UNIVERSITY OF CALIFORNIA, SAN DIEGO

Total Synthesis of Eupalinilide E and

Development of a Platform to Access Novel Thiopeptide Antibiotics

A dissertation submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy

in

Chemistry

by

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The Dissertation of Trevor Charles Johnson is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

Chair

University of California, San Diego

2016

DEDICATION

For my family

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LIST OF ABBREVIATIONS

(+)-CSA	(1S)-(+)-10-camphorsulfonic acid
$(COCl)_2$	oxalyl chloride
2,2-DMP	2,2-dimethoxypropane
2,4,6-TCBC	2,4,6-trichlorobenzoyl chloride
3,5-DMP	3,5-dimethylpyrazole
3,5-DNBC	3,5-dinitrobenzoyl chloride
Ac_2O	acetic anhydride
AcOH	acetic acid
AIBN	2,2′-azobis(2-methylpropionitrile)
Al(O*s*-Bu)$_3$	aluminum tri-*sec*-butoxide
$AlCl_3$	aluminum trichloride
B_2pin_2	bis(pinacolato)diboron
BF_3•OEt_2	boron trifluoride diethyl etherate
Boc_2O	di-*tert*-butyldicarbonate
BOPCl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
Br_2	bromine

$BrCCl_3$	bromotrichloromethane
Bu_3SnH	tributyltin hydride
$CeCl_3•7H_2O$	cerium trichloride hexahydrate
CH_2Cl_2	methylene chloride
CrO_3	chromium (VI) oxide
$Cu(OAc)_2•H_2O$	copper(II) acetate monohydrate
CuCl	copper(I) chloride
$CuSO_4$	cupper(II) sulfate
DBU	1,8-diazabicycloundec-7-ene
DCC	N,N′-dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DHP	3,4-dihydro-2H-pyran
DIBAL-H	diisobutylaluminium hydride
DIPEA	N,N-diisopropylethylamine
DMAP	4-dimethylaminopyridin
DMF	dimethylformamide
DMP	Dess–Martin periodinane

DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
EDC•HCl	N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride
Et_2AlCl	diethylaluminum chloride
Et_2O	diethyl ether
Et_3N	triethylamine
EtOH	ethanol
$H_2C{=}CHMgBr$	vinyl magnesium bromide
H_2CNMe_2I	N,N-dimethylmethyleneiminium iodide
H_2O_2	hydrogen peroxide
H_2SO_4	sulfuric acid
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3- triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HBr	hydrobromic acid
HCl	hydrochloric acid

HMPA	hexamethylphosphoramide
HOBt	hydroxybenzotriazole
IPA	isopropanol
i-PrMgCl•LiCl	isopropyl magnesium chloride lithium chloride complex
i-$PrNH_2$	isopropylamine
K_2CO_3	potassium carbonate
KH	potassium hydride
LDA	lithium diisopropylamide
Li_2CO_3	lithium carbonate
$LiAlH_4$	lithium aluminum hydride
LiCl	lithium chloride
LiOH	lithium hydroxide
mCPBA	*meta*-chloroperbenzoic acid
Me	methyl
Me_2CO	acetone
MeCN	acetonitrile
MeI	methyl iodide

MeLi	methyllithium
MeOH	methanol
$MeP(OPh_3)I$	methyltriphenoxyphosphonium iodide
$Mn(OAc)_3•2H2O$	manganese(III) acetate dihydrate
MnO_2	manganese(II) oxide
Na_2SO_4	sodium sulfate
$NaBH_4$	sodium borohydride
$NaClO_2$	sodium chlorite
NaH	sodium hydride
$NaHCO_3$	sodium bicarboante
$NaIO_4$	sodium periodate
NaOH	sodium hydroxide
NaOMe	sodium methoxide
NBS	N-bromosuccinimide
n-Bu_4NOH	*n*-tetrabutylammonium hydroxide
n-BuLi	*n*-butyllithium
NH_3	ammonia
NH_4Cl	ammonium chloride

NH_4OAc	ammonium acetate
NH_4OH	ammonium hydroxide
NBS	N-bromosuccinimide
NHS	N-hydroxysuccinimide
NMM	N-methylmorpholine
P_2O_5	phosphorus(V) oxide
$Pd(OAc)_2$	palladium(II) acetate
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
$PdCl_2(PPh_3)_2$	bis(triphenylphosphine)palladium(II) dichloride
PhMe	toluene
PhOH	phenol
PhSH	thiophenol
$PMBO(C{=}NH)CCl_3$	*para*-methoxybenzyl 2,2,2 trichloroacetimidate
PPTS	pyridinium *para*-toluenesulfonate
$Sc(OTf)_3$	scandium(III) trifluoromethanesulfonate

Sn_2Me_6	hexamethyldistannane
t-Bu	*tert*-butyl
TBAB	*n*-tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBSCl	*tert*-butyldimethylsilyl chloride
t-BuOH	*tert*-butanol
TCEP•HCl	tris(2-carboxyethyl)phosphine hydrochloride
Tf_2O	triflic anhydride
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFP	tri(2-furyl)phosphine
THF	tetrahydrofuran
TIPSOTf	triisopropylsilyl trifluoromethanesulfonate
TMSCl	trimethylsilyl chloride
TMSCN	trimethylsilyl cyanide
TMSI	trimethylsilyl iodide

TsCl	*para*-toluenesulfonyl chloride
$TsNHNH_2$	*para*-toluenesulfonyl hydrazide
p-TsOH	*para*-toluenesulfonic acid
UHP	urea hydrogen peroxide addition complex
$Yb(OTf)_3$	ytterbium(III) trifluoromethanesulfonate

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PUBLICATIONS AND PATENTS

1. Johnson, T. C.; Chin, M. R.; Han, T.; Shen, J. P.; Rana, T.; Siegel, D. Synthesis of Eupalinilide E a Promoter of Human Hematopoietic Stem and Progenitor Cell Expansion, *J. Am. Chem. Soc.* **2016**, 138, 6068-6073.

2. Camelio, A. M.; Johnson, T. C.; Siegel, D. Total Synthesis of Celastrol, Development of a Platform to Access Celastroid Natural Products, *J. Am. Chem. Soc.* **2015**, 137, 11864-11867.

3. Camelio, A. M.; Liang, Y.; Eliasen, A. M.; Johnson, T. C.; Yuan, C.; Schuppe, A. W.; Siegel, D. Computational and Experimental Studies of Phthaloyl Peroxide-Mediated Hydroxylation of Arenes Yield a More Reactive Derivative, 4,5-Dichlorophthaloyl Peroxide, *J. Org. Chem.* **2015**, 80, 8084-8095.

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ABSTRACT OF THE DISSERTAION

Total Synthesis of Eupalinilide E and

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Control of stem cell fate is a central goal of regenerative medicine. Hematopoietic stem cells (HSCs) are in high demand because they are routinely used in bone marrow transplants. This has led to a shortage of clinically viable HSCs and there are no FDA approved methods for the growth and maintenance of these cells *ex vivo*. The natural product eupalinilide E (**7**) promotes the *ex vivo* self-renewal (expansion) of HSCs with a 983-fold increase in growth after 14 days. The mode of action of eupalinilide E (**7**) remains unknown and appears to be independent of other known mechanism for HSC expansion. A synthetic route that can allow access to gram-scale quantities of eupalinilide E (**7**) has been developed.

There remains a constant need for novel antibiotics to combat the ever growing problem of antibiotic resistant infections. Thiopeptides are a well-studied family of natural products with potent antibiotic activity against several contemporary antibiotic resistant bacterial strains. Although having low toxicity against human cell lines and *in vivo* animal models, thiopeptides have only been used in the agricultural industry due to their low solubility in water. En route to the total synthesis of the thiopeptide lactocillin (**119**), a platform for the synthesis of novel thiopeptides has been developed. The route allows for rapid construction of the 29-membered macrocyclic core with synthetic handles for analog synthesis. Utilizing this route, derivative synthesis has begun with the intention of ultimately discovering novel thiopeptides with improved pharmacokinetics.

Chapter 1: Total Synthesis of Eupalinilide E

Research in the field of regenerative medicine remains predominately focused on developing stem cell based therapeutics for the treatment of various human disorders and diseases.[1–3] Pluripotent embryonic stem cells differentiate into all cell types found in an adult organism and have been used in transplantation-based therapies.[4–9] These therapies have been met with some success; however, controlling embryonic stem cell fate *ex vivo* has been inundated with problems, such as mutation, malignancy, and host-immune rejection.[10–12] Moreover, ethics surrounding the isolation and use of pluripotent embryonic stem cells remains controversial.[13]

Somatic stem cells (adult stem cells) are tissue specific and can only differentiate into cells of a specific lineage.[14–18] Like embryonic stem cells, somatic stem cells possess the ability to self-renew (expand) and differentiate in response to different biological cues. The cells persist throughout the course of an organism's lifetime and play important roles in physiological homeostasis and tissue repair. To bypass the problems associated with the use of embryonic stem cells, research has focused on promoting the *in vivo* or *ex vivo* self-renewal of somatic stem cells.

Hematopoietic stem cells (HSCs) are somatic stem cells found primarily in bone marrow tissue and give rise to all blood cell types.[19,20] They are the most well studied somatic stem cells and are routinely used in bone marrow transplants for the treatment of leukemias and anemias.[21–25] With tens of thousands of transplants performed each year, there remains a large shortage of clinically viable HSCs.[26–29] Therefore, methods that

promote the self-renewal or differentiation of HSCs are the key to unlocking their full therapeutic potential.

Within the last two decades, research has focused on identifying small molecules capable of modulating HSC homeostasis.[1–3,30] Chlamydocin (**1**), a histone deacetylases inhibitor, was found to expand human HSCs by up to 7-fold (Figure 1.1).[31] Similarly, Stemregenin 1 (SR1, **2**) along with several other purine-based small molecules were found to promote the *ex vivo* expansion of HSCs by activating the aryl hydrocarbon receptor (AHR).[32,33] SR1 (**2**) remains the most active promotor of HSC self-renewal, with treated cells displaying a 50-fold increase in growth at an EC_{50} of 120 nM. More recently, compounds related to the pyrimidoindole UM 171 (**3**) were identified to promote long term *ex vivo* expansion of HSCs.[34] Cell populations treated with UM 171 (**3**) were expanded and maintained as pure cultures for up to six months via a mechanism independent of the AHR pathway.

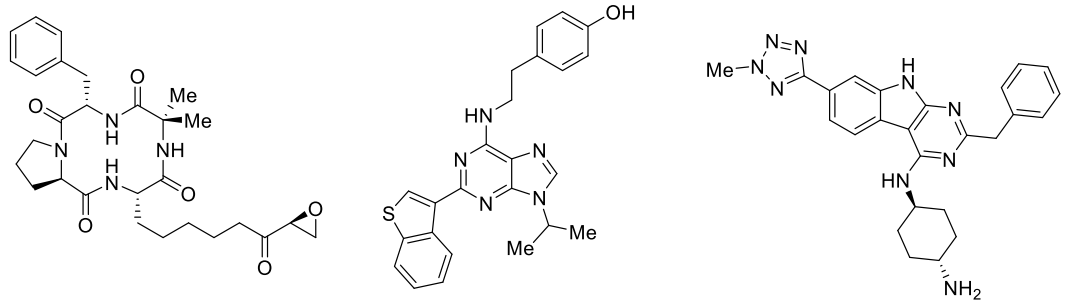


Figure 1.1. Small molecule regulators of HSC homeostasis.

Although natural products possess vast biological activities, few are known that are capable of regulating HSC homeostasis. This is likely a result of a lack of screening of natural products in this area of medicine. One report found that the plant derived natural

product euphohelioscopin A (**4**) is capable of promoting the differentiation of HSCs down the granulocyte cell lineage by activating protein kinase C (PKC, Figure 1.2).[35] Similarly, phorbol esters (**5**) were shown to activate PKC and promote macrophage differentiation.[36] The natural product garcinol (**6**) was also reported to expand HSCs by inhibiting histone acetyltransferase.[37]

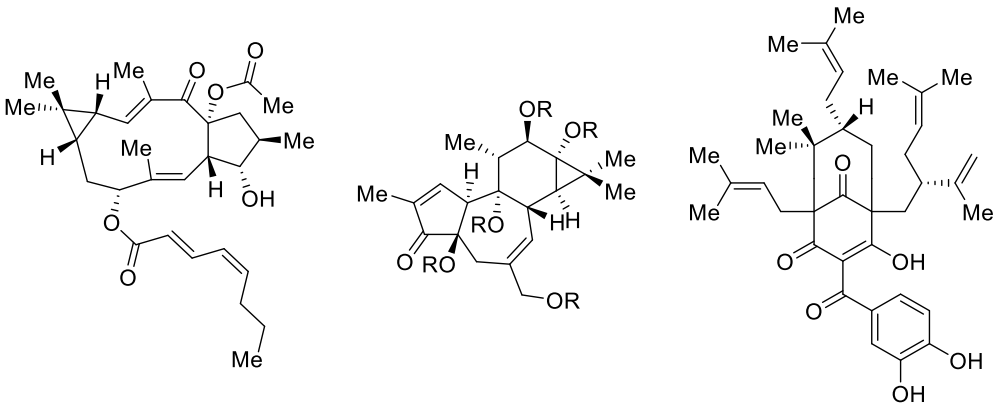


Figure 1.2. Natural products that regulate HSC homeostasis.

In an effort to find new small molecules capable of HSC self-renewal, Schultz and coworkers recently performed an unbiased screen of 704 pure natural products of microbial and plant origin.[38] The plant derived natural product eupalinilide E (**7**) was found to selectively promote the *ex vivo* expansion of HSCs and prevent the *in vivo* development of erythrocytes (Figure 1.3). Moreover, its activity was synergistic with AHR antagonists such as SR1 (**2**), suggesting that eupalinilide E (**7**) is functioning through a novel mechanism.

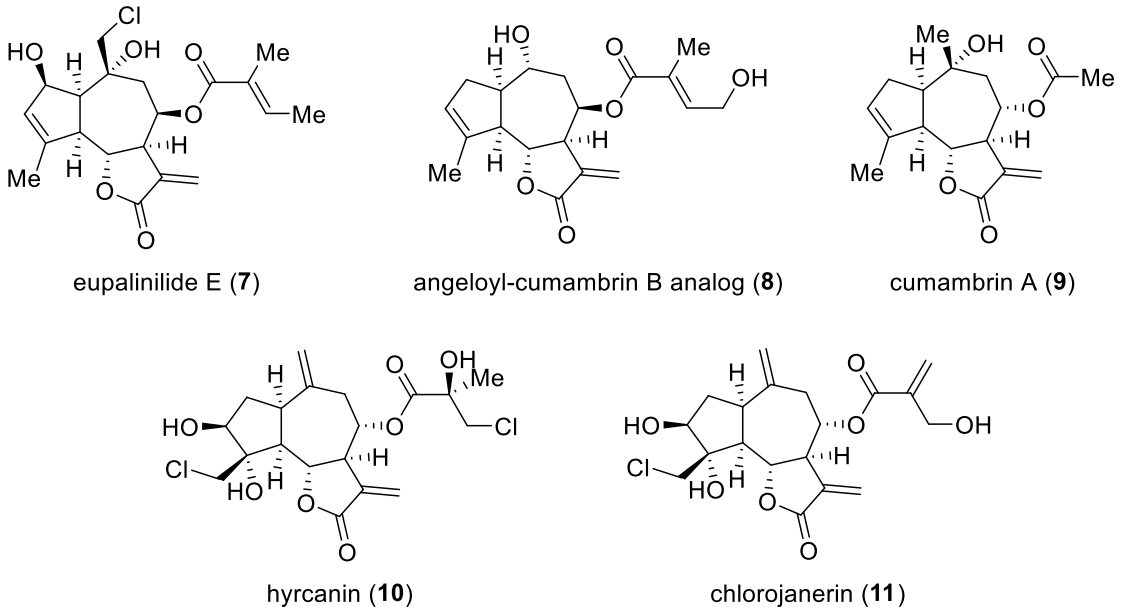


Figure 1.3. Eupalinilide E (**7**) and related sesquiterpene lactones tested for HSC expansion.

To identify compounds that promote HSC expansion, Schultz and coworkers treated human $CD34^+$ cells with 1 μM of each natural product and analyzed the cell mixtures by flow cytometry after 7 days. The quantity and percentage of HSCs, HSC progenitor cells, and lineage-committed cells were determined based on their immunophenotype. Eupalinilide E (**7**) was the only natural product found to significantly expand and maintain $CD34^+$ cells *ex vivo* at 600 nM (EC_{50} = 210 nM). Cord blood (CB) derived $CD34^+$ cells in self-renewal media showed a 45-fold increase in cell growth when treated with eupalinilide E (**7**) after 45 days. The CB $CD34^+$ cells in self-renewal media supplemented with differentiation-inducing cytokines: erythropoietin (EPO), granulocyte macrophage colony stimulating factor (GMCSF), granulocyte colony stimulating factor (GCSF), and interleukin-3 (IL-3) proliferated at a slower rate when treated with eupalinilide E (**7**), suggesting that it not only promotes expansion of an early hematopoietic progenitor but also suppresses differentiation down the erythrocyte lineage.[38]

Schultz and coworkers conducted preliminary experiments to uncover the mode of action of eupalinilide E (**7**). Initially the compound wsa tested to see if it was functioning through the aryl hydrocarbon receptor like other known small molecule regulators of HSCs.[1] Although eupalinilide E (**7**) did not give a positive response against the aryl hydrocarbon receptor, it was found to have a synergetic effect on $CD34^+$ expansion when tested in combination with SR1 (**2**).[33] This suggested that eupalinilide E (**7**) functions through a novel mechanism independent of the AHR pathway.

As eupalinilide E (**7**) is a sesquiterpene lactone, Schultz and coworkers tested the inhibition of the transcription factor NF-κB, which is the known protein target for many structurally related biologically active natural products.[39] Several other sesquiterpene lactones **8-11** were tested for their ability to promote HSC expansion; however, none of these compounds possessed this activity and were in fact cytotoxic (Figure 1.3).

The mode of action of eupalinilide E (**7**) remains unknown and throughout the course of their initial study, Schultz and coworkers exhausted their sample of the natural product.[40] Moreover, Schultz commented that: "the lack of synthetic routes to eupalinilide E hinders the generation of affinity probes for target identification." This makes eupalinilide E (**7**) an attractive target for total synthesis with the goal of ultimately synthesizing new analogs to discover its biological target.

Eupalinilide E (**7**) was isolated earlier from whole plant extracts of *Eupatorium lindleyanum* DC collected from the Songyang County of Zhejiang Province, People's Republic of China and was found to have potent cytotoxicity against the A-549 tumor cell line at 28 nM.[41] Its structure was solved using conventional methods including 1D/2D

NMR and mass spectroscopy. Along with the 5,7,5-tricyclic core found in all guaianolide sesquiterpene natural products, eupalinilide E (**7**) contains an allylic alcohol, chlorohydrin, and tigloyl ester at the C8 position (Figure 1.4). It also has a *trans*-annulated α-methylene-γ-butyrolactone, which is found in many other biologically active guaianolide natural products.[42] This functionality is a well characterized Michael acceptor of biological nucleophiles, such as cysteine residues.[43]

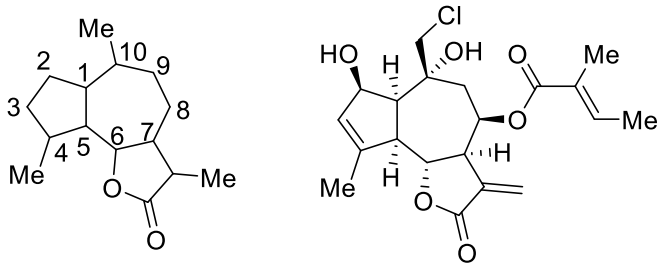
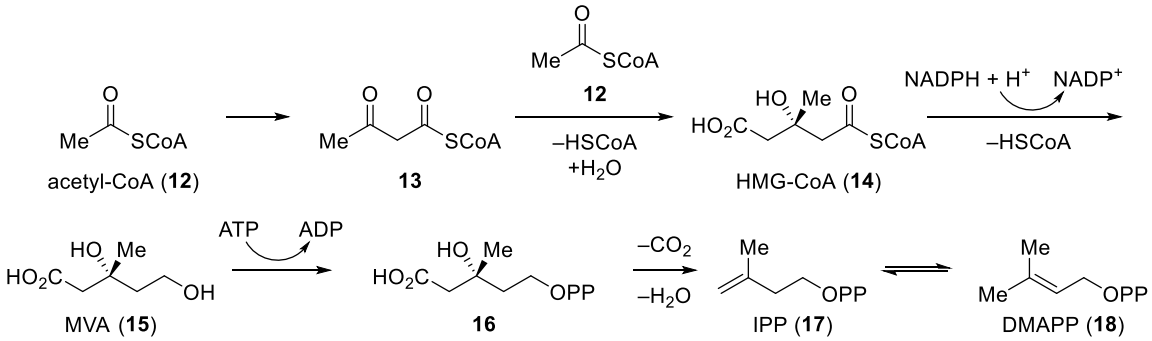


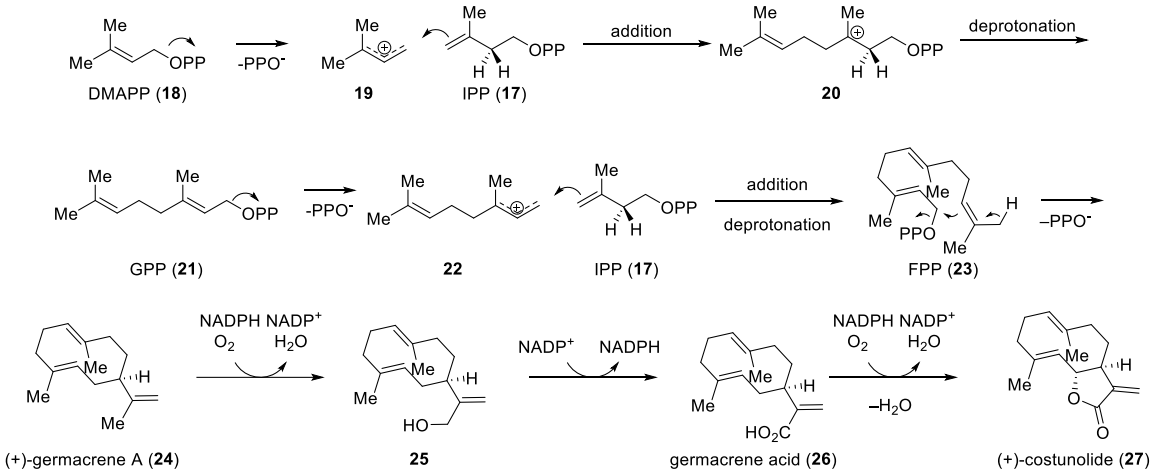
Figure 1.4. The core guaianolide framework of eupalinilide E (**7**).

The biosynthesis of guaianolide natural products has been well studied and begins with the union of three units of acetyl-CoA (**12**) via a Claisen condensation and aldol reaction to generate ß-hydroxy-ß-methylglutaryl-CoA (HMG-CoA, **14**; Scheme 1.1).[44–47] Reduction yields mevalonic acid (**15**), which is subsequently phosphorylated by mevalonate kinase. Pyrophosphomevalonic acid (**16**) then undergoes decarboxylation and dehydration to afford isopentenyl pyrophosphate (IPP, **17**), which can isomerize to γ,γ-dimethylallyl pyrophosphate (DMAPP, **18**).



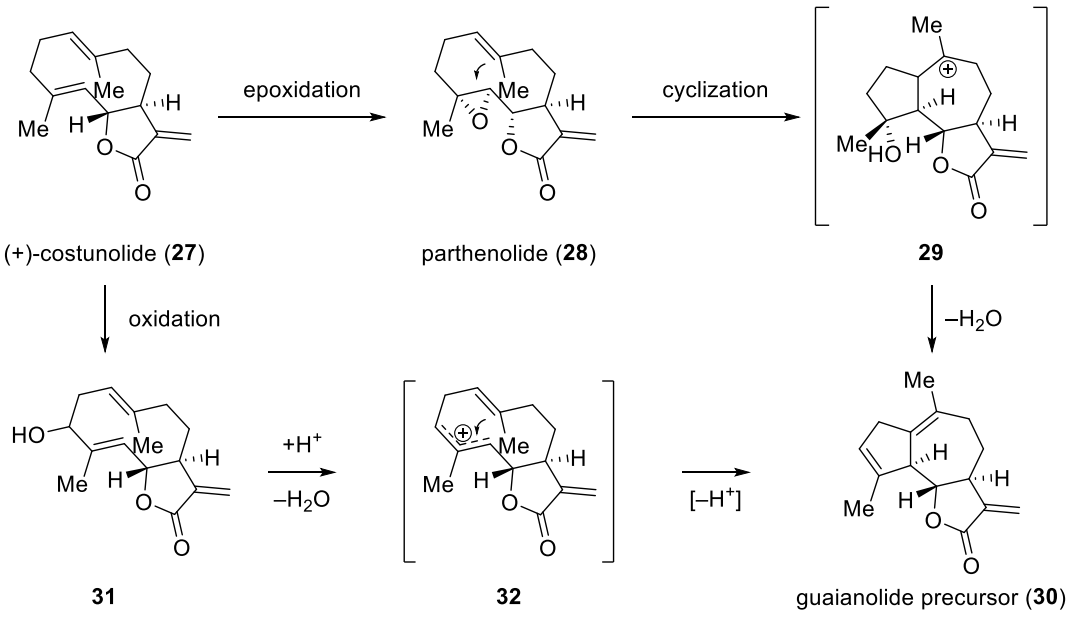
Scheme 1.1. The biosynthesis of IPP (**17**) and DMAPP (**18**).

Like many other terpenes, the C_{15} guaianolide core results from the cyclization of the linear sesquiterpene farnesyl pyrophosphate (FPP, **23**, Scheme 1.2). Ionization of DMAPP (**18**) generates an allylic cation that is trapped by electrophilic addition of IPP (**17**). Stereoselective deprotonation yields geranyl pyrophosphate (GPP, **21**), which is followed by another sequence of ionization, addition of IPP (**17**), and deprotonation to provide FPP (**23**). FPP (**23**) then cyclizes, after loss of pyrophosphate, to generate the 10 membered ring of (+)-germacrene A (**24**). The enzyme (+)-germacrene A hydroxylase installs a primary alcohol on the methyl of the isoprenyl group, which is further oxidized to the corresponding carboxylic acid to afford germacrene acid (**26**).[48–51] Finally, stereospecific C6 hydroxylation followed by lactonization yields (+)-costunolide (**27**).



Scheme 1.2. Biosynthesis (+)-costunolide (**27**) from DMAPP (**18**) and IPP (**17**).

Cyclization of (+)-costunolide (**27**) is thought to proceed via two possible routes (Scheme 1.3). Selective enzymatic epoxidation yields parthenolide (**28**), poised to undergo a *trans*-annular cyclization to provide the guaianolide precursor (**30**) after dehydration. Similarly, (+)-costunolide (**27**) can undergo enzymatic hydroxylation at the C3 position to generate alcohol **31**, which can ionize via loss of water and cyclize to give the same guaianolide precursor (**30**).[52] This precursor is then modified to provide a variety functional groups generating the large and diverse family of guaianolide natural products.



Scheme 1.3. Cyclization of (+)-costunolide (**27**) yields guaianolide precursor (**30**).

Eupalinilide E (**7**) has not been previously synthesized; however, several other guaianolides bearing the same 5,7,5-tricyclic core and γ-butyrolactone have been prepared in the laboratory (Figure 1.5). These syntheses inspired our synthesis of eupalinilide E (**7**) by providing a robust route to form the cyclopentane moiety as well as several methods for constructing the γ-butyrolactone and 7-membered ring.

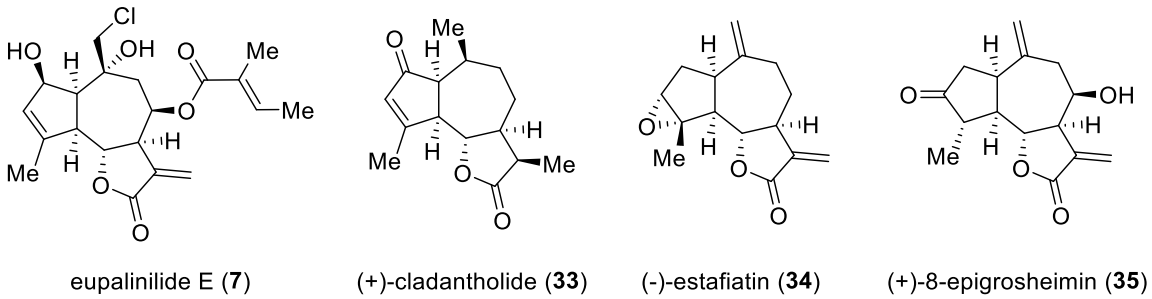
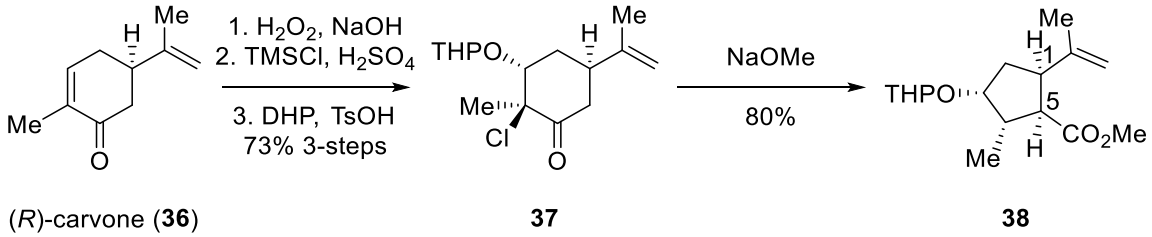


Figure 1.5. Eupalinilide E (**7**) and related guaianolide natural products.

The work pioneered by Lee and coworkers on the synthesis of the highly substituted cyclopentane **38** provided the platform for syntheses of several guaianolide natural

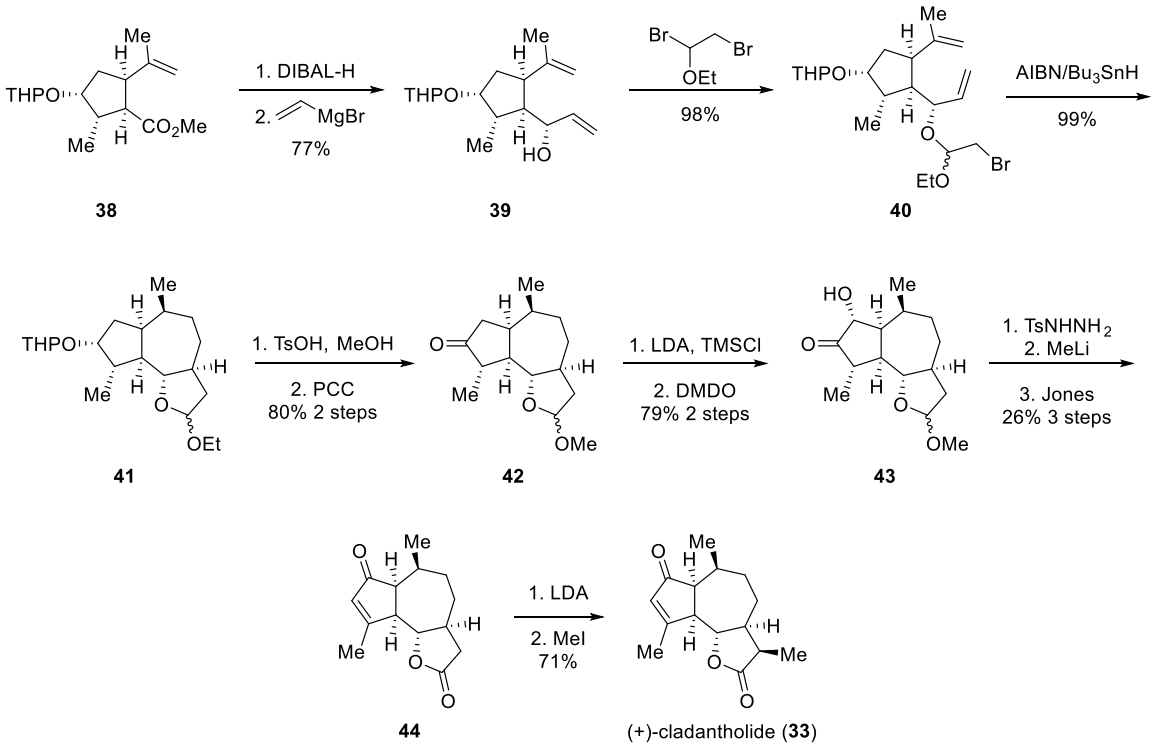
products (Scheme 1.4).[53] Importantly, the single stereocenter found in commercially available (*R*)-carvone (**36**) was used to control the stereochemical outcome of all subsequent reactions. Epoxidation of (*R*)-carvone (**36**) under basic conditions followed by opening of the epoxide and protection of the resulting secondary alcohol provided chlorohydrin **37** as a single diastereomer. Chlorohydrin **37** then underwent a sodium methoxide mediated Favorskii rearrangement to afford the highly substituted cyclopentane **38**. This intermediate provided the required methyl group at C4, the *cis* configuration between C1 and C5, and also the methyl ester and disubstituted olefin for further chemical elaboration.



Scheme 1.4. A diastereoselective Favorskii rearrangement yields the highly substituted cyclopentane **38**.

Following this work, Lee and coworkers went on to synthesize both (+)-cladantholide (**33**) and (-)-estafiatin (**34**, Scheme 1.5).[54] The methyl ester **38** was reduced to an aldehyde followed by addition of vinyl magnesium bromide to yield the secondary alcohol **39** as a single diastereomer. Alkylation provided acetal **40**, which underwent two successive radical cyclization reactions to simultaneously form both the 5 and 7-membered rings with the required stereochemistry. Following deprotection and oxidation, ketone **43** was hydroxylated at the α-position.[55] Synthesis of the enone was achieved using a Shapiro

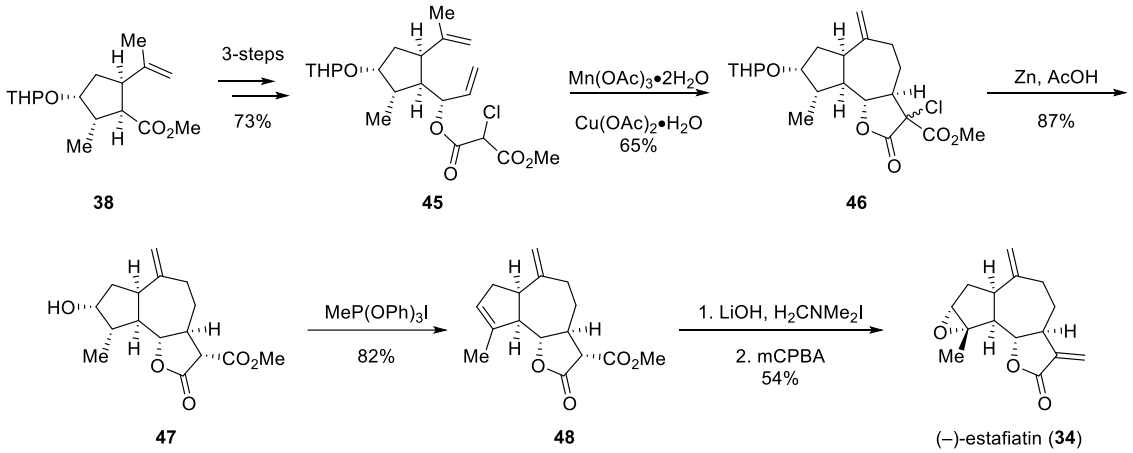
reaction followed by Jones oxidation, which also oxidized the acetal to the desired lactone.[56,57] Alkylation of the lactone with methyl iodide furnished (+)-cladantholide (**33**).



Scheme 1.5. Lee and coworkers' synthesis of (+)-cladantholide (**33**).

Using a route similar to their synthesis of (+)-cladantholide (**33**), Lee and coworkers achieved the total synthesis of (-)-estafiatin (**34**, Scheme 1.6)**.**[54] Tricycle **47** was accessed starting from the same cyclopentane **38** using a slightly different radical cyclization strategy. Selective elimination of the secondary alcohol to give the trisubstituted olefin was performed successfully using methyltriphenoxyphosphonium iodide in hexamethylphosphoramide.[58] We would later attempt to use this reaction to form the cyclopentene of eupalinilide E (**7**). The α-methylene-γ-butyrolactone was synthesized via alkylation with Eschenmoser's salt, which provided (-)-estafiatin (**34**) after epoxidation

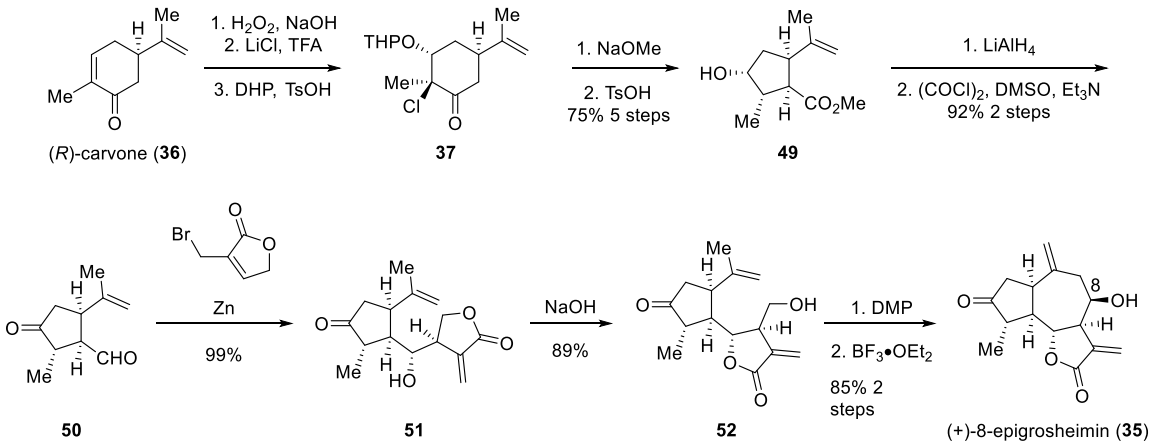
with *meta*-chloroperbenzoic acid.[59] Both of these syntheses detailed effective ring closing strategies and late stage modification of the cyclopentane ring.



Scheme 1.6. Lee and coworkers' synthesis of (-)-estafiatin (**34**).

The total synthesis of (+)-8-epigrosheimin (**35**) by Xu and coworkers provided another inspiring synthetic strategy for accessing related guaianolide natural products (Scheme 1.7).[60,61] Both eupalinilide E (**7**) and (+)-8-epigrosheimin (**35**) contain a C8 hydroxyl group, which cannot be installed easily using previous routes that relied on photochemical rearrangements, olefin metathesis or radical cyclizations to form the 7-membered ring.[62–70] Using the methodology developed in their synthesis of (+)-8-epigrosheimin (**35**), Xu and coworkers were able to overcome the problem of installing a C8 hydroxyl group. Methyl ester **49**, accessed using the same Favorskii rearrangement developed earlier by Lee, was reduced then oxidized to aldehyde **50**, which was subjected to a zinc promoted Barbier reaction to bring in the α-methylene-γ-butyrolactone as a single piece after base promoted translactonization. Oxidation of primary alcohol **52** to an aldehyde setup for an efficient diastereoselective aldehyde-ene reaction with the

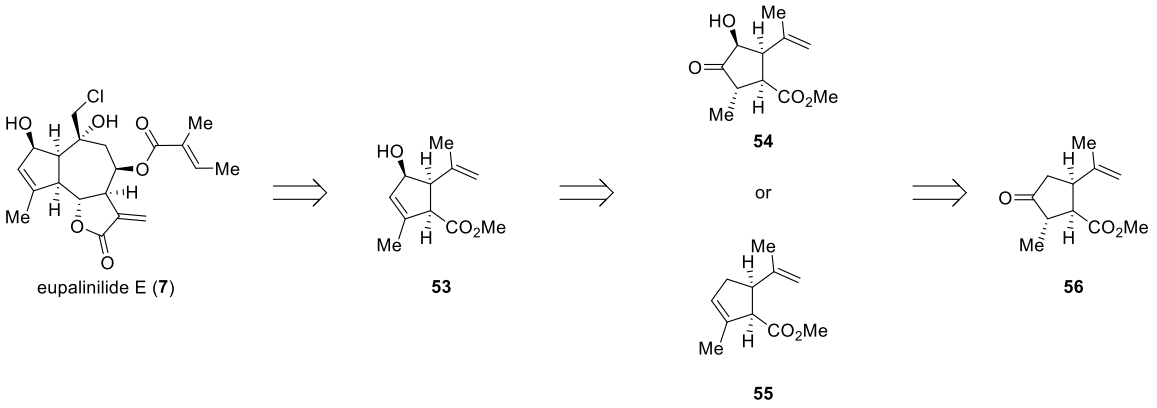
disubstituted olefin to close the 7-membered ring and install the desired C8 hydroxyl group. We would later adapt this sequence in our synthesis of eupalinilide E (**7**).



Scheme 1.7. Xu and coworkers' synthesis of (+)-8-epigrosheimin (**35**).

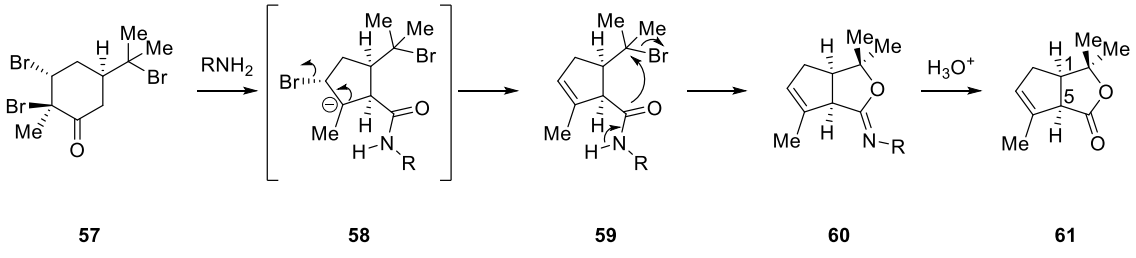
Our initial strategy for synthesizing eupalinilide E (**7**) required the synthesis of allylic alcohol **53** (Scheme 1.8). This intermediate could be accessed from either α-hydroxy ketone **54** using a Shapiro reaction or from allylic oxidation of trisubstituted olefin **55**. These intermediates were synthesized from ketone **56** using a Rubottom oxidation and a reduction/dehydration sequence, respectively. Both of these initial routes were limited by

poor yields and a lack of reaction scalability, due largely to the instability of several intermediates.



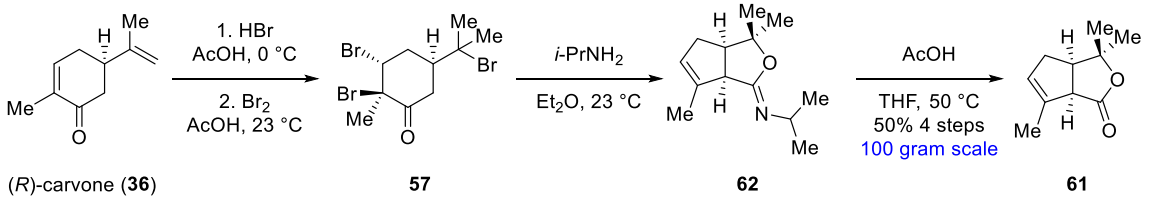
Scheme 1.8. Proposed synthesis of eupalinilide E (**7**) from cyclopentanone **56**.

While searching for alternative routes to allylic alcohol **53**, we encountered a report from Wallach in 1899 of a Favorskii rearrangement of tribromide **57** (Scheme 1.9).[71–73] Years later, Wolinsky and coworkers revisited this reaction and found tribromide **57** underwent Favorskii rearrangement with primary amines to yield bicyclic imidates **60**, which could be hydrolyzed to lactone **61** with aqueous acid.[74,75] Lactone **61** contained the same *cis* configuration between C1 and C5 and also directly provided the desired trisubstituted olefin.



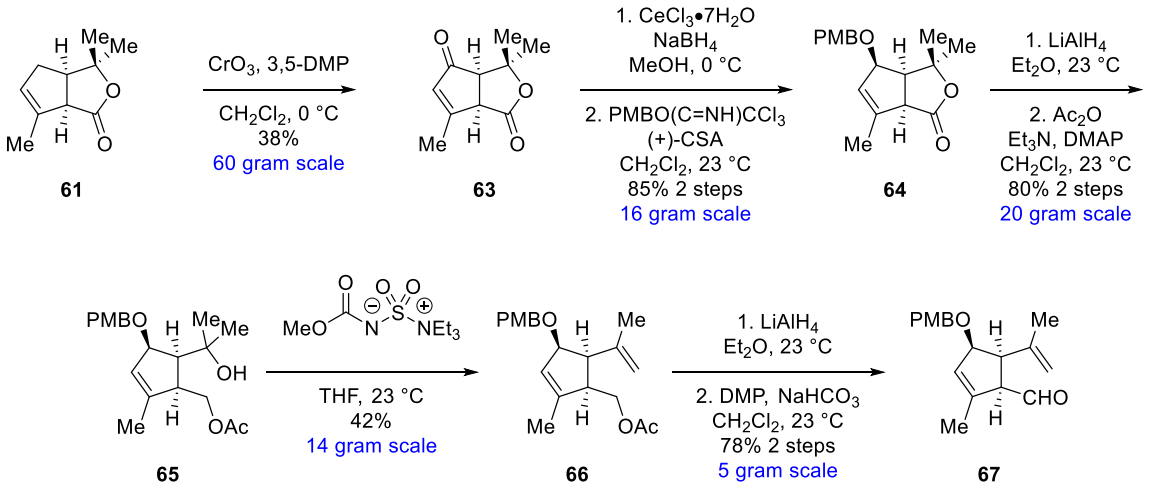
Scheme 1.9. Favorskii rearrangement of tribromide **57** to yield bicyclic lactone **61**.

The second generation route towards alcohol **53** began with hydrohalogenation of (*R)*-carvone (**36**) with dry hydrobromic acid to furnish carvone monobromide (Scheme 1.10). Further bromination of the trisubstituted olefin with bromine in acetic acid provided tribromide **57**, which afforded bicyclic imidate **62** after isopropyl amine mediated Favorskii rearrangement.[75] The imidate was hydrolyzed with aqueous acetic acid at 50 °C, yielding lactone **61** (50% yield over 4 steps) as a stable, crystalline solid after recrystallization from hexanes. This four step sequence was robust with over 300 grams of lactone **61** synthesized throughout the course of this project.



Scheme 1.10. Favorskii rearrangement of tribromide **57** mediated by isopropyl amine.

With large amounts of lactone **61** in hand, a synthetic route to aldehyde **67** was devised (Scheme 1.11). Mori and coworkers reported an allylic oxidation of lactone **61** with an excess of chromium trioxide and 3,5-dimethylpyrazole in methylene chloride to provide enone **63** with a yield of 16%.[76] After optimizing both equivalences and time, we were able to increase the yield to 38% and run the reaction on 60 gram scale. We found that using Florisil® instead of silica gel as the solid phase during purification greatly increased the yield and consistency of the reaction. Selective 1,2-reduction of enone **63** was accomplished with sodium borohydride using Luche conditions and protection of the allylic alcohol with *para*-methoxybenzyl 2,2,2-trichloroacetimidate provided *para*-methoxybenzyl alcohol **63** on 16 gram scale.[77]

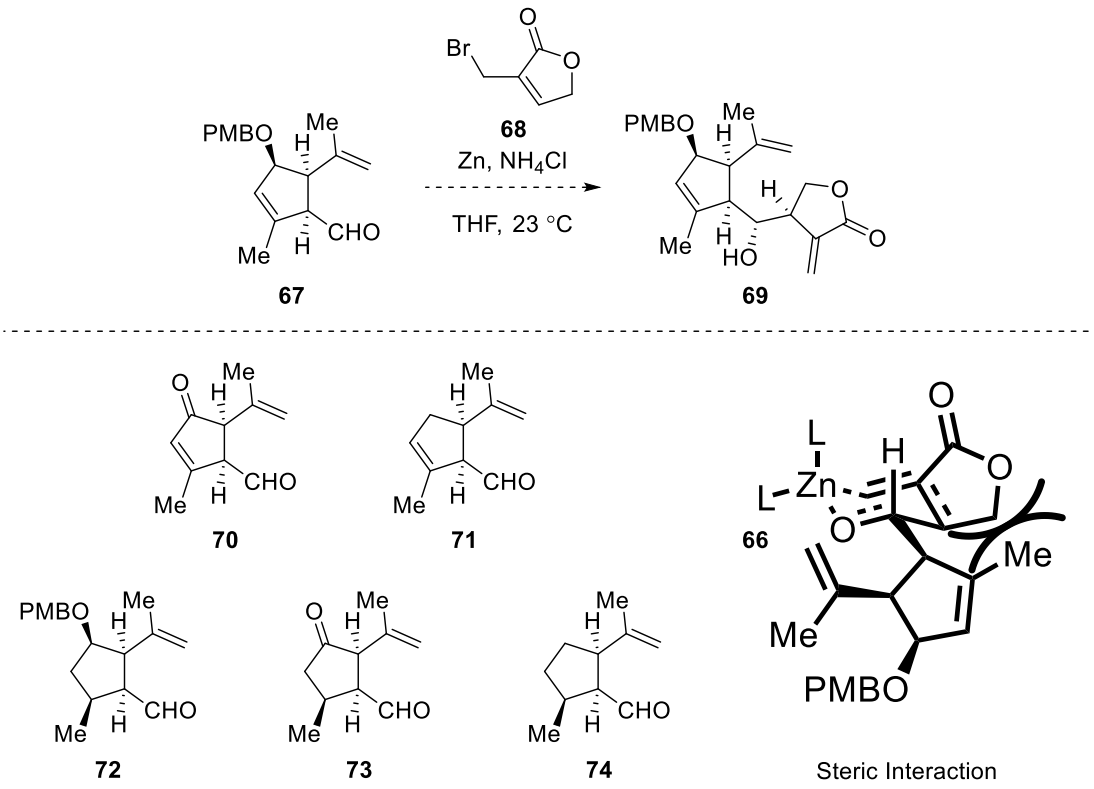


Scheme 1.11. Synthesis of aldehyde **67** from lactone **61**.

The lactone was opened with lithium aluminum hydride and the resulting primary alcohol was protected as an acetate under standard conditions in 80% yield. Elimination of the tertiary alcohol to give the desired disubstituted was difficult and often resulted in decomposition facilitated by the neighboring *para*-methoxybenzyl protected alcohol via an unknown mechanism. Ultimately, Burgess reagent in tetrahydrofuran at ambient temperature proved optimal, with a modest yield of 42%.[78] Removal of the acetate with lithium aluminum hydride and oxidation of the primary alcohol with Dess-Martin periodinane afforded aldehyde **67** on 5 gram scale.

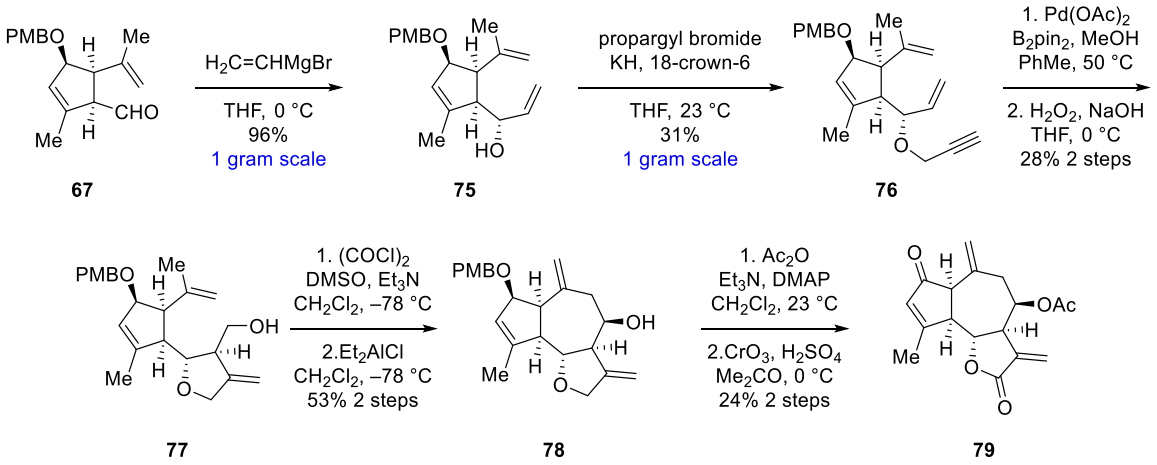
Inspired by Xu and coworkers' synthesis of (+)-8-epigrosheimin (**35**), we anticipated using a Barbier reaction between aldehyde **67** and bromide **68** to yield α-methylene-γ-butyrolactone **69** (Scheme 1.12). Unfortunately, aldehyde **67** was found to be completely unreactive under the reported conditions. Attempts to use other metals such as indium and samarium were also ineffective and upon heating, the trisubstituted olefin in **67** would isomerize. The reaction was thought to proceed through a 6-memembered

transition state and it's believed that the unsaturation between C3 and C4 in **67** created unfavorable steric interactions between the electrophile and the nucleophile. This hypothesis was later proved wrong by the fact that aldehydes **70-74** also did not successfully undergo Barbier coupling with bromide **67**.



Scheme 1.12. Failed Barbier reaction between aldehyde **67** and bromide **68**.

Instead of installing the α-methylene-γ-butyrolactone in a single reaction, we aimed to bring this piece in portion wise and use a radical or transition metal catalyzed cyclization reaction to form the 5-memebred ring. Vinyl magnesium bromide was added into aldehyde **67** to afford alcohol **75** as a single diastereomer (Scheme 1.13). This alcohol was reluctant towards alkylation and only by using potassium hydride, 18-crown-6, and propargyl bromide were we able to produce useful quantities of enyne **76** in 31% yield.

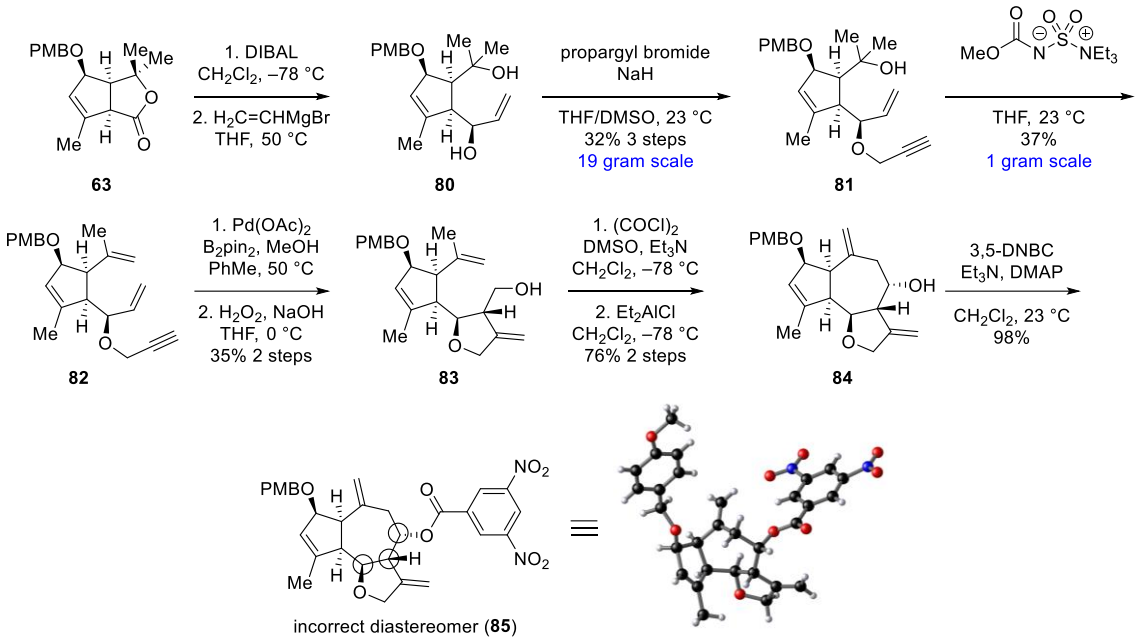


Scheme 1.13. Enyne and aldehyde-ene cyclizations form the 5,7,5-tricyclcle **79**.

Our group and others had previous experience developing palladium catalyzed borylative enyne cyclizations to synthesize highly substituted 5-membered rings with an appended primary alcohol.[79,80] We planned to use this alcohol in a subsequent aldehyde-ene reaction to close the 7-membered ring. Thus, treatment of enyne **76** with bis(pinacolato)diboron, palladium (II) acetate, and methanol in toluene at 50 °C afforded the desired cyclic ether **77** after oxidation of the intermediate primary boronate with hydrogen peroxide and sodium hydroxide. This reaction was completely diastereoselective, and provided the required *trans* configuration between C6 and C7. We were confident that the activated methylene position would undergo a late-stage oxidation to give our desired lactone. Oxidation of the primary alcohol under Swern conditions and treatment of the resulting aldehyde with diethylaluminum chloride yielded the 5,7,5-tricycle **78** as a white solid in 76% yield.[61,81] For proof of concept, the secondary alcohol was protected and the activated methylene of the 5-memebred ring was oxidized with Jones

reagent with concomitant deprotection and oxidation of the *para*-methoxybenzyl protected alcohol to give the dione **79**.[57]

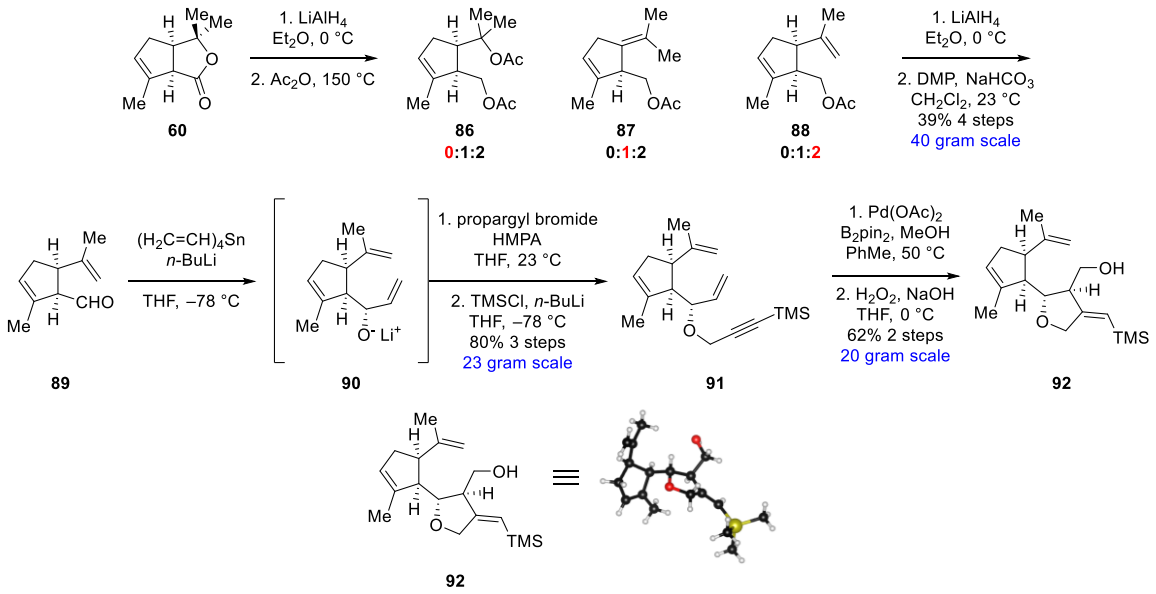
Although we successfully synthesized the core of eupalinilide E (**7**), the route was plagued with low yields and poor reaction scalability. In an attempt to streamline the route, a new synthesis of enyne **76** was devised (Scheme 1.14). Conversion of lactone **63** to the corresponding lactol and subsequent addition of vinyl magnesium bromide provided diol **80** in good yield. This sequence allowed the bypass of several functional group manipulations that were encountered en route to aldehyde **67**. Alkylation of the secondary alcohol was achieved using more mild conditions and was performed on 19 gram scale. The tertiary alcohol was eliminated using Burgess reagent and tricycle **84** was synthesized after enyne and aldehyde-ene cyclizations. This improved route allowed for multigram quantities of tricycle **84**. 3,5-dinitrobenzyl chloride was appended to the secondary alcohol to provide ester **85** and suitable crystals were grown for X-ray diffraction. Although the molecule had the correct atomic connectivity, we observed inverted stereochemistry for C6, C7, and C8. We hypothesized that this was the result of chelation controlled vinyl addition into the lactol of **63**.[82] This was opposed to the vinyl addition into discrete aldehyde **66**, which was predicted to follow the Felkin-Anh model.[83,84]



Scheme 1.14. Attempts to streamline the route leads to incorrect diastereomer **85**.

With this setback, we continued attempts to improve the yield and scalability of the route in order to explore the late stage chemistry required to complete the total synthesis. Although both allylic oxidations were performed successfully, these reactions were low yielding and it was ultimately decided to do both oxidations in a single reaction towards the end of the synthesis. Opening of lactone **61** with lithium aluminum hydride provided the diol in quantitative yield (Scheme 1.15). Poor yields with eliminating the tertiary alcohol with Burgess reagent prompted us to develop an alternative method to synthesize the desired disubstituted olefin **88**. It was found that acetate pyrolysis in neat acetic anhydride at 150 °C provided a mixture of the desired olefin **88**, the tetrasubstituted olefin **87**, and the diacetate **86**.[85,86] The ratio of these three products varied widely from reaction to reaction. It was realized that addition of activated crushed molecular sieves greatly improved the yield and consistency of this reaction, ultimately providing a 2:1 favorable

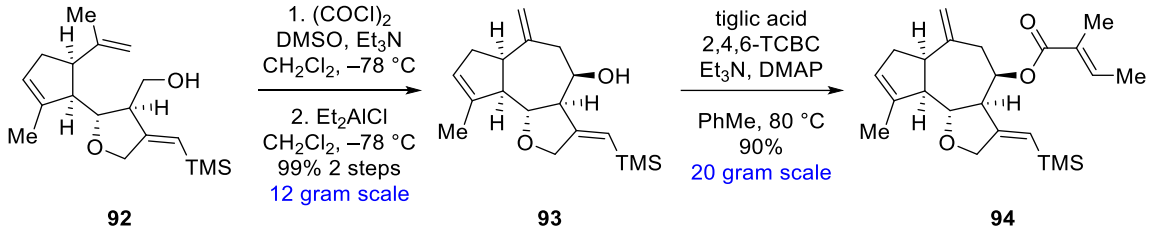
mixture of **88** and **87** in 91% yield on 40 gram scale. The two isomers were separated via silica gel column chromatography. Aldehyde **89** was synthesized after removal of the primary acetate and oxidation with Dess-Martin periodinane of the resulting alcohol.



Scheme 1.15. Synthesis of primary alcohol **92**.

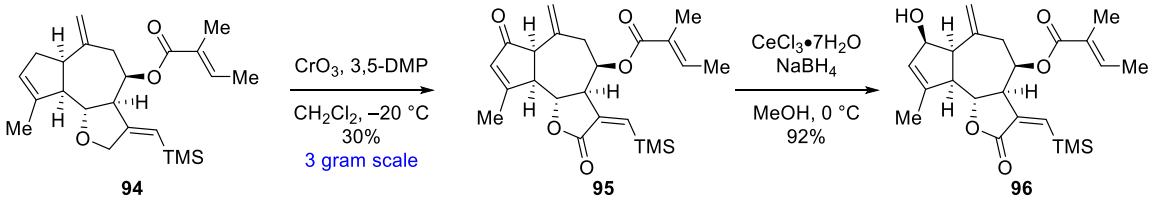
Low yields and poor scalability were still experienced for both the vinyl addition and progargylation reactions. To solve this problem, we developed a one-pot procedure for these two reactions. Vinyllithium was generated *in situ* from tetravinyltin and *n*-butyllithium at –78 °C to which a solution of aldehyde **89** in tetrahydrofuran was added to generate intermediate alkoxide **90**. Freshly distilled hexamethylphosphoramide was added followed by propargyl bromide and the reaction was warmed to ambient temperature. After workup and purification, the desired enyne was isolated in 81% yield on 23 gram scale. The alkyne was protected with a trimethylsilyl group to attenuate the reactivity of the α-methylene-γ-butyrolactone that was installed later. Remarkably, this modification more than doubled the yield of the enyne cyclization to 62%, which was run on 20 gram scale.

The structure and absolute stereochemistry of the enyne cyclization product **92** was confirmed unambiguously by X-ray diffraction, supporting the claim that vinyl addition into discrete aldehyde **89** followed Felkin-Ahn selectivity.



Scheme 1.16. Synthesis of carbocycle **94**.

Primary alcohol **92** was oxidized under Swern conditions and the intermediate aldehyde underwent cyclization at –78 °C with diethylaluminum chloride. These intermediates were more stable and allowed access to tricycle **93** in near quantitative yield on 12 gram scale. The tigloyl ester was appended using a Yamaguchi esterification with tiglic acid.[87] This improved route enabled the synthesis over 55 grams of carbocycle **94**.

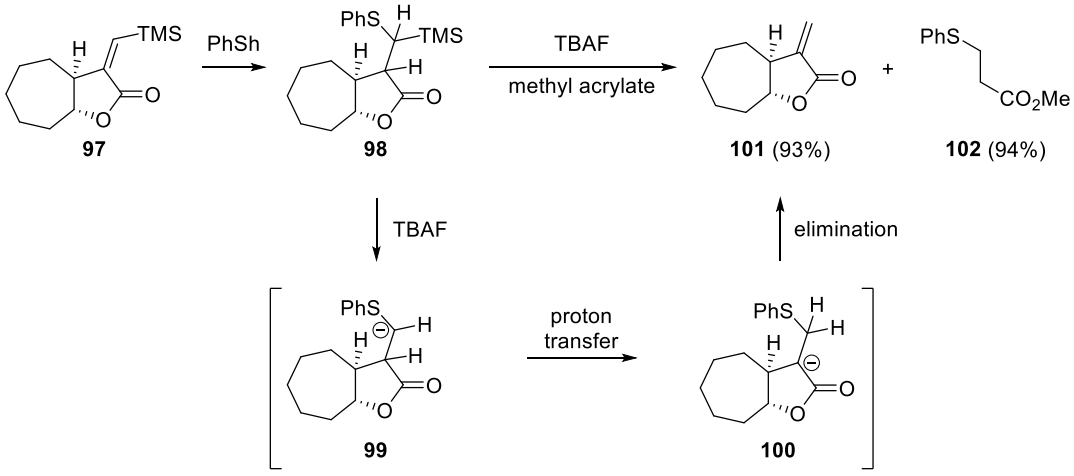


Scheme 1.17. Oxidation of the guaianolide core.

Using conditions developed in the allylic oxidation of bicycle **61**, carbocyle **94** underwent a double allylic oxidation when treated with chromium trioxide and 3,5-dimethylpyrazole to furnish dione **95** in 30% yield on 3 gram scale (Scheme 1.17). Many other reagents and conditions were investigated for this reaction including selenium dioxide, manganese(III) acetate, and other chromium base reagents such as PDC and

Collins reagent.[88–90] All of these provided little to no product. Reduction of the enone with sodium borohydride under Luche conditions afforded the allylic alcohol **96** as a single diastereomer in 92% yield.[77] In the absence of the vinyl trimethylsilyl group, significant 1,4-reduction of the α-methylene-γ-butyrolactone was observed.

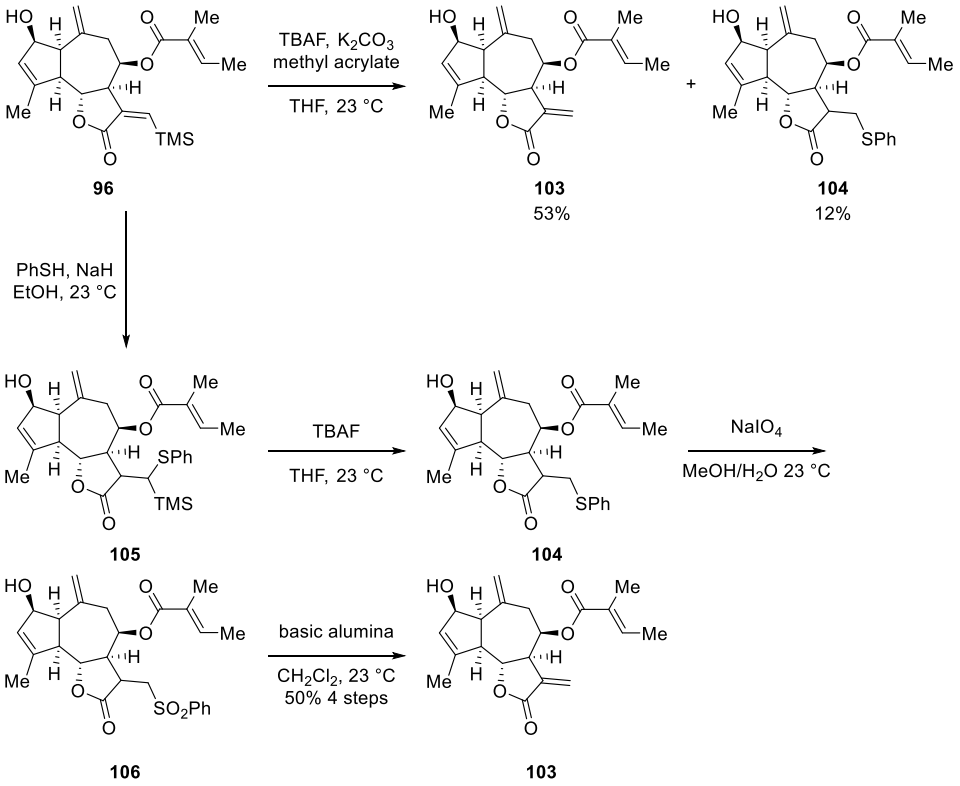
Due to the reactive nature of the α-methylene-γ-butyrolactone towards nucleophilic addition, we encounter problems with removing the vinyl trimethylsilyl group of **96**. The use of fluoride based reagents such as tetrabutylammonium fluoride, pyridinium poly(hydrofluoride), cesium fluoride, and tetrabutylammonium difluorotriphenylsilicate resulted in significant side reactions. Attempts to use acids such as trilfuoroacetic acid or hydrochloric acid lead to decomposition.



Scheme 1.18. Bachi and coworkers' vinyl trimethylsilane removal strategy.

Bachi and coworkers experienced a similar phenomenon years earlier.[28,91] Their solution was to add thiophenol into the α-methylene-γ-butyrolactone, thereby converting the Si-C_{sp2} bond to a Si-C_{sp3} bond (Scheme 1.18). Now a Si-C_{sp3}, the trimethylsilyl group was removed with tetrabutylammonium fluoride. Throughout their studies, Bachi and

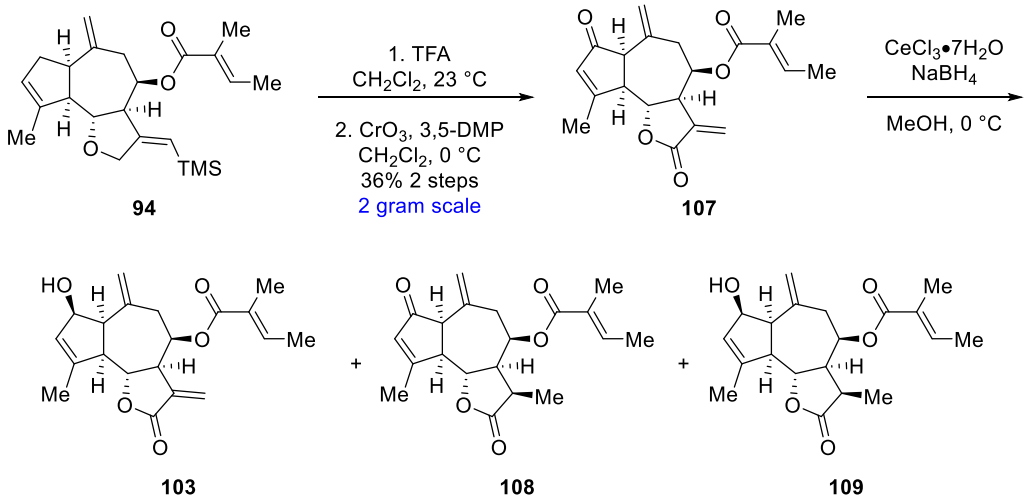
coworkers observed the expected thioether from this reaction but also a small amount of the reformed α-methylene-γ-butyrolactone, suggesting that some thiophenol was being eliminate throughout the course of the reaction. To drive elimination of thiophenol and prevent it from adding back into the α-methylene γ-butyrolactone, excess methyl acrylate was added as a Michael acceptor to trap released thiophenol. After optimization, Bachi and coworkers achieved desilylation and removal of thiophenol in a single reaction using tetrabutylammonium fluoride and an excess of methyl acrylate to regenerate their desired α-methylene-γ-butyrolactone in 93% yield.



Scheme 1.19. Desilylation of the protected α-methylene-γ-butyrolactone **96**.

We attempted to adapt this procedure for the desilylation of vinyl trimethylsilane **96** (Scheme 1.19). The desired deprotected α-methylene-γ-butyrolactone **103** was isolated

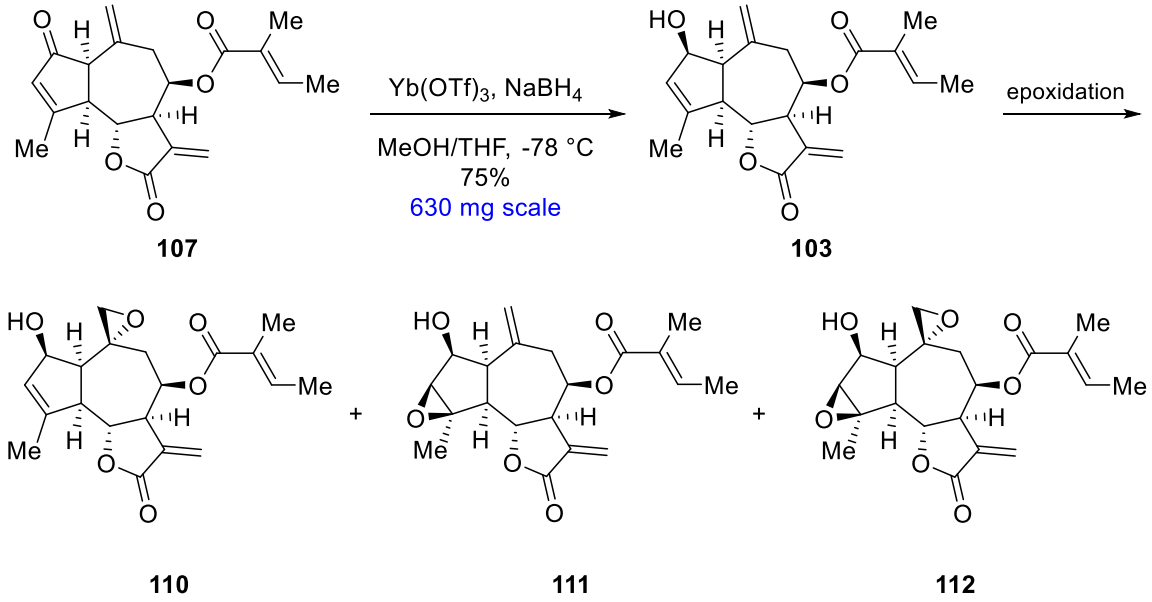
in 53% yield; however, it could not be separated from residual thioether **104**. Moreover, this impurity complicated the follow epoxidation reaction. In the end, a stepwise deprotection was developed. Addition of thiophenol using sodium hydride proceeded well to give thioether **104** after desilylation of **105** with tetrabutylammonium fluoride. The thioether was then oxidized to sulfone **106** with sodium periodate and eliminated with basic alumina to give the desired α-methylene-γ-butyrolactone **103** in 50% overall yield from **96**.



Scheme 1.20. Problems encountered when reducing enone **107**.

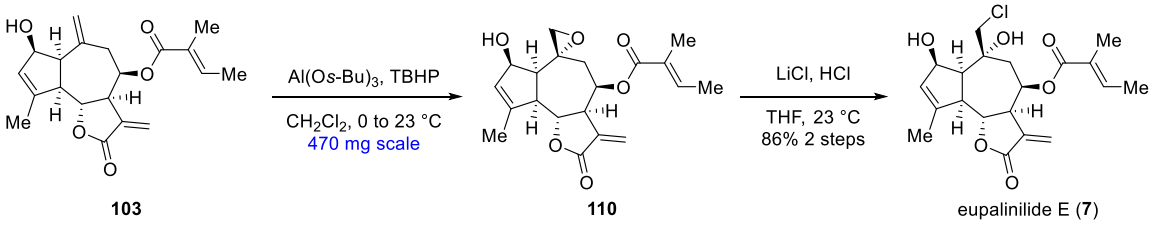
This four-step sequence was cumbersome and not scalable so we opted to desilylate prior to oxidation of the carbocyclic core **94** (Scheme 1.20). Protodesilylation proceeded well with trifluoroacetic acid in methylene chloride at ambient temperature and the resulting carbocycle underwent double allylic oxidation under the same conditions in the synthesis of **95** to form dione **107** in 36% yield on 1.6 gram scale. As previously mentioned, the bare α-methylene-γ-butyrolactone did not tolerate reduction of enone **107** with sodium borohydride under standard Luche conditions. An inseparable mixture of desired alcohol

103, 1,4-reduced α-methylene-γ-butyrolactone **108**, and over reduced **109** was observed. Attempts to use less reactive borohydrides such as zinc borohydride and sodium tris(hexafluoroisopropoxy)borohydride returned only unreacted starting material.[92,93] More bulky single hydride reducing agents such as lithium tri-sec-butylborohydride and diisobutylaluminium hydride were found to predominately give **108** and **109** even at –78 °C. Interestingly, we observed that the standard Luche conditions of sodium borohydride and cerium(III) chloride hexahydrate in methanol did not reduce the substrate at –78 °C; however, over reduction was observed upon warming the reaction to ambient temperature. It was presumed that if the reaction could be run at –78 °C then selective 1,2 reduction of the enone could be achieved. A report by Ruano and coworkers utilized ytterbium(III) trifluoromethanesulfonate at –78 °C to promote 1,2 reduction of an enone.[94] Thus, portion wise addition of sodium borohydride in the presence of stoichiometric ytterbium(III) trifluoromethanesulfonate to a solution of enone **107** at –78 °C provided the desired allylic alcohol **103** in 75% isolated yield. Importantly, residual hydride was quenched at –78 °C by the addition of 10 equivalents of acetaldehyde prior to warming the reaction to ambient temperature. This minimized the amount of over reduced product that was observed.



Scheme 1.21. Selective epoxidation of allylic alcohol **103**.

With allylic alcohol **103** in hand, attention was focused on forming the chlorohydrin and completing the synthesis of eupalinilide E (**7**). Initial attempts to selectively epoxidize the homoallylic disubstituted olefin in the presence of the allylic trisubstituted olefin produced a mixture of the desired epoxide **110**, the undesired epoxide **111**, and the over oxidized product **112** (Scheme 1.21). Peracids such as *meta*-chloroperbenzoic acid and peracetic acid gave almost exclusively **111** as a result of the directing effect of the allylic alcohol. Due to the concavity of the substrate, we sought to use a bulky oxidant in an attempt to selectively epoxidize the more accessible disubstituted olefin.



Scheme 1.22. Chlorohydrin formation completes the synthesis of eupalinilide E (**7**).

Using the catalyst derived from natural fructose developed by Shi and coworkers, a small amount of desired epoxide **110** was synthesized in 30% yield.[95] Several other Shi catalysts were also attempted but gave similar results. Abandoning this idea, epoxidation conditions developed by Sharpless were attempted.[96,97] Surprisingly, the use of *tert*-butyl hydroperoxide along with either vanadyl acetylacetonate, molybdenum hexacarbonyl, or titanium isopropoxide produced nearly a 50:50 mixture of **110** and the undesired epoxide **111** with very little over oxidized product **112**. The addition of (+)- or (-)-diethyl tartrate as ligands completely shut down the reaction, which supports the hypothesis that this observed selectivity is governed primary by the fixed conformation of the substrate. Decades earlier, Takai and coworkers investigated the use of aluminum based complexes in the epoxidation of several different olefins.[98] Initially, *tert*-butyl hydroperoxide and trimethylaluminum in a solution of methylene chloride at ambient temperature afforded **110** and **111** in a favorable 80:20 ratio. Further optimization led to the use of *tert*-butyl hydroperoxide and aluminum tri-*sec*-butoxide, which increased the selectivity and ultimately led to the isolation of **110** in 86% yield (Scheme 1.22). It's thought that the bulkier *sec*-butyl groups around aluminum further improved the selectivity of this reaction for the less hindered disubstituted olefin. Opening of epoxide **110** with dry hydrochloric acid in lithium chloride saturated tetrahydrofuran provided eupalinilide E (**7**) as a white solid. Without lithium chloride, the epoxide was engaged by the neighboring homoallylic alcohol, which resulted in the formation of a 5-memebred ring. Both ^{1}H- and ^{13}C-NMR spectra of synthetic eupalinilide E (**7**) matched reported spectra from the initial isolation and also 2D-NMR experiments of our own supported the proposed structure.

With the above synthesis, we have been able to synthesize over a gram of eupalinilide E (**7**) for *in vivo* studies with our collaborator Prof. Tariq Rana at UC San Diego. Synthetic eupalinilide E (**7**) has been retested at 600 nM for its ability to promote the *ex vivo* expansion of HSCs as described by Schultz and coworkers.[99] At 600 nM, synthetic eupalinilide E (**7**) increased the amount of total nucleated cells from an initial count of 45 thousand to 1.2 million after 7 days and 18 million after 14 days, a 406-fold increase (Figure 1.6). Eupalinilide E (**7**) displayed cytotoxicity at concentrations higher than 600 nM.

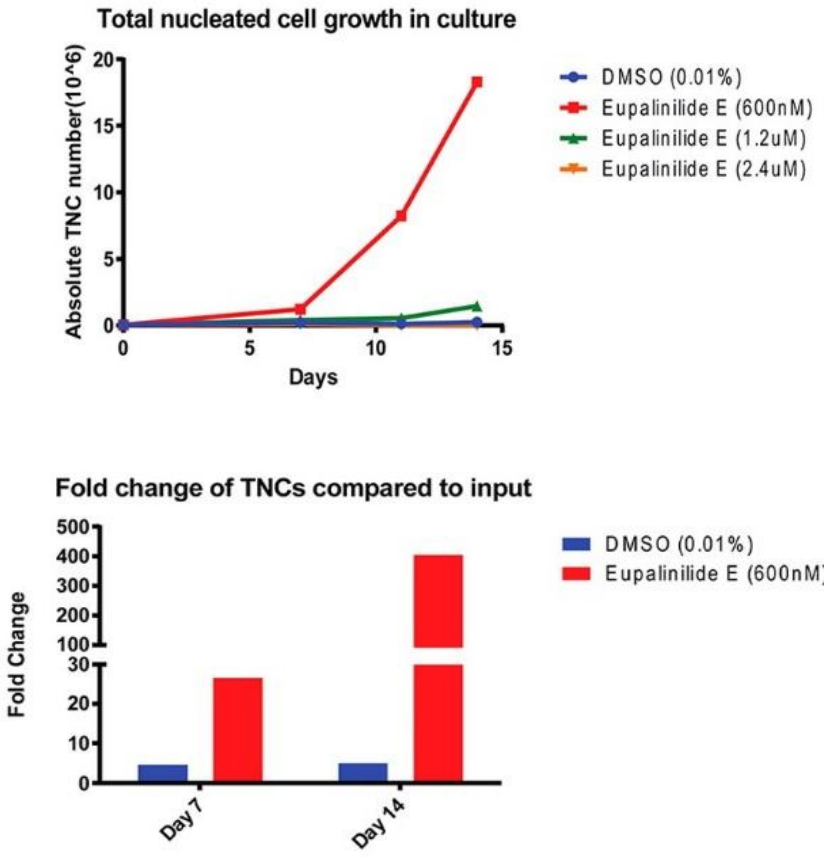


Figure 1.6. Amount of total nucleated cells promoted by eupalinilide E (**7**) at different concentrations at 7 and 14 days.

The percentage of HSCs present in culture (determined by the $CD34^+$ marker) was found to be 40.7% and 14.5% at 7 and 14 days, respectively (Figure 1.7). By multiplying the amount of total nucleated cells by the percentage of $CD34^+$ cells, we determined that treatment with 600 nM eupalinilide E led to a 983-fold increase in the amount of $CD34^+$ cells after 14 days relative to the DMSO control. Future work involves synthesizing several analogs in order to elucidate the protein target and mode of action of eupalinilide E (**7**).[100–102]

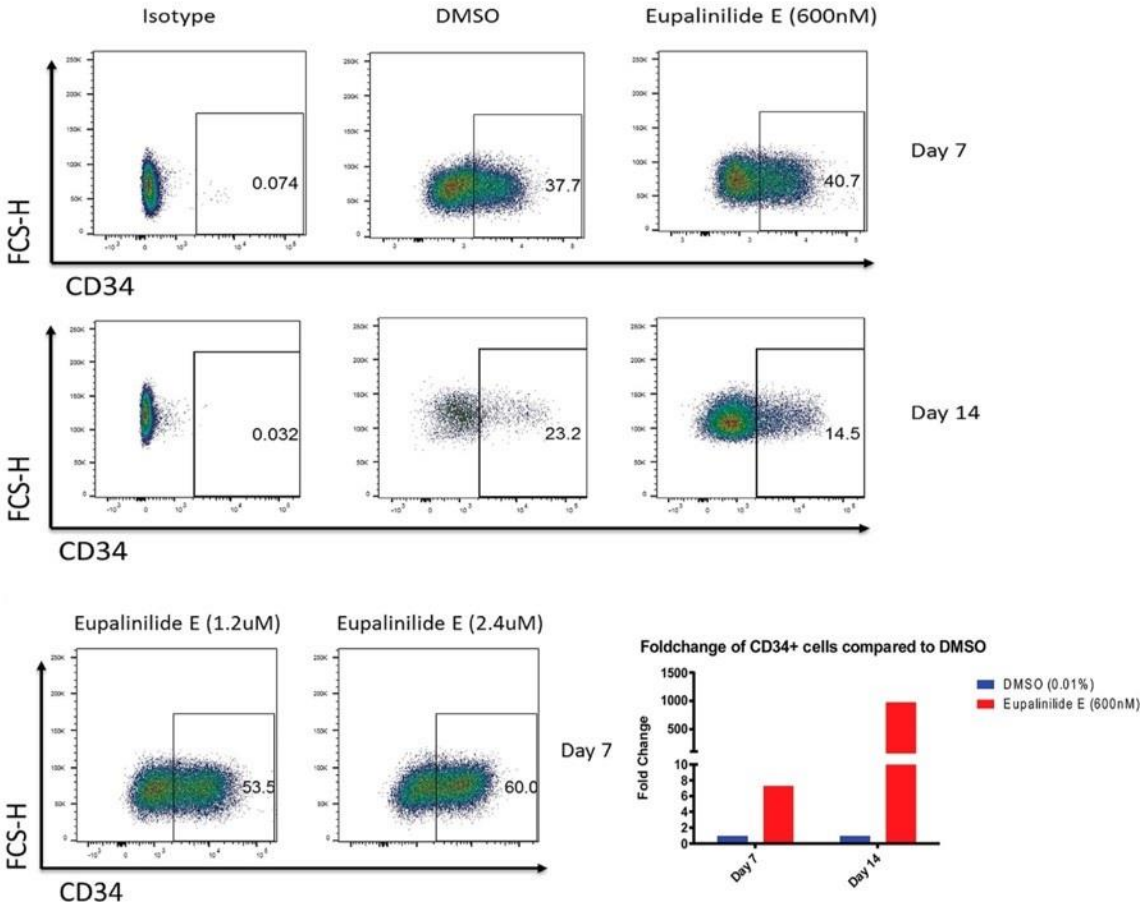


Figure 1.7. Percentage and total amount of $CD34^+$ cells after treatment with 600 nM eupalinilide E (**7**) at 7 and 14 days.

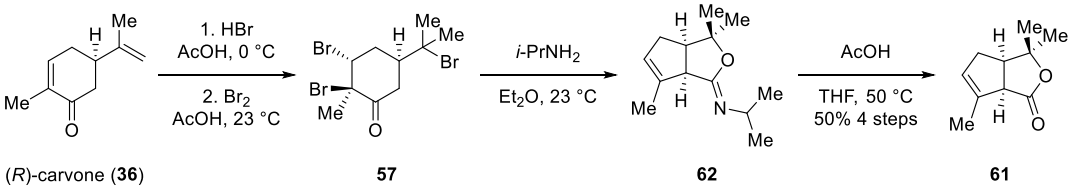
Chapter 1, in full, is a reprint of the material as it appears in Synthesis of Eupalinilide E a Promoter of Human Hematopoietic Stem and Progenitor Cell Expansion, *J. Am. Chem. Soc.* **2016**, 138, 6068-6073. Co-authors Matthew R. Chin, Tianxu Han, John Paul Shen, Tariq Rana, and Dionicio Siegel express their consent for inclusion of this published material in Chapter 1 of this dissertation. The dissertation author was an investigator and author on this paper.

Experimental Section

General Information

All reactions were performed in flame dried round bottom fitted with rubber septa under a positive pressure of argon or nitrogen, unless otherwise indicated. Air and moisture sensitive liquids and solutions were transferred via syringe or cannula. Organic solutions were concentrated by rotary evaporation at 20 torr in a water bath heated to 40 °C unless otherwise noted. Diethyl ether (Et_2O), methylene chloride (CH_2Cl_2), tetrahydrofuran (THF) and toluene (PhMe) were purified using a Pure-Solv MD-5 Solvent Purification System (Innovative Technology). Acetonitrile (MeCN), N,N,-dimethylformamide (DMF), and methanol (MeOH) were purchased from Acros (99.8%, anhydrous) and ethanol (EtOH) was purchased from Pharmco-Aaper (200 proof, absolute). The molarity of *n*-butyllithium was determined by titration against diphenylacetic acid.[103] All other reagents were used directly from the supplier without further purification unless otherwise noted. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (silica gel 60, F254, EMD chemical) and visualized using a UV lamp and/or aqueous ceric ammonium molybdate (CAM) or aqueous potassium permanganate ($KMnO_4$) stain, or ethanolic vanillin. Infrared spectra were recorded on a Nicolet 380 FTIR using neat thin film technique. High-resolution mass spectra (HRMS) were recorded on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion $[M+Na]^+$, $[M+H]^+$, [M] or $[M–H]^–$. Nuclear magnetic resonance spectra (^{1}H-NMR and ^{13}C-NMR) were recorded with a Varian Gemini [(400 MHz, ^{1}H at 400 MHz, ^{13}C at 100 MHz), (500 MHz, ^{1}H at 500 MHz, ^{13}C at 125 MHz), (600 MHz, ^{1}H at 600 MHz, ^{13}C at 150 MHz)]. For $CDCl_3$ solutions the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvent; $CHCl_3$ δ H (7.26 ppm) and $CDCl_3$ δ D (77.0 ppm). For $(CD_3)_2SO$ solutions the chemical shifts are reported as parts

per million (ppm) referenced to residual protium or carbon of the solvents; $(CD_3)(-CHD_2)SO$ δ H (2.50 ppm) or $(CD_3)_2SO$ δ C (39.5 ppm). For CD_3OD solutions the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvents; CHD_2OD δ H (3.31 ppm) or CD_3OD δ C (49.0 ppm). Coupling constants are reported in Hertz (Hz). Data for ^{1}H-NMR spectra are reported as follows: chemical shift (ppm, referenced to protium; s = singlet, d = doublet, t = triplet, q= quartet, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, ddq = doublet of doublet of quartets, bs = broad singlet, bd = broad doublet, m = multiplet, coupling constant (Hz), and integration). Melting points were measured on a MEL-TEMP device without corrections.



To a stirred solution of 33% hydrobromic acid in acetic acid (219 mL, 1.33 mmol, 2.0 equiv.) at 0 °C was slowly added a solution of *R*-carvone (**36**) (104 mL, 666 mmol, 1.0 equiv.) in acetic acid (100 mL) dropwise over 15 minutes. After 45 minutes, the reaction mixture was poured over ice H_2O (600 mL) and extracted with EtOAc (3 x 800 mL). The combined organic layers were washed with H_2O (800 mL), sat. aq. $NaHCO_3$ (800 mL) and brine (800 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give crude monobromide as an amber oil.

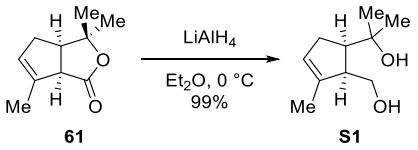
To a stirred solution of crude monobromide (154 g, 666 mmol, 1.0 equiv.) in AcOH (440 mL, 1.5 M) at 23 °C in a water bath was added a solution of bromine (41 mL, 800 mmol, 1.2 equiv.) in AcOH (70 mL) dropwise over 1 hour. After 1.5 hours, the reaction mixture was poured over ice H_2O (600 mL) and extracted with Et_2O (3 x 600 mL). The combined organic layers were washed with H_2O (600 mL), sat. aq. $NaHCO_3$ (5 x 600 mL) and brine (600 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give crude tribromide **57** as an amber oil.

To a stirred solution of crude tribromide **57** (260 g, 7.32 mol, 1.0 equiv.) in Et_2O (2.66 L, 0.25 M) at 0 °C was slowly added isopropyl amine (630 mL, 7.32 mol, 11.0 equiv.) over 30 minutes. Upon complete addition, the reaction mixture was allowed to warm to 23 °C. After 12 hours, the reaction mixture was cooled to 0 °C before carefully adding 10% aq. H_2SO_4 (600 mL). The aqueous layer was separated and the organic layer was extracted with 10% aq. H_2SO_4 (3 x 600 mL). The combined aqueous layers were cooled to 0 °C with stirring before being brought to pH = 8.0 with 10 N NaOH (600 mL). The neutralized

solution was extracted with EtOAc (4 x 600 mL), washed with brine (600 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give crude imidate **62** as an amber oil.

A stirred solution of crude imidate **62** (138 g, 666 mol, 1.0 equiv.) in a 3:1 solution of THF:10% aq. AcOH (1.33 L, 0.5 M) was heated to 50 °C. After 3 hours, the reaction mixture was cooled to 23 °C before pouring over ice and sat. aq. $NaHCO_3$ (1 L). The reaction mixture was extracted with EtOAc (4 x 600 mL), washed with brine (600 mL), dried over Na_2SO_4, and concentrated in vacuo to give an amber oil. The crude material was purified via silica gel column chromatography (5:1 hexanes:EtOAc) followed by recrystallization from hexanes to give pure bicycle **61** (55.3 g, 333 mmol, 50% over 4 steps) as a white solid (m.p. 33-35 °C).[75]

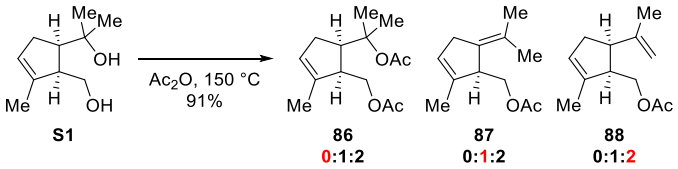
R_f = 0.41 (silica gel, 5:1 hexanes:EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.23 (bd, *J* = 2.0 Hz, 1H), 3.39 (d, *J* = 9.0 Hz, 1H), 2.81, (q, *J* = 6.3 Hz, 1H), 2.30 (t, *J* = 2.0 Hz, 2H), 2.28 (t, *J* = 2.0 Hz, 1H), 1.68 (s, 3H), 1.26 (s, 3H), 1.17 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 175.2, 135.5, 126.1, 85.2, 56.1, 47.9, 33.1, 30.2, 23.4, 14.1; **IR** (film, cm^{-1}): 1758, 1270, 1119; **HRMS** (ESI) calc. for $C_{10}H_{14}O_2$ $[M+Na]^+$: 189.08860, obs. 189.08940.



61 **S1**

To a stirred solution of bicycle **61** (32 g, 193 mmol, 1.0 equiv.) in Et_2O (960 mL, 0.2 M) at 0 °C was slowly added a 4.0 M solution of lithium aluminum hydride in Et_2O (48 mL, 193 mmol, 1.0 equiv.) over 20 minutes. After 40 minutes, the reaction mixture was carefully quenched with H_2O (7.3 mL), 15% aq. NaOH (7.3 mL), and H_2O (21.9 mL) at 0 °C. The reaction mixture was dried over Na_2SO_4, filtered through Celite, and concentrated *in vacuo* to give pure diol **S1** (32.4 g, 191 mmol, 99%) as a white solid (m.p. 73-75 °C).

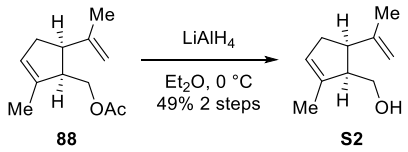
$\mathbf{R_f}$ = 0.23 (silica gel, 2:1 hexanes:EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.43 (bs, 1H), 4.57 (bs, 1H), 4.36 (bs, 1H), 3.77 (d, *J* = 12 Hz, 1H), 3.51 (dd, *J* = 11, 5.5 Hz, 1H), 2.5 (bd, *J* = 2.7 Hz, 1H), 2.31-2.23 (m, 2H), 2.09 (bd, *J* = 8.6 Hz, 1H), 1.65 (s, 1H), 1.33 (s, 1H), 1.20 (s, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 139.9, 125.8, 71.1, 60.1, 53.6, 51.4, 32.2, 29.8, 29.4, 15.1; **IR** (film, cm^{-1}): 3282, 1360, 1053, 1004; **HRMS** (ESI): calc. for $C_{10}H_{18}O_2$ $[M+Na]^+$: 193.11930, obs. 193.11990.



A stirred solution of diol **S1** (40 g, 235 mmol, 1.0 equiv.), activated 4.0 Å molecular sieves (20 g, 50% by weight), and Ac_2O (160 mL, 1.5 M) was heated to 150 °C. After 16 hours, the reaction mixture was cooled to 23 °C and passed through a short silica gel plug (10:1 hexanes:EtOAc) to give an inseparable 2:1 mixture of acetates **88** and **87** (41.5 g, 214 mmol, 91%) as an amber oil.

R_f = 0.46 (silica gel, 10:1 hexanes:EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [**88**] 5.48 (bs, 1H), 4.86 (s, 1H), 4.80 (s, 1H), 4.07 (dd, *J* = 11, 5.7 Hz, 1H), 3.83 (dd, *J* = 11, 5.7 Hz, 1H), 3.33 (bs, 1H), 2.88 (bs, 1H), 2.43 (td, *J* = 11, 2.0 Hz, 1H), 2.16 (dd, *J* = 15, 7.7 Hz, 1H), 2.00 (s, 3H), 1.79 (s, 3H), 1.75 (s, 3H), [**87**] 5.49 (bs, 1H), 4.25 (dd, *J* = 11, 6.6 Hz, 1H), , 3.97 (dd, *J* = 11, 6.6 Hz, 1H), 2.93 (q, *J* = 8.7 Hz, 1H), 2.88 (bs, 1H), 2.73 (q, *J* = 6.2 Hz, 1H), 2.03 (s, 3H), 1.77 (s, 3H), 1.73 (s, 3H), 1.63 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 171.0, 170.9, 144.5, 140.4, 133.4, 126.2, 125.4, 124.9, 110.9, 110.9, 66.2, 63.6, 63.6, 50.2, 49.6, 48.5, 36.3, 33.8, 23.1, 21.0, 20.9, 20.5, 16.0, 15.9; **IR** (film, cm^{-1}): 1741, 1379, 1252, 1038.

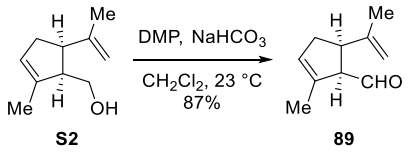
[**86**] **R_f** = 0.30 (silica gel, 10:1 hexanes:EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.47 (bs, 1H), 4.44 (dd, *J* = 11, 5.5 Hz, 1H), 3.94 (dd, *J* = 11, 7.0 Hz, 1H), 2.68 (q, *J* = 7.0 Hz, 1H), 2.40-2.30 (m, 2H), 2.15 (dd, *J* = 11, 5.5 Hz, 1H), 2.01 (s, 3H), 1.95 (s, 3H), 1.76 (s, 3H), 1.65 (s, 3H), 1.50 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 171.0, 170.2, 141.9, 125.8, 125.8, 82.1, 64.6, 55.0, 47.7, 31.2, 25.5, 22.4, 21.1, 16.6; **IR** (film, cm^{-1}): 1732, 1367, 1228, 1023.



88 **S2**

To a stirred solution of acetates **87** and **88** (41.5 g, 214 mmol, 1.0 equiv.) in Et_2O (1.1 L, 0.2 M) at 0 °C was slowly added a 4.0 M solution of lithium aluminum hydride in Et_2O (26.7 mL, 107 mmol, 0.5 equiv.) over 20 minutes. After 40 minutes, the reaction mixture was carefully quenched with H_2O (4.1 mL), 15% aq. NaOH (4.1 mL), and H_2O (12.3 mL) at 0 °C. The reaction mixture was dried over Na_2SO_4, filtered through Celite, and concentrated *in vacuo* to give a clear oil. The crude material was purified via silica gel column chromatography (50:1 to 20:1 hexanes:EtOAc) to give pure alcohol **S2** (15.9 g, 105 mmol, 49% over 2 steps) as a clear oil.

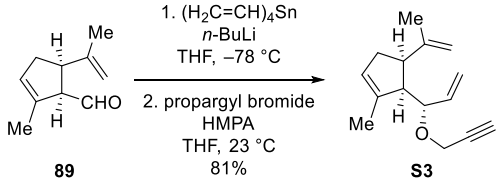
R_f = 0.36 (silica gel, 5:1 hexanes:EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.51 (s, 1H), 4.94 (s, 1H), 4.91 (s, 1H), 3.56 (dd, *J* = 9.4, 4.7, 2H), 2.96 (q, *J* = 8.6 Hz, 1H), 2.63 (bs, 1H), 2.45 (dd, *J* = 12, 6.3 Hz, 1H), 2.17 (dd, *J* = 12, 6.3 Hz, 1H), 1.83 (s, 3H), 1.73 (s, 3H), 1.59 (bs, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 146.4, 139.5, 126.2, 110.8, 61.3, 52.6, 49.3, 34.3, 23.5, 15.5; **IR** (film, cm^{-1}): 3381, 1447, 1037, 888; **HRMS** (EC-CI): calc. for $C_{10}H_{16}O$ [M]: 152.1201, obs. 152.1196.



S2 **89**

To a stirred solution of alcohol **S2** (26.2 g, 172 mmol, 1.0 equiv.) in CH_2Cl_2 (860 mL, 0.2 M) at 23 °C was added solid $NaHCO_3$ (43.4 g, 517 mmol, 3 equiv.), freshly prepared Dess-Martin periodinane (110 g, 258 mmol, 1.5 equiv.), and H_2O (1 mL). After 45 minutes, the reaction mixture was diluted with sat. aq. $NaHCO_3$ (500 mL) and sat. $Na_2S_2O_4$ and stirred for 10 minutes. The reaction mixture was extracted with CH_2Cl_2 (3 x 800 mL), washed with brine (800 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give an amber oil. The crude material was purified via silica gel column chromatography (10:1 hexanes:EtOAc) to give pure aldehyde **89** (22.5 g, 150 mmol, 87%) as a clear oil.

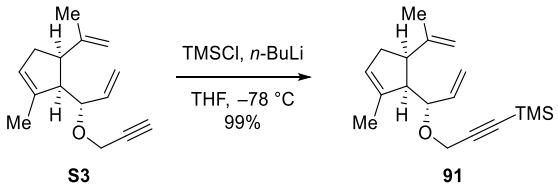
$\mathbf{R_f}$ = 0.56 (silica gel, 5:1 hexanes:EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 9.35 (d, J = 5.5 Hz, 1H), 5.77 (bs, 1H), 4.90 (s, 1H), 4.87 (s, 1H), 3.22 (q, J = 9.1 Hz, 1H), 3.17 (t, J = 6.3 Hz, 1H), 2.71 (t, J = 10 Hz, 1H), 2.43 (dd, J = 16, 8.1 Hz, 1H), 1.75 (s, 3H), 1.67 (s, 3H); **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 201.1, 143.2, 135.5, 130.0, 111.7, 63.4, 49.7, 34.6, 22.9, 15.6; **IR** (film, cm^{-1}): 1720, 1446, 892. **HRMS** (APCI-TOFMS): calc. for $C_{10}H_{14}O$ $[M+H]^+$: 151.1117, obs. 151.1119.



To a stirred solution of tetravinyl tin (11 mL, 59.9 mmol, 0.4 equiv.) in THF (600 mL) at −78 °C was added a 2.14 M solution of *n*-butyllithium in hexanes (91 mL, 195 mmol, 1.3 equiv.). The reaction mixture was warmed and stirred at 23 °C for 15 minutes before being cooled back down to −78 °C and adding a solution of aldehyde **89** (22.5 g, 150 mmol, 1.0 equiv.) in THF (150 mL). After 15 minutes, freshly distilled neat hexamethylphosphoramide (52 mL, 299 mmol, 2 equiv.) was added. After an additional 10 minutes an 80% solution of propargyl bromide in toluene (83 mL, 749 mmol, 5 equiv.) was added. Upon complete addition the reaction mixture was allowed to warm to 23 °C. After 3 hours, the reaction mixture was diluted with sat. aq. NH_4Cl (50 mL), extracted with Et_2O (3 x 50 mL), washed with 3.0 N LiCl (3 x 50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a yellow oil. The crude material was purified via silica gel column chromatography (straight hexanes to 50:1 to 20:1 hexanes:EtOAc) to give pure enyne **S3** (26.2 g, 121 mmol, 81%) as a clear oil.

R_f = 0.50 (silica gel, 2:1 hexanes:EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.86 (ddd, *J* = 17, 11, 7.4 Hz, 1H), 5.56 (bs, 1H), 5.19 (d, *J* = 10 Hz, 1H), 5.15 (d, *J* = 6.7 Hz, 1H), 4.90 (s, 2H), 4.10 (dd, *J* = 13, 2.4 Hz, 1H), 3.93 (dd, *J* = 13, 2.4 Hz, 1H), 3.88 (dd, *J* = 8.6, 2.7 Hz, 1H), 2.88 (q, *J* = 8.2 Hz, 1H), 2.63 (bd, *J* = 7.8 Hz, 1H), 2.53 (ddq, *J* = 20, 9.4, 2.4 Hz, 1H), 2.32 (t, *J* = 2.7 Hz, 1H), 2.12 (dd, *J* = 11, 7.4 Hz, 1H), 1.80 (s, 3H), 1.79 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 145.3, 139.4, 137.7, 127.4, 116.8, 111.7, 80.7, 80.4, 73.5, 55.7,

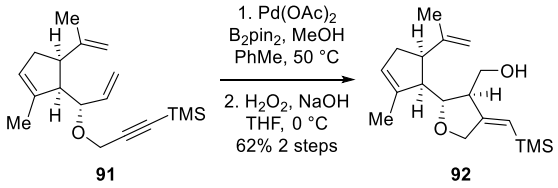
54.9, 51.1, 34.8, 23.5, 17.8; **IR** (film, cm^{-1}): 1384, 1074, 404; **HRMS** (EC-CI): calc. for $C_{15}H_{20}O$ [M]: 216.1514, obs. 216.1515.



S3 **91**

To a stirred solution of enyne **S3** (26.2 g, 121 mmol, 1.0 equiv.) in THF (1.2 L, 0.1 M) at −78 °C was added a 2.14 M solution of *n*-butyllithium in hexanes (68 mL, 145 mmol, 1.2 equiv.). After 20 minutes, freshly distilled neat trimethylsilyl chloride (31 mL, 242 mmol, 2 equiv.) was added. Upon complete addition the reaction mixture was allowed to warm to 23 °C. After 30 minutes, the reaction mixture was quenched with sat. aq. NH_4Cl (400 mL), extracted with Et_2O (3 x 400 mL), washed with brine (400 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give pure TMS enyne **91** (35 g, 121 mmol, 99%) as a clear oil.

R_f = 0.44 (silica gel, 20:1 hexanes:EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.85 (ddd, *J* = 17, 11, 7.4 Hz, 1H), 5.55 (bs, 1H), 5.28 (d, *J* = 16 Hz, 1H), 5.14 (d, *J* = 9.0 Hz, 1H), 4.88 (s, 2H), 4.11 (d, *J* = 16 Hz, 1H), 3.95 (d, *J* = 16 Hz, 1H), 3.94 (dd, *J* = 7.8, 2.7 Hz, 1H), 2.87 (q, *J* = 7.8 Hz, 1H), 2.63 (bd, *J* = 6.7 Hz, 1H), 2.50 (ddq, *J* = 20 , 9.4, 2.4 Hz, 1H), 2.13 (dd, *J* = 7.8, 2.7 Hz, 1H), 1.81 (s, 3H), 1.79 (s, 3H), 0.16 (s, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 145.1, 139.6, 137.6, 127.1, 116.8, 111.7, 102.3, 90.3, 80.2, 56.3, 54.8, 50.9, 34.8, 23.3, 17.7, -0.3; **IR** (film, cm^{-1}): 1384, 1251, 1076, 843, 403; **HRMS** (EC-CI): calc. for $C_{18}H_{28}OSi$ [M]: 288.1909, obs. 288.1901.

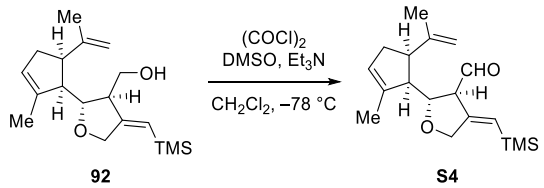


To a stirred solution of TMS enyne **91** (20.8 g, 72.1 mmol, 1.0 equiv.) in PhMe (720 mL, 0.1 M) at 23 °C was added solid bis(pinacolato)diboron (20.1 g, 79 mmol, 1.1 equiv.), palladium(II) acetate (809 mg, 3.60 mmol, 0.05 equiv.), and MeOH (2.92 mL, 72.1 mmol, 1.0 equiv.). The reaction mixture was heated to and stirred at 50 °C. After 15 hours, the reaction mixture was cooled to 23 °C and concentrated *in vacuo* to give the boronate ester as an amber oil.

To a stirred solution of crude boronate ester (30 g, 72.0 mmol, 1.0 equiv.) in THF (1.4 L, 0.05 M) at 0 °C was carefully added 3.33 N NaOH (64.9 mL, 216 mmol, 3 equiv.) and 50% aq. H_2O_2 (130 mL, 2.16 mol, 30 equiv.) over 1 hour. The reaction mixture was diluted with brine (700 mL), extracted with EtOAc (3 x 500 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a yellow oil. The crude material was purified via silica gel column chromatography (5:1 hexanes:EtOAc) to give pure alcohol **92** (13.7 g, 44.7 mmol, 62% over 2 steps) as a white solid (m.p. 62-64 °C).

R_f = 0.41 (silica gel, 5:1 hexanes:EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.54 (bs, 1H), 5.50 (q, *J* = 2.4 Hz, 1H), 4.88 (s, 1H), 4.85 (s, 1H), 4.38 (dd, *J* = 14, 2.4 Hz, 1H), 4.23 (dt, *J* = 14, 2.4 Hz, 1H), 3.91 (t, *J* = 5.1 Hz, 1H), 3.65 (dt, *J* = 11, 6.3 Hz, 1H), 3.60 (dt, *J* = 11, 6.3 Hz, 1H), 2.93 (q, *J* = 7.8 Hz, 1H), 2.70-2.66 (bm, 2H), 2.45 (ddq, *J* = 15, 8.6, 2.4 Hz, 1H), 2.20 (dd, *J* = 14, 7.8 Hz, 1H), 1.81 (s, 3H), 1.76 (s, 3H), 1.63 (t, *J* = 5.9 Hz, 1H), 0.07 (s, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 157.9, 145.9, 140.3, 127.2, 119.9, 111.9, 81.2,

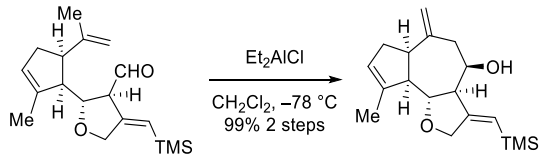
70.2, 64.0, 53.5, 51.8, 51.1, 34.7, 22.8, 17.8, -0.7; **IR** (film, cm^{-1}): 3404, 1384, 401; **HRMS** (ESI): calc. for $C_{18}H_{30}O_2Si$ $[M+Na]^+$: 329.19070, obs. 329.19090.



92 **S4**

To a stirred solution of oxalyl chloride (5.23 mL, 59.8 mmol, 1.5 equiv.) in CH_2Cl_2 (250 mL) at −78 °C was slowly added a solution of dimethyl sulfoxide (14.2 mL, 199 mmol, 5 equiv.) in CH_2Cl_2 (100 mL) over 10 minutes. After 30 minutes, a solution of alcohol **92** (12.2 g, 39.9 mmol, 1.0 equiv.) in CH_2Cl_2 (50 mL) was added. After 2 hours, neat triethylamine (28.0 mL, 199 mmol, 5 equiv.) was added in a single portion and the reaction mixture was allowed to warm to 23 °C. The reaction mixture was then diluted with 0.1 N HCl (200 mL). The organic layer was separated and washed with 0.1 N HCl (2 x 200 mL) and 3.0 N LiCl (400 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give crude aldehyde **S4** (12.1 g, 39.9 mmol, yield taken over 2 steps) as a clear oil.

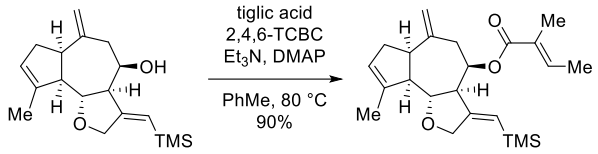
R_f = 0.69 (silica gel, 5:1 hexanes:EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 9.32 (d, *J* = 3.9 Hz, 1H), 5.55 (s, 1H), 5.53 (bs, 1H), 4.85 (s, 2H), 4.41 (dd, *J* = 14, 2.4 Hz, 1H), 4.33 (t, *J* = 6.3 Hz, 1H), 4.22 (dd, *J* = 14, 2.4 Hz, 1H) 3.40 (bt, *J* = 2.4, 1H), 2.93 (q, *J* = 7.8 Hz, 1H), 2.71 (t, *J* = 6.3 Hz, 1H), 2.46 (dd, *J* = 15, 7.4 Hz, 1H), 2.21 (dd, *J* = 15, 7.4 Hz, 1H), 1.82 (s, 3H), 1.73 (s, 3H), 0.08 (s, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 196.6, 151.9, 144.9, 139.8, 127.4, 124.0, 112.4, 78.7, 70.2, 63.7, 51.7, 50.6, 34.7, 22.9, 17.4, -0.9; **IR** (film, cm^{-1}): 1722, 1249, 840; **HRMS** (ESI): calc. for $C_{18}H_{28}O_2Si$ $[M+Na]^+$: 327.17510, obs. 327.17530.



S4 **93**

To a stirred solution of crude aldehyde **S4** (12.1 g, 39.9 mmol, 1.0 equiv.) in CH_2Cl_2 (400 mL, 0.1 M) at −78 °C was added a 1.0 M solution of diethylaluminum chloride in hexanes (19.9 mL, 19.9 mmol, 0.5 equiv.) in a single portion. After 10 minutes, the reaction mixture was quenched with 10% aq. NaOH (20 mL). The reaction mixture was warmed to 23 °C, further diluted with brine (200 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a yellow oil. The crude material was purified via silica gel column chromatography (5:1 hexanes:EtOAc) to give pure 5,7,5-tricycle **93** (12.1 g, 39.9 mmol, 99% over 2 steps) as a white solid (m.p. 64-66 °C).

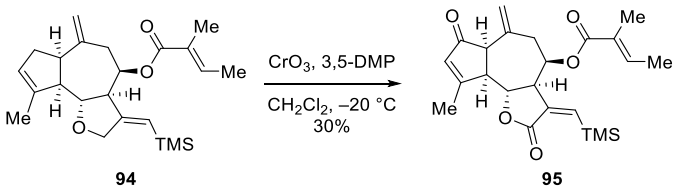
R_f = 0.60 (silica gel, 5:1 hexanes:EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.47 (s, 1H), 5.45 (d, *J* = 2.4 Hz, 1H), 4.97 (s, 1H), 4.88 (s, 1H), 4.48 (d, *J* = 14 Hz, 1H), 4.22 (dt, *J* = 8.2, 4.7 Hz, 1H), 4.09 (dt, *J* = 14, 2.4 Hz, 1H), 3.73 (t, *J* = 9.8 Hz, 1H), 3.16 (q, *J* = 8.0 Hz, 1H), 2.63 (t, *J* = 9.0 Hz, 1H), 2.54-2.40 (m, 5H), 1.96 (d, *J* = 4.7 Hz, 1H), 1.84 (s, 3H), 0.10 (s, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 158.6, 145.2, 142.3, 125.1, 117.3, 115.0, 79.3, 71.1, 66.4, 57.0, 56.1, 49.1, 36.8, 17.3, -0.6; **IR** (film, cm^{-1}): 3413, 1065, 838; **HRMS** (ESI): calc. for $C_{18}H_{28}O_2Si$ $[M+Na]^+$: 327.17510, obs. 327.17510.



93 **94**

To a stirred solution of tiglic acid (13.8 g, 138 mmol, 2.0 equiv.) in PhMe (345 mL) at 23 °C was added neat triethylamine (38.4 mL, 276 mmol, 4.0 equiv.) and neat 2,4,6-trichlorobenzoyl chloride (23.7 mL, 152 mmol, 2.2 equiv.). After 1 hour, a solution of 5,7,5-tricycle **93** (21.0 g, 69.0 mmol, 1.0 equiv.) in PhMe (345 mL) and solid dimethylaminopyridine (21.9 g, 179 mmol, 2.6 equiv.) were added. The reaction mixture was then heated to 80 °C. After 45 minutes, the reaction mixture was cooled to 23 °C, diluted with sat. aq. $NaHCO_3$, extracted with EtOAc (3 x 500 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give an amber oil. The crude material was purified via silica gel column chromatography (20:1 hexanes:EtOAc) to give pure tigloyl ester **94** (24.0 g, 62.1 mmol, 90%) as a clear oil.

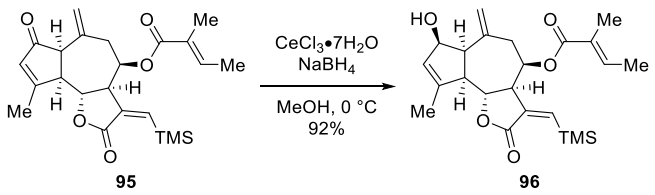
R_f = 0.18 (silica gel, 20:1 hexanes:EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.75 (q, *J* = 6.7 Hz, 1H), 5.49 (s, 1H), 5.41 (q, *J* = 5.5 Hz, 1H), 5.31 (s, 1H), 4.91 (s, 1H), 4.77 (s, 1H), 4.47 (d, *J* = 14 Hz, 1H), 4.06 (d, *J* = 14 Hz, 1H), 3.89 (t, *J* = 9.4 Hz, 1H), 3.16 (q, *J* = 7.8 Hz, 1H), 2.69 (d, *J* = 9.0 Hz, 1H), 2.68 (t, *J* = 9.0 Hz, 1H), 2.60 (dd, *J* = 14, 5.5 Hz, 1H), 2.47 (dd, *J* = 14, 5.1 Hz, 1H), 2.43 (d, *J* = 7.0 Hz, 1H), 2.42 (d, *J* = 9.0 Hz, 1H), 1.86 (s, 3H), 1.76 (s, 3H), 1.75 (d, *J* = 6.7 Hz, 3H), 0.0 (s, 9H); **^{13}C-NMR** (125 MHz, $CDCl_3$): δ 167.5, 156.6, 144.7, 142.1, 136.9, 128.6, 125.3, 117.3, 115.1, 80.5, 71.0, 69.8, 56.3, 55.1, 48.7, 39.4, 37.0, 17.3, 14.3, 12.0, -0.7; **IR** (film, cm^{-1}): 1713, 1250, 1066, 805; **HRMS** (ESI): calc. for $C_{23}H_{34}O_3Si$ $[M+Na]^+$: 409.21710, obs. 409.21690.



94 **95**

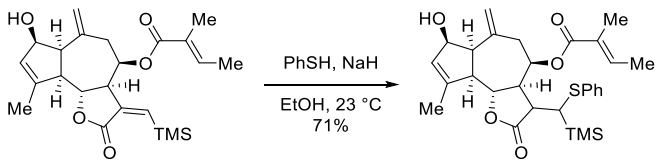
To a stirred solution of CrO_3 (20.7 g, 207 mmol, 20 equiv.) in CH_2Cl_2 (100 mL, 0.05 M) at 0 °C was added solid 3,5-dimethylpyrazole (19.9 g, 207 mmol, 20 equiv.) in a single portion. A solution of carbocycle **94** (4.0 g, 10.4 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) was then added. After 45 minutes, the reaction mixture was directly purified via florasil column chromatography (2:1 hexanes:EtOAc) to give pure guaianolide **95** (1.29 g, 3.10 mmol, 30%) as a clear oil.

R_f = 0.22 (silica gel, 2:1 hexanes:EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.70 (q, *J* = 7.0 Hz, 1H), 6.37 (d, *J* = 3.1 Hz, 1H), 6.15 (s, 1H), 5.53 (td, *J* = 4.7, 2.7 Hz, 1H), 5.07 (s, 1H), 4.96 (s, 1H), 4.54 (dd, *J* = 11, 9.0 Hz, 1H), 3.32 (d, *J* = 7.0 Hz, 1H), 3.20 (t, 9.8 Hz, 1H), 3.18 (dt, *J* = 8.6, 2.7 Hz, 1H), 2.55 (bs, 2H), 2.36 (s, 3H), 1.75 (d, *J* = 7.8 Hz, 3H), 1.74 (s, 3H), 0.15 (s, 9H); **^{13}C-NMR** (125 MHz, $CDCl_3$): δ 206.1, 177.9, 168.6, 166.9, 145.5, 138.9, 138.5, 138.1, 132.3, 127.9, 120.4, 78.1, 67.1, 56.2, 53.4, 51.2, 41.1, 19.9, 14.3, 11.9, -1.0; **IR** (film, cm^{-1}): 1765, 1707, 1249; **HRMS** (ESI): calc. for $C_{23}H_{30}O_5Si$ $[M+Na]^+$: 437.17550, obs. 437.17580.



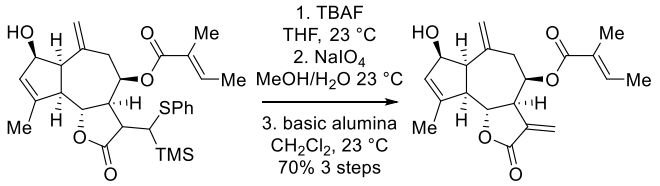
To a stirred solution of enone **95** (755 mg, 1.82 mmol, 1.0 equiv.) in MeOH (36 mL, 0.05 M) at 0 °C was added solid cerium(III) chloride heptahydrate (1.36 g, 3.64 mmol, 2.0 equiv.). After 20 minutes, solid sodium borohydride (138 mg, 3.64 mmol, 2.0 equiv.) was added in three even portions. After 15 minutes, the reaction mixture was warmed to 23 °C and diluted with 0.2 M aq. pH = 7.0 phosphate buffer. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give pure allylic alcohol **96** (700 mg, 1.68 mmol, 92%) as a clear oil.

$\mathbf{R_f}$ = 0.24 (silica gel, 3:1 hexanes:EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.69 (q, *J* = 5.5 Hz, 1H), 6.24 (d, *J* = 2.7 Hz, 1H), 5.71 (bs, 1H), 5.43 (td, *J* = 7.8, 3.9 Hz, 1H), 5.09 (s, 2H), 4.71 (bt, *J* = 5.1 Hz, 1H), 4.65 (dd, *J* = 11, 9.0 Hz, 1H), 3.16 (dt, *J* = 6.7, 2.7 Hz, 1H), 3.14 (d, *J* = 3.9 Hz, 1H), 2.88 (dd, *J* = 14, 7.4 Hz, 1H), 2.71 (dd, *J* = 14, 7.4 Hz, 1H), 2.67 (t, *J* = 9.4 Hz, 1H), 1.99 (s, 3H), 1.74 (d, *J* = 5.5 Hz, 3H), 1.73 (s, H), 0.13 (s, 9H); **^{13}C-NMR** (125 MHz, $CDCl_3$): δ 169.4, 167.2, 147.8, 144.5, 142.0, 139.9, 137.9, 128.9, 128.0, 119.0, 80.8, 79.0, 68.5, 56.2, 52.6, 49.8, 38.7, 17.3, 14.3, 11.9, -1.0; **IR** (film, cm^{-1}): 3485, 1764, 1709, 1259, 1247; **HRMS** (ESI): calc. for $C_{23}H_{32}O_5Si$ $[M+Na]^+$: 439.19110, obs. 439.19110.



To a stirred solution of vinyl silane **46** (267 mg, 0.641 mmol, 1.0 equiv.) in EtOH (6.4 mL, 0.1 M) at 23 °C was added neat thiophenol (2.88 mL, 28.2 mmol, 44 equiv.) and 60% NaH in mineral oil (103 mg, 2.56 mmol, 4.0 equiv.). After 48 hours, the reaction mixture was concentrated *in vacuo* and purified directly via silica gel column chromatography (straight hexanes to 2:1 hexanes:EtOAc) to give pure thio silane **105** (238 mg, 0.452 mmol, 71%) as a white foam.

HRMS (ESI): calc. for $C_{29}H_{38}O_5SSi$ $[M+Na]^+$: 549.21010, obs. 549.21030.



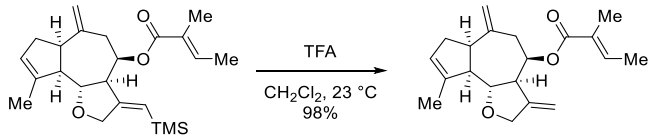
To a stirred solution of thio silane **105** (238 mg, 0.452 mmol, 1.0 equiv.) in THF (4.5 mL, 0.1 M) at 23 °C was added a 1.0 M of tetrabutylammonium fluoride in THF (0.90mL, 1.38 mmol, 1.5 equiv.). After 30 minutes, the reaction mixture was passed through a plug of silica gel (2:1 hexanes:EtOAc) to give crude thio adduct **104** as an amber oil.

To a stirred solution of crude thio adduct **104** (205 mg, 0.452 mmol, 1.0 equiv.) in MeOH (4.5 mL, 0.1 M) at 0 °C was added a solution of sodium periodate (145 mg, 0.678 mmol, 1.5 equiv.) in H_2O (4.5 mL). After 15 hours, the reaction mixture was extracted with EtOAc (3 x 10 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give crude sulfone **106** as a white solid.

A solution of crude sulfone **106** (220 mg, 0.452 mmol, 1.0 equiv.), basic alumina (440 mg, 200% by weight), and CH_2Cl_2 (4.5 mL, 0.1 M) was stirred at 23 °C. After stirring for 12 hours, the reaction mixture was passed through a plug of Celite and concentrated to give a clear oil. The crude material was purified via silica gel column chromatography (2:1 hexanes:EtOAc) to give pure butyrolactone **103** (109 mg, 0.316 mmol, 70%) as a clear oil.

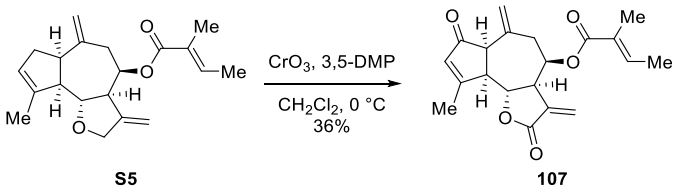
R_f = 0.54 (silica gel, 1:1 hexanes:EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.73 (q, *J* = 5.5 Hz, 1H), 6.29 (d, *J* = 3.5 Hz, 1H), 5.73 (bs, 1H), 5.52 (dd, *J* = 11, 3.5 Hz, 1H), 5.51 (d, *J* = 3.5 Hz, 1H), 5.12 (s, 1H), 5.11 (s, 1H), 4.73 (bs, 1H), 4.66 (dd, *J* = 11, 8.6 Hz, 1H), 3.19 (dd, *J* = 12, 2.7 Hz, 1H), 3.17 (d, *J* = 5.9 Hz, 1H), 2.85 (dd, *J* = 14, 6.7 Hz, 1H), 2.73 (dd,

J = 14, 7.8 Hz, 1H), 2.68 (t, *J* = 9.4 Hz, 1H), 1.99 (s, 3H), 1.76 (d, *J* = 5.9 Hz, 3H), 1.75 (s, 3H), 1.70 (d, *J* = 5.1 Hz, 1H); **^{13}C-NMR** (125 MHz, $CDCl_3$): δ 169.6, 167.2, 147.3, 141.7, 138.3, 134.2, 129.2, 128.0, 122.4, 119.2, 80.8, 78.8, 67.8, 56.1, 52.6, 47.8, 39.1, 17.3, 14.4, 12.0; **IR** (film, cm^{-1}): 3413, 1384, 1137; **HRMS** (ESI): calc. for $C_{20}H_{24}O_5$ $[M+Na]^+$: 367.15160, obs. 367.15200.



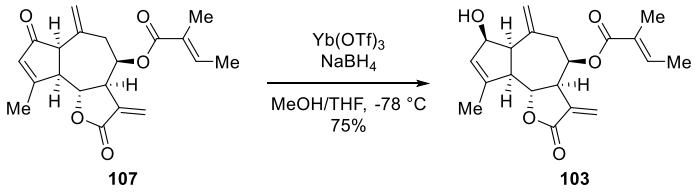
To a stirred solution of vinylsilane **94** (2 g, 5.17 mmol, 1.0 equiv.) in CH_2Cl_2 (52 mL, 0.1 M) was added neat TFA (3.96 mL, 51.7 mmol, 10 equiv.) in a single portion at 23 °C. After 2 hours, the reaction mixture was poured into sat. aq. $NaHCO_3$ (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (3 x 30 mL), brine (1 x 30 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give **S5** as an amber oil (1.6 g, 5.09 mmol, 98%). The crude material was used directly in the next reaction without purification.

R_f = 0.61 (silica gel, 20:1 hexanes:EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 6.79 (q, *J* = 6.14 Hz, 1H), 5.49 (s, 1H), 5.44 (m, 1H), 4.94 (m, 1H), 4.91 (s, 1H), 4.85 (m, 1H), 4.75 (s, 1H), 4.40 (d, *J* = 13.04 Hz, 1H), 4.10 (dt, *J* = 2.2, 13.09 Hz, 1H), 3.94 (t, *J* = 9.71 Hz, 1H), 3.15 (t, *J* = 7.70 Hz, 1H), 2.70 (m, 2H), 2.64 (dd, *J* = 5.44, 13.68 Hz, 1H), 2.42 (m, 3H), 1.86 (s, 3H), 1.77 (s, 3H), 1.75 (s, 3H). **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 167.4, 148.5, 144.6, 141.9, 137.2, 128.6, 125.4, 115.1, 103.6, 81.0, 71.5, 69.4, 56.3, 52.9, 48.4, 40.1, 37.1, 17.2, 14.3, 12.0. **IR** (film, cm^{-1}): 2367, 2078, 1640, 1401, 1114. HRMS (ESI): calc. for $C_{20}H_{26}O_3$ $[M+H]^+$: 315.1955, obs. 315.1954.



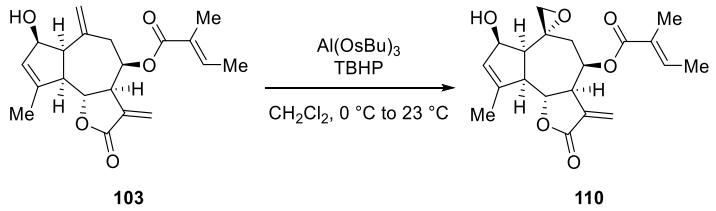
To a stirred solution of CrO_3 (10.18 g, 102 mmol, 20 equiv.) in CH_2Cl_2 (30 mL) at 0 °C was added solid 3,5-dimethylpyrazole (9.78 g, 102 mmol, 20 equiv.) in a single portion. A solution of carbocycle **S5** (1.6 g, 5.09 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) was then added in a single portion. After 45 minutes, the reaction mixture was directly purified via florasil column chromatography (1:1 hexanes:EtOAc) to give a white solid. The white solid was dissolved in EtOAc (50 ml), washed with 1.0 M HCl (3 x 20 mL), dried over Na_2SO_4, and concentrated to give pure guaianolide **107** (630 mg, 1.84 mmol, 36%) as a white foam.

R_f = 0.38 (silica gel, 1:1 hexanes:EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 6.67 (q, *J* = 7.0 Hz, 1H), 6.26 (s, 1H), 6.10 (s, 1H), 5.56 (bs, 2H), 4.98 (s, 1H), 4.98 (s, 1H), 4.48 (t, *J* = 9.7 Hz, 1H), 3.27 (d, *J* = 7.3 Hz, 1H), 3.15 (m, 2H), 2.53 (m, 1H), 2.46 (m, 1H), 2.29 (s, 3H), 1.70 (s, 3H), 1.68 (s, 3H). **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 205.9, 177.6, 168.7, 166.7, 138.5, 138.4, 133.6, 132.6, 127.8, 122.9, 120.4, 77.9, 66.3, 55.7, 53.3, 49.4, 41.8, 19.9, 14.4, 11.9. **IR** (film, cm^{-1}): 3438, 3154, 1769, 1704, 1650, 1619. **HRMS** (ESI): calc. for $C_{20}H_{22}O_5$ $[M+H]^+$: 343.1540, obs. 343.1545.



To a stirred solution of enone **107** (630 mg, 1.84 mmol, 1.0 equiv.) in 3:1 MeOH:THF (18.4 mL, 0.1 M) at –78 °C was added solid $Yb(OTf)_3$ (1.25 g, 2.02 mmol, 1.1 equiv.). After 15 minutes, solid sodium borohydride (84 mg, 2.21 mmol, 1.2 equiv.) was added in three even portions every 30 minutes for 1.5 hours. After stirring for an additional 10 minutes, neat acetaldehyde (1.0 mL, 18.4 mmol, 10 equiv.) was added in a single portion and the reaction was stirred further for 15 minutes at –78 °C. 1:1 EtOAc:H_2O (40 mL) was added and the reaction was warmed to 23 °C over 30 minutes. The reaction mixture was further diluted with brine (20 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with water (3 x 20 mL), brine (1 x 20 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give a brown oil. The crude material was purified via silica gel column chromatography (2:1 hexanes:EtOAc) to give pure allylic alcohol **103** (472 mg, 1.37 mmol, 75%) as a white foam.

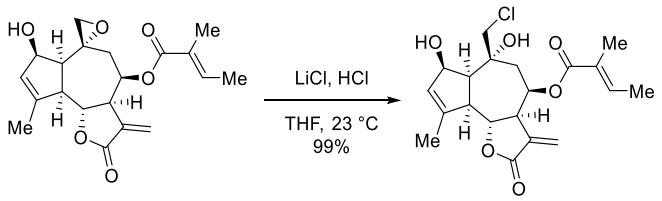
R_f = 0.54 (silica gel, 2:1 hexanes:EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.73 (q, *J* = 5.5 Hz, 1H), 6.29 (d, *J* = 3.5 Hz, 1H), 5.73 (bs, 1H), 5.52 (dd, *J* = 11, 3.5 Hz, 1H), 5.51 (d, *J* = 3.5 Hz, 1H), 5.12 (s, 1H), 5.11 (s, 1H), 4.73 (bs, 1H), 4.66 (dd, *J* = 11, 8.6 Hz, 1H), 3.19 (dd, *J* = 12, 2.7 Hz, 1H), 3.17 (d, *J* = 5.9 Hz, 1H), 2.85 (dd, *J* = 14, 6.7 Hz, 1H), 2.73 (dd, *J* = 14, 7.8 Hz, 1H), 2.68 (t, *J* = 9.4 Hz, 1H), 1.99 (s, 3H), 1.76 (d, *J* = 5.9 Hz, 3H), 1.75 (s, 3H), 1.70 (d, *J* = 5.1 Hz, 1H); **^{13}C-NMR** (125 MHz, $CDCl_3$): δ 169.6, 167.2, 147.3, 141.7, 138.3, 134.2, 129.2, 128.0, 122.4, 119.2, 80.8, 78.8, 67.8, 56.1, 52.6, 47.8, 39.1, 17.3, 14.4, 12.0; **IR** (film, cm^{-1}): 3413, 1384, 1137; **HRMS** (ESI): calc. for $C_{20}H_{24}O_5$ $[M+Na]^+$: 367.15160, obs. 367.15200.



103 **110**

To a stirred solution of allylic alcohol **103** (472 mg, 1.37 mmol, 1.0 equiv.) in CH_2Cl_2 (13.7 mL, 0.1 M) was added a 1.0 M solution of Al(O*s*-Bu)$_3$ in CH_2Cl_2 (2.1 mL, 2.1 mmol, 1.5 equiv.) dropwise at 0 °C. The reaction was stirred for 10 minutes before a 5.5-6.0 M solution of TBHP in decane (0.275 mL, 1.51 mmol, 1.1 equiv.) was added dropwise. The cooling bath was removed and the reaction was warmed to 23 °C over 30 minutes. Sat. aq. $Na_2S_2O_3$ (10 mL) was added and the mixture was stirred for 15 minutes. The crude reaction was further diluted with brine (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give epoxide **110** as a clear oil. The crude material was used immediately in the next reaction without purification.

R$_f$ = 0.54 (silica gel, 1:1 hexanes:EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 6.70 (q, *J* = 6.4 Hz, 1H), 6.33 (d, *J* = 3.2 Hz, 1H), 5.71 (bs, 1H), 5.57 (td, *J* = 8.6, 4.7 Hz, 1H), 5.55 (d, *J* = 2.8 Hz, 1H), 4.68 (bs, 1H), 4.67 (t, *J* = 8.8 Hz, 1H), 3.56 (dd, *J* = 8.6, 4.7 Hz, 1H), 2.79 (q, *J* = 7.6 Hz, 1H), 2.77 (t, *J* = 9.6 Hz, 1H), 2.61 (dd, *J* = 14, 7.6 Hz, 1H), 2.35 (d, *J* = 9.2 Hz, 1H), 2.25 (dd, *J* = 15, 8.4 Hz, 1H), 2.01 (s, 3H), 1.97 (d, *J* = 7.2 Hz, 1H), 1.77 (s, 3H), 1.73 (s, 3H); **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 169.6, 167.1, 148.9, 138.3, 133.9, 128.9, 127.9, 122.9, 81.0, 76.75, 66.7, 56.3, 55.7, 55.4, 52.3, 47.8, 36.5, 17.4, 14.3, 12.0; **IR** (film, cm^{-1}): 3477, 1768, 1339, 1140, 1037; **HRMS** (ESI): calc. for $C_{20}H_{24}O_6$ $[M+Na]^+$: 383.14650, obs. 383.14680



110 eupalinilide E (**7**)

To a stirred solution of crude epoxide **110** (490 mg, 1.36 mmol, 1.0 equiv.) in THF (13.6 mL, 0.1 M) at 23 °C was added solid lithium chloride (576 mg, 13.6 mmol, 10.0 equiv.) in a single portion. The mixture of sonicated for 5 minutes before addition of a 1.25 M solution of hydrochloric acid in MeOH (3.26 mL, 4.08 mmol, 3.0 equiv.). After 5 minutes, the reaction mixture was diluted with brine (40 mL), extracted with EtOAc (3 x 30 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a white solid. The crude material was purified via silica gel column chromatography (2:1 hexanes:EtOAc) to give pure eupalinilide E (**7**) (466 mg, 1.17 mmol, 86% over 2 steps) as a white solid (m.p. 72°C, (decomp.)).

R_f = 0.63 (silica gel, 1:1 hexanes:EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.70 (q, *J* = 5.5 Hz, 1H), 6.27 (d, *J* = 3.5 Hz, 1H), 5.75 (bs, 1H), 5.65 (td, *J* = 8.6, 4.7 Hz, 1H), 5.45 (d, *J* = 3.5 Hz, 1H), 4.59 (bs, 1H), 4.58 (t, *J* = 8.6 Hz, 1H), 3.94 (d, *J* = 11 Hz, 1H), 3.93 (bs, 1H), 3.67 (d, *J* = 11 Hz, 1H), 2.77 (dd, *J* = 11, 7.4 Hz, 1H), 2.50-2.44 (m, 4H), 2.04 (s, 3H), 1.74 (d, *J* = 5.3 Hz, 3H), 1.73 (s, 3H); **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 169.7, 167.2, 150.6, 138.1, 134.4, 128.6, 128.1, 122.1, 82.0, 75.1, 73.6, 66.4, 55.2, 55.0, 52.2, 47.4, 36.4, 18.0, 14.4, 12.0; **IR** (film, cm^{-1}): 3409, 1654, 1384, 1129; **HRMS** (ESI): calc. for $C_{20}H_{25}ClO_6$ $[M+Na]^+$: 419.12320, obs. 419.1229.

Chapter 2: Development of a Platform to Access Novel Thiopeptide Antibiotics

The rise in antibiotic resistant bacteria is one of the major threats to global health. Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Staphylococcus aureus* (VRSA) cause more than 19,000 deaths and 4 billion dollars of additional heath care costs per year in the United States alone, and these statistics are expected to rise.[104–106] There have been increased reports of untreatable, multidrug-resistant Gram-negative bacteria that are resistant to multiple types of antibiotics used today, including penicillins, cephalosporins, and tetracyclins.[107]

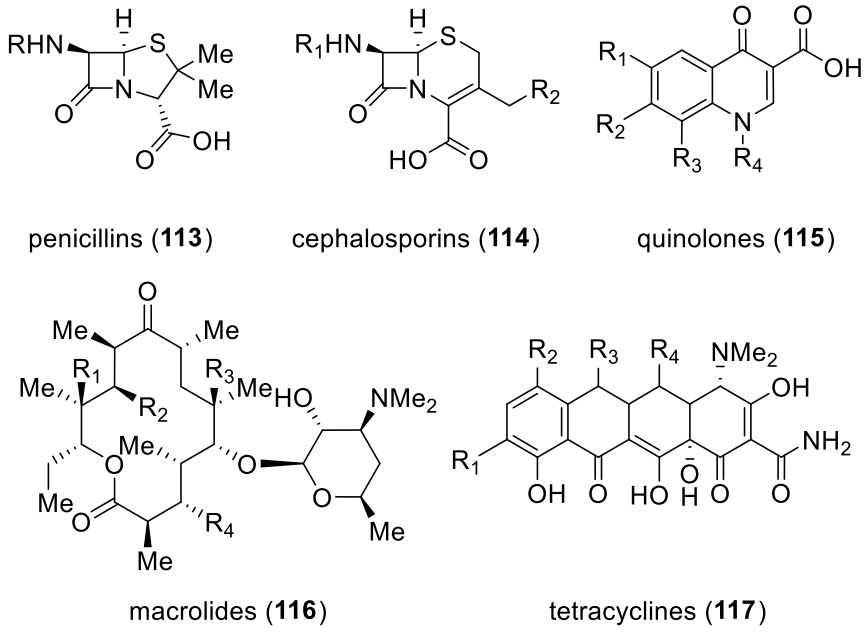


Figure 2.1. The most common antibiotic scaffolds.

The majority of all clinically approved antibiotics between 1981 and 2005 were derived from just four common scaffolds; penicillins (**113**), cephalosporins (**114**), quinolones (**115**), and macrolides (**116**, Figure 2.1).[108–112] Aside from quinolones (**115**), most of these antibiotics are made semisynthetically starting from natural sources, limiting

modifications that can be achieved using medicinal chemistry. Recently, total synthetic routes for tetracyclins (**117**) and macrolides (**116**) have widened the range of accessible synthetic derivatives; however, these new antibiotics continue to be built off of existing scaffolds.[113–115]

Thiopeptides are a large family of natural products characterized in part by their sulfur-rich, highly modified, cyclic peptide structure (Figure 2.2).[116,117] Over the past 50 years, they have garnered the attention of researchers due to their novel chemical structures and potent antibacterial properties. For example, nosiheptide (**120**) was recently found to exhibit extremely potent activity against several contemporary MRSA and *Clostridium difficile* strains in an *in vivo* murine model.[118] Moreover, it was found to be non-cytotoxic against mammalian cell lines well above its minimum inhibitory concentration (MIC). Although thiopeptides are potent antibiotics, they have not reached the clinic due to their low solubility in water. Only nosiheptide (**120**) and related thiopeptide thiostrepton are currently used in industry today as additives in chicken feed and in veterinary medicine.[119]

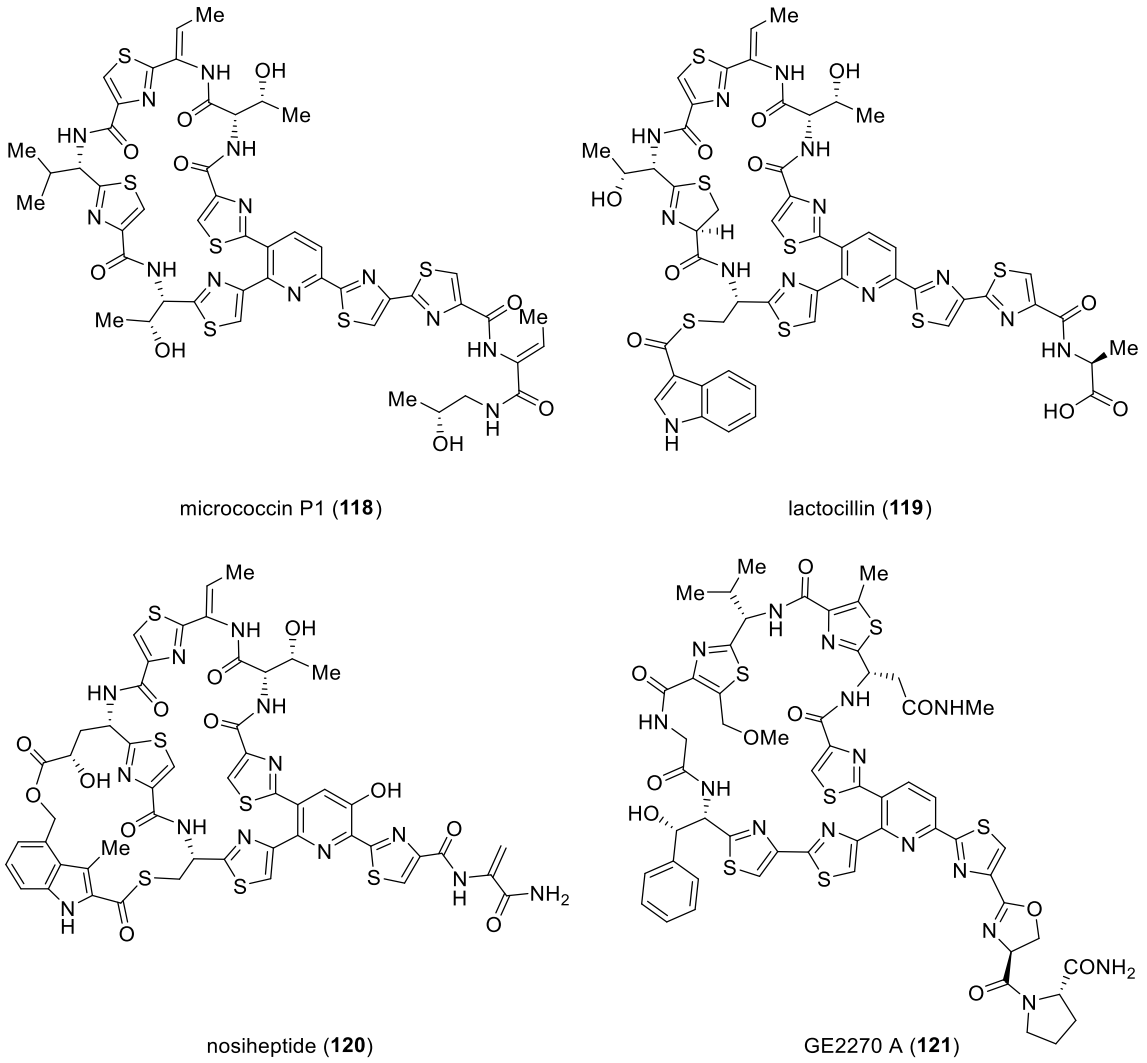


Figure 2.2. Thiopeptide antibiotics micrococcin P1 (**118**), lactocillin (**119**), nosiheptide (**120**), and GE2270 A (**121**).

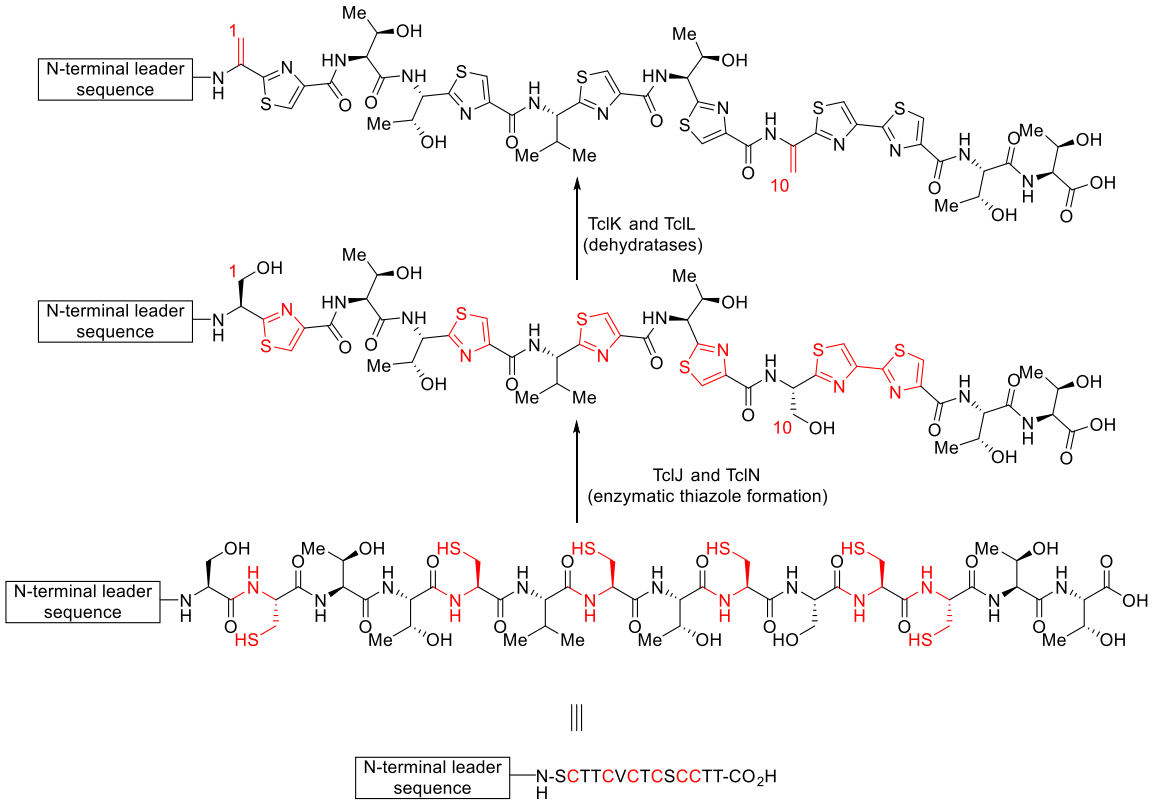
Different thiopeptides share similar structural motifs. They can contain different heterocycles including thiazolines, thiazoles, oxazolines, oxazoles, indoles, dehydropiperidines, and pyridines. They are produced ribosomally from acyclic peptides rich in cysteine, threonine, and serine. Posttranslational modification of these peptides leads to 26-, 29-, or 35-membered macrocylic rings, which can contain a variety of modified amino acid residues, such as dehydroalanines and dehydrobutyrines.

The size of the macrocyclic ring determines the biological target of the thiopeptide. Those containing a 26-membered ring, such as micrococcin P1 (**118**), lactocillin (**119**), nosiheptide (**120**), and thiostrepton, are known to selectively target the 50S ribosomal subunit and prevent interactions between the 23S rRNA and ribosomal protein L11.[120–123] It has been shown that mutations at position A1067 in H43 or A1095 in H44 leads to resistance against these thiopeptides in *Escherichia coli*.[124] Adenines A1067 and A1095 are conserved amongst all prokaryotic 23S rRNA sequences and primarily interact with the dehydrobutyrine residue found in the northern portion of these molecules (Figure 2.2).[120] Thiopeptides containing 29-membered macrocyclic rings, such as GE2270 A (**121**), GE37468, and thiomuracin, compete for the aminoacyl-tRNA binding site on the prokaryotic elongation factor EF-Tu.[125,126] The biological target of thiopeptides containing 35-membered macrocyclic rings remains unknown.[127]

Thiopeptide biosynthesis continues to be an active and dynamic area of research. Since their initial discovery in the 1940's, there has been a debate as to whether or not these natural products are synthesized ribosomally or nonribosomally. It wasn't until 2009 that there was sufficient evidence to support that thiopeptides are, in fact, produced ribosomally and the posttranscriptional machinery required to make each unique molecule is genetically encoded by the host organism.[128] Since these findings, several research groups have reported the biosynthetic gene clusters (BGCs) of more than ten different thiopeptides including thiostrepton, thiocillin, GE2270 A (**121**) and nosiheptide (**120**).[129–133] These gene clusters typically contain a N-terminal leader peptide followed by a sequence rich in cysteine, threonine, and serine, which makes up the basic backbone found in all thiopeptides. Conserved genes found in these BGCs encode for several cyclodehydratases

and dehydrogenase responsible for catalyzing the cyclization and subsequent oxidation of cysteine and serine residues to thiazoles and oxazoles. They also encode for other enzymes that aid in the synthesis of dehydro amino acids and the enzymes speculated to promote the [4+2] heterocyclization reaction that forms the core nitrogen-containing 6-membered ring of these natural products.

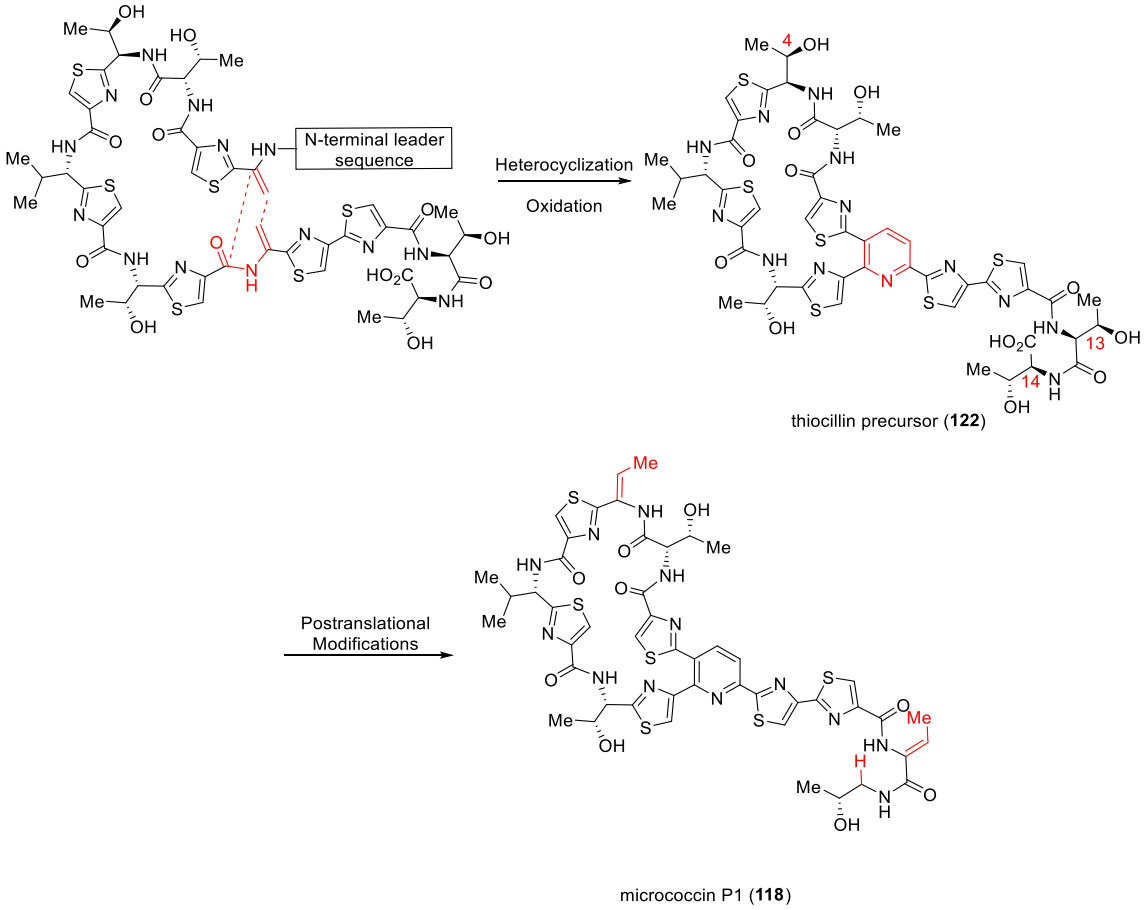
Thirteen posttranslational modifications that convert a 14-residue peptide to the natural product micrococcin P1 (**118**), a member of the thiocillin subfamily, have been recently characterized by Fischbach and coworkers.[130] Bioinformatic analysis of the *Bacillus cereus* genome afforded a sequence predicted to encode a 52-residue peptide containing the Cys/Thr/Ser rich sequence H2N-SCTTCVCTCSCCTT-CO2H. Upon further investigation, it was realized that this 14-residue peptide makes up the backbone of micrococcin P1 (**118**) and several other thiocillin antibiotics, which were later identified in extracts from cultured *B. cereus* by LC/MS and preparative HPLC. This sequence was followed by a cluster of genes (named *tcl*) whose gene products were implicated in the posttranslational modification of the initial 14-residue peptide. Of these, TclJ and TclN were found to be responsible for converting of all six cysteine residues to thiazoles (Scheme 2.1). The general sequence begins with condensation of the thiol of cysteine onto the carbonyl group of the preceding residue, followed by enzymatic dehydration and dehydrogenation to the corresponding thiazole.[134,135] Studies suggested that Ser-1 and Ser-10 provided the carbon framework of the core nitrogen-containing 6-membered ring.[117] TclK and TclL were identified as dehydratases and are predicted to dehydrate Ser-1 and Ser-10.



Scheme 2.1. Biosynthesis of micrococcin P1 (**118**).

Once dehydrated, Ser-1 and Ser-10 undergo a [4+2] heterocyclization reaction to form the core nitrogen-containing 6-membered ring (Scheme 2.2). The enzyme TclM was recently identified to catalyze this transformation; however, it's unclear whether the reaction proceeds through a concerted hetero Diels-Alder reaction or via a stepwise mechanism.[136–139] In the case of thiocillins, cleavage of the N-terminal leader is thought to assist in oxidation of the initial cyclo-adduct to the corresponding pyridine. In other thiopeptides, such as in thiostrepton, some of the N-terminal leader remains on the molecule, leading to a dehydropiperidine containing core. Following pyridine formation, TclK and TclL selectively dehydrate Thr-4 and Thr-13 to yield the dehydrobutyrine

residues found in micrococcin P1 (**118**). It's unclear which *tcl* gene is responsible for decarboxylation of Thr-14.

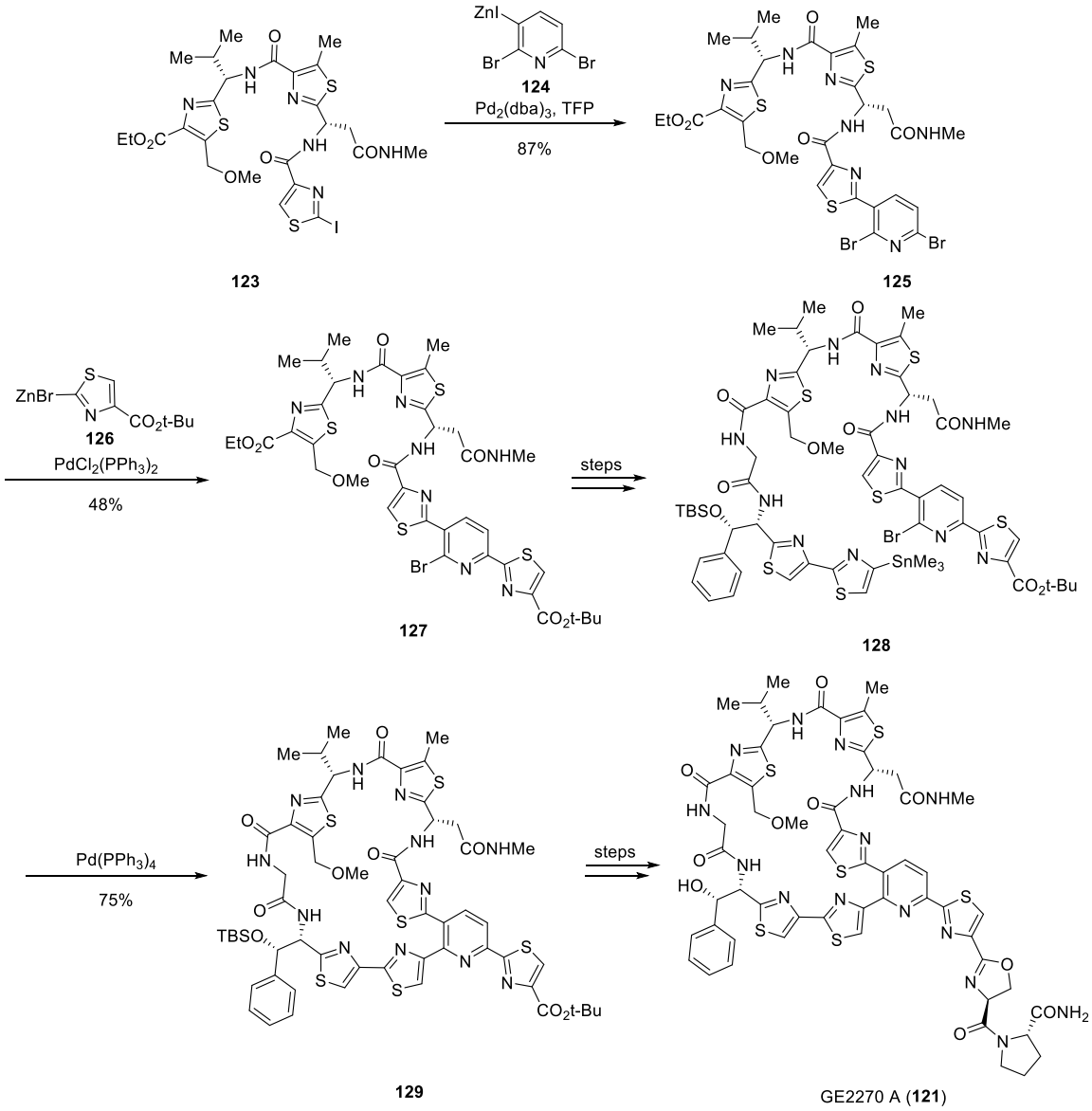


Scheme 2.2. A heterocyclization reaction completes the biosynthesis of micrococcin P1 (**118**).

The total syntheses of numerous thiopeptides have been accomplished over the past few decades.[140–145] In general, the different peptide backbones of these natural products are readily synthesized using standard peptide chemistry and Hantzsch thiazole syntheses from natural amino acids.[116,146–148] The challenge when synthesizing these molecules is in assembly of the heterocyclic cores. Strategies have involved either stepwise elaboration of

simple pyridine starting materials or pyridine synthesis from acyclic precursors using modified Chichibabin syntheses or hetero Diels-Alder reactions.

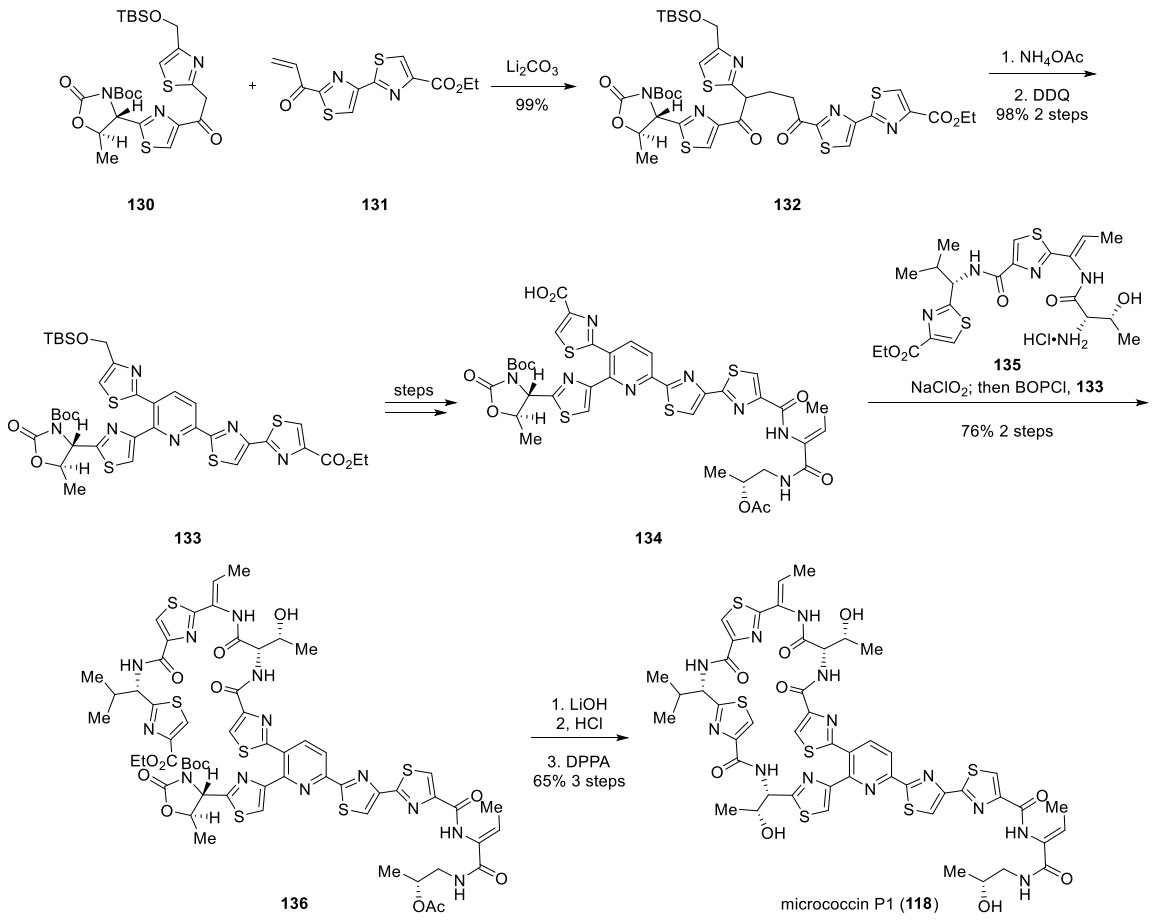
Bach and coworkers' concise synthesis of GE2270 A presents a strategy reliant on highly optimized, successive cross-coupling reactions of a trihalogenated pyridine (Scheme 2.3).[142,149] Selective halogen-metal exchange led to organozinc adduct **124** followed by Negishi cross-coupling with iodide **123**.[150] Dibromide **125** then underwent another Negishi cross-coupling with organozinc **126**, with selective coupling occurring at the most accessible bromide. Further elaboration of **127** led to stannane **128**, which cyclized via an intramolecular Stille reaction.[151] Deprotection and oxazoline formation furnished GE2270 A (**121**).



Scheme 2.3. Total synthesis of GE2270 A (**121**) by Bach and coworkers.

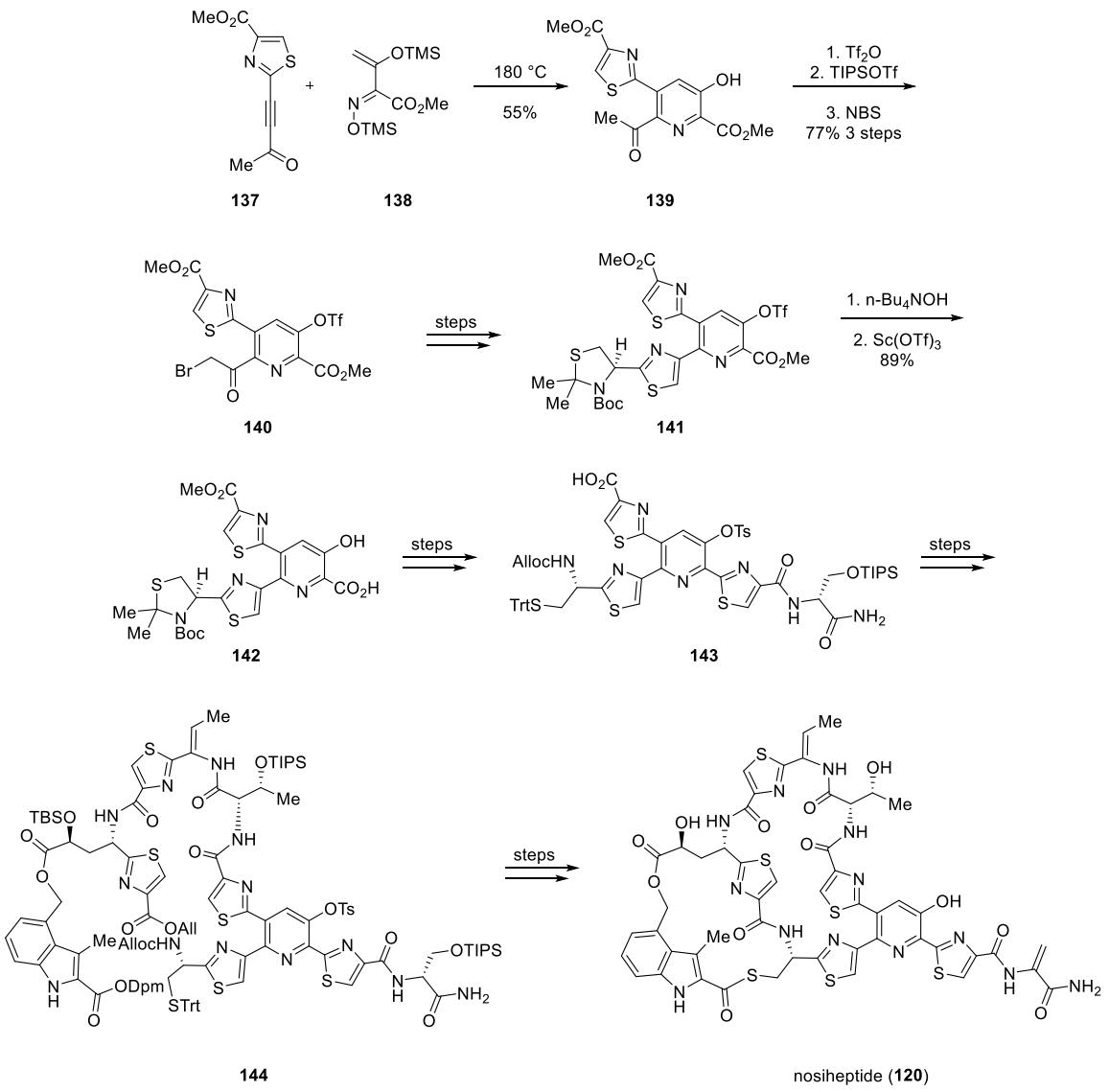
Ciufolini and coworkers took an alternative approach involving the use of a modified Chichibabin pyridine synthesis to access the core of micrococcin P1 (**118**, Scheme 2.4).[143,152,153] Conjugate addition of enolate **130** into enone **131** proceeded smoothly with catalytic base to afford dione **132**. Treatment with ammonium acetate induced cyclization to provide pyridine **133** after oxidation. Subsequent functional group

manipulation, coupling, and macrocyclization using an amide bond forming reaction completed the synthesis of micrococcin P1 (**118**).



Scheme 2.4. Ciufolini and coworkers' synthesis of micrococcin P1 (**118**).

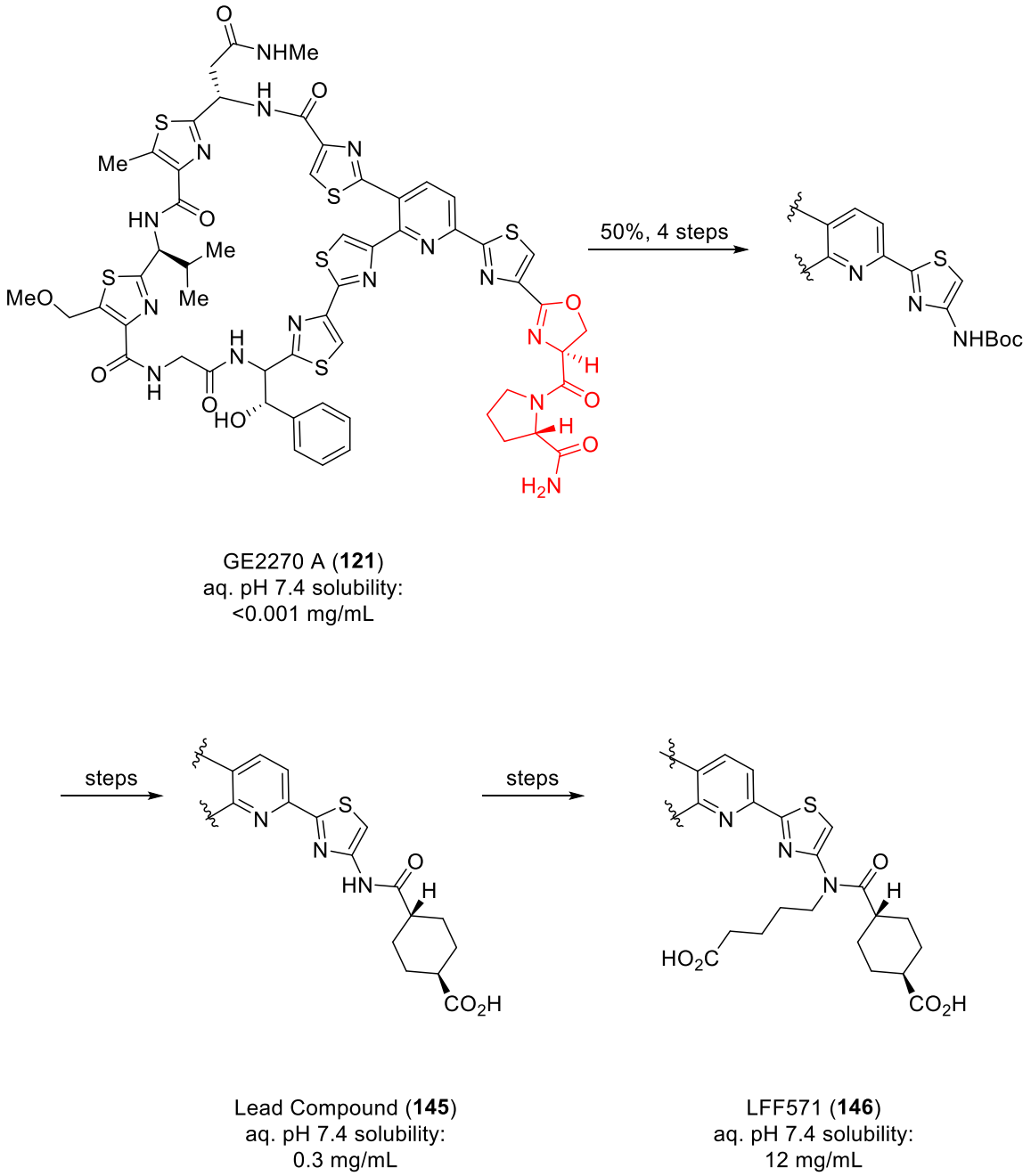
Arndt and coworkers' sought to mimic nature and use a hetero Diels-Alder reaction to access the 3-hydroxypyridyl core of nosiheptide (**120**, Scheme 2.5).[140,154,155] After much experimentation, alkyne **137** was selected for a hetero Diels-Alder reaction with diene **138** to afford 3-hydroxypyridne **140** in a single reaction. Hantzsch thiazole synthesis and several coupling reactions led to precyclized adduct **144**. Formation of the large macrocyclic ring followed by macrothiolactonization was ultimately found to be the best cyclization strategy and led to a successful synthesis of nosiheptide (**120**).



Scheme 2.5. Arndt and coworkers' synthesis of nosiheptide (**120**).

Along with efforts directed toward the total synthesis of these natural products, others have focused on late-stage derivatization of thiopeptides isolated from robust fermentation processes. With the aim of improving the efficacy and aqueous solubility of GE2270 A (**121**), LaMarche and coworkers at Novartis synthesized hundreds of analogs bearing different functional groups (Scheme 2.6).[156–158] The southern oxazoline residue of GE2270 A (**121**) was converted to an acyl azide that underwent Curtius rearrangement in

tert-butanol to afford a boc protected amine.[159,160] Derivatives were synthesized using standard peptide coupling and with the aid of molecular modeling, lead compound **145** was found to have the best antibiotic profile. Further optimization led to diacid LFF571 (**146**), which retained potent activity against several cell lines, particularly *Clostridium difficile*, and remarkably increased aqueous solubility from <0.001 to 12 mg/mL. LFF571 (**146**) remains the most soluble thiopeptide to date and has entered phase II clinical trials for the treatment of *C. difficile* infection.[161,162]



GE2270 A (**121**)
aq. pH 7.4 solubility:
<0.001 mg/mL

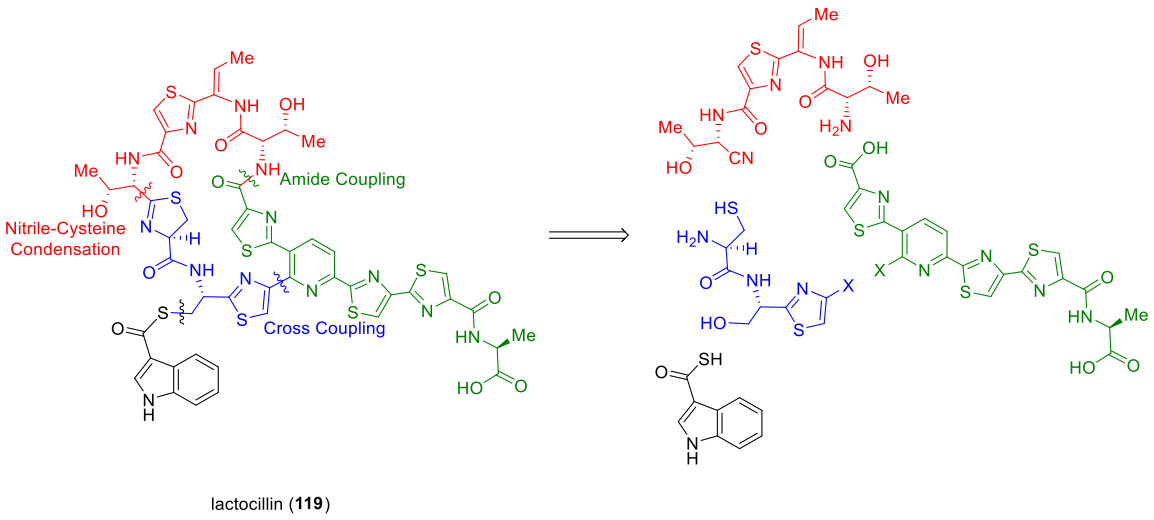
Lead Compound (**145**)
aq. pH 7.4 solubility:
0.3 mg/mL

LFF571 (**146**)
aq. pH 7.4 solubility:
12 mg/mL

Scheme 2.6. The GE2270 A analog LFF571 (**146**) entered phase II clinical trials for the treatment of *C. difficile* infection.

Fischbach and coworkers recently analyzed the genomes of hundreds of human-associated bacteria and discovered over 3,000 known BGCs, including the BGCs required for the synthesis of thiopeptides.[163] Extracts from 50 L cultures of *Lactobacillus gasseri*, a

vaginal isolate, were analyzed by LC/MS and were found to contain several structurally different thiopeptides. After extensive purification via HPLC, lactocillin (**119**) was isolated and characterized using 1D/2D NMR and mass spectrometry (Scheme 2.7). Lactocillin (**119**) was found to contain a 26-membered macrocycle with four heterocycles, two natural threonine residues, and a single dehydrobutyrine residue. It also contained an indolyl-S-cysteine moiety, two additional thiazoles that branched from the pyridyl core, and an alanine residue that terminated in a free carboxylic acid. Lactocillin (**119**) was tested and found to have an antibiotic activity spectrum similar to that of other thiopeptides.[163]

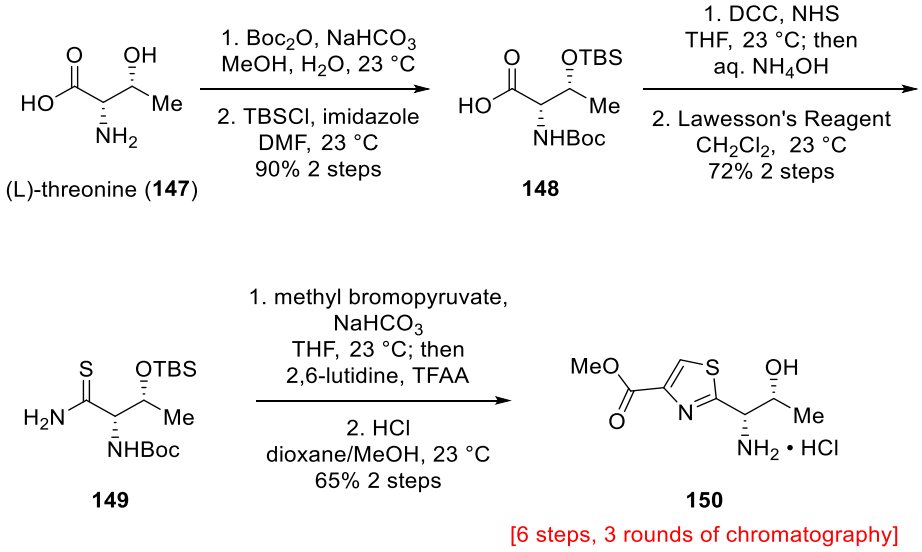


Scheme 2.7. Retrosynthetic analysis of lactocillin (**119**).

Inspired by the work on LFF571 (**146**), we set out to develop a synthesis of lactocillin (**119**) with the intention of ultimately synthesizing novel thiopeptides with improved aqueous solubility and pharmacokinetic properties (Scheme 2.7). Retrosynthetic analysis broke the molecule into essentially three core fragments that were predicted to be brought together using an amide bond coupling reaction, a cross-coupling reaction, and a nitrile-amino thiol condensation. We envisioned this approach enabling the synthesis of a

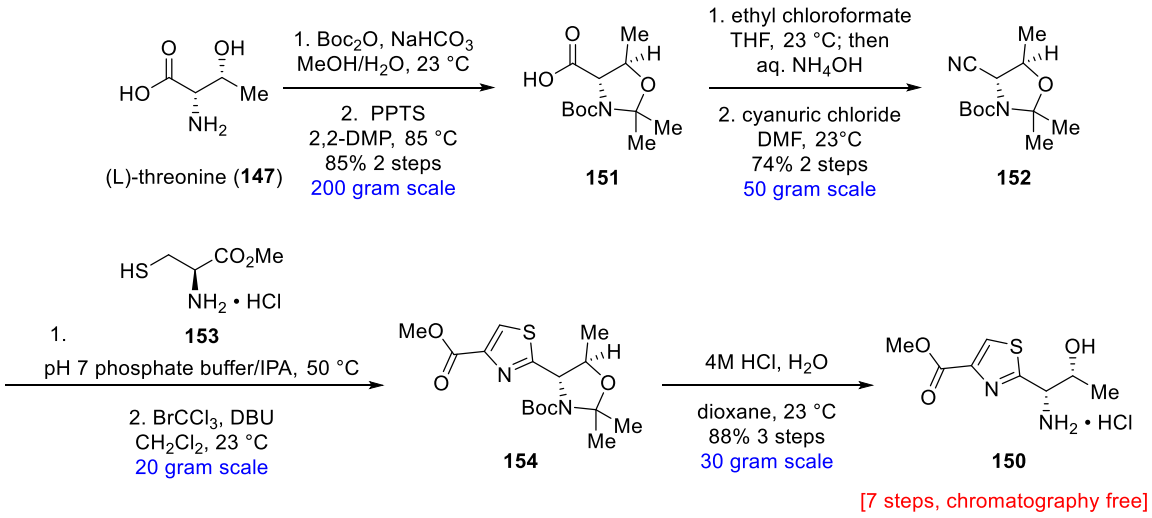
large library of novel thiopeptides by modifying each fragment and bringing them together in a systematic manner.

The northern fragment of lactocillin (**119**) is the predicted pharmacophore and can be found in related natural products including thiostrepton, micrococcin (**118**), and nosiheptide (**120**).[120,126,143,164] Traditionally, this fragment was synthesized starting from (L)-threonine (**147**, Scheme 2.8). Protection of the amine with di-*tert*-butyldicarbonate and the secondary alcohol with *tert*-butyldimethylsilyl chloride yielded protected threonine derivative **148**. The free carboxylic acid was activated with N,N'-dicyclohexylcarbodiimide and N-hydroxysuccinimide followed by conversion to the primary amide with aqueous ammonia. Lawessons reagent thiolated the primary amide to the corresponding thioamide and a Hantzch thiazole synthesis with methyl bromopyruvate was used to afford amino alcohol **150** after deprotection with anhydrous hydrochloric acid.[147,165,166]



Scheme 2.8. Previous synthesis of **150** en route to the northern fragment of lactocillin (**119**).

While current routes to **150** are high yielding and relatively concise, they are cumbersome to run on scales exceeding 10 grams. This is mostly due to the physical state of each intermediate and the use of reagents that are difficult to remove during purification. With the ultimate goal of synthesizing a large library of novel thiopeptides, we wanted to develop a new route to **150** that could easily be run on large scale (Scheme 2.9). Protection of (L)-threonine (**147**) as a *tert*-butylcarbamate and dimethyl oxazolidine group improved the crystalline properties of all subsequent intermediates, which were purified simply by recrystallization or trituration. By instead forming the mixed anhydride of **151** with ethyl chloroformate, we overcame purification issues that involved the removal of large amounts of N,N'-dicyclohexylurea when synthesizing the primary amide of **151**.



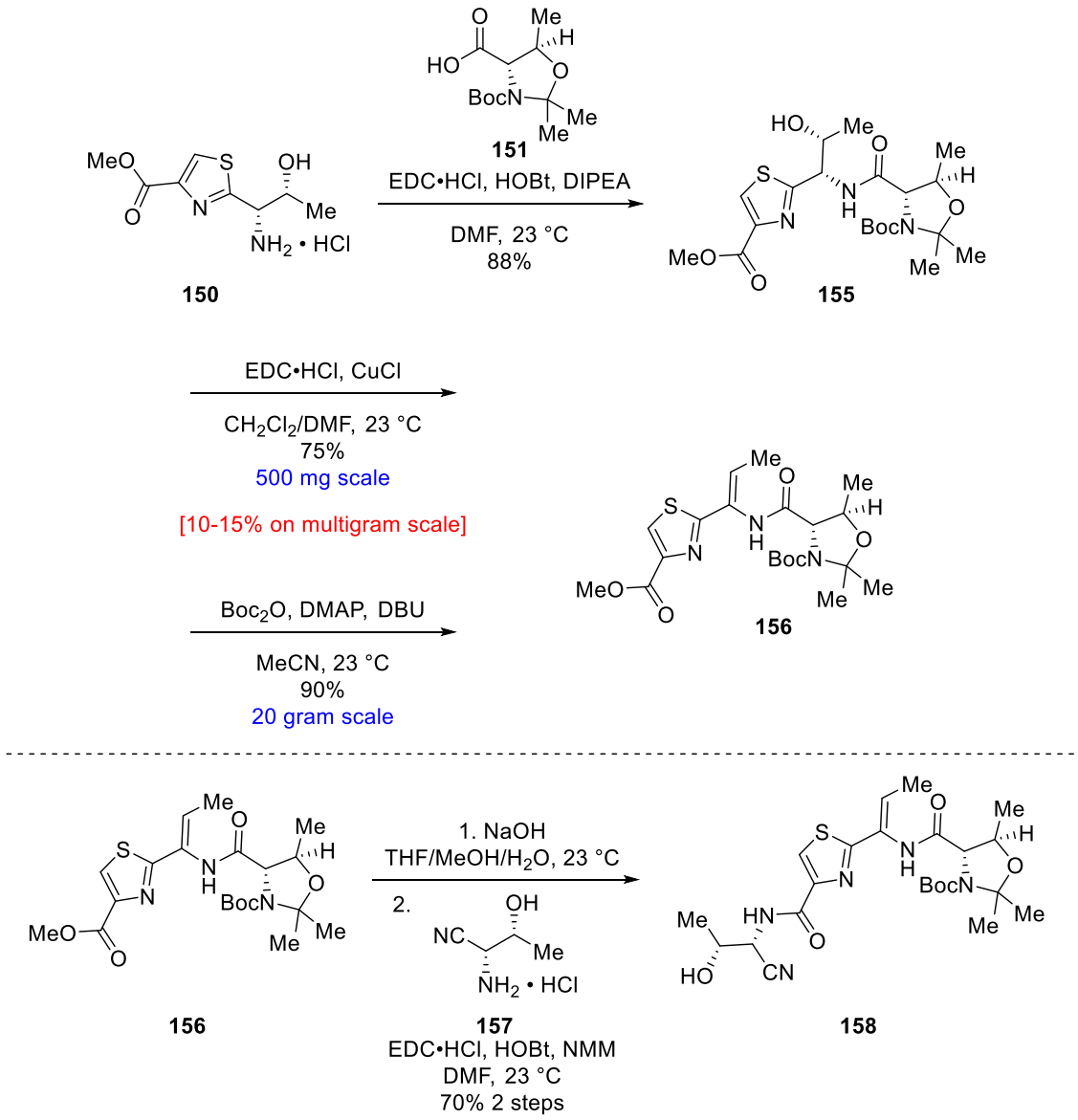
Scheme 2.9. Improved synthesis of **150** using a nitrile-amino thiol condensation.

Although originally discovered in the 1950's, the mild reaction between nitriles and amino thiols remains an underutilized method for the synthesis of thiazolines and thiazoles in total synthesis.[167,168] This method provides an attractive alternative to the Hantzch thiazole synthesis and does not require the use of reagents that complicate purification such

as Lawessons reagent and halogenated pyruvates. This was demonstrated in the synthesis of thiazole **154** (Scheme 2.9). The primary amide of **151** was readily dehydrated to nitrile **152** with cyanuric chloride, an inexpensive reagent used extensively as starting material in the synthesis of triazine-based pesticides.[169] Nitrile **152** was treated with (L)-cysteine methyl ester hydrochloride (**153**) in a 1.5:1 solution of isopropanol and 0.1 M aqueous pH 7 phosphate buffer at 50 °C to afford the corresponding thiazoline. The oxidation of thiazolines to thiazoles is well studied and many methods exist for this transformation.[170–174] The thiazoline of **154** was oxidized to the thiazole in a one-pot addition/elimination sequence with bromotrichloromethane and 1,8-diazabicycloundec-7-ene. Pure amino alcohol **150** was isolated after deprotection with aqueous hydrochloric acid. Although this new route involved an extra step, **150** was easily synthesized in 55% overall yield from (L)-threonine (**147**) on 30 gram scale without silica gel column chromatography.

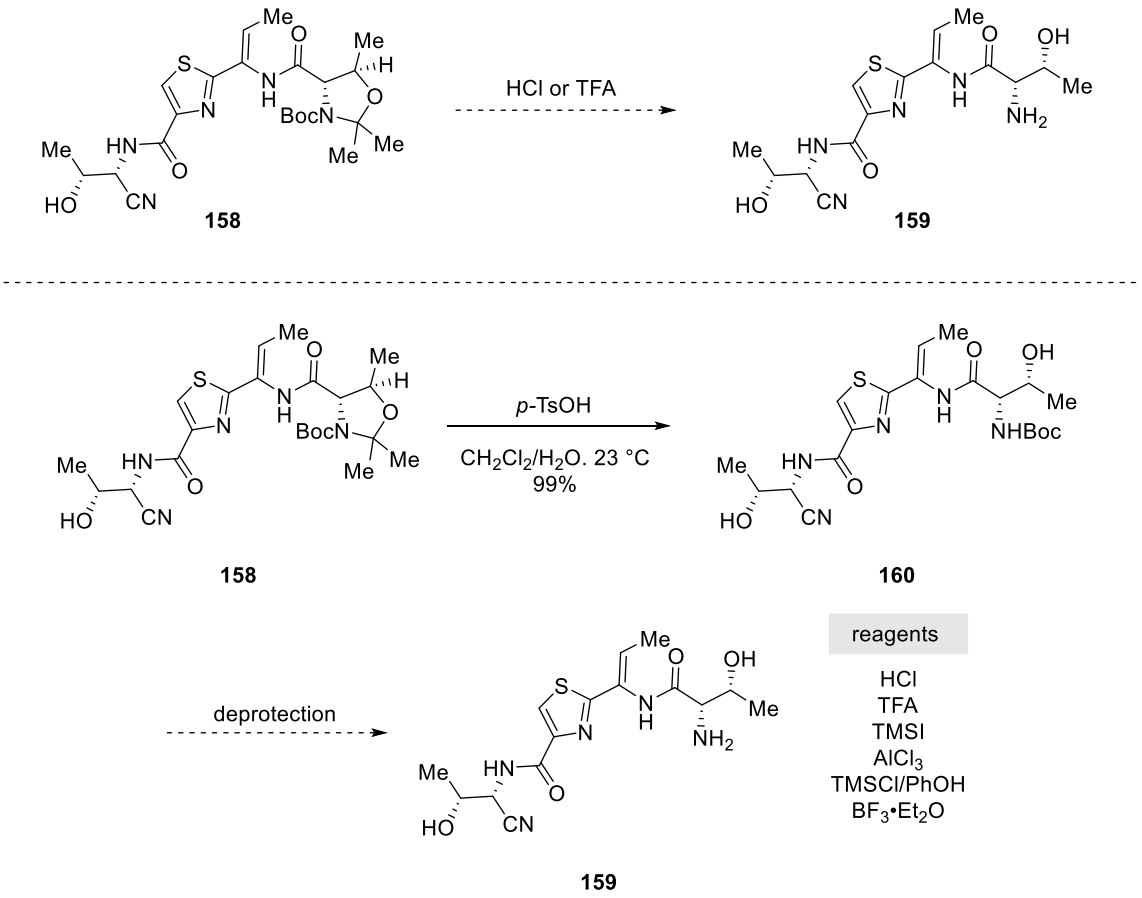
The free amine of **150** was coupled to another molecule of acid **151** under standard conditions and the secondary alcohol was selectively eliminated with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC•HCl) activated with copper(I) chloride to give the desired (E)-alkene **156** (Scheme 2.10).[175,176] This transformation worked well on several hundred milligram scale; however, any reaction larger than one gram would typically yield only a small amount of product. It's presumed that the copper salts generated throughout the course of the reaction chelate to either the starting material or product, which is then lost during workup. Although there are several other methods that exist for the synthesis of dehydro amino acids, none of them provided the desired (E)-alkene in good yield on large scale.[141,153,154,177] A simple solution was devised that involved conversion of the secondary alcohol to the *tert*-butylcarbonate followed by *in situ*

elimination with 1,8-diazabicycloundec-7-ene to provide **156** as a single olefin isomer on 20 gram scale.[178] Saponification of methyl ester **156** and coupling to the amino nitrile of threonine **157**, derived from acid deprotection of nitrile **151**, provided the protected northern fragment **158**.



Scheme 2.10. Synthesis of protected northern fragment **158**.

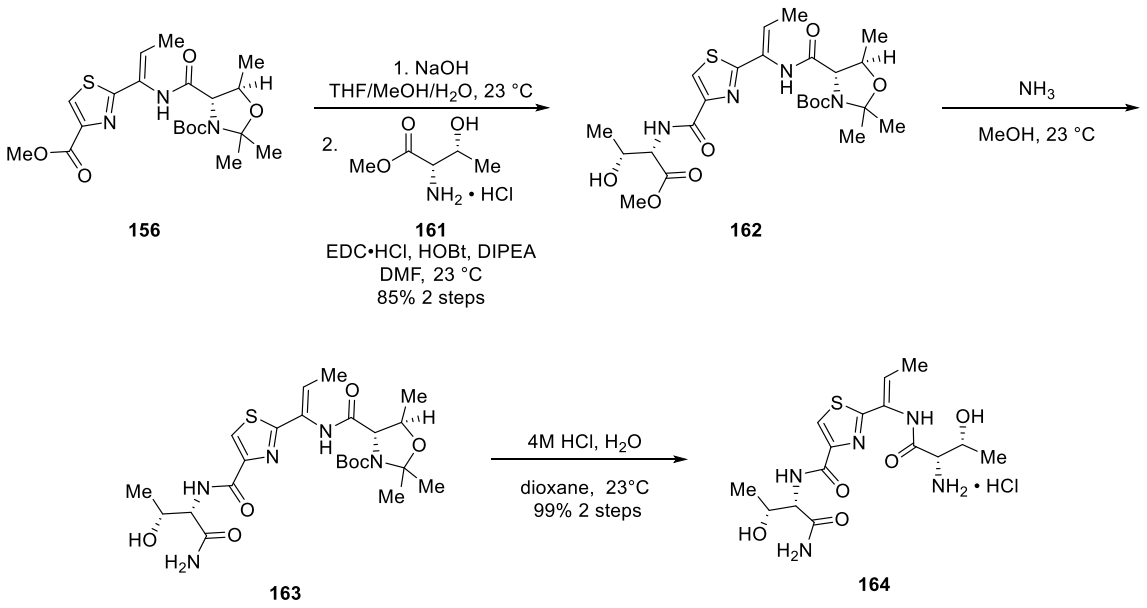
Unfortunately, **158** was found to decompose upon treatment with either aqueous hydrochloric acid or trifluoroacetic acid (Scheme 2.11). Protecting group strategies of nitrile containing peptides have not been well studied, but it's believed that the nitrile may be ionizing during the reaction. The ketal was removed by treatment of **158** with catalytic *para*-toluenesulfonic acid; however, the amine was still unable to be deprotected under a variety of known conditions.[179–182]



Scheme 2.11. Failed deprotection of protected northern fragment **158**.

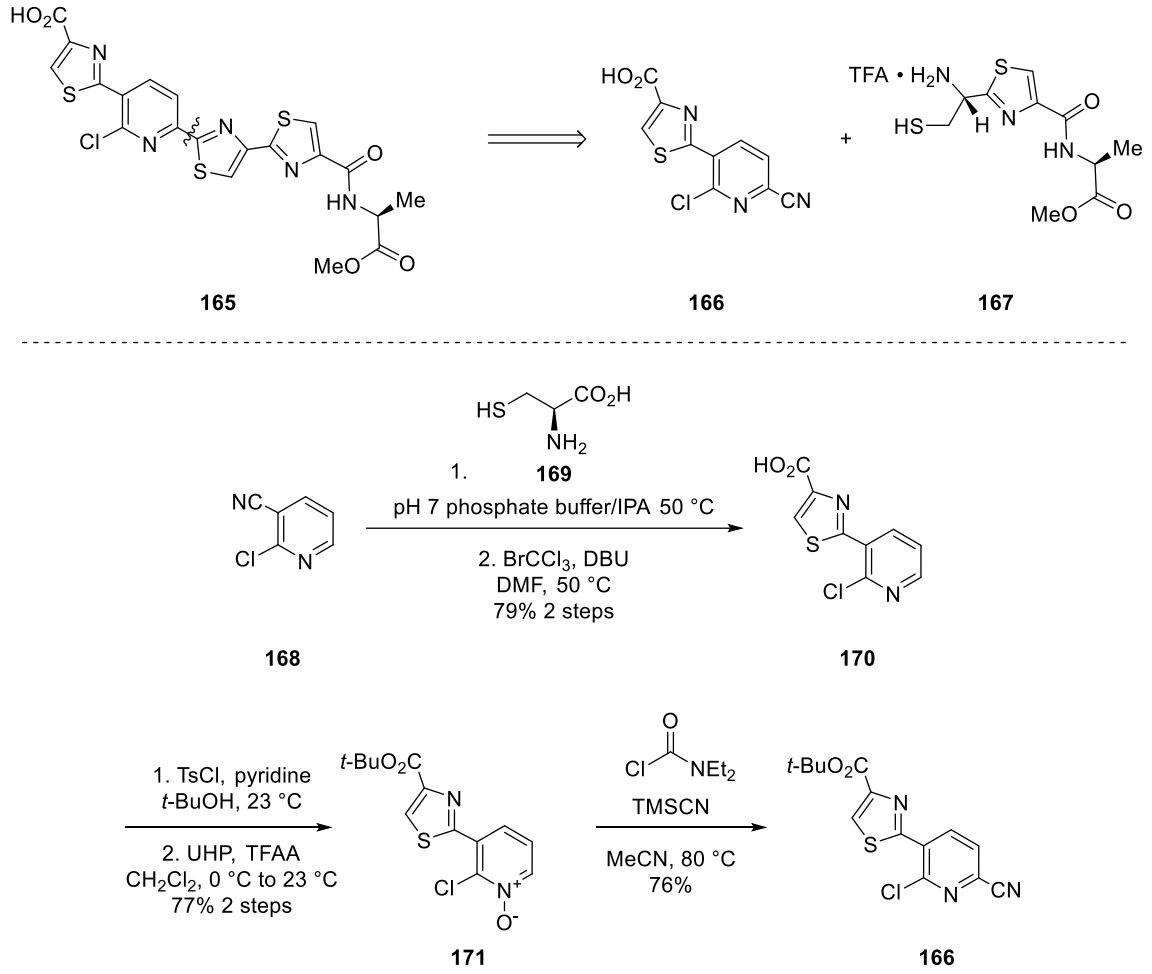
It was predicted that a primary amide should survive deprotection and could later be dehydrated to the desired nitrile (Scheme 2.12). Therefore, saponification of **156** and coupling of threonine methyl ester (**161**) provided peptide **162**, which was treated with

ammonia to afford the protected primary amide. The northern fragment was successfully deprotected with aqueous hydrochloric acid to give amino alcohol **164**.



Scheme 2.12. Synthesis of the deprotected northern fragment **164**.

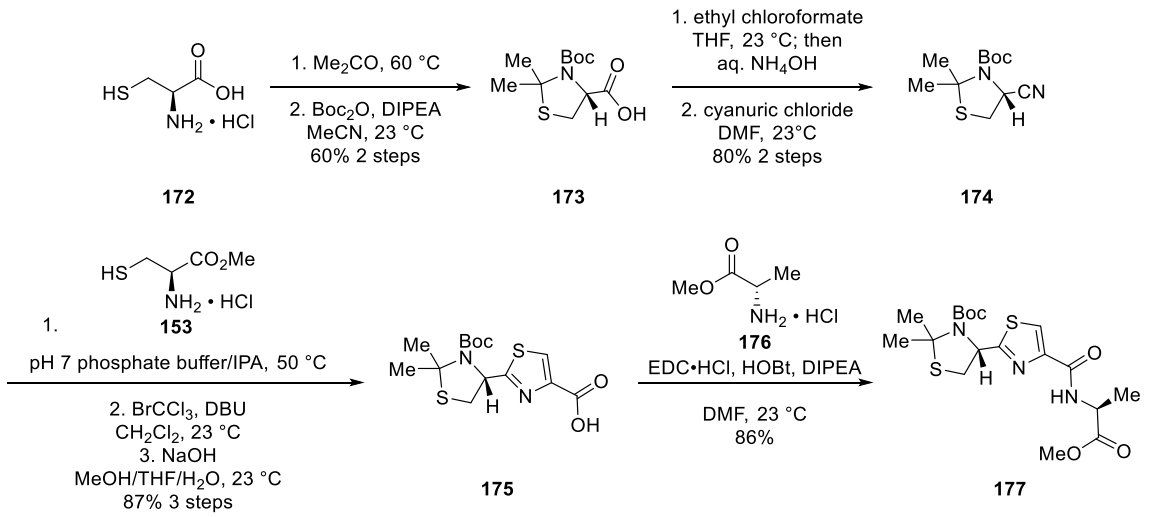
Amino alcohol **164** was to be coupled to the free acid of the pyridyl core **165**, synthesized via a condensation between nitrile **166** and amino thiol **167** (Scheme 2.13). A condensation between commercially available pyridine **168** and (L)-cysteine (**169**) afforded thiazole **170** after oxidation of the intermediate thiazoline. Protection of the free acid as a *tert*-butyl ester and oxidation to the pyridine N-oxide **171** proceeded smoothly.[183] Pyridine N-oxide **171** was subjected to a modified Reissert reaction with trimethylsilyl cyanide and diethylcarbamoyl chloride to afford the nitrile **166** as a crystalline off-white solid.[184] This sequence was robust with all intermediates being crystallized directly from the reaction mixture or purified via trituration.



Scheme 2.13. Synthesis of the nitrile **166**.

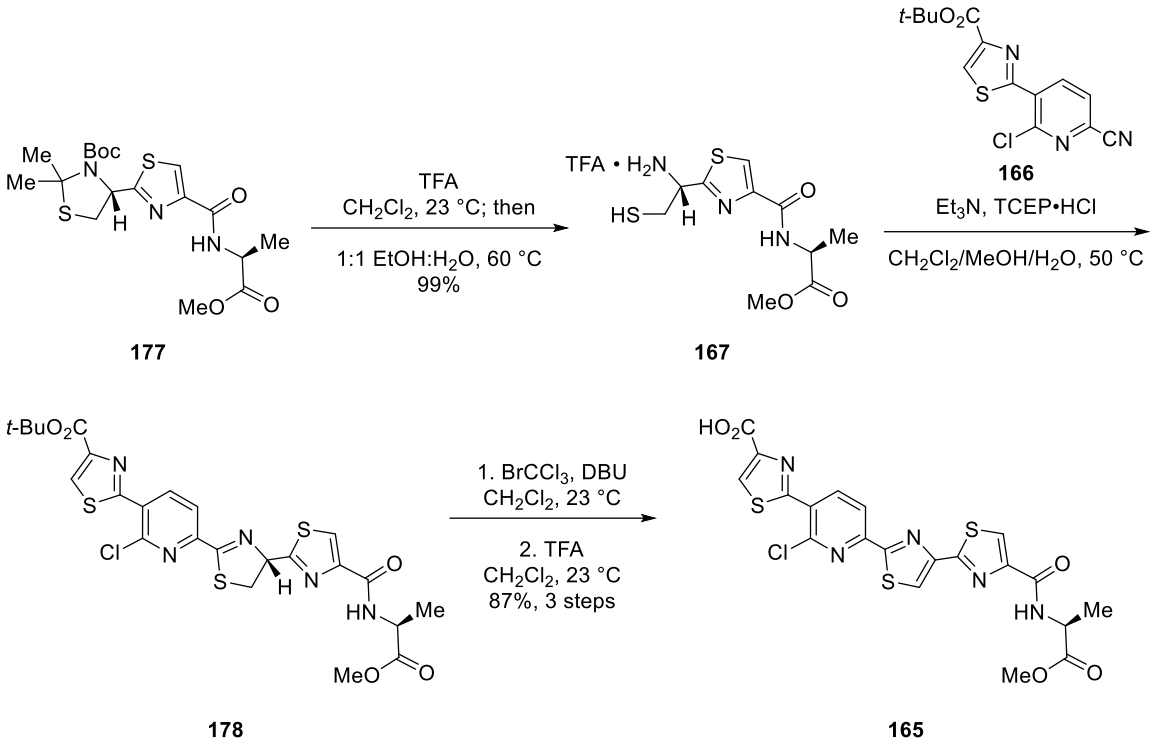
With nitrile **166** in hand, work began on the synthesis of the alanine derived southern fragment of lactocillin (**119**, Scheme 2.14). This fragment was synthesized in a very similar manner to the northern fragment and began with protection of (L)-cysteine hydrochloride (**172**) as a dimethylthiazolidine. The amine was protected once again with di-*tert*-butyldicarbonate and the free acid **173** was dehydrated via the primary amide using cyanuric chloride to provide nitrile **174**. Condensation with (L)-cysteine methyl ester hydrochloride (**153**) afforded the thiazole **175,** following oxidation and saponification of

the methyl ester. (L)-Alanine methyl ester hydrochloride (**176**) was coupled to the free acid **175** under standard conditions to yield the protected southern fragment **177**.



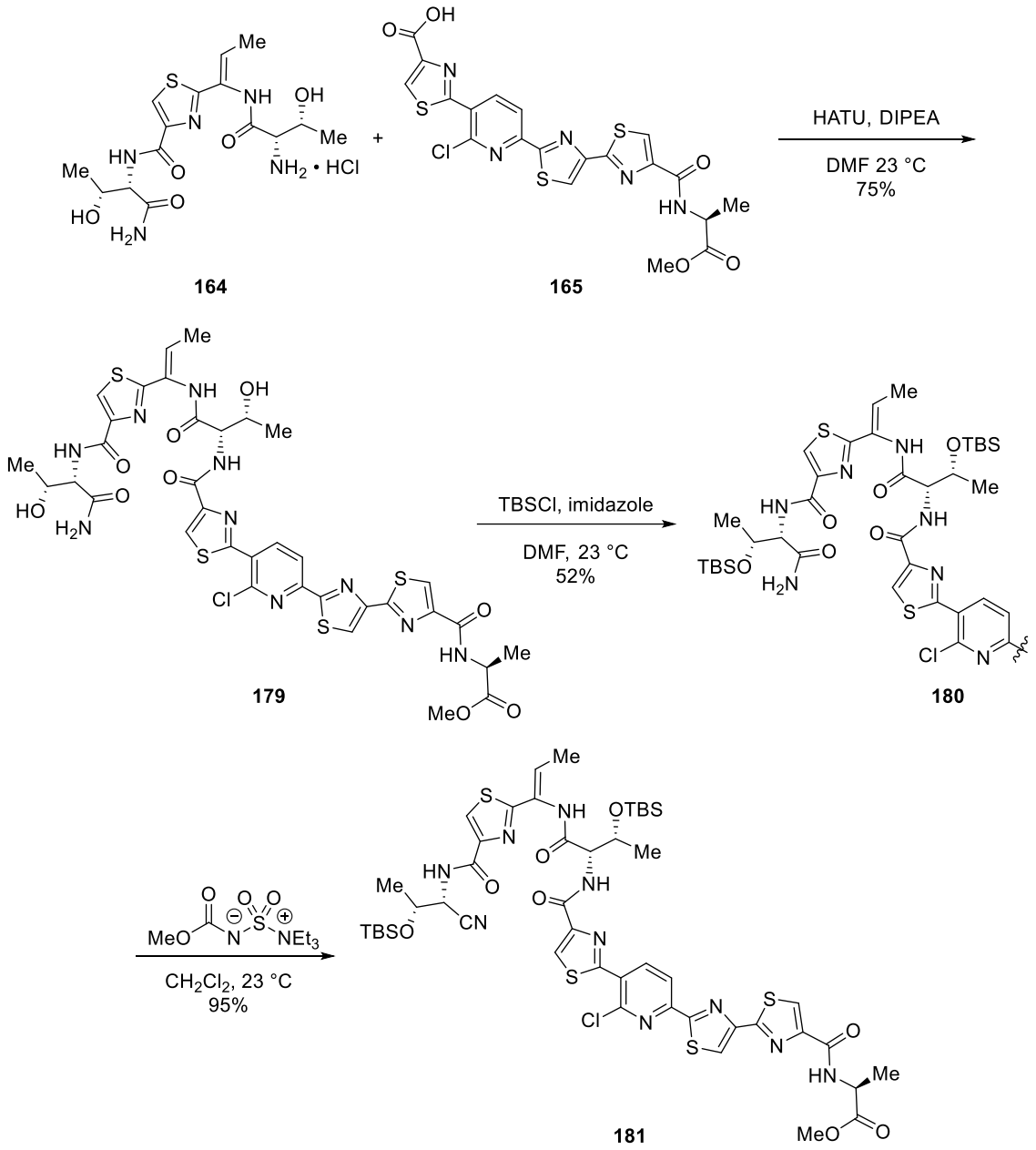
Scheme 2.14. Synthesis of protected southern fragment **177**.

Both the *tert*-butylcarbamate and ketal were removed with trifluoroacetic acid followed by treatment with a 1:1 solution of ethanol and water (Scheme 2.15). The amino thiol **167** condensed onto nitrile **166** in the presence of triethylamine and tris(2-carboxyethy1)phosphine hydrochloride in a mixed aqueous solvent system, which helped to solubilize **166**. Tris(2-carboxyethy)phosphine hydrochloride is a stoichiometric reductant of disulfide bonds and was used to prevent the *in situ* oxidation of amino thiol **167** throughout the course of the reaction.[185] Finally, oxidation of thiazoline **178** and cleavage of the *tert*-butyl ester afforded the pyridyl core **165** as a pale yellow solid after trituration with methyl *tert*-butyl ether.



Scheme 2.15. Synthesis of the pyridyl core of lactocillin (**119**).

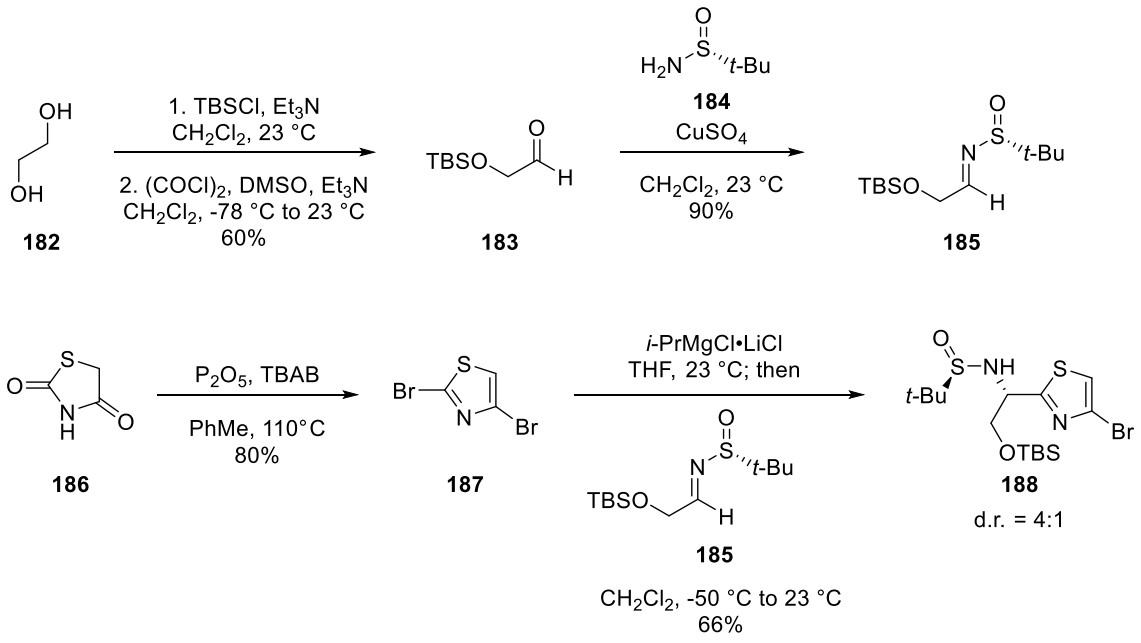
The coupling of amino alcohol **164** and free acid **165** proceeded well under standard HATU conditions with amide **179** being precipitated directly from the reaction mixture (Scheme 2.16).[186] Amide **179** was found to be incredibly difficult to work with as a result of only being slightly soluble in dimethylformamide and dimethylsulfoxide. Attempts to dehydrate the primary amide to the desired nitrile were thwarted by an inability to effectively monitor and workup these reactions. Global silylation of **179** provided a solution to the solubility problems that we were experiencing. With both alcohols now protected, the primary amide was selectively dehydrated to nitrile **181** using Burgess reagent.[187]



Scheme 2.16. Coupling of the northern fragment **164** and the pyridyl core **165**.

Completing the heterocyclic core of lactocillin (**119**) involved synthesis of stannane **191** (Scheme 2.18). Thiazoles bearing bromine at the 4-position are difficult to synthesize. They are typically accessed by selective bromination at the 5-position followed by a base-induced 1,2-rearrangement of bromine to the 4-position, a process called a "halogen

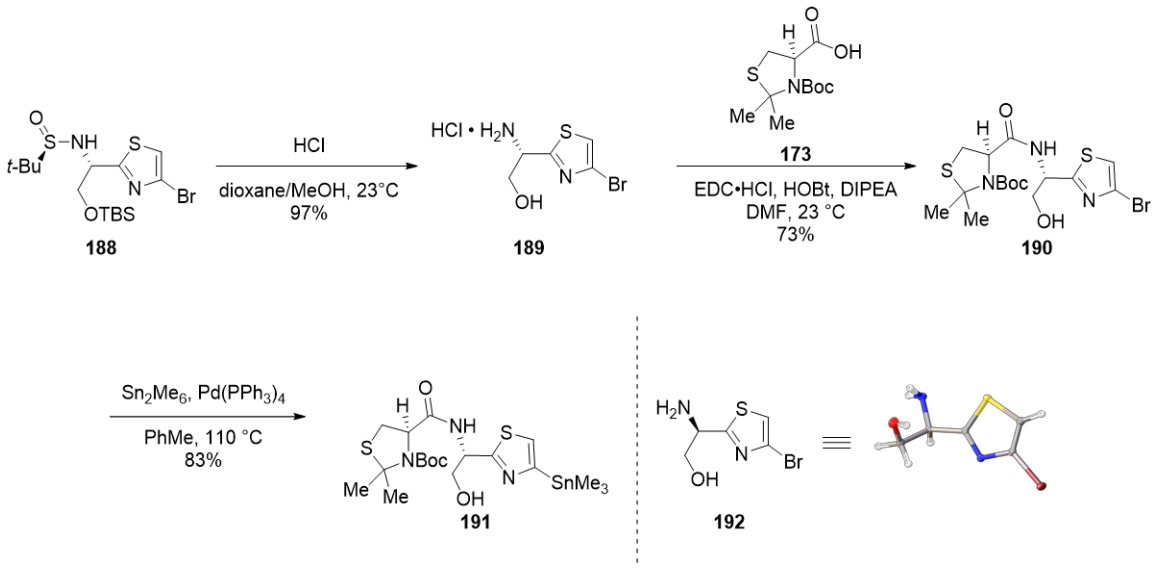
dance."[188] Alternatively, a Hunsdiecker reaction from a carboxylic acid or ester at the 4-position can lead to 4-halo thiazoles.[189,190] In the synthesis of **191**, we chose a different approach that involved a Grignard reaction between dibromide **187** and enantiopure N-*tert*-butanesulfinyl imine **185** (Scheme 2.17).



Scheme 2.17. Preparation of bromide **188**.

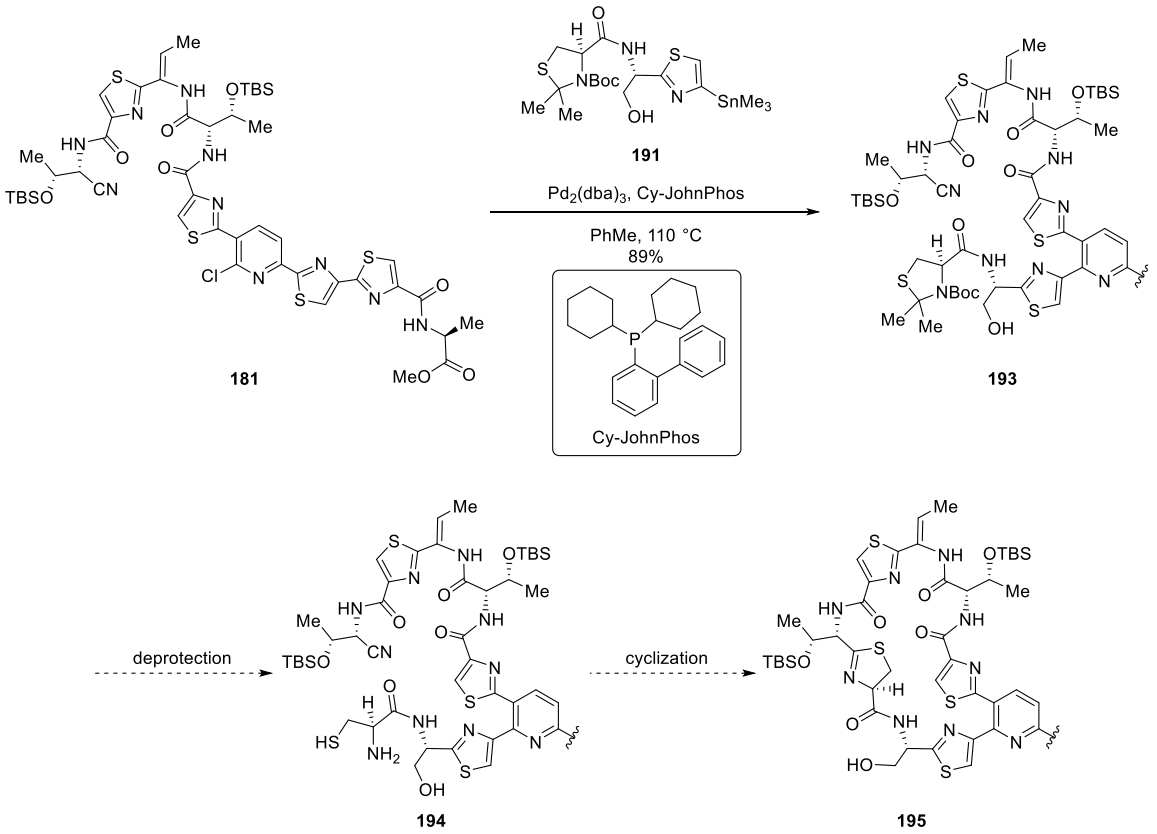
Ellman's N-*tert*-butanesulfinyl imine chemistry is widely used in the synthesis of chiral amines.[191] N-*tert*-butanesulfinyl imines are synthesized starting from aldehydes using commercially available, enantiopure 2-methyl-2-propanesulfinamide. Monosilylation of ethylene glycol **182** afforded an alcohol, which was oxidized under Swern conditions to provide aldehyde **183** (Scheme 2.17).[81] Imine formation occurred with (R)-(+)-2-methyl-2-propanesulfinamide (**184**) in the presence of copper (II) sulfate to provide N-*tert*-butanesulfinyl imine **185**.[192] Known dibromide **187** was accessed in a single

reaction using phosphorous pentoxide and tetrabutylammonium bromide from commercially available 2,4-thiazolidinedione **186**.



Scheme 2.18. Preparation of stannane **191**.

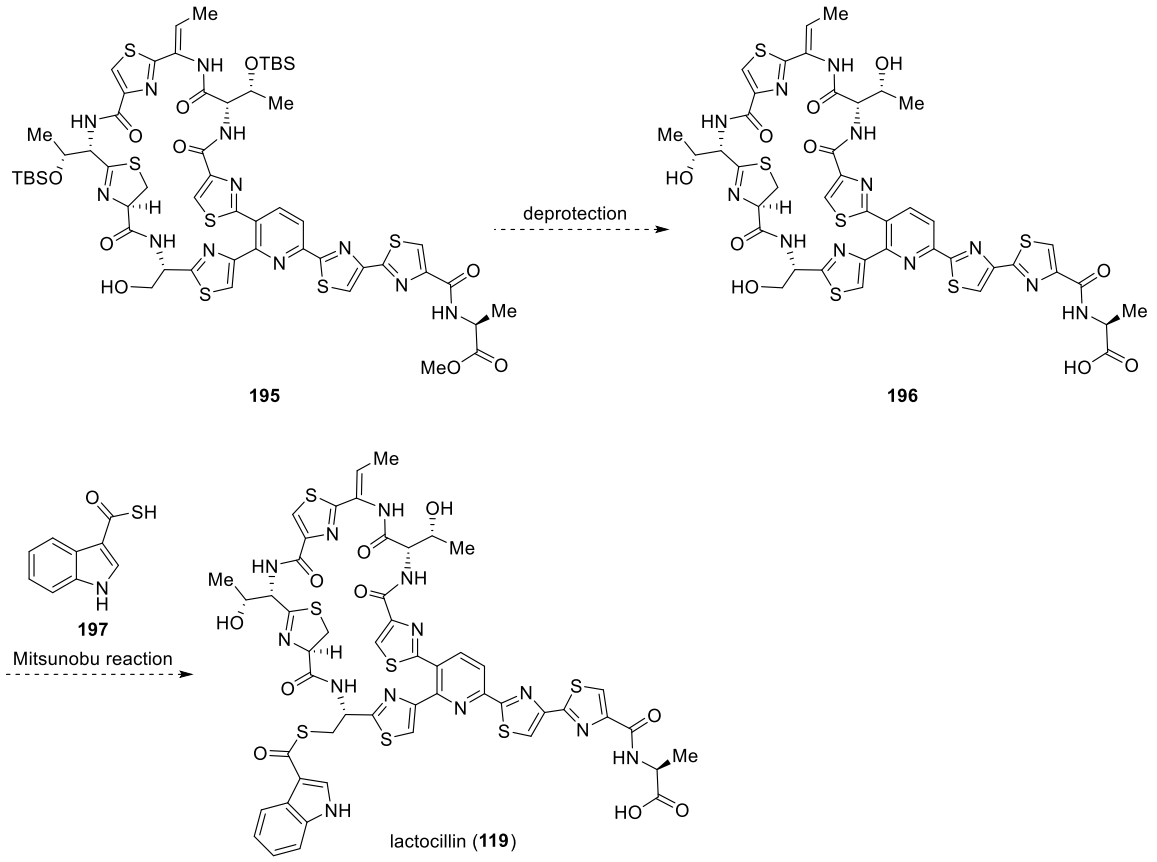
Selective magnesium-halogen exchange occurred at the 2-position using isopropylmagnesium chloride-lithium chloride complex and the resulting Grignard reagent was added to a solution of **185** in methylene chloride at –50 °C to afford the protected amine **188** as a 4:1 mixture of separable diastereomers.[149,193] The new stereocenter was confirmed by X-ray crystallography of the free base of deprotected amine **192**. Coupling of free amine **189** to acid **173** yielded the bromide **190**, which was transmetallated with hexamethyldistannane and tetrakis(triphenylphosphine) palladium(0) under standard conditions to afford stannane **191** (Scheme 2.18).[142,149,194]



Scheme 2.19. Cross coupling of chloride **181** and stannane **191** yields precyclized lactocillin (**119**).

Cross-coupling of chloride **181** and stannane **191** was achieved using tris(dibenzylideneacetone)dipalladium(0) (5 mol %) and cyclohexyl-JohnPhos (20 mol %) in toluene at 110 °C (Scheme 2.19). While other palladium/ligand combinations were tried, only tris(dibenzylideneacetone)dipalladium(0)/cyclohexyl-JohnPhos reliably provided **193**.[195–197] Interestingly, significantly destannylation of **191** was observed if the reaction was run in any solvent other than toluene. With **193** in hand, work is ongoing to selectively deprotect the *tert*-butylcarbamate and ketal to access the amino thiol **194**. Issues regarding the nitrile's stability toward acidic conditions are currently being encountered, similar to when we attempted to deprotect the northern fragment in the presence of a nitrile earlier in

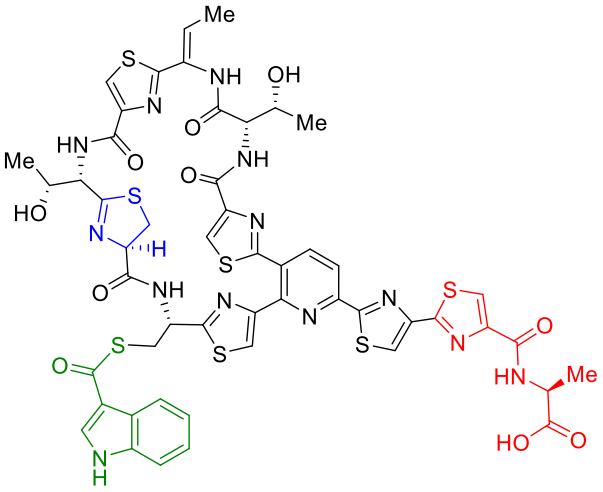
the synthesis. It may be necessary to protect nitrogen as a different functional group that can be removed under neutral or basic conditions, such as a 9-fluorenylmethyloxycarbamate or a nosyl group.[198,199] Once deprotected, amino thiol **194** is predicted to undergo an intramolecular condensation with the northern nitrile and close the macrocycle.[200] Once formed, both silyl ethers need to be removed and the methyl ester needs to be hydrolyzed prior to forming the thioester via an anticipated Mitsunobu reaction with thioacetate **197** (Scheme 2.20).[201]



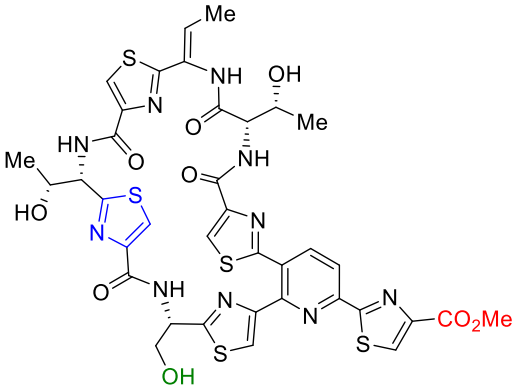
Scheme 2.20. Deprotection and thioester formation will complete the synthesis of lactocillin (**119**).

While working on the total synthesis of lactocillin (**119**), we were also working towards a simplified thiopeptide (**198**) that could be advanced as new edited thiopeptides

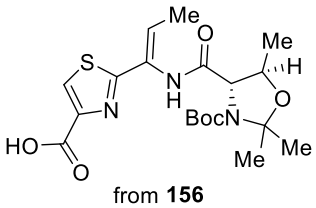
with improved physiochemical properties (Scheme 2.21). The simplified thiopeptide (**198**) retains the pharmacophore of this subfamily of thiopeptides, but has a free primary alcohol and ester, both of which can be used as handles for analog synthesis. The core thiazoline found in lactocillin (**119**) was also oxidized to a thiazole to increase stability. Retrosynthetic analysis revealed four main fragments, three of which were accessed using the chemistry developed earlier during the approach to the total synthesis of lactocillin (**119**).



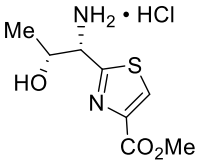
lactocillin (**119**)



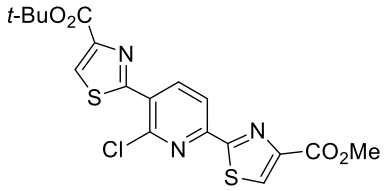
simplified thiopeptide (**198**)



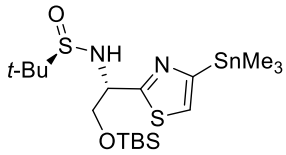
from **156**



150



from **166**

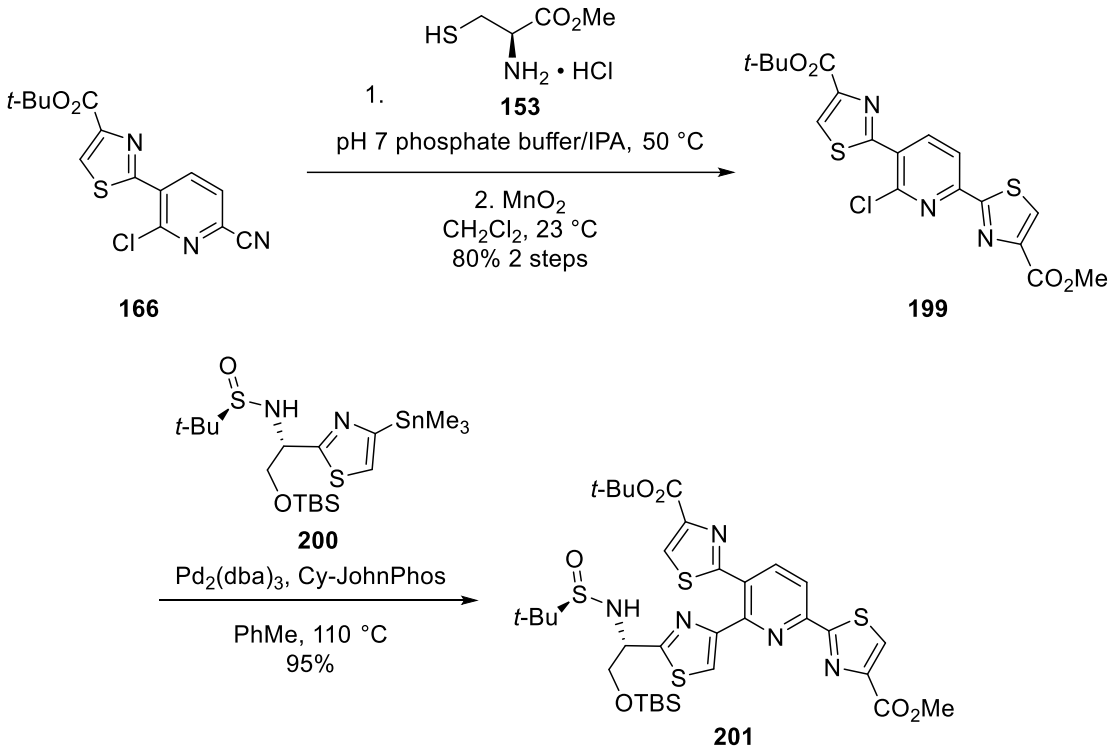


from **188**

Scheme 2.21. Retrosynthetic analysis of simplified thiopeptide (**198**).

The pyridyl core of simplified thiopeptide (**198**) was synthesized from a condensation between pyridine **166** and (L)-cysteine methyl ester hydrochloride (**153**) followed by oxidation with manganese(II) oxide (Scheme 2.22). Interestingly, significant incorporation of trichloromethane was observed when using bromotrichloromethane and 1,8-diazabicycloundec-7-ene to oxidize the intermediate thiazoline. Stille cross-coupling

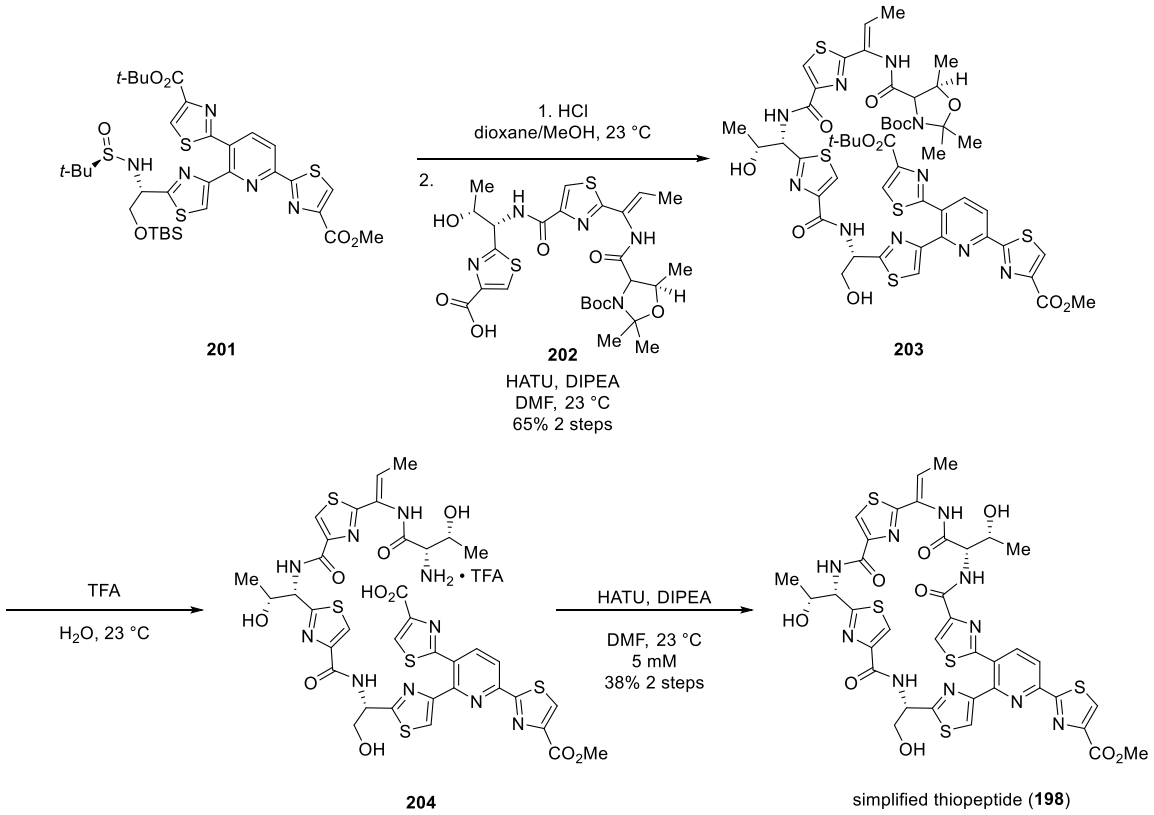
with stannane **200**, derived from transmetallation of Ellman adduct **188**, proceeded smoothly with the same conditions used in the synthesis of **193**.



Scheme 2.22. Synthesis of the core of simplified thiopeptide (**198**).

Selective deprotection of the *tert*-butyldimethylsilyl ether and *tert*-butylcarbamate in the presence of the *tert*-butyl ester was accomplished with anhydrous hydrochloric acid and the free amine was coupled to the free acid of peptide **202**, readily synthesized from free amine **150** and saponified **156** (Scheme 2.23). Simultaneous deprotection of the *tert*-butyl ester, *tert*-butylcarbamate, and ketal was achieved using aqueous trifluoroacetic acid to afford amino acid **204**. HATU mediated coupling in a 5 mM dimethylformamide solution furnished the simplified thiopeptide (**198**) as a white solid. Work has begun to synthesize an initial library of analogs with the goal of improving aqueous solubility. We

are also working closely with collaborators in molecular modeling to design new thiopeptides that may be more potent or have improved pharmacokinetic properties.



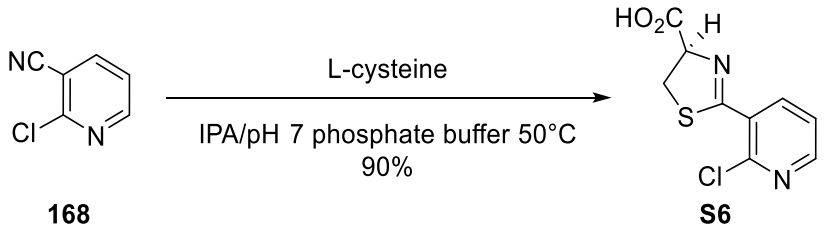
Scheme 2.23. Completing the synthesis of simplified thiopeptide (**198**).

Experimental Section

General Information

All reactions were performed in flame dried round bottom fitted with rubber septa under a positive pressure of argon or nitrogen, unless otherwise indicated. Air and moisture sensitive liquids and solutions were transferred via syringe or cannula. Organic solutions were concentrated by rotary evaporation at 20 torr in a water bath heated to 40 °C unless otherwise noted. Diethyl ether (Et_2O), methylene chloride (CH_2Cl_2), tetrahydrofuran (THF) and toluene (PhMe) were purified using a Pure-Solv MD-5 Solvent Purification System (Innovative Technology). Acetonitrile (MeCN), N,N,-dimethylformamide (DMF), and methanol (MeOH) were purchased from Acros (99.8%, anhydrous) and ethanol (EtOH) was purchased from Pharmco-Aaper (200 proof, absolute). The molarity of *n*-butyllithium was determined by titration against diphenylacetic acid.[103] All other reagents were used directly from the supplier without further purification unless otherwise noted. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (silica gel 60, F254, EMD chemical) and visualized using a UV lamp and/or aqueous ceric ammonium molybdate (CAM) or aqueous potassium permanganate ($KMnO_4$) stain, or ethanolic vanillin. Infrared spectra were recorded on a Nicolet 380 FTIR using neat thin film technique. High-resolution mass spectra (HRMS) were recorded on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion $[M+Na]^+$, $[M+H]^+$, [M] or $[M–H]^–$. Nuclear magnetic resonance spectra (^{1}H-NMR and ^{13}C-NMR) were recorded with a Varian Gemini [(400 MHz, ^{1}H at 400 MHz, ^{13}C at 100 MHz), (500 MHz, ^{1}H at 500 MHz, ^{13}C at 125 MHz), (600 MHz, ^{1}H at 600 MHz, ^{13}C at 150 MHz)]. For $CDCl_3$ solutions the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvent; $CHCl_3$ δ H (7.26 ppm) and $CDCl_3$ δ D (77.0 ppm). For $(CD_3)_2SO$ solutions the chemical shifts are reported as parts

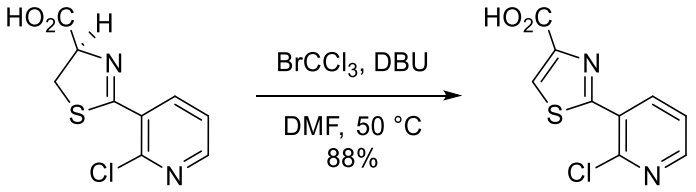
per million (ppm) referenced to residual protium or carbon of the solvents; $(CD_3)(-CHD_2)SO$ δ H (2.50 ppm) or $(CD_3)_2SO$ δ C (39.5 ppm). For CD_3OD solutions the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvents; CHD_2OD δ H (3.31 ppm) or CD_3OD δ C (49.0 ppm). Coupling constants are reported in Hertz (Hz). Data for ^{1}H-NMR spectra are reported as follows: chemical shift (ppm, referenced to protium; s = singlet, d = doublet, t = triplet, q= quartet, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, ddq = doublet of doublet of quartets, bs = broad singlet, bd = broad doublet, m = multiplet, coupling constant (Hz), and integration). Melting points were measured on a MEL-TEMP device without corrections.



168 **S6**

To a stirred solution of 2-chloro-3-cyanopyridine **168** (20 g, 144 mmol, 1.0 equiv.) in 1.5:1 IPA:0.1 M pH 7 phosphate buffer (289 mL, 0.5 M) was added solid L-cysteine (21 g, 173 mmol 1.2 equiv.). The reaction vessel was sparged with nitrogen for 10 minutes and sealed with a yellow cap. The heterogenous reaction mixture was stirred at 50 °C for 12 hours. The crude reaction was concentrated *in vacuo* to remove IPA and the resulting aqueous mixture was acidified with conc. HCl and the solids were collect by filtration. The filter cake was washed with 1.0 M HCl (2 x 100 mL) and dried under vacuum at 50 °C to yield the thiazoline **S6** (31.5 g, 130 mmol, 90%) as a white solid (m.p. 156-158 °C).

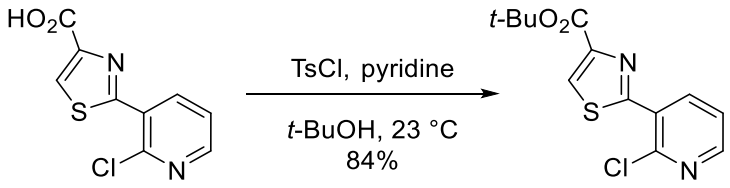
R_f = 0.13 (silica gel, 10:1 CH_2Cl_2:MeOH + 2% AcOH); **^{1}H-NMR** (600 MHz, $(CD_3)_2SO$): δ 8.55 (dd, *J* = 4.6, 1.6 Hz, 1H), 8.12 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.56 (dd, *J* = 7.6, 4.8 Hz, 1H), 5.32 (t, *J* = 9.1 Hz, 1H), 3.82 – 3.77 (m, 1H), 3.71 (dd, *J* = 11.2, 8.6 Hz, 1H); **^{13}C-NMR** (150 MHz, $(CD_3)_2SO$): δ 171.4, 164.7, 151.4, 147.5, 140.0, 128.9, 123.4, 78.4, 36.4; **IR** (film, cm^{-1}): 3134, 1744; **HRMS** (ESI): calc. for $C_9H_7ClN_2O_2S$ $[M-H]^-$: 240.9844, obs. 240.9848.



S6 **170**

To a stirred solution of **S6** (31.5 g, 130 mmol. 1.0 equiv.) in DMF (130 mL, 1.0 M) was added neat bromotrichloromethane (19.1 mL, 38.6 mmol, 1.5 equiv.) and neat DBU (40.7 mL, 273 mmol, 2.1 equiv.). The dark homogeneous reaction was stirred at 50 °C for 2 hours. Ice water (500 mL) was added and the aqueous mixture was acidified with 5.0 M HCl. The solids were collected by filtration, washed with 1.0 M HCl (2 x 100 mL), and dried under vacuum at 50 °C to yield the thiazole **170** (27.5 g, 114 mmol, 88%) as an off white solid (m.p. > 200 °C).

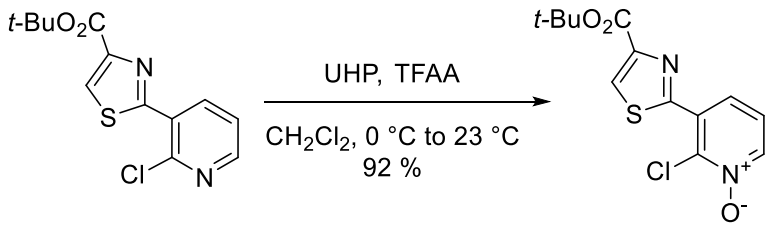
R_f = 0.27 (silica gel, 10:1 CH_2Cl_2:MeOH + 2% AcOH); **^{1}H-NMR** (600 MHz, $(CD_3)_2SO$): δ 8.70 (s, 1H), 8.62 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.57 (dd, *J* = 4.6, 1.8 Hz, 1H), 7.66 (dd, *J* = 7.8, 4.6 Hz, 1H); **^{13}C-NMR** (150 MHz, $(CD_3)_2SO$): 162.4, 161.6, 151.3, 148.0, 147.6, 140.2, 131.1, 128.3, 124.3; **IR** (film, cm^{-1}): 3133, 1721; **HRMS** (ESI): calc. for $C_9H_5ClN_2O_2S$ $[M-H]^-$: 238.9687, obs. 238.9689.



170 **S7**

To a stirred solution of **170** (10 g, 41.6 mmol, 1.0 equiv.) in a 3:1 solution of *t*-BuOH:pyridine (138 mL, 0.3 M) was added solid *p*-toluenesulfonyl chloride (15.84 g, 83 mmol, 2.0 equiv.). The heterogeneous reaction mixture was stirred at 23 °C for 15 hours. Ice water (500 mL) was added and the solids were collected by filtration. The filter cake was washed with water (2 x 100 mL) and dried under vacuum at 50 °C to yield the *t*-butyl ester **S7** (10.36 g, 34.9 mmol, 84%) as a brown powder (m.p. 115-117 °C).

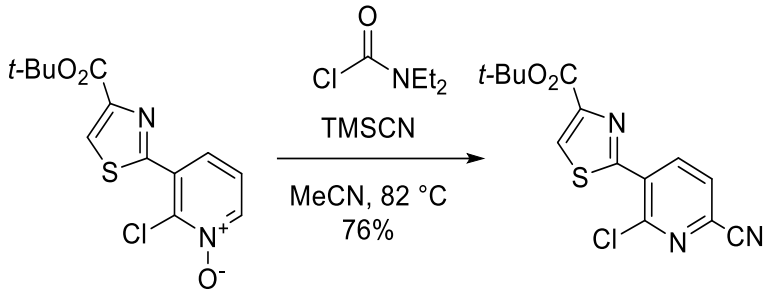
R_f = 0.58 (silica gel, 2:1 hexanes:EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 8.81 – 8.79 (m, 1H), 8.47 (dd, *J* = 4.6, 1.9 Hz, 1H), 8.21 (s, 1H), 7.40 (dd, *J* = 7.8, 4.6 Hz, 1H), 1.63 (s, 9H); **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 161.7, 160.3, 150.3, 148.5, 148.2, 139.8, 128.3, 128.2, 122.8, 82.3, 28.2; **IR** (film, cm^{-1}): 1723; **HRMS** (ESI): calc. for $C_{13}H_{13}ClN_2O_2S$ $[M+Na]^+$: 319.0278, obs. 319.0274.



S7 **171**

To a stirred solution of **S7** (10.36 g, 34.9 mmol, 1.0 equiv.) in CH_2Cl_2 (175 mL, 0.2 M) was added powdered urea-hydrogen peroxide addition complex (6.57 g, 69.8 mmol, 2.0 equiv.). The reaction vessel was cooled in an ice water bath followed by dropwise addition of neat trifluoroacetic anhydride (9.71 mL, 69.8 mmol, 2.0 equiv.) over 30 minutes. The pale yellow heterogeneous reaction was allowed to warm to 23 °C and stirred for 12 hours. The crude reaction mixture was diluted with CH_2Cl_2 (200 mL) and carefully quenched with 10% aq. K_2CO_3 (200 mL). The organic layer was washed successively with water (3 x 100 mL), sat. $Na_2S_2O_3$ (2 x 100 mL), and brine (1 x 50 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to yield pyridine N-oxide **171** (10.05 g, 32.1 mmol, 92%) as a yellow solid (m.p. 134-136 °C).

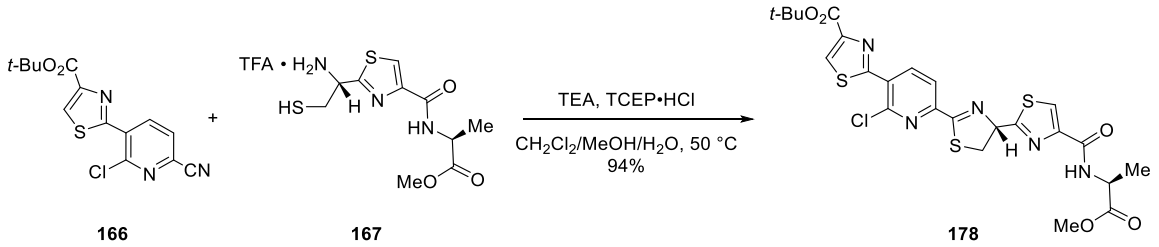
R_f = 0.80 (silica gel, 10:1 CH_2Cl_2:MeOH); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 8.45 – 8.43 (dd, *J* = 6.4, 1.4 Hz, 1H), 8.34 – 8.31 (dd, *J* = 8.3, 1.4 Hz, 1H), 8.26 (s, 1H), 7.35 – 7.32 (dd, *J* = 8.2, 6.5 Hz, 1H), 1.62 (s, 9H); **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 160.0, 159.9, 148.8, 140.4, 131.6, 128.8, 12f6.8, 122.9, 82.6, 28.1; **IR** (film, cm^{-1}): 1725; **HRMS** (ESI): calc. for $C_{13}H_{13}ClN_2O_3S$ $[M+Na]^+$: 335.0228, obs. 335.0221.



171 **166**

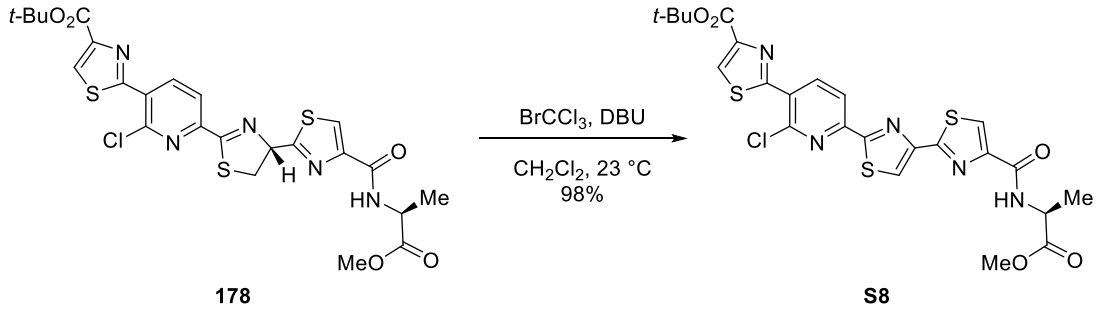
To a stirred solution of **171** (6.3 g, 20.1 mmol, 1.0 equiv.) in MeCN (134 mL, 0.15 M) was added neat diethylcarbamoyl chloride (7.66 mL, 60.4 mmol, 3.0 equiv.) and neat trimethylsilyl cyanide (8.19 mL, 60.4 mmol, 3.0 equiv.). The dark homogeneous reaction was heated to reflux for 15 hours. The crude reaction was cooled to 23 °C and 10% aq. K_2CO_3 (200 mL) was added. The solids were collected by filtration, washed with water (2 x 100 mL), and dried under vacuum at 50 °C to yield the nitrile **166** (4.92 g, 15.3 mmol, 76%) as brown solid (m.p. 151-154 °C).

R_f = 0.69 (silica gel, 2:1 hexanes:EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 9.01 (d, *J* = 8.0 Hz, 1H), 8.30 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 1.64 (s, 9H); **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 160.0, 159.6, 149.2, 148.7, 140.4, 133.0, 131.6, 129.4, 127.2, 115.6, 82.8, 28.2; **IR** (film, cm^{-1}): 2363, 1727; **HRMS** (ESI): calc. for $C_{14}H_{12}ClN_3O_2S$ $[M+Na]^+$: 344.0231, obs. 344.0227.



To a stirred solution of **166** (1.0 g, 3.11 mmol, 1.0 equiv.) in 3:3:1 CH_2Cl_2:MeOH:H_2O (31 mL, 0.1 M) was added **167** (1.44 g, 3.73 mmol, 1.2 equiv.), solid TCEP•HCl (223 mg, 0.78 mmol, 0.25 equiv.), and neat TEA (2.18 mL, 15.5 mmol, 5.0 equiv.). The reaction vessel was sparged with nitrogen for 10 minutes and sealed with a yellow cap. The homogeneous amber reaction was stirred at 50 °C for 12 hours. The reaction was diluted with EtOAc (100 mL) and washed with 1.0 M HCl (2 x 50 mL), water (1 x 50 mL), brine (1 x 25 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the thiazoline **178** (1.74 g, 2.93 mmol, 94%) as an amber oil. The product was used without further purification. An analytical sample was obtained with silica gel column chromatography using 5:1 to 1:1 hexanes:EtOAc.

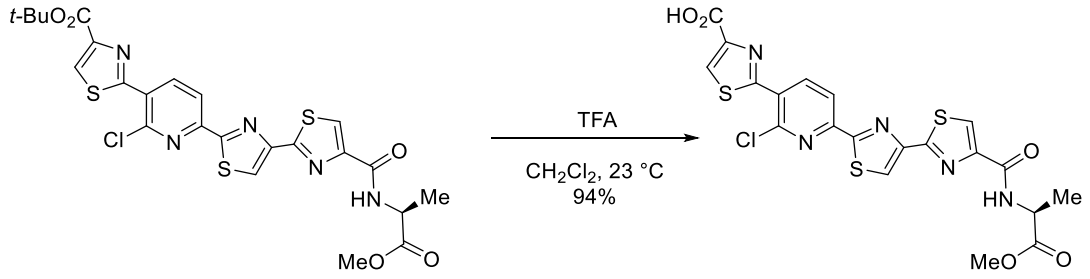
R_f = 0.52 (silica gel, 1:1 hexanes:EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$,): δ 8.91 (d, *J* = 8.1 Hz, 1H), 8.22 (s, 1H), 8.19 (dt, *J* = 2.4, 8.6 Hz, 1H), 8.05 (s, 1H), 7.75 (t, *J* = 7.0 Hz, 1H), 6.06 (dd, *J* = 6.0, 11.8 Hz, 1H), 4.75 (m, 1H), 3.92 (ddd, *J* = 1.6, 7.4, 11.1 Hz, 1H), 3.74 (m, 4H), 1.60 (s, 9H), 1.51 (dd, *J* = 1.9, 7.2 Hz, 3H); **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 173.1, 172.1, 172.0, 160.8, 160.3, 160.1, 150.6, 149.5, 148.7, 147.1, 140.2, 128.7, 124.0, 120.6, 82.4, 78.2, 52.4, 47.9, 42.8, 37.8, 28.0, 18.4; **IR** (film, cm^{-1}): 3123, 2348, 1726, 1656; **HRMS** (ESI): calc. for $C_{24}H_{24}ClN_5O_5S_3$ $[M+Na]^+$: 616.0520, obs. 616.0517.



178 **S8**

To a stirred solution of **178** (1.74 g, 2.93 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL, 0.1 M) was added neat bromotrichloromethane (0.346 mL, 3.5 mmol, 1.2 equiv.). The reaction vessel was cooled in an ice water bath before neat DBU (0.535 mL, 3.5 mmol, 1.2 equiv.) was added dropwise. The pale yellow reaction was warmed to 23 °C and stirred for 30 minutes. The reaction was diluted with 1.0 M HCl (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with water (1 x 50 mL), brine (1 x 50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude solid was triturated with MTBE (100 mL) to give **S8** (1.69 g, 2.87 mmol, 98%) as a yellow solid. (m.p. > 200 °C (decomp.))

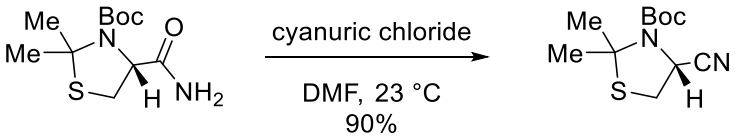
R_f = 0.64 (silica gel, 1:1 hexanes:EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 8.96 (dd, *J* = 1.3, 8.2 Hz, 1H), 8.31 (dd, *J* = 3.8, 4.4 Hz, 1H), 8.24 (s, 1H), 8.21 (d, *J* = 1.6 hz, 1H), 8.17 (s, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 4.83 (p, *J* = 7.3 Hz, 1H), 3.80 (s, 3H), 1.64 (s, 9H), 1.57 (d, *J* = 7.2 Hz, 1H); **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 173.2, 167.0, 162.2, 161.1, 160.4, 160.2, 150.8, 150.3, 150.2, 148.7, 147.5, 140.8, 129.0, 128.5, 124.3, 120.4, 118.7, 82.5, 52.5, 48.0, 28.2, 18.5 ; **IR** (film, cm^{-1}): 3123, 2982, 1744, 1723, 1681; **HRMS** (ESI): calc. for $C_{24}H_{22}ClN_5O_5S_3$ $[M+Na]^+$: 614.0360, obs. 614.0364.



S8 **165**

Solid **S8** (1.69 g, 2.85 mmol, 1.0 equiv.) was added to a stirred solution of 3:1 CH_2Cl_2:TFA (28.5 mL, 0.1 M). The pale yellow homogeneous reaction was stirred at 23 °C for 12 hours. The reaction was concentrated *in vacuo* to give a yellow solid. The crude solid was triturated with MTBE (100 mL) to give **165** (1.44 g, 2.68 mmol, 94%) as a dark yellow solid. (m.p. > 200 °C (decomp.))

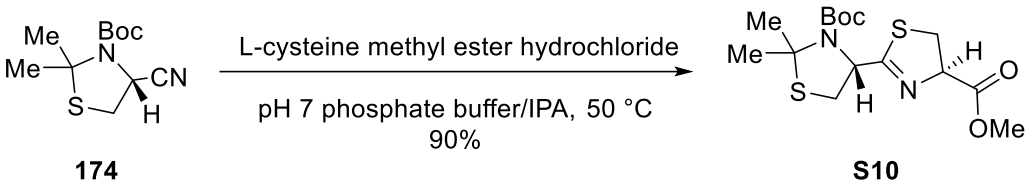
^{1}H-NMR (600 MHz, $(CD_3)_2SO$): δ 8.86 (d, J = 8.1 Hz, 1H), 8.74 (s, 1H), 8.71 (d, J = 7.3 Hz, 1H), 8.59 (s, 1H), 8.40 (s, 1H), 8.36 (d, J = 8.1 Hz, 1H), 4.56 (m, 1H), 3.68 (s, 3H), 1.46 (d, J = 7.1 Hz, 3H); **^{13}C-NMR** (150 MHz, $(CD_3)_2SO$): δ 172.7, 166.4, 161.8, 161.3, 160.2, 160.0, 150.1, 149.9, 149.4, 147.5, 146.6, 140.9, 130.9, 128.5, 125.2, 122.0, 119.0, 52.1, 47.8, 17.0; **HRMS** (ESI): calc. for $C_{20}H_{14}ClN_5O_5S_3$ $[M+Na]^+$: 557.9738, obs. 557.9734.



S9 **174**

To a stirred solution of **S9**[202] (25 g, 96.0 mmol, 1.0 equiv.) in DMF (96 mL, 1.0 M) was added solid cyanuric chloride (8.85 g, 48.0 mmol, 0.5 equiv.). The pale brown homogeneous reaction was stirred at 23 °C for 30 minutes. Ice water (500 mL) was added and the solids were collect by filtration. The filter cake was washed with water (2 x 50 mL) and dried *in vacuo* to yield the nitrile **174** (20.7 g, 85.0 mmol, 90%) as a white solid (m.p. 80-83 °C). An analytical sample was obtained with silica gel column chromatography using 5:1 to 2:1 hexanes:EtOAc.

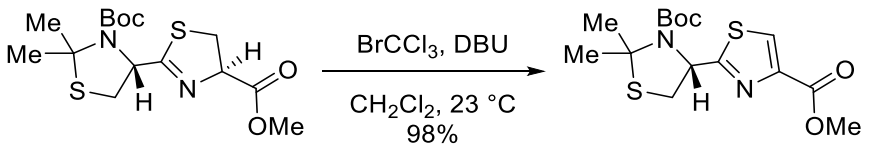
R_f = 0.69 (silica gel, 2:1 hexanes:EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 5.13 (bs, 1H), 3.28 (dd, *J* = 5.9, 12.3 Hz, 1H), 3.05 (d, *J* = 12.3 Hz, 1H), 1.82 (bs, 3H), 1.73 (bs, 3H), 1.48 (s, 9H); **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 150.7, 118.1, 82.3, 54.3, 31.2, 30.0, 29.0, 28.2; **IR** (film, cm^{-1}): 3132, 2980, 2936, 2360, 1705; **HRMS** (ESI): calc. for $C_{11}H_{18}N2O_2S$ $[M+Na]^+$: 265.0981, obs. 265.0983.



174 **S10**

To a stirred solution of **174** (10 g, 41.3 mmol, 1.0 equiv.) in 1.5:1 IPA:0.1 M pH 7 phosphate buffer (200 mL, 0.2 M) was added solid L-cysteine methyl ester hydrochloride (8.50 g, 49.5 mmol, 1.2 equiv.). The reaction vessel was sparged with nitrogen for 10 minutes and sealed with a yellow cap. The clear homogeneous reaction was stirred at 50 °C for 15 hours. The reaction was concentrated to remove IPA and the aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with 1.0 M HCl (2 x 100 mL), water (1 x 100 mL), brined (1 x 50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the thiazoline **S10** (13.4 g, 37.1 mmol, 90%) as a clear oil that solidified upon standing. The crude material was used without further purification. An analytical sample was obtained with silica gel column chromatography using 5:1 to 1:1 hexanes:EtOAc.

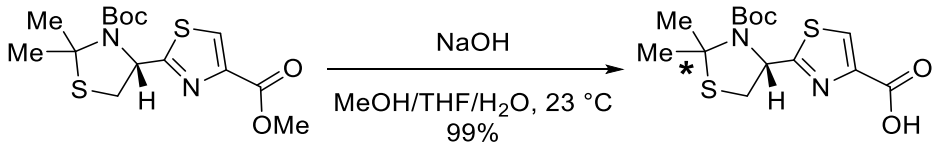
R_f = 0.50 (silica gel, 1:1 hexanes:EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 5.13 (m, 2H), 3.81 (s, 3H), 3.57 (d, *J* = 10.1 Hz, 1H), 3.53 (*J* = 9.7 Hz, 1H), 3.37 (bs, 1H), 3.09 (bs, 1H), 1.94 (bs, 3H), 1.77 (s, 3H), 1.42 (bs, 9H); **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 179.4, 170.7, 151.5, 80.7, 78.3, 65.3, 52.4, 34.8, 32.6, 28.7, 28.0, 27.6; **IR** (film, cm^{-1}): 3134, 2978, 1745, 1702; **HRMS** (ESI): calc. for $C_{15}H_{24}N_2O_4S_2$ $[M+Na]^+$: 383.1070, obs. 383.1071.



S11 **S12**

To a stirred solution of **S11** (13.4 g, 37.2 mmol, 1.0 equiv.) in CH_2Cl_2 (372 mL, 0.1 M) was added neat bromotrichloromethane (4.40 mL, 44.6 mmol, 1.2 equiv.). The reaction vessel was cooled in an ice water bath before neat DBU (6.66 mL, 44.6 mmol, 1.2 equiv.) was added dropwise. The pale yellow reaction was warmed to 23 °C and stirred for 30 minutes. The reaction was diluted with 1.0 M HCl (200 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 200 mL). The combined organic layers were washed with water (1 x 100 mL), brine (1 x 100 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the thiazole **S12** (13.1 g, 36.5 mmol, 98%) as an off white solid (m.p. 122-126 °C) which was used without further purification. An analytical sample was obtained with silica gel column chromatography using 5:1 to 1:1 hexanes:EtOAc.

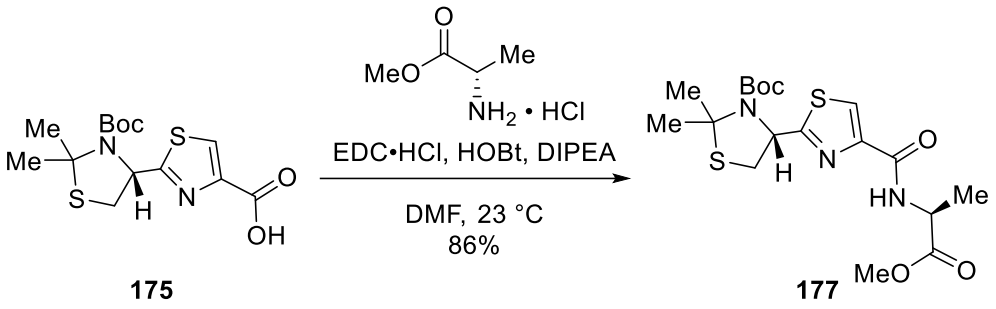
R_f = 0.61 (silica gel, 1:1 hexanes:EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 8.10 (s, 1H), 5.66 (m, 1H), 3.92 (s, 3H), 3.51 (dd, *J* = 6.5, 12.4 Hz, 1H), 3.15 (m, 1H), 1.94 (m, 3H), 1.78 (s, 3H), 1.37 (m, 9H); **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 175.9, 161.8, 151.6, 146.3, 127.4, 81.1, 72.1, 65.3, 52.4, 34.2, 28.6, 28.1, 27.9; **IR** (film, cm^{-1}): 3124, 2977, 1739, 1701; **HRMS** (ESI): calc. for $C_{15}H_{22}N_2O_4S_2$ $[M+Na]^+$: 381.0913, obs. 381.0916.



S12 **175**

To a stirred solution of **S12** (13.1 g, 36.5 mmol, 1.0 equiv.) in a 3:1 solution of THF:MeOH (180 mL, 0.2 M) was added 10% aq. NaOH (36.5 mL, 91.0 mmol, 2.5 equiv.). The clear homogeneous reaction was stirred at 23 °C for 1 hour. The reaction was diluted with 1.0 M HCl (200 mL) and the aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (1 x 50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the acid **175** (12.5 g, 36.2 mmol, 99%) as a white solid (m.p. > 200 °C) which was used without purification.

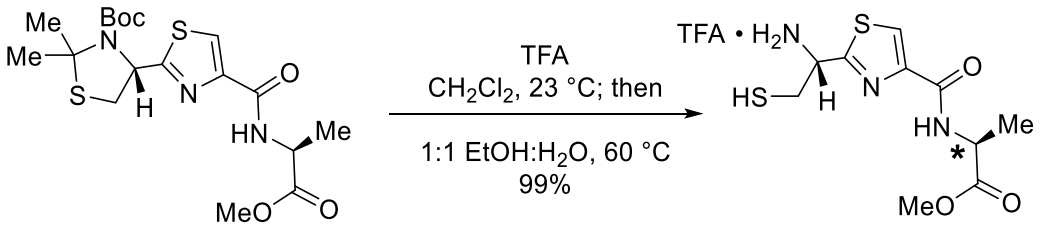
R_f = 0.54 (silica gel, 20:1 CH_2Cl_2:MeOH + 2% AcOH); **^{1}H-NMR** (600 MHz, $(CD_3)_2SO$): δ 8.31 (s, 1H), 5.58 (bs, 1H), 3.65 (dd, *J* = 6.4, 12.2 Hz, 1H), 3.09 (d, *J* = 12.4 Hz, 1H), 1.89 (bs, 3H), 1.76 (s, 3H), 1.34 (m, 9H); **^{13}C-NMR** (150 MHz, $(CD_3)_2SO$, ***** carbons were not observed): δ 174.5, 162.1, 151.1, 146.6, 128.5, 80.1, 71.4, 64.9, 33.4, 28.5, 27.8; **HRMS** (ESI): calc. for $C_{14}H_{20}N_2O_4S_2$ $[M+Na]^+$: 367.0762, obs. 367.0760.



175 **177**

To a stirred solution of **175** (3.0 g, 8.71 mmol, 1.0 equiv.) in DMF (17.4 mL, 0.5 M) was added neat DIPEA (4.55 mL, 26.1 mmol, 3.0 equiv.), solid HOBt (1.62 g, 9.58 mmol, 1.1 equiv.), solid EDC•HCl (1.84 g, 9.58 mmol, 1.1 equiv.), and solid alanine methyl ester hydrochloride (1.46 g, 10.5 mmol, 1.2 equiv.). The pale brown homogeneous reaction was stirred at 23 °C for 18 hours. The reaction was diluted with 1:1 MTBE:EtOAc (100 mL) and the organic layer was washed with 1.0 M HCl (1 x 50 mL), sat. aq. $NaHCO_3$ (1 x 50 mL), water (1 x 50 mL), brine (1 x 25 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give an amber oil. The crude material was purified via silica gel column chromatography using 5:1 to 1:1 hexanes:EtOAc to give the methyl ester **177** (3.22 g, 7.49 mmol, 86%) as a white foam.

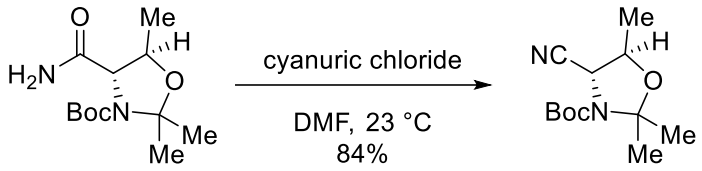
R_f = 0.61 (silica gel, 1:1 hexanes;EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 5.60 (m, 1H), 4.76 (p, *J* = 7.3 Hz, 1H), 3.77 (s, 3H), 3.52 (dd, *J* = 6.5, 12.3 Hz, 1H), 3.15 (bs, 1H), 1.93 (m, 3H), 1.82 (s, 3H), 1.51 (d, *J* = 7.2 Hz, 3H), 1.27 (s, 9H); **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 174.3, 172.7, 170.5, 160.2, 151.2, 123.2, 80.5, 71.6, 64.8, 52.0, 47.5, 33.5, 28.5, 27.8, 27.6, 17.9; **IR** (film, cm^{-1}): 3133, 1743, 1701, 1541; **HRMS** (ESI): calc. for $C_{18}H_{27}N_3O_5S_2$ $[M+Na]^+$: 452.1284, obs. 452.1285.



177 **167**

177 (2.0 g, 4.66 mmol, 1.0 equiv.) was added to a stirred solution of 3:1 CH_2Cl_2:TFA (23 mL, 0.2 M) and the pale yellow homogeneous reaction was stirred at 23 °C for 1 hour. The reaction was concentrated *in vacuo* to give a clear residue. The residue was dissolved in 1:1 EtOH:H_2O (5 mL) and concentrated *in vacuo* at 60 °C. This solvation and concentration process was repeated twice more to give the amino thiol **167** (1.78 g, 4.61 mmol, 99%) as a clear oil.

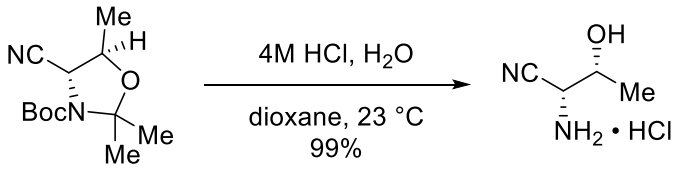
^{1}H-NMR (600 MHz, MeOD): δ 8.39 (s, 1H), 4.98 (t, *J* = 6.3 Hz, 1H), 4.69 (p, *J* = 7.2 Hz, 1H), 3.77 (s, 3H), 3.24 (m, 1H), 3.18 (m, 1H), 1.53 (d, *J* = 7.3 Hz, 3H); **^{13}C-NMR** (150 MHz, MeOD, ***** carbon overlaps with solvent): δ 174.3, 165.7, 162.3, 150.1, 127.5, 55.2, 23.0, 49.6, 28.5, 17.7; **IR** (film, cm^{-1}): 3121, 1739, 1671, 1551; **HRMS** (ESI): calc. for $C_{12}H_{15}F_3N_3O_4S_2$ $[M\text{-}TFA+Na]^+$: 312.0447, obs. 312.0448.



S13 **152**

To a stirred solution of **S13**[203] (51.4 g, 199 mmol, 1.0 equiv.) in DMF (200 mL, 1.0 M) was added solid cyanuric chloride (18.35 g, 99 mmol, 0.5 equiv.). The pale brown homogeneous reaction was stirred at 23 °C for 30 minutes. Ice water (1 L) was added and the solids were collect by filtration. The filter cake was washed with water (2 x 100 mL) and dried *in vacuo* to yield the nitrile **152** (40 g, 166 mmol, 84%) as a white solid (m.p. 41-43 °C).

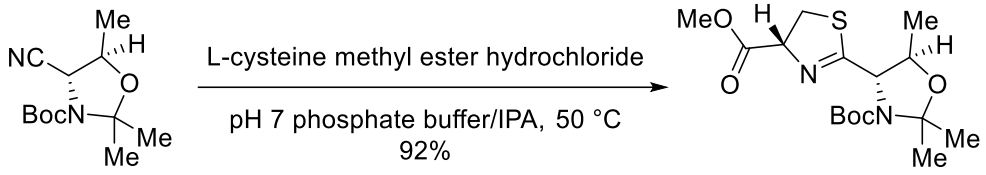
R_f = 0.70 (silica gel, 3:1 hexanes:EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 4.40 (p, *J* = 6.2 Hz, 1H), 3.99 (m, 1H), 1.59 (bs, 3H), 1.52 (bs, 4H), 1.48 (s, 9H), 1.40 (d, *J* = 6.1 Hz, 3H); **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 150.4, 117.1, 95.7, 82.0, 74.1, 52.9, 28.1, 26.4, 24.4, 18.2; **IR** (film, cm^{-1}): 2358, 1715; **HRMS** (ESI): calc. for $C_{12}H_{20}N_2O_3$ $[M+Na]^+$: 263.1366, obs. 263.1366.



152 **157**

Solid **152** (1.0 g, 4.16 mmol, 1.0 equiv.) was added to a stirred solution of 4.0 M HCl in dioxane (5.2 mL, 20.8 mmol, 5.0 equiv.) and water (0.38 mL, 20.8 mmol, 5.0 equiv.) and the clear homogeneous reaction was stirred 23 °C for 2 hours. The reaction was diluted with PhMe (25 mL) and concentrated *in vacuo*. The residue was redissolved in PhMe (25 mL) and concentrated *in vacuo.* This solvation and concentration process was repeated two more times to give the free amine **157** (560 mg, 4.10 mmol, 99%) as a clear wax which was used without further purification.

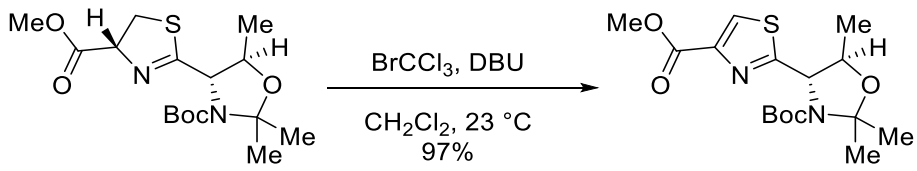
R_f = 0.38 (silica gel, 20:1 CH_2Cl_2:MeOH + 2% TEA); **^{1}H-NMR** (600 MHz, $(CD_3)_2SO$) δ 9.37 (bs, 1H), 4.38 (d, *J* = 6.2 Hz, 1H), 4.06 (p, *J* = 6.5 Hz, 1H), 1.20 (d, *J* = 6.5 Hz, 3H); **^{13}C-NMR** (150 MHz, $(CD_3)_2SO$): δ 115.7, 64.8, 46.6, 19.2; **HRMS** (ESI): calc. for $C_4H_8N_2O$ $[M+H]^+$: 101.0709, obs. 101.0709.



152 **S14**

To a stirred solution of **152** (20 g, 83 mmol, 1.0 equiv.) in 1.5:1 IPA:0.1 M pH 7 phosphate buffer (413 mL, 0.2 M) was added solid L-cysteine methyl ester hydrochloride (21.3 g, 124 mmol, 1.5 equiv.). The reaction vessel was sparged with nitrogen for 10 minutes and sealed with a yellow cap. The clear homogeneous reaction was stirred at 50 °C for 15 hours. The reaction was concentrated to remove IPA and the aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with 1.0 M HCl (2 x 100 mL), water (1 x 100 mL), brined (1 x 100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the thiazoline **S14** (27.4 g, 76 mmol, 92%) as a clear oil that solidifies upon standing. The crude material was used without further purification. An analytical sample was obtained with silica gel column chromatography using 5:1 to 1:1 hexanes:EtOAc.

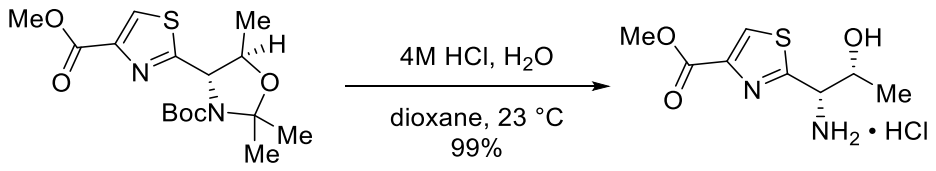
R_f = 0.53 (silica gel, 1:1 hexanes:EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 5.01 (t, *J* = 9.3 Hz, 1H), 4.16 (d, *J* = 8.1 Hz, 1H), 4.04 – 3.96 (m, 1H), 3.69 (s, 3H), 3.54 (t, *J* = 10.1 Hz, 1H), 3.42 (t, *J* = 10.5 Hz, 1H), 1.53 (s, 3H), 1.49 (s, 3H), 1.29 (s, 9H), 1.27 (d, *J* = 6.0 Hz, 3H); **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 175.9, 170.4, 151.1, 94.9, 80.4, 78.4, 74.1, 65.8, 52.5, 33.8, 27.9, 26.2, 25.1, 17.8; **IR** (film, cm^{-1}): 1745, 1707; **HRMS** (ESI): calc. for $C_{16}H_{26}N_2O_5S$ $[M+Na]^+$: 381.1455, obs. 381.1452.



S14 **154**

To a stirred solution of **S14** (27.4 g, 76 mmol, 1.0 equiv.) in CH_2Cl_2 (255 mL, 0.3 M) was added neat bromotrichloromethane (11.3 mL, 115 mmol, 1.5 equiv.). The reaction vessel was cooled in an ice water bath before neat DBU (17.1 mL, 115 mmol, 1.2 equiv.) was added dropwise. The pale yellow reaction was warmed to 23 °C and stirred for 30 minutes. The reaction was diluted with 1.0 M HCl (200 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 150 mL). The combined organic layers were washed with water (1 x 100 mL), brine (1 x 100 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the thiazole **154** (26.4 g, 74.1 mmol, 97%) as an off white solid (m.p. 120-123 °C) which was used without further purification. An analytical sample was obtained with silica gel column chromatography using 5:1 to 1:1 hexanes:EtOAc.

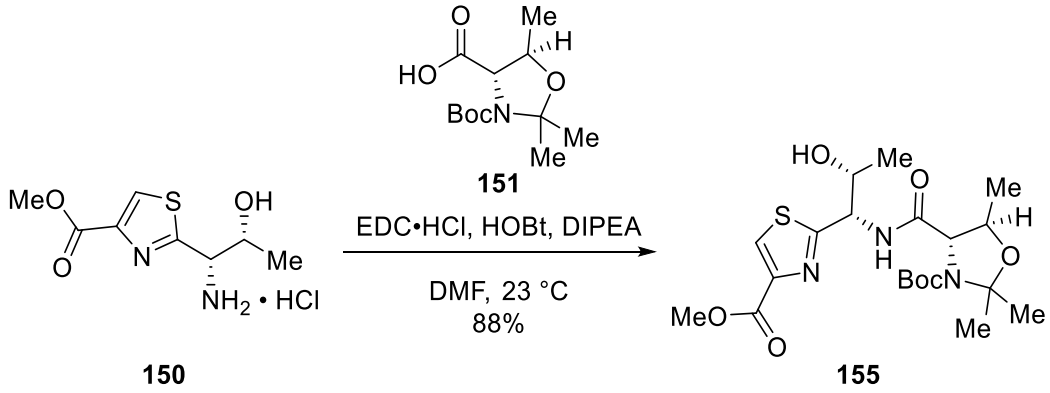
R_f = 0.63 (silica gel, 1:1 hexanes:EtOAc); **^{1}H-NMR** (600 MHz, , $CDCl_3$): δ 8.17 (bs, 1H), 4.78 (m, 1H), 4.16 (m, 1H), 3.94 (s, 3H), 1.69 (bs, 6H), 1.42 (bs, 9H), 1.18 (bs, 3H); **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 173.3, 161.3, 151.0, 146.1, 127.3, 95.0, 80.4, 77.6, 65.7, 52.1, 27.8, 26.2, 25.6, 17.6; **IR** (film, cm^{-1}): 1705; **HRMS** (ESI): calc. for $C_{16}H_{24}N_2O_5S$ $[M+Na]^+$: 379.1298, obs. 379.1295.



154 **150**

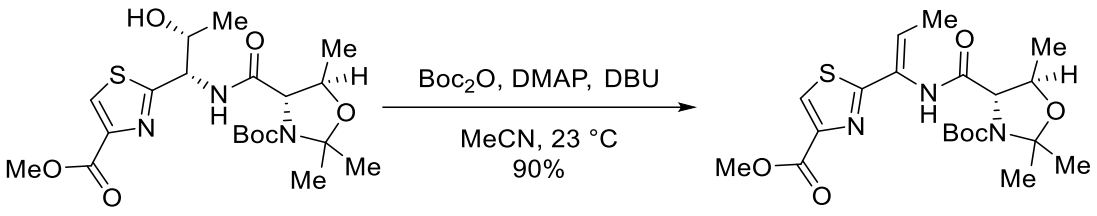
Solid **154** (26.4 g, 74.1 mmol, 1.0 equiv.) was added to a stirred solution of 4.0 M HCl in dioxane (93 mL, 370 mmol, 5.0 equiv.) and water (5.9 mL, 370 mmol, 5.0 equiv.) and the pale yellow homogeneous reaction was stirred at 23 °C for 2 hours. The reaction was diluted with PhMe (100 mL) and concentrated *in vacuo*. The residue was redissolved in PhMe (100 mL) and concentrated *in vacuo* . The residue was azeotroped with PhMe two more times to give the free amine **150** (18.5 g, 73.3 mmol, 99%) as a white solid which was used without further purification.

R_f = 0.34 (silica gel, 20:1 CH_2Cl_2:MeOH + 2% TEA); **^{1}H-NMR** (600 MHz, MeOD): δ 8.54 (s, 1H), 4.88 (s, 1H), 4.76 (d, *J* = 6.6 Hz, 1H), 4.32 – 4.26 (m, 1H), 3.92 (s, 3H), 1.23 (d, *J* = 6.4 Hz, 3H); **^{13}C-NMR** (150 MHz, MeOD): δ 165.2, 162.9, 147.3, 131.7, 68.5, 58.8, 53.0, 19.9; **IR** (film, cm^{-1}): 3408, 3124, 1724; **HRMS** (ESI): calc. for $C_8H_{13}ClN_2O_3S$ $[M+Na]^+$: 239.0461, obs. 239.0463.



To a stirred solution of **150** (18.5 g, 73.2 mmol, 1.0 equiv.) in DMF (146 mL, 0.5 M) was added neat DIPEA (38.3 mL, 220 mmol, 3.0 equiv.) solid HOBt (13.6 g, 81 mmol, 1.1 equiv.), solid EDC•HCl (15.4 g, 8 mmol, 1.1 equiv.), and the solid acid **151**[203] (19.9 g, 77 mmol, 1.05 equiv.). The pale brown homogeneous reaction was stirred at 23 °C for 18 hours. The reaction was diluted with 1:1 MTBE:EtOAc (300 mL) and the organic layer was washed with 1.0 M HCl (1 x 150 mL), sat. aq. $NaHCO_3$ (1 x 150 mL), water (1 x 150 mL), brine (1 x 50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give an amber oil. The crude material was purified via silica gel column chromatography using 1:1 to 1:2 hexanes:EtOAc to give the methyl ester **155** (29.5 g, 64.4 mmol, 88%) as a white foam.

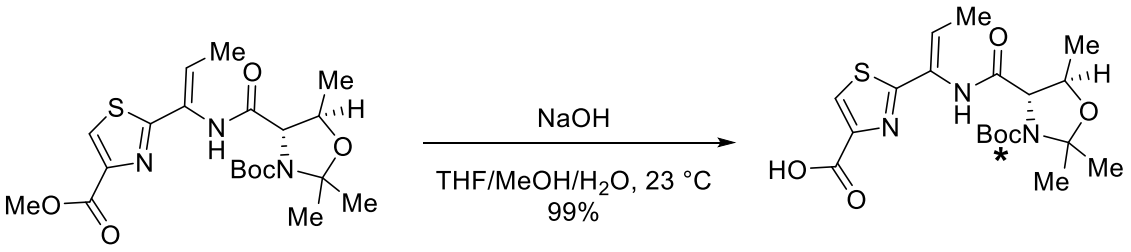
R_f = 0.30 (silica gel, 1:2 hexanes:EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.98 (s, 1H), 5.15 (bs, 1H), 4.44 (m, 1H), 4.13 (bs, 1H), 3.82 (d, J = 7.4 Hz, 1H), 3.76 (s, 3H), 1.48 (s, 3H), 1.46 (s, 3H), 1.26 (bs, 9H), 1.15 (d, J = 6.5, 3H); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 171.1, 170.1, 161.2, 151.9, 145.9, 127.6, 94.5, 80.7, 73.7, 68.7, 67.1, 55.8, 52.0, 28.0, 27.4, 25.1, 19.3, 18.7; **IR** (film, cm^{-1}): 3125, 1691; **HRMS** (ESI): calc. for $C_{20}H_{31}N_3O_7S$ $[M+Na]^+$: 480.1775, obs. 480.1778.



155 **156**

To a stirred solution of **155** (20.6 g, 45.0 mmol, 1.0 equiv.) in MeCN (150 mL, 0.3 M) was added solid DMAP (0.55 g, 4.5 mmol, 0.1 equiv.) and solid di-*tert*-butyldicarbonate (11.8 g, 54 mmol, 1.2 equiv.). The clear homogeneous reaction was stirred at 23 °C for 1 hour. Neat DBU (33.9 mL, 225 mmol, 5.0 equiv.) was added in a single portion and the clear homogeneous reaction was stirred at 23 °C for 12 hours. The reaction was diluted with EtOAc (250 mL) and the organic layer was washed with 1.0 M HCl (2 x 100 mL), water (1 x 100 mL), brine (1 x 50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a white foam. The crude material was purified via silica gel column chromatography using 1:1 to 1:2 hexanes:EtOAc to give the olefin **156** (17.8 g, 40.5 mmol, 90%) as a white foam.

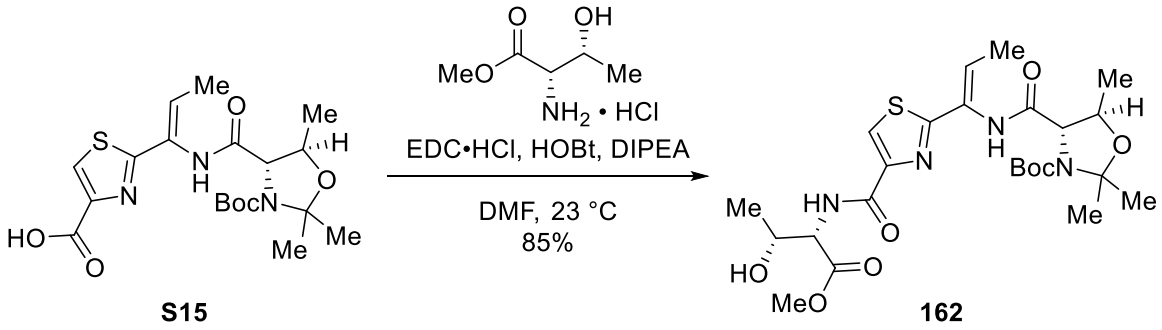
R_f = 0.31 (silica gel, 1:1 hexanes:EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.96 (bs, 1H), 6.54 (bs, 1H), 4.32 (bs, 1H), 3.97 (d, *J* = 7.7 Hz, 1H), 3.85 (s, 3H), 1.82 (d, *J* = 6.6 Hz, 3H), 1.61 (bs, 6H), 1.44 (d, *J* = 6.1 Hz, 3H), 1.40 (s, 9H); **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 168.4, 167.3, 161.7, 152.3, 146.7, 127.9, 127.1, 95.1, 81.1, 74.2, 67.8, 52.3, 28.3, 27.7, 25.5, 19.0, 14.4; **IR** (film, cm^{-1}): 3125, 2982, 2250, 1693; **HRMS** (ESI): calc. for $C_{20}H_{29}N_3O_6S$ $[M+Na]^+$: 462.1669, obs. 462.1665.



156 **S15**

To a stirred solution of **156** (10 g, 22.8 mmol, 1.0 equiv.) in 3:1 THF:MeOH (114 mL, 0.2 M) was added 10% NaOH (22.8 mL, 57.0 mmol, 2.5 equiv.). The clear homogeneous reaction was stirred at 23 °C for 30 minutes. The reaction was diluted with 1.0 M HCl (100 mL) and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (1 x 50 mL), dried over Na_2SO_4, and concentrated in vacuo to give the acid **S15** (9.58 g, 22.5 mmol, 99%) as a clear oil which was used without further purification.

R_f = 0.31 (silica gel, 20:1 CH_2Cl_2:MeOH + 2% AcOH); **^{1}H-NMR** (600 MHz, $(CD_3)_2SO$, 323 K): δ 9.71 (s, 1H), 8.30 (s, 1H), 6.63-6.49 (m, 1H), 4.15-4.04 (m, 2H), 1.78 (d, *J* = 7.1 Hz, 3H), 1.54 (s, 3H), 1.49-1.36 (m, 15H); **^{13}C-NMR** (150 MHz, $(CD_3)_2SO$, 323 K, asterisked carbons were not observed): δ 168.7, 167.7, 162.3, 148.9, 129.2, 128.0, 126.1, 94.1, 74.2, 66.7, 28.3, 27.5, 25.0, 19.5, 13.7; **IR** (film, cm^{-1}): 3132, 1696; **HRMS** (ESI): calc. for $C_{19}H_{27}N_3O_6S$ $[M+Na]^+$: 448.1513, obs. 448.1511.

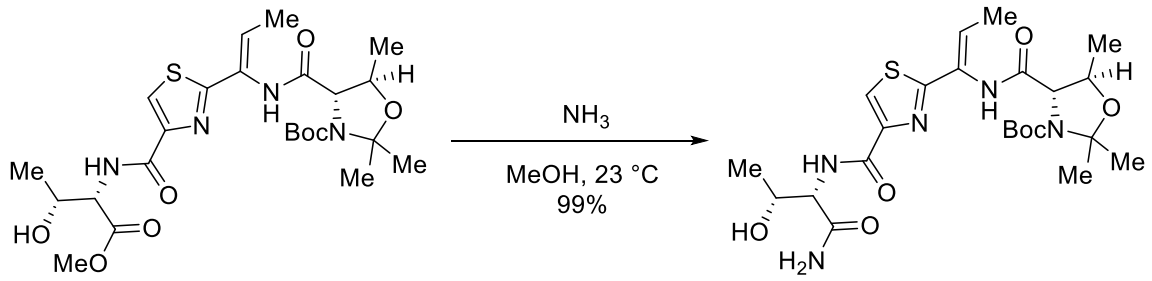


S15 **162**

To a stirred solution of **S15** (9.58 g, 22.5 mmol, 1.0 equiv.) in DMF (45.0 mL, 0.5 M) was added neat DIPEA (11.8 mL, 67.5 mmol, 3.0 equiv.) solid HOBt (4.18 g, 24.8 mmol, 1.1 equiv.), solid EDC•HCl (4.75 g, 24.8 mmol, 1.1 equiv.), and neat threonine methyl ester hydrochloride (4.20 g, 24.8 mmol, 1.1 equiv.). The pale brown homogeneous reaction was stirred at 23 °C for 18 hours. The reaction was diluted with 1:1 MTBE:EtOAc (200 mL) and the organic layer was washed with 1.0 M HCl (1 x 00 mL), sat. aq. $NaHCO_3$ (1 x 100 mL), water (1 x 50 mL), brine (1 x 50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give an amber oil. The crude material was purified via silica gel column chromatography using 2:1 to 1:2 hexanes:EtOAc to give the methyl ester **162** (10.35 g, 19.1 mmol, 85%) as a white solid (m.p. >200 °C (decomp.)).

R_f = 0.23 (silica gel, 1:2 hexanes:EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.94 (s, 1H), 6.49 (bs, 1H), 4.60 (dd, *J* = 2.7, 8.9 Hz, 1H) 4.36 (bs, 1H), 4.29 (p, *J* = 6.2 Hz, 1H), 3.99 (d, *J* = 6.7 Hz, 1H), 3.68 (s, 3H), 3.63 (bs, 1H), 1.78 (d, *J* = 6.5 Hz, 3H), 1.56 (bs, 6H), 1.41 (d, *J* = 6.1 Hz, 3H), 1.38 (bs, 9H), 1.18 (d, *J* = 6.4 Hz, 3H); **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 170.9, 168.4, 166.7, 161.3, 152.1, 149.0, 128.1, 127.5, 123.5, 94.7, 81.1, 74.0, 67.6, 67.4, 57.7, 52.3, 28.1, 27.5, 25.4, 20.0, 19.1, 14.0; **IR** (film, cm^{-1}): 3400, 3175, 2982,

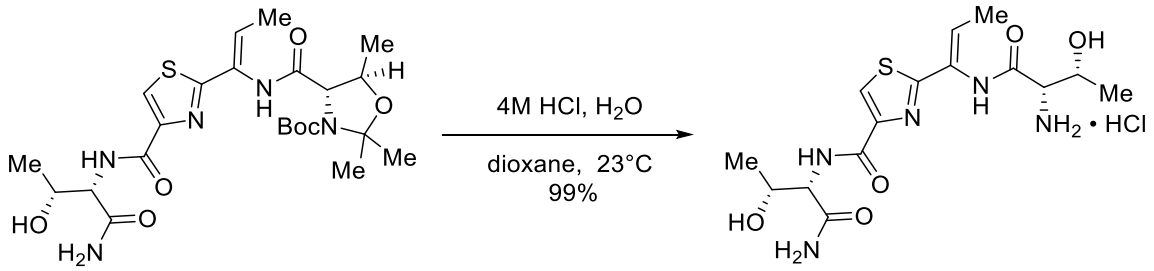
2250, 1747, 1678, 1542; **HRMS** (ESI): calc. for $C_{24}H_{36}N_4O_8S$ $[M+Na]^+$: 563.2146, obs. 563.2144.



162 **163**

Solid **162** (5.0 g, 9.25 mmol, 1.0 equiv.) was added to a stirred solution of 7 N ammonia in MeOH (66.1 mL, 462 mmol, 50.0 equiv.). The clear homogeneous reaction was stirred at 23 °C for 18 hours. The reaction was concentrated *in vacuo* to give the amide **163** (4.81 g, 9.16 mmol, 99%) as a white solid (m.p. 140 °C (decomp.)) which was used without further purification.

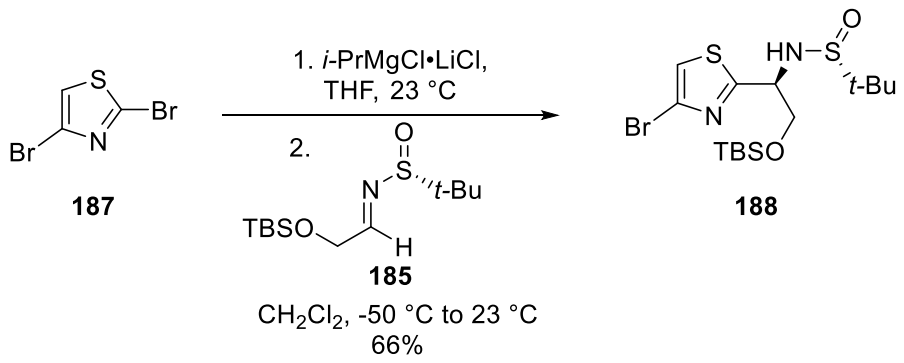
R_f = 0.41 (silica gel, 10:1 CH_2Cl_2:MeOH); **^{1}H-NMR** (600 MHz, MeOD): δ 8.13 (s, 1H), 6.86-6.60 (m, 1H), 4.47 (d, *J* = 3.1 Hz, 1H), 4.33 (bs, 1H), 4.26 (bs, 1H), 4.06 (bs, 1H), 4.05 (bs, 1H), 1.89 (d, *J* = 7.2 Hz, 3H), 1.60 (bs, 3H), 1.57-1.47 (m, 12H), 1.20 (d, *J* = 6.4 Hz, 3H); **^{13}C-NMR** (150 MHz, MeOD): δ 174.9, 168.9, 168.3, 163.2, 153.5, 150.6, 129.7, 128.0, 124.7, 95.7, 81.9, 75.4, 68.5, 68.3, 59.5, 28.6, 28.2, 25.4, 19.7, 19.2, 13.9; **IR** (film, cm^{-1}): 3173, 2981, 2936, 1671; **HRMS** (ESI): calc. for $C_{23}H_{35}N_5O_7S$ $[M+Na]^+$: 548.2149, obs. 548.2146.



163 **164**

163 (4.81 g, 9.15 mmol, 1.0 equiv.) was added to a stirred solution of 4.0 M HCl in dioxane (11.4 mL, 45.8 mmol, 5.0 equiv.) and water (0.73 mL, 45.8 mmol, 5.0 equiv.) and the pale yellow homogeneous reaction was stirred at 23 °C for 2 hours. The reaction was diluted with PhMe (10 mL) and concentrated *in vacuo*. The residue was redissolved in PhMe (10 mL) and concentrated *in vacuo.* The residue was azeotroped with PhMe two more times to give the free amine **164** (3.82 g, 9.06 mmol, 99%) as a white solid which was used without further purification.

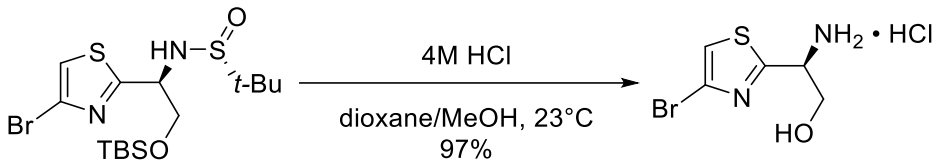
R_f = 0.11 (silica gel, 10:1 CH_2Cl_2:MeOH + 2% TEA); **^{1}H-NMR** (600 MHz, MeOD): δ 8.14 (s, 1H), 6.72 (m, 1H), 4.53 (d, *J* = 2.9 Hz, 1H), 4.33 (m, 2H), 3.94 (d, *J* = 5.1 Hz, 1H), 1.89 (d, *J* = 7.1 Hz, 3H), 1.48 (d, *J* = 6.4 Hz, 3H), 1.22 (d, *J* = 6.4 Hz, 3H); **^{13}C-NMR** (150 MHz, MeOD): δ 175.0, 168.1, 167.9, 163.1, 150.2, 130.0, 129.7, 124.9, 68.6, 67.5, 60.0, 59.4, 20.8, 20.4, 14.2; **IR** (film, cm^{-1}): 3155, 1658, 1545; **HRMS** (ESI): calc. for $C_{15}H_{24}ClN_5O_5S$ $[M+Na]^+$: 408.1312, obs. 408.1309.



To a stirred solution of **187**[204] (28.9 g, 119 mmol, 1.5 equiv.) in THF (50 mL) at 0 °C was added a 1.3 M solution of *i*-PrMgCl•LiCl in THF (98 mL, 127 mmol, 1.6 equiv.) dropwise over 10 minutes. The pale brown homogeneous reaction was warmed to 23 °C over 30 minutes. The resulting solution was added dropwise over 2 hours to a separate reaction vessel cooled to approximately –50 °C containing a solution of **185**[192] (22 g, 79 mmol, 1.0 equiv.) in CH_2Cl_2 (793 mL, 0.1 M). The pale brown homogeneous reaction was allowed to warm to 23 °C over 12 hours. The reaction was poured into brine (800 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 300 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give an amber oil. The crude material was purified via silica gel column chromatography using 10:1 to 3:1 hexanes:EtOAc to give the sulfinamide **188** (23.1 g, 52.3 mmol, 66%) as an amber oil.

R_f = 0.72 (silica gel, 1:1 hexanes:EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.16 (s, 1H), 4.83 – 4.77 (m, 1H), 4.66 (d, *J* = 6.4 Hz, 1H), 4.16 (dd, *J* = 9.8, 3.6 Hz, 1H), 4.08 (dd, *J* = 9.9, 3.5 Hz, 1H), 1.30 (s, 9H), 0.81 (s, 9H), 0.03 (s, 3H), -0.08 (s, 3H); **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 173.7, 125.0, 117.3, 66.0, 59.0, 56.3, 25.6, 22.5, 18.0, -5.5; **IR** (film, cm^{-}

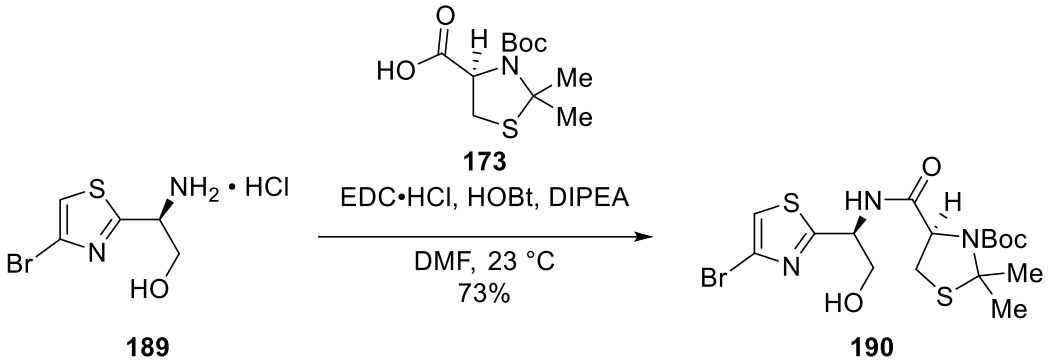
[1]): 3129, 2956, 2929, 2857, 1630; **HRMS** (ESI): calc. for $C_{15}H_{29}BrN_2O_2S_2Si$ $[M+Na]^+$: 463.0515, obs. 463.0512.



188 **189**

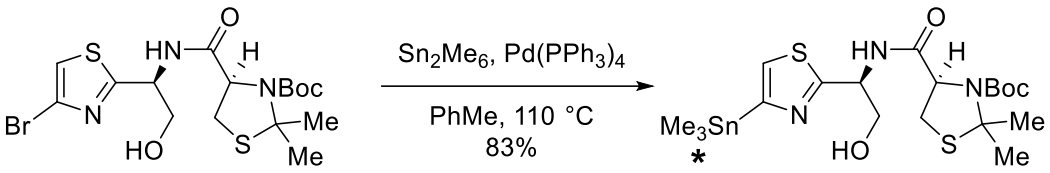
To a stirred solution of **188** (2.0 g, 4.53 mmol, 1.0 equiv.) in MeOH (6.47 mL, 0.7 M) was added a 4.0 M solution of HCl in dioxane (5.66 mL, 22.7 mmol, 5.0 equiv.). The pale yellow homogeneous reaction was stirred at 23 °C for 2 hours. The reaction was concentrated *in vacuo* to give a yellow oil. The crude material was triturated with ether (10 mL) to give **189** (1.14 g, 4.39 mmol, 97%) as a clear wax which was used without purification.

R_f = 0.39 (20:1 CH_2Cl_2:MeOH + 2% TEA); **^{1}H-NMR** (600 MHz, MeOD): δ 7.66 (s, 1H), 4.80 (under water peak, m, 1H), 4.00 (dd, *J* = 4.90, 11.6 Hz, 1H), 3.93 (dd, *J* = 6.2, 11.6 Hz, 1H); **^{13}C-NMR** (150 MHz, MeOD): δ 165.5, 125.8, 121.1, 63.2, 54.9; **IR** (film, cm^{-1}): 3123; **HRMS** (ESI): calc. for $C_5H_8BrClN_2OS$ $[M+H]^+$: 222.9535, obs. 222.9537.



To a stirred solution of **189** (1.14 g, 4.40 mmol, 1.0 equiv.) in DMF (8.78 mL, 0.5 M) was added neat DIPEA (2.29 mL, 13.2 mmol, 3.0 equiv.), solid HOBt (0.816 g, 4.83 mmol, 1.1 equiv.), solid EDC•HCl (0.926 g, 4.83 mmol, 1.1 equiv.), and the solid acid **173**[205] (1.38 g, 5.27 mmol, 1.2 equiv.). The pale brown homogeneous reaction was stirred at 23 °C for 18 hours. The reaction was diluted with 1:1 MTBE:EtOAc (100 mL) and the organic layer was washed with 1.0 M HCl (1 x 50 mL), sat. aq. $NaHCO_3$ (1 x 50 mL), water (1 x 50 mL), brine (1 x 25 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give an amber oil. The crude material was purified via silica gel column chromatography using 5:1 to 1:1 hexanes:EtOAc to give bromide **190** (1.49 g, 3.19 mmol, 73%) as a clear foam.

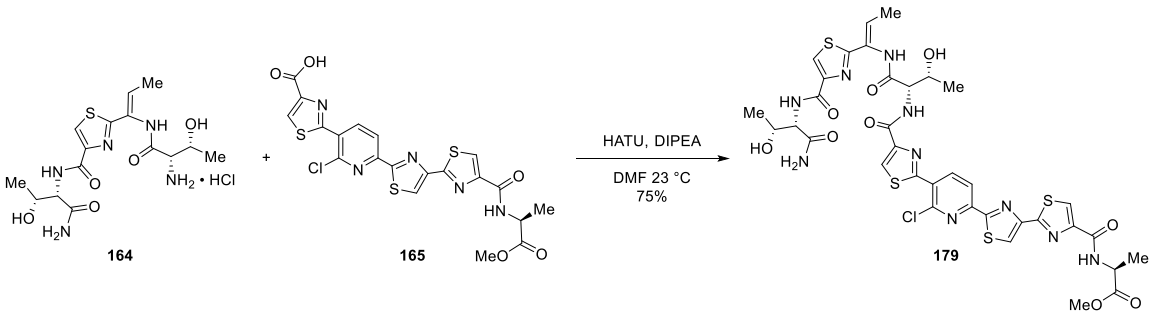
R_f = 0.52 (silica gel, 1:1 hexanes:EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.13 (s, 1H), 5.21 (dt, *J* = 3.6, 7.6 Hz, 1H), 4.73 (bs, 1H), 4.12 (d, *J* = 9.6 Hz, 1H), 3.81 (dd, *J* = 4.3, 11.2 Hz, 1H), 3.21 (dd, *J* = 6.9, 11.8 Hz, 1H), 1.82 (s, 3H), 1.70 (s, 3H), 1.38 (bs, 9H); **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 171.1, 170.1, 151.7, 124.2, 117.4, 81.5, 71.0, 67.1, 63.9, 52.6, 30.0, 29.2, 28.4, 28.2; **IR** (film, cm^{-1}): 3413, 3124, 2976, 2933, 2249, 1681; **HRMS** (ESI): calc. for $C_{16}H_{24}BrN_3O_4S_2$ $[M+Na]^+$: 488.0284, obs. 488.0280



190 **191**

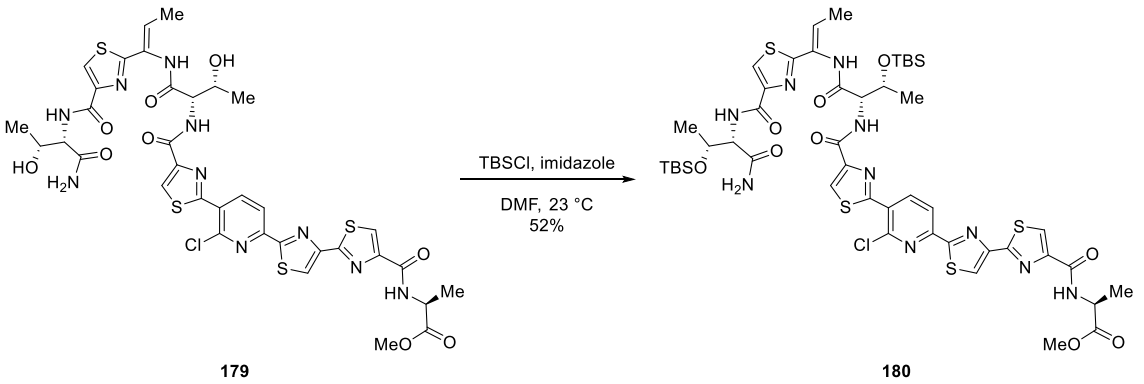
To a stirred solution of bromide **190** (1.0 g, 2.1 mmol, 1.0 equiv.) in PhMe (10.7 mL, 0.2 M) was added solid $Pd(PPh_3)_4$ (248 mg, 0.214 mmol, 0.1 equiv.) and neat hexamethyldistannane (0.889 mL, 4.29 mmol, 2.0 equiv.). The reaction vessel was sparged with nitrogen for 10 minutes and then sealed with a yellow cap. The pale yellow homogeneous reaction was stirred at 110 °C for 15 hours. The reaction was cooled to 23 °C and concentrated *in vacuo* to give a black oil. The crude material was purified directly with silica gel column chromatography using 100:1 hexanes:TEA to 5:1:0.1 hexanes:EtOAc:TEA to 1:1 hexanes:EtOAc to give the stannane **191** (979 mg, 1.78 mmol, 83%) as a clear foam.

R_f =0.50 (silica gel, 1:1 hexanes:EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.51 (bs, 1H), 7.33 (s, 1H), 5.38 (bs, 1H), 4.74 (bs, 1H), 4.23 (d, *J* = 9.4 Hz, 1H), 3.95 (dd, *J* = 3.6, 11.4 Hz, 1H), 3.27 (bs, 2H), 1.95 (bs, 3H), 1.79 (s, 3H), 1.22 (bs, 9H), 0.34 (s, 9H); **^{13}C-NMR** (150 MHz, $CDCl_3$, asterisked carbons were not observed): δ 170.8, 168.4, 159.0, 151.7, 126.0, 81.1, 72.0, 67.2, 65.4, 51.4, 30.8, 28.7, 28.4, 28.2; **IR** (film, cm^{-1}): 3135, 1676; **HRMS** (ESI): calc. for $C_{19}H_{33}N_3O_4S_2Sn$ $[M+H]^+$: 552.1004, obs. 552.1008.



To a stirred solution of acid **165** (1.0 g, 1.87 mmol, 1.0 equiv.) in DMF (9.3 mL, 0.2 M) was added the amine **164** (945 mg, 2.24 mmol, 1.2 equiv.), neat DIPEA (1.3 mL, 7.46 mmol, 4.0 equiv.), and solid HATU (780 mg, 2.05 mmol, 1.1 equiv.). The pale brown homogeneous reaction was stirred at 23 °C for 12 hours. Cold 1.0 M HCl (50 mL) was added and the solids were collected by filtration. The filter cake was washed with water (1 x 20 mL), MTBE (1 x 20 mL), and dried at 50 °C under vacuum to give **179** (1.26 g, 1.4 mmol, 75%) as a brown powder which was used without further purification. This compound was found to be soluble only in DMSO and DMF, so R_f, IR, and HRMS were not collected.

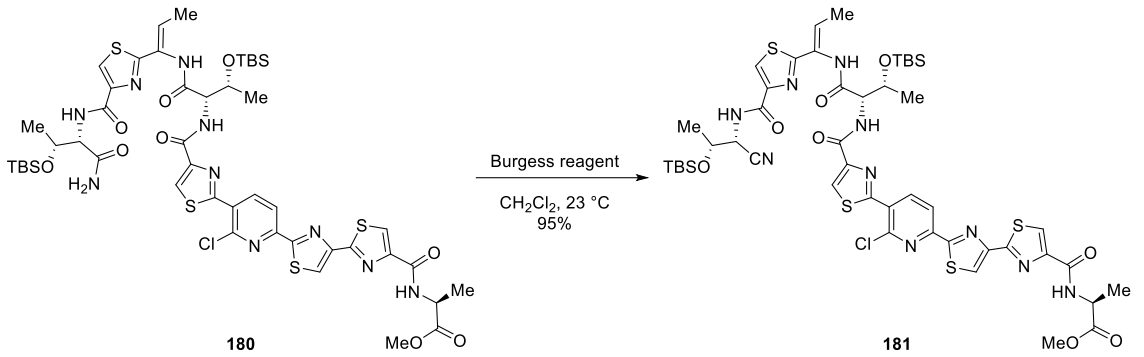
^{1}H-NMR (600 MHz, $(CD_3)_2SO$): δ 9.83 (s, 1H), 8.94 (d, *J* = 3.6 Hz, 1H), 8.73 (d, *J* = 4.1 Hz, 1H), 8.67 (s, 1H), 8.61 (s, 1H), 8.40 (m, 2H), 8.29 (d, *J* = 4.1 Hz, 1H), 8.20 (s, 1H), 7.47 (s, 1H), 7.15 (s, 1H), 6.69 (m, 1H), 4.57 (m, 2H), 4.31 (m, 2H), 4.13 (m, 1H), 3.65 (s, 1H), 1.78 (d, *J* = 5.2 Hz, 3H), 1.46 (d, *J* = 7.2 Hz, 3H), 1.26 (d, *J* = 6.2 Hz, 3H), 1.06 (d, *J* = 6.2 Hz, 3H); **^{13}C-NMR** (150 MHz, $(CD_3)_2SO$): δ 173.1, 172.1, 170.0, 167.9, 166.6, 161.5, 160.8, 160.6, 160.5, 160.4, 150.4, 150.1, 149.9, 149.8, 149.7, 147.0, 140.7, 129.0, 128.7, 127.1, 126.3, 125.1, 123.5, 121.8, 118.7, 66.8, 66.6, 58.6, 57.7, 51.9, 47.7, 20.8, 20.3, 16.9, 13.3.



179 180

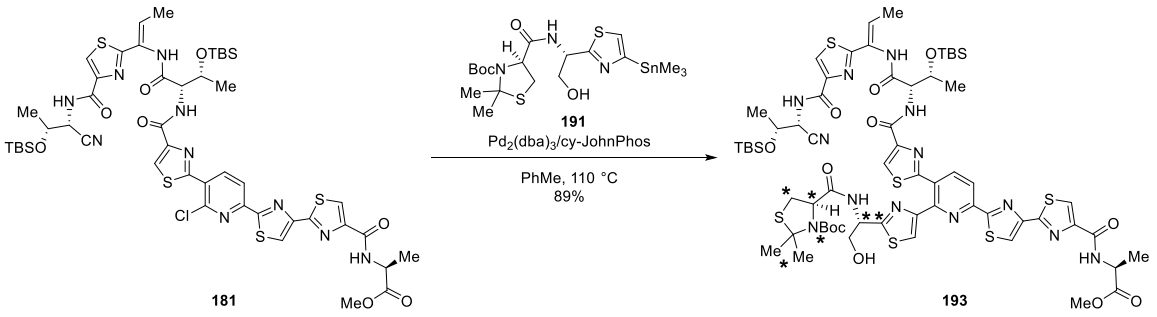
To a stirred solution of the diol **179** (495 mg, 0.548 mmol, 1.0 equiv.) in DMF (5 mL, 0.1 M) was added solid imidazole (112 mg, 1.64 mmol, 3.0 equiv.) and solid TBSCl (248 mg, 1.64 mmol, 3.0 equiv.) and the thick orange homogeneous reaction was stirred at 23 °C for 48 hours. The reaction was diluted with EtOAc (100 ml) and the organic layer was washed with water (3 x 50 mL), brine (20 mL), dried over Na_2SO_4 and concentrated to give a yellow oil. The crude material was purified via silica gel column chromatography using 1:1 hexanes:EtOAc to 50:1 CH_2Cl_2:MeOH to 20:1 CH_2Cl_2:MeOH to give the protected diol **180** (325 mg, 0.287 mmol, 52%) as a pale yellow glass.

R_f = 0.67 (silica gel, 20:1 CH_2Cl_2:MeOH); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 8.86 (d, *J* = 4.4 Hz, 1H), 8.45 (d, *J* = 6.3 Hz, 1H), 8.36 (s, 1H), 8.27 (d, *J* = 7.9 Hz, 1H), 8.23 (d, *J* = 7.0 Hz, 1H), 8.21 (s, 1H), 8.17 (s, 1H), 8.03 (s, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 6.81 (q, *J* = 7.1 Hz, 1H), 4.81 (m, 2H), 4.71 (m, 1H), 4.53 (m, 2H), 3.81 (s, 3H), 1.88 (d, *J* = 7.2 Hz, 3H), 1.57 (d, *J* = 7.2 Hz, 3H), 1.38 (d, *J* = 6.3 Hz, 3H), 1.16 (d, *J* = 6.3 Hz, 3H), 0.97 (s, 9H), 0.93 (s, 9H), 0.28 (s, 3H), 0.22 (s, 3H), 0.18 (s, 3H), 0.14 (s, 3H); **HRMS** (ESI): calc. for $C_{47}H_{63}ClN_{10}O_9S_4Si_2$ $[M+Na]^+$: 1153.2782, obs. 1153.2774.



To a stirred solution of amide **180** (75 mg, 0.066 mmol, 1.0 equiv.) in CH_2Cl_2 (1 mL, 0.07 M) was added Burgess reagent (4.7 mg, 0.199 mmol, 3.0 equiv.) and the pale yellow reaction was stirred at 23 °C for 12 hours. The reaction was concentrated *in vacuo* and the crude material was purified via silica gel column chromatography using CH_2Cl_2 to 20:1 CH_2Cl_2:MeOH to give the nitrile **181** (70 mg, 0.063 mmol, 95%) as a clear oil.

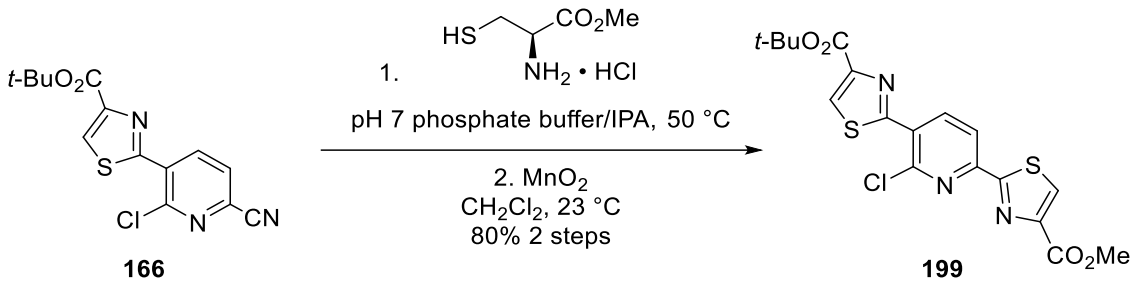
R_f = 033 (silica gel, 30:1 CH_2C_{l2}:MeOH); **^{1}H-NMR** (600 MHz, $(CD_3)_2SO$): δ 9.91 (s, 1H), 8.85 (d, *J* = 8.0 Hz, 1H), 8.73 (m, 1H), 8.70 (s, 1H), 8.63 (s, 1H), 8.42 (s, 1H), 8.33 (m, 1H), 8.24 (d, *J* = 8.9 Hz, 1H), 6.74 (q, *J* = 7 Hz, 1H), 4.95 (dd, *J* = 4.2, 9.6 Hz, 1H), 4.67 (dd, *J* = 3.5, 8.9 Hz, 1H), 4.58 (t, *J* = 7.3 Hz, 1H), 4.49 (m, 1H), 4.26 (m, 1H), 3.68 (s, 3H), 1.78 (d, *J* = 7.2 Hz, 3H), 1.47 (d, *J* = 7.2 Hz, 3H), 1.30 (d, *J* = 6.0 Hz, 3H), 1.24 (d, *J* = 6.3 Hz, 3H), 0.89 (s, 9H), 0.84 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); **^{13}C-NMR** (150 MHz, $(CD_3)_2SO$): δ173.0, 169.3, 167.7, 166.7, 160.84, 160.80, 160.48, 160.46, 160.45, 150.8, 150.5, 150.4, 149.8, 149.7, 148.6, 141.3, 127.98, 127.96, 127.7, 126.2, 125.8, 125.4, 122.7, 119.2, 118.3, 68.8, 68.0, 58.8, 52.3, 48.1, 47.0, 25.9, 25.8, 21.7, 20.4, 17.2, 13.9, -4.0, -4.5, -4.7, -4.8; **HRMS** (ESI): calc. for $C_{47}H_{61}ClN_{10}O_8S_4Si_2$ $[M+Na]^+$: 1135.2669, obs. 1135.2676.



To a stirred solution of chloride **181** (70 mg, 0.063 mmol, 1.0 equiv.) in PhMe (1.5 mL, 0.04 M) was added the stannane **191** (38 mg, 0.069 mmol, 1.1 equiv.), solid Cy-JohnPhos (4.4 mg, 0.013 mmol, 0.2 equiv.), and solid $Pd_2(dba)_3$ (1.8 mg, 3.14 μmol, 0.05 equiv.). The reaction vessel was sparged with nitrogen for 10 minutes and then sealed with a yellow cap. The dark purple homogeneous reaction was stirred at 110 °C for 18 hours. The reaction was cooled to 23 °C and concentrated *in vacuo* to give a brown oil. The crude material was purified via silica gel column chromatography using 50:1 CH_2Cl_2:MeOH to 20:1 CH_2Cl_2:MeOH to give **193** as a pale yellow glass (82 mg, 0.056 mmol, 89%).

R_f = 0.51 (silica gel, 20:1 CH_2Cl_2:MeOH); **^{1}H-NMR** (600 MHz, $CDCl_3$, ***** protons were not observed): δ 8.56 (bs, 1H), 8.36 (d, *J* = 8.1 Hz, 1H), 8.30 (d, *J* = 7.2 Hz, 1H), 8.25 (s, 1H), 8.22 (m, 2H), 8.19 (s, 1H), 8.06 (m, 2H), 8.00 (d, *J* = 9.1 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 6.80 (q, *J* = 7.1 Hz, 1H), 5.18 (m, 1H), 4.93 (dd, *J* = 2.6, 8.8 Hz, 1H), 4.84 (p, *J* = 7.3 Hz, 1H), 4.73 (m, 2H), 4.31 (m, 1H), 3.81 (s, 4H), 3.61 (bs, 1H), 1.86 (d, *J* = 7.2 Hz, 3H), 1.83 (bs, 3H), 1.75 (s, 3H), 1.58 (m, 3H), 1.28 (m, 15H), 0.95 (s, 9H), 0.90 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H), 0.17 (s, 3H), 0.13 (s, 3H); **^{13}C-NMR** (150 MHz, $CDCl_3$, ***** carbons were not observed): δ 173.2, 170.7, 169.1, 168.4, 167.1, 165.3, 162.1, 161.0, 160.5, 160.4, 151.5, 150.8, 150.5, 150.2, 150.1, 149.7, 148.8, 140.1, 128.6, 127.9, 127.5, 125.6,

124.3, 123.9, 122.0, 120.1, 118.7, 117.5, 68.3, 67.4, 64.4, 58.6, 52.6, 48.0, 46.8, 25.8, 25.7, 20.2, 19.5, 18.4, 14.0, -4.5, -4.6, -4.7, -4.8; **HRMS** (ESI): calc. for $C_{63}H_{85}N_{13}O_{12}S_6Si_2$ $[M+Na]^+$: 1486.4196, obs. 1486.4189.

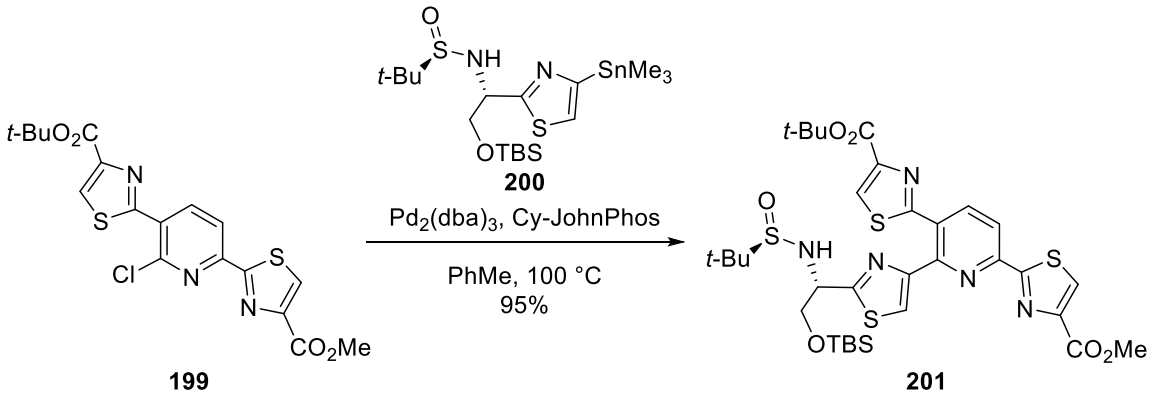


To a stirred solution of **166** (600 mg, 1.87 mmol, 1.0 equiv.) in 1.5:1 IPA:0.1 M pH 7 phosphate buffer (9.3 mL, 0.2 M) was added solid L-cysteine methyl ester hydrochloride (416 mg, 2.42 mmol, 1.3 equiv.). The reaction vessel was sparged with nitrogen for 10 minutes and sealed with a yellow cap. The clear homogeneous reaction was stirred at 50 °C for 15 hours. The reaction was concentrated to remove IPA and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with 1.0 M HCl (2 x 20 mL), water (1 x 20 mL), brined (1 x 10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the intermediate thiazoline **S16** (779 mg, 1.77 mmol, 95%) as a white solid.

To a stirred solution of thiazoline **S16** (779 mg, 1.77 mmol, 1.0 equiv.) in CH_2Cl_2 (8.8 mL, 0.2 M) was added activated MnO_2 (< 5 microns, Aldrich, 3.0 g, 35.4 mmol, 20 equiv.) and the dark heterogeneous reaction mixture was stirred at 1000 RPM at 23 °C for 12 hours. The crude reaction was filtered through Celite with CH_2Cl_2 and concentrated to give **199** as a brown solid. The crude material was triturated with MTBE (100 mL) to give pure thiazole **199** (651 mg, 1.49 mmol, 84%) as a white solid (m.p. >200 °C).

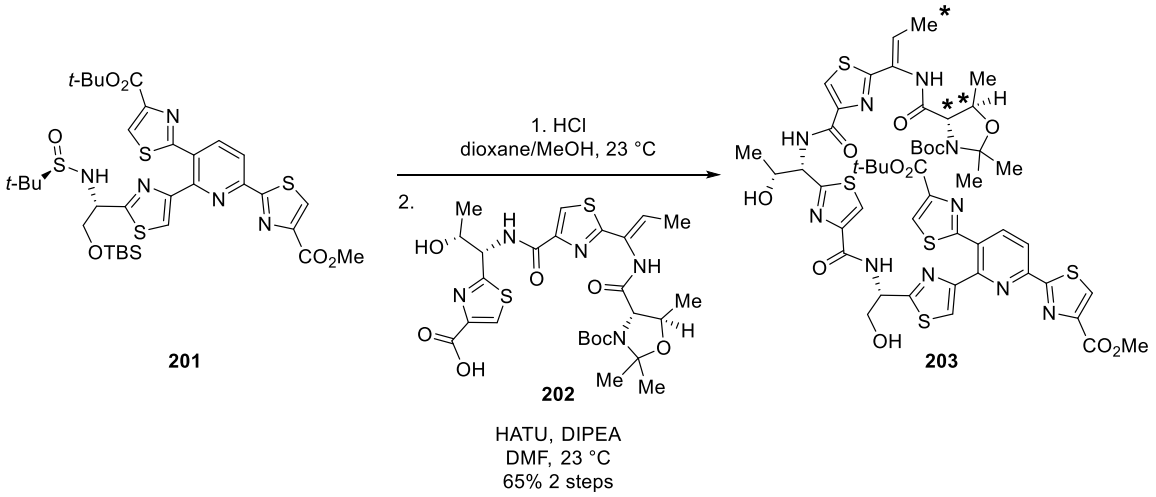
R_f = 0.65 (silica gel, 1:1 hexanes:EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 8.93 (d, *J* = 8.2 Hz, 1H), 8.35 (d, *J* = 8.2 Hz, 1H), 8.32 (s, 1H), 8.22 (s, 1H), 3.98 (s, 3H), 1.62 (s, 9H); **^{13}C-**

NMR (150 MHz, $CDCl_3$) δ 167.1, 161.6, 161.0, 160.2, 150.7, 148.7, 148.3, 147.4, 140.8, 130.7, 129.1, 128.5, 119.1, 82.4, 52.6, 28.1; **IR** (film, cm^{-1}): 1725, 1402, 1369, 1353; **HRMS** (ESI): calc. for $C_{18}H_{16}ClN_3O_4S_2$ $[M+H]^+$: 438.0344, obs. 438.0346.



To a stirred solution of chloride **199** (432 mg, 0.99 mmol, 1.0 equiv.) in PhMe (4.9 mL, 0.2 M) was added the stannane **200** (518 mg, 0.99 mmol, 1.0 equiv.), solid Cy-JohnPhos (69.1 mg, 0.2 mmol, 0.2 equiv.), and solid $Pd_2(dba)_3$ (28.4 mg, 0.049 mmol, 0.05 equiv.). The reaction vessel was sparged with nitrogen for 10 minutes and then sealed with a yellow cap. The dark purple homogeneous reaction was stirred at 110 °C for 18 hours. The reaction was cooled to 23 °C and concentrated *in vacuo* to give a brown oil. The crude material was purified via silica gel column chromatography using 2:1 hexanes:EtOAc to 1:1 hexanes:EtOAc to give **201** (716 mg, 0.937 mmol, 95%) as a pale yellow foam.

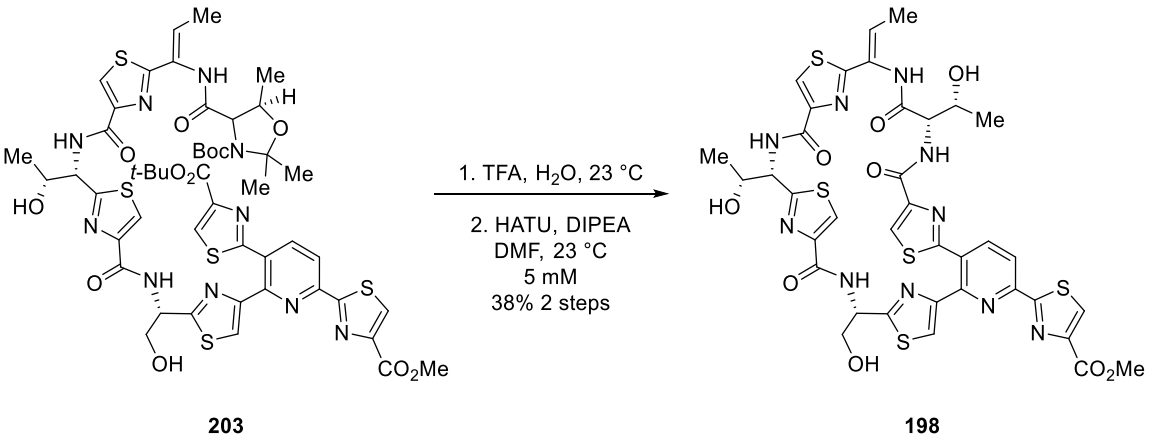
R_f = 0.42 (silica gel, 1:1 hexanes:EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 8.38 (d, *J* = 8.2 Hz, 1H), 8.35 (d, *J* = 8.2 Hz, 1H), 8.29 (s, 1H), 8.06 (s, 1H), 7.82 (s, 1H), 4.70 (dd, *J* = 5.0, 9.8 Hz, 1H), 4.57 (d, *J* = 5.6 Hz, 1H), 3.91 (s, 3H), 3.92 (m, 2H), 1.59 (s, 9H), 1.27 (s, 9H), 0.83 (s, 9H), 0.03 (s, 3H), 0.04 (s, 3H); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 171.6, 168.9, 164.8, 161.7, 160.1, 153.0, 150.8, 150.4, 148.3, 148.0, 140.2, 130.3, 129.4, 128.2, 121.5, 119.0, 82.1, 66.0, 56.2, 52.5, 28.1, 25.7, 22.5, 18.0; **IR** (film, cm^{-1}): 3124, 1726, 1401, 1343; **HRMS** (ESI): calc. for $C_{33}H_{45}N_5O_6S_4Si$ $[M+H]^+$: 764.2095, obs. 764.2094.



To a stirred solution of **201** (300 mg, 0.393 mmol, 1.0 equiv.) in MeOH (3.93 mL, 0.1 M) was added a solution of 4.0 M HCl in dioxane (0.491 mL, 1.96 mmol, 5 equiv.) and the pale yellow homogeneous reaction was stirred at 23 °C for 2 hours. The crude reaction was diluted with PhMe (50 mL) and concentrated *in vacuo* to give a pale yellow solid (240 mg, 0.388 mmol, 99%).

To a stirred solution of this crude pale yellow solid (240 mg, 0.388 mmol, 1.0 equiv.) in DMF (3.9 mL, 0.1 M) was added acid **202** (237 mg, 0.388 mmol, 1.0 equiv.), neat DIPEA (0.203 mL, 1.16 mmol, 3.0 equiv.), and solid HATU (162 mg, 0.427 mmol. 1.1 equiv.). The pale yellow homogeneous reaction a stirred at 23 °C for 15 hours. Cold 1.0 M HCl (50 mL) was added and the solids were collected by filtration. The filter cake was washed with water (1 x 20 mL), MTBE (1 x 20 mL), and dried at 50 °C under vacuum to give **203** (287 mg, 0.252 mmol, 65%) as a brown powder (m.p. > 200 °C (decomp.)) which was used without further purification. An analytical sample was obtained with silica gel column chromatography using 20:1 CH_2Cl_2:MeOH.

R_f = 0.37 (silica gel, 20:1 CH_2Cl_2:MeOH); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 8.39 (d, *J* = 8.1 Hz, 1H), 8.32 (s, 1H), 8.28 (d, *J* = 8.1 Hz, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 8.14 (s, 1H), 8.08 (s, 1H), 8.05 (s, 1H), 7.99 (s, 1H), 7.75 (bs, 1H), 6.57 (bs, 1H), 5.39 (m, 1H), 5.33 (d, *J* = 8.4 Hz, 1H), 4.73 (d, *J* = 5.8 Hz, 1H), 4.38 (bs, 1H), 4.06 (d, *J* = 9.3 Hz, 1H), 4.00 (s, 3H), 3.86 (dd, *J* = 3.7, 11.4 Hz, 1H), 1.86 (d, *J* = 6.8 Hz, 3H), 1.72 (bs, 6H), 1.60 (bs, 18H), 1.44 (d, *J* = 6.0 Hz, 3H), 1.33 (d, *J* = 6.3 Hz, 3H); **^{13}C-NMR** (150 MHz, $CDCl_3$; ***** carbons were not observed): δ 171.8, 168.9, 168.8, 168.3, 167.0, 165.1, 161.8, 161.3, 160.7, 160.6, 152.5, 150.7, 150.6, 149.1, 149.0, 148.6, 148.2, 140.3, 130.5, 129.2, 128.5, 127.7, 124.5, 124.0, 122.2, 119.1, 95.0, 82.6, 81.5, 68.3, 64.2, 56.3, 52.6, 51.6, 28.3, 28.2, 26.0, 20.1, 19.4 **IR** (film, cm^{-1}): 3122, 1666, 1480, 1401; **HRMS** (ESI): calc. for $C_{49}H_{56}N_{10}O_{12}S_5$ $[M+Na]^+$: 1159.2575, obs. 1159.2572.



203 **198**

Solid **203** (10 mg, 8.76 μmol, 1.0 equiv.) was dissolved in 10:1 TFA:H_2O (1.1 mL, 8.0 mM) and the clear homogeneous reaction was stirred at 23 °C for 2 hours. PhMe (20 mL) was added and the crude reaction was concentrated *in vacuo* to give a clear residue (9 mg, 8.70 μmol, 99%).

To a stirred solution of this crude residue (9.0 mg, 8.70 μmol, 99%) in DMF (1.7 mL, 5 mM) was added neat DIPEA (7.6 μL, 0.043 mmol, 5 equiv.) and solid HATU (6.6 mg, 0.017 mmol, 2 equiv.). The clear homoegeneous reaction was stirred at 23 °C for 15 hours. The crude reaction was diluted with EtOAc (50 mL) and the organic layer was washed with 1.0 M HCl (1 x 10 mL), sat. aq. $NaHCO_3$ (1 x 10 mL), water (1 x 10 mL), brine (1 x 5 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give an amber oil. The crude material was purified via preparative TLC using 10:1 CH_2Cl_2:MeOH to give **198** (3.0 mg, 3.9 μmol, 38%) as a white solid (m.p. >200 °C).

R_f = 0.21 (silica gel, 10:1 CH_2Cl_2:MeOH); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 8.65 (bs, 2H), 8.38 (d, *J* = 8.1 Hz, 1H), 8.33 (s, 1H), 8.23 (d, *J* = 9.4 Hz, 1H), 8.17 (s, 1H), 8.15 (bs, 1H), 8.03 (d, *J* = 8.1 Hz, 1H), 8.00 (s, 1H), 7.98 (s, 1H), 7.92 (d, *J* = 7. Hz, 1H), 6.42 (q, *J* = 7.0

Hz, 1H), 5.42 (m, 2H), 4.88 (d, *J* = 5.9 Hz, 1H), 4.68 (m, 1H), 4.38 (dd, *J* = 2.1, 6.2 Hz, 1H), 4.01 (s, 3H), 3.97 (dd, *J* = 2.8, 11.0 Hz, 1H), 3.74 (dd, *J* = 4.6, 10.9 Hz, 1H), 1.83 (d, *J* = 7.0 Hz, 3H), 1.47 (d, *J* = 6.3 Hz, 3H), 1.35 (d, *J* = 6.3 Hz, 3H); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 169.8, 168.9, 168.8, 168.7, 166.2, 165.8, 161.8, 161.2, 161.0, 160.4, 153.7, 150.8, 150.6, 149.8, 149.5, 148.5, 148.2, 140.3, 130.5, 128.9, 128.6, 128.3, 125.1, 124.9, 123.7, 121.5, 118.9, 69.0, 67.9, 63.7, 57.5, 54.6, 52.6, 51.4, 20.1, 19.0, 14.5; **IR** (film, cm^{-1}): 3128, 1656, 1401; **HRMS** (ESI): calc. for $C_{37}H_{34}N_{10}O_9S_5$ $[M+Na]^+$: 945.1006, obs. 945.1011.

APPENDIX A: CRYSTALLOGRAPHIC DATA FOR 85

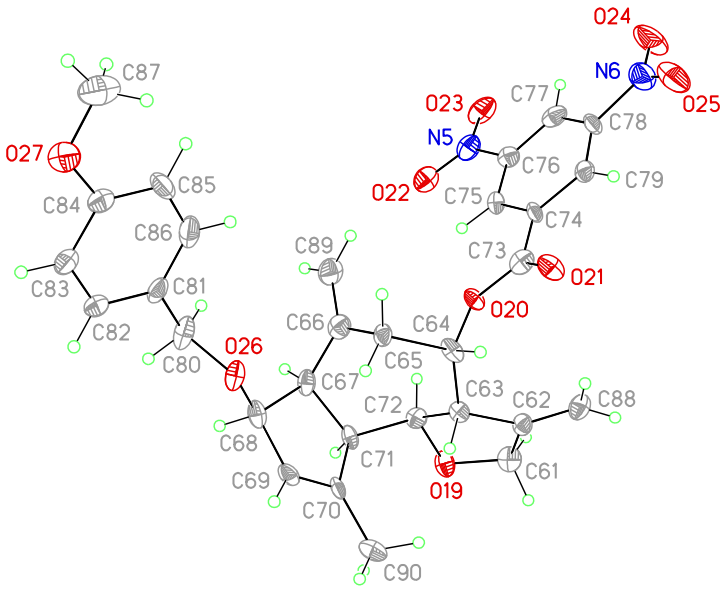


Table 1. Crystal data and structure refinement for **85**.

Empirical formula	C30 H30 N2 O9	
Formula weight	562.56	
Temperature	140(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P 21	
Unit cell dimensions	a = 25.044(3) Å	α = 90°.
	b = 5.4847(12) Å	ß = 97.558(6)°.
	c = 29.751(4) Å	γ = 90°.
Volume	4051.1(11) $Å^3$	
Z	6	
Density (calculated)	1.384 Mg/m^3	
Absorption coefficient	0.103 mm^{-1}	
F(000)	1776	
Crystal size	0.300 x 0.050 x 0.040 mm	
Theta range for data collection	1.640 to 24.999°.	
Index ranges	-29<=h<=29, -6<=k<=6, -35<=l<=35	
Reflections collected	53001	
Independent reflections	14309 [R(int) = 0.1855]	
Completeness to theta = 25.242°	97.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.854	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	14309 / 1 / 1114
Goodness-of-fit on F^2	0.980
Final R indices [I>2sigma(I)]	R1 = 0.0737, wR2 = 0.1139
R indices (all data)	R1 = 0.1907, wR2 = 0.1502
Absolute structure parameter	-0.6(10)
Extinction coefficient	n/a
Largest diff. peak and hole	0.278 and -0.315 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **85**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C1	-1326(3)	7658(16)	3274(3)	25(2)
C2	-1166(3)	5296(17)	3086(3)	21(2)
C3	-675(3)	4387(15)	3391(2)	16(2)
C4	-271(3)	2970(16)	3167(2)	18(2)
C5	253(3)	2409(15)	3482(2)	16(2)
C6	566(3)	4643(16)	3649(3)	20(2)
C7	455(3)	5860(16)	4078(3)	21(2)
C8	597(3)	4116(17)	4496(3)	24(2)
C9	58(3)	3235(18)	4593(2)	25(2)
C10	-342(3)	4545(16)	4401(3)	19(2)
C11	-151(3)	6487(15)	4098(2)	16(2)
C12	-472(3)	6753(15)	3629(3)	20(2)
C13	-89(3)	3234(19)	2404(3)	21(2)
C14	183(3)	4770(16)	2087(2)	15(2)
C15	475(3)	6817(16)	2247(3)	19(2)
C16	759(3)	8050(16)	1950(3)	20(2)
C17	771(3)	7365(16)	1505(3)	21(2)
C18	481(3)	5271(16)	1365(2)	16(2)
C19	198(3)	3955(17)	1643(2)	21(2)

C20	1505(3)	2930(18)	4481(3)	30(2)
C21	1844(3)	1005(17)	4317(3)	23(2)
C22	1865(3)	692(19)	3853(3)	34(3)
C23	2172(3)	-1109(17)	3691(3)	28(2)
C24	2476(3)	-2622(18)	3982(3)	28(2)
C25	2480(3)	-2298(19)	4446(3)	35(3)
C26	2171(3)	-532(19)	4607(3)	35(3)
C27	2717(3)	-5080(20)	3382(3)	43(3)
C28	-1403(3)	4243(18)	2711(3)	35(3)
C29	942(3)	5548(17)	3419(3)	29(2)
C30	-923(3)	4409(18)	4487(3)	31(2)
C31	4504(3)	3555(18)	86(3)	34(3)
C32	4255(3)	1330(17)	274(3)	21(2)
C33	3797(3)	542(16)	-77(3)	17(2)
C34	3287(3)	-302(16)	88(2)	21(2)
C35	2845(3)	-904(16)	-291(2)	18(2)
C36	2642(3)	1288(16)	-572(3)	18(2)
C37	2898(3)	1955(15)	-990(2)	18(2)
C38	2809(3)	-126(16)	-1351(3)	22(2)
C39	3352(3)	-1248(16)	-1348(2)	22(2)
C40	3743(3)	31(17)	-1115(3)	22(2)
C41	3523(3)	2245(16)	-898(3)	22(2)
C42	3736(3)	2725(17)	-403(2)	23(2)
C43	3016(3)	1034(19)	796(3)	23(2)

C44	2701(3)	3002(17)	999(3)	18(2)
C45	2407(3)	4736(17)	734(3)	26(2)
C46	2103(3)	6420(17)	939(3)	20(2)
C47	2088(3)	6444(18)	1398(3)	26(2)
C48	2371(3)	4653(19)	1651(3)	25(2)
C49	2674(3)	2921(17)	1463(3)	21(2)
C50	1879(3)	-1067(17)	-1433(3)	26(2)
C51	1481(3)	-2766(16)	-1262(3)	20(2)
C52	1261(3)	-4718(17)	-1517(3)	23(2)
C53	928(3)	-6382(17)	-1345(3)	26(2)
C54	814(3)	-6088(17)	-903(3)	22(2)
C55	1007(3)	-4097(16)	-649(3)	20(2)
C56	1337(3)	-2458(17)	-829(3)	26(2)
C57	490(3)	-7994(18)	-269(2)	35(3)
C58	4399(3)	381(18)	678(3)	35(3)
C59	2235(3)	2639(17)	-465(3)	26(2)
C60	4333(3)	-427(19)	-1103(3)	35(3)
C61	7746(3)	12627(16)	3645(3)	27(2)
C62	7581(3)	10201(16)	3812(3)	20(2)
C63	7113(3)	9303(15)	3475(2)	17(2)
C64	6696(3)	7723(16)	3660(2)	19(2)
C65	6198(3)	7229(15)	3320(2)	19(2)
C66	5876(3)	9458(17)	3158(3)	25(2)
C67	6011(3)	10825(16)	2748(2)	21(2)

C68	5921(3)	9217(17)	2304(3)	24(2)
C69	6476(3)	8578(16)	2220(2)	21(2)
C70	6849(3)	9898(16)	2455(3)	18(2)
C71	6612(3)	11576(16)	2773(2)	17(2)
C72	6902(3)	11710(15)	3254(3)	20(2)
C73	6576(3)	7755(18)	4445(3)	23(2)
C74	6348(3)	9158(16)	4800(3)	18(2)
C75	6041(3)	11239(16)	4699(3)	19(2)
C76	5816(3)	12390(17)	5039(3)	23(2)
C77	5850(3)	11479(18)	5471(3)	27(2)
C78	6153(3)	9408(19)	5562(3)	27(2)
C79	6401(3)	8217(17)	5237(3)	22(2)
C80	5021(3)	7825(18)	2222(3)	33(3)
C81	4668(3)	5639(18)	2232(3)	26(2)
C82	4450(3)	4500(19)	1830(3)	30(2)
C83	4096(3)	2596(19)	1836(3)	33(3)
C84	3965(3)	1759(18)	2248(3)	30(3)
C85	4172(3)	2846(19)	2645(3)	33(3)
C86	4526(3)	4767(19)	2633(3)	33(3)
C87	3461(4)	-1130(20)	2623(3)	49(3)
C88	7806(3)	9080(17)	4187(3)	27(2)
C89	5472(3)	10191(17)	3367(3)	31(2)
C90	7436(3)	9986(17)	2389(3)	29(2)
N1	1091(3)	10165(14)	2121(2)	24(2)

N2	515(3)	4361(17)	905(2)	29(2)
N3	1797(3)	8310(16)	660(3)	30(2)
N4	2324(3)	4562(19)	2142(2)	41(2)
N5	5473(3)	14554(15)	4927(3)	30(2)
N6	6164(3)	8291(19)	6016(3)	41(2)
O1	-949(2)	8131(11)	3668(2)	24(2)
O2	-118(2)	4395(10)	2794(2)	18(1)
O3	-251(2)	1186(12)	2308(2)	28(2)
O4	1085(2)	10769(11)	2514(2)	32(2)
O5	1348(2)	11211(12)	1859(2)	30(2)
O6	761(2)	5621(12)	657(2)	36(2)
O7	303(2)	2387(12)	794(2)	30(2)
O8	951(2)	2162(10)	4420(2)	24(2)
O9	2778(2)	-4511(12)	3857(2)	35(2)
O10	4271(2)	3728(11)	-378(2)	28(2)
O11	3088(2)	1622(10)	368(2)	20(1)
O12	3171(2)	-776(12)	998(2)	28(2)
O13	1765(2)	8084(12)	247(2)	36(2)
O14	1600(2)	9974(12)	857(2)	37(2)
O15	2061(3)	6174(14)	2295(2)	46(2)
O16	2564(3)	2921(16)	2358(2)	59(2)
O17	2414(2)	-1907(10)	-1273(2)	20(1)
O18	498(2)	-7897(11)	-752(2)	25(2)
O19	7376(2)	13203(11)	3249(2)	24(2)

O20	6518(2)	8977(10)	4050(2)	19(1)
O21	6778(2)	5764(11)	4508(2)	26(2)
O22	5401(2)	15205(11)	4529(2)	31(2)
O23	5297(2)	15604(12)	5239(2)	37(2)
O24	5981(3)	9452(15)	6307(2)	56(2)
O25	6367(3)	6249(15)	6073(2)	48(2)
O26	5584(2)	7163(10)	2320(2)	25(2)
O27	3607(2)	-186(13)	2208(2)	39(2)

Table 3. Bond lengths [Å] and angles [°] for **85**.

C1-O1	1.428(8)	C5-C6	1.504(11)
C1-C2	1.487(11)	C5-H5A	0.99
C1-H1A	0.99	C5-H5B	0.99
C1-H1B	0.99	C6-C29	1.332(10)
C2-C28	1.325(10)	C6-C7	1.498(11)
C2-C3	1.513(10)	C7-C11	1.565(10)
C3-C4	1.500(10)	C7-C8	1.571(10)
C3-C12	1.532(11)	C7-H7	1.00
C3-H3	1.00	C8-O8	1.427(9)
C4-O2	1.450(8)	C8-C9	1.498(11)
C4-C5	1.539(10)	C8-H8	1.00
C4-H4	1.00	C9-C10	1.302(10)

C9-H9	0.95	C20-H20B	0.99
C10-C30	1.512(10)	C21-C26	1.393(11)
C10-C11	1.512(11)	C21-C22	1.400(11)
C11-C12	1.523(9)	C22-C23	1.377(12)
C11-H11	1.00	C22-H22	0.95
C12-O1	1.432(9)	C23-C24	1.359(11)
C12-H12	1.00	C23-H23	0.95
C13-O3	1.215(10)	C24-O9	1.362(10)
C13-O2	1.333(9)	C24-C25	1.391(11)
C13-C14	1.494(11)	C25-C26	1.365(12)
C14-C15	1.389(11)	C25-H25	0.95
C14-C19	1.400(10)	C26-H26	0.95
C15-C16	1.383(10)	C27-O9	1.435(9)
C15-H15	0.95	C27-H27A	0.98
C16-C17	1.378(10)	C27-H27B	0.98
C16-N1	1.478(10)	C27-H27C	0.98
C17-C18	1.393(11)	C28-H28A	0.95
C17-H17	0.95	C28-H28B	0.95
C18-C19	1.366(10)	C29-H29A	0.95
C18-N2	1.470(10)	C29-H29B	0.95
C19-H19	0.95	C30-H30A	0.98
C20-O8	1.439(9)	C30-H30B	0.98
C20-C21	1.477(11)	C30-H30C	0.98
C20-H20A	0.99	C31-O10	1.429(8)

C31-C32	1.510(11)	C40-C60	1.495(10)
C31-H31A	0.99	C40-C41	1.513(11)
C31-H31B	0.99	C41-C42	1.521(10)
C32-C58	1.314(10)	C41-H41	1.00
C32-C33	1.509(10)	C42-O10	1.443(9)
C33-C34	1.502(10)	C42-H42	1.00
C33-C42	1.537(11)	C43-O12	1.199(10)
C33-H33	1.00	C43-O11	1.346(9)
C34-O11	1.472(9)	C43-C44	1.509(12)
C34-C35	1.510(9)	C44-C45	1.385(11)
C34-H34	1.00	C44-C49	1.391(10)
C35-C36	1.513(11)	C45-C46	1.389(11)
C35-H35A	0.99	C45-H45	0.95
C35-H35B	0.99	C46-C47	1.372(10)
C36-C59	1.332(11)	C46-N3	1.477(11)
C36-C37	1.517(10)	C47-C48	1.377(11)
C37-C41	1.561(10)	C47-H47	0.95
C37-C38	1.563(10)	C48-C49	1.379(11)
C37-H37	1.00	C48-N4	1.482(10)
C38-O17	1.429(9)	C49-H49	0.95
C38-C39	1.492(11)	C50-O17	1.439(8)
C38-H38	1.00	C50-C51	1.500(11)
C39-C40	1.324(10)	C50-H50A	0.99
C39-H39	0.95	C50-H50B	0.99

C51-C52	1.385(11)	C61-H61A	0.99
C51-C56	1.392(11)	C61-H61B	0.99
C52-C53	1.379(11)	C62-C88	1.333(10)
C52-H52	0.95	C62-C63	1.520(10)
C53-C54	1.392(10)	C63-C64	1.516(10)
C53-H53	0.95	C63-C72	1.536(11)
C54-C55	1.378(11)	C63-H63	1.00
C54-O18	1.381(10)	C64-O20	1.466(8)
C55-C56	1.376(11)	C64-C65	1.524(9)
C55-H55	0.95	C64-H64	1.00
C56-H56	0.95	C65-C66	1.509(11)
C57-O18	1.438(8)	C65-H65A	0.99
C57-H57A	0.98	C65-H65B	0.99
C57-H57B	0.98	C66-C89	1.316(10)
C57-H57C	0.98	C66-C67	1.510(11)
C58-H58A	0.95	C67-C71	1.555(10)
C58-H58B	0.95	C67-C68	1.579(10)
C59-H59A	0.95	C67-H67	1.00
C59-H59B	0.95	C68-O26	1.413(9)
C60-H60A	0.98	C68-C69	1.484(10)
C60-H60B	0.98	C68-H68	1.00
C60-H60C	0.98	C69-C70	1.309(10)
C61-O19	1.435(8)	C69-H69	0.95
C61-C62	1.497(11)	C70-C71	1.496(10)

C70-C90	1.510(10)	C81-C82	1.395(11)
C71-C72	1.520(9)	C82-C83	1.373(12)
C71-H71	1.00	C82-H82	0.95
C72-O19	1.444(9)	C83-C84	1.388(11)
C72-H72	1.00	C83-H83	0.95
C73-O21	1.207(10)	C84-C85	1.363(11)
C73-O20	1.345(9)	C84-O27	1.388(10)
C73-C74	1.480(11)	C85-C86	1.381(12)
C74-C75	1.387(10)	C85-H85	0.95
C74-C79	1.389(10)	C86-H86	0.95
C75-C76	1.375(11)	C87-O27	1.431(10)
C75-H75	0.95	C87-H87A	0.98
C76-C77	1.370(11)	C87-H87B	0.98
C76-N5	1.478(11)	C87-H87C	0.98
C77-C78	1.372(12)	C88-H88A	0.95
C77-H77	0.95	C88-H88B	0.95
C78-C79	1.381(11)	C89-H89A	0.95
C78-N6	1.479(11)	C89-H89B	0.95
C79-H79	0.95	C90-H90A	0.98
C80-O26	1.448(9)	C90-H90B	0.98
C80-C81	1.492(12)	C90-H90C	0.98
C80-H80A	0.99	N1-O5	1.217(8)
C80-H80B	0.99	N1-O4	1.219(8)
C81-C86	1.376(11)	N2-O6	1.232(9)

N2-O7	1.233(9)	N5-O23	1.225(8)
N3-O14	1.223(9)	N5-O22	1.227(8)
N3-O13	1.227(8)	N6-O24	1.213(9)
N4-O16	1.217(10)	N6-O25	1.232(10)
N4-O15	1.225(10)		

O1-C1-C2	106.6(7)	O2-C4-H4	109.2
O1-C1-H1A	110.4	C3-C4-H4	109.2
C2-C1-H1A	110.4	C5-C4-H4	109.2
O1-C1-H1B	110.4	C6-C5-C4	113.8(7)
C2-C1-H1B	110.4	C6-C5-H5A	108.8
H1A-C1-H1B	108.6	C4-C5-H5A	108.8
C28-C2-C1	125.6(8)	C6-C5-H5B	108.8
C28-C2-C3	126.9(8)	C4-C5-H5B	108.8
C1-C2-C3	107.4(7)	H5A-C5-H5B	107.7
C4-C3-C2	116.5(6)	C29-C6-C7	119.8(8)
C4-C3-C12	116.2(7)	C29-C6-C5	120.4(8)
C2-C3-C12	101.0(7)	C7-C6-C5	119.8(7)
C4-C3-H3	107.5	C6-C7-C11	114.9(6)
C2-C3-H3	107.5	C6-C7-C8	110.7(7)
C12-C3-H3	107.5	C11-C7-C8	102.9(6)
O2-C4-C3	108.8(7)	C6-C7-H7	109.4
O2-C4-C5	106.6(6)	C11-C7-H7	109.4
C3-C4-C5	113.8(6)	C8-C7-H7	109.4

O8-C8-C9	112.5(8)	O3-C13-O2	126.2(8)
O8-C8-C7	114.4(7)	O3-C13-C14	122.6(8)
C9-C8-C7	103.4(6)	O2-C13-C14	111.2(8)
O8-C8-H8	108.8	C15-C14-C19	120.2(8)
C9-C8-H8	108.8	C15-C14-C13	120.2(7)
C7-C8-H8	108.8	C19-C14-C13	119.1(8)
C10-C9-C8	113.5(8)	C16-C15-C14	117.9(7)
C10-C9-H9	123.2	C16-C15-H15	121.0
C8-C9-H9	123.2	C14-C15-H15	121.0
C9-C10-C30	126.9(8)	C17-C16-C15	123.9(8)
C9-C10-C11	111.3(8)	C17-C16-N1	117.5(8)
C30-C10-C11	121.5(7)	C15-C16-N1	118.5(7)
C10-C11-C12	116.3(7)	C16-C17-C18	115.9(8)
C10-C11-C7	104.6(6)	C16-C17-H17	122.1
C12-C11-C7	112.5(6)	C18-C17-H17	122.1
C10-C11-H11	107.7	C19-C18-C17	123.1(8)
C12-C11-H11	107.7	C19-C18-N2	118.9(8)
C7-C11-H11	107.7	C17-C18-N2	117.9(8)
O1-C12-C11	108.7(6)	C18-C19-C14	118.9(8)
O1-C12-C3	104.8(6)	C18-C19-H19	120.5
C11-C12-C3	116.4(7)	C14-C19-H19	120.5
O1-C12-H12	108.9	O8-C20-C21	109.6(7)
C11-C12-H12	108.9	O8-C20-H20A	109.7
C3-C12-H12	108.9	C21-C20-H20A	109.7

O8-C20-H20B	109.7	O9-C27-H27C	109.5
C21-C20-H20B	109.7	H27A-C27-H27C	109.5
H20A-C20-H20B	108.2	H27B-C27-H27C	109.5
C26-C21-C22	116.2(8)	C2-C28-H28A	120.0
C26-C21-C20	123.0(8)	C2-C28-H28B	120.0
C22-C21-C20	120.7(8)	H28A-C28-H28B	120.0
C23-C22-C21	121.9(8)	C6-C29-H29A	120.0
C23-C22-H22	119.1	C6-C29-H29B	120.0
C21-C22-H22	119.1	H29A-C29-H29B	120.0
C24-C23-C22	120.5(8)	C10-C30-H30A	109.5
C24-C23-H23	119.7	C10-C30-H30B	109.5
C22-C23-H23	119.7	H30A-C30-H30B	109.5
C23-C24-O9	125.2(8)	C10-C30-H30C	109.5
C23-C24-C25	118.9(9)	H30A-C30-H30C	109.5
O9-C24-C25	115.9(8)	H30B-C30-H30C	109.5
C26-C25-C24	120.7(9)	O10-C31-C32	106.0(7)
C26-C25-H25	119.7	O10-C31-H31A	110.5
C24-C25-H25	119.7	C32-C31-H31A	110.5
C25-C26-C21	121.7(8)	O10-C31-H31B	110.5
C25-C26-H26	119.1	C32-C31-H31B	110.5
C21-C26-H26	119.1	H31A-C31-H31B	108.7
O9-C27-H27A	109.5	C58-C32-C33	127.6(8)
O9-C27-H27B	109.5	C58-C32-C31	125.5(8)
H27A-C27-H27B	109.5	C33-C32-C31	106.8(7)

C34-C33-C32	117.6(6)	C36-C37-H37	109.5
C34-C33-C42	115.3(7)	C41-C37-H37	109.5
C32-C33-C42	102.6(7)	C38-C37-H37	109.5
C34-C33-H33	106.9	O17-C38-C39	111.5(7)
C32-C33-H33	106.9	O17-C38-C37	115.4(6)
C42-C33-H33	106.9	C39-C38-C37	104.5(6)
O11-C34-C33	109.3(7)	O17-C38-H38	108.4
O11-C34-C35	108.0(6)	C39-C38-H38	108.4
C33-C34-C35	113.2(6)	C37-C38-H38	108.4
O11-C34-H34	108.7	C40-C39-C38	113.3(8)
C33-C34-H34	108.7	C40-C39-H39	123.4
C35-C34-H34	108.7	C38-C39-H39	123.4
C34-C35-C36	113.5(7)	C39-C40-C60	125.7(8)
C34-C35-H35A	108.9	C39-C40-C41	111.3(7)
C36-C35-H35A	108.9	C60-C40-C41	122.6(8)
C34-C35-H35B	108.9	C40-C41-C42	116.8(7)
C36-C35-H35B	108.9	C40-C41-C37	104.8(7)
H35A-C35-H35B	107.7	C42-C41-C37	113.8(6)
C59-C36-C35	121.5(8)	C40-C41-H41	106.9
C59-C36-C37	118.7(8)	C42-C41-H41	106.9
C35-C36-C37	119.8(7)	C37-C41-H41	106.9
C36-C37-C41	113.7(6)	O10-C42-C41	108.8(6)
C36-C37-C38	110.4(7)	O10-C42-C33	104.3(6)
C41-C37-C38	104.2(6)	C41-C42-C33	118.0(7)

O10-C42-H42	108.4	O17-C50-C51	108.7(7)
C41-C42-H42	108.4	O17-C50-H50A	109.9
C33-C42-H42	108.4	C51-C50-H50A	109.9
O12-C43-O11	126.8(9)	O17-C50-H50B	110.0
O12-C43-C44	122.8(8)	C51-C50-H50B	110.0
O11-C43-C44	110.4(8)	H50A-C50-H50B	108.3
C45-C44-C49	119.7(8)	C52-C51-C56	117.9(8)
C45-C44-C43	122.0(7)	C52-C51-C50	121.9(8)
C49-C44-C43	118.1(8)	C56-C51-C50	120.2(8)
C44-C45-C46	119.2(8)	C53-C52-C51	121.6(8)
C44-C45-H45	120.4	C53-C52-H52	119.2
C46-C45-H45	120.4	C51-C52-H52	119.2
C47-C46-C45	122.1(8)	C52-C53-C54	119.0(8)
C47-C46-N3	118.2(8)	C52-C53-H53	120.5
C45-C46-N3	119.6(7)	C54-C53-H53	120.5
C46-C47-C48	117.3(8)	C55-C54-O18	124.4(8)
C46-C47-H47	121.3	C55-C54-C53	120.5(9)
C48-C47-H47	121.3	O18-C54-C53	115.0(8)
C47-C48-C49	122.7(8)	C56-C55-C54	119.3(8)
C47-C48-N4	117.5(8)	C56-C55-H55	120.3
C49-C48-N4	119.8(8)	C54-C55-H55	120.3
C48-C49-C44	118.9(8)	C55-C56-C51	121.5(8)
C48-C49-H49	120.6	C55-C56-H56	119.2
C44-C49-H49	120.6	C51-C56-H56	119.2

O18-C57-H57A	109.5	C88-C62-C61	125.6(8)
O18-C57-H57B	109.5	C88-C62-C63	127.4(8)
H57A-C57-H57B	109.5	C61-C62-C63	107.0(7)
O18-C57-H57C	109.5	C64-C63-C62	116.9(6)
H57A-C57-H57C	109.5	C64-C63-C72	115.6(7)
H57B-C57-H57C	109.5	C62-C63-C72	101.2(7)
C32-C58-H58A	120.0	C64-C63-H63	107.5
C32-C58-H58B	120.0	C62-C63-H63	107.5
H58A-C58-H58B	120.0	C72-C63-H63	107.5
C36-C59-H59A	120.0	O20-C64-C63	108.4(6)
C36-C59-H59B	120.0	O20-C64-C65	107.5(6)
H59A-C59-H59B	120.0	C63-C64-C65	113.7(6)
C40-C60-H60A	109.5	O20-C64-H64	109.0
C40-C60-H60B	109.5	C63-C64-H64	109.0
H60A-C60-H60B	109.5	C65-C64-H64	109.0
C40-C60-H60C	109.5	C66-C65-C64	115.1(7)
H60A-C60-H60C	109.5	C66-C65-H65A	108.5
H60B-C60-H60C	109.5	C64-C65-H65A	108.5
O19-C61-C62	106.9(7)	C66-C65-H65B	108.5
O19-C61-H61A	110.3	C64-C65-H65B	108.5
C62-C61-H61A	110.3	H65A-C65-H65B	107.5
O19-C61-H61B	110.3	C89-C66-C65	120.6(8)
C62-C61-H61B	110.3	C89-C66-C67	119.8(9)
H61A-C61-H61B	108.6	C65-C66-C67	119.5(7)

C66-C67-C71	114.3(6)	O19-C72-C71	108.0(6)
C66-C67-C68	112.2(7)	O19-C72-C63	104.7(6)
C71-C67-C68	102.6(6)	C71-C72-C63	117.1(7)
C66-C67-H67	109.2	O19-C72-H72	108.9
C71-C67-H67	109.2	C71-C72-H72	108.9
C68-C67-H67	109.2	C63-C72-H72	108.9
O26-C68-C69	113.2(7)	O21-C73-O20	125.6(8)
O26-C68-C67	115.8(7)	O21-C73-C74	123.5(8)
C69-C68-C67	103.9(6)	O20-C73-C74	110.9(8)
O26-C68-H68	107.9	C75-C74-C79	119.4(8)
C69-C68-H68	107.9	C75-C74-C73	121.9(7)
C67-C68-H68	107.9	C79-C74-C73	118.4(8)
C70-C69-C68	113.4(8)	C76-C75-C74	119.1(8)
C70-C69-H69	123.3	C76-C75-H75	120.4
C68-C69-H69	123.3	C74-C75-H75	120.4
C69-C70-C71	111.4(7)	C77-C76-C75	122.8(9)
C69-C70-C90	125.9(8)	C77-C76-N5	117.9(8)
C71-C70-C90	122.4(7)	C75-C76-N5	119.0(8)
C70-C71-C72	116.4(7)	C76-C77-C78	116.9(8)
C70-C71-C67	105.5(6)	C76-C77-H77	121.6
C72-C71-C67	113.5(6)	C78-C77-H77	121.6
C70-C71-H71	107.0	C77-C78-C79	122.7(8)
C72-C71-H71	107.0	C77-C78-N6	117.9(9)
C67-C71-H71	107.0	C79-C78-N6	119.1(9)

C78-C79-C74	118.9(9)	C81-C86-C85	121.8(9)
C78-C79-H79	120.5	C81-C86-H86	119.1
C74-C79-H79	120.5	C85-C86-H86	119.1
O26-C80-C81	110.9(7)	O27-C87-H87A	109.5
O26-C80-H80A	109.4	O27-C87-H87B	109.5
C81-C80-H80A	109.5	H87A-C87-H87B	109.5
O26-C80-H80B	109.4	O27-C87-H87C	109.5
C81-C80-H80B	109.4	H87A-C87-H87C	109.5
H80A-C80-H80B	108.0	H87B-C87-H87C	109.5
C86-C81-C82	118.2(9)	C62-C88-H88A	120.0
C86-C81-C80	121.2(8)	C62-C88-H88B	120.0
C82-C81-C80	120.6(9)	H88A-C88-H88B	120.0
C83-C82-C81	120.6(9)	C66-C89-H89A	120.0
C83-C82-H82	119.7	C66-C89-H89B	120.0
C81-C82-H82	119.7	H89A-C89-H89B	120.0
C82-C83-C84	119.5(9)	C70-C90-H90A	109.5
C82-C83-H83	120.3	C70-C90-H90B	109.5
C84-C83-H83	120.3	H90A-C90-H90B	109.5
C85-C84-C83	120.9(9)	C70-C90-H90C	109.5
C85-C84-O27	125.4(9)	H90A-C90-H90C	109.5
C83-C84-O27	113.7(8)	H90B-C90-H90C	109.5
C84-C85-C86	119.0(9)	O5-N1-O4	124.1(8)
C84-C85-H85	120.5	O5-N1-C16	118.0(7)
C86-C85-H85	120.5	O4-N1-C16	117.9(7)

O6-N2-O7	124.4(8)	O25-N6-C78	117.5(9)
O6-N2-C18	117.4(8)	C1-O1-C12	107.8(6)
O7-N2-C18	118.2(8)	C13-O2-C4	117.3(7)
O14-N3-O13	125.2(8)	C8-O8-C20	111.6(6)
O14-N3-C46	117.9(7)	C24-O9-C27	116.2(7)
O13-N3-C46	116.9(8)	C31-O10-C42	106.5(6)
O16-N4-O15	126.2(8)	C43-O11-C34	117.4(7)
O16-N4-C48	116.5(8)	C38-O17-C50	111.2(6)
O15-N4-C48	117.3(9)	C54-O18-C57	115.8(6)
O23-N5-O22	125.0(8)	C61-O19-C72	108.0(6)
O23-N5-C76	117.6(8)	C73-O20-C64	116.6(6)
O22-N5-C76	117.4(8)	C68-O26-C80	111.3(6)
O24-N6-O25	124.5(9)	C84-O27-C87	116.1(7)
O24-N6-C78	118.0(9)		

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **85**. 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}
C1	17(5)	28(6)	28(5)	1(5)	-9(4)	-1(5)
C2	20(5)	24(6)	20(5)	3(5)	3(4)	-3(5)
C3	19(5)	17(5)	15(5)	2(4)	10(4)	2(4)

C4	35(6)	16(5)	6(4)	3(4)	8(4)	-8(5)
C5	18(5)	18(5)	12(4)	-3(4)	3(4)	0(4)
C6	19(5)	19(6)	22(5)	-1(5)	-2(4)	-4(5)
C7	20(5)	18(6)	23(5)	2(4)	-5(4)	-6(5)
C8	24(5)	22(6)	24(5)	-6(5)	-4(4)	0(5)
C9	32(6)	28(6)	14(5)	-4(5)	-1(4)	-2(5)
C10	22(5)	20(6)	15(5)	-1(4)	-3(4)	2(5)
C11	20(5)	13(5)	15(5)	-8(4)	-6(4)	3(4)
C12	15(5)	16(6)	28(5)	2(4)	3(4)	0(4)
C13	20(5)	28(6)	15(5)	4(5)	-1(4)	8(5)
C14	21(5)	18(5)	7(5)	7(4)	0(4)	3(4)
C15	14(5)	29(6)	14(5)	0(4)	4(4)	0(5)
C16	28(5)	11(5)	19(5)	-3(4)	0(4)	6(5)
C17	19(5)	25(6)	18(5)	5(5)	1(4)	-1(5)
C18	17(5)	23(6)	7(5)	-4(4)	-2(4)	3(4)
C19	19(5)	27(6)	18(5)	3(5)	3(4)	4(5)
C20	25(6)	34(7)	28(5)	-5(5)	-8(4)	-3(5)
C21	9(5)	22(6)	37(6)	-11(5)	-3(4)	0(5)
C22	36(6)	36(7)	28(6)	9(5)	-5(5)	-1(6)
C23	31(6)	27(6)	25(5)	7(5)	4(5)	1(5)
C24	23(6)	34(7)	29(6)	0(5)	5(4)	1(5)
C25	30(6)	45(8)	28(6)	-5(5)	-9(5)	13(6)
C26	26(6)	52(8)	23(5)	-3(6)	-10(5)	1(6)
C27	47(6)	60(8)	24(6)	-8(5)	7(5)	13(6)

C28	37(6)	40(7)	27(6)	-5(5)	-1(5)	7(6)
C29	24(5)	29(6)	33(6)	6(5)	4(4)	-2(5)
C30	29(5)	40(7)	22(5)	6(5)	5(4)	-2(5)
C31	28(6)	44(8)	28(6)	-6(5)	-5(5)	-5(5)
C32	15(5)	30(6)	17(5)	-9(5)	3(4)	-6(5)
C33	9(5)	22(6)	20(5)	1(4)	0(4)	1(4)
C34	23(5)	22(6)	18(5)	-1(4)	-3(4)	-8(5)
C35	12(5)	25(6)	18(5)	3(4)	4(4)	-1(4)
C36	15(5)	19(5)	19(5)	-6(4)	0(4)	-1(4)
C37	15(5)	15(5)	22(5)	-2(4)	-6(4)	-1(4)
C38	22(5)	24(6)	19(5)	8(4)	1(4)	-6(5)
C39	30(6)	18(6)	22(5)	2(4)	11(4)	2(5)
C40	21(5)	30(6)	14(5)	5(4)	3(4)	4(5)
C41	19(5)	19(6)	27(5)	6(5)	5(4)	-1(4)
C42	18(5)	29(6)	19(5)	-2(5)	-5(4)	-6(5)
C43	21(5)	33(7)	15(6)	-12(5)	-1(4)	-15(5)
C44	16(5)	22(6)	15(5)	2(5)	1(4)	-4(5)
C45	31(5)	29(6)	19(5)	-10(5)	9(4)	-17(5)
C46	18(5)	28(6)	15(5)	-1(5)	5(4)	2(5)
C47	10(5)	40(7)	28(6)	-11(5)	1(4)	1(5)
C48	20(5)	39(7)	15(5)	-6(5)	0(4)	1(5)
C49	17(5)	31(6)	15(5)	0(5)	0(4)	2(5)
C50	22(5)	32(6)	20(5)	3(5)	-10(4)	1(5)
C51	17(5)	16(5)	22(5)	3(5)	-10(4)	-6(4)

C52	15(5)	35(7)	18(5)	0(5)	-3(4)	3(5)
C53	23(6)	25(6)	29(6)	-13(5)	-1(4)	-4(5)
C54	20(5)	27(6)	21(5)	1(5)	5(4)	4(5)
C55	19(5)	22(6)	18(5)	4(5)	3(4)	4(5)
C56	21(5)	21(6)	34(6)	-9(5)	2(4)	3(5)
C57	40(6)	45(7)	22(5)	12(5)	13(4)	-7(5)
C58	29(6)	42(7)	32(6)	-2(5)	-2(5)	-10(5)
C59	28(6)	31(6)	18(5)	-2(5)	-1(4)	-7(5)
C60	33(6)	48(7)	25(5)	-5(5)	12(4)	5(6)
C61	31(6)	21(6)	29(5)	-3(5)	2(5)	-1(5)
C62	20(5)	22(6)	18(5)	-6(4)	0(4)	-1(5)
C63	22(5)	12(5)	17(5)	-5(4)	2(4)	-2(4)
C64	35(6)	10(5)	12(5)	-9(4)	4(4)	3(5)
C65	19(5)	20(5)	18(5)	0(4)	-3(4)	-6(4)
C66	24(5)	25(6)	26(5)	-8(5)	1(4)	-2(5)
C67	23(5)	16(5)	22(5)	-4(4)	-6(4)	3(4)
C68	31(6)	22(6)	18(5)	-4(5)	-5(4)	1(5)
C69	29(6)	22(6)	13(5)	-3(4)	4(4)	8(5)
C70	23(5)	21(6)	9(5)	2(4)	-3(4)	-3(5)
C71	27(5)	11(5)	13(5)	-2(4)	-4(4)	-1(4)
C72	21(5)	17(6)	21(5)	-4(4)	2(4)	-9(4)
C73	22(5)	15(6)	31(6)	-7(5)	0(4)	-12(5)
C74	21(5)	20(6)	12(5)	5(4)	-2(4)	-6(5)
C75	20(5)	16(5)	18(5)	0(4)	-2(4)	1(5)

C76	22(5)	21(6)	25(5)	-3(5)	4(4)	-2(5)
C77	19(6)	31(7)	30(6)	-14(5)	6(4)	-5(5)
C78	27(6)	39(7)	14(5)	9(5)	-2(4)	-13(5)
C79	19(5)	27(6)	17(5)	-6(5)	-1(4)	-2(4)
C80	24(6)	31(7)	40(6)	-8(5)	-12(5)	4(5)
C81	13(5)	36(7)	28(6)	-12(5)	-1(4)	5(5)
C82	17(5)	47(7)	27(5)	-2(5)	5(4)	3(5)
C83	18(5)	50(7)	30(6)	-8(5)	2(4)	-6(5)
C84	19(6)	41(7)	30(6)	-2(5)	6(5)	0(5)
C85	34(6)	50(8)	14(5)	3(5)	4(4)	11(6)
C86	25(6)	44(8)	28(6)	-10(5)	-7(5)	10(6)
C87	40(7)	50(8)	62(7)	10(6)	20(6)	1(6)
C88	20(5)	29(6)	31(6)	-1(5)	-2(4)	-4(5)
C89	29(6)	29(6)	35(6)	7(5)	2(5)	7(5)
C90	38(6)	29(6)	21(5)	-4(5)	12(4)	-1(5)
N1	30(5)	22(5)	19(5)	4(4)	3(4)	-3(4)
N2	20(4)	47(6)	20(5)	5(5)	4(4)	12(5)
N3	27(5)	32(6)	29(5)	5(5)	-1(4)	-13(4)
N4	32(5)	66(8)	25(5)	-21(5)	3(4)	2(5)
N5	26(5)	25(5)	37(5)	-7(5)	-1(4)	-6(4)
N6	42(6)	52(7)	27(5)	-1(5)	2(4)	-9(5)
O1	26(3)	23(4)	22(3)	-6(3)	-2(3)	8(3)
O2	23(3)	20(4)	13(3)	2(3)	6(3)	1(3)
O3	36(4)	28(4)	19(3)	-7(3)	4(3)	-5(3)

O4	41(4)	30(4)	27(4)	-8(3)	10(3)	-13(3)
O5	31(4)	28(4)	33(4)	-4(3)	14(3)	-10(3)
O6	44(4)	45(5)	21(4)	-5(3)	13(3)	-14(4)
O7	38(4)	23(4)	29(4)	-8(3)	6(3)	-5(4)
O8	28(4)	23(4)	19(3)	-1(3)	-5(3)	3(3)
O9	39(4)	47(5)	20(4)	-5(3)	4(3)	12(4)
O10	28(4)	35(4)	21(3)	1(3)	-1(3)	-15(3)
O11	28(3)	21(4)	14(3)	-5(3)	9(3)	0(3)
O12	41(4)	26(4)	20(3)	5(3)	10(3)	2(4)
O13	45(4)	45(5)	20(4)	7(4)	12(3)	10(4)
O14	48(4)	24(4)	41(4)	-6(4)	14(3)	0(4)
O15	56(5)	63(6)	21(4)	-5(4)	14(3)	18(5)
O16	64(5)	88(7)	23(4)	6(4)	-4(4)	45(5)
O17	16(3)	21(4)	23(3)	4(3)	-1(3)	3(3)
O18	22(3)	32(4)	22(3)	-1(3)	3(3)	-7(3)
O19	32(4)	18(4)	21(3)	-4(3)	-4(3)	-3(3)
O20	28(3)	13(4)	16(3)	7(3)	3(3)	3(3)
O21	40(4)	18(4)	22(3)	2(3)	8(3)	4(3)
O22	28(4)	23(4)	42(4)	2(3)	3(3)	5(3)
O23	26(4)	34(5)	52(4)	-17(4)	7(3)	6(3)
O24	78(5)	71(6)	25(4)	1(4)	22(4)	9(5)
O25	67(5)	48(5)	30(4)	8(4)	8(4)	-15(5)
O26	23(4)	18(4)	30(3)	-2(3)	-8(3)	1(3)
O27	34(4)	47(5)	37(4)	3(4)	7(3)	0(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for **85**.

	x	y	z	U(eq)
H1A	-1314	8977	3048	30
H1B	-1696	7555	3355	30
H3	-804	3304	3625	19
H4	-437	1405	3047	22
H5A	163	1474	3747	19
H5B	485	1364	3317	19
H7	675	7380	4126	25
H8	766	5099	4760	29
H9	12	1853	4776	30
H11	-165	8087	4257	20
H12	-249	7659	3429	24
H15	479	7354	2551	23
H17	964	8266	1307	25
H19	14	2509	1537	26
H20A	1624	3256	4806	36
H20B	1542	4456	4310	36
H22	1661	1752	3643	41
H23	2170	-1296	3373	33

H25	2699	-3315	4652	42
H26	2180	-346	4925	42
H27A	2860	-3734	3217	65
H27B	2335	-5311	3271	65
H27C	2915	-6576	3335	65
H28A	-1703	5006	2538	42
H28B	-1273	2726	2616	42
H29A	1138	6961	3526	35
H29B	1014	4781	3147	35
H30A	-979	5521	4735	46
H30B	-1007	2738	4572	46
H30C	-1160	4880	4212	46
H31A	4422	5033	256	41
H31B	4900	3372	109	41
H33	3933	-853	-246	21
H34	3368	-1789	280	26
H35A	2540	-1645	-160	22
H35B	2981	-2130	-492	22
H37	2734	3500	-1123	21
H38	2699	629	-1655	26
H39	3411	-2731	-1499	27
H41	3618	3699	-1074	26
H42	3498	3961	-282	28
H45	2414	4774	415	31

H47	1891	7648	1536	32
H49	2861	1695	1647	26
H50A	1823	-1033	-1768	31
H50B	1828	606	-1321	31
H52	1342	-4917	-1818	27
H53	780	-7708	-1525	31
H55	913	-3858	-353	23
H56	1469	-1084	-655	31
H57A	237	-6772	-182	53
H57B	851	-7654	-113	53
H57C	375	-9620	-185	53
H58A	4205	-961	776	42
H58B	4697	1038	870	42
H59A	2065	2234	-208	31
H59B	2115	4008	-646	31
H60A	4492	870	-1269	52
H60B	4388	-2003	-1245	52
H60C	4505	-447	-788	52
H61A	7731	13887	3882	33
H61B	8119	12550	3569	33
H63	7268	8332	3238	20
H64	6866	6133	3764	23
H65A	6313	6397	3053	23
H65B	5961	6094	3460	23

H67	5780	12316	2702	25
H68	5759	10282	2049	29
H69	6552	7334	2016	25
H71	6619	13253	2642	21
H72	6660	12503	3452	24
H75	5986	11861	4398	22
H77	5673	12245	5696	32
H79	6605	6779	5311	26
H80A	4955	8596	1919	40
H80B	4931	9028	2448	40
H82	4548	5048	1549	36
H83	3941	1857	1561	39
H85	4075	2291	2925	39
H86	4676	5508	2910	40
H87A	3292	157	2783	74
H87B	3785	-1722	2813	74
H87C	3207	-2484	2557	74
H88A	8098	9824	4374	33
H88B	7675	7536	4267	33
H89A	5381	9313	3621	38
H89B	5271	11596	3262	38
H90A	7518	11577	2265	43
H90B	7512	8697	2179	43
H90C	7660	9743	2682	43

Table 6. Torsion angles [°] for **85**.

O1-C1-C2-C28	-177.8(8)	C11-C7-C8-C9	19.8(8)
O1-C1-C2-C3	0.2(8)	O8-C8-C9-C10	-140.1(7)
C28-C2-C3-C4	30.9(12)	C7-C8-C9-C10	-16.2(9)
C1-C2-C3-C4	-147.0(7)	C8-C9-C10-C30	-169.5(8)
C28-C2-C3-C12	157.9(9)	C8-C9-C10-C11	4.8(10)
C1-C2-C3-C12	-20.0(8)	C9-C10-C11-C12	133.6(8)
C2-C3-C4-O2	53.3(9)	C30-C10-C11-C12	-51.7(10)
C12-C3-C4-O2	-65.7(8)	C9-C10-C11-C7	8.8(9)
C2-C3-C4-C5	172.0(7)	C30-C10-C11-C7	-176.5(7)
C12-C3-C4-C5	53.0(9)	C6-C7-C11-C10	102.9(8)
O2-C4-C5-C6	56.9(8)	C8-C7-C11-C10	-17.6(8)
C3-C4-C5-C6	-63.0(9)	C6-C7-C11-C12	-24.3(10)
C4-C5-C6-C29	-90.8(9)	C8-C7-C11-C12	-144.7(7)
C4-C5-C6-C7	89.2(8)	C10-C11-C12-O1	79.7(8)
C29-C6-C7-C11	127.9(8)	C7-C11-C12-O1	-159.7(7)
C5-C6-C7-C11	-52.1(10)	C10-C11-C12-C3	-38.3(10)
C29-C6-C7-C8	-116.1(8)	C7-C11-C12-C3	82.4(9)
C5-C6-C7-C8	64.0(9)	C4-C3-C12-O1	160.2(6)
C6-C7-C8-O8	19.2(9)	C2-C3-C12-O1	33.1(7)
C11-C7-C8-O8	142.5(7)	C4-C3-C12-C11	-79.7(9)
C6-C7-C8-C9	-103.5(8)	C2-C3-C12-C11	153.2(7)

O3-C13-C14-C15	-164.2(8)	O9-C24-C25-C26	-176.9(8)
O2-C13-C14-C15	15.0(10)	C24-C25-C26-C21	-0.1(14)
O3-C13-C14-C19	7.7(12)	C22-C21-C26-C25	-2.2(13)
O2-C13-C14-C19	-173.1(7)	C20-C21-C26-C25	179.9(9)
C19-C14-C15-C16	2.4(12)	O10-C31-C32-C58	172.9(8)
C13-C14-C15-C16	174.2(7)	O10-C31-C32-C33	-10.5(9)
C14-C15-C16-C17	-0.1(12)	C58-C32-C33-C34	36.8(13)
C14-C15-C16-N1	-177.3(7)	C31-C32-C33-C34	-139.7(8)
C15-C16-C17-C18	-1.2(12)	C58-C32-C33-C42	164.5(9)
N1-C16-C17-C18	176.0(7)	C31-C32-C33-C42	-11.9(8)
C16-C17-C18-C19	0.3(12)	C32-C33-C34-O11	56.0(9)
C16-C17-C18-N2	-175.3(7)	C42-C33-C34-O11	-65.3(8)
C17-C18-C19-C14	1.9(12)	C32-C33-C34-C35	176.6(7)
N2-C18-C19-C14	177.5(7)	C42-C33-C34-C35	55.2(10)
C15-C14-C19-C18	-3.2(12)	O11-C34-C35-C36	55.4(8)
C13-C14-C19-C18	-175.1(7)	C33-C34-C35-C36	-65.8(10)
O8-C20-C21-C26	-104.4(9)	C34-C35-C36-C59	-90.1(9)
O8-C20-C21-C22	77.8(10)	C34-C35-C36-C37	91.1(8)
C26-C21-C22-C23	3.0(13)	C59-C36-C37-C41	127.6(8)
C20-C21-C22-C23	-179.1(8)	C35-C36-C37-C41	-53.6(10)
C21-C22-C23-C24	-1.4(14)	C59-C36-C37-C38	-115.8(8)
C22-C23-C24-O9	177.5(8)	C35-C36-C37-C38	63.1(9)
C22-C23-C24-C25	-1.0(13)	C36-C37-C38-O17	13.9(9)
C23-C24-C25-C26	1.7(14)	C41-C37-C38-O17	136.4(7)

C36-C37-C38-C39	-108.8(7)	O12-C43-C44-C49	11.9(12)
C41-C37-C38-C39	13.7(8)	O11-C43-C44-C49	-168.5(7)
O17-C38-C39-C40	-135.7(7)	C49-C44-C45-C46	2.0(12)
C37-C38-C39-C40	-10.5(9)	C43-C44-C45-C46	176.6(8)
C38-C39-C40-C60	-171.0(8)	C44-C45-C46-C47	0.8(13)
C38-C39-C40-C41	2.3(10)	C44-C45-C46-N3	178.7(7)
C39-C40-C41-C42	133.8(8)	C45-C46-C47-C48	-2.7(13)
C60-C40-C41-C42	-52.6(11)	N3-C46-C47-C48	179.4(7)
C39-C40-C41-C37	6.9(9)	C46-C47-C48-C49	1.9(13)
C60-C40-C41-C37	-179.6(7)	C46-C47-C48-N4	-175.6(7)
C36-C37-C41-C40	107.8(7)	C47-C48-C49-C44	0.9(13)
C38-C37-C41-C40	-12.5(8)	N4-C48-C49-C44	178.3(7)
C36-C37-C41-C42	-21.1(10)	C45-C44-C49-C48	-2.9(12)
C38-C37-C41-C42	-141.3(7)	C43-C44-C49-C48	-177.6(8)
C40-C41-C42-O10	76.0(9)	O17-C50-C51-C52	-93.6(9)
C37-C41-C42-O10	-161.6(7)	O17-C50-C51-C56	84.2(9)
C40-C41-C42-C33	-42.6(10)	C56-C51-C52-C53	-2.9(12)
C37-C41-C42-C33	79.9(9)	C50-C51-C52-C53	174.9(7)
C34-C33-C42-O10	159.4(6)	C51-C52-C53-C54	-0.3(12)
C32-C33-C42-O10	30.2(8)	C52-C53-C54-C55	3.3(12)
C34-C33-C42-C41	-79.7(9)	C52-C53-C54-O18	-177.1(7)
C32-C33-C42-C41	151.1(7)	O18-C54-C55-C56	177.4(7)
O12-C43-C44-C45	-162.7(8)	C53-C54-C55-C56	-3.2(12)
O11-C43-C44-C45	16.9(11)	C54-C55-C56-C51	-0.1(12)

C52-C51-C56-C55	3.1(12)	O26-C68-C69-C70	-140.8(7)
C50-C51-C56-C55	-174.8(7)	C67-C68-C69-C70	-14.3(10)
O19-C61-C62-C88	-176.3(8)	C68-C69-C70-C71	4.3(10)
O19-C61-C62-C63	3.4(8)	C68-C69-C70-C90	-169.1(8)
C88-C62-C63-C64	30.9(12)	C69-C70-C71-C72	134.8(8)
C61-C62-C63-C64	-148.9(7)	C90-C70-C71-C72	-51.6(11)
C88-C62-C63-C72	157.4(8)	C69-C70-C71-C67	7.9(9)
C61-C62-C63-C72	-22.4(8)	C90-C70-C71-C67	-178.5(7)
C62-C63-C64-O20	51.4(9)	C66-C67-C71-C70	106.2(7)
C72-C63-C64-O20	-67.6(8)	C68-C67-C71-C70	-15.5(8)
C62-C63-C64-C65	170.9(7)	C66-C67-C71-C72	-22.5(10)
C72-C63-C64-C65	51.9(9)	C68-C67-C71-C72	-144.1(7)
O20-C64-C65-C66	57.7(9)	C70-C71-C72-O19	77.1(9)
C63-C64-C65-C66	-62.3(9)	C67-C71-C72-O19	-160.0(7)
C64-C65-C66-C89	-92.1(10)	C70-C71-C72-C63	-40.7(10)
C64-C65-C66-C67	89.2(9)	C67-C71-C72-C63	82.1(9)
C89-C66-C67-C71	128.4(8)	C64-C63-C72-O19	161.0(6)
C65-C66-C67-C71	-52.9(10)	C62-C63-C72-O19	33.6(8)
C89-C66-C67-C68	-115.3(9)	C64-C63-C72-C71	-79.4(9)
C65-C66-C67-C68	63.3(9)	C62-C63-C72-C71	153.2(7)
C66-C67-C68-O26	19.2(10)	O21-C73-C74-C75	-169.0(8)
C71-C67-C68-O26	142.3(7)	O20-C73-C74-C75	9.9(11)
C66-C67-C68-C69	-105.6(8)	O21-C73-C74-C79	4.7(12)
C71-C67-C68-C69	17.5(8)	O20-C73-C74-C79	-176.4(7)

C79-C74-C75-C76	3.0(12)	C17-C16-N1-O5	1.3(11)
C73-C74-C75-C76	176.6(8)	C15-C16-N1-O5	178.6(7)
C74-C75-C76-C77	-4.7(13)	C17-C16-N1-O4	-179.5(7)
C74-C75-C76-N5	-177.8(7)	C15-C16-N1-O4	-2.1(11)
C75-C76-C77-C78	4.1(13)	C19-C18-N2-O6	178.1(7)
N5-C76-C77-C78	177.3(7)	C17-C18-N2-O6	-6.1(11)
C76-C77-C78-C79	-2.0(13)	C19-C18-N2-O7	-2.6(11)
C76-C77-C78-N6	-175.7(7)	C17-C18-N2-O7	173.2(7)
C77-C78-C79-C74	0.6(13)	C47-C46-N3-O14	8.6(11)
N6-C78-C79-C74	174.2(7)	C45-C46-N3-O14	-169.3(8)
C75-C74-C79-C78	-1.0(12)	C47-C46-N3-O13	-171.7(8)
C73-C74-C79-C78	-174.9(7)	C45-C46-N3-O13	10.4(11)
O26-C80-C81-C86	83.4(10)	C47-C48-N4-O16	177.8(8)
O26-C80-C81-C82	-100.1(9)	C49-C48-N4-O16	0.3(12)
C86-C81-C82-C83	1.3(13)	C47-C48-N4-O15	-4.2(12)
C80-C81-C82-C83	-175.4(8)	C49-C48-N4-O15	178.3(8)
C81-C82-C83-C84	-1.7(13)	C77-C76-N5-O23	9.5(11)
C82-C83-C84-C85	1.9(14)	C75-C76-N5-O23	-177.0(8)
C82-C83-C84-O27	-179.4(8)	C77-C76-N5-O22	-172.7(7)
C83-C84-C85-C86	-1.5(13)	C75-C76-N5-O22	0.8(11)
O27-C84-C85-C86	179.8(8)	C77-C78-N6-O24	-11.6(12)
C82-C81-C86-C85	-1.0(13)	C79-C78-N6-O24	174.4(8)
C80-C81-C86-C85	175.7(8)	C77-C78-N6-O25	169.2(8)
C84-C85-C86-C81	1.1(14)	C79-C78-N6-O25	-4.7(12)

C2-C1-O1-C12	21.9(8)	C35-C34-O11-C43	113.5(7)
C11-C12-O1-C1	-160.2(7)	C39-C38-O17-C50	-159.2(6)
C3-C12-O1-C1	-35.1(8)	C37-C38-O17-C50	81.9(8)
O3-C13-O2-C4	11.4(12)	C51-C50-O17-C38	-168.9(6)
C14-C13-O2-C4	-167.8(6)	C55-C54-O18-C57	-16.1(11)
C3-C4-O2-C13	-135.9(7)	C53-C54-O18-C57	164.4(7)
C5-C4-O2-C13	101.0(7)	C62-C61-O19-C72	18.9(8)
C9-C8-O8-C20	-160.3(6)	C71-C72-O19-C61	-159.0(6)
C7-C8-O8-C20	82.1(8)	C63-C72-O19-C61	-33.5(8)
C21-C20-O8-C8	-169.5(7)	O21-C73-O20-C64	2.6(12)
C23-C24-O9-C27	-7.1(12)	C74-C73-O20-C64	-176.2(6)
C25-C24-O9-C27	171.4(8)	C63-C64-O20-C73	-123.0(7)
C32-C31-O10-C42	30.7(9)	C65-C64-O20-C73	113.7(7)
C41-C42-O10-C31	-165.3(7)	C69-C68-O26-C80	-157.2(6)
C33-C42-O10-C31	-38.5(8)	C67-C68-O26-C80	83.0(8)
O12-C43-O11-C34	11.9(12)	C81-C80-O26-C68	179.0(7)
C44-C43-O11-C34	-167.7(6)	C85-C84-O27-C87	-1.7(12)
C33-C34-O11-C43	-122.9(7)	C83-C84-O27-C87	179.6(8)

APPENDIX B: CRYSTALLOGRAPHIC DATA FOR 92

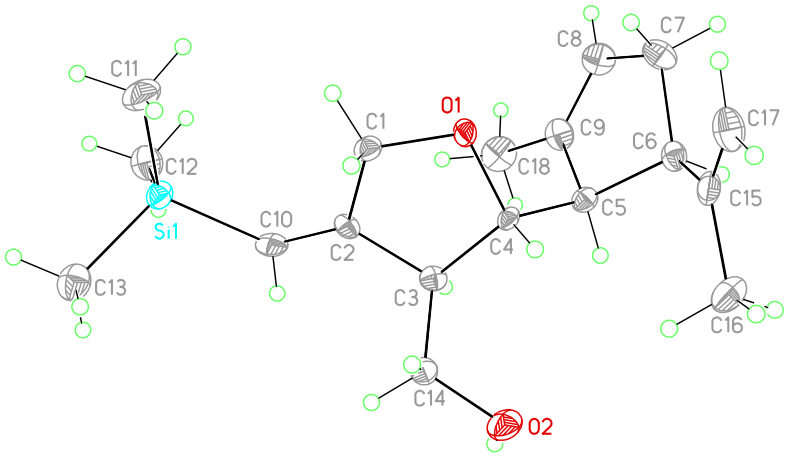


Table 1. Crystal data and structure refinement for **92**.

Empirical formula	C18 H30 O2 Si	
Formula weight	306.51	
Temperature	133(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P 21	
Unit cell dimensions	a = 10.9429(18) Å	α = 90°.
	b = 6.4395(12) Å	ß = 102.480(6)°.
	c = 13.070(3) Å	γ = 90°.
Volume	899.2(3) $Å^3$	
Z	2	
Density (calculated)	1.132 Mg/m^3	
Absorption coefficient	0.134 mm^{-1}	
F(000)	336	
Crystal size	0.39 x 0.15 x 0.10 mm	
Theta range for data collection	3.544 to 25.464°.	
Index ranges	-13<=h<=9, -7<=k<=7, -15<=l<=15	
Reflections collected	5362	
Independent reflections	3151 [R(int) = 0.0478]	
Completeness to theta = 25.242°	98.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.923	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	3151 / 1 / 199
Goodness-of-fit on F^2	1.062
Final R indices [I>2sigma(I)]	R1 = 0.0606, wR2 = 0.1078
R indices (all data)	R1 = 0.0926, wR2 = 0.1184
Absolute structure parameter	0.02(16)
Extinction coefficient	n/a
Largest diff. peak and hole	0.395 and -0.235 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **92**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C1	5035(5)	6449(7)	2871(4)	16(1)
C2	5046(4)	8692(8)	2499(4)	13(1)
C3	4088(5)	9811(8)	2976(4)	14(1)
C4	3341(4)	8073(7)	3380(4)	12(1)
C5	1921(4)	8183(8)	2992(4)	15(1)
C6	1135(5)	6748(7)	3579(4)	17(1)
C7	917(5)	4763(8)	2903(4)	24(1)
C8	939(5)	5602(9)	1831(5)	24(1)
C9	1482(5)	7454(8)	1866(4)	21(1)
C10	5753(4)	9550(8)	1899(4)	18(1)
C11	7376(6)	5758(8)	1539(5)	35(2)
C12	6430(5)	8968(9)	-189(5)	34(2)
C13	8431(5)	10151(9)	1705(5)	28(2)
C14	4774(5)	11226(8)	3853(4)	18(1)
C15	1615(5)	6523(8)	4739(4)	20(1)
C16	1716(5)	8541(10)	5356(4)	29(1)
C17	1880(5)	4720(9)	5225(5)	28(2)
C18	1693(5)	8661(10)	934(4)	30(1)
O1	3809(3)	6122(5)	3058(3)	20(1)

O2	3913(4)	12361(6)	4328(3)	26(1)
Si1	6991(1)	8566(2)	1248(1)	18(1)

Table 3. Bond lengths [Å] and angles [°] for **92**.

C1-O1	1.430(5)	C7-C8	1.507(8)
C1-C2	1.525(7)	C7-H7A	0.99
C1-H1A	0.99	C7-H7B	0.99
C1-H1B	0.99	C8-C9	1.329(7)
C2-C10	1.335(6)	C8-H8	0.95
C2-C3	1.513(7)	C9-C18	1.505(7)
C3-C14	1.528(7)	C10-Si1	1.860(5)
C3-C4	1.544(6)	C10-H10	0.95
C3-H3	1.00	C11-Si1	1.877(6)
C4-O1	1.453(6)	C11-H11A	0.98
C4-C5	1.528(6)	C11-H11B	0.98
C4-H4	1.00	C11-H11C	0.98
C5-C9	1.521(7)	C12-Si1	1.864(6)
C5-C6	1.571(7)	C12-H12A	0.98
C5-H5	1.00	C12-H12B	0.98
C6-C15	1.500(7)	C12-H12C	0.98
C6-C7	1.543(7)	C13-Si1	1.864(6)
C6-H6	1.00	C13-H13A	0.98

C13-H13B	0.98	C16-H16B	0.98
C13-H13C	0.98	C16-H16C	0.98
C14-O2	1.435(6)	C17-H17A	0.95
C14-H14A	0.99	C17-H17B	0.95
C14-H14B	0.99	C18-H18A	0.98
C15-C17	1.325(7)	C18-H18B	0.98
C15-C16	1.521(8)	C18-H18C	0.98
C16-H16A	0.98	O2-H2O	0.83(6)
O1-C1-C2	105.5(4)	O1-C4-C3	106.4(4)
O1-C1-H1A	110.6	C5-C4-C3	115.4(4)
C2-C1-H1A	110.6	O1-C4-H4	108.3
O1-C1-H1B	110.6	C5-C4-H4	108.3
C2-C1-H1B	110.6	C3-C4-H4	108.3
H1A-C1-H1B	108.8	C9-C5-C4	113.1(4)
C10-C2-C3	125.9(5)	C9-C5-C6	101.5(4)
C10-C2-C1	128.7(4)	C4-C5-C6	115.8(4)
C3-C2-C1	105.4(4)	C9-C5-H5	108.7
C2-C3-C14	108.7(4)	C4-C5-H5	108.7
C2-C3-C4	105.1(4)	C6-C5-H5	108.7
C14-C3-C4	112.7(4)	C15-C6-C7	118.4(4)
C2-C3-H3	110.0	C15-C6-C5	116.2(4)
C14-C3-H3	110.0	C7-C6-C5	103.9(4)
C4-C3-H3	110.0	C15-C6-H6	105.8
O1-C4-C5	109.9(4)	C7-C6-H6	105.8

C5-C6-H6	105.8	H12A-C12-H12B	109.5
C8-C7-C6	101.8(4)	Si1-C12-H12C	109.5
C8-C7-H7A	111.4	H12A-C12-H12C	109.5
C6-C7-H7A	111.4	H12B-C12-H12C	109.5
C8-C7-H7B	111.4	Si1-C13-H13A	109.5
C6-C7-H7B	111.4	Si1-C13-H13B	109.5
H7A-C7-H7B	109.3	H13A-C13-H13B	109.5
C9-C8-C7	112.7(5)	Si1-C13-H13C	109.5
C9-C8-H8	123.6	H13A-C13-H13C	109.5
C7-C8-H8	123.6	H13B-C13-H13C	109.5
C8-C9-C18	125.5(6)	O2-C14-C3	111.4(4)
C8-C9-C5	110.9(5)	O2-C14-H14A	109.3
C18-C9-C5	123.5(5)	C3-C14-H14A	109.3
C2-C10-Si1	134.4(4)	O2-C14-H14B	109.3
C2-C10-H10	112.8	C3-C14-H14B	109.3
Si1-C10-H10	112.8	H14A-C14-H14B	108.0
Si1-C11-H11A	109.5	C17-C15-C6	124.2(5)
Si1-C11-H11B	109.5	C17-C15-C16	120.7(5)
H11A-C11-H11B	109.5	C6-C15-C16	115.0(5)
Si1-C11-H11C	109.5	C15-C16-H16A	109.5
H11A-C11-H11C	109.5	C15-C16-H16B	109.5
H11B-C11-H11C	109.5	H16A-C16-H16B	109.5
Si1-C12-H12A	109.5	C15-C16-H16C	109.5
Si1-C12-H12B	109.5	H16A-C16-H16C	109.5

H16B-C16-H16C	109.5	H18B-C18-H18C	109.5
C15-C17-H17A	120.0	C1-O1-C4	109.0(3)
C15-C17-H17B	120.0	C14-O2-H2O	102(4)
H17A-C17-H17B	120.0	C10-Si1-C13	108.4(2)
C9-C18-H18A	109.5	C10-Si1-C12	107.4(3)
C9-C18-H18B	109.5	C13-Si1-C12	108.6(3)
H18A-C18-H18B	109.5	C10-Si1-C11	112.9(2)
C9-C18-H18C	109.5	C13-Si1-C11	109.0(3)
H18A-C18-H18C	109.5	C12-Si1-C11	110.4(3)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **92**. 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}
C1	17(3)	12(3)	18(3)	0(2)	5(2)	3(2)
C2	14(2)	10(3)	15(3)	5(3)	2(2)	-1(3)
C3	18(3)	12(3)	13(3)	3(2)	3(3)	1(2)
C4	14(2)	10(3)	14(3)	1(2)	6(2)	3(2)
C5	16(3)	14(3)	16(3)	1(2)	4(2)	3(2)
C6	12(3)	18(3)	21(4)	3(2)	4(3)	2(2)
C7	22(3)	23(3)	24(4)	-2(3)	0(3)	-6(3)
C8	21(3)	32(4)	17(4)	-6(3)	-3(3)	-4(3)
C9	13(3)	25(3)	21(4)	2(3)	-1(3)	2(2)

C10	21(3)	9(3)	21(4)	2(2)	0(3)	3(2)
C11	44(4)	17(3)	49(5)	-1(3)	24(4)	5(3)
C12	35(3)	32(4)	37(4)	-1(3)	17(3)	-5(3)
C13	27(3)	26(3)	31(4)	5(3)	7(3)	6(3)
C14	17(3)	13(3)	27(4)	1(3)	7(3)	2(2)
C15	17(3)	26(3)	20(4)	-1(3)	10(3)	0(3)
C16	33(3)	30(3)	25(3)	-6(3)	12(3)	3(3)
C17	27(3)	34(4)	24(4)	8(3)	9(3)	-2(3)
C18	30(3)	34(3)	22(3)	2(3)	0(3)	3(3)
O1	13(2)	12(2)	36(3)	2(2)	11(2)	3(2)
O2	37(3)	15(2)	31(3)	0(2)	15(2)	3(2)
Si1	21(1)	16(1)	20(1)	2(1)	9(1)	2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for 92.

	x	y	z	U(eq)
H1A	5199	5481	2327	19
H1B	5679	6234	3521	19
H3	3519	10652	2429	17
H4	3536	8124	4163	14
H5	1647	9654	3043	18
H6	296	7427	3491	21
H7A	1593	3735	3136	28

H7B	100	4116	2918	28
H8	600	4884	1198	29
H10	5586	10987	1776	21
H11A	8083	5356	1232	52
H11B	6647	4901	1238	52
H11C	7599	5549	2300	52
H12A	6193	10426	-326	50
H12B	5702	8080	-448	50
H12C	7099	8611	-549	50
H13A	8245	11613	1529	41
H13B	9090	9667	1361	41
H13C	8714	10007	2466	41
H14A	5328	10376	4394	22
H14B	5305	12215	3565	22
H16A	2006	8244	6105	43
H16B	893	9211	5237	43
H16C	2313	9469	5125	43
H17A	1767	3463	4835	33
H17B	2182	4684	5963	33
H18A	2587	8660	929	44
H18B	1406	10094	976	44
H18C	1223	8015	289	44
H2O	3720(50)	13360(100)	3920(50)	40(20)

Table 6. Torsion angles [°] for 92.

O1-C1-C2-C10	-154.5(5)	C7-C8-C9-C18	177.5(5)
O1-C1-C2-C3	26.7(5)	C7-C8-C9-C5	-0.2(6)
C10-C2-C3-C14	-71.2(6)	C4-C5-C9-C8	106.6(5)
C1-C2-C3-C14	107.7(5)	C6-C5-C9-C8	-18.2(5)
C10-C2-C3-C4	167.9(5)	C4-C5-C9-C18	-71.1(6)
C1-C2-C3-C4	-13.3(5)	C6-C5-C9-C18	164.1(5)
C2-C3-C4-O1	-4.3(5)	C3-C2-C10-Si1	178.7(4)
C14-C3-C4-O1	-122.6(4)	C1-C2-C10-Si1	0.1(9)
C2-C3-C4-C5	-126.5(4)	C2-C3-C14-O2	179.0(4)
C14-C3-C4-C5	115.2(5)	C4-C3-C14-O2	-64.8(5)
O1-C4-C5-C9	-43.9(5)	C7-C6-C15-C17	0.7(8)
C3-C4-C5-C9	76.4(6)	C5-C6-C15-C17	-124.1(6)
O1-C4-C5-C6	72.7(5)	C7-C6-C15-C16	-175.8(5)
C3-C4-C5-C6	-167.0(4)	C5-C6-C15-C16	59.4(6)
C9-C5-C6-C15	160.4(4)	C2-C1-O1-C4	-30.4(5)
C4-C5-C6-C15	37.5(6)	C5-C4-O1-C1	147.5(4)
C9-C5-C6-C7	28.6(5)	C3-C4-O1-C1	21.9(5)
C4-C5-C6-C7	-94.4(5)	C2-C10-Si1-C13	-123.5(5)
C15-C6-C7-C8	-159.1(4)	C2-C10-Si1-C12	119.3(5)
C5-C6-C7-C8	-28.6(5)	C2-C10-Si1-C11	-2.6
C6-C7-C8-C9	18.8(6)		

Table 7. Hydrogen bonds for 92 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O2-H2O...O1#1	0.83(6)	2.12(6)	2.924(6)	163(5)

Symmetry transformations used to generate equivalent atoms:

#1 x,y+1,z

APPENDIX C: CRYSTALLOGRAPHIC DATA FOR 192

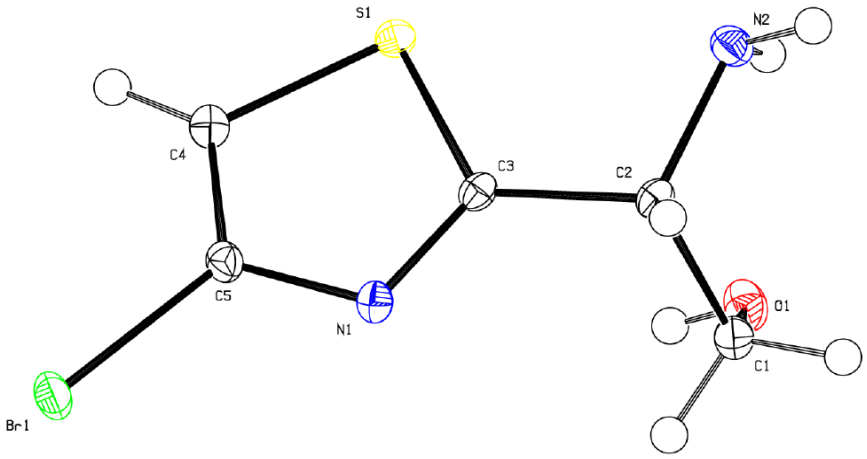


Table 1 Crystal data and structure refinement for **192.**

Identification code	**192**
Empirical formula	$C_5H_7BrN_2OS$
Formula weight	223.10
Temperature/K	100.0
Crystal system	monoclinic
Space group	$P2_1$
a/Å	4.9945(3)
b/Å	9.0674(5)
c/Å	8.2336(5)
α/°	90
β/°	93.053(2)
γ/°	90
Volume/Å^3	372.35(4)
Z	2
ρ_{calc}g/cm^3	1.990
μ/mm^{-1}	5.729
F(000)	220.0
Crystal size/mm^3	0.15 × 0.15 × 0.12
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.954 to 56.592
Index ranges	-5 ≤ h ≤ 6, -12 ≤ k ≤ 12, -10 ≤ l ≤ 10
Reflections collected	6750
Independent reflections	1770 [R_{int} = 0.0462, R_{sigma} = 0.0433]
Data/restraints/parameters	1770/4/100
Goodness-of-fit on F^2	1.010
Final R indexes [I>=2σ (I)]	R_1 = 0.0191, wR_2 = 0.0432
Final R indexes [all data]	R_1 = 0.0196, wR_2 = 0.0433
Largest diff. peak/hole / e Å^{-3}	0.28/-0.42
Flack parameter	0.085(8)

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for 192. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
Br(1)	9597.6(5)	-2584.6(4)	9809.1(3)	16.39(9)
S(1)	5017.7(14)	1009.3(7)	7548.7(8)	11.81(14)
O(1)	4627(5)	-344(2)	3185(3)	16.7(5)
N(1)	8887(5)	-774(2)	7086(3)	11.1(5)
N(2)	6629(5)	2362(3)	4516(3)	13.2(4)
C(1)	7432(7)	-166(3)	3437(4)	14.7(6)
C(2)	8112(5)	973(3)	4783(3)	10.9(5)
C(3)	7548(5)	340(3)	6421(3)	10.2(5)
C(4)	5781(6)	-286(3)	9023(4)	12.6(6)
C(5)	7879(6)	-1093(3)	8556(3)	11.9(5)

Table 3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for **192**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Br(1)	17.81(15)	17.38(13)	14.26(15)	6.59(12)	3.44(10)	5.15(13)
S(1)	11.0(3)	12.8(3)	11.9(3)	0.5(2)	2.7(2)	2.6(2)
O(1)	19.4(13)	14.9(10)	15.5(13)	2.7(8)	-2.4(9)	-3.8(8)
N(1)	10.6(12)	13(1)	9.8(12)	1.2(9)	0.8(9)	-0.5(8)
N(2)	14.0(11)	11.1(9)	14.6(11)	1.5(12)	1.9(9)	0.4(12)
C(1)	19.8(18)	12.6(12)	11.5(16)	0.7(9)	0.7(12)	-0.5(10)
C(2)	9.6(13)	12.9(10)	10.4(13)	-0.3(10)	2.8(10)	-0.5(10)
C(3)	9.9(14)	11.5(11)	9.2(13)	-1.7(9)	0.6(10)	-1.9(10)
C(4)	12.7(15)	13.4(12)	11.7(15)	0.7(9)	0.3(11)	-0.8(10)
C(5)	14.4(15)	11.0(11)	10.0(14)	0.5(10)	-2.1(11)	-0.8(11)

Table 4 Bond Lengths for **192**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
Br(1)	C(5)	1.881(3)	N(1)	C(5)	1.366(4)
S(1)	C(3)	1.718(3)	N(2)	C(2)	1.471(4)
S(1)	C(4)	1.717(3)	C(1)	C(2)	1.540(4)
O(1)	C(1)	1.414(4)	C(2)	C(3)	1.506(4)
N(1)	C(3)	1.315(4)	C(4)	C(5)	1.351(4)

Table 5 Bond Angles for **192**.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C(4)	S(1)	C(3)	89.92(14)	N(1)	C(3)	C(2)	123.4(2)
C(3)	N(1)	C(5)	109.2(2)	C(2)	C(3)	S(1)	121.8(2)
O(1)	C(1)	C(2)	111.2(2)	C(5)	C(4)	S(1)	108.4(2)
N(2)	C(2)	C(1)	112.1(2)	N(1)	C(5)	Br(1)	117.3(2)
N(2)	C(2)	C(3)	110.0(2)	C(4)	C(5)	Br(1)	124.9(2)
C(3)	C(2)	C(1)	110.1(2)	C(4)	C(5)	N(1)	117.7(3)
N(1)	C(3)	S(1)	114.8(2)				

Table 6 Torsion Angles for **192**.

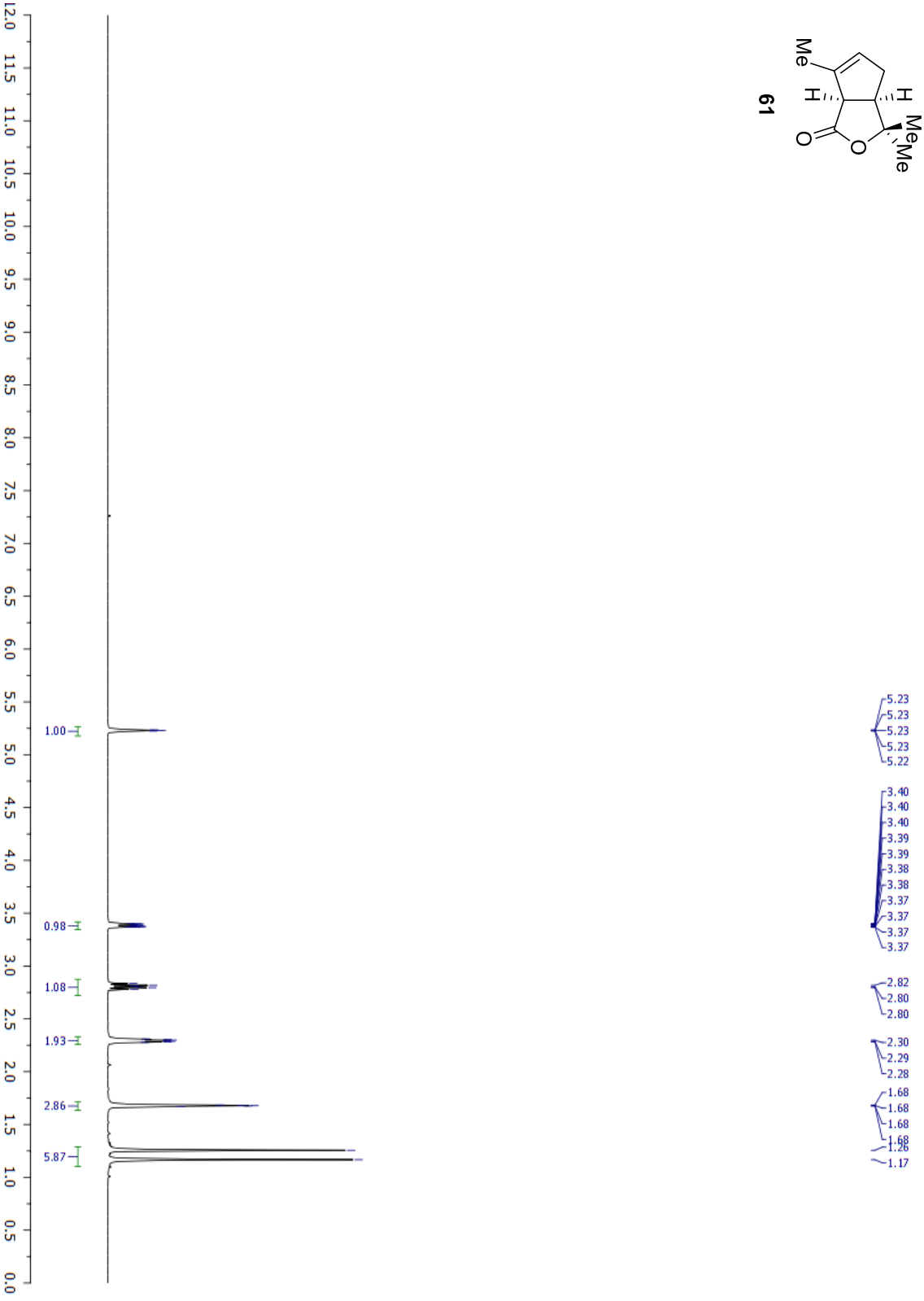
A	B	C	D	Angle/°	A	B	C	D	Angle/°
S(1)	C(4)	C(5)	Br(1)	176.39(16)	C(3)	S(1)	C(4)	C(5)	0.8(2)
S(1)	C(4)	C(5)	N(1)	-1.4(3)	C(3)	N(1)	C(5)	Br(1)	-176.55(18)
O(1)	C(1)	C(2)	N(2)	-50.7(3)	C(3)	N(1)	C(5)	C(4)	1.4(3)
O(1)	C(1)	C(2)	C(3)	72.2(3)	C(4)	S(1)	C(3)	N(1)	0.0(2)
N(2)	C(2)	C(3)	S(1)	11.7(3)	C(4)	S(1)	C(3)	C(2)	178.6(2)
N(2)	C(2)	C(3)	N(1)	-169.8(2)	C(5)	N(1)	C(3)	S(1)	-0.7(3)

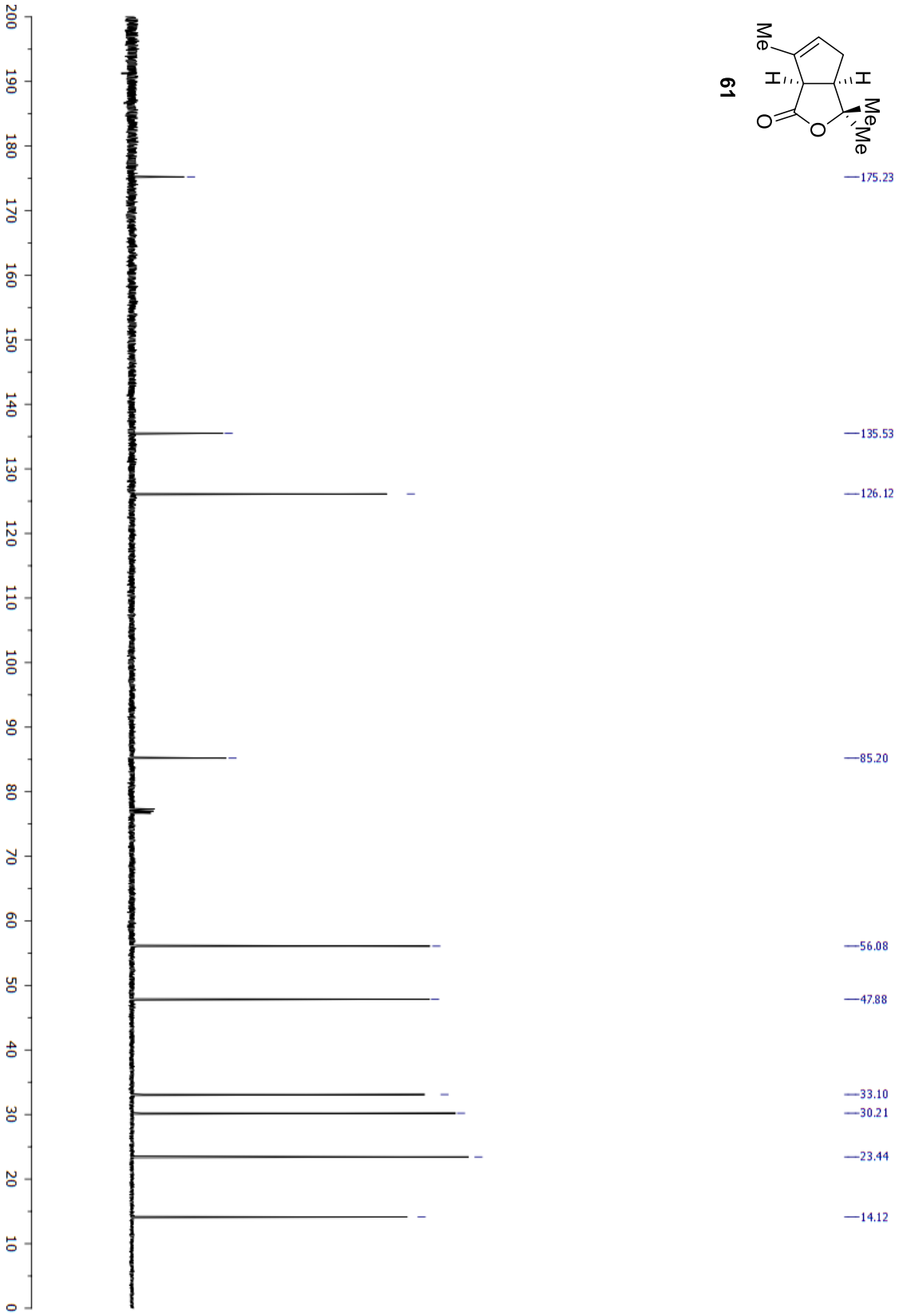
C(1) C(2) C(3) S(1)	-112.4(2)	C(5) N(1) C(3) C(2)	-179.3(2)
C(1) C(2) C(3) N(1)	66.1(3)		

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for **192**.

Atom	*x*	*y*	*z*	U(eq)
H(1)	4150(90)	-870(40)	3770(50)	25
H(2A)	7450(60)	2970(30)	3910(40)	20
H(2B)	5130(40)	2130(30)	4010(40)	20
H(1A)	8194	161	2412	18
H(1B)	8256	-1126	3746	18
H(2)	10073	1197	4777	13
H(4)	4881	-413	10001	15

APPENDIX D: CATALOG OF SPECTRA

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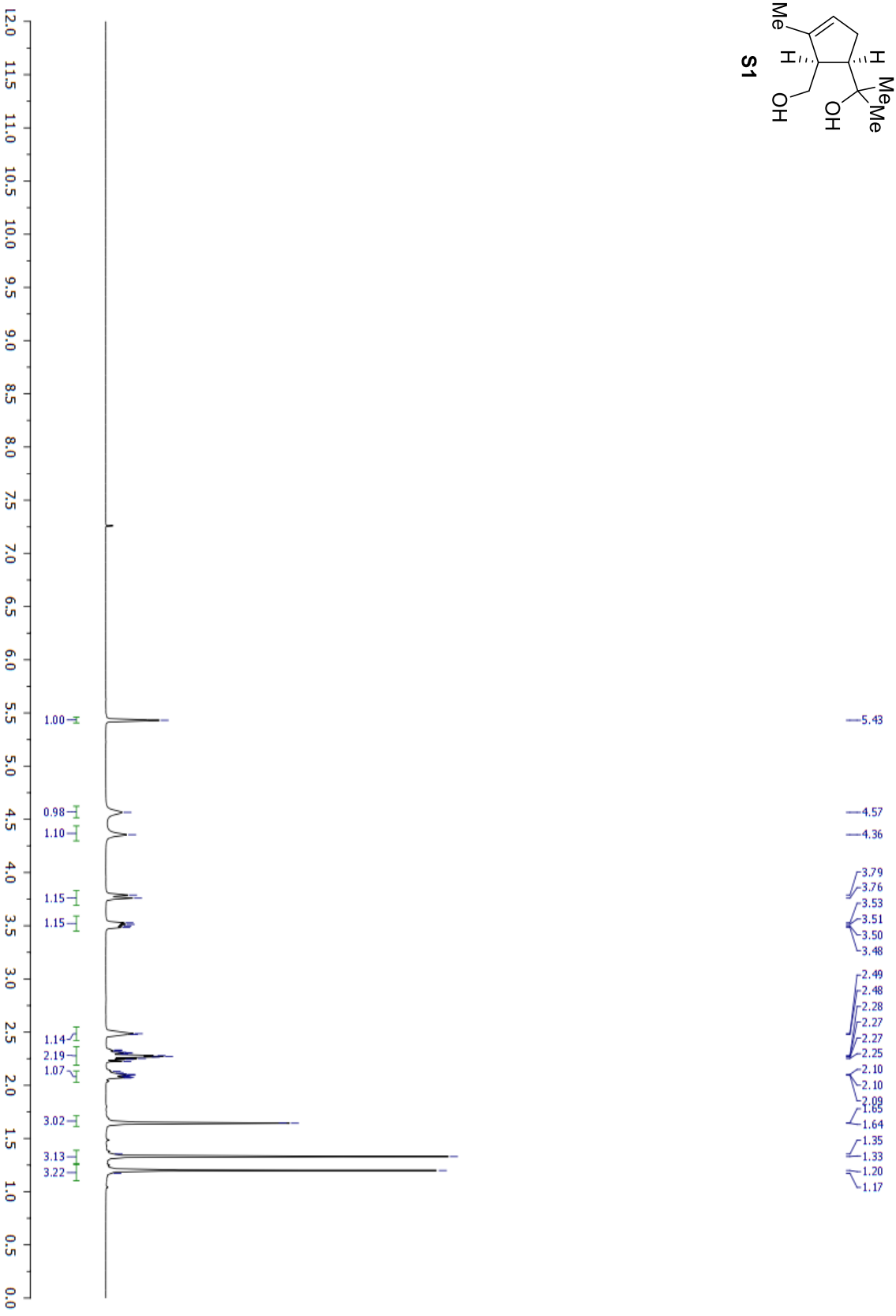
H
H
Me
Me
O
O
61
175.23
135.53
126.12
85.20
56.08
47.88
33.10
30.21
23.44
14.12
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0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H
OH
H
Me
Me
OH
S1
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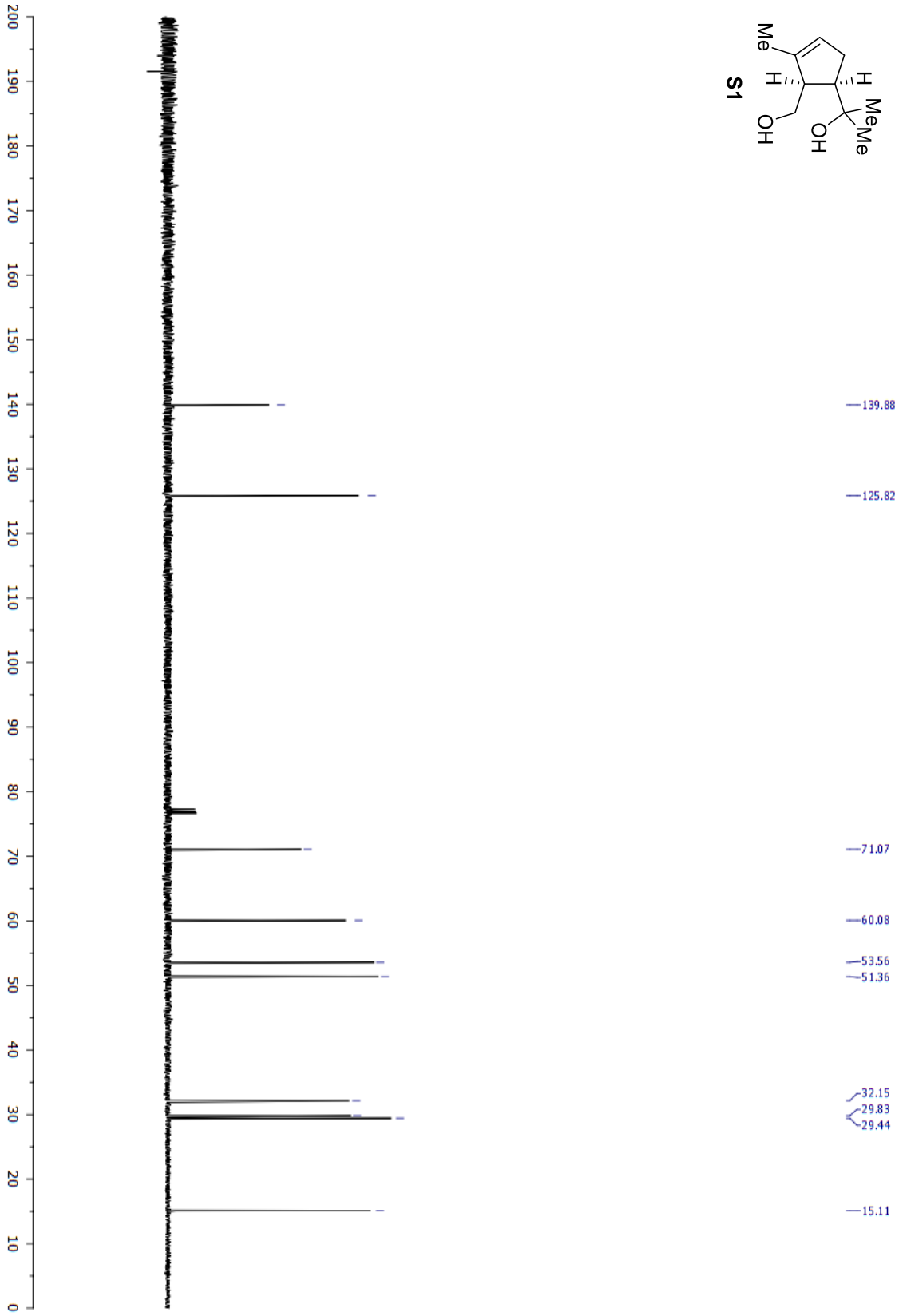
1.00
0.98
1.10
1.15
1.15
1.14
2.19
1.07
3.02
3.13
3.22
5.43
4.57
4.36
3.79
3.76
3.53
3.51
3.50
3.48
2.49
2.48
2.28
2.27
2.27
2.25
2.10
2.10
2.09
1.65
1.64
1.35
1.33
1.20
1.17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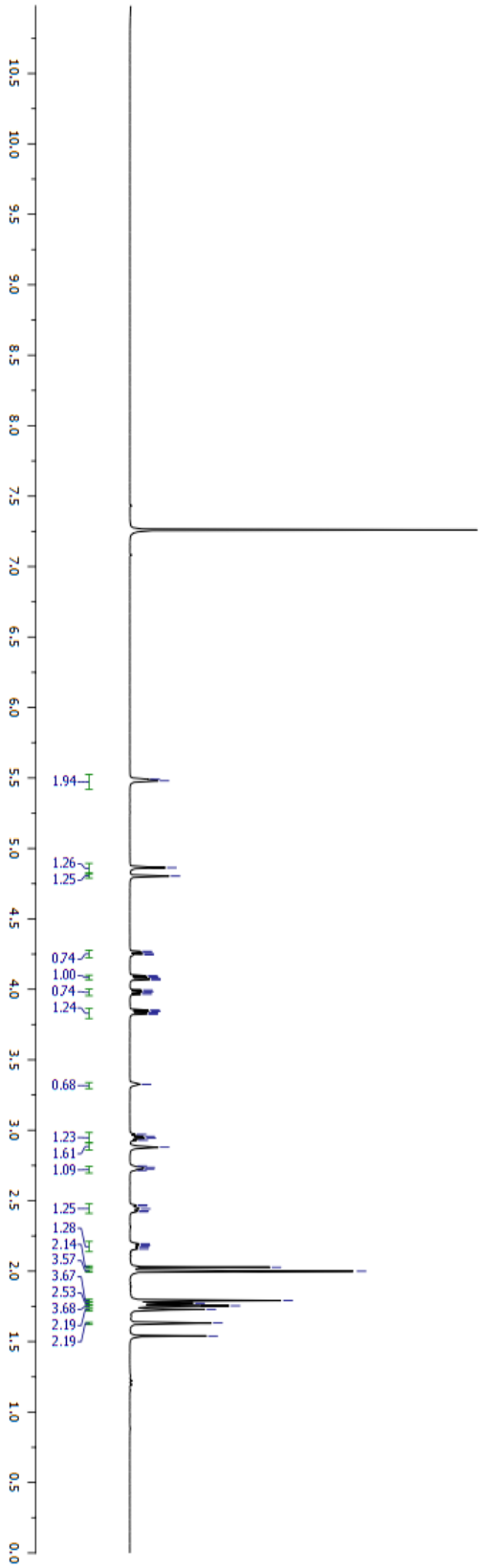
H
OH
H
Me
Me
OH
S1
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
139.88
125.82
71.07
60.08
53.56
51.36
32.15
29.83
29.44
15.11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10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.94
1.26
1.25
0.74
1.00
0.74
1.24
0.68
1.23
1.61
1.09
1.25
1.28
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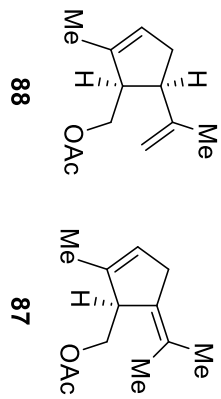
3.57
3.67
2.53
3.68
2.19
2.19


Me
H
OAc
H
Me
Me
H
OAc
Me
Me

88

87


5.49
5.48
4.86
4.80
4.25
4.10
4.09
4.08
4.07
3.85
3.84
3.83
3.82
3.33
2.96
2.94
2.93
2.88
2.75
2.74
2.73
2.47
2.46
2.44
2.43
2.42
2.20
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2.17
2.16
2.03
2.00
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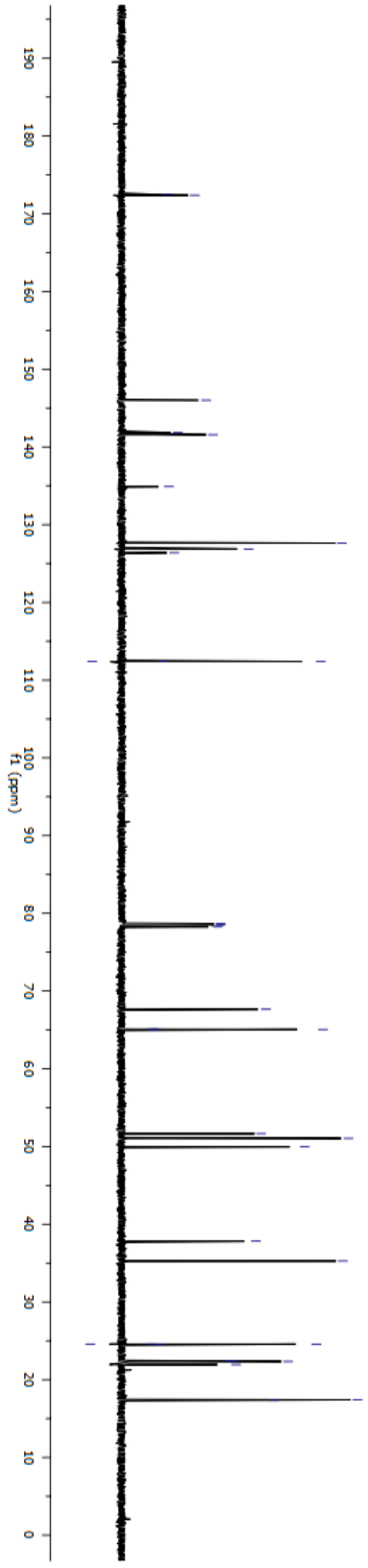
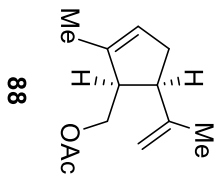
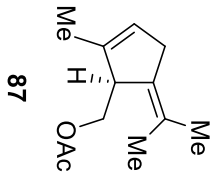
1.77
1.75
1.73
1.63
1.54



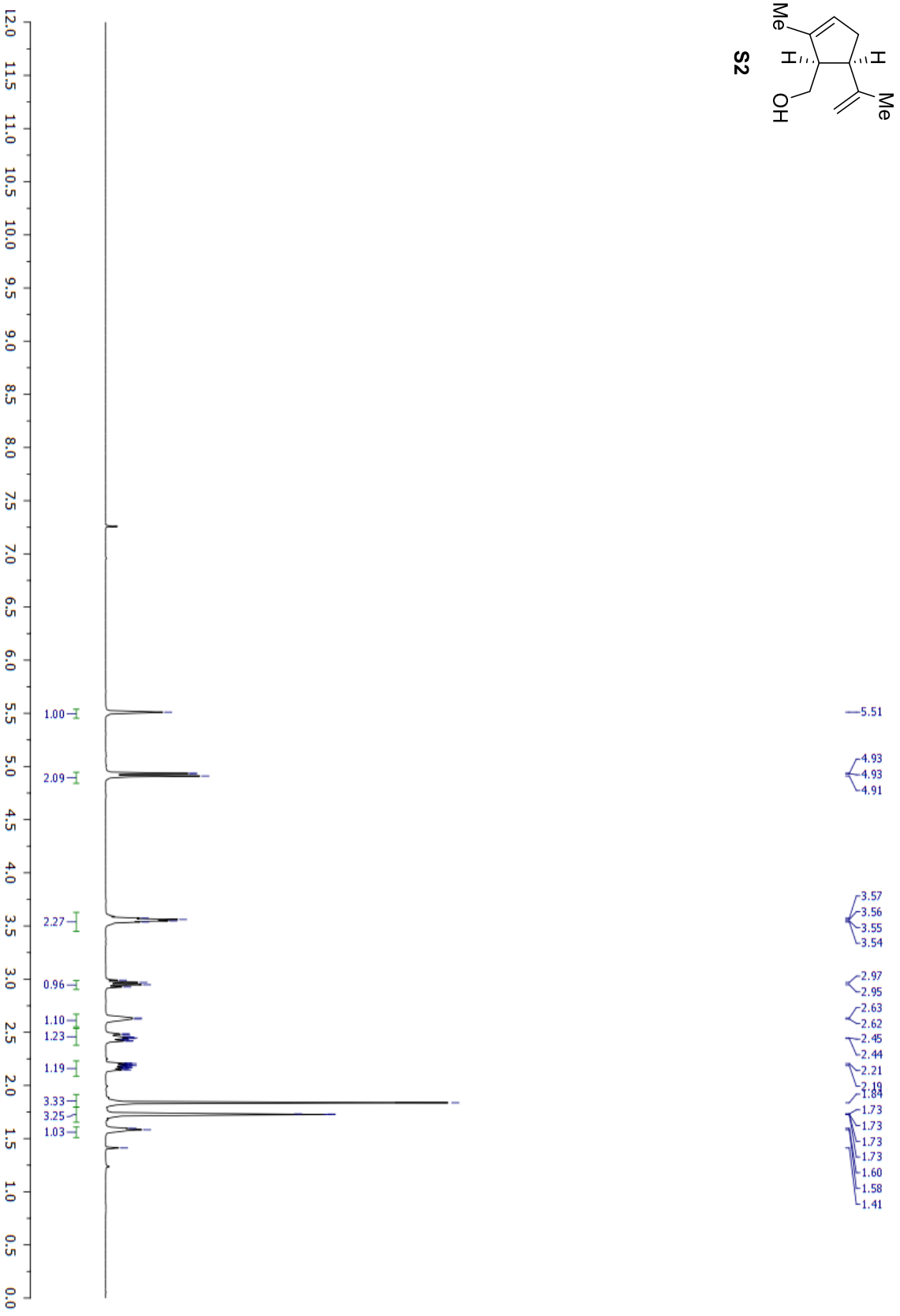


88



87

172.46
172.39
146.01
141.84
141.57
134.89
127.62
126.88
126.39
112.40
112.39
112.38
78.68
78.47
78.26
67.65
65.08
65.07
65.06
51.64
51.05
49.96
37.82
35.27
24.59
24.59
24.59
24.57
22.46
22.42
22.34
21.95
17.42
17.38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H
H
OH
Me
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1.00
2.09
2.27
0.96
1.10
1.23
1.19
3.33
3.25
1.03
5.51
4.93
4.93
4.91
3.57
3.56
3.55
3.54
2.97
2.95
2.63
2.62
2.45
2.44
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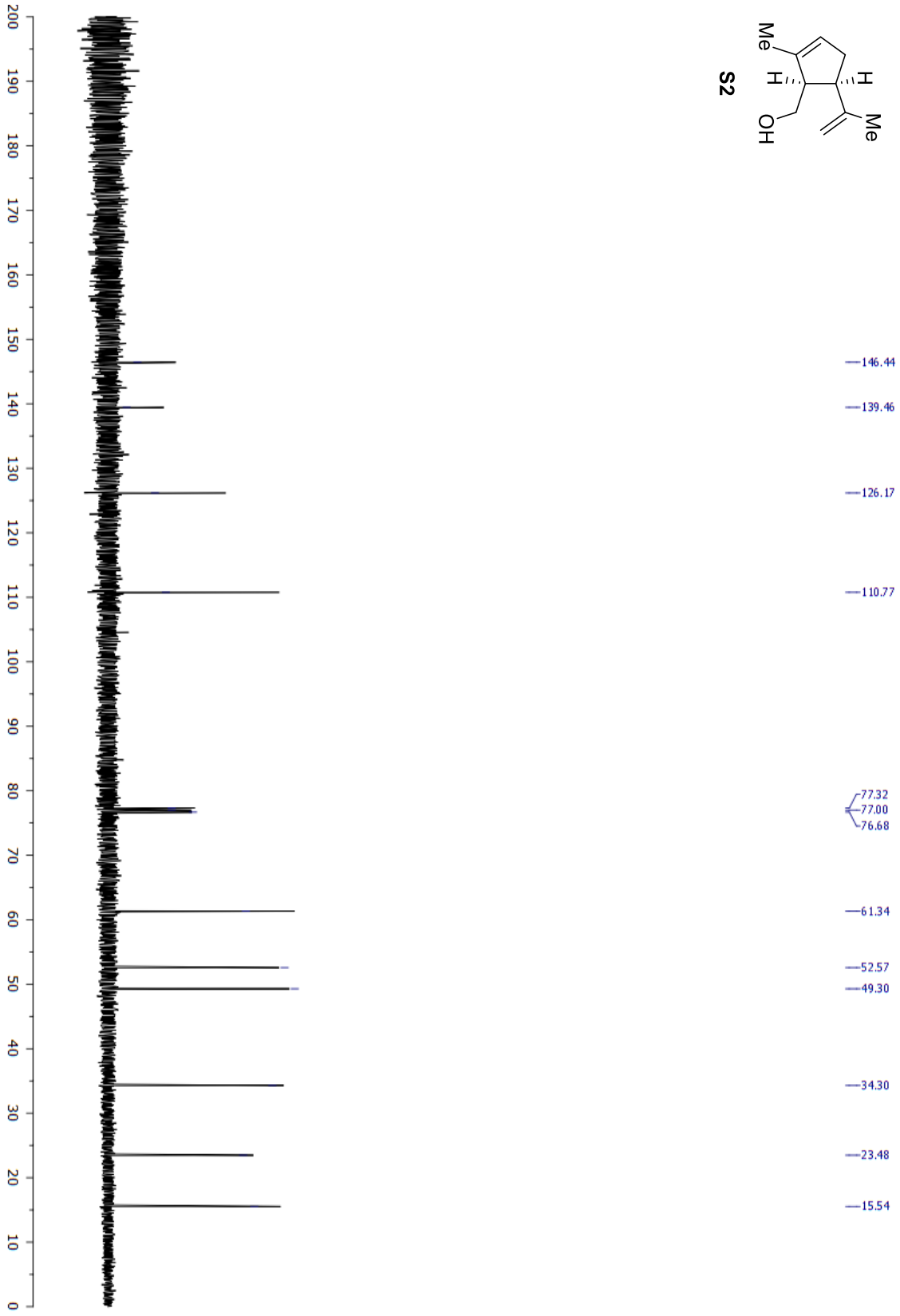
2.10
1.84
1.73
1.73
1.73
1.73
1.60
1.58
1.41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H
H
Me
OH
S2
146.44
139.46
126.17
110.77
77.32
77.00
76.68
61.34
52.57
49.30
34.30
23.48
15.54
200
190
180
170
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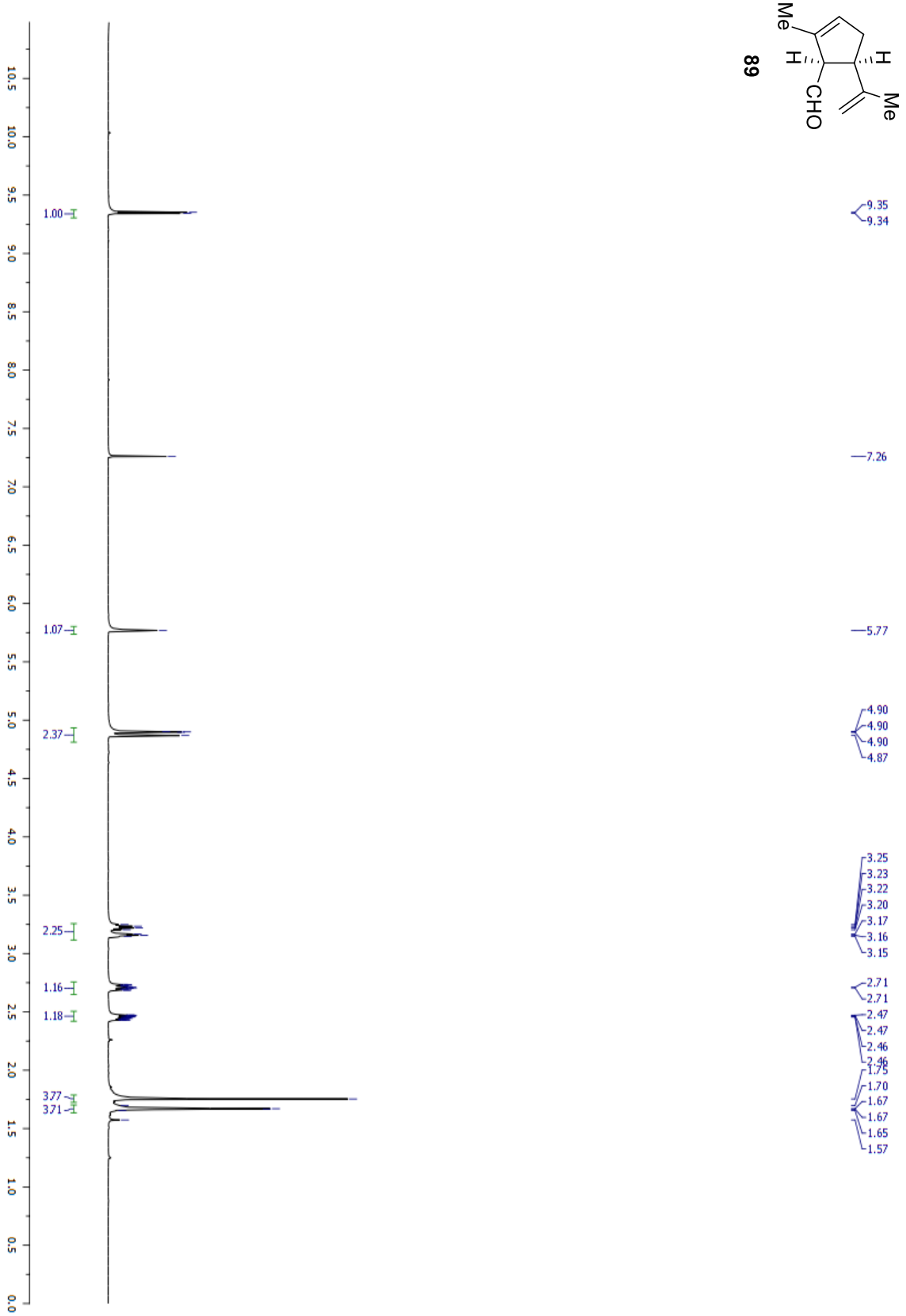
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0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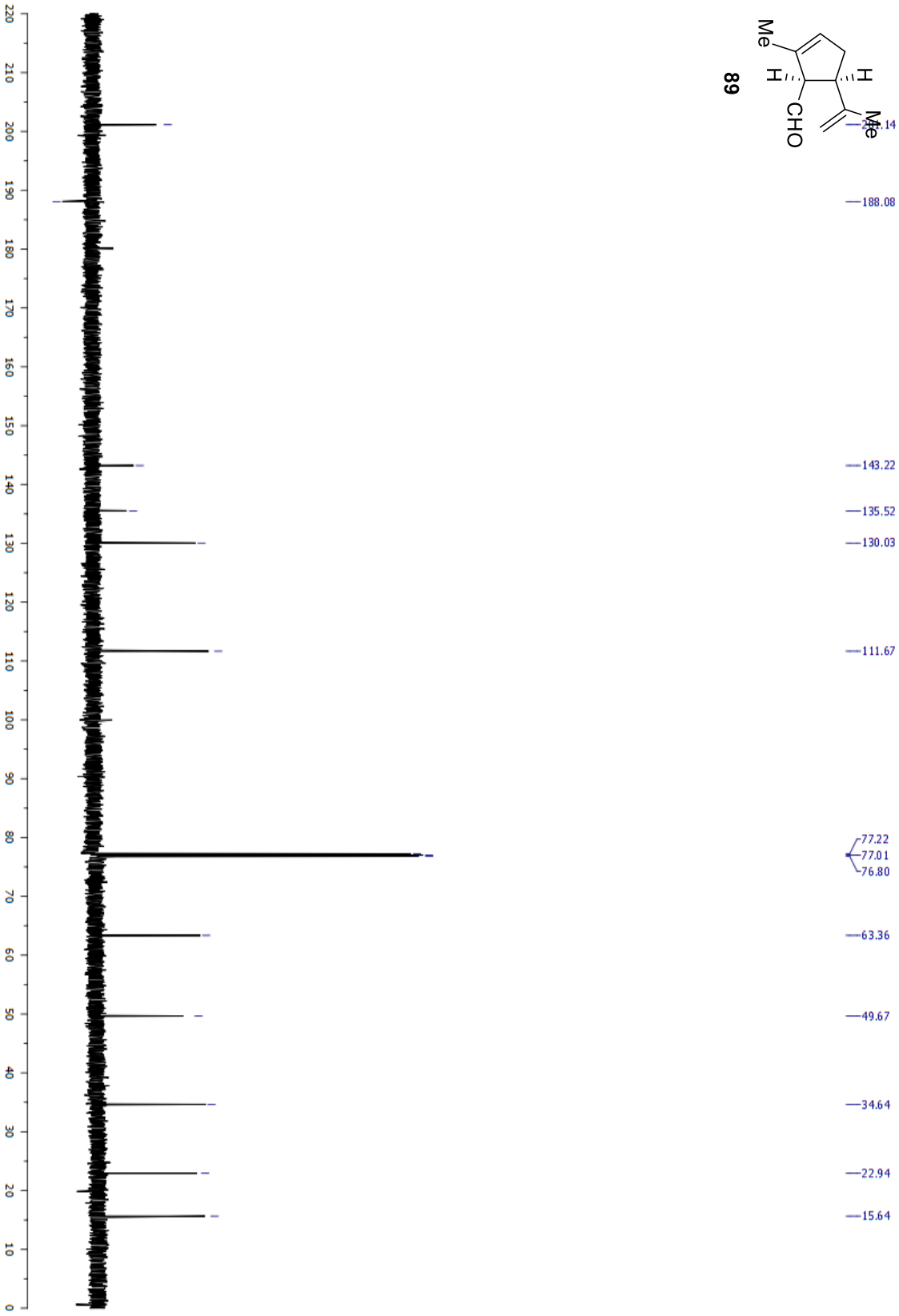
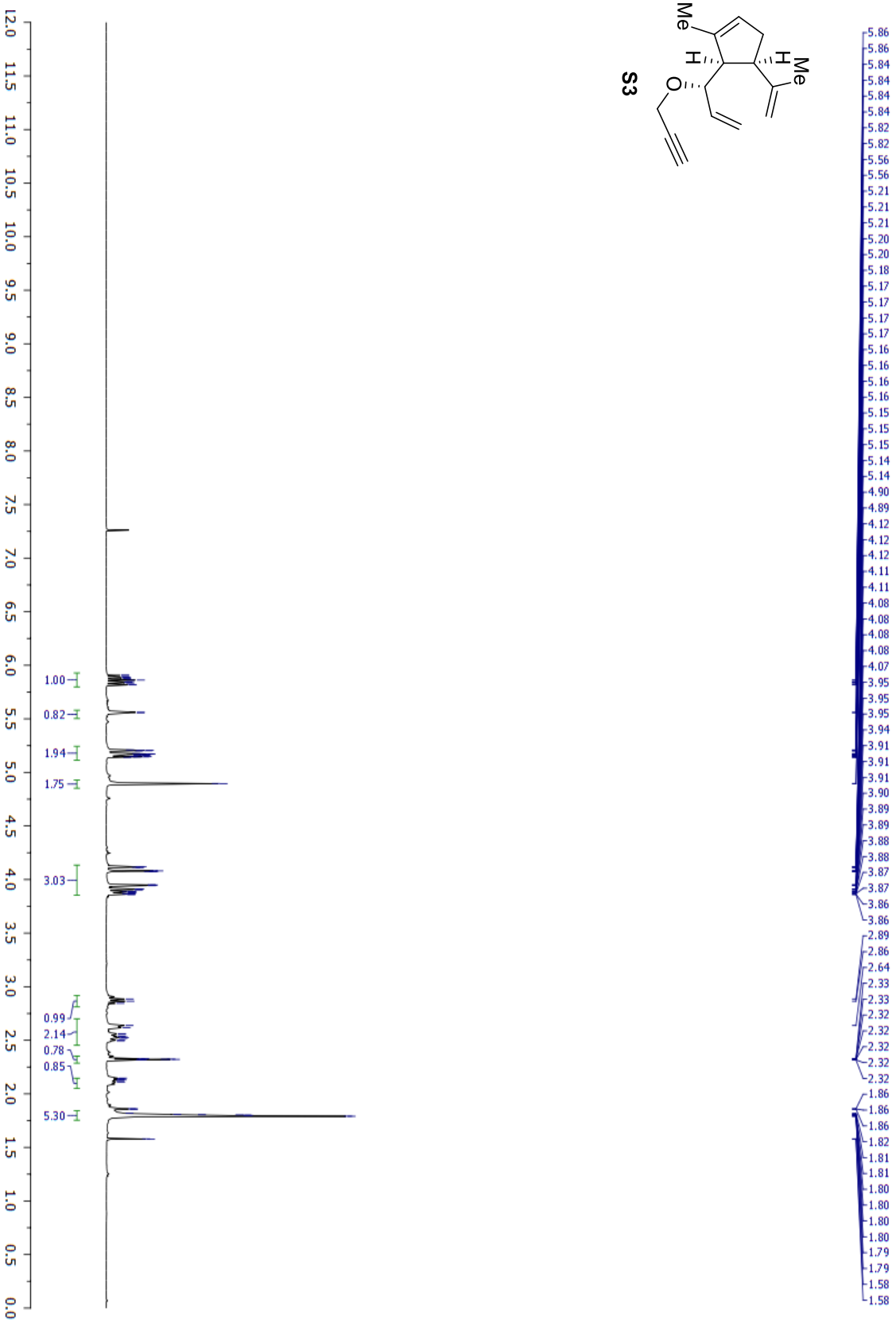
H
H
CHO
Me
89
1.00
1.07
2.37
2.25
1.16
1.18
3.77
3.71
9.35
9.34
7.26
5.77
4.90
4.90
4.90
4.87
3.25
3.23
3.22
3.20
3.17
3.16
3.15
2.71
2.71
2.47
2.47
2.46
2.46
1.75
1.70
1.67
1.67
1.65
1.57


89
Me
H
H
CHO
Me
144.14
188.08
143.22
135.52
130.03
111.67
77.22
77.01
76.80
63.36
49.67
34.64
22.94
15.64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Me
H
O
H
Me
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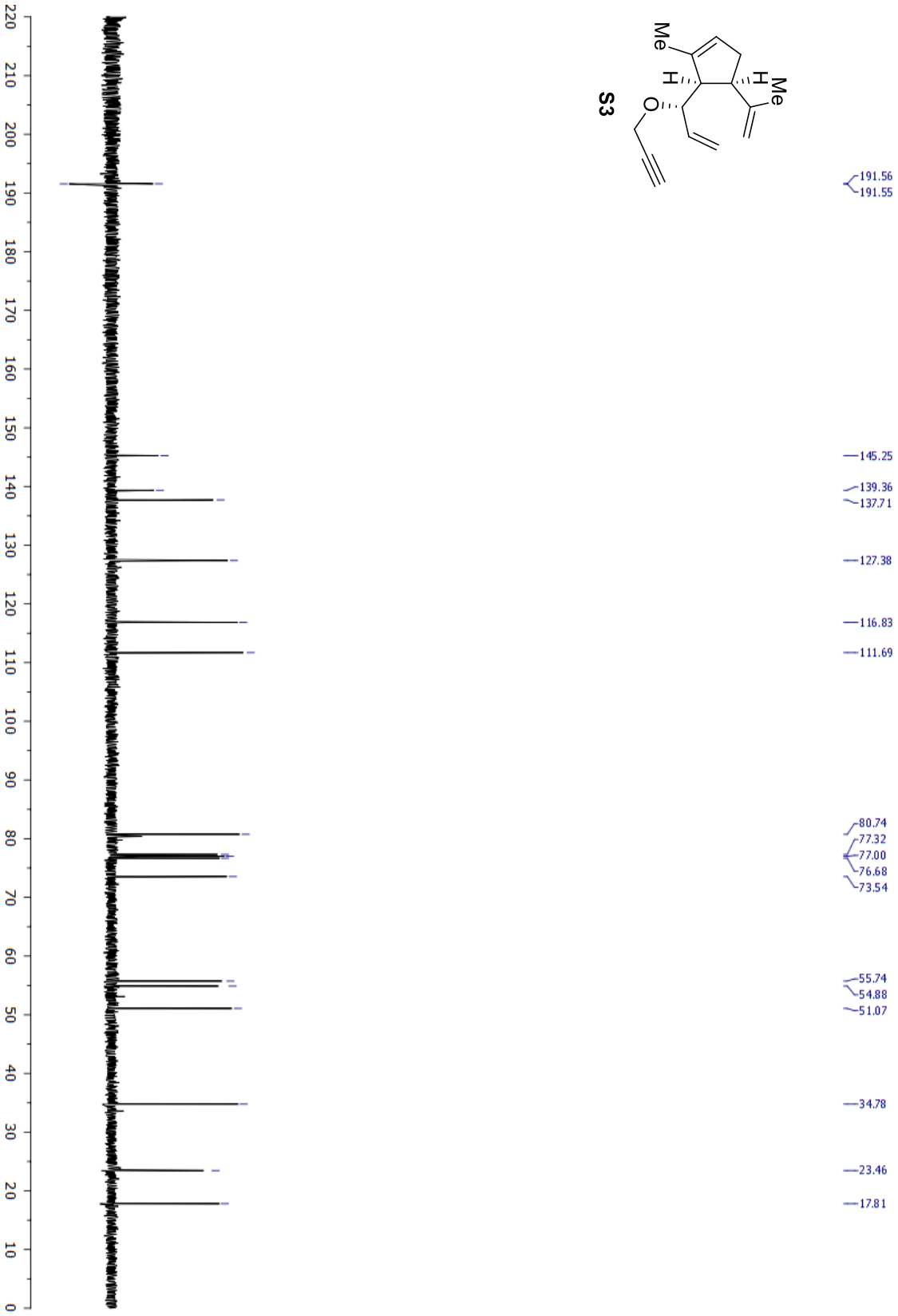
1.00
0.82
1.94
1.75
3.03
0.99
2.14
0.78
0.85
5.30
5.86 5.86 5.84 5.84 5.84 5.84 5.82 5.82 5.56 5.56 5.21 5.21 5.21 5.20 5.20 5.18 5.17 5.17 5.17 5.17 5.16 5.16 5.16 5.16 5.15 5.15 5.15 5.14 5.14 4.90 4.89 4.12 4.12 4.12 4.11 4.11 4.08 4.08 4.08 4.08 4.07 3.95 3.95 3.95 3.94 3.91 3.91 3.91 3.90 3.89 3.89 3.88 3.88 3.87 3.87 3.86 3.86 2.89 2.86 2.64 2.33 2.33 2.32 2.32 2.32 2.32 2.32 1.86 1.86 1.86 1.82 1.81 1.81 1.80 1.80 1.80 1.80 1.79 1.79 1.58 1.58


S3
Me
H
O
H
Me
191.56
191.55
145.25
139.36
137.71
127.38
116.83
111.69
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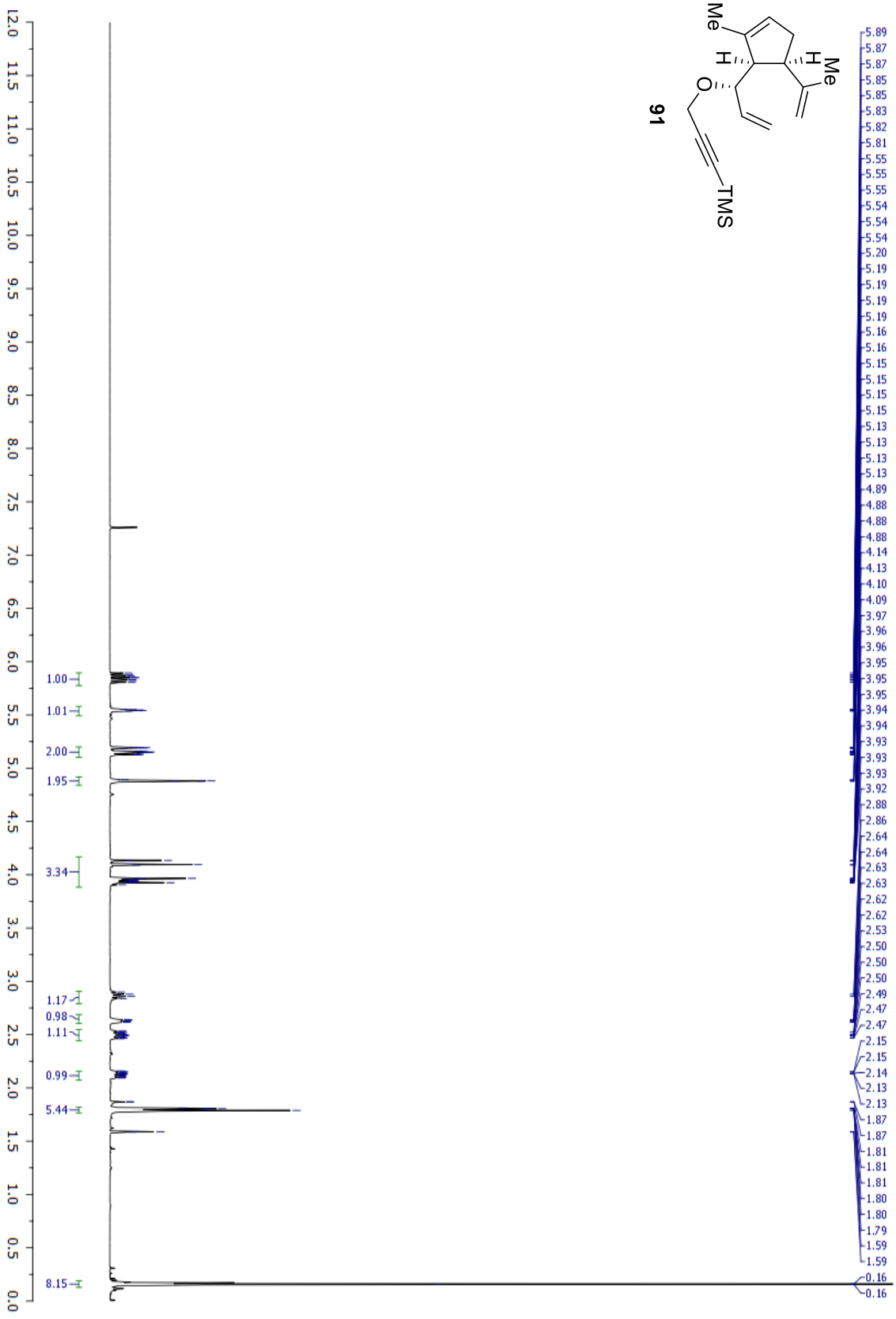
55.74
54.88
51.07
34.78
23.46
17.81


Me
H
O
H
Me
TMS
91
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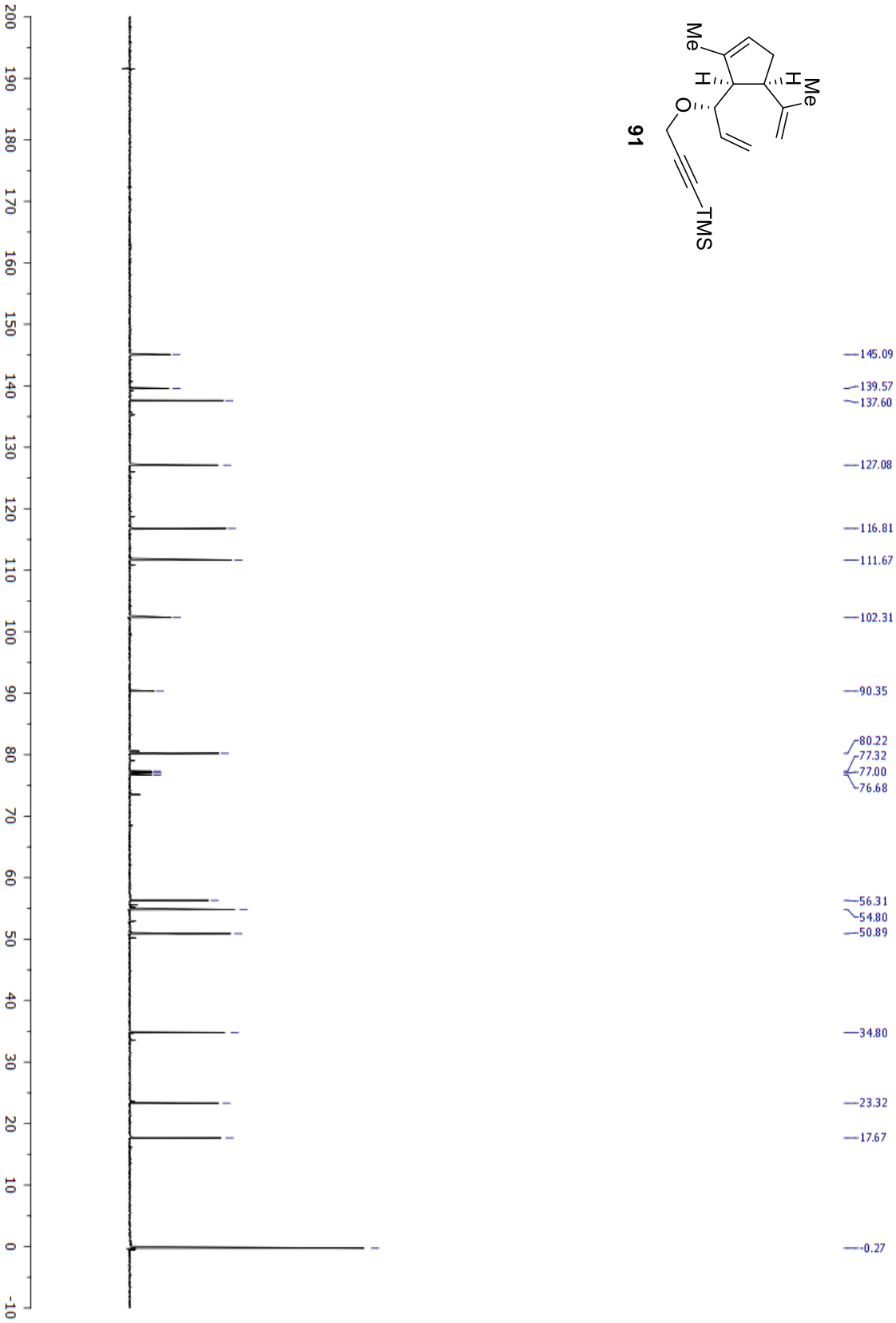
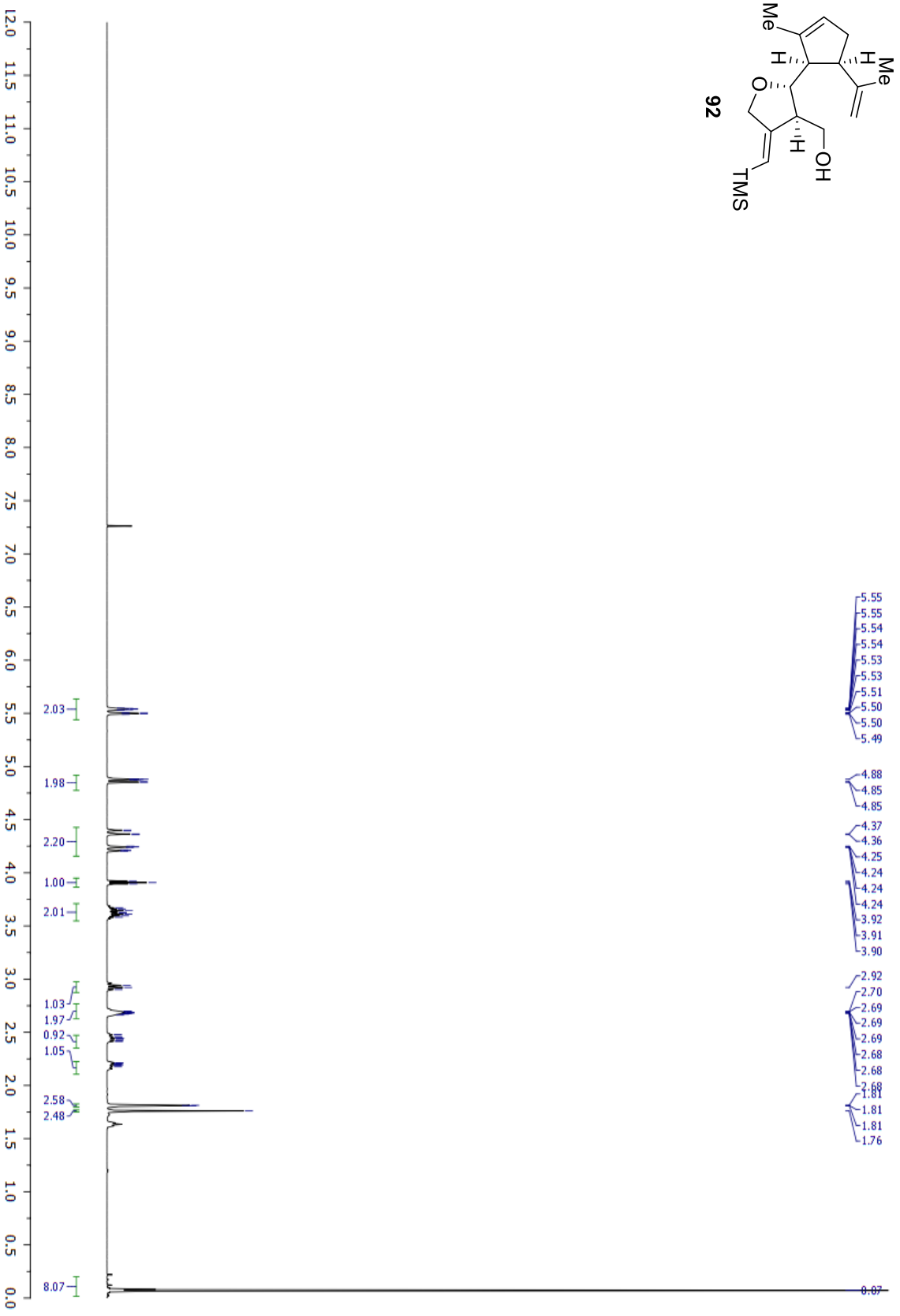
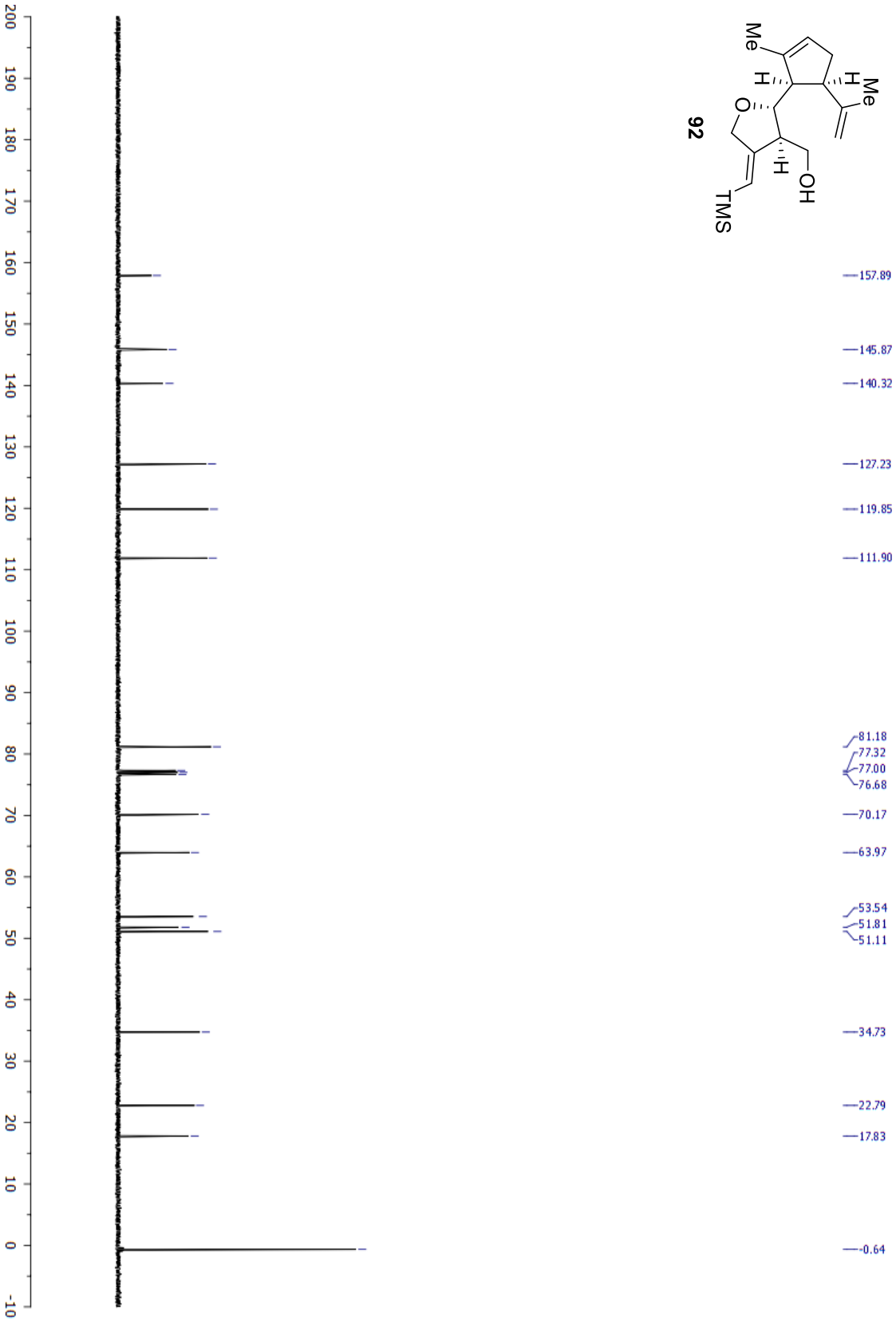
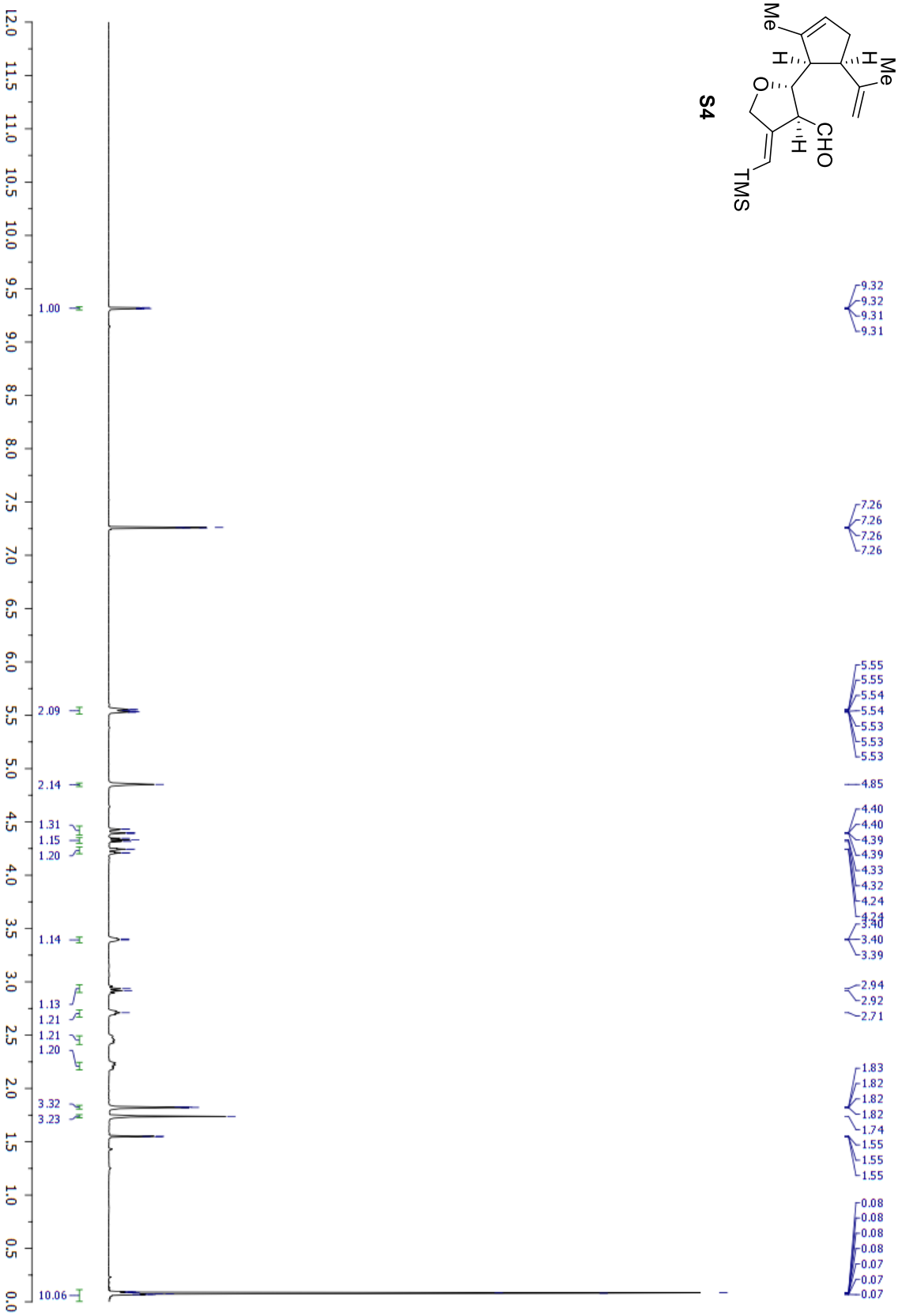
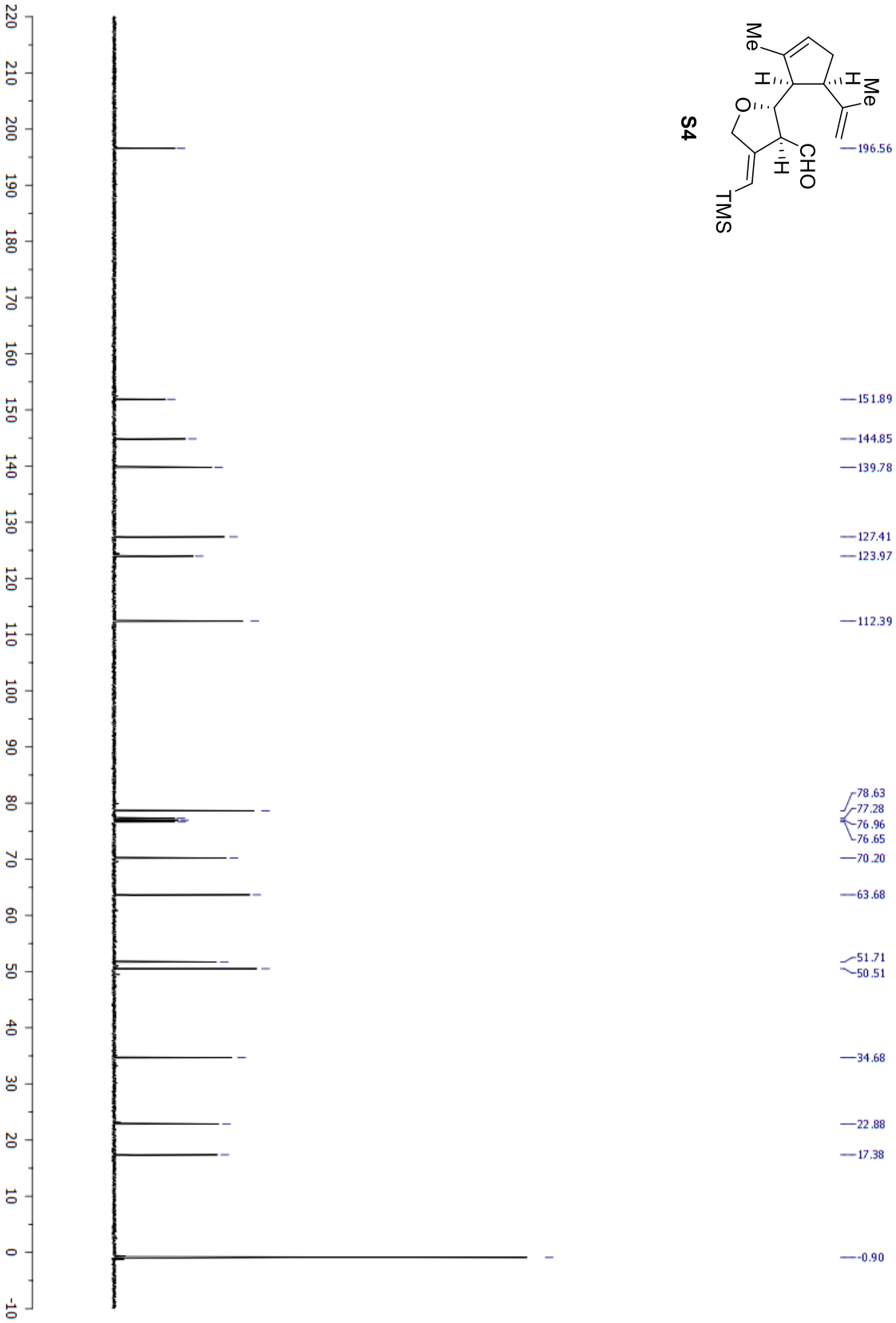
1.00
1.01
2.00
1.95
3.34
1.17
0.98
1.11
0.99
5.44
8.15
5.89 5.87 5.87 5.85 5.85 5.83 5.82 5.81 5.55 5.55 5.55 5.54 5.54 5.54 5.20 5.19 5.19 5.19 5.19 5.19 5.16 5.16 5.15 5.15 5.15 5.15 5.13 5.13 5.13 5.13 5.13 4.89 4.88 4.88 4.88 4.88 4.14 4.13 4.10 4.09 3.97 3.96 3.96 3.95 3.95 3.95 3.94 3.94 3.93 3.93 3.93 3.92 2.88 2.86 2.64 2.64 2.63 2.63 2.62 2.62 2.53 2.50 2.50 2.50 2.49 2.47 2.47 2.15 2.15 2.14 2.13 2.13 1.87 1.87 1.81 1.81 1.81 1.80 1.80 1.79 1.59 1.59 0.16 0.16


Me
H
O
Me
TMS
91
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
145.09
139.57
137.60
127.08
116.81
111.67
102.31
90.35
80.22
77.32
77.00
76.68
56.31
54.80
50.89
34.80
23.32
17.67
0.27


Me
H
O
H
Me
H
OH
TMS
92
12.0 11.5 11.0 10.5 10.0 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 0.0
2.03
1.98
2.20
1.00
2.01
1.03
1.97
0.92
1.05
2.58
2.48
8.07
5.55 5.55 5.54 5.54 5.53 5.53 5.51 5.50 5.50 5.49
4.88 4.85 4.85
4.37 4.36 4.25 4.24 4.24 4.24 3.92 3.91 3.90
2.92 2.70 2.69 2.69 2.69 2.68 2.68 2.66
1.81 1.81 1.81 1.76
0.07


Me
H
Me
H
O
H
OH
TMS
92
157.89
145.87
140.32
127.23
119.85
111.90
81.18
77.32
77.00
76.68
70.17
63.97
53.54
51.81
51.11
34.73
22.79
17.83
0.64
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


S4
Me
H
O
H
Me
CHO
H
TMS
9.32
9.32
9.31
9.31
7.26
7.26
7.26
7.26
5.55
5.55
5.54
5.54
5.53
5.53
5.53
4.85
4.40
4.40
4.39
4.39
4.33
4.32
4.24
4.24
3.40
3.40
3.39
2.94
2.92
2.71
1.83
1.82
1.82
1.82
1.74
1.55
1.55
1.55
0.08
0.08
0.08
0.08
0.07
0.07
0.07
1.00
2.09
2.14
1.31
1.15
1.20
1.14
1.13
1.21
1.21
1.20
3.32
3.23
10.06


Me
H
Me
H
O
CHO
H
TMS
S4
196.56
151.89
144.85
139.78
127.41
123.97
112.39
78.63
77.28
76.96
76.65
70.20
63.68
51.71
50.51
34.68
22.88
17.38
-0.90
220
210
200
190
180
170
160
150
140
130
120
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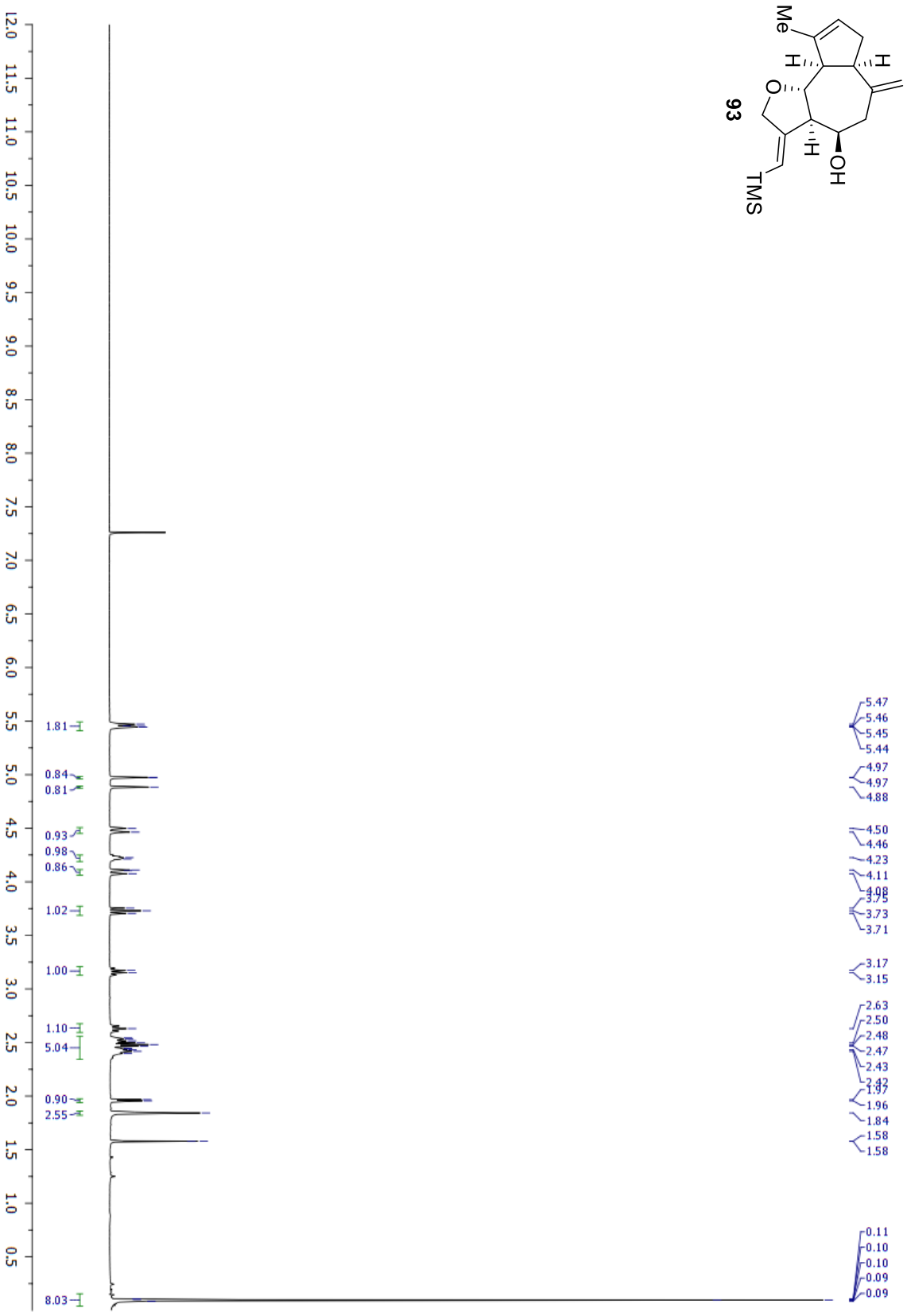
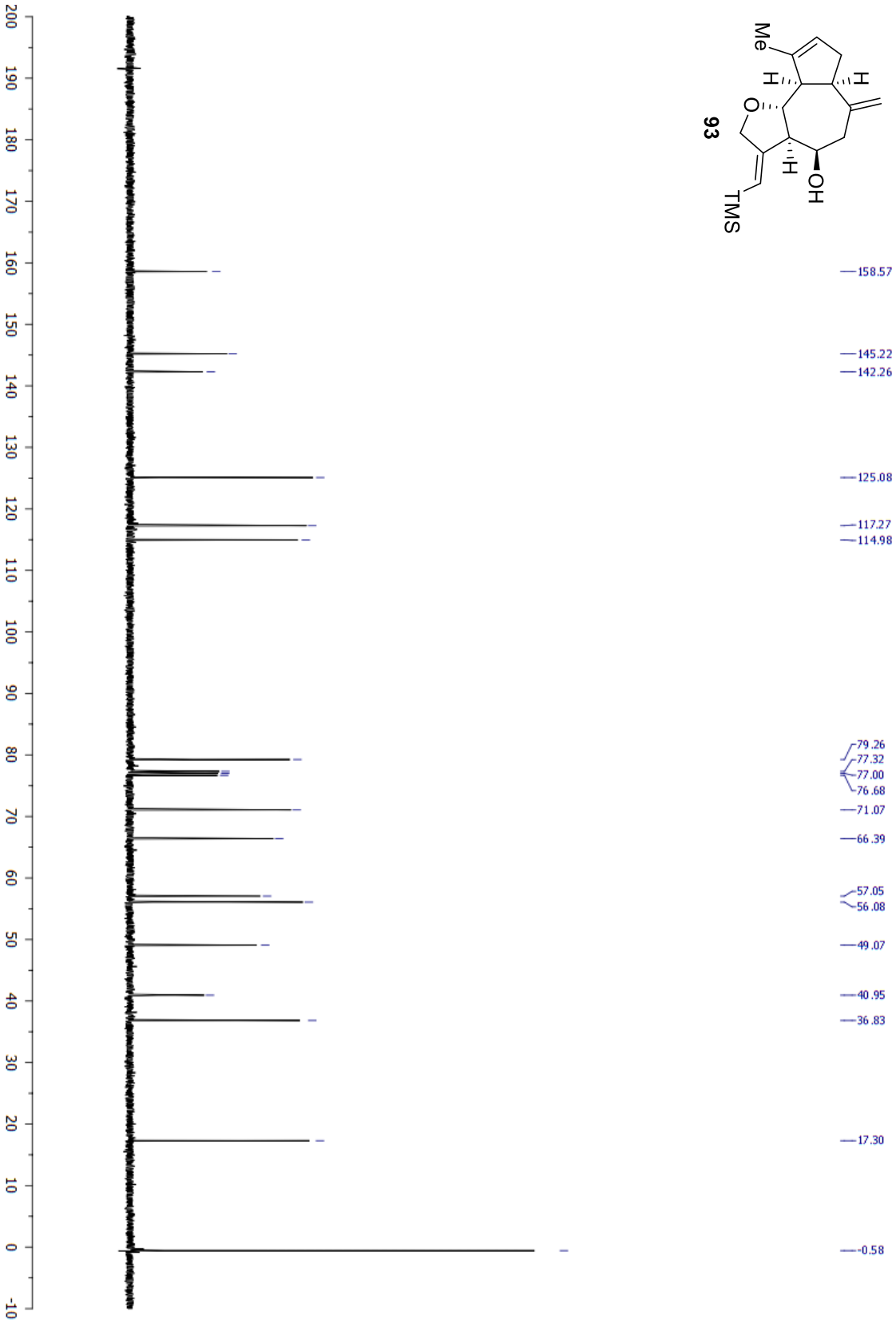
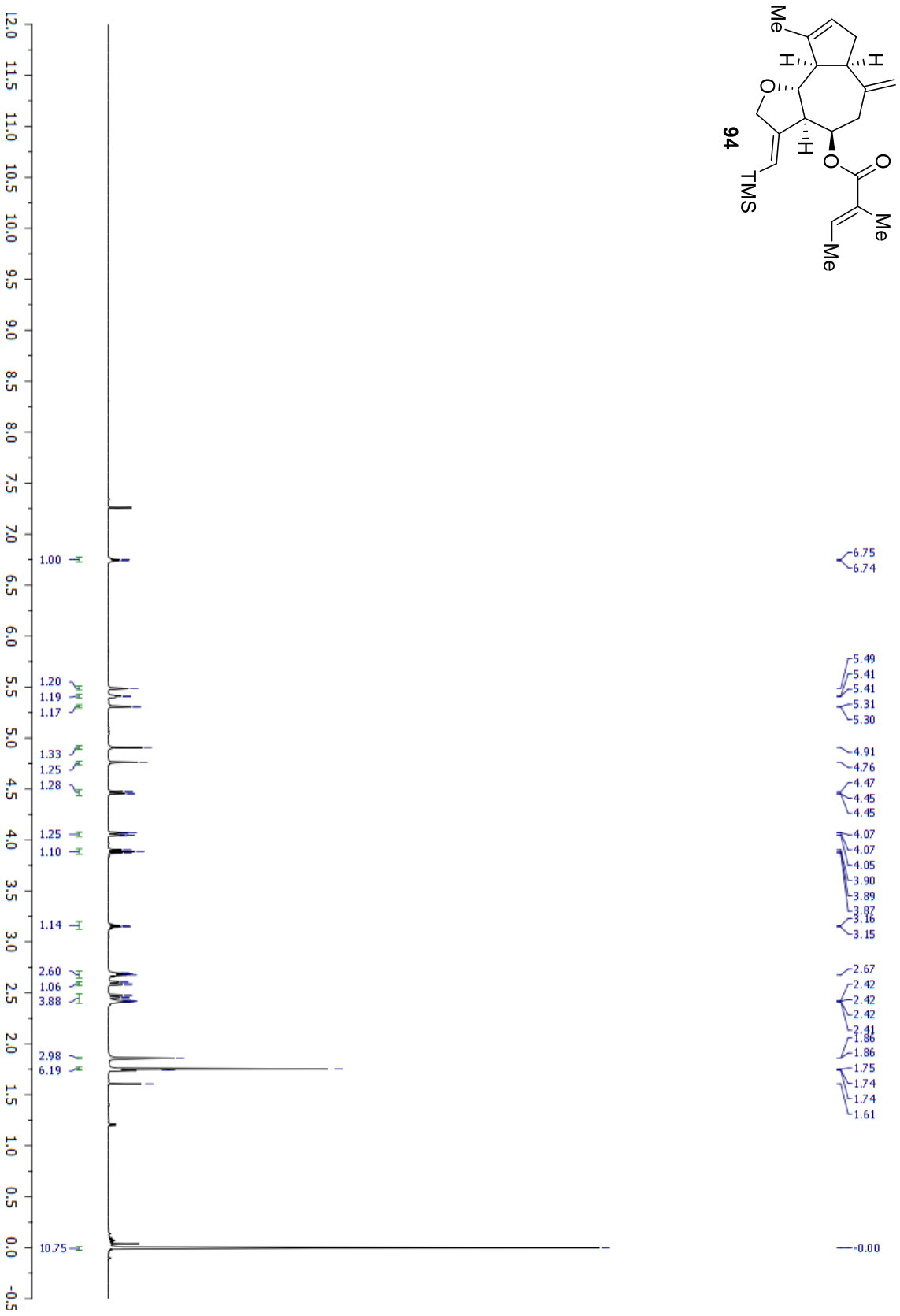
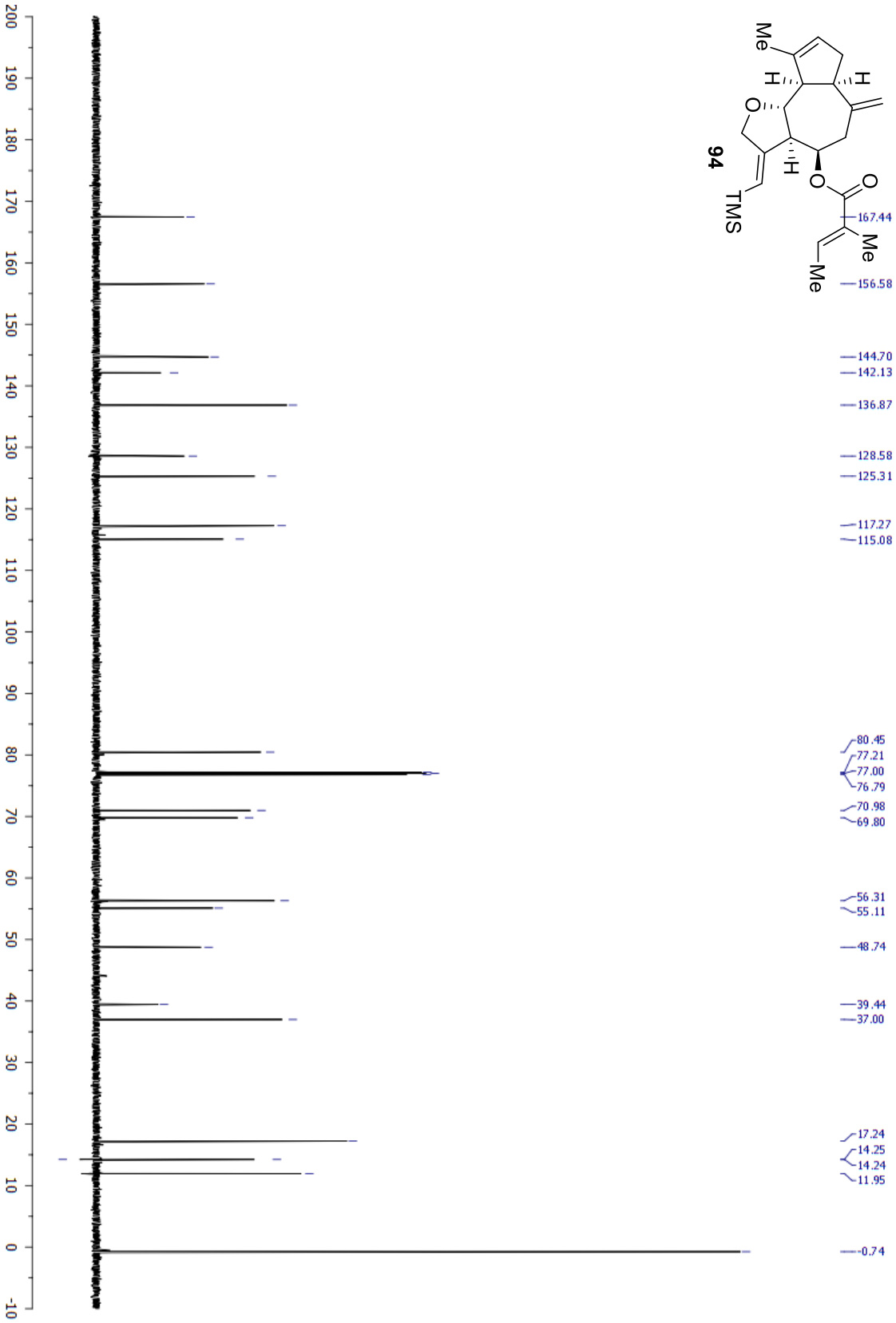
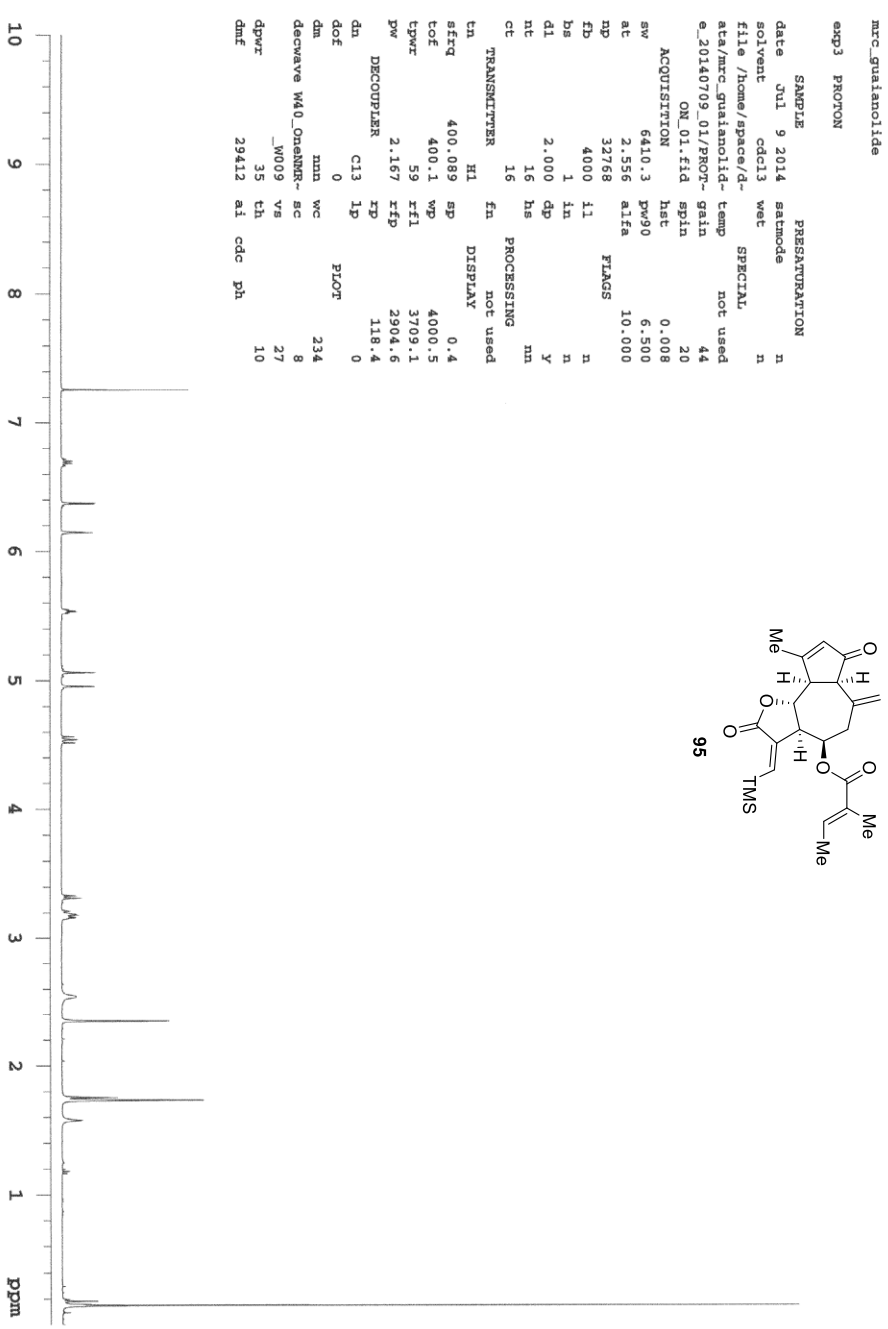
100
90
80
70
60
50
40
30
20
10
0
-10

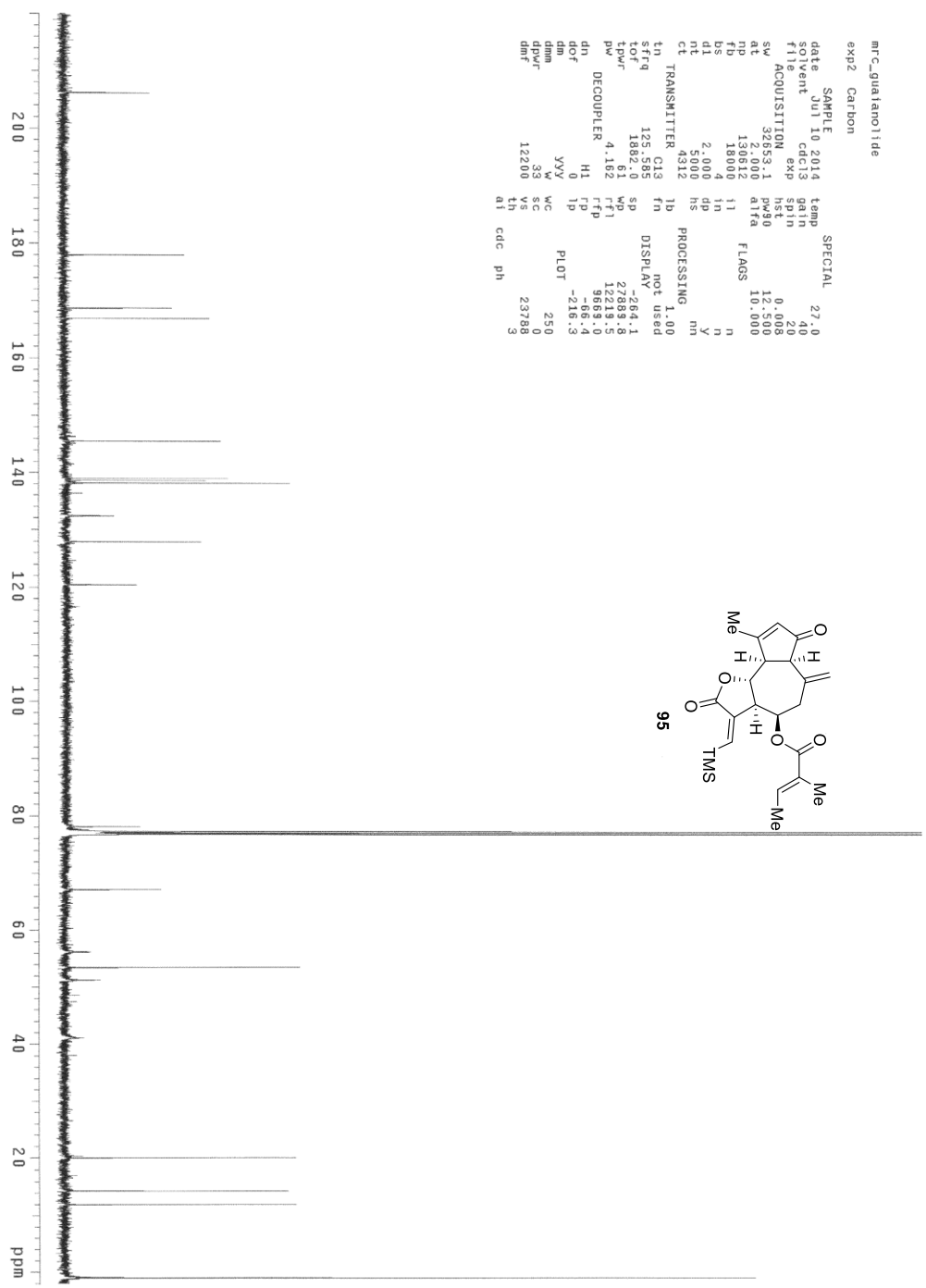

Me
H
H
O
H
OH
TMS
93
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
1.81
0.84
0.81
0.93
0.98
0.86
1.02
1.00
1.10
5.04
0.90
2.55
8.03
5.47
5.46
5.45
5.44
4.97
4.97
4.88
4.50
4.46
4.23
4.11
4.08
3.75
3.73
3.71
3.17
3.15
2.63
2.50
2.48
2.47
2.43
2.42
1.97
1.96
1.84
1.58
1.58
0.11
0.10
0.10
0.09
0.09

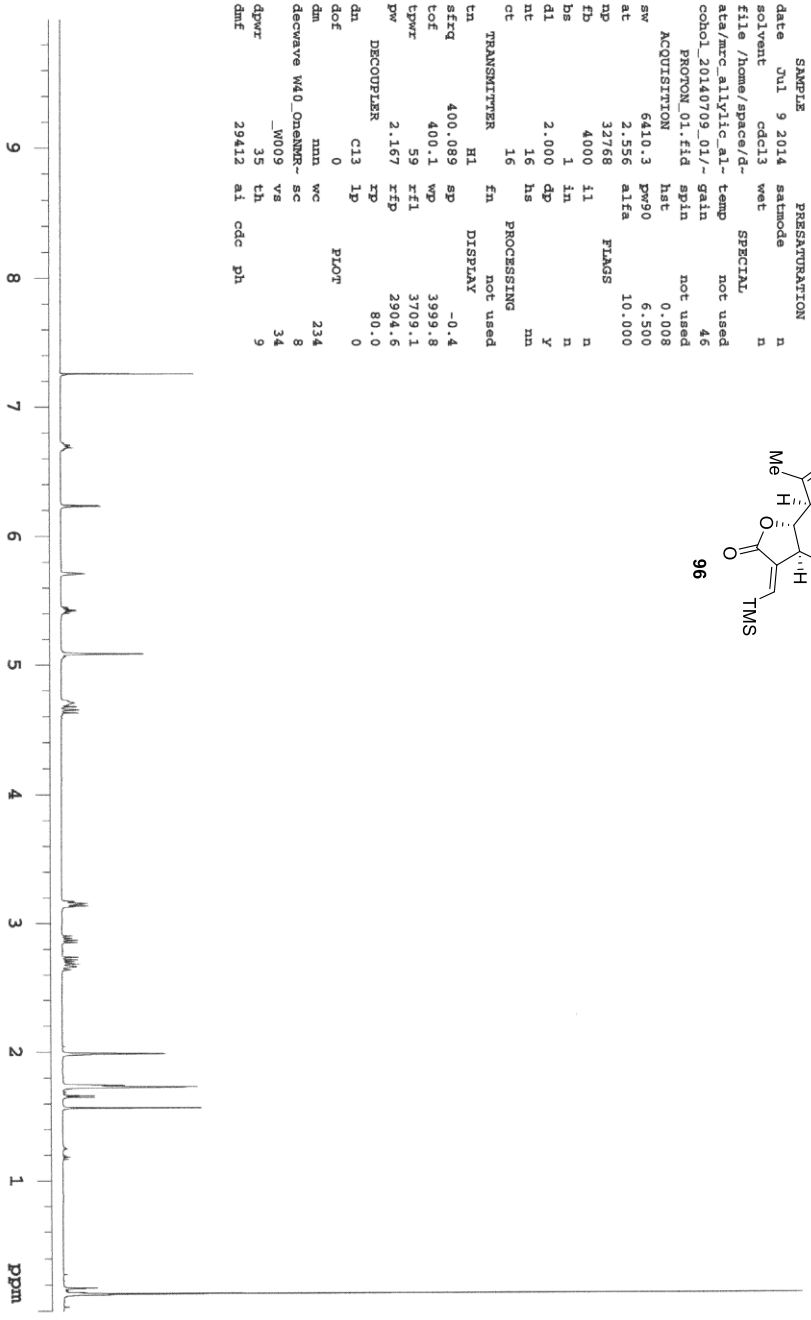

Me
H
H
O
H
OH
TMS
93
158.57
145.22
142.26
125.08
117.27
114.98
79.26
77.32
77.00
76.68
71.07
66.39
57.05
56.08
49.07
40.95
36.83
17.30
-0.58


Me
H
H
O
H
O
O
Me
Me
TMS
94
12.0 11.5 11.0 10.5 10.0 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 0.0 -0.5
1.00
1.20
1.19
1.17
1.33
1.25
1.28
1.25
1.10
1.14
2.60
1.06
3.88
2.98
6.19
10.75
6.75
6.74
5.49
5.41
5.41
5.31
5.30
4.91
4.76
4.47
4.45
4.45
4.07
4.07
4.05
3.90
3.89
3.87
3.16
3.15
2.67
2.42
2.42
2.42
2.41
1.86
1.86
1.75
1.74
1.74
1.61
-0.00


Me
H
H
O
H
O
O
TMS
Me
Me
94
167.44
156.58
144.70
142.13
136.87
128.58
125.31
117.27
115.08
80.45
77.21
77.00
76.79
70.98
69.80
56.31
55.11
48.74
39.44
37.00
17.24
14.25
14.24
11.95
-0.74


mrc_guianolide
exp3 PROTON
SAMPLE PRESATURATION
date Jul 9 2014 satmode n
solvent cdcl3 wet n
file /home/space/d-
ata/mrc_guianolid- SPECIAL
e_20140709_01/PROT- temp not used
ON_01.fid gain 44
ACQUISITION spin 20
6410.3 hst 0.008
sw 2.556 pw90 6.500
at 32768 alfa 10.000
np 4000 FLAGS
fb 1 il n
bs 2.000 in n
d1 16 dp y
nt 16 hs nn
ct TRANSMITTER PROCESSING
16 fn not used
H1 DISPLAY
tn 400.089 sp 0.4
sfrq 400.1 wp 4000.5
tof 59 rfl 3709.1
tpwr 2.167 rfp 2904.6
pw DECOUPLER rp 118.4
C13 lp 0
dn PLOT
0
dof nnn wc 234
dm decwave W40_OneNMR- sc 8
__W009 vs 27
dpwr 35 th 10
dmf 29412 ai cdc ph
Me
H
O
O
H
O
O
Me
Me
TMS
95
10
9
8
7
6
5
4
3
2
1
ppm

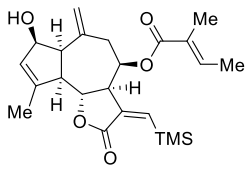

mrc_guaianolide
exp2 Carbon
SAMPLE
date Jul 10 2014
solvent cdcl3
file exp
ACQUISITION
sw 32653.1
at 2.000
np 130612
fb 18000
bs 4
d1 2.000
nt 5000
ct 4312
TRANSMITTER
tn C13
sfrq 125.585
tof 1862.1
tpwr 61
pw 4.162
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 33
dmf 12200
temp 27.0
gain 40
spin 20
hst 0.008
pw90 12.500
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp -264.1
wp 2788.8
rfl 12219.5
rfp 9669.0
rp -66.4
lp -216.3
PLOT
wc 250
sc 0
vs 23788
th 3
ai cdc ph
Me
H
O
O
H
O
O
H
Me
O
Me
TMS
95
200
180
160
140
120
100
80
60
40
20
ppm


mrc_allylic_alcohol
exp3 PROTON
SAMPLE PRESATURATION
date Jul 9 2014 satmode n
solvent cdcl3 wet n
file /home/space/d- SPECIAL
ata/mrc_allylic_al- temp not used
cohol_20140709_01/- gain 46
PROTON_01.fid spin not used
ACQUISITION hst 0.008
sw 6410.3 pw90 6.500
at 2.556 alfa 10.000
np 32768 FLAGS
fb 4000 il n
bs 1 in n
d1 2.000 dp y
nt 16 hs nn
ct 16 PROCESSING
TRANSMITTER fn not used
tn H1 DISPLAY
sfrq 400.089 sp -0.4
tof 400.1 wp 3999.8
tpwr 59 rfl 3709.1
pw 2.167 rfp 2904.6
DECOUPLER rp 80.0
dn C13 lp 0
dof 0 PLOT
dm nnn wc 234
decwave W40_OneNMR- sc 8
_W009 vs 34
dpwr 35 th 9
dmf 29412 ai cdc ph
HO
H
Me
H
O
O
H
O
Me
Me
TMS
96
9
8
7
6
5
4
3
2
1
ppm

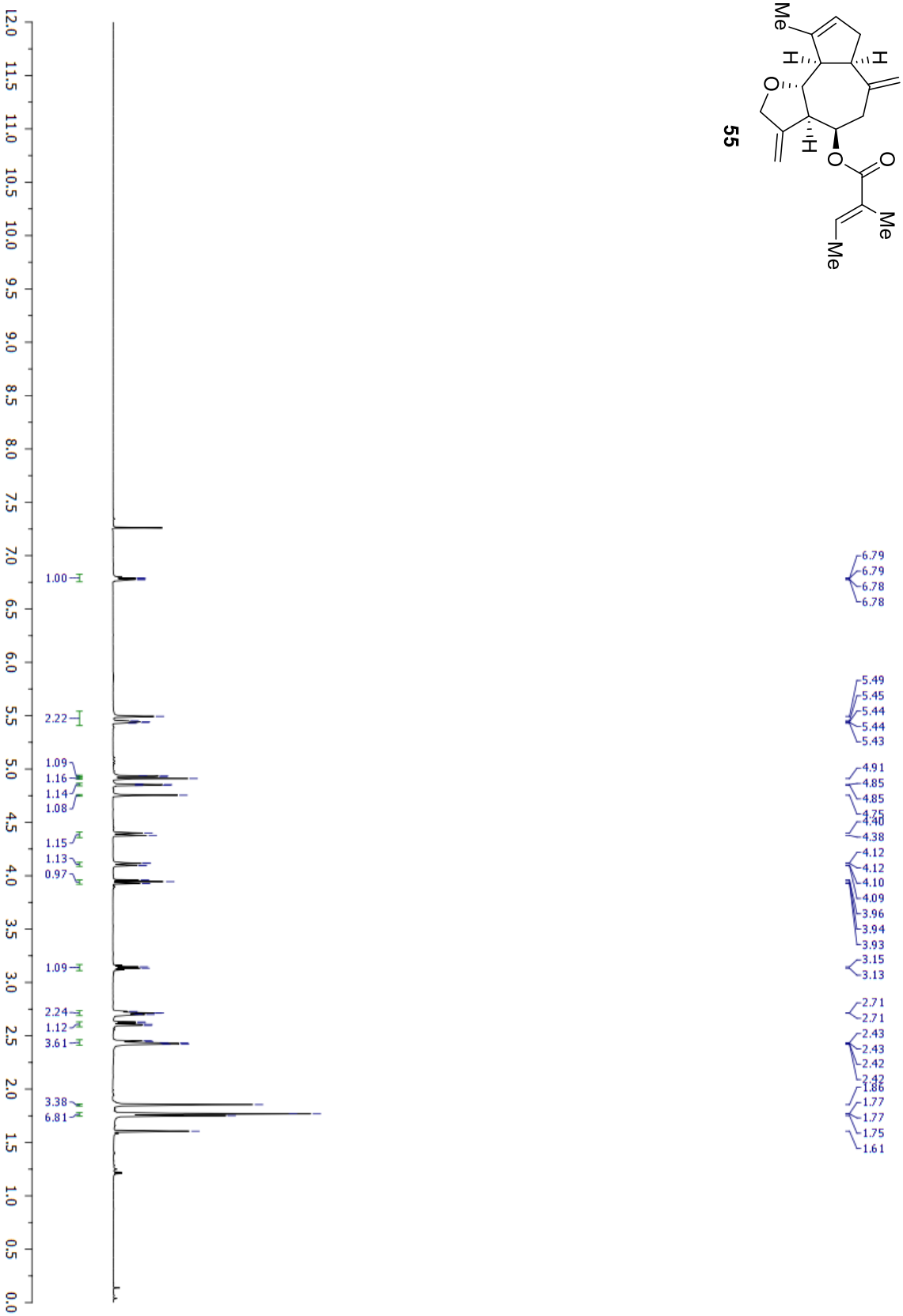
mrc_allylic_alcohol

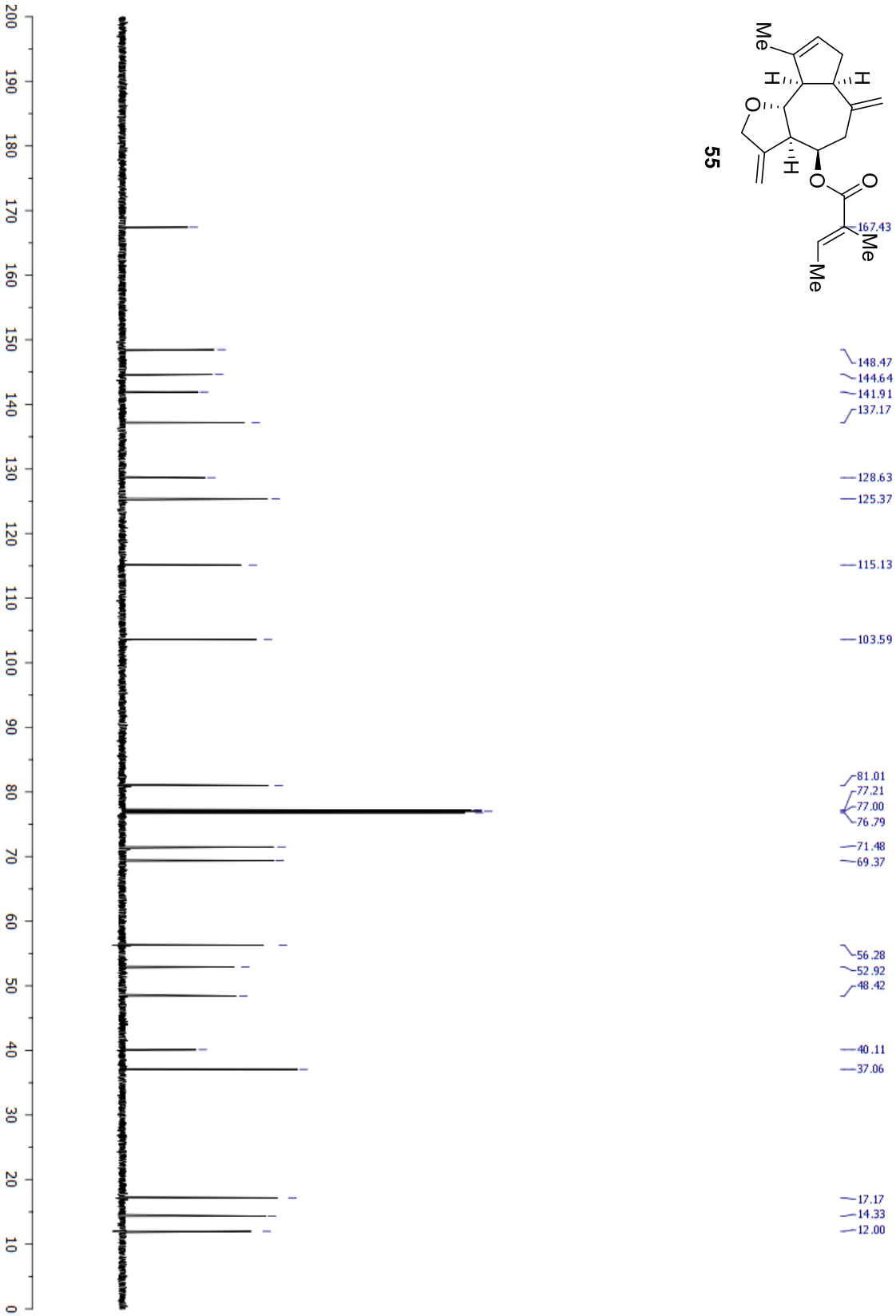
exp2 Carbon

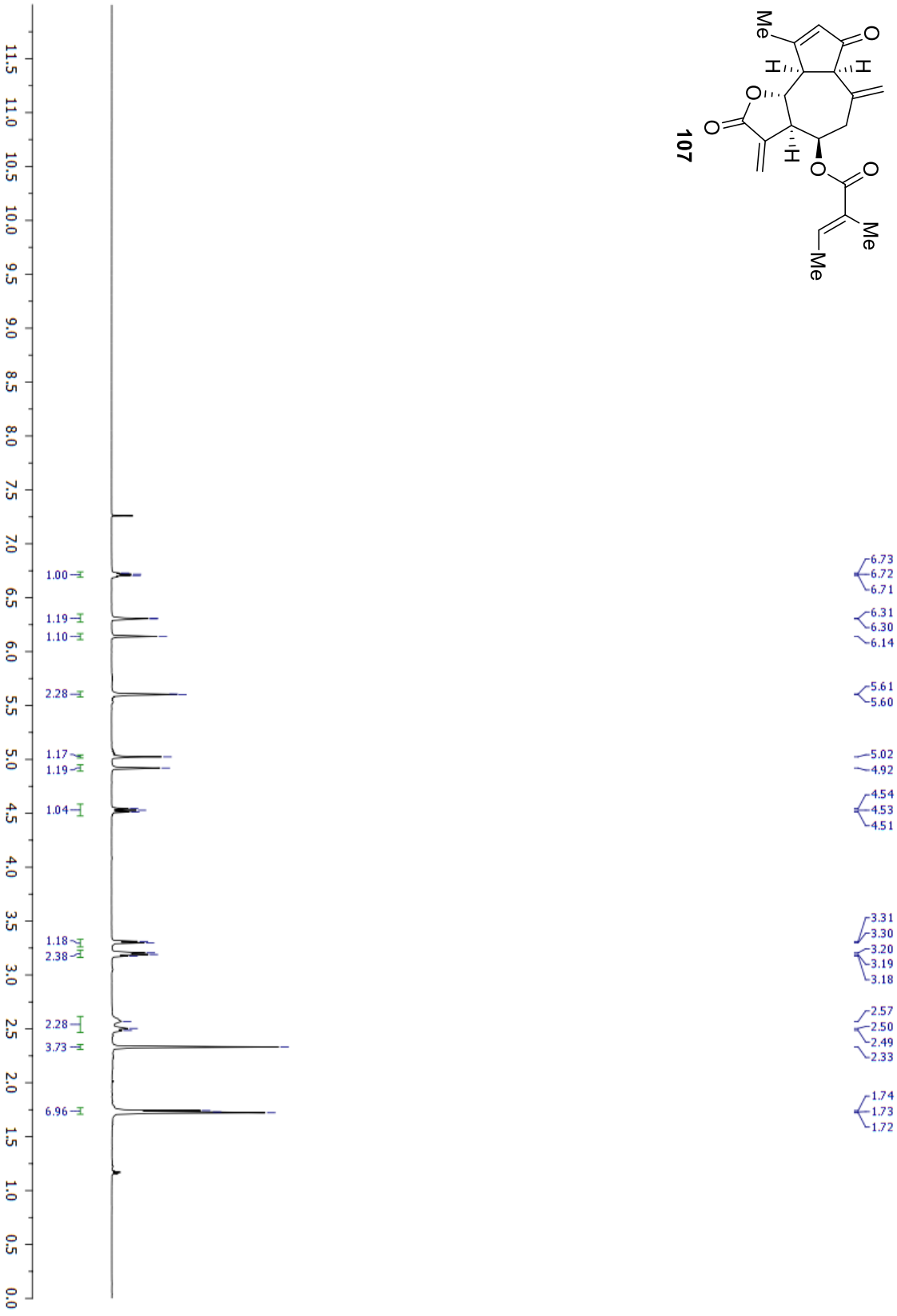
SAMPLE		SPECIAL	
date	Jul 10 2014	temp	27.0
solvent	cdcl3	gain	40
file	exp	spin	20
ACQUISITION		hst	0.008
sw	32653.1	pw90	12.500
at	2.000	alfa	10.000
np	130612	FLAGS	
fb	18000	il	n
bs	4	in	n
d1	2.000	dp	y
nt	5000	hs	nn
ct	2808	PROCESSING	
TRANSMITTER		lb	1.00
tn	C13	fn	not used
sfrq	125.585	DISPLAY	
tof	1882.0	sp	-259.1
tpwr	61	wp	25375.2
pw	4.162	rfl	12214.5
DECOUPLER		rfp	9669.0
dn	H1	rp	-59.0
dof	0	lp	-235.1
dm	yyy	PLOT	
dmm	w	wc	250
dpwr	33	sc	0
dmf	12200	vs	27908
		th	6
		ai cdc ph	



96

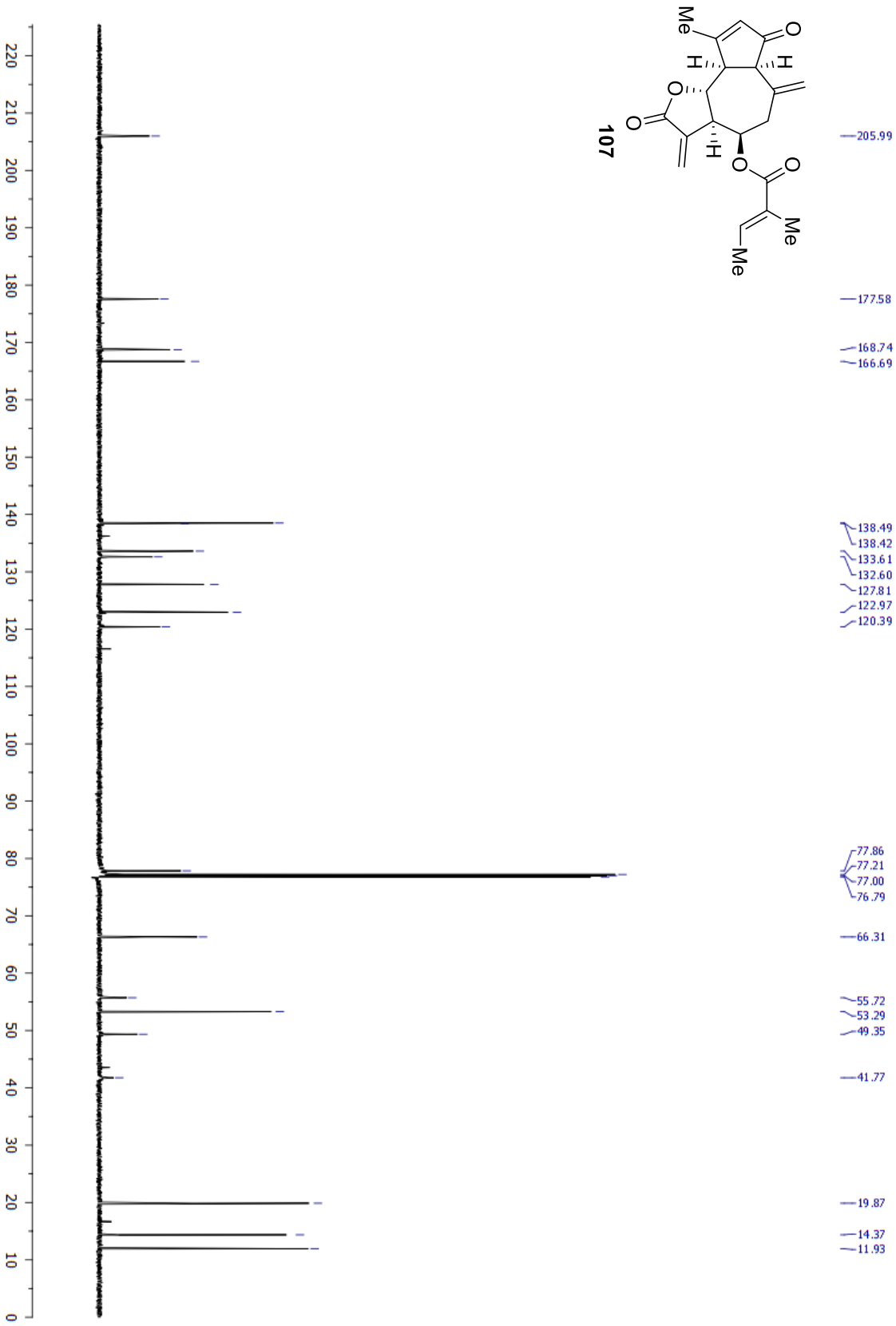

Me
H
H
O
H
O
O
Me
Me
55
6.79
6.79
6.78
6.78
5.49
5.45
5.44
5.44
5.43
4.91
4.85
4.85
4.75
4.40
4.38
4.12
4.12
4.10
4.09
3.96
3.94
3.93
3.15
3.13
2.71
2.71
2.43
2.43
2.42
2.42
1.86
1.77
1.77
1.75
1.61
1.00
2.22
1.09
1.16
1.14
1.08
1.15
1.13
0.97
1.09
2.24
1.12
3.61
3.38
6.81
12.0
11.5
11.0
10.5
10.0
9.5
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
0.0

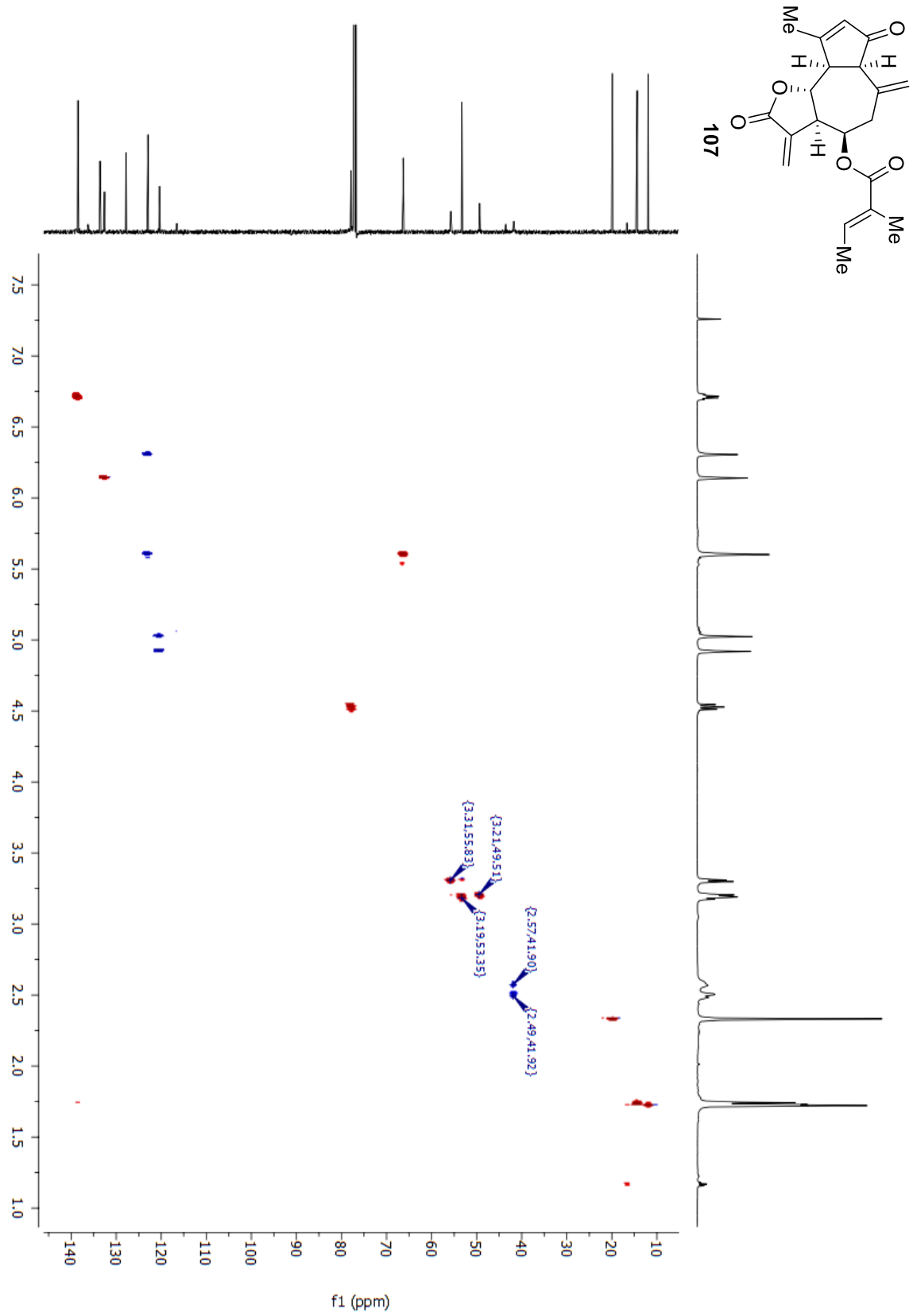

55
Me
H
H
O
H
O
O
Me
Me
167.43
148.47
144.64
141.91
137.17
128.63
125.37
115.13
103.59
81.01
77.21
77.00
76.79
71.48
69.37
56.28
52.92
48.42
40.11
37.06
17.17
14.33
12.00
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

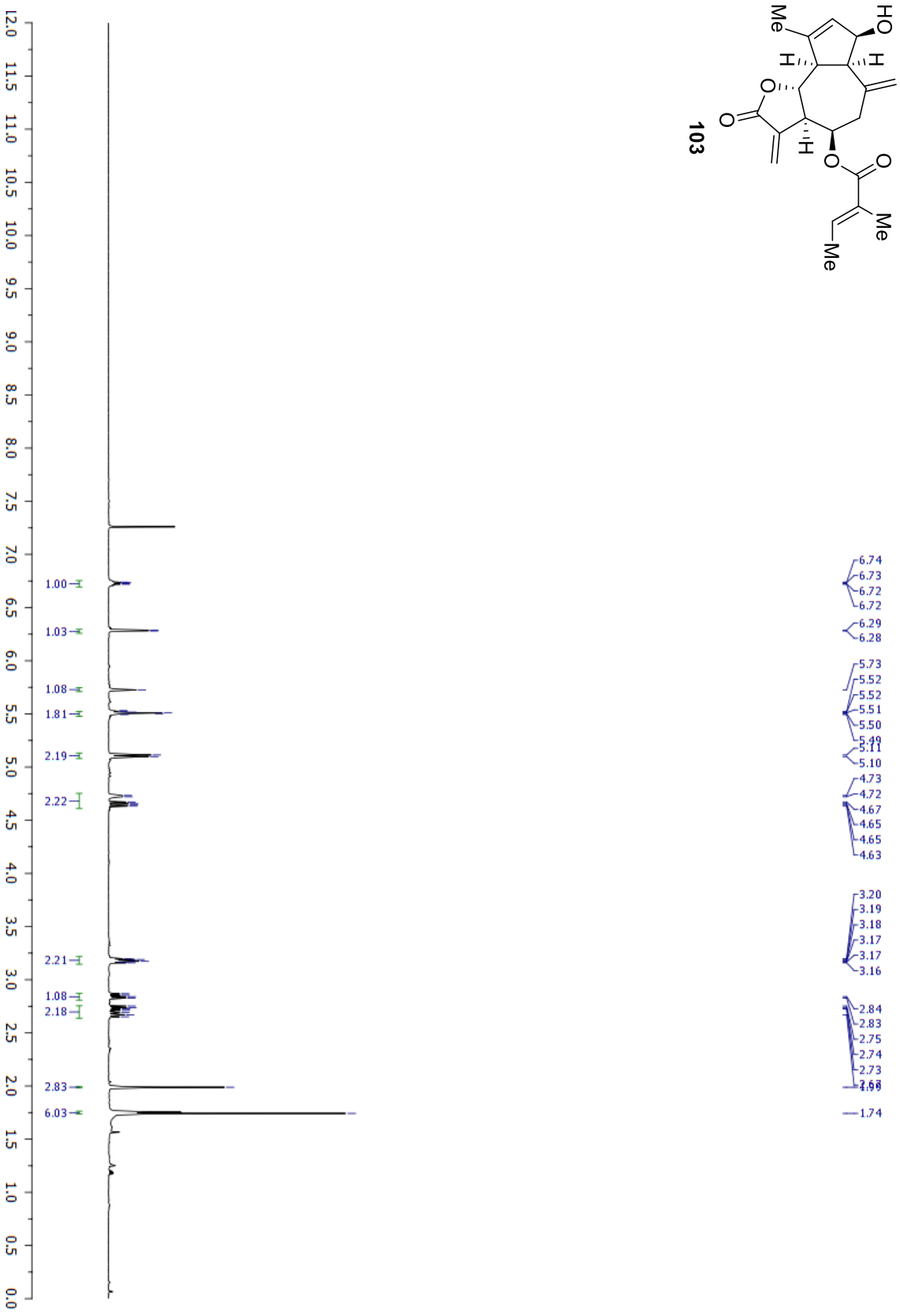

11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
1.00
1.19
1.10
2.28
1.17
1.19
1.04
1.18
2.38
2.28
3.73
6.96
6.73
6.72
6.71
6.31
6.30
6.14
5.61
5.60
5.02
4.92
4.54
4.53
4.51
3.31
3.30
3.20
3.19
3.18
2.57
2.50
2.49
2.33
1.74
1.73
1.72

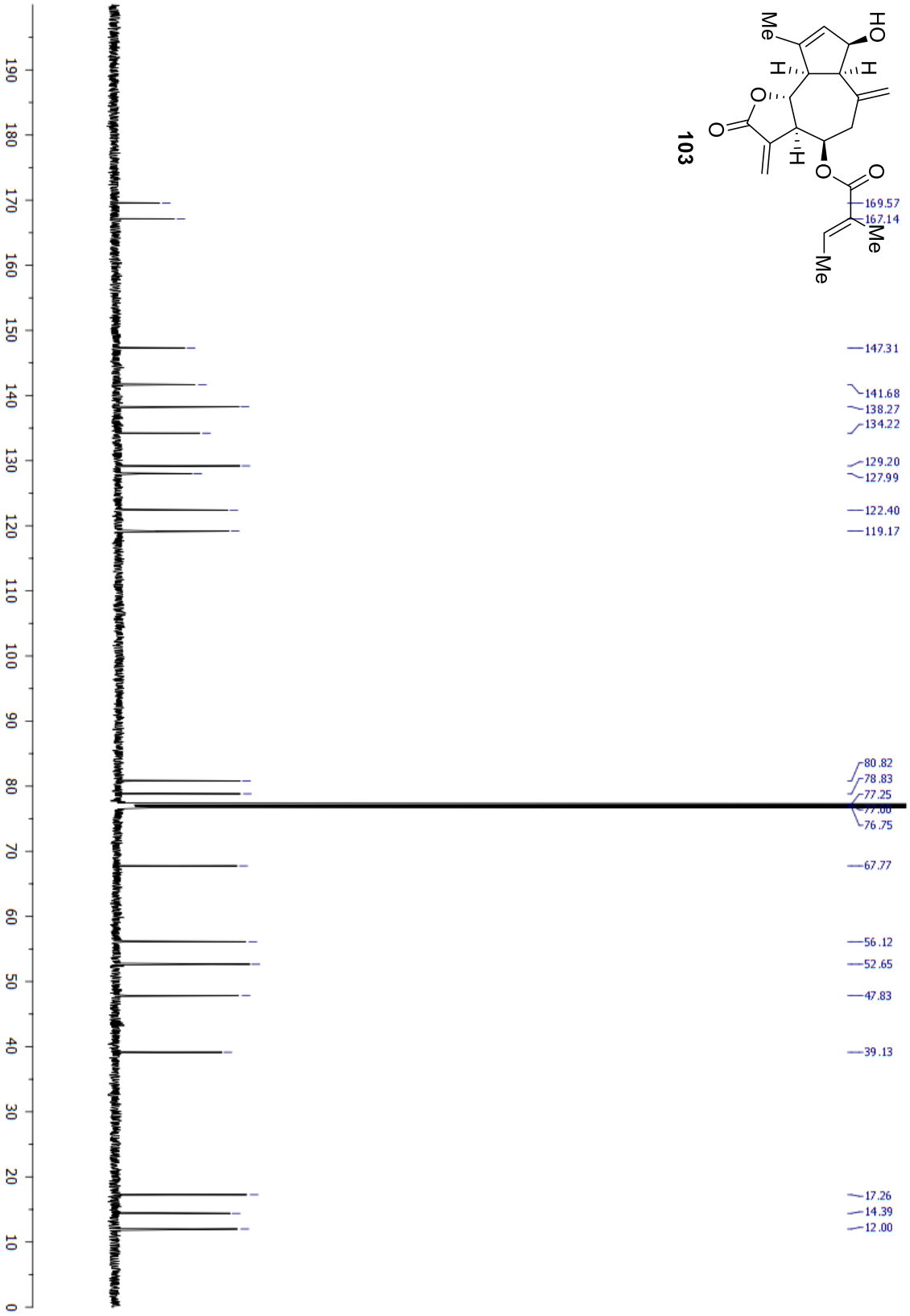
Me
H
O
O
H
O
H
O
O
Me
Me

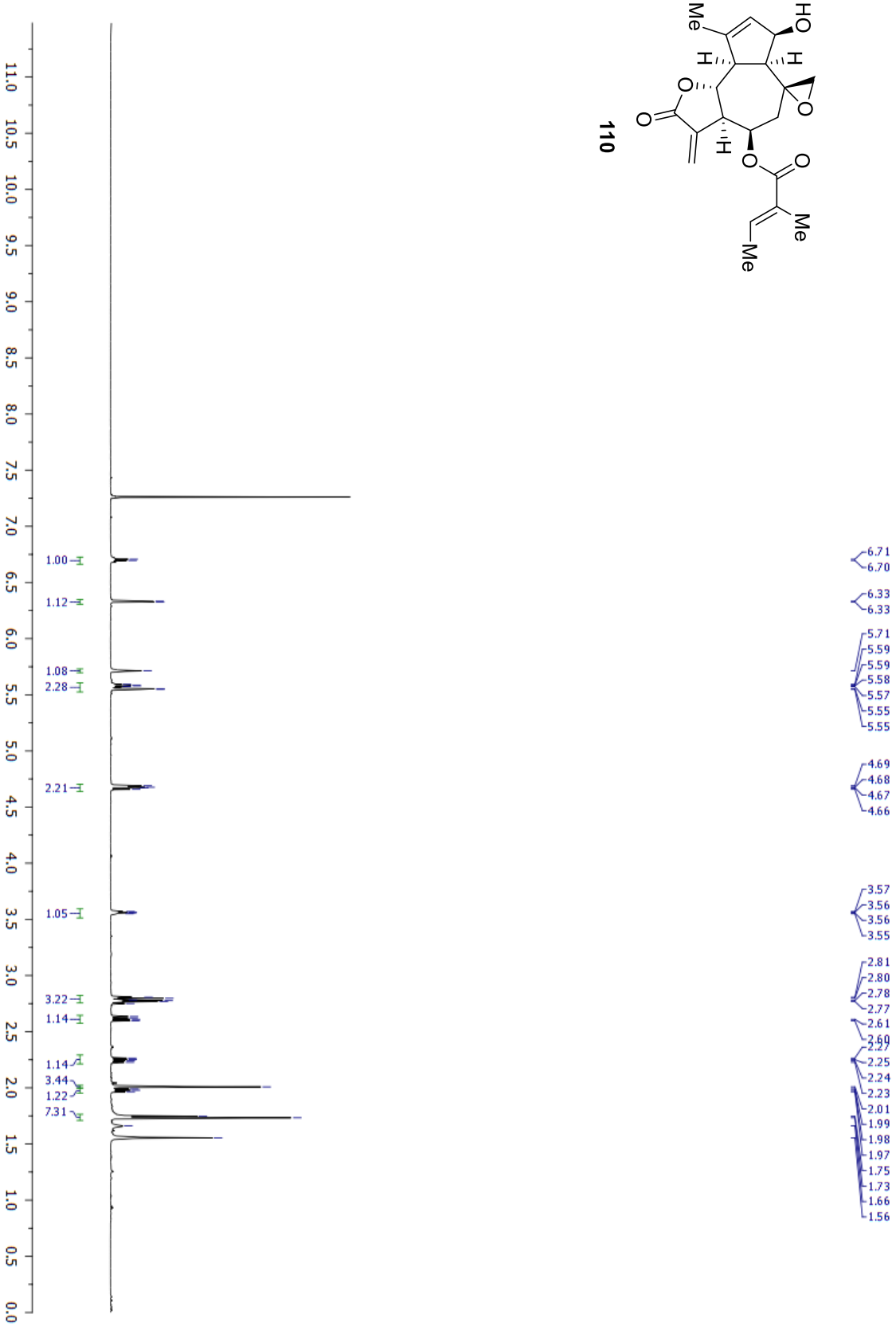
107


107
205.99
177.58
168.74
166.69
138.49
138.42
133.61
132.60
127.81
122.97
120.39
77.86
77.21
77.00
76.79
66.31
55.72
53.29
49.35
41.77
19.87
14.37
11.93


Me
H
O
O
O
H
O
O
Me
Me
107
{3.21,49.51}
{3.31,55.83}
{3.19,53.35}
{2.57,41.90}
{2.49,41.92}
f1 (ppm)

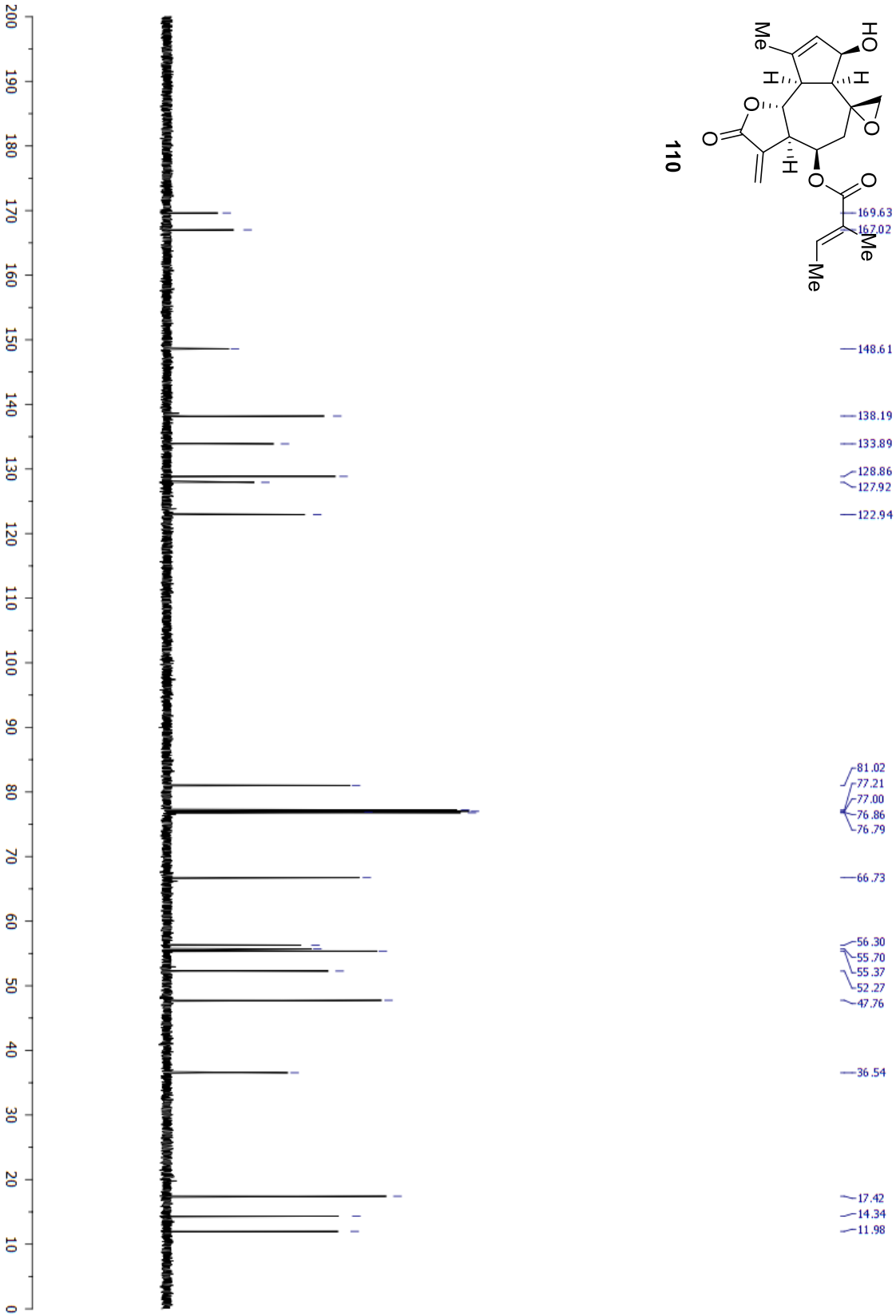

103
Me
HO
H
H
O
O
H
O
O
Me
Me
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
1.00
1.03
1.08
1.81
2.19
2.22
2.21
1.08
2.18
2.83
6.03
6.74
6.73
6.72
6.72
6.29
6.28
5.73
5.52
5.52
5.51
5.50
5.49
5.11
5.10
4.73
4.72
4.67
4.65
4.65
4.63
3.20
3.19
3.18
3.17
3.17
3.16
2.84
2.83
2.75
2.74
2.73
1.74


103
Me
HO
H
H
O
O
H
O
O
169.57
167.14
Me
Me
147.31
141.68
138.27
134.22
129.20
127.99
122.40
119.17
80.82
78.83
77.25
76.75
67.77
56.12
52.65
47.83
39.13
17.26
14.39
12.00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


11.0
10.5
10.0
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
0.0
1.00
1.12
1.08
2.28
2.21
1.05
3.22
1.14
1.14
3.44
1.22
7.31
6.71
6.70
6.33
6.33
5.71
5.59
5.59
5.58
5.57
5.55
5.55
4.69
4.68
4.67
4.66
3.57
3.56
3.56
3.55
2.81
2.80
2.78
2.77
2.61
2.60
2.27
2.25
2.24
2.23
2.01
1.99
1.98
1.97
1.75
1.73
1.66
1.56

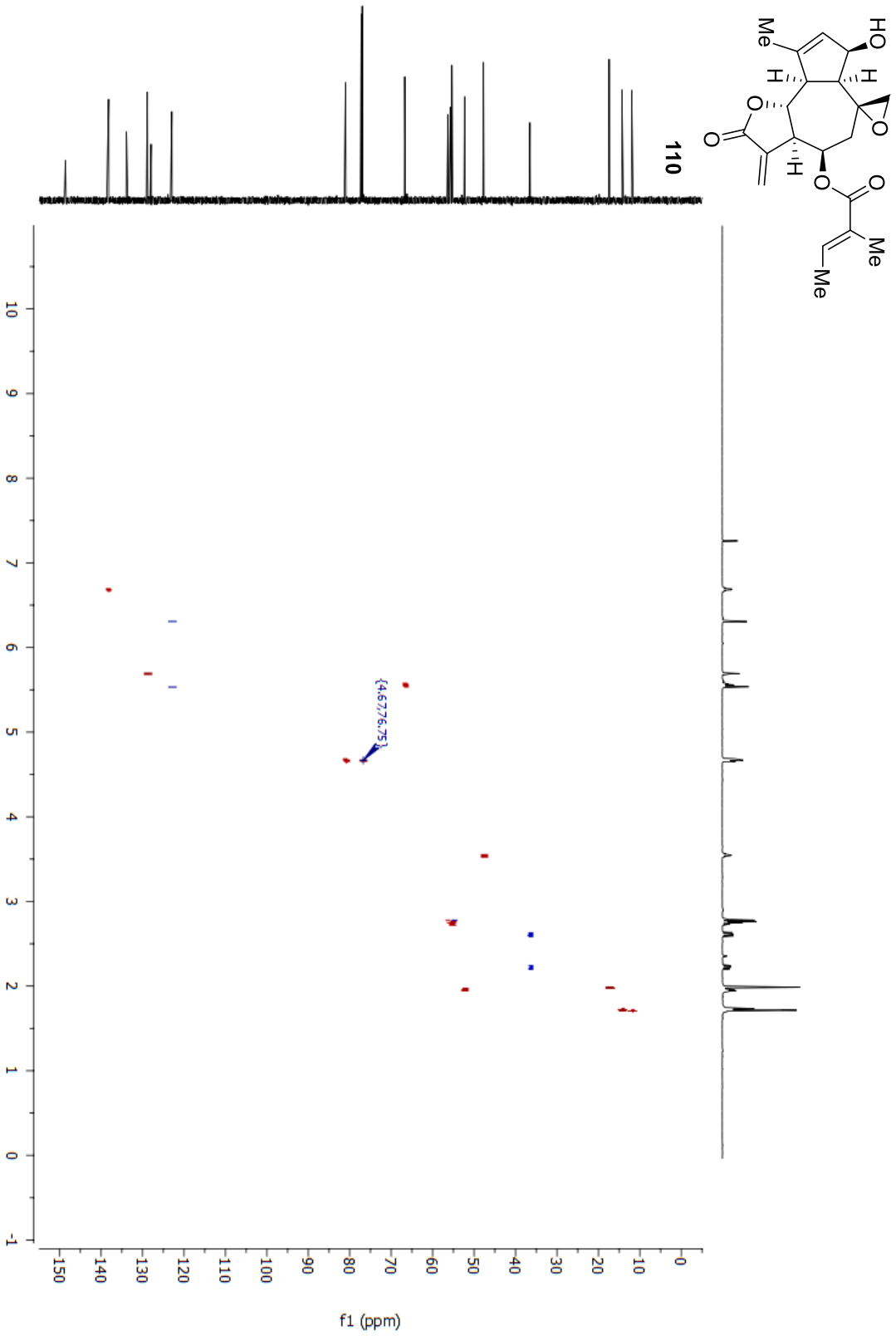
110

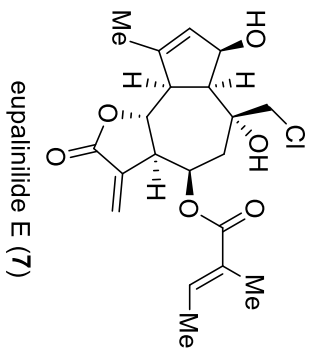
Me
HO
H
H
O
O
O
H
O
O
Me
Me


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
169.63
167.02
148.61
138.19
133.89
128.86
127.92
122.94
81.02
77.21
77.00
76.86
76.79
66.73
56.30
55.70
55.37
52.27
47.76
36.54
17.42
14.34
11.98

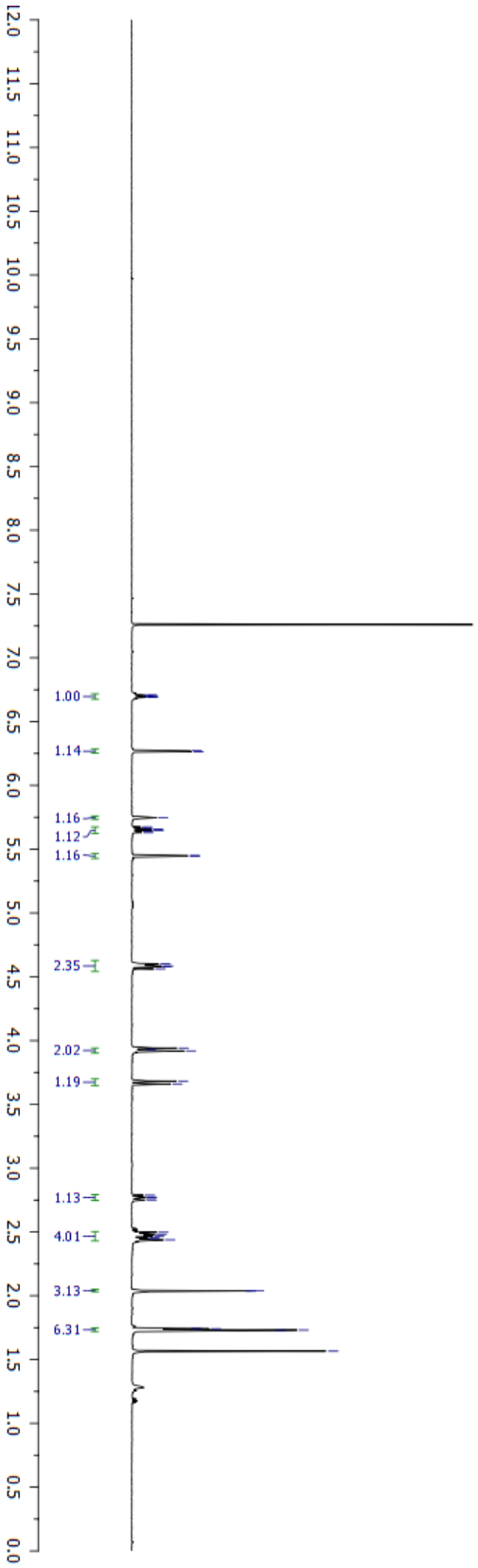
Me
HO
H
H
O
O
O
O
O
H
O
Me
Me

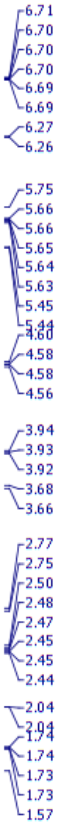
110

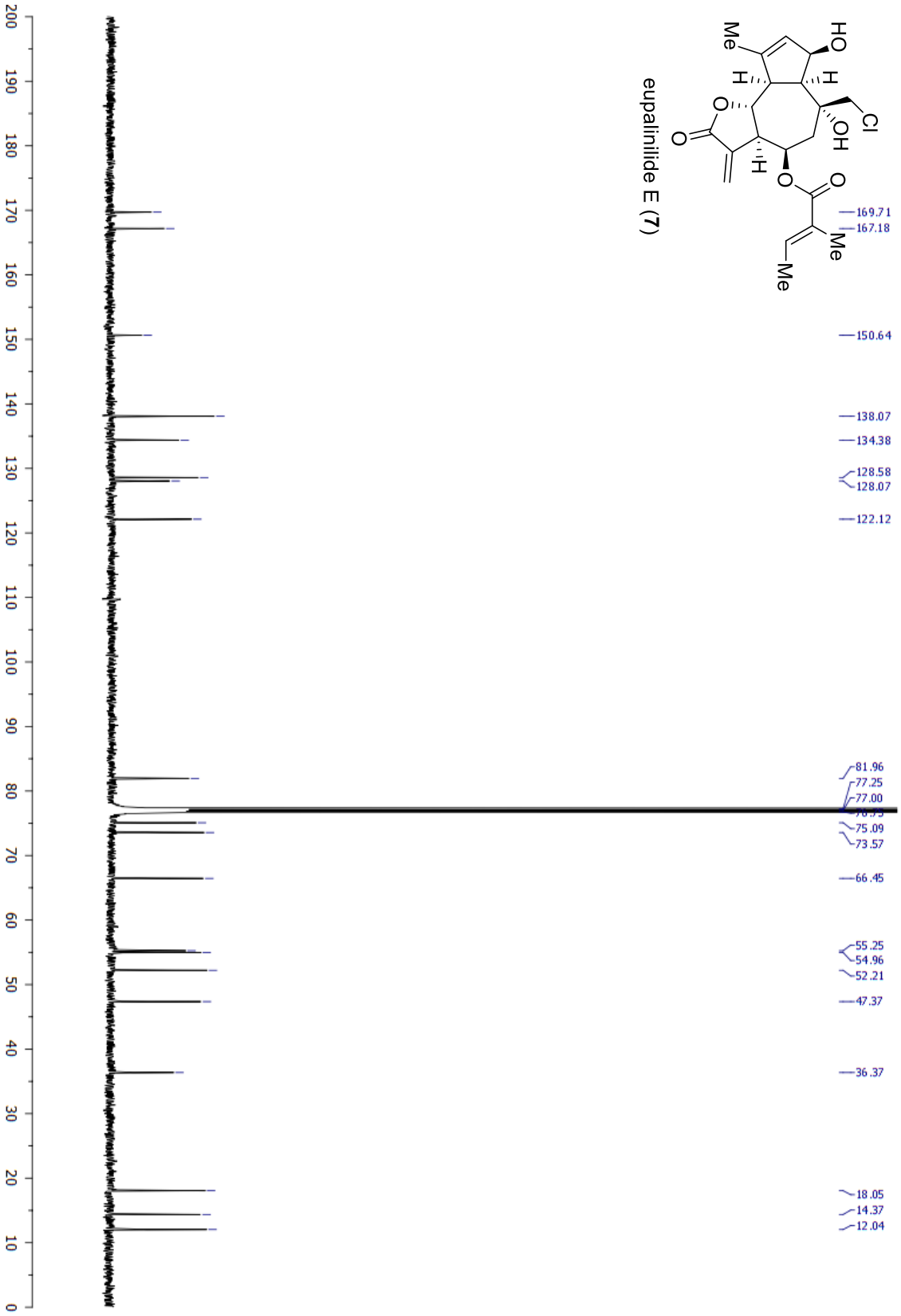

110
{4.67/76.75}
f1 (ppm)



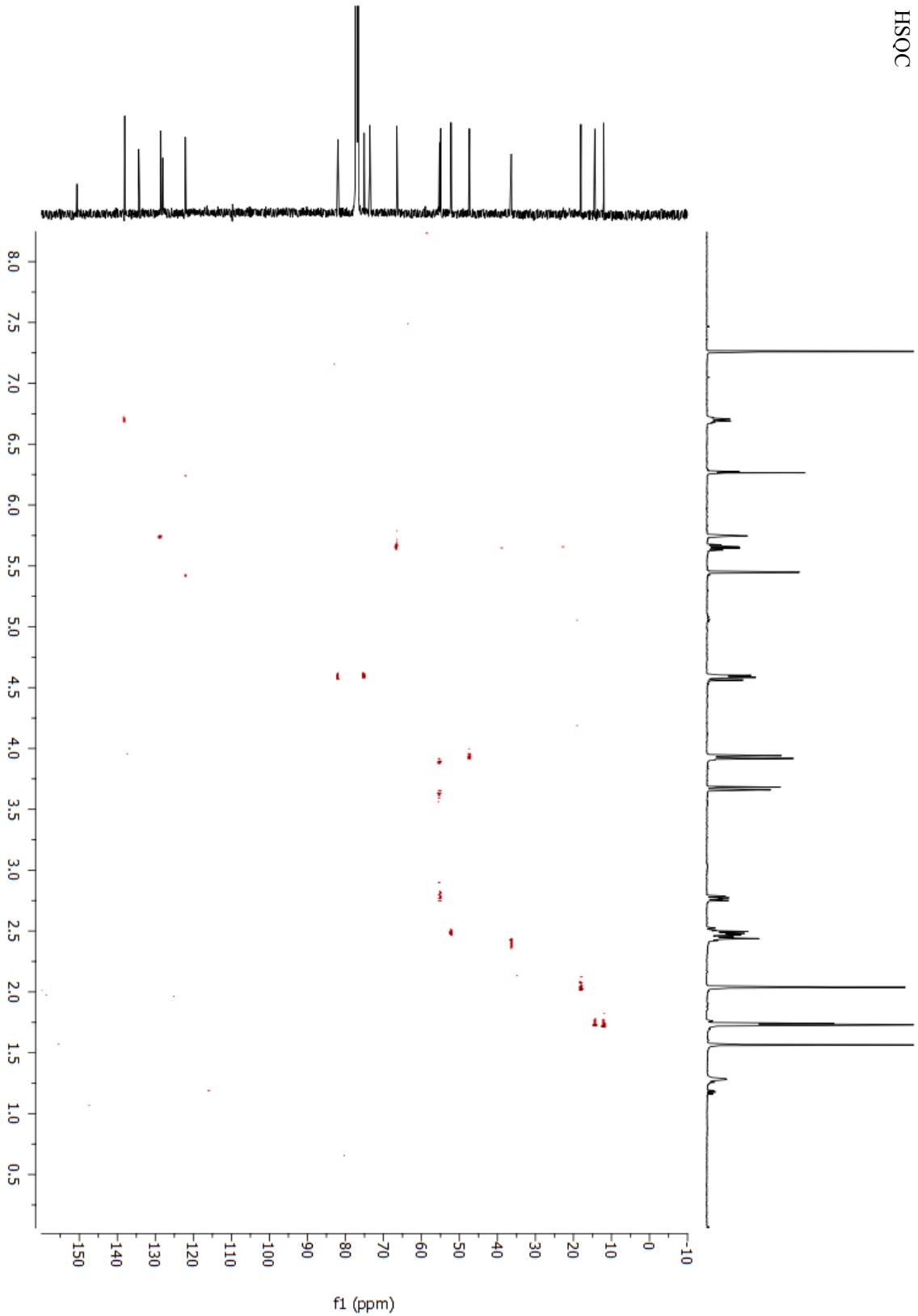
eupalinilide E (**7**)



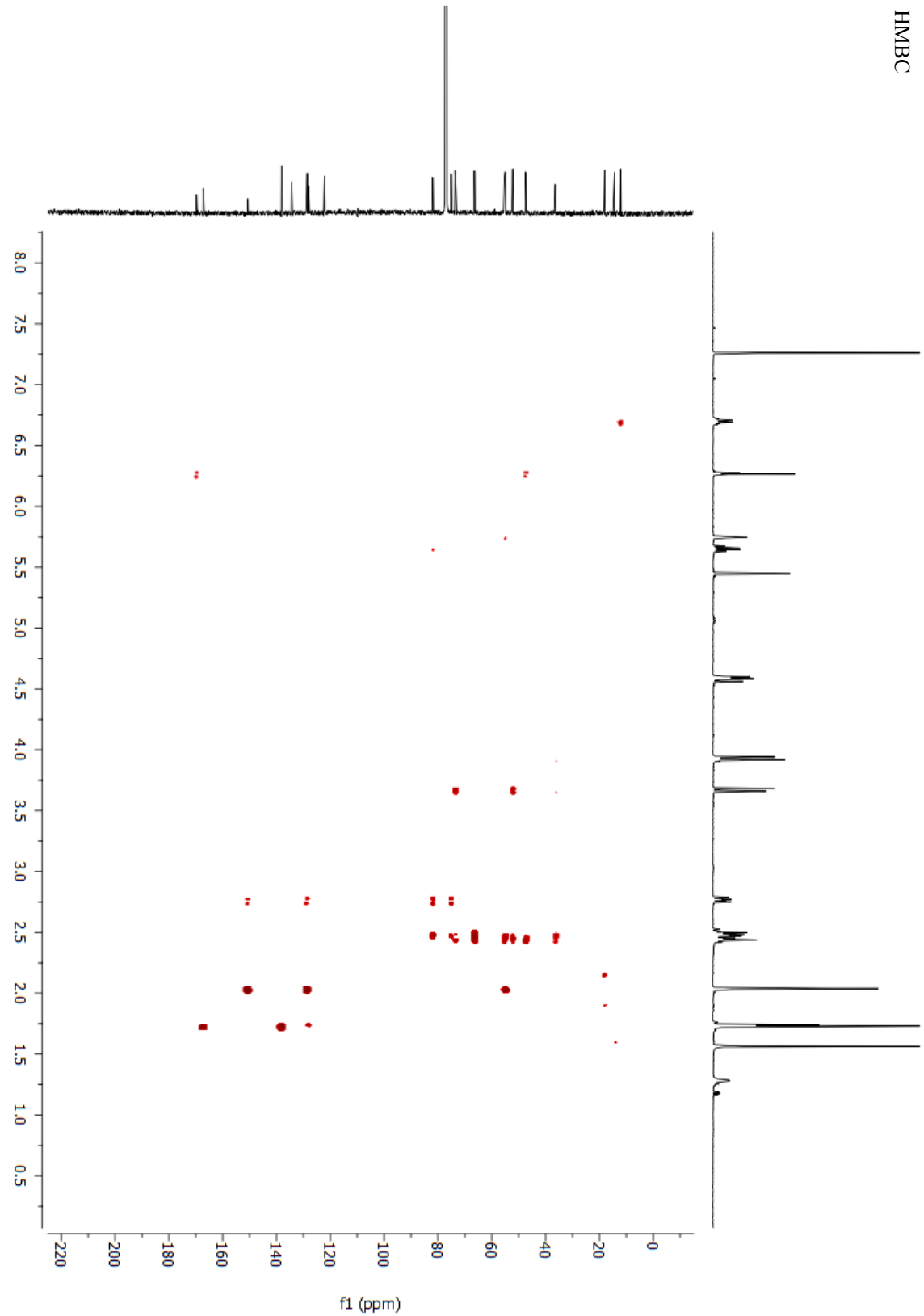



eupalinilide E (7)
169.71
167.18
150.64
138.07
134.38
128.58
128.07
122.12
81.96
77.25
77.00
75.09
73.57
66.45
55.25
54.96
52.21
47.37
36.37
18.05
14.37
12.04
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

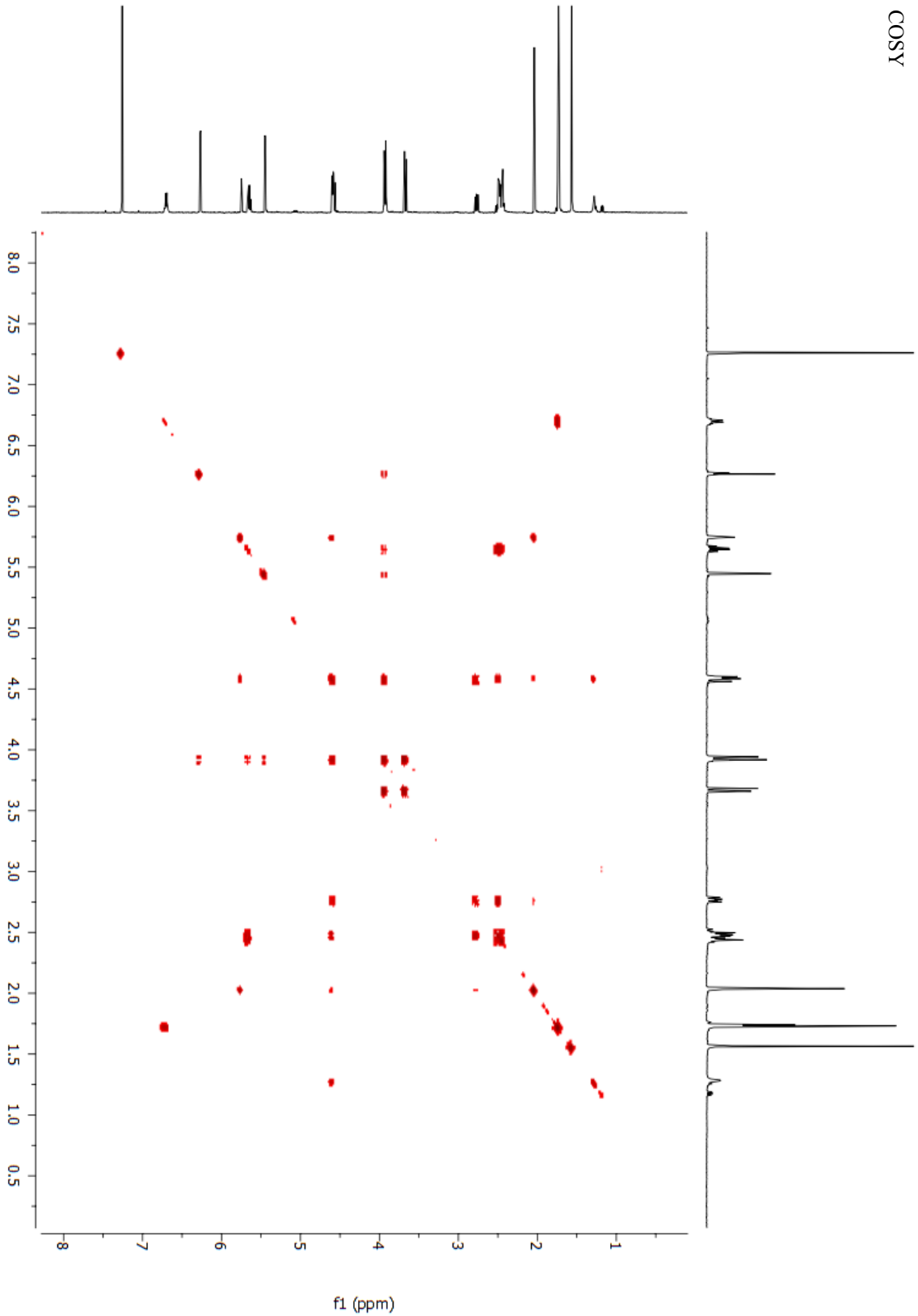
HSQC


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
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

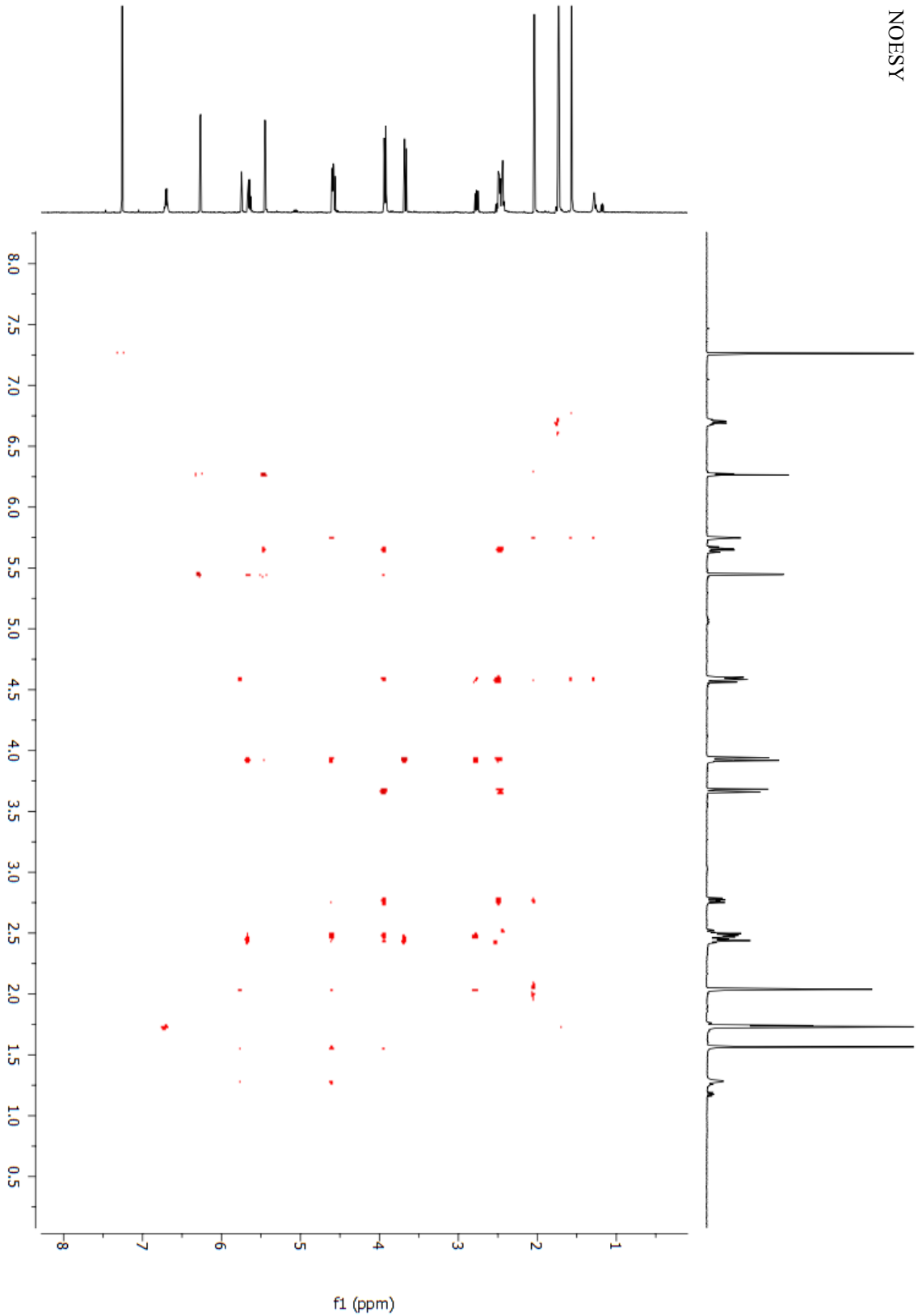
HMBC

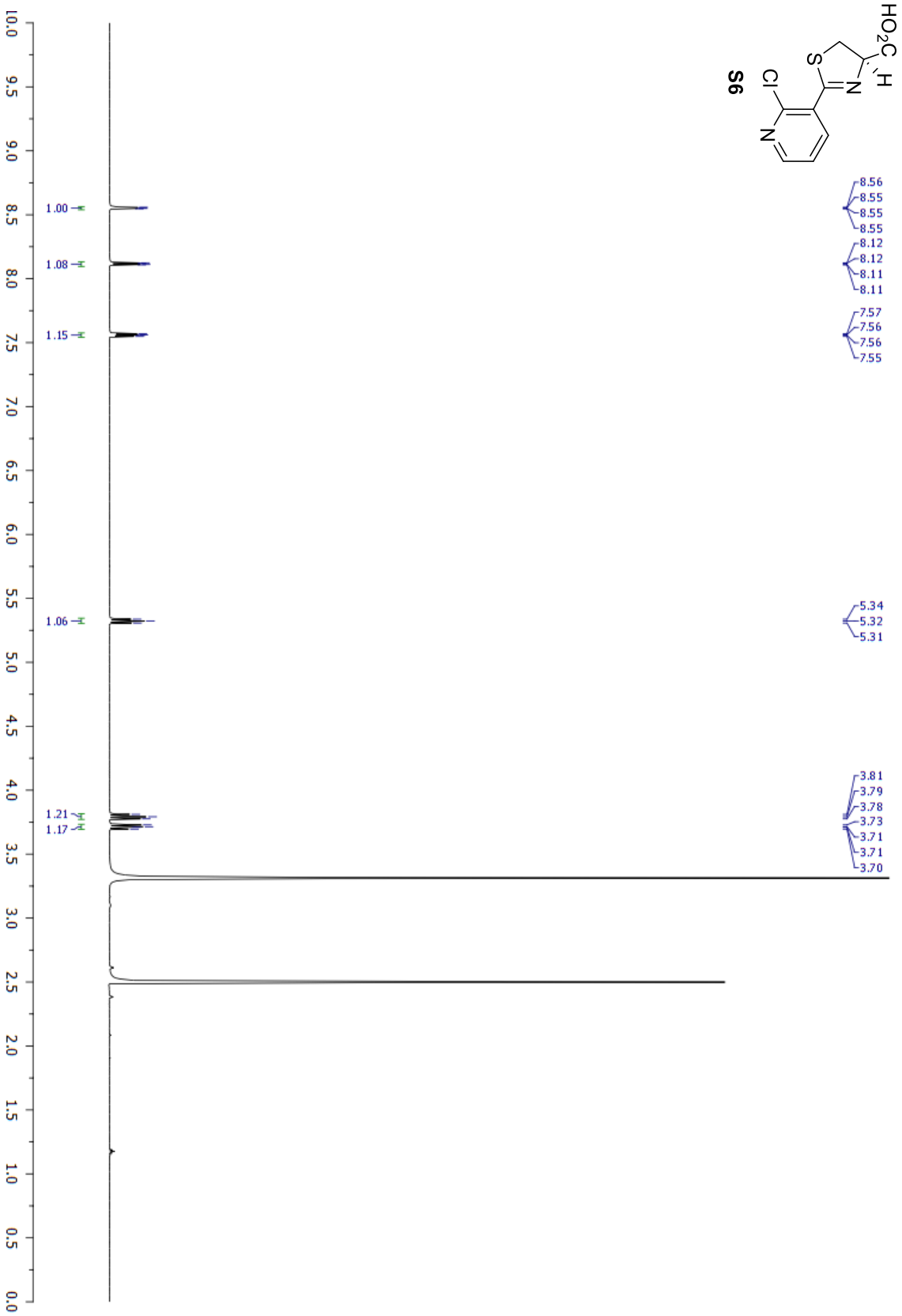

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

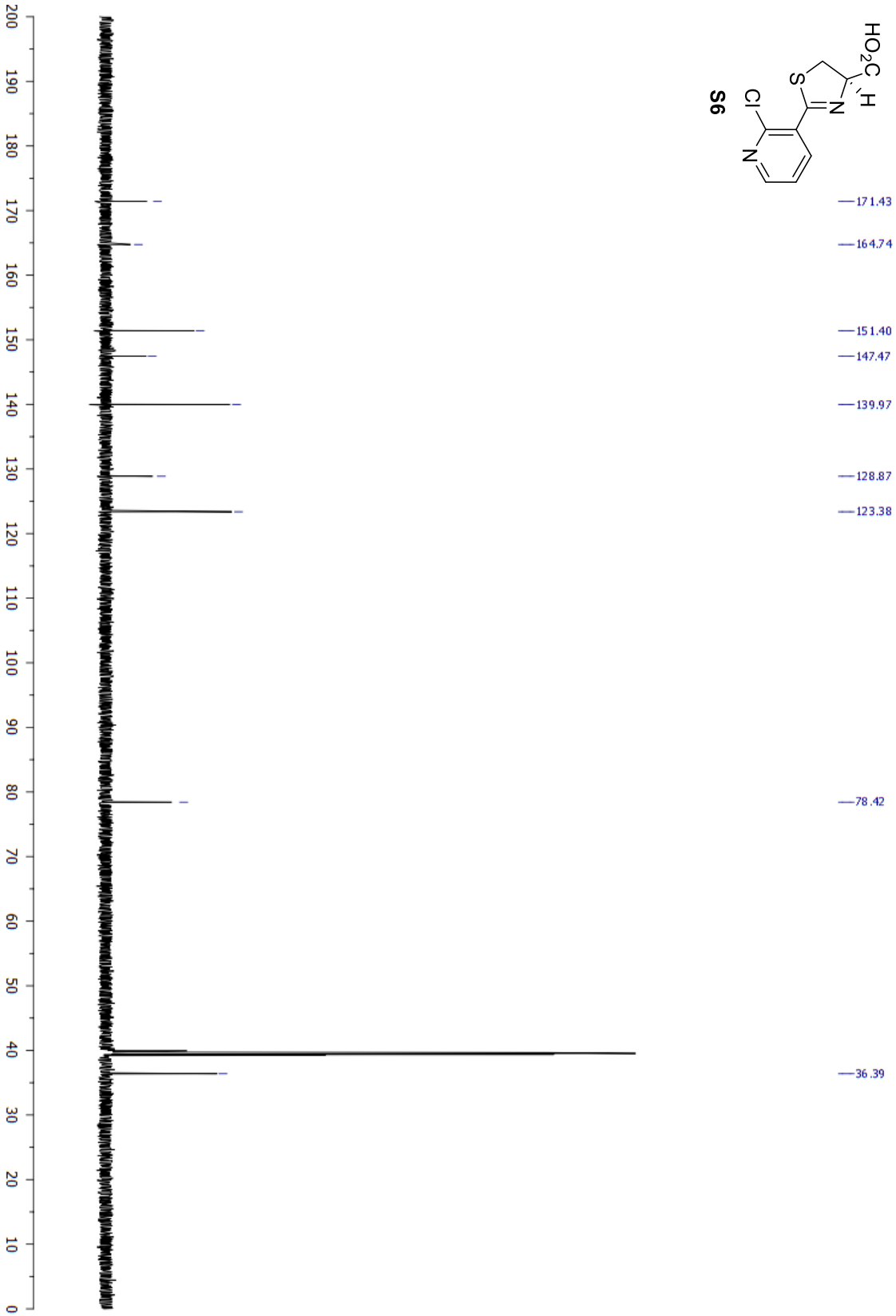
COSY

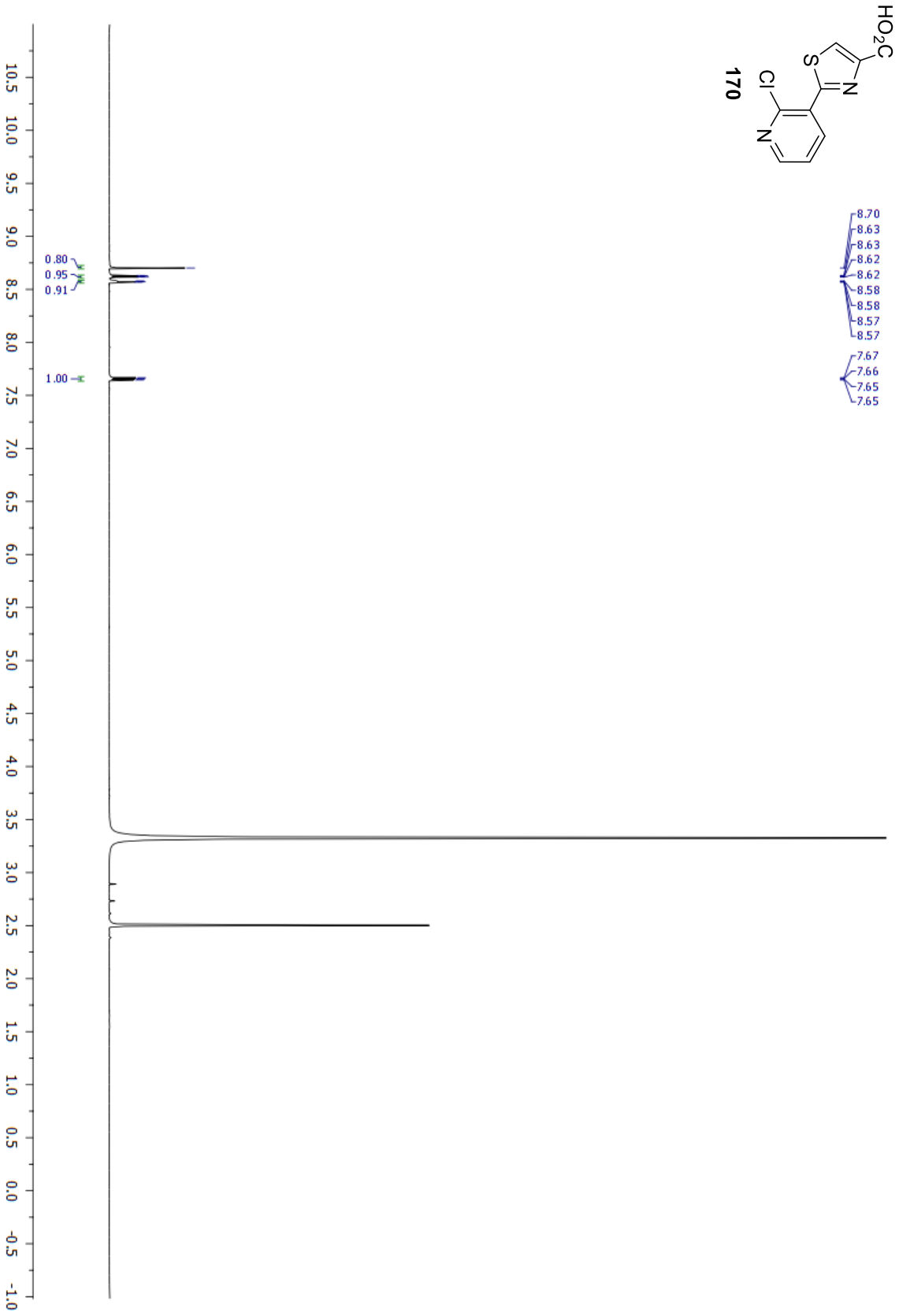


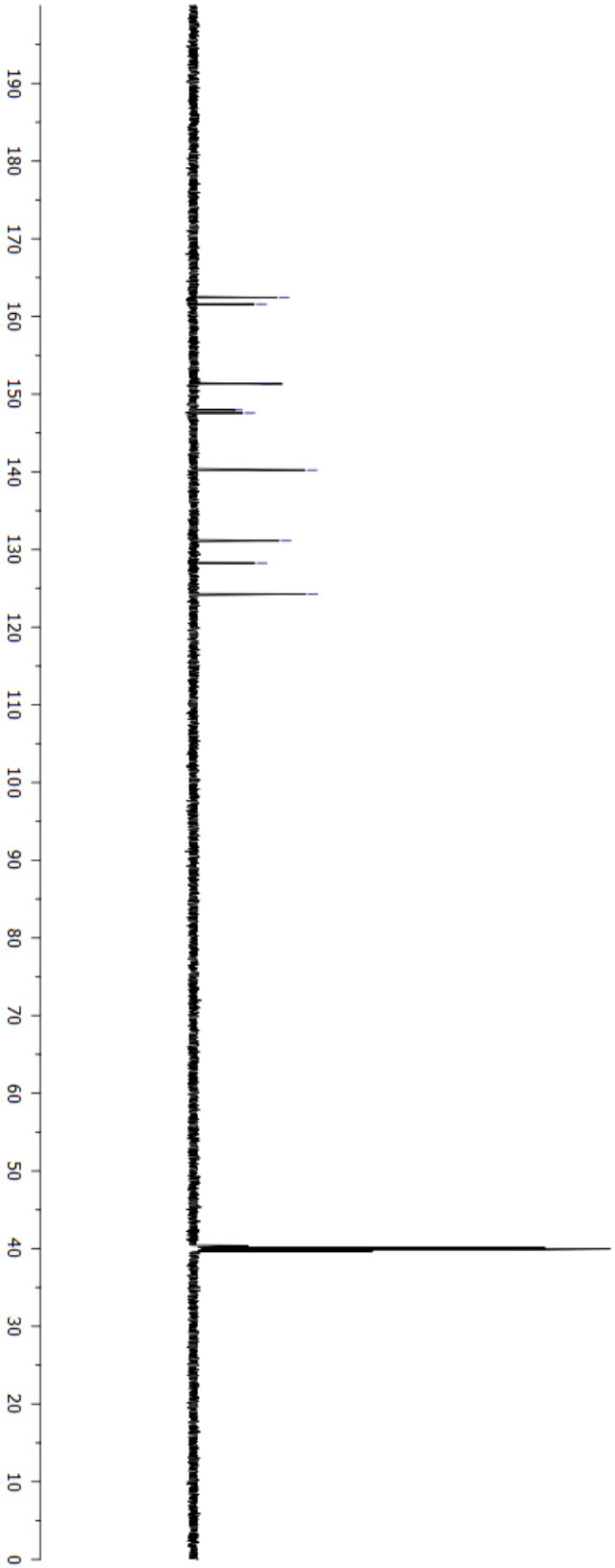
NOESY

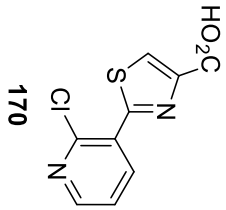



S6
Cl
N
S
N
HO2C
H
8.56
8.55
8.55
8.55
8.12
8.12
8.11
8.11
7.57
7.56
7.56
7.55
5.34
5.32
5.31
3.81
3.79
3.78
3.73
3.71
3.71
3.70
1.00
1.08
1.15
1.06
1.21
1.17


S6
171.43
164.74
151.40
147.47
139.97
128.87
123.38
78.42
36.39

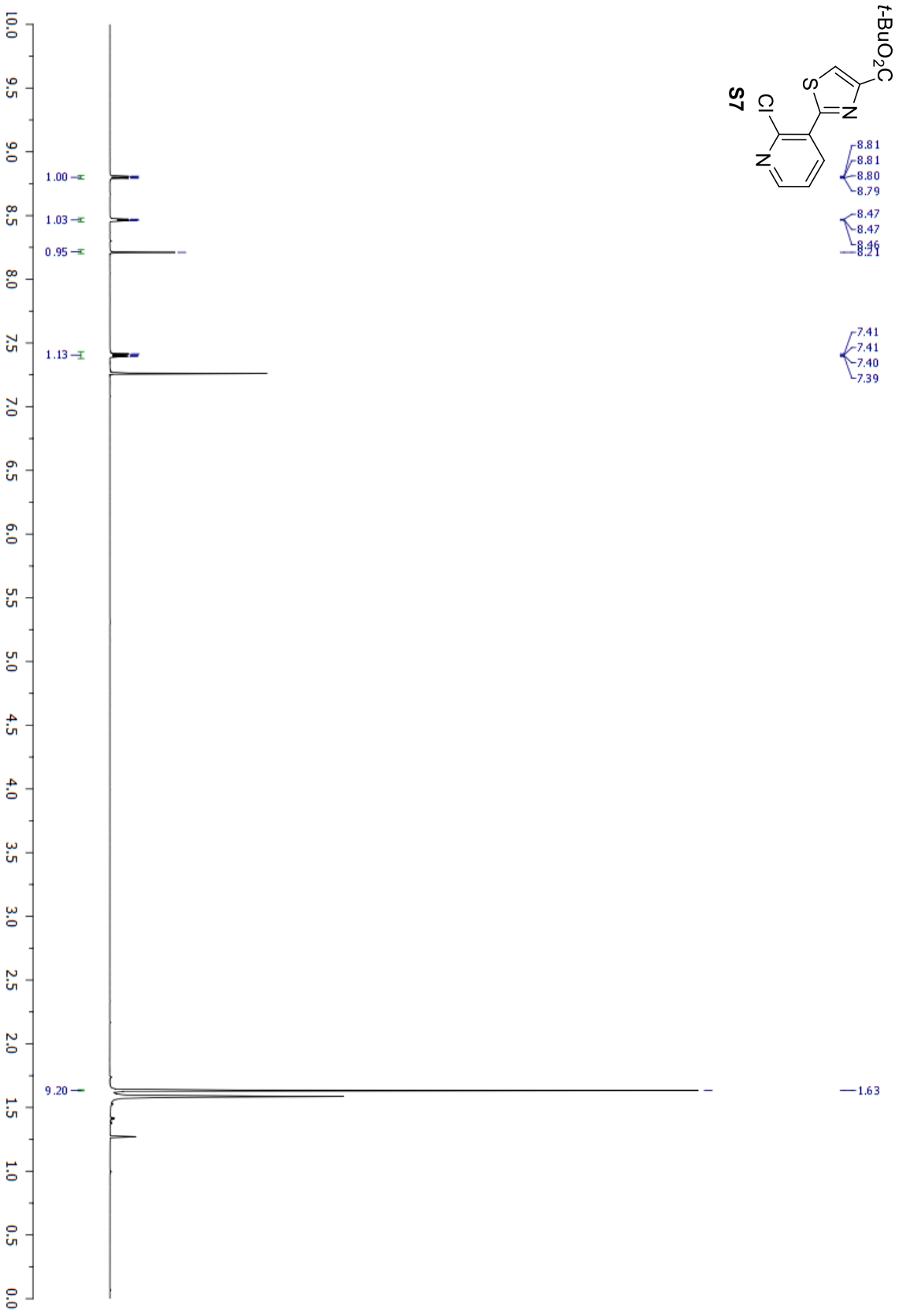

HO2C
S
N
Cl
N
170
8.70
8.63
8.63
8.62
8.62
8.58
8.58
8.57
8.57
7.67
7.66
7.65
7.65
0.80
0.95
0.91
1.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0

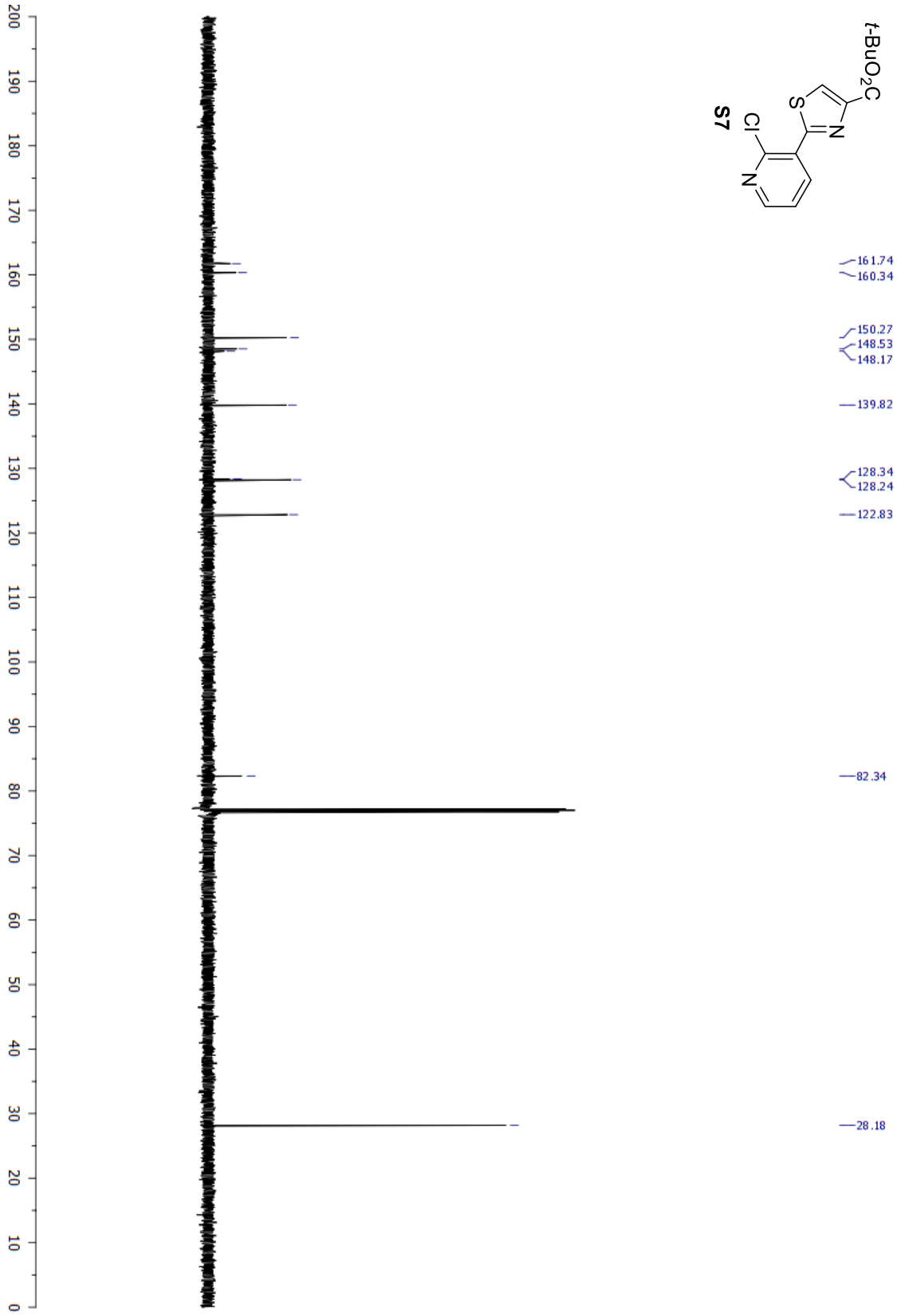


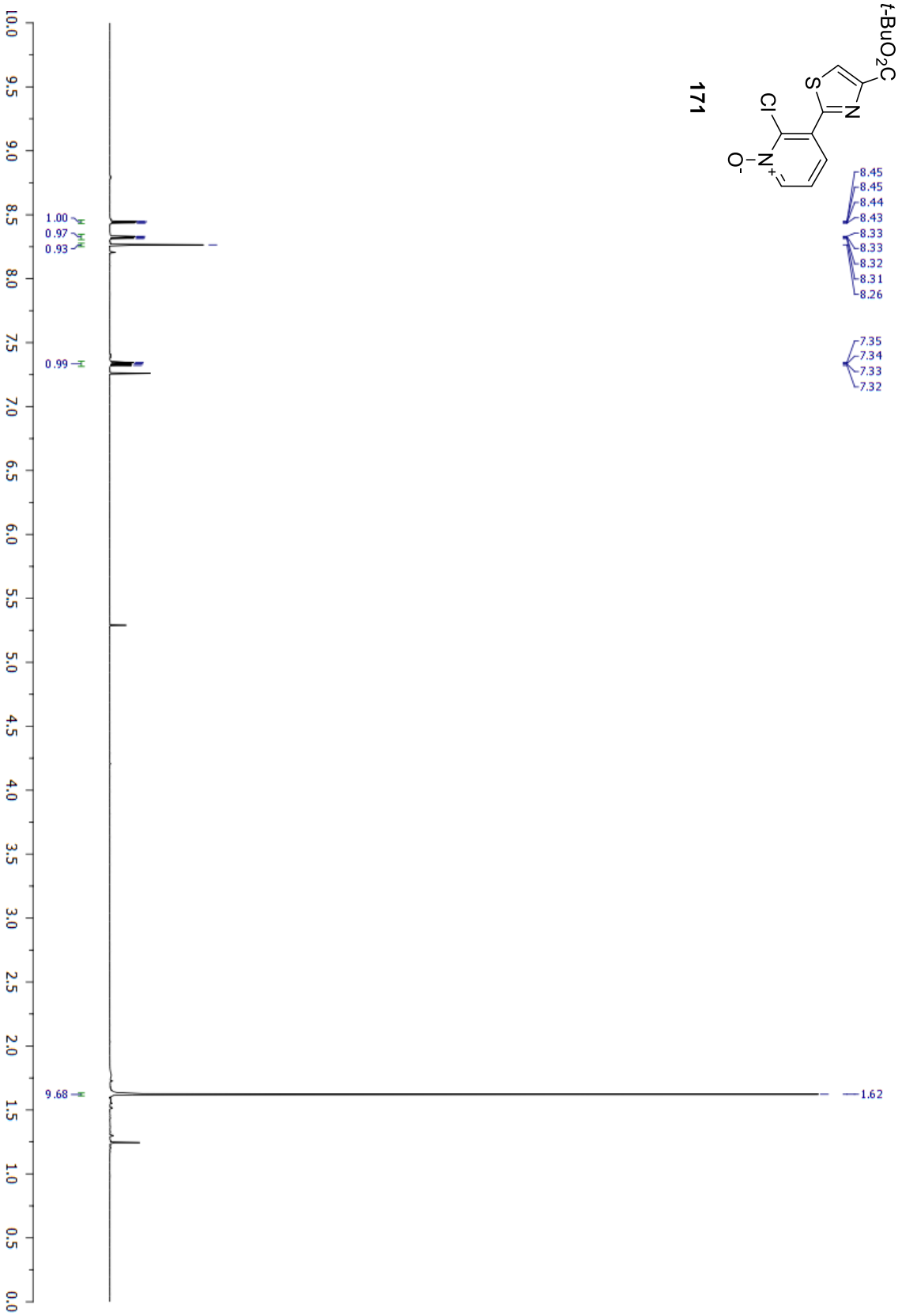


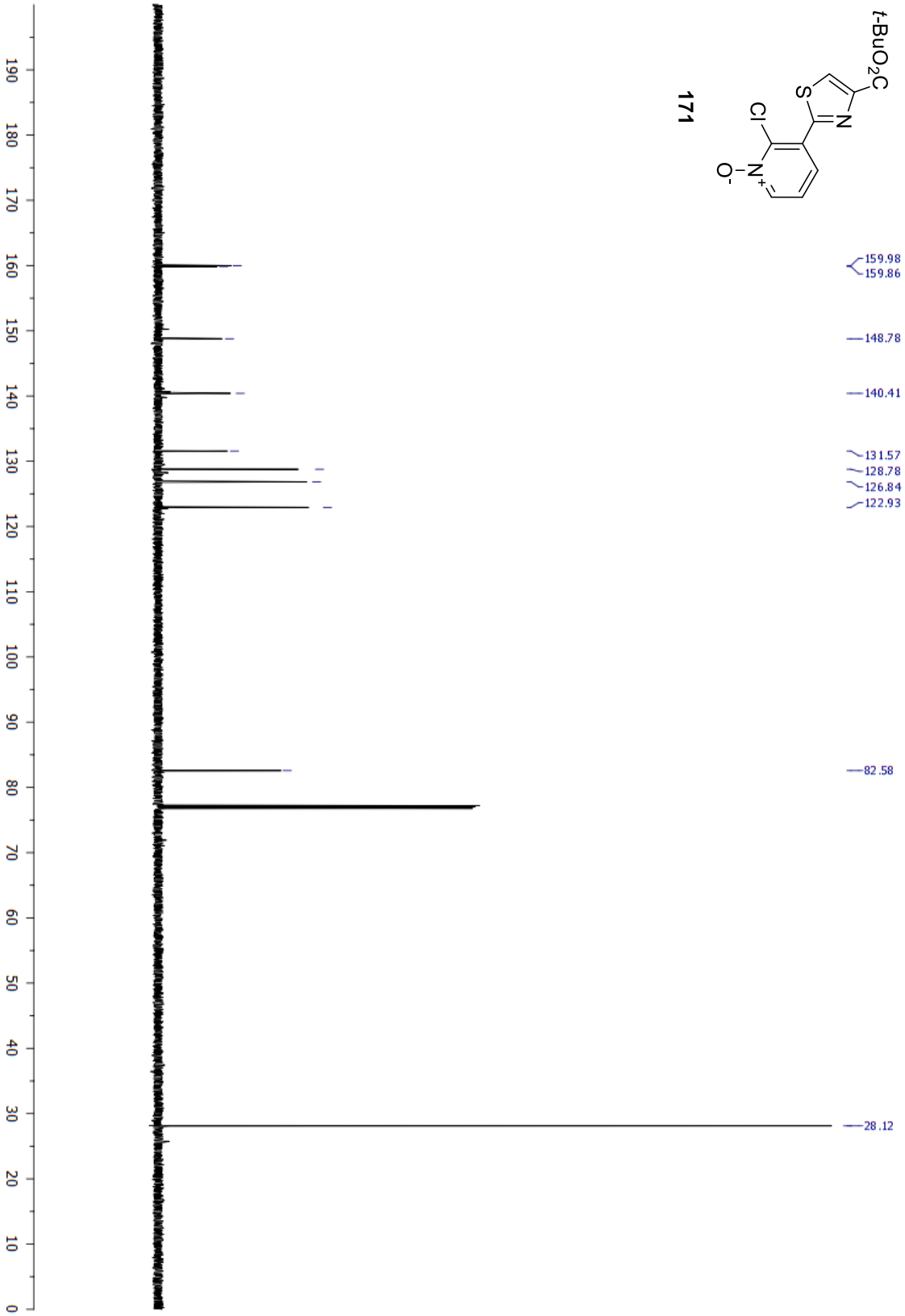
170

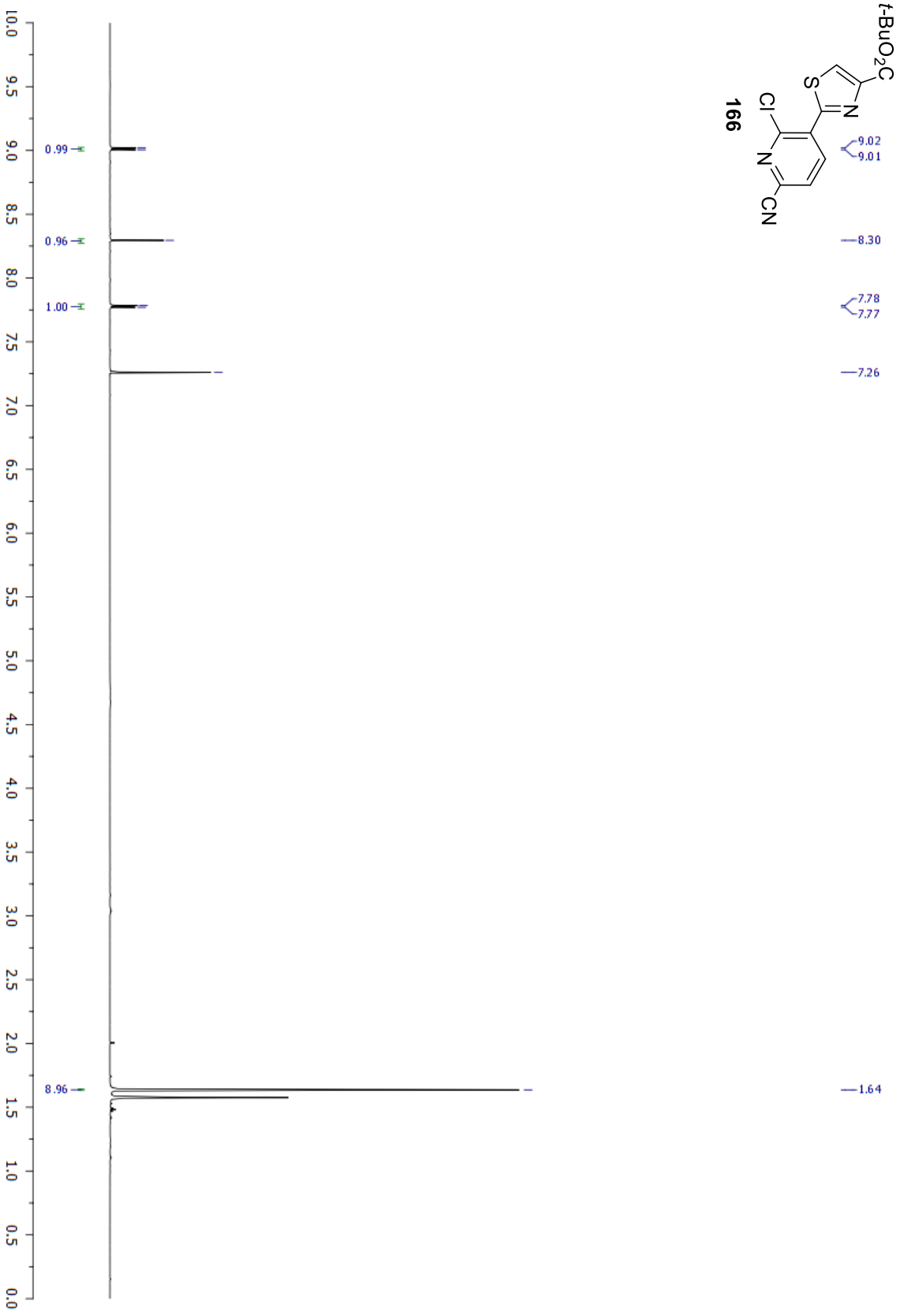
162.42
161.58
151.32
147.96
147.56
140.21
131.13
128.25
124.27

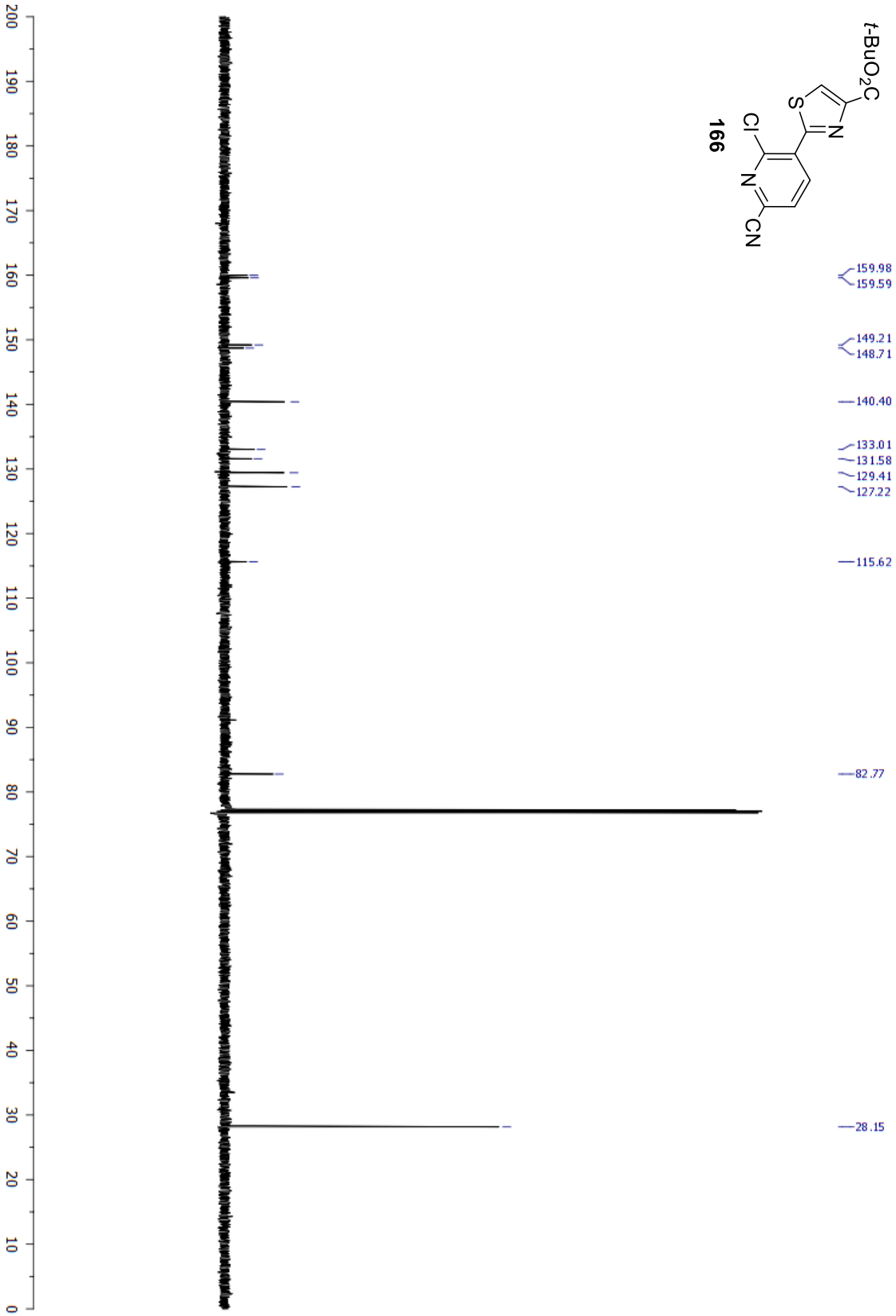

S7
t-BuO2C
S
N
Cl
N
8.81
8.81
8.80
8.79
8.47
8.47
8.46
8.21
7.41
7.41
7.40
7.39
1.00
1.03
0.95
1.13
9.20
1.63
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

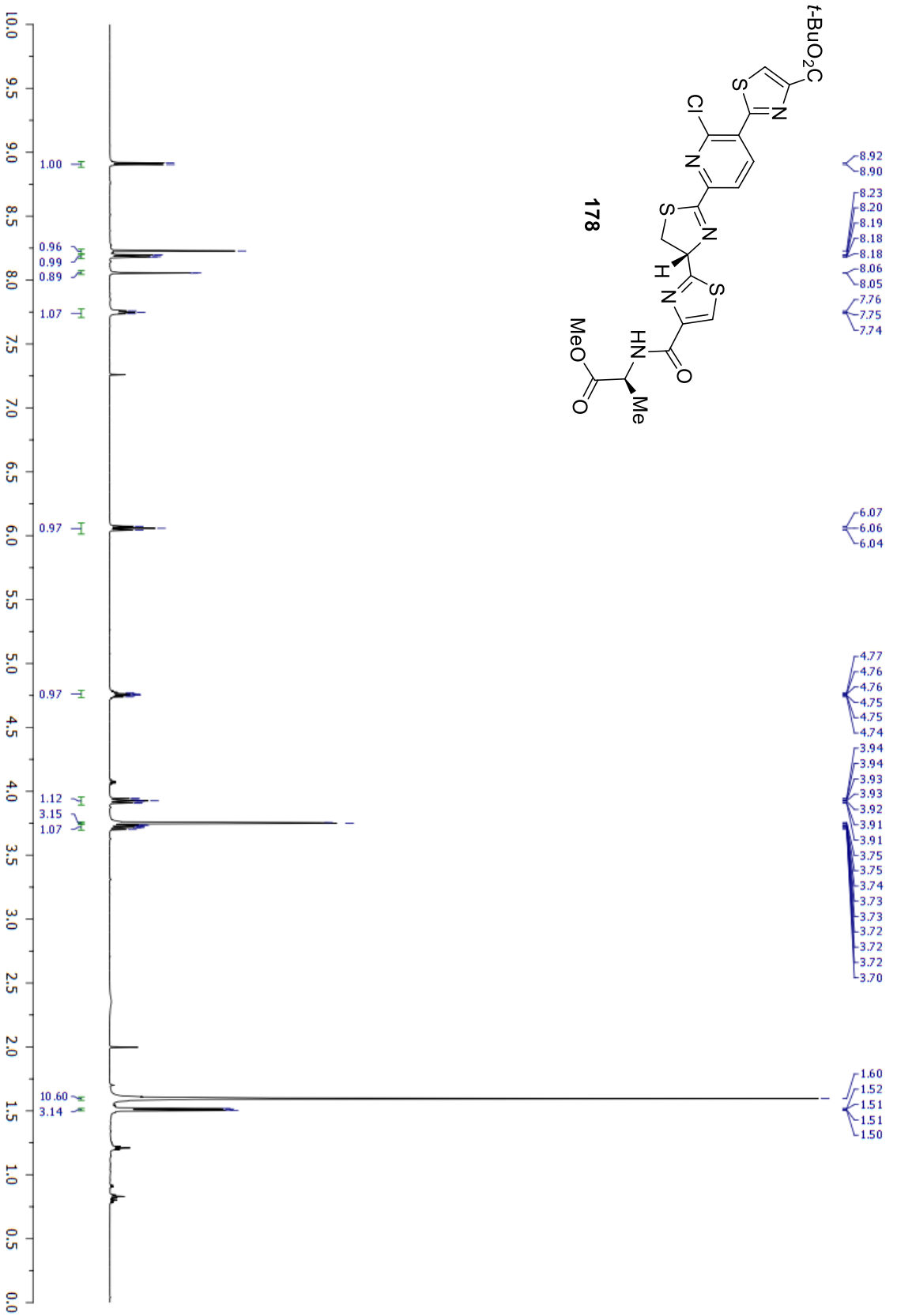

S7
t-BuO2C
Cl
S
N
N
161.74
160.34
150.27
148.53
148.17
139.82
128.34
128.24
122.83
82.34
28.18
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


t-BuO2C
S
N
Cl
O-
N+
171
8.45
8.45
8.44
8.43
8.33
8.33
8.32
8.31
8.26
7.35
7.34
7.33
7.32
1.00
0.97
0.93
0.99
9.68
1.62
10.0
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
0.0


171
t-BuO2C
S
N
Cl
O-
N+
159.98
159.86
148.78
140.41
131.57
128.78
126.84
122.93
82.58
28.12
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


t-BuO2C
S
N
Cl
N
CN
166
9.02
9.01
8.30
7.78
7.77
7.26
1.64
0.99
0.96
1.00
8.96
10.0
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
0.0


166
t-BuO2C
S
N
Cl
N
CN
159.98
159.59
149.21
148.71
140.40
133.01
131.58
129.41
127.22
115.62
82.77
28.15
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


178
t-BuO2C
Cl
MeO
HN
Me
O
10.0
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
0.0
1.00
0.96
0.99
0.89
1.07
0.97
0.97
1.12
3.15
1.07
10.60
3.14
8.92
8.90
8.23
8.20
8.19
8.18
8.18
8.06
8.05
7.76
7.75
7.74
6.07
6.06
6.04
4.77
4.76
4.76
4.75
4.75
4.74
3.94
3.94
3.93
3.93
3.92
3.91
3.91
3.75
3.75
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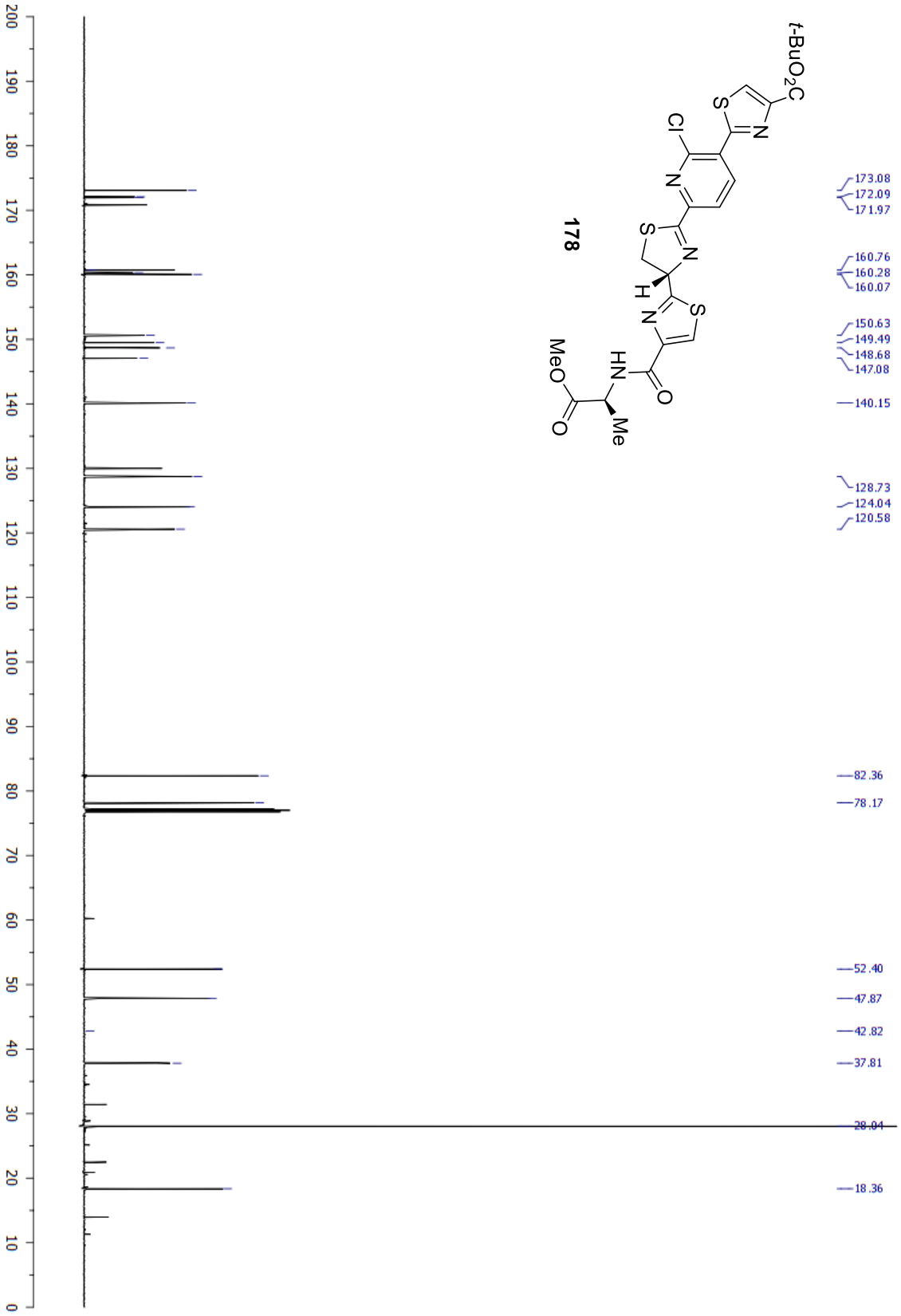
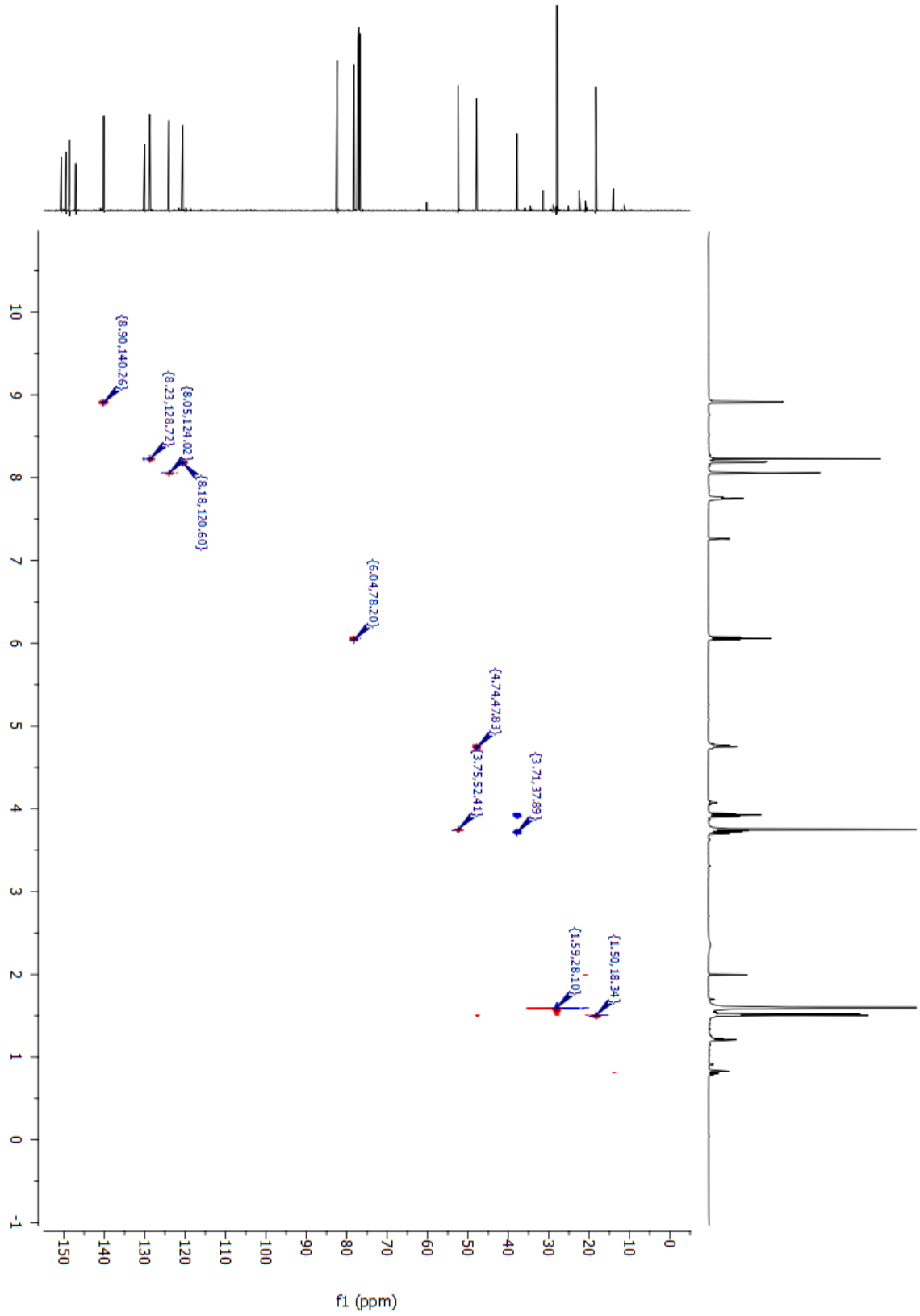
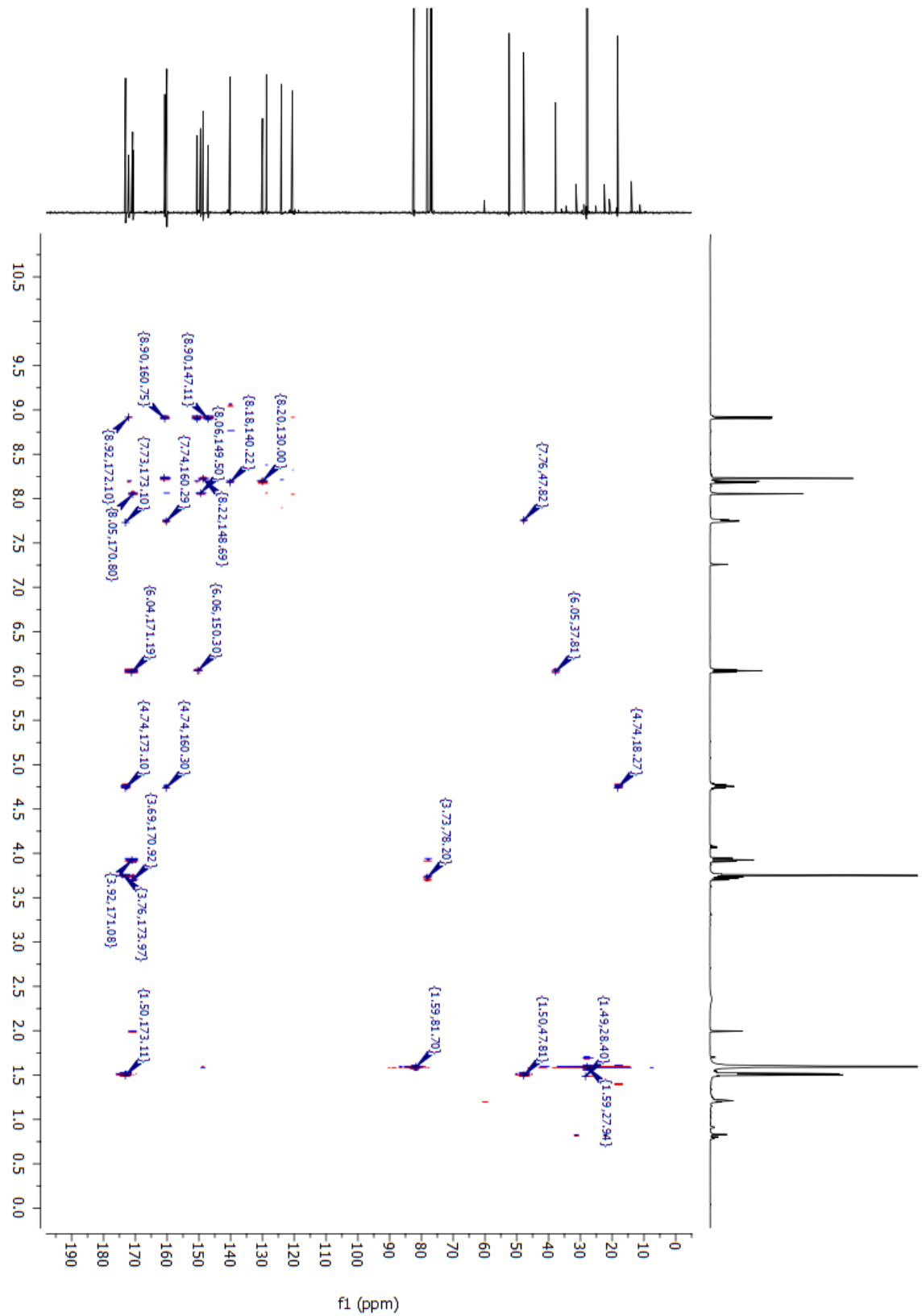
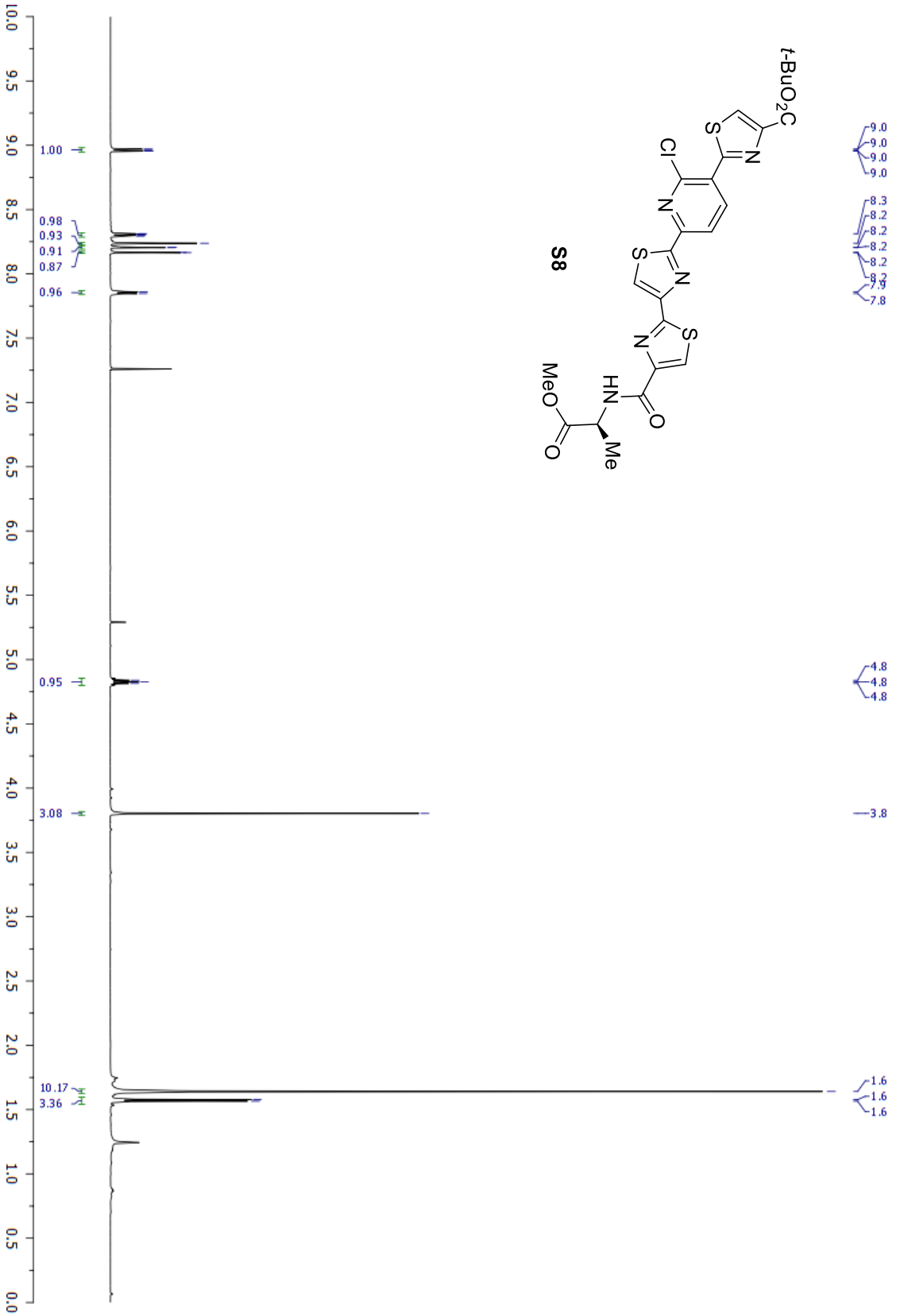
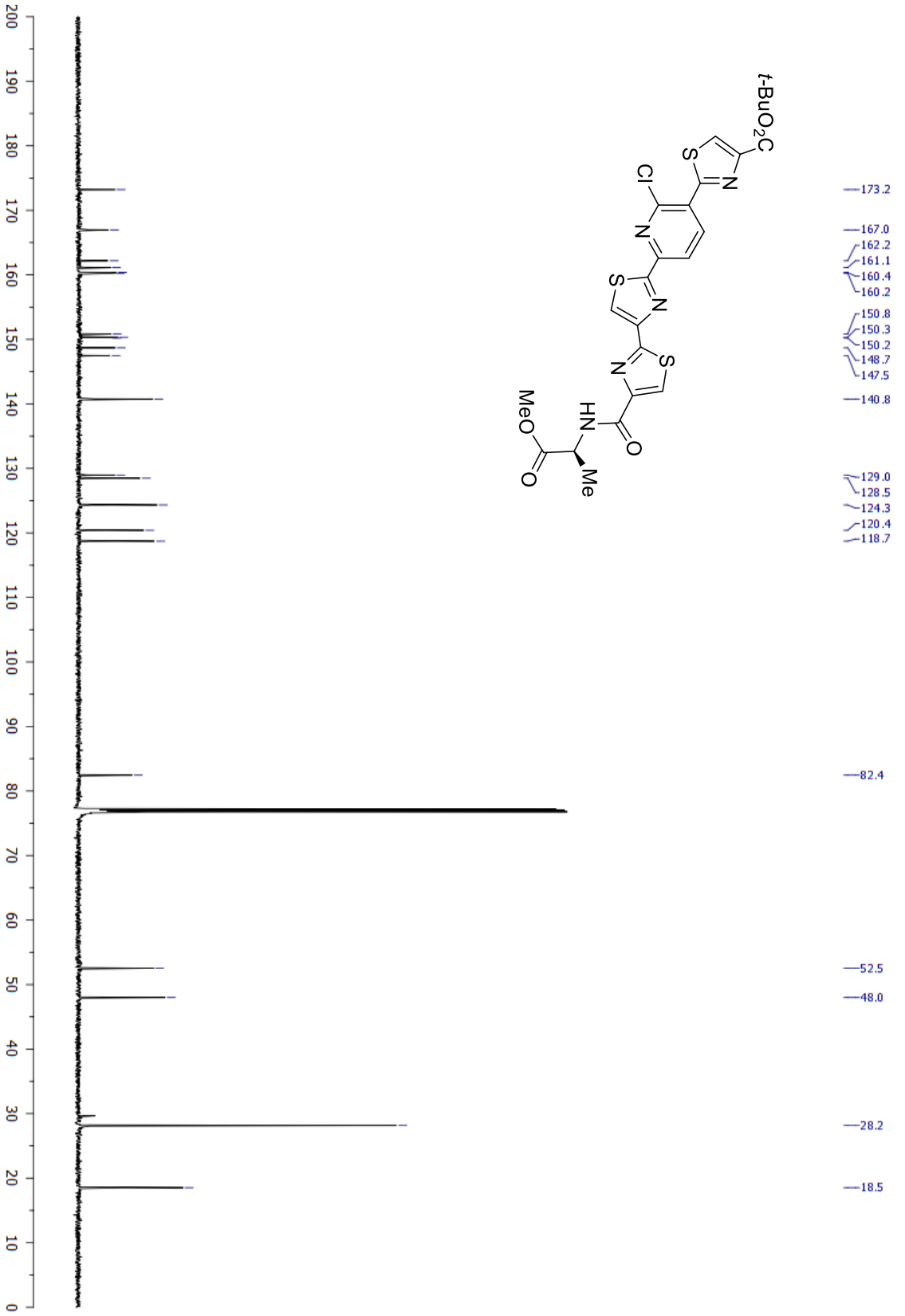
3.70
1.60
1.52
1.51
1.51
1.50

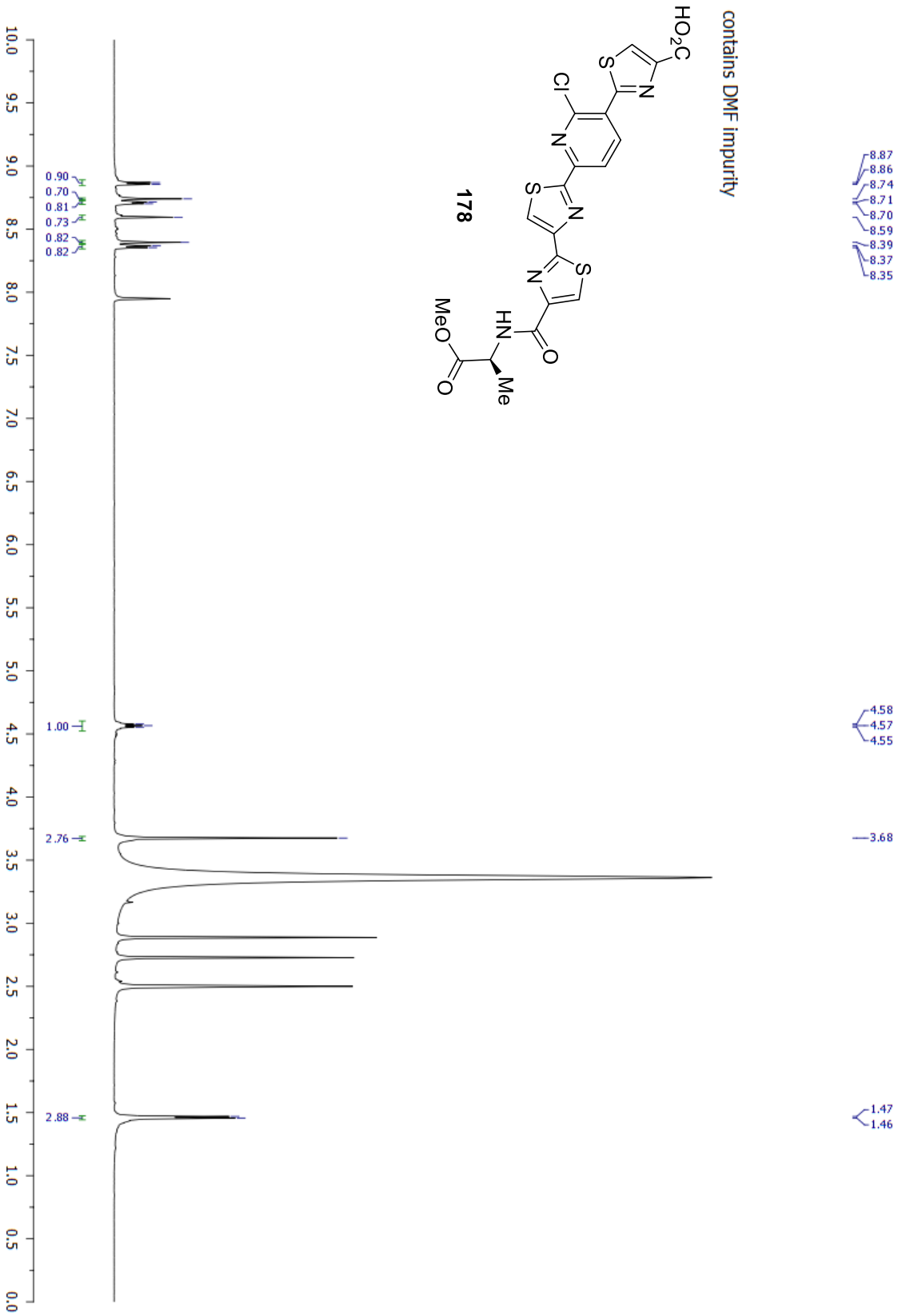

178
t-BuO2C
Cl
MeO
HN
Me
O
173.08
172.09
171.97
160.76
160.28
160.07
150.63
149.49
148.68
147.08
140.15
128.73
124.04
120.58
82.36
78.17
52.40
47.87
42.82
37.81
28.04
18.36

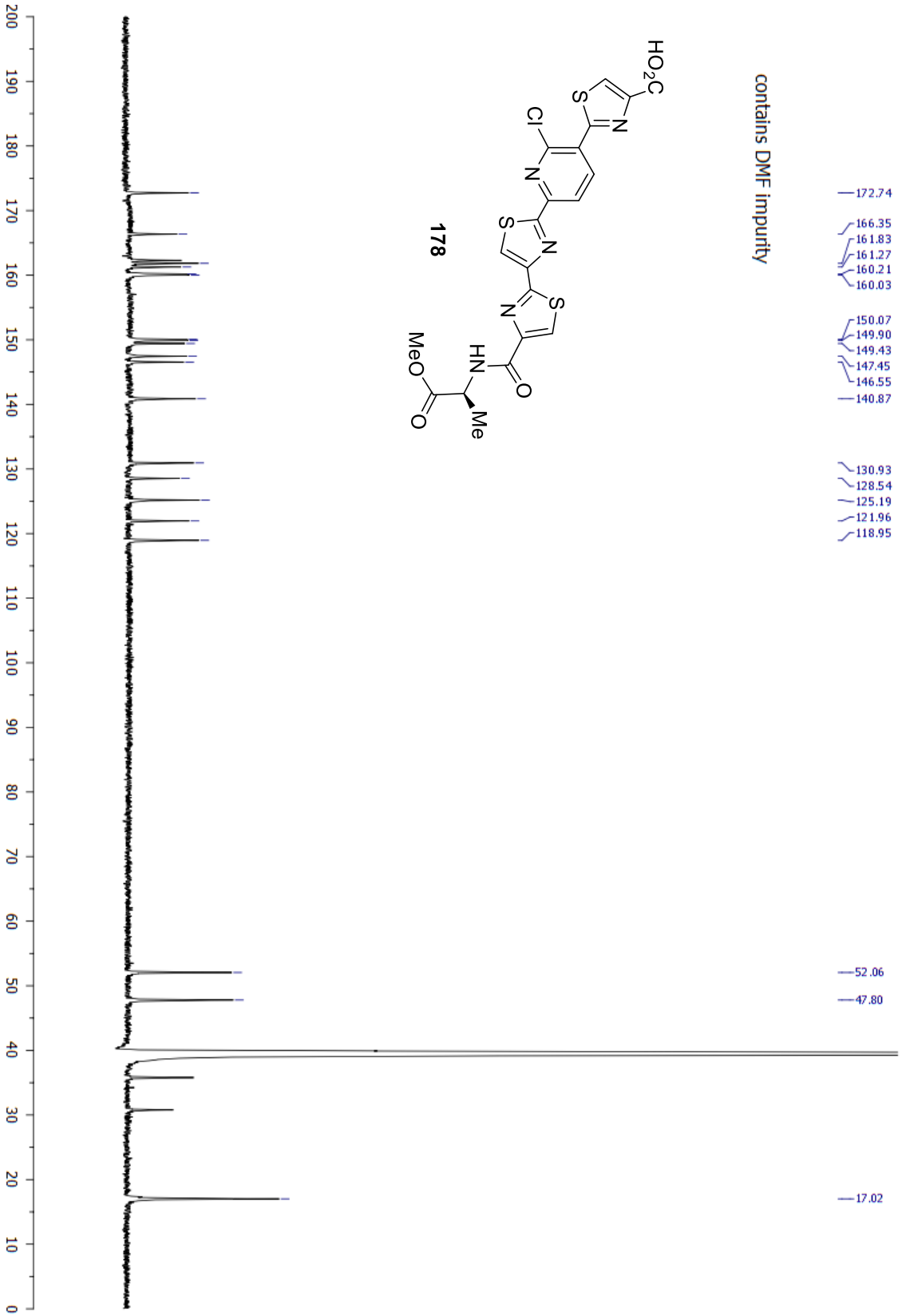

{8.90,140.26}
{8.23,128.72}
{8.05,124.02}
{8.18,120.60}
{6.04,78.20}
{4.74,47.83}
{3.75,52.41}
{3.71,37.89}
{1.59,28.10}
{1.50,18.34}
f1 (ppm)

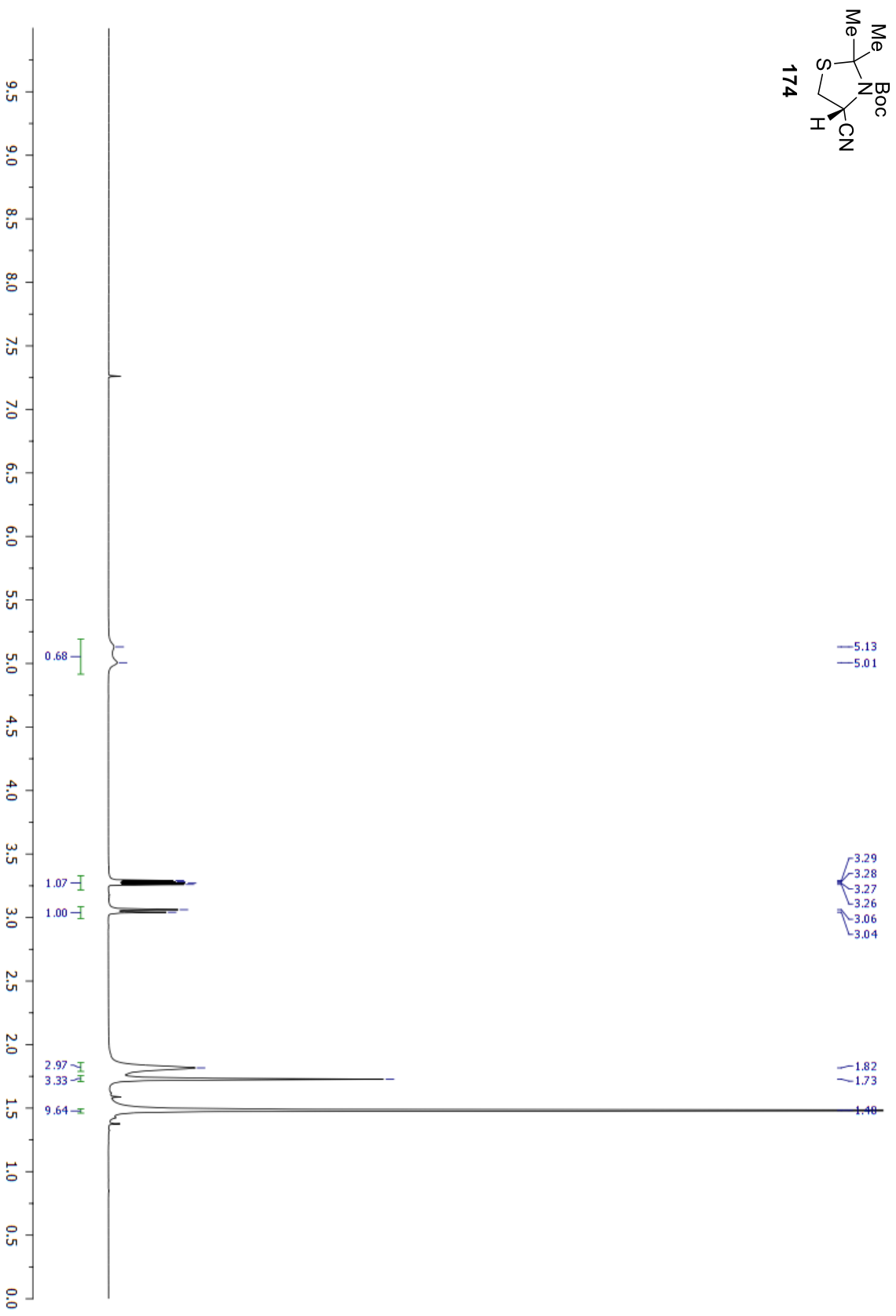

{8.90,160.75}
{8.92,172.10}
{8.05,170.80}
{7.73,173.10}
{8.90,147.11}
{8.06,149.50}
{7.74,160.29}
{8.22,148.69}
{8.18,140.22}
{8.20,130.00}
{7.76,47.82}
{6.04,171.19}
{6.06,150.30}
{6.05,37.81}
{4.74,173.10}
{4.74,160.30}
{4.74,18.27}
{3.69,170.92}
{3.92,171.08}
{3.76,173.97}
{3.73,78.20}
{1.50,173.11}
{1.59,81.70}
{1.50,47.81}
{1.49,28.40}
{1.59,27.94}
f1 (ppm)

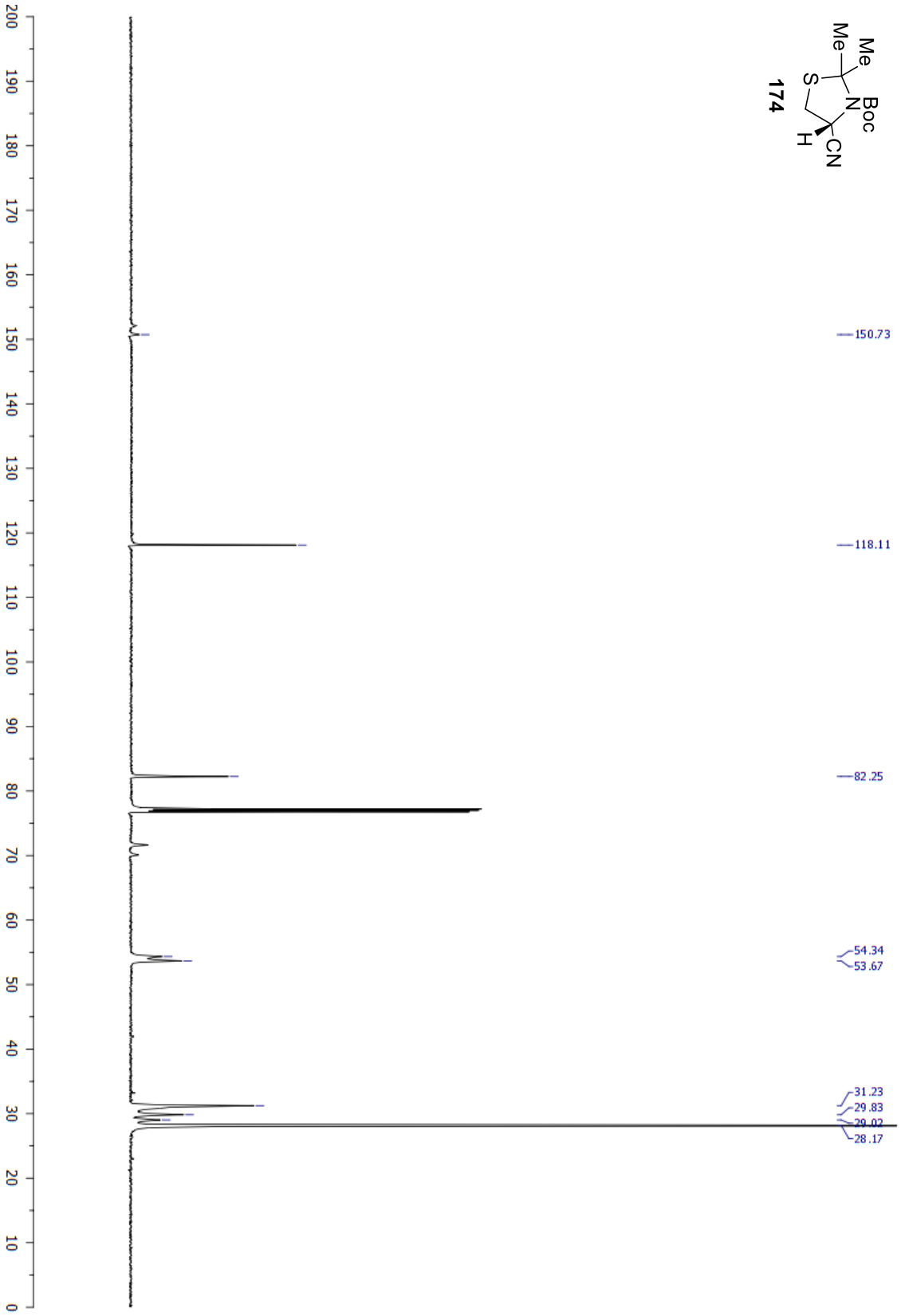

S8
t-BuO2C
Cl
MeO
HN
Me
O
N
S
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.00
0.98
0.93
0.91
0.87
0.96
0.95
3.08
10.17
3.36
9.0
8.3
8.2
7.9
7.8
4.8
3.8
1.6

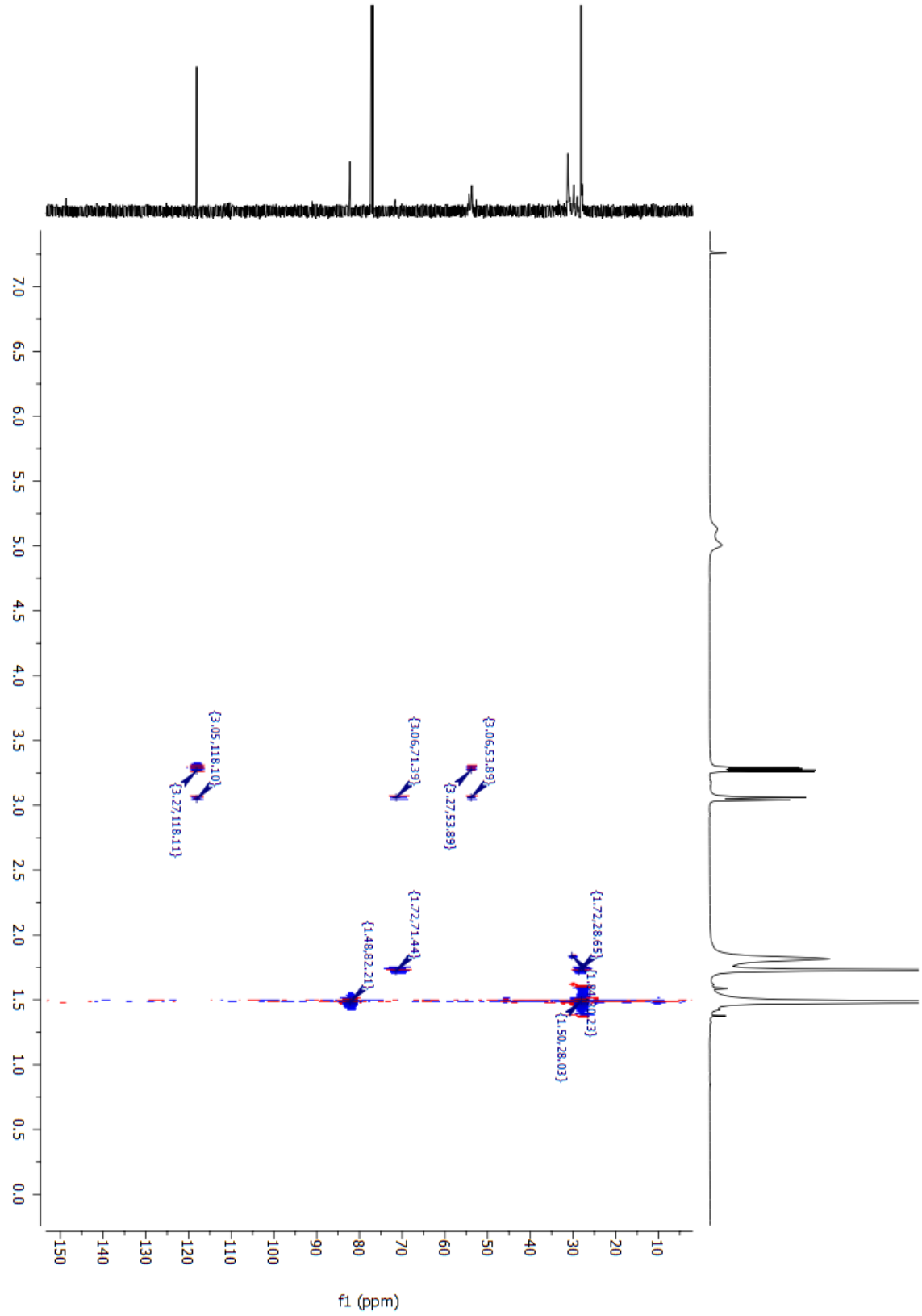

t-BuO2C
Cl
N
S
HN
Me
MeO
O
173.2
167.0
162.2
161.1
160.4
160.2
150.8
150.3
150.2
148.7
147.5
140.8
129.0
128.5
124.3
120.4
118.7
82.4
52.5
48.0
28.2
18.5

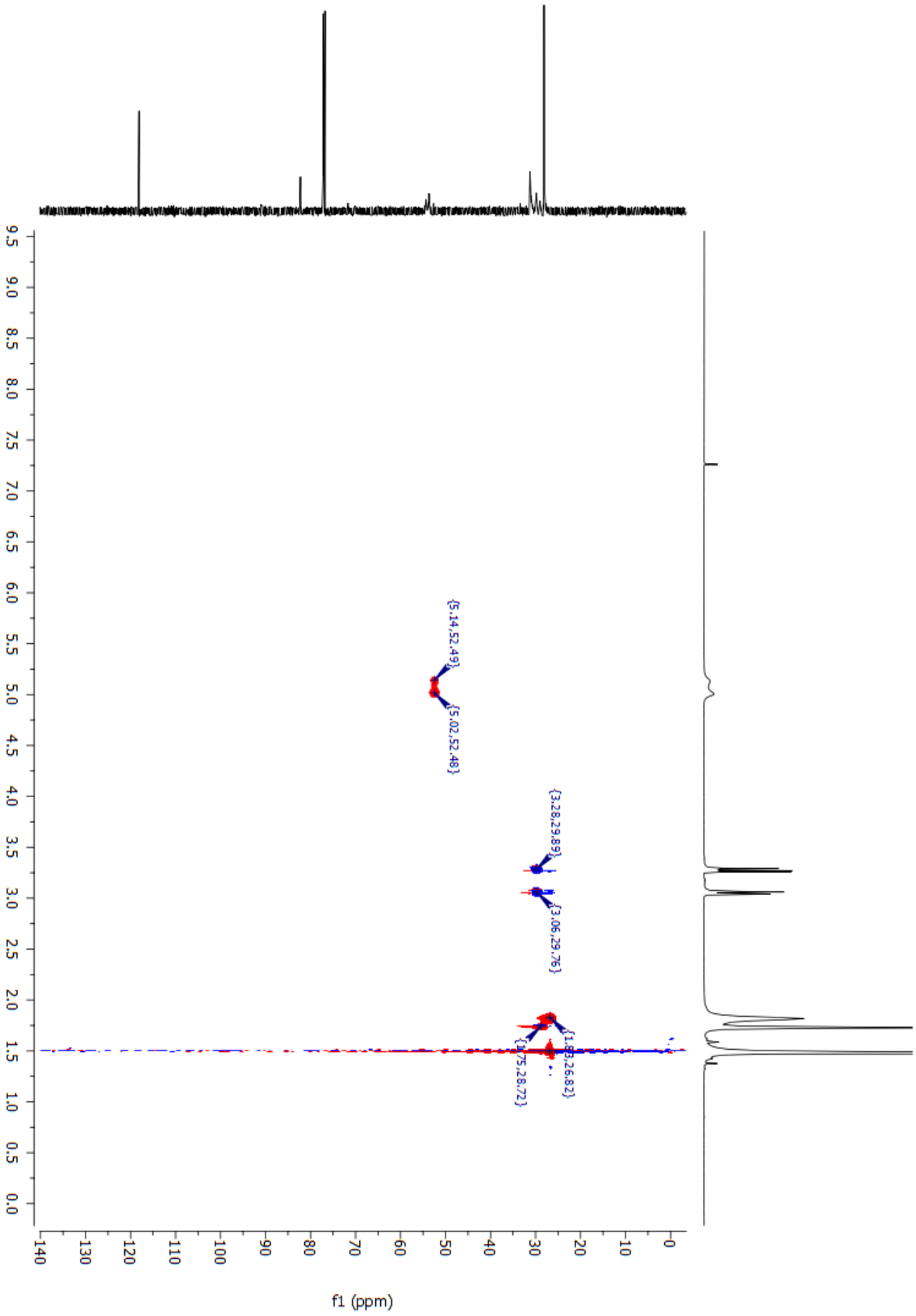

contains DMF impurity
178
HO2C
Cl
N
S
HN
Me
MeO
O
8.87
8.86
8.74
8.71
8.70
8.59
8.39
8.37
8.35
4.58
4.57
4.55
3.68
1.47
1.46
0.90
0.70
0.81
0.73
0.82
0.82
1.00
2.76
2.88

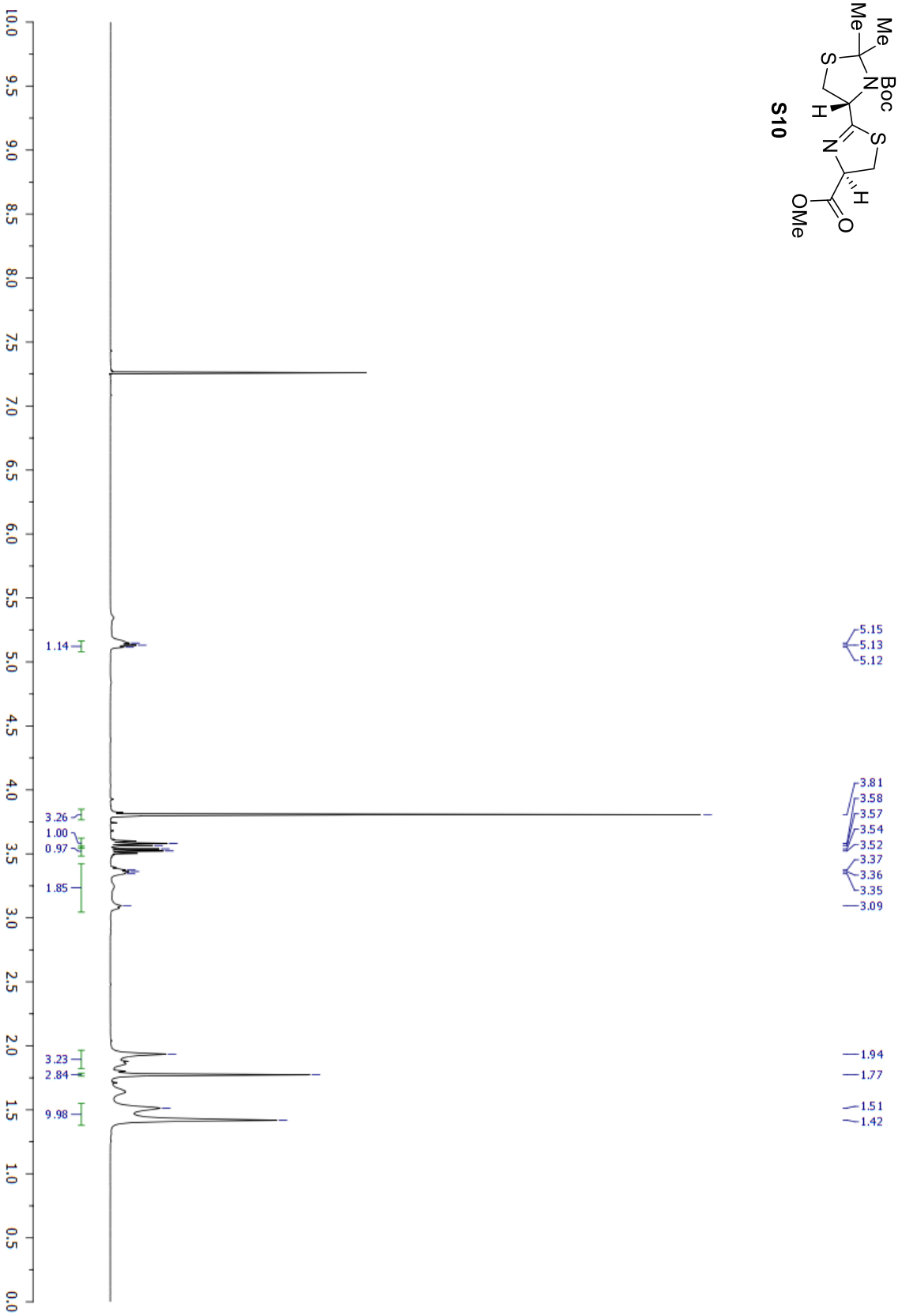

HO2C
Cl
N
S
N
S
N
S
N
HN
O
MeO
O
Me
178
contains DMF impurity
172.74
166.35
161.83
161.27
160.21
160.03
150.07
149.90
149.43
147.45
146.55
140.87
130.93
128.54
125.19
121.96
118.95
52.06
47.80
17.02
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

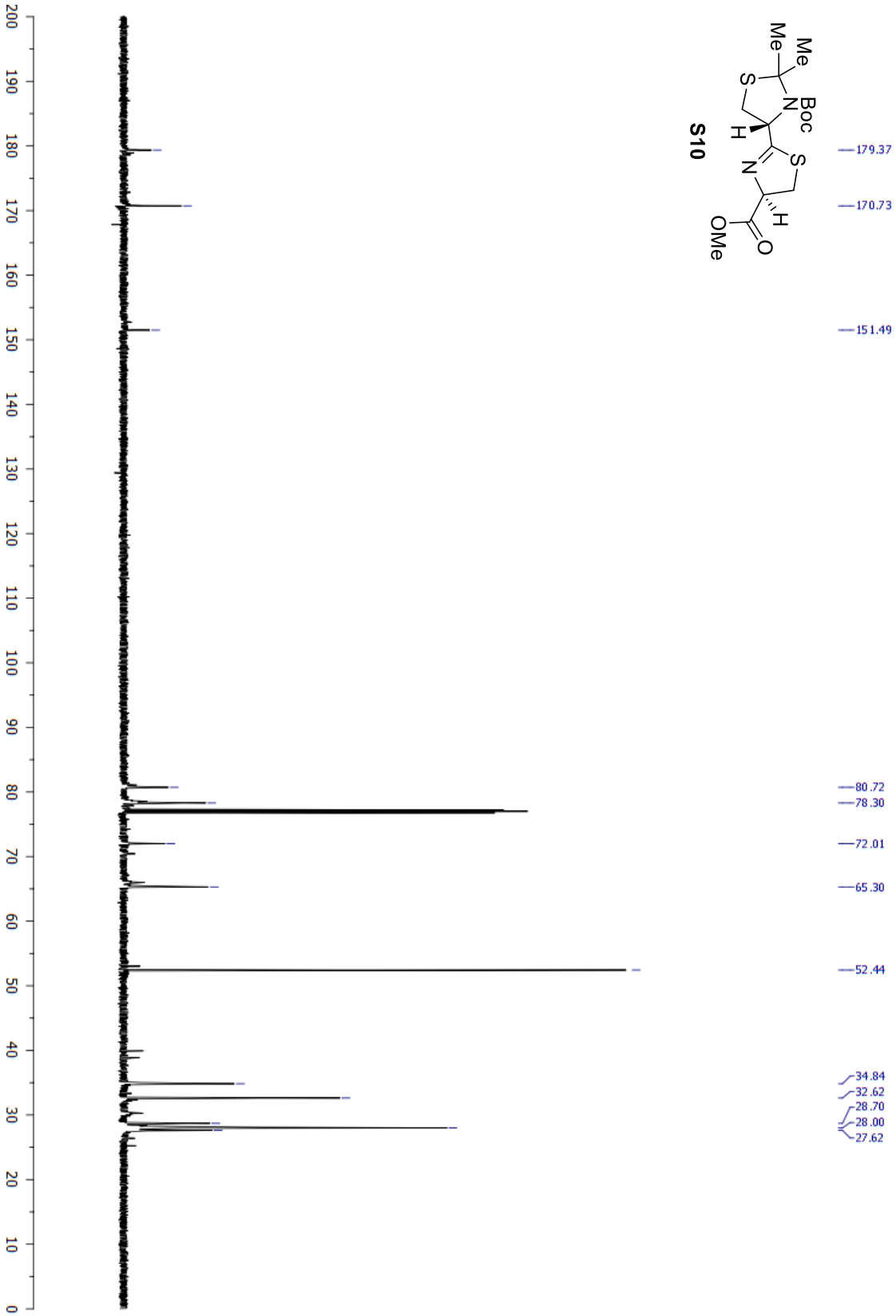

Me
Me
S
N
Boc
CN
H
174
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0.68
1.07
1.00
2.97
3.33
9.64
5.13
5.01
3.29
3.28
3.27
3.26
3.06
3.04
1.82
1.73
1.48

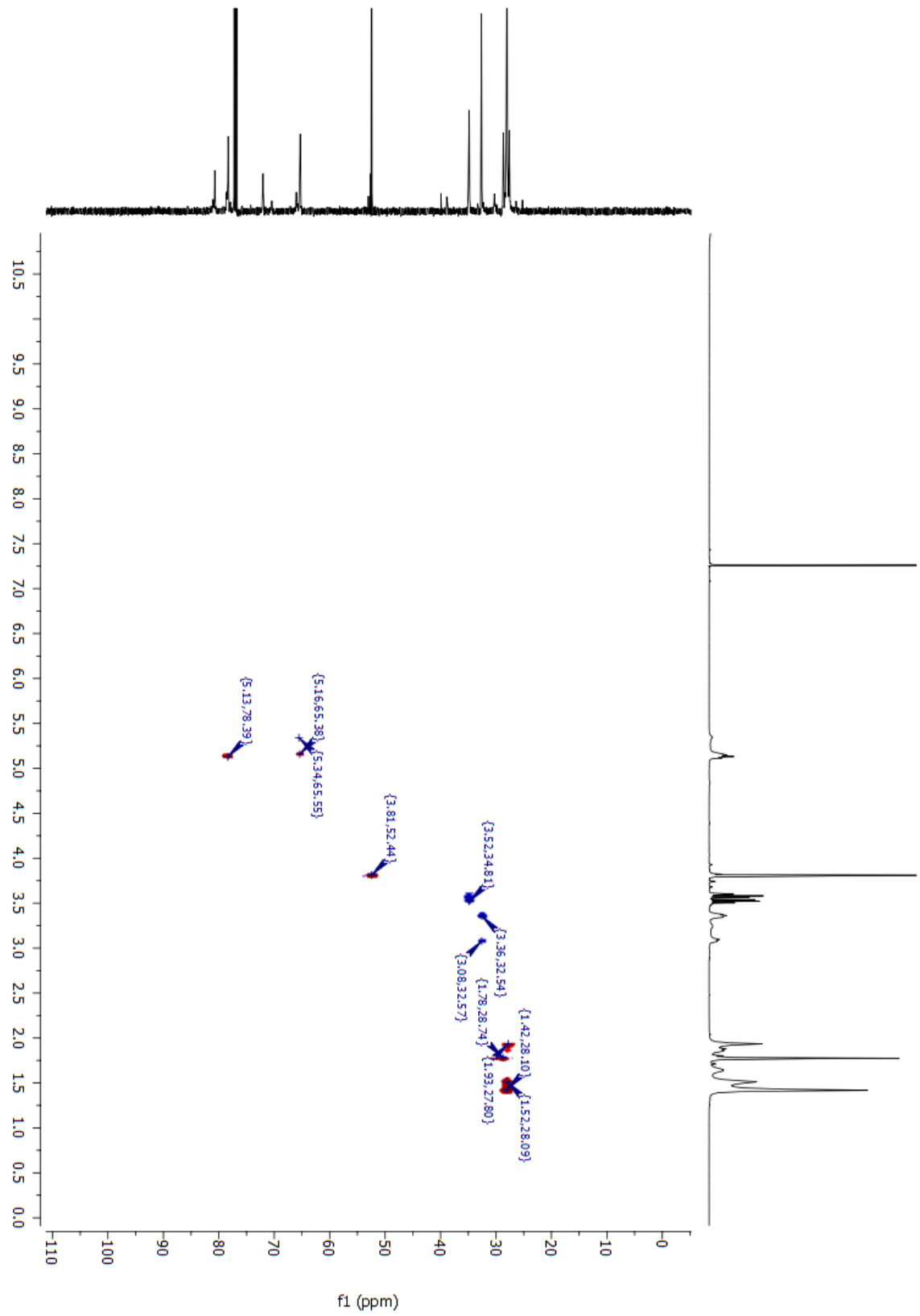

Me
Me
S
N
Boc
CN
H
174
150.73
118.11
82.25
54.34
53.67
31.23
29.83
29.02
28.17
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

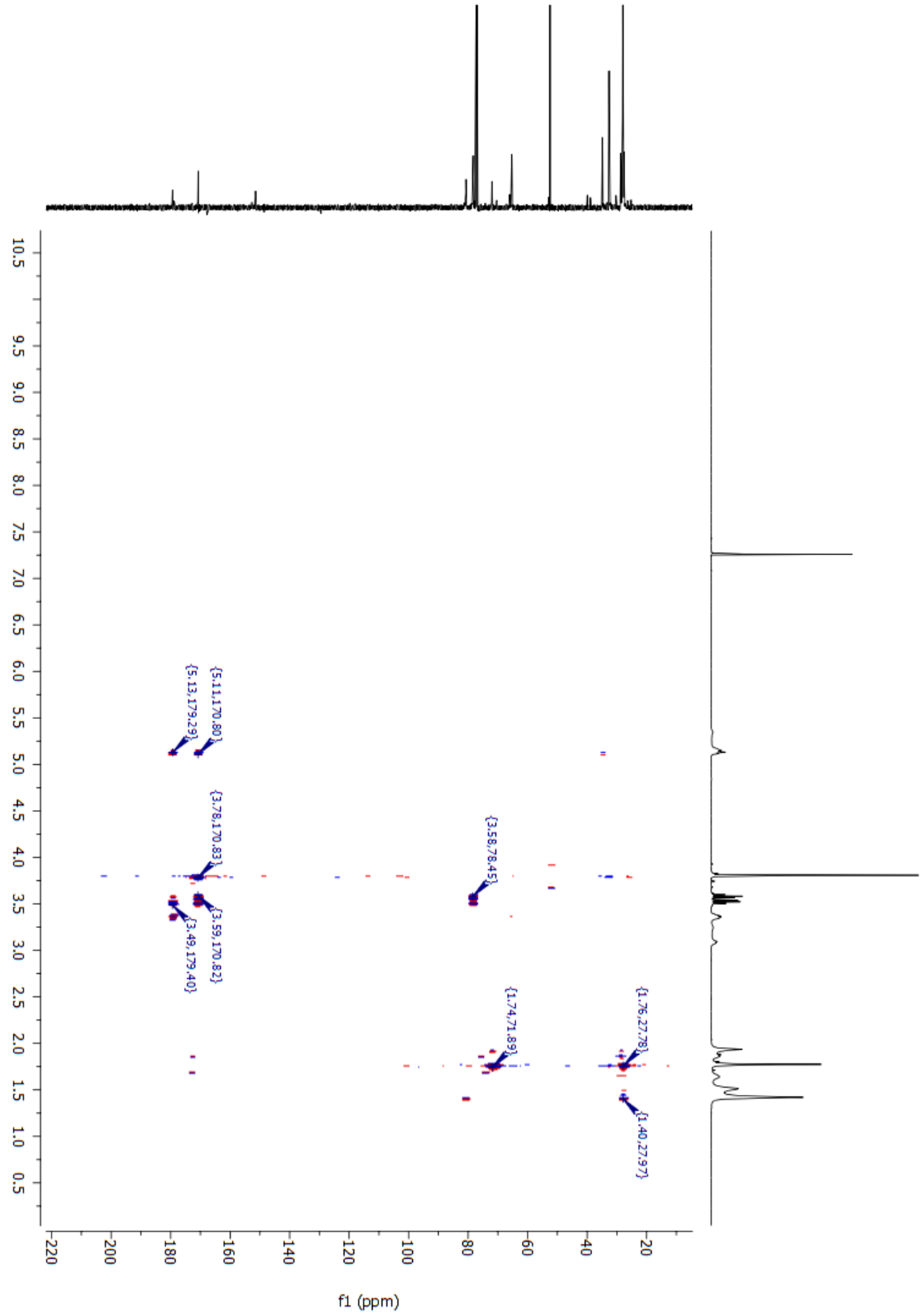

{3.05,118.10}
{3.27,118.11}
{3.06,71.39}
{3.06,53.89}
{3.27,53.89}
{1.72,71.44}
{1.48,82.21}
{1.72,28.65}
{1.50,28.03}
f1 (ppm)

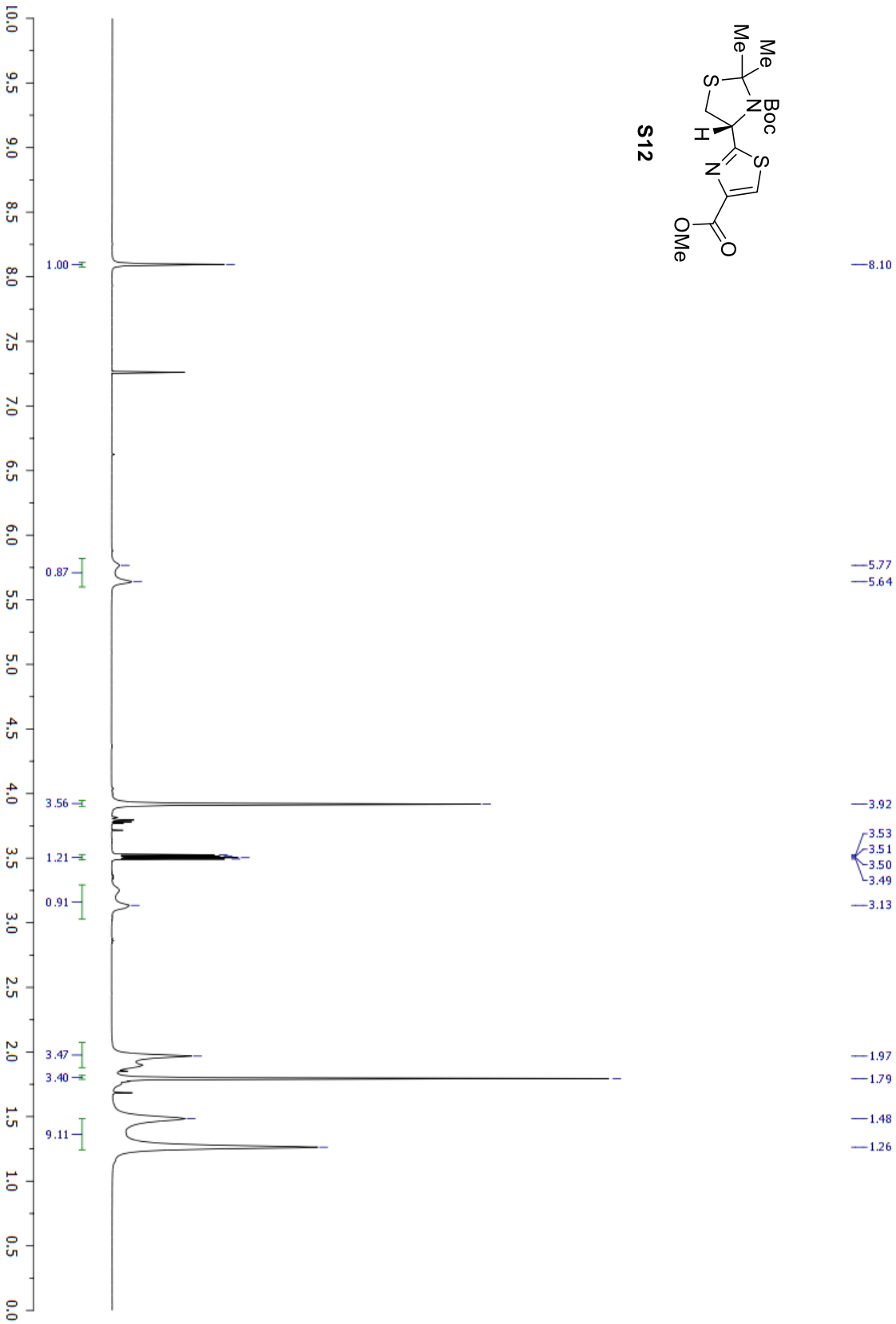

{5.14,52.49}
{5.02,52.48}
{3.28,29.89}
{3.06,29.76}
{1.75,28.72}
{1.63,26.82}
f1 (ppm)

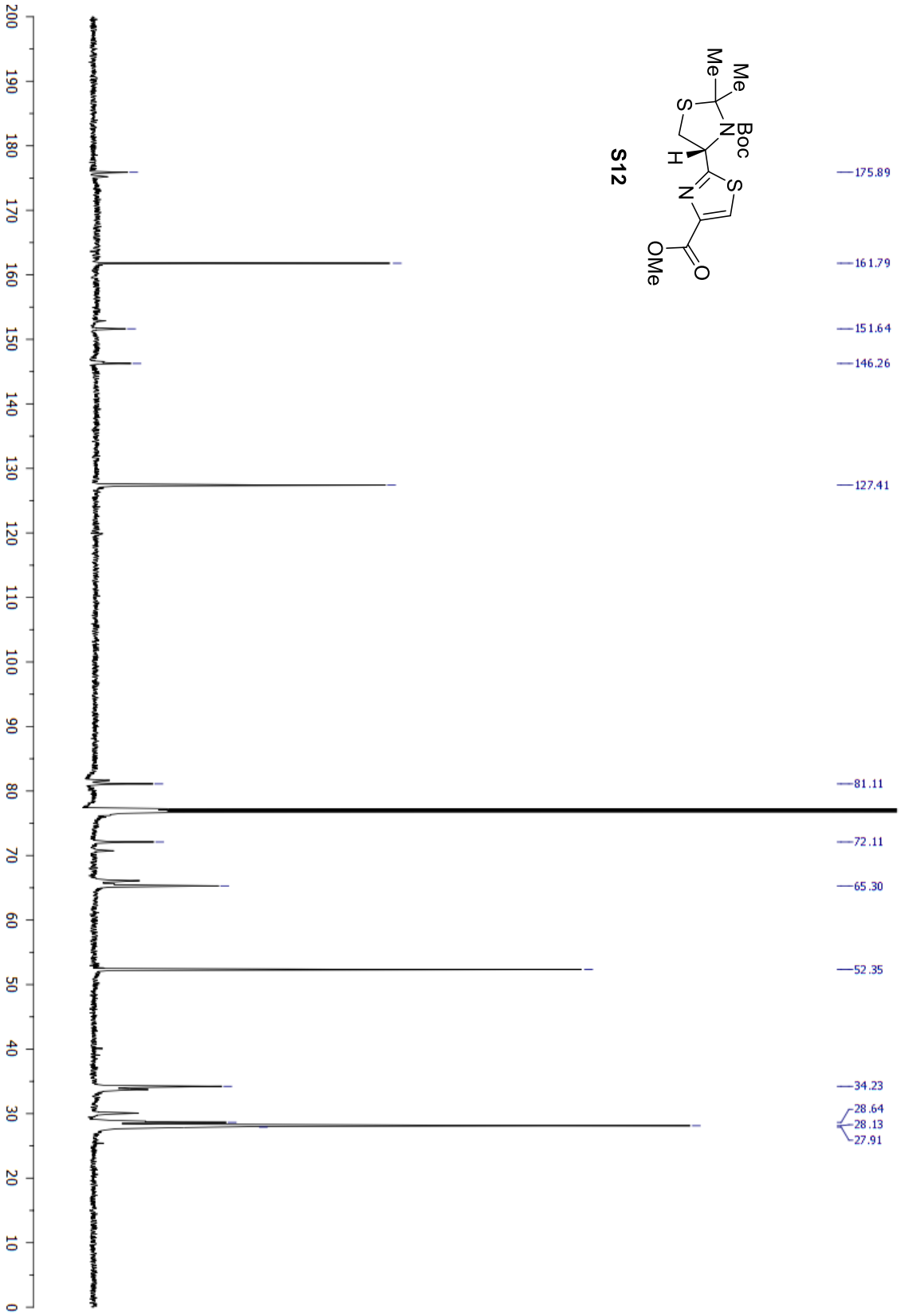

Me
Me
S
N
Boc
H
S
N
H
O
OMe
S10
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.14
3.26
1.00
0.97
1.85
3.23
2.84
9.98
5.15
5.13
5.12
3.81
3.58
3.57
3.54
3.52
3.37
3.36
3.35
3.09
1.94
1.77
1.51
1.42

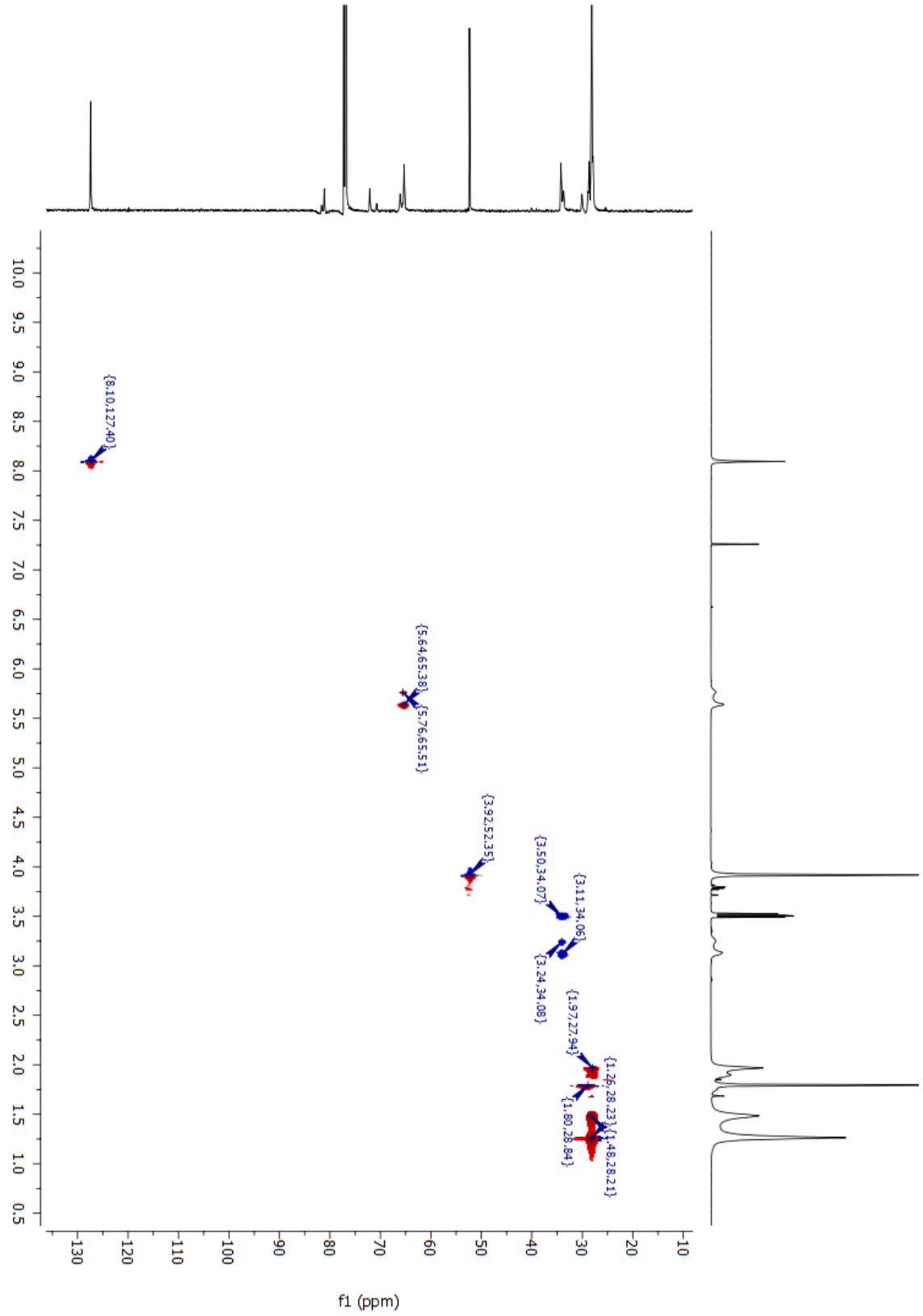

S10
Me
Me
Boc
N
S
H
N
S
H
O
OMe
179.37
170.73
151.49
80.72
78.30
72.01
65.30
52.44
34.84
32.62
28.70
28.00
27.62
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

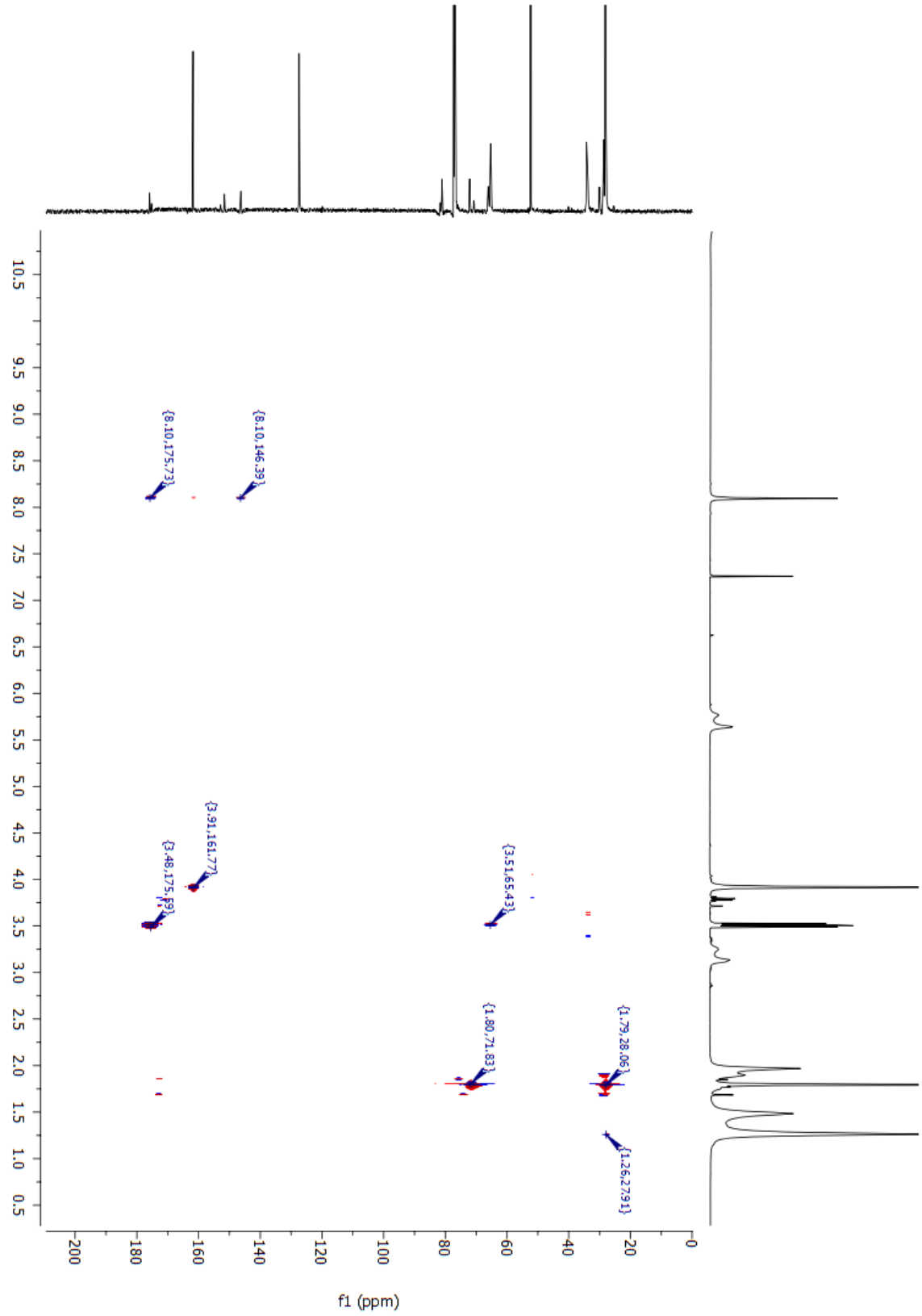

{5.13,78.39}
{5.16,65.38}
{5.34,65.55}
{3.81,52.44}
{3.52,34.81}
{3.36,32.54}
{3.08,32.57}
{1.78,28.74}
{1.42,28.10}
{1.93,27.80}
{1.52,28.09}
f1 (ppm)

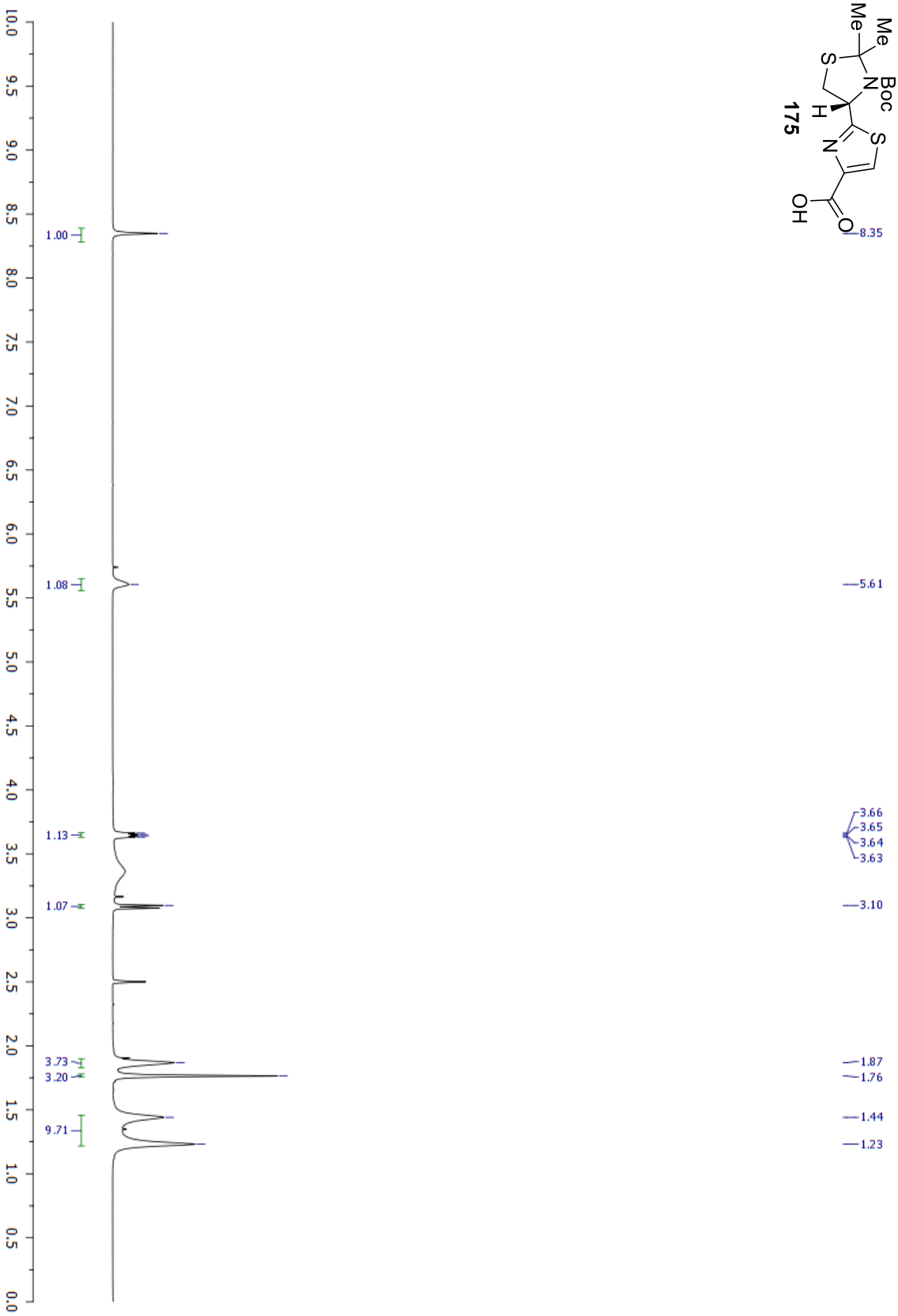

{5.11,170.80}
{5.13,179.29}
{3.78,170.83}
{3.58,78.45}
{3.59,170.82}
{3.49,179.40}
{1.74,71.89}
{1.76,27.78}
{1.40,27.97}
f1 (ppm)

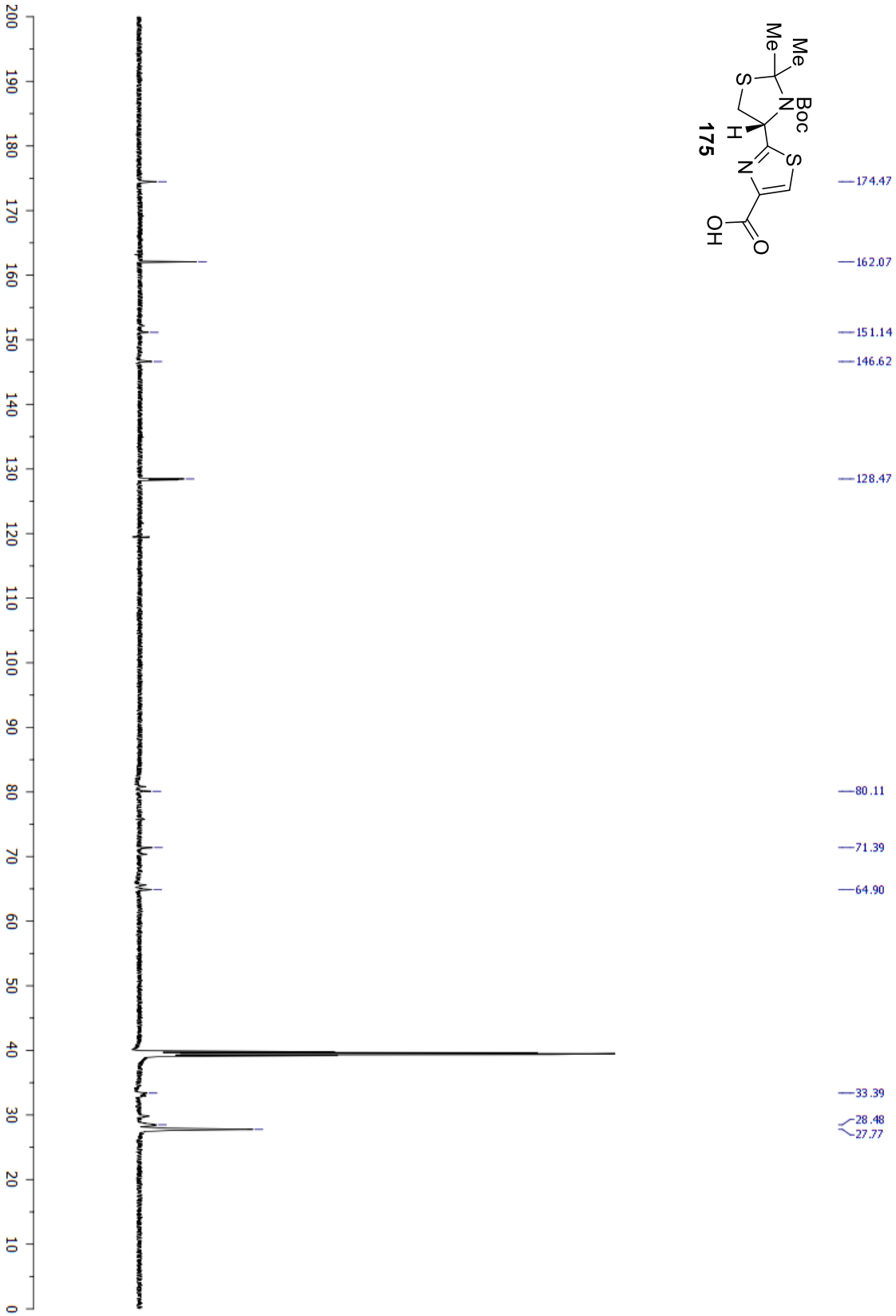

S12
Me
Me
S
N
Boc
H
S
N
OMe
O
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.00
0.87
3.56
1.21
0.91
3.47
3.40
9.11
8.10
5.77
5.64
3.92
3.53
3.51
3.50
3.49
3.13
1.97
1.79
1.48
1.26

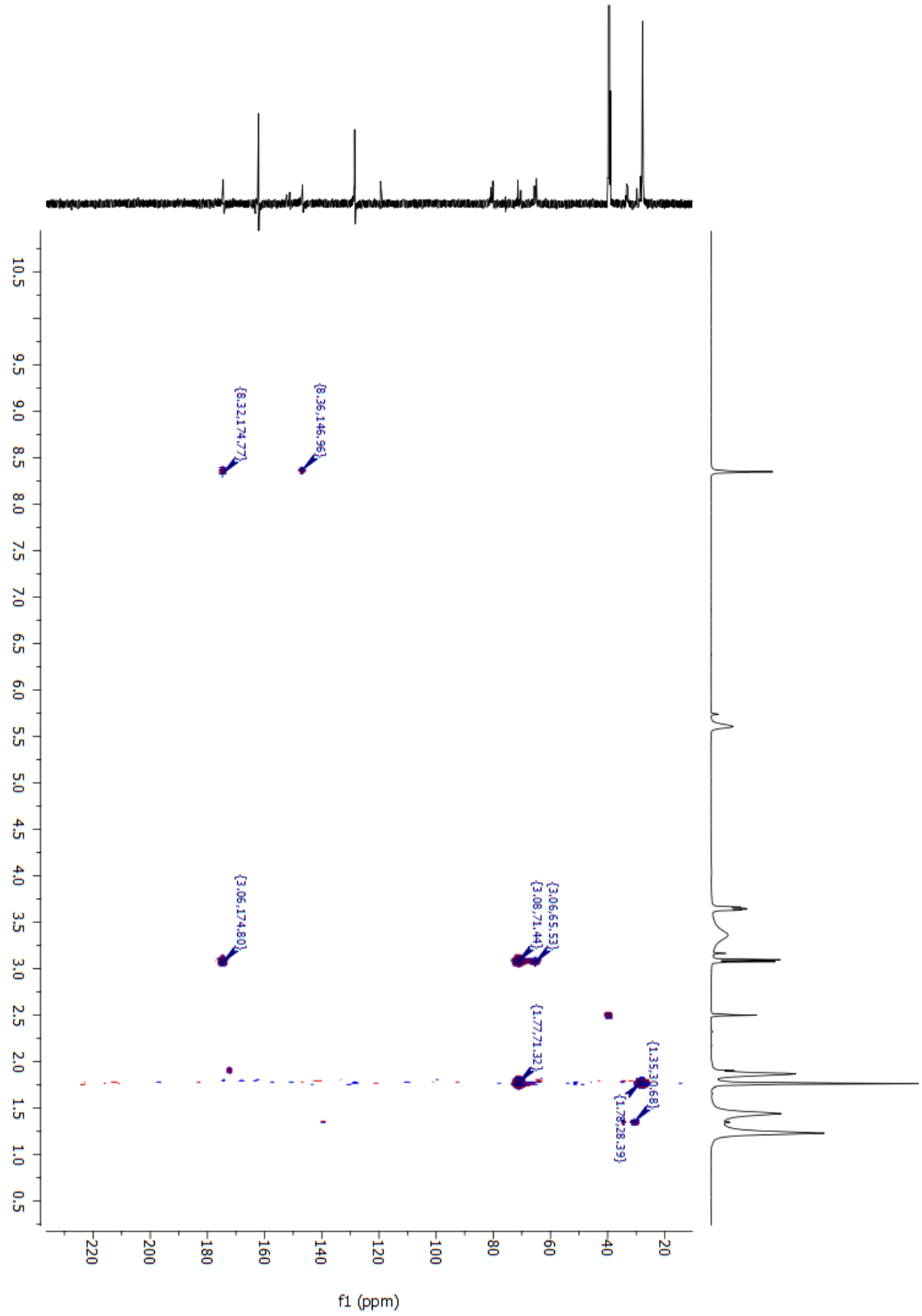

S12
Me
Me
S
N
Boc
H
S
N
OMe
O
175.89
161.79
151.64
146.26
127.41
81.11
72.11
65.30
52.35
34.23
28.64
28.13
27.91
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

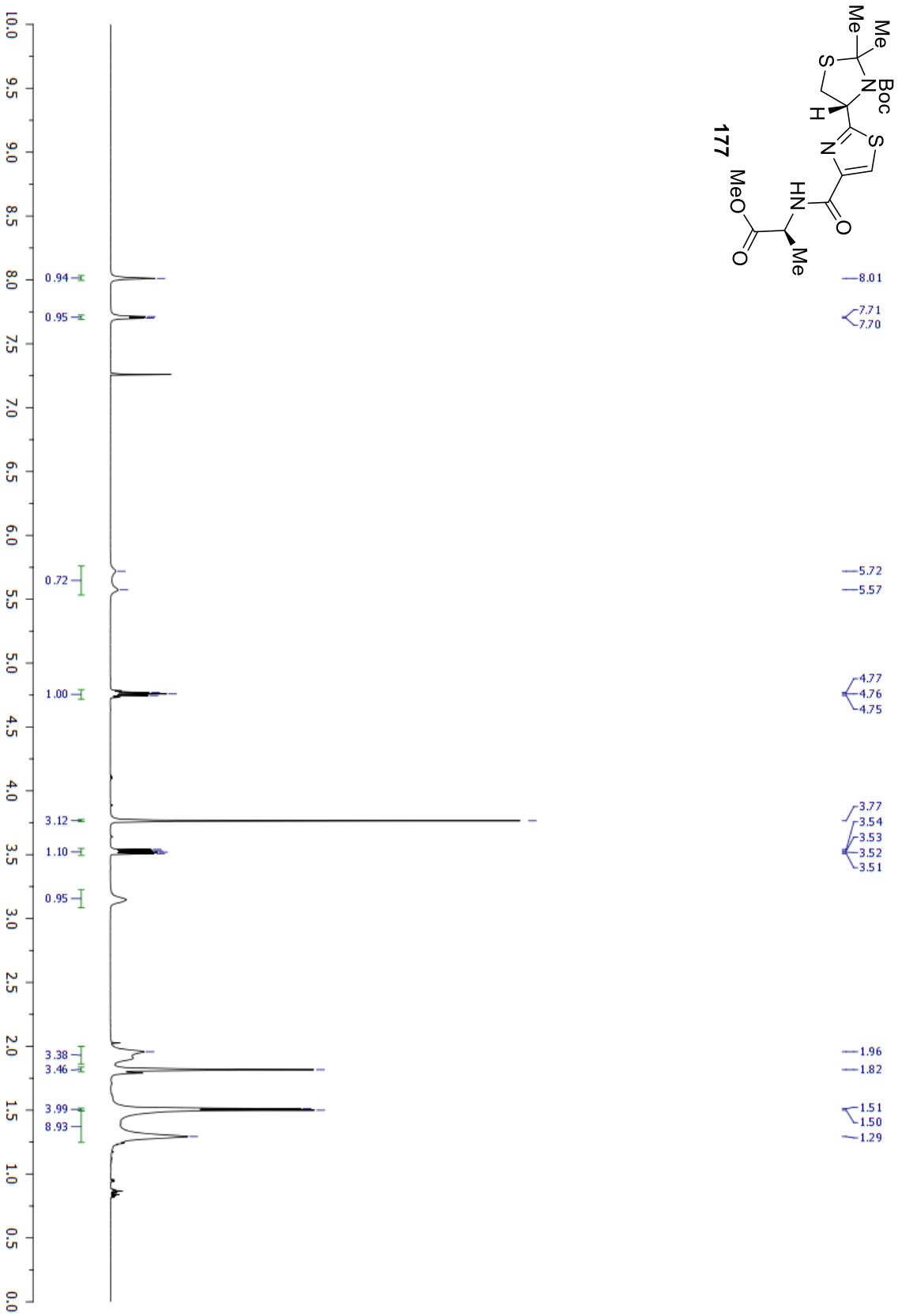

{8.10,127.40}
{5.64,65.38}
{5.76,65.51}
{3.92,52.35}
{3.50,34.07}
{3.11,34.06}
{3.24,34.08}
{1.97,27.94}
{1.26,28.23}
{1.80,28.84}
{1.48,28.21}
f1 (ppm)

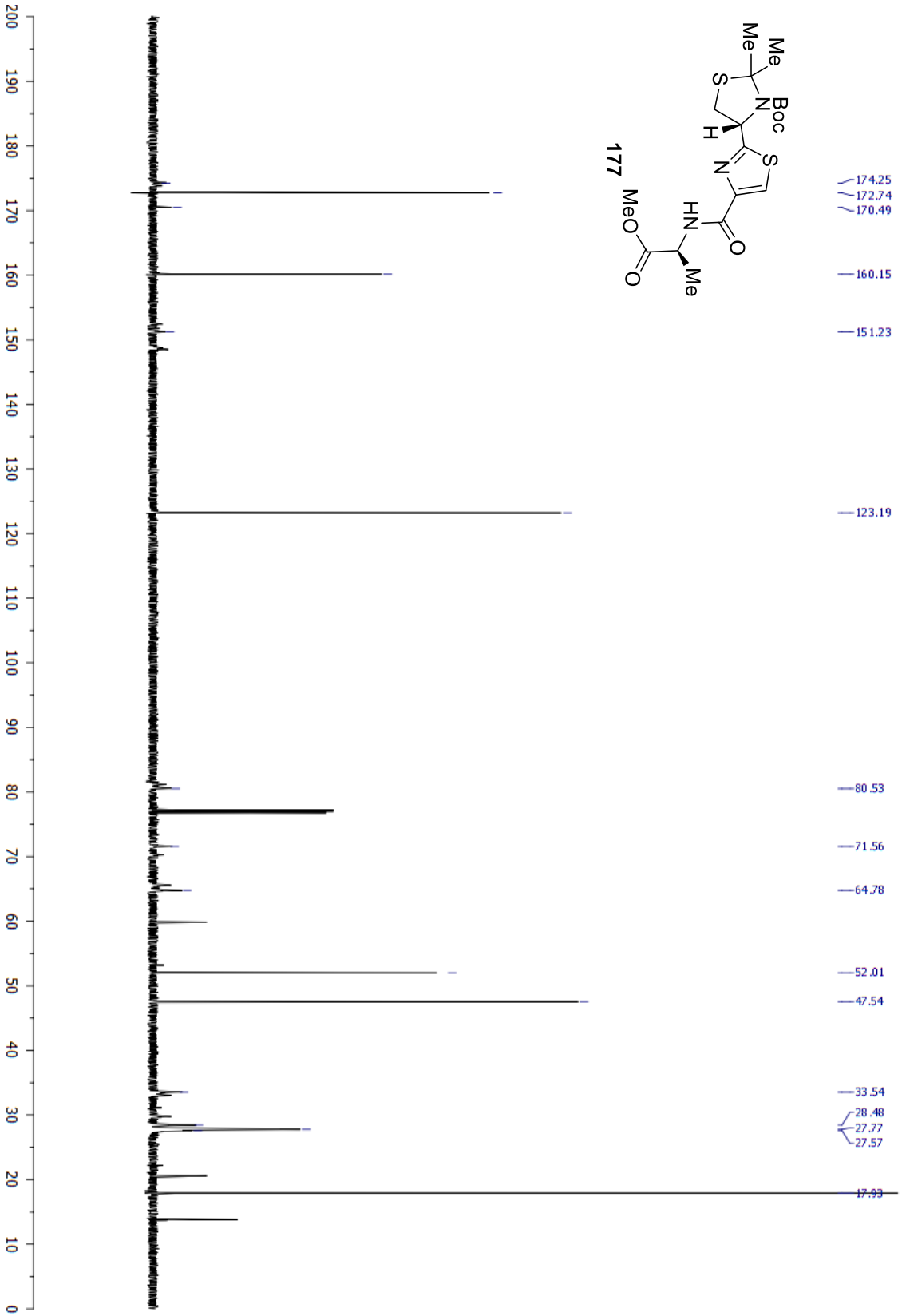

{8.10,175.73}
{8.10,146.39}
{3.91,161.77}
{3.48,175.69}
{3.51,65.43}
{1.80,71.83}
{1.79,28.06}
{1.26,27.91}
f1 (ppm)

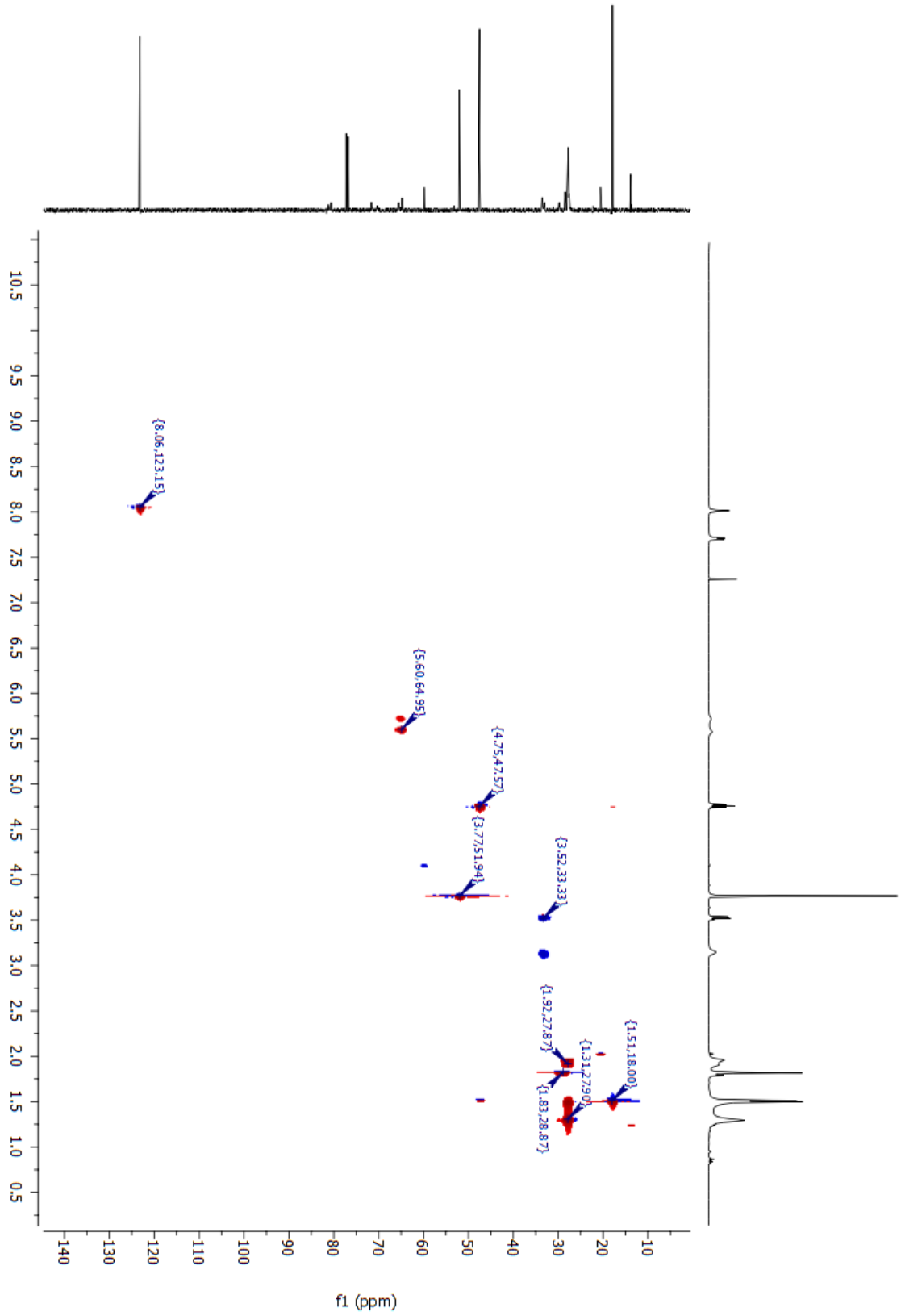

Me
Me
S
N
Boc
H
175
N
S
OH
O
8.35
5.61
3.66
3.65
3.64
3.63
3.10
1.87
1.76
1.44
1.23
1.00
1.08
1.13
1.07
3.73
3.20
9.71
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

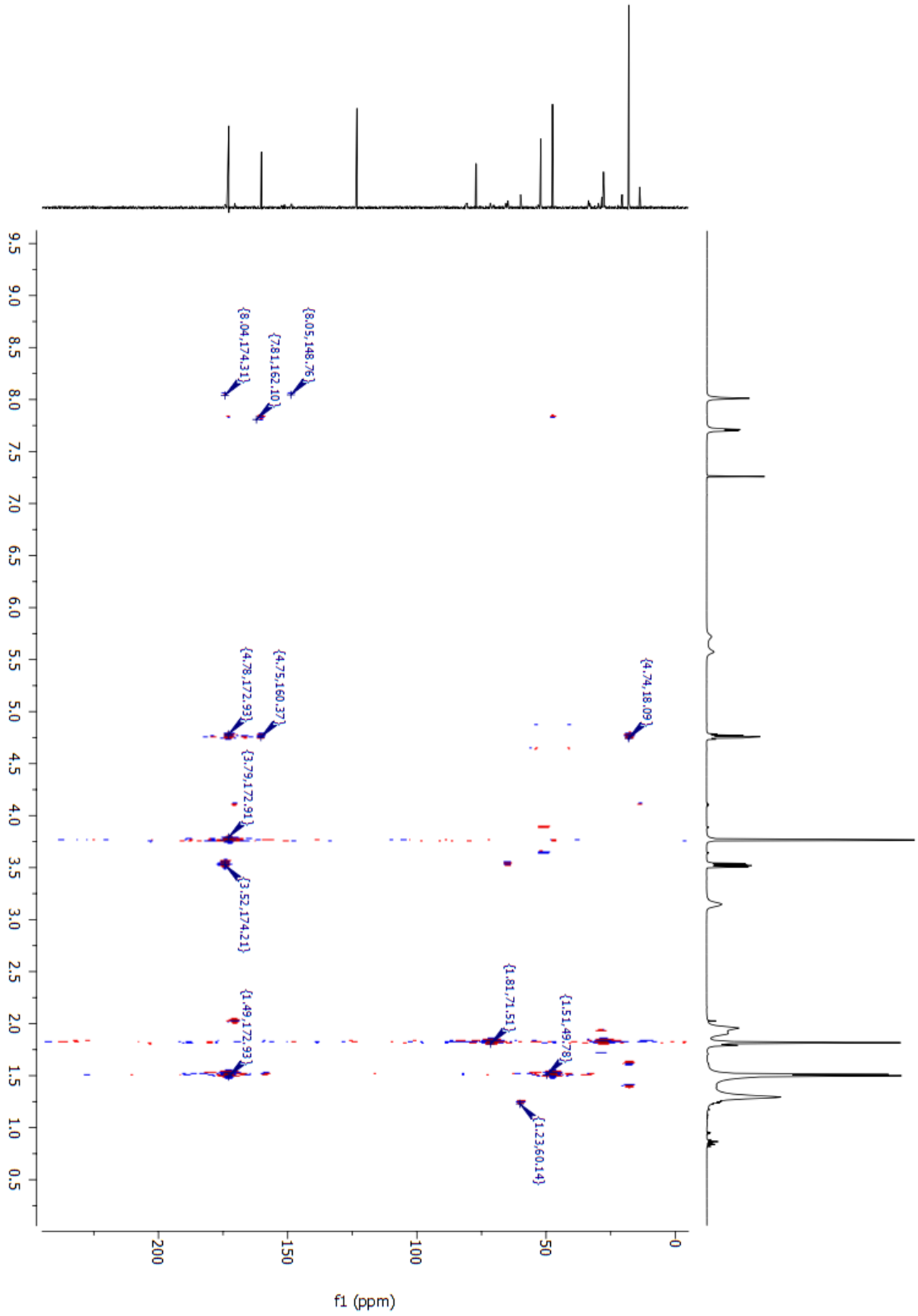

Me
Me
S
N
Boc
H
175
N
S
OH
O
174.47
162.07
151.14
146.62
128.47
80.11
71.39
64.90
33.39
28.48
27.77
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

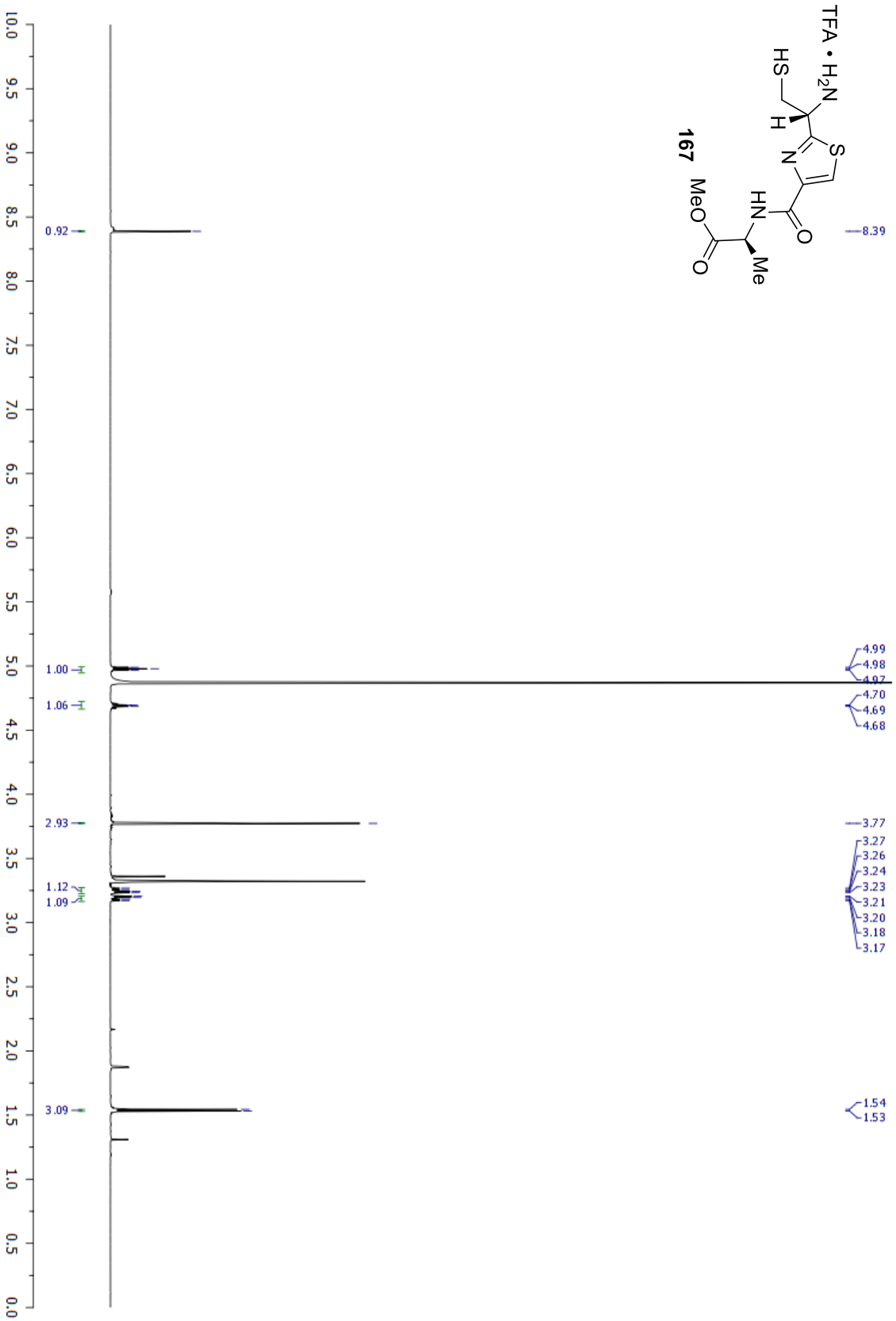

{8.32,174.77}
{8.36,146.96}
{3.06,174.80}
{3.06,65.53}
{3.08,71.44}
{1.77,71.32}
{1.35,30.68}
{1.78,28.39}
f1 (ppm)

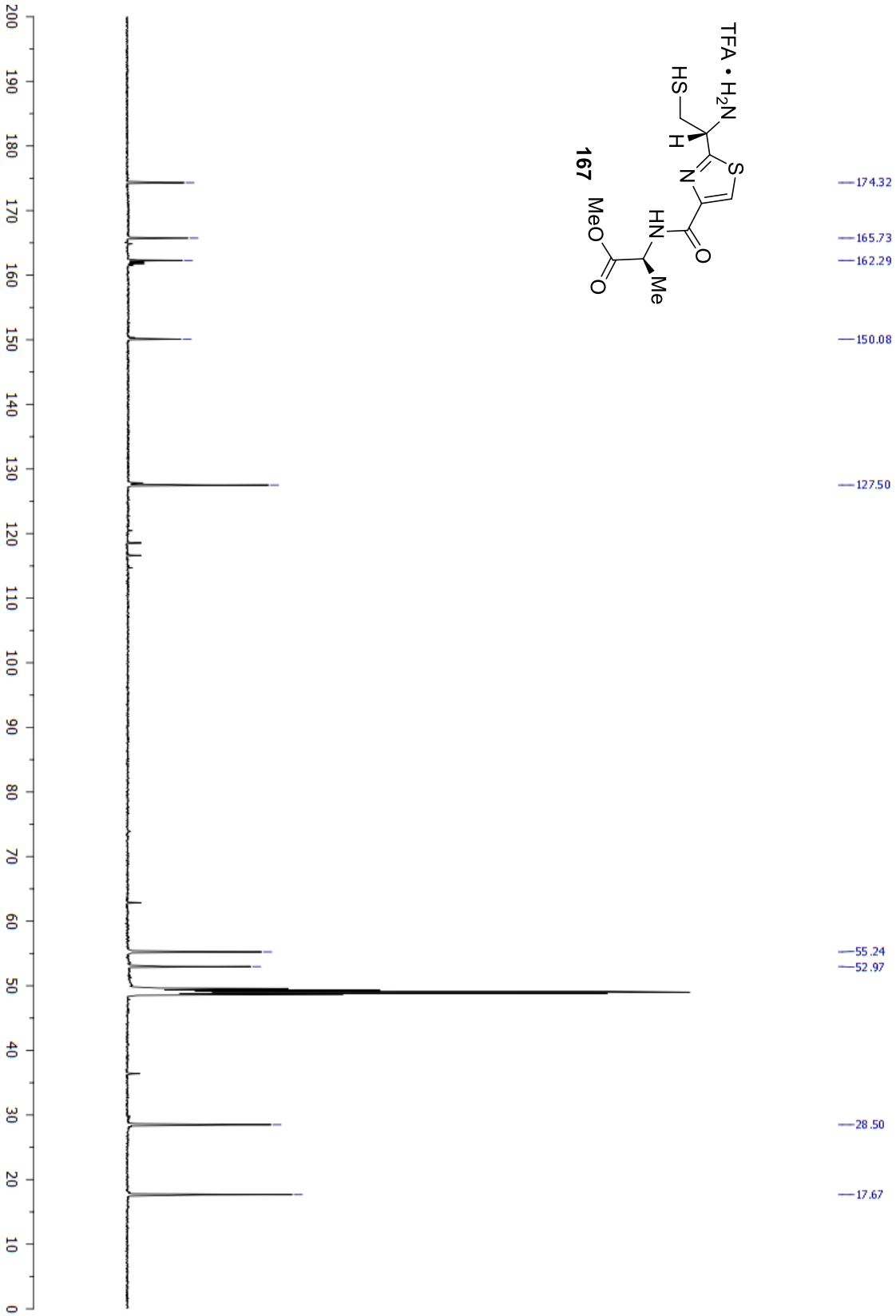

177
Me
Me
S
N
Boc
H
S
N
HN
O
MeO
O
Me
0.94
0.95
0.72
1.00
3.12
1.10
0.95
3.38
3.46
3.99
8.93
8.01
7.71
7.70
5.72
5.57
4.77
4.76
4.75
3.77
3.54
3.53
3.52
3.51
1.96
1.82
1.51
1.50
1.29


177
Me
Me
S
N
Boc
H
N
S
HN
O
MeO
O
Me
174.25
172.74
170.49
160.15
151.23
123.19
80.53
71.56
64.78
52.01
47.54
33.54
28.48
27.77
27.57
17.93
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


{8.06,123.15}
{5.60,64.95}
{4.75,47.57}
{3.77,51.94}
{3.52,33.33}
{1.92,27.87}
{1.31,27.90}
{1.83,28.87}
{1.51,18.00}
f1 (ppm)


{8.04,174.31}
{7.81,162.10}
{8.05,148.76}
{4.78,172.93}
{4.75,160.37}
{4.74,18.09}
{3.79,172.91}
{3.52,174.21}
{1.81,71.51}
{1.51,49.78}
{1.49,172.93}
{1.23,60.14}
f1 (ppm)


TFA • H2N
HS
H
N
S
HN
O
MeO
O
Me
167
8.39
4.99
4.98
4.97
4.70
4.69
4.68
3.77
3.27
3.26
3.24
3.23
3.21
3.20
3.18
3.17
1.54
1.53
0.92
1.00
1.06
2.93
1.12
1.09
3.09


TFA • H2N
HS
H
N
S
O
HN
Me
MeO
O
167
174.32
165.73
162.29
150.08
127.50
55.24
52.97
28.50
17.67
200
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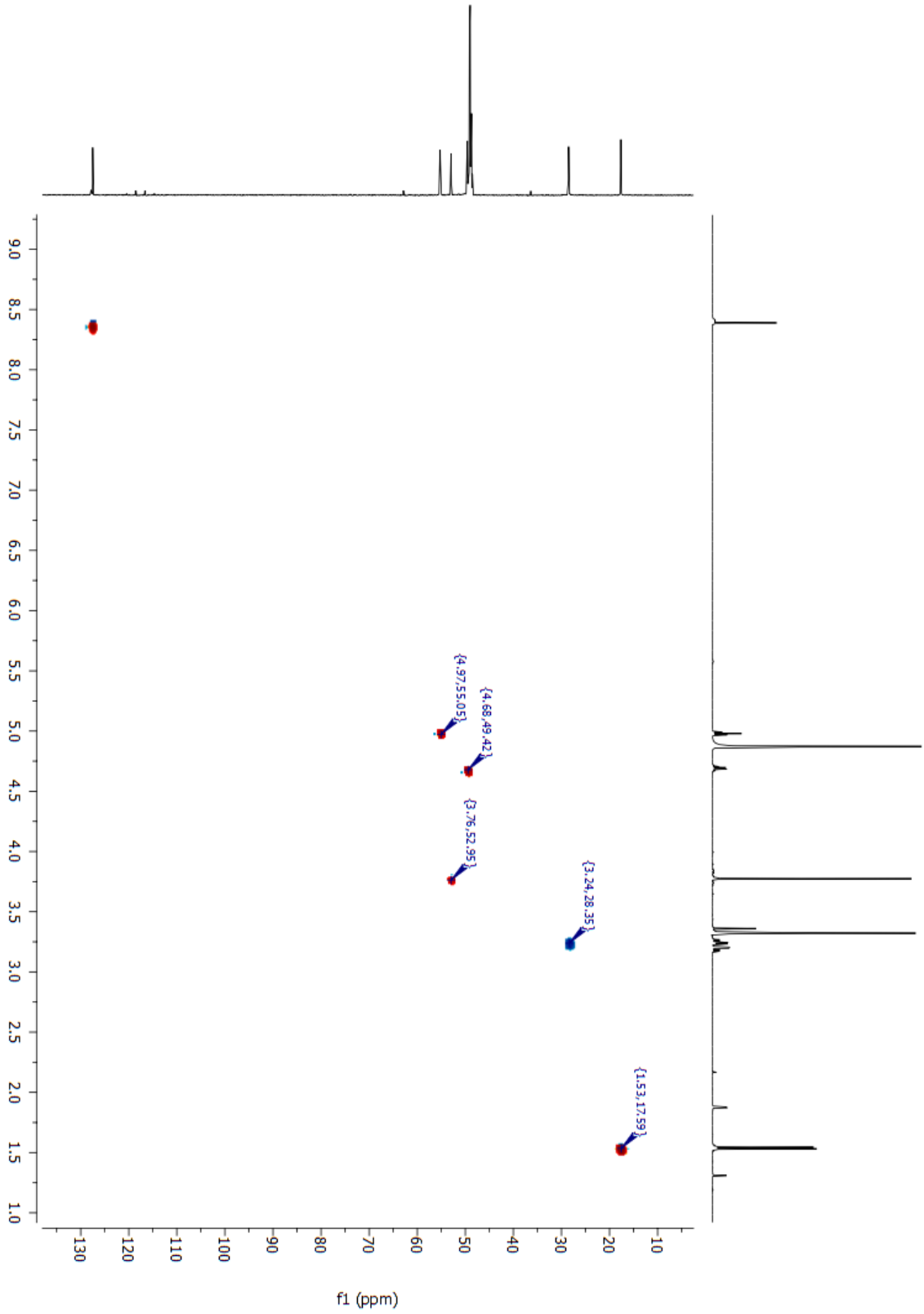
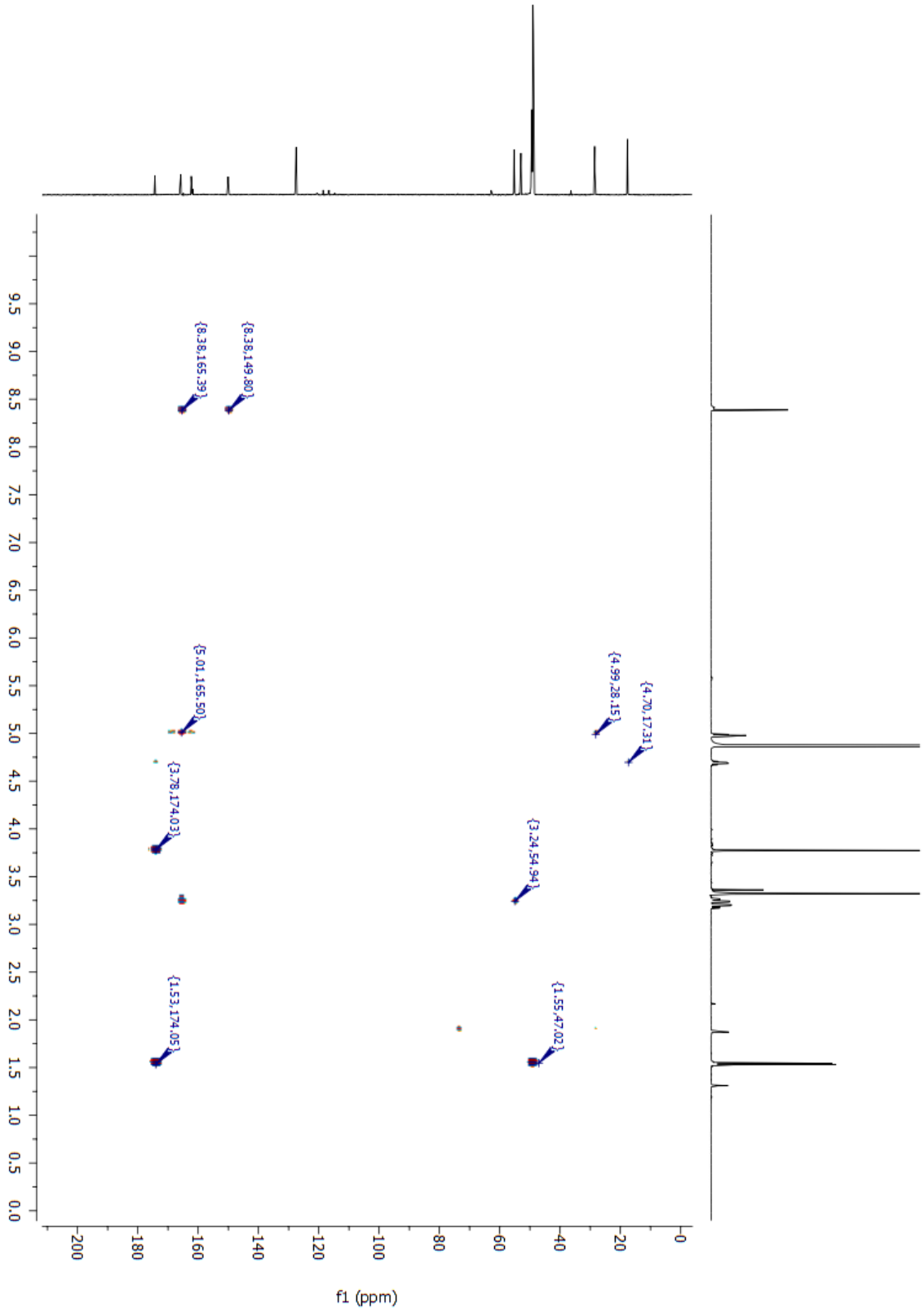
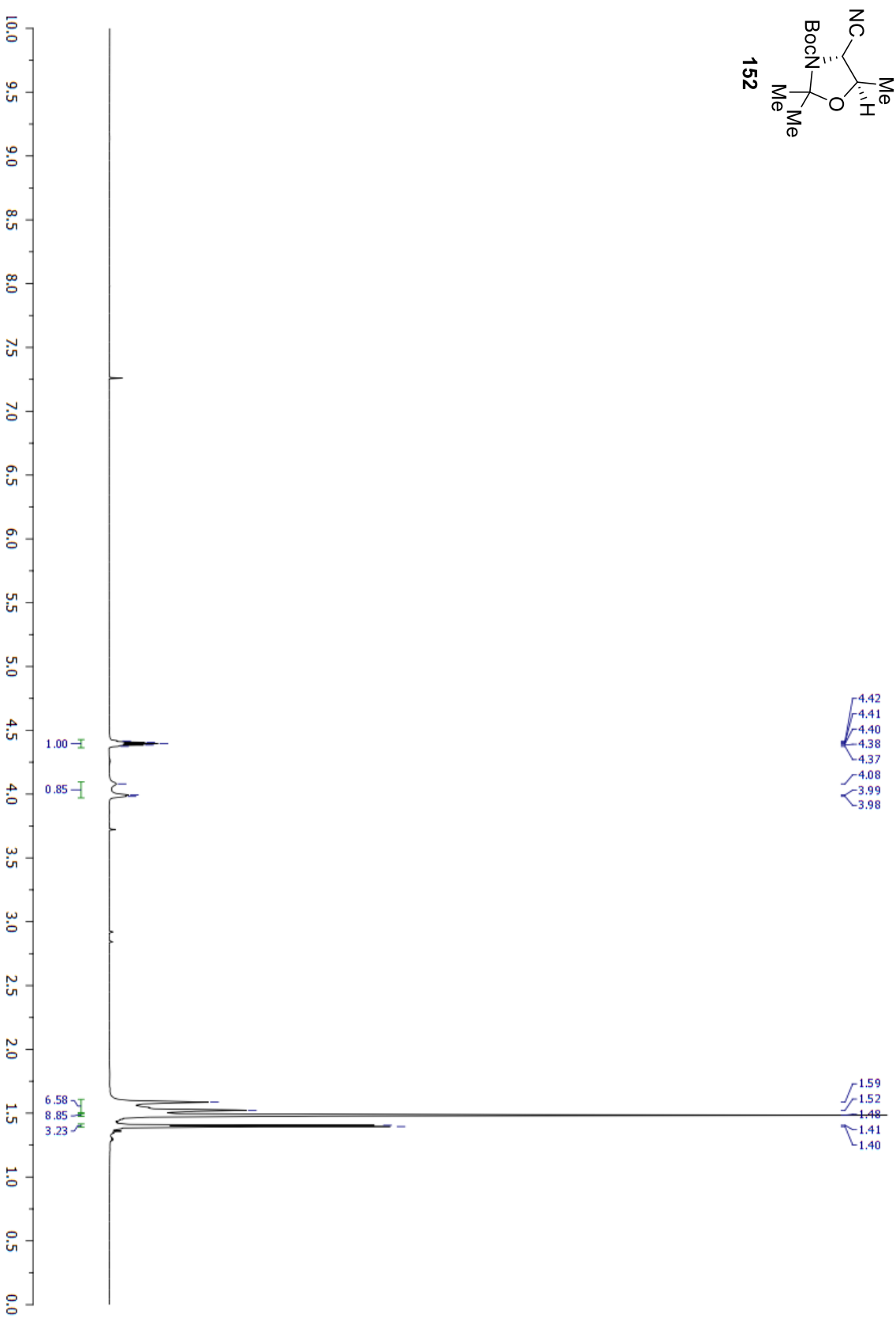
90
80
70
60
50
40
30
20
10
0


{4.97,55.05}
{4.68,49.42}
{3.76,52.95}
{3.24,28.35}
{1.53,17.59}
f1 (ppm)


{8.38,165.39}
{8.38,149.80}
{5.01,165.50}
{4.99,28.15}
{4.70,17.31}
{3.78,174.03}
{3.24,54.94}
{1.53,174.05}
{1.55,47.02}
f1 (ppm)


NC
BocN
Me
H
O
Me
Me
152
10.0
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
0.0
1.00
0.85
6.58
8.85
3.23
4.42
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3.99
3.98
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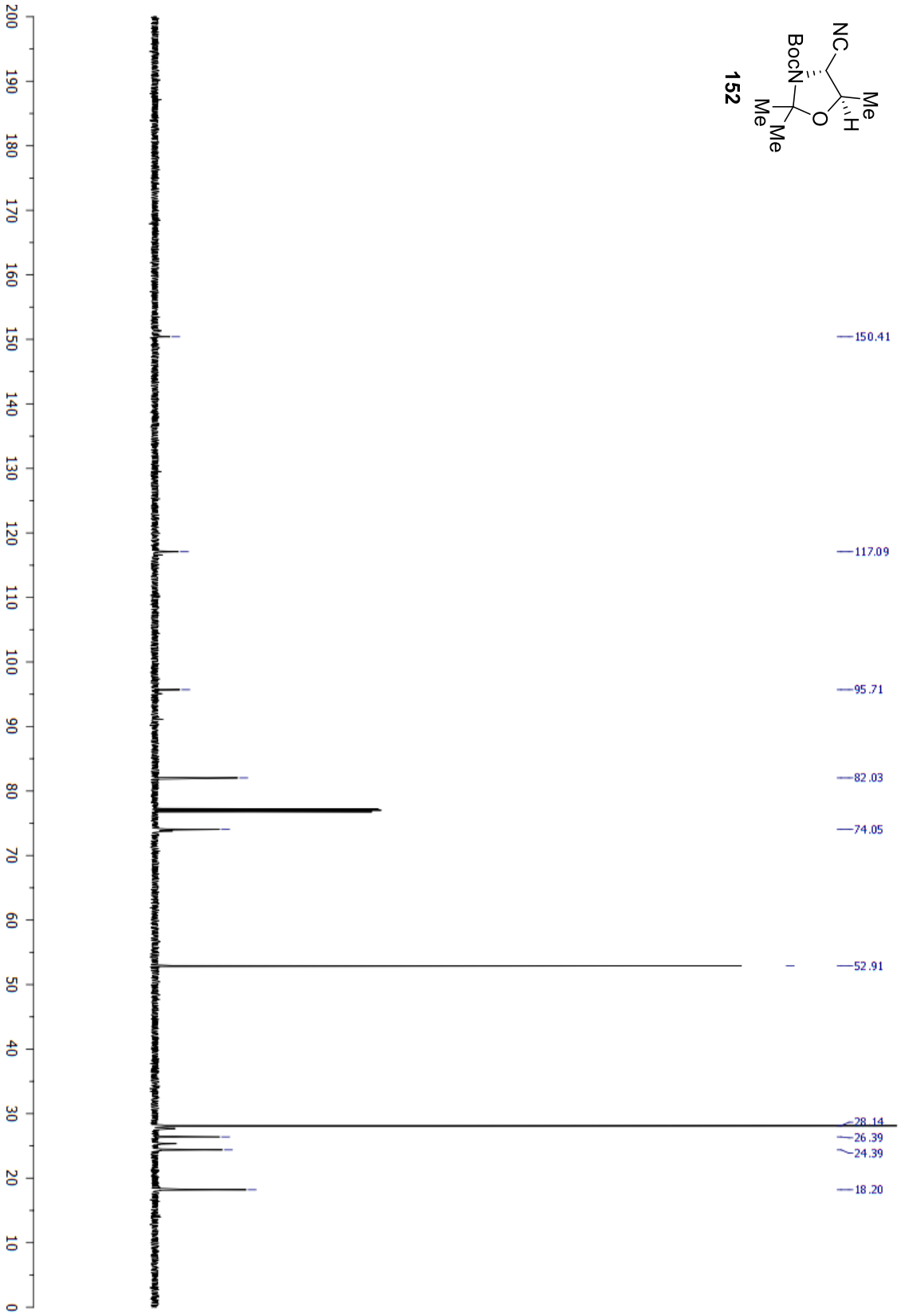
1.52
1.48
1.41
1.40


NC
BocN
Me
H
O
Me
Me
152
150.41
117.09
95.71
82.03
74.05
52.91
28.14
26.39
24.39
18.20
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
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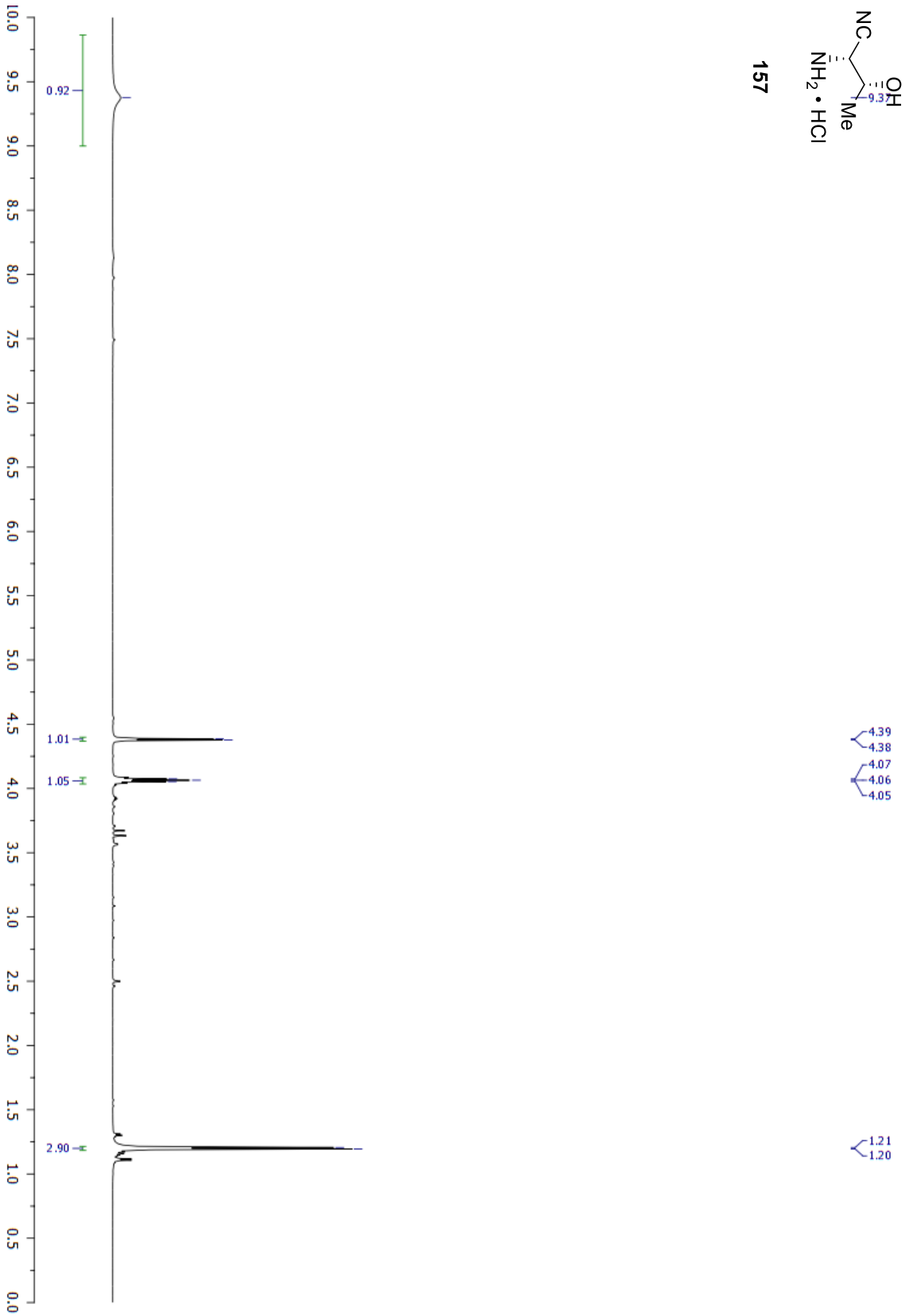
NC
OH
Me
NH2 • HCl
9.37
157
4.39
4.38
4.07
4.06
4.05
1.21
1.20
0.92
1.01
1.05
2.90
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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2.0
1.5
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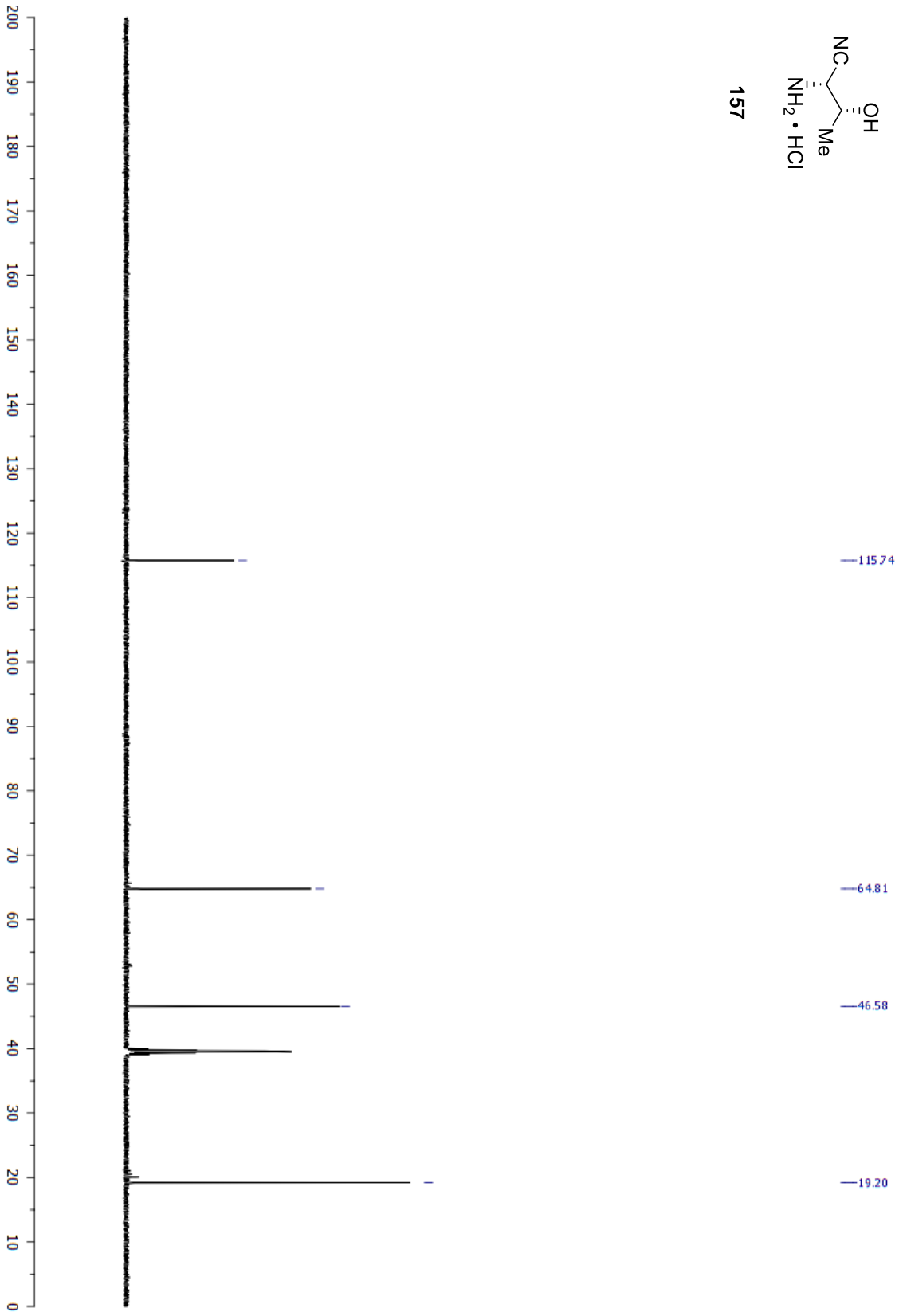
NC
OH
NH2 • HCl
Me
157
115.74
64.81
46.58
19.20
200
190
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150
140
130
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110
100
90
80
70
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50
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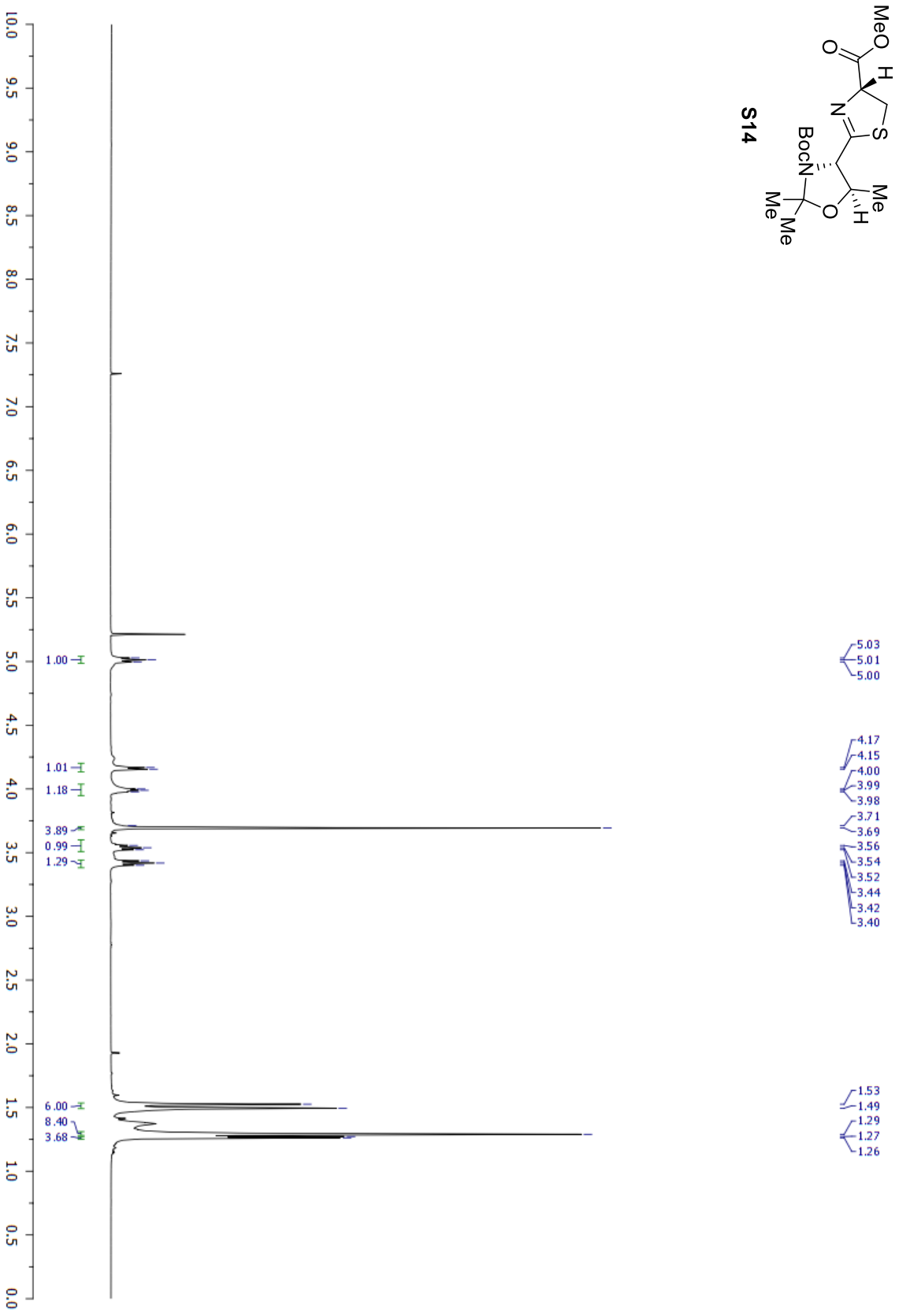
30
20
10
0


MeO
O
H
N
S
BocN
Me
H
O
Me
Me
S14
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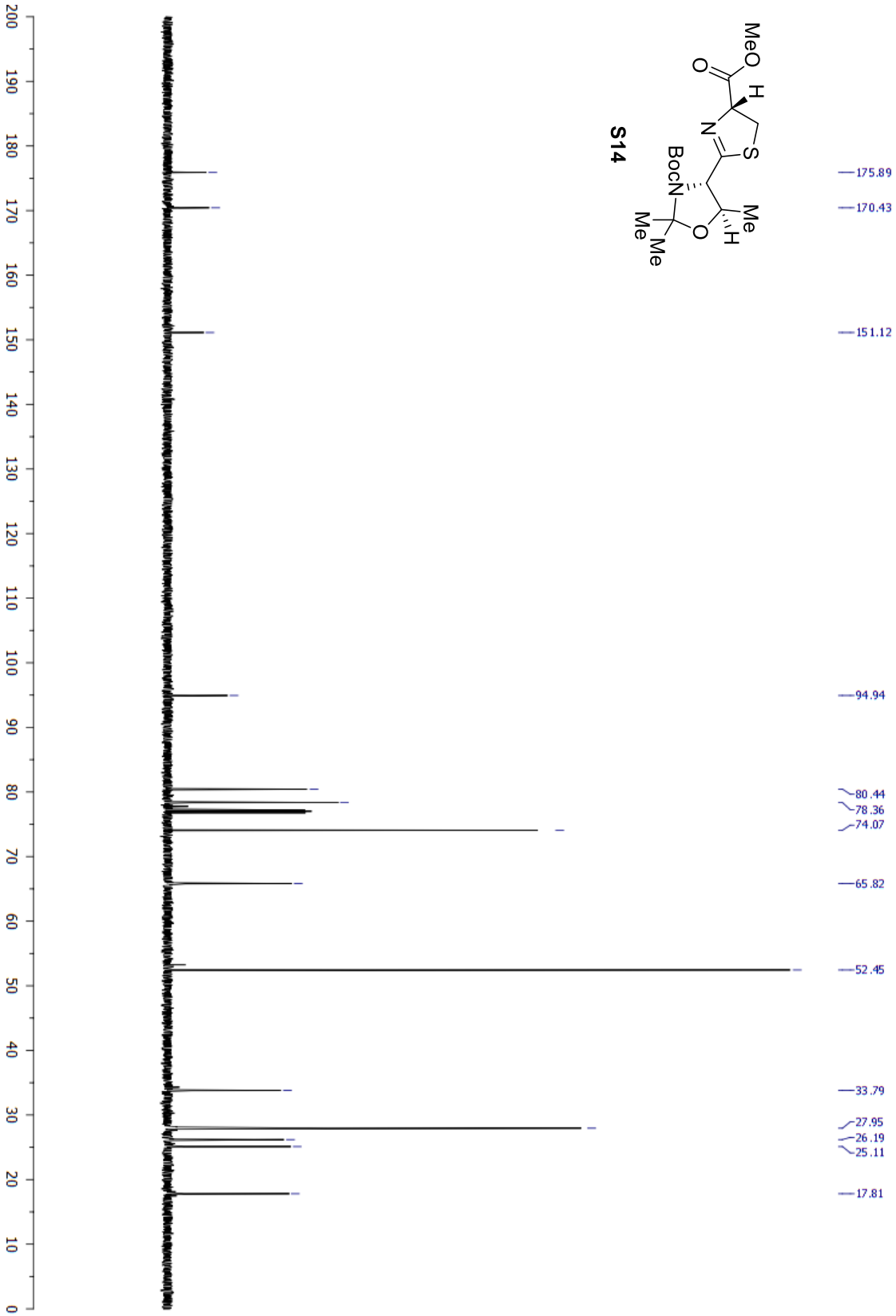
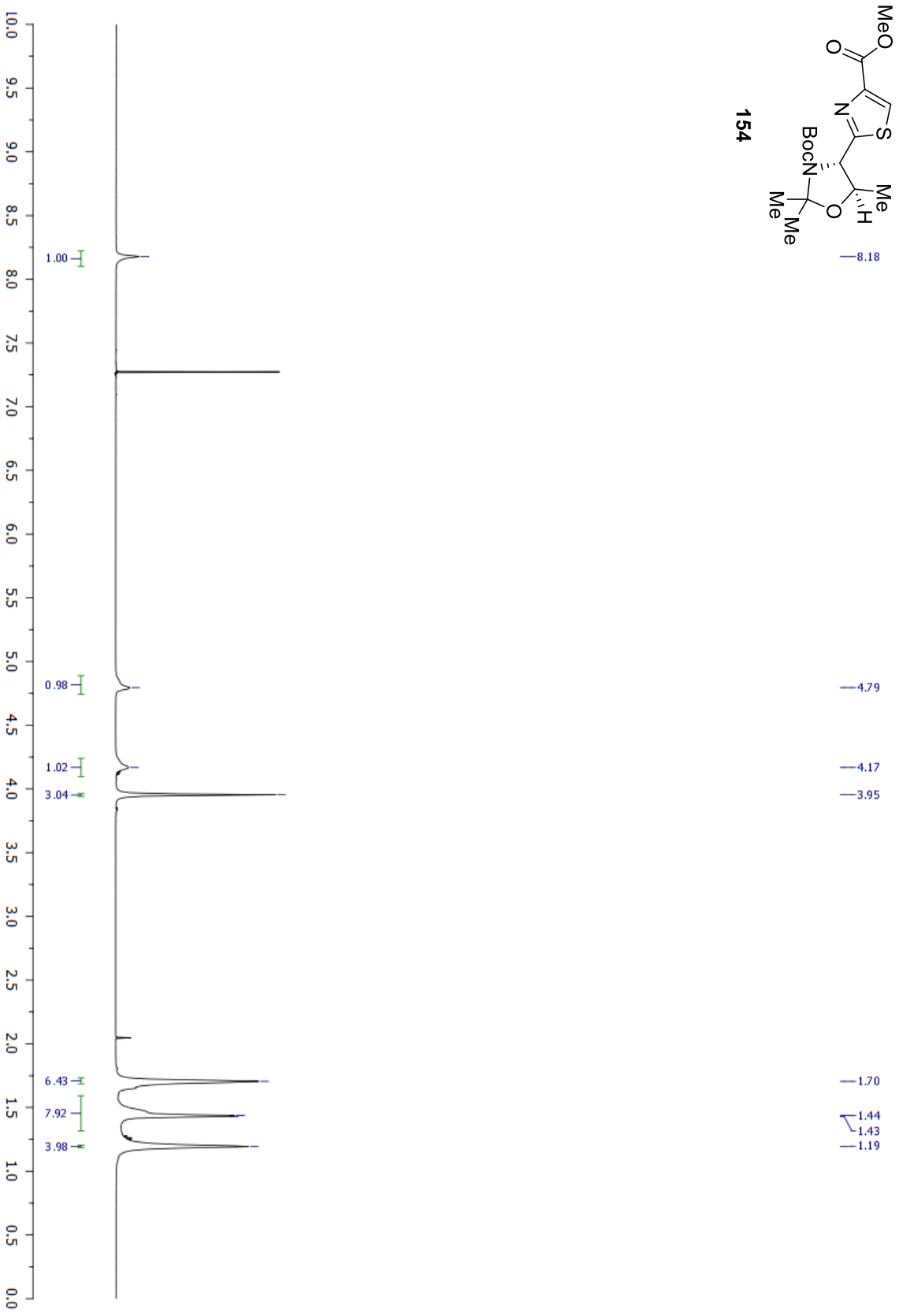
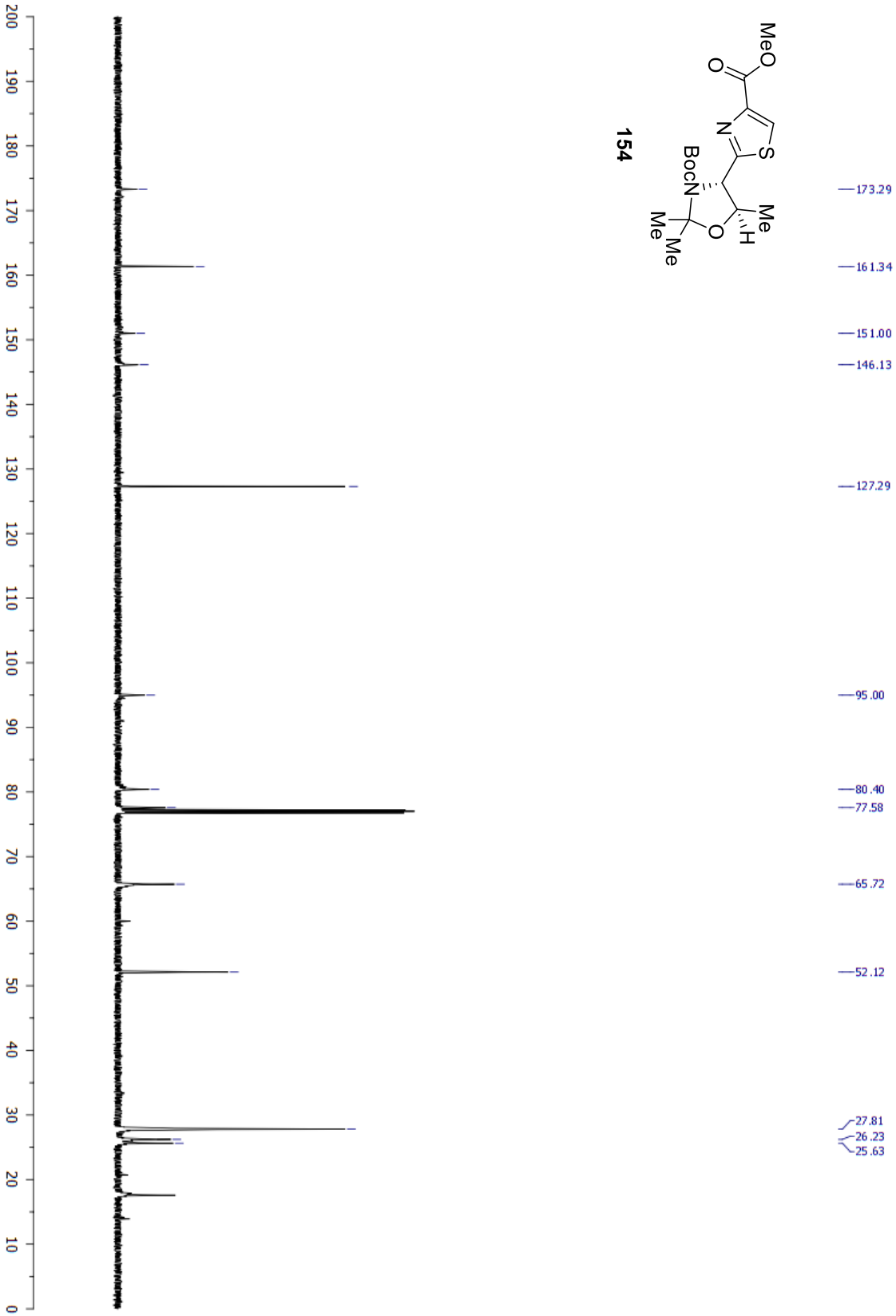
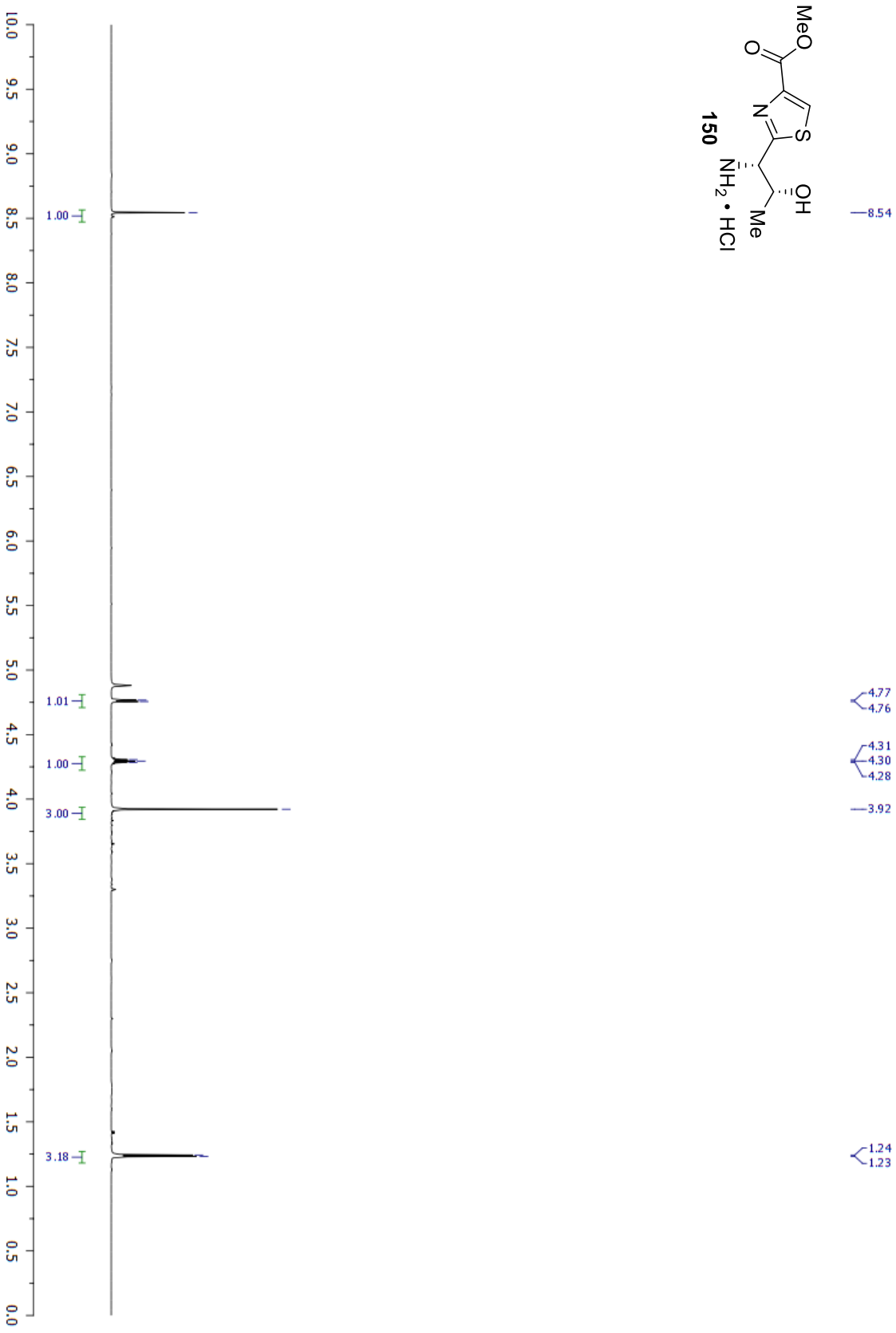
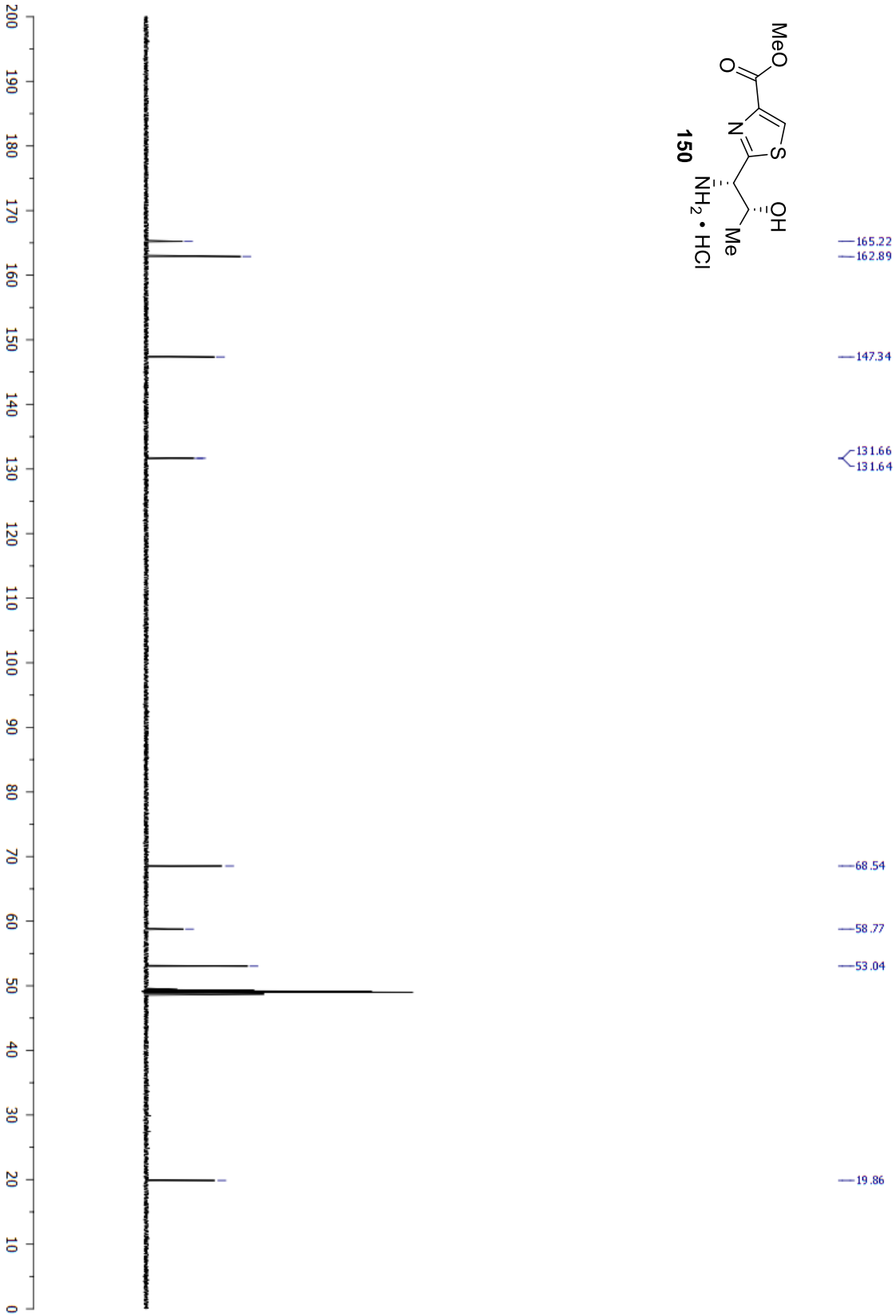
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.00
1.01
1.18
3.89
0.99
1.29
6.00
8.40
3.68
5.03
5.01
5.00
4.17
4.15
4.00
3.99
3.98
3.71
3.69
3.56
3.54
3.52
3.44
3.42
3.40
1.53
1.49
1.29
1.27
1.26

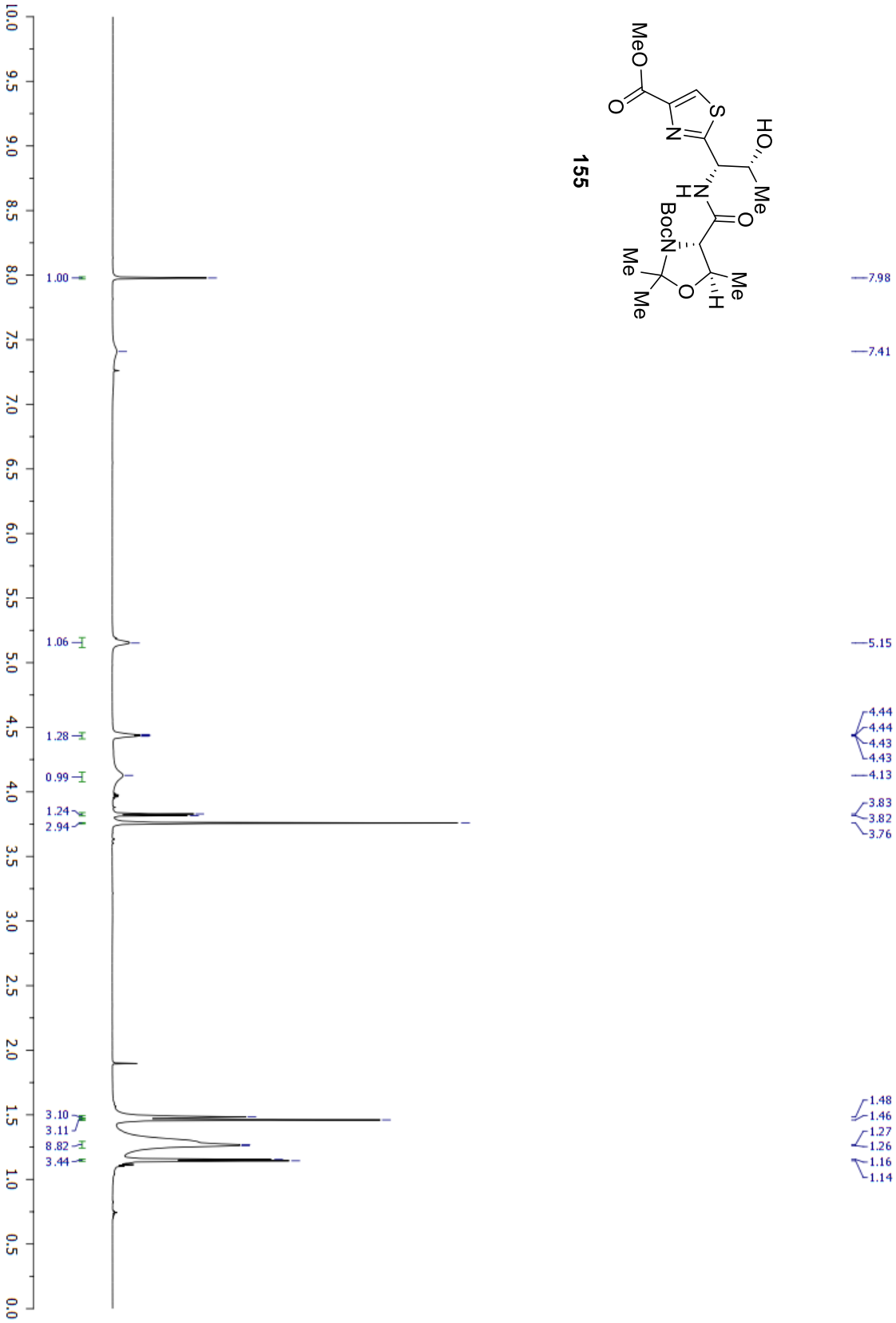

S14
MeO
O
H
N
S
BocN
Me
Me
Me
O
H
175.89
170.43
151.12
94.94
80.44
78.36
74.07
65.82
52.45
33.79
27.95
26.19
25.11
17.81
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

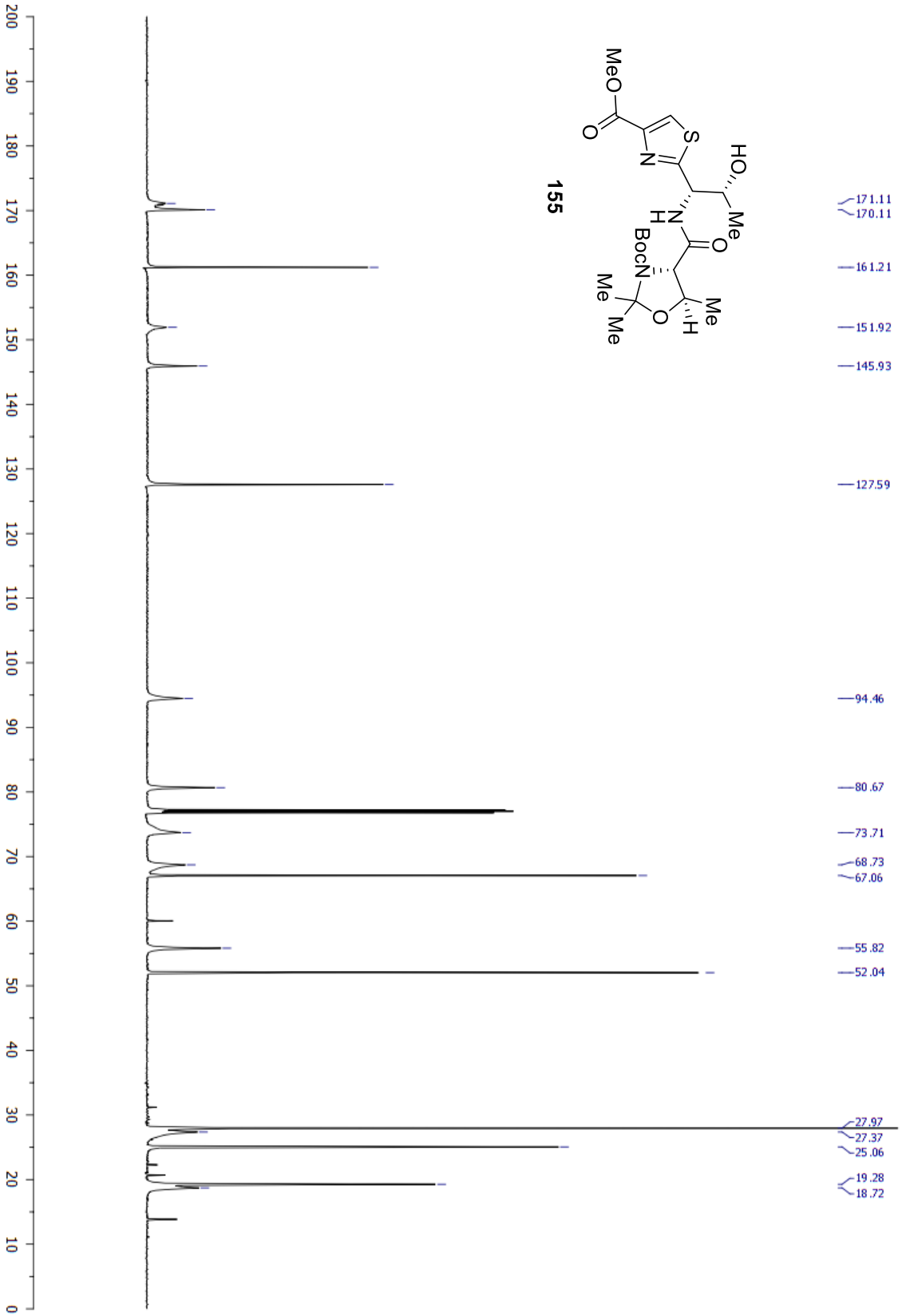

MeO
O
N
S
BocN
Me
H
O
Me
Me
154
8.18
4.79
4.17
3.95
1.70
1.44
1.43
1.19
1.00
0.98
1.02
3.04
6.43
7.92
3.98
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

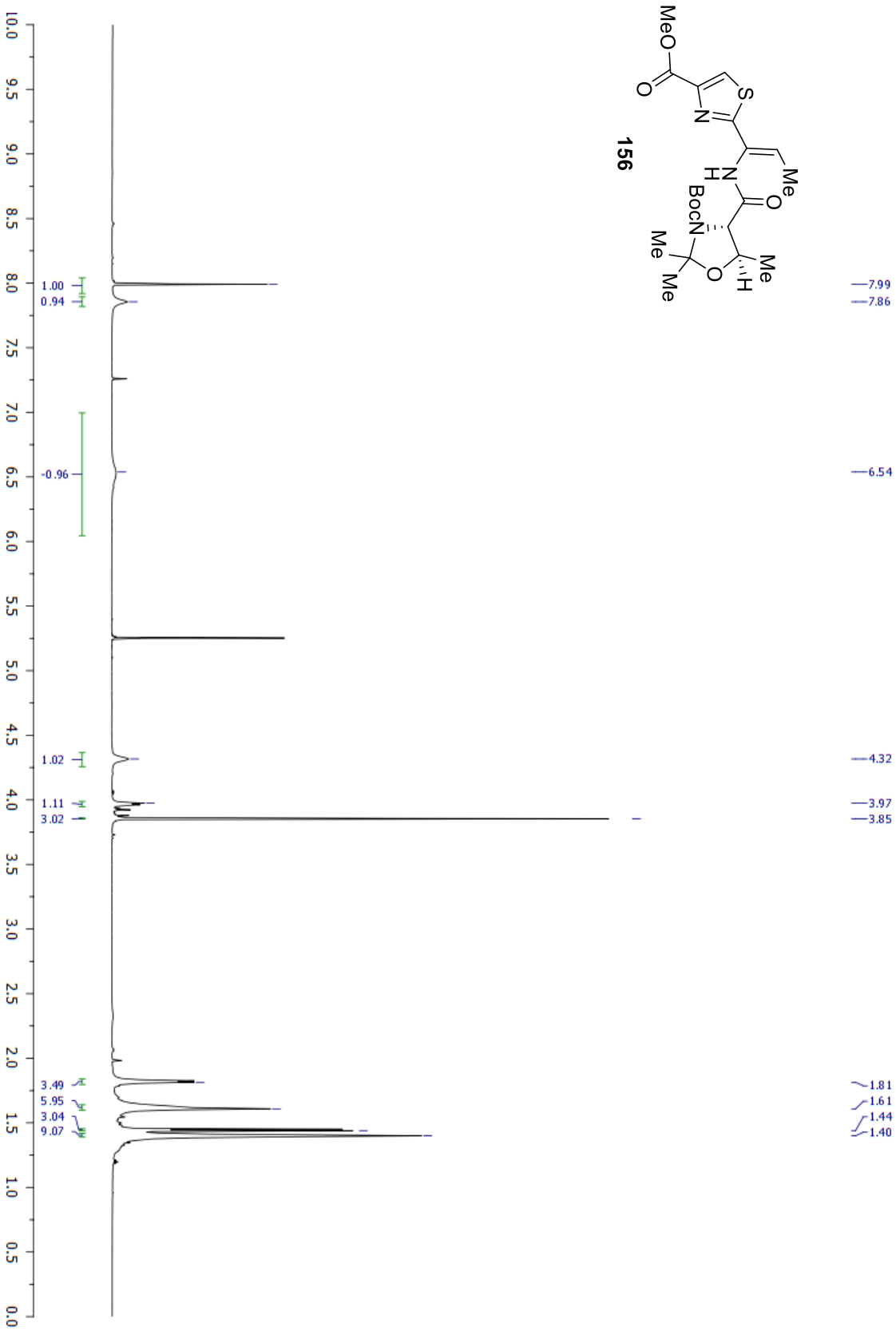

MeO
O
N
S
BocN
Me
H
O
Me
Me
154
173.29
161.34
151.00
146.13
127.29
95.00
80.40
77.58
65.72
52.12
27.81
26.23
25.63
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


MeO
O
N
S
OH
Me
NH2 • HCl
150
8.54
4.77
4.76
4.31
4.30
4.28
3.92
1.24
1.23
1.00
1.01
1.00
3.00
3.18
10.0
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
0.0


MeO
O
N
S
OH
Me
NH2 • HCl
150
165.22
162.89
147.34
131.66
131.64
68.54
58.77
53.04
19.86
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


MeO
O
S
N
HO
Me
N
H
O
BocN
Me
Me
O
Me
H
155
10.0
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
0.0
1.00
1.06
1.28
0.99
1.24
2.94
3.10
3.11
8.82
3.44
7.98
7.41
5.15
4.44
4.44
4.43
4.43
4.13
3.83
3.82
3.76
1.48
1.46
1.27
1.26
1.16
1.14


MeO
O
S
N
HO
Me
H
N
O
BocN
Me
Me
Me
O
H
155
171.11
170.11
161.21
151.92
145.93
127.59
94.46
80.67
73.71
68.73
67.06
55.82
52.04
27.97
27.37
25.06
19.28
18.72
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


MeO
O
S
N
N
H
Me
O
BocN
Me
Me
O
Me
H
156
10.0
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
0.0
1.00
0.94
0.96
1.02
1.11
3.02
3.49
5.95
3.04
9.07
7.99
7.86
6.54
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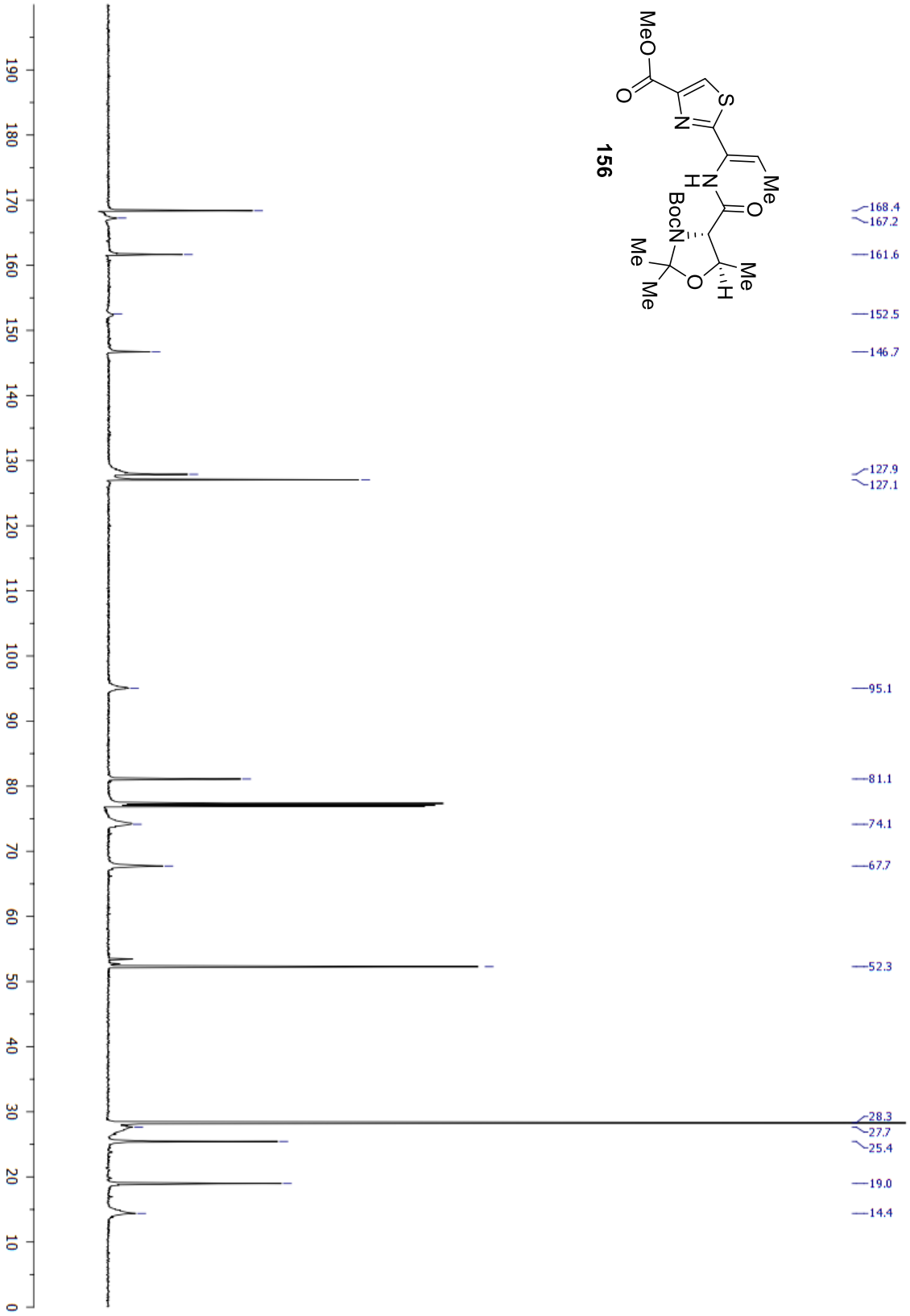
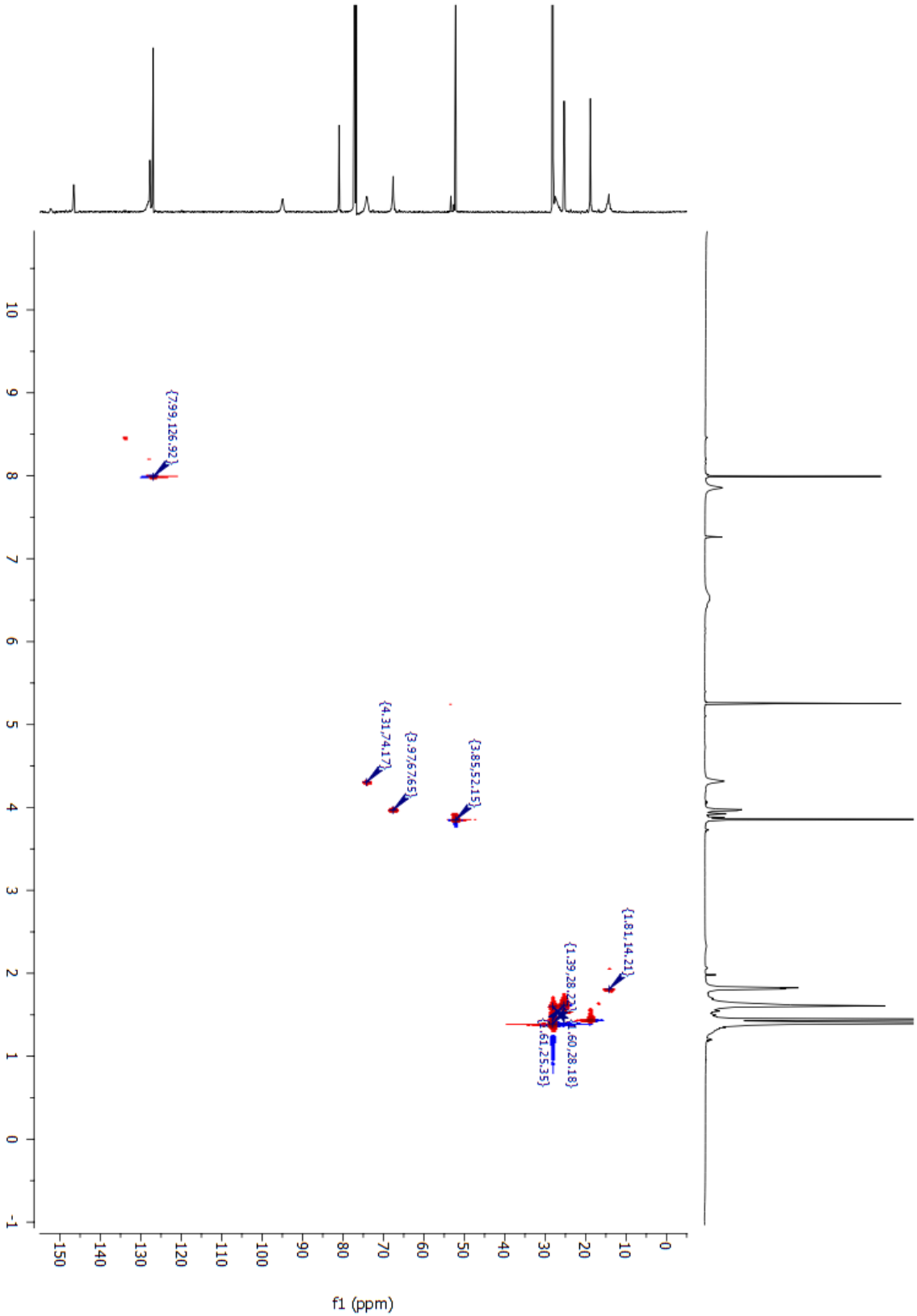
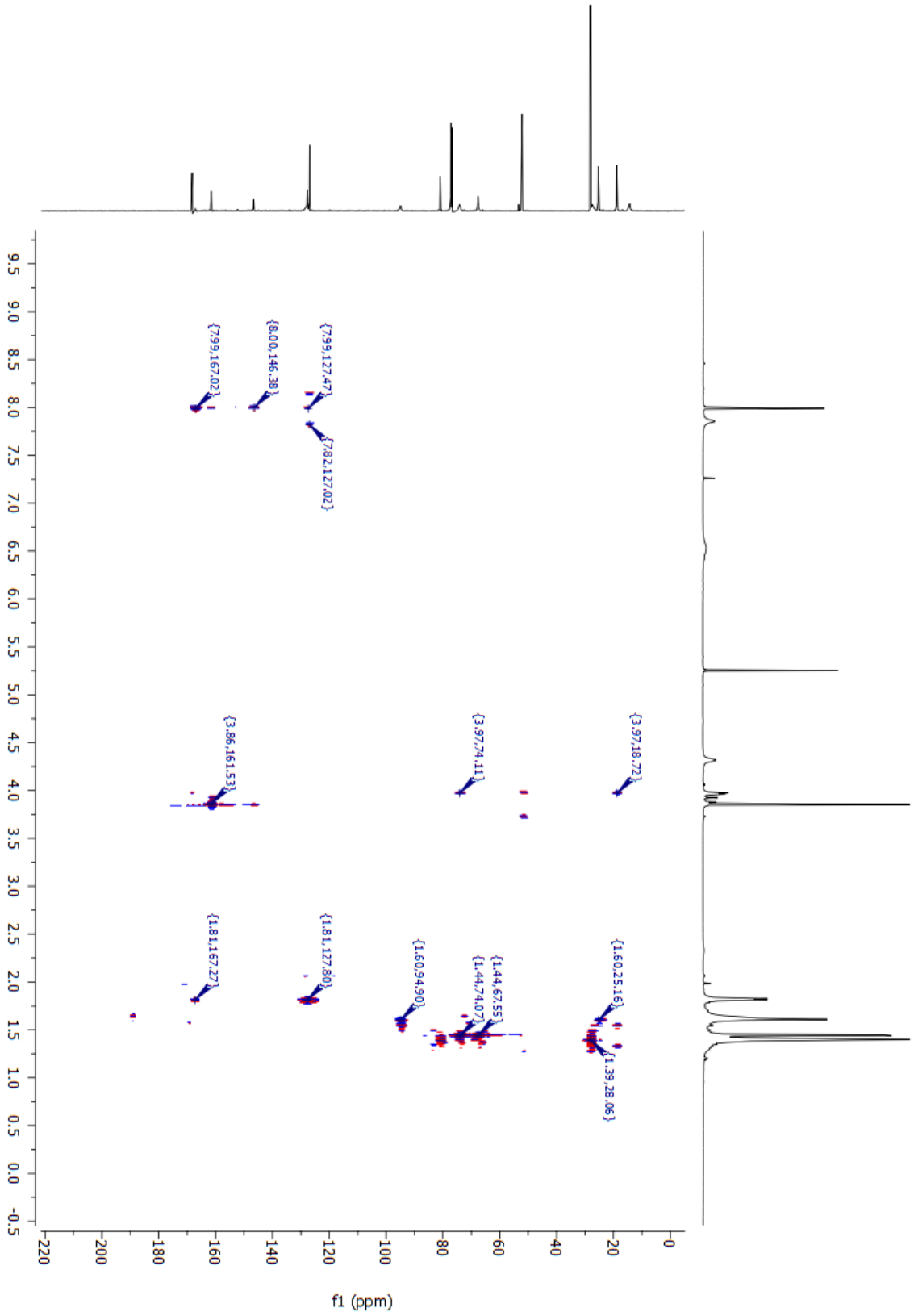
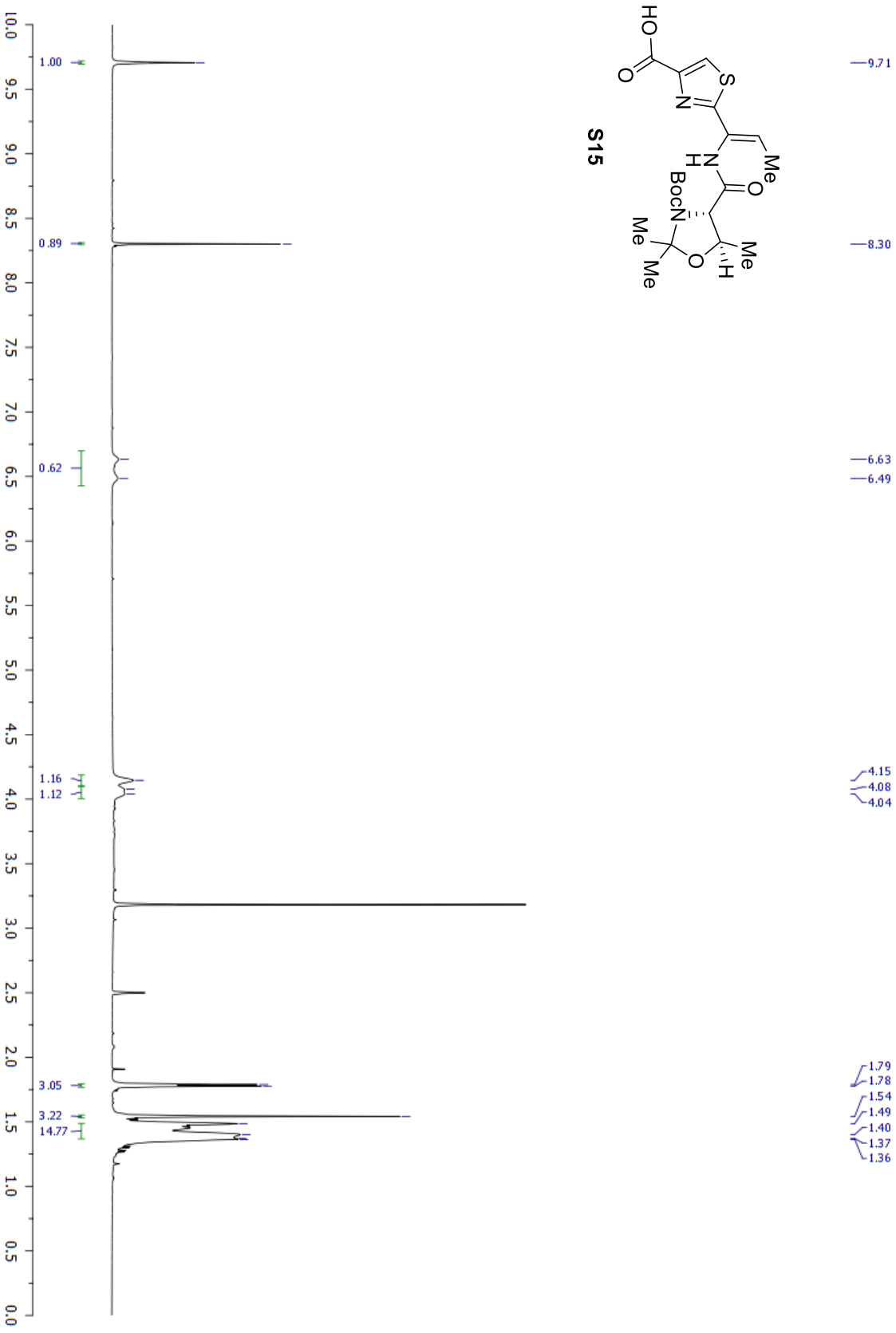
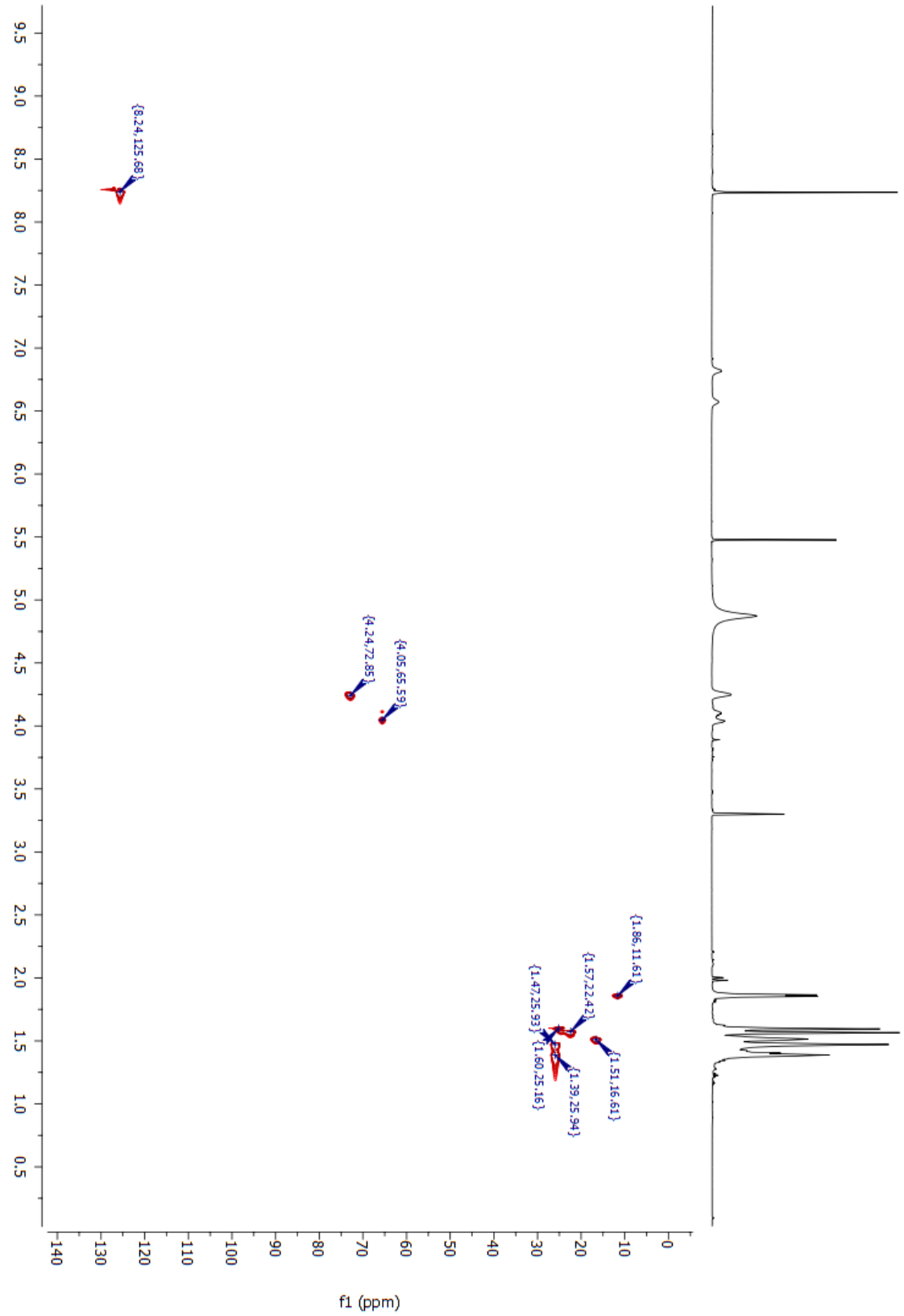
3.97
3.85
1.81
1.61
1.44
1.40

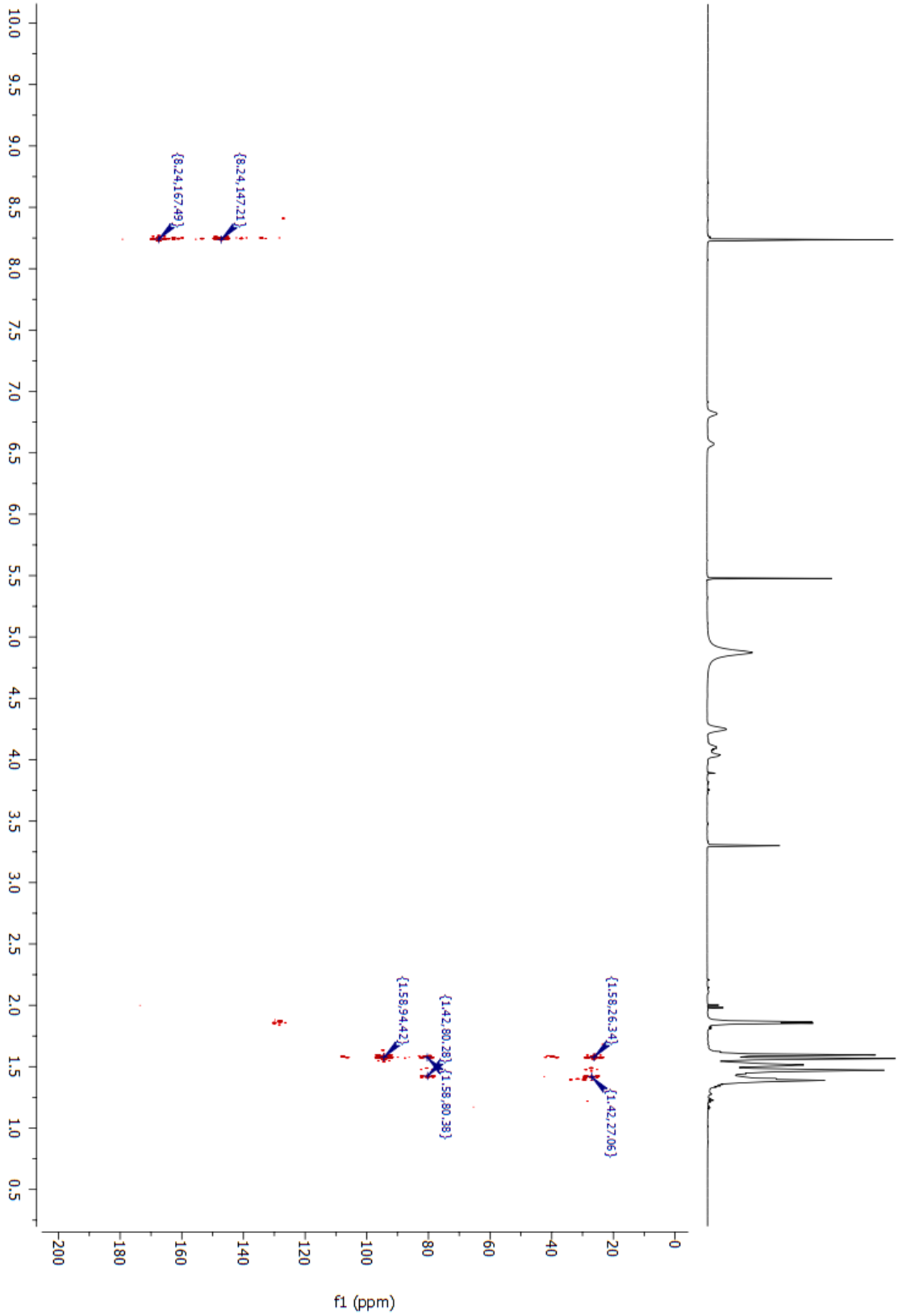

MeO
O
S
N
H
N
Me
O
BocN
Me
Me
O
Me
H
156
168.4
167.2
161.6
152.5
146.7
127.9
127.1
95.1
81.1
74.1
67.7
52.3
28.3
27.7
25.4
19.0
14.4
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

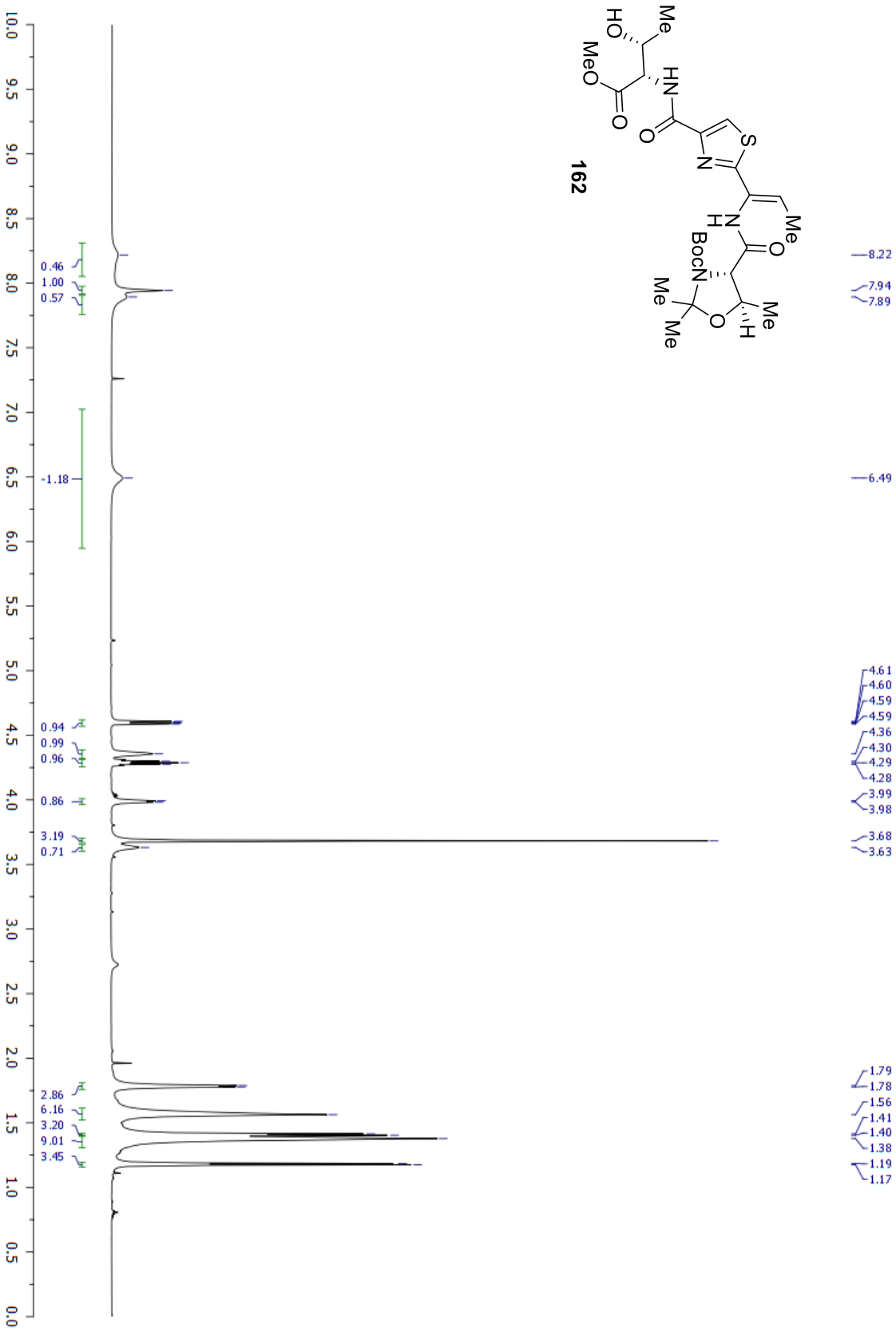

{7.99,126.92}
{4.31,74.17}
{3.97,67.65}
{3.85,52.15}
{1.81,14.21}
{1.39,28.22}
{1.60,28.18}
{1.61,25.35}
f1 (ppm)

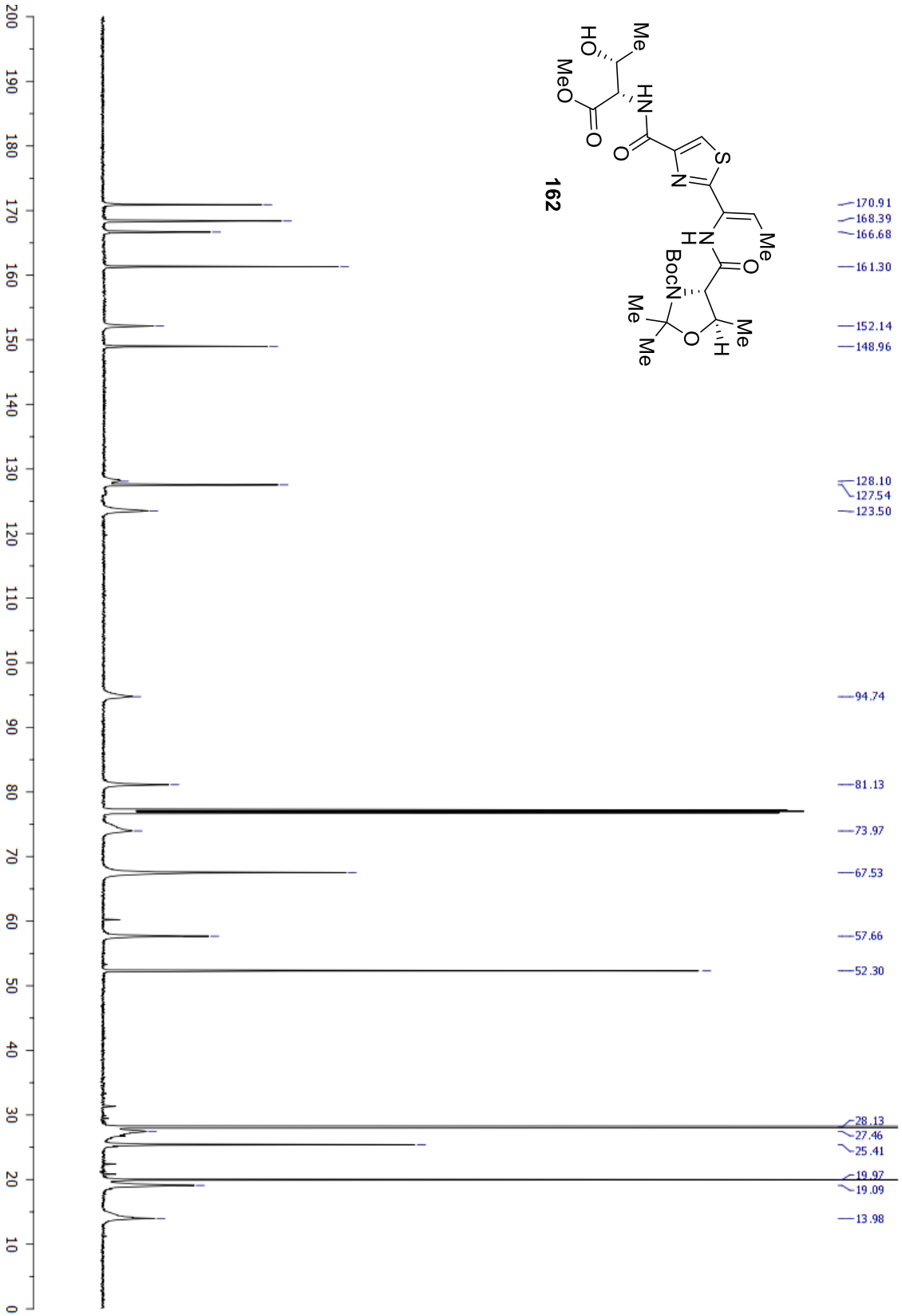

{7.99,167.02}
{8.00,146.38}
{7.99,127.47}
{7.82,127.02}
{3.86,161.53}
{3.97,74.11}
{3.97,18.72}
{1.81,167.27}
{1.81,127.80}
{1.60,94.90}
{1.44,74.07}
{1.44,67.55}
{1.60,25.16}
{1.39,28.06}
f1 (ppm)

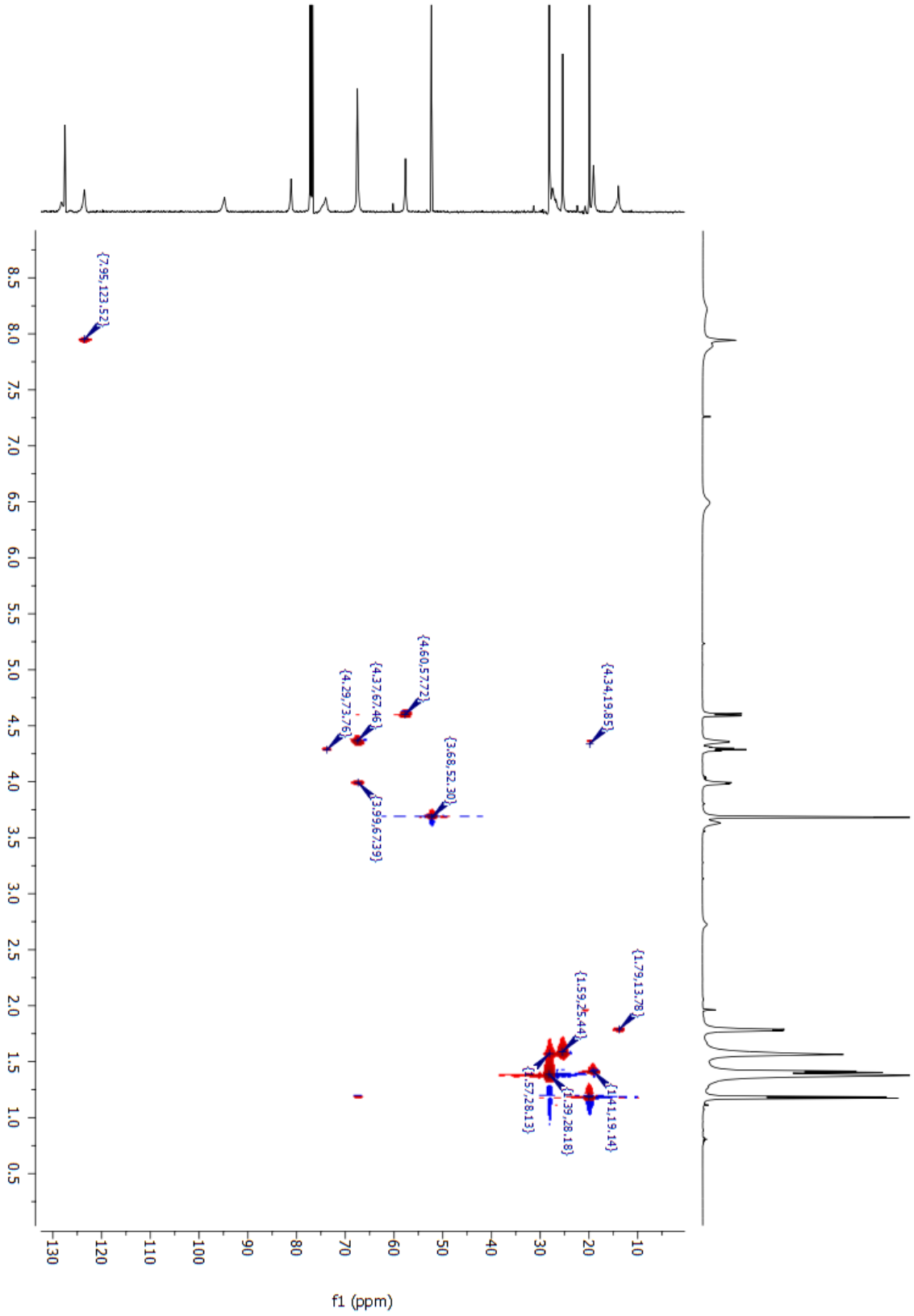

HO
O
S
N
N
H
Me
O
BocN
Me
Me
O
Me
H
S15
9.71
8.30
6.63
6.49
4.15
4.08
4.04
1.79
1.78
1.54
1.49
1.40
1.37
1.36
1.00
0.89
0.62
1.16
1.12
3.05
3.22
14.77
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


{8.24,125.68}
{4.24,72.85}
{4.05,65.59}
{1.86,11.61}
{1.57,22.42}
{1.47,25.93}
{1.60,25.16}
{1.51,16.61}
{1.39,25.94}
f1 (ppm)


{8.24,167.49}
{8.24,147.21}
{1.58,94.42}
{1.42,80.28}
{1.58,80.38}
{1.58,26.34}
{1.42,27.06}
f1 (ppm)


162
10.0
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
0.0
0.46
1.00
0.57
1.18
0.94
0.99
0.96
0.86
3.19
0.71
2.86
6.16
3.20
9.01
3.45
8.22
7.94
7.89
6.49
4.61
4.60
4.59
4.59
4.36
4.30
4.29
4.28
3.99
3.98
3.68
3.63
1.79
1.78
1.56
1.41
1.40
1.38
1.19
1.17


162
170.91
168.39
166.68
161.30
152.14
148.96
128.10
127.54
123.50
94.74
81.13
73.97
67.53
57.66
52.30
28.13
27.46
25.41
19.97
19.09
13.98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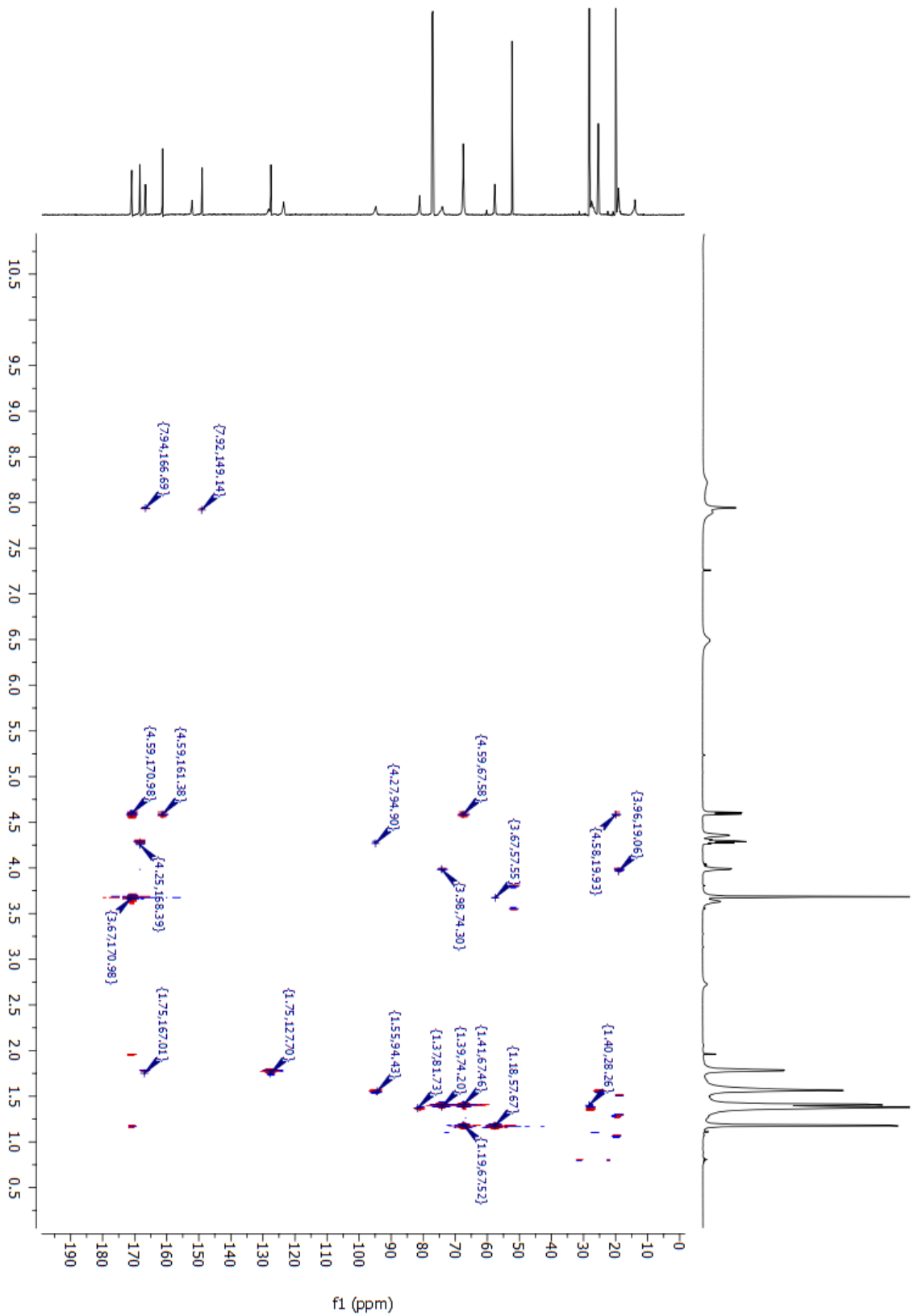
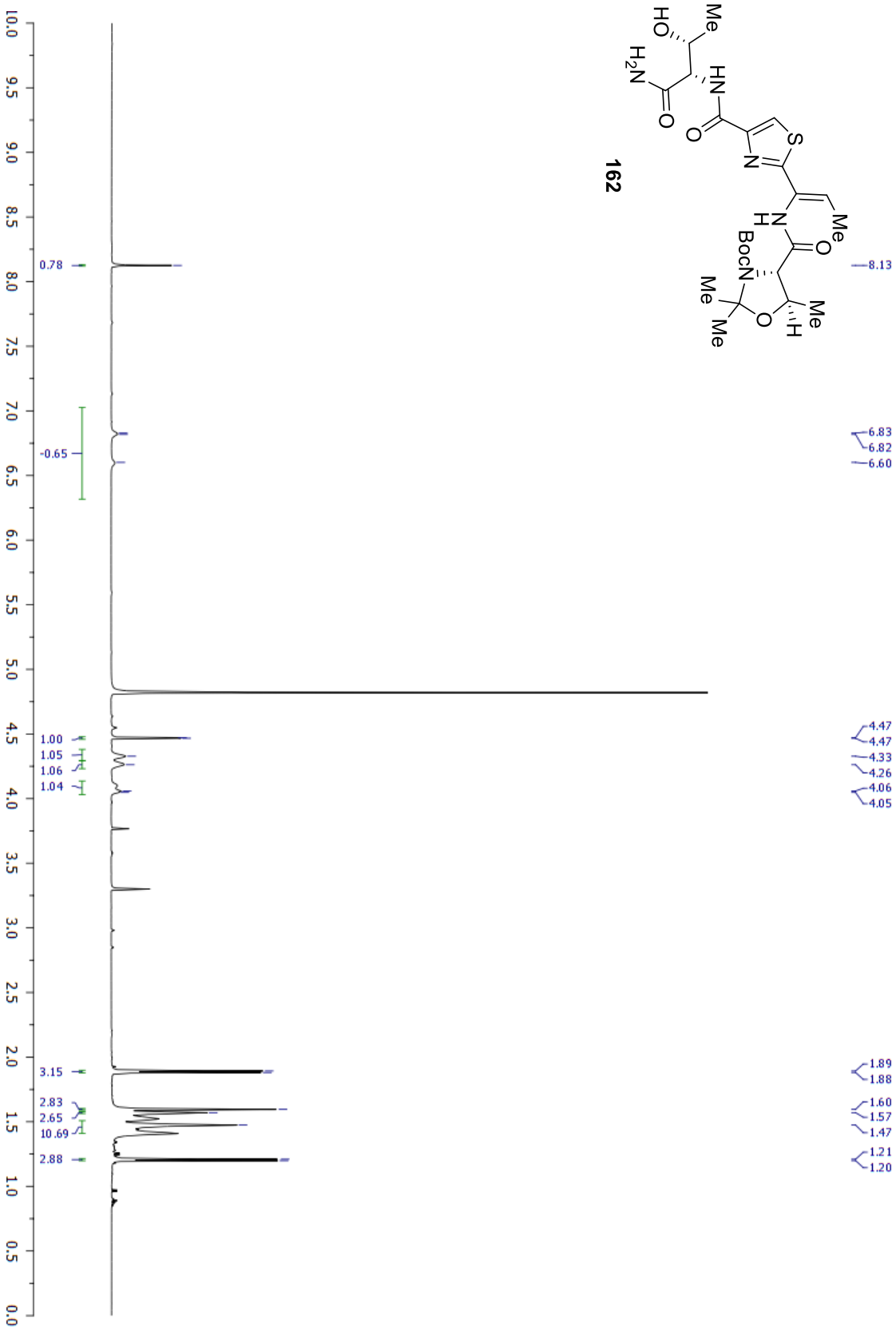
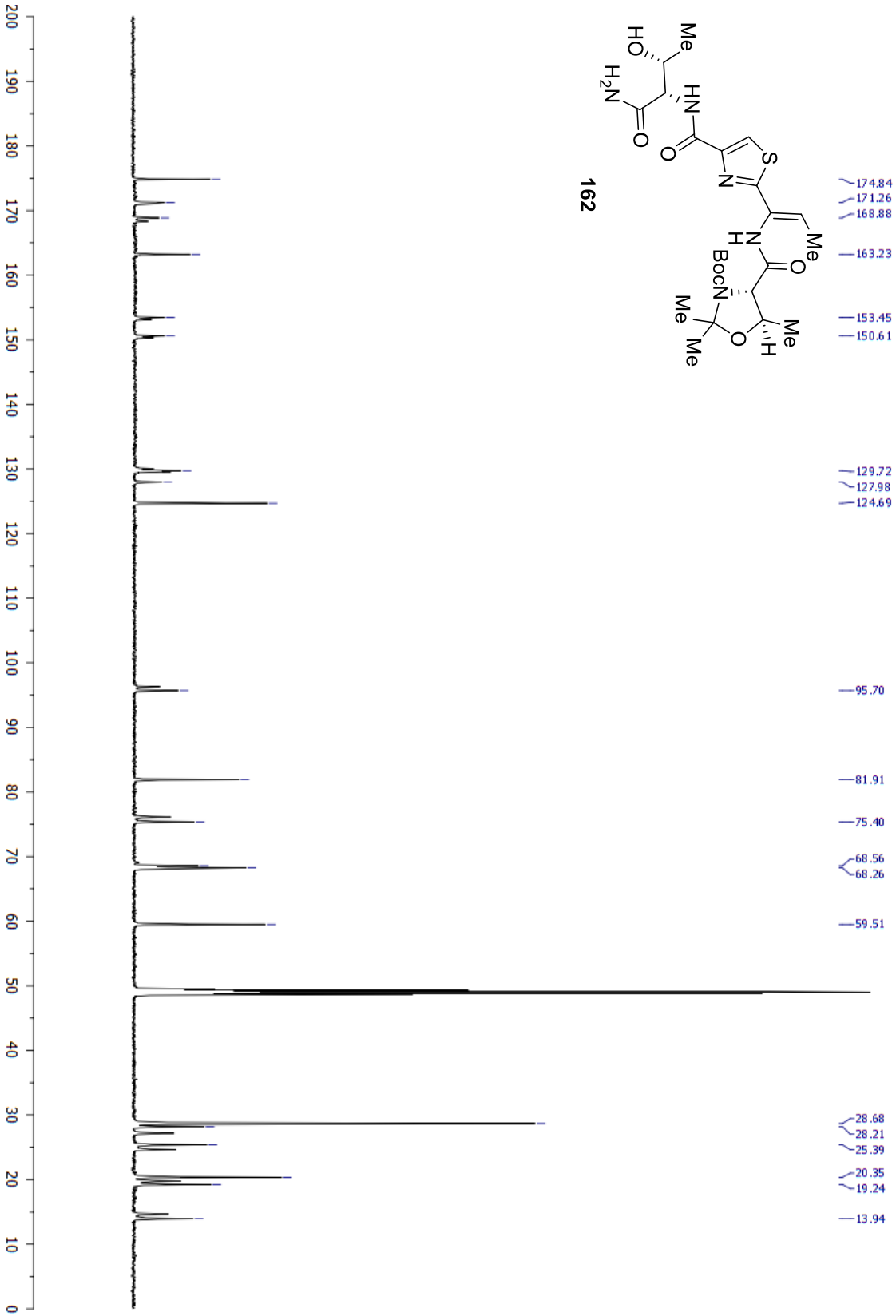
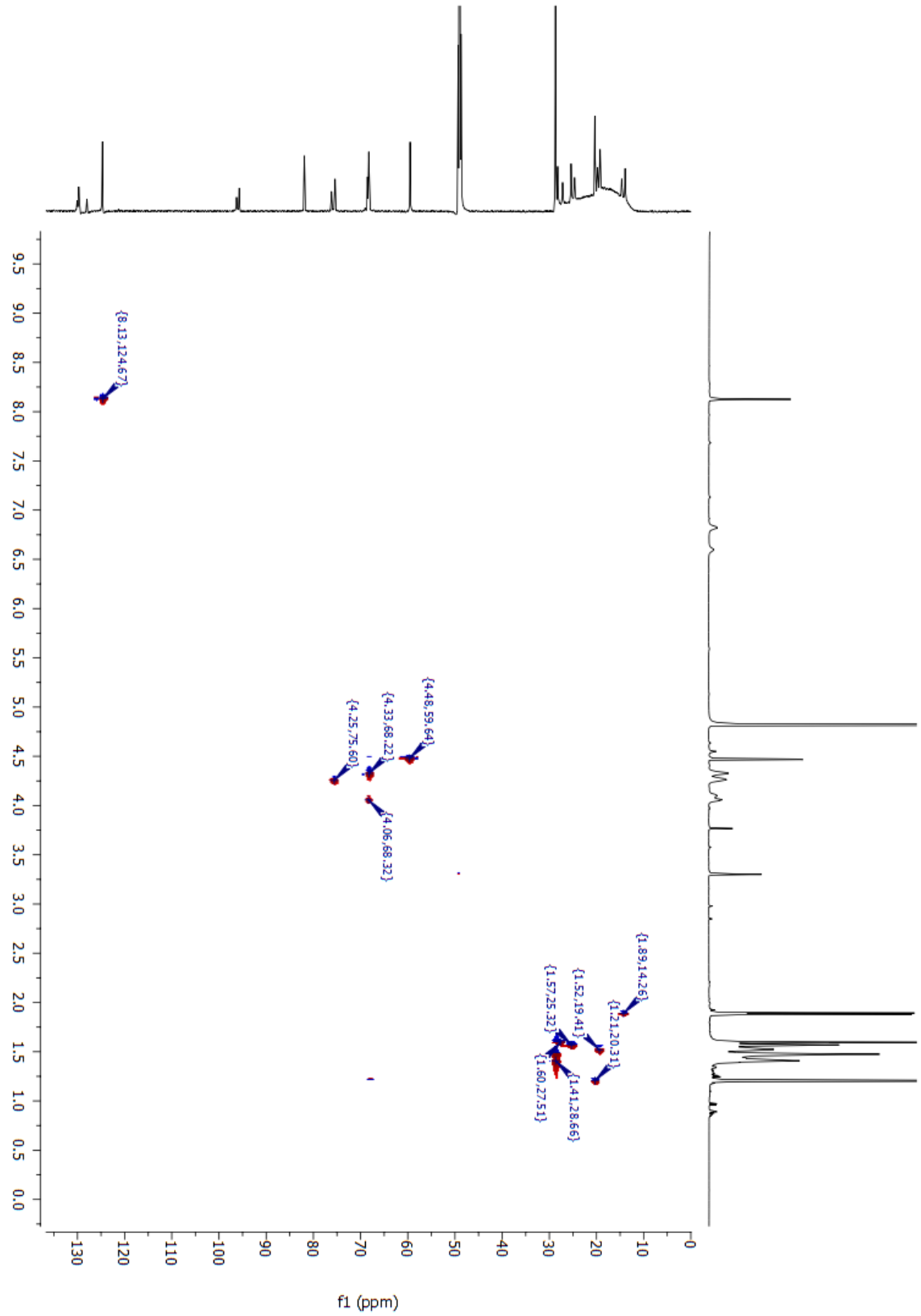
{4.60,57.72}
{4.37,67.46}
{4.29,73.76}
{4.34,19.85}
{3.68,52.30}
{3.99,67.39}
{1.79,13.78}
{1.59,25.44}
{1.57,28.13}
{1.39,28.18}
{1.41,19.14}
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

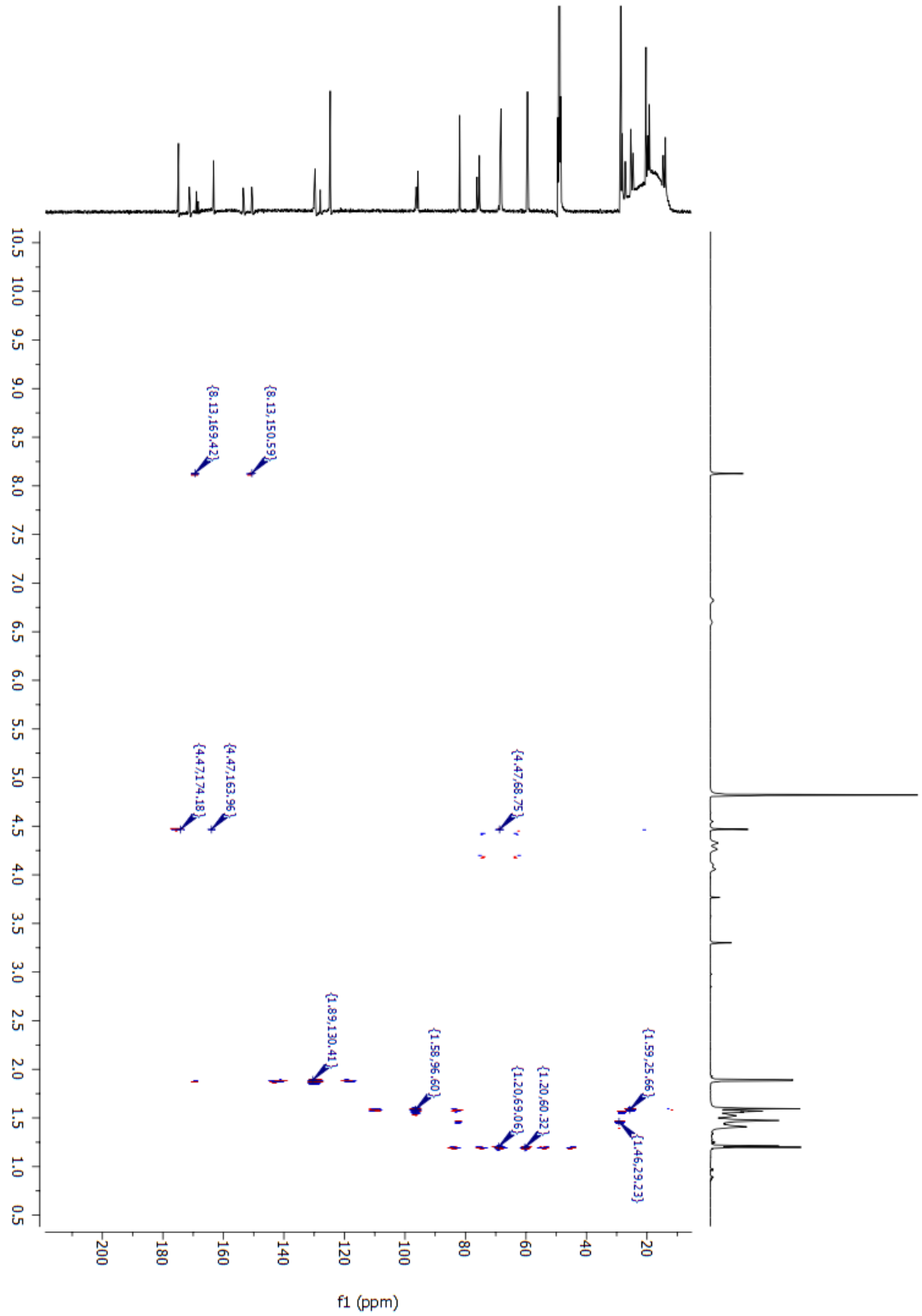

{7.94,166.69}
{7.92,149.14}
{4.59,170.98}
{4.59,161.38}
{4.25,168.39}
{3.67,170.98}
{1.75,167.01}
{1.75,127.70}
{4.27,94.90}
{4.59,67.58}
{3.67,57.55}
{3.98,74.30}
{1.55,94.43}
{1.37,81.73}
{1.39,74.20}
{1.41,67.46}
{1.18,57.67}
{1.19,67.52}
{3.96,19.06}
{4.58,19.93}
{1.40,28.26}
f1 (ppm)

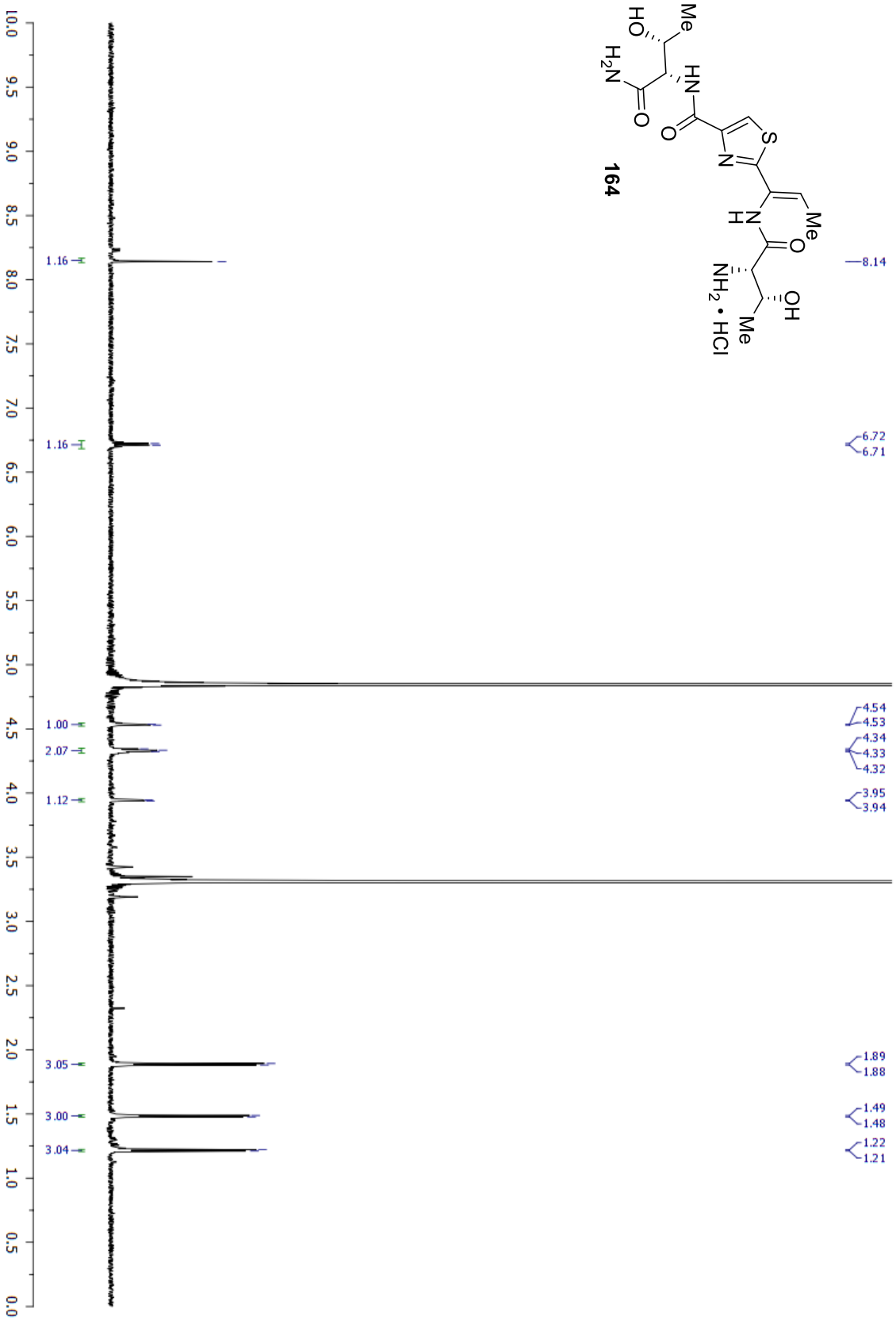

162
Me
HO
H2N
HN
O
S
N
N
H
Me
O
BocN
Me
Me
O
Me
H
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0.78
-0.65
1.00
1.05
1.06
1.04
3.15
2.83
2.65
10.69
2.88
8.13
6.83
6.82
6.60
4.47
4.47
4.33
4.26
4.06
4.05
1.89
1.88
1.60
1.57
1.47
1.21
1.20

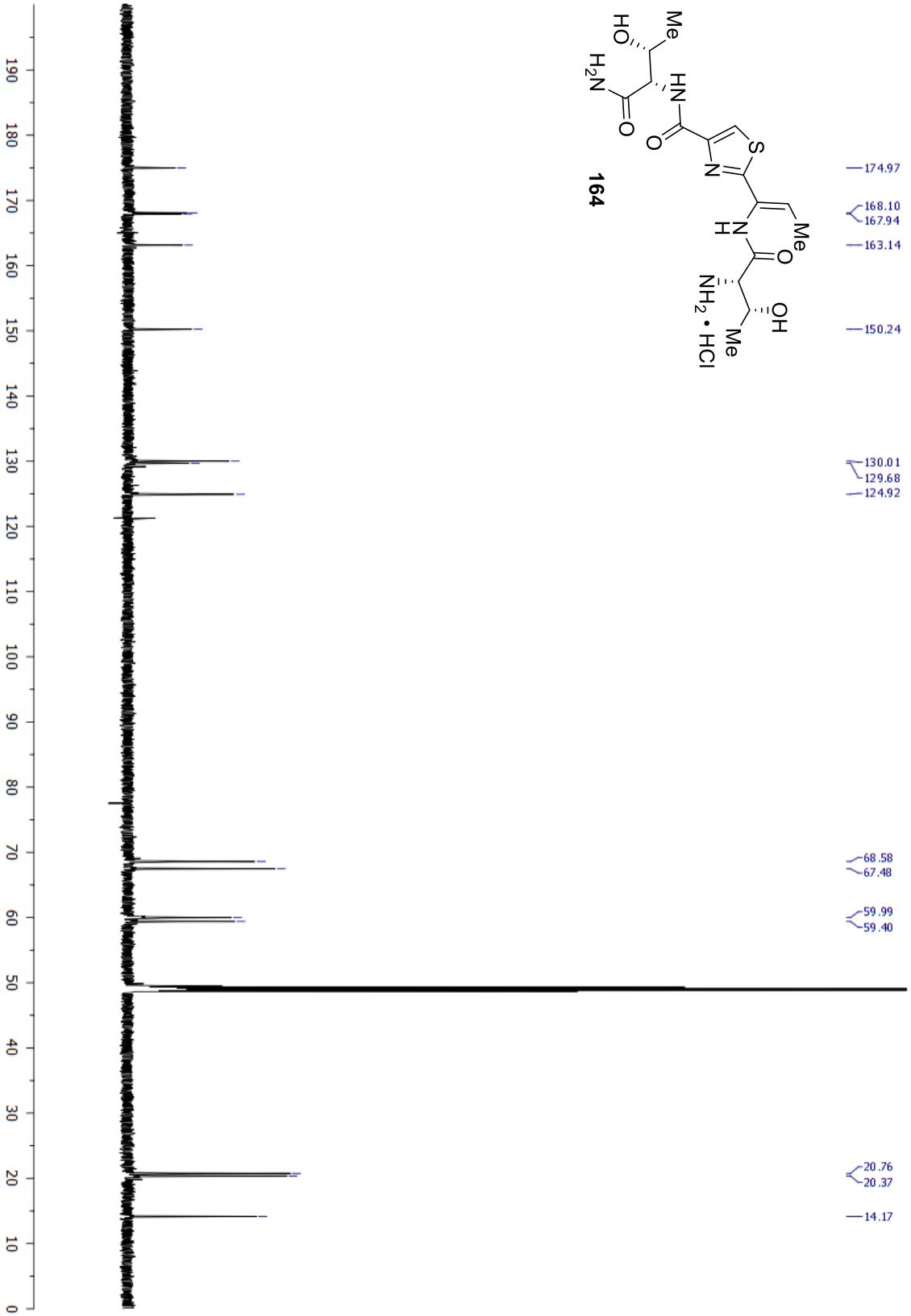

174.84
171.26
168.88
163.23
153.45
150.61
129.72
127.98
124.69
95.70
81.91
75.40
68.56
68.26
59.51
28.68
28.21
25.39
20.35
19.24
13.94
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

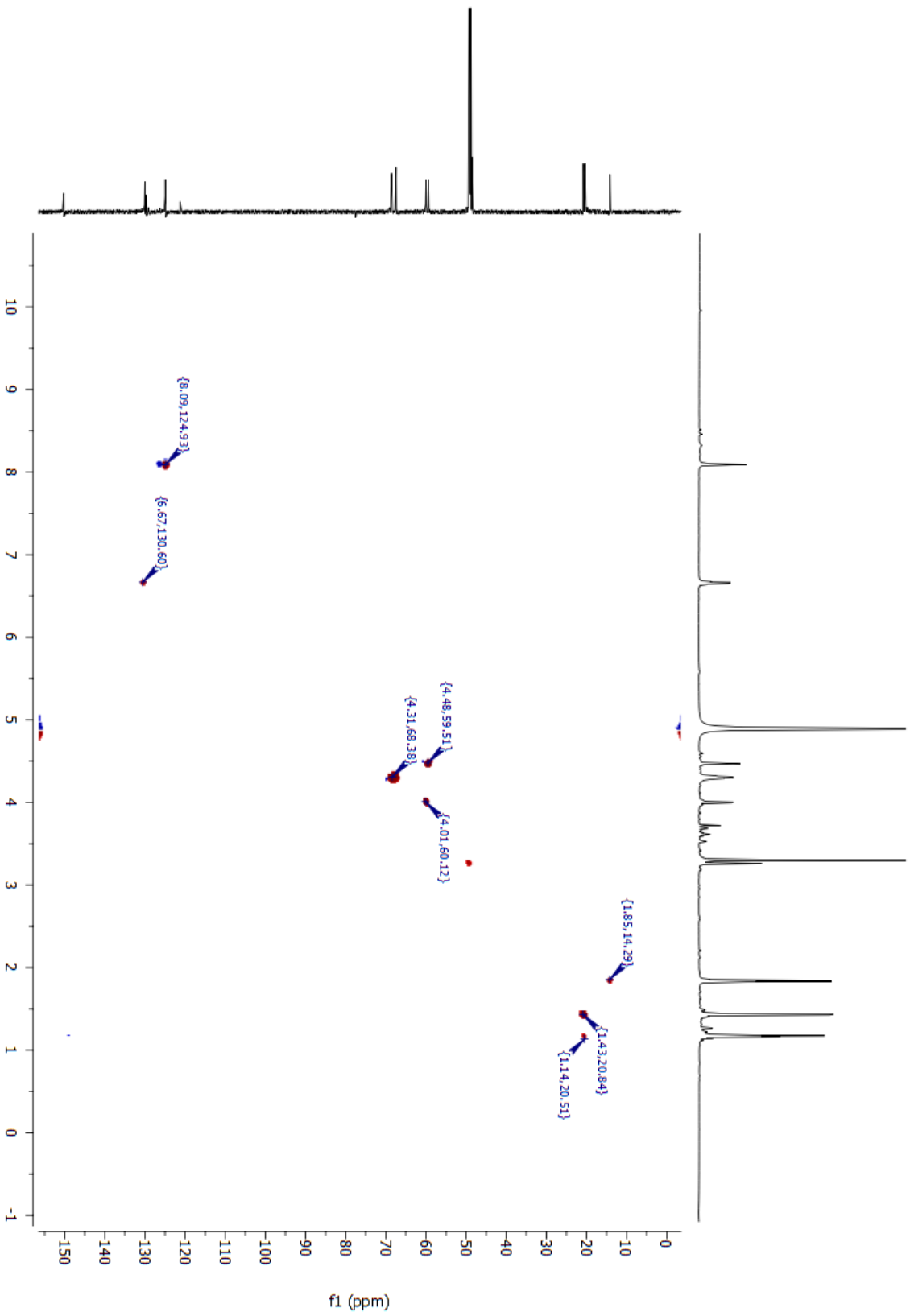
162

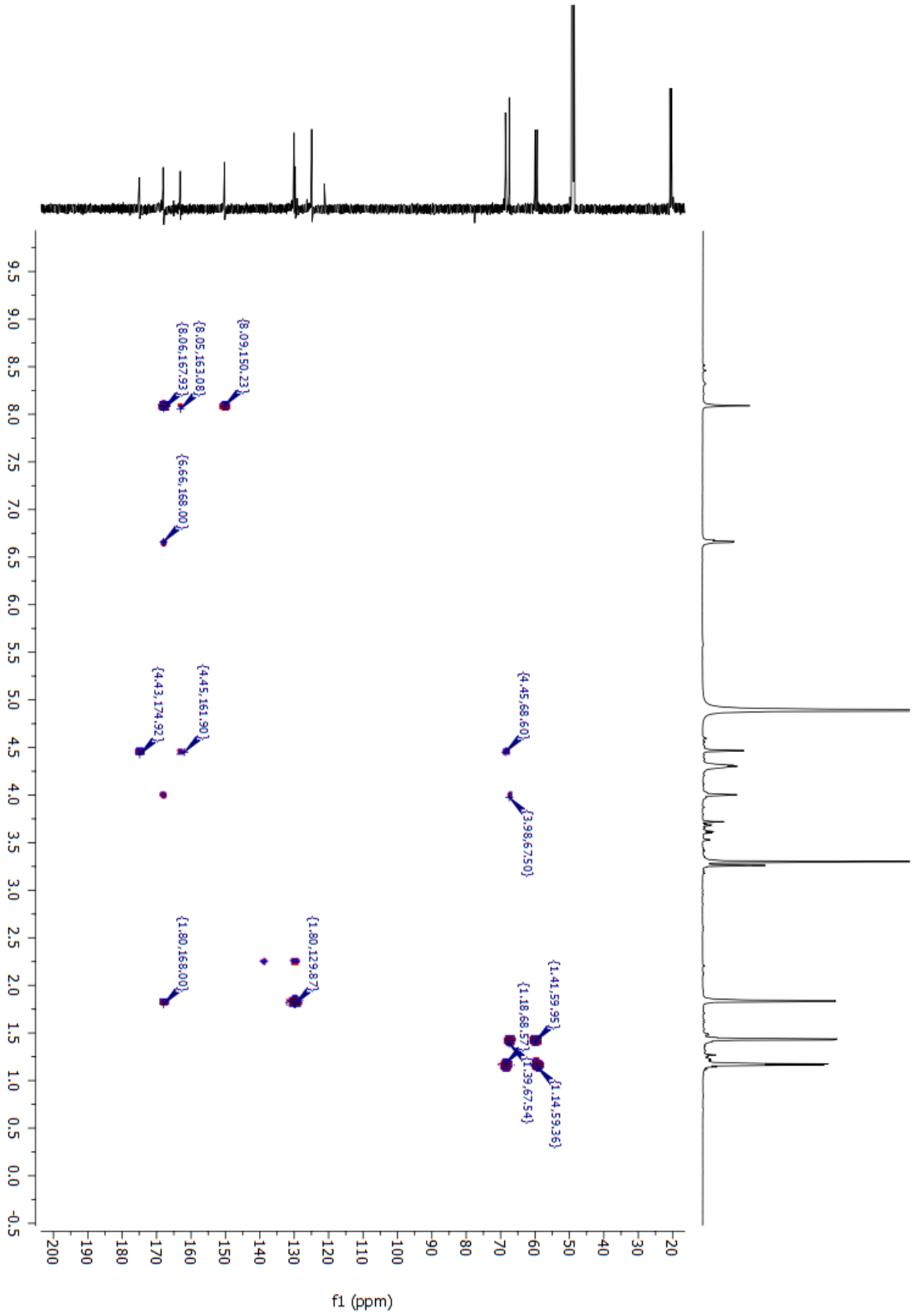

{8.13,124.67}
{4.48,59.64}
{4.33,68.22}
{4.25,75.60}
{4.06,68.32}
{1.89,14.26}
{1.52,19.41}
{1.57,25.32}
{1.21,20.31}
{1.60,27.51}
{1.41,28.66}
f1 (ppm)

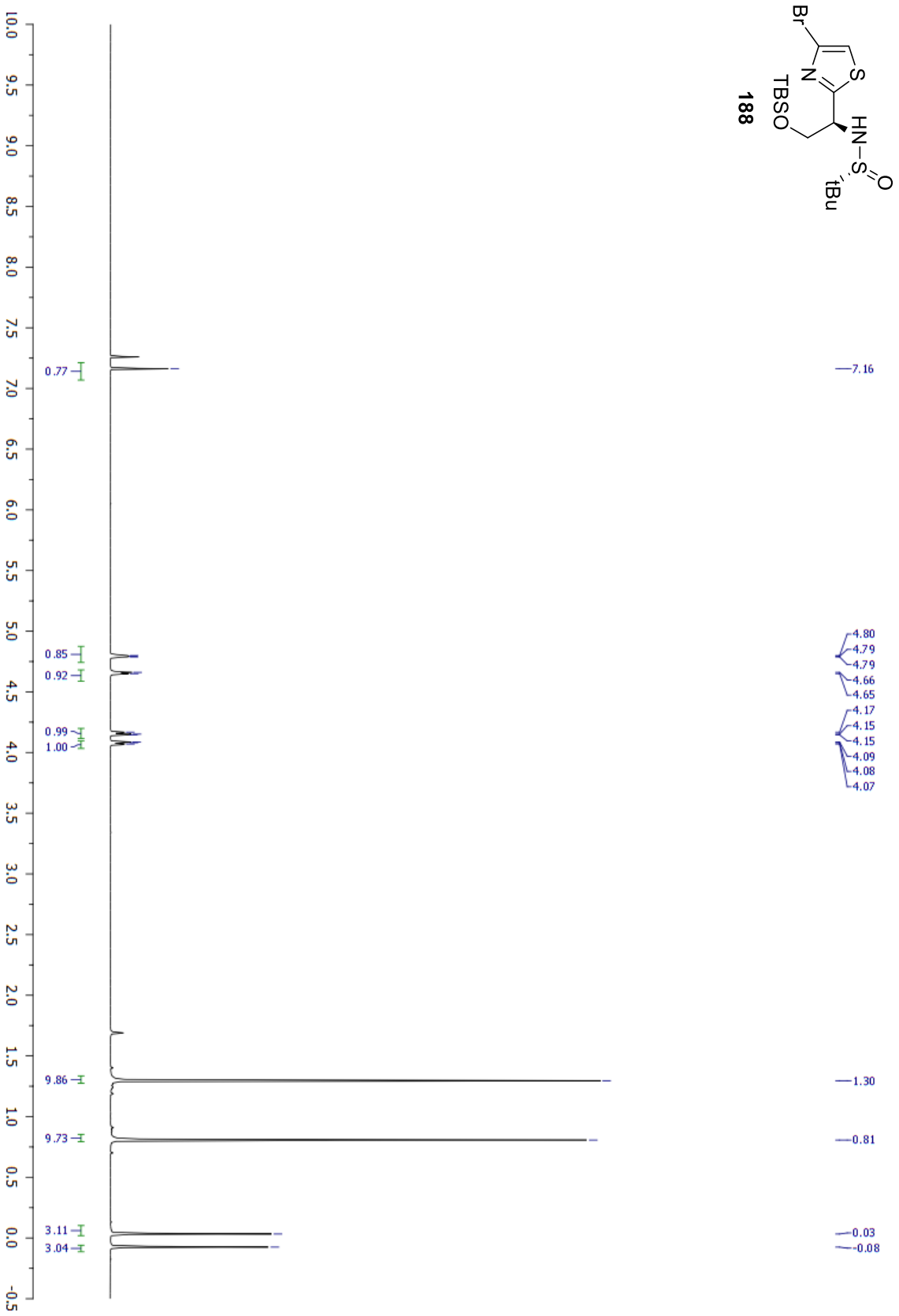

{8.13,169.42}
{8.13,150.59}
{4.47,174.18}
{4.47,163.96}
{4.47,68.75}
{1.89,130.41}
{1.58,96.60}
{1.59,25.66}
{1.20,69.06}
{1.20,60.32}
{1.46,29.23}
f1 (ppm)

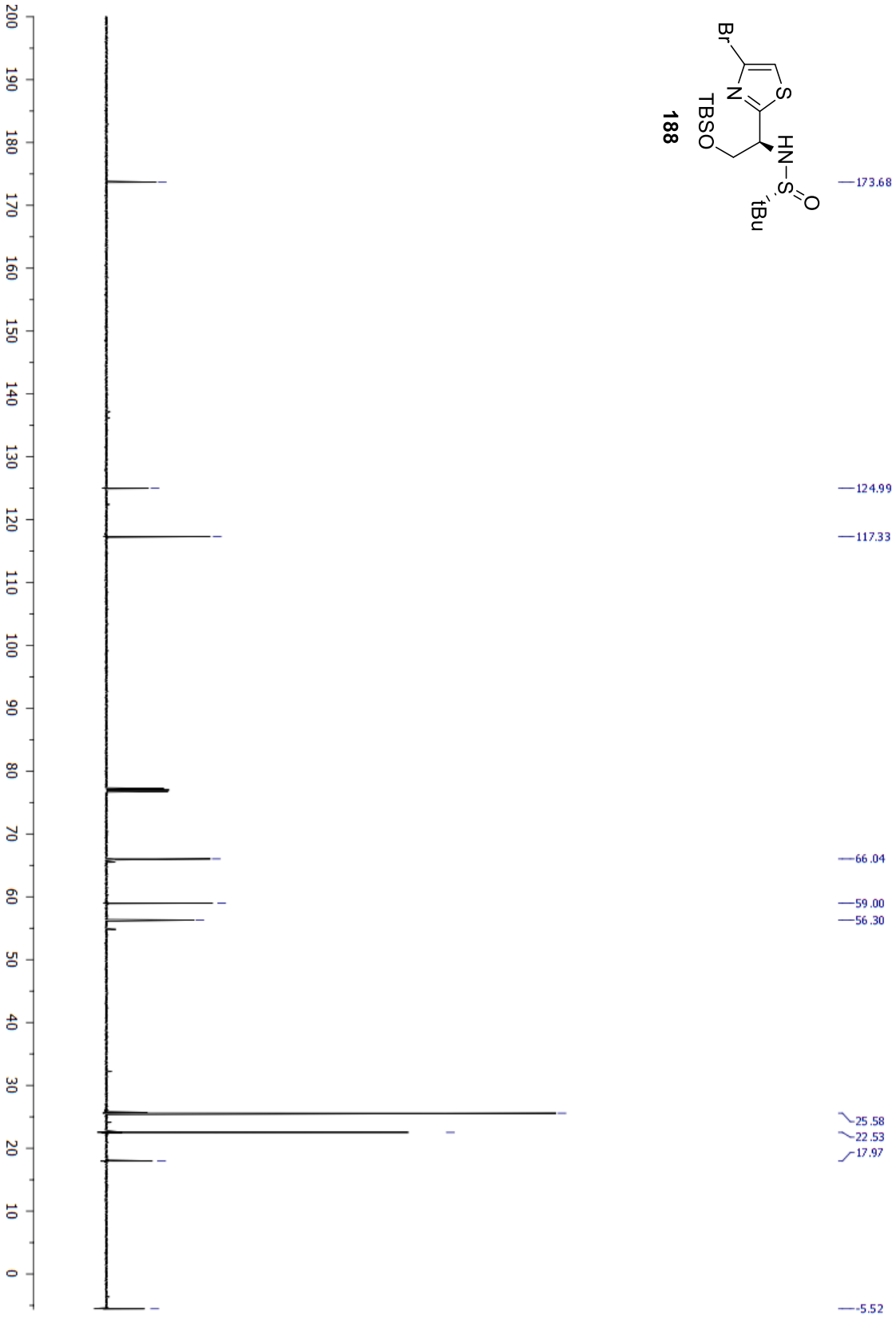

164
1.16
1.16
1.00
2.07
1.12
3.05
3.00
3.04
8.14
6.72
6.71
4.54
4.53
4.34
4.33
4.32
3.95
3.94
1.89
1.88
1.49
1.48
1.22
1.21

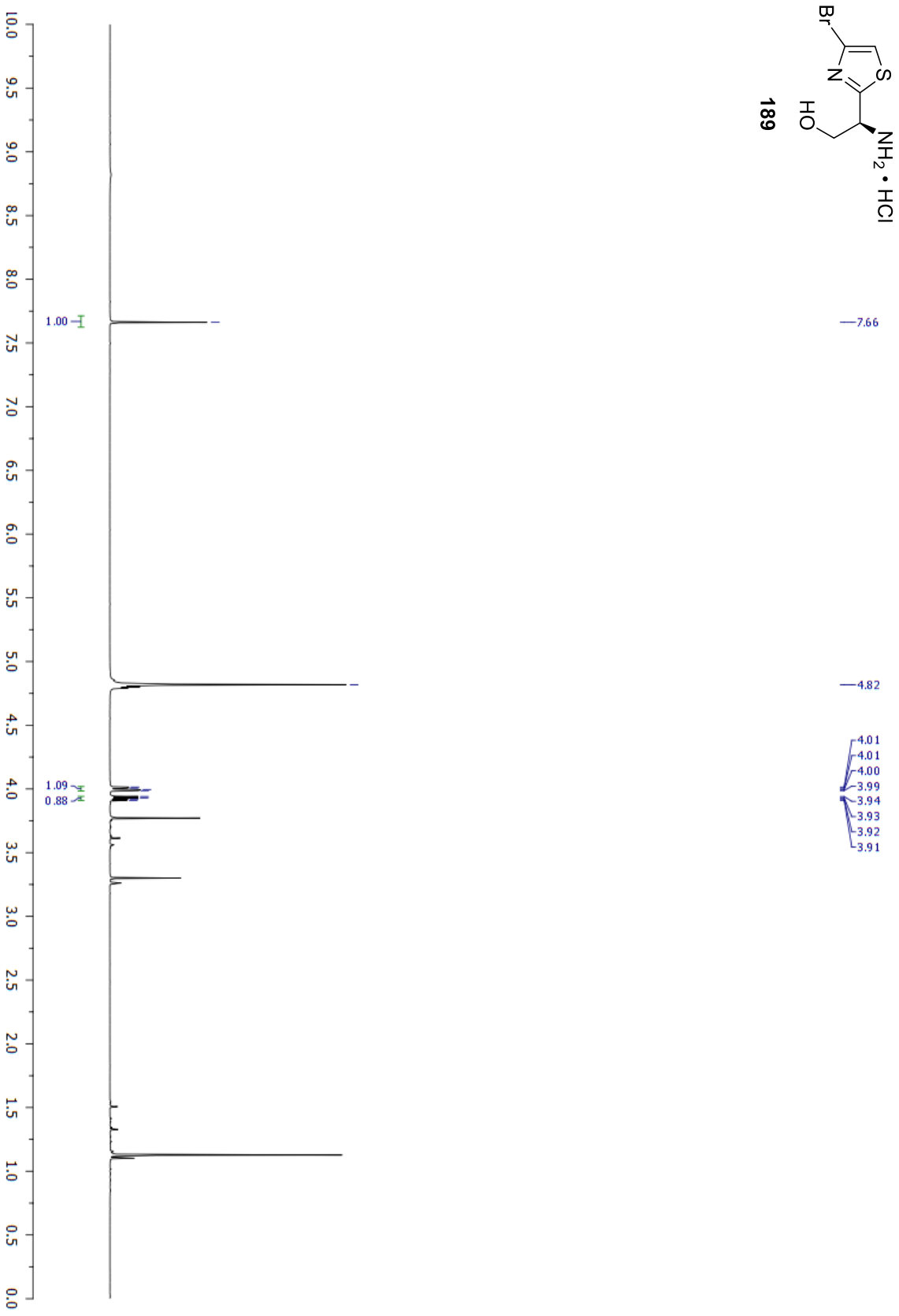

174.97
168.10
167.94
163.14
150.24
130.01
129.68
124.92
68.58
67.48
59.99
59.40
20.76
20.37
14.17
164

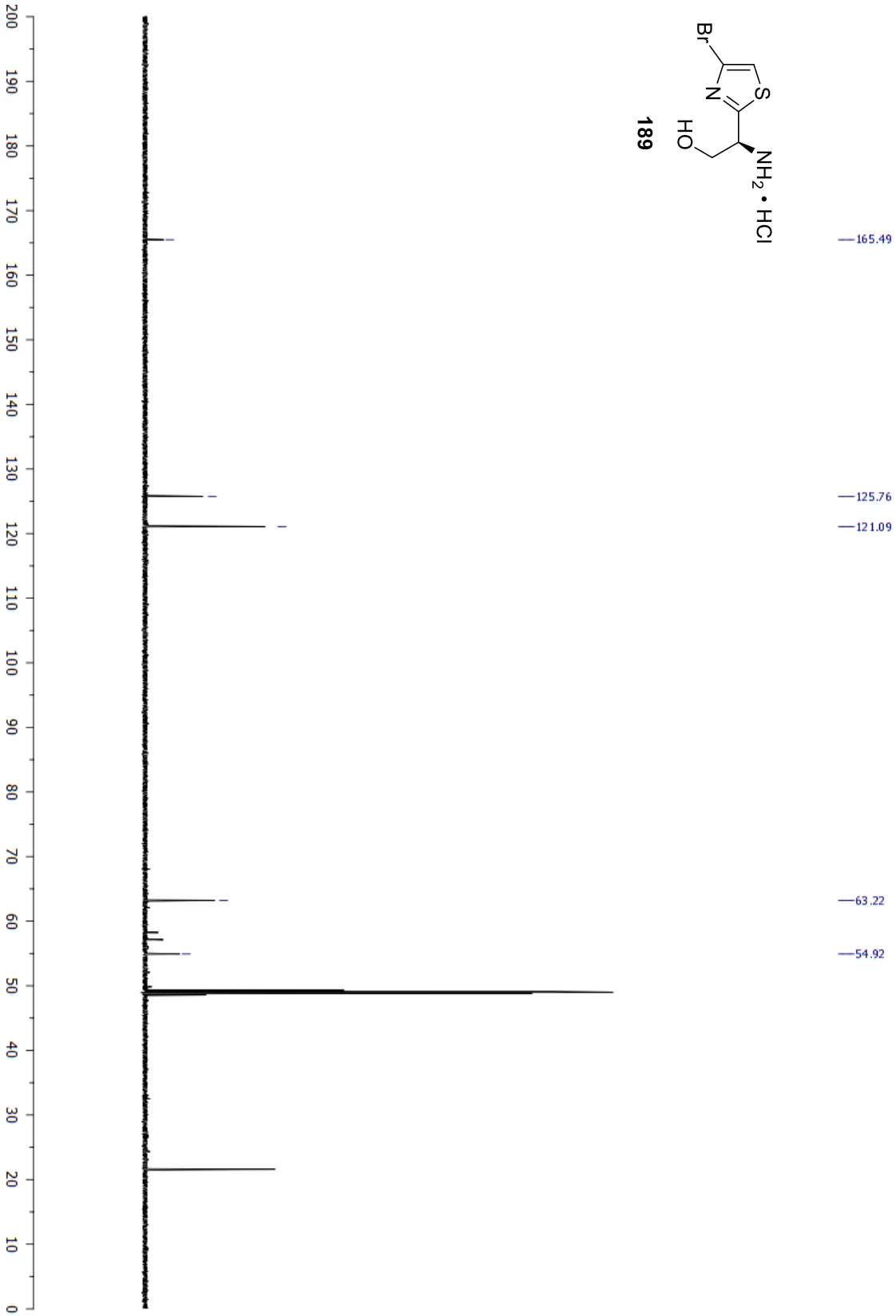

{8.09,124.93}
{6.67,130.60}
{4.48,59.51}
{4.31,68.38}
{4.01,60.12}
{1.85,14.29}
{1.43,20.84}
{1.14,20.51}
f1 (ppm)

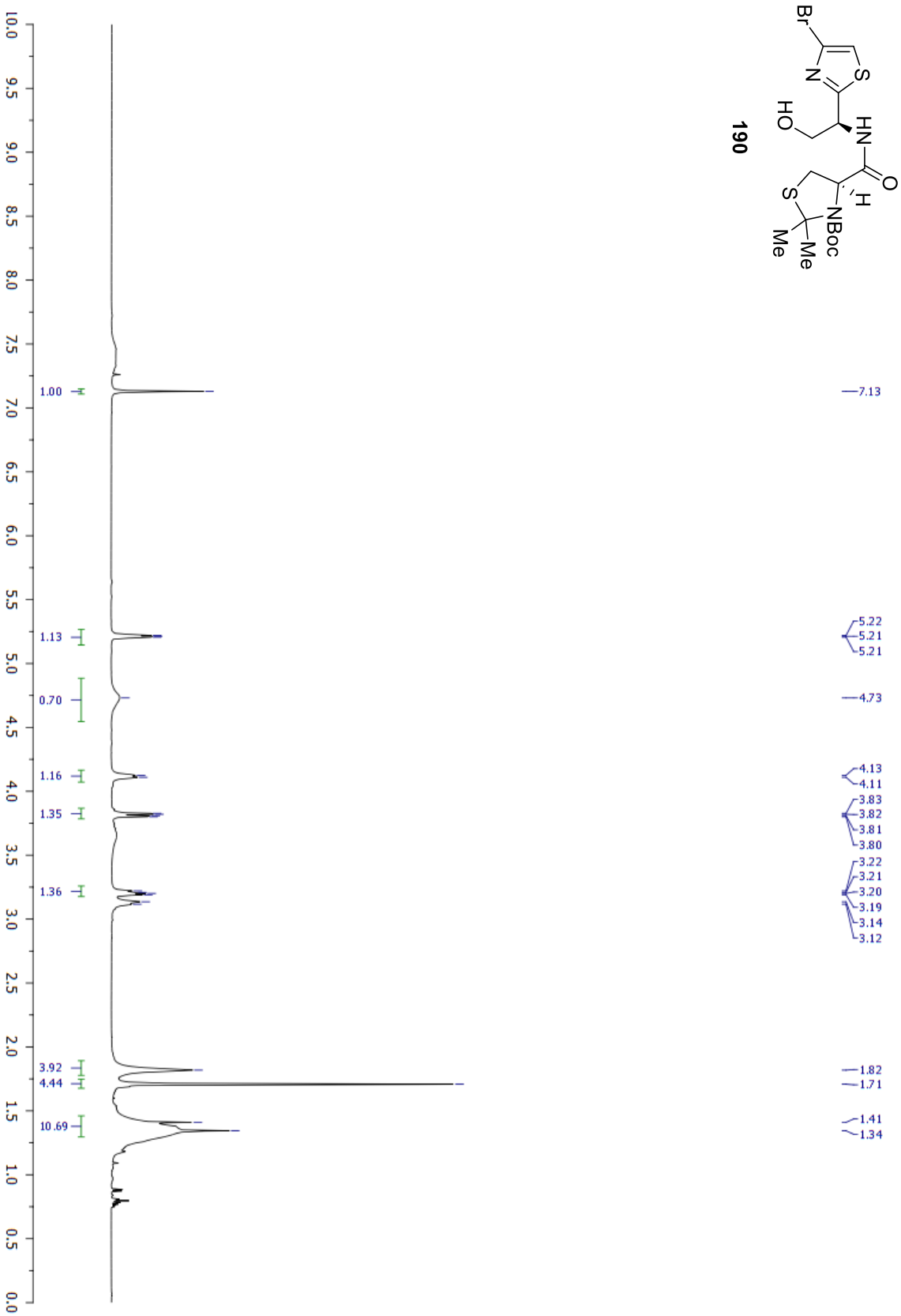

{8.09,150.23}
{8.05,163.08}
{8.06,167.93}
{6.66,168.00}
{4.43,174.92}
{4.45,161.90}
{4.45,68.60}
{3.98,67.50}
{1.80,168.00}
{1.80,129.87}
{1.41,59.95}
{1.18,68.57}
{1.39,67.54}
{1.14,59.36}
f1 (ppm)

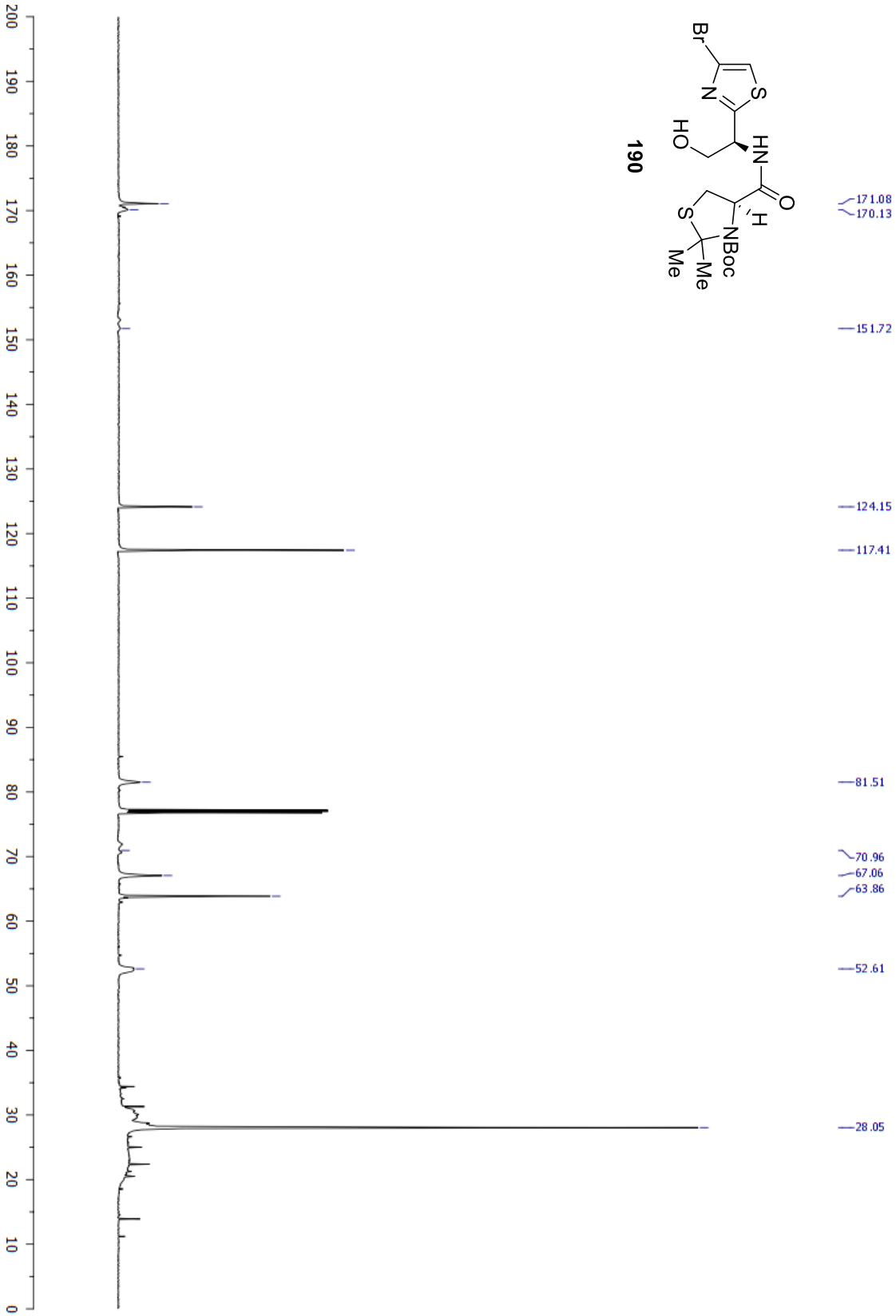

Br
N
S
TBSO
HN
S
O
tBu
188
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
0.77
0.85
0.92
0.99
1.00
9.86
9.73
3.11
3.04
7.16
4.80
4.79
4.79
4.66
4.65
4.17
4.15
4.15
4.09
4.08
4.07
1.30
0.81
0.03
-0.08

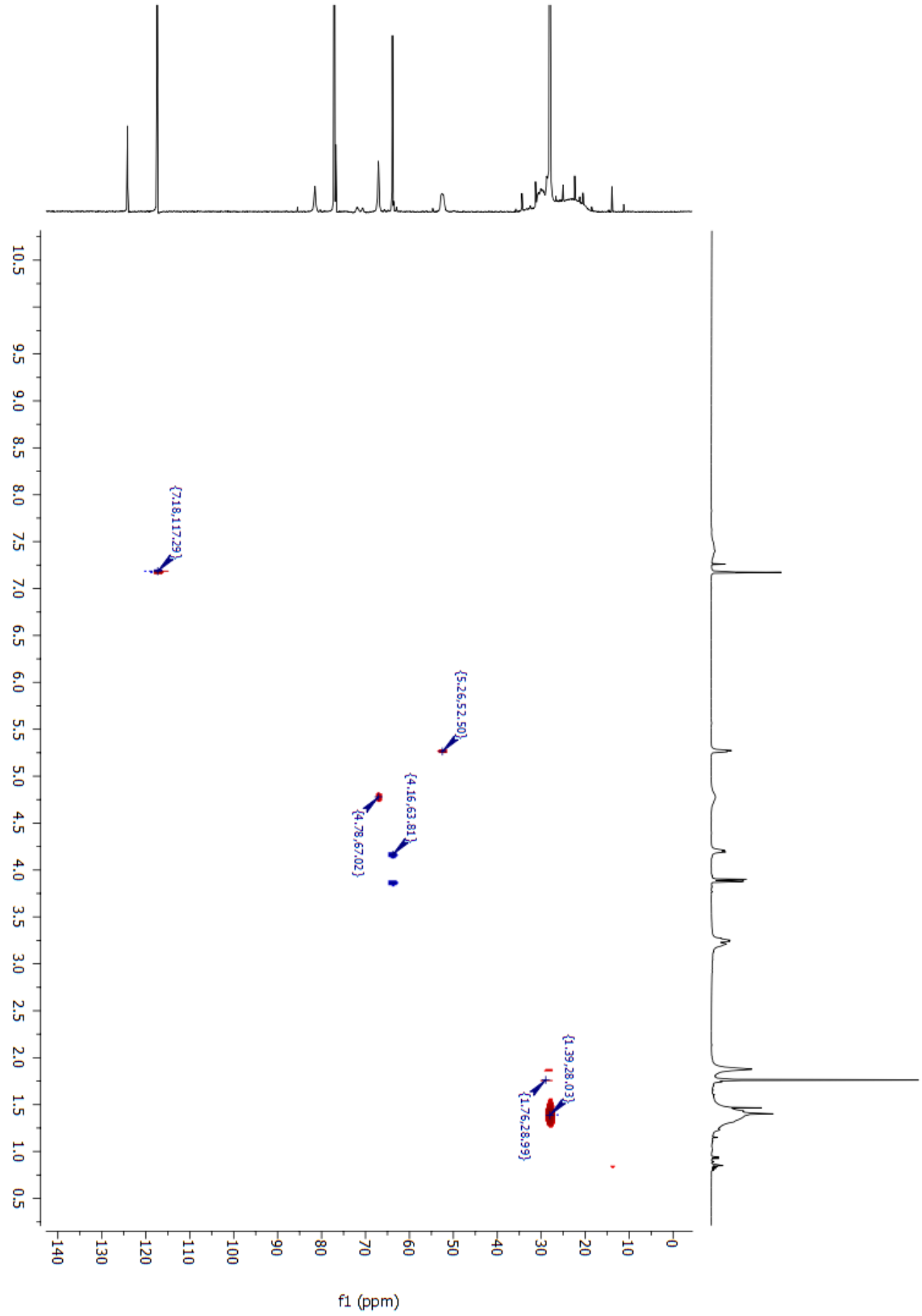

Br
N
S
TBSO
HN
S
O
tBu
188
173.68
124.99
117.33
66.04
59.00
56.30
25.58
22.53
17.97
-5.52
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

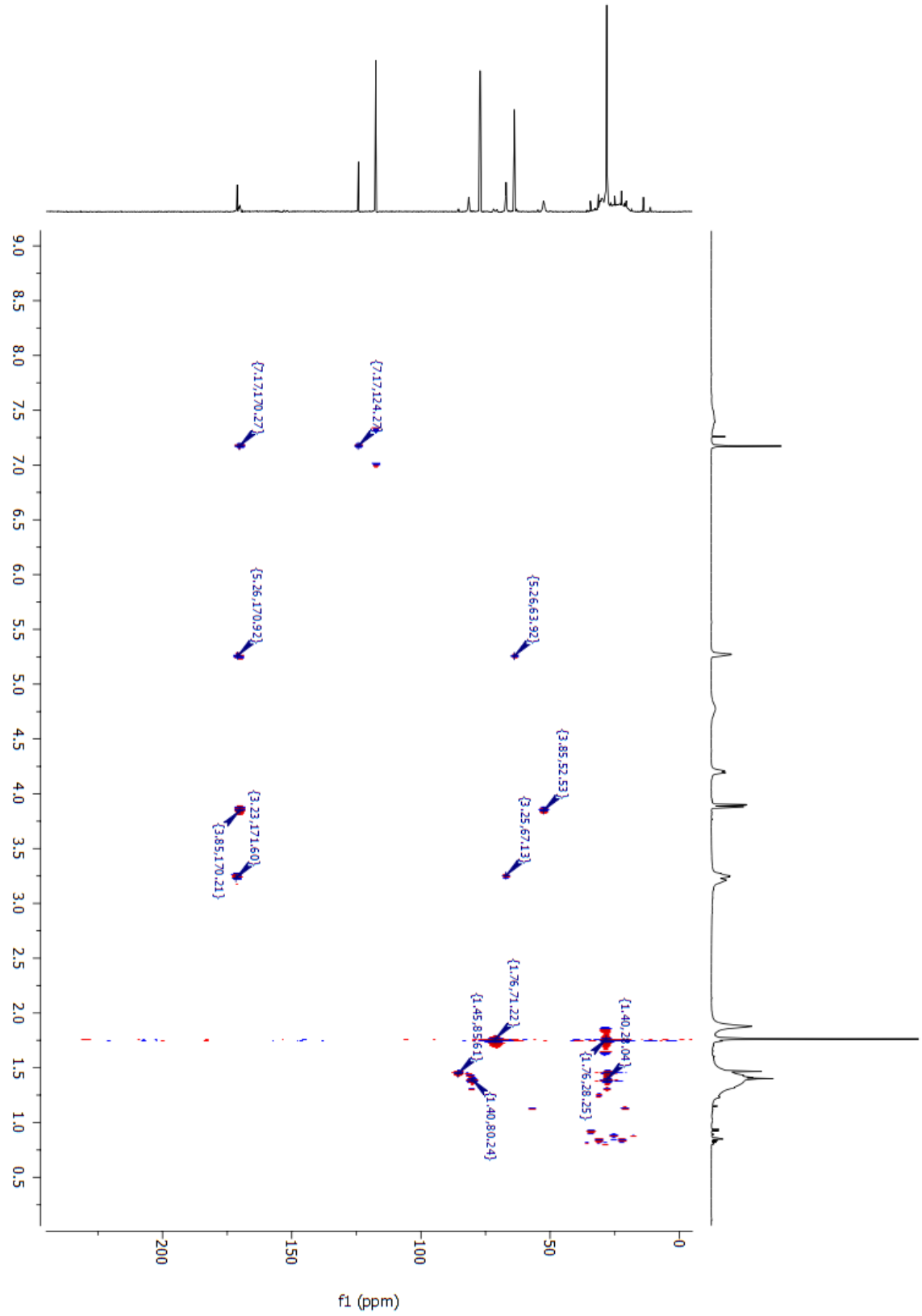

Br
N
S
HO
NH2 • HCl
189
7.66
4.82
4.01
4.01
4.00
3.99
3.94
3.93
3.92
3.91
1.00
1.09
0.88

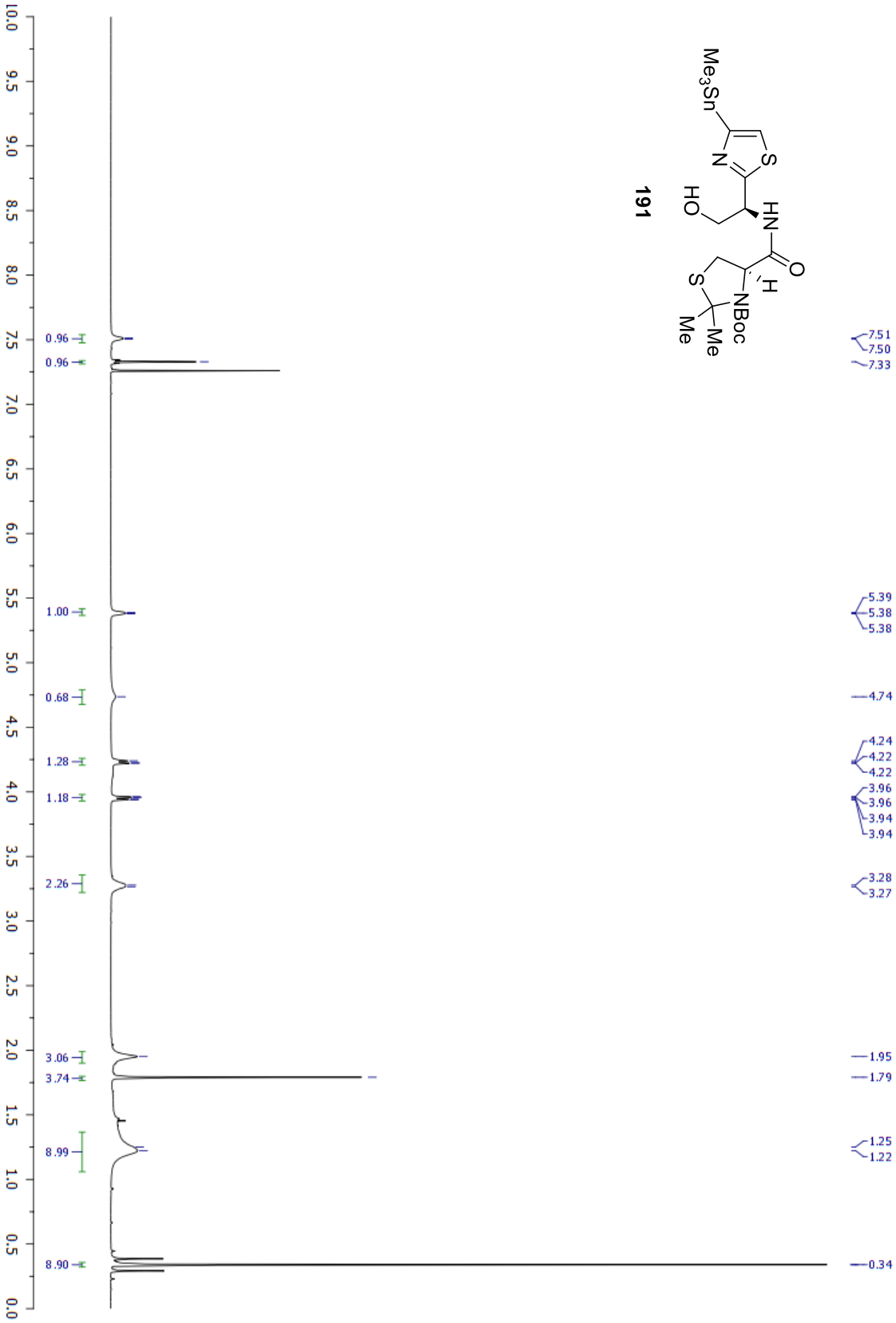

Br
S
N
HO
NH2 • HCl
189
165.49
125.76
121.09
63.22
54.92
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

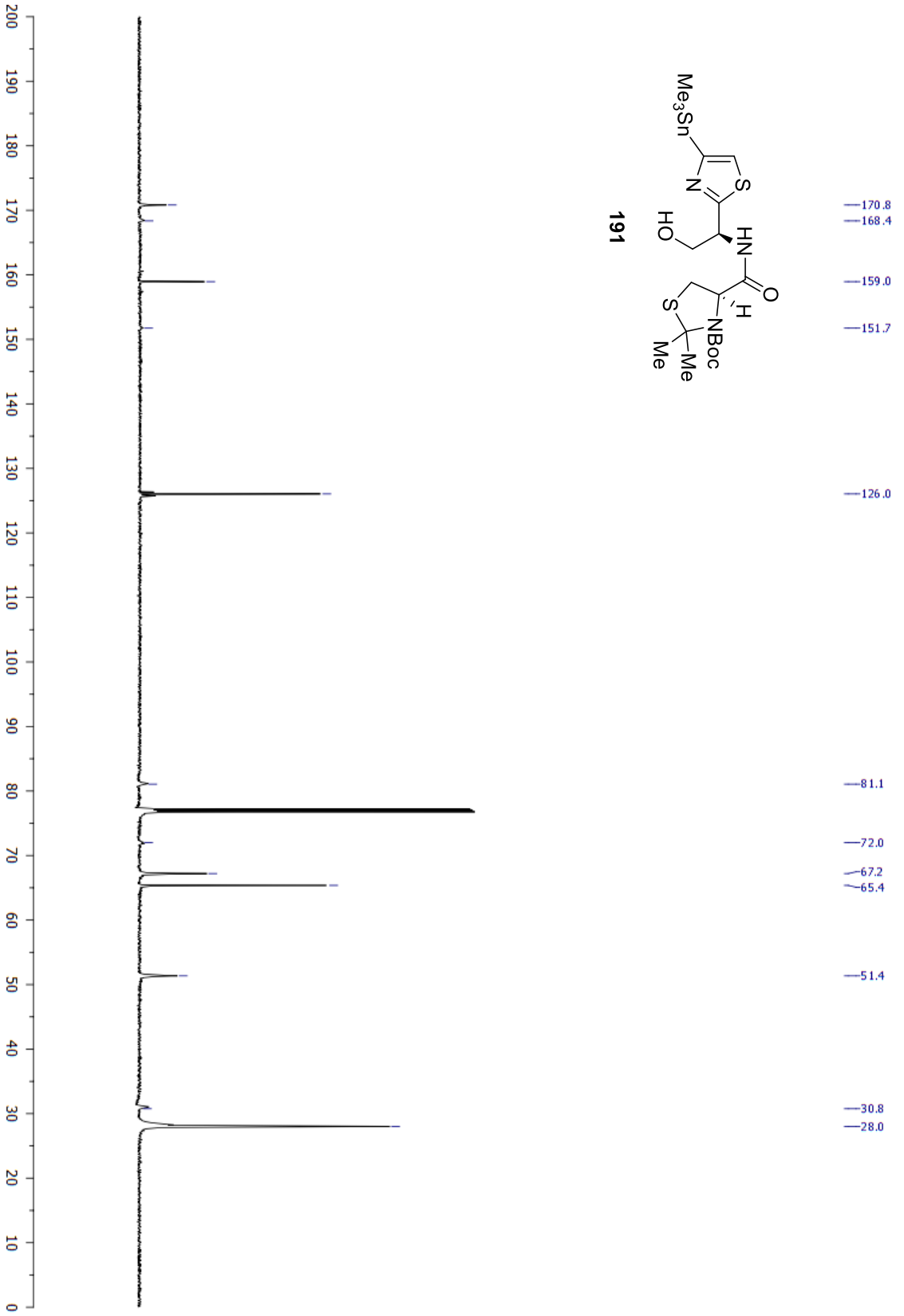

Br
N
S
HO
HN
O
H
S
NBoc
Me
Me
190
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.00
1.13
0.70
1.16
1.35
1.36
3.92
4.44
10.69
7.13
5.22
5.21
5.21
4.73
4.13
4.11
3.83
3.82
3.81
3.80
3.22
3.21
3.20
3.19
3.14
3.12
1.82
1.71
1.41
1.34

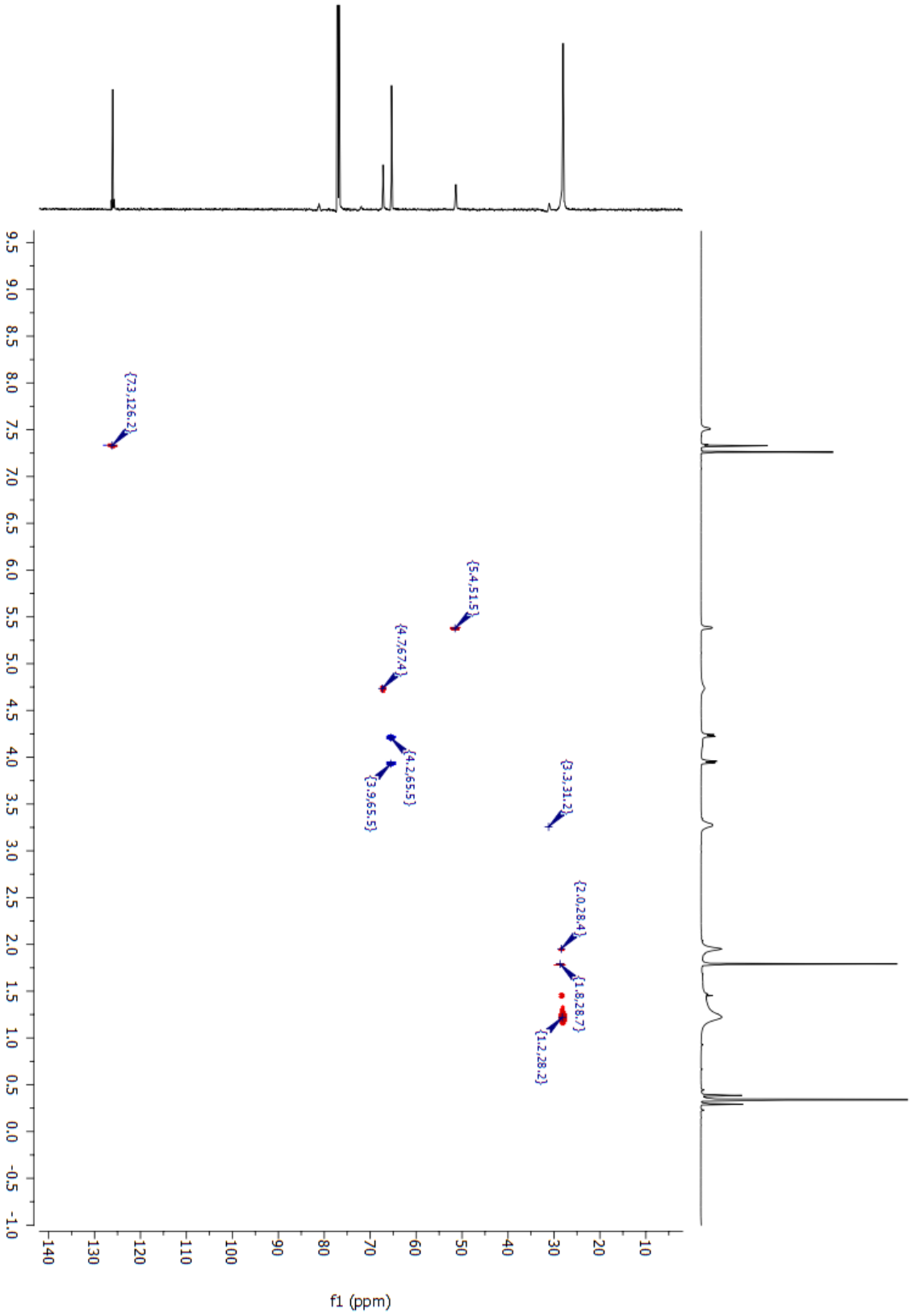

190
Br
N
S
HO
HN
O
H
S
NBoc
Me
Me
171.08
170.13
151.72
124.15
117.41
81.51
70.96
67.06
63.86
52.61
28.05
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

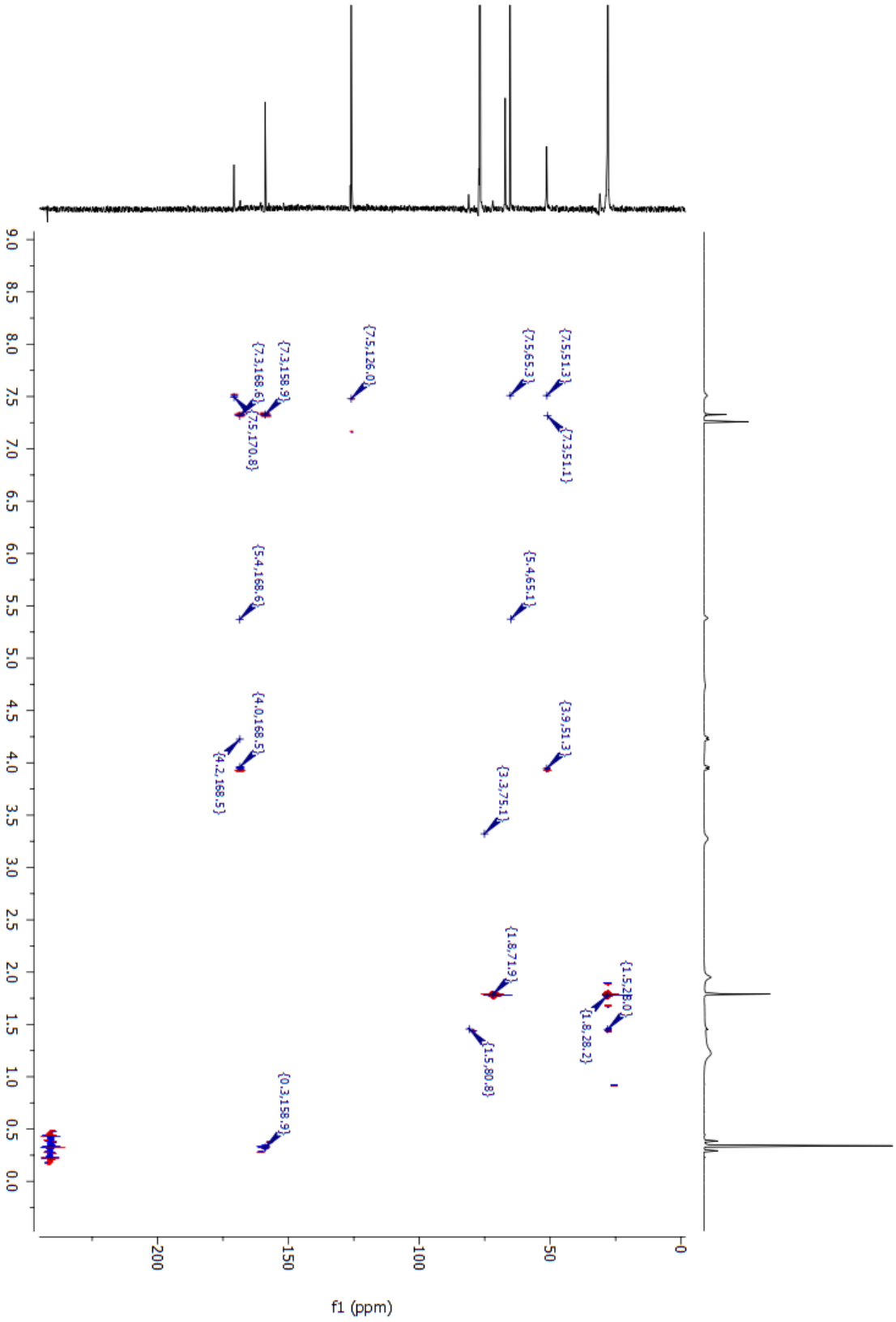

{7.18,117.29}
{5.26,52.50}
{4.16,63.81}
{4.78,67.02}
{1.39,28.03}
{1.76,28.99}
f1 (ppm)

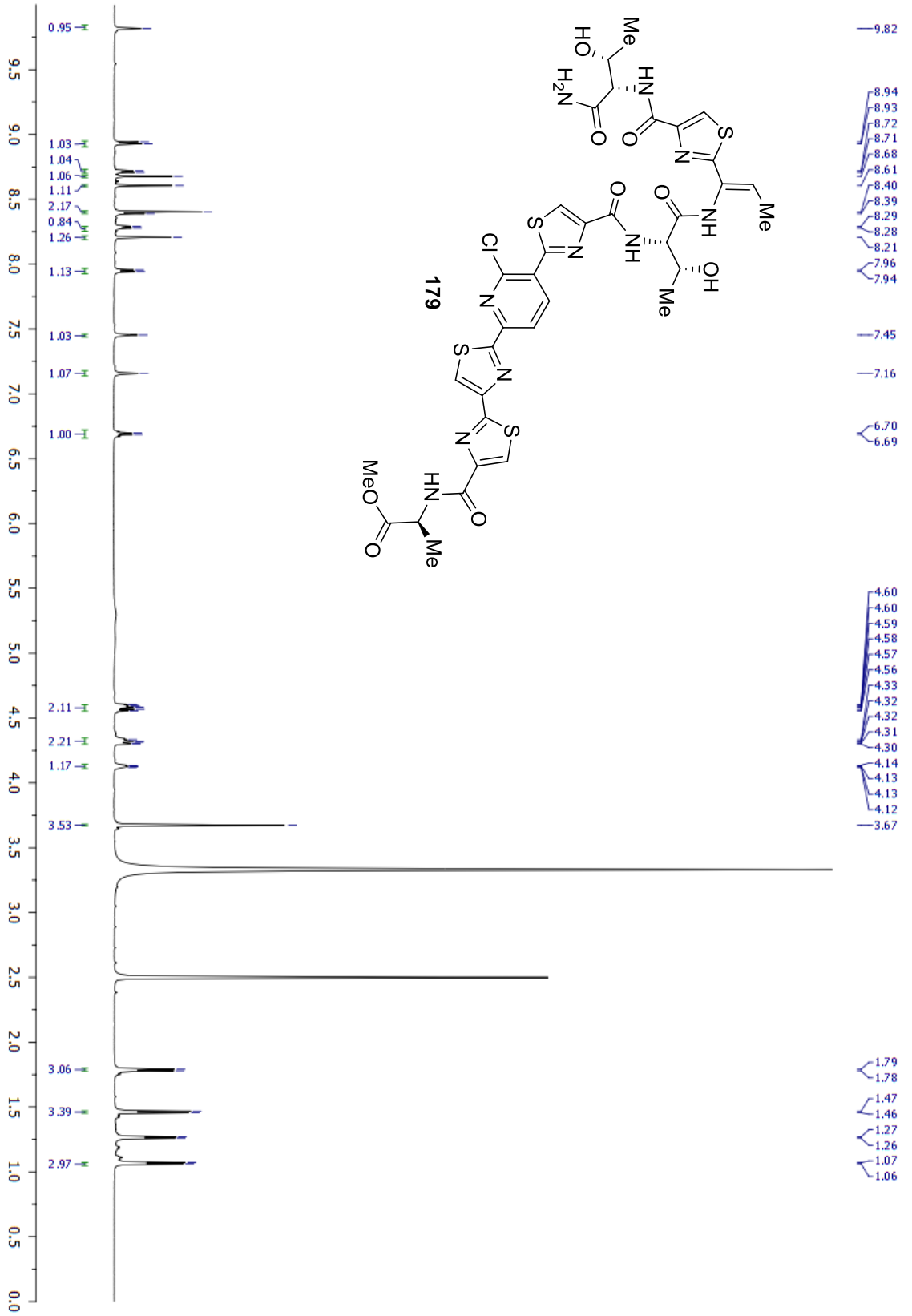

{7.17,170.27}
{7.17,124.27}
{5.26,170.92}
{5.26,63.92}
{3.85,52.53}
{3.23,171.60}
{3.85,170.21}
{3.25,67.13}
{1.76,71.22}
{1.45,85.61}
{1.40,28.04}
{1.76,28.25}
{1.40,80.24}
f1 (ppm)

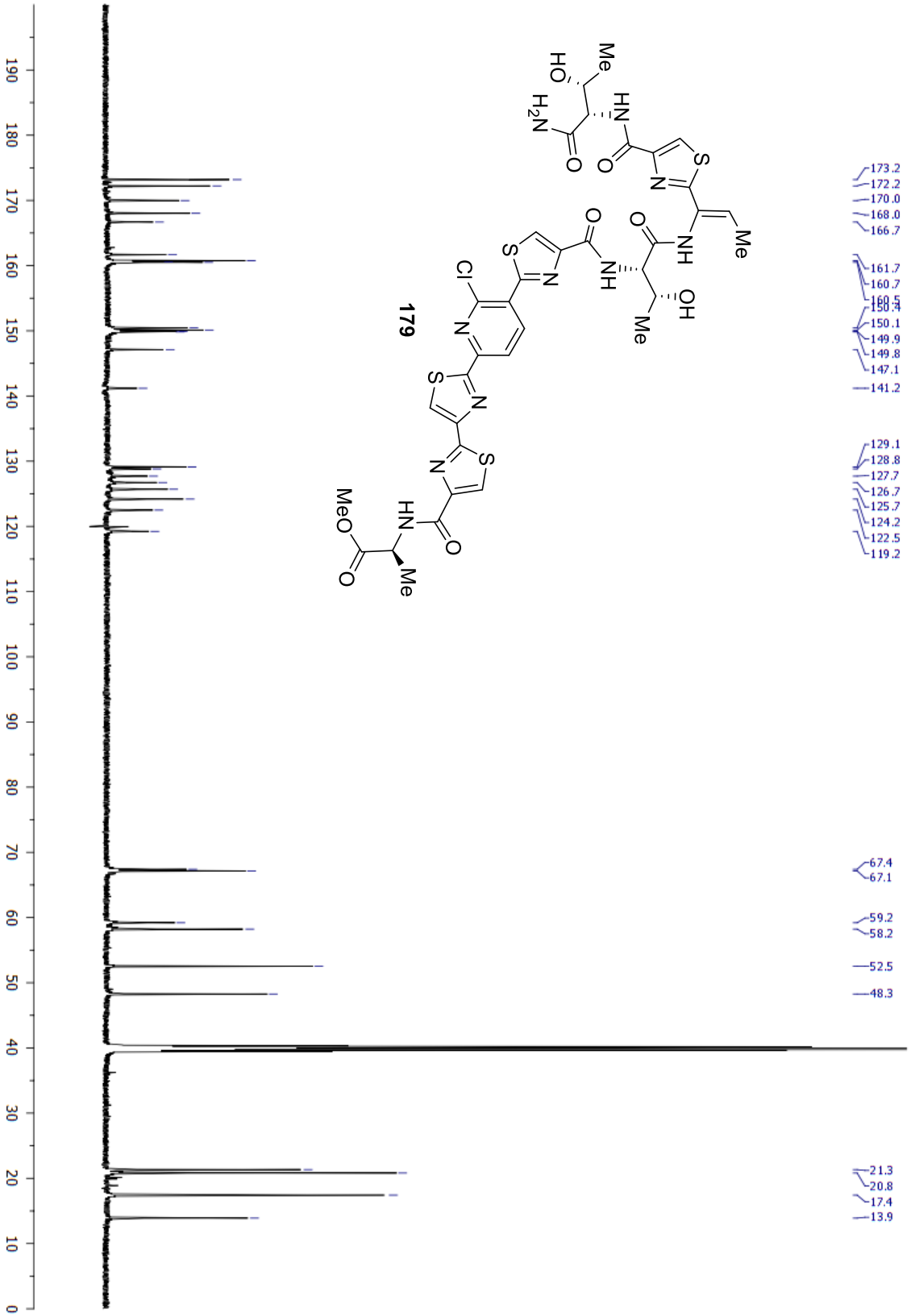

Me3Sn
N
S
HO
HN
O
H
S
NBoc
Me
Me
191
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0.96
0.96
1.00
0.68
1.28
1.18
2.26
3.06
3.74
8.99
8.90
7.51
7.50
7.33
5.39
5.38
5.38
4.74
4.24
4.22
4.22
3.96
3.96
3.94
3.94
3.28
3.27
1.95
1.79
1.25
1.22
0.34

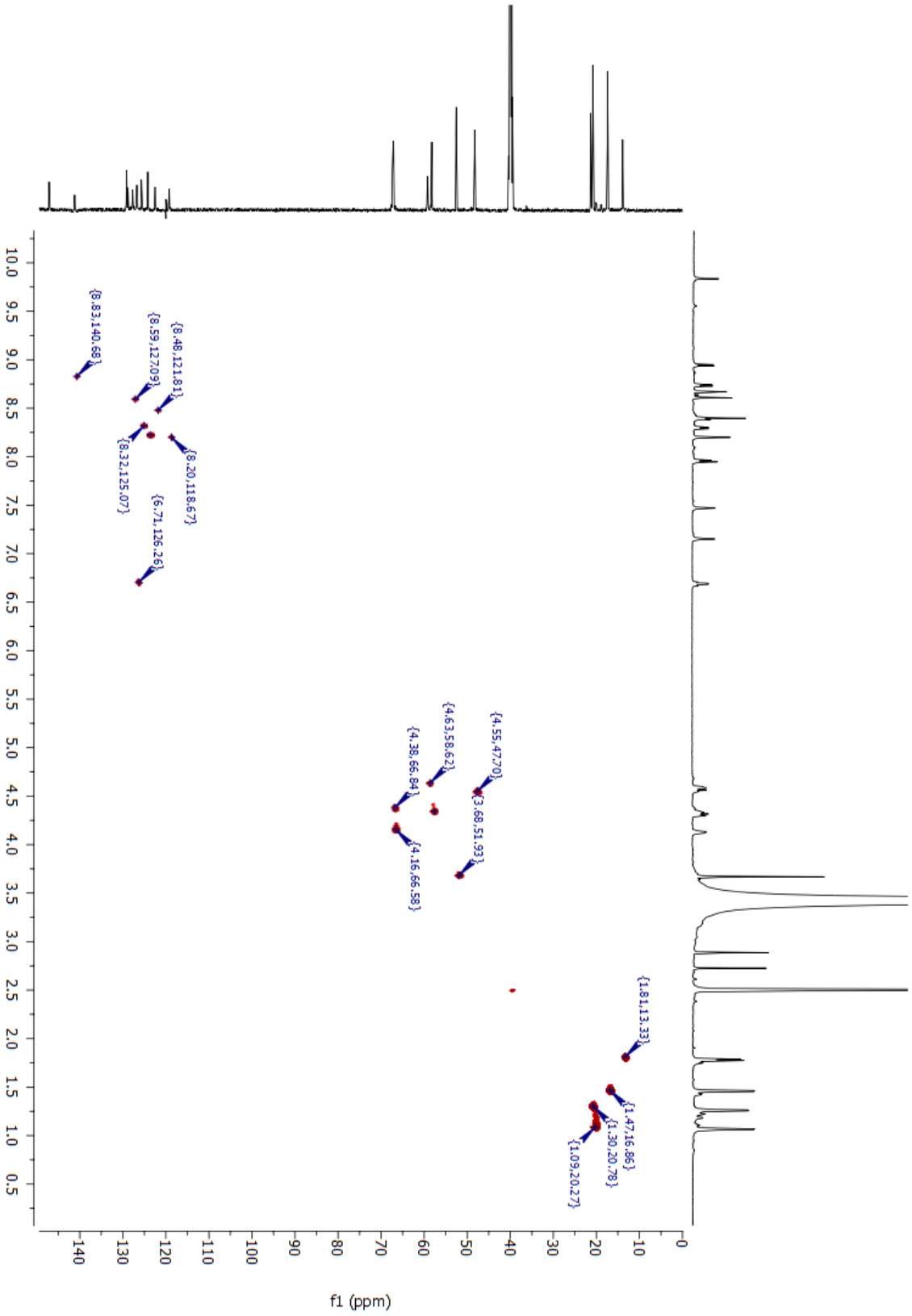

Me3Sn
N
S
HO
HN
O
H
S
NBoc
Me
Me
191
170.8
168.4
159.0
151.7
126.0
81.1
72.0
67.2
65.4
51.4
30.8
28.0
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

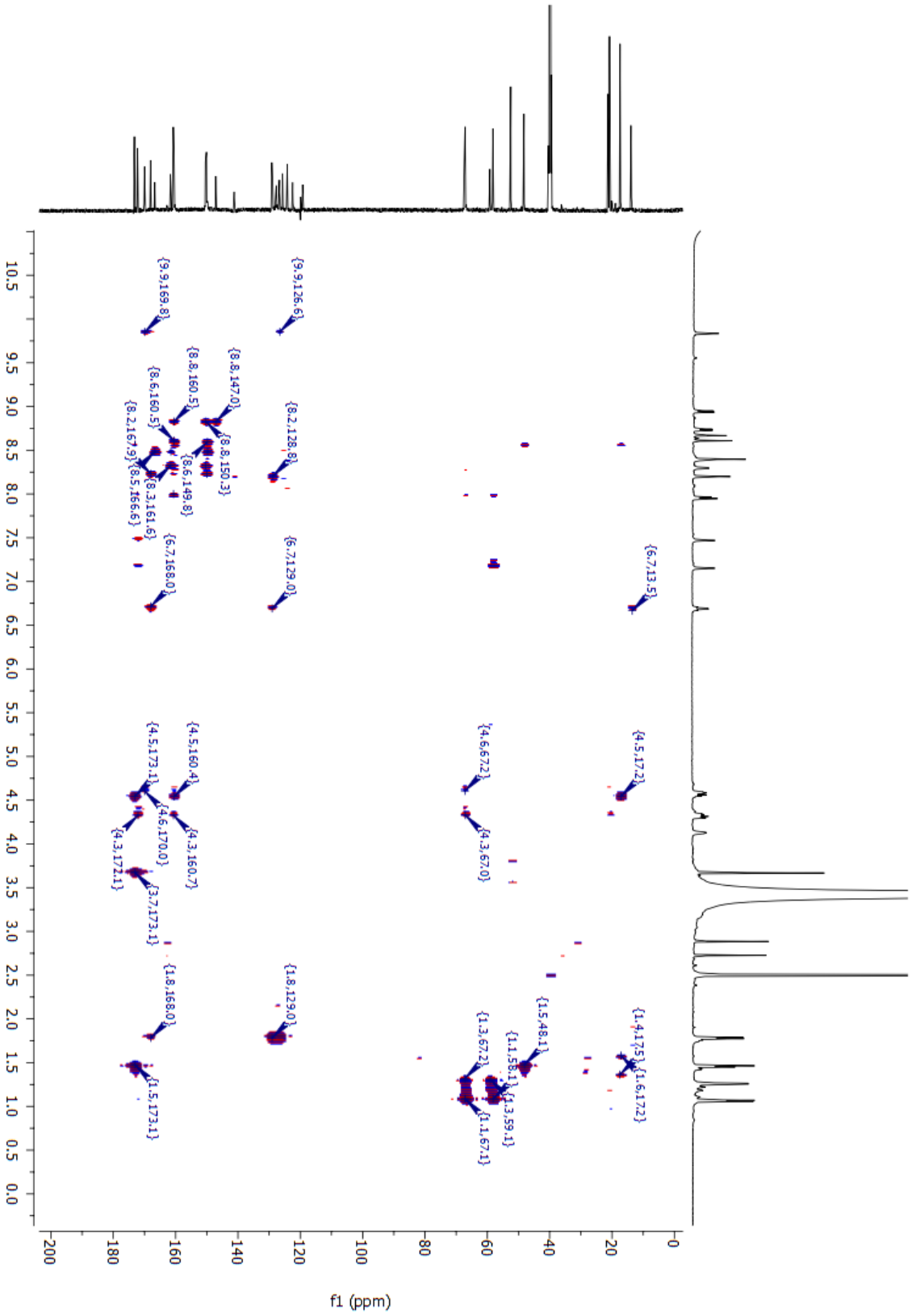

{7.3,126.2}
{5.4,51.5}
{4.7,67.4}
{4.2,65.5}
{3.9,65.5}
{3.3,31.2}
{2.0,28.4}
{1.8,28.7}
{1.2,28.2}
f1 (ppm)

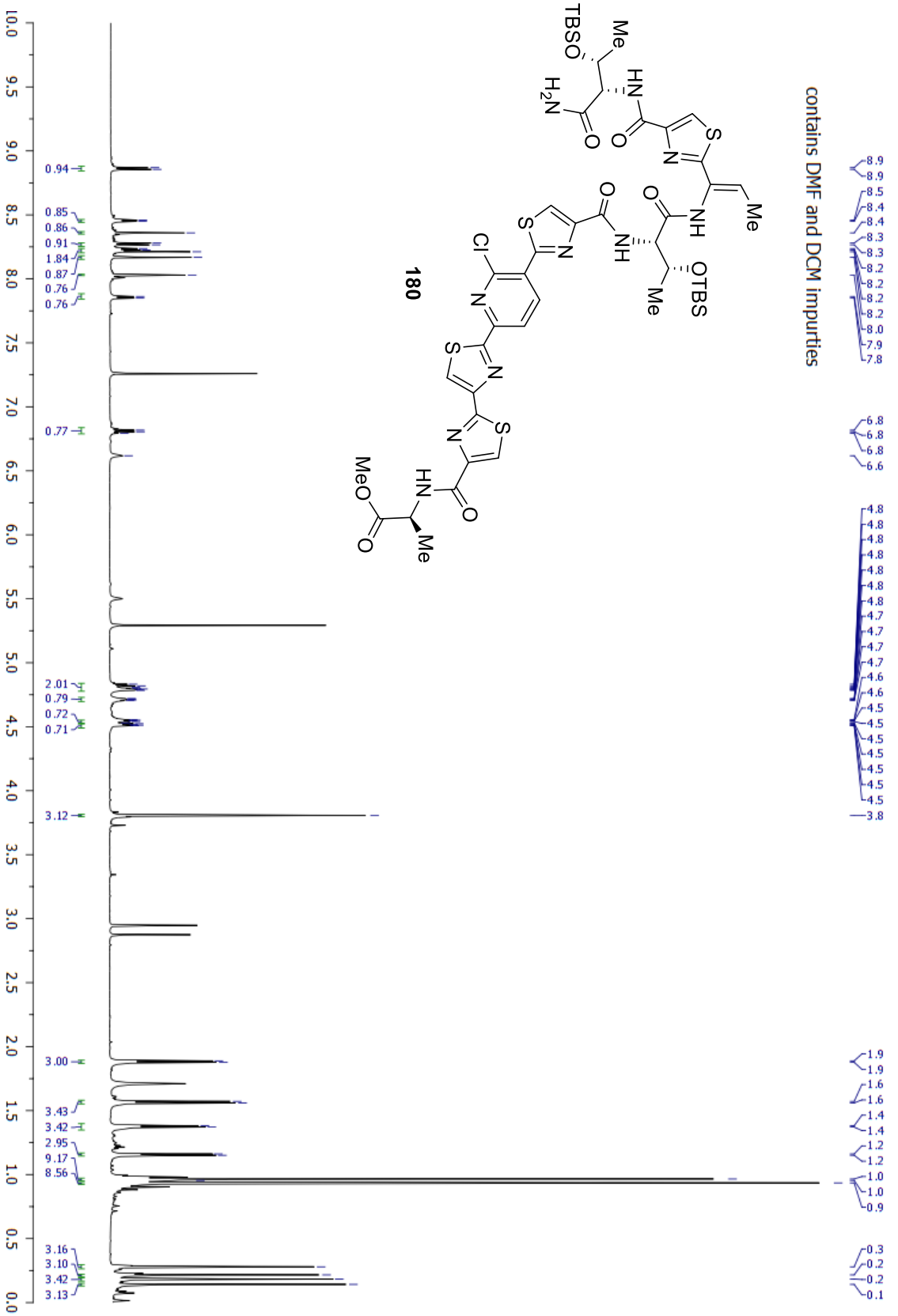

{7.5,126.0}
{7.5,65.3}
{7.5,51.3}
{7.3,158.9}
{7.3,168.6}
{7.5,170.8}
{7.3,51.1}
{5.4,168.6}
{5.4,65.1}
{4.0,168.5}
{4.2,168.5}
{3.9,51.3}
{3.3,75.1}
{1.8,71.9}
{1.5,28.0}
{1.8,28.2}
{1.5,80.8}
{0.3,158.9}
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
200
150
100
50
0
f1 (ppm)

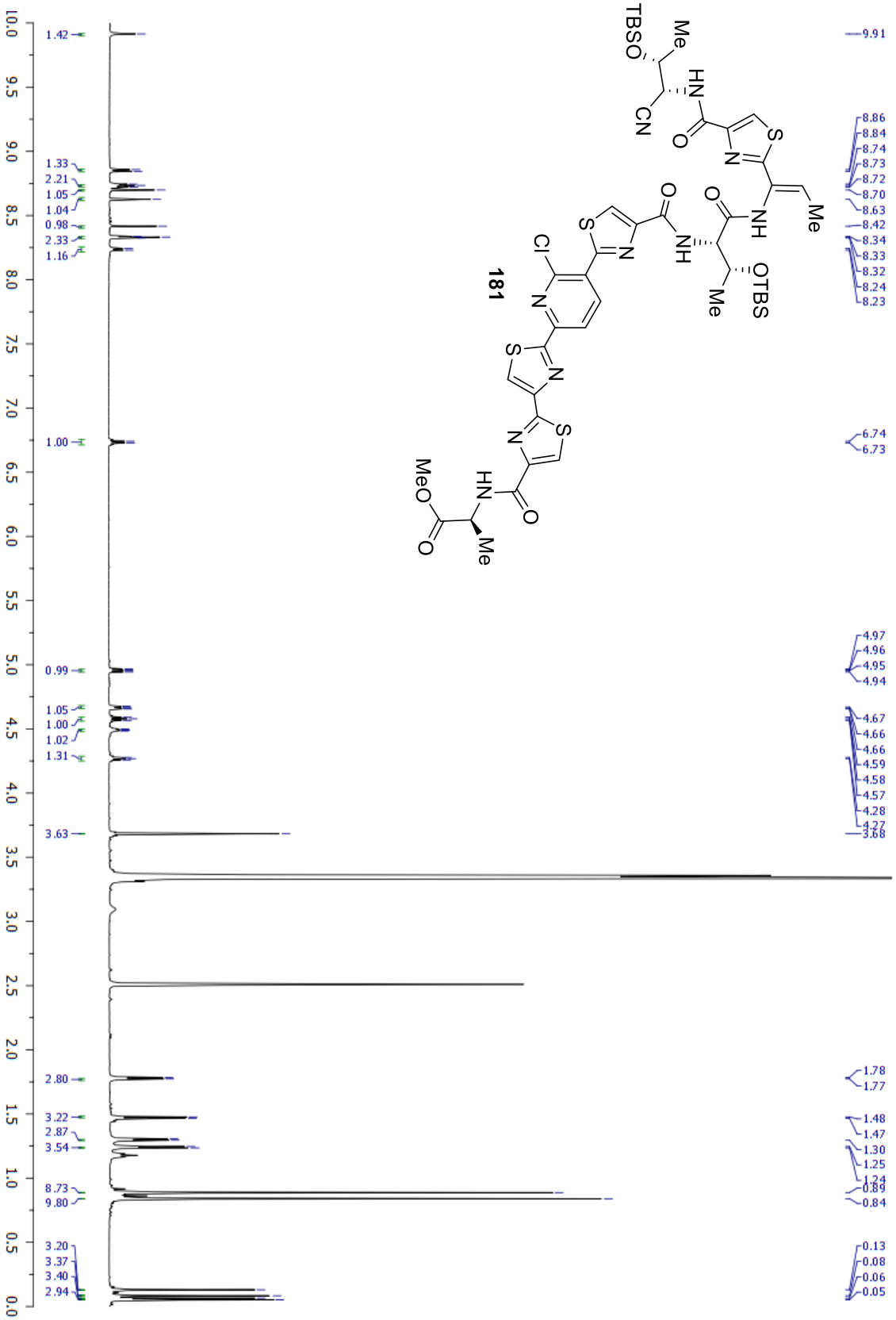

179
0.95
1.03
1.04
1.06
1.11
2.17
0.84
1.26
1.13
1.03
1.07
1.00
2.11
2.21
1.17
3.53
3.06
3.39
2.97
9.82
8.94
8.93
8.72
8.71
8.68
8.61
8.40
8.39
8.29
8.28
8.21
7.96
7.94
7.45
7.16
6.70
6.69
4.60
4.60
4.59
4.58
4.57
4.56
4.33
4.32
4.32
4.31
4.30
4.14
4.13
4.13
4.12
3.67
1.79
1.78
1.47
1.46
1.27
1.26
1.07
1.06

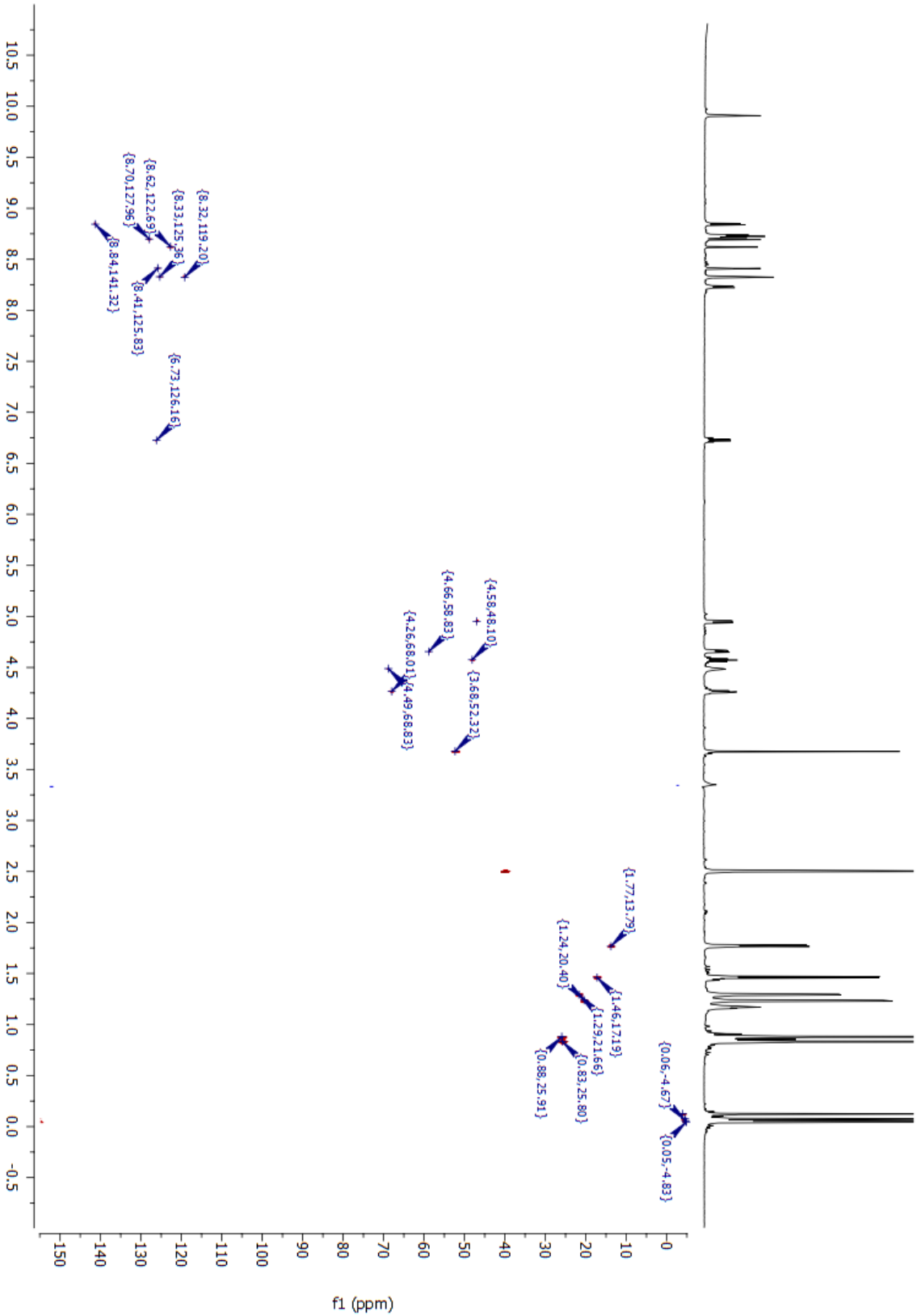

179
173.2
172.2
170.0
168.0
166.7
161.7
160.7
160.5
160.4
150.1
149.9
149.8
147.1
141.2
129.1
128.8
127.7
126.7
125.7
124.2
122.5
119.2
67.4
67.1
59.2
58.2
52.5
48.3
21.3
20.8
17.4
13.9


{8.83,140.68}
{8.59,127.09}
{8.48,121.81}
{8.32,125.07}
{8.20,118.67}
{6.71,126.26}
{4.63,58.62}
{4.55,47.70}
{4.38,66.84}
{3.68,51.93}
{4.16,66.58}
{1.81,13.33}
{1.47,16.86}
{1.30,20.78}
{1.09,20.27}
f1 (ppm)


f1 (ppm)


180
contains DMF and DCM impurities


181
TBSO
Me
HN
CN
O
S
N
NH
OTBS
Cl
MeO
1.42
1.33
2.21
1.05
1.04
0.98
2.33
1.16
1.00
0.99
1.05
1.00
1.02
1.31
3.63
2.80
3.22
2.87
3.54
8.73
9.80
3.20
3.37
3.40
2.94
9.91
8.86
8.84
8.74
8.73
8.72
8.70
8.63
8.42
8.34
8.33
8.32
8.24
8.23
6.74
6.73
4.97
4.96
4.95
4.94
4.67
4.66
4.66
4.59
4.58
4.57
4.28
4.27
3.68
1.78
1.77
1.48
1.47
1.30
1.25
1.24
0.89
0.84
0.13
0.08
0.06
0.05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{8.70,127.96}
{8.84,141.32}
{8.41,125.83}
{6.73,126.16}
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{3.68,52.32}
{4.26,68.01}
{4.49,68.83}
{1.77,13.79}
{1.24,20.40}
{1.46,17.19}
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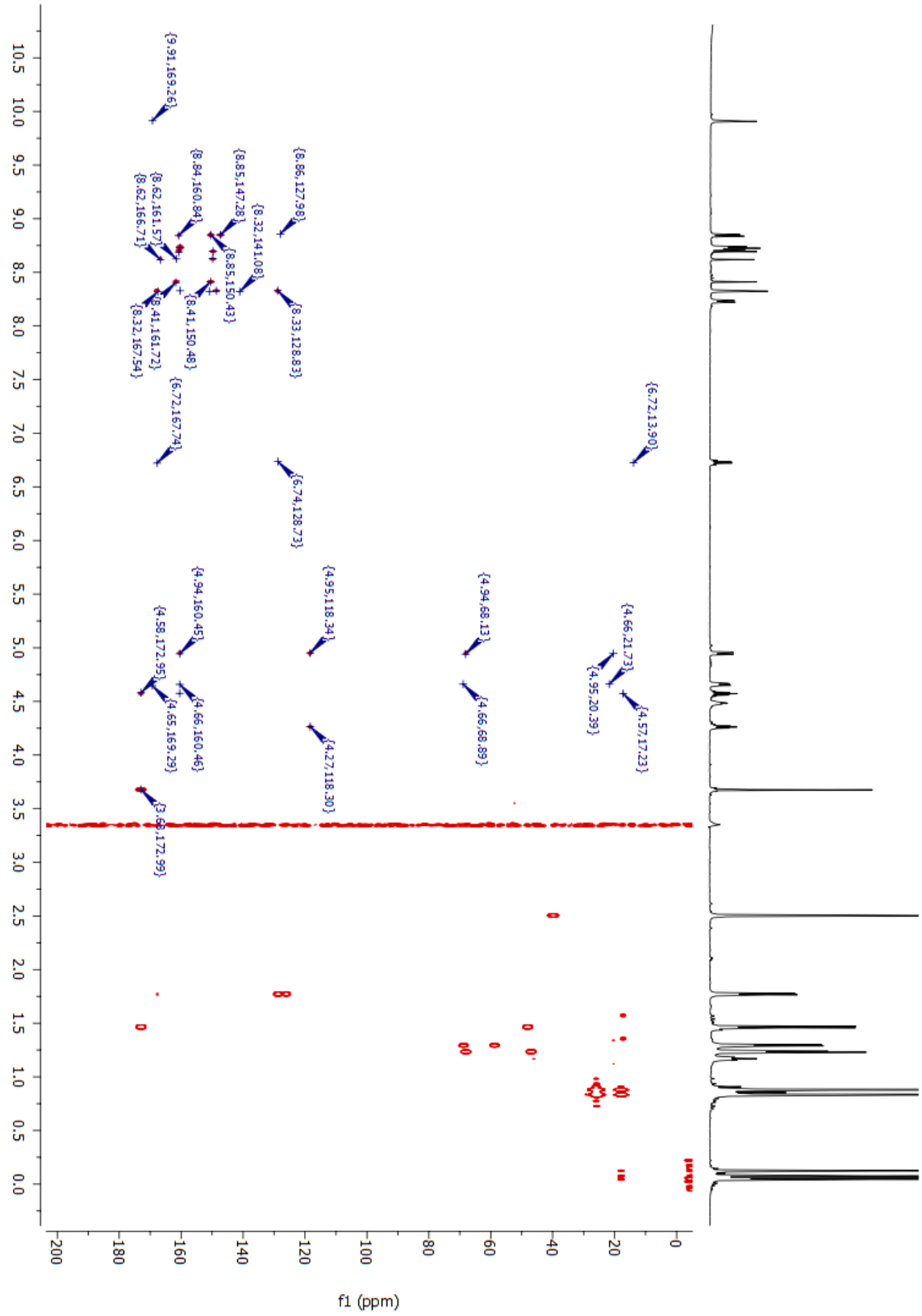
f1 (ppm)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{8.85,147.28}
{8.62,161.57}
{8.62,166.71}
{8.32,141.08}
{8.85,150.43}
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{8.33,128.83}
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{6.74,128.73}
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{4.66,160.46}
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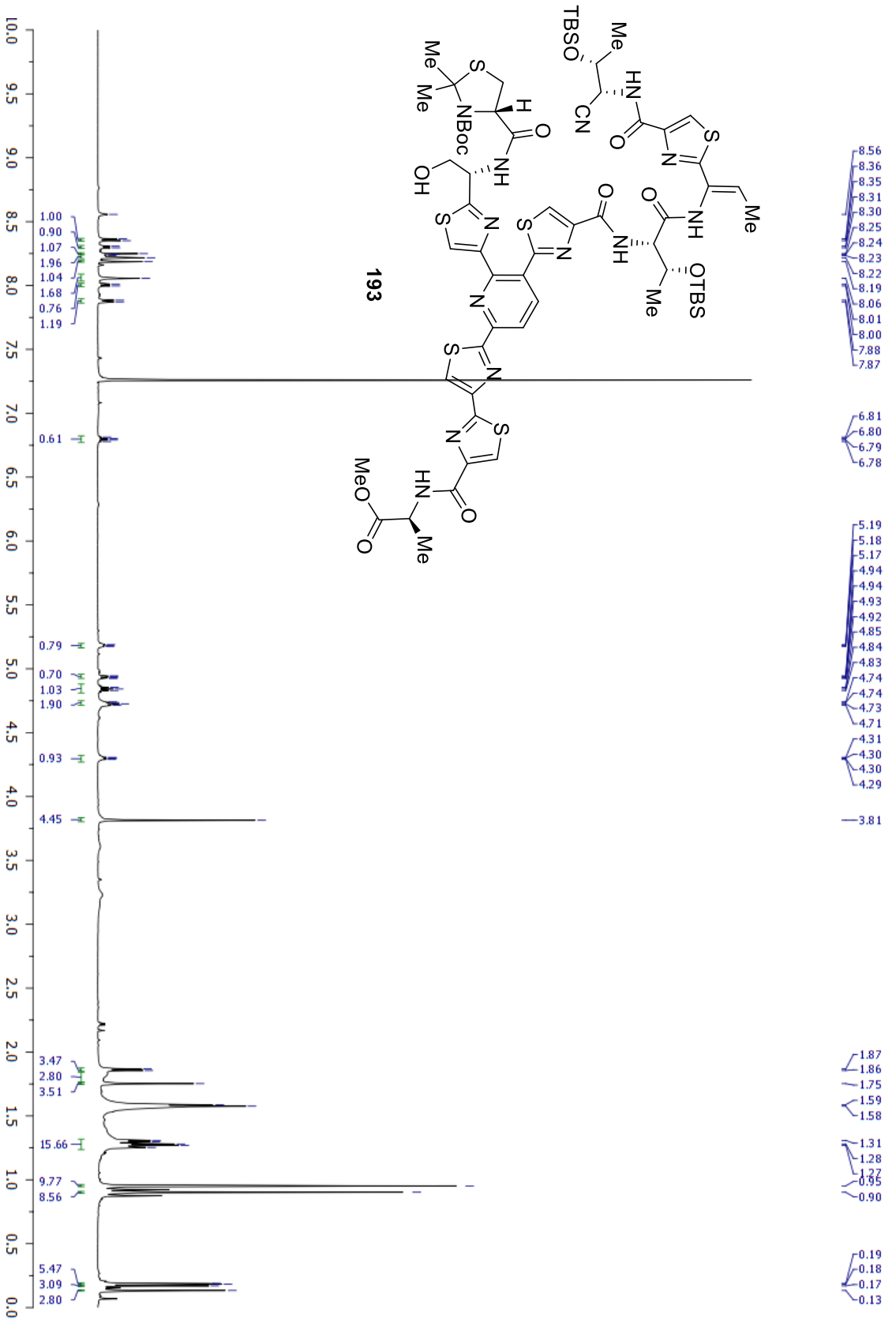
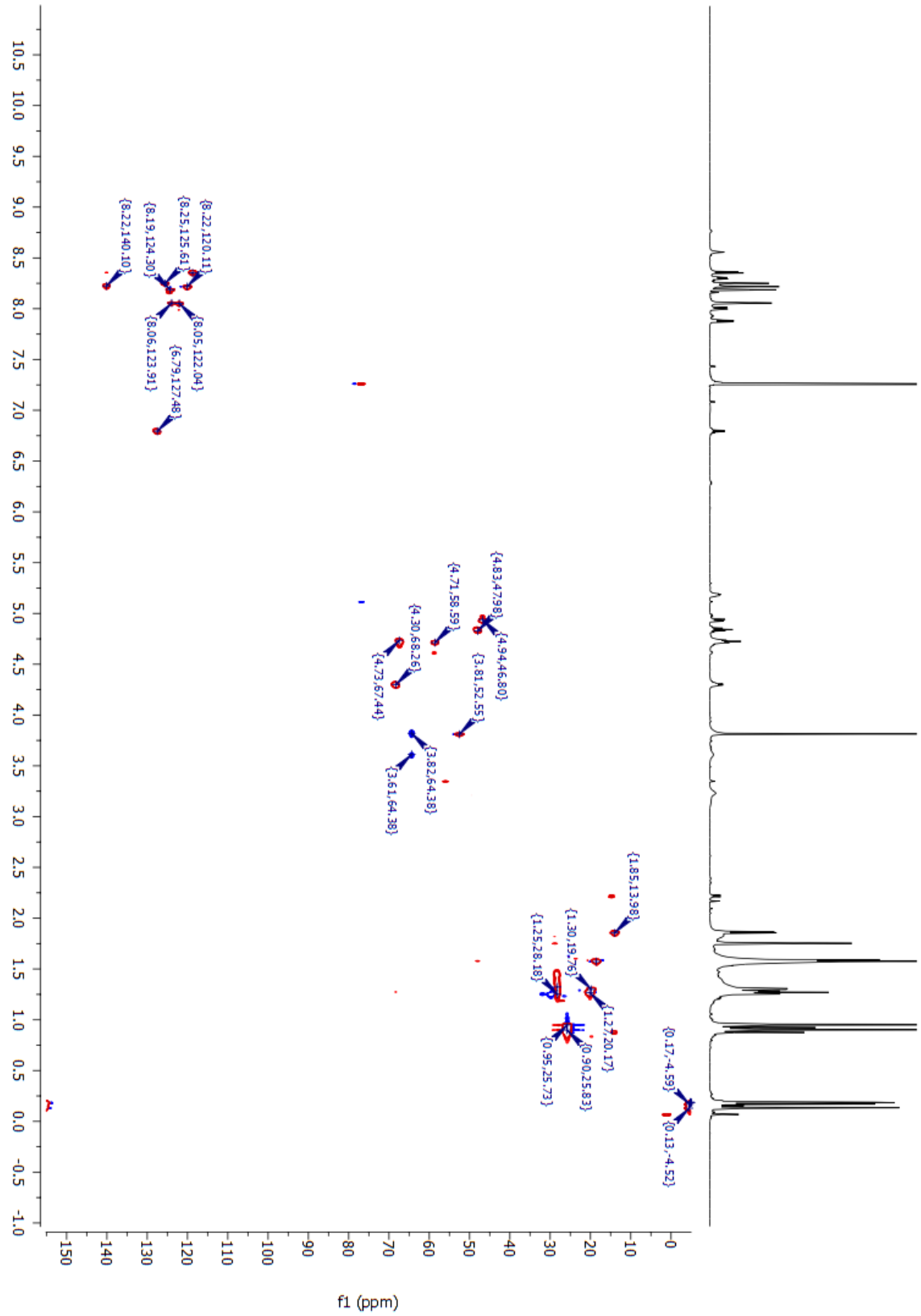
f1 (ppm)


193
Me
Me
S
H
NBoc
O
NH
OH
TBSO
Me
HN
CN
O
S
N
Me
O
NH
OTBS
Me
MeO
HN
Me
10.0
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
0.0
1.00
0.90
1.07
1.96
1.04
1.68
0.76
1.19
0.61
0.79
0.70
1.03
1.90
0.93
4.45
3.47
2.80
3.51
15.66
9.77
8.56
5.47
3.09
2.80
8.56
8.36
8.35
8.31
8.30
8.25
8.24
8.23
8.22
8.19
8.06
8.01
8.00
7.88
7.87
6.81
6.80
6.79
6.78
5.19
5.18
5.17
4.94
4.94
4.93
4.92
4.85
4.84
4.83
4.74
4.74
4.73
4.71
4.31
4.30
4.30
4.29
3.81
1.87
1.86
1.75
1.59
1.58
1.31
1.28
1.27
0.95
0.90
0.19
0.18
0.17
0.13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{8.25,125.61}
{8.19,124.30}
{8.22,140.10}
{8.05,122.04}
{6.79,127.48}
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{3.61,64.38}
{1.85,13.98}
{1.30,19.76}
{1.25,28.18}
{1.27,20.17}
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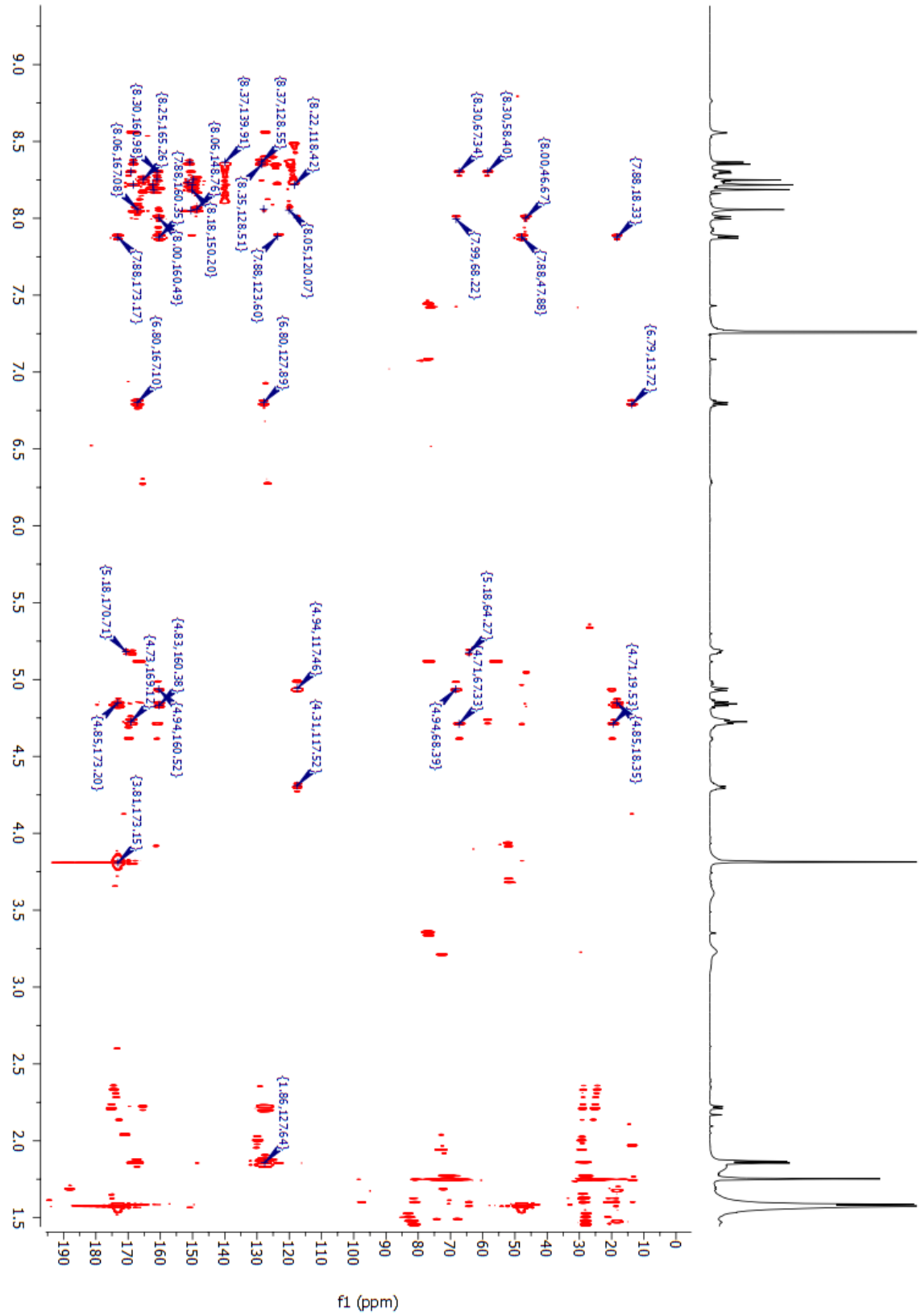
{0.17,-4.59}
{0.13,-4.52}
f1 (ppm)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{8.25,165.26}
{8.06,148.76}
{8.18,150.20}
{8.35,128.51}
{8.05,120.07}
{7.88,123.60}
{6.80,127.89}
{7.88,160.35}
{8.00,160.49}
{7.88,173.17}
{6.80,167.10}
{8.30,67.34}
{8.30,58.40}
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{7.88,47.88}
{7.99,68.22}
{7.88,18.33}
{6.79,13.72}
{5.18,64.27}
{4.71,67.33}
{4.94,68.39}
{4.71,19.53}
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{4.94,117.46}
{4.31,117.52}
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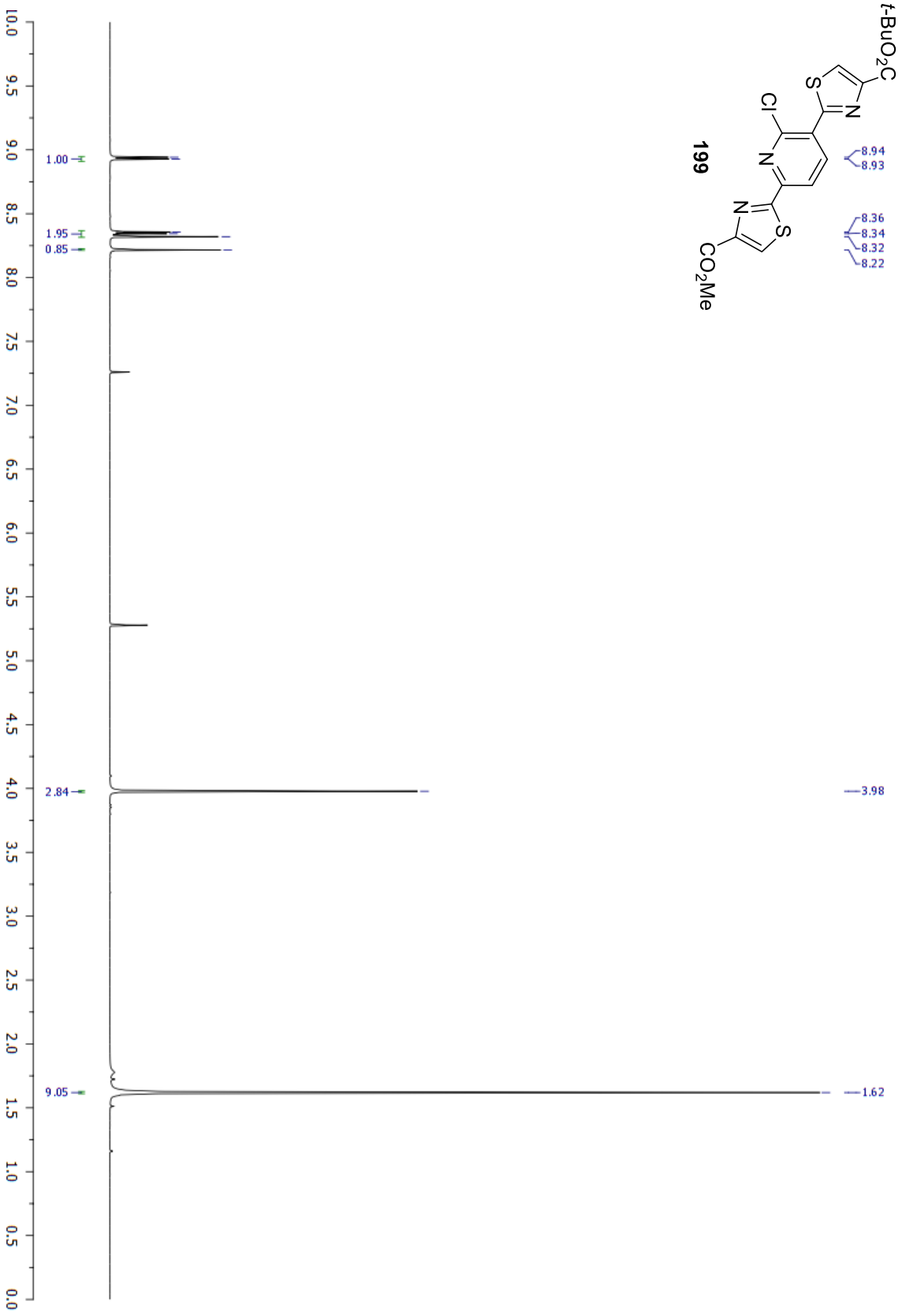
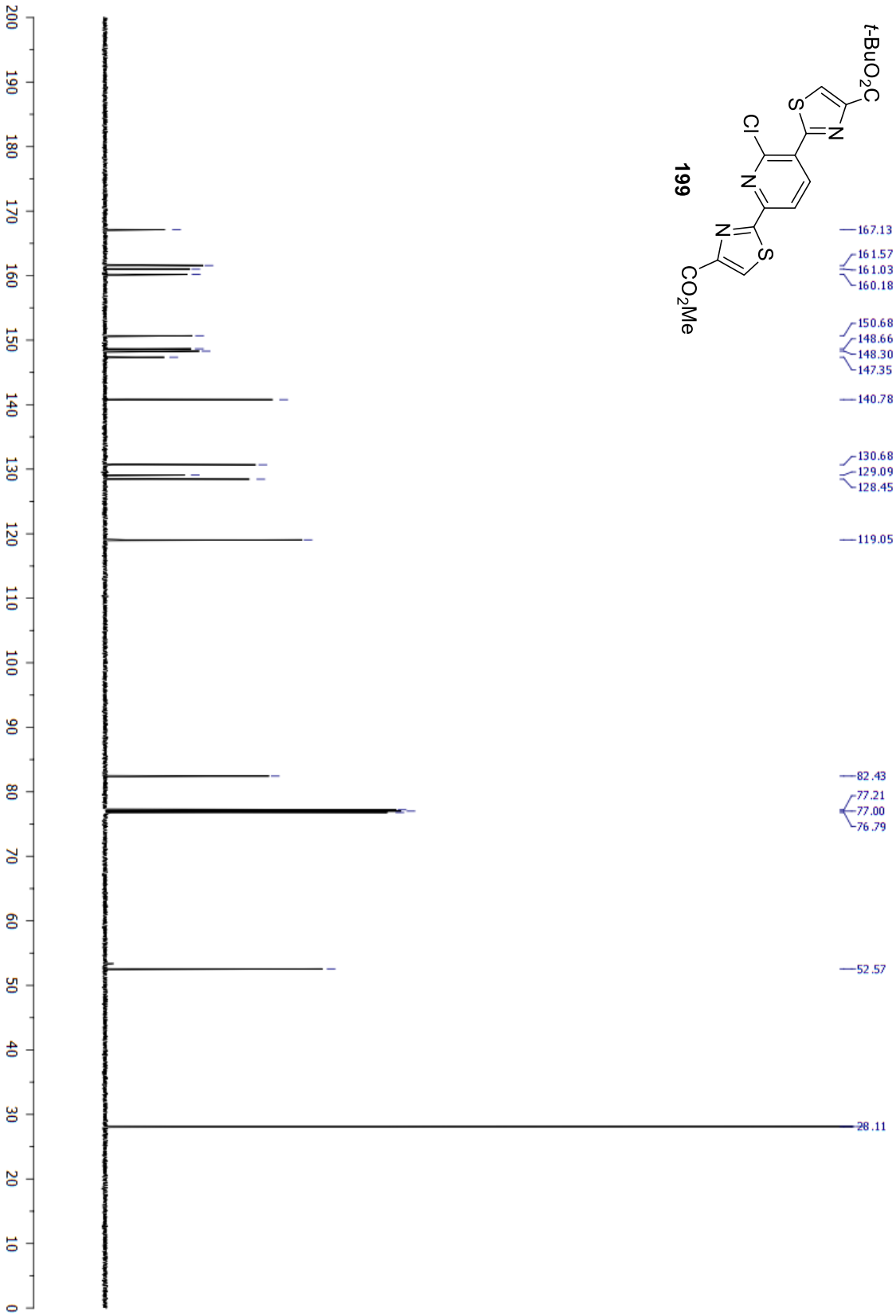
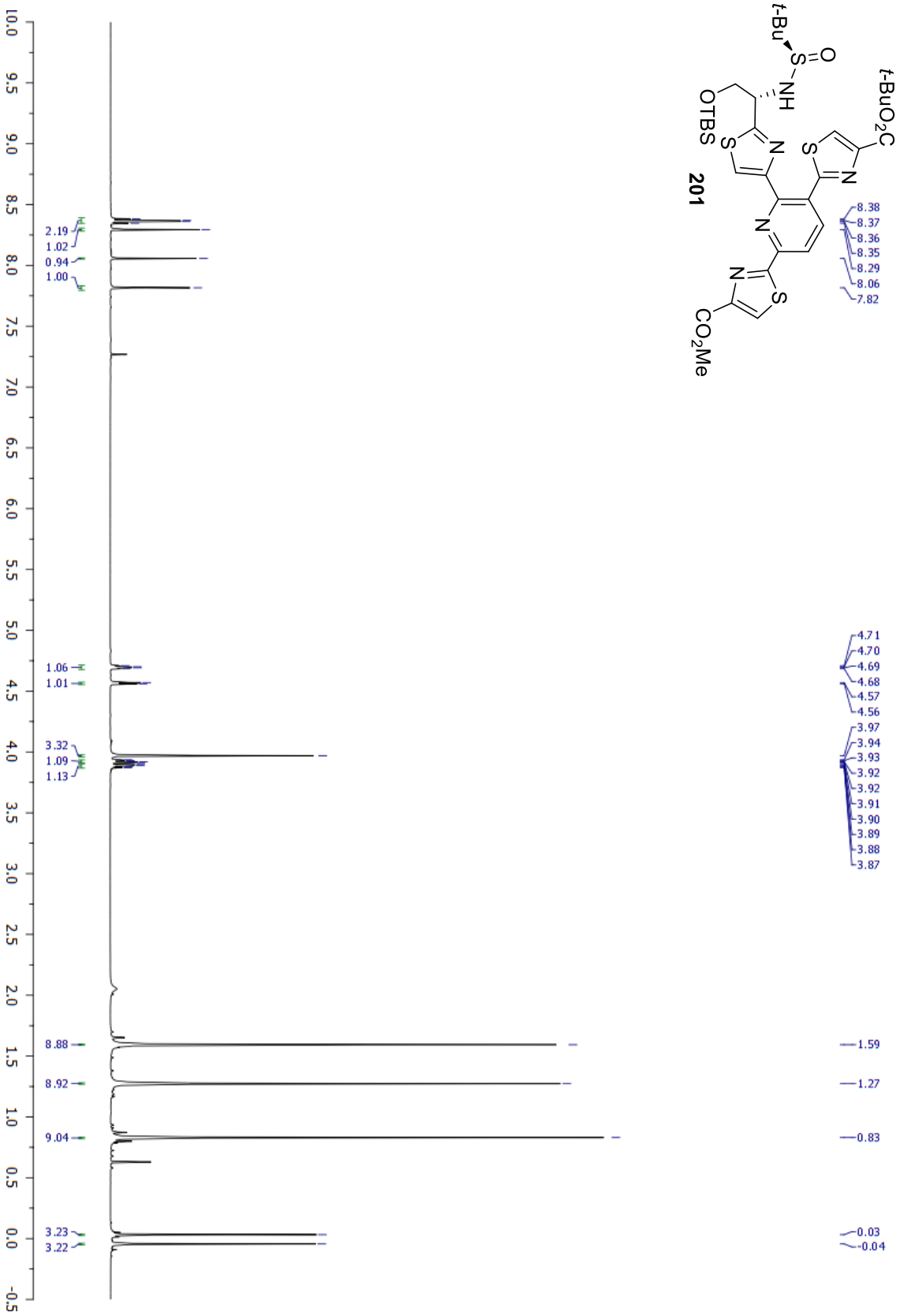
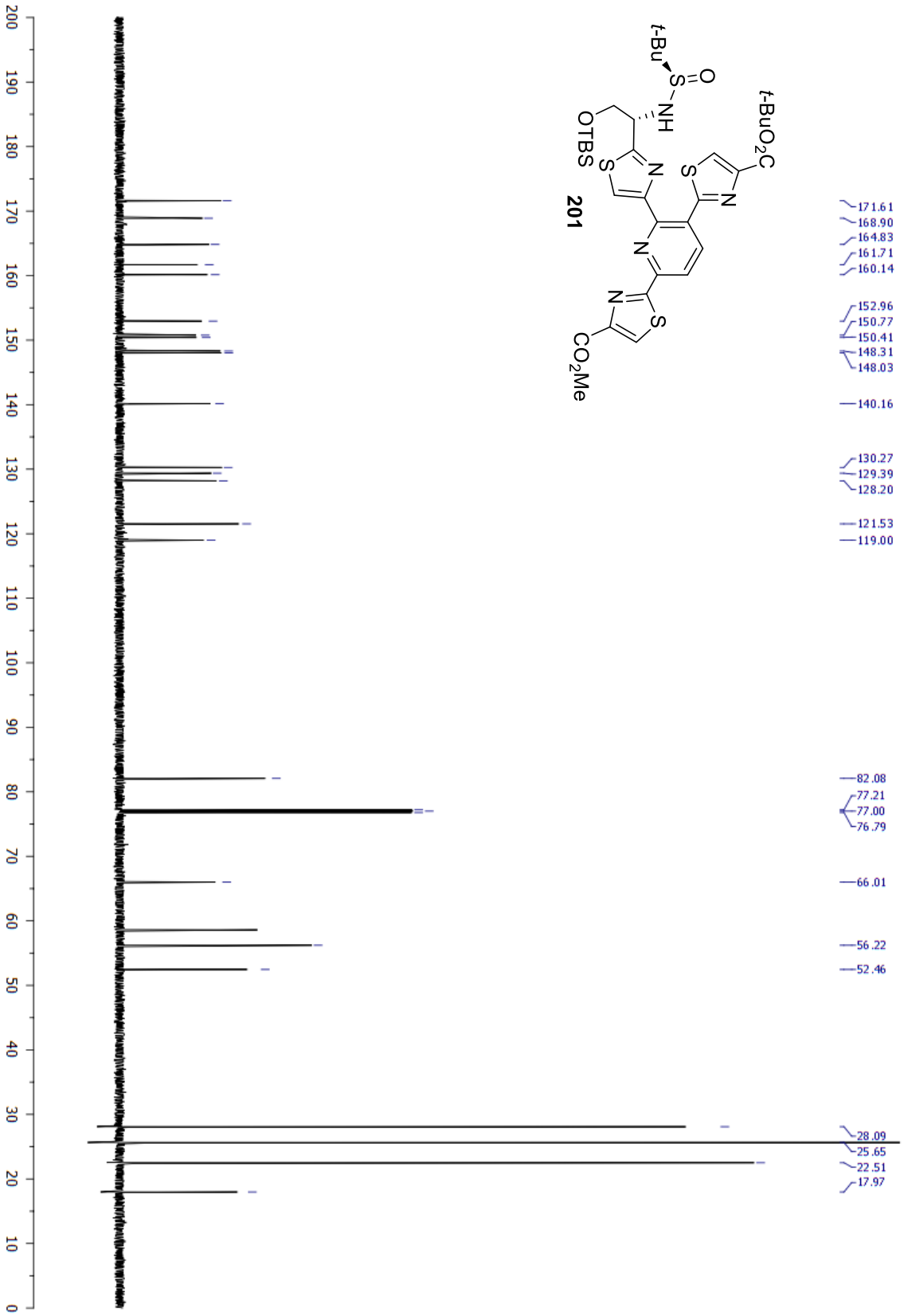
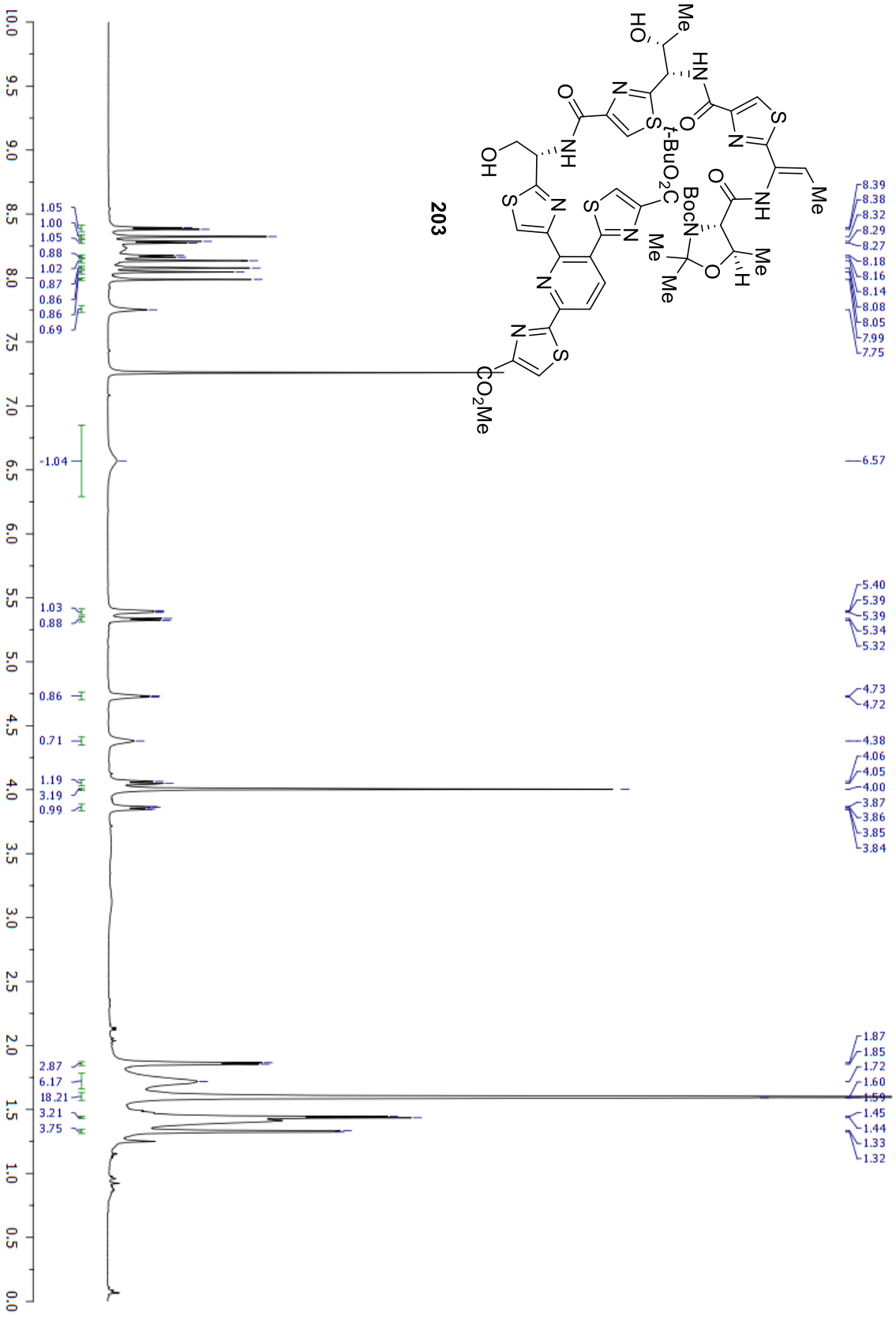
f1 (ppm)


199
t-BuO2C
Cl
N
S
N
N
S
CO2Me
8.94
8.93
8.36
8.34
8.32
8.22
1.00
1.95
0.85
2.84
9.05
3.98
1.62


t-BuO2C
Cl
N
S
N
N
S
CO2Me
199
167.13
161.57
161.03
160.18
150.68
148.66
148.30
147.35
140.78
130.68
129.09
128.45
119.05
82.43
77.21
77.00
76.79
52.57
28.11
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


t-Bu
S=O
NH
OTBS
t-BuO2C
CO2Me
201
8.38
8.37
8.36
8.35
8.29
8.06
7.82
4.71
4.70
4.69
4.68
4.57
4.56
3.97
3.94
3.93
3.92
3.92
3.91
3.90
3.89
3.88
3.87
2.19
1.02
0.94
1.00
1.06
1.01
3.32
1.09
1.13
8.88
8.92
9.04
3.23
3.22
1.59
1.27
0.83
0.03
-0.04


t-Bu
S
O
NH
OTBS
S
N
S
N
t-BuO2C
N
N
S
CO2Me
201
171.61
168.90
164.83
161.71
160.14
152.96
150.77
150.41
148.31
148.03
140.16
130.27
129.39
128.20
121.53
119.00
82.08
77.21
77.00
76.79
66.01
56.22
52.46
28.09
25.65
22.51
17.97
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


203
Me
HO
HN
O
N
S
NH
OH
t-BuO2C
BocN
Me
Me
Me
H
O
NH
Me
CO2Me
10.0
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
0.0
1.05
1.00
1.05
0.88
1.02
0.87
0.86
0.86
0.69
1.04
1.03
0.88
0.86
0.71
1.19
3.19
0.99
2.87
6.17
18.21
3.21
3.75
8.39
8.38
8.32
8.29
8.27
8.18
8.16
8.14
8.08
8.05
7.99
7.75
6.57
5.40
5.39
5.39
5.34
5.32
4.73
4.72
4.38
4.06
4.05
4.00
3.87
3.86
3.85
3.84
1.87
1.85
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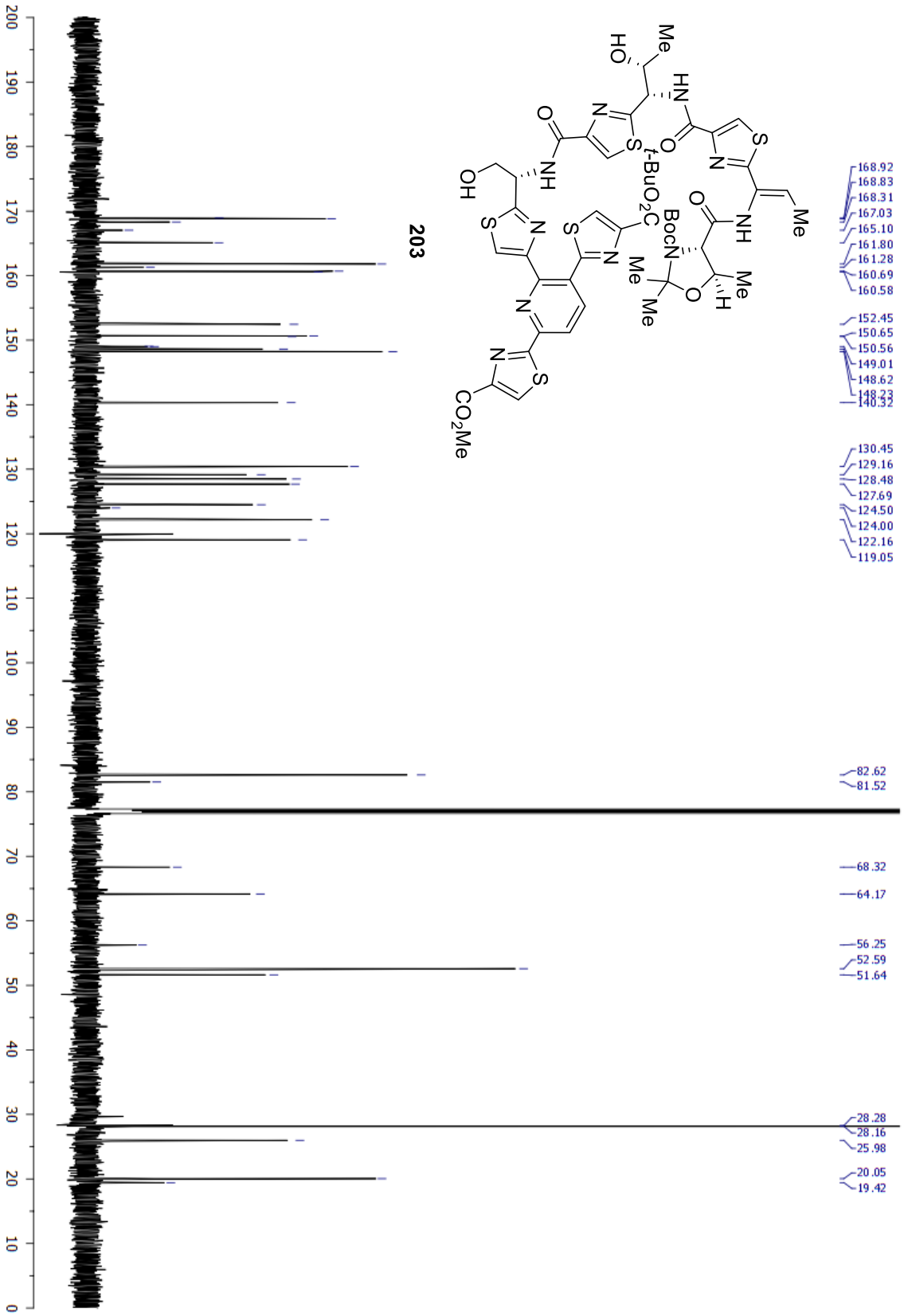
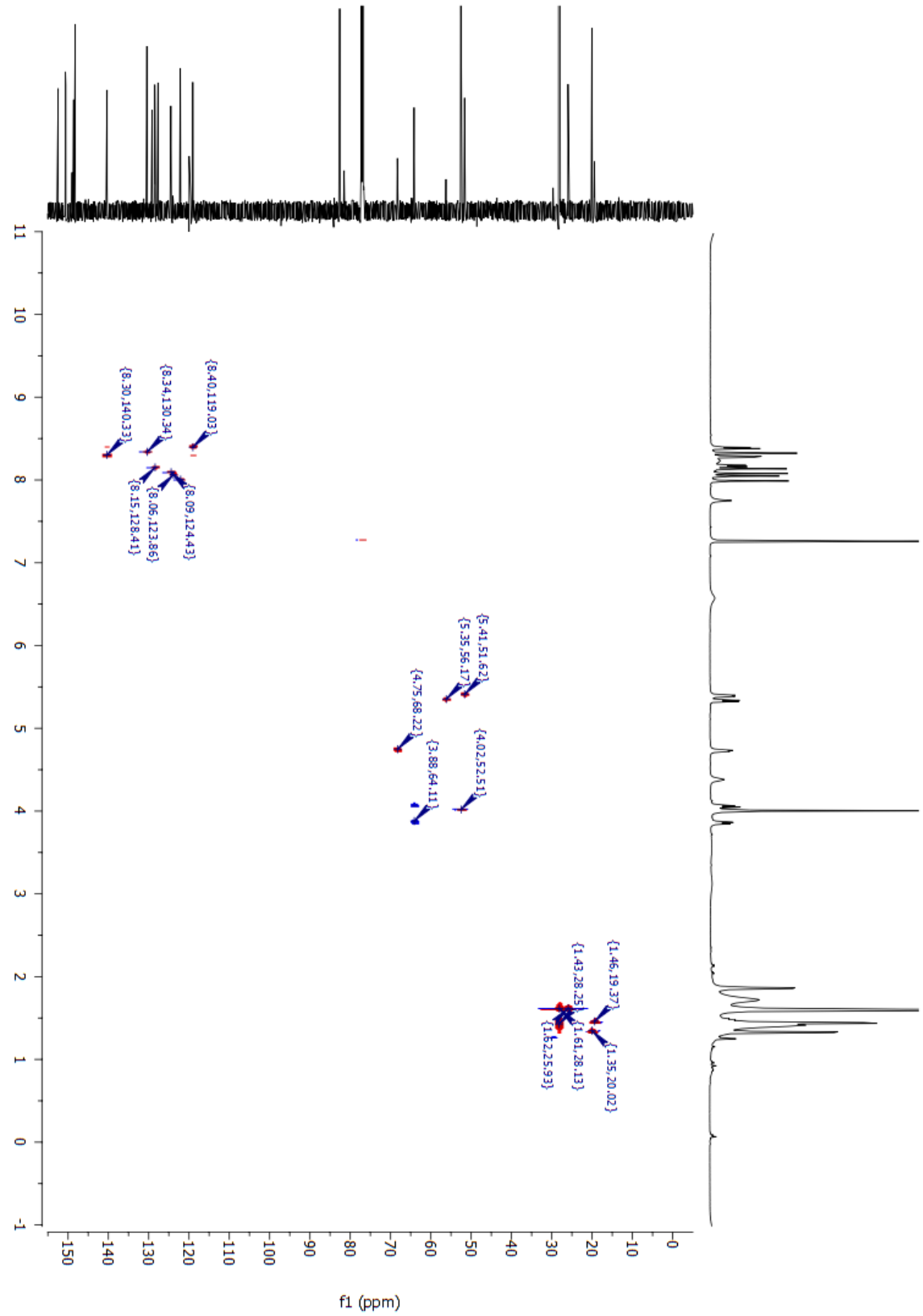
1.60
1.59
1.45
1.44
1.33
1.32


203
168.92
168.83
168.31
167.03
165.10
161.80
161.28
160.69
160.58
152.45
150.65
150.56
149.01
148.62
148.23
140.32
130.45
129.16
128.48
127.69
124.50
124.00
122.16
119.05
82.62
81.52
68.32
64.17
56.25
52.59
51.64
28.28
28.16
25.98
20.05
19.42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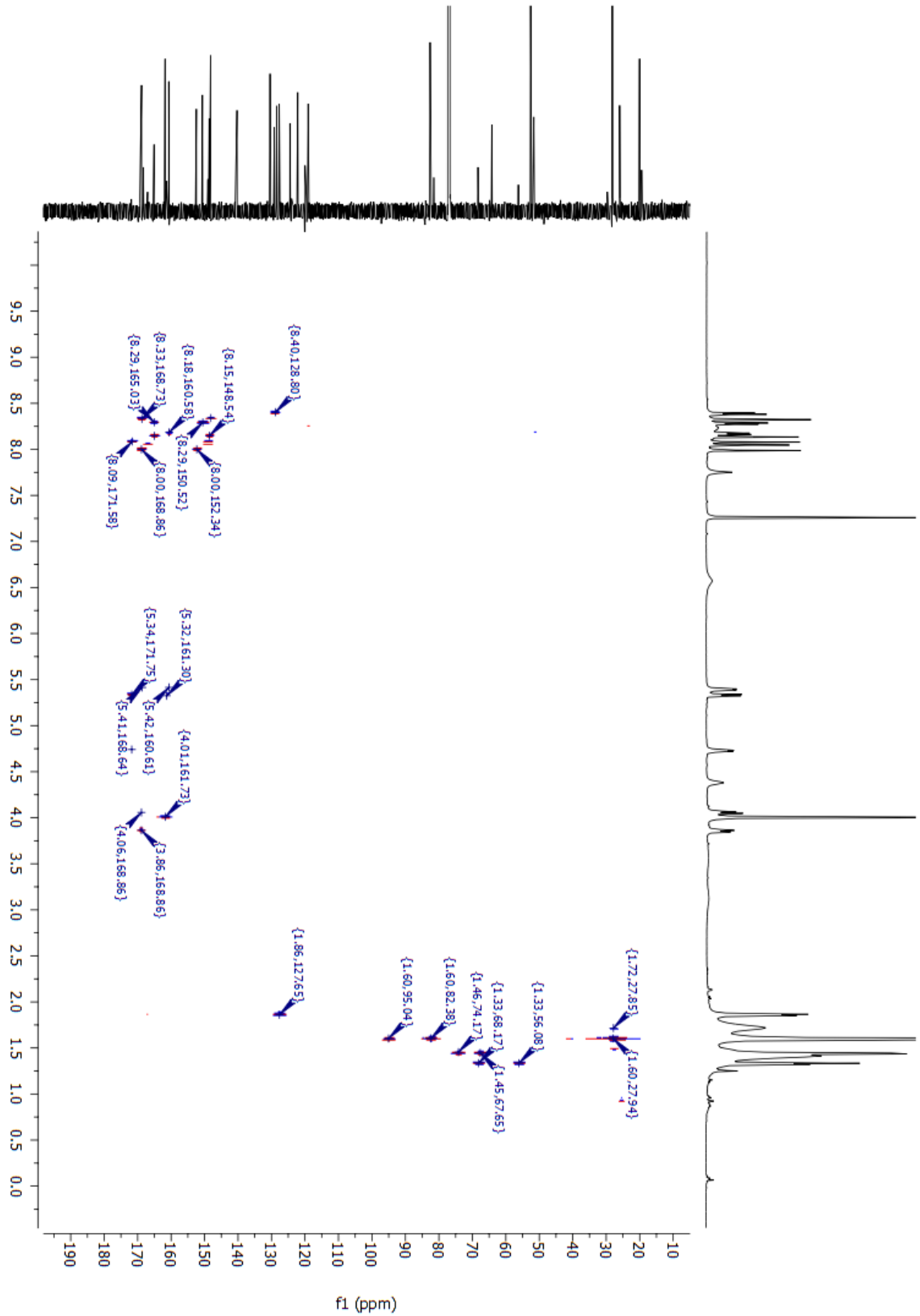
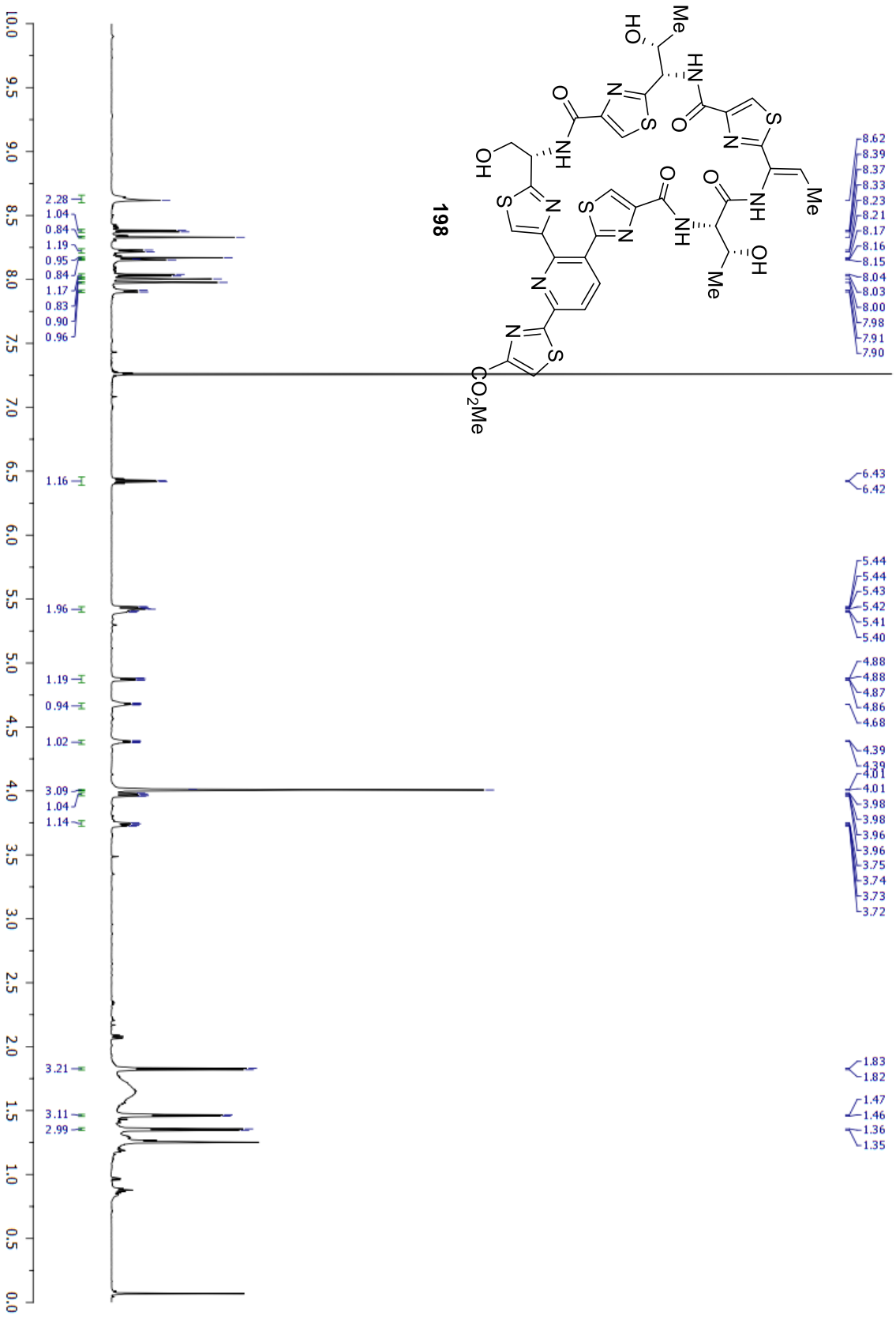
{8.34,130.34}
{8.30,140.33}
{8.09,124.43}
{8.06,123.86}
{8.15,128.41}
{5.41,51.62}
{5.35,56.17}
{4.75,68.22}
{4.02,52.51}
{3.88,64.11}
{1.46,19.37}
{1.43,28.25}
{1.61,28.13}
{1.62,25.93}
{1.35,20.02}
f1 (ppm)


{8.40,128.80}
{8.15,148.54}
{8.18,160.58}
{8.33,168.73}
{8.29,165.03}
{8.09,171.58}
{8.00,168.86}
{8.29,150.52}
{8.00,152.34}
{5.32,161.30}
{5.34,171.75}
{5.41,168.64}
{5.42,160.61}
{4.01,161.73}
{4.06,168.86}
{3.86,168.86}
{1.86,127.65}
{1.72,27.85}
{1.60,27.94}
{1.33,56.08}
{1.33,68.17}
{1.46,74.17}
{1.45,67.65}
{1.60,95.04}
{1.60,82.38}
f1 (ppm)


198
Me
HO
HN
O
N
S
NH
OH
Me
CO2Me
10.0
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
0.0
2.28
1.04
0.84
1.19
0.95
0.84
1.17
0.83
0.90
0.96
1.16
1.96
1.19
0.94
1.02
3.09
1.04
1.14
3.21
3.11
2.99
8.62
8.39
8.37
8.33
8.23
8.21
8.17
8.16
8.15
8.04
8.03
8.00
7.98
7.91
7.90
6.43
6.42
5.44
5.44
5.43
5.42
5.41
5.40
4.88
4.88
4.87
4.86
4.68
4.39
4.39
4.01
4.01
3.98
3.98
3.96
3.96
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3.74
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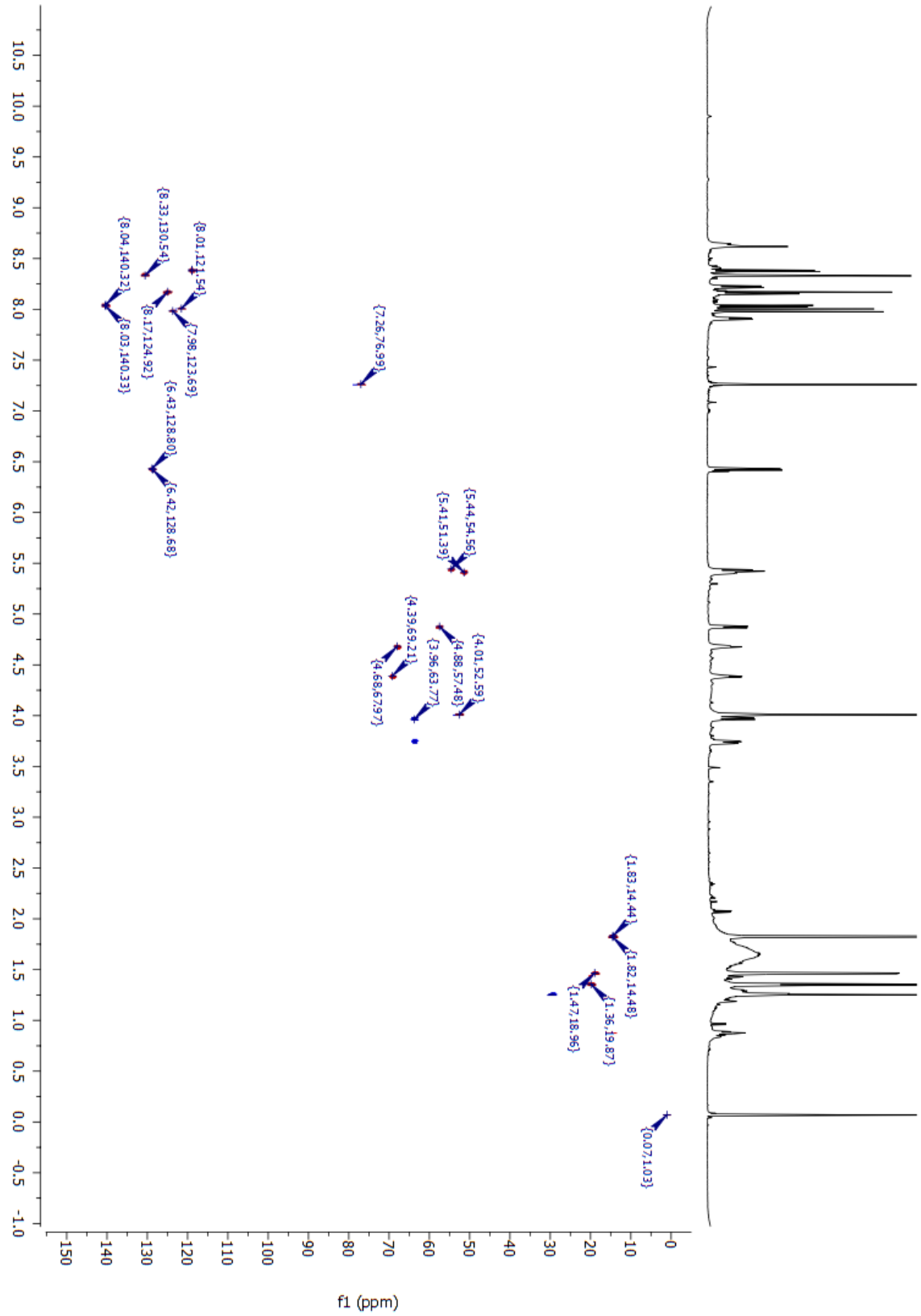
3.72
1.83
1.82
1.47
1.46
1.36
1.35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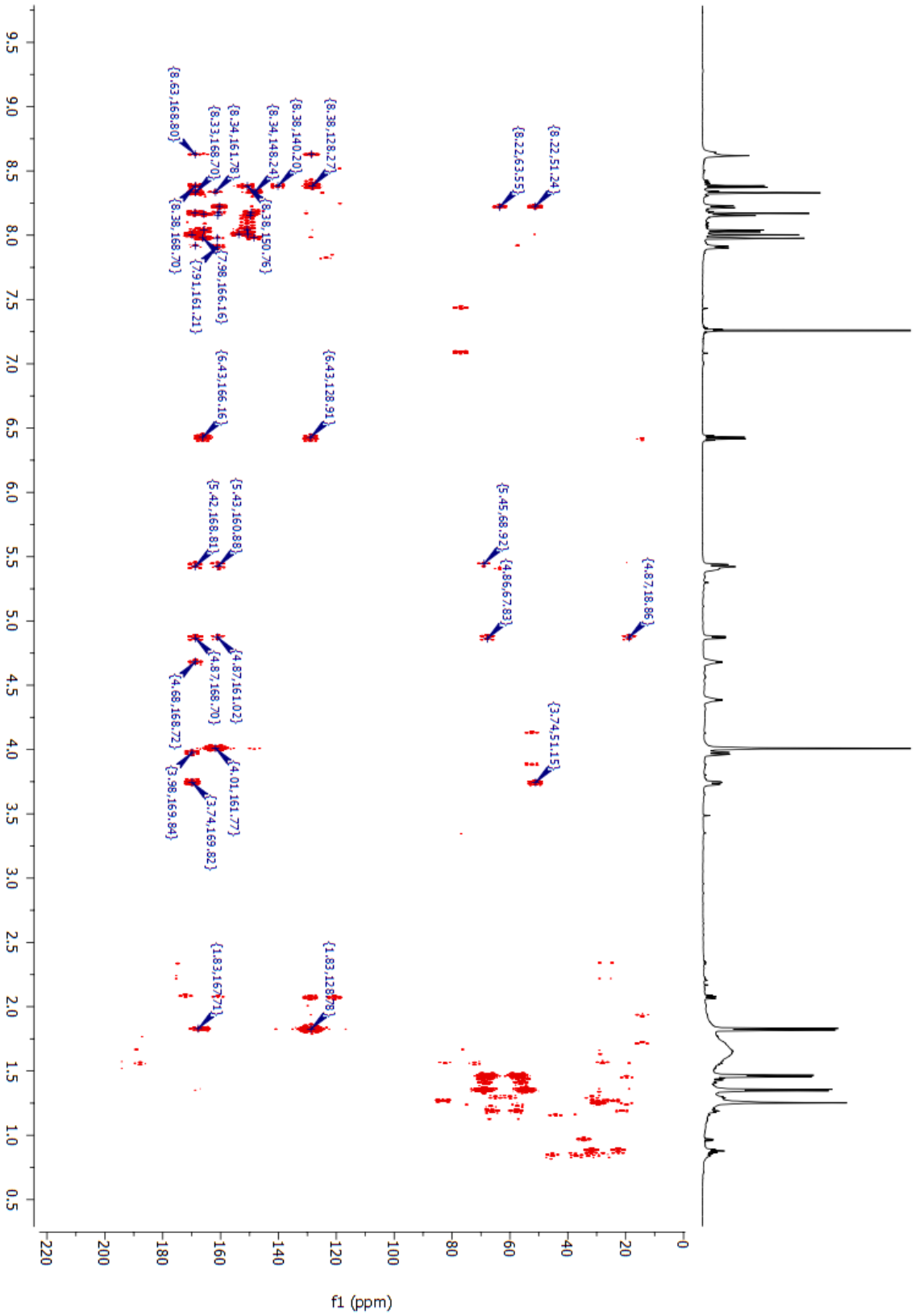
{4.88,57.48}
{5.44,54.56}
{5.41,51.39}
{4.39,69.21}
{4.68,67.97}
{3.96,63.77}
{7.26,76.99}
{8.01,121.54}
{7.98,123.69}
{8.33,130.54}
{8.17,124.92}
{8.04,140.32}
{8.03,140.33}
{6.43,128.80}
{6.42,128.68}
f1 (ppm)


{8.63,168.80}
{8.33,168.70}
{8.38,168.70}
{8.34,161.78}
{7.91,161.21}
{7.98,166.16}
{8.38,128.27}
{8.38,140.20}
{8.34,148.24}
{8.38,150.76}
{6.43,166.16}
{6.43,128.91}
{8.22,51.24}
{8.22,63.55}
{5.42,168.81}
{5.43,160.89}
{5.45,68.92}
{4.86,67.83}
{4.87,18.86}
{4.68,168.72}
{4.87,168.70}
{4.87,161.02}
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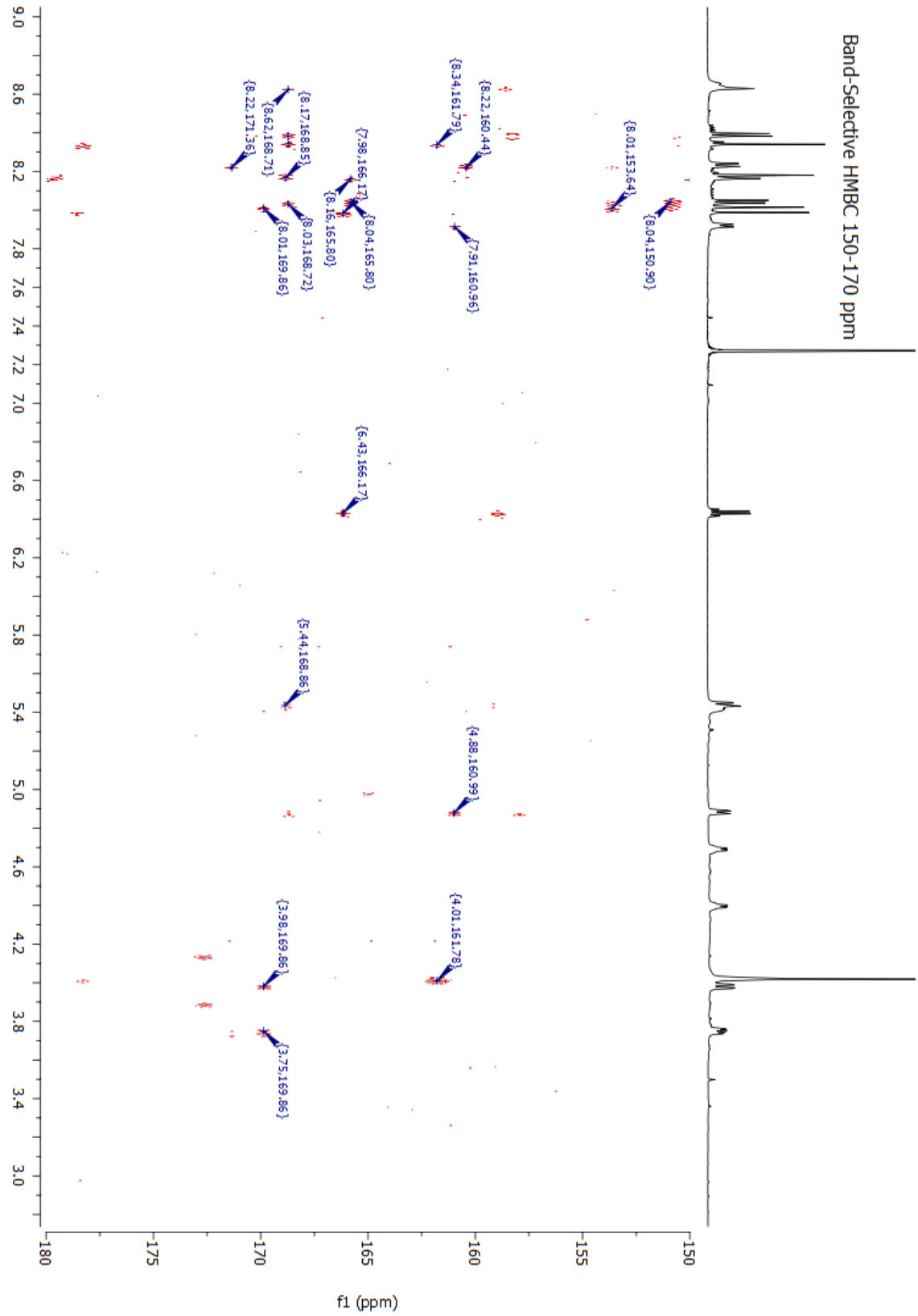
{4.01,161.77}
{3.74,51.15}
{1.83,167.71}
{1.83,128.78}
f1 (ppm)


Band-Selective HMBC 150-170 ppm
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{8.34,161.79}
{7.91,160.96}
{7.98,166.17}
{8.04,165.80}
{8.16,165.80}
{8.17,168.85}
{8.03,168.72}
{8.01,169.86}
{8.62,168.71}
{8.22,171.36}
{6.43,166.17}
{5.44,168.86}
{4.88,160.99}
{4.01,161.78}
{3.98,169.86}
{3.75,169.86}
f1 (ppm)

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