THE UNIVERSITY OF CHICAGO

# TOTAL SYNTHESIS OF ANNOTINOLIDES AND THE EXPLORATION OF THEIR BIOSYNTHETIC RELATIONSHIPS

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# ABSTRACT


**Total Synthesis of Annotinolides and the Exploration of Their Biosynthetic Relationships**

**Pei Qu**

Total synthesis of novel structures from Mother Nature inspires organic chemists to develop new methods and tactics. It also shapes the new discipline of synthetic chemistry. In this dissertation, we will introduce our recent total synthesis of several annotinolides, which belong to a new family of *Lycopodium* alkaloids discovered by the Hu group in 2016. The inspiration of new transformations and strategies during the synthesis of annotinolides will be illustrated. Also, our exploration of the transformation between annotinolides provide some insight to their potential biosynthetic pathway.

First, we will analyze the novel structures of annotinolides. We are particularly interested in the cage-shaped molecules within this family. Then we will introduce the inspiring biosynthetic pathway proposed by the Hu group and the synthetic efforts from the She group and the Tu group.

Next, we will discuss our synthetic effort towards annotinolide B in Chapter 2. Based on the four-membered ring within the molecule, we envisioned an intramolecularly [2+2] reaction as the key reaction. We successfully constructed the C ring system, featuring a Michael addition/triflation sequence and the Mitsunobu reaction or oxidation/recution sequence to install the desired stereochemistry. However, the key [2+2] reaction failed in multiple substrates due to the potential ring strain.

In Chapter 3, our synthesis of 4-*epi*-annotinolide C, 4-*epi*-annotinolide D, annotinolide C, annotinolide D and annotinolide E will be introduced. We first attempted to use the

intramolecular oxidative coupling reaction to construct the key [3.2.1] bicycle but only led to an unexpected [3.3.1] hemiketal. Based on this result, we used a Conia-ene reaction and iodolactonization to introduce the key caged structure moiety. The stereochemistry was controlled by the tactical application of a nitrile group and the detailed analysis of the conformations for the advanced intermediates. Deiodination on different substrates could lead to different diastereomers, and we were able to access 3 natural products and 2 natural product epimers. The transformations between annotinolide C, D and E were also explored, which delivered interesting results comparing to the proposed biosynthetic pathway.

The asymmetric solution for our total synthesis will be discussed in Chapter 4. We developed an enzymatic resolution approach, which highlights the recovery of the undesired enantiomer. The *ee* erosion was observed in the following steps, but we could still get 79% *ee* with detailed optimization.

Finally, we will summary the discoveries and conclusions in Chapter 5. Those results would be inspiring for the synthesis of similar systems.

# LIST OF ABBREVIATIONS

| | |
|---|---|
| **9-BBN** | 9-borabicyclo[3.3.1]nonane |
| **BDSB** | bromodiethylsulfonium Bromopentachloroantimonate |
| ***n*-BuLi** | *n*-butyllithium |
| **Boc** | *tert*-butylcarbonyl |
| **Bn** | benzyl |
| **brsm** | based on recovered starting material |
| **Bz** | benzoyl |
| **CuTC** | copper(I)-thiophene-2-carboxylate |
| **DBU** | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| **DCC** | *N*,*N'*-dicyclohexylcarbodiimide |
| **DCE** | 1,2-dichloroethane |
| **DDQ** | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| **DEAD** | diethyl azidocarboxylate |
| **DIAD** | diisopropyl azidocarboxylate |
| **DIBAL-H** | diisobutylaluminum hydride |
| **DMAP** | 4-(*N*,*N*-dimethyl)pyridine |

**DME** dimethoxyethane

**DMF** *N*,*N*-dimethylformamide

**DMP** Dess-Martin periodinane

**DMSO** dimethyl sulfoxide

**DPPA** diphenyl phosphoryl azide

**EtOAc** ethyl acetate

**HMPA** hexamethylphosphoramide

**HRMS** high-resolution mass spectroscopy

**IBX** 2-iodoxybenzoic acid

**IR** infrared

**LDA** lithium diisopropylamide

**LiTMP** lithium 2,2,6,6-tetramethylpiperidide

***m*CPBA** *meta*-chloroperbenzoic aacid

**MeOH** methanol

**Mn(dpm)$_3$** tris(2,2,6,6-tetramethyl-3,5-heptanedionato)manganese(III)

**MOM** methypxymethyl

**Ms** methanesulfonyl

**MS** molecular sieves

| | |
|---|---|
| **MTBE** | *tert*-butyl methyl ether |
| **NIS** | *N*-iodosuccinimide |
| **NMO** | *N*-methylmorpholine *N*-oxide |
| **NMR** | nuclear magnetic resonance |
| **N. R.** | no reaction |
| **Ns** | 2-nitrobenzenesulfonyl |
| **PCC** | pyridinium chlorochromate |
| **PMB** | *p*-methoxybenzyl |
| **PTSA** | *p*-toluenesulfonic acid |
| **py** | pyridine |
| **TBAF** | tetrabutylammonium fluoride |
| **TBHP** | *tert*-butyl hydroperoxide |
| **TES** | triethylsilyl |
| **TBS** | *tert*-butyldimethylsilyl |
| **Tf** | trifluoromethanesulfonate |
| **TFA** | trifluoroacetic acid |
| **THF** | tetrahydrofuran |
| **TIPS** | triisopropylsilyl |

**TMS** trimethylsilyl

**TsOH** *p*-toluenesulfonic acid

**VO(acac)$_2$** vanadyl acetylacetonate

# ACKNOWLEDGMENT

When I first step into the field of organic chemistry, I was fascinated by the way how chemists could build and manipulate molecules. And the molecules that created by the hands of chemists, significantly changed our life. So, I want to become a synthetic chemist, with the skills to make any molecules one could imagine and make a different to the world. Fortunately, I am here, approaching the finish line of my Ph. D. in total synthesis. This is possible only by the help and support of many people I met along the way.

First and foremost, I want to thank my mentor, Prof. Scott Snyder. Without his encouragement and support, I could not make it to the last. The freedom of choosing projects by myself, builds up my confidence in chemistry step by step and let me reach my utmost potential. Also, when I encountered the challenges and got frustrated, he could share his experience and help me to walk out of it. I think the most important thing he taught, is to find your own way and make the decision by your own. An independent Ph. D. could survive in any situation in the future.

Also, I am honored and grateful to have Professor Viresh Rawal and Professor Guangbin Dong to on my defense committee. Thanks for their valuable time and comments.

There are many collegues in the group helped me a lot in the projects I have worked on. Thanks for sharing and the discussion in chemistry, and many of them helped to accommodate the life in UChicago: Dr. Pei Gan (arboridinine project), Dr. Qinda Ye (scaparvins project), Dr. Minxing Shen (first-generation route of annotinolide C), Chang Liu (first-generation route of annotinolide C), Jose Little (second-generation of annotinolide C), Colin Cooper (antroalbocin A).

A special thanks to my roommates and colleagues, Dr. Fangjie Yin and Cheng Peng. Thanks for their support, no matter inside or outside the lab. They are the mentors for my cooking, and shared a lot of stuff, like chemistry, photography, traveling… I really missed three years we shared together. And luckily, we all survived in the warzone of Chicago. To Dr. Fangjie Yin, congratulations to reunion with your girlfriend after 5-year long distance relationship. Also, thanks to the experience for finding jobs, hope to have opportunities to collaborate in the process industry. To Cheng Peng, thanks for all the help and friendship since undergraduate school and hope to see your perfect defense next year.

Thanks to my dearest friends Haoyuan Liu and Hongxin Ge. 3 years in high school, 4 years in undergraduate school, studying chemistry together. Although we went to different graduate schools, but we always share opinion in chemistry and graduate school life. Waiting to see your defenses in the near future!

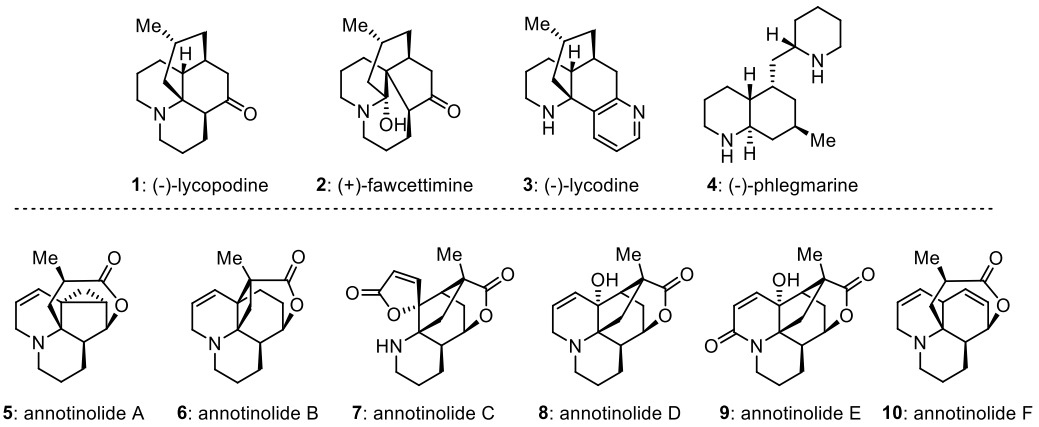
And the most important, thanks to my parents. Their supports are the strongest encouragement to continue my chosen path. At the finish line of my Ph. D., I want to share the most exciting moment with them.

A road to Ph. D. of total synthesis is not easy, the time in my graduate schools will be unforgettable. Hope I could always remember why I chose this path and finish it. And also, hope my meager knowledge could make some difference, at least a little.

# CHAPTER 1

# INTRODUCTION OF ANNOTINOLIDES

## *1.1 Isolation and the Structure of Annotinolides*

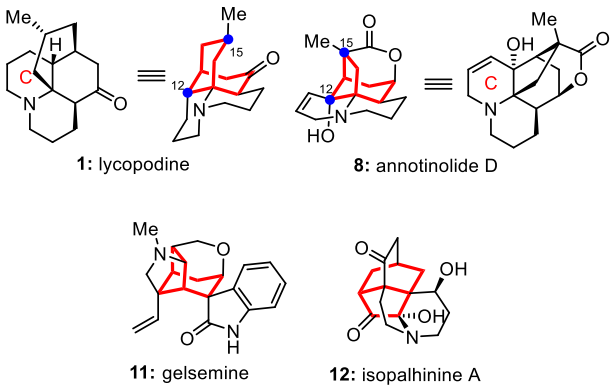



**Scheme 1.1** The four major types of *Lycopodium* alkaloids and the structure of annotinolides

Since the first isolation of lycopodine from *L. complanatum* by Bödeker in 1881,[1] *Lycopodium* alkaloids have interested chemists with continually emerging novel structures and biological activities.[2] To date, there are four major classes of alkaloids in the *Lycopodium* family as shown in scheme 1.1: the lycopodine type, the fawcettimine type, the lycodine type and the phlegmarine type. Those alkaloids have served as inspiring targets for synthetic chemists for over a half century.[3] In 2016, the Hu group isolated a new family of *Lycopodium* alkaloids — annotinolides.[4] The annotinolide family has 6 members and they all possess fascinating structures. Among those alkaloids, annotinolide B (**6**), C (**7**), D (**8**), and E (**9**) contain a caged lactone structure and unique bicycle systems compared to the common *Lycopodium* alkaloids. The analysis of the structural features is listed in scheme 1.2.

Taking annotinolide D (**8**) as a representative example, we find three major differences with the classic lycopodine (**1**) skeleton: 1) There is an all-carbon quaternary stereocenter at C15, unique among *Lycopodium* alkaloids; 2) The conformation of the carbon-carbon bond at the C12 stereocenter has changed, and C12 exhibits a higher oxidation stage compared to lycopodine (**1**);

3) Instead of a [3.3.1] bicycle, a [3.2.1] bicycle is embedded in the skeleton of annotinolide D (**8**). This [3.2.1] bicycle coupled with quaternary stereocenters is quite synthetic challenging, as was illustrated in the previous syntheses of the famous compounds gelsemine (**11**)[5] and isopalhinine A (**12**).[6]

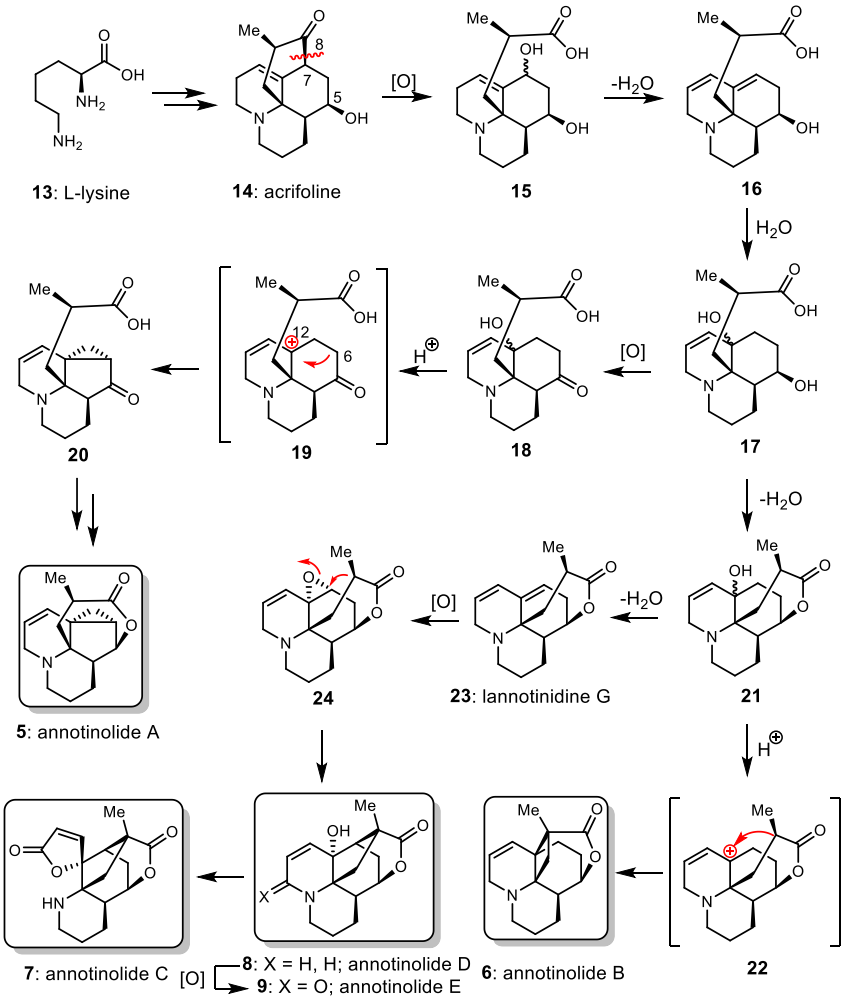



**Scheme 1.2** The structural comparison of lycopodine (**1**) and annodinolide D (**8**)

Intrigued by the structure of this class and as part of the group's dedicated efforts towards seeking family-level solutions for complex natural products, we targeted annotinolide B (**6**), C (**7**), D (**8**), and E (**9**) for total synthesis. In this dissertation, we will introduce the stories behind the total syntheses of those targets and reveal the discoveries along the way.

## *1.2 Proposed Biosynthetic Pathway*

Before we dive into the total synthesis of annotinolides, we must review the biosynthetic pathway since the unique structures of annotinolides make us wonder how Mother Nature creates them. Based on the known biosynthetic pathway of other *Lycopodium* alkaloids, the Hu group proposed their thoughts in the isolation paper.[4a] This proposal starts from the known acrifoline (**14**), which has a double bond at C11-C12 and the similar oxidation state at C5 and C8. Acrifoline (**14**) initially undergoes oxidative cleavage, forming carboxylic acid **15**. Then, a




**Scheme 1.3** The Hu group's proposed biosynthetic pathway of annotinolides

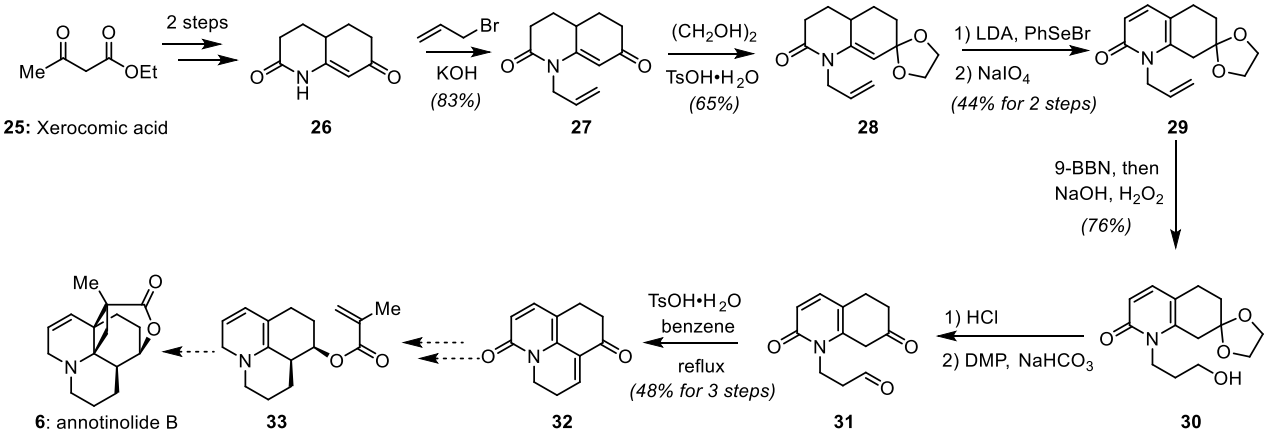
dehydration/hydration isomerization sequence leads to key allylic alcohol **17**. From **17**, if C5 gets oxidized to a ketone, an intramolecular attack of the carbocation at C12 by the would deliver the 5/3 ring system as in **20**. Thus, annotinolide A (**5**) was constructed by the following reduction/lactonization sequence. The rest of annotinolides are synthesized via another pathway. Also, from intermediate **17**, the signature lactone ring in annotinolides was formed through direct lactonization with the secondary alcohol at C5. Lactone **21** serves as the common intermediate for annotinolide B (**6**), C (**7**), D (**8**), and E (**9**). If the allylic carbocation is directly formed as in intermediate **22**, the α carbon of the lactone (C15) attacks and closes the four-membered ring,

providing annotinolide B (**6**). If **21** dehydrates and form lannotinidine G (**23**) first, annotinolide D (**8**) would be constructed through the epoxidation of the double bond at C7-C12 and subsequent nucleophilic attack at C15. Then, an allylic oxidation leads to annotinolide E (**9**) from which annotinolide C (**7**) could arise via hydrolysis and isomerization.

### *1.3 Synthetic Efforts from Other Groups*

The annotinolides drew broad attention in the total synthesis community with their fascinating structures. Many groups proposed the annotinolides as potential targets, and to date there are two groups who have disclosed their synthetic studies towards annotinolides.[7,8] The She group was interested in annotinolide B (**6**) and constructed the A/B/C ring system. Additionally, the Tu group has published their synthetic study towards annotinolide C (**7**).

#### *1.3.1 The She Group's Synthetic Study*

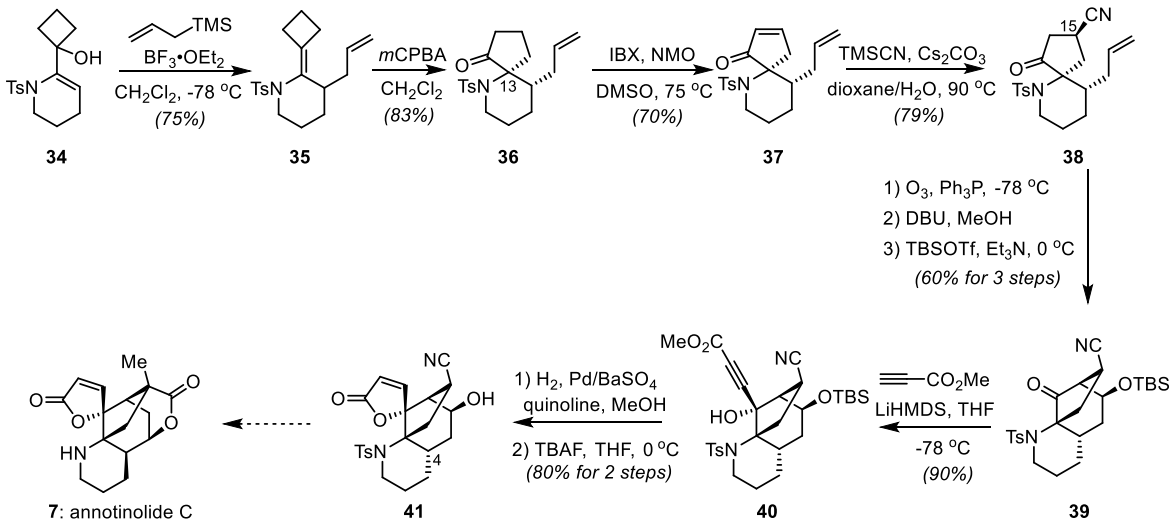



**Scheme 1.4** The She group's synthetic study towards annotinolide B (**6**)

The She group's plan for synthesizing annotinolide B (**6**) was based on a key [2+2] cycloaddition as the final step. Thus, they constructed the A/B/C ring system first. A reported cyclic amide **26** synthesized from xerocomic acid **25** in 2 steps was chosen as the precursor for

their synthetic study. Allylation of amide **26** using allyl bromide in basic KOH solution succeeded with 83% yield. Then, the ketone was masked with glycol, and the C ring was oxidized in 44% yield by employing a selenium oxidation/double bond migration sequence. One benefit of this approach is that the pyridone moiety in product **29** contributes significantly to the stability of the molecule, making it easier to handle. Pushing forward, hydroboration/oxidation, glycol deprotection with HCl, and DMP oxidation delivered keto aldehyde **31**. After an acid catalyzed aldol reaction, product **32** was formed in 35% yield overall from pyridine **29**. Of note, **32** possessed the A/B/C ring system with the desired functional group handle at C4 and C5. The She group then envisioned converting tricyclic compound **32** to ester **33**, which could lead to natural product annotinolide B (**6**) through an intramolecular [2+2] reaction.

### *1.3.2 The Tu Group's Synthetic Study*




**Scheme 1.5** The Tu group's synthetic study towards annotinolide C (**7**)

The Tu group utilized their state-of-art semi-pinacol rearrangement in their synthetic study as shown in scheme 1.5. Starting from the known building block **34**, a Sakurai type allylation followed by the epoxidation/semipinacol sequence provided spirocyclic ketone **36**. The C13

stereocenter was established efficiently in only 2 steps and 62% yield. Then, nitrile **38** was obtained in 55% yield via an IBX oxidation and a cyanide conjugate addition, successfully installingthe ester equivalent on C15. Next, they chose to construct the [3.2.1] bicycle structure via an intramolecular aldol reaction. The ozonolysis revealed the aldehyde group, and a DBU-catalyzed aldol reaction followed by TBS protection furnished the bicyclic compound **39** in 60% yield over three steps. Then, the butenolide ring was introduced. A nucleophilic addition reaction with in-situ generated lithium propiolate on **39** gave tertiary alcohol **40** in 90% yield as a single diastereomer. The addition product **40** was then subjected to Lindlar reduction condition and the lactone ring formed concomitantly. Further TBAF deprotection led to advanced intermediate **41**. Comparing **41** with natural product annotinolide C (**7**), the final tasks would be to adjust the oxidation state, convert the C4 stereocenter, and form the final lactone ring. Unfortunately, these late-stage transformations listed above are difficult to achieve with the functional groups and stereocenters in **41**, and subsequent attempts to access these structures were not fruitfulDespite this challenge, the Tu group provided a great solution to construct the ABCD ring system in annotinolide C (**7**), especially the [3.2.1] bicyclicand butenolide moieties.

### *1.4 Reference*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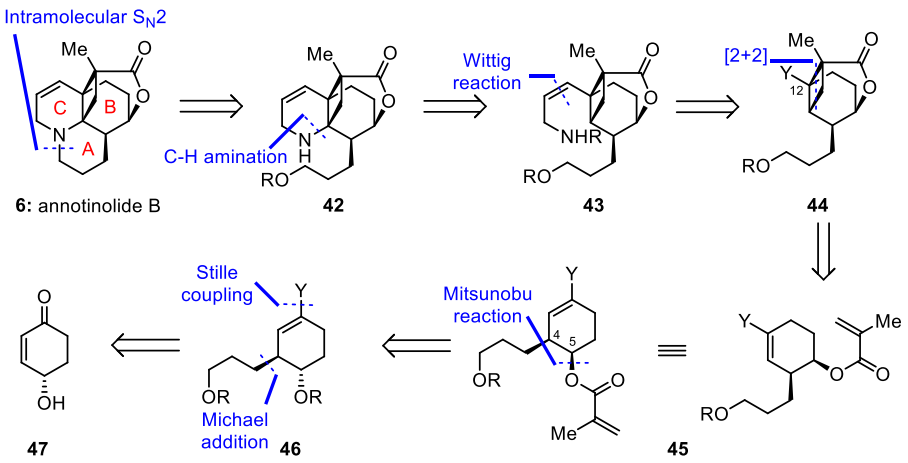
# CHAPTER 2

# SYNTHETIC STUDY TOWARDS ANNOTINOLIDE B

## *2.1 Retrosynthetic Analysis*




**Scheme 2.1** Our retrosynthetic analysis of annotinolide B (**6**)

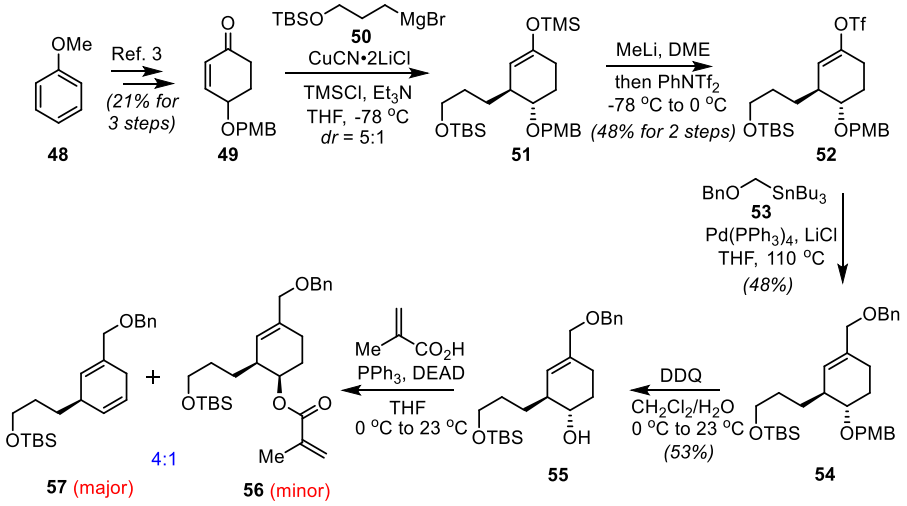
The classical way to construct the signature four-member D ring in annotinolide B (**6**) is the photochemical [2+2] reaction. Early in 1968, the Ayer group successfully obtained a four-member ring intermediate through a photochemical [2+2] reaction in their total synthesis of lycopodine (**1**).[1] Based on the [2+2] as the key reaction, we designed our route as shown in scheme 2.1. In our proposal, we proposed the A ring would be the simplest of the rings to construct in the final stage. Then, the C ring could be closed through a C-H amination reaction. This disconnection utilizes state-of-art C-H activation chemistry[2] and would avoid superfluous functional group transformations in the synthesis. With the rigid framework of the four-membered ring/lactone system and desired *Z* configuration of olefin, the envisioned reaction has a great chance to succeed. In intermediate **43**, the olefin moiety would be introduced via Wittig reaction, tracing back to a Y group handle at C12. This Y group could be aldehyde, ester or any other group that facilitates the [2+2] reaction. From here, the intramolecular [2+2] reaction leads to a monocyclic substrate **45**. Analyzing C4 and C5 stereocenter in **45**, we proposed that C5 stereocenter could be inverted through a Mitsunobu reaction. Then the *trans* relationship of C4

and C5 would be conveniently established using a Michael addition. And of course, the Y group could be introduced through the coupling reaction of a triflate functional group, which could be installed alongside the conjugate addition. Finally, we can trace this compound back to the simple literature reported precursor **47**.[3]

Our designed route for annotinolide B (**6**) is a very concise approach, highlighting an intramolecular [2+2] reaction and a C-H amination reaction. The successful realization of these two key steps would avoid unnecessary functional group manipulations, and both precisely and efficiently install the functional groups desired, while constructing the unique framework of annotinolide B (**6**).

## *2.2 Synthetic Study of Annotinolide B (6)*

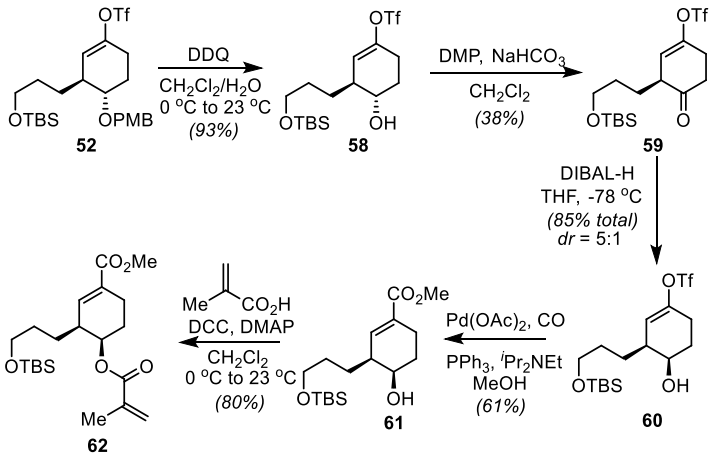
### *2.2.1 Construction of C4 and C5 Stereocenters on B Ring System*




**Scheme 2.2** Constructing C5 stereocenter using Mitsunobu reaction

Following the designed route in Scheme 2.2, we initiated our synthesis with cyclohexenone **49** (3 steps from commercially available **48**). First, we introduced the 3-carbon

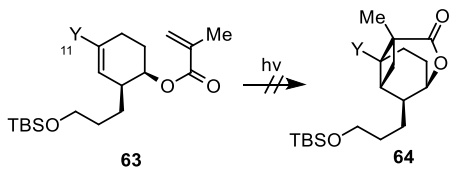
side chain using a Michael addition,[4] and quenched the enolate with TMSCl. With PMB protection on the secondary alcohol, the conjugate addition afforded a 5:1 dr favoring trans product **51**. The silyl enol ether **51** is stable enough to be purified via column. And it was subjected to MeLi and $PhNTf_2$, delivering our coupling precursor **52** in 48% yield from cyclohexanone **49**. Then we planned to install a one-carbon side chain with Bn protected primary alcohol as Y group in **54**. The standard Stille coupling reaction with **53**[5] delivered **54** in 48% yield. The next obvious challenge would be to invert the C5 stereocenter. After a 53%-yield deprotection of PMB group, we performed a Mitsunobu reaction[6] with methacrylic acid. Unfortunately, the deprotected alcohol gave elimination product **57** as the major one. The inverted ester **56** was only obtained in poor ~15% yield. Further screening of Mitsunobu reaction conditions such as reagents, solvents, and temperature did not provide significant improvements. We propose the steric hinderance around C5 might be the main reason for elimination being the preferential reaction pathway. Although this approach enabled us to access the designed [2+2] substrate, the efficiency was not optimal due to the side reaction evident in the final Mitsunobu step. Thus, we were seeking alternative solutions to improve material throughput.




**Scheme 2.3** Constructing C5 stereocenter using oxidation/reduction sequence

Because the Mitsunobu reaction did not provide satisfactory synthetic efficiency, we turned to a classic oxidation/reduction sequence to reverse the C5 stereocenter. We hypothesized that the adjacent carbon chain on C4 would block the hydride approach from the undesired top face, affording the desired *syn* disposed product preferentially. The experimental results supported our assumption. DDQ deprotection and DMP oxidation led to ketone **59** in 35% yield overall. Of note, **59** was not air stable due to its propensity for aerobic oxidation to the aromatic system. We subjected **59** to reduction after a rudimentary column purification, using DIBAL-H as the reducing reagent at -78 °C, delivering alcohol **60** in 5:1 diastereomeric ratio. Additionally, the undesired diastereomer **58** could be recycled through this pathway. The total 85% yield of **58** and **60** was much better compared to the Mitsunobu result. With **60** in hand, we transformed the OTf group into an ester through Pd-catalyzed carbonylation,[7] and a subsequent DCC esterification gave [2+2] substrate **62** in overall 49% yield.

### *2.2.2 Exploration of [2+2] Reaction*




**63** **64**

| Y | Additive | Solvent | Time | Result |
|---|---|---|---|---|
| -$CH_2OBn$ (**56**) | None | $CH_3CN$ | 4 h | No reaction |
| | PhCOPh (1 equiv.) | $CH_3CN$ | 3 h | Decomposition |
| -$CO_2Me$ (**62**) | None | $CH_3CN$ | 6.5 h | No reaction |
| | $PhCOCH_3$ (1 equiv.) | $CH_3CN$ | 9 h | No reaction |
| | None | $CH_3CN$/ac = 9:1 | 6 h | Decomposition |
| | None[a] | $CH_3CN$/ac = 9:1 | 6 h | No reaction |
| | None[a] | acetone | 11 h | No reaction |

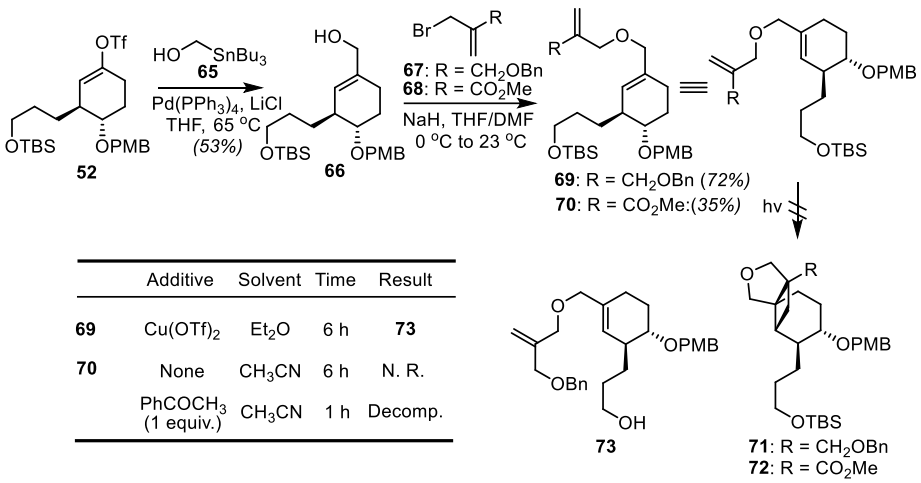
a: Pyrex filter was used

**Table 2.1** Condition screening for [2+2] reaction

With synthetic access to two different [2+2] addition substrates **56** and **62**, we hoped they would provide some insights into the photochemical reaction efficacy with both the unactivated double bond and the conjugated, electron deficient double bond. The 500 W medium-pressure

mercury lamp was chosen as the light source, which is typical in [2+2] reactions. We screened a number of reaction parameters, including solvent, wavelengths, and additives, but the only results we obtained on the two substrates were decomposition or no reaction at all.[8] It quickly became evident we needed to modify our substrate since no matter in substrate **56** or **62**, our designed [2+2] reaction failed to form the 7-membered lactone ring. This transformation might be too challenging since the strain energy of the transition state for forming such a lactone would exceptionally high. Therefore, it is likely the two olefins would never have a chance to approach each other. In that spirit, we were wondering if we could move the linkage of double bond to C11. Now the intramolecular [2+2] would form a 5/4 ring system. And according to the "rule of five" in [2+2] reaction,[8] this would be much more favorable compared to the previous 7/4 ring system.

Starting from coupling precursor **52** again, we accessed the primary alcohol **66** through Stille coupling with organotin reagent **65** in 53% yield. Then we synthesized two substrates, **69** and **70,** through a simple NaH deprotonation and allylic substitution reaction. For the $CH_2OBn$ substrate, we used $Cu(OTf)_2$ as the additive. We hoped the Cu cation would coordinate the two double bonds and placing them in close proximity and facilitating the [2+2] reaction, but only deprotection product **73** was observed. The other $CO_2Me$ substrate was subjected to normal [2+2] conditions. Without any additives we did not observe any reaction, however; when we add the triplet sensitizer $PhCOCH_3$, the substrate quickly decomposed in the reaction system, prompting us to reconsider the viability of this approach.




| | Additive | Solvent | Time | Result |
|---|---|---|---|---|
| **69** | $Cu(OTf)_2$ | $Et_2O$ | 6 h | **73** |
| **70** | None | $CH_3CN$ | 6 h | N. R. |
| | $PhCOCH_3$ (1 equiv.) | $CH_3CN$ | 1 h | Decomp. |

**Scheme 2.4** Ether linkage substrate for [2+2] reaction

## *2.3 Conclusion and Outlook*

Overall, we established a concise, reliable route to access B ring stereocenters featuring a Michael addition, oxidation/reduction sequence, and coupling reaction. This approach enabled us to access different substrates and thoroughly examine the possibility of constructing the highly substituted four-membered D ring in annotinolide B (**6**) via an intramolecular [2+2] reaction. With the results obtained above, we proposed that an intramolecular approach for the D ring system might be too strained to proceed effectively. The highly substituted four-membered ring therefore would need to be synthesized first, or through an intermolecular reaction with highly reactive allenes like in Ayer's work. In addition, the designed route for annotinolide B (**6**) laid a foundation for the following first-generation route of annotinolide C (**7**).

## *2.4 Experimental Section*

**General procedures.** All reactions were carried out under an argon atmosphere with dry solvents under anhydrous condition, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, dimethylformamide (DMF), diethyl ether ($Et_2O$) and dichloromethane ($CH_2Cl_2$) were obtained by

passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically ($^{1}$H and $^{13}$C NMR) homogenous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 nm E. SiliCycle silica gel plates (60F-254) using UV light as visualizing agent, and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040-0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker 500 MHz and 400 MHz instruments and calibrated using residual undeuterated solvents as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on an Agilent 6244 Tof-MS using ESI (Electronspray Ionization) at the University of Chicago Mass Spectroscopy Core Facility.

**Abbreviations.** THF = tetrahydrofuran, $Et_3N$ = triethylamine, EtOAc = ethyl acetate, DME = 1,2-dimethoxyethane, MeLi = methyl lithium, $PhNTf_2$ = *N*,*N*-bis(trifluoromethylsulfonyl)aniline, $Pd(PPh_3)_4$ = tetrakis(triphenylphosphine)palladium(0), DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone, $Ph_3P$ = triphenylphosphine, DEAD = diethyl azodicarboxylate, DMP= Dess-Martin periodinane, DIBAL-H = diisobutylaluminium hydride, MeOH = methanol, $Pd(OAc)_2$ = palladium(II) acetate, DMAP = 4-dimethylaminopyridine, DCC

= *N*,*N*′-dicyclohexylcarbodiimide, DMF = *N*,*N*-Dimethylformamide, $Et_2O$ = diethyl ether, KHMDS = potassium bis(trimethylsilyl)amide.

**Silyl enol ether 51.** To a round-bottom flask was charged with Mg turnings (2.07 g, 85.2 mmol, 9.0 equiv) and a magnetic stir bar. Heated the flask under vacuum for 3 min with propane gun. After the flask was cooled to 23 ℃ under vacuum, a small portion of THF (10 mL) was added, followed by 5 drops of 1,2-dibromomethane via syringe. The suspension was vigorously stirred until the bubbles formed from the surface of Mg turnings. Then bromide **50**[4] (12.71 g, 50.2 mmol, 5.3 equiv) in THF (40 mL) was added via syringe pump at 23 ℃ over 40 min. The suspension gradually turned cloudy and gray. When the addition was finished, the suspension was further stirred for 30 min and then diluted with THF (50 mL). A clear solution was obtained and transferred to a flame-dried flask. The solution was cooled to -78 ℃ using a dry ice-acetone bathe and CuCN·2LiCl (1.0 M in THF, 18.9 mL, 18.9 mmol, 2.0 equiv) was added. The resulting suspension was vigorously stirred at -45 ℃ for 30 min and cooled back to -78 ℃. Then $Et_3N$ (2.63 mL, 18.9 mmol, 2.0 equiv), TMSCl (2.40 mL, 18.9 mmol, 2.0 equiv), and **49**[3] (2.20 g, 9.47 mmol, 1.0 equiv) in THF (45 mL) were added subsequently. Use a small amount of THF (5.0 mL) to ensure a complete transfer of **49**. After the reaction was completed at -78 ℃ by TLC monitoring (typically 40 min), the cold bath was removed and directly concentrated in vacuo. The crude slurry obtained was redissolved in hexanes (100 mL) and filtered through Celite (eluted with hexanes). Repeated this procedure twice until there was no participate observed after concentration. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 50:1→20:1) to give silyl enol ether **51** as a colorless oil and directly used in next step. **26**: $R_f$ = 0.57 (silica gel, hexanes/EtOAc, 4:1).

**Triflate 52.** The crude silyl enol ether **51** obtained above was dissolved in DME (47 mL) and cooled to -78 ℃ using a dry ice-acetone bath. MeLi (1.6 M in ether, 8.9 mL, 14.2 mmol, 1.5 equiv) was added dropwise. The solution turned brown and was directly warmed up to 0 ℃ using an ice-water bath. Stirred at 0 ℃ and after the silyl enol ether was fully consumed based on TLC analysis (typically 30 min), the solution was cooled back to -78 ℃. Then $PhNTf_2$ (6.77 g, 18.9 mmol, 2.0 equiv) in THF (47 mL) was added slowly. Warmed up the reaction solution directly to 0 ℃ after the addition. When the reaction was completed based on TLC analysis (typically 1 h), quenched the reaction with saturated $NH_4Cl$ solution (40 mL) and EtOAc (40 mL). Removed the cold bath and transferred the reaction contents into a separatory funnel. After separation, the aqueous layer was extracted with EtOAc (3 × 40 mL). The organic layers were combined and washed with brine (100 mL), dried ($Na_2SO_4$), filtered and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 20:1) to give triflate **52** (2.44 g, 48% yield for 2 steps) as a colorless oil. **52**: $R_f$ = 0.58 (silica gel, hexanes/EtOAc, 4:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 5.63 (d, *J* = 3.6 Hz, 1 H), 4.54 (d, *J* = 11.3 Hz, 1 H), 4.42 (d, *J* = 11.4 Hz, 1 H), 3.80 (s, 3 H), 3.58 (t, *J* = 6.0 Hz, 2 H), 3.38 (td, *J* = 7.7, 6.5, 2.8 Hz, 1 H), 2.47 (dt, *J* = 15.1, 8.7 Hz, 1 H), 2.43–2.36 (m, 1 H), 2.36–2.26 (m, 1 H), 2.00 (ddt, *J* = 10.5, 6.6, 3.8 Hz, 1 H), 1.86 (dq, *J* = 13.5, 6.8 Hz, 1 H), 1.63–1.44 (m, 3H), 1.38 (ddd, *J* = 18.1, 11.5, 7.2 Hz, 1 H), 0.89 (s, 9 H), 0.04 (s, 6 H).

**Benzyl ether 54.** The triflate **52** (280 mg, 0.520 mmol, 1.0 equiv) was dissolved in THF (3.0 mL) in a seal tube. Tin reagent **53** (641 mg, 1.56 mmol, 3.0 equiv)[5] and LiCl (441 mg, 10.4 mmol, 20 equiv) were added and bubbled the reaction solution through Ar for 20 min. Then $Pd(PPh_3)_4$ (120 mg, 0.104 mmol, 0.20 equiv) were added and the reaction system was sealed.

Directly heated the reaction solution at 110 ℃ using an oil bath. When the reaction was completed based on TLC analysis (typically 1.5 h), directly concentrated the reaction contents in vacuo. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 50:1→20:1) to give benzyl ether **54** (127 mg, 48% yield) as a pale-yellow oil. **54**: $R_f$ = 0.88 (silica gel, hexanes/EtOAc, 4:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.37–7.32 (m, 3 H), 7.30–7.26 (m, 4 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 5.55 (s, 1 H), 4.58 (d, *J* = 11.4 Hz, 1 H), 4.45 (s, 2 H), 4.41 (d, *J* = 11.4 Hz, 1 H), 3.90 (s, 2 H), 3.80 (s, 3 H), 3.58 (t, *J* = 6.2 Hz, 2 H), 3.35–3.28 (m, 1 H), 2.20 (d, *J* = 13.8 Hz, 2 H), 2.09–1.96 (m, 2 H), 1.64 (p, *J* = 8.1, 7.6 Hz, 1 H), 1.61–1.53 (m, 1 H), 1.53–1.46 (m, 1 H), 1.39–1.28 (m, 2 H), 0.89 (s, 9 H), 0.04 (s, 6 H).

**Alcohol 55.** The benzyl ether **54** (120 mg, 0.235 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (2.0 mL) and deionized $H_2O$ (0.10 mL). The solution was cooled to 0 ℃ using an ice-water bath and DDQ (64.2 mg, 0.282 mmol, 1.2 equiv) was added in one portion. The solution turned dark-green, and the cold bath was directly removed after addition. When the starting material was fully consumed based on TLC analysis (typically 30 min), the reaction was with saturated $NaHCO_3$ solution (3.0 mL). The reaction contents were transferred into a separatory funnel. After separation, the aqueous layer was extracted with $CH_2Cl_2$ (3 × 3.0 mL). The organic layers were combined and washed with brine (10 mL), dried ($Na_2SO_4$), filtered and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 10:1) to give alcohol **55** (48.9 mg, 53% yield) as a colorless oil. **55**: $R_f$ = 0.21 (silica gel, hexanes/EtOAc, 4:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.41–7.31 (m, 3 H), 7.31–7.25 (m, 2 H), 5.54 (s, 1 H), 4.46 (s, 2 H), 3.90 (s, 2 H), 3.66–3.59 (m, 3 H), 2.24–2.15 (m, 1 H), 2.14–2.06 (m, 2 H), 1.91 (ddd, *J* = 12.8, 8.6, 5.0 Hz, 1H), 1.73–1.57 (m, 4 H), 1.43–1.33 (m, 1 H), 0.89 (s, 9 H), 0.05 (s, 6 H).

**Ester 56 and alkene 57.** The alcohol **55** (23.1 mg, 0.0589 mmol, 1.0 equiv) was dissolved in THF (0.60 mL) and cooled to 0 ℃ using an ice-water bath. methyl acrylate (25 μL, 0.295 mmol, 5.0 equiv) and $Ph_3P$ (77.4 mg, 0.295 mmol, 5.0 equiv) were added subsequently. After stirring at 0 ℃ for 5 min, DEAD (0.13 mL, 40% in toluene, 0.295 mmol, 5.0 equiv) was added and the cold bath was removed. When the starting material was fully consumed based on TLC analysis (typically 3.5 h), the reaction was diluted with deionized $H_2O$ (2.0 mL) and EtOAc (2.0 mL). The reaction contents were transferred into a separatory funnel and separated. Then the aqueous layer was extracted with EtOAc (3 × 2.0 mL). The organic layers were combined and washed with brine (5 mL), dried ($Na_2SO_4$), filtered and concentrated. The resultant residue was purified by PTLC (silica gel, hexanes/EtOAc, 5:1) to give alcohol **56** and alkene **57** as colorless oils. The relative ratio was determined by crude NMR. **56**: $R_f$ = 0.79 (silica gel, hexanes/EtOAc, 4:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.39–7.32 (m, 3 H), 7.26 (s, 2 H), 6.10–6.02 (m, 1 H), 5.57 (s, 1 H), 5.51 (q, *J* = 1.7 Hz, 1 H), 5.23–5.17 (m, 1 H), 4.46 (d, *J* = 2.1 Hz, 2 H), 3.97–3.89 (m, 2 H), 3.60 (t, *J* = 6.1 Hz, 2 H), 2.40 (d, *J* = 10.2 Hz, 1 H), 2.16–2.04 (m, 3 H), 1.92 (d, *J* = 1.3 Hz, 3 H), 1.79–1.69 (m, 1 H), 1.67–1.48 (m, 3 H), 1.41–1.30 (m, 1 H), 0.88 (s, 9 H), 0.03 (d, *J* = 1.4 Hz, 6 H). **57**: $R_f$ = 0.83 (silica gel, hexanes/EtOAc, 4:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.40–7.33 (m, 4 H), 7.32–7.27 (m, 1 H), 5.77 (dtd, *J* = 9.1, 3.4, 1.9 Hz, H), 5.69–5.57 (m, 2 H), 4.47 (s, 2 H), 3.94 (s, 2 H), 3.61 (t, *J* = 6.4 Hz, 2 H), 2.82 (s, 1 H), 2.71–2.63 (m, 2 H), 1.63–1.52 (m, 2 H), 1.51– 1.42 (m, 2 H), 0.89 (s, 9 H), 0.04 (s, 6 H).

**Alcohol 58.** The triflate **52** (275 mg, 0.510 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (5.0 mL) and deionized $H_2O$ (0.25 mL). The substrate solution was cooled to 0 ℃ and DDQ (139 mg, 0.613 mmol, 1.2 equiv) was added. Removed the cold bath and after the starting material was fully consumed based on TLC analysis (typically 25 min), the reaction was

quenched by saturated $NaHCO_3$ (5.0 mL). The reaction contents were transferred into a separatory funnel and separated. Then the aqueous layer was extracted with $CH_2Cl_2$ (3 × 5.0 mL). The organic layers were combined and washed with brine (12 mL), dried ($Na_2SO_4$), filtered and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 10:1) to give alcohol **58** (199 mg, 93% yield) as a colorless oil. **58**: $R_f$ = 0.22 (silica gel, hexanes/EtOAc, 4:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 5.62 (dt, *J* = 3.1, 1.5 Hz, 1 H), 3.72–3.66 (m, 1 H), 3.64 (t, *J* = 5.9 Hz, 2 H), 2.51–2.36 (m, 2 H), 2.33–2.26 (m, 1 H), 1.98 (dtd, *J* = 13.1, 5.9, 3.1 Hz, 1 H), 1.90–1.81 (m, 1 H), 1.76 (d, *J* = 4.7 Hz, 1 H), 1.65 (qq, *J* = 6.1, 3.7, 2.7 Hz, 2 H), 1.47–1.39 (m, 1 H), 0.89 (s, 9 H), 0.05 (s, 6 H).

**Ketone 59.** The alcohol **58** (200 mg, 0.478 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (4.8 mL) and $NaHCO_3$ (402 mg, 4.78 mmol, 10.0 equiv). Then the suspension was cooled to 0 ℃ and DMP (811 mg, 1.91 mmol, 4.0 equiv) was added. Removed the cold bath and after the starting material was fully consumed based on TLC analysis (typically 1 h), the reaction was quenched by $Na_2S_2O_3$ (3.0 M in $H_2O$, 5.0 mL). The reaction contents were transferred into a separatory funnel and separated. Then the aqueous layer was extracted with $CH_2Cl_2$ (3 × 5.0 mL). The organic layers were combined and washed with brine (12 mL), dried ($Na_2SO_4$), filtered and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 10:1) to give ketone **59** (76.6 mg, 38% yield) as a colorless oil. **58**: $R_f$ = 0.24 (silica gel, hexanes/EtOAc, 4:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 5.86 (d, *J* = 3.7 Hz, 1 H), 3.64 (t, *J* = 6.1 Hz, 2 H), 3.03 (s, 1 H), 2.80 (t, *J* = 6.7 Hz, 2 H), 2.70 (dq, *J* = 13.8, 6.9 Hz, 2 H), 1.78 (tt, *J* = 13.6, 6.7 Hz, 2 H), 1.57–1.50 (m, 2 H), 0.91 (s, 9 H), 0.07 (s, 6 H). [Note: the product was not stable under vacuum, so the reaction was set up in a multiple parallel fashion and combined in the next step.]

**Alcohol 60.** The ketone **59** (257 mg, 0.617 mmol, 1.0 equiv) was dissolved in THF (6.2 mL) and cooled to -78 ℃. Then DIBAL-H (1.0 M in THF, 2.22 mL, 2.22 mmol, 3.6 equiv) was added dropwise. The reaction solution was stirred at – 78 ℃ until the starting material was fully consumed based on TLC analysis (typically 30 min), the reaction was quenched by saturated Rochelle's salt (6.0 mL). Removed the cold bath and stirred for another 30 min. The reaction contents were transferred into a separatory funnel and separated. Then the aqueous layer was extracted with EtOAc (3 × 6.0 mL). The organic layers were combined and washed with brine (14 mL), dried ($Na_2SO_4$), filtered and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 10:1) to give alcohol **60** (172 mg, 67% yield) and alcohol **58** (46.3 mg, 18% yield) as colorless oils. **60**: $R_f$ = 0.25 (silica gel, hexanes/EtOAc, 4:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 5.51 (s, 1 H), 4.05 (s, 1 H), 3.66 (p, *J* = 5.4, 4.8 Hz, 2 H), 2.65–2.52 (m, 1 H), 2.42 (s, 1 H), 2.36–2.24 (m, 1 H), 2.08 (dtd, *J* = 15.0, 6.0, 3.4 Hz, 1 H), 1.80 (dd, *J* = 12.9, 5.7 Hz, 2 H), 1.65 (dddd, *J* = 14.9, 11.5, 8.2, 4.9 Hz, 3 H), 0.90 (s, 9 H), 0.06 (s, 6 H).

**Ester 61.** The alcohol **59** (46.0 mg, 0.110 mmol, 1.0 equiv) was dissolved in MeOH (1.1 mL). Then Hünig base (0.96 mL, 0.550 mmol, 5.0 equiv) and $Ph_3P$ (5.8 mg, 0.0220 mmol, 0.20 equiv) was added. The reaction solution was bubbled through CO gas using a balloon and syringe needle for 15 min. $Pd(OAc)_2$ (2.5 mg, 0.0110 mmol, 0.10 equiv) was added subsequently and the reaction solution was stirred at 23 ℃ until the starting material was fully consumed based on TLC analysis (typically 30 min). The reaction was quenched by saturated aqueous $NH_4Cl$ (4.0 mL) and ether (4.0 mL). The reaction contents were transferred into a separatory funnel and separated. Then the aqueous layer was extracted with ether (3 × 4.0 mL). The organic layers were combined and washed with brine (8.0 mL), dried ($MgSO_4$), filtered and

concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 8:1) to give ester **61** (22.2 mg, 61% yield) as a colorless oil. **61**: $R_f$ = 0.27 (silica gel, hexanes/EtOAc, 4:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 6.75 (s, 1 H), 4.07 (s, 1 H), 3.73 (s, 3 H), 3.66 (tt, *J* = 6.9, 3.4 Hz, 2 H), 2.44–2.37 (m, 2 H), 2.36–2.28 (m, 1 H), 2.03–1.96 (m, 1 H), 1.75–1.61 (m, 4 H), 1.53–1.44 (m, 1 H), 0.90 (s, 9 H), 0.06 (s, 6 H).

**Ester 62.** The ester **61** (22.2 mg, 0.0670 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (1.32 mL) and DMAP (8.2 mg, 0.0670 mmol, 1.0 equiv), methyl acrylate (8.5 μL, 100 mmol, 1.5 equiv) were added. The reaction solution was cooled to 0 °C using an ice-water bath and DCC (20.6 mg, 0.100 mmol, 1.5 equiv) was added. Then the cold bath was removed, and a pale-yellow suspension was formed. After the starting material was fully consumed based on TLC analysis (typically 24 h), the reaction was quenched by saturated $NaHCO_3$ (2.0 mL). The reaction contents were then transferred into a separatory funnel and separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 3.0 mL). The organic layers were combined and washed with brine (6.0 mL), dried ($Na_2SO_4$), filtered and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 15:1) to give ester **62** (21.3 mg, 80% yield) as a colorless oil. **62**: $R_f$ = 0.47 (silica gel, hexanes/EtOAc, 4:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 6.82 (s, 1 H), 6.05 (s, 1 H), 5.53 (p, *J* = 1.6 Hz, 1 H), 5.22 (d, *J* = 5.5 Hz, 1 H), 3.75 (s, 3 H), 3.61 (t, *J* = 5.9 Hz, 2 H), 2.56–2.47 (m, 1 H), 2.38 (dd, *J* = 13.6, 8.8 Hz, 1 H), 2.35–2.24 (m, 1 H), 2.14 (dtd, *J* = 14.9, 5.8, 3.7 Hz, 1 H), 1.91 (t, *J* = 1.4 Hz, 3 H), 1.75–1.66 (m, 1 H), 1.65–1.56 (m, 3 H), 1.48–1.40 (m, 1 H), 0.88 (d, *J* = 2.2 Hz, 9 H), 0.03 (d, *J* = 1.5 Hz, 6 H).

**Alcohol 66.** The triflate **52** (235 mg, 0.436 mmol, 1.0 equiv) was dissolved in THF (2.2 mL) in a microwave tube and tin reagent **65** (280 mg, 0.872 mmol, 2.0 equiv), LiCl (370 mg, 8.72 mmol, 20 equiv) were added. The reaction solution was bubbled through Ar for 20 min

before $Pd(PPh_3)_4$ was added. Then the reaction system was sealed and directly heated at 65 ℃ using an oil bath. After the starting material was fully consumed based on TLC analysis (typically 1 h), the reaction was cooled to 23 ℃ and directly concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 5:1→2:1) to give alcohol **66** (97.7 mg, 53% yield) as a colorless oil. **66**: $R_f$ = 0.15 (silica gel, hexanes/EtOAc, 4:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.5 Hz, 2 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 5.54 (s, 1 H), 4.58 (d, *J* = 11.4 Hz, 1 H), 4.41 (d, *J* = 11.4 Hz, 1 H), 4.00 (d, *J* = 6.0 Hz, 2 H), 3.80 (s, 3 H), 3.58 (t, *J* = 6.1 Hz, 2 H), 3.48 (q, *J* = 7.0 Hz, 1 H), 3.35–3.30 (m, 1 H), 2.18 (d, *J* = 12.2 Hz, 2 H), 2.07–1.93 (m, 2 H), 1.65 (tt, *J* = 15.9, 8.2 Hz, 1 H), 1.38–1.23 (m, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H).

**Ether 69.** The alcohol **66** (95.1 mg, 0.226 mmol, 1.0 equiv) was dissolved in THF (1.80 mL) and DMF (0.45 mL) and the solution was cooled to 0 ℃ using an ice-water bath. Then NaH (27.1 mg, 0.677 mmol, 3.0 equiv) was added and stirred the suspension at 0 ℃ for 30 min. Bromide **67**[9] (65.1 mg, 0.271 mmol, 1.2 equiv) was added subsequently and the cold bath was removed after addition. When the starting material was fully consumed based on TLC analysis (typically 6 h), the reaction was quenched by saturated $NH_4Cl$ (2.0 mL). The reaction contents were then transferred into a separatory funnel and separated. The aqueous layer was extracted with $Et_2O$ (3 × 4.0 mL). The organic layers were combined and washed with brine (8.0 mL), dried ($Na_2SO_4$), filtered and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 20:1) to give ether **69** (94.0 mg, 72% yield) as a colorless oil. **69**: $R_f$ = 0.65 (silica gel, hexanes/EtOAc, 4:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 4.4 Hz, 4 H), 7.29–7.26 (m, 3 H), 6.93–6.78 (m, 2 H), 5.51 (s, 1 H), 5.21 (d, *J* = 8.6 Hz, 2 H), 4.58 (d, *J* = 11.4 Hz, 1 H), 4.51 (s, 2 H), 4.40 (d, *J* = 11.4 Hz, 1H), 4.04 (s, 2 H), 3.95 (s, 2

H), 3.84 (s, 2 H), 3.80 (s, 3 H), 3.57 (t, *J* = 6.1 Hz, 2 H), 3.34–3.26 (m, 1 H), 2.23–2.10 (m, 2 H), 2.05–1.94 (m, 2 H), 1.67–1.57 (m, 4 H), 1.34–1.28 (m, 1 H), 0.89 (s, 9 H), 0.04 (s, 6 H).

**Ether 70.** The alcohol **66** (35.0 mg, 0.0832 mmol, 1.0 equiv) was dissolved in THF (0.80 mL) and DMF (0.20 mL) and the solution was cooled to 0 ℃ using an ice-water bath. Then NaH (10.0 mg, 0.250 mmol, 3.0 equiv) was added and stirred the suspension at 0 ℃ for 30 min. Bromide **68** (12.0 μL, 0.100 mmol, 1.2 equiv) was added subsequently and the cold bath was removed after addition. When the starting material was fully consumed based on TLC analysis (typically 5 h), the reaction was quenched by saturated $NH_4Cl$ (1.0 mL). The reaction contents were then transferred into a separatory funnel and separated. The aqueous layer was extracted with $Et_2O$ (3 × 4.0 mL). The organic layers were combined and washed with brine (8.0 mL), dried ($Na_2SO_4$), filtered and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 20:1) to give ether **70** (14.9 mg, 35% yield) as a colorless oil. **70**: $R_f$ = 0.46 (silica gel, hexanes/EtOAc, 4:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 7.9 Hz, 2 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 6.37–6.25 (m, 1 H), 5.89 (dq, *J* = 21.1, 1.8 Hz, 1 H), 5.54 (s, 1 H), 4.58 (d, *J* = 11.3 Hz, 1 H), 4.40 (d, *J* = 11.3 Hz, 1 H), 4.31–4.20 (m, 1 H), 4.12 (t, *J* = 1.7 Hz, 2 H), 3.90 (s, 2 H), 3.80 (s, 3 H), 3.77 (s, 1 H), 3.76 (s, 2 H), 3.58 (t, *J* = 6.2 Hz, 2 H), 3.32 (tq, *J* = 6.9, 3.5, 2.7 Hz, 1 H), 2.26–2.13 (m, 2 H), 2.04–1.93 (m, 2 H), 1.69–1.56 (m, 3 H), 1.33 (ddd, *J* = 10.7, 7.8, 3.1 Hz, 1 H), 0.89 (s, 9 H), 0.04 (s, 6 H).

**General procedure for photochemical [2+2] reaction.** The substrate was dissolved in indicated solvents (0.04 M) in a quartz test tube. Additives was added at this stage if mentioned. Then the solution was bubbled through Ar for 20 min. After the Ar bubbling, the test tube was sealed and subjected to the irradiation of medium-pressured Hg lamp in the photoreactor. The

reaction was directly concentrated and purified by PTLC (silica gel, hexanes/EtOAc, 4:1) after subjecting to the indicated time.

### *2.5 Reference*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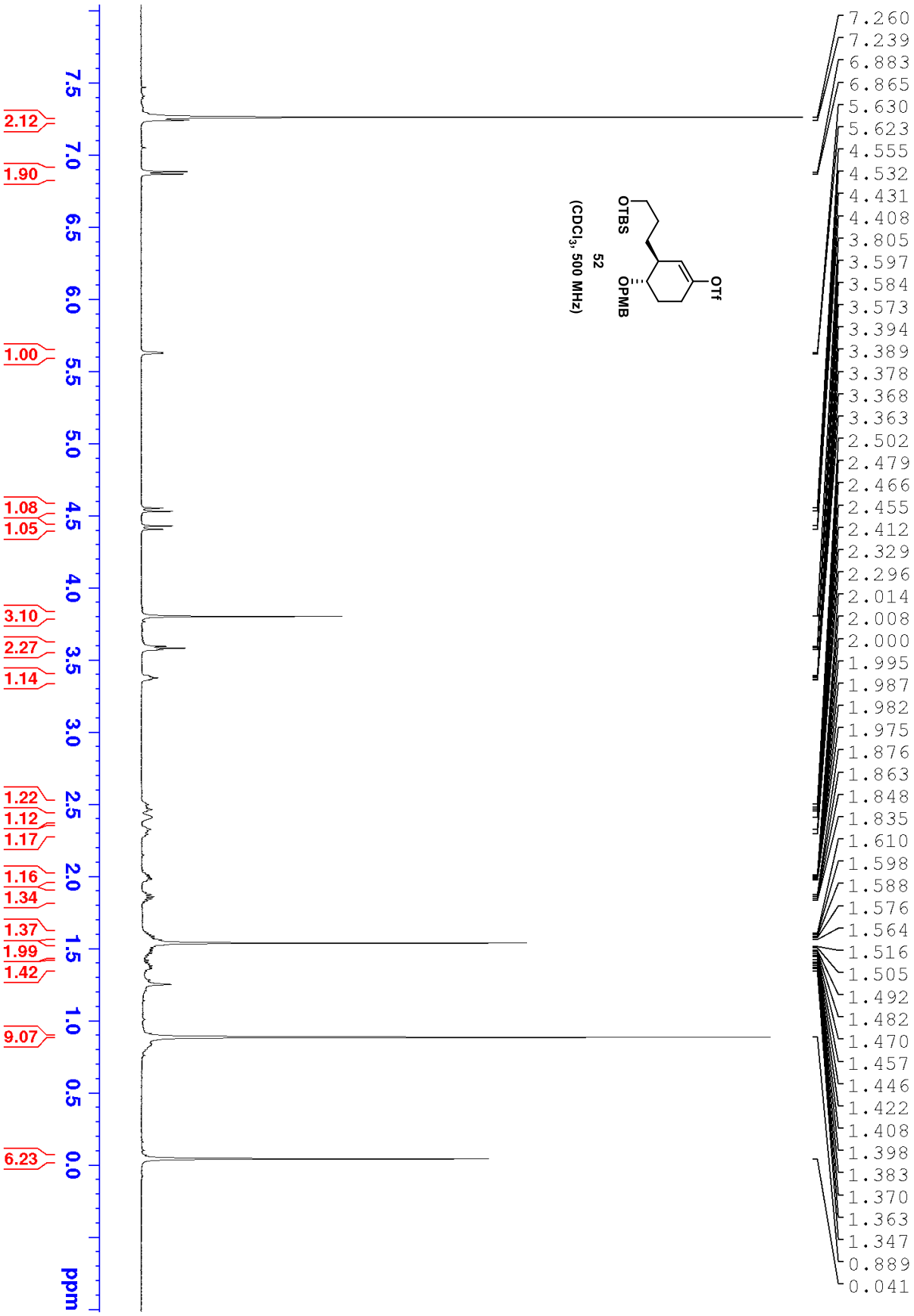
### *2.6 NMR Spectra of Selected Intermediates*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4.532
4.431
4.408
3.805
3.597
3.584
3.573
3.394
3.389
3.378
3.368
3.363
2.502
2.479
2.466
2.455
2.412
2.329
2.296
2.014
2.008
2.000
1.995
1.987
1.982
1.975
1.876
1.863
1.848
1.835
1.610
1.598
1.588
1.576
1.564
1.516
1.505
1.492
1.482
1.470
1.457
1.446
1.422
1.408
1.398
1.383
1.370
1.363
1.347
0.889
0.041
2.12
1.90
1.00
1.08
1.05
3.10
2.27
1.14
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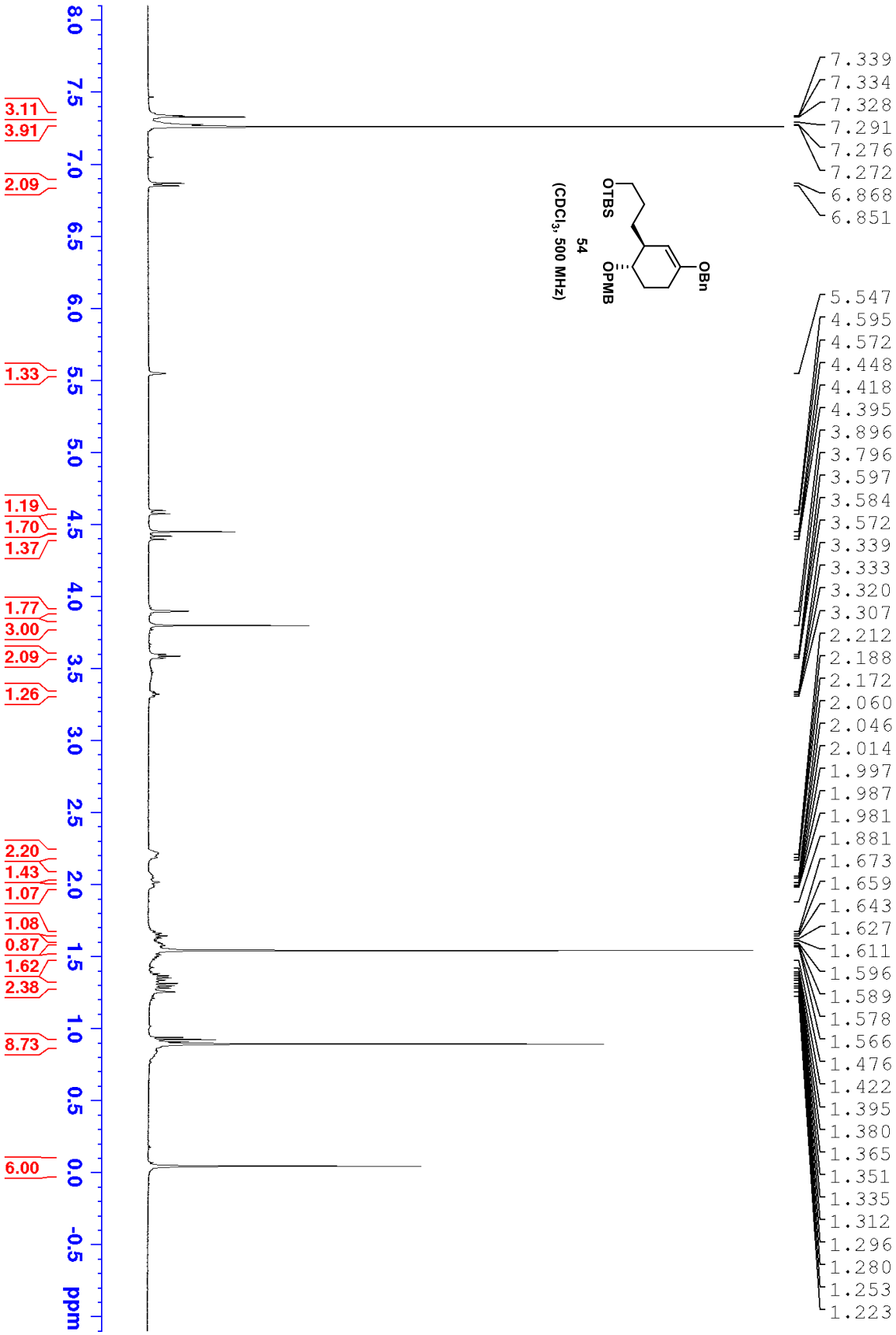
1.12
1.17
1.16
1.34
1.37
1.99
1.42
9.07
6.23
ppm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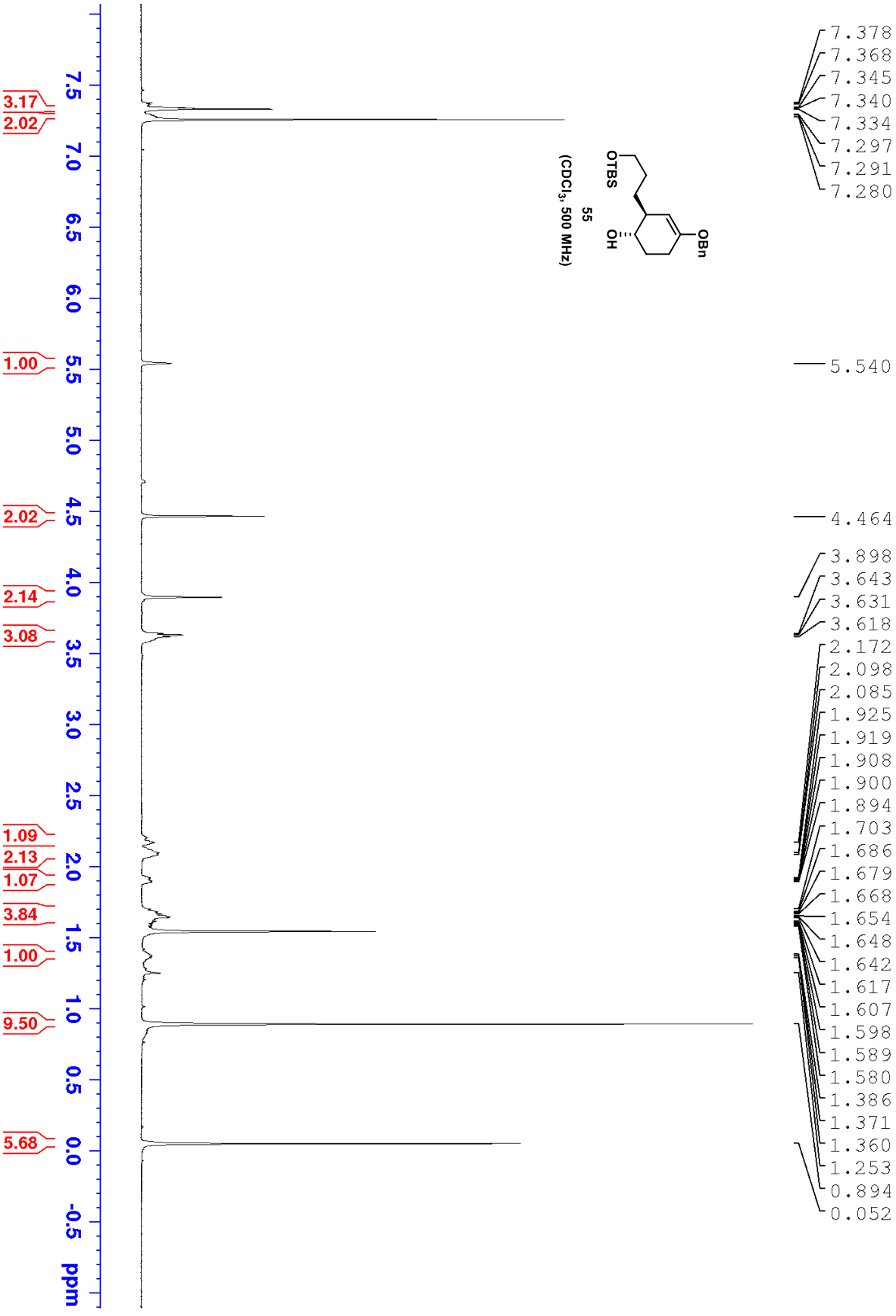
6.851
5.547
4.595
4.572
4.448
4.418
4.395
3.896
3.796
3.597
3.584
3.572
3.339
3.333
3.320
3.307
2.212
2.188
2.172
2.060
2.046
2.014
1.997
1.987
1.981
1.881
1.673
1.659
1.643
1.627
1.611
1.596
1.589
1.578
1.566
1.476
1.422
1.395
1.380
1.365
1.351
1.335
1.312
1.296
1.280
1.253
1.223
3.11
3.91
2.09
1.33
1.19
1.70
1.37
1.77
3.00
2.09
1.26
2.20
1.43
1.07
1.08
0.87
1.62
2.38
8.73
6.00
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
ppm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7.280
5.540
4.464
3.898
3.643
3.631
3.618
2.172
2.098
2.085
1.925
1.919
1.908
1.900
1.894
1.703
1.686
1.679
1.668
1.654
1.648
1.642
1.617
1.607
1.598
1.589
1.580
1.386
1.371
1.360
1.253
0.894
0.052
3.17
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1.00
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2.14
3.08
1.09
2.13
1.07
3.84
1.00
9.50
5.68
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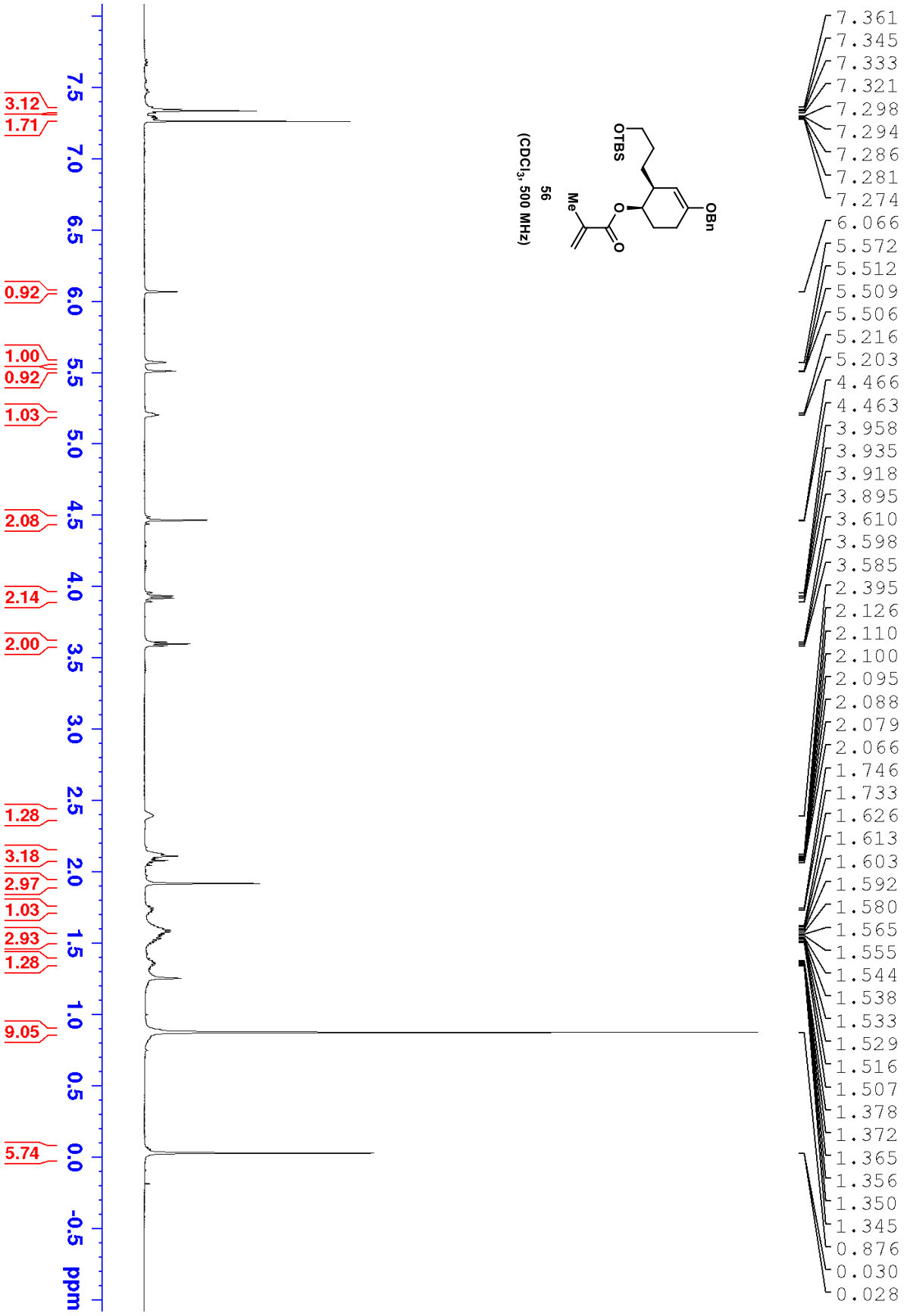
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7.286
7.281
7.274
6.066
5.572
5.512
5.509
5.506
5.216
5.203
4.466
4.463
3.958
3.935
3.918
3.895
3.610
3.598
3.585
2.395
2.126
2.110
2.100
2.095
2.088
2.079
2.066
1.746
1.733
1.626
1.613
1.603
1.592
1.580
1.565
1.555
1.544
1.538
1.533
1.529
1.516
1.507
1.378
1.372
1.365
1.356
1.350
1.345
0.876
0.030
0.028
3.12
1.71
0.92
1.00
0.92
1.03
2.08
2.14
2.00
1.28
3.18
2.97
1.03
2.93
1.28
9.05
5.74
7.5
7.0
6.5
6.0
5.5
5.0
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3.5
3.0
2.5
2.0
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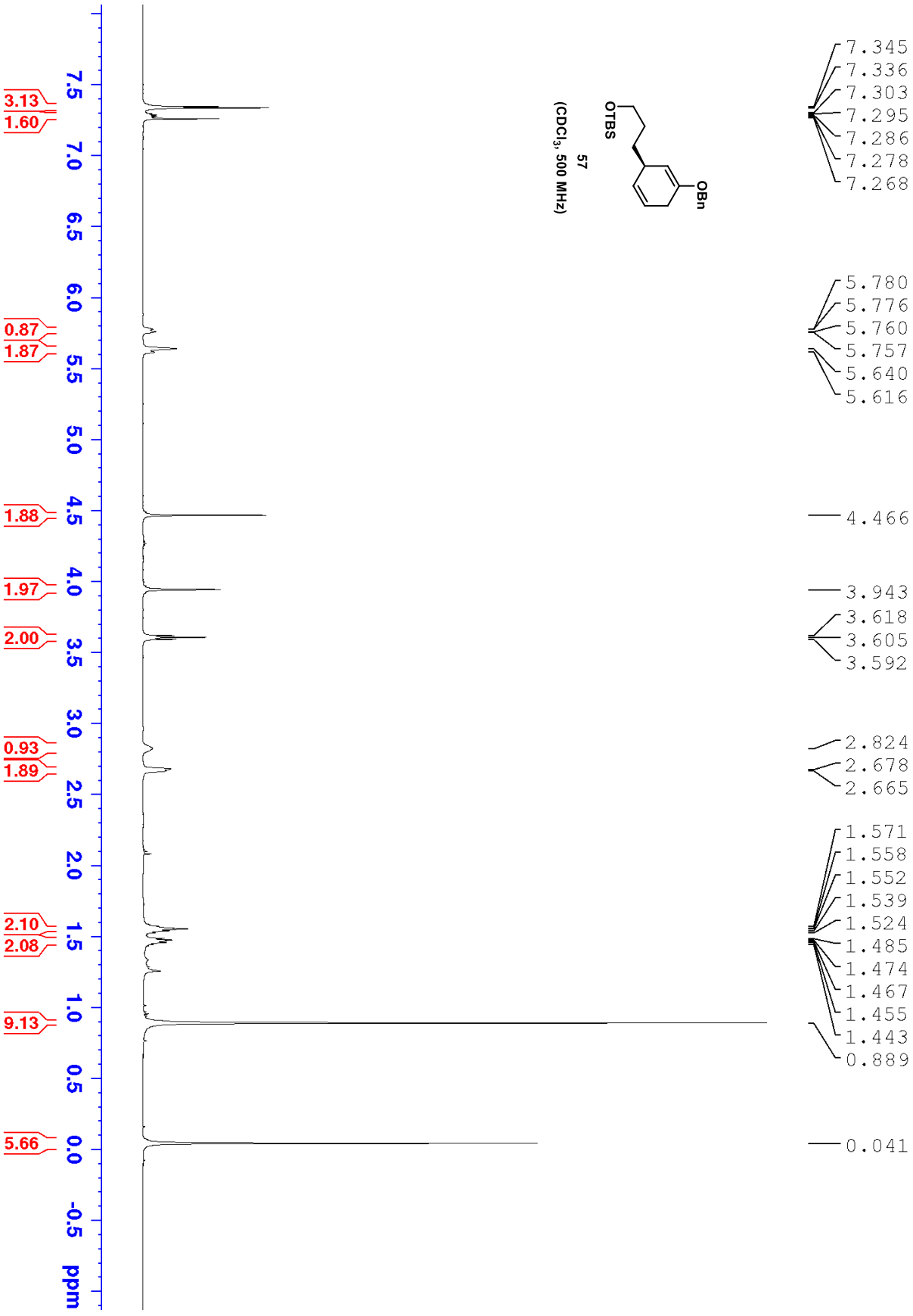
1.0
0.5
0.0
-0.5
ppm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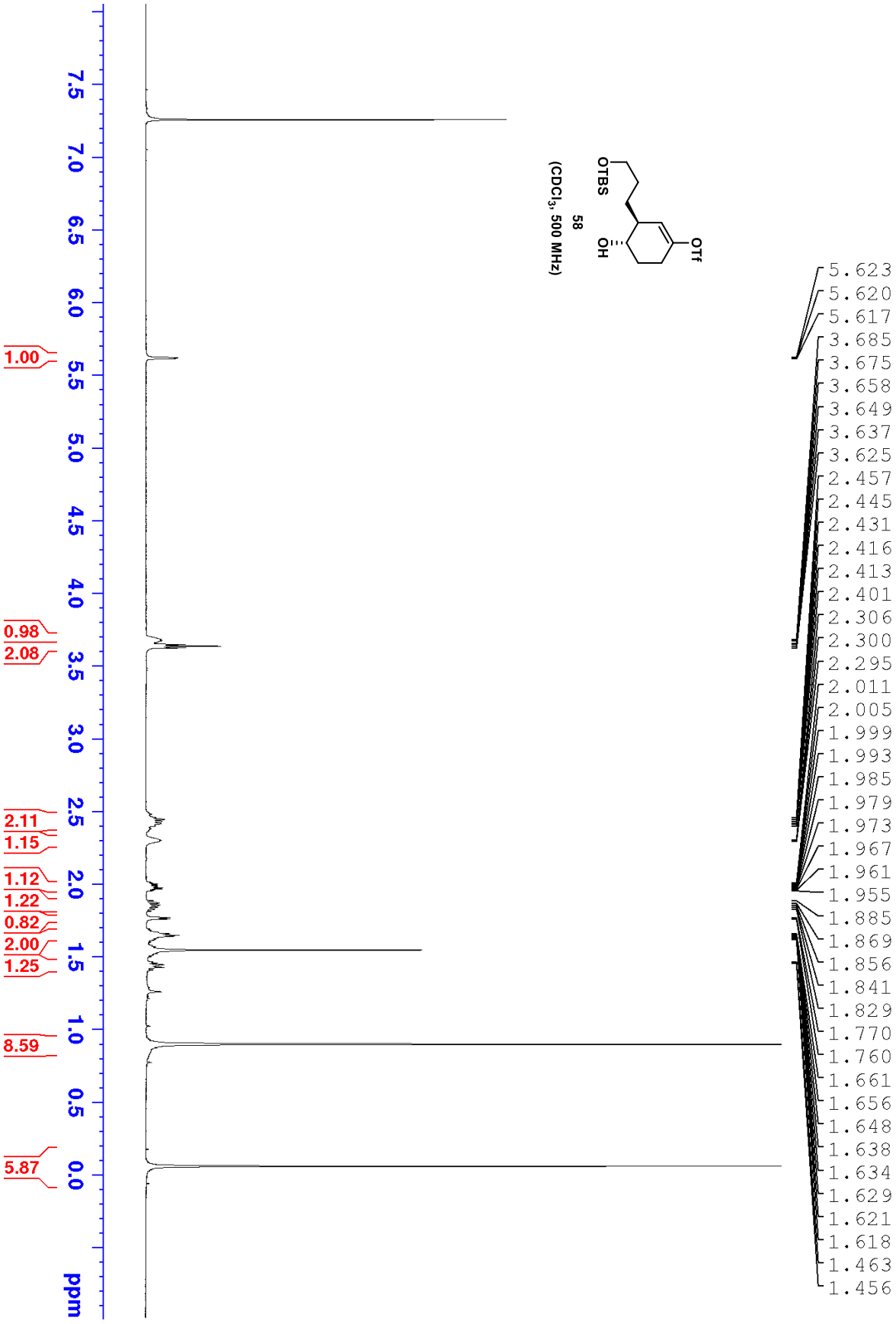
5.776
5.760
5.757
5.640
5.616
4.466
3.943
3.618
3.605
3.592
2.824
2.678
2.665
1.571
1.558
1.552
1.539
1.524
1.485
1.474
1.467
1.455
1.443
0.889
0.041
3.13
1.60
0.87
1.87
1.88
1.97
2.00
0.93
1.89
2.10
2.08
9.13
5.66
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm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3.649
3.637
3.625
2.457
2.445
2.431
2.416
2.413
2.401
2.306
2.300
2.295
2.011
2.005
1.999
1.993
1.985
1.979
1.973
1.967
1.961
1.955
1.885
1.869
1.856
1.841
1.829
1.770
1.760
1.661
1.656
1.648
1.638
1.634
1.629
1.621
1.618
1.463
1.456
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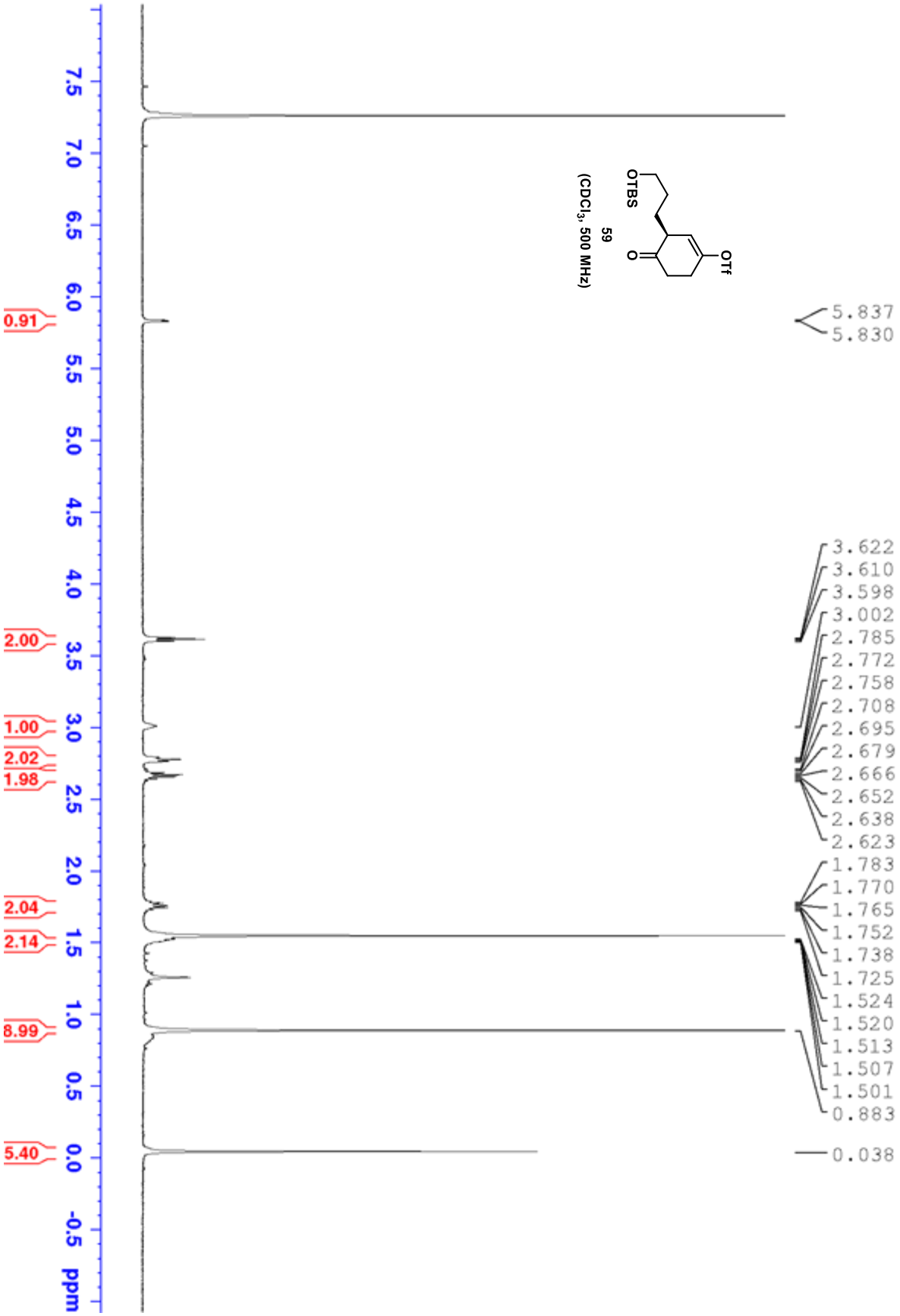
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2.708
2.695
2.679
2.666
2.652
2.638
2.623
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1.770
1.765
1.752
1.738
1.725
1.524
1.520
1.513
1.507
1.501
0.883
0.038
0.91
2.00
1.00
2.02
1.98
2.04
2.14
8.99
5.40
7.5
7.0
6.5
6.0
5.5
5.0
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3.5
3.0
2.5
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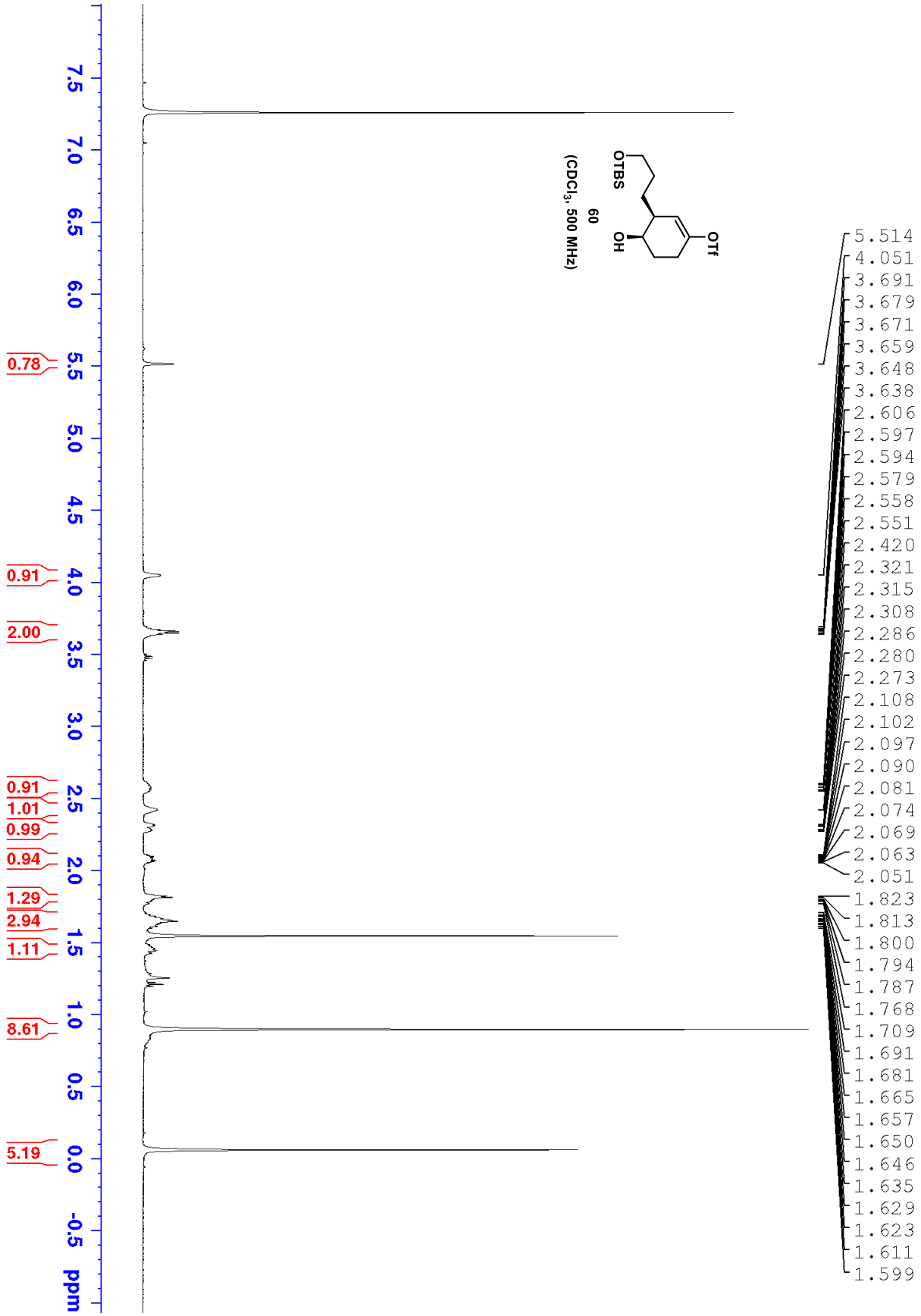
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0.99
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1.29
2.94
1.11
8.61
5.19
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
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3.679
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3.648
3.638
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2.308
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2.108
2.102
2.097
2.090
2.081
2.074
2.069
2.063
2.051
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1.800
1.794
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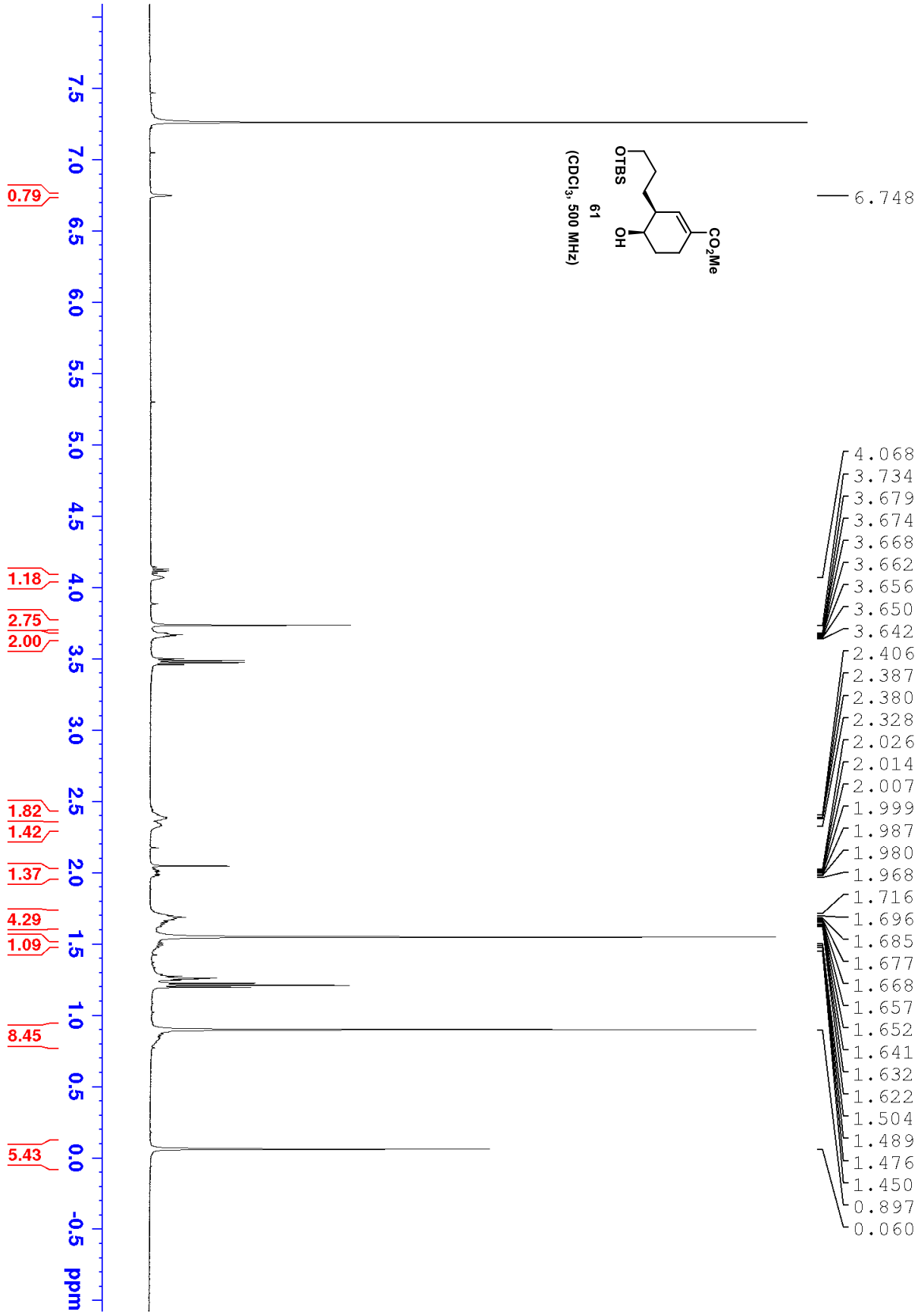
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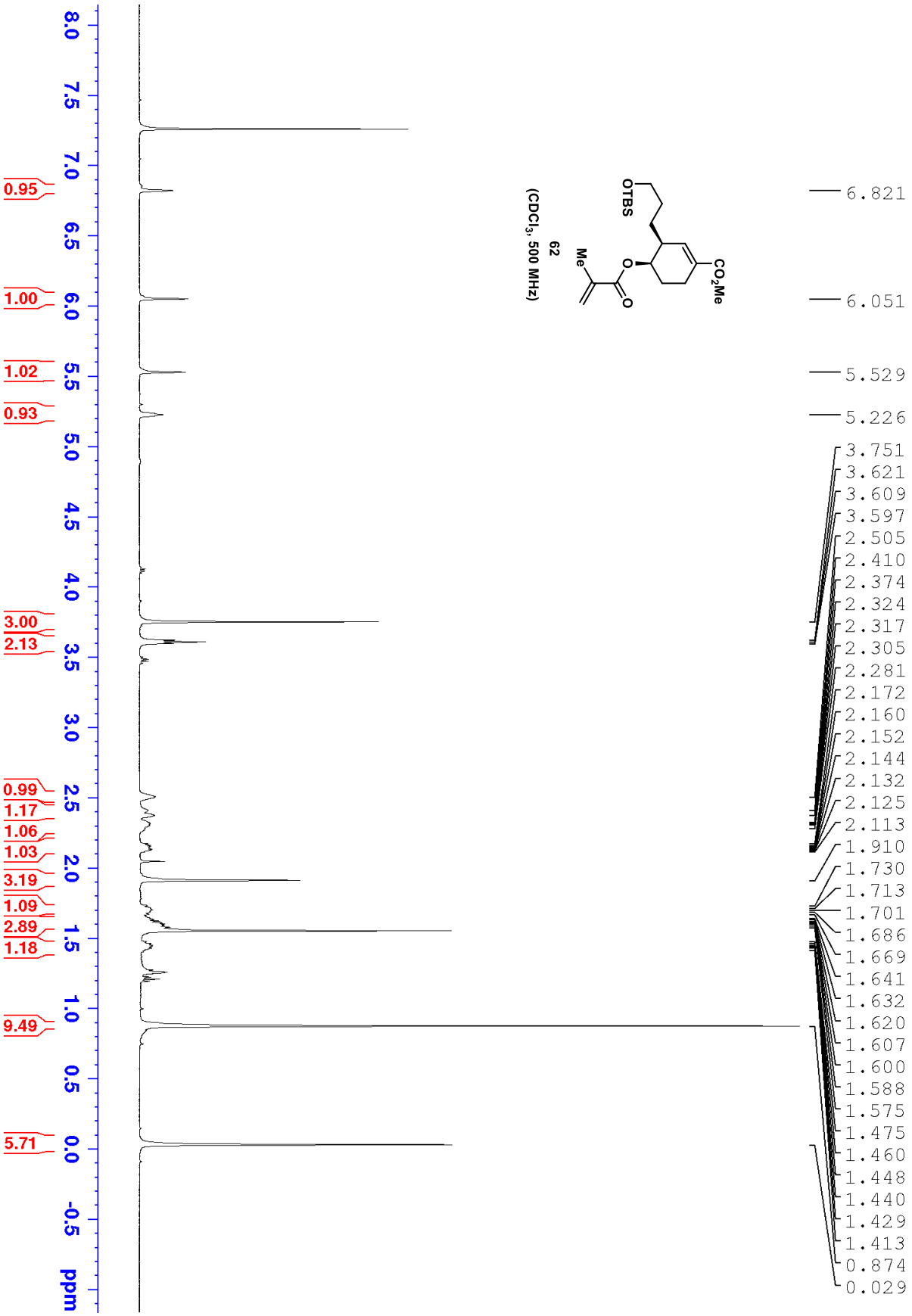
ppm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1.460
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1.440
1.429
1.413
0.874
0.029
0.95
1.00
1.02
0.93
3.00
2.13
0.99
1.17
1.06
1.03
3.19
1.09
2.89
1.18
9.49
5.71
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7.5
7.0
6.5
6.0
5.5
5.0
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1.0
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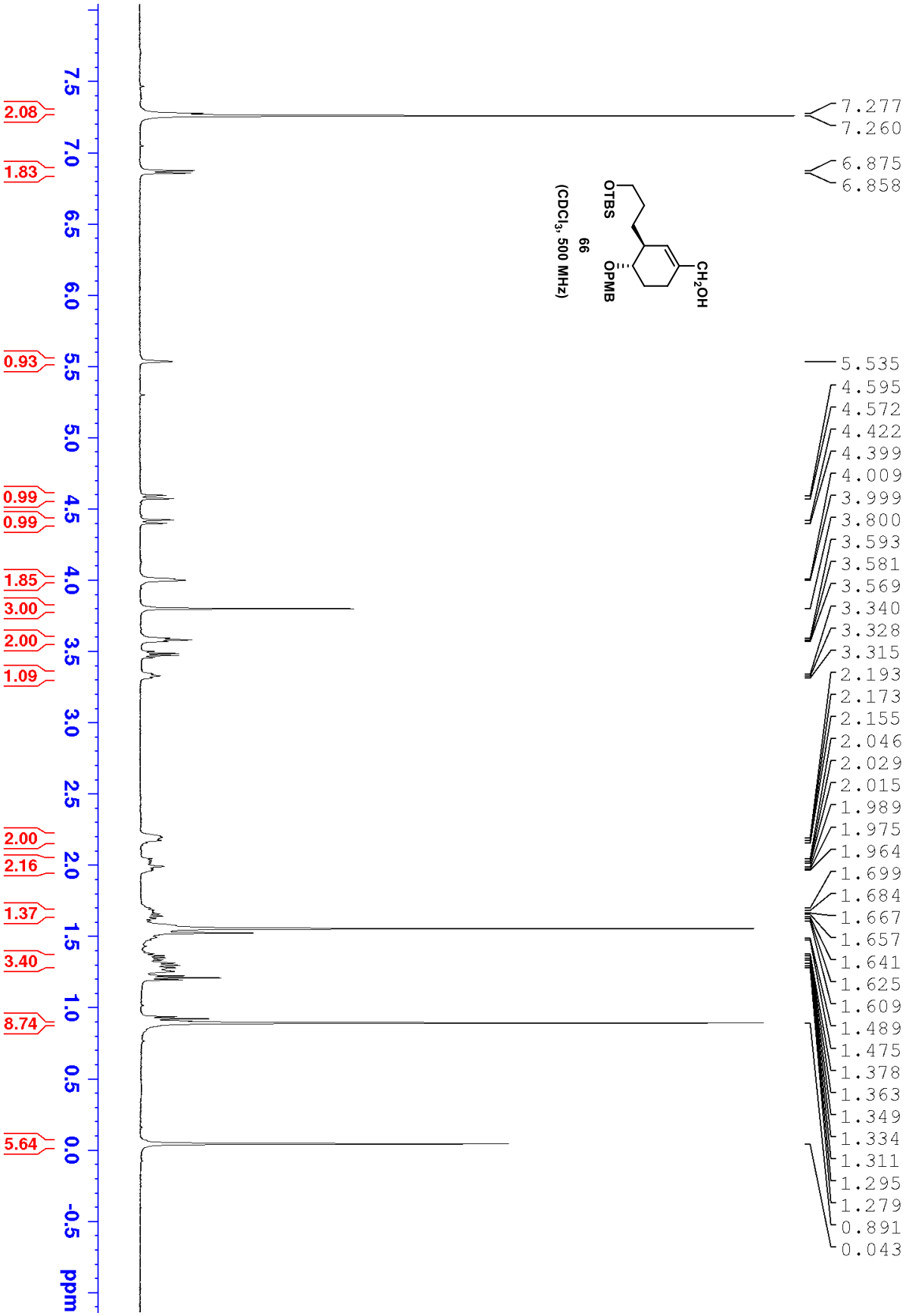
ppm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4.422
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3.999
3.800
3.593
3.581
3.569
3.340
3.328
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2.173
2.155
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2.029
2.015
1.989
1.975
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1.699
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1.667
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1.349
1.334
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0.043
2.08
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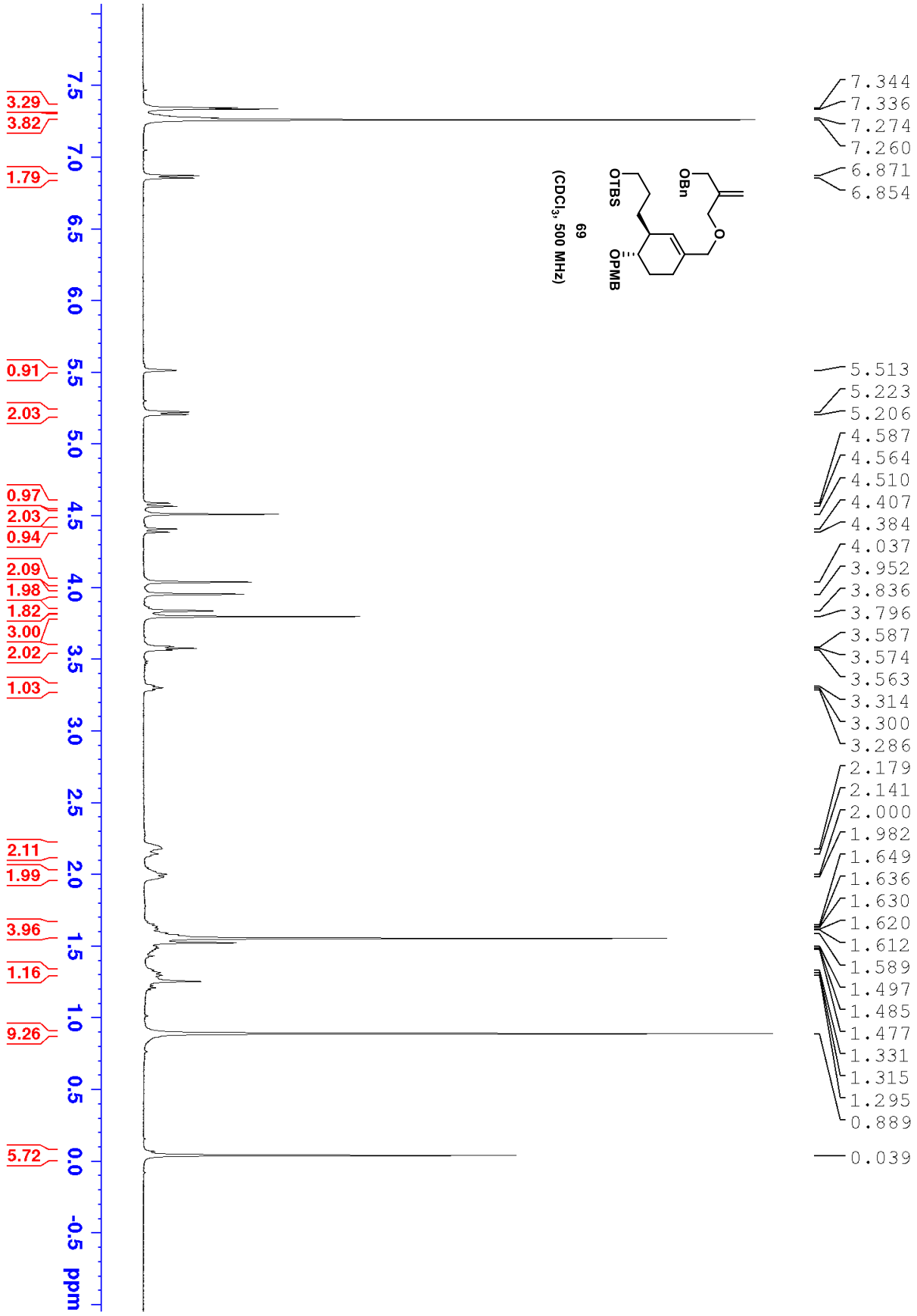
ppm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4.587
4.564
4.510
4.407
4.384
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1.485
1.477
1.331
1.315
1.295
0.889
0.039
3.29
3.82
1.79
0.91
2.03
0.97
2.03
0.94
2.09
1.98
1.82
3.00
2.02
1.03
2.11
1.99
3.96
1.16
9.26
5.72
7.5
7.0
6.5
6.0
5.5
5.0
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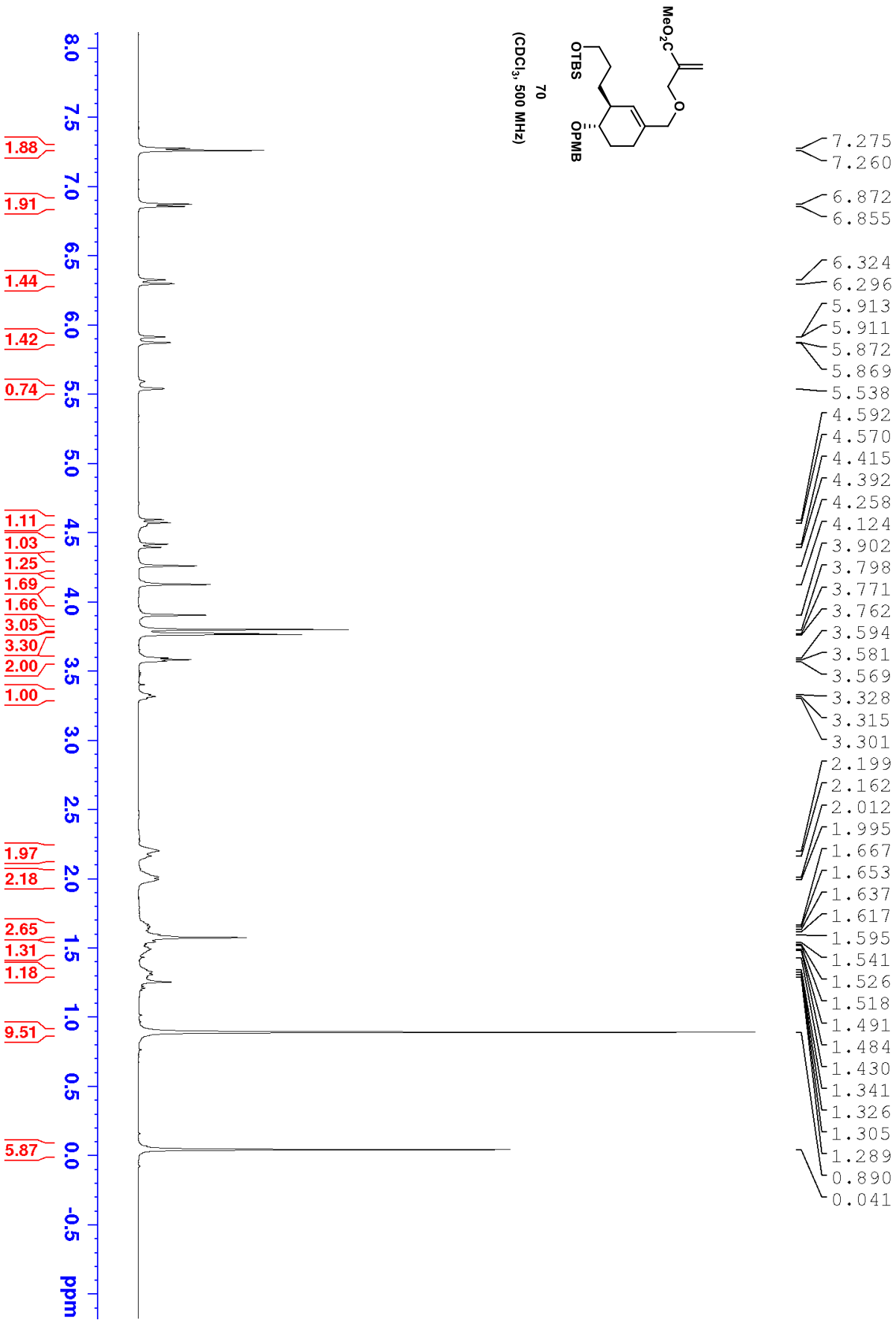
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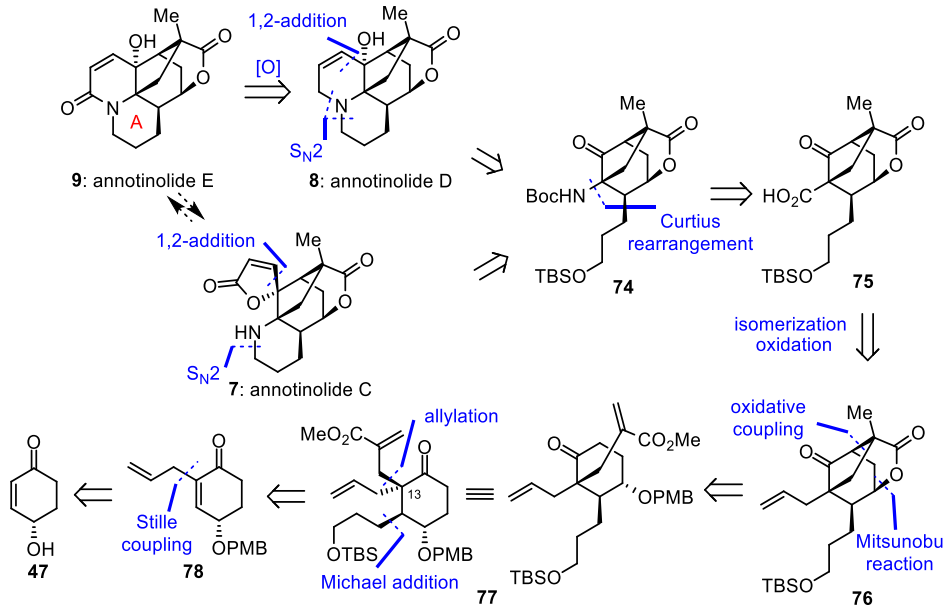
1.03
1.25
1.69
1.66
3.05
3.30
2.00
1.00
1.97
2.18
2.65
1.31
1.18
9.51
5.87
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
7.275
7.260
6.872
6.855
6.324
6.296
5.913
5.911
5.872
5.869
5.538
4.592
4.570
4.415
4.392
4.258
4.124
3.902
3.798
3.771
3.762
3.594
3.581
3.569
3.328
3.315
3.301
2.199
2.162
2.012
1.995
1.667
1.653
1.637
1.617
1.595
1.541
1.526
1.518
1.491
1.484
1.430
1.341
1.326
1.305
1.289
0.890
0.041

# CHAPTER 3

# TOTAL SYNTHESES OF 4-EPI-ANNOTINOLIDE C, 4-EPI-ANNOTINOLIDE D, ANNOTINOLIDE C, ANNOTINOLIDE D, AND ANNOTINOLIDE E

## *3.1 First-Generation Route*

### *3.1.1 Retrosynthetic Analysis*

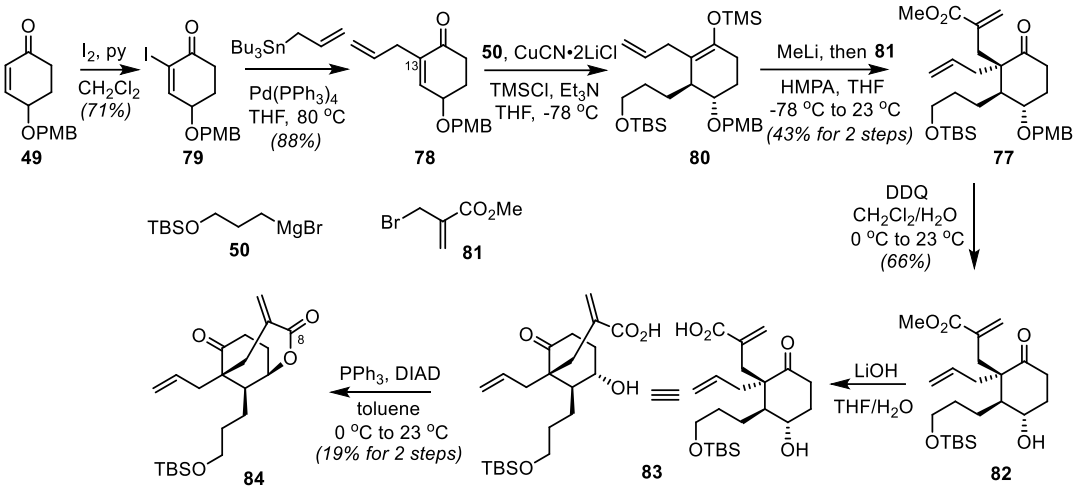



**Scheme 3.1** Retrosynthetic analysis of fisrt-generation route

Since annotinolide C (**7**), D (**8**), and E (**9**) possess the same [3.2.1] bicycle lactone skeleton, we designed a divergent route to access all of these natural products. Furthermore, with all three natural products in hand, we could examine their biosynthetic relationships proposed in scheme 1.3. The Hu group has proposed a possible biosynthetic pathway from annotinolide D (**8**) to E (**9**), and further to annotinolide C (**7**). The allylic oxidation from annotinolide D (**8**) to annotinolide E (**9**) would be simple and straightforward, but we anticipate the isomerization from annotinolide E (**9**) to annotinolide C (**7**) might be difficult since normally a lactam is much more stable than the analogous lactone. We hoped to address these concerns using experimental results if we could successfully obtain these three natural products in the lab.

As shown in scheme 3.1, annotinolide C (**7**) and E (**8**) could be synthesized by similar $S_N2$ cyclizations of A ring, and a subsequent 1,2-addition reaction. This disconnection leads to a common intermediate ketone **74**. The tertiary amine on **74** could be introduced via Curtius rearrangement. Furthermore, it is possible to obtain the carboxylic acid group through the Stoltz group's method.[1] Using allyl group here is crucial for the stereocontrol at C13 according to the Danishefsky group's precedent.[2] After these functional group interconversions, we choose **76** as the initial [3.2.1] bicycle product. The two carbonyl groups in **76** exhibit a 1,4-dicarbonyl motif through the C7-C15 bond, so an oxidative coupling might be an ideal disconnection.[3] As for the lactone moiety, the Mitsunobu reaction is convenient considering the stereochemical requirement of the C4 position. This disconnection also finally traces the synthesis back to monocyclic substrate **77**. **77** is an ideal Michael addition/allylation product from cyclohexanone **78**. This disconnection is inspired from our synthetic study of annotinolide B (**6**). Moreover, we predicted that the C13 stereocenter could be established based on the precedent established by Danishefsky.[2] This retrosynthetic analysis will also lead to **47** if we disconnect the allyl group from **78** via Stille coupling.

### *3.1.2 Construction of 7-Membered Lactone Ring System*




**Scheme 3.2** Construction of 7-membered lactone ring

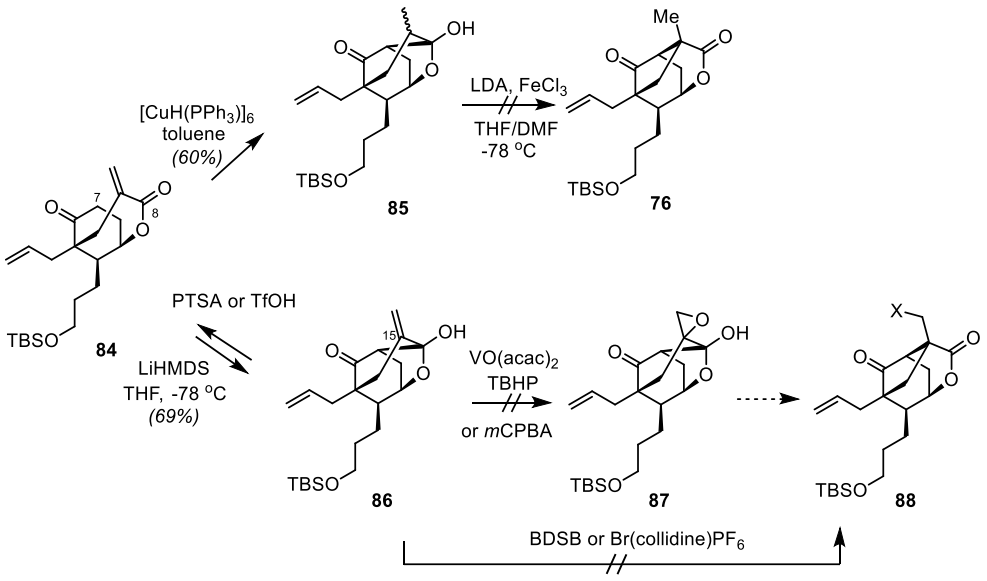
Having previously established a route to synthesize **49** during our synthetic study towards annotinolide B (**6**), we were able to access this starting material in decagram scale. From here, α-iodination of **49** gave iodo enone **79** in decent 71% yield. Then the Stille coupling was executed with $(Ph_3P)_4Pd$ as the catalyst in a sealed tube at 80 °C. The reaction went well and gave us 88% yield. After successfully installing the allyl group handle, we screened the best conditions for the Michael addition/allylation sequenceand found that a two-step which used silyl enol ether **80** as the key intermediate procedure appeared to be optimal. As shown in scheme 3.2, the initial Michael addition product was quenched with TMSCl.[4] Then, the crude silyl enol either was desilylated with MeLi, and the allylation was accomplished in just 30 minutes with the subsequent addition of HMPA and allyl bromide **81** at -78 °C. The desired diastereomer **77** was isolated in 43% yield over 2 steps. In this reaction sequence, the allyl group we installed in **78** was crucial for the diastereocontrol at C13 according to the report from the Danishefsky group.[2] Thankfully, it worked as predicted on our substrate.

With all the side chains and stereocenters introduced, we pressed forward to construct the lactone moiety. The two functional groups for necessary for the lactonization should be

deprotected first. Treatment with DDQ removed the PMB group in 66% yield, and the methyl ester was hydrolyzed with mild LiOH in THF/$H_2O$ conditions.[5] Without purification on column, carboxylic acid **83** was directly lactonized using a Mitsunobu reaction. The signature 7-membered lactone **84** was obtained in 19% overall yield from **82**. We also examined the possibility of mesylating **82**, then in-situ hydrolyzation and $S_N2$ substitution under basic condition for lactonization, however; this approach only gave us decomposition at the second step.

### *3.1.3 Attempts for Constructing [3.2.1] Bicycle Moiety*

The success of constructing the lactone ring finally enabled us to explore methods to synthesize the [3.2.1] bicycle. In the first-generation route, we envisioned an intramolecular oxidative coupling reaction. In order to obtain the coupling substrate, we first need to reduce the conjugated ester. For this purpose, Stryker's reagent[6] was chosen since it would provide the best chemoselectivity. However, the experiment delivered an unexpected product **85**. We could imagine this product was obtained via a reduction/intramolecular aldol reaction sequence. Examining a molecular model of **84** we could find that C7 and C8 are very close in space, hence the intramolecular aldol reaction occurs facilely under basic conditions.




**Scheme 3.3** Attempts to construct [3.2.1] bicycle system

Although the [3.3.1] bicycle in hemiketal **85** is not our desired product, there are also some approaches that could manipulate the hemiketal and transform it into the [3.2.1] bicycle framework. First, we tried to subject **85** to classic oxidative coupling conditions.[3] With excess strong base, it might be possible the hemiketal would be converted to the double enolate. This double enolate would be an ideal intermediate for oxidative coupling reactions. Unfortunately, no reaction occurred under this condition.

There is another approach to access [3.2.1] bicycle. With the hemiketal and double bond moiety in **86**, a cationic rearrangement would lead to product **88**. This would require initiation of the reaction by generating carbocation at C15. Treating conjugated ester **84** with LiHMDS led to hemiketal **86** as expected in 72% yield. Initial trials using strong protic acids like TfOH or PTSA only transformed **86** back to **84**. Therefore, we turned to halogen cation reagents as the initiator. BDSB reagent or Br(collidine)$PF_6$ would be selective for the double bond at C15, but both of

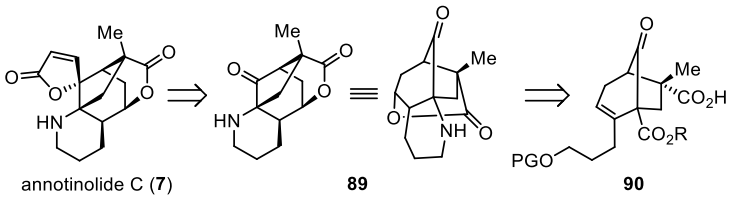
them resulted in complex mixtures. A semi-pinacol rearrangement would be a promising solution, but we were never able to introduce the epoxide like **87** at C15.

### *3.1.4 Summary*

We have developed an approach to the C13 stereocenter and the 7-membered lactone ring in our first-generation route. The unexpected intramolecular aldol reaction was the biggest challenge. We attempted to overcome this problem with cationic rearrangement initiating from C15 in **86**, but experimental results indicated such reactivity is difficult to achieve on this substrate. Although accessing [3.2.1] bicycle failed, the intramolecular aldol reaction emphasized that the C7-C15 bond would be hard to make, since a [3.2.1] bicycle with a caged lactone and quaternary carbon C15 is very sterically encumbered.

## *3.2 Second-Generation Route*

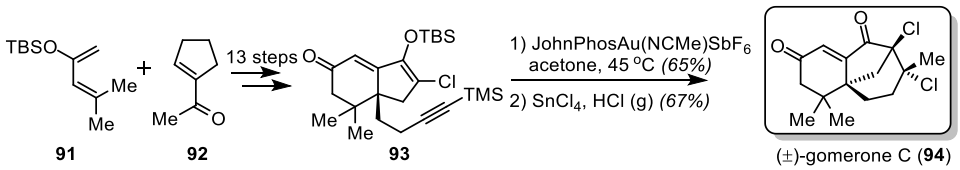
### *3.2.1 Retrosynthetic Analysis*




**Scheme 3.4** Analysis of [3.2.1] bicycle in intermediate **89**

The result of intramolecular aldol reaction in the first-generation route sheds some insights to the novel cage structure of annotinolide C (**7**), D (**8**), and E (**9**). The Common [3.3.1] bicycle in lycopodine class alkaloids is much easier to form, suggesting that the [3.2.1] bicycle is more strained and maybe the most challenging moiety in these molecules. Thus, establishing the bicyclic skeleton could be a better choice for our synthetic plan. From that perspective, we

examined the key [3.2.1] bicyclic structure shown as **89**. If we consider the lactone in **89** as being formed by lactonization of carboxylic acid and alkene, and the nitrogen is introduced via a Curtis rearrangement, the precursor could be a β-keto ester **90**. The β-keto ester **90** is clearly a typical Conia-ene reaction product. Conia-ene reaction has been employed in total synthesis to construct bicycles, especially after the discovery of gold as the reaction catalyst.[7] The relatively mild conditions and excellent chemoselectivity of gold catalyst make it ideal for complicated substrates in total synthesis. We found two recent examples of total syntheses from the Carreira group[8] and our group[9] which have applied gold-catalyzed Conia-ene reactions to build similar bicyclic structures.

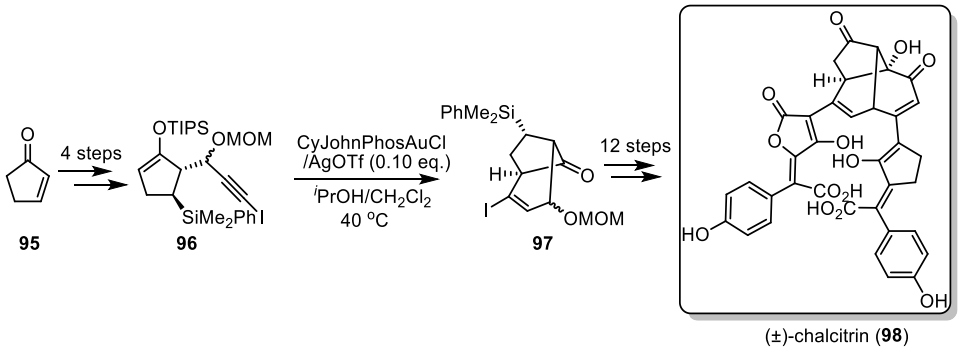



**Scheme 3.5** The Carreira group's total synthesis of (±)-gomerone C (**94**)

In the synthesis of gomerone C (**94**), the Carreira group initiated the synthesis with a classic Diels-Alder reaction to form the 6/5 bicycle system and obtained **93** in 13 steps. Silyl enol ether **93** serve as the substrate for Conia-ene reaction. Using a JohnPhos gold catalyst, they were able to access the key [3.2.1] bridge cycle in 65% yield. Furthermore, HCl addition finished the total synthesis of gomerone C (**94**). The excellent functional group tolerance of the Conia-ene reaction avoided the protection of other functional group and enabled the Carreira group finished the total synthesis in only 15 steps.

Our group also reported a gold-catalyzed Conia-ene reaction in the sysnthesis of [3.2.1] bridged bicyclic containing natural product (±)-chalcitrin (**99**). From simple 2-cyclopentenone, a Micheal addition/aldol reaction sequence and subsequent functional group manipulations gave

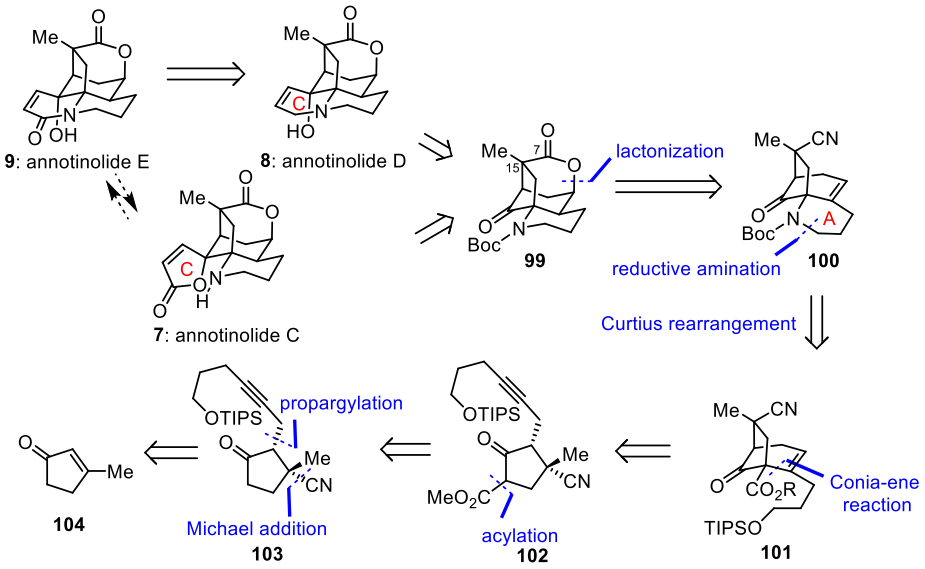
silyl enol ether **96** in 4 steps. Next, the Conia-ene reaction was conducted to construct the [3.2.1] bridged bicycle core. The vinyl iodide moiety in the product served as a handle for later coupling reaction. 12 further steps install all the required parts, resulting in a 17 linear step synthesis of chalcitrin (**98**). The core skeleton and the vinyl iodide handle from the Conia-ene reaction was pivotal to the success.




**Scheme 3.6** Our group's total synthesis of (±)-chalcitrin (**98**)

As we could see from the two syntheses above, gold-catalyzed Conia-ene reactions are very efficient in constructing [3.2.1] bicycles and can tolerate many sensitive functional groups. Although it appears promising to apply in our synthesis, there still might be two major concerns. First, our substrate is a β-keto ester, normally it would be less nucleophilic compared to silyl enol ethers. Second, we are forming an all-carbon quaternary center, so the steric hinderance and the strain in the product would increase the barrier for this reaction. On the other hand, these challenges could present an opportunity for us to explore more reactivities of gold-catalyzed Conia-ene reactions. The success of this reaction on our substrate would provide a new approach to build all carbon quaternary centers, and the ester group in the product could be transformed to other moieties like amines, allyl groups and so on. This will extensively expand the scope of application of gold-catalyzed Conia-ene reactions in total synthesis.

Based on the analysis of **89** in scheme 3.4 and the inspiration from the literature, we chose the Conia-ene reaction as our key reaction for the [3.2.1] bicycle. The whole retrosynthetic analysis of our second-generation route is depicted below:

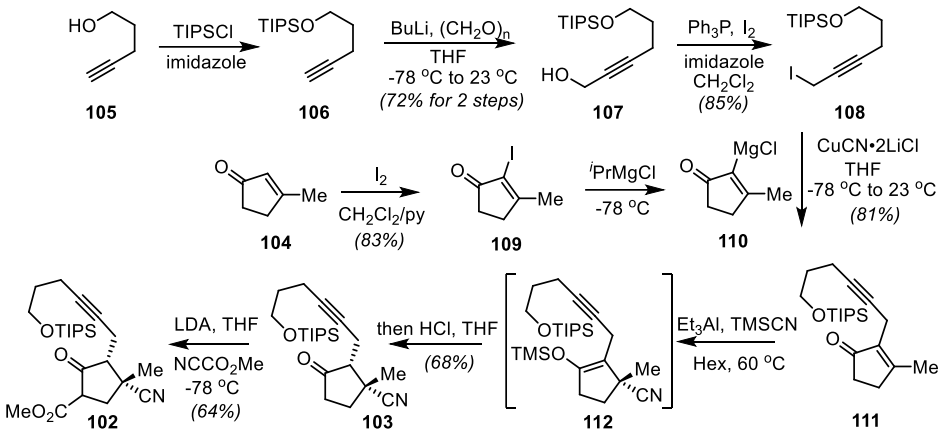



**Scheme 3.7** Retrosynthetic analysis of second-generation route

The proposed transformations of annotinolide C (**7**), D (**8**), and E (**9**) have been discussed in section 2.1. Similar with the first-generation route, annotinolide C (**7**) and D (**8**) could be synthesized through a common intermediate **99** if we cyclize C ring last. Then the caged lactone on the right-hand part could be built by acid-alkene lactonization. We traced the carboxylic acid group on C15 to a nitrile group as in **100** for 2 reasons: 1) The nitrile group could tolerate more reaction conditions;2) The steric difference between a methyl group and nitrile group is used to control the stereocenter at C7. The A ring could be introduced by a reductive amination, and a preceding Curtis rearrangement trace back to β-keto ester **101**. As discussed above, a Conia-ene reaction would deliver the monocyclic substrate **102**. The ester group would be introduced by a direct acylation with Mander's reagent. The ketone precursor **103** was a typical Micheal addition/nucleophilic propargylation product. The stereocenter could be controlled by the nitrile

group according to a previous report by the Huet group. And finally, we arrived at commercially available 3-methyl-2-cyclopentenone (**104**) as the starting point.

### *3.2.2 Synthesis of β-keto Ester **102***

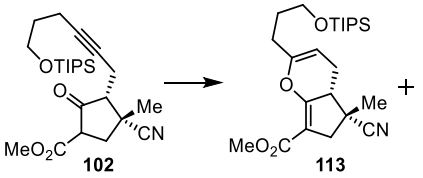



**Scheme 3.8** Synthesis of β-keto ester **102**

The synthesis began with a literature reported TIPS protection/formaldehyde addition of 4-pentyn-1-ol (**105**) to access propargyl alcohol **107**.[11] Treatment of **107** under Appel reaction condition afforded propargyl iodide **108** in 85% yield. Moving forward, we first tried the cyanide conjugate addition to obtain the analogous silyl enol ether, and then added MeLi to generate an enolate in a similar procedure as in the second-generation synthesis. Unfortunately, the silyl enol ether decomposed when MeLi was added. Thus, we changed the protocol to a coupling/cyanide addition sequence. The iodide **109** was prepared via iodine/pyridine reaction system with 83% yield[12] and then was treated with $^{i}$PrMgCl solution. Iodine-Mg exchange formed the Gringnard reagent **110** and further treatment of CuCN·2LiCl and propargyl iodide **108** furnished coupling product **111**.[13] This coupling reaction could be performed on decagram scale with a reliable 81% yield. Huet's $Et_3Al$/TMSCN condition was applied to conduct the cyanide addition.[10] The resulting silyl enol ether **112** was directly treated with 3 M HCl, and the thermodynamic

protonation of C7 gave desired diastereomer **103** as the major product in decent 68% yield. A subsequent 64%-yield acylation using LDA and Mander's reagent finally led to our Conia-ene reaction substrate **102**.

### *3.2.3 Exploration of Key Conia-ene Reaction*




| Entry | Catalyst | Condition | Result |
|---|---|---|---|
| 1 | $Ph_3PAuNTf_2$ (0.2 eq.) | $CH_2Cl_2$, 23 °C | **113** : **114** = 4:1 |
| 2 | $Ph_3PAuCl/AgOTf$ (0.2 eq.) | $CH_2Cl_2$, 23 °C | Only **113** |
| 3 | CyJohnPhosAuCl/AgOTf (0.2 eq.) | $CH_2Cl_2$, 40 °C | **113** : **114** = 2:1 |
| 4 | CyJohnPhosAuCl/AgOTf (0.2 eq.) | tol, 40 °C | **113** : **114** = 1:1 |
| 5 | CyJohnPhosAuCl/AgOTf (0.2 eq.) | tol/$^t$BuOH, 40 °C | **113** : **114** = 10:1 |
| 6 | CyJohnPhosAuCl/AgOTf (0.2 eq.) | acetone, 40 °C | Only **113** |
| 7 | CyJohnPhosAuCl/AgOTf (0.2 eq.) | MeCN, 40 °C | Unkown product |
| 8 | CyJohnPhosAuCl/$AgBF_4$ (0.2 eq.) | tol, 40 °C | **113** : **114** = 8:1 |
| 9 | CyJohnPhosAuCl/$AgSbF_6$ (0.2 eq.) | tol, 40 °C | **113** : **114** = 10:1 |
| 10 | CyJohnPhosAuCl (0.2 eq.) /AgOTf (1.0 eq.) | tol, 40 °C | **113** : **114** = 3:1 |
| 11 | $LAuNTf_2$ (0.2 eq.) | tol, 40 °C | No reaction |

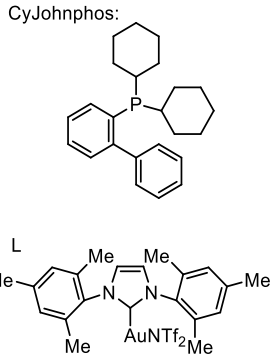
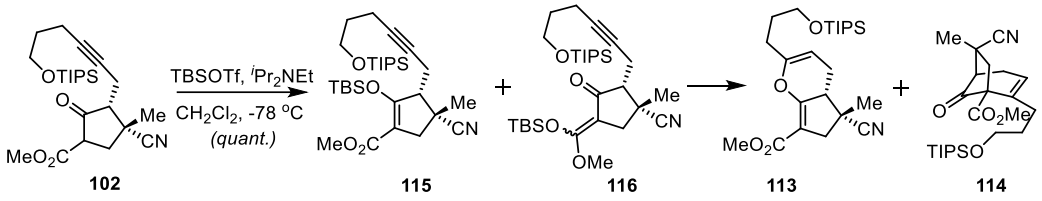



**Table 3.1** Condition screening of Au(I) catalyzed Conia-ene reaction

With the desired β-keto ester **102** in hand, we initiated the attempts for the key Conia-ene reaction. First, we tried the common $Ph_3PAuNTf_2$ as the catalyst, but we found that two major products with the ratio of 4:1 were formed in the reaction and they were very close on TLC. After careful separation on PTLC and $^1H$, $^{13}C$ NMR analysis, it turned out that the major product was an O-cyclization product **113** and the minor product was the desired one **114**. The mixed reaction results suggested that maybe we could tune the reaction selectivity through manipulating reaction conditions. Next, we screened the ligand on gold, counterion, solvent and temperature, and while the ratio of the two products did change, the best result we got was only 1:1. Experiments indicated OTf was the best counterion, the best ligand would be sterically hindered

CyJohnPhos, and the best solvent for this reaction is toluene. The 1:1 result is unsatisfactory because of the poor selectivity and the difficulty in separation. Considering the general mechanism of gold-catalyzed alkyne addition, we suspected that the steric hinderance might inhibit C-cyclization. Additionally, we also tried to initiate the reaction using In (III) catalyst or Mn (III) catalyst, but all of those conditions led to fast decomposition of the starting material.




| Entry | Catalyst | Condition | Result |
|---|---|---|---|
| 1 | JohnPhosAu(NCMe)$SbF_6$ (0.2 eq.) | acetone | No reaction |
| 2 | CyJohnPhosAuCl/AgOTf (0.2 eq.) | tol/$^t$BuOH, 40 °C | No reaction |
| 3 | $Ph_3PAuNTf_2$ (0.2 eq.) | $CH_2Cl_2$, 40 °C | **113** : **114** = 1:10 *(72%)* |

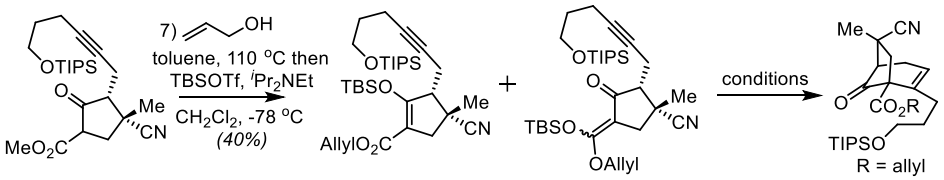
**Table 3.2** Condition screening on silyl enol ether substrate

Since simply changing the reaction condition proved incapable of reversing the reaction selectivity, we decided to mask the promiscuous oxygen atom with silyl group. This could completely shut off the O-cyclization pathway and give us the desired selectivity. In addition, the silyl enol ether would be more electron-rich compared to the corresponding β-keto ester, enhancing the reactivity for C-cyclization. Subjecting β-keto ester **102** to Hünig's base and TBSOTf gave silyl enol ether mixture **115** and **116** near quantitatively. Then we examined the Conia-ene reaction condition again. To our delight, the selectivity was completely reversed when using $Ph_3PAuNTf_2$ as catalyst, and the decent yield enabled us to move forward to the next stage of our synthesis.

The initial results in entry 3 is promising. But we found two major problems of that reaction: 1) When we performed the hydrolysis for the methyl ester, hoping to introduce the

nitrogen in our molecule, however, classic hydrolysis conditions for methyl esters such as LiOH, LiI/pyridine, or $Me_3SnOH$ all failed on our substrate; 2) The reaction suffers conversion issues above 100 mg scales. On large scale, a black precipitate could be observed from the system, which we believe was the decomposed catalyst. With 0.20 equivalent of Au(I) catalyst, the conversion never exceeded 50%.

The first problem may relate to the instability of the β-keto ester structure in **114** due to potential retro-aldol decomposition pathway. Thus, an ester that could be hydrolyzed in acidic or neutral conditions was needed. The ketone could also be masked to further enhance the stability of **114**. As indicated in table 3.3, our final successful ester choice is allyl ester. A transesterification[14] followed by addition of TBSOTf and Hunig's base after removal of excess allyl alcohol and toluene gave allyl ester substrate mixture **117** and **118** in 40% yield.




**102** **117** **118** **119**

| | Catalyst | Condition | Result |
|---|---|---|---|
| 1 | $Ph_3PAuNTf_2$ (0.2 eq.) | $CH_2Cl_2$, 40 °C | 20% (42% brsm) |
| 2 | $Ph_3PAuCl/AgSbF_6$ (0.2 eq.) | $CH_2Cl_2$/$^i$PrOH, 40 °C | low conversion |
| 3 | JohnPhosAu(NCMe)$SbF_6$ (0.2 eq.) | acetone, 40 °C | 50% (55% brsm) |
| 4 | $Ph_3PAuNTf_2$ (0.2 eq.) | tol/$^t$BuOH, 40 °C | 22% (31% brsm) |
| 5[a] | JohnPhosAu(NCMe)$SbF_6$ (0.2 eq.) | acetone, 40 °C | 30% conversion |
| 6[a] | JohnPhosAu(NCMe)$SbF_6$(0.2 eq.) | acetone, 23 °C | No reaction |
| 7[a] | $Ph_3PAuNTf_2$ (0.2 eq.) | $CH_2Cl_2$/$^i$PrOH, 23 °C | No reaction |
| 8 | JohnPhosAu(NCMe)$SbF_6$ (0.3 eq.) | $CH_2Cl_2$/$^i$PrOH, 40 °C | 62% |

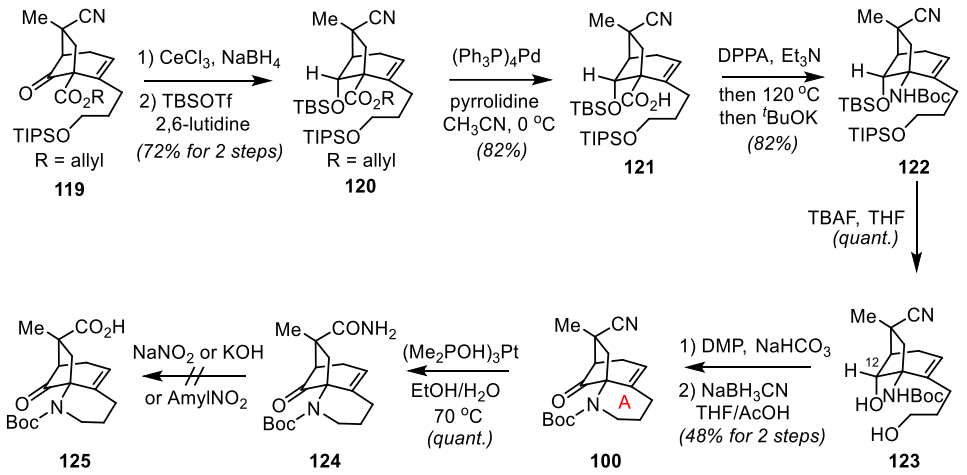
a: with additives 4 Å MS and 2,4,6-tri-tert-butylpyrimidine

**Table 3.3** Optimization of the Conia-ene reaction

We began to solve the conversion issue on the large scale Conia-ene reaction with the allyl ester substituent in hand. The trial run for the allyl ester substrate on small scale gave comparable results to the methyl ester. This illustrated simply changing the ester did not

negatively affect the reactivity of the Conia-ene, and thus wewere confident to optimize above 100 mg scale. As we have discussed above, the observation of precipitates was probably caused by catalyst decomposition. Examining the Au(I) catalyzed Conia-ene reaction mechanism we would find that the Au(I) needs a proton exchange to turn over the catalytic cycle. The simple solution would be introducing protonic solvent in the reaction system. Our successful reaction solvent system (toluene/$^{t}$BuOH = 10:1) in the synthesis of chalcitrin (**98**)[9] was applied, and we observed much better conversion in entry 2. But the yield was far from satisfactory. The TLC indicated some unknown products, which might come from the hydrolysis of silyl enol ether. To further avoid this hydrolysis reaction, the acid and water in the reaction system would need to be extinguished. Taking inspiration from the Li group,[15] we found that using 2,4,6-tri-tert-butylpyrimidine as the trap for the acid generated in the reaction and 4 Å molecular sieve to remove the trace amount water (as shown in entry 3), greatly reduced the observed hydrolysis of the substrate, but the reaction was also inhibited. Then we examined the impact of phosphine ligands on Au(I) and the counterion. Commercially available JohnPhosAu(NCMe)$SbF_6$ proved to be capable of complete the reaction with decent 62% yield, even on gram scale. Ultimately, the optimal condition we found is entry 8, as JohnPhosAu(NCMe)$SbF_6$ was more stable in the reaction system, and the isopropanol solvent resolved the issue of catalyst turnover.

### *3.2.4 Cyclization of A Ring and Attempts for the Nitrile Hydrolysis*




**Scheme 3.9** Cyclization of A ring and attempts for the nitrile hydrolysis

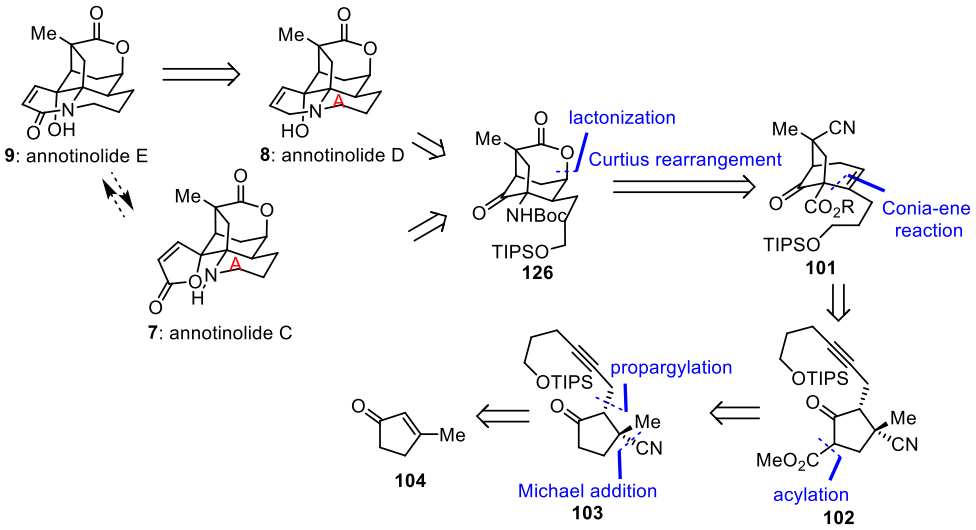
After all the problems in the Conia-ene reaction were solved, we continued our journey to construct the caged lactone. The ketone was first masked to avoid any decomposition or selectivity issues in the later synthesis. A classic Luche reduction and subsequent TBS protection converted the ketone to protected alcohol **120** as a single diastereomer. Then, the allyl ester was removed with $(Ph_3P)_4Pd$, with overall 59% yield from β-keto ester **119**.[16] The carboxylic acid product **121** was a nice solid and we obtained X-ray data, confirming all the stereocenters in the molecule. An interesting result from the X-ray data was the hydride approached the ketone on the [3.2.1] bicycle from the 5-membered ring side. This implied the nucleophilic addition we designed in the late stage would present the similar outcome. Analyzing the configuration of the [3.2.1] bicycle, the 5-membered ring side would be less hindered if we consider the trajectory of nucleophilic addition. Another possible explanation would be the tortional strain during the nucleophilic attack. The tortional strain generated when the attack occurred from the 6-membered ring side might be much larger than from the 5-membered ring side.

Pressing forward, the carboxylic acid group was transformed to an amide with a one-pot procedure from the Fukuyama group,[17] followed by Boc protection, providing **122** in 82% yield.

Then, the two silyl groups were removed simultaneously by treatment with excess TBAF, producing diol **123** quantitively. We preferred oxidation/reductive amination as the method to close A ring. This approach would be more efficient since the ketone at C12 could also be introduced during the oxidation. Just as we expected, the double oxidation was accomplished with excess DMP, forming a hemiaminal intermediate. Of note, the hemiaminal was immediately subjected to $NaBH_3CN$ in THF/AcOH due to stability issues.[18] The cyclized product **100**, along with desired ketone on it, could be obtained in 48% for 2 steps. Considering the functional groups on the C ring of annotinolides are quite delicate, we decided to construct the lactone ring first. Then, the nitrile group would need to be converted into a carboxylic acid. Parkin's catalyst[19] selectively hydrolyzed the nitrile group into the amide, but further hydrolysis conditions, like KOH and nitrite oxidation all failed. Another alternative solution would be a reduction/oxidation sequence. Since ketone at C12 would not be compatible with the reduction of the nitrile group, we decided to perform the reaction sequence on the earlier intermediate **100** and explore the lactonization with the rest of material **100**. We tested the nucleophilic addition of the ketone at this stage. Initial attempts showed the addition was difficult, vinyl magnesium bromide addition only gave ~10% yield. The addition might also need to be examined before the cyclization of the A ring,since the additional ring on the bicyclic system might provide more rigidity to the substrate and change the conformation unfavorably for addition.

## *3.3 Third-Generation Route*

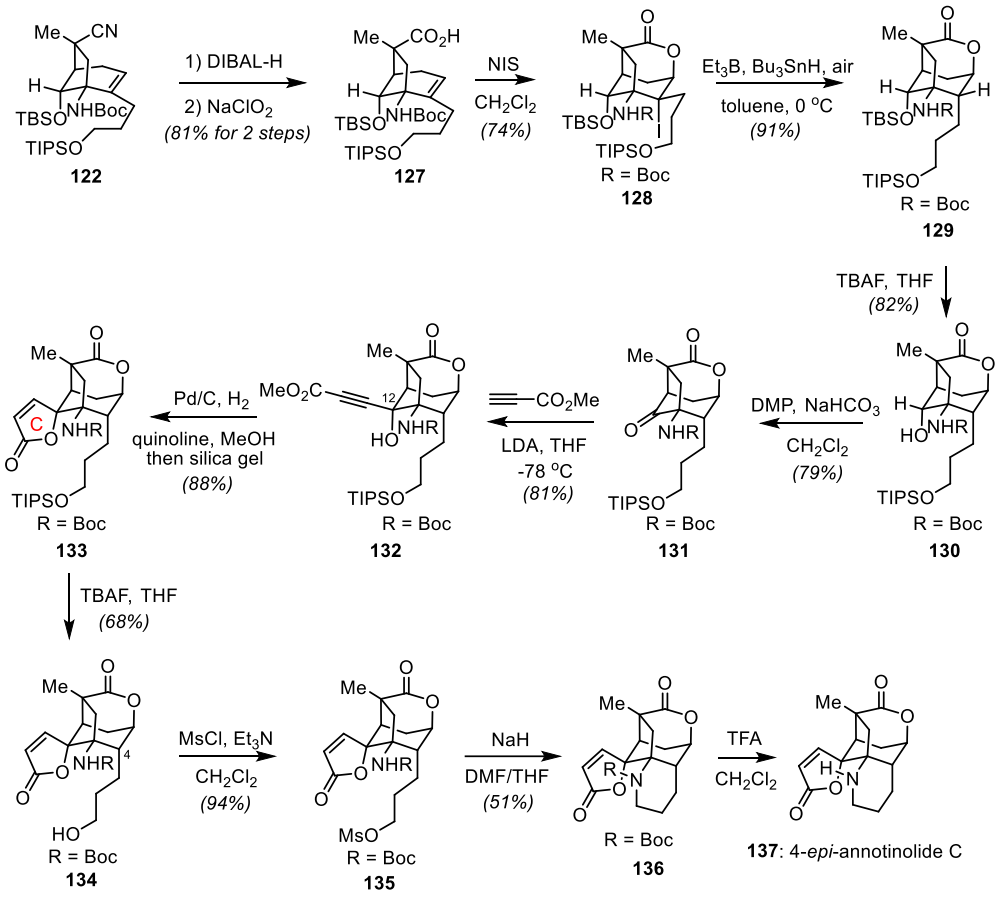
### *3.3.1 Retrosynthetic Analysis*




**Scheme 3.10** Retrosynthetic analysis of third-generation route

The design of our third-generation route was quite similar to the second-generation route. The major difference would be the order of lactonization and A ring closure. As we have discussed in section 3.2.4, introducing the lactone moiety first would maximize the general efficiency of our synthetic route.

### *3.3.2 Lactonization and the Total Synthesis of 4-epi-Annotinolide C (**137**)*




**Scheme 3.11** Lactonization and the total synthesis of 4-*epi*-annotinolide C (**137**)

The synthesis of **122** remained the same as in the second-generation route. DIBAL-H was selected to reduce the nitrile into the aldehyde, and the subsequent Pinnick oxidation delivered carboxylic acid **127** in 91% yield overall. Lactonization for a carboxylic acid with an alkene could be accomplished by the Ag(I) catalyzed lactonization or the traditional iodo-lactonization. Initial attempts were focused on Ag(I) catalyzed lactonization since it could furnish the lactone in one step. The condition from the He group[20] was applied, but only gave us decomposition no matter how we attempted to change the solvent or the reaction temperature. The issue might be most of the functional groups would not be tolerated in the relative harsh condition. Then we turned to the iodo-lactonization. Although it would take 2 steps to reach our desired product, the reaction conditions were much milder. Excess NIS in $CH_2Cl_2$ could directly lead us to

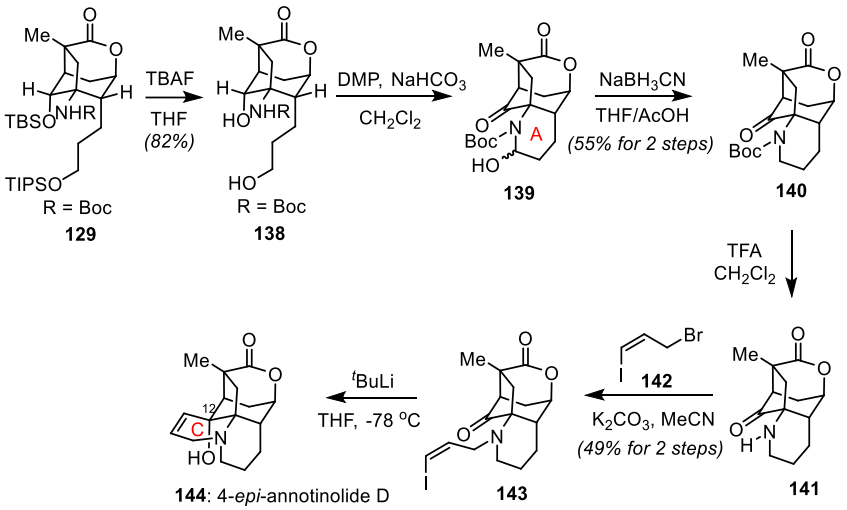
lactonization product **128** in 74% yield. The removal of iodine was straightforward, using radical $Et_3B/Bu_3SnH$ conditions. We obtained a single diastereomer in 91% yield through the deiodination, but we were not sure about the stereochemistry at this point. The natural product would be only few steps away and the intermediates along the route might be ideal for X-ray analysis. So, we carried on with the current diastereomer.

According to the previous result, the nucleophilic addition with the presence of the A ring would be difficult. Thus, we planned to test the nucleophilic addition first. With 1 equivalent of TBAF, the TBS group could be selectively removed. Then, a simple DMP oxidation led to the common intermediate **131** in 65% yield overall. To achieve annotinolide C (**7**), we chose lithium propiolate as the nucleophile.[21] Methyl propiolate was treated with LDA, generating a nucleophile for the addition. The addition worked well at -78 ℃, providing **132** in 81% yield. Product **132** was obtained as a single diastereomer, and we proposed the C12 stereocenter would be the same as **120** in the early Luche reduction, but solid evidence was needed to prove our theory. We were planning to proceed to the late stage to obtain such evidence. The C ring was constructed via a simple Lindlar reduction and a lactonization on silica gel (due to its slight acidity). The cyclization sequence was accomplished in 88% yield. Now, the only task remained would be A ring system. The traditional $S_N2$ cyclization was depicted this time due to the butanolide ring might not be compatible with the reduction.

The TIPS group was removed by TBAF in 68% yield. Primary alcohol **134** was a nice solid and we could get the X-ray data to clarify the stereochemistry for C4 and C12. C12 stereocenter was the same as we expected. However, the C4 stereocenter was completely different from our desired one. The optimization would be discussed in the later chapter. At this point, we continued the synthesis with the material in hand since it would also provide the

information for our later A ring cyclization on the desired substrate. In order to affect an $S_N2$ cyclization, alcohol **134** was transformed to mesylate **135** in 94% yield. NaH was selected as the base to deprotonate the NHBoc group for the subsequent intramolecular substitution. The cyclization product **136** could be synthesized, but the yield was not consistent. We suspect adventitious NaOH was responsible for this variability the amount of it depends on the quality of NaH, DMF and THF. Despite the variable yield, we were able to produce enough material to perform the final deprotection of Boc group. TFA successfully removed the Boc group and 4-*epi*-annotinolide C (**7**) was accomplished through this approach.

### *3.3.3 The Total Synthesis of 4-epi-Annotinolide D (**144**)*

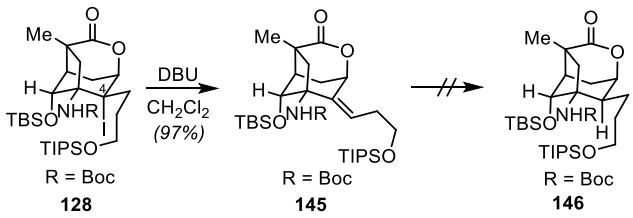



**Scheme 3.12** The total synthesis of 4-*epi*-annotinolide D (**144**)

We also explored the closure of the C ring in annotinolide D (**8**) with the diastereomer **131**. Considering the intramolecular nucleophilic addition would require the side chain on nitrogen to be in a relatively fixed conformation, we synthesized the A ring first. Similar to our second-generation route, TBAF desilylation, oxidation, and reductive amination cyclization delivered Boc protected amine **140** in 45% yield over 3 steps. Then the Boc group was removed

by TFA and the iodo alkene moiety was introduced through the reaction with allyl bromide **142**,[22] which was prepared according to the literature precedent. Vinyl iodide **143** was successfully prepared in 49% yield from **140**. Our final step would be metal-iodine exchange, followed by intramolecular attack to ketone at C12. Potentially promising reagents such as $^{n}$BuLi, $^{i}$MgCl, and $^{t}$BuLi were all tested. We found $^{t}$BuLi was the optimal exchanging reagent and 4-*epi*-annotinolide D (**144**) was achieved as a single diastereomer.

### *3.3.4 Reverse of C4 Stereocenter*

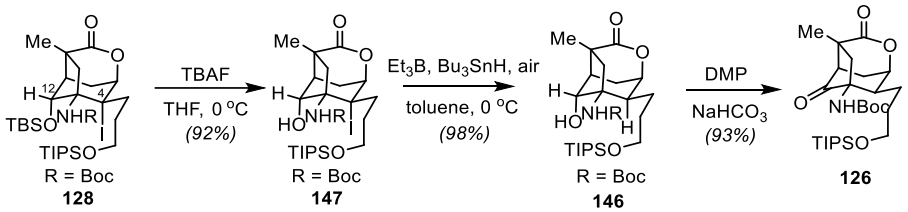



| Entry | Condition | Result |
|---|---|---|
| 1 | Pd/C, EtOH, $H_2$ | **129** |
| 2 | $PtO_2$, EtOH, $H_2$ | complex mixture |
| 3 | Crabtree's catalyst, $H_2$, $CH_2Cl_2$ | no reaction |
| 4 | $Mn(dpm)_3$, $PhSiH_3$, TBHP, $^{i}$PrOH | hydration product |

**Table 3.4** Failed attempts to reverse C4 stereocenter

Through the syntheses of 4-*epi*-annotinolide C (**137**) and 4-*epi*-annotinolide D (**144**), we have established a possible way to cyclize the final ring and construct the C12 stereocenter as the desired one. To achieve the synthesis of the actual natural products, we had to solve the issue for deiodination at C4. Other than direct radical deiodination, elimination/hydrogenation might be a solution. There was a chance that double bond on C4 would change the conformation of the molecule and then hydrogen came from the bottom face. The elimination reaction happened smoothly with DBU, giving the single alkene isomer **145** in 97% yield. We did not determine the actual configuration of the double bond because it would be removed in the following reduction step. The representative conditions we explored are listed in table 3.4. Classic Pd/C

hydrogenation led to the same diastereomer as the previous radical deiodination. Other hydrogenation catalysts, $PtO_2$ gave a very complex mixture and Crabtree's catalyst gave no reaction at all. The HAT reaction was also examined on **145**, but only a hydration product was obtained.

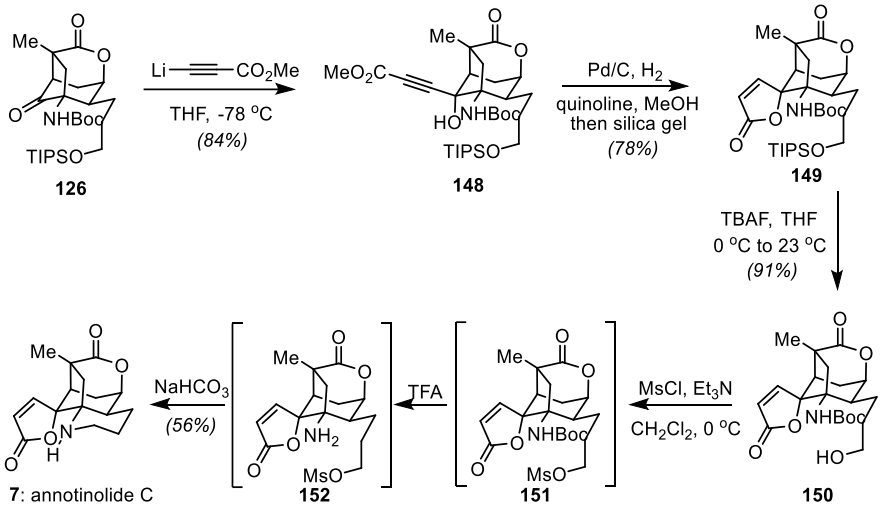



**Scheme 3.13** Synthesis of desired common intermediate ketone **126**

All of the failed results indicated that in iodide **128**, the bottom face is much more difficult to access by external reagents compared to the top face. With that conclusion, we examined the functional groups in **128** and found that a large OTBS group exhibits a [1,3] relation with the iodine at C4. Thus, the TBS group on the alcohol at C12 would contribute most to the steric hinderance of the bottom face. Thus, we ran a simple deprotection of TBS group before deiodination. 1 equivalent of TBAF worked well on **128**, delivering secondary alcohol **147** in 98% yield. Deiodination of **147** showed extraordinary selectivity towards our desired **146**. A single diastereomer was obtained in excellent 95% yield. The steric hinderance could be responsible as we analyzed before, but an intramolecular [1,6] HAT could also be possible, similar to the Zard group's case.[23] In our system this would consist of the free hydroxy group reacting with $Et_3B$, and the radical at C4 abstracting an H from the methylene of the Et group. From alcohol **146**, a DMP oxidation led to the desired common intermediate ketone **126** as in our retrosynthetic analysis in 93% yield.

### *3.3.5 The Total Synthesis of Annotinolide C (7)*

Having successfully tested the route to cyclize the final A ring and C ring, we then sought to apply the same route to the correct diastereomer However we still faced the issue that the NaH initiated $S_N2$ cyclization demonstrated a variable yield and needed to be optimized. Fortunately, the cyclization that Fangjie used in our group's synthesis of strychnochromine would be a perfect solution to this problem. In that synthesis, we removed Boc group first and use the free amine to furnish an $S_N2$ reaction under basic aqeuous conditions like $NaHCO_3$ solution. The basic conditions applied are much milder than NaH and would tolerate the butanolide moiety in our substrate. Furthermore, these transformations could be accomplished in just one pot.

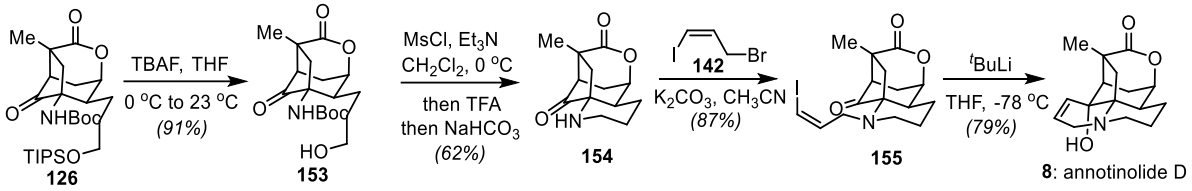



**Scheme 3.14** The total synthesis of annotinolide C (**7**)

Starting from ketone **126**, the sequence in 4-*epi*-annotinolide C (**137**): lithium propiolate addition, reduction/lactonization, and TBAF deprotection all proceeded smoothly. Primary alcohol **150** was prepared in three steps in 60% overall yield. Then, the cyclization sequence described above was applied. Mesylation of **150** only took 30 minutes, followed by TFA addition toremove the Boc group. Final quenching of the TFA with excess $NaHCO_3$ successfully led to annotinolide C (**7**). This reaction sequence could be performed in 20 mg scale in 56% yield. The

spectrum matched perfectly with the date from the isolation paper, and we also obtained the single crystal X-ray data for further confirmation of the synthetic sample.

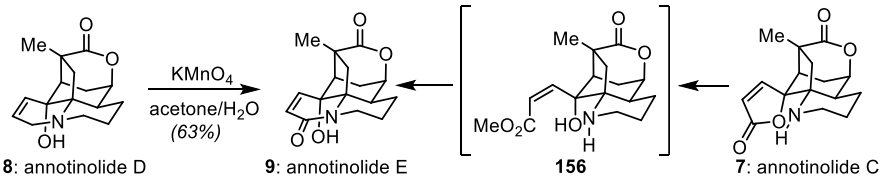
### *3.3.6 The Total Synthesis of Annotinolide D (**8**)*




**Scheme 3.15** The total synthesis of annotinolide D (**8**)

With the success in annotinolide C (**7**) and the previous route to 4-*epi*-annotinolide D (**144**), the route towards annotinolide D (**8**) would be straightforward. After TBAF deprotection, a one-pot cyclization similar to the synthesis of annotinolide C (**7**) led to **154** in 57% overall yield. Then iodinated alkene **142** was coupled, and a lithium-iodine exchange with $^{t}$BuLi gave natural product annotinolide D (**8**) in 69% yield from secondary amine **154**.

### *3.3.7 The Total Synthesis of Annotinolide E (**9**) and the Transformation Between Annotinolide C (**7**) and E (**9**)*




| | |
|---|---|
| NaOH, MeOH | no reaction |
| DMAP, toluene, 110 °C | no reaction |
| MeOH,MeONa | **7**:**9** = 1:1 |
| TBD, tol/MeOH | **7**:**9** = 4:1 |

**Table 3.5** The transformations between annotinolide C (**7**), D (**8**) and E (**9**)

Annotinolide C (**7**) and annotinolide D (**8**) were accomplished through our third-generation route and we were now able to explore the potentially biomimetic transformations

between annotinolide C (**7**), D (**8**), and E (**9**). The synthesis of annotinolide E (**9**) from annotinolide D (**8**) was achieved by a $KMnO_4$ allylic oxidation in 63% yield.[24] This result further supports the biosynthetic proposal. However, when we examine the isomerization between annotinolide E (**9**) and annotinolide C (**7**), only isomerization from annotinolide C (**7**) to annotinolide E (**9**) was possible. Table 3.5 lists the typical lactone-lactam isomerization conditions we tested. No isomerization was observed if we started from annotinolide E (**9**) under those conditions. When we used annotninolide C (**7**) as the starting material, only strong nucleophilic conditions displayed the possibility of conversion. We believe methyl ester **156** is the key intermediate. Catalyst TBD[25] could form a 4:1 mixture of annotinolide C (**7**) and E (**9**). Meanwhile, NaOMe in methanol delivered the best conversion. The ratio of annotinolide C (**7**) and E (**9**) was approxiomately 1:1, but there was a significant amount of a side product, whichwe suspect would be the lactone-opening product.

The results we obtained in the chemistry lab indicated the isomerization could only happen from annotinolide C (**7**) to E (**9**). This is a reasonable result since the activation energy from the lactam of annotinolide E (**9**) to intermediate **156** would be much higher than that of the lactone in annotinolide C (**7**). Comparing this conclusion with the biosynthetic proposal, it seems that annotinolide C (**7**) might came from a different biosynthetic pathway than annotinolide D (**8**) and E (**9**). There is also another possibility that a special lactam-lactone isomerase exists in the plant *Lycopodium annotinum*.

### *3.3.8 Summary*

Throughout our third-generation route, we have finally achieved a collection of natural products in the annotinolide family. Contrasting this route to the second-generation route, we

changed the order of constructing the A ring and lactone moiety and optimized the A ring cyclization sequence. In this synthetic campaign, we encountered a stereoselectivity issue at C4 during the deiodination and resolved it by removing the TBS group on the secondary alcohol at C12. The strategy we applied in the total synthesis has taken advantage of the conformation of the scaffold and delivered perfect stereocontrol at C4 and C12. In addition, synthesizing annotinolide C (**7**), D (**8**), and E (**9**) enabled us to explore the potential biosynthetic relationship between these natural products.

### *3.4 Experimental Section*

**General procedures.** All reactions were carried out under an argon atmosphere with dry solvents under anhydrous condition, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, dimethylformamide (DMF), diethyl ether ($Et_2O$) and dichloromethane ($CH_2Cl_2$) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically ($^1H$ and $^{13}C$ NMR) homogenous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 nm E. SiliCycle silica gel plates (60F-254) using UV light as visualizing agent, and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040-0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker 500 MHz and 400 MHz instruments and calibrated using residual undeuterated solvents as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d =

doublet, t = triplet, q = quartet, m = multiplet. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on an Agilent 6244 Tof-MS using ESI (Electronspray Ionization) at the University of Chicago Mass Spectroscopy Core Facility.

**Abbreviations.** EtOAc = ethyl acetate, THF = tetrahydrofuran, $Pd(PPh_3)_4$ = tetrakis(triphenylphosphine)palladium(0), $Et_3N$ = triethylamine, TMSCl = trimethylsilyl chloride, MeLi = methyl lithium, HMPA = hexamethylphosphoramide, DDQ = dimethyl sulfoxide, $PPh_3$ = triphenylphosphine, DIAD = diisopropyl azodicarboxylate, LiHMDS = lithium bis(trimethylsilyl)amide, TIPSCl = triisopropylsilyl chloride, MeOH = methanol, *n*-BuLi = *n*-butyl lithium, *i*-PrMgCl = isopropyl magnesium chloride, $Et_3Al$ = triethylaluminum, TMSCN = trimethylsilyl cyanide, *i*-$Pr_2NH$ = diisopropylamine, *i*-$Pr_2NEt$ = *N*,*N*-diisopropylethylamine, TBSOTf = tert-butyldimethylsilyl trifluoromethanesulfonate, *i*-PrOH = isopropanol, JohnPhosAu(NCMe)$SbF_6$ = (acetonitrile)[(2-biphenyl)di-tert-butylphosphine]gold(I) hexafluoroantimonate, $NaBH_4$ = sodium boron hydride, MeCN = acetonitrile, *t*-BuOK = potassium tert-butoxide, *t*-BuOH = tert-butanol, $NaBH_3CN$ = sodium cyanoborohydride, DIBAL-H = diisobutylaluminum hydride, *n*-$Bu_3SnH$ = tributyltin hydride, $Et_3B$ = triethylborane, TBAF = tetrabutylammonium fluoride, MsCl = methanesulfonyl chloride, DMF = dimethylformamide, TFA = trifluoroacetic acid, *t*-BuLi = tert-butyl lithium, DBU = 1,8-diazabicyclo(5.4.0)undec-7-ene, NaOMe = sodium methoxide, M.S. = molecular sieves, KHMDS = potassium bis(trimethylsilyl)amide.

**Iodide 79.** Enone **49** (5.02 g, 21.6 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (216 mL) and pyridine (14 mL). Then iodine (6.58 g, 25.9 mmol, 1.2 equiv) was added in one portion. The dark brown solution was stirred at 23 ℃ until the substrate was fully consumed based on TLC

analysis (typically 14 h). Then the reaction was quenched by $Na_2S_2O_3$ solution (1.0 M, 150 mL). The reaction contents turned yellow and were transferred to a separatory funnel. After separation, the aqueous layer was extracted with $CH_2Cl_2$ (3 × 150 mL). The organic layers were combined and washed with brine (450 mL), dried ($Na_2SO_4$), filtered and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 8:1→4:1) to give iodide **79** (5.51 g, 71% yield) as an orange solid. **79**: $R_f$ = 0.52 (silica gel, hexanes/EtOAc, 2:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 3.0, 1.3 Hz, 1 H), 7.30–7.27 (m, 2 H), 6.95–6.87 (m, 2 H), 4.57 (s, 2 H), 4.25–4.20 (m, 1 H), 3.82 (s, 3 H), 2.85 (ddd, *J* = 16.7, 5.4, 4.3 Hz, 1 H), 2.56–2.46 (m, 1 H), 2.39–2.29 (m, 1 H), 2.10 (dddd, *J* = 13.0, 11.9, 8.8, 4.4 Hz, 1 H).

**Enone 78.** Iodide **79** (5.50 g, 15.4 mmol, 1.0 equiv) was dissolved in THF (50 mL) in a seal tube, and allyltributylstanne (9.5 mL, 30.8 mmol, 2.0 equiv) was added. The obtained orange solution was bubbled through Ar for 20 min. Then $Pd(PPh_3)_4$ (1.78 g, 1.54 mmol, 0.10 equiv) was added and the reaction system was sealed. Directly heated the reaction solution at 80 ℃ using an oil bath. After the substrate was fully consumed based on TLC analysis (typically 15 h), the reaction solution was cooled to 23 ℃ and directly concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 10:1) to give enone **78** (3.68 g, 88% yield) as a yellow oil. **78**: $R_f$ = 0.25 (silica gel, hexanes/EtOAc, 4:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.32–7.27 (m, 2 H), 6.95–6.85 (m, 2 H), 6.71 (dq, *J* = 2.7, 1.4 Hz, 1 H), 5.79 (ddt, *J* = 15.2, 10.8, 6.8 Hz, 1 H), 5.08 (t, *J* = 1.3 Hz, 1 H), 5.06–5.03 (m, 1 H), 4.59 (d, *J* = 11.4 Hz, 1 H), 4.55 (d, *J* = 11.4 Hz, 1 H), 4.24 (ddd, *J* = 9.2, 4.7, 2.3 Hz, 1 H), 3.81 (s, 3 H), 2.94 (dq, *J* = 6.8, 1.5 Hz, 2 H), 2.68–2.59 (m, 1 H), 2.37–2.27 (m, 2 H), 2.04–1.95 (m, 1H).

**Silyl enol ether 80.** To a round-bottom flask was charged with Mg turnings (3.33 g, 0.137 mol, 9.0 equiv) and a magnetic stir bar. Heated the flask under vacuum for 3 min with propane gun. After the flask was cooled to 23 ℃ under vacuum, a small portion of THF (11 mL) was added, followed by 5 drops of 1,2-dibromomethane via syringe. The suspension was vigorously stirred until the bubbles formed from the surface of Mg turnings. Then bromide **50** (20.46 g, 0.0808 mmol, 5.3 equiv) in THF (70 mL) was added via syringe pump at 23 ℃ over 40 min. The suspension gradually turned cloudy and gray. When the addition was finished, the suspension was further stirred for 30 min and then diluted with THF (81 mL). A clear solution was obtained and transferred to a flame-dried flask. The solution was cooled to -78 ℃ using a dry ice-acetone bathe and CuCN·2LiCl (1.0 M in THF, 30.5 mL, 0.0305 mol, 2.0 equiv) was added. The resulting suspension was vigorously stirred at -45 ℃ for 30 min and cooled back to -78 ℃. Then $Et_3N$ (2.55 mL, 0.0183 mol, 1.2 equiv), TMSCl (2.33 mL, 0.0183 mol, 2.0 equiv), and **78** (4.15 g, 0.0152 mol, 1.0 equiv) in THF (75 mL) were added subsequently. Use a small amount of THF (6.0 mL) to ensure a complete transfer of **78**. The reaction mixture was gradually warmed up in cold bath overnight. After the substrate was fully consumed by TLC analysis (typically 12 h), the suspension was directly concentrated in vacuo. The crude slurry obtained was redissolved in hexanes (100 mL) and filtered through Celite (eluted with hexanes). Repeated this procedure twice until there was no participate observed after concentration. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 50:1→20:1) to give silyl enol ether **80** as a colorless oil and directly used in next step. **80**: $R_f$ = 0.68 (silica gel, hexanes/EtOAc, 4:1).

**Ketone 77.** The crude silyl enol ether **80** obtained above was dissolved in THF (76 mL) and cooled to -78 ℃ using a dry ice-acetone bath. MeLi (1.6 M in ether, 14.2 mL, 0.0228 mol,

2.5 equiv) was added dropwise. The solution turned brown and was directly warmed up to 0 ℃ using an ice-water bath. Stirred at 0 ℃ and after the silyl enol ether was fully consumed based on TLC analysis (typically 30 min), the solution was cooled back to -78 ℃. Then HMPA (26.4 mL, 0.152 mol, 10 equiv) was added and stirred at -78 ℃ for another 15 min. **81** (3.60 mL, 0.0304 mol, 2.0 equiv) was added dropwise and the reaction solution as gradually warmer up to 23 ℃ overnight. When the substrate was fully consumed based on TLC analysis (typically 12 h), quenched the reaction with saturated $NH_4Cl$ solution (80 mL). The reaction contents were transferred into a separatory funnel and separated. After separation, the aqueous layer was extracted with EtOAc (3 × 80 mL). The organic layers were combined and washed with brine (200 mL), dried ($Na_2SO_4$), filtered and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 16:1) to give ketone **77** (3.60 g, 43% yield for 2 steps) as a colorless oil. **77**: $R_f$ = 0.56 (silica gel, hexanes/EtOAc, 2:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.28–7.26 (m, 2 H), 6.92–6.84 (m, 2 H), 6.20 (d, *J* = 1.2 Hz, 1 H), 5.59–5.50 (m, 1 H), 5.49 (d, *J* = 1.2 Hz, 1 H), 5.03–4.97 (m, 2 H), 4.59 (d, *J* = 11.0 Hz, 1 H), 4.43 (d, *J* = 11.0 Hz, 1 H), 3.81 (s, 3 H), 3.77 (dt, *J* = 9.0, 4.3 Hz, 1 H), 3.69 (s, 3 H), 3.61–3.54 (m, 2 H), 2.81 (d, *J* = 13.7 Hz, 1 H), 2.74–2.68 (m, 2 H), 2.43–2.35 (m, 3 H), 1.98–1.89 (m, 3 H), 1.67 (dt, *J* = 14.1, 9.0 Hz, 2 H), 1.58–1.55 (m, 1 H), 1.33 (td, *J* = 14.5, 13.6, 7.9 Hz, 1 H), 0.91 (s, 9 H), 0.05 (s, 6 H).

**Alcohol 82.** The ketone **77** (690 mg, 1.27 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (12 mL) and deionized $H_2O$ (0.60 mL). The solution was cooled to 0 ℃ using an ice-water bath and DDQ (345 mg, 1.52 mmol, 1.2 equiv) was added in one portion. The solution turned dark-green, and the cold bath was directly removed after addition. When the starting material was fully consumed based on TLC analysis (typically 30 min), the reaction was quenched with saturated

$NaHCO_3$ solution (12 mL). The reaction contents were transferred into a separatory funnel. After separation, the aqueous layer was extracted with $CH_2Cl_2$ (3 × 12 mL). The organic layers were combined and washed with brine (30 mL), dried ($Na_2SO_4$), filtered and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 10:1) to give alcohol **82** (355 mg, 66% yield) as a colorless oil. **82**: $R_f$ = 0.24 (silica gel, hexanes/EtOAc, 2:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 6.19 (d, *J* = 1.2 Hz, 1 H), 5.62–5.51 (m, 1 H), 5.47 (s, 1 H), 5.03 (d, *J* = 1.7 Hz, 1 H), 5.00 (dt, *J* = 7.5, 2.2 Hz, 1 H), 4.17–4.07 (m, 2 H), 3.69 (s, 3 H), 3.66 (td, *J* = 6.1, 2.6 Hz, 2 H), 2.96 (d, *J* = 4.3 Hz, 1 H), 2.83 (dt, *J* = 13.3, 2.9 Hz, 2 H), 2.71 (ddd, *J* = 14.2, 4.4, 2.2 Hz, 1 H), 2.43 (d, *J* = 13.8 Hz, 1 H), 2.38 (dt, *J* = 15.8, 5.1 Hz, 1 H), 2.26 (ddt, *J* = 13.8, 9.6, 4.5 Hz, 1 H), 1.93–1.83 (m, 3 H), 1.83–1.71 (m, 2 H), 1.71–1.61 (m, 1 H), 0.92 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H).

**Carboxylic acid 83.** The alcohol **82** (285 mg, 0.671 mmol, 1.0 equiv) was dissolved in THF (27 mL) and deionized $H_2O$ (6.7 mL). $LiOH{\cdot}H_2O$ (282 mg, 6.71 mmol, 10 equiv) was added in one portion. The cloudy suspension turned yellow. When the starting material was fully consumed based on TLC analysis (typically 14 h), the reaction was acidified by HCl (3 M in $H_2O$) until the pH reached below 4. Then the reaction contents were transferred into a separatory funnel. After separation, the aqueous layer was extracted with EtOAc (3 × 15 mL). The organic layers were combined and washed with brine (30 mL), dried ($Na_2SO_4$), filtered and concentrated. The resultant crude carboxylic acid **83** was directly used in the next step without purification.

**Ester 84.** To a flame-dried flask was charged with $PPh_3$ (215 mg, 0.818 mmol, 1.2 equiv) and toluene (6.8 mL). The solution was cooled to 0 ℃ using an ice-water bath and DIAD (0.16 mL, 0.818 mmol, 1.2 equiv) was added. The resulting yellow solution was stirred at 0 ℃ for 15 min. Then the crude carboxylic acid **83** obtained above in toluene (6.0 mL) was added at that

temperature via syringe pump over 40 min. The could bath was removed after addition. When the starting material was fully consumed based on TLC analysis (typically 12), the reaction was quenched with deionized $H_2O$ (10 mL). The reaction contents were transferred into a separatory funnel. After separation, the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined and washed with brine (25 mL), dried ($Na_2SO_4$), filtered and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 10:1) to ester **84** (61.0 mg, 19% yield for 2 steps) as a colorless oil. **84**: $R_f$ = 0.32 (silica gel, hexanes/EtOAc, 2:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 5.75 (d, *J* = 1.4 Hz, 1 H), 5.53 (dddd, *J* = 16.7, 10.2, 8.7, 6.3 Hz, 1 H), 5.33 (t, *J* = 1.2 Hz, 1 H), 5.14–5.07 (m, 2 H), 5.01 (dt, *J* = 10.7, 4.5 Hz, 1 H), 3.73 (dt, *J* = 10.2, 5.1 Hz, 1 H), 3.60 (dtd, *J* = 10.2, 7.7, 6.3, 3.4 Hz, 1 H), 2.71 (dd, *J* = 13.7, 6.3 Hz, 1 H), 2.56 (dddd, *J* = 15.7, 10.8, 7.7, 3.1 Hz, 1 H), 2.41–2.38 (m, 2 H), 2.37–2.32 (m, 1 H), 2.26 (qt, *J* = 8.0, 3.6 Hz, 2 H), 2.17 (dd, *J* = 13.7, 8.7 Hz, 1 H), 2.01–1.91 (m, 1 H), 1.81 (tdd, *J* = 9.0, 7.1, 4.4 Hz, 1 H), 1.72 (td, *J* = 10.4, 9.1, 3.0 Hz, 1 H), 1.55–1.48 (m, 2 H), 0.89 (s, 9 H), 0.06 (s, 6 H).

**Hemiketal 86.** Ester **84** (60.1 mg, 0.153 mmol, 1.0 equiv) was dissolved in THF (1.5 mL) and cooled to -78 ℃ using a dry ice-acetone bath. Then LiHMDS (1.0 M in THF, 0.18 mL, 0.183 mmol, 1.2 equiv) was added dropwise and the reaction was kept stirring at -78 ℃ for 1.5 h. Quenched the reaction with saturated $NH_4Cl$ (3.0 mL) and removed the cold bath. The reaction contents were warmed up to 23 ℃ and transferred into a separatory funnel. After separation, the aqueous layer was extracted with EtOAc (3 × 3.0 mL). The organic layers were combined and washed with brine (5.0 mL), dried ($Na_2SO_4$), filtered and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 10:1) to hemiketal **86** (41.3 mg, 69% yield) as a colorless oil. **86**: $R_f$ = 0.32 (silica gel, hexanes/EtOAc,

2:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 5.79–5.68 (m, 1 H), 5.29 (d, *J* = 2.8 Hz, 1 H), 5.04 (q, *J* = 2.0 Hz, 1 H), 5.02 (dt, *J* = 10.5, 2.1 Hz, 1 H), 4.94 (d, *J* = 2.6 Hz, 1 H), 4.50 (d, *J* = 4.9 Hz, 1 H), 3.63 (dt, *J* = 10.0, 5.9 Hz, 1 H), 3.57 (dt, *J* = 9.9, 6.4 Hz, 1 H), 2.85 (t, *J* = 2.8 Hz, 1 H), 2.83–2.79 (m, 2 H), 2.63 (ddd, *J* = 12.1, 6.1, 5.0 Hz, 1 H), 2.50 (ddt, *J* = 14.2, 5.2, 1.6 Hz, 1 H), 2.01 (dd, *J* = 14.2, 9.5 Hz, 1 H), 1.91 (dd, *J* = 14.0, 7.6 Hz, 2 H), 1.69 (d, *J* = 10.5 Hz, 1 H), 1.65–1.59 (m, 1 H), 1.58–1.50 (m, 1 H), 1.45–1.35 (m, 2 H), 0.89 (s, 9 H), 0.05 (s, 6 H).

**Propargyl alcohol 107.** To a solution of **105** (16.8 g, 0.200 mol, 1.0 equiv) in $CH_2Cl_2$ (400 mL) at 23 °C was sequentially added imidazole (20.4 g, 0.300 mol, 1.5 equiv) and TIPSCl (51.4 mL, 0.240 mol, 1.2 equiv), after which a white participate formed. The resultant suspension was then stirred at 23 °C for 4 h. Next, MeOH (1.72 mL, 1.36 g, 0.0400 mol) was added and the reaction contents were stirred for an additional 30 min. Upon completion, the reaction contents were filtered through a pad of Celite (eluting with hexanes) and concentrated directly. Pressing forward without any further purification, the so-obtained TIPS-protected alcohol was dissolved in THF (1.05 L) and the reaction contents were cooled to –78 °C. Next, *n*-BuLi (100 mL, 2.5 M in hexane, 0.250 mol, 1.25 equiv) was then added at –78 °C via cannula over the course of 5 min, during which time the solution turned bright yellow. The reaction contents were then stirred for an additional 30 min at –78 °C. Solid paraformaldehyde (12.7 g, 0.420 mol, 2.1 equiv) was then added to the solution in a single portion, and the resultant suspension was then slowly warmed to 23 °C and stirred for 12 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NH_4Cl$ (600 mL) and poured into a separatory funnel. After separating the layers, the aqueous phase was extracted with EtOAc (2 × 600 mL). The combined organic layers were then washed with brine (1 L), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash chromatography

chromatography (silica gel, hexanes/EtOAc, 10:1) provided the desired propargyl alcohol **107** (38.4 g, 72% yield over 2 steps) as a pale-yellow oil. Its spectral data matched that previously reported.

**Propargyl iodide 108.** To a flame-dried flask containing $CH_2Cl_2$ (800 mL) at 23 °C was sequentially added $Ph_3P$ (45.86 g, 0.175 mol, 1.2 equiv) and imidazole (11.9 g, 0.175 mol, 1.2 equiv). The resultant solution was then cooled to 0 °C using an ice-water bath and $I_2$ (44.4 g, 0.175 mol, 1.2 equiv) was added in a single portion, forming an orange-brown suspension. The resultant suspension was then stirred at 0 °C for 30 min before a solution of propargyl alcohol **107** (39.4 g, 0.146 mol, 1.0 equiv) in $CH_2Cl_2$ (200 mL) was added, rinse that flask with a minimal amount of $CH_2Cl_2$ to ensure a complete transfer. Next, the ice-water bath was removed, at which time the suspension turned bright yellow. After stirring the resultant suspension at 23 °C for 1 h, the reaction was filtered directly through Celite (eluting with hexanes) and concentrated. The resultant residue was redissolved in hexanes (600 mL) and filtered a second time through a pad of Celite (eluting with hexanes) again. The resultant filtrate was concentrated and purification of the resultant residue by flash chromatography chromatography (silica gel, hexanes/EtOAc, 50:1), provided the desired propargyl iodid**e 108** (47.0 g, 85% yield) as a yellow oil. **108**: $R_f$ = 0.87 (silica gel, hexanes/EtOAc, 4:1); IR (film) $\nu_{max}$ 2930, 2892, 2866, 2361, 2339, 1464, 1171, 1109, 680 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 3.76 (t, *J* = 6.0 Hz, 2 H), 3.70 (t, *J* = 2.5 Hz, 2 H), 2.32 (tt, *J* = 7.1, 2.5 Hz, 2 H), 1.72 (p, *J* = 6.6 Hz, 2 H), 1.11–1.06 (m, 21 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 86.4, 77.1, 61.7, 31.6, 18.0, 15.6, 12.0, –16.9; HRMS (ESI) calcd for $C_{15}H_{30}IOSi^+$ [M + $H^+$] 380.1032, found 380.1030.

**Iodide 109.** A flame-dried flask at 23 °C was charged sequentially with **104** (9.81 mL, 9.61 g, 0.100 mol, 1.0 equiv), $CH_2Cl_2$ (800 mL), and pyridine (200 mL). Next, $I_2$ (55.9 g, 0.220

mol, 2.2 equiv) was added, forming a dark-brown solution. The resultant mixture was then stirred at 23 °C for 48 h. Upon completion, the reaction contents were quenched the addition of saturated aqueous $Na_2S_2O_3$ (600 mL) and poured into a separatory funnel. After separating the layers, the organic phase was washed with 3 N HCl (1 L), $H_2O$ (600 mL), and brine (600 mL). The organic layer was then dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4:1→2:1) afforded the desired iodide **109** (18.5 g, 83% yield) as a pale-yellow solid. Its spectral data matched that previously reported.

**Enone 111.** Iodide **109** (21.2 g, 95.6 mmol, 1.5 equiv) was dissolved in THF (350 mL) in a flame-dried flask at 23 °C and then was cooled to –78 °C using a dry ice-acetone bath, forming a yellow suspension. Next, *i*-PrMgCl (2.0 M in THF, 47.8 mL, 95.6 mmol, 1.5 equiv) was added dropwise at –78 °C, during which time the yellow suspension turned into a pale brown solution. After stirring the resultant solution for 30 min at –78 °C, freshly prepared CuCN•2LiCl (1.0 M in THF, 96 mL, 95.6 mmol, 1.5 equiv) was added, and the resultant gray/green suspension was stirred for a further 15 min at –78 °C. Next, a solution of propargyl iodide **108** (24.2 g, 63.7 mmol, 1.0 equiv) in THF (40 mL) was added to the suspension, rinsing the flask with additional THF (10 mL) to ensure a complete transfer. Once the transfer was complete, the cold bath was removed and the suspension was slowly warmed to 23 °C over the course of 30 min with stirring, during which time the suspension turned brown. Upon completion, the reaction contents were quenched by the sequential addition of saturated aqueous $NH_4Cl$ (200 mL) and 3 M NaOH (200 mL) and poured into a separatory funnel. After separating the layers, the aqueous layer was extracted with EtOAc (2 × 400 mL). The combined organic layers were then washed with brine (800 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant

residue by flash column chromatography (silica gel, hexanes/EtOAc, 10:1→4:1), providing the desired enone **111** (17.9 g, 81% yield) as a yellow oil. **111**: $R_f$ = 0.29 (silica gel, hexanes/EtOAc, 4:1); IR (film) $\nu_{max}$ 2942, 2865, 2360, 2339, 1700, 1653, 1457, 1107, 668 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 3.72 (t, *J* = 6.1 Hz, 2 H), 3.06 (s, 2 H), 2.58–2.47 (m, 2 H), 2.44–2.34 (m, 2 H), 2.23 (tt, *J* = 7.1, 2.5 Hz, 2 H), 2.17 (s, 3 H), 1.68 (p, *J* = 6.7 Hz, 2 H), 1.06–1.03 (m, 21 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 207.6, 171.8, 136.1, 79.7, 76.0, 61.8, 33.9, 32.0, 31.6, 17.9, 17.3, 15.1, 12.5, 11.8; HRMS (ESI) calcd for $C_{21}H_{37}O_2Si^+$ [M + $H^+$] 349.2558, found 349.2553.

**Nitrile 103.** $Et_3Al$ (1.0 M in heptane, 40.4 mL, 40.4 mmol, 1.2 equiv) and hexanes (19 mL) were added sequentially to a flame-dried flask at 23 °C. Next, TMSCN (9.2 mL, 74.0 mmol, 2.2 equiv) was added and the resultant colorless solution was stirred for 15 min at 23 °C. A solution of enone **111** (11.7 g, 33.6 mmol, 1.0 equiv) in hexanes (200 mL) was then added, using an additional portion of hexanes (60 mL) to complete the transfer. The reaction solution turned a red-brown color and then was warmed to 60 °C using a pre-heated oil bath. After stirring the resultant solution at 60 °C for 1 h. Upon completion, the reaction contents were then cooled to 0 °C using an ice-water bath and quenched by the addition of $H_2O$ until no bubble formation was observed from the solution. The reaction contents were then warmed to 23 °C and stirred for 30 min before being filtered through a pad of $Na_2SO_4$ (eluting with hexanes) and concentrated directly. The resultant crude silyl enol ether was then dissolved in THF (100 mL) and 3 M HCl (25 mL) was added at 23 °C. The resultant solution was stirred at 23 °C until the presence of the silyl enol ether had disappeared based on TLC monitoring (typically 10 min). Upon completion, the reaction contents were quenched by the addition of $H_2O$ (25 mL) and poured into a separatory funnel. After separating the layers, the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were then washed with brine (300 mL), dried ($Na_2SO_4$),

filtered, and concentrated. Purification of the resultant crude product by flash column chromatography (silica gel, hexanes/EtOAc, 10:1→4:1) providing the desired nitrile (8.67 g, 68% yield) as a pale brown oil. **103**: $R_f$ = 0.29 (silica gel, hexanes/EtOAc, 4:1); IR (film) $\nu_{max}$ 2943, 2892, 2866, 2235, 1751, 1490, 1246, 1108 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 3.73 (t, *J* = 6.0 Hz, 2 H), 2.87 (ddq, *J* = 17.4, 4.1, 2.2 Hz, 1 H), 2.53 (ddt, *J* = 12.9, 8.0, 2.0 Hz, 1 H), 2.46–2.40 (m, 2 H), 2.35 (ddt, *J* = 19.6, 12.2, 2.6 Hz, 1 H), 2.25 (td, *J* = 7.2, 3.4 Hz, 2 H), 2.14 (dd, *J* = 10.1, 3.7 Hz, 1 H), 1.86 (ddd, *J* = 12.8, 11.2, 8.9 Hz, 1 H), 1.74 (d, *J* = 1.2 Hz, 3 H), 1.72–1.66 (m, 2 H), 1.09–1.00 (m, 21 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 212.6, 121.3, 82.3, 76.2, 61.8, 57.5, 41.7, 35.2, 34.2, 31.9, 25.3, 17.9, 16.7, 15.1, 11.9; HRMS (ESI) calcd for $C_{22}H_{38}NO_2Si^+$ [M + $H^+$] 376.2667, found 376.2667.

**β-ketoester 102.** To a flame-dried flask at 23 °C was added *i*-$Pr_2NH$ (3.71 mL, 26.5 mmol, 2.1 equiv) and THF (27 mL), and the resultant solution was cooled to 0 °C using an ice-water bath. Next, *n*-BuLi (1.6 M in hexanes, 16.6 mL, 26.5 mmol, 2.1 equiv) was added dropwise, generating a colorless solution. After stirring the reaction contents for 10 min at 0 °C, the ice-water bath was exchanged for a dry ice-acetone bath to cool the solution to –78 °C. A solution of nitrile **103** (4.74 g, 12.6 mmol, 1.0 equiv) in THF (90 mL) was then added quickly, using an additional portion of THF (10 mL) to complete the transfer. The reaction solution turned a red-brown color and was stirred for an additional 30 min at –78 °C before Mander's reagent (**14**, 1.52 mL, 18.9 mmol, 1.5 equiv) was added dropwise. The resultant solution was then stirred at –78 °C for another 1 h. Upon completion, the reaction contents were quenched at –78 °C by the addition of saturated aqueous $NH_4Cl$ (100 mL) and warmed to 23 °C. The contents were then poured into a separatory funnel and the layers were separated. The aqueous layer was further extracted with EtOAc (2 × 100 mL). The combined organic layers were then washed with

brine (300 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8:1→4:1) provided the desired β-ketoester **102** (3.51 g, 64% yield) as a pale-yellow oil and as an inseparable mixture of diastereomers, also with enol form based on NMR analysis. $R_f$ = 0.29 (silica gel, hexanes/EtOAc, 4:1); IR (film) $\nu_{max}$ 2943, 2893, 2865, 2230, 1734, 1717, 1705, 1635, 1464, 1386, 1254, 1124, 672 $cm^{-1}$; $^1H$ NMR (500 MHz, $CHCl_3$, list major two diastereomers) δ 3.79–3.76 (m, 3 H), 3.76–3.72 (m, 2 H), 3.47 (dd, *J* = 12.2, 8.4 Hz, 0.71 H), 3.26 (dd, *J* = 11.4, 8.7 Hz, 0.28 H), 3.07 (dd, *J* = 14.0, 5.4 Hz, 0.28 H), 2.94–2.88 (m, 1 H), 2.88–2.80 (m, 0.28 H), 2.78–2.72 (m, 1 H), 2.72–2.67 (m, 0.28 H), 2.66–2.56 (m, 0.71 H), 2.55–2.49 (m, 0.56 H), 2.39 (ddt, *J* = 16.9, 10.1, 2.3 Hz, 1 H), 2.35–2.33 (m, 1 H), 2.30–2.23 (m, 3 H), 2.22–2.14 (m, 0.56 H), 1.81 (s, 2 H), 1.77–1.67 (m, 3 H), 1.08–1.01 (m, 21H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 205.3, 168.1, 120.8, 82.9, 75.6, 61.8, 57.4, 53.0, 52.3, 51.5, 51.2, 50.8, 39.8, 37.7, 32.1, 32.0, 31.7, 25.0, 19.2, 18.0, 16.8, 15.2, 15.1, 15.0, 12.2, 12.0; HRMS (ESI) calcd for $C_{24}H_{40}NO_4Si^+$ [M + $H^+$] 434.2721, found 434.2719.

**General procedure for Conia-ene reactions performed as part of condition screening:** To a flame-dried flask at 23 °C was added a solution of substrate **102** (1.0 equiv) in the indicated solvent (at a final concentration of 0.10 M). The indicated gold salt (0.20 equiv) and (if applicable) silver salt (0.20 equiv) were then added subsequently, forming a pale-yellow suspension. If needed, the suspension was then directly placed in pre-heated oil bath, and the resultant solution was either stirred at 23 °C or 40 °C for 24 h. Upon completion, the reaction contents were filtered through a pad of Celite (eluting with $CH_2Cl_2$). The filtrate was then concentrated directly and characterized by NMR analysis. (See NMR section pure spectrum of **113** and **114**)

**Silyl enol ether 115 and 116**. Pushing forward, the newly formed β-ketoester **102** (31.9 mg, 0.0738 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (0.74) and *i*-$Pr_2NEt$ (64 μL, 0.369 mmol, 5.0 equiv) was added at 23 °C. The resultant solution was then cooled to –78 °C using a dry ice-acetone bath and TBSOTf (64 μL, 0.111 mmol, 1.5 equiv) was added dropwise. After stirring the resultant solution for 30 min at –78 °C, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (2.0 mL). The reaction contents were then warmed to 23 °C, poured into a separatory funnel, and the layers were separated. The aqueous layer was further extracted with $CH_2Cl_2$ (2 × 3.0 mL). The combined organic layers were then washed with brine (5.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 20:1), providing a mixture of silyl enol ethers **115** and **116** (28.4 mg, 70% yield) as a pale-yellow oil. **115** and **116**: $R_f$ = 0.59 (silica gel, hexanes/EtOAc, 4:1).

**Silyl enol ether 117 and 118**. Pushing forward, the newly formed β-ketoester **102** (3.51 g, 8.09 mmol, 1.0 equiv) was dissolved in a mixture of toluene (40 mL) and allyl alcohol (10 mL), and the reaction contents were then heated directly to 110 °C using a pre-heated oil bath. After stirring at 110 °C for 3 h, the reaction contents were then cooled to 23 °C and concentrated directly. Finally, the resultant crude product was then dissolved in $CH_2Cl_2$ (81 mL) and *i*-$Pr_2NEt$ (7.04 mL, 40.4 mmol, 5.0 equiv) was added at 23 °C. The resultant solution was then cooled to –78 °C using a dry ice-acetone bath and TBSOTf (3.72 mL, 16.2 mmol, 2.0 equiv) was added dropwise. After stirring the resultant solution for 30 min at –78 °C, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (60 mL). The reaction contents were then warmed to 23 °C, poured into a separatory funnel, and the layers were separated. The aqueous layer was further extracted with $CH_2Cl_2$ (2 × 60 mL). The combined organic layers were then washed with

brine (150 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 20:1), providing a mixture of silyl enol ethers **117** and **118** (1.86 g, 40% yield) as a pale-yellow oil. **117** and **118**: $R_f$ = 0.59 (silica gel, hexanes/EtOAc, 4:1); IR (film) $\nu_{max}$ 2942, 2893, 2865, 2232, 1720, 1703, 1635, 1463, 1390, 1251, 1231, 1133, 1108, 1067, 1057, 1013, 995, 841, 788 $cm^{-1}$; $^1H$ NMR (400 MHz, $C_6D_6$) δ 5.73 (ddtd, *J* = 18.0, 10.7, 5.6, 2.0 Hz, 1 H), 5.09 (ddt, *J* = 17.2, 3.6, 1.7 Hz, 1 H), 4.97 (ddt, *J* = 10.4, 2.7, 1.4 Hz, 1 H), 4.45 (dd, *J* = 5.6, 1.5 Hz, 2 H), 3.71–3.60 (m, 2 H), 3.24 (dd, *J* = 14.9, 1.9 Hz, 0.67 H), 2.98–2.87 (m, 0.67 H), 2.68 (ddt, *J* = 17.1, 4.5, 2.4 Hz, 0.67 H), 2.61–2.54 (m, 0.67 H), 2.51 (dd, *J* = 15.0, 1.6 Hz, 0.33 H), 2.40–2.31 (m, 1 H), 2.22 (tq, *J* = 6.9, 2.4 Hz, 2 H), 2.14 (ddd, *J* = 6.2, 4.0, 1.5 Hz, 0.67 H), 2.10 (dt, *J* = 9.2, 2.4 Hz, 0.33 H), 1.70–1.61 (m, 2 H), 1.17 (s, 1 H), 1.11–1.06 (m, 23 H), 0.95–0.90 (m, 9 H), 0.31 (d, *J* = 18.3 Hz, 3 H), 0.15 (d, *J* = 17.8 Hz, 3 H); $^{13}C$ NMR (100 MHz, $C_6D_6$) δ 163.70, 163.67, 163.65, 163.1, 133.64, 133.61, 125.9, 122.9, 118.2, 107.5, 106.5, 83.9, 83.7, 76.67, 76.65, 64.9, 62.8, 57.1, 55.2, 42.5, 42.2, 37.2, 36.5, 33.0, 32.9, 27.7, 26.5, 26.44, 21.1, 20.2, 19.29, 19.25, 18.89, 18.87, 18.7, 17.9, 16.2, 16.1, 12.9, –3.2, –3.3, –3.6, –3.8; HRMS (ESI) calcd for $C_{32}H_{55}NNaO_4Si_2^+$ [M + $Na^+$] 596.3562, found 596.3560.

**General procedure for Conia-ene reactions performed as part of condition screening:** To a flame-dried flask at 23 °C was added a solution of substrate mixture **117** and **118** (1.0 equiv) in the indicated solvent (at a final concentration of 0.10 M). The indicated gold salt (0.20 equiv) and (if applicable) silver salt (0.20 equiv) were then added subsequently, forming a pale-yellow suspension. If needed, the suspension was then directly placed in pre-heated oil bath, and the resultant solution was either stirred at 23 °C or 40 °C for 48 h. Upon completion or no further conversion based on TLC analysis, the reaction contents were filtered

through a pad of Celite (eluting with $CH_2Cl_2$). The filtrate was then concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 16:1→4:1).

**β-ketoester 119.** A mixture of silyl enol ethers **117** and **118** (2.98 g, 5.20 mmol, 1.0 equiv) were dissolved in $CH_2Cl_2$ (47 mL) and *i*-PrOH (4.7 mL) at 23 °C and then JohnPhosAu(NCMe)$SbF_6$ (1.20 g, 1.56 mmol, 0.30 equiv) was added. The resultant solution was then warmed to 40 °C using a pre-heated oil bath and stirred at that temperature for 48 h, during which time the original yellow solution gradually turned a dark brown and a participate formed. Once the reaction appeared complete, as judged by no obvious turnover based on TLC analysis, the reaction contents were cooled to 23 °C and concentrated directly. Purified the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 16:1→4:1), providing the desired β-ketoester **119** (1.48 g, 62% yield) as a pale brown oil. **119**: $R_f$ = 0.43 (silica gel, hexanes/EtOAc, 4:1); IR (film) $\nu_{max}$ 2943, 2892, 2867, 2238, 1768, 1734, 1652, 1463, 1386, 1248, 1106, 995, 882 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.93 (ddt, *J* = 17.3, 10.4, 5.9 Hz, 1 H), 5.50 (dd, *J* = 4.5, 2.3 Hz, 1 H), 5.38 (dq, *J* = 17.2, 1.5 Hz, 1 H), 5.27 (dt, *J* = 10.4, 1.3 Hz, 1 H), 4.74 (ddt, *J* = 13.1, 6.0, 1.4 Hz, 1 H), 4.66 (ddt, *J* = 13.1, 6.0, 1.4 Hz, 1 H), 3.69 (t, *J* = 6.0 Hz, 2 H), 3.03 (ddd, *J* = 18.1, 4.4, 2.2 Hz, 1 H), 2.98–2.90 (m, 1 H), 2.87 (d, *J* = 13.8 Hz, 1 H), 2.60 (d, *J* = 13.8 Hz, 1 H), 2.44 (dd, *J* = 4.4, 2.5 Hz, 1 H), 2.30–2.19 (m, 1 H), 2.17–2.06 (m, 1 H), 1.69 (dddd, *J* = 10.1, 7.8, 6.8, 3.7 Hz, 2 H), 1.50 (s, 3 H), 1.07–1.03 (m, 21 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 204.8, 167.4, 143.3, 131.4, 122.7, 119.5, 119.2, 66.4, 62.5, 62.0, 53.0, 46.5, 36.5, 33.9, 31.1, 29.9, 28.4, 25.9, 18.0, 12.0, 11.9; HRMS (ESI) calcd for $C_{26}H_{42}NO_4Si^+$ [M + $H^+$] 460.2878, found 460.2876.

**Silyl ether 120.** β-ketoester **119** (1.48 g, 3.22 mmol, 1.0 equiv) was dissolved in MeOH (32 mL) at 23 °C and then $CeCl_3 \bullet 7H_2O$ (1.44 g, 3.86 mmol, 1.2 equiv) was added. After all the solids had dissolved, the resultant solution was then cooled to 0 °C using an ice-water bath and $NaBH_4$ (0.180 g, 4.83 mmol, 1.5 equiv) was added in a single portion. After the solution stopped bubbling, the reaction contents were stirred at 0 °C for another 5 min and then the ice-water bath was removed. The resultant contents were then stirred at 23 °C for 30 min. Upon completion, the reaction contents were diluted by the addition of $CH_2Cl_2$ (32 mL) and quenched with saturated aqueous $NH_4Cl$ (60 mL). The reaction contents were the poured into a separatory funnel and the resultant layers were separated. The aqueous layer was then further extracted with $CH_2Cl_2$ (3 × 60 mL). The combined organic layers were then washed with brine (120 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4:1→2:1) provided the desired alcohol (1.25 g, 84% yield) as a colorless oil. Pushing forward, the obtained alcohol (1.25 g, 2.71 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (27 mL) and 2,6-lutidine (1.57 mL, 13.5 mmol, 5.0 equiv) was added at 23 °C. Next, TBSOTf (0.93 mL, 4.06 mmol, 1.5 equiv) was added dropwise. The resultant solution was then stirred for 4 h Stirred the reaction for 4 h at 23 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NaHCO_3$ (25 mL), poured into a separatory funnel, and the resultant layers were separated. The aqueous layer was then further extracted with (2 × 30 mL). The combined organic layers were then washed with brine (90 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant crude residue by flash column chromatography (silica gel, hexanes/EtOAc, 16:1) provided the desired silyl ether **120** (1.34 g, 86% yield) as a colorless oil. **120**: $R_f$ = 0.69 (silica gel, hexanes/EtOAc, 4:1); IR (film) $\nu_{max}$ 2939, 2892, 2865, 2235, 1733, 1653, 1472, 1457, 1247, 1138, 1102, 873, 838 $cm^{-1}$; $^1H$ NMR

(500 MHz, $CDCl_3$) δ 5.92 (ddt, *J* = 16.7, 10.3, 6.1 Hz, 1 H), 5.46 (br s, 1 H), 5.38–5.28 (m, 1 H), 5.24 (dq, *J* = 10.4, 1.3 Hz, 1 H), 4.66 (ddt, *J* = 13.1, 6.0, 1.4 Hz, 1 H), 4.50 (ddt, *J* = 13.0, 6.1, 1.4 Hz, 1 H), 4.20 (d, *J* = 5.3 Hz, 1 H), 3.71–3.62 (m, 2 H), 2.64 (d, *J* = 17.9 Hz, 1 H), 2.50 (d, *J* = 13.8 Hz, 1 H), 2.39–2.27 (m, 2 H), 2.23–2.13 (m, 1 H), 2.05 (s, 2 H), 1.66 (ddt, *J* = 24.6, 12.3, 6.1 Hz, 2 H), 1.52 (s, 3 H), 1.08 -1.00 (m, 21 H), 0.87 (s, 9 H), 0.03 (d, *J* = 5.2 Hz, 6 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 172.4, 137.0, 131.8, 124.3, 119.7, 119.1, 73.5, 65.8, 62.9, 57.4, 48.1, 47.6, 35.7, 31.5, 31.2, 3.1, 29.1, 28.0, 26.0, 25.7, 18.0, 11.9, –5.0, –5.1; HRMS (ESI) calcd for $C_{32}H_{58}NO_4Si_2^+$ [M + $H^+$] 576.3899, found 576.3896.

**Carboxylic acid 121.** Silyl ether **120** (1.34 g, 2.33 mmol, 1.0 equiv) was dissolved in MeCN (23 mL) and pyrrolidine (0.229 mL, 2.79 mmol, 1.2 equiv) was added at 23 °C. The resultant solution was then cooled to 0 °C using an ice-water bath, and $Pd(Ph_3P)_4$ (1.07 g, 0.930 mmol, 0.4 equiv) was added. After the reaction contents were stirred at 0 °C for 5 min, the ice-water bath was removed, and the reaction contents were stirred at 23 °C for 1 h. Upon completion, the reaction contents were diluted with EtOAc (10 mL) and quenched by the addition of 3 M HCl (20 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with brine (90 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 6:1→4:1) provided the desired carboxylic acid **121** (1.03 g, 82% yield) as a white solid. **121**: $R_f$ = 0.57 (silica gel, hexanes/EtOAc, 4:1); IR (film) $\nu_{max}$ 2940, 2892, 2865, 2236, 1700, 1653, 1457, 1436, 1254, 1140, 1108, 872, 838 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.56 (s, 1 H), 4.24 (d, *J* = 5.3 Hz, 1 H), 3.69 (td, *J* = 6.3, 2.5 Hz, 2 H), 2.63–2.53 (m, 2 H), 2.45 (d, *J* = 18.4 Hz, 1 H), 2.21–1.98 (m, 4 H), 1.76–1.65 (m, 2 H), 1.52 (s, 3 H), 1.10 -1.02

(m, 21 H), 0.92 (s, 9 H), 0.15 (s, 6 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.9, 135.8, 123.8, 120.2, 72.8, 62.6, 57.2, 16.9, 46.7, 35.7, 31.17, 29.5, 29.0, 27.9, 25.6, 18, 11.9, –4.6, –5.3; HRMS (ESI) calcd for $C_{29}H_{54}NO_4Si_2^+$ [M + $H^+$] 536.3586, found 536.3587.

**Boc amide 122.** Carboxylic acid **121** (1.03 g, 1.92 mmol, 1.0 equiv) was dissolved in toluene (20 mL) at 23 °C and then $Et_3N$ (0.535 mL, 3.84 mmol, 2.0 equiv) and diphenyl phosphoryl azide (0.620 mL, 2.88 mmol, 1.5 equiv) were added sequentially. After stirring the resultant solution for 30 min at 23 °C, the reaction contents were heated at 120 °C using a pre-heated oil bath and stirred for an additional 1 h at that temperature. Upon completion, the reaction contents were cooled to 23 °C and *t*-BuOK (1.0 M in *t*-BuOH, 3.84 mL, 3.84 mmol, 2.0 equiv) was added and the reaction contents were stirred for another 1 h at 23 °C, during which time the color of the reaction solution transformed into a pale-yellow suspension. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NH_4Cl$ (20 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (2 × 20 mL). The combined organic layers were then washed with brine (50 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 10:1) provided the desired Boc amide intermediate **122** (0.971 g, 82% yield) as a colorless oil. **122**: $R_f$ = 0.62 (silica gel, hexanes/EtOAc, 4:1); IR (film) $\nu_{max}$ 3470, 3438, 2940, 2894, 2865, 2235, 1719, 1496, 1472, 1463, 1390, 1366, 1250, 1165, 1135, 1105, 1010, 880, 838 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 5.41–5.32 (m, 1 H), 4.68 (s, 1 H), 4.40 (d, *J* = 5.2 Hz, 1 H), 3.70 (t, *J* = 6.2 Hz, 2 H), 2.64 (d, *J* = 13.4 Hz, 1 H), 2.56–2.46 (m, 2 H), 2.32 (ddd, *J* = 18.0, 4.4, 2.2 Hz, 1 H), 2.14–2.06 (m, 2 H), 2.00–1.93 (m, 1 H), 1.67 (ddd, *J* = 14.0, 7.8, 6.2 Hz, 2 H), 1.54 (s, 3 H), 1.42 (s, 9 H), 1.05 (s, 21 H), 0.88 (s, 9 H), 0.08 (d, *J* = 7.5 Hz, 6 H); $^{13}$C NMR (100 MHz,

$CDCl_3$) δ 154.8, 139.4, 124.5, 119.8, 79.2, 72.0, 63.0, 62.7, 47.1, 45.9, 35.7, 32.1, 29.2, 28.4, 28.1, 27.5, 25.6, 18.0, 17.9, 11.9, –4.8, –5.0; HRMS (ESI) calcd for $C_{33}H_{62}N_2NaO_4Si_2^+$ [M + $Na^+$] 629.4140, found 629.4137.

**Diol 123.** Boc amide **122** (33.2 mg, 0.0544 mmol, 1.0 equiv) was dissolved in THF (0.54 mL) and cooled to 0 °C using an ice-water bath. Then TBAF (1.0 M in THF, 0.12 mL, 0.120 mmol, 2.2 equiv) was added dropwise. The cold bath was removed after the addition and the resulting yellow solution was stirred at 23 °C for 2 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NH_4Cl$ (2.0 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (2 × 3.0 mL). The combined organic layers were then washed with brine (5.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/acetone, 2:1) provided the desired diol **123** (18.3 mg, 99% yield) as a colorless oil. **123**: $R_f$ = 0.02 (silica gel, hexanes/EtOAc, 4:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 5.54 (dt, *J* = 4.2, 2.1 Hz, 1 H), 5.04 (s, 1 H), 4.23 (d, *J* = 5.6 Hz, 1 H), 3.70 (qt, *J* = 10.5, 6.2 Hz, 2 H), 2.75 (dd, *J* = 17.9, 4.0 Hz, 1 H), 2.66 (d, *J* = 12.9 Hz, 1 H), 2.42–2.35 (m, 1 H), 2.27–2.22 (m, 1 H), 2.10–2.05 (m, 2 H), 1.84–1.72 (m, 3 H), 1.70–1.58 (m, 1 H), 1.54 (s, 3 H), 1.44 (s, 9 H).

**Amide 100.** Diol **123** (13.0 mg, 0.0386 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (0.77 mL) and $NaHCO_3$ (32.4 mg, 0.386 mmol, 10 equiv) was added. Dess-Martin periodinane (65.7 mg, 0.155 mmol, 4.0 equiv) was added into the white suspension and stirred at 23 °C for 30 min. Upon completion, the reaction contents were quenched by the addition of aqueous $Na_2S_2O_3$ (3.0 M, 2.0 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with $CH_2Cl_2$ (2 × 3.0 mL). The

combined organic layers were then washed with saturated aqueous $NaHCO_3$ (5.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. The crude residue was directly dissolved in THF (0.36 mL) and AcOH (0.04 mL). Then $NaBH_3CN$ (12.1 mg, 0.193 mmol, 5.0 equiv) was added in one portion. The reaction solution was stirred at 23 °C for 12 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NaHCO_3$ (2.0 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (2 × 3.0 mL). The combined organic layers were then washed with brine (5.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 6:1) provided the desired amide **100** (5.9 mg, 48% yield for 2 steps) as a colorless oil. **100**: $R_f$ = 0.31 (silica gel, hexanes/EtOAc, 4:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 5.28 (s, 1 H), 3.78 (dt, *J* = 12.7, 4.8 Hz, 1 H), 3.12–3.06 (m, 1 H), 3.06–2.91 (m, 2 H), 2.78–2.72 (m, 1 H), 2.61 (d, *J* = 12.3 Hz, 1 H), 2.46 (d, *J* = 19.5 Hz, 1 H), 2.33 (d, *J* = 14.4 Hz, 1 H), 2.29–2.20 (m, 1 H), 1.77–1.71 (m, 1H), 1.57 (s, 3 H), 1.45 (s, 9 H).

**Amide 124.** Amide **100** (5.9 mg, 0.0186 mmol, 1.0 equiv) was dissolved in EtOH (0.48 mL) and deionized $H_2O$ (0.12 mL) in a microwave vial. Parkin's catalyst (4.0 mg, 0.0093 mmol, 0.50 equiv) was then added. The vial was sealed and directly heated the reaction solution at 70 °C using a pre-heated oil bath for 24 h. Upon completion, the reaction contents were cooled to 23 °C and filtered through a small pad of silica gel (eluted with hexanes/EtOAc, 4:1). Concentration in vacuo provided the desired amide **124** (6.0 mg, 99% yield) as a white solid. **124**: $R_f$ = 0.31 (silica gel, hexanes/EtOAc, 4:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 5.60–5.49 (m, 2 H), 5.12 (s, 1 H), 3.78 (d, *J* = 12.4 Hz, 1 H), 3.20–3.06 (m, 2 H), 2.77 (d, *J* = 18.1 Hz, 1 H),

2.71–2.61 (m, 1 H), 2.40 (d, *J* = 5.0 Hz, 1 H), 2.35–2.24 (m, 2 H), 2.16 (d, *J* = 12.2 Hz, 1 H), 1.76–1.68 (m, 1 H), 1.60 (s, 3 H), 1.46 (s, 9 H).

**Carboxylic acid 127.** The Boc amide intermediate **122** (0.960 g, 1.58 mmol, 1.0 equiv) was dissolved in toluene (16 mL) and then the reaction solution was cooled to 0 °C using an ice-water bath. Next, DIBAL-H (20 wt % in toluene, 5.27 mL, 6.32 mmol, 4.0 equiv) was added dropwise, and then the reaction contents were stirred for an additional 15 min at 0 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous Rochelle's salt (16 mL). The resultant biphasic reaction contents were then warmed to 23 °C and stirred for 40 min until both layers became clear. The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (2 × 15 mL). The combined organic layers were then washed with brine (20 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 10:1), providing the desired aldehyde (0.828 g, 85% yield) as a colorless oil. Pushing forward, the obtained aldehyde (0.825 g, 1.35 mmol, 1.0 equiv) was dissolved in *t*-BuOH (13.5 mL) at 23 °C and then $H_2O$ (13.5 mL), 2-methyl-2-butene (4.5 mL), and $NaH_2PO_4$•$2H_2O$ (4.21 g, 27.0 mmol, 20 equiv) were added sequentially. After all the solids had dissolved, $NaClO_2$ (1.22 g, 13.5 mmol, 10 equiv) was then added and the initially cloudy solution turned yellow in color. The resultant solution was stirred for an additional 40 min at 23 °C for 40 min during which time it became colorless. Upon completion, the reaction contents were diluted with EtOAc (15 mL), poured into a separatory funnel, and the layers were separated. The aqueous layer was further extracted with EtOAc (2 × 15 mL). The combined organic layers were then washed with brine (20 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc,

4:1) provided the desired carboxylic acid **127** (0.801 g, 95% yield) as a colorless oil. **127**: $R_f$ = 0.30 (silica gel, hexanes/EtOAc, 4:1); IR (film) $\nu_{max}$ 3470, 2940, 2893, 2865, 1718, 1654, 1496, 1463, 1390, 1251, 1165, 1127, 1104, 880, 837 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 5.14 (d, *J* = 3.8 Hz, 1 H), 4.71 (s, 1 H), 4.59 (s, 1 H), 3.67 (t, *J* = 6.3 Hz, 2 H), 2.89 (d, *J* = 13.4 Hz, 1 H), 2.37 (d, *J* = 17.8 Hz, 1 H), 2.20 (d, *J* = 13.4 Hz, 1 H), 2.09–1.95 (m, 4 H), 1.64 (p, *J* = 7.0 Hz, 2 H), 1.48 (s, 3 H), 1.42 (s, 9 H), 1.11–0.97 (m, 21 H), 0.86 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 182.1, 154.8, 139.2, 119.0, 78.8, 73.0, 72.9, 68.0, 63.3, 62.9, 47.6, 46.9, 42.8, 32.1, 29.7, 29.5, 28.4, 27.7, 26.6, 25.7, 18.0, 17.9, 12.0, –4.7, –4.9; HRMS (ESI) calcd for $C_{33}H_{63}NNaO_6Si_2^+$ [M + $Na^+$] 648.4086, found 648.4086.

**Iodolactone 128.** Carboxylic acid **127** (0.800 g, 1.28 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (13 mL) at 23 °C and *N*-iodosuccinimide (1.44 g, 6.39 mmol, 5.0 equiv) was then added in a single portion, leading initially to the formation of a white participate and eventually a purple-colored solution. The reaction contents were stirred at 23 °C for 6 h. Upon completion, the reaction was quenched by the addition of 3 M $Na_2S_2O_3$ (13 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with $CH_2Cl_2$ (2 × 15 mL). The combined organic layers were then washed with brine (20 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 16:1), providing the iodolactone **128** (0.712 g, 74% yield) as a colorless oil. **128**: $R_f$ = 0.58 (silica gel, hexanes/EtOAc, 4:1); IR (film) $\nu_{max}$ 3362, 2941, 2880, 1735, 1700, 1653, 1472, 1455, 1367, 1167, 1110, 1012, 619 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 4.93 (s, 1 H), 4.86 (d, *J* = 3.0 Hz, 1 H), 4.46 (s, 1 H), 3.78 (dt, *J* = 10.9, 5.5 Hz, 1 H), 3.70 (dt, *J* = 9.9, 6.2 Hz, 1 H), 2.93 (dd, *J* = 14.2, 2.5 Hz, 1 H), 2.57 (d, *J* = 14.5 Hz, 1 H), 2.49–2.38 (m, 1 H), 2.04–1.88 (m, 4 H), 1.82–1.70

(m, 2 H), 1.41 (s, 9 H), 1.31 (s, 3 H), 1.03 (d, *J* = 5.1 Hz, 21 H), 0.95 (s, 9 H), 0.17 (s, 3 H), 0.10 (s, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 175.8, 154.1, 80.6, 64.1, 62.6, 60.6, 41.9, 41.5, 35.6, 34.6, 31.5, 29.2, 28.3, 25.9, 25.2, 24.6, 23.7, 22.6, 18.0, 11.9, –4.5, –5.2; HRMS (ESI) calcd for $C_{33}H_{63}INO_6Si_2^+$ [M + $H^+$] 752.3233, found 752.3232.

**Lactone 129.** Iodoalcohol **128** (0.270 g, 0.359 mmol, 1.0 equiv) was dissolved in toluene (7.2 mL) at 23 °C and then cooled to 0 °C with an ice-water bath. Next, *n*-$Bu_3SnH$ (0.157 g, 0.538 mmol, 1.5 equiv) and $Et_3B$ (1.0 M in hexane, 0.359 mL, 0.359 mmol, 1.0 equiv) were then added sequentially, and 1.0 mL of air from syringe was subsequently bubbled through the solution to initiate the reaction. The reaction contents were then stirred for 15 min at 0 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NaHCO_3$ (5.0 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (2 × 5.0 mL). The combined organic layers were then washed with brine (10 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8:1) provided the desired lactone **129** (0.201 g, 91% yield) as a colorless oil. **129**: $R_f$ = 0.54 (silica gel, hexanes/EtOAc, 4:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 4.79 (s, 1 H), 4.43 (s, 1 H), 4.33–4.22 (m, 1 H), 3.68 (t, *J* = 6.5 Hz, 2 H), 2.45 (d, *J* = 14.0 Hz, 1 H), 2.38 (d, *J* = 13.4 Hz, 1 H), 2.34–2.29 (m, 1 H), 2.07–1.98 (m, 1 H), 1.95 (d, *J* = 6.2 Hz, 1 H), 1.87–1.77 (m, 1 H), 1.71–1.59 (m, 3 H), 1.42 (s, 9 H), 1.39–1.34 (m, 1 H), 1.31 (s, 3 H), 1.07–1.03 (m, 21 H), 0.92 (s, 9 H), 0.13 (s, 3 H), 0.08 (s, 3 H).

**Alcohol 130.** Lactone **129** (0.310 g, 0.495 mmol, 1.0 equiv) was dissolved in THF (9.8 mL) and cooled to 0 °C with an ice-water bath. Next, TBAF (1.0 M in THF, 0.449 mL, 0.49 mmol, 1.0 equiv) was added dropwise. The resultant pale-yellow solution was stirred for an

additional 30 min at 0 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NH_4Cl$ (8.0 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (2 × 10.0 mL). The combined organic layers were then washed with brine (15 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4:1) provided the desired alcohol **130** (0.208 g, 82% yield) as a colorless oil. **130**: $R_f$ = 0.18 (silica gel, hexanes/EtOAc, 4:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 5.16 (s, 1 H), 4.85 (s, 1 H), 4.52 (p, *J* = 2.4 Hz, 1 H), 4.45 (d, *J* = 6.0 Hz, 1 H), 3.68 (t, *J* = 6.1 Hz, 2 H), 2.69 (d, *J* = 14.1 Hz, 1 H), 2.26–2.19 (m, 1 H), 2.01 (d, *J* = 12.7 Hz, 1 H), 1.95 (d, *J* = 9.8 Hz, 1 H), 1.85–1.76 (m, 1 H), 1.70–1.56 (m, 4 H), 1.49 (dtd, *J* = 12.8, 6.4, 2.4 Hz, 1 H), 1.44 (s, 9 H), 1.32 (s, 3 H), 1.07–1.02 (m, 21 H).

**Ketone 131.** Alcohol **130** (0.115 g, 0.225 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (4.5 mL) at 23 °C and then $NaHCO_3$ (0.189 g, 2.25 mmol, 10 equiv) and Dess–Martin periodinane (0.191 g, 0.449 mmol, 2.0 equiv) were added sequentially in single portions. The reaction contents were then stirred for 30 min at 23 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $Na_2S_2O_3$ (5.0 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (2 × 5.0 mL). The combined organic layers were then washed with brine (10 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8:1) provided the desired lactone **131** (0.0905 g, 79% yield) as a colorless oil. **131**: $R_f$ = 0.48 (silica gel, hexanes/EtOAc, 4:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 5.51 (s, 1 H), 4.52 (s, 1 H), 3.64 (td, *J* = 10.4, 4.9 Hz, 2 H),

3.20 (d, *J* = 10.3 Hz, 1 H), 3.15 (d, *J* = 13.7 Hz, 1 H), 2.44–2.28 (m, 3 H), 1.75 (d, *J* = 13.8 Hz, 1 H), 1.67–1.51 (m, 3 H), 1.48–1.44 (m, 1 H), 1.41 (s, 9 H), 1.34 (s, 3 H), 1.07–1.00 (m, 21 H).

**Alkynyl ester 132.** Methyl propiolate (0.042 mL, 0.471 mmol, 2.5 equiv) was dissolved in THF (0.71 mL) at 23 °C and then the reaction contents were cooled to –78 °C with a dry ice-acetone bath. Next, freshly prepared LDA (1.0 M in THF, 0.46 mL, 0.461 mmol, 2.45 equiv) was added and the resulting orange solution was stirred for an additional 30 min at –78 °C. A solution of ketone **131** (95.8 mg, 0.188 mmol, 1.0 equiv) in THF (0.60 mL) was then added, using another aliquot of THF (0.10 mL) to complete the transfer. The reaction contents were stirred for an additional 15 min at –78 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NH_4Cl$ (2.0 mL) and warmed to 23 °C. The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (2 × 2.0 mL). The combined organic layers were then washed with brine (3.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexane/EtOAc, 4:1) to provide the desired alkynyl ester **132** (90.6 mg, 81% yield) as a pale-yellow oil. **132**: $R_f$ = 0.33 (silica gel, hexanes/EtOAc, 3:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 6.86 (s, 1 H), 5.51 (s, 1 H), 4.95 (s, 1 H), 4.51–4.48 (m, 1 H), 3.77 (s, 3 H), 3.66 (qt, *J* = 8.3, 4.6 Hz, 2 H), 2.89–2.77 (m, 1 H), 2.48 (d, *J* = 5.1 Hz, 1 H), 2.43–2.32 (m, 1 H), 2.30 (d, *J* = 13.2 Hz, 1 H), 2.07–2.00 (m, 2 H), 1.86–1.76 (m, 1 H), 1.75–1.69 (m, 1 H), 1.63 (td, *J* = 12.7, 12.0, 5.6 Hz, 1 H), 1.49 (s, 3 H), 1.46 (s, 9 H), 1.13–0.98 (m, 21 H).

**Butenolide 133.** Alkynyl ester **132** (81.0 mg, 0.842 mmol, 1.0 equiv) and quinoline (0.0048 mL, 0.409 mmol, 3.0 equiv) were sequentially dissolved in MeOH (2.7 mL) at 23 °C. Next, Pd/C (10% wt., 14.5 mg, 0.10 equiv based on Pd) was added, and the resulting black

suspension was degassed with a $H_2$ atmosphere. The resultant suspension was then stirred for 1 h at 23 °C in the presence of a $H_2$ atmosphere (from a balloon). Upon completion, the reaction contents were filtered directly through a pad of Celite (eluting with EtOAc). The resultant filtrate was then washed with 3 M HCl (3.0 mL), poured into a separatory funnel, and the layers were separated. The aqueous layer was then further extracted with EtOAc (3 × 3.0 mL). The combined organic layers were then washed with brine (4.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. The resultant crude residue was then dissolved in $CH_2Cl_2$ (0.84 mL) at 23 °C and silica gel (136 mg, 1.0 g/mmol substrate) was added. The resultant slurry was stirred for 30 min, before being loaded directly on a silica gel column and purified by flash column chromatography (silica gel, hexane/acetone, 4:1) to provide the desired butenolide **133** (67.0 mg, 88% yield) as a white solid. **133**: $R_f$ = 0.40 (silica gel, hexanes/acetone, 2:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 5.8 Hz, 1 H), 6.20 (d, *J* = 5.8 Hz, 1 H), 4.59 (s, 1 H), 4.47 (s, 1 H), 3.74–3.62 (m, 2 H), 2.90 (d, *J* = 14.5 Hz, 1 H), 2.72 (d, *J* = 9.9 Hz, 1 H), 2.67–2.58 (m, 1 H), 2.31 (s, 1 H), 2.13 (d, *J* = 5.1 Hz, 1 H), 1.91 (d, *J* = 15.0 Hz, 1 H), 1.74–1.62 (m, 2 H), 1.60–1.51 (m, 2 H), 1.43 (s, 3 H), 1.39 (s, 9 H), 1.08–1.02 (m, 21 H).

**Alcohol 134.** Butenolide **133** (67.0 mg, 0.119 mmol, 1.0 equiv) was dissolved in THF (2.4 mL) at 23 °C and TBAF (1.0 M in THF, 0.18 mL, 0.0178 mmol, 1.5 equiv) was added dropwise. The resultant light brown solution was stirred for an additional 1 h at 23 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NH_4Cl$ (2.0 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (2 × 3.0 mL). The combined organic layers were then washed with brine (5.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel,

hexanes/acetone, 2:1→1:1), to provide the desired alcohol **134** (33.1 mg, 68% yield) as a white solid. **134**: $R_f$ = 0.02 (silica gel, hexanes/acetone, 2:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 5.8 Hz, 1 H), 6.22 (d, *J* = 5.8 Hz, 1 H), 4.64 (s, 1 H), 4.56 (s, 1 H), 3.72–3.60 (m, 3 H), 2.91 (d, *J* = 14.4 Hz, 1 H), 2.78 (d, *J* = 9.9 Hz, 1 H), 2.65 (dd, *J* = 14.9, 3.0 Hz, 1 H), 2.38–2.24 (m, 1 H), 2.15 (d, *J* = 5.1 Hz, 1 H), 1.97–1.89 (m, 1 H), 1.73 (tt, *J* = 10.6, 4.4 Hz, 2 H), 1.63–1.55 (m, 1 H), 1.53–1.46 (m, 1 H), 1.43 (s, 3 H), 1.40 (s, 9 H).

**Mesylate 135.** Alcohol **134** (13.2 mg, 0.0319 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (0.64 mL) at 23 °C and then was cooled to 0 °C with an ice-water bath. Next, $Et_3N$ (0.044 mL, 0.319 mmol, 10 equiv) and MsCl (0.0074 mL, 0.0957 mmol, 3.0 equiv) were added. The reaction solution turned into a light brown suspension and was stirred for an additional 30 min at 0 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NaHCO_3$ (2.0 mL) and the cold bath was removed. The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with $CH_2Cl_2$ (2 × 2.0 mL). The combined organic layers were then washed with brine (5.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/acetone, 2:1) provided the desired mesylate **135** (14.6 mg, 94% yield) as a white solid. **135**: $R_f$ = 0.05 (silica gel, hexanes/acetone, 1:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 5.8 Hz, 1 H), 6.26 (d, *J* = 5.7 Hz, 1 H), 4.54 (s, 1 H), 4.46 (s, 1 H), 4.22 (td, *J* = 6.3, 2.6 Hz, 2 H), 3.42 (q, *J* = 7.3 Hz, 1 H), 3.02 (s, 3 H), 2.70–2.58 (m, 1 H), 2.19–2.13 (m, 2 H), 1.98–1.85 (m, 2 H), 1.73 (s, 3 H), 1.52–1.46 (m, 1 H), 1.43 (s, 3 H), 1.41 (s, 9 H).

**Boc amide 136.** Mesylate **135** (7.1 mg, 0.0146 mmol, 1.0 equiv) was dissolved in THF (0.32 mL) and DMF (0.08 mL) at 23 °C and then was cooled to 0 °C with an ice-water bath.

Next, NaH (60% in mineral oil, 2.9 mg, 0.0732 mmol, 5.0 equiv) was added. The reaction suspension was stirred for an additional 30 min at 0 °C. Upon completion, the reaction contents were quenched by the addition of deionized $H_2O$ (2.0 mL) and EtOAc (2.0 mL). The cold bath was removed after work up. The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (2 × 2.0 mL). The combined organic layers were then washed with brine (5.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/acetone, 4:1) provided the desired Boc amide **136** (2.9 mg, 51% yield) as a white solid. **136**: $R_f$ = 0.58 (silica gel, hexanes/acetone, 1:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 5.7 Hz, 1 H), 6.09 (d, *J* = 5.7 Hz, 1 H), 4.40 (s, 1 H), 3.89 (d, *J* = 13.6 Hz, 1 H), 3.78 (d, *J* = 14.8 Hz, 1 H), 2.97–2.89 (m, 1 H), 2.76–2.63 (m, 1 H), 2.41 (d, *J* = 14.8 Hz, 1 H), 2.36 (dd, *J* = 14.3, 5.7 Hz, 2 H), 2.11–2.00 (m, 2 H), 1.95–1.88 (m, 1 H), 1.80–1.72 (m, 1 H), 1.72–1.61 (m, 1 H), 1.44 (s, 3 H), 1.39 (s, 9 H).

**4-*epi*-annotinolide C (137).** Boc amide **136** (2.9 mg, 0.00745 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (0.30 mL) at 23 °C. Next, TFA (0.030 mL) was added dropwise. The reaction solution was stirred for an additional 15 min at 23 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NaHCO_3$ (2.0 mL) and $CH_2Cl_2$ (2.0 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with $CH_2Cl_2$ (2 × 2.0 mL). The combined organic layers were then washed with brine (3.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. 4-*epi*-annotinolide C (**137**) was directly obtained as a white solid without further purification. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 5.7 Hz, 1 H), 6.24 (d, *J* = 5.8 Hz, 1 H), 4.44–4.40 (m, 1 H), 2.77–2.64 (m, 3 H), 2.20–2.09 (m, 2 H), 2.05 (d, *J* = 13.8 Hz, 1 H), 1.98–

1.93 (m, 1 H), 1.89 (d, *J* = 13.8 Hz, 1 H), 1.81 (d, *J* = 13.3 Hz, 1 H), 1.69–1.58 (m, 2 H), 1.52–1.45 (m, 1 H), 1.42 (s, 3 H).

**Diol 138.** Lactone **129** (94.8 mg, 0.152 mmol, 1.0 equiv) was dissolved in THF (1.5 mL) and cooled to 0 °C with an ice-water bath. Next, TBAF (1.0 M in THF, 0.67 mL, 0.668 mmol, 4.4 equiv) was added dropwise. The cold bath was removed, and the resultant pale-yellow solution was stirred for an additional 4 h at 23 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NH_4Cl$ (2.0 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (2 × 3.0 mL). The combined organic layers were then washed with brine (4.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/acetone, 2:1) provided the desired diol **138** (49.4 mg, 82% yield) as a colorless oil. **138**: $R_f$ = 0.02 (silica gel, hexanes/EtOAc, 1:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 5.14 (s, 1 H), 5.08 (s, 1 H), 4.49 (s, 1 H), 4.37 (s, 1 H), 3.64 (t, *J* = 6.2 Hz, 2 H), 3.02– 2.95 (m, 1 H), 2.67 (d, *J* = 14.3 Hz, 1 H), 2.21 (s, 1 H), 2.10 (d, *J* = 33.6 Hz, 1 H), 1.88–1.67 (m, 4 H), 1.62 (ddt, *J* = 14.4, 4.7, 2.1 Hz, 2 H), 1.44 (s, 9 H), 1.32 (s, 3 H).

**Amide 140.** Diol **138** (26.2 mg, 0.0732 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (1.5 mL) and $NaHCO_3$ (61.5 mg, 0.732 mmol, 10 equiv) was added. Dess-Martin periodinane (124 mg, 0.293 mmol, 4.0 equiv) was added into the white suspension and stirred at 23 °C for 40 min. Upon completion, the reaction contents were quenched by the addition of aqueous $Na_2S_2O_3$ (3.0 M, 2.0 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with $CH_2Cl_2$ (2 × 3.0 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (5.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. The crude residue was directly dissolved in THF (1.3 mL)

and AcOH (0.14 mL). Then $NaBH_3CN$ (1.0 M in THF, 0.15 mL, 0.146 mmol, 2.0 equiv) was added dropwise. The reaction solution was stirred at 23 °C for 12 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NaHCO_3$ (2.0 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (2 × 3.0 mL). The combined organic layers were then washed with brine (5.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 2:1) provided the desired amide **140** (13.6 mg, 55% yield for 2 steps) as a colorless oil. **140**: $R_f$ = 0.55 (silica gel, hexanes/EtOAc, 2:1).

**Vinyl iodide 143.** Boc amide **140** (12.0 mg, 0.0358 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (0.70 mL) at 23 °C. Next, TFA (0.070 mL) was added dropwise. The reaction solution was stirred for an additional 15 min at 23 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NaHCO_3$ (2.0 mL) and $CH_2Cl_2$ (2.0 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with $CH_2Cl_2$ (2 × 2.0 mL). The combined organic layers were then washed with brine (3.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. The crude amine **141** was directly used in next step without further purification. Pushing forward, the crude **141** was dissolved in MeCN (0.40 mL) at 23 °C. Then $K_2CO_3$ (49.5 mg, 0.358 mmol, 10.0 equiv) and allyl bromide **142** (44.2 mg, 0.179 mmol, 5.0 equiv) were added. The reaction suspension was stirred at 23 °C for an additional 24 h. Upon completion, the reaction suspension was filtered through a pad of Celite (eluted with EtOAc) and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/acetone, 4:1) provided the desired amide **143** (7.0 mg, 49% yield for 2 steps) as a

colorless oil. **143**: $R_f$ = 0.62 (silica gel, hexanes/acetone, 2:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 6.31–6.25 (m, 2 H), 4.32 (tt, *J* = 2.7, 1.6 Hz, 1 H), 3.52–3.43 (m, 2 H), 3.37–3.30 (m, 1 H), 2.79 (ddt, *J* = 12.5, 4.2, 2.0 Hz, 1 H), 2.58–2.51 (m, 1 H), 2.32 (dp, *J* = 5.0, 2.5 Hz, 2 H), 2.27 (dt, *J* = 5.3, 1.7 Hz, 1 H), 2.17 (d, *J* = 13.4 Hz, 1 H), 2.07 (d, *J* = 13.4 Hz, 1 H), 1.75–1.67 (m, 2 H), 1.66–1.59 (m, 2 H), 1.35 (s, 3 H).

**4-*epi*-annotinolide D (144).** Vinyl iodide **143** (2.0 mg, 0.00498 mmol, 1.0 equiv) was dissolved in THF (0.30 mL) at 23 °C and was cooled to –78 °C with a dry ice-acetone bath. Next, *t*-BuLi (1.7 M in pentane, 0.0062 mL, 0.0105 mmol, 2.1 equiv) was added dropwise. The reaction solution was stirred for an additional 30 min at –78 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NH_4Cl$ (2.0 mL) and EtOAc (2.0 mL). Then the cold bath was removed. The reaction contents were poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (2 × 2.0 mL). The combined organic layers were then washed with brine (3.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. 4-*epi*-annotinolide D (**144**) was directly obtained as a white solid without further purification. $^1$H NMR (500 MHz, $CDCl_3$) δ 5.92–5.87 (m, 1 H), 5.87–5.82 (m, 1 H), 4.39 (s, 1 H), 3.90 (d, *J* = 20.0 Hz, 1 H), 3.49 (t, *J* = 11.3 Hz, 1 H), 3.25–3.17 (m, 1 H), 2.82 (dd, *J* = 13.5, 3.1 Hz, 1 H), 2.69 (d, *J* = 11.0 Hz, 1 H), 2.25–2.13 (m, 2 H), 2.12–2.03 (m, 2 H), 1.85–1.73 (m, 3 H), 1.71–1.51 (m, 2 H), 1.23 (s, 3 H).

**Alkene 145.** Iodide **128** (94.9 mg, 0.126 mmol, 1.0 equiv) was dissolved in toluene (1.3 mL) at 23 °C. Next, DBU (0.19 mL, 1.26 mmol, 10.0 equiv) was added dropwise. The reaction solution was stirred for an additional 2.5 h at 23 °C. Upon completion, the reaction contents were quenched by the addition of HCl (1.0 M in $H_2O$, 2.0 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was

further extracted with EtOAc (2 × 2.0 mL). The combined organic layers were then washed with brine (3.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 10:1) provided the desired alkene **145** (76.3 mg, 97% yield) as a colorless oil. **145**: $R_f$ = 0.46 (silica gel, hexanes/acetone, 2:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 5.59 (t, *J* = 7.4 Hz, 1 H), 5.28 (s, 1 H), 4.71 (s, 1 H), 4.11 (s, 1 H), 3.74–3.59 (m, 2 H), 2.70 (d, *J* = 13.5 Hz, 1 H), 2.52–2.39 (m, 2 H), 2.28 (d, *J* = 14.1 Hz, 1 H), 2.13–2.02 (m, 2 H), 1.82–1.72 (m, 1 H), 1.43 (s, 9 H), 1.38 (s, 3 H), 1.06–1.02 (m, 21 H), 0.88 (s, 9 H), 0.13 (s, 3 H), 0.07 (s, 3 H).

**Iodoalcohol 147.** Iodolactone **128** (0.340 g, 0.452 mmol, 1.0 equiv) was dissolved in THF (4.5 mL) at 23 °C and then was cooled to 0 °C with an ice-water bath. Next, TBAF (1.0 M in THF, 0.452 mL, 0.452 mmol, 1.0 equiv) was added dropwise. The resultant pale-yellow solution was stirred for an additional 15 min at 0 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NH_4Cl$ (4.0 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (2 × 6.0 mL). The combined organic layers were then washed with brine (10 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8:1) provided the desired iodoalcohol **147** (0.266 g, 92% yield) as a colorless oil. **147**: $R_f$ = 0.34 (silica gel, hexanes/EtOAc, 4:1); IR (film) $\nu_{max}$ 3365, 2942, 2880, 2865, 1734, 1700, 1653, 1472, 1457, 1367, 1166, 1105, 1012, 622 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 5.41 (s, 1 H), 5.20 (s, 1 H), 4.86 (s, 1 H), 4.56 (s, 1 H), 3.82 (dt, *J* = 10.5, 5.1 Hz, 1 H), 3.71 (dt, *J* = 12.5, 6.2 Hz, 1 H), 3.10 (d, *J* = 14.4 Hz, 1 H), 2.47 (d, *J* = 14.0 Hz, 1 H), 2.25 (s, 1 H), 2.07 (q, *J* = 18.3, 16.3 Hz, 2 H), 1.87–1.74 (m, 4 H), 1.43 (s, 9 H), 1.31 (s, 3 H), 1.13–0.97 (m, 21 H); $^{13}$C NMR (126 MHz,

$CDCl_3$) δ 175.7, 154.9, 80.7, 74.6, 65.1, 62.3, 57.8, 45.4, 43.1, 42.0, 35.1, 29.6, 28.8, 28.2, 24.2, 24.1, 18.0, 11.9; HRMS (ESI) calcd for $C_{27}H_{48}INNaO_6Si^+$ [M + $Na^+$] 660.2188, found 660.2184.

**Lactone 146.** Iodoalcohol **147** (0.260 g, 0.408 mmol, 1.0 equiv) was dissolved in toluene (8.2 mL) at 23 °C and then was cooled to 0 °C with an ice-water bath. Next, *n*-$Bu_3SnH$ (0.178 g, 0.612 mmol, 1.5 equiv) and $Et_3B$ (1.0 M in hexane, 0.41 mL, 0.408 mmol, 1.0 equiv) were then added sequentially and 1.0 mL of air from syringe was subsequently bubbled through the solution to initiate the reaction. The reaction contents were then stirred for 15 min at 0 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NaHCO_3$ (6.0 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (2 × 6.0 mL). The combined organic layers were then washed with brine (10 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8:1) provided the desired lactone **146** (0.205 g, 98% yield) as a colorless oil. **146**: $R_f$ = 0.32 (silica gel, hexanes/EtOAc, 4:1); IR (film) $\nu_{max}$ 3335, 2942, 2881, 2865, 1734, 1700, 1653, 1473, 1457, 1367, 1168, 1100, 1009 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 6.09 (s, 1 H), 5.10–4.99 (m, 1 H), 4.62 (q, *J* = 2.8 Hz, 1 H), 4.28 (dd, *J* = 6.4, 2.7 Hz, 1 H), 3.71 (qd, *J* = 5.7, 2.5 Hz, 1 H), 3.66–3.55 (m, 1 H), 2.62 (d, *J* = 13.0 Hz, 2 H), 2.17 (q, *J* = 4.5 Hz, 1 H), 2.02 (d, *J* = 13.1 Hz, 1 H), 1.70 (tdd, *J* = 11.6, 6.3, 2.5 Hz, 1 H), 1.65–1.59 (m, 1 H), 1.55–1.46 (m, 3 H), 1.43–1.37 (m, 10 H), 1.27 (s, 3 H), 1.08–0.98 (m, 21 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 177.0, 156.6, 80.9, 76.6, 76.5, 63.7, 63.4, 44.6, 43.03, 42.96, 38.1, 30.3, 28.1, 26.8, 24.3, 21.7, 18.0, 11.8; HRMS (ESI) calcd for $C_{27}H_{49}NNaO_6Si^+$ [M + $Na^+$] 534.3221, found 534.3217.

**Ketone 126.** Lactone **146** (0.200 g, 0.391 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (7.8 mL) at 23 °C and then $NaHCO_3$ (0.328 g, 3.91 mmol, 10 equiv) and Dess–Martin periodinane (0.332 g, 0.782 mmol, 2.0 equiv) were added sequentially in single portions. The reaction contents were then stirred for 30 min at 23 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $Na_2S_2O_3$ (6.0 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (2 × 6.0 mL). The combined organic layers were then washed with brine (10 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8:1) provided the desired lactone **126** (0.186 g, 93% yield) as a colorless oil. **126**: $R_f$ = 0.32 (silica gel, hexanes/EtOAc, 4:1); IR (film) $\nu_{max}$ 3335, 2942, 2881, 2865, 1734, 1700, 1653, 1473, 1457, 1367, 1168, 1100, 1009 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 5.41 (s, 1 H), 5.20 (s, 1 H), 4.86 (s, 1 H), 4.56 (s, 1 H), 3.82 (dt, *J* = 10.5, 5.1 Hz, 1 H), 3.71 (dt, *J* = 12.5, 6.2 Hz, 1 H), 3.10 (d, *J* = 14.4 Hz, 1 H), 2.47 (d, *J* = 14.0 Hz, 1 H), 2.25 (s, 1 H), 2.07 (q, *J* = 18.3, 16.3 Hz, 2 H), 1.87–1.74 (m, 4 H), 1.43 (s, 9 H), 1.31 (s, 3 H), 1.13–0.97 (m, 21 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 175.7, 154.9, 80.7, 74.6, 65.1, 62.3, 57.8, 45.4, 43.1, 42.0, 35.1, 29.6, 28.8, 28.2, 24.2, 24.1, 18.0, 11.9; HRMS (ESI) calcd for $C_{27}H_{47}NNaO_6Si^+$ [M + $Na^+$] 532.3065, found 532.3059.

**Alkynyl ester 148.** Methyl propiolate (0.022 mL, 0.250 mmol, 2.5 equiv) was dissolved in THF (0.75 mL) at 23 °C and then the reaction contents were cooled to –78 °C with a dry ice-acetone bath. Next, freshly prepared LDA (1.0 M in THF, 0.250 mL, 0.250 mmol, 2.5 equiv) was added and the resulting orange solution was stirred for an additional 30 min at –78 °C. A solution of ketone **7** (51.1 mg, 0.100 mmol, 1.0 equiv) in THF (0.90 mL) was then added, using another aliquot of THF (0.10 mL) to complete the transfer. The reaction contents were stirred for

an additional 15 min at –78 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NH_4Cl$ (1.5 mL) and warmed to 23 °C. The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (2 × 2.0 mL). The combined organic layers were then washed with brine (3.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexane/EtOAc, 4:1) to provide the desired alkynyl ester **148** (50.1 mg, 84% yield) as a pale-yellow oil. **148**: $R_f$ = 0.65 (silica gel, hexanes/EtOAc, 2:1); IR (film) $\nu_{max}$ 3313, 2943, 2880, 2866, 2233, 1750, 1734, 1717, 1473, 1457, 1382, 1254, 1159, 1093 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.22 (s, 1 H), 5.02–4.95 (m, 1 H), 4.63 (q, *J* = 2.6 Hz, 1 H), 3.79–3.76 (m, 3 H), 3.74 (t, *J* = 5.3 Hz, 1 H), 3.66–3.61 (m, 1 H), 2.78–2.72 (m, 2 H), 2.45 (dt, *J* = 5.3, 1.7 Hz, 1 H), 2.10 (d, *J* = 13.4 Hz, 1 H), 1.96 (dd, *J* = 13.3, 2.0 Hz, 1 H), 1.77–1.67 (m, 3 H), 1.62–1.51 (m, 2 H), 1.44 (s, 3 H), 1.43 (s, 9 H), 1.06–1.00 (m, 21 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 176.3, 156.9, 153.5, 88.0, 81.9, 77.5, 77.2, 75.9, 67.0, 63.4, 52.8, 50.6, 43.5, 43.1, 38.5, 30.4, 28.3, 28.1, 24.1, 22.1, 18.0, 11.9; HRMS (ESI) calcd for $C_{31}H_{51}NNaO_8Si^+$ [M + $Na^+$] 616.3276, found 616.3273.

**Butenolide 149.** Alkynyl ester **148** (50.1 mg, 0.842 mmol, 1.0 equiv) and quinoline (0.0030 mL, 0.253 mmol, 3.0 equiv) were sequentially dissolved in MeOH (1.7 mL) at 23 °C. Next, Pd/C (10% wt., 8.9 mg, 0.10 equiv based on Pd) was added, and the resulting black suspension was degassed with a $H_2$ atmosphere. The resultant suspension was then stirred for 1 h at 23 °C in the presence of a $H_2$ atmosphere (from a balloon). Upon completion, the reaction contents were filtered directly through a pad of Celite (eluting with EtOAc). The resultant filtrate was then washed with 3 M HCl (3.0 mL), poured into a separatory funnel, and the layers were separated. The aqueous layer was then further extracted with EtOAc (3 × 3.0 mL). The

combined organic layers were then washed with brine (4.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. The resultant crude residue was then dissolved in $CH_2Cl_2$ (0.84 mL) at 23 °C and silica gel (84.2 mg, 1.0 g/mmol substrate) was added. The resultant slurry was stirred for 30 min, before being loaded directly on a silica gel column and purified by flash column chromatography (silica gel, hexane/acetone, 4:1) to provide the desired butenolide **149** (37.2 mg, 78% yield) as a white solid. **149**: $R_f$ = 0.53 (silica gel, hexanes/acetone, 2:1); IR (film) $\nu_{max}$ 3342, 2941, 2878, 2866, 1772, 1748, 1715, 1464, 1457, 1388, 1255, 1245, 1165, 1099 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 5.9 Hz, 1 H), 6.04 (d, *J* = 5.7 Hz, 1 H), 4.65 (s, 1 H), 4.38 (s, 1 H), 3.77 (p, *J* = 5.7, 5.2 Hz, 1 H), 3.67 (td, *J* = 10.4, 8.7, 4.5 Hz, 1 H), 3.12 (d, *J* = 14.7 Hz, 1 H), 2.52 (dd, *J* = 14.4, 3.0 Hz, 1 H), 2.31 (d, *J* = 14.5 Hz, 1 H), 2.16 (t, *J* = 9.2 Hz, 2 H), 1.97 (ddd, *J* = 14.4, 5.2, 2.5 Hz, 1 H), 1.80–1.59 (m, 3 H), 1.56–1.47 (m, 1 H), 1.43 (s, 3 H), 1.33 (s, 9 H), 1.13–0.97 (m, 21 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 175.5, 170.8, 156.2, 154.5, 119.6, 95.0, 80.1, 74.5, 65.9, 62.9, 44.7, 44.2, 42.9, 36.6, 30.4, 30.0, 28.1, 24.5, 21.3, 18.0, 11.9; HRMS (ESI) calcd for $C_{30}H_{49}NNaO_7Si^+$ [M + $Na^+$] 586.3171, found 586.3165.

**Alcohol 150.** Butenolide **149** (35.5 mg, 0.0621 mmol, 1.0 equiv) was dissolved in THF (1.24 mL) at 23 °C and TBAF (1.0 M in THF, 0.093 mL, 0.0931 mmol, 1.5 equiv) was added dropwise. The resultant light brown solution was stirred for an additional 1 h at 23 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NH_4Cl$ (2.0 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (2 × 3.0 mL). The combined organic layers were then washed with brine (5.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/acetone, 2:1→1:1), to provide the desired alcohol **150** (23.0 mg, 91% yield) as a white

solid. **150**: $R_f$ = 0.49 (silica gel, hexanes/acetone, 1:1); IR (film) $\nu_{max}$ 3335, 2975, 2936, 2873, 1771, 1744, 1717, 1472, 1457, 1388, 1367, 1270, 1247, 1165, 1096, 1050 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 5.8 Hz, 1 H), 6.06 (d, *J* = 5.7 Hz, 1 H), 4.71 (d, *J* = 7.9 Hz, 1 H), 4.65 (t, *J* = 2.8 Hz, 1 H), 3.73 (dt, *J* = 10.9, 6.9 Hz, 1 H), 3.67 (dt, *J* = 10.8, 6.2 Hz, 1 H), 3.00 (d, *J* = 14.1 Hz, 1 H), 2.53 (dd, *J* = 14.6, 3.0 Hz, 1 H), 2.35 (d, *J* = 14.6 Hz, 1 H), 2.30–2.22 (m, 1 H), 2.18–2.15 (m, 1 H), 1.98 (ddd, *J* = 14.5, 5.1, 2.5 Hz, 1 H), 1.85–1.75 (m, 2 H), 1.72–1.61 (m, 2 H), 1.54 (ddt, *J* = 12.7, 8.8, 6.3 Hz, 1 H), 1.43 (s, 3 H), 1.35 (s, 9 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 175.5, 170.8, 156.2, 154.7, 119.8, 95.1, 80.2, 74.5, 69.5, 65.9, 62.3, 53.7, 43.0, 31.7, 30.5, 29.4, 28.1, 24.5, 21.2; HRMS (ESI) calcd for $C_{21}H_{29}NNaO_7^+$ [M + $Na^+$] 430.1836, found 430.1832.

**Annotinolide C (7).** Alcohol **150** (17.5 mg, 0.0429 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (0.86 mL) at 23 °C and then the reaction contents were cooled to 0 °C using an ice-water bath. Next, $Et_3N$ (0.062 mL, 0.429 mmol, 10 equiv) and MsCl (0.010 mL, 0.129 mmol, 3.0 equiv) were added sequentially, affording a pale-yellow solution. The resultant solution was then stirred for 30 min at 0 °C. TFA (0.22 mL) was then added at 0 °C and the cold bath was removed. The resultant solution was then stirred for 1 h at 23 °C. Upon completion, the reaction contents were quenched by the portion-wise addition of saturated aqueous $NaHCO_3$ until the mixture stopped bubbling. Next, an additional aliquot of saturated aqueous $NaHCO_3$ (3.0 mL) and $CH_2Cl_2$ (4.0 mL) were then added, and the resultant biphasic mixture was stirred vigorously for 30 min at 23 °C. The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with $CH_2Cl_2$ (4 × 5.0 mL). The combined organic layers were then washed with brine (8.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography

(silica gel, $CH_2Cl_2$/MeOH, 50:1→5:1), provided the desired annotinolide C (**7**, 6.7 mg, 56% yield) as a white amorphous solid. **7**: $R_f$ = 0.22 (silica gel, hexanes/acetone, 1:1); IR (film) $\nu_{max}$ 3306, 2933, 2887, 2860, 1762, 1734, 1653, 1465, 1457, 1248, 1220, 1128, 1097, 678 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 5.8 Hz, 1 H), 6.16 (d, *J* = 5.8 Hz, 1 H), 4.40 (p, *J* = 2.7 Hz, 1 H), 2.90 (ddt, *J* = 13.6, 4.1, 1.8 Hz, 1 H), 2.75 (d, *J* = 14.1 Hz, 1 H), 2.61 (ddd, *J* = 13.8, 3.0, 1.3 Hz, 1 H), 2.55 (br d, *J* = 12.5 Hz, 1 H), 2.25 (br d, *J* = 12.5 Hz, 1 H), 2.20–2.17 (m, 1 H), 1.96 (ddd, *J* = 14.1, 5.1, 2.5 Hz, 1 H), 1.83 (dddd, *J* = 12.9, 12.9, 12.9, 4.2 Hz, 1 H), 1.79–1.75 (m, 1 H), 1.74–1.70 (m, 1 H), 1.68 (dd, *J* = 14.1, 1.8 Hz, 1 H), 1.46–1.40 (m, 1 H), 1.43 (s, 3 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 176.0, 170.6, 156.0, 121.3, 94.6, 77.9, 65.3, 47.3, 43.2 ,42.9, 42.2, 41.2, 31.5, 27.2, 24.2, 23.6; HRMS (ESI) calcd for $C_{16}H_{20}NO_4^+$ [M + $H^+$] 290.1387, found 290.1389.

**Alcohol 153.** Ketone **126** (60.1 mg, 0.118 mmol, 1.0 equiv) was dissolved in THF (2.4 mL) at 23 °C and then was cooled to 0 °C with an ice-water bath. Next, TBAF (1.0 M in THF, 0.177 mL, 0.177 mmol, 1.5 equiv) was added dropwise. The resultant pale-yellow solution was stirred for an additional 1 h at 0 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NH_4Cl$ (2.0 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (2 × 3.0 mL). The combined organic layers were then washed with brine (5.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/acetone, 2:1→1:1) provided the desired alcohol **153** (37.8 mg, 91% yield) as a colorless oil. **153**: $R_f$ = 0.48 (silica gel, hexanes/acetone, 1:1); IR (film) $\nu_{max}$ 3362, 2973, 2934, 2872, 1734, 1700, 1457, 1387, 1367, 1165, 1131, 1007 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 5.27 (s, 1 H), 4.62 (dq, *J* = 4.2, 2.4 Hz, 1 H), 3.68 (dt, *J* = 11.8, 6.0

Hz, 1 H), 3.63 (dt, *J* = 10.9, 6.0 Hz, 1 H), 2.87 (d, *J* = 14.1 Hz, 1 H), 2.51–2.42 (m, 2 H), 2.24 (s, 1 H), 2.15 (td, *J* = 6.3, 3.0 Hz, 1 H), 2.12–1.98 (m, 1 H), 1.92 (d, *J* = 14.0 Hz, 1 H), 1.87–1.65 (m, 2 H), 1.51 (dtd, *J* = 12.3, 6.0, 3.0 Hz, 1 H), 1.41 (s, 9 H), 1.34 (s, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 209.2, 174.8, 154.8, 80.1, 73.9, 66.7, 62.3, 52.1, 48.4, 40.8, 39.2, 37.0, 29.9, 28.2, 24.3, 21.5; HRMS (ESI) calcd for $C_{18}H_{27}NNaO_6^+$ [M + $Na^+$] 376.1731, found 376.1724.

**Amine 154.** Alcohol **153** (35.2 mg, 0.099 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (2.0 mL) at 23 °C and then the reaction contents were cooled to 0 °C using an ice-water bath. Next, $Et_3N$ (0.138 mL, 0.990 mmol, 10.0 equiv) and MsCl (0.026 mL, 0.297 mmol, 3.0 equiv) were added sequentially, affording a pale-yellow solution. The resultant solution was then stirred for 30 min at 0 °C. TFA (0.5 mL) was then added at 0 °C and the cold bath was removed. The resultant solution was then stirred for 1 h at 23 °C. Upon completion, the reaction contents were quenched by the portion-wise addition of saturated aqueous $NaHCO_3$ until the mixture stopped bubbling. Next, an additional aliquot of saturated aqueous $NaHCO_3$ (3.0 mL) and $CH_2Cl_2$ (4.0 mL) were then added, and the resultant biphasic mixture was stirred vigorously for 30 min at 23 °C. The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with $CH_2Cl_2$ (4 × 5.0 mL). The combined organic layers were then washed with brine (8.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, $CH_2Cl_2$/MeOH, 50:1→5:1) provided the desired amine **154** (14.4 mg, 62% yield) as a white amorphous solid. **154**: $R_f$ = 0.13 (silica gel, hexanes/acetone = 1:1); IR (film) $\nu_{max}$ 3333, 2924, 2865, 2844, 1751, 1735, 1457, 1134, 1025 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 4.38 (t, *J* = 2.4 Hz, 1 H), 3.04 (d, *J* = 13.2 Hz, 1 H), 2.85 (s, 1 H), 2.63 (t, *J* = 13.0 Hz, 1 H), 2.44–2.38 (m, 2 H), 2.26–2.19 (m, 1 H), 2.06 (dt, *J* = 12.4, 2.7 Hz, 1 H), 1.91 (qd, *J* = 13.0, 3.9 Hz, 1 H), 1.81 (dd, *J*

= 13.7, 3.5 Hz, 1 H), 1.74 (d, *J* = 13.6 Hz, 1 H), 1.56 (dd, *J* = 13.4, 1.8 Hz, 1 H), 1.48 (dt, *J* = 13.1, 4.4 Hz, 1 H), 1.34 (d, *J* = 1.3 Hz, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 211.7, 175.4, 76.7, 67.1, 50.3, 49.1, 42.1, 40.6, 39.5, 37.9, 26.5, 24.4, 23.0; HRMS (ESI) calcd for $C_{13}H_{17}NNaO_3^+$ [M + $Na^+$] 258.1101, found 258.1100.

**Vinyl iodide 155.** Amine **154** (13.2 mg, 0.0553 mmol, 1.0 equiv) was dissolved in MeCN (0.55 mL) at 23 °C and then $K_2CO_3$ (76.4 mg, 0.553 mmol, 10 equiv) and allylic bromide **142** (68.1 mg, 0.276 mmol, 5.0 equiv) were added sequentially. The resultant white suspension was then stirred for 24 h at 23 °C. Upon completion, the reaction contents were filtered through Celite (eluting with EtOAc). The filtrate was then concentrated, and the resultant residue was purified by flash column chromatography (silica gel, hexanes/acetone, 2:1) to provide the desired vinyl iodide **155** (19.4 mg, 87% yield) as a white amorphous solid. **155**: $R_f$ = 0.70 (silica gel, hexanes/acetone = 1:1); IR (film) $\nu_{max}$ 2932, 2868, 2835, 1748, 1736, 1653, 1457, 1122, 1033, 667 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 6.41–6.37 (m, 1 H), 6.36–6.33 (m, 1 H), 4.40 (t, *J* = 2.8 Hz, 1 H), 3.22 (ddq, *J* = 14.2, 4.7, 2.1 Hz, 1 H), 2.92–2.84 (m, 1 H), 2.79 (d, *J* = 12.2 Hz, 1 H), 2.57–2.52 (m, 1 H), 2.40 (ddq, *J* = 14.4, 6.4, 2.2 Hz, 1 H), 2.33 (dt, *J* = 5.7, 2.5 Hz, 1 H), 2.27–2.14 (m, 3 H), 1.88–1.76 (m, 3 H), 1.72 (dt, *J* = 13.5, 2.9 Hz, 1 H), 1.65–1.57 (m, 1 H), 1.38 (s, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 213.4, 175.3, 138.9, 83.6, 76.9, 72.7, 55.4, 50.7, 49.0, 48.4, 39.9, 38.8, 31.2, 24.8, 24.7, 23.0; HRMS (ESI) calcd for $C_{16}H_{21}INO_3^+$ [M + $Na^+$] 402.0561, found 402.0570.

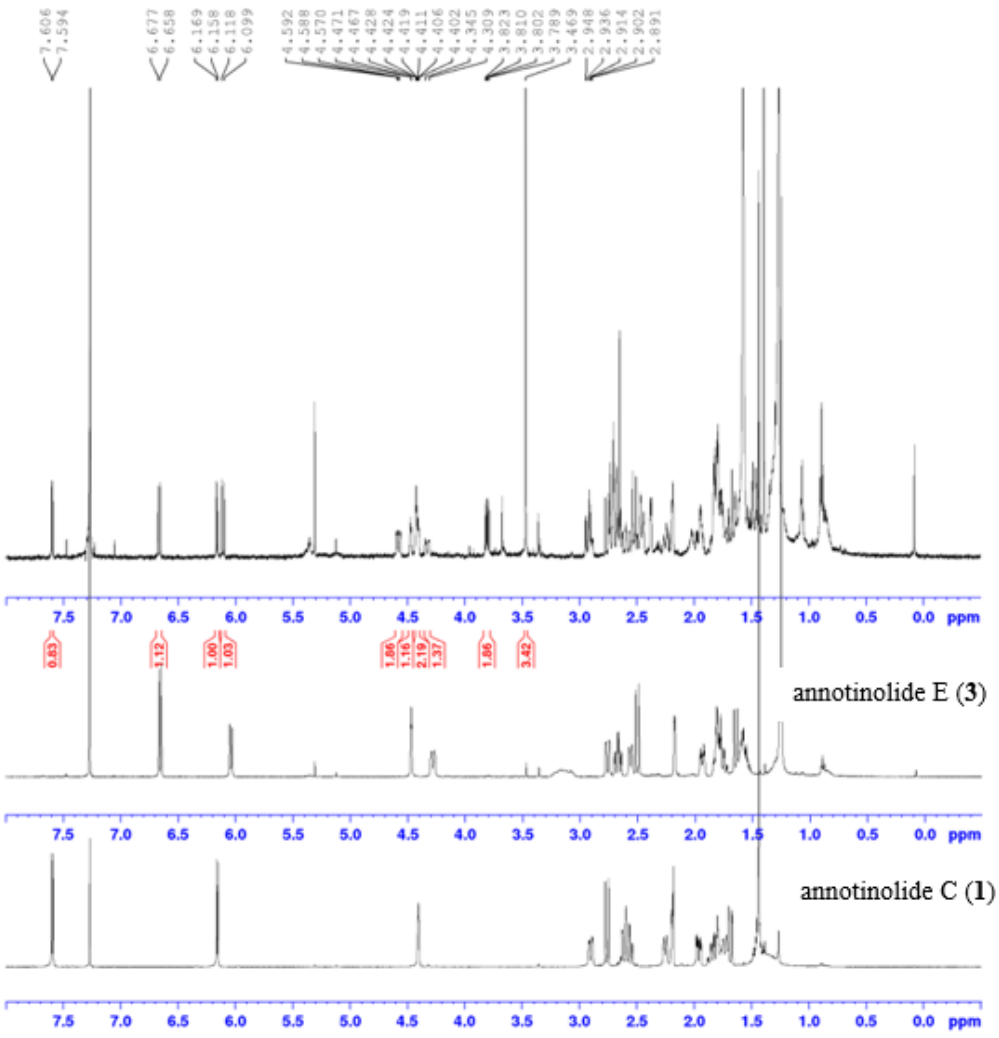
**Annotinolide D (8).** Vinyl iodide **155** (16.0 mg, 39.9 mmmol, 1.0 equiv) was dissolved in THF (0.79 mL) at 23 °C and then the reaction contents were cooled to –78 °C with a dry ice-acetone bath. Next, *t*-BuLi (1.7 M in pentanes, 0.049 mL, 83.7 mmol, 2.1 equiv) was added dropwise, during which time the solution turned a pale-yellow color. The reaction contents were

then stirred for 30 min at –78 °C. Upon completion, the reaction contents were quenched by the addition of $H_2O$ (1.5 mL) and warmed to 23 °C with stirring. The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (2 × 3.0 mL). The combined organic layers were then washed with brine (4.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, $CH_2Cl_2$/MeOH, 50:1→5:1) provided annotinolide D (**8**, 8.7 mg, 79% yield) as a white amorphous solid. **8**: $R_f$ = 0.24 (silica gel, hexanes/acetone, 1:1); IR (film) $\nu_{max}$ 3245, 2930, 2869, 2837, 1734, 1653, 1473, 1457, 1383, 1288, 1125, 1071, 1017 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 5.82 (dt, *J* = 10.1, 1.9 Hz, 1 H), 5.78 (ddd, *J* = 9.9, 3.8, 1.9 Hz, 1 H), 4.36 (p, *J* = 2.7 Hz, 1 H), 3.33 (ddd, *J* = 18.3, 3.5, 1.5 Hz, 1 H), 2.85 (ddd, *J* = 18.3, 2.2, 2.2 Hz, 1 H), 2.71 (br d, *J* = 11.3 Hz, 1 H), 2.67 (ddd, *J* = 14.0, 3.0, 1.3 Hz, 1 H), 2.27 (m, 1 H), 2.24 (dd, *J* = 11.5, 3.1 Hz, 1 H), 2.05 (d, *J* = 13.3 Hz, 1 H), 1.93 (ddd, *J* = 5.0, 1.6, 1.6 Hz, 1 H), 1.75–1.67 (m, 6 H), 1.24 (s, 3 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 178.2, 130.6, 127.3, 79.1, 72.7, 65.8, 51.4, 49.8, 46.2, 42.6, 39.6, 31.5, 29.9, 25.0, 24.3, 23.6; HRMS (ESI) calcd for $C_{16}H_{22}NO_3^+$ [M + $H^+$] 276.1594, found 276.1579.

**Annotinolide E (9).** Annotinolide D (**8**, 1.9 mg, 0.0069 mmol, 1.0 equiv) was dissolved in acetone (0.56 mL) and deionized water (0.14 mL) at 23 °C and then the resultant solution was cooled 0 °C using an ice-water bath. $KMnO_4$ (1.6 mg, 0.0104 mmol, 1.5 equiv) was then added in a single portion, leading to a purple-colored solution. The reaction contents were stirred for 15 min at 0 °C. Upon completion, the reaction contents were quenched by the addition of saturated $Na_2S_2O_3$ (0.50 mL) and warmed to 23 °C. The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (3 × 3.0 mL). The combined organic layers were then washed with brine

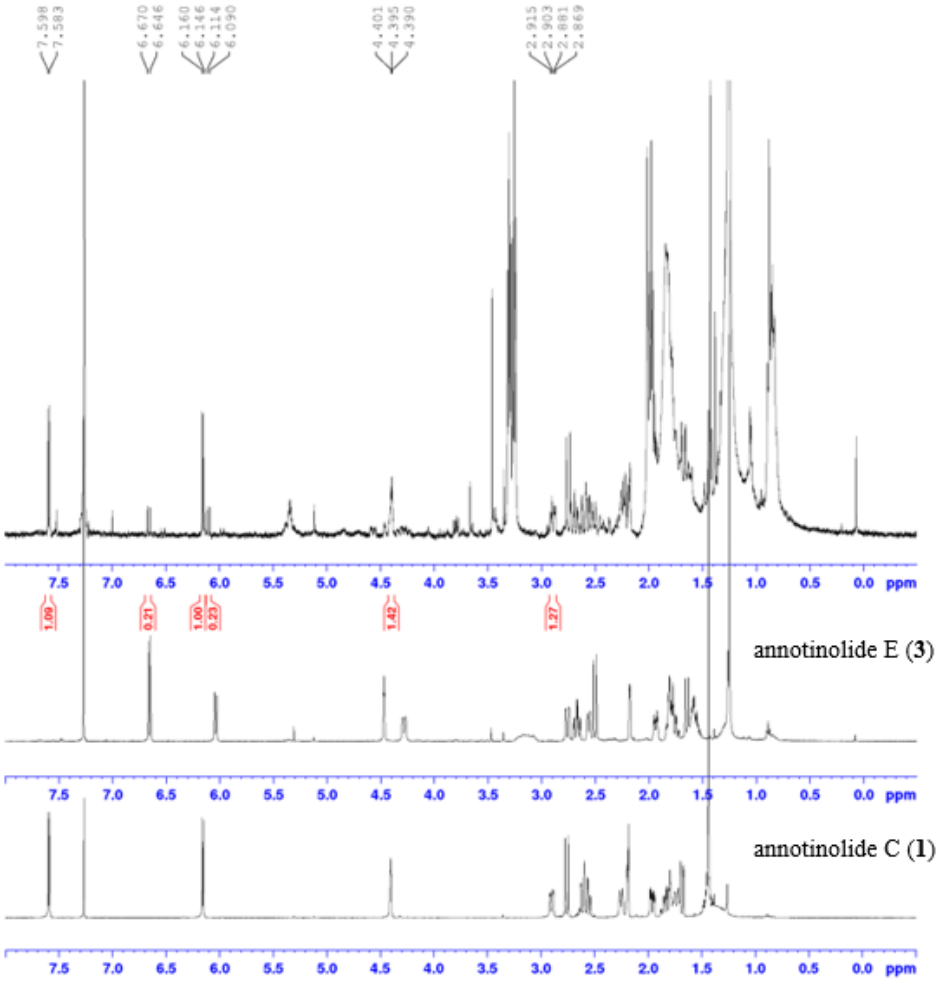
(4.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, $CH_2Cl_2$/MeOH, 50:1→5:1) to provide annotinolide E (**9**, 1.2 mg, 63% yield) as a white amorphous solid. **9**: $R_f$ = 0.27 (silica gel, hexanes/acetone, 1:1); IR (film) $\nu_{max}$ 3312, 2931, 2865, 1734, 1653, 1602, 1436, 1383, 1127, 1059, 1021, 988 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 6.66 (d, *J* = 9.7 Hz, 1 H), 6.04 (d, *J* = 9.7 Hz, 1 H), 4.37 (p, *J* = 2.5 Hz, 1 H), 2.76 (ddd, *J* = 14.2, 3.2, 1.4 Hz, 1 H), 2.67 (ddd, *J* = 13.5, 13.5, 3.6 Hz, 1 H), 2.56 (br d, *J* = 12.4 Hz, 1 H), 2.50 (d, *J* = 13.7 Hz, 1 H), 2.18 (ddd, *J* = 5.1, 1.6, 1.6 Hz, 1 H), 1.94 (dp, *J* = 13.3, 3.4 Hz, 1 H), 1.85–1.78 (m, overlapping, 2 H), 1.76 (dddd, *J* = 13.2, 13.2, 13.2, 3.5 Hz, 1 H), 1.65 (dd, *J* = 13.7, 1.8 Hz, 1 H), 1.61–1.53 (m, 1 H), 1.25 (s, 3 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 176.9, 163.2, 142.7, 126.4, 78.0, 72.8, 66.1, 48.6, 42.8, 41.5, 39.9, 38.9, 30.3, 23.9, 22.7, 22.6; HRMS (ESI) calcd for $C_{16}H_{20}NO_4^+$ [M + $H^+$] 290.1387, found 290.1393.

**Annotinolide E (9).** Annotinolide C (**7**, 0.6 mg, 0.0021 mmol, 1.0 equiv) was dissolved in MeOH (0.30 mL) at 23 °C and NaOMe (0.6 mg, 0.01 mmol, 5.0 equiv) was added. The resultant solution was stirred for 1.5 h at 23 °C, at which point TLC analysis indicated no further change. The reaction contents were then diluted with EtOAc (1.0 mL) and quenched by the addition of saturated aqueous $NH_4Cl$ (0.50 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (3 × 1.0 mL). The combined organic layers were then washed with brine (2.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. The resultant residue was then analyzed directly by $^1H$ NMR, affording the result shown below indicating a mixture of annotinolide C (**7**), annotinolide E (**9**), and some unknown products in an approximate ratio of 1:1:1.




**Annotinolide E (9).** Annotinolide C (**7**, 0.6 mg, 0.0021 mmol, 1.0 equiv) was dissolved in toluene (0.30 mL) and MeOH (0.030 mL) at 23 °C and triazabicyclo decene (0.3 mg, 0.0021 mmol, 1.0 equiv) was added in one portion. The reaction solution was stirred at 23 °C for 2 h, at which point TLC analysis indicated no further change. The reaction contents were diluted with EtOAc (1.0 mL) and quenched by saturated $NH_4Cl$ solution (0.50 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (3 × 1.0 mL). The combined organic layers were then washed with brine (2.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. The resultant residue

was then analyzed directly by $^{1}$H NMR, affording the result shown below indicating a mixture of annotinolide C (**7**) and annotinolide E (**9**) in an approximate ratio of 4:1.

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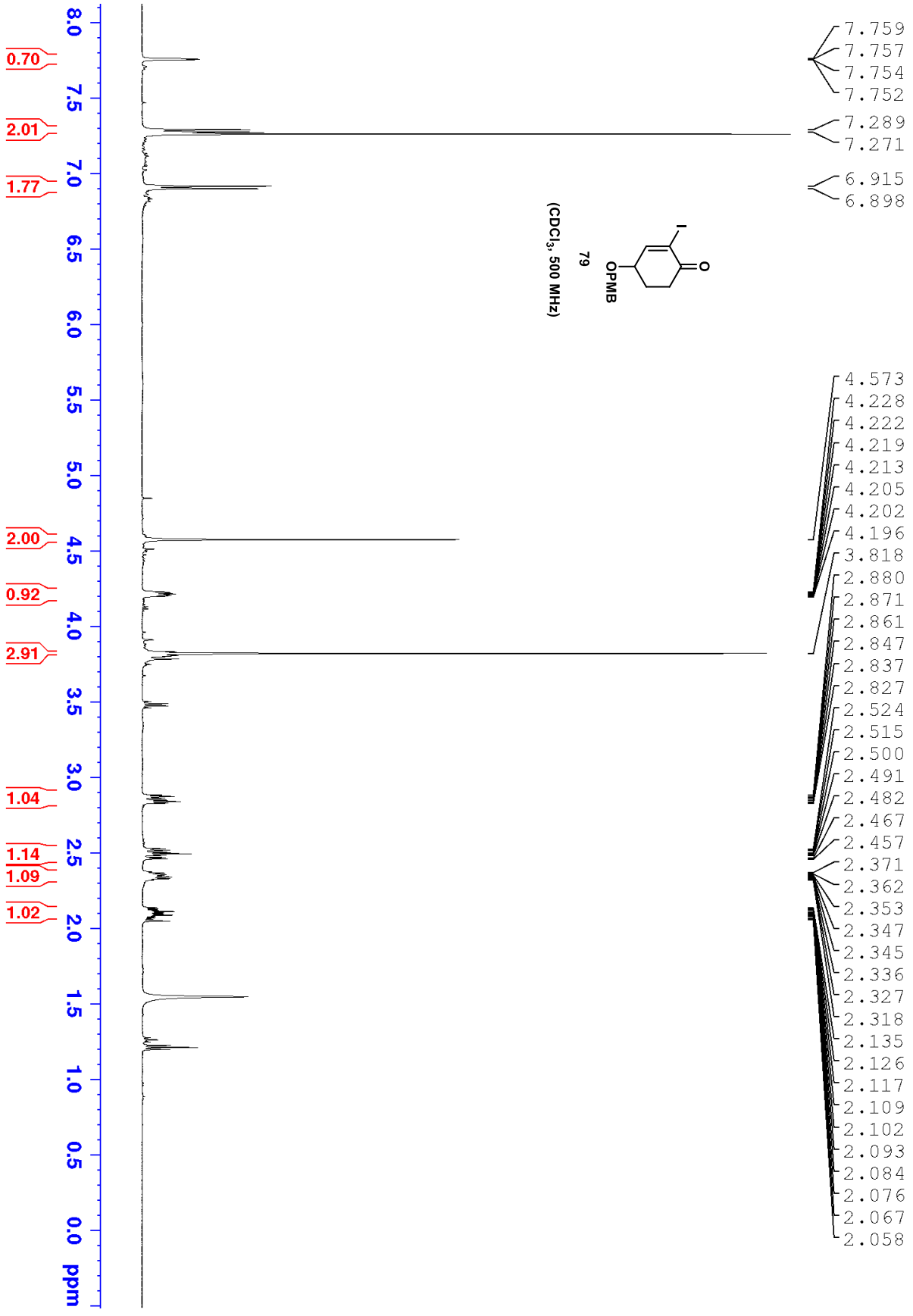
### *3.6 NMR Spectra of Selected Intermediates*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2.515
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OPMB
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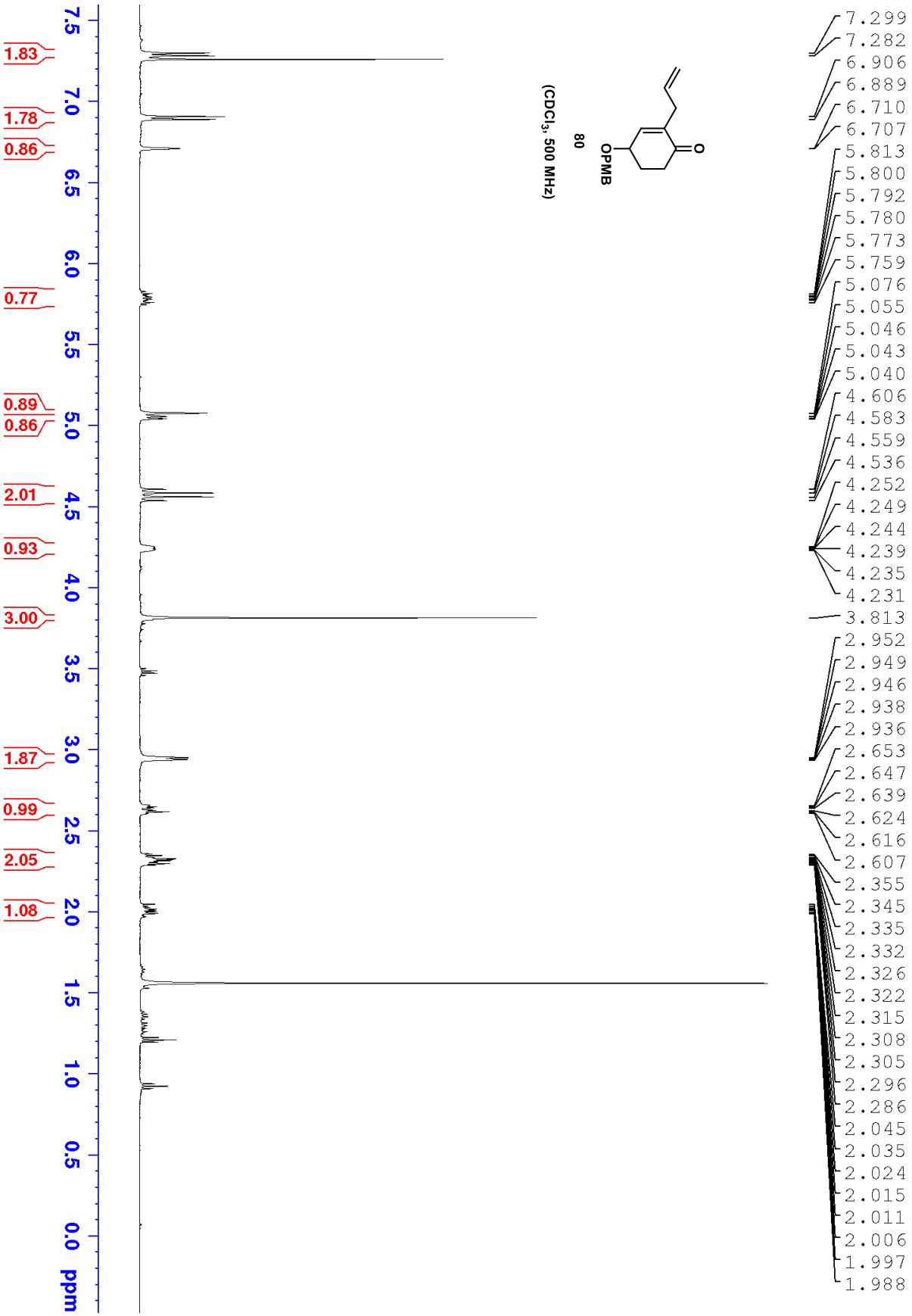
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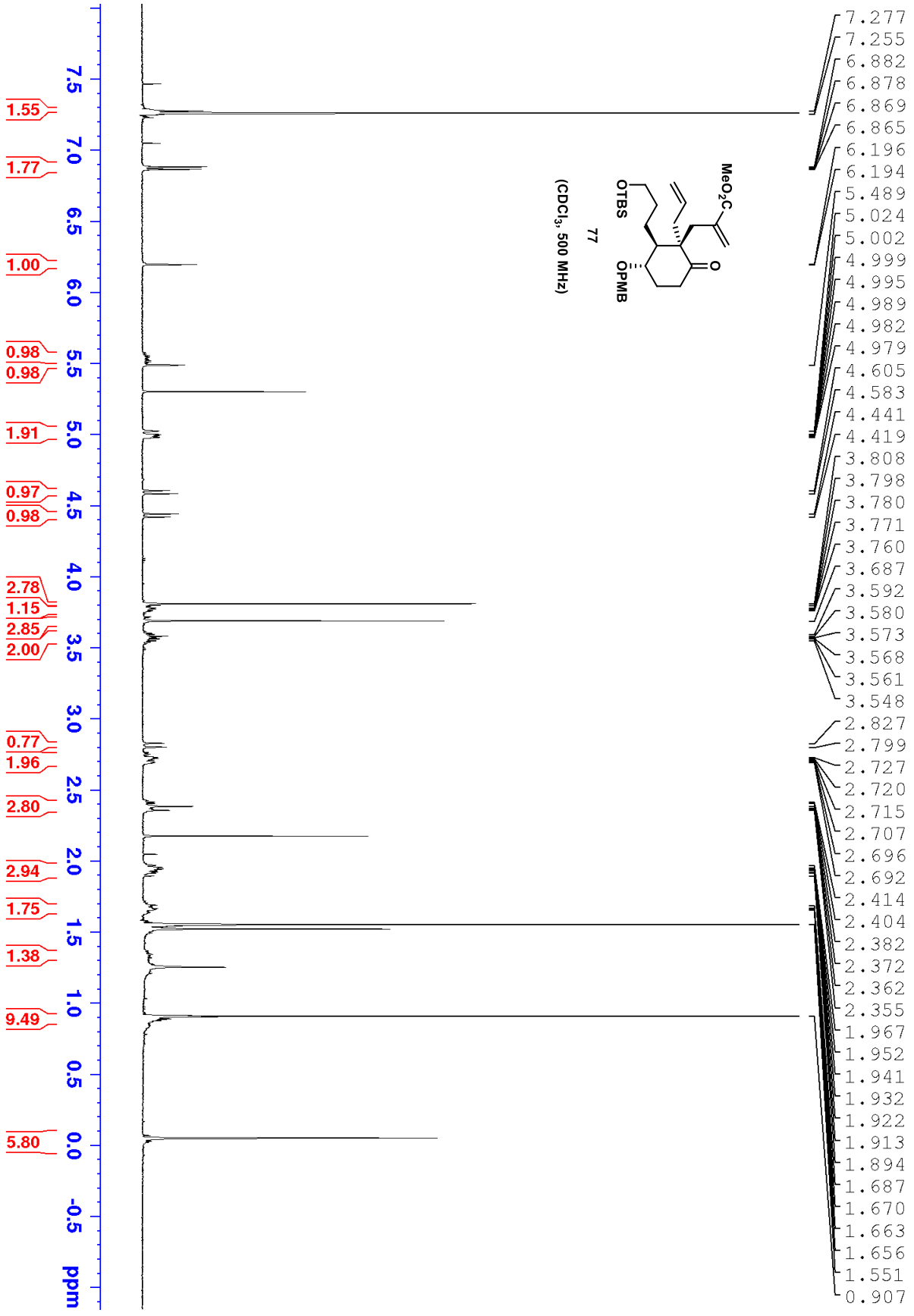
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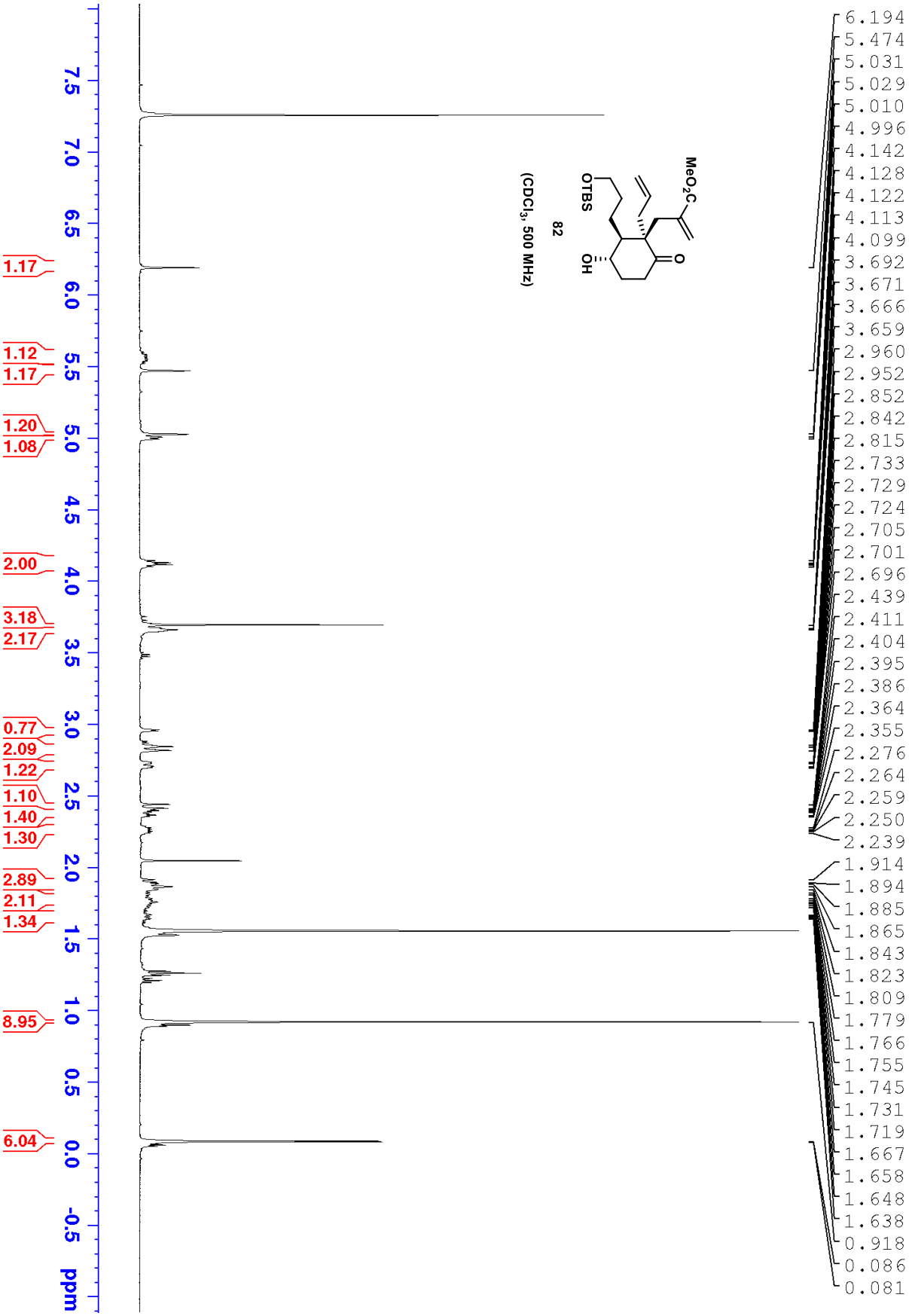
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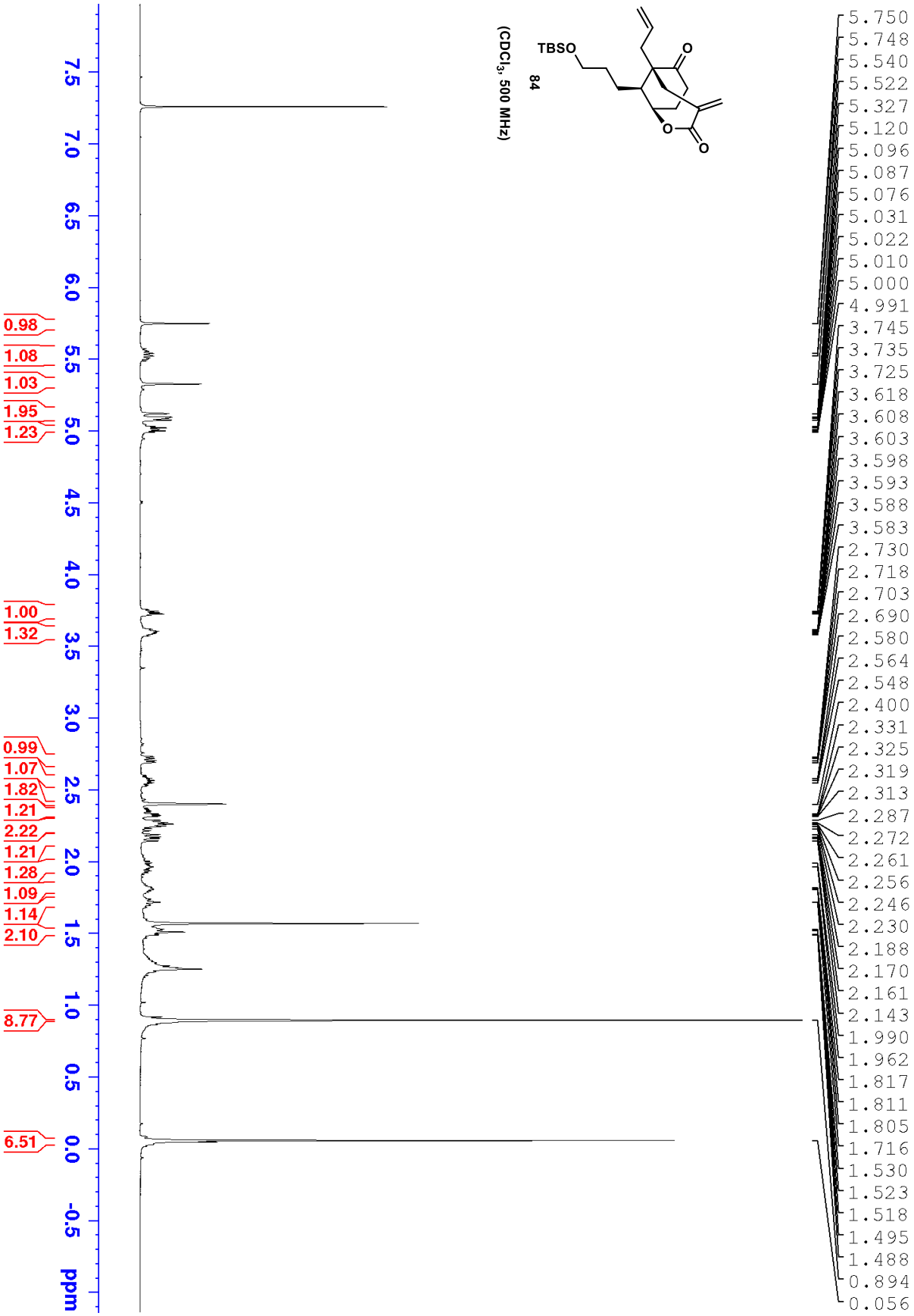
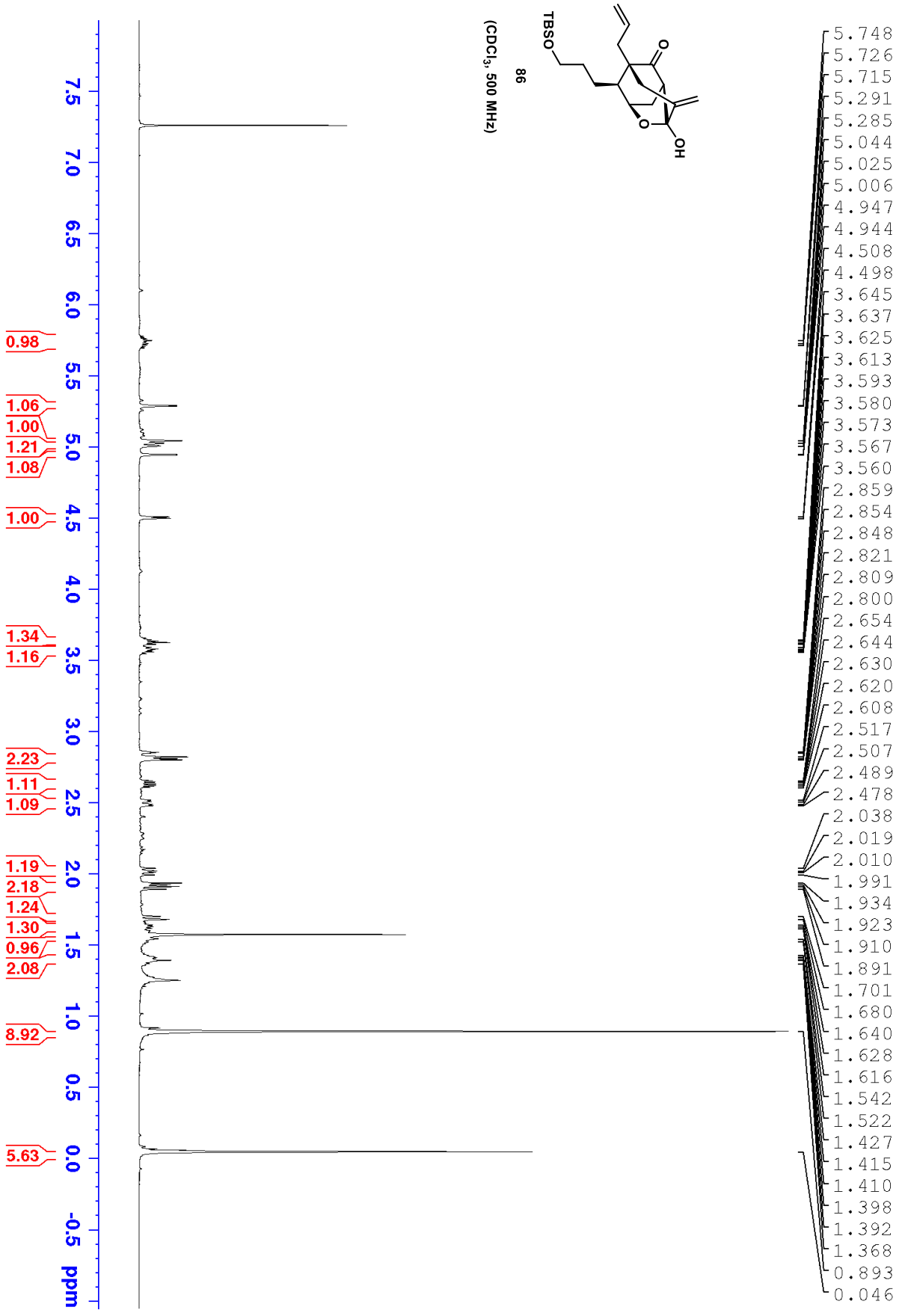
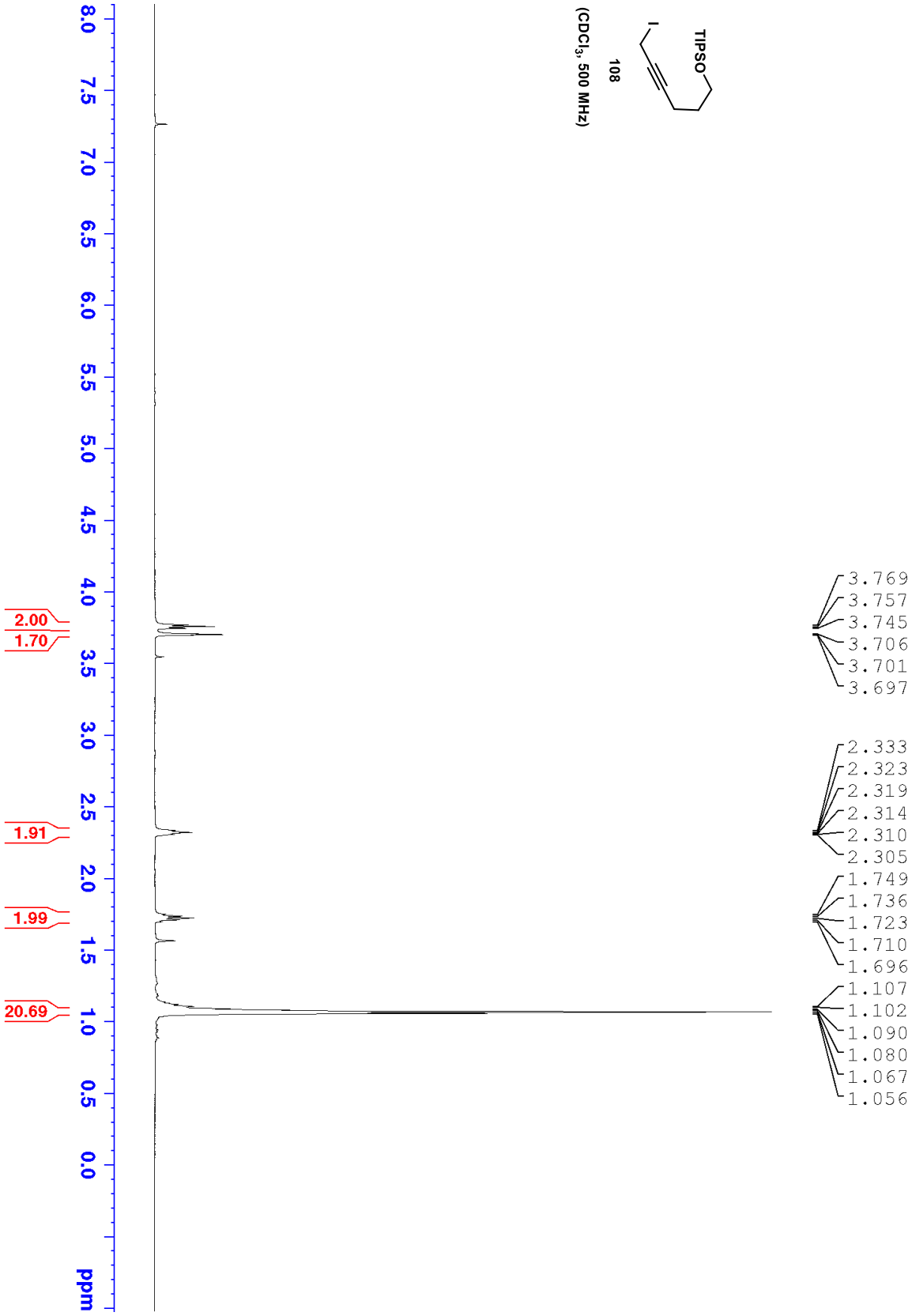
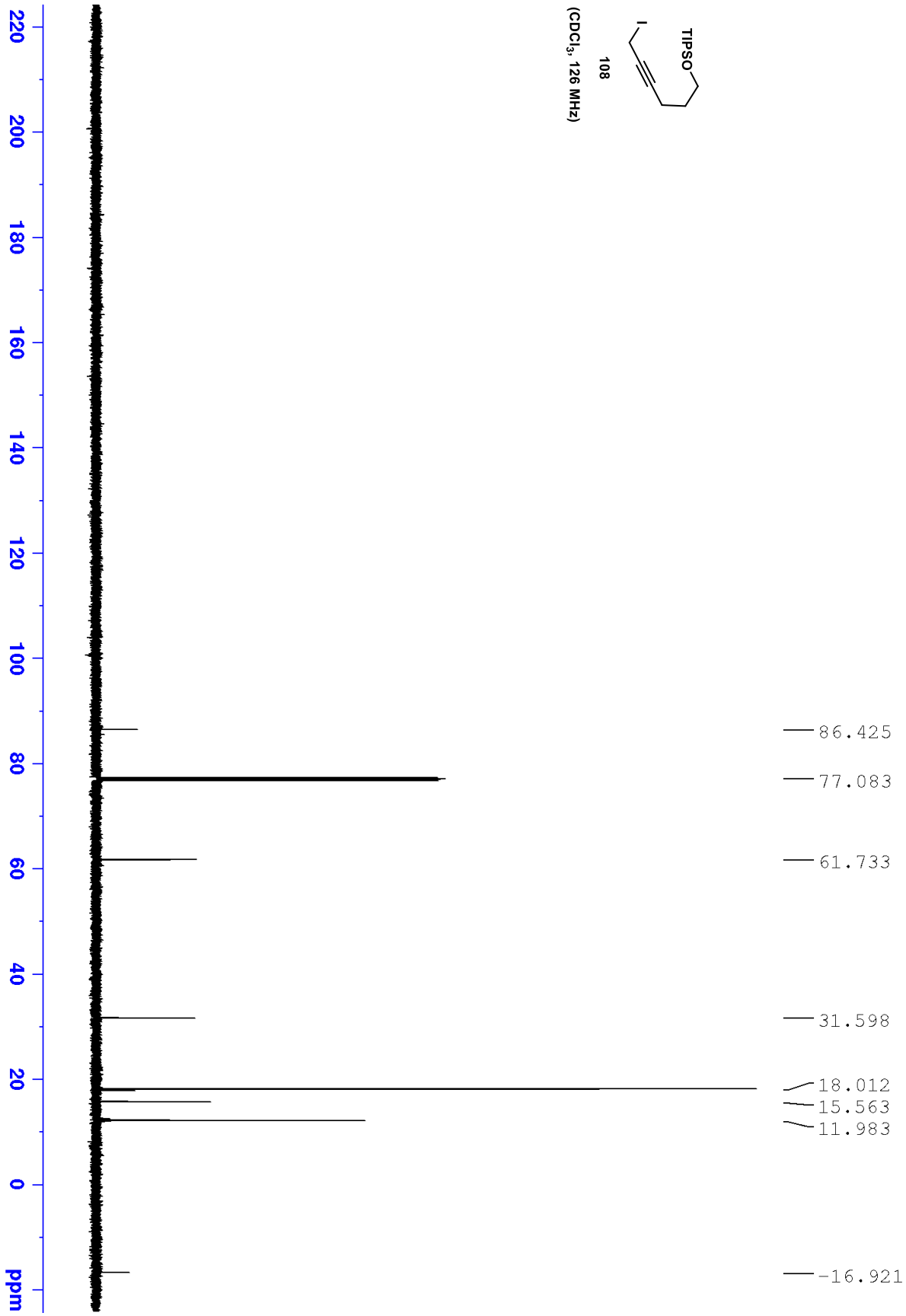
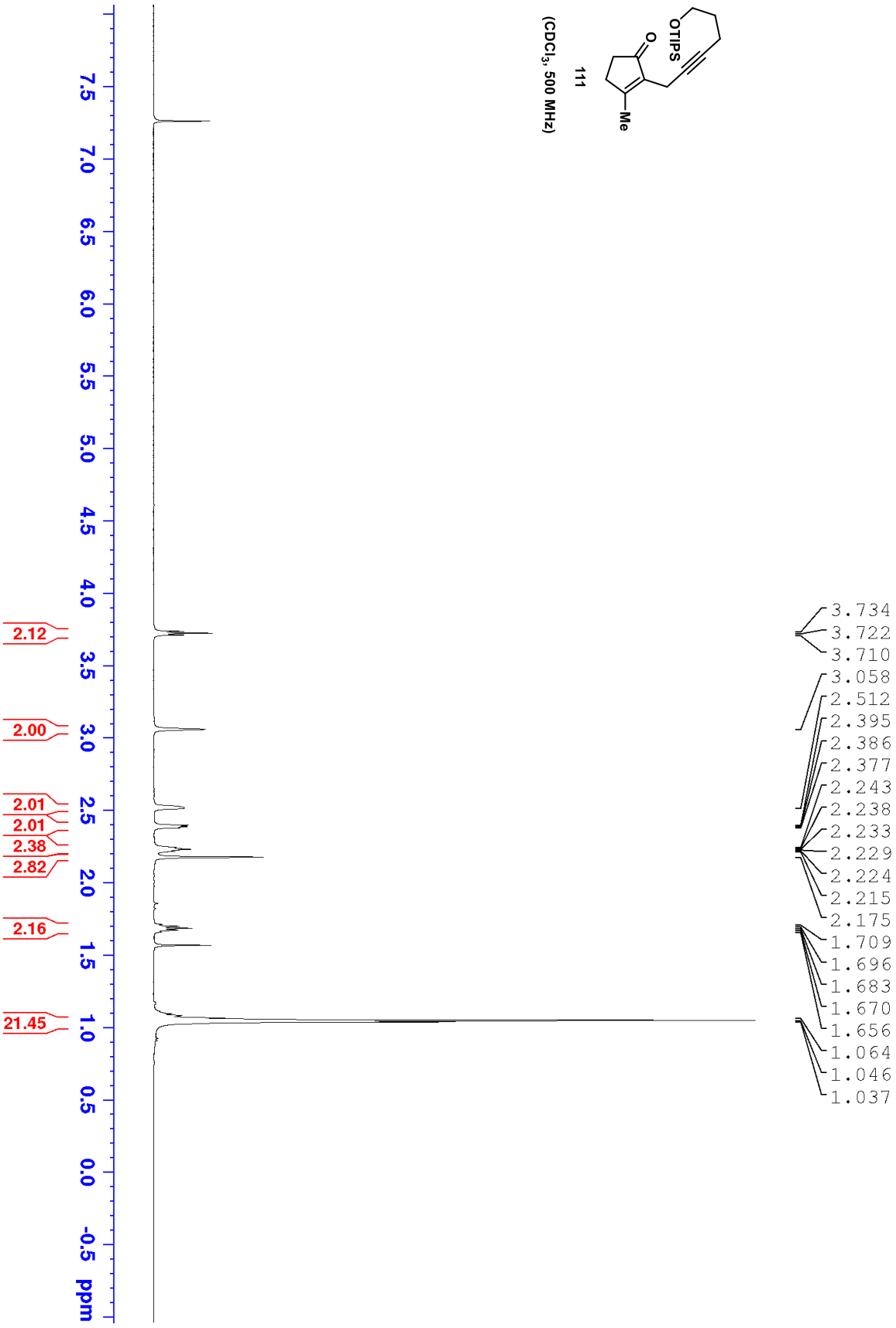
-0.5
ppm

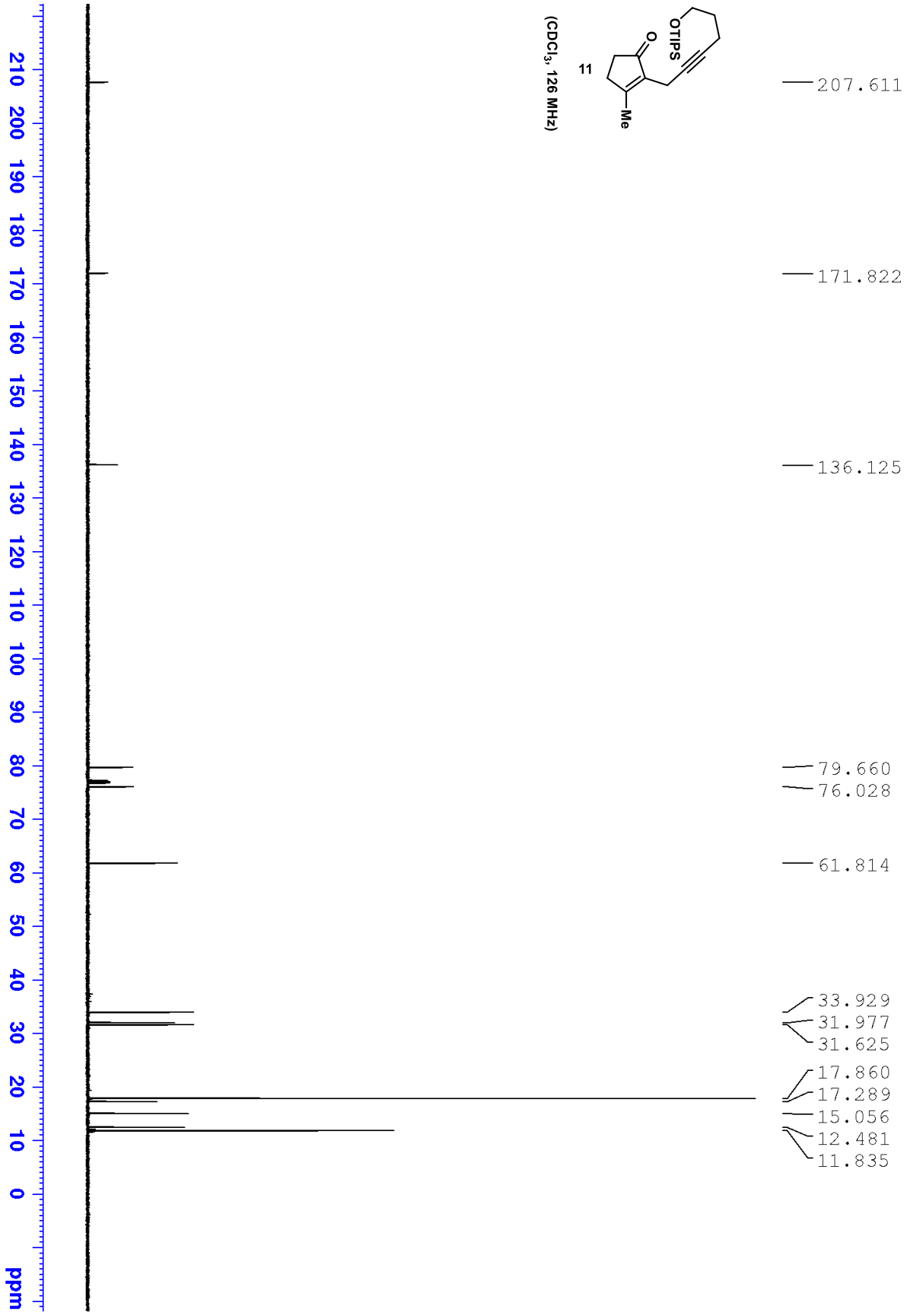

84
(CDCl3, 500 MHz)
TBSO
O
O
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
0.98
1.08
1.03
1.95
1.23
1.00
1.32
0.99
1.07
1.82
1.21
2.22
1.21
1.28
1.09
1.14
2.10
8.77
6.51
5.750
5.748
5.540
5.522
5.327
5.120
5.096
5.087
5.076
5.031
5.022
5.010
5.000
4.991
3.745
3.735
3.725
3.618
3.608
3.603
3.598
3.593
3.588
3.583
2.730
2.718
2.703
2.690
2.580
2.564
2.548
2.400
2.331
2.325
2.319
2.313
2.287
2.272
2.261
2.256
2.246
2.230
2.188
2.170
2.161
2.143
1.990
1.962
1.817
1.811
1.805
1.716
1.530
1.523
1.518
1.495
1.488
0.894
0.056

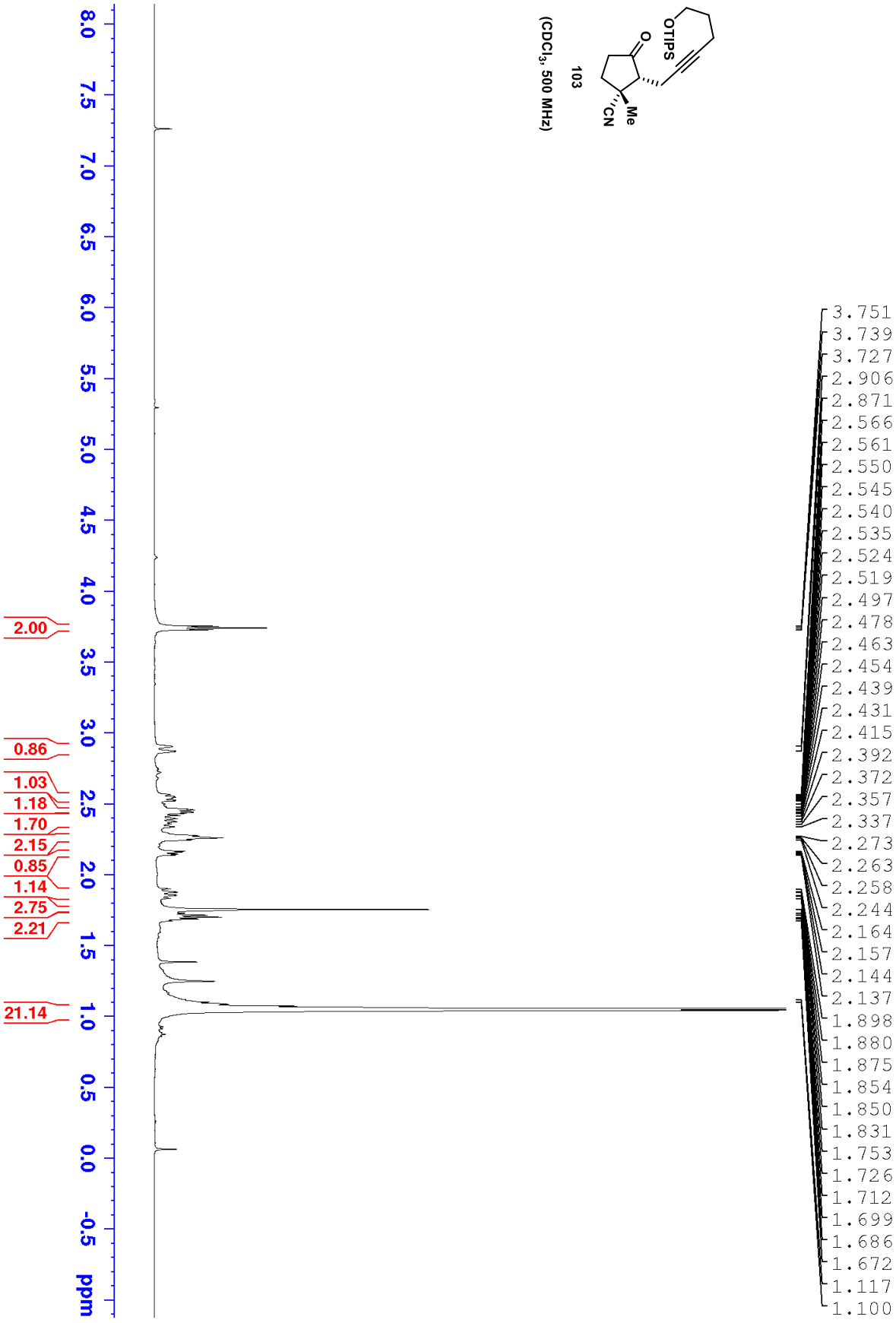

86
(CDCl3, 500 MHz)
TBSO
O
O
OH
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
0.98
1.06
1.00
1.21
1.08
1.00
1.34
1.16
2.23
1.11
1.09
1.19
2.18
1.24
1.30
0.96
2.08
8.92
5.63
5.748
5.726
5.715
5.291
5.285
5.044
5.025
5.006
4.947
4.944
4.508
4.498
3.645
3.637
3.625
3.613
3.593
3.580
3.573
3.567
3.560
2.859
2.854
2.848
2.821
2.809
2.800
2.654
2.644
2.630
2.620
2.608
2.517
2.507
2.489
2.478
2.038
2.019
2.010
1.991
1.934
1.923
1.910
1.891
1.701
1.680
1.640
1.628
1.616
1.542
1.522
1.427
1.415
1.410
1.398
1.392
1.368
0.893
0.046

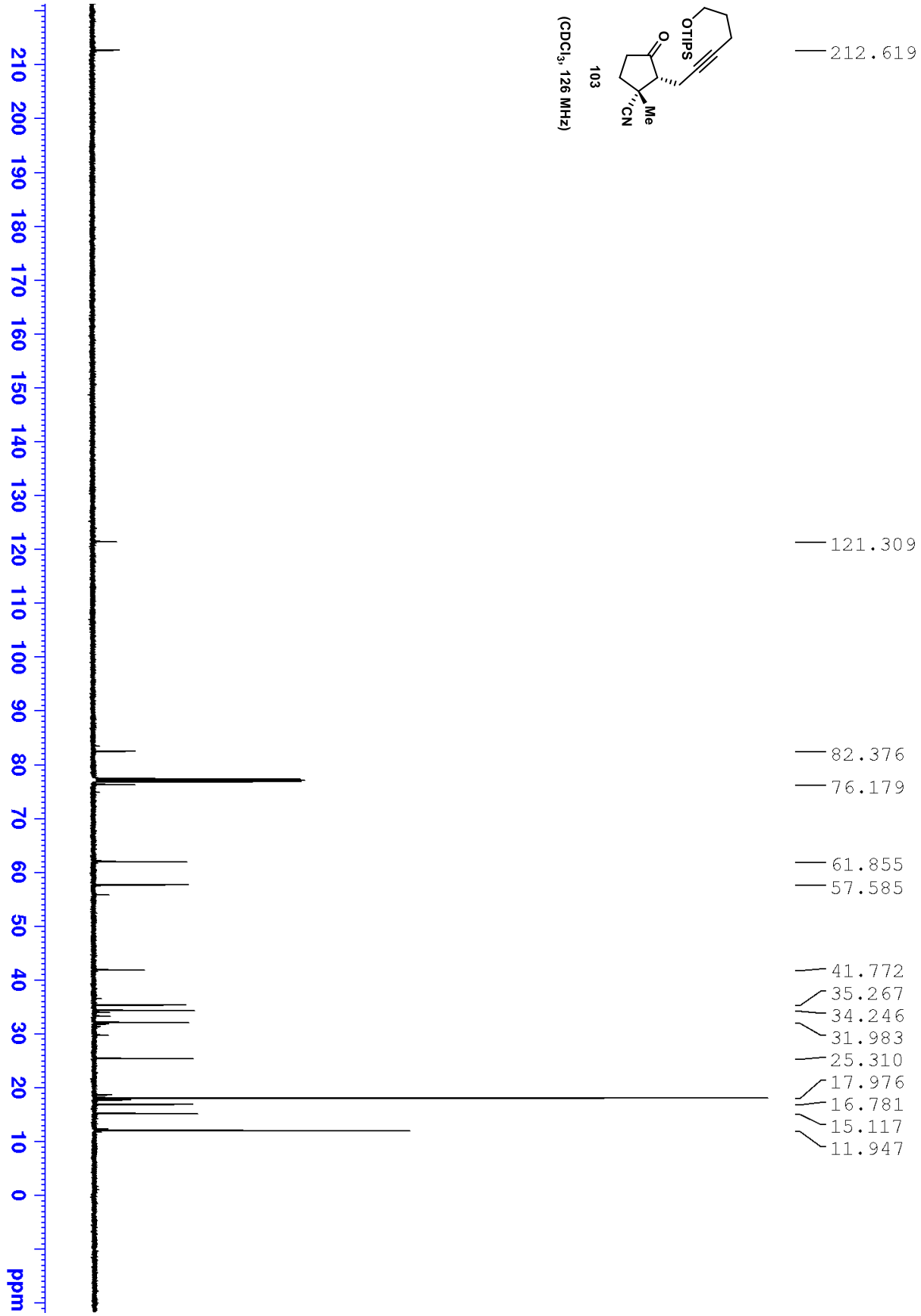

TIPSO
I
108
(CDCl3, 500 MHz)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.00
1.70
1.91
1.99
20.69
3.769
3.757
3.745
3.706
3.701
3.697
2.333
2.323
2.319
2.314
2.310
2.305
1.749
1.736
1.723
1.710
1.696
1.107
1.102
1.090
1.080
1.067
1.056

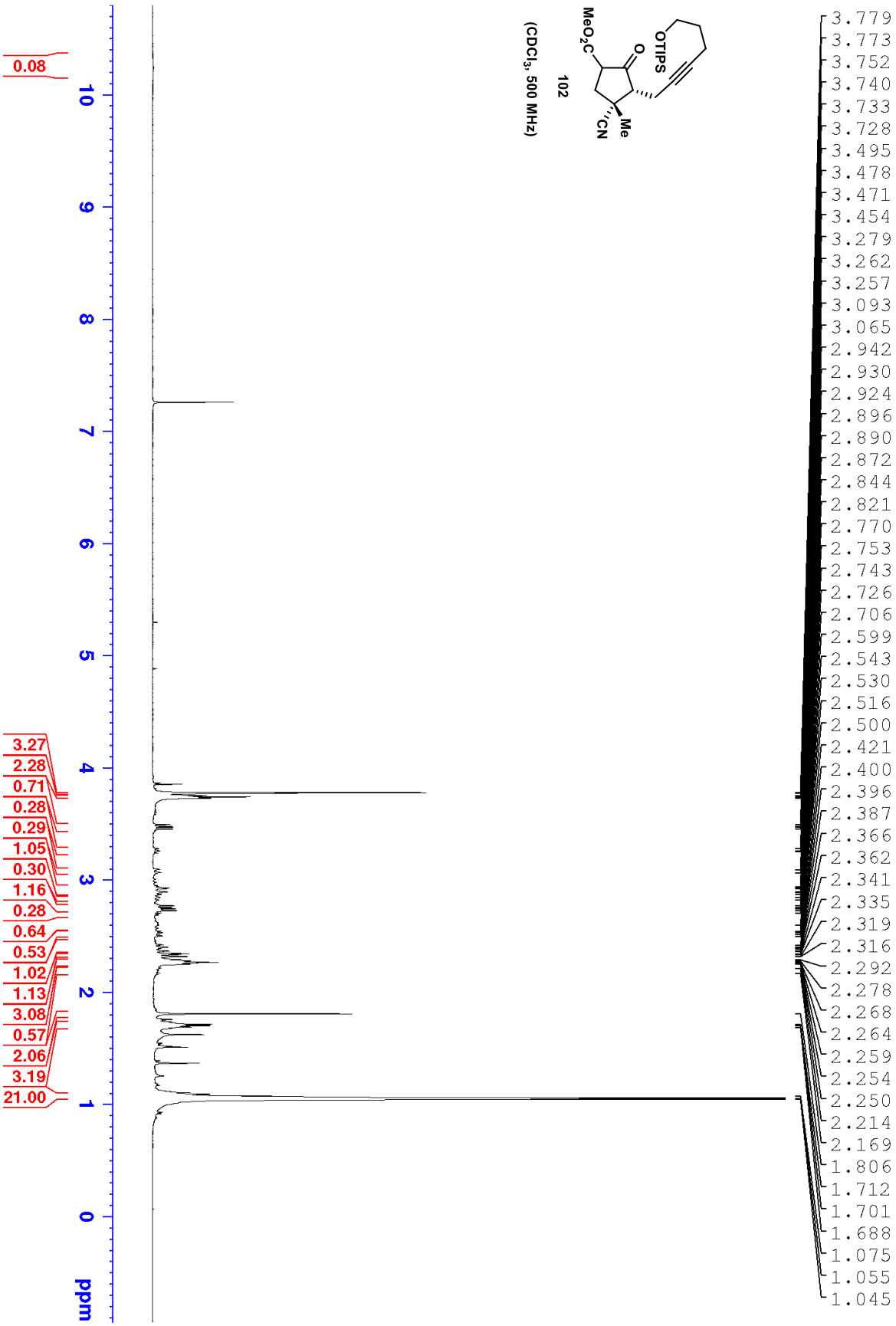

TIPSO
I
108
(CDCl3, 126 MHz)
220
200
180
160
140
120
100
80
60
40
20
0
ppm
86.425
77.083
61.733
31.598
18.012
15.563
11.983
-16.921

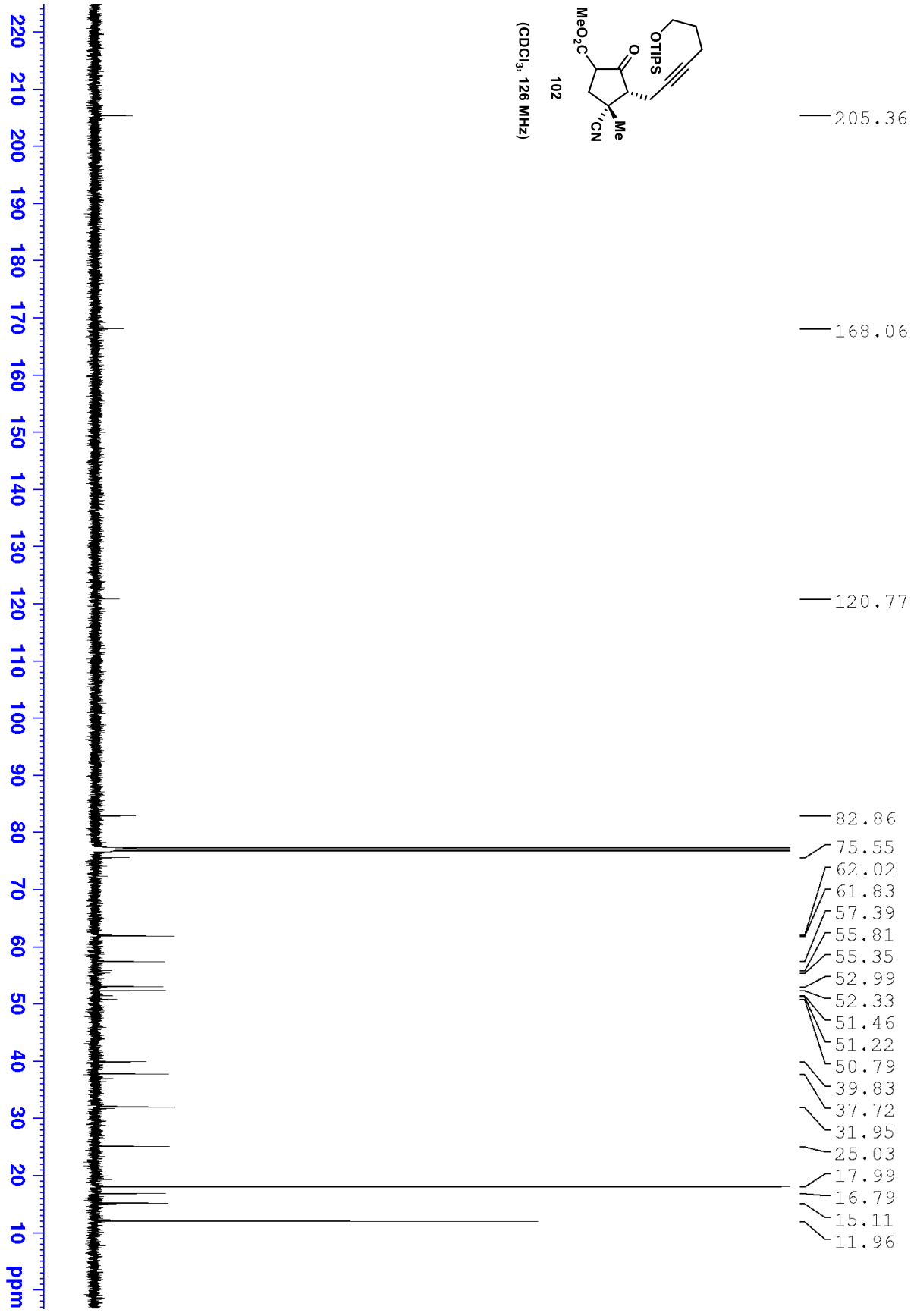

111
(CDCl3, 500 MHz)
OTIPS
O
Me
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
2.12
2.00
2.01
2.01
2.38
2.82
2.16
21.45
3.734
3.722
3.710
3.058
2.512
2.395
2.386
2.377
2.243
2.238
2.233
2.229
2.224
2.215
2.175
1.709
1.696
1.683
1.670
1.656
1.064
1.046
1.037

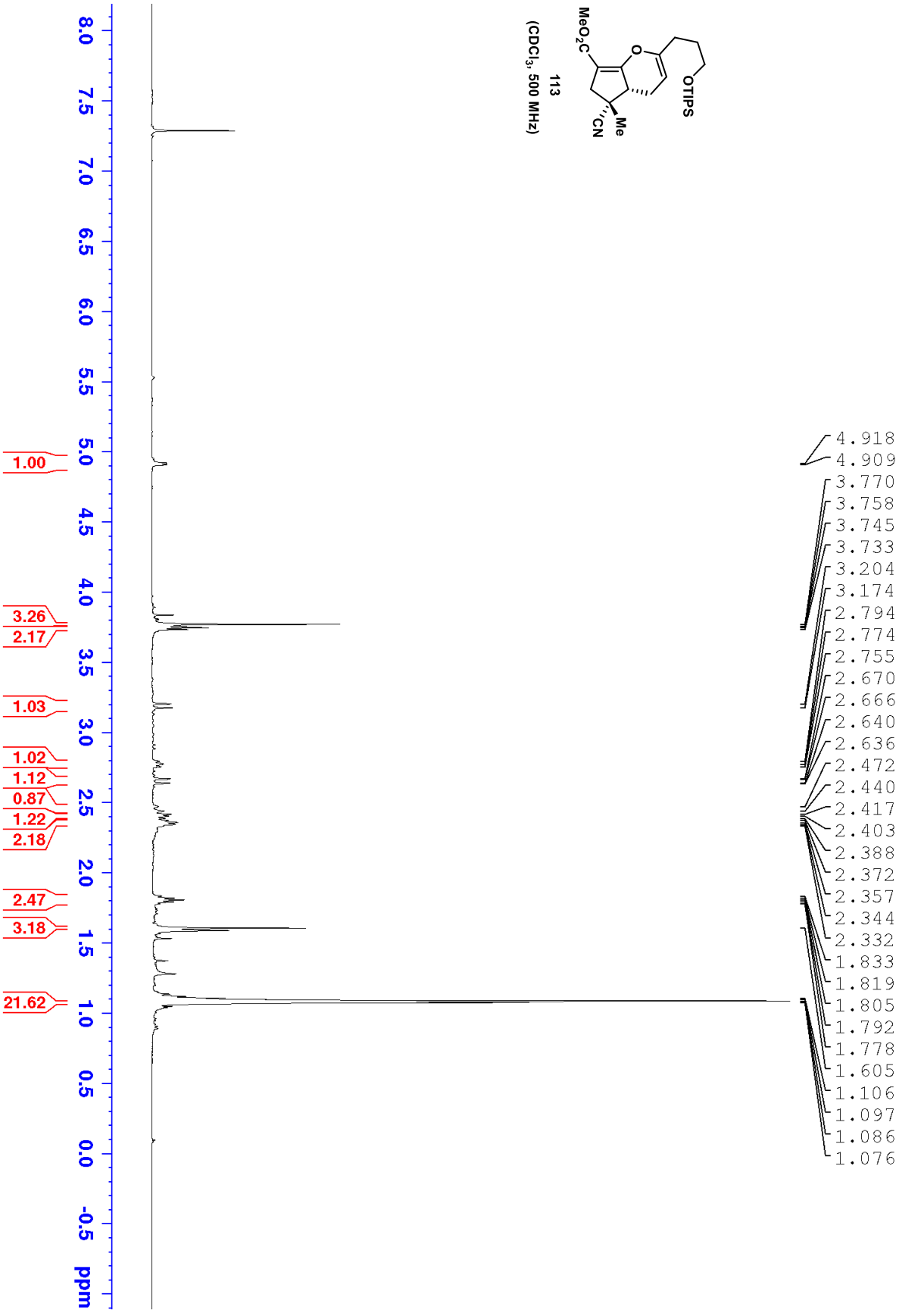

(CDCl3, 126 MHz)
11
OTIPS
O
Me
207.611
171.822
136.125
79.660
76.028
61.814
33.929
31.977
31.625
17.860
17.289
15.056
12.481
11.835
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

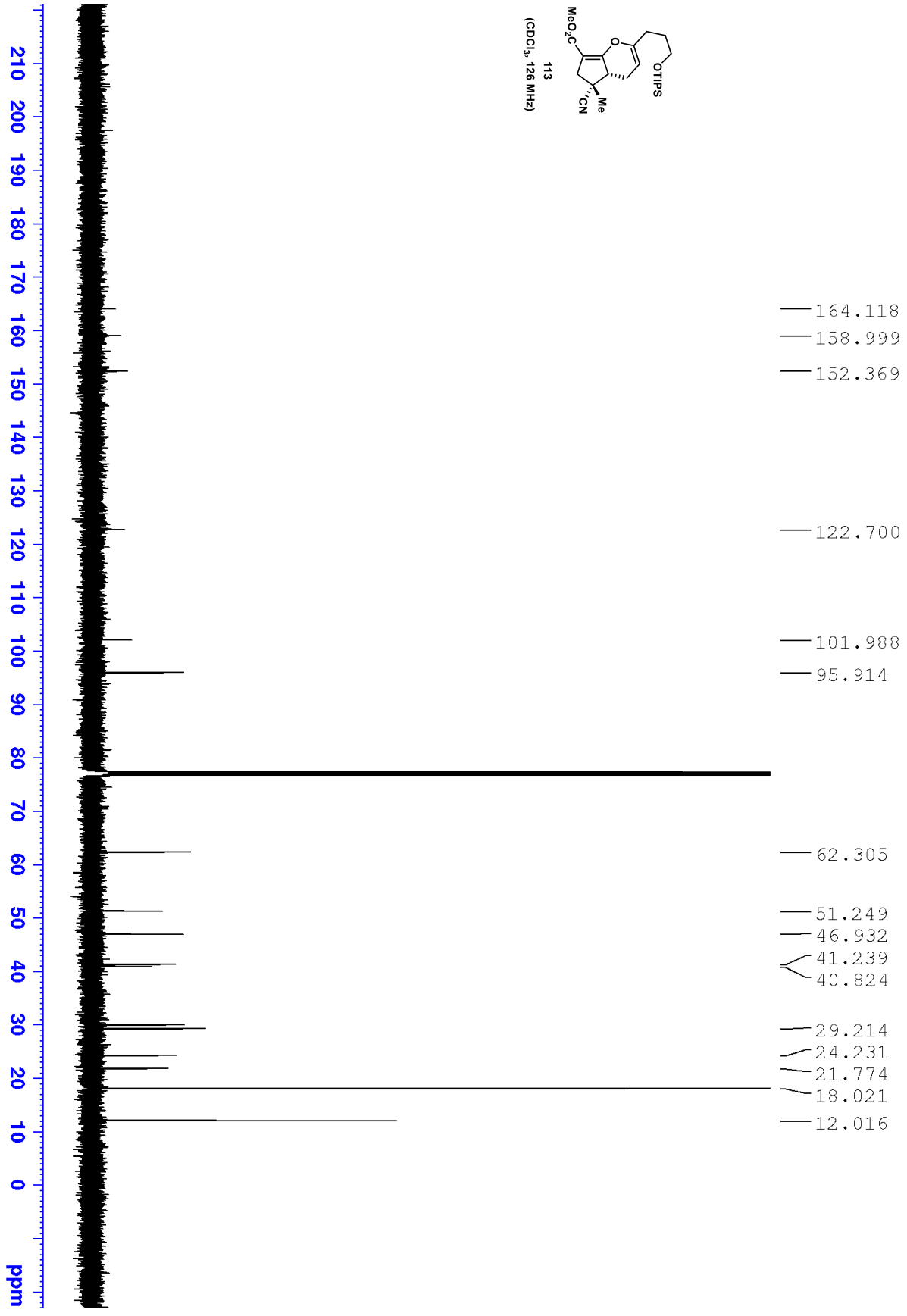

OTIPS
O
Me
CN
103
(CDCl3, 500 MHz)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
2.00
0.86
1.03
1.18
1.70
2.15
0.85
1.14
2.75
2.21
21.14
3.751
3.739
3.727
2.906
2.871
2.566
2.561
2.550
2.545
2.540
2.535
2.524
2.519
2.497
2.478
2.463
2.454
2.439
2.431
2.415
2.392
2.372
2.357
2.337
2.273
2.263
2.258
2.244
2.164
2.157
2.144
2.137
1.898
1.880
1.875
1.854
1.850
1.831
1.753
1.726
1.712
1.699
1.686
1.672
1.117
1.100

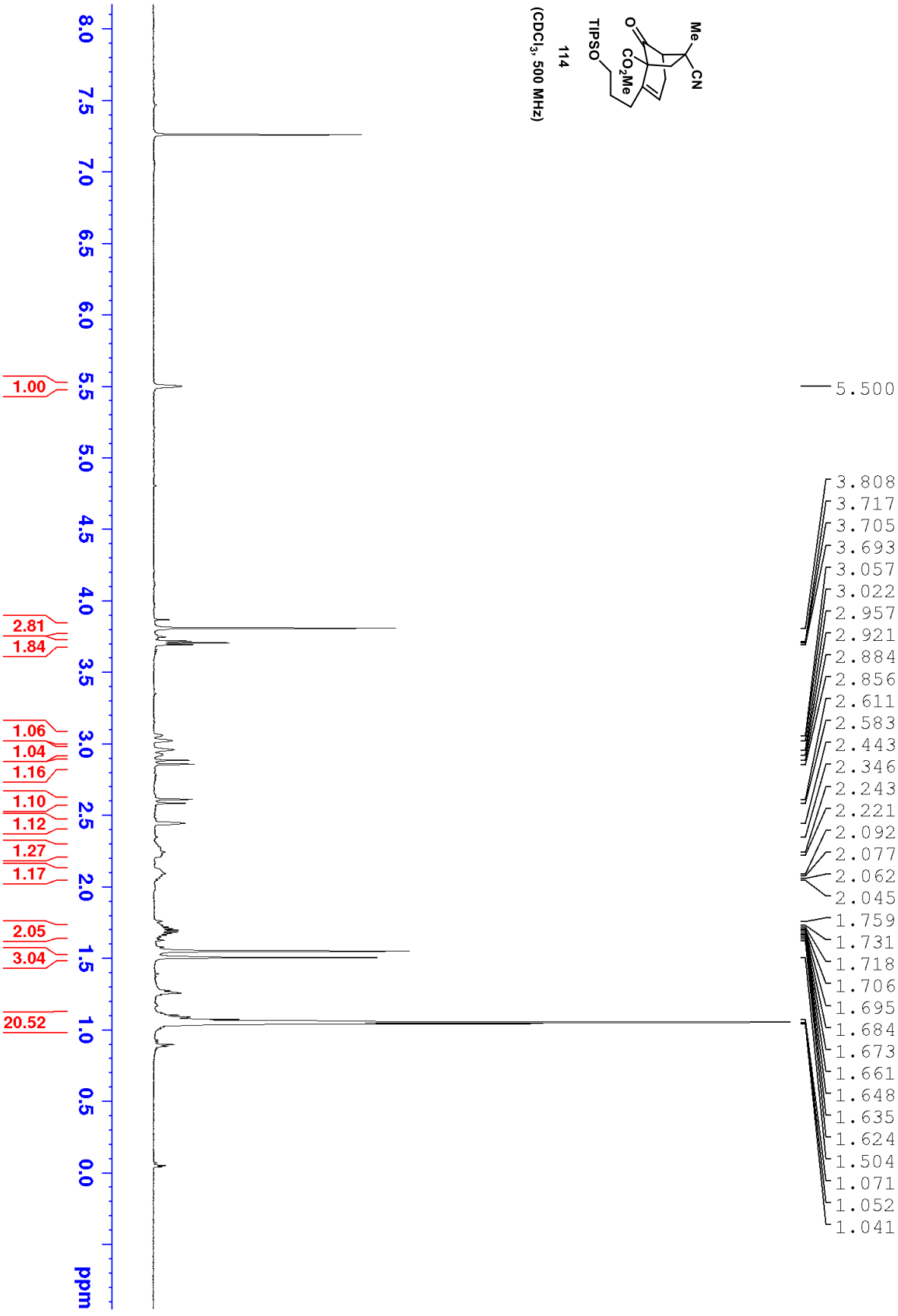

103
(CDCl3, 126 MHz)
OTIPS
O
Me
CN
212.619
121.309
82.376
76.179
61.855
57.585
41.772
35.267
34.246
31.983
25.310
17.976
16.781
15.117
11.947
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

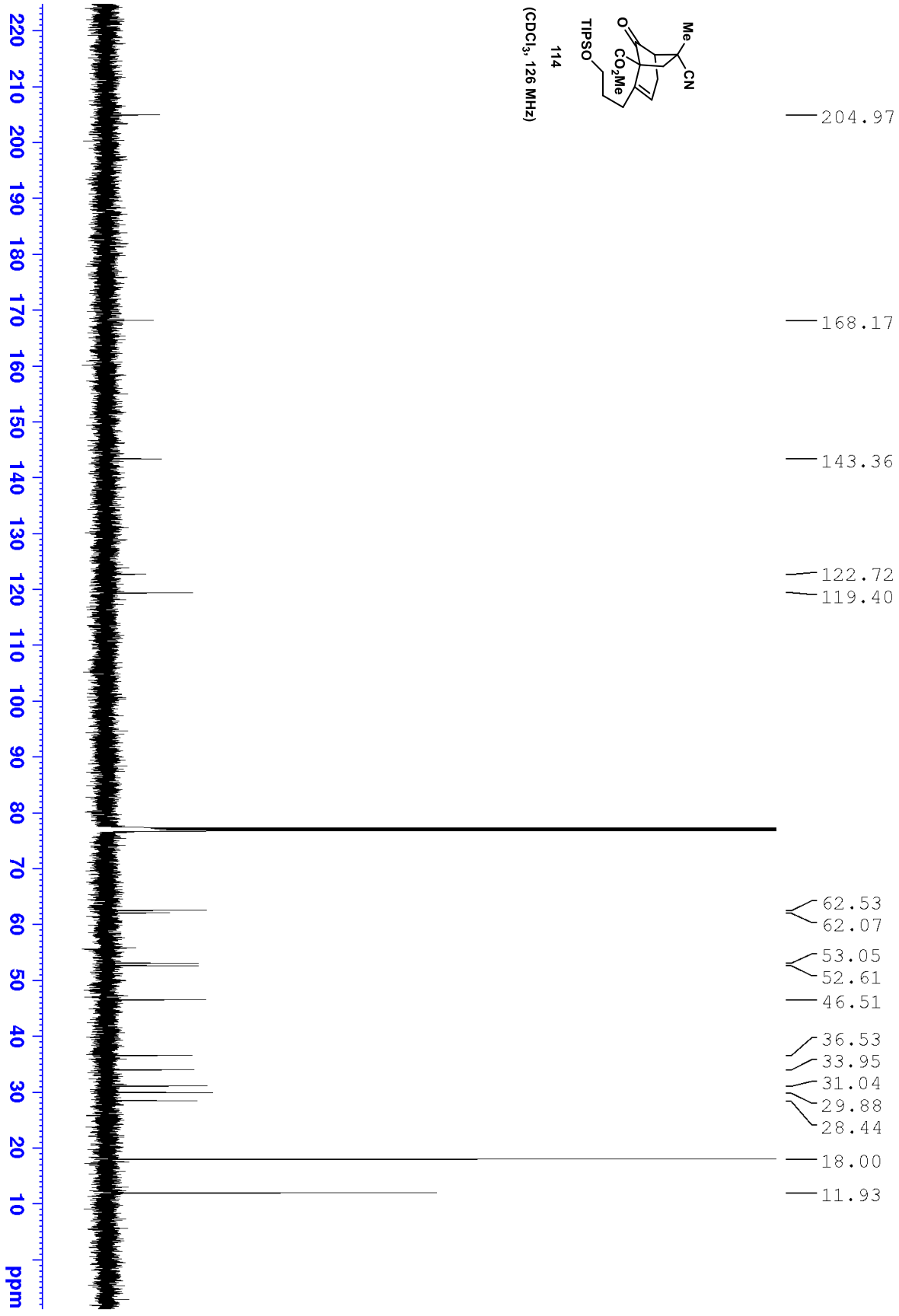

102
(CDCl3, 500 MHz)
MeO2C
O
OTIPS
Me
CN
0.08
3.27
2.28
0.71
0.28
0.29
1.05
0.30
1.16
0.28
0.64
0.53
1.02
1.13
3.08
0.57
2.06
3.19
21.00
ppm
3.779
3.773
3.752
3.740
3.733
3.728
3.495
3.478
3.471
3.454
3.279
3.262
3.257
3.093
3.065
2.942
2.930
2.924
2.896
2.890
2.872
2.844
2.821
2.770
2.753
2.743
2.726
2.706
2.599
2.543
2.530
2.516
2.500
2.421
2.400
2.396
2.387
2.366
2.362
2.341
2.335
2.319
2.316
2.292
2.278
2.268
2.264
2.259
2.254
2.250
2.214
2.169
1.806
1.712
1.701
1.688
1.075
1.055
1.045

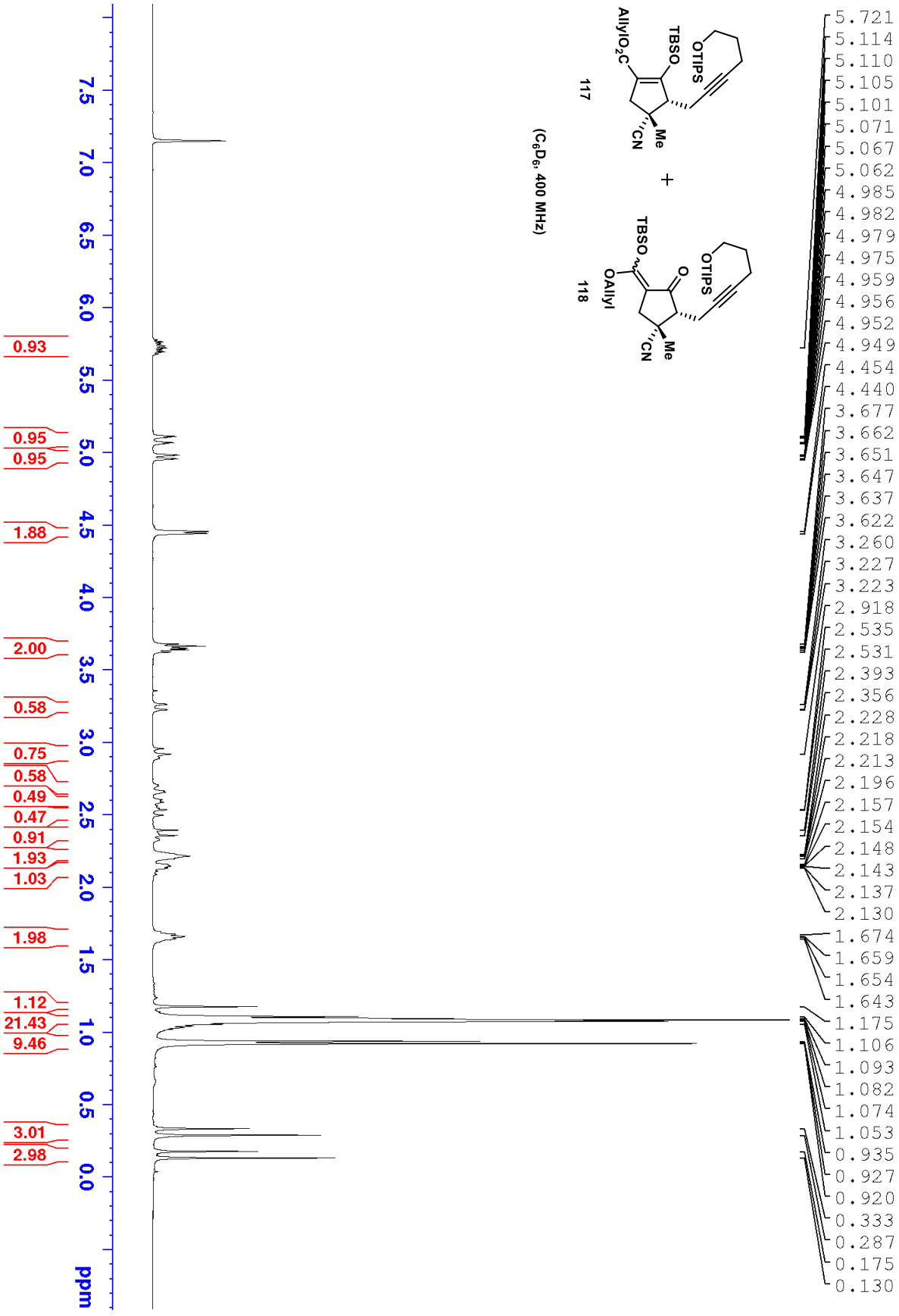

MeO2C
O
OTIPS
CN
Me
102
(CDCl3, 126 MHz)
205.36
168.06
120.77
82.86
75.55
62.02
61.83
57.39
55.81
55.35
52.99
52.33
51.46
51.22
50.79
39.83
37.72
31.95
25.03
17.99
16.79
15.11
11.96
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

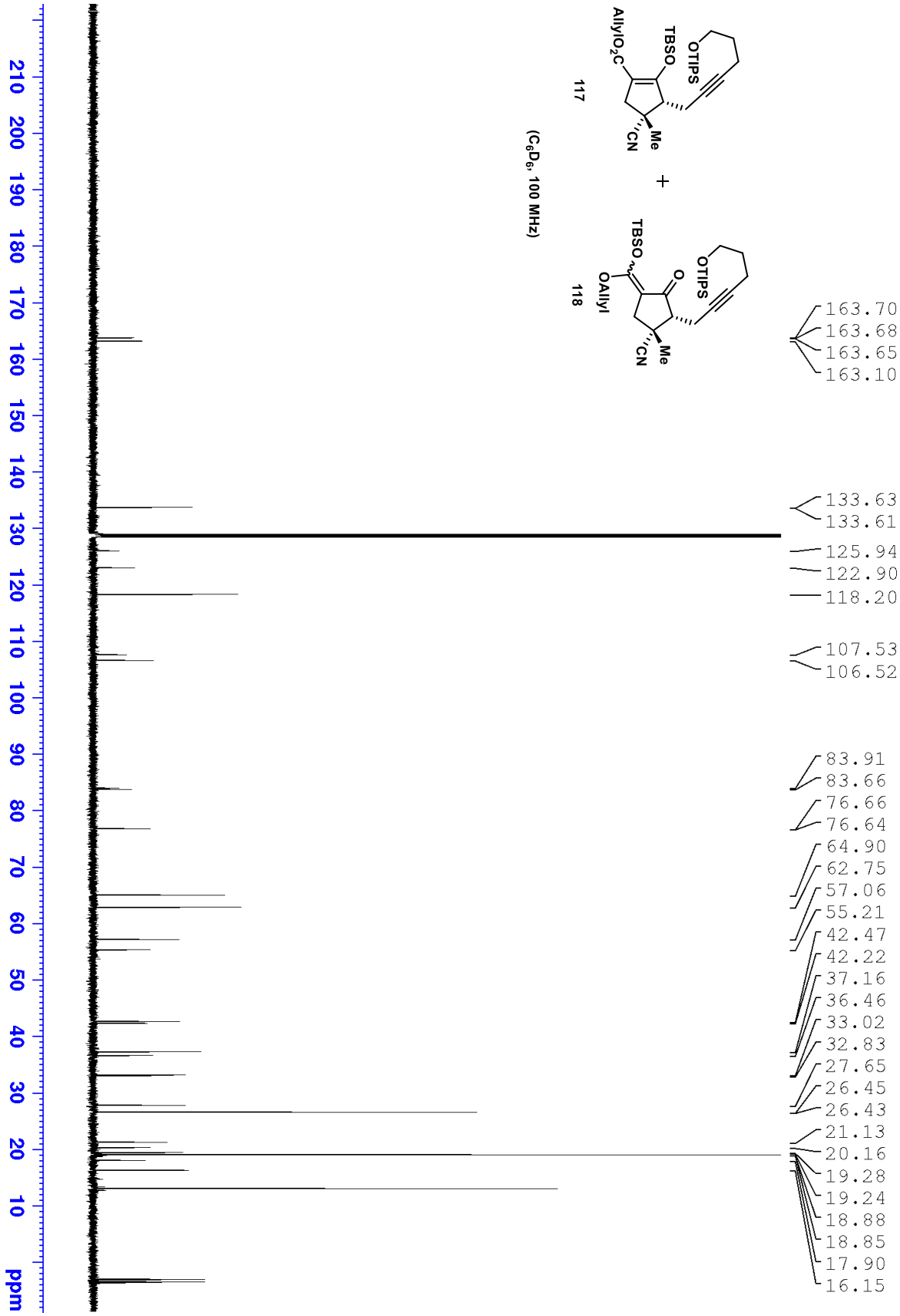

113
(CDCl3, 500 MHz)
MeO2C
O
OTIPS
CN
Me
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
1.00
3.26
2.17
1.03
1.02
1.12
0.87
1.22
2.18
2.47
3.18
21.62
4.918
4.909
3.770
3.758
3.745
3.733
3.204
3.174
2.794
2.774
2.755
2.670
2.666
2.640
2.636
2.472
2.440
2.417
2.403
2.388
2.372
2.357
2.344
2.332
1.833
1.819
1.805
1.792
1.778
1.605
1.106
1.097
1.086
1.076

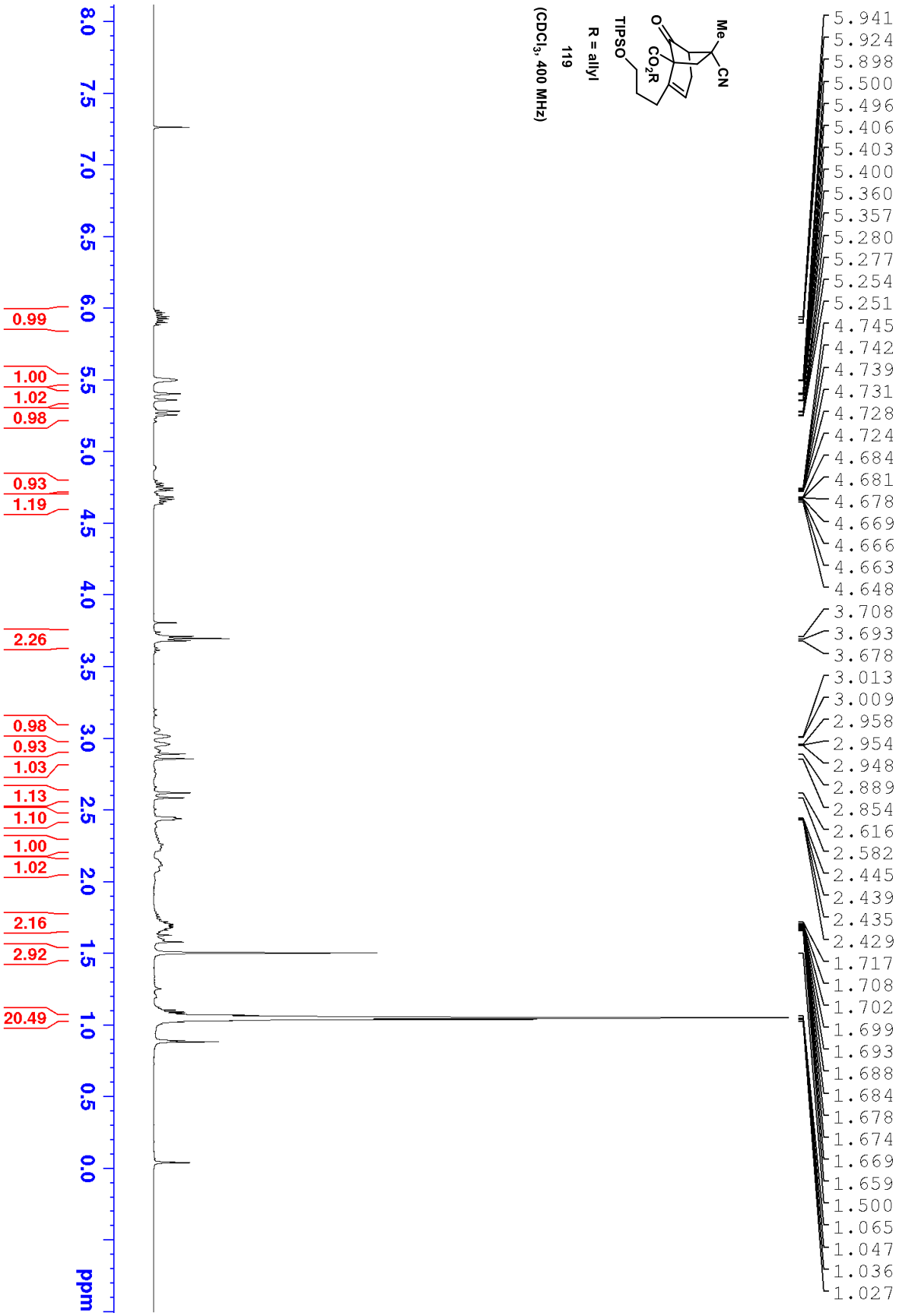

MeO2C
Me
CN
OTIPS
113
(CDCl3, 126 MHz)
164.118
158.999
152.369
122.700
101.988
95.914
62.305
51.249
46.932
41.239
40.824
29.214
24.231
21.774
18.021
12.016
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

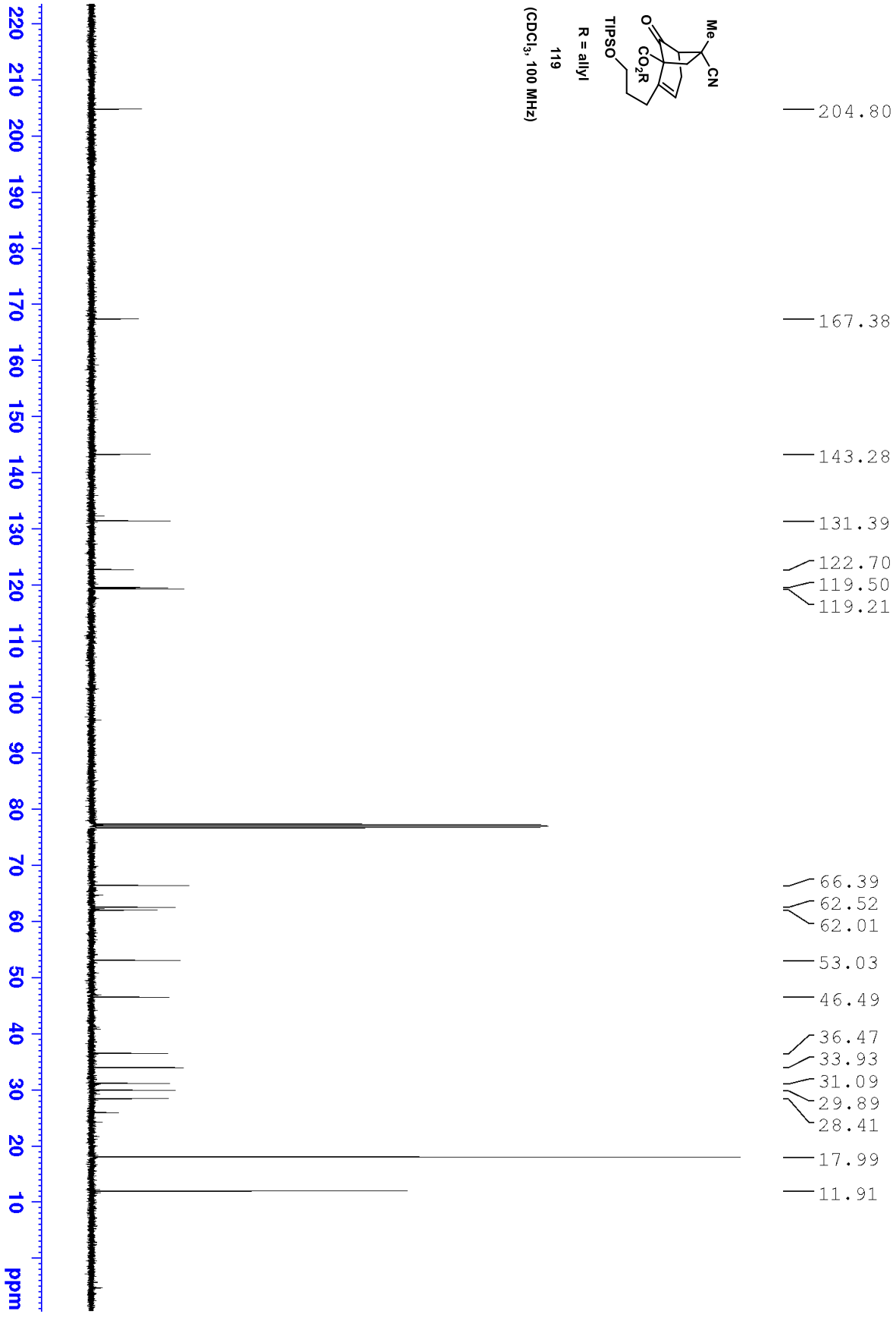

114
(CDCl3, 500 MHz)
TIPSO
O
CO2Me
Me
CN
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
2.81
1.84
1.06
1.04
1.16
1.10
1.12
1.27
1.17
2.05
3.04
20.52
5.500
3.808
3.717
3.705
3.693
3.057
3.022
2.957
2.921
2.884
2.856
2.611
2.583
2.443
2.346
2.243
2.221
2.092
2.077
2.062
2.045
1.759
1.731
1.718
1.706
1.695
1.684
1.673
1.661
1.648
1.635
1.624
1.504
1.071
1.052
1.041

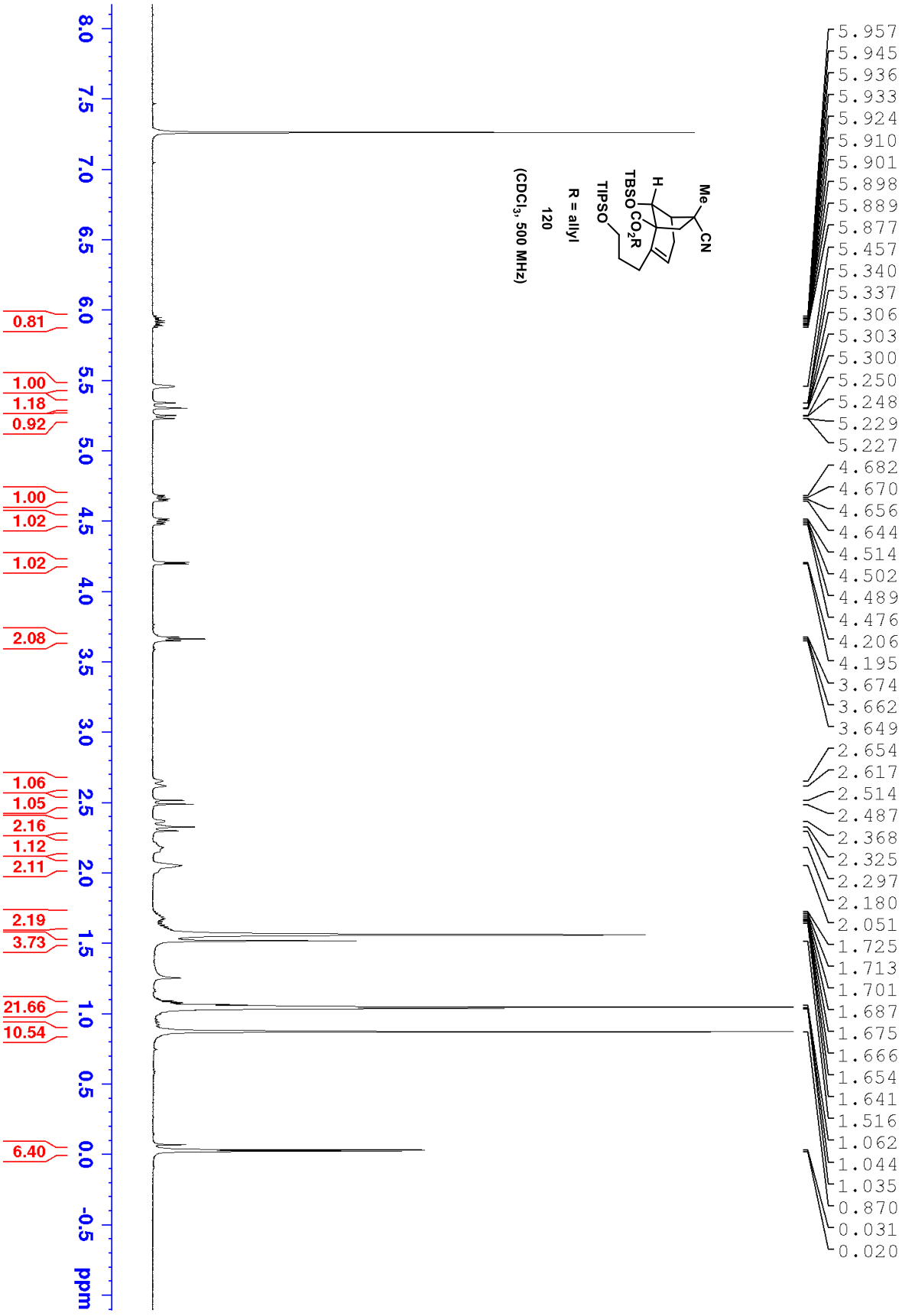

114
(CDCl3, 126 MHz)
TIPSO
O
CO2Me
Me
CN
204.97
168.17
143.36
122.72
119.40
62.53
62.07
53.05
52.61
46.51
36.53
33.95
31.04
29.88
28.44
18.00
11.93
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

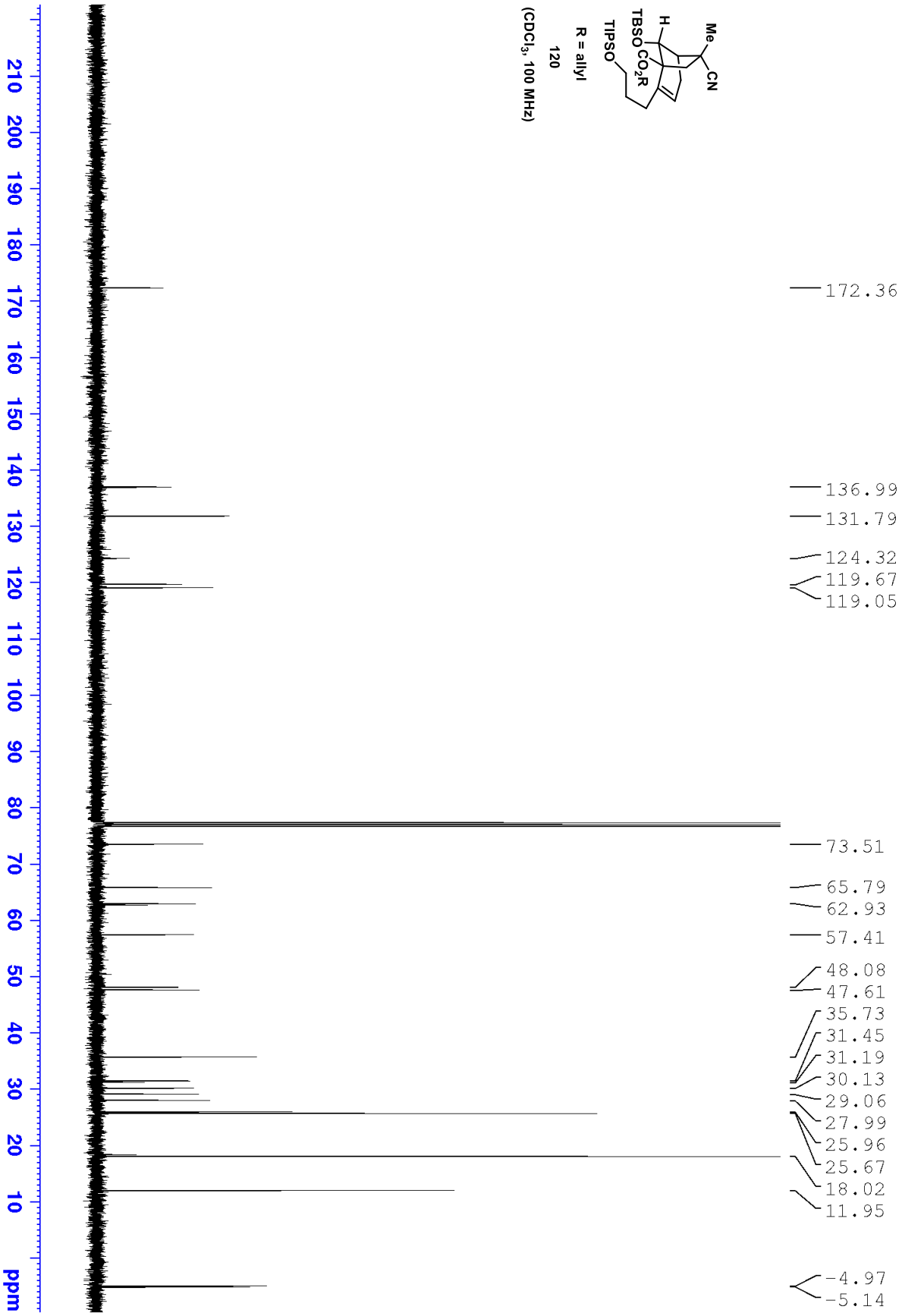

117
118
+
(C6D6, 400 MHz)
5.721
5.114
5.110
5.105
5.101
5.071
5.067
5.062
4.985
4.982
4.979
4.975
4.959
4.956
4.952
4.949
4.454
4.440
3.677
3.662
3.651
3.647
3.637
3.622
3.260
3.227
3.223
2.918
2.535
2.531
2.393
2.356
2.228
2.218
2.213
2.196
2.157
2.154
2.148
2.143
2.137
2.130
1.674
1.659
1.654
1.643
1.175
1.106
1.093
1.082
1.074
1.053
0.935
0.927
0.920
0.333
0.287
0.175
0.130
0.93
0.95
0.95
1.88
2.00
0.58
0.75
0.58
0.49
0.47
0.91
1.93
1.03
1.98
1.12
21.43
9.46
3.01
2.98
ppm

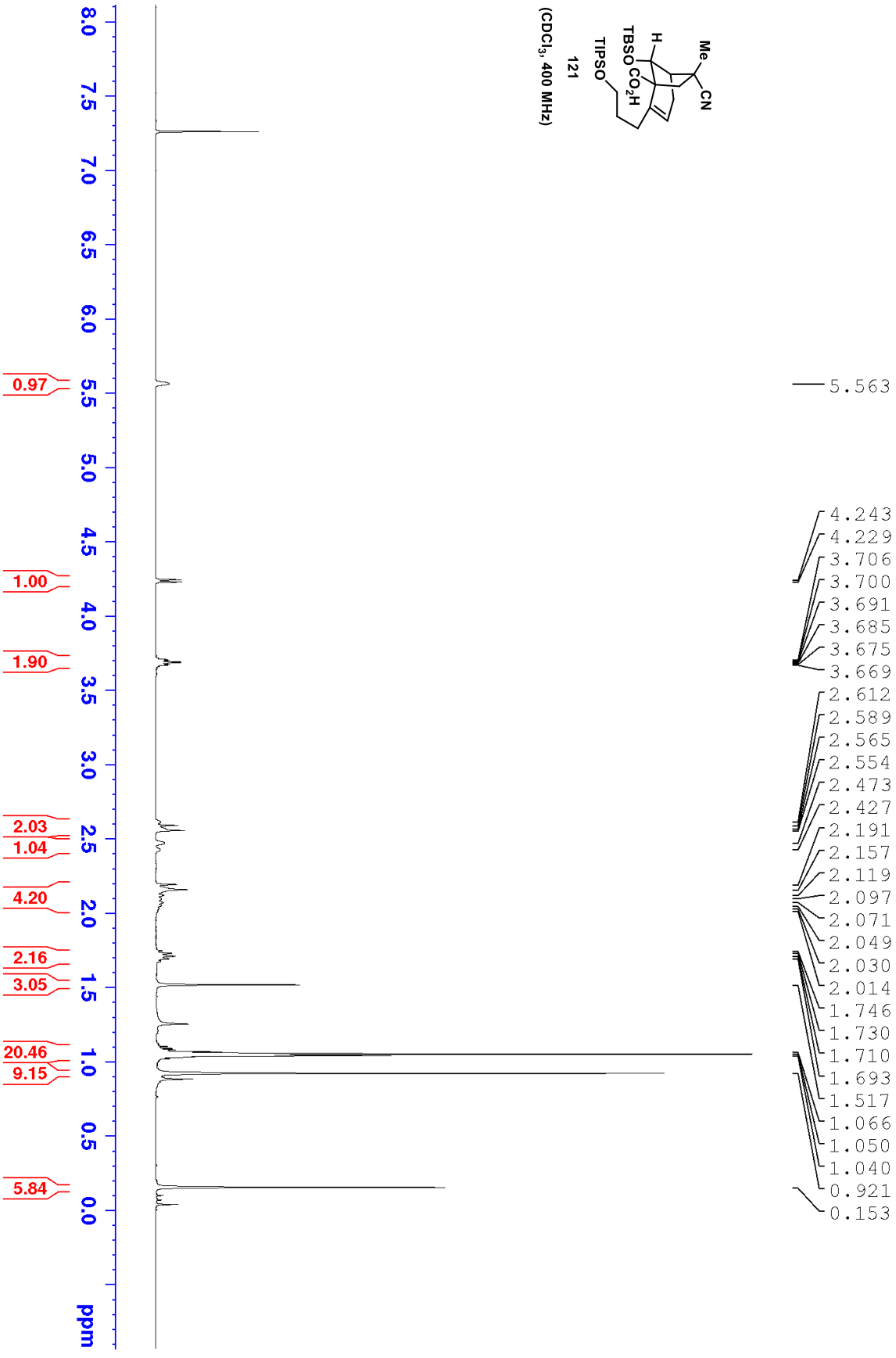

117
118
(C6D6, 100 MHz)
163.70
163.68
163.65
163.10
133.63
133.61
125.94
122.90
118.20
107.53
106.52
83.91
83.66
76.66
76.64
64.90
62.75
57.06
55.21
42.47
42.22
37.16
36.46
33.02
32.83
27.65
26.45
26.43
21.13
20.16
19.28
19.24
18.88
18.85
17.90
16.15
ppm

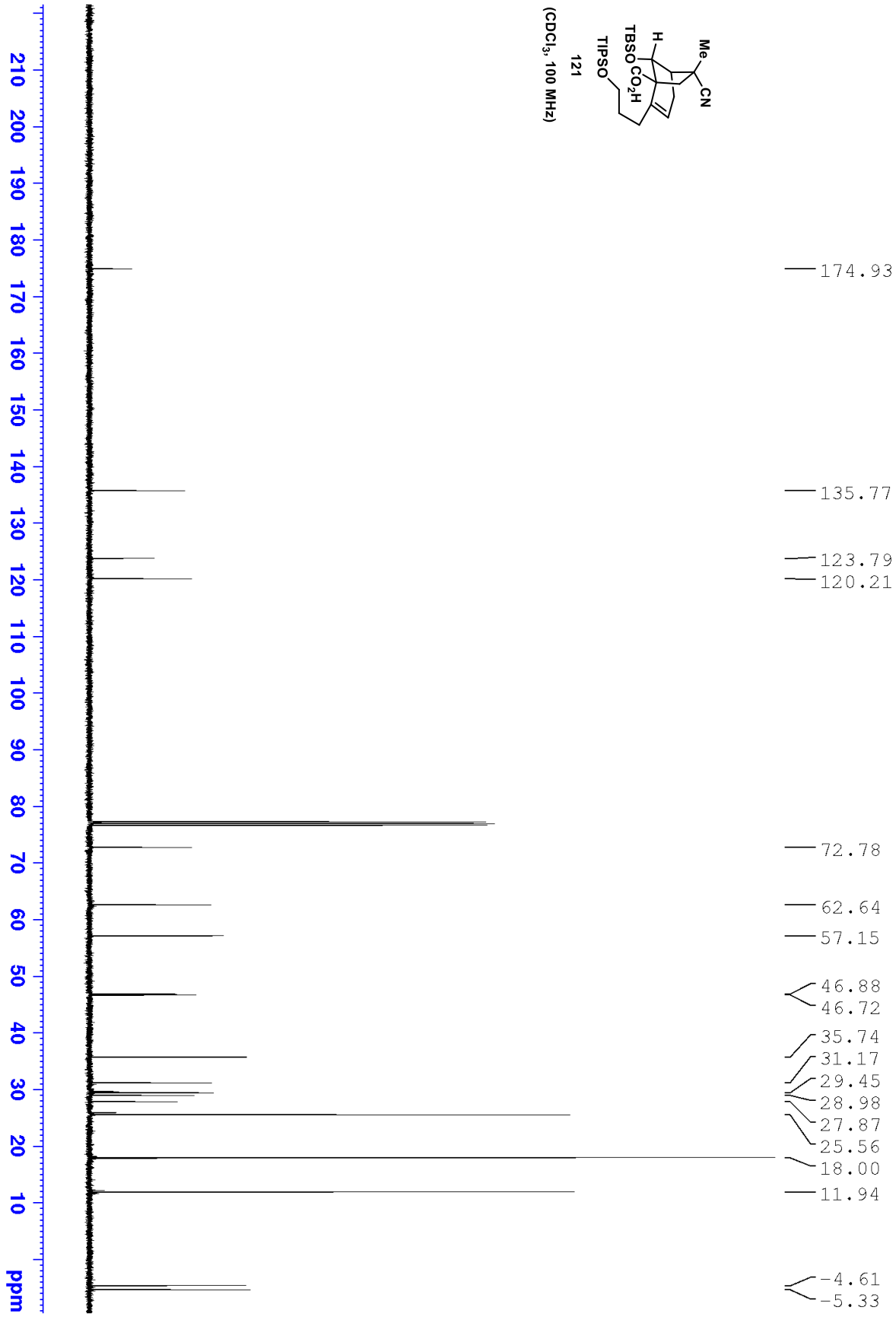

TIPSO
O
CO2R
Me
CN
R = allyl
119
(CDCl3, 400 MHz)
5.941
5.924
5.898
5.500
5.496
5.406
5.403
5.400
5.360
5.357
5.280
5.277
5.254
5.251
4.745
4.742
4.739
4.731
4.728
4.724
4.684
4.681
4.678
4.669
4.666
4.663
4.648
3.708
3.693
3.678
3.013
3.009
2.958
2.954
2.948
2.889
2.854
2.616
2.582
2.445
2.439
2.435
2.429
1.717
1.708
1.702
1.699
1.693
1.688
1.684
1.678
1.674
1.669
1.659
1.500
1.065
1.047
1.036
1.027
0.99
1.00
1.02
0.98
0.93
1.19
2.26
0.98
0.93
1.03
1.13
1.10
1.00
1.02
2.16
2.92
20.49
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
ppm

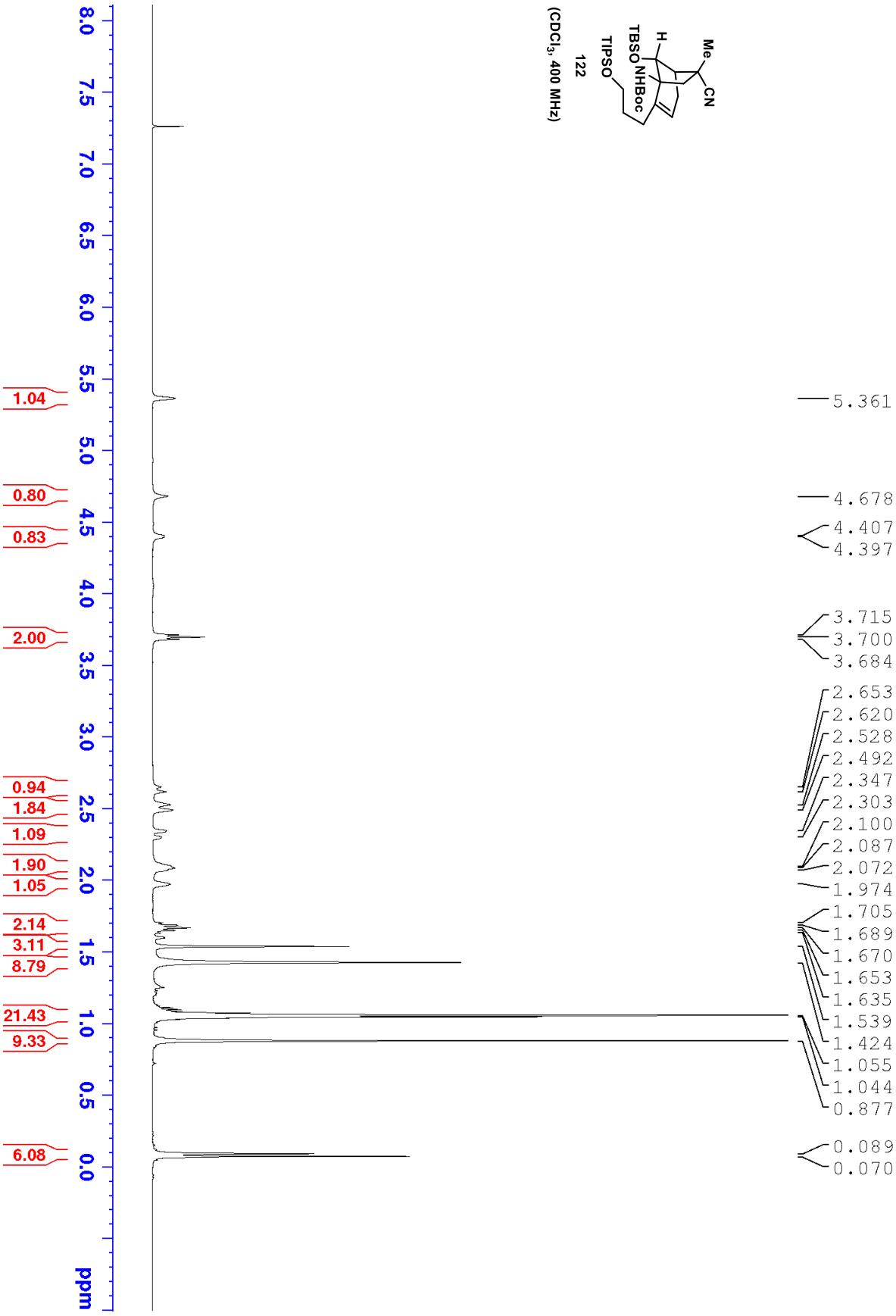

TIPSO
O
CO2R
Me
CN
R = allyl
119
(CDCl3, 100 MHz)
204.80
167.38
143.28
131.39
122.70
119.50
119.21
66.39
62.52
62.01
53.03
46.49
36.47
33.93
31.09
29.89
28.41
17.99
11.91
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

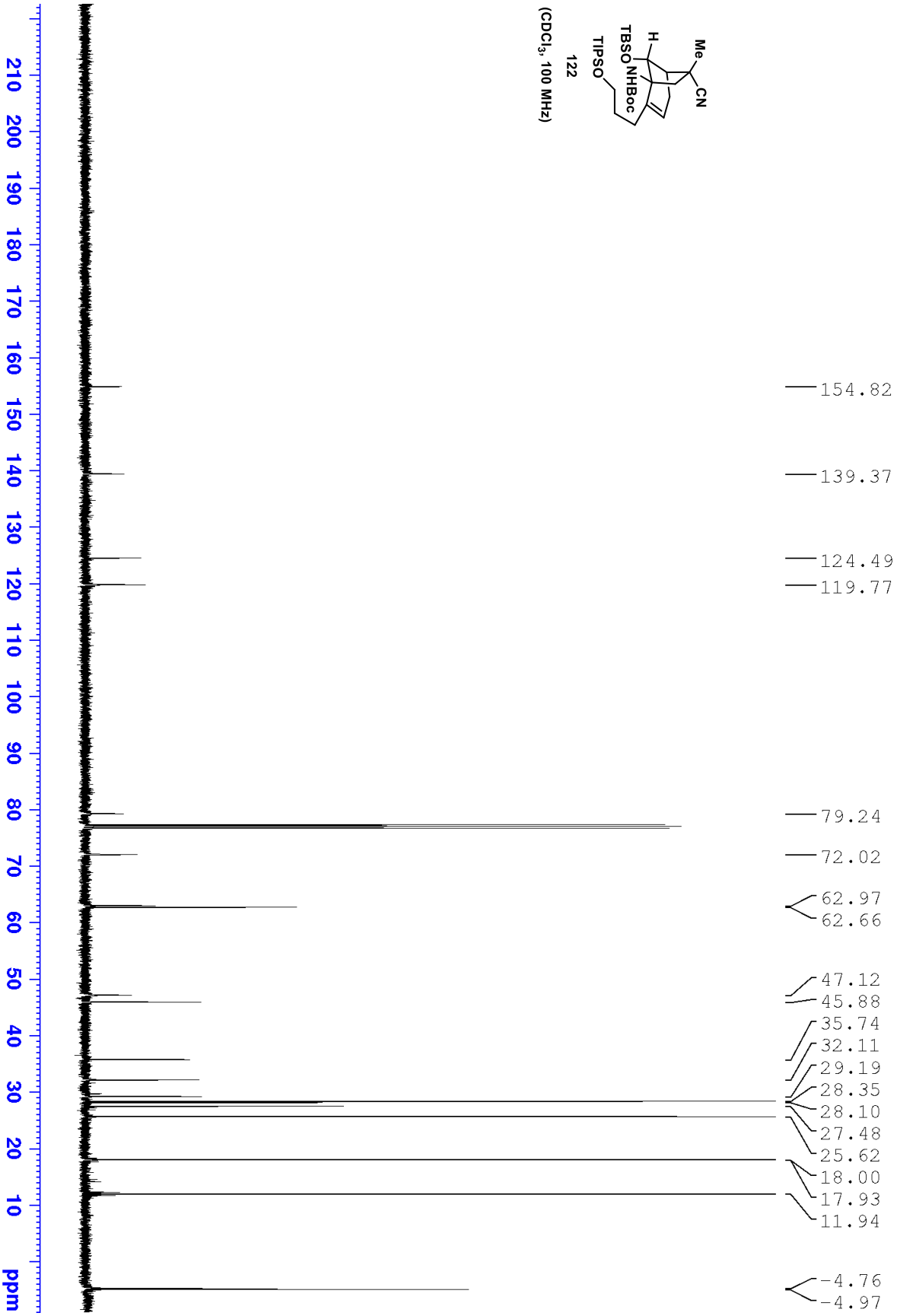

120
R = allyl
(CDCl3, 500 MHz)
TIPSO
TBSO
CO2R
H
Me
CN
0.81
1.00
1.18
0.92
1.00
1.02
1.02
2.08
1.06
1.05
2.16
1.12
2.11
2.19
3.73
21.66
10.54
6.40
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
5.957
5.945
5.936
5.933
5.924
5.910
5.901
5.898
5.889
5.877
5.457
5.340
5.337
5.306
5.303
5.300
5.250
5.248
5.229
5.227
4.682
4.670
4.656
4.644
4.514
4.502
4.489
4.476
4.206
4.195
3.674
3.662
3.649
2.654
2.617
2.514
2.487
2.368
2.325
2.297
2.180
2.051
1.725
1.713
1.701
1.687
1.675
1.666
1.654
1.641
1.516
1.062
1.044
1.035
0.870
0.031
0.020

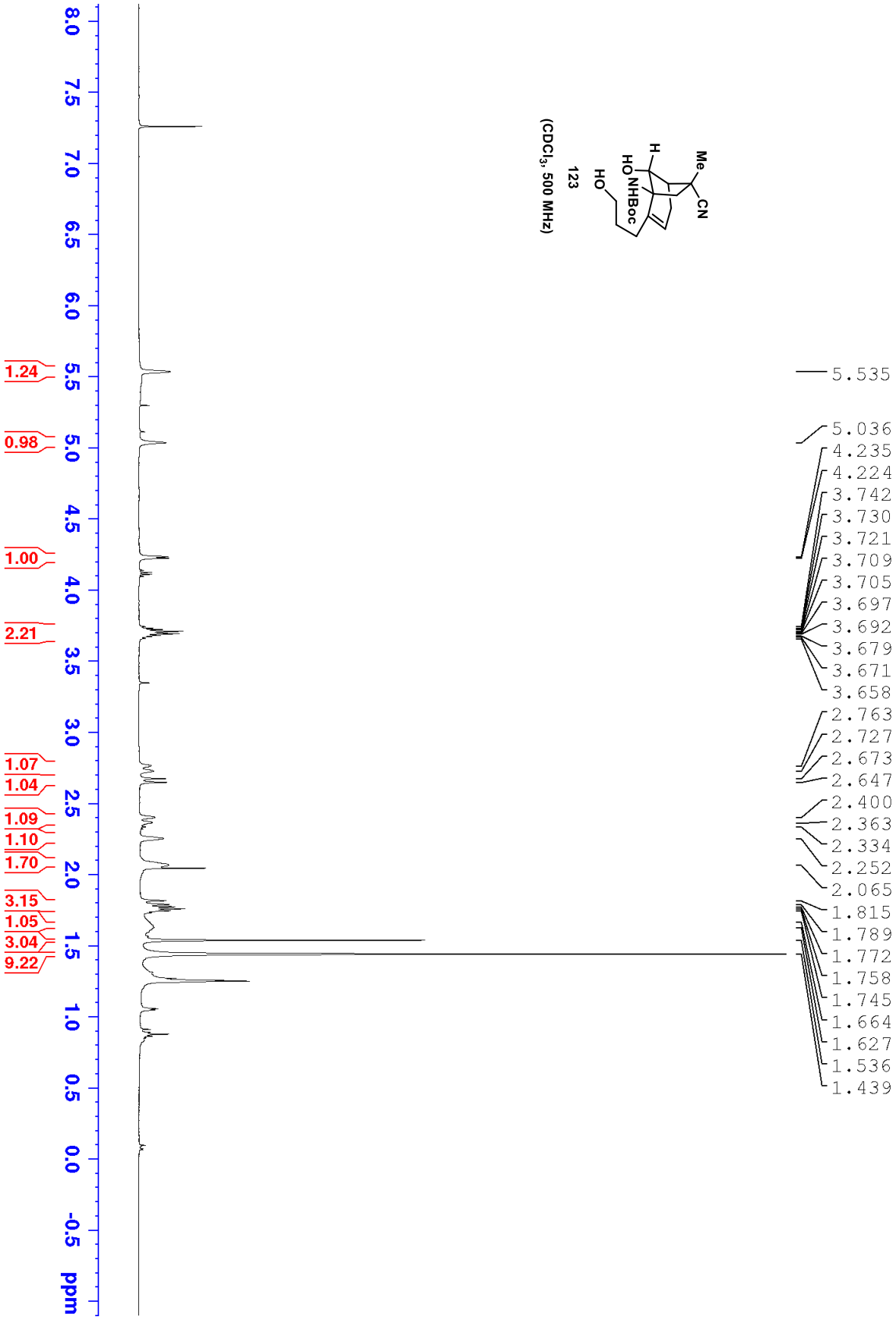

TIPSO
TBSO
CO2R
H
Me
CN
R = allyl
120
(CDCl3, 100 MHz)
172.36
136.99
131.79
124.32
119.67
119.05
73.51
65.79
62.93
57.41
48.08
47.61
35.73
31.45
31.19
30.13
29.06
27.99
25.96
25.67
18.02
11.95
-4.97
-5.14
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

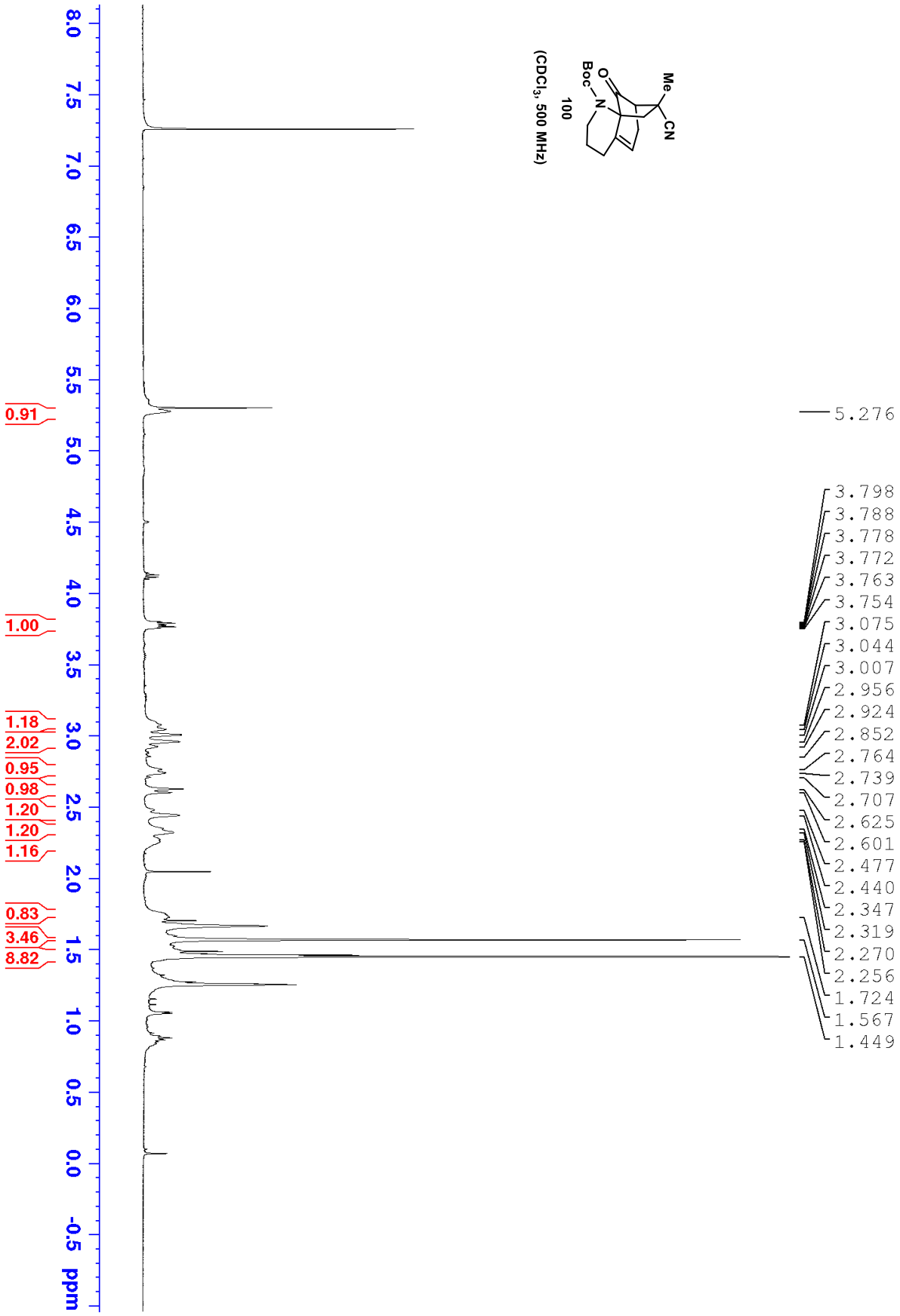

121
(CDCl3, 400 MHz)
TIPSO
TBSO
CO2H
H
Me
CN
5.563
4.243
4.229
3.706
3.700
3.691
3.685
3.675
3.669
2.612
2.589
2.565
2.554
2.473
2.427
2.191
2.157
2.119
2.097
2.071
2.049
2.030
2.014
1.746
1.730
1.710
1.693
1.517
1.066
1.050
1.040
0.921
0.153
0.97
1.00
1.90
2.03
1.04
4.20
2.16
3.05
20.46
9.15
5.84
8.0
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
ppm

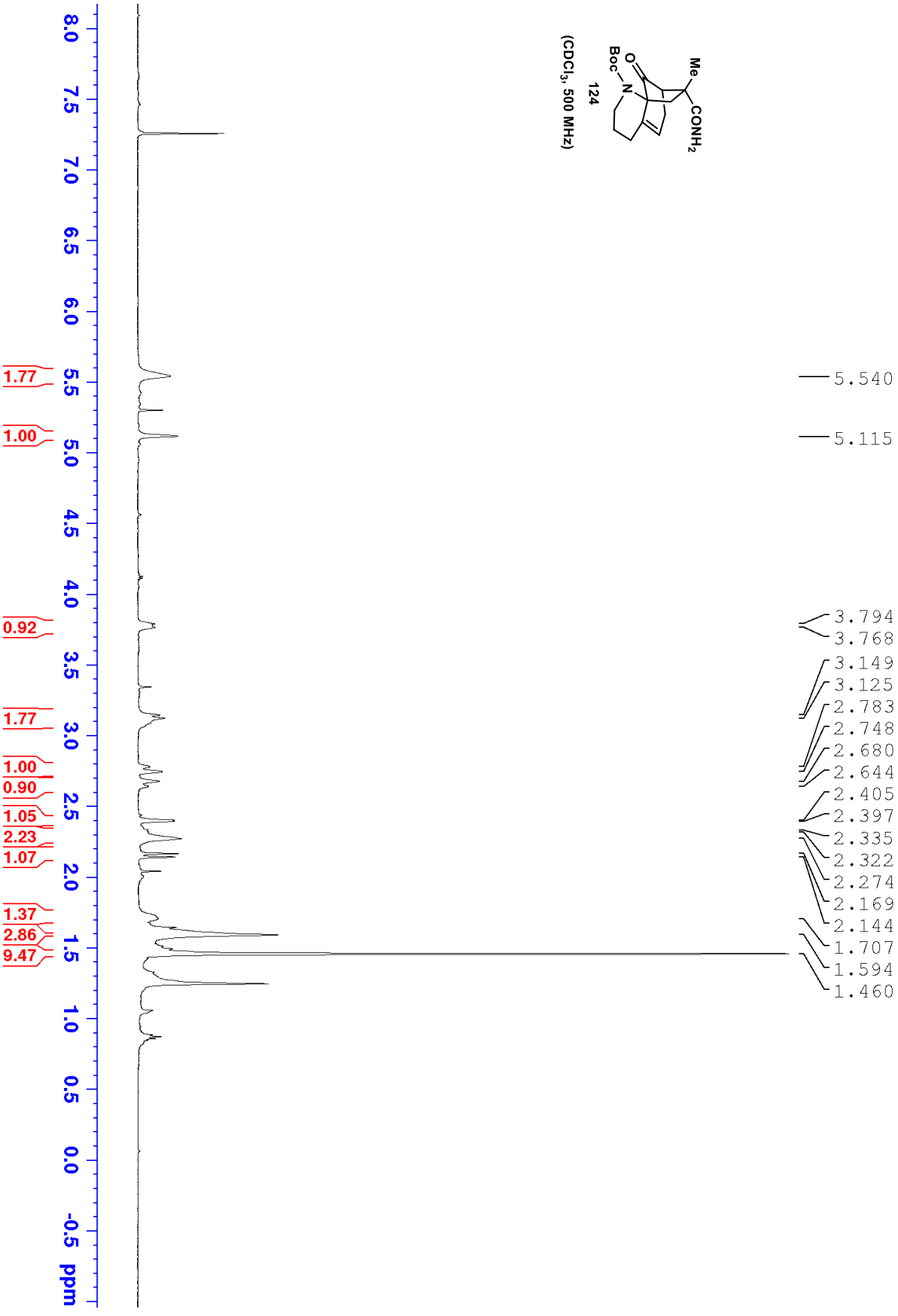

121
(CDCl3, 100 MHz)
TIPSO
TBSO
CO2H
H
Me
CN
174.93
135.77
123.79
120.21
72.78
62.64
57.15
46.88
46.72
35.74
31.17
29.45
28.98
27.87
25.56
18.00
11.94
-4.61
-5.33
ppm

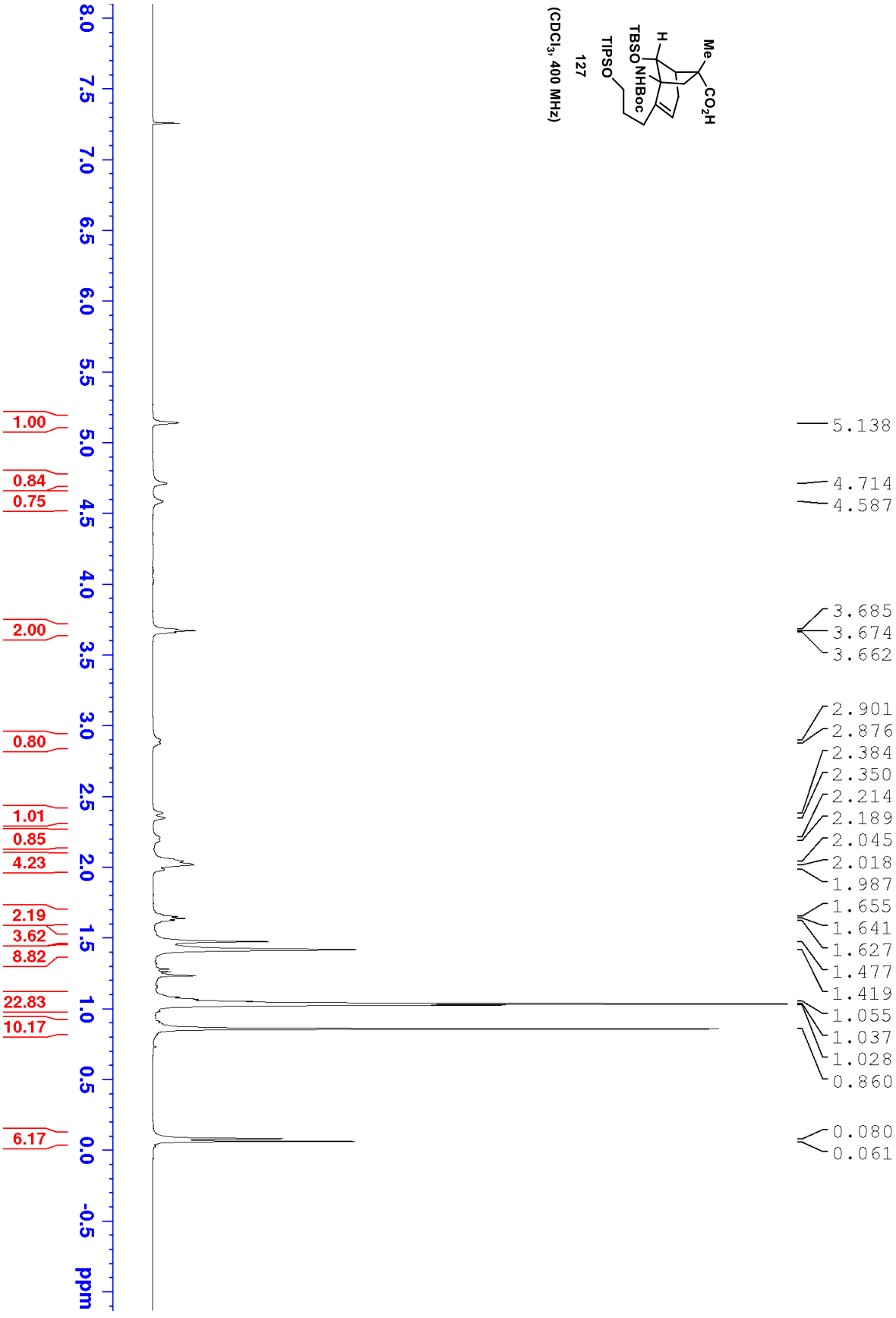

122
(CDCl3, 400 MHz)
TIPSO
TBSO
NHBoc
H
Me
CN
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.04
0.80
0.83
2.00
0.94
1.84
1.09
1.90
1.05
2.14
3.11
8.79
21.43
9.33
6.08
5.361
4.678
4.407
4.397
3.715
3.700
3.684
2.653
2.620
2.528
2.492
2.347
2.303
2.100
2.087
2.072
1.974
1.705
1.689
1.670
1.653
1.635
1.539
1.424
1.055
1.044
0.877
0.089
0.070

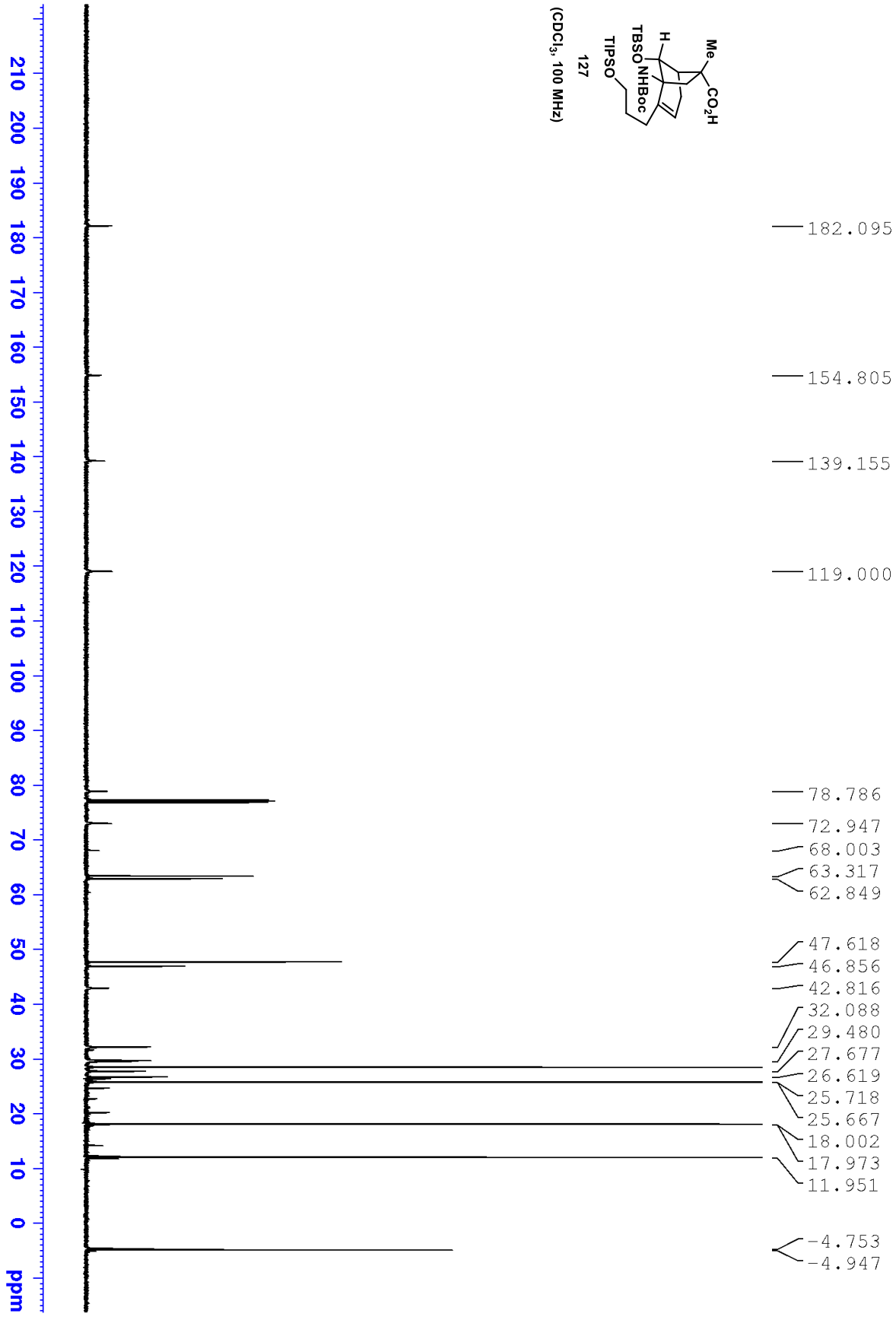

122
(CDCl3, 100 MHz)
TIPSO
TBSO
NHBoc
H
Me
CN
154.82
139.37
124.49
119.77
79.24
72.02
62.97
62.66
47.12
45.88
35.74
32.11
29.19
28.35
28.10
27.48
25.62
18.00
17.93
11.94
-4.76
-4.97
ppm

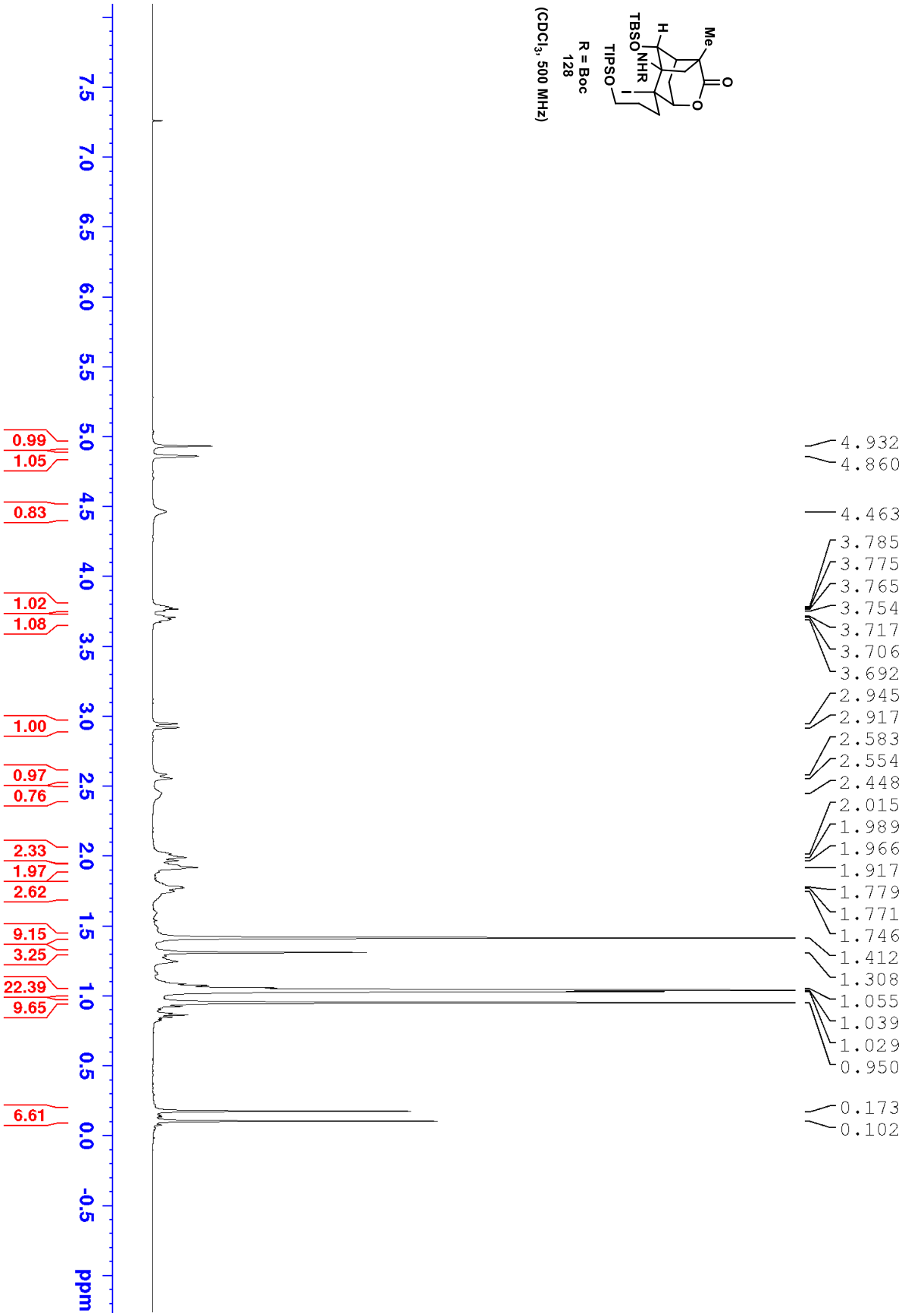

123
(CDCl3, 500 MHz)
HO
HO
NHBoc
H
Me
CN
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
1.24
0.98
1.00
2.21
1.07
1.04
1.09
1.10
1.70
3.15
1.05
3.04
9.22
5.535
5.036
4.235
4.224
3.742
3.730
3.721
3.709
3.705
3.697
3.692
3.679
3.671
3.658
2.763
2.727
2.673
2.647
2.400
2.363
2.334
2.252
2.065
1.815
1.789
1.772
1.758
1.745
1.664
1.627
1.536
1.439

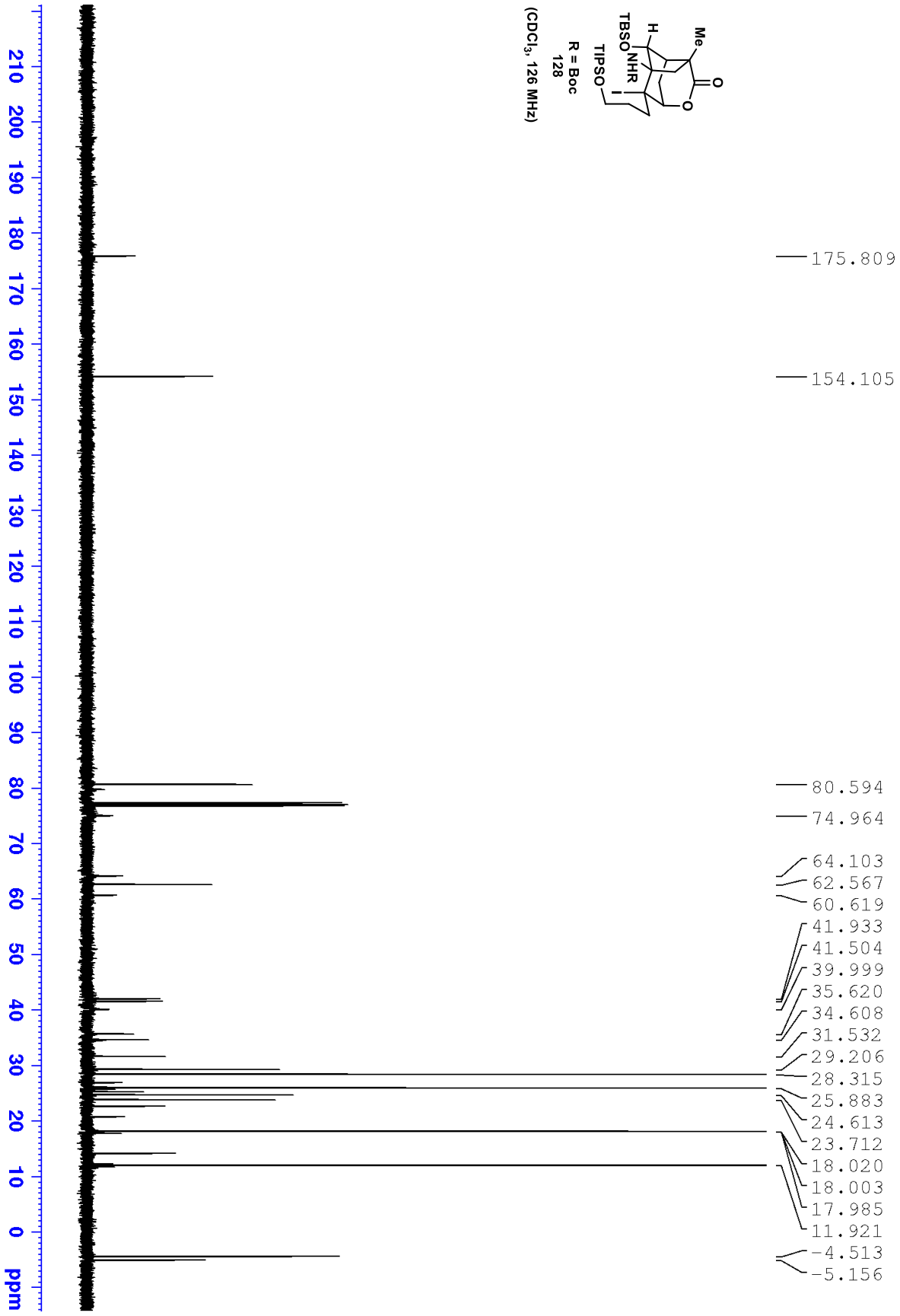

100
(CDCl3, 500 MHz)
Boc
N
O
Me
CN
5.276
3.798
3.788
3.778
3.772
3.763
3.754
3.075
3.044
3.007
2.956
2.924
2.852
2.764
2.739
2.707
2.625
2.601
2.477
2.440
2.347
2.319
2.270
2.256
1.724
1.567
1.449
0.91
1.00
1.18
2.02
0.95
0.98
1.20
1.20
1.16
0.83
3.46
8.82
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

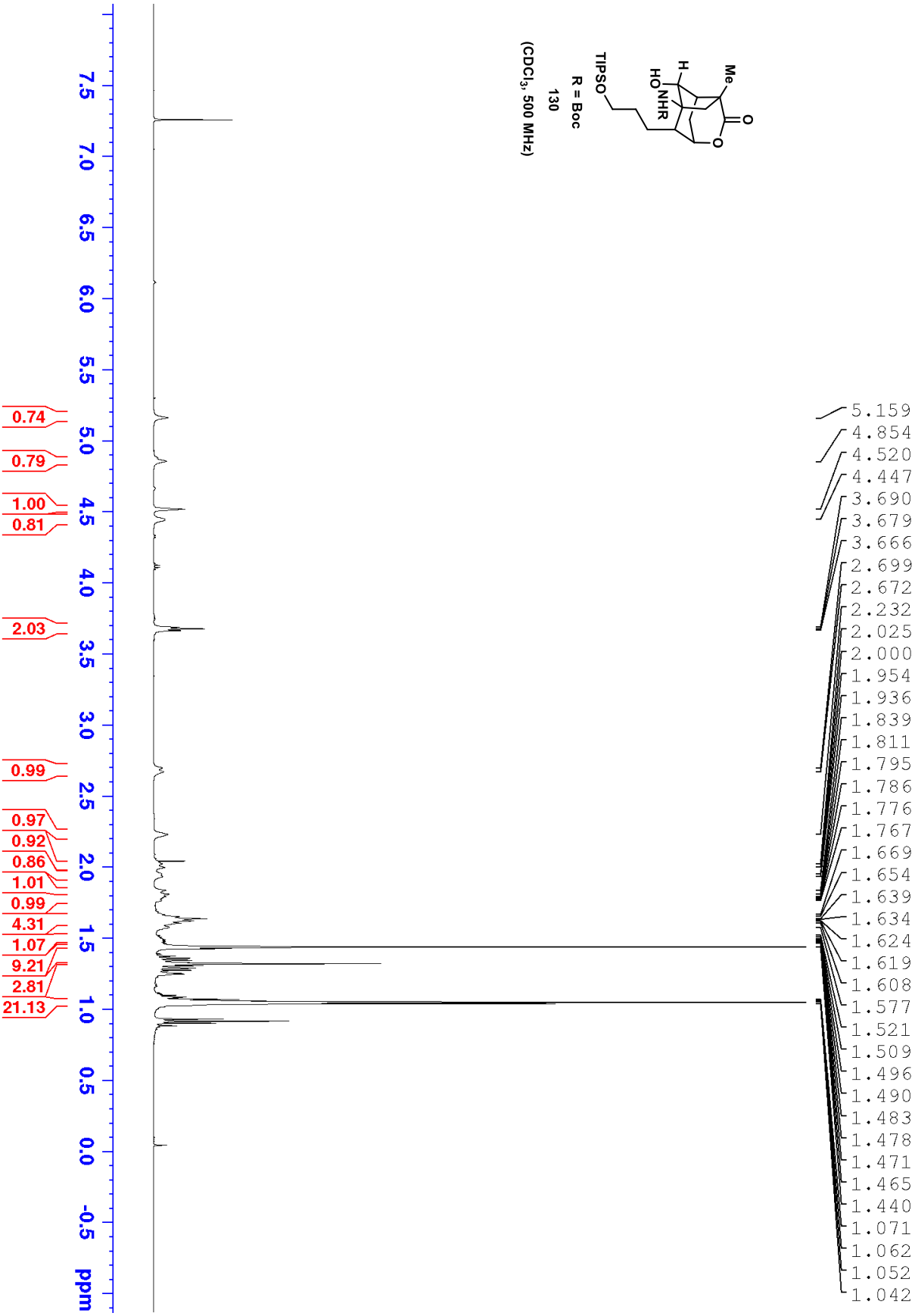

124
(CDCl3, 500 MHz)
Boc
N
O
Me
CONH2
5.540
5.115
3.794
3.768
3.149
3.125
2.783
2.748
2.680
2.644
2.405
2.397
2.335
2.322
2.274
2.169
2.144
1.707
1.594
1.460
1.77
1.00
0.92
1.77
1.00
0.90
1.05
2.23
1.07
1.37
2.86
9.47
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

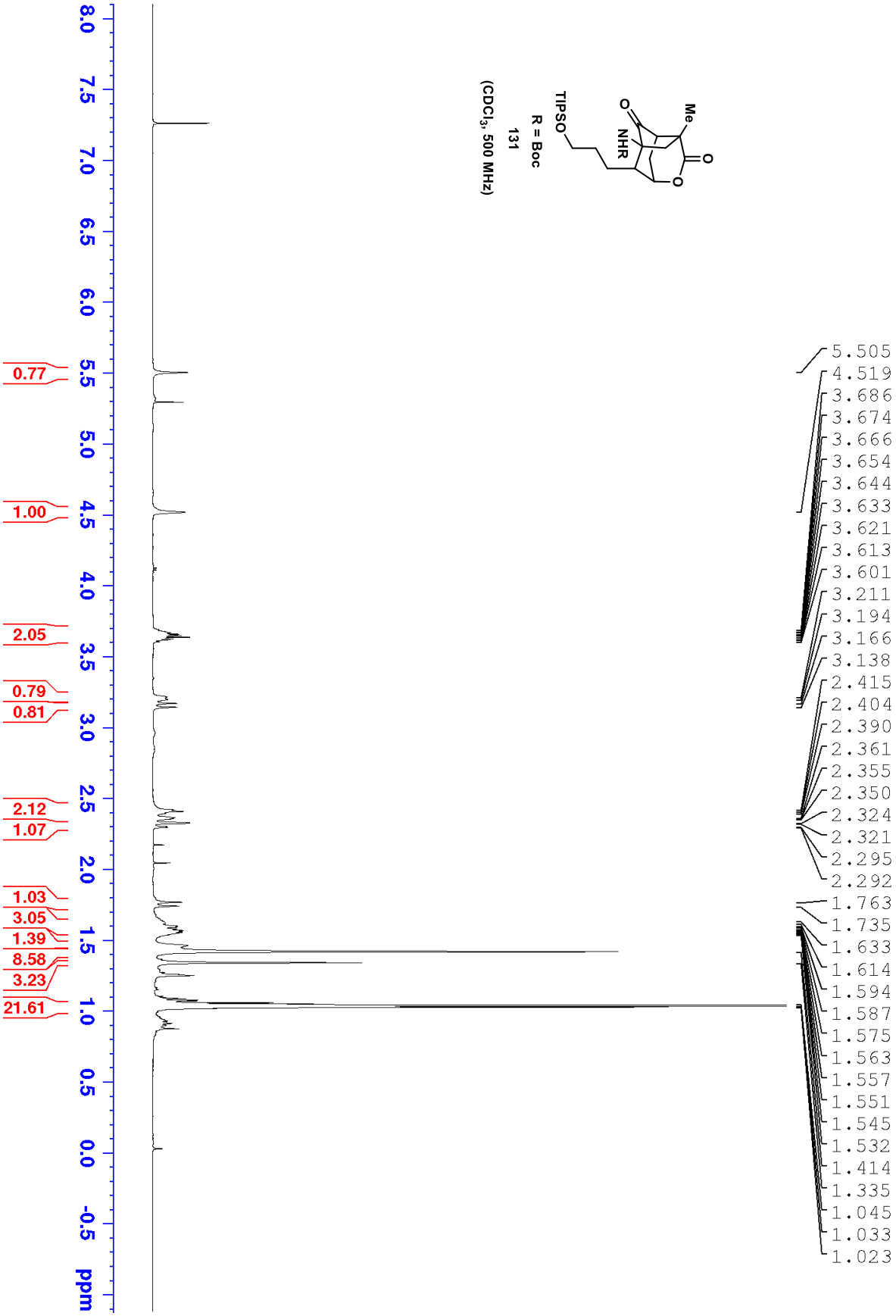

127
(CDCl3, 400 MHz)
TIPSO
TBSO
NHBoc
H
Me
CO2H
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
1.00
0.84
0.75
2.00
0.80
1.01
0.85
4.23
2.19
3.62
8.82
22.83
10.17
6.17
5.138
4.714
4.587
3.685
3.674
3.662
2.901
2.876
2.384
2.350
2.214
2.189
2.045
2.018
1.987
1.655
1.641
1.627
1.477
1.419
1.055
1.037
1.028
0.860
0.080
0.061

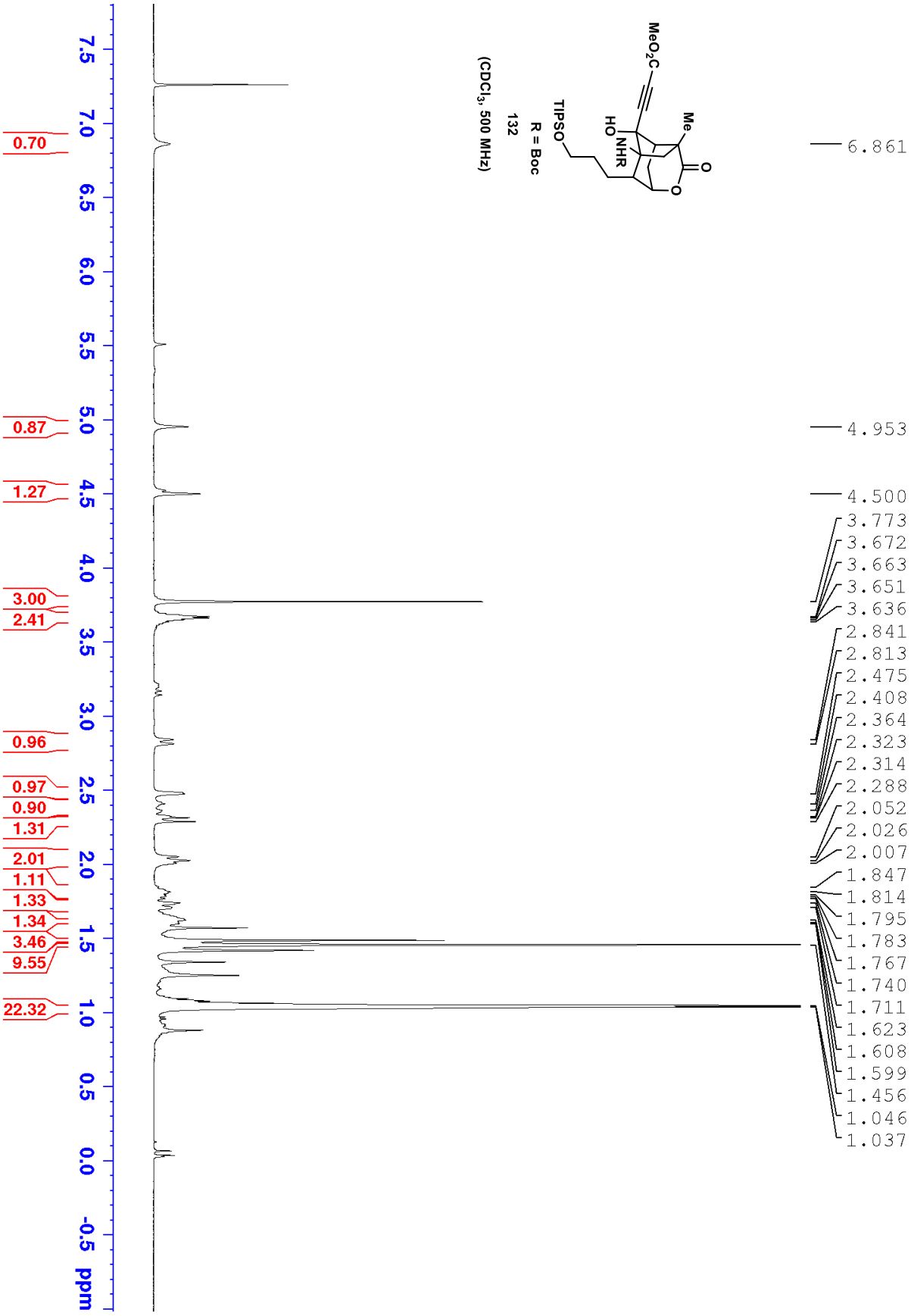

127
(CDCl3, 100 MHz)
TIPSO
TBSO
NHBoc
H
Me
CO2H
182.095
154.805
139.155
119.000
78.786
72.947
68.003
63.317
62.849
47.618
46.856
42.816
32.088
29.480
27.677
26.619
25.718
25.667
18.002
17.973
11.951
-4.753
-4.947
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

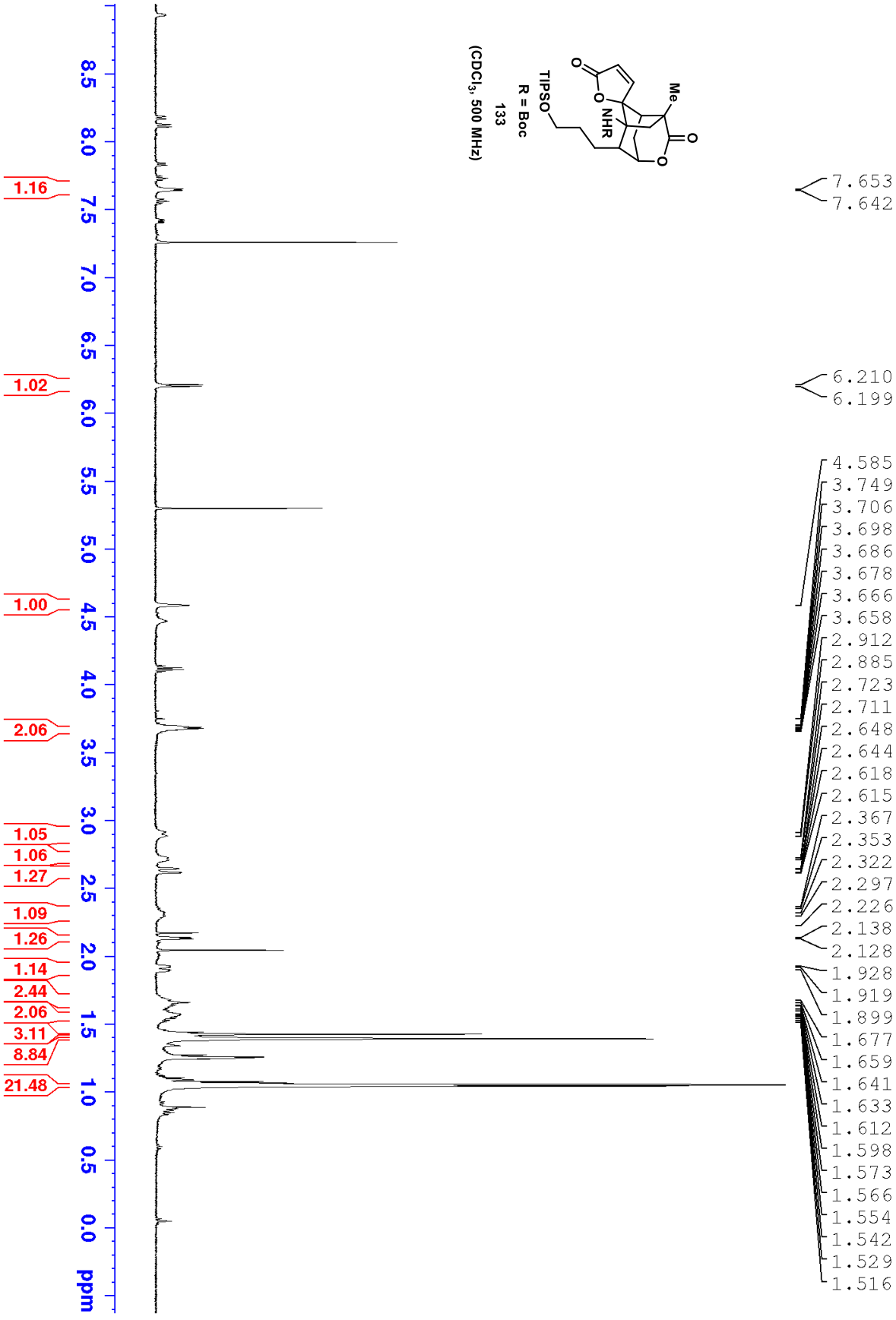

TBSO
NHR
H
Me
TIPSO
O
O
R = Boc
128
(CDCl3, 500 MHz)
4.932
4.860
4.463
3.785
3.775
3.765
3.754
3.717
3.706
3.692
2.945
2.917
2.583
2.554
2.448
2.015
1.989
1.966
1.917
1.779
1.771
1.746
1.412
1.308
1.055
1.039
1.029
0.950
0.173
0.102
0.99
1.05
0.83
1.02
1.08
1.00
0.97
0.76
2.33
1.97
2.62
9.15
3.25
22.39
9.65
6.61
ppm

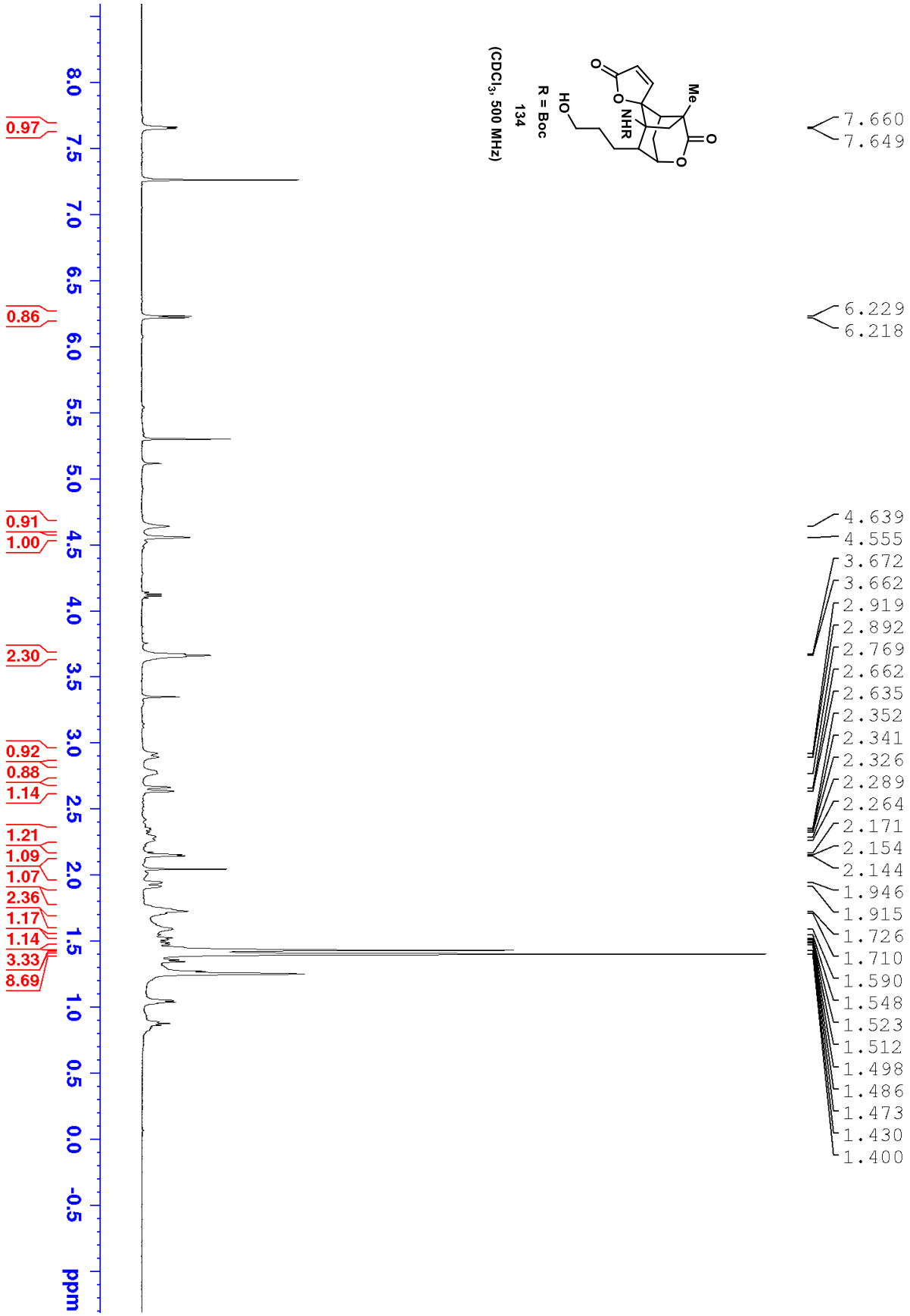

R = Boc
128
(CDCl3, 126 MHz)
TIPSO
TBSO
NHR
H
Me
O
O
O
175.809
154.105
80.594
74.964
64.103
62.567
60.619
41.933
41.504
39.999
35.620
34.608
31.532
29.206
28.315
25.883
24.613
23.712
18.020
18.003
17.985
11.921
-4.513
-5.156
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

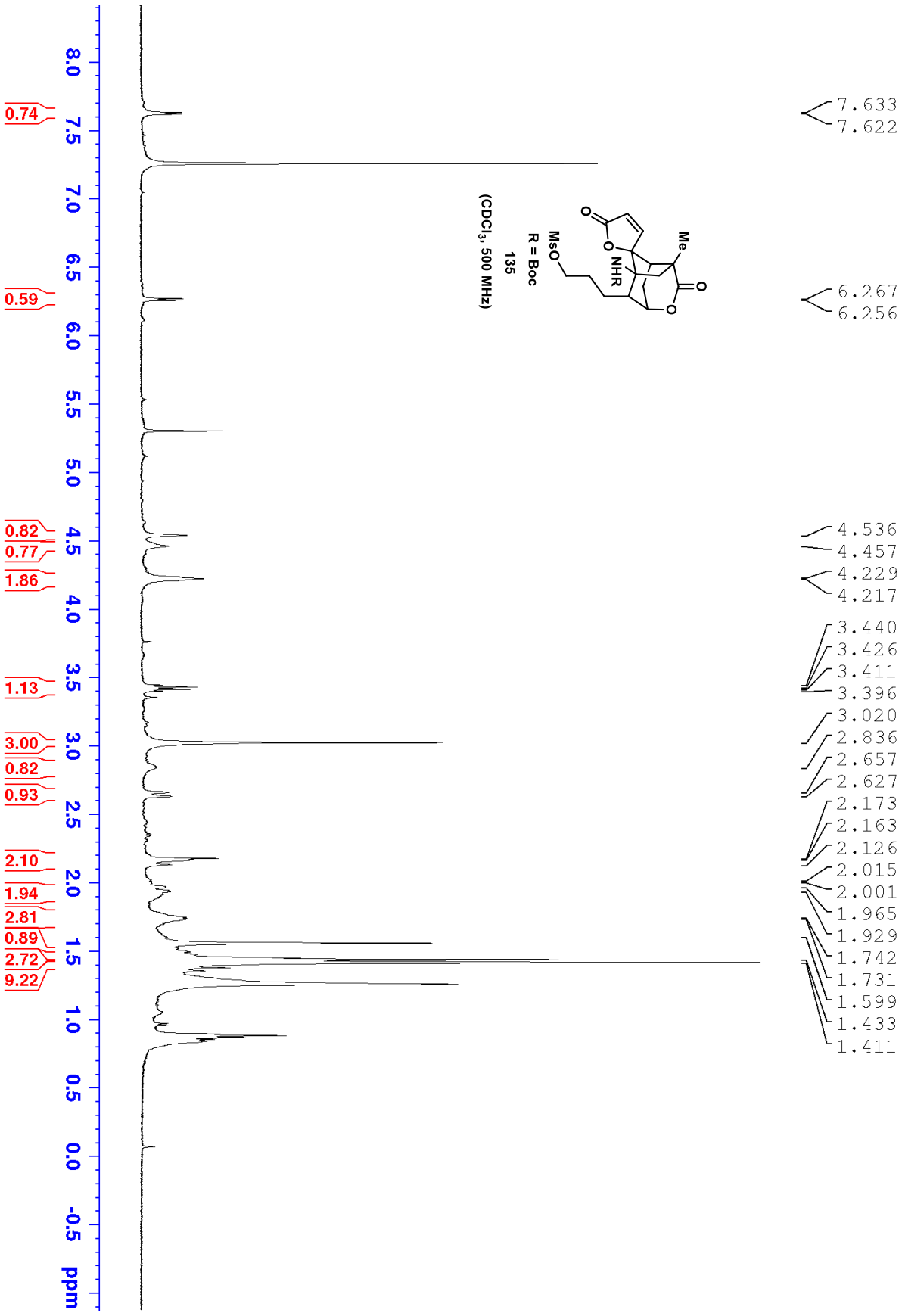

TIPSO
HO
NHR
H
Me
O
O
R = Boc
130
(CDCl3, 500 MHz)
0.74
0.79
1.00
0.81
2.03
0.99
0.97
0.92
0.86
1.01
0.99
4.31
1.07
9.21
2.81
21.13
5.159
4.854
4.520
4.447
3.690
3.679
3.666
2.699
2.672
2.232
2.025
2.000
1.954
1.936
1.839
1.811
1.795
1.786
1.776
1.767
1.669
1.654
1.639
1.634
1.624
1.619
1.608
1.577
1.521
1.509
1.496
1.490
1.483
1.478
1.471
1.465
1.440
1.071
1.062
1.052
1.042
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
ppm

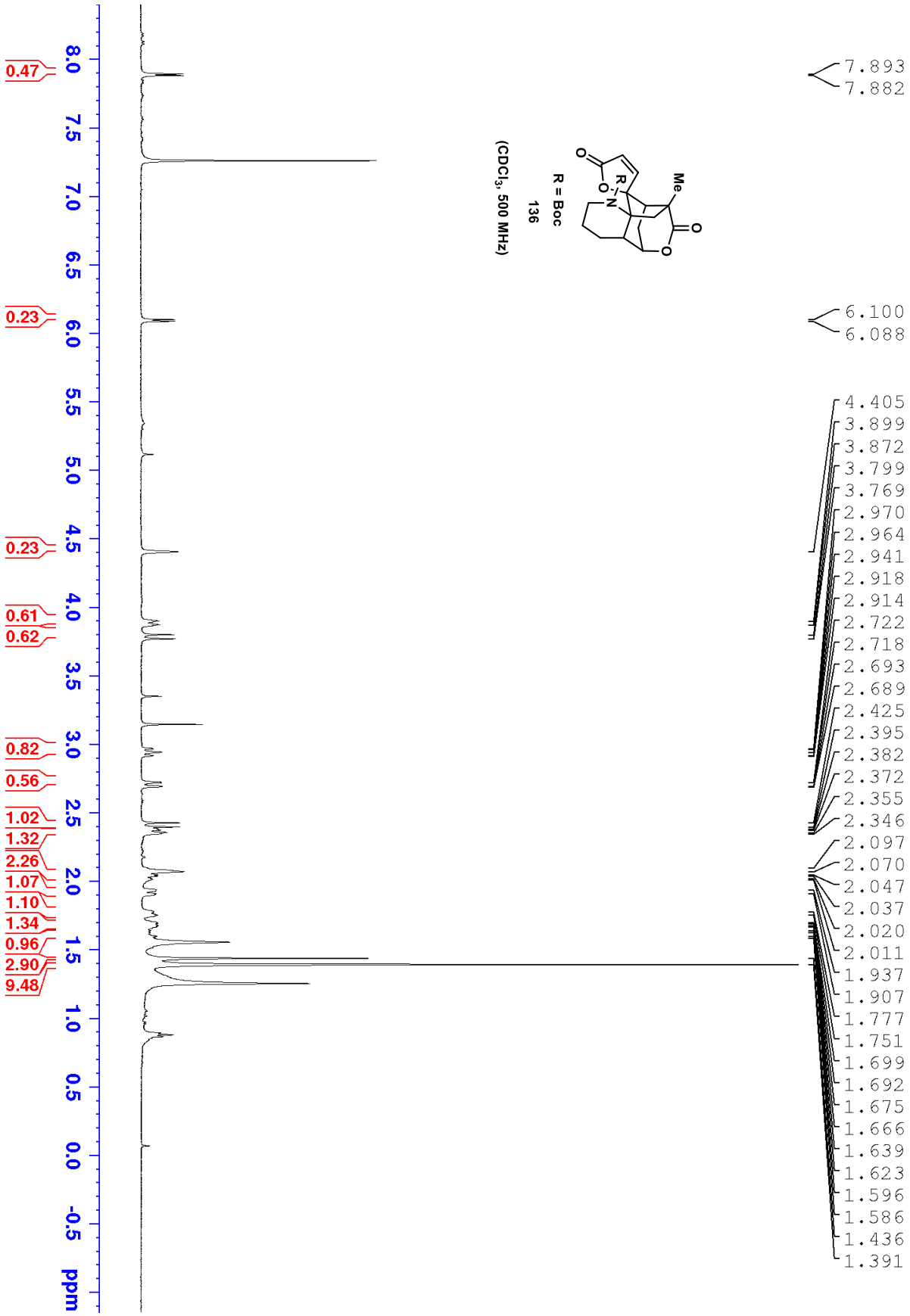

TIPSO
NHR
O
O
Me
O
O
R = Boc
131
(CDCl3, 500 MHz)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
0.77
1.00
2.05
0.79
0.81
2.12
1.07
1.03
3.05
1.39
8.58
3.23
21.61
5.505
4.519
3.686
3.674
3.666
3.654
3.644
3.633
3.621
3.613
3.601
3.211
3.194
3.166
3.138
2.415
2.404
2.390
2.361
2.355
2.350
2.324
2.321
2.295
2.292
1.763
1.735
1.633
1.614
1.594
1.587
1.575
1.563
1.557
1.551
1.545
1.532
1.414
1.335
1.045
1.033
1.023

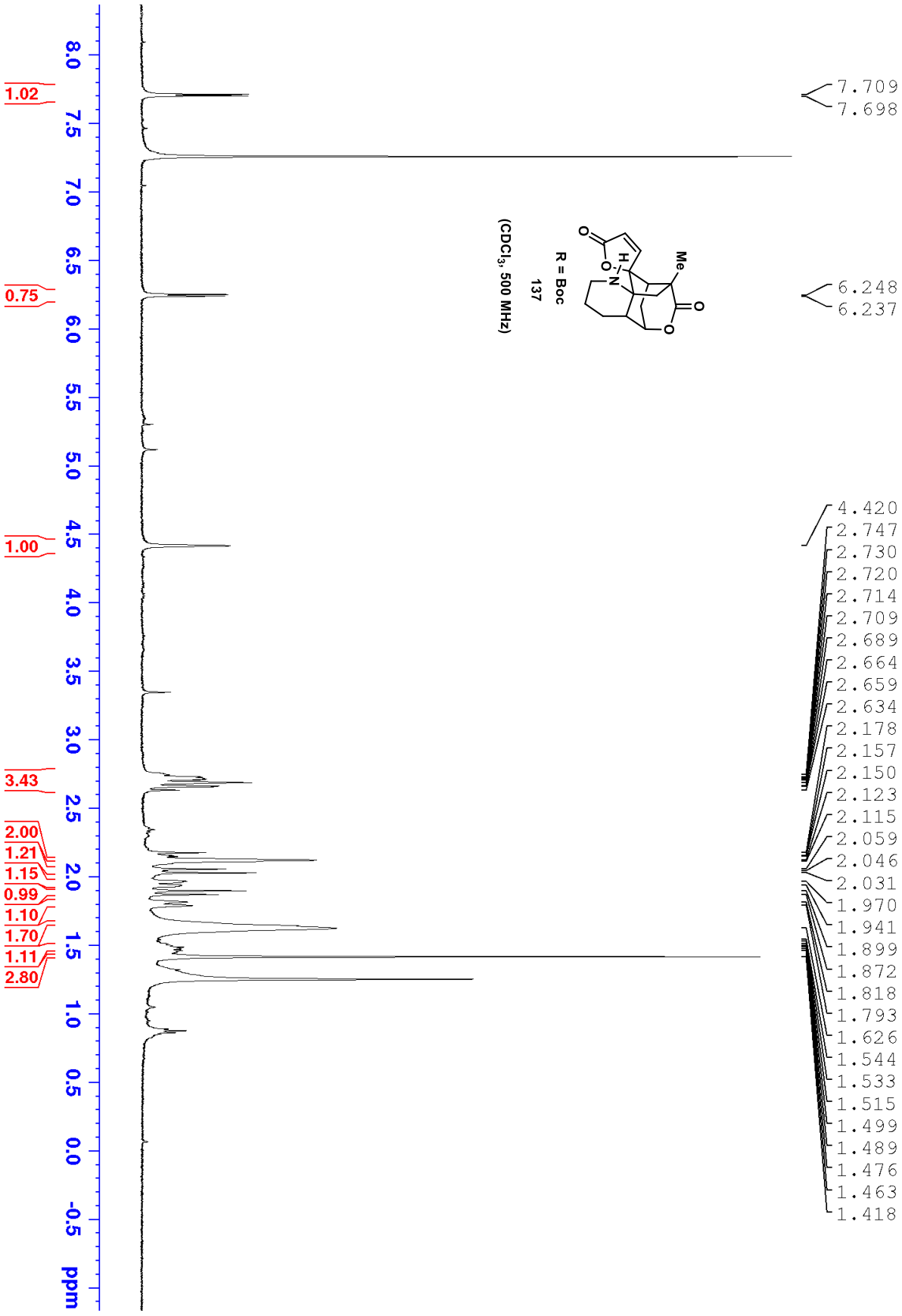

132
R = Boc
(CDCl3, 500 MHz)
TIPSO
HO
NHR
MeO2C
Me
O
O
6.861
4.953
4.500
3.773
3.672
3.663
3.651
3.636
2.841
2.813
2.475
2.408
2.364
2.323
2.314
2.288
2.052
2.026
2.007
1.847
1.814
1.795
1.783
1.767
1.740
1.711
1.623
1.608
1.599
1.456
1.046
1.037
0.70
0.87
1.27
3.00
2.41
0.96
0.97
0.90
1.31
2.01
1.11
1.33
1.34
3.46
9.55
22.32
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
ppm

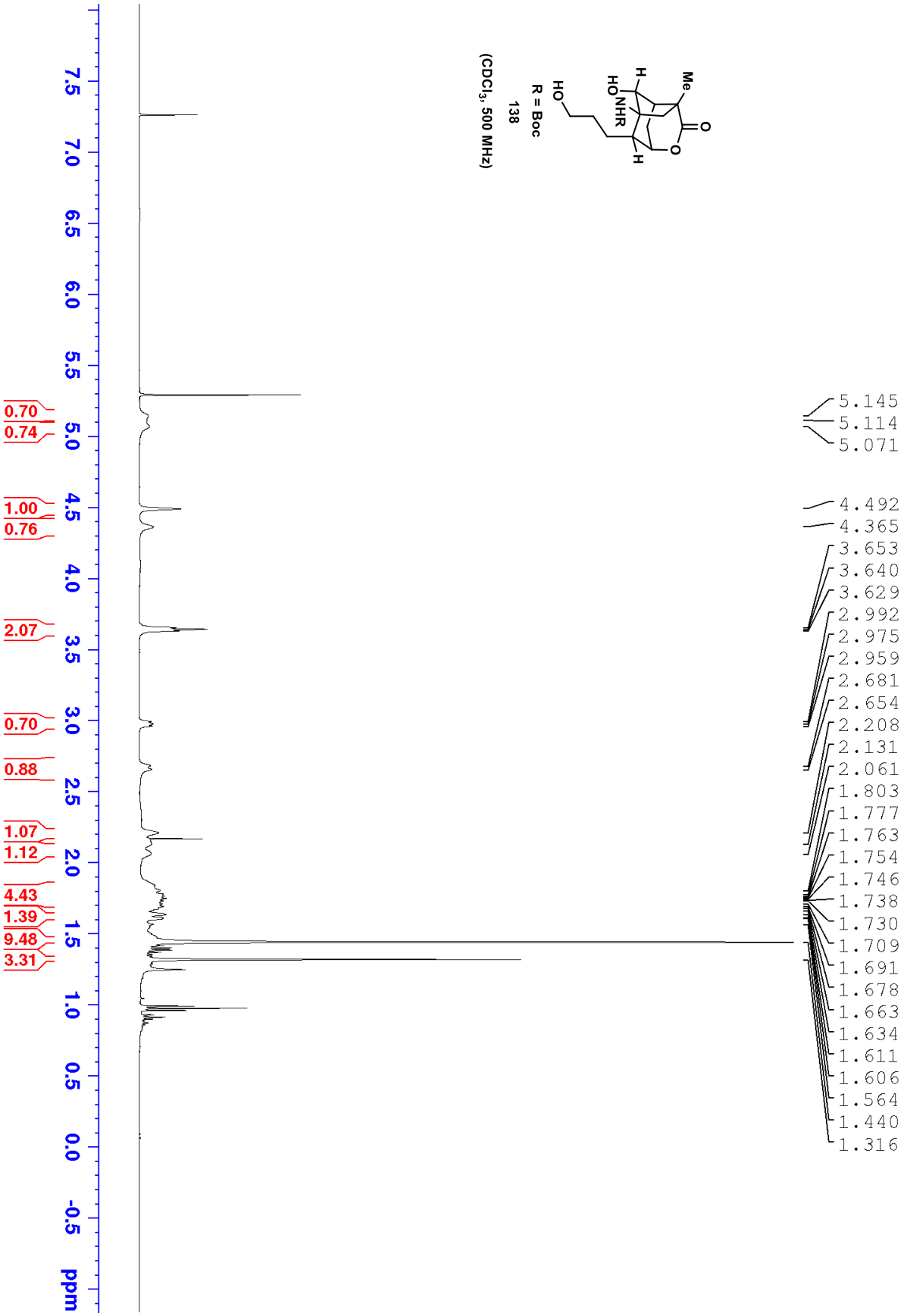

133
(CDCl3, 500 MHz)
R = Boc
TIPSO
NHR
Me
7.653
7.642
6.210
6.199
4.585
3.749
3.706
3.698
3.686
3.678
3.666
3.658
2.912
2.885
2.723
2.711
2.648
2.644
2.618
2.615
2.367
2.353
2.322
2.297
2.226
2.138
2.128
1.928
1.919
1.899
1.677
1.659
1.641
1.633
1.612
1.598
1.573
1.566
1.554
1.542
1.529
1.516
1.16
1.02
1.00
2.06
1.05
1.06
1.27
1.09
1.26
1.14
2.44
2.06
3.11
8.84
21.48
ppm

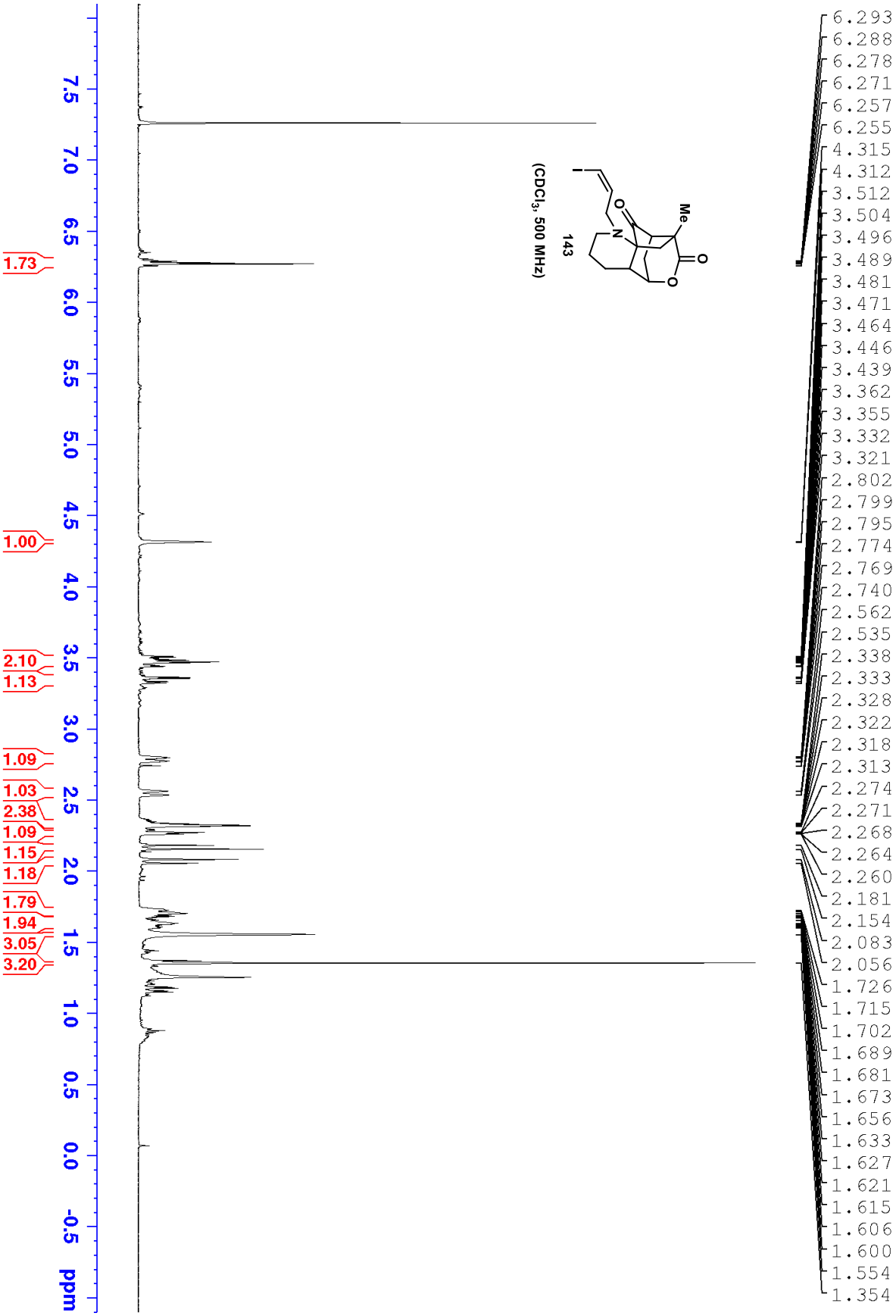

134
R = Boc
(CDCl3, 500 MHz)
HO
NHR
Me
O
O
O
O
O
7.660
7.649
6.229
6.218
4.639
4.555
3.672
3.662
2.919
2.892
2.769
2.662
2.635
2.352
2.341
2.326
2.289
2.264
2.171
2.154
2.144
1.946
1.915
1.726
1.710
1.590
1.548
1.523
1.512
1.498
1.486
1.473
1.430
1.400
0.97
0.86
0.91
1.00
2.30
0.92
0.88
1.14
1.21
1.09
1.07
2.36
1.17
1.14
3.33
8.69
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
ppm

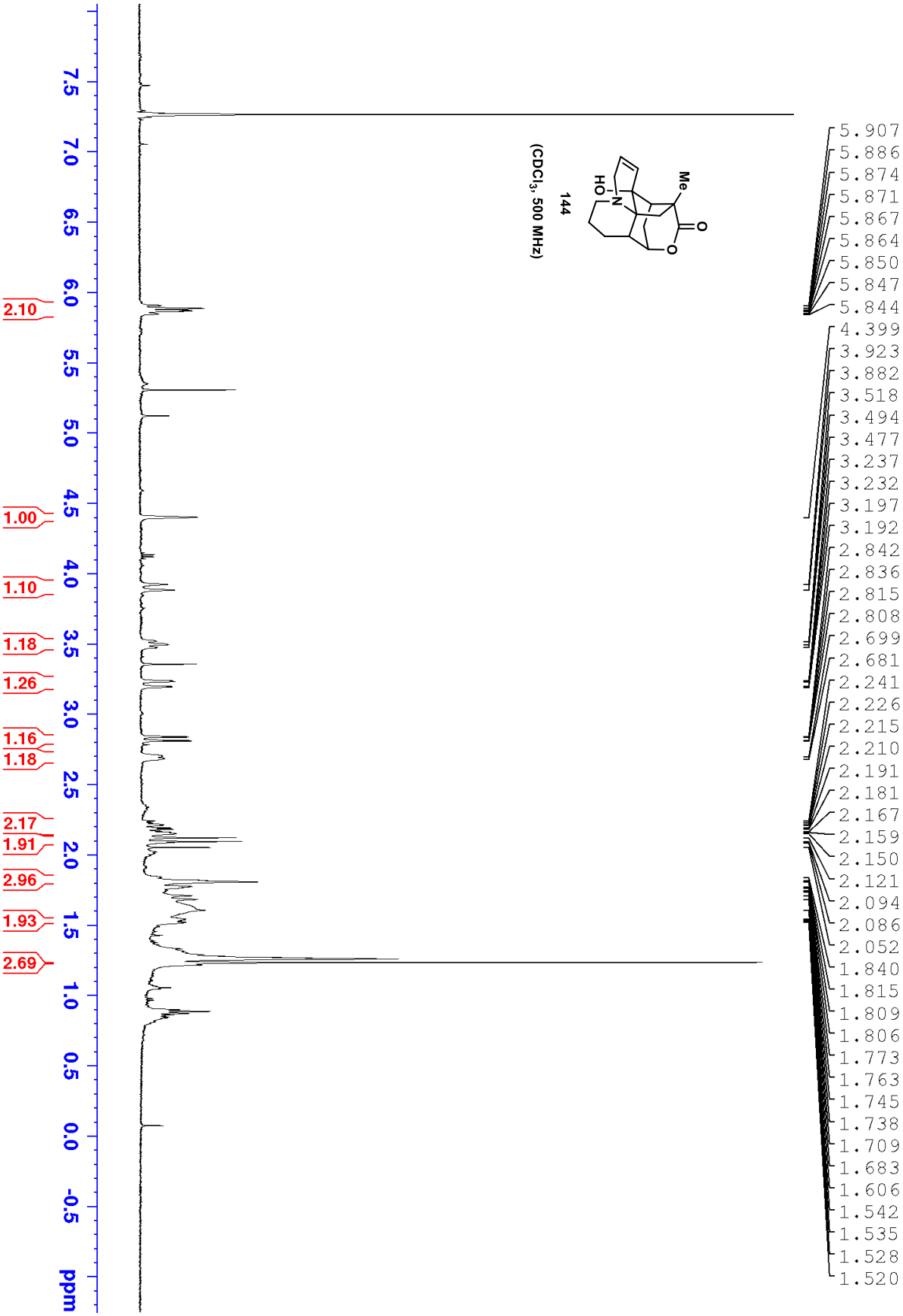

135
R = Boc
(CDCl3, 500 MHz)
MsO
NHR
Me
O
O
O
O
O
O
7.633
7.622
6.267
6.256
4.536
4.457
4.229
4.217
3.440
3.426
3.411
3.396
3.020
2.836
2.657
2.627
2.173
2.163
2.126
2.015
2.001
1.965
1.929
1.742
1.731
1.599
1.433
1.411
0.74
0.59
0.82
0.77
1.86
1.13
3.00
0.82
0.93
2.10
1.94
2.81
0.89
2.72
9.22
8.0
7.5
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
ppm

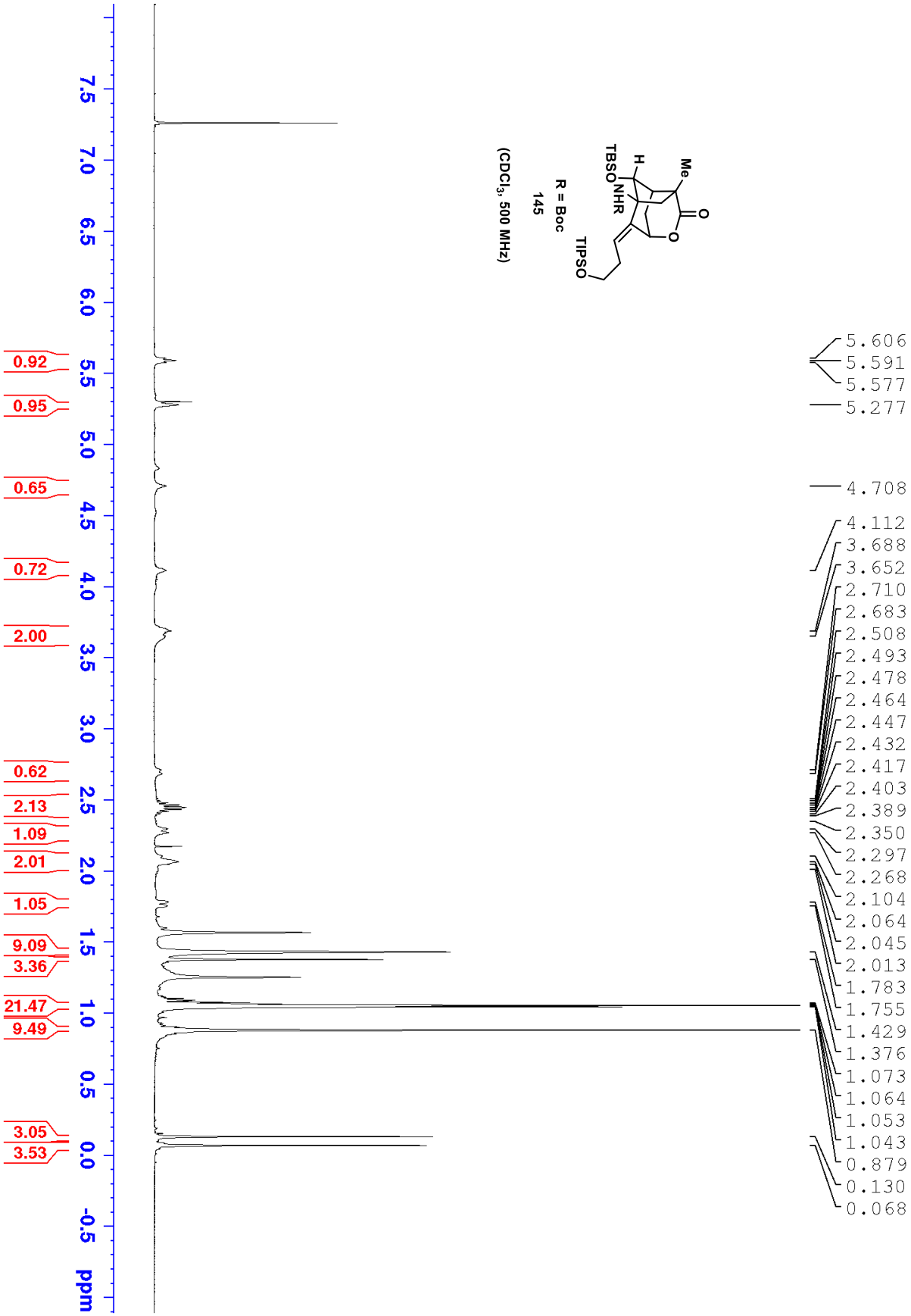

136
R = Boc
(CDCl3, 500 MHz)
Me
7.893
7.882
6.100
6.088
4.405
3.899
3.872
3.799
3.769
2.970
2.964
2.941
2.918
2.914
2.722
2.718
2.693
2.689
2.425
2.395
2.382
2.372
2.355
2.346
2.097
2.070
2.047
2.037
2.020
2.011
1.937
1.907
1.777
1.751
1.699
1.692
1.675
1.666
1.639
1.623
1.596
1.586
1.436
1.391
0.47
0.23
0.23
0.61
0.62
0.82
0.56
1.02
1.32
2.26
1.07
1.10
1.34
0.96
2.90
9.48
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
ppm

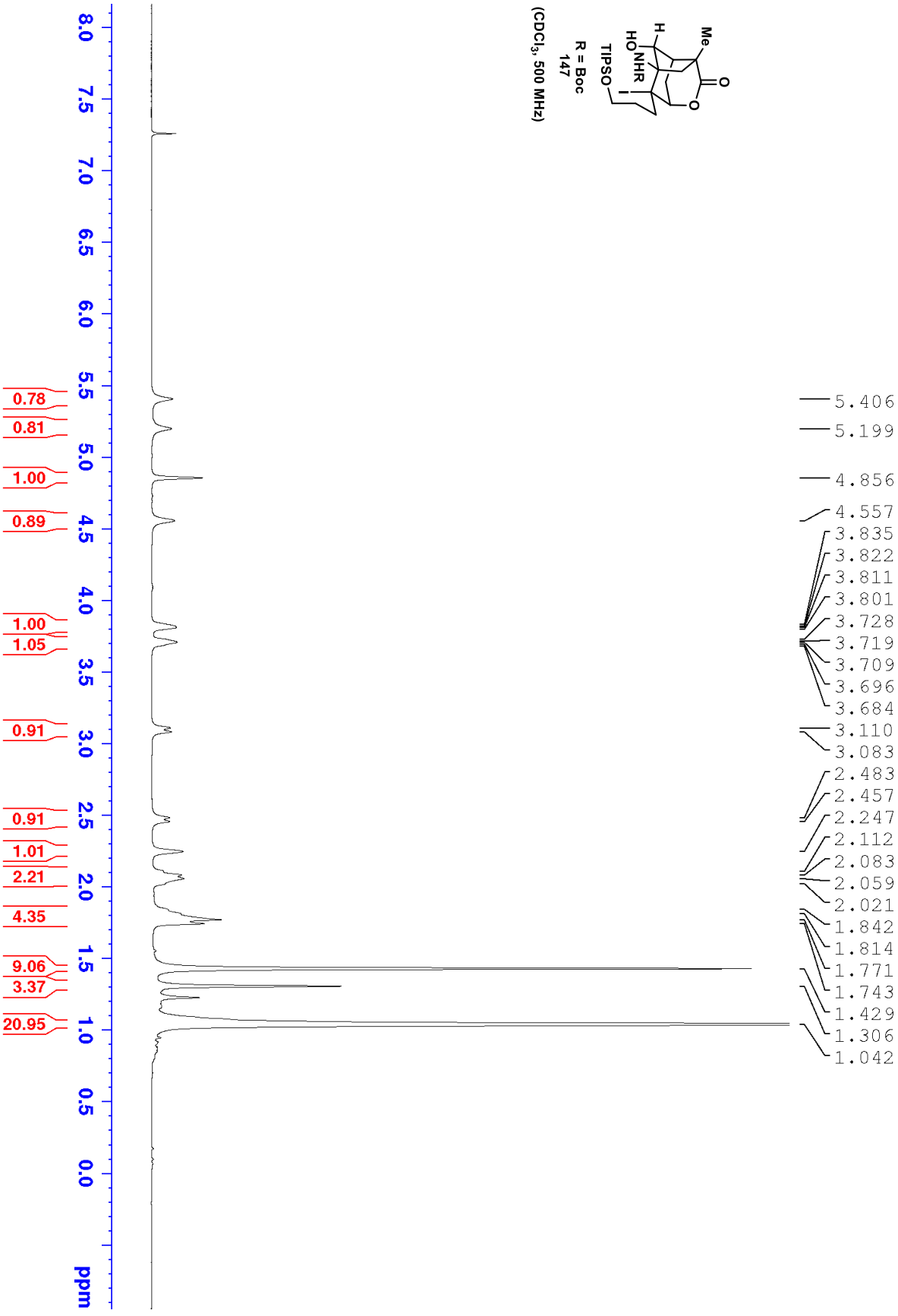

7.709
7.698
6.248
6.237
4.420
2.747
2.730
2.720
2.714
2.709
2.689
2.664
2.659
2.634
2.178
2.157
2.150
2.123
2.115
2.059
2.046
2.031
1.970
1.941
1.899
1.872
1.818
1.793
1.626
1.544
1.533
1.515
1.499
1.489
1.476
1.463
1.418
1.02
0.75
1.00
3.43
2.00
1.21
1.15
0.99
1.10
1.70
1.11
2.80
8.0
7.5
7.0
6.5
6.0
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
ppm
(CDCl3, 500 MHz)
R = Boc
137
Me

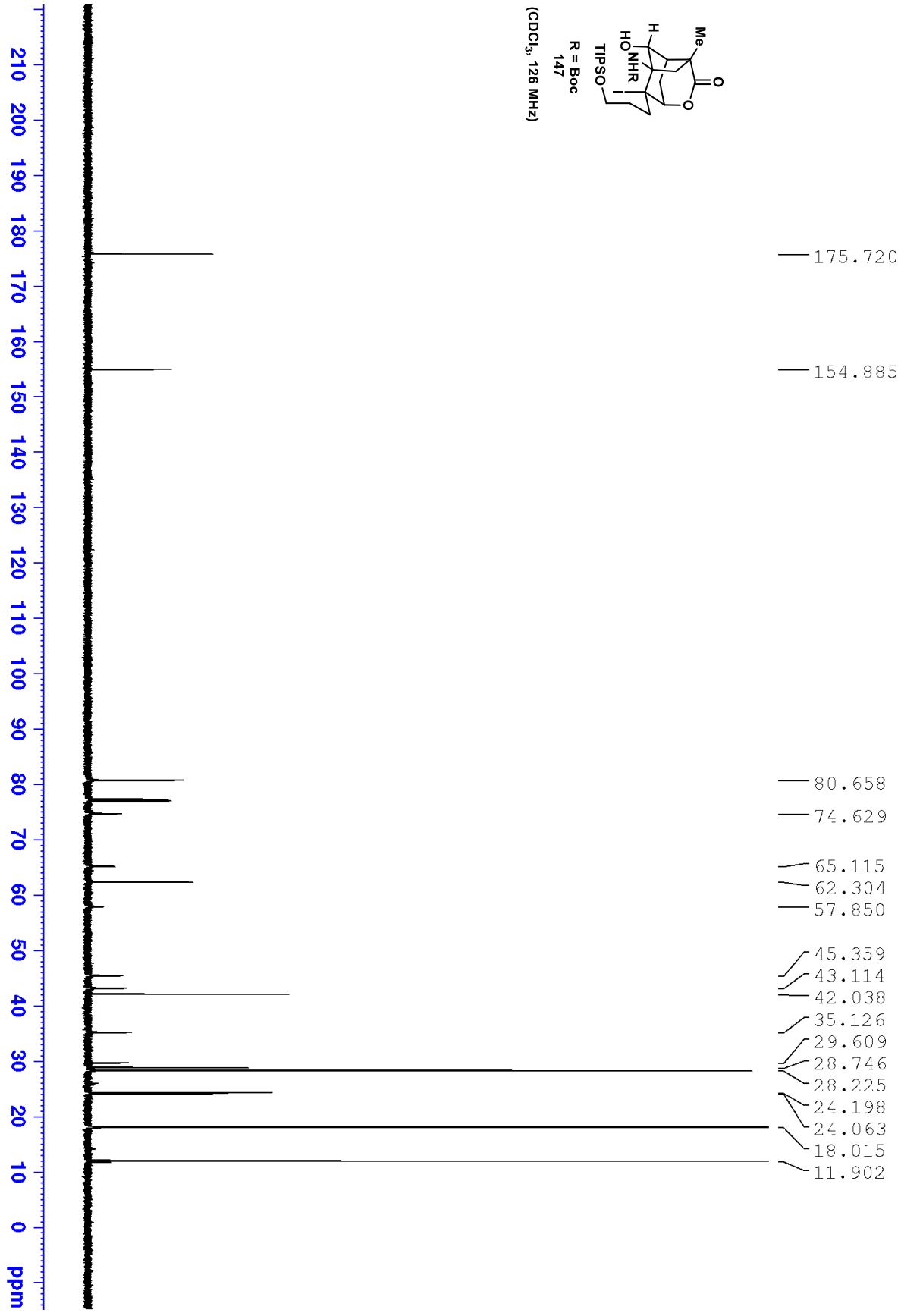

138
R = Boc
(CDCl3, 500 MHz)
HO
HO
NHR
H
H
Me
O
O
5.145
5.114
5.071
4.492
4.365
3.653
3.640
3.629
2.992
2.975
2.959
2.681
2.654
2.208
2.131
2.061
1.803
1.777
1.763
1.754
1.746
1.738
1.730
1.709
1.691
1.678
1.663
1.634
1.611
1.606
1.564
1.440
1.316
0.70
0.74
1.00
0.76
2.07
0.70
0.88
1.07
1.12
4.43
1.39
9.48
3.31
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
ppm

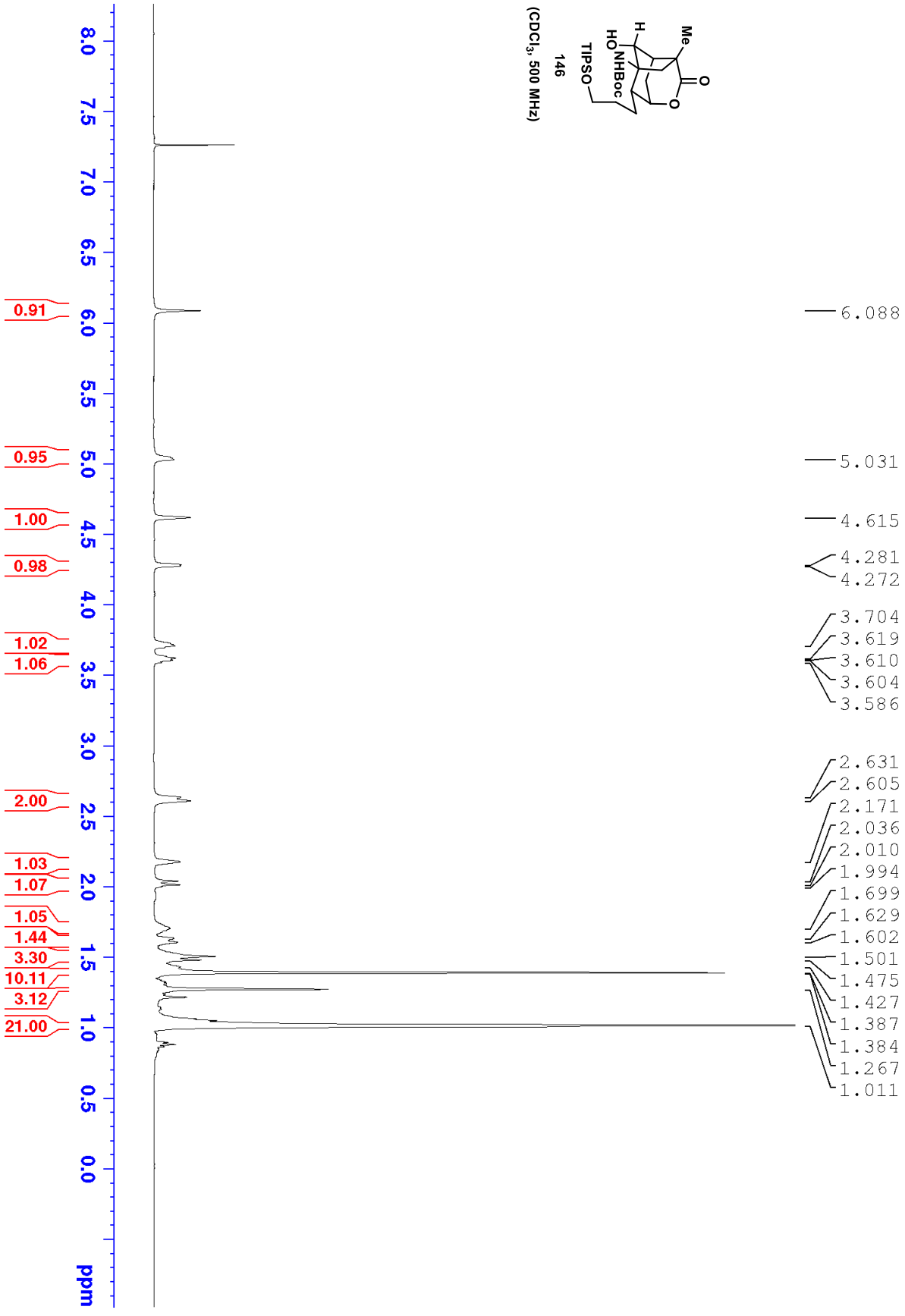

143
(CDCl3, 500 MHz)
Me
O
N
O
O
O
1.73
1.00
2.10
1.13
1.09
1.03
2.38
1.09
1.15
1.18
1.79
1.94
3.05
3.20
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
6.293
6.288
6.278
6.271
6.257
6.255
4.315
4.312
3.512
3.504
3.496
3.489
3.481
3.471
3.464
3.446
3.439
3.362
3.355
3.332
3.321
2.802
2.799
2.795
2.774
2.769
2.740
2.562
2.535
2.338
2.333
2.328
2.322
2.318
2.313
2.274
2.271
2.268
2.264
2.260
2.181
2.154
2.083
2.056
1.726
1.715
1.702
1.689
1.681
1.673
1.656
1.633
1.627
1.621
1.615
1.606
1.600
1.554
1.354

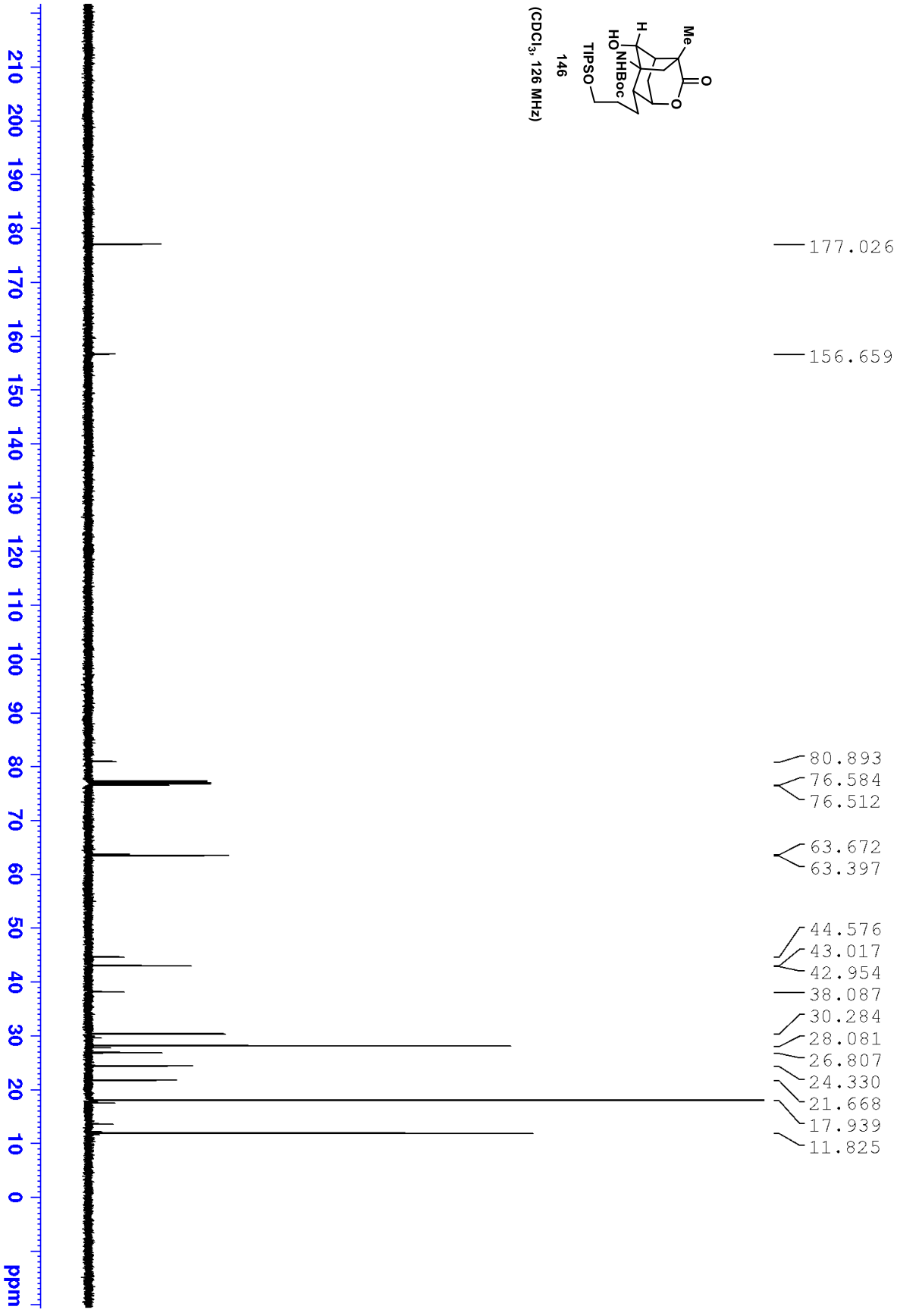

144
(CDCl3, 500 MHz)
Me
HO
N
O
O
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
2.10
1.00
1.10
1.18
1.26
1.16
1.18
2.17
1.91
2.96
1.93
2.69
5.907
5.886
5.874
5.871
5.867
5.864
5.850
5.847
5.844
4.399
3.923
3.882
3.518
3.494
3.477
3.237
3.232
3.197
3.192
2.842
2.836
2.815
2.808
2.699
2.681
2.241
2.226
2.215
2.210
2.191
2.181
2.167
2.159
2.150
2.121
2.094
2.086
2.052
1.840
1.815
1.809
1.806
1.773
1.763
1.745
1.738
1.709
1.683
1.606
1.542
1.535
1.528
1.520

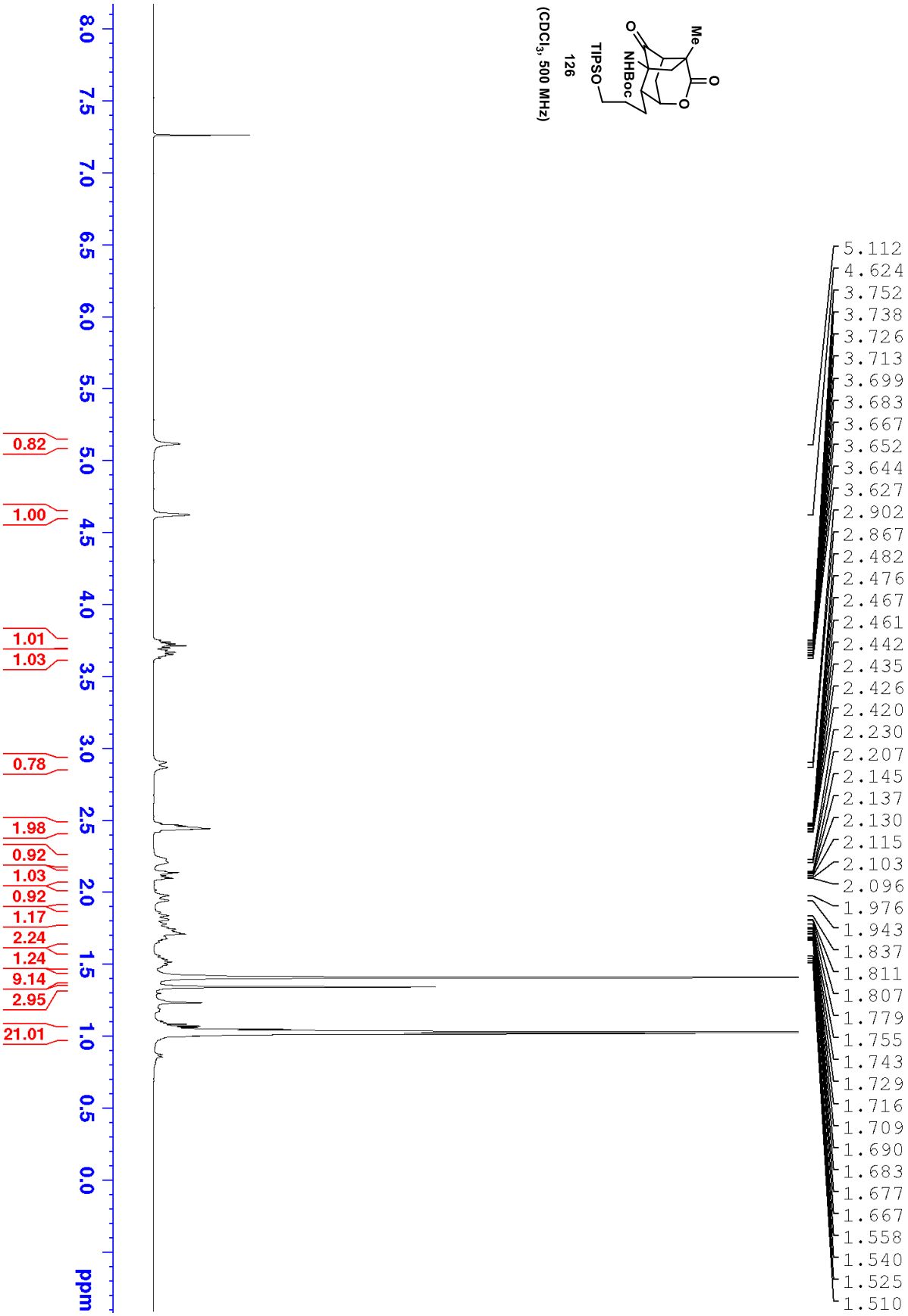

(CDCl3, 500 MHz)
R = Boc
145
TIPSO
TBSO
NHR
H
Me
O
O
5.606
5.591
5.577
5.277
4.708
4.112
3.688
3.652
2.710
2.683
2.508
2.493
2.478
2.464
2.447
2.432
2.417
2.403
2.389
2.350
2.297
2.268
2.104
2.064
2.045
2.013
1.783
1.755
1.429
1.376
1.073
1.064
1.053
1.043
0.879
0.130
0.068
0.92
0.95
0.65
0.72
2.00
0.62
2.13
1.09
2.01
1.05
9.09
3.36
21.47
9.49
3.05
3.53
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
ppm

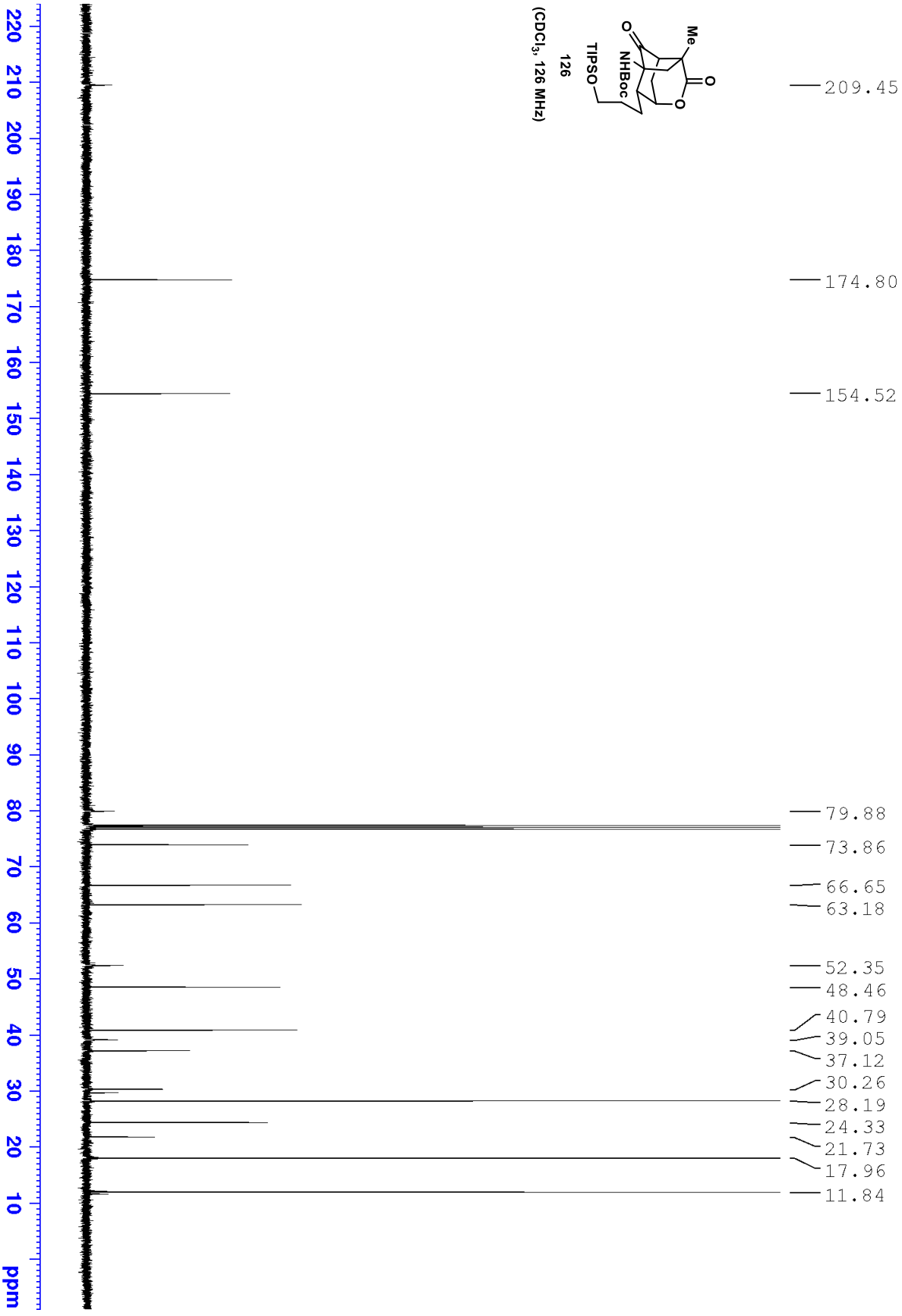

R = Boc
147
(CDCl3, 500 MHz)
TIPSO
HO
NHR
H
Me
O
O
O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.78
0.81
1.00
0.89
1.00
1.05
0.91
0.91
1.01
2.21
4.35
9.06
3.37
20.95
5.406
5.199
4.856
4.557
3.835
3.822
3.811
3.801
3.728
3.719
3.709
3.696
3.684
3.110
3.083
2.483
2.457
2.247
2.112
2.083
2.059
2.021
1.842
1.814
1.771
1.743
1.429
1.306
1.042

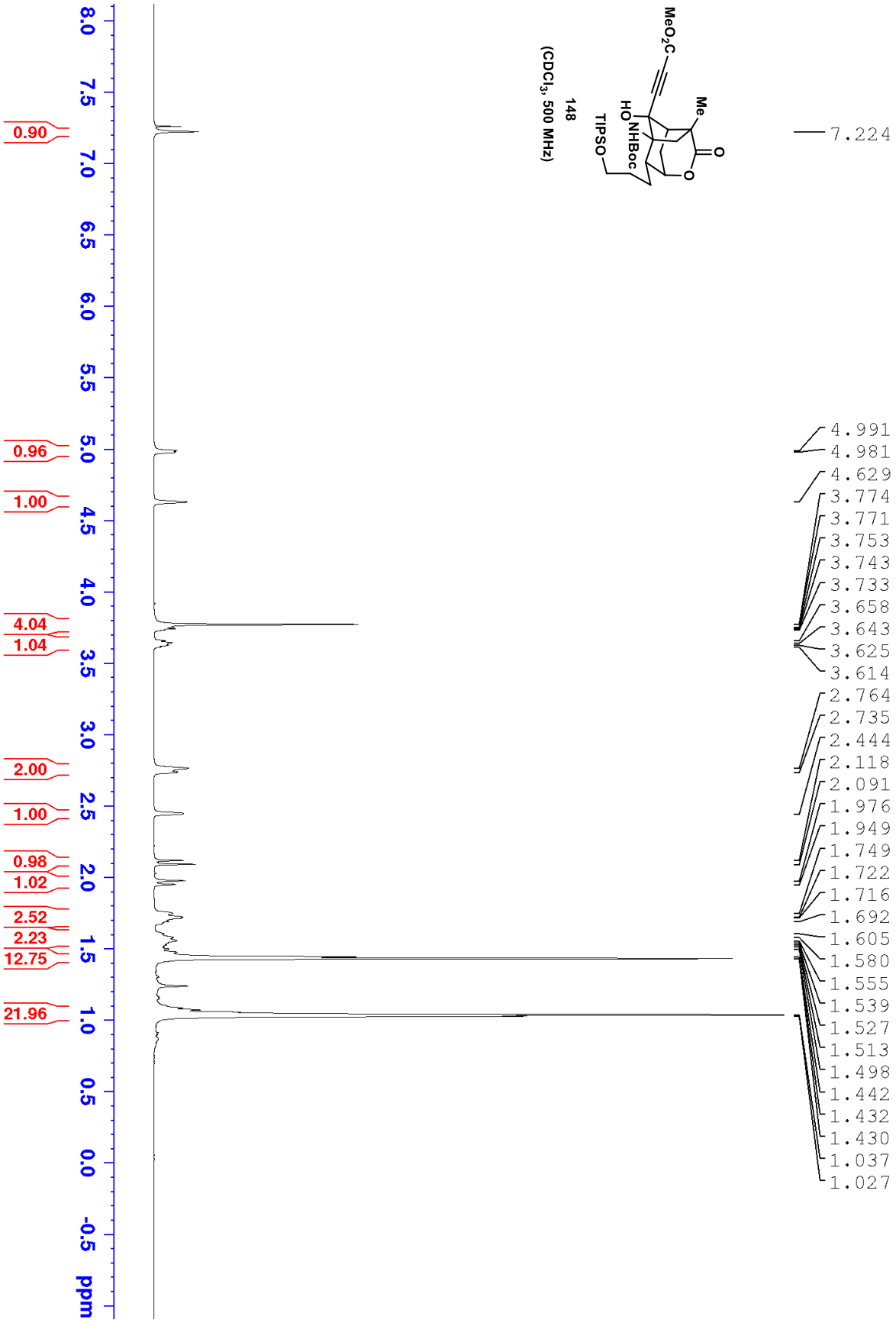

147
R = Boc
(CDCl3, 126 MHz)
TIPSO
HO
NHR
H
Me
O
O
O
175.720
154.885
80.658
74.629
65.115
62.304
57.850
45.359
43.114
42.038
35.126
29.609
28.746
28.225
24.198
24.063
18.015
11.902
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

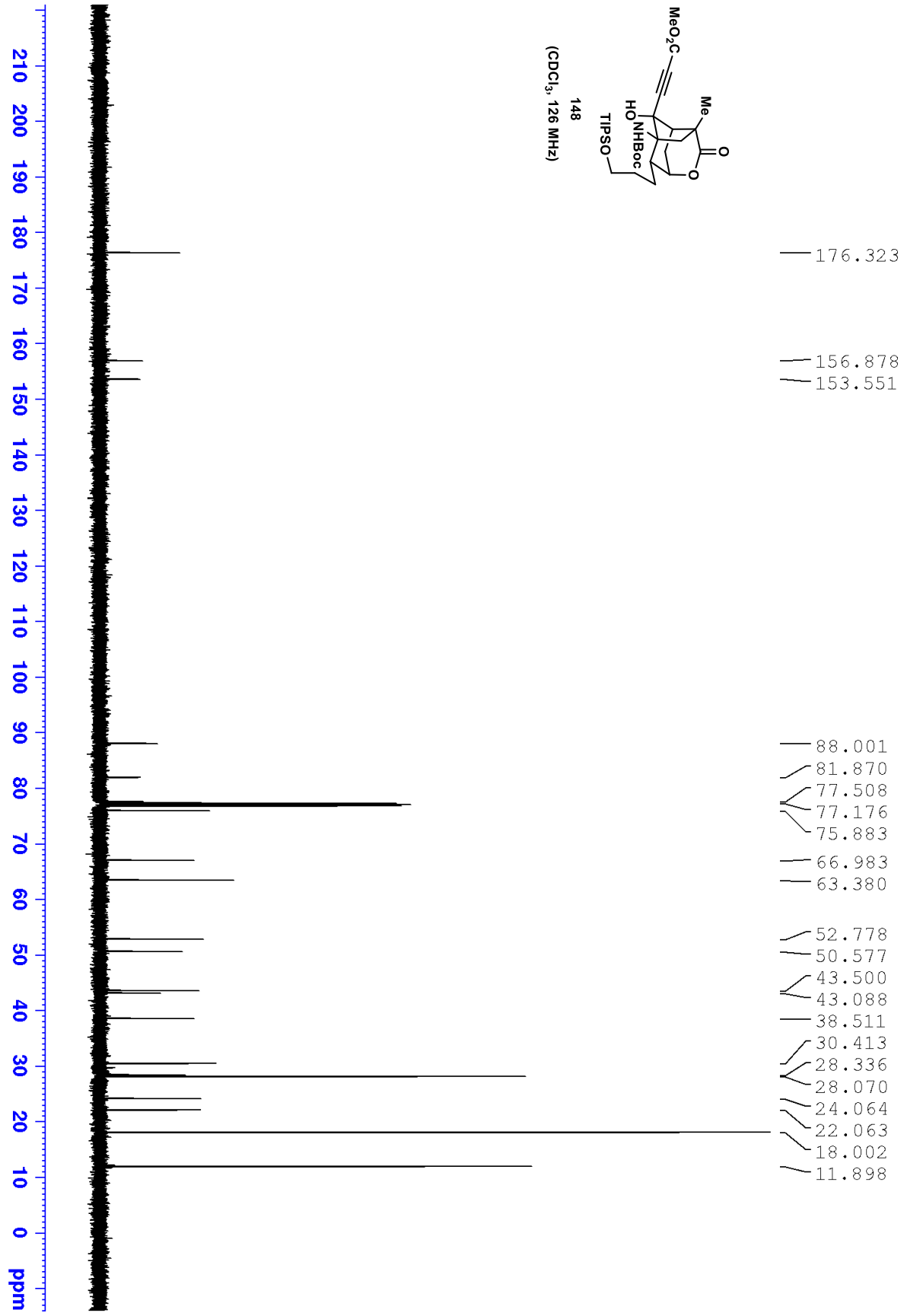

146
(CDCl3, 500 MHz)
TIPSO
HO
NHBoc
H
Me
O
O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.91
0.95
1.00
0.98
1.02
1.06
2.00
1.03
1.07
1.05
1.44
3.30
10.11
3.12
21.00
6.088
5.031
4.615
4.281
4.272
3.704
3.619
3.610
3.604
3.586
2.631
2.605
2.171
2.036
2.010
1.994
1.699
1.629
1.602
1.501
1.475
1.427
1.387
1.384
1.267
1.011

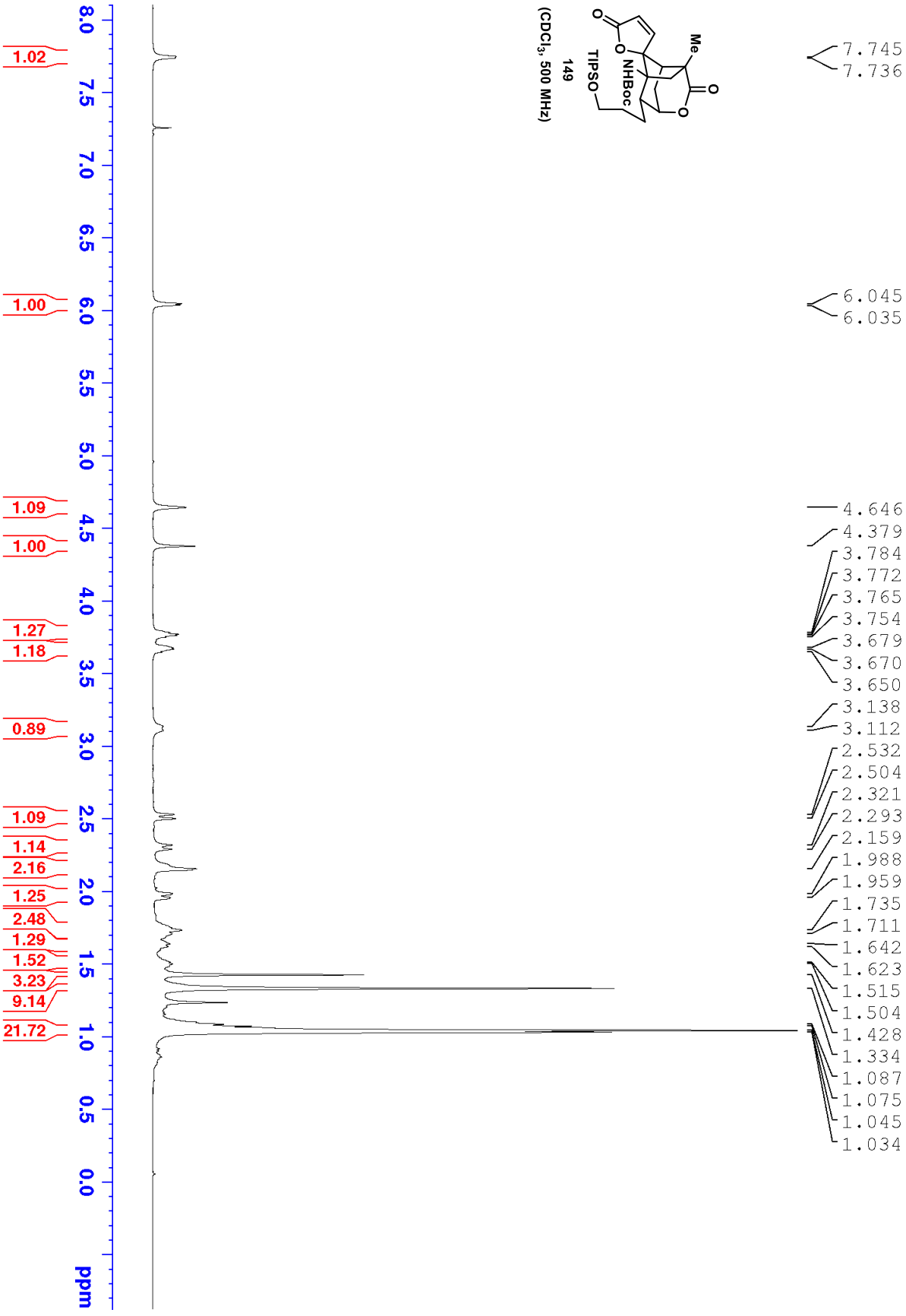

146
(CDCl3, 126 MHz)
TIPSO
HO
NHBoc
H
Me
O
O
177.026
156.659
80.893
76.584
76.512
63.672
63.397
44.576
43.017
42.954
38.087
30.284
28.081
26.807
24.330
21.668
17.939
11.825
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

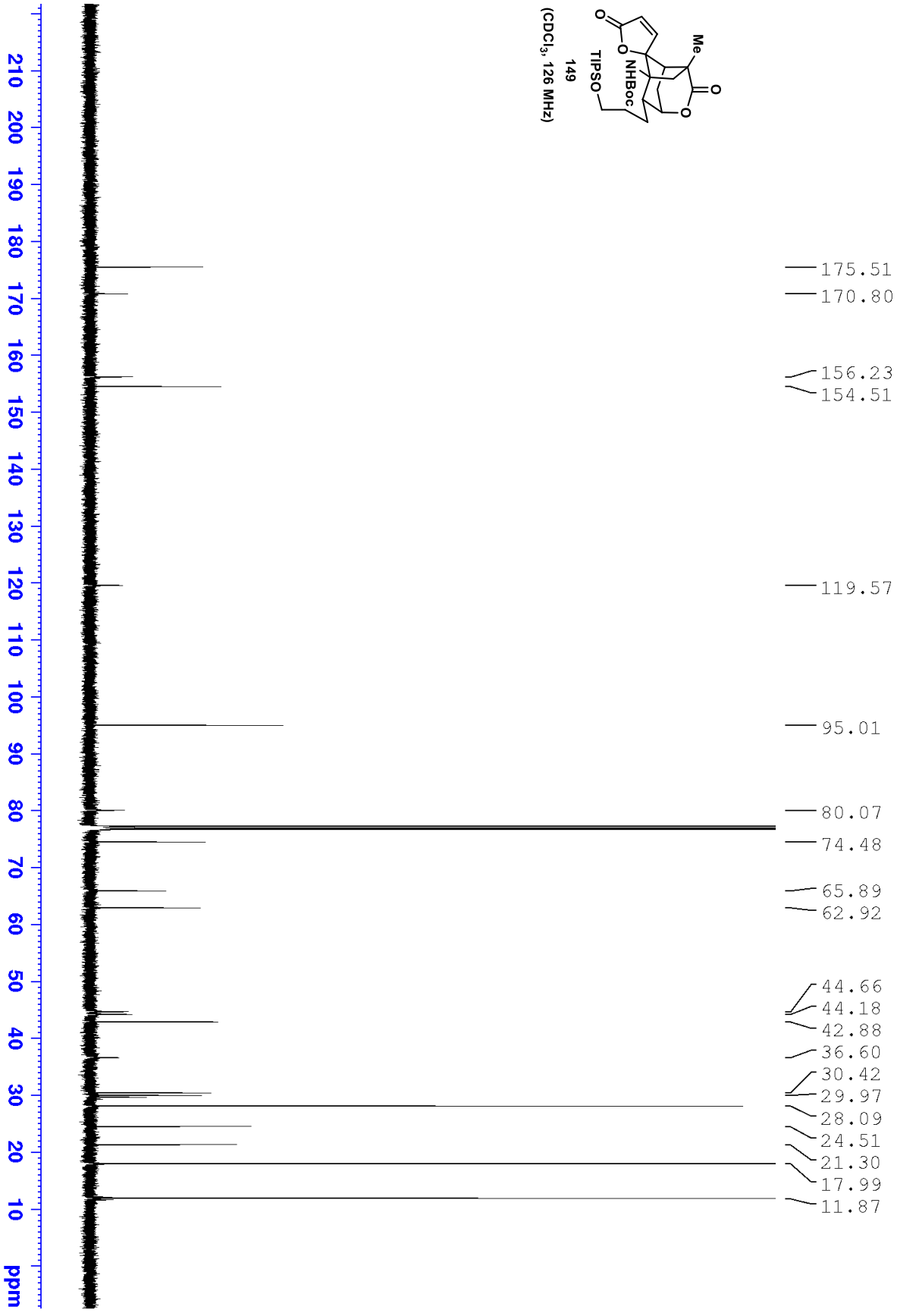

126
(CDCl3, 500 MHz)
TIPSO
NHBoc
Me
O
O
O
O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.82
1.00
1.01
1.03
0.78
1.98
0.92
1.03
0.92
1.17
2.24
1.24
9.14
2.95
21.01
5.112
4.624
3.752
3.738
3.726
3.713
3.699
3.683
3.667
3.652
3.644
3.627
2.902
2.867
2.482
2.476
2.467
2.461
2.442
2.435
2.426
2.420
2.230
2.207
2.145
2.137
2.130
2.115
2.103
2.096
1.976
1.943
1.837
1.811
1.807
1.779
1.755
1.743
1.729
1.716
1.709
1.690
1.683
1.677
1.667
1.558
1.540
1.525
1.510

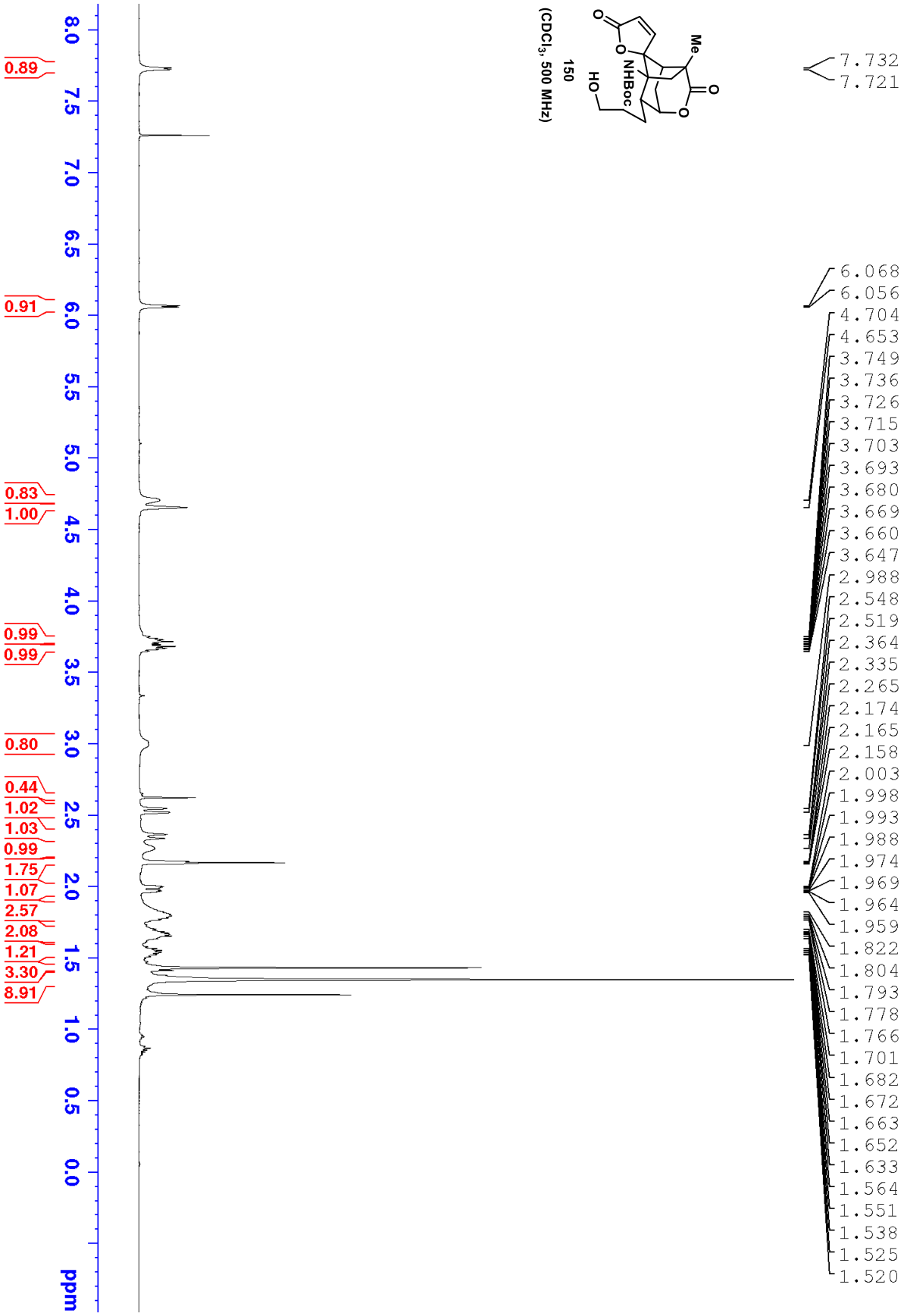

126
(CDCl3, 126 MHz)
TIPSO
NHBoc
O
Me
O
O
209.45
174.80
154.52
79.88
73.86
66.65
63.18
52.35
48.46
40.79
39.05
37.12
30.26
28.19
24.33
21.73
17.96
11.84
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

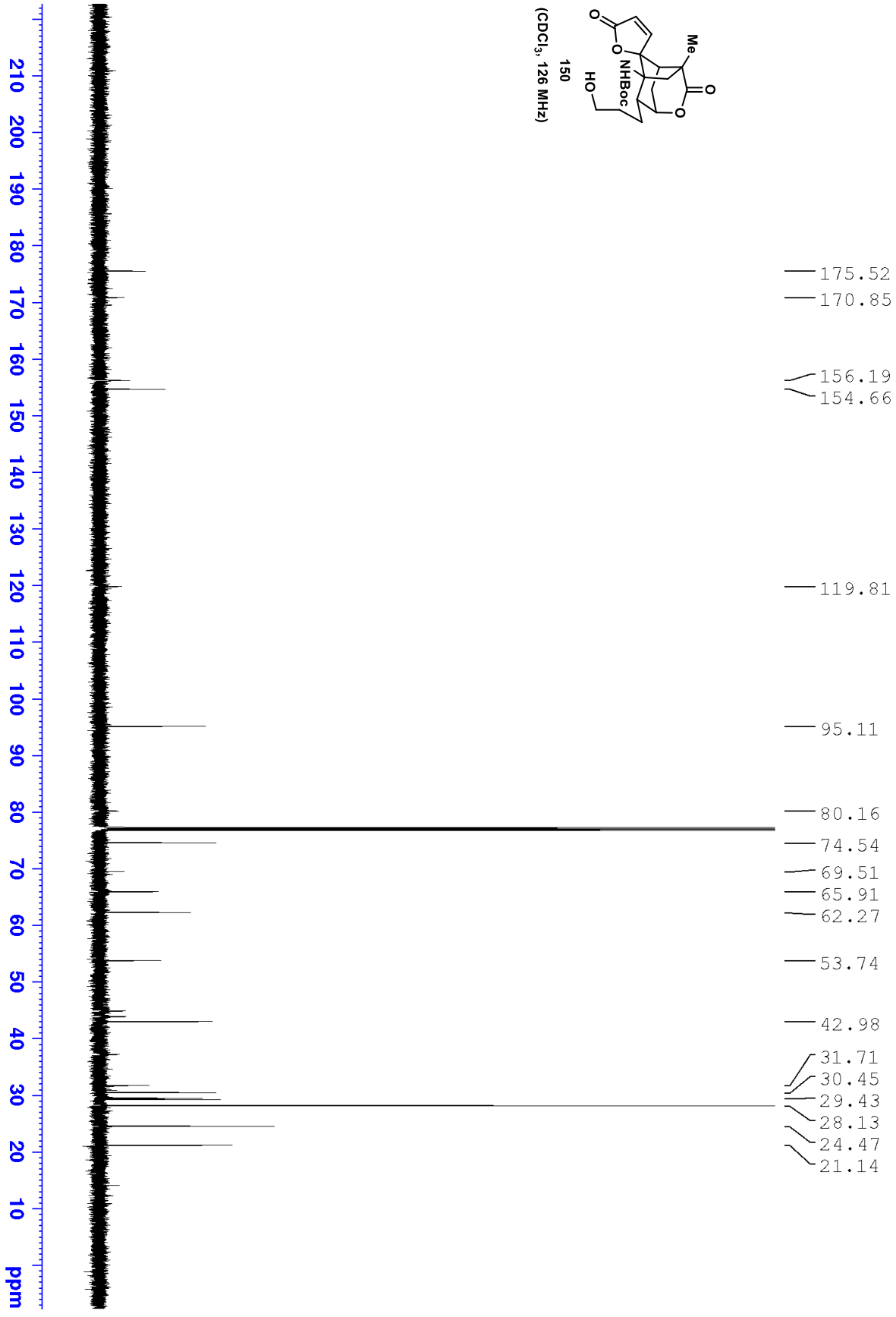

148
(CDCl3, 500 MHz)
MeO2C
Me
HO
NHBoc
TIPSO
O
O
7.224
4.991
4.981
4.629
3.774
3.771
3.753
3.743
3.733
3.658
3.643
3.625
3.614
2.764
2.735
2.444
2.118
2.091
1.976
1.949
1.749
1.722
1.716
1.692
1.605
1.580
1.555
1.539
1.527
1.513
1.498
1.442
1.432
1.430
1.037
1.027
0.90
0.96
1.00
4.04
1.04
2.00
1.00
0.98
1.02
2.52
2.23
12.75
21.96
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
ppm

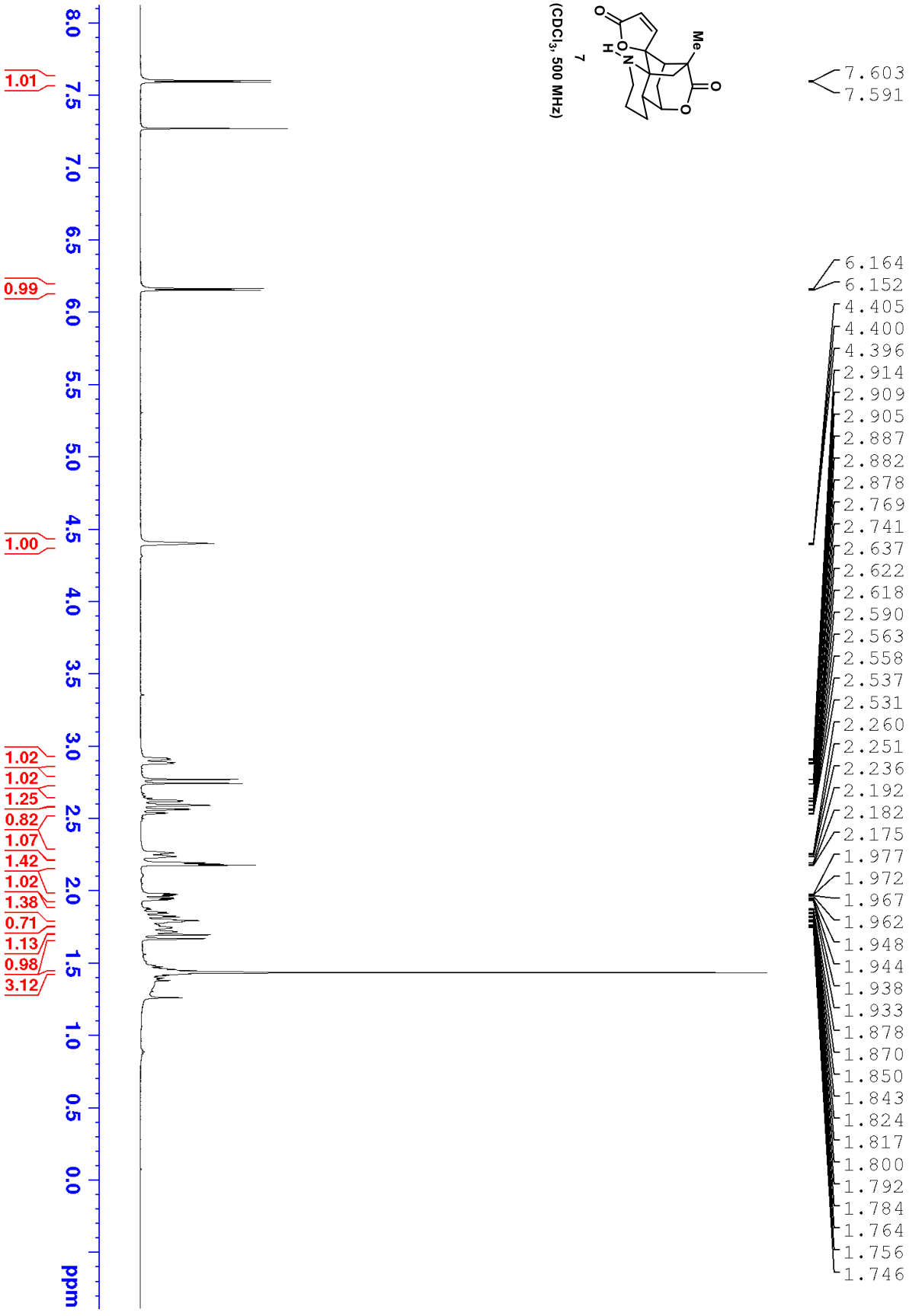

148
(CDCl3, 126 MHz)
MeO2C
Me
HO
NHBoc
TIPSO
O
O
176.323
156.878
153.551
88.001
81.870
77.508
77.176
75.883
66.983
63.380
52.778
50.577
43.500
43.088
38.511
30.413
28.336
28.070
24.064
22.063
18.002
11.898
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


149
(CDCl3, 500 MHz)
TIPSO
NHBoc
Me
O
O
O
O
O
7.745
7.736
6.045
6.035
4.646
4.379
3.784
3.772
3.765
3.754
3.679
3.670
3.650
3.138
3.112
2.532
2.504
2.321
2.293
2.159
1.988
1.959
1.735
1.711
1.642
1.623
1.515
1.504
1.428
1.334
1.087
1.075
1.045
1.034
1.02
1.00
1.09
1.00
1.27
1.18
0.89
1.09
1.14
2.16
1.25
2.48
1.29
1.52
3.23
9.14
21.72
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
ppm


149
(CDCl3, 126 MHz)
TIPSO
NHBoc
Me
O
O
O
O
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm
175.51
170.80
156.23
154.51
119.57
95.01
80.07
74.48
65.89
62.92
44.66
44.18
42.88
36.60
30.42
29.97
28.09
24.51
21.30
17.99
11.87


150
(CDCl3, 500 MHz)
Me
O
O
NHBoc
HO
O
O
7.732
7.721
6.068
6.056
4.704
4.653
3.749
3.736
3.726
3.715
3.703
3.693
3.680
3.669
3.660
3.647
2.988
2.548
2.519
2.364
2.335
2.265
2.174
2.165
2.158
2.003
1.998
1.993
1.988
1.974
1.969
1.964
1.959
1.822
1.804
1.793
1.778
1.766
1.701
1.682
1.672
1.663
1.652
1.633
1.564
1.551
1.538
1.525
1.520
0.89
0.91
0.83
1.00
0.99
0.99
0.80
0.44
1.02
1.03
0.99
1.75
1.07
2.57
2.08
1.21
3.30
8.91
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
ppm


150
(CDCl3, 126 MHz)
Me
NHBoc
HO
O
O
O
O
O
175.52
170.85
156.19
154.66
119.81
95.11
80.16
74.54
69.51
65.91
62.27
53.74
42.98
31.71
30.45
29.43
28.13
24.47
21.14
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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O
N
O
O
O
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7.591
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6.152
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4.400
4.396
2.914
2.909
2.905
2.887
2.882
2.878
2.769
2.741
2.637
2.622
2.618
2.590
2.563
2.558
2.537
2.531
2.260
2.251
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2.192
2.182
2.175
1.977
1.972
1.967
1.962
1.948
1.944
1.938
1.933
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1.850
1.843
1.824
1.817
1.800
1.792
1.784
1.764
1.756
1.746
1.01
0.99
1.00
1.02
1.02
1.25
0.82
1.07
1.42
1.02
1.38
0.71
1.13
0.98
3.12
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7.0
6.5
6.0
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1.5
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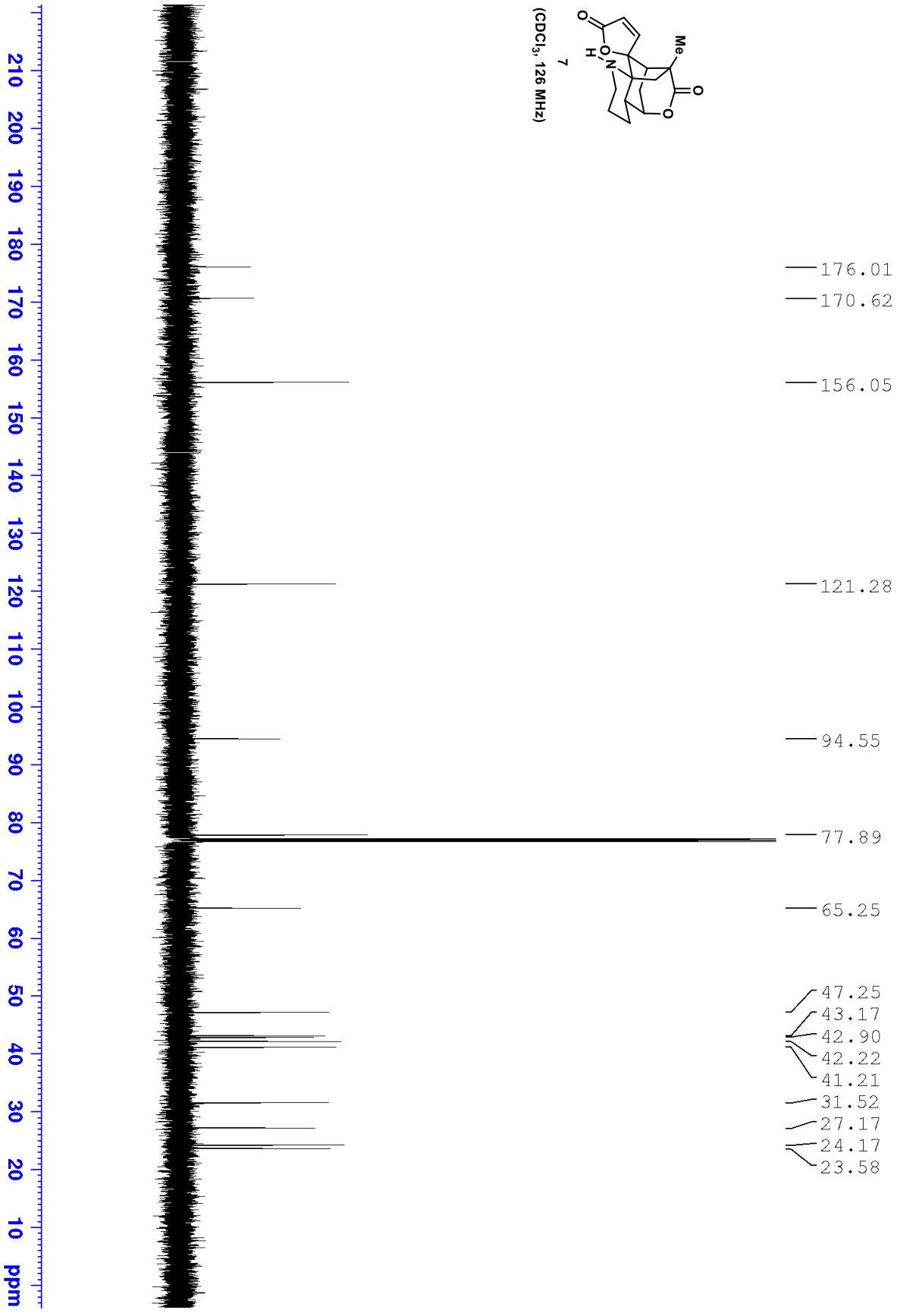
ppm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O
N
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O
O
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200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm
176.01
170.62
156.05
121.28
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77.89
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41.21
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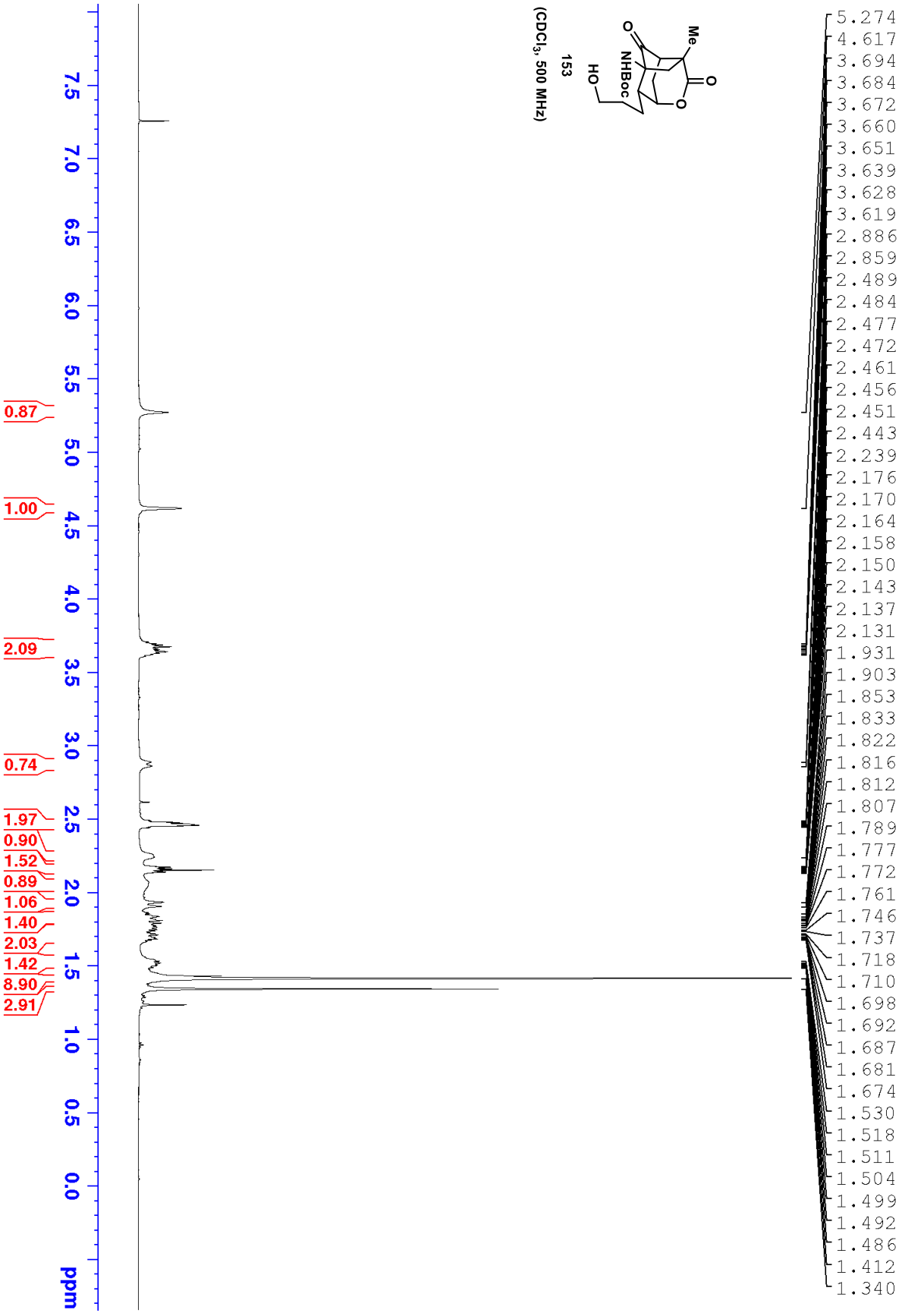
23.58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O
O
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3.694
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3.660
3.651
3.639
3.628
3.619
2.886
2.859
2.489
2.484
2.477
2.472
2.461
2.456
2.451
2.443
2.239
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2.170
2.164
2.158
2.150
2.143
2.137
2.131
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1.903
1.853
1.833
1.822
1.816
1.812
1.807
1.789
1.777
1.772
1.761
1.746
1.737
1.718
1.710
1.698
1.692
1.687
1.681
1.674
1.530
1.518
1.511
1.504
1.499
1.492
1.486
1.412
1.340
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1.00
2.09
0.74
1.97
0.90
1.52
0.89
1.06
1.40
2.03
1.42
8.90
2.91
7.5
7.0
6.5
6.0
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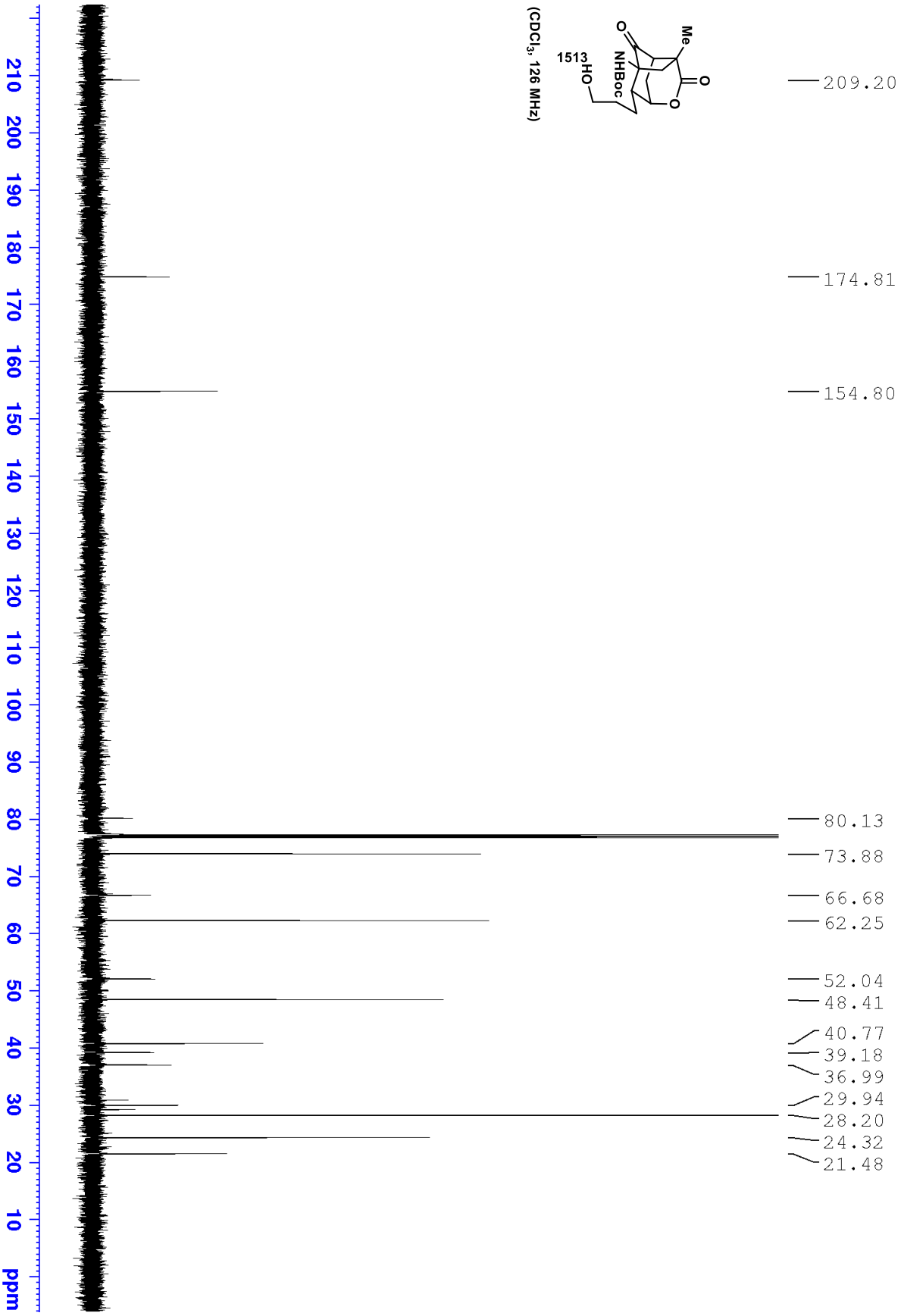
ppm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O
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66.68
62.25
52.04
48.41
40.77
39.18
36.99
29.94
28.20
24.32
21.48
210
200
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140
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120
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100
90
80
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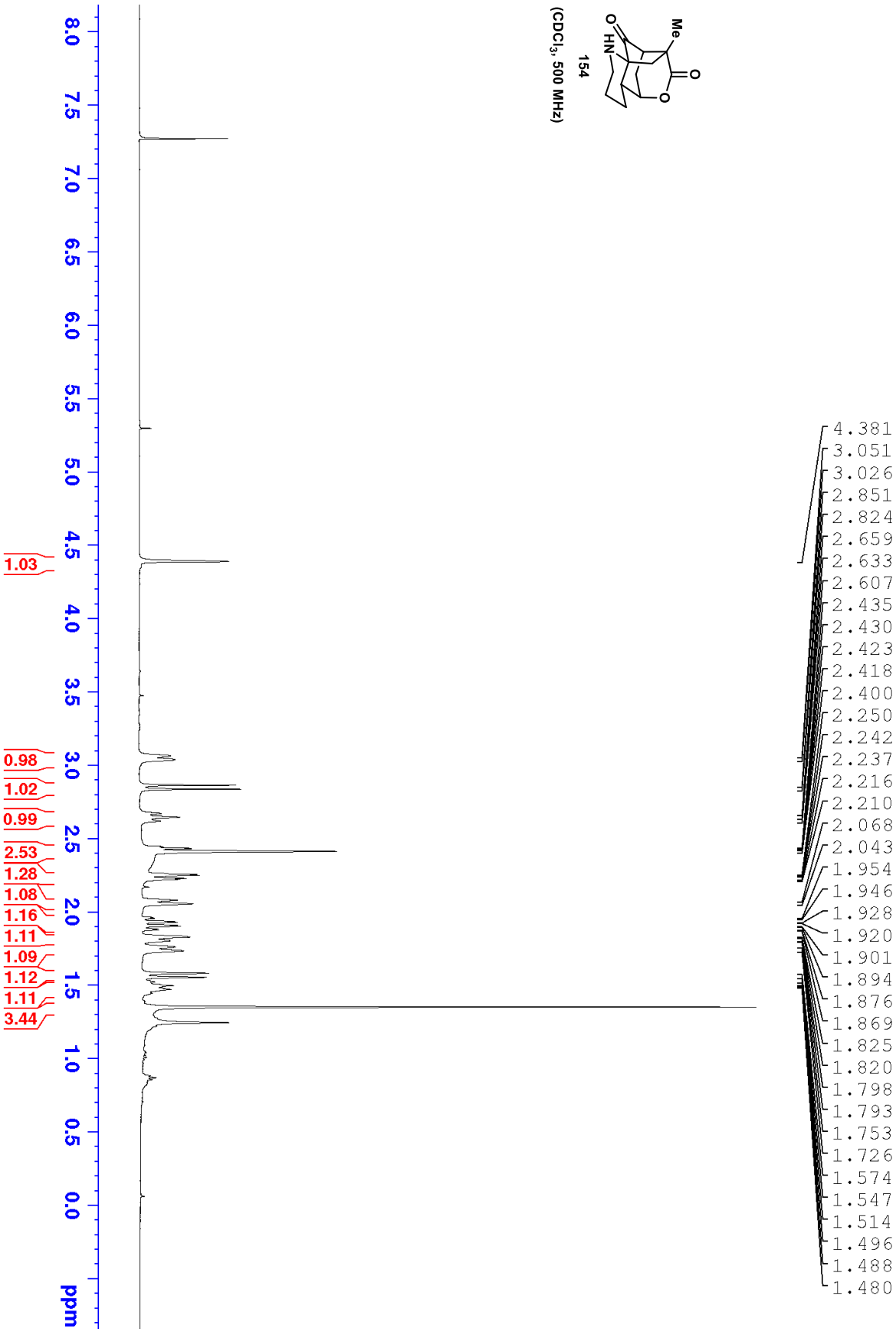
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ppm
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0.99
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1.09
1.12
1.11
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2.824
2.659
2.633
2.607
2.435
2.430
2.423
2.418
2.400
2.250
2.242
2.237
2.216
2.210
2.068
2.043
1.954
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1.928
1.920
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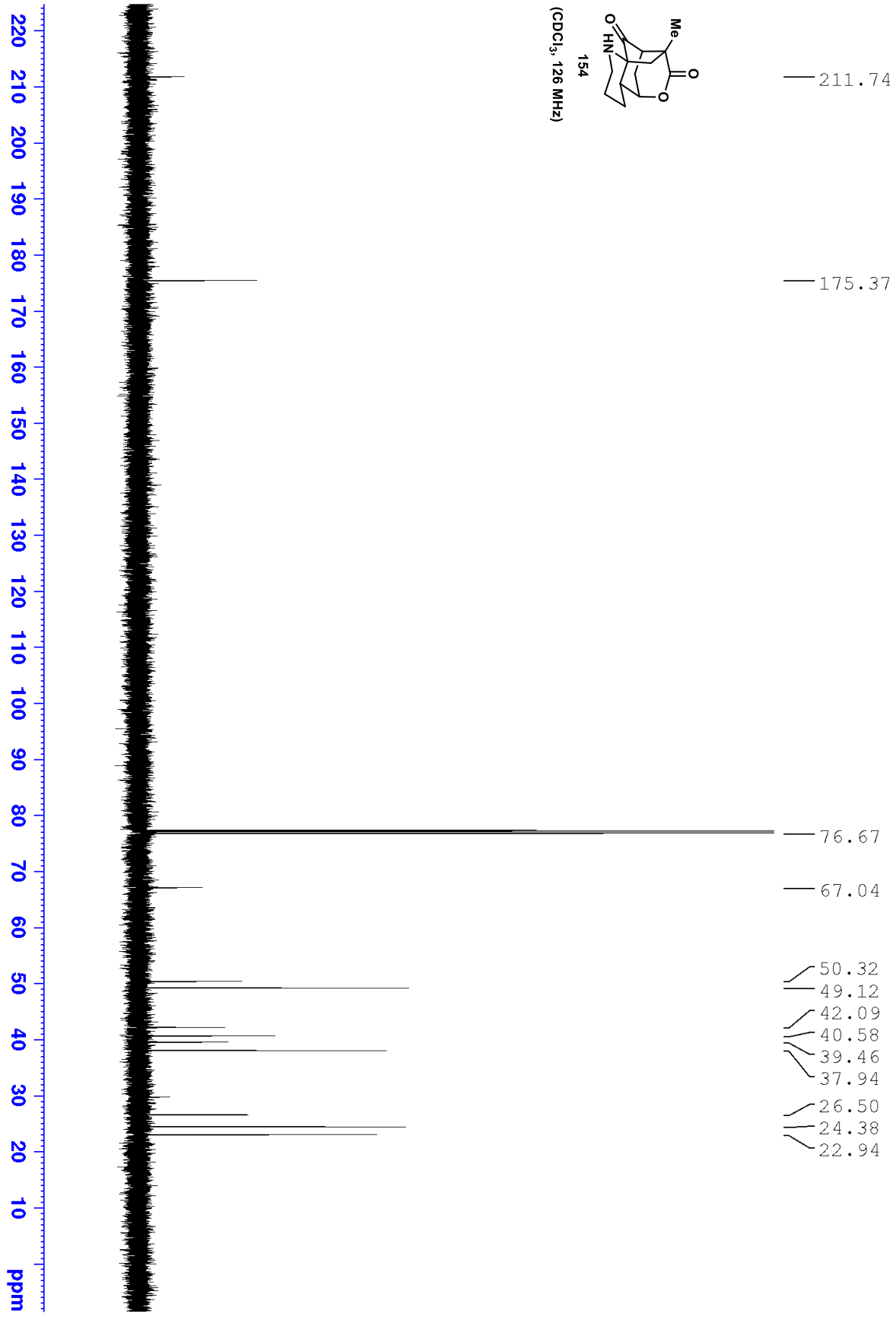
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HN
O
O
O
Me
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67.04
50.32
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26.50
24.38
22.94
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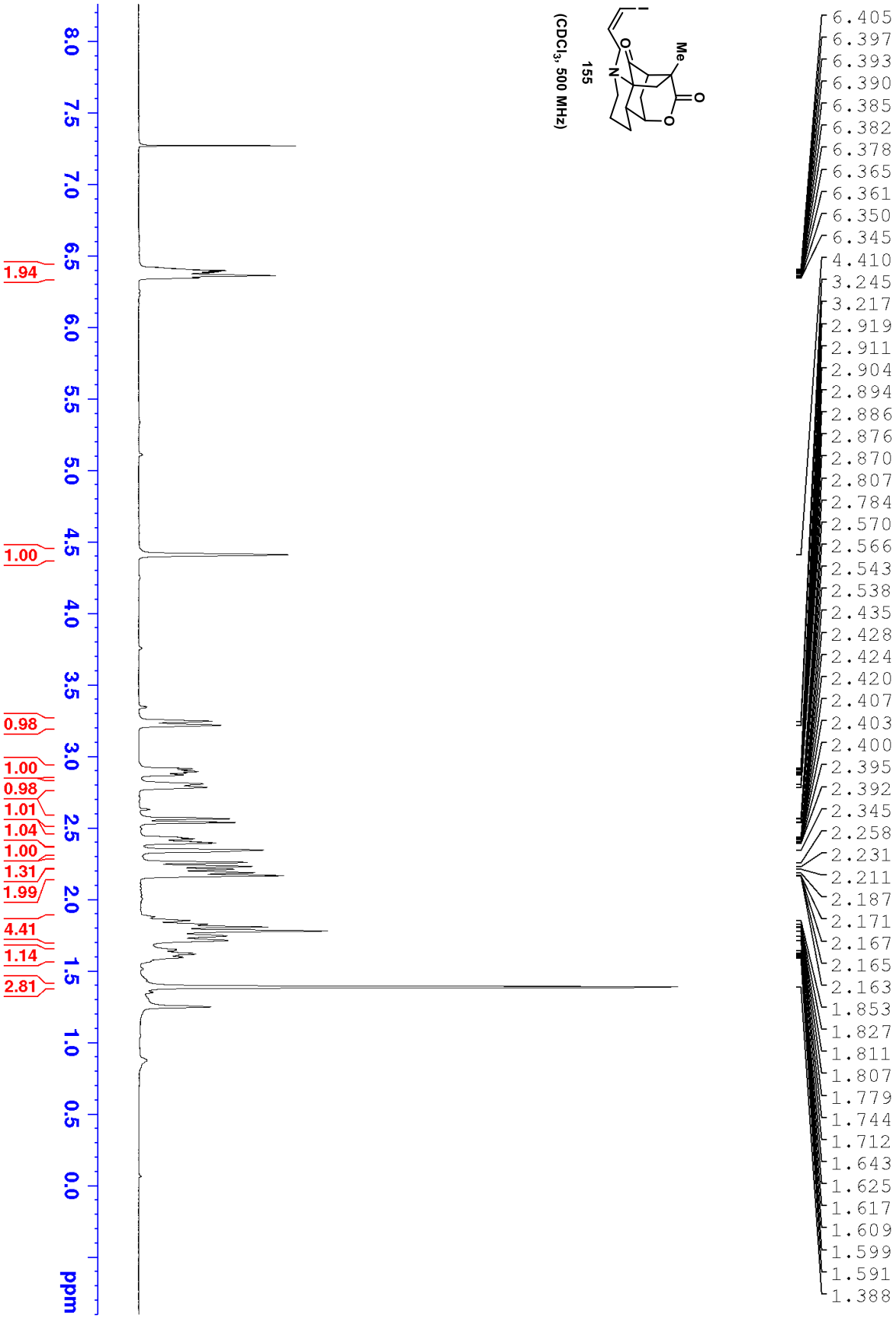
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O
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6.365
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3.217
2.919
2.911
2.904
2.894
2.886
2.876
2.870
2.807
2.784
2.570
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2.538
2.435
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2.420
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2.403
2.400
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2.165
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1.744
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1.609
1.599
1.591
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0.98
1.00
0.98
1.01
1.04
1.00
1.31
1.99
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1.14
2.81
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7.0
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6.0
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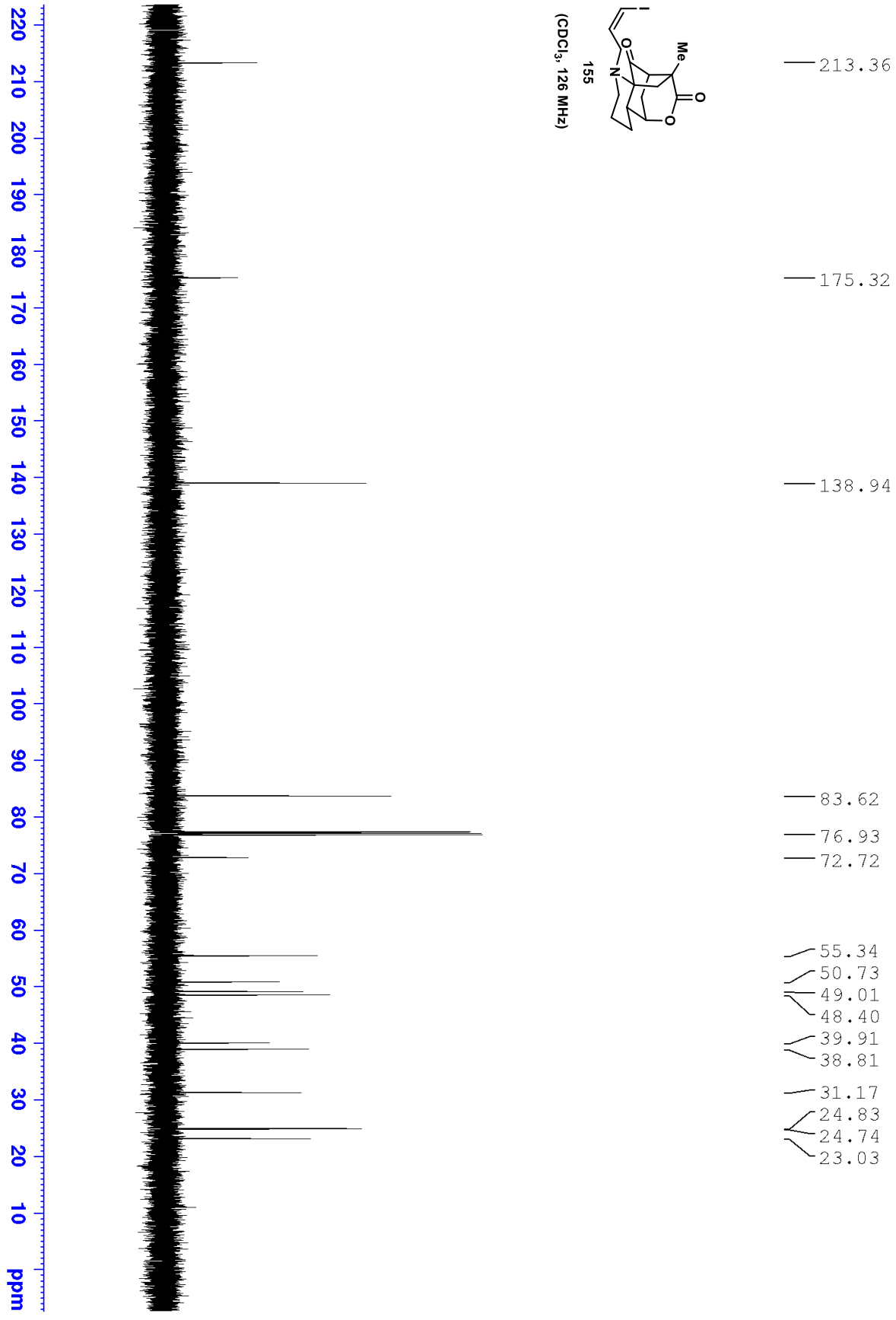
ppm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N
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O
O
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76.93
72.72
55.34
50.73
49.01
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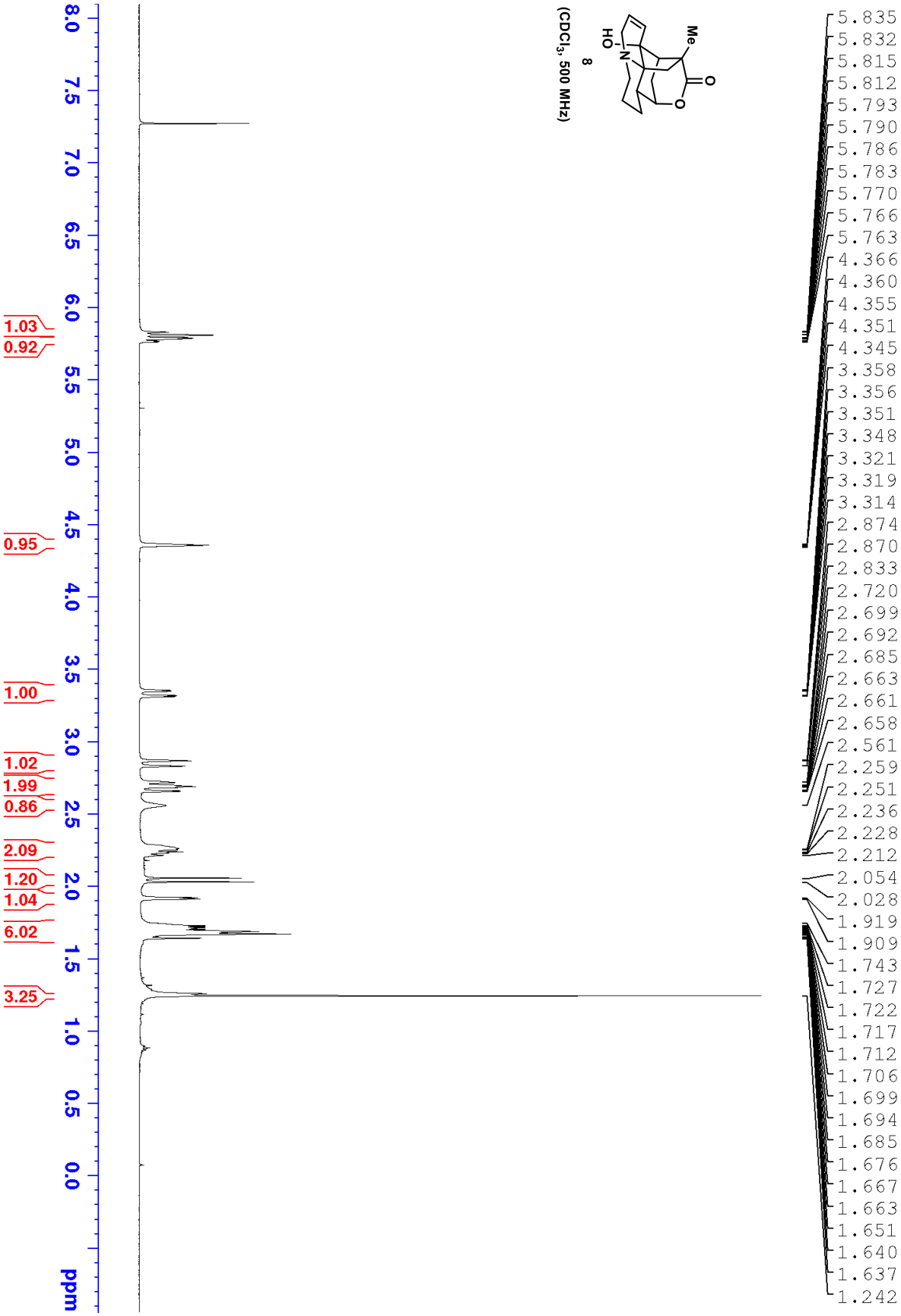
24.74
23.03
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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O
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4.0
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0.0
ppm
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1.00
1.02
1.99
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1.04
6.02
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5.766
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3.348
3.321
3.319
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2.870
2.833
2.720
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2.685
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2.251
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2.228
2.212
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1.722
1.717
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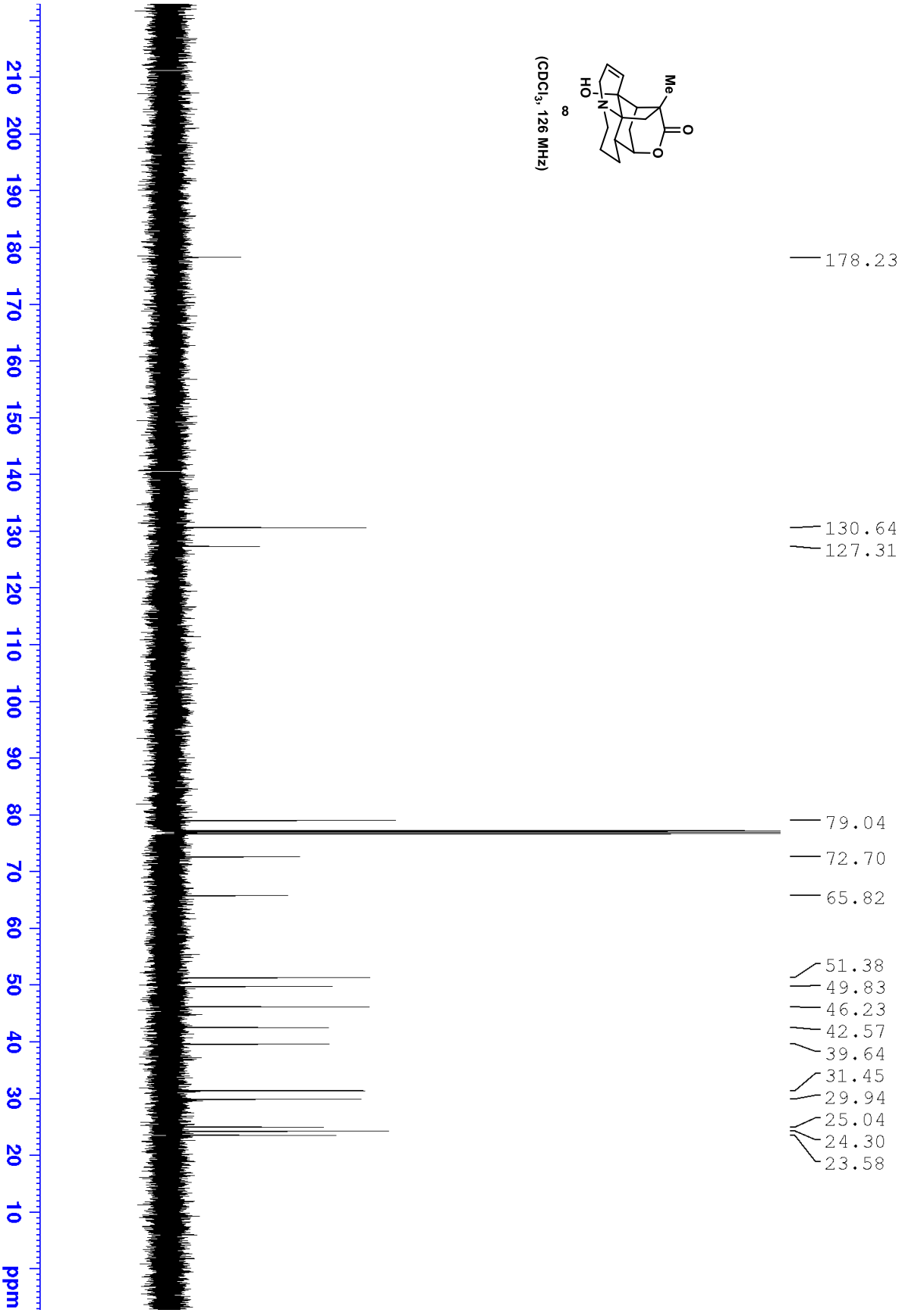
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Me
HO
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O
O
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127.31
79.04
72.70
65.82
51.38
49.83
46.23
42.57
39.64
31.45
29.94
25.04
24.30
23.58
210
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120
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90
80
70
60
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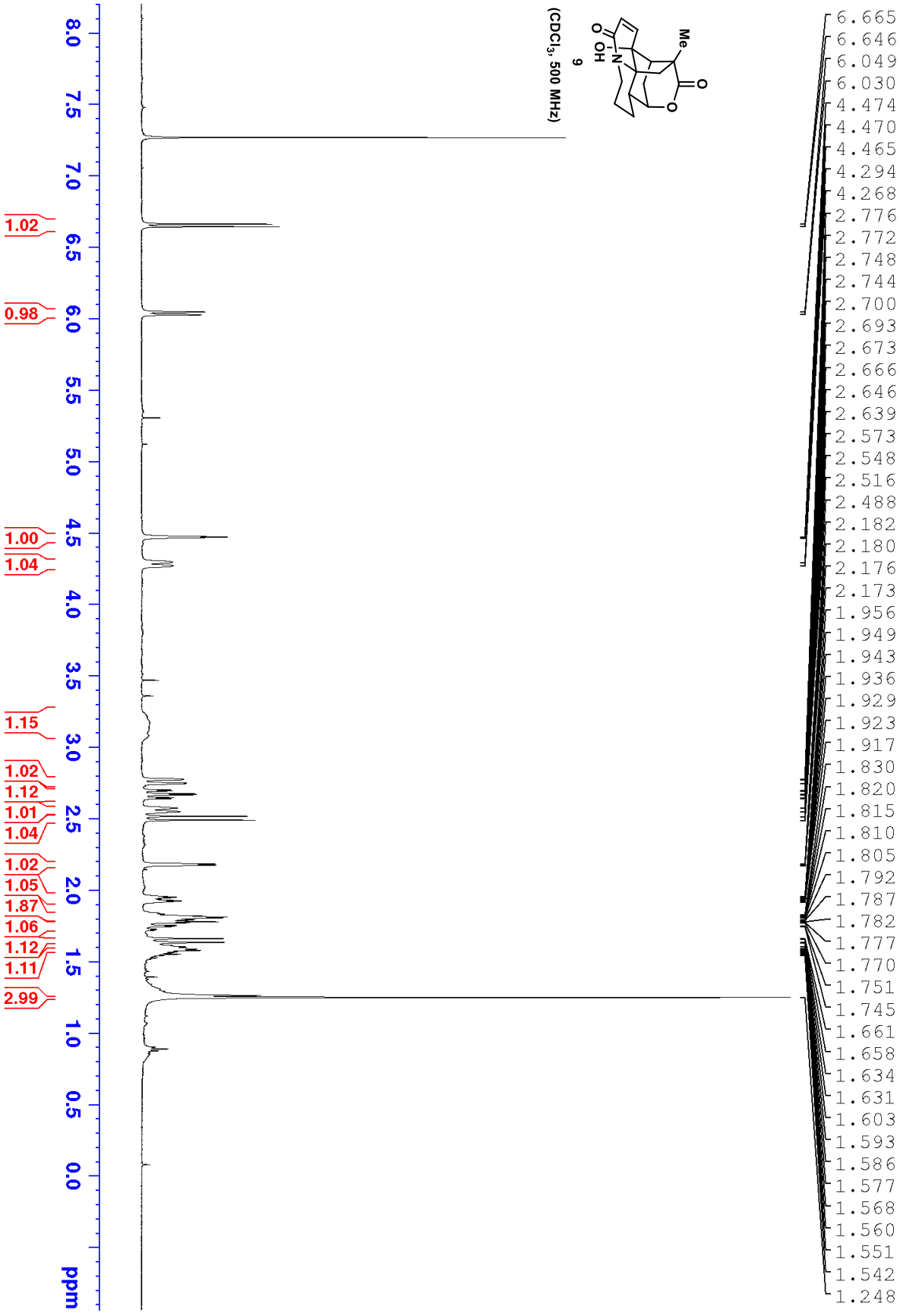
40
30
20
10
ppm


9
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O
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7.5
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6.5
6.0
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5.0
4.5
4.0
3.5
3.0
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2.0
1.5
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0.5
0.0
ppm
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1.00
1.04
1.15
1.02
1.12
1.01
1.04
1.02
1.05
1.87
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2.666
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2.180
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1.943
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1.929
1.923
1.917
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1.815
1.810
1.805
1.792
1.787
1.782
1.777
1.770
1.751
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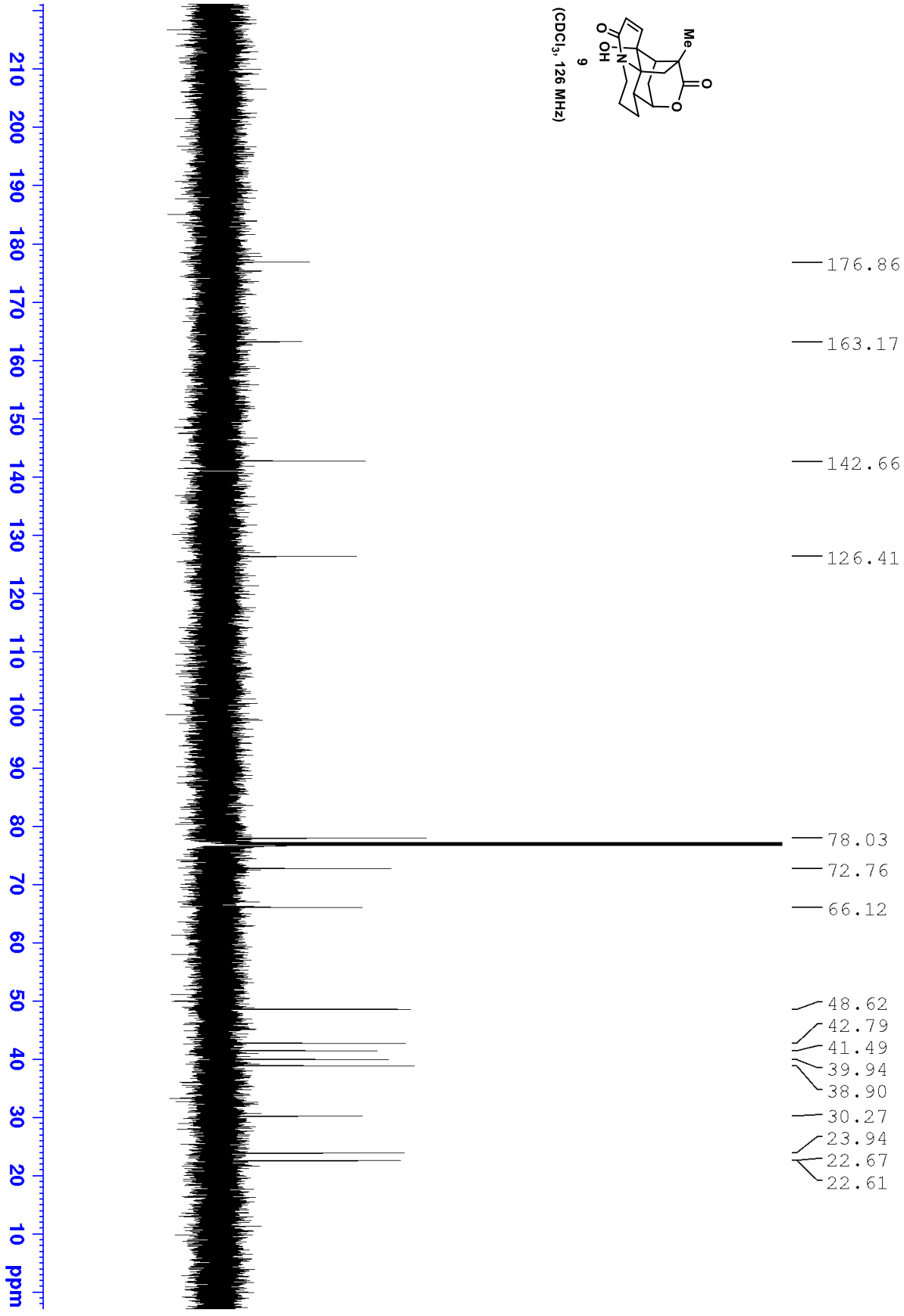
1.568
1.560
1.551
1.542
1.248


9
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126.41
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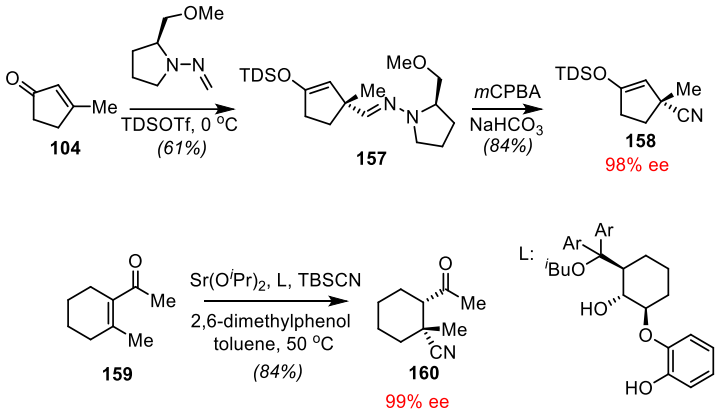
72.76
66.12
48.62
42.79
41.49
39.94
38.90
30.27
23.94
22.67
22.61
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

# CHAPTER 4

# FORMAL ASYMMETRIC SYNTHESIS ROUTE

## *4.1 Asymmetric Synthesis of the Nitrile-Containing Quaternary Center*

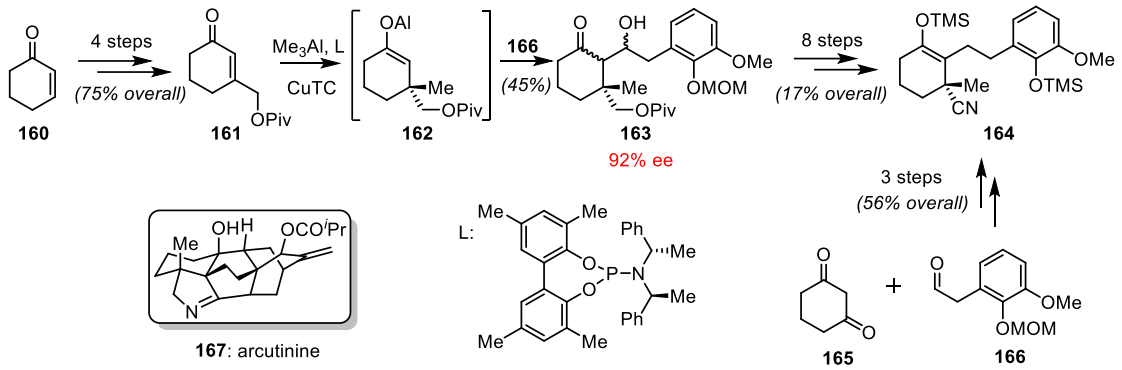
### *4.1.1 Reported Direct Asymmetric Synthesis Methods*




**Scheme 4.1** Reported direct construction methods for nitrile-containing quaternary centers

In the previous chapter, we have achieved the synthesis of multiple annotinolides and their epimers. The potential biosynthetic transformations of annotinolide C (**7**), D (**8**) and E (**9**) were also examined in our lab. The only remaining issue in our third-generation route was developing an asymmetric version. To address this problem, we need to construct ketone **103** asymmetrically. It would be challenging since there is a nitrile-containing quaternary center and so far, only two direct construction methods on similar substrates have been reported.[1,2] As shown in scheme 4.1, the Lassaletta group utilized SAMP imine to perform a conjugative addition. Then the silyl enol ether **157** was transformed to nitrile **158** in 51% yield overall, with an excellent 98% *ee*. The Shibasaki group developed a Sr (II) catalyzed approach, which could apply to cyclic ester **159** in 84% yield, 99% *ee*.

### *4.1.2 The Qin Group's Approach in the Total Synthesis of Arcutinine (**167**)*

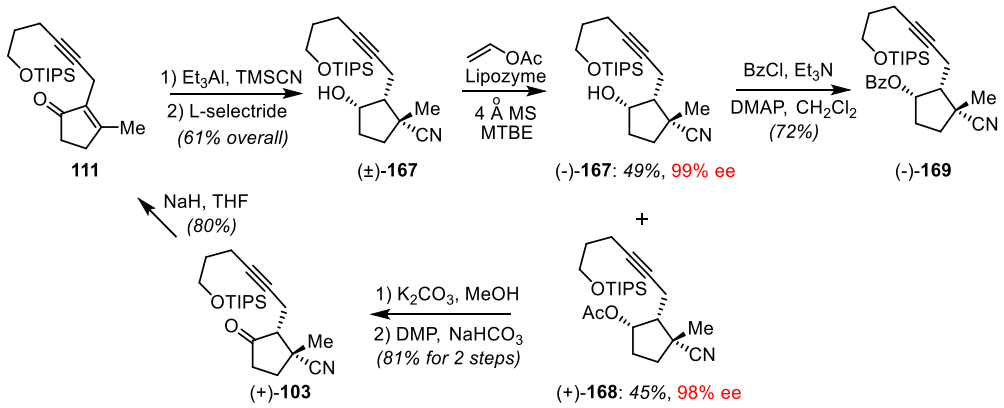



**Scheme 4.2** The racemic and aymmetric approach to **164** from the Qin group

There are fewer repots for the construction of nitrile-containing quaternary stereocenters in total synthesis. In 2019, the Qin group reported their total synthesis of arcutinine (**167**),[3] and they encountered a similar problem to our synthesis. For the construction of the nitrile-containing quaternary stereocenter on the six-membered ring system, they examined some asymmetric cyanide addition methods. Unfortunately, none of the direct additions succeeded. They finally chose a detoured approach, which used $CH_2OPiv$ group in **161** as a surrogate for the nitrile. By converting the problem to asymmetric addition, they found the Alekxis group's method is optimal and could furnish the aldol reaction with aldehyde **166** in one pot. This solution delivered 45% yield and 92% *ee*, however; the disadvantage of this approach was they had to go through 8 steps to adjust the functional groups. The racemic route for the same intermediate **164** took only 3 steps from **165** and **166**.

## *4.2 Formal Asymmetric Synthesis Route*

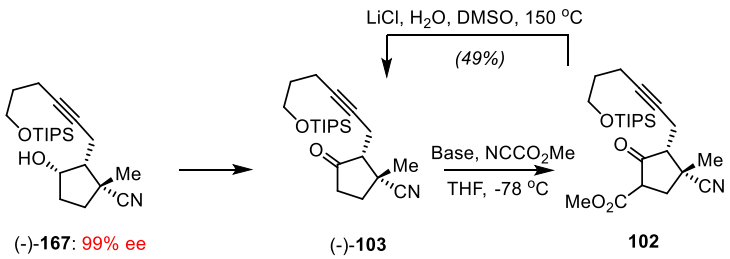
### *4.2.1 Enzymatic Resolution Approach*




**Scheme 4.3** Our enzymatic resolution approach for the asymmetric synthesis

According to the precedents mentioned in the previous sections, synthesizing a nitrile-containing quaternary center asymmetrically would be very challenging. There are no direct asymmetric cyanide addition methods from enone **111** to **103**, and the Qin group's solution will take many more steps. Examining our nitrile **103** intermediate, we found that the ketone group could potentially serve as a handle for the resolution. Reducing **103** with L-selectride at -78 ℃ delivered alcohol **167** as a single diastereomer in 92% yield. **167** was subjected to the Lipozyme resolution condition,[4] and the two enantiomers could be separated perfectly in a total 94% yield. The *ee* value was measured after transforming the product to its benzoate derivative **169**. The levo-isomer was retained as the secondary alcohol in 99% *ee*, and the dextro-isomer was acylated by Lipozyme in 98% *ee*. The advantage of this approach is that both enantiomers could be recycled. Taking the acylated (+)-**168** as example, hydrolysis and DMP oxidation led to (+)-**103**. Then, upon treatment of (+)-**103** with NaH, a retro-Michael reaction occurred and planar enone **111** was obtained. With the recycled **111**, the efficiency of the enzymatic resolution approach was much higher since half of the enantiomers did not need to be discarded.

### *4.2.2 Optimization for the Formal Asymmetric Synthesis Route*




(-)-**167**: 99% ee (-)-**103** **102**

| Entry | Condition | Result[a] |
|---|---|---|
| 1 | PCC, $CH_2Cl_2$, 23 °C | 96% ee[b] |
| 2 | DMP, $CH_2Cl_2$, 23 °C | 96%, 95% ee[c] |
| 3 | DMP, $NaHCO_3$, $CH_2Cl_2$, 23 °C | 88%, 91% ee[d] |
| 4 | $(COCl)_2$, DMSO, $Et_3N$ $CH_2Cl_2$, -78 °C to -40 °C | 87% ee[b] |

a: ee value was measured after transforming **103** to benzoate **169**
b: yield not determined
c: the reaction was performed on 0.2 g scale
d: the reaction was performed on 0.8 g scale

| Entry[a] | Base (1.9 equiv) | Variants | Result[b] |
|---|---|---|---|
| 5 | LDA | none | 72% ee[c] |
| 6 | LDA | pre-mix **103** with $NCCO_2Me$ | unkown product |
| 7 | LDA | $Et_2O$ as solvent | unkown product |
| 8 | LDA | toluene as solvent | unkown product |
| 9 | LiHMDS | none | unkown product |
| 10 | NaHMDS | none | complex mixture |
| 11 | KHMDS | none | 69% ee[c] |
| 12 | LiTMP | none | 76% ee[c] |
| 13[d] | LDA | none | 62%, 79% ee |

a: ketone **103** was 91% ee and the reaction was performed on 50 mg scale. The procedures were kept the same as the recamic procdure except the base and variants in this table
b: ee value was measured after transforming **103** to benzoate **169**
c: yield not determined
d: the reaction was performed on 0.2 g scale and ketone **103** was 95% ee

**Table 4.1** Optimization of the formal aysmmetric route

The enzymatic resolution approach enabled us to get enantiopure **167**. Since the absolute confirmation has not been determined, we chose the levo-enantiomer as the starting material to prepare β-keto ester **102**. This would accomplish the formal asymmetric synthesis. However, there was an *ee* erosion problem with our route. This problem was first observed for the oxidation of **167**. Classic DMP oxidation with $NaHCO_3$ gave us a 91% *ee* product. Considering that ketone **103** could undergo a retro-Michael reaction with NaH as in scheme 4.3, we suspected the cyanide addition/elimination would be reversable under basic conditions. This phenomenon was also observed in some previous literature reports.[5] Through further screening of oxidation conditions, we found that removal of $NaHCO_3$ from DMP oxidation or acidic PCC oxidation would minimize the *ee* erosion. 95% *ee* and 96% *ee* respectively were obtained under those conditions. For a more basic Swern oxidation condition, the *ee* of **103** dropped to 87%.

With the acceptable 95% *ee* result for DMP oxidation, we pushed forward to the acylation reaction. It turned out the *ee* erosion was demonstrably worse with strong bases like LDA. When we performed the same LDA mediated acylation reaction as in the racemic route, the ee of **102** dropped to 79%. Switching the solvents or the procedure sequence did not improve the results. Surprisingly, we observed an unknown product similar to the byproduct we attained when using LiHMDS as the base. We suspect this side product might be the product of acylation on the other side of the ketone in **103**, the regioisomer of **102**. With KHMDS and LiTMP base, the *ee* never exceeded that with LDA. NaHMDS did not provide any isolable product. Considering the equilibrium hypothesis, we also tried to add KCN to inhibit the elimination reaction, but no fruitful results were obtained.

### *4.3 Experimental Section*

**General procedures.** All reactions were carried out under an argon atmosphere with dry solvents under anhydrous condition, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, dimethylformamide (DMF), diethyl ether ($Et_2O$) and dichloromethane ($CH_2Cl_2$) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically ($^1H$ and $^{13}C$ NMR) homogenous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 nm E. SiliCycle silica gel plates (60F-254) using UV light as visualizing agent, and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040-0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography separations were carried out on

0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker 500 MHz and 400 MHz instruments and calibrated using residual undeuterated solvents as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on an Agilent 6244 Tof-MS using ESI (Electronspray Ionization) at the University of Chicago Mass Spectroscopy Core Facility.

**Abbreviations.** THF = tetrahydrofuran, EtOAc = ethyl acetate, MTBE = methyl tert-butyl ether, MeOH = methanol, $Et_3N$ = triethylamine, 4-DMAP = 4-dimethylaminopyridine, BzCl = benzoyl chloride, DMSO = dimethyl sulfoxide.

**Alcohol 167.** Ketone **103** (1.90 g, 5.06 mmol, 1.0 equiv) was dissolved in THF (51 mL) and then the reaction solution was cooled to –78 °C with a dry ice-acetone bath. Next, L-selectride (1.0 M in THF, 5.56 mL, 5.56 mmol, 1.1 equiv) was added dropwise, and the resulting pale-yellow solution was stirred at –78 °C for 30 min. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NH_4Cl$ (40 mL) at –78 °C. After warming the reaction contents to 23 °C, they were poured into a separatory funnel and the resultant layers were separated. The aqueous layer was further extracted with EtOAc (2 × 40 mL). The combined organic layers were then washed with brine (100 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 6:1→3:1), providing desired alcohol **167** (1.74 g, 92% yield) as a colorless oil. **167**: $R_f$ = 0.26 (silica gel, hexanes/EtOAc, 4:1); IR (film) $\nu_{max}$ 3482, 2943, 2890, 2866, 2234, 1462, 1457, 1248, 1107, 1068 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 4.48–4.40 (m, 1 H), 3.74 (t, *J* = 6.1 Hz, 2 H), 2.65–2.57 (m, 1 H), 2.51–2.47 (m, 1 H), 2.47–2.40 (m, 1 H), 2.26 (tt, *J* = 7.1, 2.4 Hz, 2 H),

2.09–2.01 (m, 1 H), 1.91 (d, *J* = 4.2 Hz, 1 H), 1.86 (dddd, *J* = 14.5, 8.6, 6.4, 2.3 Hz, 1 H), 1.75 (dt, *J* = 10.4, 5.3 Hz, 1 H), 1.72–1.64 (m, 3 H), 1.43 (s, 3H), 1.08–1.01 (m, 21 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 123.8, 84.7, 77.3, 73.9, 61.8, 54.7, 39.6, 38.1 ,32.4, 32.1, 25.45, 18.0, 15.8, 15.1, 11.9; HRMS (ESI) calcd for $C_{22}H_{40}NO_2Si^+$ [M + $H^+$] 378.2823, found 378.2819.

**Acetate 168.** 4 Å molecular sieves (4.05 g, 180 mg/mL solvent) were added to a round bottom flask and subsequently dried by flame heating under vacuum until any chunks in the original sample had disappeared to leave only a residual powder. The flask was then cooled to 23 °C under vacuum and charged with argon. A stir bar and a solution of alcohol **167** (1.65 g, 4.37 mmol, 1.0 equiv) in MTBE (20 mL) were then added at 23 °C. Another portion of MTBE (2.5 mL) was used to rinse the flask to complete the transfer of alcohol **39**. Finally, vinyl acetate (2.08 mL, 22.5 mmol, 5.0 equiv) and Lipozyme (0.450 g, 20 mg/mL solvent) were added, and the resulting suspension was stirred at 23 °C for 24 h. Upon completion, the reaction suspension was filtered through a pad of Celite (eluting with EtOAc) and concentrated directly. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8:1→4:1) provided desired acetate **168** (0.826 g, 45% yield, 98% *ee*) as a colorless oil and unreacted alcohol **167** (0.813 g, 49% yield, 99% *ee*) as a colorless oil. [Note: The *ee* values of (+)-**168** and (–)-**167** were measured after they had been transformed separately into benzoate **169** as delineated below]. **168**: $R_f$ = 0.31 (silica gel, hexanes/EtOAc, 4:1); IR (film) $\nu_{max}$ 2943, 2893, 2866, 2234, 1740, 1464, 1457, 1239, 1107, 1067 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 5.31 (td, *J* = 5.3, 1.9 Hz, 1 H), 3.72 (t, *J* = 6.1 Hz, 2 H), 2.58–2.51 (m, 1 H), 2.47–2.38 (m, 2 H), 2.22 (tt, *J* = 7.2, 2.0 Hz, 2 H), 2.12 (ddd, *J* = 15.2, 9.7, 5.5 Hz, 1H), 2.07 (s, 3 H), 1.94–1.85 (m, 2 H), 1.76–1.70 (m, 1 H), 1.70–1.64 (m, 2 H), 1.52–1.48 (m, 3 H), 1.07–1.01 (m, 21 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 170.3, 123.1, 81.5, 76.7, 76.0, 61.9, 53.1, 40.4, 38.1, 32.1, 30.7, 25.6, 20.9,

18.0, 16.0, 15.1, 11.9; HRMS (ESI) calcd for $C_{24}H_{42}NO_3Si^+$ [M + $H^+$] 420.2928, found 420.2930. $[\alpha]_D^{23}$ = +22° (*c* = 1.0, $CHCl_3$). Alcohol (–)-**167**: $[\alpha]_D^{23}$ = –26° (*c* = 1.0, $CHCl_3$).

**Alcohol 167.** Acetate **168** (0.770 g, 1.83 mmol, 1.0 equiv) was dissolved in MeOH (92 mL) at 23 °C and then $K_2CO_3$ (2.54 g, 18.3 mmol, 10.0 equiv) was added. The reaction suspension was then vigorously stirred at 23 °C for 1 h. Upon completion, the reaction mixture was filtered through Celite (eluting with EtOAc) and concentrated directly. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4:1) providing the desired alcohol **167** (0.658 g, 95% yield) as a colorless oil. (+)-**167**: $[\alpha]_D^{23}$ = +25° (*c* = 1.0, $CHCl_3$).

**General procedure to prepare benzoate 169 for *ee* measurement.** Alcohol **167** (10.2 mg, 0.0270 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (0.54 mL) at 23 °C. Then $Et_3N$ (13.7 mg, 0.135 mmol, 5.0 equiv), 4-DMAP (3.3 mg, 0.0270 mmol, 1.0 equiv), and BzCl (5.7 mg, 0.0405 mmol, 1.5 equiv) were added sequentially, forming a yellow solution. The reaction contents were then stirred at 23 °C for 24 h. Upon completion, the reaction solution was quenched by the addition of saturated $NaHCO_3$ solution (0.5 mL) and poured into a separatory funnel. After separating the layers, the aqueous layer was extracted further with $CH_2Cl_2$ (2 × 2.0 mL). The combined organic layers were then washed with brine (4.0 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 10:1) providing the desired benzoate **169** (9.4 mg, 72% yield) as a colorless oil. IR (film) $\nu_{max}$ 2942, 2894, 2865, 2233, 1722, 1462, 1452, 1272, 1110, 1070, 711 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.15–8.11 (m, 2 H), 7.58–7.51 (m, 2 H), 7.48–7.43 (m, 1 H), 5.60 (td, *J* = 5.2, 1.9 Hz, 1 H), 3.68 (t, *J* = 6.0 Hz, 2 H), 2.68 (ddt, *J* = 16.7, 9.1, 2.5 Hz, 1 H), 2.54 (ddt, *J* = 14.8, 6.4, 4.1 Hz, 2 H), 2.28–2.16 (m, 3 H), 2.10–2.00 (m, 2 H), 1.83 (ddd, *J* = 13.7, 10.0, 6.1

Hz, 1 H), 1.64 (dddd, $J$ = 13.3, 7.3, 6.1, 2.7 Hz, 2 H), 1.58 (s, 3 H), 1.06–0.99 (m, 21 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 165.8, 133.1, 129.9, 128.5, 123.5, 81.8, 76.8, 76.7, 61.8, 53.8, 40.5, 38.3, 32.1, 30.8, 25.7, 18.0, 17.9, 16.1, 15.1, 11.9; HRMS (ESI) calcd for $C_{29}H_{43}NNaO_3Si^+$ [M + $Na^+$] 504.2904, found 504.2905. (+)-**169**: $[\alpha]_D^{23}$ = +45° ($c$ = 1.0, $CHCl_3$); (–)-**169**: $[\alpha]_D^{23}$ = –43° ($c$ = 1.0, $CHCl_3$). HPLC condition: OD-H column, 4.6 × 250 mm, hexanes/*i*-PrOH = 99:1, 1 mL/min, UV detector at 240 nm, $R_T$[(+)-**169**] = 7.14 min, $R_T$[(–)-**169**] = 8.13 min.

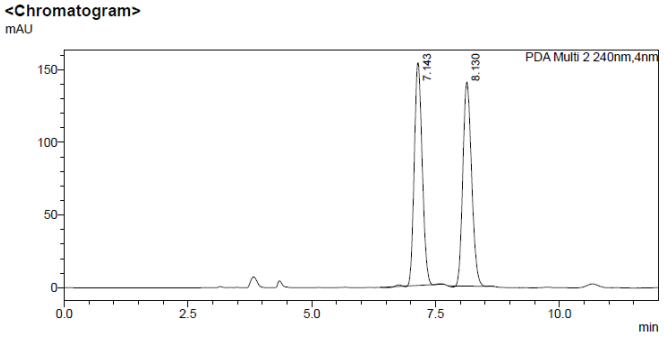
Racemic **169**:

SHIMADZU LabSolutions Analysis Report

<Sample Information>

| | | | |
|---|---|---|---|
| Sample Name | : PQ-1669-7 | | |
| Sample ID | : PQ-1669-7 | | |
| Data Filename | : PQ-1669-7.lcd | | |
| Method Filename | : Default Method.lcm | | |
| Batch Filename | : | | |
| Vial # | : -1 | Sample Type | : Unknown |
| Injection Volume | : 20 uL | | |
| Date Acquired | : 11/16/2020 4:16:53 PM | Acquired by | : Snyder Group |
| Date Processed | : 11/25/2020 6:08:39 PM | Processed by | : Snyder Group |

<Chromatogram>




<Peak Table>

PDA Ch2 240nm

| Peak# | Ret. Time | Height | Area | Height% | Area% |
|---|---|---|---|---|---|
| 1 | 7.143 | 153147 | 1711250 | 52.174 | 49.808 |
| 2 | 8.130 | 140387 | 1724411 | 47.826 | 50.192 |
| Total | | 293534 | 3435661 | 100.000 | 100.000 |

(+)-**169** (from resolution product **168**):

SHIMADZU LabSolutions **Analysis Report**

**<Sample Information>**

| | | | |
|---|---|---|---|
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| Sample ID | : PQ-1683 | | |
| Data Filename | : PQ-1683.lcd | | |
| Method Filename | : Default Method.lcm | | |
| Batch Filename | : | | |
| Vial # | : -1 | Sample Type | : Unknown |
| Injection Volume | : 20 uL | | |
| Date Acquired | : 11/25/2020 5:40:49 PM | Acquired by | : Snyder Group |
| Date Processed | : 3/17/2021 9:06:02 AM | Processed by | : Snyder Group |

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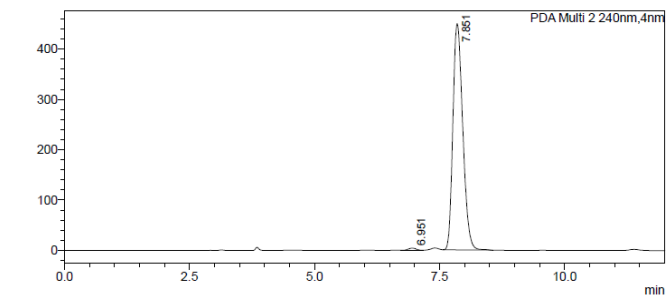


**<Peak Table>**

PDA Ch2 240nm

| Peak# | Ret. Time | Height | Area | Height% | Area% |
|---|---|---|---|---|---|
| 1 | 6.951 | 4635 | 53451 | 1.021 | 0.859 |
| 2 | 7.851 | 449529 | 6168288 | 98.979 | 99.141 |
| Total | | 454164 | 6221739 | 100.000 | 100.000 |

(–)-**169** (from resolution product **167**):

SHIMADZU LabSolutions **Analysis Report**

**<Sample Information>**

| | | | |
|---|---|---|---|
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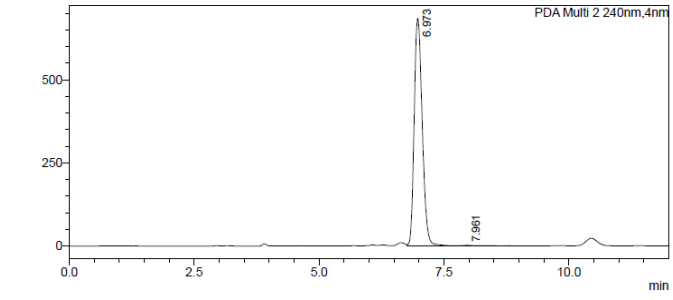
| Sample ID | : PQ-1684-2 | | |
| Data Filename | : PQ-1684-2.lcd | | |
| Method Filename | : Default Method.lcm | | |
| Batch Filename | : | | |
| Vial # | : -1 | Sample Type | : Unknown |
| Injection Volume | : 20 uL | | |
| Date Acquired | : 11/26/2020 5:26:05 PM | Acquired by | : Snyder Group |
| Date Processed | : 3/17/2021 9:03:46 AM | Processed by | : Snyder Group |

**<Chromatogram>**




**<Peak Table>**

PDA Ch2 240nm

| Peak# | Ret. Time | Height | Area | Height% | Area% |
|---|---|---|---|---|---|
| 1 | 6.973 | 685158 | 7725821 | 99.807 | 99.804 |
| 2 | 7.961 | 1324 | 15203 | 0.193 | 0.196 |
| Total | | 686482 | 7741024 | 100.000 | 100.000 |

**Ketone 103.** Alcohol **169** (0.650 g, 1.72 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (17 mL) at 23 °C and then $NaHCO_3$ (1.44 g, 17.2 mmol, 10 equiv) and Dess–Martin periodinane (1.45 g, 34.4 mmol, 2.0 equiv) were added sequentially. The resultant suspension was then vigorously stirred at 23 °C for 45 min. Upon completion, the reaction contents were quenched by the addition of 3 M $Na_2S_2O_3$ (15 mL) and poured into a separatory funnel. After separating the layers, the aqueous layer was further extracted with $CH_2Cl_2$ (2 × 15 mL). The combined organic layers were then washed with brine (40 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8:1) provided desired ketone **103** (0.604 g, 93% yield) as a colorless oil. (+)-**103**: $[\alpha]_D^{23}$ = +81° (*c* = 1.0, $CHCl_3$).

**Enone 111.** Ketone **103** (0.550 g, 1.42 mmol, 1.0 equiv) was dissolved in THF (14 mL) at 23 °C and then the resultant solution was cooled to 0 °C using an ice-water bath. Then NaH (60% dispersion in mineral oil, 0.284 g, 7.10 mmol, 5.0 equiv) was added in a single portion, forming a pale yellow suspension. The reaction mixture was then stirred at 0 °C for 1 h. Upon completion, the reaction contents were quenched by the addition of $H_2O$ (10 mL), warmed to 23 °C, and poured into a separatory funnel. After separating the layers, the aqueous layer was further extracted with EtOAc (2 × 10 mL). The combined organic layers were then washed with brine (30 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 10:1) provided desired enone **111** (0.405 g, 82% yield) as a pale-yellow oil whose spectral data fully matched that of previously characterized material.

**Procedure for entry 2 in table 4.1.** Alcohol **167** (0.181 g, 0.477 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (4.77 mL) at 23 °C and then Dess–Martin periodinane (0.404 g, 0.953

mmol, 2.0 equiv) was added. The resultant suspension was then vigorously stirred at 23 °C for 30 min. Upon completion, the reaction contents were quenched by the addition of 3 M $Na_2S_2O_3$ (5.0 mL) and poured into a separatory funnel. After separating the layers, the aqueous layer was further extracted with $CH_2Cl_2$ (2 × 5.0 mL). The combined organic layers were then washed with brine (10 mL), dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8:1) provided desired ketone **103** (0.173 g, 96% yield) as a colorless oil. (–)-**103**: $[\alpha]_D^{23}$ = –84° (*c* = 1.0, $CHCl_3$).

HPLC trace for entry 1 in table 4.1:

SHIMADZU LabSolutions Analysis Report

<Sample Information>

| | | | |
|---|---|---|---|
| Sample Name | : PQ-1798-2 | | |
| Sample ID | : PQ-1798-2 | | |
| Data Filename | : PQ-1798-2.lcd | | |
| Method Filename | : Default Method.lcm | | |
| Batch Filename | : | | |
| Vial # | : -1 | Sample Type | : Unknown |
| Injection Volume | : 20 uL | | |
| Date Acquired | : 3/18/2021 10:13:40 AM | Acquired by | : Snyder Group |
| Date Processed | : 3/18/2021 10:27:22 AM | Processed by | : Snyder Group |

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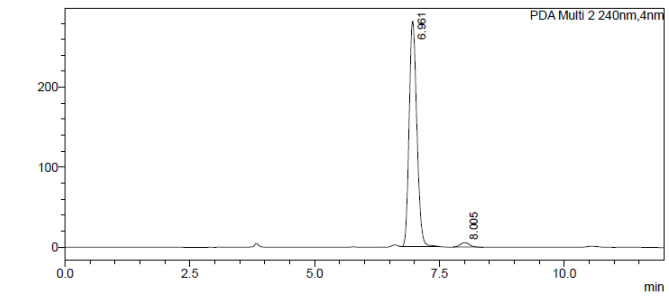


<Peak Table>

PDA Ch2 240nm

| Peak# | Ret. Time | Height | Area | Height% | Area% |
|---|---|---|---|---|---|
| 1 | 6.961 | 281849 | 3019970 | 98.052 | 97.716 |
| 2 | 8.005 | 5600 | 70590 | 1.948 | 2.284 |
| Total | | 287449 | 3090559 | 100.000 | 100.000 |

HPLC trace for entry 2 in table 4.1:

SHIMADZU LabSolutions **Analysis Report**

**<Sample Information>**

| | | | |
|---|---|---|---|
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| Sample ID | : PQ-1793 | | |
| Data Filename | : PQ-1793.lcd | | |
| Method Filename | : Default Method.lcm | | |
| Batch Filename | : | | |
| Vial # | : -1 | Sample Type | : Unknown |
| Injection Volume | : 20 uL | | |
| Date Acquired | : 3/6/2021 10:37:55 AM | Acquired by | : Snyder Group |
| Date Processed | : 3/17/2021 9:12:44 AM | Processed by | : Snyder Group |

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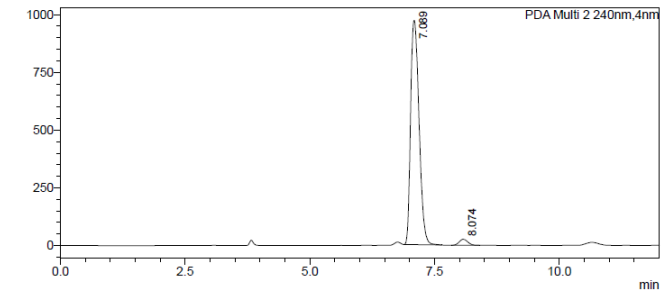


**<Peak Table>**

PDA Ch2 240nm

| Peak# | Ret. Time | Height | Area | Height% | Area% |
|---|---|---|---|---|---|
| 1 | 7.089 | 971303 | 11454802 | 97.390 | 97.369 |
| 2 | 8.074 | 26032 | 309567 | 2.610 | 2.631 |
| Total | | 997335 | 11764369 | 100.000 | 100.000 |

HPLC trace for entry 3 in table 4.1:

SHIMADZU LabSolutions **Analysis Report**

**<Sample Information>**

| | | | |
|---|---|---|---|
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| Sample ID | : PQ-1783 | | |
| Data Filename | : PQ-1783.lcd | | |
| Method Filename | : Default Method.lcm | | |
| Batch Filename | : | | |
| Vial # | : -1 | Sample Type | : Unknown |
| Injection Volume | : 20 uL | | |
| Date Acquired | : 2/28/2021 11:34:56 AM | Acquired by | : Snyder Group |
| Date Processed | : 3/17/2021 9:15:38 AM | Processed by | : Snyder Group |

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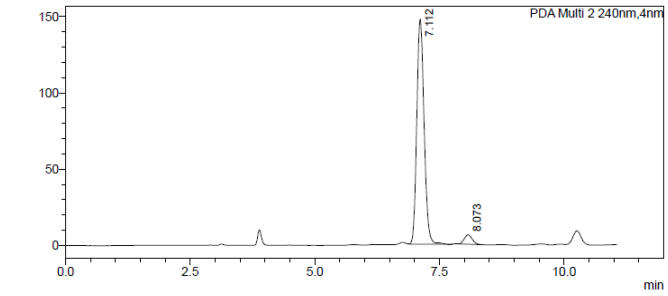


**<Peak Table>**

PDA Ch2 240nm

| Peak# | Ret. Time | Height | Area | Height% | Area% |
|---|---|---|---|---|---|
| 1 | 7.112 | 147484 | 1503542 | 95.988 | 95.603 |
| 2 | 8.073 | 6164 | 69156 | 4.012 | 4.397 |
| Total | | 153647 | 1572698 | 100.000 | 100.000 |

HPLC trace for entry 4 in table 4.1:

SHIMADZU LabSolutions **Analysis Report**

**<Sample Information>**

| | | | |
|---|---|---|---|
| Sample Name | : PQ-1812 | | |
| Sample ID | : PQ-1812 | | |
| Data Filename | : PQ-1812.lcd | | |
| Method Filename | : Default Method.lcm | | |
| Batch Filename | : | | |
| Vial # | : -1 | Sample Type | : Unknown |
| Injection Volume | : 20 uL | | |
| Date Acquired | : 3/17/2021 1:28:59 PM | Acquired by | : Snyder Group |
| Date Processed | : 3/17/2021 1:43:40 PM | Processed by | : Snyder Group |

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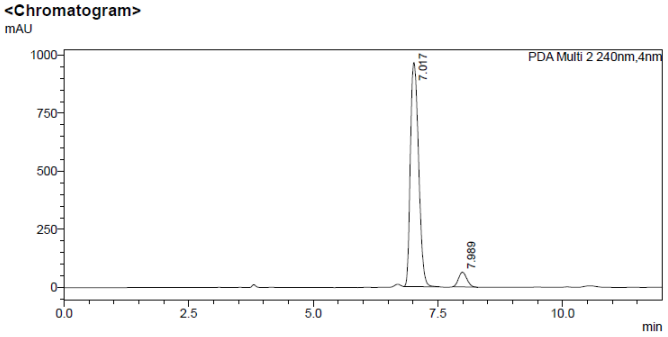



**<Peak Table>**

PDA Ch2 240nm

| Peak# | Ret. Time | Height | Area | Height% | Area% |
|---|---|---|---|---|---|
| 1 | 7.017 | 964041 | 11057125 | 93.857 | 93.795 |
| 2 | 7.989 | 63095 | 731494 | 6.143 | 6.205 |
| Total | | 1027136 | 11788619 | 100.000 | 100.000 |

**General procedure for preparing ketone 103 from β-ketoester 102.** β-ketoester **102** (16.1 mg, 0.0369 mmol, 1.0 equiv) was dissolved in DMSO (0.19 mL) at 23 °C, and then LiCl (3.1 mg, 0.0738 mmol, 2.0 equiv) and $H_2O$ (3.3 mg, 0.184 mmol, 5.0 equiv) were added subsequently. The resultant reaction solution was then warmed to 150 °C using a pre-heated oil bath and stirred at that temperature for 2 h. Upon completion, the reaction contents were cooled to 23 °C and diluted by the addition of $Et_2O$ (4.0 mL). The reaction contents were then poured into a separatory funnel, the layers were separated, and the organic layer was washed with 1:1 mixture of brine and water (2 × 2.0 mL). The organic layer was then dried ($Na_2SO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8:1) provided desired ketone **103** (6.0 mg, 49% yield) as a colorless oil.

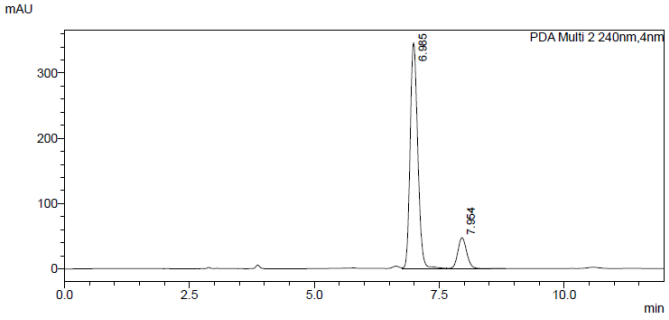
HPLC trace for entry 5 in table 4.1:

SHIMADZU LabSolutions **Analysis Report**

**<Sample Information>**

| | | | |
|---|---|---|---|
| Sample Name | : PQ-1695-2 | | |
| Sample ID | : PQ-1695-2 | | |
| Data Filename | : PQ-1695-3.lcd | | |
| Method Filename | : Default Method.lcm | | |
| Batch Filename | : | | |
| Vial # | : -1 | Sample Type | : Unknown |
| Injection Volume | : 20 uL | | |
| Date Acquired | : 3/17/2021 12:35:35 PM | Acquired by | : Snyder Group |
| Date Processed | : 3/17/2021 1:03:58 PM | Processed by | : Snyder Group |

**<Chromatogram>**




**<Peak Table>**

PDA Ch2 240nm

| Peak# | Ret. Time | Height | Area | Height% | Area% |
|---|---|---|---|---|---|
| 1 | 6.985 | 345925 | 3676198 | 87.924 | 85.961 |
| 2 | 7.954 | 47510 | 600400 | 12.076 | 14.039 |
| Total | | 393435 | 4276597 | 100.000 | 100.000 |

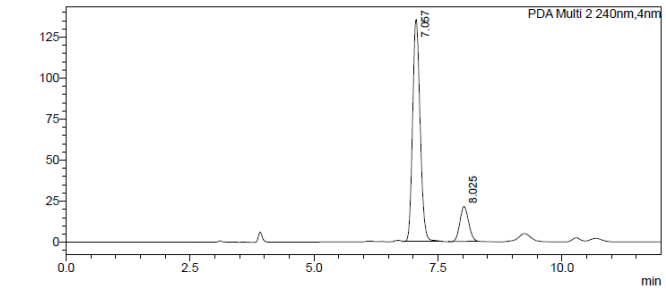
HPLC trace for entry 11 in table 4.1:

SHIMADZU LabSolutions **Analysis Report**

**<Sample Information>**

| | | | |
|---|---|---|---|
| Sample Name | : PQ-1706 | | |
| Sample ID | : PQ-1706 | | |
| Data Filename | : PQ-1706.lcd | | |
| Method Filename | : Default Method.lcm | | |
| Batch Filename | : | | |
| Vial # | : -1 | Sample Type | : Unknown |
| Injection Volume | : 20 uL | | |
| Date Acquired | : 12/10/2020 5:56:06 PM | Acquired by | : Snyder Group |
| Date Processed | : 3/17/2021 9:00:03 AM | Processed by | : Snyder Group |

**<Chromatogram>**




**<Peak Table>**

PDA Ch2 240nm

| Peak# | Ret. Time | Height | Area | Height% | Area% |
|---|---|---|---|---|---|
| 1 | 7.057 | 135380 | 1425525 | 86.440 | 84.523 |
| 2 | 8.025 | 21238 | 261035 | 13.560 | 15.477 |
| Total | | 156618 | 1686560 | 100.000 | 100.000 |

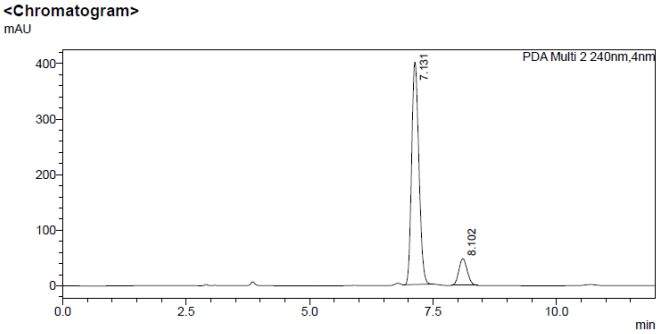
HPLC trace for entry 12 in table 4.1:

SHIMADZU LabSolutions **Analysis Report**

**<Sample Information>**

| | | | |
|---|---|---|---|
| Sample Name | : PQ-1700-2 | | |
| Sample ID | : PQ-1700-2 | | |
| Data Filename | : PQ-1700-2.lcd | | |
| Method Filename | : Default Method.lcm | | |
| Batch Filename | : | | |
| Vial # | : -1 | Sample Type | : Unknown |
| Injection Volume | : 20 uL | | |
| Date Acquired | : 3/18/2021 9:57:45 AM | Acquired by | : Snyder Group |
| Date Processed | : 3/18/2021 10:30:32 AM | Processed by | : Snyder Group |

**<Chromatogram>**




**<Peak Table>**

PDA Ch2 240nm

| Peak# | Ret. Time | Height | Area | Height% | Area% |
|---|---|---|---|---|---|
| 1 | 7.131 | 399781 | 4097706 | 89.327 | 87.850 |
| 2 | 8.102 | 47765 | 566708 | 10.673 | 12.150 |
| Total | | 447546 | 4664414 | 100.000 | 100.000 |

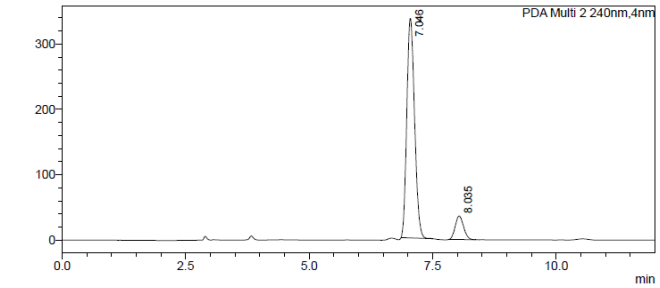
HPLC trace for entry 13 in table 4.1:

SHIMADZU LabSolutions **Analysis Report**

**<Sample Information>**

| | | | |
|---|---|---|---|
| Sample Name | : PQ-1810-1 | | |
| Sample ID | : PQ-1810-1 | | |
| Data Filename | : PQ-1810-1.lcd | | |
| Method Filename | : Default Method.lcm | | |
| Batch Filename | : | | |
| Vial # | : -1 | Sample Type | : Unknown |
| Injection Volume | : 20 uL | | |
| Date Acquired | : 3/17/2021 1:14:31 PM | Acquired by | : Snyder Group |
| Date Processed | : 3/17/2021 1:34:28 PM | Processed by | : Snyder Group |

**<Chromatogram>**




**<Peak Table>**

PDA Ch2 240nm

| Peak# | Ret. Time | Height | Area | Height% | Area% |
|---|---|---|---|---|---|
| 1 | 7.046 | 335603 | 3677124 | 90.316 | 89.666 |
| 2 | 8.035 | 35984 | 423779 | 9.684 | 10.334 |
| Total | | 371586 | 4100903 | 100.000 | 100.000 |

## *4.4 Reference*

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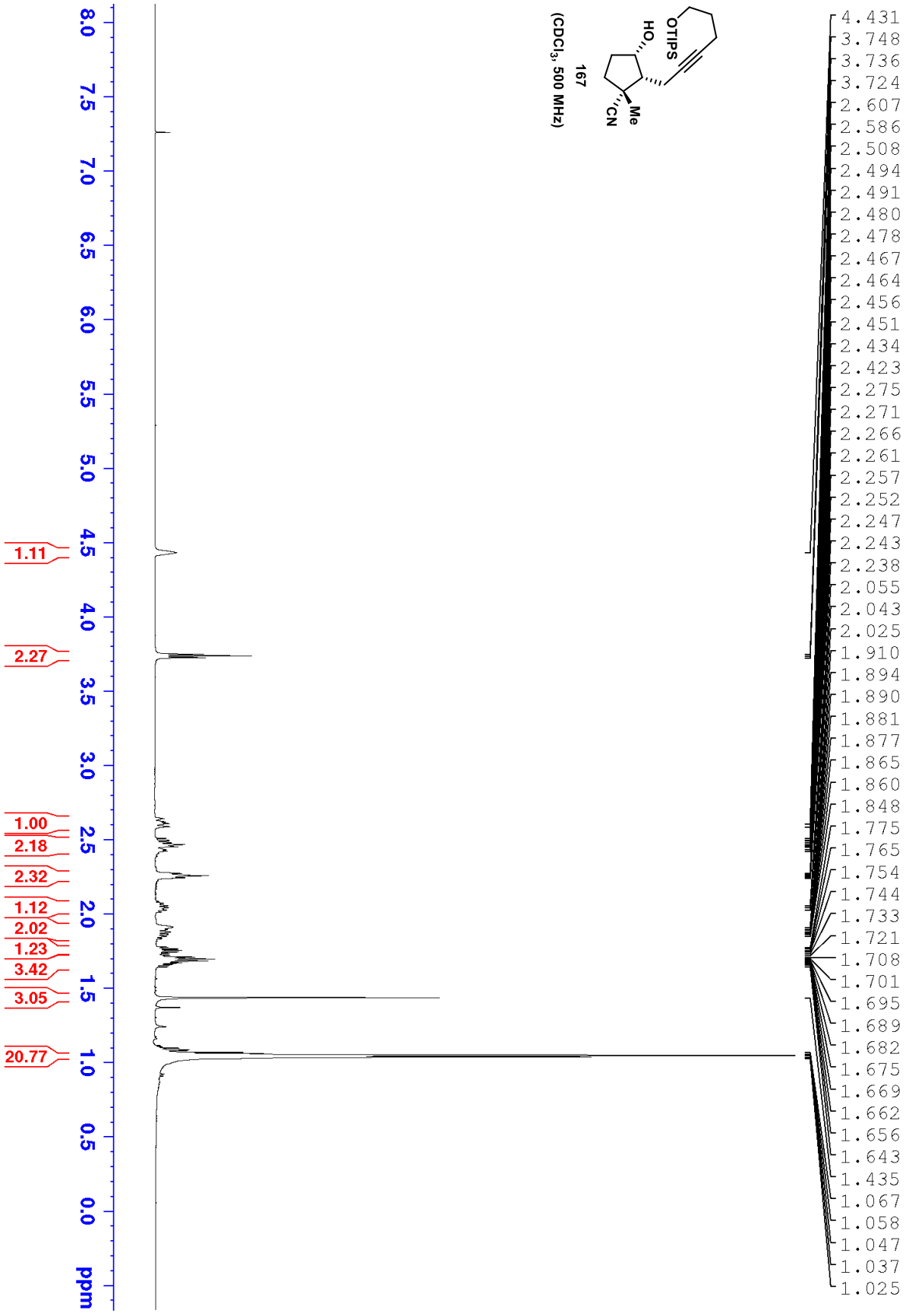
2. Tanaka, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2010**, *132*, 8862.

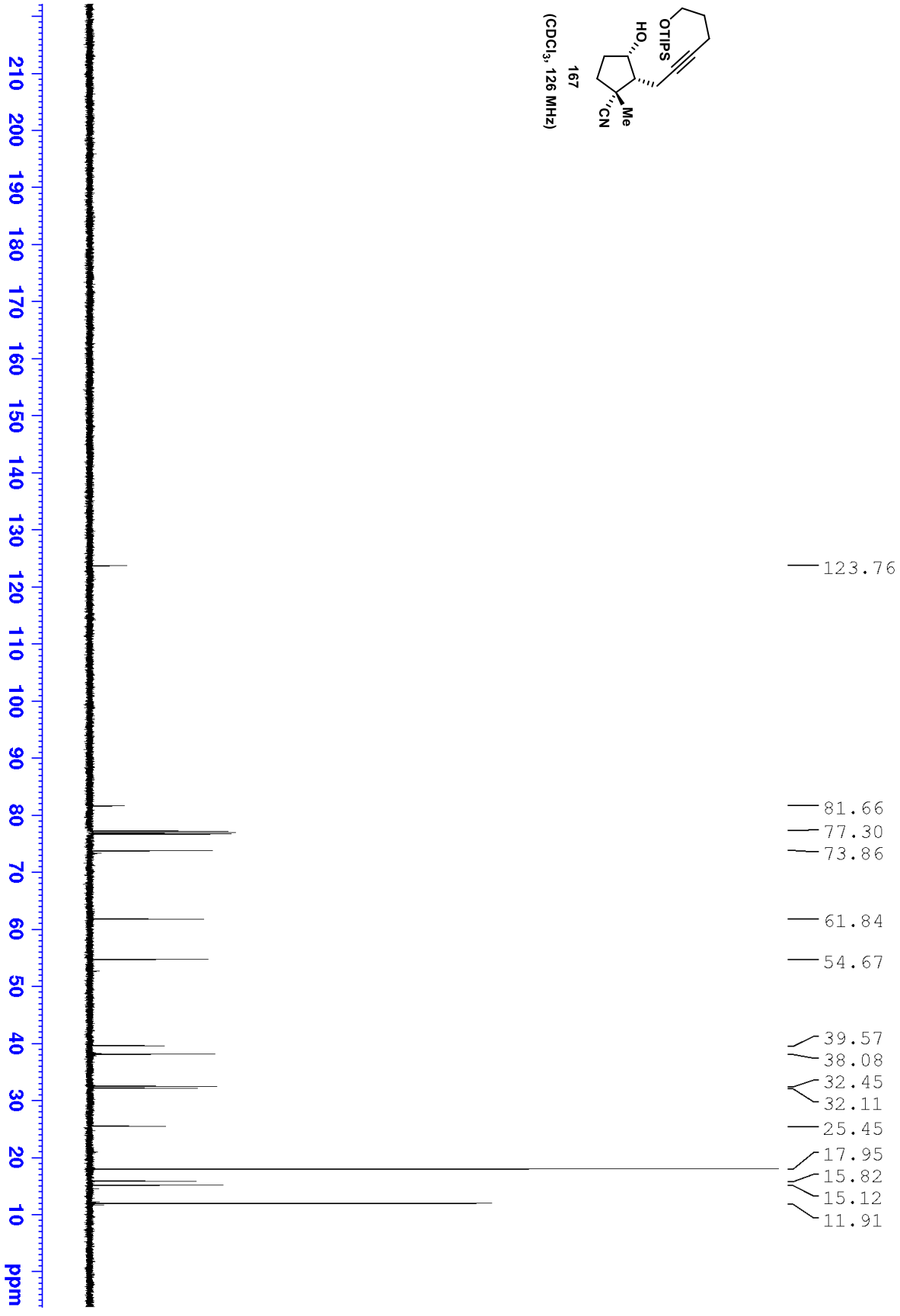
3. Nie, W.; Gong, J.; Chen, Z.; Liu, J.; Tian, D.; Song, H.; Liu, X.-Y.; Qin, Y. *J. Am. Chem. Soc.* **2019**, *141*, 9712.

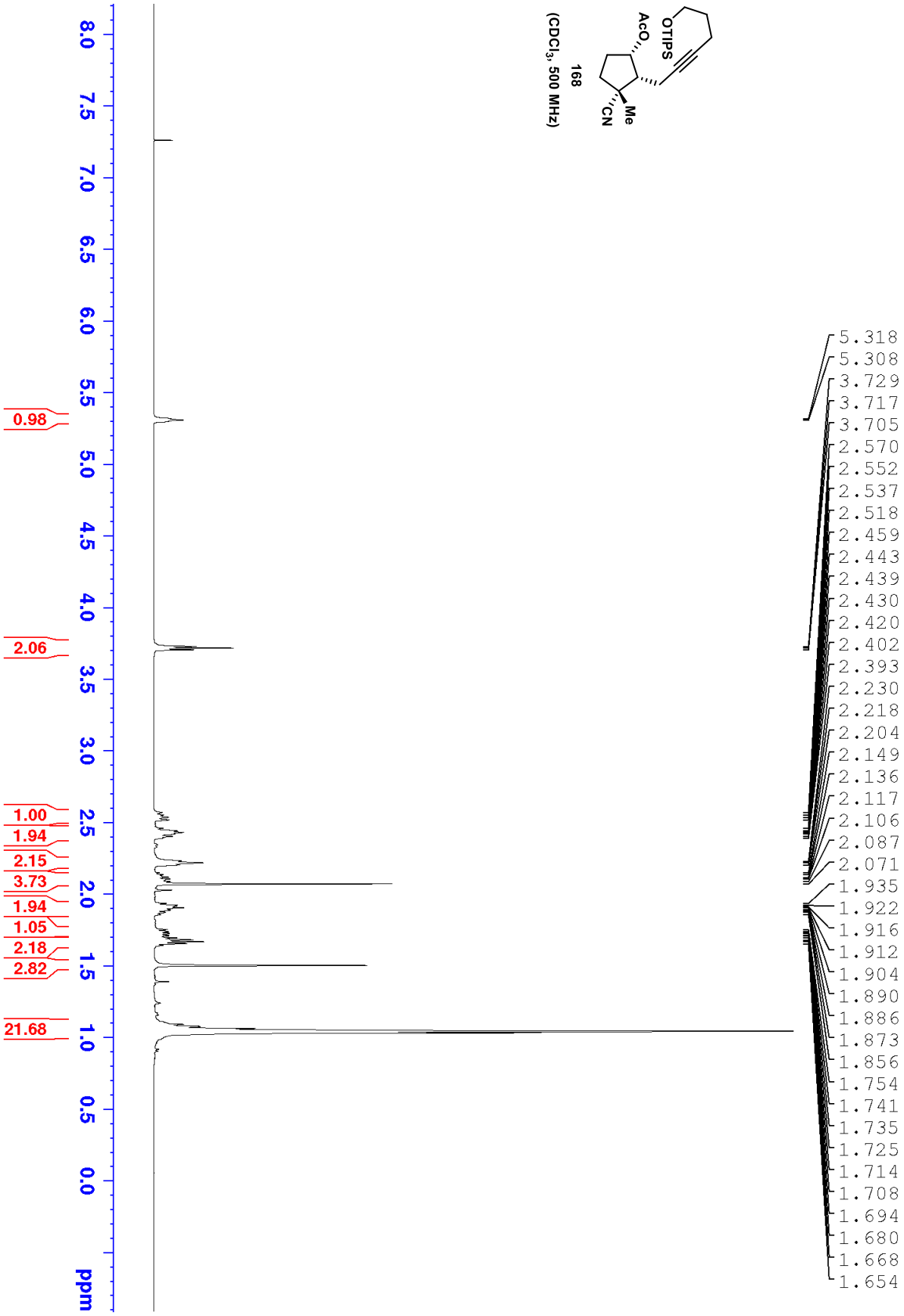
4. De Yan, H. D.; Li, Q.; Wang, Z. *Biotechnol. Appl. Biochem.* **2017**, *64*, 87.

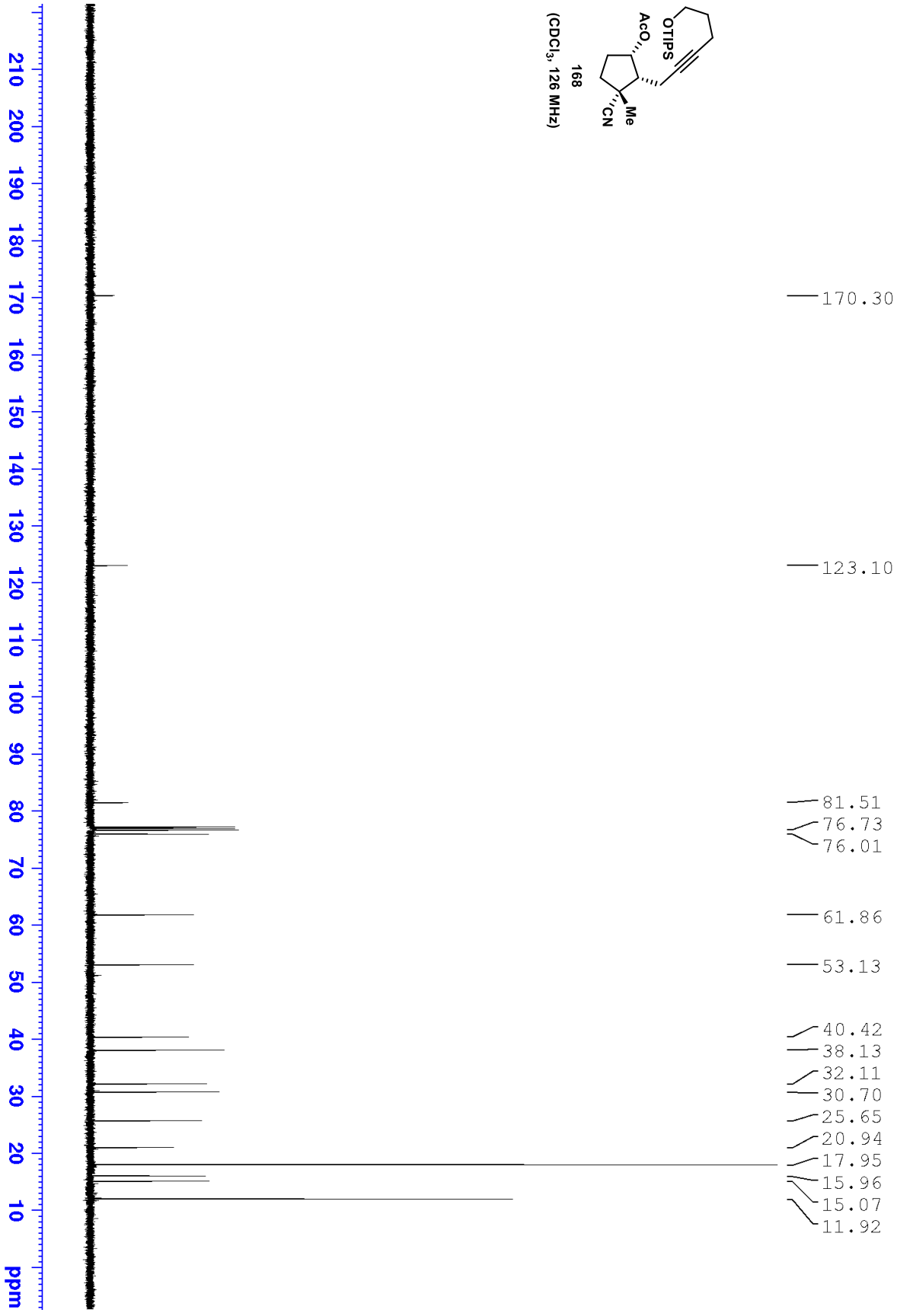
5. a) Vassil, I. O.; Hesse, M. *Helv. Chim. Acta* **1987**, *70*, 1393; b) Zeng, M.; Murphy, S. K.; Herzon, S. B. *J. Am. Chem. Soc.* **2017**, *139*, 16377.

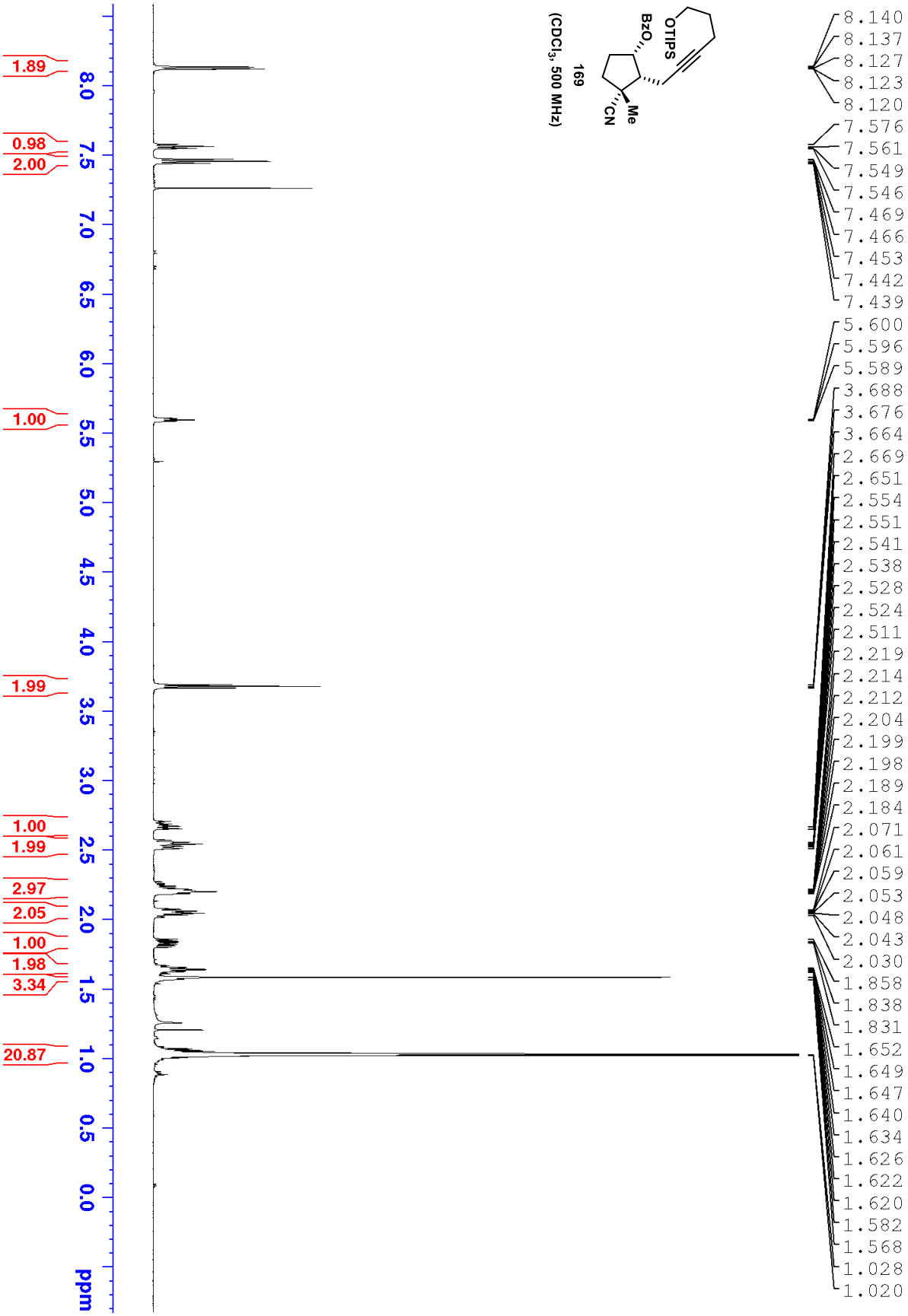
### *4.5 NMR Spectra of Selected Intermediates*

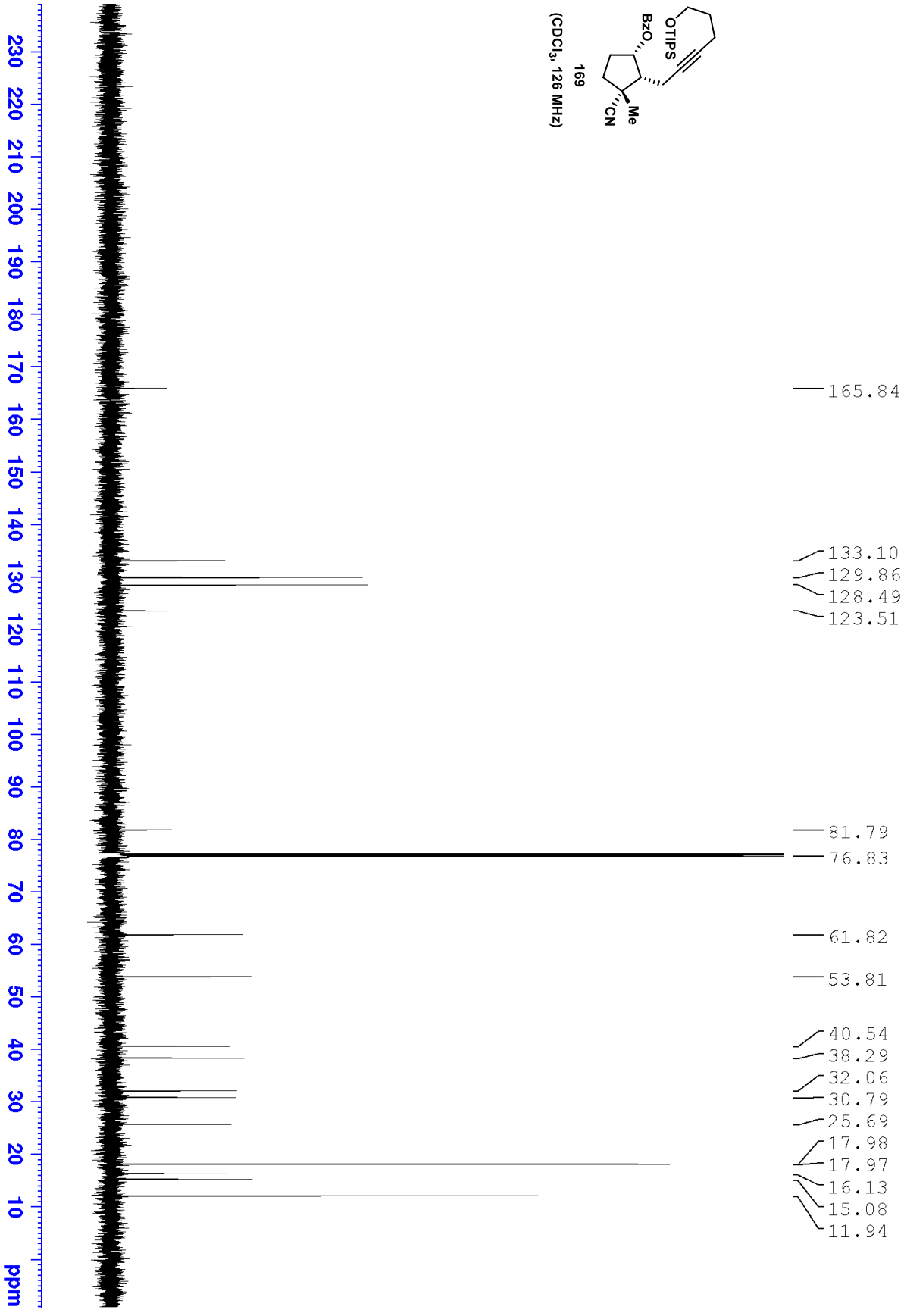

OTIPS
HO
Me
CN
167
(CDCl3, 500 MHz)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.11
2.27
1.00
2.18
2.32
1.12
2.02
1.23
3.42
3.05
20.77
4.431
3.748
3.736
3.724
2.607
2.586
2.508
2.494
2.491
2.480
2.478
2.467
2.464
2.456
2.451
2.434
2.423
2.275
2.271
2.266
2.261
2.257
2.252
2.247
2.243
2.238
2.055
2.043
2.025
1.910
1.894
1.890
1.881
1.877
1.865
1.860
1.848
1.775
1.765
1.754
1.744
1.733
1.721
1.708
1.701
1.695
1.689
1.682
1.675
1.669
1.662
1.656
1.643
1.435
1.067
1.058
1.047
1.037
1.025


OTIPS
HO
Me
CN
167
(CDCl3, 126 MHz)
123.76
81.66
77.30
73.86
61.84
54.67
39.57
38.08
32.45
32.11
25.45
17.95
15.82
15.12
11.91
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


OTIPS
AcO
Me
CN
168
(CDCl3, 500 MHz)
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
ppm
0.98
2.06
1.00
1.94
2.15
3.73
1.94
1.05
2.18
2.82
21.68
5.318
5.308
3.729
3.717
3.705
2.570
2.552
2.537
2.518
2.459
2.443
2.439
2.430
2.420
2.402
2.393
2.230
2.218
2.204
2.149
2.136
2.117
2.106
2.087
2.071
1.935
1.922
1.916
1.912
1.904
1.890
1.886
1.873
1.856
1.754
1.741
1.735
1.725
1.714
1.708
1.694
1.680
1.668
1.654


OTIPS
AcO
Me
CN
168
(CDCl3, 126 MHz)
170.30
123.10
81.51
76.73
76.01
61.86
53.13
40.42
38.13
32.11
30.70
25.65
20.94
17.95
15.96
15.07
11.92
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


169
(CDCl3, 500 MHz)
OTIPS
BzO
Me
CN
8.140
8.137
8.127
8.123
8.120
7.576
7.561
7.549
7.546
7.469
7.466
7.453
7.442
7.439
5.600
5.596
5.589
3.688
3.676
3.664
2.669
2.651
2.554
2.551
2.541
2.538
2.528
2.524
2.511
2.219
2.214
2.212
2.204
2.199
2.198
2.189
2.184
2.071
2.061
2.059
2.053
2.048
2.043
2.030
1.858
1.838
1.831
1.652
1.649
1.647
1.640
1.634
1.626
1.622
1.620
1.582
1.568
1.028
1.020
1.89
0.98
2.00
1.00
1.99
1.00
1.99
2.97
2.05
1.00
1.98
3.34
20.87
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
ppm


OTIPS
BzO
Me
CN
169
(CDCl3, 126 MHz)
165.84
133.10
129.86
128.49
123.51
81.79
76.83
61.82
53.81
40.54
38.29
32.06
30.79
25.69
17.98
17.97
16.13
15.08
11.94
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

# CHAPTER 5

# CONCLUSION AND SUMMARY

We extensively studied the annotinolide family of natural products from the perspective of synthetic chemists. The novel structure of annotinolides led to several inspiring results. These results, especially the ones from the failed route, provided us a lot of insights into the structural properties of the annotinolides:

1) In the synthetic study of annotinolide B (**6**), we developed a concise route for the construction of the C4 and C5 stereocenters in the B ring system in the annotinolides. The exploration of the intramolecular [2+2] reaction did not provide our desired product, but this taught us that with the 7-membered lactone ring, the key cyclobutene ring in annotinolide B (**6**) is difficult to make. Maybe an intermolecular [2+2] with a more reactive alkene partner like in the Ayer's synthesis would have a better chance to succeed.

2) For our first-generation route towards annotinolide C (**7**), D (**8**), and E (**9**), we depicted a similar route to the synthetic study of annotinolide B (**6**). By utilizing Danishefsky's method and a Mitsunobu reaction, we successfully constructed the 7-membered lactone ring moiety with the desired stereochemistry. The envisioned oxidative coupling reaction did not work, but the [3.3.1] hemiketal product **85** and **86** gave us some insights to the strain of the [3.2.1] bicycle system.

3) Based on our analysis of the first-generation route, we chose to synthesize the strained [3.2.1] bicyclic skeleton first. The second-generation route highlights a gold (I)-catalyzed Conia-ene reaction, which built up the strained [3.2.1] bicycle and an all-carbon quaternary center. The use of the nitrile group is also crucial to the stereocontrol. We were unable to construct the lactone ring after the A ring was formed, indicating the lactone ring system should be introduced before the cyclization of the A ring system.

4) By adjusting the reaction sequence, we were finally able to build up all of the ring systems in the annotinolides. The lactone ring was constructed via a classic iodolactonization reaction. The removal of iodine at C4 accidentally led us to the epimers of annotinolide C (**7**) and D (**8**). With the deprotection of the cumbersome TBS group, we could obtain the desired diastereomer and accomplished the divergent synthesis of annotinolide C (**7**), D (**8**), and E (**9**). It is noteworthy that the reactions in the late stage are all diastereoselective, which perfectly illustrates the advantage of our synthetic design and conformational analysis. This route gave us opportunities to explore the potential biosynthetic transformations between these annotinolides. The results from our lab proved the oxidation from annotinolide D (**8**) to E (**9**) and annotinolide C (**7**) to E (**9**) were straightforward, but the isomerization from annotinolide E (**9**) to C (**7**) was difficult. These isomerization results did not match the biosynthetic proposal from the Hu group. This indicates there might be another biosynthetic pathway for annotinolide C (**7**) or a special lactam-lactone isomerase needs to be found.

5) We also developed a formal asymmetric synthesis approach by enzymatic resolution. This allowed us to circumnavigate a challenging asymmetric synthesis of a nitrile-containing quaternary center. Our solution has the advantages of short step count, and the ability to recycle the undesired diastereomer. Although the route suffered from erosion of the enantiomeric excess at later steps, the overall 79% *ee* was ultimately practical in the synthesis.