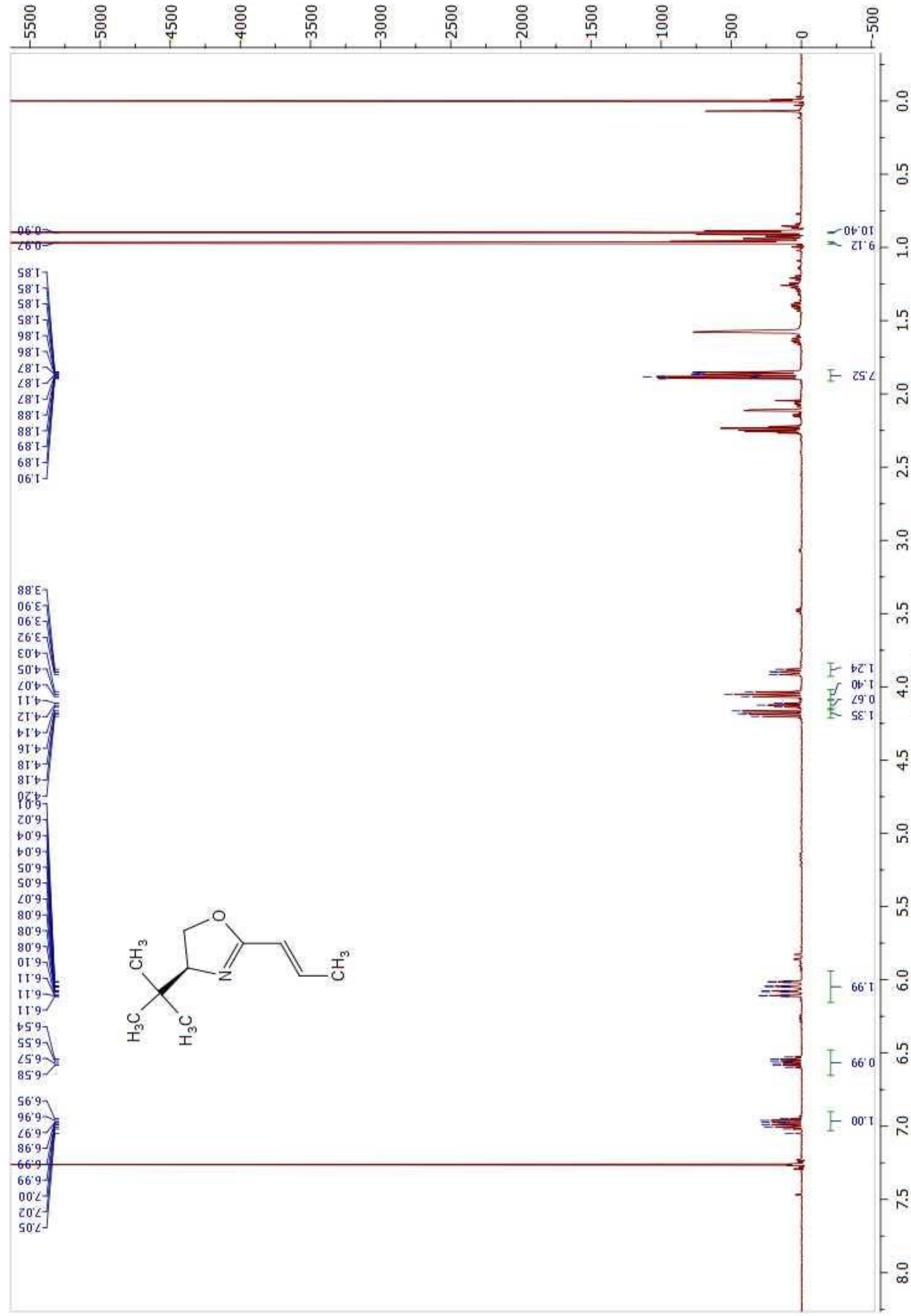


Figure 91. ^{1}H NMR spectrum of **129d** (500 MHz, $CDCl_3$).

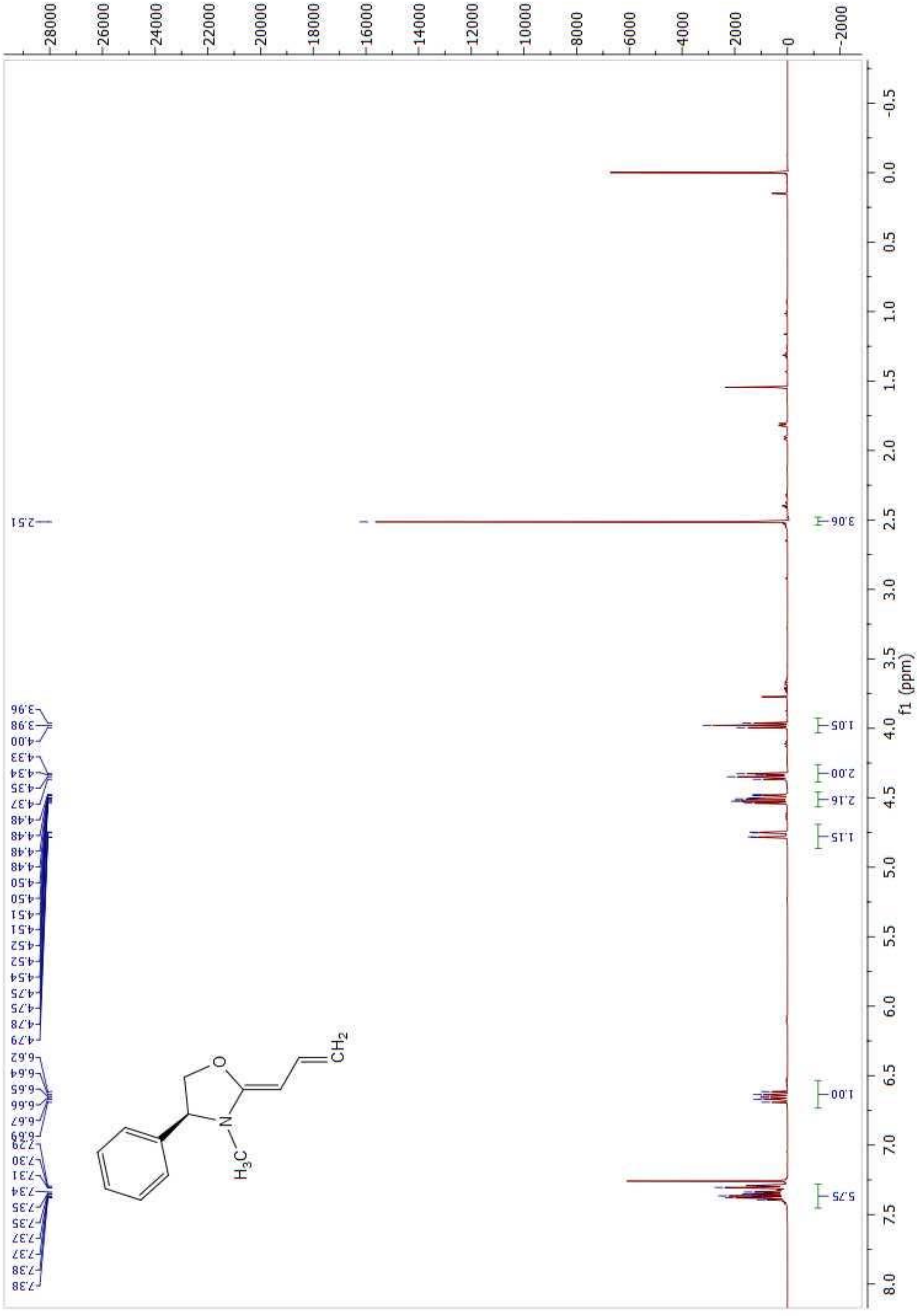


Figure 92. ^{1}H NMR spectrum of **130a** (500 MHz, $CDCl_3$).

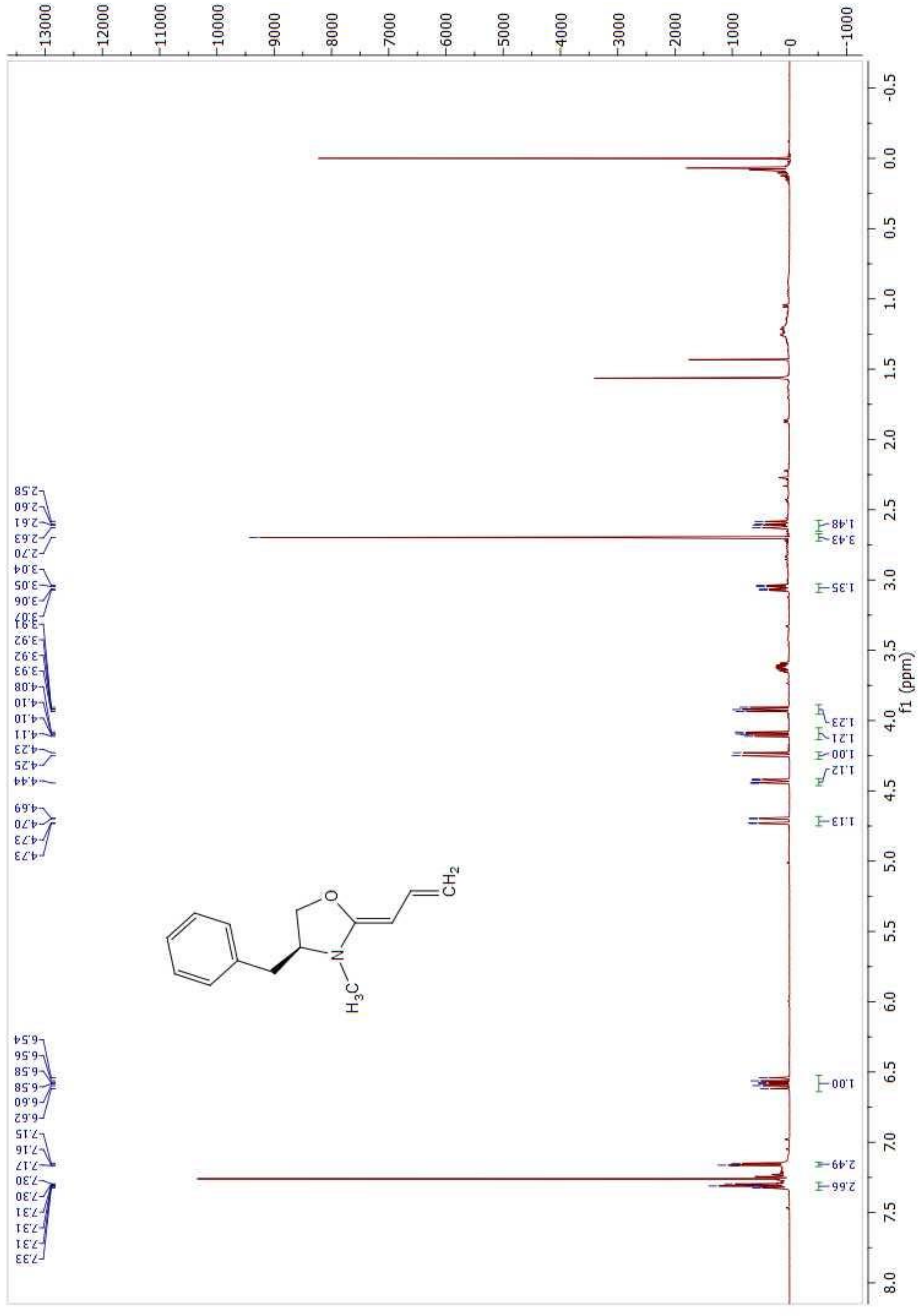


Figure 93. ^{1}H NMR spectrum of **130b** (500 MHz, $CDCl_3$).

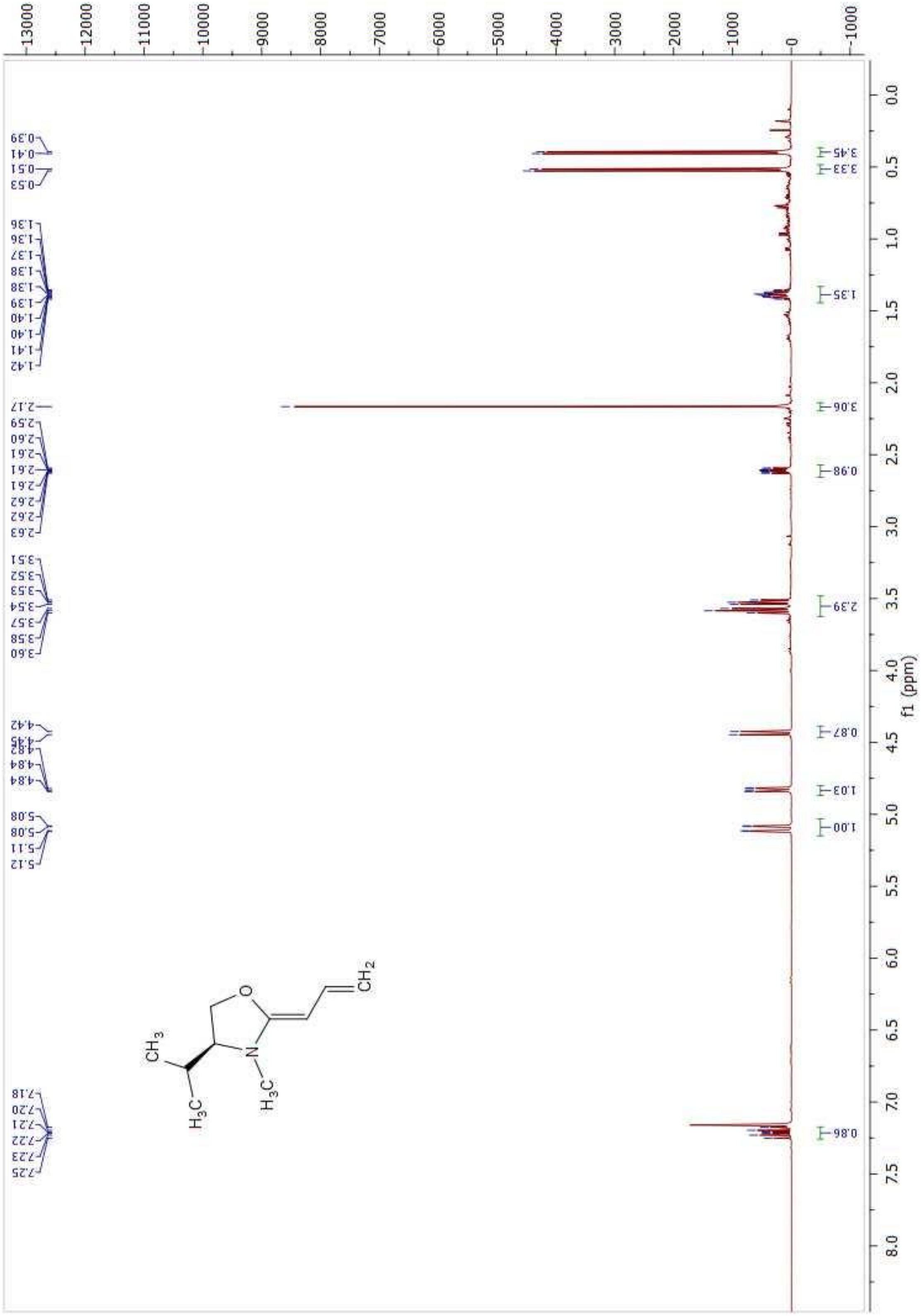


Figure 94. ^{1}H NMR spectrum of **130c** (500 MHz, $CDCl_3$).

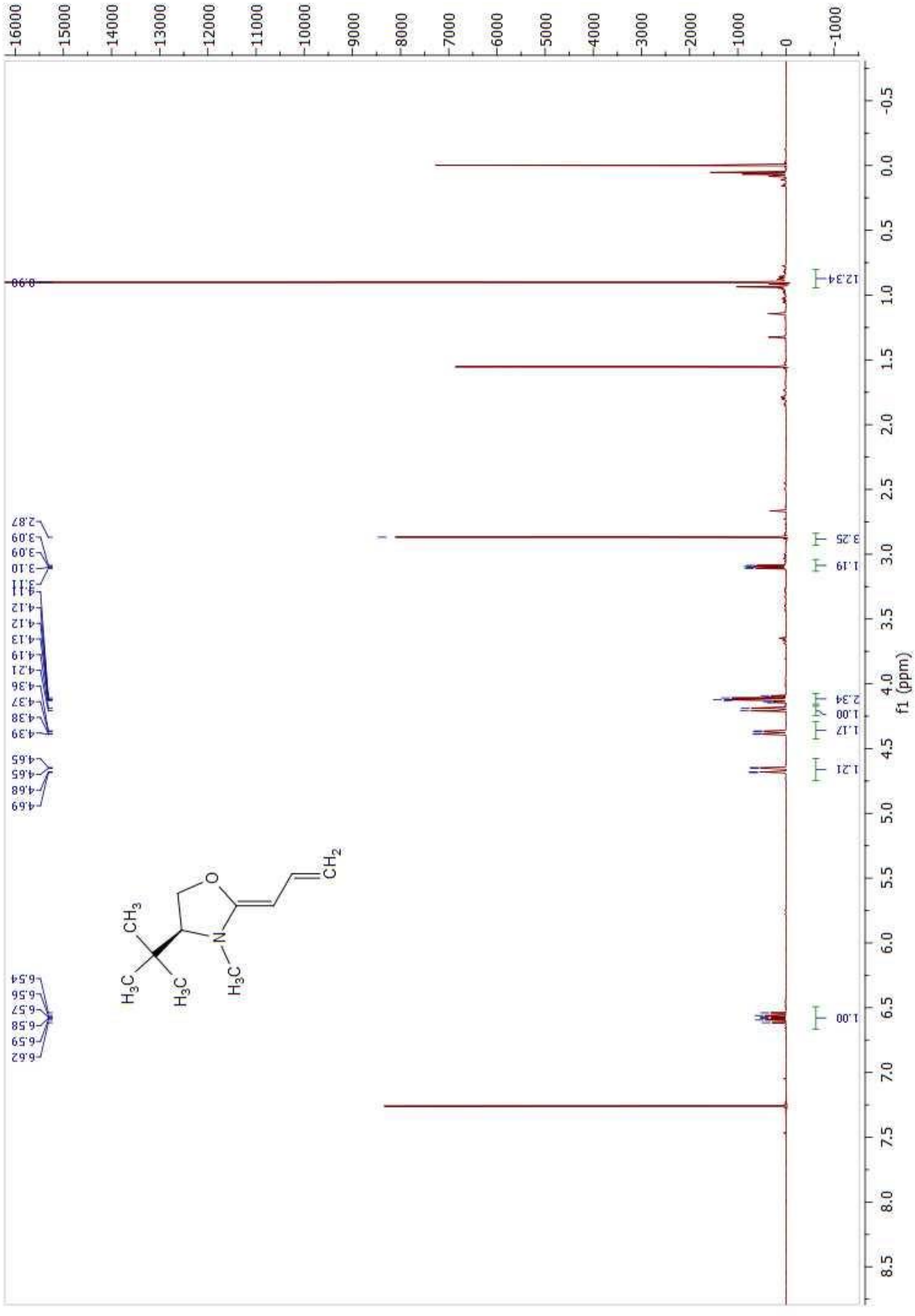


Figure 95. ^{1}H NMR spectrum of **130d** (500 MHz, CDCl$_3$).

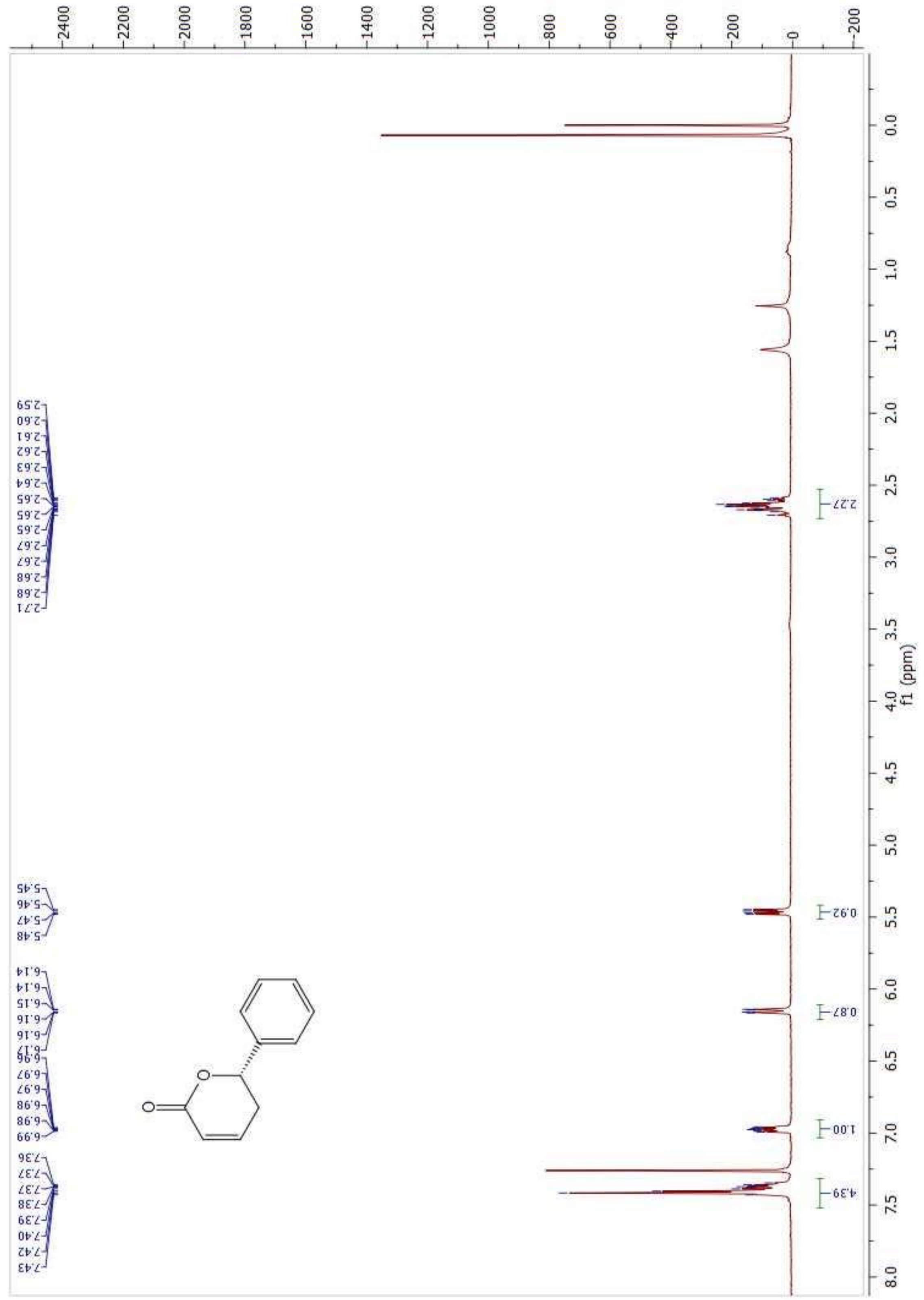


Figure 96. ^{1}H NMR spectrum of **134a** (500 MHz, $CDCl_3$).

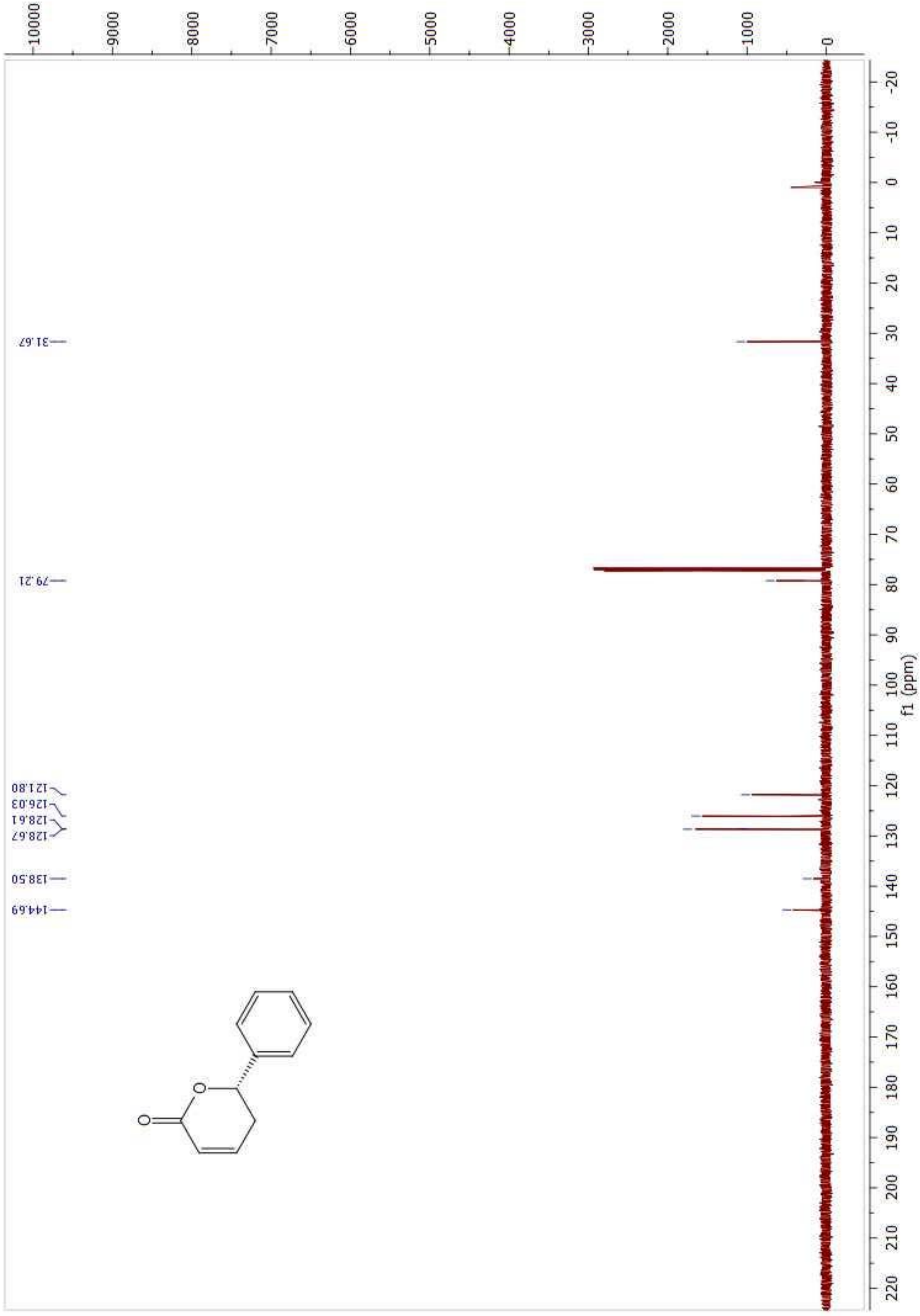


Figure 97. ^{13}C NMR spectrum of **134a** (125 MHz, $CDCl_3$).

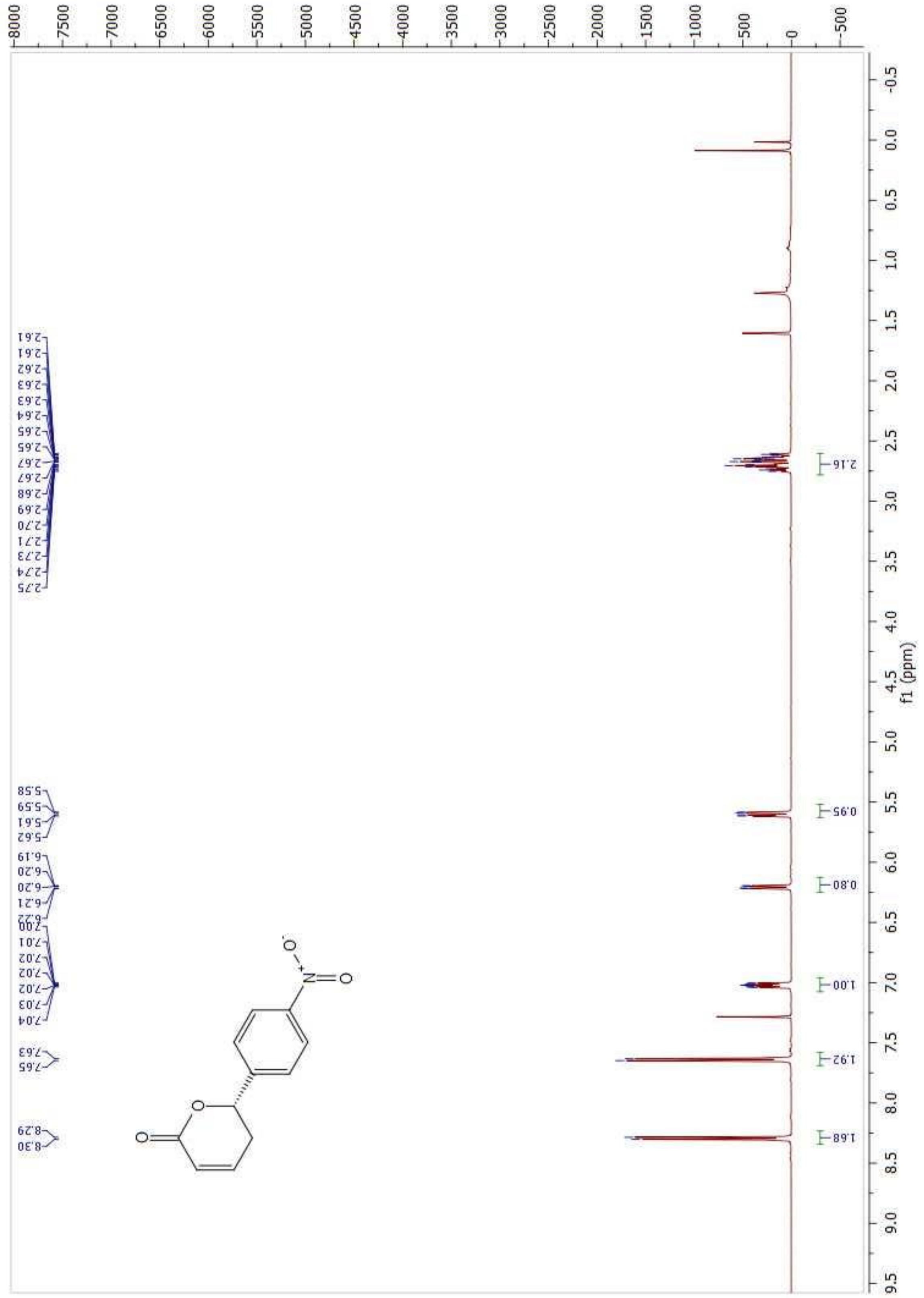


Figure 98. ^{1}H NMR spectrum of **134b** (500 MHz, $CDCl_3$).

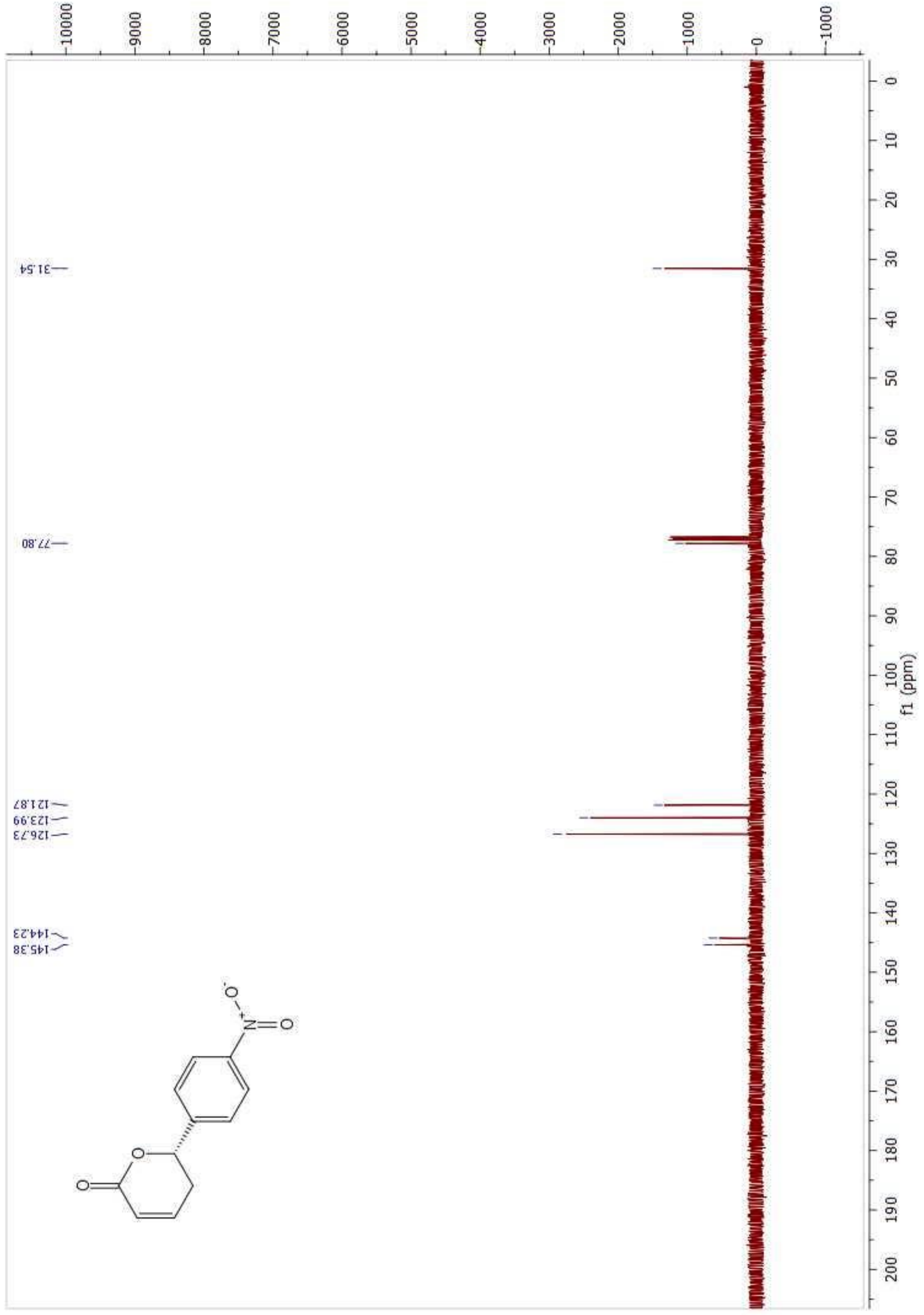


Figure 99. ^{13}C NMR spectrum of **134b** (125 MHz, $CDCl_3$).

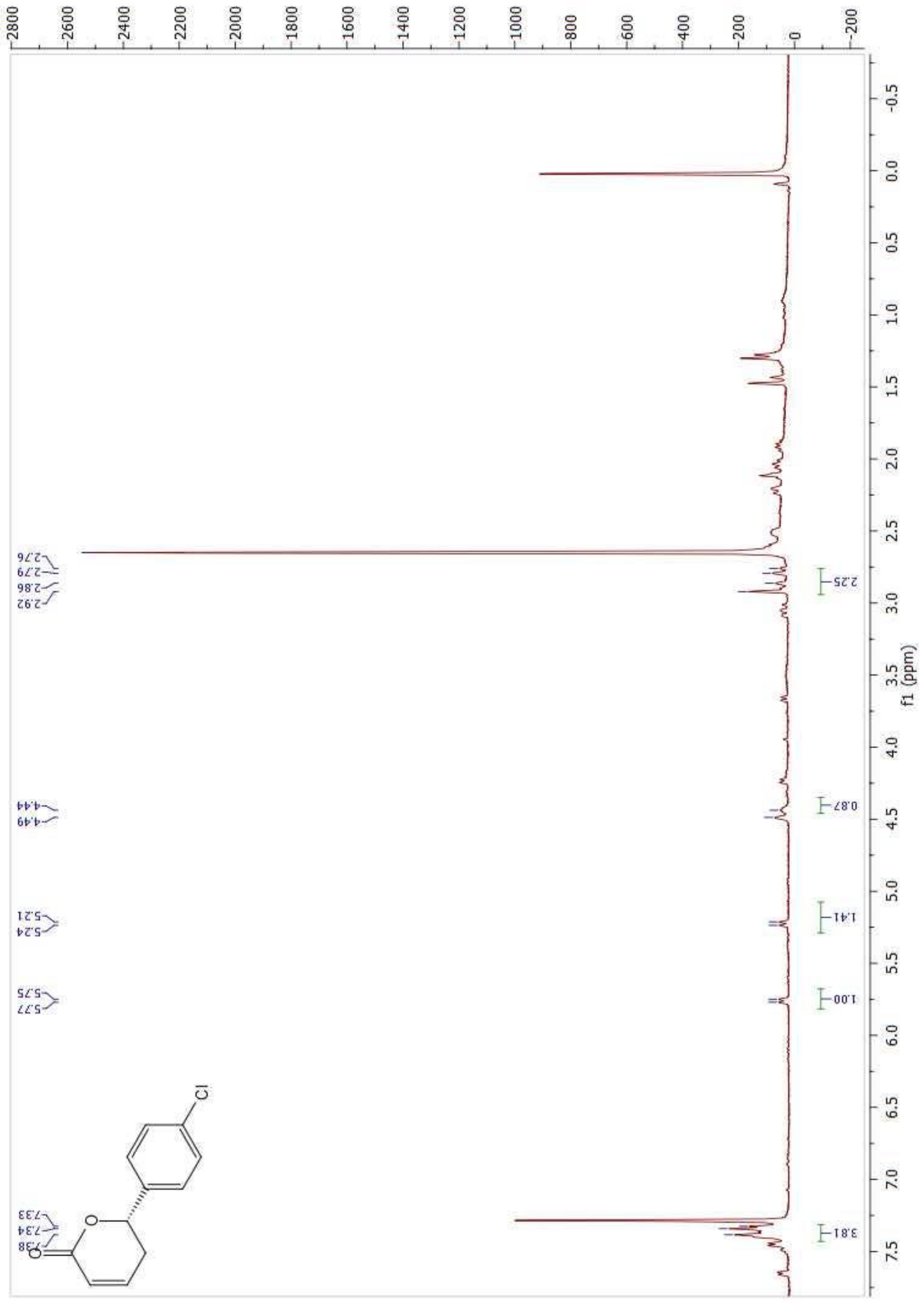


Figure 100. ^{1}H NMR spectrum of **134c** (500 MHz, $CDCl_3$).

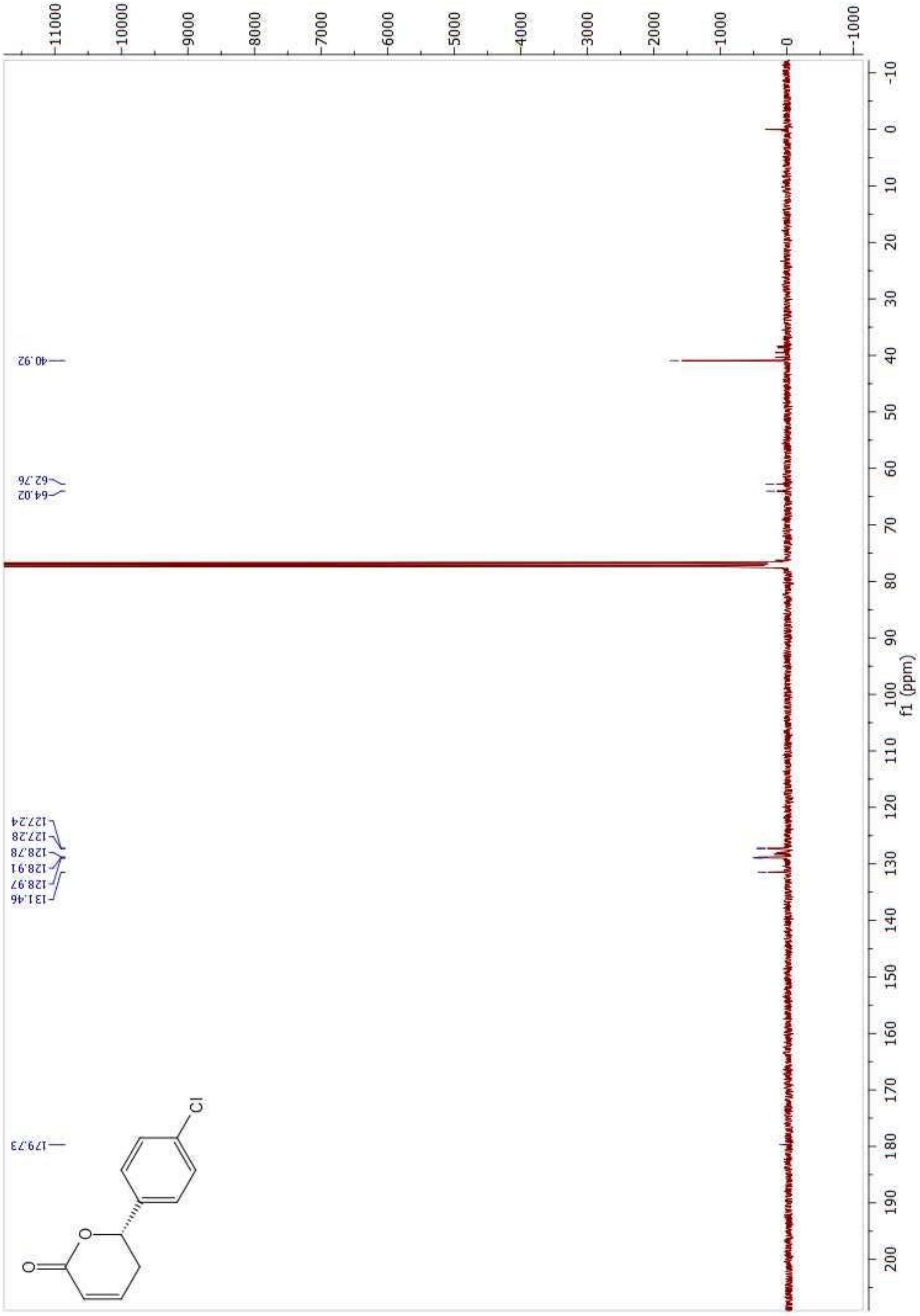


Figure 101. ^{13}C NMR spectrum of **134c** (125 MHz, $CDCl_3$).

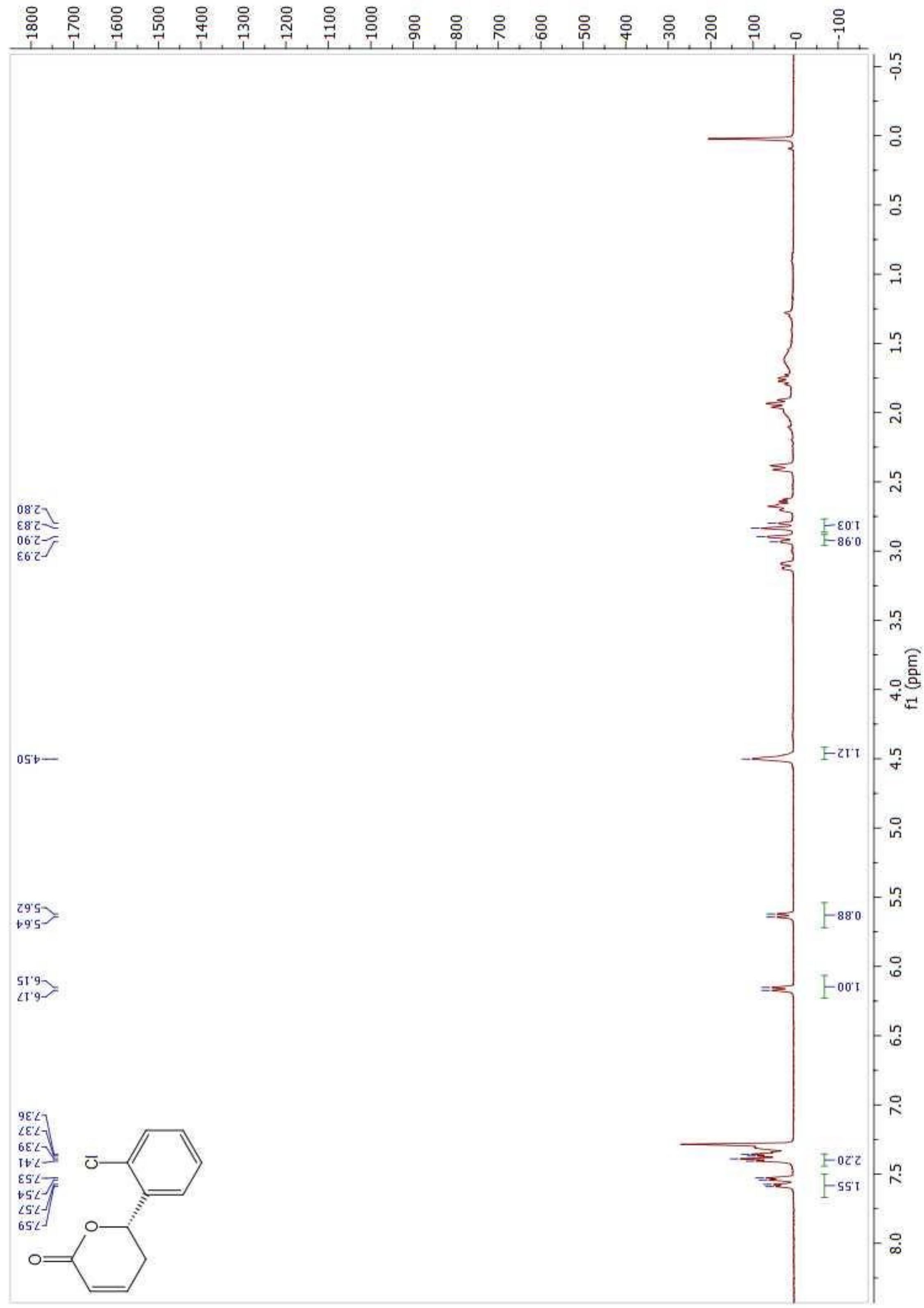


Figure 102. ^{1}H NMR spectrum of **134d** (500 MHz, $CDCl_3$).

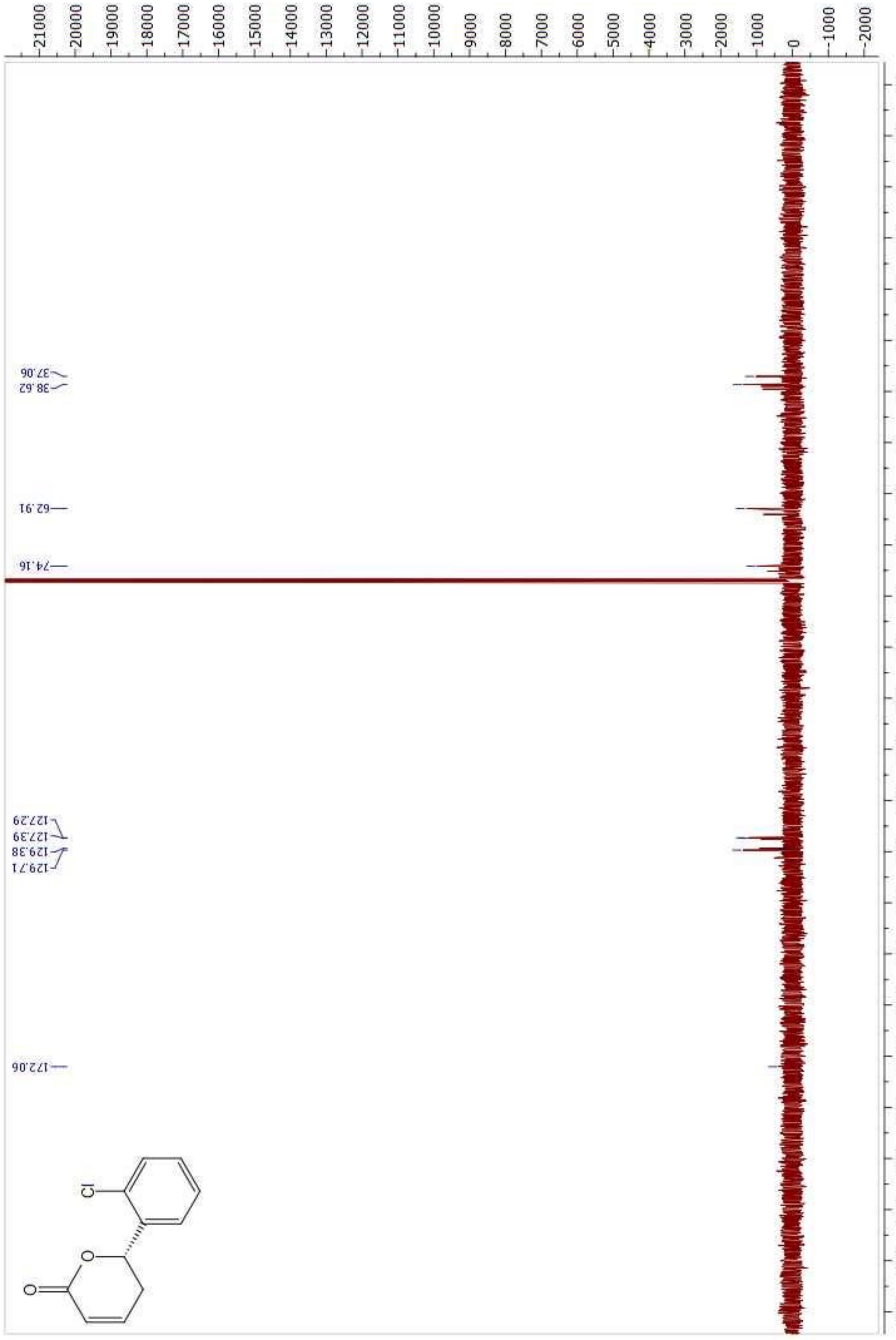


Figure 103. ^{13}C NMR spectrum of **134d** (125 MHz, $CDCl_3$).

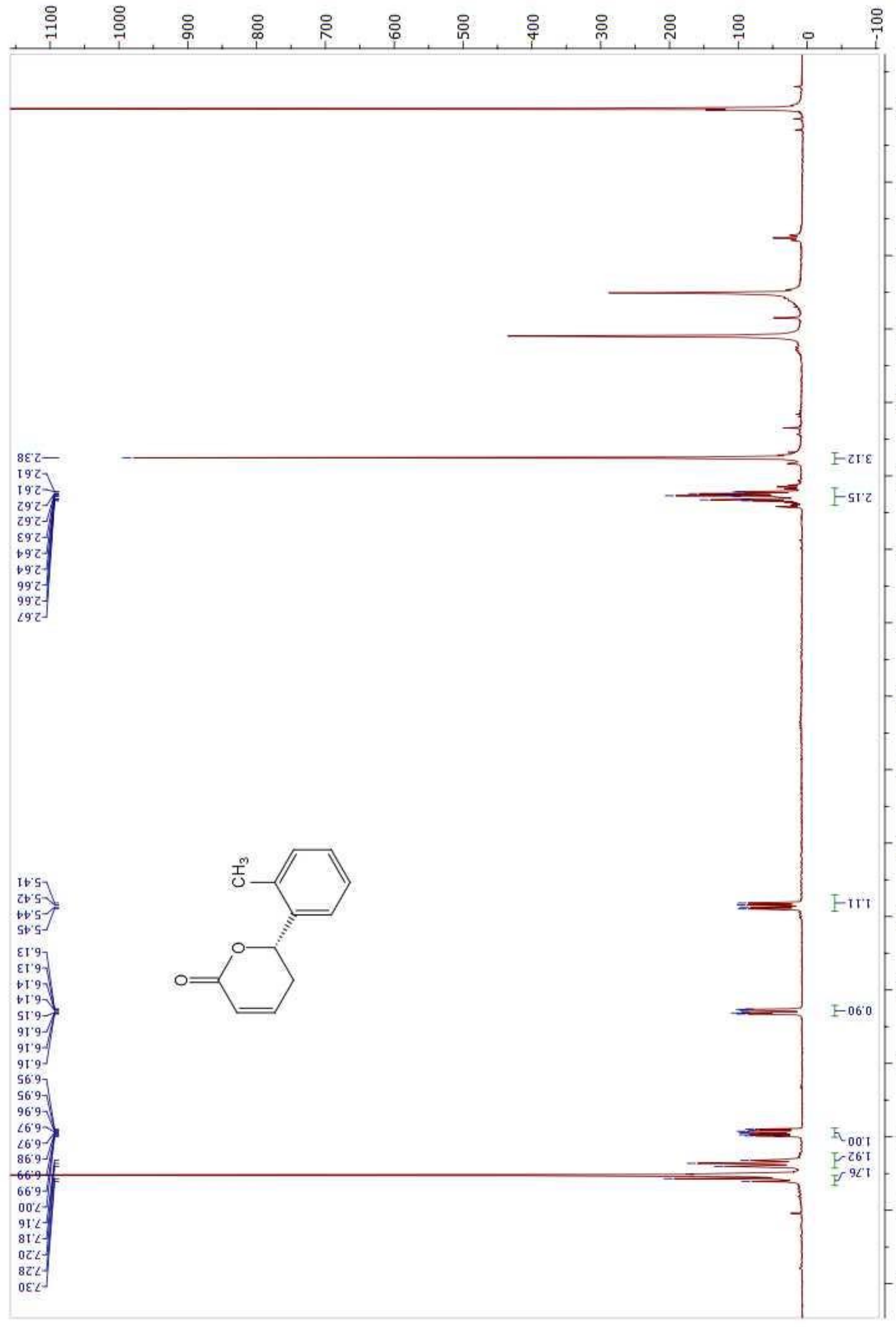


Figure 104. ^{1}H NMR spectrum of **134e** (500 MHz, $CDCl_3$).

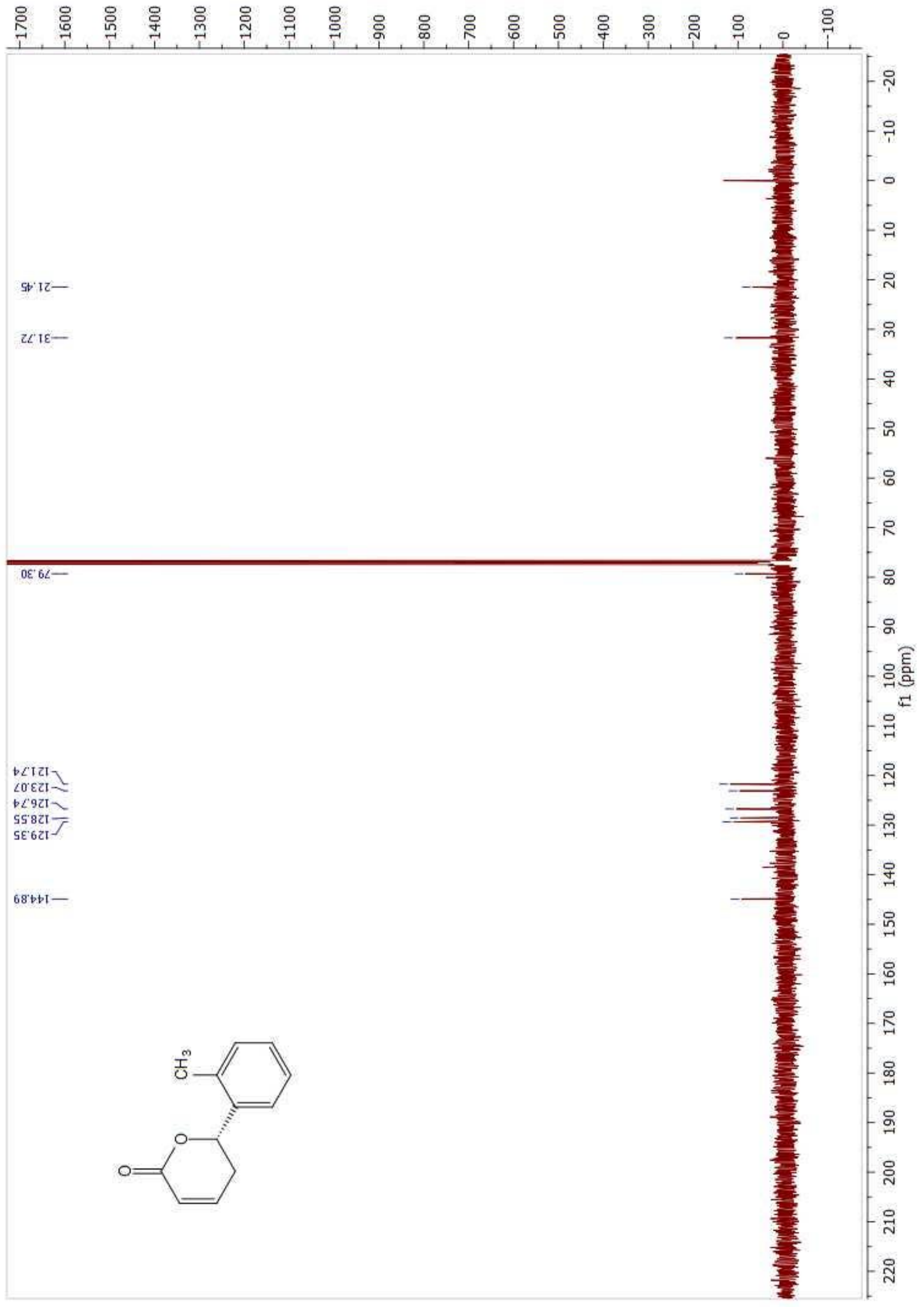


Figure 105. ^{13}C NMR spectrum of **134e** (125 MHz, $CDCl_3$).

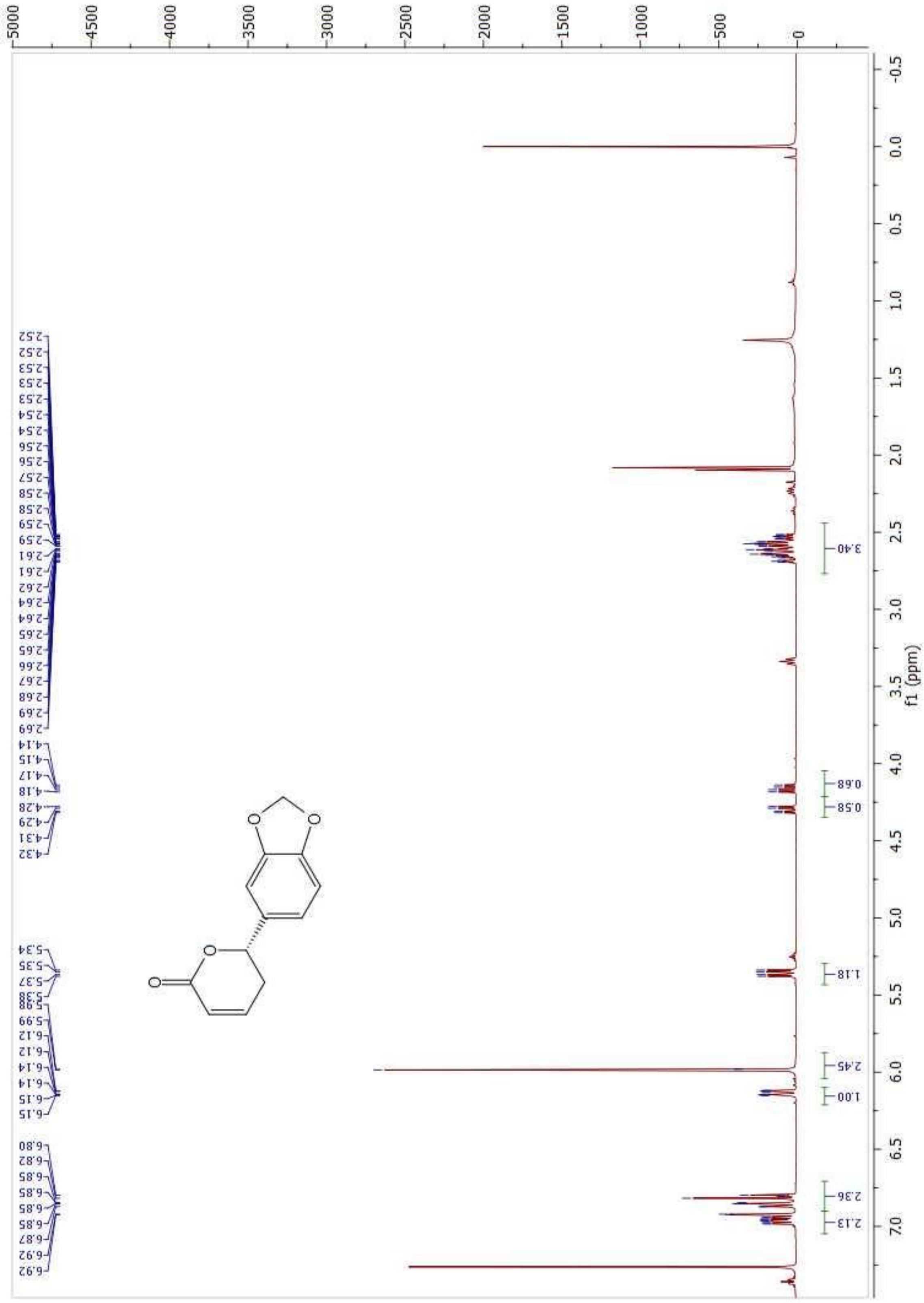


Figure 106. ^{1}H NMR spectrum of **134f** (500 MHz, $CDCl_3$).

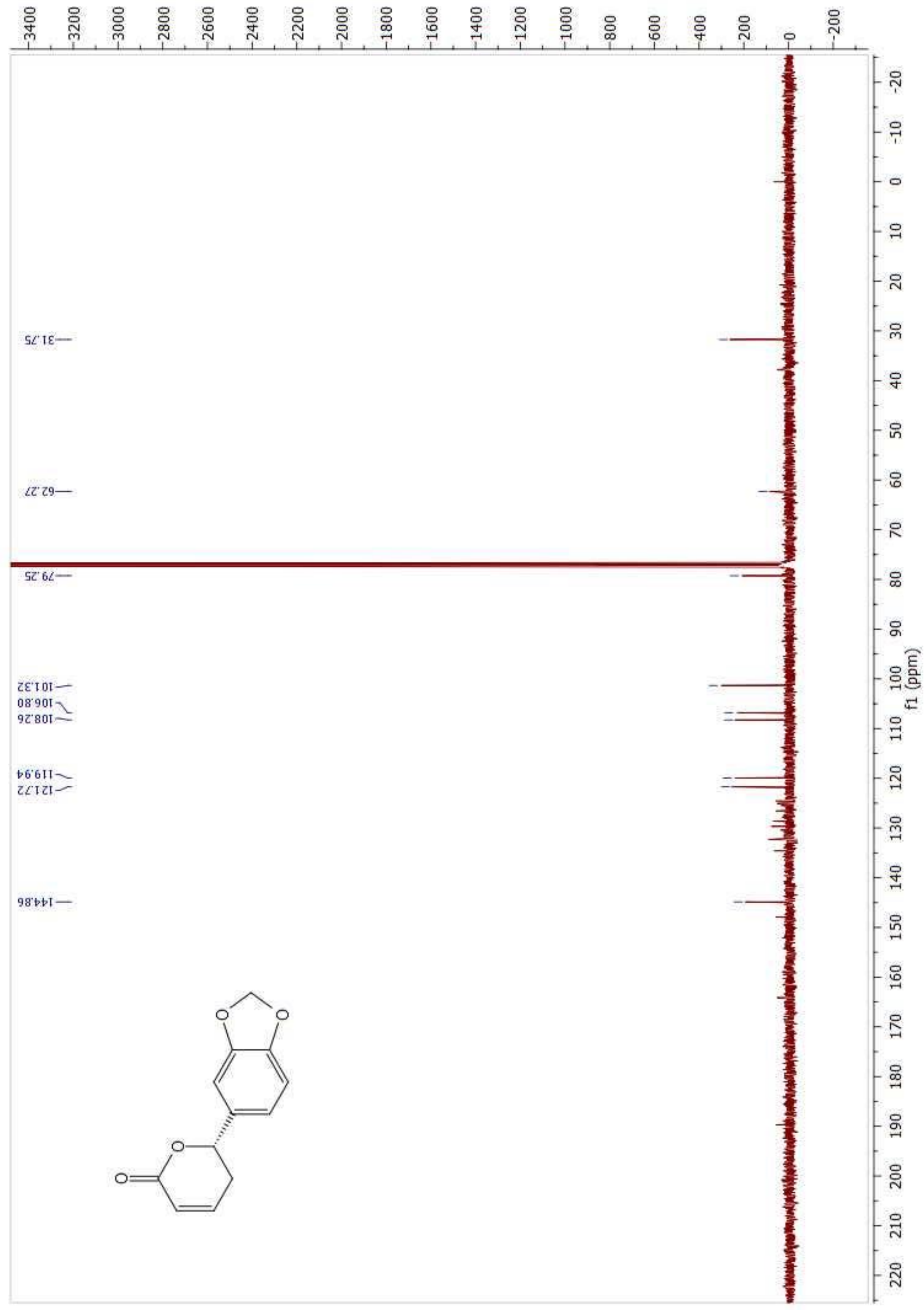


Figure 107. ^{13}C NMR spectrum of **134f** (125 MHz, CDCl$_3$).

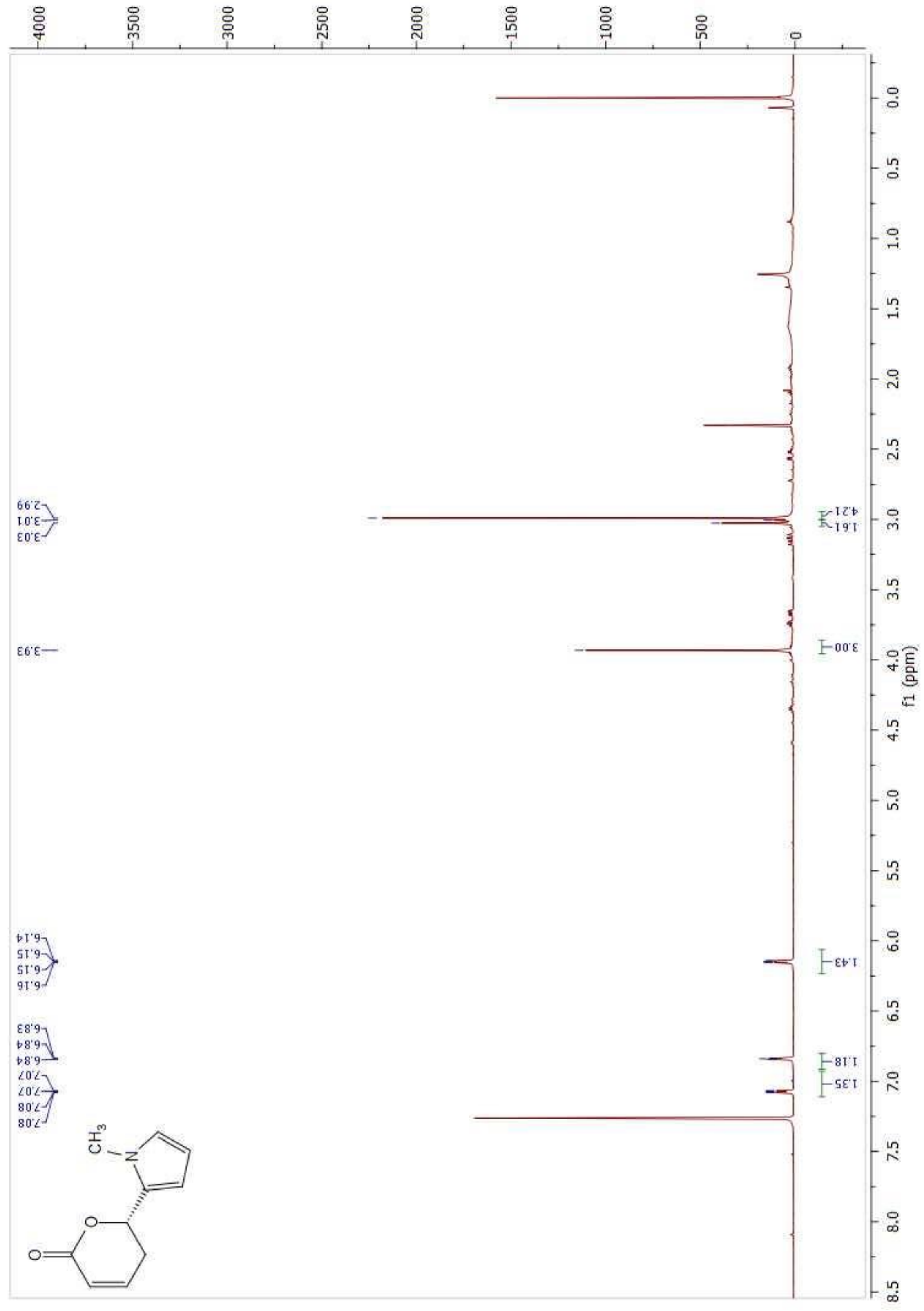


Figure 108. ^{1}H NMR spectrum of **134g** (500 MHz, $CDCl_3$).

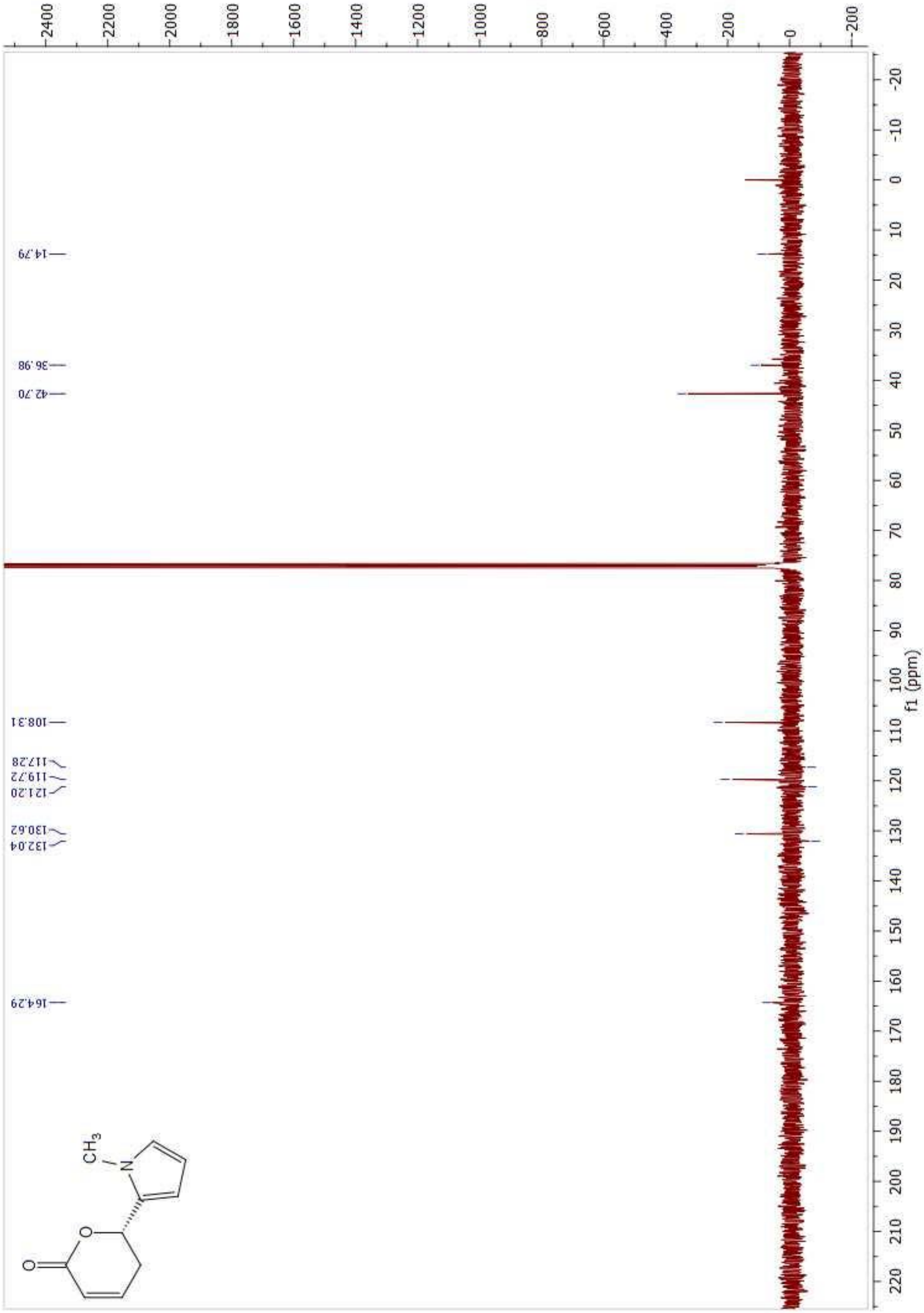


Figure 109. ^{13}C NMR spectrum of **134g** (125 MHz, $CDCl_3$).

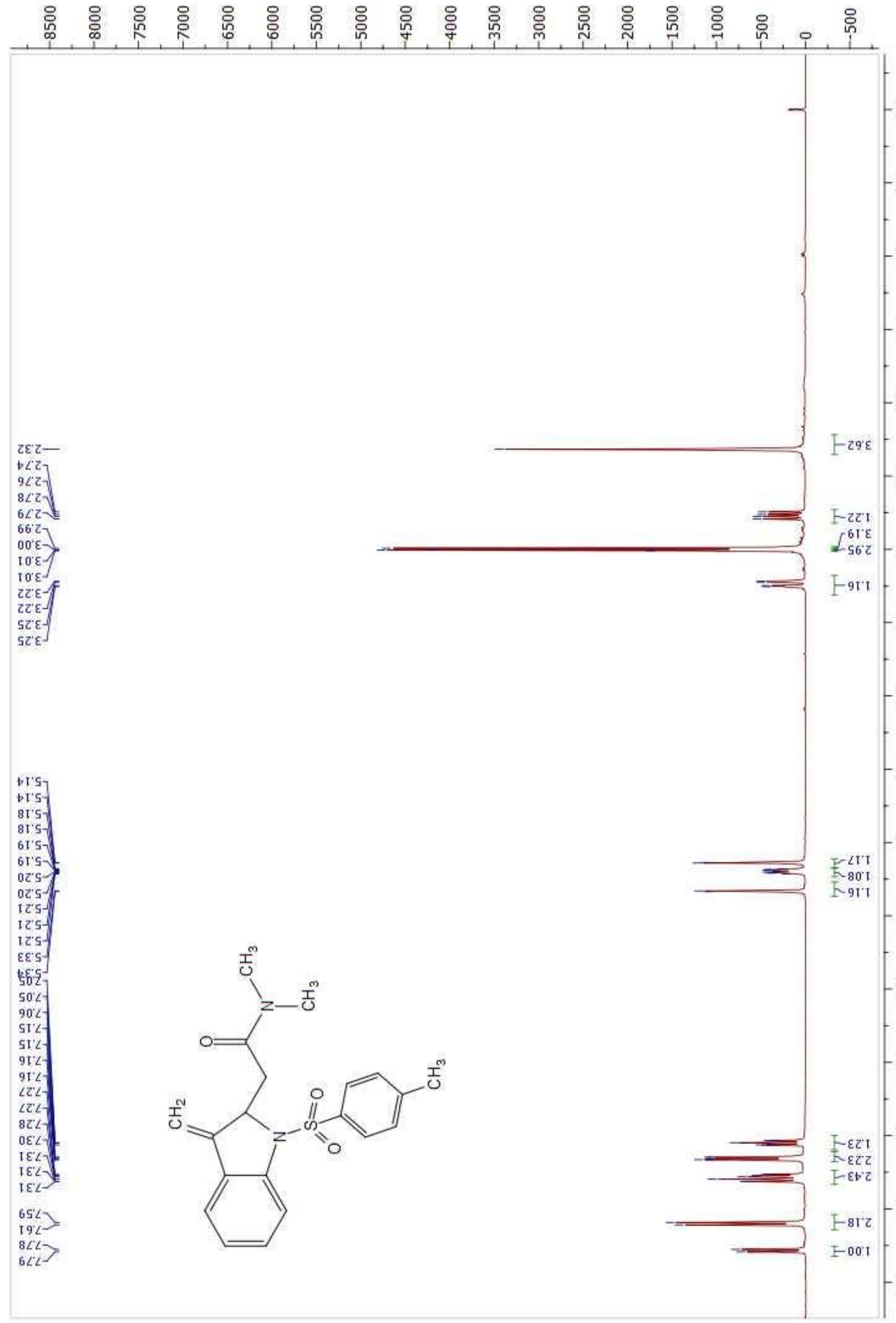


Figure 110. ^{1}H NMR spectrum of **171** (500 MHz, $CDCl_3$).

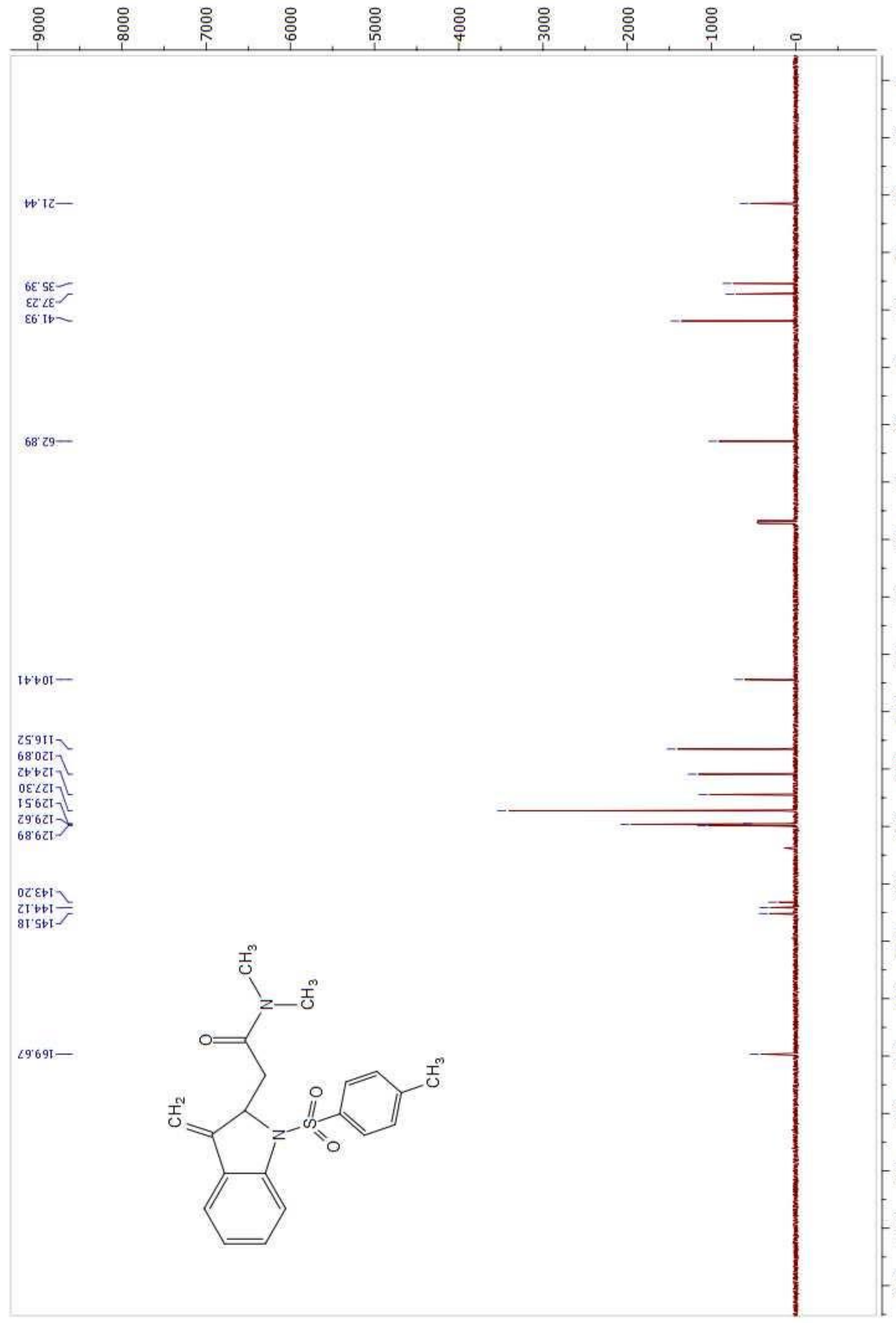


Figure 111. ^{13}C NMR spectrum of **171** (125 MHz, $CDCl_3$).

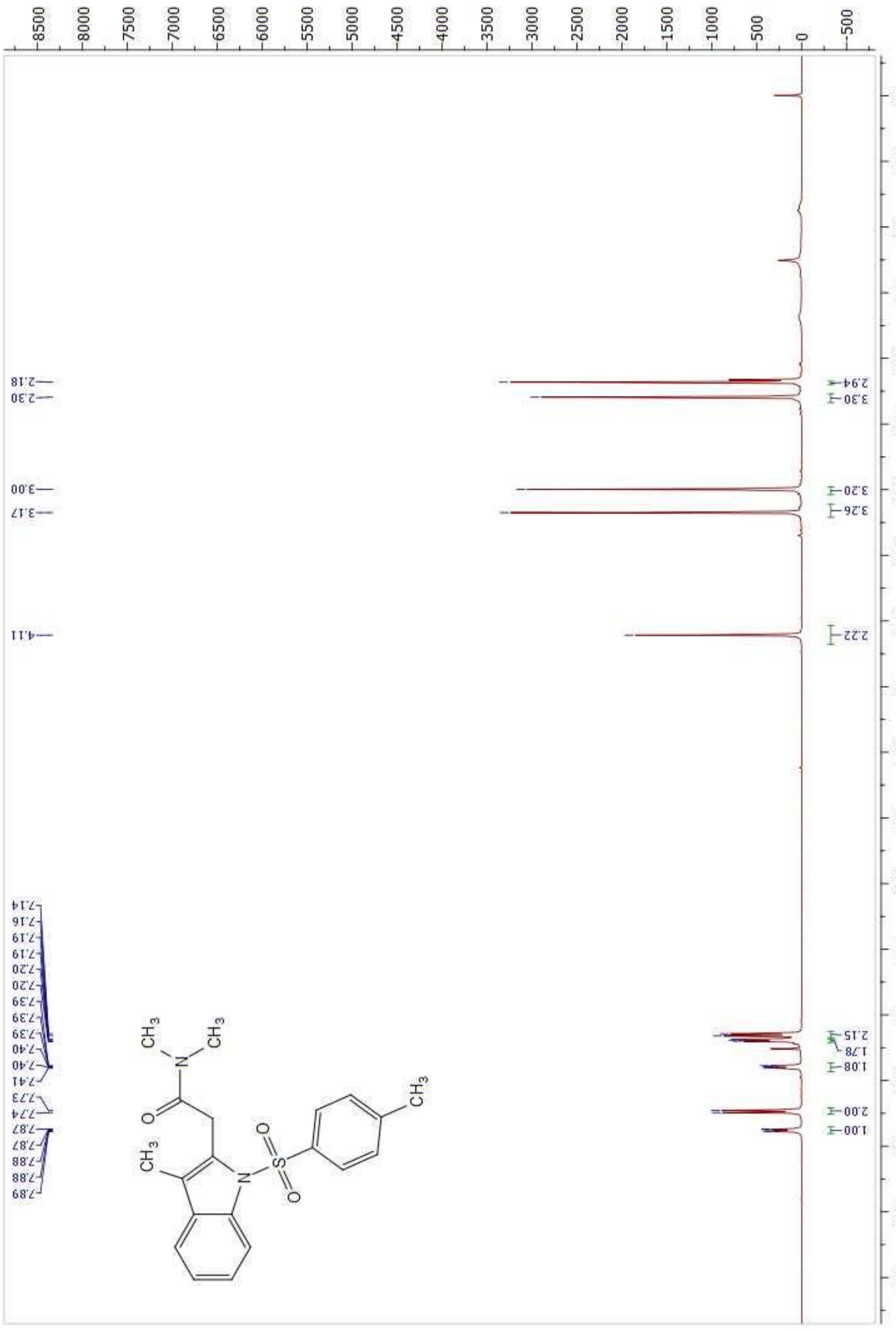


Figure 112. ^{1}H NMR spectrum of **172** (500 MHz, $CDCl_3$).

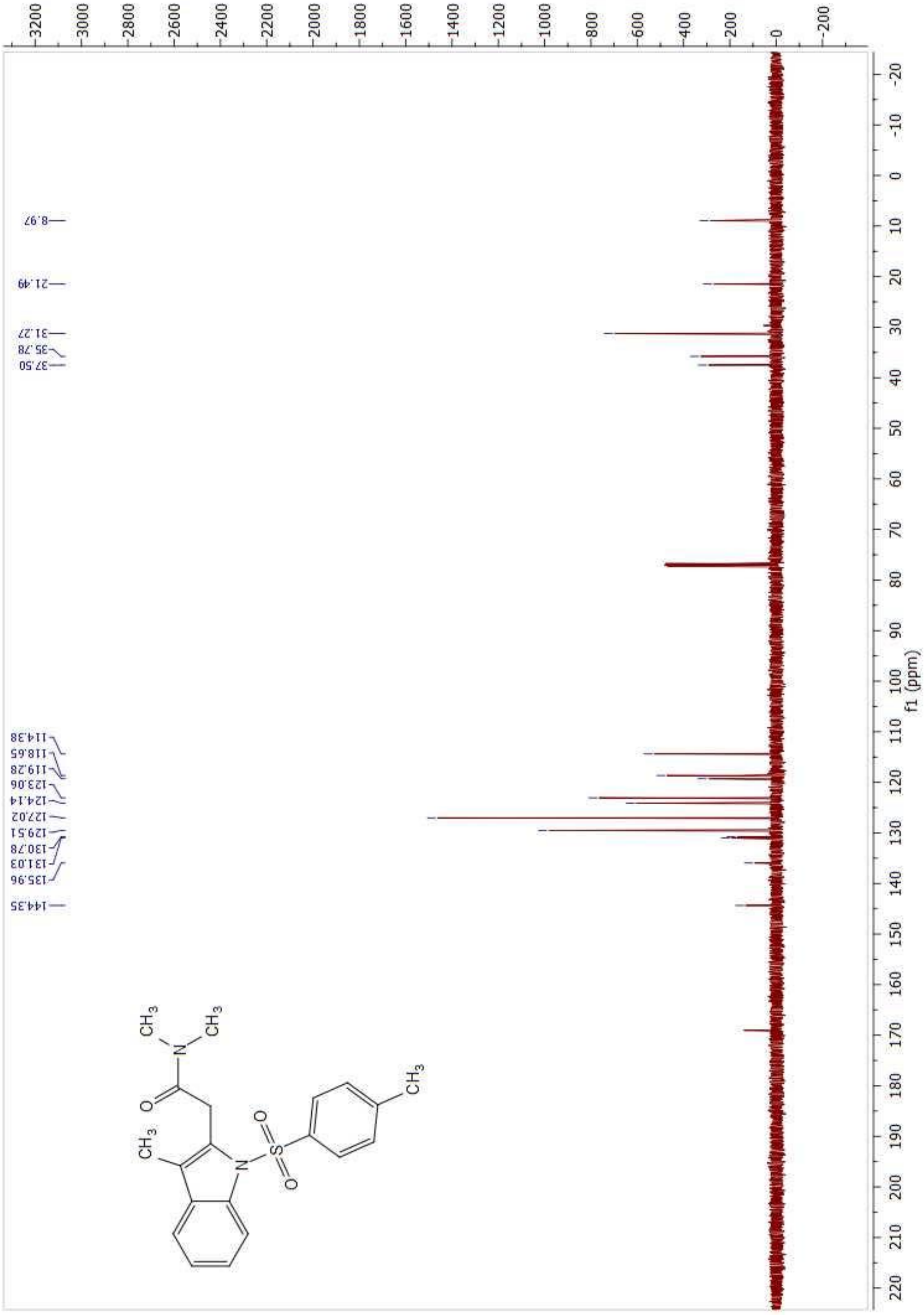


Figure 113. ^{13}C NMR spectrum of **172** (125 MHz, $CDCl_3$).

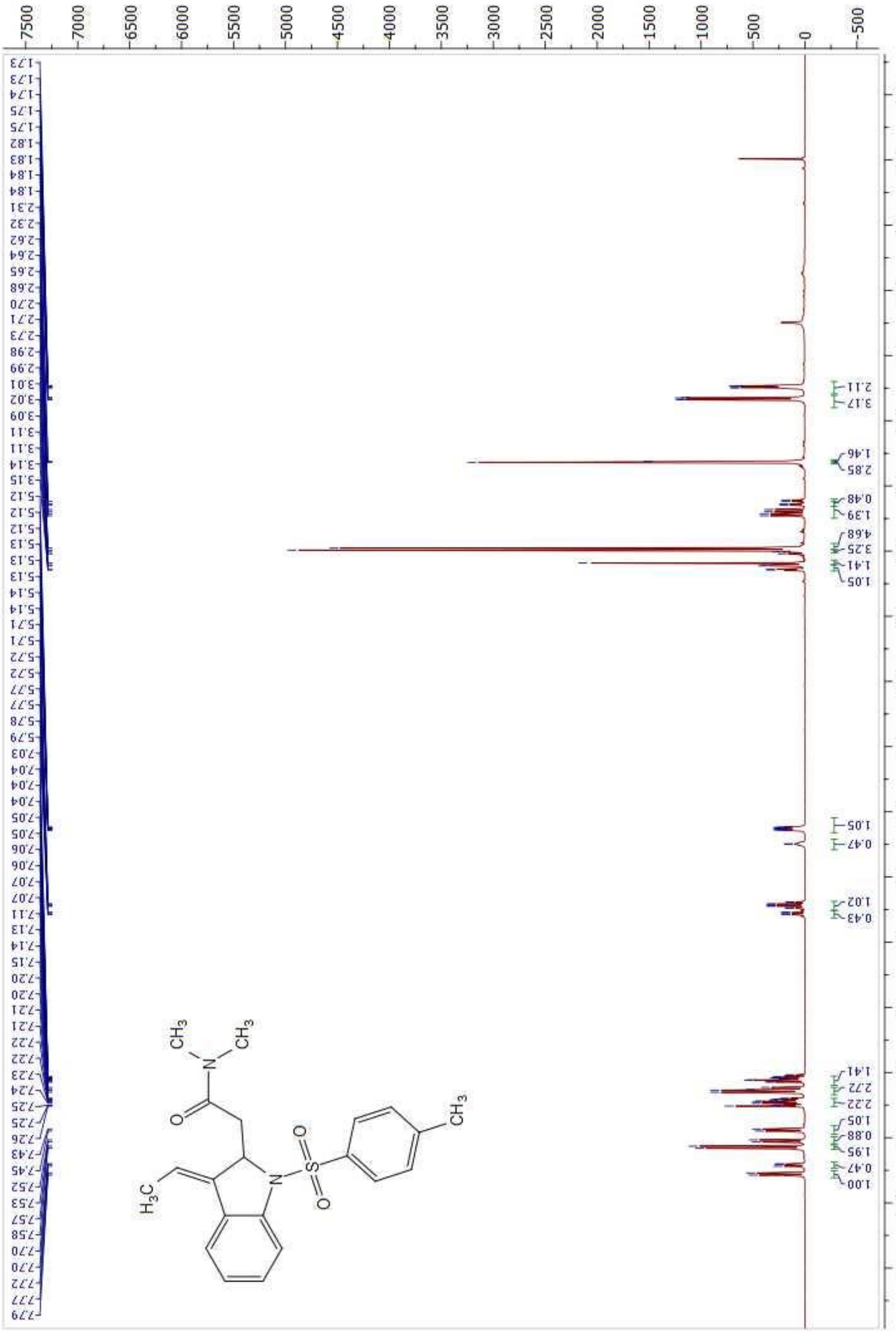


Figure 114. ^{1}H NMR spectrum of **173a** (500 MHz, $CDCl_3$).

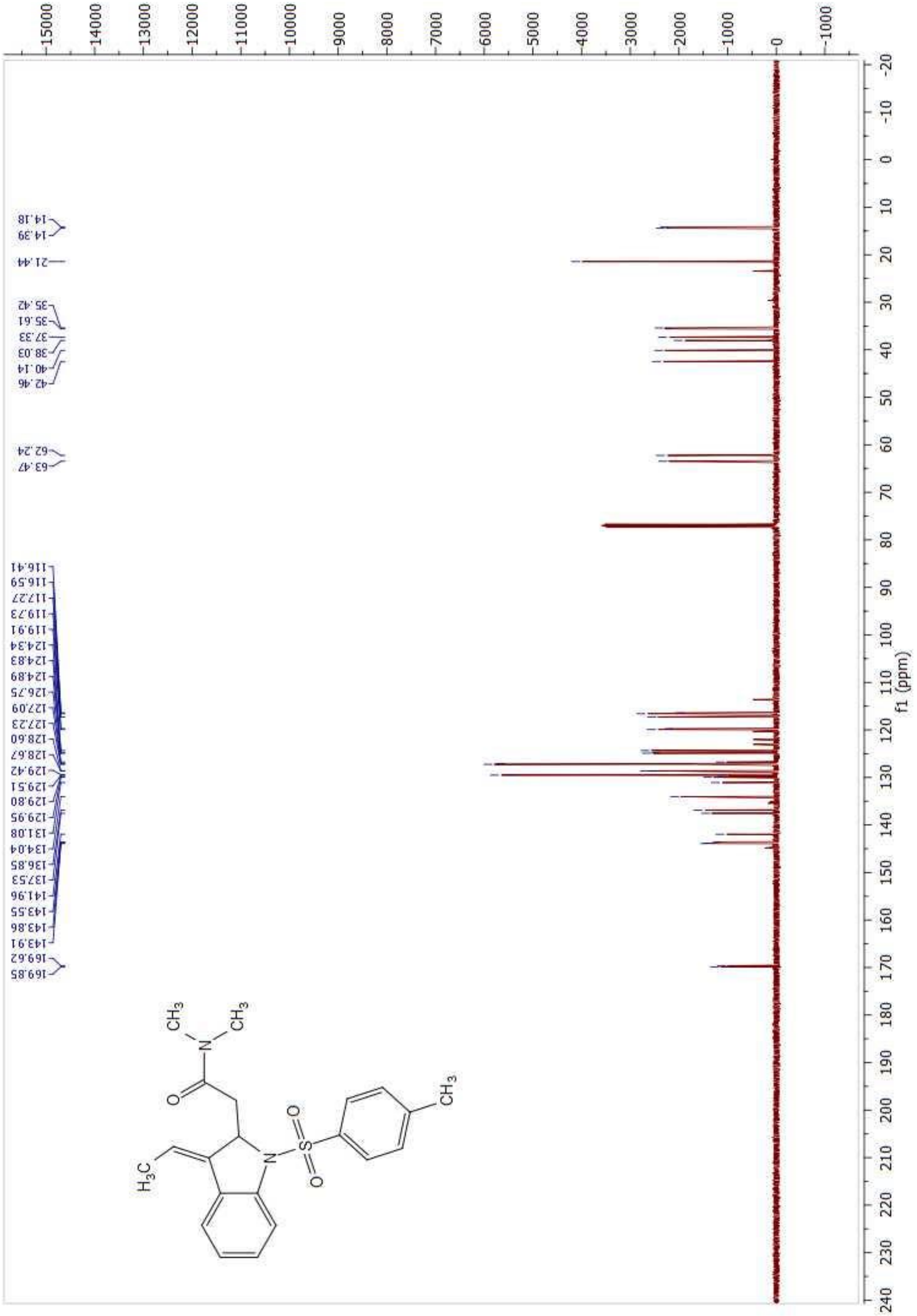


Figure 115. ^{13}C NMR spectrum of **173a** (125 MHz, $CDCl_3$).

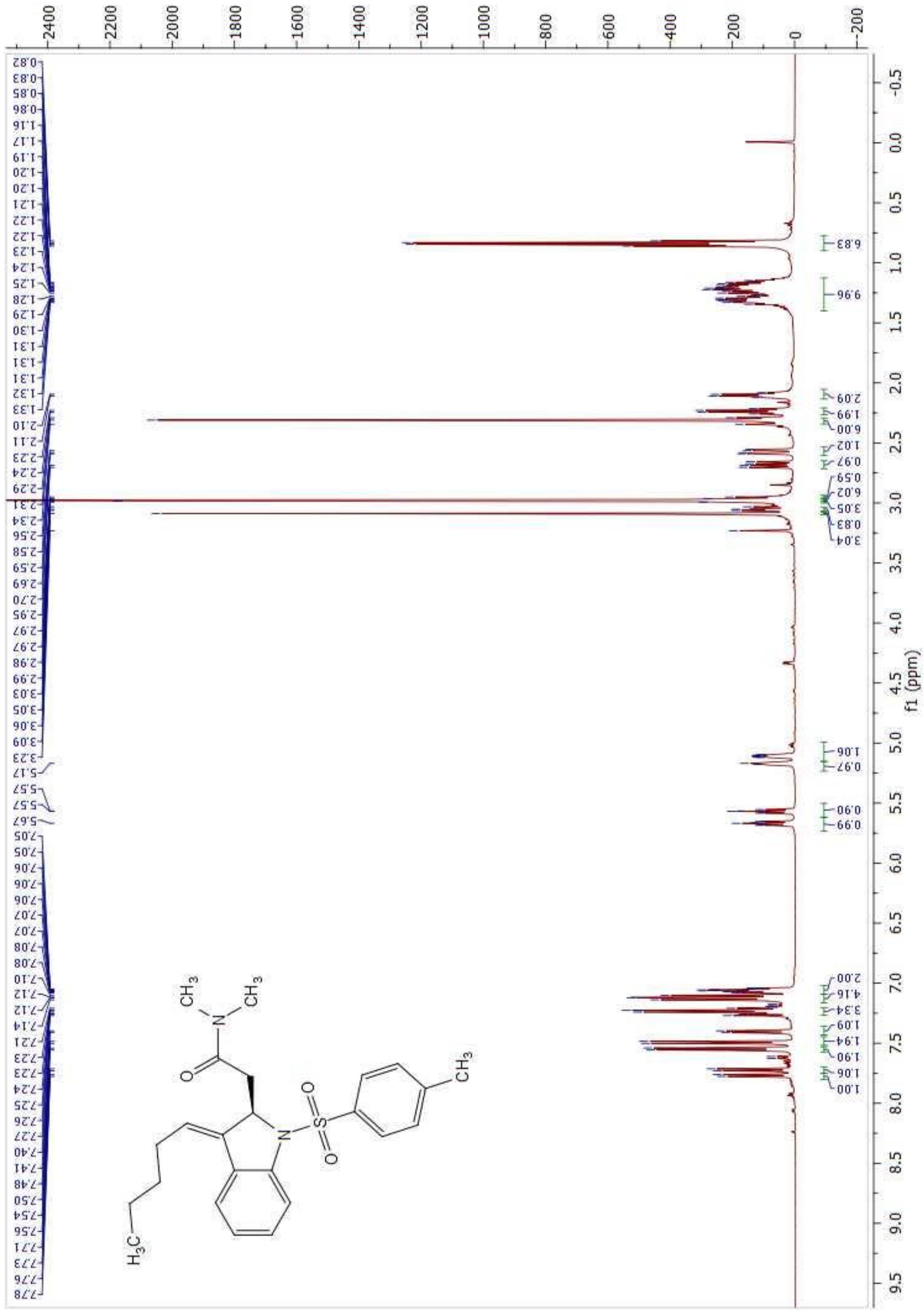


Figure 116. ^{1}H NMR spectrum of **173b** (500 MHz, $CDCl_3$).

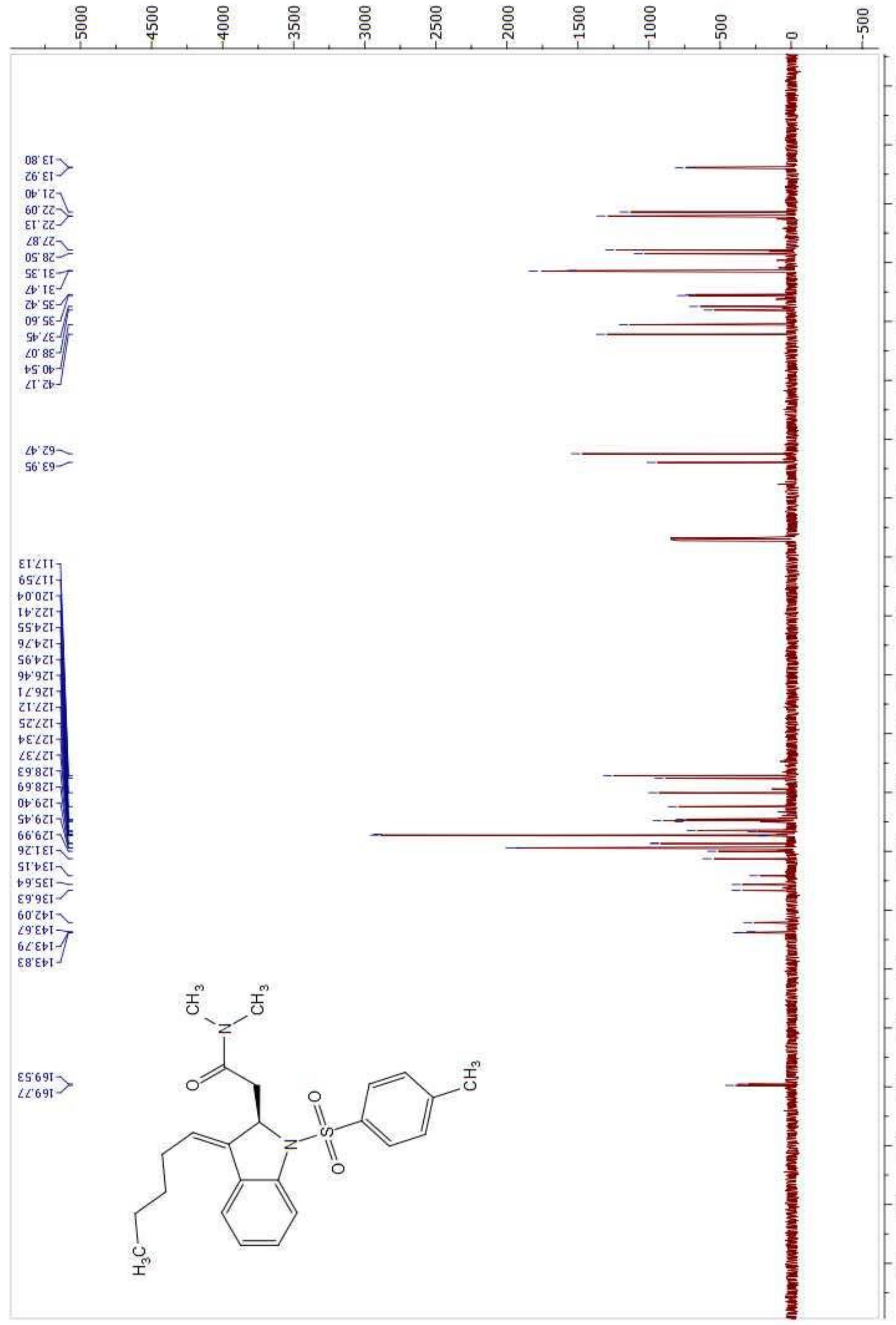


Figure 117. ^{13}C NMR spectrum of **173b** (125 MHz, CDCl$_3$).

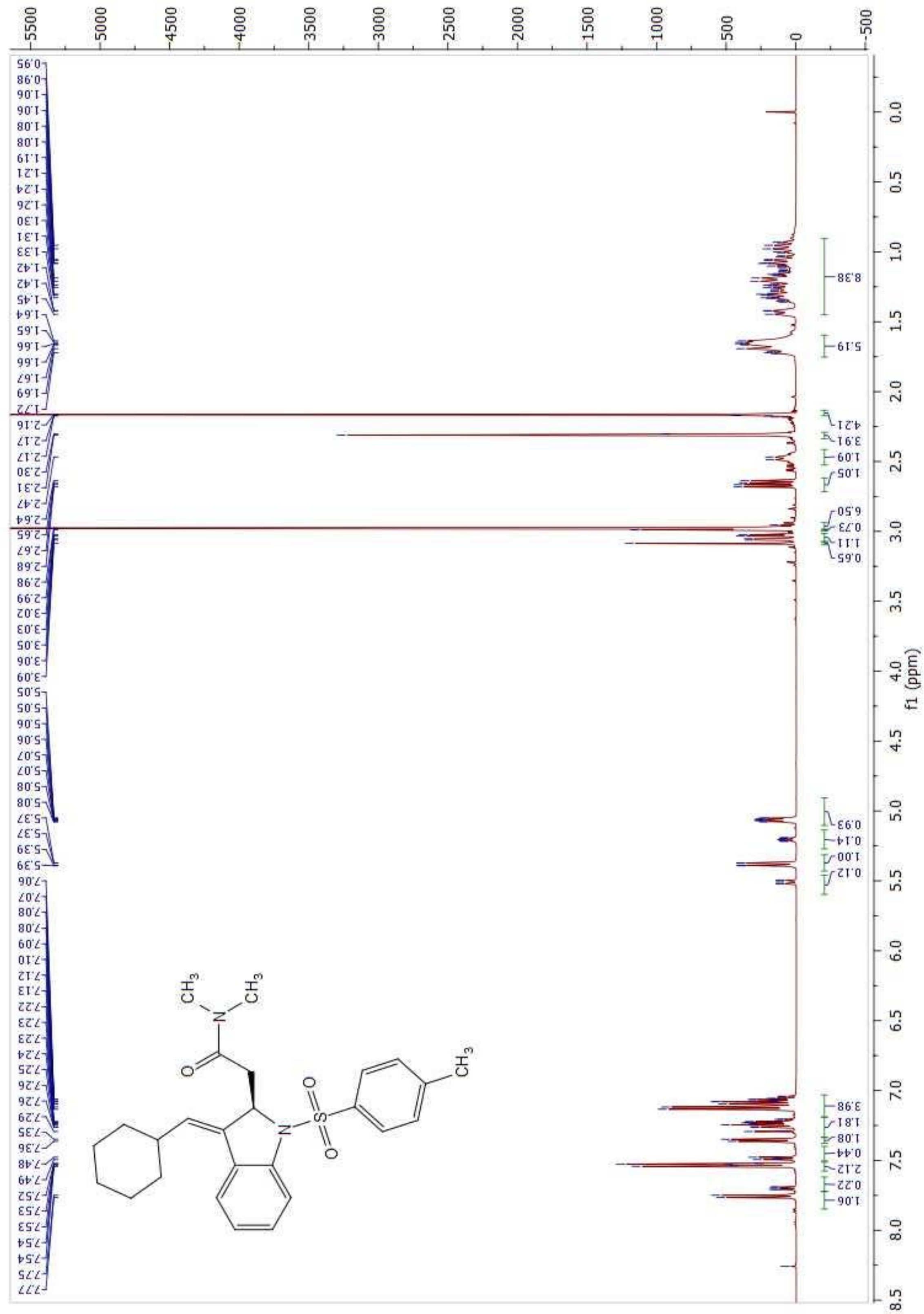


Figure 118. ^{1}H NMR spectrum of **173c** (500 MHz, $CDCl_3$).

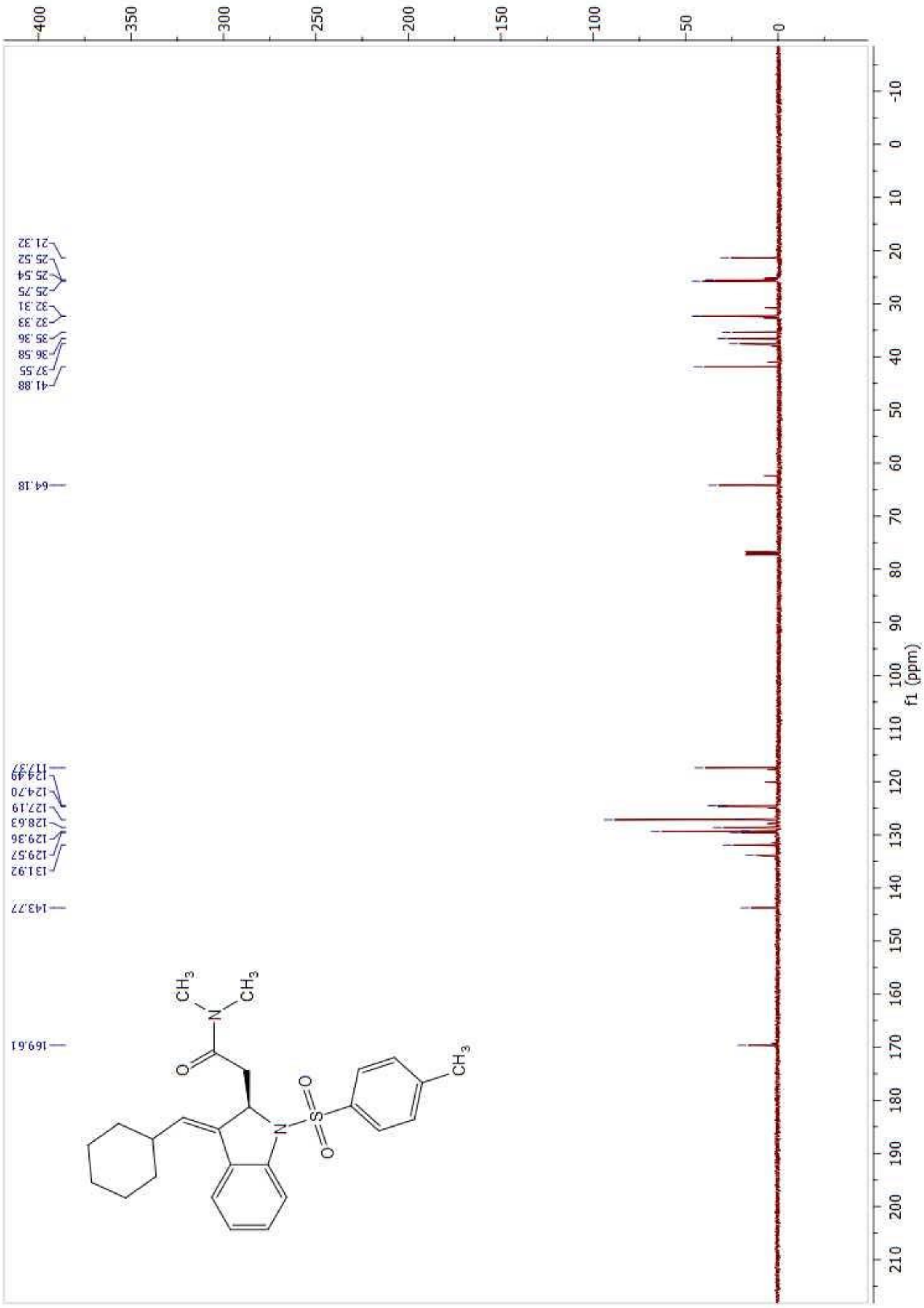


Figure 119. ^{13}C NMR spectrum of **173c** (125 MHz, $CDCl_3$).

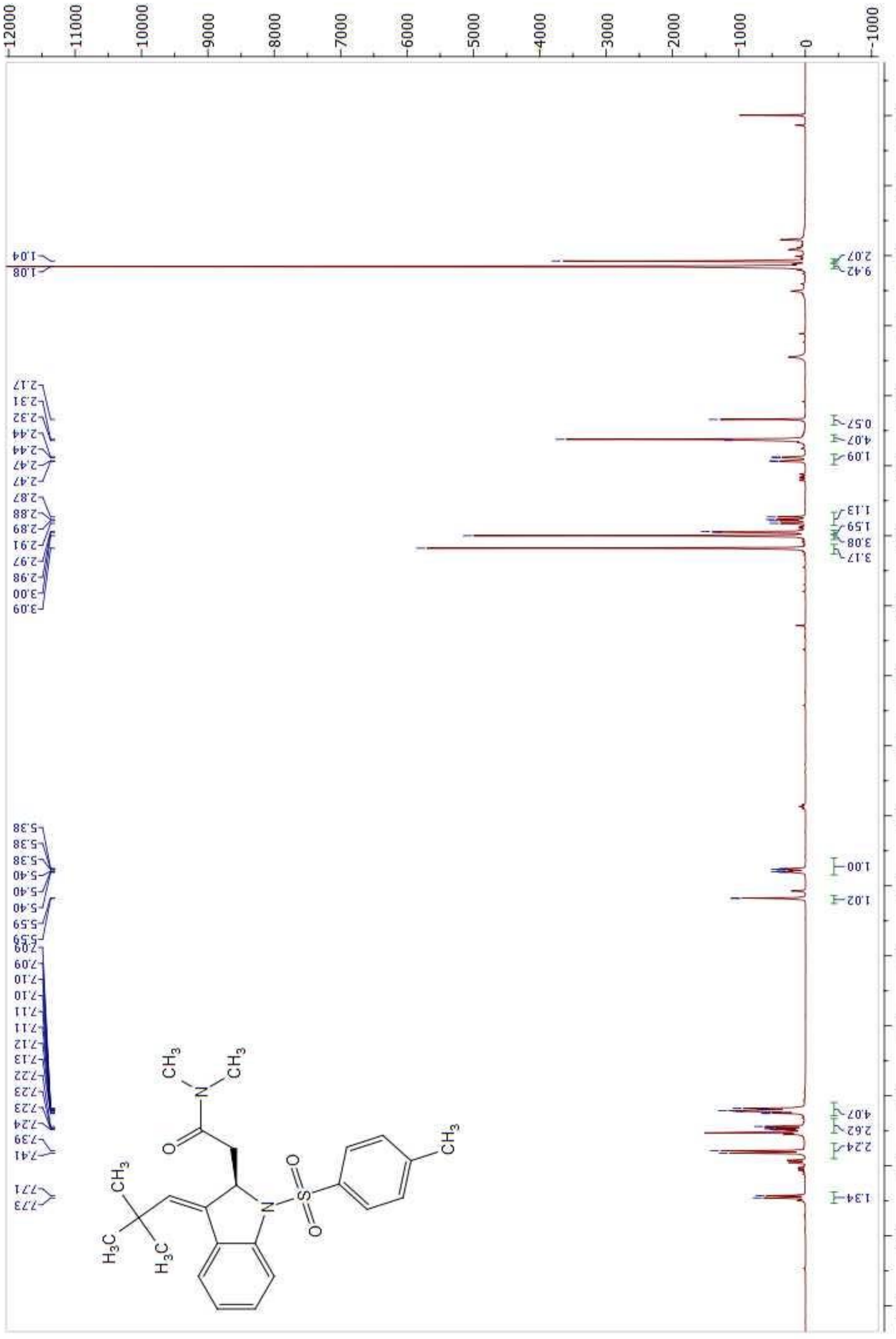


Figure 120. ^{1}H NMR spectrum of **173d** (500 MHz, $CDCl_3$).

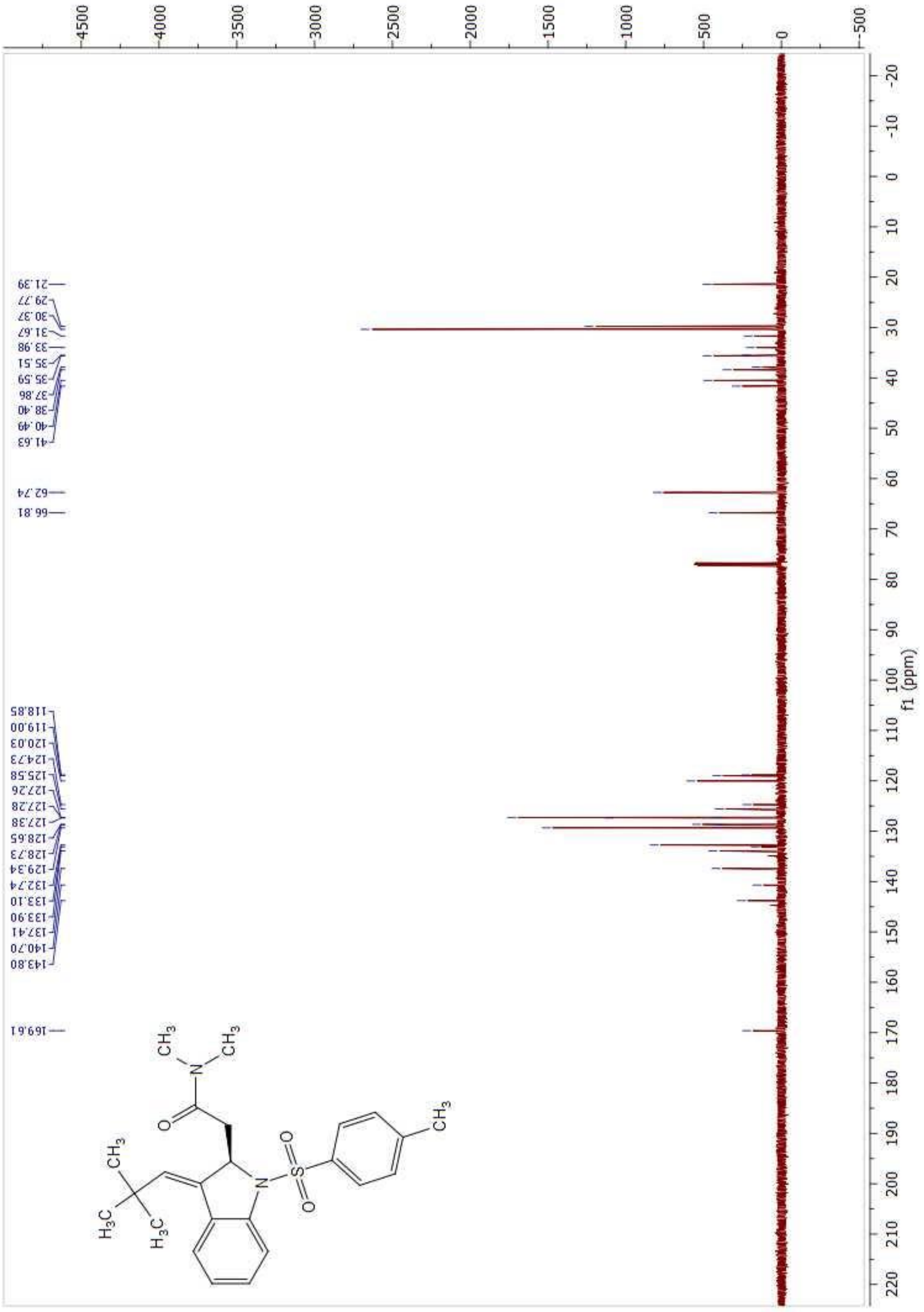


Figure 121. ^{13}C NMR spectrum of **173d** (125 MHz, CDCl$_3$).

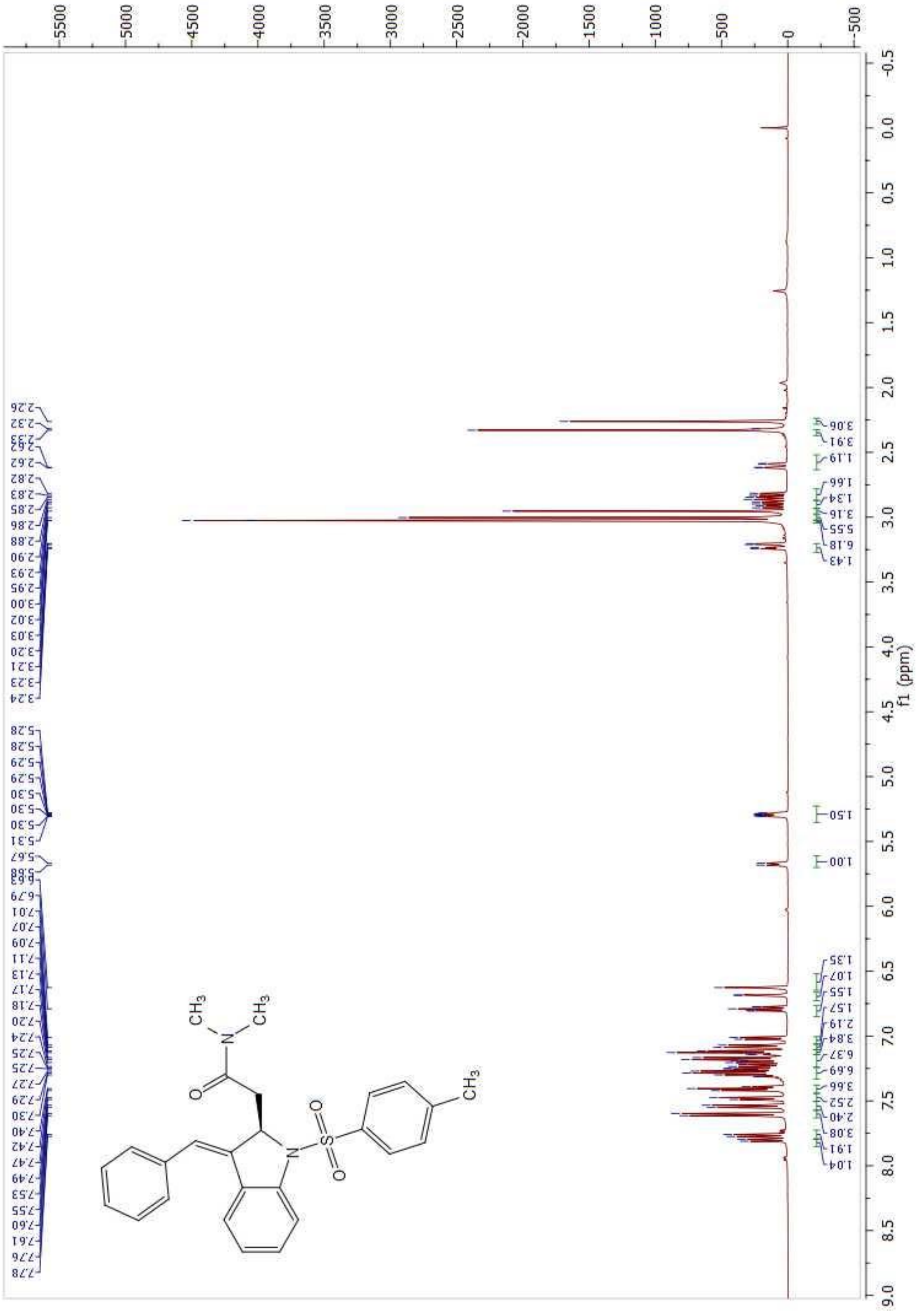


Figure 122. ^{1}H NMR spectrum of **173e** (500 MHz, CDCl$_3$).

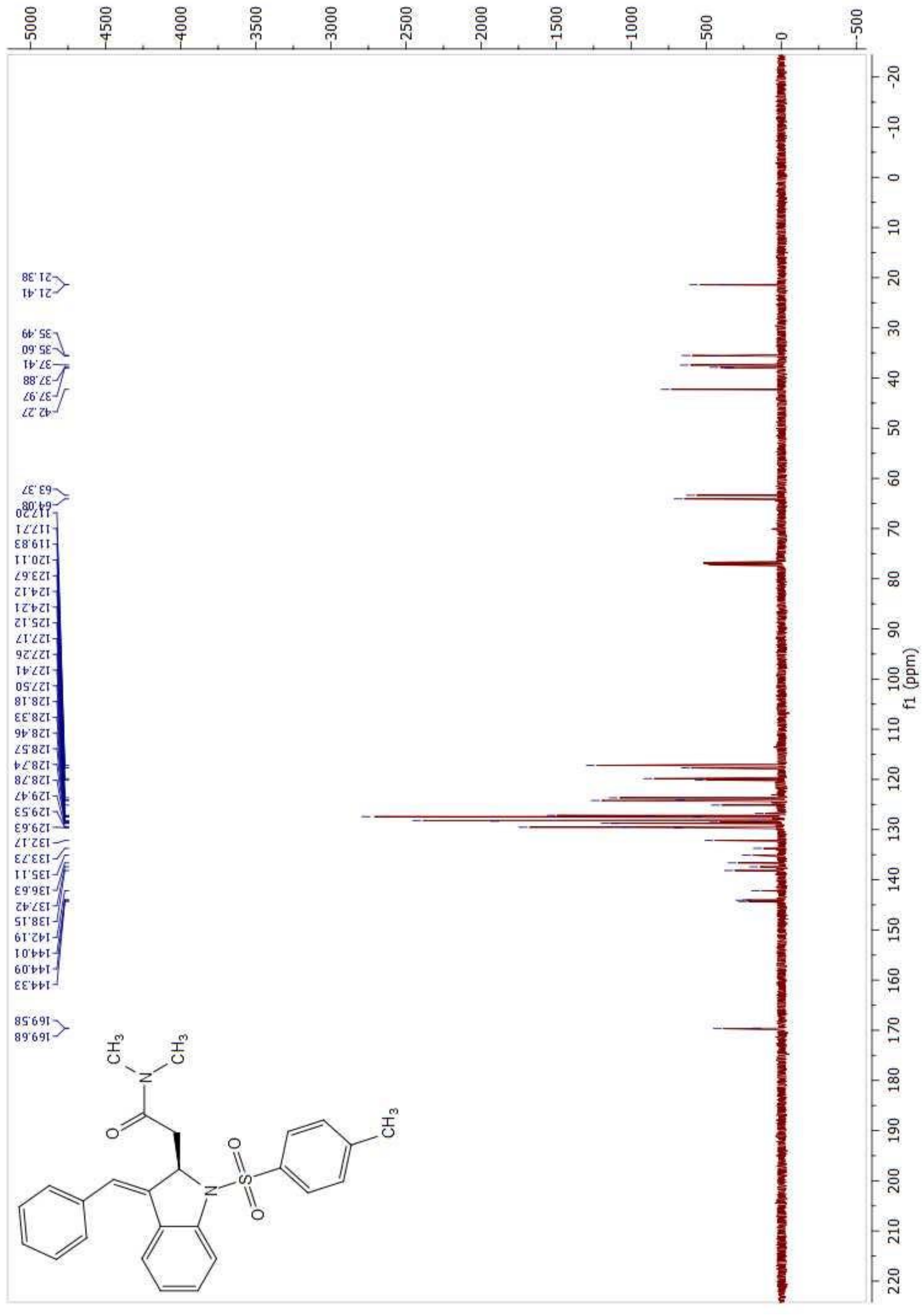


Figure 123. ^{13}C NMR spectrum of **173e** (125 MHz, CDCl$_3$).

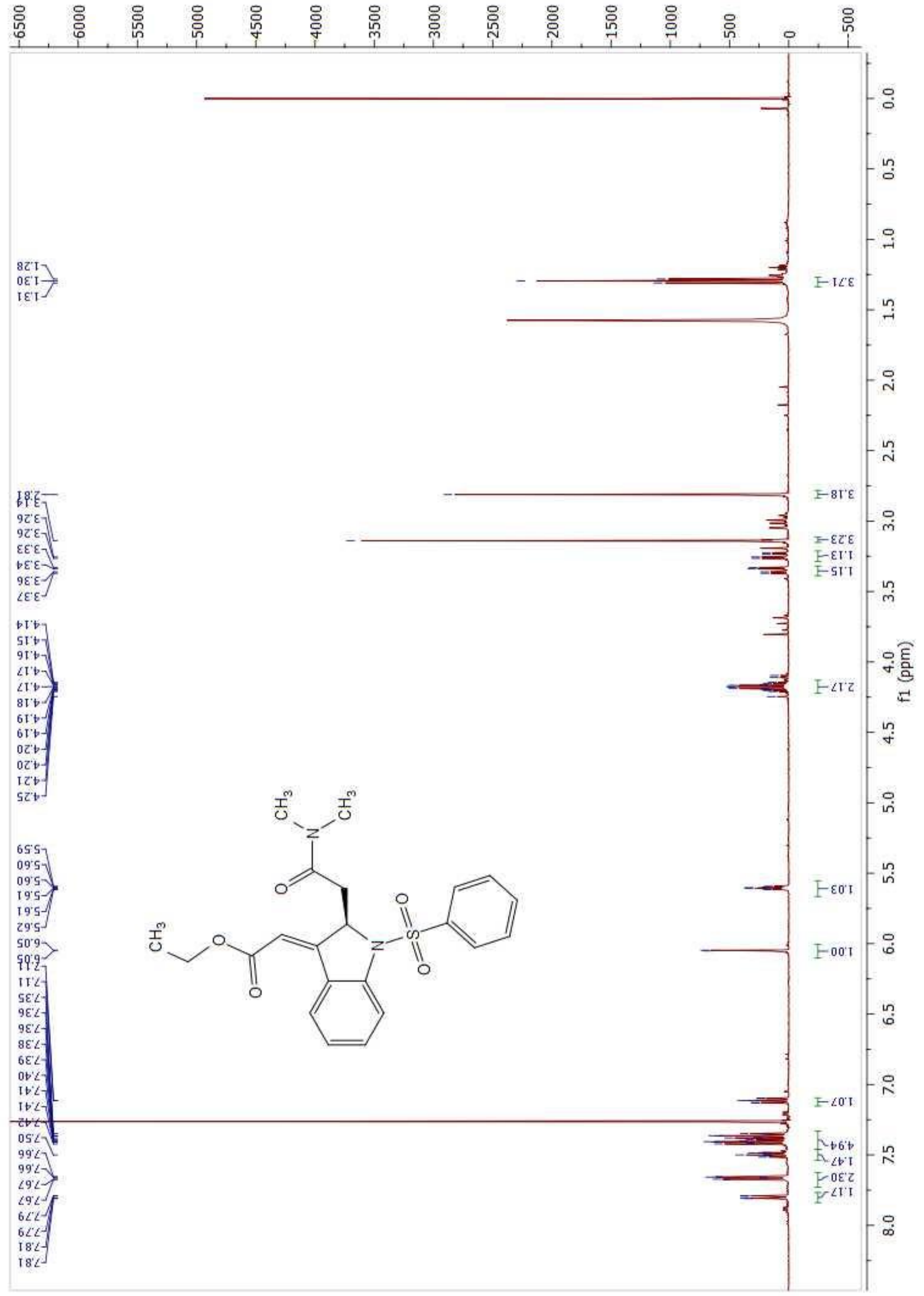


Figure 124. ^{1}H NMR spectrum of **173f** (500 MHz, $CDCl_3$).

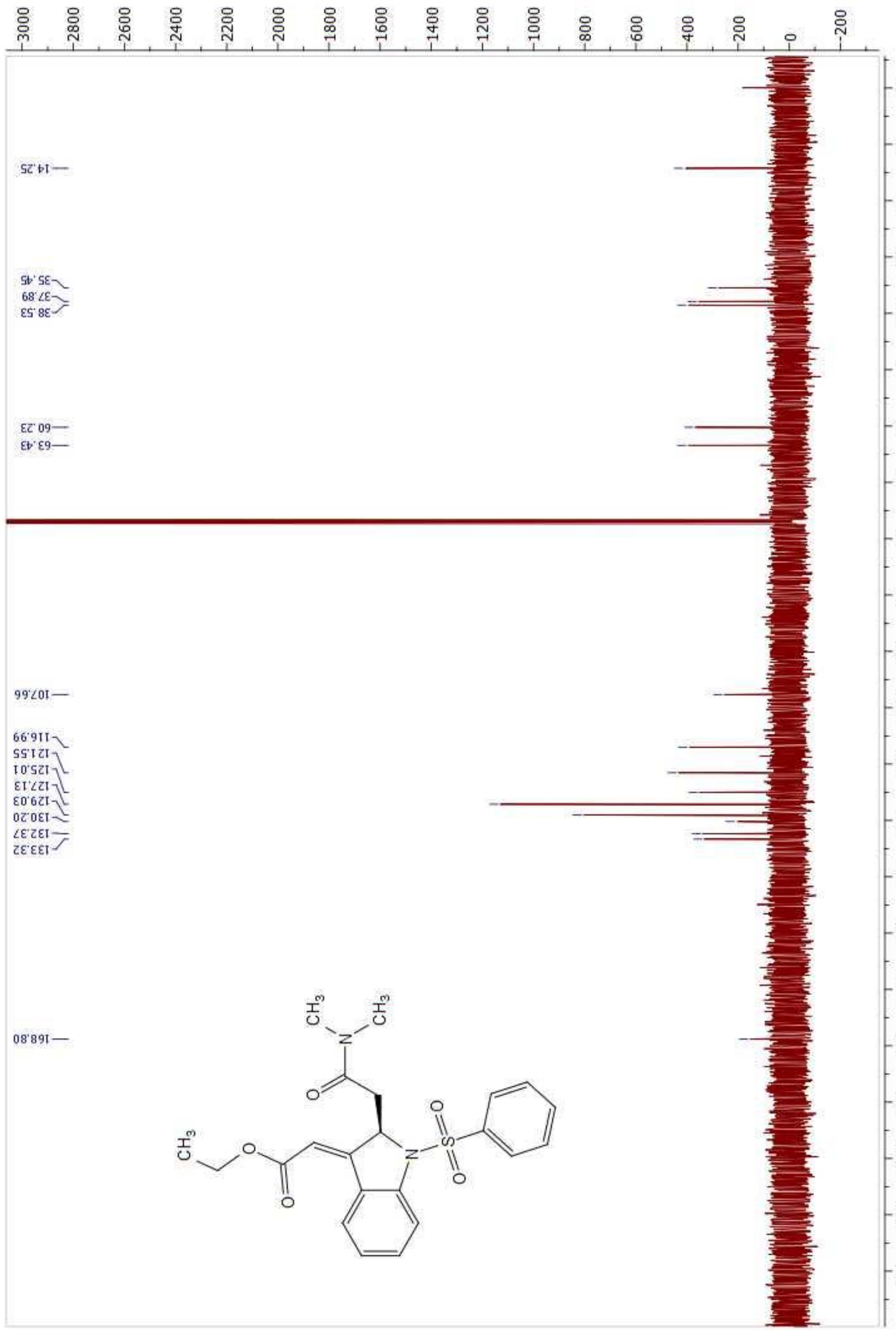


Figure 125. ^{13}C NMR spectrum of **173f** (125 MHz, $CDCl_3$).

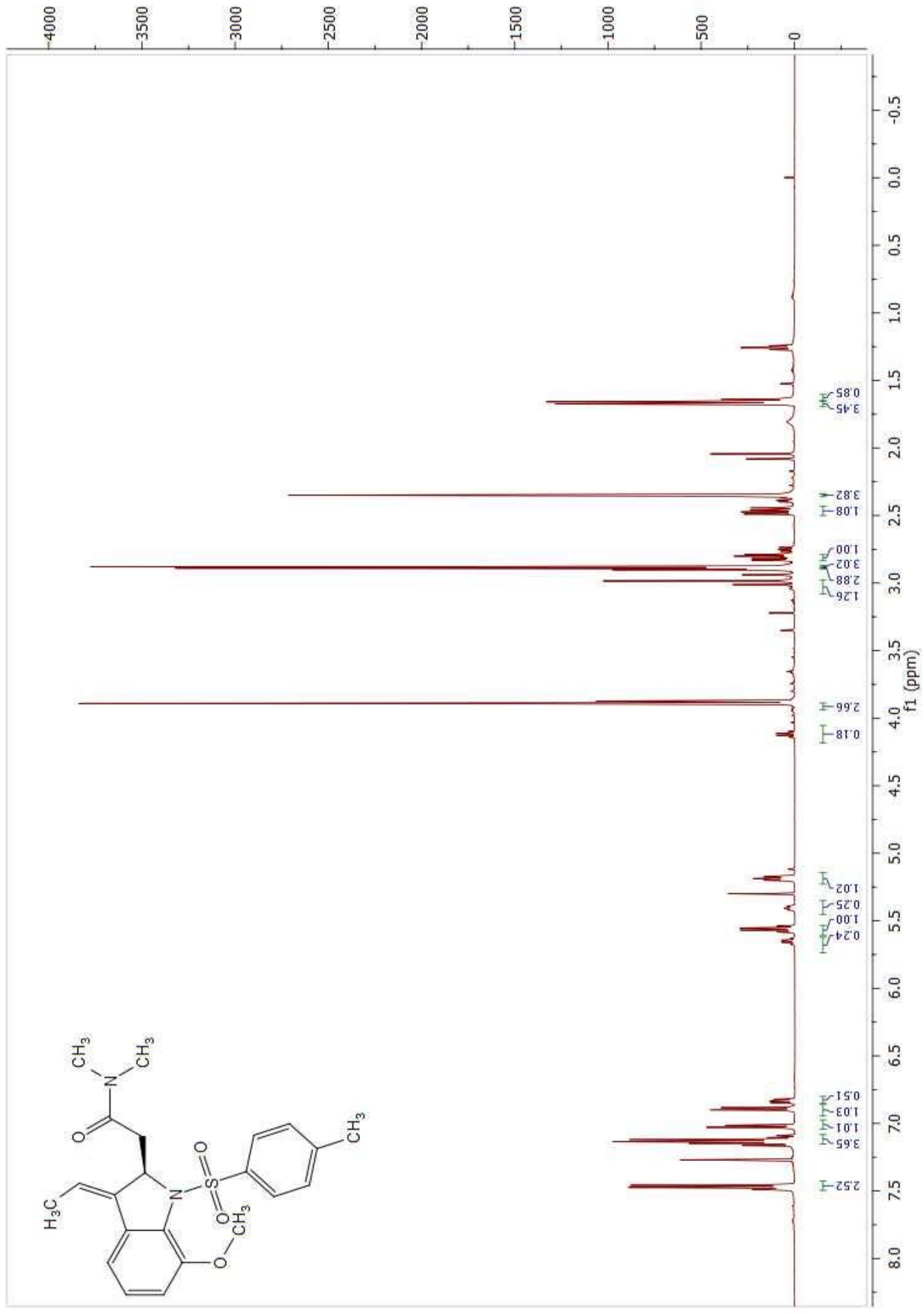


Figure 126. ^{1}H NMR spectrum of **173g** (500 MHz, $CDCl_3$).

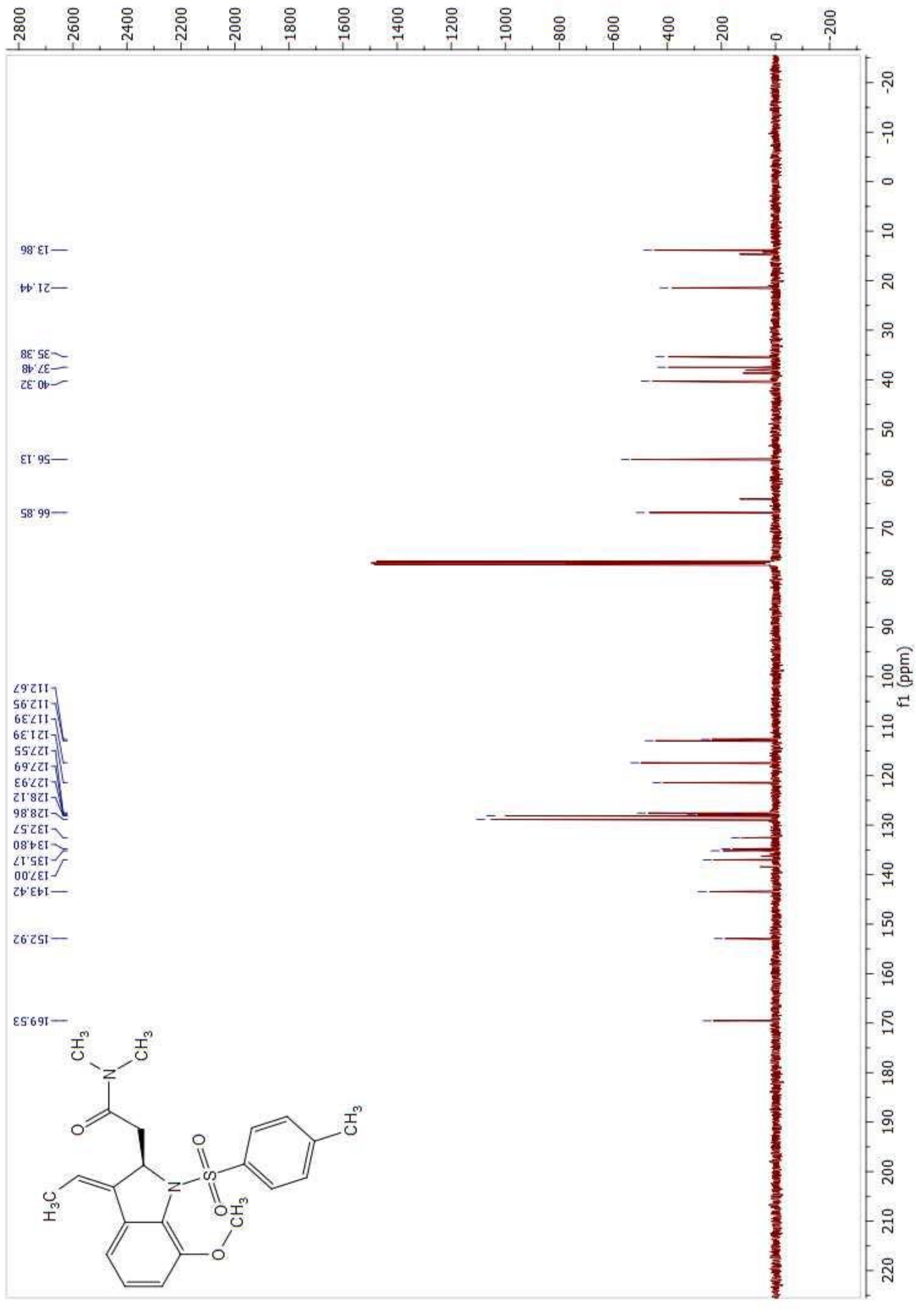


Figure 127. ^{13}C NMR spectrum of **173g** (125 MHz, $CDCl_3$).

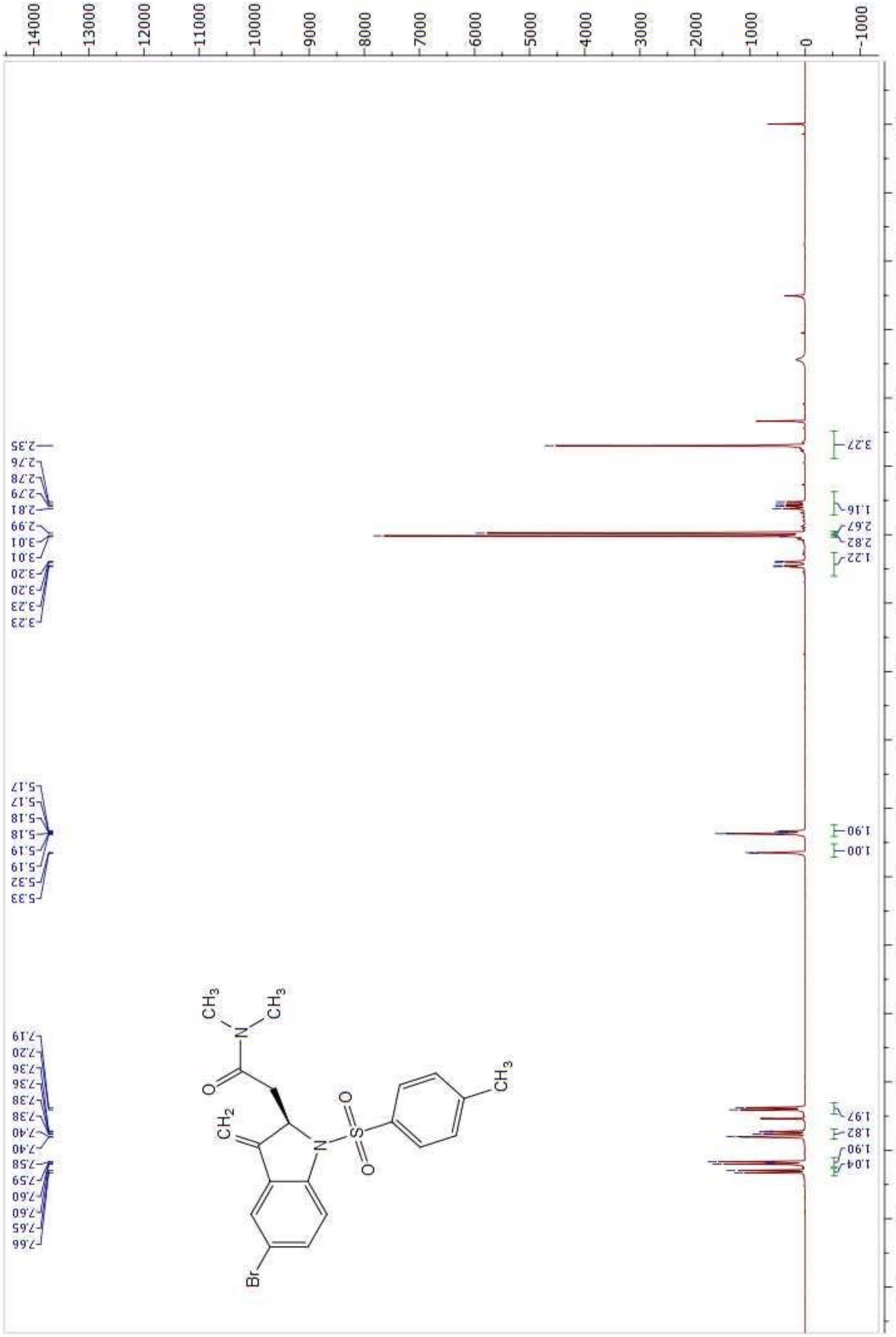


Figure 128. ^{1}H NMR spectrum of **173h** (500 MHz, $CDCl_3$).

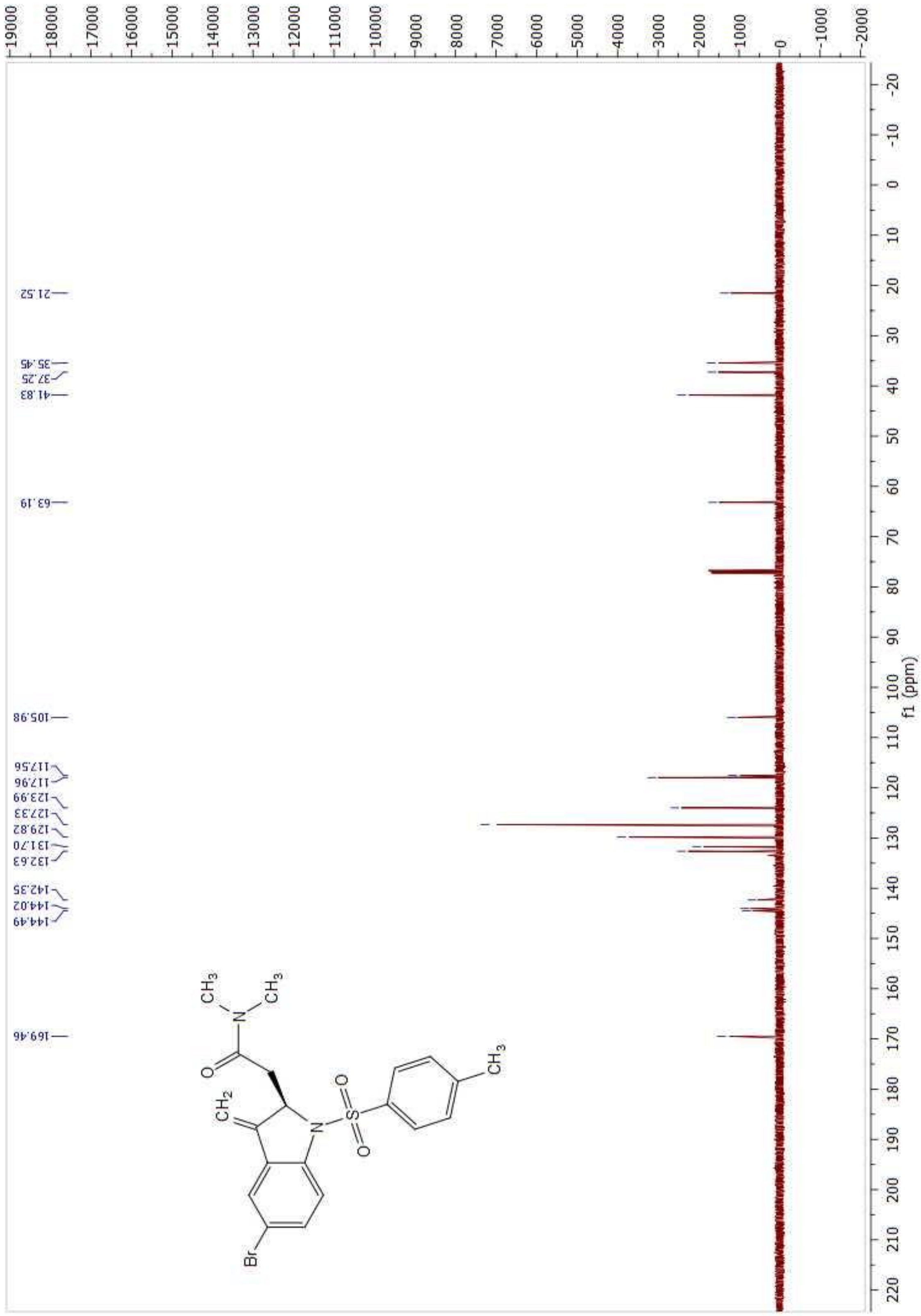


Figure 129. ^{13}C NMR spectrum of **173h** (125 MHz, CDCl$_3$).

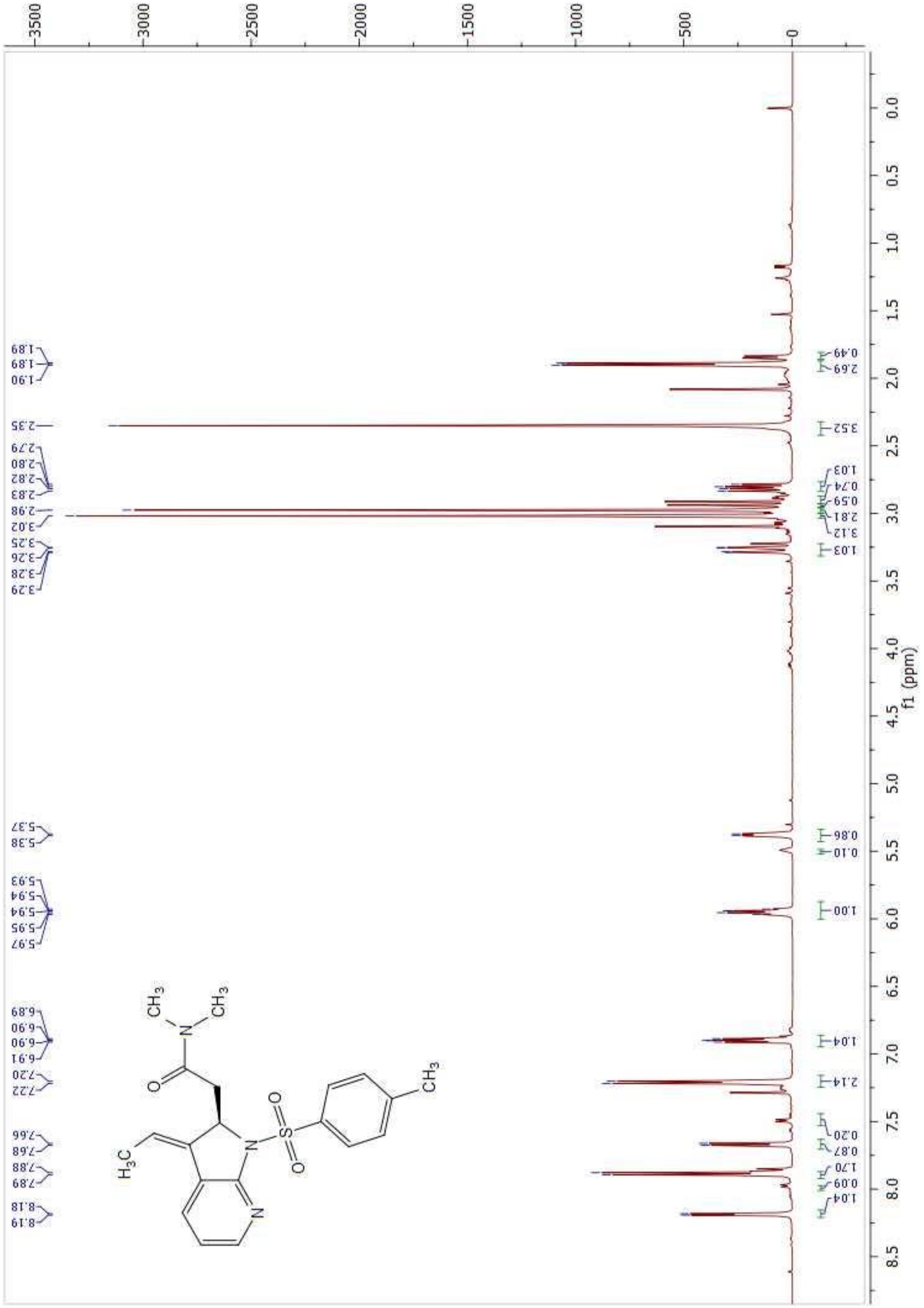


Figure 130. ^{1}H NMR spectrum of **173i** (500 MHz, $CDCl_3$).

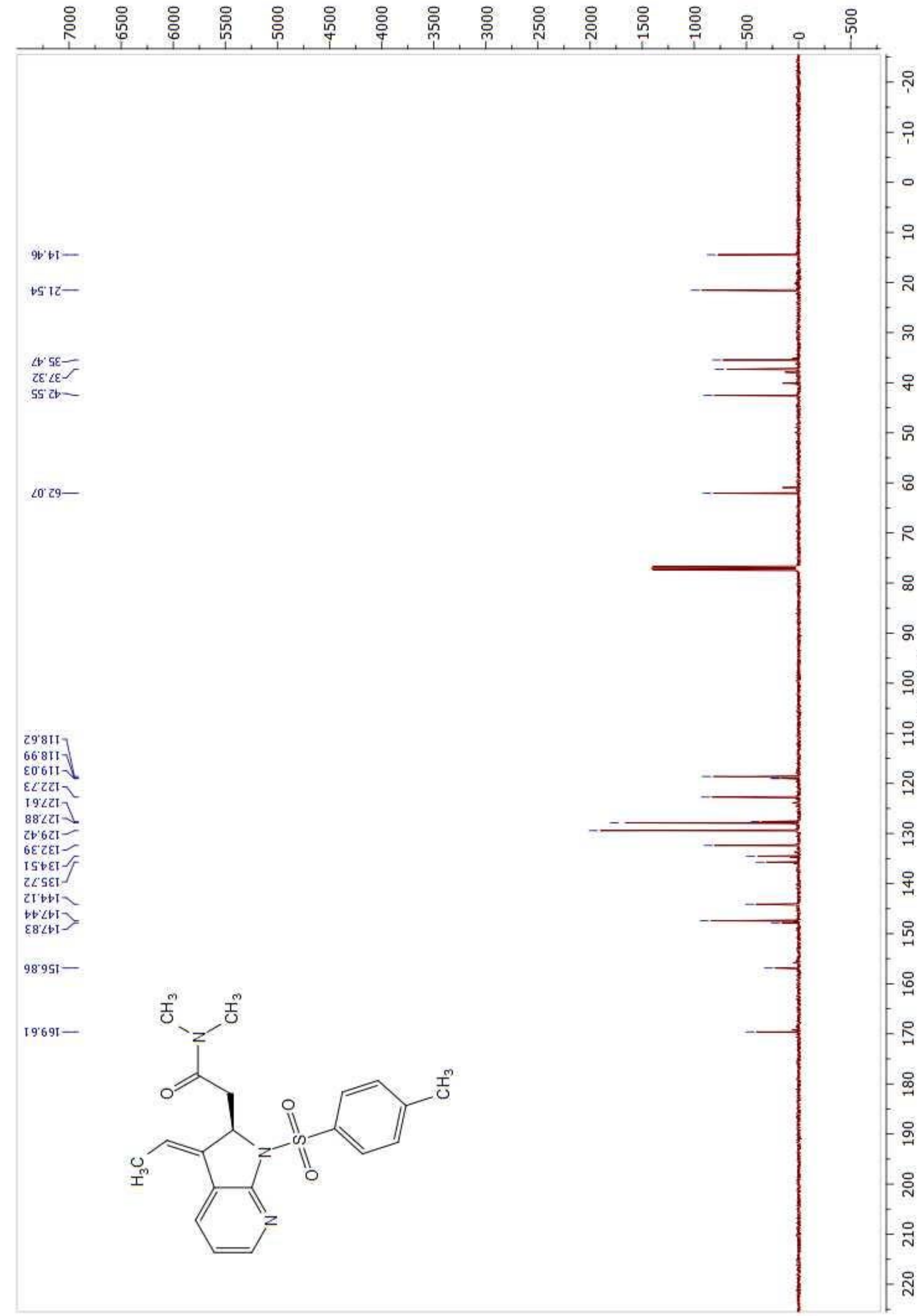


Figure 131. ^{13}C NMR spectrum of **173i** (125 MHz, $CDCl_3$).

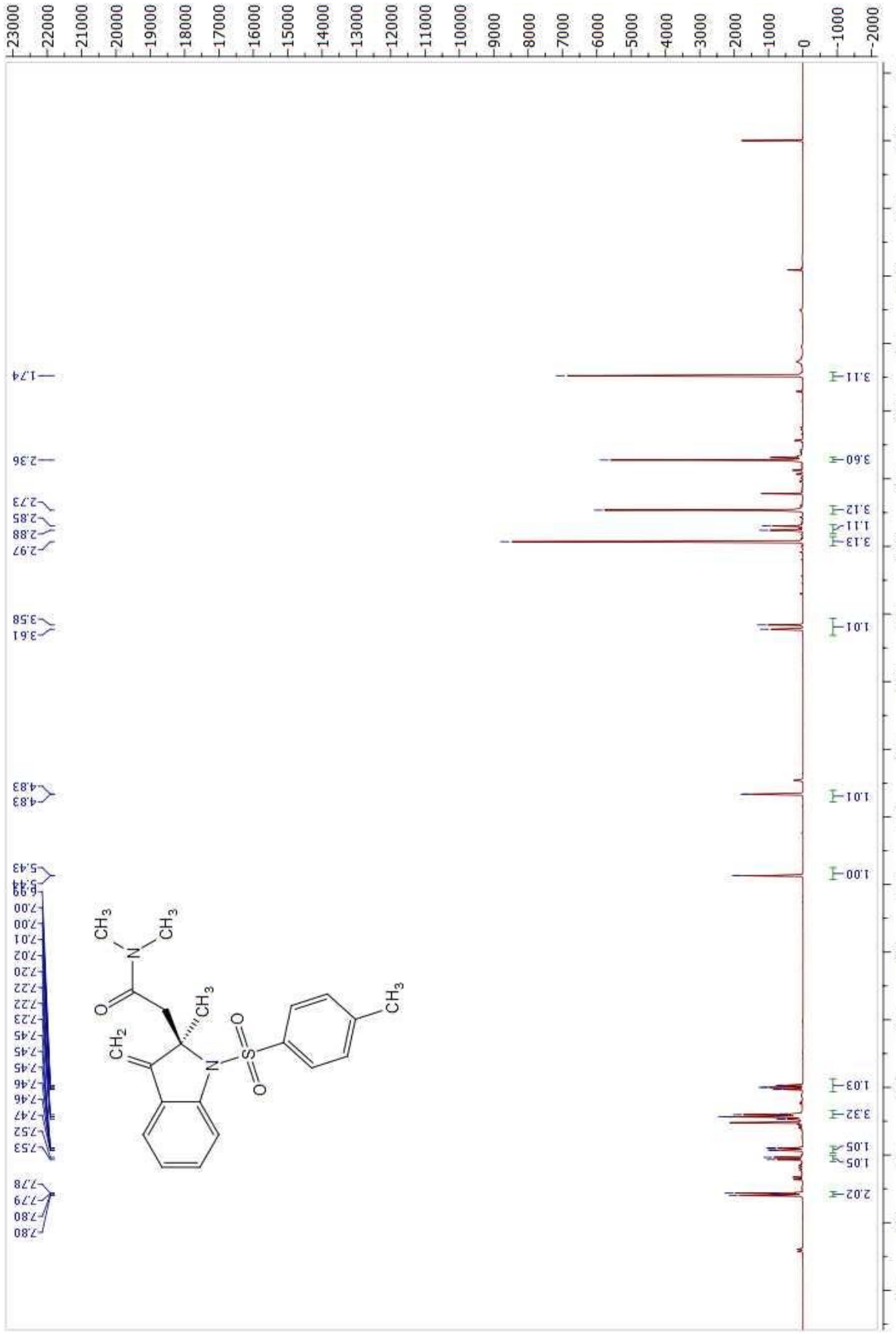


Figure 132. ^{1}H NMR spectrum of **173k** (500 MHz, $CDCl_3$).

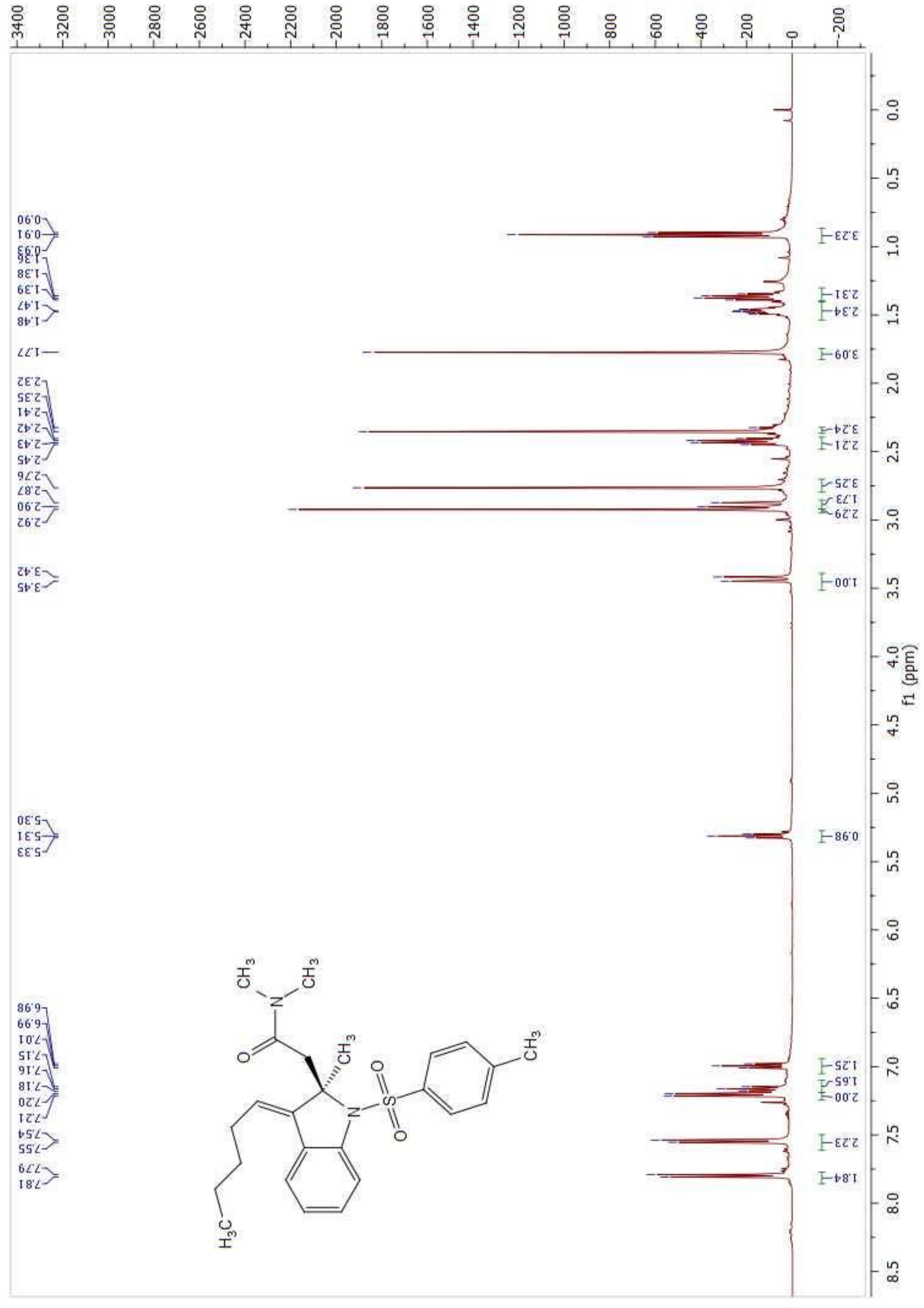


Figure 133. ^{1}H NMR spectrum of **173l** (500 MHz, $CDCl_3$).

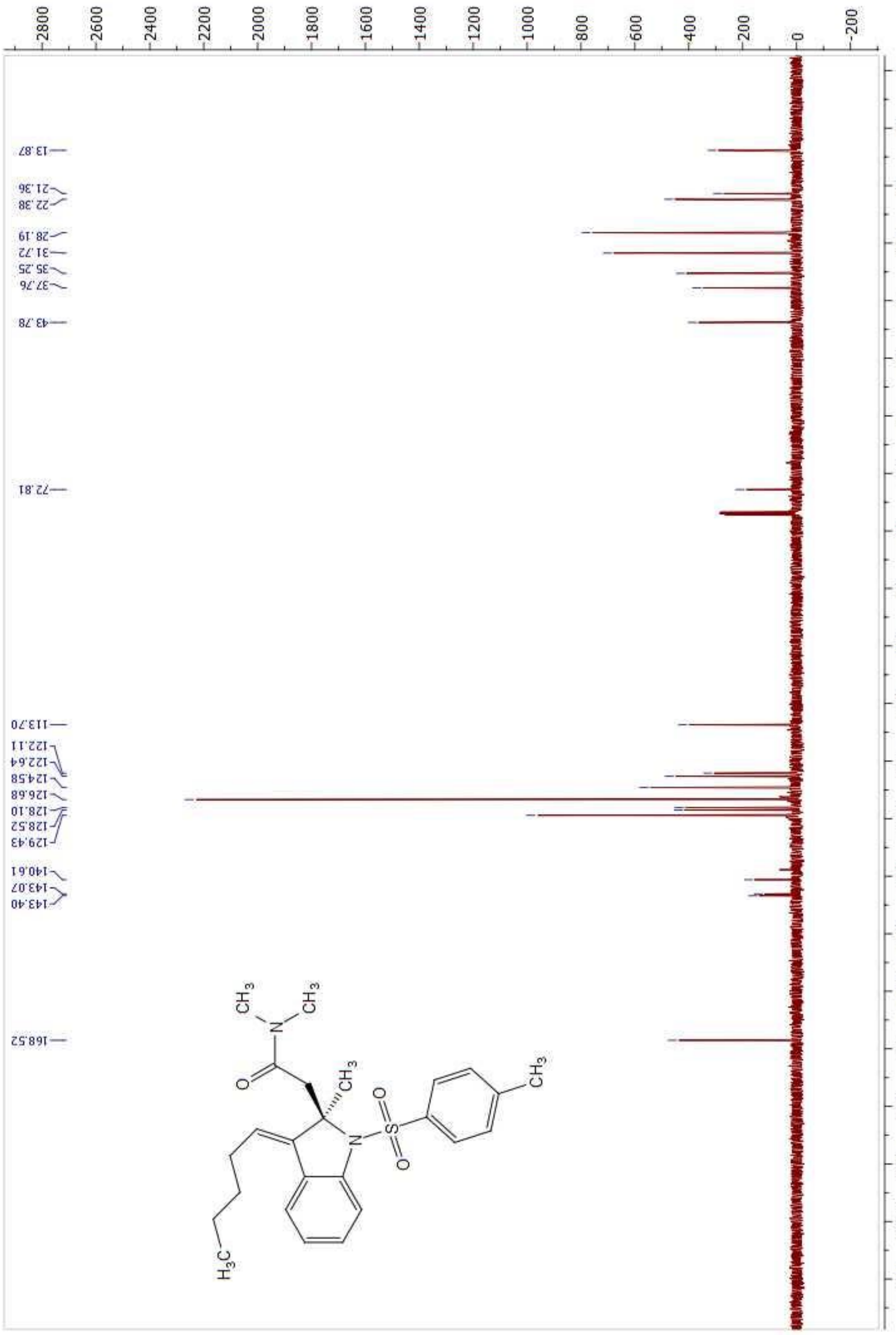


Figure 134. ^{13}C NMR spectrum of **173l** (125 MHz, $CDCl_3$).

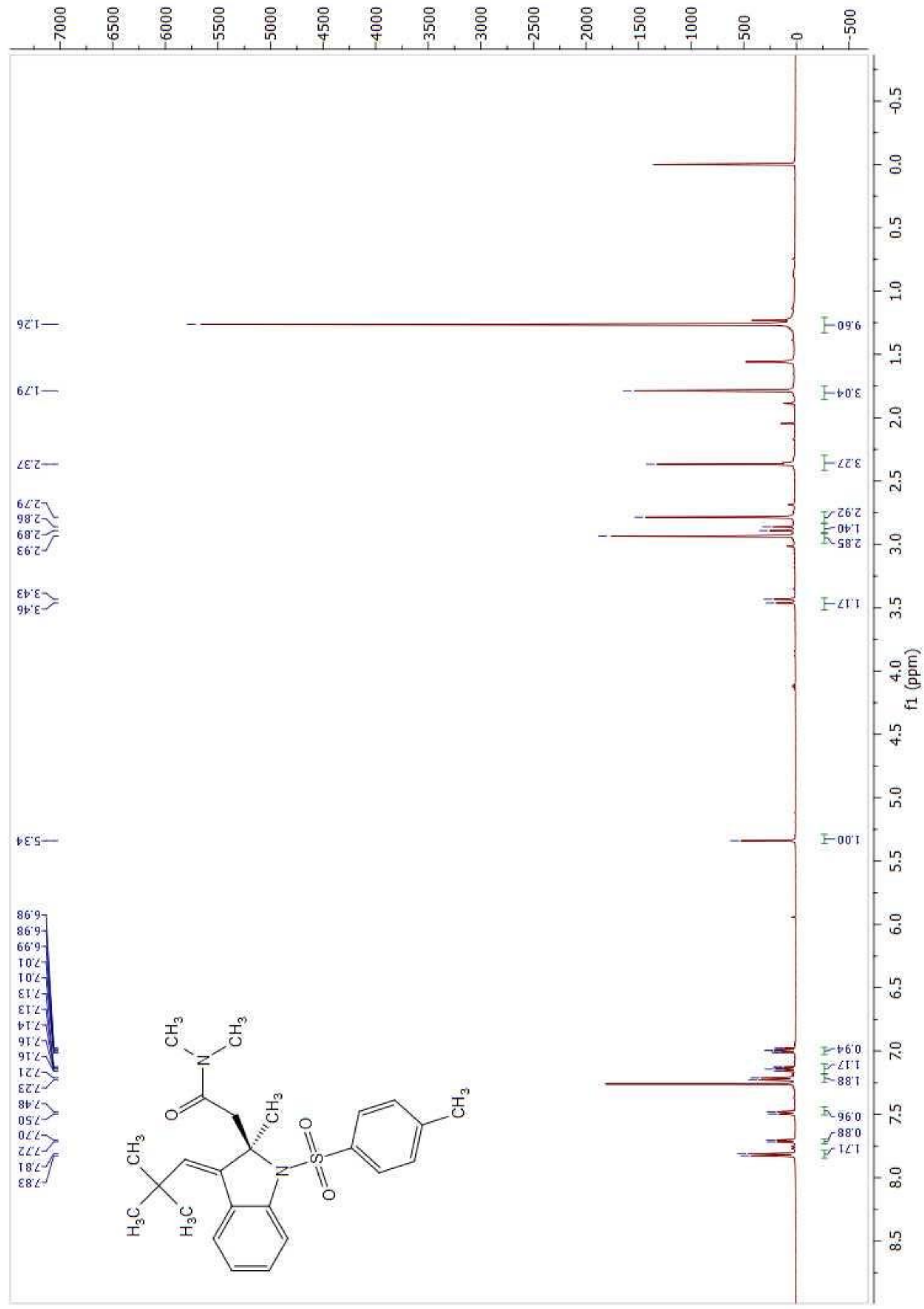


Figure 135. ^{1}H NMR spectrum of **173m** (500 MHz, $CDCl_3$).

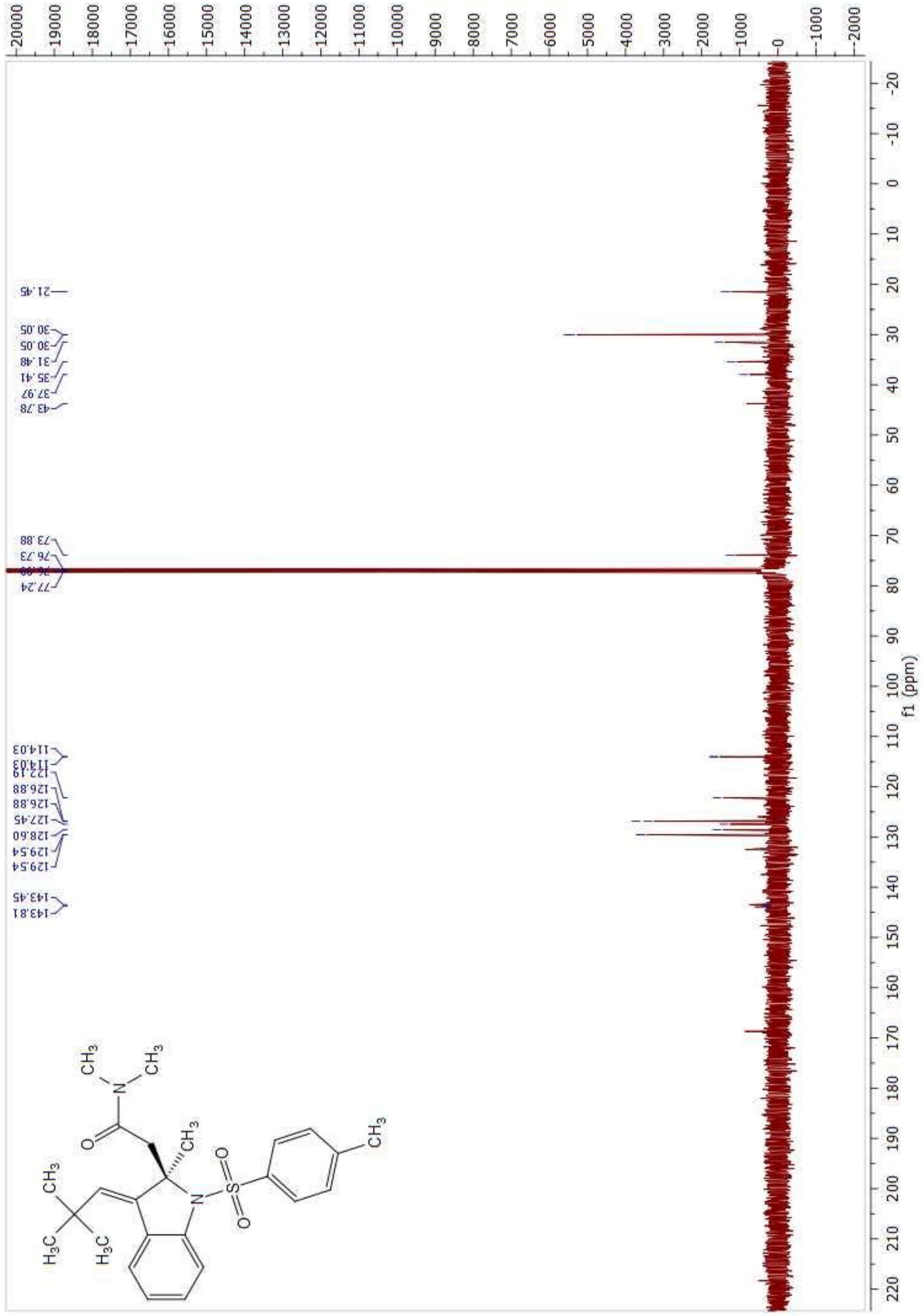


Figure 136. ^{13}C NMR spectrum of **173m** (125 MHz, CDCl$_3$).

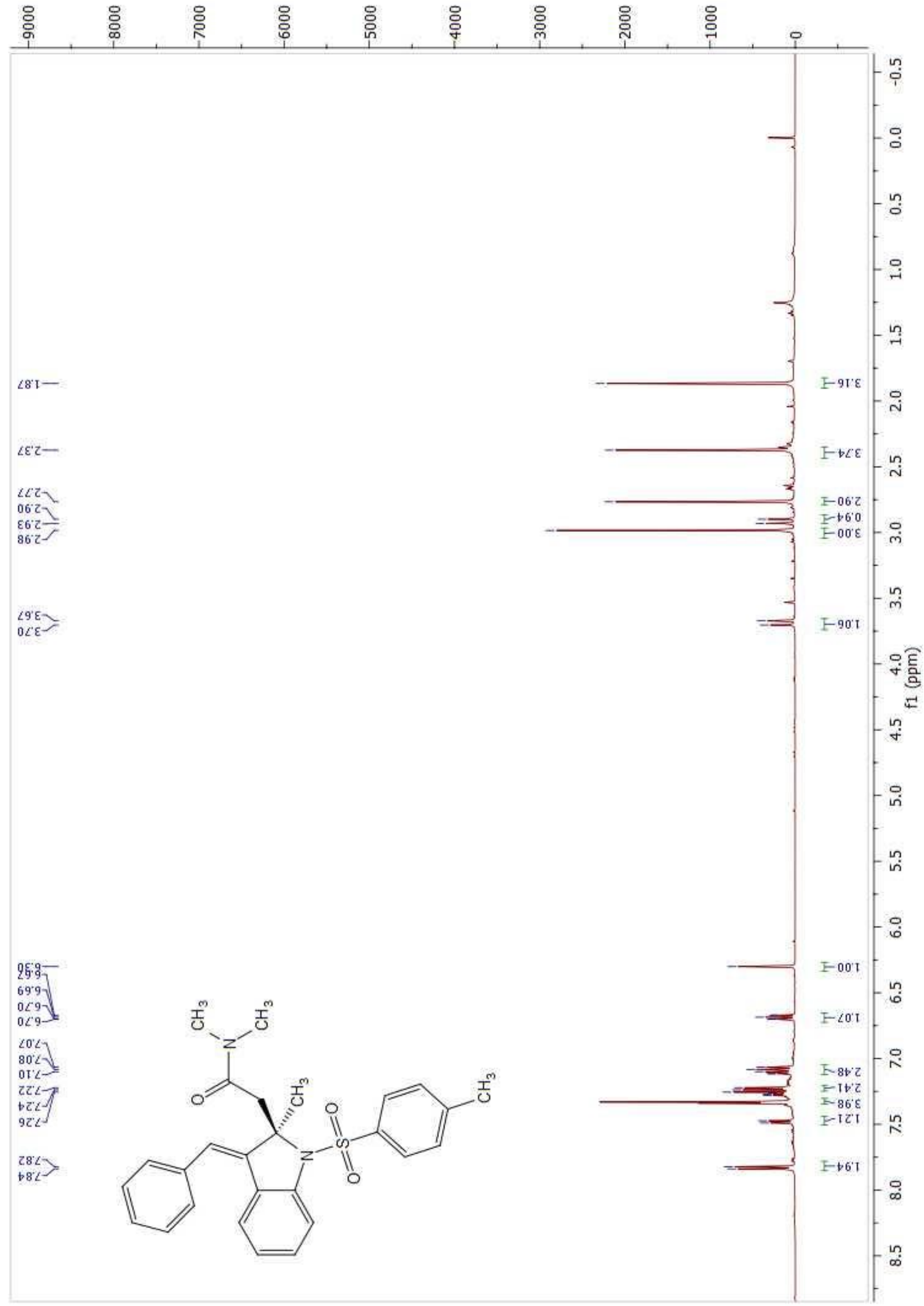


Figure 137. ^{1}H NMR spectrum of **173n** (500 MHz, $CDCl_3$).

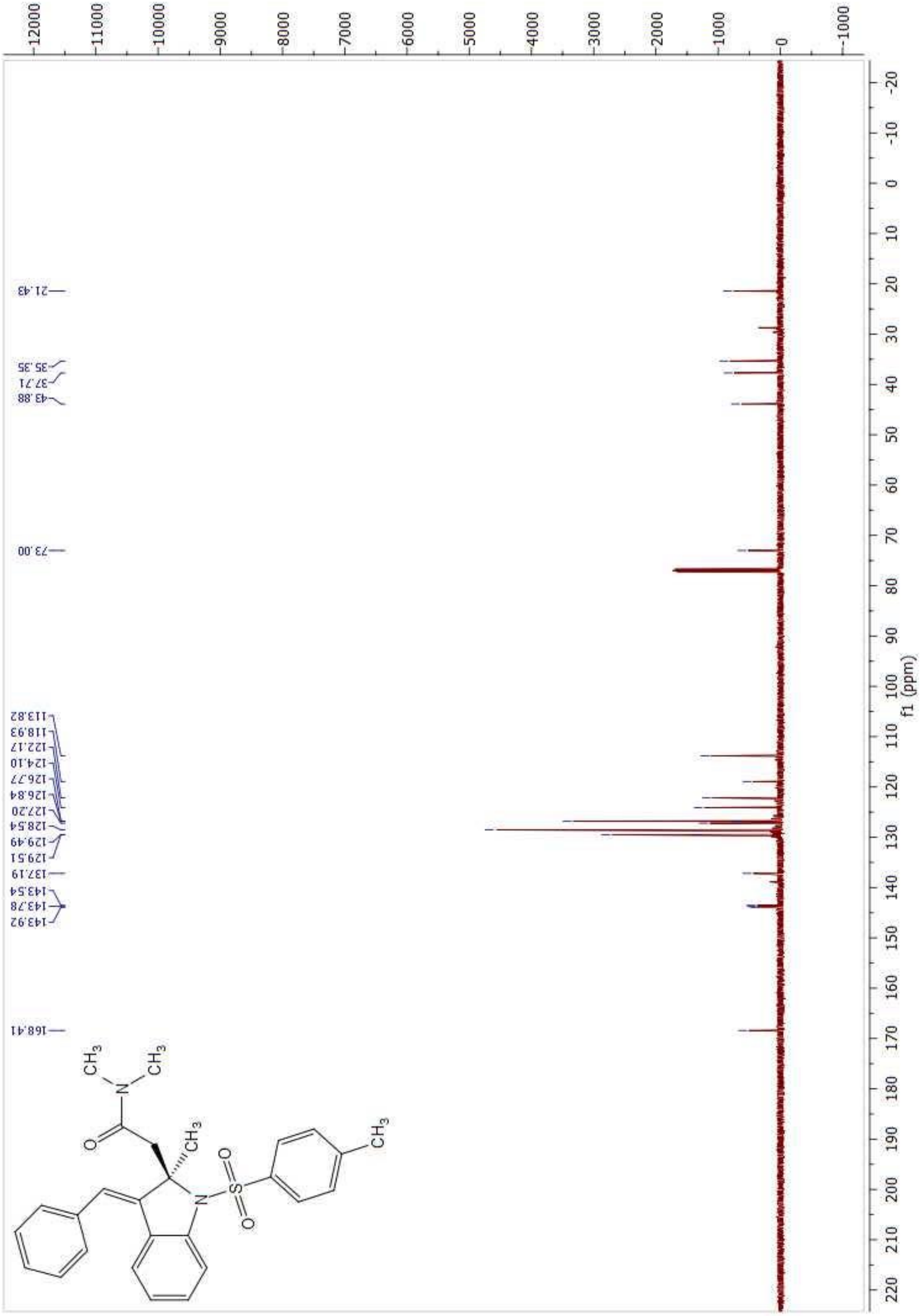


Figure 138. ^{13}C NMR spectrum of **173n** (125 MHz, $CDCl_3$).

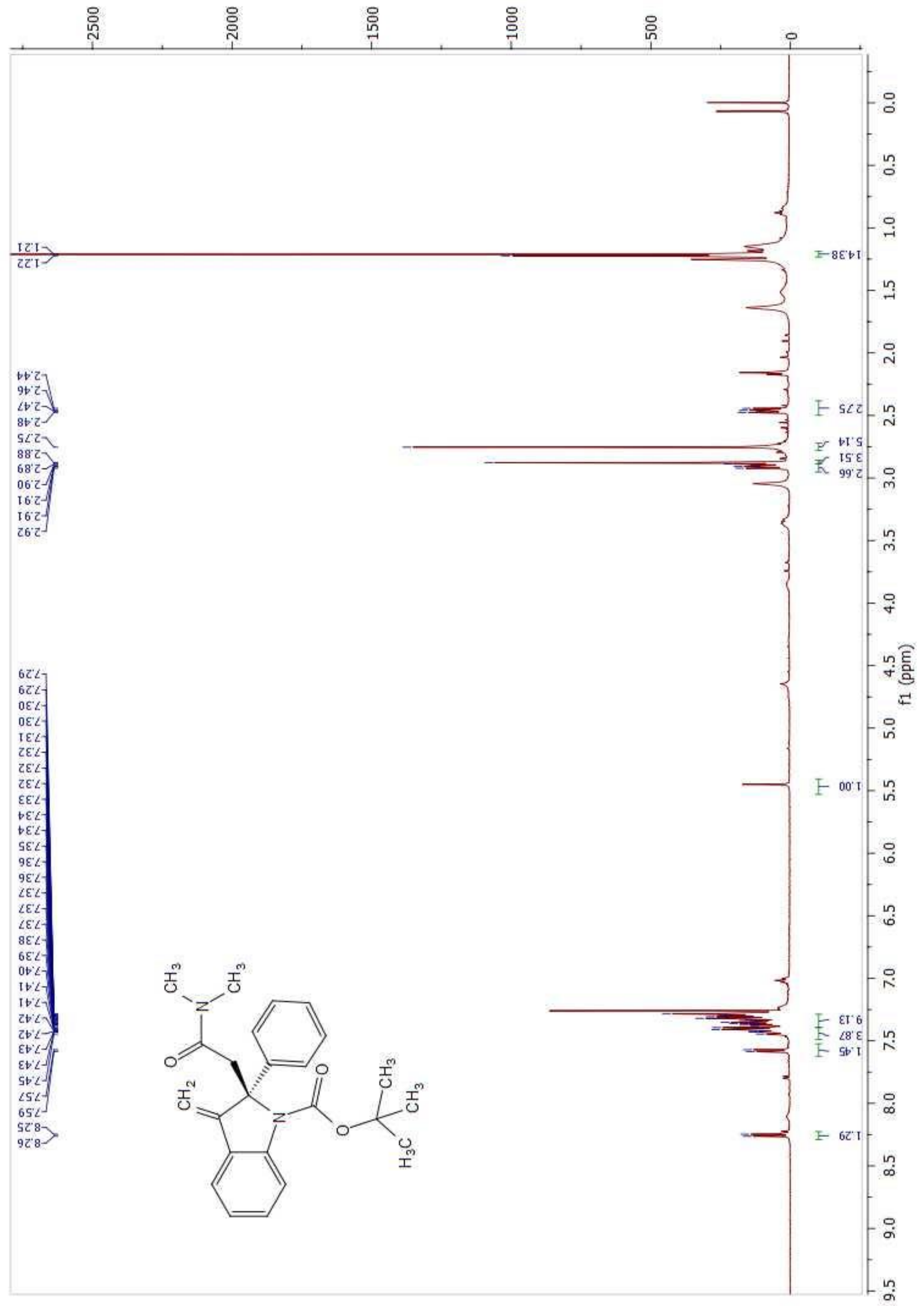


Figure 139. ^{1}H NMR spectrum of **173o** (500 MHz, $CDCl_3$).

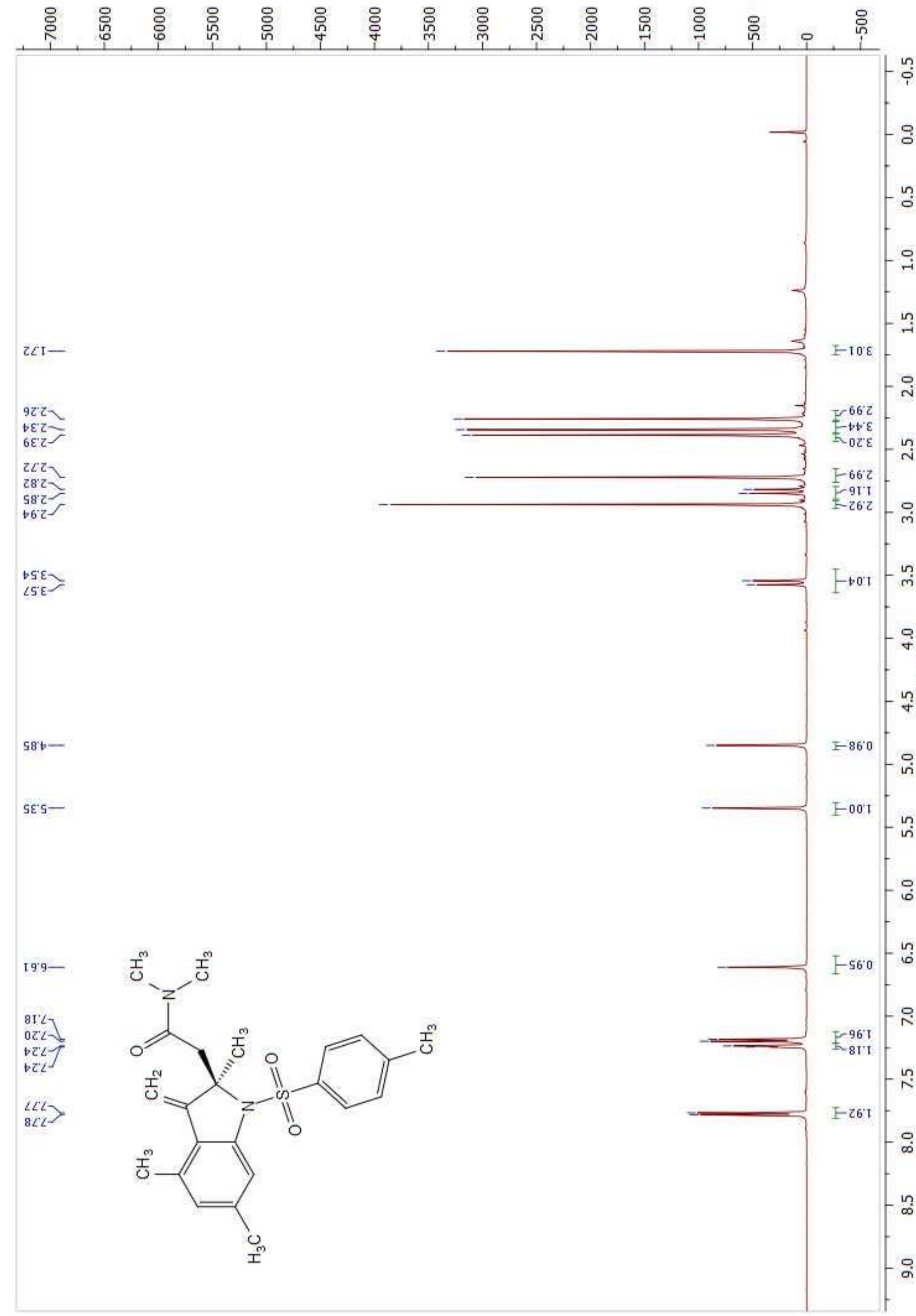


Figure 140. ^{1}H NMR spectrum of **173p** (500 MHz, CDCl$_3$).

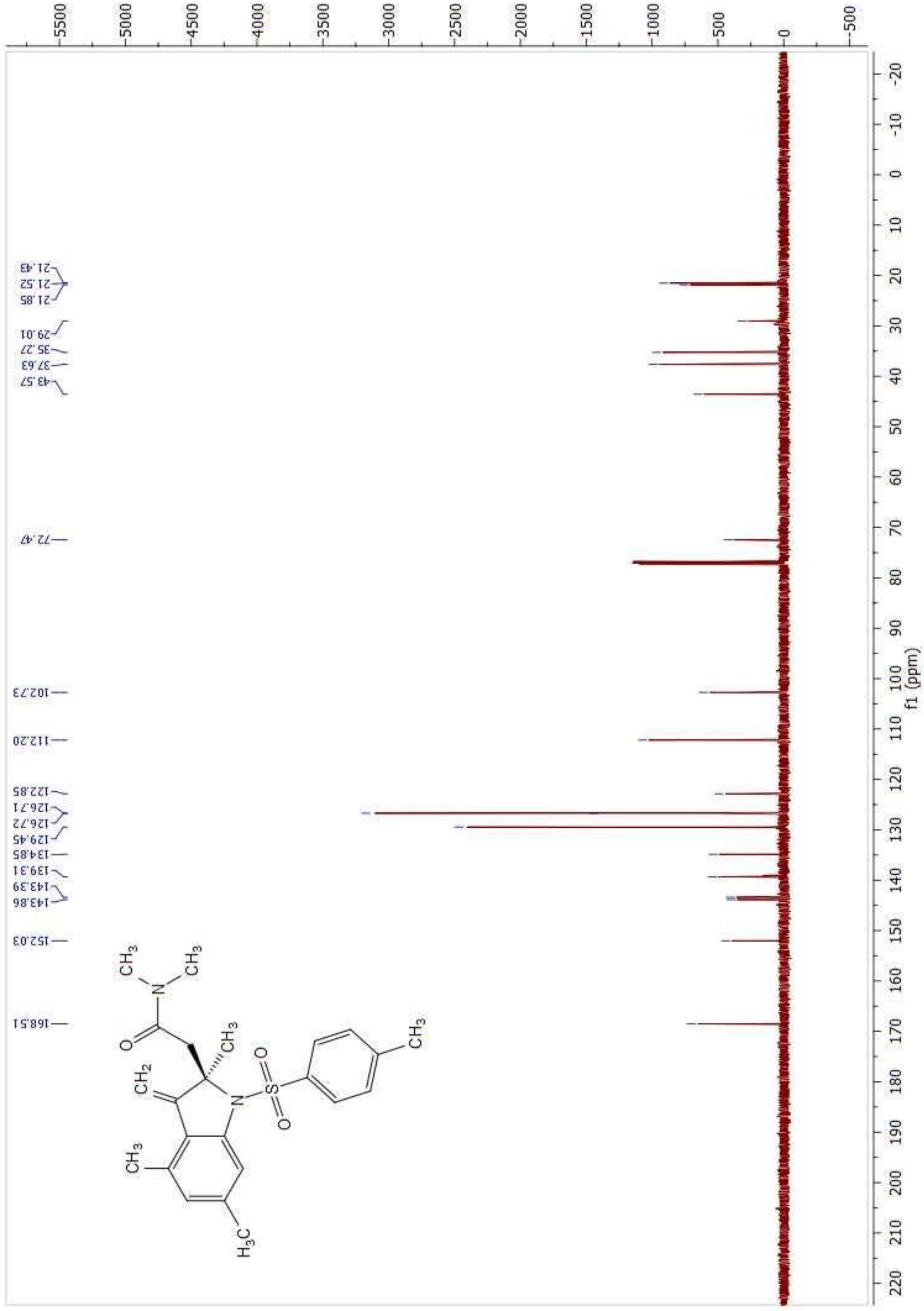


Figure 141. ^{13}C NMR spectrum of **173p** (125 MHz, $CDCl_3$).

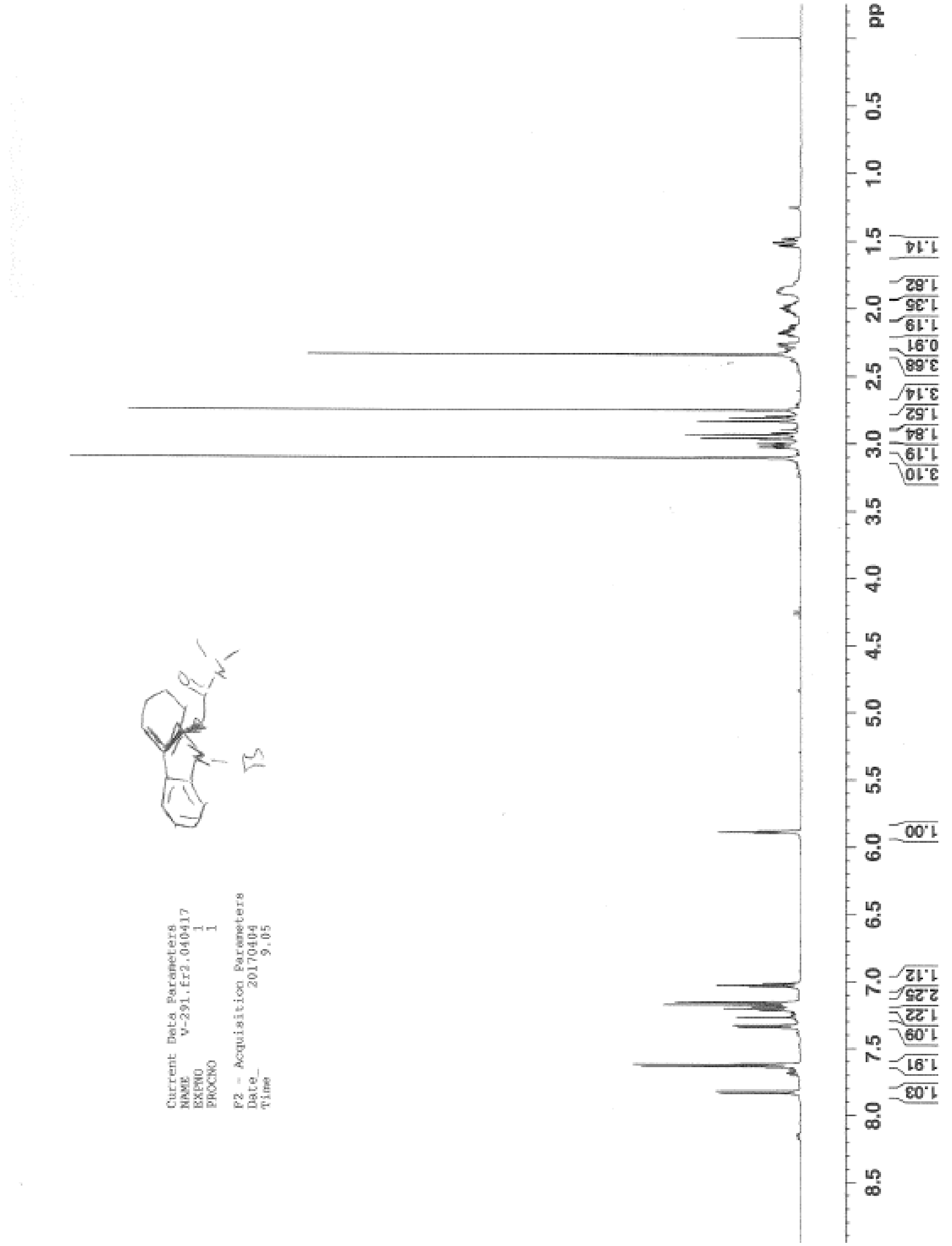


Figure 142. ^{1}H NMR spectrum of **173q** (500 MHz, $CDCl_3$).

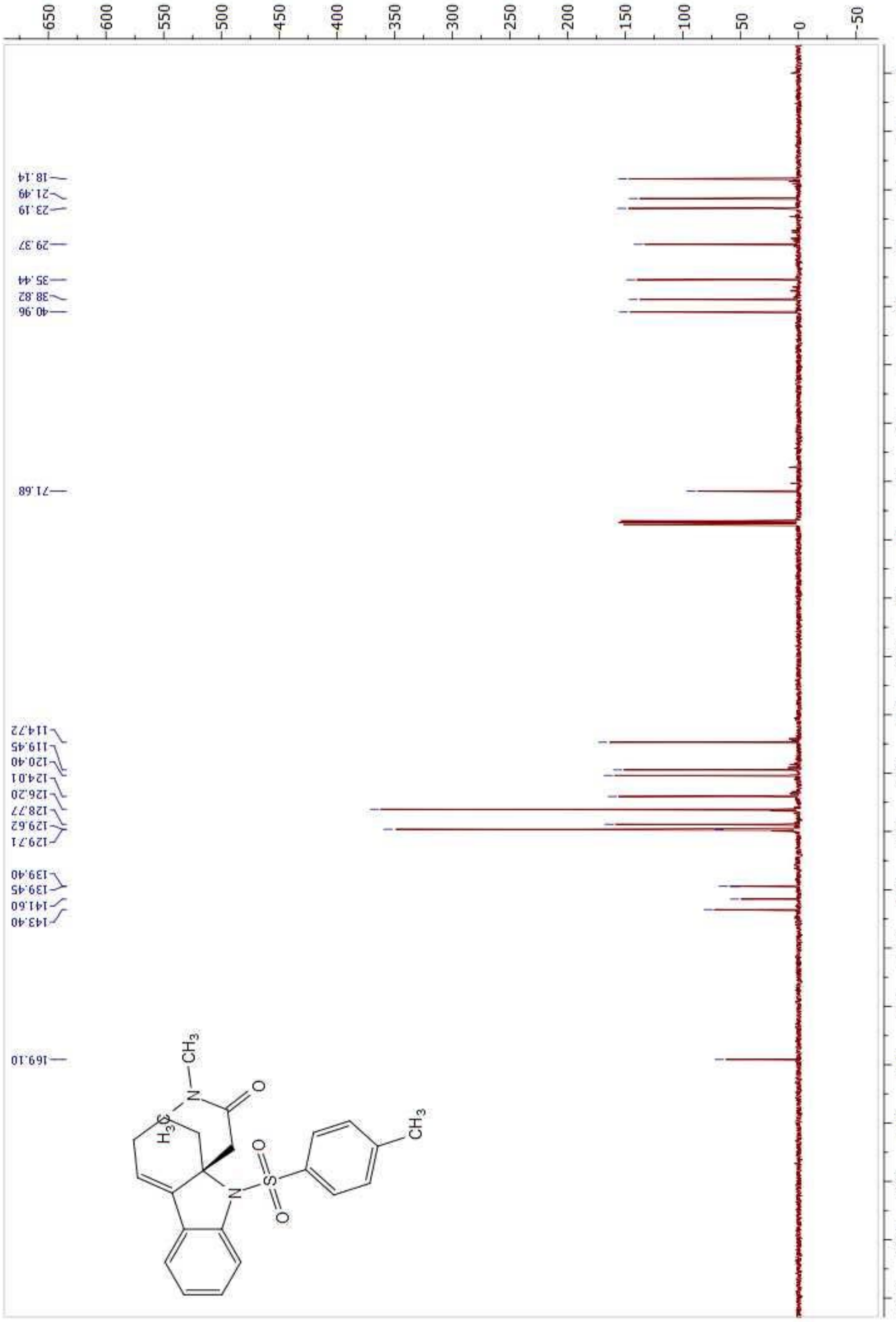


Figure 143. ^{13}C NMR spectrum of **173q** (125 MHz, $CDCl_3$).

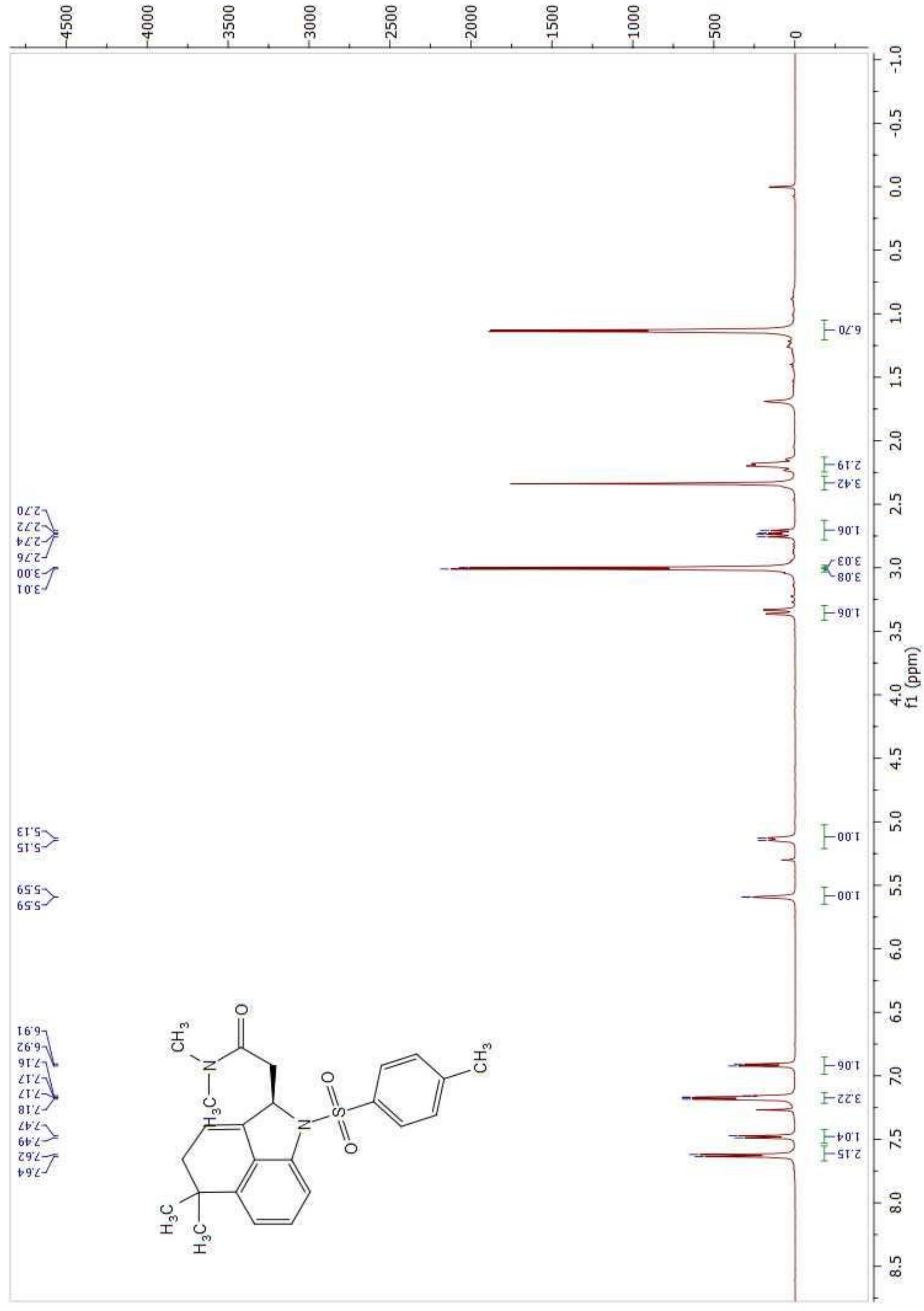


Figure 144. ^{1}H NMR spectrum of **173r** (500 MHz, $CDCl_3$).

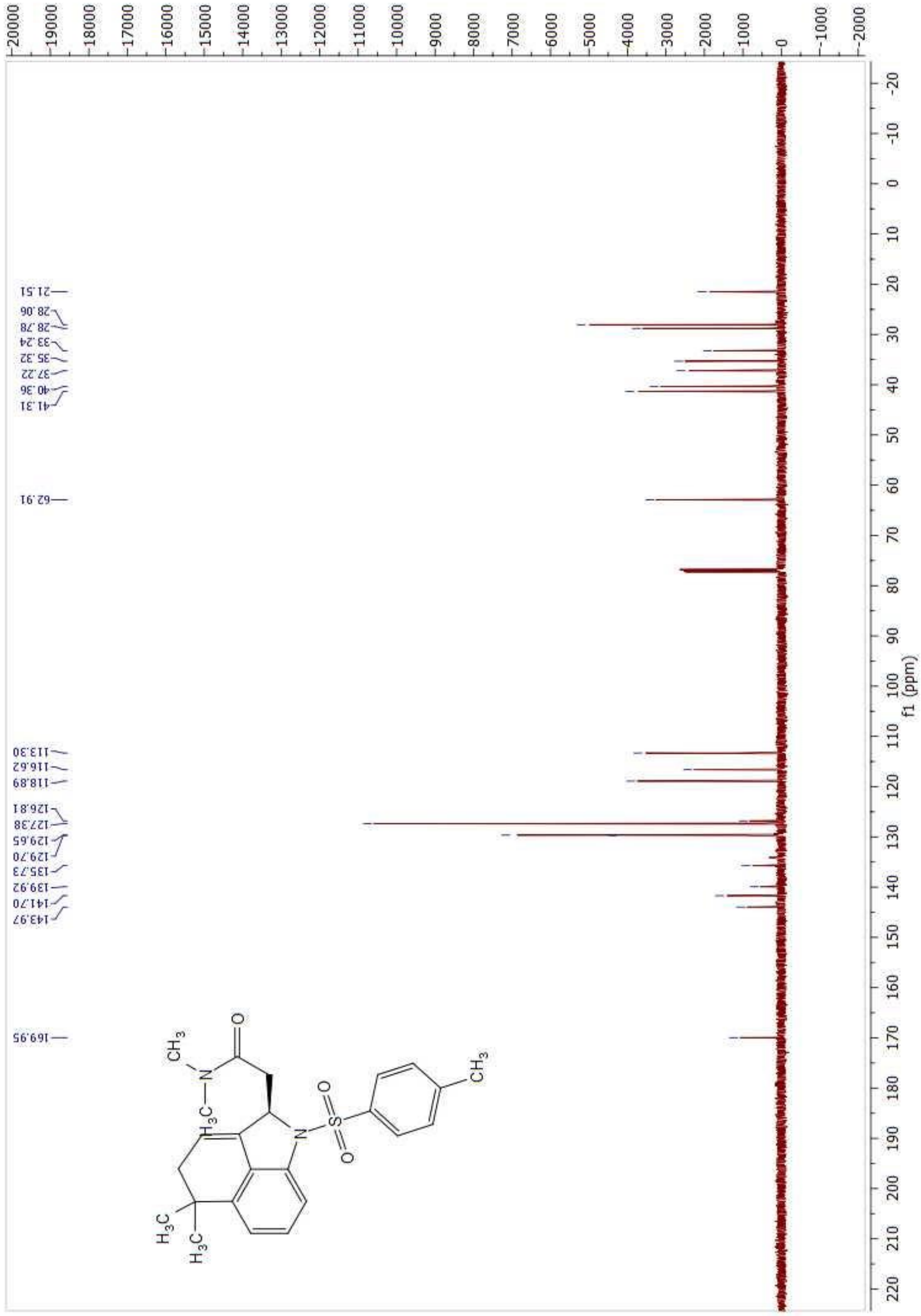


Figure 145. ^{13}C NMR spectrum of **173r** (125 MHz, $CDCl_3$).

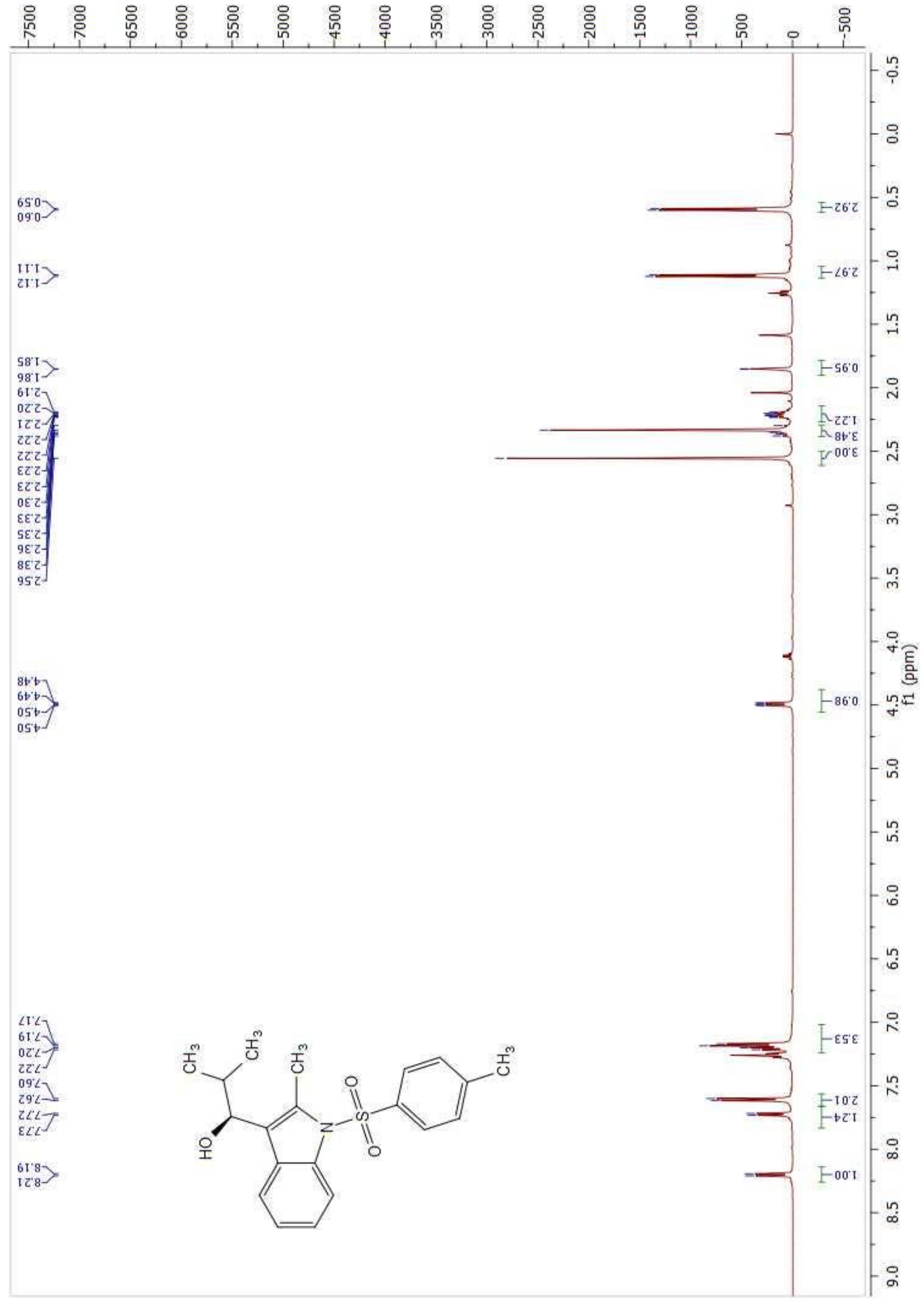


Figure 146. ^{1}H NMR spectrum of **175c** (500 MHz, $CDCl_3$).

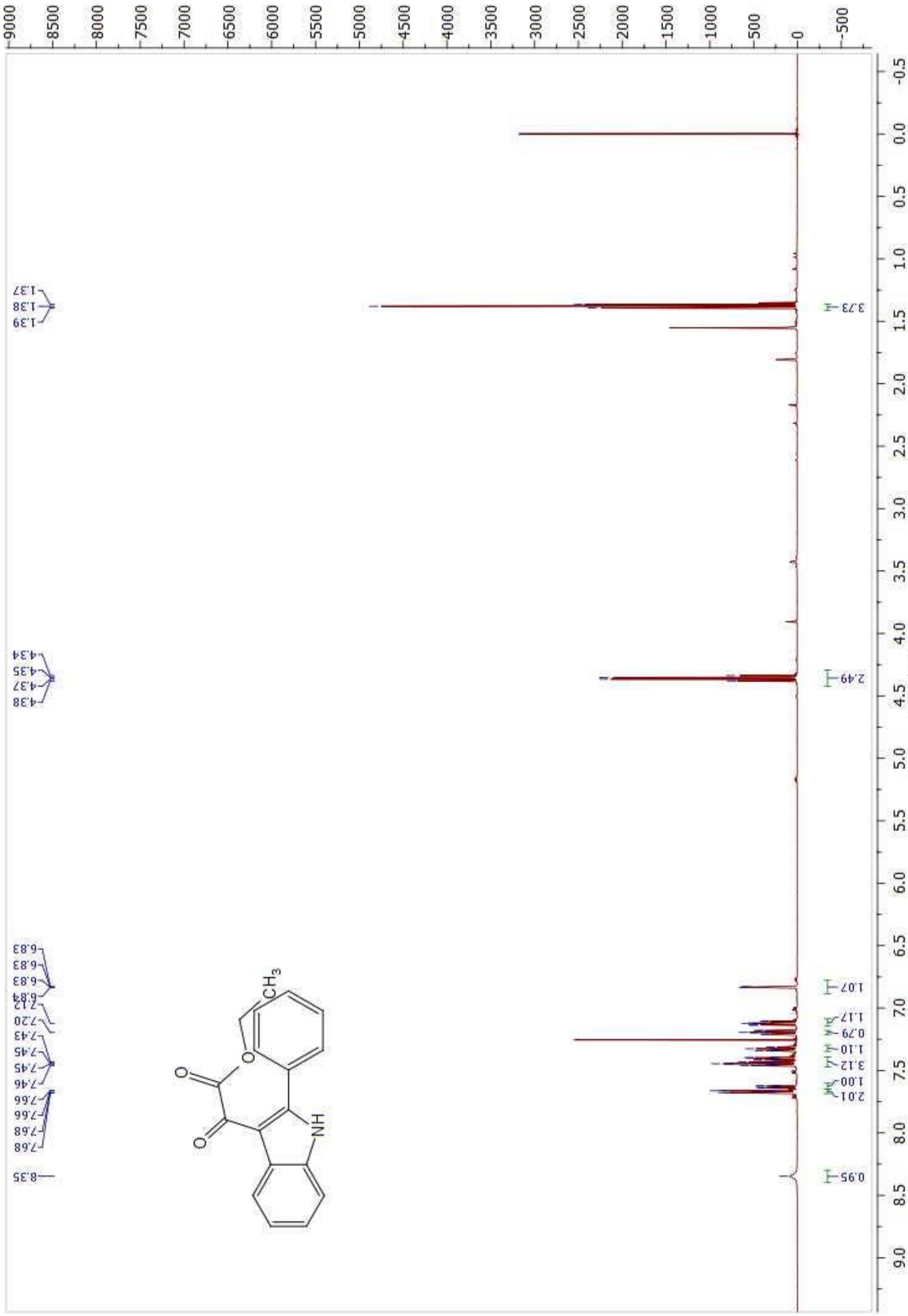


Figure 147. ^{1}H NMR spectrum of **211b** (500 MHz, $CDCl_3$).

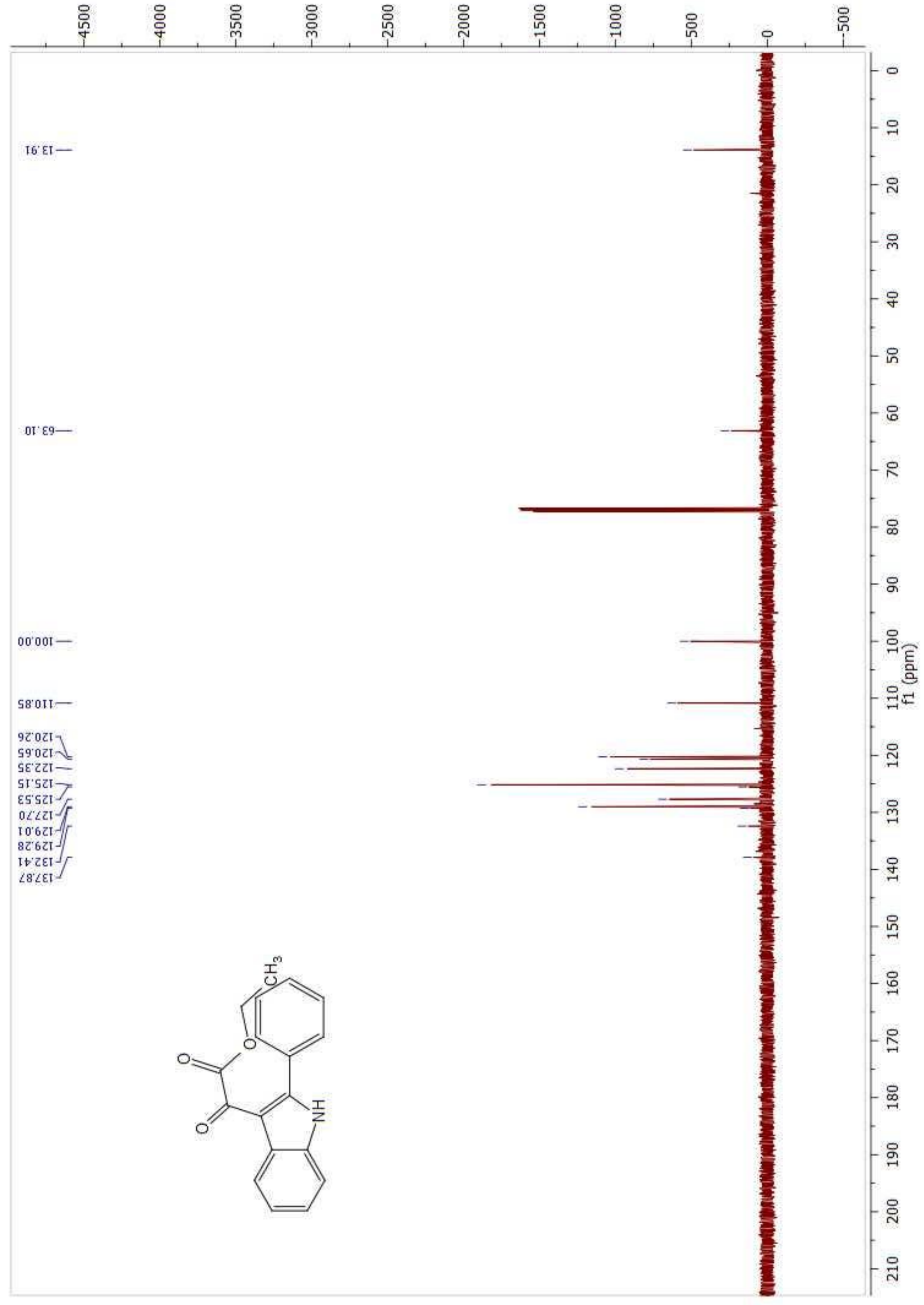


Figure 148. ^{13}C NMR spectrum of **211b** (125 MHz, $CDCl_3$).

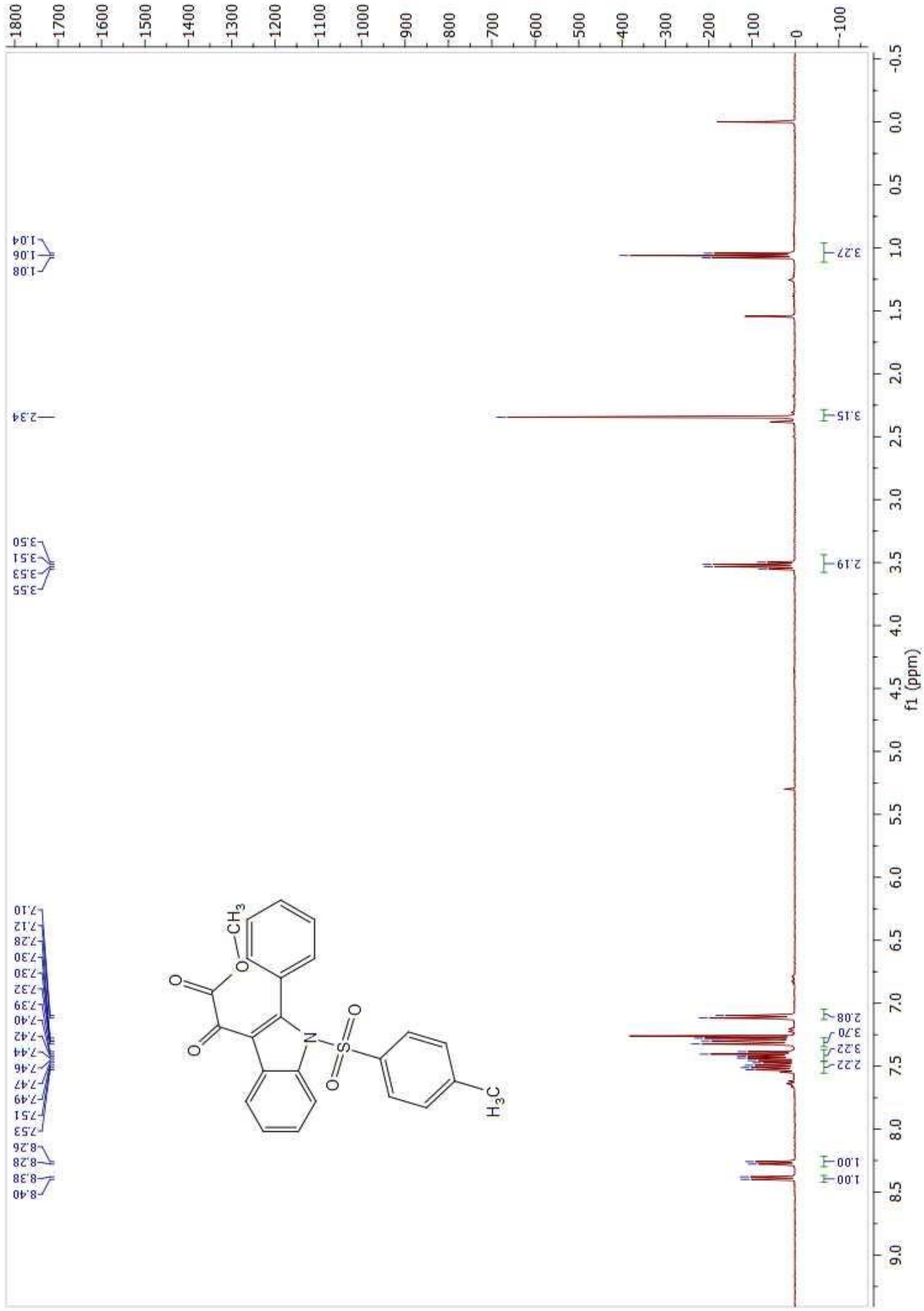


Figure 149. ^{1}H NMR spectrum of **211** (500 MHz, $CDCl_3$).

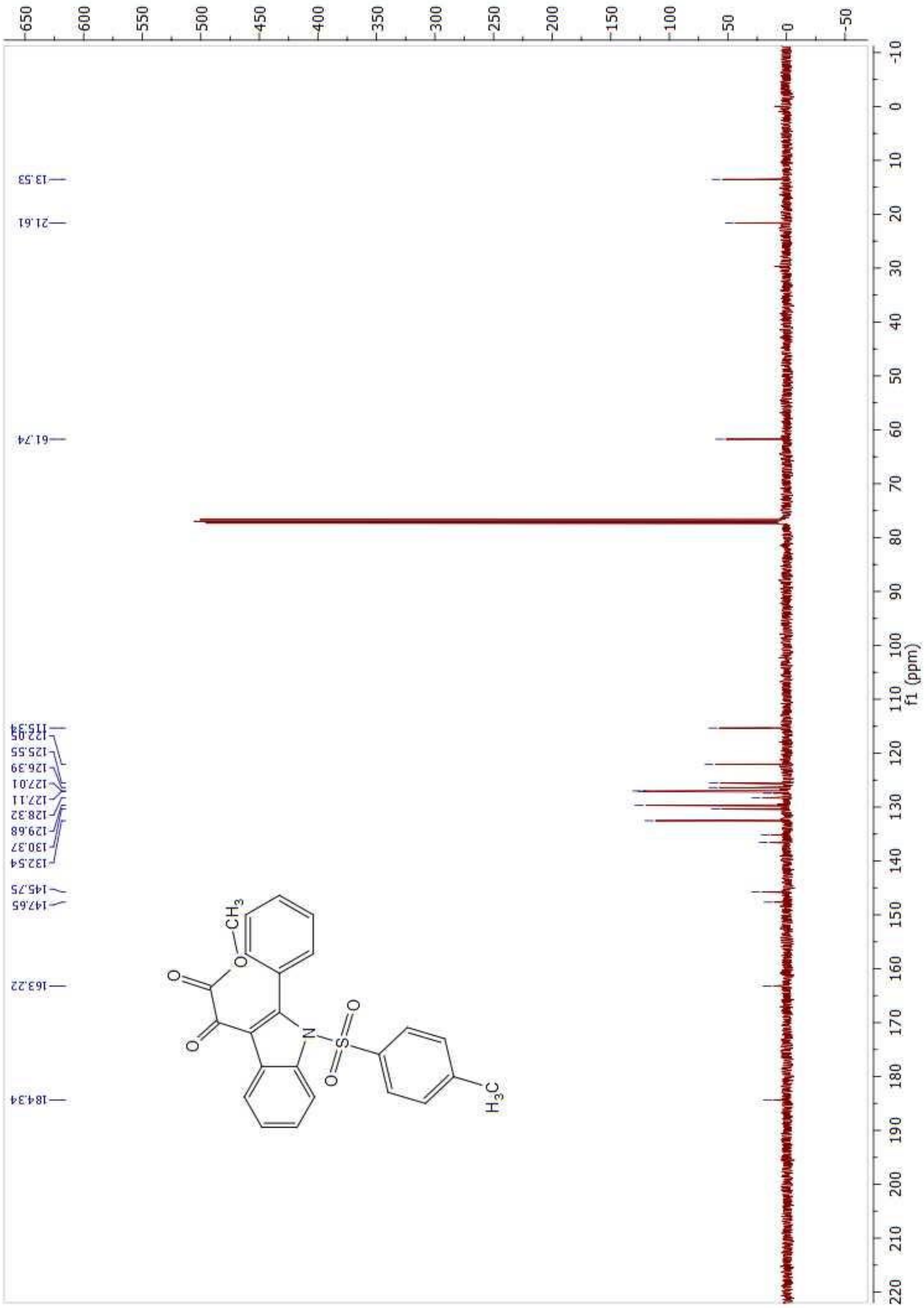


Figure 150. ^{13}C NMR spectrum of **211** (125 MHz, CDCl$_3$).

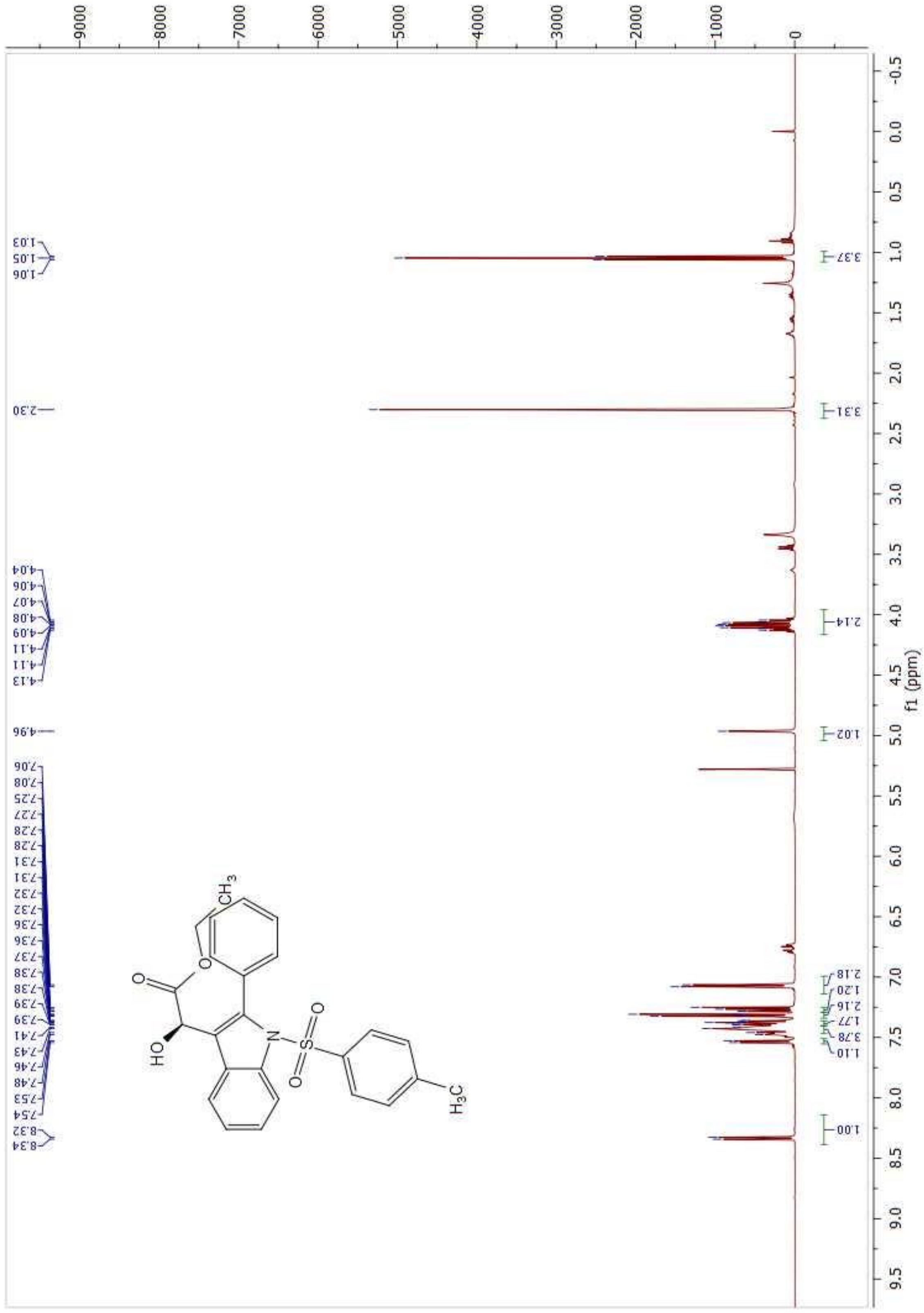


Figure 151. ^{1}H NMR spectrum of **212** (500 MHz, $CDCl_3$).

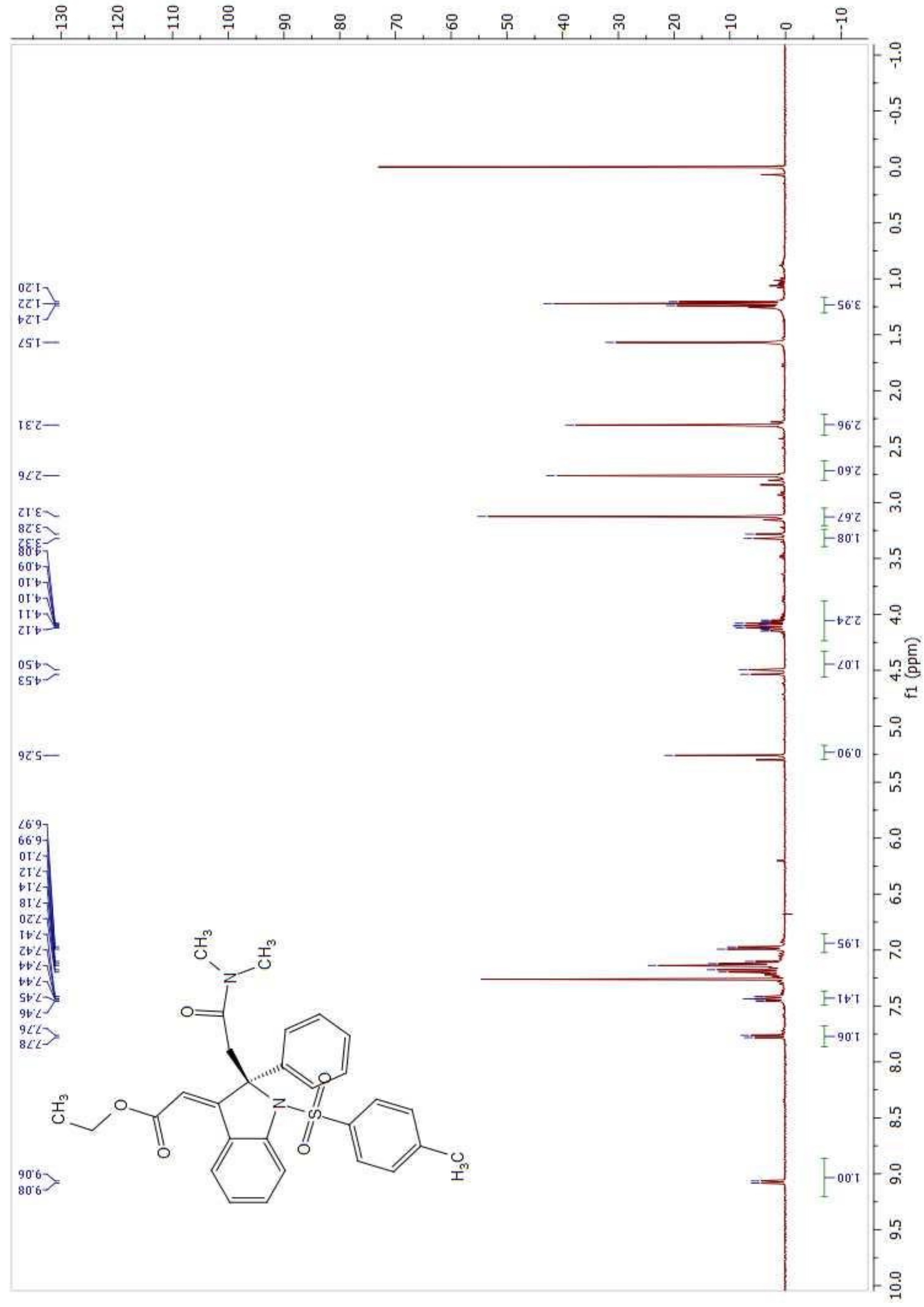


Figure 152. ^{1}H NMR spectrum of **213** (500 MHz, CDCl$_3$).

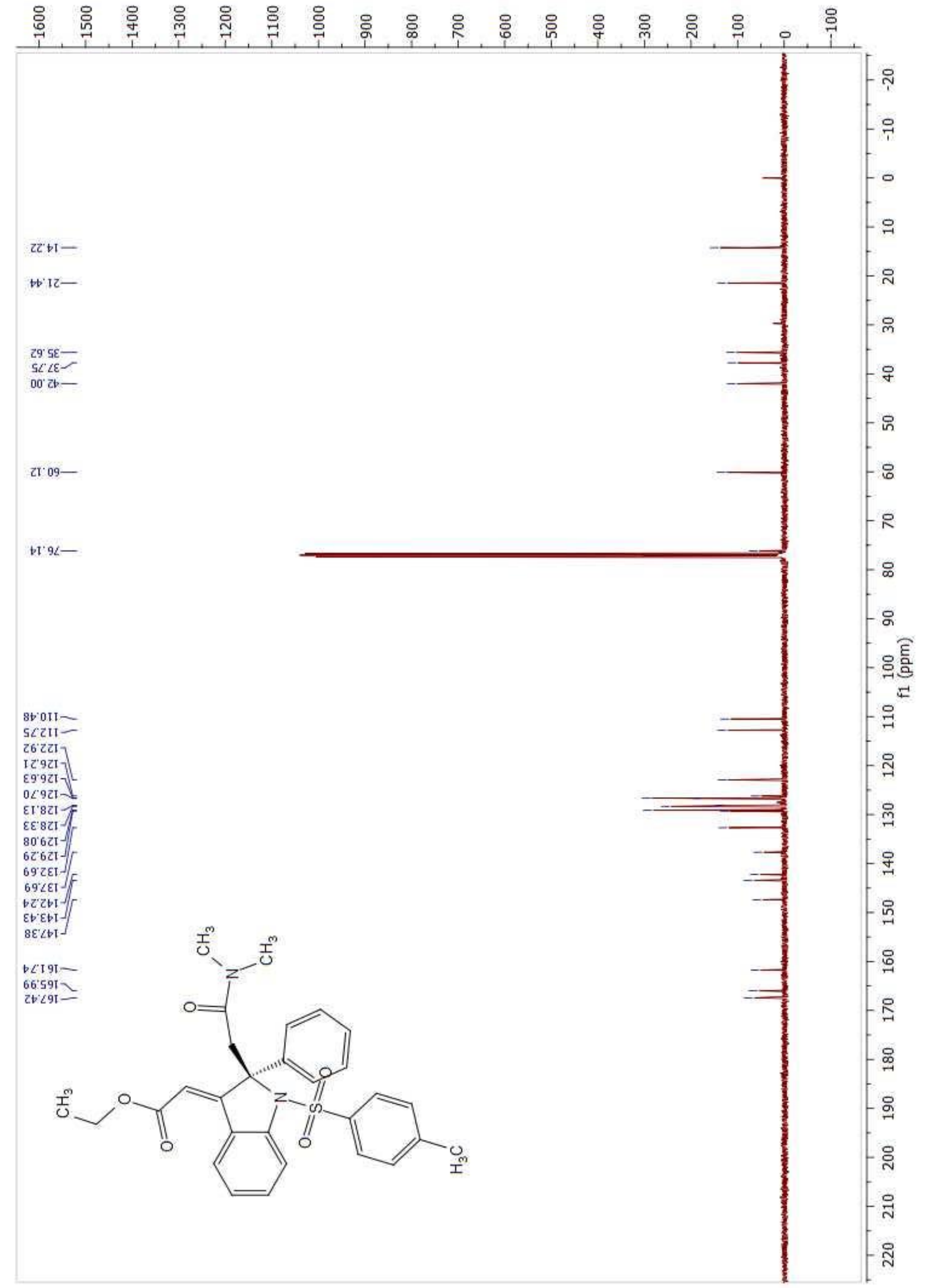


Figure 153. ^{13}C NMR spectrum of **213** (125 MHz, CDCl$_3$).

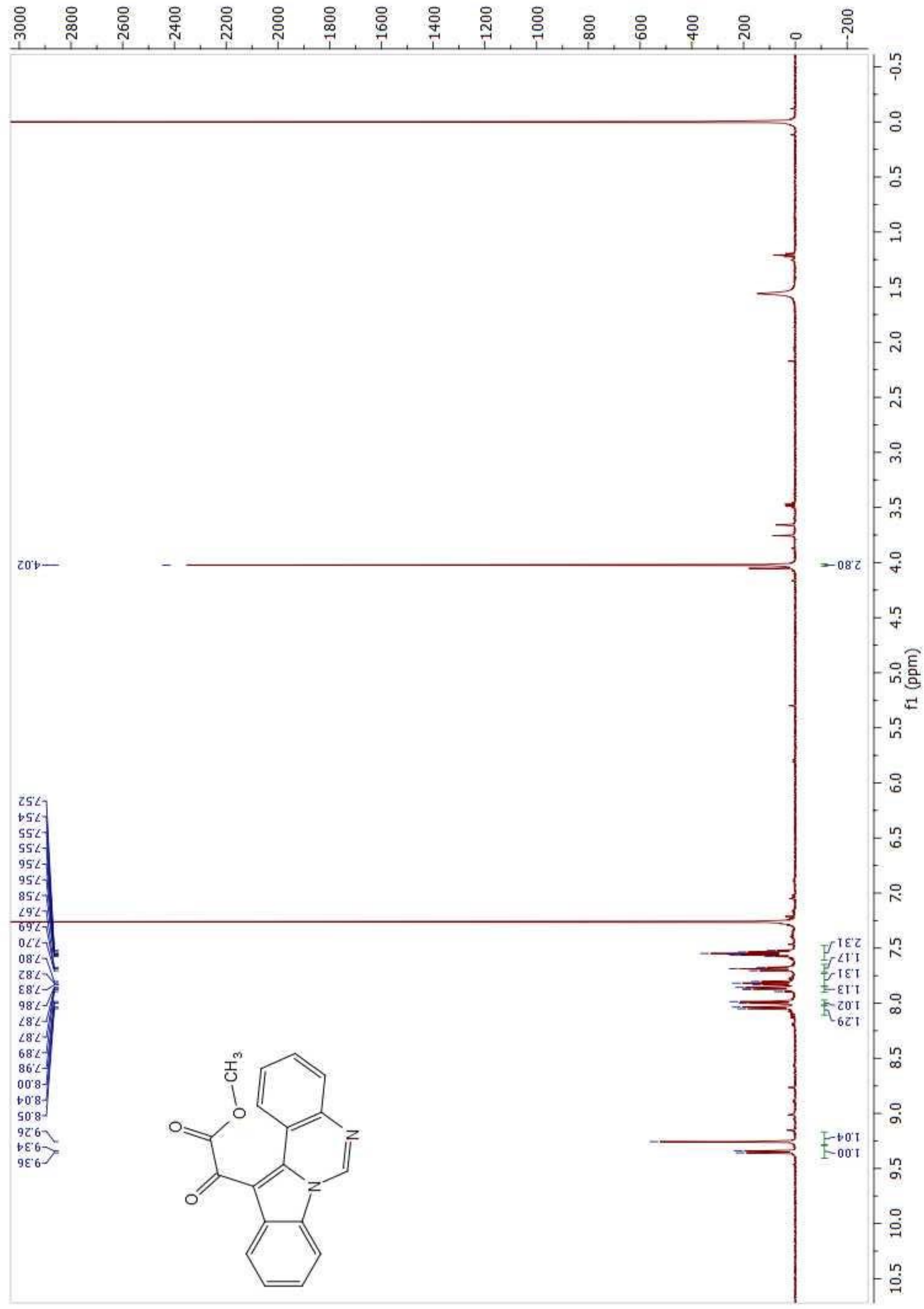


Figure 154. ^{1}H NMR spectrum of **234** (500 MHz, $CDCl_3$).

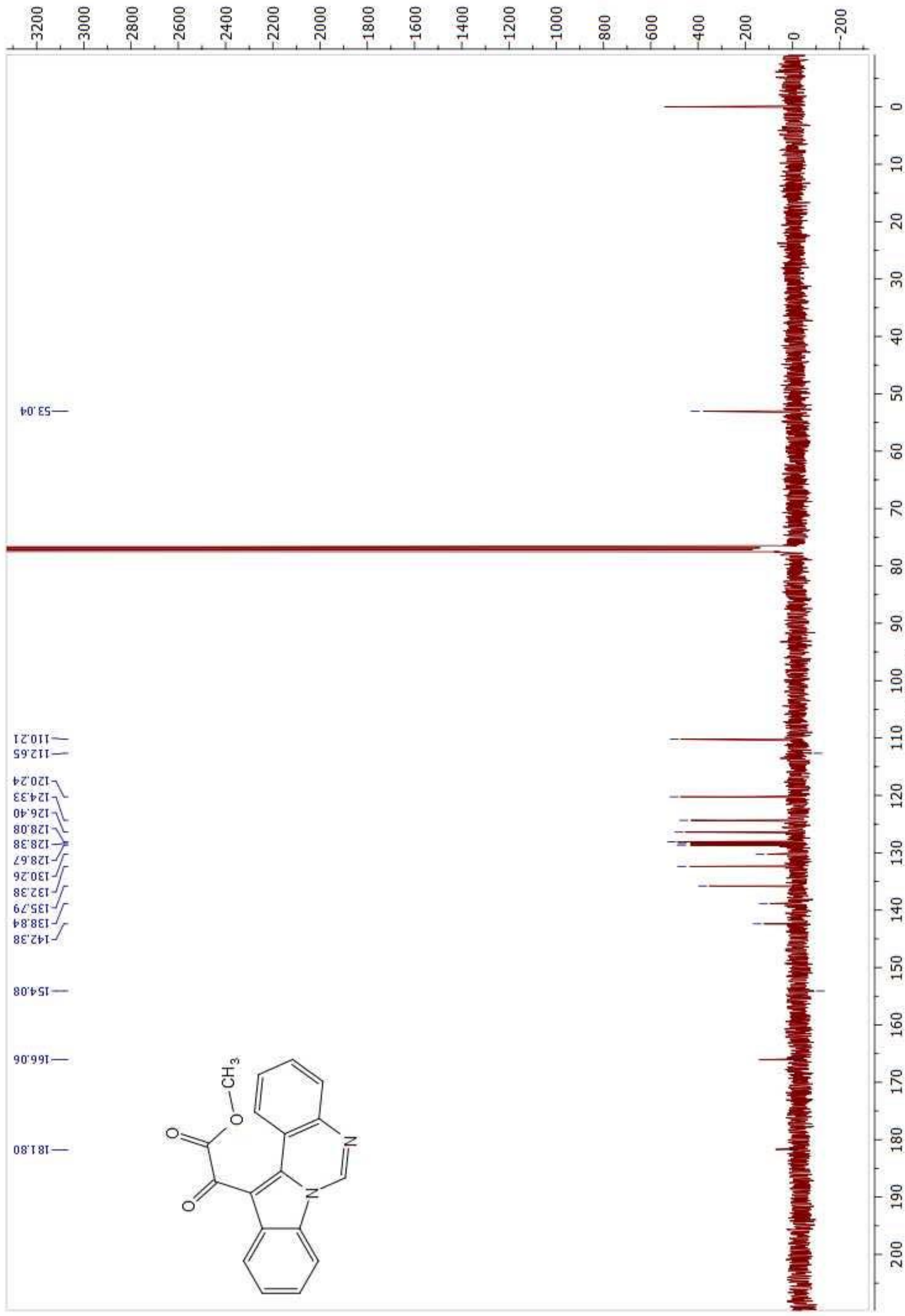


Figure 155. ^{13}C NMR spectrum of **234** (125 MHz, $CDCl_3$).

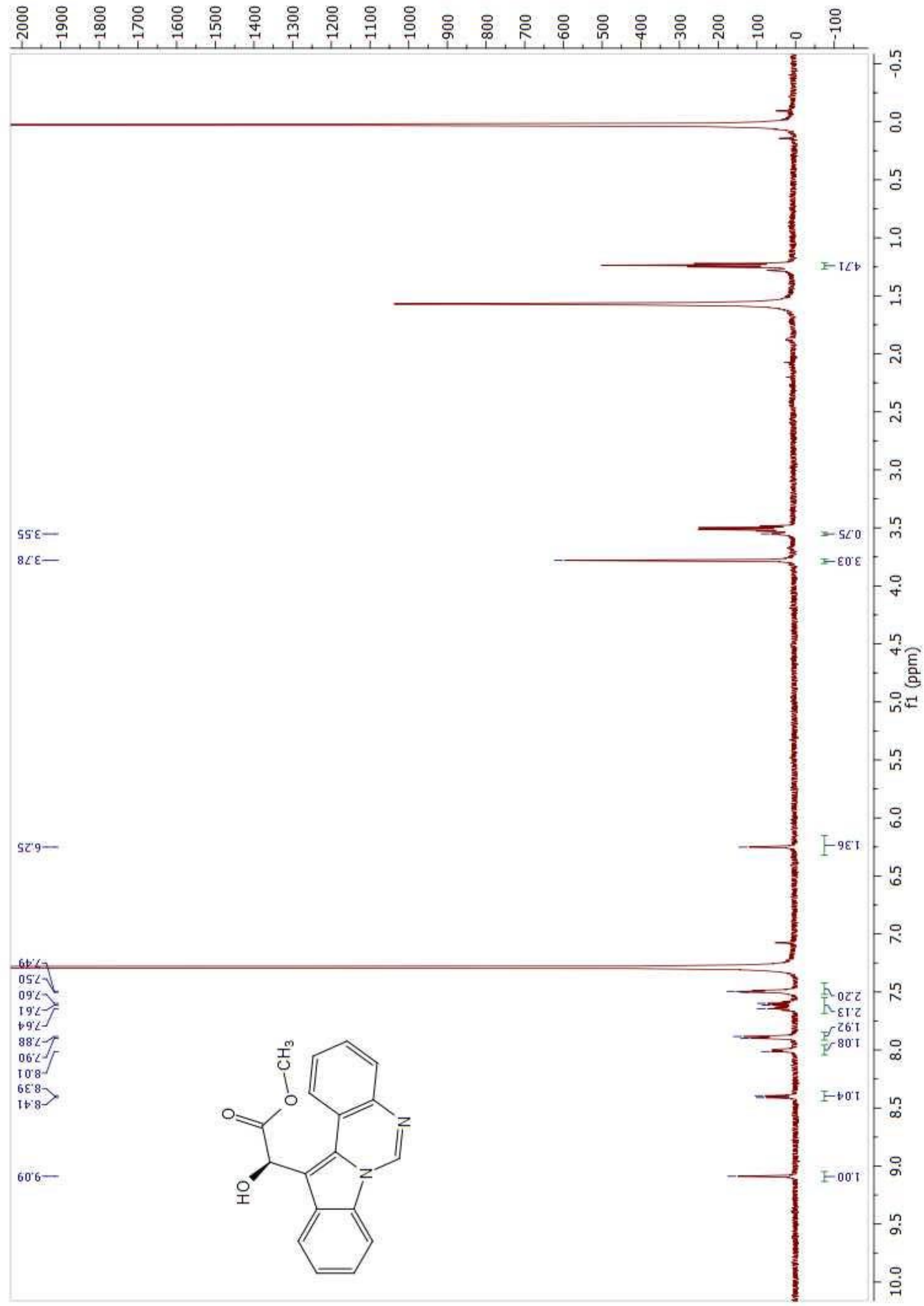


Figure 156. ^{1}H NMR spectrum of **232** (500 MHz, $CDCl_3$).

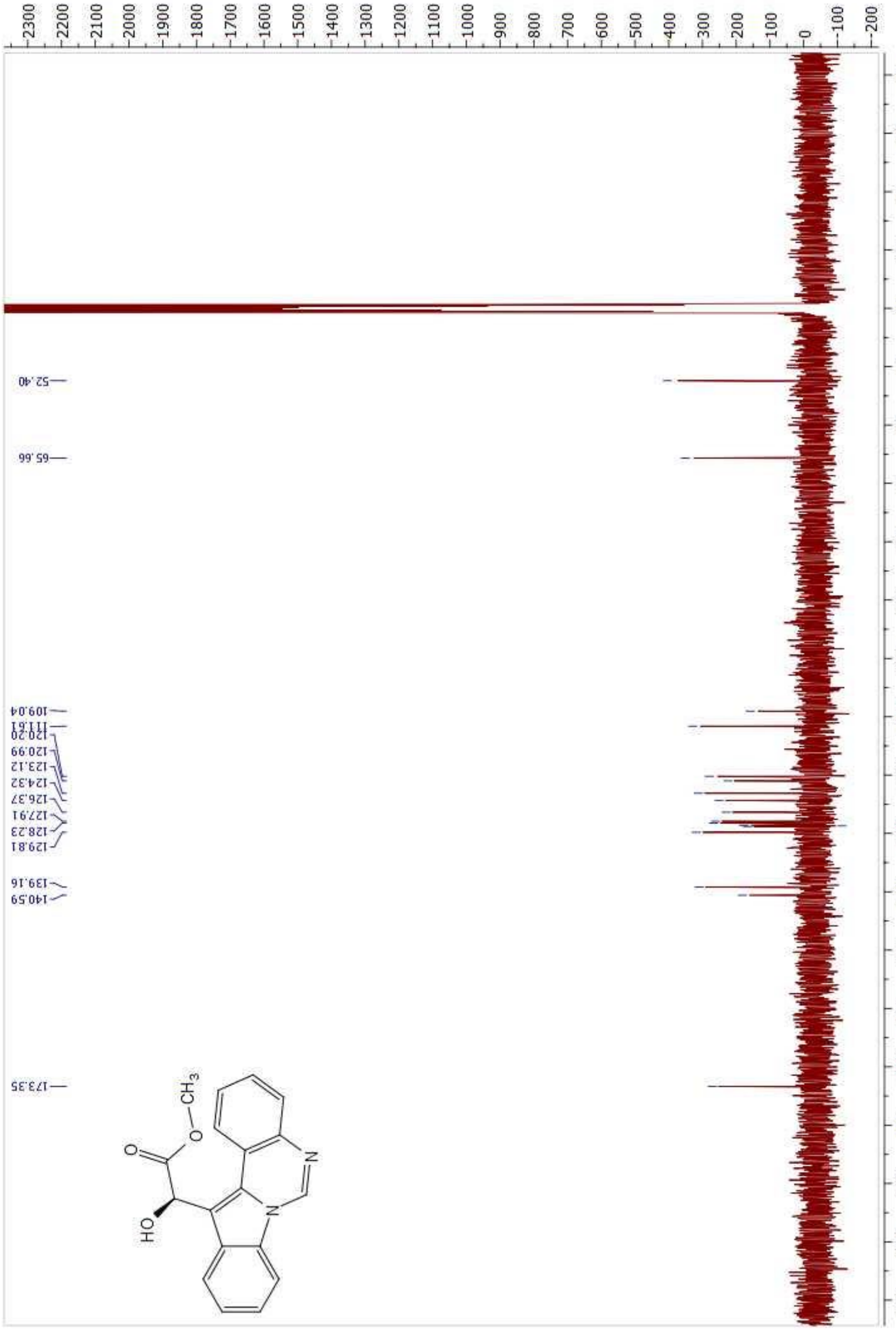


Figure 157. ^{13}C NMR spectrum of **232** (125 MHz, DMSO-D6).

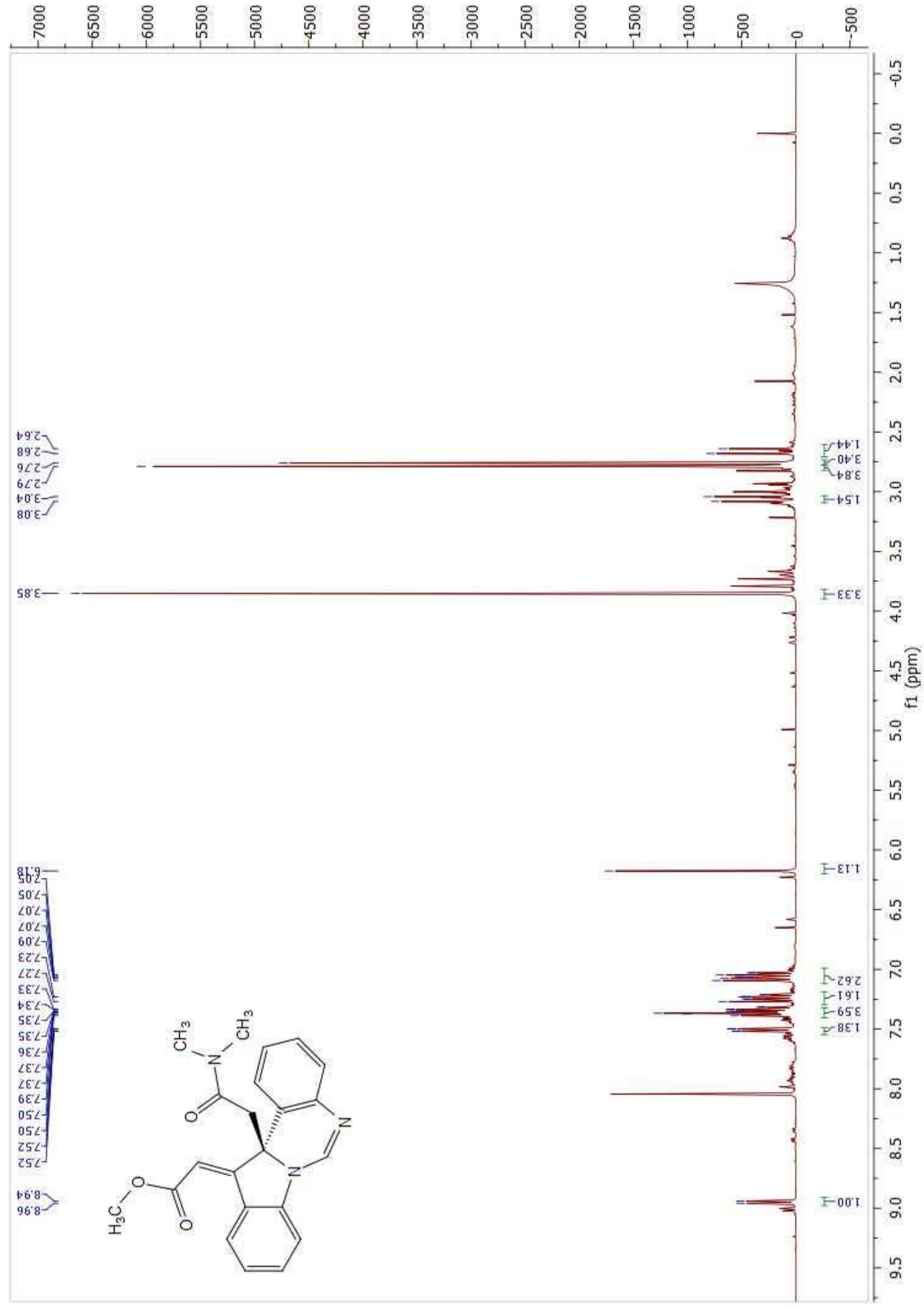


Figure 158. ^{1}H NMR spectrum of **231** (500 MHz, $CDCl_3$).

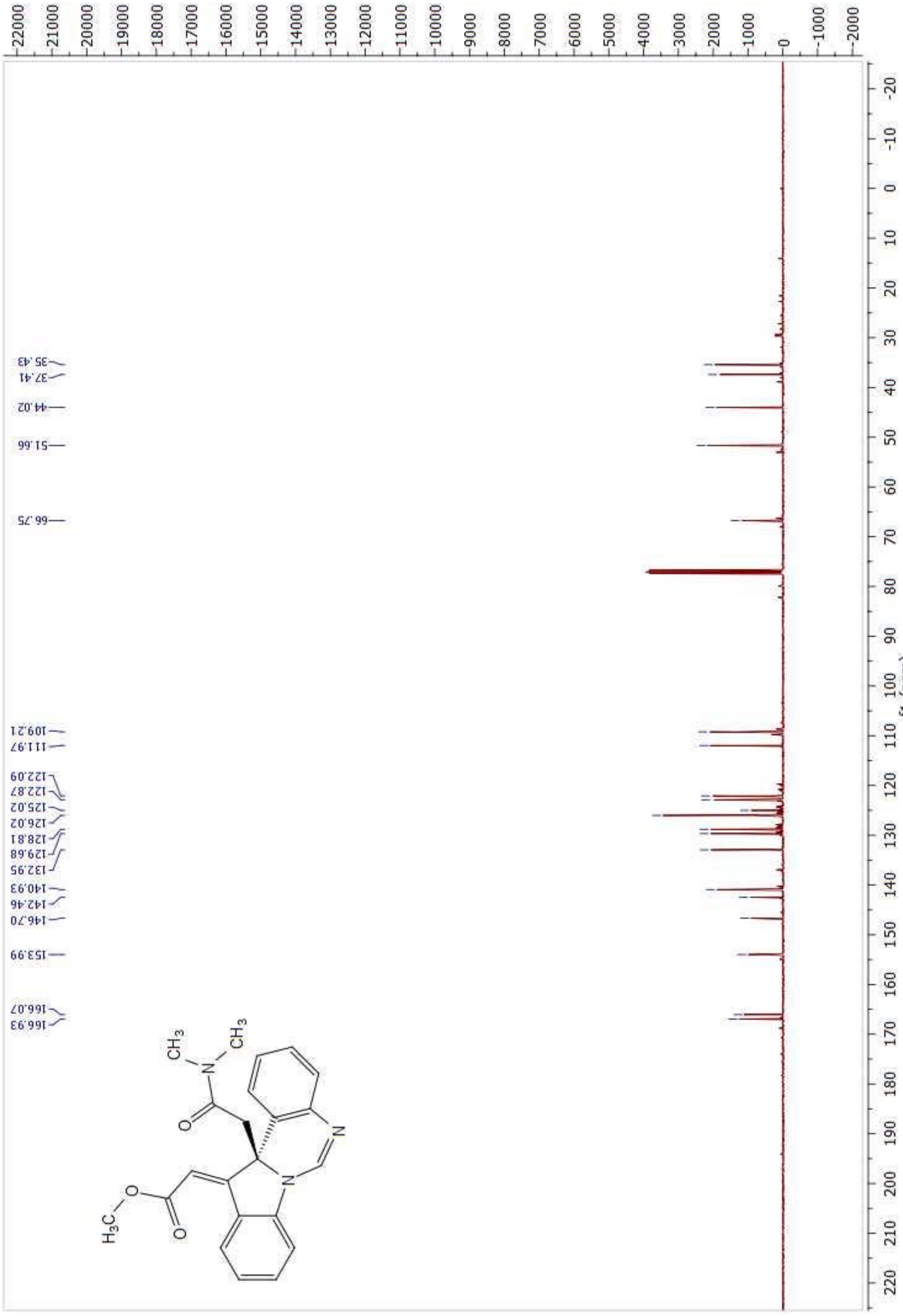


Figure 159. ^{13}C NMR spectrum of **231** (125 MHz, $CDCl_3$).

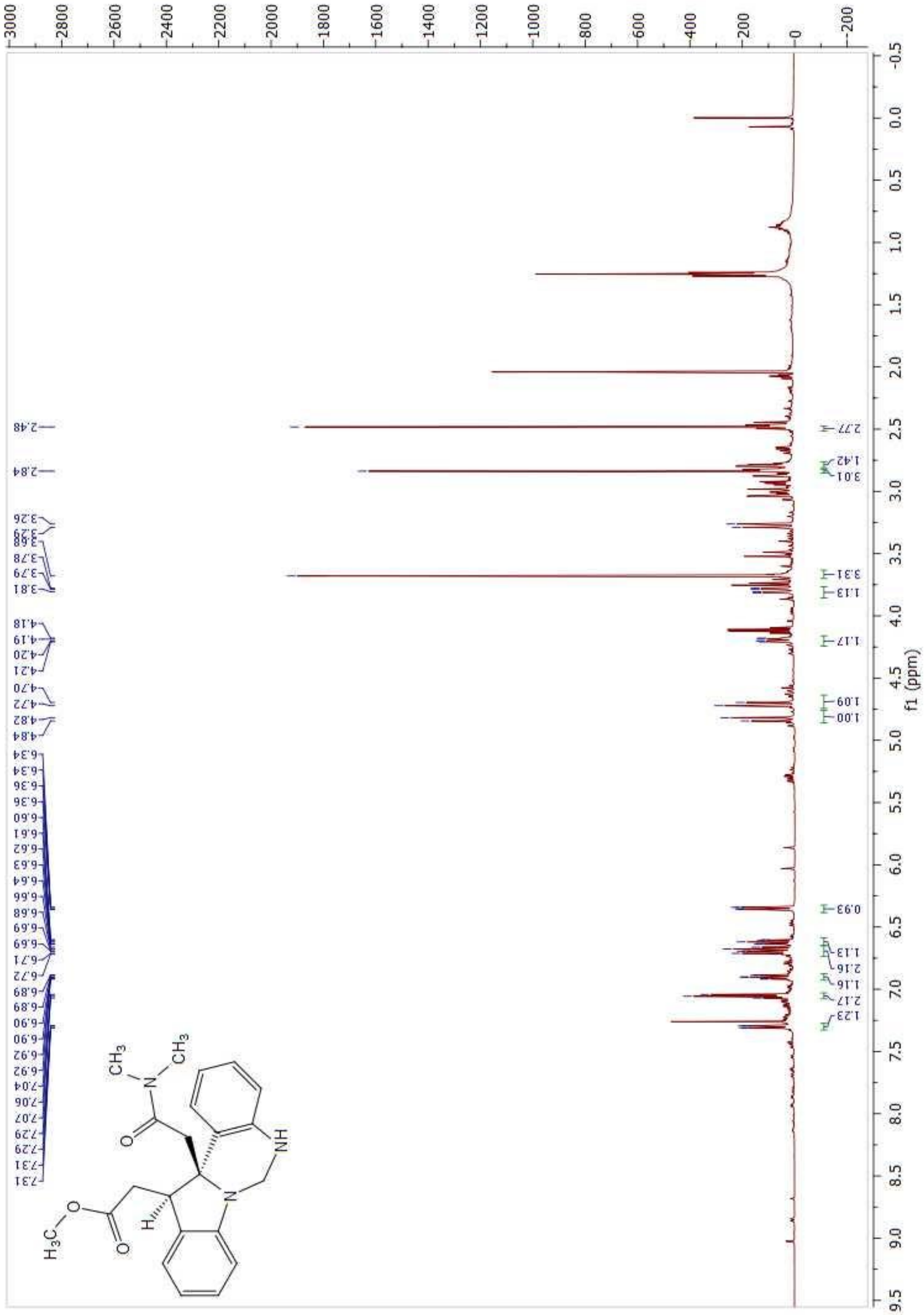


Figure 160. ^{1}H NMR spectrum of **233b** (500 MHz, $CDCl_3$).

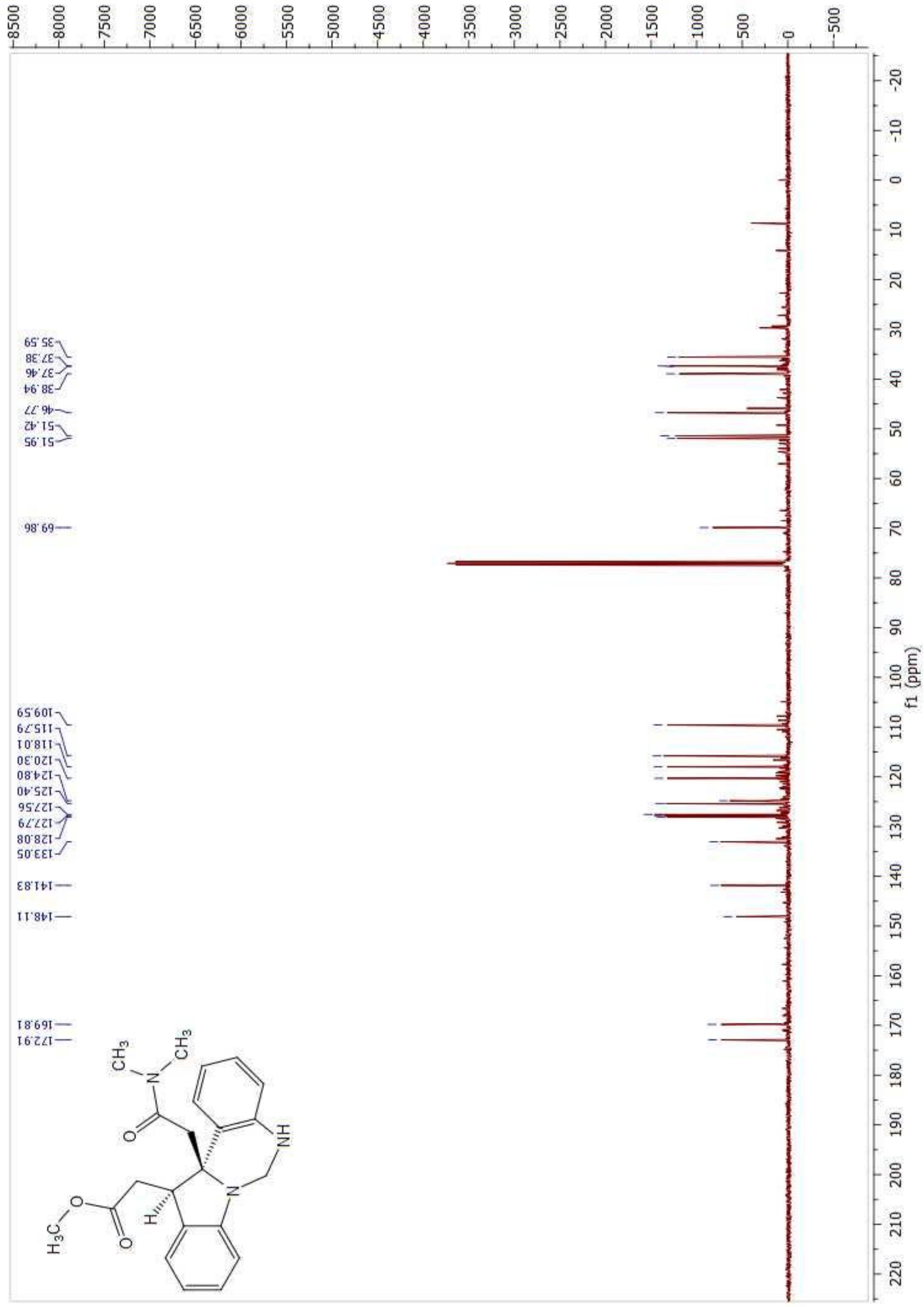


Figure 161. ^{13}C NMR spectrum of **233b** (125 MHz, $CDCl_3$).

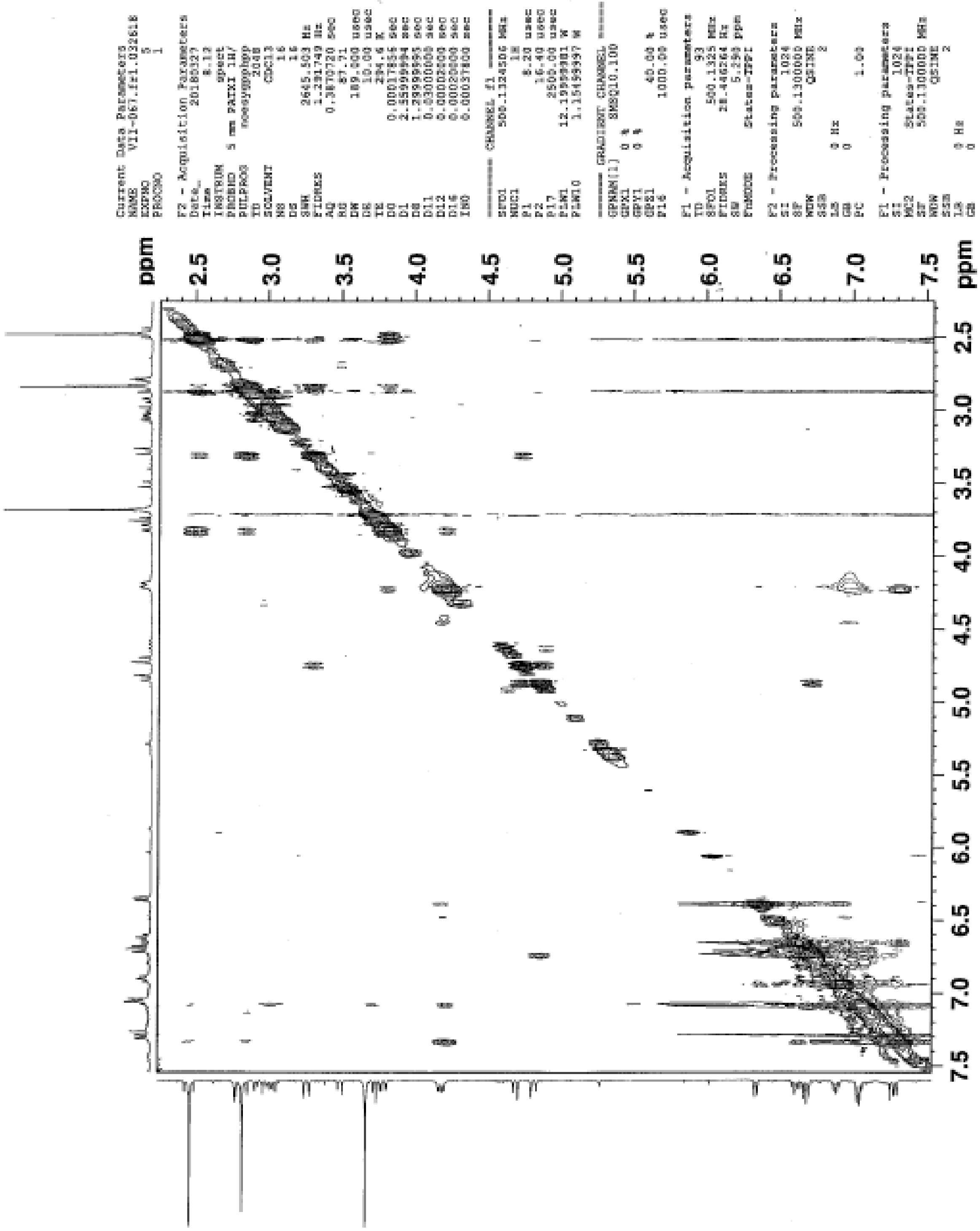


Figure 162. NOESY spectrum of **233b** (500 MHz, $CDCl_3$).

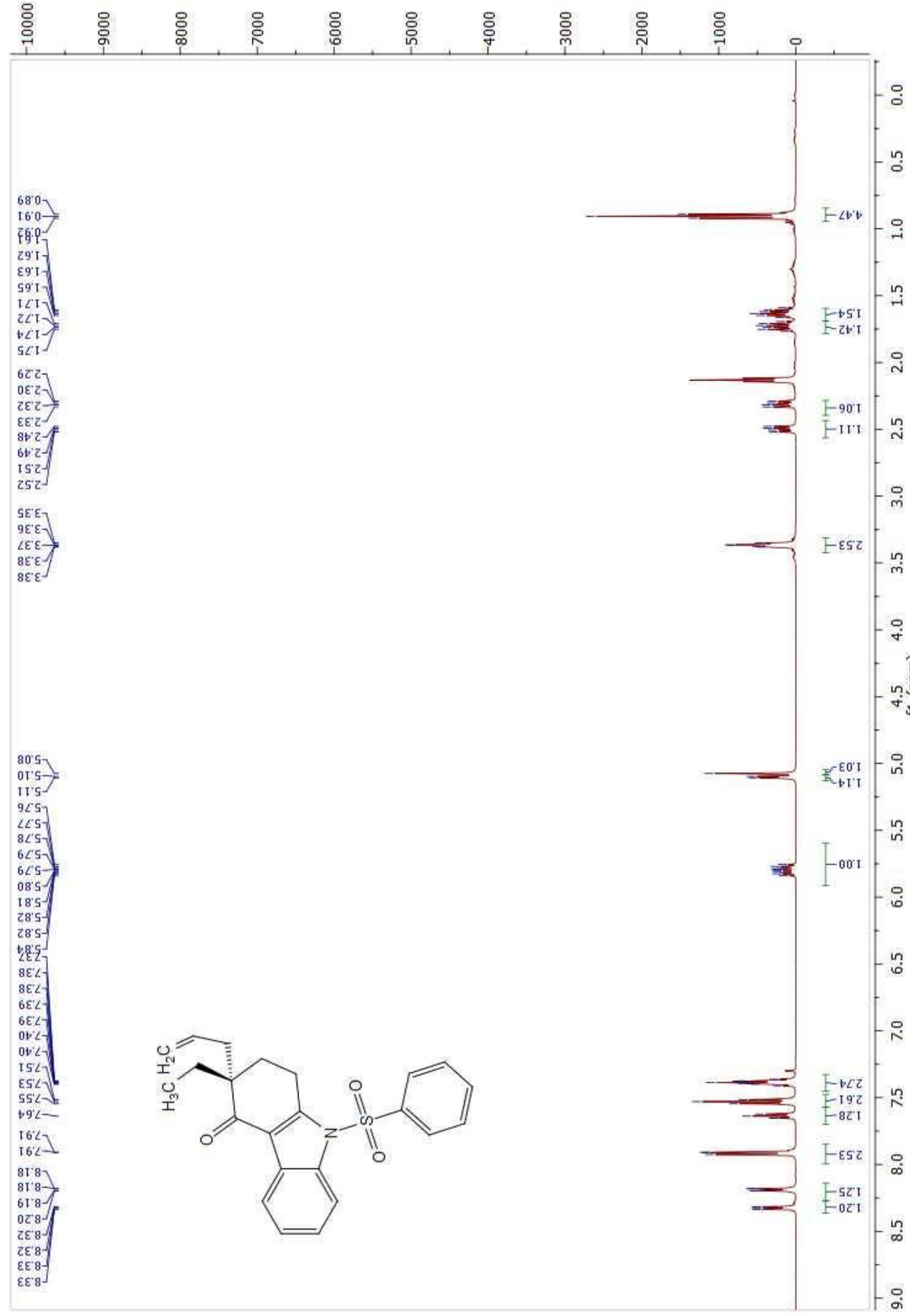


Figure 163. ^{1}H NMR spectrum of **249** (500 MHz, $CDCl_3$).

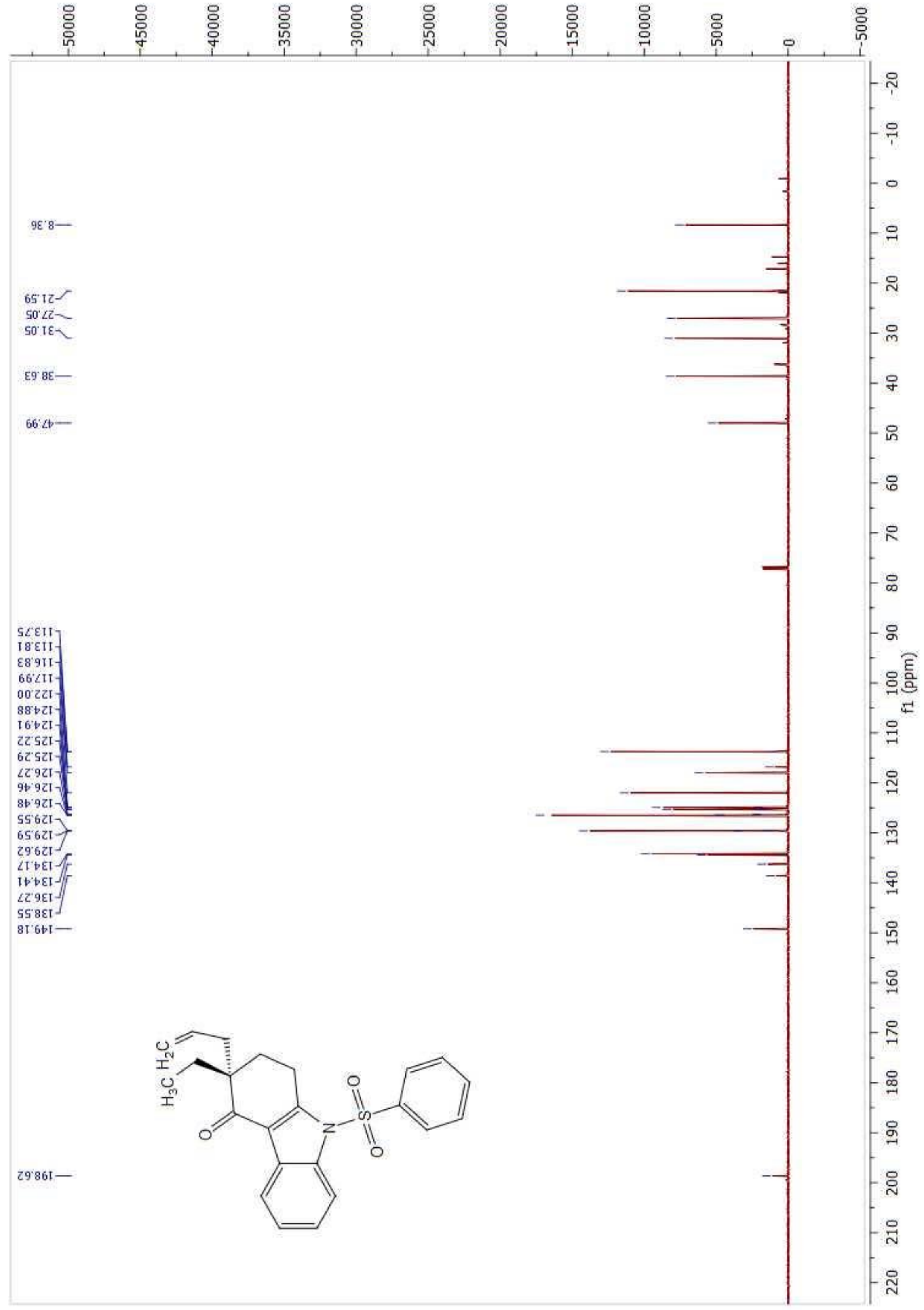


Figure 164. ^{13}C NMR spectrum of **249** (125 MHz, $CDCl_3$).

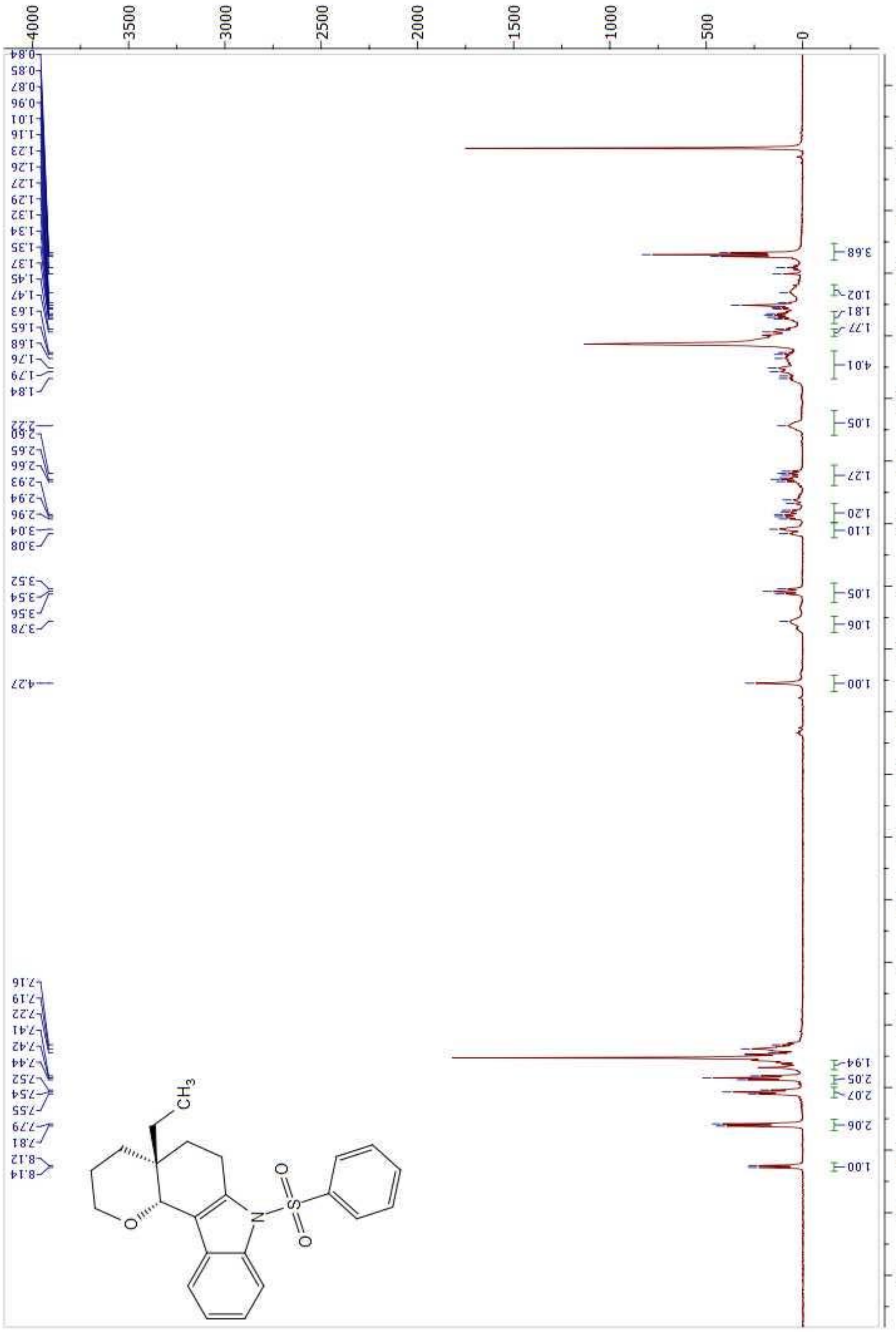


Figure 165. ^{1}H NMR spectrum of **252** (500 MHz, $CDCl_3$).

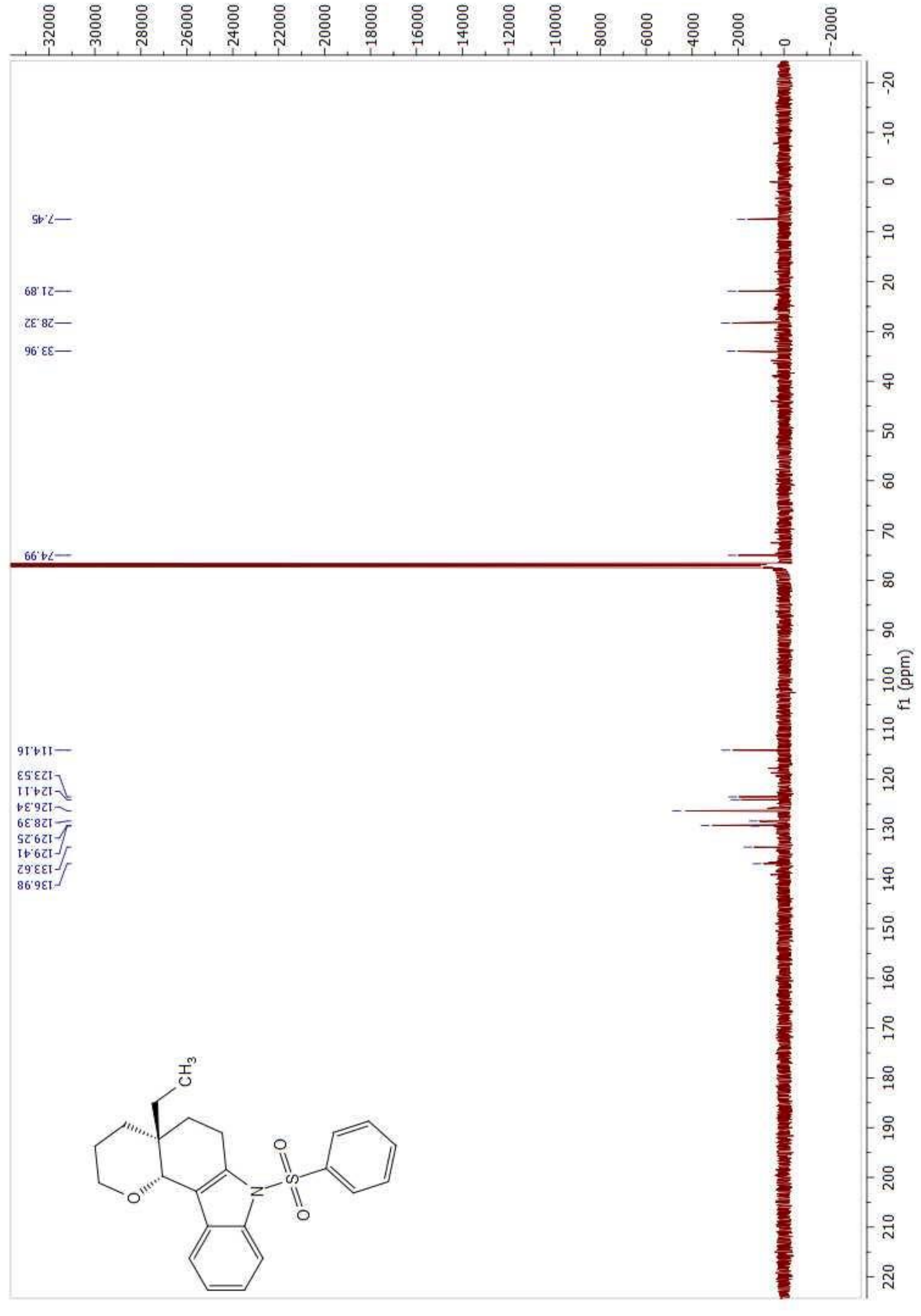


Figure 166. ^{13}C NMR spectrum of **252** (125 MHz, $CDCl_3$).

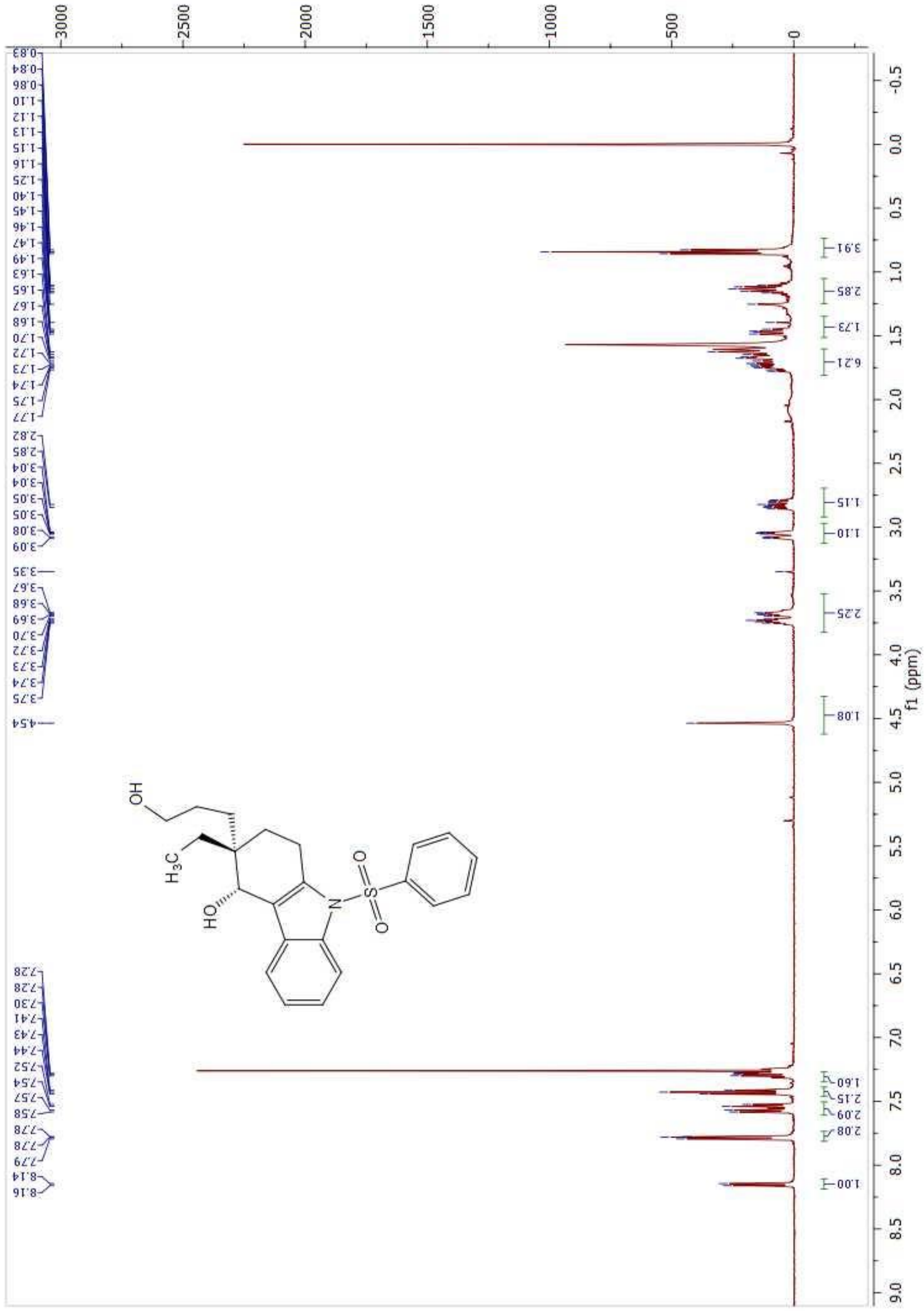


Figure 167. ^{1}H NMR spectrum of **253** (500 MHz, $CDCl_3$).

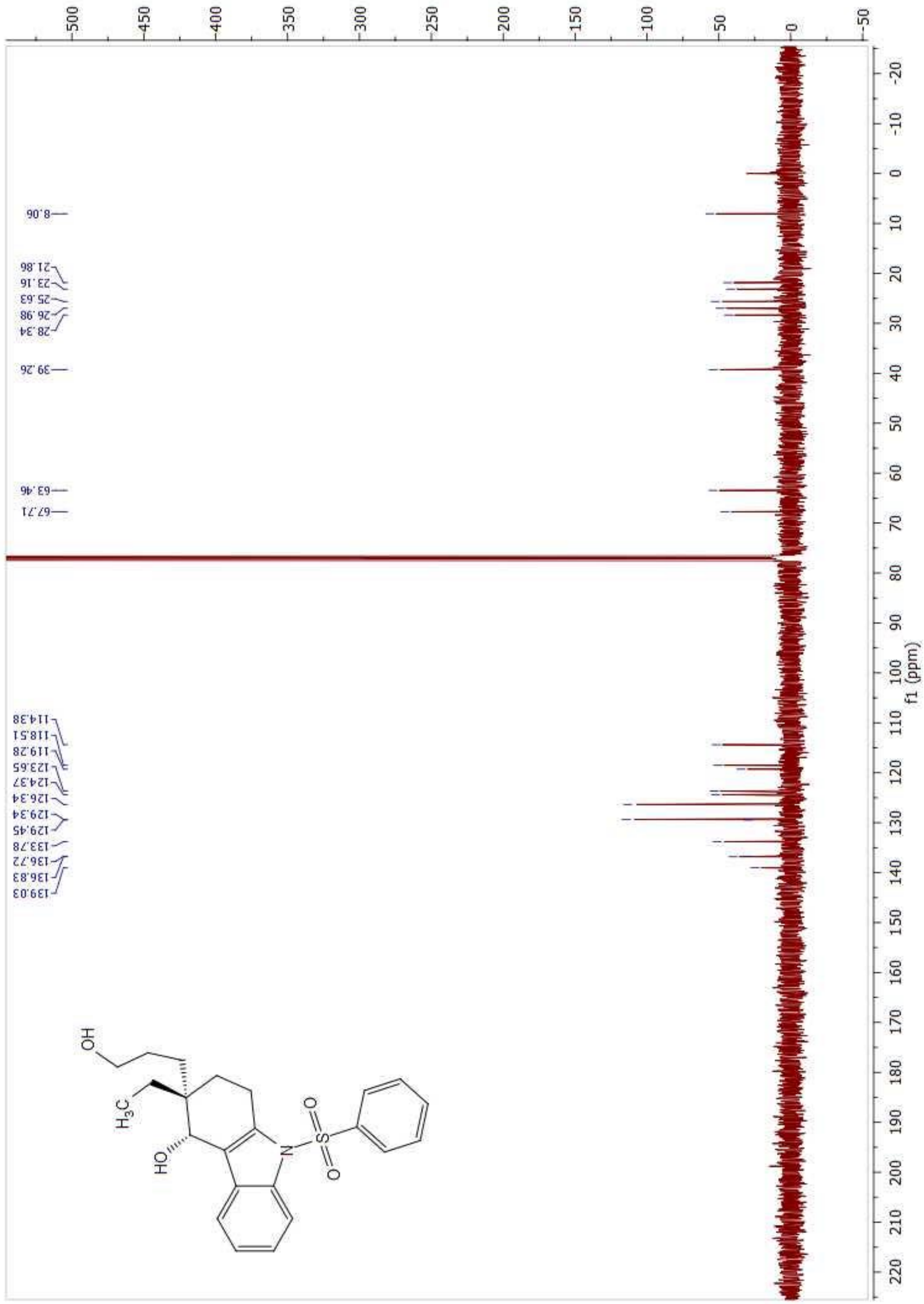


Figure 168. ^{13}C NMR spectrum of **253** (125 MHz, $CDCl_3$).

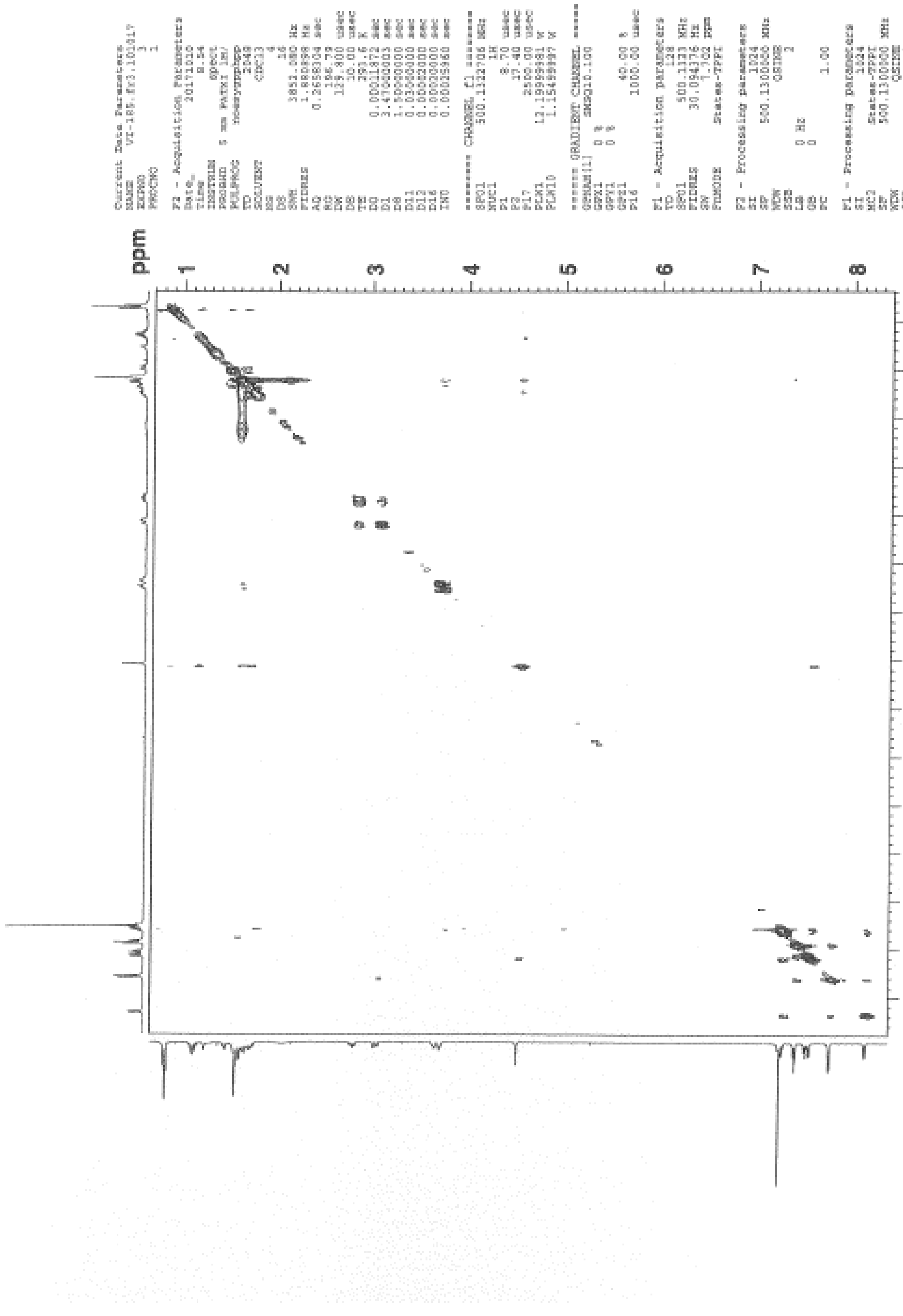


Figure 169. NOESY NMR spectrum of **253** (500 MHz, $CDCl_3$).

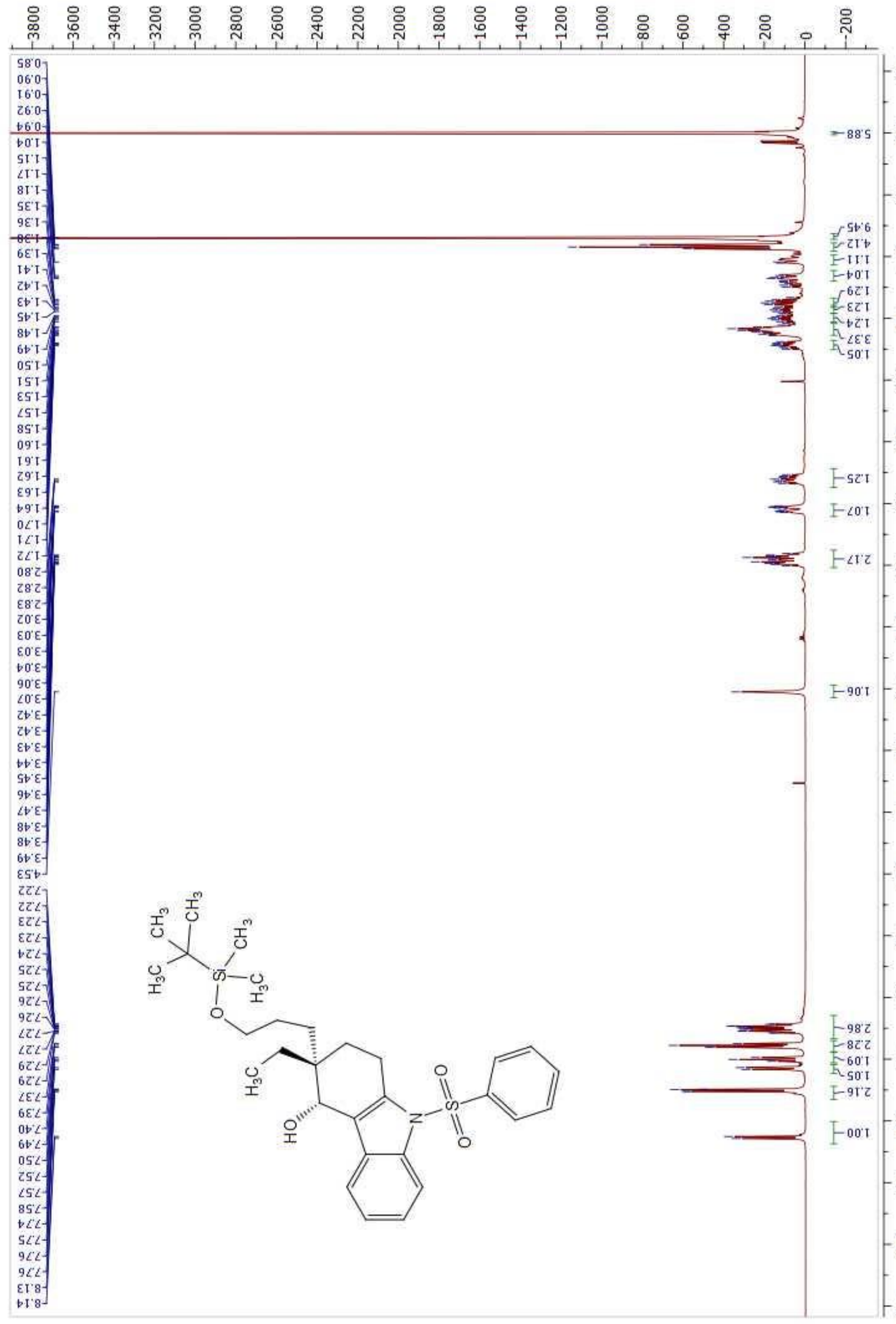


Figure 170. ^{1}H NMR spectrum of **254** (500 MHz, $CDCl_3$).

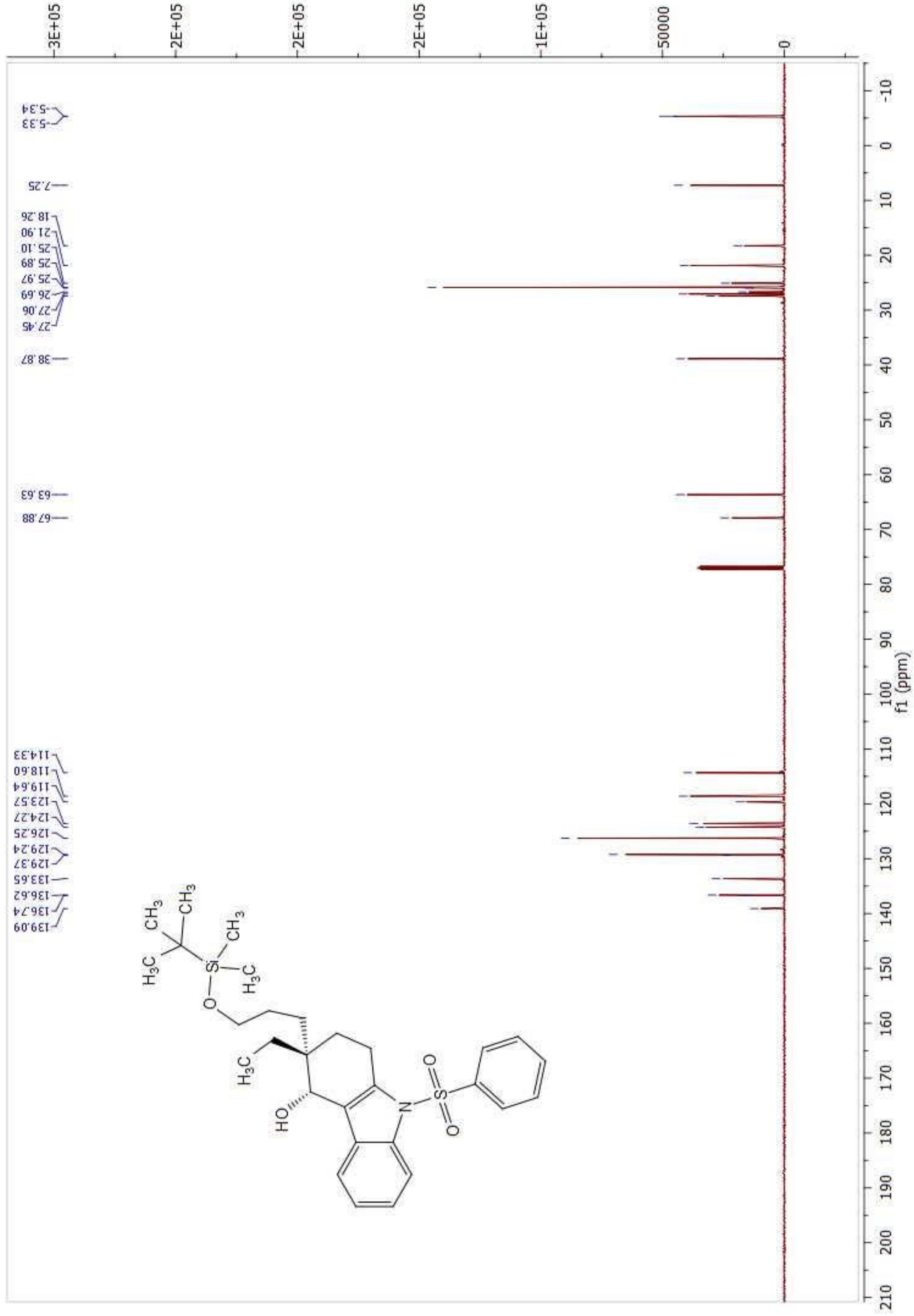


Figure 171. ^{13}C NMR spectrum of **254** (125 MHz, CDCl$_3$).

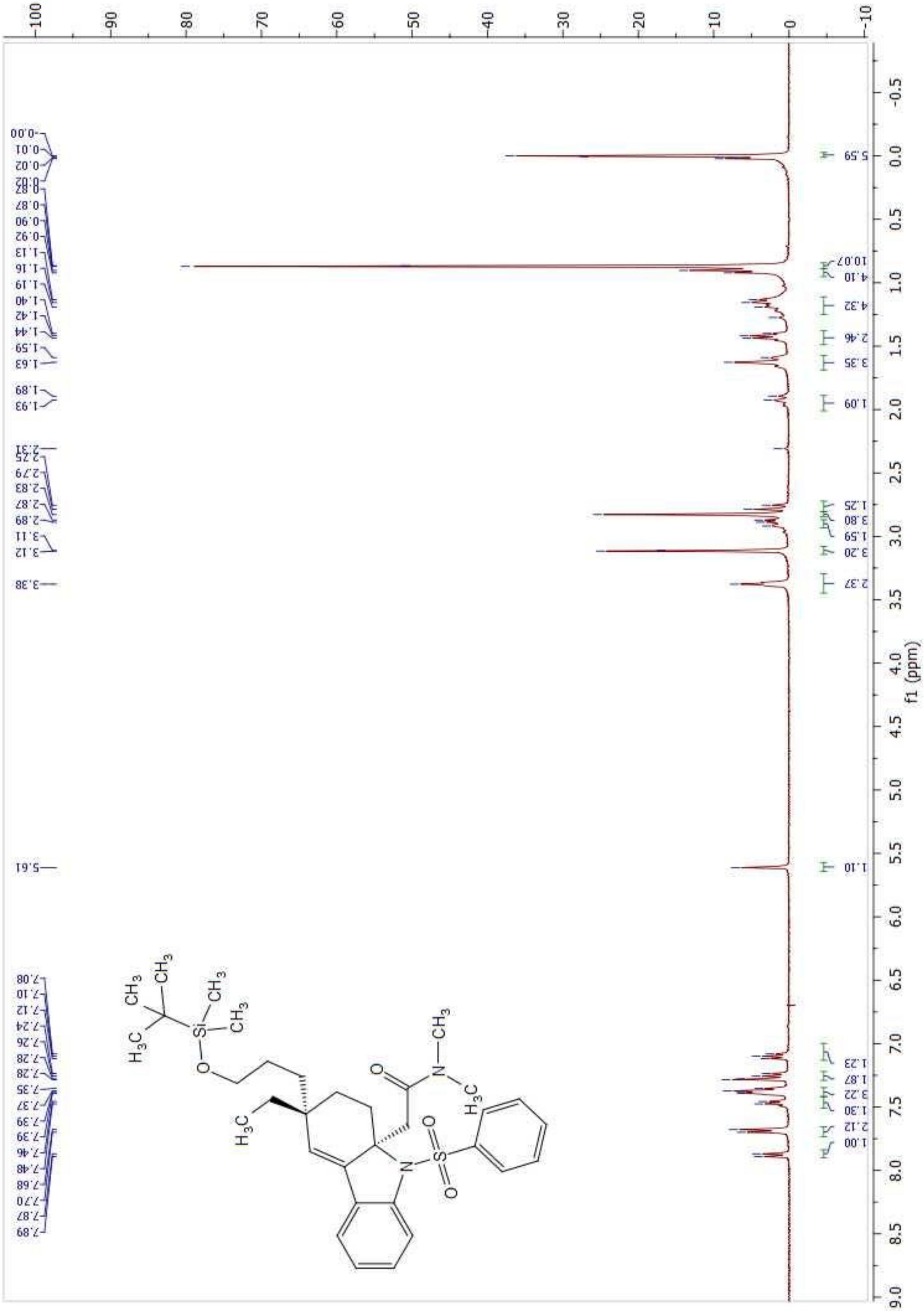


Figure 172. ^{1}H NMR spectrum of **255** (500 MHz, CDCl$_3$).

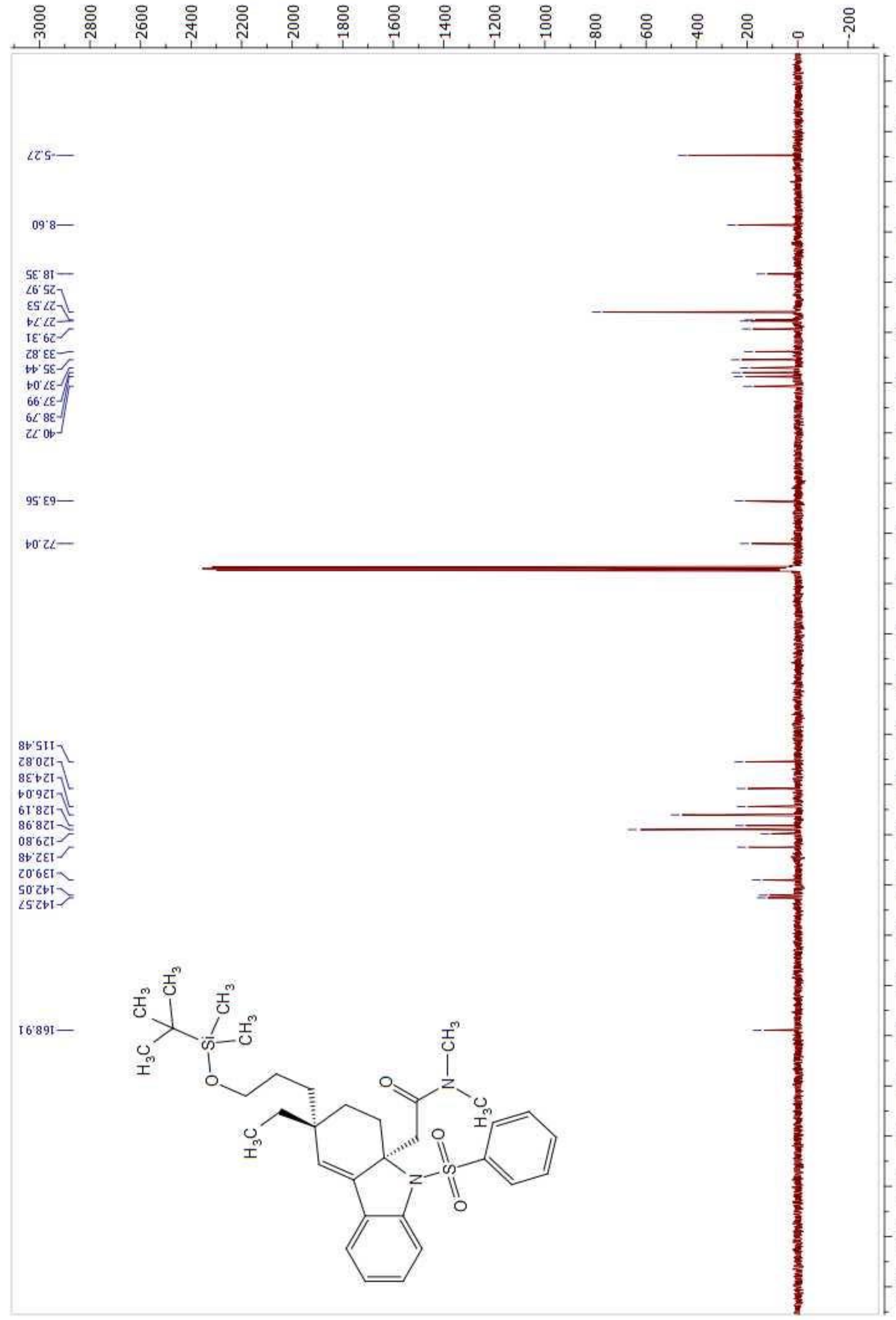


Figure 173. ^{13}C NMR spectrum of **255** (125 MHz, $CDCl_3$).

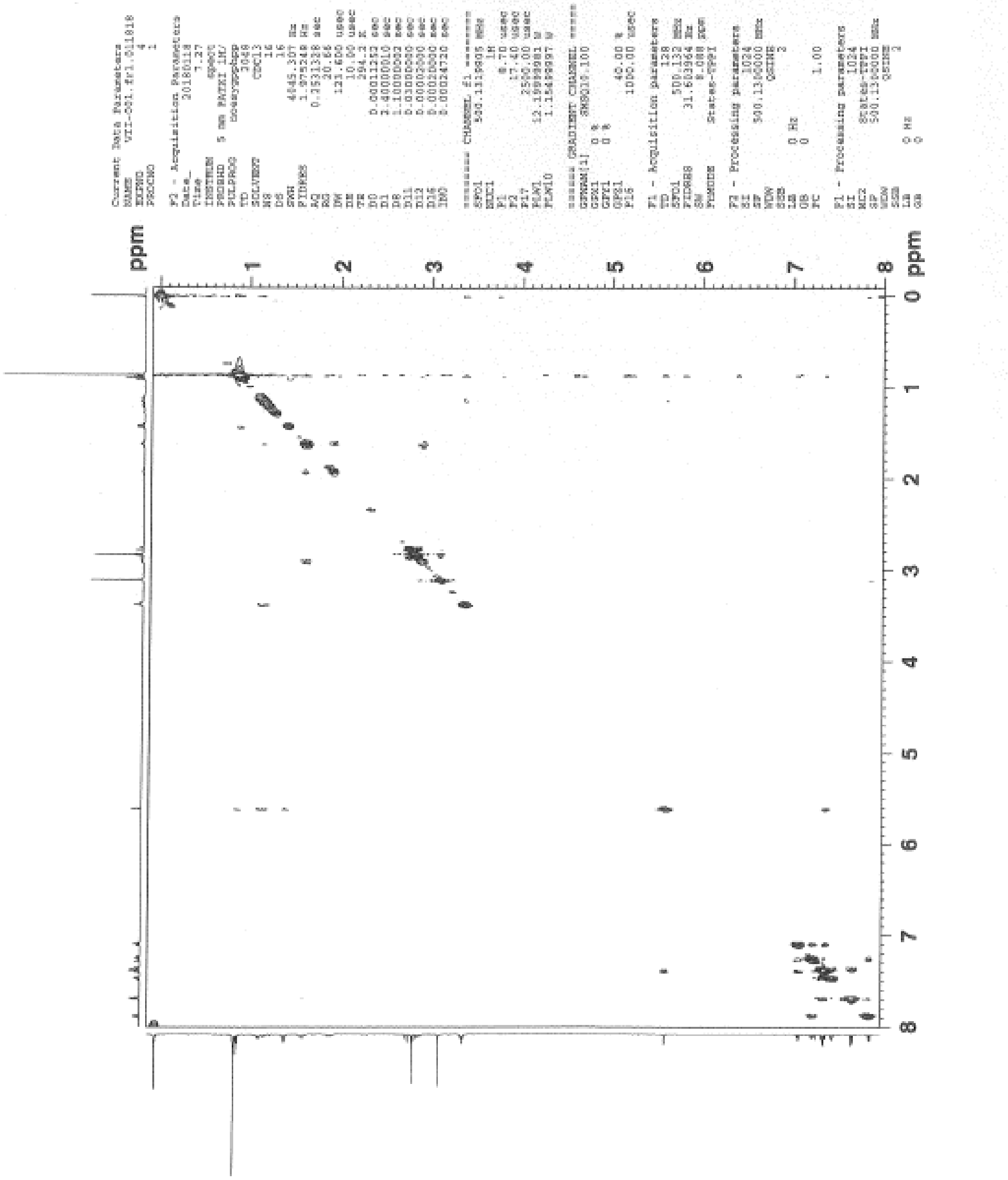


Figure 174. NOESY spectrum of **255** (500 MHz, $CDCl_3$).

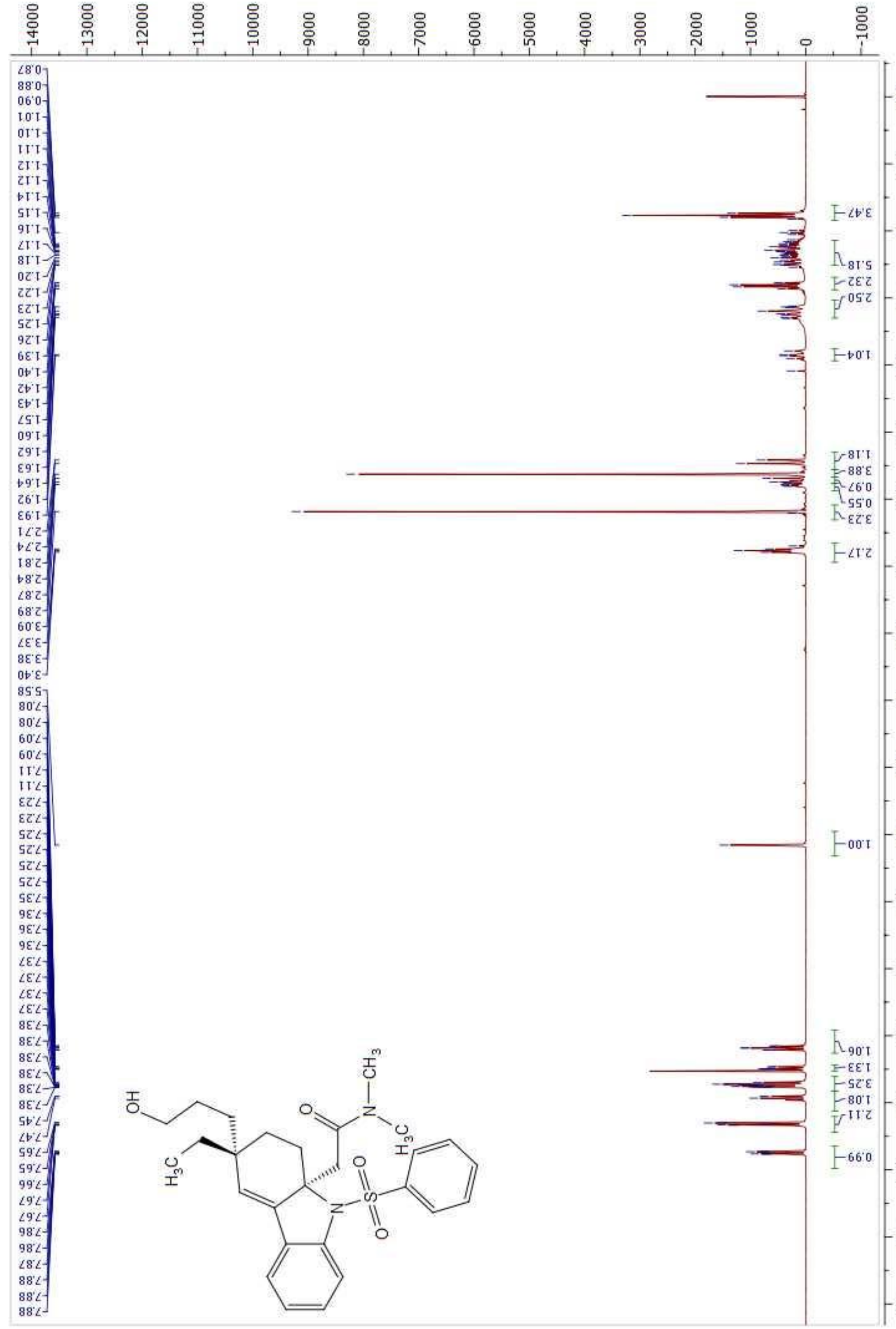


Figure 175. ^{1}H NMR spectrum of **255a** (500 MHz, CDCl$_3$).

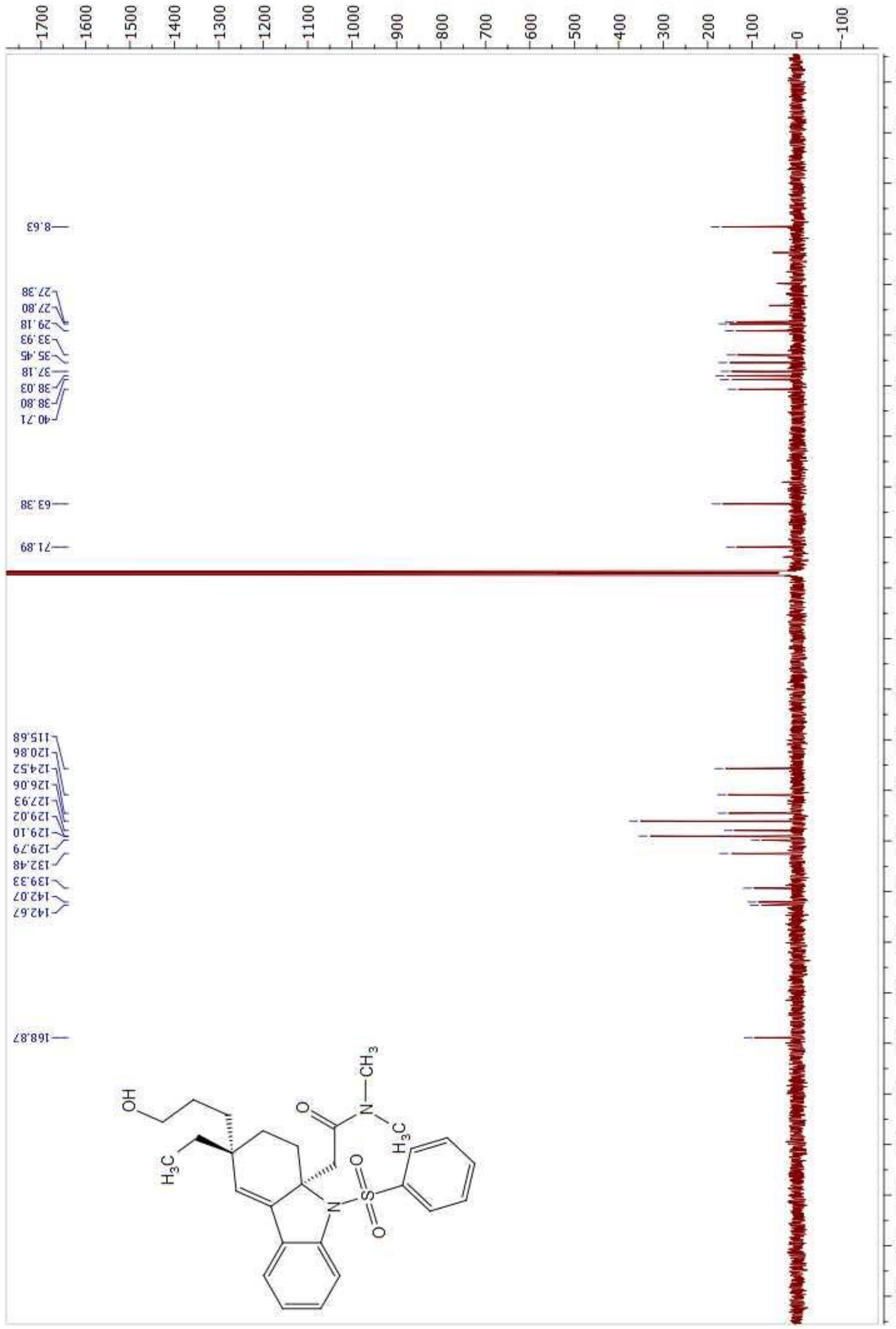


Figure 176. ^{13}C NMR spectrum of **255a** (125 MHz, $CDCl_3$).

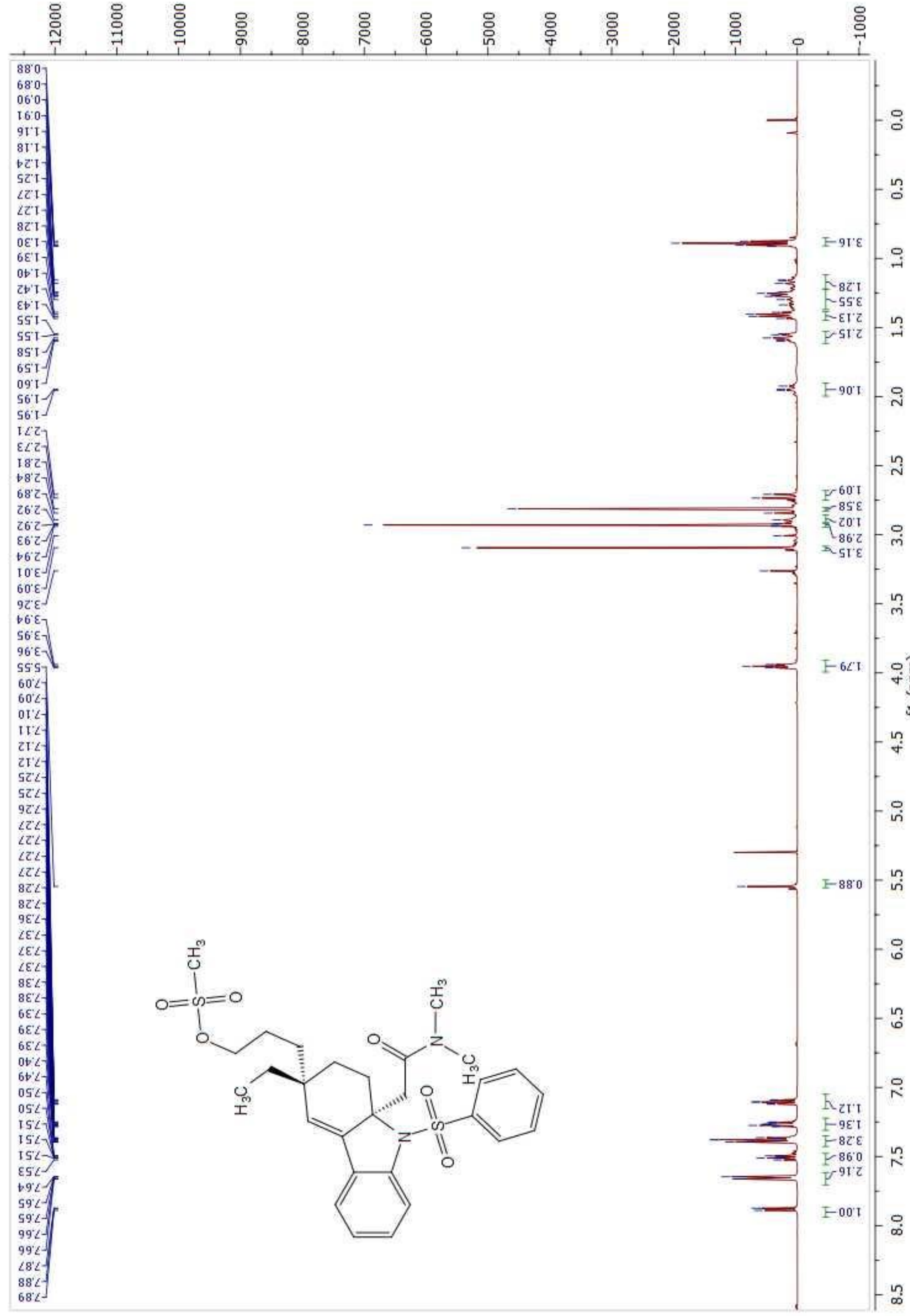


Figure 177. ^{1}H NMR spectrum of **256** (500 MHz, $CDCl_3$).

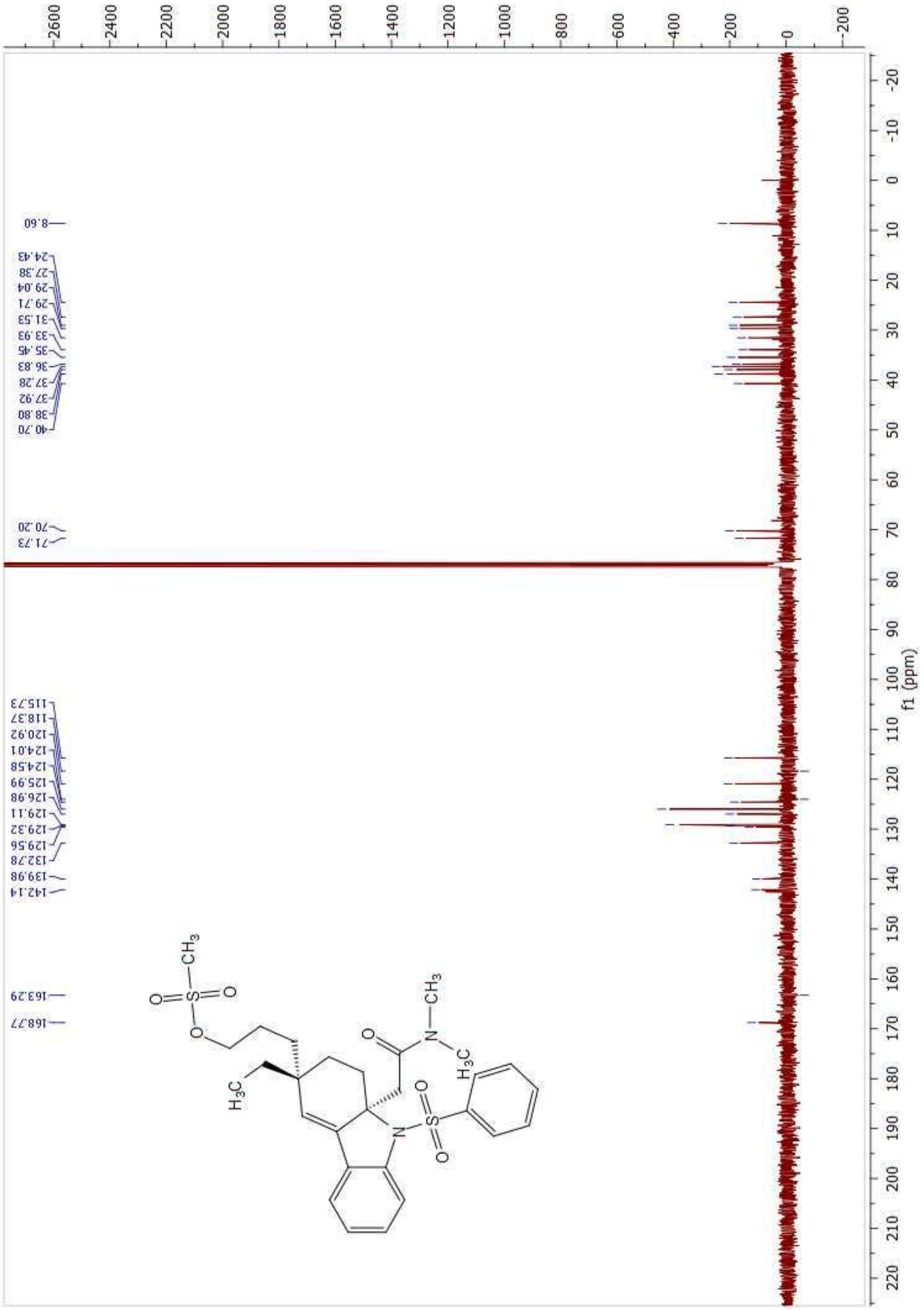


Figure 178. ^{13}C NMR spectrum of **256** (125 MHz, $CDCl_3$).

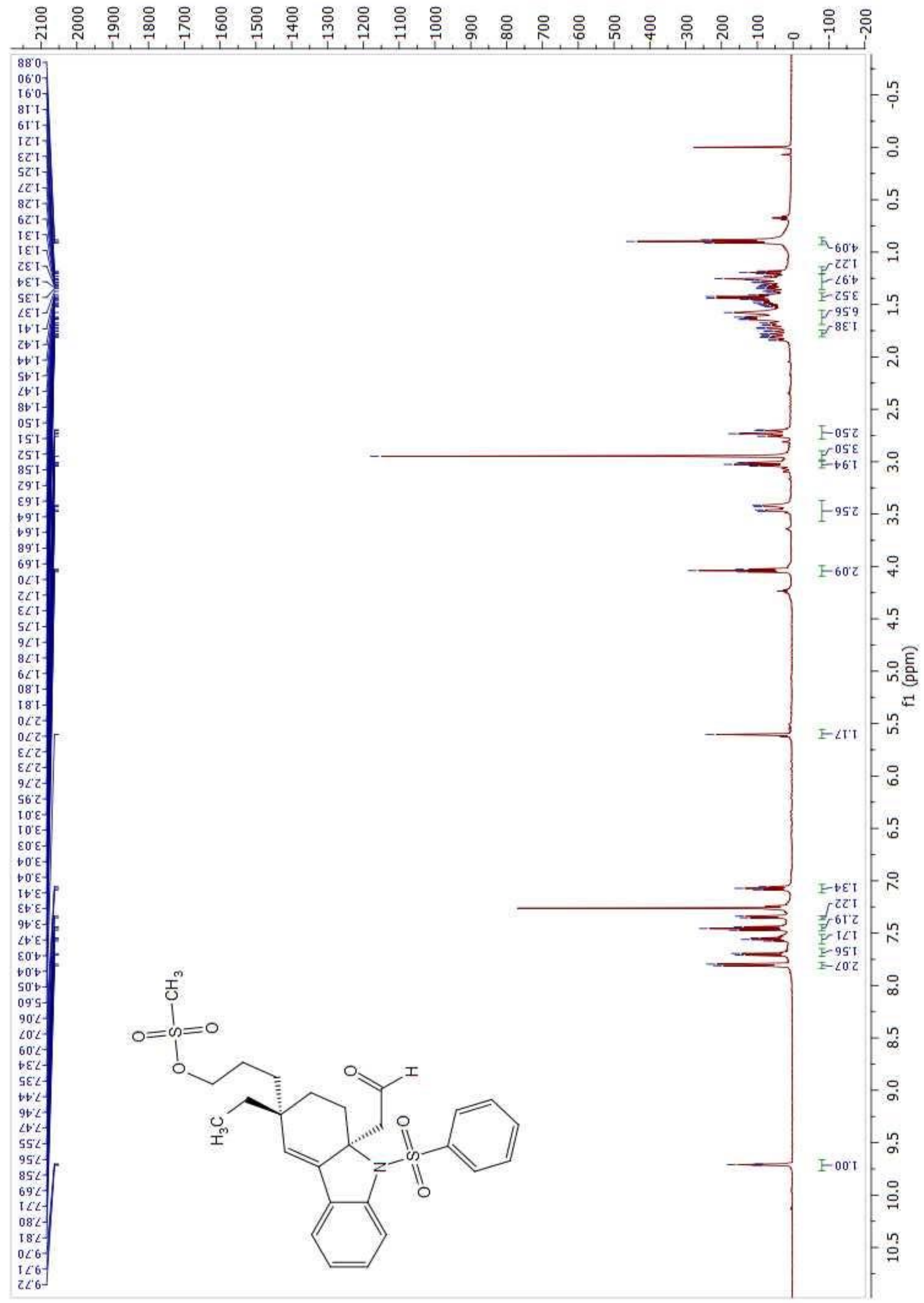


Figure 179. ^{1}H NMR spectrum of **257** (500 MHz, $CDCl_3$).

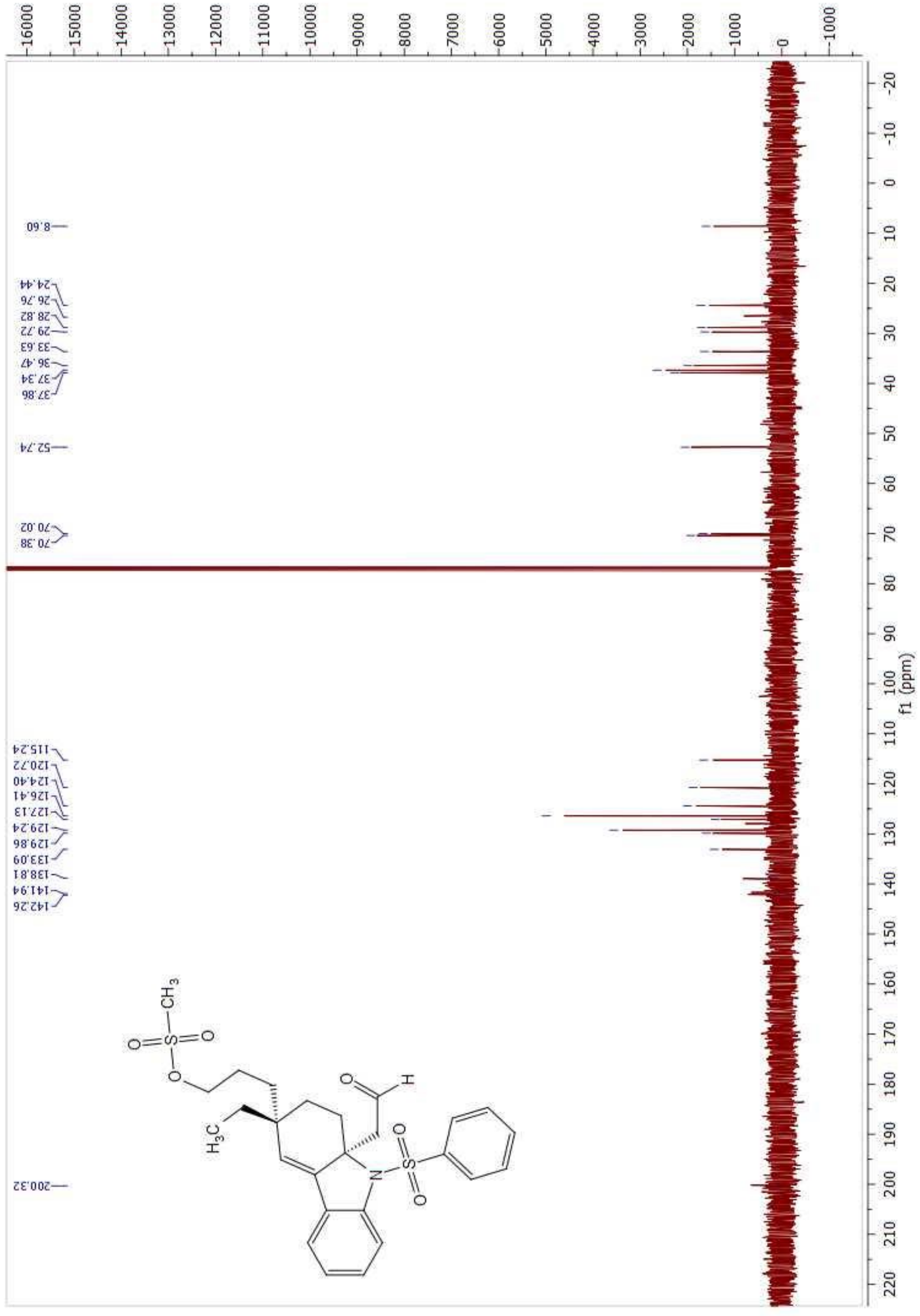


Figure 180. ^{13}C NMR spectrum of **257** (125 MHz, $CDCl_3$).

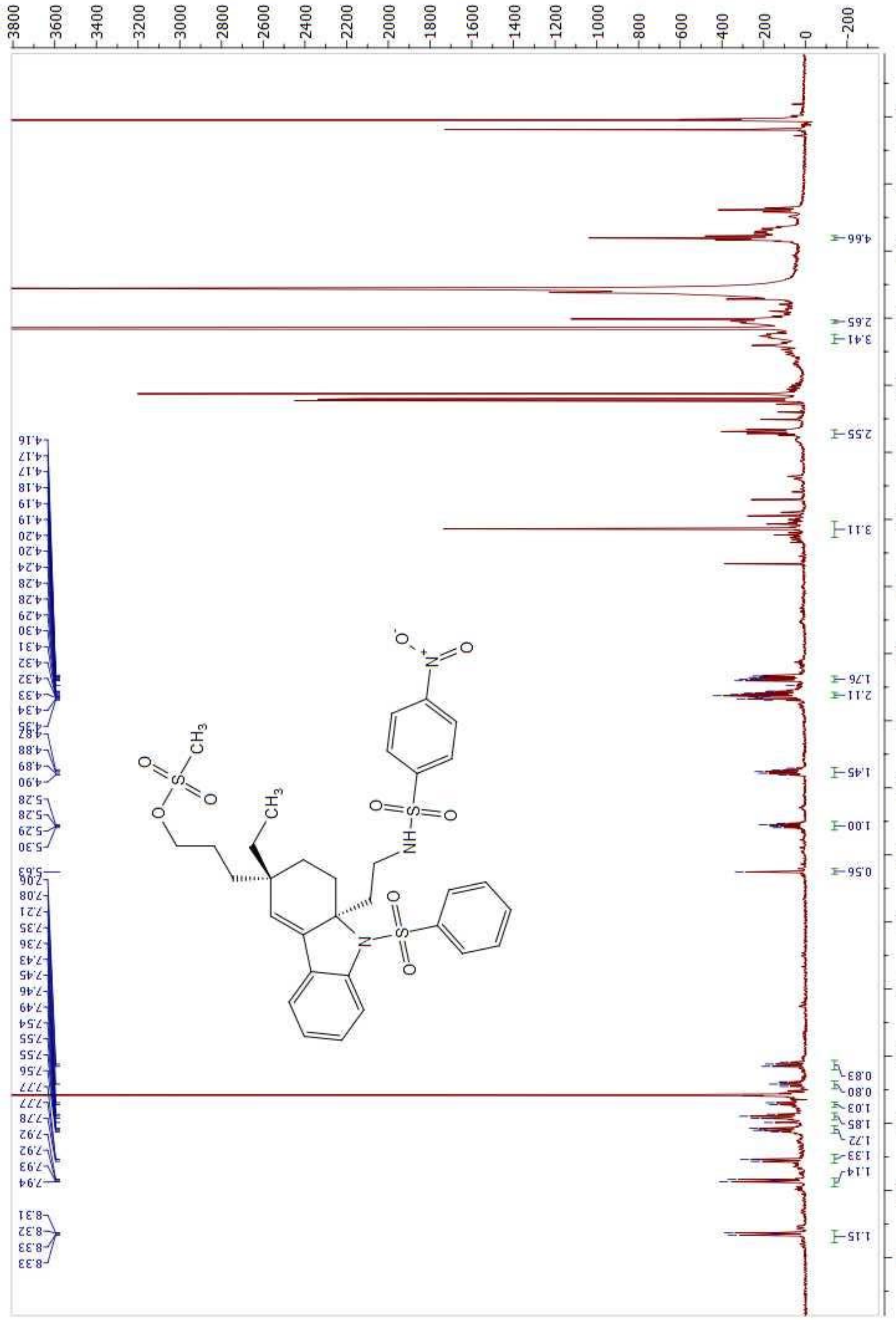


Figure 181. ^{1}H NMR spectrum of **258** (500 MHz, CDCl$_3$).

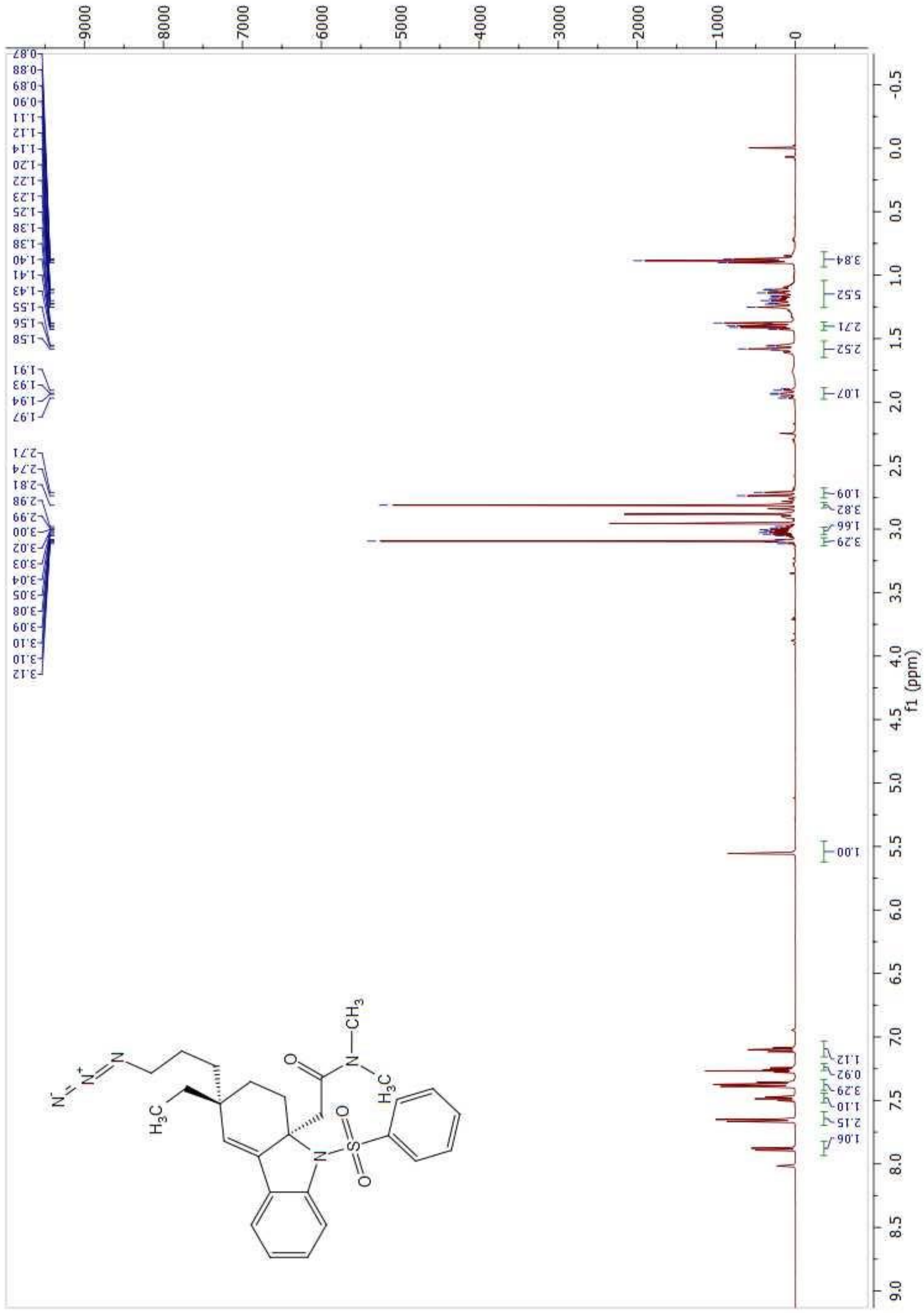


Figure 182. ^{1}H NMR spectrum of **260** (500 MHz, $CDCl_3$).

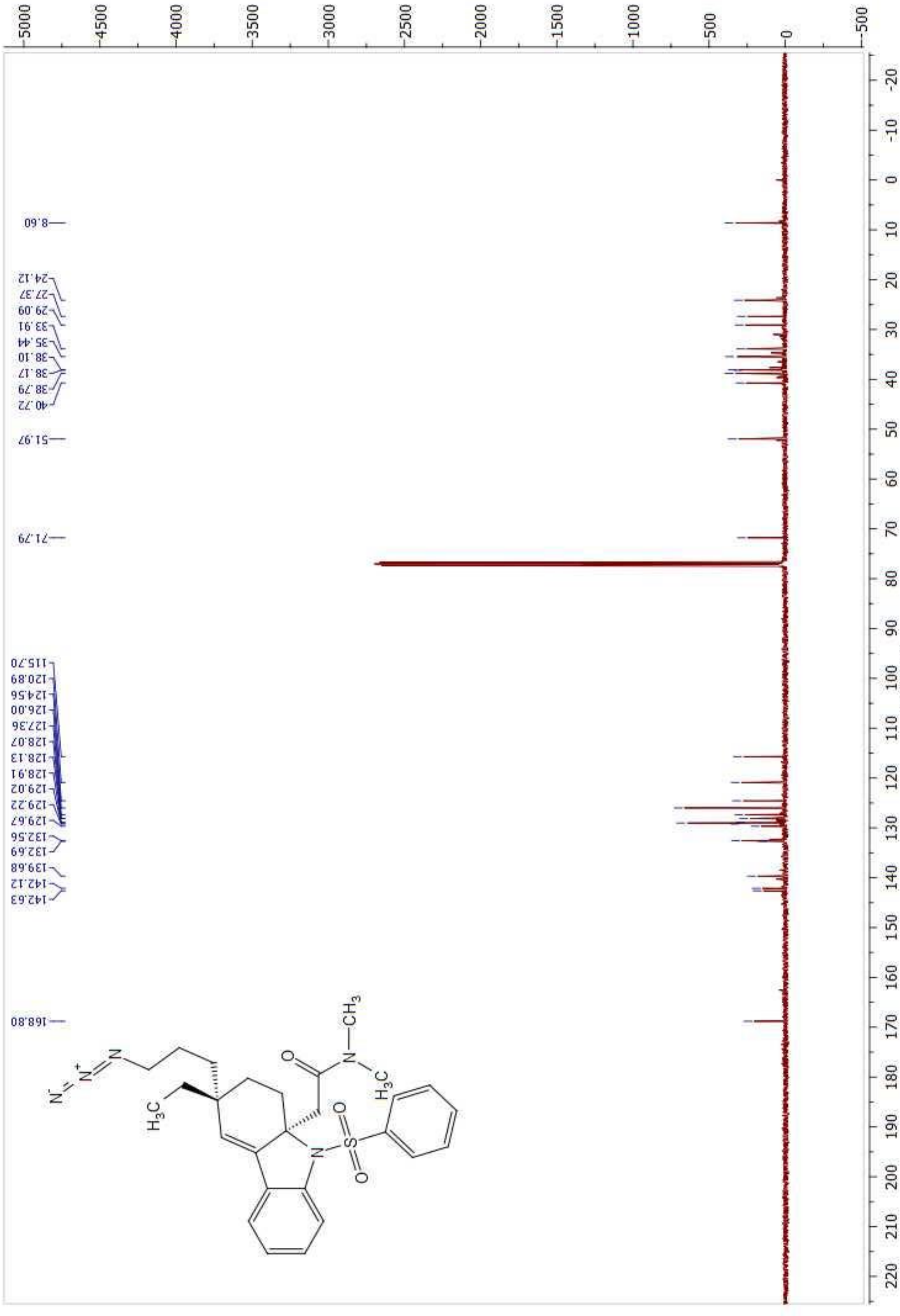


Figure 183. ^{13}C NMR spectrum of **260** (125 MHz, $CDCl_3$).

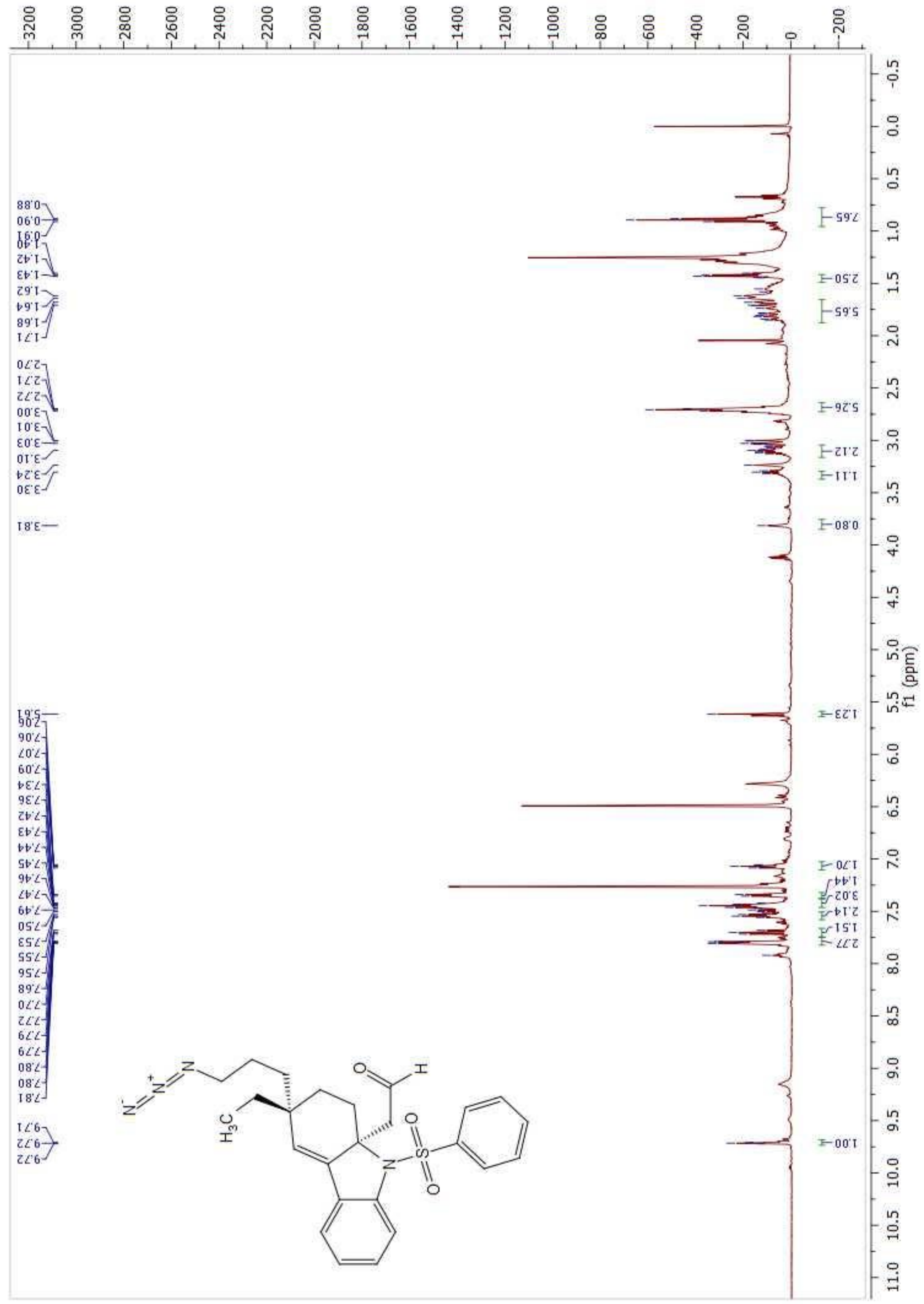


Figure 184. ^{1}H NMR spectrum of **261** (500 MHz, $CDCl_3$).

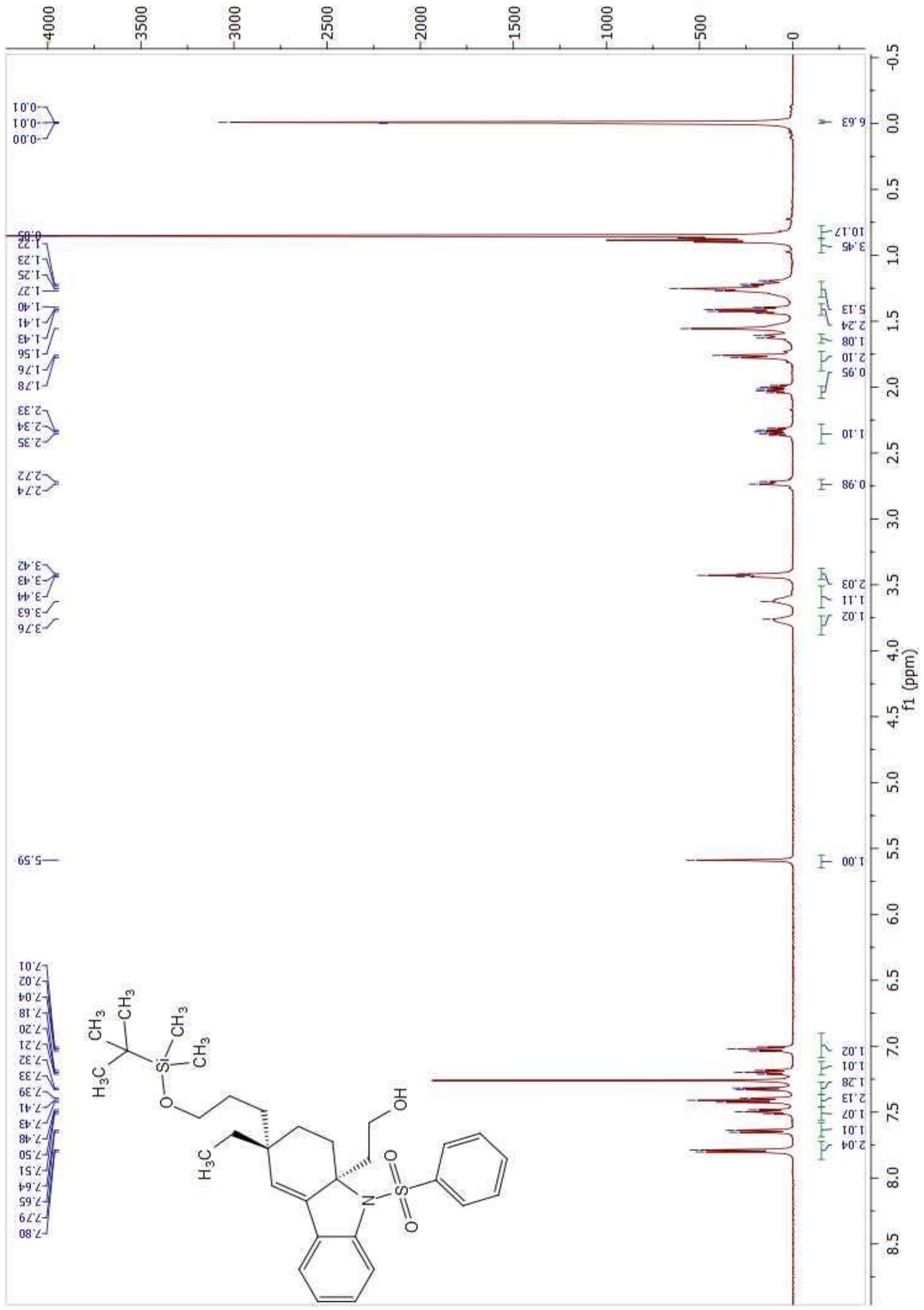


Figure 185. ^{1}H NMR spectrum of **270** (500 MHz, $CDCl_3$).

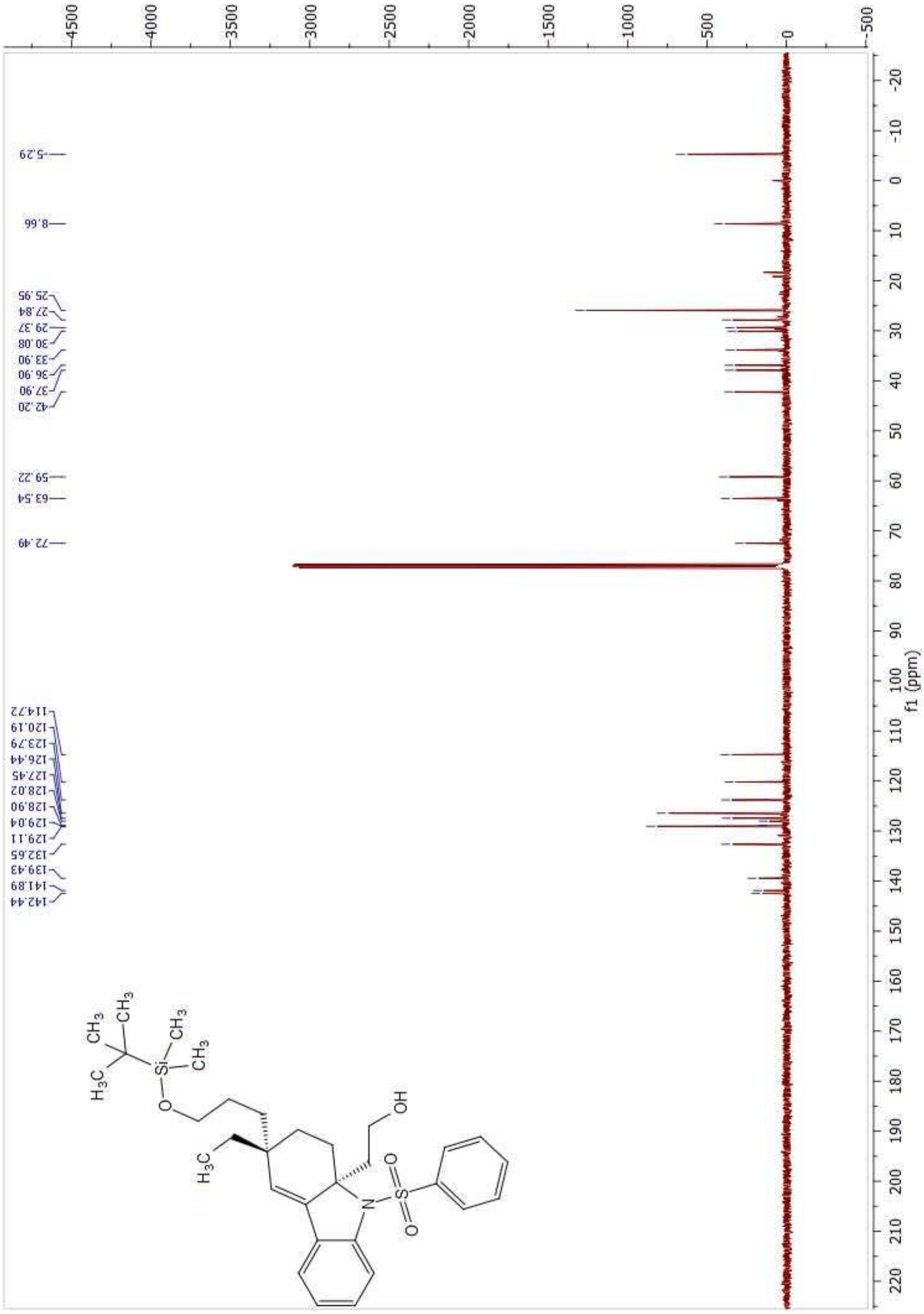


Figure 186. ^{13}C NMR spectrum of **270** (125 MHz, $CDCl_3$).

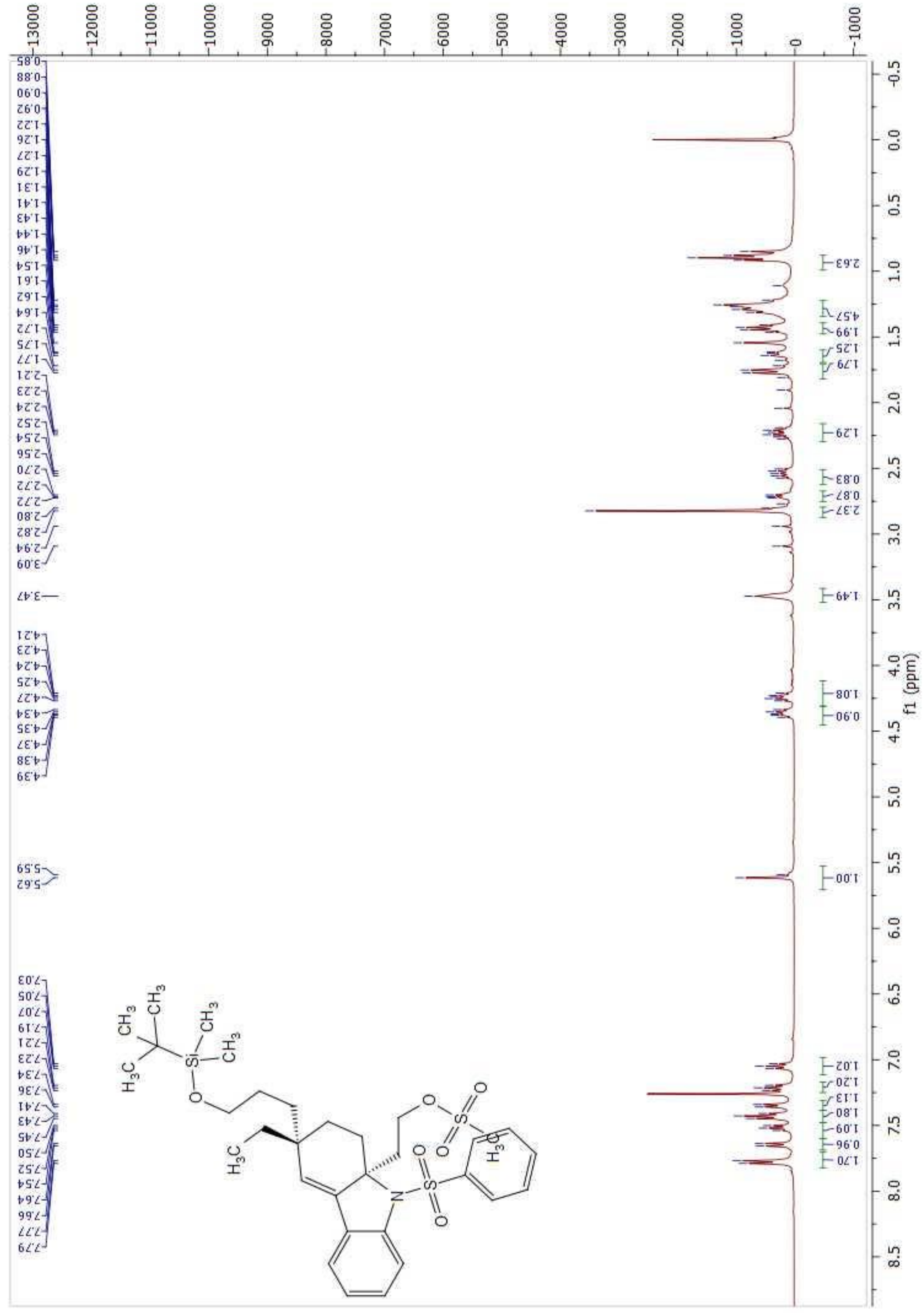


Figure 187. ^{1}H NMR spectrum of **271a** (500 MHz, $CDCl_3$).

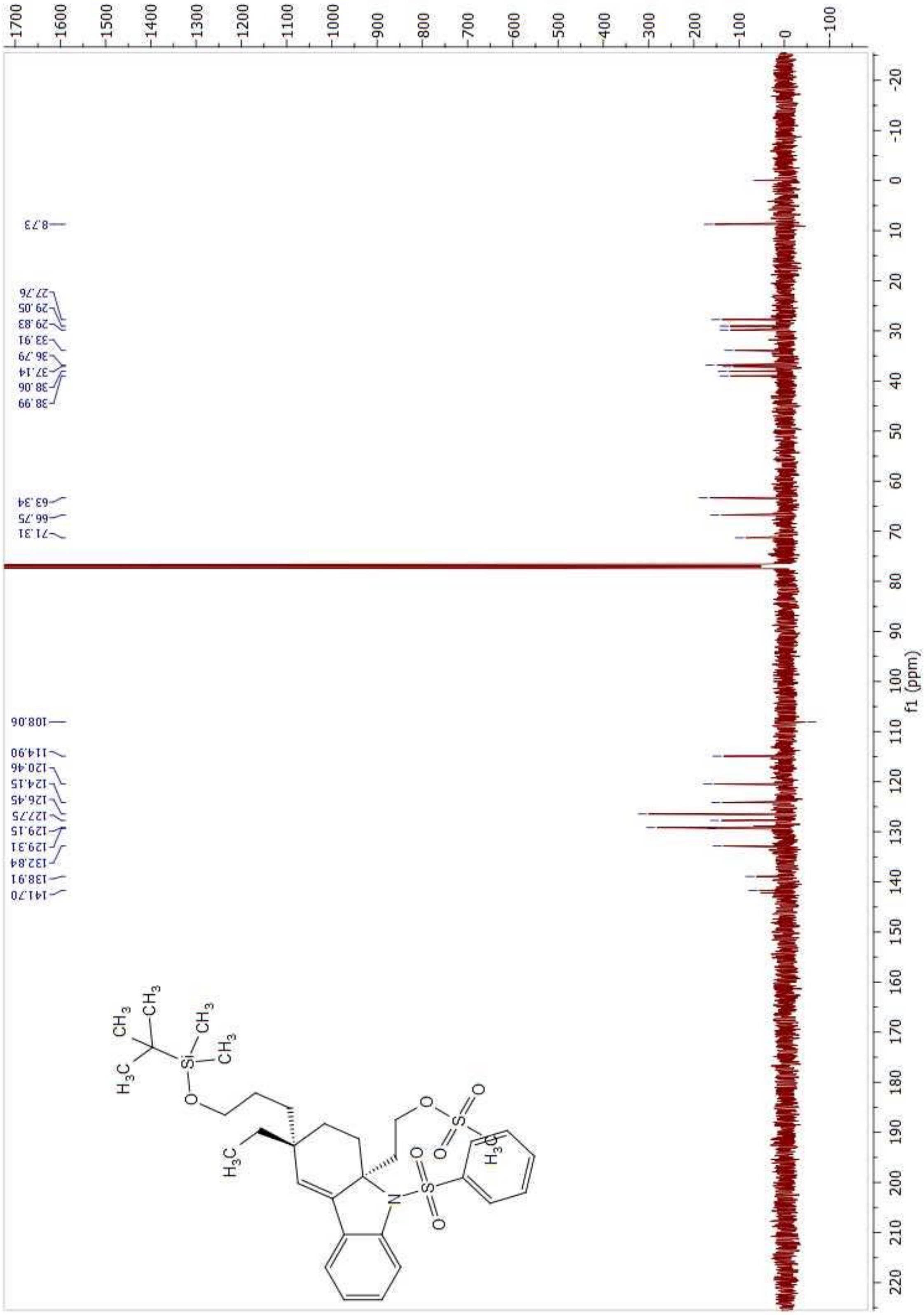


Figure 188. ^{13}C NMR spectrum of **271a** (125 MHz, CDCl$_3$).

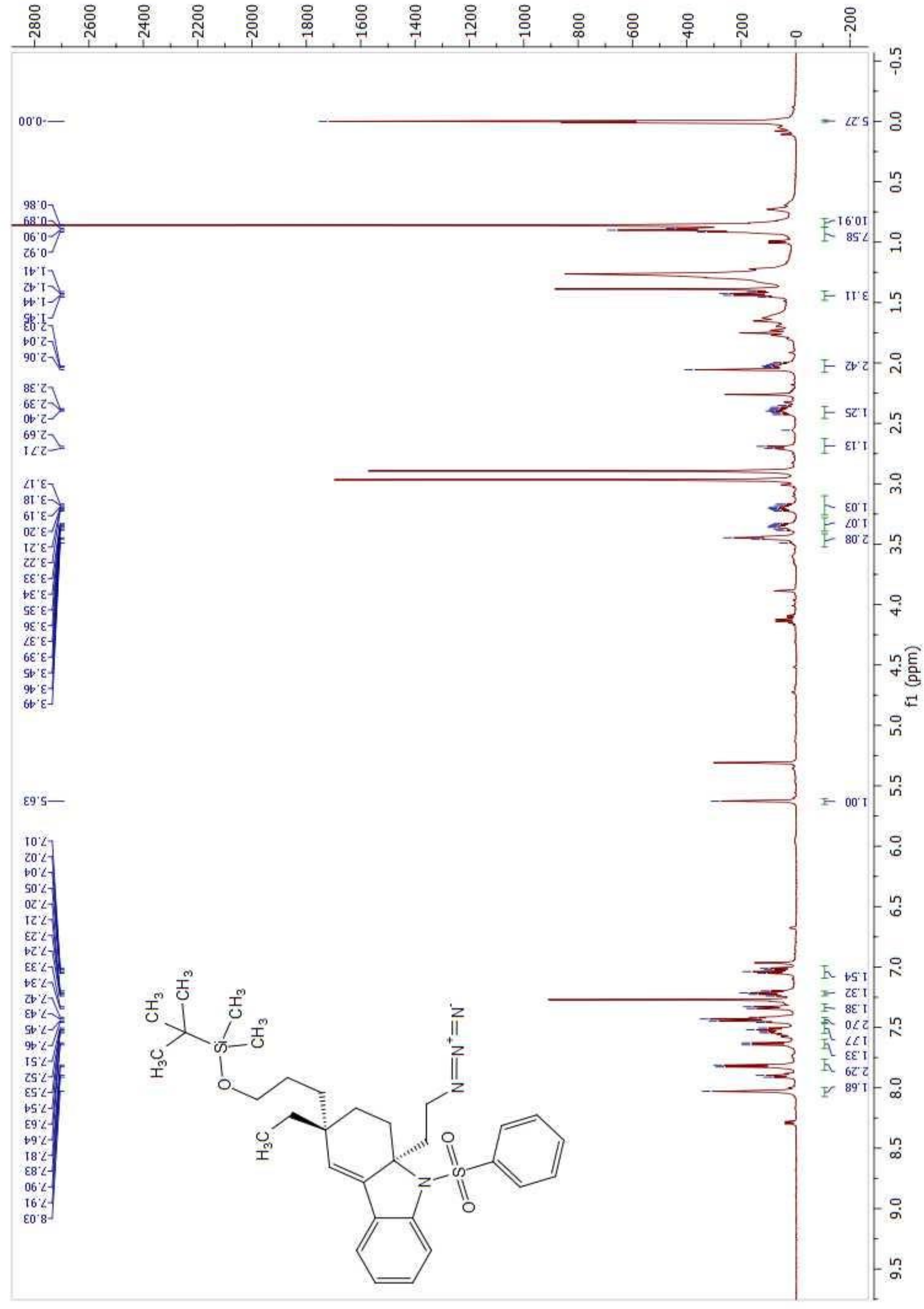


Figure 189. ^{1}H NMR spectrum of **271** (500 MHz, $CDCl_3$).

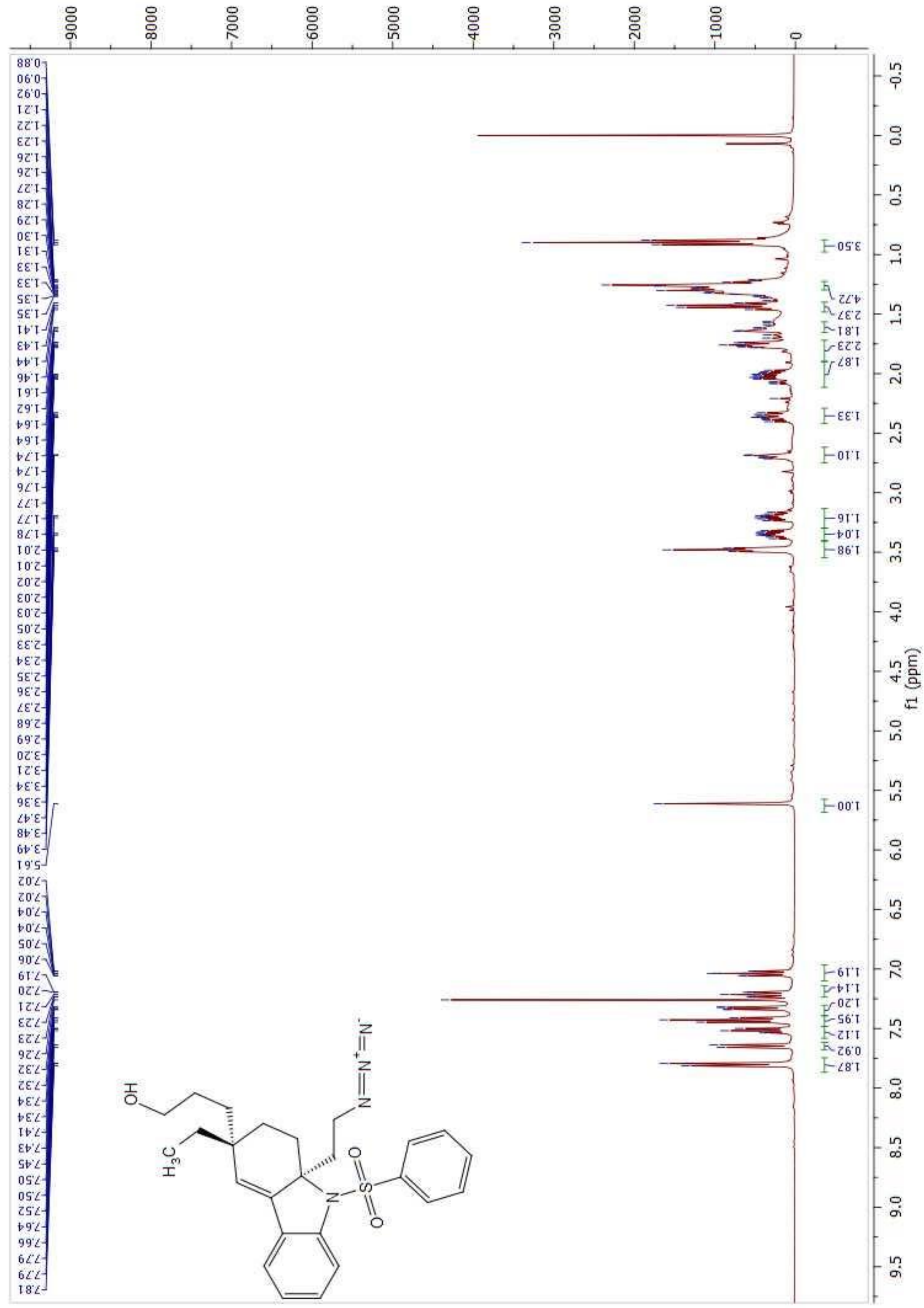


Figure 190. ^{1}H NMR spectrum of **269a** (500 MHz, $CDCl_3$).

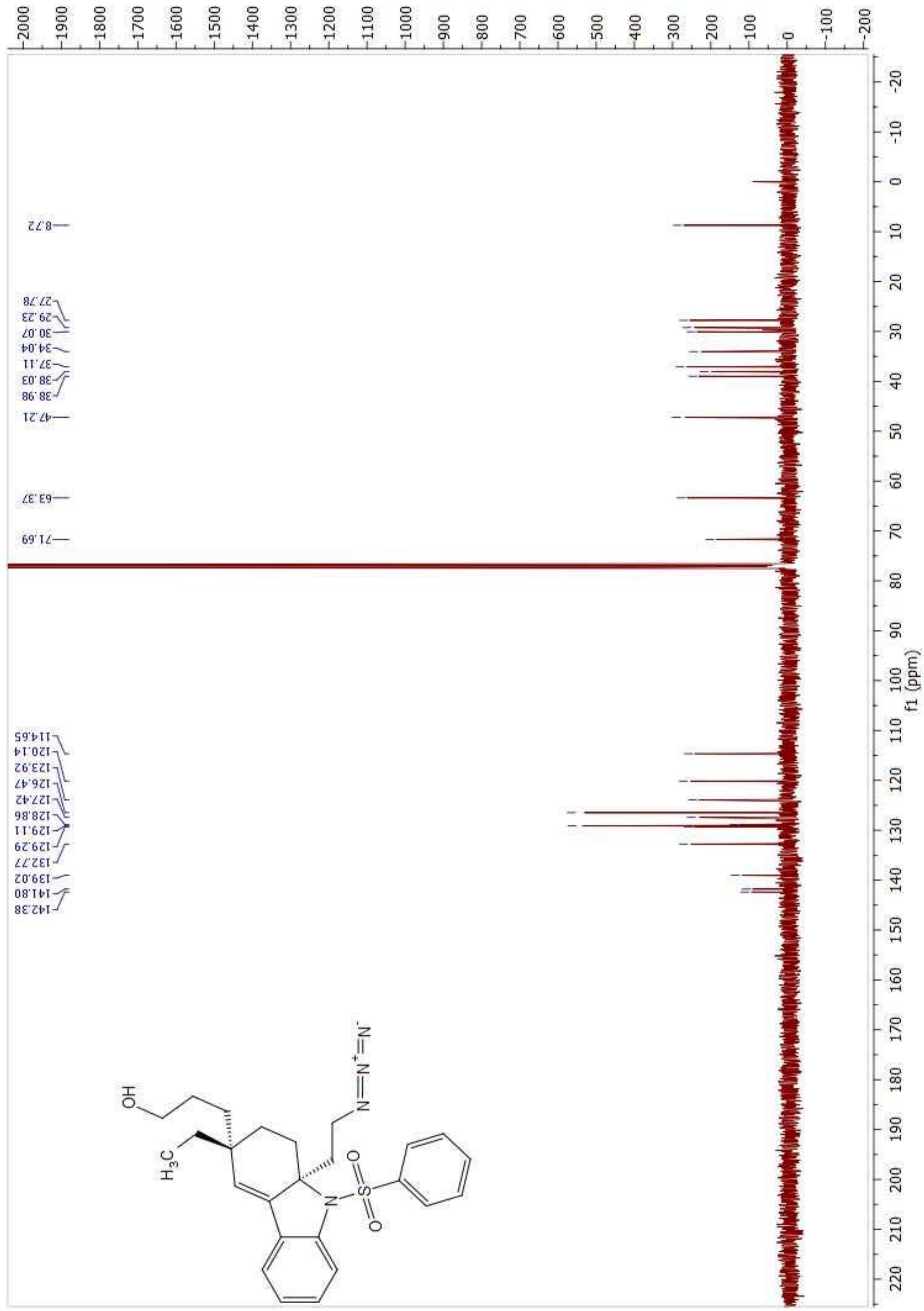


Figure 191. ^{13}C NMR spectrum of **269a** (125 MHz, $CDCl_3$).

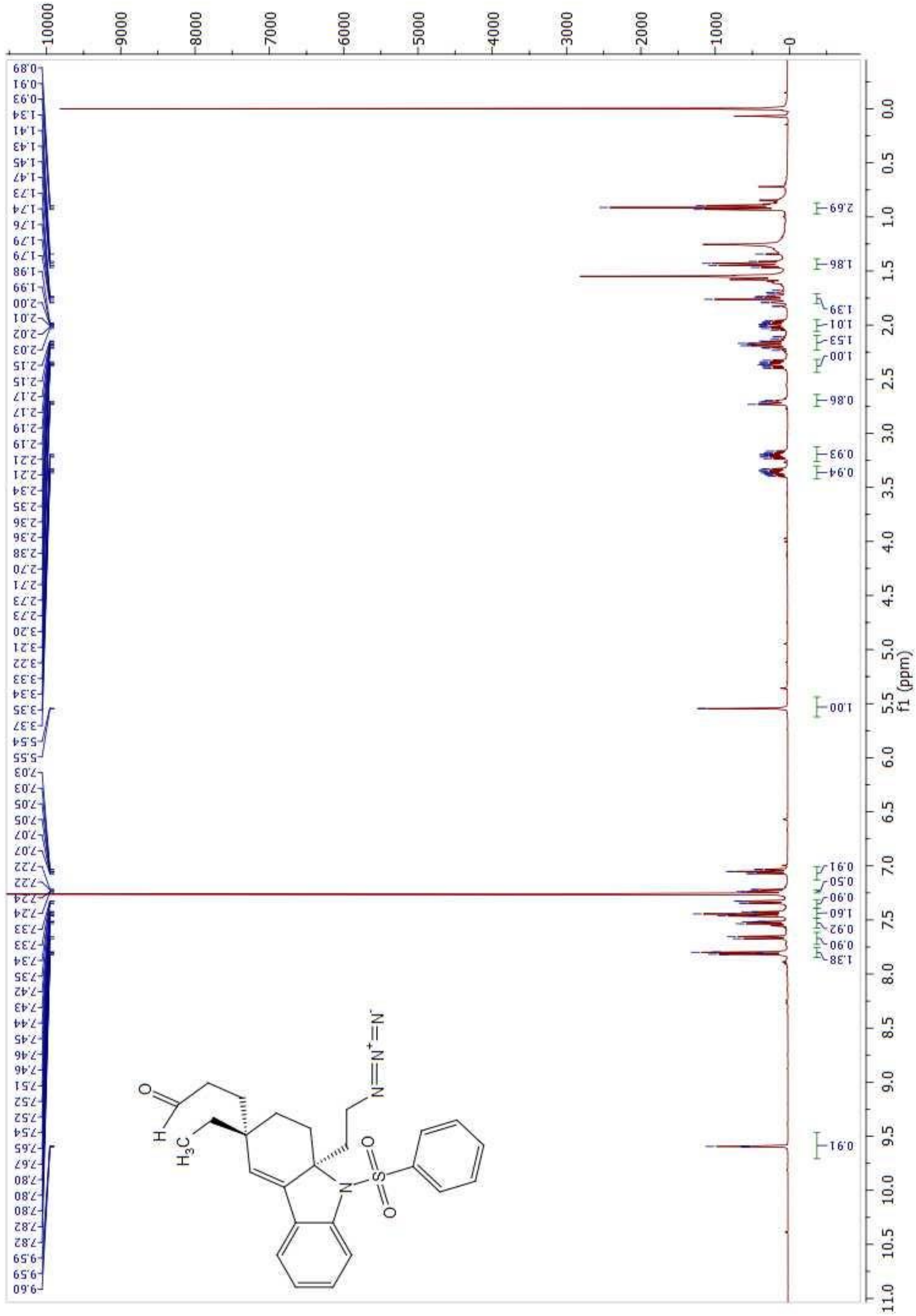


Figure 192. ^{1}H NMR spectrum of **269b** (500 MHz, $CDCl_3$).

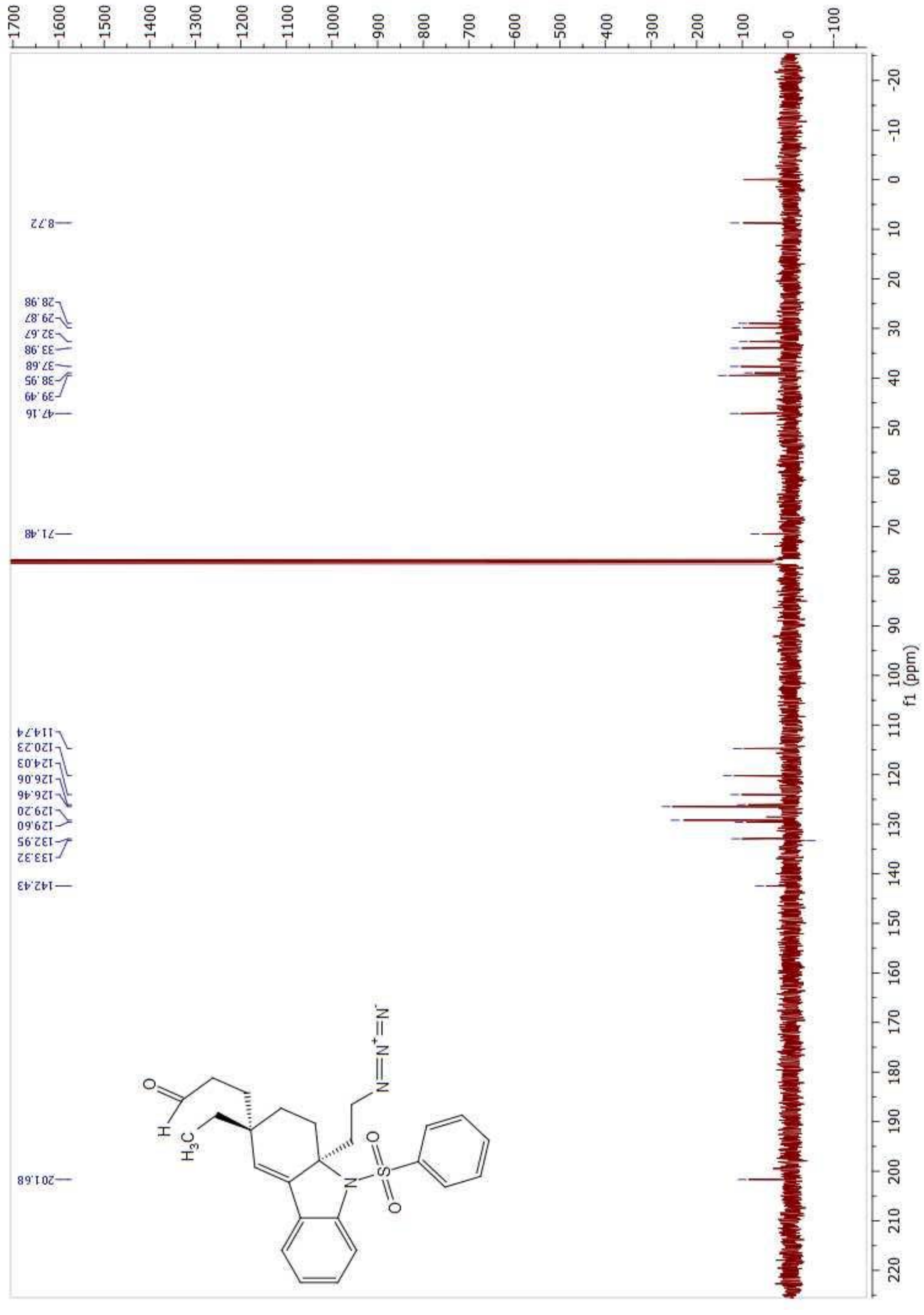


Figure 193. ^{13}C NMR spectrum of **269b** (125 MHz, CDCl$_3$).

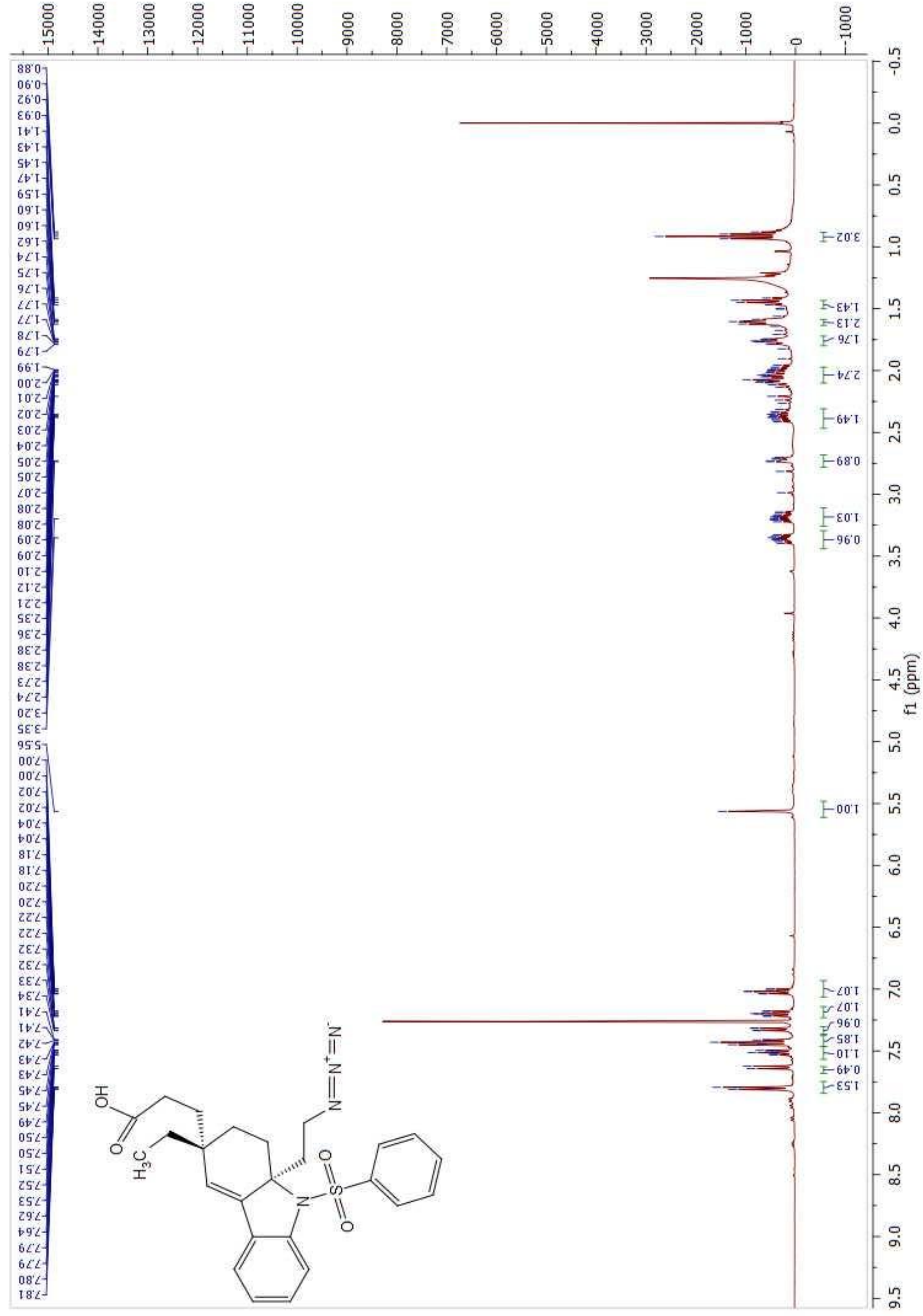


Figure 194. ^{1}H NMR spectrum of **269** (500 MHz, $CDCl_3$).

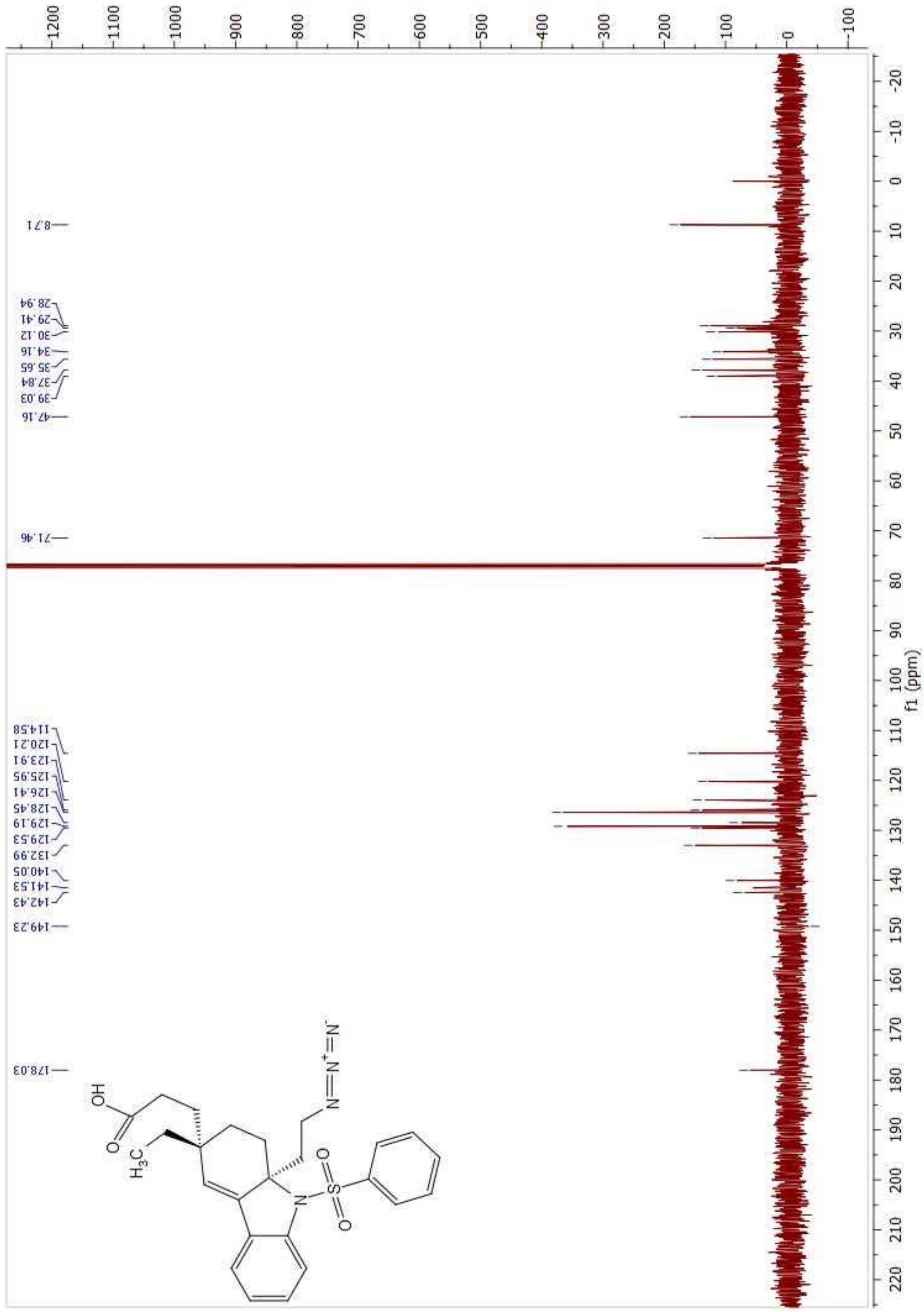


Figure 195. ^{13}C NMR spectrum of **269** (125 MHz, $CDCl_3$).