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Total Synthesis of Caulamidine A

By
Zhouyang Zhu

A dissertation submitted in partial satisfaction of the
requirements for the degree of
Doctor of Philosophy
in
Chemistry
in the
Graduate Division
of the
University of California, Berkeley

Committee in Charge:
Professor Thomas Maimone, Chair
Professor Richmond Sarpong
Professor Wenjun Zhang

Summer 2024

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Abstract

Total Synthesis of Caulamidine A

by

Zhouyang Zhu

Doctor of Philosophy in Chemistry

University of California, Berkeley

Professor Thomas Maimone, Chair

Marine bryozoans continue to provide architecturally fascinating halogenated alkaloids that pose unique challenges for chemical synthesis. This dissertation documents the evolution of a synthetic program aimed at accessing the trihalogenated alkaloid caulamidine A.

In Chapter 1, we provide an introduction to the caulamidine alkaloids, detailing their isolation, structural elucidation, and synthetic challenges. In our discussion, we compare and contrast the caulamidine alkaloids to the well-studied and topologically homologous C_{20} bis(cyclotryptamine) alkaloids, highlighting how the caulamidine alkaloids require the development of new synthetic strategies.

In Chapter 2, we describe our efforts in developing a synthetic strategy toward caulamidine A. Initially, we proposed to install the challenging neopentylic chloride motif leveraging an alkene chlorination strategy, which culminated in a 16-step racemic synthesis of caulamidine A. To achieve an asymmetric synthesis and to optimize the formation of key stereogenic centers, we truncated the synthetic route to an 11-step sequence featuring a rapid, diastereoselective ketone-amidine annulation reaction facilitated by glycol bistriflate and a highly diastereoselective hydrogen atom transfer that correctly established the key chlorine-bearing stereogenic center.

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To the past Maimone group members

Xirui: Huge thanks for sharing your job experience and advice with me. They are incredibly helpful. Wishing you all the best in your career, and please don't forget about me when you and Danny have your own startup☺.

Bingqi: Thanks a bunch for helping me during those tough times and giving me your advice. You're truly the nicest person I know, always smiling and willing to listen. I have no doubt you'll be an awesome PI!

Karl: I'm sorry I never quite caught your jokes (I'll blame my poor English for that)! Nonetheless, you are a very fun and caring person. Thank you for always brainstorming for my projects and being there to help. Wishing you all the success in the industry!

Claire: Thank you for always maintaining the group culture and helping communicate with the other groups during the NMR war lol. I wish you and your family all the best!

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Linus: 沈老板, thank you for being a great 师兄 who's always there to help. And thanks for giving us valuable advice and helping us make connections outside the lab. I wish you 生意兴隆, 早日财富自由!

Rachel: You might have seen it several times in other people's theses, but I still want to say—you are a very nice lady! Thank you for baking all those delicious pastries and for taking care of the lab. I wish you and Danny all the best! (I'm still waiting for the wedding invite!☺)

Vasil: I was lucky to have you as my deskmate in 909 when I first joined the lab. Your kindness and patience were exactly what I needed at that time, and I'm truly grateful for it. Also, a big thank

you for all the help you gave me during my job search process. I wish you all the luck in your career ahead!

Andre: I'll never forget that night after my first lab Christmas party when you and Danny came over while I was struggling with scaleup alone. You suggested I start my own project, which turned out to be the perfect direction for my PhD. Thanks to your advice, I've experienced tremendous growth and success during my PhD. I can't thank you enough for that! I have full confidence that you'll be a great PI, and I wish you all the best in your career!

Paulo: Thank you for always being so nice and caring! I felt like a princess with how you treated me♡. You were always there to listen whenever I wanted to talk, and you always gave me a ride whenever I needed one. You also drove so far away to grab my favorite Bonchon! Plus, you taught me all the tricks even though I have never bought you boba or dim sum in return lol. Now that we will be working at the same company, we can have dim sum, hotpot, and many other foods together soon!

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Jun: Congratulations on your recent papers! Not long ago you were still worried about your tenure track. Now you have a Science and a JACS in a row! How amazing! I can't wait to see more papers coming out from your lab. Best of luck in your career, although I'm sure you won't need it!

Naifeng: I'm glad I had the chance to work in the same room as such a brilliant scientist like you. I learned a great deal of useful lab tips and, most importantly, how not to let chemistry control my emotions. Thank you for all the valuable lessons, and I wish you and your family all the best!

To the current Maimone group members

Danny H.: The summer before you joined, Danny told me you were a math guy who didn't know much chemistry, just like me. Well, turns out he was completely wrong! When the three of you showed up, I felt completely left behind and stressed out. I couldn't be more grateful to you for helping me catch up. The weekly Classics and quizzes really taught me a lot, and I miss them a bunch. Throughout my PhD, you never hesitated to help me no matter how much time and effort it took. Your kindness is incredible, and I'm certain you'll be an exceptional professor in the future. Best wishes for your career!

Yi: My best partner in chemistry and in life, I can't thank you enough for always being there for me. I know dealing with my bad temper isn't easy, but you always handle it like a champ. Over the past four (nearly five) years, I've grown so much as a person and a chemist, and it's all thanks to you. I know you've been feeling really stressed about the future lately, but I want you to know

that no matter what happens, we'll tackle it together. Here's to many more years of growth and support!

Kelvin: I'm really impressed by how you manage to balance skating with your chemistry PhD, even though it means missing out on a bunch of dim sum parties☹. Are all Harvard students as versatile as you and Danny (our pro CS:GO player lol)? You both are also incredibly skilled at writing and presentations—my go-to folks for help with editing manuscripts and slides (and rewriting angry emails lol). I know you lean toward the east coast for work, but since you will be travelling often for tournaments, let's definitely catch up whenever we can!

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Dad, mom, and grandma: I'm really sorry it's been four years since I last visited home. I know you've been missing me a lot, and I miss you too. Thank you for believing in me and patiently waiting for my return. And a heartfelt thank you for your unconditional love, unwavering support,

and understanding over the past 27 years. Pursuing a PhD can be challenging, and life can be tough, but knowing you've got my back makes it all less scary. I couldn’t love you more, and I can't wait to see you soon back home.

List of Abbreviations

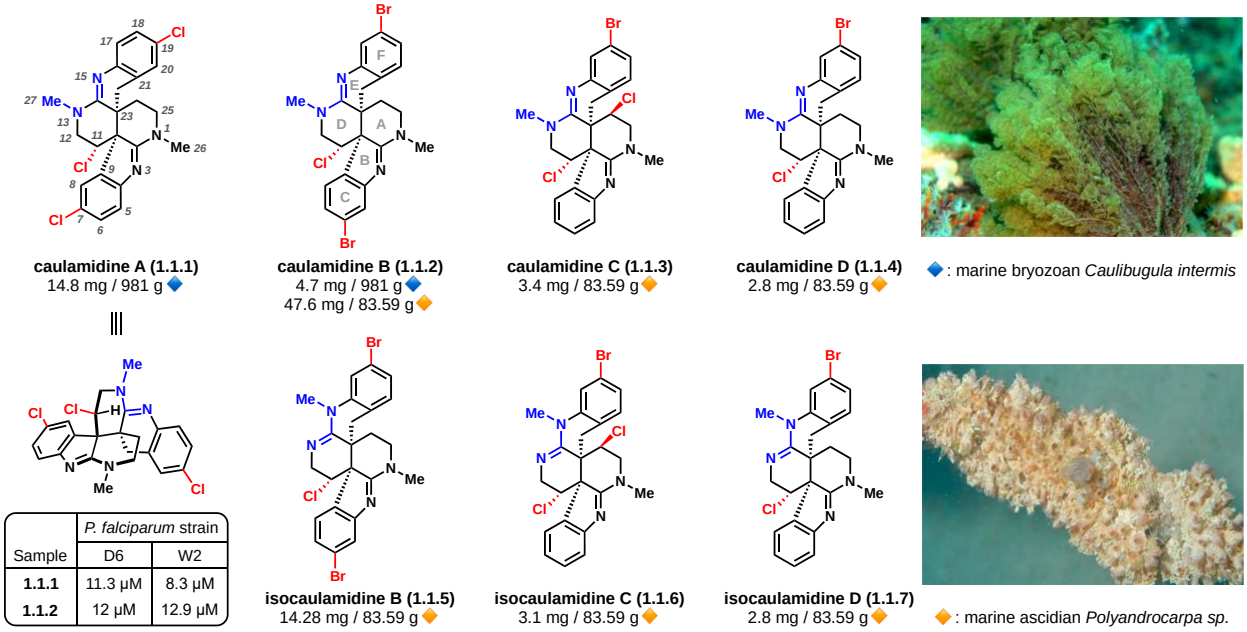
acac	acetylacetonate
Alloc	allyloxycarbonyl
9-BBN	9- borabicyclo[3.3.1]nonane
BF_3•Et_2O	boron trifluoride diethyl etherate
BINOL	1,1'-bi-2-naphthol
Boc	*tert*-butyloxycarbonyl
CAN	ceric ammonium nitrate
CASE	computer-assisted structural elucidation
CSA	camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCDMH	1,3-dichloro-5,5-dimethylhydantoin
DCM	dichloromethane
DIC	*N,N'*-diisopropylcarbodiimide
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMPU	*N,N'*-dimethylpropyleneurea
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
dtbpy	di-*tert*-butyl bipyridine
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
EI	electron ionization
ESI	electrospray ionization
HAT	hydrogen atom transfer
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
i-Pr	isopropyl
IC_{50}	half maximal inhibitory concentration
IR	infrared
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LED	light emitting diode
LiHMDS	lithium bis(trimethylsilyl)amide
LLS	longest linear sequence
LPO	lauroyl peroxide
Me	methyl
MS	molecular sieves
MWI	microwave irradiation
NaHMDS	sodium bis(trimethylsilyl)amide

NCS	*N*-chlorosuccinimide
NHPI	*N*-hydroxyphthalimide
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
PMB	*p*-methoxybenzyl
ppm	parts per million
ppy	2-phenylpyridine
PTSA	*p*-toluenesulfonic acid
pyr	pyridine
RCSA	residual chemical shift anisotropy
RDC	residual dipolar coupling
Red-Al	sodium bis(2-methoxyethoxy)aluminium hydride
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TPAP	tetrapropylammonium perruthenate
UV	ultraviolet
VT	variable temperature

Chapter 1. Introduction to the Caulamidine Alkaloids

1.1 Caulamidines Isolation and Structural Elucidation

The caulamidine alkaloids (**1.1.1**–**1.1.7**, Figure 1.1.1) are a group of polyhalogenated natural products characterized by a hexahydro-2,6-naphthyridine core fused by a dihydroindole-derived and tetrahydroquinoline-based ring system. Among these, caulamidines A (**1.1.1**) and B (**1.1.2**) were the first to be isolated and characterized.[1] These two compounds were originally isolated as minor constituents from the marine bryozoan *Caulibugula intermis* by Gustafson and coworkers in 2004. The principal constituents, named caulibugulones, were identified to be a series of cytotoxic isoquinoline quinones and iminoquinones.[2] Despite being non-toxic to human cells, both **1.1.1** and **1.1.2** exhibited antimalarial activities toward chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum* (IC_{50} = 8.3–12.9 μM). This favorable concentration difference between the antimalarial activity and cytotoxic effects suggests that the caulamidines could serve as novel antimalarial agents.



Sample	*P. falciparum* strain	
	D6	W2
1.1.1	11.3 μM	8.3 μM
1.1.2	12 μM	12.9 μM

Figure 1.1.1 Structures of caulamidines and isocaulamidines. D6 = chloroquine sensitive; W2 = chloroquine resistant.

The structures of **1.1.1** and **1.1.2** were unambiguously identified using a suite of contemporary NMR methods, complemented by computer-assisted structural elucidation (CASE) analysis and DFT-computational studies. While conventional 1D and 2D NMR analyses were sufficient for establishing the hexacyclic framework and relative configuration of **1.1.1** and **1.1.2**, newly developed NMR experiments were necessary for verifying the carbon-carbon and carbon-nitrogen connectivities. A novel band-selective CLIP-HSQMBC experiment, capable of detecting the $^{35,37}Cl$ isotopic effect on chlorinated carbons, was employed to support the assignments of chlorine substituents. In addition to spectroscopic analyses, CASE analysis of the NMR and HRMS data was applied to identify and rank possible alternative structures. One viable structural alternative was identified for **1.1.1** but was ruled out through a comparison of the experimental and calculated NMR data and free energy levels of the proposed and alternate structures. Final confirmation of the assigned structures was achieved using two anisotropic NMR parameters—residual chemical shift anisotropy (RCSA) and residual dipolar coupling (RDC). These parameters can define the relative orientations of chemical bonds regardless of their separation, thus providing

an orthogonal and unequivocal methods to assess the validity of the overall structure and stereochemical configuration.

Recently, the same group isolated and identified two new caulamidines, C (**1.1.3**) and D (**1.1.4**), along with three new homologues named isocaulamidines B, C, and D (**1.1.5**–**1.1.7**) from the marine ascidian *Polyandrocarpa sp*.[3] Compared to **1.1.1** and **1.1.2**, these ascidian-derived congeners exhibit different halogen contents and substitution patterns on the peripheral aromatic rings and within the bis-amidine core (highlighted in red in Figure 1.1.1). While **1.1.1** and **1.1.2** have a single chlorine substituent at C11 in the bis-amidine core, caulamidine C (**1.1.3**) and isocaulamidine C (**1.1.6**) contain an extra chlorine at C24 in the A ring. Furthermore, in the isocaulamidine skeleton, an altered pattern of *N*-methyl substitution was noted (N15 vs N13 in the caulamidines, highlighted in blue in Figure 1.1.1). The intriguing and unprecedented structures of these caulamidines piqued our interest and we endeavored to design a concise synthetic route for their synthesis.

1.2 Structurally Similar Alkaloids

The hexacyclic skeleton of caulamidines and isocaulamidines is reminiscent of the C_{20} bis(cyclotryptamine) alkaloids (see **1.2.3**−**1.2.7**, Figure 1.2.1)—a broad class of natural products biosynthetically derived from the dimerization of two tryptamine units. The structural diversity within this class of alkaloids is remarkable, as the initial dimer (**1.2.1**) can undergo hydrolysis to form a hypothetical common biosynthon (**1.2.2**), which can then rearrange into five distinct skeletal isomers.[4]

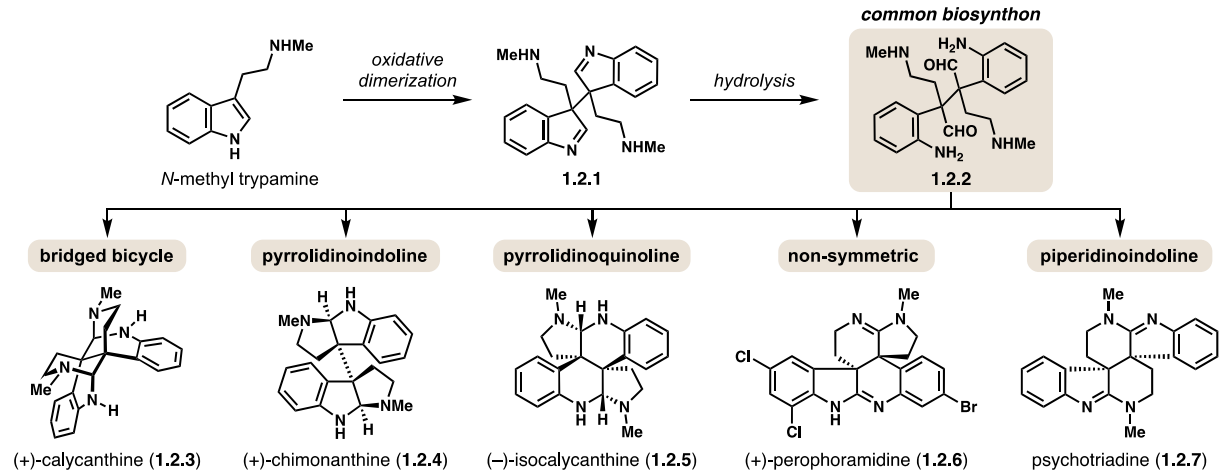


Figure 1.2.1 Representative C_{20} bis(cyclotryptamine) alkaloids and proposed biosynthesis.

(+)-calycanthine (**1.2.3**) corresponds to the bridged bicycle arrangement and was first isolated in 1888. Its structure was initially proposed through chemical degradation studies by Robinson[5] and Woodward,[6] and later confirmed by X-ray crystallography of its dihydrobromide dihydrate salt by Hamor and Robertson.[7] In their subsequent work, Hamor and Robertson established the structure of chimonanthine (**1.2.4**),[8,9] which features two 3,3'-connected indoline units, each with an annulated pyrrolidine, corresponding to the pyrrolidinoindoline arrangement. Isocalycanthine (**1.2.5**), isolated from the South American shrub *Psychotria forsteriana*, corresponds to the skeletal arrangement known as pyrrolidinoquinoline.[10] An oxidized version of it, which contains two amidines in place of the aminals, was later isolated from the same plant.[11] In addition to these symmetric isomers, non-symmetric skeletons have been observed in

perophoramidine (**1.2.6**) and communesins. Communesins, in particular, exhibit a densely functionalized heptacyclic skeleton, which further contributes to the structural diversity of bis(cyclotryptamine) alkaloids. While these aforementioned scaffolds have been found in many isolated natural products, the remaining piperidinoindoline skeleton has only been observed recently when Garg's group synthesized a compound, now termed psychotriadine (**1.2.7**), bearing this skeleton and subsequently identified it in the extracts of *Psychotria colorata* flower.[12,13]

The bis(cyclotryptamine) alkaloids exhibit a wide range of biological activities, including anti-convulsant, anti-fungal, anti-viral, analgesic, anti-tumor, and anti-melanogenesis properties.[14] Due to their diverse biological profile and intriguing skeletal structures, these alkaloids have attracted significant attention from the synthetic communities over the past few decades. One of the biggest synthetic challenges lies in the construction of sterically hindered vicinal all-carbon quaternary stereocenters at C3a and C3a'. To address this challenge, efficient strategies have been developed, one of which relies on the biomimetic oxidative dimerization of indole[15–20] and oxindole[21–23] derivatives. An early example of this strategy was demonstrated by Scott's group in 1964 (Figure 1.2.2A), where they treated the magnesium salt of *N*-methyl tryptamine with iron(III) chloride to form the C3a-C3a' quaternary linkage, albeit with no stereocontrol.[24] In addition to the commonly employed tryptamine, tryptophan, and oxindole starting materials, recent work by Jiang's group[25] identified tryptophan isomer (**1.2.8**) as a novel substrate for oxidative dimerization. Iron-mediated single-electron oxidation of the chiral monomer led to the formation of three challenging bonds with two congested quaternary stereocenters in a one-step transformation,

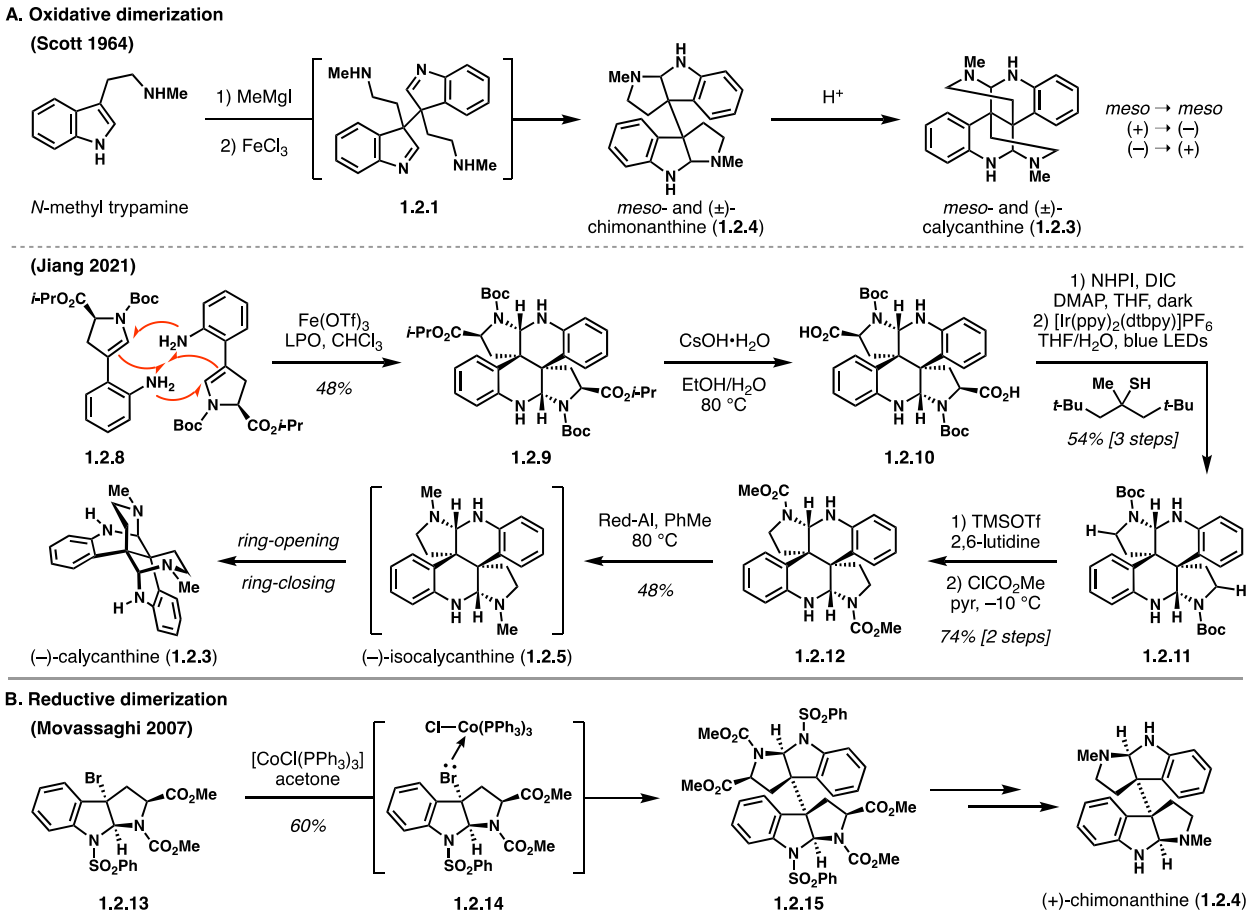


Figure 1.2.2 Dimerization strategies for bis(cyclotryptamine) alkaloids.

resulting in the pyrrolidinoquinoline scaffold (see **1.2.9**) with high stereoselectivity and efficiency. However, further elaboration toward (–)-isocalycanthine (**1.2.5**) primarily produced (–)-calycanthine (**1.2.3**) as the major product, presumably through ring opening and closing of the transient isocalycanthine intermediate.

Apart from bioinspired oxidative strategies, reductive dimerization has also been explored.[26,27] In the seminal studies by Movassaghi's group (Figure 1.2.2B),[26] highly reactive tris(triphenylphosphine)cobalt(I) chloride [$CoCl(PPh_3)_3$] was employed as a stoichiometric reducing agent to promote the reductive dimerization of bromide **1.2.13**. In an efficient bond-forming step, they were able to simultaneously secure the vicinal quaternary stereocenters and rapidly access the pyrrolidinoindoline skeleton (see **1.2.15**), which ultimately led to the synthesis (+)-chimonanthine, (+)-folicanthine, and (–)-calycanthine.

Another strategy for constructing the two quaternary centers in the bis(cyclotryptamine) alkaloids is by dialkylation of 3,3'-bisoxindoles. In 1996, Overman reported the stereocontrolled synthesis of *meso*-chimonanthine *via* a samarium-mediated reductive dialkylation of isoindigo

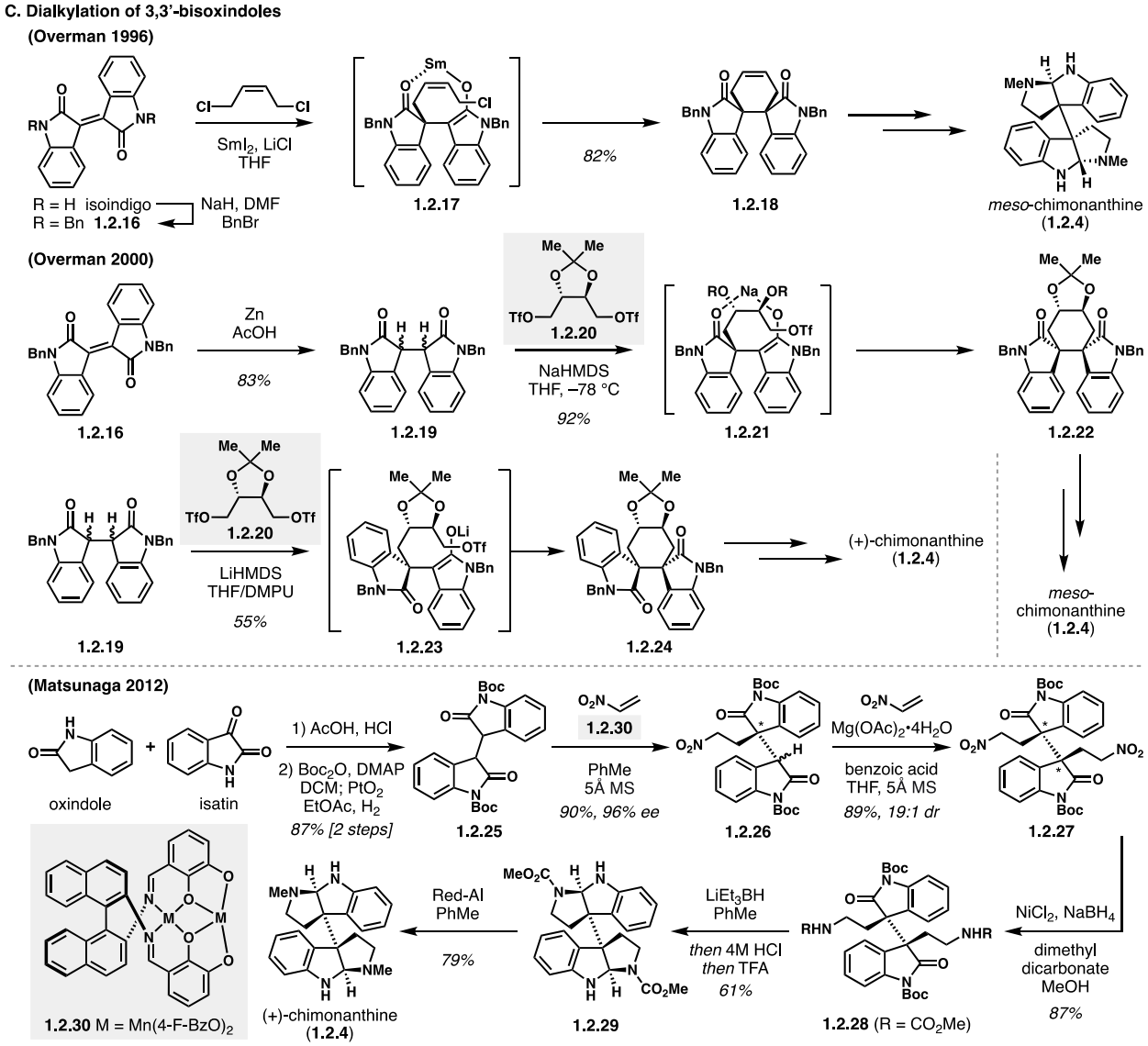


Figure 1.2.2 (continued) Dimerization strategies for bis(cyclotryptamine) alkaloids.

(Figure 1.2.2C).[28] The relative stereochemistry of the two quaternary centers was dictated by the chelate assembly **1.2.17**. A few years later, Overman's group developed a more efficient, enantioselective synthesis by reaction of dihydroisoindigo (**1.2.16**) with a chiral, enantiopure dielectrophile (**1.2.20**).[29] By exploiting the nature of the metal enolate (chelated or nonchelated), the relative configuration of the products could be controlled. While alkylation of the disodium dienolate of **1.2.16** with bistriflate **1.2.20** led to *cis* relationship of the two spirooxindole groups (see **1.2.22**) and ultimately to *meso*-chimonanthine, alkylation of the dilithium dienolate of **1.2.16** in the presence of DMPU provided C_2-symmetric bisoxindole **1.2.24** as the major product, which was converted to (+)-chimonanthine. In a similar disconnection, the Matsunaga's group reported a catalytic asymmetric synthesis of (+)-chimonanthine in 2012.[30] Their approach involved sequential Michael reactions of *N*-Boc-protected dihydroisoindigo (**1.2.25**) with nitroethylene. A chiral Mn-Schiff base complex was used to catalyze the first Michael reaction, securing the first quaternary stereocenter (see **1.2.26**) with 96 % *ee*. The second Michael reaction, catalyzed by $Mg(OAc)_2$/benzoic acid, established the other quaternary stereocenter (see **1.2.27**) with high diastereoselectivity (19:1 *dr*).

More recently, innovative strategies based on fragmentation and solvent-caged radical recombination have been developed for directed C3a–C3a' bond formation at the quaternary stereocenters (Figure 1.2.2D). Building on their previous work on Co^{I}-mediated reductive homodimerization of cyclotryptamine derivatives (Figure 1.2.2B), the Movassaghi group introduced a new approach for selective C–C bond formation at the C_{3a} quaternary stereocenters of two different cyclotryptamine fragments.[31] This method leverages photolytic fragmentation of

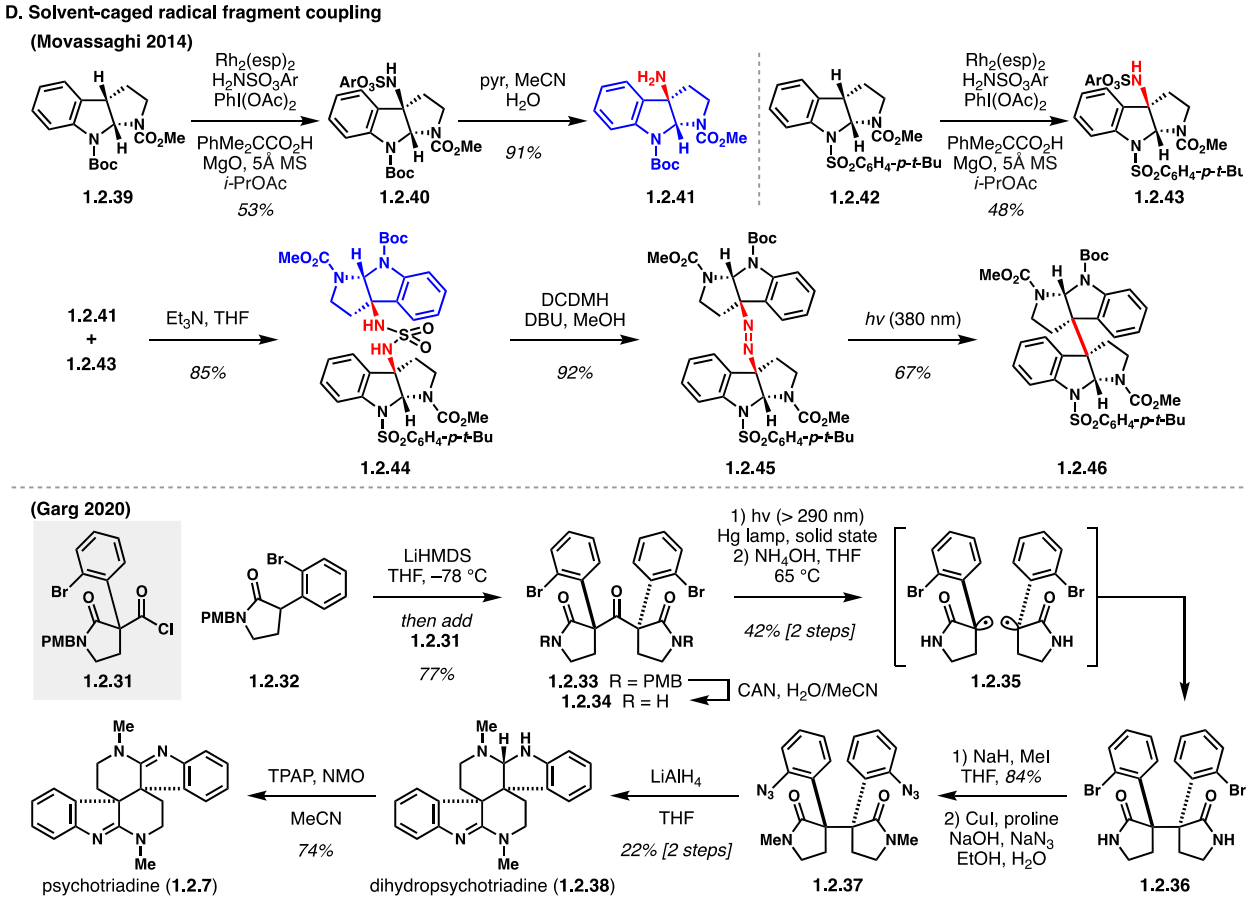


Figure 1.2.2 (continued) Dimerization strategies for bis(cyclotryptamine) alkaloids.

unsymmetrical diazene (see **1.2.45**) to form a pair of carbon-centered radicals, whose recombination within the solvent cage would result in the selective formation of the desired heterodimeric products. With the aid of this newly developed strategy, a variety of bis(cyclotryptamine)[32] and oligomeric cyclotryptamine[33] natural products have been successfully synthesized with complete control over the absolute and relative stereochemistry. Complementary to Movassaghi's approach, Garg reported a stereospecific photodecarbonylation of a crystalline ketone (**1.2.34**) in the synthesis of psychotriadine (**1.2.7**).[12] In this method, the rigidity of the crystal lattice ensures that the radical pair (**1.2.35**) recombines with retention of stereochemistry, thus securing the key vicinal quaternary stereocenters.

1.3 Challenges Associated with the Syntheses of Caulamidines

While the C_{20} bis(cyclotryptamine) alkaloids could be efficiently accessed using various dimerization strategies, such strategies are not readily applicable to the caulamidines as they are neither symmetric nor dimeric due to the presence of a single additional carbon atom (C22) of unknown biosynthetic origins. Of even greater concern is the presence of a chlorine-bearing neopentylic stereocenter (two in caulamidine and isocaulamidine C)—a structural motif of well-appreciated challenge in alkaloid synthesis. To provide a clearer understanding of the issues associated with the neopentylic chloride motif, a detailed overview is presented herein.

Despite over 8,000 halogenated natural products being documented,[34,35] natural products with neopentylic chloride are exceptionally rare, not to mention neopentylic chloride-containing alkaloids. The known examples of these alkaloids include (–)-acutumine (**1.3.1**, Figure 1.3.1) and members of the welwitindolinone, hapalindole, fischerindole, and ambiguine families.

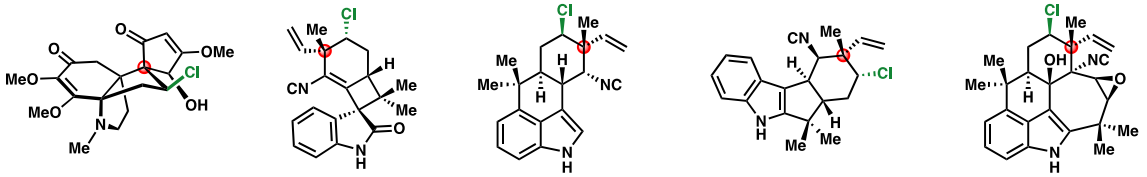


Figure 1.3.1 Representative alkaloids bearing neopentylic chlorides.

In nature, the formation of these neopentylic chlorides is primarily catalyzed by non-heme iron/α-ketoglutarate-dependent halogenases (NHFeHs) *via* a radical mechanism (Figure 1.3.2).[36–38] The consensus reaction mechanism starts with the displacement of water by substrate followed by O_2 binding (**1.3.6→1.3.7**). Subsequent oxidative decarboxylation of the co-substrate α-

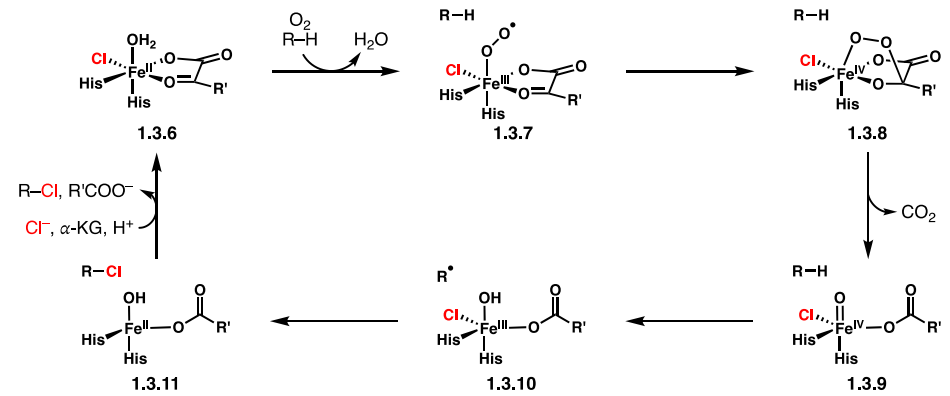


Figure 1.3.2 Mechanism of non-heme iron/α-ketoglutarate-dependent halogenases (NHFeHs).

ketoglutarate forms an Fe^{IV}–oxo species (**1.3.9**), which abstracts a hydrogen atom from the substrate, forming an Fe^{III}–OH intermediate (**1.3.10**) and a carbon radical. A halogen rebound step then follows to produce the chlorinated product (**1.3.10→1.3.11**).

In many of these enzymes, the overall reaction is highly regio- and stereoselective. However, replicating such transformation in a laboratory setting is extremely challenging, and no examples of direct C–H chlorination are yet known in natural product synthesis. Typically, stereoselective chlorination is achieved through S_N2 displacement of activated alcohols. However, when applied to sterically hindered neopentylic chlorides, this strategy often suffers from lack of reactivity, possible chloride equilibration, and/or elimination.[39] For instance, in the attempted synthesis of (–)-*N*-methylwelwitindolinone B isothiocyanate by Rawal and co-workers (Figure 1.3.3A),[40] deoxygenative chlorination of alcohol **1.3.12** resulted in either no reaction or slow decomposition under various conditions. Similarly, S_N2 displacement of oxo-phosphonium **1.3.13** proved unfruitful even under forcing conditions. In another example, during the attempted synthesis of (–)-acutuminine by Reisman's group (Figure 1.3.3B),[41] a number of heterolytic and radical deoxychlorination conditions were investigated for hindered neopentyl alcohol **1.3.15**, but these attempts only led to unreacted starting material or decomposition.

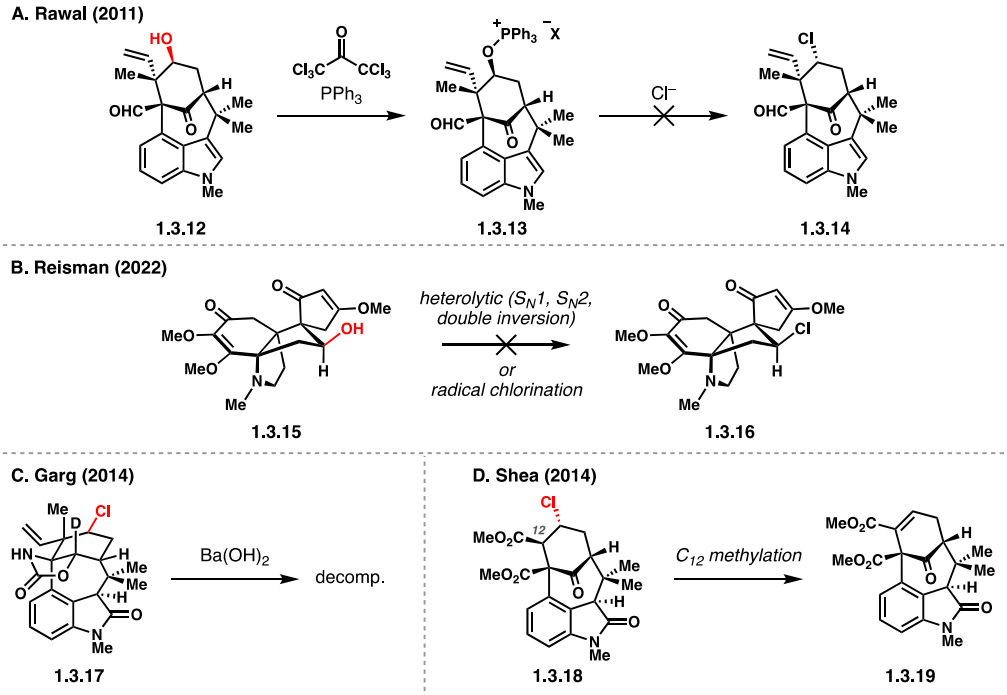


Figure 1.3.3 Synthetic challenges associated with neopentylic chlorides.

Beyond steric hindrance, the lability of the chlorine atom further exacerbates the synthetic challenges associated with neopentylic chlorides. Alkyl chlorides are prone to undergo a variety of undesired side reactions in the presence of nucleophiles and bases. For example, in the synthesis of (–)-*N*-methylwelwitindolinone B isothiocyanate by Garg and coworkers (Figure 1.3.3C),[42] attempted hydrolysis of carbamate **1.3.17** with $Ba(OH)_2$ led to decomposition of the alkyl chloride. This necessitated a survey of milder methods for cleaving the carbamate. Similarly, in the synthetic studies by Shea (Figure 1.3.3D),[43] alkyl chloride **1.3.18** underwent unwanted elimination during the late-stage construction of the final quaternary center by methylation.

1.4 Other Synthetic Work Toward Caulamidines

At the outset of our synthetic program aimed at caulamidine A (**1.1.1**),[44] no syntheses or synthetic studies had been reported toward the caulamidines. Shortly after we published our synthetic route to **1.1.1**, the Xu group disclosed the first enantioselective total syntheses of (–)-caulamidine D (**1.1.4**) and (–)-isocaulamidine D (**1.1.7**, Figure 1.4.1).[45]

Their synthesis relies on a stereospecific Meerwein−Eschenmoser−Claisen rearrangement to construct a key quaternary center from indole ether **1.4.3**. The chirality was successfully transferred from the chiral allyl alcohol (**1.4.2**) to afford the oxindole product **1.4.4** with high stereoselectivity. Following the removal of the Boc group, treatment with Red-Al afforded tricycle **1.4.6**. Further functional group manipulations led to nitrile **1.4.7**, which was deprotonated and treated with benzyl bromide **1.4.8** to form the second key quaternary center (see **1.4.9**) with 4:1 *dr*. The desired diastereomer was then converted into aldehyde **1.4.10**, which was subsequently subjected to *L*-proline catalyzed electrophilic chlorination, albeit with modest diastereoselectivity (1.2:1 *dr*). With the neopentylic chloride installed, the aldehyde was transformed into a mesylate (see **1.4.11**), setting the stage for the key reductive cyclization cascade. Through a survey of reducing metals, iron powder in aqueous NH_4Cl solution with EtOH was identified as the optimal condition to reduce the nitro group in **1.4.11** and trigger the following cyclization cascade. The desired 6-*exo*-dig/6-*exo*-tet product (**1.4.12**) bearing the full hexacyclic skeleton in caulamidines was obtained in 60% yield, with a minor product (24%) arising from the competing 6-*exo*-dig/5-*exo*-tet pathway. Finally, *N*-methylation using NaH and MeI completed the syntheses of caulamidine D (**1.1.4**) and isocaulamidine D (**1.1.7**) in a total of 16 steps (LLS). The optical rotation values of synthetic **1.1.4** and **1.1.7** closely matched those reported for the natural samples. However, X-ray crystallography revealed that the synthetic compounds were enantiomers of the structures proposed by Gustafson and coworkers.[3] Thus, the structures of natural **1.1.4** and **1.1.7** were reassigned to be the enantiomers of the originally proposed configurations.

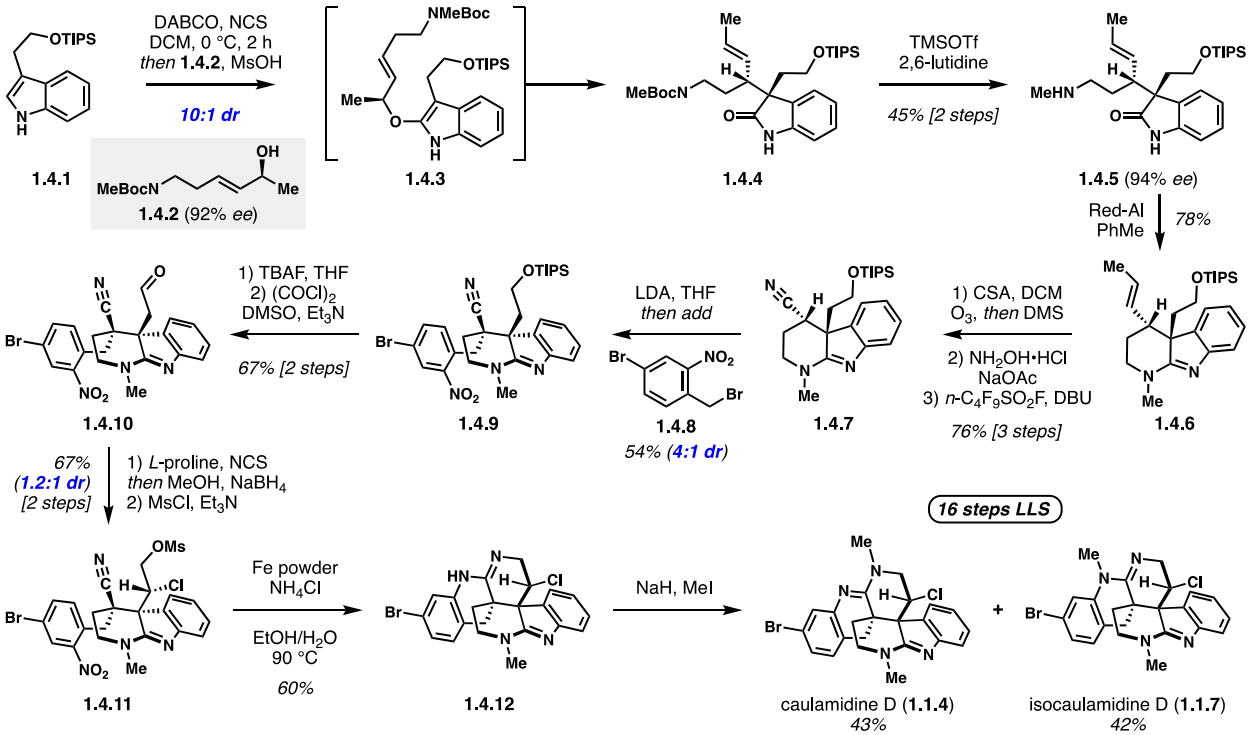


Figure 1.4.1 Total synthesis of (–)-caulamidine D and (–)-isocaulamidine D.

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Chapter 2. Total Synthesis of Caulamidine A

2.1 Retrosynthetic Analysis

Recognizing the synthetic challenges posed by the neopentylic chloride motif as discussed in Chapter 1.3, it was clear to us that our retrosynthetic design should focus on the installation of the C_{11} chlorine. Given the potential pitfalls associated with direct C–H chlorination and S_N2 displacement strategies, we directed our attention to electrophilic chlorination of enamine at C11–C12 (see **2.1.1**, Figure 2.1.1). While the two tricyclic "halves" of **2.1.1** are approximately perpendicular, we envisioned that the chlorinating reagent would approach from the desired *si* face of the enamine because the methylene protons at C24 and C25 partially shield the alternative diastereoface (see optimized ground state geometry of **2.1.1** in Figure 2.4.1).

Retrosynthetically, enamine **2.1.1** could be accessed through dehydration of hemiaminal **2.1.2**, which, in turn, could be derived from precursor **2.1.3** *via* oxidative cleavage of the pendant allyl side chain. However, concerns about potential oxidation of the amidine groups during oxidative cleavage prompted us to perform this transformation on a simpler substrate (**2.1.7**) and test our key electrophilic chlorination on enamide **2.1.6**. From chloride **2.1.5**, the remaining carbons of the natural product could be introduced through allylation and benzylation at C23 *via* enolate alkylation. The exact order of these two alkylation events would be determined by the inherent stereochemical environment of the spirocycle. Finally, straightforward functional group manipulations would convert **2.1.4** to caulamidine A (**1.1.1**).

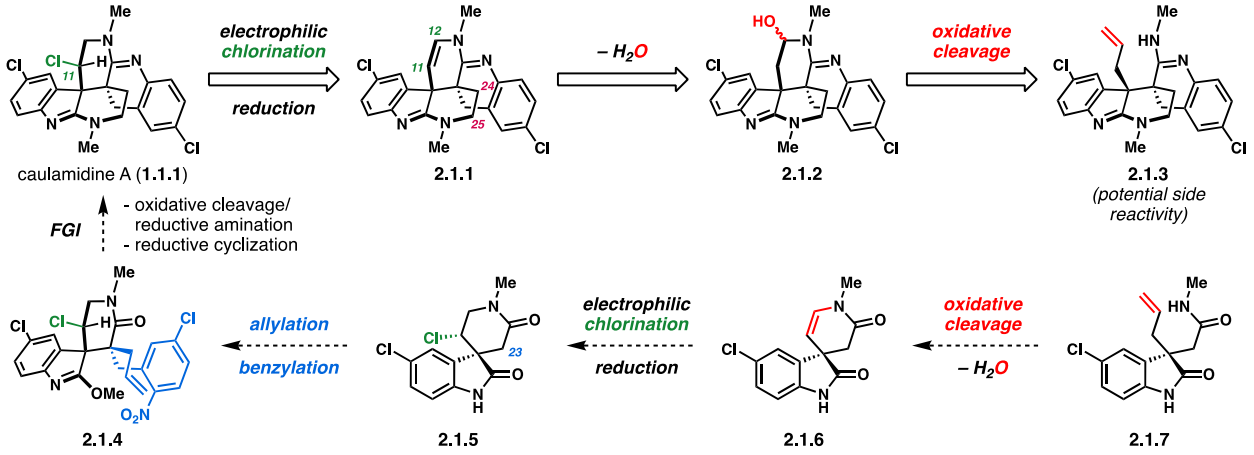


Figure 2.1.1 Retrosynthetic plan.

2.2 Initial Investigations into the Electrophilic Chlorination Strategy

We initiated our synthetic studies by preparing the spirocyclic enamide (**2.1.6**). To synthesize the allyl oxindole (**2.1.7**), we selected commercially available 5-chloroindole-3-acetic acid as the starting material and envisioned installing the allyl side chain using well-established indole C_3 allylation methods from the literature. We first *N*-protected the free indole with an allyloxycarbonyl (Alloc) group (see **2.2.1,** Figure 2.2.1), serving as a π-allyl precursor for subsequent C_3 allylation. Next, the acid functionality in *N*-Alloc indole **2.2.1** was converted into Boc-protected *N*-methyl amide (see **2.2.2**) through a two-step process. With compound **2.2.2** in hand, we performed a decarboxylative allylic rearrangement using $Pd(PPh_3)_4$ and triethylborane,[1] which furnished the C3-allylated product (**2.2.3**) in 66% yield. This indolenine intermediate was found to be unstable and was immediately subjected to Lindgren–Kraus oxidation conditions,[2] producing a stable oxindole product (**2.2.4**) in 81% yield. Following our retrosynthetic plan, the allyl side chain in **2.2.4** underwent oxidative cleavage by ozonolysis to form an aldehyde handle

(see **2.2.5**). Subsequent removal of the Boc group revealed a secondary amide that condensed with the pendant aldehyde, yielding the desired spirocyclic enamide **2.1.6** in 48% yield, along with 18% of hemiaminal product (**2.2.6**). The hemiaminal (**2.2.6**) could be further converted into the enamide (**2.1.6**) by acid-catalyzed dehydration.

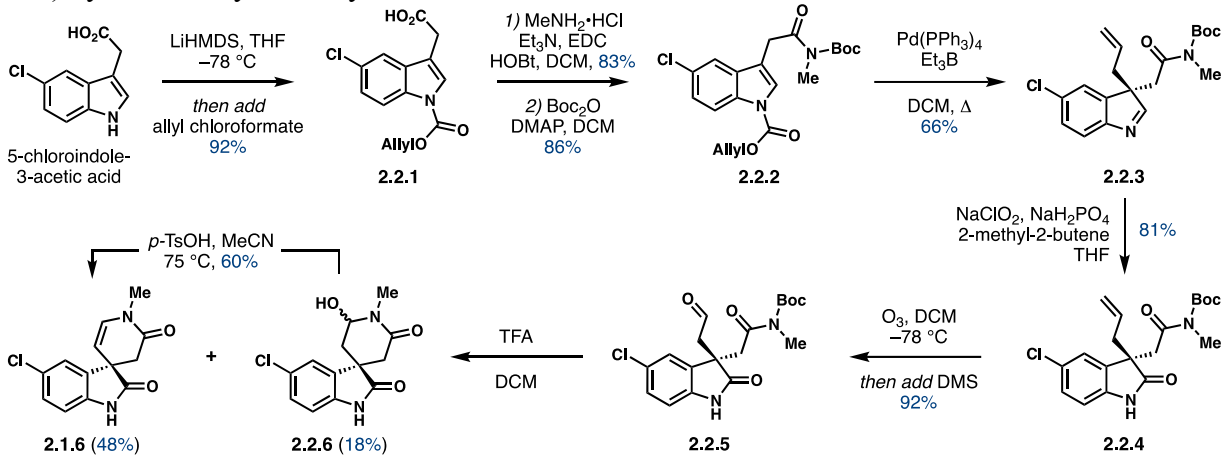


Figure 2.2.1 Preparation of spirocyclic enamide **2.1.6.**

From this key spirocyclic intermediate (**2.1.6**), we proceeded to evaluate our key electrophilic chlorination reaction (Figure 2.2.2). The enamide moiety in **2.1.6** was reactive toward *N*-chlorosuccinimide (NCS) in THF/H_2O, forming chlorohydrin **2.2.7** as a single diastereomer. To our delight, the C_{11} stereocenter was formed selectively with the desired configuration as determined by X-ray crystallography. However, our attempts to reduce the hemiaminal moiety in **2.2.7** were unsuccessful, yielding only the recovered starting material. To facilitate a smoother reduction process, we prepared a methyl ether derivative (**2.2.8**), which was not only acquired in higher yield but was also successfully reduced to chloride **2.1.5** using the canonical conditions (BF_3•Et_2O, Et_3SiH).

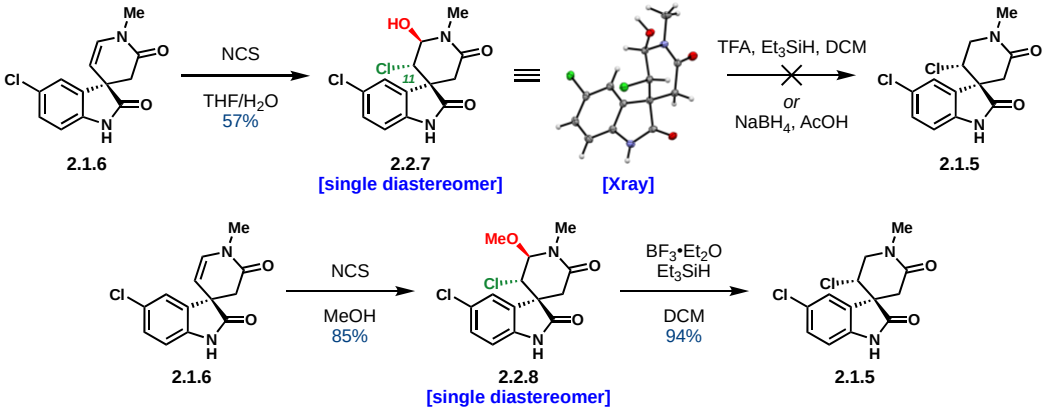


Figure 2.2.2 Electrophilic chlorination and reduction.

With the C_{11} chlorine installed, we next sought to construct the remaining three rings in the natural product through alkylations at C23. To prevent unwanted *N*-alkylation of the free oxindole and to activate C2 for future amidine formation, we converted oxindole **2.1.5** (Figure 2.2.3A) to methyl imidate **2.2.9** with Meerwein's salt. Unfortunately, attempts to generate an enolate from **2.2.9** with LDA only led to cyclopropane product **2.2.10** through unwanted intramolecular chloride displacement.

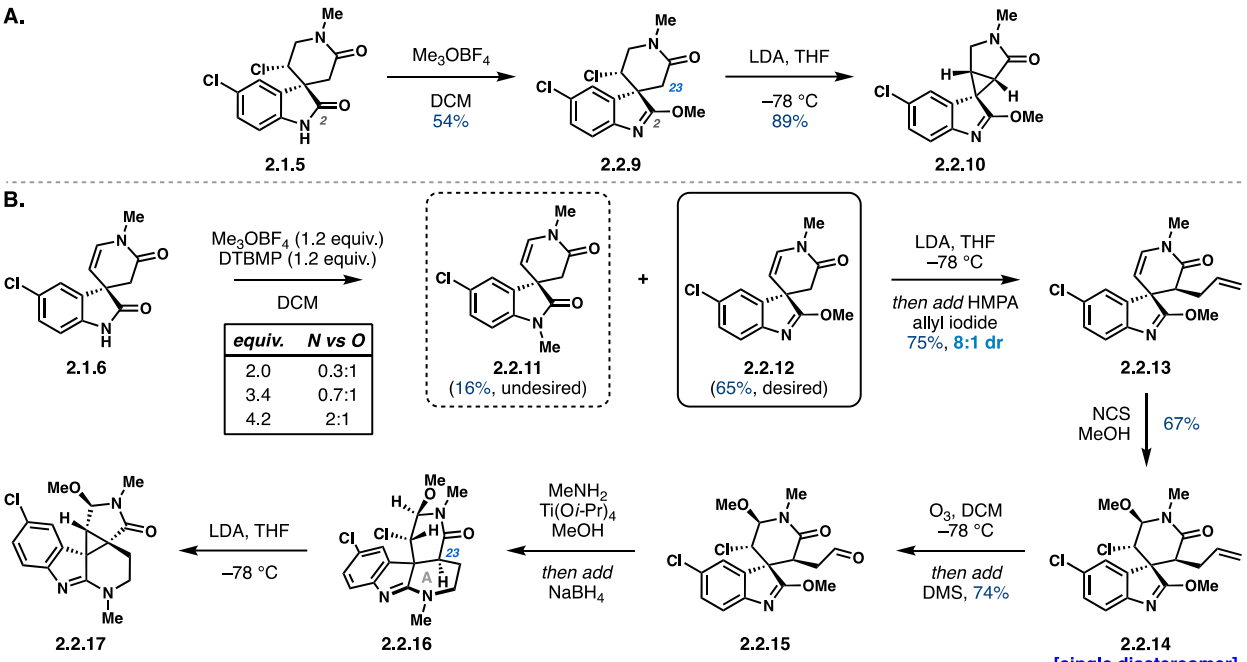


Figure 2.2.3 Failed attempts at C_{23} alkylations in the presence of C_{11} chlorine.

To avoid this side reaction, we decided to perform the C_{23} alkylations before the chlorination. Returning to spirocyclic enamide **2.1.6** (Figure 2.2.3B), we carried out *O*-methylation using Meerwein's salt and an additional amine base to prevent protonation of the enamide by in-situ generated fluoroboric acid. Consistent with the results reported by Somfai and Danielsson,[3] the use of Hünig's base in this transformation resulted in almost exclusive *N*-methylation (**2.2.11**), while 2,6-di-tert-butyl-4-methylpyridine (DTBMP) gave predominantly *O*-methylation (**2.2.12**) with some *N*-methylation and recovered starting material. Surprisingly, increasing the amount of Meerwein's salt and DTBMP increased the formation of *N*-methylation product. Further experiments showed that **2.2.12** could be converted into **2.2.11** in the presence of Meerwein's salt and DTBMP. Therefore, to maximize yield and minimize unwanted *N*-methylation, we identified 1.2 equiv. of Meerwein's salt and DTBMP as the optimal conditions, producing the desired *O*-methylation product (**2.2.12**) in 65% yield.

Next, we attempted α-allylation as the first alkylation event to prove the stereochemical outcome. The allylated spirocycle (**2.2.13**) was obtained in 75% yield with 8:1 *dr*, where the major diastereomer was the result of allylation from the β face. This result suggested the subsequent benzylation of **2.2.13** would also occur from the β face, leading to an undesired configuration at C23. Nevertheless, we envisioned we could construct the A ring from **2.2.13**, and the resultant rigid tetracyclic core (see **2.2.16**) could alter the stereochemical outcome of the benzylation. To this end, we needed to perform an oxidative cleavage of the allyl side chain and a reductive amination with the resultant aldehyde. To avoid potential chemoselectivity issues, we converted the enamide (**2.2.13**) to methyl chloroether (**2.2.14**). Although there remained a risk of intramolecular chloride displacement during benzylation, we hoped the formation of a strained cyclopropane-containing pentacycle would render this event less likely. Proceeding with **2.2.14**, we cleaved the allyl side chain by ozonolysis to unveil an aldehyde. Subsequent reductive amination with in-situ cyclization afforded tetracycle **2.2.16**. Unfortunately, when we deprotonated **2.2.16** with LDA, the undesired chloride displacement occurred again, generating pentacyclic cyclopropane adduct **2.2.17**.

This result indicated to us the need to reverse the sequence of alkylation events in order to achieve the desired configuration at C23. Despite this strategic adjustment, our efforts to install the benzyl group on **2.2.12** were unsuccessful (Figure 2.2.4). With various bases and electrophiles screened, we mostly obtained recovered starting material, with only small amounts of α-iodo product observed under certain conditions when **2.2.21** was used as the electrophile.

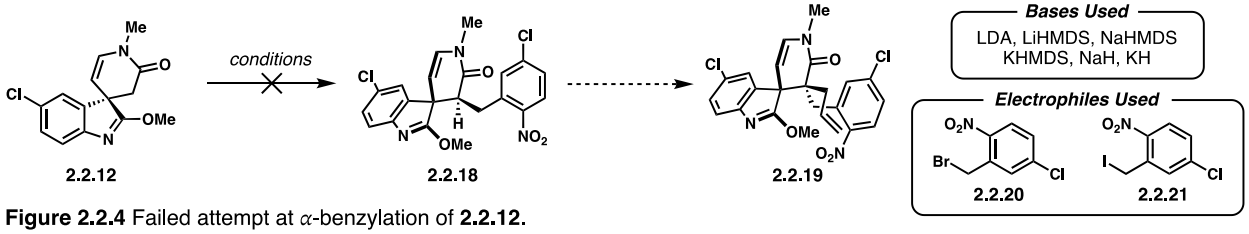


Figure 2.2.4 Failed attempt at α-benzylation of **2.2.12.**

2.3 16-Step Racemic Route to Caulamidine A

We hypothesized that the low reactivity of **2.2.12** in benzylation was due to steric hindrance from the adjacent spirocenter. Therefore, we decided to return to an earlier intermediate **2.2.2**. To our delight, the benzylation (see **2.3.1**, Figure 2.3.1) proceeded smoothly in 70% yield. Decarboxylative allylic rearrangement of **2.3.1** produced two separable diastereomeric indolenine products, which were then converted to oxindoles **2.3.2a** and **2.3.2b**. Since the C_{23} stereocenter would later be ablated during deprotonation, both diastereomers were carried forward for subsequent reactions.

Ozonolysis followed by Boc group removal delivered spirocyclic enamides **2.3.3a** and **2.3.3b**. Interestingly, these two diastereomers exhibited significantly different physical properties. While **2.3.3a** was soluble in most organic solvents, **2.3.3b** was only soluble in polar solvents such as DMSO. Due to these differences in solubility, **2.3.3a** was converted to methyl imidate (**2.3.4a**) in 64% yield, whereas **2.3.3b** had low conversion in DCM, yielding methyl imidate (**2.3.4b**) in only 28% yield along with a significant amount of undesired *N*-methylation product. Furthermore,

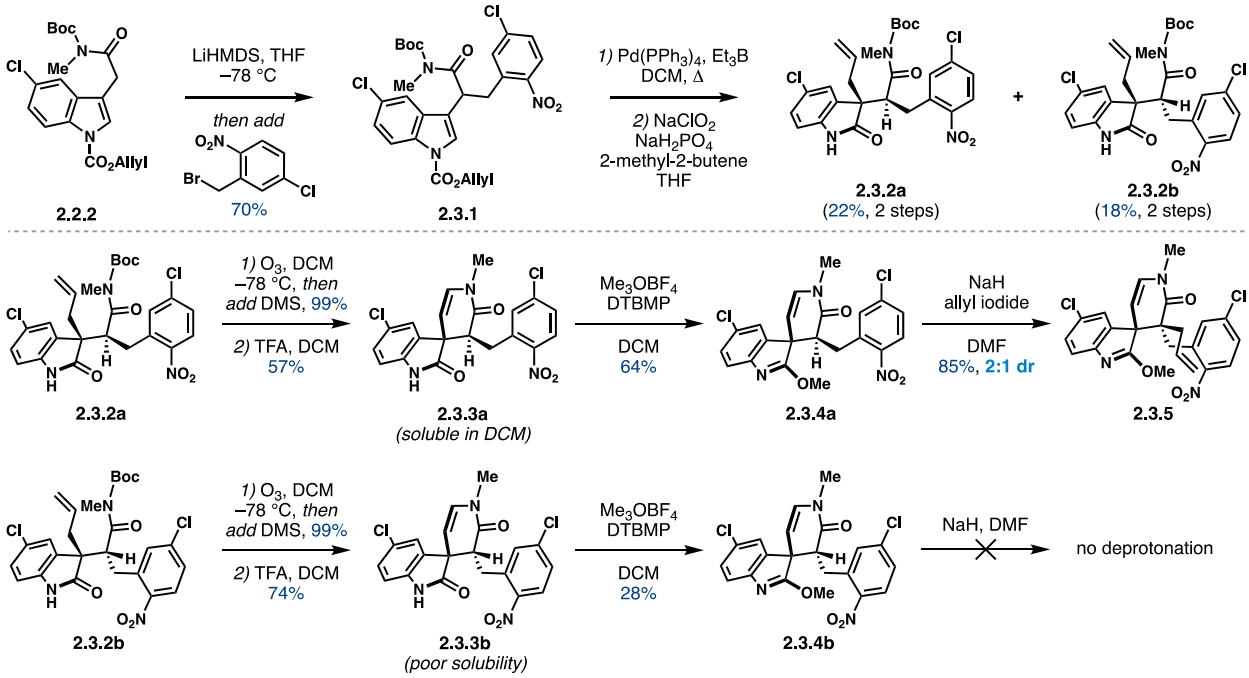


Figure 2.3.1 Preparation of C_{23} fully substituted spirocycle **2.3.5.**

while imidate **2.3.4a** underwent allylation to form the desired product (**2.3.5**) in 85% yield with 2:1 *dr*, imidate **2.3.4b** could not be deprotonated under the same conditions. We postulated that in **2.3.4a**, the unfavorable 1,3-diaxial interaction between the -OMe and benzyl groups forces the benzyl group into the pseudoequatorial position and the α-proton into the pseudoaxial position, allowing for facile deprotonation, whereas in **2.3.4b** the α-proton is in the pseudoequatorial position disfavoring deprotonation.

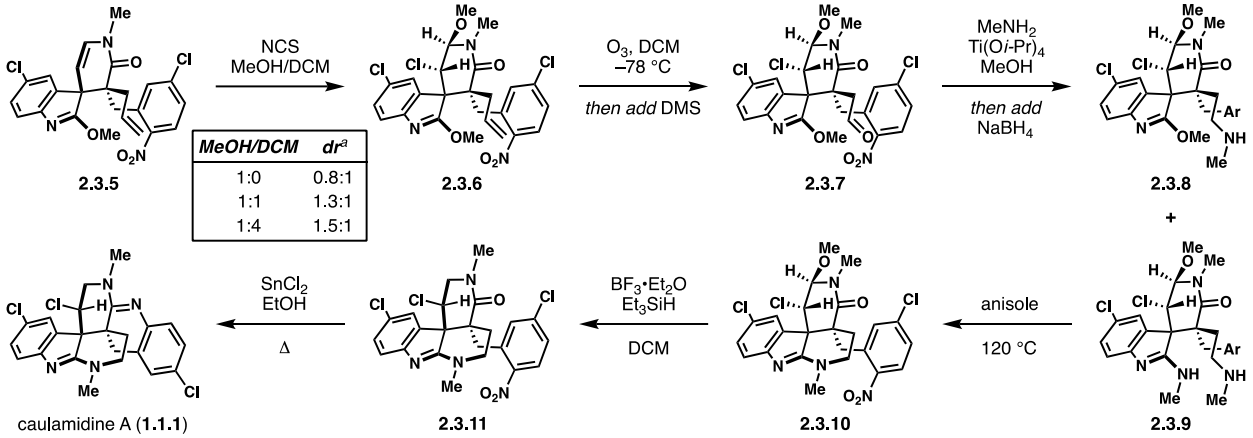


Figure 2.3.2 Completed synthesis of caulamidine A (**1.1.1**). [a]Desired vs. undesired.

With **2.3.5** in hand, we proceeded with electrophilic chlorination as previously described. However, contrary to the single diastereomers obtained from previous substrates, this reaction proceeded with 0.8:1 *dr*, with moderate preference for the undesired diastereomer. Notably, the addition of DCM as a cosolvent reversed the diastereoselectivity, now favoring the desired diastereomer. By employing a 1:4 ratio of MeOH to DCM, we achieved a *dr* of 1.5:1. We suspected this fortuitous switch in facial selectivity could be elucidated by our observations in the ^{1}H NMR spectra of **2.3.5** (Figure 2.3.3). At room temperature, the ^{1}H NMR spectrum displayed broad signals at 4.0 ppm and 2.9 ppm for benzylic protons, and at 2.6 ppm and 2.3 ppm for allylic protons. The signal at 3.6 ppm corresponding to the -OMe protons was also broadened. However, upon heating, the broad signals coalesced to form peaks with clear splitting patterns. The peak broadening suggests the existence of several discrete conformations that are accessible at room temperature. The effect of rapid interconversion between these conformations is attenuated at higher temperatures, resulting in sharper peaks in the NMR. We speculate that the conformation

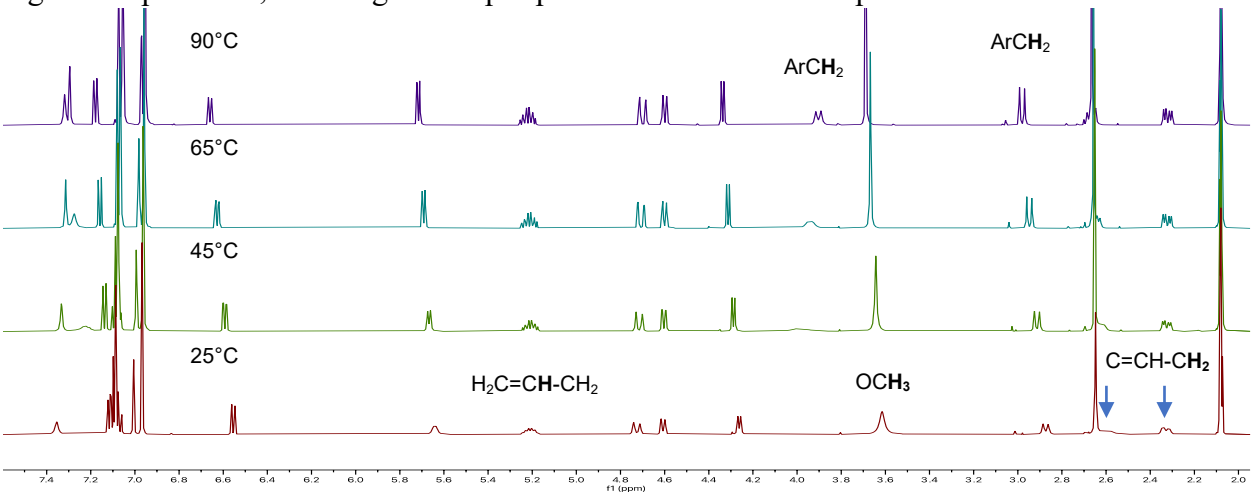


Figure 2.2.3 VT ^{1}H NMR spectra of **2.3.5** in toluene-d_8.

adopted by **2.3.5** is heavily dependent upon the solvent system, causing the diastereoselectivity of the reaction to be fairly sensitive to the precise identity of the solvent.

With **2.3.6** in hand, we proceeded to cleave the allyl side chain by ozonolysis. Subsequent reductive amination yielded a mixture of products—some retaining the methyl imidate moiety (see **2.3.8**) and others possessing an *N*-methyl amidine moiety (see **2.3.9**). Both compounds underwent cyclization upon heating at 120°C in anisole,[4] forming tetracycle **2.3.10**. Subsequent reduction of the *N,O*-aminal with BF_3•Et_2O and triethylsilane produced intermediate **2.3.11**, positioning us one step away from the target natural product. Finally, stannous chloride-mediated reductive cyclization[5] completed the synthesis of caulamidine A (**1.1.1**) in a total of 16 steps.

2.4 Optimized 11-Step Asymmetric Route to Caulamidine A

Although we were able to successfully synthesize caulamidine A, there remained several outstanding problems in this 16-step route. Firstly, our route was racemic, and our attempts to achieve an asymmetric synthesis through enantioselective decarboxylative allylation[6] only yielded trace amounts of the C3-allylated product. This was likely due to the steric hindrance encountered during the formation of a quaternary center adjacent to a tertiary center. Secondly, approximately half of our material was lost because one of the diastereomers (**2.3.3b**) exhibited poor solubility and could not be progressed beyond imidate **2.3.4b**. Thirdly, the *dr* for the C_{23} quaternary center and C_{11} chlorine were suboptimal. We hoped that further optimization would result in a more ideal synthetic solution to caulamidine A.

Our initial analysis of the highlighted issues suggested that condition screening would not be productive as many of our concerns are fundamentally related to the inherent structures of our synthetic intermediates. Thus, a redesign of our synthetic route would be necessary. Our optimized route would begin with commercially available methyl-5-chloroindole-3-acetate (Figure 2.4.1). We planned to perform an asymmetric allylation as the first reaction to avoid the steric encumbrance present in more advanced intermediates. From oxindole **2.4.1**, we would conduct amidation and ozonolysis to obtain spirocyclic enamide **2.1.6**. After that, instead of alkylating C23 and closing the A ring by amidine formation, we proposed forming the amidine moiety first (see **2.4.2**) and then closing the A ring by C_{23} alkylation. This strategic adjustment not only shortens the sequence for A ring assembly but also provides a rigid tetracyclic template (**2.4.3**) for diastereoselective benzylation, allowing us to construct the C_{23} quaternary center with complete stereocontrol. Finally, after obtaining **2.1.1** through reductive cyclization, we planned to proceed with our key electrophilic chlorination and reduction sequence as previously established.

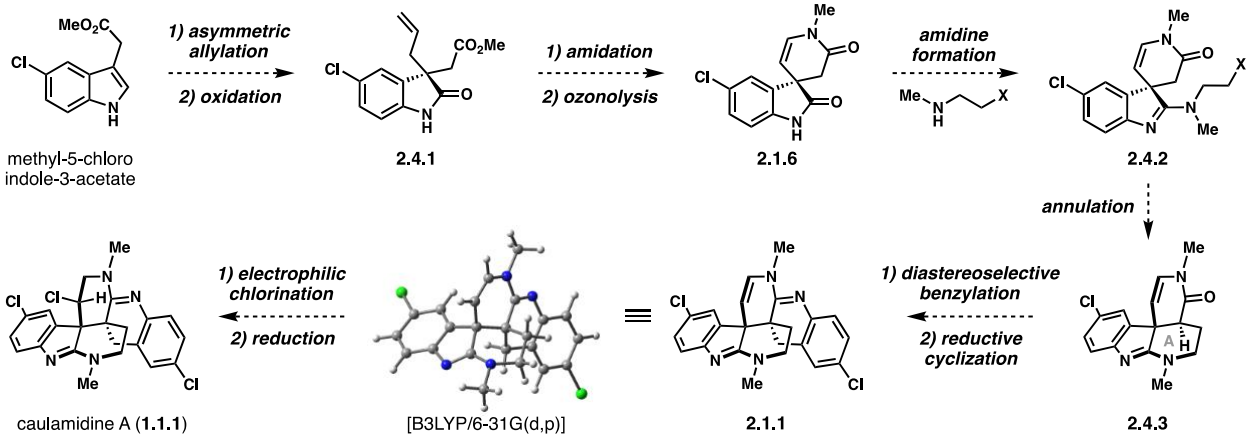


Figure 2.4.1 Revised synthetic plan.

Our efforts on this revised synthetic plan began with examination of Trost' enantioselective C_3 allylation conditions with methyl-5-chloroindole-3-acetate (Figure 2.4.2).[6] Due to the relative instability of the indolenine intermediate (**2.4.4**), the *ee* was measured on the oxindole product (**2.4.1**). However, we were disappointed to observe very low enantioenrichment (30% *ee*) in the oxindole product. To construct the stereocenter with greater enantioselectivity, we explored alternative allylic alkylation conditions beyond simple allylation reactions. Our investigations led us to You's palladium catalyzed prenylation conditions,[7] which successfully produced the prenylated product (**2.4.5**) with a high degree of enantioenrichment (84% *ee*).

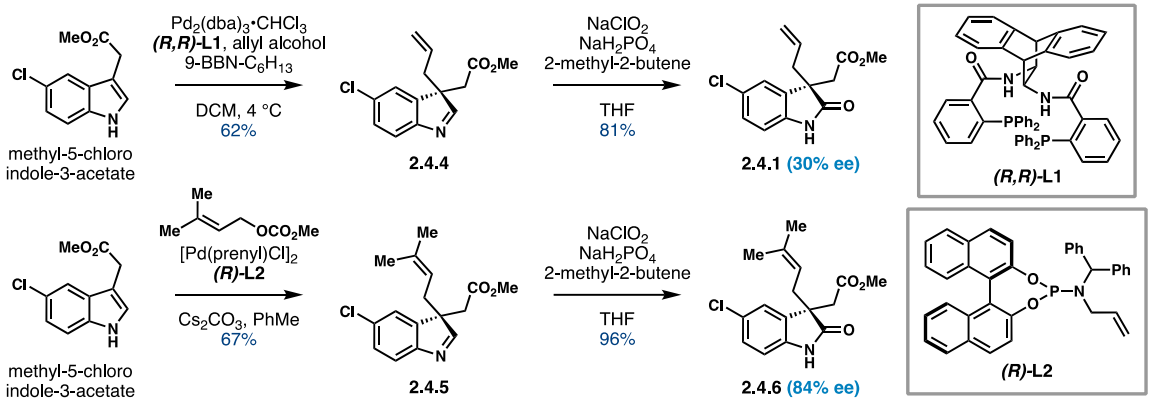


Figure 2.4.2 Investigations into asymmetric allylic alkylations.

We then advanced enantioenriched oxindole **2.4.6** to spirocyclic enamide **2.1.6** through a two-step sequence (Figure 2.4.3). First, amidation using methylamine in the presence of calcium chloride converted the methyl ester moiety in **2.4.6** to *N*-methyl amide (see **2.4.7**).[8] Subsequent ozonolysis forged spirocycle **2.1.6** in a total of 4 steps from methyl-5-chloroindole-3-acetate, a significant improvement over the original 7-step sequence. Recrystallization of **2.1.6** from methanol further enriched the enantiomeric purity of this compound to 92% *ee*. Next, we sought to convert oxindole **2.1.6** to amidine **2.4.8** by Lewis acid activation of the oxindole in the presence of *N*-methyl-2-chloroethylamine. However, none of the tested conditions delivered the desired amidine product (**2.4.8**). Reflecting on our previous work, we recalled observing amidine formation during the reductive amination of **2.3.7** (Figure 2.4.3), where some products had the methyl imidate converted to *N*-methyl amidine. This conversion appeared to be facilitated by the Lewis acid Ti(O*i*-Pr)$_4$. Therefore, we treated methyl imidate **2.2.12** with *N*-methyl-2-

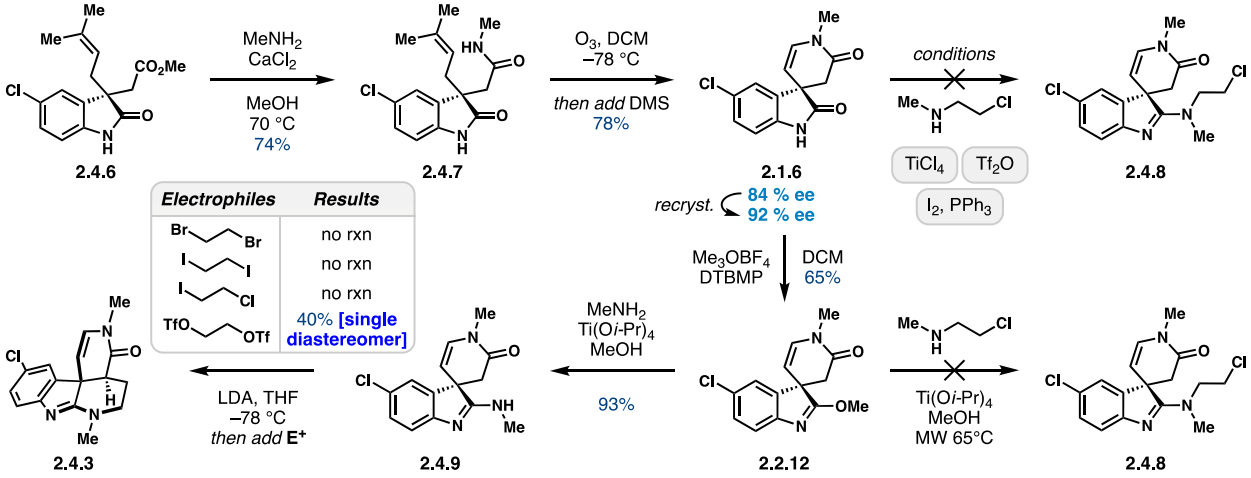


Figure 2.4.3 Synthesis of tetracycle **2.4.3**.

chloroethylamine and Ti(O*i*-Pr)$_4$, but no reaction occurred. We postulated that steric hindrance from the neighboring spirocenter was impeding the reaction, so we replaced the secondary amine with methylamine, successfully synthesizing *N*-methyl amidine (**2.4.9**) in 93% yield. From here, we envisioned alkylating the *N*-methyl amidine with a 1,2-dihaloethane to reach the previously planned amidine intermediate **2.4.8**. Additionally, we speculated that it might be possible to form the tetracycle (**2.4.3**) directly in one pot by using a suitable base to deprotonate both the amidine and the lactam. We thus treated **2.4.9** with LDA followed by addition of symmetric or nonsymmetric 1,2-dihaloethanes (e.g., 1,2-diiodoethane, 1,2-dibromoethane, 1-chloro-2-iodoethane). Unfortunately, these biselectrophiles did not produce either amidine **2.4.8** or tetracycle **2.4.3**. Suspecting that the 1,2-dihaloethanes were not reactive enough to undergo alkylation with this sterically encumbered substrate, we turned to the more reactive glycol bistriflate, which has been previously shown to be superior to 1,2-dihaloethanes in double displacement reactions.[9–11] To our delight, treating the enolate of **2.4.9** with glycol bistriflate successfully yielded the desired tetracycle (**2.4.3**) in 40% yield as a single diastereomer.

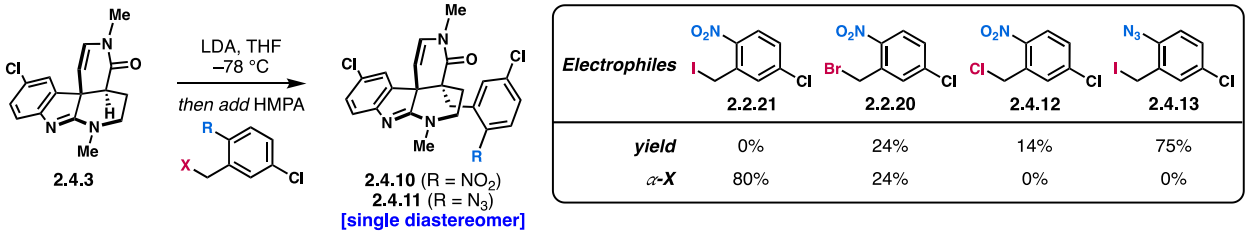


Figure 2.4.4 Benzylation of **2.4.3**.

With tetracycle **2.4.3** in hand, we were poised to investigate the diastereoselective benzylation to set the C$_{23}$ quaternary stereocenter (Figure 2.4.4). Our initial attempt at benzylation using 4-chloro-2-(iodomethyl)-1-nitrobenzene (**2.2.21**) resulted exclusively in α-iodination of the tetracycle, a side reaction we had previously observed in small quantities during the benzylation of spirocycle **2.2.12** (Figure 2.2.4). We attributed this side reaction to the large and soft electrophilic nature of iodine. Switching benzyl iodide to benzyl bromide (**2.2.20**) yielded the desired benzylated product (**2.4.10**) with reduced α-halogenation. Further improvement was achieved by using benzyl chloride (**2.4.12**), which eliminated α-halogenation but significantly decreased reaction conversion. We postulated that the *ortho*-nitro group and the electron-withdrawing chlorine atom acidified the benzylic protons, resulting in protonation of the nascently formed enolate of **2.4.3**. To address this issue, we switched to more electron rich benzyl halides. Using azidobenzyl iodide (**2.4.13**), we successfully obtained the desired benzylated product (**2.4.11**) in 75% yield without any α-halogenation and as a single diastereomer.

With the challenging quaternary stereocenters secured, we aimed to complete the hexacyclic core of caulamidine A (**1.1.1**) using a Staudinger-aza-Wittig reaction (Figure 2.4.5). Treatment with PBu$_3$ under microwave irradiation smoothly transformed azide **2.4.11** into bisamidine **2.1.1**. However, subsequent exposure of **2.1.1** to previously described electrophilic chlorination conditions resulted in a single diastereomer with an undesired configuration at C11 (see **2.4.14**). To explore if a different outcome could be achieved, we performed the same reaction on a substrate lacking the full hexacyclic skeleton (see **2.4.11**). Again, the undesired diastereomer (**2.4.15a**) was exclusively isolated. Additionally, we evaluated other chlorination conditions using chiral cinchona alkaloids, but the best result achieved was 6:1 *dr* favoring the undesired diastereomer.

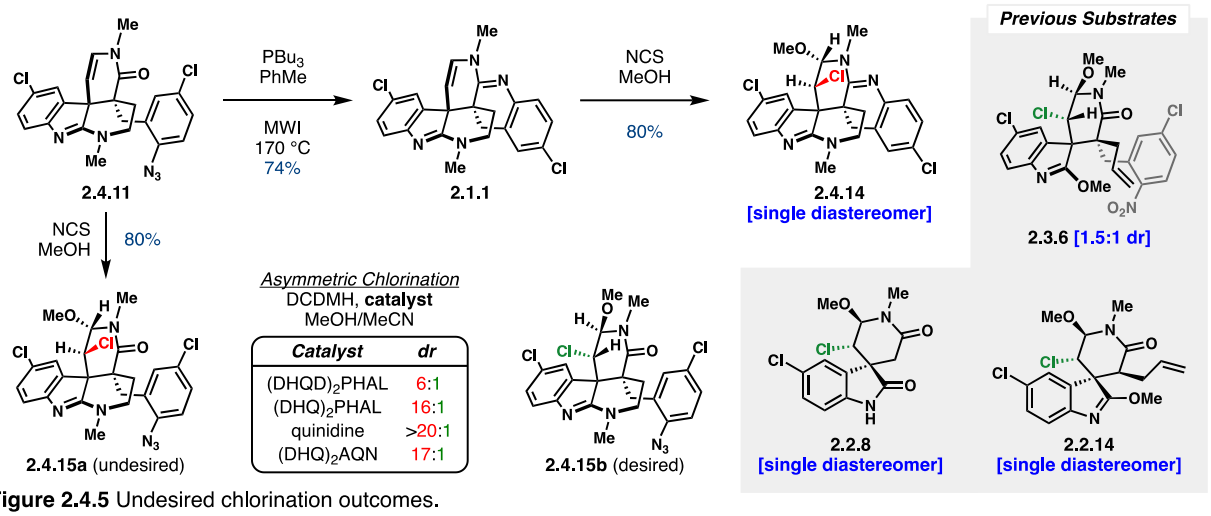


Figure 2.4.5 Undesired chlorination outcomes.

While these outcomes indicated that the *re* face approach was operative in this system, contrary to our initial hypothesis presented in Chapter 2.1, we envisioned that C=C bond reduction of a β-chloro enamine (**2.4.16**, Figure 2.4.6) might allow for the desired stereochemical outcome at C11. Although attempts to directly transform **2.1.1** into its chlorinated counterpart **2.4.16** failed, we were able to install the β-chloro enamine moiety in an earlier step in the synthesis (Figure 2.4.7). Treatment of spirocyclic enamide **2.1.6** with NCS in acetonitrile smoothly furnished vinyl chloride **2.4.17**. This resulting product was carried through the same 5-step sequence as before to ultimately arrive at hexacycle **2.4.16**.

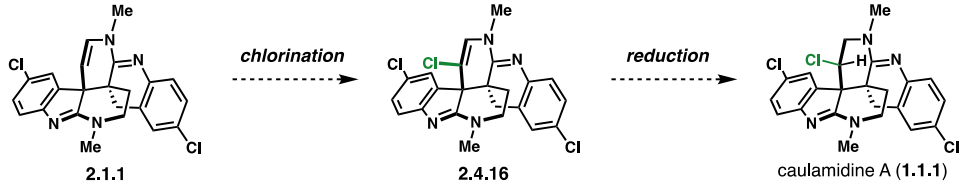
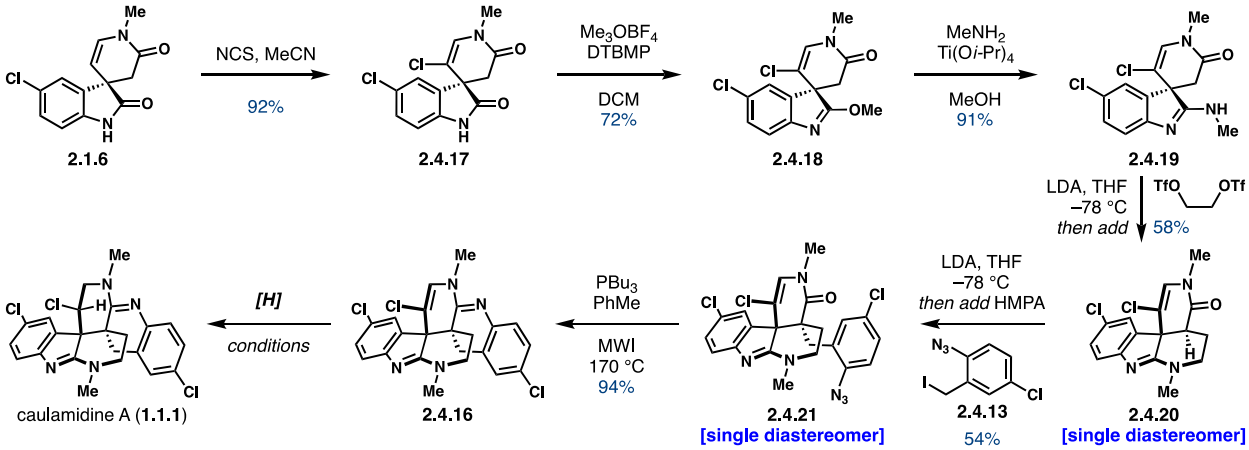


Figure 2.4.6 Revised plan for C_{11} chlorine introduction.

Extensive investigations were carried out to selectively reduce **2.4.16**, a task that proved incredibly challenging. Ionic reductions (entry 1) failed to achieve the desired transformation and were complicated by the two basic amidine groups, which were preferentially protonated. While classic hydrogenation conditions (Adams' catalyst, H_2, AcOH/EtOAc) (entry 2) delivered **1.1.1** as a single diastereomer, only a trace amount of the product was detected, with the major product formed being dechlorocaulamidine A (**2.4.22**). Given recent developments in hydrogen atom transfer (HAT)-based hydrogenations of alkenyl halides,[12,13] we decided to survey reported conditions in this challenging molecular context (entries 3–7).[12–16] While Fe- and Co-based conditions did not afford the desired product (entries 3-5), Shenvi's reduction protocol generated trace amounts of product, provided Ph(O*i*-Pr)SiH_2 was used as the reductant (entry 7).[15] Suspecting catalyst deactivation, we increased the amount of $Mn(dpm)_3$ to 2 equiv and found the overall yield of **1.1.1** was increased to 15% (entry 8). With increased conversion, a significant number of byproducts (see **2.4.23**–**2.4.25**) with differing oxidation patterns at the distal C_{25} position were also identified. Given the reduction of the C_{11}–C_{12} double bond in **2.4.23**–**2.4.25** as well as the very close spatial arrangement of C11 and C25 in this polycyclic framework, we suspected that after the initial HAT at C12, the resulting α-chloro radical at C11 underwent a 1,5-HAT to deliver a carbon-centered radical at C25. Subsequent trapping of this species with oxygen and fragmentation,



Entry	Conditions	Reaction Products [a]
1	TFA, Et_3SiH, DCM	**2.4.16**
2	H_2, PtO_2, AcOH/EtOAc	**2.4.16**, **2.4.22** (14%), **1.1.1** (6%)
3	$Fe_2(ox)_3$, $NaBH_4$, EtOH/H_2O	**2.4.16**
4	$Co(acac)_2$, Et_3SiH, 1,4-CHD, TBHP, *n*-PrOH, air	**2.4.16**
5	$Fe(acac)_3$, $PhSiH_3$, PhSH, EtOH	**2.4.16**
6	$Mn(dpm)_3$, $PhSiH_3$, TBHP, *i*-PrOH	**2.4.16**
7[b]	$Mn(dpm)_3$, Ph(*i*-PrO)SiH_2, TBHP, *i*-PrOH	**2.4.16**, **1.1.1** (trace)
8[c]	$Mn(dpm)_3$, Ph(*i*-PrO)SiH_2, TBHP, *i*-PrOH	**2.4.16** (21%), **1.1.1** (15%), **2.4.23** (16%), **2.4.24** (9%), **2.4.25** (7%)
9[d]	$Mn(dpm)_3$, Ph(*i*-PrO)SiH_2, PhSH, *i*-PrOH	**2.4.16** (62%), **1.1.1** (12%)
10[e]	$Mn(dpm)_3$, Ph(*i*-PrO)SiH_2, PhSH, B(O*i*-Pr)$_3$, *i*-PrOH	**2.4.16** (24%), **1.1.1** (49%)[f]

[a]Yields determined by ^{1}H NMR analysis. [b]Mn^{III} (5 mol%), silane (2 equiv.), TBHP (2 equiv.). [c]Mn^{III} (2 equiv.), silane (4 equiv.), TBHP (2 equiv.). [d]Mn^{III} (2 equiv.), silane (2 equiv.), PhSH (2 equiv.). [e]Mn^{III} (10 equiv.), silane (10 equiv.), PhSH (10 equiv.), B(O*i*-Pr)$_3$ (2 equiv.), with *aq.* NH_4OH workup. [f]Isolated yield. TFA = trifluoroacetic acid, TBHP = tert-butyl hydroperoxide.

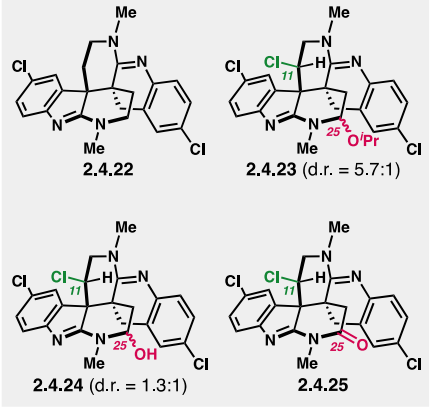


Figure 2.4.7 Completed asymmetric synthesis of caulamidine A (**1.1.1**).

or oxidation and nucleophilic trapping of the resulting iminium then generated these oxidized products. Of note, C_{25} oxidation products were not formed if **1.1.1** was resubjected to the reaction conditions, further suggesting the C_{25} oxidation is coupled to the HAT process across the C_{11}–C_{12} double bond.

Recognizing that **2.4.23**–**2.4.25** accounted for a considerable fraction of the mass balance, we sought to suppress these side reactivities by accelerating the final, product forming HAT with a thiol mediator.[16–20] The inclusion of thiophenol reduced the formation of byproducts **2.4.23**–**2.4.25** (entry 9), but conversion to **1.1.1** remained low. Given the possibility that the Lewis basic nitrogens in **2.4.16** interfere with the manganese complexes formed in this reaction, we included B(O*i*-Pr)$_3$ to the reaction as a sacrificial Lewis acid and found it to be beneficial to the reaction outcome.[21] By further increasing the quantity of manganese and including an ammonium hydroxide workup for metal decomplexation, we were able to generate enantioenriched caulamidine A (**1.1.1**) in 49% isolated yield. Although the optical rotation value of our synthetic sample (–113) does not match the reported value of –5.6, we obtained a very small sample (~0.4 mg) of natural **1.1.1** from the NIH natural product repository, and this small sample possessed an optical rotation of −54 in our hands. Thus, we believe the initially reported optical rotation value of **1.1.1** to be inaccurate.

To better understand the HAT-mediated reduction of **2.4.16**, several deuterium labelling experiments were performed (Figure 2.4.8A). Using deuterated ethylene glycol, a deuterated variant of intermediate **2.4.16** (see **2.4.16-*d*$_4$**) could be prepared wherein the C_{24} and C_{25} methylene groups were replaced by CD_2 units. Subjecting this material to conditions from entry 8 (Figure

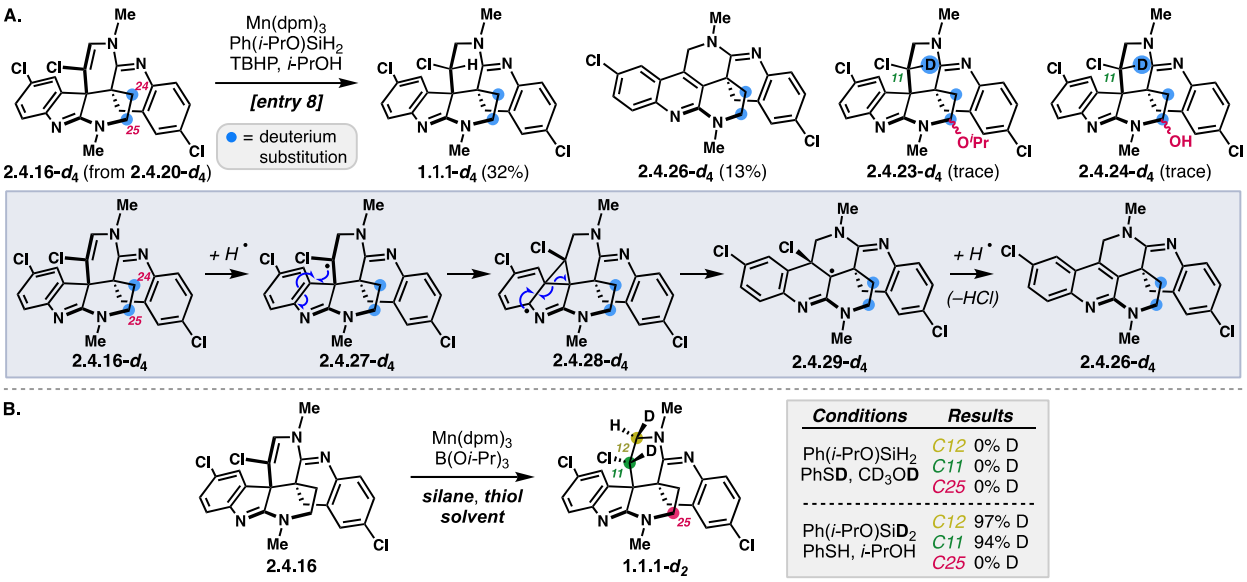


Figure 2.4.7 Deuterium labelling and incorporation studies.

2.4.7) afforded two main products, tetradeuterated caulamidine A (**1.1.1-*d*4**) and quinoline **2.4.26-*d*4** in 32% and 13% yields respectively. Not surprisingly, the formation of C_{25} oxidation products were significantly reduced, with compounds **2.4.23-*d*4** and **2.4.24-*d*4** formed in only trace quantities (~3% yield). Nevertheless, we confirmed these compounds possessed C_{11} deuteration (*via* 1,5-HAT) unlike compound **1.1.1-*d*4** which possesses a proton at C11. Quinoline **2.4.26-*d*4** is presumably formed *via* the dearomative 3-*exo* cyclization of radical **2.4.27-*d*4** to generate radical **2.4.28-*d*4** and ultimately **2.4.29-*d*4** after cyclopropane fragmentation. Quinoline-forming rearomatization then generates **2.4.26-*d*4**. Notably, we had observed trace amounts (1-3%) of this quinoline previously in the non-deuterated series, but with the rate of intramolecular 1,5-HAT retarded in this system, this product was formed in substantial quantities.

Additionally, we performed several experiments using **2.4.16** and deuterated reagents of relevance to our thiol-containing conditions (Figure 2.4.8B). Notably, no deuterium atoms were incorporated into **1.1.1** when deuterated thiophenol and methanol were employed, suggesting the silane delivers these atoms. Moreover, when deuterated Ph(*i*-PrO)SiD_2 was employed, the C_{11} and C_{12} positions were both deuterated, and high facial selectively was noted in both presumed HAT events. In both experiments in Figure 2.4.8B, incorporation of deuterium was not observed at C25. Overall, these finding suggest the major pathway to caulamidine A is *via* a diastereoselective intermolecular HAT process.

2.5 Conclusion

In this chapter, we have chronicled the evolution of a total synthetic strategy toward the structurally unique antimalarial alkaloid caulamidine A. Although our initial alkene chlorination strategy ultimately led to a 16-step synthesis of caulamidine A, there were several challenges that still needed to be addressed. Installation of the C_{11} chlorine at an early stage proved to be a liability, necessitating a reorganization of the reaction sequence. This reorganization impaired our ability to render the synthesis asymmetric and resulted in suboptimal stereochemical control over the formation of C_{23} quaternary center and C_{11} stereocenter. Through extensive optimization, we were able to achieve an 11-step asymmetric total synthesis of caulamidine A, thus confirming its absolute configuration. An enantioselective prenylation highlights the rapid formation of an

enantioenriched spirocyclic oxindole in only four steps from commercial materials. A glycol bistriflate-mediated annulation reaction then quickly constructs the hexahydro-2,6-naphthyridine core with complete diastereoselectivity. Given the importance of spirocyclic oxindoles in drug discovery,[22] we feel this maneuver may have uses in other contexts. The rigid tetracyclic core formed then served to direct formation of the final all-carbon quaternary center via diastereoselective alkylation. A one-pot azide reduction/cyclization forged the caulamidine core in 10-steps setting the stage for a diastereoselective HAT hydrogenation to form the key neopentylic chlorine stereocenter of the target.

2.6 References

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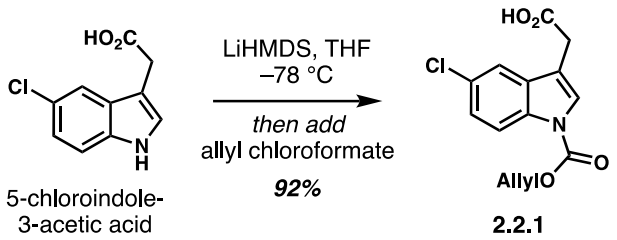
2.7 Experimental Procedure and Characterization Data

General Procedures:

All reactions were performed in flame- or oven-dried glassware under positive pressure of nitrogen or argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe. When indicated, solvents or reagents were degassed by sparging with argon for 15 minutes in an ultrasound bath at 25 ºC. Volatile solvents were removed under reduced pressure rotary evaporation. Analytical and preparative thin-layer chromatography (TLC) were performed using glass plates coated with silica gel (0.25-mm, 60-Å pore size, Merck TLC Silicagel 60 F254) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) and then were stained by submersion in an ethanolic anisaldehyde solution or potassium permanganate solution followed by brief heating on a hot plate. Flash column chromatography was performed with silica gel purchased from Fisher Scientific (230-40 mesh, Grade 60). All samples were loaded onto the column either as solutions in DCM or dry loaded by resuspension of the crude mixture in DCM or MeOH with an appropriate amount of silica gel followed by careful concentration to dryness under reduced pressure. HMPA was distilled over calcium hydride at reduced pressure and stored under N_2 over molecular sieves. Anhydrous acetonitrile (MeCN), tetrahydrofuran (THF), toluene (PhMe), and dichloromethane (DCM) were obtained by passing these previously degassed solvents through activated alumina columns. Anhydrous methanol (MeOH) and isopropanol (*i*-PrOH) were purchased from Sigma Aldrich. [Pd(prenyl)Cl]$_2$ was synthesized from $PdCl_2$ and 1-chloro-3-methyl-2-butene according to a literature procedure.[1] Methyl prenyl carbonate was synthesized from 3-methylbut-2-en-1-ol according to a literature procedure.[2] Ozone was produced using A$_2$Z® S-0.5G LAB Ozone Generator. All other reagents were used as received from commercial sources, unless otherwise noted. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker AVB400, AV500, AV600, and AV700 spectrometers at 23 ºC. Proton chemical shifts are expressed as parts per million (ppm, δ scale) and are referenced to residual solvent ($CHCl_3$, δ 7.26 (s); C_6D_5H, δ 7.16 (s); $CHDCl_2$, δ 5.32 (t); CHD_2CN, δ 1.94 (p); CHD_2OD, δ 3.31 (p); THF-d_7, δ 1.72 (m); $CHD_2S(O)CD_3$, δ 2.50 (p)). Carbon chemical shifts are expressed as parts per million (ppm, δ scale) and are referenced to the solvent ($CDCl_3$, δ 77.16; C_6D_6, δ 128.06; CD_2Cl_2, δ 53.84; CD_3CN, δ 118.26; CD_3OD, δ 49.00; THF-d_8, δ 25.31; $(CD_3)_2SO$, δ 39.52). Data is presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublet, dt = triplet of doublet, t = triplet, q = quartet, m = multiplet, br = broad, coupling constant (*J*) in Hertz (Hz), and integration. Infrared spectra were recorded on a Bruker Alpha FT-IR spectrometer as thin films and are reported as frequency of absorption (cm^{-1}). Only selected resonances are reported. High-resolution mass spectra (HRMS) were obtained by the mass spectrometry facility at the University of California, Berkeley using a Finnigan LTQFT mass spectrometer (Thermo Electron Corporation). Chiral HPLC analyses were performed on a Waters Alliance e2695 Separations Module using Chiralpak® columns (AD-3, IA) eluting with *i*-PrOH/hexanes mixtures as indicated. Optical rotations were measured on a PerkinElmer 241 polarimeter using a 1 dm path-length cell at 589 nm. X-ray diffraction data was collected at the Small Molecule X-ray Crystallography Facility (CheXray) at the University of California, Berkeley using a Rigaku XtaLAB P200 equipped with a MicroMax 007HF rotating anoted an Pilatus3 R 200K-A hybrid pixel array detector. Data were collected using CuKa radiation (l = 1.5418 Å).

Compound Preparation and Characterization Data

Preparation of *N*-Alloc indole 2.2.1:



5-chloroindole-3-acetic acid — **2.2.1**

A flame-dried round bottom flask equipped with a stir bar was charged with 5-chloroindole-3-acetic acid (1.10 g, 5.25 mmol, 1 equiv). The atmosphere was exchanged three times with argon before anhydrous THF (9.5 mL) was added. The resulting solution was cooled to –78 ºC, and LiHMDS (11.5 mL, 1 M in THF, 11.5 mmol, 2.2 equiv) was added dropwise with vigorous stirring. After the mixture was stirred at –78 ºC for 30 minutes, allyl chloroformate (0.61 mL, 5.7 mmol, 1.1 equiv) was added dropwise. The resulting mixture was stirred at –78 ºC for an additional 1.5 hours before being quenched by the addition of 3N HCl (20 mL). The layers were separated, and the aqueous phase was extracted further with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2 to 3% MeOH/DCM) to afford *N*-Alloc indole **2.2.1** (1.42 g, 4.83 mmol, 92%) as a white solid.

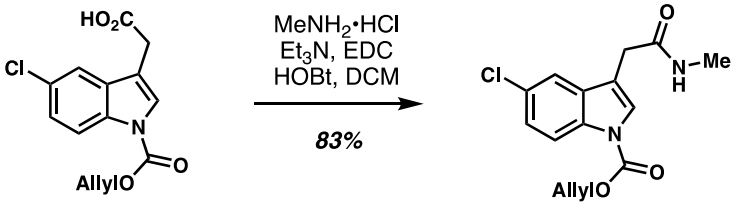
TLC: R_f = 0.49 (10% MeOH/DCM)

^{1}H NMR (600 MHz, THF-d_8) δ 10.81 (br, 1H), 8.12 (d, *J* = 8.8 Hz, 1H), 7.71 (d, *J* = 1.2 Hz, 1H), 7.61 (d, *J* = 2.1 Hz, 1H), 7.27 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.09 (ddt, *J* = 17.4, 10.5, 5.8 Hz, 1H), 5.45 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.30 (dt, *J* = 10.5, 1.3 Hz, 1H), 4.90 (dt, *J* = 5.9, 1.4 Hz, 2H), 3.66 (d, *J* = 1.1 Hz, 2H), 2.52 (br, 1H).

^{13}C NMR (150 MHz, THF-d_8) δ 171.86, 150.91, 134.94, 133.00, 132.83, 129.14, 126.25, 125.22, 120.08, 119.17, 116.89, 115.42, 68.32, 30.61.

HRMS (m/z): (ESI) calcd for $^{12}C_{14}H_{11}O_4N^{35}Cl$ $[M–H]^-$: 292.0377, found 292.0378.

Preparation of amide SI-1:

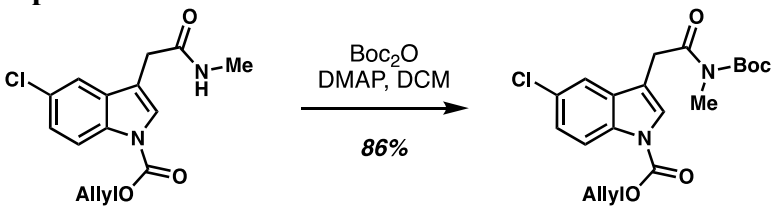


2.2.1 — **SI-1**

To a vigorously stirred suspension of **2.2.1** (1.42 g, 4.83 mmol, 1 equiv) in DCM (48 mL) at 0 ºC were added triethylamine (2.2 mL, 16 mmol, 3.3 equiv), *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC•HCl) (1.02 g, 5.32 mmol, 1.1 equiv), hydroxybenzotriazole (HOBt) (719 mg, 5.32 mmol, 1.1 equiv), and methylamine hydrochloride (359 mg, 5.32 mmol, 1.1 equiv) in sequence. The mixture was stirred for 1 hour at 0 ºC and then 24 hours at ambient temperature. Upon completion of the reaction as indicated by TLC, the reaction was quenched by the addition of 1 N HCl (50 mL). The layers were separated, and the aqueous phase was extracted further with DCM (3 x 30 mL). The combined organic layers were washed with saturated *aq.* $NaHCO_3$ (100 mL), dried over Na_2SO_4, filtered, and concentrated under

reduced pressure. The residue was purified by silica gel column chromatography (1 to 1.6% MeOH/DCM) to afford amide **SI-1** (1.23 g, 4.01 mmol, 83%) as a white solid.
TLC: R_f = 0.48 (5% MeOH/DCM)
^{1}H NMR (600 MHz, CD_2Cl_2) δ 8.11 (d, *J* = 8.8 Hz, 1H), 7.62 (s, 1H), 7.53 (d, *J* = 2.1 Hz, 1H), 7.32 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.09 (ddt, *J* = 17.2, 10.5, 5.9 Hz, 1H), 5.61 (br, 1H), 5.47 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.36 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.91 (dt, *J* = 5.9, 1.4 Hz, 2H), 3.57 (s, 2H), 2.73 (d, *J* = 4.8 Hz, 3H).
^{13}C NMR (150 MHz, CD_2Cl_2) δ 170.12, 150.63, 134.48, 131.87, 131.80, 129.16, 126.09, 125.47, 119.67, 119.37, 116.76, 115.02, 68.26, 33.18, 26.64.
HRMS (m/z): (ESI) calcd for $^{12}C_{15}H_{16}O_3N_2{}^{35}Cl$ $[M+H]^+$: 307.0844, found 307.0844.

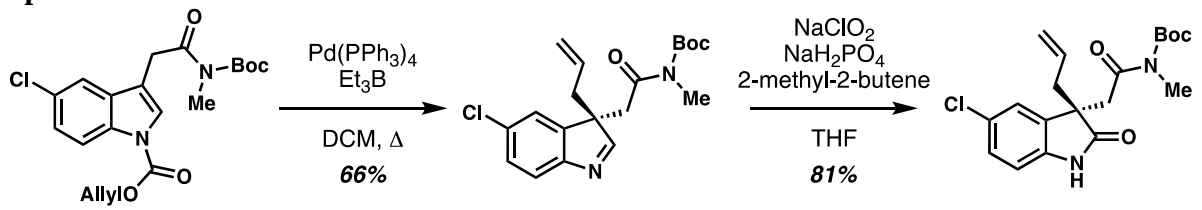
Preparation of Boc-protected amide 2.2.2:



SI-1 **2.2.2**

To a solution of **SI-1** (3.26 g, 10.6 mmol, 1 equiv) and DMAP (130 mg, 1.06 mmol, 0.1 equiv) in DCM (53 mL), di-*tert*-butyl dicarbonate (4.6 mL, 20 mmol, 1.9 equiv) was added dropwise. The resulting mixture was stirred at ambient temperature until completion of the reaction as indicated by TLC (~4 hours). The reaction was quenched by the addition of 0.5 N HCl (50 mL). The layers were separated, and the aqueous phase was extracted further with EtOAc (3 x 30 mL). The combined organic layers were washed with saturated *aq.* $NaHCO_3$ (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (3 to 6% EtOAc/hexanes) to afford Boc-protected amide **2.2.2** (3.69 g, 9.07 mmol, 86%) as a white solid.
TLC: R_f = 0.32 (10% EtOAc/hexanes)
^{1}H NMR (600 MHz, CD_2Cl_2) δ 8.10 (d, *J* = 8.9 Hz, 1H), 7.61 (d, *J* = 1.1 Hz, 1H), 7.50 (d, *J* = 1.9 Hz, 1H), 7.29 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.08 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.46 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.35 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.90 (dt, *J* = 5.8, 1.4 Hz, 2H), 4.27 (d, *J* = 1.1 Hz, 2H), 3.14 (s, 3H), 1.54 (s, 9H).
^{13}C NMR (150 MHz, CD_2Cl_2) δ 173.13, 153.81, 150.72, 134.26, 132.46, 132.00, 128.81, 126.02, 124.98, 119.62, 119.45, 116.59, 115.40, 83.62, 68.06, 34.66, 31.96, 28.17.
HRMS (m/z): (ESI) calcd for $^{12}C_{20}H_{23}O_5N_2{}^{35}Cl^{23}Na$ $[M+Na]^+$: 429.1188, found 429.1188.

Preparation of oxindole 2.2.4:



2.2.2 **2.2.3** **2.2.4**

Following a published procedure,[3] a flame-dried round bottom flask equipped with a reflux condenser and stir bar was charged with **2.2.2** (188 mg, 462 μmol, 1 equiv) and $Pd(PPh_3)_4$ (5.3

mg, 4.6 μmol, 0.01 equiv). The atmosphere was exchanged three times with argon before anhydrous DCM (2.3 mL) was added. To the resulting yellow solution, triethylborane (0.46 mL, 1 M in hexanes, 0.46 mmol, 1.0 equiv) was added dropwise, and the mixture was heated at reflux for 16 hours. After being cooled to ambient temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (4:48:48 EtOAc/DCM/hexanes to 10:45:45 EtOAc/DCM/hexanes) to afford indolenine **2.2.3** (111 mg, 306 μmol, 66%) as a slightly yellow oil, which was used immediately for the next step.

Following a published procedure,[4] to a solution of **2.2.3** (111 mg, 306 μmol, 1 equiv) in THF (3 ml), 2-methyl-2-butene (0.32 mL, 3.0 mmol, 9.9 equiv) and $NaClO_2$ (138 mg, 1.53 mmol, 5.0 equiv) were added in sequence. The resulting suspension was stirred vigorously, and NaH_2PO_4 (0.46 mL, 1 M in H_2O, 0.46 mmol, 1.5 equiv) was added dropwise. After completion of addition, the reaction mixture was stirred at ambient temperature for 1.5 hours before being quenched by the addition of saturated *aq*. $Na_2S_2O_3$ (3 mL) at 0 ºC. The layers were separated, and the aqueous phase was extracted further with EtOAc (3 x 3 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (21 to 35% EtOAc/hexanes) to afford oxindole **2.2.4** (93.4 mg, 247 μmol, 81%) as a white foam.

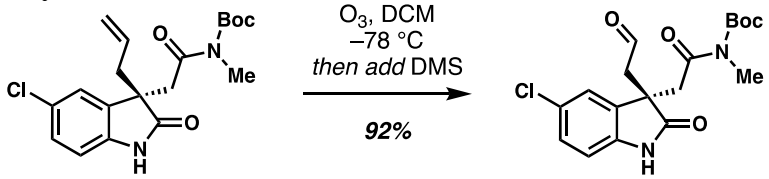
TLC: R_f = 0.21 (30% EtOAc/hexanes)

^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.76 (br, 1H), 7.17 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.09 (d, *J* = 2.1 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 5.54 (dddd, *J* = 17.1, 10.2, 7.7, 7.0 Hz, 1H), 5.07 – 4.99 (m, 2H), 3.68 (d, *J* = 18.6 Hz, 1H), 3.50 (d, *J* = 18.6 Hz, 1H), 2.94 (s, 3H), 2.49 (ddt, *J* = 13.5, 7.1, 1.2 Hz, 1H), 2.42 (ddt, *J* = 13.5, 7.6, 1.1 Hz, 1H), 1.53 (s, 9H).

^{13}C NMR (150 MHz, CD_2Cl_2) δ 180.95, 172.48, 153.43, 140.72, 135.12, 131.71, 127.84, 127.19, 123.34, 119.80, 110.62, 83.74, 50.89, 45.19, 43.21, 31.42, 28.17.

HRMS (m/z): (ESI) calcd for $^{12}C_{19}H_{24}O_4N_2{}^{35}Cl$ $[M+H]^+$: 379.1419, found 379.1415.

Preparation of aldehyde 2.2.5:



2.2.4 **2.2.5**

A solution of **2.2.4** (37.2 mg, 98.2 μmol, 1 equiv) in DCM (2 mL) was cooled to –78 ºC and sparged with a stream of ozone until a blue color persisted. At this point, TLC analysis indicated the complete consumption of starting material and dimethyl sulfide (1 mL) was added. The resulting reaction mixture was allowed to slowly warm to ambient temperature and stirred at that temperature overnight. The crude reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (2% MeOH/DCM) to afford aldehyde **2.2.5** (34.2 g, 89.8 μmol, 92%) as a white foam.

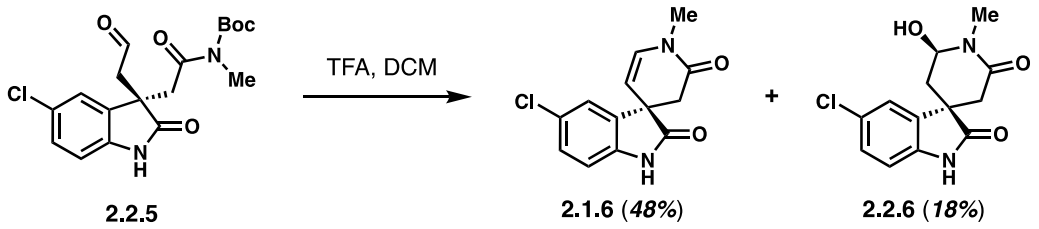
TLC: R_f = 0.50 (10% MeOH/DCM)

^{1}H NMR (600 MHz, CD_2Cl_2) δ 9.55 (t, *J* = 1.6 Hz, 1H), 7.77 (br, 1H), 7.26 (d, *J* = 2.2 Hz, 1H), 7.20 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 3.88 (d, *J* = 18.4 Hz, 1H), 3.46 (d, *J* = 18.4 Hz, 1H), 3.03 (dd, *J* = 17.2, 1.8 Hz, 1H), 2.96 (s, 3H), 2.82 (dd, *J* = 17.2, 1.4 Hz, 1H), 1.52 (s, 9H).

^{13}C NMR (150 MHz, CD_2Cl_2) δ 198.69, 180.19, 172.09, 153.39, 140.64, 133.96, 128.47, 127.61, 124.48, 110.99, 83.92, 50.46, 48.02, 44.77, 31.44, 28.13.

HRMS (m/z): (ESI) calcd for $^{12}C_{18}H_{22}O_5N_2{}^{35}Cl$ $[M+H]^+$: 381.1212, found 381.1210.

Preparation of enamide 2.1.6:



2.2.5 **2.1.6** (*48%*) **2.2.6** (*18%*)

To a solution of **2.2.5** (90.0 mg, 236 μmol, 1 equiv) in DCM (2.5 mL), TFA (0.50 mL, 6.5 mmol, 27 equiv) was added dropwise. The resulting mixture was stirred at ambient temperature for 1.5 hours before being quenched by the addition of saturated *aq.* $NaHCO_3$ (3 mL) at 0 ºC. The layers were separated, and the aqueous phase was extracted further with EtOAc (3 x 3 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1.8 to 3.4% MeOH/DCM) to afford enamide **2.1.6** (30.0 mg, 114 μmol, 48%) as a white solid and hemiaminal **2.2.6** (11.6 mg, 41.3 μmol, 18%) as a white solid.

Enamide 2.1.6

TLC: R_f = 0.28 (5% MeOH/DCM)

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.22 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.11 (d, *J* = 2.1 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.37 (d, *J* = 7.7 Hz, 1H), 4.90 (dd, *J* = 7.7, 0.9 Hz, 1H), 3.20 (s, 3H), 3.03 (d, *J* = 16.3 Hz, 1H), 2.69 (dd, *J* = 16.3, 1.0 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 179.33, 166.50, 138.18, 134.14 (2C), 129.15, 128.73, 124.26, 111.31, 104.56, 49.35, 39.15, 34.27.

IR (thin film) ν_{max} (cm^{-1}): 3221, 1718, 1654, 1477, 1364, 1295, 1175, 819, 716, 601, 557.

HRMS (m/z): (ESI) calcd for $^{12}C_{13}H_{11}{}^{35}ClN_2{}^{23}NaO_2$ $[M+Na]^+$: 285.0401, found 285.0403.

Hemiaminal 2.2.6

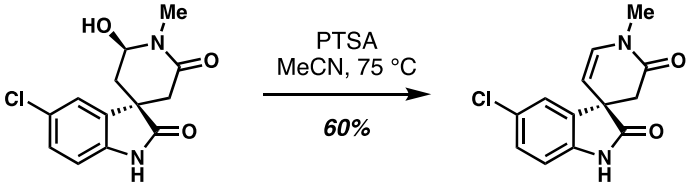
TLC: R_f = 0.22 (5% MeOH/DCM)

^{1}H NMR (600 MHz, DMSO-d_6): δ 10.83 (s, 1H), 7.30 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.97 (d, *J* = 2.2 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.11 (d, *J* = 8.7 Hz, 1H), 4.98 (q, *J* = 6.9 Hz, 1H), 2.95 (s, 3H), 2.58 (d, *J* = 16.6 Hz, 1H), 2.28 (dd, *J* = 16.7, 2.5 Hz, 1H), 2.17 (ddd, *J* = 13.9, 5.9, 2.4 Hz, 1H), 1.99 (dd, *J* = 13.9, 7.1 Hz, 1H).

^{13}C NMR (150 MHz, DMSO-d_6): δ 179.11, 166.58, 140.18, 134.05, 128.40, 125.88, 123.23, 111.51, 79.17, 46.32, 39.10, 38.33, 36.92, 29.91.

HRMS (m/z): (ESI) calcd for $^{12}C_{13}H_{14}O_3N_2{}^{35}Cl$ $[M+H]^+$: 281.0687, found 281.0686.

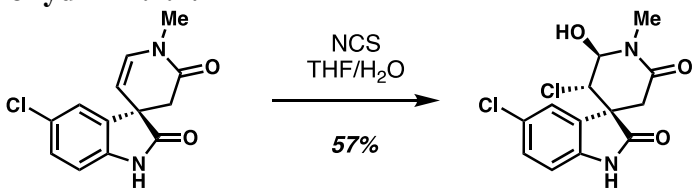
Conversion of hemiaminal 2.2.6 to enamide 2.1.6:



2.2.6 **2.1.6**

A suspension of **2.2.6** (97.7 mg, 348 μmol, 1 equiv) and TsOH·H_2O (6.6 mg, 35 μmol, 0.1 equiv) in MeCN (5 mL) was heated at 75 ºC for 12 hours. After being cooled to ambient temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1.8 to 2.7% MeOH/DCM) to afford enamide **2.1.6** (55.1 mg, 210 μmol, 60%) as a white solid.

Preparation of chlorohydrin 2.2.7:



2.1.6 **2.2.7**

[single diastereomer]

To a reaction tube charged with **2.1.6** (18.6 mg, 70.8 μmol, 1 equiv) and NCS (11.4 mg, 85.4 μmol, 1.2 equiv), THF (0.71 mL) and H_2O (0.14 mL) were added. The reaction mixture was stirred vigorously at ambient temperature for 3 hours before being quenched by the addition of saturated *aq*. $Na_2S_2O_3$ (1 mL). The layers were separated, and the aqueous phase was extracted further with EtOAc (3 x 1 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1 to 1.3 to 2% MeOH/DCM) to afford chlorohydrin **2.2.7** (12.7 mg, 40.3 μmol, 57%) as a white solid.

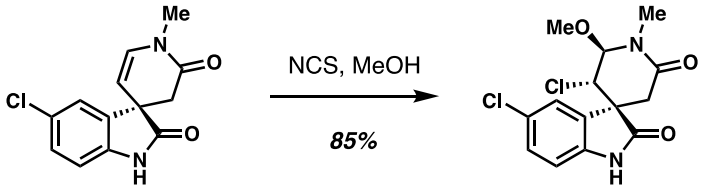
TLC: R_f = 0.17 (5% MeOH/DCM)

^{1}H NMR (600 MHz, CD_3OD) δ 7.35 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.95 (d, *J* = 2.1 Hz, 1H), 5.05 (d, *J* = 7.4 Hz, 1H), 4.33 (d, *J* = 7.5 Hz, 1H), 3.09 (s, 3H), 2.97 (d, *J* = 17.2 Hz, 1H), 2.48 (d, *J* = 17.2 Hz, 1H).

^{13}C NMR (150 MHz, CD_3OD) δ 177.66, 168.59, 142.56, 130.78, 130.60, 129.01, 125.08, 112.92, 85.83, 63.14, 53.68, 39.56, 30.34.

HRMS (m/z): (ESI) calcd for $^{12}C_{13}H_{11}O_3N_2{}^{35}Cl_2$ $[M–H]^-$: 313.0152, found 313.0149.

Preparation of chloroether 2.2.8:



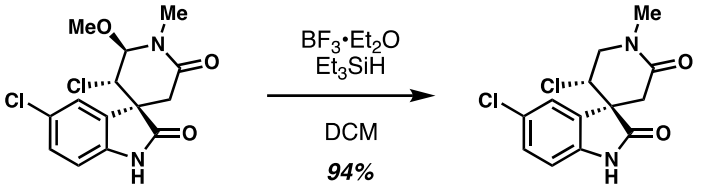
2.1.6 **2.2.8**

[single diastereomer]

A flame-dried reaction tube equipped with a stir bar was charged with **2.1.6** (29.0 mg, 110 μmol, 1 equiv) and NCS (17.7 mg, 133 μmol, 1.2 equiv). The atmosphere was exchanged three times with argon before anhydrous MeOH (1.5 mL) was added. The reaction mixture was stirred at ambient temperature overnight before being quenched by the addition of saturated *aq*. $Na_2S_2O_3$ (1 mL). The layers were separated, and the aqueous phase was extracted further with EtOAc (3 x 1 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (40 to 50% EtOAc/hexanes) to afford chloroether **2.2.8** (30.9 mg, 93.9 μmol, 85%) as a white solid.

TLC: R_f = 0.29 (60% EtOAc/hexanes)
^{1}H NMR (600 MHz, CD_2Cl_2) δ 8.09 (br, 1H), 7.33 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.95 – 6.92 (m, 2H), 4.88 (d, *J* = 7.2 Hz, 1H), 4.50 (d, *J* = 7.2 Hz, 1H), 3.54 (s, 3H), 3.08 (s, 3H), 2.96 (dd, *J* = 17.1, 0.7 Hz, 1H), 2.51 (d, *J* = 17.2 Hz, 1H).
^{13}C NMR (150 MHz, CD_2Cl_2) δ 175.63, 166.52, 140.26, 130.14, 129.13, 128.73, 124.89, 111.98, 92.78, 59.37, 56.16, 52.79, 39.02, 30.61.
HRMS (m/z): (ESI) calcd for $^{12}C_{14}H_{15}O_3N_2{}^{35}Cl_2$ $[M+H]^+$: 329.0454, found 329.0454.

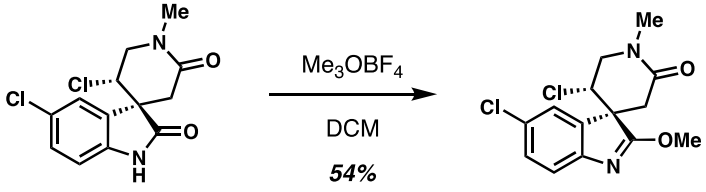
Preparation of chloride 2.1.5:



2.2.8 **2.1.5**

A flame-dried reaction tube equipped with a stir bar was charged with **2.2.8** (30.1 mg, 91.4 µmol, 1 equiv). After the atmosphere was exchanged three times with argon, anhydrous DCM (1.8 mL) and triethylsilane (0.06 mL, 0.4 mmol, 4 equiv) were added in sequence. The resulting solution was cooled to 0 ºC, and BF_3•OEt_2 (0.05 mL, 0.4 mmol, 4 equiv) was added dropwise. After completion of addition, the reaction mixture was allowed to warm to ambient temperature and stirred at that temperature for 12 hours before being quenched by the addition of saturated *aq.* $NaHCO_3$ (2 mL). The layers were separated, and the aqueous phase was extracted further with EtOAc (3 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1.1 to 1.7% MeOH/DCM) to afford chloride **2.1.5** (25.6 mg, 85.6 µmol, 94%) as a white solid.
TLC: R_f = 0.22 (5% MeOH/DCM)
^{1}H NMR (600 MHz, CD_2Cl_2) δ 8.19 (br, 1H), 7.32 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.12 (d, *J* = 2.1 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 4.54 (dd, *J* = 9.9, 5.9 Hz, 1H), 3.87 (dd, *J* = 13.0, 6.0 Hz, 1H), 3.71 (dd, *J* = 13.0, 9.9 Hz, 1H), 3.07 (s, 3H), 2.87 (d, *J* = 17.5 Hz, 1H), 2.56 (d, *J* = 17.4 Hz, 1H).
^{13}C NMR (150 MHz, CD_2Cl_2) δ 176.25, 165.80, 140.22, 129.93, 129.64, 128.59, 125.44, 111.77, 54.68, 53.29, 52.92, 38.08, 34.58.
HRMS (m/z): (ESI) calcd for $^{12}C_{13}H_{13}O_2N_2{}^{35}Cl_2$ $[M+H]^+$: 299.0349, found 299.0348.

Preparation of imidate 2.2.9:

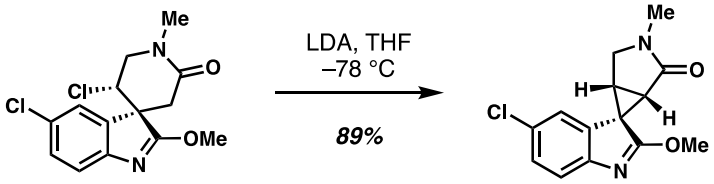


2.1.5 **2.2.9**

In a nitrogen-filled glovebox, trimethyloxonium tetrafluoroborate (107 mg, 723 µmol, 5.0 equiv) was added to a flame-dried reaction tube charged with **2.1.5** (43.4 mg, 145 µmol, 1 equiv). The reaction tube was sealed and removed from the glovebox. Anhydrous DCM (4 mL) was added, and the resulting suspension was stirred at ambient temperature for 16 hours before being quenched by the addition of saturated *aq.* $NaHCO_3$ (3 mL). The layers were separated, and the

aqueous phase was extracted further with EtOAc (3 x 3 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (15 to 25% Et_2O/DCM) to afford imidate **2.2.9** (24.3 mg, 77.6 µmol, 54%) as a white solid.
TLC: R_f = 0.20 (33% Et_2O/DCM)
^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.34 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.28 (d, *J* = 8.3 Hz, 1H), 7.07 (d, *J* = 2.1 Hz, 1H), 4.53 (dd, *J* = 10.1, 6.1 Hz, 1H), 4.08 (s, 3H), 3.83 (dd, *J* = 12.8, 6.1 Hz, 1H), 3.73 (dd, *J* = 12.9, 10.1 Hz, 1H), 3.06 (s, 3H), 2.87 (d, *J* = 17.4 Hz, 1H), 2.44 (d, *J* = 17.4 Hz, 1H).
^{13}C NMR (150 MHz, CD_2Cl_2) δ 178.60, 165.47, 152.31, 136.54, 129.92, 129.65, 123.83, 120.30, 57.63, 56.81, 53.33, 53.27, 37.22, 34.48.
HRMS (m/z): (ESI) calcd for $^{12}C_{14}H_{15}O_2N_2{}^{35}Cl_2$ $[M+H]^+$: 313.0505, found 313.0503.

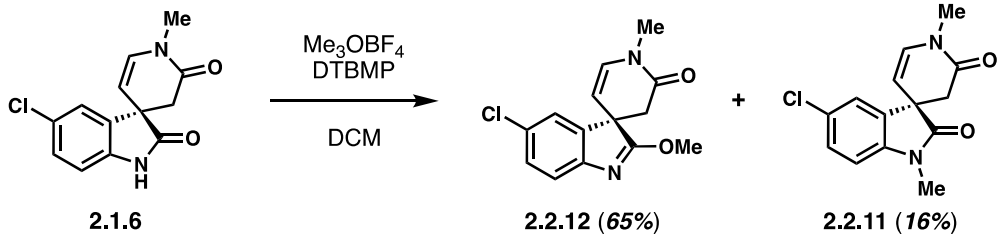
Cyclopropane 2.2.10:



2.2.9 2.2.10

A flame-dried reaction tube equipped with a stir bar was charged with **2.2.9** (19.7 mg, 62.9 µmol, 1 equiv). The atmosphere was exchanged three times with argon before anhydrous THF (0.44 mL) was added. The resulting solution was cooled to –78 ºC, and a solution of freshly made LDA (0.15 mL, 0.5 M in THF, 75 µmol, 1.2 equiv) was added dropwise. After the mixture was stirred at –78 ºC for 30 minutes, TLC analysis indicated disappearance of the starting material. Saturated *aq.* NH_4Cl (1 mL) was added in one portion at –78 ºC, and then the mixture was warmed to ambient temperature. The layers were separated, and the aqueous phase was extracted further with EtOAc (3 x 1 mL). The combined layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (80% EtOAc/Hexanes) to afford cyclopropane **2.2.10** (15.4 mg, 55.7 µmol, 89%) as a white solid.
TLC: R_f = 0.21 (EtOAc)
^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.32 (dd, *J* = 8.3, 0.5 Hz, 1H), 7.28 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.44 (dd, *J* = 2.1, 0.5 Hz, 1H), 4.01 (s, 3H), 3.85 (dd, *J* = 12.3, 5.7 Hz, 1H), 3.53 (dd, *J* = 12.2, 1.4 Hz, 1H), 2.98 (dd, *J* = 6.9, 1.4 Hz, 1H), 2.94 (s, 3H), 2.88 (ddd, *J* = 6.8, 5.7, 0.6 Hz, 1H).
^{13}C NMR (150 MHz, CD_2Cl_2) δ 178.06, 168.61, 153.78, 133.41, 128.68, 128.11, 121.30, 120.35, 57.01, 48.54, 36.55, 35.43, 28.93, 28.46.
HRMS (m/z): (ESI) calcd for $^{12}C_{14}H_{14}O_2N_2{}^{35}Cl$ $[M+H]^+$: 277.0738, found 277.0736.

Preparation of imidate 2.2.12:



2.1.6 2.2.12 (*65%*) 2.2.11 (*16%*)

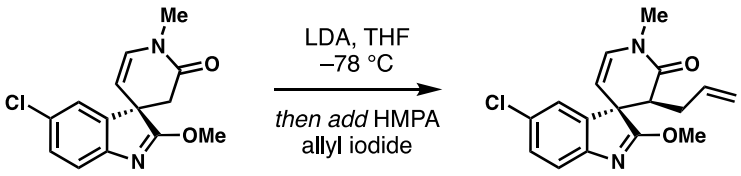
In a nitrogen-filled glovebox, 2,6-di-*tert*-butyl-4-methylpyridine (104 mg, 507 µmol, 1.2 equiv) and trimethyloxonium tetrafluoroborate (75.0 mg, 507 µmol, 1.2 equiv) were added to a flame-

dried round bottom flask charged with **2.1.6** (111 mg, 423 μmol, 1 equiv). The flask was sealed and removed from the glovebox. Anhydrous DCM (21 mL) was added, and the resulting suspension was stirred at ambient temperature overnight before being quenched by the addition of saturated *aq*. $NaHCO_3$ (20 mL). The layers were separated, and the aqueous phase was extracted further with DCM (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (31% EtOAc/hexanes) to afford imidate **2.2.12** (76.4 mg, 276 μmol, 65%) as a white foam along with 16% of **2.2.11**.

Desired *O*-methylation (2.2.12)
TLC: R_f = 0.24 (50% EtOAc/hexanes)
^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.24 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.20 (dd, *J* = 8.2, 0.5 Hz, 1H), 7.14 (dd, *J* = 2.1, 0.5 Hz, 1H), 6.38 (d, *J* = 7.7 Hz, 1H), 4.76 (d, *J* = 7.7 Hz, 1H), 4.02 (s, 3H), 3.14 (s, 3H), 2.76 (d, *J* = 16.2 Hz, 1H), 2.64 (d, *J* = 16.2 Hz, 1H).
^{13}C NMR (150 MHz, $CDCl_3$): δ 182.25, 166.98, 151.30, 141.91, 134.65, 129.57, 129.16, 122.79, 119.86, 103.76, 57.49, 52.50, 38.32, 34.16.
IR (thin film) ν_{max} (cm^{-1}): 3055, 2951, 2923, 2854, 1657, 1610, 1580, 1453, 1353, 1292, 1268, 1168, 1046, 959, 907, 820, 733, 604, 546, 439.
HRMS (m/z): (ESI) calcd for $^{12}C_{14}H_{14}O_2N_2{}^{35}Cl$ $[M+H]^+$: 277.0738, found 277.0739.

Undesired *N*-methylation (2.2.11)
TLC: R_f = 0.17 (50% EtOAc/hexanes)
^{1}H NMR (600 MHz, THF-d_8) δ 7.27 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.15 (d, *J* = 2.2 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 6.44 (d, *J* = 7.7 Hz, 1H), 4.74 (dt, *J* = 7.7, 0.7 Hz, 1H), 3.13 (s, 3H), 3.08 (s, 3H), 2.80 (d, *J* = 16.0 Hz, 1H), 2.56 (dd, *J* = 16.0, 1.0 Hz, 1H).
^{13}C NMR (150 MHz, THF-d_8): δ 177.23, 166.25, 142.87, 135.25, 134.75, 129.32, 128.36, 124.23, 110.15, 104.81, 49.56, 39.71, 33.56, 26.40.
HRMS (m/z): (ESI) calcd for $^{12}C_{14}H_{14}O_2N_2{}^{35}Cl$ $[M+H]^+$: 277.0738, found 277.0736.

Preparation of allyl 2.2.13:

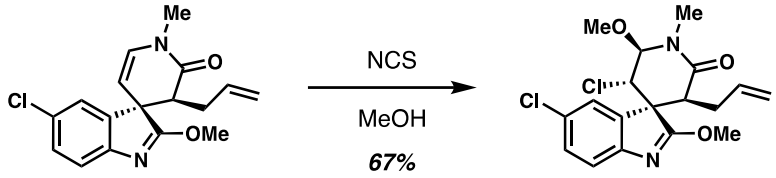


2.2.12 **2.2.13**

A flame-dried reaction tube equipped with a stir bar was charged with **2.2.12** (43.6 mg, 158 μmol, 1 equiv). The atmosphere was exchanged three times with argon before anhydrous THF (1.3 mL) was added. The resulting solution was cooled to –78 ºC, and a solution of freshly made LDA (0.38 mL, 0.5 M in THF, 0.19 mmol, 1.2 equiv) was added dropwise. After the mixture was stirred at –78 ºC for 30 minutes, HMPA (0.08 mL, 0.5 mmol, 3 equiv) was added followed by dropwise addition of allyl iodide (20 μL, 0.22 mmol, 1.4 equiv). The reaction mixture was allowed to warm to ambient temperature over 4 hours before being quenched by the addition of saturated *aq.* NH_4Cl (1 mL). The layers were separated, and the aqueous phase was extracted further with EtOAc (3 x 1 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (17 to 28 to 40%

EtOAc/hexanes) to afford allyl **2.2.13** (33.2 mg, 105 μmol, 67%) as a white solid along with 8% of 23-*epi*-**2.2.13**.
TLC: R_f = 0.45 (50% EtOAc/hexanes)
^{13}C NMR (150 MHz, CD_2Cl_2) δ 180.79, 169.45, 152.51, 141.60, 137.25, 134.81, 129.56, 129.10, 122.84, 119.74, 115.55, 104.32, 57.19, 56.49, 46.11, 34.47, 30.01.
HRMS (m/z): (ESI) calcd for $^{12}C_{17}H_{18}O_2N_2{}^{35}Cl$ $[M+H]^+$: 317.1051, found 317.1048.

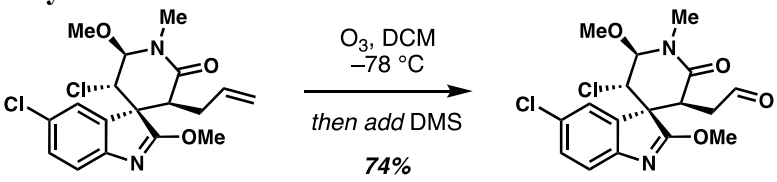
Preparation of chloroether 2.2.14:



2.2.13 **2.2.14** **[single diastereomer]**

A flame-dried reaction tube equipped with a stir bar was charged with **2.2.13** (162 mg, 511 μmol, 1 equiv) and NCS (82.1 mg, 615 μmol, 1.2 equiv). The atmosphere was exchanged three times with argon before anhydrous MeOH (5.2 mL) was added. The reaction mixture was stirred at ambient temperature for 30 minutes before being quenched by the addition of saturated *aq*. $Na_2S_2O_3$ (5 mL). The layers were separated, and the aqueous phase was extracted further with EtOAc (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20% EtOAc/hexanes) to afford chloroether **2.2.14** (132 mg, 344 μmol, 67%) as a white solid.
TLC: R_f = 0.44 (50% EtOAc/Hexanes)
^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.32 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 1H), 6.90 (d, *J* = 2.0 Hz, 1H), 5.83 – 5.74 (m, 1H), 5.04 – 5.01 (m, 1H), 5.00 (t, *J* = 1.4 Hz, 1H), 4.79 (d, *J* = 6.0 Hz, 1H), 4.61 (d, *J* = 6.0 Hz, 1H), 4.06 (s, 3H), 3.55 (s, 3H), 3.06 (s, 3H), 2.79 – 2.70 (m, 1H), 2.65 (dd, *J* = 7.6, 5.5 Hz, 1H), 2.53 (dtt, *J* = 14.7, 7.4, 1.2 Hz, 1H).
^{13}C NMR (150 MHz, CD_2Cl_2) δ 178.17, 168.86, 151.86, 137.70, 135.87, 129.96, 129.67, 123.44, 120.37, 116.93, 93.87, 59.39, 57.37, 57.15, 56.98, 47.91, 33.17, 31.24.
HRMS (m/z): (ESI) calcd for $^{12}C_{18}H_{21}O_3N_2{}^{35}Cl_2$ $[M+H]^+$: 383.0924, found 383.0920.

Preparation of aldehyde 2.2.15:

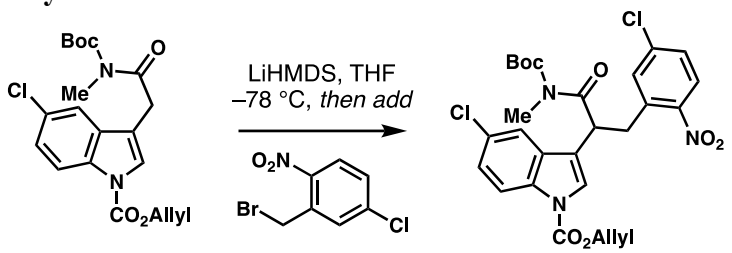


2.2.14 **2.2.15**

A solution of **2.2.14** (44.6 mg, 116 μmol, 1 equiv) in DCM (4.6 mL) was cooled to –78 ºC and sparged with a stream of ozone until a blue color persisted. At this point, TLC analysis indicated the complete consumption of starting material and dimethyl sulfide (2.2 mL) was added. The resulting reaction mixture was allowed to slowly warm to ambient temperature and stirred at that temperature overnight. The crude reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (1.8% MeOH/DCM) to afford aldehyde **2.2.15** (33.3 mg, 86.4 μmol, 74%) as a slightly yellow solid.

TLC: R_f = 0.37 (5% MeOH/DCM)
^{13}C NMR (150 MHz, CD_2Cl_2) δ 198.25, 177.69, 168.87, 151.92, 137.31, 130.22, 129.70, 124.16, 120.47, 93.86, 57.88, 57.69, 57.43, 57.41, 42.06, 40.07, 31.71.
HRMS (m/z): (ESI) calcd for $^{12}C_{17}H_{19}O_4N_2{}^{35}Cl_2$ [M+H]$^+$: 385.0716, found 385.0713.

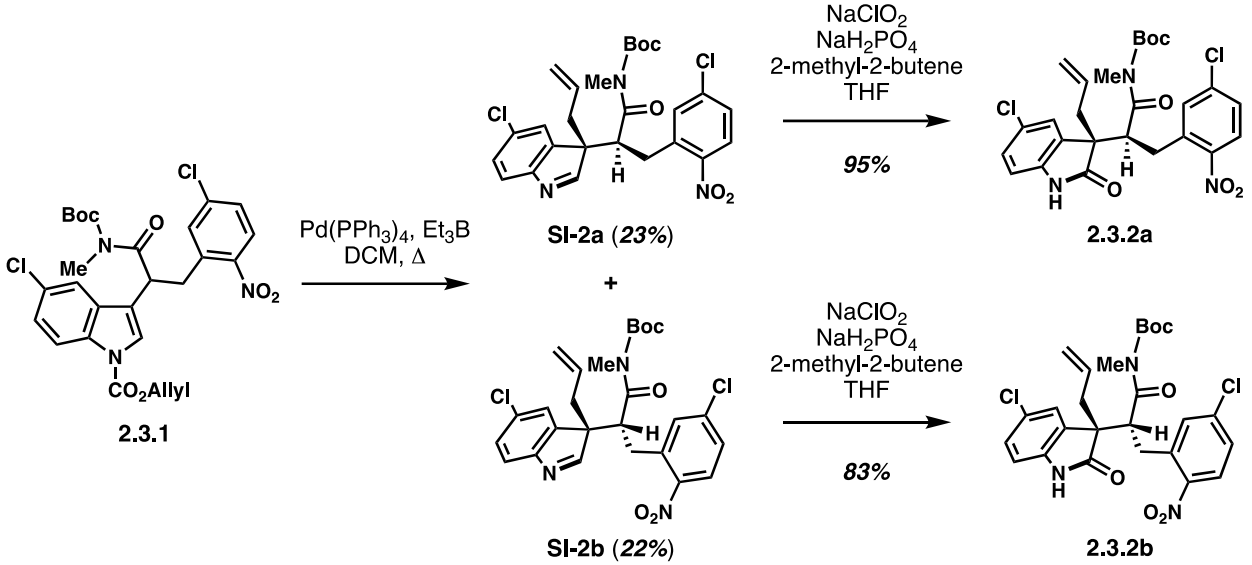
Preparation of *α*-benzyl substituted amide 2.3.1:



2.2.2 **2.3.1**

A flame-dried round bottom flask equipped with a stir bar was charged with **2.2.2** (667 mg, 1.64 mmol, 1 equiv). The atmosphere was exchanged three times with argon before anhydrous THF (16 mL) was added. The resulting solution was cooled to –78 ºC, and LiHMDS (1.97 mL, 1 M in THF, 1.97 mmol, 1.2 equiv) was added dropwise. After the mixture was stirred at –78 ºC for 40 minutes, a solution of (2-bromomethyl)-4-chloro-1-nitrobenzene (452 mg, 1.80 mmol, 1.1 equiv) in THF (16 mL) was added dropwise. The reaction mixture was allowed to slowly warm to ambient temperature and stirred at that temperature overnight before being quenched by the addition of saturated *aq.* NH_4Cl (30 mL). The layers were separated, and the aqueous phase was extracted further with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1:30:69 Et_2O/DCM/hexanes) to afford *α*-benzyl substituted amide **2.3.1** (661 mg, 1.15 mmol, 70%) as a white solid.
TLC: R_f = 0.30 (3:29:68 Et_2O/DCM/hexanes)
^{1}H NMR (600 MHz, CD_2Cl_2) δ 8.11 (d, *J* = 8.9 Hz, 1H), 7.89 (d, *J* = 8.7 Hz, 1H), 7.63 (d, *J* = 2.1 Hz, 1H), 7.58 (s, 1H), 7.33 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.30 – 7.25 (m, 2H), 6.08 (ddt, *J* = 17.2, 10.5, 5.9 Hz, 1H), 5.70 (dd, *J* = 8.4, 6.3 Hz, 1H), 5.45 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.36 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.95 – 4.84 (m, 2H), 3.66 (dd, *J* = 13.5, 8.4 Hz, 1H), 3.47 (dd, *J* = 13.5, 6.3 Hz, 1H), 3.04 (s, 3H), 1.38 (s, 9H).
^{13}C NMR (150 MHz, CD_2Cl_2) δ 175.30, 153.44, 150.59, 148.27, 139.35, 136.83, 134.37, 133.37, 131.89, 130.96, 129.03, 128.27, 126.77, 126.10, 125.24, 119.84, 119.65, 118.73, 116.60, 83.83, 68.23, 43.32, 36.79, 32.41, 27.93.
HRMS (m/z): (ESI) calcd for $^{12}C_{27}H_{27}O_7N_3{}^{35}Cl_2{}^{23}Na$ [M+Na]$^+$: 598.1118, found 598.1120.

Preparation of oxindole 2.3.2a and 2.3.2b:



Following a published procedure,[3] a flame-dried round bottom flask equipped with a reflux condenser and stir bar was charged with **2.3.1** (1.14 mg, 1.98 mmol, 1 equiv) and $Pd(PPh_3)_4$ (45.6 mg, 39.5 μmol, 0.02 equiv). The atmosphere was exchanged three times with argon before anhydrous DCM (10 mL) was added. To the resulting yellow solution, triethylborane (2.0 mL, 1 M in hexanes, 2.0 mmol, 1.0 equiv) was added dropwise, and the mixture was heated at reflux for 16 hours. After being cooled to ambient temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2:49:49 Et_2O/DCM/hexanes to 4:48:48 Et_2O/DCM/hexanes) to afford indolenine **SI-2a** (243 mg, 456 μmol, 23%) as a white foam and indolenine **SI-2b** (236 mg, 443 μmol, 22%) as a white foam, which were used immediately for the next step.

2.3.2a: Following a published procedure,[4] to a solution of **SI-2a** (243 mg, 456 μmol, 1 equiv) in THF (4.6 ml), 2-methyl-2-butene (0.48 mL, 4.5 mmol, 9.9 equiv) and $NaClO_2$ (206 mg, 2.28 mmol, 5.0 equiv) were added in sequence. The resulting suspension was stirred vigorously, and NaH_2PO_4 (0.68 mL, 1 M in H_2O, 0.68 mmol, 1.5 equiv) was added dropwise. After completion of addition, the reaction mixture was stirred at ambient temperature for 1.5 hours before being quenched by the addition of saturated *aq*. $Na_2S_2O_3$ (4 mL) at 0 ºC. The layers were separated, and the aqueous phase was extracted further with EtOAc (5 x 4 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (19% EtOAc/hexanes) to afford oxindole **2.3.2a** (237 mg, 432 μmol, 95%) as a white solid.

TLC: R_f = 0.32 (30% EtOAc/hexanes)

^{1}H NMR (600 MHz, CD_2Cl_2) δ 8.10 (br, 1H), 7.95 (d, *J* = 8.8 Hz, 1H), 7.33 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.25 (d, *J* = 2.3 Hz, 1H), 7.21 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.12 (d, *J* = 2.1 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 5.27 (ddt, *J* = 17.2, 10.1, 7.2 Hz, 1H), 5.07 – 5.00 (m, 2H), 4.88 (ddt, *J* = 10.1, 1.9, 0.9 Hz, 1H), 3.99 (dd, *J* = 12.8, 3.1 Hz, 1H), 3.24 (t, *J* = 12.4 Hz, 1H), 3.03 (ddt, *J* = 13.5, 6.9, 1.2 Hz, 1H), 2.90 (s, 3H), 2.86 (ddt, *J* = 13.6, 7.5, 1.1 Hz, 1H), 1.27 (s, 9H).

^{13}C NMR (150 MHz, CD_2Cl_2) δ 179.11, 175.13, 152.96, 147.98, 140.19, 139.54, 136.60, 133.28, 132.82, 132.10, 128.52, 128.29, 127.66, 127.01, 125.14, 119.66, 110.99, 83.85, 55.28, 48.95, 37.67, 32.42, 31.98, 27.78.

2.3.2b: Following a published procedure,[4] to a solution of **SI-2b** (236 mg, 443 μmol, 1 equiv) in THF (4.4 ml), 2-methyl-2-butene (0.47 mL, 4.4 mmol, 10 equiv) and $NaClO_2$ (201 mg, 2.22 mmol, 5.0 equiv) were added in sequence. The resulting suspension was stirred vigorously, and NaH_2PO_4 (0.67 mL, 1 M in H_2O, 0.67 mmol, 1.5 equiv) was added dropwise. After completion of addition, the reaction mixture was stirred at ambient temperature for 1.5 hours before being quenched by the addition of saturated *aq*. $Na_2S_2O_3$ (4 mL) at 0 ºC. The layers were separated, and the aqueous phase was extracted further with EtOAc (5 x 4 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (19% EtOAc/hexanes) to afford oxindole **2.3.2b** (202 mg, 368 μmol, 83%) as a white solid.

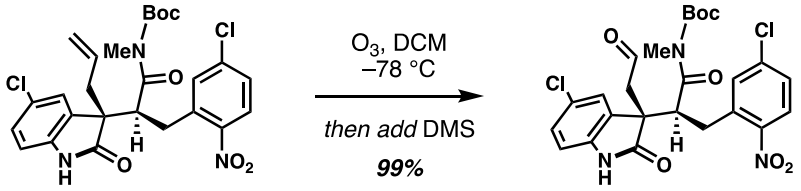
TLC: R_f = 0.32 (30% EtOAc/hexanes)

^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.99 (d, *J* = 8.8 Hz, 1H), 7.66 (br, 1H), 7.37 (d, *J* = 2.1 Hz, 1H), 7.34 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.19 – 7.14 (m, 2H), 6.77 (d, *J* = 8.3 Hz, 1H), 5.45 – 5.35 (m, 1H), 5.25 (dd, *J* = 11.6, 3.8 Hz, 1H), 5.02 (dq, *J* = 17.0, 1.4 Hz, 1H), 4.94 (ddt, *J* = 10.1, 1.9, 0.9 Hz, 1H), 3.77 (dd, *J* = 13.0, 3.8 Hz, 1H), 3.35 (dd, *J* = 13.0, 11.6 Hz, 1H), 2.90 (ddt, *J* = 13.4, 7.7, 1.1 Hz, 1H), 2.67 (ddt, *J* = 13.4, 6.8, 1.2 Hz, 1H), 2.64 (s, 3H), 1.37 (s, 9H).

^{13}C NMR (150 MHz, CD_2Cl_2) δ 178.84, 176.14, 153.10, 147.82, 140.21, 139.57, 136.88, 133.43, 132.81, 131.77, 128.61, 128.29, 127.55, 127.12, 125.48, 119.84, 110.68, 84.10, 54.74, 50.58, 40.06, 32.76, 31.67, 27.84.

HRMS (m/z): (ESI) calcd for $^{12}C_{26}H_{28}O_6N_3{}^{35}Cl_2$ $[M+H]^+$: 548.1350, found 548.1347.

Preparation of aldehyde SI-3a:



2.3.2a **SI-3a**

A solution of **2.3.2a** (237 mg, 432 μmol, 1 equiv) in DCM (10.5 mL) was cooled to –78 ºC and sparged with a stream of ozone until a blue color persisted. At this point, TLC analysis indicated the complete consumption of starting material and dimethyl sulfide (5.2 mL) was added. The resulting reaction mixture was allowed to slowly warm to ambient temperature and stirred at that temperature overnight. The crude reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (2% MeOH/DCM) to afford aldehyde **SI-3a** (236 g, 429 μmol, 99%) as a white foam.

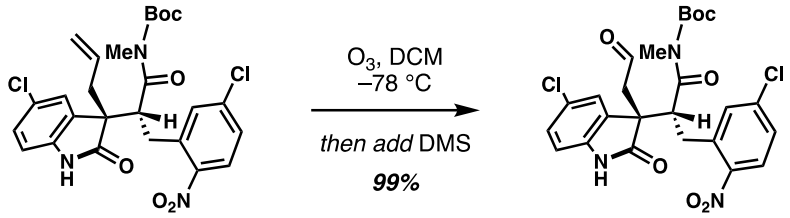
TLC: R_f = 0.44 (10% MeOH/DCM)

^{1}H NMR (600 MHz, CD_2Cl_2) δ 9.52 (s, 1H), 7.94 (d, *J* = 8.8 Hz, 1H), 7.84 (s, 1H), 7.33 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.26 (d, *J* = 2.3 Hz, 1H), 7.19 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.89 – 6.84 (m, 2H), 4.88 (dd, *J* = 11.9, 2.9 Hz, 1H), 4.02 (dd, *J* = 12.8, 3.0 Hz, 1H), 3.76 (d, *J* = 18.8 Hz, 1H), 3.43 (d, *J* = 18.8 Hz, 1H), 3.18 (t, *J* = 12.4 Hz, 1H), 2.93 (s, 3H), 1.19 (s, 9H).

^{13}C NMR (150 MHz, CD_2Cl_2): δ 198.60, 178.75, 174.76, 152.73, 147.86, 140.30, 139.69, 136.31, 133.28, 132.70, 128.82, 128.41, 127.47, 127.07, 123.84, 111.19, 84.05, 50.39, 48.04, 45.61, 31.91, 31.62, 27.63.

HRMS (m/z): (ESI) calcd for $^{12}C_{25}H_{26}O_7N_3{}^{35}Cl_2$ $[M+H]^+$: 550.1142, found 550.1136.

Preparation of aldehyde SI-3b:

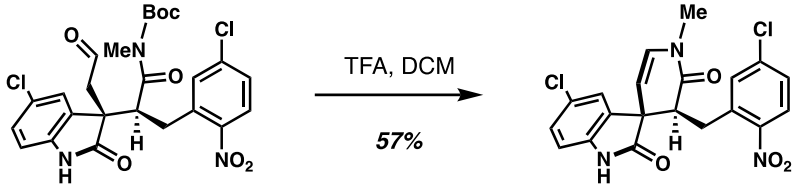


2.3.2b **SI-3b**

A solution of **2.3.2b** (202 g, 368 μmol, 1 equiv) in DCM (9 mL) was cooled to –78 ºC and sparged with a stream of ozone until a blue color persisted. At this point, TLC analysis indicated the complete consumption of starting material and dimethyl sulfide (4.4 mL) was added. The resulting reaction mixture was allowed to slowly warm to ambient temperature and stirred at that temperature overnight. The crude reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (2% MeOH/DCM) to afford aldehyde **SI-3b** (200 mg, 363 μmol, 99%) as a white foam.

TLC: R_f = 0.44 (10% MeOH/DCM)

Preparation of enamide 2.3.3a:



SI-3a **2.3.3a**

To a solution of **SI-3a** (236 mg, 429 μmol, 1 equiv) in DCM (4.2 mL) at 0 °C, TFA (0.83 mL, 11 mmol, 25 equiv) was added dropwise. The resulting mixture was allowed to warm to ambient temperature and stirred at that temperature for 6 hours before being concentrated under reduced pressure. The residue was redissolved in EtOAc (10 mL) and washed with saturated *aq*. $NaHCO_3$ (10 mL). The layers were separated, and the aqueous phase was extracted further with EtOAc (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0.8% MeOH/DCM) to afford enamide **2.3.3a** (105 mg, 243 μmol, 57%) as a white solid.

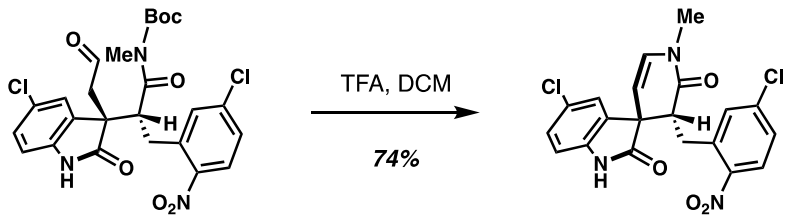
TLC: R_f = 0.27 (5% MeOH/DCM)

^{1}H NMR (600 MHz, CD_2Cl_2) δ 8.25 (s, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.20 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.15 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.10 (d, *J* = 2.3 Hz, 1H), 6.99 (dt, *J* = 2.2, 0.6 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 6.35 (d, *J* = 7.7 Hz, 1H), 4.74 (d, *J* = 7.7 Hz, 1H), 3.81 (dd, *J* = 14.6, 7.1 Hz, 1H), 3.39 (t, *J* = 6.8 Hz, 1H), 3.09 (d, *J* = 0.6 Hz, 3H), 2.58 (dd, *J* = 14.7, 6.5 Hz, 1H).

^{13}C NMR (150 MHz, CD_2Cl_2) δ 177.54, 168.41, 147.75, 139.85, 138.96, 137.57, 134.57, 133.14, 133.08, 129.49, 128.63, 127.98, 126.44, 124.34, 111.60, 105.84, 53.32, 47.17, 34.60, 29.82.

HRMS (m/z): (ESI) calcd for $^{12}C_{20}H_{16}O_4N_3{}^{35}Cl_2$ $[M+H]^+$: 432.0512, found 432.0509.

Preparation of enamide 2.3.3b:



SI-3b **2.3.3b**

To a solution of **SI-3b** (206 mg, 374 μmol, 1 equiv) in DCM (3.6 mL) at 0 °C, TFA (0.72 mL, 9.3 mmol, 25 equiv) was added dropwise. The resulting mixture was allowed to warm to ambient temperature and stirred at that temperature for 6 hours before being concentrated under reduced pressure. The residue was suspended in DCM and poured onto a fritted funnel. The filter cake was washed successively with DCM (5 x 2 mL), saturated *aq*. $NaHCO_3$ (3 x 2 mL), and H_2O (3 x 2 mL), and then dried under high vacuum to afford enamide **2.3.3b** (120 mg, 278 μmol, 74%) as a white solid.

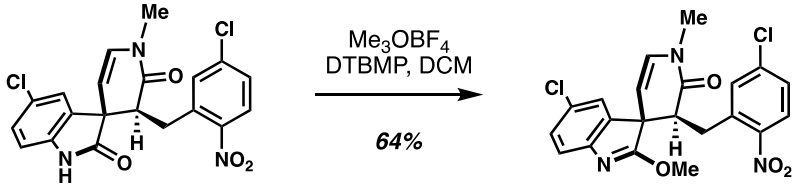
TLC: R_f = 0.32 (5% MeOH/DCM)

^{1}H NMR (600 MHz, DMSO-d_6) δ 10.67 (s, 1H), 7.91 (d, *J* = 8.7 Hz, 1H), 7.51 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.35 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.99 (d, *J* = 2.2 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.53 (d, *J* = 7.7 Hz, 1H), 4.92 (d, *J* = 7.7 Hz, 1H), 3.50 – 3.41 (m, 2H), 3.05 (s, 3H), 2.37 – 2.29 (m, 1H).

^{13}C NMR (150 MHz, DMSO-d_6): δ 177.79, 167.74, 147.99, 140.31, 137.33, 136.25, 132.91, 132.08, 130.71, 129.16, 127.78, 126.36, 126.21, 123.41, 111.65, 105.26, 52.73, 45.35, 33.90, 28.28.

HRMS (m/z): (ESI) calcd for $^{12}C_{20}H_{16}O_4N_3{}^{35}Cl_2$ $[M+H]^+$: 432.0512, found 432.0510.

Preparation of imidate 2.3.4a:



2.3.3a **2.3.4a**

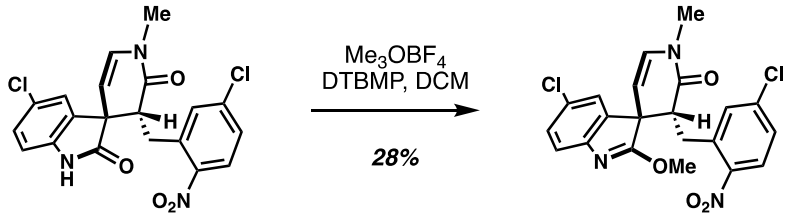
In a nitrogen-filled glovebox, 2,6-di-*tert*-butyl-4-methylpyridine (75.0 mg, 365 μmol, 1.35 equiv) and trimethyloxonium tetrafluoroborate (54.1 mg, 366 μmol, 1.35 equiv) were added to a flame-dried round bottom flask charged with **2.3.3a** (117 mg, 271 μmol, 1 equiv). The flask was sealed and removed from the glovebox. Anhydrous DCM (27 mL) was added, and the resulting suspension was stirred at ambient temperature overnight before being quenched by the addition of saturated *aq*. $NaHCO_3$ (30 mL). The layers were separated, and the aqueous phase was extracted further with DCM (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (18 to 20% EtOAc/hexanes) to afford imidate **2.3.4a** (77.0 mg, 173 μmol, 64%) as a white solid.

TLC: R_f = 0.40 (50% EtOAc/hexanes)

^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.75 (d, *J* = 8.7 Hz, 1H), 7.20 (dd, *J* = 8.2, 0.5 Hz, 1H), 7.18 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.16 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.94 (dd, *J* = 2.2, 0.5 Hz, 1H), 6.88 (d, *J* = 2.3 Hz, 1H), 6.34 (d, *J* = 7.7 Hz, 1H), 4.62 (d, *J* = 7.7 Hz, 1H), 4.05 (s, 3H), 3.80 (dd, *J* = 14.7, 6.4 Hz, 1H), 3.36 – 3.30 (m, 1H), 3.09 (d, *J* = 0.6 Hz, 3H), 2.19 (dd, *J* = 14.7, 6.8 Hz, 1H).

^{13}C NMR (150 MHz, CD_2Cl_2) δ 180.43, 168.50, 152.09, 147.63, 140.55, 138.88, 137.60, 134.87, 132.97, 129.77, 129.56, 127.85, 126.34, 122.71, 119.97, 104.48, 57.64, 56.43, 46.45, 34.66, 29.44.
HRMS (m/z): (ESI) calcd for $^{12}C_{21}H_{18}O_4N_3{}^{35}Cl_2$ $[M+H]^+$: 446.0669, found 446.0664.

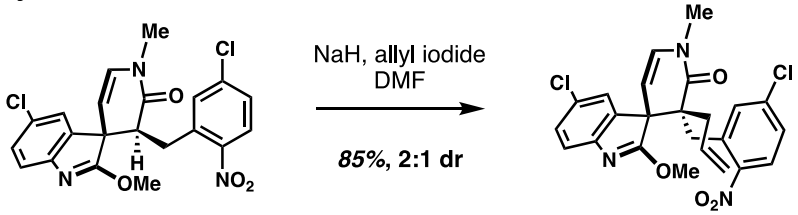
Preparation of imidate 2.3.4b:



2.3.3b **2.3.4b**

In a nitrogen-filled glovebox, 2,6-di-*tert*-butyl-4-methylpyridine (13.5 mg, 65.7 μmol, 1.35 equiv) and trimethyloxonium tetrafluoroborate (9.7 mg, 66 μmol, 1.3 equiv) were added to a flame-dried round bottom flask charged with **2.3.3b** (21.0 mg, 48.6 μmol, 1 equiv). The flask was sealed and removed from the glovebox. Anhydrous DCM (5.0 mL) was added, and the resulting suspension was stirred at ambient temperature overnight before being quenched by the addition of saturated *aq*. $NaHCO_3$ (5 mL). The layers were separated, and the aqueous phase was extracted further with DCM (3 x 3 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (16 to 18% EtOAc/hexanes) to afford imidate **2.3.4b** (6.1 mg, 14 μmol, 28%) as a white solid.
TLC: R_f = 0.47 (50% EtOAc/hexanes)
^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.86 (d, *J* = 8.7 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.21 (dd, *J* = 8.2, 0.5 Hz, 1H), 7.07 (dd, *J* = 2.1, 0.5 Hz, 1H), 6.86 (d, *J* = 2.3 Hz, 1H), 6.34 (d, *J* = 7.7 Hz, 1H), 4.76 (d, *J* = 7.7 Hz, 1H), 3.77 (s, 3H), 3.64 (dd, *J* = 14.6, 6.8 Hz, 1H), 3.49 – 3.43 (m, 1H), 3.15 (d, *J* = 0.6 Hz, 3H), 2.31 (dd, *J* = 14.6, 7.3 Hz, 1H).
^{13}C NMR (150 MHz, CD_2Cl_2) δ 181.26, 168.54, 151.55, 148.01, 138.98, 137.79, 136.65, 134.22, 133.47, 129.99, 129.81, 128.20, 126.45, 123.12, 120.32, 105.33, 57.34, 56.26, 44.06, 34.80, 29.97.
HRMS (m/z): (ESI) calcd for $^{12}C_{21}H_{18}O_4N_3{}^{35}Cl_2$ $[M+H]^+$: 446.0669, found 446.0666.

Preparation of allyl 2.3.5:



2.3.4a **2.3.5**

A flame-dried reaction tube equipped with a stir bar was charged with **2.3.4a** (81.2 mg, 182 μmol, 1 equiv). The atmosphere was exchanged three times with argon before anhydrous DMF (3.6 mL) was added. The resulting solution was cooled to 0 ºC, and NaH (39 mg, 60% dispersion in mineral oil, 0.98 mmol, 5.4 equiv) was added in three portions. After the mixture was stirred at 0 ºC for 20 minutes, allyl iodide (0.17 mL, 1.9 mmol, 10 equiv) was added dropwise. The resulting mixture was allowed to warm to ambient temperature and stirred at that temperature for 6 hours before being quenched by the addition of saturated *aq*. $NaHCO_3$ (3 mL) at 0 ºC. The layers were separated, and the aqueous phase was extracted further with Et_2O (3 x 3 mL). The combined organic layers

were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (11 to 13 to 18% EtOAc/hexanes) to afford allyl **2.3.5** (50.2 mg, 103 μmol, 57%) as a white solid along with 28% of 23-*epi*-**2.3.5**.

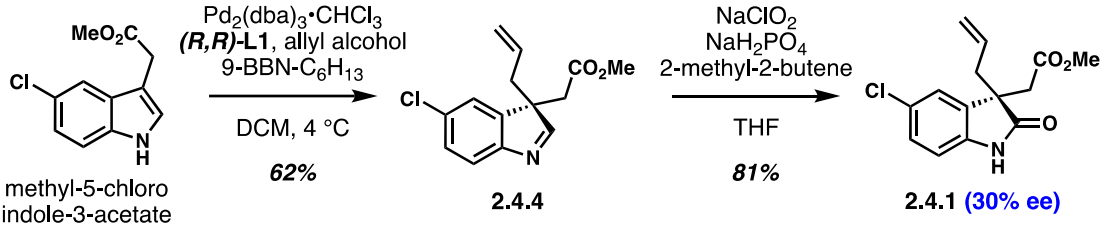
TLC: R_f = 0.23 (30% EtOAc/hexanes)

^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.76 (d, *J* = 8.7 Hz, 1H), 7.46 – 7.31 (m, 3H), 7.31 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 6.35 (d, *J* = 7.6 Hz, 1H), 5.26 – 5.14 (m, 1H), 4.80 (dq, *J* = 16.9, 1.7 Hz, 1H), 4.77 – 4.71 (m, 2H), 4.12 (br, 1H), 3.94 (s, 3H), 3.18 (br, 1H), 2.97 (s, 3H), 2.49 (br, 1H), 2.23 (dd, *J* = 15.7, 6.5 Hz, 1H).

^{13}C NMR (150 MHz, CD_2Cl_2) δ 180.68, 169.46, 152.66, 149.77, 139.30, 138.39, 134.61, 134.27, 133.92, 133.14, 129.51, 129.34, 128.46, 126.76, 124.45, 120.10, 118.17, 105.62, 60.27, 57.26, 50.96, 35.55, 34.75, 31.50.

HRMS (m/z): (ESI) calcd for $^{12}C_{24}H_{22}O_4N_3{}^{35}Cl_2$ $[M+H]^+$: 486.0982, found 486.0977.

Preparation of 2.4.1:



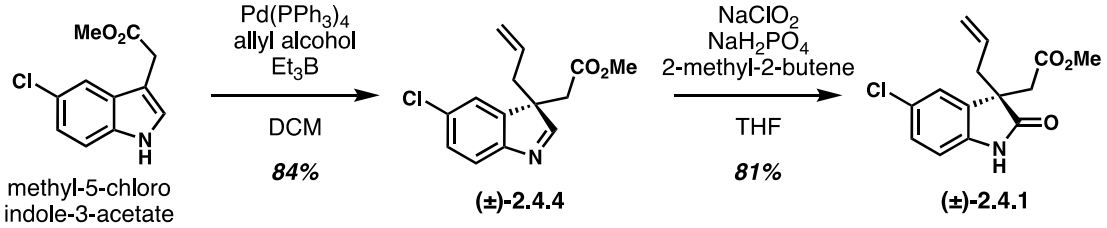
Following a published procedure,[5] a flame-dried reaction tube equipped with a stir bar was charged with methyl-5-chloroindole-3-acetate (14.9 mg, 66.6 μmol, 1 equiv), $Pd_2(dba)_3$•$CHCl_3$ (1.7 mg, 1.6 μmol, 0.025 equiv), and (*R*,*R*)-ANDEN-Phenyl Trost Ligand (4.1 mg, 5.0 μmol, 0.076 equiv). The atmosphere was exchanged three times with argon before anhydrous DCM (0.67 mL) was added. The resulting solution was stirred at ambient temperature for 15 min and then a solution of 9-BBN-C_6H_{13} (0.14 mL, 0.25 M in THF, 35 μmol, 0.53 equiv) was added. After completion of addition, the resulting mixture was stirred for 5 min and cooled to 0 ºC. Allyl alcohol (13.6 μL, 200 μmol, 3.0 equiv) was then added dropwise and the resulting solution was stirred for 20 hours at 4 ºC before being quenched by the addition of saturated *aq.* $NaHCO_3$ (1 mL). The layers were separated, and the aqueous phase was extracted further with EtOAc (3 x 1 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (10% Et_2O/DCM) to afford indolenine **2.4.5** (10.8 mg, 41.0 μmol, 62%) as a colorless oil, which was used immediately for the next step.

***Borane generation:** A flame-dried reaction tube equipped with a stir bar was charged with 9-BBN dimer (30.4 mg, 125 μmol). The atmosphere was exchanged three times with argon before anhydrous THF (0.5 mL) was added. 1-hexene (37.1 μL, 297 μmol) was then added and the resulting mixture was stirred at ambient temperature for 4 hours.

Following a published procedure,[4] to a solution of **2.4.5** (10.8 mg, 41.0 μmol, 1 equiv) in THF (0.41 ml), 2-methyl-2-butene (43.4 μL, 410 μmol, 10 equiv) and $NaClO_2$ (18.5 mg, 205 μmol, 5.0 equiv) were added in sequence. The resulting suspension was stirred vigorously, and NaH_2PO_4 (61.4 μL, 1 M in H_2O, 61.4 μmol, 1.5 equiv) was added dropwise. After completion of addition, the reaction mixture was stirred at ambient temperature for 1.5 hours before being quenched by the addition of saturated *aq*. $Na_2S_2O_3$ (0.5 mL) at 0 ºC. The layers were separated, and the aqueous phase was extracted further with EtOAc (5 x 0.5 mL). The combined organic layers were dried

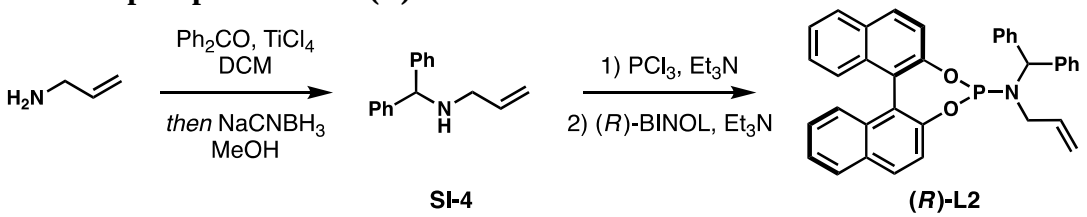
over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (40% EtOAc/hexanes) to afford oxindole **2.4.1** (9.3 mg, 33 μmol, 81%) as a colorless oil.

Preparation of racemic standard of 2.4.1:



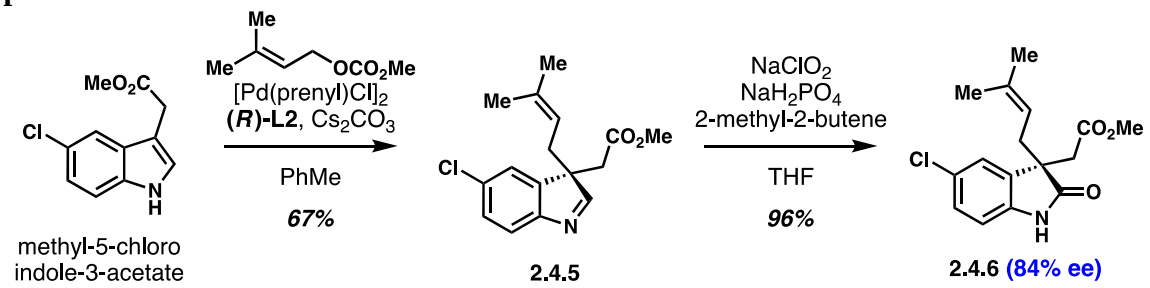
A flame-dried reaction tube equipped with a stir bar was charged with methyl-5-chloroindole-3-acetate (179 mg, 800 μmol, 1 equiv) and $Pd(PPh_3)_4$ (23.1 mg, 20.0 μmol, 0.025 equiv). The atmosphere was exchanged three times with argon before anhydrous DCM (16 mL) was added. To the resulting yellow solution, triethylborane (0.88 mL, 1 M in hexanes, 0.88 mmol, 1.1 equiv) and allyl alcohol (0.16 mL, 2.4 mmol, 2.9 equiv) were added dropwise in sequence. The reaction mixture was stirred for 23 hours at ambient temperature before being concentrated under reduced pressure. The residue was purified by by silica gel column chromatography (13 to 20% EtOAc/hexanes) to afford indolenine **(±)-2.4.5** (178 mg, 675 μmol, 84%) as a colorless oil, which was converted into **(±)-2.4.1** following the procedure mentioned above.

Preparation of phosphoramidite (*R*)-L2:



Phosphoramidite ligand **(*R*)-L2** was prepared from *N*-allyl-benzhydryl-amine (**SI-4**) according to the procedure reported in ref. 6. **SI-4** was synthesized from allylamine according to the procedure reported in ref. 7. The spectral data were found to match those reported in the literature.

Preparation of 2.4.6:



Following a published procedure,[6] to a flame-dried round bottom flask charged with methyl-5-chloroindole-3-acetate (101 mg, 452 μmol, 1 equiv), $[Pd(prenyl)Cl]_2$[1] (9.6 mg, 23 μmol, 0.05 equiv), phosphoramidite ligand **(*R*)-L2** (12.2 mg, 22.7 μmol, 0.05 equiv), and Cs_2CO_3 (221 mg, 678 μmol, 1.5 equiv) were added toluene (9.1 mL) and methyl prenyl carbonate[2] (97.9 mg, 679 μmol, 1.5 equiv) in sequence. The reaction mixture was stirred at ambient temperature for 20 hours

before being quenched by the addition of water (9 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1.2 to 2.4 to 4.8% Et_2O/DCM) to afford indolenine **2.4.5** (88.9 mg, 305 μmol, 67%) as a slightly yellow oil, which was used immediately for the next step. ***Note:** The best yield was obtained on 100-mg scale. Yield was lower on larger scale (44% on 8-mmol scale).

Following a published procedure,[4] 2-methyl-2-butene (0.37 mL, 3.5 mmol, 11 equiv) and $NaClO_2$ (156 mg, 1.72 mmol, 5.7 equiv) were added to a solution of **2.4.5** in THF (3.5 ml). The resulting suspension was stirred vigorously and treated with dropwise addition of NaH_2PO_4 (0.52 mL, 1 M in H_2O, 0.52 mmol, 1.7 equiv). After completion of addition, the reaction mixture was stirred at ambient temperature for 1 hour before being quenched by the addition of saturated *aq*. $Na_2S_2O_3$ (3 mL) at 0 ºC. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 3 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5.4 to 14% Et_2O/DCM) to afford oxindole **2.4.6** (90.2 mg, 293 μmol, 96%) as a slightly yellow oil. Enantiomeric excess was determined to be 84% by chiral HPLC (Chiralpak AD-3, 10% *i*-PrOH/hexanes, 1 mL/min, 9.63 min minor, 14.76 min major).

TLC: R_f = 0.37 (20% Et_2O/DCM)

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.17 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.11 (d, *J* = 2.1 Hz, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 4.92 (tp, *J* = 7.5, 1.4 Hz, 1H), 3.50 (s, 3H), 3.04 (d, *J* = 16.8 Hz, 1H), 2.90 (d, *J* = 16.8 Hz, 1H), 2.46 (dd, *J* = 14.0, 7.4 Hz, 1H), 2.41 (dd, *J* = 14.1, 7.9 Hz, 1H), 1.62 (d, *J* = 1.4 Hz, 3H), 1.49 (d, *J* = 1.4 Hz, 3H).

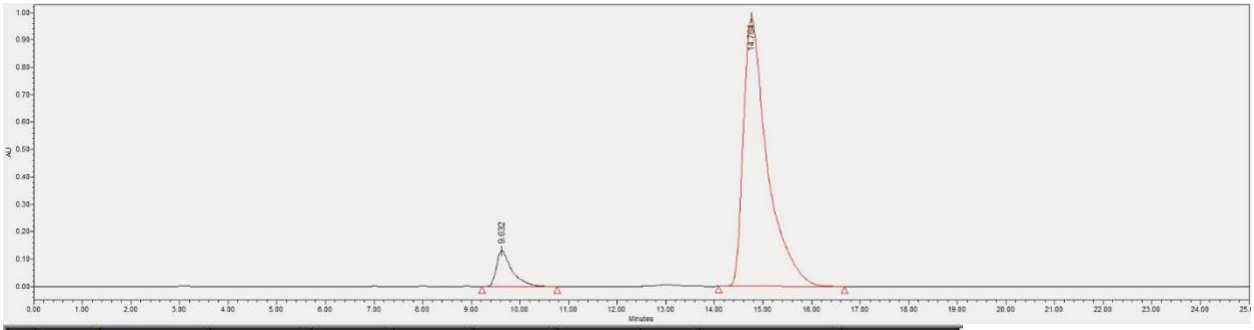
^{13}C NMR (150 MHz, $CDCl_3$): δ 180.97, 170.41, 139.93, 137.14, 133.70, 128.15, 127.51, 123.79, 116.44, 110.67, 51.88, 50.67, 39.72, 36.53, 26.04, 18.12.

IR (thin film) ν_{max} (cm^{-1}): 3222, 2914, 2855, 1710, 1618, 1477, 1437, 1350, 1300, 1200, 1173, 1066, 989, 887, 815, 736, 645, 570, 455.

HRMS (m/z): (ESI) calcd for $^{12}C_{16}H_{18}{}^{35}ClN^{23}NaO_3$ $[M+Na]^+$: 330.0867, found 330.0869.

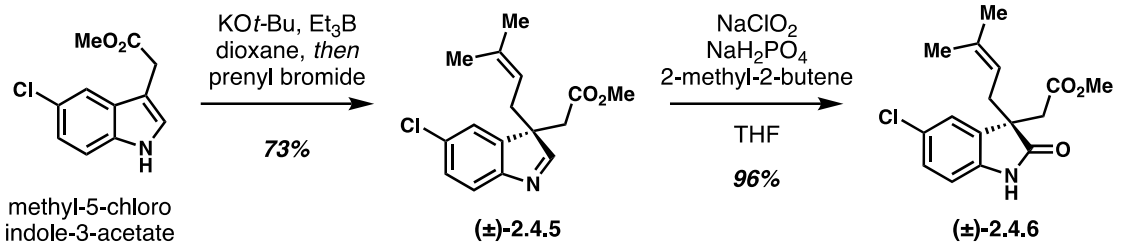
$[\alpha]_D^{26}$ +8° (*c* 0.1, CH_3CN)

HPLC traces:



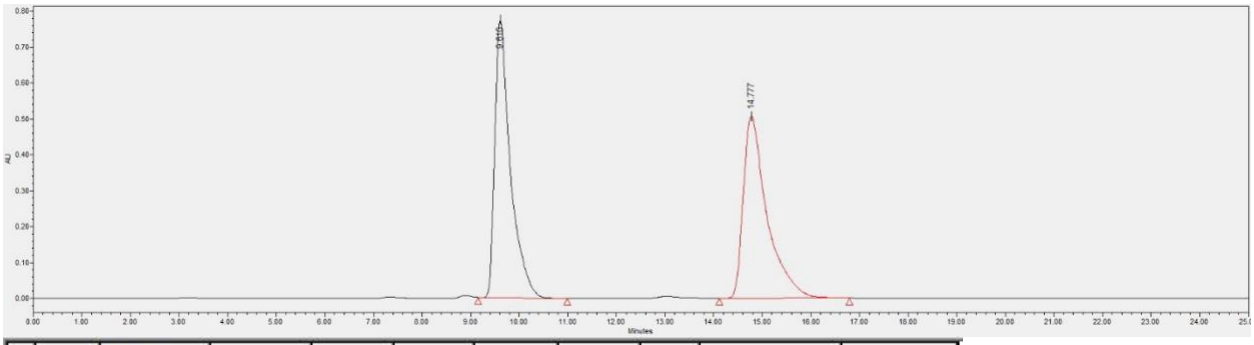
	Name	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		9.632	2840608	7.82	130166	bb			Unknown	
2		14.764	33502643	92.18	978154	bb			Unknown	

Preparation of racemic standard of 2.4.6:



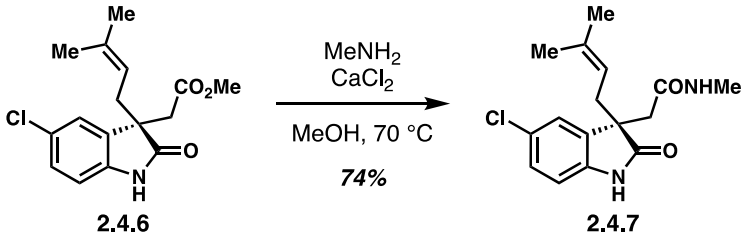
Following a published procedure,[8] potassium *tert*-butoxide (0.74 mL, 1 M in THF, 0.74 mmol, 1.1 equiv) was added dropwise to a solution of methyl-5-chloroindole-3-acetate (150 mg, 671 μmol, 1 equiv) in 1,4-dioxane (2.6 mL). After stirring at ambient temperature for 30 minutes, triethylborane (0.74 mL, 1 M in hexanes, 0.74 mmol, 1.1 equiv) was added dropwise. The resulting mixture was stirred for another 30 minutes before prenyl bromide (0.09 mL, 0.8 mmol, 1.2 equiv) was added. The reaction mixture was stirred at ambient temperature for 15 hours before being quenched by the addition of saturated *aq*. NH_4Cl (3 mL). The aqueous layer was extracted with EtOAc (3 x 3 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1.2 to 2.4 to 4.8% Et_2O/DCM) to afford **(±)-2.4.5** (142 mg, 487 μmol, 73%) as a slightly yellow oil, which was converted into **(±)-2.4.6** following the procedure mentioned above.

HPLC traces:



	Name	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		9.610	17250011	50.05	772811	bb			Unknown	
2		14.777	17217511	49.95	507171	bb			Unknown	

Preparation of amide 2.4.7:



To a flame-dried pressure vessel charged with **2.4.6** (1.16 g, 3.77 mmol, 1 equiv) and $CaCl_2$ (419 mg, 3.78 mmol, 1 equiv) was added $MeNH_2$ (18.9 mL, 2 M in MeOH, 37.8 mmol, 10 equiv). The pressure vessel was sealed and heated at 70 ºC for 14 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was taken in EtOAc (50 mL) and treated with saturated *aq*. NH_4Cl (50 mL). The aqueous layer was extracted with

EtOAc (3 x 50 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2 to 3.3% MeOH/DCM) to afford amide **2.4.7** (858 mg, 2.80 mmol, 74%) as a white foam.

TLC: R_f = 0.22 (5% MeOH/DCM)

^{1}H NMR (600 MHz, C_6D_6): δ 9.34 (s, 1H), 7.19 (d, *J* = 2.1 Hz, 1H), 7.02 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.60 (d, *J* = 8.2 Hz, 1H), 5.45 (q, *J* = 5.7 Hz, 1H), 5.04 (tdt, *J* = 8.3, 3.0, 1.4 Hz, 1H), 2.87 (d, *J* = 15.4 Hz, 1H), 2.60 (dd, *J* = 14.0, 8.1 Hz, 1H), 2.51 (dd, *J* = 14.1, 7.1 Hz, 1H), 2.41 (d, *J* = 15.4 Hz, 1H), 2.28 (d, *J* = 4.7 Hz, 3H), 1.49 (d, *J* = 1.4 Hz, 3H), 1.46 (d, *J* = 1.4 Hz, 3H).

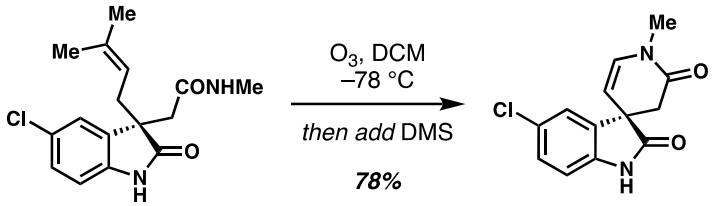
^{13}C NMR (150 MHz, C_6D_6): δ 181.72, 169.81, 141.55, 136.08, 135.11, 127.7 (under solvent peak, see provided HSQC), 127.02, 123.71, 117.83, 111.51, 51.43, 41.94, 36.86, 25.99, 25.91, 18.07.

IR (thin film) ν_{max} (cm^{-1}): 3285, 2914, 1711, 1648, 1559, 1477, 1325, 1235, 1163, 817, 735, 566, 499, 455.

HRMS (m/z): (ESI) calcd for $^{12}C_{16}H_{19}{}^{35}ClN_2{}^{23}NaO_2$ $[M+Na]^+$: 329.1027, found 329.1029.

$[\alpha]_D^{26}$ +27° (*c* 0.1, CH_3CN)

Preparation of spirocycle 2.1.6:



A round bottom flask was charged with amide **2.4.7** (1.84 g, 6.00 mmol, 1 equiv) and dry DCM (230 mL). The resulting solution was cooled to –78 ºC and sparged with a stream of ozone until a blue color persisted. At this point, TLC analysis indicated the complete consumption of starting material and dimethyl sulfide (120 mL) was added. The resulting reaction mixture was allowed to slowly warm to ambient temperature and stirred at that temperature overnight. The crude reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (1.8% MeOH/DCM) to afford spirocycle **2.1.6** (1.23 g, 4.68 mmol, 78%) as a white solid. Recrystallization from MeOH provided **2.1.6** with 92% ee as determined by chiral HPLC (Chiralpak IA, 10% *i*-PrOH/hexanes, 1 mL/min, 26.13 min minor, 29.38 min major).

TLC: R_f = 0.28 (5% MeOH/DCM)

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.22 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.11 (d, *J* = 2.1 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.37 (d, *J* = 7.7 Hz, 1H), 4.90 (dd, *J* = 7.7, 0.9 Hz, 1H), 3.20 (s, 3H), 3.03 (d, *J* = 16.3 Hz, 1H), 2.69 (dd, *J* = 16.3, 1.0 Hz, 1H).

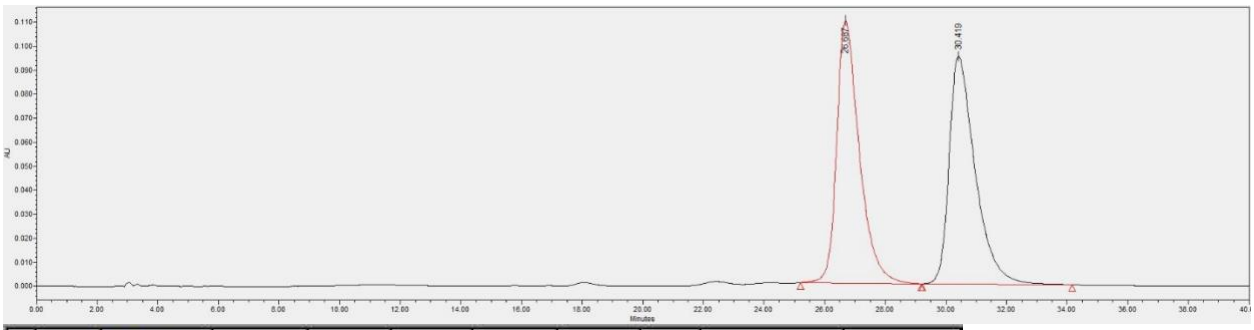
^{13}C NMR (150 MHz, $CDCl_3$): δ 179.33, 166.50, 138.18, 134.14 (2C), 129.15, 128.73, 124.26, 111.31, 104.56, 49.35, 39.15, 34.27.

IR (thin film) ν_{max} (cm^{-1}): 3221, 1718, 1654, 1477, 1364, 1295, 1175, 819, 716, 601, 557.

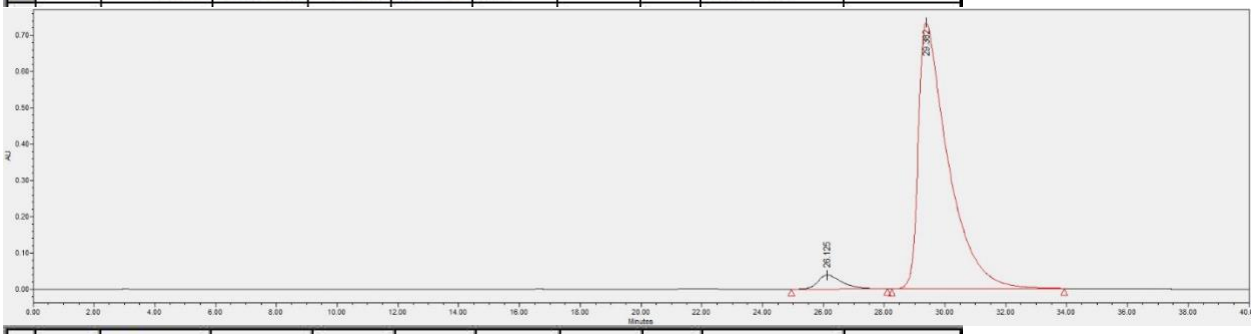
HRMS (m/z): (ESI) calcd for $^{12}C_{13}H_{11}{}^{35}ClN_2{}^{23}NaO_2$ $[M+Na]^+$: 285.0401, found 285.0403.

$[\alpha]_D^{26}$ –152° (*c* 0.1, CH_3CN)

HPLC traces (racemic, enantioenriched):

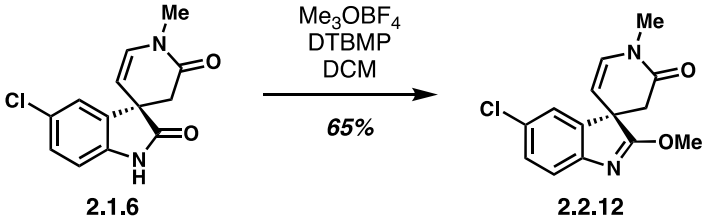


	Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		26.687	5681849	50.02	109327	bb			Unknown	
2		30.419	5678329	49.98	94926	Bb			Unknown	



	Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		26.125	2139491	4.11	38804	bb			Unknown	
2		29.382	49885702	95.89	732664	Bb			Unknown	

Preparation of imidate 2.2.13:



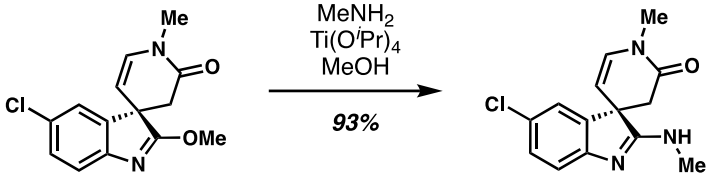
2.1.6 **2.2.12**

To a flame-dried round bottom flask charged with **2.1.6** (111 mg, 423 µmol, 1 equiv) 2,6-di-*tert*-butyl-4-methylpyridine (104 mg, 507 µmol, 1.2 equiv), and trimethyloxonium tetrafluoroborate (75.0 mg, 507 µmol, 1.2 equiv) was added dry DCM (21 mL). The reaction mixture was stirred at ambient temperature overnight before being quenched by the addition of saturated *aq*. $NaHCO_3$ (20 mL). The layers were separated, and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (31% EtOAc/hexanes) to afford imidate **2.2.12** (76.4 mg, 276 µmol, 65%) as a white foam.

TLC: R_f = 0.24 (50% EtOAc/hexanes)

^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.24 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.20 (dd, *J* = 8.2, 0.5 Hz, 1H), 7.14 (dd, *J* = 2.1, 0.5 Hz, 1H), 6.38 (d, *J* = 7.7 Hz, 1H), 4.76 (d, *J* = 7.7 Hz, 1H), 4.02 (s, 3H), 3.14 (s, 3H), 2.76 (d, *J* = 16.2 Hz, 1H), 2.64 (d, *J* = 16.2 Hz, 1H).
^{13}C NMR (150 MHz, $CDCl_3$): δ 182.25, 166.98, 151.30, 141.91, 134.65, 129.57, 129.16, 122.79, 119.86, 103.76, 57.49, 52.50, 38.32, 34.16.
IR (thin film) ν_{max} (cm^{-1}): 3055, 2951, 2923, 2854, 1657, 1610, 1580, 1453, 1353, 1292, 1268, 1168, 1046, 959, 907, 820, 733, 604, 546, 439.
HRMS (m/z): (ESI) calcd for $^{12}C_{14}H_{14}{}^{35}ClN_2O_2$ $[M+H]^+$: 277.0738, found 277.0739.
$[\alpha]_D^{29}$ –216° (*c* 0.1, CH_3CN)

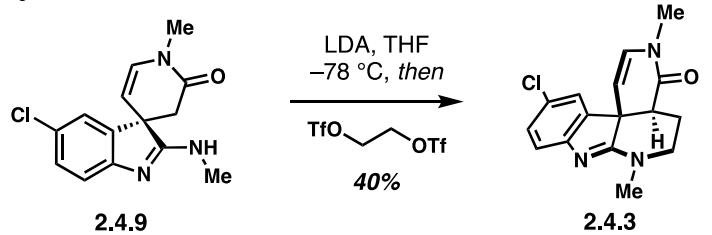
Preparation of amidine 2.4.9:



2.2.12 **2.4.9**

To a flame-dried round bottom flask charged with imidate **2.2.12** (71.0 mg, 257 μmol, 1 equiv) were added $MeNH_2$ (11 mL, 2 M in MeOH, 22 mmol, 86 equiv) and titanium isopropoxide (0.15 mL, 0.51 mmol, 2 equiv). The reaction mixture was stirred at ambient temperature for 3 days before being concentrated under reduced pressure. The residue was taken in EtOAc (20 mL) and stirred vigorously with saturated *aq.* Rochelle salt (40 mL) for 2 hours. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2 to 3 to 5% MeOH/DCM) to afford amidine **2.4.9** (65.6 mg, 238 μmol, 93%) as a while solid.
TLC: R_f = 0.17 (5% MeOH/DCM)
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.18 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 7.03 (d, *J* = 2.1 Hz, 1H), 6.38 (d, *J* = 7.8 Hz, 1H), 4.85 (d, *J* = 7.8 Hz, 1H), 4.81 (s, 1H), 3.20 (s, 3H), 3.07 (s, 3H), 2.73 (d, *J* = 16.7 Hz, 1H), 2.67 (d, *J* = 16.7 Hz, 1H).
^{13}C NMR (150 MHz, $CDCl_3$): δ 175.87, 166.80, 153.92, 140.48, 133.96, 129.20, 127.23, 122.04, 117.96, 105.82, 52.99, 40.46, 34.34, 30.04.
IR (thin film) ν_{max} (cm^{-1}): 3312, 3054, 2940, 2901, 1655, 1619, 1566, 1450, 1409, 1361, 1228, 1084, 1027, 912, 824, 733, 605, 551, 435.
HRMS (m/z): (ESI) calcd for $^{12}C_{14}H_{15}{}^{35}ClN_3O$ $[M+H]^+$: 276.0898, found 276.0896.
$[\alpha]_D^{29}$ –268° (*c* 0.025, CH_3CN)

Preparation of tetracycle 2.4.3:



2.4.9 **2.4.3**

A flame-dried reaction tube was charged with amidine **2.4.9** (31.5 mg, 114 μmol, 1 equiv) and dry THF (1.05 mL). The resulting solution was cooled to –78 ºC and a solution of freshly made LDA

(0.50 mL, 0.5 M in THF, 0.25 mmol, 2.2 equiv) was added dropwise. After the mixture was stirred at –78 ºC for 30 minutes, a solution of 1,2-bis[(trifluoromethylsulfonyl)oxy]ethane[9] (74.5 mg, 228 μmol, 2 equiv) in THF (0.45 mL) was added dropwise. The reaction mixture was allowed to warm to ambient temperature over 4 hours before being quenched by the addition of saturated *aq*. $NaHCO_3$ (2 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (5 x 3 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2 to 3% MeOH/DCM) to afford tetracycle **2.4.3** (13.8 mg, 45.7 μmol, 40%) as a while solid.

TLC: R_f = 0.26 (5% MeOH/DCM)

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.16 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.13 (d, *J* = 8.3 Hz, 1H), 6.98 (d, *J* = 2.1 Hz, 1H), 6.21 (d, *J* = 7.6 Hz, 1H), 4.78 (dd, *J* = 7.6, 1.8 Hz, 1H), 3.65 (ddd, *J* = 12.2, 6.7, 5.3 Hz, 1H), 3.21 (s, 3H), 3.15 (ddd, *J* = 12.6, 7.6, 5.3 Hz, 1H), 3.11 (s, 3H), 2.76 (ddd, *J* = 8.5, 7.7, 1.8 Hz, 1H), 2.19 (dddd, *J* = 13.8, 8.5, 7.5, 5.3 Hz, 1H), 2.11 (dddd, *J* = 14.2, 7.7, 6.7, 5.3 Hz, 1H).

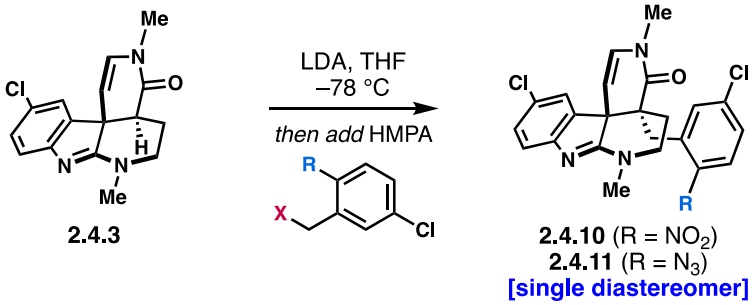
^{13}C NMR (150 MHz, $CDCl_3$): δ 175.21, 169.67, 153.53, 139.71, 131.18, 129.18, 127.07, 121.84, 117.82, 107.29, 53.24, 50.34, 42.26, 38.24, 34.47, 25.06.

IR (thin film) ν_{max} (cm^{-1}): 3332, 3053, 2931, 2865, 1666, 1626, 1588, 1567, 1444, 1409, 1357, 1266, 1116, 1032, 911, 821, 731, 624, 532, 416.

HRMS (m/z): (ESI) calcd for $^{12}C_{16}H_{17}{}^{35}ClN_3O$ $[M+H]^+$: 302.1055, found 302.1052.

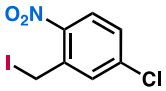
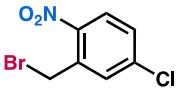
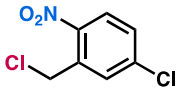
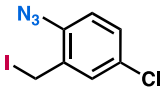
$[\alpha]_D^{29}$ –483° (*c* 0.1, CH_3CN)

Electrophile screening for benzylation of 2.4.3:



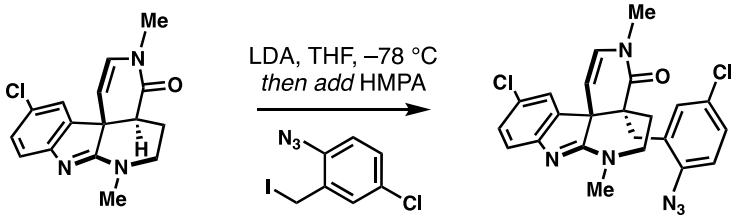
2.4.3

2.4.10 (R = NO_2)
2.4.11 (R = N_3)
[single diastereomer]

Electrophiles	 **2.2.21**	 **2.2.20**	 **2.4.12**	 **2.4.13**
yield	0%	24%	14%	75%
***α*-X**	80%	24%	0%	0%

Typical procedure for benzylation of 2.4.3: A flame-dried reaction tube was charged with **2.4.3** (1 equiv) and anhydrous THF. The resulting solution was cooled to –78 ºC and a solution of freshly made LDA (0.5M in THF, 1.05 equiv) was added dropwise. After the mixture was stirred at –78 ºC for 30 minutes, HMPA (3 equiv) was added followed by dropwise addition of a solution of electrophile (1.1 equiv) in THF. The reaction mixture was allowed to warm to ambient temperature over 4 hours before being quenched by the addition of saturated *aq*. NH_4Cl. The layers were separated, and the aqueous phase was extracted further with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC or silica gel column chromatography.

Preparation of azide 2.4.11:



2.4.3 *75%* **2.4.11**

A flame-dried reaction tube was charged with tetracycle **2.4.3** (43.2 mg, 143 μmol, 1 equiv) and dry THF (1.3 mL). The resulting solution was cooled to –78 ºC and a solution of freshly made LDA (300 μL, 0.5M in THF, 150 μmol, 1.05 equiv) was added dropwise. After the mixture was stirred at –78 ºC for 30 minutes, HMPA (0.07 mL, 0.4 mmol, 3 equiv) was added followed by dropwise addition of a solution of 2-azido-5-chlorobenzyl iodide[10] (46.2 mg, 157 μmol, 1.1 equiv) in THF (0.4 mL). The reaction mixture was allowed to warm to ambient temperature over 4 hours before being quenched by the addition of saturated *aq*. NH_4Cl (2 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (5 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0.4 to 0.6 to 0.8 % MeOH/DCM) to afford azide **2.4.11** (50.4 mg, 108 μmol, 75%) as a while solid.

TLC: R_f = 0.35 (3% MeOH/DCM)

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.71 (d, *J* = 2.5 Hz, 1H), 7.12 – 7.07 (m, 2H), 7.04 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.68 (d, *J* = 8.5 Hz, 1H), 6.59 (d, *J* = 2.1 Hz, 1H), 6.13 (d, *J* = 7.6 Hz, 1H), 4.75 (d, *J* = 7.6 Hz, 1H), 3.42 (ddd, *J* = 12.2, 7.4, 2.8 Hz, 1H), 3.25 (s, 3H), 3.18 – 3.12 (m, 1H), 3.10 (s, 3H), 3.00 (d, *J* = 14.6 Hz, 1H), 2.70 (d, *J* = 14.6 Hz, 1H), 2.47 (ddd, *J* = 14.1, 10.1, 7.5 Hz, 1H), 1.82 (ddd, *J* = 14.1, 6.3, 2.8 Hz, 1H).

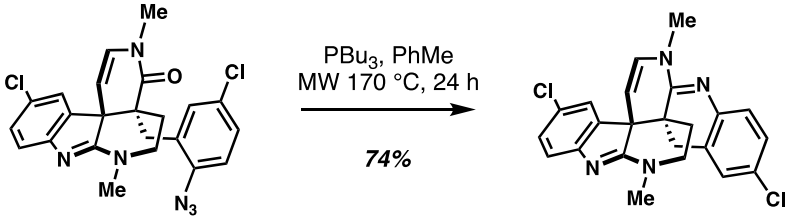
^{13}C NMR (150 MHz, $CDCl_3$): δ 174.31, 171.76, 153.39, 137.63, 136.99, 133.24, 131.39, 130.04, 129.95, 128.71, 128.30, 126.81, 122.01, 118.57, 117.39, 109.92, 57.33, 48.02, 47.33, 38.06, 35.41, 29.51, 27.93.

IR (thin film) ν_{max} (cm^{-1}): 2957, 2929, 2872, 2123, 2086, 1660, 1620, 1569, 1481, 1445, 1409, 1362, 1299, 1254, 1194, 1116, 1072, 816, 734, 530.

HRMS (m/z): (ESI) calcd for $^{12}C_{23}H_{21}{}^{35}Cl_2N_6O$ $[M+H]^+$: 467.1148, found 467.1143.

$[\alpha]_D^{29}$ –486° (*c* 0.1, CH_3CN)

Preparation of hexacycle 2.1.1:

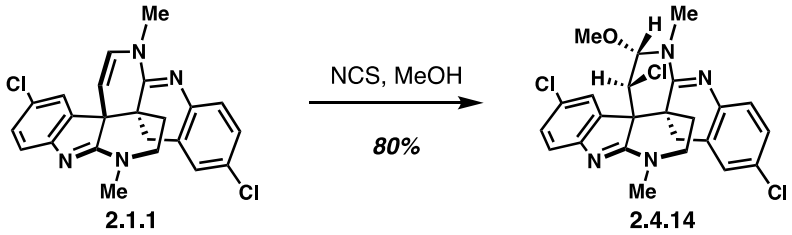


2.4.11 *74%* **2.1.1**

A Biotage microwave vial was charged with azide **2.4.11** (80.0 mg, 171 μmol, 1 equiv), PBu_3 (0.09 mL, 0.4 mmol, 2 equiv), and dry PhMe (10 mL) under N_2 atmosphere. The vial was capped and heated at 170 ˚C for 24 hours in a Biotage microwave reactor. After decapping the vial, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel

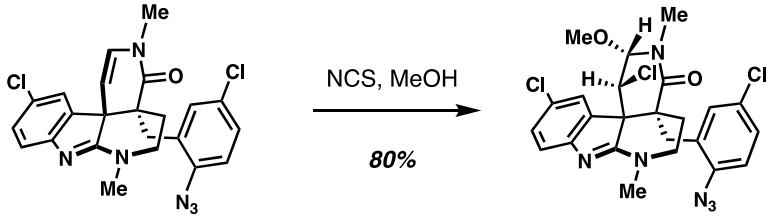
column chromatography (5.6 to 8.4 to 11.2% Et_2O/DCM) to afford hexacycle **2.1.1** (53.8 mg, 127 μmol, 74%) as a while solid.
***Note:** Organic azides can be heat- and shock-sensitive. Caution should be exercised when using azides.
TLC: R_f = 0.18 (10% Et_2O/DCM)
^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.14 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.10 (ddd, *J* = 8.4, 2.4, 1.0 Hz, 1H), 7.07 – 7.04 (m, 2H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.86 (dd, *J* = 2.5, 1.3 Hz, 1H), 6.25 (d, *J* = 7.6 Hz, 1H), 4.70 (d, *J* = 7.6 Hz, 1H), 3.46 (ddd, *J* = 12.5, 6.6, 4.6 Hz, 1H), 3.36 (s, 3H), 3.17 (ddd, *J* = 12.5, 8.8, 6.0 Hz, 1H), 3.07 (s, 3H), 2.77 (dd, *J* = 16.2, 1.3 Hz, 1H), 2.35 (dddd, *J* = 14.1, 8.8, 6.6, 1.4 Hz, 1H), 2.18 (d, *J* = 16.2 Hz, 1H), 1.85 (ddd, *J* = 14.1, 5.9, 4.6 Hz, 1H).
^{13}C NMR (150 MHz, CD_2Cl_2): δ 176.16, 158.19, 154.35, 143.75, 139.89, 132.36, 129.06, 128.44, 127.96, 127.92, 126.98, 126.46, 126.05, 122.95, 117.91, 104.96, 56.01, 47.98, 40.89, 37.99, 37.32, 30.38, 26.02.
IR (thin film) ν_{max} (cm^{-1}): 2927, 1565, 1445, 1381, 1301, 1257, 1193, 1077, 1017, 905, 822, 734, 602, 526, 453.
HRMS (m/z): (ESI) calcd for $^{12}C_{23}H_{21}{}^{35}Cl_2N_4$ $[M+H]^+$: 423.1138, found 423.1140.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{29}}$ –1297° (*c* 0.1, CH_3CN)

Chloroetherification of 2.1.1:



A flame-dried reaction tube charged with hexacycle **2.1.1** (13.9 mg, 32.8 μmol, 1 equiv) and NCS (5.3 mg, 40 μmol, 1.2 equiv) was evacuated and refilled with argon for three times. Dry MeOH (3.4 mL) was added, and the reaction mixture was stirred at ambient temperature overnight before being quenched by the addition of saturated *aq*. $Na_2S_2O_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0.43 to 0.86% MeOH/DCM) to afford **2.4.14** (12.9 mg, 26.3 μmol, 80%) as a white solid.
TLC: R_f = 0.35 (3% MeOH/DCM)
^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.30 (d, *J* = 2.2 Hz, 1H), 7.17 – 7.11 (m, 2H), 7.07 – 7.02 (m, 2H), 6.88 (dd, *J* = 2.5, 1.2 Hz, 1H), 4.91 (d, *J* = 1.4 Hz, 1H), 4.22 (d, *J* = 1.4 Hz, 1H), 3.36 (ddd, *J* = 12.5, 8.2, 1.2 Hz, 1H), 3.27 (s, 3H), 3.26 – 3.16 (m, 4H), 3.10 (s, 3H), 2.75 – 2.60 (m, 2H), 2.13 (d, *J* = 16.1 Hz, 1H), 1.76 (ddd, *J* = 14.6, 6.5, 1.2 Hz, 1H).
^{13}C NMR (150 MHz, CD_2Cl_2): δ 174.17, 159.78, 154.92, 143.49, 136.73, 129.47, 128.41, 127.98, 127.79, 127.05, 125.88 (2C), 125.12, 117.80, 97.67, 58.62, 56.68, 56.63, 47.55, 37.76, 36.77, 36.28, 31.72, 25.18.
IR (thin film) ν_{max} (cm^{-1}): 2927, 1623, 1567, 1470, 1447, 1400, 1348, 1298, 1258, 1188, 1123, 1066, 955, 825, 739, 700, 564, 529, 486.
HRMS (m/z): (ESI) calcd for $^{12}C_{24}H_{24}{}^{35}Cl_3N_4O$ $[M+H]^+$: 489.1010, found 489.1004.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{29}}$ –188° (*c* 0.1, CH_3CN)

Chloroetherification of 2.4.11:



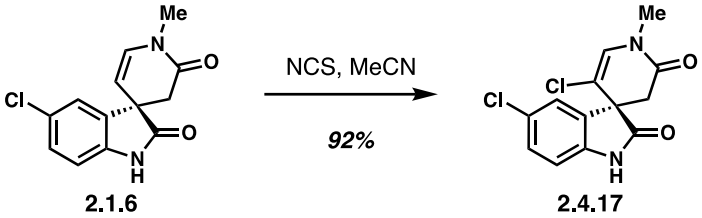
2.4.11 2.4.15a

A flame-dried reaction tube charged with azide **2.4.11** (3.5 mg, 7.5 μmol, 1 equiv) and NCS (3.0 mg, 22 μmol, 3.0 equiv) was evacuated and refilled with argon for three times. Dry MeOH (0.4 mL) was added, and the reaction mixture was stirred at ambient temperature overnight before being quenched by the addition of saturated *aq*. $Na_2S_2O_3$ (1 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 1 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (Et_2O) to afford **2.4.15a** (3.2 mg, 6.0 μmol, 80%) as a white solid.

^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.22 (d, *J* = 2.5 Hz, 1H), 7.16 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.11 – 7.06 (m, 2H), 7.04 (dd, *J* = 7.9, 0.8 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 4.81 (d, *J* = 1.7 Hz, 1H), 4.05 (d, *J* = 1.7 Hz, 1H), 3.39 (ddd, *J* = 12.8, 6.6, 4.8 Hz, 1H), 3.32 (d, *J* = 14.0 Hz, 1H), 3.28 (s, 3H), 3.16 (s, 3H), 3.15 – 3.07 (m, 1H), 3.08 (s, 3H), 2.70 – 2.63 (m, 2H), 1.79 (ddd, *J* = 14.2, 6.1, 4.8 Hz, 1H).

^{13}C NMR (150 MHz, CD_2Cl_2) δ 174.26, 171.71, 155.15, 138.18, 137.02, 132.89, 130.98, 129.70, 129.06, 128.57, 127.98, 124.37, 119.17, 117.25, 96.91, 60.46, 59.38, 56.63, 48.36, 46.72, 37.78, 35.88, 35.59, 31.98.

Preparation of vinyl chloride 2.4.17:



2.1.6 2.4.17

A flame-dried round bottom flask charged with spirocycle **2.1.6** (811 mg, 3.09 mmol, 1 equiv) and NCS (495 mg, 3.71 mmol, 1.2 equiv) was evacuated and refilled with argon for three times. Dry MeCN (80 mL) was added, and the reaction mixture was stirred at ambient temperature. Conversion was monitored by TLC and an additional portion of NCS (0.1 equiv) was added after 3 hours if starting material was still present in the reaction mixture. Once conversion was complete as judged by TLC, the reaction was quenched by the addition of saturated *aq*. $Na_2S_2O_3$ (80 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 80 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0.7 to 1.4 to 1.7% MeOH/DCM) to afford vinyl chloride **2.4.17** (840 mg, 2.83 mmol, 92%) as a white solid.

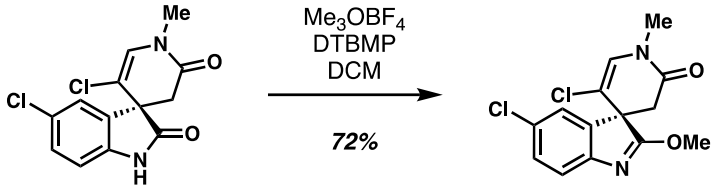
TLC: R_f = 0.29 (5% MeOH/DCM)

^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.61 (s, 1H), 7.28 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.17 (d, *J* = 2.1 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 6.55 (s, 1H), 3.19 – 3.13 (m, 4H), 2.73 (d, *J* = 16.5 Hz, 1H).

^{13}C NMR (150 MHz, CD_2Cl_2): δ 176.10, 165.16, 139.17, 132.29, 132.18, 130.03, 128.86, 124.76, 111.63, 110.18, 54.46, 40.15, 34.58.

IR (thin film) ν_{max} (cm^{-1}): 3205, 1725, 1657, 1477, 1387, 1293, 1221, 1172, 1115, 1038, 875, 818, 746, 678, 562.
HRMS (m/z): (ESI) calcd for $^{12}C_{13}H_{11}{}^{35}Cl_2N_2O_2$ $[M+H]^+$: 297.0192, found 297.0194.
$[\alpha]_D^{26}$ –126° (*c* 0.1, CH_3CN)

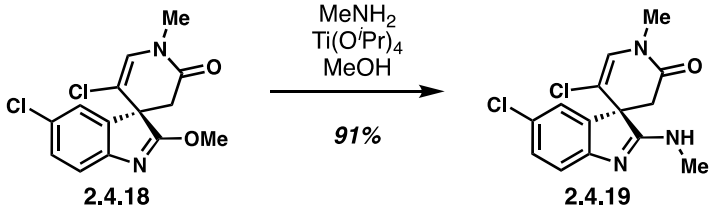
Preparation of imidate 2.4.18:



2.4.17 **2.4.18**

To a flame-dried round bottom flask charged with vinyl chloride **2.4.17** (371 mg, 1.25 mmol, 1 equiv) 2,6-di-*tert*-butyl-4-methylpyridine (307 mg, 1.50 mmol, 1.2 equiv), and trimethyloxonium tetrafluoroborate (221 mg, 1.49 mmol, 1.2 equiv) was added dry DCM (62 mL). The reaction mixture was stirred at ambient temperature overnight before being quenched by the addition of saturated *aq*. $NaHCO_3$ (60 mL). The layers were separated, and the aqueous layer was extracted with DCM (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20.6% EtOAc/hexanes) to afford **2.4.18** (281 mg, 903 μmol, 72%) as a white foam.
TLC: R_f = 0.36 (50% EtOAc/hexanes)
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.12 (d, *J* = 2.0 Hz, 1H), 6.52 (s, 1H), 4.09 (s, 3H), 3.19 (s, 3H), 3.05 (d, *J* = 16.5 Hz, 1H), 2.73 (d, *J* = 16.5 Hz, 1H).
^{13}C NMR (150 MHz, $CDCl_3$): δ 179.25, 165.59, 150.96, 138.90, 131.50, 129.97, 129.87, 122.73, 120.03, 109.99, 57.59, 56.99, 38.55, 34.51.
IR (thin film) ν_{max} (cm^{-1}): 2948, 1677, 1616, 1584, 1453, 1375, 1349, 1289, 1267, 1134, 1039, 945, 826, 736, 627, 545, 438.
HRMS (m/z): (ESI) calcd for $^{12}C_{14}H_{13}{}^{35}Cl_2N_2O_2$ $[M+H]^+$: 311.0349, found 311.0349.
$[\alpha]_D^{28}$ –155° (*c* 0.1, CH_3CN)

Preparation of amidine 2.4.19:

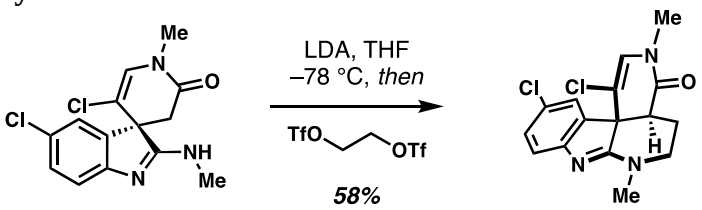


2.4.18 **2.4.19**

To a flame-dried round bottom flask charged with imidate **2.4.18** (281 mg, 903 μmol, 1 equiv) were added $MeNH_2$ (23 mL, 2 M in MeOH, 46 mmol, 51 equiv) and titanium isopropoxide (0.53 mL, 1.8 mmol, 2 equiv). The reaction mixture was stirred at ambient temperature for 3 days before being concentrated under reduced pressure. The residue was taken in EtOAc (50 mL) and stirred vigorously with saturated *aq.* Rochelle salt (100 mL) for 2 hours. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica

gel column chromatography (1.2 to 2.3 to 3.5% MeOH/DCM) to afford amidine **2.4.19** (256 mg, 825 μmol, 91%) as a while solid.
TLC: R_f = 0.22 (5% MeOH/DCM)
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.22 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.16 (d, *J* = 8.3 Hz, 1H), 7.04 (d, *J* = 2.1 Hz, 1H), 6.55 (s, 1H), 4.86 (s, 1H), 3.19 (s, 3H), 3.11 (s, 3H), 2.88 (d, *J* = 16.8 Hz, 1H), 2.79 (d, *J* = 16.9 Hz, 1H).
^{13}C NMR (150 MHz, $CDCl_3$): δ 173.29, 165.35, 154.14, 138.26, 131.46, 129.87, 127.45, 122.11, 118.21, 111.40, 57.79, 41.15, 34.61, 30.17.
IR (thin film) ν_{max} (cm^{-1}): 3354, 3223, 3058, 2937, 1661, 1622, 1569, 1452, 1408, 1378, 1332, 1266, 1229, 1115, 1030, 950, 825, 732, 552, 462.
HRMS (m/z): (ESI) calcd for $^{12}C_{14}H_{14}{}^{35}Cl_2N_3O$ $[M+H]^+$: 310.0508, found 310.0506.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{28}}$ –177° (*c* 0.1, CH_3CN)

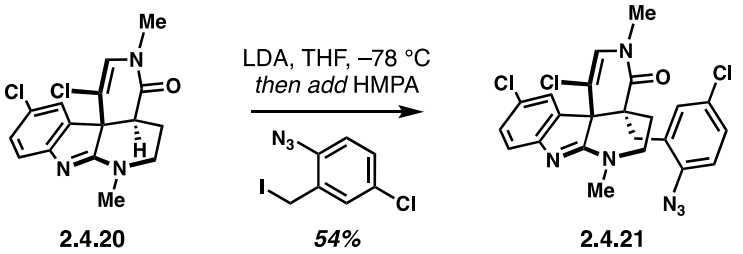
Preparation of tetracycle 2.4.20:



2.4.19 **2.4.20**

A flame-dried reaction tube was charged with amidine **2.4.19** (58.0 mg, 0.187 mmol, 1 equiv) and dry THF (0.94 mL). The resulting solution was cooled to –78 ºC and a solution of freshly made LDA (0.82 mL, 0.5 M in THF, 0.41 mmol, 2.2 equiv) was added dropwise. After the mixture was stirred at –78 ºC for 30 minutes, a solution of 1,2-bis[(trifluoromethylsulfonyl)oxy]ethane[9] (122 mg, 374 mmol, 2 equiv) in THF (1.17 mL) was added dropwise. The reaction mixture was allowed to warm to ambient temperature over 4 hours before being quenched by the addition of saturated *aq*. $NaHCO_3$ (2 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (5 x 3 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1.7% MeOH/DCM) to afford tetracycle **2.4.20** (36.3 mg, 108 μmol, 58%) as a while solid.
TLC: R_f = 0.29 (5% MeOH/DCM)
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.21 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.98 (dd, *J* = 2.1, 0.5 Hz, 1H), 6.38 (s, 1H), 3.71 (ddd, *J* = 13.1, 8.1, 5.4 Hz, 1H), 3.24 – 3.20 (m, 4H), 3.18 (s, 3H), 2.78 (dd, *J* = 8.6, 7.9 Hz, 1H), 2.23 – 2.16 (m, 1H), 2.11 (dddd, *J* = 14.0, 7.9, 6.0, 5.4 Hz, 1H).
^{13}C NMR (150 MHz, $CDCl_3$): δ 171.68, 168.63, 154.52, 137.41, 129.97, 128.72, 127.04, 121.95, 117.97, 112.76, 57.45, 49.56, 43.19, 38.17, 34.63, 24.78.
IR (thin film) ν_{max} (cm^{-1}): 3070, 2934, 2878, 1674, 1630, 1570, 1446, 1374, 1300, 1268, 1116, 1054, 825, 733, 648, 533, 442.
HRMS (m/z): (ESI) calcd for $^{12}C_{16}H_{16}{}^{35}Cl_2N_3O$ $[M+H]^+$: 336.0665, found 336.0661.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{28}}$ –379° (*c* 0.1, CH_3CN)

Preparation of azide 2.4.21:



2.4.20 **2.4.21**

A flame-dried reaction tube was charged with tetracycle **2.4.20** (152 mg, 452 μmol, 1 equiv) and dry THF (1.4 mL). The resulting solution was cooled to –78 ºC and a solution of freshly made LDA (950 μL, 0.5 M in THF, 475 μmol, 1.05 equiv) was added dropwise. After the mixture was stirred at –78 ºC for 30 minutes, HMPA (0.24 mL, 1.4 mmol, 3.1 equiv) was added followed by dropwise addition of a solution of 2-azido-5-chlorobenzyl iodide[10] (146 mg, 497 μmol, 1.1 equiv) in THF (1 mL). The reaction mixture was allowed to warm to ambient temperature over 4 hours before being quenched by the addition of saturated *aq.* NH_4Cl (2 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (5 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0.3 % MeOH/DCM) to afford azide **2.4.21** (123 mg, 245 μmol, 54%) as a while solid.

TLC: R_f = 0.24 (1% MeOH/DCM)

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.77 (d, *J* = 2.5 Hz, 1H), 7.16 – 7.11 (m, 3H), 6.79 (d, *J* = 8.5 Hz, 1H), 6.71 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.35 (s, 1H), 3.55 (ddd, *J* = 12.4, 7.5, 4.7 Hz, 1H), 3.26 (s, 3H), 3.23 – 3.17 (m, 4H), 2.94 (d, *J* = 14.7 Hz, 1H), 2.50 (d, *J* = 14.7 Hz, 1H), 2.27 (dt, *J* = 14.8, 7.6 Hz, 1H), 1.88 (ddd, *J* = 14.4, 7.0, 4.7 Hz, 1H).

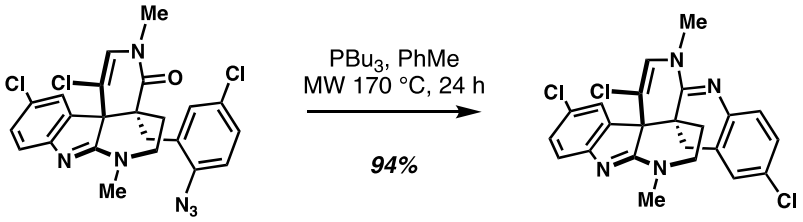
^{13}C NMR (150 MHz, $CDCl_3$): δ 171.00, 170.75, 154.87, 137.76, 134.78, 133.69, 130.73, 130.08, 129.80, 128.44, 128.05, 126.88, 122.22, 118.78, 117.67, 113.91, 62.00, 48.12, 47.83, 38.09, 35.53, 30.54, 27.62.

IR (thin film) ν_{max} (cm^{-1}): 3072, 2932, 2122, 1671, 1572, 1449, 1368, 1299, 1253, 1187, 1115, 905, 822, 736, 636, 530, 441.

HRMS (m/z): (ESI) calcd for $^{12}C_{23}H_{20}{}^{35}Cl_3N_6O$ $[M+H]^+$: 501.0759, found 501.0764.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ –390° (*c* 0.1, CH_3CN)

Preparation of hexacycle 2.4.16:



2.4.21 **2.4.16**

A Biotage microwave vial was charged with azide **2.4.21** (123 mg, 245 μmol, 1 equiv), PBu_3 (0.12 mL, 0.49 mmol, 2 equiv), and dry PhMe (10 mL) under N_2 atmosphere. The vial was capped and heated at 170 °C for 24 hours in a Biotage microwave reactor. After decapping the vial, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2.7 to 4% Et_2O/DCM) to afford hexacycle **2.4.16** (105 mg, 229 μmol, 94%) as a while solid.

***Note:** Organic azides can be heat- and shock-sensitive. Caution should be exercised when using azides.

TLC: R_f = 0.37 (10% Et_2O/DCM)

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.21 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 1H), 7.11 (ddd, *J* = 8.5, 2.5, 1.0 Hz, 1H), 7.05 (d, *J* = 2.1 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.84 (dd, *J* = 2.5, 1.2 Hz, 1H), 6.41 (s, 1H), 3.59 (dt, *J* = 12.9, 6.5 Hz, 1H), 3.39 (s, 3H), 3.24 (dt, *J* = 13.0, 6.6 Hz, 1H), 3.20 (s, 3H), 2.77 (dd, *J* = 16.1, 1.3 Hz, 1H), 2.24 (dtd, *J* = 14.4, 6.6, 1.2 Hz, 1H), 2.14 (d, *J* = 16.2 Hz, 1H), 2.01 (dt, *J* = 14.3, 6.5 Hz, 1H).

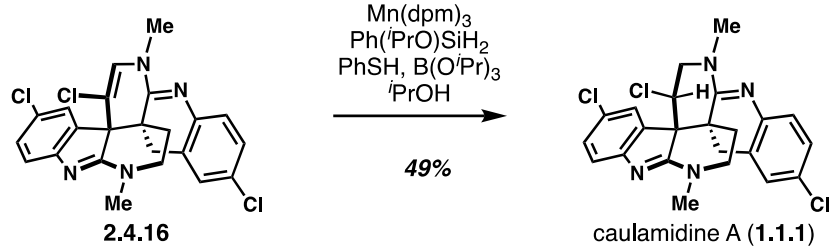
^{13}C NMR (150 MHz, $CDCl_3$): δ 172.35, 156.59, 154.43, 142.72, 137.12, 129.99, 129.79, 129.17, 128.06, 127.92, 127.34, 126.09, 125.05, 122.77, 118.13, 108.97, 60.49, 47.58, 42.34, 37.98, 37.35, 31.60, 27.04.

IR (thin film) ν_{max} (cm^{-1}): 3047, 2926, 1565, 1445, 1380, 1299, 1255, 1072, 1020, 916, 825, 733, 605, 540, 440.

HRMS (m/z): (ESI) calcd for $^{12}C_{23}H_{20}{}^{35}Cl_3N_4$ $[M+H]^+$: 457.0748, found 457.0752.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ –1039° (*c* 0.1, CH_3CN)

Preparation of (–)-caulamidine A (1.1.1):

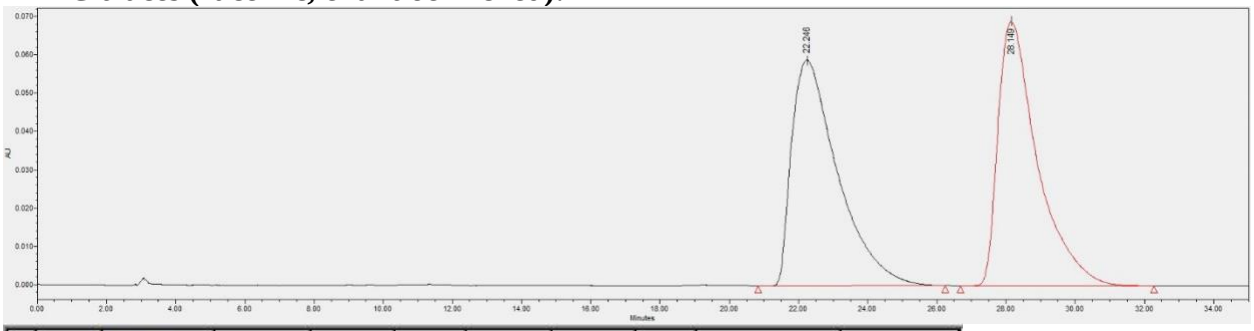


To a flame-dried reaction tube charged with **2.4.16** (10.2 mg, 22.3 μmol, 1 equiv) and $Mn(dpm)_3$ (135 mg, 223 μmol, 10 equiv) were added *i*-PrOH (2.2 mL) and triisopropyl borate (10.3 μL, 44.6 μmol, 2 equiv) in sequence. The resulting mixture was stirred at ambient temperature for 10 minutes. After 10 minutes, isopropoxy(phenyl)silane (40.0 μL, 223 μmol, 10 equiv) and thiophenol (22.9 μL, 223 μmol, 10 equiv) were added in sequence. The reaction mixture was stirred at ambient temperature overnight before being quenched by the addition of ammonium hydroxide (3 mL). The aqueous layer was extracted with EtOAc (5 x 3 mL), and the combined organic layers were washed with saturated *aq*. NH_4Cl (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified with a short plug of silica gel (0.6 to 1% MeOH/DCM) and then repurified by preparative TLC (3% MeOH/DCM) to afford **1.1.1** (5.0 mg, 11 μmol, 49%) as a glassy solid. Enantiomeric excess was determined to be 96% by chiral HPLC (Chiralpak AD-3, 10% *i*-PrOH/hexanes, 1 mL/min, 22.03 min major, 28.63 min minor).

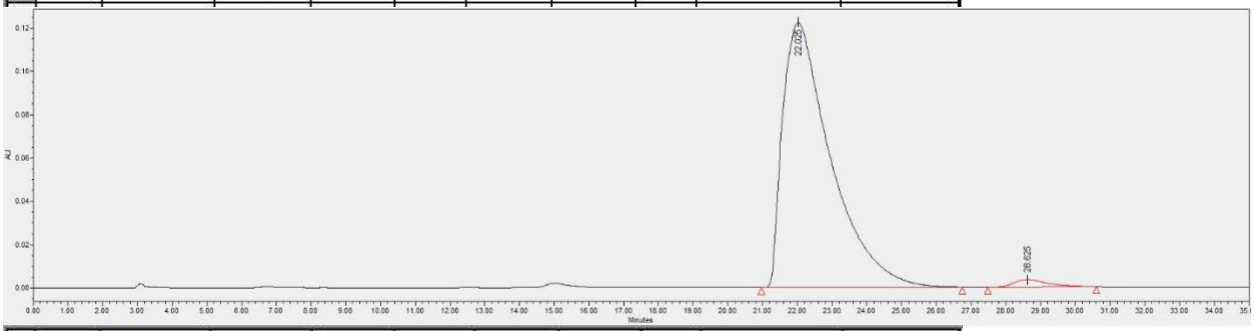
TLC: R_f = 0.24 (3% MeOH/DCM)

^{1}H NMR (600 MHz, CD_3CN): δ 7.29 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 7.10 (ddd, *J* = 8.4, 2.5, 1.0 Hz, 1H), 6.94 (dd, *J* = 2.5, 1.2 Hz, 1H), 6.93 (d, *J* = 1.9 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 5.00 (dd, *J* = 11.0, 6.3 Hz, 1H), 3.85 (dd, *J* = 12.8, 6.4 Hz, 1H), 3.69 (dd, *J* = 12.7, 11.0 Hz, 1H), 3.36 (ddd, *J* = 12.3, 7.3, 1.6 Hz, 1H), 3.22 (s, 3H), 3.15 (td, *J* = 12.0, 5.9 Hz, 1H), 2.98 (s, 3H), 2.45 (ddt, *J* = 16.0, 2.3, 1.2 Hz, 1H), 2.26 (d, *J* = 16.0 Hz, 1H), 2.25 – 2.19 (m, 1H), 1.72 (ddd, *J* = 15.0, 5.9, 1.6 Hz, 1H).

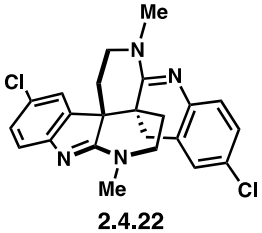
^{13}C NMR (150 MHz, CD_3CN): δ 174.95, 160.00, 157.20, 145.00, 134.45, 130.29, 128.27, 128.20, 127.23, 126.84, 126.37, 125.24, 124.69, 118.86, 59.99, 55.94, 53.72, 48.55, 40.88, 38.26, 36.75, 30.62, 25.83.
IR (thin film) ν_{max} (cm^{-1}): 2924, 2869, 1560, 1451, 1404, 1297, 1249, 1195, 1116, 1024, 904, 825, 735, 530.
HRMS (m/z): (ESI) calcd for $^{12}C_{23}H_{22}{}^{35}Cl_3N_4$ $[M+H]^+$: 459.0905, found 459.0904.
$[\alpha]_D^{25}$ –113° (*c* 0.1, CH_3CN)
CD (CH_3CN, 2.56 × 10^{-5} M) λ_{ext} (Δε) 319 (1.01), 312 (0.0), 270 (-15.43), 250 (0.0), 232 (31.70), 224 (0.0), 216 (-31.06) nm.
HPLC traces (racemic, enantioenriched):



	Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		22.246	5463379	50.01	58953	bb			Unknown	
2		28.149	5460292	49.99	68998	bb			Unknown	



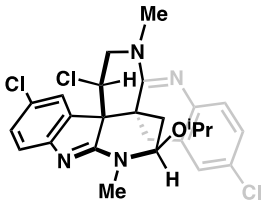
	Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		22.025	11730769	98.02	122186	bb			Unknown	
2		28.625	237056	1.98	3462	bb			Unknown	



2.4.22

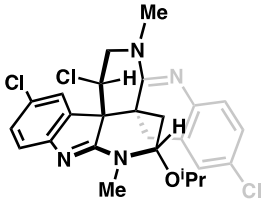
Dechlorocaulamidine A (2.4.22)
TLC: R_f = 0.32 (5% MeOH/DCM)
^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.22 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.17 (d, *J* = 8.2 Hz, 1H), 7.08 (ddd, *J* = 8.4, 2.5, 1.0 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 2.1 Hz, 1H), 6.84 (dd, *J* = 2.6, 1.2 Hz, 1H), 3.69 (td, *J* = 12.6, 5.7 Hz, 1H), 3.50 (ddd, *J* = 13.0, 6.8, 1.2 Hz, 1H), 3.29 (ddd, *J* = 12.2, 7.0, 1.5 Hz, 1H), 3.26 (s, 3H), 3.12 (td, *J* = 12.2, 5.5 Hz, 1H), 3.01 (s, 3H), 2.75 (ddd, *J* = 13.9, 12.3, 6.7 Hz, 1H), 2.55 (d, *J* = 16.0 Hz, 1H), 2.27 (dddd, *J* = 14.3, 12.1, 7.0, 2.0

Hz, 1H), 2.10 (d, *J* = 16.1 Hz, 1H), 1.77 (ddd, *J* = 14.7, 5.5, 1.5 Hz, 1H), 1.38 (ddd, *J* = 14.0, 5.7, 1.1 Hz, 1H).
^{13}C NMR (150 MHz, CD_2Cl_2): δ 178.17, 160.80, 154.45, 144.60, 138.33, 128.93, 127.79, 127.42, 126.61, 126.44, 126.00, 124.58, 123.63, 118.85, 54.14, 48.26, 46.93, 38.05, 37.53, 37.18, 31.74, 29.94, 25.53.
IR (thin film) ν_{max} (cm^{-1}): 2922, 2863, 1562, 1448, 1347, 1264, 1199, 1150, 1080, 1032, 986, 903, 825, 735, 517, 428.
HRMS (m/z): (ESI) calcd for $^{12}C_{23}H_{23}{}^{35}Cl_2N_4$ $[M+H]^+$: 425.1294, found 425.1299.



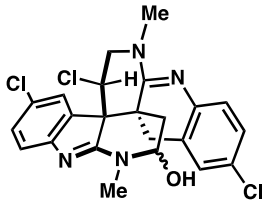
2.4.23-minor

HAT-O*i*-Pr 2.4.23-minor
TLC: R_f = 0.27 (3% MeOH/DCM)
^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.28 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 7.10 (ddd, *J* = 8.5, 2.5, 1.0 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 2.1 Hz, 1H), 6.85 (dd, *J* = 2.5, 1.2 Hz, 1H), 5.43 (dd, *J* = 10.9, 6.5 Hz, 1H), 4.67 (dd, *J* = 7.6, 3.9 Hz, 1H), 3.83 (dd, *J* = 12.6, 6.6 Hz, 1H), 3.79 – 3.74 (m, 2H), 3.28 (s, 3H), 3.24 (s, 3H), 2.41 (d, *J* = 15.6 Hz, 1H), 2.35 (dd, *J* = 15.4, 7.6 Hz, 1H), 1.95 (d, *J* = 15.9 Hz, 1H), 1.87 (ddd, *J* = 15.4, 4.0, 2.0 Hz, 1H), 1.21 (d, *J* = 6.1 Hz, 3H), 1.12 (d, *J* = 6.1 Hz, 3H).
^{13}C NMR (150 MHz, CD_2Cl_2): δ 172.11, 158.75, 156.54, 144.34, 133.53, 130.04, 128.08, 127.95, 127.16 (2C), 125.00 (2C), 124.12, 118.61, 86.17, 71.15, 59.81, 53.36 (under solvent peak, see provided HSQC), 53.15, 40.90, 36.88, 36.48, 34.17, 33.39, 22.91, 22.72.
IR (thin film) ν_{max} (cm^{-1}): 2967, 2926, 2856, 1722, 1567, 1451, 1405, 1196, 1122, 970, 903, 823, 739, 596, 531, 439.
HRMS (m/z): (ESI) calcd for $^{12}C_{26}H_{28}{}^{35}Cl_3N_4O$ $[M+H]^+$: 517.1323, found 517.1318.



2.4.23-major

HAT-O*i*-Pr 2.4.23-major
TLC: R_f = 0.25 (3% MeOH/DCM)
^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.31 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 7.10 (ddd, *J* = 8.4, 2.5, 1.0 Hz, 1H), 6.96 – 6.93 (m, 2H), 6.87 (dd, *J* = 2.5, 1.2 Hz, 1H), 4.76 (dd, *J* = 10.7, 6.7 Hz, 1H), 4.63 (dd, *J* = 4.5, 1.4 Hz, 1H), 3.78 – 3.70 (m, 2H), 3.52 (hept, *J* = 6.2 Hz, 1H), 3.25 (s, 3H), 3.01 (s, 3H), 2.64 (d, *J* = 15.5 Hz, 1H), 2.45 (d, *J* = 15.5 Hz, 1H), 2.14 (ddd, *J* = 15.2, 4.6, 2.0 Hz, 1H), 1.94 (dd, *J* = 15.1, 1.4 Hz, 1H), 1.16 (d, *J* = 6.1 Hz, 3H), 0.86 (d, *J* = 6.1 Hz, 3H).
^{13}C NMR (150 MHz, CD_2Cl_2): δ 173.53, 158.74, 155.95, 143.92, 133.73, 129.93, 128.27, 128.00, 127.60, 127.05, 126.49, 124.60, 124.37, 119.37, 89.40, 72.92, 59.91, 55.22, 53.36 (under solvent peak, see provided HSQC), 39.97, 36.92, 35.64, 32.36, 31.57, 22.60, 22.34.
IR (thin film) ν_{max} (cm^{-1}): 2969, 2925, 2871, 1722, 1565, 1452, 1403, 1325, 1264, 1195, 1123, 970, 904, 824, 738, 604, 517, 437.
HRMS (m/z): (ESI) calcd for $^{12}C_{26}H_{28}{}^{35}Cl_3N_4O$ $[M+H]^+$: 517.1323, found 517.1328.



2.4.24

HAT-OH 2.4.24

TLC: R_f = 0.07 (3% MeOH/DCM)

bold = major epimer

normal = minor epimer

underline = superimposed peaks of major and minor epimer

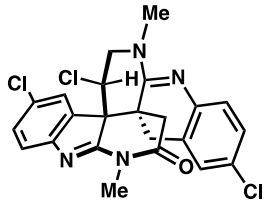
italicized = indistinguishable peaks of major and minor epimer

^{1}H NMR (600 MHz, CD_2Cl_2): δ **7.32** (dd, *J* = 8.3, 2.1 Hz, 1H), 7.30 (dd, *J* = 8.5, 2.3 Hz, 1H), **7.28** (d, *J* = 8.3 Hz, 1H), 7.22 (d, *J* = 8.3 Hz, 1H), 7.12 – 7.09 (m, 2H), 6.97 – 6.94 (m, 3H), **6.92** (d, *J* = 2.1 Hz, 1H), **6.87** (dd, *J* = 2.5, 1.2 Hz, 1H), 6.85 (dd, *J* = 2.5, 1.2 Hz, 1H), 5.16 (dd, *J* = 10.4, 5.9 Hz, 1H), **5.07** (td, *J* = 4.3, 1.3 Hz, 1H), 4.83 (q, *J* = 6.6 Hz, 1H), **4.78** (dd, *J* = 10.7, 6.7 Hz, 1H), 3.84 (dd, *J* = 12.7, 6.4 Hz, 1H), 3.80 – 3.71 (m, 3H), 3.28 (s, 3H), **3.26** (s, 3H), 3.19 (s, 3H), **3.06** (s, 3H), 2.80 (d, *J* = 6.6 Hz, 1H), **2.69 – 2.66** (m, 2H), 2.52 – 2.48 (m, 2H), 2.35 (dd, *J* = 15.3, 6.9 Hz, 1H), **2.24 – 2.17** (m, 1H), 2.03 – 1.97 (m, 2H), 1.92 (ddd, *J* = 15.3, 6.4, 2.1 Hz, 1H).

^{13}C NMR (150 MHz, CD_2Cl_2): δ **173.45**, 172.91, **158.65**, 158.23, 156.36, **155.84**, 144.05, **143.98**, **133.74**, 133.57, 130.13, **129.99**, **128.23**, 128.15, *127.78*, *127.75*, **127.72**, 127.67, *127.32*, *127.30*, **126.77**, 125.07, 124.94, **124.67**, **124.43**, 124.14, **119.53**, 119.03, **84.06**, 81.93, **59.98**, 59.70, **55.17**, 53.84 (under solvent peak, see provided HSQC), 53.36 (2C, under solvent peak, see provided HSQC), 41.05, **40.12**, **36.95**, 36.91, **35.46**, 35.07, 34.62, **32.91**, **32.64**, 32.53.

IR (thin film) ν_{max} (cm^{-1}): 3145, 2924, 2856, 1564, 1452, 1404, 1292, 1193, 1122, 1068, 970, 905, 820, 735, 589, 532, 435.

HRMS (m/z): (ESI) calcd for $^{12}C_{23}H_{22}{}^{35}Cl_3N_4O$ $[M+H]^+$: 475.0854, found 475.0860.



2.4.25

HAT-ketone 2.4.25

TLC: R_f = 0.27 (3% MeOH/DCM)

^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.46 – 7.44 (m, 1H), 7.43 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.12 (ddd, *J* = 8.4, 2.5, 0.9 Hz, 1H), 7.04 (d, *J* = 2.0 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.84 (dd, *J* = 2.5, 1.2 Hz, 1H), 4.76 (dd, *J* = 10.9, 6.3 Hz, 1H), 3.88 (dd, *J* = 12.8, 6.4 Hz, 1H), 3.80 (dd, *J* = 12.8, 10.9 Hz, 1H), 3.48 (s, 3H), 3.30 (s, 3H), 2.85 (d, *J* = 19.2 Hz, 1H), 2.66 (dd, *J* = 19.1, 2.3 Hz, 1H), 2.54 – 2.49 (m, 1H), 2.09 (d, *J* = 15.9 Hz, 1H).

^{13}C NMR (150 MHz, CD_2Cl_2): δ 170.10, 167.60, 156.45, 154.97, 143.72, 133.35, 130.75, 130.66, 128.46, 128.22, 127.85, 125.34, 124.54, 123.84, 121.32, 60.43, 53.24, 52.35, 37.79, 37.06, 35.59, 33.39, 30.06.

IR (thin film) ν_{max} (cm^{-1}): 2924, 2856, 1693, 1575, 1452, 1333, 1199, 1125, 1037, 964, 893, 826, 736, 668, 594, 528, 438.

HRMS (m/z): (ESI) calcd for $^{12}C_{23}H_{20}{}^{35}Cl_3N_4O$ $[M+H]^+$: 473.0697, found 473.0703.

Natural Product Spectral Comparisons

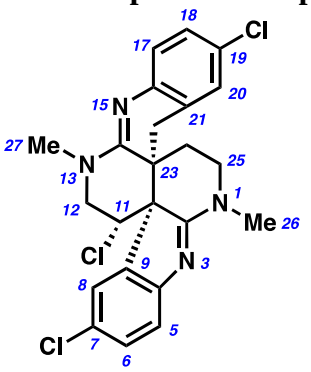


Table S1. Comparison of ^{1}H NMR data of natural and synthetic caulamidine A.

Position	^{1}H (δ) Natural Sample (ref. 11)* (600 MHz, CD_3CN)	^{1}H (δ) Natural Sample (ref. 12)** (600 MHz, CD_3CN)	^{1}H (δ) Synthetic Sample (600 MHz, CD_3CN)
5-H	7.17 (d, *J* = 8.5 Hz, 1H)	7.14 (d, *J* = 8.3 Hz, 1H)	7.14 (d, *J* = 8.3 Hz, 1H)
6-H	7.31 (dd, *J* = 8.4, 2.0 Hz, 1H)	7.29 (dd, *J* = 8.3, 2.2 Hz, 1H)	7.29 (dd, *J* = 8.3, 2.1 Hz, 1H)
8-H	6.95 (bs, 1H)	6.93 – 6.91 (m, 1H) {overlaps with 17-H}	6.93 (d, *J* = 1.9 Hz, 1H) {overlaps with 17-H}
11-H	5.02 (dd, *J* = 10.8, 4.7 Hz, 1H)	5.00 (dd, *J* = 11.0, 6.3 Hz, 1H)	5.00 (dd, *J* = 11.0, 6.3 Hz, 1H)
12-H_a	3.87 (dd, *J* = 13.3, 6.6 Hz, 1H)	3.85 (dd, *J* = 12.8, 6.4 Hz, 1H)	3.85 (dd, *J* = 12.8, 6.4 Hz, 1H)
12-H_b	3.66 (dd, *J* = 13.3, 10.5 Hz, 1H)	3.69 (dd, *J* = 12.8, 11.0 Hz, 1H)	3.69 (dd, *J* = 12.7, 11.0 Hz, 1H)
17-H	6.94 (d, *J* = 8.2 Hz, 1H)	6.93 – 6.91 (m, 1H) {overlaps with 8-H}	6.92 (d, *J* = 8.3 Hz, 1H) {overlaps with 8-H}
18-H	7.12 (dd, *J* = 8.2, 2.4 Hz, 1H)	7.10 (dd, *J* = 8.4, 2.5 Hz, 1H)	7.10 (ddd, *J* = 8.4, 2.5, 1.0 Hz, 1H)
20-H	6.96 (bs, 1H)	6.95 – 6.93 (m, 1H)	6.94 (dd, *J* = 2.5, 1.2 Hz, 1H)
22-H_a	2.48 (d, *J* = 15.9 Hz, 1H)	2.48 – 2.42 (m, 1H)	2.45 (ddt, *J* = 16.0, 2.3, 1.2 Hz, 1H)
22-H_b	2.28 (d, *J* = 15.9 Hz, 1H)	2.26 (d, *J* = 16.1 Hz, 1H) {overlaps with 24-H_a}	2.26 (d, *J* = 16.0 Hz, 1H)
24-H_a	2.25 (m, 1H)	2.22 (m, 1H) {overlaps with 22-H_b and H_2O}	2.22 (m, 1H)
24-H_b	1.73 (dd, *J* = 15.0, 6.2 Hz, 1H)	1.72 (ddd, *J* = 14.9, 6.0, 1.6 Hz, 1H)	1.72 (ddd, *J* = 15.0, 5.9, 1.6 Hz, 1H)
25-H_a	3.38 (ddd, *J* = 12.5, 7.5, 1.6 Hz, 1H)	3.36 (ddd, *J* = 12.3, 7.3, 1.6 Hz, 1H)	3.36 (ddd, *J* = 12.3, 7.3, 1.6 Hz, 1H)
25-H_b	3.18 (dt, *J* = 11.7, 5.9 Hz, 1H)	3.16 (dt, *J* = 11.8, 5.9 Hz, 1H)	3.15 (dt, *J* = 12.0, 5.9 Hz, 1H)
26-H	3.00 (s, 3H)	2.98 (s, 3H)	2.98 (s, 3H)
27-H	3.24 (s, 3H)	3.22 (s, 3H)	3.22 (s, 3H)

* Tabular values reported in ref. 11. Not referenced to CD_3CN residual signal at 1.94 ppm.
** Referenced to CD_3CN satellite peak at 1.8250 ppm.

Table S2. Comparison of ^{13}C NMR data of natural and synthetic caulamidine A.

Position	^{13}C (δ) Natural Sample (ref. 11)* (150 MHz, CD_3CN)	^{13}C (δ) Natural Sample (ref. 12)** (150 MHz, CD_3CN)	^{13}C (δ) Synthetic Sample (150 MHz, CD_3CN)
2	174.0	174.9	175.0
4	156.0	157.0	157.2
5	117.8	118.8	118.9
6	129.4	130.3	130.3
7	126.3	127.2	127.2
8	123.8	124.6	124.7
9	133.3	134.3	134.4
10	58.9	59.9	60.0
11	54.8	55.9	55.9
12	52.6	53.7	53.7
14	159.1	160.0	160.0
16	143.9	144.9	145.0
17	124.2	125.2	125.2
18	127.2	128.2	128.2
19	125.8	126.8	126.8
20	127.3	128.2	128.3
21	125.4	126.3	126.4
22	29.6	30.6	30.6
23	39.8	40.8	40.9
24	24.7	25.7	25.8
25	47.4	48.5	48.5
26	37.2	38.2	38.3
27	35.8	36.7	36.8

* Tabular values reported in ref. 11. Not referenced to CD_3CN signal at 118.26 ppm.
** Referenced to CD_3CN signal at 118.26 ppm.

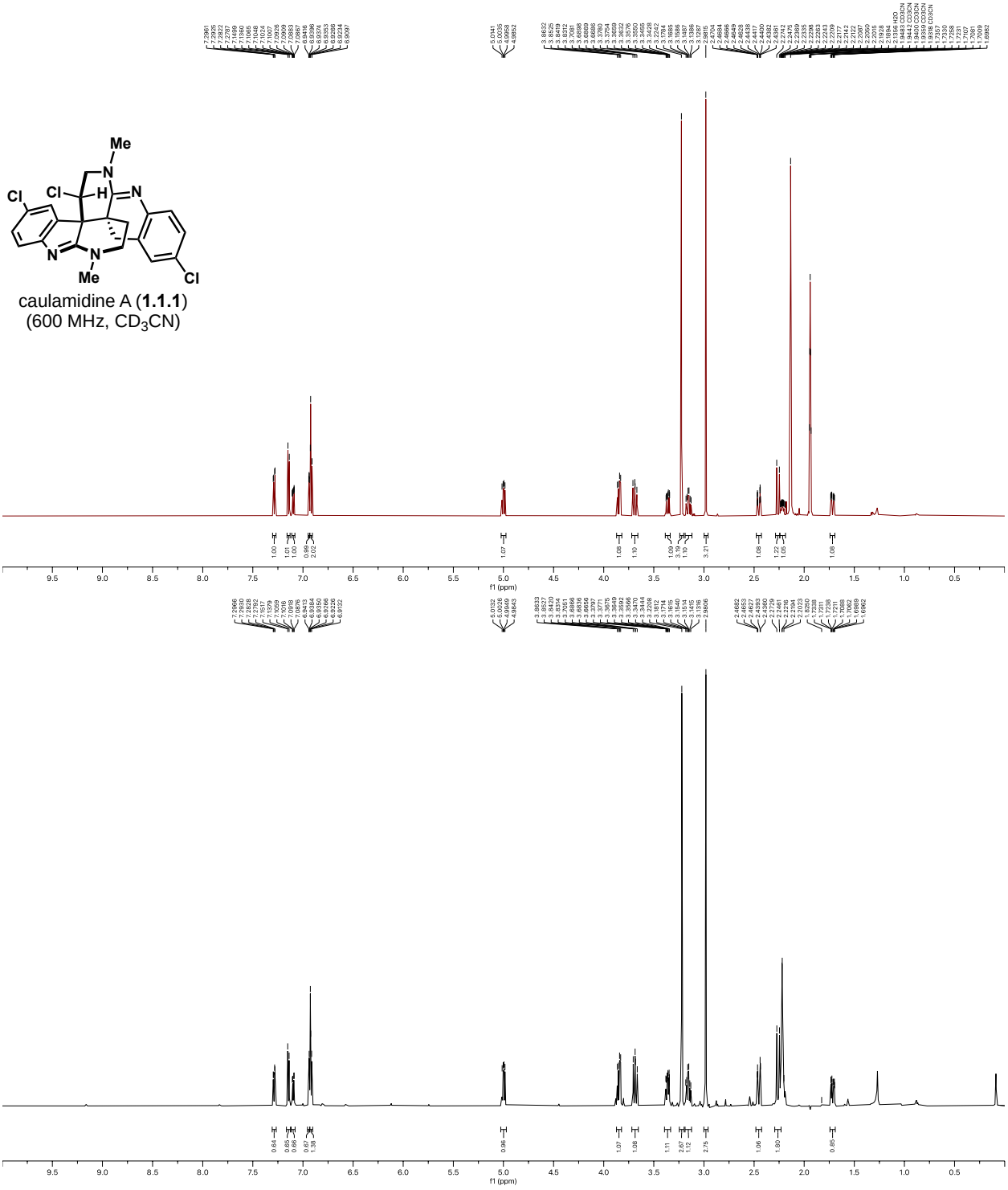


Figure SI-1. ^{1}H NMR spectra of synthetic and natural[12] caulamidine A.

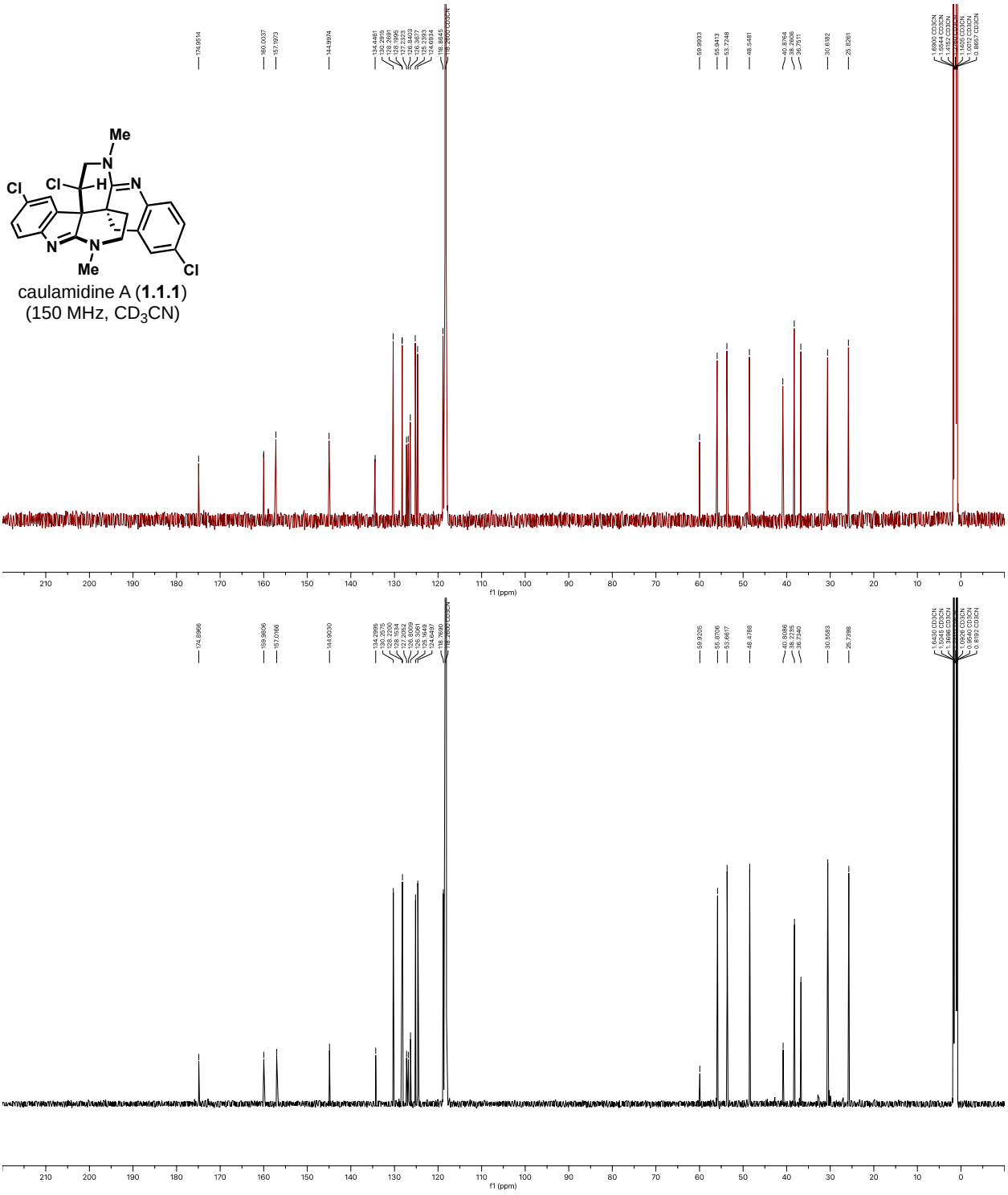


Figure SI-2. ^{13}C NMR spectra of synthetic and natural[12] caulamidine A.

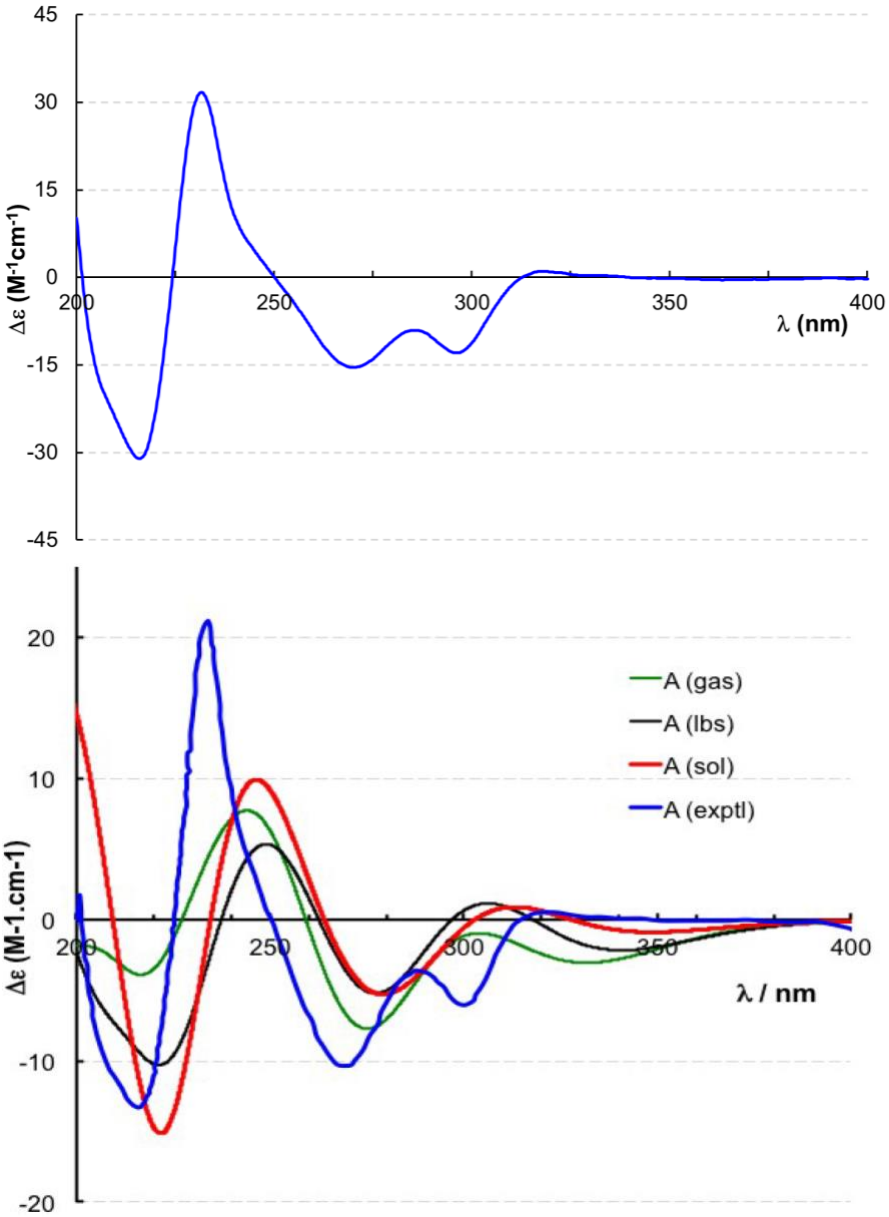


Figure SI-3. ECD spectra of synthetic and natural[11] caulamidine A.

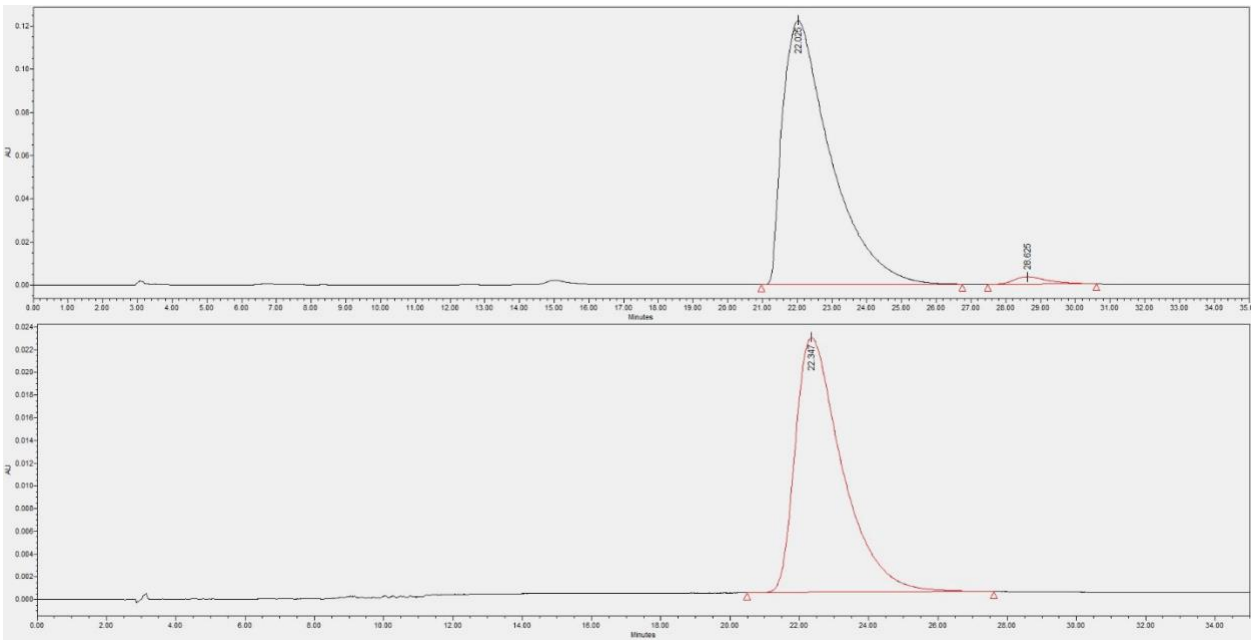
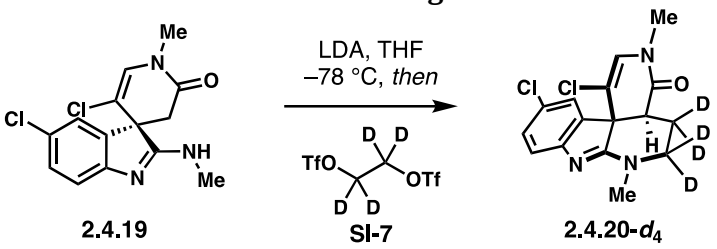


Figure SI-4. HPLC traces of synthetic and natural[13] caulamidine A.

Deuterium-Labeling Studies



Tetracycle 2.4.20-*d*$_4$: A flame-dried reaction tube was charged with amidine **2.4.19** (89.6 mg, 0.289 mmol, 1 equiv) and dry THF (1.45 mL). The resulting solution was cooled to –78 ºC and a solution of freshly made LDA (1.27 mL, 0.5 M in THF, 0.635 mmol, 2.2 equiv) was added dropwise. After the mixture was stirred at –78 ºC for 30 minutes, a solution of **SI-7** (prepared from ethylene glycol-*d*$_6$ following the same procedure[9] for glycol bistriflate, 191 mg, 0.578 mmol, 2 equiv) in THF (1.8 mL) was added dropwise. The reaction mixture was allowed to warm to ambient temperature over 4 hours before being quenched by the addition of saturated *aq*. $NaHCO_3$ (3 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (5 x 3 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0.9 to 1.7 to 2% MeOH/DCM) to afford tetracycle **2.4.20-*d*$_4$** (74.0 mg, 217 μmol, 75%) as a while solid.

TLC: R_f = 0.29 (5% MeOH/DCM)

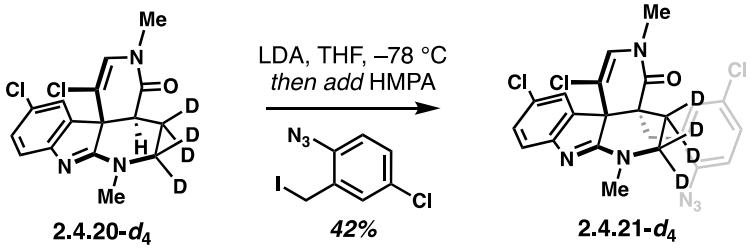
^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.19 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.07 (d, *J* = 8.3 Hz, 1H), 7.02 (d, *J* = 2.2 Hz, 1H), 6.42 (s, 1H), 3.17 (s, 3H), 3.13 (s, 3H), 2.70 (s, 1H).

^{13}C NMR (150 MHz, CD_2Cl_2): δ 171.99, 168.67, 155.29, 138.18, 129.89, 129.48, 126.63, 122.16, 117.75, 112.08, 57.60, 48.81 (pentet), 43.27, 38.02, 34.64, 24.02 (pentet).

IR (thin film) ν_{max} (cm^{-1}): 2927, 1674, 1626, 1567, 1447, 1409, 1374, 1335, 1303, 1267, 1183, 1121, 1035, 824, 735, 662, 521.

HRMS (m/z): (ESI) calcd for $^{12}C_{16}H_{12}{}^2H_4{}^{35}Cl_2N_3O$ $[M+H]^+$: 340.0916, found 340.0913.

$[\alpha]_D^{30}$ –398° (*c* 0.1, CH_3CN)



Azide 2.4.21-*d*$_4$: A flame-dried reaction tube was charged with tetracycle **2.4.20-*d*$_4$** (70.2 mg, 206 μmol, 1 equiv) and dry THF (0.6 mL). The resulting solution was cooled to –78 ºC and a solution of freshly made LDA (0.43 mL, 0.5 M in THF, 0.22 mmol, 1.0 equiv) was added dropwise. After the mixture was stirred at –78 ºC for 30 minutes, HMPA (0.11 mL, 0.63 mmol, 3.1 equiv) was added followed by dropwise addition of a solution of 2-azido-5-chlorobenzyl iodide[10] (66.6 mg, 227 μmol, 1.1 equiv) in THF (0.6 mL). The reaction mixture was allowed to warm to ambient temperature over 4 hours before being quenched by the addition of saturated *aq*. NH_4Cl (2 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (5 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced

pressure. The residue was purified by silica gel column chromatography (0.2 to 0.3 to 0.4 % MeOH/DCM) to afford azide **2.4.21-*d*$_4$** (43.7 mg, 86.4 μmol, 42%) as a while solid.

TLC: R_f = 0.24 (1% MeOH/DCM)

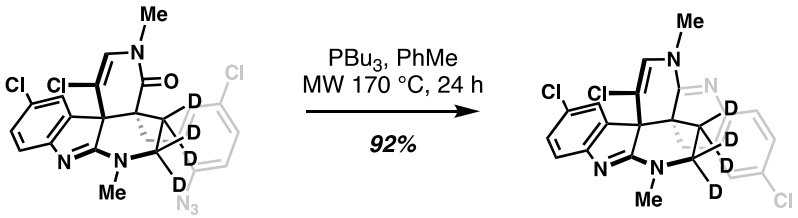
^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.72 (d, *J* = 2.5 Hz, 1H), 7.14 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.11 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 6.80 (d, *J* = 8.5 Hz, 1H), 6.72 (d, *J* = 2.1 Hz, 1H), 6.38 (s, 1H), 3.23 (s, 3H), 3.14 (s, 3H), 2.91 (d, *J* = 14.6 Hz, 1H), 2.53 (d, *J* = 14.6 Hz, 1H).

^{13}C NMR (150 MHz, CD_2Cl_2): δ 171.14, 171.10, 155.63, 138.15, 135.56, 133.72, 131.32, 129.99, 129.81, 128.77, 128.56, 126.72, 122.62, 119.27, 117.53, 113.58, 62.11, 48.44, 47.15 (pentet), 38.00, 35.62, 30.70, 27.34 (pentet).

IR (thin film) ν_{max} (cm^{-1}): 2926, 2120, 1669, 1629, 1568, 1449, 1407, 1367, 1301, 1265, 1195, 1115, 905, 818, 735, 528, 440.

HRMS (m/z): (ESI) calcd for $^{12}C_{23}H_{16}{}^{2}H_4{}^{35}Cl_3N_6O$ $[M+H]^+$: 505.1010, found 505.1004.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{30}}$ –380° (*c* 0.1, CH_3CN)



2.4.21-*d*$_4$ **2.4.16-*d*$_4$**

Hexacycle 2.4.16-*d*$_4$: A Biotage microwave vial was charged with azide **2.4.21-*d*$_4$** (33.9 mg, 67.0 μmol, 1 equiv), PBu_3 (33.1 μL, 134 μmol, 2 equiv), and dry PhMe (2.7 mL) under N_2 atmosphere. The vial was capped and heated at 170 °C for 24 hours in a Biotage microwave reactor. After decapping the vial, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2.7 to 4% Et_2O/DCM) to afford hexacycle **2.4.16-*d*$_4$** (28.6 mg, 61.9 μmol, 92%) as a while solid.

***Note:** Organic azides can be heat- and shock-sensitive. Caution should be exercised when using azides.

TLC: R_f = 0.37 (10% Et_2O/DCM)

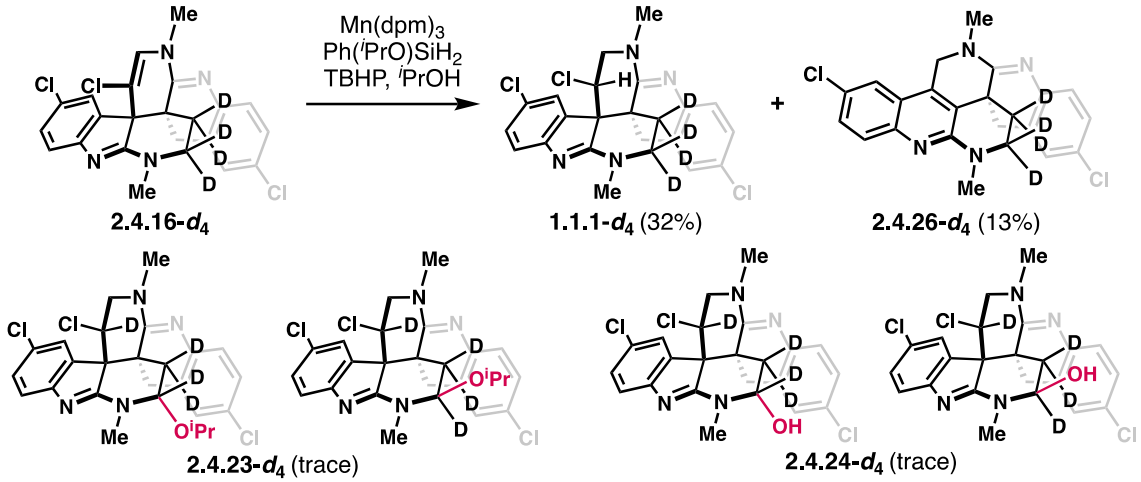
^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.20 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.12 – 7.08 (m, 3H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.88 – 6.86 (m, 1H), 6.45 (s, 1H), 3.37 (s, 3H), 3.15 (s, 3H), 2.73 (dt, *J* = 16.2, 1.2 Hz, 1H), 2.16 (d, *J* = 16.2 Hz, 1H).

^{13}C NMR (150 MHz, CD_2Cl_2): δ 172.61, 157.02, 155.33, 143.37, 137.88, 130.44, 129.99, 129.01, 128.11 (2C), 127.10, 126.25, 125.73, 123.13, 118.02, 108.86, 60.71, 46.93 (pentet), 42.48, 37.90, 37.45, 31.74, 26.47 (pentet).

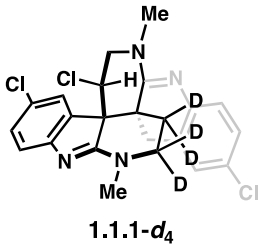
IR (thin film) ν_{max} (cm^{-1}): 2927, 1565, 1449, 1381, 1302, 1257, 1196, 1126, 1080, 825, 736, 541.

HRMS (m/z): (ESI) calcd for $^{12}C_{23}H_{16}{}^{2}H_4{}^{35}Cl_3N_4$ $[M+H]^+$: 461.0999, found 461.0994.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{26}}$ –1003° (*c* 0.1, CH_3CN)



1,5-HAT confirmed by deuterium-labeling: To a flame-dried reaction tube charged with **2.4.16-*d*4** (5.3 mg, 11 μmol, 1 equiv) and Mn(dpm)3 (14 mg, 23 μmol, 2 equiv) were added *i*-PrOH (1.2 mL), isopropoxy(phenyl)silane (8.2 μL, 46 μmol, 4 equiv), and *tert*-butyl hydroperoxide (4.2 μL, 23 μmol, 2 equiv) in sequence. The reaction mixture was stirred at ambient temperature overnight before being concentrated under reduced pressure. The crude mixture was filtered through a short plug of silica gel to remove the baseline Mn complexes (DCM for loading, 5% MeOH/DCM for flushing). Yields were determined by ^{1}H NMR using 1.97 μmol methyl 3,5-dinitrobenzoate as internal standard. Preparative TLC (3% MeOH/DCM) afforded pure **1.1.1-*d*4**, **2.4.26-*d*4**, **2.4.23-*d*4**, and **2.4.24-*d*4** for characterization.



Caulamidine A-*d*4 (1.1.1-*d*4)

TLC: R_f = 0.24 (3% MeOH/DCM)

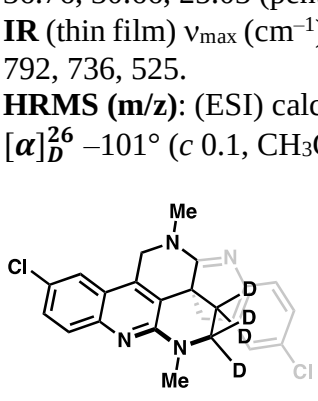
^{1}H NMR (600 MHz, CD_3CN): δ 7.29 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 7.10 (dd, *J* = 8.4, 2.4 Hz, 2H), 6.94 (dd, *J* = 2.5, 1.2 Hz, 1H), 6.93 – 6.90 (m, 2H), 4.99 (dd, *J* = 10.9, 6.3 Hz, 1H), 3.85 (dd, *J* = 12.8, 6.4 Hz, 1H), 3.69 (dd, *J* = 12.7, 11.0 Hz, 1H), 3.23 (s, 3H), 2.98 (s, 3H), 2.48 – 2.43 (m, 1H), 2.25 (d, *J* = 16.0 Hz, 1H).

^{13}C NMR (150 MHz, CD_3CN): δ 174.96, 160.04, 157.27, 145.03, 134.44, 130.31, 128.29, 128.22, 127.22, 126.87, 126.38, 125.26, 124.71, 118.86, 59.99, 55.91, 53.75, 47.75 (pentet), 40.73, 38.21, 36.76, 30.66, 25.03 (pentet).

IR (thin film) ν_{max} (cm^{-1}): 2925, 2871, 1561, 1450, 1402, 1316, 1255, 1194, 1128, 1063, 905, 826, 792, 736, 525.

HRMS (m/z): (ESI) calcd for $^{12}C_{23}H_{18}{}^2H_4{}^{35}Cl_3N_4$ $[M+H]^+$: 463.1156, found 463.1151.

$[\alpha]_D^{26}$ –101° (*c* 0.1, CH_3CN)

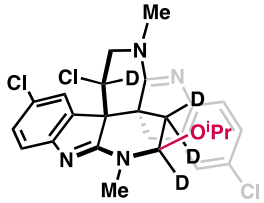


2.4.26-*d*4

TLC: R_f = 0.29 (3% MeOH/DCM)

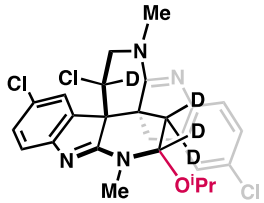
^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.60 (d, *J* = 8.9 Hz, 1H), 7.55 (d, *J* = 2.3 Hz, 1H), 7.44 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.21 (ddd, *J* = 8.3, 2.4, 0.9 Hz, 1H), 7.18 (dd, *J* = 2.5, 1.2 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 4.73 (d, *J* = 16.7 Hz, 1H), 4.56 (d, *J* = 16.7 Hz, 1H), 3.23 (s, 3H), 3.22 (s, 3H), 2.99 (d, *J* = 15.8 Hz, 1H), 2.52 (dt, *J* = 15.8, 1.2 Hz, 1H).

^{13}C NMR (150 MHz, CD_2Cl_2): δ 164.66, 153.43, 145.81, 145.74, 132.03, 129.66, 128.46, 128.15, 127.98, 127.97, 127.34, 127.00, 124.72, 121.48, 121.03, 119.69, 51.51, 45.51 (signal absent due to ^{2}H coupling, see provided HMBC), 37.43, 35.73, 34.36, 33.88, 26.18 (signal absent due to ^{2}H coupling, see provided HMBC).
IR (thin film) ν_{max} (cm^{-1}): 2924, 2853, 1635, 1572, 1470, 1402, 1313, 1190, 1121, 968, 823.
HRMS (m/z): (ESI) calcd for $^{12}C_{23}H_{17}{}^2H_4{}^{35}Cl_2N_4$ $[M+H]^+$: 427.1389, found 427.1383.
$[\alpha]_D^{27}$ +110° (*c* 0.05, CH_2Cl_2)



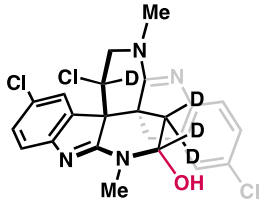
2.4.23-d_4-minor

2.4.23-d_4-minor
TLC: R_f = 0.27 (3% MeOH/DCM)
^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.28 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 7.10 (ddd, *J* = 8.4, 2.5, 1.0 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 2.1 Hz, 1H), 6.85 (dd, *J* = 2.3, 1.0 Hz, 2H), 3.82 (d, *J* = 12.6 Hz, 1H), 3.80 – 3.75 (m, 2H), 3.28 (s, 3H), 3.25 (s, 3H), 2.40 (d, *J* = 15.9 Hz, 1H), 1.95 (d, *J* = 15.9 Hz, 1H), 1.21 (d, *J* = 6.1 Hz, 3H), 1.13 (d, *J* = 6.1 Hz, 3H).
HRMS (m/z): (ESI) calcd for $^{12}C_{26}H_{24}{}^2H_4{}^{35}Cl_3N_4O$ $[M+H]^+$: 521.1574, found 521.1573.
***Note:** The amount of **22-d_4-minor** was not enough for full characterization. Please find ^{1}H NMR comparison of **22-minor** and **22-d_4-minor** on page SI-144.

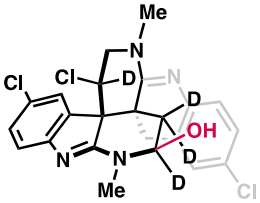


2.4.23-d_4-major

2.4.23-d_4-major
TLC: R_f = 0.25 (3% MeOH/DCM)
^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.31 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 7.10 (ddd, *J* = 8.4, 2.5, 1.0 Hz, 1H), 6.97 – 6.93 (m, 2H), 6.87 (dd, *J* = 2.5, 1.2 Hz, 1H), 3.78 – 3.70 (m, 2H), 3.52 (hept, *J* = 6.0 Hz, 1H), 3.26 (s, 3H), 3.01 (s, 3H), 2.65 (d, *J* = 15.5 Hz, 1H), 2.45 (d, *J* = 15.4 Hz, 1H), 1.16 (d, *J* = 6.1 Hz, 3H), 0.86 (d, *J* = 6.1 Hz, 3H).
HRMS (m/z): (ESI) calcd for $^{12}C_{26}H_{24}{}^2H_4{}^{35}Cl_3N_4O$ $[M+H]^+$: 521.1574, found 521.1571.
***Note:** The amount of **22-d_4-major** was not enough for full characterization. Please find ^{1}H NMR comparison of **22-major** and **22-d_4-major** on page SI-145.

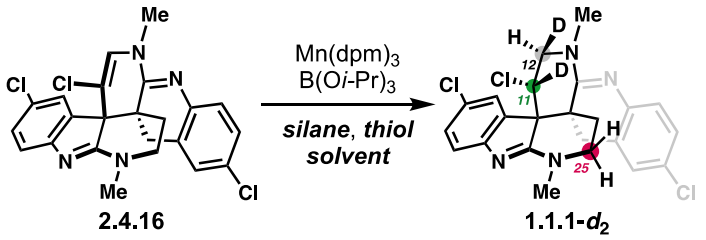


2.4.24-d_4-major



2.4.24-d_4-minor

2.4.24-d_4
TLC: R_f = 0.07 (3% MeOH/DCM)
bold = major epimer
normal = minor epimer
<u>underline</u> = superimposed peaks of major and minor epimer
^{1}H NMR (600 MHz, CD_2Cl_2): δ **7.32** (dd, *J* = 8.3, 2.1 Hz, 1H), 7.30 (dd, *J* = 8.3, 2.1 Hz, 1H), **7.28** (d, *J* = 8.3 Hz, 1H), 7.22 (d, *J* = 8.3 Hz, 1H), <u>7.13 – 7.08</u> (m, 2H), <u>6.98 – 6.94</u> (m, 3H), **6.92** (d, *J* = 2.1 Hz, 1H), **6.87** (dd, *J* = 2.5, 1.2 Hz, 1H), 6.85 (dd, *J* = 2.5, 1.2 Hz, 1H), 3.83 (d, *J* = 12.7 Hz, 1H), <u>3.80 – 3.70</u> (m, 3H), 3.28 (s, 3H), **3.26** (s, 3H), 3.19 (s, 3H), **3.06** (s, 3H), 2.85 (s, 1H), **2.71 – 2.64** (m, 2H), <u>2.53 – 2.46</u> (m, 2H), 1.99 (d, *J* = 16.0 Hz, 1H).
HRMS (m/z): (ESI) calcd for $^{12}C_{23}H_{18}{}^2H_4{}^{35}Cl_3N_4O$ $[M+H]^+$: 479.1105, found 479.1103.
***Note:** The amount of **23-d_4** was not enough for full characterization. Please find ^{1}H NMR comparison of **23** and **23-d_4** on page SI-146.



Entry	Conditions	Results
1	Ph(*i*-PrO)SiH_2 PhS**D**, CD_3O**D**	C12 0% D C11 0% D C25 0% D
2	Ph(*i*-PrO)Si**D**$_2$ PhSH, *i*-PrOH	C12 97% D C11 94% D C25 0% D

Experiment 1: Reaction was performed using the same procedure on page 62. In this case, PhSD[14] was used instead of regular PhSH. CD_3OD was used as the solvent instead of *i*-PrOH. No deuterium incorporation was observed at C11 or C25.

Experiment 2: Reaction was performed using the same procedure on page 62. In this case, Ph(*i*-PrO)SiD_2 (prepared from $PhSiD_3$[15] using the procedure reported in ref. 16) was used instead of regular Ph(*i*-PrO)SiH_2. 97% and 94% deuterium incorporation were observed at C12 and C11, respectively. No deuterium incorporation was observed at C25.

Caulamidine A-d_2 (1.1.1-d_2):

TLC: R_f = 0.24 (3% MeOH/DCM)

^{1}H NMR (600 MHz, CD_3CN): δ 7.29 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 7.10 (ddd, *J* = 8.4, 2.5, 1.0 Hz, 1H), 6.94 (dd, *J* = 2.6, 1.3 Hz, 1H), 6.93 – 6.90 (m, 2H), 4.99 (d, *J* = 10.7 Hz, 0.06H), 3.86 – 3.82 (m, 0.03H), 3.67 (s, 1H), 3.36 (ddd, *J* = 12.3, 7.3, 1.6 Hz, 1H), 3.22 (s, 3H), 3.16 (td, *J* = 11.9, 6.0 Hz, 1H), 2.98 (s, 3H), 2.48 – 2.43 (m, 1H), 2.26 (d, *J* = 16.0 Hz, 1H), 2.21 (dddd, *J* = 14.9, 11.6, 7.3, 2.1 Hz, 1H), 1.72 (ddd, *J* = 15.0, 6.0, 1.6 Hz, 1H).

^{13}C NMR (150 MHz, CD_3CN): δ 174.96, 160.04, 157.24, 145.03, 134.47, 130.31, 128.29, 128.22, 127.25, 126.87, 126.38, 125.26, 124.71, 118.88, 59.93, 55.94 (signal absent due to ^{2}H coupling), 53.72 (signal absent due to ^{2}H coupling), 48.56, 40.91, 38.27, 36.72, 30.65, 25.85.

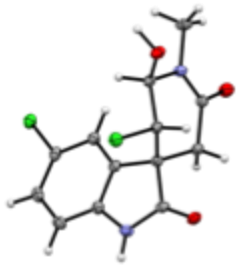
IR (thin film) ν_{max} (cm^{-1}): 2924, 2853, 1674, 1620, 1557, 1451, 1401, 1298, 1258, 1196, 947, 823, 526.

HRMS (m/z): (ESI) calcd for $^{12}C_{23}H_{20}{}^2H_2{}^{35}Cl_3N_4$ $[M+H]^+$: 461.1030, found 461.1024.

$[\alpha]_D^{27}$ –176° (*c* 0.025, CH_3CN)

X-Ray Crystallography Data

Chlorohydrin 2.2.7 (grown via slow evaporation from MeOH at –20 ºC)



chlorohydrin **2.2.7** **[Xray]**

A colorless block 0.21 x 0.18 x 0.18 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using omega scans. Crystal-to-detector distance was 33.00 mm and exposure time was 0.50 seconds per frame at low and high angles, using a scan width of 0.5°. Data collection was 99% complete to 74.000° in θ. A total of 13912 reflections were collected covering the indices -9<=h<=7, -16<=k<=16, -16<=l<=16. 2683 reflections were founded to be symmetry independent, with an R_{int} of 0.0334. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/n (No. 14). The data were integrated using the CrysAlis^{Pro} 1.171.41.116a software program and scaled using the SCALE3 ABSPACK scaling algorithm. Solution by intrinsic phasing (SHELXT-2015) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Table 1. Crystal data and structure refinement for ZZhu01_Maimone.

Identification code	ZZhu01_Maimone	
Empirical formula	C13 H12 Cl2 N2 O3	
Formula weight	315.15	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 7.64310(10) Å	α= 90°.
	b = 13.4434(2) Å	β= 101.9210(10)°.
	c = 13.16580(10) Å	γ = 90°.
Volume	1323.60(3) $Å^3$	
Z	4	
Density (calculated)	1.581 Mg/m^3	
Absorption coefficient	4.507 mm^{-1}	
F(000)	648	
Crystal size	0.210 x 0.180 x 0.180 mm^3	
Theta range for data collection	4.754 to 74.473°.	
Index ranges	-9<=h<=7, -16<=k<=16, -16<=l<=16	
Reflections collected	13912	
Independent reflections	2683 [R(int) = 0.0334]	
Completeness to theta = 74.000°	99.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.84620	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2683 / 0 / 190	
Goodness-of-fit on F^2	1.073	
Final R indices [I>2sigma(I)]	R1 = 0.0317, wR2 = 0.0818	
R indices (all data)	R1 = 0.0333, wR2 = 0.0832	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.555 and -0.277 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for zzhu01_maimone. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	4837(1)	2821(1)	8740(1)	20(1)
Cl(2)	1381(1)	4454(1)	4187(1)	20(1)
O(1)	4471(2)	7087(1)	8014(1)	23(1)
O(2)	2507(2)	4366(1)	9464(1)	19(1)
O(3)	8960(1)	4061(1)	8833(1)	19(1)
N(1)	3189(2)	5668(1)	8418(1)	16(1)
N(2)	7868(2)	3389(1)	7213(1)	18(1)
C(1)	6207(2)	5620(1)	8013(1)	15(1)
C(2)	4544(2)	6177(1)	8144(1)	16(1)
C(3)	1570(2)	6209(1)	8530(1)	21(1)
C(4)	3129(2)	4582(1)	8564(1)	15(1)
C(5)	4998(2)	4144(1)	8698(1)	15(1)
C(6)	5967(2)	4494(1)	7851(1)	15(1)
C(7)	7801(2)	3966(1)	8041(1)	16(1)
C(8)	6322(2)	3502(1)	6427(1)	16(1)
C(9)	5973(2)	3076(1)	5451(1)	19(1)
C(10)	4393(2)	3352(1)	4773(1)	18(1)
C(11)	3264(2)	4048(1)	5079(1)	17(1)
C(12)	3607(2)	4464(1)	6073(1)	16(1)
C(13)	5150(2)	4170(1)	6755(1)	15(1)

Table 3. Bond lengths [Å] and angles [°] for zzhu01_maimone.

Cl(1)-C(5)	1.7848(16)
Cl(2)-C(11)	1.7457(16)
O(1)-C(2)	1.236(2)
O(2)-C(4)	1.3961(19)
O(3)-C(7)	1.228(2)
N(1)-C(2)	1.350(2)
N(1)-C(3)	1.468(2)
N(1)-C(4)	1.475(2)
N(2)-C(7)	1.347(2)
N(2)-C(8)	1.409(2)
C(1)-C(2)	1.516(2)
C(1)-C(6)	1.534(2)
C(4)-C(5)	1.521(2)
C(5)-C(6)	1.534(2)
C(6)-C(13)	1.513(2)
C(6)-C(7)	1.545(2)
C(8)-C(9)	1.381(2)
C(8)-C(13)	1.399(2)
C(9)-C(10)	1.395(2)
C(10)-C(11)	1.388(2)
C(11)-C(12)	1.397(2)
C(12)-C(13)	1.384(2)
C(2)-N(1)-C(3)	119.01(13)
C(2)-N(1)-C(4)	125.58(13)
C(3)-N(1)-C(4)	115.31(13)
C(7)-N(2)-C(8)	111.49(13)
C(2)-C(1)-C(6)	115.12(13)
O(1)-C(2)-N(1)	121.55(15)
O(1)-C(2)-C(1)	119.25(14)
N(1)-C(2)-C(1)	119.20(14)
O(2)-C(4)-N(1)	109.99(13)
O(2)-C(4)-C(5)	107.30(12)
N(1)-C(4)-C(5)	110.16(12)
C(4)-C(5)-C(6)	112.33(13)
C(4)-C(5)-Cl(1)	108.67(10)
C(6)-C(5)-Cl(1)	112.03(11)
C(13)-C(6)-C(1)	115.51(13)
C(13)-C(6)-C(5)	116.00(13)
C(1)-C(6)-C(5)	105.23(12)
C(13)-C(6)-C(7)	101.80(12)
C(1)-C(6)-C(7)	110.66(12)
C(5)-C(6)-C(7)	107.42(12)
O(3)-C(7)-N(2)	127.29(15)

O(3)-C(7)-C(6)	124.13(14)
N(2)-C(7)-C(6)	108.57(13)
C(9)-C(8)-C(13)	122.68(15)
C(9)-C(8)-N(2)	127.64(15)
C(13)-C(8)-N(2)	109.62(14)
C(8)-C(9)-C(10)	117.43(15)
C(11)-C(10)-C(9)	120.10(15)
C(10)-C(11)-C(12)	122.25(15)
C(10)-C(11)-Cl(2)	119.43(12)
C(12)-C(11)-Cl(2)	118.29(12)
C(13)-C(12)-C(11)	117.62(15)
C(12)-C(13)-C(8)	119.82(15)
C(12)-C(13)-C(6)	131.72(14)
C(8)-C(13)-C(6)	108.32(13)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for zzhu01_maimone. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	21(1)	14(1)	26(1)	2(1)	6(1)	0(1)
Cl(2)	19(1)	22(1)	16(1)	-1(1)	0(1)	-1(1)
O(1)	20(1)	15(1)	34(1)	2(1)	8(1)	-1(1)
O(2)	16(1)	24(1)	18(1)	2(1)	5(1)	-2(1)
O(3)	13(1)	24(1)	21(1)	0(1)	1(1)	0(1)
N(1)	13(1)	16(1)	20(1)	2(1)	5(1)	1(1)
N(2)	16(1)	17(1)	21(1)	0(1)	4(1)	3(1)
C(1)	13(1)	16(1)	17(1)	-1(1)	4(1)	-2(1)
C(2)	15(1)	16(1)	15(1)	-1(1)	2(1)	-1(1)
C(3)	16(1)	21(1)	26(1)	5(1)	7(1)	5(1)
C(4)	13(1)	16(1)	16(1)	1(1)	3(1)	-2(1)
C(5)	14(1)	14(1)	16(1)	0(1)	3(1)	-1(1)
C(6)	13(1)	16(1)	15(1)	-1(1)	3(1)	-1(1)
C(7)	14(1)	16(1)	18(1)	2(1)	5(1)	-1(1)
C(8)	16(1)	14(1)	18(1)	1(1)	4(1)	0(1)
C(9)	22(1)	15(1)	21(1)	-1(1)	8(1)	1(1)
C(10)	24(1)	16(1)	15(1)	-3(1)	5(1)	-2(1)
C(11)	18(1)	16(1)	16(1)	1(1)	2(1)	-4(1)
C(12)	16(1)	16(1)	18(1)	-1(1)	4(1)	-1(1)
C(13)	15(1)	14(1)	16(1)	0(1)	5(1)	-2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for zzhu01_maimone.

	x	y	z	U(eq)
H(1A)	7158	5736	8636	18
H(1B)	6624	5903	7411	18
H(3A)	1436	6175	9253	31
H(3B)	523	5907	8079	31
H(3C)	1669	6906	8331	31
H(4)	2324	4272	7950	18
H(5)	5708	4374	9382	18
H(9)	6777	2614	5249	22
H(10)	4089	3062	4102	22
H(12)	2809	4931	6273	20
H(2)	1270(40)	4240(20)	9240(20)	45(7)
H(2A)	8760(30)	2984(18)	7154(19)	33(6)

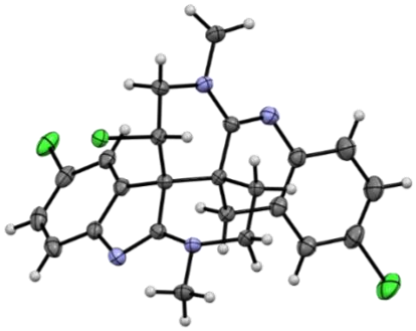
Table 6. Torsion angles [°] for zzhu01_maimone.

C(3)-N(1)-C(2)-O(1)	2.0(2)
C(4)-N(1)-C(2)-O(1)	178.28(15)
C(3)-N(1)-C(2)-C(1)	-179.14(14)
C(4)-N(1)-C(2)-C(1)	-2.8(2)
C(6)-C(1)-C(2)-O(1)	-161.64(14)
C(6)-C(1)-C(2)-N(1)	19.4(2)
C(2)-N(1)-C(4)-O(2)	135.72(15)
C(3)-N(1)-C(4)-O(2)	-47.84(18)
C(2)-N(1)-C(4)-C(5)	17.6(2)
C(3)-N(1)-C(4)-C(5)	-165.92(13)
O(2)-C(4)-C(5)-C(6)	-169.42(12)
N(1)-C(4)-C(5)-C(6)	-49.70(17)
O(2)-C(4)-C(5)-Cl(1)	66.05(14)
N(1)-C(4)-C(5)-Cl(1)	-174.23(10)
C(2)-C(1)-C(6)-C(13)	81.35(17)
C(2)-C(1)-C(6)-C(5)	-47.94(17)
C(2)-C(1)-C(6)-C(7)	-163.68(13)
C(4)-C(5)-C(6)-C(13)	-64.42(17)
Cl(1)-C(5)-C(6)-C(13)	58.22(16)
C(4)-C(5)-C(6)-C(1)	64.58(16)
Cl(1)-C(5)-C(6)-C(1)	-172.77(10)
C(4)-C(5)-C(6)-C(7)	-177.47(13)
Cl(1)-C(5)-C(6)-C(7)	-54.82(14)
C(8)-N(2)-C(7)-O(3)	-177.40(15)
C(8)-N(2)-C(7)-C(6)	3.79(17)
C(13)-C(6)-C(7)-O(3)	176.56(14)
C(1)-C(6)-C(7)-O(3)	53.3(2)
C(5)-C(6)-C(7)-O(3)	-61.10(19)
C(13)-C(6)-C(7)-N(2)	-4.58(16)
C(1)-C(6)-C(7)-N(2)	-127.88(14)
C(5)-C(6)-C(7)-N(2)	117.76(14)
C(7)-N(2)-C(8)-C(9)	175.88(16)
C(7)-N(2)-C(8)-C(13)	-1.27(18)
C(13)-C(8)-C(9)-C(10)	1.2(2)
N(2)-C(8)-C(9)-C(10)	-175.59(15)
C(8)-C(9)-C(10)-C(11)	1.7(2)
C(9)-C(10)-C(11)-C(12)	-2.9(2)
C(9)-C(10)-C(11)-Cl(2)	175.13(12)
C(10)-C(11)-C(12)-C(13)	1.1(2)
Cl(2)-C(11)-C(12)-C(13)	-176.95(12)
C(11)-C(12)-C(13)-C(8)	1.8(2)
C(11)-C(12)-C(13)-C(6)	176.92(15)
C(9)-C(8)-C(13)-C(12)	-3.0(2)
N(2)-C(8)-C(13)-C(12)	174.31(14)

C(9)-C(8)-C(13)-C(6)	-179.19(15)
N(2)-C(8)-C(13)-C(6)	-1.87(17)
C(1)-C(6)-C(13)-C(12)	-51.8(2)
C(5)-C(6)-C(13)-C(12)	72.0(2)
C(7)-C(6)-C(13)-C(12)	-171.76(16)
C(1)-C(6)-C(13)-C(8)	123.73(14)
C(5)-C(6)-C(13)-C(8)	-112.45(15)
C(7)-C(6)-C(13)-C(8)	3.79(16)

Symmetry transformations used to generate equivalent atoms:

(–)-Caulamidine A (1.1.1) (grown via slow evaporation from Et_2O at –20 ºC)



caulamidine A (**1.1.1**) **[Xray]**

A colorless block 0.23 x 0.12 x 0.08 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using omega scans. Crystal-to-detector distance was 30.21 mm and exposure time was 0.50 seconds per frame using a scan width of 0.5°. Data collection was 100% complete to 74.000° in θ. A total of 38775 reflections were collected covering the indices -11<=h<=10, -12<=k<=12, -18<=l<=18. 5749 reflections were found to be symmetry independent, with an R_{int} of 0.0530. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21 (No. 4). The data were integrated using the CrysAlis^{Pro} 1.172.42.81a software program and scaled using the SCALE3 ABSPACK scaling algorithm. Solution by intrinsic phasing (SHELXT-2015) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Table 1. Crystal data and structure refinement for ZZhu02_Maimone.

Identification code	ZZhu02_Maimone	
Empirical formula	C27 H31 Cl3 N4 O	
Formula weight	533.91	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 9.55600(10) Å	a= 90°.
	b = 10.26580(10) Å	b= 101.2400(10)°.
	c = 14.65900(10) Å	g = 90°.
Volume	1410.46(2) $Å^3$	
Z	2	
Density (calculated)	1.257 Mg/m^3	
Absorption coefficient	3.143 mm^{-1}	
F(000)	560	
Crystal size	0.230 x 0.120 x 0.080 mm^3	
Theta range for data collection	3.074 to 74.493°.	
Index ranges	-11<=h<=10, -12<=k<=12, -18<=l<=18	
Reflections collected	38775	
Independent reflections	5749 [R(int) = 0.0530]	
Completeness to theta = 74.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.77843	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5749 / 61 / 368	
Goodness-of-fit on F^2	1.074	
Final R indices [I>2sigma(I)]	R1 = 0.0462, wR2 = 0.1322	
R indices (all data)	R1 = 0.0471, wR2 = 0.1333	
Absolute structure parameter	0.003(6)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.626 and -0.395 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for zzhu02_maimone. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	5043(1)	7985(1)	2728(1)	37(1)
Cl(2)	2241(1)	5500(1)	5855(1)	25(1)
Cl(3)	-2312(1)	2330(2)	-832(1)	51(1)
N(1)	-243(3)	6926(3)	4102(2)	24(1)
N(2)	-1293(3)	4882(3)	4269(2)	22(1)
N(3)	3308(3)	3069(3)	3966(2)	24(1)
N(4)	2288(3)	2302(3)	2532(2)	28(1)
C(1)	3174(4)	6435(4)	3392(3)	25(1)
C(2)	3511(4)	7718(4)	3187(3)	30(1)
C(3)	2668(5)	8764(4)	3306(3)	32(1)
C(4)	1404(5)	8571(4)	3646(3)	30(1)
C(5)	1049(4)	7305(4)	3850(2)	24(1)
C(6)	1925(4)	6246(3)	3722(2)	22(1)
C(7)	1185(4)	5030(3)	3974(2)	20(1)
C(8)	-216(4)	5654(3)	4114(2)	21(1)
C(9)	-2591(4)	5535(4)	4419(3)	29(1)
C(10)	-1587(4)	3706(3)	3684(3)	25(1)
C(11)	-239(3)	3000(4)	3538(2)	22(1)
C(12)	891(4)	3913(3)	3252(2)	20(1)
C(13)	1964(4)	4391(3)	4885(2)	21(1)
C(14)	3407(4)	3889(3)	4782(2)	23(1)
C(15)	4577(4)	2288(4)	3930(3)	30(1)
C(16)	2212(4)	3079(3)	3220(2)	22(1)
C(17)	1155(4)	2327(4)	1751(3)	28(1)
C(18)	1017(5)	1268(5)	1131(3)	39(1)
C(19)	-64(5)	1268(5)	343(3)	43(1)
C(20)	-984(5)	2302(5)	172(3)	37(1)
C(21)	-894(4)	3352(4)	786(3)	29(1)
C(22)	188(4)	3354(4)	1578(3)	26(1)
C(23)	376(4)	4452(3)	2272(3)	23(1)
O(1)	3101(17)	4830(20)	8630(14)	148(6)
C(24)	4690(30)	6920(40)	8764(16)	175(13)
C(25)	3708(16)	6012(19)	8403(12)	99(5)
C(26)	1900(20)	4150(20)	8225(17)	120(6)
C(27)	1399(13)	2910(20)	8409(12)	88(5)
O(2)	5718(16)	5440(20)	980(13)	152(6)
C(28)	7412(18)	7310(20)	1096(12)	105(5)
C(29)	6970(14)	6095(18)	1399(11)	93(5)

C(30)	5189(18)	4480(20)	1478(15)	122(6)
C(31)	5970(30)	3390(30)	1605(16)	137(7)

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Table 3. Bond lengths [Å] and angles [°] for zzhu02_maimone.

Cl(1)-C(2)	1.747(4)
Cl(2)-C(13)	1.800(4)
Cl(3)-C(20)	1.746(4)
N(1)-C(8)	1.306(5)
N(1)-C(5)	1.410(5)
N(2)-C(8)	1.354(5)
N(2)-C(9)	1.464(4)
N(2)-C(10)	1.476(4)
N(3)-C(16)	1.359(5)
N(3)-C(14)	1.451(5)
N(3)-C(15)	1.463(5)
N(4)-C(16)	1.299(5)
N(4)-C(17)	1.415(5)
C(1)-C(6)	1.386(5)
C(1)-C(2)	1.402(5)
C(1)-H(1)	0.9500
C(2)-C(3)	1.374(6)
C(3)-C(4)	1.407(6)
C(3)-H(3)	0.9500
C(4)-C(5)	1.391(5)
C(4)-H(4)	0.9500
C(5)-C(6)	1.407(5)
C(6)-C(7)	1.515(5)
C(7)-C(8)	1.533(5)
C(7)-C(13)	1.542(5)
C(7)-C(12)	1.549(5)
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(10)-C(11)	1.529(5)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-C(12)	1.547(5)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-C(23)	1.529(5)
C(12)-C(16)	1.533(4)
C(13)-C(14)	1.507(5)
C(13)-H(13)	1.0000
C(14)-H(14A)	0.9900
C(14)-H(14B)	0.9900
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800

C(17)-C(22)	1.393(6)
C(17)-C(18)	1.406(6)
C(18)-C(19)	1.391(7)
C(18)-H(18)	0.9500
C(19)-C(20)	1.370(7)
C(19)-H(19)	0.9500
C(20)-C(21)	1.396(6)
C(21)-C(22)	1.395(6)
C(21)-H(21)	0.9500
C(22)-C(23)	1.506(5)
C(23)-H(23A)	0.9900
C(23)-H(23B)	0.9900
O(1)-C(26)	1.376(18)
O(1)-C(25)	1.415(18)
C(24)-C(25)	1.355(18)
C(24)-H(24A)	0.9800
C(24)-H(24B)	0.9800
C(24)-H(24C)	0.9800
C(25)-H(25A)	0.9900
C(25)-H(25B)	0.9900
C(26)-C(27)	1.401(19)
C(26)-H(26A)	0.9900
C(26)-H(26B)	0.9900
C(27)-H(27A)	0.9800
C(27)-H(27B)	0.9800
C(27)-H(27C)	0.9800
O(2)-C(30)	1.377(19)
O(2)-C(29)	1.406(17)
C(28)-C(29)	1.419(19)
C(28)-H(28A)	0.9800
C(28)-H(28B)	0.9800
C(28)-H(28C)	0.9800
C(29)-H(29A)	0.9900
C(29)-H(29B)	0.9900
C(30)-C(31)	1.34(2)
C(30)-H(30A)	0.9900
C(30)-H(30B)	0.9900
C(31)-H(31A)	0.9800
C(31)-H(31B)	0.9800
C(31)-H(31C)	0.9800

C(8)-N(1)-C(5)	105.2(3)
C(8)-N(2)-C(9)	116.9(3)
C(8)-N(2)-C(10)	116.5(3)
C(9)-N(2)-C(10)	113.1(3)
C(16)-N(3)-C(14)	125.1(3)

C(16)-N(3)-C(15)	119.3(3)
C(14)-N(3)-C(15)	115.2(3)
C(16)-N(4)-C(17)	117.8(3)
C(6)-C(1)-C(2)	117.1(4)
C(6)-C(1)-H(1)	121.4
C(2)-C(1)-H(1)	121.4
C(3)-C(2)-C(1)	122.8(4)
C(3)-C(2)-Cl(1)	118.8(3)
C(1)-C(2)-Cl(1)	118.3(3)
C(2)-C(3)-C(4)	120.0(4)
C(2)-C(3)-H(3)	120.0
C(4)-C(3)-H(3)	120.0
C(5)-C(4)-C(3)	118.1(4)
C(5)-C(4)-H(4)	121.0
C(3)-C(4)-H(4)	121.0
C(4)-C(5)-C(6)	121.1(3)
C(4)-C(5)-N(1)	125.3(3)
C(6)-C(5)-N(1)	113.3(3)
C(1)-C(6)-C(5)	120.9(3)
C(1)-C(6)-C(7)	132.5(3)
C(5)-C(6)-C(7)	106.6(3)
C(6)-C(7)-C(8)	98.6(3)
C(6)-C(7)-C(13)	113.1(3)
C(8)-C(7)-C(13)	110.4(3)
C(6)-C(7)-C(12)	118.3(3)
C(8)-C(7)-C(12)	110.7(3)
C(13)-C(7)-C(12)	105.6(3)
N(1)-C(8)-N(2)	125.0(3)
N(1)-C(8)-C(7)	115.6(3)
N(2)-C(8)-C(7)	119.4(3)
N(2)-C(9)-H(9A)	109.5
N(2)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
N(2)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
N(2)-C(10)-C(11)	113.5(3)
N(2)-C(10)-H(10A)	108.9
C(11)-C(10)-H(10A)	108.9
N(2)-C(10)-H(10B)	108.9
C(11)-C(10)-H(10B)	108.9
H(10A)-C(10)-H(10B)	107.7
C(10)-C(11)-C(12)	113.7(3)
C(10)-C(11)-H(11A)	108.8
C(12)-C(11)-H(11A)	108.8
C(10)-C(11)-H(11B)	108.8

C(12)-C(11)-H(11B)	108.8
H(11A)-C(11)-H(11B)	107.7
C(23)-C(12)-C(16)	106.8(3)
C(23)-C(12)-C(11)	111.1(3)
C(16)-C(12)-C(11)	107.0(3)
C(23)-C(12)-C(7)	110.9(3)
C(16)-C(12)-C(7)	113.2(3)
C(11)-C(12)-C(7)	107.9(3)
C(14)-C(13)-C(7)	110.8(3)
C(14)-C(13)-Cl(2)	107.4(2)
C(7)-C(13)-Cl(2)	112.7(2)
C(14)-C(13)-H(13)	108.6
C(7)-C(13)-H(13)	108.6
Cl(2)-C(13)-H(13)	108.6
N(3)-C(14)-C(13)	111.6(3)
N(3)-C(14)-H(14A)	109.3
C(13)-C(14)-H(14A)	109.3
N(3)-C(14)-H(14B)	109.3
C(13)-C(14)-H(14B)	109.3
H(14A)-C(14)-H(14B)	108.0
N(3)-C(15)-H(15A)	109.5
N(3)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
N(3)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
N(4)-C(16)-N(3)	117.9(3)
N(4)-C(16)-C(12)	122.6(3)
N(3)-C(16)-C(12)	119.3(3)
C(22)-C(17)-C(18)	119.5(4)
C(22)-C(17)-N(4)	122.5(3)
C(18)-C(17)-N(4)	118.0(4)
C(19)-C(18)-C(17)	119.8(4)
C(19)-C(18)-H(18)	120.1
C(17)-C(18)-H(18)	120.1
C(20)-C(19)-C(18)	119.9(4)
C(20)-C(19)-H(19)	120.1
C(18)-C(19)-H(19)	120.1
C(19)-C(20)-C(21)	121.5(4)
C(19)-C(20)-Cl(3)	120.2(3)
C(21)-C(20)-Cl(3)	118.3(4)
C(22)-C(21)-C(20)	118.7(4)
C(22)-C(21)-H(21)	120.6
C(20)-C(21)-H(21)	120.6
C(17)-C(22)-C(21)	120.5(4)
C(17)-C(22)-C(23)	117.1(3)

C(21)-C(22)-C(23)	122.3(4)
C(22)-C(23)-C(12)	109.8(3)
C(22)-C(23)-H(23A)	109.7
C(12)-C(23)-H(23A)	109.7
C(22)-C(23)-H(23B)	109.7
C(12)-C(23)-H(23B)	109.7
H(23A)-C(23)-H(23B)	108.2
C(26)-O(1)-C(25)	133(2)
C(25)-C(24)-H(24A)	109.5
C(25)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
C(25)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5
C(24)-C(25)-O(1)	142(2)
C(24)-C(25)-H(25A)	101.6
O(1)-C(25)-H(25A)	101.6
C(24)-C(25)-H(25B)	101.6
O(1)-C(25)-H(25B)	101.6
H(25A)-C(25)-H(25B)	104.6
O(1)-C(26)-C(27)	131(2)
O(1)-C(26)-H(26A)	104.4
C(27)-C(26)-H(26A)	104.4
O(1)-C(26)-H(26B)	104.4
C(27)-C(26)-H(26B)	104.4
H(26A)-C(26)-H(26B)	105.6
C(26)-C(27)-H(27A)	109.5
C(26)-C(27)-H(27B)	109.5
H(27A)-C(27)-H(27B)	109.5
C(26)-C(27)-H(27C)	109.5
H(27A)-C(27)-H(27C)	109.5
H(27B)-C(27)-H(27C)	109.5
C(30)-O(2)-C(29)	118.6(18)
C(29)-C(28)-H(28A)	109.5
C(29)-C(28)-H(28B)	109.5
H(28A)-C(28)-H(28B)	109.5
C(29)-C(28)-H(28C)	109.5
H(28A)-C(28)-H(28C)	109.5
H(28B)-C(28)-H(28C)	109.5
O(2)-C(29)-C(28)	124.4(17)
O(2)-C(29)-H(29A)	106.2
C(28)-C(29)-H(29A)	106.2
O(2)-C(29)-H(29B)	106.2
C(28)-C(29)-H(29B)	106.2
H(29A)-C(29)-H(29B)	106.4
C(31)-C(30)-O(2)	114.8(19)

C(31)-C(30)-H(30A)	108.6
O(2)-C(30)-H(30A)	108.6
C(31)-C(30)-H(30B)	108.6
O(2)-C(30)-H(30B)	108.6
H(30A)-C(30)-H(30B)	107.5
C(30)-C(31)-H(31A)	109.5
C(30)-C(31)-H(31B)	109.5
H(31A)-C(31)-H(31B)	109.5
C(30)-C(31)-H(31C)	109.5
H(31A)-C(31)-H(31C)	109.5
H(31B)-C(31)-H(31C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for zzhu02_maimone. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	30(1)	50(1)	30(1)	10(1)	1(1)	-16(1)
Cl(2)	26(1)	24(1)	24(1)	-3(1)	0(1)	0(1)
Cl(3)	52(1)	65(1)	30(1)	-12(1)	-10(1)	-5(1)
N(1)	25(2)	20(1)	26(2)	0(1)	4(1)	0(1)
N(2)	17(1)	19(1)	30(2)	-1(1)	3(1)	2(1)
N(3)	18(1)	25(1)	27(1)	-3(1)	2(1)	1(1)
N(4)	25(2)	29(2)	29(2)	-4(1)	4(1)	4(1)
C(1)	25(2)	28(2)	21(2)	1(1)	-1(1)	-4(1)
C(2)	26(2)	38(2)	23(2)	4(2)	0(1)	-11(2)
C(3)	44(2)	26(2)	25(2)	2(2)	0(2)	-12(2)
C(4)	40(2)	20(2)	27(2)	2(1)	3(2)	-2(2)
C(5)	27(2)	20(2)	22(2)	-1(1)	1(1)	-3(1)
C(6)	24(2)	21(2)	20(2)	1(1)	0(1)	-3(1)
C(7)	18(2)	18(2)	22(2)	1(1)	1(1)	1(1)
C(8)	22(2)	19(2)	22(2)	0(1)	2(1)	1(1)
C(9)	21(2)	28(2)	37(2)	-2(2)	7(2)	5(2)
C(10)	19(2)	22(2)	35(2)	-3(1)	3(1)	-1(1)
C(11)	20(2)	18(1)	26(2)	-1(1)	2(1)	-1(1)
C(12)	17(2)	19(2)	22(2)	-2(1)	0(1)	-1(1)
C(13)	21(2)	21(2)	21(2)	-1(1)	2(1)	-1(1)
C(14)	22(2)	20(2)	26(2)	2(1)	1(1)	3(1)
C(15)	20(2)	32(2)	37(2)	-5(2)	2(1)	3(2)
C(16)	19(2)	19(2)	27(2)	1(1)	5(1)	1(1)
C(17)	27(2)	30(2)	27(2)	-7(2)	4(1)	-2(2)
C(18)	43(2)	39(2)	35(2)	-14(2)	6(2)	3(2)
C(19)	48(3)	44(2)	33(2)	-16(2)	2(2)	0(2)
C(20)	36(2)	46(2)	28(2)	-10(2)	2(2)	-7(2)
C(21)	30(2)	32(2)	25(2)	0(2)	4(2)	-2(2)
C(22)	29(2)	29(2)	21(2)	-1(1)	4(1)	-4(1)
C(23)	23(2)	21(2)	24(2)	0(1)	0(1)	-1(1)
O(1)	102(9)	213(13)	144(12)	-43(9)	60(8)	-34(8)
C(24)	170(20)	290(20)	77(12)	-61(15)	67(13)	-110(20)
C(25)	50(7)	182(13)	74(9)	-49(8)	34(6)	-3(7)
C(26)	88(9)	161(13)	116(13)	-2(9)	36(9)	-13(8)
C(27)	35(6)	148(12)	76(9)	5(8)	1(6)	-5(6)
O(2)	87(7)	215(13)	144(11)	-18(9)	-1(7)	20(7)
C(28)	86(9)	173(13)	65(8)	-24(7)	33(7)	49(7)
C(29)	48(6)	167(12)	65(8)	-22(7)	11(5)	48(6)
C(30)	60(8)	191(14)	103(12)	-41(9)	-11(7)	19(7)
C(31)	108(14)	216(14)	86(12)	-26(10)	18(11)	42(10)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for zzhu02_maimone.

	x	y	z	U(eq)
H(1)	3776	5727	3309	30
H(3)	2937	9617	3159	39
H(4)	812	9285	3734	36
H(9A)	-2348	6161	4930	43
H(9B)	-3258	4886	4577	43
H(9C)	-3037	5995	3851	43
H(10A)	-2154	3957	3070	30
H(10B)	-2171	3097	3977	30
H(11A)	-509	2330	3050	26
H(11B)	193	2548	4122	26
H(13)	1379	3641	5032	26
H(14A)	4045	4635	4733	28
H(14B)	3831	3383	5343	28
H(15A)	4328	1361	3916	45
H(15B)	5313	2468	4481	45
H(15C)	4940	2511	3369	45
H(18)	1660	555	1250	47
H(19)	-164	552	-75	51
H(21)	-1555	4051	667	35
H(23A)	-542	4913	2240	28
H(23B)	1082	5084	2123	28
H(24A)	4663	7640	8324	262
H(24B)	5646	6520	8876	262
H(24C)	4489	7243	9352	262
H(25A)	4017	5779	7818	119
H(25B)	2848	6557	8205	119
H(26A)	1939	4126	7555	143
H(26B)	1099	4745	8275	143
H(27A)	390	2833	8115	132
H(27B)	1507	2795	9082	132
H(27C)	1953	2246	8158	132
H(28A)	7476	7254	438	158
H(28B)	8348	7542	1466	158
H(28C)	6716	7985	1175	158
H(29A)	7766	5482	1389	112
H(29B)	6910	6210	2061	112
H(30A)	5117	4837	2094	146
H(30B)	4212	4256	1151	146

H(31A)	5426	2670	1264	205
H(31B)	6197	3177	2269	205
H(31C)	6856	3517	1374	205

Table 6. Torsion angles [°] for zzhu02_maimone.

C(6)-C(1)-C(2)-C(3)	0.5(6)
C(6)-C(1)-C(2)-Cl(1)	-177.6(3)
C(1)-C(2)-C(3)-C(4)	-0.1(6)
Cl(1)-C(2)-C(3)-C(4)	178.0(3)
C(2)-C(3)-C(4)-C(5)	-0.2(6)
C(3)-C(4)-C(5)-C(6)	0.0(6)
C(3)-C(4)-C(5)-N(1)	-173.0(3)
C(8)-N(1)-C(5)-C(4)	172.0(4)
C(8)-N(1)-C(5)-C(6)	-1.4(4)
C(2)-C(1)-C(6)-C(5)	-0.6(5)
C(2)-C(1)-C(6)-C(7)	177.0(3)
C(4)-C(5)-C(6)-C(1)	0.4(6)
N(1)-C(5)-C(6)-C(1)	174.2(3)
C(4)-C(5)-C(6)-C(7)	-177.8(3)
N(1)-C(5)-C(6)-C(7)	-4.0(4)
C(1)-C(6)-C(7)-C(8)	-171.1(4)
C(5)-C(6)-C(7)-C(8)	6.7(3)
C(1)-C(6)-C(7)-C(13)	72.3(5)
C(5)-C(6)-C(7)-C(13)	-109.9(3)
C(1)-C(6)-C(7)-C(12)	-51.9(5)
C(5)-C(6)-C(7)-C(12)	125.9(3)
C(5)-N(1)-C(8)-N(2)	-175.9(3)
C(5)-N(1)-C(8)-C(7)	6.5(4)
C(9)-N(2)-C(8)-N(1)	1.1(5)
C(10)-N(2)-C(8)-N(1)	139.0(4)
C(9)-N(2)-C(8)-C(7)	178.6(3)
C(10)-N(2)-C(8)-C(7)	-43.5(4)
C(6)-C(7)-C(8)-N(1)	-8.5(4)
C(13)-C(7)-C(8)-N(1)	110.1(4)
C(12)-C(7)-C(8)-N(1)	-133.3(3)
C(6)-C(7)-C(8)-N(2)	173.7(3)
C(13)-C(7)-C(8)-N(2)	-67.6(4)
C(12)-C(7)-C(8)-N(2)	49.0(4)
C(8)-N(2)-C(10)-C(11)	41.6(4)
C(9)-N(2)-C(10)-C(11)	-178.8(3)
N(2)-C(10)-C(11)-C(12)	-48.0(4)
C(10)-C(11)-C(12)-C(23)	-68.7(4)
C(10)-C(11)-C(12)-C(16)	175.1(3)
C(10)-C(11)-C(12)-C(7)	53.0(4)
C(6)-C(7)-C(12)-C(23)	-41.4(4)
C(8)-C(7)-C(12)-C(23)	71.3(3)
C(13)-C(7)-C(12)-C(23)	-169.2(3)
C(6)-C(7)-C(12)-C(16)	78.5(4)
C(8)-C(7)-C(12)-C(16)	-168.8(3)

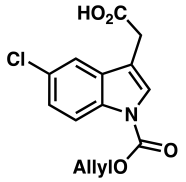
C(13)-C(7)-C(12)-C(16)	-49.3(4)
C(6)-C(7)-C(12)-C(11)	-163.3(3)
C(8)-C(7)-C(12)-C(11)	-50.6(4)
C(13)-C(7)-C(12)-C(11)	68.9(3)
C(6)-C(7)-C(13)-C(14)	-65.1(4)
C(8)-C(7)-C(13)-C(14)	-174.5(3)
C(12)-C(7)-C(13)-C(14)	65.8(3)
C(6)-C(7)-C(13)-Cl(2)	55.3(3)
C(8)-C(7)-C(13)-Cl(2)	-54.1(3)
C(12)-C(7)-C(13)-Cl(2)	-173.8(2)
C(16)-N(3)-C(14)-C(13)	21.0(5)
C(15)-N(3)-C(14)-C(13)	-165.7(3)
C(7)-C(13)-C(14)-N(3)	-51.6(4)
Cl(2)-C(13)-C(14)-N(3)	-175.1(2)
C(17)-N(4)-C(16)-N(3)	-179.2(3)
C(17)-N(4)-C(16)-C(12)	6.0(5)
C(14)-N(3)-C(16)-N(4)	178.8(3)
C(15)-N(3)-C(16)-N(4)	5.8(5)
C(14)-N(3)-C(16)-C(12)	-6.2(5)
C(15)-N(3)-C(16)-C(12)	-179.2(3)
C(23)-C(12)-C(16)-N(4)	-41.4(4)
C(11)-C(12)-C(16)-N(4)	77.7(4)
C(7)-C(12)-C(16)-N(4)	-163.6(3)
C(23)-C(12)-C(16)-N(3)	143.8(3)
C(11)-C(12)-C(16)-N(3)	-97.1(4)
C(7)-C(12)-C(16)-N(3)	21.6(4)
C(16)-N(4)-C(17)-C(22)	17.6(6)
C(16)-N(4)-C(17)-C(18)	-162.5(4)
C(22)-C(17)-C(18)-C(19)	1.3(7)
N(4)-C(17)-C(18)-C(19)	-178.6(4)
C(17)-C(18)-C(19)-C(20)	0.3(7)
C(18)-C(19)-C(20)-C(21)	-1.9(7)
C(18)-C(19)-C(20)-Cl(3)	178.2(4)
C(19)-C(20)-C(21)-C(22)	1.8(6)
Cl(3)-C(20)-C(21)-C(22)	-178.3(3)
C(18)-C(17)-C(22)-C(21)	-1.4(6)
N(4)-C(17)-C(22)-C(21)	178.5(3)
C(18)-C(17)-C(22)-C(23)	179.2(4)
N(4)-C(17)-C(22)-C(23)	-1.0(5)
C(20)-C(21)-C(22)-C(17)	-0.1(6)
C(20)-C(21)-C(22)-C(23)	179.3(4)
C(17)-C(22)-C(23)-C(12)	-35.7(4)
C(21)-C(22)-C(23)-C(12)	144.9(3)
C(16)-C(12)-C(23)-C(22)	52.7(4)
C(11)-C(12)-C(23)-C(22)	-63.6(4)
C(7)-C(12)-C(23)-C(22)	176.4(3)

C(26)-O(1)-C(25)-C(24)	166(3)
C(25)-O(1)-C(26)-C(27)	172(2)
C(30)-O(2)-C(29)-C(28)	-161.4(16)
C(29)-O(2)-C(30)-C(31)	-71(3)

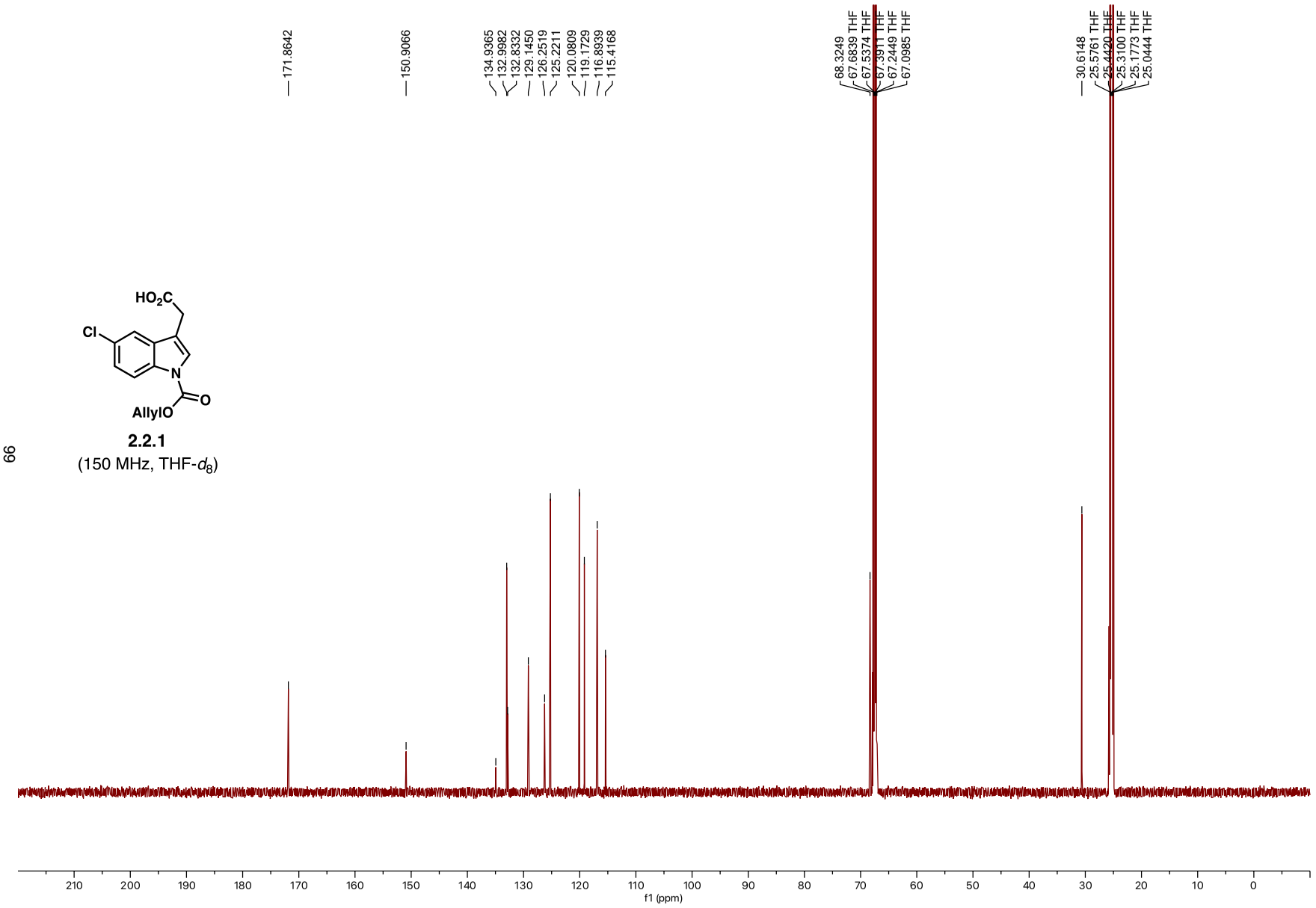
Symmetry transformations used to generate equivalent atoms:

References:

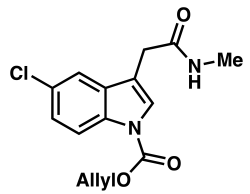
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2.2.1
(600 MHz, THF-d_8)


171.8642
150.9066
134.9365
132.9982
132.8332
129.1450
126.2519
125.2211
120.0809
119.1729
116.8939
115.4168
68.3249
67.6839 THF
67.5374 THF
67.3911 THF
67.2449 THF
67.0985 THF
30.6148
25.5761 THF
25.4420 THF
25.3100 THF
25.1773 THF
25.0444 THF
HO2C
Cl
N
O
AllylO
2.2.1
(150 MHz, THF-d8)
f1 (ppm)

8.1217
8.1070
7.6232
7.5291
7.5256
7.3264
7.3228
7.3117
7.3081
6.1179
6.1081
6.1005
6.0983
6.0907
6.0892
6.0810
6.0795
6.0719
6.0697
6.0621
6.0523
5.6096
5.4868
5.4844
5.4819
5.4795
5.4582
5.4557
5.4533
5.4509
5.3754
5.3734
5.3714
5.3693
5.3581
5.3560
5.3540
5.3520
5.3218 CD2Cl2
5.3200 CD2Cl2
5.3181 CD2Cl2
4.9181
4.9158
4.9135
4.9085
4.9060
4.9037
3.5710
2.7336
2.7256
1.5786 H2O

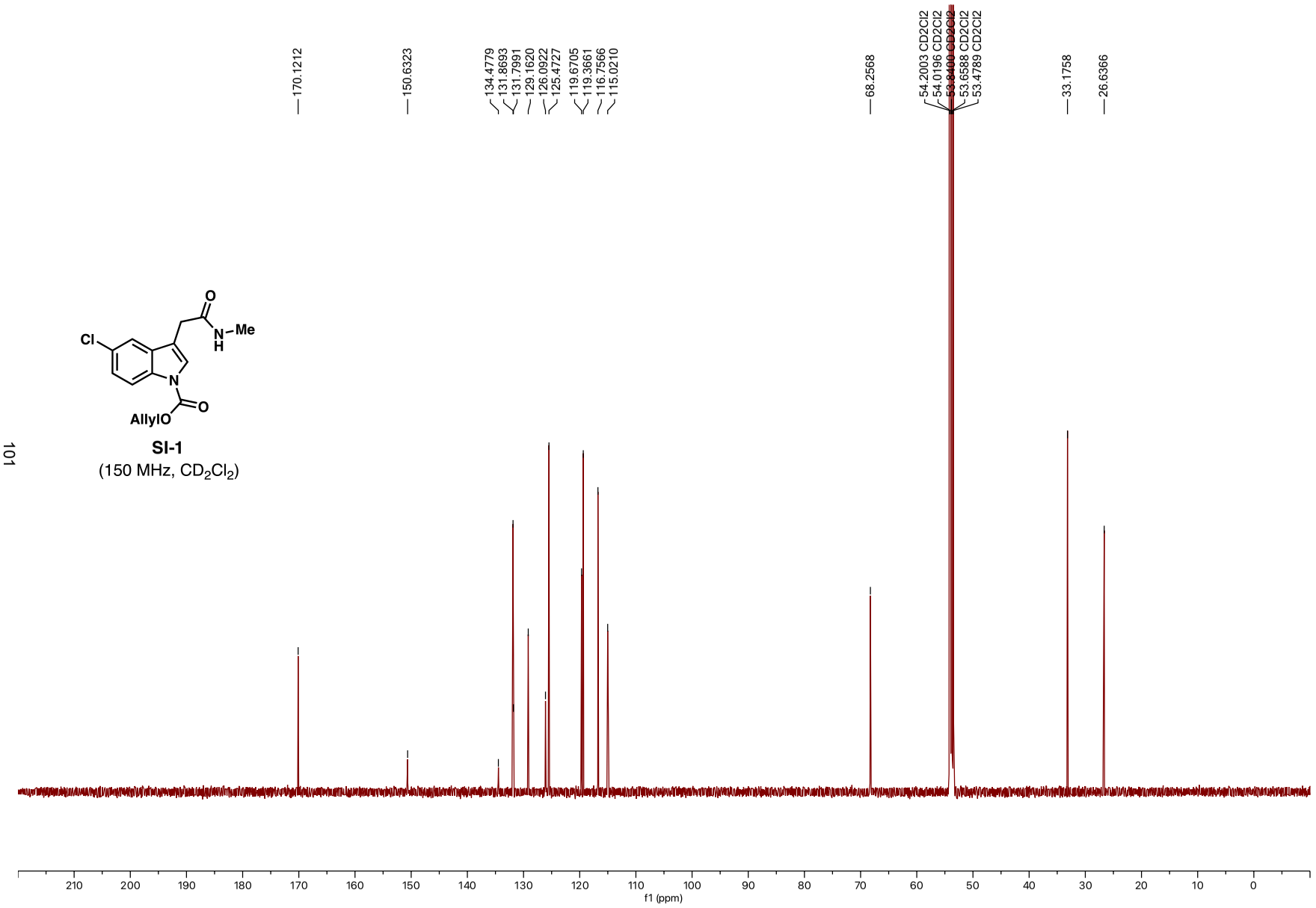


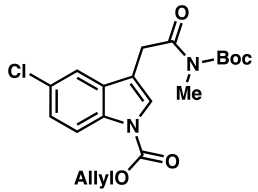
SI-1
(600 MHz, CD_2Cl_2)

100

0.99
1.00
1.00
1.07
0.98
1.01
1.08
1.08
2.27
2.34
3.36

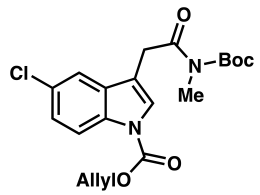
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


170.1212
150.6323
134.4779
131.8693
131.7991
129.1620
126.0922
125.4727
119.6705
119.3661
116.7566
115.0210
68.2568
54.2003 CD2Cl2
54.0196 CD2Cl2
53.8400 CD2Cl2
53.6588 CD2Cl2
53.4789 CD2Cl2
33.1758
26.6366
O
N–Me
H
Cl
N
O
AllylO
SI-1
(150 MHz, CD2Cl2)
101
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



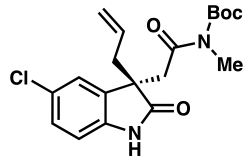
2.2.2

(600 MHz, CD_2Cl_2)



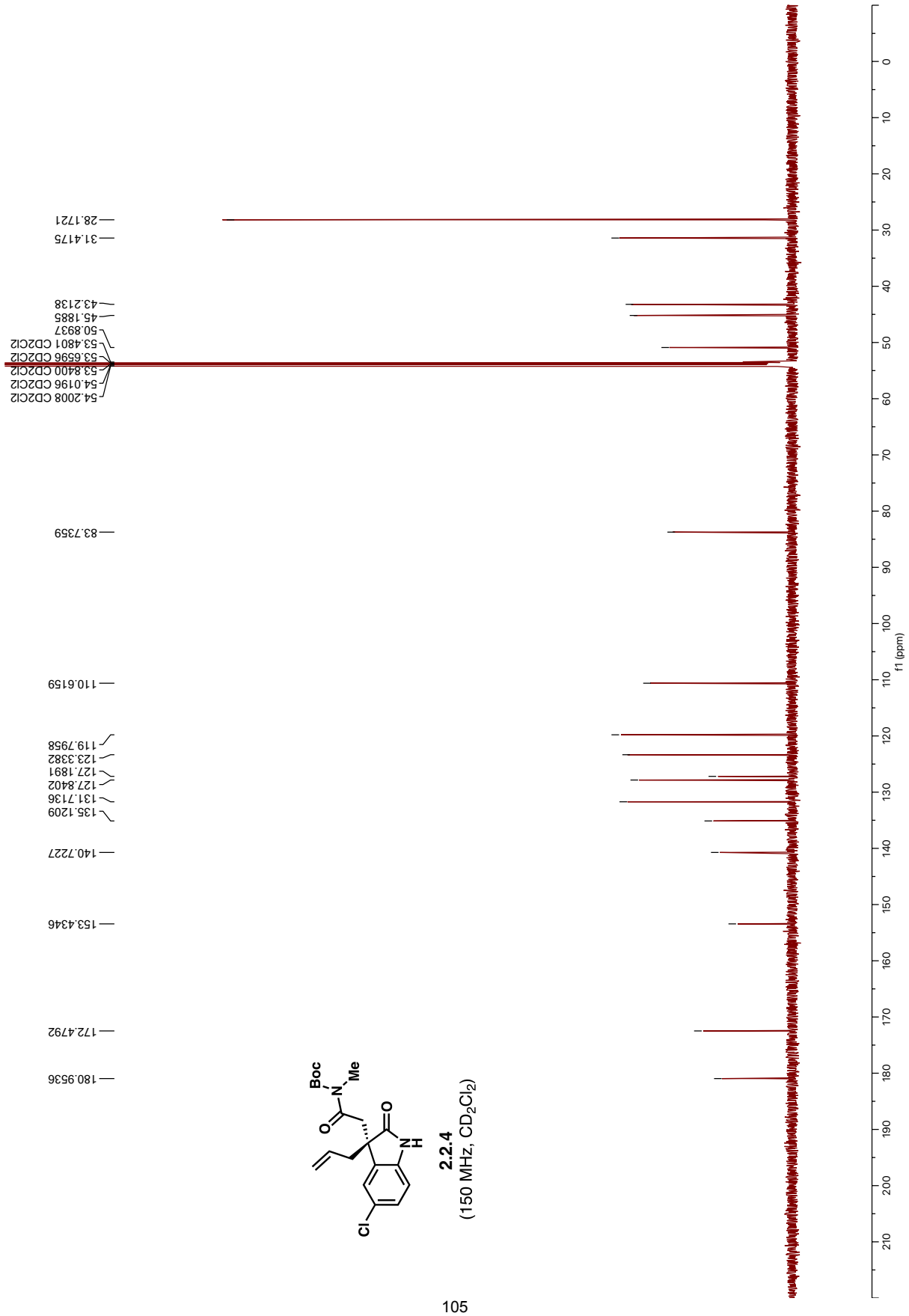
2.2.2

(150 MHz, CD_2Cl_2)

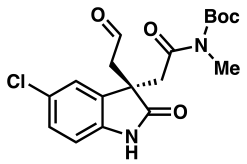


2.2.4

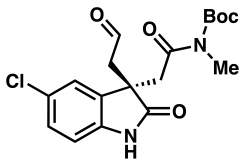
(600 MHz, CD_2Cl_2)



2.2.4
(150 MHz, CD_2Cl_2)



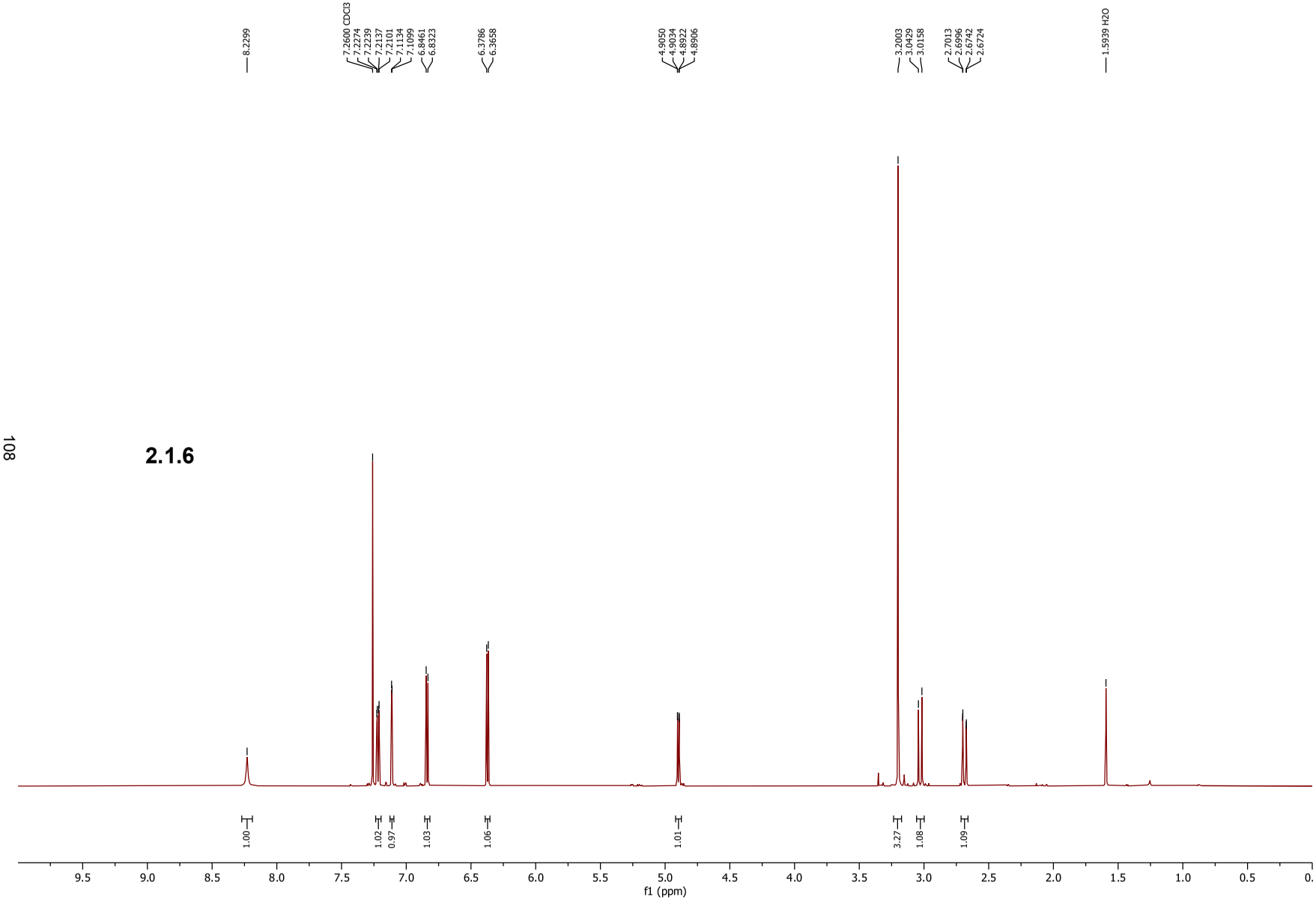
2.2.5
(600 MHz, CD_2Cl_2)



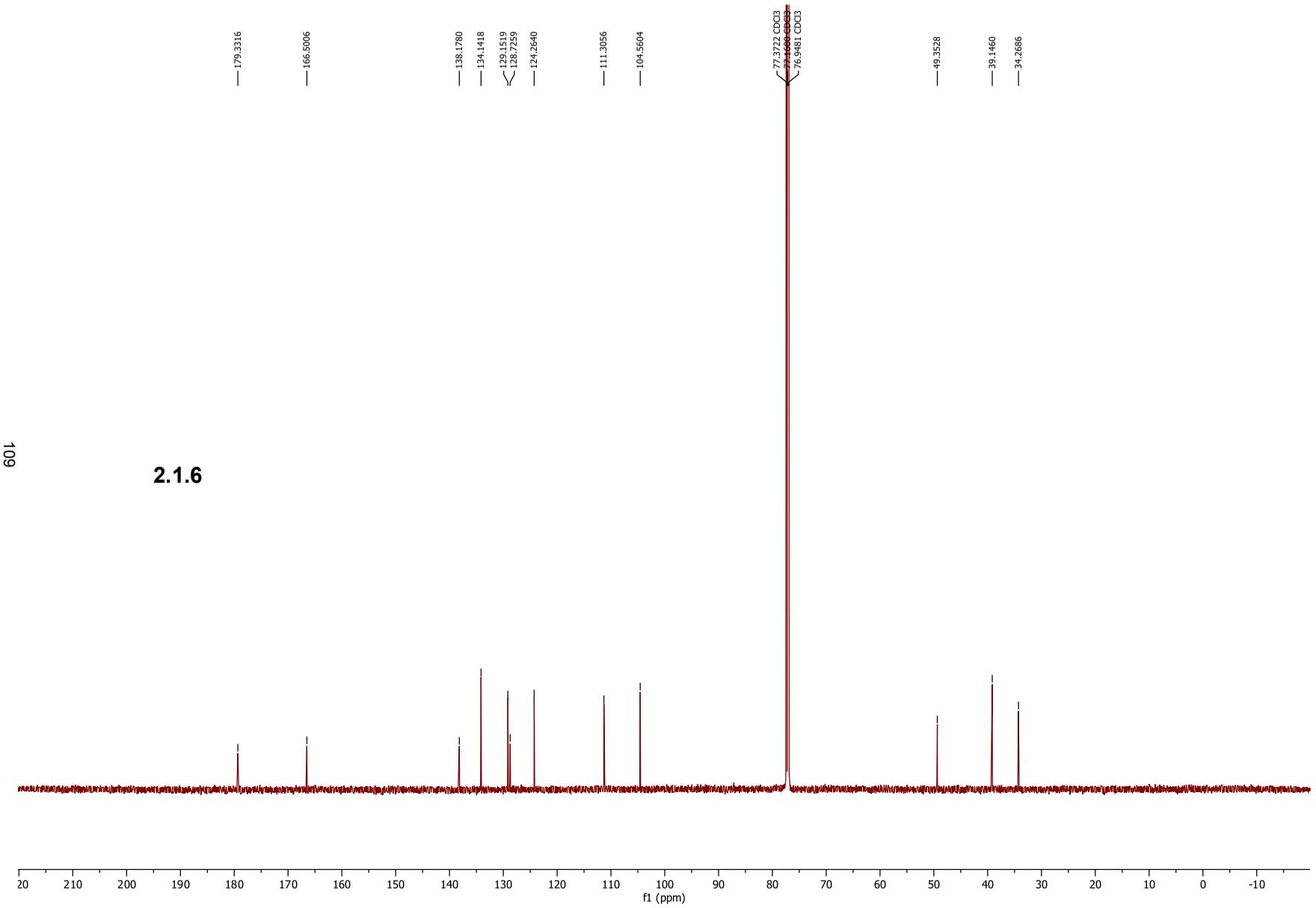
2.2.5

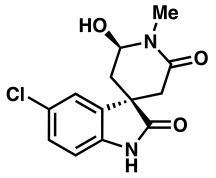
(150 MHz, CD_2Cl_2)

2.1.6


8.2299
7.2600 CDCl3
7.2274
7.2239
7.2137
7.2101
7.1134
7.1099
6.8461
6.8323
6.3786
6.3658
4.9050
4.9034
4.8922
4.8906
3.2003
3.0429
3.0158
2.7013
2.6996
2.6742
2.6724
1.5939 H2O
1.00
1.02
0.97
1.03
1.06
1.01
3.27
1.08
1.09
f1 (ppm)

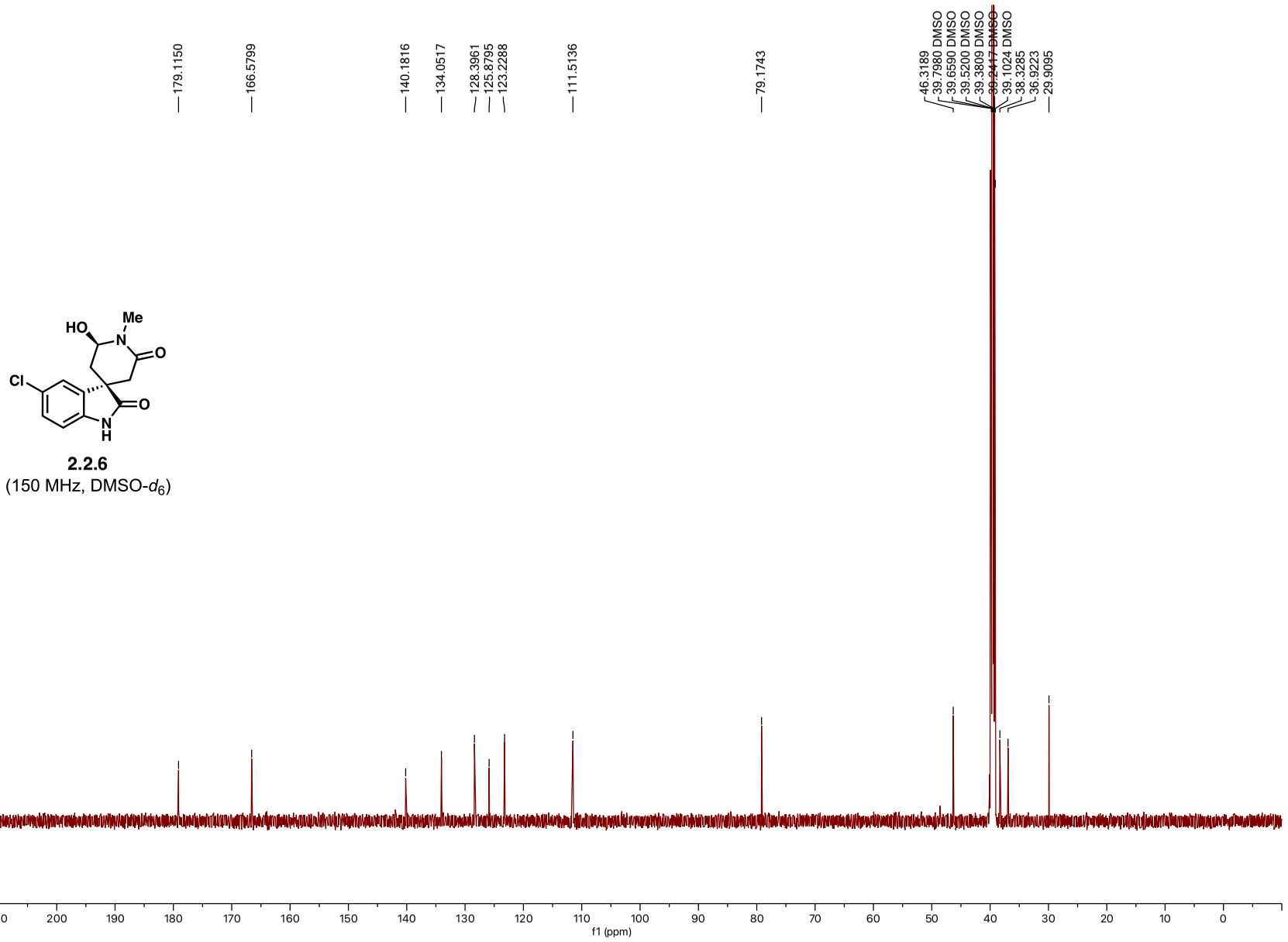
2.1.6

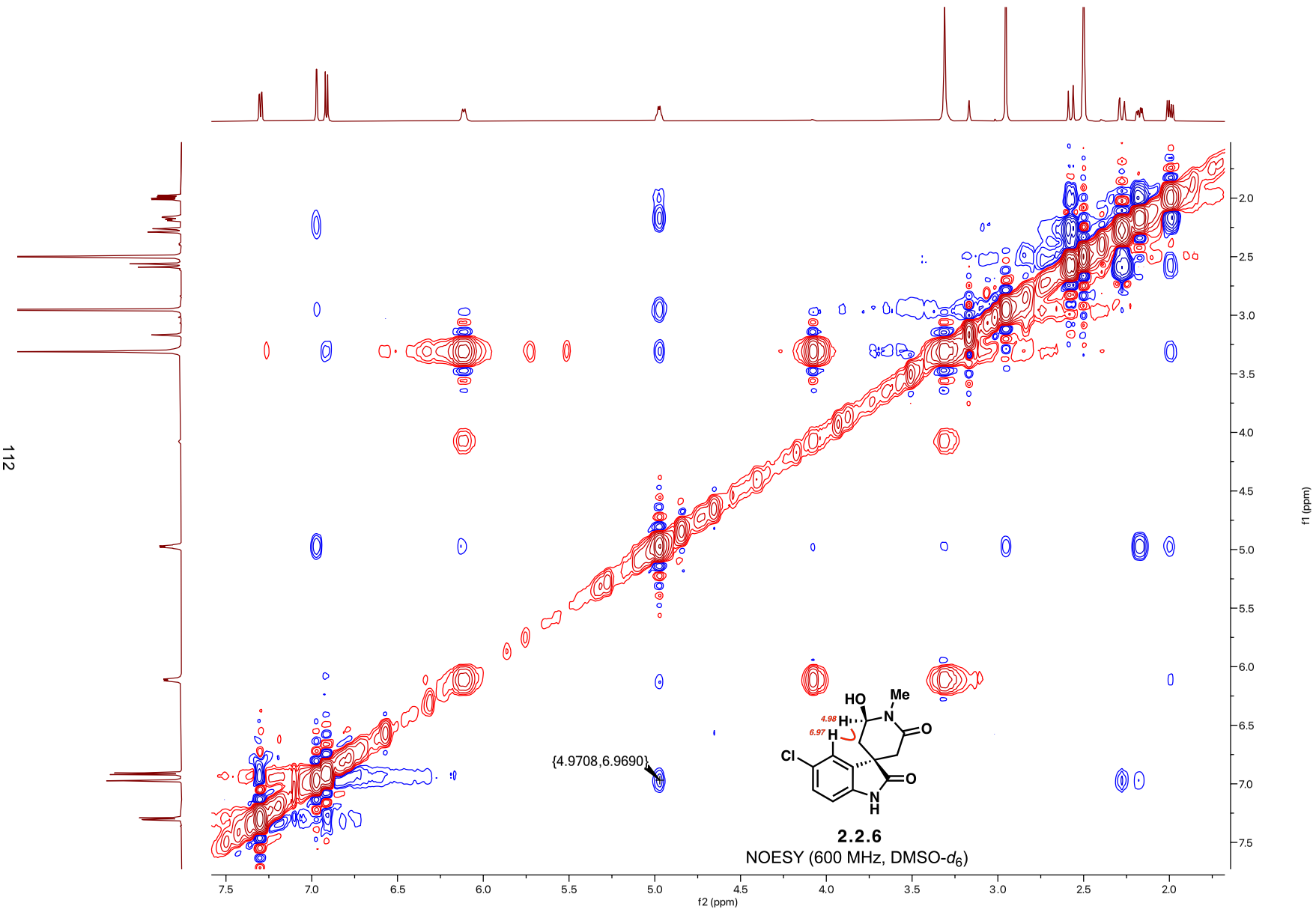

179.3316
166.5006
138.1780
134.1418
129.1519
128.7259
124.2640
111.3056
104.5604
77.3722 CDCl3
77.1600 CDCl3
76.9481 CDCl3
49.3528
39.1460
34.2686
f1 (ppm)



2.2.6

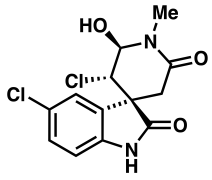
(600 MHz, DMSO-d_6)


179.1150
166.5799
140.1816
134.0517
128.3961
125.8795
123.2288
111.5136
79.1743
46.3189
39.7980 DMSO
39.6590 DMSO
39.5200 DMSO
39.3809 DMSO
39.2417 DMSO
39.1024 DMSO
38.3285
36.9223
29.9095
HO
Me
N
O
Cl
O
N
H
2.2.6
(150 MHz, DMSO-d_6)
f1 (ppm)



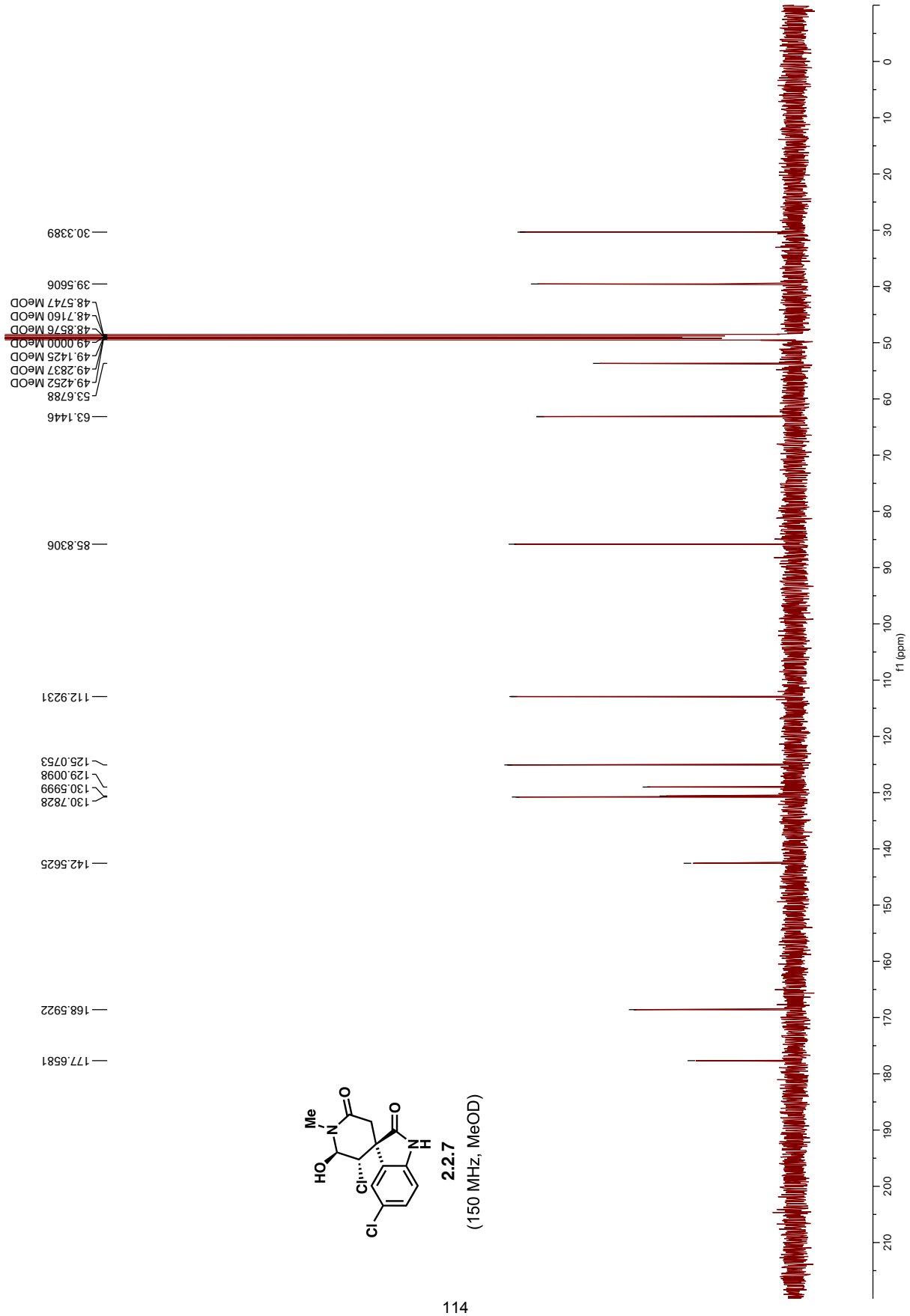
2.2.6

NOESY (600 MHz, DMSO-d_6)



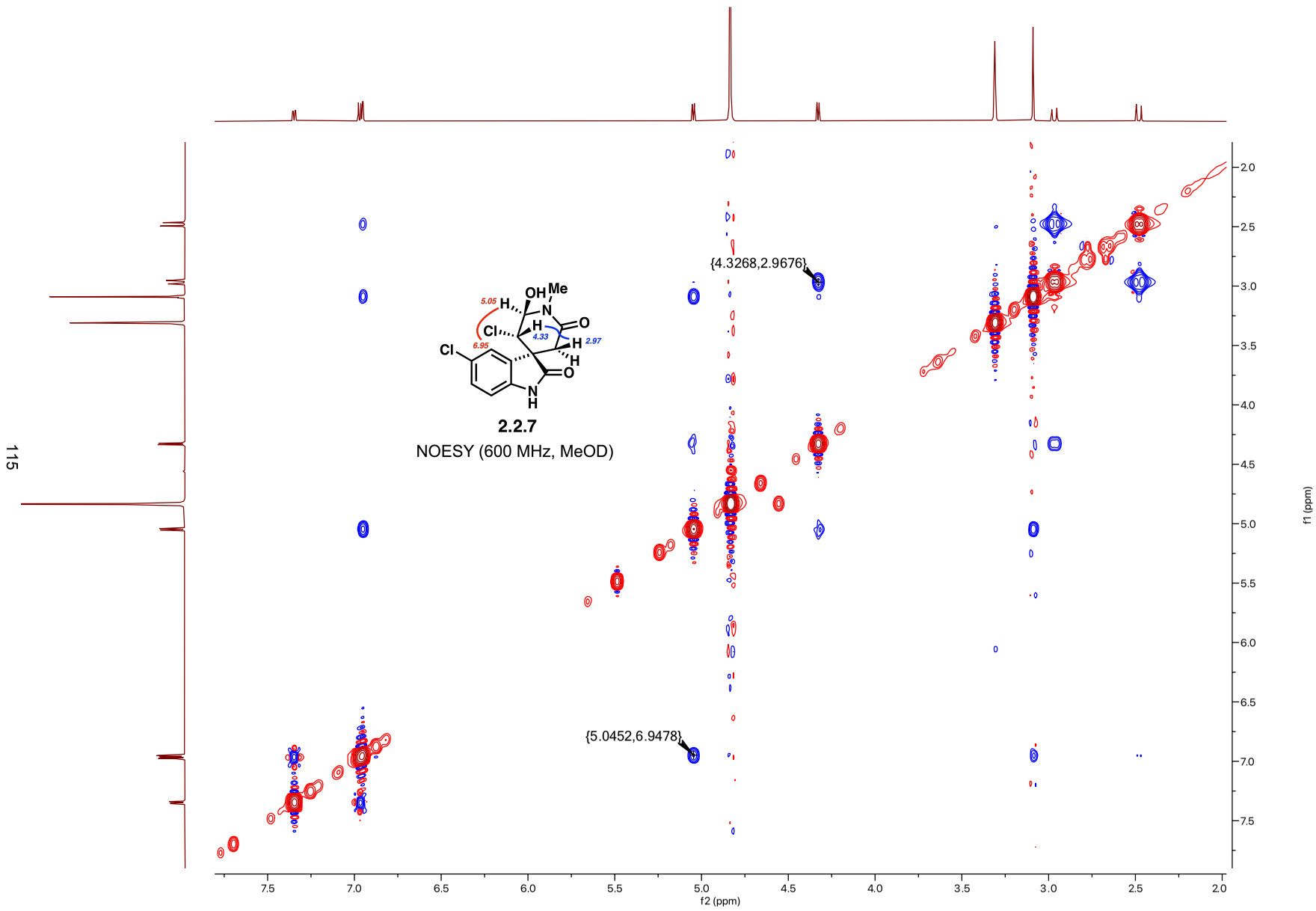
2.2.7

(600 MHz, MeOD)



2.2.7

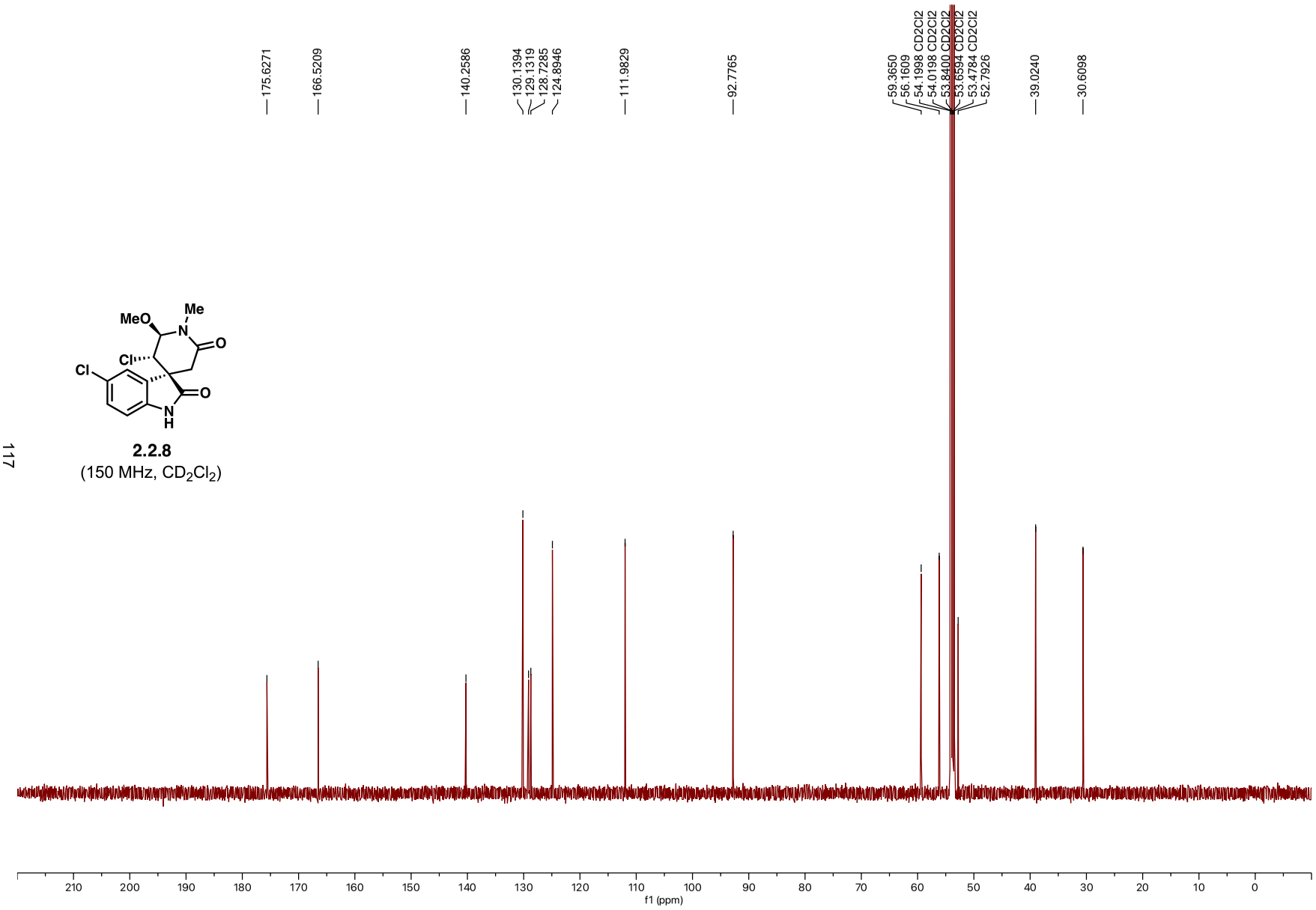
(150 MHz, MeOD)

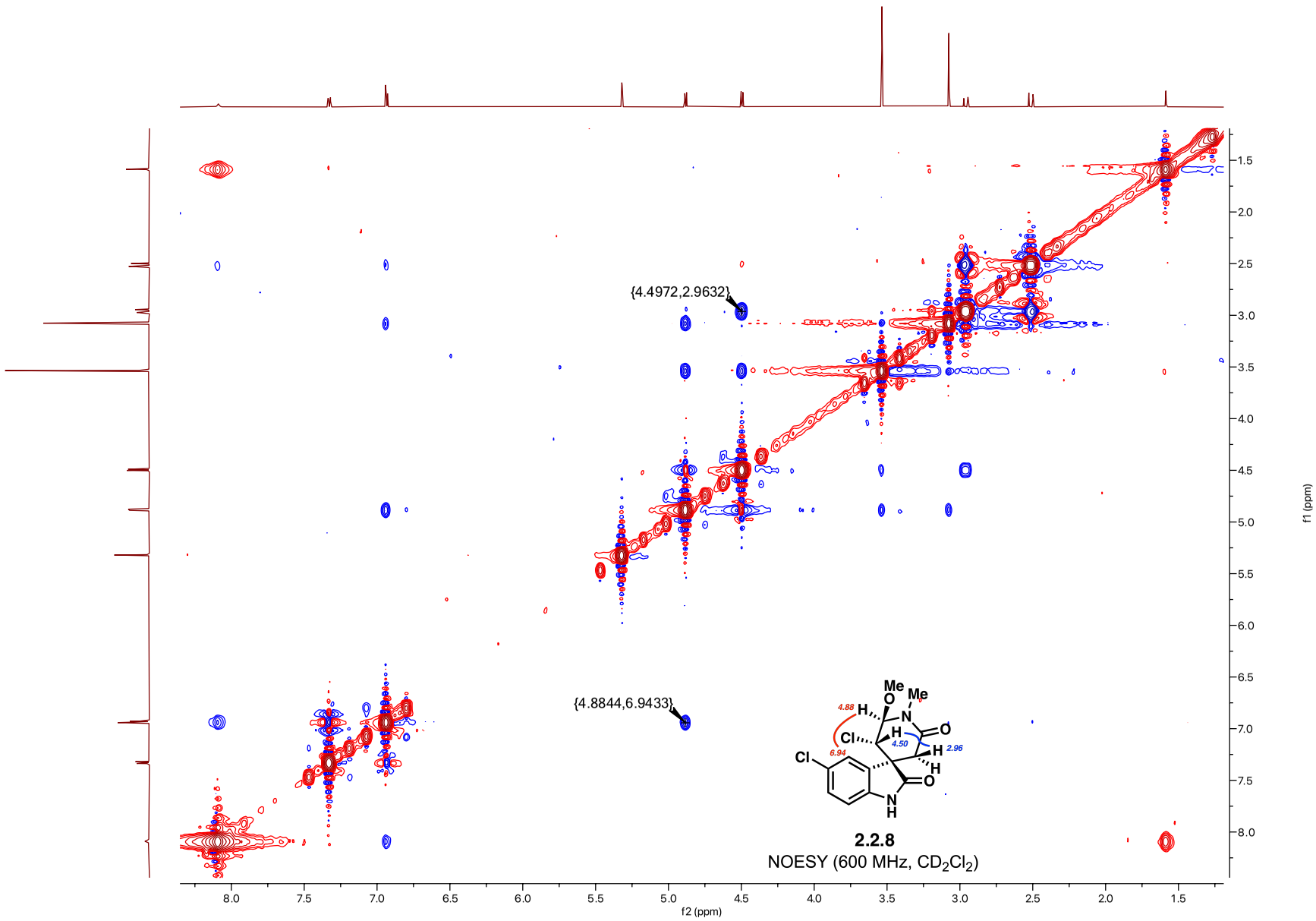


2.2.7

NOESY (600 MHz, MeOD)

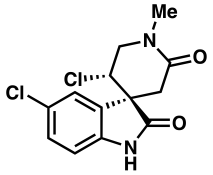
2.2.8
(600 MHz, CD_2Cl_2)


175.6271
166.5209
140.2586
130.1394
129.1319
128.7285
124.8946
111.9829
92.7765
59.3650
56.1609
54.1998 CD2Cl2
54.0198 CD2Cl2
53.8400 CD2Cl2
53.6594 CD2Cl2
53.4784 CD2Cl2
52.7926
39.0240
30.6098
MeO
Me
N
O
Cl
Cl
O
N
H
2.2.8
(150 MHz, CD2Cl2)
f1 (ppm)

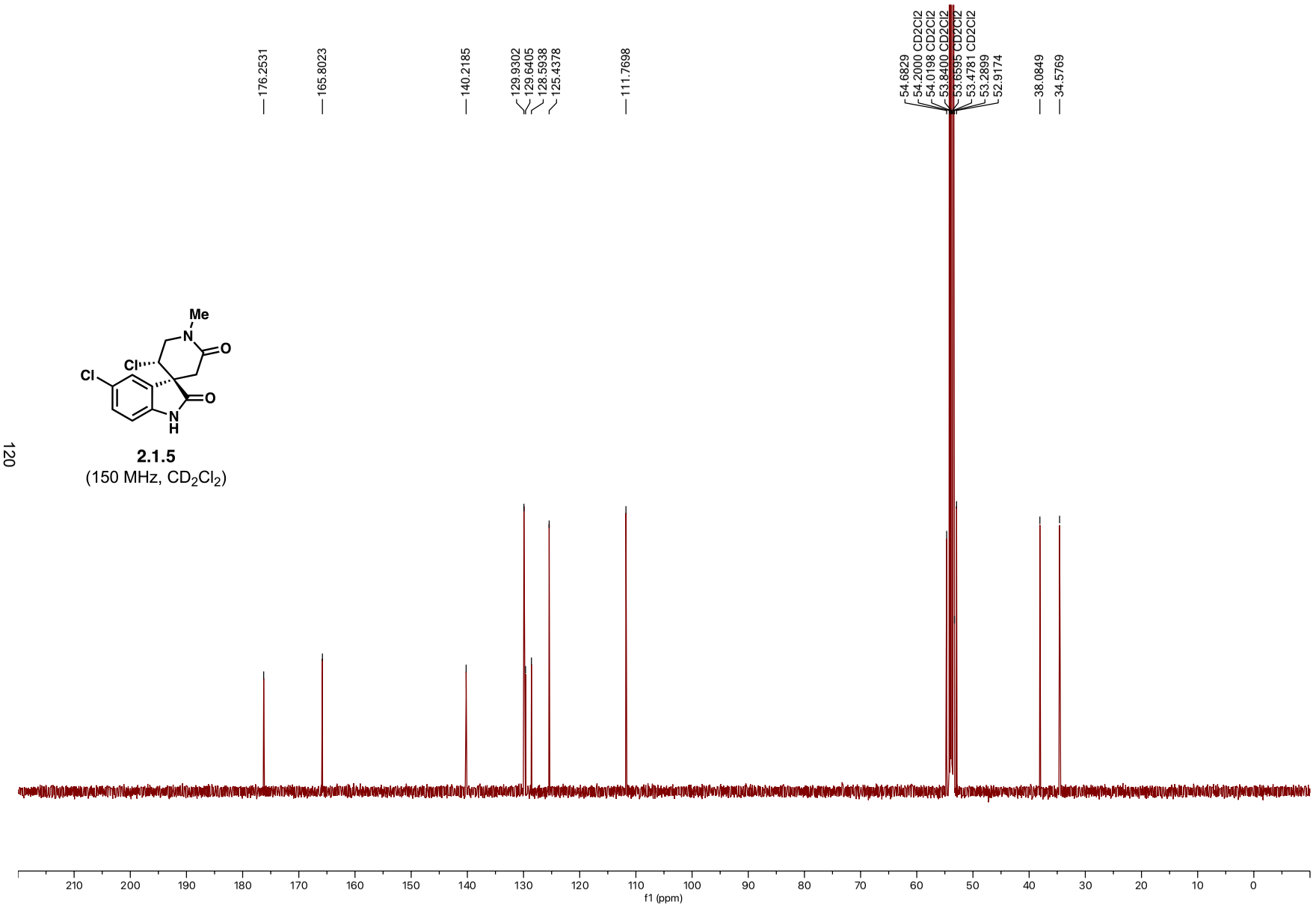


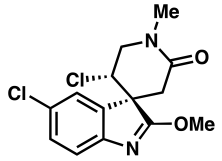
2.2.8

NOESY (600 MHz, CD_2Cl_2)



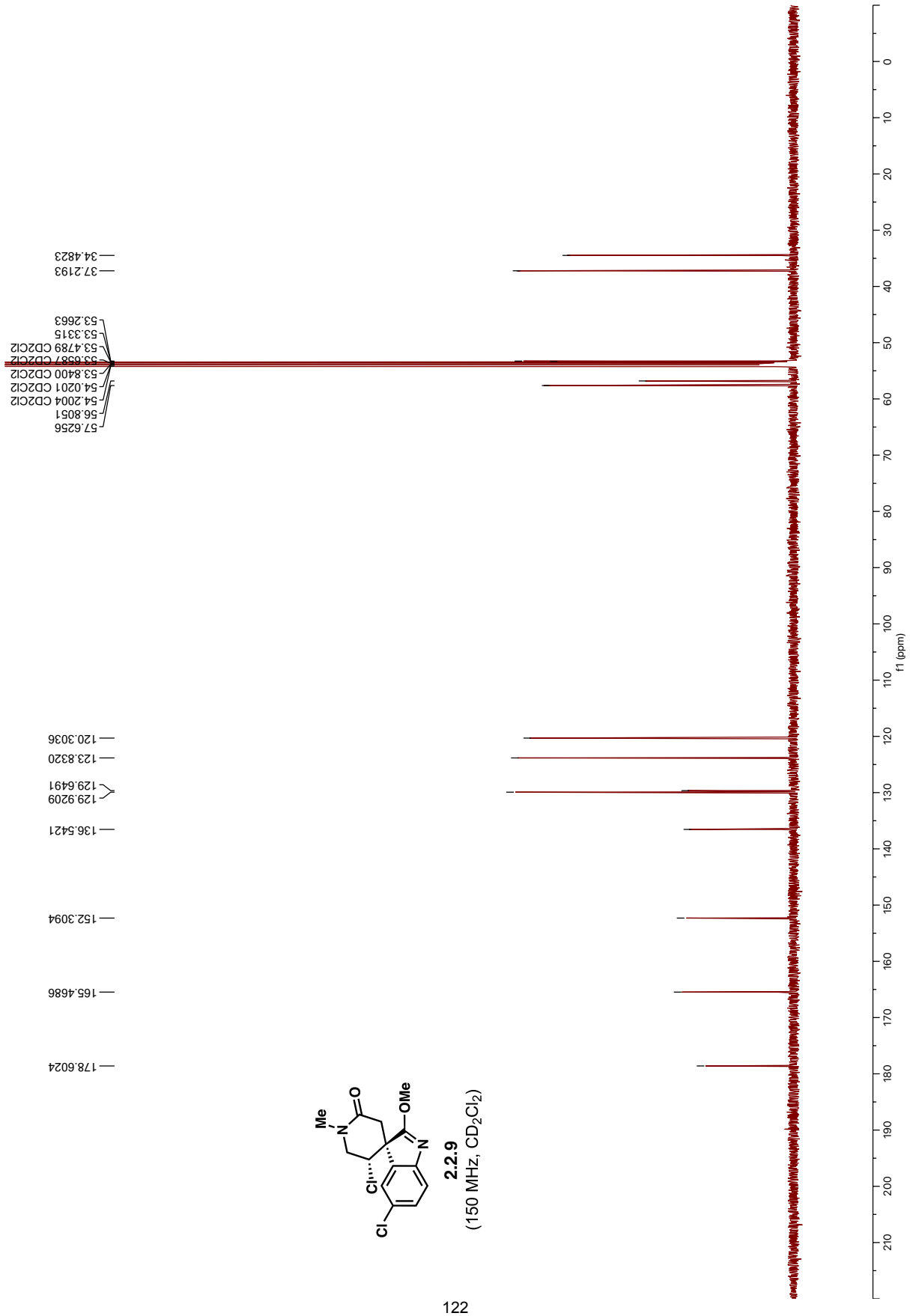
2.1.5
(600 MHz, CD_2Cl_2)

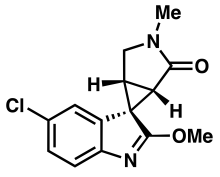

176.2531
165.8023
140.2185
129.9302
129.6405
128.5938
125.4378
111.7698
54.6829
54.2000 CD2Cl2
54.0198 CD2Cl2
53.8400 CD2Cl2
53.6595 CD2Cl2
53.4781 CD2Cl2
53.2899
52.9174
38.0849
34.5769
Me
N
O
Cl
Cl
O
N
H
2.1.5
(150 MHz, CD2Cl2)
120
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



2.2.9

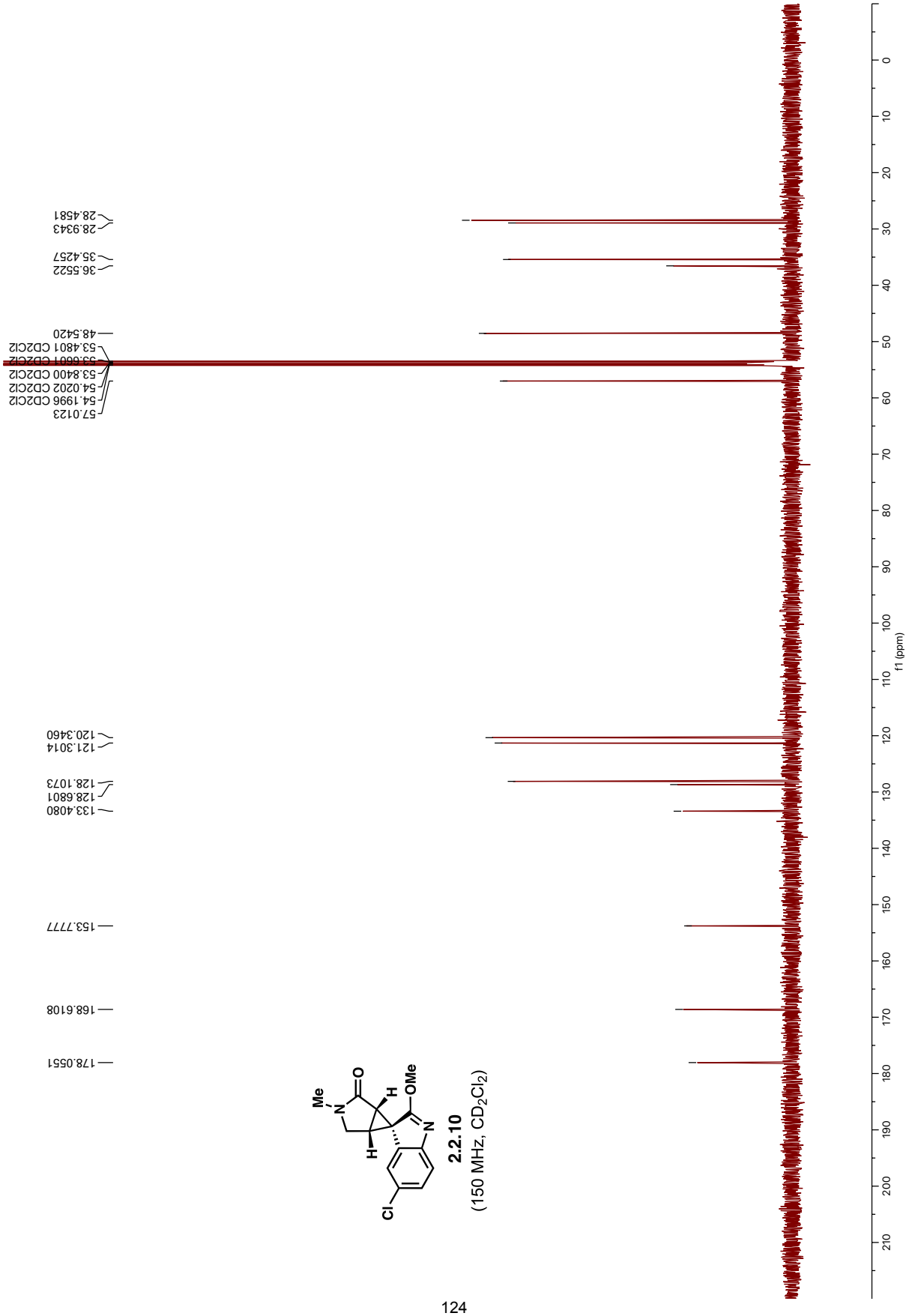
(600 MHz, CD_2Cl_2)


178.6024
165.4686
152.3094
136.5421
129.9209
129.6491
123.8320
120.3036
57.6256
56.8051
54.2004 CD2Cl2
54.0201 CD2Cl2
53.8400 CD2Cl2
53.6587 CD2Cl2
53.4789 CD2Cl2
53.3315
53.2663
37.2193
34.4823
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
Me
N
O
OMe
N
Cl
Cl
2.2.9
(150 MHz, CD2Cl2)



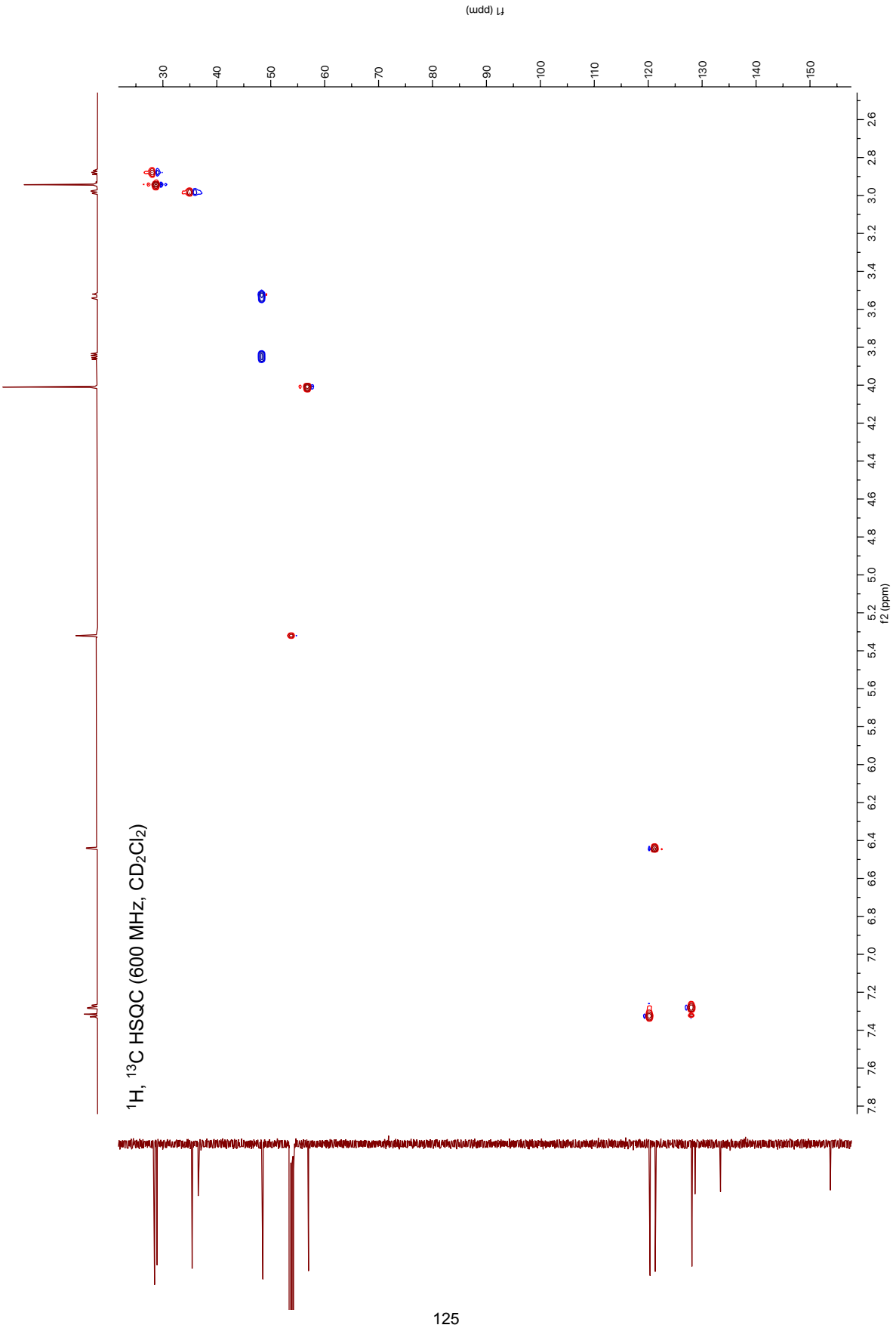
2.2.10

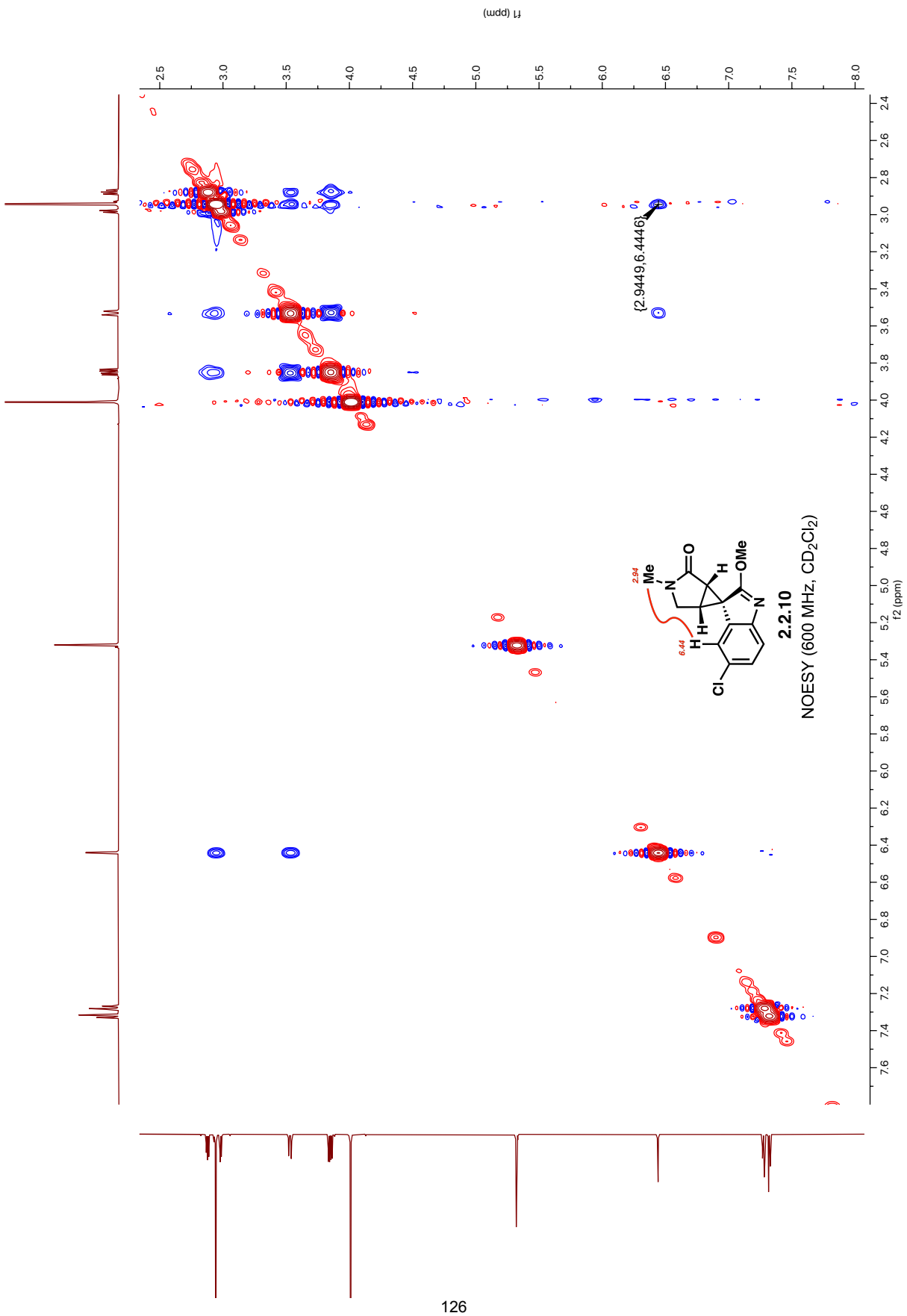
(600 MHz, CD_2Cl_2)

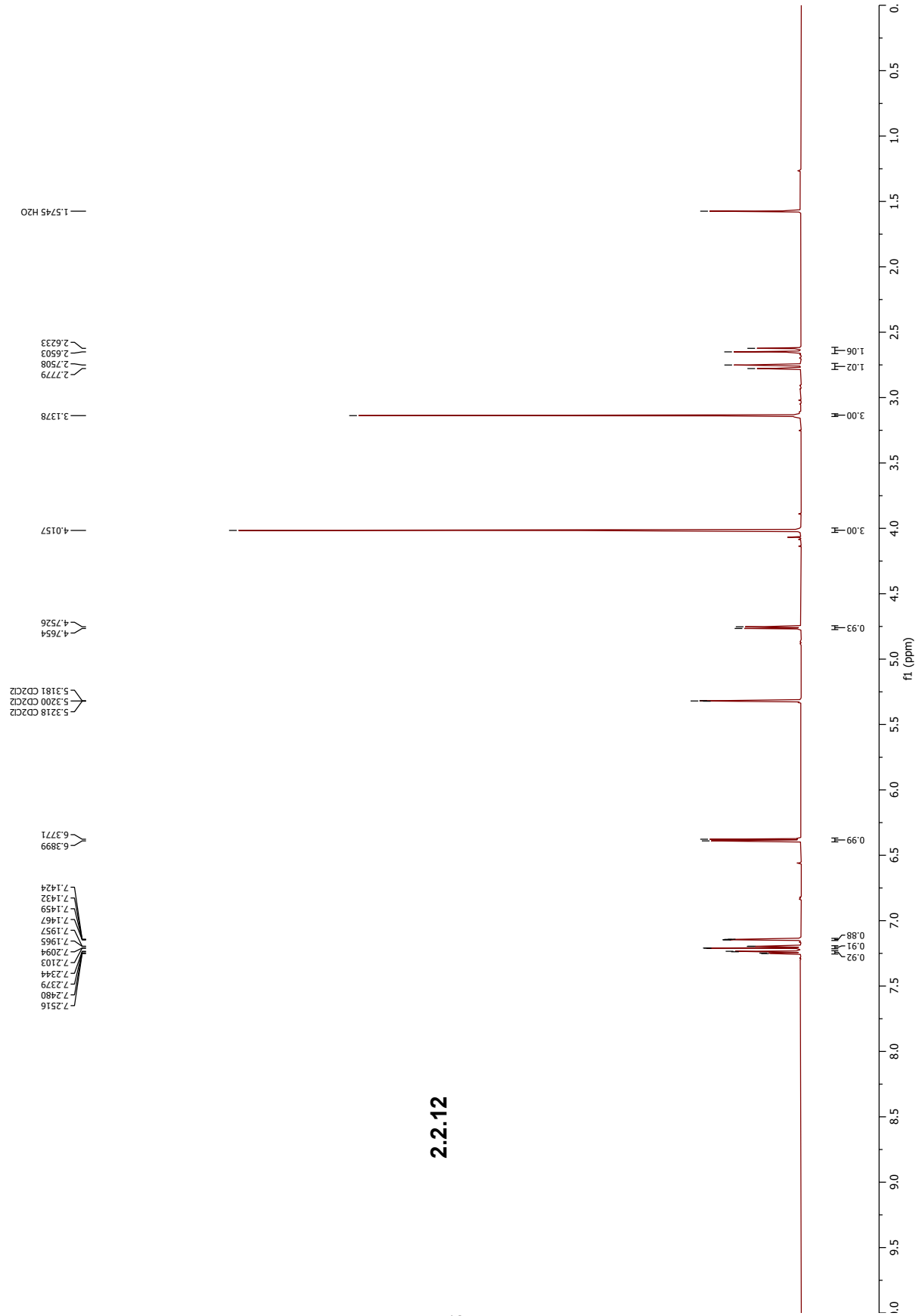


2.2.10

(150 MHz, CD_2Cl_2)

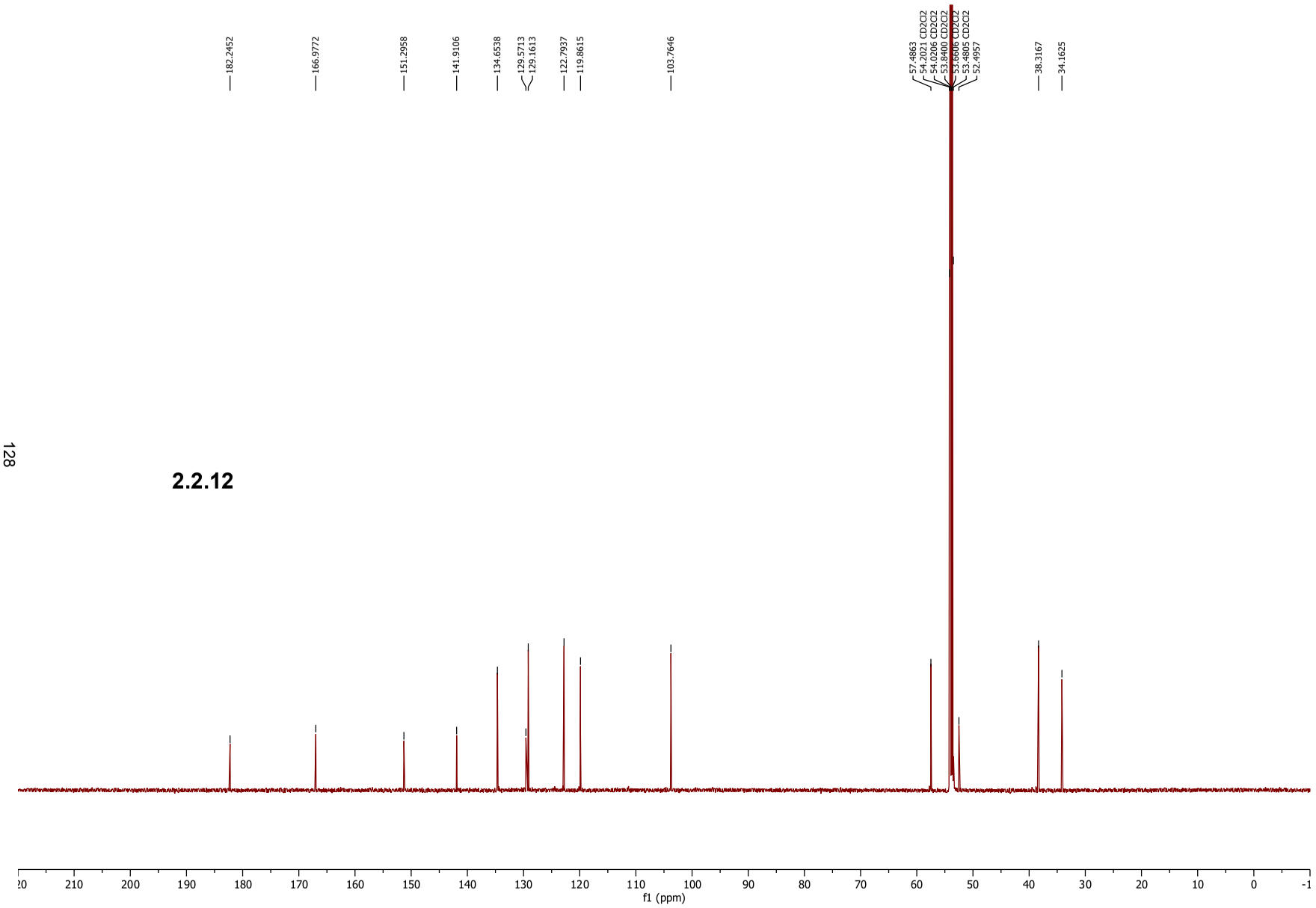

^{1}H, ^{13}C HSQC (600 MHz, CD_2Cl_2)
f2 (ppm)
f1 (ppm)

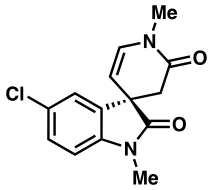

f1 (ppm)
f2 (ppm)
{2.9449,6.4446}
2.94
6.44
Me
N
O
H
OMe
N
H
Cl
2.2.10
NOESY (600 MHz, CD_2Cl_2)


7.2516
7.2480
7.2379
7.2344
7.2103
7.2094
7.1965
7.1957
7.1467
7.1459
7.1432
7.1424
6.3899
6.3771
5.3218 CDZCl2
5.3200 CDZCl2
5.3181 CDZCl2
4.7654
4.7526
4.0157
3.1378
2.7779
2.7508
2.6503
2.6233
1.5745 H2O
0.92
0.91
0.88
0.99
3.00
0.93
3.00
3.00
1.02
1.06
f1 (ppm)

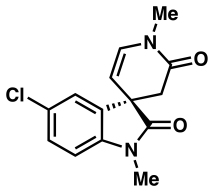
2.2.12

2.2.12


182.2452
166.9772
151.2958
141.9106
134.6538
129.5713
129.1613
122.7937
119.8615
103.7646
57.4863
54.2021 CD2Cl2
54.0206 CD2Cl2
53.8400 CD2Cl2
53.6606 CD2Cl2
53.4805 CD2Cl2
52.4957
38.3167
34.1625
f1 (ppm)

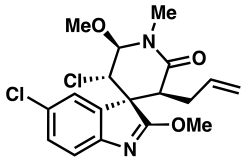


2.2.11
(600 MHz, THF-d_8)



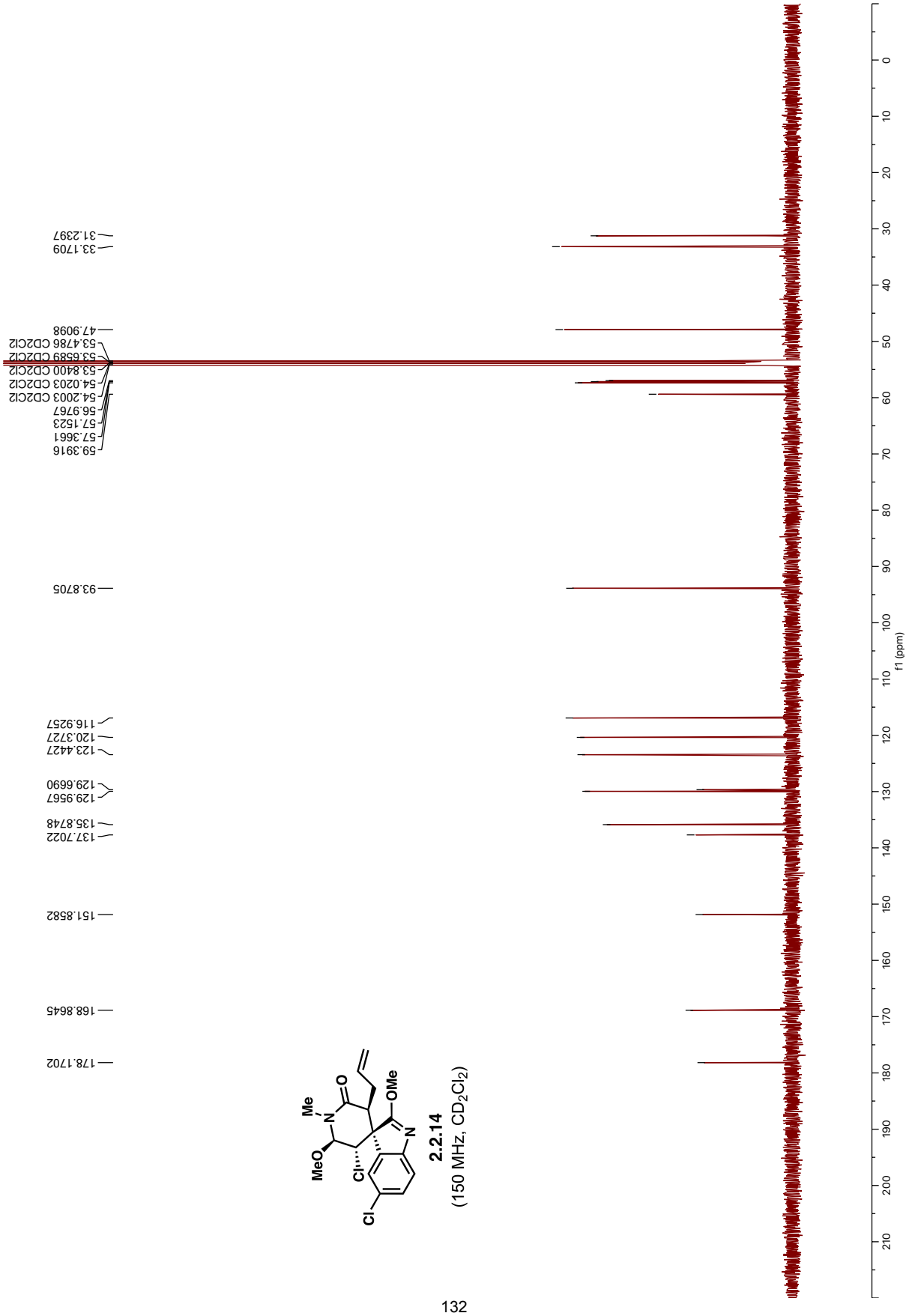
2.2.11

(150 MHz, THF-d_8)



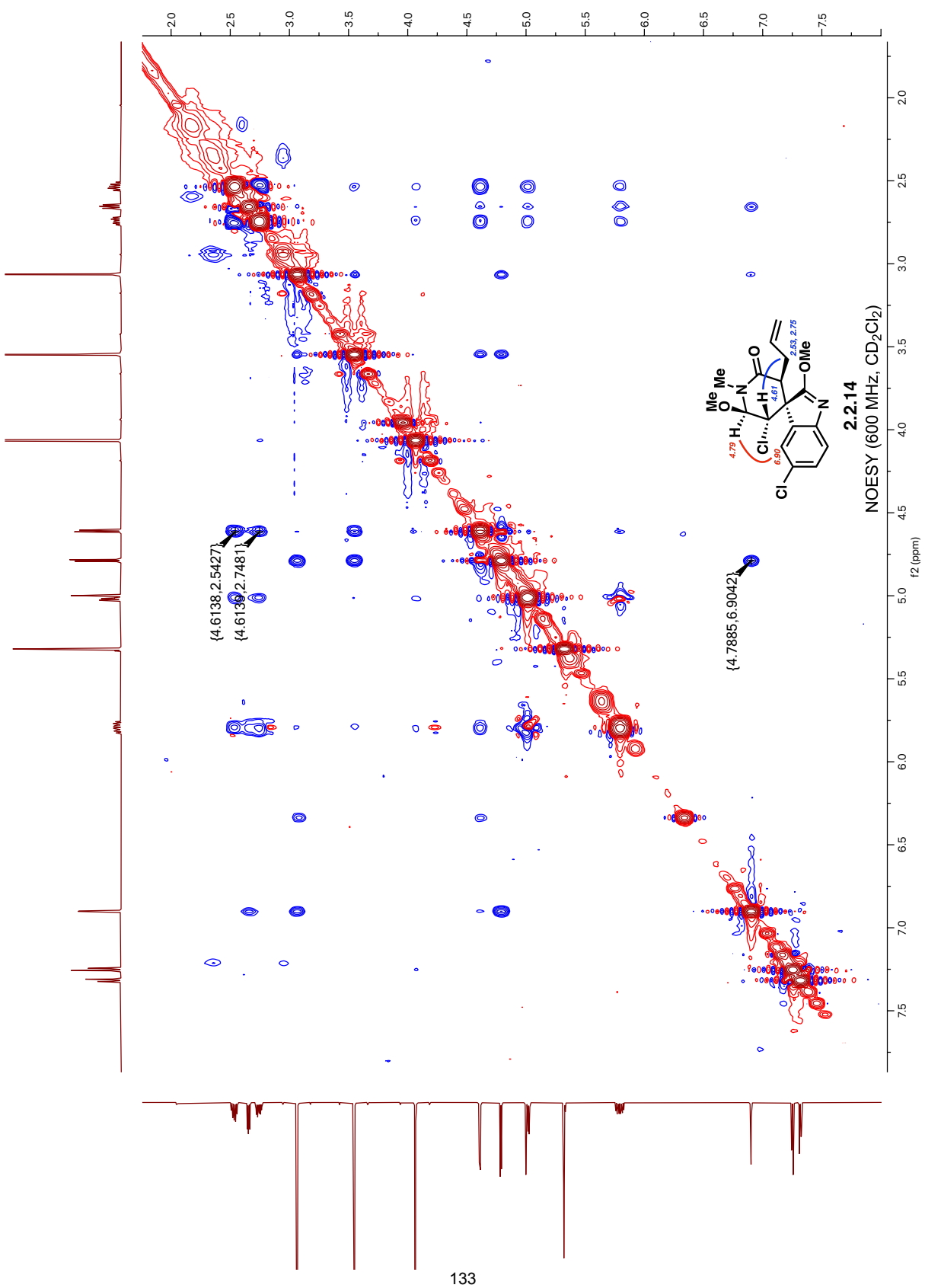
2.2.14

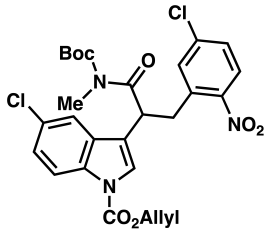
(600 MHz, CD_2Cl_2)



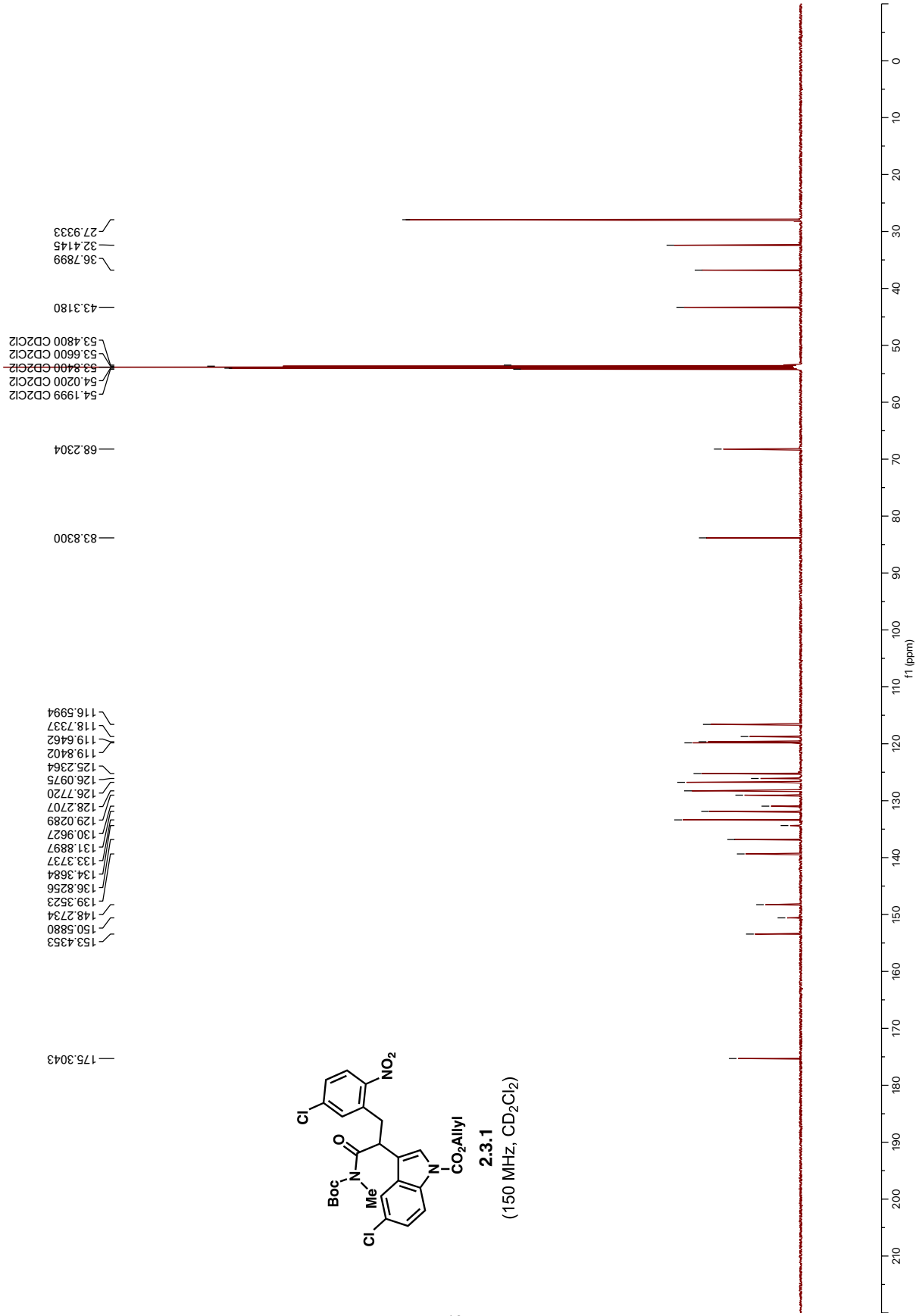
2.2.14

(150 MHz, CD_2Cl_2)


f1 (ppm)
f2 (ppm)
{4.6138,2.5427}
{4.6139,2.7481}
{4.7885,6.9042}
2.2.14
NOESY (600 MHz, CD2Cl2)
Me
Me
O
N
O
H
4.61
2.53, 2.75
OMe
N
4.79
H
Cl
6.90
Cl

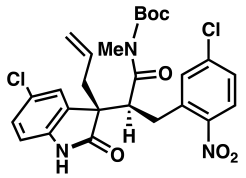


2.3.1
(600 MHz, CD_2Cl_2)



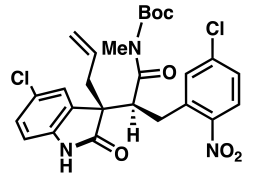
2.3.1

(150 MHz, CD_2Cl_2)



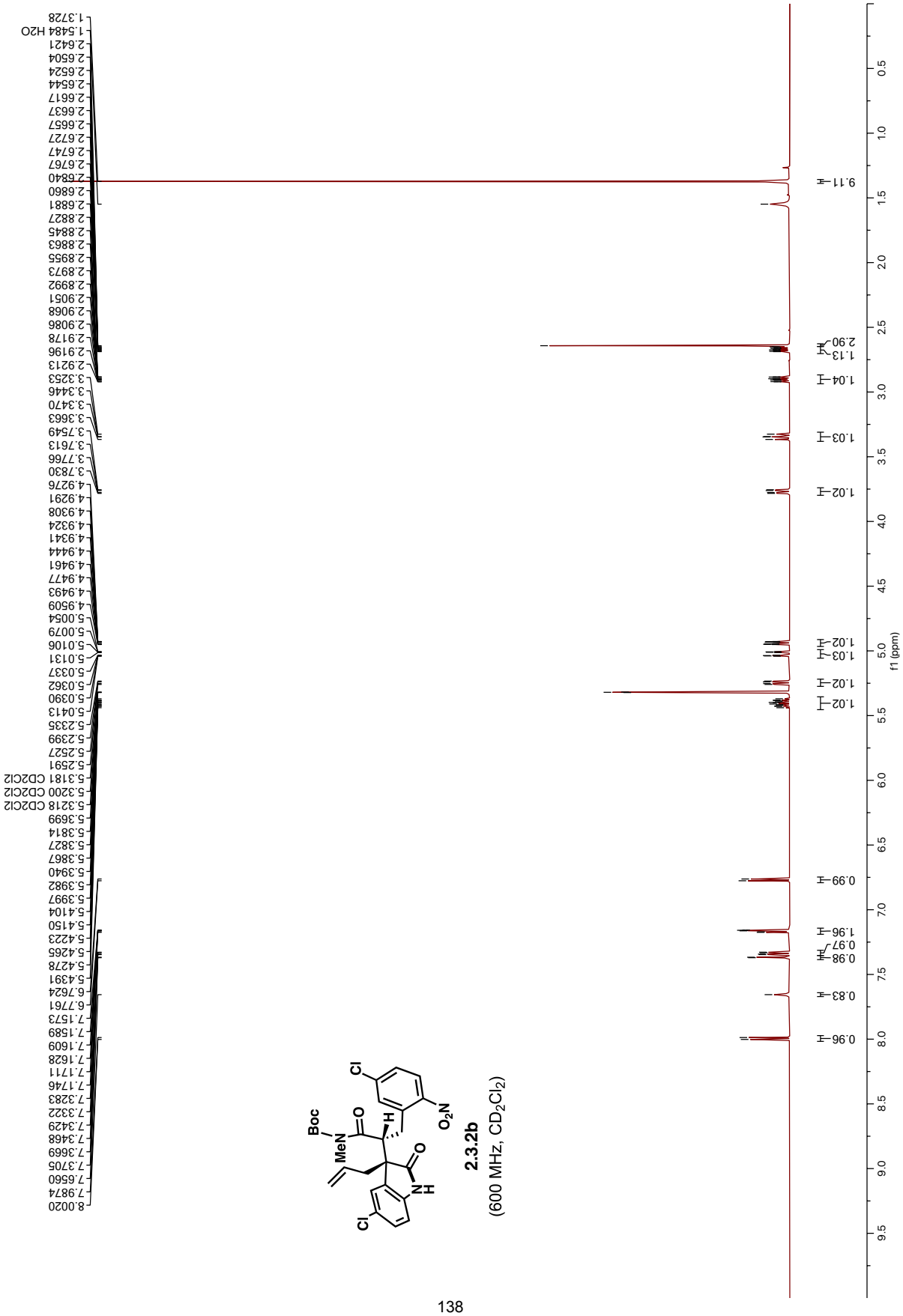
2.3.2a

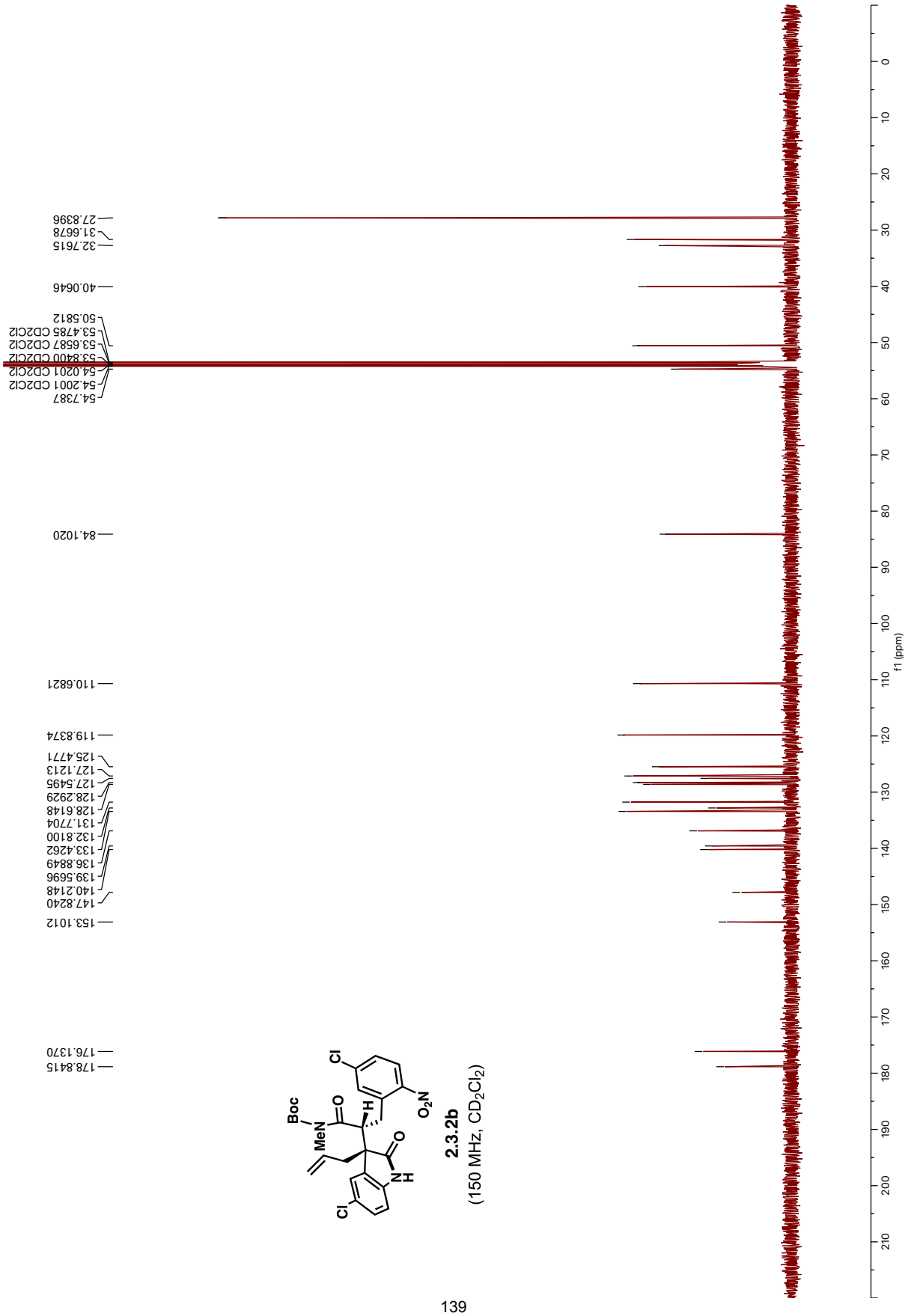
(600 MHz, CD_2Cl_2)



2.3.2a

(150 MHz, CD_2Cl_2)

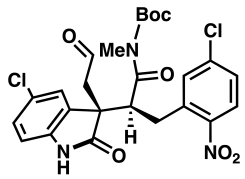

Boc
MeN
O
H
O
N
H
Cl
Cl
O2N
2.3.2b
(600 MHz, CD2Cl2)
f1 (ppm)



2.3.2b

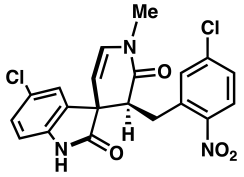
(150 MHz, CD_2Cl_2)

SI-3a
(600 MHz, CD_2Cl_2)

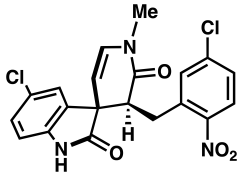


SI-3a

(150 MHz, CD_2Cl_2)

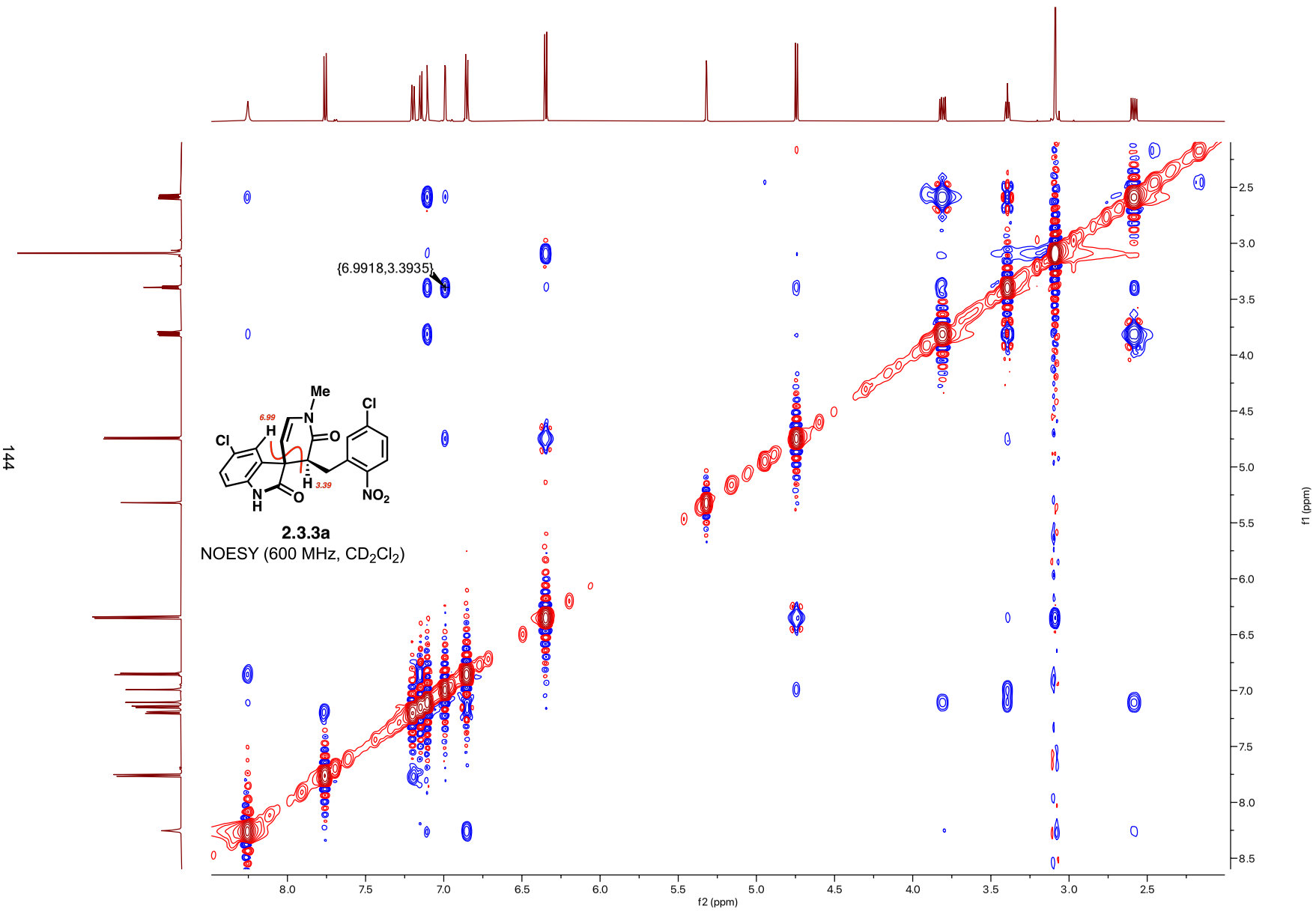


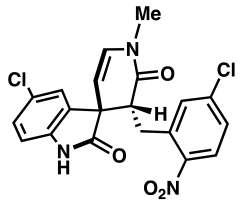
2.3.3a
(600 MHz, CD_2Cl_2)



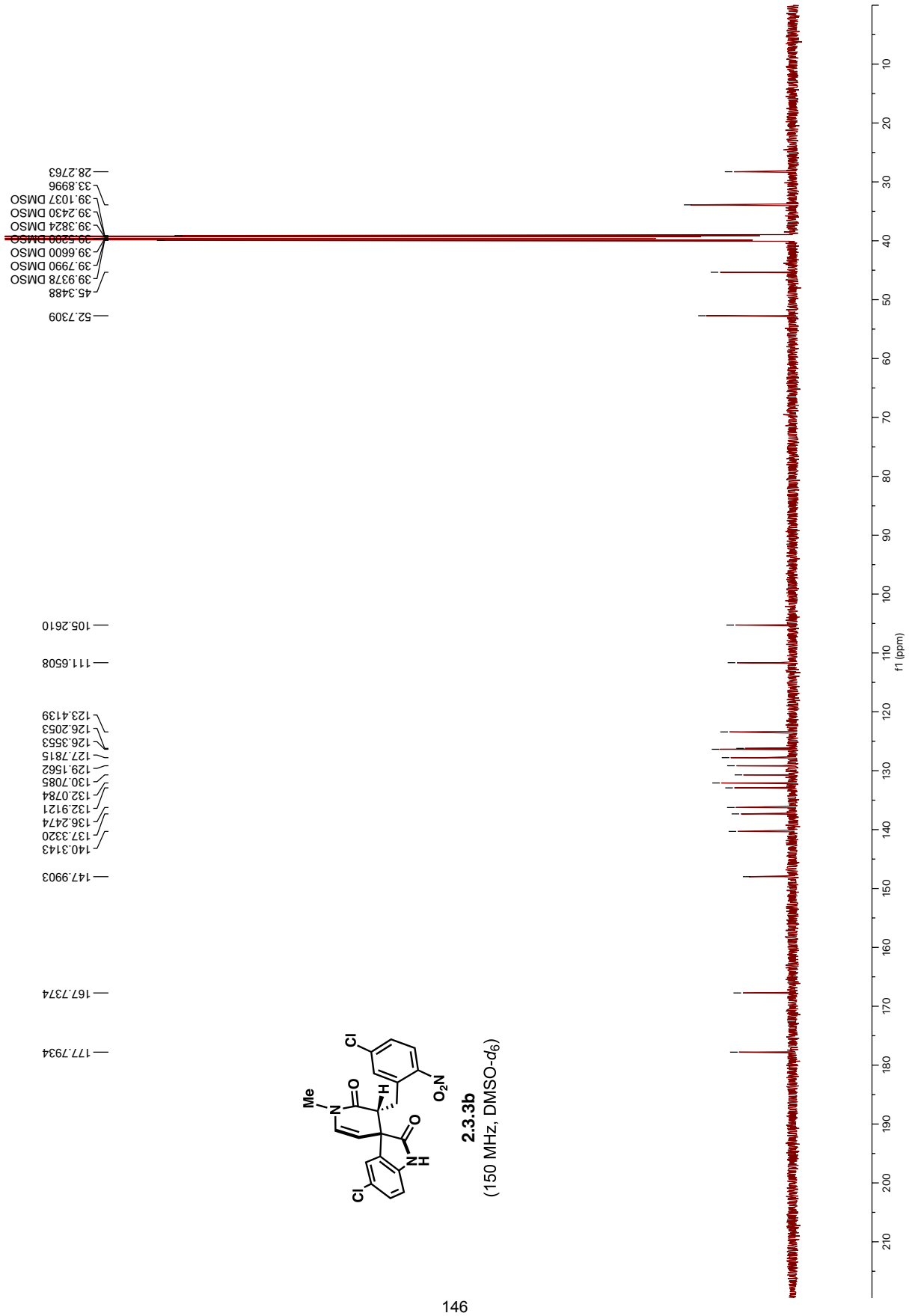
2.3.3a

(150 MHz, CD_2Cl_2)


{6.9918,3.3935}
Me
N
O
Cl
6.99
H
Cl
H
3.39
N
H
O
NO2
2.3.3a
NOESY (600 MHz, CD2Cl2)
f2 (ppm)
f1 (ppm)

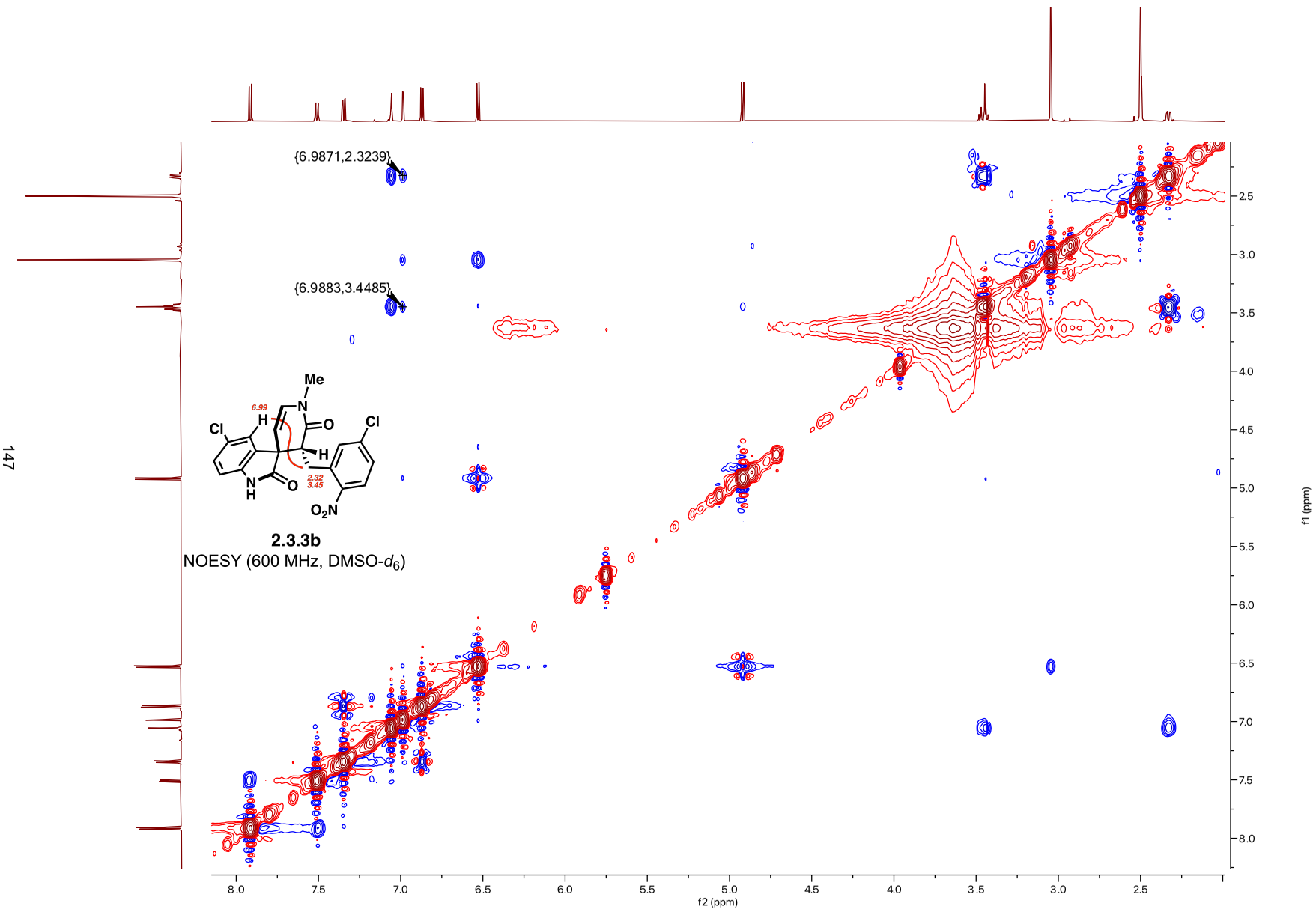


2.3.3b
(600 MHz, DMSO-d_6)



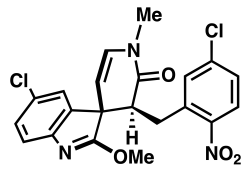
2.3.3b

(150 MHz, DMSO-d_6)

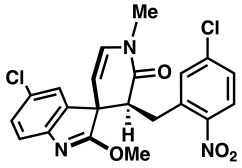


2.3.3b

NOESY (600 MHz, DMSO-d_6)

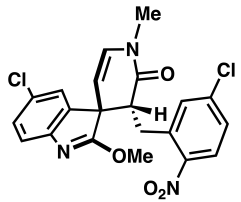


2.3.4a
(600 MHz, CD_2Cl_2)



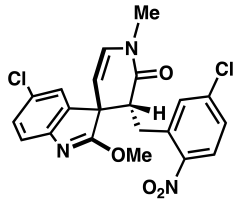
2.3.4a

(150 MHz, CD_2Cl_2)



2.3.4b

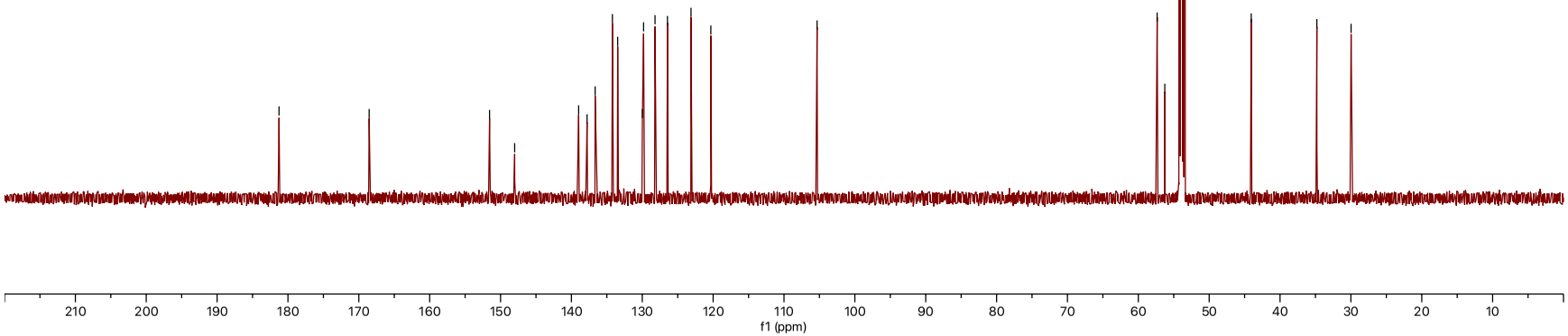
(600 MHz, CD_2Cl_2)

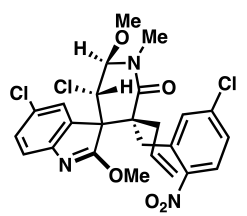


2.3.4b

(150 MHz, CD_2Cl_2)

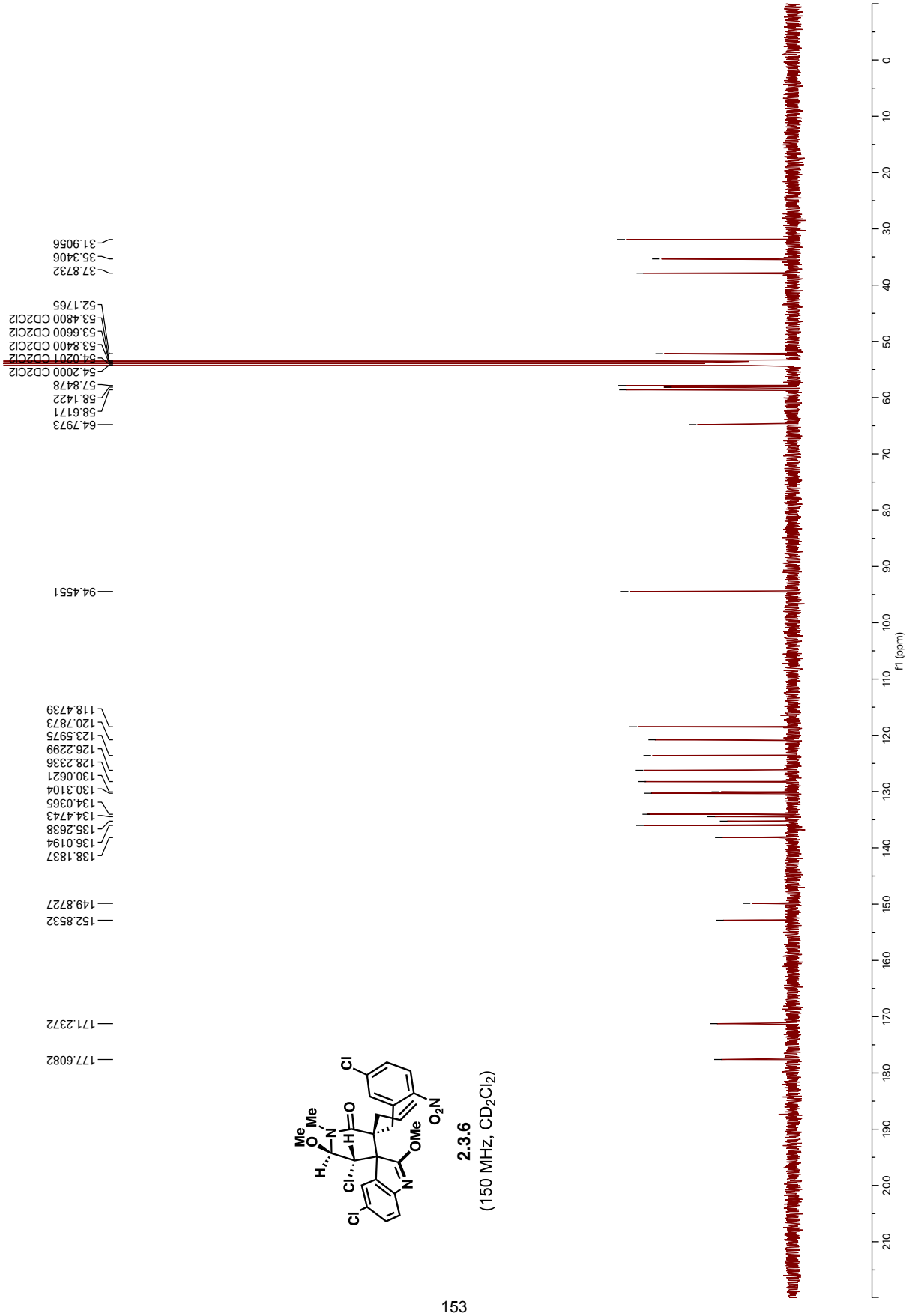
181.2617
168.5420
151.5527
148.0092
138.9792
137.7917
136.6492
134.2170
133.4700
129.9854
129.8134
128.2010
126.4458
123.1234
120.3230
105.3319
57.3431
56.2622
54.2002 CD2Cl2
54.0200 CD2Cl2
53.8400 CD2Cl2
53.6604 CD2Cl2
53.4794 CD2Cl2
44.0626
34.8034
29.9743





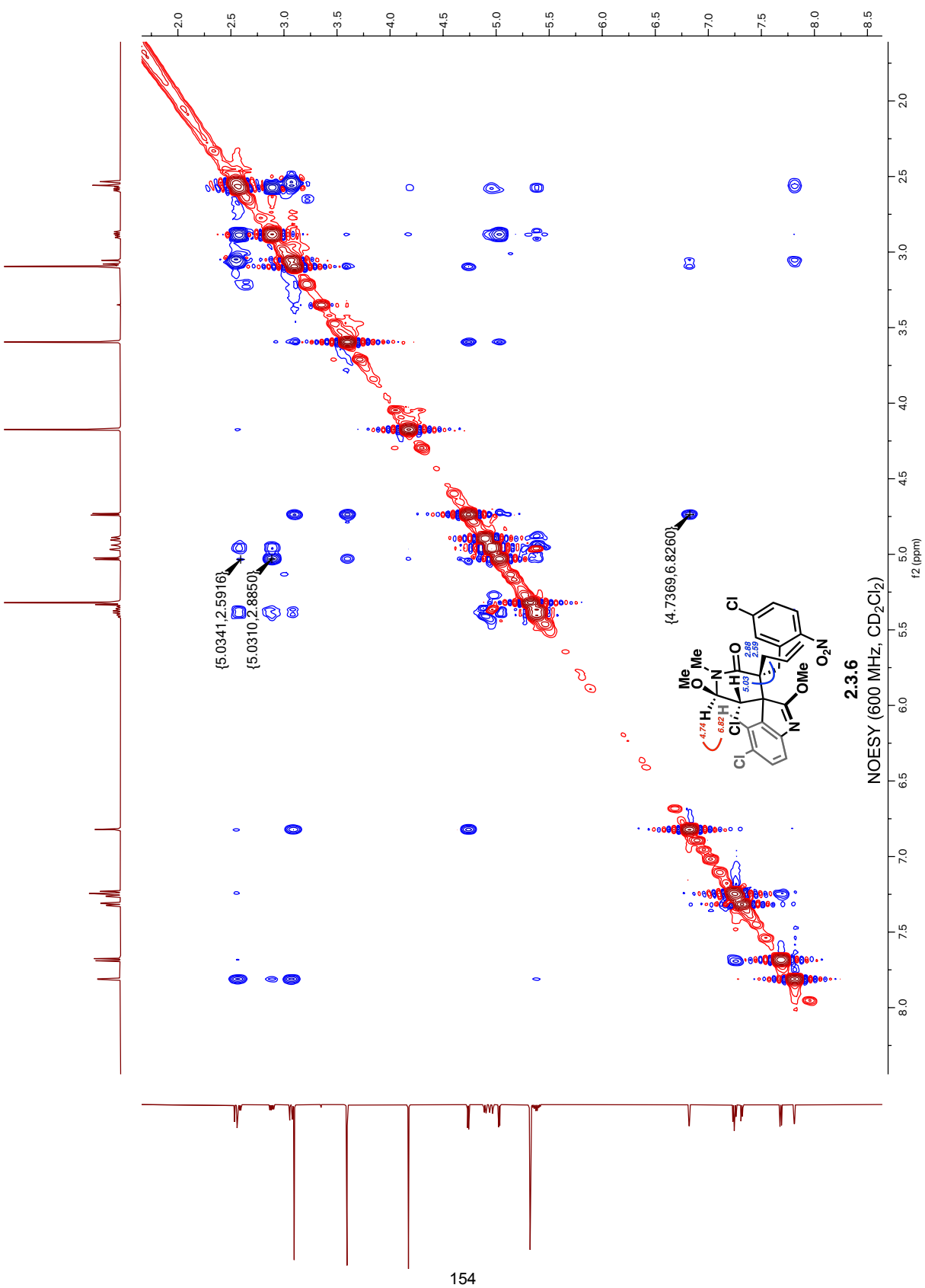
2.3.6

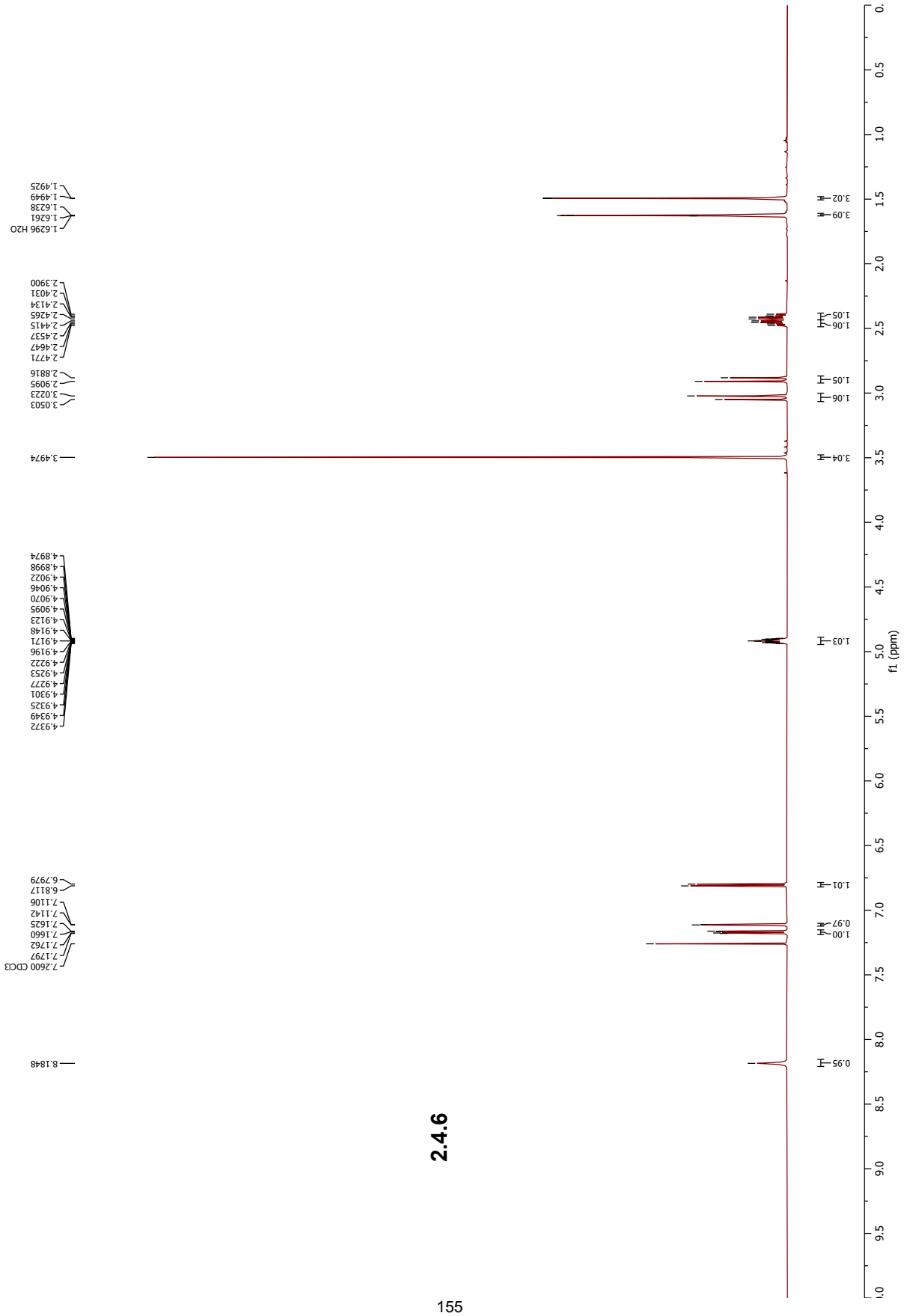
(600 MHz, CD_2Cl_2)



2.3.6

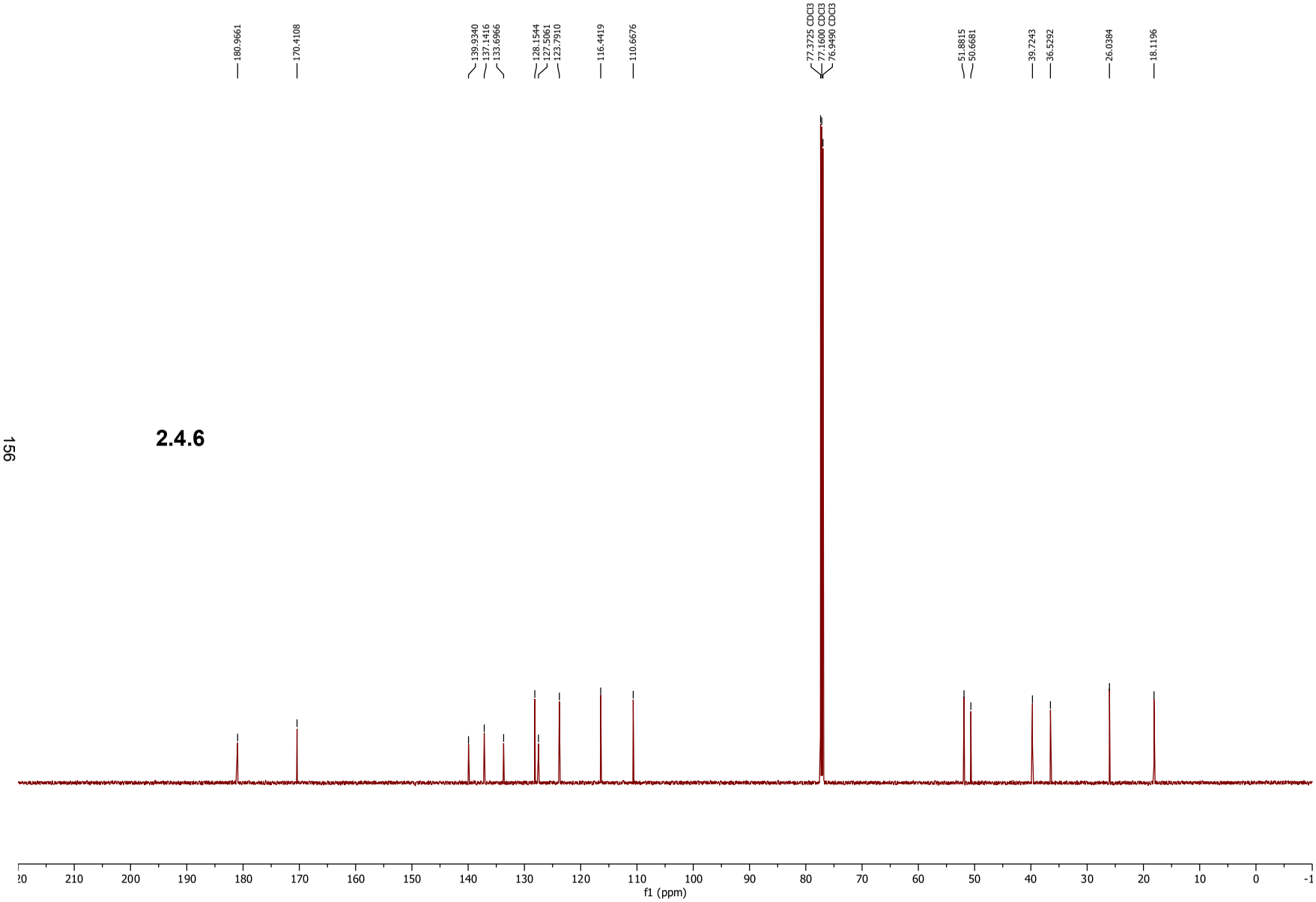
(150 MHz, CD_2Cl_2)


{5.0341,2.5916}
{5.0310,2.8850}
{4.7369,6.8260}
2.3.6
NOESY (600 MHz, CD2Cl2)
f2 (ppm)
f1 (ppm)

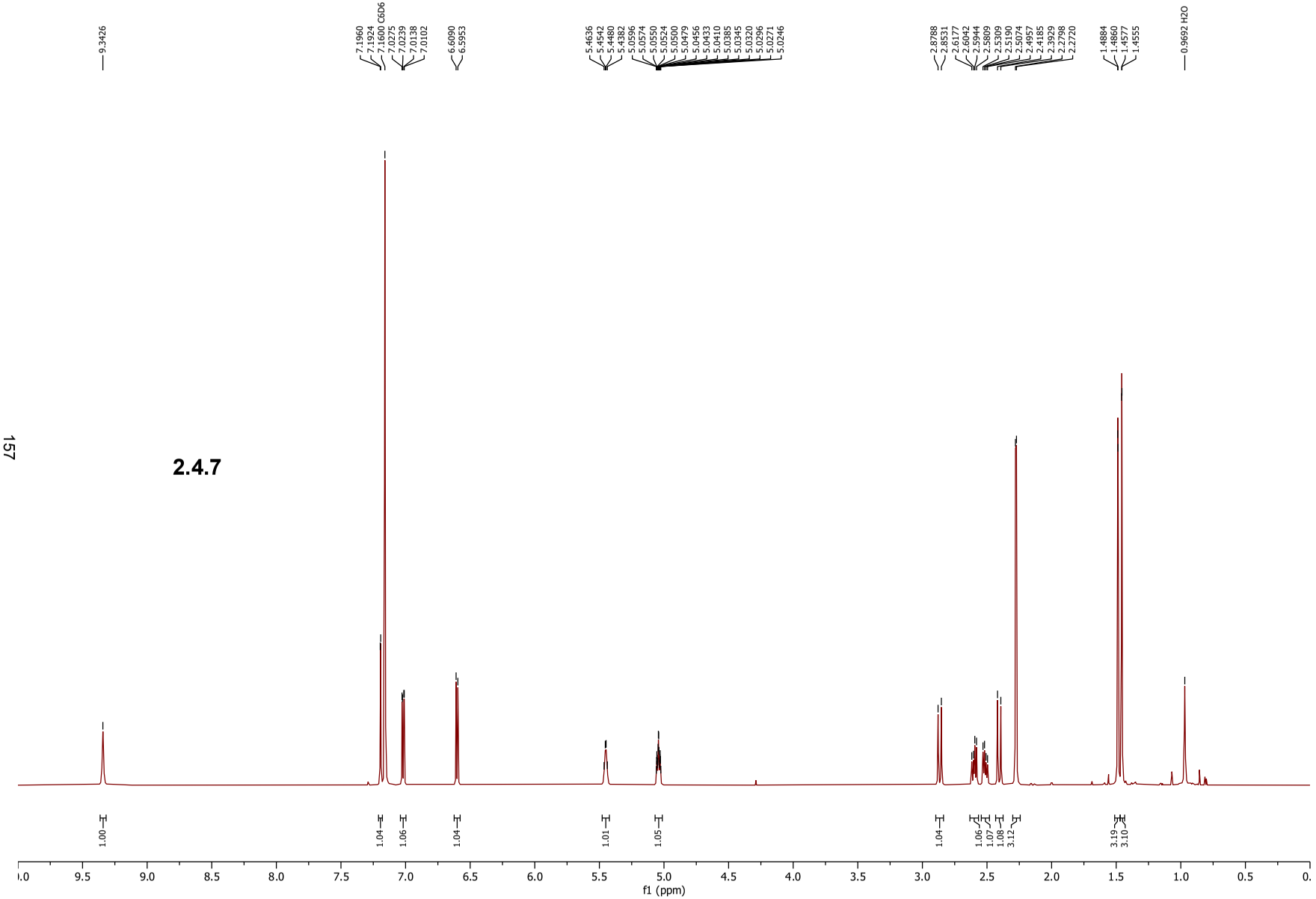

8.1848
7.2600 CDCl3
7.1797
7.1762
7.1660
7.1625
7.1142
7.1106
6.8117
6.7979
4.9372
4.9349
4.9325
4.9301
4.9277
4.9253
4.9222
4.9196
4.9171
4.9148
4.9123
4.9095
4.9070
4.9046
4.9022
4.8998
4.8974
3.4974
3.0503
3.0223
2.9095
2.8816
2.4771
2.4647
2.4537
2.4415
2.4265
2.4134
2.4031
2.3900
1.6296 H2O
1.6261
1.6238
1.4949
1.4925
0.95
1.00
0.97
1.01
1.03
3.04
1.06
1.05
1.06
1.05
3.09
3.02
f1 (ppm)

2.4.6

2.4.6

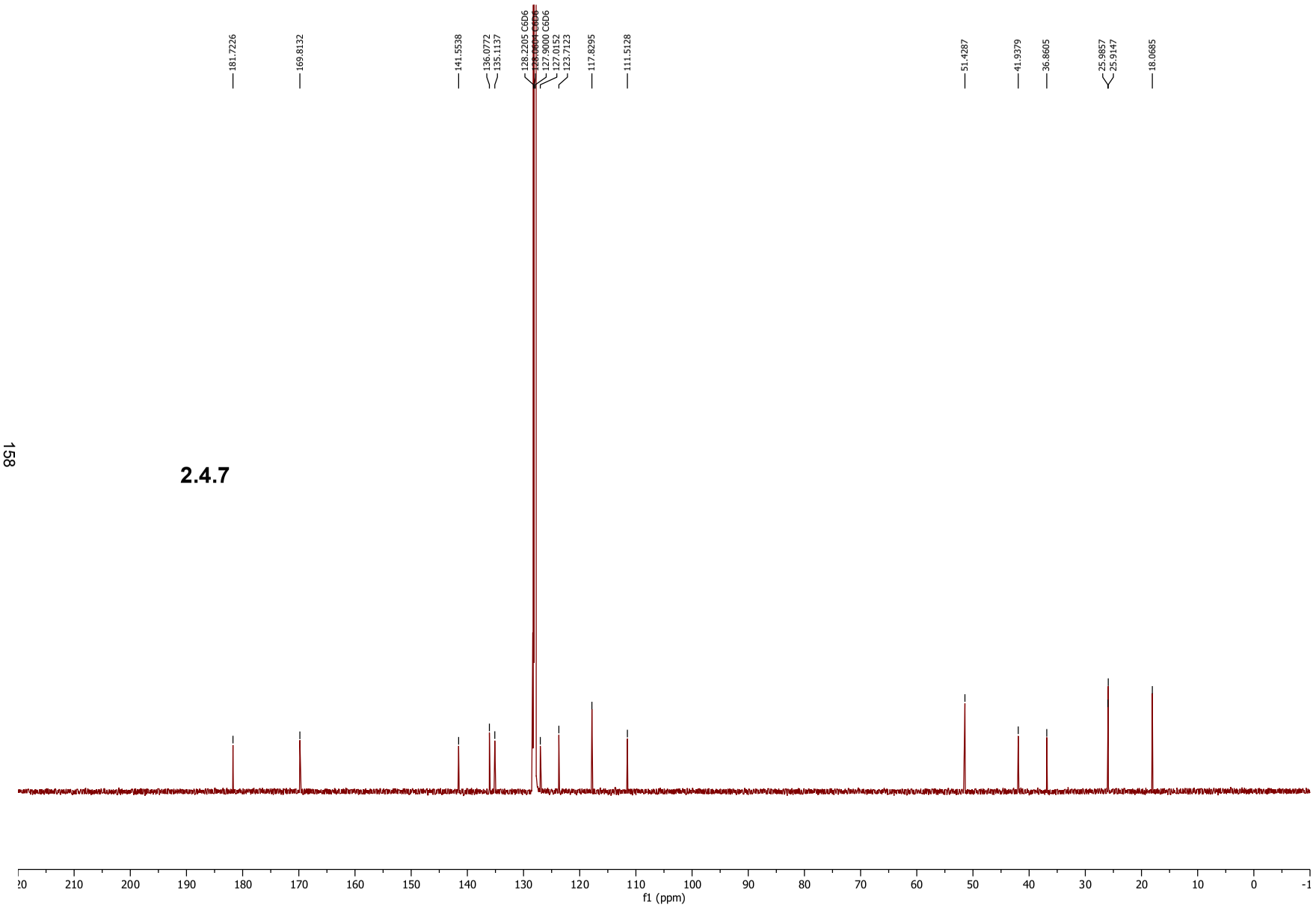

180.9661
170.4108
139.9340
137.1416
133.6966
128.1544
127.5061
123.7910
116.4419
110.6676
77.3725 CDCl3
77.1600 CDCl3
76.9490 CDCl3
51.8815
50.6681
39.7243
36.5292
26.0384
18.1196
f1 (ppm)

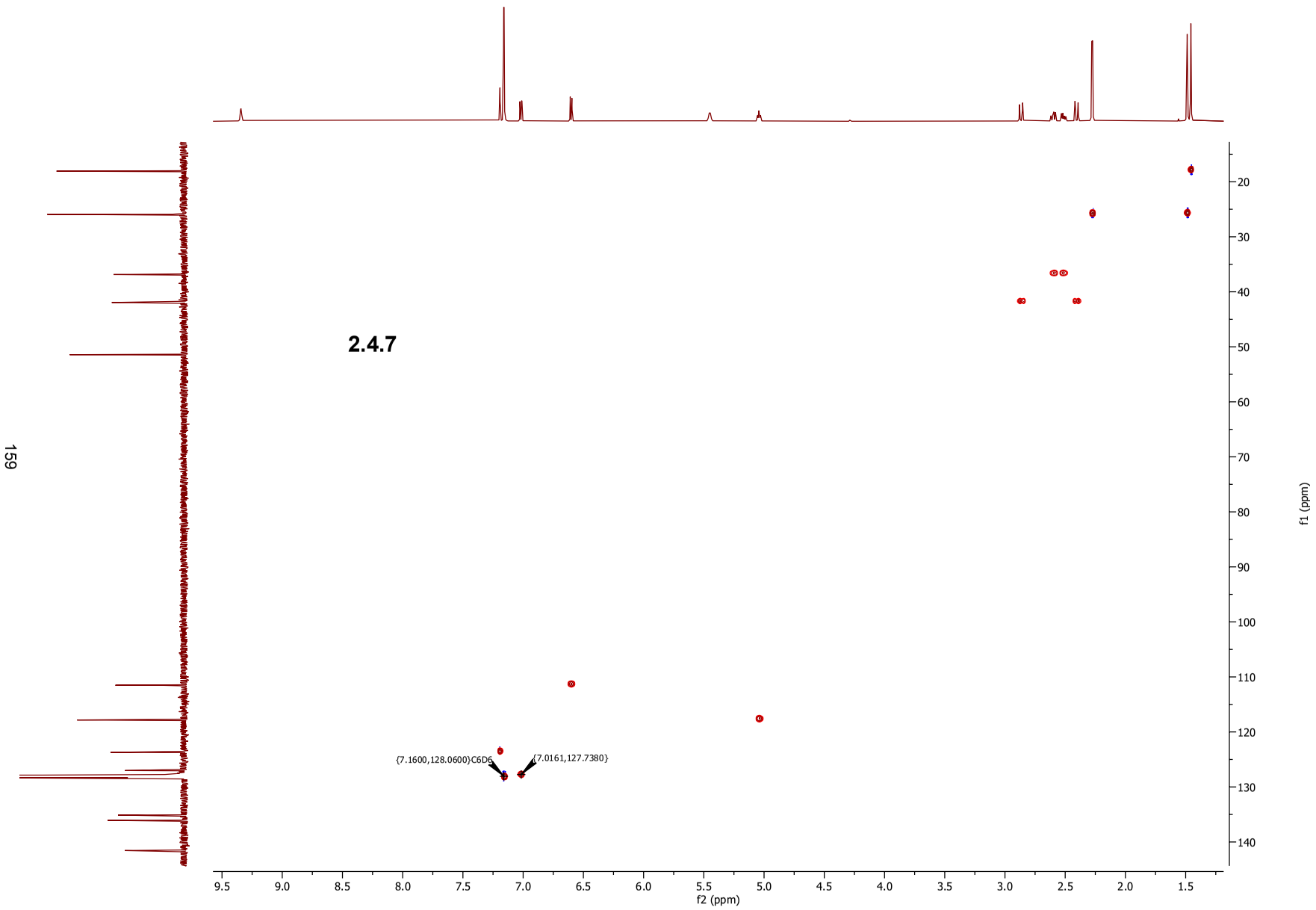
2.4.7


9.3426
7.1960
7.1924
7.1600 C6D6
7.0275
7.0239
7.0138
7.0102
6.6090
6.5953
5.4636
5.4542
5.4480
5.4382
5.0596
5.0574
5.0550
5.0524
5.0500
5.0479
5.0456
5.0433
5.0410
5.0385
5.0345
5.0320
5.0296
5.0271
5.0246
2.8788
2.8531
2.6177
2.6042
2.5944
2.5809
2.5309
2.5190
2.5074
2.4957
2.4185
2.3929
2.2798
2.2720
1.4884
1.4860
1.4577
1.4555
0.9692 H2O
1.00
1.04
1.06
1.04
1.01
1.05
1.04
1.06
1.07
1.08
3.12
3.19
3.10
f1 (ppm)

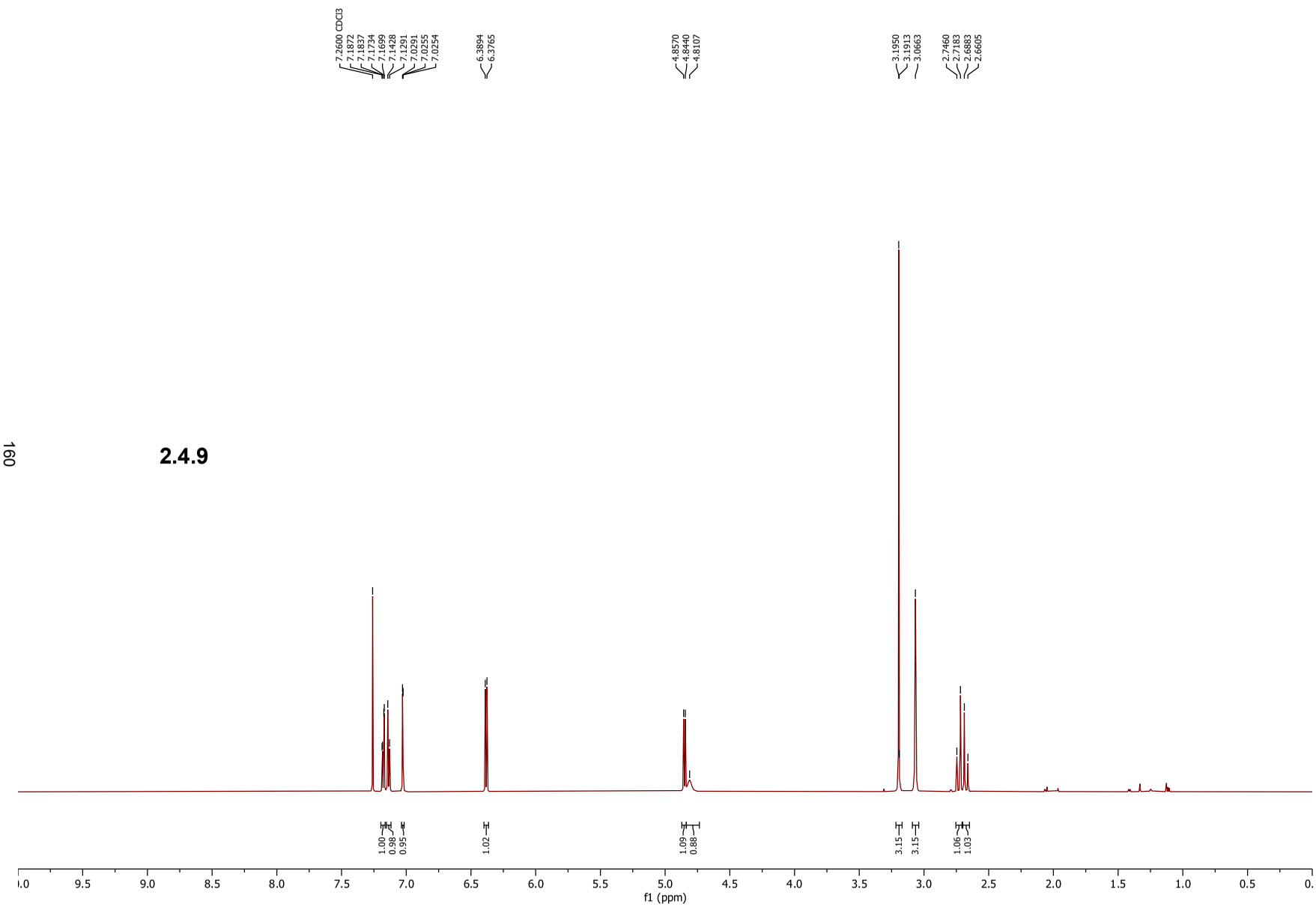
158

2.4.7

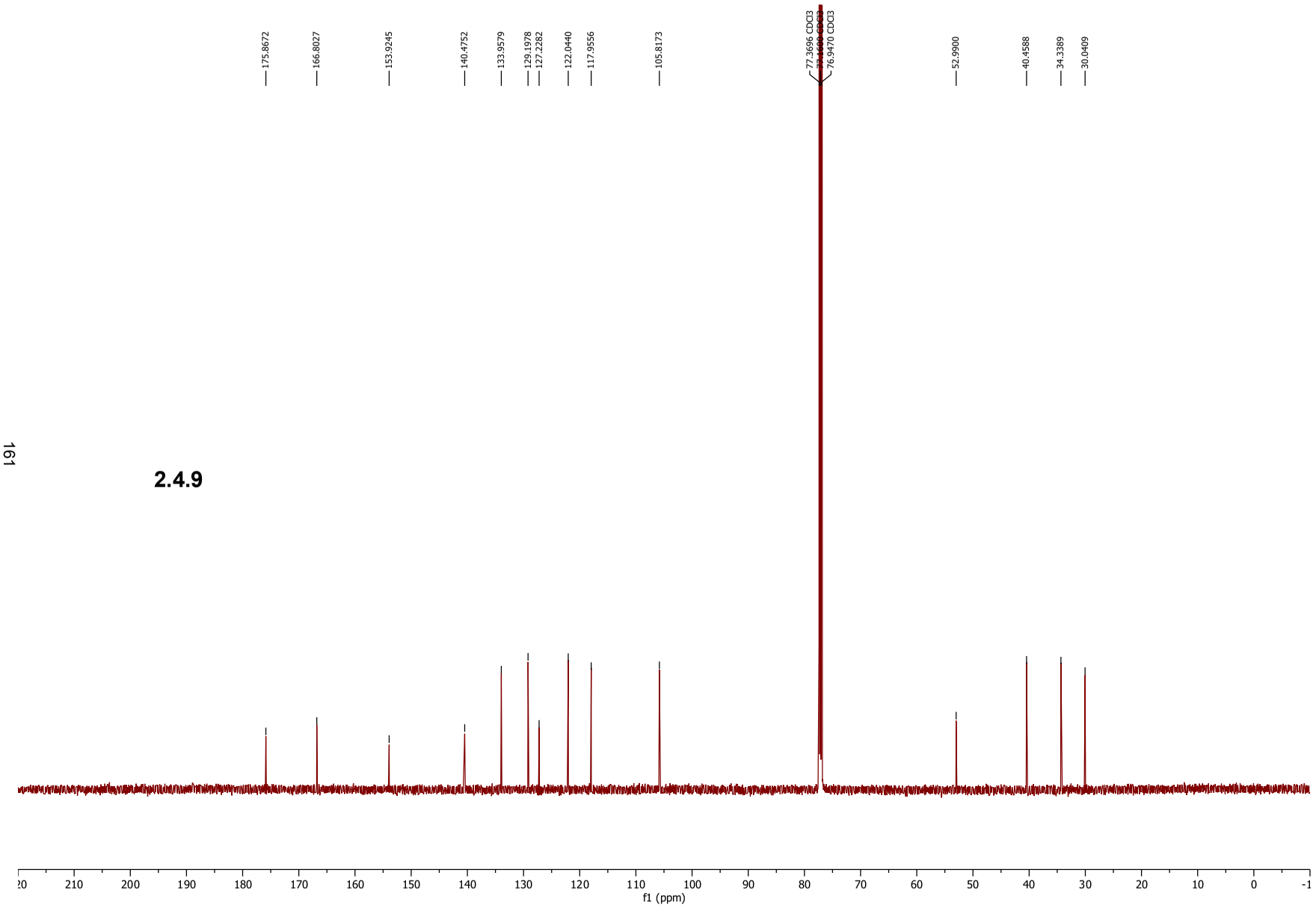

181.7226
169.8132
141.5538
136.0772
135.1137
128.2205 C6D6
127.9000 C6D6
127.0152
123.7123
117.8295
111.5128
51.4287
41.9379
36.8605
25.9857
25.9147
18.0685
f1 (ppm)


2.4.7
159
{7.1600,128.0600}C6D6
{7.0161,127.7380}
f2 (ppm)
f1 (ppm)

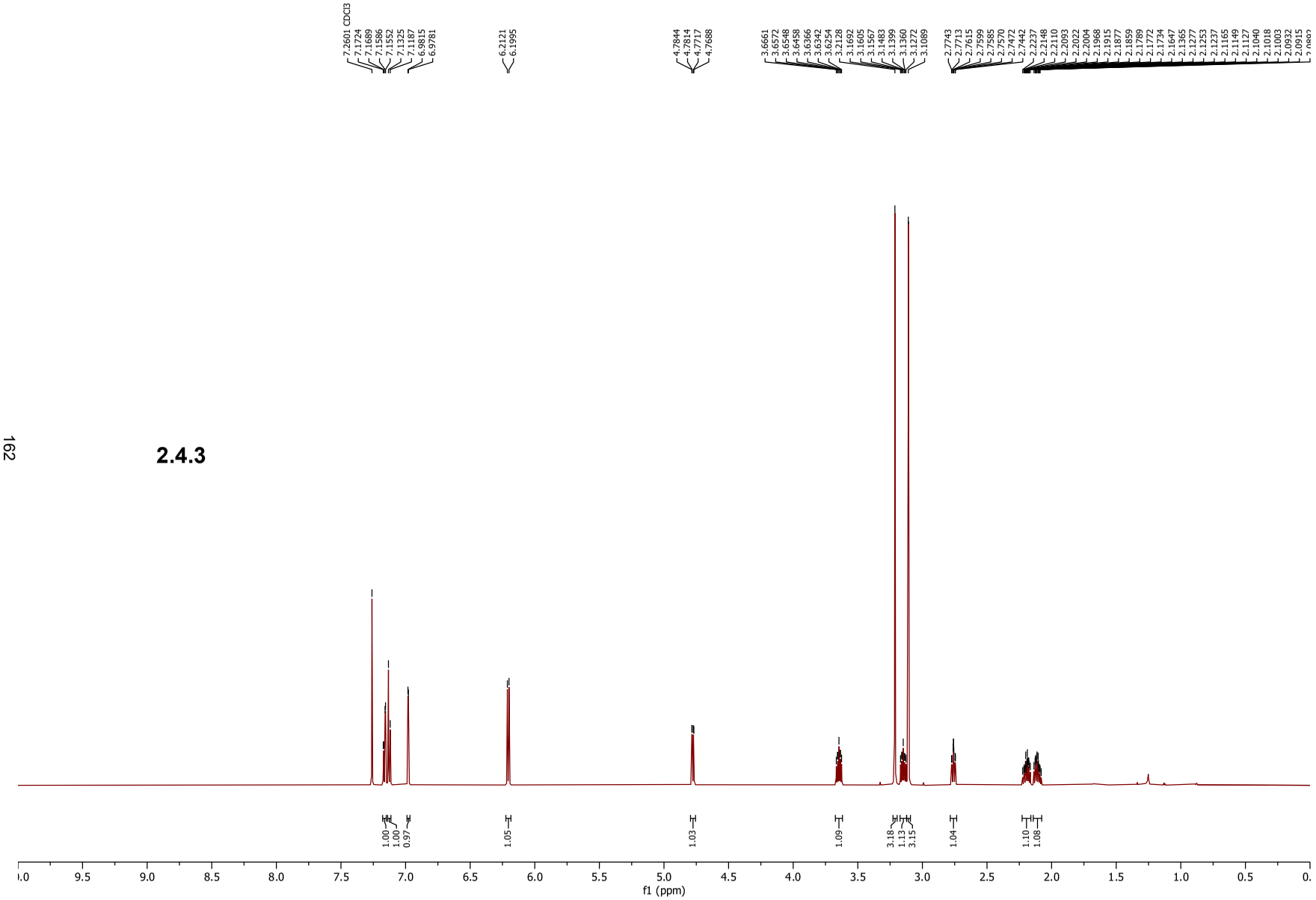
2.4.9

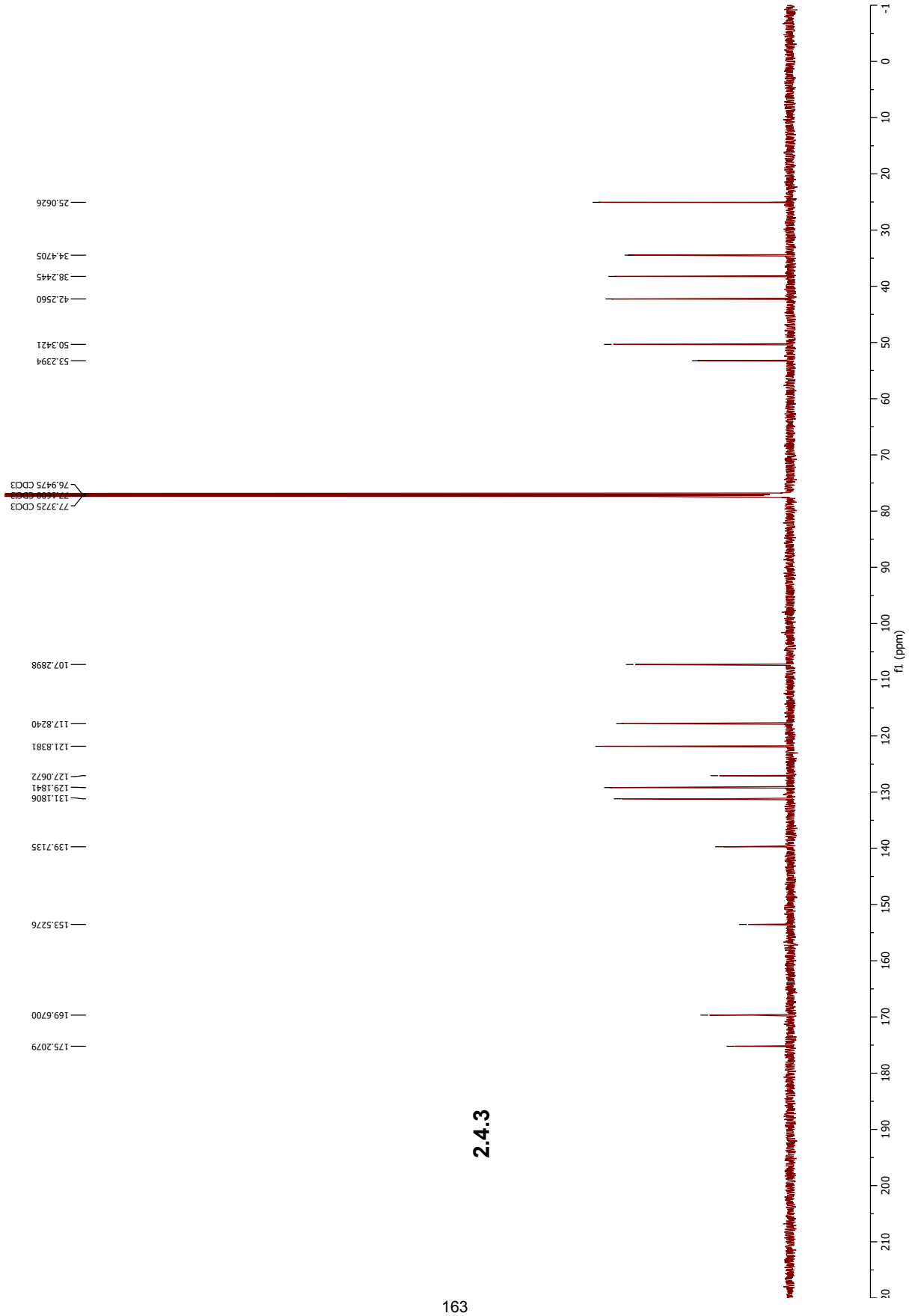

7.2600 CDCl3
7.1872
7.1837
7.1734
7.1699
7.1428
7.1291
7.0291
7.0255
7.0254
6.3894
6.3765
4.8570
4.8440
4.8107
3.1950
3.1913
3.0663
2.7460
2.7183
2.6883
2.6605
1.00
0.98
0.95
1.02
1.09
0.88
3.15
3.15
1.06
1.03
f1 (ppm)

2.4.9

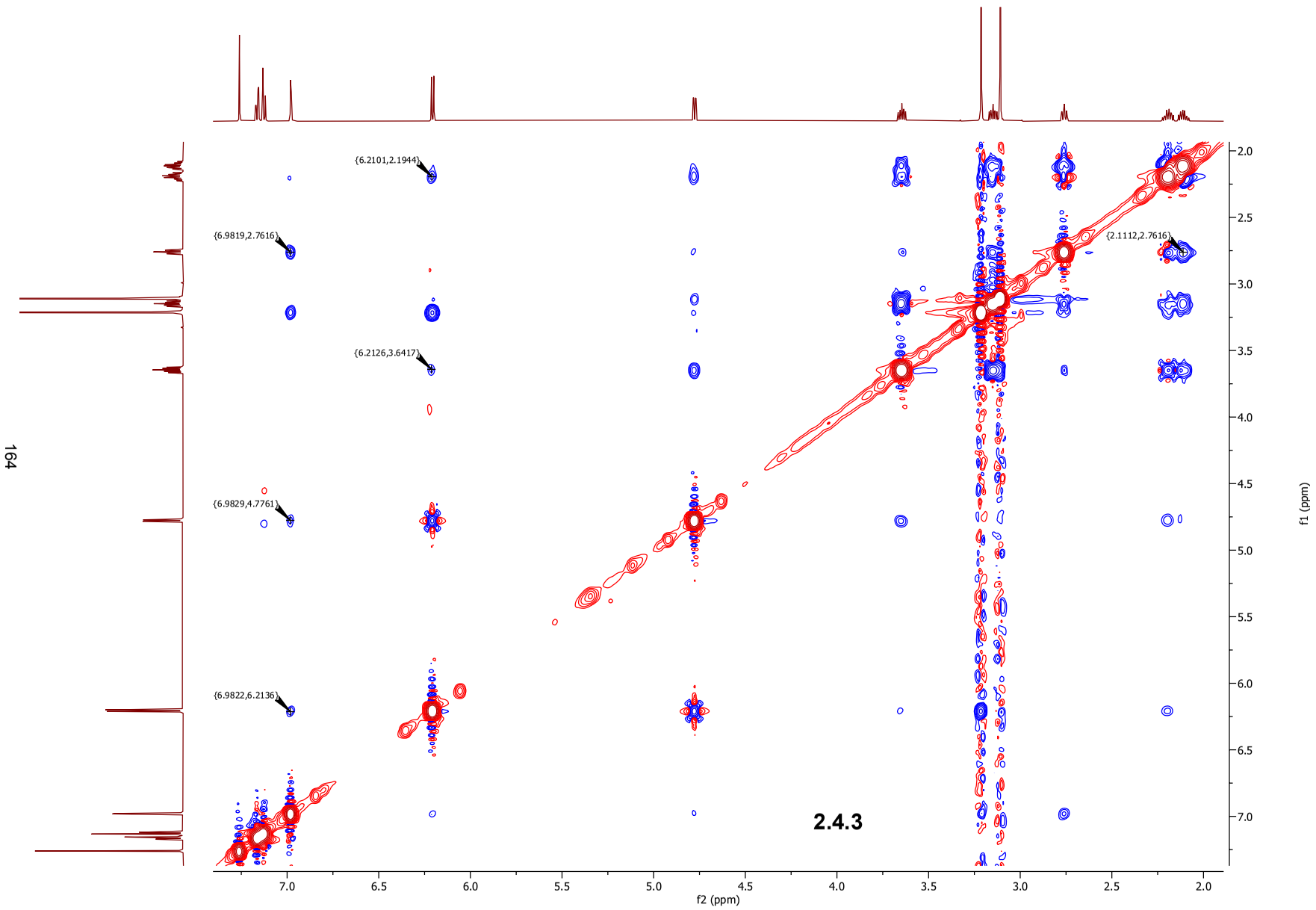

175.8672
166.8027
153.9245
140.4752
133.9579
129.1978
127.2282
122.0440
117.9556
105.8173
77.3696 CDCl3
76.9470 CDCl3
52.9900
40.4588
34.3389
30.0409
f1 (ppm)

2.4.3

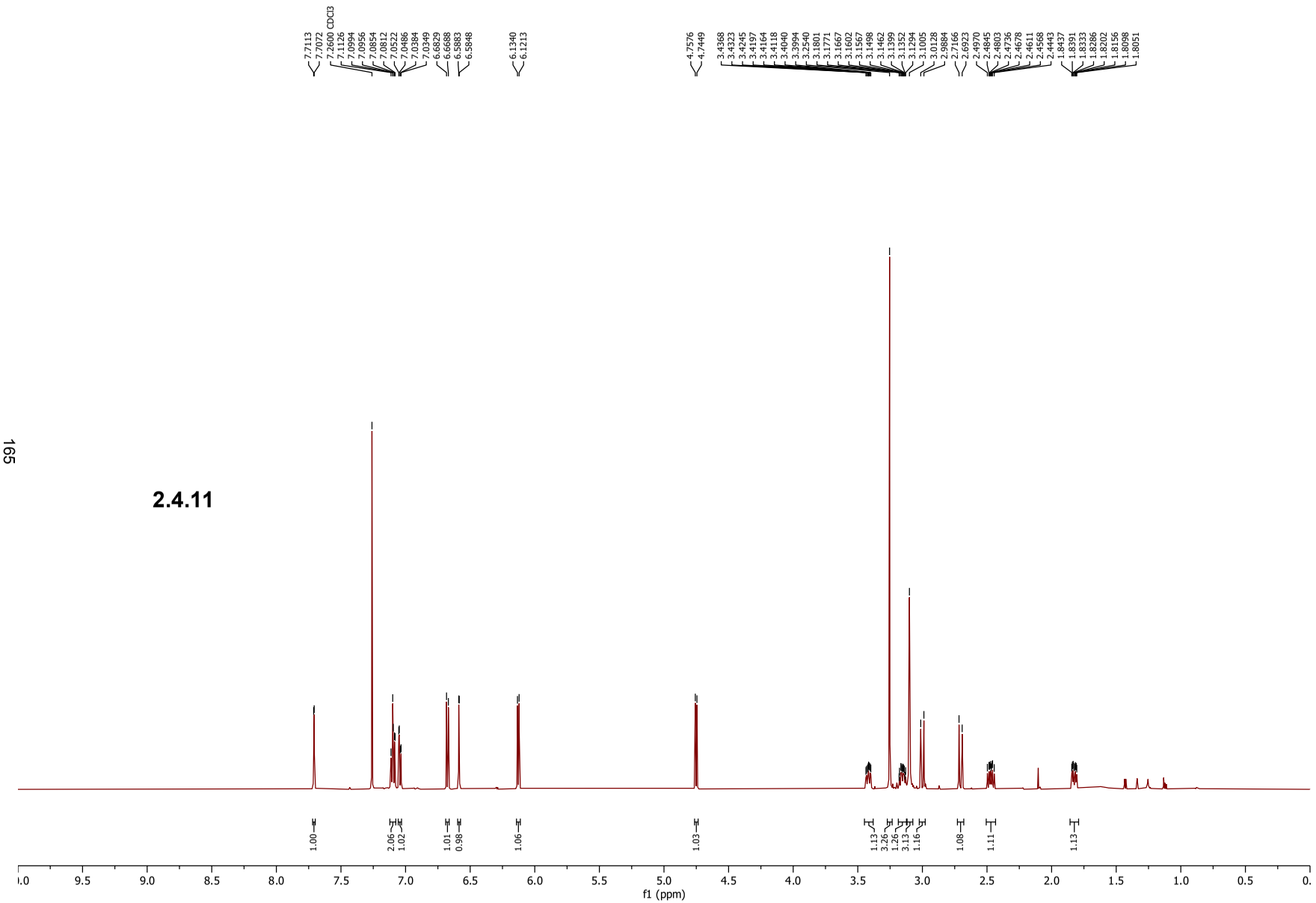

7.2601 CDCl3
7.1724
7.1689
7.1586
7.1552
7.1325
7.1187
6.9815
6.9781
6.2121
6.1995
4.7844
4.7814
4.7717
4.7688
3.6661
3.6572
3.6548
3.6458
3.6366
3.6342
3.6254
3.2128
3.1692
3.1605
3.1567
3.1483
3.1399
3.1360
3.1272
3.1089
2.7743
2.7713
2.7615
2.7599
2.7585
2.7570
2.7472
2.7442
2.2237
2.2148
2.2110
2.2093
2.2022
2.2004
2.1968
2.1915
2.1877
2.1859
2.1789
2.1772
2.1734
2.1647
2.1365
2.1277
2.1253
2.1237
2.1165
2.1149
2.1127
2.1040
2.1018
2.1003
2.0932
2.0915
1.00
1.00
0.97
1.05
1.03
1.09
3.18
1.13
3.15
1.04
1.10
1.08
f1 (ppm)


175.2079
169.6700
153.5276
139.7135
131.1806
129.1841
127.0672
121.8381
117.8240
107.2898
77.3725 CDCl3
76.9475 CDCl3
53.2394
50.3421
42.2560
38.2445
34.4705
25.0626
f1 (ppm)

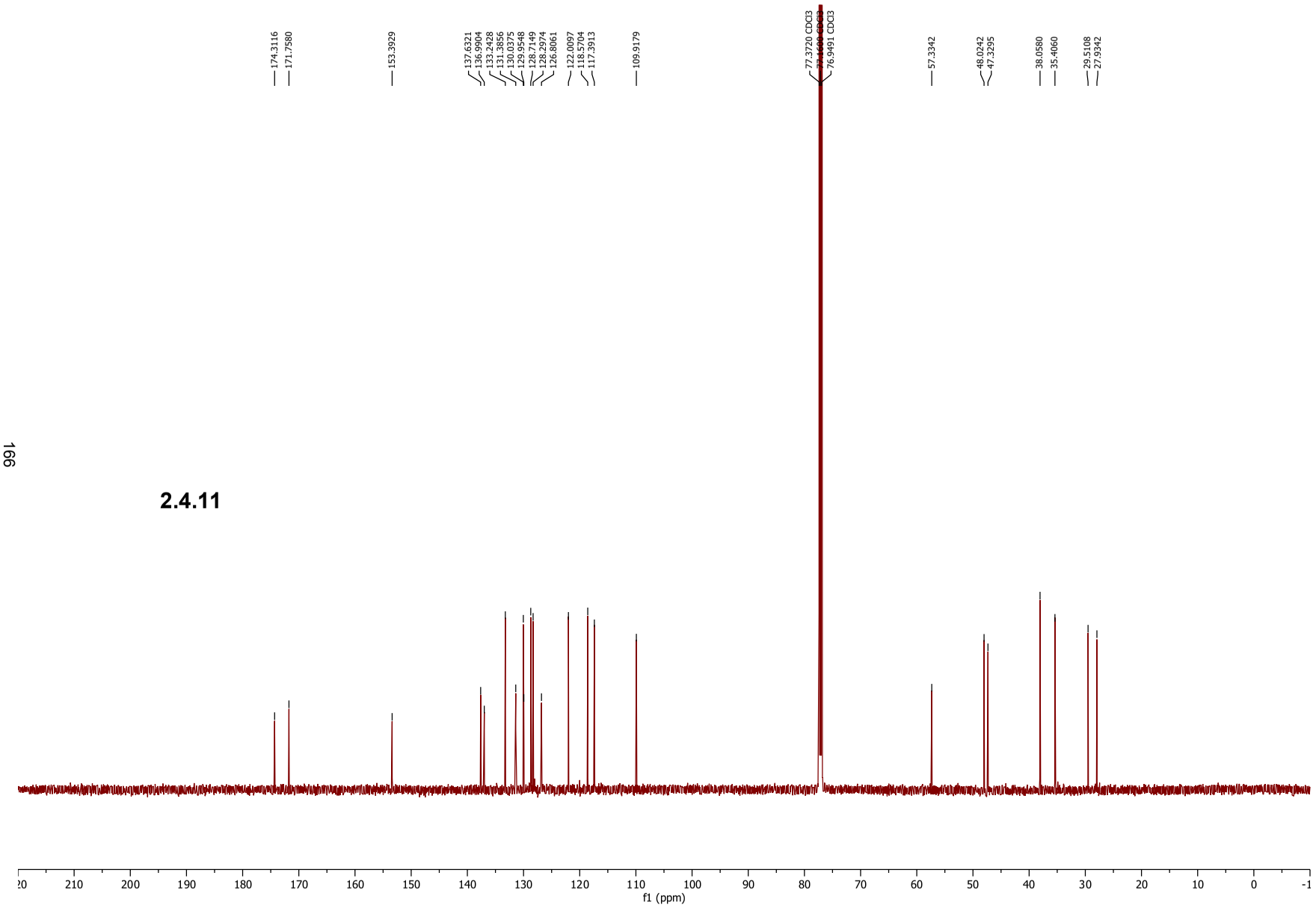
2.4.3

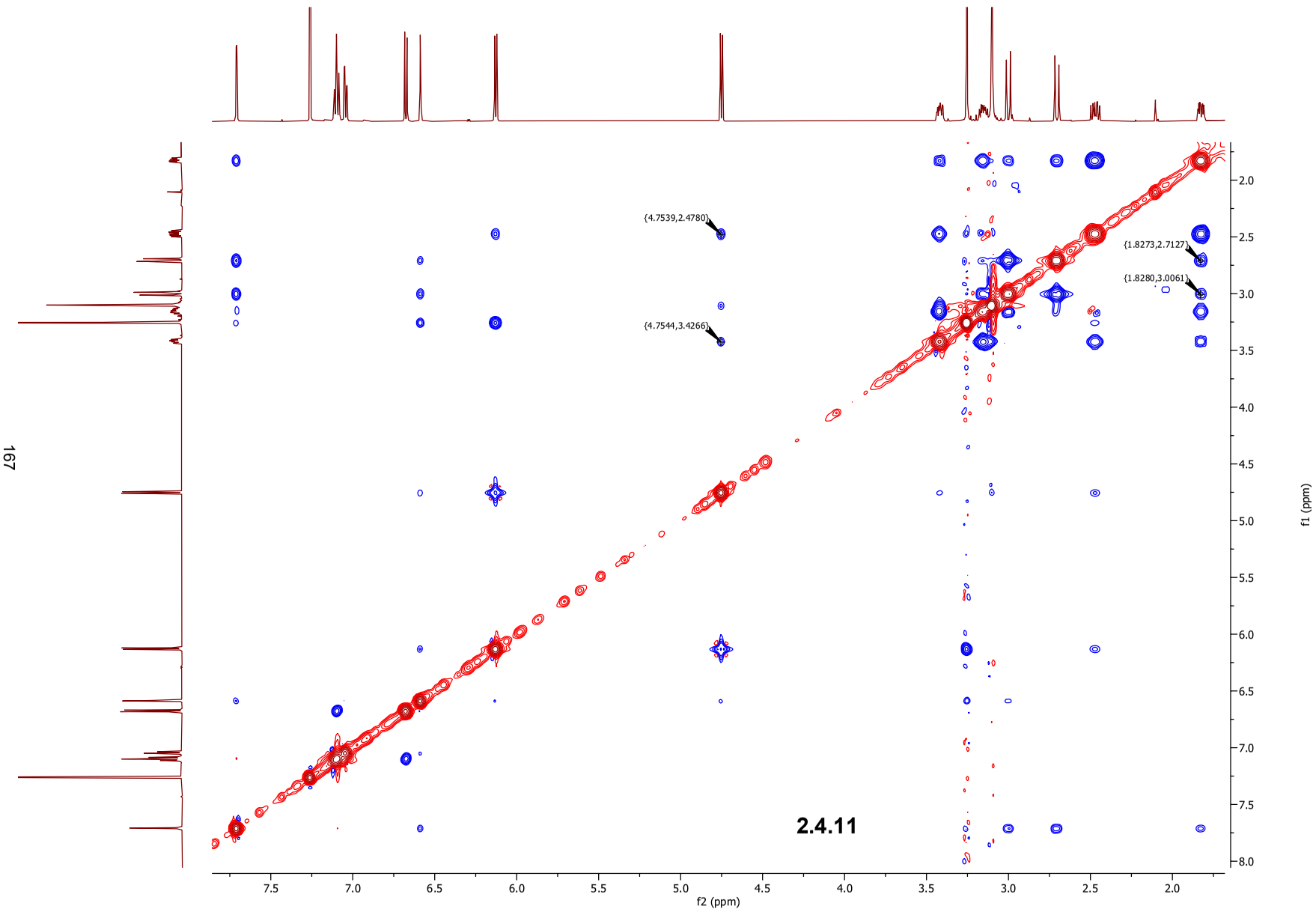

{6.2101,2.1944}
{6.9819,2.7616}
{6.2126,3.6417}
{6.9829,4.7761}
{6.9822,6.2136}
{2.1112,2.7616}
2.4.3
f2 (ppm)
f1 (ppm)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0

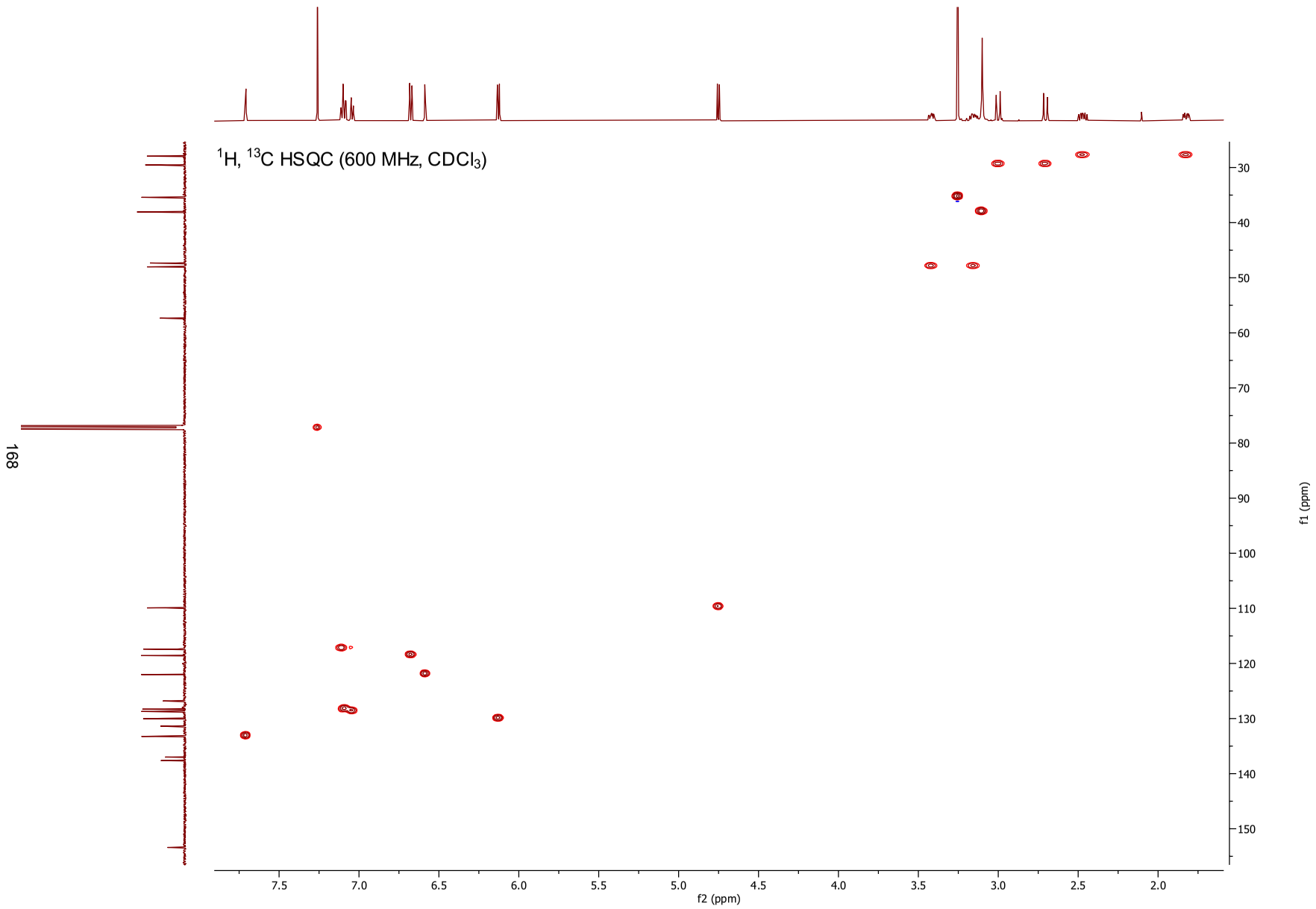
2.4.11


7.7113
7.7072
7.2600 CDCl3
7.1126
7.0994
7.0956
7.0854
7.0812
7.0522
7.0486
7.0384
7.0349
6.6829
6.6688
6.5883
6.5848
6.1340
6.1213
4.7576
4.7449
3.4368
3.4323
3.4245
3.4197
3.4164
3.4118
3.4040
3.3994
3.2540
3.1801
3.1771
3.1667
3.1602
3.1567
3.1498
3.1462
3.1399
3.1352
3.1294
3.1005
3.0128
2.9884
2.7166
2.6923
2.4970
2.4845
2.4803
2.4736
2.4678
2.4611
2.4568
2.4443
1.8437
1.8391
1.8333
1.8286
1.8202
1.8156
1.8098
1.8051
1.00
2.06
1.02
1.01
0.98
1.06
1.03
1.13
3.26
1.26
3.13
1.16
1.08
1.11
1.13
f1 (ppm)

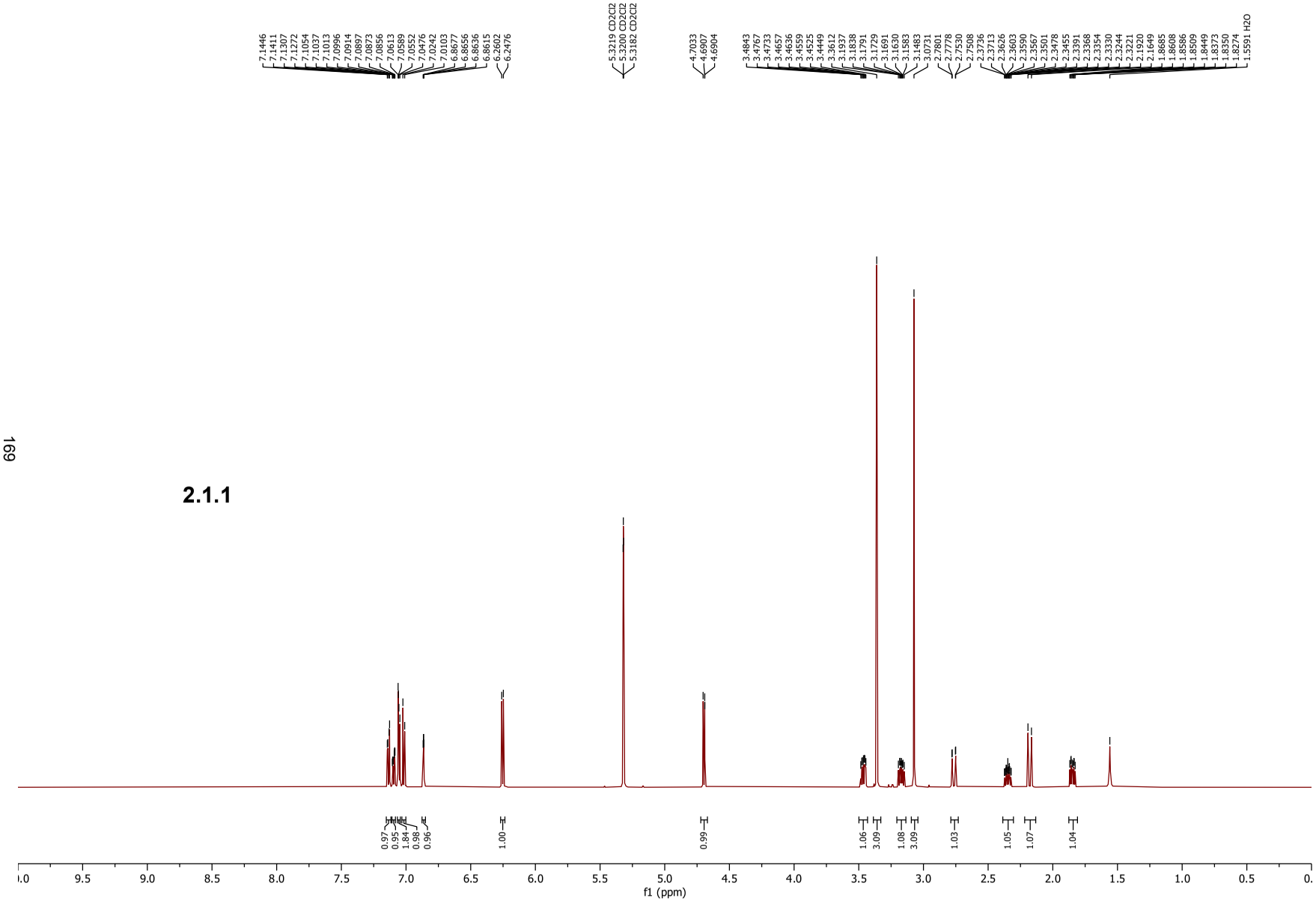
2.4.11

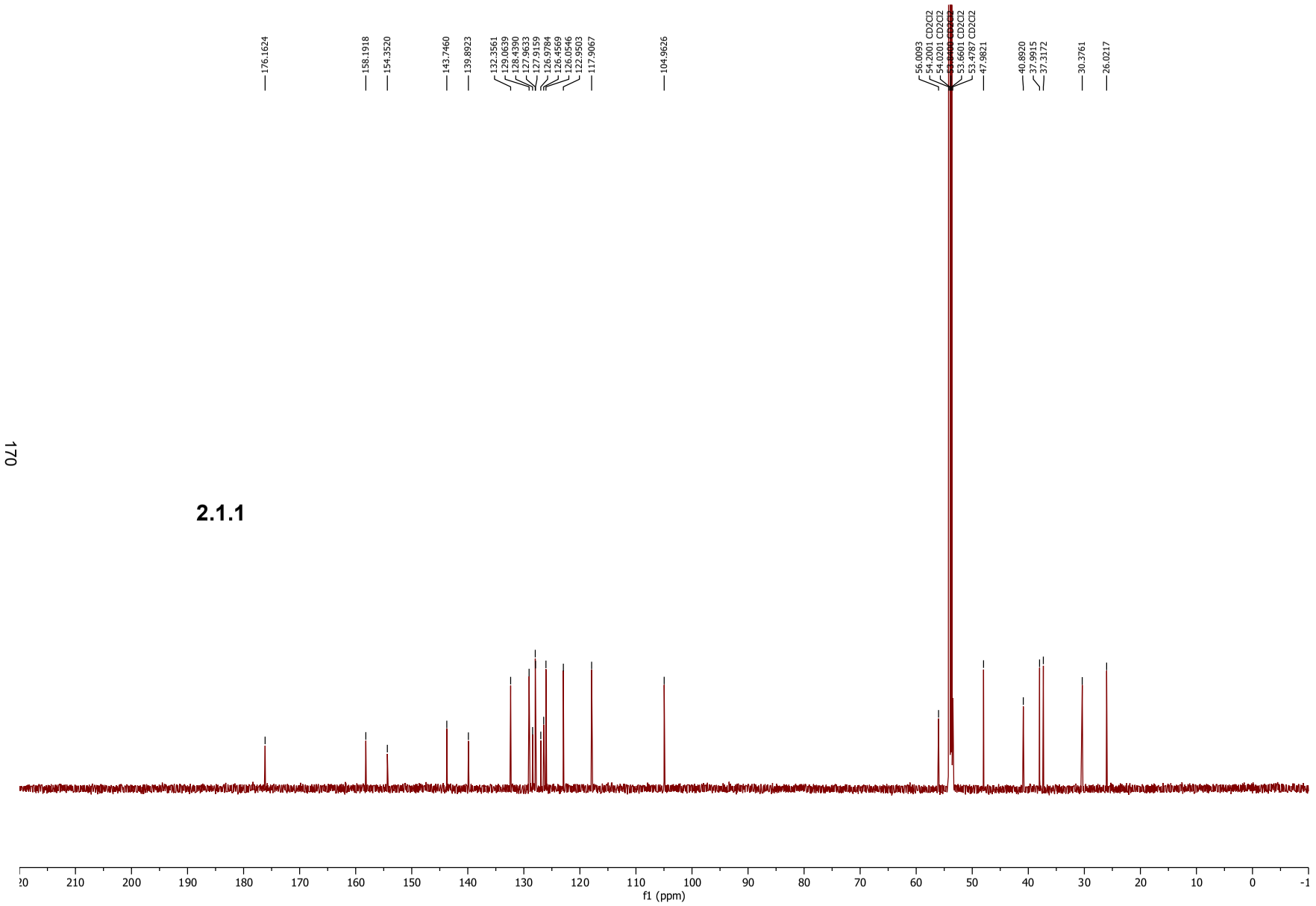

174.3116
171.7580
153.3929
137.6321
136.9904
133.2428
131.3856
130.0375
129.9548
128.7149
128.2974
126.8061
122.0097
118.5704
117.3913
109.9179
77.3720 CDCl3
77.1668 CDCl3
76.9491 CDCl3
57.3342
48.0242
47.3295
38.0580
35.4060
29.5108
27.9342
f1 (ppm)

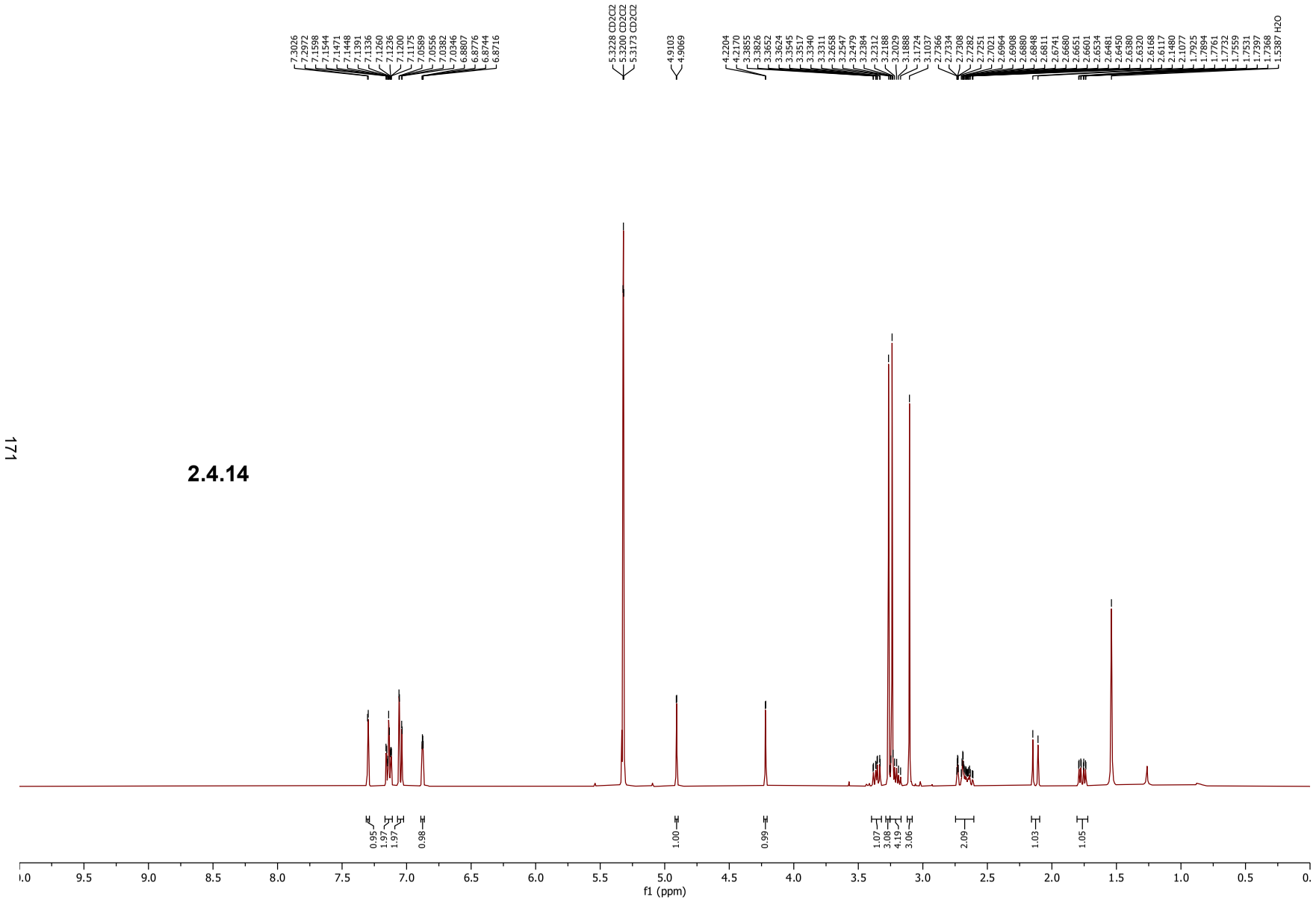

{4.7539,2.4780}
{4.7544,3.4266}
{1.8273,2.7127}
{1.8280,3.0061}
2.4.11
f2 (ppm)
f1 (ppm)

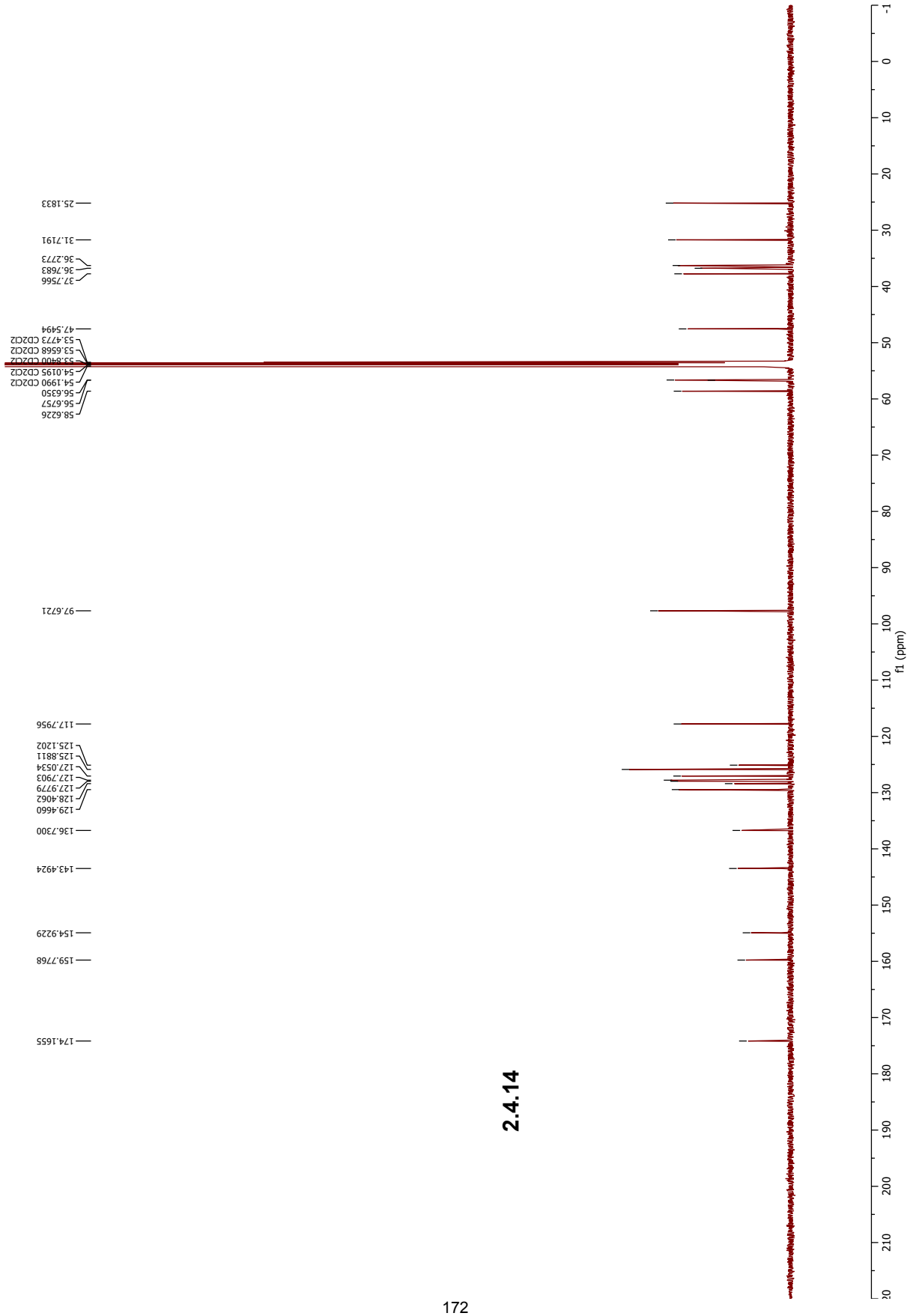

^{1}H, ^{13}C HSQC (600 MHz, $CDCl_3$)
168
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f2 (ppm)
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)

2.1.1

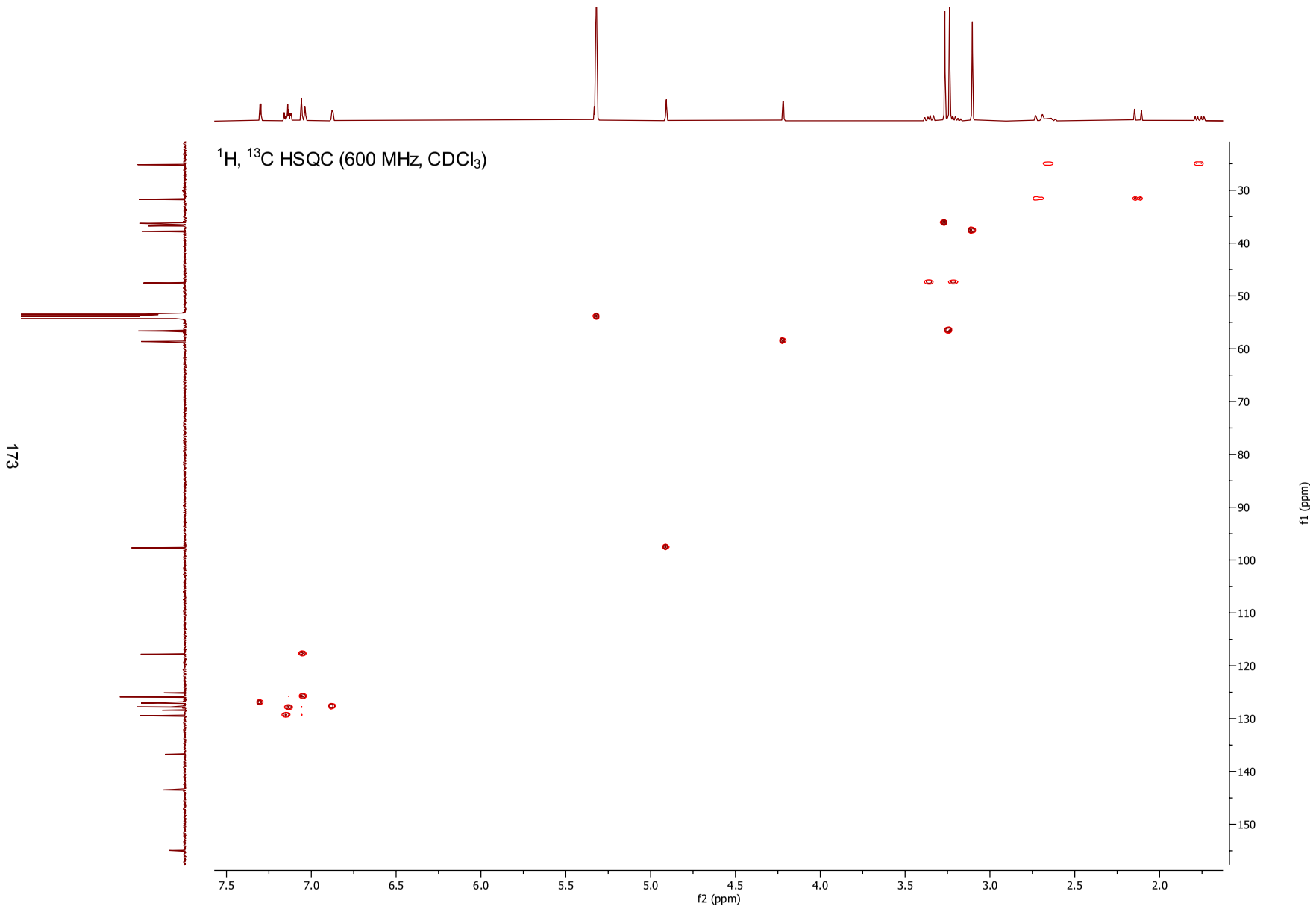

7.1446
7.1411
7.1307
7.1272
7.1054
7.1037
7.1013
7.0996
7.0914
7.0897
7.0873
7.0856
7.0613
7.0589
7.0552
7.0476
7.0242
7.0103
6.8677
6.8656
6.8636
6.8615
6.2602
6.2476
5.3219 CD2Cl2
5.3200 CD2Cl2
5.3182 CD2Cl2
4.7033
4.6907
4.6904
3.4843
3.4767
3.4733
3.4657
3.4636
3.4559
3.4525
3.4449
3.3612
3.1937
3.1838
3.1791
3.1729
3.1691
3.1630
3.1583
3.1483
3.0731
2.7801
2.7778
2.7530
2.7508
2.3736
2.3713
2.3626
2.3603
2.3590
2.3567
2.3501
2.3478
2.3455
2.3391
2.3368
2.3354
2.3330
2.3244
2.3221
2.1920
2.1649
1.8685
1.8608
1.8586
1.8509
1.8449
1.8373
1.8350
1.8274
1.5591 H2O
0.97
0.95
1.84
0.98
0.96
1.00
0.99
1.06
3.09
1.08
3.09
1.03
1.05
1.07
1.04
f1 (ppm)

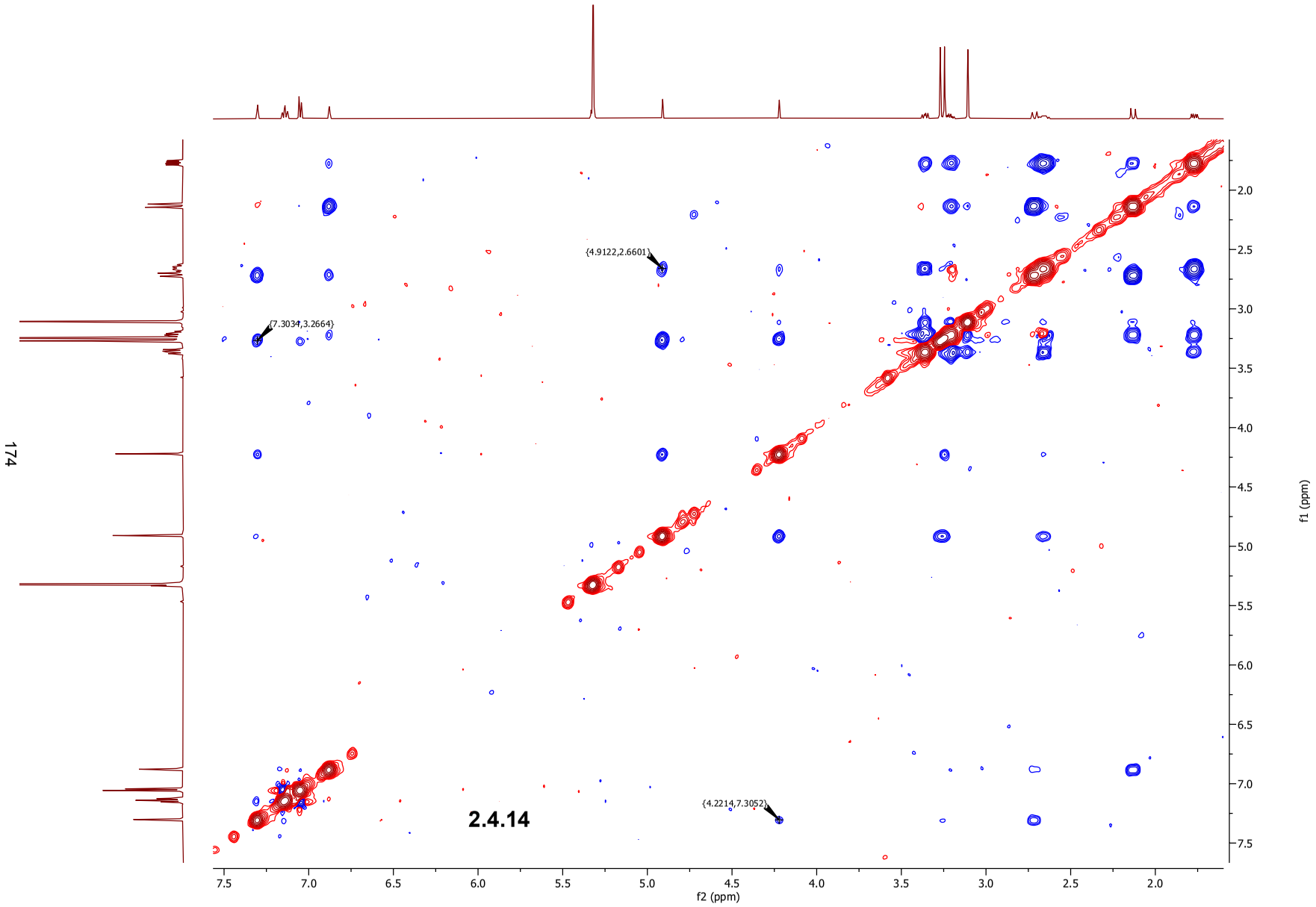

176.1624
158.1918
154.3520
143.7460
139.8923
132.3561
129.0639
128.4390
127.9633
127.9159
126.9784
126.4569
126.0546
122.9503
117.9067
104.9626
56.0093
54.2001 CD2Cl2
54.0201 CD2Cl2
53.8401 CD2Cl2
53.6601 CD2Cl2
53.4787 CD2Cl2
47.9821
40.8920
37.9915
37.3172
30.3761
26.0217
170
2.1.1
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

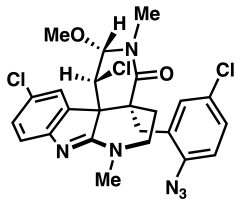

7.3026
7.2972
7.1598
7.1544
7.1471
7.1448
7.1391
7.1336
7.1260
7.1236
7.1200
7.1175
7.0589
7.0556
7.0382
7.0346
6.8807
6.8776
6.8744
6.8716
5.3228 CD2Cl2
5.3200 CD2Cl2
5.3173 CD2Cl2
4.9103
4.9069
4.2204
4.2170
3.3855
3.3826
3.3652
3.3624
3.3545
3.3517
3.3340
3.3311
3.2658
3.2547
3.2479
3.2384
3.2312
3.2188
3.2029
3.1888
3.1724
3.1037
2.7366
2.7334
2.7308
2.7282
2.7251
2.7021
2.6964
2.6908
2.6880
2.6848
2.6811
2.6741
2.6680
2.6651
2.6601
2.6534
2.6481
2.6450
2.6380
2.6320
2.6168
2.6117
2.1480
2.1077
1.7925
1.7894
1.7761
1.7732
1.7559
1.7531
1.7397
1.7368
1.5387 H2O
171
2.4.14
0.95
1.97
1.97
0.98
1.00
0.99
1.07
3.08
4.19
3.06
2.09
1.03
1.05
f1 (ppm)


174.1655
159.7768
154.9229
143.4924
136.7300
129.4660
128.4062
127.9779
127.7903
127.0534
125.8811
125.1202
117.7956
97.6721
58.6226
56.6757
56.6350
54.1990 CDCl2
54.0195 CDCl2
53.8400 CDCl2
53.6568 CDCl2
53.4773 CDCl2
47.5494
37.7566
36.7683
36.2773
31.7191
25.1833
f1 (ppm)

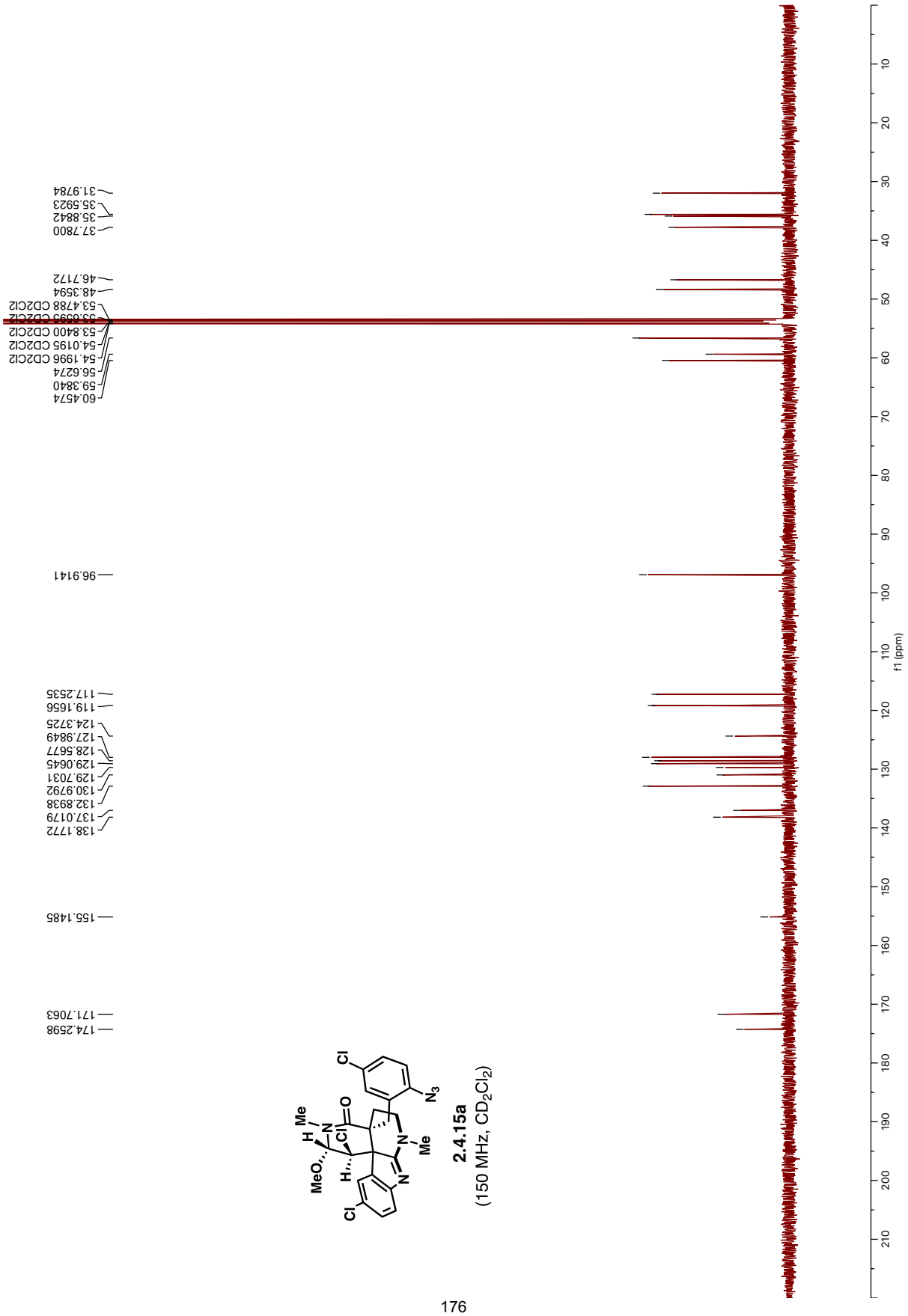
2.4.14


^{1}H, ^{13}C HSQC (600 MHz, $CDCl_3$)
173
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f2 (ppm)
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)


{4.9122,2.6601}
{7.3034,3.2664}
{4.2214,7.3052}
2.4.14
174
f2 (ppm)
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0

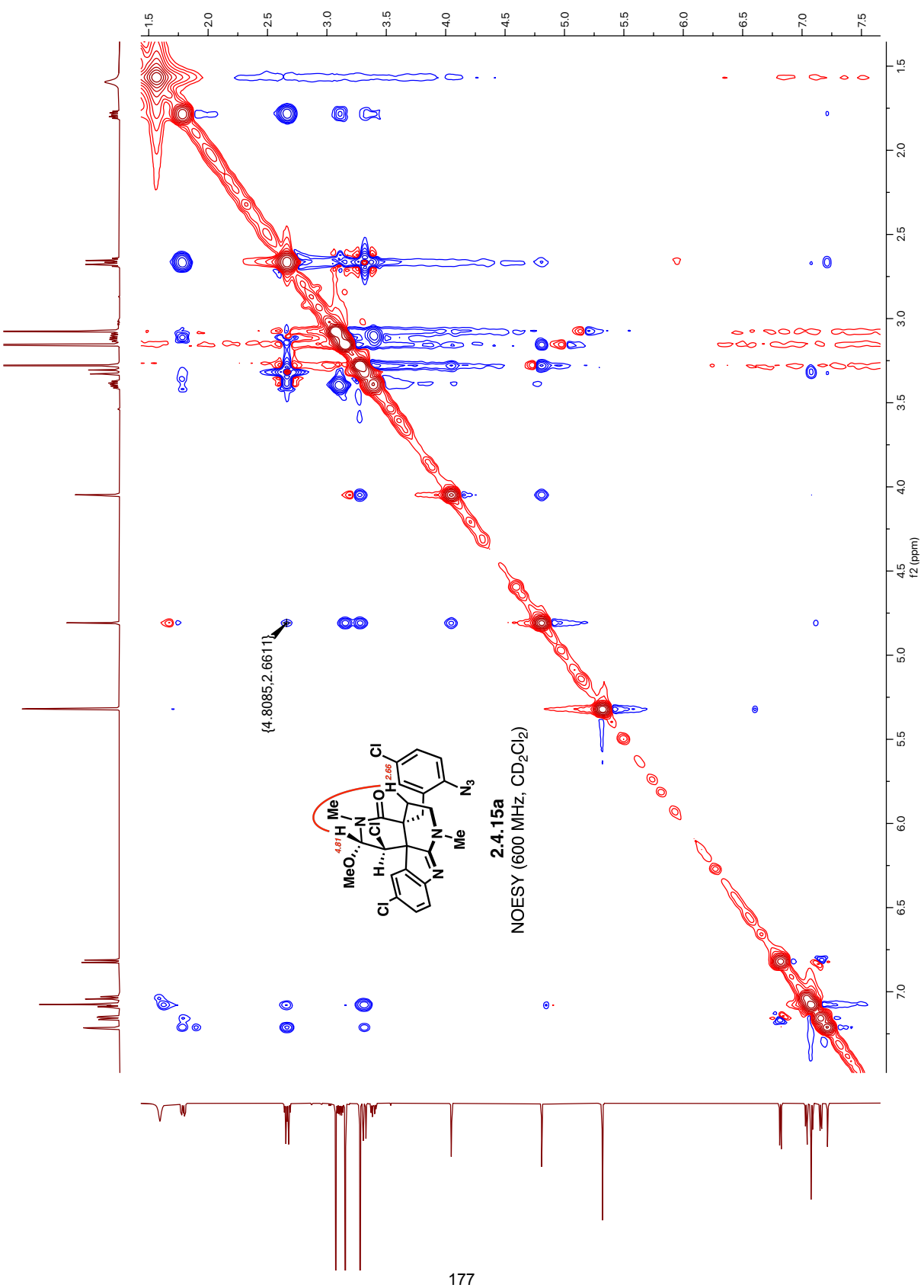


2.4.15a
(600 MHz, CD_2Cl_2)

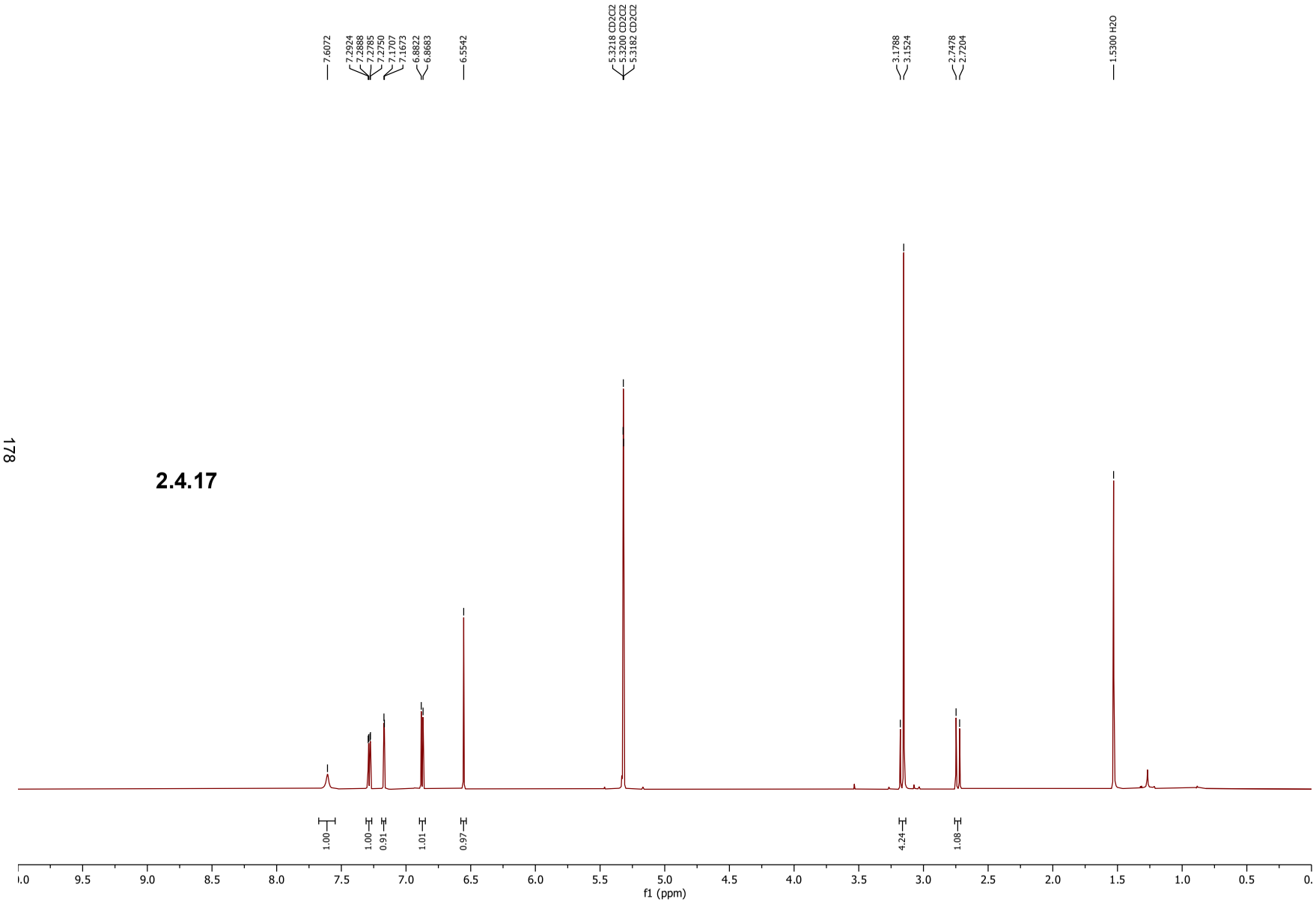


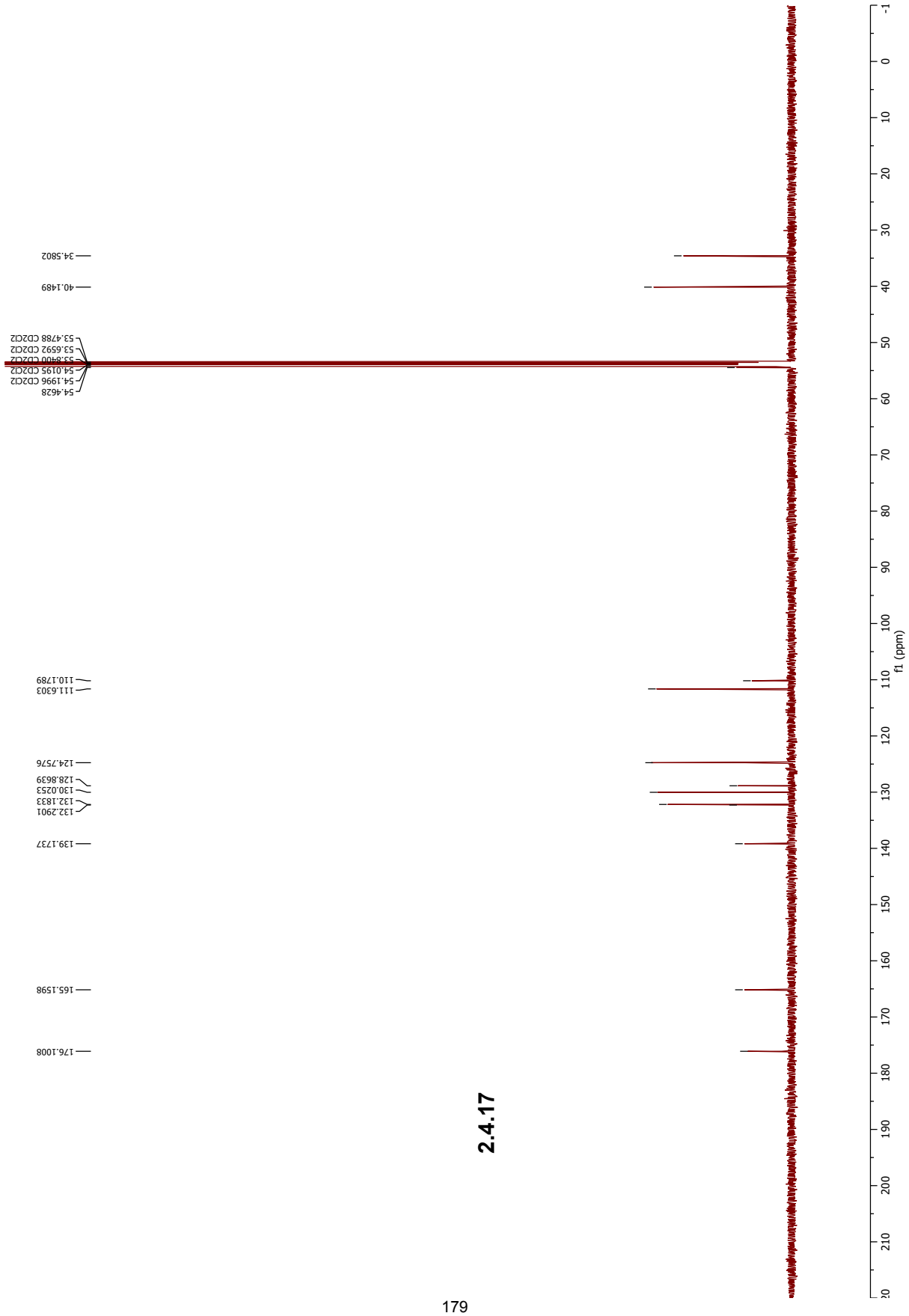
2.4.15a

(150 MHz, CD_2Cl_2)


f1 (ppm)
f2 (ppm)
{4.8085,2.6611}
2.4.15a
NOESY (600 MHz, CD_2Cl_2)
Me
MeO
Cl
O
H
2.66
4.81
N_3
Me

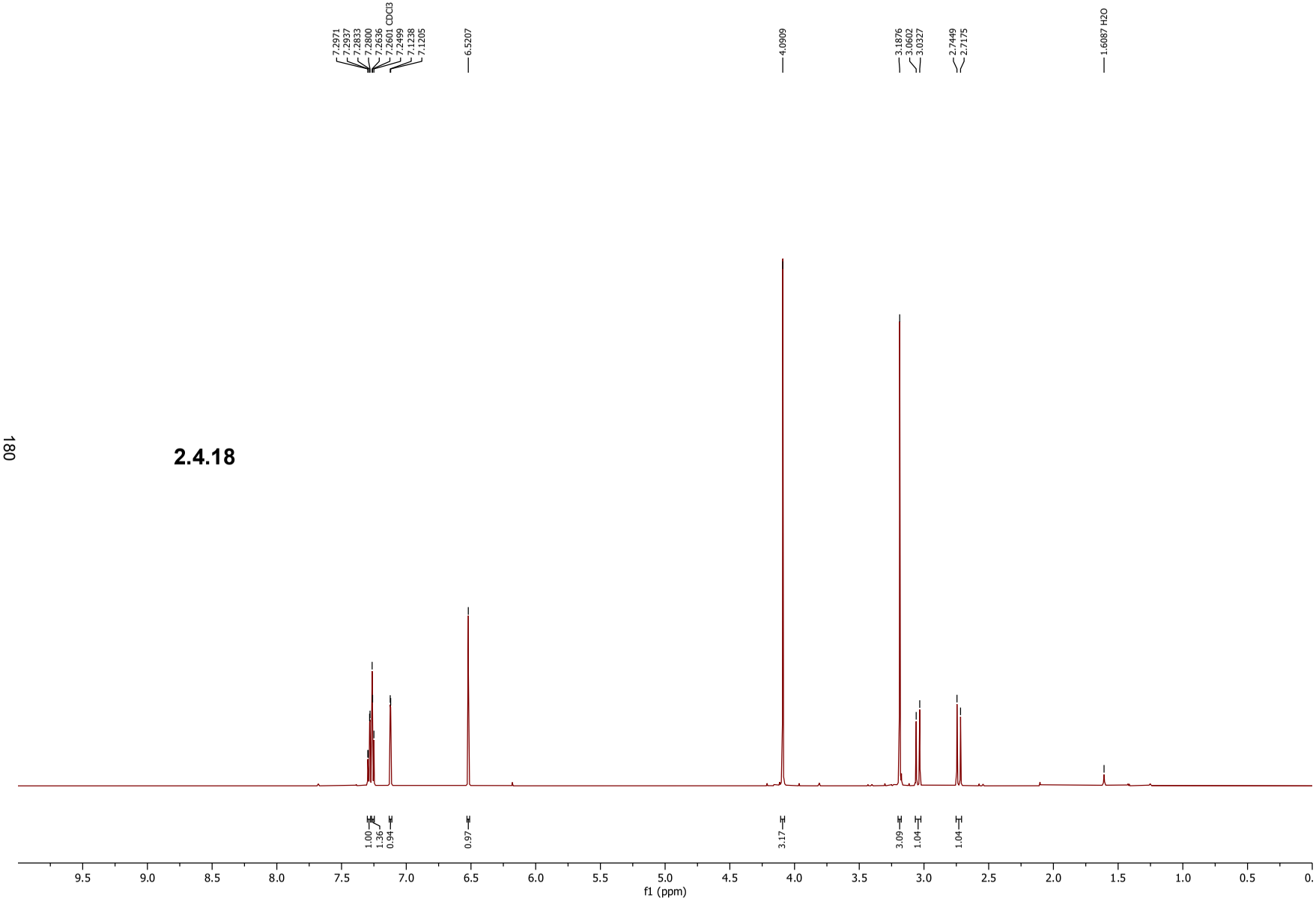
2.4.17

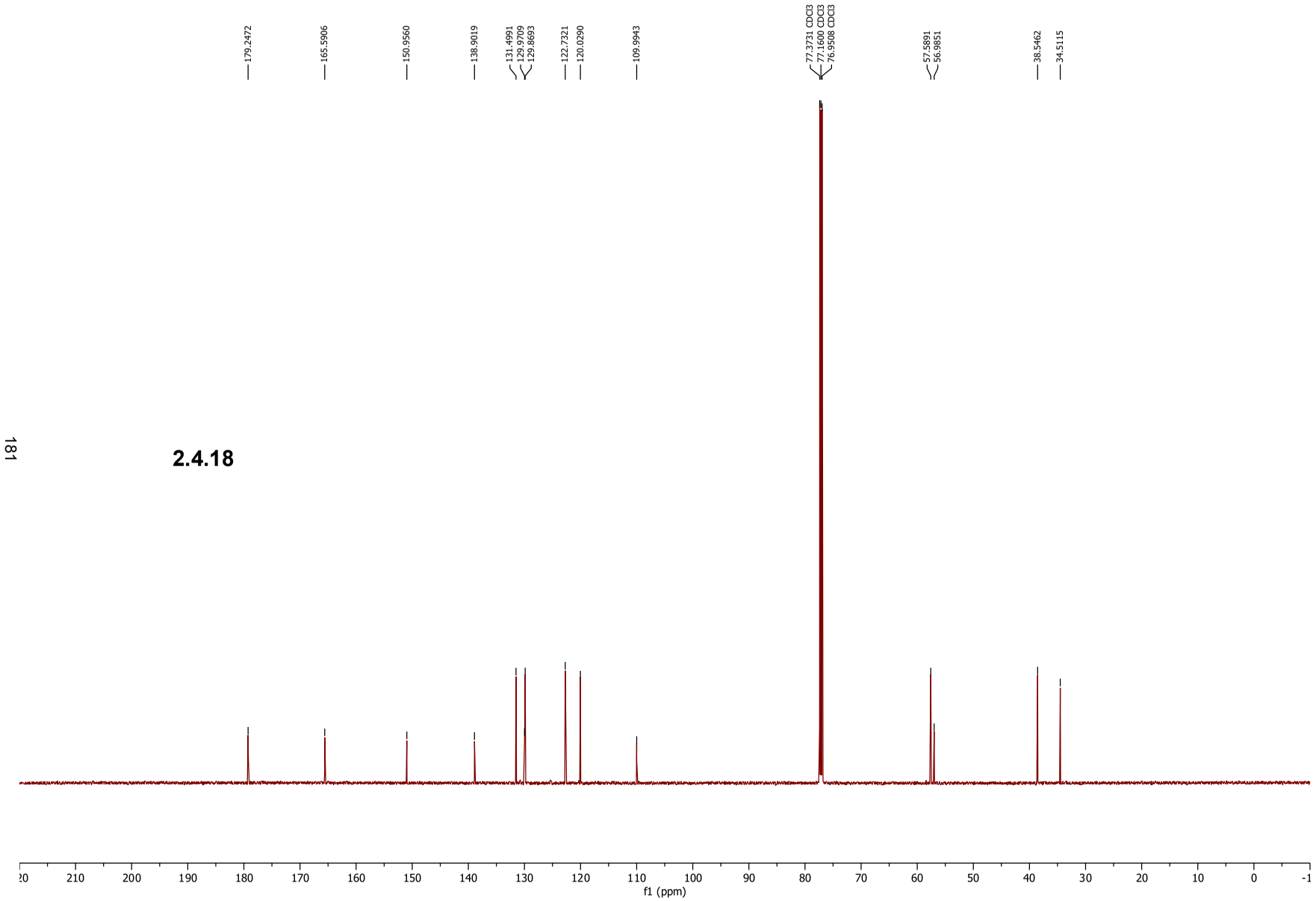

7.6072
7.2924
7.2888
7.2785
7.2750
7.1707
7.1673
6.8822
6.8683
6.5542
5.3218 CD2Cl2
5.3200 CD2Cl2
5.3182 CD2Cl2
3.1788
3.1524
2.7478
2.7204
1.5300 H2O
1.00
1.00
0.91
1.01
0.97
4.24
1.08
f1 (ppm)

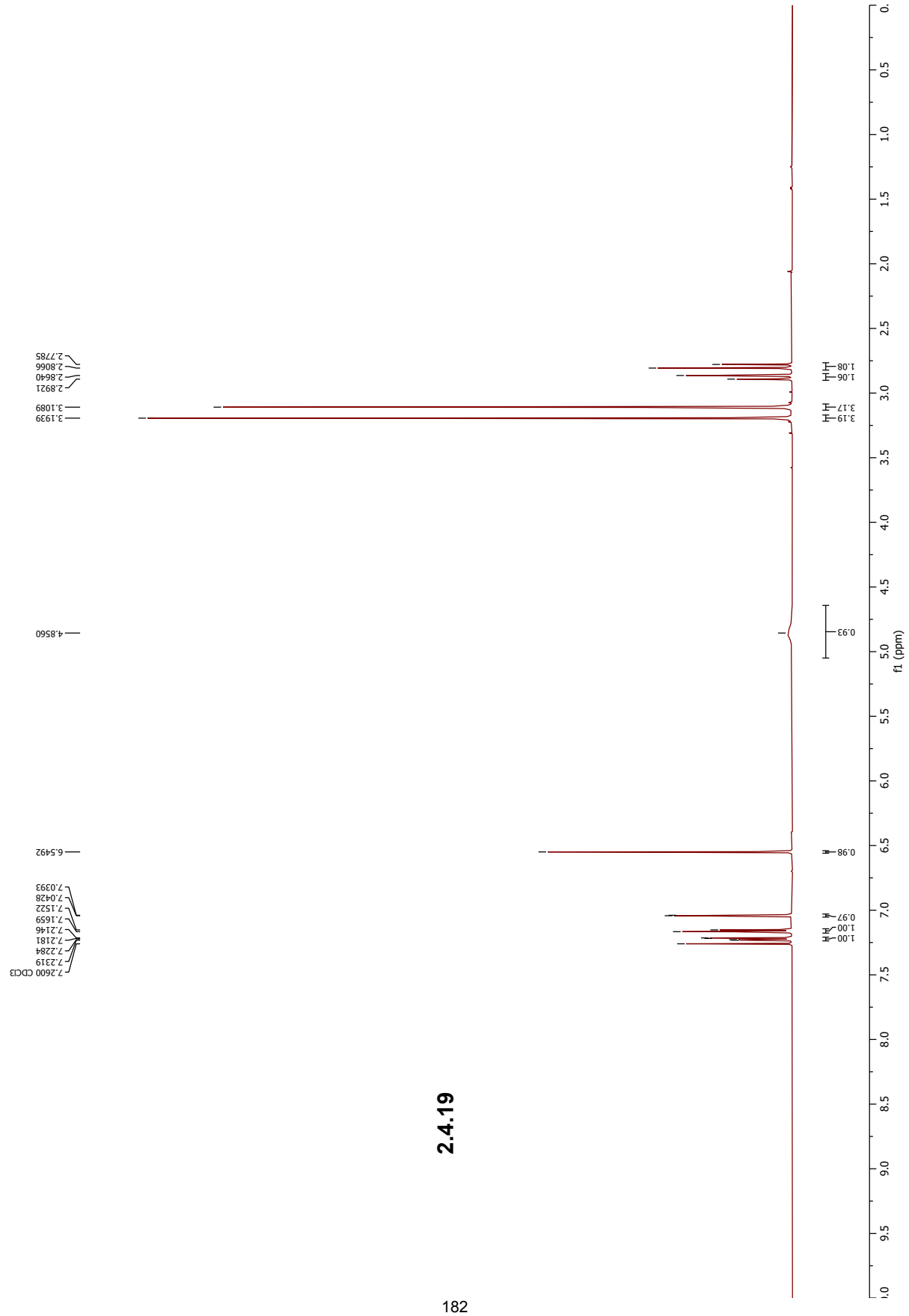

34.5802
40.1489
53.4788 CDCl2
53.6592 CDCl2
53.8400 CDCl2
54.0195 CDCl2
54.1996 CDCl2
54.4628
110.1789
111.6303
124.7576
128.8639
130.0253
132.1833
132.2901
139.1737
165.1598
176.1008
f1 (ppm)

2.4.17

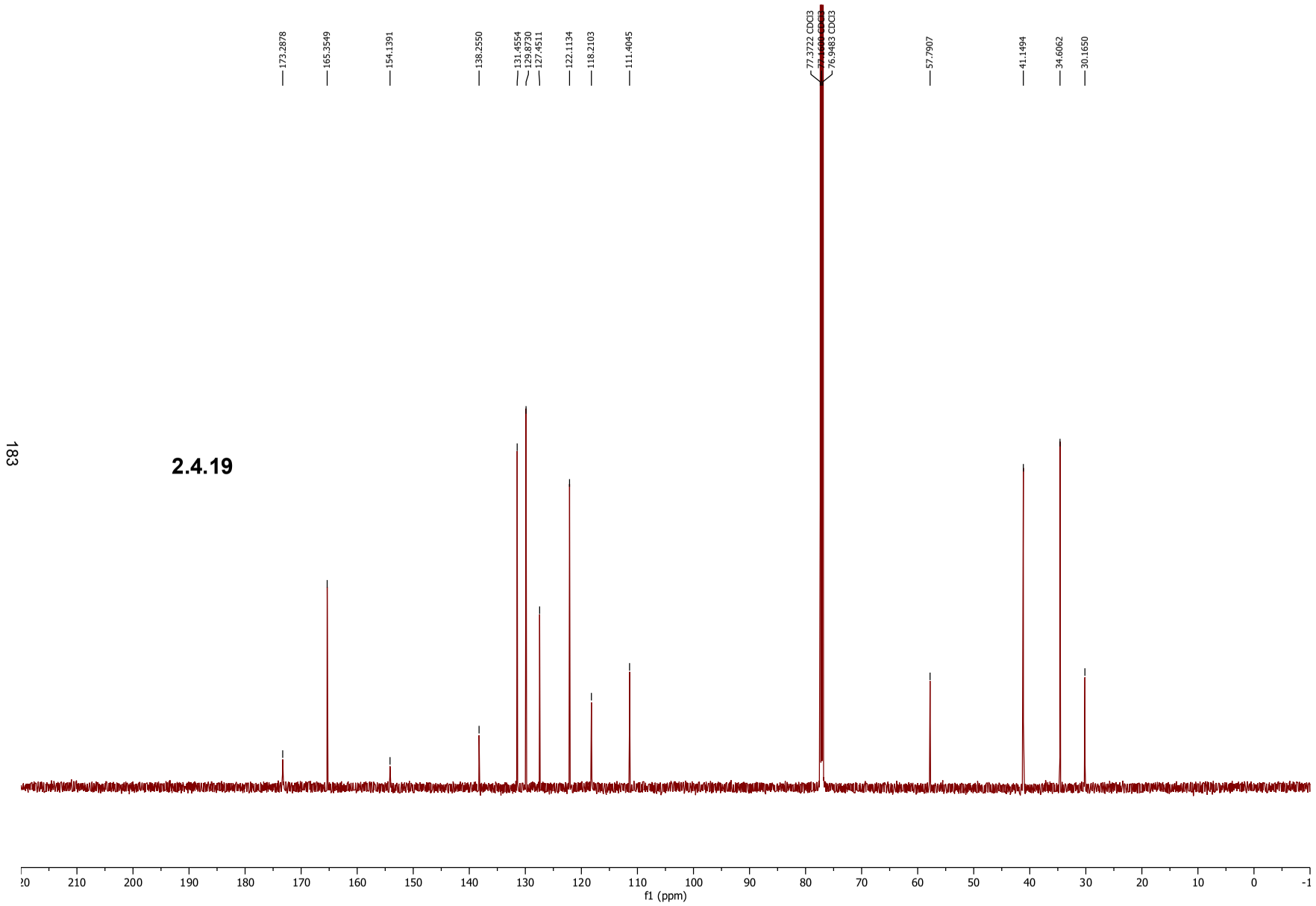
2.4.18


7.2971
7.2937
7.2833
7.2800
7.2636
CDCl3
7.2601
7.2499
7.1238
7.1205
6.5207
4.0909
3.1876
3.0602
3.0327
2.7449
2.7175
1.6087 H2O
1.00
1.36
0.94
0.97
3.17
3.09
1.04
1.04
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

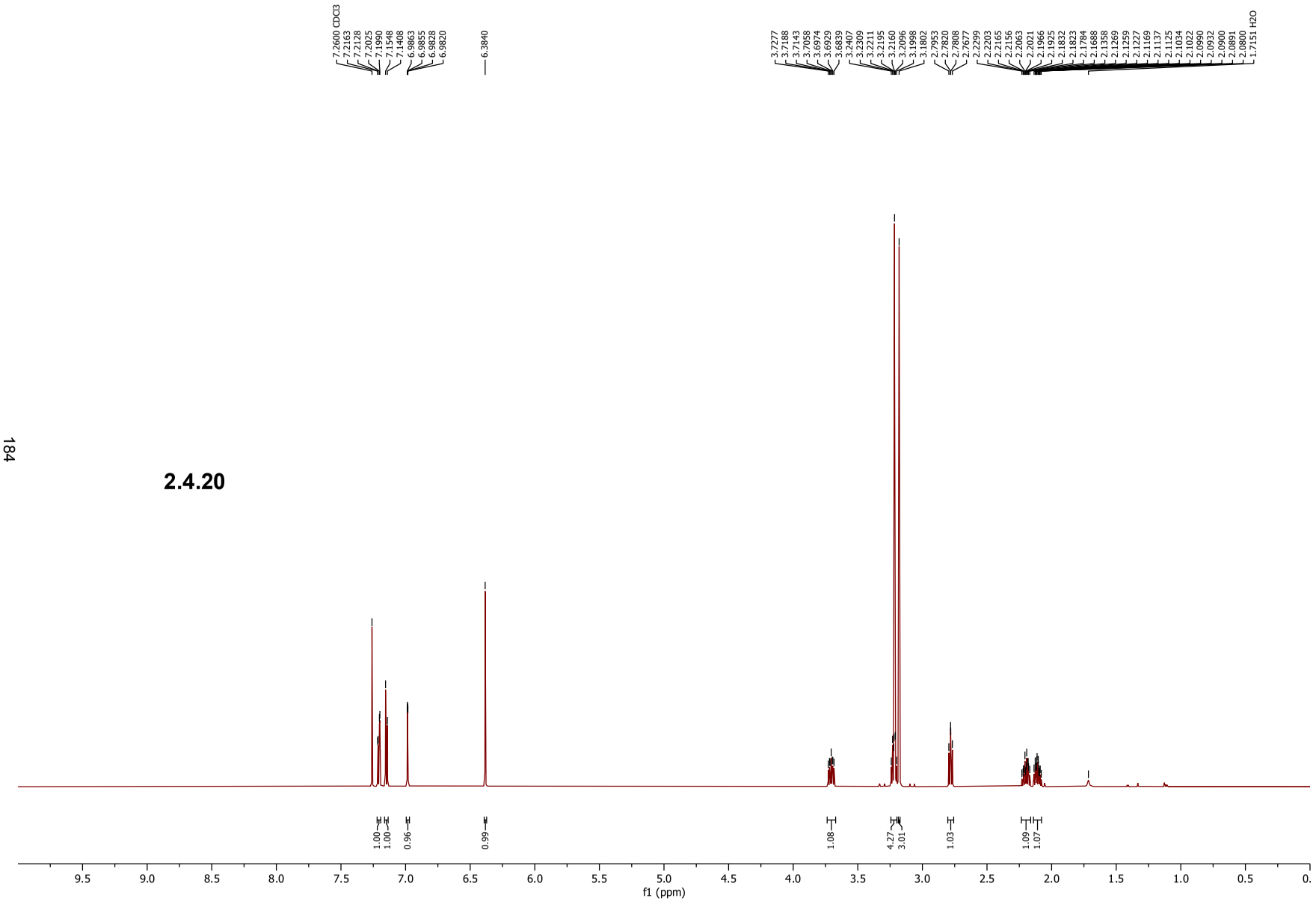

179.2472
165.5906
150.9560
138.9019
131.4991
129.9709
129.8693
122.7321
120.0290
109.9943
77.3731 CDCl3
77.1600 CDCl3
76.9508 CDCl3
57.5891
56.9851
38.5462
34.5115
181
2.4.18
f1 (ppm)


7.2600 CDCl3
7.2319
7.2284
7.2181
7.2146
7.1659
7.1522
7.0428
7.0393
6.5492
4.8560
3.1939
3.1089
2.8921
2.8640
2.8066
2.7785
0.98
1.00
1.00
0.97
0.93
3.19
3.17
1.06
1.08
f1 (ppm)

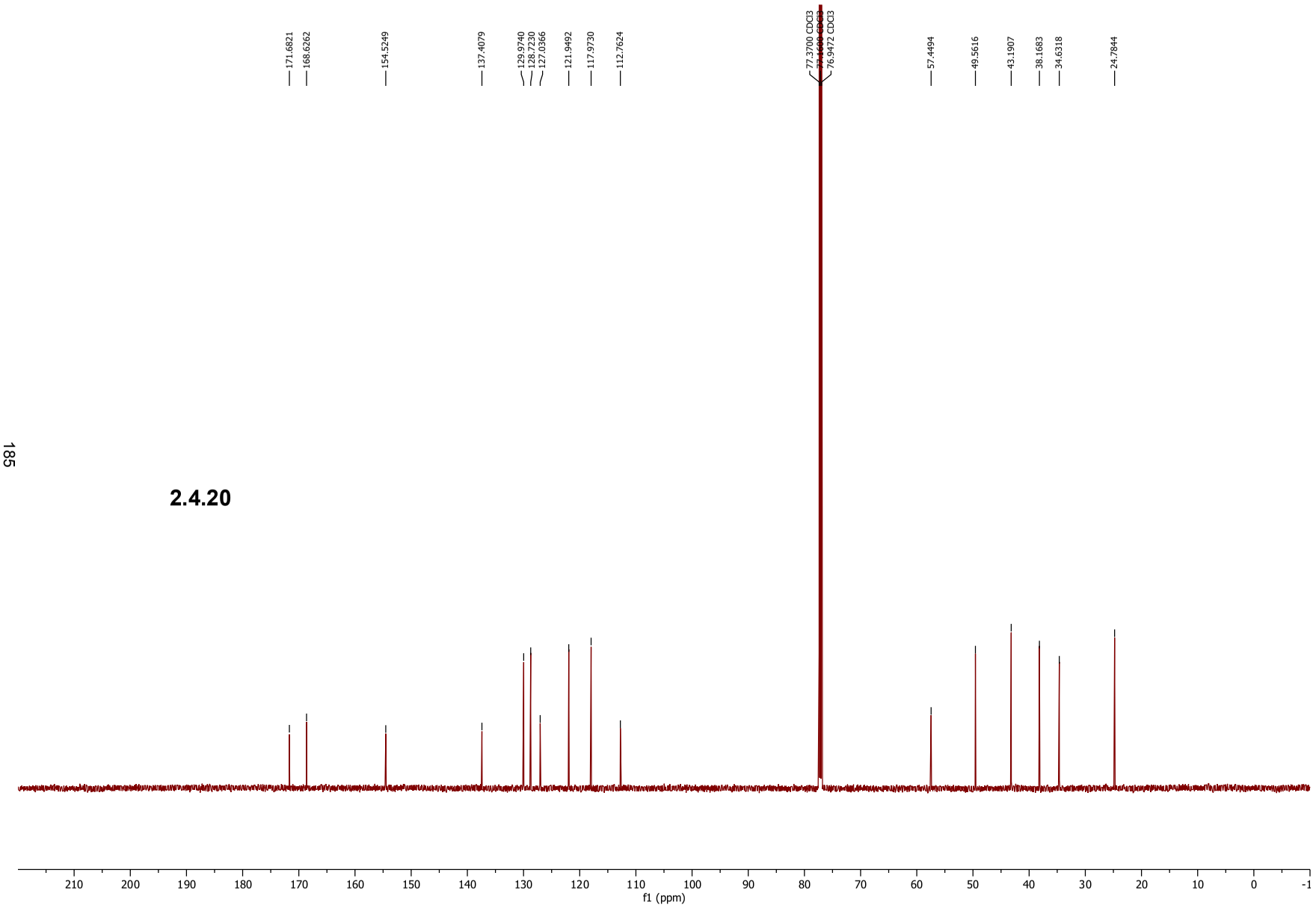
2.4.19


173.2878
165.3549
154.1391
138.2550
131.4554
129.8730
127.4511
122.1134
118.2103
111.4045
77.3722 CDCl3
77.1668 CDCl3
76.9483 CDCl3
57.7907
41.1494
34.6062
30.1650
183
2.4.19
f1 (ppm)

2.4.20

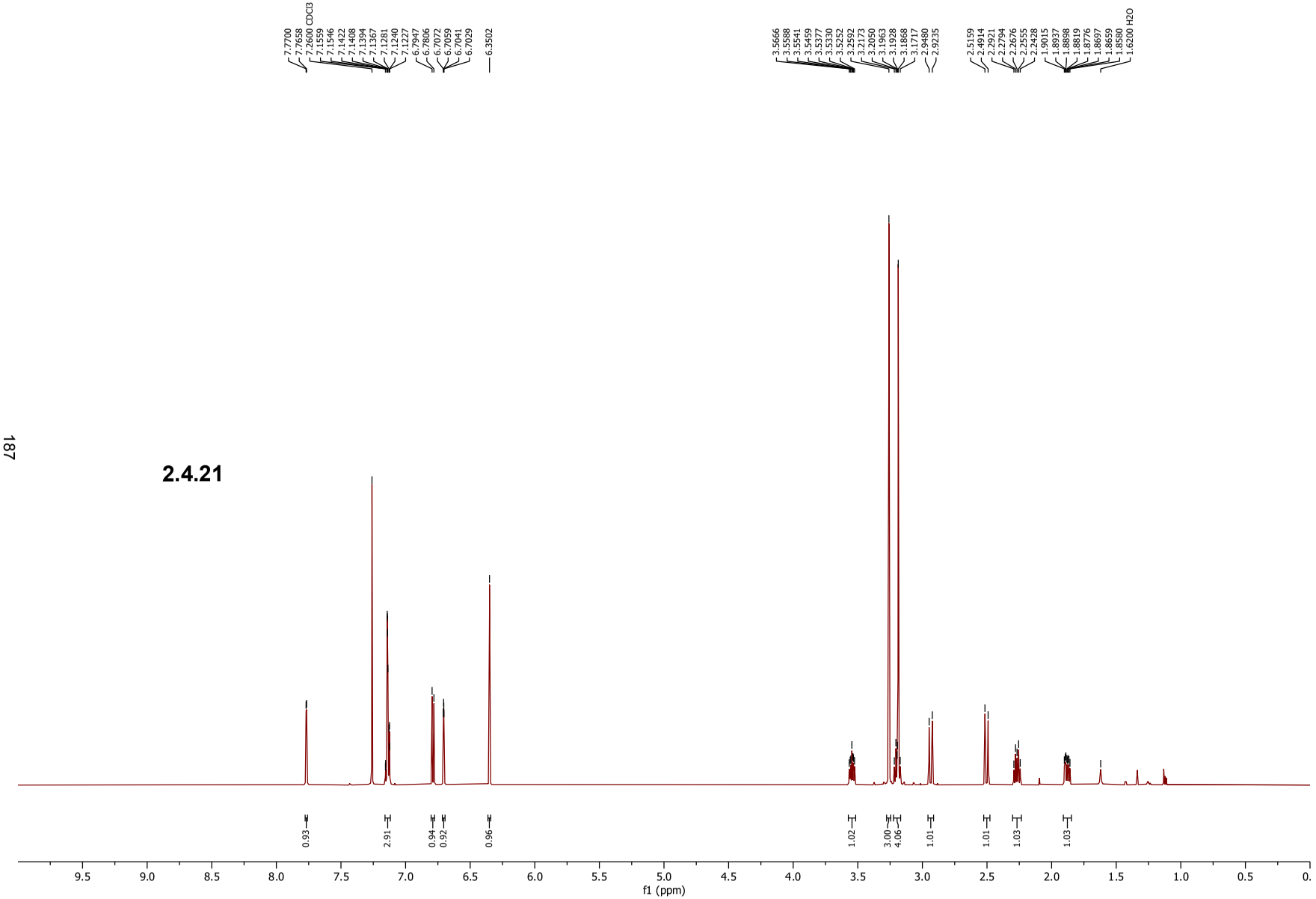

7.2600 CDCl3
7.2163
7.2128
7.2025
7.1990
7.1548
7.1408
6.9863
6.9855
6.9828
6.9820
6.3840
3.7277
3.7188
3.7143
3.7058
3.6974
3.6929
3.6839
3.2407
3.2309
3.2211
3.2195
3.2160
3.2096
3.1998
3.1802
2.7953
2.7820
2.7808
2.7677
2.2299
2.2203
2.2165
2.2156
2.2063
2.2021
2.1966
2.1925
2.1832
2.1823
2.1784
2.1688
2.1358
2.1269
2.1259
2.1227
2.1169
2.1137
2.1125
2.1034
2.1022
2.0990
2.0932
2.0900
2.0891
2.0800
1.7151 H2O
1.00
1.00
0.96
0.99
1.08
4.27
3.01
1.03
1.09
1.07
f1 (ppm)

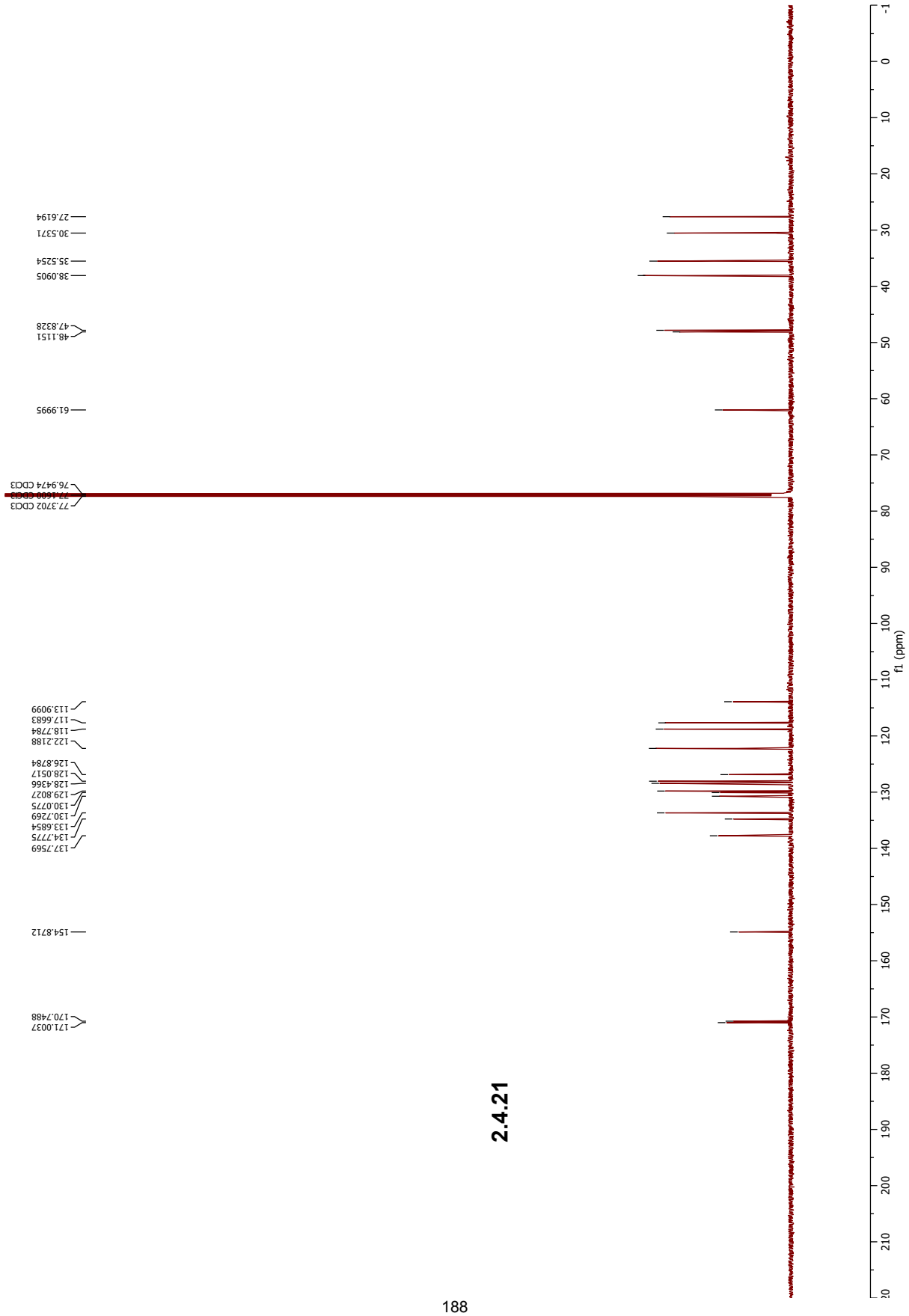
2.4.20


171.6821
168.6262
154.5249
137.4079
129.9740
128.7230
127.0366
121.9492
117.9730
112.7624
77.3700 CDCl3
77.1668 CDCl3
76.9472 CDCl3
57.4494
49.5616
43.1907
38.1683
34.6318
24.7844
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

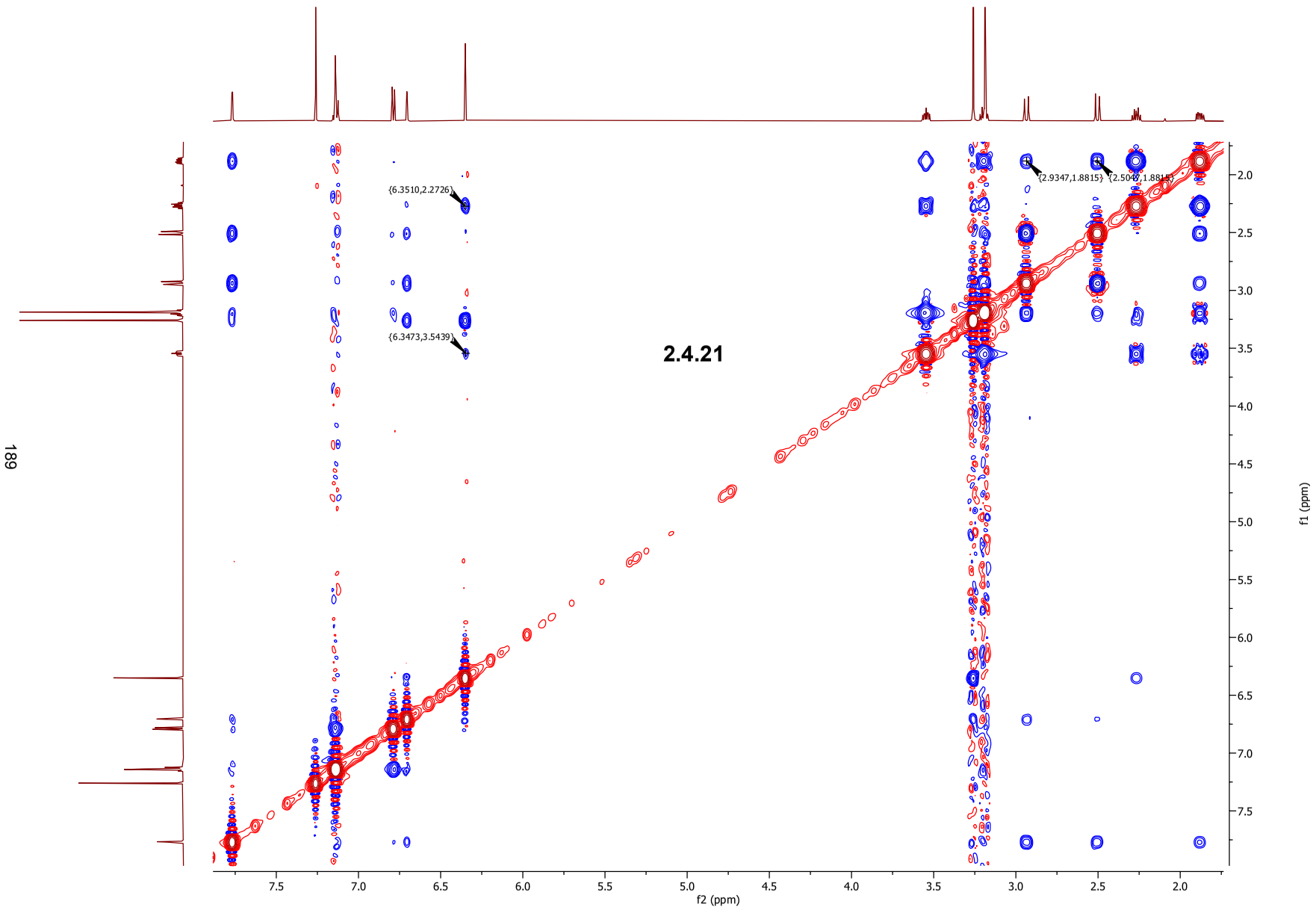
f1 (ppm)
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
(2.1907,2.7909)
(2.7774,6.9862)
(6.3851,2.1162)
(6.3832,3.7102)
(6.3854,6.9960)
2.4.20
f2 (ppm)
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.6
3.8
4.0
4.2
4.4
4.6
4.8
5.0
5.2
5.4
5.6
5.8
6.0
6.2
6.4
6.6
6.8
7.0
7.2

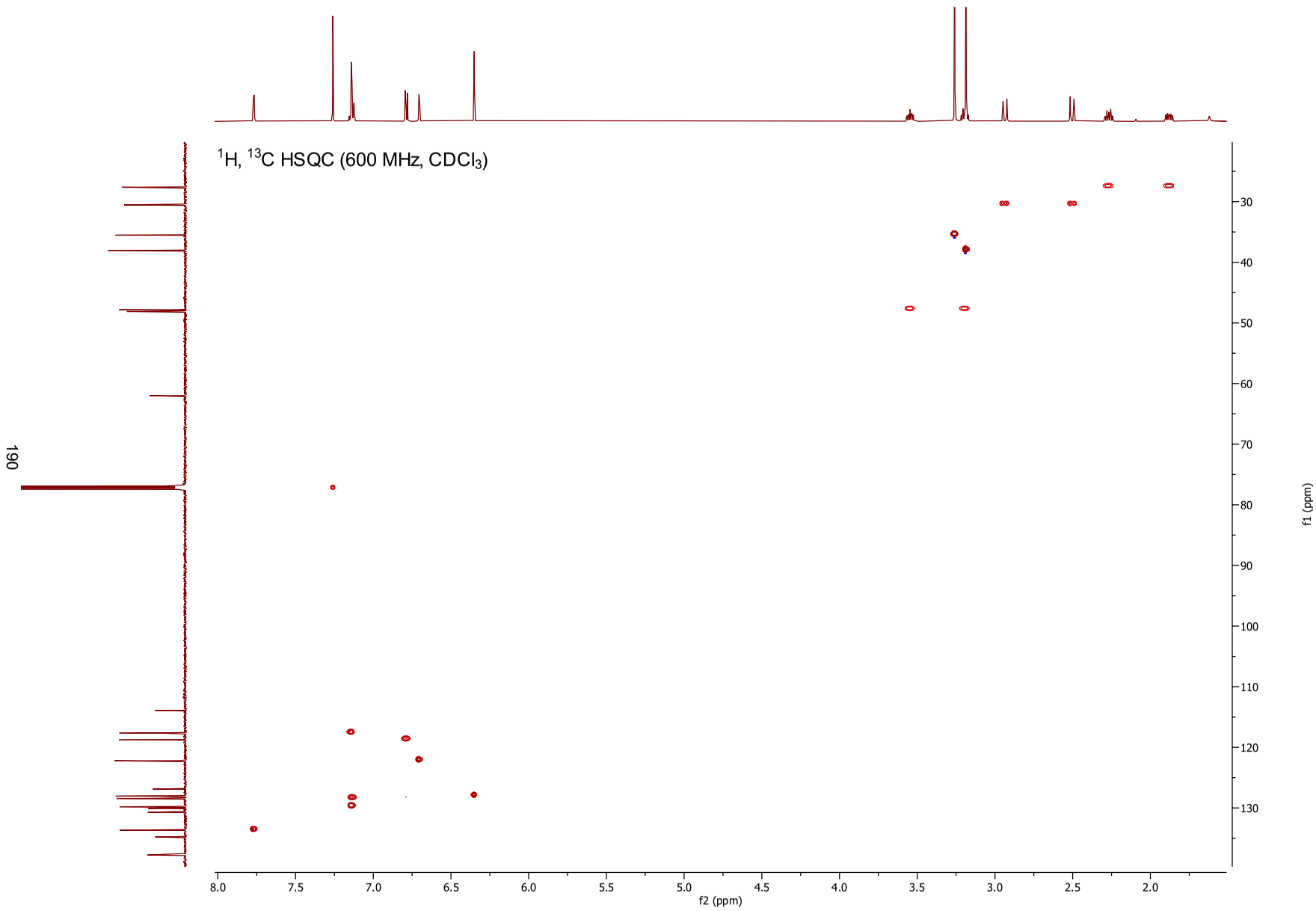
2.4.21

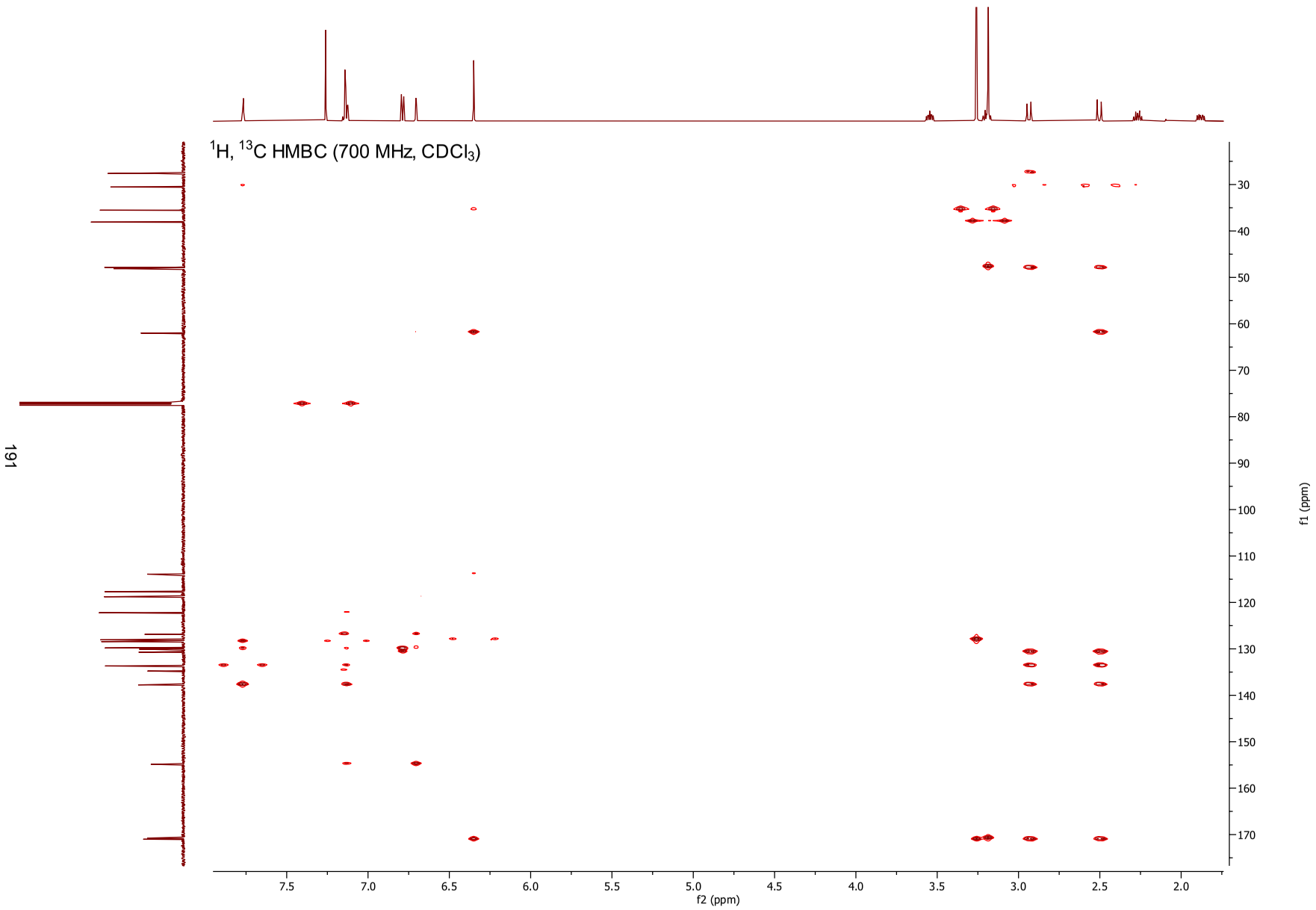

7.7700
7.7658
7.2600 CDCl3
7.1559
7.1546
7.1422
7.1408
7.1394
7.1367
7.1281
7.1240
7.1227
6.7947
6.7806
6.7072
6.7059
6.7041
6.7029
6.3502
3.5666
3.5588
3.5541
3.5459
3.5377
3.5330
3.5252
3.2592
3.2173
3.2050
3.1963
3.1928
3.1868
3.1717
2.9480
2.9235
2.5159
2.4914
2.2921
2.2794
2.2676
2.2555
2.2428
1.9015
1.8937
1.8898
1.8819
1.8776
1.8697
1.8659
1.8580
1.6200 H2O
0.93
2.91
0.94
0.92
0.96
1.02
3.00
4.06
1.01
1.01
1.03
1.03
f1 (ppm)


171.0037
170.7488
154.8712
137.7569
134.7775
133.6854
130.7269
130.0775
129.8027
128.4366
128.0517
126.8784
122.2188
118.7784
117.6683
113.9099
77.3702 CDCl3
77.1690 CDCl3
76.9474 CDCl3
61.9995
48.1151
47.8328
38.0905
35.5254
30.5371
27.6194
f1 (ppm)

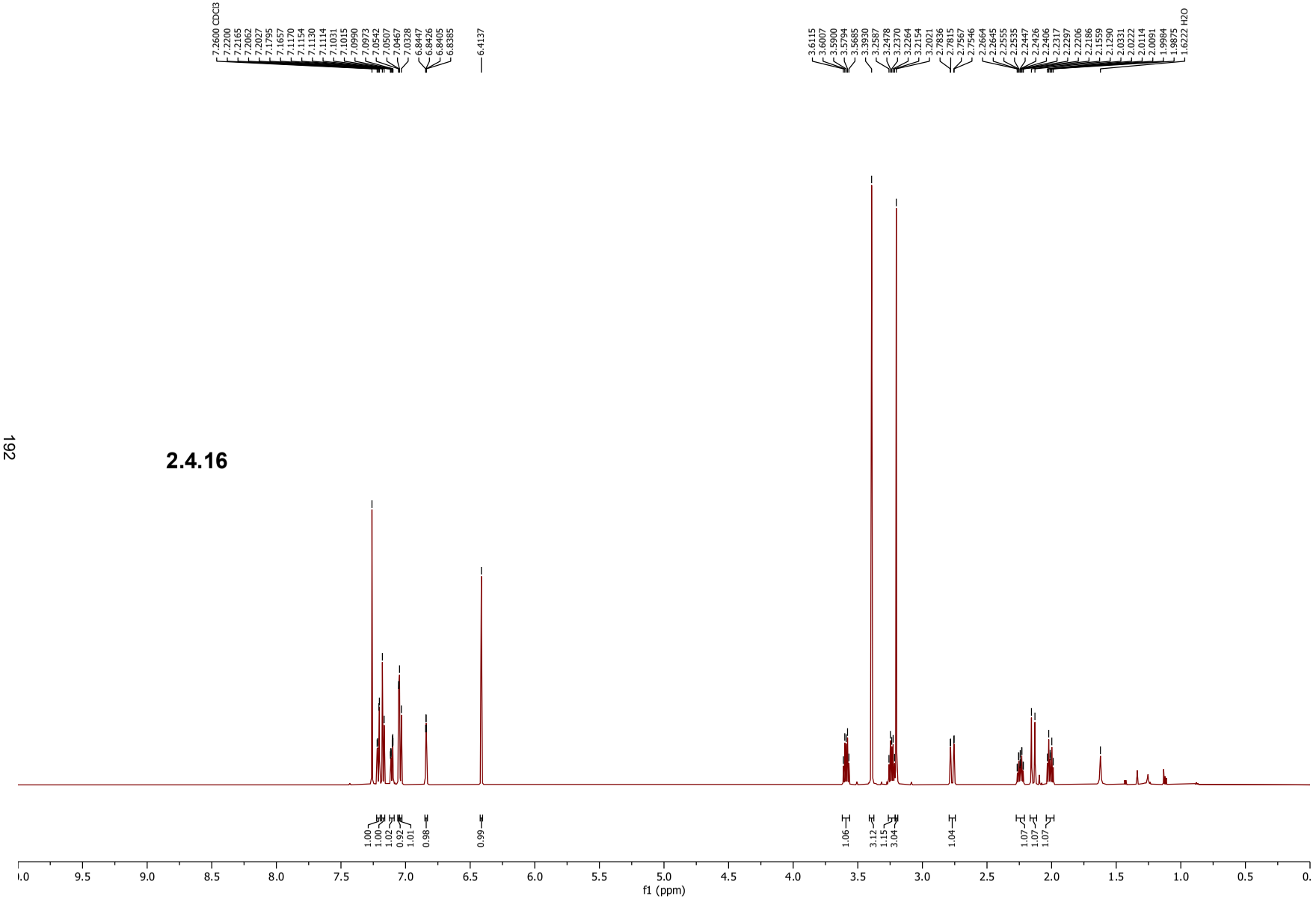
2.4.21

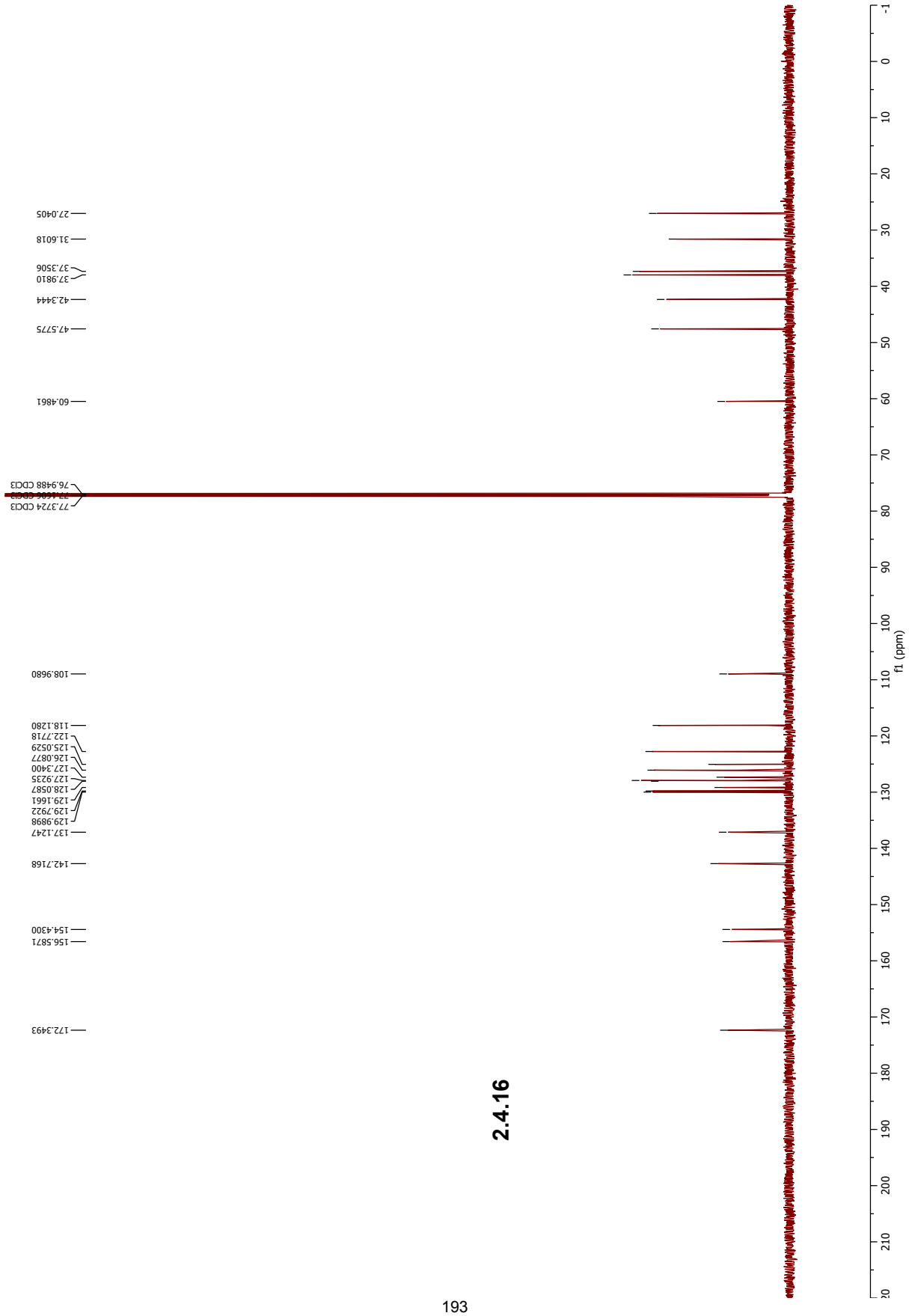

{6.3510,2.2726}
{6.3473,3.5439}
{2.9347,1.8815}
{2.5042,1.8815}
2.4.21
f2 (ppm)
f1 (ppm)


^{1}H, ^{13}C HSQC (600 MHz, $CDCl_3$)
190
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f2 (ppm)
30
40
50
60
70
80
90
100
110
120
130
f1 (ppm)


^{1}H, ^{13}C HMBC (700 MHz, CDCl$_3$)
191
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f2 (ppm)
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)

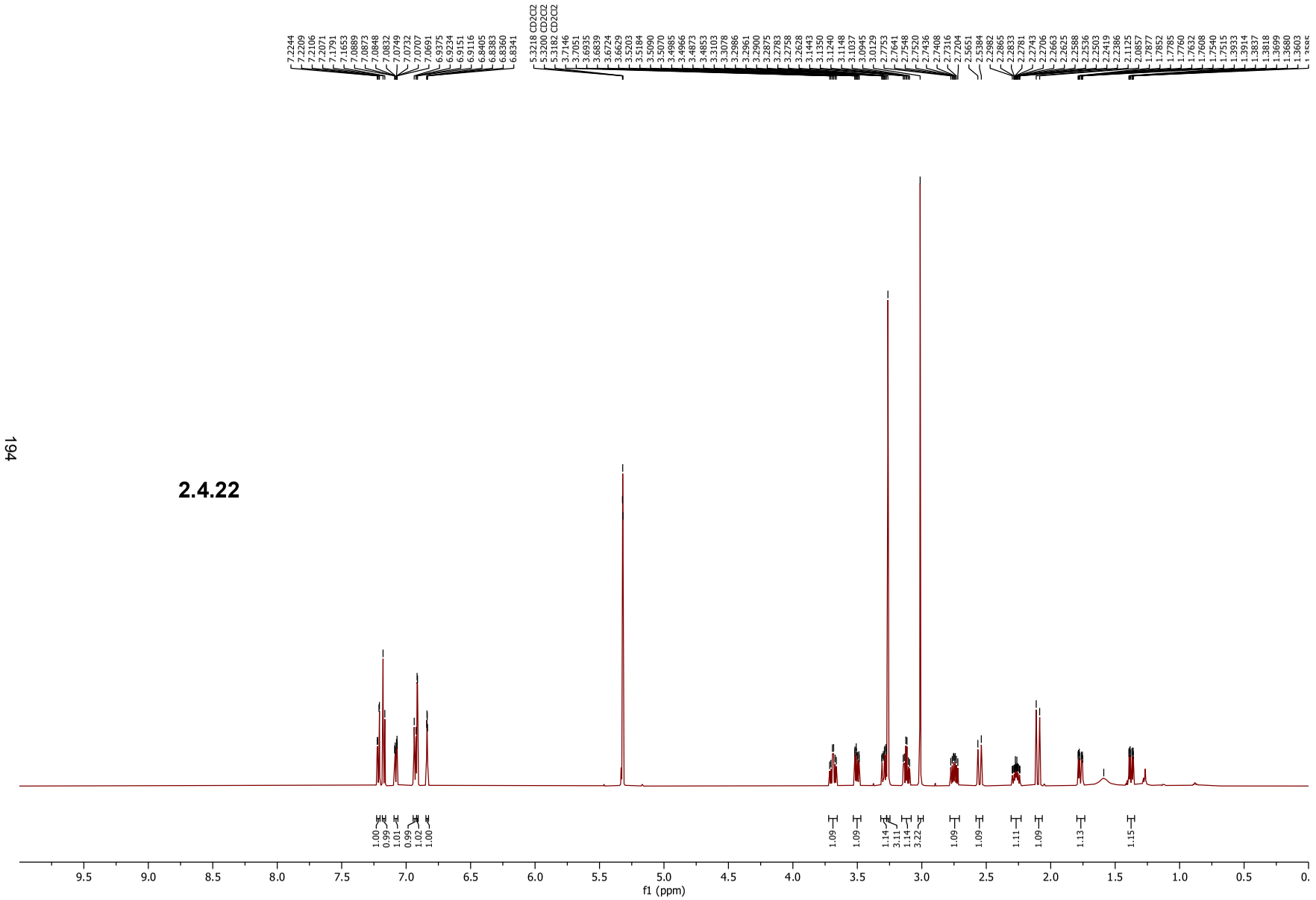
2.4.16

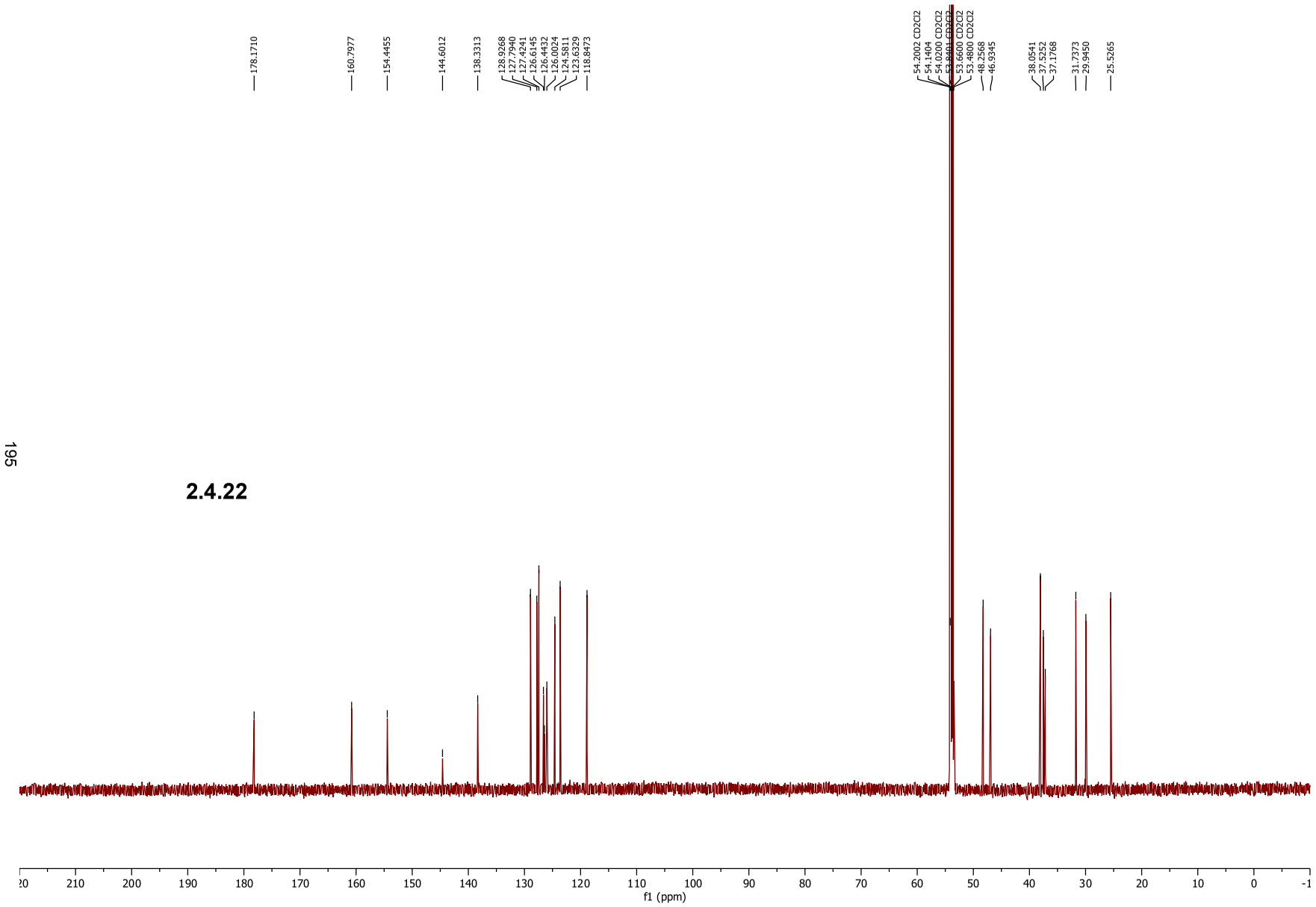

7.2600 CDCl3
7.2200
7.2165
7.2062
7.2027
7.1795
7.1657
7.1170
7.1154
7.1130
7.1114
7.1031
7.1015
7.0990
7.0973
7.0542
7.0507
7.0467
7.0328
6.8447
6.8426
6.6405
6.6385
6.4137
3.6115
3.6007
3.5900
3.5794
3.5685
3.3930
3.2587
3.2478
3.2370
3.2264
3.2154
3.2021
2.7836
2.7815
2.7567
2.7546
2.2664
2.2645
2.2555
2.2535
2.2447
2.2426
2.2406
2.2317
2.2297
2.2206
2.2186
2.1599
2.1290
2.0331
2.0222
2.0114
2.0091
1.9984
1.9875
1.6222 H2O
1.00
1.00
1.02
0.92
1.01
0.98
0.99
1.06
3.12
1.15
3.04
1.04
1.07
1.07
1.07
f1 (ppm)


172.3493
156.5871
154.4300
142.7168
137.1247
129.9898
129.7922
129.1661
128.0587
127.9235
127.3400
126.0877
125.0529
122.7718
118.1280
108.9680
77.3724 CDCl3
76.9488 CDCl3
60.4861
47.5775
42.3444
37.9810
37.3506
31.6018
27.0405
f1 (ppm)

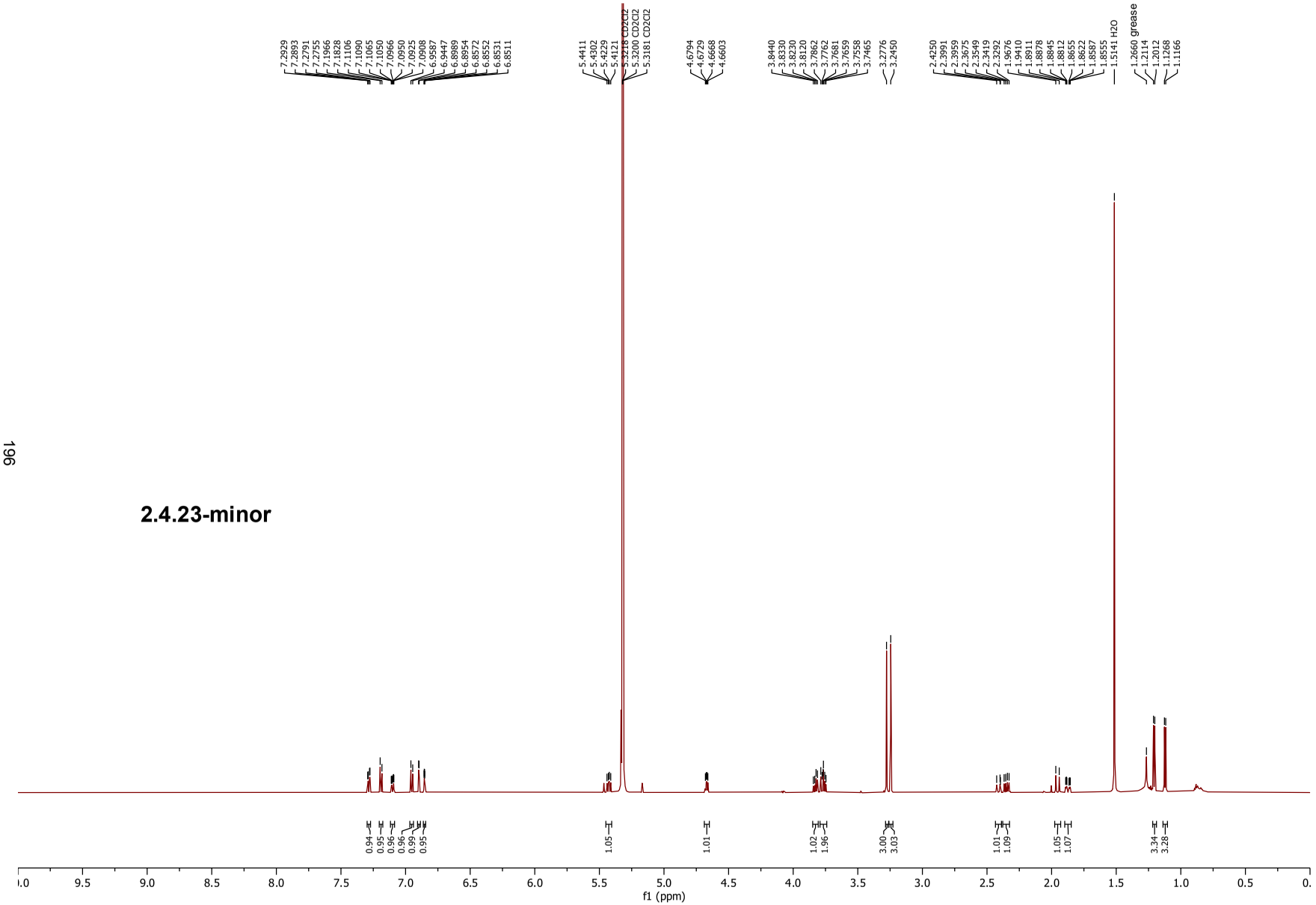
2.4.16

2.4.22

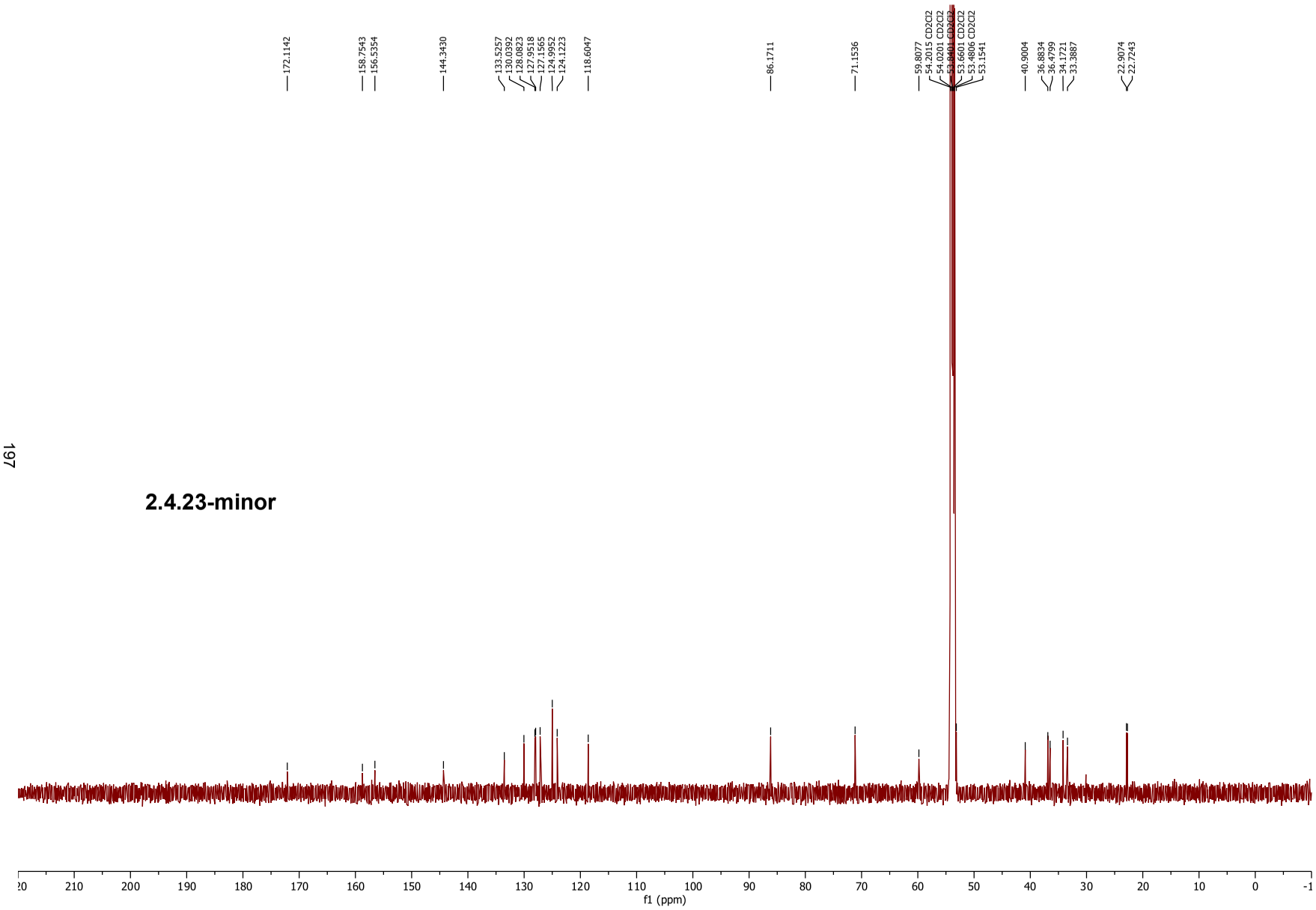

7.2244
7.2209
7.2106
7.2071
7.1791
7.1653
7.0889
7.0873
7.0848
7.0832
7.0749
7.0732
7.0707
7.0691
6.9375
6.9234
6.9151
6.9116
6.8405
6.8383
6.8360
6.8341
5.3218 CD2Cl2
5.3200 CD2Cl2
5.3182 CD2Cl2
3.7146
3.7051
3.6835
3.6839
3.6724
3.6629
3.5203
3.5184
3.5090
3.5070
3.4985
3.4966
3.4873
3.4853
3.3103
3.3078
3.2986
3.2961
3.2900
3.2875
3.2783
3.2758
3.2628
3.1443
3.1350
3.1240
3.1148
3.1037
3.0945
3.0129
2.7753
2.7641
2.7548
2.7520
2.7436
2.7408
2.7316
2.7204
2.5651
2.5384
2.2982
2.2865
2.2833
2.2781
2.2743
2.2706
2.2663
2.2625
2.2588
2.2536
2.2503
2.2419
2.2386
2.1125
2.0857
1.7877
1.7852
1.7785
1.7760
1.7632
1.7608
1.7540
1.7515
1.3933
1.3914
1.3837
1.3818
1.3699
1.3680
1.3603
1.00
0.99
1.01
0.99
1.02
1.00
1.09
1.09
1.14
3.11
1.14
3.22
1.09
1.09
1.11
1.09
1.13
1.15
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

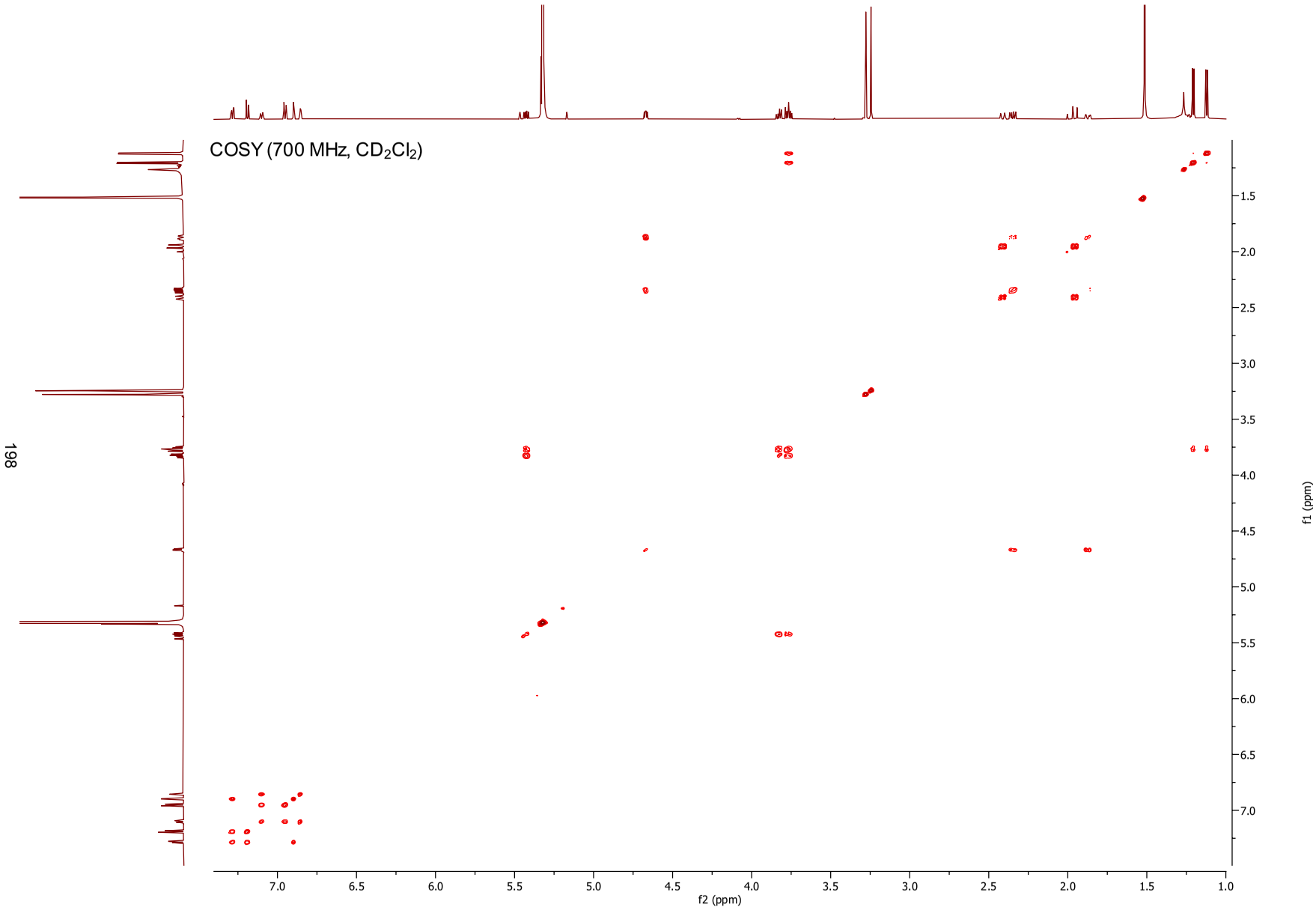

178.1710
160.7977
154.4455
144.6012
138.3313
128.9268
127.7940
127.4241
126.6145
126.4432
126.0024
124.5811
123.6329
116.8473
54.2002 CD2Cl2
54.1404
54.0200 CD2Cl2
53.8401 CD2Cl2
53.6600 CD2Cl2
53.4800 CD2Cl2
48.2568
46.9345
38.0541
37.5252
37.1768
31.7373
29.9450
25.5265
195
2.4.22
f1 (ppm)

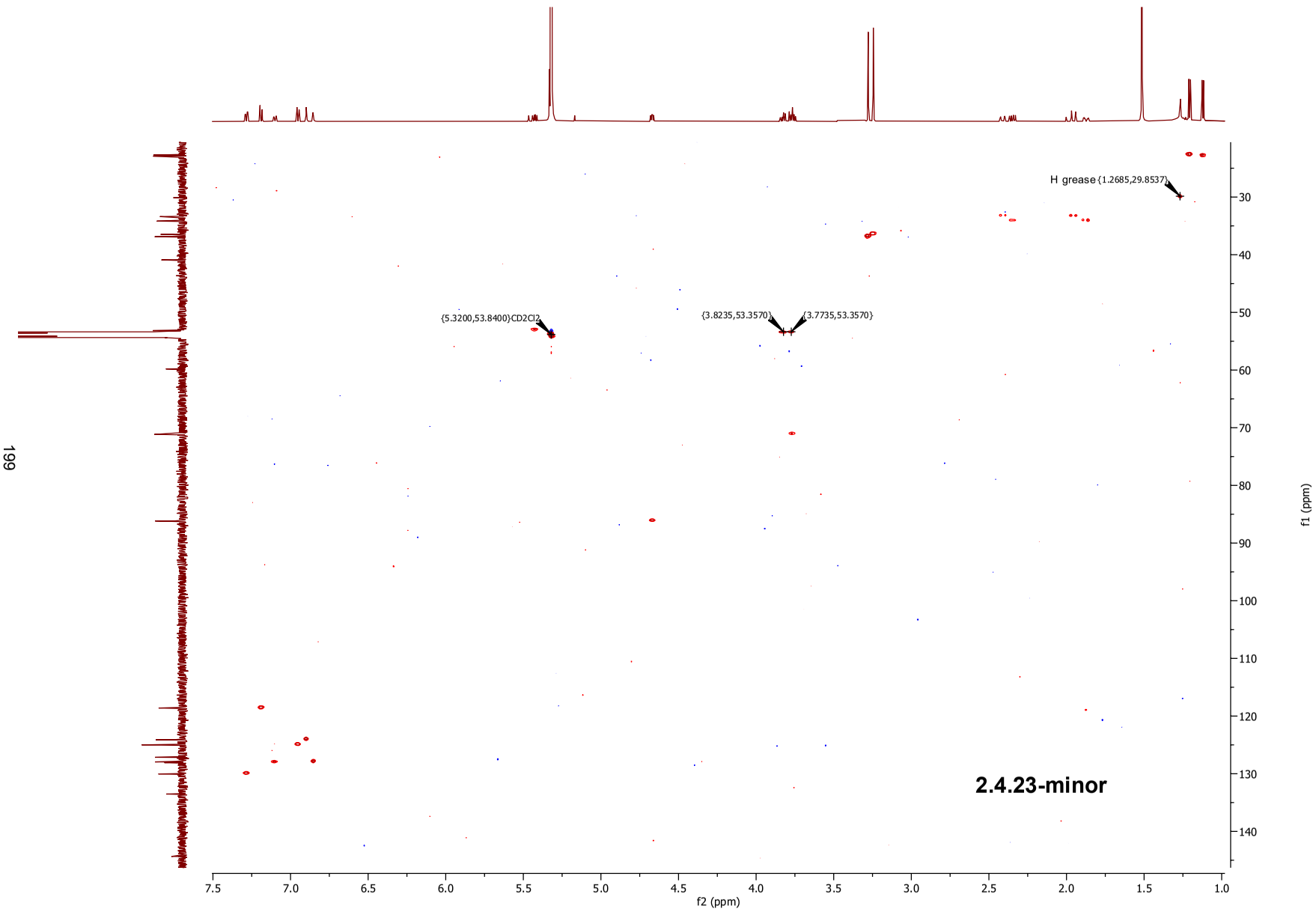
2.4.23-minor

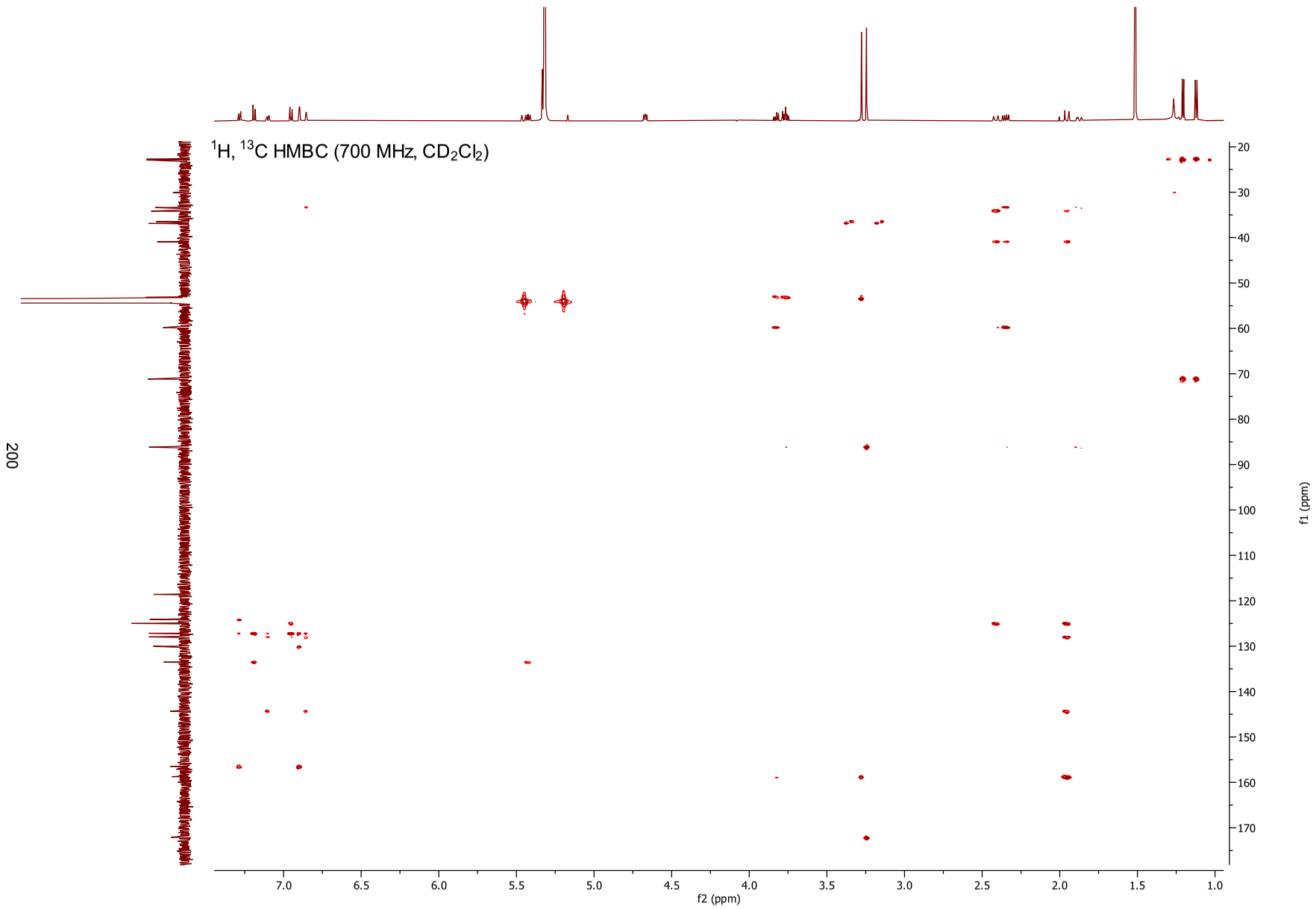

7.2929
7.2893
7.2791
7.2755
7.1966
7.1828
7.1106
7.1090
7.1065
7.1050
7.0966
7.0950
7.0925
7.0908
6.9587
6.9447
6.8989
6.8954
6.8572
6.8552
6.8531
6.8511
5.4411
5.4302
5.4229
5.4121
5.3218 CD2Cl2
5.3200 CD2Cl2
5.3181 CD2Cl2
4.6794
4.6729
4.6668
4.6603
3.8440
3.8330
3.8230
3.8120
3.7862
3.7762
3.7681
3.7659
3.7558
3.7465
3.2776
3.2450
2.4250
2.3991
2.3959
2.3675
2.3549
2.3419
2.3292
1.9676
1.9410
1.8911
1.8878
1.8845
1.8812
1.8655
1.8622
1.8587
1.8555
1.5141 H2O
1.2660 grease
1.2114
1.2012
1.1268
1.1166
0.94
0.95
0.96
0.96
0.99
0.95
1.05
1.01
1.02
1.96
3.00
3.03
1.01
1.09
1.05
1.07
3.34
3.28
f1 (ppm)

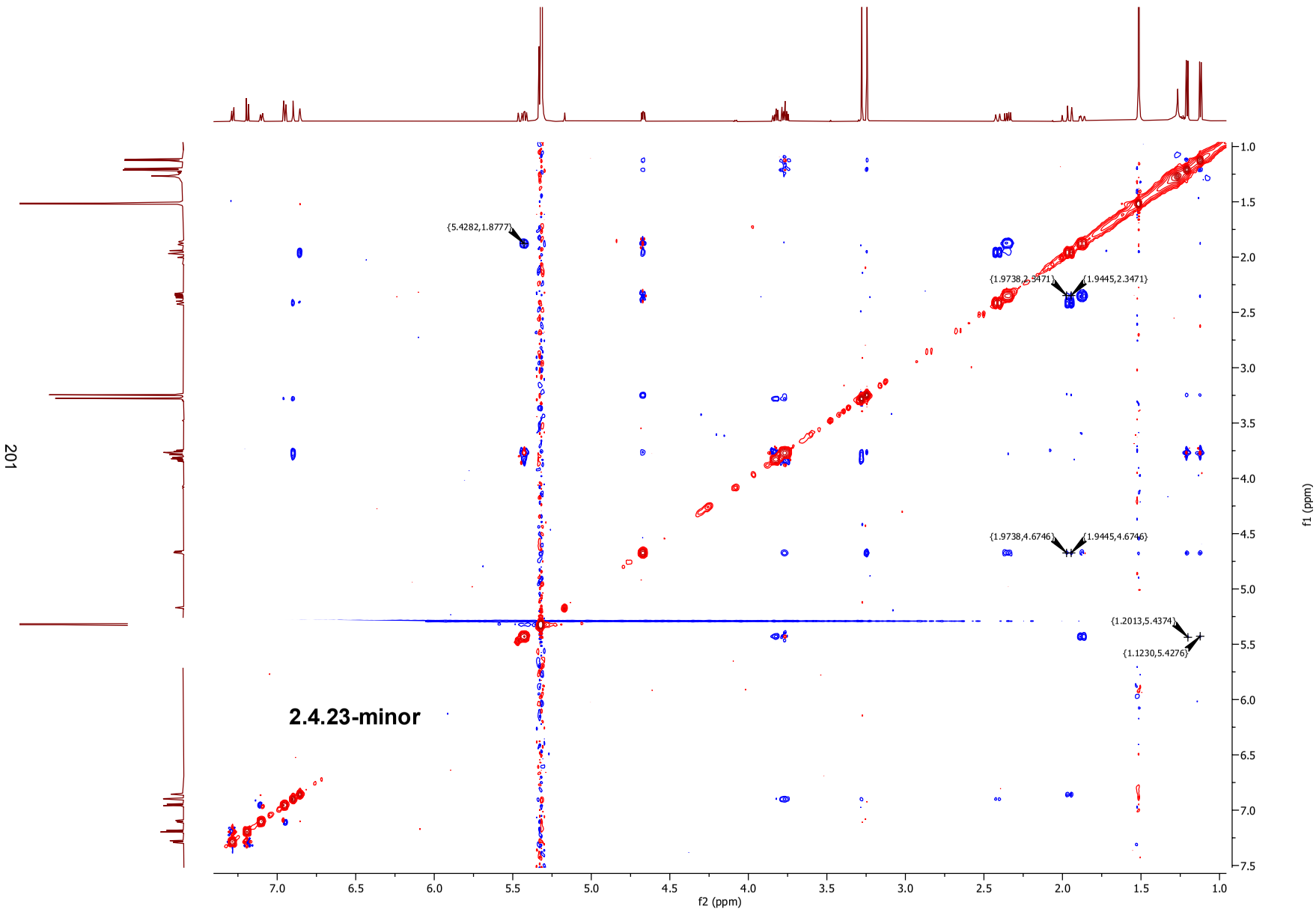
2.4.23-minor


172.1142
158.7543
156.5354
144.3430
133.5257
130.0392
128.0823
127.9518
127.1565
124.9952
124.1223
118.6047
86.1711
71.1536
59.8077
54.2015 CD2Cl2
54.0201 CD2Cl2
53.8401 CD2Cl2
53.6601 CD2Cl2
53.4806 CD2Cl2
53.1541
40.9004
36.8834
36.4799
34.1721
33.3887
22.9074
22.7243
f1 (ppm)

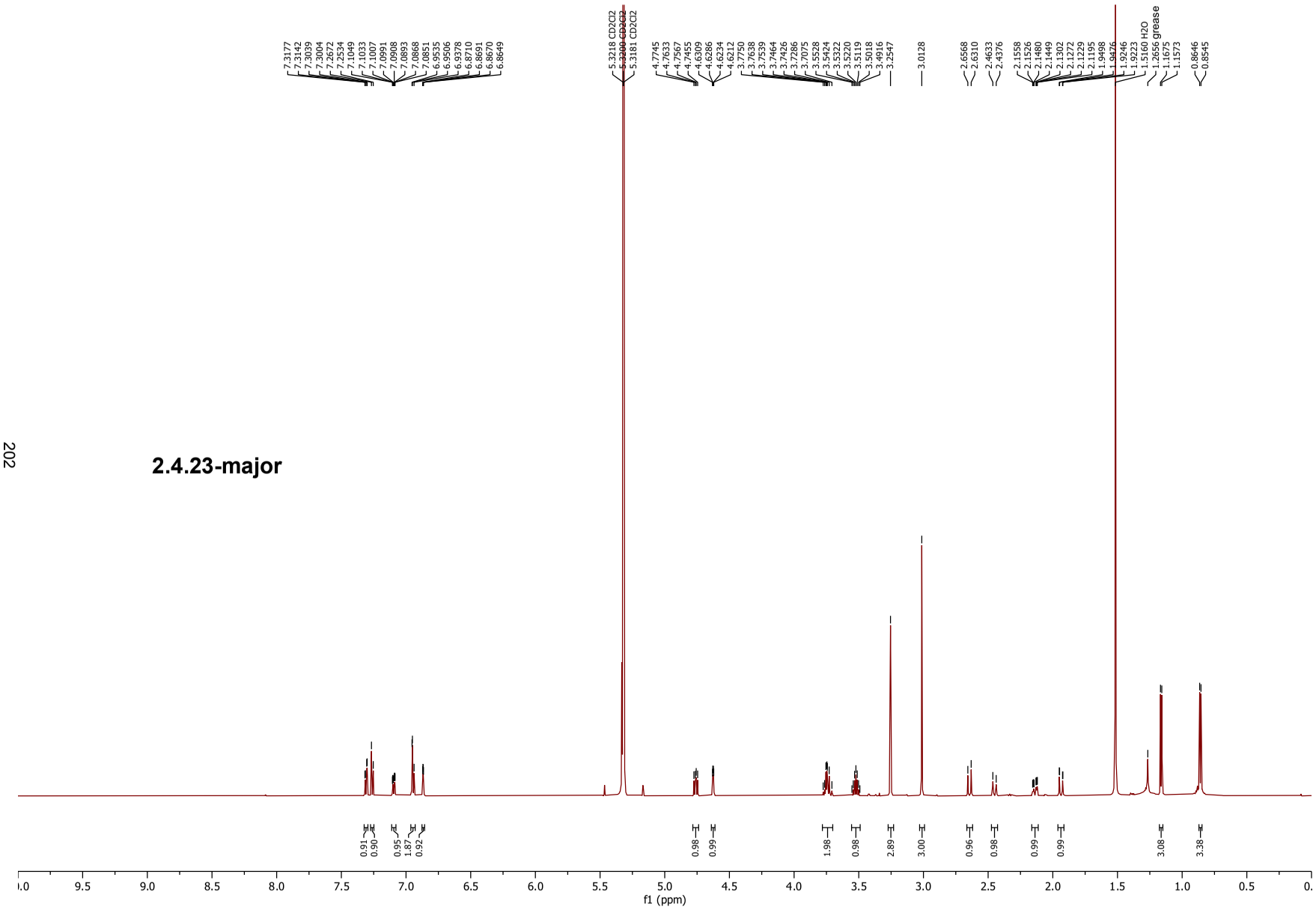

COSY (700 MHz, CD_2Cl_2)
198
f2 (ppm)
f1 (ppm)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

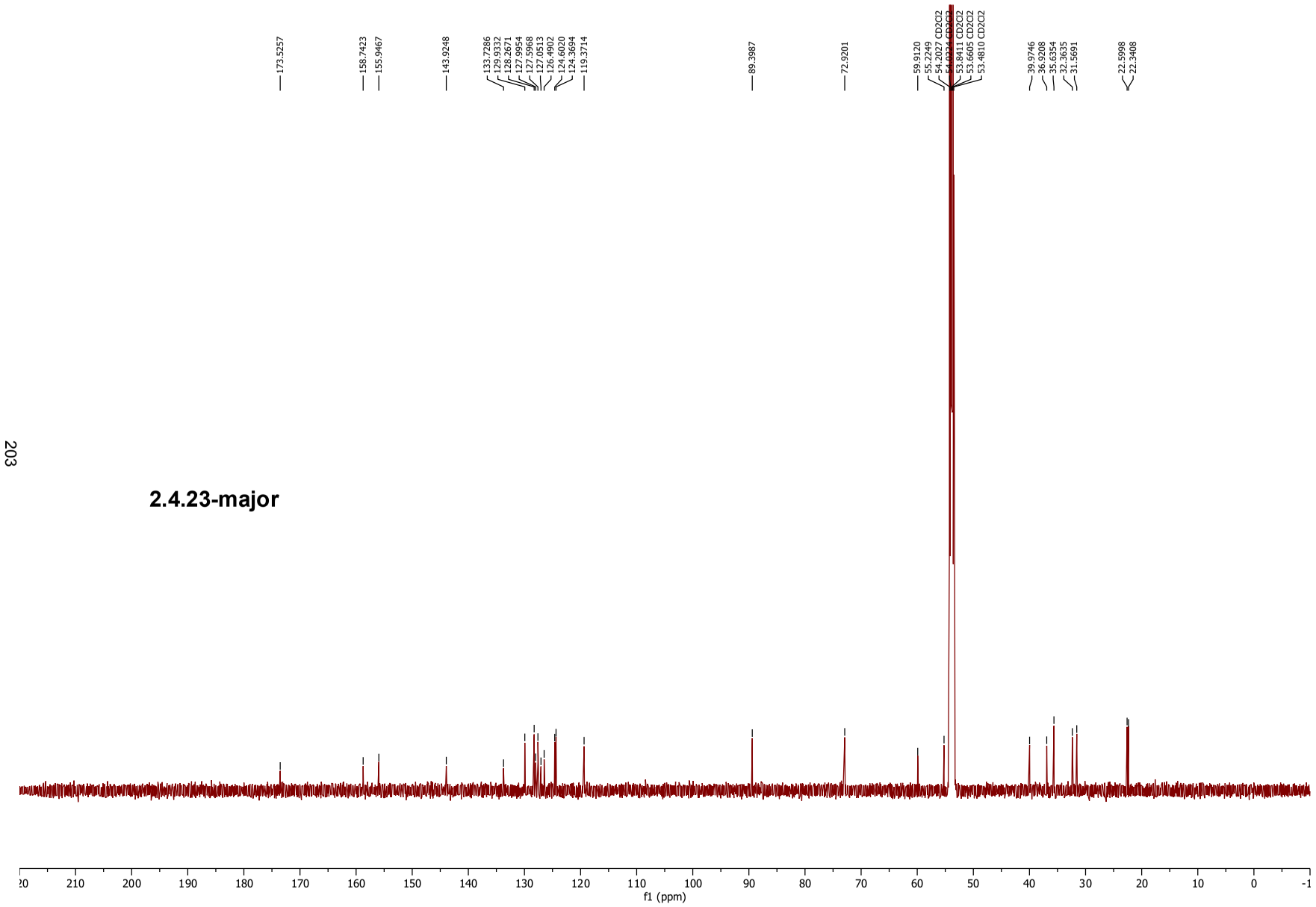

H grease {1.2685,29.8537}
{5.3200,53.8400}CD2Cl2
{3.8235,53.3570}
{3.7735,53.3570}
2.4.23-minor
f2 (ppm)
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
30
40
50
60
70
80
90
100
110
120
130
140

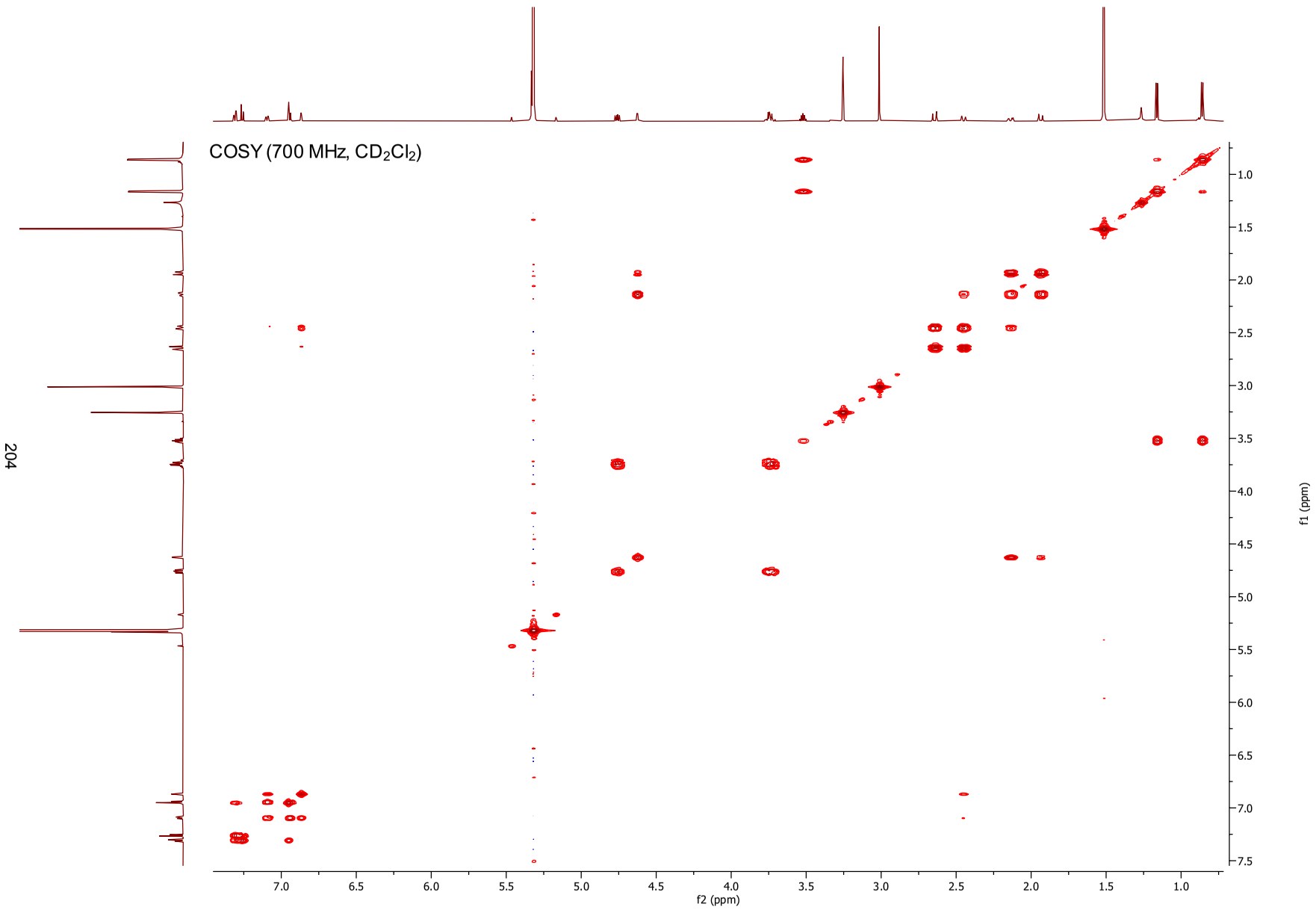

^{1}H, ^{13}C HMBC (700 MHz, CD_2Cl_2)
200
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)

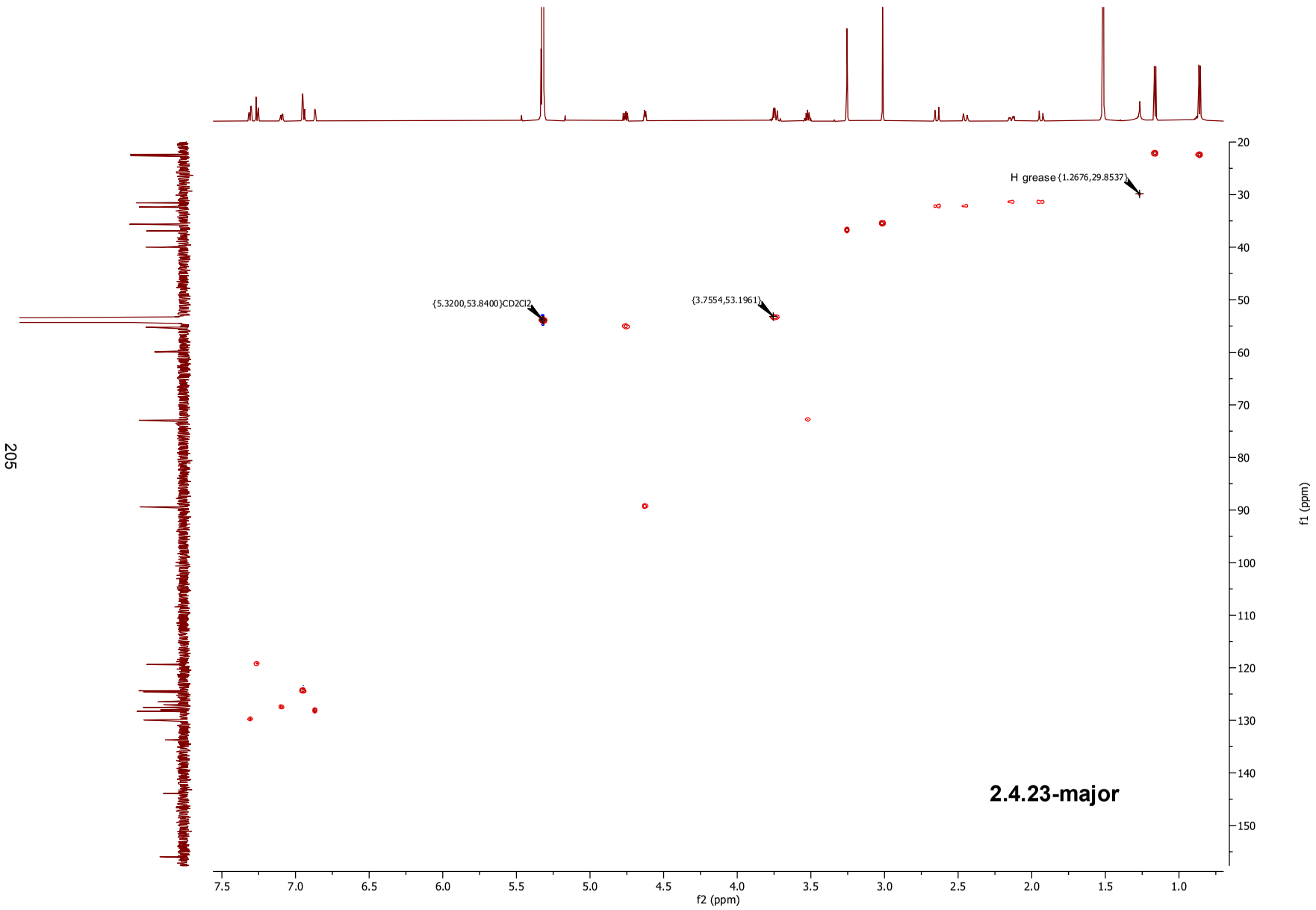

201
{5.4282,1.8777}
{1.9738,2.3471}
{1.9445,2.3471}
{1.9738,4.6746}
{1.9445,4.6746}
{1.2013,5.4374}
{1.1230,5.4276}
2.4.23-minor
f2 (ppm)
f1 (ppm)

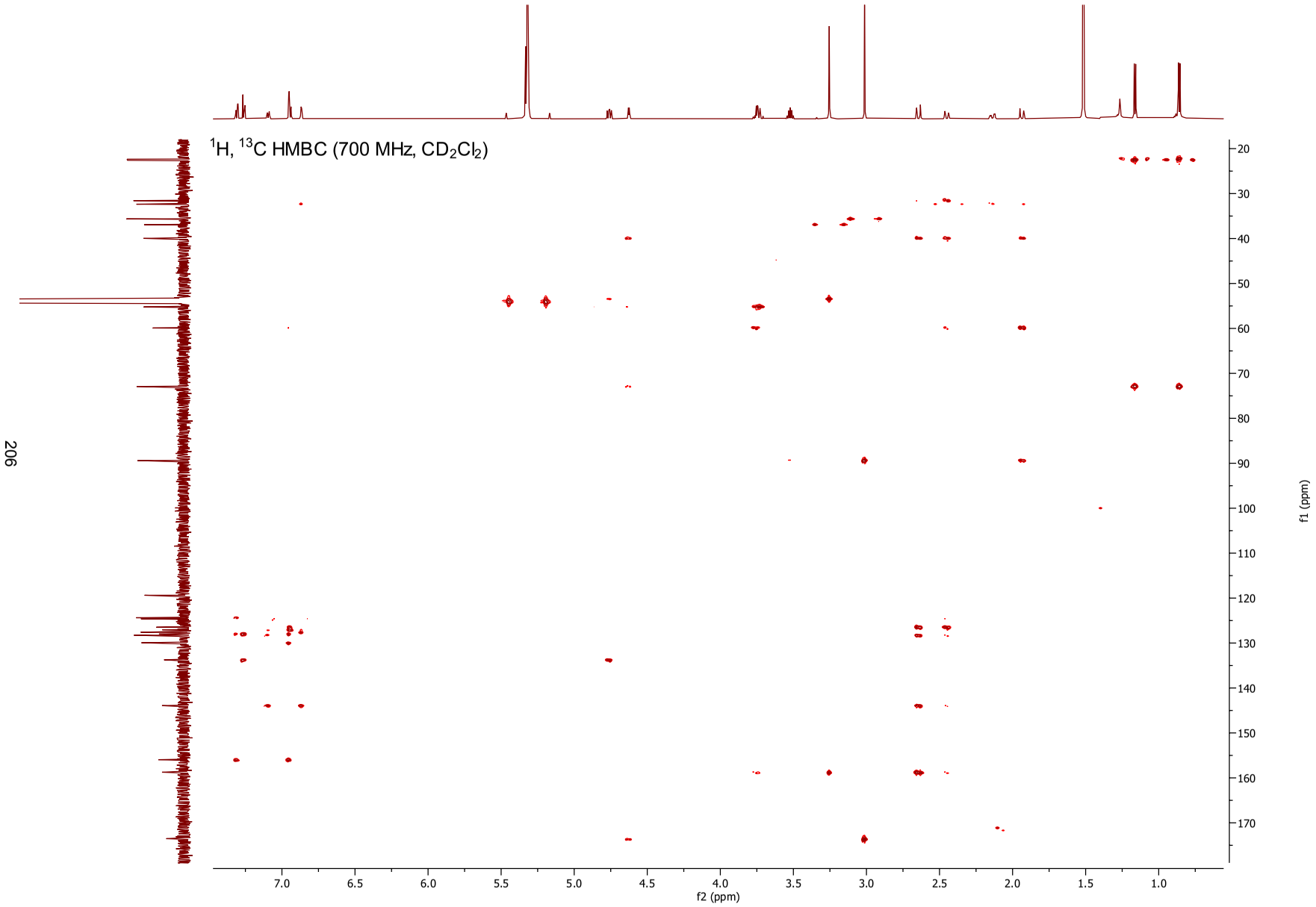
2.4.23-major

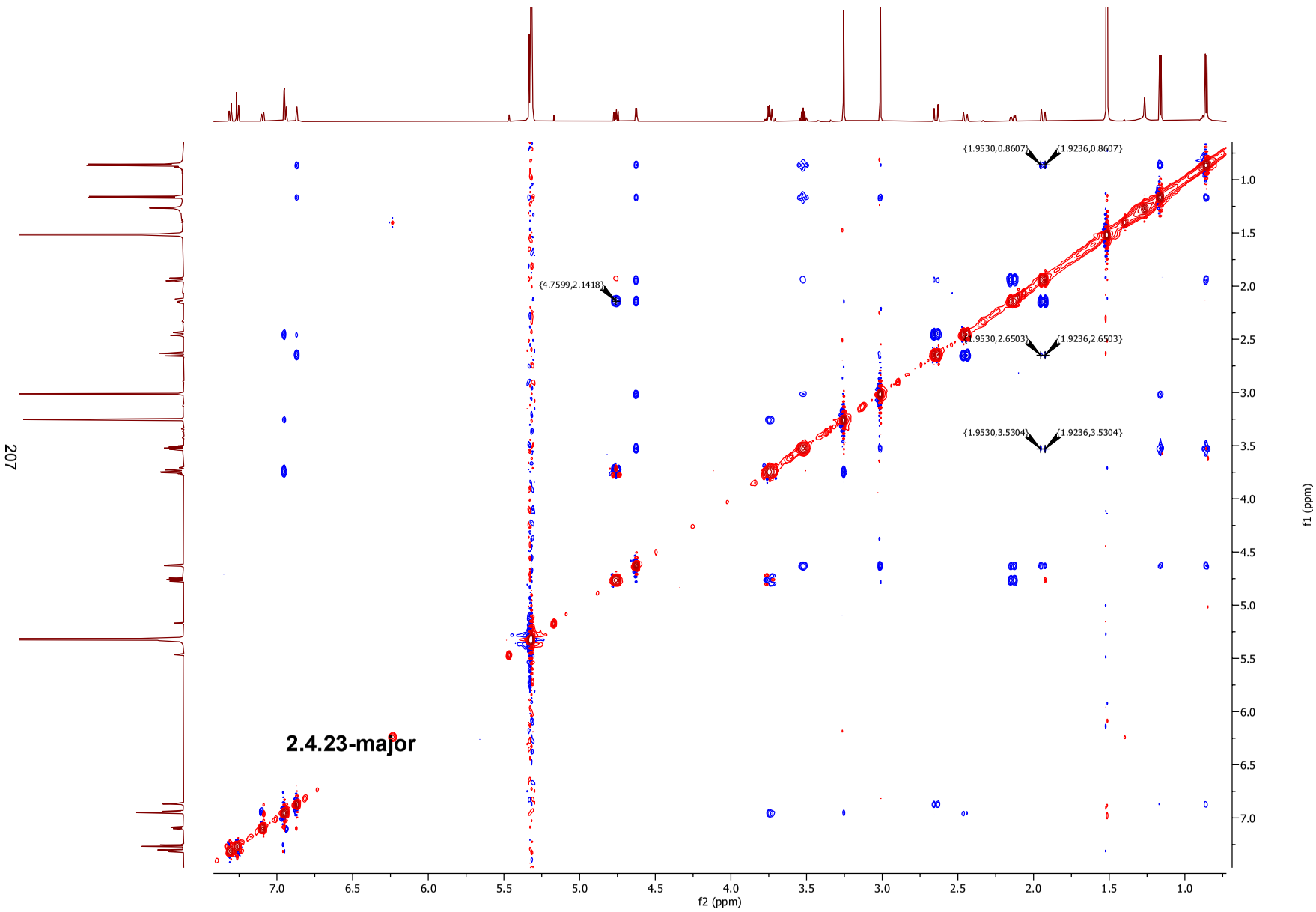

7.3177
7.3142
7.3039
7.3004
7.2672
7.2534
7.1049
7.1033
7.1007
7.0991
7.0908
7.0893
7.0868
7.0851
6.9535
6.9506
6.9378
6.8710
6.8691
6.8670
6.8649
5.3218 CD2Cl2
5.3200 CD2Cl2
5.3181 CD2Cl2
4.7745
4.7633
4.7567
4.7455
4.6309
4.6286
4.6234
4.6212
3.7750
3.7638
3.7539
3.7464
3.7426
3.7286
3.7075
3.5528
3.5424
3.5322
3.5220
3.5119
3.5018
3.4916
3.2547
3.0128
2.6568
2.6310
2.4633
2.4376
2.1558
2.1526
2.1480
2.1449
2.1302
2.1272
2.1229
2.1195
1.9998
1.9476
1.9246
1.9223
1.5160 H2O
1.2656 grease
1.1675
1.1573
0.8646
0.8545
0.91
0.90
0.95
1.87
0.92
0.98
0.99
1.98
0.98
2.89
3.00
0.96
0.98
0.99
0.99
3.08
3.38
f1 (ppm)

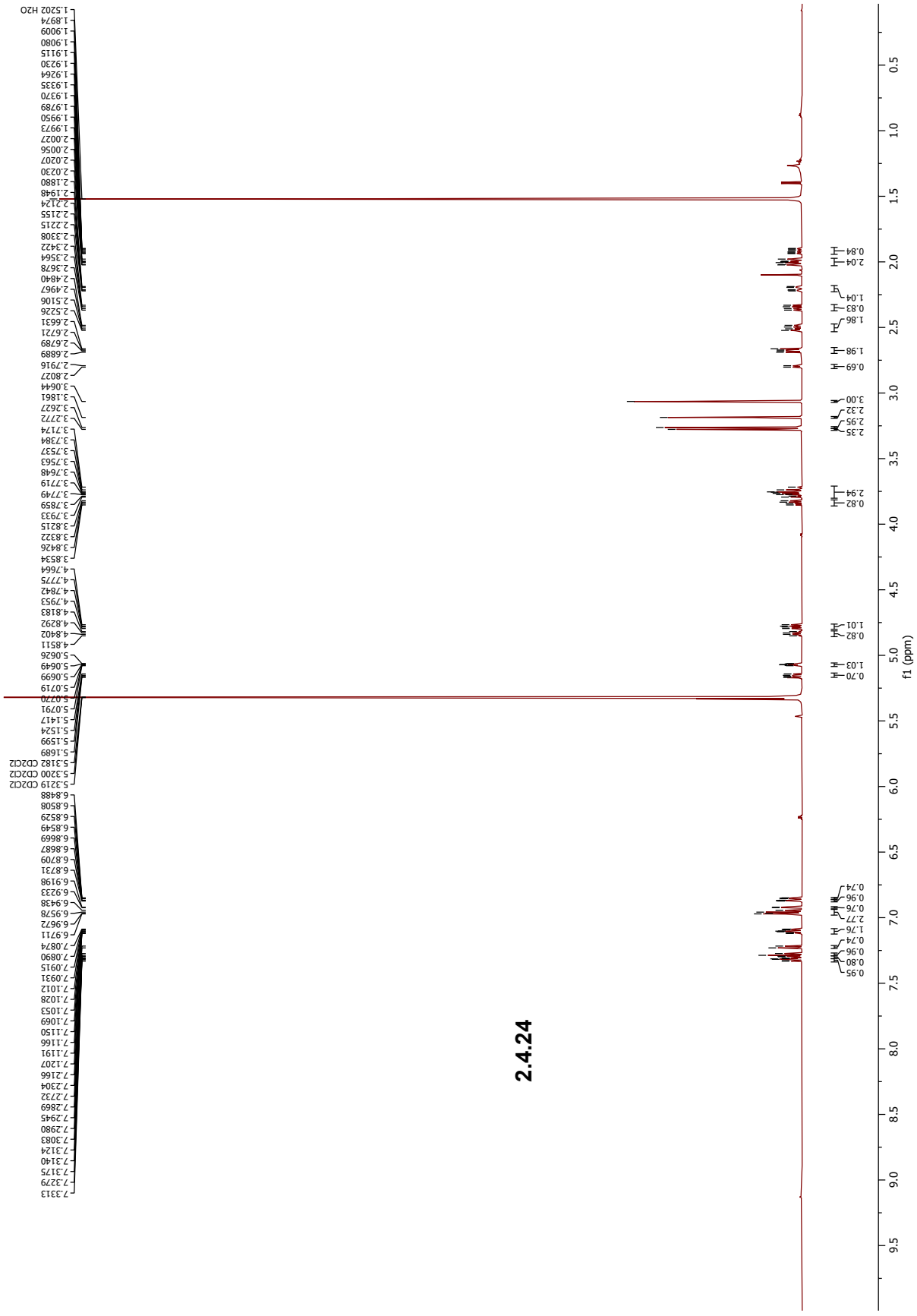

173.5257
158.7423
155.9467
143.9248
133.7286
129.9332
128.2671
127.9954
127.5968
127.0513
126.4902
124.6020
124.3694
119.3714
89.3987
72.9201
59.9120
55.2249
54.2027 CD2Cl2
54.0324 CD2Cl2
53.8411 CD2Cl2
53.6605 CD2Cl2
53.4810 CD2Cl2
39.9746
36.9208
35.6354
32.3635
31.5691
22.5998
22.3408
203
2.4.23-major
f1 (ppm)


COSY (700 MHz, CD2Cl2)
f2 (ppm)
f1 (ppm)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
7.5


H grease {1.2676,29.8537}
{5.3200,53.8400}CD2Cl2
{3.7554,53.1961}
2.4.23-major
f2 (ppm)
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
20
30
40
50
60
70
80
90
100
110
120
130
140
150

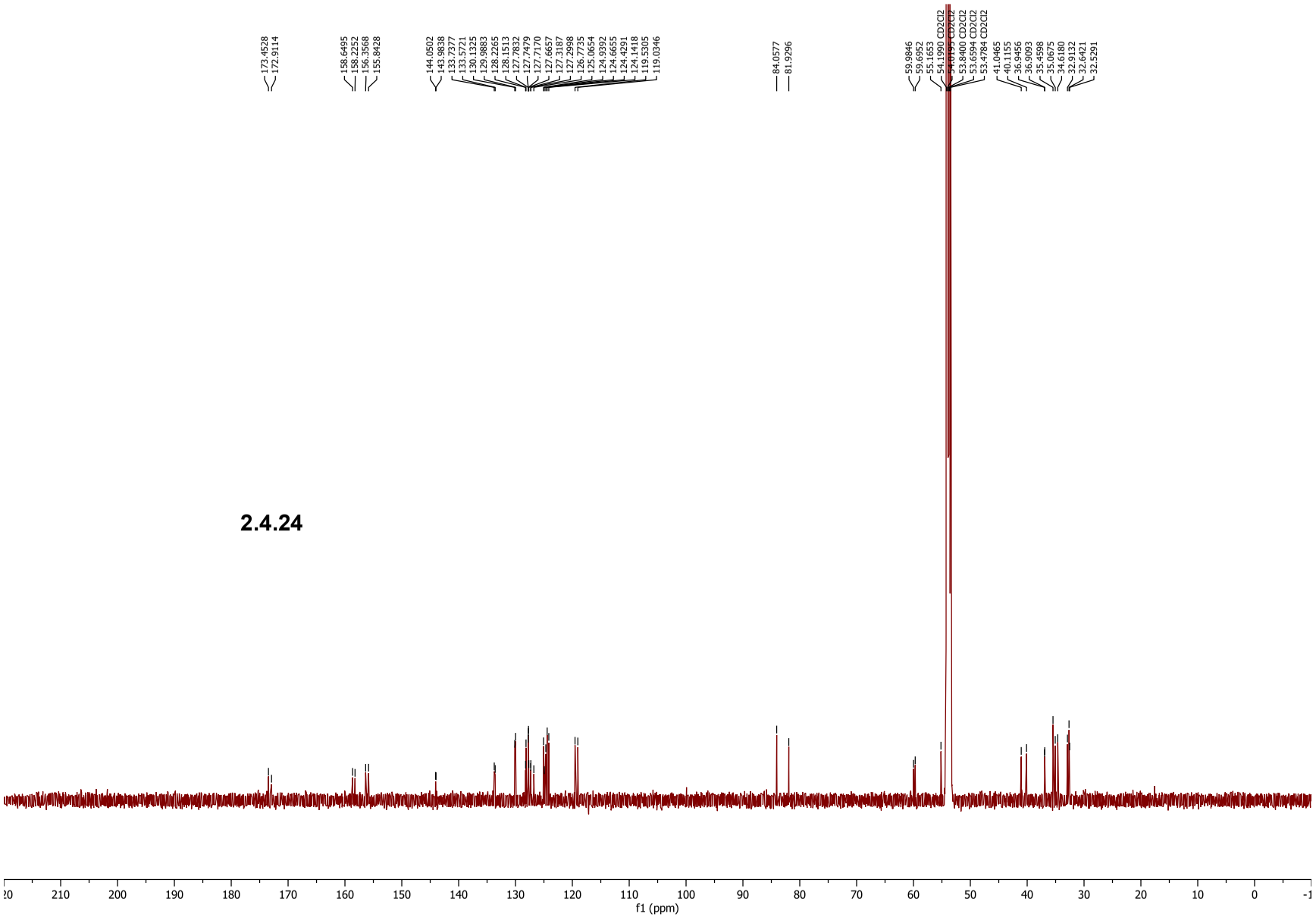

^{1}H, ^{13}C HMBC (700 MHz, CD_2Cl_2)
206
f2 (ppm)
f1 (ppm)

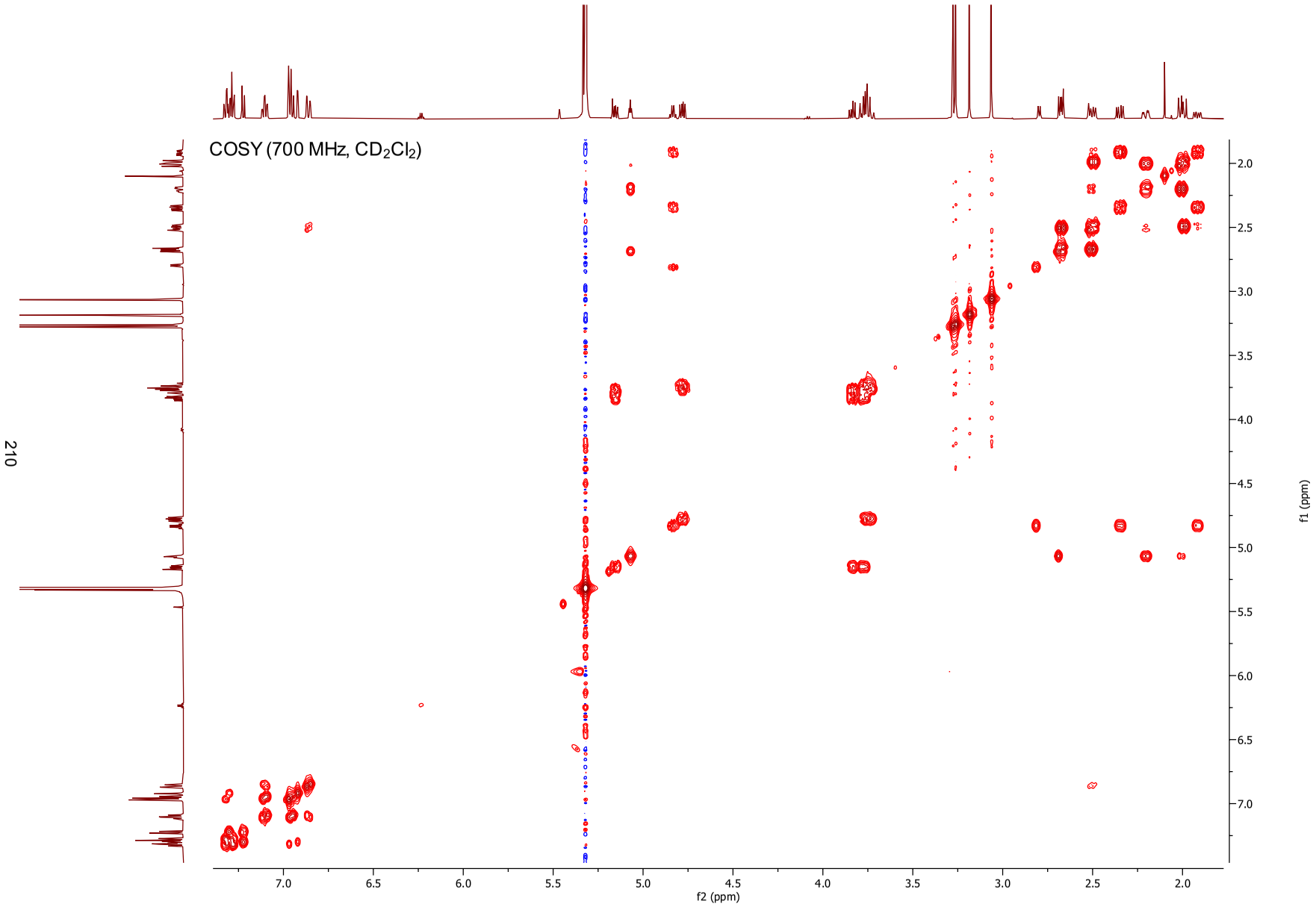

{1.9530,0.8607}
{1.9236,0.8607}
{4.7599,2.1418}
{1.9530,2.6503}
{1.9236,2.6503}
{1.9530,3.5304}
{1.9236,3.5304}
2.4.23-major
207
f2 (ppm)
f1 (ppm)

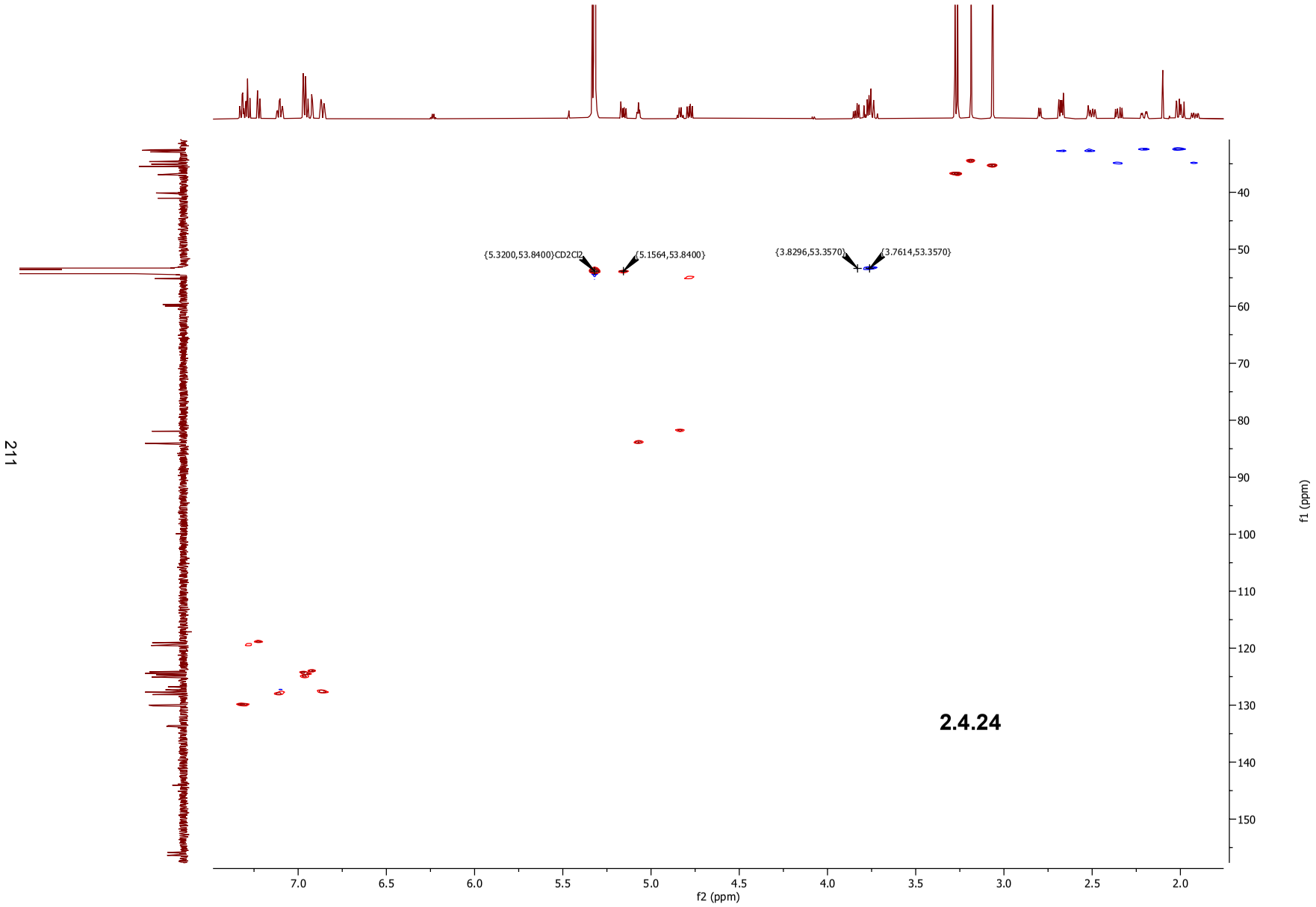

7.3313
7.3279
7.3175
7.3140
7.3124
7.3083
7.2980
7.2945
7.2869
7.2732
7.2304
7.2166
7.1207
7.1191
7.1166
7.1150
7.1069
7.1053
7.1028
7.1012
7.0931
7.0915
7.0890
7.0874
6.9711
6.9672
6.9578
6.9438
6.9233
6.9198
6.8731
6.8709
6.8687
6.8669
6.8549
6.8529
6.8508
6.8488
5.3219 CD2Cl2
5.3200 CD2Cl2
5.3182 CD2Cl2
5.1689
5.1599
5.1524
5.1417
5.0791
5.0720
5.0719
5.0699
5.0649
5.0626
4.8511
4.8402
4.8292
4.8183
4.7953
4.7842
4.7775
4.7664
3.8534
3.8426
3.8322
3.8215
3.7933
3.7859
3.7749
3.7719
3.7648
3.7563
3.7537
3.7384
3.7174
3.7772
3.7627
3.1861
3.0644
2.8027
2.7916
2.6889
2.6789
2.6721
2.6631
2.5226
2.5106
2.4967
2.4840
2.3678
2.3564
2.3422
2.3308
2.2215
2.2155
2.1274
2.1948
2.1880
2.0230
2.0207
2.0056
2.0027
1.9950
1.9973
1.9789
1.9370
1.9335
1.9264
1.9230
1.9115
1.9080
1.9009
1.8974
1.5202 H2O
0.95
0.80
0.96
0.74
1.76
2.77
0.76
0.96
0.74
0.84
2.04
1.04
0.83
1.86
1.98
0.69
3.00
2.35
2.95
2.32
2.94
0.82
1.01
0.82
1.03
0.70
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
f1 (ppm)

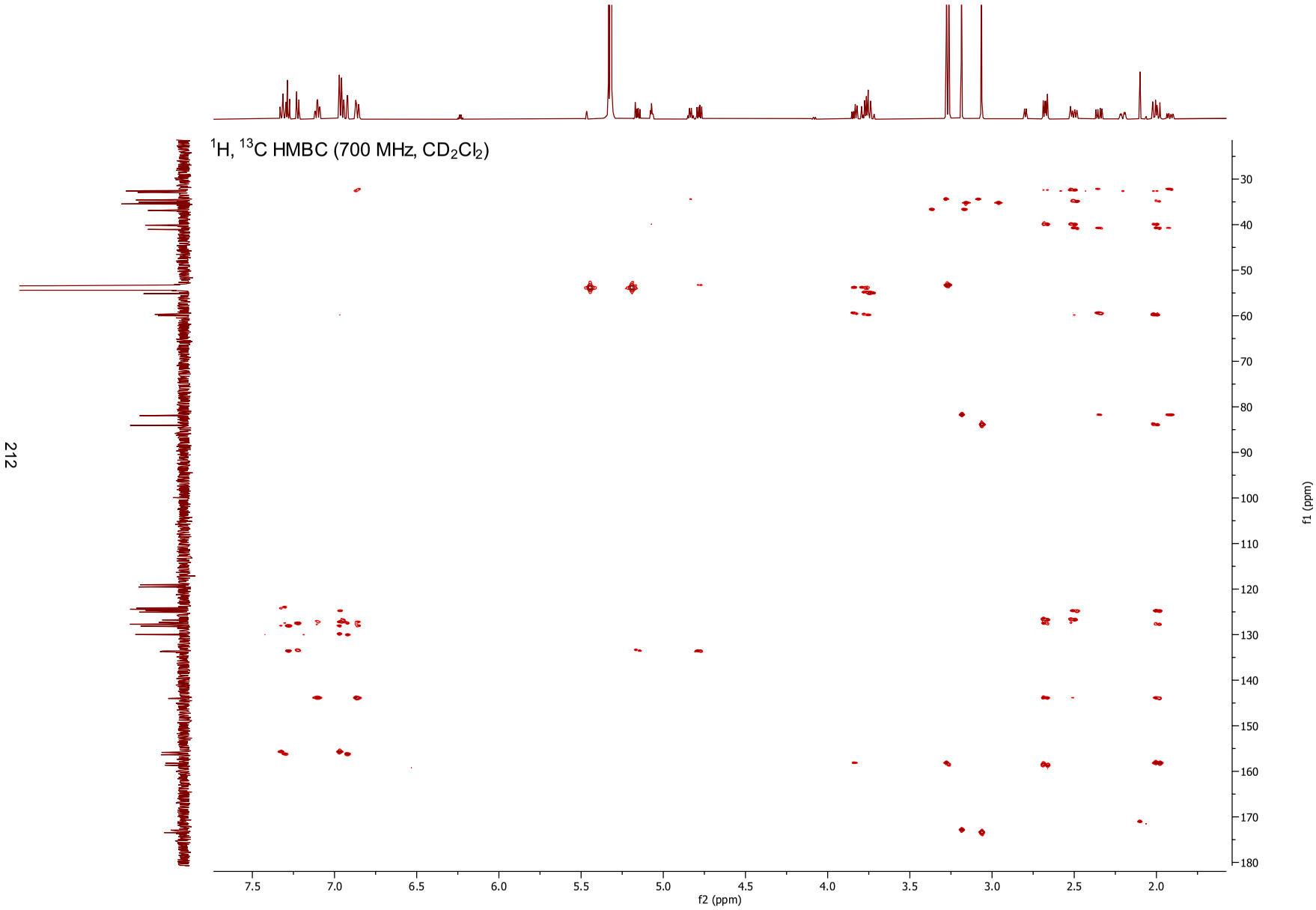
2.4.24

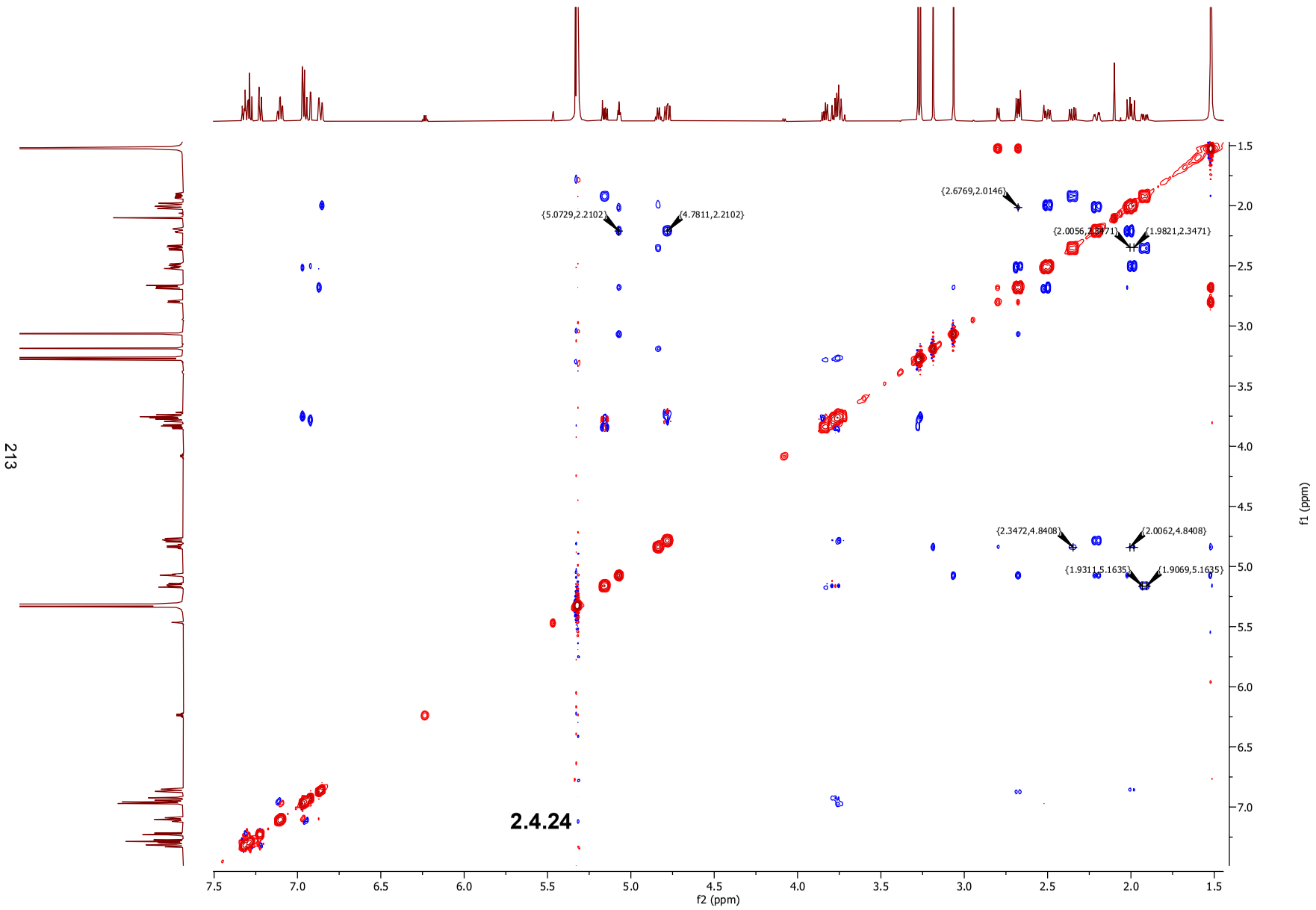
2.4.24


173.4528
172.9114
158.6495
158.2252
156.3568
155.8428
144.0502
143.9838
133.7377
133.5721
130.1325
129.9883
128.2265
128.1513
127.7832
127.7479
127.7170
127.6657
127.3187
127.2998
126.7735
125.0654
124.9392
124.6655
124.4291
124.1418
119.5305
119.0346
84.0577
81.9296
59.9846
59.6952
55.1653
54.1990 CD2Cl2
53.8400 CD2Cl2
53.6594 CD2Cl2
53.4784 CD2Cl2
41.0465
40.1155
36.9456
36.9093
35.4598
35.0675
34.6180
32.9132
32.6421
32.5291
f1 (ppm)

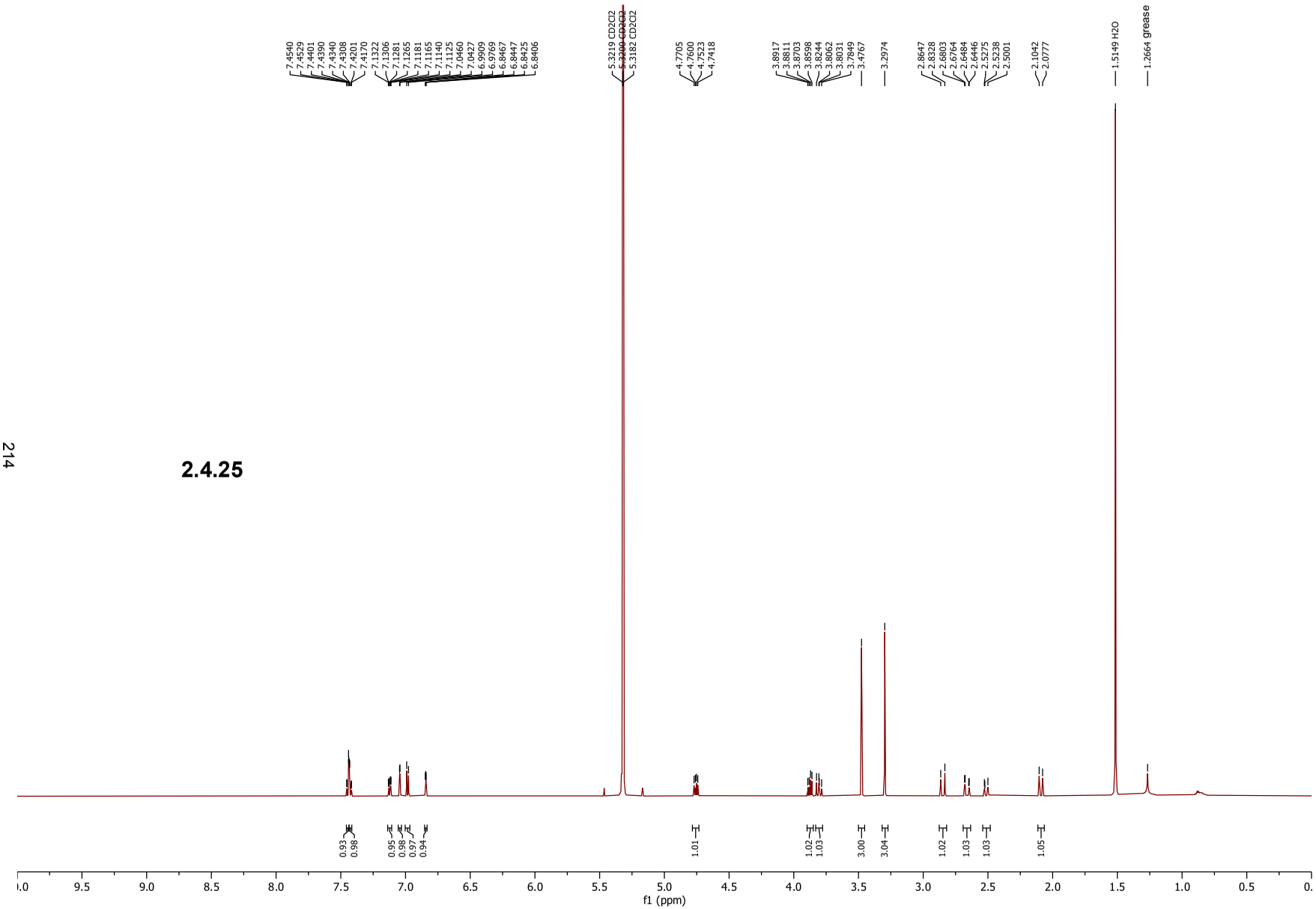

COSY (700 MHz, CD_2Cl_2)
f2 (ppm)
f1 (ppm)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0


{5.3200,53.8400}CD2Cl2
{5.1564,53.8400}
{3.8296,53.3570}
{3.7614,53.3570}
2.4.24
211
f2 (ppm)
f1 (ppm)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
40
50
60
70
80
90
100
110
120
130
140
150

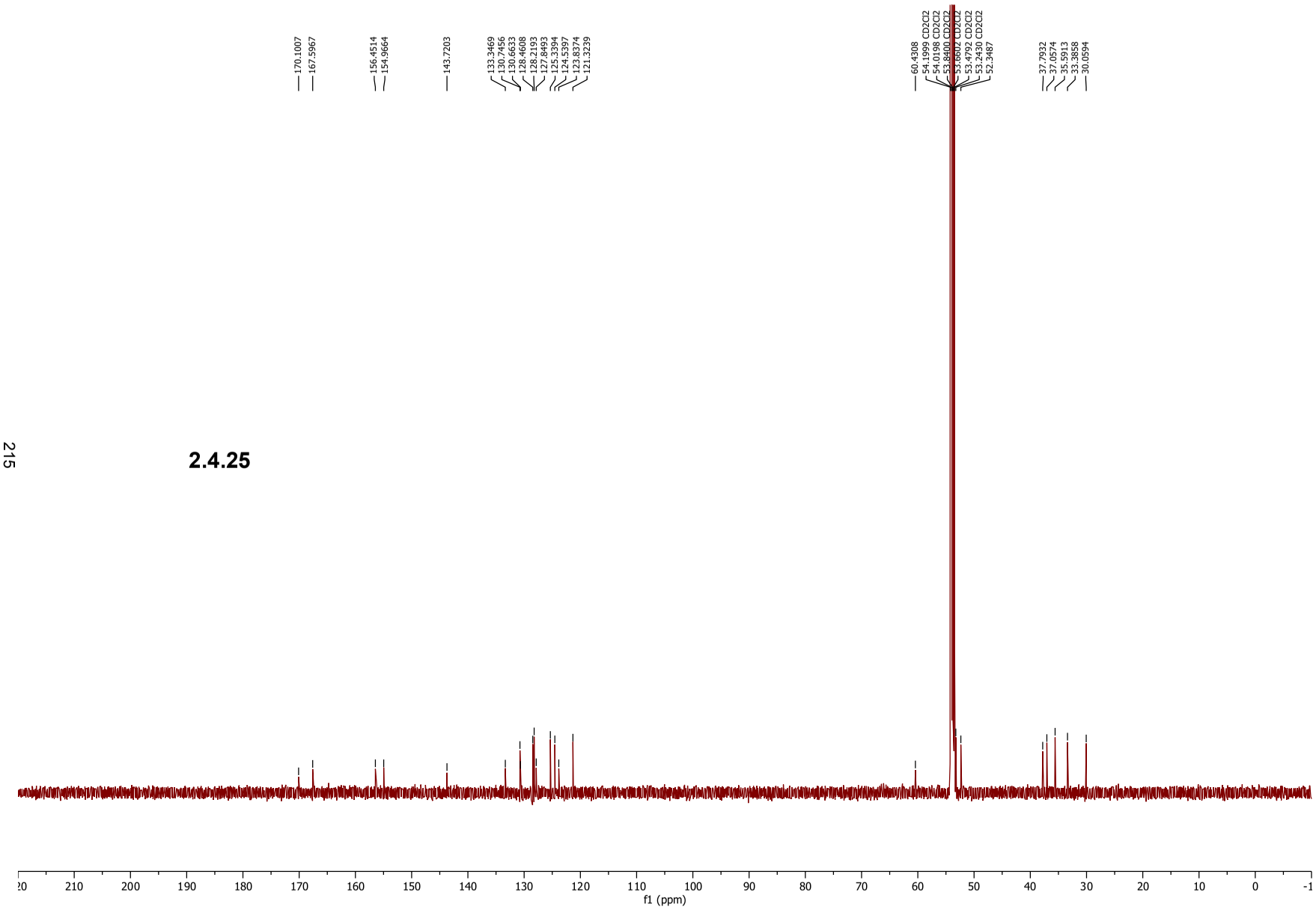

^{1}H, ^{13}C HMBC (700 MHz, CD_2Cl_2)
212
f2 (ppm)
f1 (ppm)

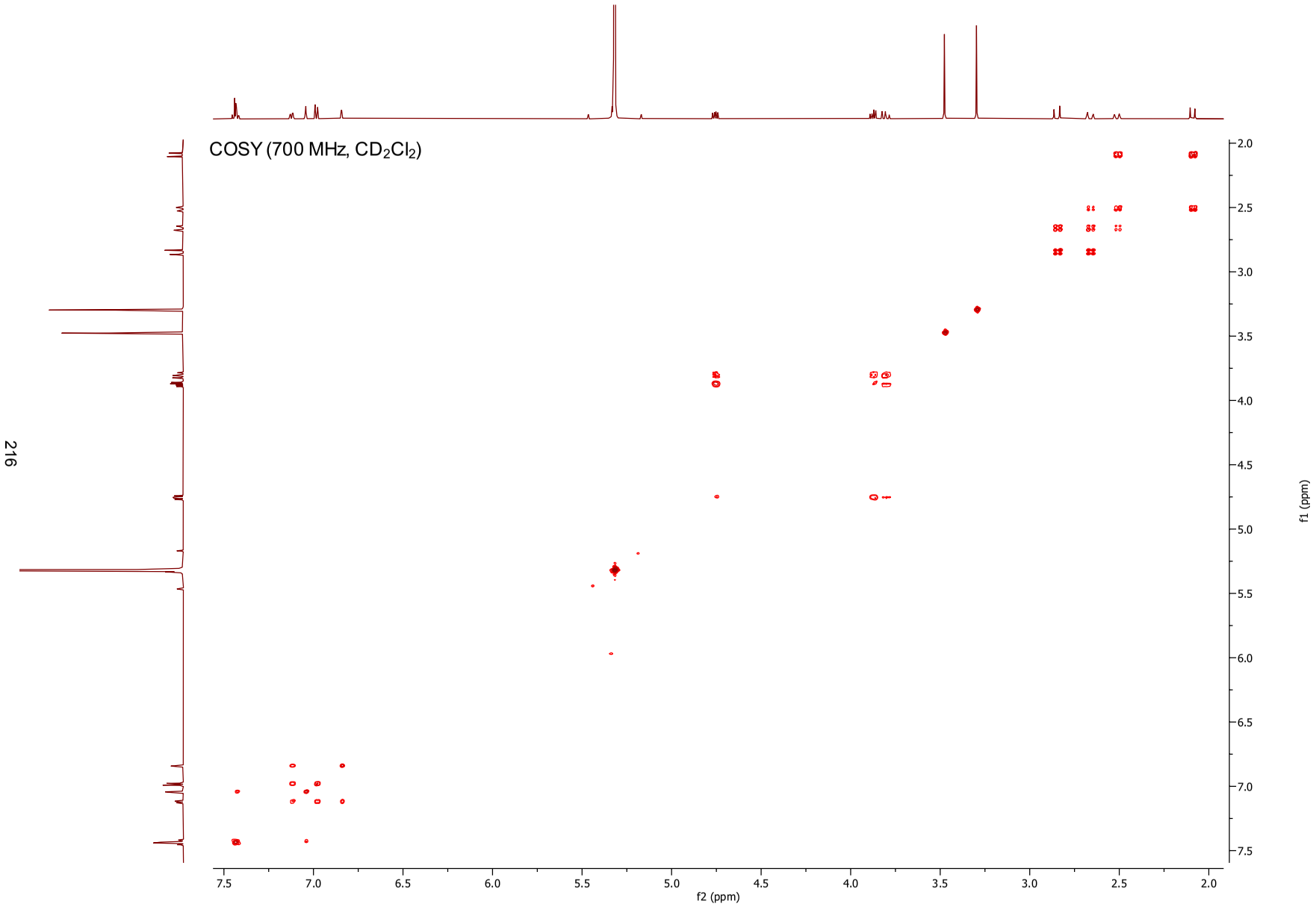

{5.0729,2.2102}
{4.7811,2.2102}
{2.6769,2.0146}
{2.0056,2.3471}
{1.9821,2.3471}
{2.3472,4.8408}
{2.0062,4.8408}
{1.9311,5.1635}
{1.9069,5.1635}
2.4.24
213
f2 (ppm)
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5

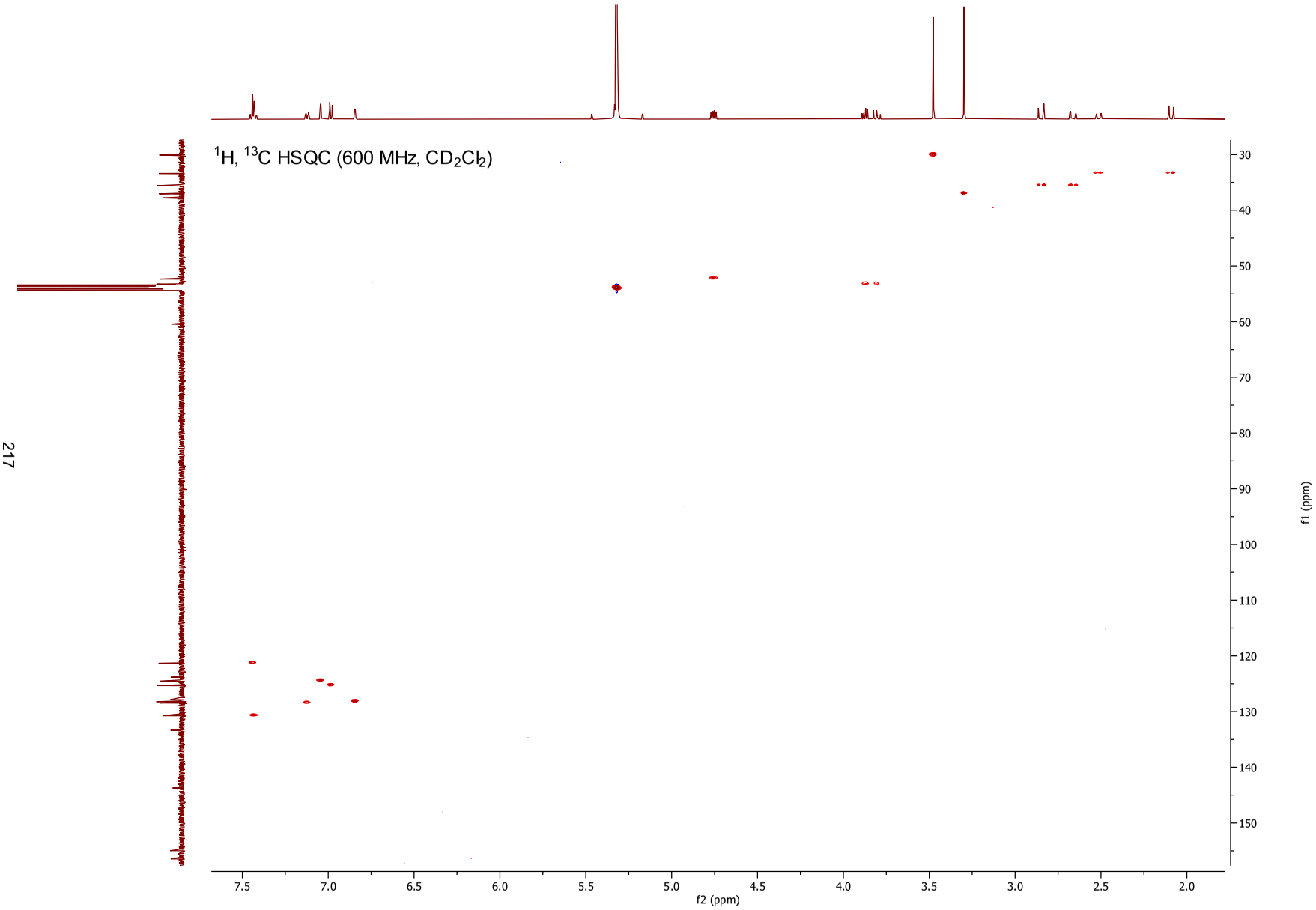
2.4.25

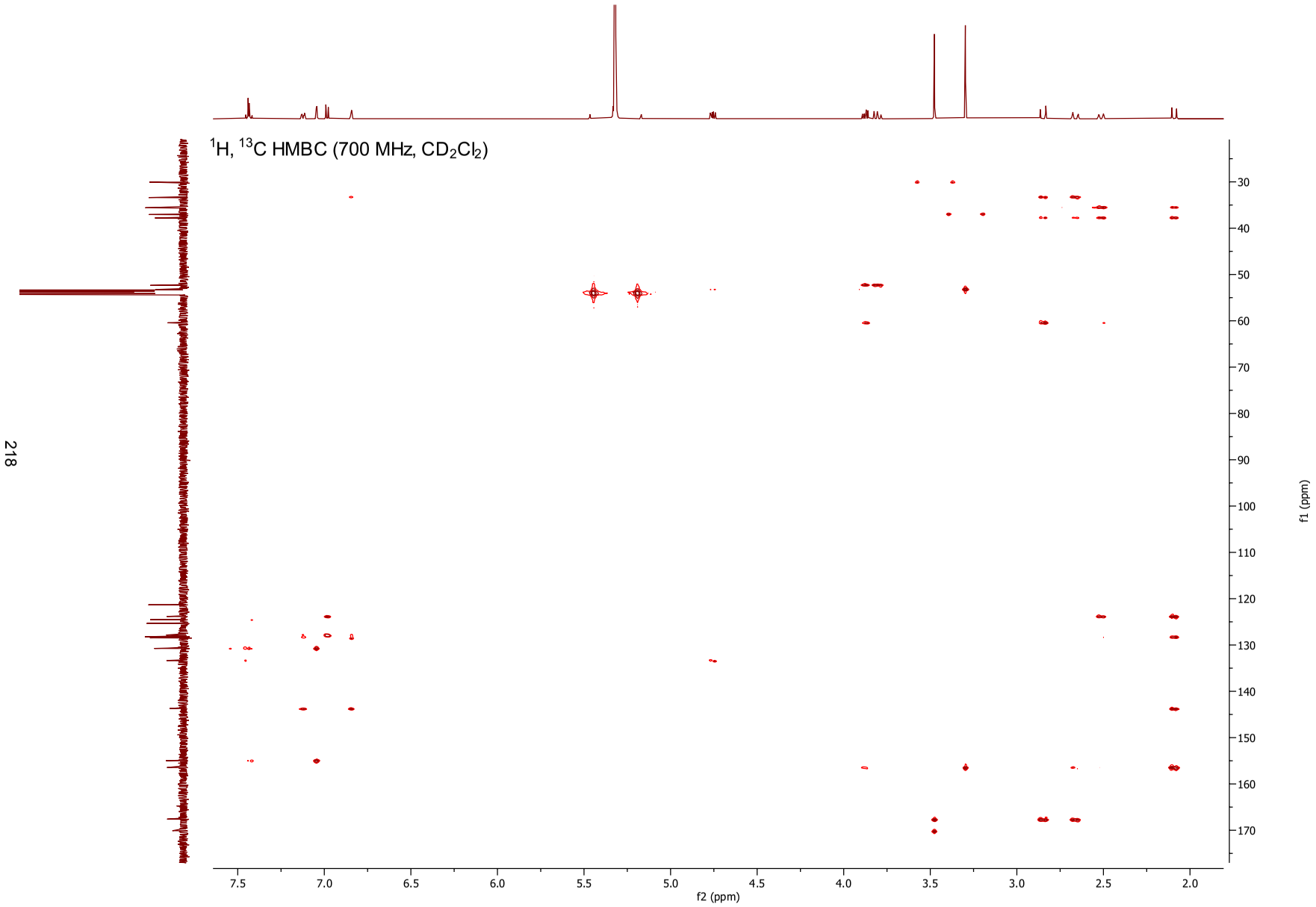

7.4540
7.4529
7.4401
7.4390
7.4340
7.4308
7.4201
7.4170
7.1322
7.1306
7.1281
7.1265
7.1181
7.1165
7.1140
7.1125
7.0460
7.0427
6.9909
6.9769
6.8467
6.8447
6.8425
6.8406
5.3219 CD2Cl2
5.3200 CD2Cl2
5.3182 CD2Cl2
4.7705
4.7600
4.7523
4.7418
3.8917
3.8811
3.8703
3.8598
3.8244
3.8062
3.8031
3.7849
3.4767
3.2974
2.8647
2.8328
2.6803
2.6764
2.6484
2.6446
2.5275
2.5238
2.5001
2.1042
2.0777
1.5149 H2O
1.2664 grease
0.93
0.98
0.95
0.98
0.97
0.94
1.01
1.02
1.03
3.00
3.04
1.02
1.03
1.03
1.05
f1 (ppm)

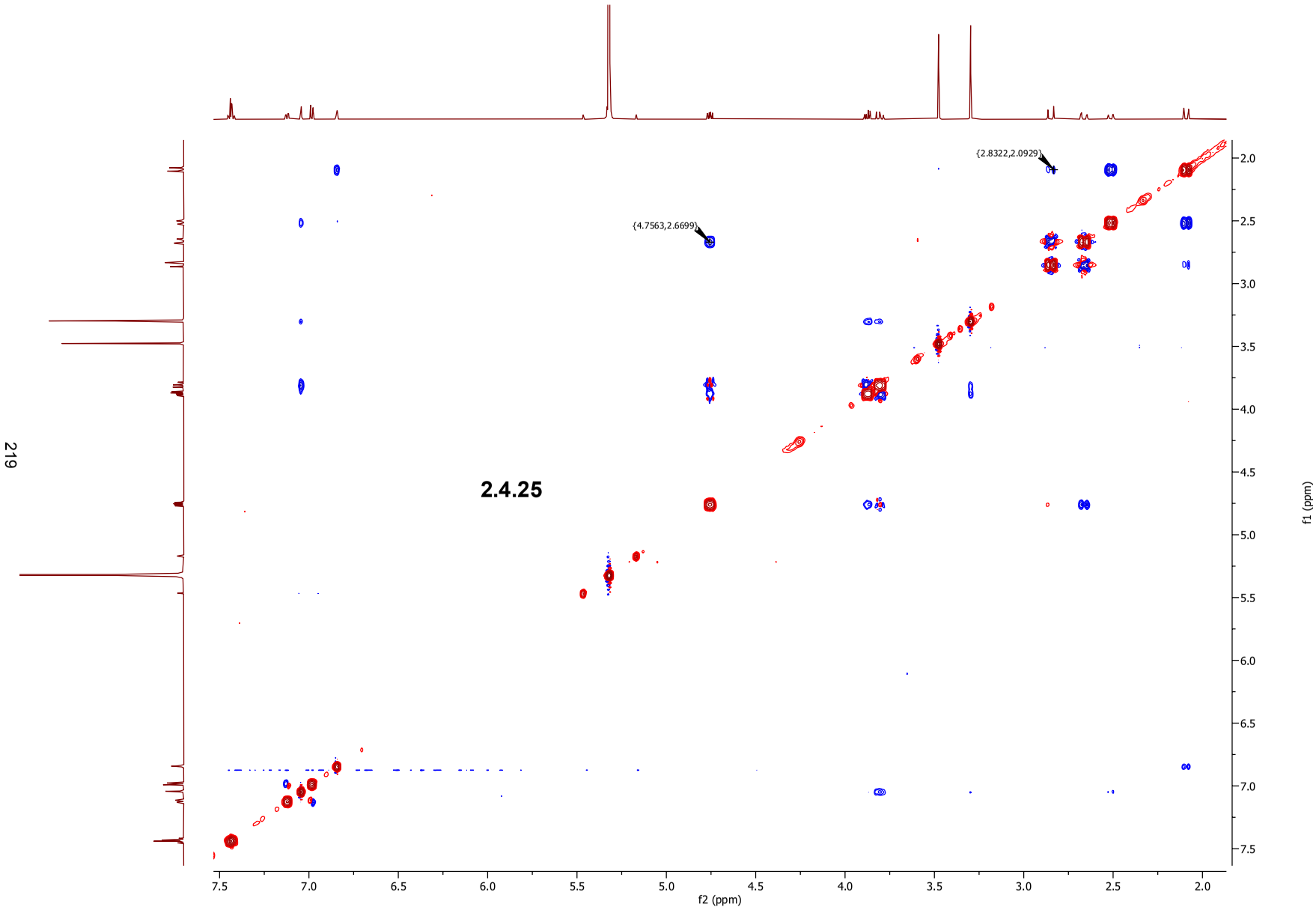
2.4.25

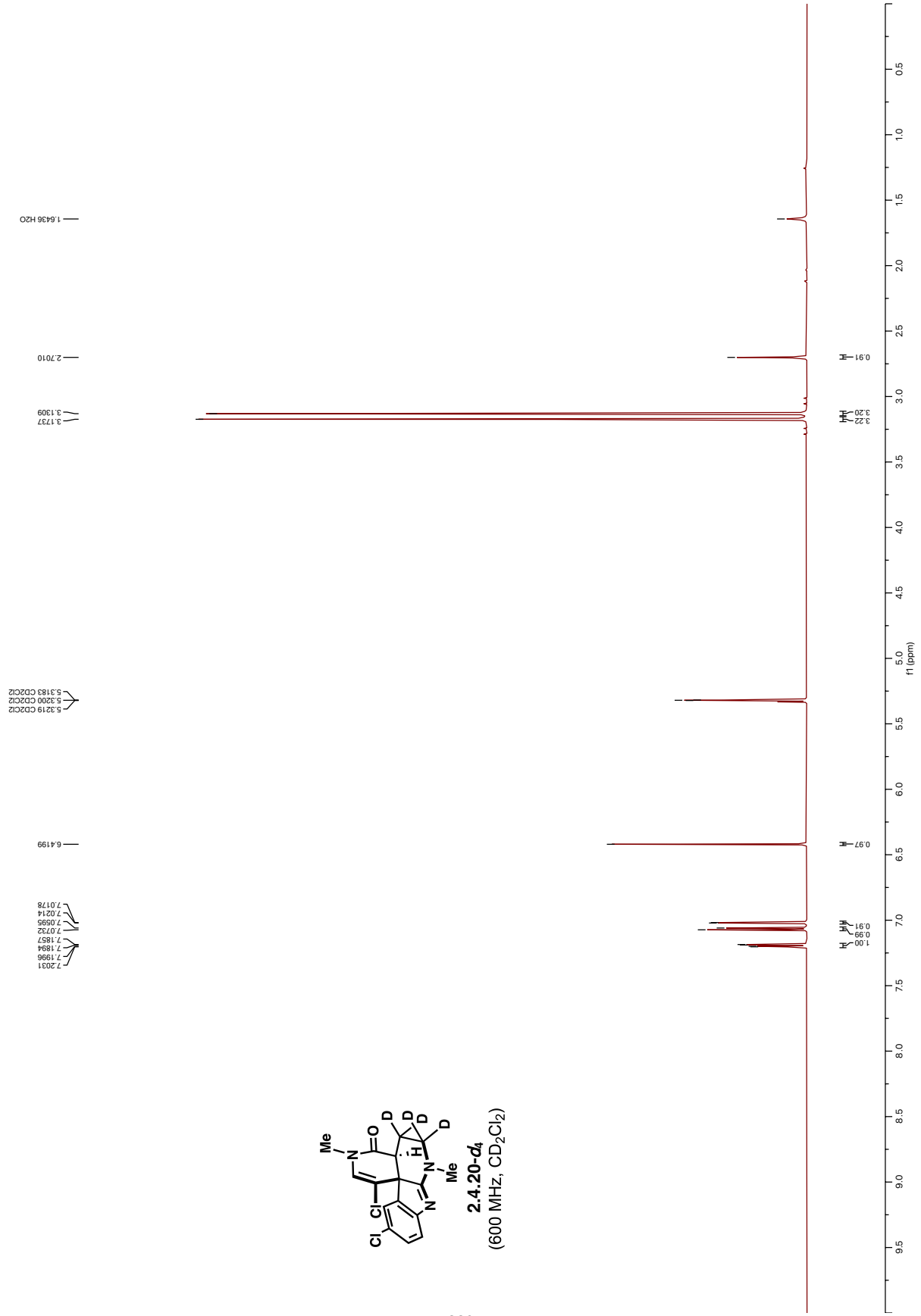

170.1007
167.5967
156.4514
154.9664
143.7203
133.3469
130.7456
130.6633
128.4608
128.2193
127.8493
125.3394
124.5397
123.8374
121.3239
60.4308
54.1999 CD2Cl2
54.0198 CD2Cl2
53.8400 CD2Cl2
53.6602 CD2Cl2
53.4792 CD2Cl2
53.2430 CD2Cl2
52.3487
37.7932
37.0574
35.5913
33.3858
30.0594
f1 (ppm)


COSY (700 MHz, CD_2Cl_2)
f2 (ppm)
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0

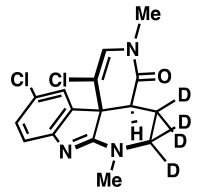

^{1}H, ^{13}C HSQC (600 MHz, CD_2Cl_2)
f2 (ppm)
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
30
40
50
60
70
80
90
100
110
120
130
140
150


^{1}H, ^{13}C HMBC (700 MHz, CD_2Cl_2)
f2 (ppm)
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170


{2.8322,2.0929}
{4.7563,2.6699}
2.4.25
f2 (ppm)
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0

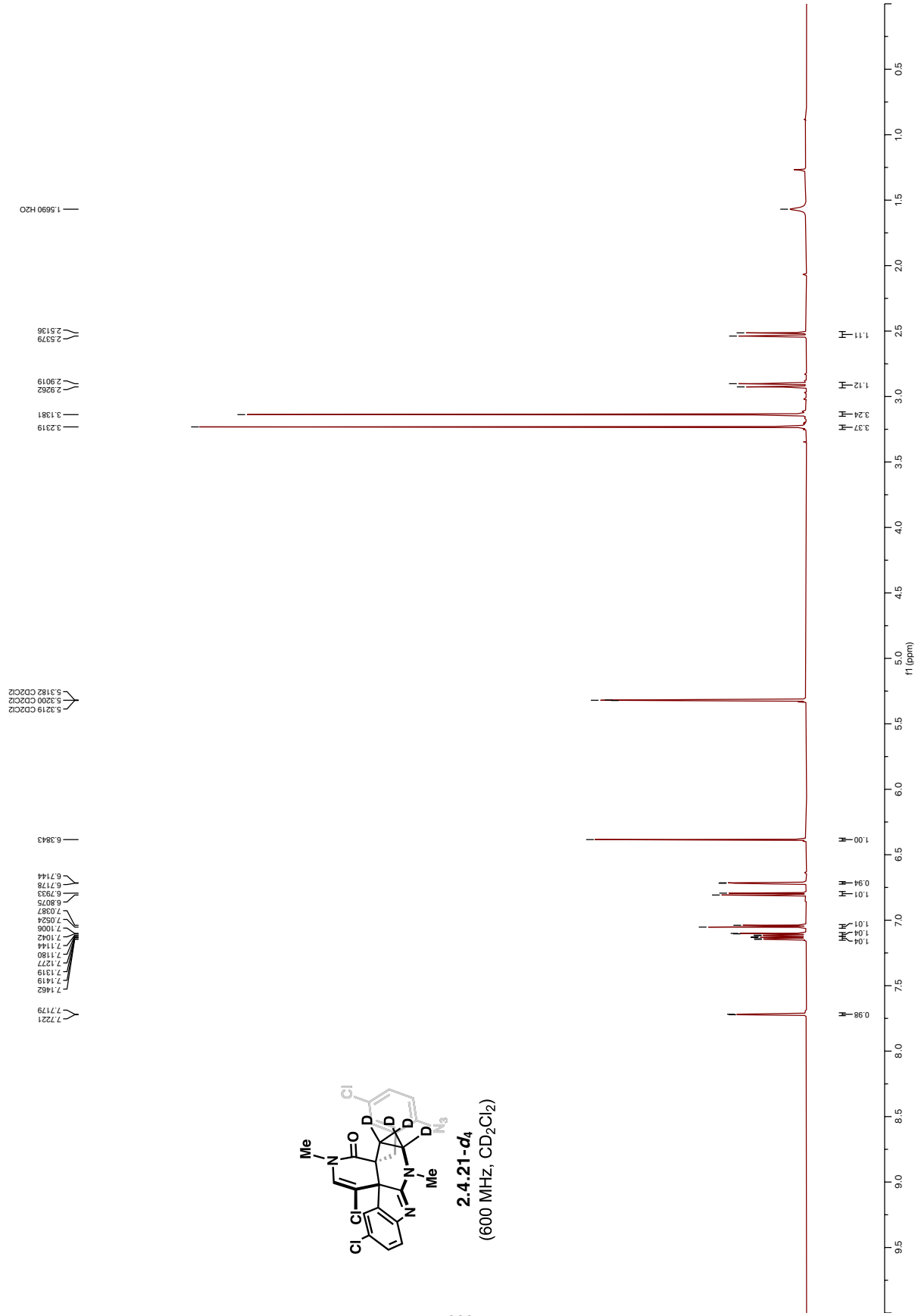


2.4.20-*d*$_4$
(600 MHz, CD_2Cl_2)



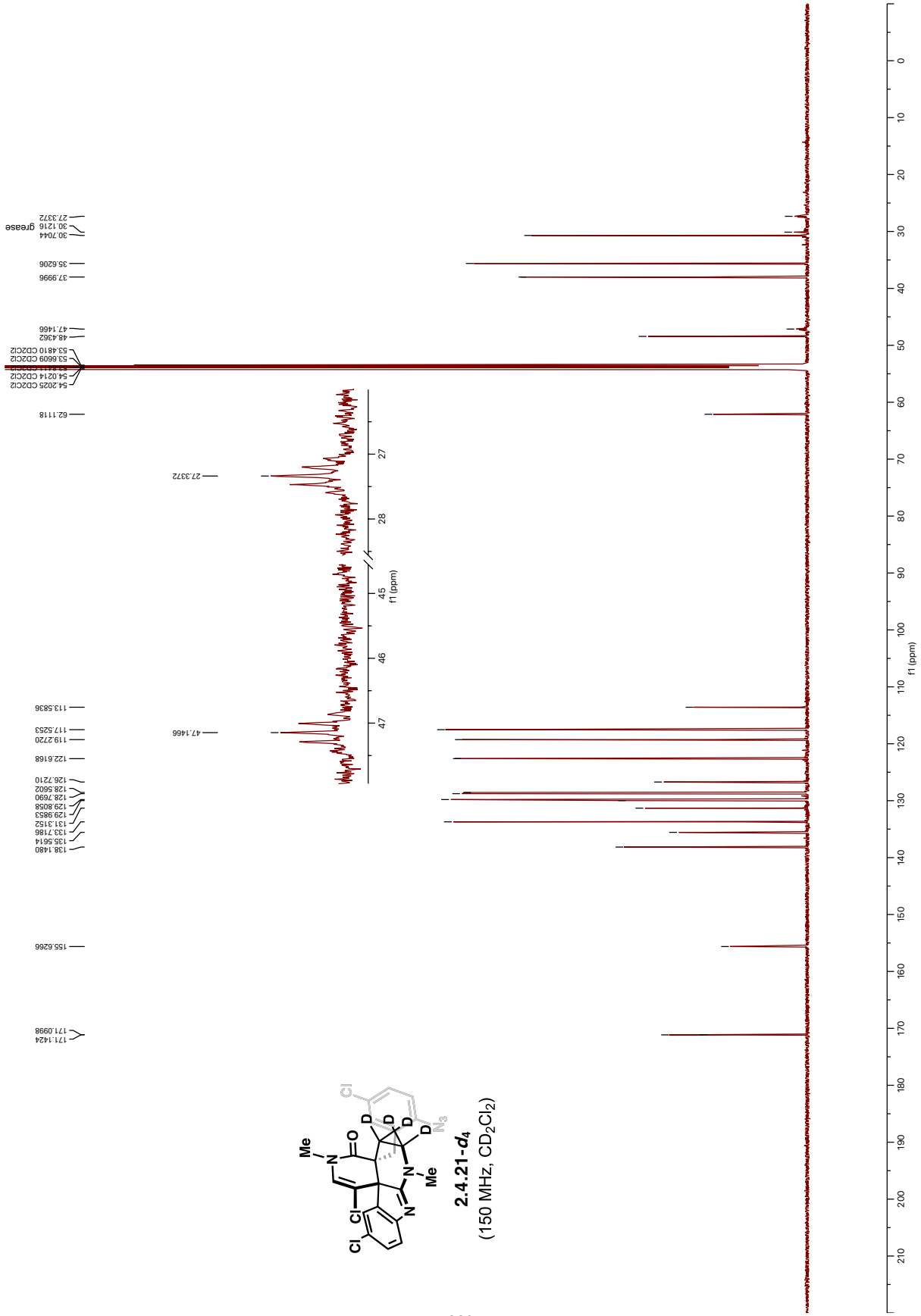
2.4.20-*d*$_4$

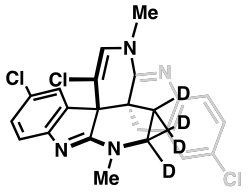
(150 MHz, CD_2Cl_2)



2.4.21-*d*$_4$

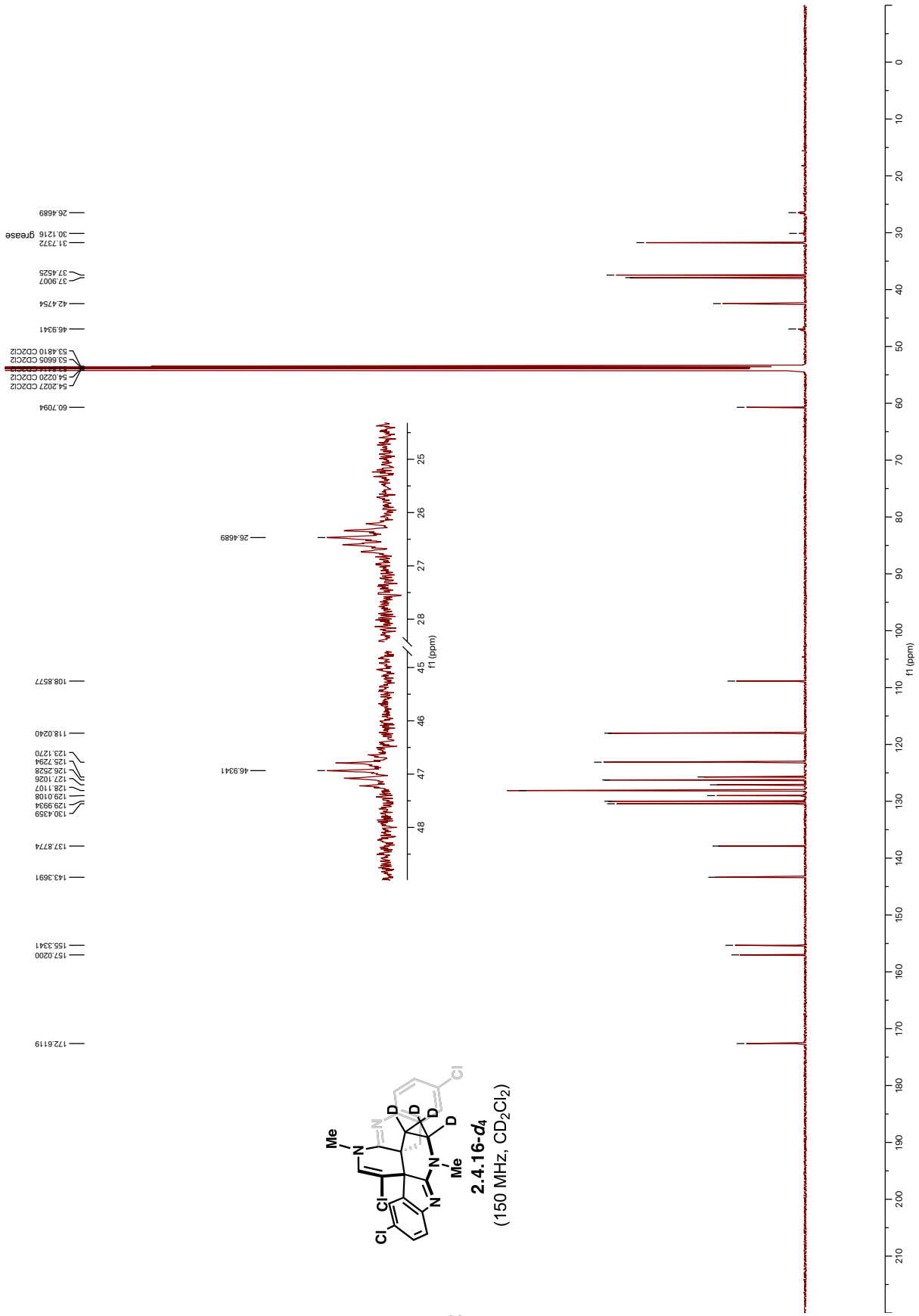
(600 MHz, CD_2Cl_2)

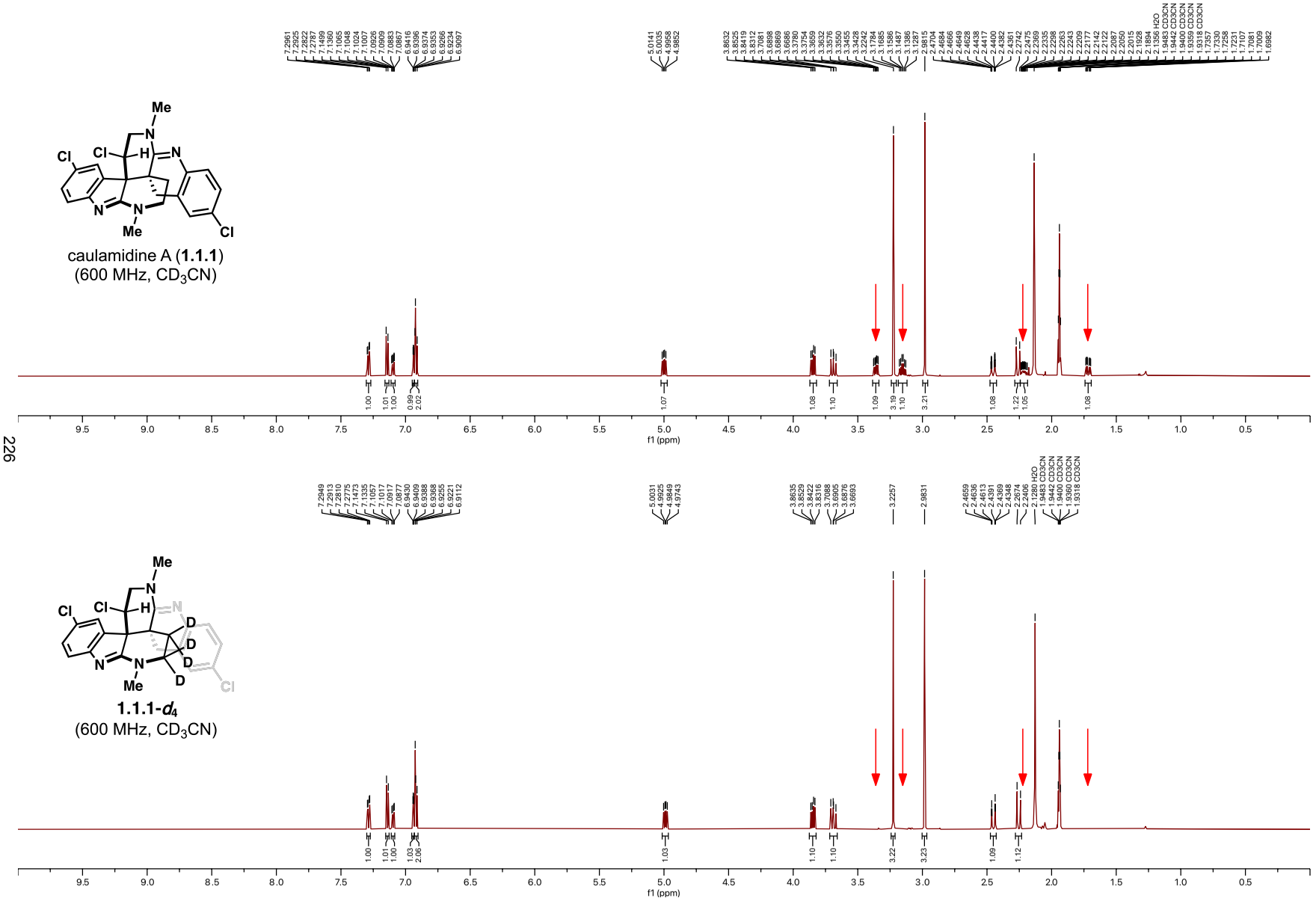

171.0998
171.1424
155.6266
138.1480
135.5614
133.7186
131.3152
129.9853
129.8058
128.7690
128.5602
126.7210
122.6168
119.2720
117.5253
113.5836
62.1118
54.2025 CD2Cl2
54.0214 CD2Cl2
53.4810 CD2Cl2
53.6609 CD2Cl2
48.4362
47.1466
37.9996
35.6206
30.7044
30.1216 grease
27.3372
f1 (ppm)
Me
N
O
D
D
D
D
N
N
Me
Cl
Cl
Cl
N3
2.4.21-d4
(150 MHz, CD2Cl2)

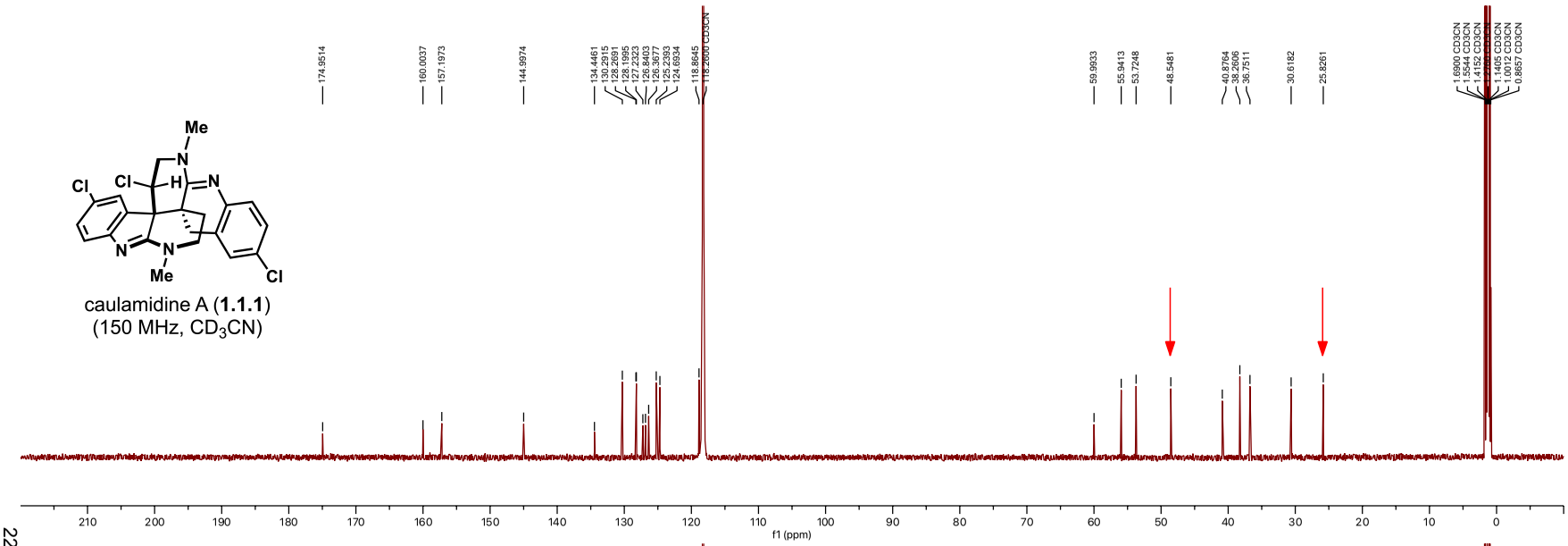


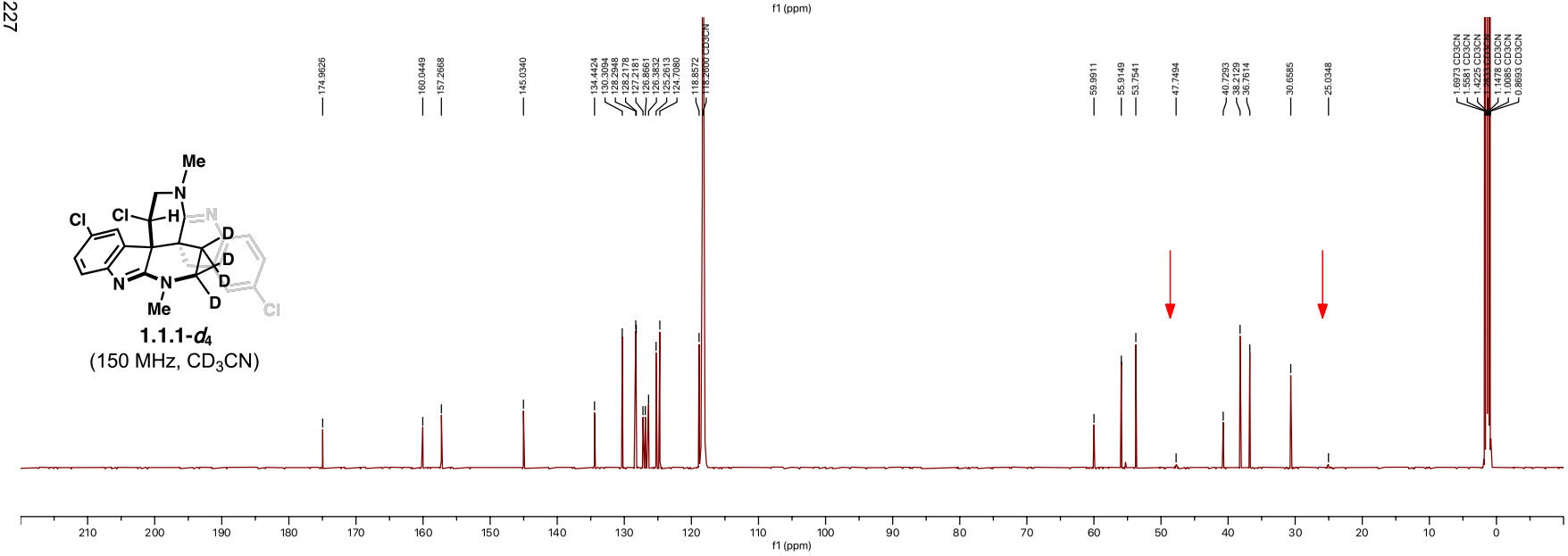
2.4.16-*d*$_4$

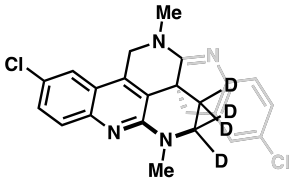
(600 MHz, CD_2Cl_2)


26.4689
30.1216 grease
31.7372
37.9007
37.4525
42.4754
46.9341
53.4810 CD2Cl2
53.6605 CD2Cl2
54.0220 CD2Cl2
54.3027 CD2Cl2
60.7094
108.8577
118.0240
123.1270
125.7294
126.2528
127.1026
128.1107
129.0108
129.9934
130.4359
137.8774
143.3691
155.3341
157.0200
172.6119
f1 (ppm)
Me
N
Cl
Cl
N
D
D
D
D
N
Me
N
Cl
2.4.16-d_4
(150 MHz, CD_2Cl_2)

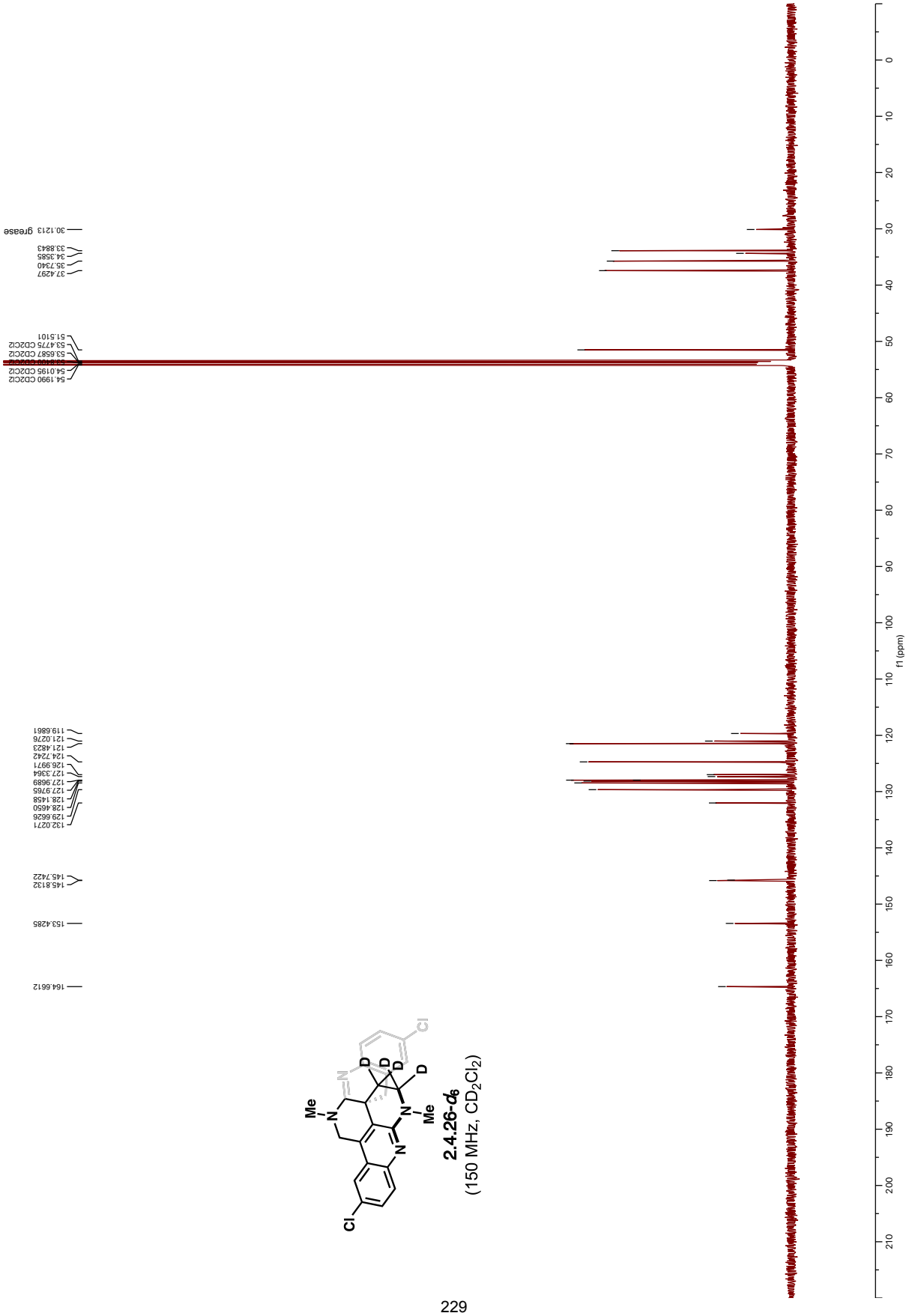

caulamidine A (1.1.1)
(600 MHz, CD3CN)
1.1.1-d4
(600 MHz, CD3CN)
f1 (ppm)


caulamidine A (1.1.1)
(150 MHz, CD3CN)
f1 (ppm)


1.1.1-d4
(150 MHz, CD3CN)
f1 (ppm)

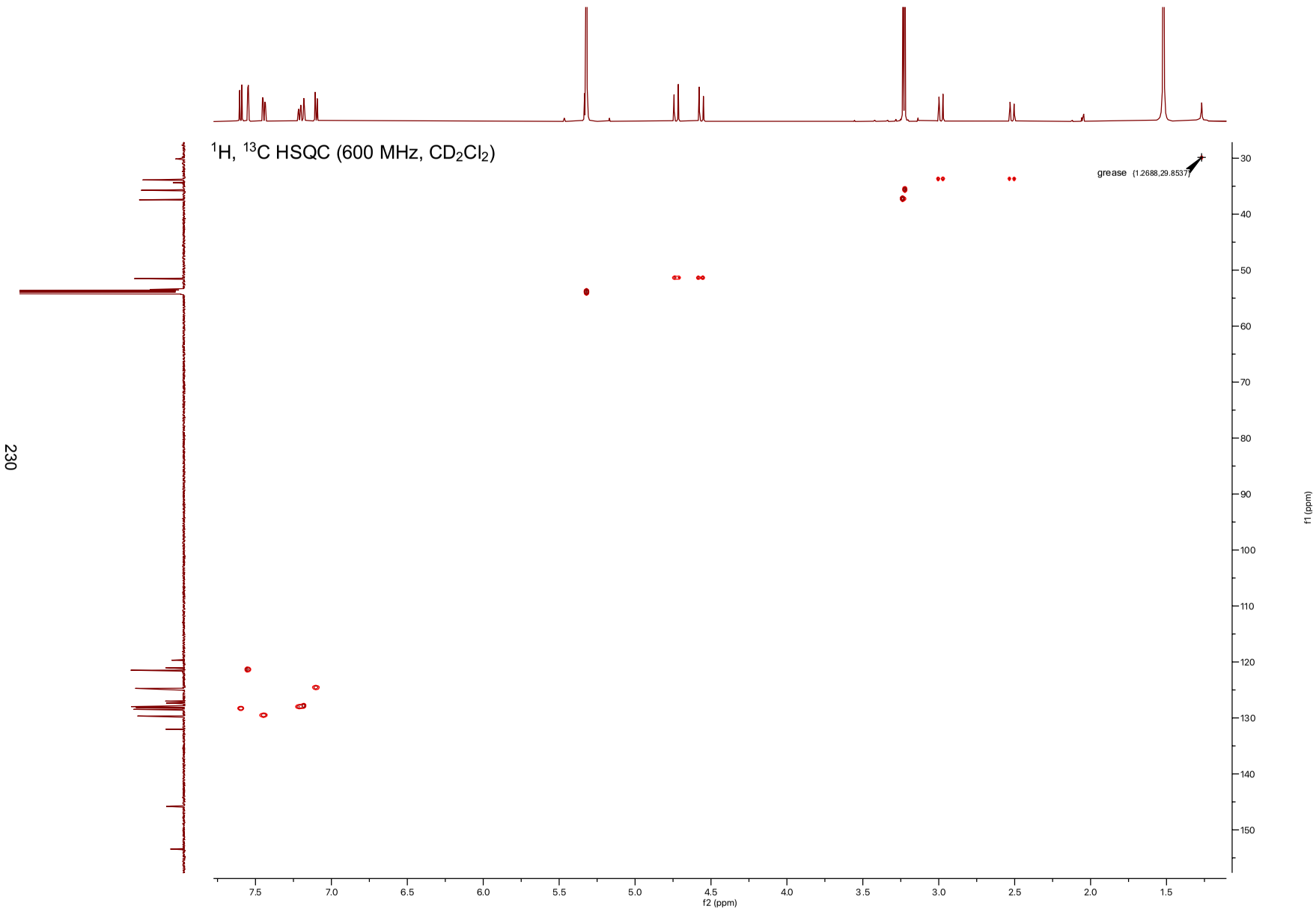


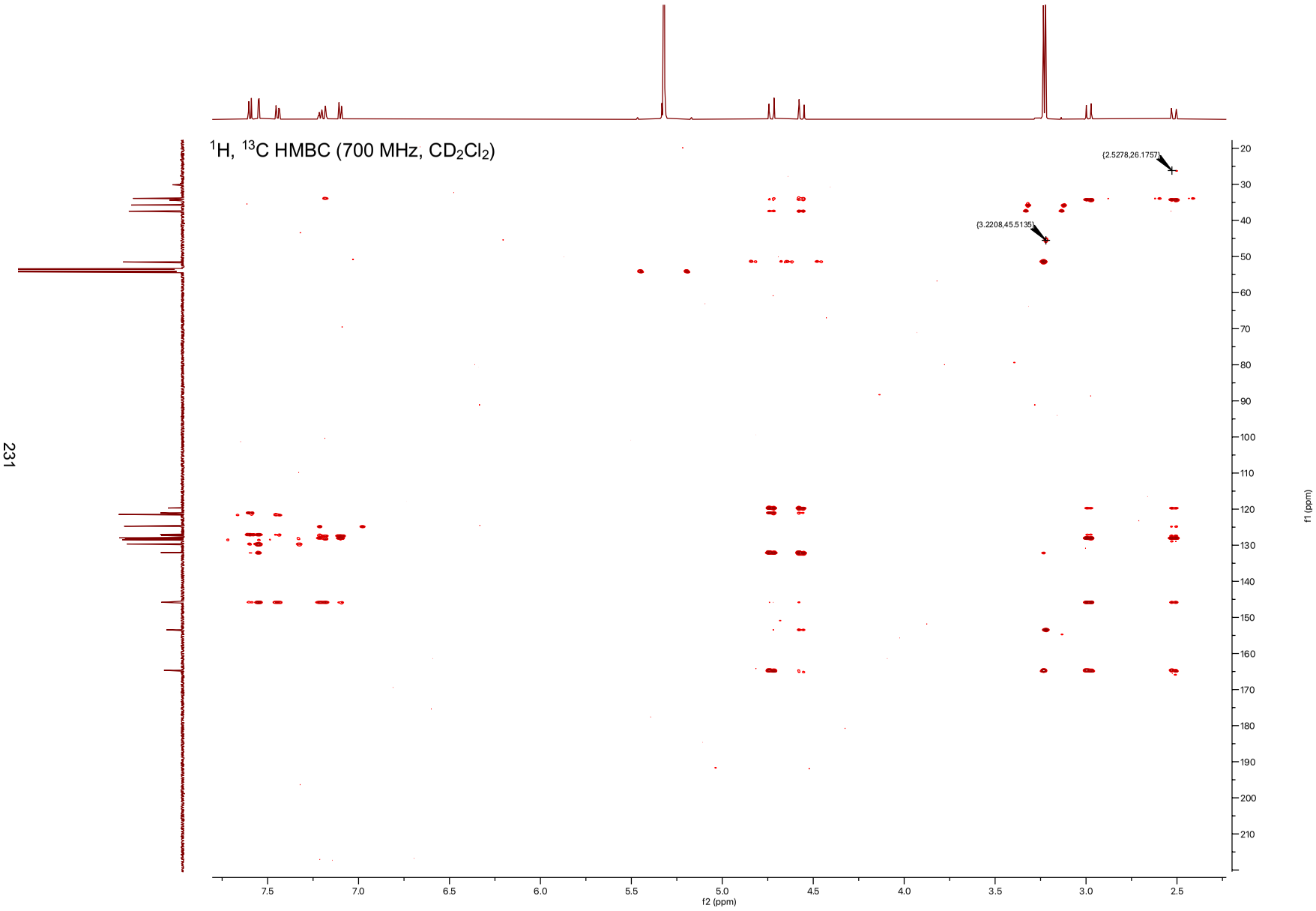
2.4.26-d_6
(600 MHz, CD_2Cl_2)

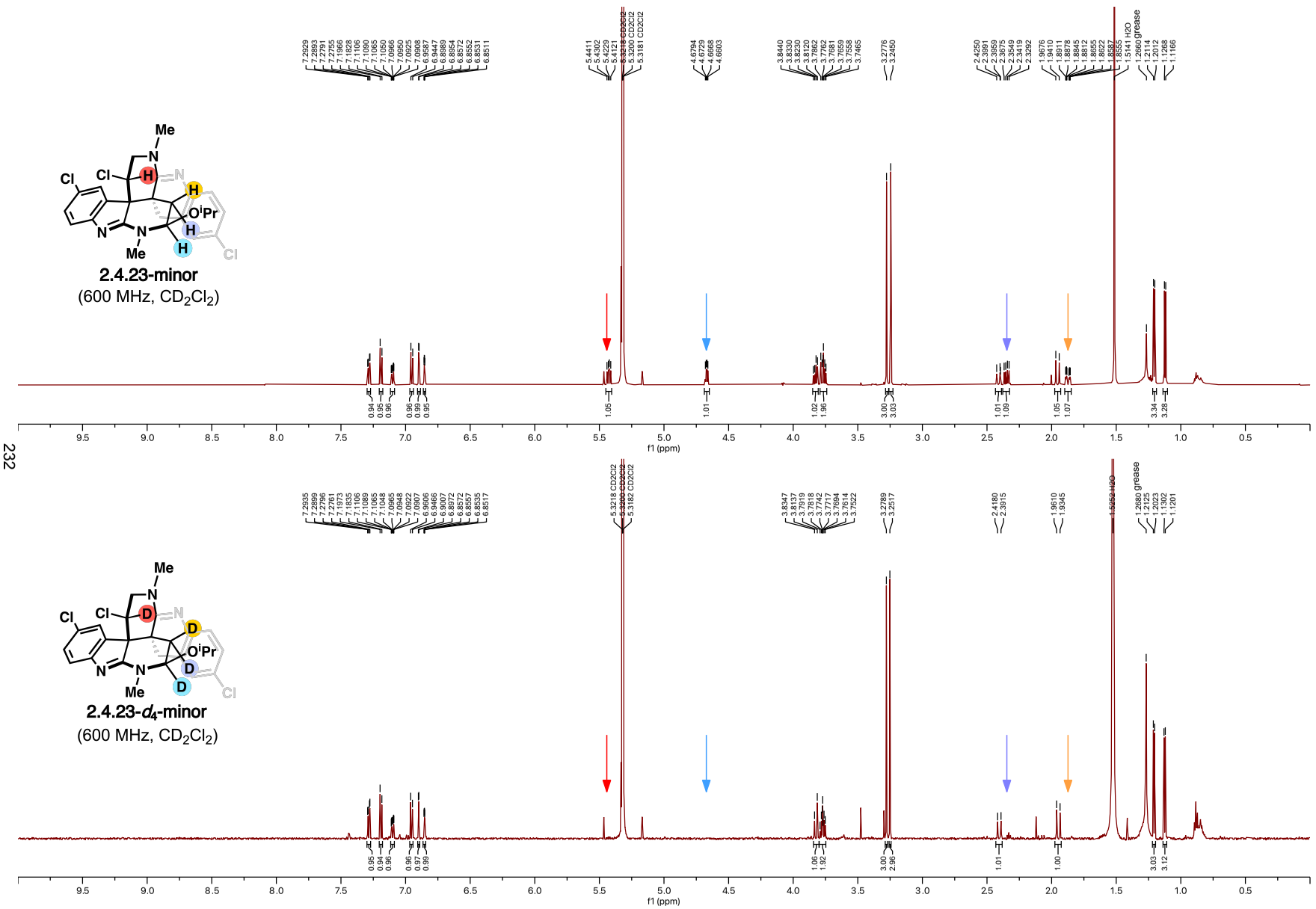


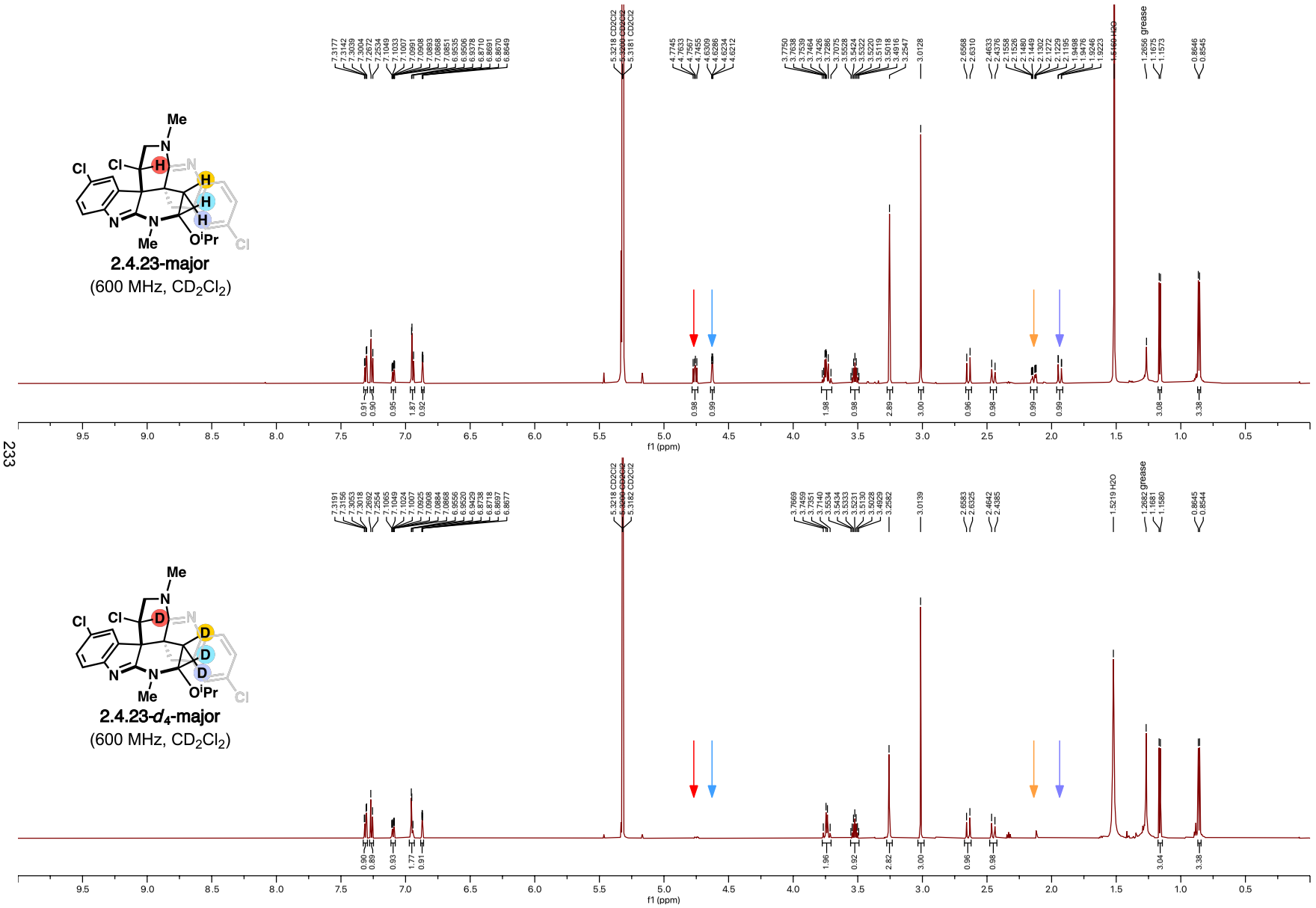
2.4.26-d_6

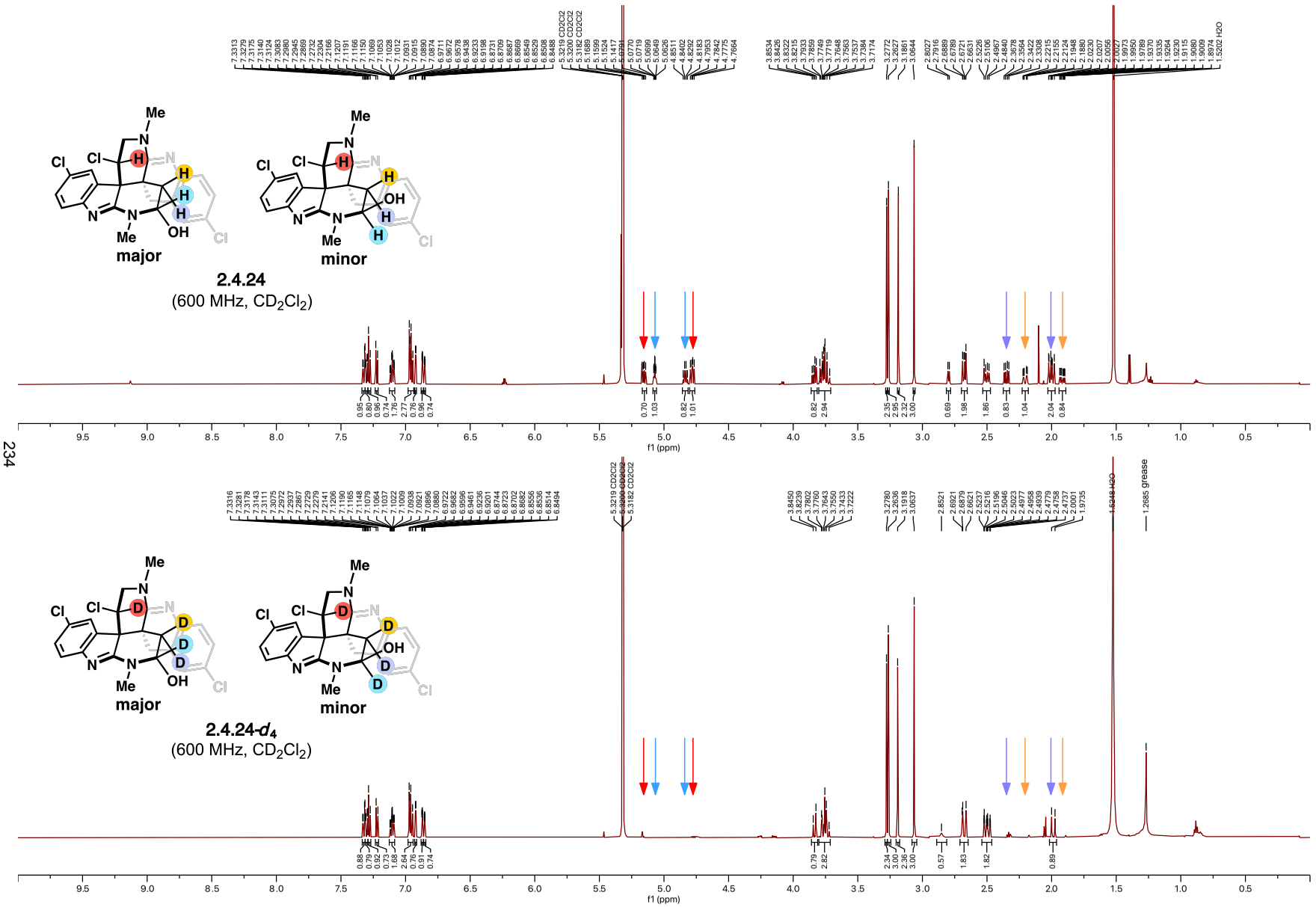
(150 MHz, CD_2Cl_2)

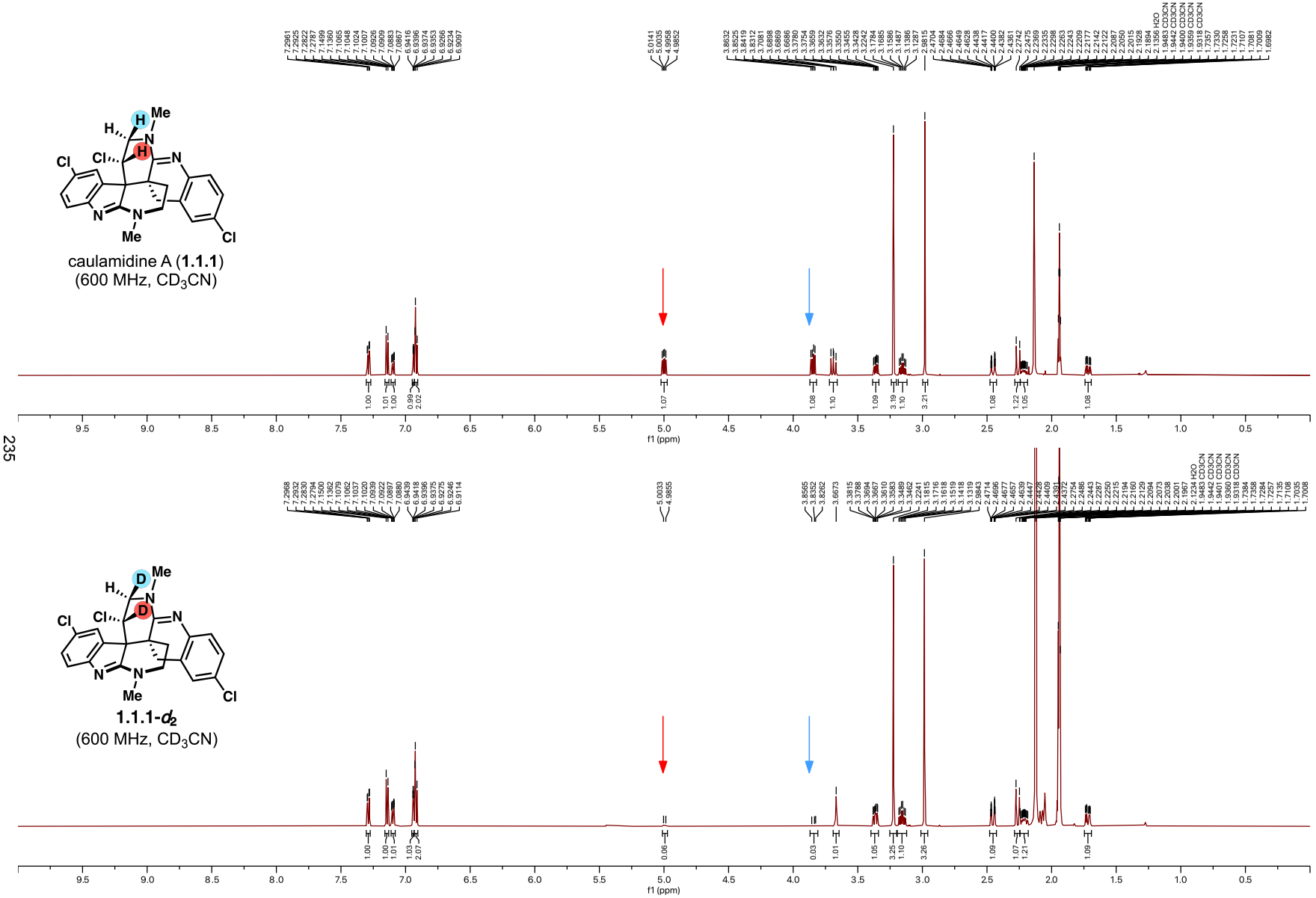

^{1}H, ^{13}C HSQC (600 MHz, CD_2Cl_2)
grease (1.2688,29.8537)
f2 (ppm)
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
30
40
50
60
70
80
90
100
110
120
130
140
150

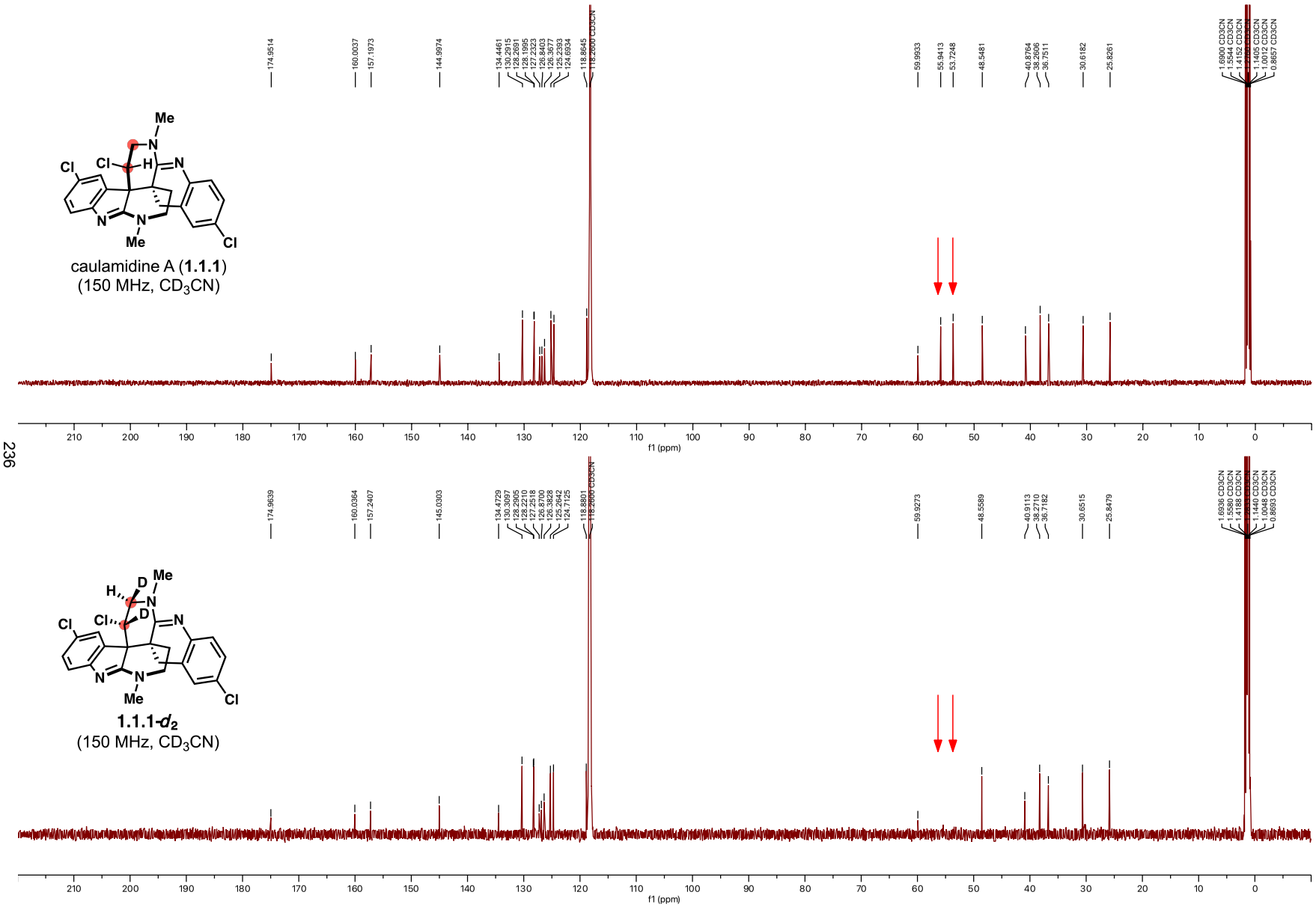

^{1}H, ^{13}C HMBC (700 MHz, CD_2Cl_2)
(2.5278,26.1757)
(3.2208,45.5135)
f2 (ppm)
f1 (ppm)

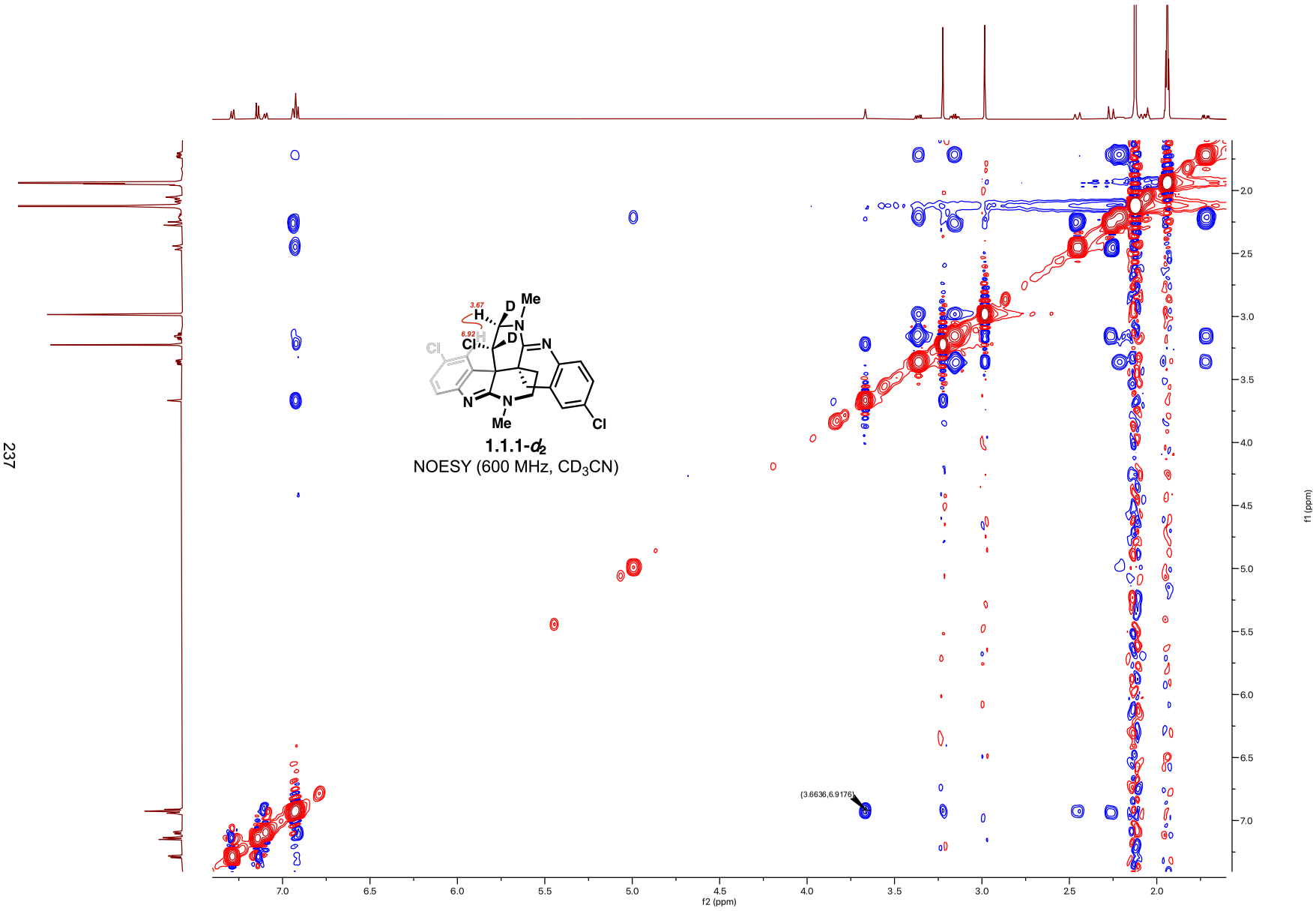

Me
N
Cl
Cl
H
N
H
O^{i}Pr
N
N
H
Me
H
Cl
2.4.23-minor
(600 MHz, CD_2Cl_2)
f1 (ppm)
D
2.4.23-d_4-minor
(600 MHz, CD_2Cl_2)
f1 (ppm)


Me
N
Cl
Cl
H
N
H
H
H
N
N
Me
O^{i}Pr
Cl
2.4.23-major
(600 MHz, CD_2Cl_2)
f1 (ppm)
D
2.4.23-d_4-major
(600 MHz, CD_2Cl_2)


major
minor
2.4.24
(600 MHz, CD2Cl2)
major
minor
2.4.24-d4
(600 MHz, CD2Cl2)
f1 (ppm)
grease


caulamidine A (1.1.1)
(600 MHz, CD3CN)
1.1.1-d2
(600 MHz, CD3CN)
f1 (ppm)


caulamidine A (1.1.1)
(150 MHz, CD3CN)
1.1.1-d2
(150 MHz, CD3CN)
f1 (ppm)



1.1.1-d_2

NOESY (600 MHz, CD_3CN)