Title
Strategies Towards the Synthesis of Welwitindolinone C

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Strategies Towards the Synthesis of Welwitindolinone C

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Chemistry

by

Jennifer Pitzen

Dissertation Committee:
Professor Kenneth J. Shea, Chair
Professor David Van Vranken
Professor Sergey Pronin

2015

DEDICATION

For my family, for supporting me.

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- "Studies toward the synthesis of (–)-stenine." Cleary, L.; Mak, V. M.; Pitzen, J.; McCallum, M. E.; Loo, M. M.; Shea, K. J. *Tetrahedron Lett.* **2015**, *56*, 3497–3499.

Presentations

- "Progress Towards the Total Synthesis of Welwitindolinone C." Poster, American Chemical Society Division of Organic Chemistry Graduate Research Symposium, Irvine CA, 2014.

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ABSTRACT OF THE DISSERTATION

Strategies Towards the Synthesis of Welwitindolinone C

By

Jennifer Pitzen

Doctor of Philosophy in Chemistry

University of California, Irvine, 2015

Professor Kenneth J. Shea, Chair

Progress towards the total synthesis of *N*-methylwelwitindolinone C isothiocyanate is reported. The tetracyclic core is established by a key alkylation–type 2 intramolecular Diels–Alder cascade reaction, forming three new carbon-carbon bonds and five stereocenters in one step. Mechanistic studies suggest that alkylation proceeds via a zinc enolate intermediate instead of a silyl ketene aminal, shortening the synthesis by one step. Elaboration of the welwitindolinone core was accomplished with novel use of chlorinating agent $MoCl_5$ to selectively convert a ketone to the vinyl chloride found in the natural product. To circumvent the problematic differentiation of two esters and install a bridgehead amine at an early stage in the synthesis, a series of new dienophiles were prepared. Ultimately selective protection of a diol intermediate allowed for differentiation, but methylation to install the final quaternary center proved to be challenging and remains one of the last hurdles in completing the synthesis.

Chapter 1: Isolation and Bioactivity of Welwitindolinone Alkaloids.

1.1. Isolation and Bioactivity.

The welwitindolinones are a family of alkaloids isolated from the Stigonemataceae family of blue-green algae (cyanobacteria). Welwitindolinones A-C (**1.1**-**1.7**) were first isolated in 1994 from *Hapalosiphon welwitschii* and *Westiella intricata*,[1] while welwitindolinone D (**1.11**) and oxidized welwitindolinones (**1.8**-**1.10**) were isolated in 1999 from *Fischerella muscicola* and *Fischerella major* (Figure 1.1).[2] *N*-methylwelwitindolinone C isothiocyanate (**1.7**) was the major component of the lipophilic extracts. The structurally related fischerindoles (**1.12)**, hapalindoles (**1.13**, **1.14**), and hapalindolinones (**1.15**) were also isolated from these cyanobacteria.

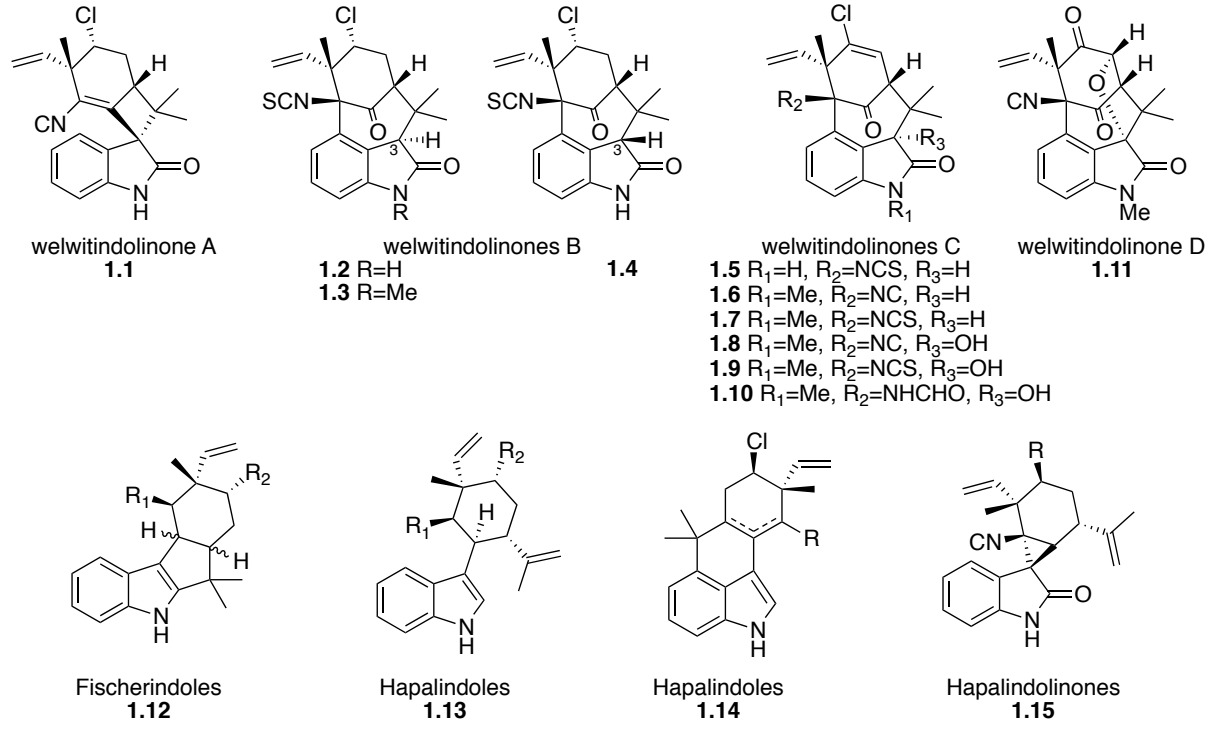


Figure 1.1: *The welwitindolinone alkaloids and related natural products.*

The welwitindolinone alkaloids share many structural similarities but each provides unique synthetic challenges. For example, welwitindolinone A (**1.1**) is the only member that

contains a fused spirocenter while welwitindolinone D's (**1.11**) ethereal bridge makes it more highly oxidized than other members of the family. Additionally, both C3 epimers of welwitindolinone B (**1.3**, **1.4**) are naturally occurring and welwitindolinones C (**1.5**-**1.10**) contain a vinyl chloride moiety. Welwitindolinone A (**1.1**) was the first to be synthesized in 2005,[3] followed by welwitindolinone D (**1.11**) in 2011.[4] Seventeen years after its isolation, the first total synthesis of *N*-methylwelwitindolinone C isothiocyanate (**1.7**) was reported by the Garg group. The welwitindolinones remain a popular target, with many groups reporting syntheses of the core and a number of total and formal syntheses.[5,6] All members of the family have been synthesized, with welwitindolinone B (**1.3**) being the last to be prepared.[7]

Of the welwitindolinones tested, *N*-methylwelwitindolinone C isothiocyanate (**1.7**) had the most interesting biological activity. Several members of the family were shown to reverse P-glycoprotein-mediated multiple drug resistance (MDR).[8] P-glycoprotein (P-gp) is a 170 kDa transmembrane protein. It functions as an ATP-binding cassette (ABC) transporter and is found in epithelial cells of the liver, intestines, and brain capillaries.[9] P-gp transports a wide variety of substrates including many drug molecules out of the cell. It is believed to have a protective function, preventing the accumulation of toxic substances within cells and protecting sensitive organs such as the brain.[10]

The mechanism by which P-gp transports substrates is not fully understood but the active transporter uses energy released by ATP hydrolysis to transport substrates out of the cell. P-gp either acts as a hydrophobic vacuum cleaner, transporting substrate molecules from inside the plasma membrane outside the cell or as a flippase, transporting substrates from the inner leaflet of the plasma membrane to the outer leaflet, where the substrate can then diffuse out of the cell.[11]

Because P-gp substrates are relatively hydrophobic and readily partition into the plasma membrane it is difficult to differentiate between the two proposed transport mechanisms.

The overexpression of P-gp has been implicated in MDR, a condition in which cells acquire simultaneous resistance to a wide variety of structurally and functionally unrelated drugs. MDR has been attributed to over 90% of chemotherapeutic failure in patients with metastatic cancer.[12] P-gp acts as a drug efflux pump to reduce cellular retention of chemotherapeutic drugs. Additionally, P-gp limits the efficacy of treatment for HIV and parasitic diseases such as Malaria and Leishmaniasis.[9]

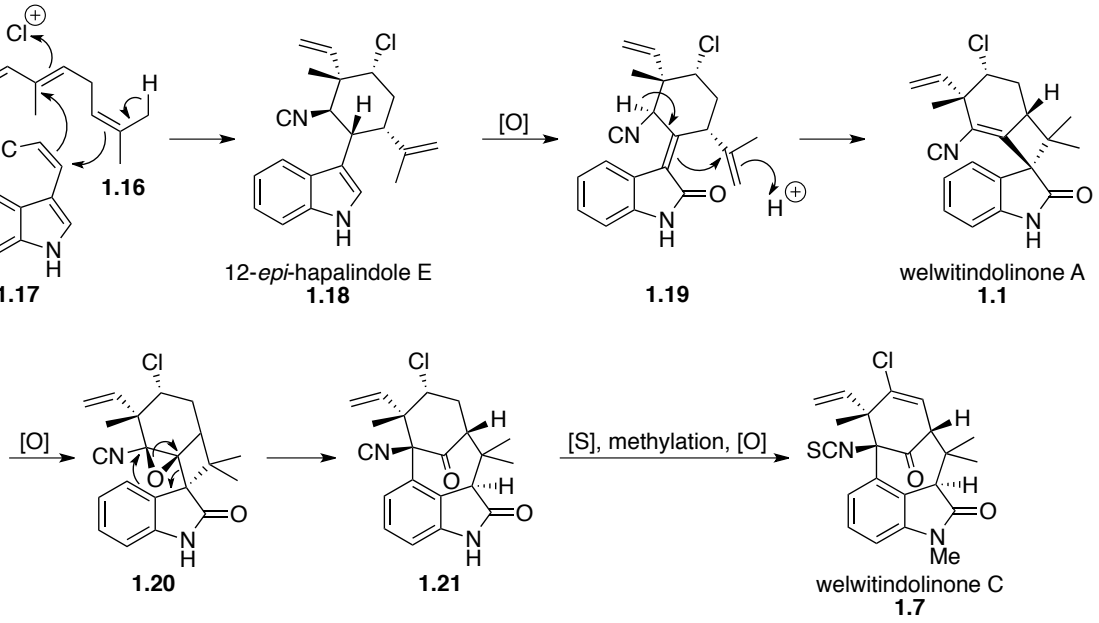
A wide variety of drugs are known substrates for P-gp and there appear to be few structural requirements for substrates. Most have one or two hydrophobic centers or aromatic rings. Substrates with electron donor groups have two groups 2.5 ± 0.3 Å apart or two or three groups 4.6 ± 0.6 Å apart.[13] Efforts to modify drugs to avoid P-gp usually results in a decrease in the desired activity of the drug. Little is known about how inhibitors function or the structural requirements for inhibitors. Many of the first P-gp inhibitors discovered act as P-gp substrates at low concentrations and P-gp inhibitors at high concentrations.[14] A proposed mechanism states that P-gp inhibitors are transported out of the cell then diffuse back into the cell rapidly. At high concentrations the inhibitor is constantly being transported out of the cell, outcompeting other P-gp substrates.[15] Compounds that inhibit P-gp are of interest both for their potential clinical use and to gain a better understanding of P-gp activity.

Welwitindolinone **1.7** was shown to promote the accumulation of known P-gp substrates vinblastine and taxol in vinblastine resistant cells (SK-VLB).[8] It was also significantly less cytotoxic than welwitindolinone **1.5** (IC_{50} = 2.88 μM vs 0.15 μM, respectively). The compounds inhibit P-gp without being transported themselves, as evidenced by no change in cytotoxicity

between MCF-7/ADR cells which overexpress P-gp compared with MCF-7 cells. This otherwise unknown mechanism of action makes the welwitindolinones attractive synthetic targets.

1.2 Proposed Biosynthesis.

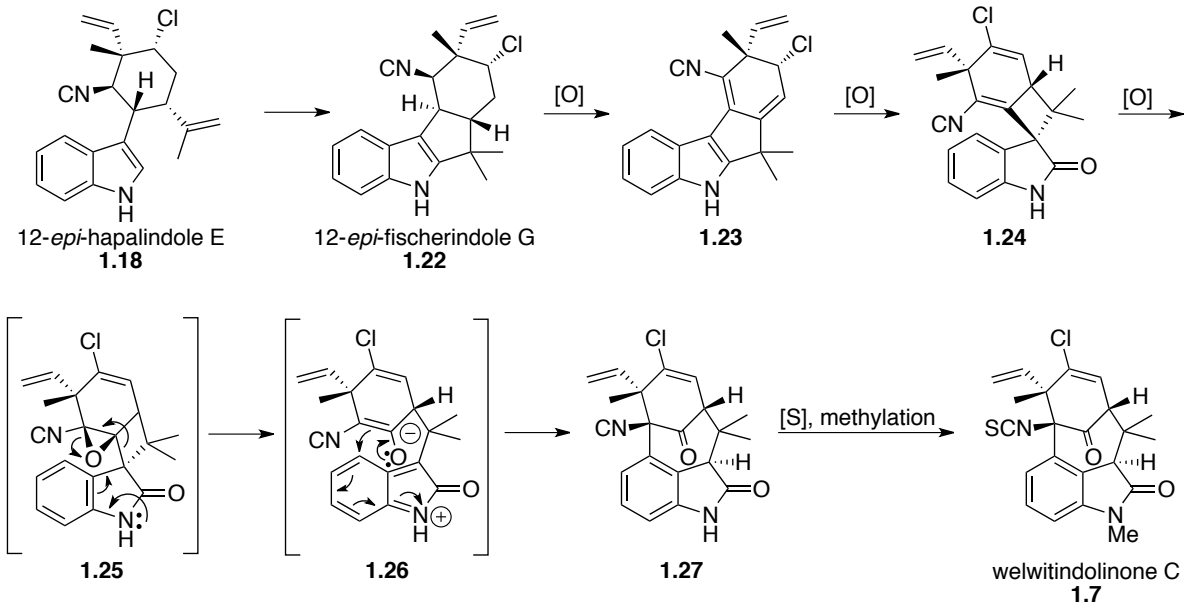
In addition to isolating and evaluating the biological activity of the welwitindolinones, the Moore group proposed the biosynthetic pathway outlined in Scheme 1.1.[1] An enzymatic chloronium-induced polyene cyclization between terpene **1.16** and tryptophan **1.17** could result in formation of 12-*epi*-hapalindole E (**1.18**). Oxidation to proposed intermediate **1.19** could then undergo acid catalyzed cyclization to form welwitindolinone A (**1.1**). Oxidation followed by rearrangement would afford [4.3.1] bicycle **1.21**. Sulfurization, methylation and oxidation would afford welwitindolinone C (**1.7**).



Scheme 1.1: *Moore's proposed biosynthesis.*

Some concerns have been raised about this proposed biosynthetic pathway. Oxidized hapalindole **1.19** has not been isolated, despite the discovery of 63 other members of the family,

suggesting it may not be a biosynthetic intermediate. Additionally, there is little precedent for the rearrangement from epoxide **1.20** to oxindole **1.21**. In response to these criticisms, the Baran group proposed an alternate biosynthetic pathway (Scheme 1.2).[16] Acid catalyzed cyclization of hapalindole **1.18** would lead to fischerindole **1.22**. Allylic oxidation could afford diene **1.23**, and subsequent oxidative ring contraction could result in spirocycle **1.24**. Oxidative ring expansion via enolate **1.26** would then afford welwitindolinone intermediate **1.27**. Sulfurization and methylation and would then afford welwitindolinone C (**1.7**).

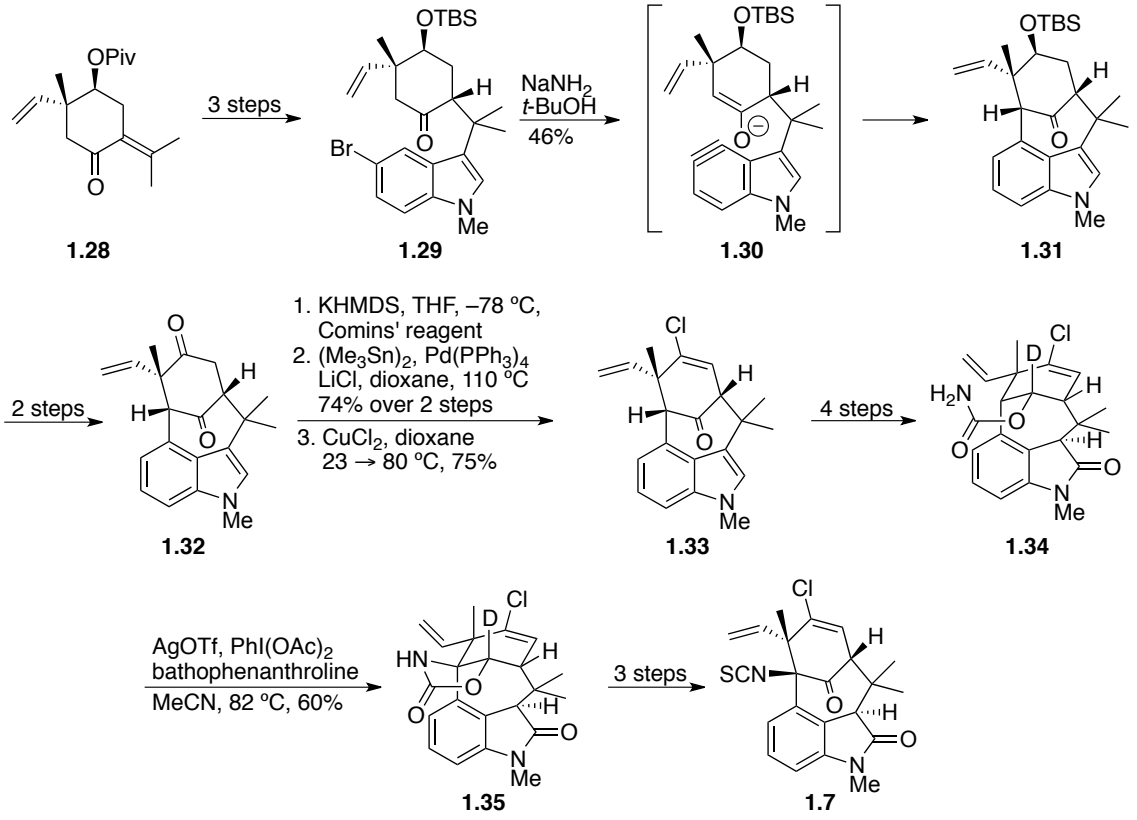


Scheme 1.2: *Baran's alternative proposed biosynthesis.*

1.3 Reported Total and Formal Syntheses.

As the major component of the lipophilic extracts and with the alkaloid with the most interesting biological activity, welwitindolinone C (**1.7**) has been the most popular synthetic target within the welwitindolinone family.[5,6] As a result, a number of groups have developed unique routes to target the core. Overall the synthetic strategies can be divided into three groups. The Garg and Rawal groups couple indole and cyclohexyl fragments, forming the seven-

membered ring last. The Martin & Wood groups begin with an indole fragment, forming the seven-membered ring followed by the cyclohexyl ring.[5] Finally, the Trost and Funk groups begin with the [4.3.1] bicycle and construct the oxindole last.[6]

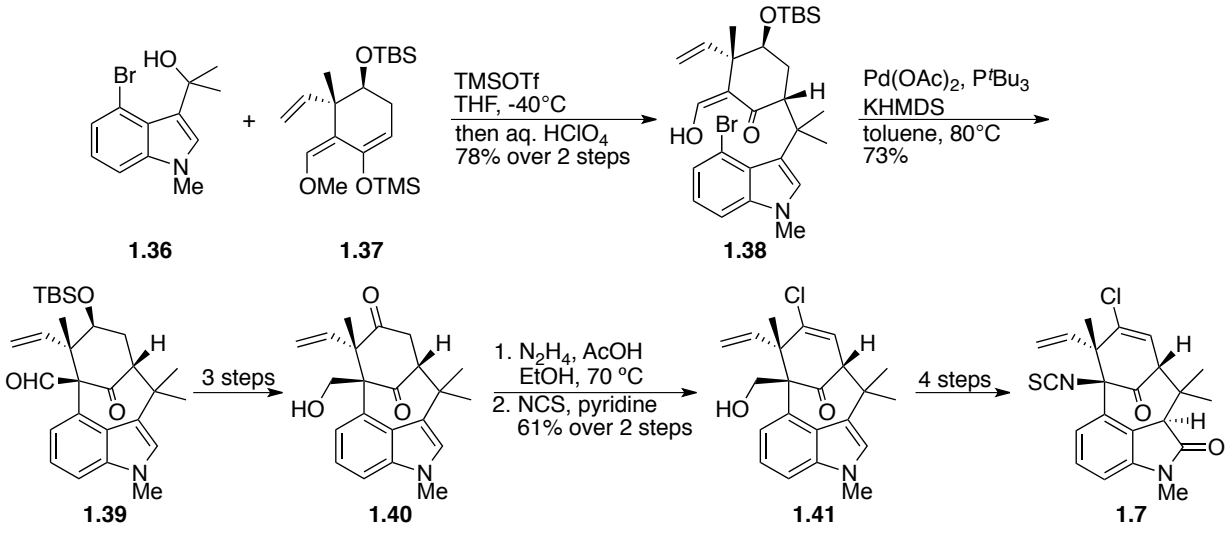


Scheme 1.3: *Garg's synthesis of welwitindolinone C (**1.7**).*

The Garg group was the first to report a total synthesis, and their key step used an aryne cyclization to form the carbon skeleton.[5a,b] From known enone **1.28**, cyclization precursor **1.29** was prepared in three steps (Scheme 1.3). Indolyne cyclization afforded tetracycle **1.31** in moderate yield, which could be elaborated to ketone **1.32**. Installation of the vinyl chloride proved challenging, and a three-step procedure was necessary to prepare the desired functional group from ketone **1.32**. The final challenge in the synthesis was installation of the bridgehead isothiocyanate. Intermolecular functionalization of the sterically congested bridgehead center

was unsuccessful, but intramolecular nitrene insertion provided the desired substitution. Welwitindolinone **1.7** was prepared in 17 steps from known enone **1.28**.

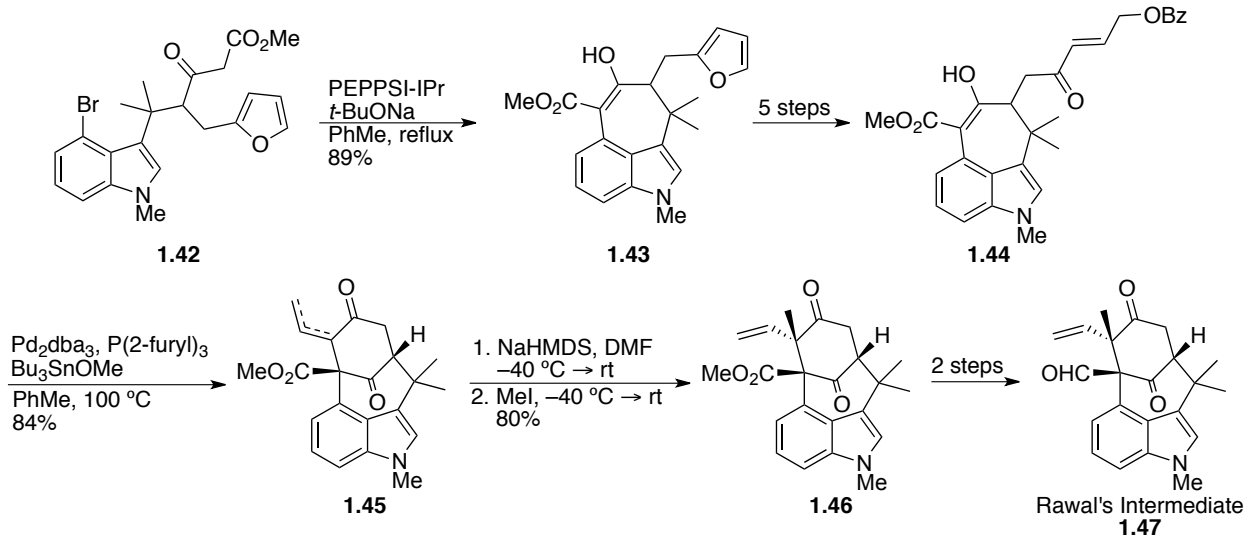
The Rawal group reported the second total synthesis of welwitindolinone C. Keys steps include a palladium-catalyzed enolate arylation and hydrazone chlorination.[5c] Similar to the Garg group's strategy, the synthesis builds off an indole scaffold to prepare tricycle **1.38** (Scheme 1.4). Palladium-catalyzed enolate arylation allows formation of tetracycle **1.39** as a single diastereomer in good yield. Chlorination proved challenging, but hydrazone condensation followed by electrophilic chlorination allowed the preparation of vinyl chloride **1.41** in two steps from ketone **1.40**. Finally, indole oxidation and isothiocyanate installation allowed for the completion of the synthesis. Welwitindolinone C (**1.7**) was prepared in 16 linear steps from commercially available starting materials.



Scheme 1.4: *Rawal's synthesis of welwitindolinone C (**1.7**).*

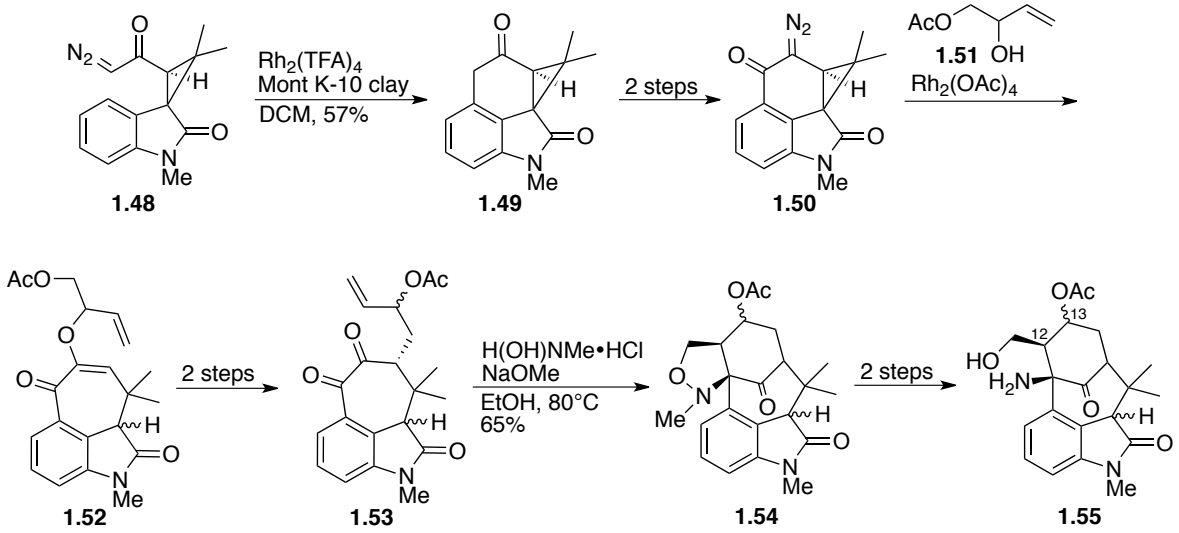
The Martin group reported a formal synthesis in 2012.[5d,e] Their approach was sequential construction of the seven-membered ring followed by the cyclohexanone onto an indole scaffold. Enolate arylation was used to prepare tetracycle **1.43** in high yield (Scheme 1.5). Oxidative cleavage of the furan proved to be challenging, but allowed for the synthesis of enol **1.44**.

Palladium-catalyzed intramolecular allylic alkylation of enol **1.44** afforded tetracycle **1.45** and subsequent diastereoselective methylation provided enone **1.46**. Two additional steps allowed the Martin group to intercept Rawal's intermediate **1.47** in the formal synthesis.



Scheme 1.5: *Martin's synthesis of welwitindolinone C (**1.7**).*

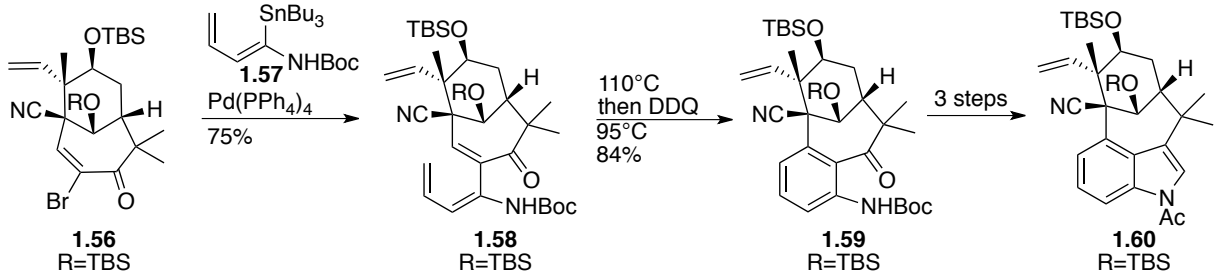
1.4 Selected Alternative Synthetic Approaches.



Scheme 1.6: *Wood's approach to welwitindolinone C (**1.7**).*

In addition to the reported total syntheses, a number of groups have developed unique routes to target the welwitindolinone core. The Wood group utilized a rhodium-catalyzed C–H insertion to construct tetracycle **1.49** (Scheme 1.6)[6a,m]. Ring expansion afforded tricycle **1.52** which was followed by late stage cyclohexanone construction via transannular nitrone cycloaddition to afford [4.3.1] bicycle **1.54**. Amino alcohol **1.55** was revealed after an additional two steps. Key challenges that remain include installation of the methyl group at C12 and vinyl chloride at C13.

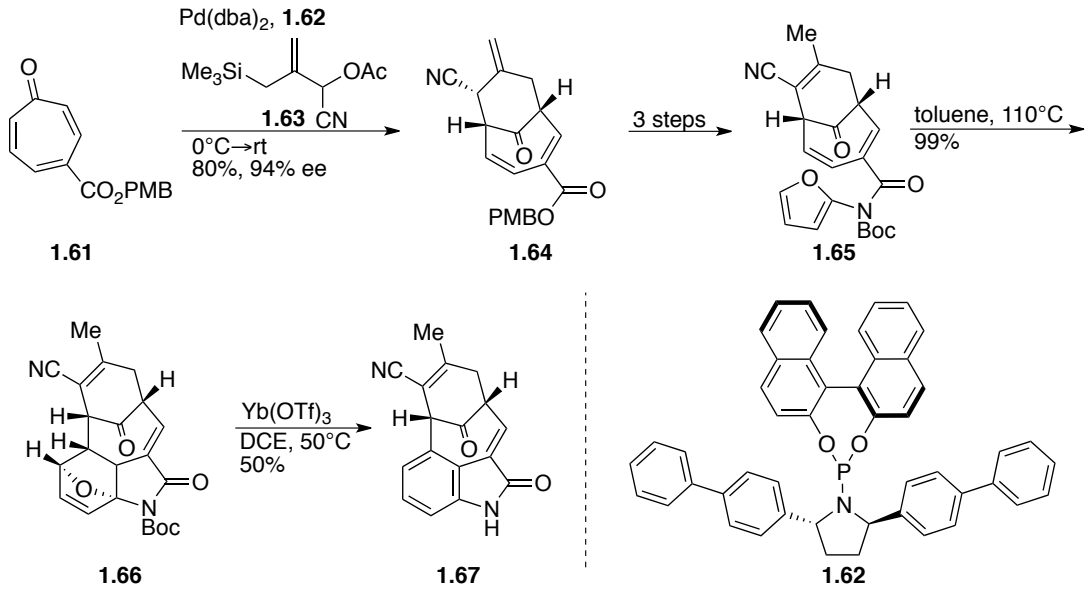
The Funk group took a different approach, constructing the oxindole last.[6e] Stille coupling of bicycle **1.56** (prepared in 11 steps from known compounds) afforded triene **1.58** which underwent clean electrocyclization to tricycle **1.59** (Scheme 1.7). Indole **1.60** was formed in an additional three steps. Early construction of the [4.3.1] bicycle allows the necessary cyclohexanone substitution to be installed with a high degree of diastereoselectivity but adds to the length of the synthesis. At the time of Funk's publication in 2006, indole **1.60** was the most advanced welwitindolinone intermediate reported, but the group has not completed the total synthesis.



Scheme 1.7: *Funk's approach to welwitindolinone C (**1.7**).*

The Trost group uses an approach similar to the Funk group, with a late-stage oxindole construction.[6j] Key steps include an enantioselective [6+3] cycloaddition to construct bicycle **1.64** (Scheme 1.8). Three additional steps converted bicycle **1.64** to triene **1.65** which then

underwent an intramolecular Diels–Alder reaction followed by aromatization to afford welwitindolinone core **1.67**. This route showcases the utility of the [6+3] and [4+2] cycloaddition reactions to rapidly construct complex frameworks.



Scheme 1.8: *Trost's approach to welwitindolinone C (**1.7**).*

1.5 Conclusion.

Due to their interesting biological activity and chemical structure, the welwitindolinones have attracted substantial attention from the synthetic community. A number of different approaches towards the core have been reported, showcasing the utility of various reactions in complex settings. While all members of the family have been prepared, the molecules remain popular synthetic targets.

1.6 References.

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Chapter 2: Initial Studies Toward the Welwitindolinone Core.

2.1. Previous Work in the Shea lab.

While other groups focus on the C4–C11 bond as a key disconnection, we envisioned using the type 2 intramolecular Diels–Alder (IMDA) reaction pioneered in our laboratory to quickly establish the welwitindolinone core and showcase the utility of this reaction. Unlike a type 1 IMDA that results in fused bicyclic systems, a type 2 IMDA provides bridged bicyclic systems with a highly strained bridgehead olefin (Figure 2.1).[1] Two possible type 2 IMDA reactions could give rise to the welwitindolinone core (Scheme 2.1). Retrosynthetic disconnections are possible either at the C13–C14 and C10–C15 bonds (Route A) or the C12–C13 and C10–11 bonds (Route B) to give reasonable intermediates for the type 2 IDMA reaction.

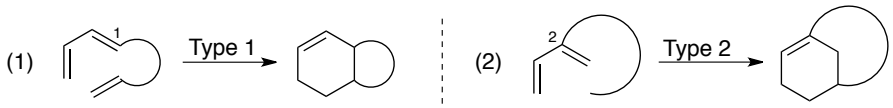
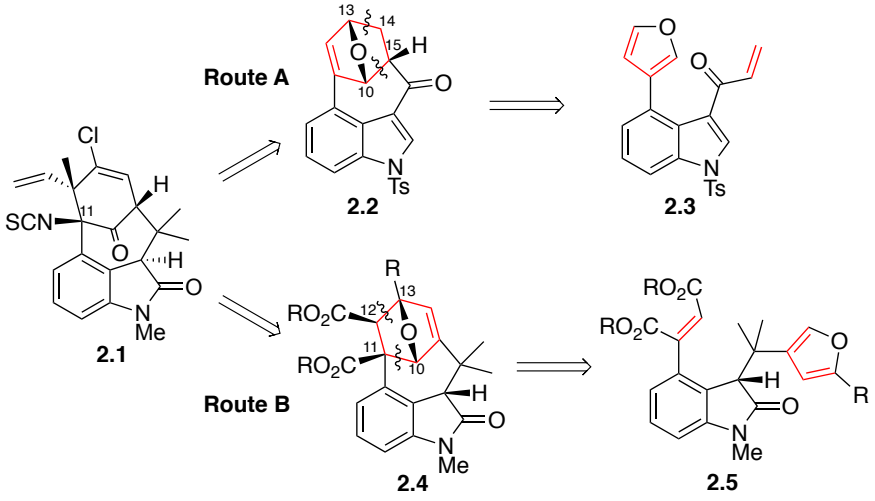
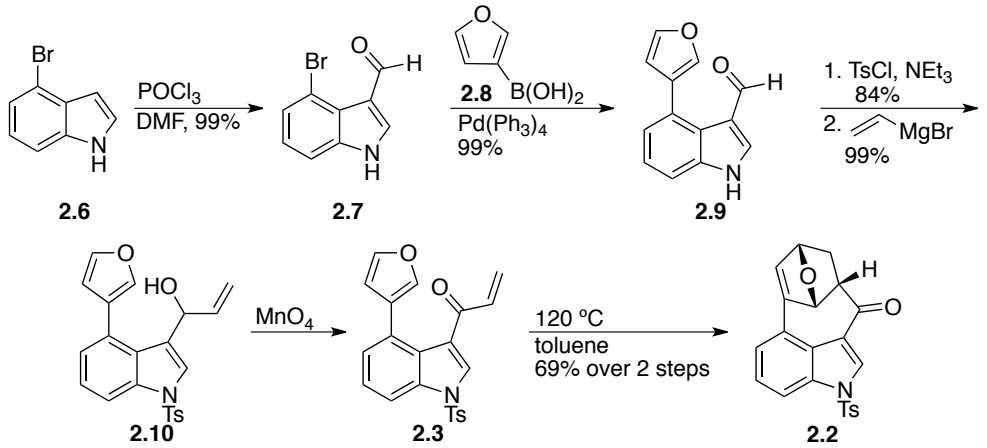


Figure 2.1: *Intramolecular Diels–Alder reactions.*



Scheme 2.1: *Two possible type 2 IMDA reactions to establish the welwitindolinone core.*

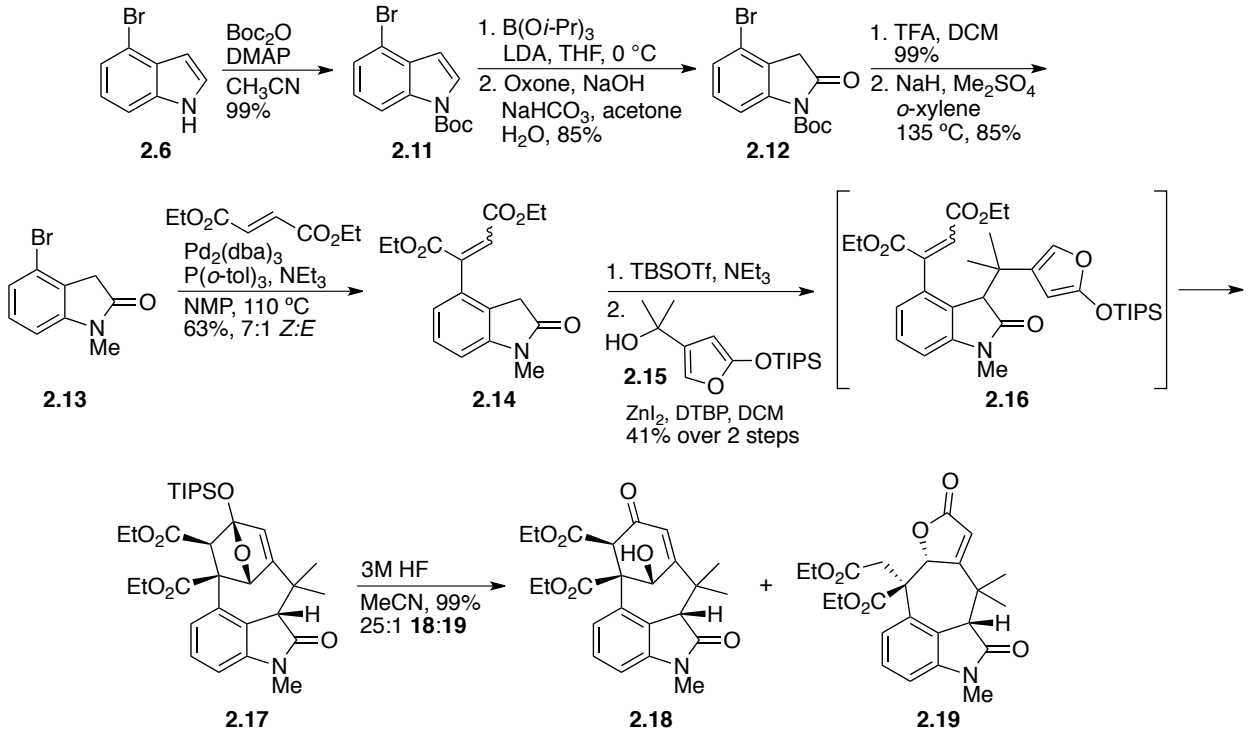
Dr Ryan Lauchli, a former Shea lab graduate student began by investigating the first strategy.[2] Commercially available 4-bromoindole (**2.6**) could be formylated followed by a Suzuki cross–coupling to prepare diene **2.9** (Scheme 2.1). Tosylation, Grignard addition and oxidation afforded IMDA precursor **2.3**. Cyclization of triene **2.3** occurred upon heating, to provide the welwitindolinone core and the first example of a type 2 IMDA reaction with a furan diene. While this route provided quick access to the welwitindolinone core, cycloadduct **2.2** is missing a substantial portion of the carbon skeleton of natural product **2.1**. The second retrosynthetic strategy would provide a more highly functionalized cycloadduct and therefore a more concise route to welwitindolinone **2.1**.



Scheme 2.2: *Initial synthesis of the welwitindolinone core.*

The second strategy was investigated by Dr. John Brailsford.[3] Starting from 4-bromoindole (**2.6**), Boc protection and selective oxidation afforded oxindole **2.12** (Scheme 2.3). Protection was necessary to allow oxidation of the C-2 carbon, following a previously reported industrial procedure.[4] Deprotection, *N*-methylation, and a Heck reaction with diethylfumarate provided oxindole **2.14** in good yield but as a mixture of *E/Z* isomers. Formation of a silyl ketene aminal followed by alkylation with furan **2.15**[5] formed intermediate triene **2.16**, which gratifyingly cyclized under the Lewis acidic reaction conditions providing cycloadduct **2.17** as a

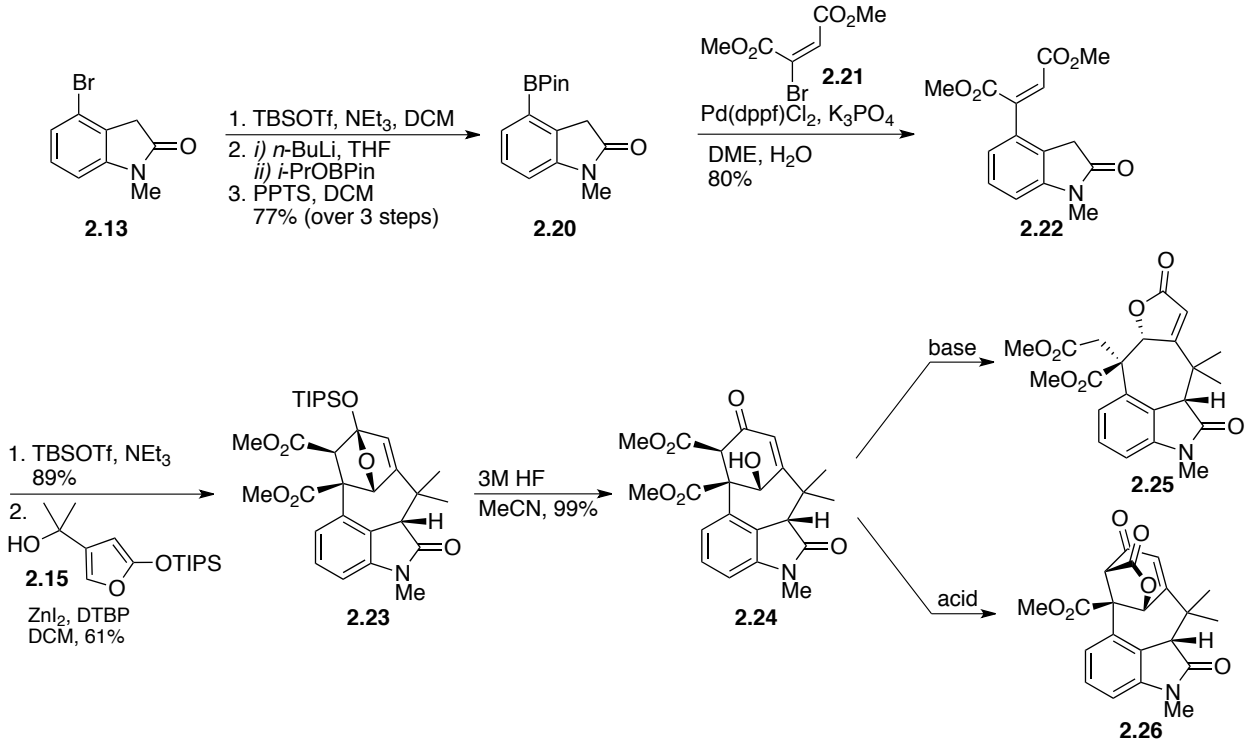
single diastereomer. This reaction forms three new carbon–carbon bonds and five stereocenters in a single step. Surprisingly, hydrogenation of the bridgehead alkene in cycloadduct **2.17** was not observed, even under high pressures of hydrogen with various heterogeneous catalysts. Instead, silyl acetal **2.17** was cleaved with hydrofluoric acid to give enone **2.18**, but a narrow pH range must be maintained during isolation to avoid formation of retro-Claisen product **2.19**. While this strategy led to a more highly functionalized welwitindolinone core, challenges still remain. The yield for the cycloaddition is low, the two esters must be differentiated, and C-12 is lacking a methyl substituent found in the carbon skeleton. Therefore a revised approach was designed by Dr. Leah Cleary to address some of these problems.



Scheme 2.3: *Second generation synthesis.*

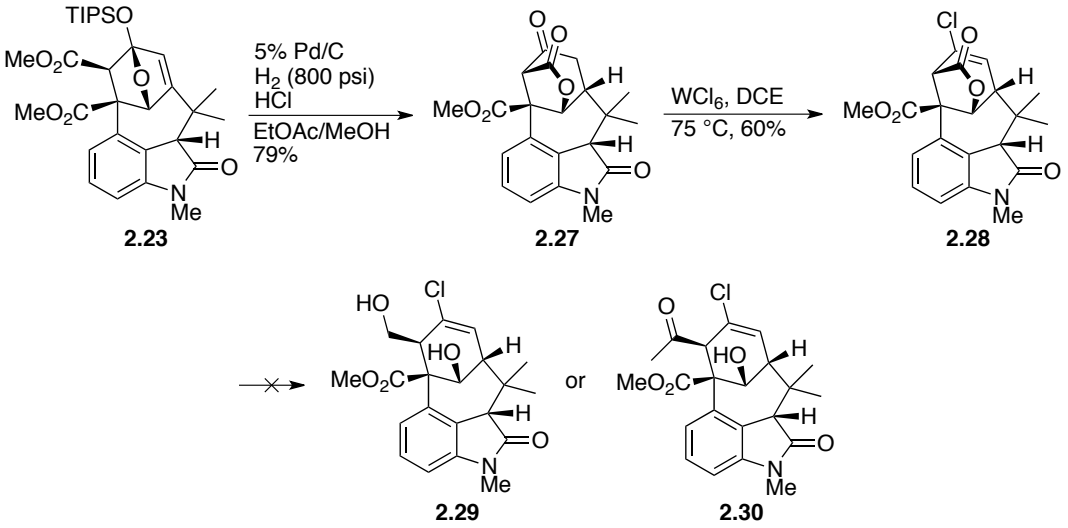
To address the low IMDA yields, methyl esters were proposed as an alternative to the ethyl esters in dienophile **2.14**. Surprisingly, replacing diethylfumarate with dimethylfumarate in the Heck reaction resulted in low yields.[6] A Suzuki cross–coupling reaction was used to solve

this challenge. Bromoindole **2.13** was first protected as the silylketene aminal, followed by lithiation, installation of the pinacol borane and deprotection to boronic ester **2.20** (Scheme 2.4). Subsequent Suzuki cross–coupling proceeded with high yields to prepare dienophile **2.22** as a single isomer. Using previously established conditions, cycloadduct **2.23** was formed in slightly improved yields compared with ethyl cycloadduct **2.17** (54% compared with 41% over 2 steps, respectively). Deprotection to enone **2.24** proceeded as expected, but protection or oxidation of the alcohol proved challenging. Under basic conditions retro–Claisen reaction occurs to form rearranged lactone **2.25**, while under acidic conditions lactonization occurs between the bridging alcohol and the C-12 ester to form ß-ketolactone **2.26**. The solution to this problem was to wait to remove the silyl protecting group until a later stage in the synthesis. Reduction of the C12 ester would prevent both retro–Claisen and lactone formation. Efforts were redirected on reduction of the bridgehead alkene, which had also been problematic.



Scheme 2.4: *Revised second generation approach.*

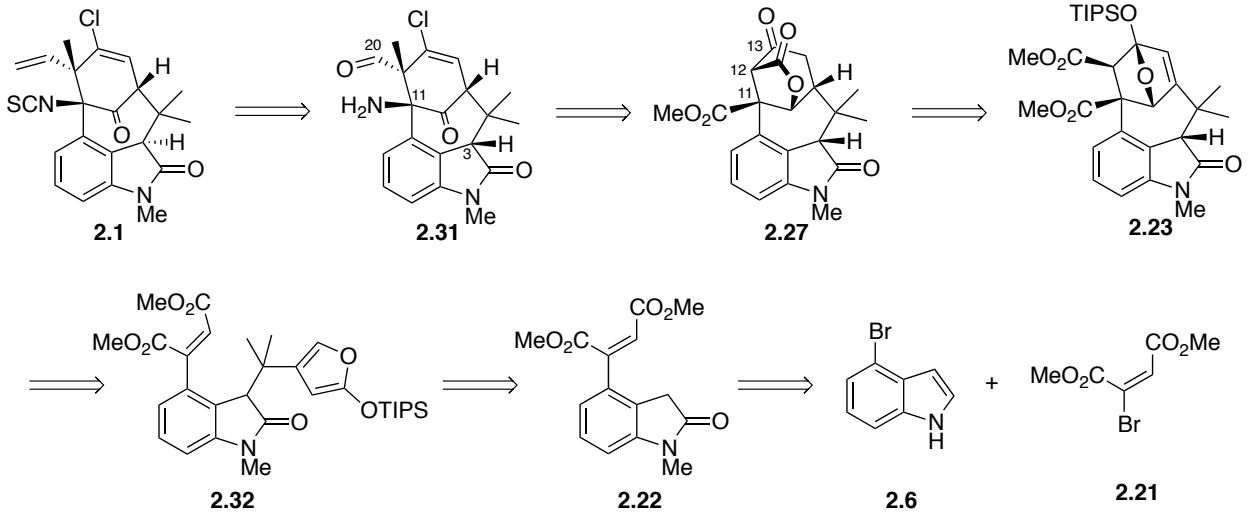
Reduction of the bridgehead alkene prior to deprotection should relieve ring strain and allow the cyclohexane ring to adopt a chair conformation. This would bring the bridging alcohol further from the ketone and ester, hopefully preventing retro–Claisen and lactonization. Despite the expected reactivity of bridgehead alkene **2.23**, reduction was not observed with a variety of heterogeneous catalysts, even under pressures up to 800 psi of hydrogen (Scheme 2.5). Addition of acid in an attempt to accelerate reaction resulted in silyl deprotection, lactonization and subsequent hydrogenation to ß-ketolactone **2.27**.[7] From there, the ketone could chemo and regioselectively be converted to vinyl chloride **2.28** in a single step, showcasing an improvement over the multistep methods used by the Garg and Rawal groups.[8,9] Elaboration of vinyl chloride **2.28** also proved to be challenging, due to the crystalline and unreactive nature of the molecule. Selective reduction of the lactone to diol **2.29** was not observed, nor was nucleophilic opening to ketone **2.30**. At this point I joined the Shea group and Dr. Leah Cleary focused instead on a route towards welwitindolinone B.



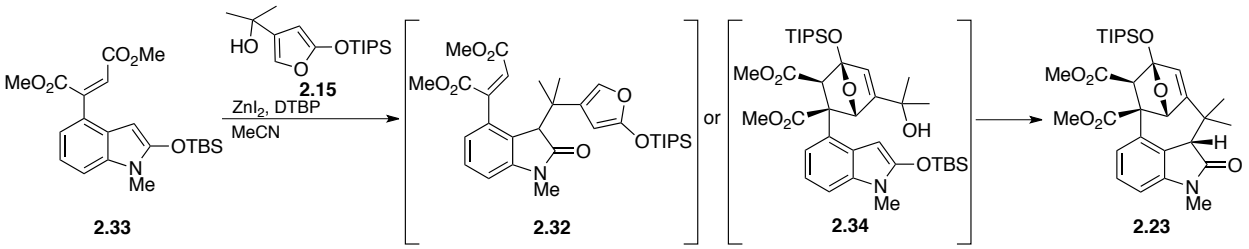
Scheme 2.5: *Hydrogenation and vinyl chloride installation.*

2.2 Type 2 IMDA Optimization and Mechanistic Studies.

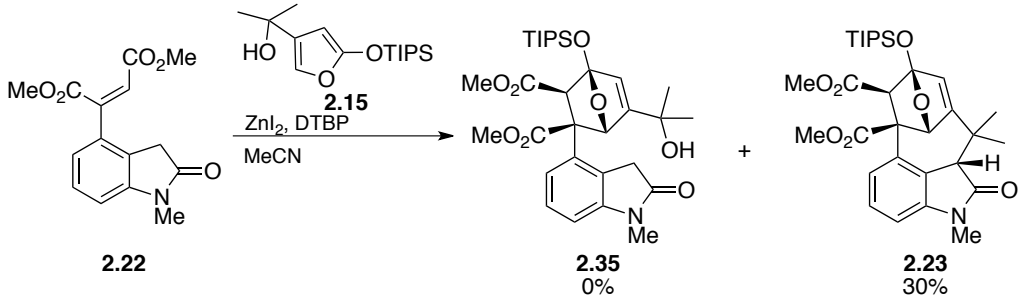
Based on previous work in the group, the welwitindolinone core could be prepared rapidly, and key challenges that remained were late stage methylation and epimerization. Our retrosynthetic strategy using a type 2 IMDA reaction is outlined in Scheme 2.6. Welwitindolinone **2.1** could be prepared from aldehyde **2.31** by epimerization at C3, isothiocyanate installation at C11 and a Wittig olefination at C20. Aldehyde **2.31** would result from methylation at C12, chlorination at C13 and differentiation between the methyl ester at C11 and lactone at C12 in pentacycle **2.27**. Lactone **2.27** would arise from hydrogenation and deprotection of cycloadduct **2.23**, the product of the key type 2 IMDA reaction of triene **2.32**. Triene **2.32** can be prepared from alkylation of vinyl oxindole **2.22**, the cross-coupling product of bromo-alkene **2.21** and a suitably functionalized arene derived from commercially available 4-bromoindole (**2.6**). This strategy provides rapid access to the welwitindolinone core and allows the modular use of alkene coupling partners to incorporate other functionality necessary to complete the total synthesis.



Scheme 2.6: *Retrosynthetic strategy.*



Scheme 2.7: *Possible alkylation-IMDA cascade intermediates.*

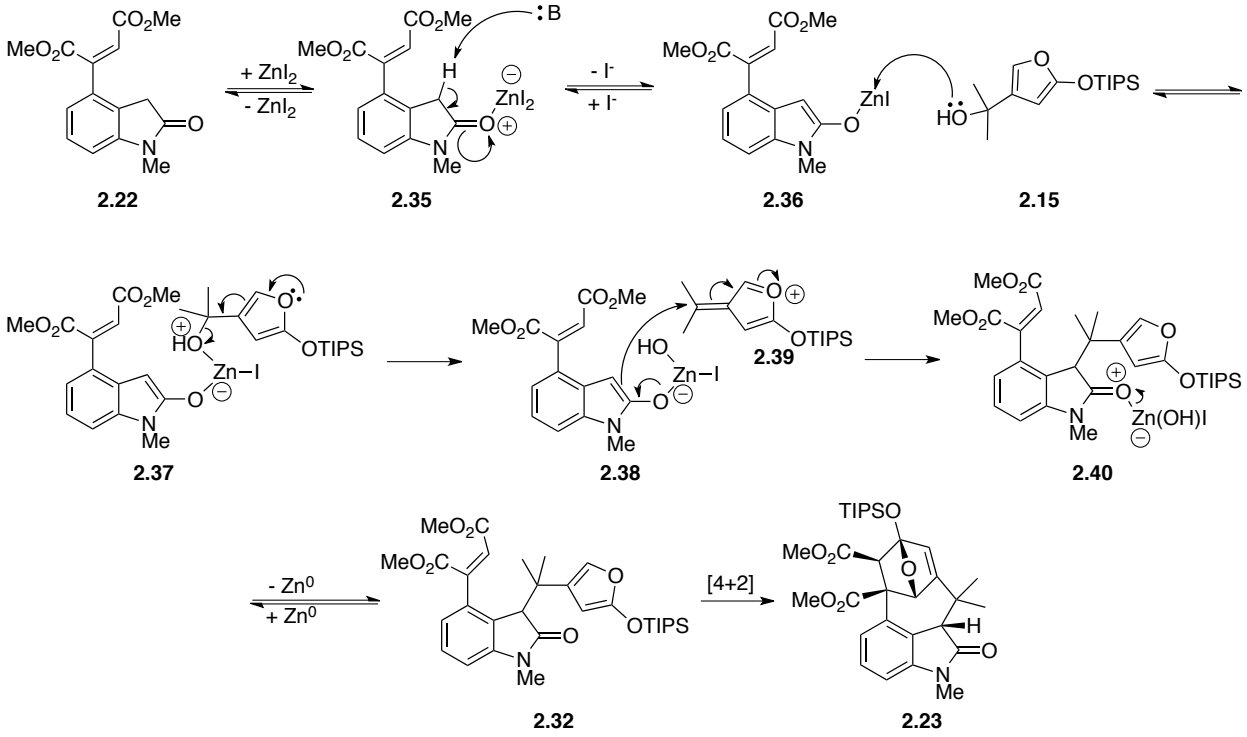


Scheme 2.8: One-step alkylation-IMDA cascade reaction.

Upon joining the project, my initial focus was on further improving the yield of the key type 2 IMDA reaction. While we had initially proposed that alkylation occurs prior to cycloaddition we have no evidence to support that claim. Under the alkylation reaction conditions cycloaddition also occurs without the need to first isolate a triene intermediate (see **2.16**, Scheme 2.3). However, as shown in Scheme 2.7, two different intermediates are possible in this reaction cascade. If the alkylation occurs first, triene **2.32** would be formed, while if an intermolecular cycloaddition occurs first, tetracycle **2.34** would be formed. To determine if the intermolecular Diels–Alder reaction occurs prior to alkylation, vinyl oxindole **2.22** (lacking the silylketene aminal for alkylation) was subjected to the alkylation Diels–Alder cascade reaction conditions (Scheme 2.8). If alkylation occurs prior to cycloaddition, only unreacted starting material is expected, but if intermolecular cycloaddition can occur, tetracycle **2.35** is the expected product. Instead, cascade product **2.23** was isolated, where both alkylation and cycloaddition have occurred, demonstrating that preparation of the silyl ketene aminal is not

necessary for alkylation to occur. This result did not provide information about the order of events during the reaction but allows us to prepare cycloadduct **2.23** directly from oxindole **2.22**.

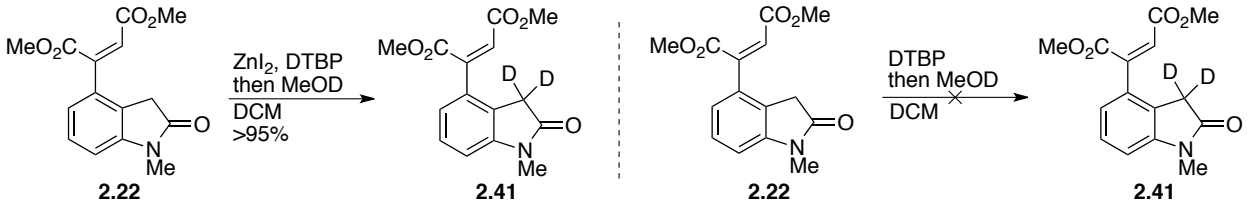
The proposed mechanism of this cascade reaction involves formation of zinc enolate **2.36** prior to alkylation (Scheme 2.9). Loss of iodide allows coordination of zinc enolate **2.38** to furan **2.15**. Formation of oxocarbenium **2.39** and nucleophilic attack by enolate **2.38** results in triene **2.40**. Loss of zinc followed by a type 2 IMDA affords cycloadduct **2.23**, ultimately forming three new carbon–carbon bonds and five new stereocenters. An alternative possible mechanism involves furan coordination prior to enolate formation, and the coordination state of zinc in each intermediate is unknown. In order to optimize the reaction conditions, we want to focus on how zinc facilitates alkylation and whether alkylation or cycloaddition occurs first.



Scheme 2.9: *Proposed mechanism of the alkylation-IMDA cascade.*

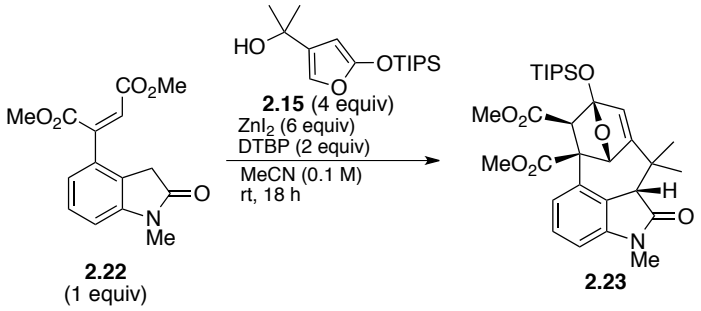
Deuterium incorporation studies were performed to determine the conditions needed for enolization. Vinyl oxindole **2.22** was treated with zinc iodide and di-*tert*-butylpyridine (DTBP)

then quenched with CD_3OD (Scheme 2.10). Analysis of the ^1H NMR spectrum showed >95% deuterium incorporation. When vinyl oxindole **2.22** was treated with only DTBP then CD_3OD, no disappearance in the ^1H NMR spectrum of the oxindole protons was observed, indicating that zinc iodide is required for enolization. Additional experiments suggest alkylation occurs prior to cyclization (see chapter 3).



Scheme 2.10: *Deuterium incorporation into vinyl oxindole **2.22**.*

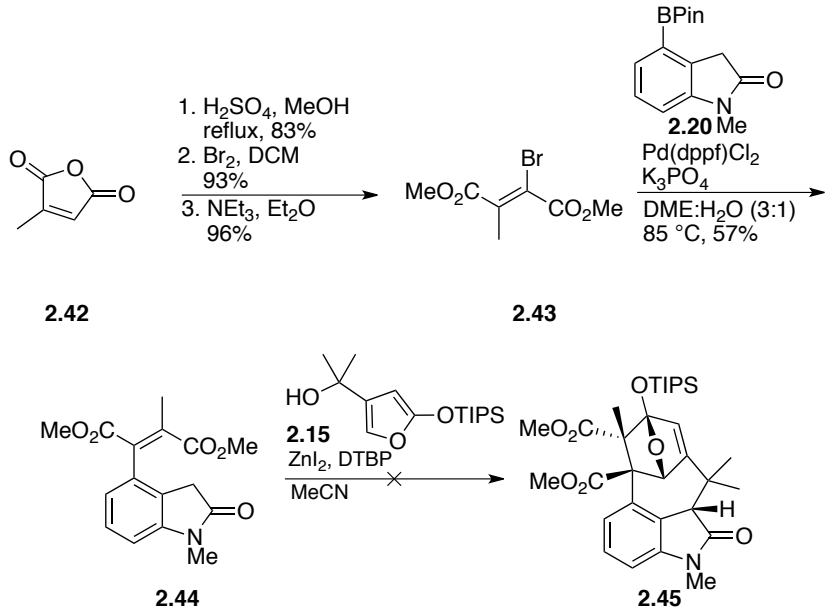
Table 2.1: *Optimization of the alkylation-IMDA cascade reaction.*



Entry	Conditions	Yield	Entry	Conditions	Yield
1	Original conditions	20-40%	10	1.5 equiv **2.15**	15%
2	1 equiv H_2O	NR	11	5 equiv DTBP	NR
3	4Å MS	NR	12	5 equiv DTBP, 65 ºC	30%
4	1 equiv $MgSO_4$	38%	13	1.5 equiv ZnI_2	30%
5	0.2M	38%	14	3 equiv ZnI_2	40%
6	0.05M	30%	15	12 equiv ZnI_2	40%
7	0 ºC	NR	16	Add **2.15** after 12 h	40%
8	40 ºC	20%	17	Add **2.15** over 2 days	45%
9	4 days	45%			

After confirming the formation of a zinc enolate, efforts were made to optimize the alkylation–IMDA cascade reaction. Low yields in this reaction were generally attributed to incomplete consumption of vinyl oxindole **2.22** and competing decomposition of furan **2.15**

under the Lewis acidic reaction conditions. Increasing reaction times from 18 hours to four days or heating did not improve the yield (Table 2.1). The reaction is extremely sensitive to water but when desiccants such as molecular sieves or anhydrous magnesium sulfate were added to the reaction, yields did not improve. The amount of zinc iodide can be decreased to from six to three equivalents without affecting the yield but with 1.5 equivalents the yield decreased. Increasing the concentration of DTBP caused the zinc to dissolve in acetonitrile but stopped the reaction. Sequentially adding one equivalent of furan **2.15** every 12 hours over two days lead to the highest yields. It was found that furan **2.15** is unstable under the reaction conditions and deprotection to the butenolide is a competing side reaction. Cycloadduct **2.23** was isolated in 47% yield using the optimized conditions.

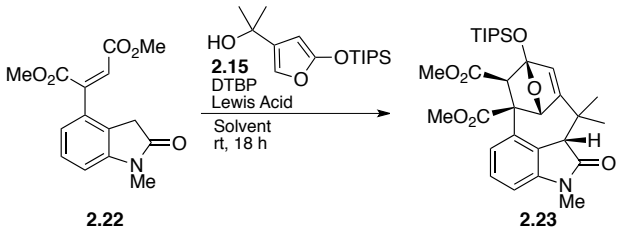


Scheme 2.11: *Synthesis of vinyl oxindole **2.44**.*

To introduce the methyl group at C12 present in the natural product at an early stage, tetrasubstituted vinyl oxindole **2.44** was prepared according to previously established procedures (Scheme 2.11).[10] Unfortunately, when subjected to the alkylation IMDA cascade conditions, cycloadduct **2.44** was not observed. Lewis acids were screened in order to find conditions that

induced the alkylation–cycloaddition cascade but did not contribute to the rapid decomposition of furan **2.15**. Vinyl oxindole **2.22** was used instead of tetrasubstituted oxindole **2.44** because it is more readily available and the formation of cycloadduct **2.23** can be easily quantified by ^{1}H NMR. Of the metals screened, only zinc, copper and silver resulted in the formation of cycloadduct **2.23** (Table 2.2). A solvent screen with zinc iodide showed that DCM as a solvent improved the yield while using DMF and THF dissolved the zinc iodide but resulted in no detectable formation of cycloadduct **2.23**. Switching from zinc iodide to copper (II) triflate also improved the yield compared to the original conditions. These results suggest that further screening of Lewis acids and solvents can further increase the yield of the cascade reaction and tetrasubstituted vinyl oxindole **2.44** will be subjected to the optimized conditions to determine if cycloadduct **2.45** can be prepared. The use of copper Lewis acids also provides an opportunity to add chiral ligands to make the cascade enantioselective.

Table 2.2: *Screening Lewis acid and solvent effects on the alkylation-IMDA cascade reaction.*



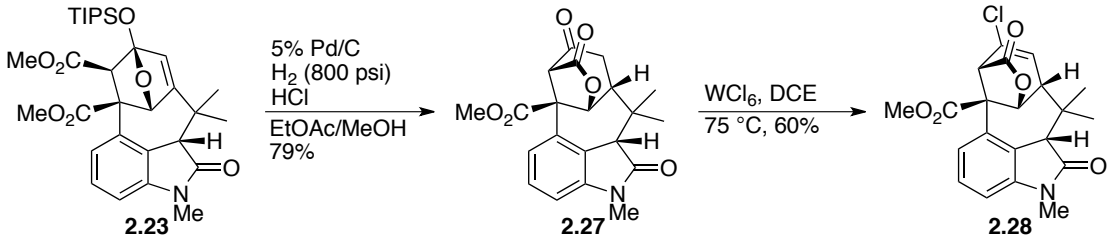
2.22 **2.23**

Entry	Lewis Acid	Solvent	Yield	Entry	Lewis Acid	Solvent	Yield
1	$Sc(OTf)_3$	MeCN	NR	13	ZnI_2	$CHCl_3$	20%[a]
2	$NiCl_2$	MeCN	NR	14	ZnI_2	DCE	50%[a]
3	$Ir(OTf)_3$	DCE	NR	15	ZnI_2	DCM	65%[a]
4	Me_3Al	DCE	NR	16	$ZnCl_2$	DCM	17%[a]
5	LiI	THF	NR	17	$ZnBr_2$	DCM	16%[a]
6	AgOTf	MeCN	35%[a]	18	$Zn(OTf)_2$	DCM	6%[a]
7	$Cu(OTf)_2$	DCE	50%	19	CuI	DCM	NR
8	$Zn(OTf)_2$	MeCN	14%[a]	20	CuBr	DCM	NR
9	ZnI_2	MeCN	20-40%	21	CuCl	DCM	NR
10	ZnI_2	DMF	NR	22	$CuBr_2$	DCM	decomp
11	ZnI_2	THF	NR	23	$CuCl_2$	DCM	decomp
12	ZnI_2	Toluene	20%[a]	24	$Cu(OTf)_2$	DCM	15%[a]

a) Determined by ^{1}H NMR

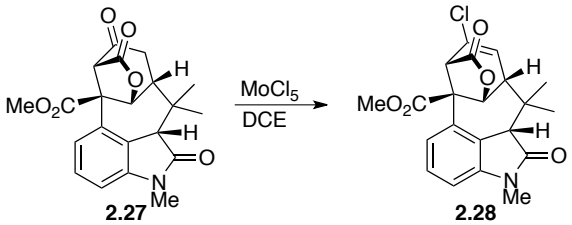
2.3. Cycloadduct Elaboration.

After optimization of the alkylation–IMDA cascade reaction, efforts were directed towards the elaboration of cycloadduct **2.23**. Based on the work by Dr. Leah Cleary, hydrogenation at high pressure in the presence of hydrochloric acid afforded lactone **2.27** (Scheme 2.12).[6] Acid facilitates deprotection of the silyl ether and the resulting free alcohol forms a stable five-membered lactone. Ketone **2.27** was then converted to vinyl chloride **2.28** using tungsten (VI) chloride.[8]



Scheme 2.12: *Hydrogenation and installation of the vinyl chloride.*

Table 2.3: *Optimization of the $MoCl_5$ chlorination.*

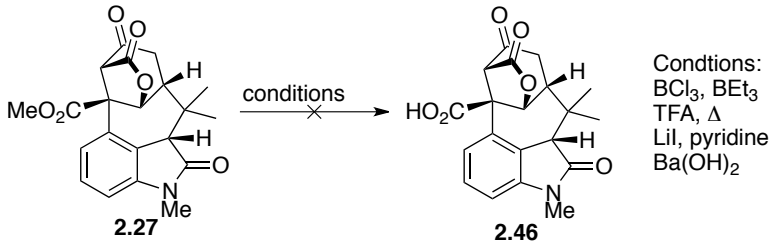


Entry	Temperature	Concentration	Time	$MoCl_5$	Yield
1	75 ºC	0.2 M	15 h	4 equiv	decomp
2	45 ºC	0.2 M	15 h	4 equiv	41%
3	rt	0.2 M	15 h	4 equiv	20%
4	45 ºC	0.05 M	24 h	2 equiv	80%

The Rawal group experienced difficulties installing the alkyl chloride adjacent to the quaternary center at C12 in welwitindolinone **2.1** and the Garg group used a three step procedure to convert the ketone into a vinyl chloride to complete the synthesis of welwitindolinone **2.1** (see chapter 1).[9] In order to avoid difficulties in installing the vinyl chloride at a late stage, we

searched for a chlorinating reagent that is smaller and more reactive than tungsten (VI) chloride. Following periodic trends we chose to use molybdenum (V) chloride, which is not known to produce vinyl chlorides but has been used to chlorinate alkenes and alkynes.[11] At high temperatures $MoCl_5$ lead exclusively to decomposition of ketone **2.27** but lowered temperatures led to formation of desired chloride **2.28** (Table 2.3). Compared to WCl_6, $MoCl_5$ allows for shorter reaction times and less decomposition of the starting material is observed. The use of $MoCl_5$ to convert ketones to vinyl chlorides has not been reported in the literature and the scope of this reagent is being investigated.

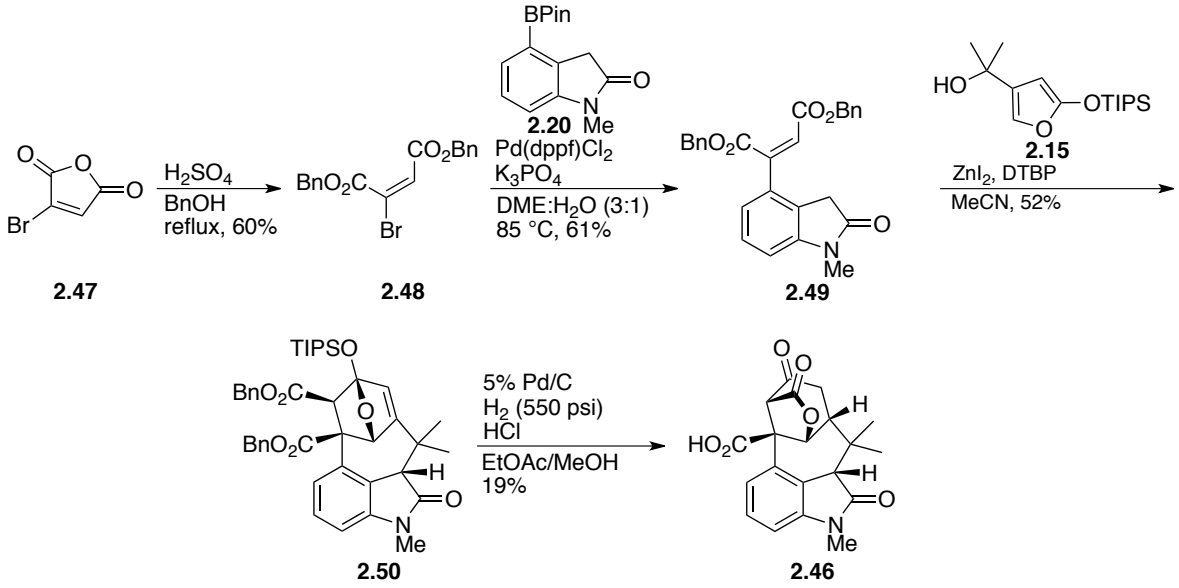
Based on the work by Dr. Leah Cleary, selective reaction of the lactone was ruled out as a strategy for elaboration. Instead, saponification of the methyl ester of lactone **2.27** was investigated (Scheme 2.13). Subsequent reduction of either the carboxylic acid or lactone group of **2.46** could then be used to differentiate the two carbonyl groups. The conditions screened were limited to those that are selective for methyl esters due to the presence of a lactone and an amide. To further complicate hydrolysis, the methyl ester is adjacent to a quaternary bridgehead carbon making it fairly hindered. None of the conditions screened resulted in the formation of a new compound. We attribute the lack to reactivity to the low solubility of pentacycle **2.27** in a variety of organic solvents.



Scheme 2.13: *Attempted methyl ester hydrolysis.*

To circumvent the difficult hydrolysis, the synthesis was revised to include benzyl esters on the oxindole dienophile instead of methyl esters (Scheme 2.14). The benzyl esters would be

cleaved during hydrogenation of the bridgehead alkene to afford carboxylic acids without the need for an additional deprotection step. Esterification of commercially available bromomaleic anhydride (**2.47**) provided alkene **2.48**. Suzuki cross-coupling between boronic ester **2.20** and alkene **2.48** afforded vinyl oxindole **2.49** and subjection to alkylation–IMDA cascade conditions gave cycloadduct **2.50**. Hydrogenation afforded pentacycle **2.46**. Low yields in this unoptimized reaction are attributed to difficulties in isolation and insolubility of pentacycle **2.46** in most solvents. Once again elaboration of acid **2.46** provided problematic, with attempts to chlorinate the ketone, induce a Curtius rearrangement on the carboxylic acid or reduce the lactone were unsuccessful. Again the highly crystalline nature of the compound and lack of solubility severely hindered both isolation and elaboration of acid **2.46**.



Scheme 2.14: *Synthesis and cycloaddition of the revised dienophile.*

2.4 Conclusion.

Given the challenges encountered in elaborating cycloadduct **2.23**, the need to introduce differentiation at an earlier stage in the synthesis was recognized. The vinyl bromide Suzuki

cross–coupling partner was targeted as ideal component to modify, as it had already been demonstrated that a variety of alkenes are tolerated in the reaction. Making an unsymmetrical alkene prior to cross–coupling would also make the synthesis more concise.

2.5. References.

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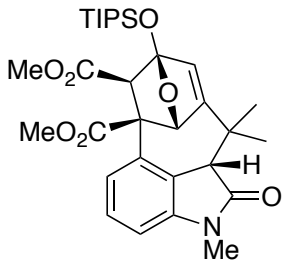
2.6. Supporting Information.

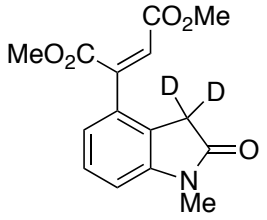
All reactions were carried out under nitrogen, unless otherwise noted, in oven– or flame– dried glassware. Extra-dry acetonitrile (99.9%, >10 ppm water) in an AcroSeal bottle was purchased from Fisher Scientific. Thin layer chromatography was performed using glass-backed EM Science Silica Gel 60 PF254 Plates. Flash chromatography was performed using EM Science Silica Gel 60 (230-400 mesh). All volatile solvents were removed, *in vacuo*, under reduced pressure using a Büchi rotary evaporator. ^{1}H NMR spectra were recorded at 500 MHz, using a Bruker DRX 500 spectrophotometer, or at 600 MHz using an Avance 600 spectrometer. ^{13}C NMR spectra were recorded at 125 MHz. All spectra were taken at 298 K. ^{1}H NMR and ^{13}C NMR spectra were run in $CDCl_3$, CD_2Cl_2, or CD_3OD with shifts reported as δ values in ppm and referenced to residual solvent proton(s). Splitting patterns are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sep = septet, m = multiplet, br = broad. Infrared (IR) spectra were acquired on a Perkin & Elmer FT IR System 2000 Series spectrometer. High resolution mass spectra were obtained on a MicroMass LCT (ES) spectrometer. High pressure hydrogenations were performed in a Parr Instrument 4767 Pressure Vessel.



2.23

Cycloadduct 2.23 To a solution of vinyl oxindole **2.22** (0.400 g, 1.34 mmol) in acetonitrile (13 mL) under argon was added zinc iodide (2.57 g, 8.05 mmol), di-*tert*-butyl pyridine (0.58 mL, 2.58 mmol), then furan **2.15** (0.40 mL, 1.34 mmol). Furan **2.15** (0.40 mL, 1.34 mmol) was

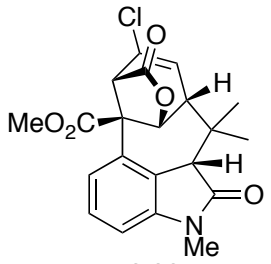
added every 12 hours for 2 days while stirring at room temperature. After 2 days the reaction was washed with saturated aqueous NH_4Cl (20 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organics were washed with water (2 x 40 mL) and brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel flash column chromatography (4:1 hexanes/EtOAc) affording a pale yellow solid (0.359 g, 47%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, J = 8.1, 1H), 7.24 (t, J = 7.9, 1 H), 6.66 (d, J = 7.5, 1H), 5.77 (s, 1H), 5.60 (s, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.67 (s, 1H), 3.53 (s, 1H), 3.16 (s, 3H), 1.66 (s, 3H), 1.13–1.04 (m, 21H), 0.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 171.8, 170.8, 158.6, 144.1, 137.5, 128.7, 127.8, 125.4, 124.5, 110.7, 106.8, 76.1, 67.6, 64.4, 53.1, 52.2, 51.7, 39.9, 26.3, 25.6, 19.5, 17.9, 12.7. Spectra are identical to literature report.[1]



2.41

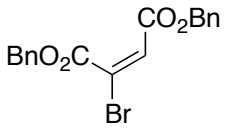
Vinyl oxindole 2.41 To a suspension of zinc iodide (0.067 g, 0.210 mmol) in CD_2Cl_2 (0.7 mL) was added vinyl oxindole **2.22** (0.020 g, 69.1[1] μmol), di-*tert*-butyl pyridine (0.030 mL, 0.138 mmol), and CD_3OD (0.010 mL, 0.210 mmol). After 5 minutes, ^{1}H NMR showed >95% deuterium incorporation. The reaction was quenched with saturated aqueous NH_4Cl (2 mL) and extracted into EtOAc (3 x 3 mL). The combined organics were washed with water (2 x 3 mL) and brine (3 mL), dried over Na_2SO_4 and concentrated *in vacuo*. A mixture of protonated and deuterated vinyl oxindole was isolated due to NH_4Cl quench.

[1] Brailsford, J. PhD. Thesis, University of California, Irvine, **2009**.



2.28

Vinyl chloride 2.28 A suspension of lactone **2.27** (10 mg, 0.026 mmol) and $MoCl_5$ (14 mg, 0.052 mmol) in DCE (0.5 mL) under argon was sealed and heated to 45 ºC. After 15 hours the reaction was cooled to room temperature and loaded directly onto a column of silica gel. The reaction was purified by flash column chromatography (4:1 → 2:1 hexanes/EtOAc) affording a white solid (4.8 mg, 48%, 65% brsm). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.9, 1H), 6.83 (d, *J* = 7.9, 1H), 6.73 (d, *J* = 8.1, 1H), 5.85 (s, 1H), 5.54 (s, 1H), 4.01 (s, 1H), 3.77 (s, 3H), 3.47 (s, 1H), 3.18 (s, 3H), 2.58 (s, 1H), 1.68 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 170.6, 170.1, 144.8, 130.1, 129.8, 126.5, 124.7, 124.5, 119.5, 107.9, 78.5, 59.1, 53.9, 52.9, 52.5, 50.4, 38.6, 29.6, 26.2, 21.4; IR (CaF_2 cell, 0.2 mm, $CHCl_3$ solution) ν[cm^{-1}] = 3060, 2959, 1803, 1712, 1612, 1469; HRMS (TOF MS+) *m* / *z* calcd for $C_{21}H_{20}NO_5ClNa$ $(M + Na)^+$ 424.0928, found 424.0926. ^{1}H and ^{13}C NMR spectra match vinyl chloride **2.28** prepared with WCl_6.[2]

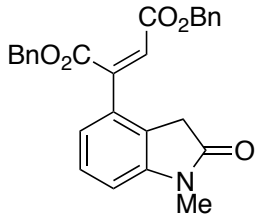


2.48

Alkene 2.48 To a solution of bromomaleic anhydride (**2.47**) (1.00 g, 5.65 mmol) in benzyl alcohol (5.6 mL) was added concentrated H_2SO_4 (0.2 mL), precipitating a brown oil. The

[2] Cleary, L. PhD. Thesis, University of California, Irvine, **2013**.

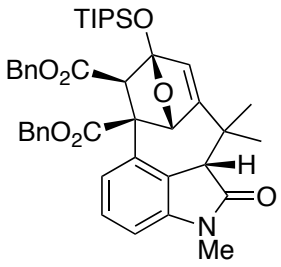
reaction was heated to reflux for 24 hours, cooled to 75 ºC for 24 hours then cooled to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc (3 x 10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting oil was purified by silica gel flash column chromatography (hexanes → 50:1 hexanes/EtOAc) affording a pale yellow oil (1.27 g, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.32 (m, 10H), 6.54 (s, 1H), 5.17 (s, 2H), 5.12 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 162.6, 134.8, 134.5, 128.61, 128.60, 128.57, 128.53, 128.4, 127.4, 126.6, 68.4, 67.3; IR (CaF_2 cell, 0.2 mm, $CHCl_3$ solution) ν[cm^{-1}] = 3092, 3023, 2921, 1732, 1322, 1161; HRMS (TOF ES+) *m* / *z* calcd for $C_{18}H_{15}O_4BrNa$ $(M + Na)^+$ 397.0051, found 397.0058.



2.49

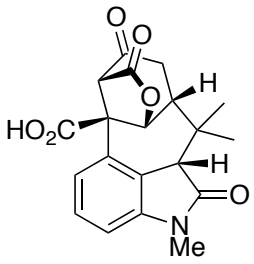
Vinyl oxindole 2.49 To a degassed solution of alkene **2.48** (0.500 g, 1.33 mmol) in DME was added to oxindole **2.20** (0.243 g, 0.888 mmol), $Pd(dppf)Cl_2$ (0.036 g, 0.044 mmol) and K_3PO_4 (0.377 g, 1.78 mmol). Degassed water (0.6 mL) was then added and the reaction was heated to 85 ºC. After 4 hours the reaction was cooled to room temperature, filtered through Celite, washed with excess EtOAc and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10:1 → 7:1 → 4:1 → 2:1 hexanes/EtOAc) affording a yellow oil (0.243 g, 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.33 (m, 10H), 7.31 (t, *J* = 8.1, 1H), 7.07 (d, *J* = 8.3, 1H), 6.86 (d, *J* = 7.8, 1H), 6.28 (s, 1H), 5.25 (s, 2H), 5.20 (s, 2H), 3.48 (s, 2H), 3.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 167.1, 164.4, 146.8, 146.0, 135.3, 134.8, 130.4, 128.8, 128.71, 128.68, 128.64, 128.62, 128.57, 123.0, 122.0, 121.3, 109.7, 68.0, 67.1,

35.6, 26.4; IR (CaF_2 cell, 0.2 mm, $CHCl_3$ solution) ν[cm^{-1}] = 3018, 2986, 1732, 1375, 1250, 1046; HRMS (TOF ES+) *m* / *z* calcd for $C_{27}H_{23}NO_5Na$ $(M + Na)^+$ 464.1474, found 464.1473.



2.50

Cycloadduct 2.50 To a solution of vinyl oxindole **2.49** (15 mg, 35.1 μmol) in acetonitrile (0.35 mL) under argon was added zinc iodide (67 mg, 211 μmol), di-*tert*-butyl pyridine (15 μL, 70.2 μmol), then furan **2.15** (10 mg, 35.1 μmol). Furan **2.15** (10 mg, 35.1 μmol) was added every 12 hours for 2 days while stirring at room temperature. After 2 days the reaction was washed with saturated acqueous NH_4Cl (1 mL). The aqueous layer was extracted with EtOAc (3 x 1 mL) and the combined organics were washed with water (3 x 2 mL), brine (2 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel flash column chromatograpy (hexanes → 10:1 → 7:1 hexanes/EtOAc) affording a white solid (13.1 mg, 52%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.28 (m, 8H), 7.23–7.19 (m, 3H), 6.66 (d, *J* = 7.5, 1H), 5.82 (s, 1H), 5.61 (s, 1H), 5.06 (d, *J* = 12.7, 1H), 5.00 (appar dd, *J* = 15.6, 12.8, 2H), 4.83 (d, *J* = 12.5, 1H), 3.53 (s, 1H), 3.30 (s, 1H), 3.16 (s, 3H), 1.66 (s, 3H), 1.10–1.07 (m, 3H), 1.05–1.03 (m, 18H), 0.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 170.9, 169.9, 158.5, 144.0, 137.2, 135.9, 135.4, 128.49, 128.47, 128.43, 128.14, 128.10, 128.0, 127.9, 127.7, 125.4, 124.5, 110.7, 106.6, 76.0, 67.6, 66.7, 64.0, 51.6, 39.8, 26.1, 25.4, 19.4, 17.9, 17.8, 12.6; IR (CaF_2 cell, 0.2 mm, $CHCl_3$ solution) ν[cm^{-1}] = 2895, 2407, 1737, 1706, 1524, 1213; HRMS (TOF ES+) *m* / *z* calcd for $C_{43}H_{51}NO_7SiNa$ $(M + Na)^+$ 744.3333, found 74.3319; mp = 182–185 ºC.



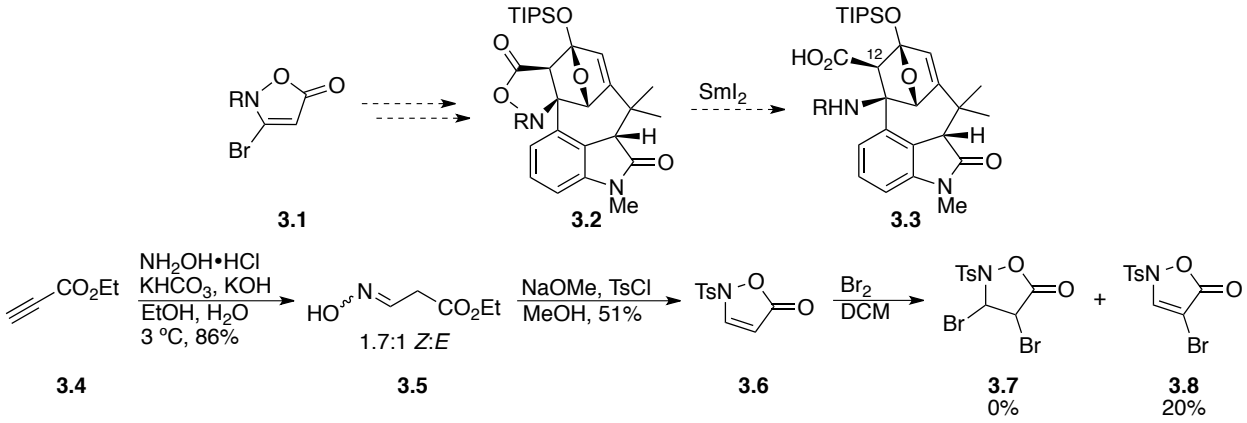
2.46

Lactone 2.46 To a solution of cycloadduct **2.50** (100 mg, 139 μmol) in EtOAc (0.55 mL) and MeOH (3.1 mL) was added concentrated HCl (0.36 mL) then Pd/C (5%, 59 mg, 27.7 μmol). The reaction was purged with H_2 (3 x) then pressurized to 550 psi. After two days the reaction was filtered through Celite, washed with excess MeCN, EtOAc, MeOH and DCM (3 x 10 mL each) and concentrated *in vacuo*. The crude reaction was suspended in acetone and a white solid (9.8 mg, 19%) was removed by vacuum filtration. Lactone **2.46** is only sparingly soluble in boiling MeOH and insoluble in all other solvents screened including DMSO and water. With the help of Dr. Phillip Dennison, no acceptable ^{13}C NMR spectrum could be obtained due to solubility difficulties. ^1H NMR (600 MHz, CD_3OD) δ 7.41–7.35 (m, 1H), 7.02 (d, J = 6.6, 1H), 6.89 (d, J = 7.2, 1H), 5.95 (s, 1H), 4.24 (s, 1H), 3.76 (s, 1H), 3.23 (s, 3H), 2.62–2.46 (m, 2H), 2.01–1.93 (m, 1H), 1.69 (s, 3H), 0.81 (s, 3H); IR (KBr pellet) ν[cm^{-1}] = 1799, 1711, 1640, 1410, 1130; HRMS (TOF ES-) m / z calcd for $C_{20}H_{18}NO_6$ $(M - H)^-$ 368.1134, found 368.1138.

Chapter 3: Targeting Alternative Dienophiles.

3.1. First Differentiated Dienophiles.

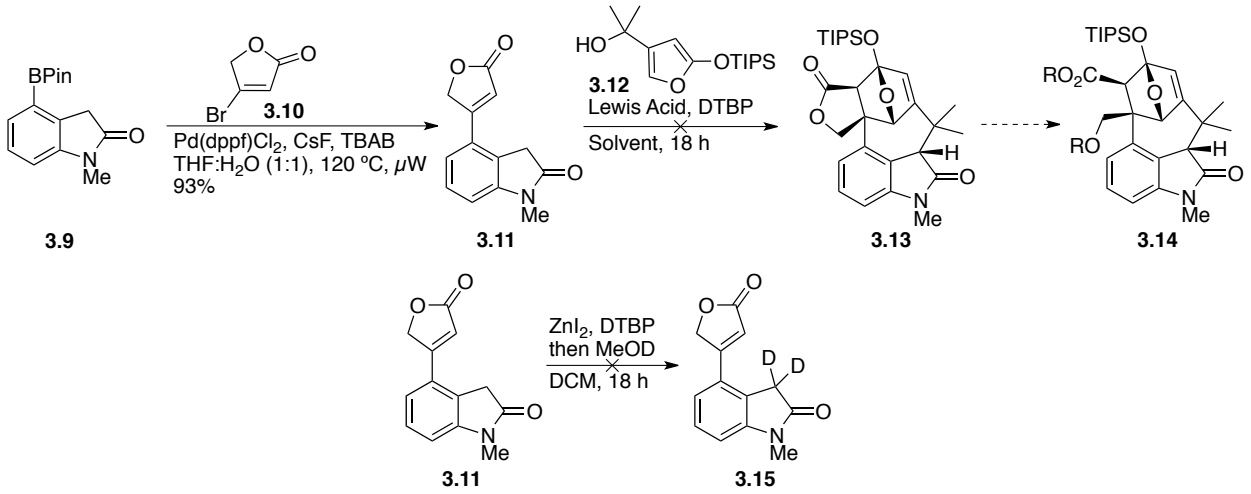
All of our previously studied vinyl bromide Suzuki cross–coupling partners have contained two esters, which have caused problems in differentiating them after synthesizing the welwitindolinone core. Therefore a revised strategy was introduced to include a vinyl bromide with two different substituents. The bridgehead substituent must be converted to an isothiocyanate, so incorporating nitrogen at that position was determined to be a priority. C12 will need to be methylated, so a carbonyl substituent will provide the most flexibility. An isoxazolidone was chosen to fulfill these requirements.



Scheme 3.1: *Isoxazolidone dienophile synthesis.*

Isoxazolidone dienophile **3.1** would provide an opportunity to form protected bridgehead amine **3.3** after reductive N–O bond cleavage of cycloadduct **3.2** and would bypass unreactive bridgehead carboxylic acid intermediates (Scheme 3.1). Synthesis of the dienophile began with the formation of oxime **3.5**.[1] Cyclization under basic conditions followed by alkylation afforded isoxazolinone **3.6**. To facilitate cross coupling, alkene **3.6** must be brominated. However, upon treatment with bromine, none of desired dibromide **3.7** was formed and vinyl bromide **3.8** with the undesired regiochemistry was isolated. Attempts to install bromine at an earlier stage in the

synthesis were unsuccessful and the route was set aside for more promising alkenes.

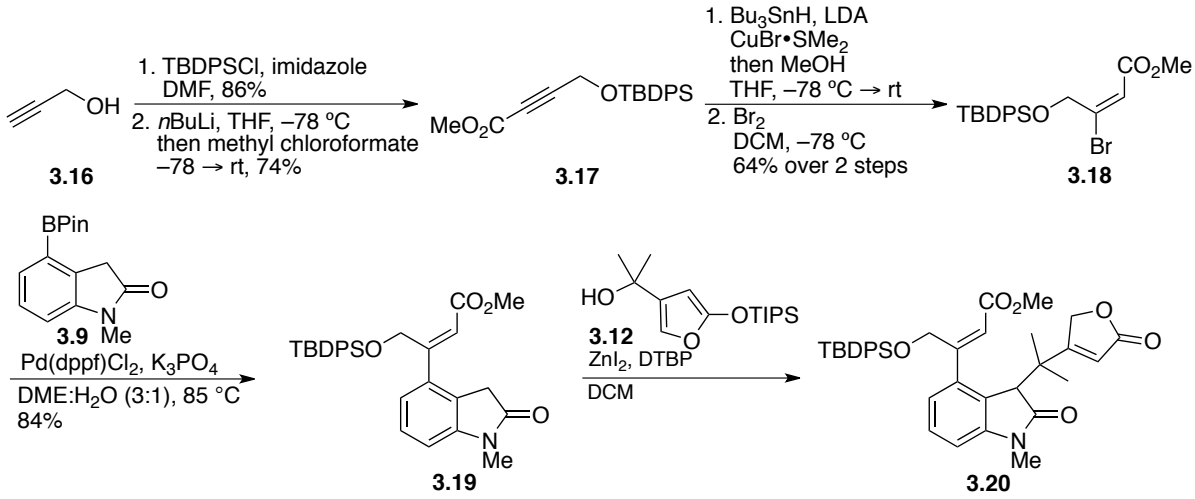


Scheme 3.2: *Attempted lactone dienophile cycloaddition.*

Lactone **3.10**, an intermediate in the synthesis of furan diene **3.12** was chosen as the second dienophile. This dienophile would result in hexacyclic cycloadduct **3.13** and upon transesterification to pentacycle **3.14** the bridgehead carbon would be differentiated from the adjacent ester (Scheme 3.2). The Suzuki cross-coupling conditions used for previous dienophiles only lead to trace amounts of vinyl oxindole **3.11**, as lactone **3.10** was found to be unstable under basic conditions. Switching to cesium fluoride as a Lewis base and adding tetrabutylammonium bromide (TBAB) as a phase transfer catalyst allowed improved the yield of the reaction to 93% when heated by microwave irradiation.[2] However, when oxindole **3.11** was subjected to optimized alkylation Diels–Alder reaction conditions, only trace amounts of cycloadduct **3.12** were present in a complex mixture. Using other solvents and Lewis acids that had been successful with diester dienophiles (see chapter 2) only resulted in unreacted starting material. In order to determine whether enolate formation was occurring under the reaction conditions, a deuterium incorporation experiment was performed. However, when oxindole **3.11** was treated with zinc iodide, base, and a deuterium source, no deuterium incorporation was observed after 18

hours, compared with complete incorporation after one hour in oxindole **2.22**. This suggests that relatively small changes in the oxindole dienophile significantly affect the ability to alkylate.

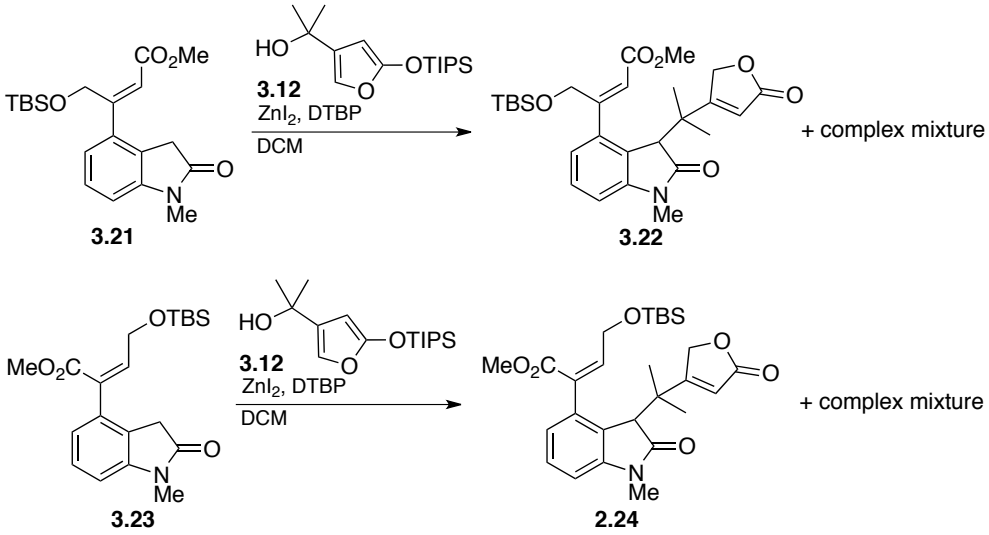
Efforts at finding a suitably functionalized alkene dienophile were directed towards a linear, differentiated alkene. Protection of propargyl alcohol (**3.16**) followed by alkylation afforded alkyne **3.19** (Scheme 3.3).[3] Copper catalyzed hydrostannylation then bromination resulted in vinyl bromide **3.18** with the desired regiochemistry.[4] A Suzuki cross-coupling reaction with boronic ester **3.9** provided alkylation–IMDA precursor **3.19**. Unfortunately, instead of the desired cycloadduct, alkylated oxindole **3.20** was isolated from the complex reaction mixture. Two possible causes for the lack of reactivity in the cycloaddition were proposed. Either the silyl protecting group is too large and hinders rotation or the electronics of the diene and dienophile are not aligned correctly. The rate of cycloaddition is slower than competing deprotection of the silyl acetal.



Scheme 3.3: *Linear dienophile synthesis.*

Two related dienophiles were prepared to determine whether steric or electronic problems were slowing cycloaddition. TBS alcohol **3.21** was prepared by a method analogous to TBDPS alcohol **3.19**. Again, deprotection of the silyl acetal was faster than cycloaddition, resulting in

formation of lactone **3.22** (Scheme 3.4). Alternate alkene regioisomer **3.23** also failed to produce the desired cycloadduct. Decomposition of furan **3.12** under the reaction conditions has always been of concern but when the dienophile contains two esters, cycloaddition is fast enough that the desired product is formed in modest yields. When the dienophile only contains one ester, decomposition is faster than cycloaddition. Two possible strategies were developed to counteract this problem. Either an alkene dienophile with two different electron withdrawing groups can be synthesized or a more stable furan with a different protecting group can be prepared.

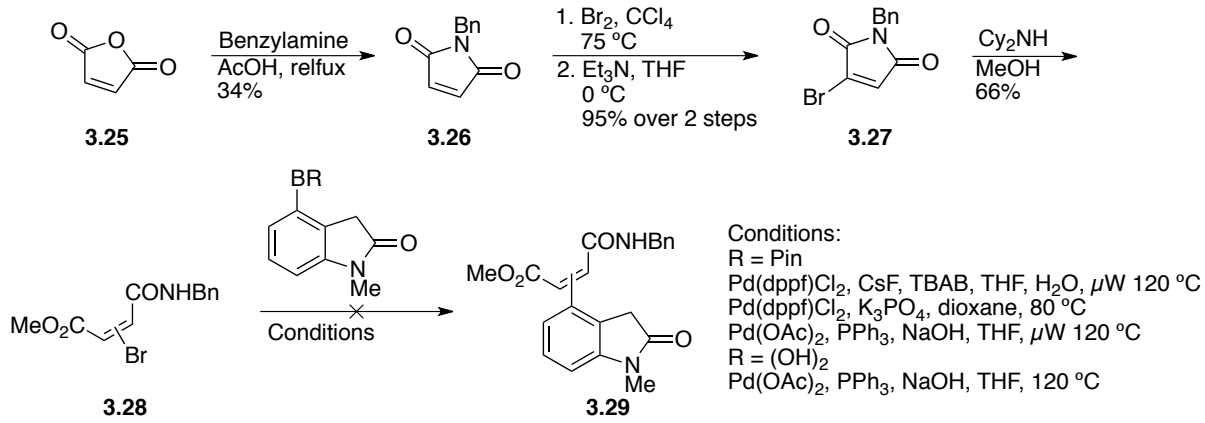


Scheme 3.4: *Investigation of steric and electronic effects on cycloaddition.*

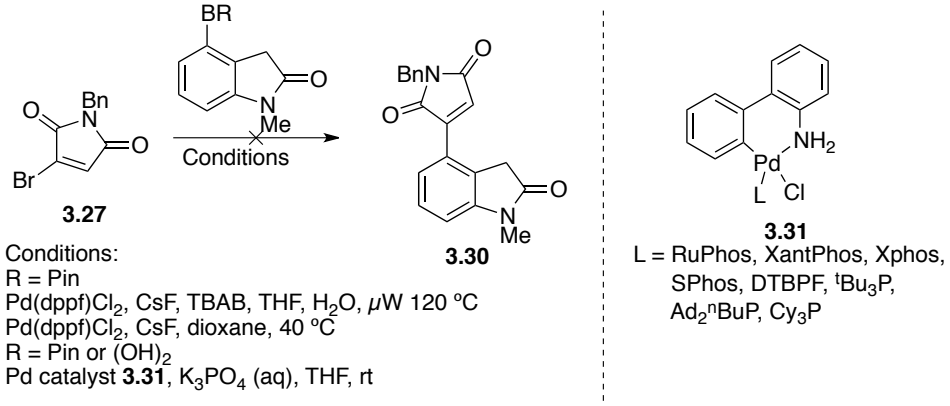
3.2. Doubly Electron Withdrawing Dienophiles.

Initial efforts were focused on preparing an alkene dienophile with two different electron withdrawing groups. An amide was chosen as the second substituent on the alkene due to its similar polarity as compared with an ester, and the ability to be rearranged to the necessary bridgehead amine. Maleimide **3.26** was prepared from maleic anhydride (**3.25**), (Scheme 3.5).[5] Dibromination followed by elimination afforded bromomaleimide **3.27** and subsequent esterification with methanol afforded amide **3.28** as a single regioisomer.[6] Attempts to cross–

couple amide **3.28** were unsuccessful, resulting in decomposition of amide **3.28**. While cross–coupling reactions of secondary amides are known, tertiary amides are more widely used.[7] Attempts to methylate amide **3.28** were unsuccessful.



Scheme 3.5: *Synthesis and attempted cross-coupling of an amide dienophile.*



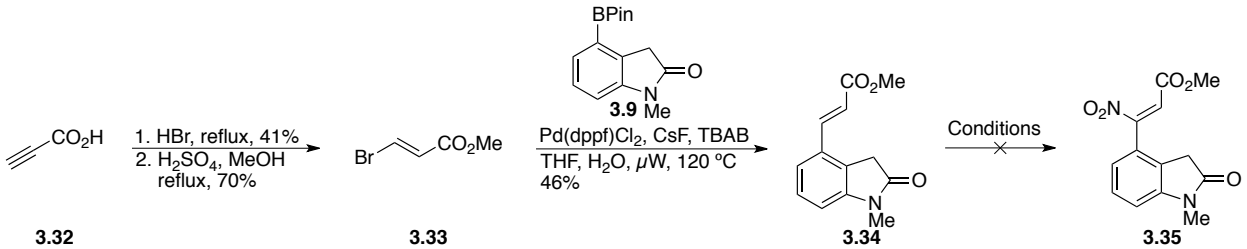
Scheme 3.6: *Attempted cross-coupling of a maleimide dienophile.*

An alternative route to amide dienophile **3.29** was proposed. Maleimides are known to undergo Suzuki cross–coupling reactions and maleimide **3.30** could be esterified to afford amide **3.29** or taken into the alkylation–cycloaddition cascade reaction directly. However, bromomaleimide **3.27** was unreactive under standard Suzuki cross–coupling reaction conditions (Scheme 3.6). Alternative palladium precatalysts (**3.31**) were also screened.[8] When boronic ester **3.9** was used, only decomposition of maleimide **3.27** was observed, suggesting that

transmetallation is slow. Using a boronic acid resulted in trace formation of dienophile **3.30** within a complex mixture, detected by mass spectrometry. Difficulties in identifying and isolating trace quantities of the desired product have hindered optimization attempts.

Instead of installing nitrogen-containing functionality before the Suzuki cross–coupling reaction, efforts were directed at nitrating oxindole dienophiles. Hydrobromination and methylation of propiolic acid (**3.32**) afforded vinyl bromide **3.33** followed by Suzuki cross–coupling with to provide oxindole **3.34** (Table 3.1).[9] Silver nitrite in the presence of TEMPO was recently reported as a new method to nitrate alkenes.[10] Unfortunately, nitration of alkene **3.34** was not regioselective. Protecting the oxindole as silyl ketene aminal also resulted in non-selective nitration. Finally, treatment with CAN and sodium nitrite resulted in nitration of the aromatic ring while N_2O_4 caused decomposition. While a dienophile with a nitro substituent remains a desirable synthetic target, difficulties with nitration have directed us towards alternate routes.

Table 3.1: *Attempted nitration of alkene dienophiles.*

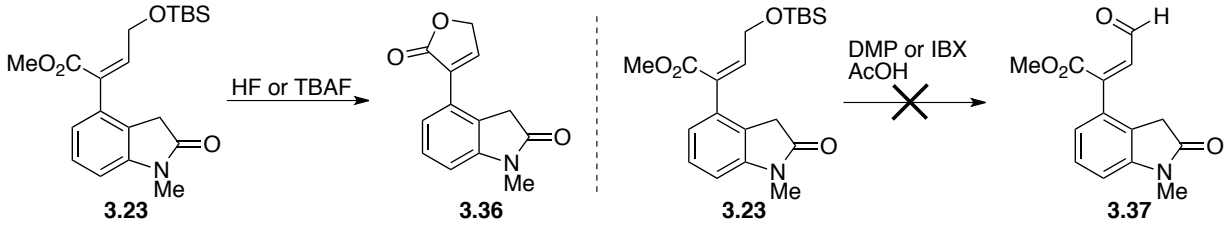


3.32 **3.33** **3.34** **3.35**

Entry	Conditions	Result
1	$AgNO_2$, TEMPO, 4Å MS	not selective
2	TBSOTf, NEt_3 then $AgNO_2$, TEMPO, 4Å MS	not selective
3	CAN, $NaNO_2$	polynitration
4	I_2, N_2O_4	decomp

Due to the difficulties incorporating nitrogen–containing groups, alternate electron withdrawing groups were investigated. Aldehyde **3.37** was targeted first. Deprotection of silyl alcohol **3.23** did not afford the desired free alcohol but instead formed lactone **3.36** under the

reaction conditions (Scheme 3.7). Lactone **3.36** has previously been shown to not undergo cycloaddition. Attempted deprotection in the presence of oxidizing agents was also unsuccessful, and only unreacted starting material was isolated. The stability of the five-membered lactone necessitates avoiding a free alcohol intermediate, but the desire to avoid aluminum based reducing agents due to possible reduction of the oxindole meant selective reduction of an ester to aldehyde was not a viable strategy to prepare the desired aldehyde. Given the challenges in preparing various oxindole dienophiles, efforts were directed back to esters as electron-withdrawing substituents.

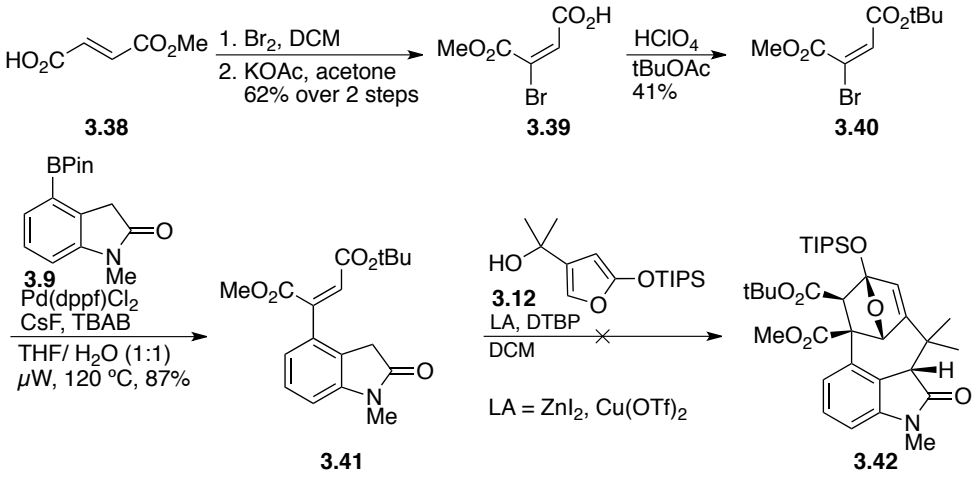


Scheme 3.7: *Attempted aldehyde synthesis.*

3.3. Diester Dienophiles.

Alkene dienophiles with two different ester substituents were targeted. Known alkene **3.38**[11] was dibrominated then eliminated to afford bromoalkene **3.39** as a single isomer (Scheme 3.8). Esterification provided differentiated ester **3.40** which was cross–coupled to produce dienophile **3.41**.[12] Under the previously optimized alkylation–cycloaddition conditions, cycloadduct **3.42** was not observed. In addition, no starting alkene **3.41** or alkylated product was present in the complex reaction mixture. Changing the Lewis acid from zinc iodide to copper triflate gave the same result. This result was somewhat unexpected due to the similarities between alkene **3.41** and diester alkene **2.22**, which does react under these conditions. As with the case of lactone **3.36**, it is proposed that changes to the alkene substituents can have a

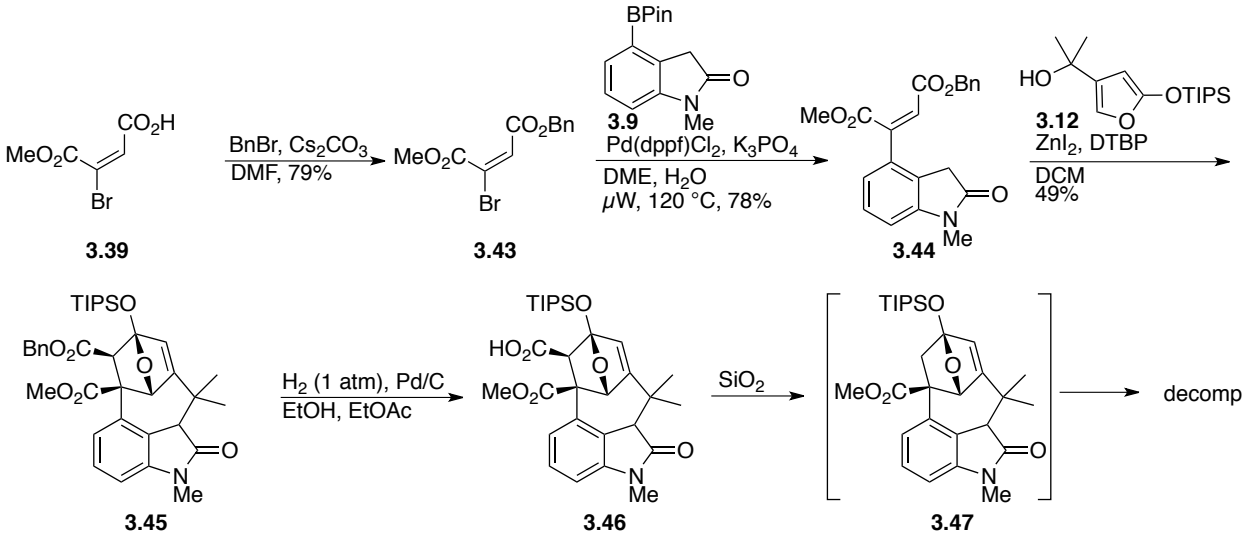
dramatic effect on the rate of alkylation of the oxindole. The increased size of the t-butyl ester compared with methyl appears to substantially hinder reactivity.



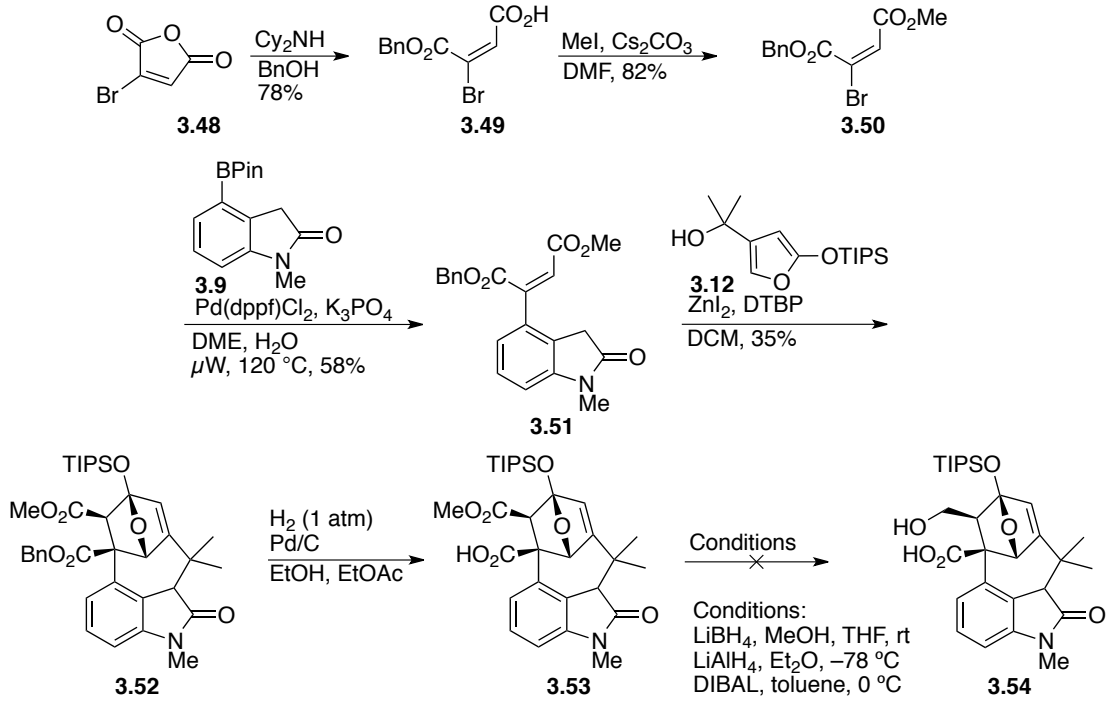
Scheme 3.8: *Attempted differentiated diester synthesis.*

The limits for successful cycloaddition have been narrowed further. In addition to two electron-withdrawing groups, the dienophile must remain relatively small. Nitrogen-containing alkenes could not be cross coupled, and only methyl, ethyl, and benzyl esters are small enough to facilitate cycloaddition. For this reason, alkenes with one benzyl and one methyl ester were prepared. The benzyl ester could then be selectively removed by hydrogenation, differentiating the two groups. Acid **3.39** was benzyl protected and cross–coupled to afford dienophile **3.44** (Scheme 3.9). The alkylation-cycloaddition cascade reaction affords cycloadduct **3.45** as a single diastereomer. Hydrogenation at 1 atm cleanly results in hydrogenolysis of the benzyl ester without reducing the bridgehead alkene. Unfortunately, when exposed to silica or simply upon standing decarboxylation of acid **3.46** is rapid to form ester **3.47**, followed by further decomposition. Attempted reduction of acid **3.46** with lithium borohydride, boranes and aluminum reducing agents resulted predominantly in competing decarboxylation. These results are unexpected because decarboxylation usually does not occur without significant heating, but

in this case may occur via a mechanism similar to the retro–Claisen reaction observed upon silyl deprotection.



Scheme 3.9: *Differentiated benzyl ester alkene dienophile.*

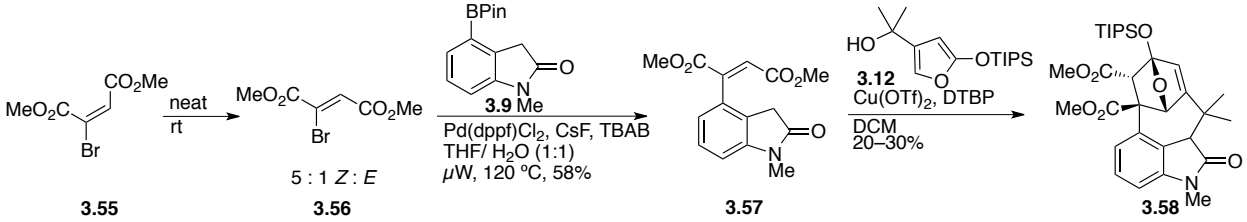


Scheme 3.10: *Alternate differentiated benzyl ester regioisomer.*

To prevent decarboxylation, regioisomeric alkene **3.51** was the next synthetic target (Scheme 3.10). Without the adjacent silyl acetal, decarboxylation is not expected to occur.

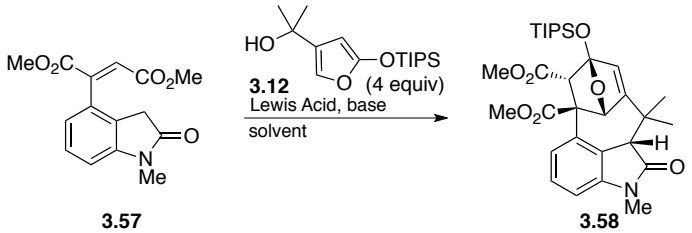
Esterification and cross coupling proceed as expected, and cycloadduct **3.52** was obtained in moderate yield.[6] Hydrogenolysis of benzyl ester **3.52** revealed carboxylic acid **3.53**, but subsequent ester reduction was not successful. Reduction of the carboxylic acid was not attempted due to expected subsequent lactone formation.

When attempting to prepare diester **2.22** it was discovered that an aliquot of bromoalkene **3.55** had isomerized upon standing at room temperature (Scheme 3.11). Suzuki cross–coupling to afford diester **3.57** was followed by alkylation–cycloaddition to form cycloadduct **3.58**. When zinc iodide was used instead of copper triflate, no reaction occurred. Cycloadduct **3.58** is potentially useful because the two esters are found in different local environments and can possibly be differentiated.



Scheme 3.11: *Alternate diester alkene isomer.*

Table 3.2: *Optimization of copper-catalyzed alkylation–cycloaddition reaction.*

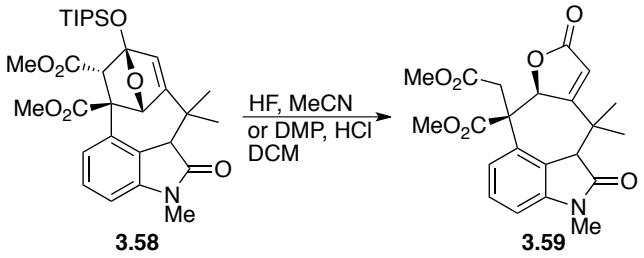


Entry	Lewis Acid	Base	Solvent	Yield[a]	Entry	Lewis Acid	Base	Solvent	Yield[a]
1	$Cu(OTf)_2$	DTBP	DCM	57%	8	CuBr	DTBP	DCM	NR
2	$Cu(OTf)_2$	DTBP	DCE	46%	9	CuCl	DTBP	DCM	NR
3	$Cu(OTf)_2$	DTBP	MeCN	trace	10	$CuBr_2$	DTBP	DCM	40% side pdt
4	$Cu(OTf)_2$	DTBP	DMF	trace	11	$CuCl_2$	DTBP	DCM	60% side pdt
5	$Cu(OTf)_2$	DTBP	Toluene	NR	12	$Cu(OTf)_2$	NEt_3	DCM	25%[b]
6	$Cu(OTf)_2$	DTBP	THF	NR	13	$Cu(OTf)_2$	iPr_2NEt	DCM	55%[b]
7	CuI	DTBP	DCM	NR	14	$Cu(OTf)_2$	pyridine	DCM	NR[b]

a) Determined by ^1H NMR b) With 1.5 equiv furan **3.12**

Using the conditions optimized for dienophile **2.22**, cycloadduct **3.58** was only isolated in low yields. In order to increase the yield, different copper sources, solvents and bases were screened (Table 3.2). Using DCM as the solvent gave the highest yields and copper triflate was found to be the best copper source. Screening bases revealed that Hünig's base gave similar yields while using fewer equivalents of furan **3.12**. Increasing the amount of furan **3.12** used did not improve the yield. Additionally, the yield of this reaction was found to be highly dependent on scale. Cycloadduct **3.58** could only be isolated in small quantities and all efforts to obtain more material failed.

Despite the challenges in obtaining material, elaboration of cycloadduct **3.48** was investigated. Deprotection did not give the desired alcohol but retro–Claisen product **3.59** was isolated (Scheme 3.12). Deprotection in the presence of an oxidizing agent in an attempt to prevent rearrangement was also unsuccessful, which is consistent with previous results from our lab.[13] Difficulties in obtaining and elaborating cycloadduct **3.58** lead us to focus instead on preparing more stable furan dienes.



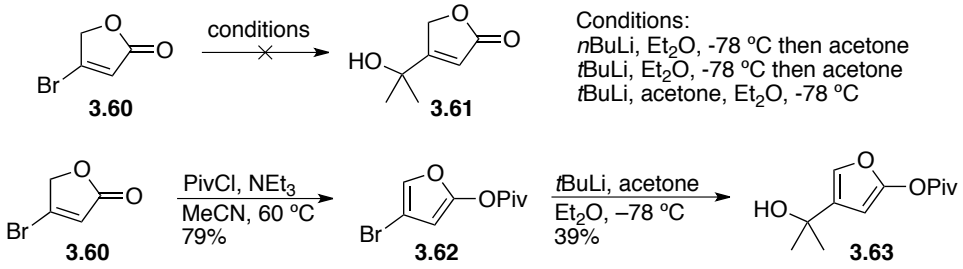
3.58 **3.59**

Scheme 3.12: *Attempted silyl deprotection.*

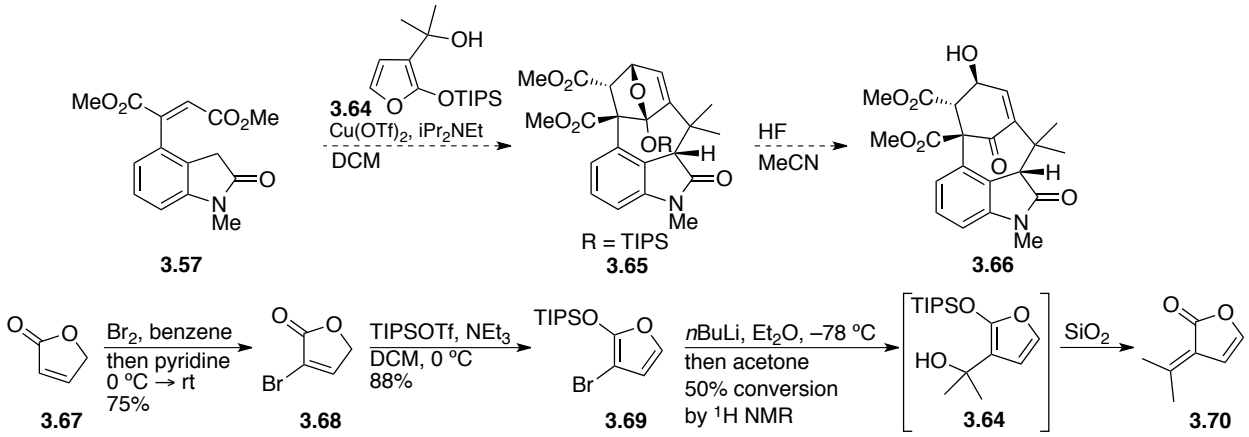
3.4. Alternate Furan Syntheses.

In addition to dienophiles with two different electron withdrawing groups, efforts were also directed towards a more stable furan diene. Attempts to lithiate bromolactone **3.60** directly

did not afford alcohol **3.61** (Scheme 3.13). Instead, enolization followed by pivaloyl protection afforded diene **3.62** which was then lithiated and converted to alcohol **3.63**.[14] Low yields are attributed to difficulties purifying alcohol **3.63** which does not appear to be stable to silica gel purification. This also suggests that it won't show improved stability under the Lewis acid alkylation-IMDA cascade reaction conditions compared with silyl furan **3.12**. Preliminary results support reduced stability and no cycloadduct could be isolated.



Scheme 3.13: *Furan synthesis with an alternative protecting group.*



Scheme 3.14: *Alternative furan regioisomer synthesis.*

Alternative furan **3.64** was also targeted. Cycloadduct **3.65** could be prepared from alkene dienophile **3.57**, differing only from related cycloadduct **3.58** in the position of the silyl acetal (Scheme 3.14). Upon deprotection of cycloadduct **3.65**, alcohol **3.66** is expected to be stable and should not undergo a retro–Claisen reaction. Enone **3.67** was converted to vinyl bromide **3.68** *via* a one-pot bromination elimination sequence.[15] Enolization and protection

afforded diene **3.69**[16] which was lithiated and treated with acetone to produce alcohol **3.64**. Upon exposure to silica gel during column chromatography, alcohol **3.64** decomposed to enone **3.70**.[17] The instability of alcohol **3.64** suggests it is also not be suited to the Lewis acidic conditions necessary to form cycloadduct **3.65**.

3.5. Conclusion.

A variety of dienophiles were prepared, with varying degrees of success. Initial studies showed that due to the sensitivity of furan **3.12** under the Lewis acidic cyclization conditions, a highly electron-withdrawn, and sterically compact dienophile is necessary to allow cycloaddition to be faster than competing deprotection. Challenges incorporating nitrogen-containing functional groups and unexpected lactonization and decarboxylation further demonstrate the challenges associated with this family of compounds.

Most of the cycloaddition cascade reactions are low yielding, and only when both esters are methyl can we obtain an appreciable quantity of material. For that reason, efforts were directed back at elaborating cycloadduct **2.23**.

3.6. References

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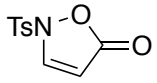
3.7. Supporting Information.

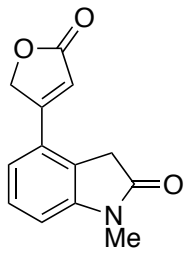
All reactions were carried out under nitrogen, unless otherwise noted, in oven– or flame– dried glassware. Thin layer chromatography was performed using glass-backed EM Science Silica Gel 60 PF254 Plates. Flash chromatography was performed using EM Science Silica Gel 60 (230-400 mesh). All volatile solvents were removed, *in vacuo*, under reduced pressure using a Büchi rotary evaporator. ^{1}H NMR spectra were recorded at 500 MHz, using a Bruker DRX 500 spectrophotometer, or at 600 MHz using an Avance 600 spectrometer. ^{13}C NMR spectra were recorded at 125 MHz. All spectra were taken at 298 K. ^{1}H NMR and ^{13}C NMR spectra were run in $CDCl_3$, CD_2Cl_2, or CD_3OD with shifts reported as δ values in ppm and referenced to residual solvent proton(s). Splitting patterns are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sep = septet, m = multiplet, br = broad. Infrared (IR) spectra were acquired on a Perkin & Elmer FT IR System 2000 Series spectrometer. High resolution mass spectra were obtained on a MicroMass LCT (ES) spectrometer. High pressure hydrogenations were performed in a Parr Instrument 4767 Pressure Vessel.



3.6

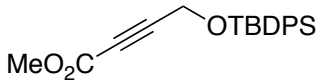
Isoxazolinone 3.6 To a solution of sodium methoxide (0.67 mL, 2.5 M in methanol) was added oxime **3.5** (200 mg, 1.53 mmol) followed by *p*-toluenesulfonyl chloride (291 mg, 1.53 mmol). After 90 minutes the reaction slurry was extracted into dry ether (3 x 1 mL), filtered through Celite and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel column chromatography (hexanes → 10:1 hexanes/EtOAc) to afford a white solid (185 mg, 51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, J = 3,9, 1H), 7.76 (d, J = 8.6, 2H), 7.38 (d, J = 8.1, 2H), 5.62

(d, J = 3.9, 1H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 151.5, 147.5, 130.3, 129.4, 128.4, 102.1, 21.9; IR (ATR) ν[cm^{-1}] = 3154, 3113, 1775, 1755, 1566, 1381; HRMS (TOF ES+) m / z calcd for $C_{10}H_9O_4NSNa$ $(M + Na)^+$ 262.0150, found 262.0143; mp = 128–129 ºC.



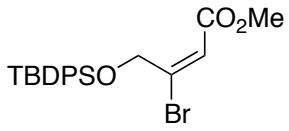
3.11

Lactone 3.11 To a solution of oxindole **3.9** (50 mg, 0.183 mmol), alkene **3.10** (20 mg, 0.122 mmol), $Pd(dppf)Cl_2$ (5 mg, 6.1 μmol) and tetrabutylammonium bromide (39 mg, 0.122 mmol) in degassed THF (0.4 mL) was added a solution of CsF (74 mg, 0.488 mmol) in water (0.4 mL). The reaction was heated to 120 ºC (200 W) in the microwave for 6 minutes then diluted with DCM (2 mL) and washed with 1M HCl (2 mL). The aqueous layer was extracted with DCM (2 x 2 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel column chromatography (5:1 → 2:1 → 1:1 → 1:2 hexanes/EtOAc) to afford a pale orange solid (26 mg, 93%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (t, J = 7.9, 1H), 7.08 (d, J = 7.8, 1H), 6.98 (d, J = 8.1, 1H), 6.31 (s, 1H), 5.27 (s, 2H), 3.63 (s, 2H), 3.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ173.7, 173.6, 161.7, 146.5, 129.2, 126.1, 123.6, 120.3, 115.9, 111.0, 71.8, 36.6, 26.5; IR (ATR) ν[cm^{-1}] = 3098, 2901, 1753, 1705, 1350, 1061; HRMS (TOF ES+) m / z calcd for $C_{13}H_{11}O_3NNa$ $(M + Na)^+$ 252.0637, found 252.0630.



3.17

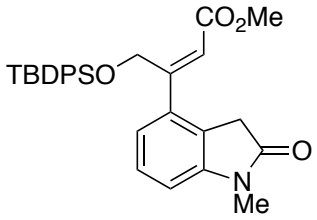
Alkyne 3.17 To a solution of TBDPS protected propargyl alcohol (200 mg, 0.680 mmol) in THF (7 mL) at –78 ºC was added dropwise a solution of *n*BuLi (0.27 mL, 2.5 M) in hexanes. After 15 minutes, methyl chloroformate (43 μL, 0.680 mmol) was added and the reaction was warmed to room temperature then diluted with H_2O (5 mL). The reaction was extracted into ether (3 x 5 mL), washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel column chromatography (40:1 → 20:1 hexanes/EtOAc) to afford a clear oil (176 mg, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74–7.70 (m, 4H), 7.48–7.40 (m, 6H), 4.42 (s, 2H), 3.79 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 135.7, 132.5, 130.0, 138.1, 85.9, 76.5, 52,8, 52.3, 26.7, 19.2; IR (ATR) ν[cm^{-1}] = 2951, 2858, 2241, 1716, 1250; HRMS (TOF ES+) *m* / *z* calcd for $C_{21}H_{24}O_3SiNa$ $(M + Na)^+$ 375.1392, found 375.1388.



3.18

Alkene 3.18 To a solution of diisopropylamine (60 μL, 0.426 mmol) in THF (0.5 mL) at 0 ºC was added dropwise a solution of *n*BuLi (0.15 mL, 2.5 M) in hexanes. After 15 minutes, freshly distilled tributyltin hydride (100 μL, 0.369 mmol) was added. After stirring for 15 minutes, the reaction was cooled to –78 ºC and CuBr•SMe_2 (76 mg, 0.369 mmol) was added. After 1 hour, alkyne **3.17** (100 mg, 0.284 mmol) was added and the reaction was allowed to warm slowly to room temperature. After 12 hours the reaction was diluted with brine (1 mL) and extracted into ether (3 x 1 mL). The combined organic extracts were washed with water (1 mL), brine (1 mL),

dried over $MgSO_4$ and concentrated *in vacuo* to a pale yellow oil (91 mg) which was dissolved in DCM (1.4 mL) and cooled to –78 ºC. To the solution was added dropwise bromine (8 µL, 0.156 mmol). After 3 hours the reaction was diluted with DCM (2 mL), washed with saturated aqueous $Na_2S_2O_3$, water, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel column chromatography (hexanes → 97:3 hexanes/EtOAc) to afford a pale yellow oil (39 mg, 64% over 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 7.3, 4H), 7.44 (t, J = 7.2, 2H), 7.40 (t, J = 7.2, 4H), 6.36 (s, 1H), 4.92 (s, 2H), 3.60 (s, 3H), 1.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.1, 148.4, 135.7, 133.0, 129.8, 127.7, 123.1, 63.3, 51.7, 26.8, 19.4; IR (ATR) ν[cm^{-1}] = 2951, 2857, 1720, 1327, 1105; HRMS (TOF ES+) m / z calcd for $C_{21}H_{25}O_3SiBrNa$ $(M + Na)^+$ 455.0654, found 455.0649.

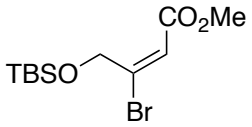


3.19

Oxindole 3.19

A solution of alkene **3.18** (15 mg, 34.6 µmol) in DME (65 µL) was added to a vial containing borane **3.9** (14 mg, 51.9 µmol), K_3PO_4 (15 mg, 69.2 µmol), and $Pd(dppf)Cl_2$ (1.5 mg, 1.73 µmol) followed by water (22 µL). The vial was sealed and heated to 85 ºC. After 4 hours the reaction as filtered through Celite, washed with excess EtOAc and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel column chromatography (EtOAc) to afford a pale yellow oil (14.3 mg, 84%). (10:1 hexanes/EtOAc is a more appropriate elution solvent). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (dd, J = 7.7, 1.4 Hz, 1H), 7.47–7.45 (m, 4H), 7.42–7.39 (m, 2H), 7.33–

7.29 (m, 4H), 6.91 (d, J = 7.9 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 5.81 (t, J = 1.7 Hz, 1H), 5.18 (d, J = 1.6 Hz, 1H), 3.65 (s, 3H), 3.47 (s, 2H), 3.25 (s, 3H), 0.81 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 165.9, 135.6, 134.9, 133.2, 129.8, 129.7, 127.82, 127.76, 127.6, 122.9, 122.7, 118.4, 107.8, 61.6, 51.4, 35.6, 26.6, 19.1, 14.3.

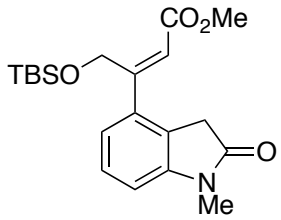


S1

Alkene S1

To a solution of DIPA (0.46 mL, 3.29 mmol) in THF (4 mL) at 0 ºC was added dropwise *n*BuLi (1.14 mL, 2.85 mmol, 2.5M in hexanes). After 15 minutes, freshly distilled Bu_3SnH (0.77 mL, 2.85 mmol) was added dropwise. The reaction was stirred for 15 minutes then cooled to –78 ºC and $CuBrSMe_2$ (586 mg, 2.85 mmol) was added. After 1 hour, alkyne (500 mg, 2.19 mmol) in THF (0.2 mL) was added and the reaction was stirred for an additional hour. MeOH (0.4 mL) was added dropwise and the reaction was allowed to warm slowly to room temperature. The reaction was diluted with brine (25 mL), extracted into Et_2O (3 x 25 mL), washed with water (50 mL), brine (50 mL), dried of $MgSO_4$ and concentrated *in vacuo*. The crude vinyl stannane was dissolved in DCM (22 mL) and cooled to –78 ºC and Br_2 (123 µL, 2.41 mmol) was added dropwise. After 2 hours, warmed to 0 ºC and quenched with sat. aq $Na_2S_2O_3$ (20 mL) and warmed to room temperature. The organic layer was washed with 1M NaOH (20 mL), water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purified by silica gel column chromatography (hexanes → 100:1 → 50:1 hexanes/EtOAc) to afford a yellow oil (314 mg, 46%

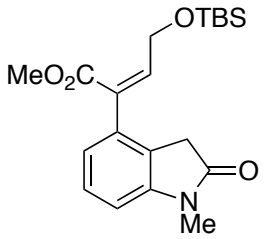
over 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.41 (s, 1H), 4.88 (s, 2H), 3.72 (s, 3H), 0.93 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 149.6, 122.9, 62.8, 51.8, 25.9, 18.4, –5.2.



3.21

Oxindole 3.21

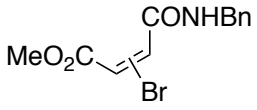
To a microwave reaction vessel was added borane **3.9** (50 mg, 0.183 mmol), Pd(dppf)Cl_2 (5 mg, 6.1 μmol), K_3PO_4 (52 mg, 0.244 mmol) followed by alkene **S1** (46 mg, 0.122 mmol) in DME (0.46 ml). Reaction was stirred then water (0.15 mL) was added. The reaction was heated to 120 ºC in the microwave for 10 minutes then filtered through Celite, washed with excess EtOAc and concentrated *in vacuo*. Purified by silica gel column chromatography (hexanes → 10:1 → 7:1 hexanes:EtOAc) to afford a yellow oil (trace solvent could not be removed). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (t, J = 7.9 Hz, 1H), 6.95 (d, J = 7.9 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 5.89 (s, 1H), 5.12 (s, 2H), 3.76 (s, 3H), 3.59 (s, 2H), 3.23 (s, 3H), 0.65 (s, 9H), –0.01 (s, 6H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 166.2, 159.9, 144.9, 136.4, 127.8, 123.1, 122.4, 118.1, 107.9, 60.9, 51.6, 35.8, 26.4, 25.5, 17.9, –5.5.



3.23

Oxindole 3.23

To a microwave reaction vessel was added borane **3.9** (50 mg, 0.183 mmol), $Pd(dppf)Cl_2$ (5 mg, 6.1 μmol), K_3PO_4 (52 mg, 0.244 mmol) followed by alkene (46 mg, 0.122 mmol) in DME (0.46 ml). Reaction was stirred then water (0.15 mL) was added. The reaction was heated to 120 ºC in the microwave for 10 minutes, added $Pd(dppf)Cl_2$ (5 mg, 6.1 μmol) and heated to 120 ºC in the microwave for 1 hour. Filtered through Celite, washed with excess EtOAc and concentrated *in vacuo*. Purified by silica gel column chromatography (hexanes → 10:1 → 7:1 → 4:1 hexanes:EtOAc) to afford a yellow oil (12 mg, 26%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (t, J = 7.6 Hz, 1H), 6.94 (d, J = 7.8 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.38 (t, J = 5.1 Hz, 1H), 4.75 (d, J = 4.4 Hz, 2H), 3.75 (s, 3H), 3.39 (s, 2H), 3.22 (s, 3H), 0.92 (s, 9H), 0.11 (s, 6H).

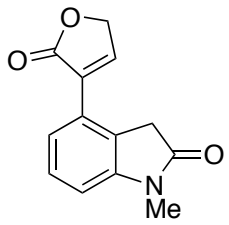


3.28

Amide 3.28

To a suspension of maleimide **3.27** (50 mg, 0.188 mmol) in MeOH (0.15 mL) was added dicyclohexylamine (37 mg, 0.207 mmol). After 2 hours the reaction was concentrated *in vacuo*. The crude solid was suspended in EtOAc (1 mL), washed with $NaHCO_3$ (1 mL), extracted into EtOAc (3 x 1 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purified by silica gel column

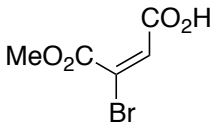
chromatography (hexanes → 7:1 → 4:1 hexanes/EtOAc) to afford a white solid (37 mg, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.17 (m, 5H), 5.33 (s, 1H), 4.58 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 165.3, 161.1, 136.3, 128.7, 128.4, 127.8, 96.4, 58.9, 41.2.



3.36

Lactone 3.36

To a solution of ether **3.23** (5 mg, 13.3 μmol) in MeCN (0.3 mL) was added 1 drop aqueous HF. After 15 minutes, quenched with sat. aq $NaHCO_3$ (0.2 mL), extracted into DCM (3 x 0.2 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purified by silica gel column chromatography (4:1 → 2:1 hexanes/EtOAc) to afford lactone **3.36**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 6.89 (d, J = 7.0 Hz, 1H), 5.01 (s, 2H), 3.65 (s, 2H), 3.25 (s, 3H).

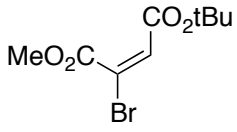


3.39

Vinyl bromide 3.39

To a suspension of alkene **3.38** (200 mg, 1.54 mmol) in DCM (6 mL) was added Br_2 (0.12 mL, 2.31 mmol). After 18 hours, diluted with EtOAc (10 mL) and quenched with sat. aq $Na_2S_2O_3$. Extracted into EtOAc (3 x 10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude

dibromide was dissolved in acetone (15 mL) and KOAc (151 mg, 1.54 mmol) was added. After 18 hours the reaction was diluted with DCM (15 mL), washed with 1M HCl (20 mL, saturated with NaCl), dried over Na_2SO_4 and concentrated *in vacuo*. Purified by silica gel column chromatography (2:1 hexanes/EtOAc, 2% AcOH) to afford a white solid (220 mg, 67% over 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.65 (br s, 1H), 6.49 (s, 1H), 3.86 (s, 3H). Spectra matches the literature report for this compound.[1]

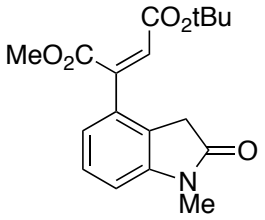


3.40

Ester 3.40

To a solution of alkene **3.39** (100 mg, 0.478 mmol) in *t*BuOAc (1.2 mL) at 0 ºC was added dropwise $HClO_4$ (62 μL, 0.718 mmol) then warmed to room temperature. After 18 hours, washed with water (1 mL), dried of Na_2SO_4 and concentrated *in vacuo*. Purified by silica gel column chromatography (25:1 hexanes/EtOAc) to afford a pale yellow oil (52 mg, 41%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.43 (s, 1H), 3.88 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 162.0, 129.0, 125.2, 82.8, 53.4, 27.9.

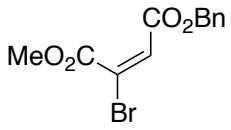
[1] Batchelor, M. J.; Mellor, J. M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 985–995.



3.41

Oxindole 3.41

To a microwave vial was added borane **3.9** (67 mg, 0.245 mmol), $Pd(dppf)Cl_2$ (8 mg, 9.43 μmol), TBAB (61 mg, 0.189 mmol) then alkene **3.40** (50 mg, 0.189 mmol) in THF (0.6 mL). Stirred for 5 minutes then added CsF (115 mg, 0.754 mmol) in water (0.6 mL). Heated to 120 ºC in the microwave for 10 minutes. Diluted with DCM (5 mL), washed with 1M HCl (5 mL), extracted the aqueous layer into DCM (3 x 5 mL), dried the combined organics over Na_2SO_4 and concentrated *in vacuo*. Purified by silica gel column chromatography (10:1 → 7:1 → 4:1 hexanes/EtOAc) to afford a yellow solid (54.5 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.9 Hz, 1H), 7.08 (d, *J* = 7.9 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.16 (s, 1H), 3.89 (s, 3H), 3.54 (s, 2H), 3.22 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 167.9, 163.8, 145.9, 144.8, 130.9, 128.7, 124.2, 122.9, 122.0, 109.4, 82.1, 52.7, 35.6, 28.1, 26.4.

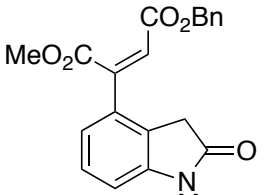


3.43

Alkene 3.43

To a solution of carboxylic acid **3.39** (100 mg, 0.478mmol) in DMF (2.4 mL) was added Cs_2CO_3 (234 mg, 0.718 mmol) then benzyl bromide (85 μL, 0.718 mmol) and stirred at room temperature. After 18 hours, quenched with 1M HCl (5 mL), and extracted into EtOAc (3 x 5

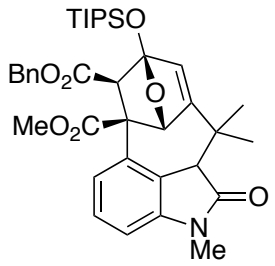
mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo.* Purified by silica gel column chromatography (hexanes → 25:1 → 10:1 hexanes/EtOAc) to afford a white solid (113 mg, 79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.35 (m, 5H), 6.40 (s, 1H), 5.18 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.1, 162.7, 134.8, 128.7, 128.6, 127.5, 126.6, 67.5, 53.4.



3.44

Oxindole 3.44

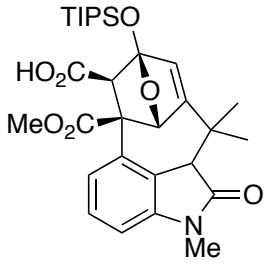
To a microwave vial was added borane **3.9** (119 mg, 0.435 mmol), K_3PO_4 (142 mg, 0.669 mol) and Pd(dppf)Cl_2 (14 mg, 16.7 μmol). Alkene **3.43** (90 mg, 0.301 mmol) was added in DME (0.6 mL) and the reaction was stirred for 5 minutes. Added water (0.2 mL) then heated the reaction in the microwave to 120 ºC for 10 minutes. Filtered through Celite, washed with excess EtOAc and concentrated *in vacuo*. Purified by silica gel column chromatography (7:1 → 4:1 → 2:1 hexanes/EtOAc) to afford a yellow oil (86 mg, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.32 (m, 6H), 7.10 (d, J = 7.8 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 6.28 (s, 1H), 5.23 (s, 2H), 3.80 (s, 3H), 3.53 (s, 2H), 3.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 167.7, 164.4, 146.9, 146.1, 135.2, 130.5, 128.8, 128.72, 128.67, 128.64, 123.0, 122.0, 121.3, 109.7, 67.2, 52.8, 35.6, 26.4.



3.45

Cycloadduct 3.45

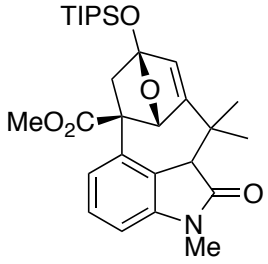
To a solution of oxindole **3.44** (150 mg, 0.411 mmol) in DCM (2 mL) was added ZnI_2 (393 mg, 1.23 mmol) followed by DTPB (178 μL, 0.822 mmol). Furan **3.12** (490 mg, 1.64 mmol) in DCM (2 mL) was added via syringe pump (0.14 mL/hour). After 18 hours, diluted with EtOAc (10 mL) and quenched with sat. aq NH_4Cl (10 mL). Extracted into EtOAc (3 x 20 mL), washed with water (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purified by silica gel column chromatography (7:1 hexanes/EtOAc) to afford a yellow solid (130 mg, 49%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.33 (d, *J* = 7.0 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 6.66 (d, *J* = 7.7 Hz, 1H), 5.79 (s, 1H), 5.61 (s, 1H), 5.26 (d, *J* = 12.7 Hz, 1H), 5.16 (d, *J* = 12.6 Hz, 1H), 3.53 (s, 1H), 3.43 (s, 3H), 3.29 (s, 1H), 3.16 (s, 3H), 1.66 (s, 3H), 1.11–1.03 (m, 21), 0.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 171.5, 170.0, 158.5, 144.0, 137.4, 136.1, 128.6, 128.5, 128.1, 128.0, 127.6, 125.2, 124.4, 110.7, 106.6, 76.0, 67.6, 66.7, 64.1, 52.7, 51.5, 39.8, 26.1, 25.4, 19.4, 17.8, 12.6.



3.46

Carboxylic acid 3.46

To a suspension of cycloadduct (30 mg, 46.4 μmol) in EtOH (0.5 mL) was added EtOAc (0.1 mL) followed by Pd/C (20 mg, 9.3 μmol, 5%). Purged with H_2 3 x then stirred under 1 atm H_2. After 2.5 hours, filtered through Celite, washed with excess EtOAc and concentrated *in vacuo*. Product is not silica stable and decomposes upon standing at room temperature. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.2 Hz, 1H), 7.26 (t, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 7.5 Hz, 1H), 5.78 (s, 1H), 5.60 (s, 1H), 3.69 (s, 3H), 3.52 (s, 1H), 3.26 (s, 1H), 3.16 (s, 3H), 1.67 (s, 3H), 1.15–1.05 (m, 21H), 0.76 (s, 3H).

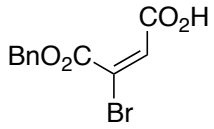


3.47

Ester 3.47

Crude carboxylic acid **3.46** was purified by silica gel column chromatography (4:1 → 2:1 hexanes/EtOAc) followed by preparatory TLC (2:1 hexanes/EtOAc). Ester **3.47** further decomposed upon standing for 24 hours, preventing full characterization. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (t, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 7.9 Hz, 1H), 6.62 (d, *J* = 7.7 Hz, 1H), 5.58 (s, 1H),

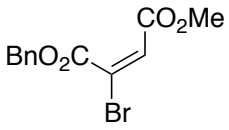
5.40 (s, 1H), 5.14 (d, J = 10.5 Hz, 1H), 4.06 (s, 1H), 3.74 (s, 3H), 3.14 (s, 3H), 2.87 (d, J = 10.9 Hz, 1H), 1.69 (s, 3H), 1.19 (sep, J = 7.5 Hz, 3H), 1.09–1.01 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 172.6, 154.0, 150.5, 144.4, 139.1, 128.5, 125.5, 122.9, 120.2, 106.8, 104.1, 66.6, 61.0, 57.1, 53.0, 43.0, 26.0, 24.0, 20.1, 17.9, 12.5.



3.49

Carboxylic acid 3.49

To a solution of bromomaleic anhydride (1.0 g, 5.65 mmol) in BnOH (4.5 mL) at 0 ºC was added slowly dicyclohexylamine (1.2 mL, 6.22 mmol). After 2 hours, added EtOAc (20 mL), stirred for 1 hour and collected the resulting solid by vacuum filtration. The solid was suspended in EtOAc (100 mL) and water (100 mL). Added $KHSO_4$ until the aqueous layer reached pH 3, extracted into EtOAc, dried over Na_2SO_4 and concentrated *in vacuo* to afford an off white solid (1.25 g, 78%). Taken on directly without further purification. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39–7.35 (m, 5H), 6.52 (s, 1H), 5.30 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 163.4, 129.6, 128.8, 128.7, 128.6, 126.1, 68.7.

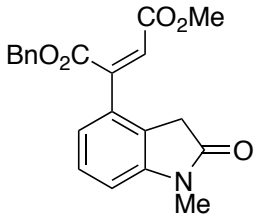


3.50

Alkene 3.50

To a solution of carboxylic acid **3.49** (1.25 g, 4.38 mmol) in DMF (22 mL) was added Cs_2CO_3 (2.14 g, 6.58 mmol) followed by MeI (0.41 mL, 6.58 mmol). After 2 hours, quenched with 1M

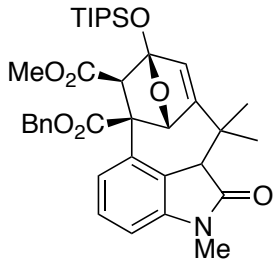
HCl (20 ml), extracted into EtOAc (3 x 40 mL), washed the combined organic layers with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purified by silica gel column chromatography (hexanes → 50:1 → 10:1 hexanes/EtOAc) to afford a white solid (1.07 g, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.25 (m, 5H), 6.51 (s, 1H), 5.31 (s, 2H), 3.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 163.4, 134.6, 128.8, 128.7, 127.2, 126.7, 126.6, 68.5, 52.3.



3.51

Oxindole 3.51

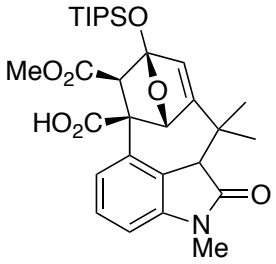
To a microwave vial was added borane **3.9** (351 mg, 1.28 mmol), K_3PO_4 (545 mg, 2.57 mmol), Pd(dppf)Cl_2 (53 mg, 64 μmol) followed by alkene **3.50** (500 mg, 1.67 mmol) in DME (2.4 mL). Stirred for 5 minutes then added water (0.8 mL). Heated in the microwave to 120 ºC for 10 minutes. Filtered through Celite, washed with excess EtOAc and concentrated *in vacuo*. Purified by silica gel column chromatography (7:1 → 4:1 → 2:1 hexanes/EtOAc) to afford oxindole **3.51** (271 mg, 58%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.34 (m, 5H), 7.31 (t, J = 7.8 Hz, 1H), 7.06 (d, J = 7.9 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.23 (s, 1H), 5.34 (s, 2H), 3.71 (s, 3H), 3.49 (s, 2H), 3.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 167.2, 165.1, 146.8, 146.0, 134.9, 130.5, 129.0, 128.75, 128.71, 128.68, 123.0, 122.0, 121.4, 109.6, 68.1, 52.2, 35.7, 31.6.



3.52

Cycloadduct 3.52

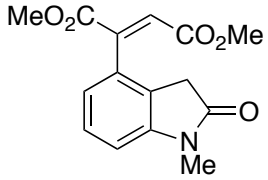
To a solution of oxindole **3.51** (80 mg, 0.219 mmol) in DCM (1 mL) was added ZnI_2 (210 mg, 0.657 mmol) then DTBP (95 μL, 0.438 mmol). Added furan **3.12** (0.27 mL, 0.876 mmol) in DCM (1.2 mL) via syringe pump (0.07 mL/hour). After 24 hours, quenched with sat. aq NH_4Cl (2 mL), and extracted into EtOAc (3 x 5 mL). Washed the organic layer with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo.* Purified by silica gel column chromatography (7:1 hexanes/EtOAc) to afford a pale yellow solid (49 mg, 35%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.31 (m, 4H), 7.27–7.25 (m, 2H), 7.22 (t, *J* = 8.1 Hz, 1H), 6.67 (d, *J* = 7.7 Hz, 1H) 5.81 (s, 1H), 5.61 (s, 1H), 5.15 (d, *J* = 12.6 Hz, 1H), 5.00 (d, *J* = 12.5 Hz, 1H), 3.57 (s, 3H), 3.53 (s, 1H), 3.24 (s, 1H), 3.17 (s, 3H), 1.67 (s, 3H), 1.13–1.06 (m, 21H), 0.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 170.9, 170.5, 158.4, 144.0, 137.3, 135.5, 128.5, 128.1, 127.9, 127.8, 127.4, 125.3, 124.4, 110.6, 106.7, 76.0, 67.7, 67.4, 64.2, 51.8, 51.5, 39.8, 26.1, 25.4, 19.4, 17.8, 12.5.



3.53

Carboxylic acid 3.53

To a solution of cycloadduct **3.52** (5 mg, 7.7 μmol) in EtOAc (30 μL) was added EtOH (0.17 mL) followed by Pd/C (3 mg, 1.6 μmol, 5%). The reaction was purged with H_2 3 x then stirred under 1 atm H_2. After 2 hours, filtered through Celite, washed with excess EtOAc and concentrated *in vacuo*. Taken on without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.24 (m, 2H), 6.66 (d, J = 7.3 Hz, 1H), 5.70 (s, 1H), 5.60 (s, 1H), 3.72 (s, 3H), 3.52 (s, 1H), 3.23 (s, 1H), 3.16 (s, 3H), 1.65 (s, 3H), 1.05–1.04 (m, 21H), 0.75 (s, 3H).

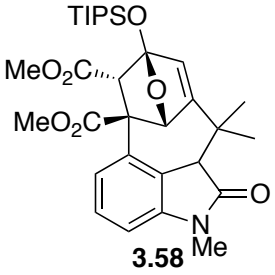


3.57

Oxindole 3.57

To a microwave vial was added borane **3.9** (246 mg, 0.900 mmol), TBAB (290 mg, 0.900 mmol), Pd(dppf)Cl_2 (37 mg, 45 μmol) followed by alkene **3.56** (261 mg, 1.17 mmol) in THF (3 mL). Stirred for 5 minutes then added CsF (547 mg, 3.60 mmol) in water (3 mL). Heated in the microwave to 120 ºC for 10 minutes. Diluted with DCM (20 mL), washed with 1M HCl (20 mL). Extracted into DCM (3 x 20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purified by silica gel column chromatography (7:1 → 4:1 → 2:1 → 1:1 hexanes/EtOAc) followed by a

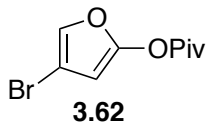
second silica gel column (4:1 hexanes/EtOAc) to afford oxindole **3.57** (151 mg, 58%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.8 Hz, 1H), 7.10 (s, 1H), 6.84 (app dd, *J* = 8.0, 2.8 Hz, 2H), 3.81 (s, 3H), 3.63 (s, 3H), 3.34 (s, 2H), 3.23 (s, 3H).



3.58

Cycloadduct 3.58

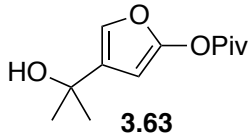
To a solution of oxindole **3.57** (50 mg, 0.173 mmol) and $Cu(OTf)_2$ (375 mg, 1.04 mmol) in DCM (1.7 mL) was added DTBP (75 μL, 0.346 mmol) followed by furan **3.12** (206 mg, 0.691 mmol). Stirred for 18 hours, then quenched with NH_4Cl (3 mL). Extracted into Et_2O (3 x 5 mL), washed with water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purified by silica gel column chromatography (7:1 hexanes/EtOAc) to afford cycloadduct **3.58** (16.2 mg, 17%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (t, *J* = 7.9 Hz, 1H), 6.72 (d, *J* = 7.9 Hz, 1H), 6.65 (d, *J* = 7.5 Hz, 1H), 5.93 (s, 1H), 5.58 (s, 1H), 4.16 (s, 1H), 3.71 (s, 3H), 3.60 (s, 1H), 3.52 (s 3H), 3.16 (s, 3H), 1.70 (s, 3H), 1.12 (sep, *J* = 7.0 Hz, 3H), 1.06 (d, *J* = 6.0 Hz, 18H), 0.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 173.0, 170.8, 153.4, 144.9, 134.8, 129.3, 128.2, 125.3, 121.8, 111.3, 107.0, 79.3, 69.6, 61.6, 53.4, 52.0, 51.7, 39.2, 26.7, 26.1, 20.1, 17.8, 12.6.



3.62

Furan 3.62

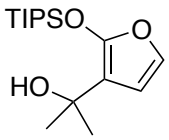
To a solution of lactone **3.60** (750 mg, 4.60 mmol) and PivCl (1.7 mL, 13.8 mmol) in MeCN (23 mL) was added NEt_3 (1.9 mL, 13.8 mmol) and heated to 60 ºC. After 2 hours, cooled to room temperature and filtered through Celite. Diluted with DCM (25 mL), washed with 10% Na_2CO_3 (50 mL), brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purified by silica gel column chromatography (hexanes) to afford a clear oil (893 mg, 79%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.09 (s, 1H), 6.00 (s, 1H), 1.34 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 151.4, 133.4, 100.6, 96.2, 39.2, 26.5.



3.63

Furan alcohol 3.63

To a solution of furan **3.62** (20 mg, 80.9 μmol) and acetone (6.5 μL, 89.0 μmol) in Et_2O (0.23 mL) at –78 ºC was added dropwise *t*BuLi (0.11 mL, 0.17 mmol, 1.52 M in hexanes). After 2 hours, quenched with sat. aq NH_4Cl (0.2 mL) and warmed to room temperature. Extracted into EtOAc (1 mL), washed with water (1 mL), brine (1 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purified by silica gel column chromatography (hexanes → 50:1 hexanes/EtOAc) to afford a yellow oil (7 mg, 39%). Crude ^{1}H NMR prior to purification showed 66% conversion. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (s, 1H), 5.93 (s, 1H), 1.52 (s, 6H), 1.35 (s, 9H).



3.64

Furan alcohol 3.64

To a solution of furan **3.69** (1.45 g, 4.54 mmol) in Et_2O (13 mL) at –78 ºC was added dropwise *n*BuLi (2.0 mL, 4.54 mmol, 2.22 M in hexanes). After 1.5 hours, added acetone (0.37 mL, 5.00 mmol) dropwise in Et_2O (4.5 mL). After 2.5 hours, quenched with NH_4Cl (10 mL). Extracted into EtOAc (20 mL), washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. ^{1}H NMR showed 50% conversion, product is not silica stable and could not be purified. Upon expose to silica gel, product decomposes to enone **3.70** whose spectra match literature reports.[2] ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, *J* = 2.2 Hz, 1H), 6.27 (d, *J* = 2.2 Hz, 1H), 1.53 (s, 6H), 1.35–1.25 (m, 3H), 1.12 (d, *J* = 3.2 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.2, 130.3, 110.6, 103.3, 68.6, 30.5, 17.6, 12.3.

[2] Sigman, M. S.; Kerr, C. E.; Eaton, B. E. *J. Am. Chem. Soc.* **1993**, *115*, 7545–7546.

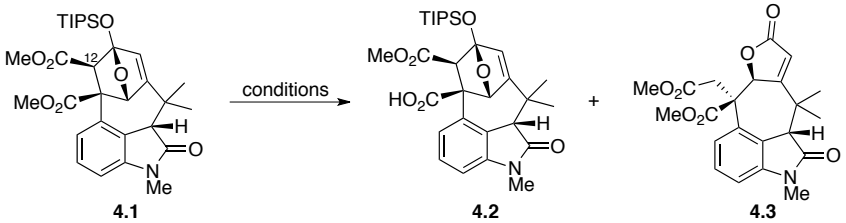
Chapter 4: Differentiation and Elaboration.

4.1. Cycloadduct Reduction and Elaboration.

All the various differentiated dienophiles that have been prepared failed at various stages during the synthesis. Ultimately the steric and electronic demands of the type 2 IMDA reaction as well as the sensitivity of the furan diene to the Lewis acidic reaction conditions could not be successfully overcome except in the case of the cycloadduct **4.1** with two methyl ester substituents. For this reason efforts were directed back at elaborating and differentiating this compound.

Comparing the two esters in cycloadduct **4.1** it is unclear which group is more reactive or if selective reactivity can be achieved. The bridgehead ester, despite being neopentylic, is expected to be slightly less hindered than the ester at C12 with its adjacent silyl protecting group. The concave structure of the ring system also helps the bridgehead ester sit in a more exposed environment, hopefully making it more reactive. Attempts to hydrolyze ester **4.1** to acid **4.2** resulted in no reaction, decomposition, or hydrolysis of the silyl protecting group resulting in a retro–Claisen rearrangement to lactone **4.3** (Table 4.1). None of conditions surveyed resulted in any detectable ester hydrolysis.

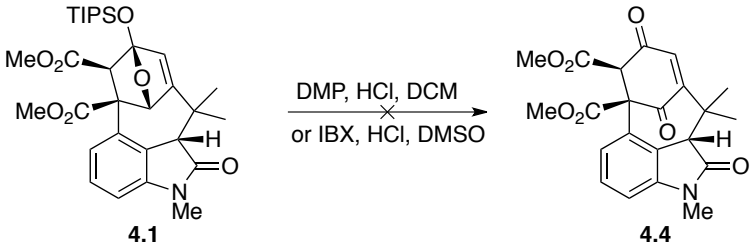
Table 4.1: *Attempted hydrolysis of cycloadduct **4.1**.*



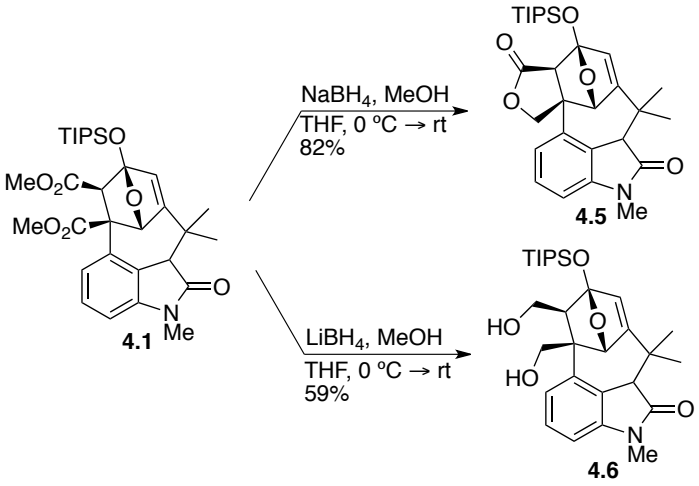
4.1 **4.2** **4.3**

Entry	Conditions	Result
1	LiOH, acetone, H_2O, rt	NR
2	LiOH, acetone, H_2O, 50 °C	NR
3	TMSOK, THF	NR
4	LiI, pyridine, reflux	decomp
5	KOtBu, DMSO	decomp
6	BCl_3, DCM, –78 °C to rt	**4.3**
7	$AlCl_3$, THF	**4.3**

The sensitivity of silyl acetal **4.1** is problematic due to the retro–Claisen rearrangement that occurs upon deprotection. To avoid this non-productive rearrangement, oxidative deprotections were attempted. DMP or IBX alone are not acidic enough to remove the TIPS group but in the presence of HCl, enone **4.4** was not formed (Scheme 4.1).[1] Again, retro–Claisen product **4.3** is the major product of the reaction, suggesting that rearrangement is faster than oxidation.



Scheme 4.1: *Attempted oxidative deprotection.*

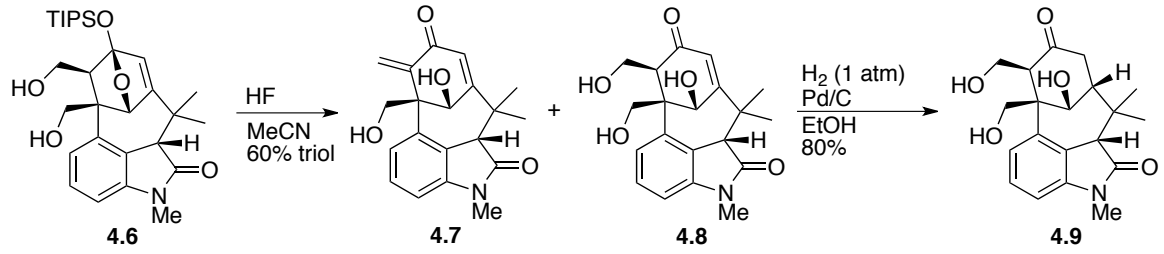


Scheme 4.2: *Cycloadduct reduction.*

Reduction of the esters of cycloadduct **4.1** was also targeted as a potential method for differentiation. The silyl acetal is expected to be stable under the reaction conditions, removing the potential for rearranged side products. Sodium borohydride reduced the less hindered bridgehead alkene followed by lactonization to form lactone **4.5** (Scheme 4.2). This confirms

that the bridgehead ester is less hindered and differentiation is possible. However, opening the stable 5-membered lactone is expected to be problematic in the presence of the silyl acetal. Alternately, reduction with lithium borohydride resulted in formation of diol **4.6**. The lack of a carbonyl substituent at C12 should allow silyl deprotection of diol **4.6** to proceed without lactonization or retro–Claisen reaction.

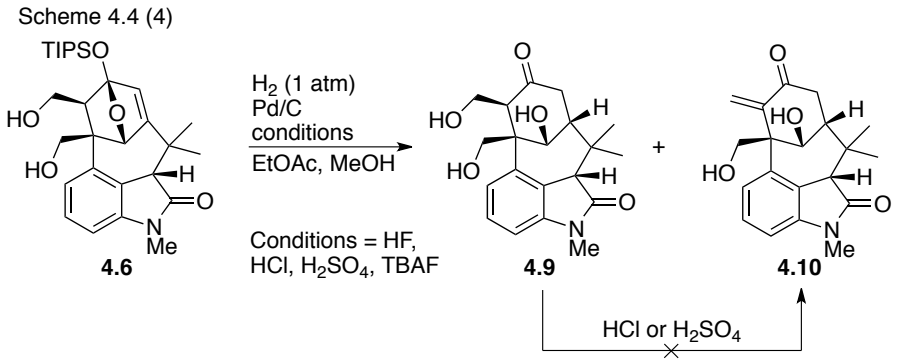
Therefore, synthetic efforts were focused on elaborating reduced cycloadduct **4.6**. Deprotection with a variety of fluoride sources afforded mixtures of diol **4.7** and triol **4.8** (Scheme 4.3). None of the conditions screened gave good selectivity but desired triol **4.8** could be separated from the reaction mixture. Subsequent hydrogenation of alkene **4.8** under atmospheric pressure afforded triol **4.9**. While triol **4.9** could be accessed via this route, formation of side product **4.7** limited the amount of material that could be accessed.



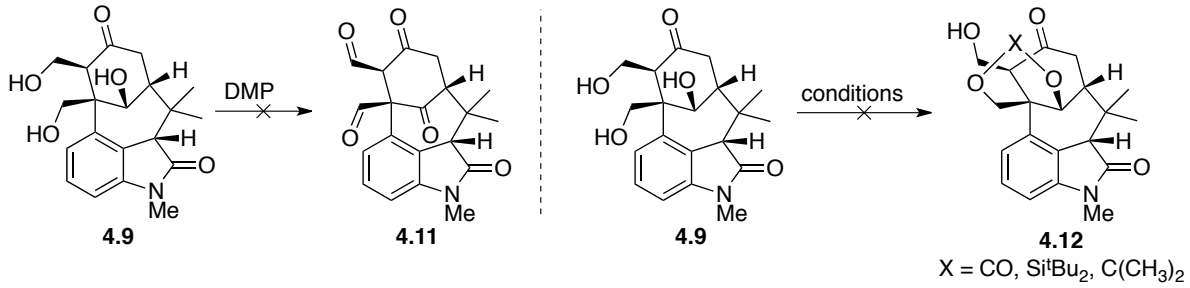
Scheme 4.3: *Reduced cycloadduct deprotection attempts.*

To improve the yield of triol **4.9**, one-pot deprotection-hydrogenation conditions were screened.[2] Again competing elimination to enone **4.10** was observed (Scheme 4.4). Additionally, triol **4.9** was not stable to silica gel purification and could not be separated from enone **4.10**. Elimination of the alcohol is proposed to occur after hydrogenation, as hydrogenation of the exocyclic alkene is generally not observed. Attempts to favor elimination by using stronger acids or longer reaction times were unsuccessful, resulting in decomposition or hydrogenation of the exocyclic alkene. Isolation of the mixture and subjection to dilute acid also did not promote

elimination to enone **4.10**. Instead, triol **4.9** could be formed selectively by shortening the reaction time to 30 minutes and used without further purification.



Scheme 4.4: *One-pot deprotection-hydrogenation reaction.*

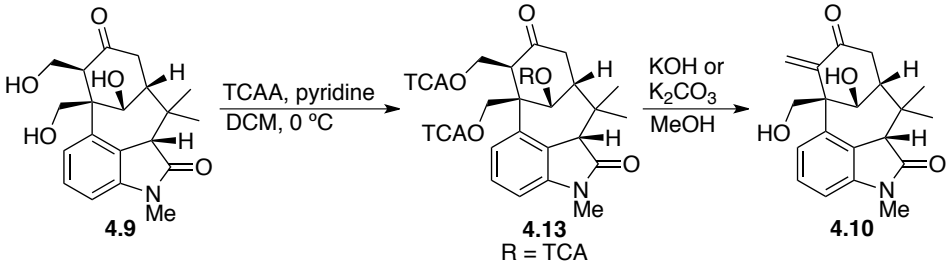


Scheme 4.5: *Triol elaboration attempts.*

Several approaches to elaborate triol **4.9** were considered. First, global oxidation to keto-aldehyde **4.11** was investigated (Scheme 4.5). While keto-aldehyde **4.11** lacks differentiation, it would provide an opportunity to screen methylation conditions. However, even in the presence of excess oxidant, only a single oxidation was observed by mass spectrometry. The compound formed decomposed upon isolation but it is proposed that oxidation of a primary alcohol occurs followed by formation of a lactol. The lactol and secondary alcohol are not oxidized under the reaction conditions but the resulting compound could not be isolated for characterization. Selective protection to form alcohol **4.12** was also unsuccessful. Desired alcohol **4.12** relies on formation of the thermodynamically more stable six-membered ring instead of the two other possible seven-membered rings.[3] However, protected alcohol **4.12** with a carbonate, silyl ether or

acetal could not be formed. Conditions screened resulted either in no reaction or decomposition of triol **4.9**, motivating us to search for milder elaboration conditions.

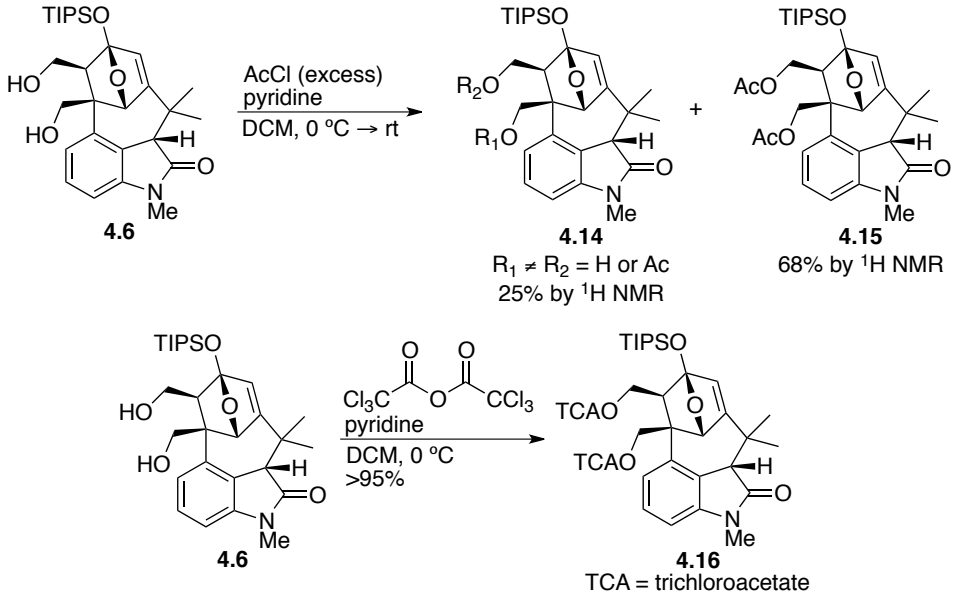
Acetate protection of triol **4.9** was investigated. Global protection with trichloroacetate anhydride (TCAA) afforded ketone **4.13** (Scheme 4.6). Attempted selective deprotection of the less hindered primary acetate resulted in global deprotection and elimination to enone **4.10**. Switching from trichloroacetate to the more stable acetate analog was also unsuccessful. Attempted global protection resulted in a mixture of mono-, di-, and triprotected products due to the lower reactivity of acetyl chloride compared with TCAA. Ultimately these intermediates did not solve the problem of differentiation, and difficulties in isolating triol **4.9** lead to an alternate elaboration strategy.



Scheme 4.6: *Triol global protection and elimination.*

Alcohol protection prior to hydrogenation was considered as a strategy to avoid unstable triol **4.9**. Acetate and trichloroacetate (TCA) protecting groups were chosen to promote elimination after silyl deprotection. Acetate protection was incomplete provided an inseparable mixture of diacetate **4.15** and monoacetate **4.14** (Scheme 4.7). Only a single regioisomer of acetate **4.14** was observed, suggesting that selective protection of one of the primary alcohols is possible. Diprotection with trichloroacetic anhydride cleanly afforded diacetate **4.16** without the need for further purification. Unfortunately, further elaboration again proved to be problematic. The silyl protecting group must be cleaved prior to bridgehead alkene hydrogenation, but the

TCA esters were also removed under those conditions. Similarly, hydrogenation of the mixture of acetate protected diols **4.14** and **4.15** did not afford the desired ketone. Selective monoacetate protection was also not observed.

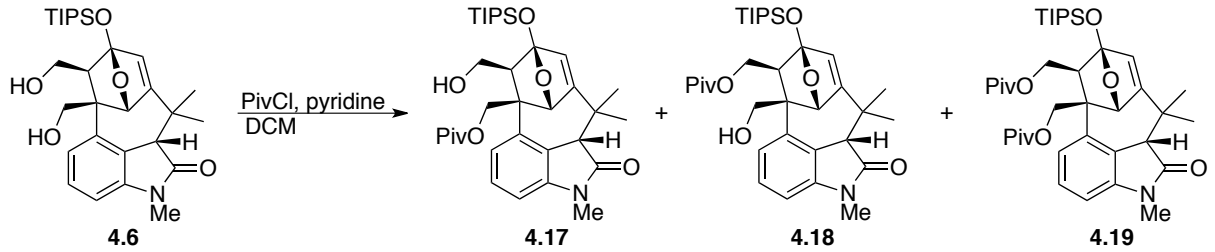


Scheme 4.7: *Reduced cycloadduct protection.*

4.2. Selective Diol Protection and Elaboration.

Instead, efforts were focused on a larger protecting group. Protection with pivaloyl chloride led to separable mixtures of mono- and diprotected products, allowing the assignment of regioisomers **4.17** and **4.18** (Table 4.2). Screening protection conditions showed that the addition of DMAP increased the regioselectivity to 6:1 favoring bridgehead ester **4.17**, while shortened reaction times and lower temperatures decreased formation of diprotected cycloadduct **4.19**. Attempts to further increase the regioselectivity of protection using *N*-pivaloyl imidazole were unsuccessful, with no reaction occurring even at elevated temperatures.[4] Reasonable quantities of protected diol **4.17** could be obtained, with a highest isolated yield of 57%.

Table 4.2: *Optimization of selective Piv protection.*

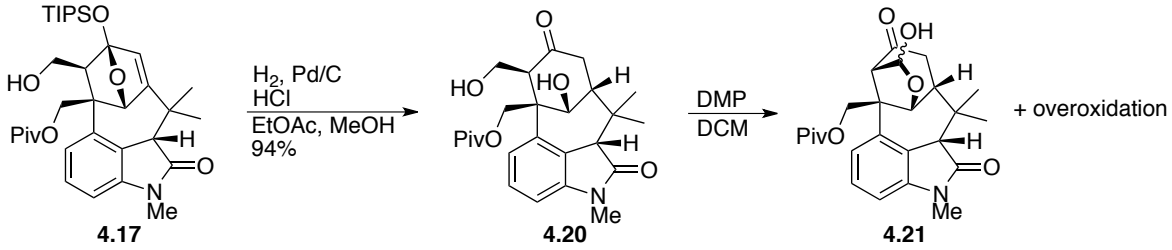


4.6 **4.17** **4.18** **4.19**

Entry	Temperature	Equiv PivCl	Additive	Time	**4.6 : 4.17 : 4.18 : 4.19**	Yield **4.17**
1	0º C to rt	1.05	none	7 h	4 : 1.4 : 1 : 0	22% [1]
2	0º C to rt	2.2	none	7 h	3.3 : 6.3 : 4 : 1	43% [1]
3	0º C	2.2	none	36 h	1.4 : 3.7 : 2.2 : 1	50%
4	0º C	2.2	DMAP	36 h	7.5 : 4 : 1 : 0	34% [1]
5	0º C to rt	2.2	DMAP	1.5 h	**4.19** only	0%
6	0º C to rt	1.05	DMAP	24 h	5.5 : 1.6 : 1 : 0	20% [1]
7	0º C to rt	2.2	DMAP	45 min	0 : 1 : 0 : 1.2	34% [1]
8	rt	2.2	DMAP	45 min	0 : 1 : 0 : 3.7	21% [1]
9	rt	1.05	DMAP	2.5 h	17 : 5 : 1 : 0	22% [1]
10	0º C to rt	2.2	DMAP	30 min	0 : 6 : 1 : 3	63% [1]

[1] Determined by ^{1}H NMR

Elaboration of diol **4.17** proceeded smoothly to afford triol **4.20** (Scheme 4.8). Unfortunately, oxidation did not lead to aldehyde formation but instead gave a mixture of products including lactol **4.21** in addition to overoxidation. This suggests that protection of the secondary alcohol is necessary before oxidation.

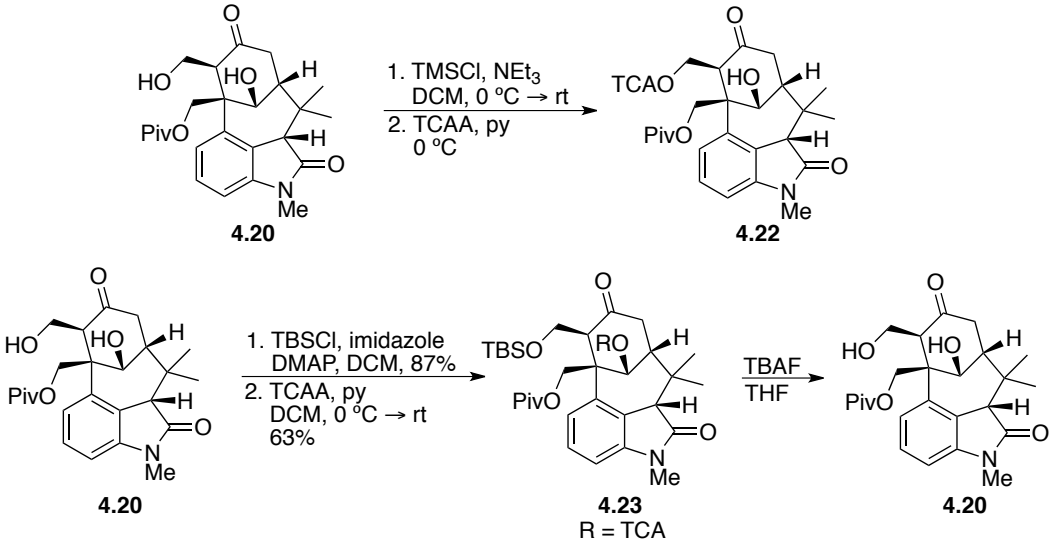


4.17 **4.20** **4.21**

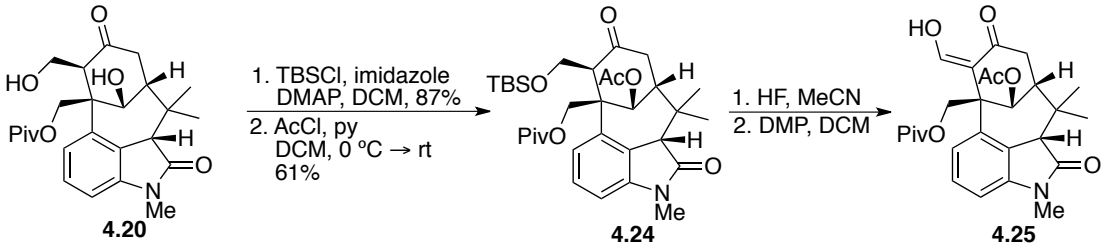
Scheme 4.8: *Selectively protected diol elaboration.*

Efforts were then directed towards selectively protecting secondary alcohol **4.20**. One-pot procedures to first silyl protect the primary alcohol followed by trichloroacetate protection of the secondary alcohol instead lead to selective trichloroacetate protection of the primary alcohol (Scheme 4.9).[5] This is hypothesized to occur via silyl transfer to the secondary alcohol, leaving

the primary alcohol free to react with trichloroacetic anhydride. Switching to a larger silyl protecting group and isolating the intermediate protected diol allowed formation of globally protected triol **4.23**. Unfortunately, upon treatment with TBAF, both the silyl and trichloroacetate protecting groups were cleaved. To avoid deprotection of the secondary alcohol, an acetate protecting group was used instead of trichloroacetate.



Scheme 4.9: *Secondary alcohol protection attempts*.



Scheme 4.10: *Synthesis of methylation precursor **4.25***.

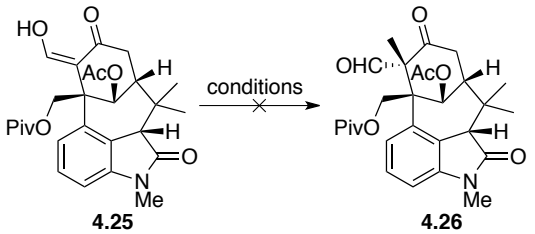
Acetate protection of the secondary alcohol proved to be somewhat more challenging than trichloroacetate protection. A large excess of acetyl chloride was required as no reaction was observed with acetic anhydride, and the reaction proceeded slowly with unreacted starting material recovered after 18 hours (Scheme 4.10). Silyl deprotection of triol **4.24** followed by

oxidation led to enol **4.25**, which was then subjected to various methylation conditions.

4.3. Screening Methylation Conditions.

While there are few examples of methylating α-formyl ketones, the reaction is not entirely unprecedented.[6] Attempts to use methyl iodide to favor C-methylation were unsuccessful, and only O-methylation was observed. Strong bases tended to cause decomposition (Table 4.3) while weaker bases resulted in O-methylation or no reaction. While a wide variety of conditions remain to be screened, this route was ultimately abandoned due to the number of steps required to manipulate protecting groups, instability of enol **4.25** and lack of the desired reactivity in methylating.

Table 4.3: *Screening methylation conditions.*

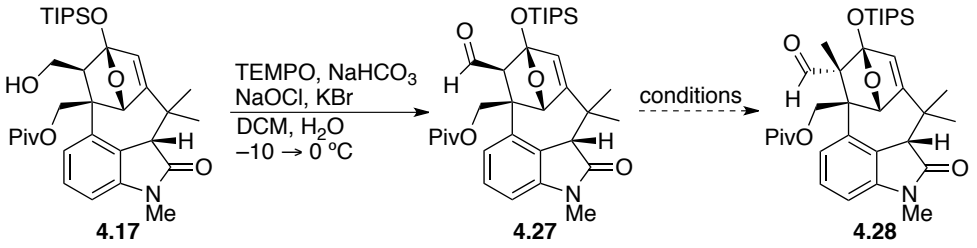


4.25 **4.26**

Entry	Base	Me Source	Solvent	Result
1	NaHMDS	MeI	THF	decomp
2	NaH	MeI	THF	decomp
3	KOtBu	MeI	THF	O-methylation
4	K_2CO_3	MeI	THF	O-methylation
5	K_2CO_3	MeI	DMSO	O-methylation
6	K_2CO_3	MeI	HMPA	O-methylation
7	K_2CO_3	MeI	none	O-methylation
8	K_2CO_3	MeI	Et_2O	NR
9	Li_2CO_3	MeI	Et_2O	NR
10	Li_2CO_3	Me_2SO_4	Et_2O	NR

Enamine alkylation was considered as an alternative solution.[7] Aldehyde **4.27** was targeted as a suitable substrate (Scheme 4.11). Surprisingly, oxidation of primary alcohol **4.17** proved to be difficult. Hypervalent iodine, chromium, and sulfoxide based oxidations all failed to

oxidize the primary alcohol, possibly due to the crowded steric environment. Only TEMPO-mediated oxidation was successful in preparing small quantities of aldehyde **4.27**, but the conditions failed upon increasing the scale of the reaction beyond 5 mg. A preliminary survey of methylation conditions also failed to provide the desired reactivity, again attributed to steric crowding. Methylation of the welwitindolinone core does not appear to be the optimal approach, and introducing the quaternary center earlier would solve most of the problems encountered.



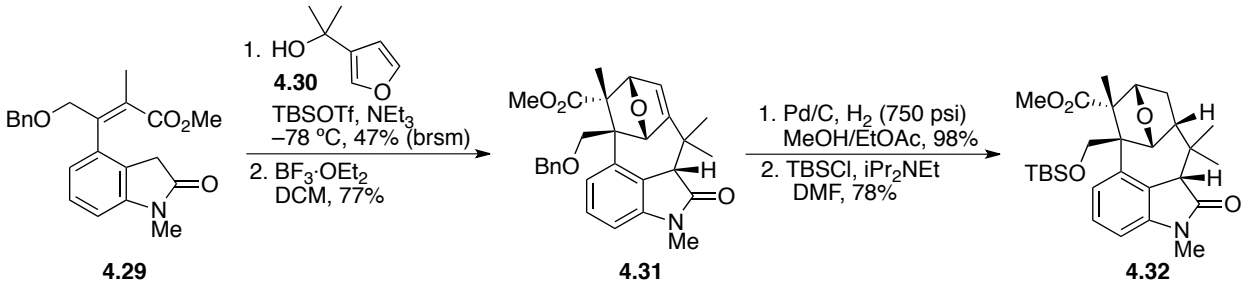
Scheme 4.11: *Alternative methylation substrate*.

4.4. Conclusions and Future Directions.

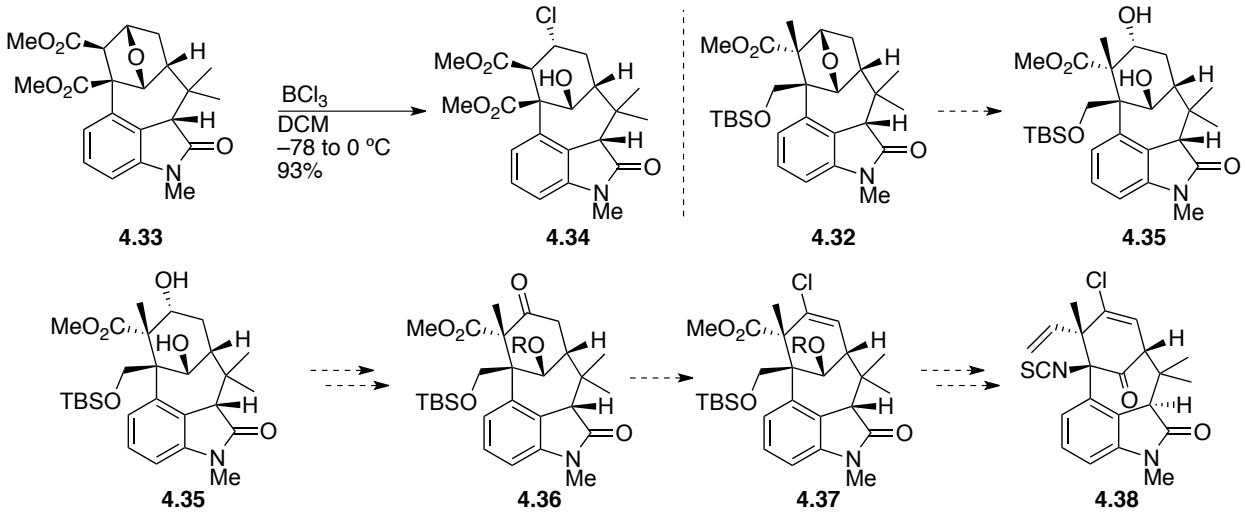
Installing the quaternary center at C12 is one of the major challenges remaining in completing the total synthesis of welwitindolinone C (**4.38**). The acidity of the C3 proton has limited which substrates are potentially amenable to selective deprotonation and/or methylation and lead to the synthesis of unstable dicarbonyl **4.25**. Observed *O*-methylation instead of the desired *C*-methylation has further complicated the process, and the current route is not well suited to our natural product target.

In her work towards welwitindolinone B, Dr. Leah Cleary reported T2IMDA reactions with tetrasubstituted alkene dienophiles.[8] Cycloadduct **4.31** could be prepared with the desired quaternary center in place, followed by hydrogenation and protection to afford ether **4.32** (Scheme 4.12). Further elaboration of ether **4.32** could allow the synthesis of welwitindolinone

C. Nucleophilic hydroxide opening, analogous to the chlorination reaction in the welwitindolinone B route could afford diol **4.35** (Scheme 4.13).[9] From there, oxidation and chlorination would afford vinyl chloride **4.37**. Functional group manipulations would then allow the synthesis of welwitindolinone C (**4.38**).



Scheme 4.12: *Cycloaddition with a tetrasubstituted alkene dienophile*.



Scheme 4.13: *Proposed endgame strategy based on our welwitindolinone B strategy*.

While selective pivaloyl protection has allowed the differentiation of reduced cycloadduct **4.6**, difficulties in methylating have ultimately limited the utility of our route towards welwitindolinone C (**4.38**). A strategy that allows the use of tetrasubstituted alkene dienophile in the IMDA-cascade reaction would install the desired C12 quaternary center while avoiding unstable 1,3-dicarbonyl intermediates.

4.5. References.

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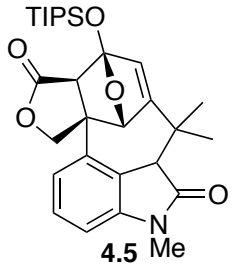
4.6. Supporting Information.

All reactions were carried out under nitrogen, unless otherwise noted, in oven– or flame– dried glassware. Thin layer chromatography was performed using glass-backed EM Science Silica Gel 60 PF254 Plates. Flash chromatography was performed using EM Science Silica Gel 60 (230-400 mesh). All volatile solvents were removed, *in vacuo*, under reduced pressure using a Büchi rotary evaporator. ^{1}H NMR spectra were recorded at 500 MHz, using a Bruker DRX 500 spectrophotometer, or at 600 MHz using an Avance 600 spectrometer. ^{13}C NMR spectra were recorded at 125 MHz. All spectra were taken at 298 K. ^{1}H NMR and ^{13}C NMR spectra were run in $CDCl_3$, CD_2Cl_2, or CD_3OD with shifts reported as δ values in ppm and referenced to residual solvent proton(s). Splitting patterns are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sep = septet, m = multiplet, br = broad. Infrared (IR) spectra were acquired on a Perkin & Elmer FT IR System 2000 Series spectrometer. High resolution mass spectra were obtained on a MicroMass LCT (ES) spectrometer. High pressure hydrogenations were performed in a Parr Instrument 4767 Pressure Vessel.

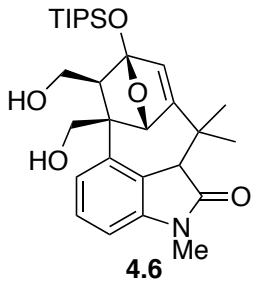


4.5

Lactone 4.5

To a solution of cycloadduct **4.1** (10 mg, 17.6 μmol) in THF (0.2 mL) at 0 ºC was added MeOH (17 μL) then $NaBH_4$ (8 mg, 0.211 mmol) and the reaction was warmed to room temperature. After 4 hours, diluted with EtOAc (1 mL), quenched with sat. aq NH_4Cl (1mL). Extracted into

EtOAc (3 x 1 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purified by silica gel column chromatography (4:1 hexanes/EtOAc) to afford a white solid (7.4 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 5.73 (s, 1H), 5.04 (s, 1H), 4.56 (t, *J* = 10.8 Hz, 2H), 3.52 (s, 1H), 3.19 (s, 3H), 2.84 (s, 1H), 2.11 (s, 3H), 1.16 (sep, *J* = 7.5 Hz, 3H), 1.11–1.08 (m, 18H), 0.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 171.5, 158.1, 144.4, 140.0, 129.8, 128.4, 123.4, 122.4, 111.8, 106.5, 79.23, 79.17, 62.8, 62.3, 51.6, 38.9, 26.3, 26.2, 20.2, 17.8, 12.6.

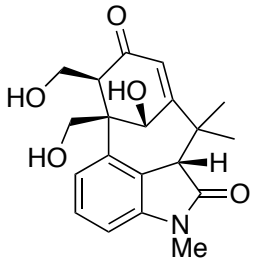


4.6

Diol 4.6

To a solution of cycloadduct **4.1** (410 mg, 0.720 mmol) in THF (7 mL) at 0 ºC was added MeOH (0.35 mL) then $LiBH_4$ (2.16 mL, 4.32 mmol, 2M in THF) dropwise. The reaction was then warmed to room temperature. After 4 hours, quenched with sat. aq NH_4Cl (10 mL) and stirred until gas evolution stopped. Extracted into EtOAc (3 x 30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purified by silica gel column chromatography (2:1 → 1:1 hexanes/EtOAc) to afford a white solid (217 mg, 59%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.65 (d, *J* = 7.6 Hz, 1H), 5.60 (s, 1H), 5.09 (s, 1H), 4.15 (dd, *J* = 11.7, 7.8 Hz, 1H), 4.03–3.98 (m, 2H), 3.92 (d, *J* = 11.2 Hz, 1H), 3.94 (s, 1H), 3.17 (s, 3H), 2.24 (dd, *J* = 7.3, 5.1 Hz, 1H), 1.65 (s, 3H), 1.18 (sep, *J* = 7.8 Hz, 3H), 1.10 (d, *J* = 7.8 Hz, 18H), 0.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 156.8, 144.1, 141.6, 128.9, 126.9,

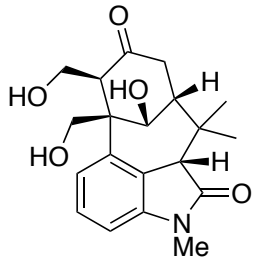
124.5, 122.6, 111.0, 105.9, 99.9, 75.5, 67.1, 61.2, 57.3, 51.8, 39.5, 26.1, 25.7, 19.7, 17.9, 12.6; IR (ATR) ν[cm^{-1}] = 3559, 3010, 2946, 2869, 1707, 1463; HRMS (TOF ES+) *m* / *z* calcd for $C_{29}H_{43}NO_5SiNa$ $(M + Na)^+$ 536.2808, found 536.2819.



4.8

Enone triol 4.8

To a suspension of diol **4.6** (5 mg, 9.73 μmol) in MeCN (0.3 mL) was added HF (0.3 mL, 6M in MeCN). After 1 hour, adjusted pH to 4 with sat. aq $NaHCO_3$, extracted into EtOAc (3 x 1 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purified by silica gel column chromatography (EtOAc) to afford triol **4.8** (2.1 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.7 Hz, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 6.68 (d, *J* = 7.7 Hz, 1H), 5.69 (s, 1H), 5.34 (s, 1H), 4.36 (d, *J* = 9.9 Hz, 1H), 4.28 (d, *J* = 10.8 Hz, 1H), 4.09 (d, *J* = 9.9 Hz, 1H), 4.02 (d, *J* = 10.9 Hz, 1H), 3.76 (s, 1H), 3.17 (s, 3H), 2.92 (s, 1H), 1.77 (s, 3H), 1.01 (s, 3H). Enone **4.7** is the minor product of this reaction.



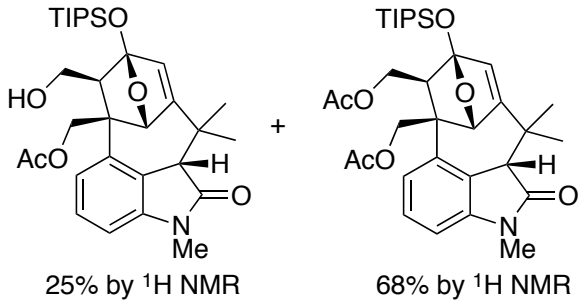
4.9

Triol 4.9

To a solution of alkene **4.8** (5 mg, 14.0 μmol) in EtOH (0.35 mL) was added Pd/C (6 mg, 2.8 μmol, 5%). Stirred under 1 atm H_2 for 7 hours, then filtered through Celite, washed with excess DCM then MeOH and concentrated *in vacuo* to afford a white solid (4 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 1H), 6.74 (d, *J* = 7.7 Hz, 1H), 4.97 (s, 1H), 4.22–4.19 (m, 2H), 4.12 (dd, *J* = 11.1, 3.2 Hz, 1H), 3.89 (d, *J* = 11.0 Hz, 1H), 3.58 (s, 1H), 3.19 (s, 3H), 3.05 (t, *J* = 4.5 Hz, 1H), 2.32–2.26 (m, 1H), 2.20–2.10 (m, 2H), 1.62 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.9, 175.3, 144.4, 141.6, 129.3, 124.4, 121.4, 106.8, 68.8, 68.1, 60.8, 60.4, 55.7, 53.6, 52.4, 40.2, 37.8, 30.4, 26.2, 19.7.

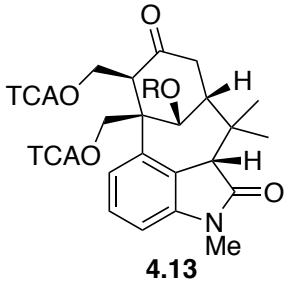
Alternate 1-step deprotection and reduction

To a solution of diol **4.6** (10 mg, 19.5 μmol) in EtOAc (80 μL) and MeOH (0.43 mL) was added HCl (50 μL, 5M) then Pd/C (8 mg, 3.89 μmol, 5%). Stirred under 1 atm H_2 for 40 minutes, then filtered through Celite and diluted with EtOAc (5 mL). Washed with water (3 x 4 mL), brine (4 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Taken on without further purification, was not stable to silica gel column chromatography. Spectra matches product from the two-step procedure.



Acetate 4.14 and Diacetate 4.15

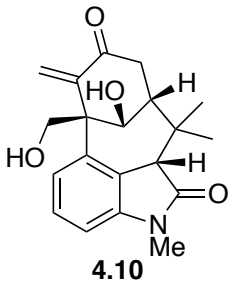
To a solution of diol (5 mg, 9.73 μmol) in DCM (0.1 mL) was added pyridine (2.4 μL, 29.2 μmol) then cooled to 0 ºC. Added acetyl chloride (1.5 μL, 20.4 μL), stirred for 1 hour then warmed to room temperature. After 4 hours, diluted with EtOAc (2 mL). Washed with sat. aq $NaHCO_3$ (2 x 1 mL), 10% aq $CuSO_4$ (2 x 1 mL), water (1 mL), brine (1 mL), dried over Na_2SO_4 and concentrated *in vacuo*. ^{1}H NMR of the crude mixture showed a 2.7:1 mixture of diacetate **4.15** to acetate **4.14**. Not separable by silica gel column chromatography. **Acetate 4.14**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.62 (d, *J* = 7.9 Hz, 1H), 5.61 (s, 1H), 5.03 (s, 1H), 4.63 (d, *J* = 10.7 Hz, 1H), 4.28 (d, *J* = 10.6 Hz, 1H), 3.98 (dd, *J* = 11.1, 5.0 Hz, 1H), 3.45 (s, 1H), 3.17 (s, 3H), 2.28 (dd, *J* = 8.7, 4.8 Hz, 1H), 1.84 (s, 3H), 1.65 (s, 3H), 1.18–1.12 (m, 3H), 1.08 (d, *J* = 8.2 Hz, 18H), 0.79 (s, 3H). **Diacetate 4.15**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 6.62 (d, *J* = 7.8 Hz, 1H), 5.59 (s, 1H), 5.06 (s, 1H), 4.77–4.73 (m, 2H), 4.28 (d, *J* = 10.6 Hz, 1H), 4.22 (dd, *J* = 11.9, 9.4 Hz, 1H), 3.46 (s, 1H), 3.18 (s, 3H), 2.37 (dd, *J* = 9.4, 5.3 Hz, 1H), 2.17 (s, 3H), 1.84 (s, 3H), 1.65 (s, 3H), 1.18–1.12 (m, 3H), 1.08 (d, *J* = 8.2 Hz, 18H), 0.78 (s, 3H).



4.13
R = TCA

Trichloroaceate 4.13

To a solution of triol **4.9** (2 mg, 5.56 μmol) in DCM (0.1 mL) was added pyridine (1.8 μL, 22.3 μmol) then cooled to 0 ºC. Added trichloroacetic anhydride (3.4 μL, 18.4 μmol) and stirred for 2 hours then warmed to room temperature. Diluted with EtOAc (2 mL). Washed with sat. aq $NaHCO_3$ (2 x 1 mL), 10% aq $CuSO_4$ (2 x 1 mL), water (1 mL), brine (1 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purified by silica gel column chromatography (4:1 → 2:1 hexanes/EtOAc) to afford acetate **4.13** (1.1 mg, 31% from triol **4.x**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (t, *J* = 7.9 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.28 (s, 1H), 5.39 (dd, *J* = 12.2, 3.1 Hz, 1H), 5.11 (d, *J* = 11.0 Hz, 1H), 4.84 (dd, *J* = 12.3, 9.1 Hz, 1H), 4.50 (d, *J* = 11.1 Hz, 1H), 3.71 (s, 1H), 3.59 (dd, *J* = 8.8, 3.1 Hz, 1H), 3.22 (s, 3H), 2.48–2.43 (m, 1H), 2.36–2.29 (m, 2H), 1.77 (s, 3H), 0.85 (s, 3H).



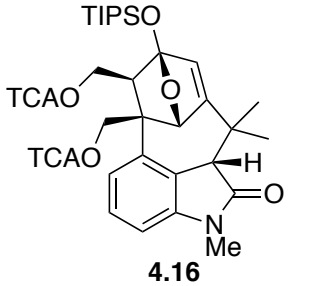
4.10

Diol 4.10

To a solution of protected triol **4.13** (0.5 mg, 0.63 μmol) in MeOH (50 μL) was added K_2CO_3

(0.1 mg, 0.16 μmol) in water (5 μL). After 2 hours, diluted with water (0.2 mL), extracted into EtOAc (3 x 0.5 mL), washed with brine (1 mL), dried over Na_2SO_4 and concentrated *in vacuo*.

Diol **4.10** can also be found as a side product in the 1 step deprotection and reduction of diol **4.9** if the reaction is allowed to stir for too long. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.72 (d, *J* = 7.7 Hz, 1H), 6.48 (s, 1H), 5.64 (s, 1H), 5.06 (s, 1H), 4.30 (d, *J* = 11.1 Hz, 1H), 4.02 (d, *J* = 11.1 Hz, 1H), 3.60 (s, 1H), 3.19 (s, 3H), 2.41 (dd, *J* = 15.0, 8.7 Hz, 1H), 2.16–2.10 (m, 1H), 1.96 (dd, *J* = 15.0, 10.0 Hz, 1H), 1.64 (s, 3H), 0.78 (s, 3H).



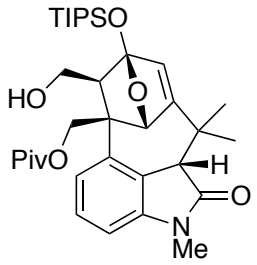
4.16

TCA = trichloroacetate

Diester 4.16

To a suspension of diol **4.6** (5 mg, 9.73 μmol) in MeCN (0.1 mL) and DCM (0.1 mL) was added pyridine (2.4 μL, 29.2 μmol) and cooled to 0 ºC. Added trichloroacetic anhydride (4 μL, 21.4 μmol) and stirred for 1 hour then warmed to room temperature. After an additional hour, the reaction was diluted with EtOAc (2 mL). Washed with sat. aq $NaHCO_3$ (2 x 1 mL), 10% aq $CuSO_4$ (2 x 1 mL), water (1 mL), brine (1 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford diester **4.16**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.21 (m, 2H), 6.63 (d, *J* = 7.2 Hz, 1H), 5.65 (s, 1H), 5.24 (d, *J* = 10.3 Hz, 1H), 5.19 (s, 1H), 5.11 (dd, *J* = 12.2, 4.3 Hz, 1H), 4.53 (d, *J* = 10.3 Hz, 1H), 4.40 (t, *J* = 11.7 Hz, 1H), 3.52 (s, 1H), 3.17 (s, 3H), 2.67 (dd, *J* = 11.6, 4.2 Hz,

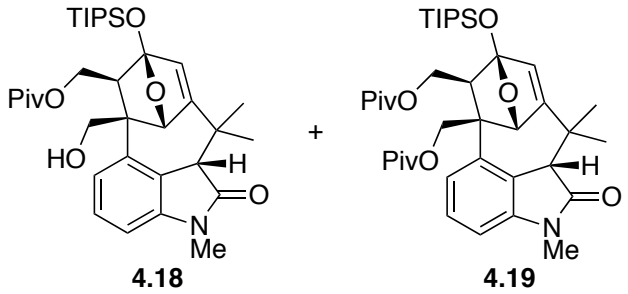
1H), 1.68 (s, 3H), 1.16 (sep, J = 6.5 Hz, 3H), 1.11 (d, J = 5.6 Hz, 18H), 0.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 161.8, 161.0, 157.3, 144.0, 139.4, 129.1, 126.9, 125.0, 123.2, 110.1, 106.2, 75.6, 73.4, 68.1, 57.3, 54.9, 51.7, 39.2, 26.1, 25.7, 19.7, 17.9, 12.6.



4.17

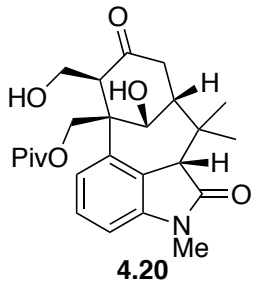
Piv diol 4.17

To a suspension of diol **4.6** (100 mg, 0.195 mmol) in DCM (4 mL) at 0 ºC was added DMAP (54 mg, 0.438 mmol), pyridine (35 μL, 0.438 mmol), then PivCl (36 μL, 0.292 mmol). After 10 minutes, quenched with sat. aq $NaHCO_3$ (4 mL). Diluted with EtOAc (20 mL), washed with sat. aq $NaHCO_3$ (20 mL), 10% aq $CuSO_4$ (2 x 20 mL), water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purified by silica gel column chromatography (7:1 → 4:1 hexanes/EtOAc) to afford a white solid (66.4 mg, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (t, J = 8.0 Hz, 1H), 7.00 (d, J = 8.1 Hz, 1H), 6.60 (d, J = 7.6 Hz, 1H), 5.63 (s, 1H), 5.02 (s, 1H), 4.70 (d, J = 10.6 Hz, 1H), 4.18–4.13 (m, 2H), 3.99 (dd, J = 11.2, 4.5 Hz, 1H), 3.45 (s, 1H), 3.17 (s, 3H), 2.78 (br s, 1H), 2.29 (dd, J = 8.7, 4.6 Hz, 1H), 1.66 (s, 3H), 1.17 (sep, J = 7.3 Hz, 3H), 1.10 (d, J = 7.8 Hz, 18 H), 0.89 (s, 9H), 0.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7, 174.9, 156.1, 143.6, 141.5, 128.8, 127.2, 124.0, 122.72, 122.66, 111.2, 105.7, 75.7, 68.2, 61.2, 57.5, 56.7, 52.0, 39.3, 27.0, 26.1, 25.9, 19.7, 17.9, 12.6; HRMS (TOF ES+) m / z calcd for $C_{34}H_{51}NO_6SiNa$ $(M + Na)^+$ 620.3383, found 620.3395.



Piv diol regioisomer 4.18 and Diprotected diol 4.19

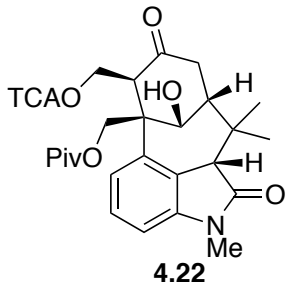
To a suspension of diol **4.6** (5 mg, 9.73 μmol) in DCM (0.2 mL) was added pyridine (2.4 μL, 29.2 μmol) then cooled to 0 ºC. Added PivCl (2.6 μL, 21.4 μmol), stirred for 3 hours then warmed to room temperature and stirred overnight. Diluted with EtOAc (1 mL), washed with sat. aq $NaHCO_3$ (2 x 1 mL), 10% aq $CuSO_4$ (2 x 1 mL), water (1 mL), brine (1 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purified by preparatory TLC (2:1 hexanes/EtOAc) to separate regioisomers **4.17** and **4.18** from diester **4.19**. **Regioisomer 4.18:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.23 (m, 2H), 6.65 (d, *J* = 7.0 Hz, 1H), 5.58 (s, 1H), 5.20 (s, 1H), 4.76 (dd, *J* = 11.9, 4.2 Hz, 1H), 4.18–4.13 (m, 2H), 3.96 (t, *J* = 9.2 Hz, 1H), 3.53 (s, 1H), 3.18 (s, 3H), 2.37 (dd, *J* = 10.6, 4.2 Hz, 1H), 1.66 (s, 3H), 1.32 (s, 9H), 1.46 (sep, *J* = 6.7 Hz, 3H), 1.09 (d, *J* = 5.8 Hz, 18H), 0.78 (s, 3H). **Diprotected diol 4.19:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21–7.20 (m, 2H), 6.60 (dd, *J* = 5.9, 2.5 Hz, 1H), 5.60 (s, 1H), 5.09 (s, 1H), 4.95 (d, *J* = 10.6 Hz, 1H), 4.82 (dd, *J* = 12.0, 4.4 Hz, 1H), 4.15–4.09 (m, 2H), 3.48 (s, 1H), 3.17 (s, 3H), 2.45 (dd, *J* = 11.2, 4.1 Hz, 1H), 1.66 (s, 3H), 1.34 (s, 9H), 1.14 (sep, *J* = 7.3 Hz, 3H), 1.09 (d, *J* = 7.2 Hz, 18H), 0.89 (s, 9H), 0.79 (s, 3H).



4.20

Monoprotected triol 4.20

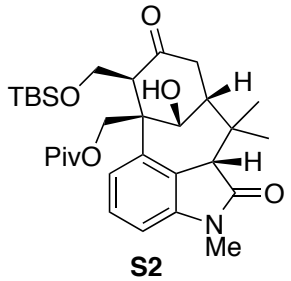
To a solution of diol **4.17** (55 mg, 92.0 μmol) in EtOAc (1.25 mL) and MeOH (4.1 mL) was added HCl (0.25 mL, 5M) then Pd/C (39 mg, 18.4 μmol, 5%). Stirred under 1 atm H_2 for 75 minutes then filtered through Celite. Diluted with EtOAc (30 mL), washed with water (2 x 20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purified by silica gel column chromatography (3:2 → 1:1 hexanes/EtOAc) to afford a white solid (38.4 mg, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 8.1, 1H), 7.11 (d, *J* = 8.2, 1H), 6.72 (d, *J* = 7.7 Hz, 1H), 4.79 (s, 1H), 4.53 (app t, *J* = 11.5 Hz, 2H), 4.16–4.12 (m, 1H), 4.09 (dd, *J* = 11.6, 3.3 Hz, 1H), 3.53 (s, 1H), 3.20 (s, 3H), 3.06 (dd, *J* = 5.4, 3.6 Hz, 1H), 2.33 (dd, *J* = 11.8, 8.0 Hz, 1H), 2.25 (t, *J* = 10.4 Hz, 1H), 2.17 (dd, *J* = 11.5, 4.0 Hz, 1H), 1.63 (s, 3H), 0.94 (s, 9H), 0.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.3, 178.1, 175.1, 144.0, 141.6, 129.2, 124.2, 121.5, 106.6, 67.03, 66.96, 60.05, 59.75, 54.4, 54.0, 52.6, 40.2, 38.8, 37.8, 30.5, 27.0, 26.2, 19.8; HRMS (TOF ES+) *m* / *z* calcd for $C_{25}H_{33}NO_6Na$ $(M + Na)^+$ 466.2206, found 466.2223.



4.22

Acetate 4.22

To a solution of triol **4.20** (2 mg, 4.5 μmol) in DCM (100 μL) at 0 ºC was added TMSCl (0.6 μL, 4.6 μmol) then NEt_3 (0.7 μL, 5.0 μmol) then warmed to room temperature. After 2 hours, cooled to 0 ºC, added trichloroacetic anhydride (0.9 μL, 4.7 μmol) and pyridine (0.4 μL, 5.0 μL). Stirred for 1 hour then warmed to room temperature. After 15 minutes at room temperature, diluted with EtOAc (1 mL). Washed with sat. aq $NaHCO_3$ (2 x 1 mL), 10% aq $CuSO_4$ (2 x 1 mL), water (1 mL), brine (1 mL), dried over Na_2SO_4 and concentrated *in vacuo*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, *J* = 8.1 Hz, 1H), 7.08 (d, *J* = 8.2 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 5.29 (dd, *J* = 12.0, 2.9 Hz, 1H), 4.90 (s, 1H), 4.76 (dd, *J* = 12.0, 8.0 Hz, 1H), 4.67 (d, *J* = 10.9 Hz, 1H), 4.61 (d, *J* = 11.0 Hz, 1H), 3.50 (s, 1H), 3.28 (dd, *J* = 7.1, 2.6 Hz, 1H, 3.21 (s, 1H), 2.38–2.29 (m, 2H), 2.19–2.16 (m, 1H), 1.62 (s, 3H), 0.94 (s, 9H), 0.81 (s, 3H).

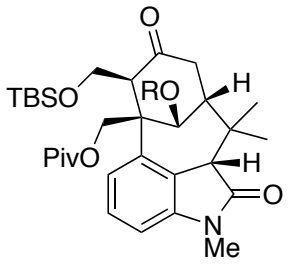


S2

Silyl alcohol S2

To a solution of ester **4.20** (38.4 mg, 86.6 μmol) in DCM (0.9 mL) was added TBSCl (20 mg,

0.130 mmol), imidazole (12 mg, 0.173 mmol), and DMAP (5 mg, 43.3 μmol). After stirring for 1.5 hours, diluted with DCM (20 mL). Washed with water (15 mL), brine (15 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purified by silica gel column chromatography (2:1 hexanes/EtOAc) to afford a white solid (41.8 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 4.87 (d, *J* = 6.0 Hz, 1H), 4.81 (d, *J* = 6.2 Hz, 1H), 4.72 (d, *J* = 11.1 Hz, 1H), 4.55 (d, *J* = 10.9 Hz, 1H), 4.43 (dd, *J* = 10.8, 3.4 Hz, 1H), 3.94 (dd, *J* = 10.8, 2.0, 1H), 3.61 (s, 1H), 3.0 (s, 3H), 2.98 (br s, 1H), 2.37–2.32 (m, 2H), 2.11 (t, *J* = 14.1 Hz, 1H), 1.66 (s, 3H), 0.95 (s, 9H), 0.88 (s, 9H), 0.79 (s, 3H), 0.21 (s, 3H), 0.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.4, 177.9, 175.3, 144.1, 142.3, 129.0, 124.7, 121.2, 106.4, 66.5, 66.3, 60.0, 58.1, 54.4, 54.0, 52.8, 40.1, 38.7, 37.9, 30.6, 27.0, 26.2, 25.8, 20.0, 18.3, –5.7, –5.8; HRMS (TOF ES+) *m* / *z* calcd for $C_{31}H_{47}NO_6SiNa$ $(M + Na)^+$ 580.3070, found 580.3156.

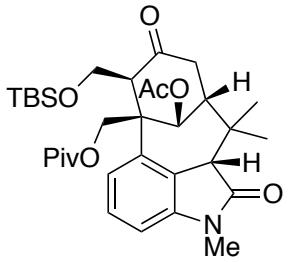


4.23
R = TCA

Triprotected triol 4.23

To a solution of alcohol **S2** (1.5 mg, 2.7 μmol) in DCM (0.1 mL) at 0 ºC was added pyridine (0.4 μL, 5.4 μmol) then trichloroacetic anhydride (0.5 μL, 3.0 μmol) and stirred for 1.5 hours then warmed to room temperature. After 2 hours, added excess pyridine (2 μL) then excess trichloroacetic anhydride (2 μL) and stirred for an additional 2 hours. Diluted with EtOAc (2

mL), washed with sat. aq $NaHCO_3$ (2 x 1 mL), 10% aq $CuSO_4$ (2 x 1 mL), water (1 mL), brine (1 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purified by silica gel column chromatography (4:1 hexanes/EtOAc) to afford a white solid (1.2 mg, 63%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (t, *J* = 8.1 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 6.26 (s, 1H), 4.90 (d, *J* = 11.5 Hz, 1H), 4.51 (dd, *J* = 11.4, 2.8 Hz, 1H), 4.31 (t, *J* = 9.3 Hz, 1H), 3.68 (s, 1H), 3.27 (d, *J* = 9.4 Hz, 1H), 3.23 (s, 3H), 2.37–2.32 (m, 1H), 2.30–2.23 (m, 2H), 1.76 (s, 3H), 0.98 (s, 9H), 0.94 (s, 9H), 0.83 (s, 3H), 0.15 (s, 6H).

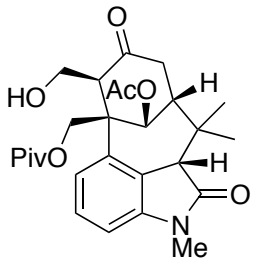


4.24

Acetate 4.24

To a solution of alcohol **S2** (5.0 mg, 9.0 μmol) in DCM (0.1 mL) at 0 ºC was added pyridine (2.2 μL, 27 μmol), acetyl chloride (1.3 μL, 28 μmol), then DMAP (1.1 mg, 9.0 μmol) and the reaction was warmed to room temperature. After 18 hours, diluted with EtOAc (2 mL), washed with sat. aq $NaHCO_3$ (1 mL), 10% aq $CuSO_4$ (2 x 1 mL), water (1 mL), brine (2 x 1 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purified by silica gel column chromatography (hexanes → 7:1 → 4:1 hexanes/EtOAc) to afford a white solid (3.3 mg, 61%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (t, *J* = 7.9 Hz, 1H), 7.13 (d, *J* = 8.2, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 6.16 (s, 1H), 4.77 (d, *J* = 11.6 Hz, 1H), 4.52 (dd, *J* = 11.2, 2.8 Hz, 1H), 4.21 (d, *J* = 11.6 Hz, 1H), 3.93 (dd, *J* = 10.9, 9.0 Hz, 1H), 3.71 (s, 1H), 3.21 (s, 3H), 3.18–3.14 (m, 1H), 2.28 (dd, *J* = 12.5, 8.5 Hz, 1H), 2.23–2.19 (m, 1H), 2.14–2.11 (m, 1H), 2.06 (s, 3H), 1.69 (s, 3H), 0.98 (s, 9H), 0.91 (s, 9H),

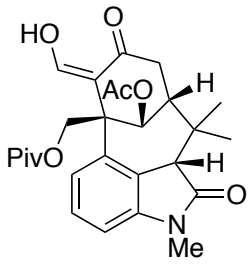
0.78 (s, 3H), 0.16 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.9, 177.6, 175.0, 168.9, 143.7, 142.0, 129.4, 124.2, 121.4, 106.4, 70.5, 68.0, 62.9, 61.6, 52.6, 52.5, 51.1, 40.0, 38.7, 38.0, 30.2, 27.0, 26.3, 26.0, 21.1, 19.8, 18.2, –5.4, –5.5.



S3

Alcohol S3

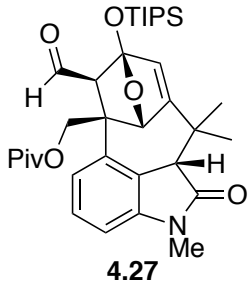
To a solution of acetate **4.24** (9.2 mg, 15.4 μmol) in MeCN (0.47 mL) was added HF (0.47 mL, 6M in MeCN). After 1 hour, the reaction was quenched with sat. aq. $NaHCO_3$ (1 mL), extracted into DCM (3 x 1 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Taken on directly to enol **4.25**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.06 (s, 1H), 4.41 (d, *J* = 11.0 Hz, 1H), 4.28 (t, *J* = 9.9 Hz, 1H), 4.01 (d, *J* = 10.9 Hz, 1H), 3.82 (td, *J* = 10.6, 3.7 Hz, 1H), 3.67 (s, 1H), 3.35 (d, *J* = 10.3, 1H), 3.21 (s, 3H), 3.18 (dd, *J* = 8.2, 3.5 Hz, 1H), 2.34–2.21 (m, 2H), 2.16–2.12 (m, 1H), 2.09 (s, 3H), 1.69 (s, 3H), 0.91 (s, 9H), 0.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.5, 177.7, 174.8, 168.9, 144.1, 140.8, 129.5, 124.1, 121.2, 106.8, 69.6, 66.3, 61.6, 60.5, 52.5, 52.4, 51.2, 40.3, 38.1, 30.1, 29.8, 26.9, 26.3, 21.3, 19.8.



4.25

Enol 4.25

To a solution of alcohol **S3** (8.1 mg, 16.7 μmol) in DCM (0.17 mL) was added DMP (10.6 mg, 25.0 μmol). After 1 hour, the reaction was quenched with 1:1 sat aq $NaHCO_3$: $Na_2S_2O_3$ (1 mL). Extracted into EtOAc (3 x 1 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Used immediately without further purification or stored in benzene at –20 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 14.22 (br s, 1H), 7.52 (br s, 1H), 7.26 (t, *J* = 7.3 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 6.26 (s, 1H), 4.45 (d, *J* = 10.6 Hz, 1H), 4.12 (d, *J* = 10.8 Hz, 1H), 3.72 (s, 1H), 3.20 (s, 3H), 2.37 (dd, *J* = 15.8, 8.4 Hz, 1H), 2.09–2.06 (m, 4), 2.01–1.97 (m, 1H), 1.70 (s, 3H), 0.98 (s, 9H), 0.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.9, 177.8, 175.0, 169.5, 162.5, 143.9, 137.1, 128.9, 123.9, 122.0, 114.8, 106.7, 68.9, 66.3, 52.2, 49.8, 48.7, 38.4, 37.5, 30.2, 29.8, 27.9, 26.3, 21.3, 20.0.



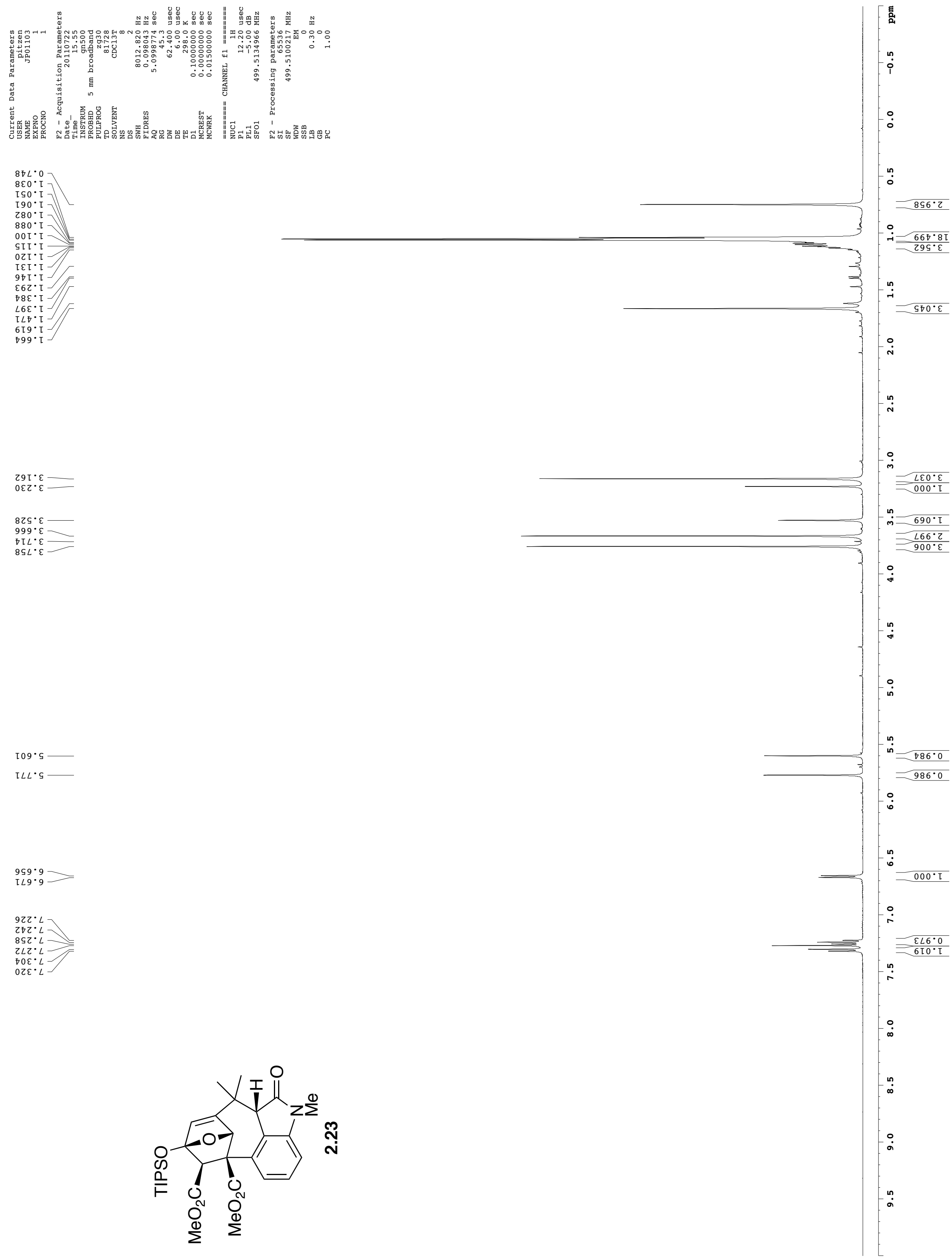
4.27

Aldehyde 4.27

To a solution of alcohol **4.17** (2 mg, 3.3 μmol) in DCM (0.1 mL) at –10 ºC was added KBr (10

μL, 2M in H_2O), TEMPO (0.1 mg, 3.3 μmol), then buffered NaOCl (5 μL, 0.78M, 20 mg $NaHCO_3$/mL). After 90 minutes, added buffered NaOCl (10 μL) and stirred for 30 minutes. Diluted with water (1 mL), extracted into DCM (3 x 1 mL), washed with ½ sat. aq $Na_2S_2O_3$ (1 mL), sat. aq. $NaHCO_3$ (1 mL), brine (1 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.90 (d, *J* = 5.8 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 5.64 (s, 1H), 5.14 (s, 1H), 4.57 (d, *J* = 10.8 Hz, 1H), 4.33 (d, *J* = 10.9 Hz, 1H), 3.48 (s, 1H), 3.19 (s, 3H), 2.73 (d, *J* = 5.6 Hz, 1H), 1.71 (s, 3H), 1.19–1.07 (m, 21H), 0.96 (s, 9H), 0.82 (s, 3H).

Appendix A: Selected NMR Spectroscopy Data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N
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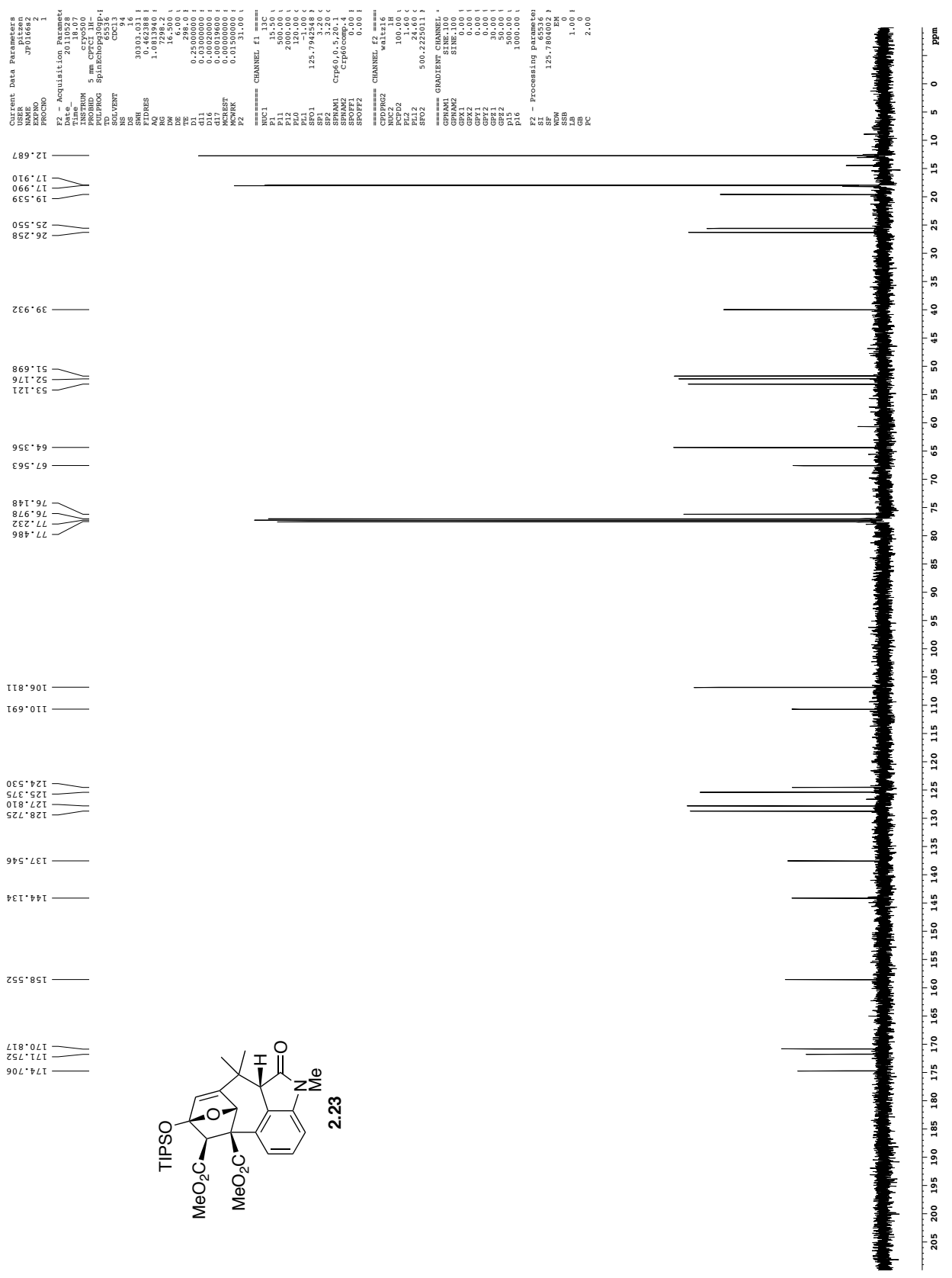
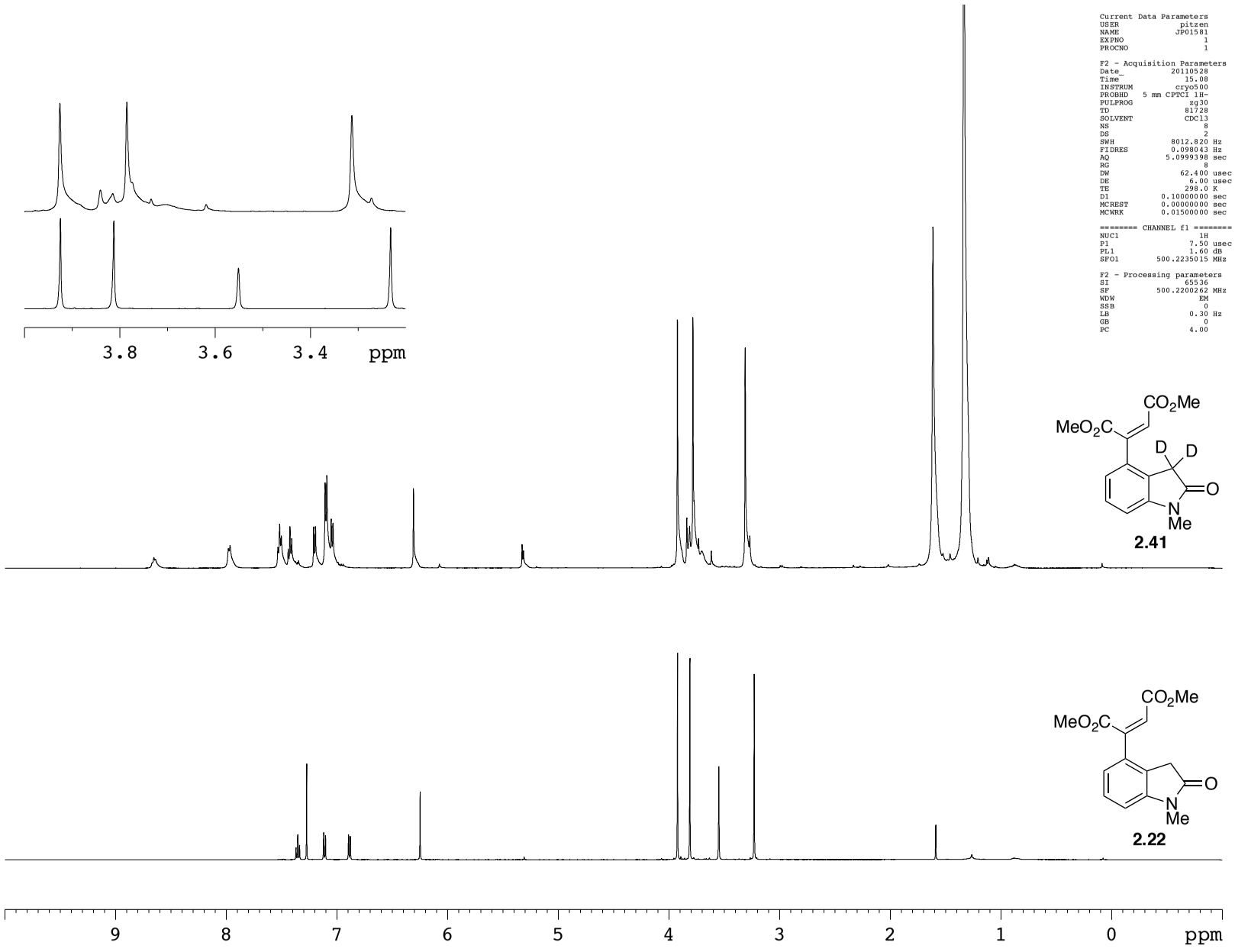
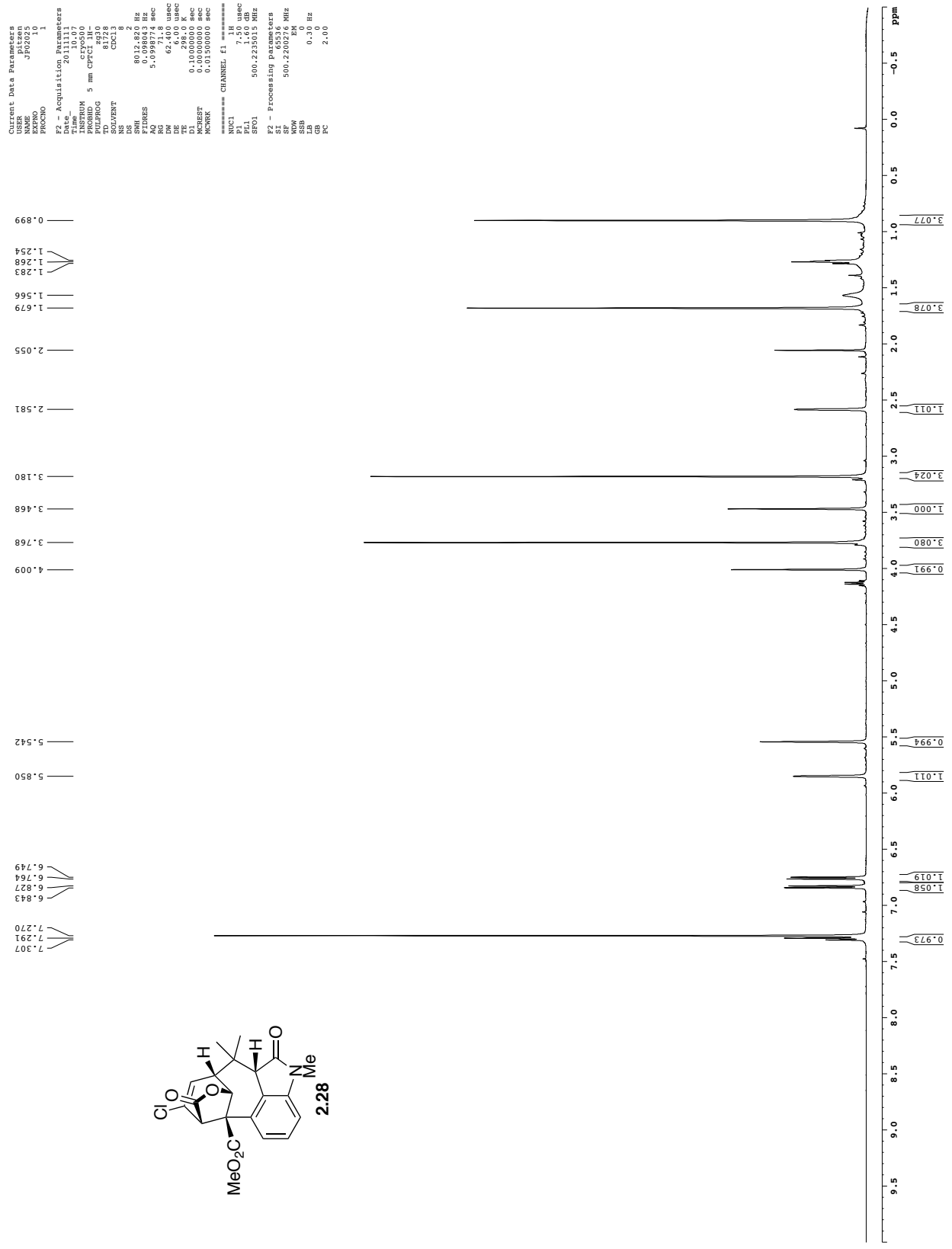
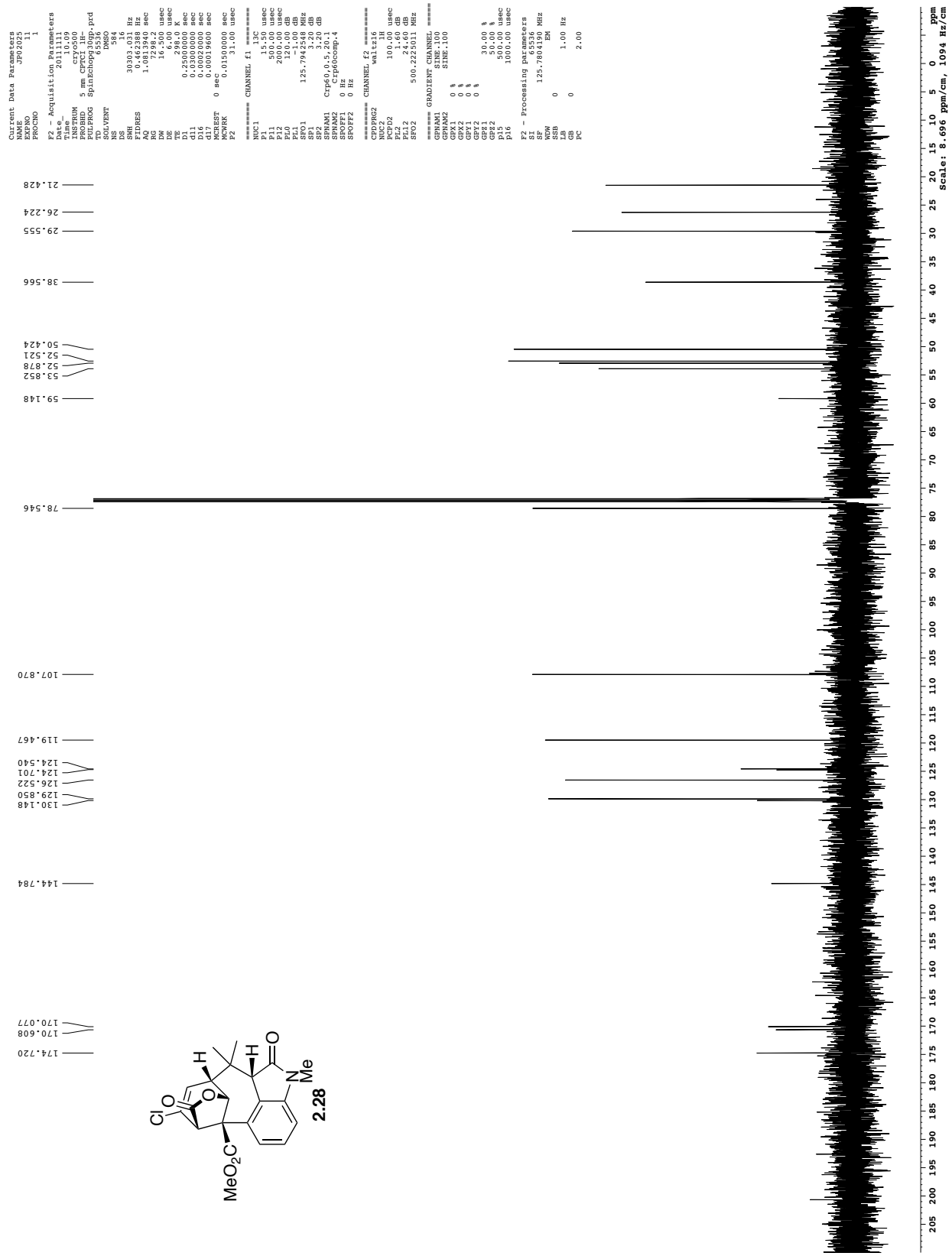
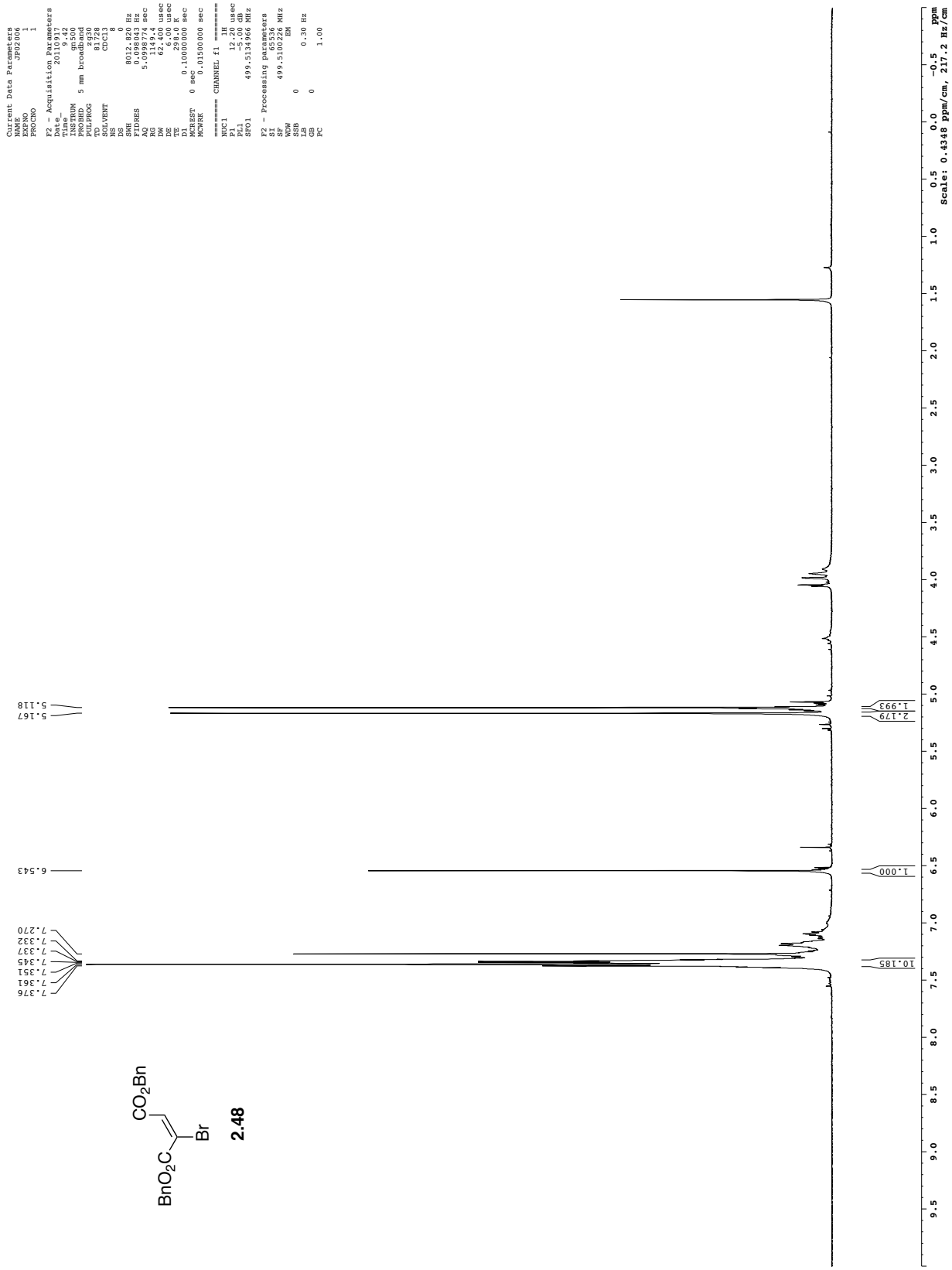
O
2.23

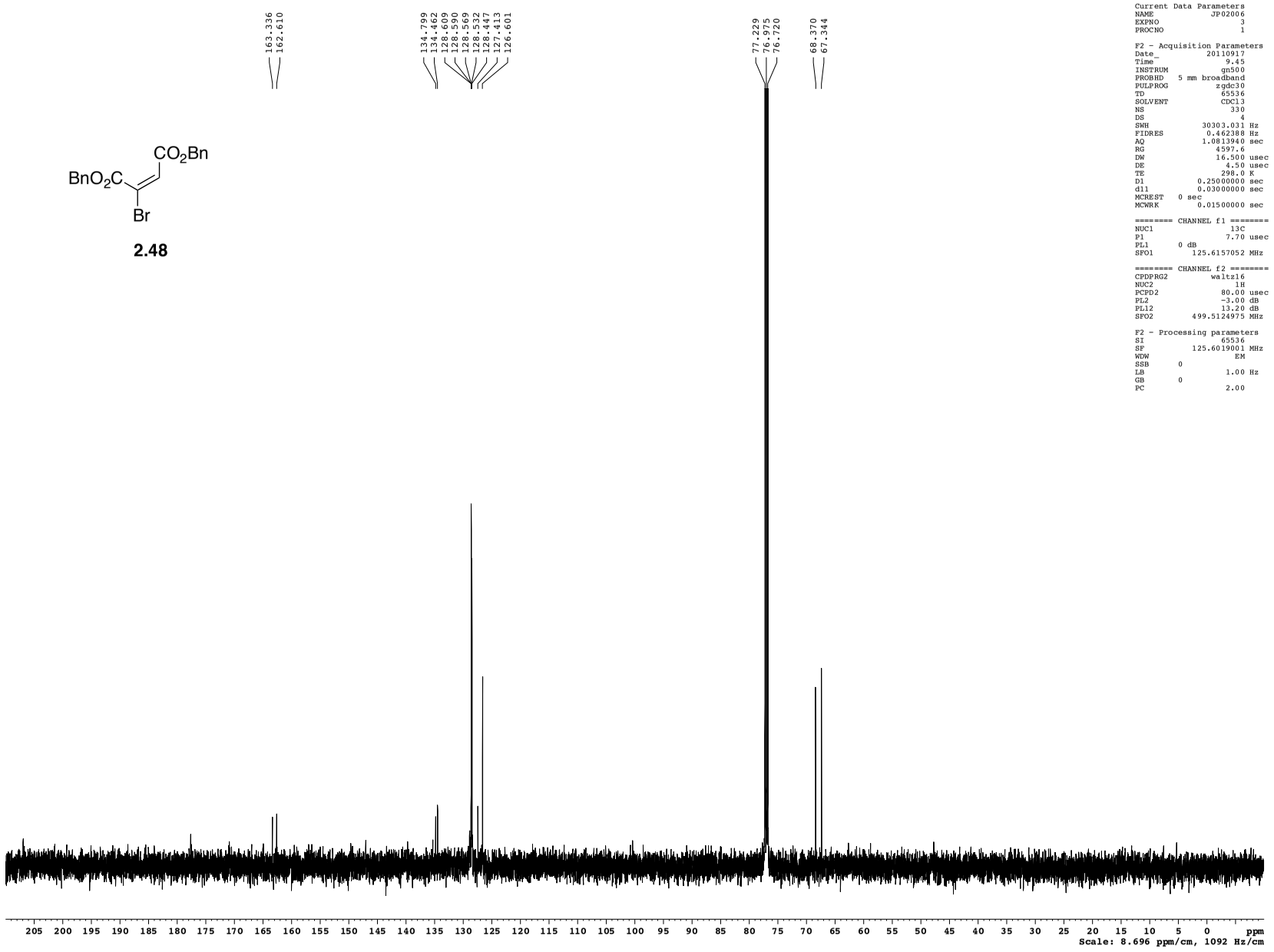

Current Data Parameters
NAME
EXPNO
PROCNO
F2 - Acquisition Parameters
Time
INSTRUM
PROBHD
PULPROG
TD
SOLVENT
NS
DS
SWH
FIDRES
AQ
DW
DE
TE
D1
d11
d16
d17
MCREST
MCWRK
P2
NUC1
P1
P11
P12
PL0
PL1
SFO1
SP1
SP2
SPNAM1
SPNAM2
SPOFF1
SPOFF2
CPDPRG2
NUC2
PCPD2
PL2
PL12
SFO2
GPNAM1
GPNAM2
GPZ1
GPX2
GPY1
GPZ12
GPZ11
GPZ22
p15
p16
F2 - Processing parameters
SI
SF
WDW
SSB
LB
GB
PC
12.687
17.910
17.990
19.539
25.550
26.258
39.932
51.698
52.176
53.121
64.356
67.563
76.148
76.978
77.232
77.486
106.811
110.691
124.530
125.375
127.810
128.725
137.546
144.134
158.552
170.817
171.752
174.706
TIPSO
MeO2C
MeO2C
O
O
H
N
Me
2.23
ppm

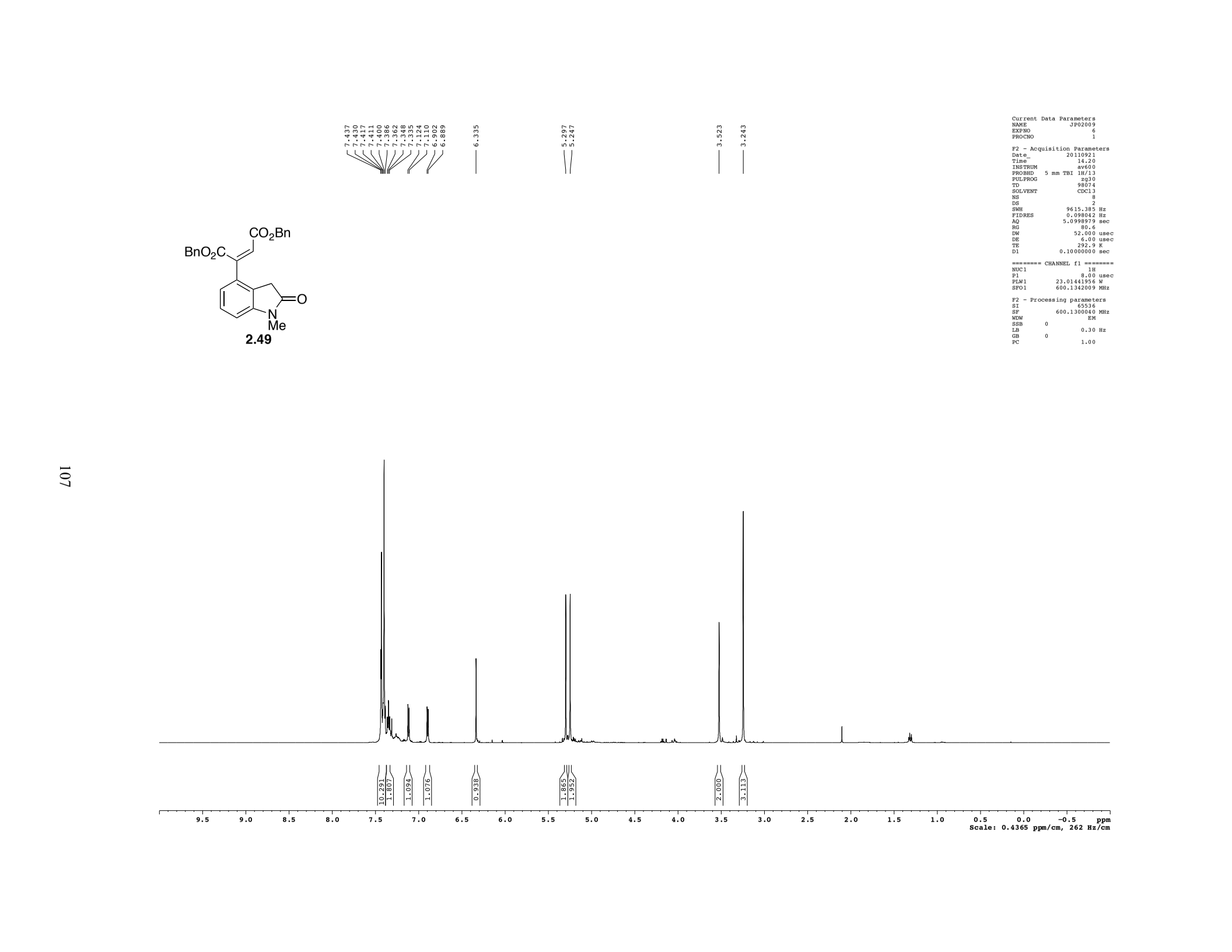

Current Data Parameters
USER pitzen
NAME JP01581
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20110528
Time 15.08
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0999398 sec
RG 8
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200262 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00
3.8
3.6
3.4
ppm
CO2Me
MeO2C
D
D
O
N
Me
2.41
CO2Me
MeO2C
O
N
Me
2.22
9
8
7
6
5
4
3
2
1
0
ppm

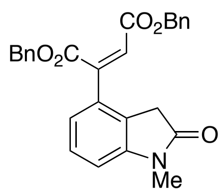

Current Data Parameters
USER pizen
NAME JF02025
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20111111
Time 10.07
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.098774 sec
RG 71.8
DW 62.400 usec
DE 6.00 usec
TE 298.1 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200276 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00
0.899
1.254
1.268
1.283
1.566
1.679
2.055
2.581
3.180
3.468
3.768
4.009
5.542
5.850
6.449
6.764
6.827
6.843
7.270
7.291
7.307
0.973
1.058
1.019
0.994
1.011
3.077
3.078
1.011
3.024
1.000
3.080
0.991
ppm
Cl
O
H
O
H
O
N
Me
MeO2C
2.28


Current Data Parameters
NAME JP02025
EXPNO 11
PROCNO 1
F2 - Acquisition Parameters
Date_ 20111111
Time 16.03
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 584
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813940 sec
RG 72.042
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
D12 0.00019600 sec
MCREST 0 sec
MCWRK 0.01500000 sec
P2 31.00 usec
CHANNEL f1
NUC1 13C
P1 15.50 usec
P11 500.000 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 1.50 dB
PL11 125.794248 MHz
SP1 3.20 dB
SP2 3.20 dB
SPNAM1 Crp60,0.5,20.1
SPNAM2 Crp4comp.4
SPOFF1 0 Hz
SPOFF2 0 Hz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.60 dB
SFO2 500.2225011 MHz
GRADIENT CHANNEL
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec
F2 - Processing parameters
SI 65536
SF 500.1900400 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
21.428
26.224
29.555
38.566
50.424
52.521
52.878
53.852
59.148
78.546
107.870
119.467
124.540
124.701
126.522
129.850
130.148
144.784
170.077
170.608
174.720
ppm
Scale: 8.696 ppm/cm, 1094 Hz/cm
Cl
O
H
O
H
O
N
Me
MeO2C
2.28

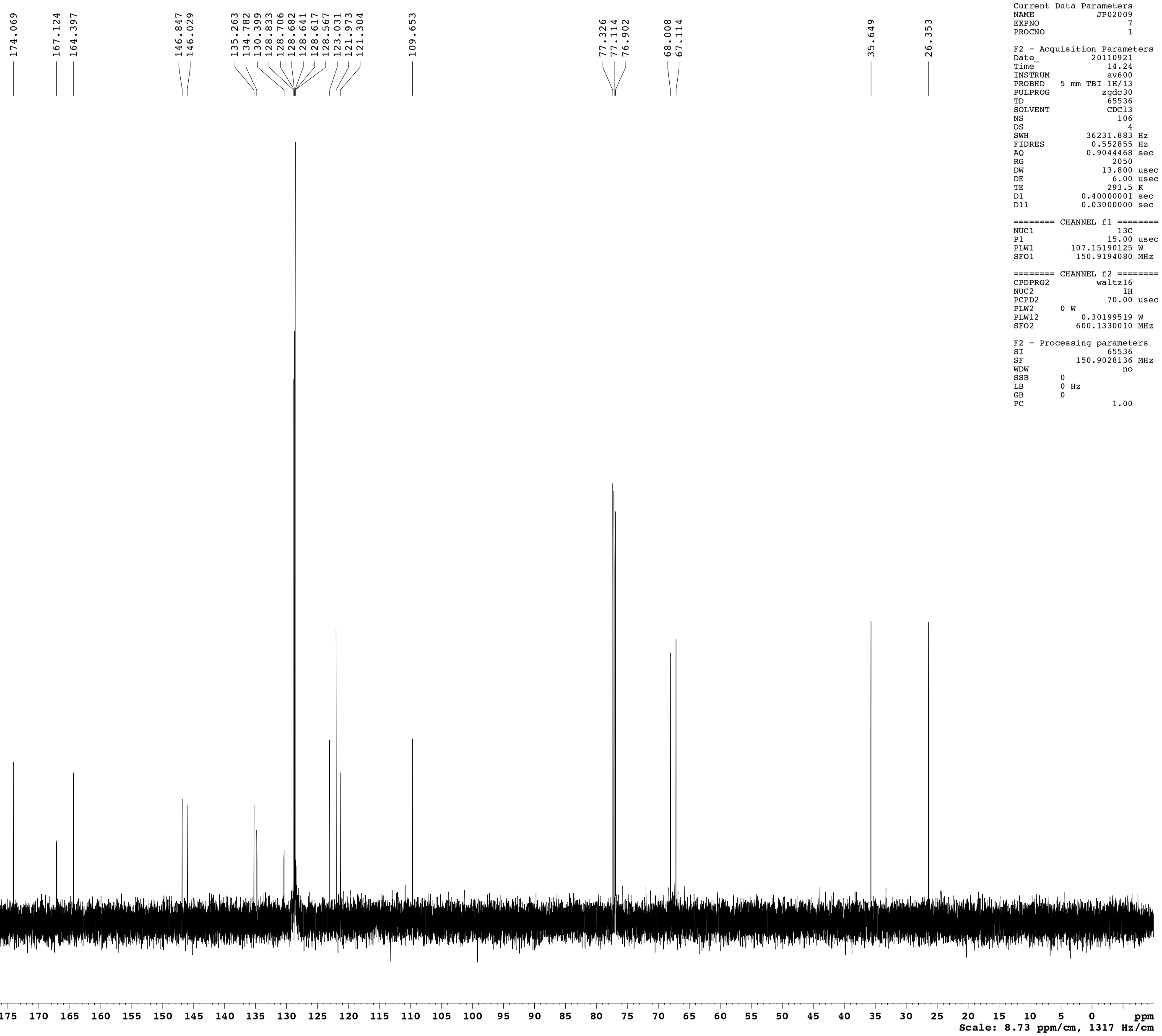

Current Data Parameters
NAME JPD2106
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20110917
Time 9.42
INSTRUM spect
PROBHD 5 mm broadband
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 0
SWH 8012.820 Hz
FIDRES 0.098146 Hz
AQ 5.0998774 sec
RG 1149.4
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
D11 0.03000000 sec
MCREST 0 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 12.20 usec
PL1 -5.00 dB
SFO1 499.5134966 MHz
F2 - Processing parameters
SI 65536
SF 499.5100226 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
5.118
5.167
6.543
7.270
7.332
7.337
7.345
7.351
7.361
7.376
1.993
2.179
1.000
10.185
ppm
Scale: 0.4348 ppm/cm, 217.2 Hz/cm
CO2Bn
BnO2C
Br
2.48


163.336
162.610
134.799
134.462
128.609
128.590
128.569
128.532
128.447
127.413
126.601
77.229
76.975
76.720
68.370
67.344
CO2Bn
BnO2C
Br
2.48
Current Data Parameters
NAME JP02006
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20110917
Time 9.45
INSTRUM qn500
PROBHD 5 mm broadband
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 330
DS 4
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813940 sec
RG 4597.6
DW 16.500 usec
DE 4.50 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
MCREST 0 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 7.70 usec
PL1 0 dB
SFO1 125.6157052 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -3.00 dB
PL12 13.20 dB
SFO2 499.5124975 MHz
F2 - Processing parameters
SI 65536
SF 125.6019001 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
205 200 195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 ppm
Scale: 8.696 ppm/cm, 1092 Hz/cm


7.437
7.430
7.417
7.411
7.400
7.386
7.362
7.348
7.335
7.124
7.110
6.902
6.889
6.335
5.297
5.247
3.523
3.243
Current Data Parameters
NAME JP02009
EXPNO 6
PROCNO 1
F2 - Acquisition Parameters
Date_ 20110921
Time 14.20
INSTRUM av600
PROBHD 5 mm TBI 1H/13
PULPROG zg30
TD 98074
SOLVENT CDCl3
NS 8
DS 2
SWH 9615.385 Hz
FIDRES 0.098042 Hz
AQ 5.0998979 sec
RG 80.6
DW 52.000 usec
DE 6.00 usec
TE 292.9 K
D1 0.10000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PLW1 23.01441956 W
SFO1 600.1342009 MHz
F2 - Processing parameters
SI 65536
SF 600.1300040 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
CO2Bn
BnO2C
O
N
Me
2.49
10.291
1.807
1.094
1.076
0.938
1.865
1.952
2.000
3.113
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
Scale: 0.4365 ppm/cm, 262 Hz/cm



2.49



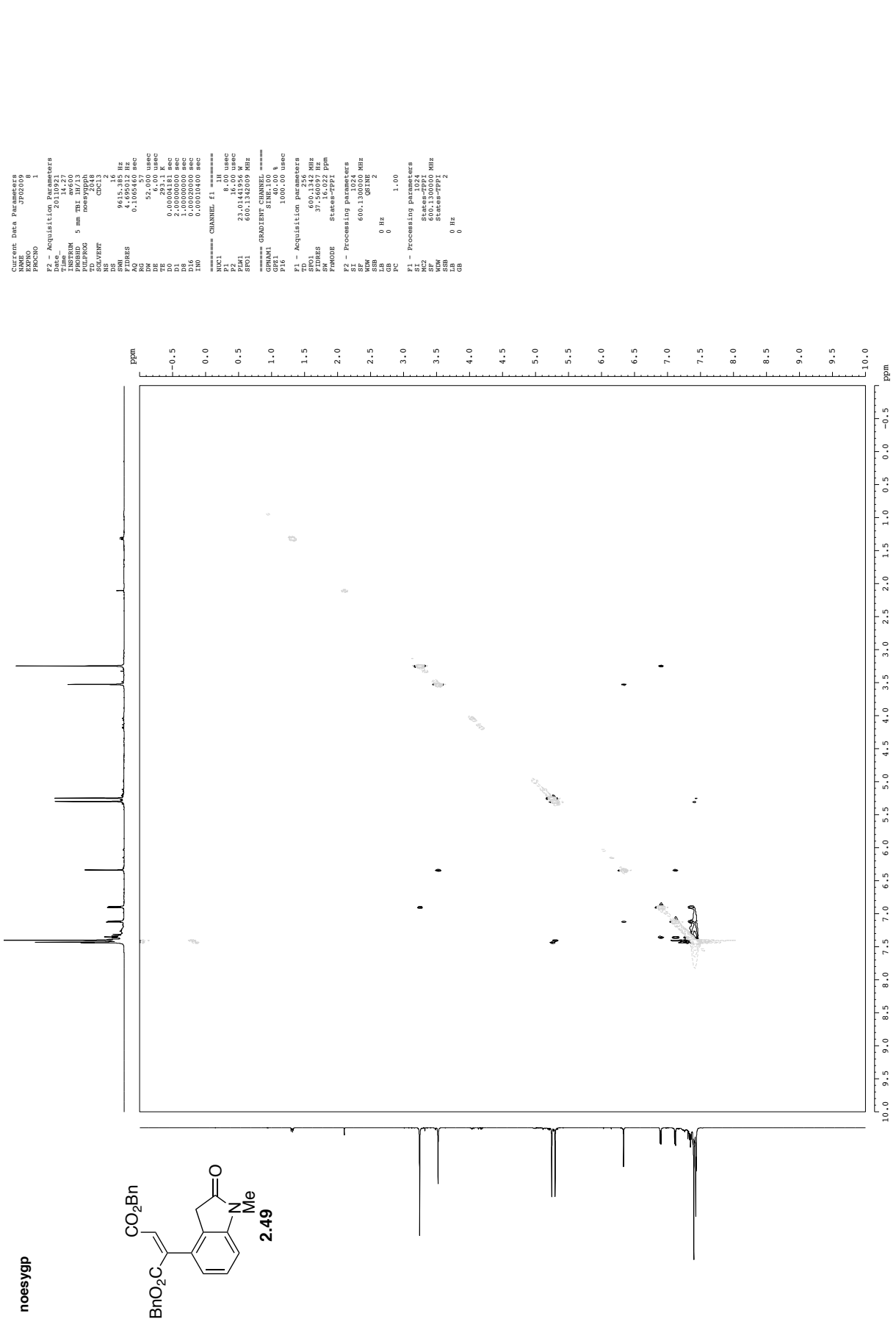

```
Current Data Parameters
NAME             JP02009
EXPNO                  7
PROCNO                 1

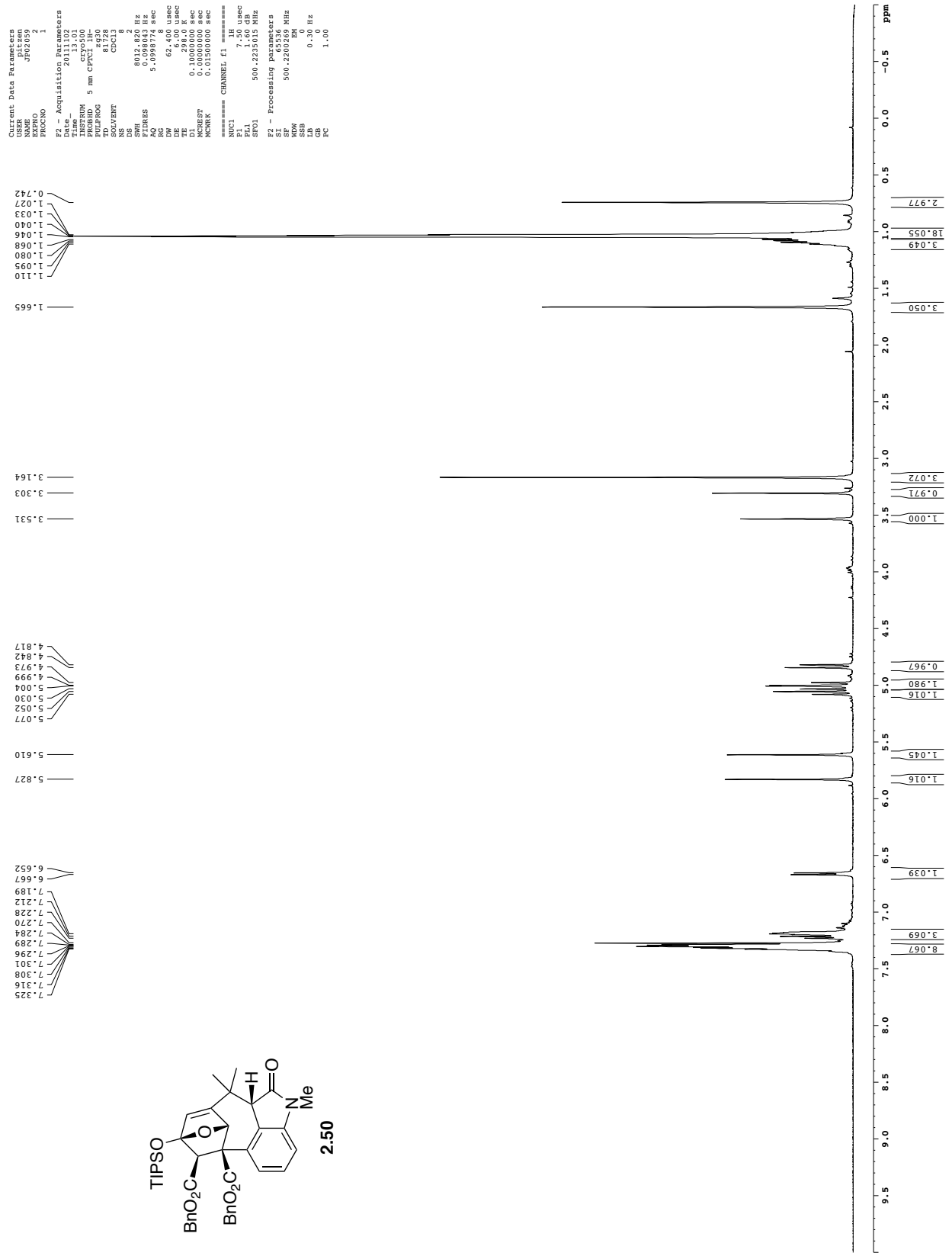
F2 - Acquisition Parameters
Date_           20110921
Time               14.24
INSTRUM            av600
PROBHD   5 mm TBI 1H/13
PULPROG          zgdc30
TD                 65536
SOLVENT            CDCl3
NS                   106
DS                     4
SWH            36231.883 Hz
FIDRES          0.552855 Hz
AQ             0.9044468 sec
RG                  2050
DW                13.800 usec
DE                  6.00 usec
TE                 293.5 K
D1            0.40000001 sec
D11           0.03000000 sec

======== CHANNEL f1 ========
NUC1                 13C
P1                 15.00 usec
PLW1        107.15190125 W
SFO1         150.9194080 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              70.00 usec
PLW2      0 W
PLW12         0.30199519 W
SFO2         600.1330010 MHz

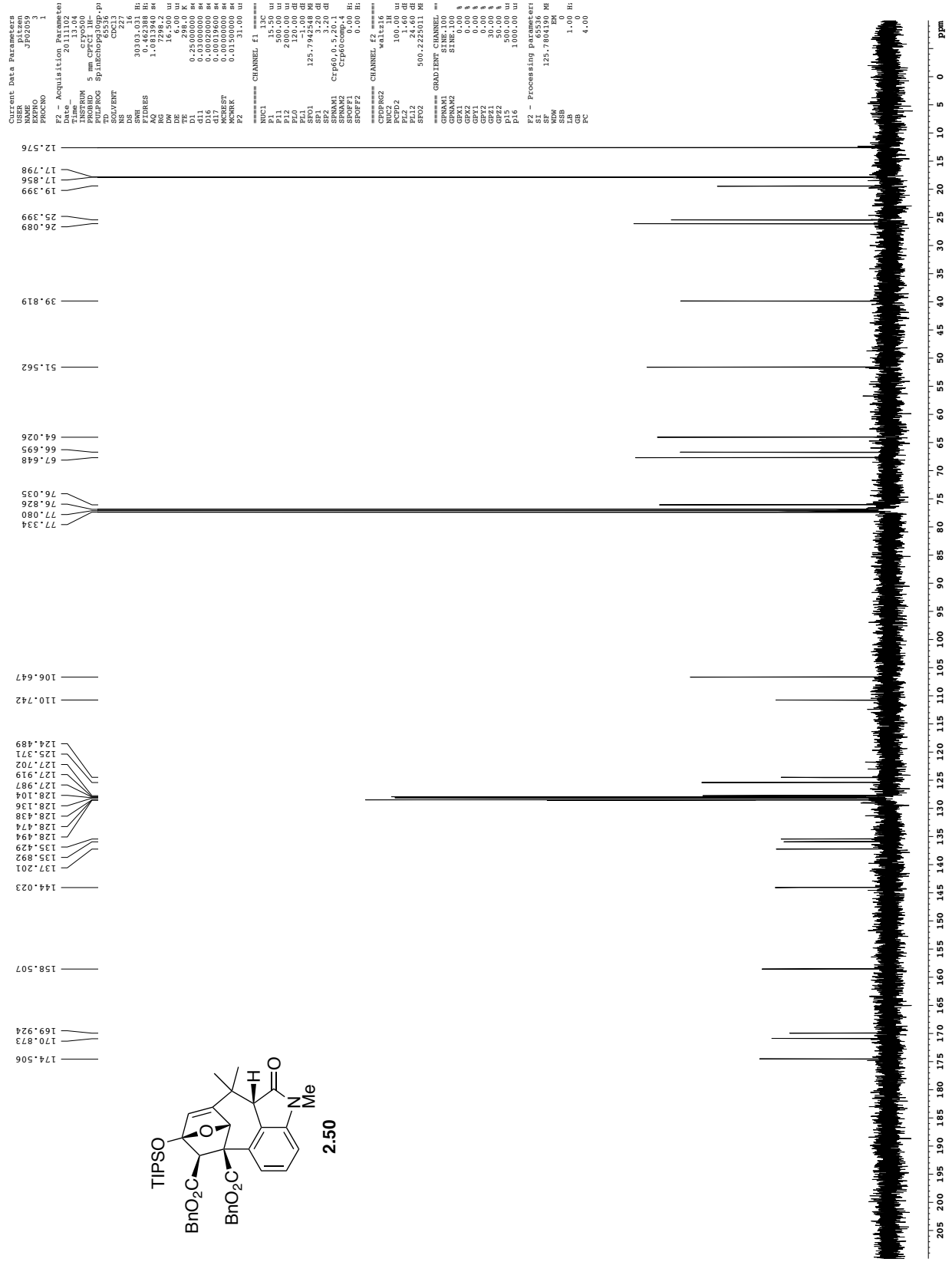
F2 - Processing parameters
SI                 65536
SF           150.9028136 MHz
WDW                   no
SSB       0
LB        0 Hz
GB        0
PC                  1.00
```

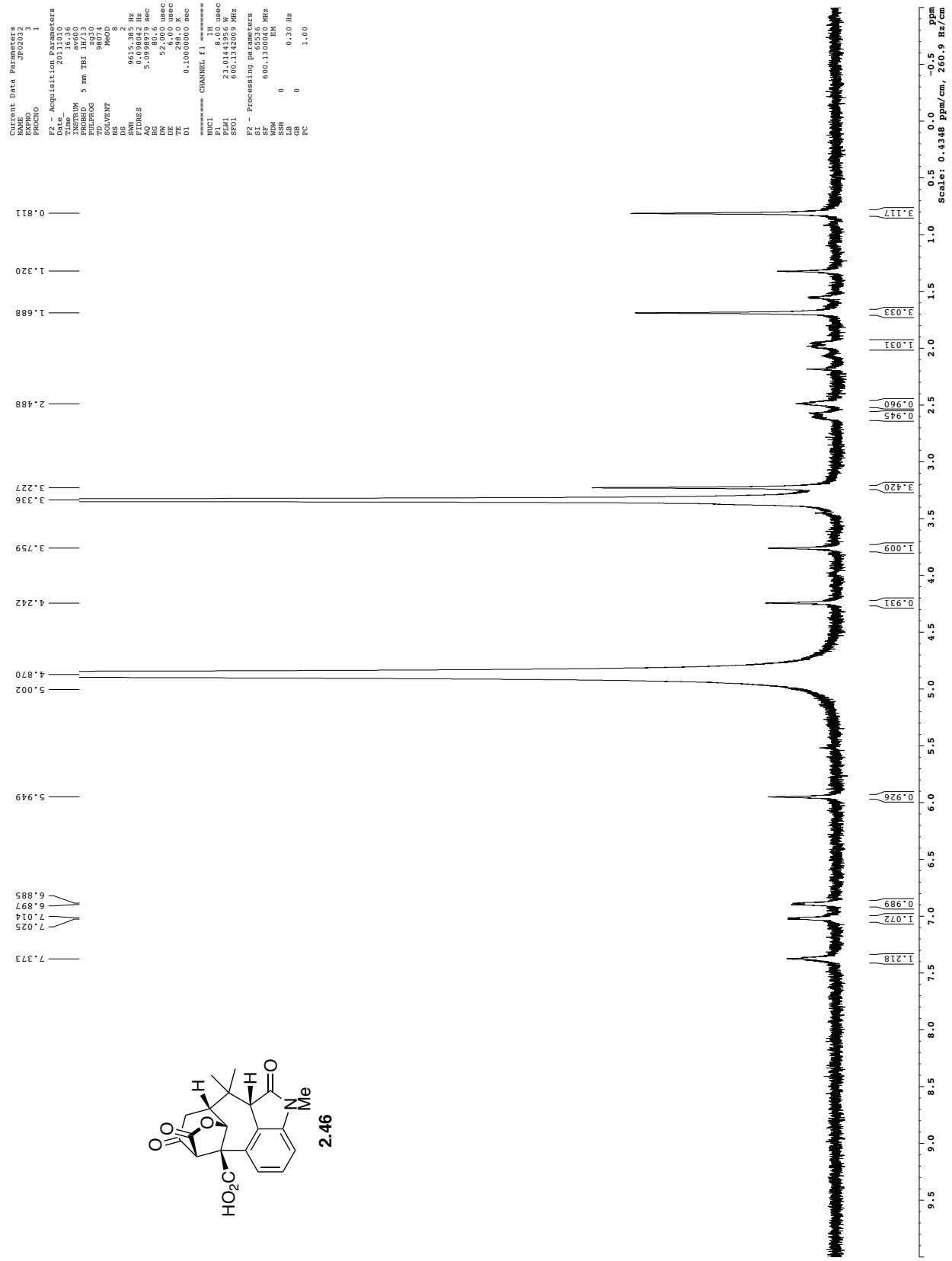

noesygp
CO2Bn
BnO2C
O
N
Me
2.49
ppm


Current Data Parameters
USER pitzen
NAME JF02059
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20111102
Time 13.01
INSTRUM ctyo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0998775 sec
RG 8
DW 62.400 usec
DE 6.00 usec
TE 294.2 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.55 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200269 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
ppm
1.110
1.095
1.080
1.068
1.046
1.040
1.033
1.027
0.742
1.665
3.164
3.303
3.531
5.077
5.052
5.030
5.004
4.999
4.973
4.842
4.817
5.610
5.827
6.652
6.667
7.189
7.212
7.228
7.270
7.284
7.289
7.296
7.301
7.308
7.316
7.325
2.977
18.055
3.049
3.050
3.072
0.971
1.000
0.967
1.980
1.016
1.045
1.016
1.039
3.069
8.067

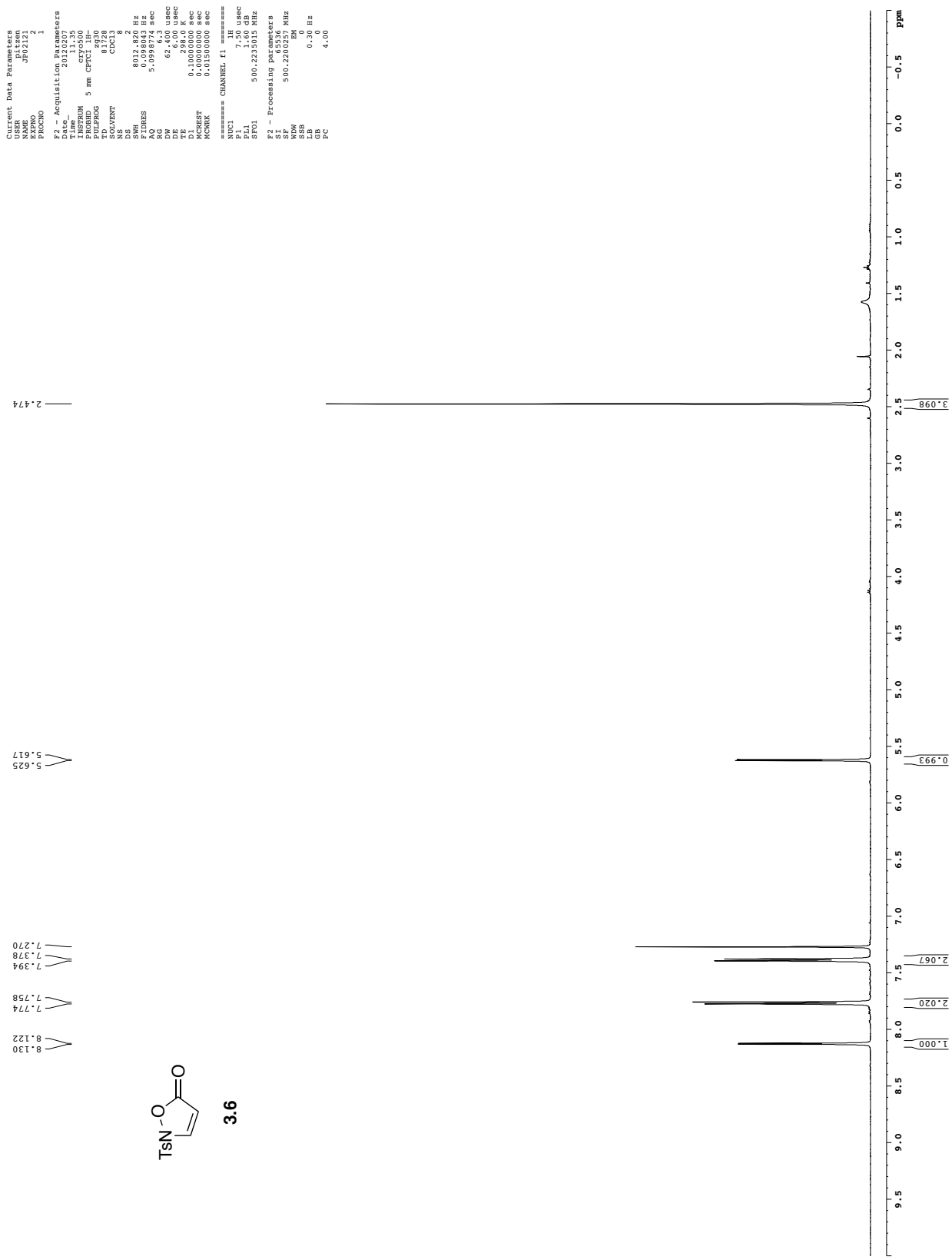
TIPSO
BnO2C
BnO2C
O
H
O
N
Me

2.50

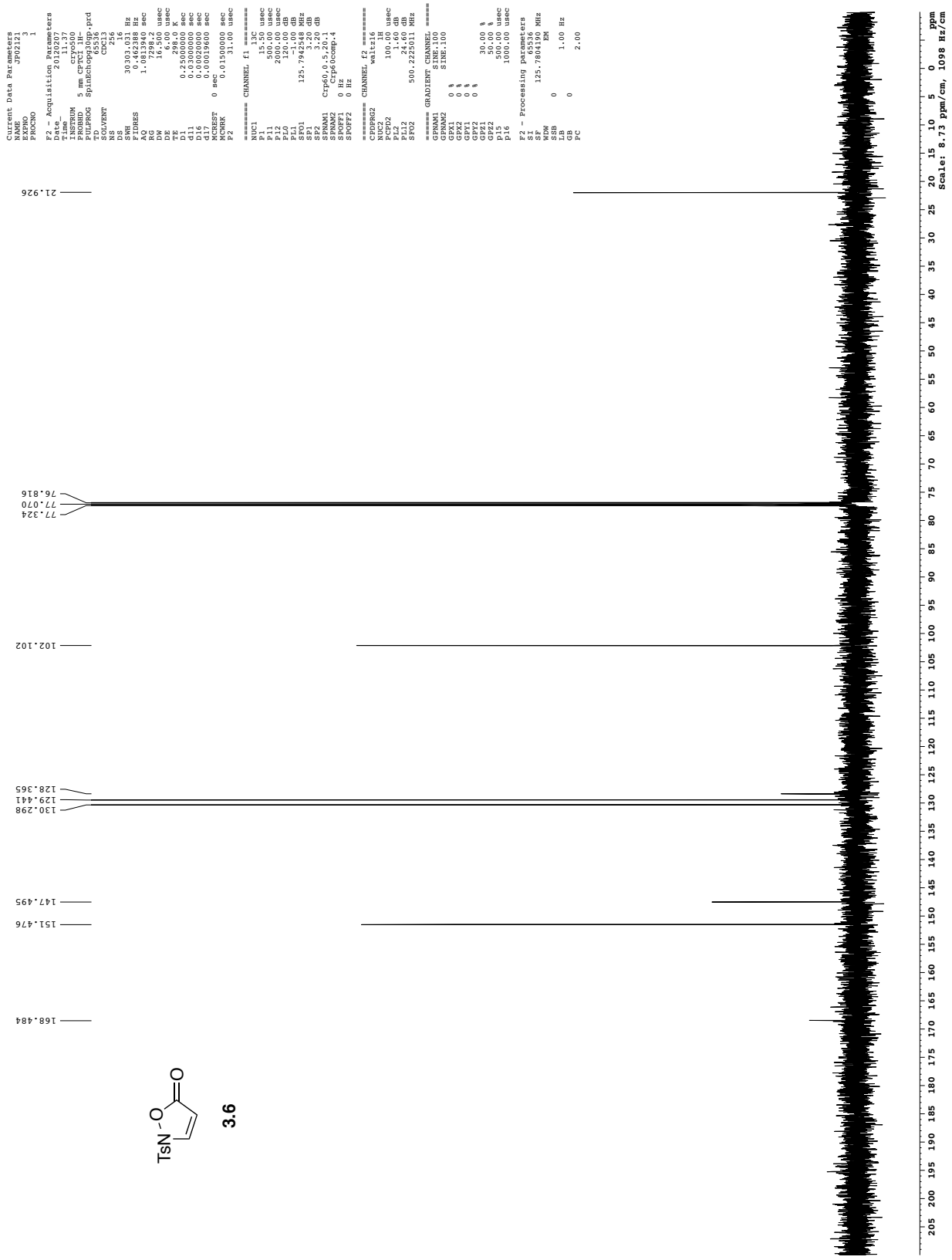

Current Data Parameters
NAME pizen
EXPNO 1
PROCNO 1
F2 - Acquisition Parameter
Date_ 20111102
Time 13.04
INSTRUM cryo500
PROBHD 5 mm CPPFCH1H-
PULPROG SpinEchopg30gp.pi
TD 65536
SOLVENT CDCl3
NS 272
DS 16
SWH 30303.031 Hz
FIDRES 0.462348 Hz
AQ 1.0813940 sec
RG 7298.2
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
P2 31.100 usec
======== CHANNEL f1 ========
NUC1 13C
P1 15.50 usec
P11 500.00 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 21.00 dB
SFO1 125.7942548 MHz
SP1 3.20 dB
SP2 3.20 dB
SPNAM1 Crp60,0.5,20.1
SPNAM2 Crp60comp.4
SPOFF1 0.00 Hz
SPOFF2 0.00 Hz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.60 dB
SFO2 500.2225011 MHz
===== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0.00 %
GPX2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec
F2 - Processing parameter
SI 65536
SF 125.7804190 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 4.00
12.576
17.798
17.856
19.399
25.399
26.089
39.819
51.562
64.026
66.695
67.648
76.035
76.826
77.080
77.334
106.647
110.742
124.489
125.371
127.702
127.919
127.987
128.104
128.136
128.438
128.474
128.494
135.429
135.892
137.201
144.023
158.507
169.924
170.873
174.506
ppm
TIPSO
BnO2C
BnO2C
O
H
O
N
Me
2.50


Current Data Parameters
NAME JP02032
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20111010
Time 11.16
INSTRUM av600
PROBHD 5 mm TBI 1H/13
PULPROG zg30
TD 98074
SOLVENT MeOD
NS 8
DS 2
SWH 9615.385 Hz
FIDRES 0.098042 Hz
AQ 5.0998979 sec
RG 406.6
DW 52.000 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PLW1 23.01441956 W
SFO1 600.1342009 MHz
F2 - Processing parameters
SI 65536
SF 600.1300040 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
0.811
1.320
1.688
2.488
3.227
3.336
3.759
4.242
4.870
5.002
5.949
6.885
6.897
7.014
7.025
7.373
3.117
3.033
1.031
0.960
0.945
3.420
1.009
0.931
0.926
0.989
1.072
1.218
ppm
Scale: 0.4348 ppm/cm, 260.9 Hz/cm
O
H
H
O
O
O
N
Me
HO2C

2.46

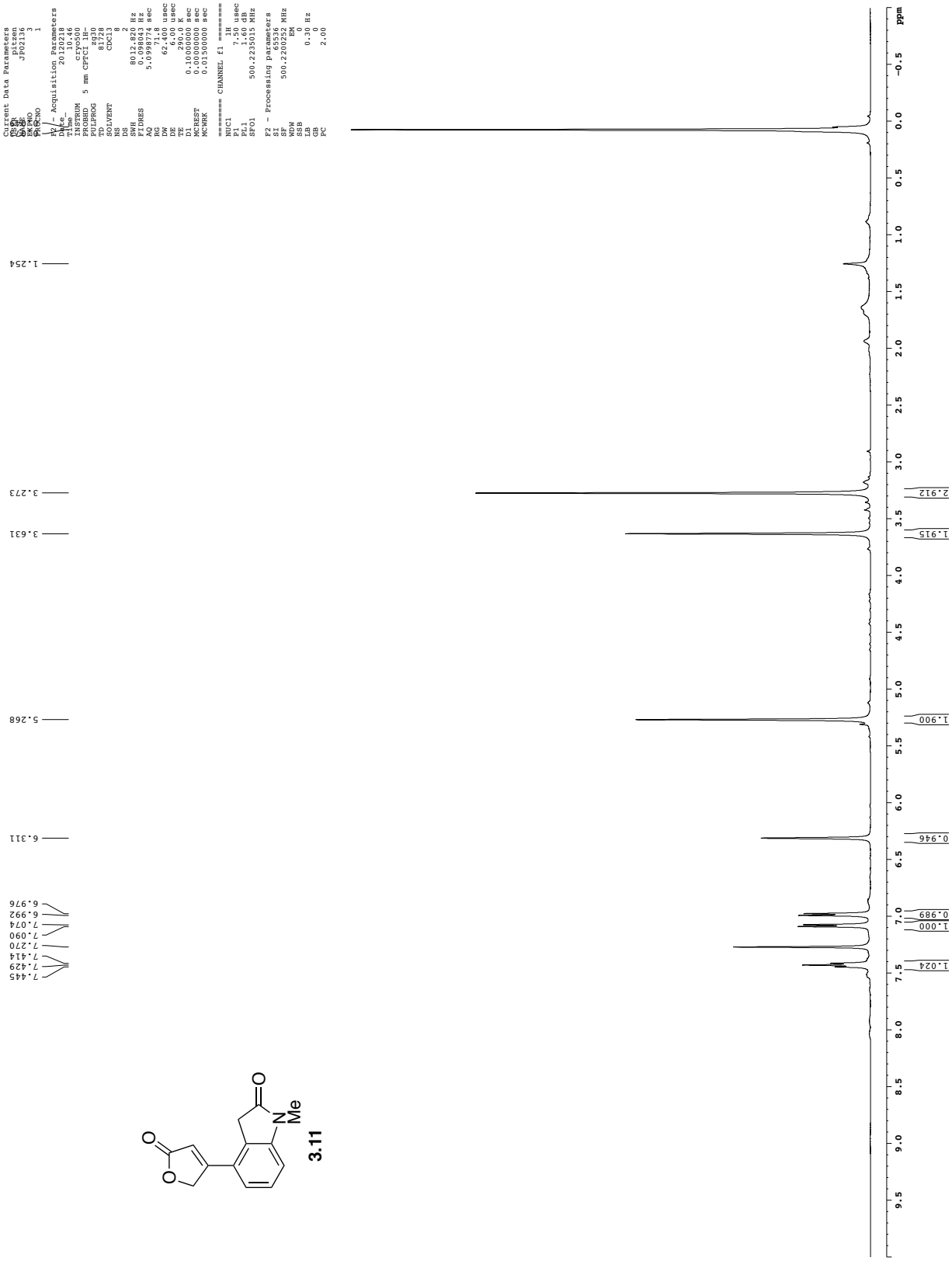

Current Data Parameters
USER pitzen
NAME JP02121
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20120717
Time 11.35
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 4
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.099574 sec
RG 6.3
DW 62.400 usec
DE 6.00 usec
TE 294.1 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.55 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200257 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00
2.474
5.625
5.617
7.394
7.378
7.270
7.774
7.758
8.130
8.122
3.098
0.993
2.067
2.020
1.000
ppm

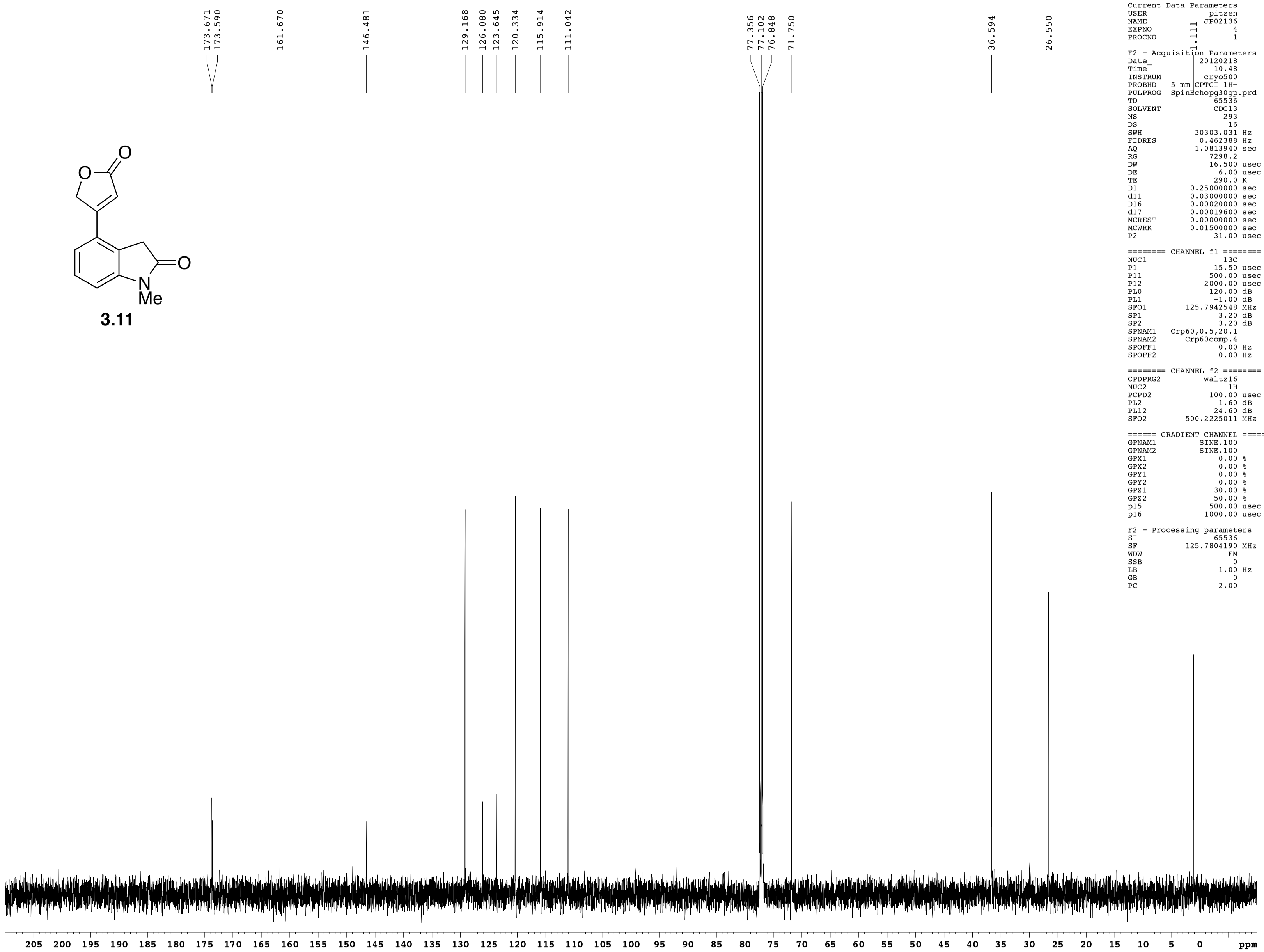
3.6


Current Data Parameters
NAME JP02121
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20110207
Time 13.13
INSTRUM cryo300
PROBHD 5 mm CPTCI 1H-
PULPROG spinEchopr2536.prd
TD 65536
SOLVENT CDCl3
NS 256
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813940 sec
RG 72984.2
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019000 sec
MCREST 0 sec
MCWRK 0.01500000 sec
P2 31.00 usec
======== CHANNEL f1 ========
NUC1 13C
P1 15.50 usec
PL1 500.00 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 0.00 dB
SFO1 125.7942548 MHz
SP1 3.20 dB
SP2 3.20 dB
SPNAM1 Crp60,0.5,20.1
SPNAM2 Crp60comp.4
SPOFF1 0 Hz
SPOFF2 0 Hz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.60 dB
SFO2 500.2225011 MHz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 50.00 %
P16 500.00 usec
p16 1000.00 usec
F2 - Processing parameters
SI 65536
SF 125.7804190 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
21.926
76.816
77.070
77.324
102.102
128.365
129.441
130.298
147.495
151.476
168.484
ppm
Scale: 8.73 ppm/cm, 1098 Hz/cm

TsN
O
O

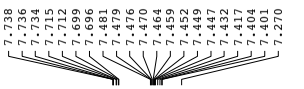
3.6


Current Data Parameters
NAME JF02136
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20120218
Time 10.46
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81920
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.098774 sec
RG 718
DW 62.400 usec
DE 6.00 usec
TE 290.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235010 MHz
F2 - Processing parameters
SI 65536
SF 500.2200252 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00
1.254
3.273
3.631
5.268
6.311
6.976
6.992
7.074
7.090
7.270
7.414
7.429
7.445
2.912
1.915
1.900
0.946
0.989
1.000
1.024
ppm
3.11



173.671
173.590
161.670
146.481
129.168
126.080
123.645
120.334
115.914
111.042
77.356
77.102
76.848
71.750
36.594
26.550
1.111
Current Data Parameters
USER pitzen
NAME JP02136
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20120218
Time 10.48
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD 65536
SOLVENT CDCl3
NS 293
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813940 sec
RG 7298.2
DW 16.500 usec
DE 6.00 usec
TE 290.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
P2 31.00 usec
======== CHANNEL f1 ========
NUC1 13C
P1 15.50 usec
P11 500.00 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 3.20 dB
SP2 3.20 dB
SPNAM1 Crp60,0.5,20.1
SPNAM2 Crp60comp.4
SPOFF1 0.00 Hz
SPOFF2 0.00 Hz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.60 dB
SFO2 500.2225011 MHz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0.00 %
GPX2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec
F2 - Processing parameters
SI 65536
SF 125.7804190 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
205 200 195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 ppm

3.11

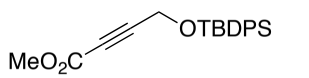



```
Current Data Parameters
USER                pitzen
NAME              JP03008
EXPNO                   3
PROCNO                  1

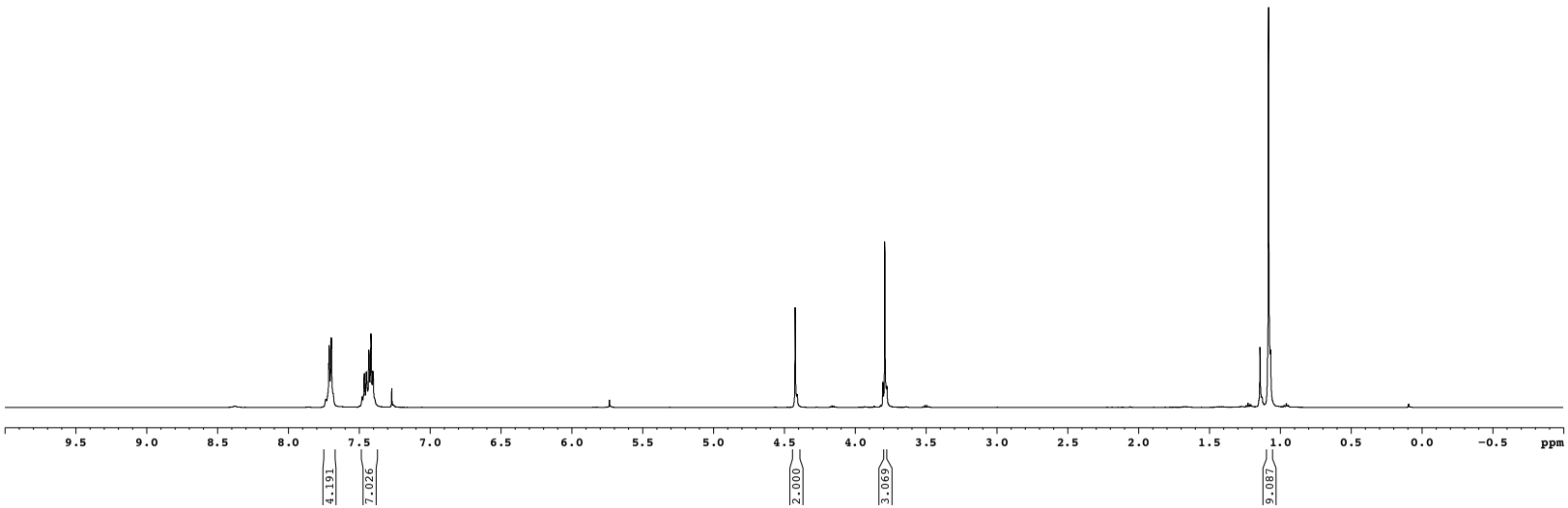
F2 - Acquisition Parameters
Date_            20120506
Time                11.47
INSTRUM             qn500
PROBHD   5 mm broadband
PULPROG              zg30
TD                  81728
SOLVENT           CDCl3T
NS                      8
DS                      2
SWH              8012.820 Hz
FIDRES           0.098043 Hz
AQ               5.0998774 sec
RG                  161.3
DW                 62.400 usec
DE                  6.00 usec
TE                298.0 K
D1           0.10000000 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 12.20 usec
PL1                -5.00 dB
SFO1         499.4034958 MHz

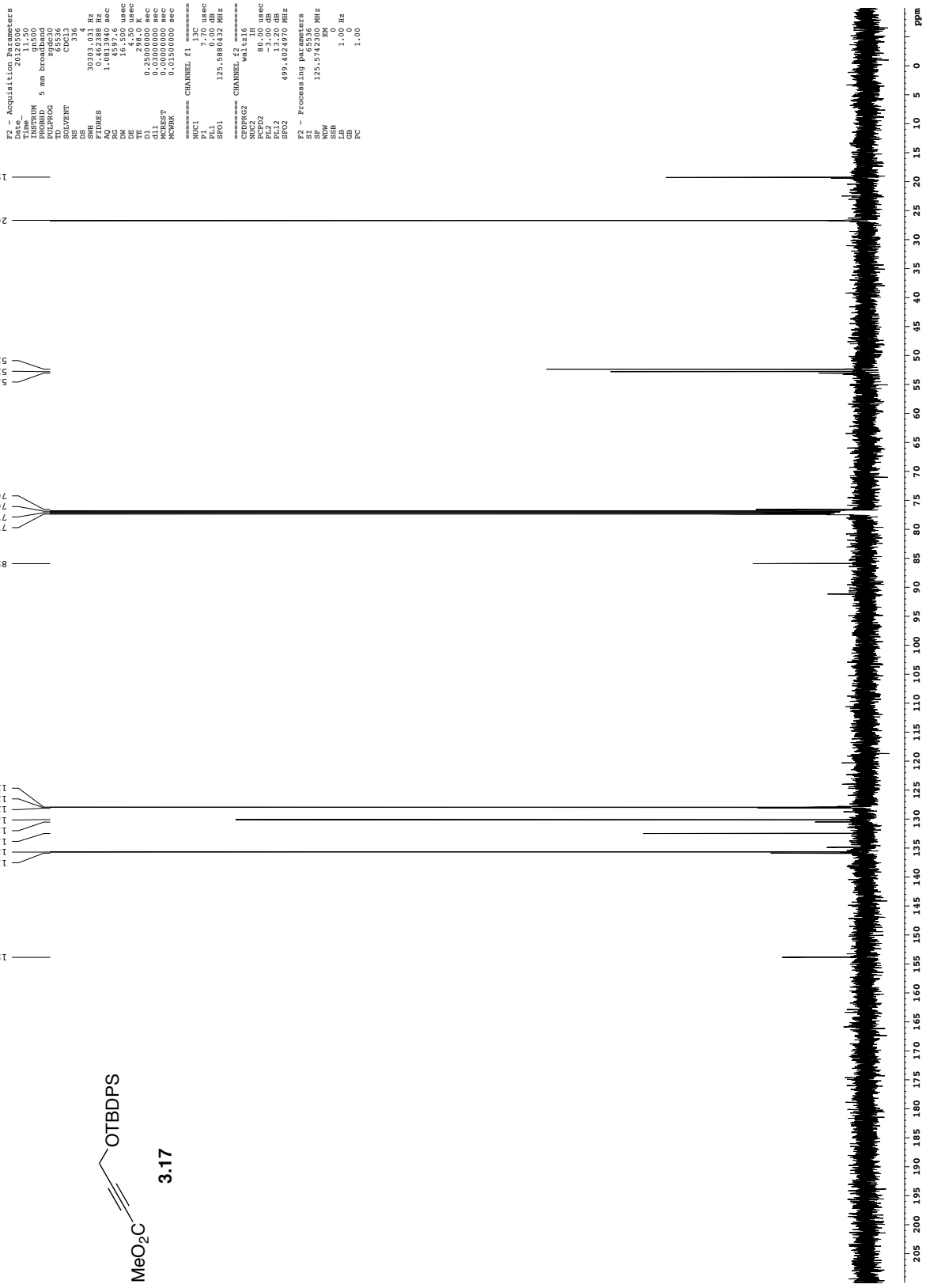
F2 - Processing parameters
SI                  65536
SF           499.4000272 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   2.00
```

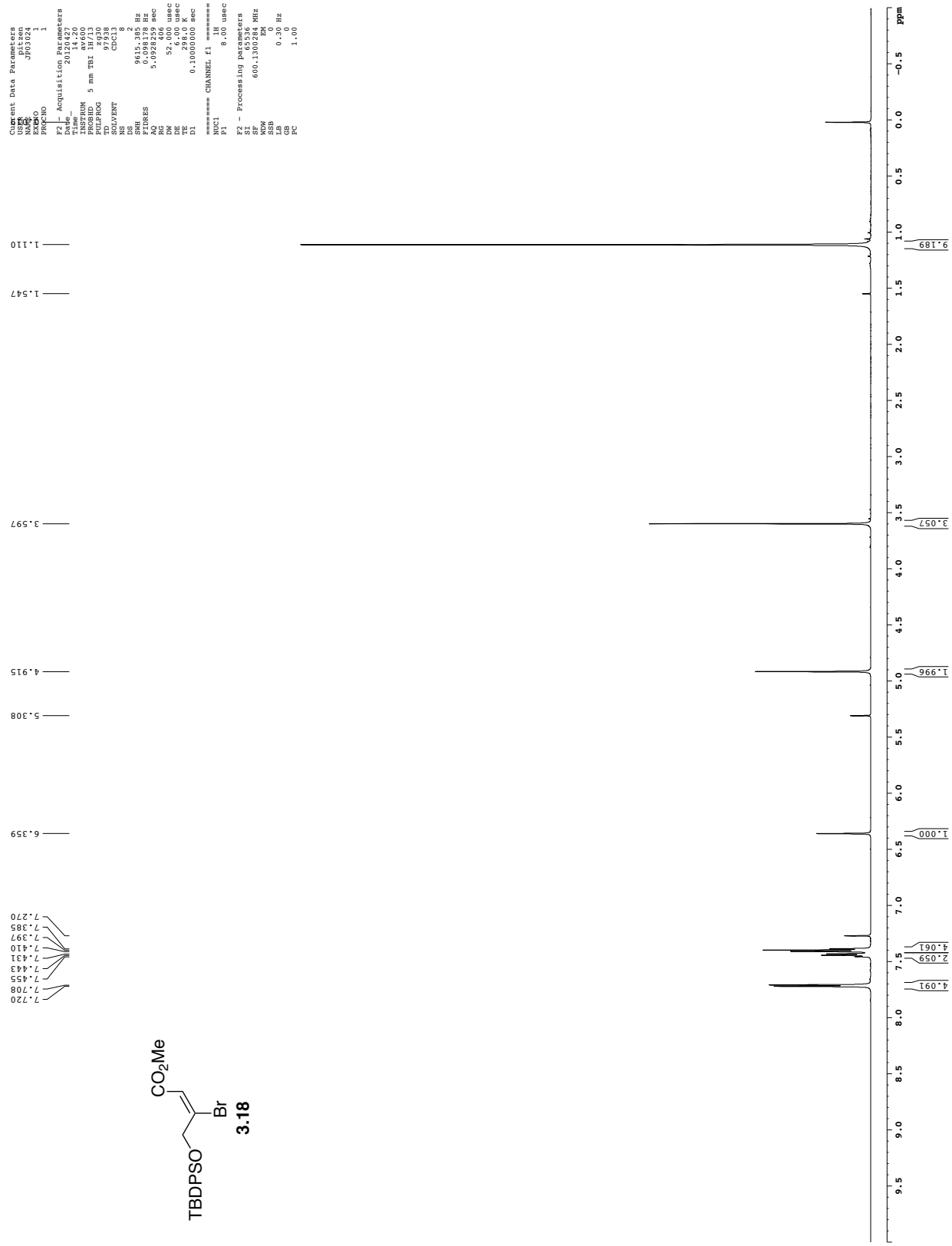


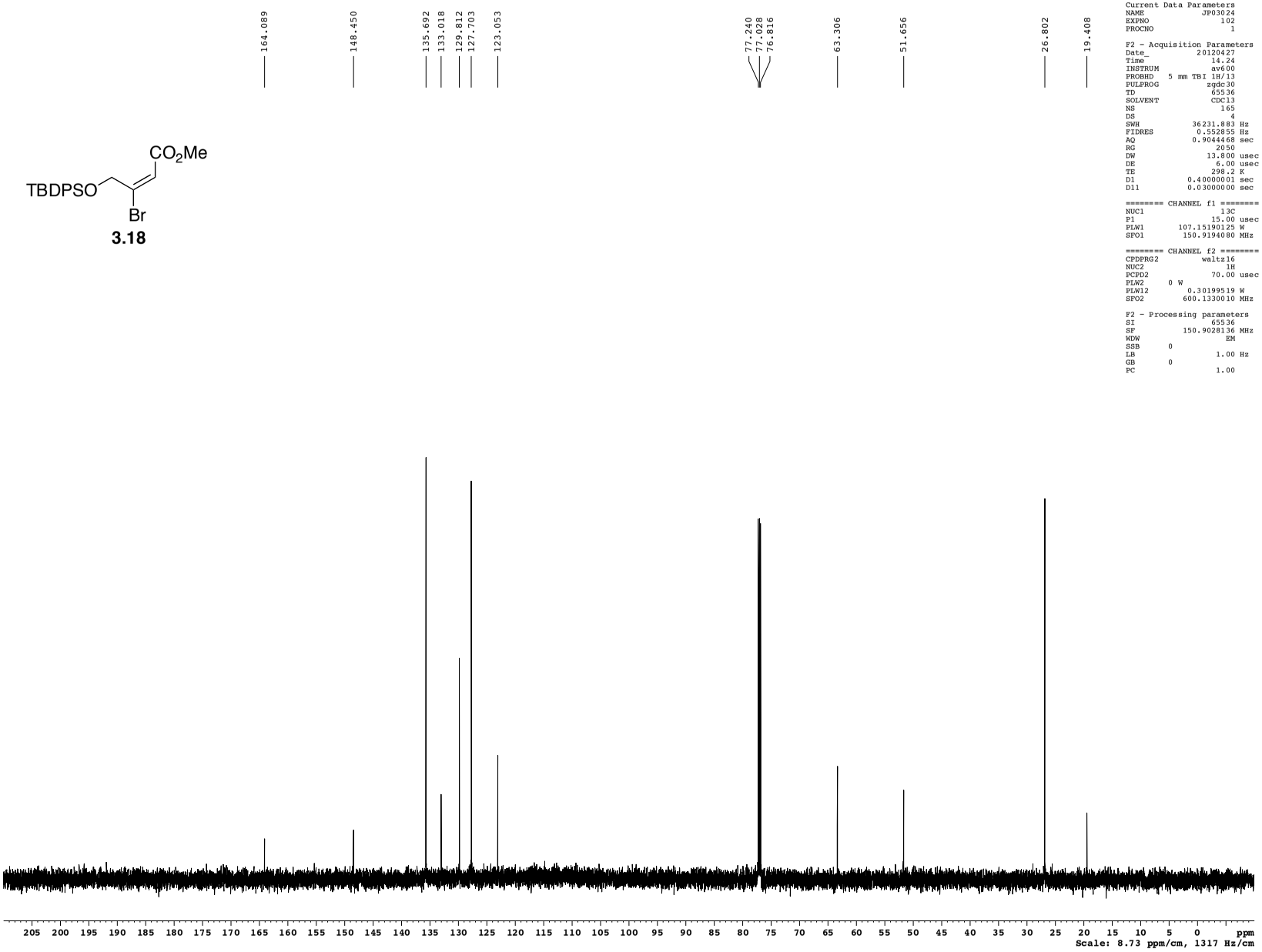
3.17

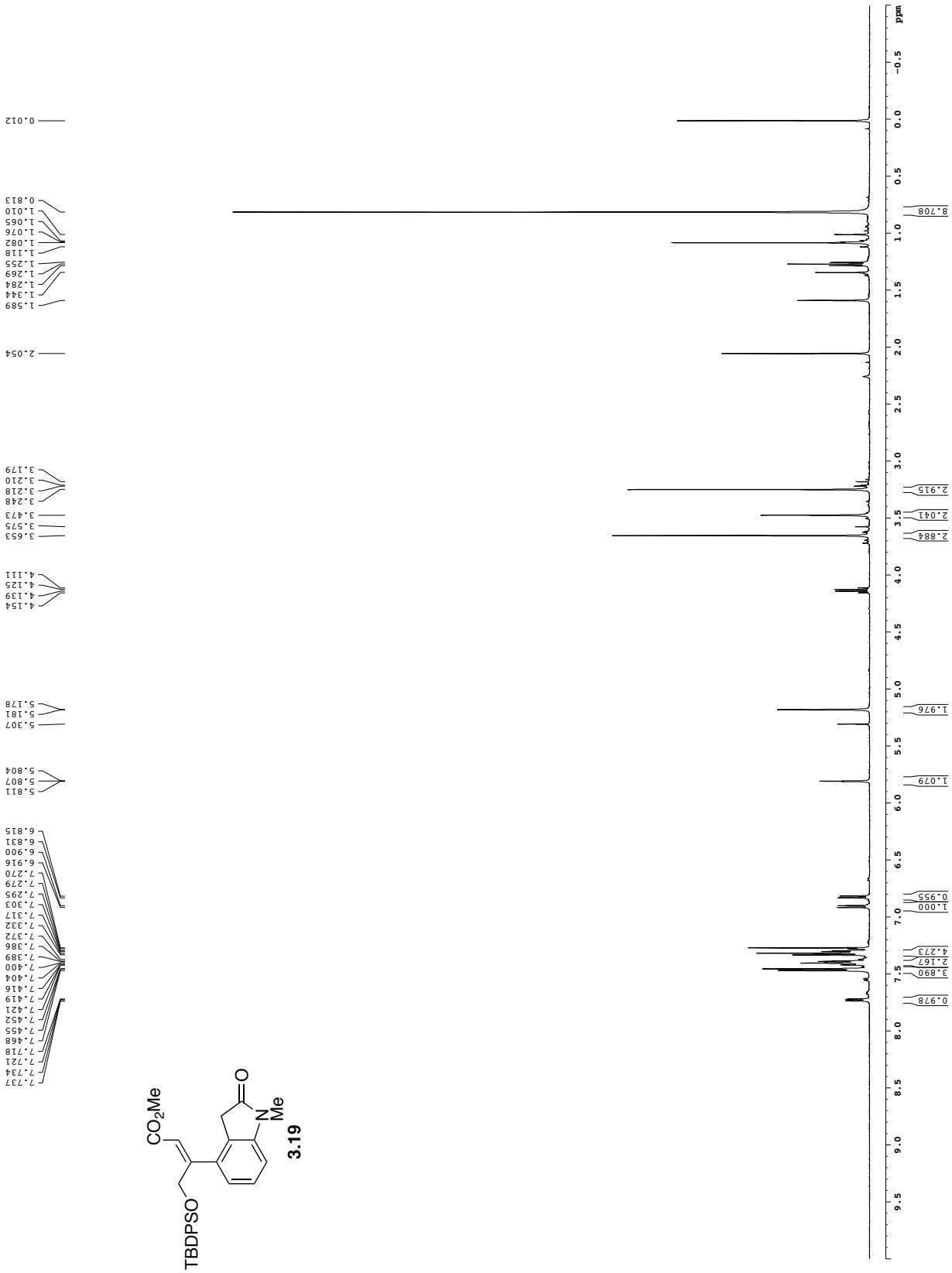


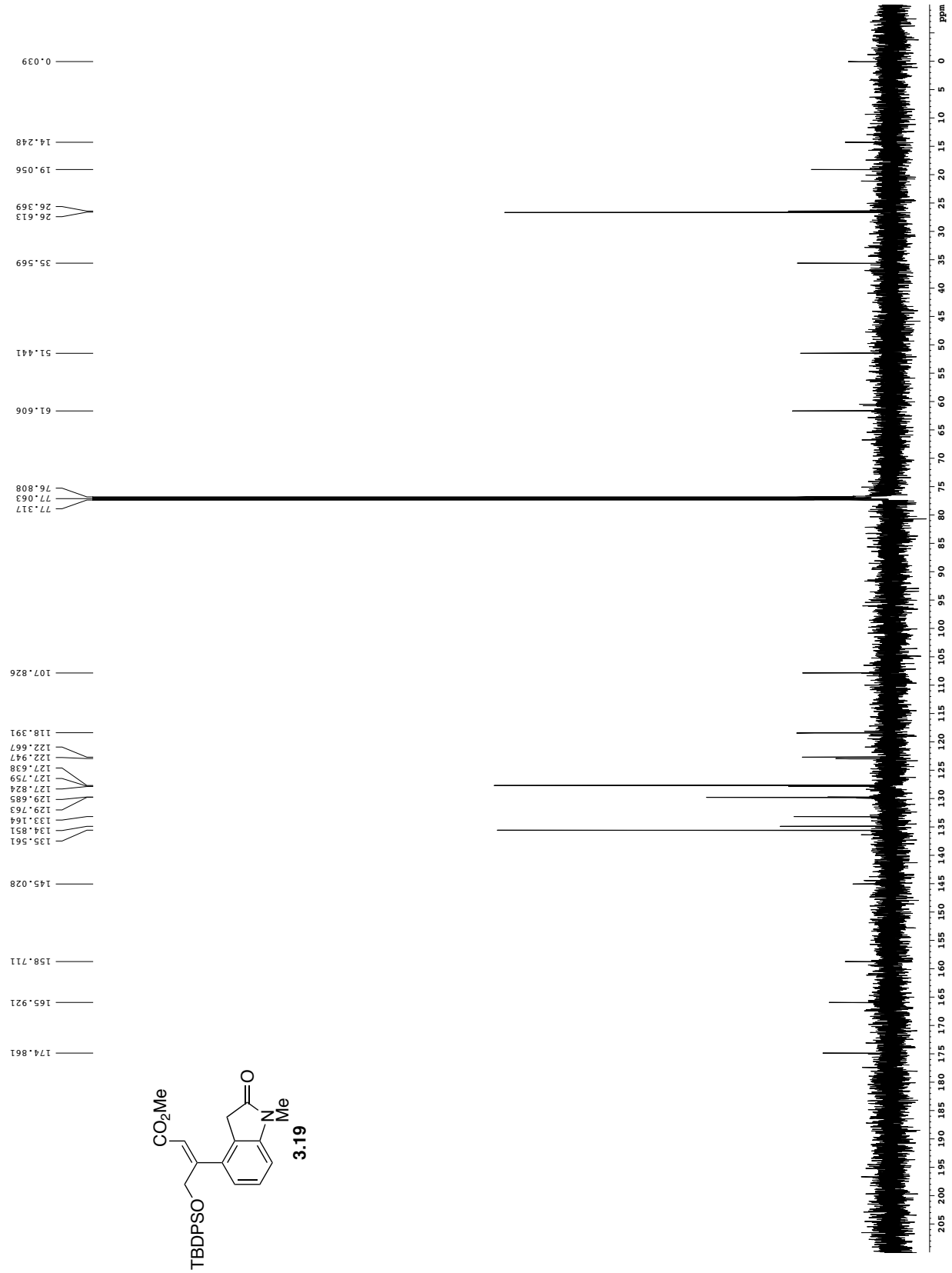
13C spectrum with 1H decoupling

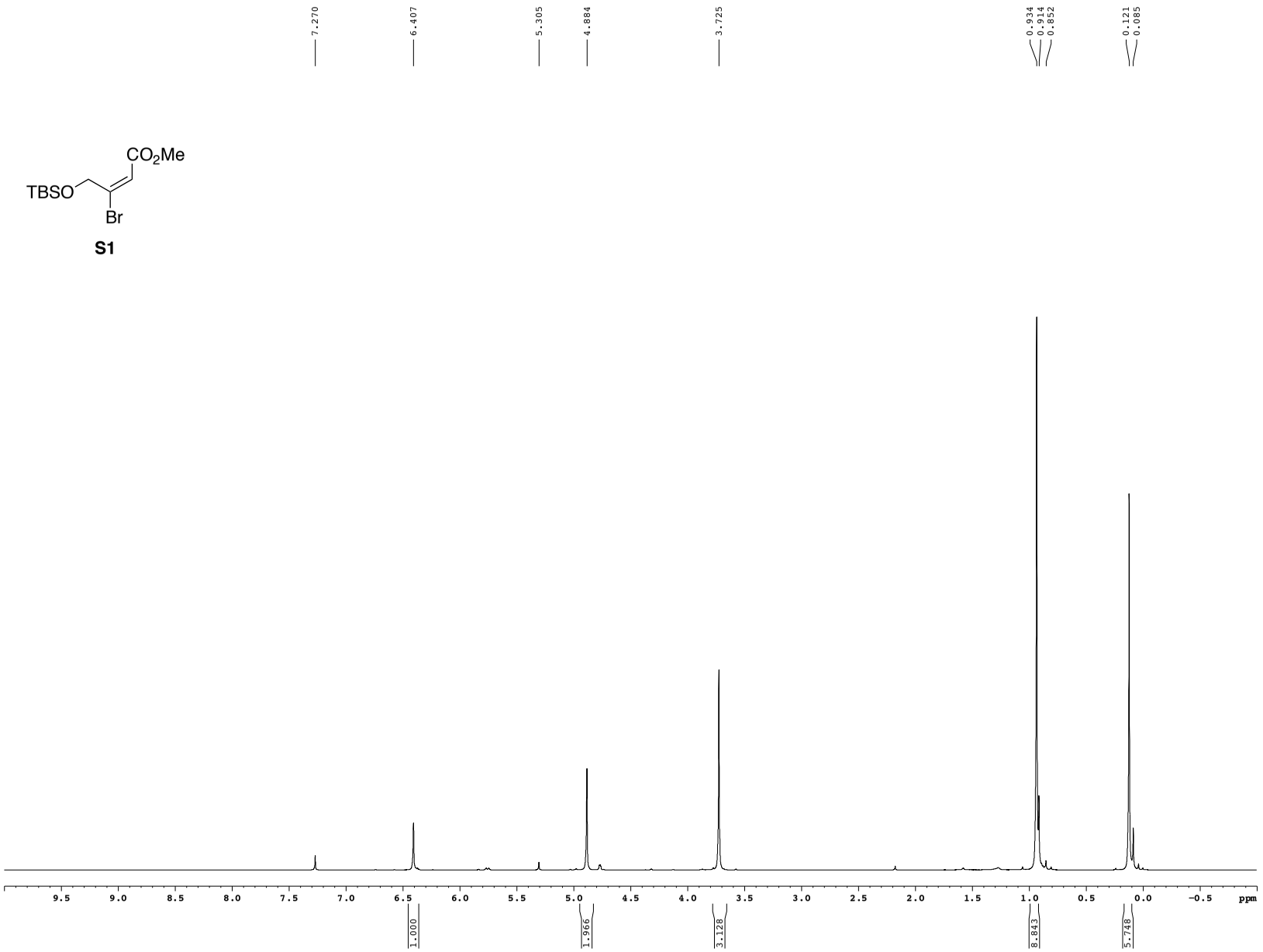


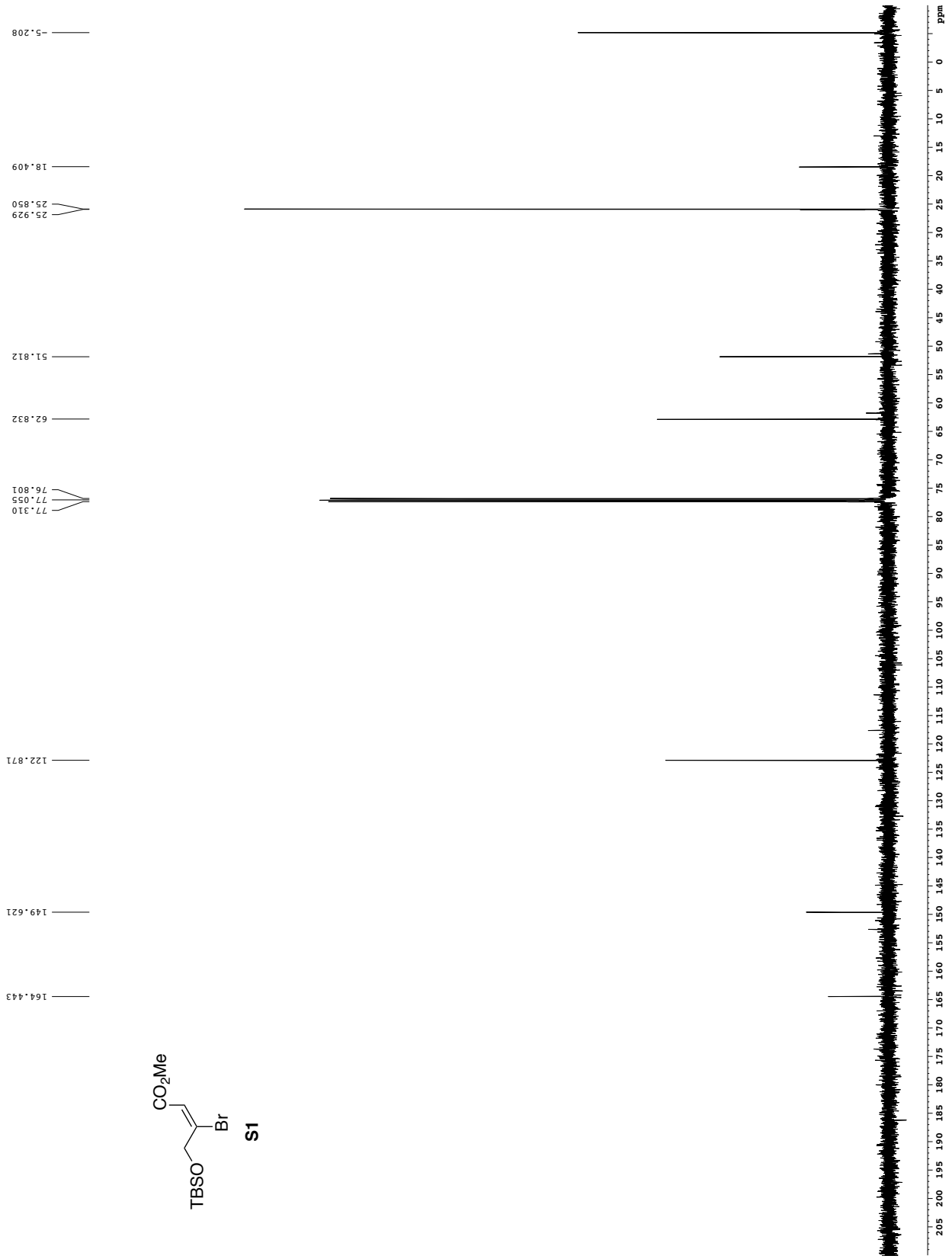

Current Data Parameters
USER pitzen
NAME JF03024
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20120427
Time 14.20
INSTRUM av600
PROBHD 5 mm TBI 1H/13
PULPROG zg30
TD 97938
SOLVENT CDCl3
NS 8
DS 2
SWH 9615.385 Hz
FIDRES 0.098218 Hz
AQ 5.0928256 sec
RG 406
DW 52.000 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
F2 - Processing parameters
SI 65536
SF 600.1300284 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1.110
1.547
3.597
4.915
5.308
6.359
7.270
7.385
7.397
7.410
7.431
7.443
7.455
7.708
7.720
9.189
3.057
1.996
1.000
4.061
2.059
4.091
ppm
CO2Me
Br
TBDPSO
3.18

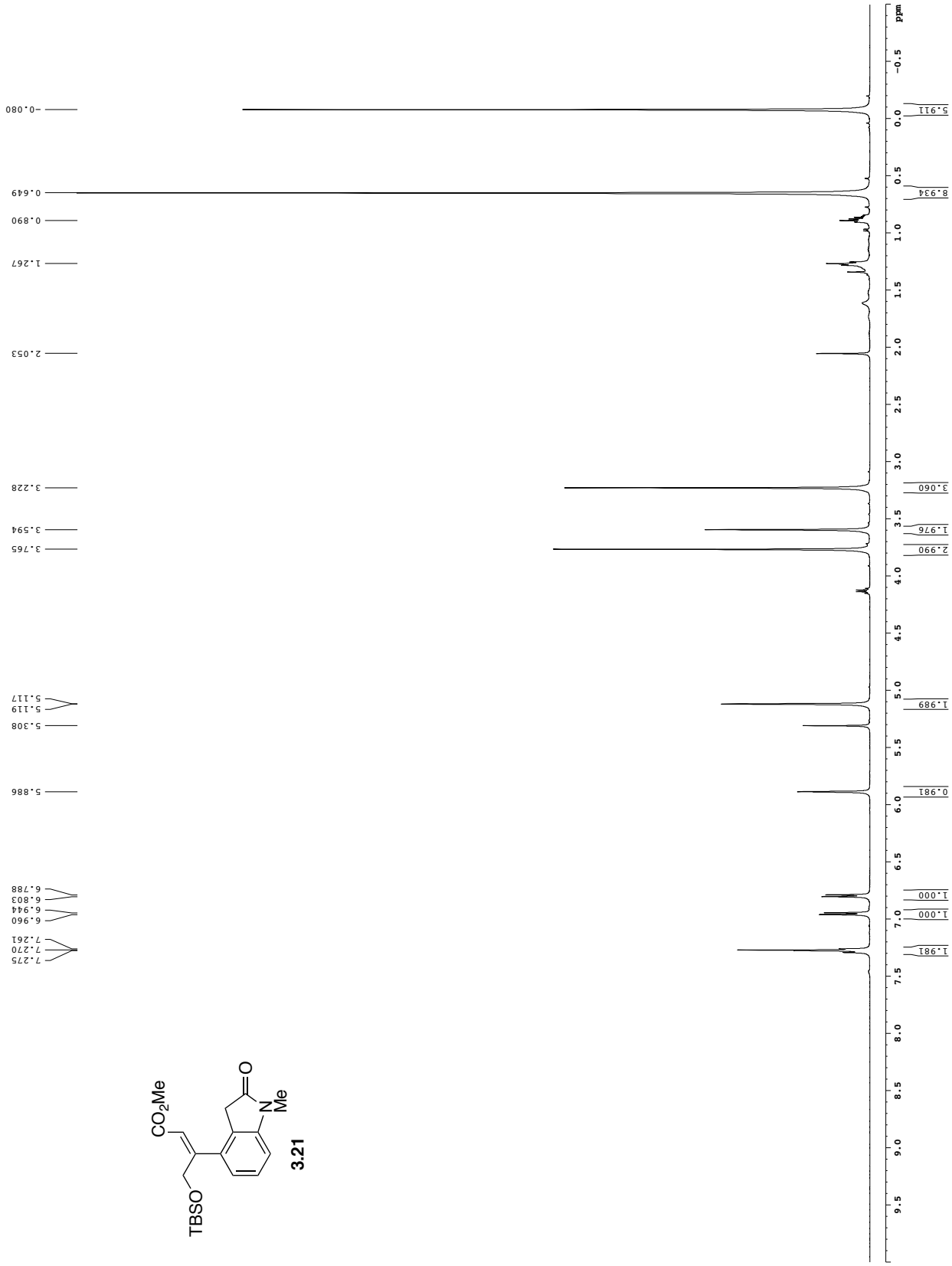

164.089
148.450
135.692
133.018
129.812
127.703
123.053
77.240
77.028
76.816
63.306
51.656
26.802
19.408
CO2Me
TBDPSO
Br
3.18
Current Data Parameters
NAME JP03024
EXPNO 102
PROCNO 1
F2 - Acquisition Parameters
Date_ 20120427
Time 14.24
INSTRUM av600
PROBHD 5 mm TBI 1H/13
PULPROG zgdc30
TD 65536
SOLVENT CDC13
NS 165
DS 4
SWH 36231.883 Hz
FIDRES 0.552855 Hz
AQ 0.9044468 sec
RG 2050
DW 13.800 usec
DE 6.00 usec
TE 298.2 K
D1 0.40000001 sec
D11 0.03000000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 15.00 usec
PLW1 107.15190125 W
SFO1 150.9194080 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 70.00 usec
PLW2 0 W
PLW12 0.30199519 W
SFO2 600.1330010 MHz
F2 - Processing parameters
SI 65536
SF 150.9028136 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
205 200 195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 ppm
Scale: 8.73 ppm/cm, 1317 Hz/cm


0.012
0.813
1.010
1.065
1.076
1.082
1.118
1.255
1.269
1.284
1.344
1.589
2.054
3.179
3.210
3.218
3.248
3.473
3.575
3.653
4.111
4.125
4.139
4.154
5.178
5.181
5.307
5.804
5.807
5.811
6.815
6.831
6.900
6.916
7.270
7.279
7.295
7.303
7.317
7.332
7.372
7.386
7.389
7.400
7.404
7.416
7.419
7.421
7.452
7.455
7.468
7.718
7.721
7.734
7.737
8.708
0.978
3.890
2.167
4.273
1.000
0.955
1.079
1.976
2.884
2.041
2.915
ppm
CO2Me
TBDPSO
O
N
Me
3.19

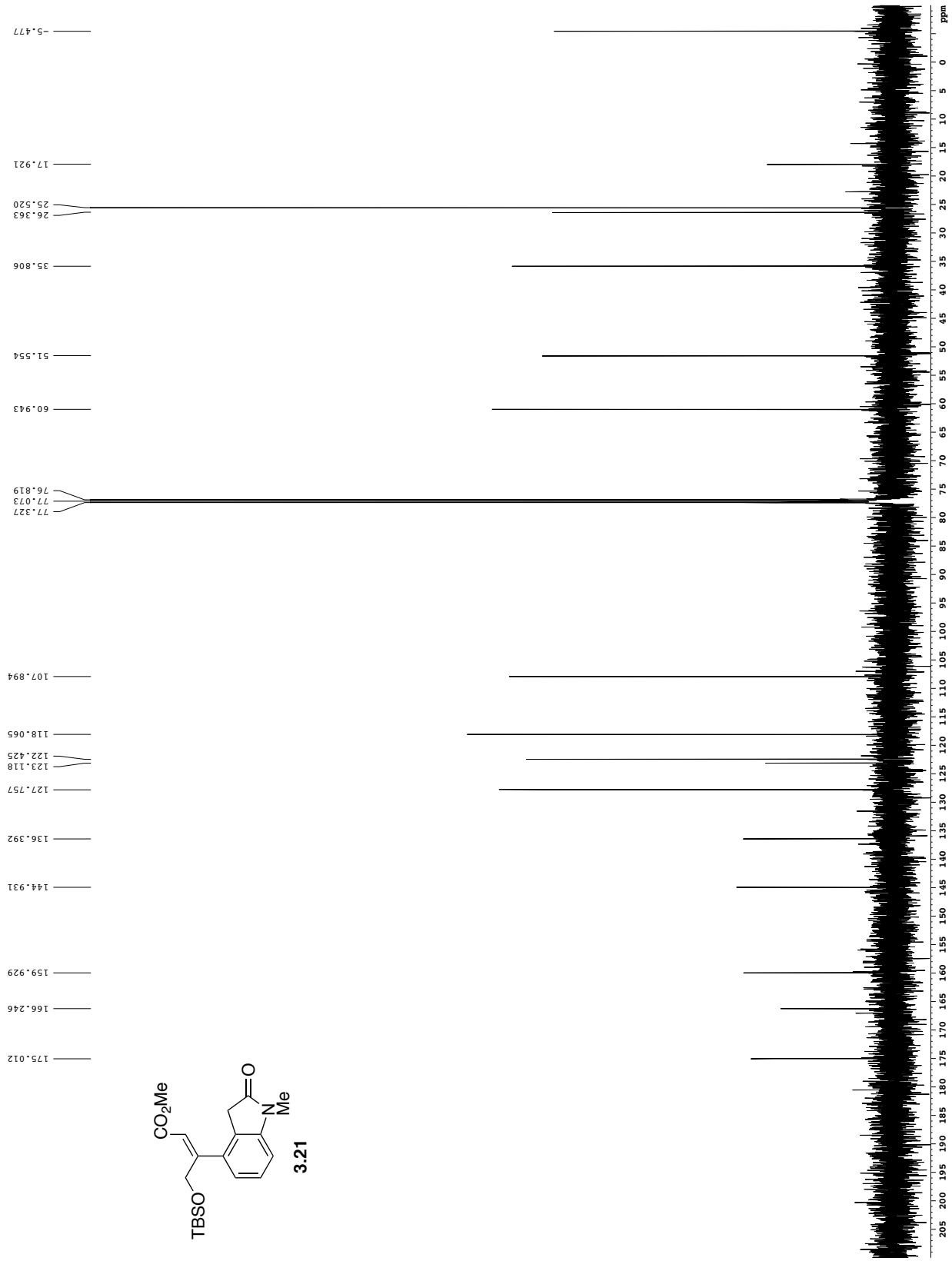

0.039
14.248
19.056
26.369
26.613
35.569
51.441
61.606
76.808
77.063
77.317
107.826
118.391
122.667
122.947
127.638
127.759
127.824
129.685
129.763
133.164
134.851
135.561
145.028
158.711
165.921
174.861
ppm
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
140
145
150
155
160
165
170
175
180
185
190
195
200
205
CO2Me
TBDPSO
O
N
Me
3.19

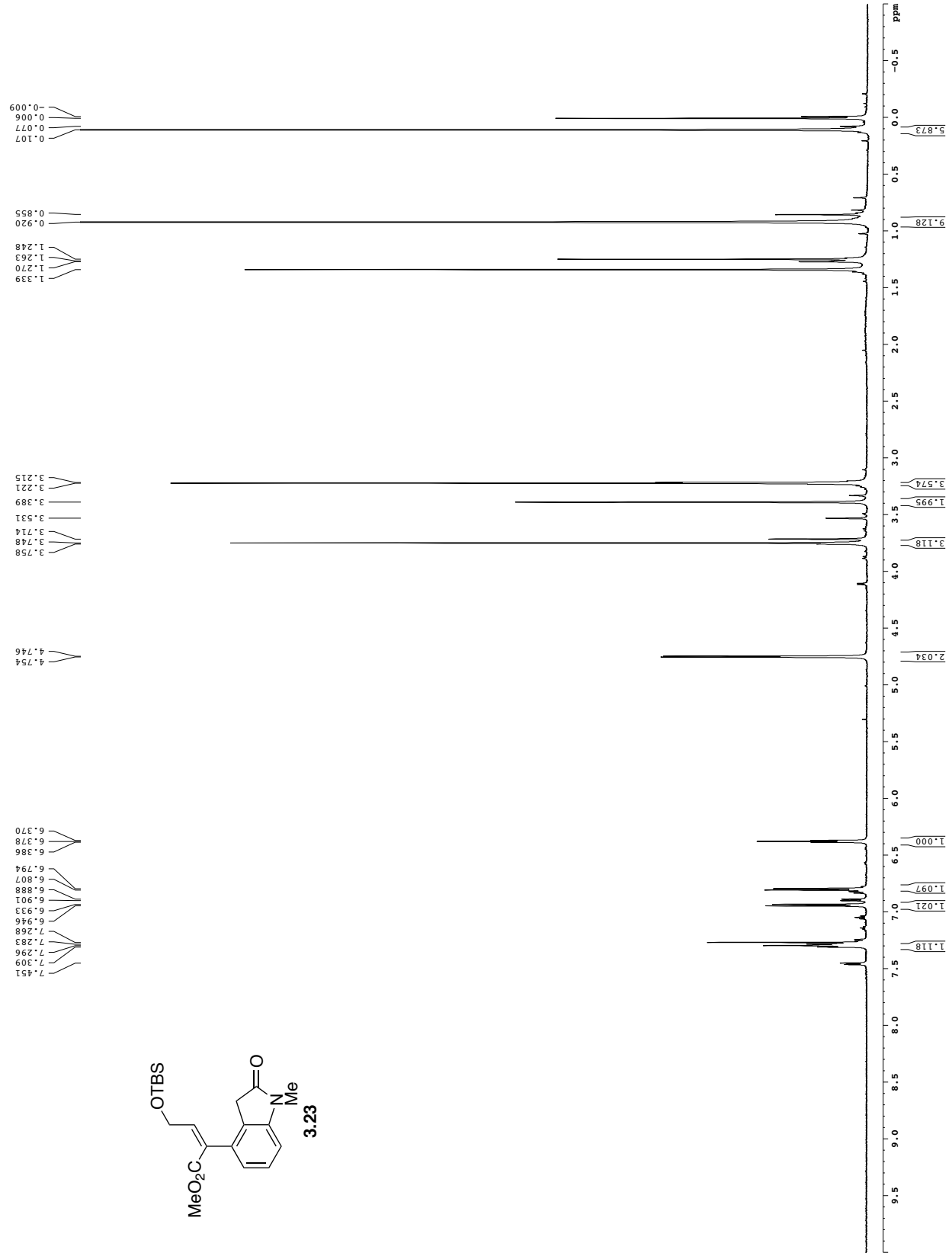

7.270
6.407
5.305
4.884
3.725
0.934
0.914
0.852
0.121
0.085
CO2Me
TBSO
Br
S1
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
1.000
1.966
3.128
8.843
5.748

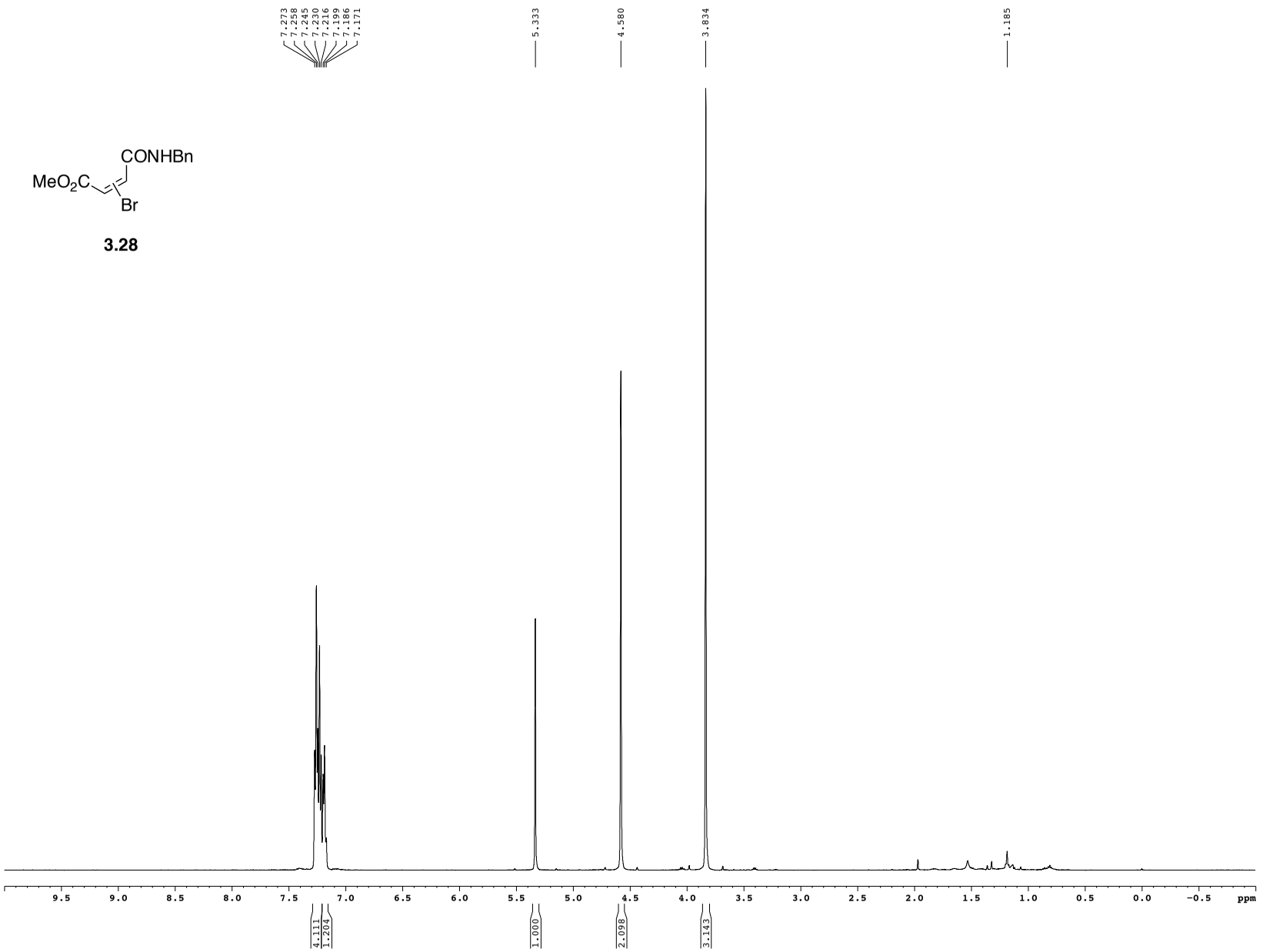

-5.208
18.409
25.850
25.929
51.812
62.832
76.801
77.055
77.310
122.871
149.621
164.443
ppm
TBSO
CO2Me
Br
S1

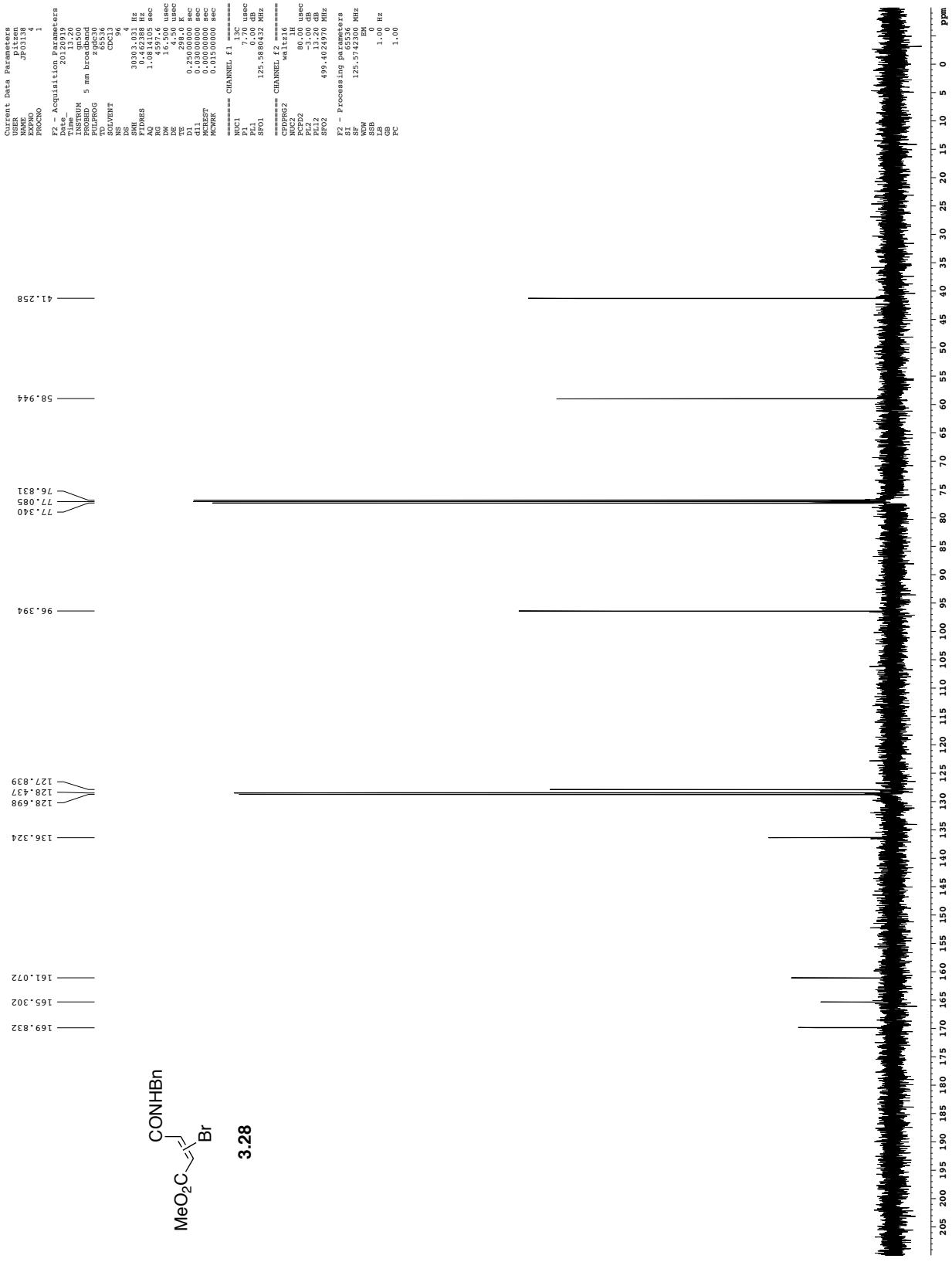

-0.080
0.649
0.890
1.267
2.053
3.228
3.594
3.765
5.117
5.119
5.308
5.886
6.788
6.803
6.944
6.960
7.261
7.270
7.275
5.911
8.934
3.060
1.976
2.990
1.989
0.981
1.000
1.000
1.981
ppm
CO2Me
TBSO
O
N
Me

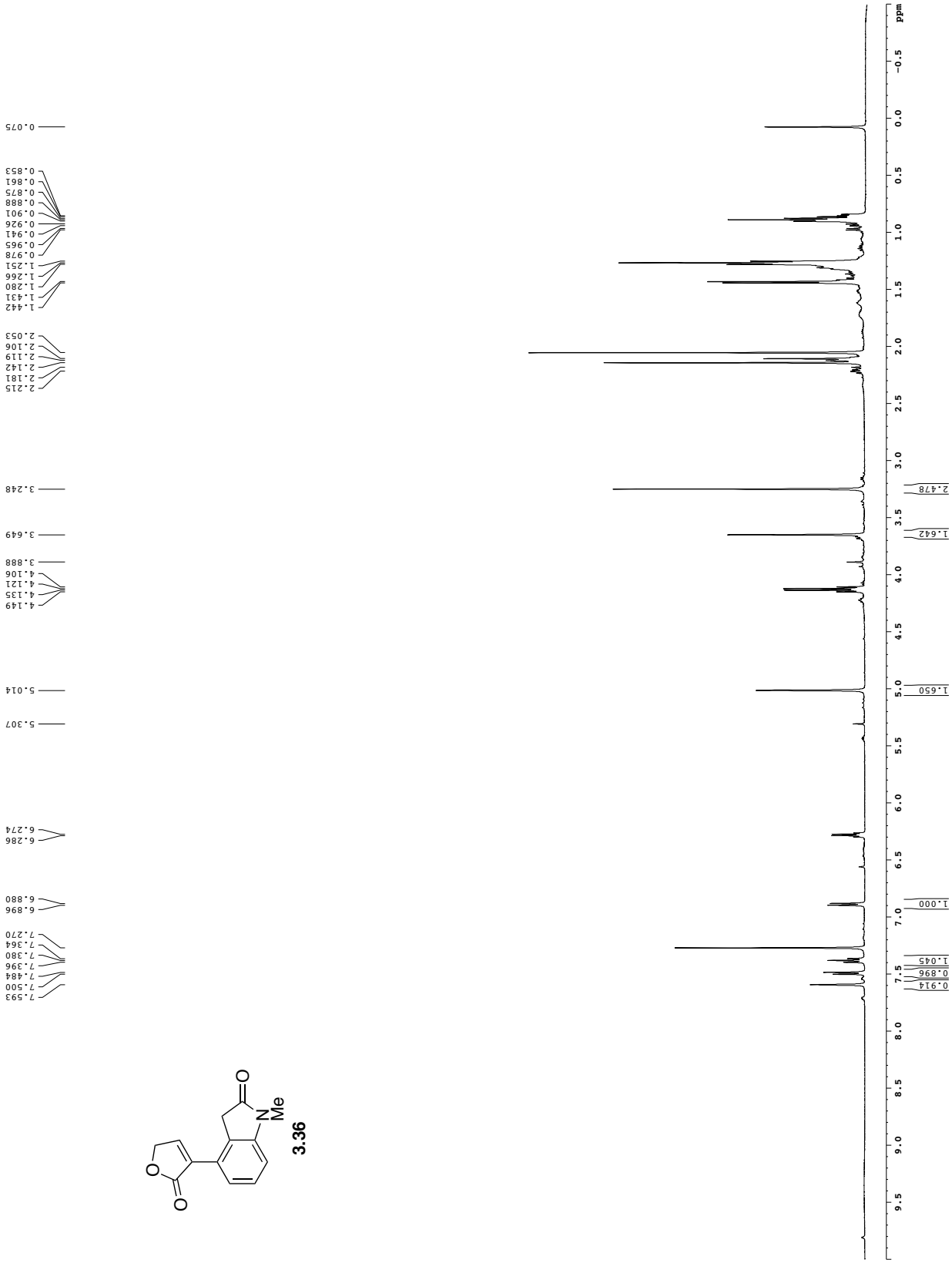
3.21


-5.477
17.921
25.520
26.363
35.806
51.554
60.943
76.819
77.073
77.327
107.894
118.065
122.425
123.118
127.757
136.392
144.931
159.929
166.246
175.012
ppm
CO2Me
TBSO
N
Me
O
3.21


OTBS
MeO2C
O
N
Me
3.23

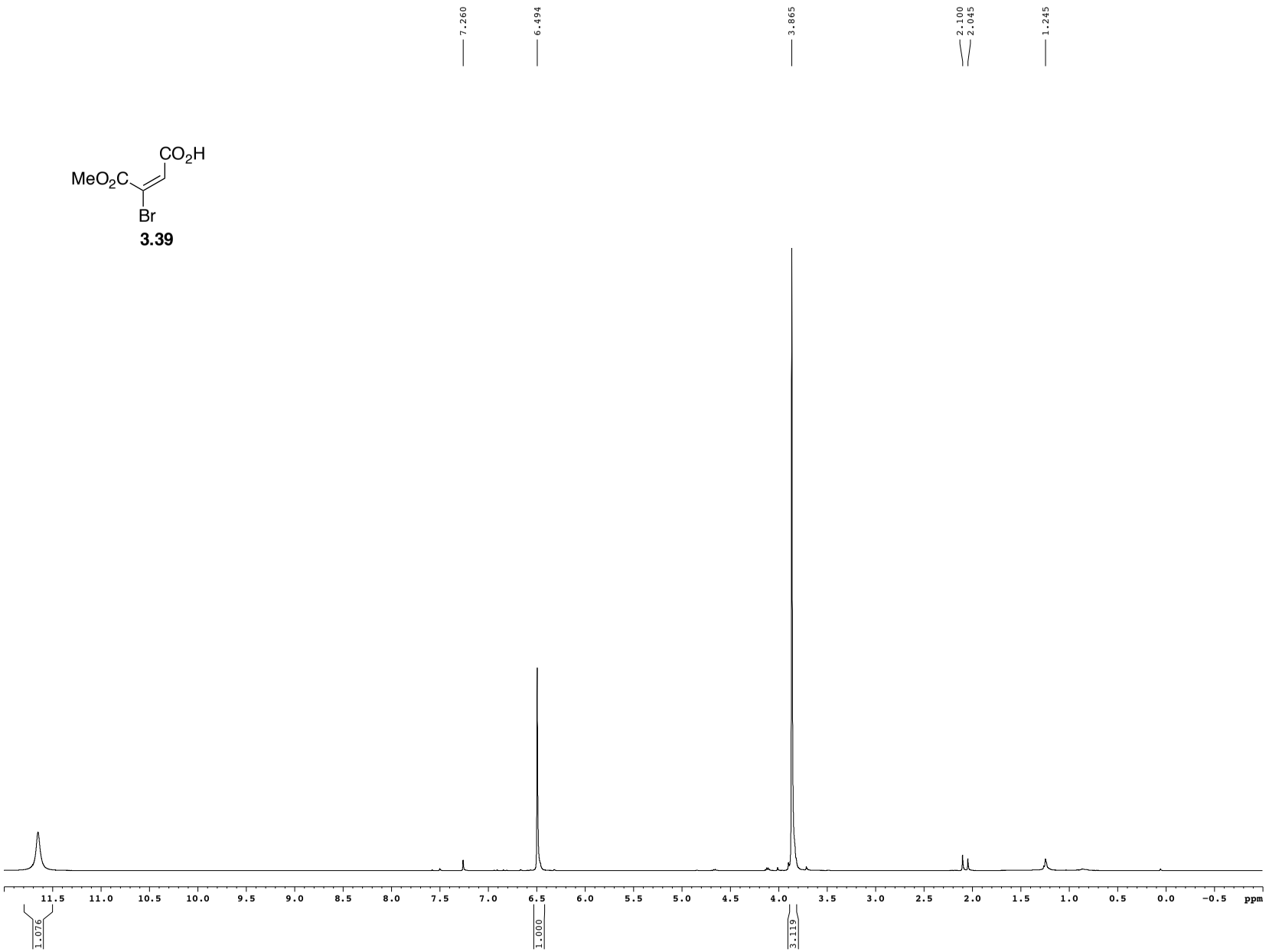

7.273
7.258
7.245
7.230
7.216
7.199
7.186
7.171
5.333
4.580
3.834
1.185
CONHBn
MeO2C
Br
3.28
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
4.111
1.204
1.000
2.098
3.143

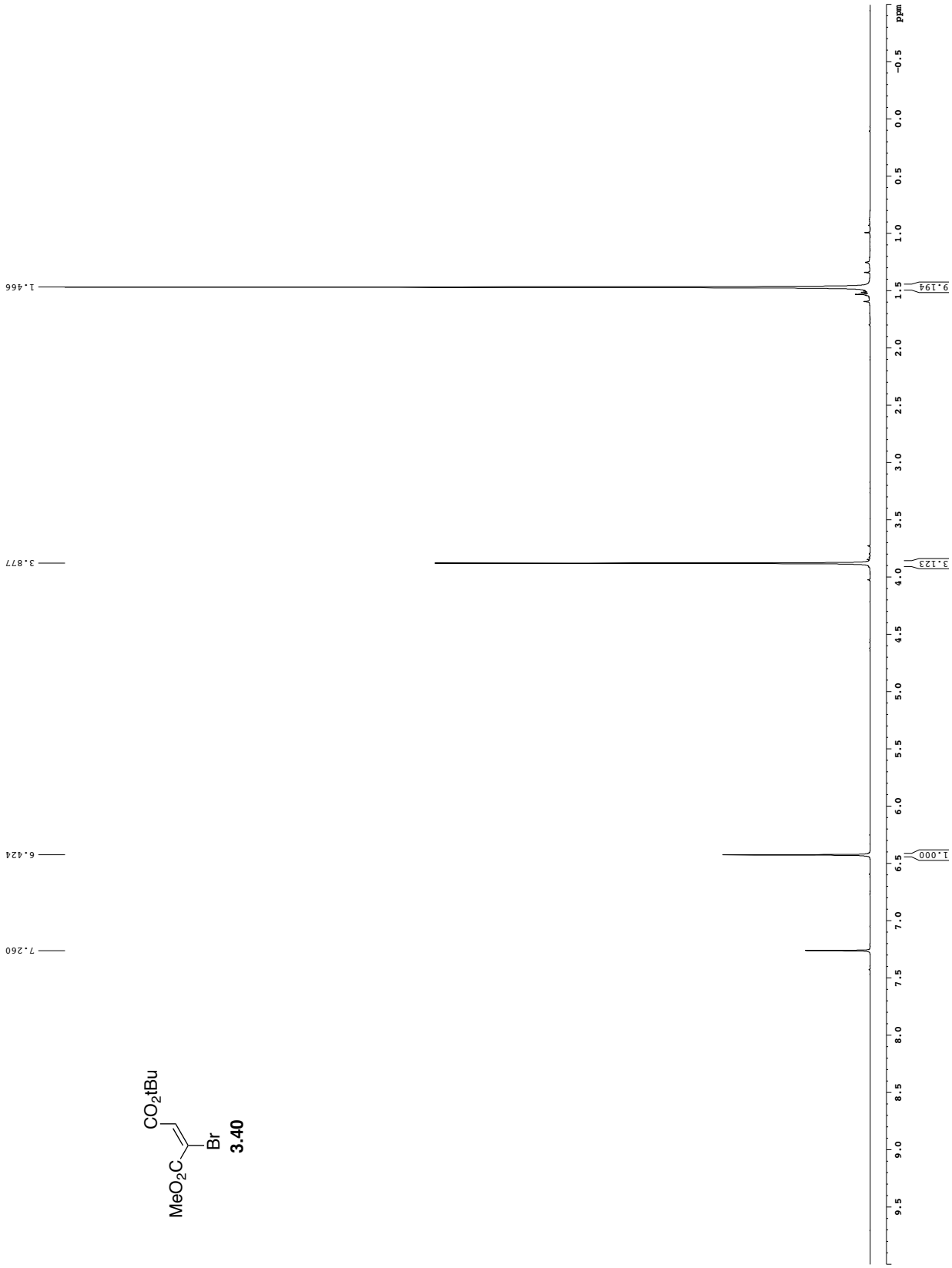

Current Data Parameters
USER pitzen
NAME JF03134
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20120919
Time_ 13.20
INSTRUM qn500
PROBHD 5 mm broadband
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 96
DS 4
SWH 30303.031 Hz
FIDRES 0.462308 Hz
AQ 1.0814105 sec
RG 4597.6
DW 16.500 usec
DE 6.50 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
MCWGEST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 13C ========
NUC1 13C
P1 7.70 usec
PL1 0.00 dB
SFO1 125.5880432 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -3.00 dB
PL12 13.20 dB
SFO2 499.4024970 MHz
F2 - Processing parameters
SI 65536
SF 125.5742300 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
41.258
58.944
76.831
77.085
77.340
96.394
127.839
128.437
128.698
136.324
161.072
165.302
169.832
CONHBn
Br
MeO2C
3.28
ppm

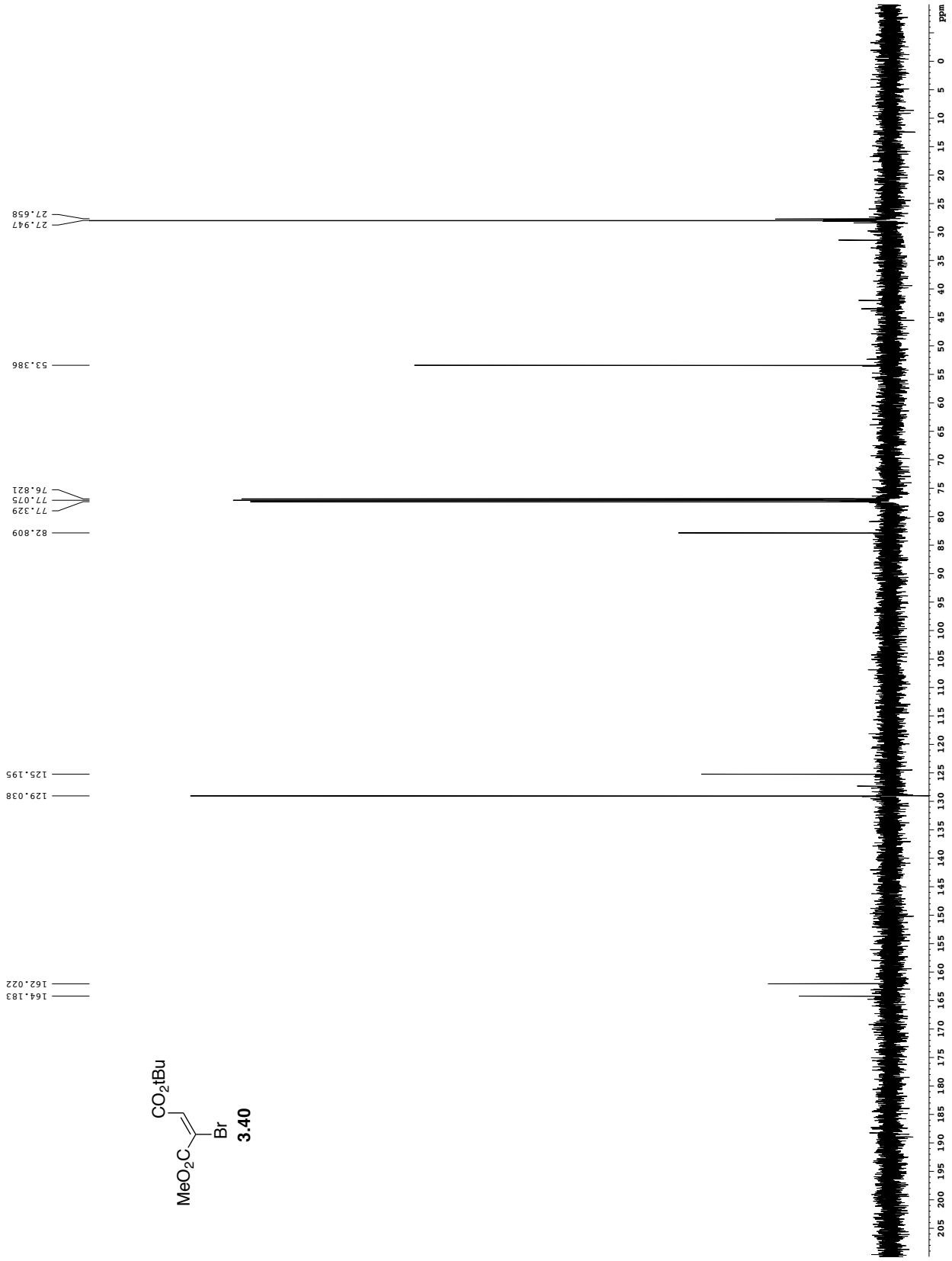

0.075
0.853
0.861
0.875
0.888
0.901
0.926
0.941
0.965
0.978
1.251
1.266
1.280
1.431
1.442
2.053
2.106
2.119
2.142
2.181
2.215
3.248
3.649
3.888
4.106
4.121
4.135
4.149
5.014
5.307
6.274
6.286
6.880
6.896
7.270
7.364
7.380
7.396
7.484
7.500
7.593
ppm
2.478
1.642
1.650
1.000
1.045
0.896
0.914

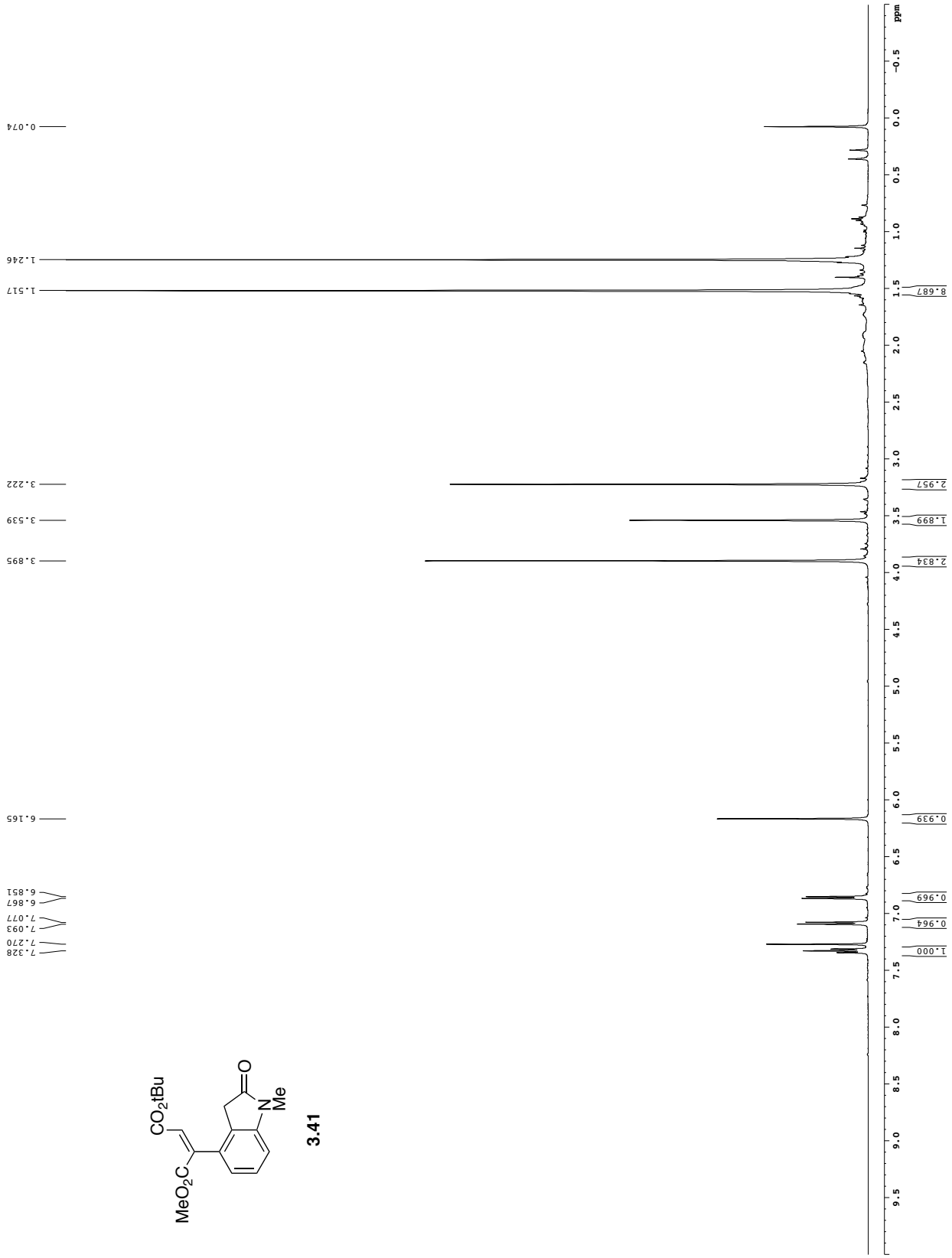
O
N
Me
O
O

3.36


7.260
6.494
3.865
2.100
2.045
1.245
CO2H
MeO2C
Br
3.39
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm
1.076
1.000
3.119

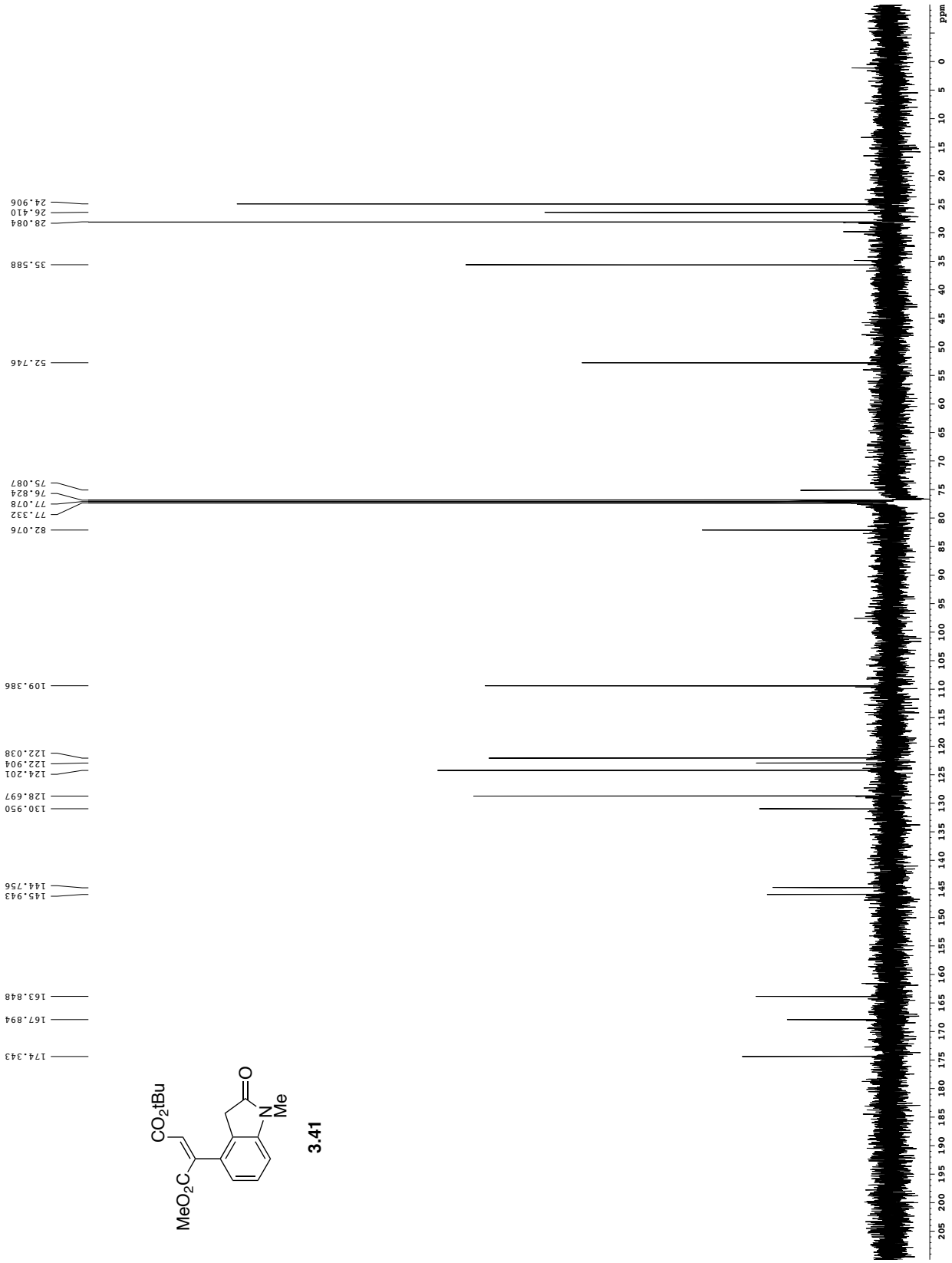

1.466
3.877
6.424
7.260
9.194
3.123
1.000
ppm
CO2tBu
MeO2C
Br
3.40


27.658
27.947
53.386
76.821
77.075
77.329
82.809
125.195
129.038
162.022
164.183
ppm
MeO_2C
Br
CO_2tBu
3.40


0.074
1.246
1.517
3.222
3.539
3.895
6.165
6.851
6.867
7.077
7.093
7.270
7.328
8.687
2.957
1.899
2.834
0.939
0.969
0.964
1.000
ppm

CO2tBu
MeO2C
O
N
Me

3.41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77.078
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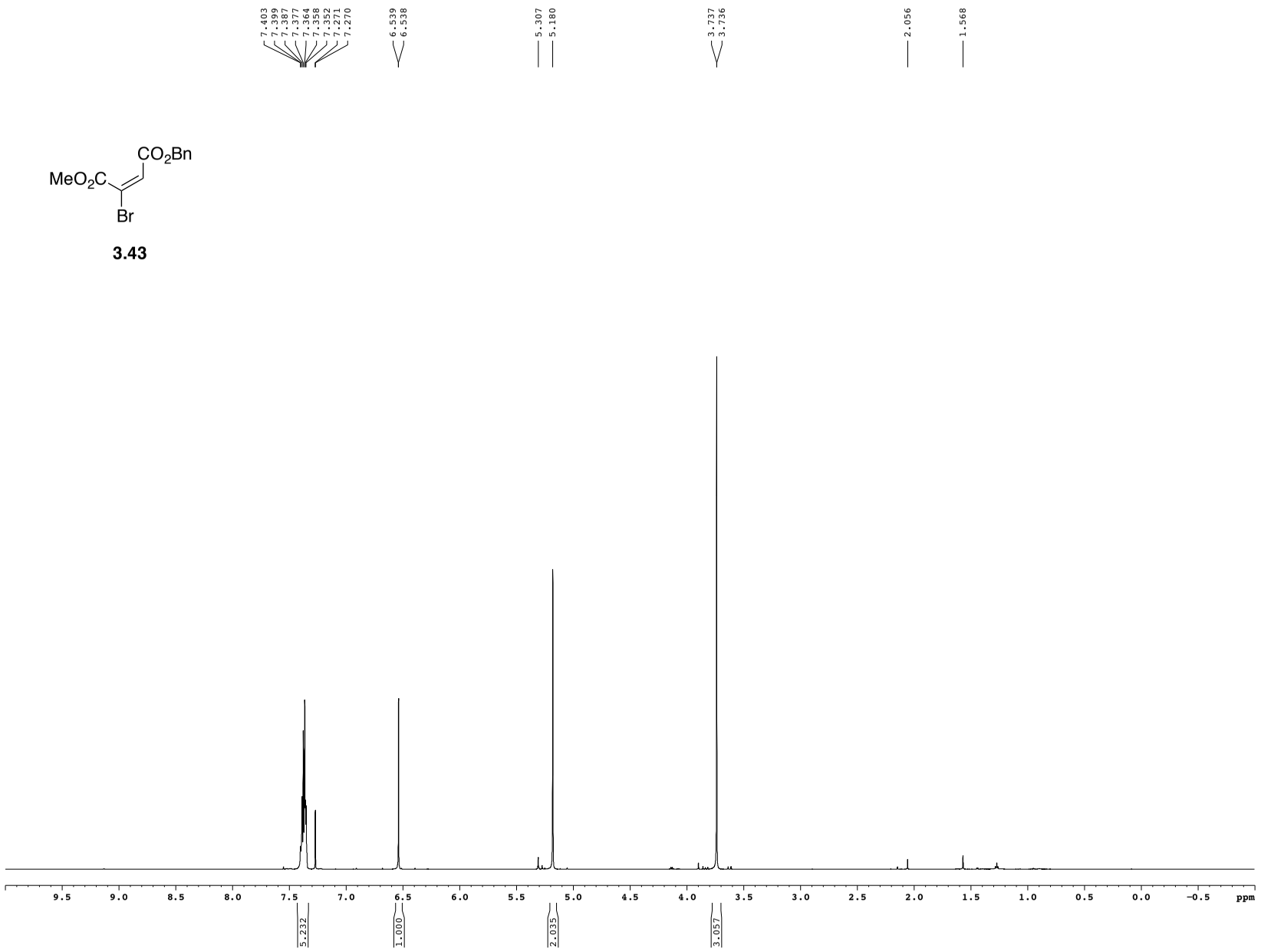
122.904
124.201
128.697
130.950
144.756
145.943
163.848
167.894
174.343
ppm
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
140
145
150
155
160
165
170
175
180
185
190
195
200
205

CO2tBu
MeO2C
O
N
Me

3.41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7.399
7.387
7.377
7.364
7.358
7.352
7.271
7.270
6.539
6.538
5.307
5.180
3.737
3.736
2.056
1.568
CO2Bn
MeO2C
Br
3.43
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
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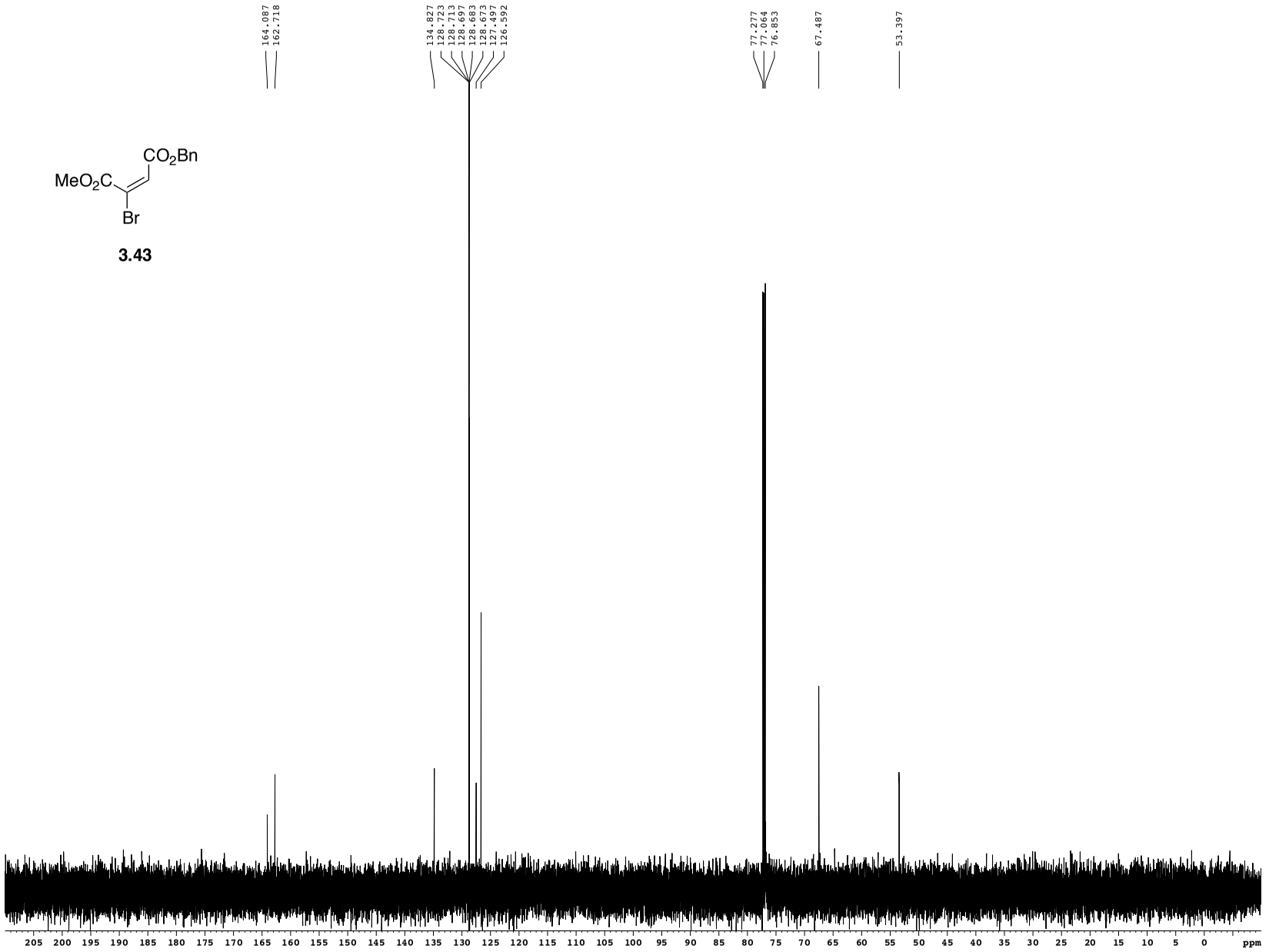
2.035
3.057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134.827
128.723
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128.683
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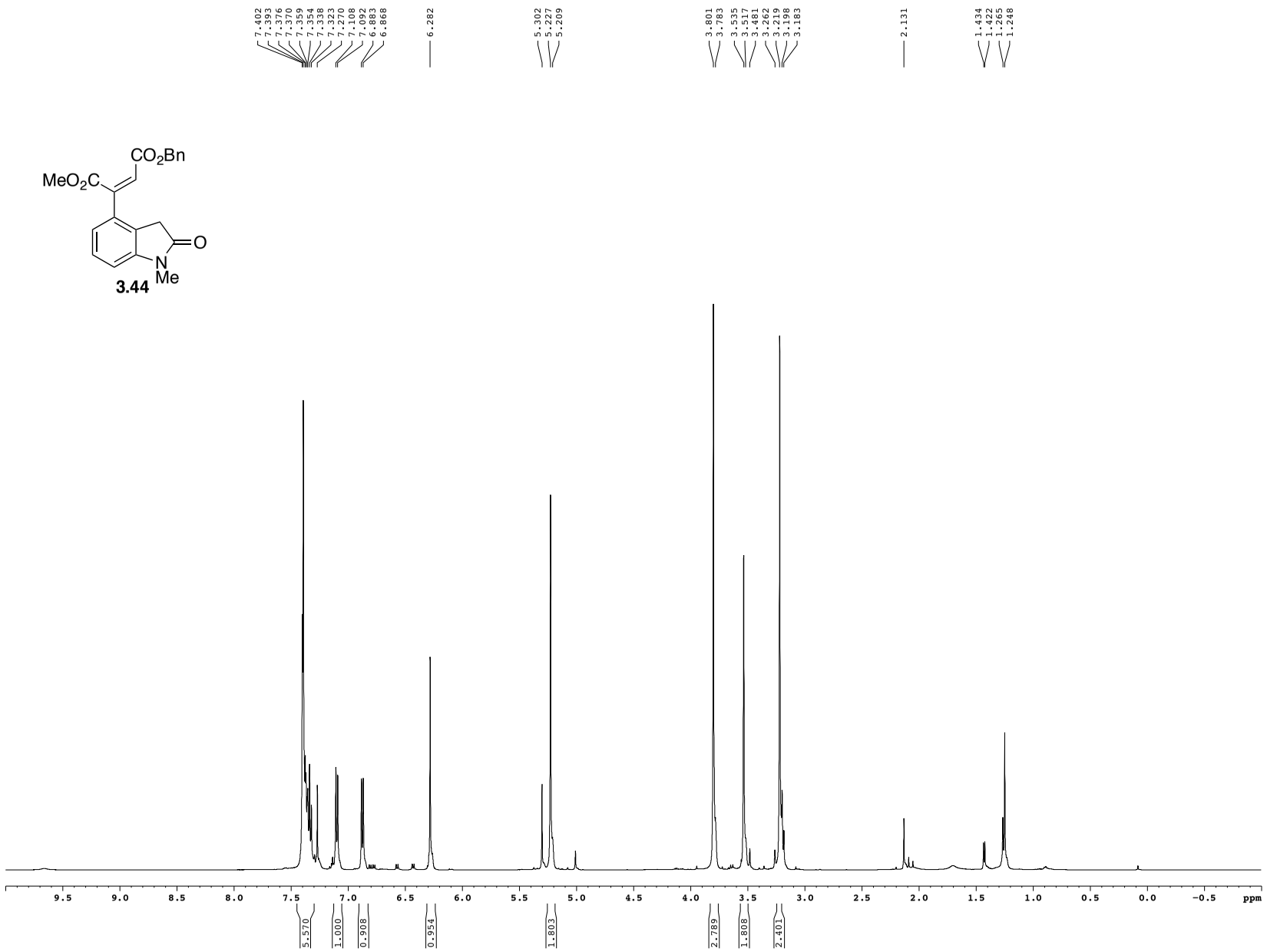
77.277
77.064
76.853
67.487
53.397
CO2Bn
MeO2C
Br
3.43
205 200 195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 ppm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7.323
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7.108
7.092
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6.868
6.282
5.302
5.227
5.209
3.801
3.783
3.535
3.517
3.481
3.262
3.219
3.198
3.183
2.131
1.434
1.422
1.265
1.248
CO2Bn
MeO2C
O
N
Me
3.44
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
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0.954
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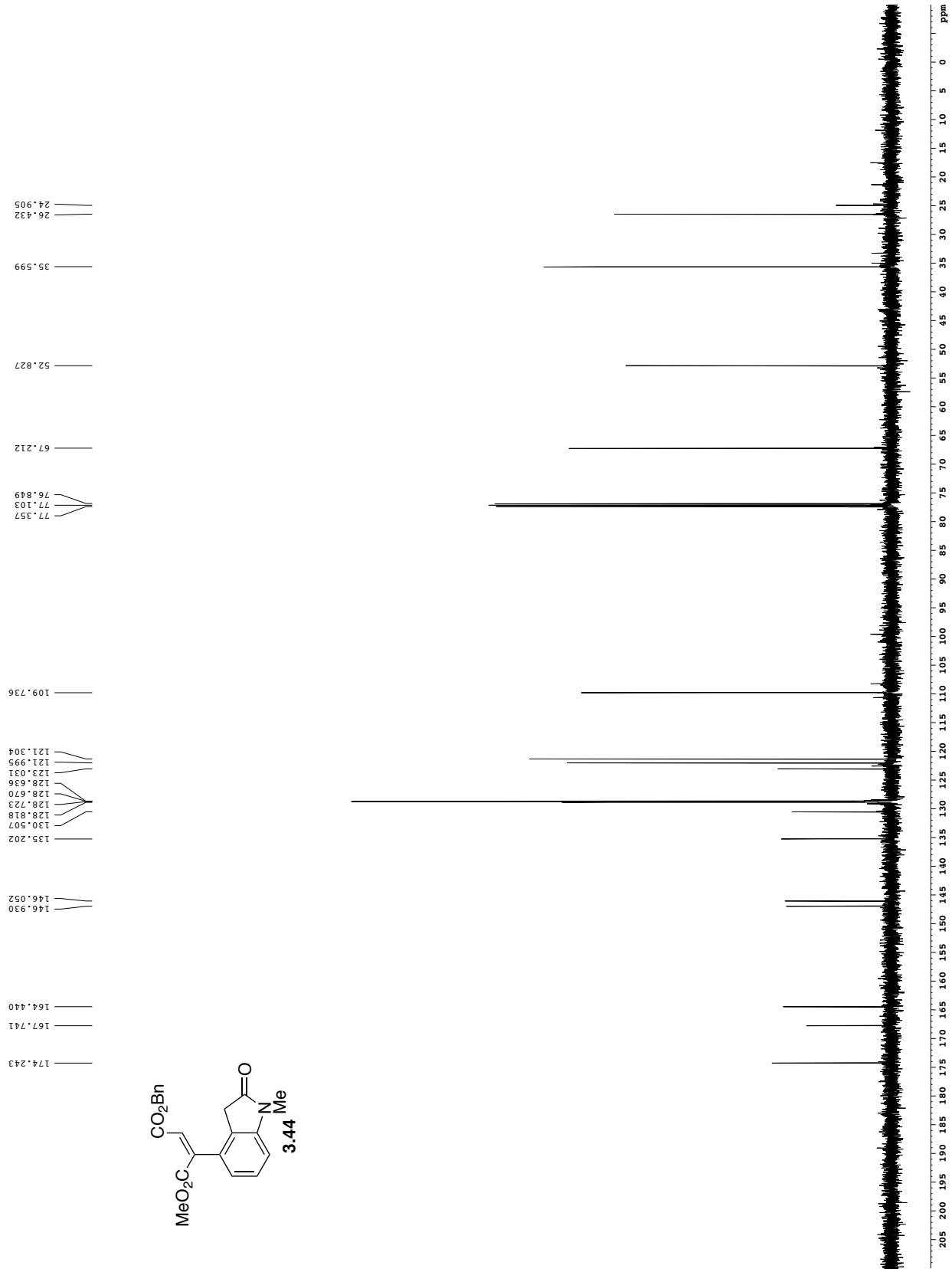
2.789
1.808
2.401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167.741
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130.507
128.818
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128.670
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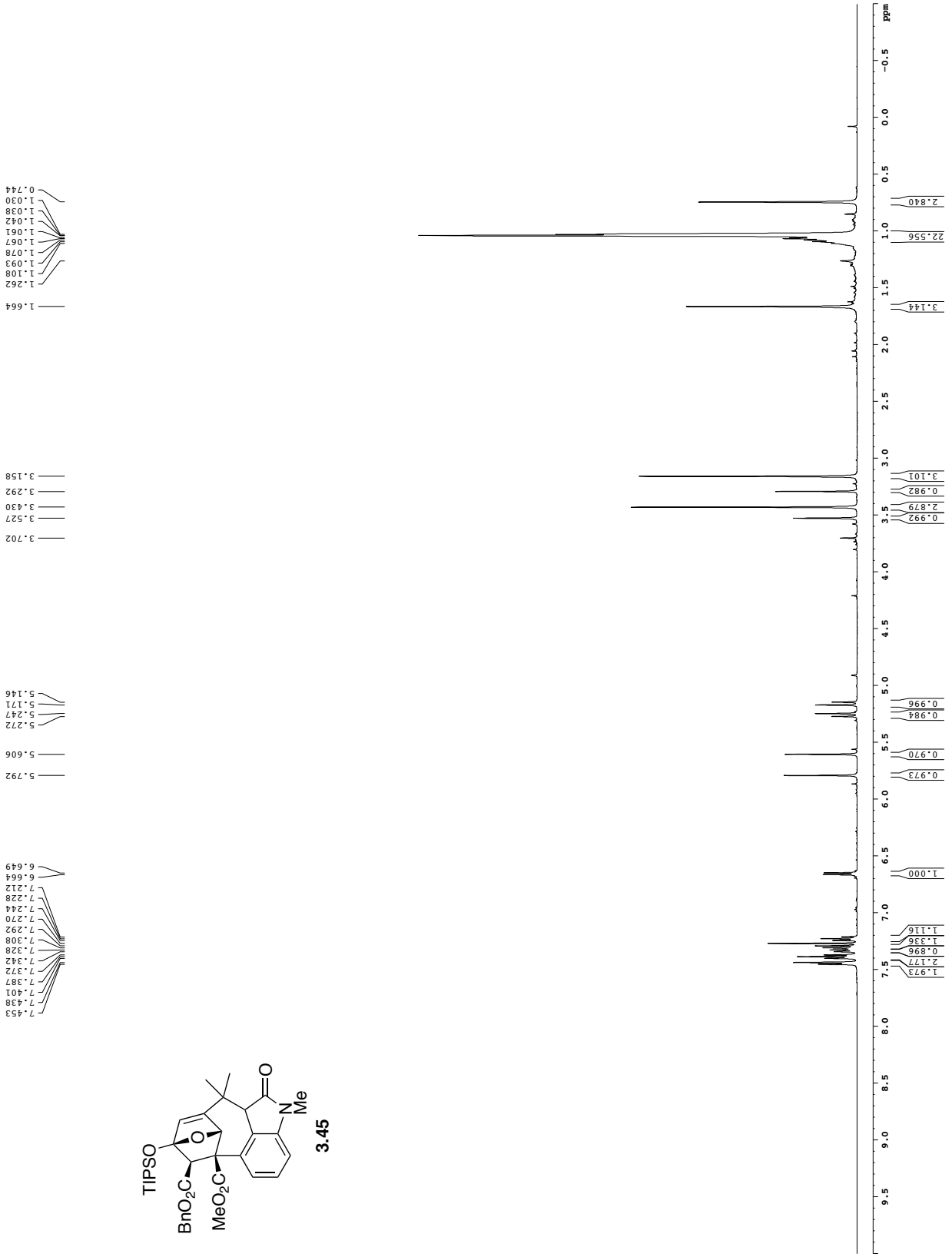
121.995
121.304
109.736
77.357
77.103
76.849
67.212
52.827
35.599
26.432
24.905
ppm
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
140
145
150
155
160
165
170
175
180
185
190
195
200
205
CO2Bn
MeO2C
O
N
Me
3.44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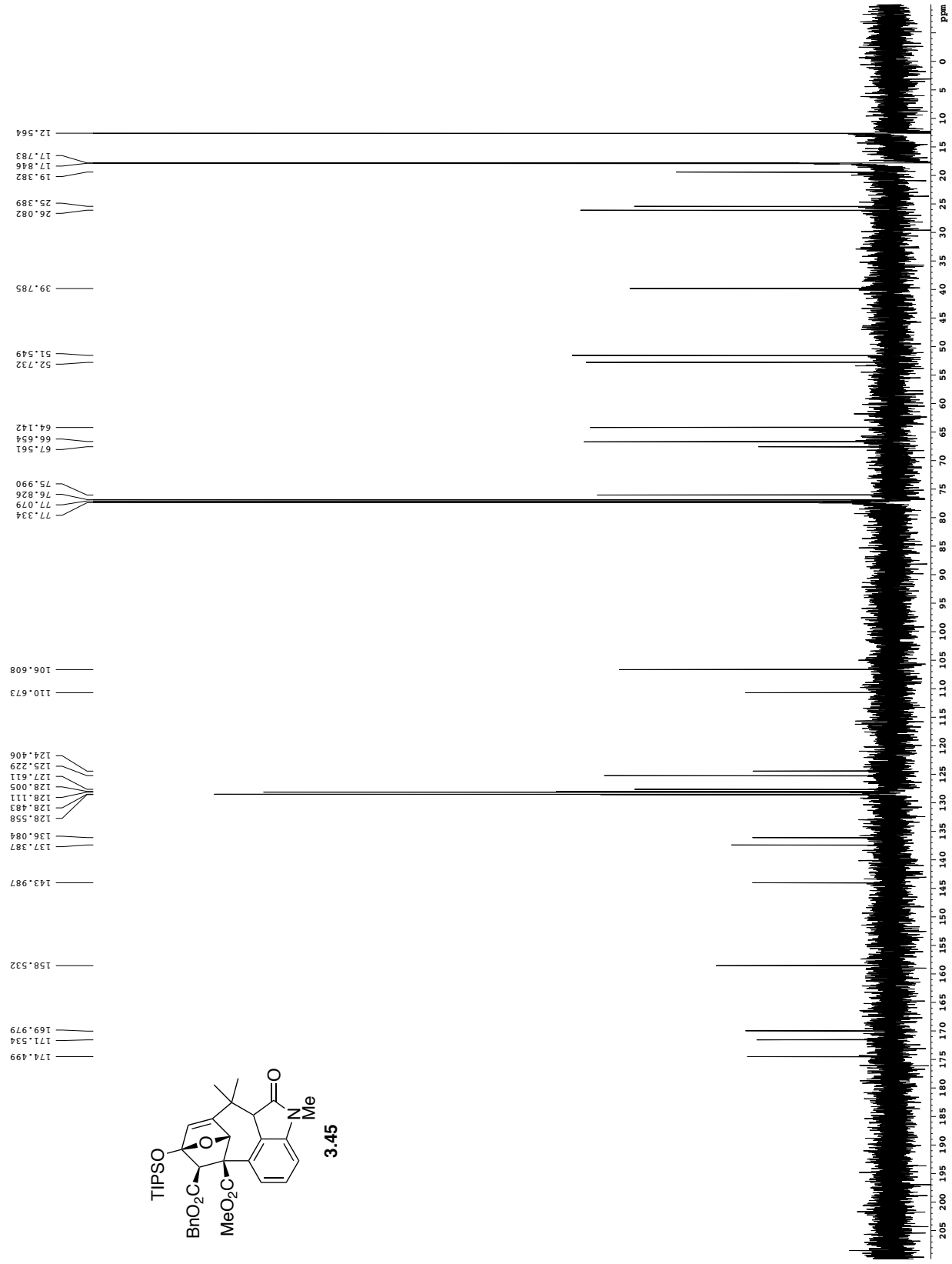
7.401
7.387
7.372
7.342
7.328
7.308
7.292
7.270
7.244
7.228
7.212
6.664
6.649
5.792
5.606
5.272
5.247
5.171
5.146
3.702
3.527
3.430
3.292
3.158
1.664
1.262
1.108
1.093
1.078
1.067
1.061
1.042
1.038
1.030
0.744
ppm
1.973
2.177
0.896
1.336
1.116
1.000
0.973
0.970
0.984
0.996
0.992
2.879
0.982
3.101
3.144
22.556
2.840

TIPSO
BnO2C
MeO2C
O
N
Me
O

3.45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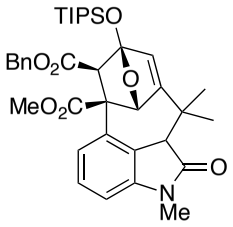
17.783
17.846
19.382
25.389
26.082
39.785
51.549
52.732
64.142
66.654
67.561
75.990
76.826
77.079
77.334
106.608
110.673
124.406
125.229
127.611
128.005
128.111
128.483
128.558
136.084
137.387
143.987
158.532
169.979
171.534
174.499
TIPSO
BnO2C
MeO2C
O
N
Me
3.45

gnoesy



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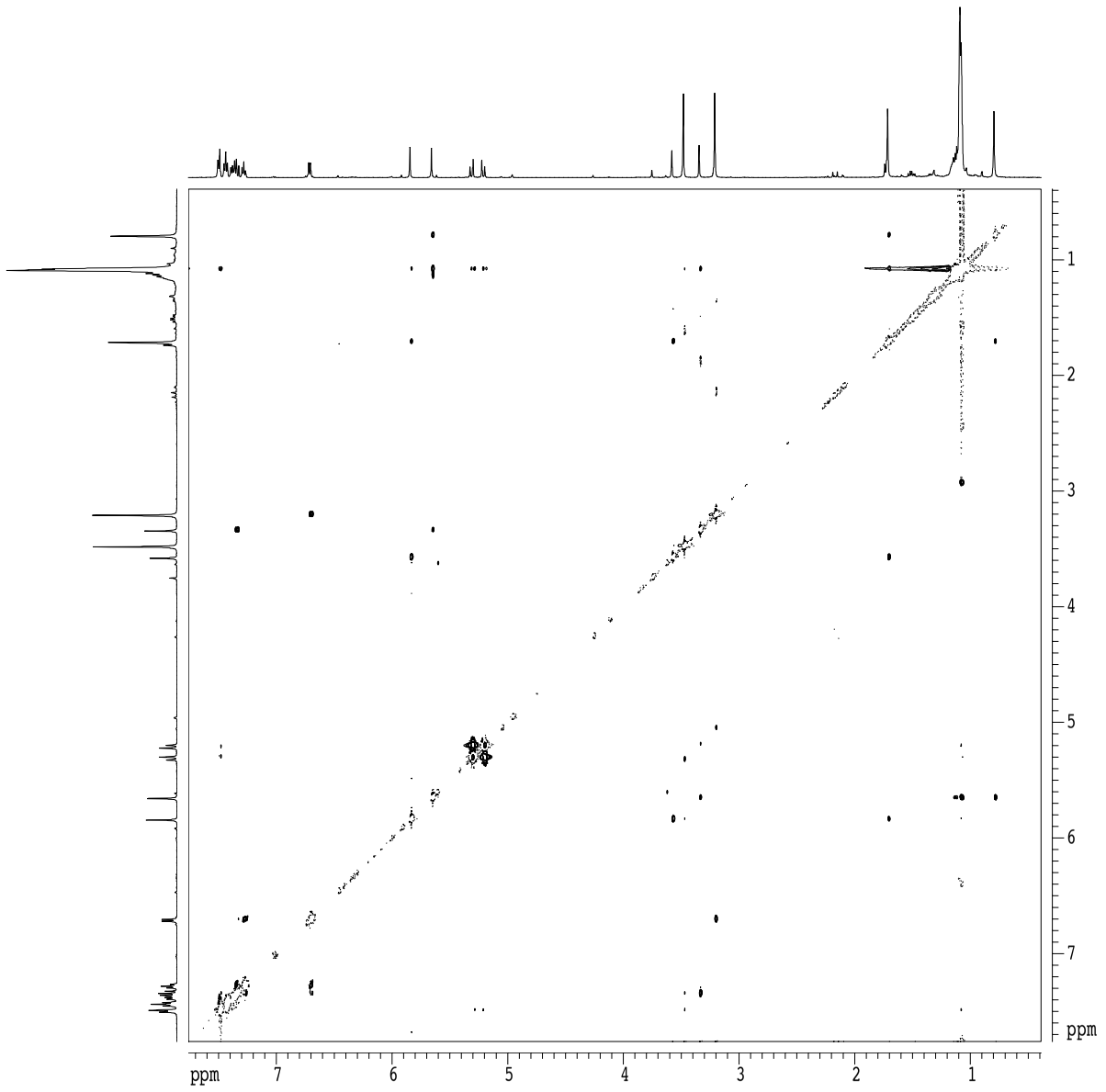


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USER              pitzen
NAME              JP05049
EXPNO                   3
PROCNO                  1

      F2 - Acquisition Parameters
Date_           20130617
Time              19.00
INSTRUM         cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG       noesygptp
TD                2048
SOLVENT           CDCl3
NS                   2
DS                  16
SWH            3687.316 Hz
FIDRES            1.800447 Hz
AQ              0.2777588 sec
RG                  57
DW               135.600 usec
DE                 6.00 usec
TE               298.0 K
D0              0.00000300 sec
D1              2.00000000 sec
D8              0.80000001 sec
D16             0.00020000 sec
d20             0.39880002 sec
IN0             0.00013560 sec

    ======== CHANNEL f1 ========
NUC1                  1H
P1                 7.50 usec
P2                15.00 usec
PL1                1.60 dB
SFO1         500.2220437 MHz

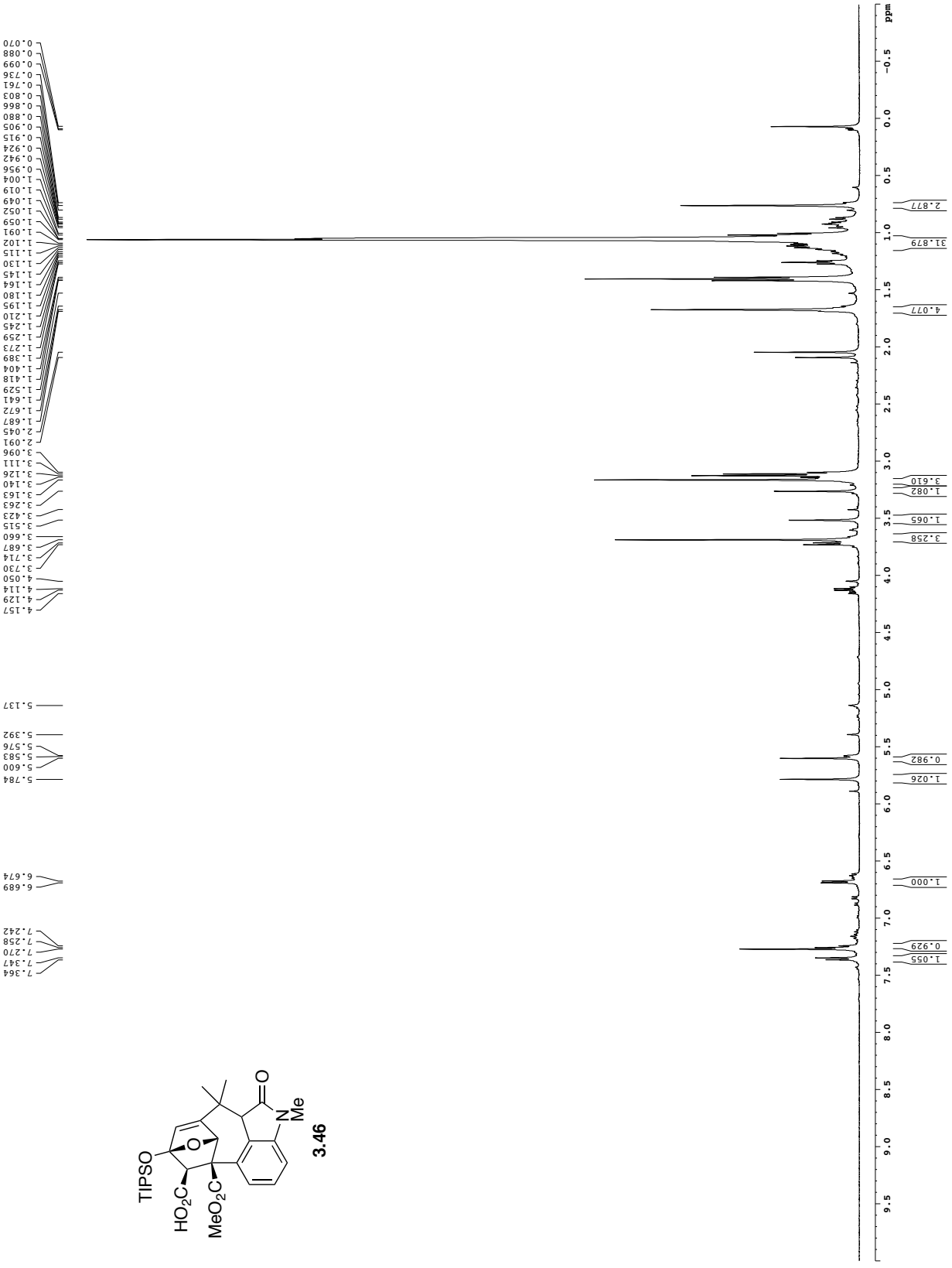
    ====== GRADIENT CHANNEL =====
GPNAM1          sine.100
GPNAM2          sine.100
GPX1               0.00 %
GPX2               0.00 %
GPY1               0.00 %
GPY2               0.00 %
GPZ1              40.00 %
GPZ2             -40.00 %
P16             1000.00 usec

      F1 - Acquisition parameters
ND0                   2
TD                  256
SFO1            500.222 MHz
FIDRES         14.403577 Hz
SW                7.371 ppm
FnMODE        undefined

      F2 - Processing parameters
SI                 1024
SF           500.2200054 MHz
WDW               QSINE
SSB                   2
LB                 0.00 Hz
GB                    0
PC                 4.00

      F1 - Processing parameters
SI                 1024
MC2                TPPI
SF           500.2200059 MHz
WDW               QSINE
SSB                   2
LB                 0.00 Hz
GB                    0

      2D NMR plot parameters
CX2               15.00 cm
CX1               15.00 cm
F2PLO              7.760 ppm
F2LO            3881.90 Hz
F2PHI              0.389 ppm
F2HI             194.59 Hz
F1PLO              7.759 ppm
F1LO            3881.40 Hz
F1PHI              0.388 ppm
F1HI             194.09 Hz
F2PPMCM         0.49143 ppm/cm
F2HZCM        245.82104 Hz/cm
F1PPMCM         0.49143 ppm/cm
F1HZCM        245.82104 Hz/cm
```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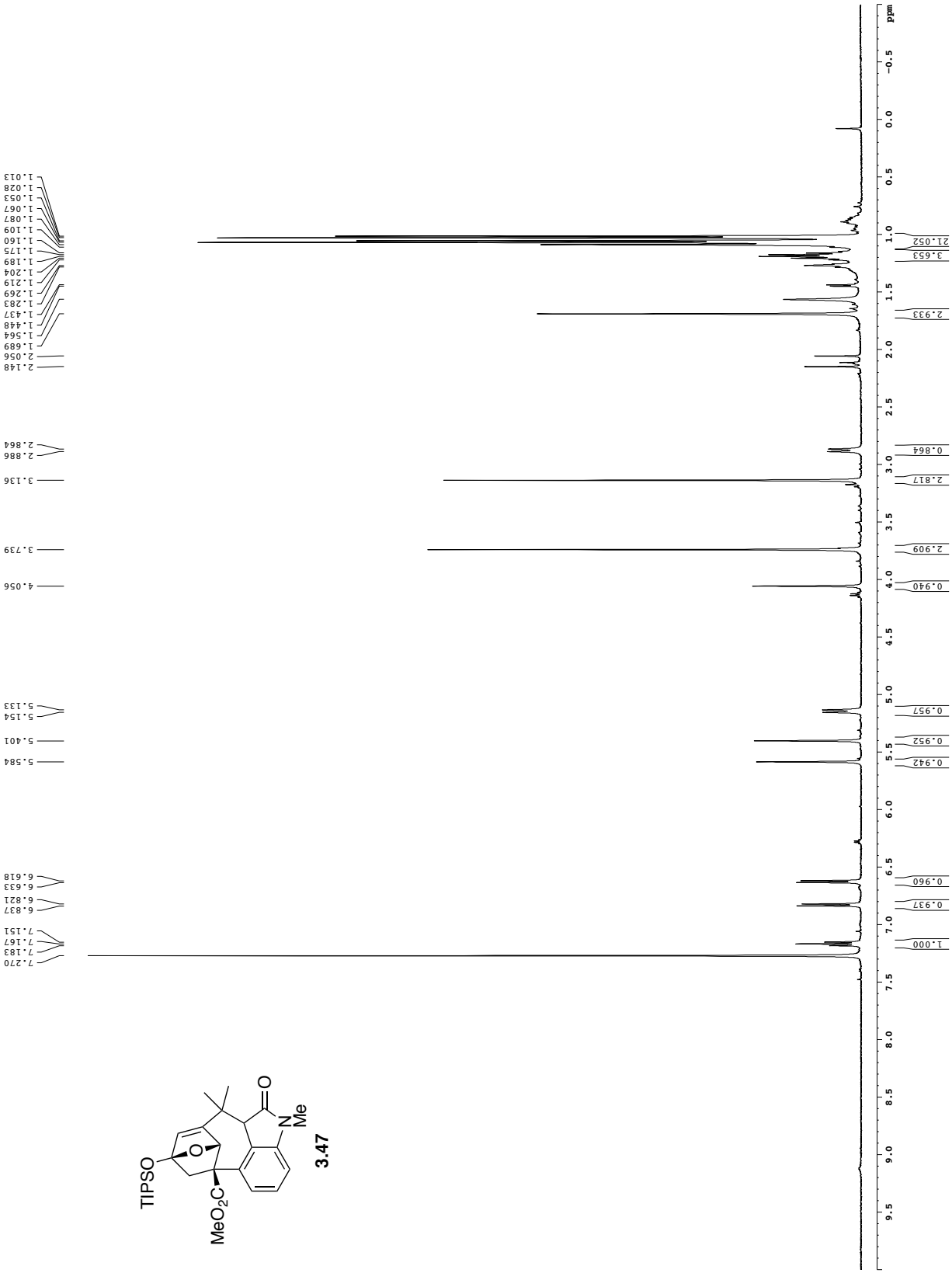
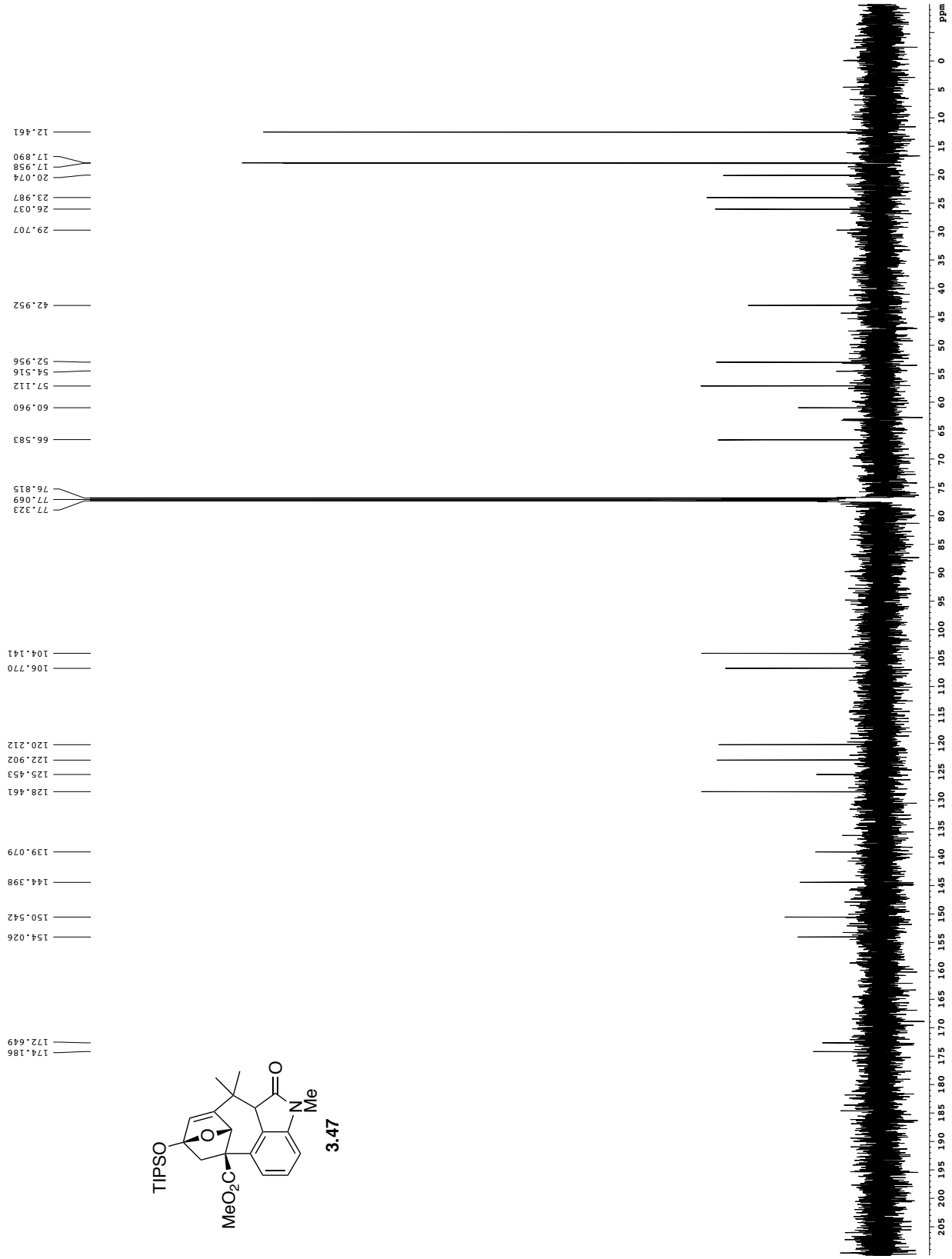
0.099
0.736
0.761
0.803
0.866
0.880
0.905
0.915
0.924
0.942
0.956
1.004
1.019
1.049
1.052
1.059
1.091
1.102
1.115
1.130
1.145
1.164
1.180
1.195
1.210
1.245
1.259
1.273
1.389
1.404
1.418
1.529
1.641
1.672
1.687
2.045
2.091
3.096
3.111
3.126
3.140
3.163
3.263
3.423
3.515
3.660
3.687
3.714
3.730
4.050
4.114
4.129
4.157
5.137
5.392
5.576
5.583
5.600
5.784
6.674
6.689
7.242
7.258
7.270
7.347
7.364
2.877
31.879
4.077
3.610
1.082
1.065
3.258
0.982
1.026
1.000
0.929
1.055
ppm
TIPSO
HO2C
MeO2C
O
N
Me
O
3.46


7.270
7.183
7.167
7.151
6.837
6.821
6.633
6.618
5.584
5.401
5.154
5.133
4.056
3.739
3.136
2.886
2.864
2.148
2.056
1.689
1.564
1.448
1.437
1.283
1.269
1.219
1.204
1.189
1.175
1.160
1.109
1.087
1.067
1.053
1.028
1.013
1.000
0.937
0.960
0.942
0.952
0.957
0.940
2.909
2.817
0.864
2.933
3.653
21.052
ppm
TIPSO
MeO2C
O
N
Me
3.47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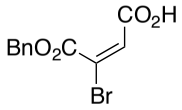
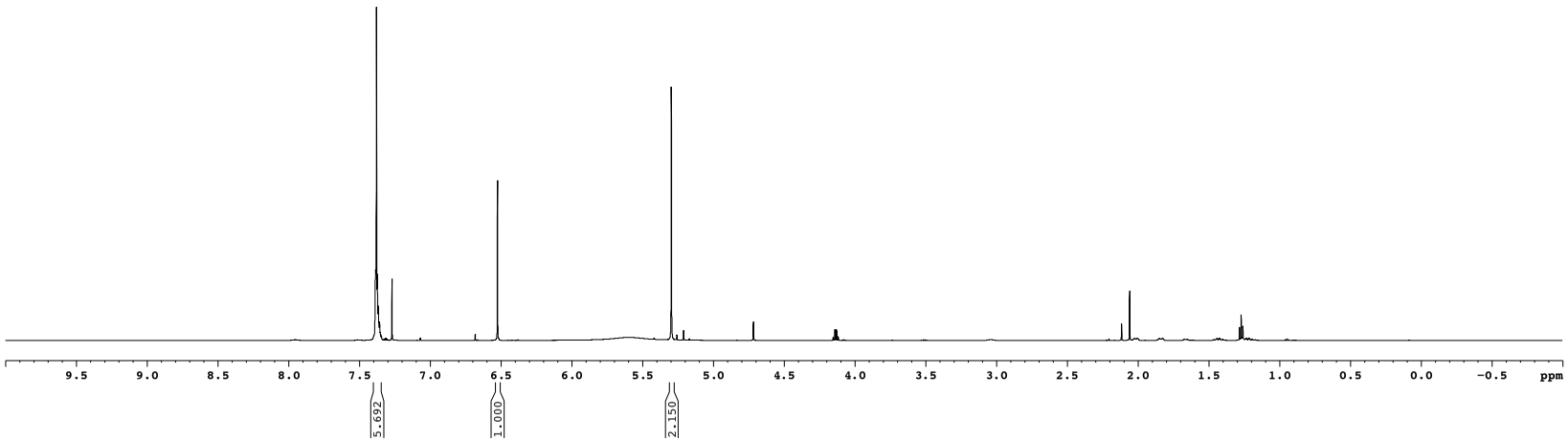
17.890
17.958
20.074
23.987
26.037
29.707
42.952
52.956
54.516
57.112
60.960
66.583
76.815
77.069
77.323
104.141
106.770
120.212
122.902
125.453
128.461
139.079
144.398
150.542
154.026
172.649
174.186
ppm
TIPSO
MeO2C
O
N
Me
3.47


7.387
7.384
7.380
7.374
7.369
7.367
7.362
7.359
7.353
7.350
7.346
7.270
6.682
6.525
5.297
5.258
5.210
4.717
4.141
4.129
2.116
2.059
1.283
1.271
1.259


CO2H
BnO2C
Br

3.49


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
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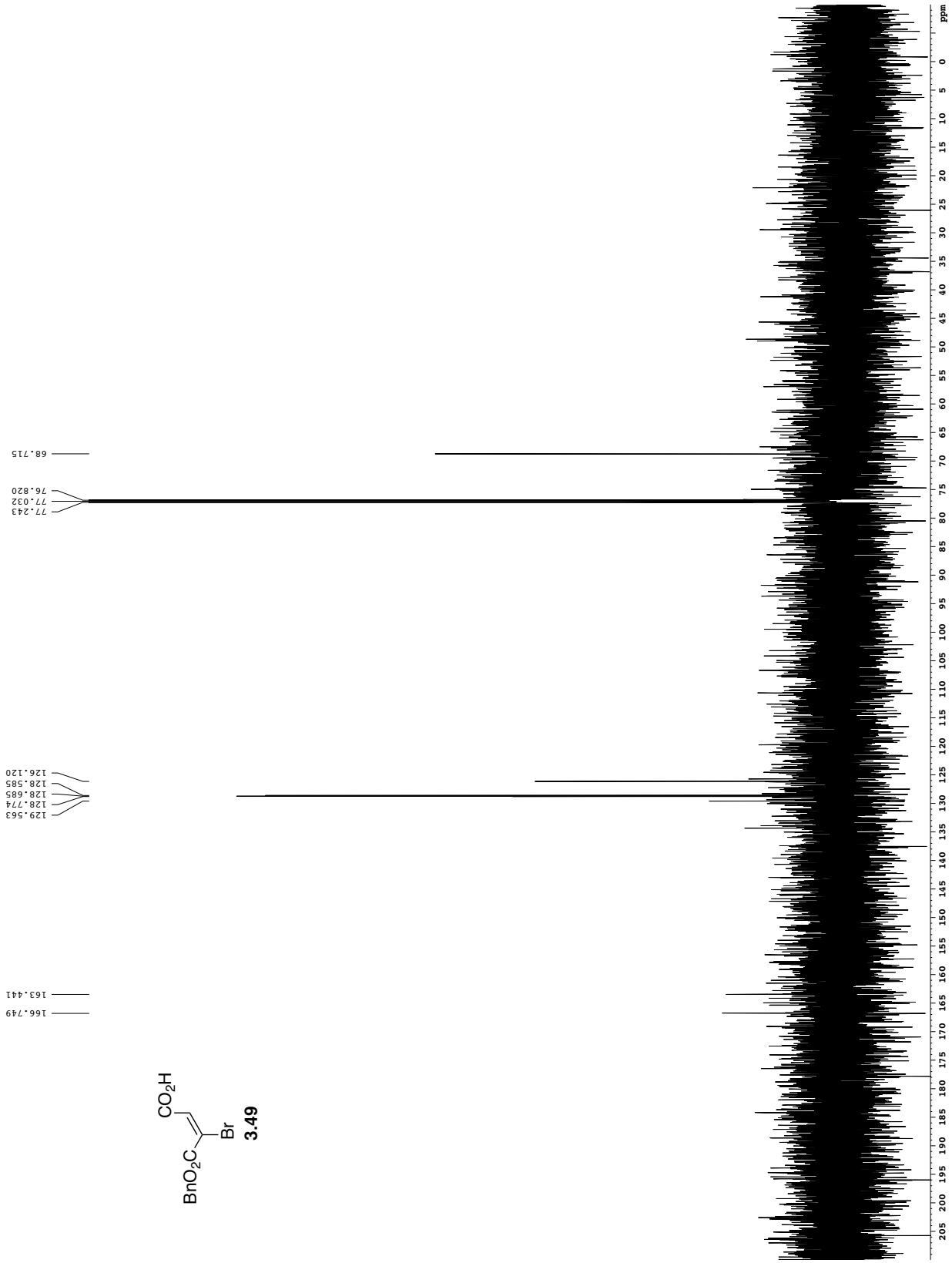
1.000
2.150


CO2H
BnO2C
Br
3.49
166.749
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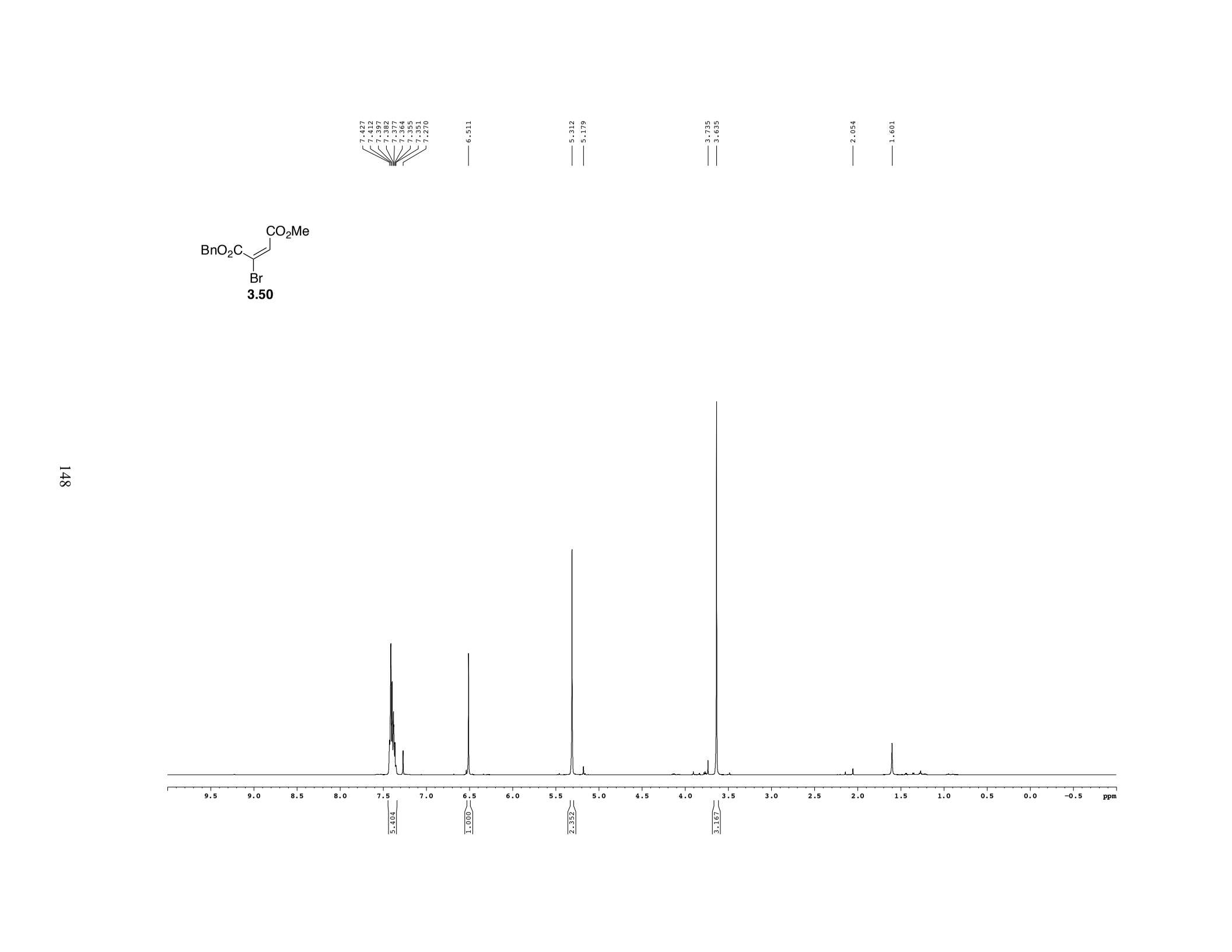
129.563
128.774
128.685
128.585
126.120
77.243
77.032
76.820
68.715
ppm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7.412
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7.382
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7.351
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6.511
5.312
5.179
3.735
3.635
2.054
1.601
CO2Me
BnO2C
Br
3.50
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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1.5
1.0
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ppm
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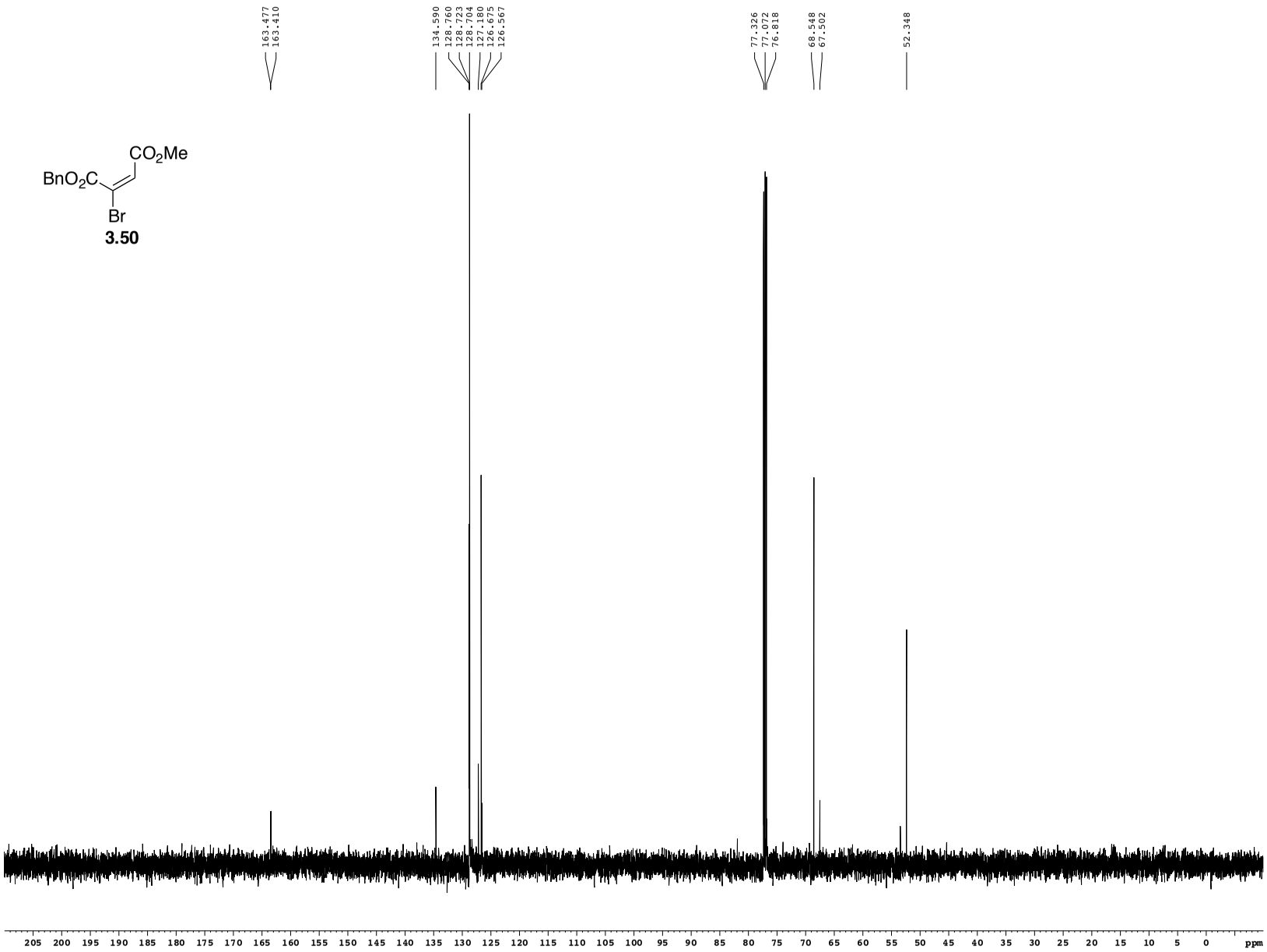
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128.760
128.723
128.704
127.180
126.675
126.567
77.326
77.072
76.818
68.548
67.502
52.348
CO2Me
BnO2C
Br
3.50
205 200 195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 ppm


7.409
7.396
7.385
7.378
7.367
7.353
7.341
7.323
7.306
7.290
7.260
7.073
7.057
6.861
6.845
6.273
6.230
5.335
5.222
3.792
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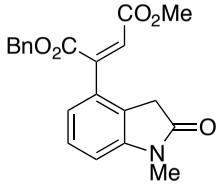
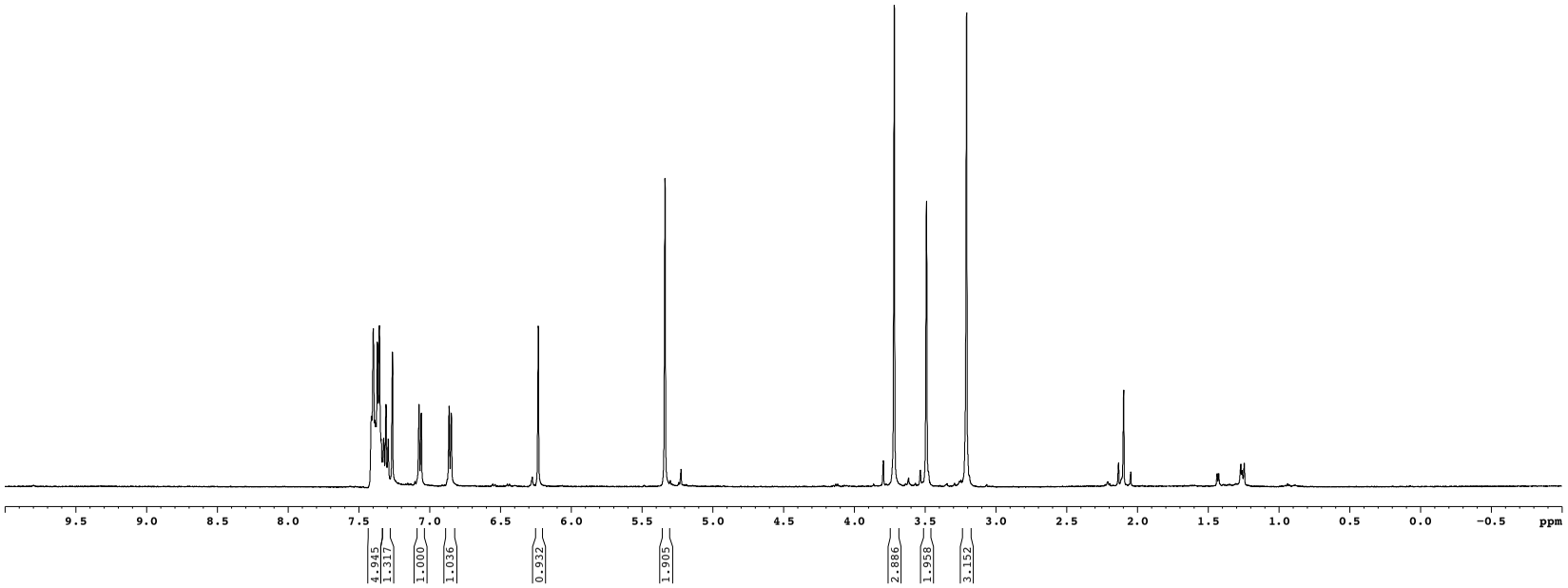
1.258
1.243


CO2Me
BnO2C
O
N
Me

3.51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8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
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1.317
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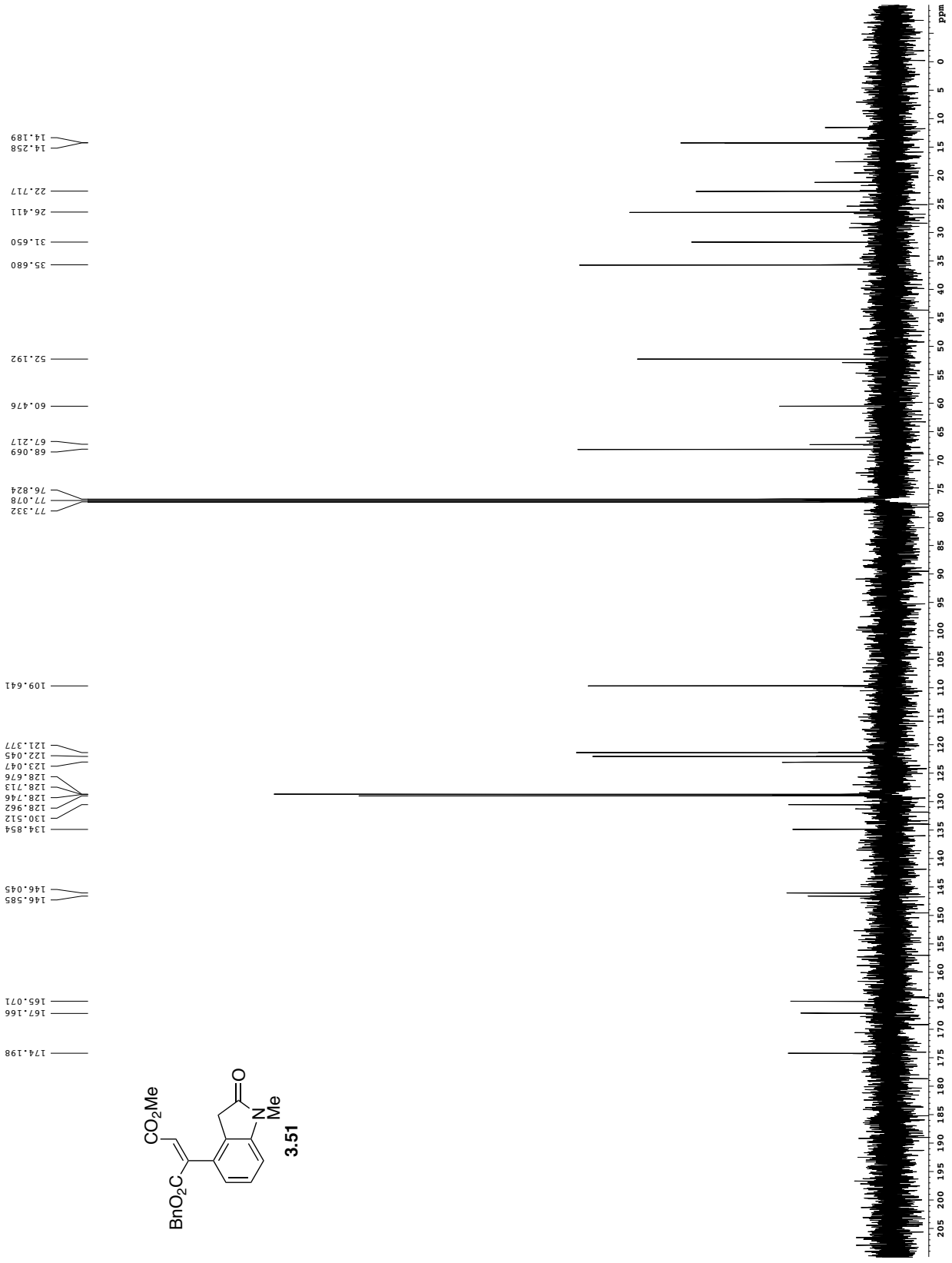
1.036
0.932
1.905
2.886
1.958
3.152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14.258
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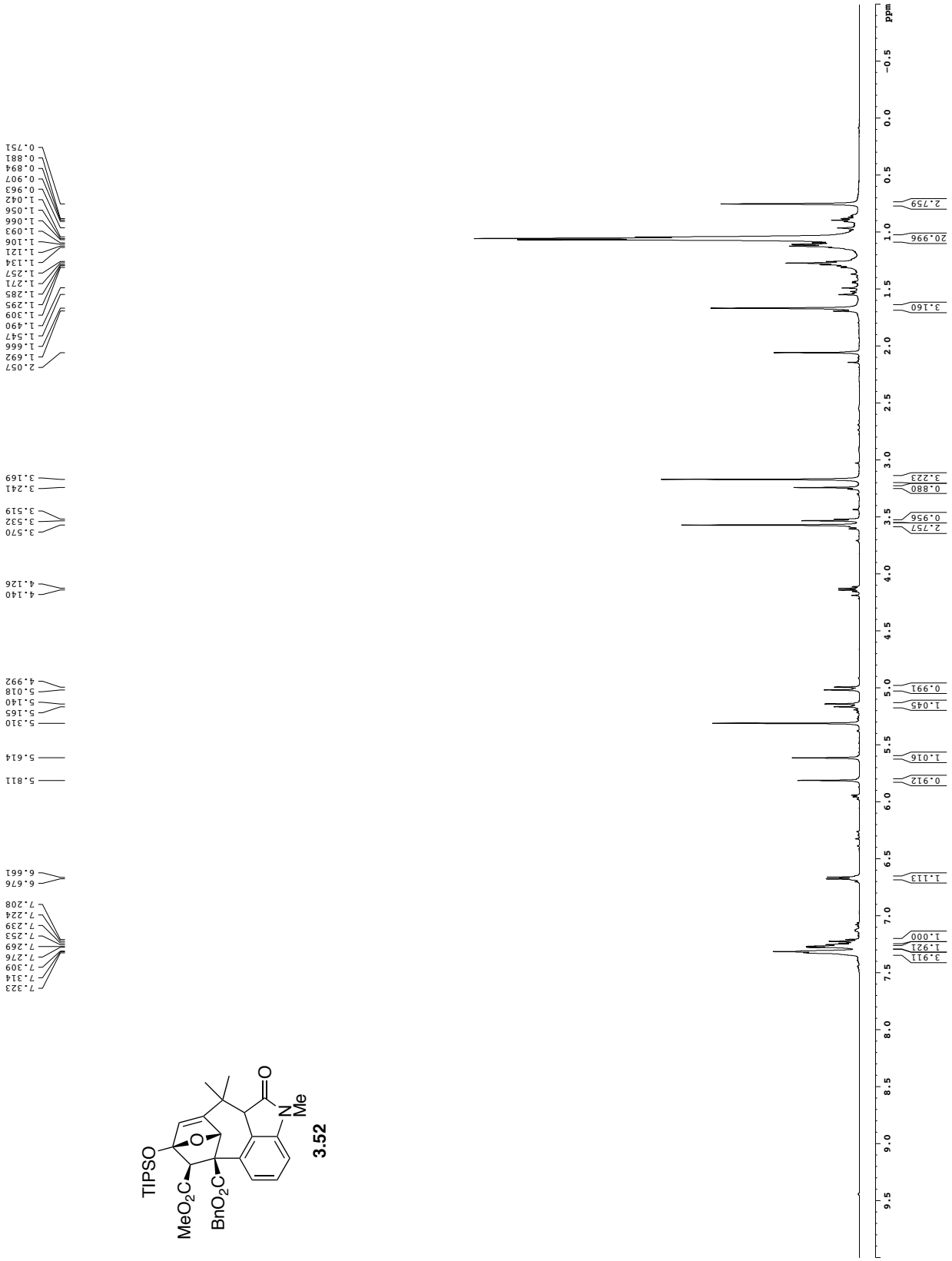
26.411
31.650
35.680
52.192
60.476
67.217
68.069
76.824
77.078
77.332
109.641
121.377
122.045
123.047
128.676
128.713
128.746
128.962
130.512
134.854
146.045
146.585
165.071
167.166
174.198
ppm
CO2Me
BnO2C
N
Me
O
3.51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1.066
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1.121
1.134
1.257
1.271
1.285
1.295
1.309
1.490
1.547
1.666
1.692
2.057
3.169
3.241
3.519
3.532
3.570
4.126
4.140
4.992
5.018
5.140
5.165
5.310
5.614
5.811
6.661
6.676
7.208
7.224
7.239
7.253
7.269
7.276
7.309
7.314
7.323
TIPSO
MeO2C
BnO2C
O
N
Me
3.52
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
3.911
1.921
1.000
1.113
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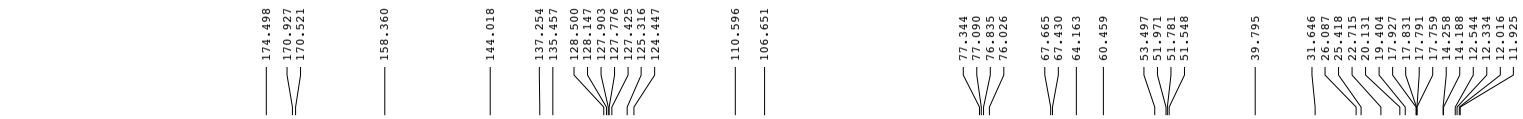
2.759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170.521
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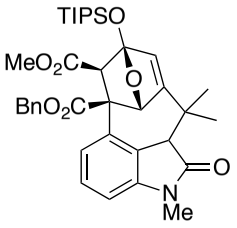
128.500
128.147
127.903
127.776
127.425
125.316
124.447
110.596
106.651
77.344
77.090
76.835
76.026
67.665
67.430
64.163
60.459
53.497
51.971
51.781
51.548
39.795
31.646
26.087
25.418
22.715
20.131
19.404
17.927
17.831
17.791
17.759
14.258
14.188
12.544
12.334
12.016
11.925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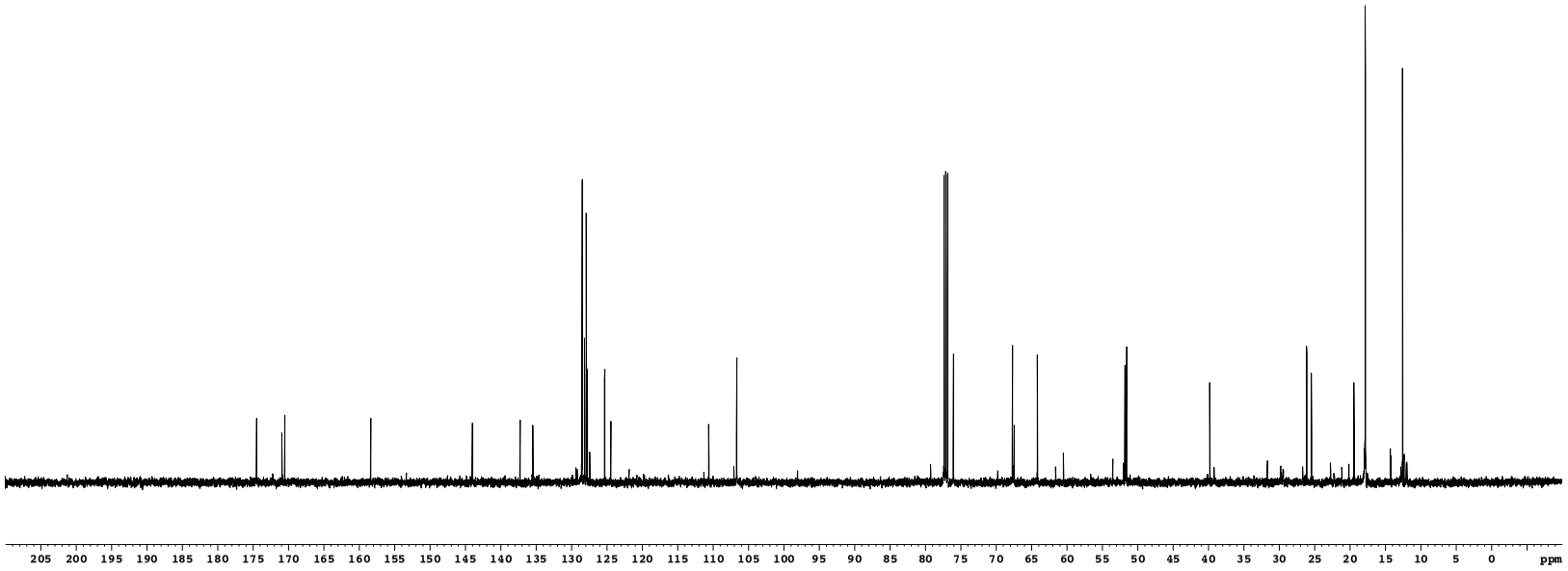
MeO2C
BnO2C
O
O
N
Me

3.52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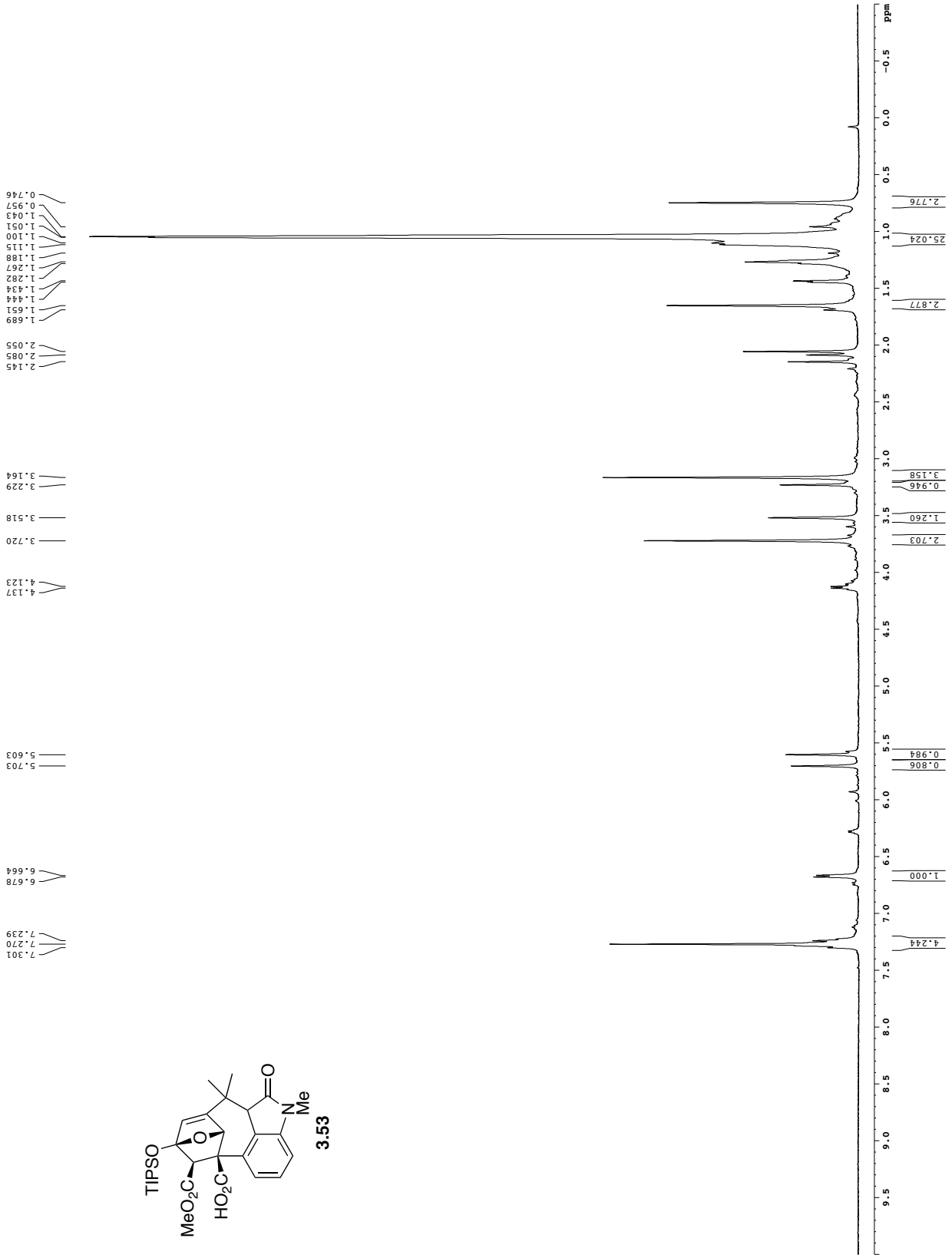
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0.957
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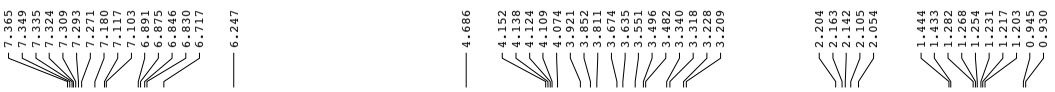
1.051
1.100
1.115
1.188
1.267
1.282
1.434
1.444
1.651
1.689
2.055
2.085
2.145
3.164
3.229
3.518
3.720
4.123
4.137
5.603
5.703
6.664
6.678
7.239
7.270
7.301
ppm
4.244
1.000
0.806
0.984
2.703
1.260
0.946
3.158
2.877
25.024
2.776
TIPSO
MeO2C
HO2C
O
N
Me
O
3.53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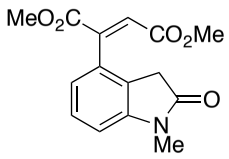
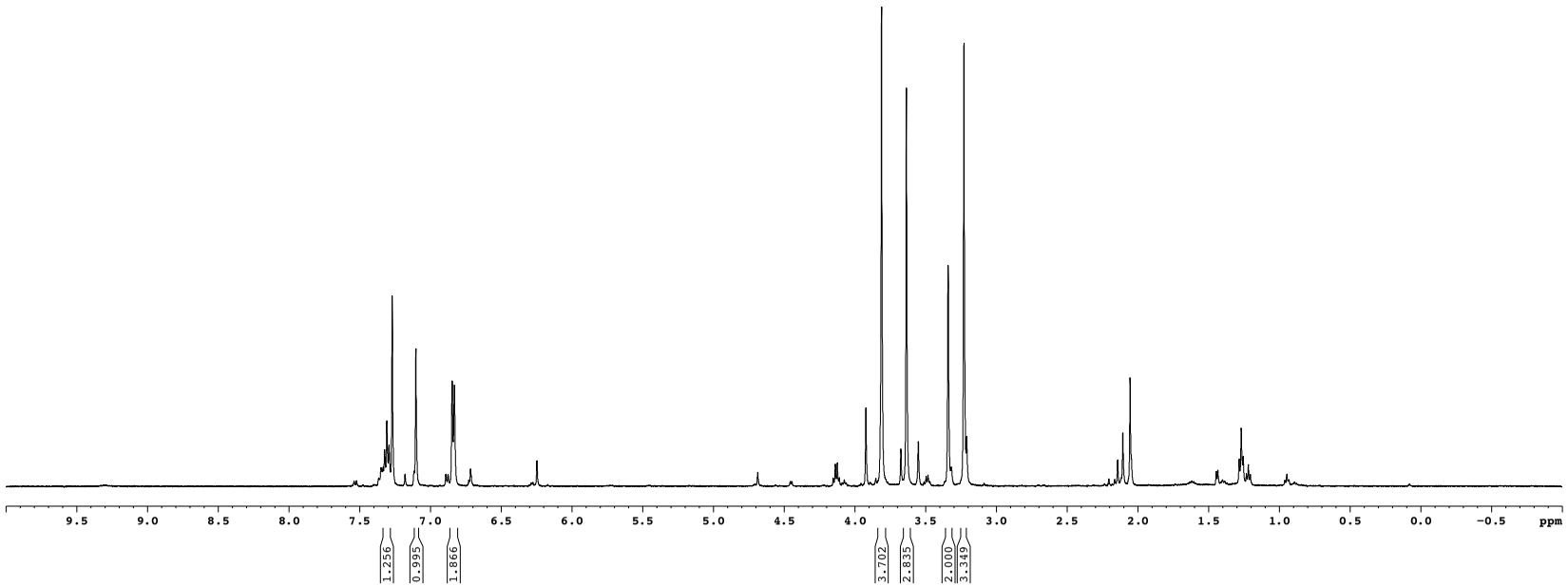
7.349
7.335
7.324
7.309
7.293
7.271
7.180
7.117
7.103
6.891
6.875
6.846
6.830
6.717
6.247
4.686
4.152
4.138
4.124
4.109
4.074
3.921
3.852
3.811
3.674
3.635
3.551
3.496
3.482
3.340
3.318
3.228
3.209
2.204
2.163
2.142
2.105
2.054
1.444
1.433
1.282
1.268
1.254
1.231
1.217
1.203
0.945
0.930


MeO2C
CO2Me
O
N
Me

3.57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8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
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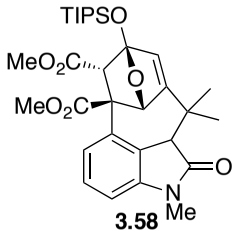
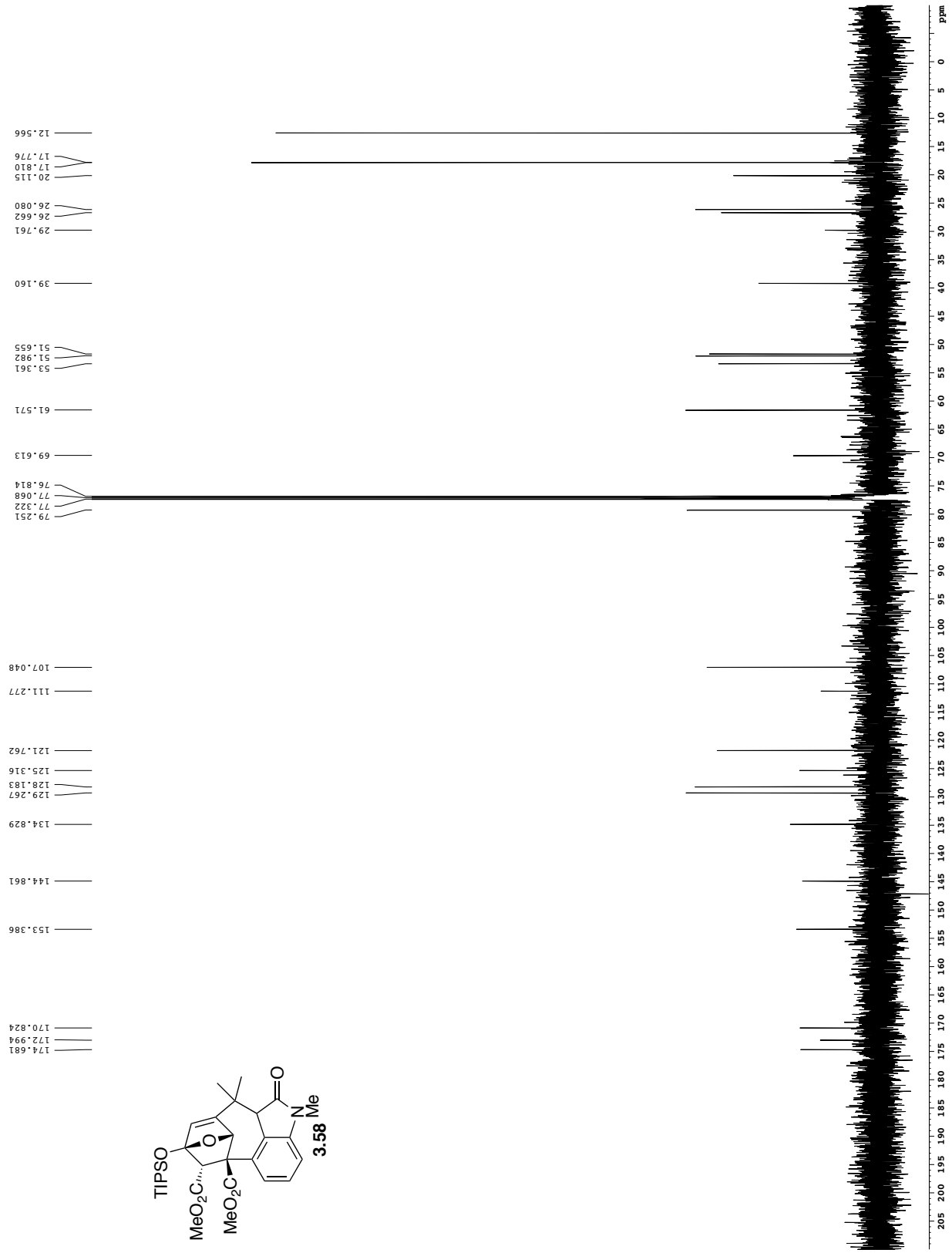
0.995
1.866
3.702
2.835
2.000
3.349


TIPSO
MeO2C
MeO2C
O
O
N
Me

3.58

7.270
7.130
7.114
7.099
6.724
6.708
6.663
6.647
5.929
5.578
4.163
3.715
3.600
3.523
3.165
2.148
2.113
2.047
1.699
1.567
1.448
1.437
1.263
1.219
1.146
1.130
1.116
1.102
1.091
1.063
1.052
1.038
0.964
ppm
1.000
0.996
1.019
1.012
0.986
0.990
2.995
1.040
3.016
3.095
3.091
3.556
19.859
3.065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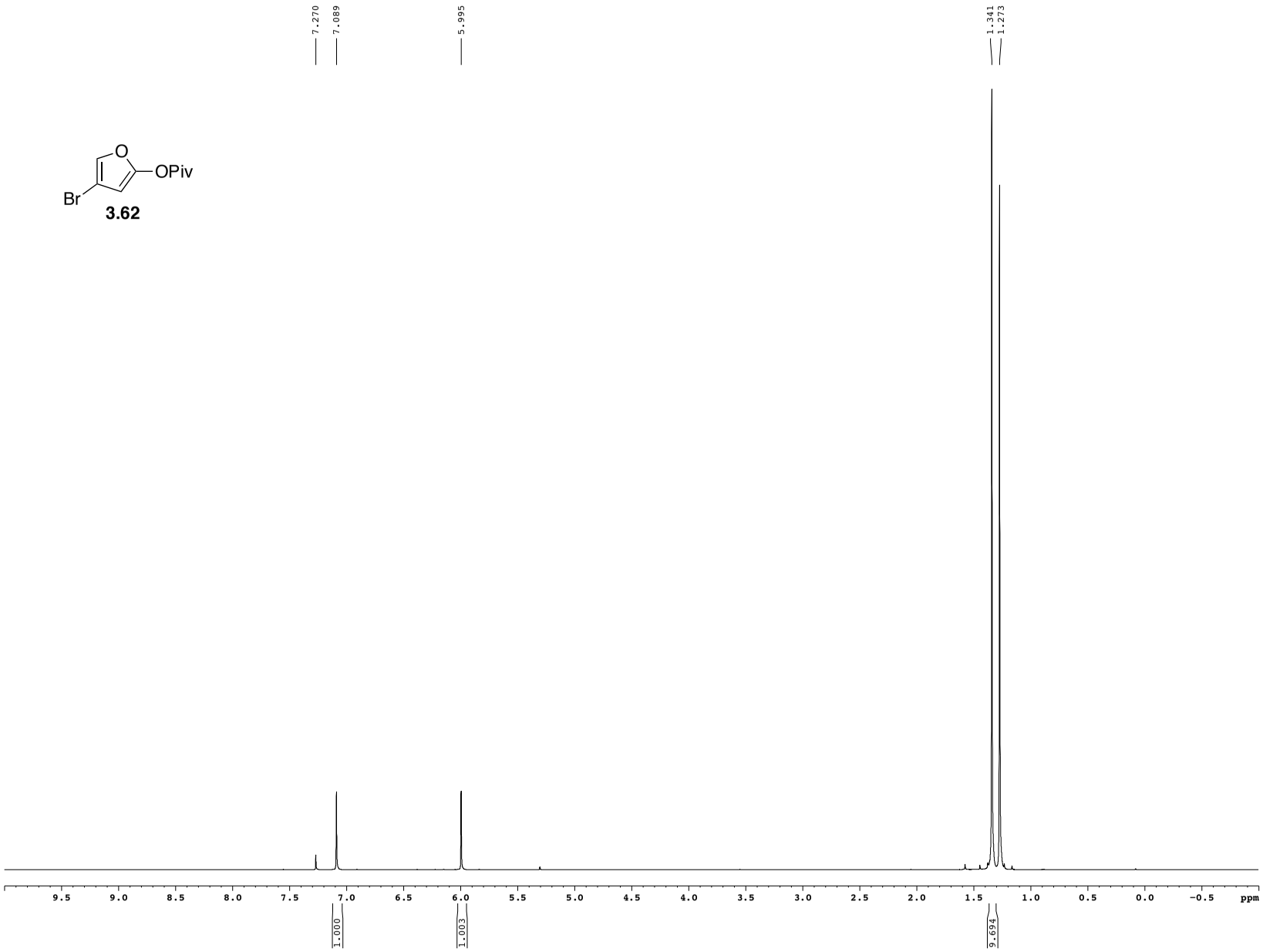
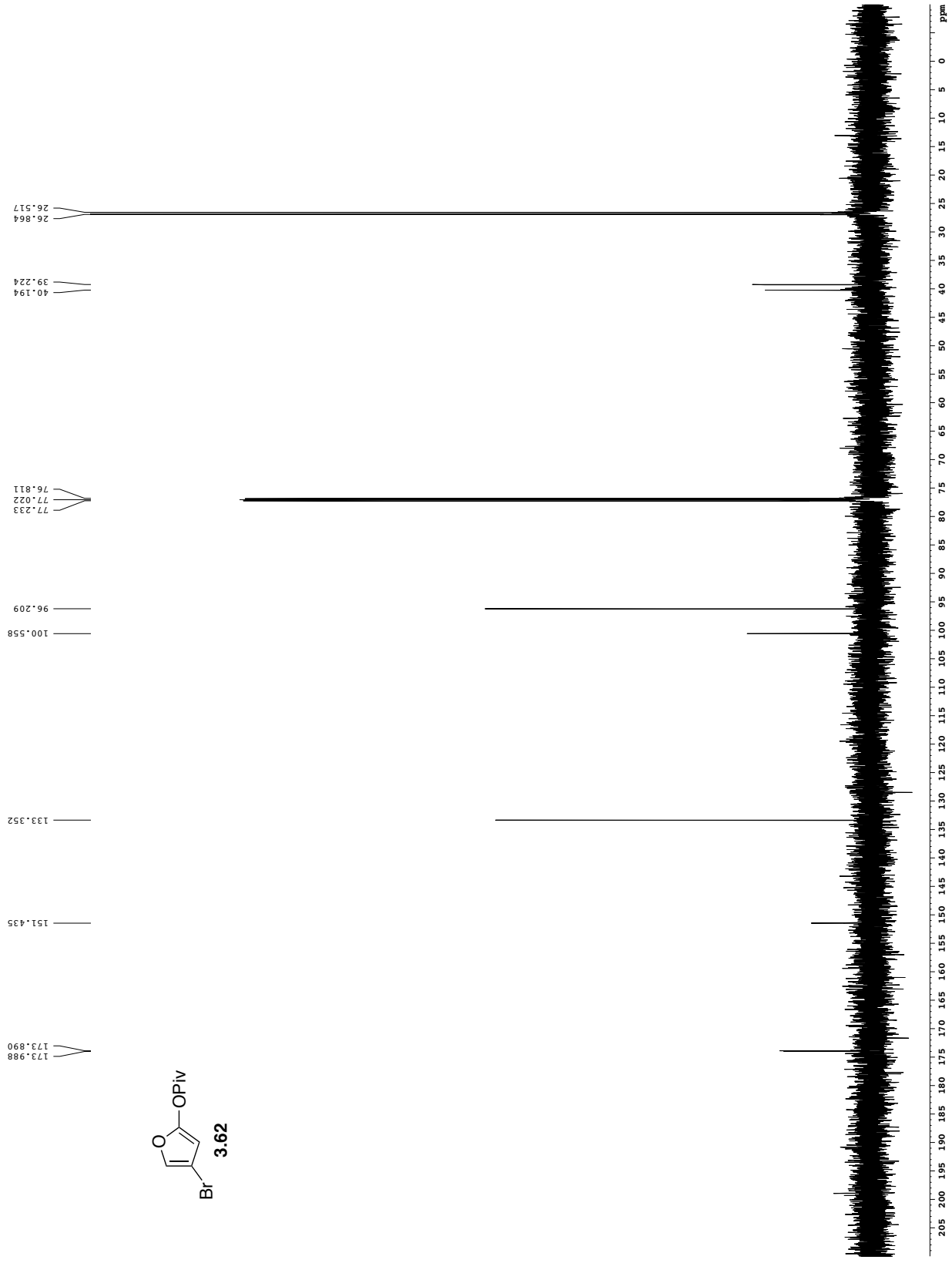
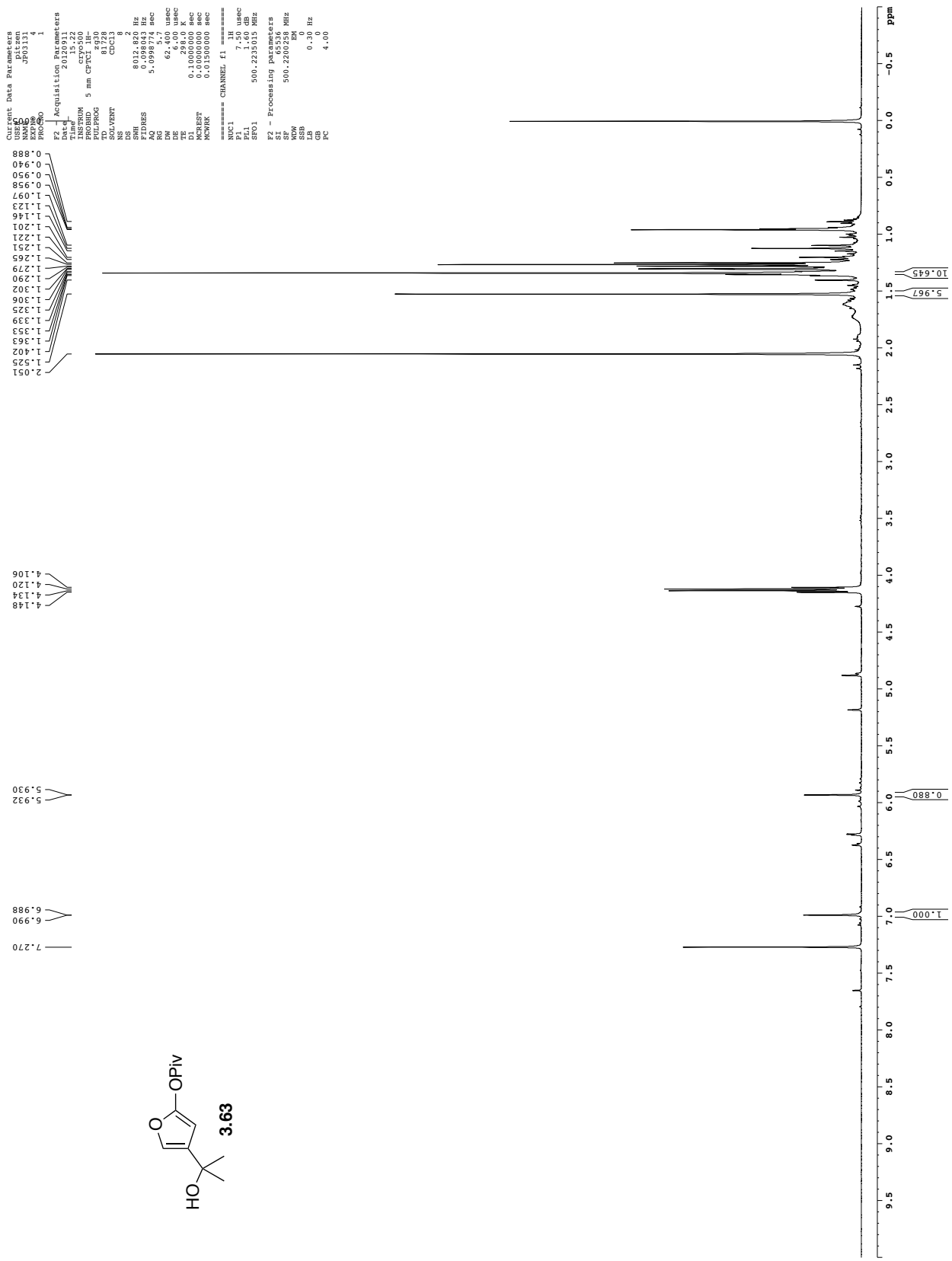
17.810
20.115
26.080
26.662
29.761
39.160
51.655
51.982
53.361
61.571
69.613
76.814
77.068
77.322
79.251
107.048
111.277
121.762
125.316
128.183
129.267
134.829
144.861
153.386
170.824
172.994
174.681
TIPSO
MeO2C
MeO2C
O
O
N
Me
3.58
ppm


7.270
7.089
5.995
1.341
1.273
O
OPiv
Br
3.62
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
1.000
1.003
9.694


26.517
26.864
39.224
40.194
76.811
77.022
77.233
96.209
100.558
133.352
151.435
173.890
173.988
OPiv
O
Br
3.62
ppm


Current Data Parameters
F2 - Acquisition Parameters
F2 - Processing parameters
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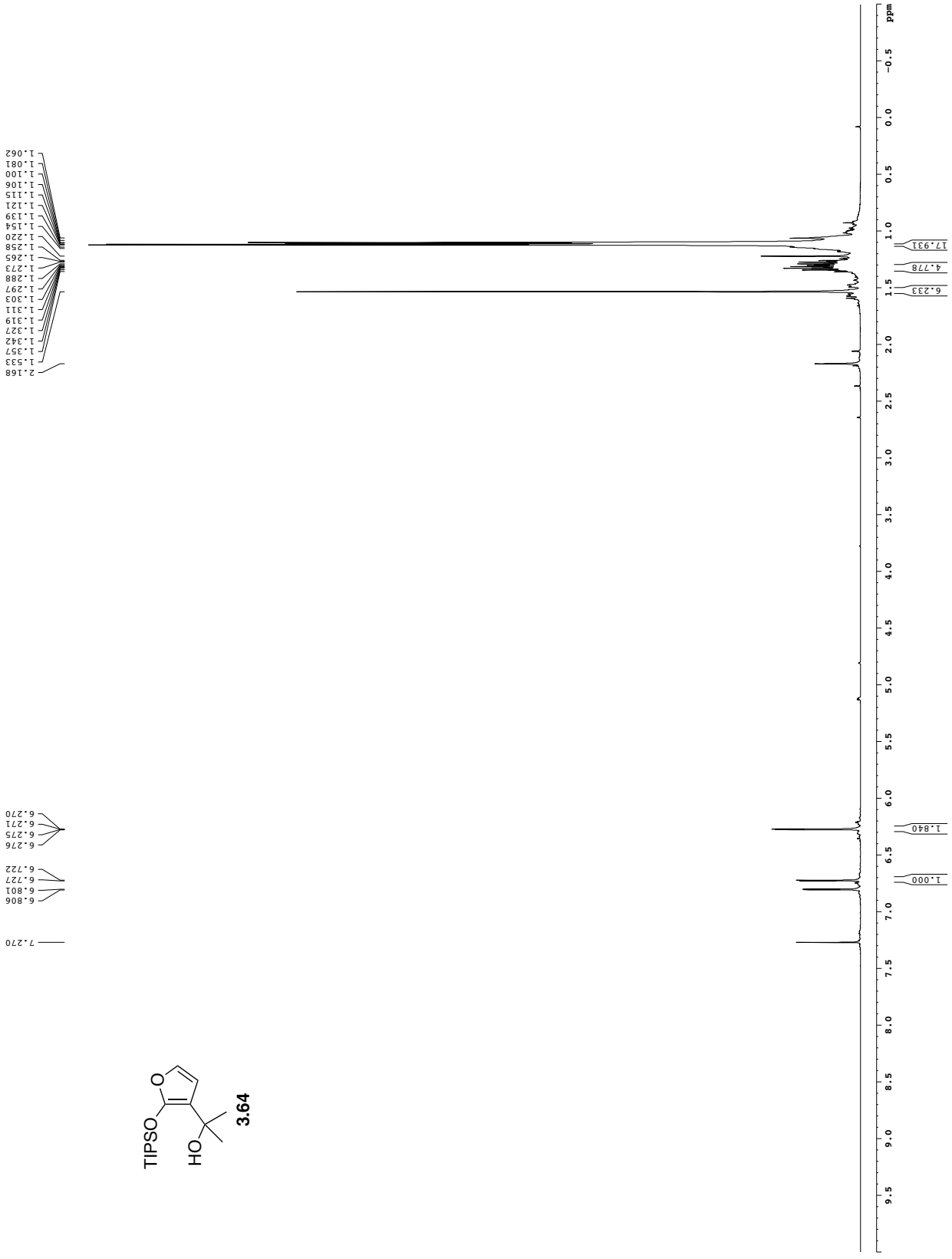
0.950
0.958
1.097
1.123
1.146
1.201
1.221
1.251
1.265
1.279
1.290
1.302
1.306
1.325
1.339
1.353
1.363
1.402
1.525
2.051
4.106
4.120
4.134
4.148
5.930
5.932
6.988
6.990
7.270
10.645
5.967
0.880
1.000
ppm
OPiv
O
HO
3.63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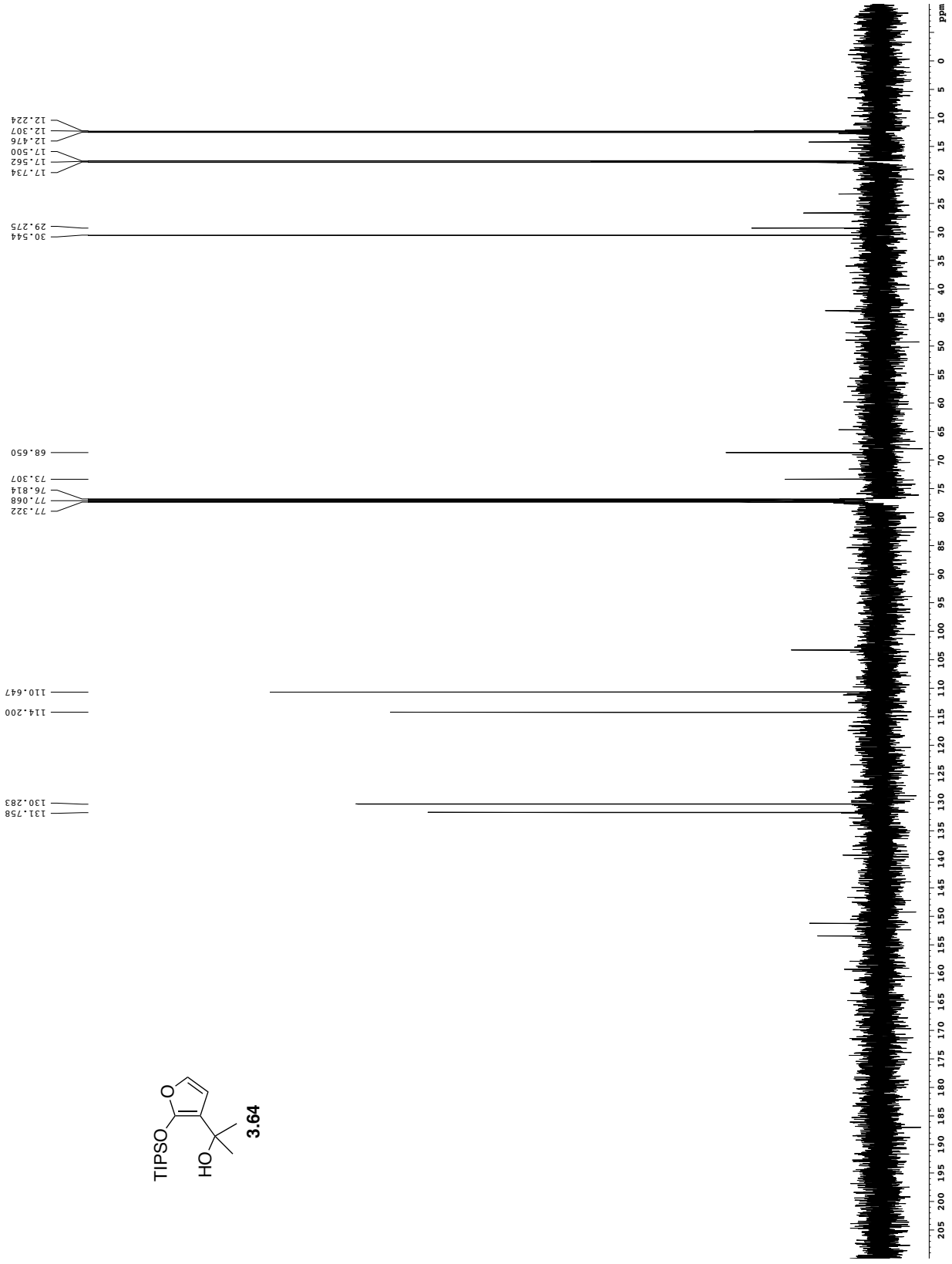
1.081
1.100
1.106
1.115
1.121
1.139
1.154
1.220
1.258
1.265
1.273
1.288
1.297
1.303
1.311
1.319
1.327
1.342
1.357
1.533
2.168
6.270
6.271
6.275
6.276
6.722
6.727
6.801
6.806
7.270
17.931
4.778
6.233
1.840
1.000
ppm
TIPSO
HO
3.64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12.307
12.476
17.500
17.562
17.734
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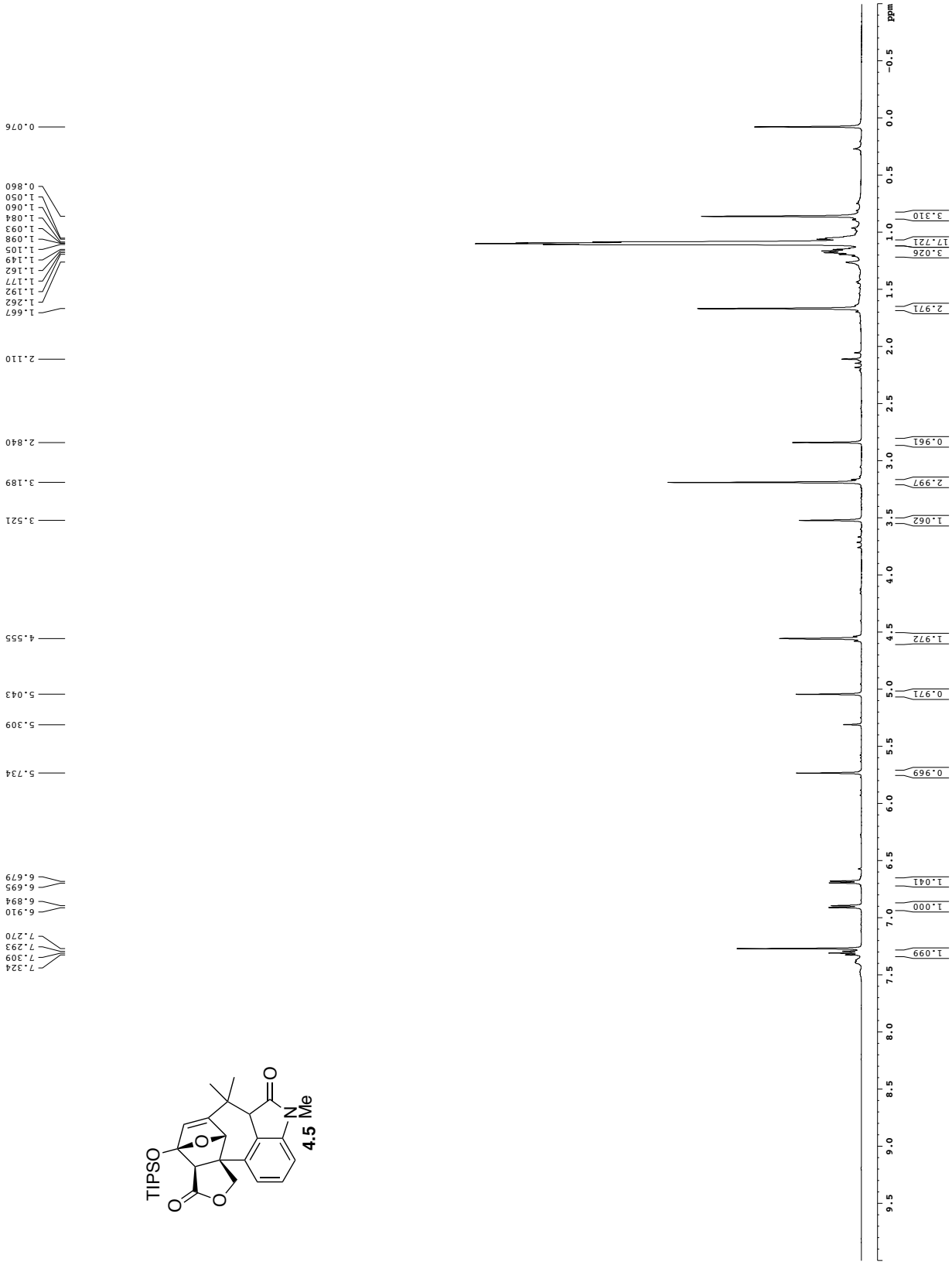
30.544
68.650
73.307
76.814
77.068
77.322
110.647
114.200
130.283
131.758
TIPSO
O
HO
3.64
ppm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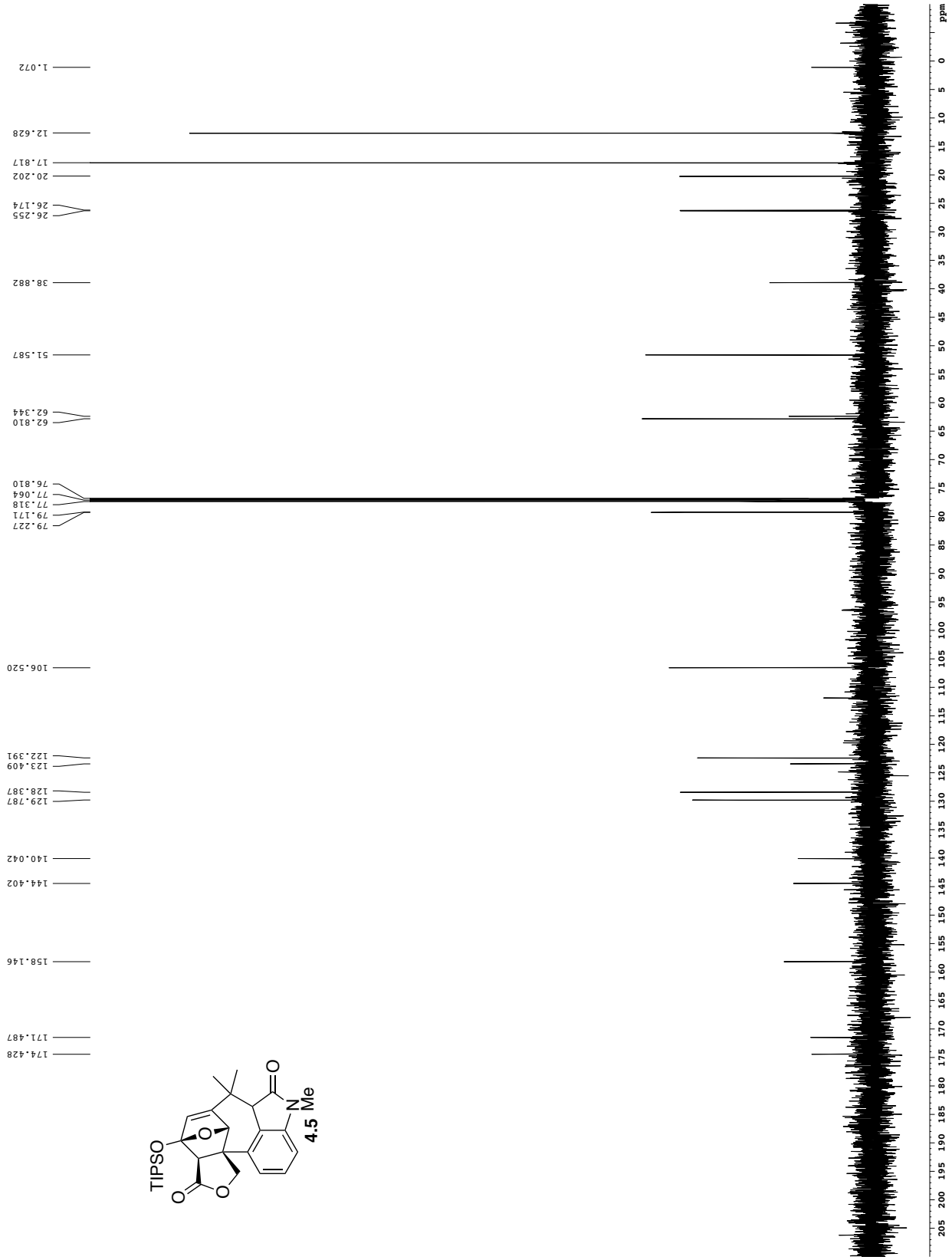
1.098
1.105
1.149
1.162
1.177
1.192
1.262
1.667
2.110
2.840
3.189
3.521
4.555
5.043
5.309
5.734
6.679
6.695
6.894
6.910
7.270
7.293
7.309
7.324
ppm
1.099
1.000
1.041
0.969
0.971
1.972
1.062
2.997
0.961
2.971
3.026
17.721
3.310
TIPSO
O
O
O
O
N
Me
4.5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51.587
62.344
62.810
76.810
77.064
77.318
79.171
79.227
106.520
122.391
123.409
128.387
129.787
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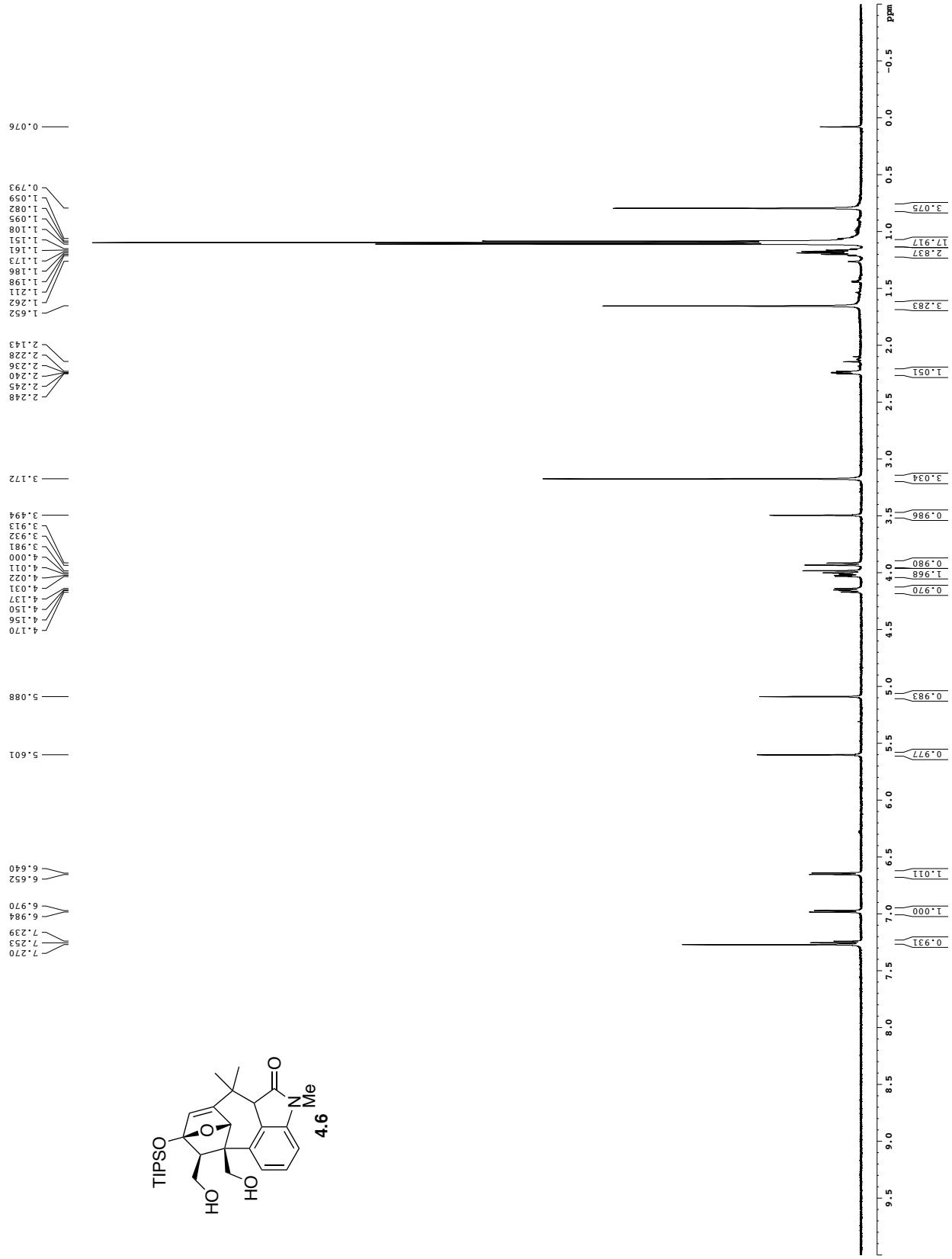
144.402
158.146
171.487
174.428
ppm
TIPSO
O
O
O
N
Me
4.5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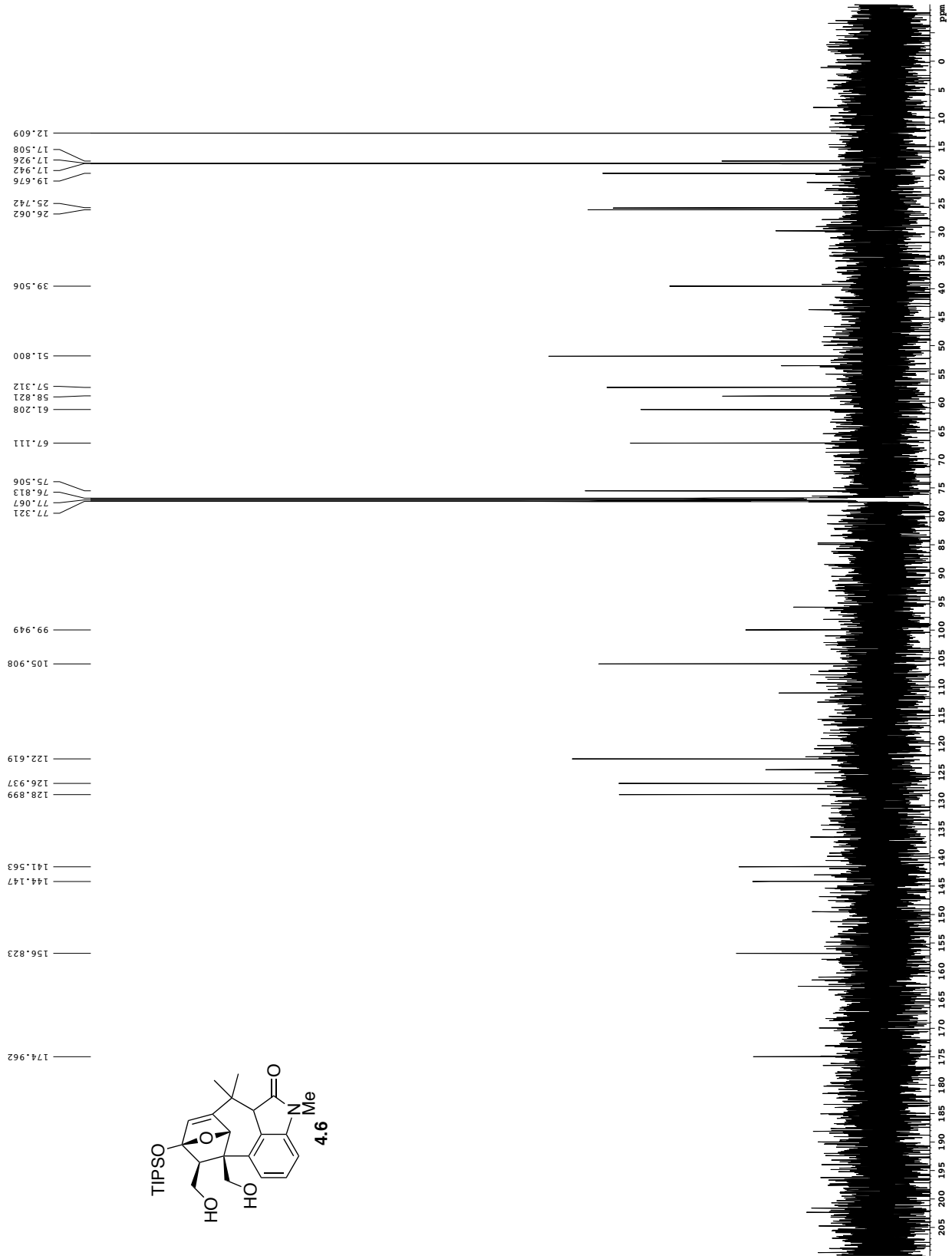
1.082
1.095
1.108
1.151
1.161
1.173
1.186
1.198
1.211
1.262
1.652
2.143
2.228
2.236
2.240
2.245
2.248
3.172
3.494
3.913
3.932
3.981
4.000
4.011
4.022
4.031
4.137
4.150
4.156
4.170
5.088
5.601
6.640
6.652
6.970
6.984
7.239
7.253
7.270
ppm
3.075
17.917
2.837
3.283
1.051
3.034
0.986
0.980
1.968
0.970
0.983
0.977
1.011
1.000
0.931
TIPSO
HO
HO
O
N
Me
O
4.6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17.942
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39.506
51.800
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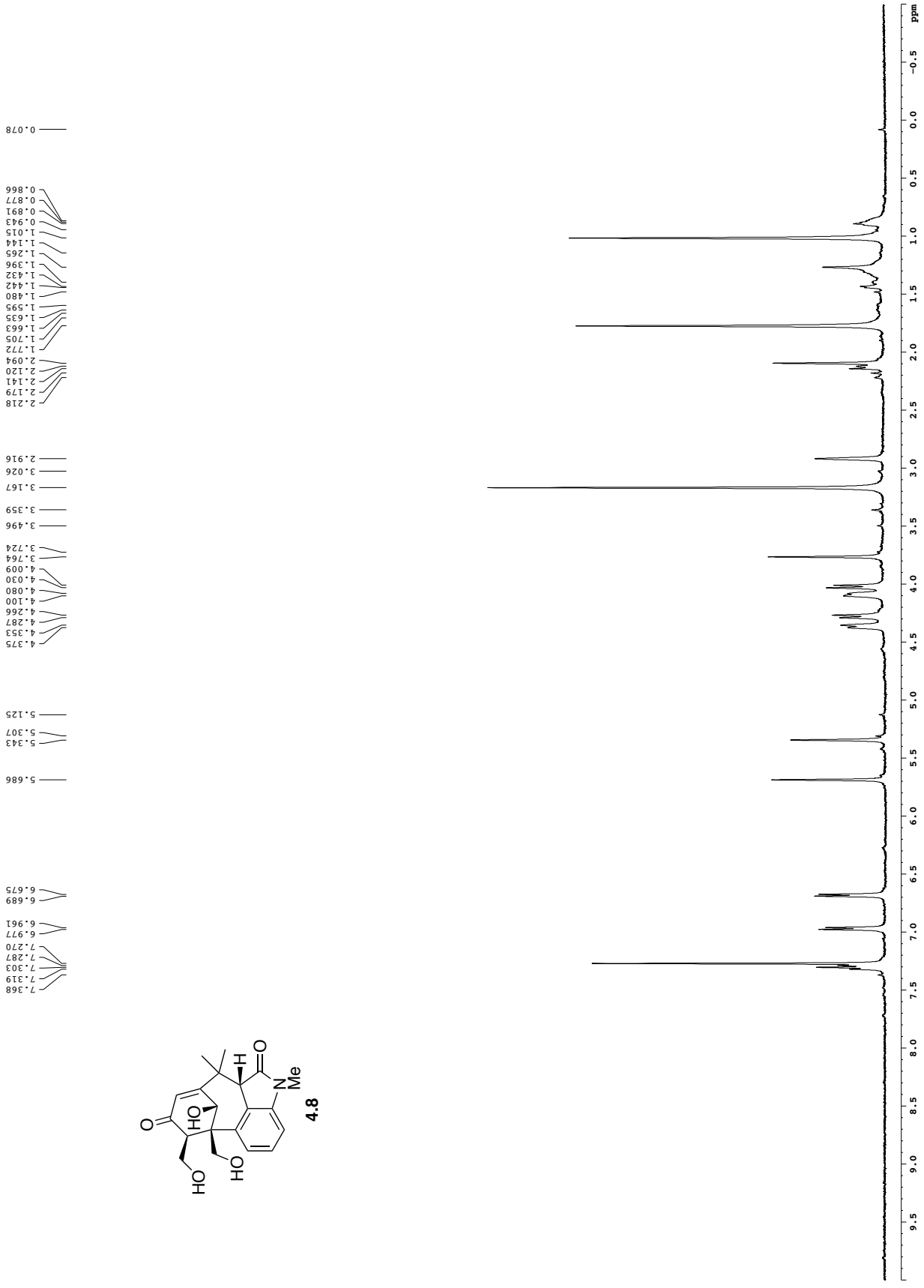
58.821
61.208
67.111
75.506
76.813
77.067
77.321
99.949
105.908
122.619
126.937
128.899
141.563
144.147
156.823
174.962
TIPSO
HO
HO
O
N
Me
O
4.6
ppm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1.265
1.396
1.432
1.442
1.480
1.595
1.635
1.663
1.705
1.772
2.094
2.120
2.141
2.179
2.218
2.916
3.026
3.167
3.359
3.496
3.724
3.764
4.009
4.030
4.080
4.100
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4.353
4.375
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6.675
6.689
6.961
6.977
7.270
7.287
7.303
7.319
7.368
ppm
9.5
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8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5

O
HO
HO
HO
H
O
N
Me

4.8

0.076
0.782
0.850
0.873
0.887
1.261
1.386
1.616
1.777
2.100
2.122
2.144
2.154
2.167
2.182
2.203
2.259
2.278
2.293
2.301
2.316
3.052
3.193
3.579
3.875
3.897
4.116
4.131
4.186
4.200
4.222
4.967
6.729
6.745
7.075
7.091
7.257
7.270
7.344
7.360
7.375
ppm
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7.5
7.0
6.5
6.0
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5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5
1.000
0.992
1.024
0.884
1.951
1.068
1.153
1.103
3.324
0.964
3.058
1.258
2.327
3.907
3.146

O
HO
H
O
N
Me
H
HO
HO

4.9

213.937
175.310
144.421
141.610
129.300
124.352
121.374
106.791
77.325
77.071
76.817
68.804
68.099
60.799
60.431
55.729
53.648
52.425
40.248
37.797
30.395
26.208
19.718
ppm
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5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
140
145
150
155
160
165
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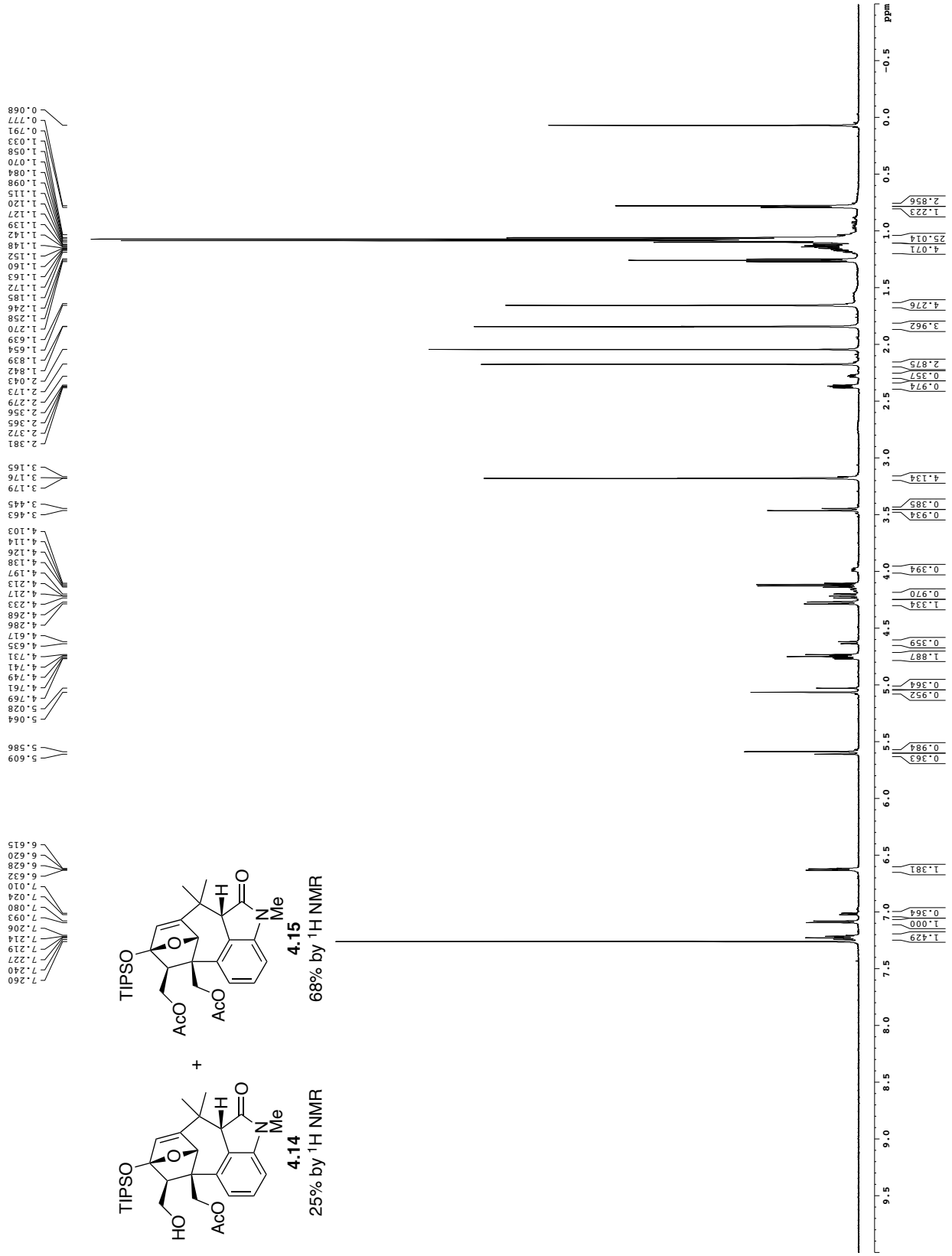
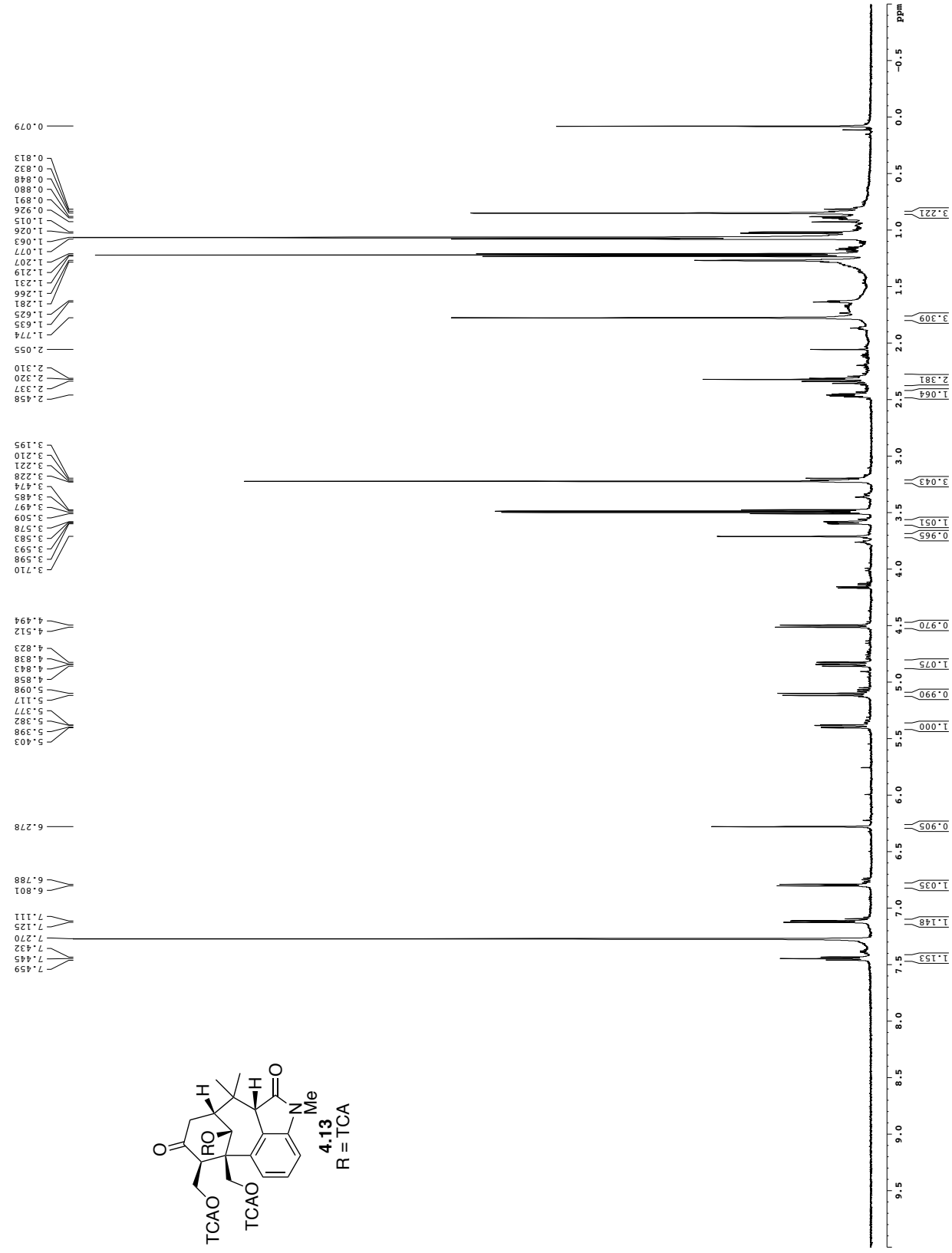
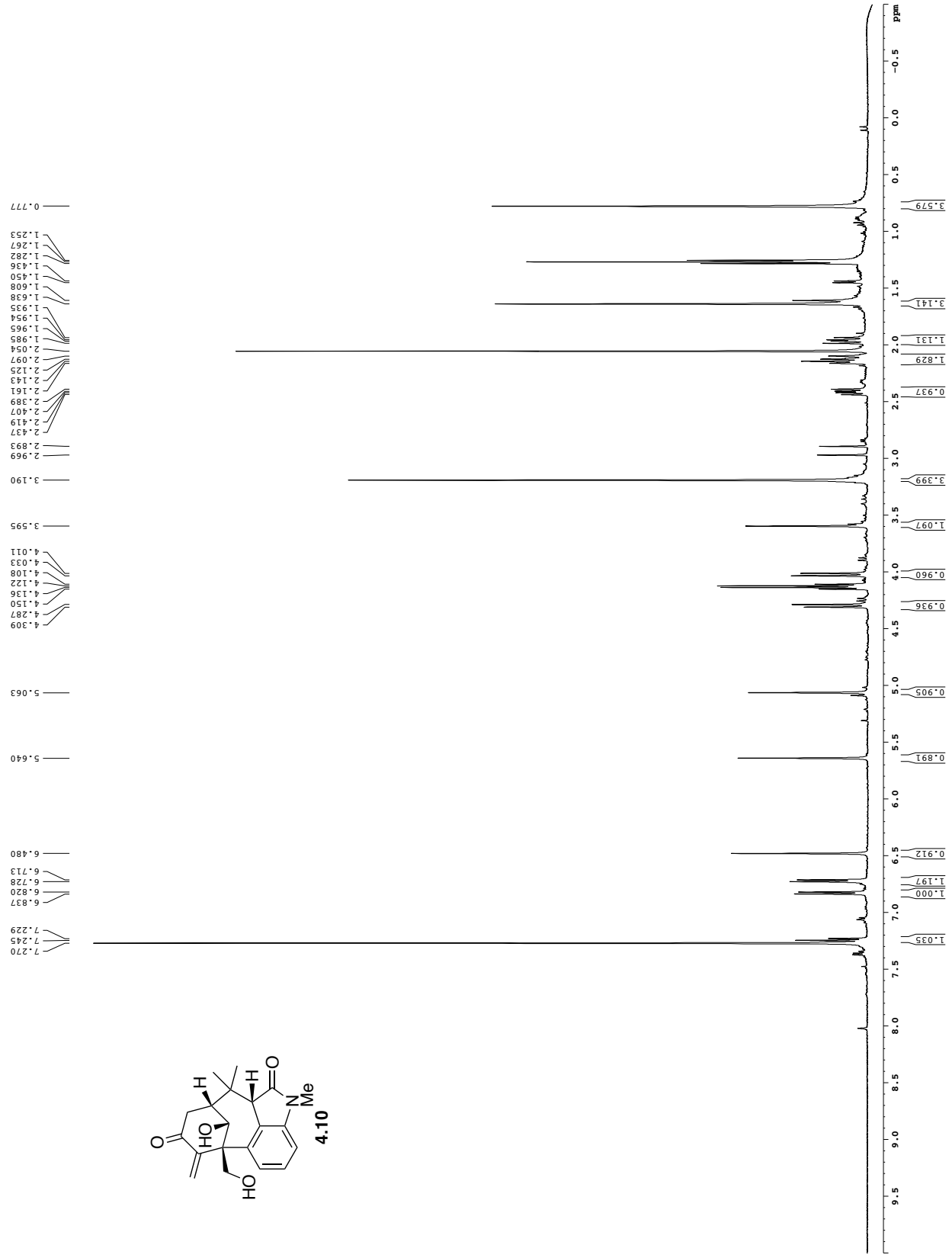
180
185
190
195
200
205
210
215
O
H
HO
HO
HO
H
O
N
Me

4.9


TIPSO
AcO
AcO
N
Me
O
H
O
4.15
68% by ^{1}H NMR
+
TIPSO
HO
AcO
4.14
25% by ^{1}H NMR


0.079
0.813
0.832
0.848
0.880
0.891
0.926
1.015
1.026
1.063
1.077
1.207
1.219
1.231
1.266
1.281
1.625
1.635
1.774
2.055
2.310
2.320
2.337
2.458
3.195
3.210
3.221
3.228
3.474
3.485
3.497
3.509
3.578
3.583
3.593
3.598
3.710
4.494
4.512
4.823
4.838
4.843
4.858
5.098
5.117
5.377
5.382
5.398
5.403
6.278
6.788
6.801
7.111
7.125
7.270
7.432
7.445
7.459
1.153
1.148
1.035
0.905
1.000
0.990
1.075
0.970
0.965
1.051
3.043
1.064
2.381
3.309
3.221
ppm
TCAO
TCAO
RO
H
H
O
O
N
Me
4.13
R = TCA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1.954
1.965
1.985
2.054
2.097
2.125
2.143
2.161
2.389
2.407
2.419
2.437
2.893
2.969
3.190
3.595
4.011
4.033
4.108
4.122
4.136
4.150
4.287
4.309
5.063
5.640
6.480
6.713
6.728
6.820
6.837
7.229
7.245
7.270
3.579
3.141
1.131
1.829
0.937
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0.936
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0.891
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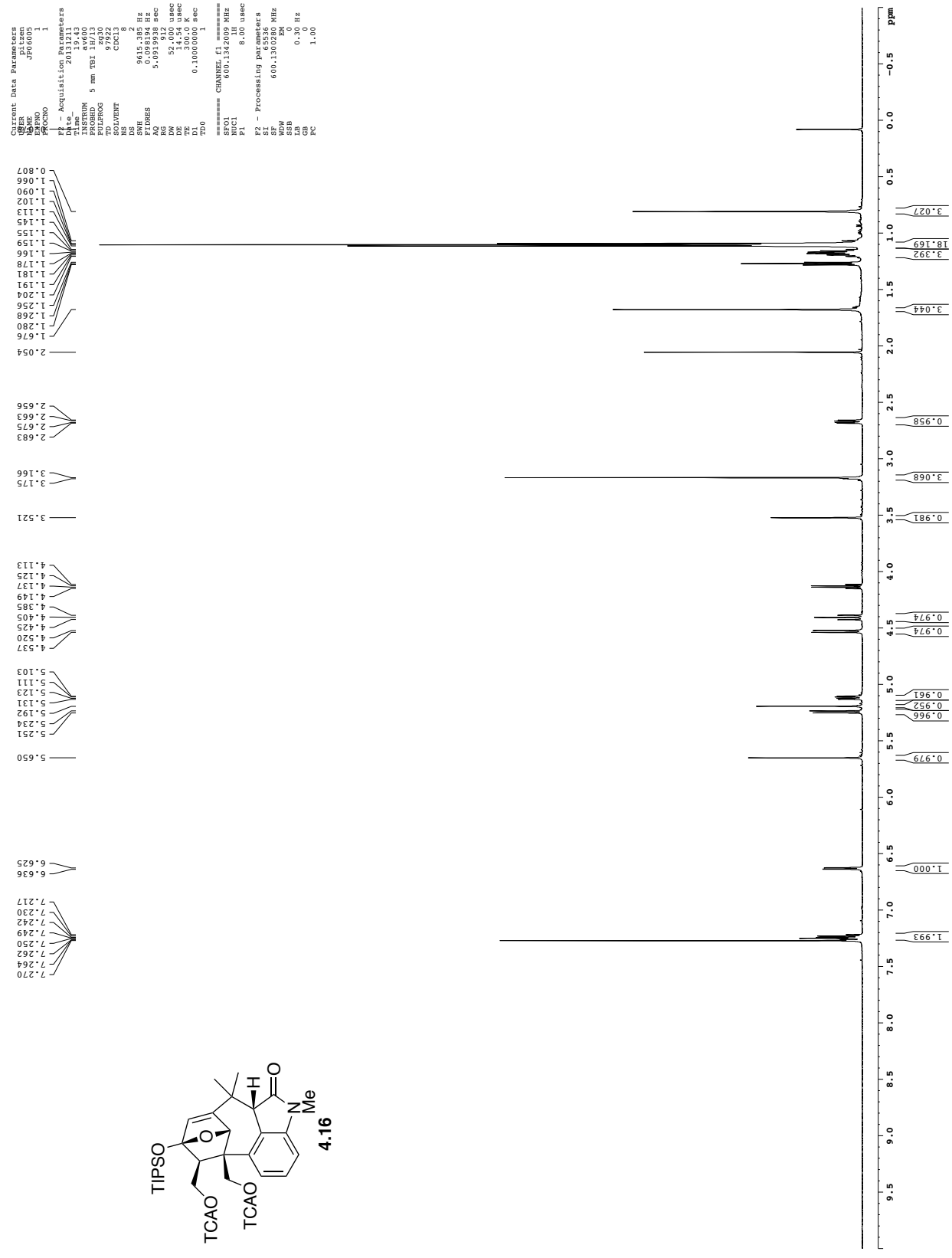
1.035
ppm
4.10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EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20131211
Time 19.43
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PROBHD 5 mm TBI 1H/13
PULPROG zg30
TD 79922
SOLVENT CDCl3
NS 8
DS 2
SWH 9615.385 Hz
FIDRES 0.098194 Hz
AQ 5.0919936 sec
RG 32
DW 52.000 usec
DE 14.54 usec
TE 300.0 K
D1 0.10000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 600.1342009 MHz
NUC1 1H
P1 8.00 usec
F2 - Processing parameters
SI 65536
SF 600.1300280 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
0.807
1.066
1.090
1.102
1.113
1.145
1.155
1.159
1.166
1.178
1.181
1.191
1.204
1.256
1.268
1.280
1.676
2.054
2.656
2.663
2.675
2.683
3.166
3.175
3.521
4.113
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4.137
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4.405
4.425
4.520
4.537
5.103
5.111
5.123
5.131
5.192
5.234
5.251
5.650
6.625
6.636
7.217
7.230
7.242
7.249
7.250
7.262
7.264
7.270
3.027
18.169
3.392
3.044
0.958
3.068
0.981
0.974
0.974
0.961
0.952
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1.993
ppm
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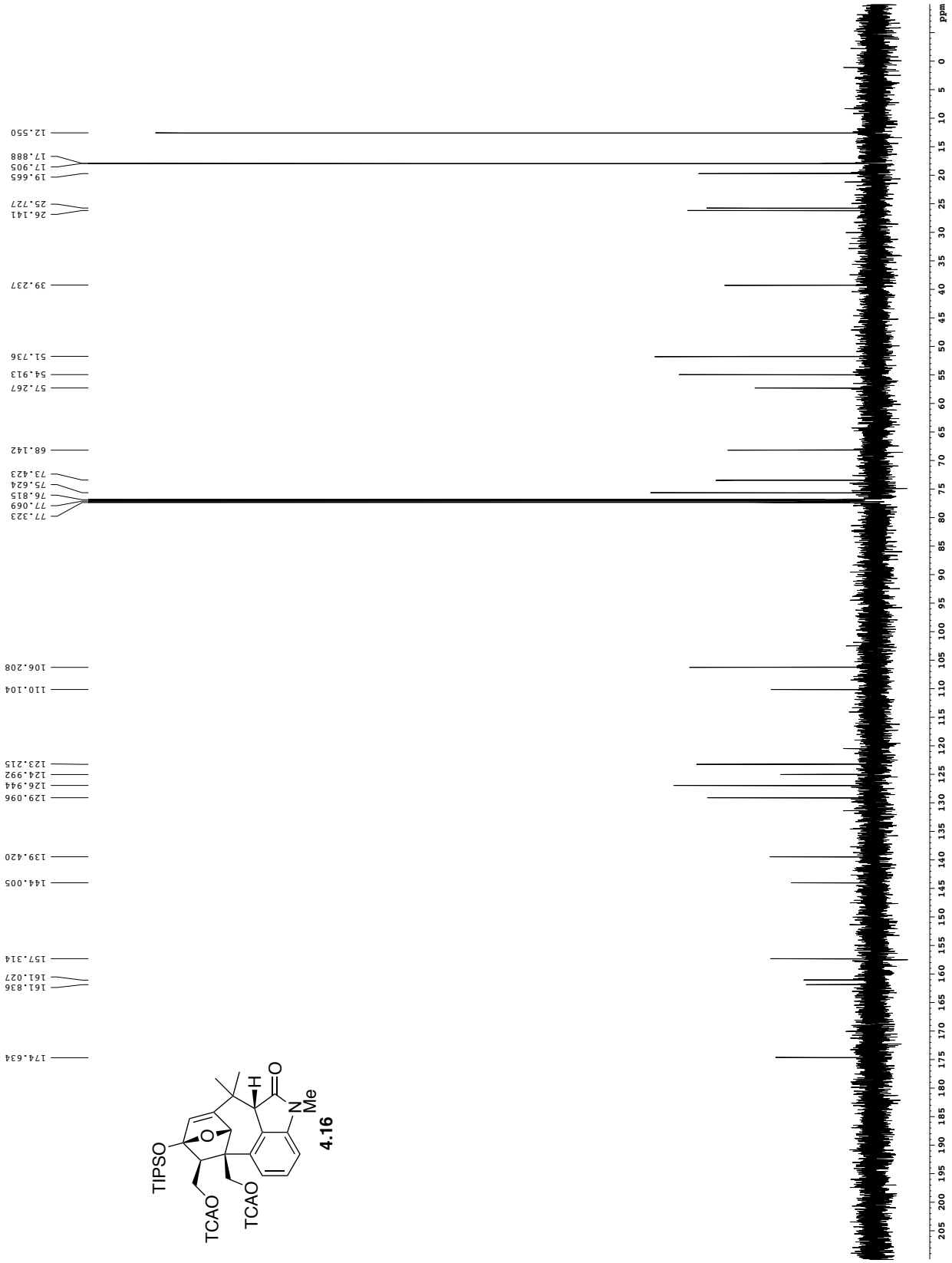
TCAO
TCAO
O
H
O
N
Me
4.16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25.727
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73.423
75.624
76.815
77.069
77.323
106.208
110.104
123.215
124.992
126.944
129.096
139.420
144.005
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174.634
ppm
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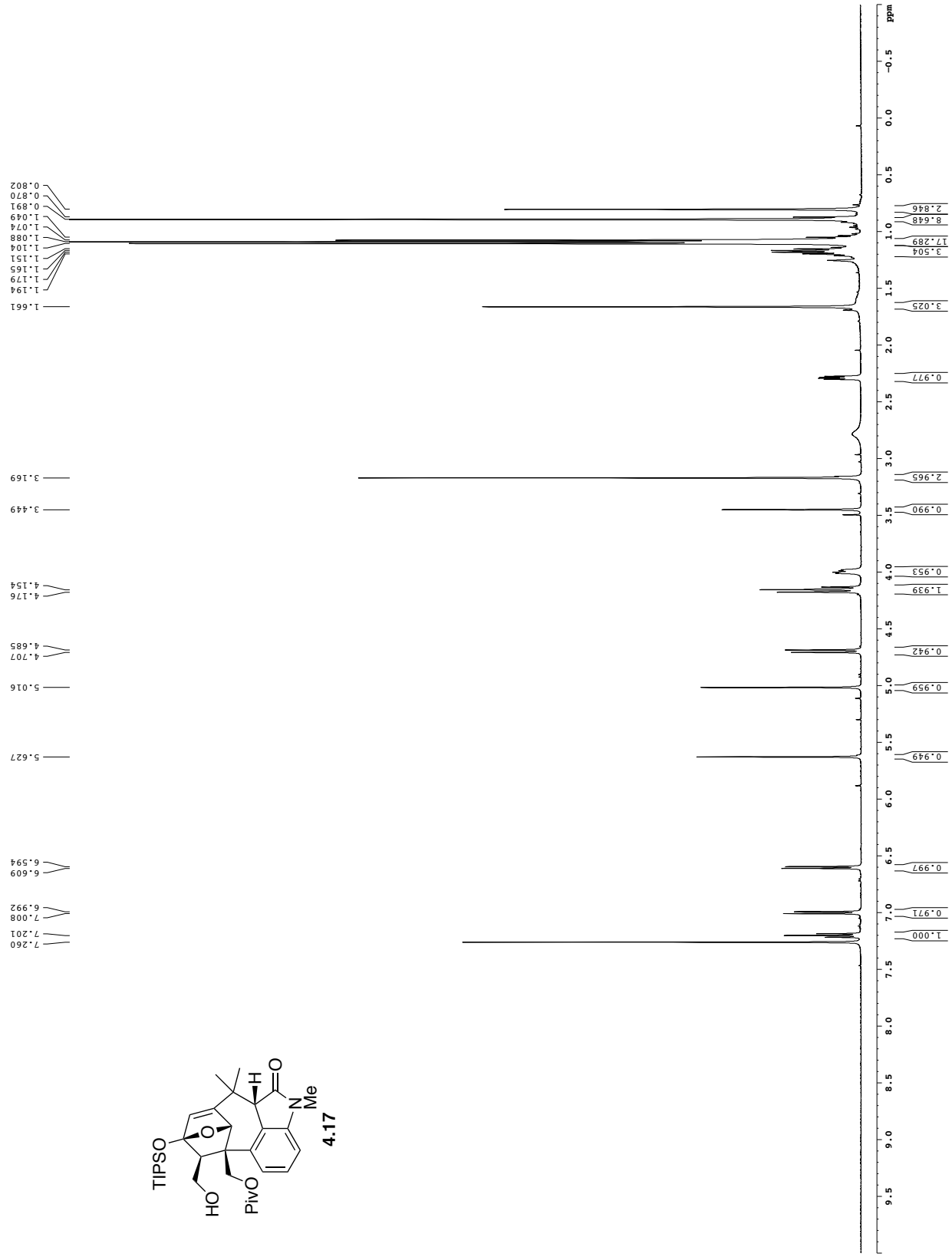
TCAO
TCAO
O
H
O
N
Me
4.16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3.449
4.154
4.176
4.685
4.707
5.016
5.627
6.594
6.609
6.992
7.008
7.201
7.260
ppm
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0.997
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0.949
5.0
0.959
4.5
0.942
4.0
1.939
0.953
3.5
0.990
3.0
2.965
2.5
0.977
2.0
3.025
1.5
17.289
3.504
1.0
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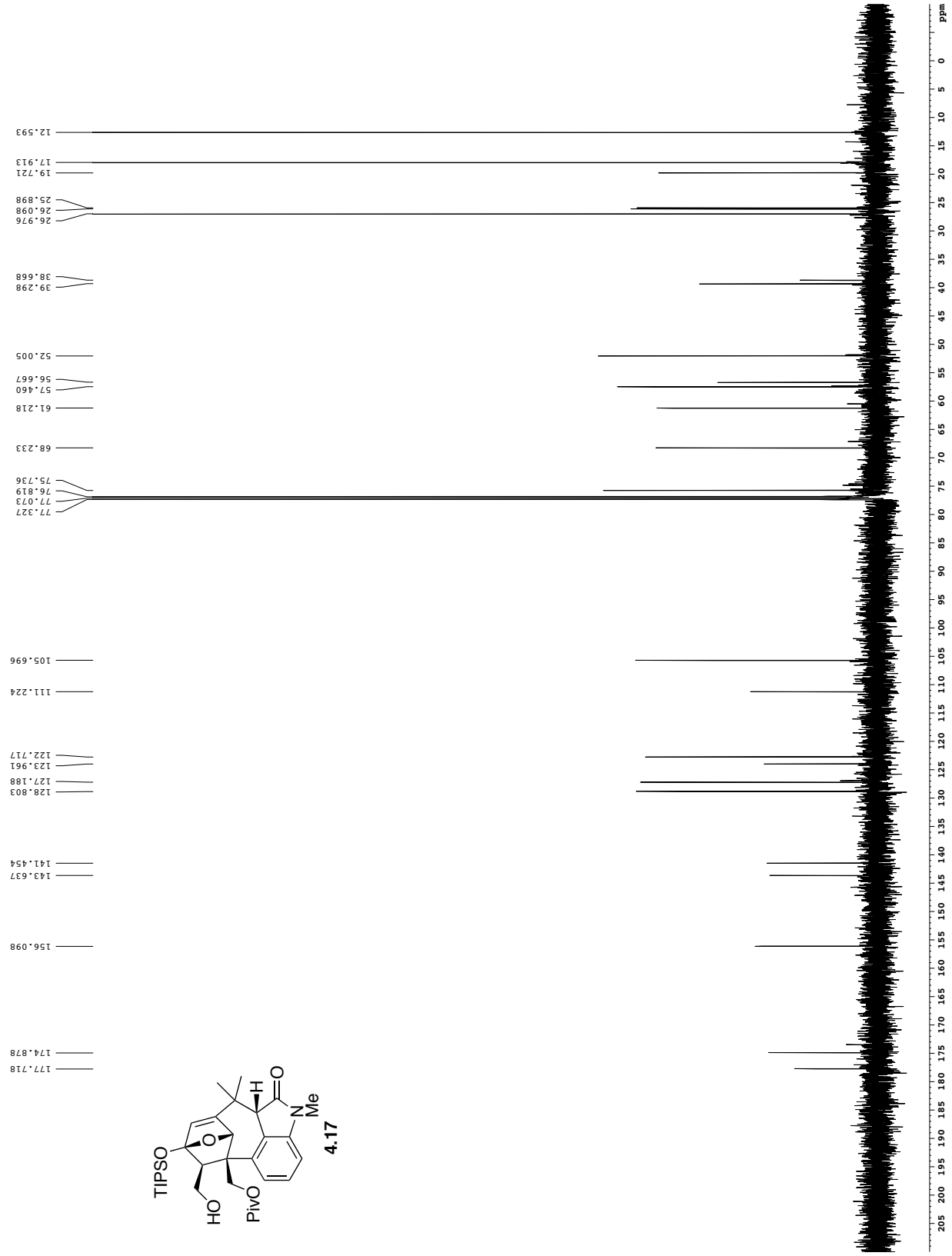
0.0
−0.5
TIPSO
O
HO
PivO
H
O
N
Me
4.17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19.721
25.898
26.098
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61.218
68.233
75.736
76.819
77.073
77.327
105.696
111.224
122.717
123.961
127.188
128.803
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174.878
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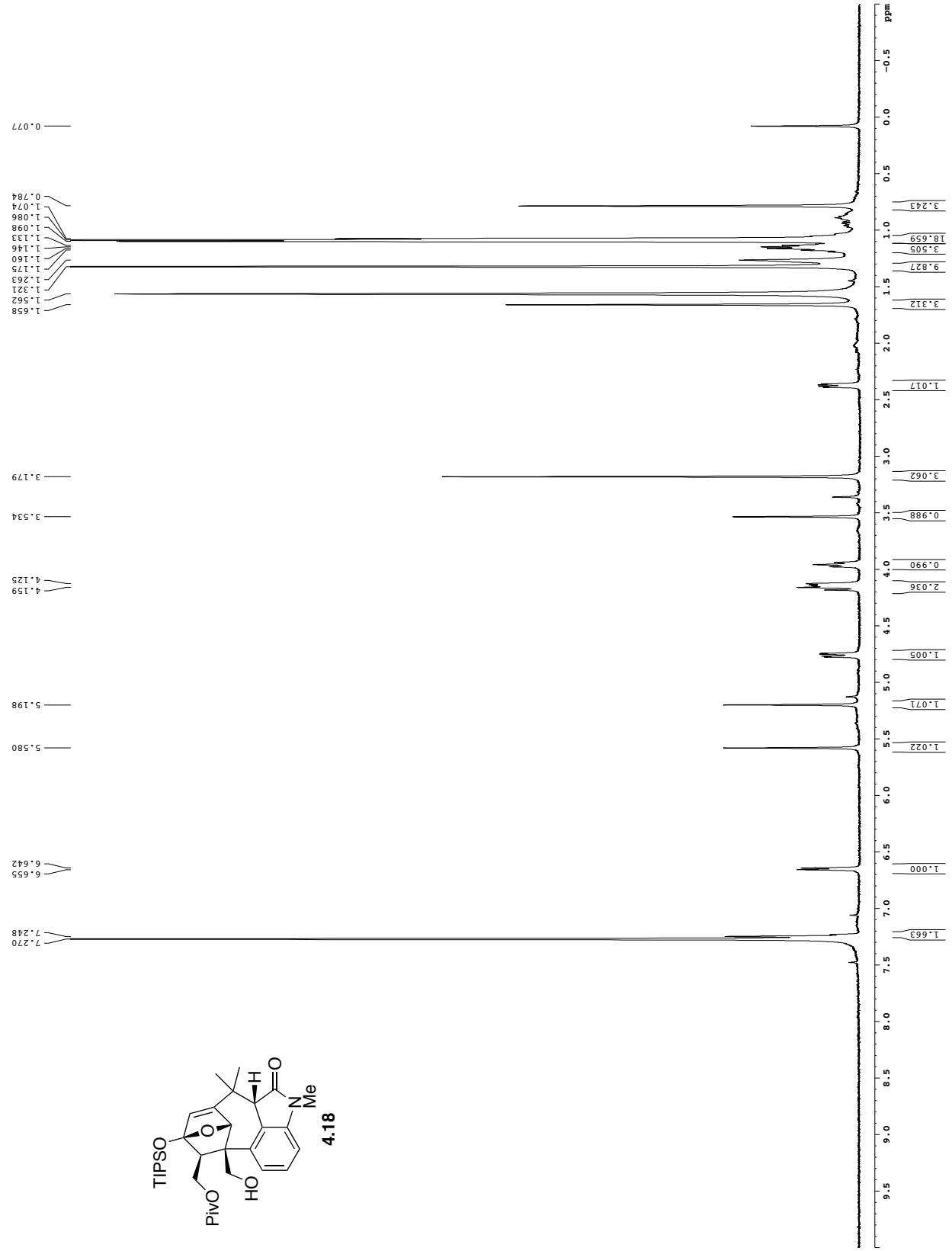
HO
PivO
O
H
O
N
Me
4.17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0.784
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1.086
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1.146
1.160
1.175
1.263
1.321
1.562
1.658
3.179
3.534
4.125
4.159
5.198
5.580
6.642
6.655
7.248
7.270
ppm
3.243
18.659
3.505
9.827
3.312
1.017
3.062
0.988
0.990
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1.071
1.022
1.000
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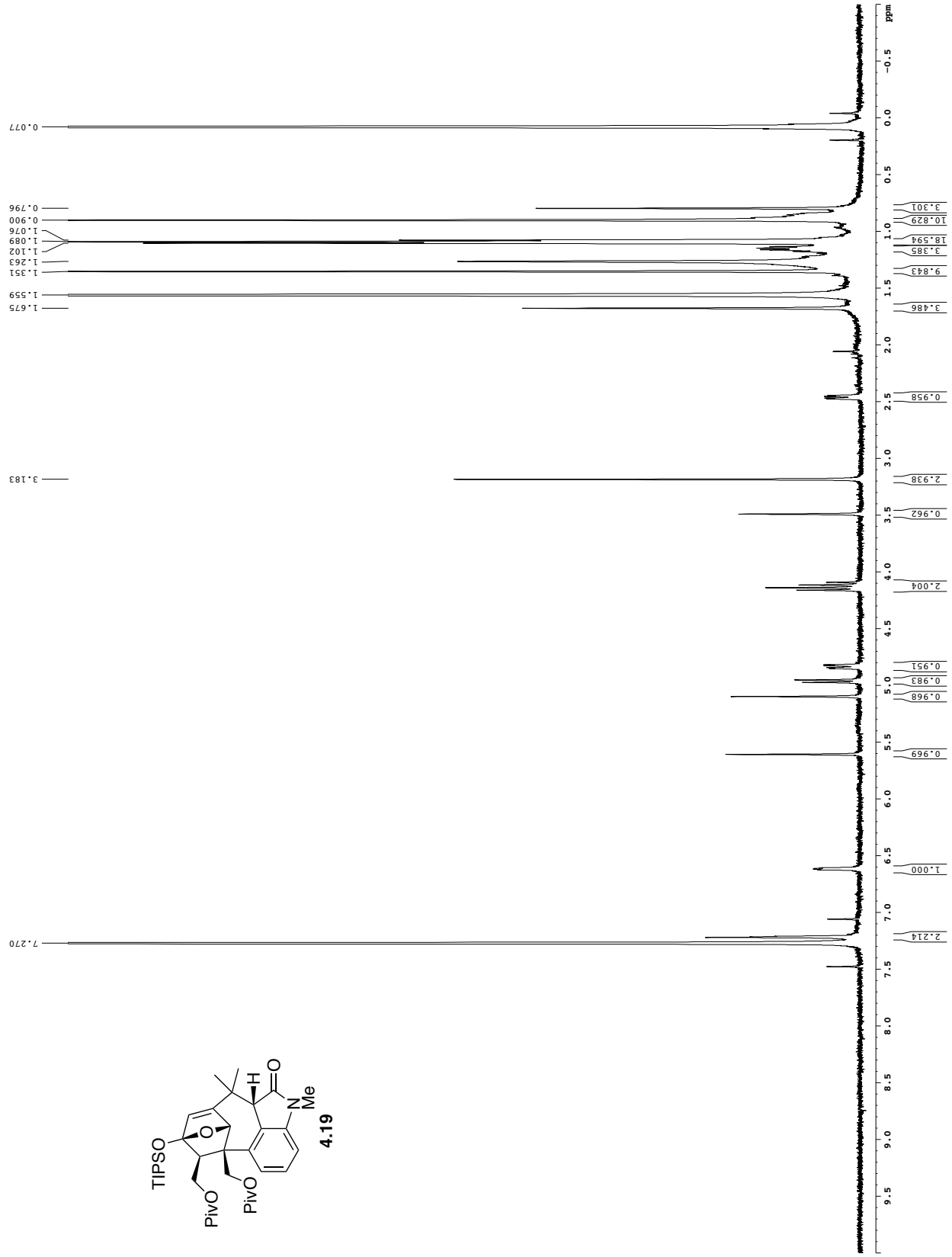
PivO
HO
O
H
O
N
Me
4.18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1.089
1.076
0.900
0.796
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10.829
18.594
3.385
9.843
3.486
0.958
2.938
0.962
2.004
0.951
0.983
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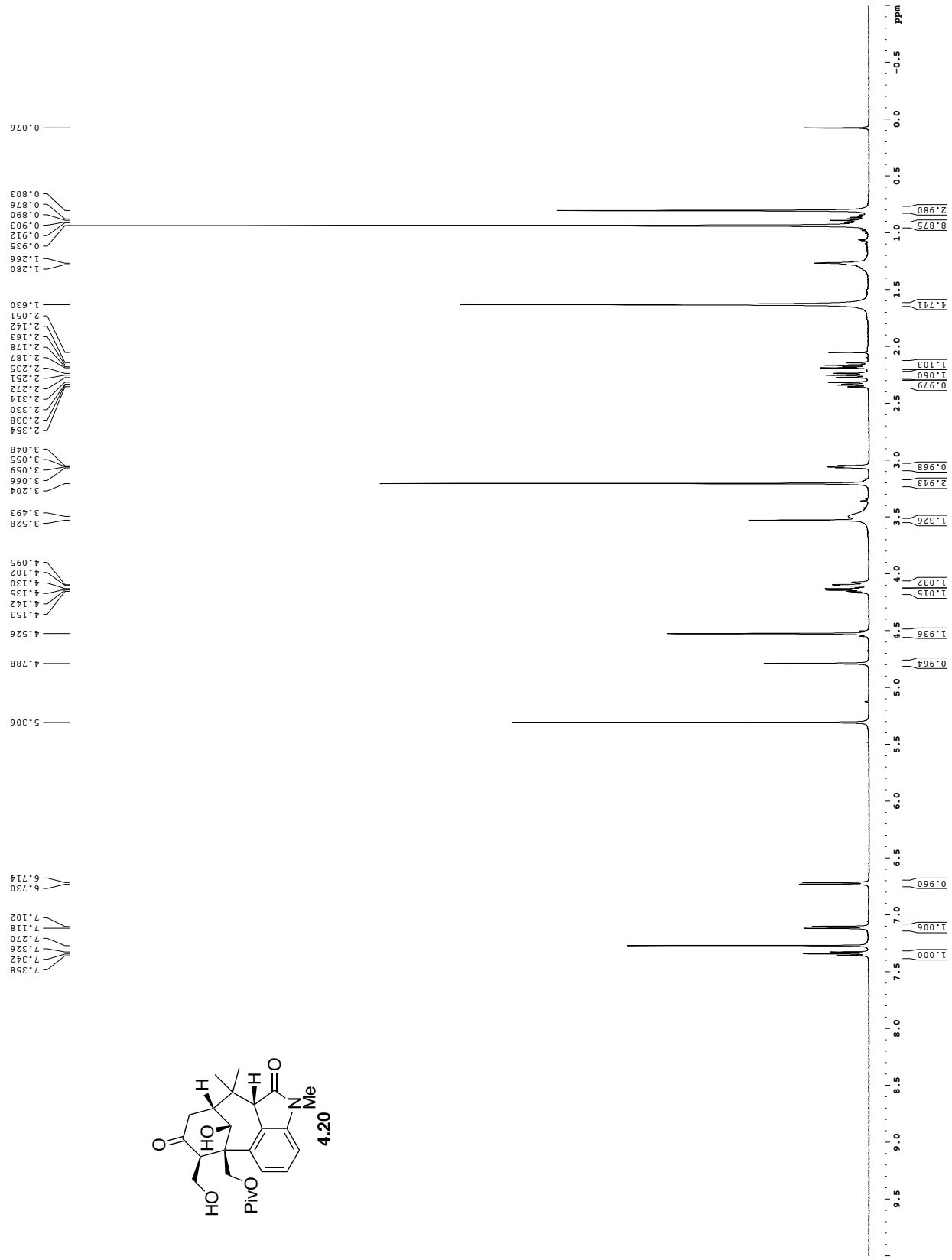
1.000
2.214
ppm
TIPSO
PivO
PivO
O
H
O
N
Me

4.19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0.890
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2.163
2.178
2.187
2.235
2.251
2.272
2.314
2.330
2.338
2.354
3.048
3.055
3.059
3.066
3.204
3.493
3.528
4.095
4.102
4.130
4.135
4.142
4.153
4.526
4.788
5.306
6.714
6.730
7.102
7.118
7.270
7.326
7.342
7.358
2.980
8.875
4.741
1.103
1.060
0.979
0.968
2.943
1.326
1.032
1.015
1.936
0.964
0.960
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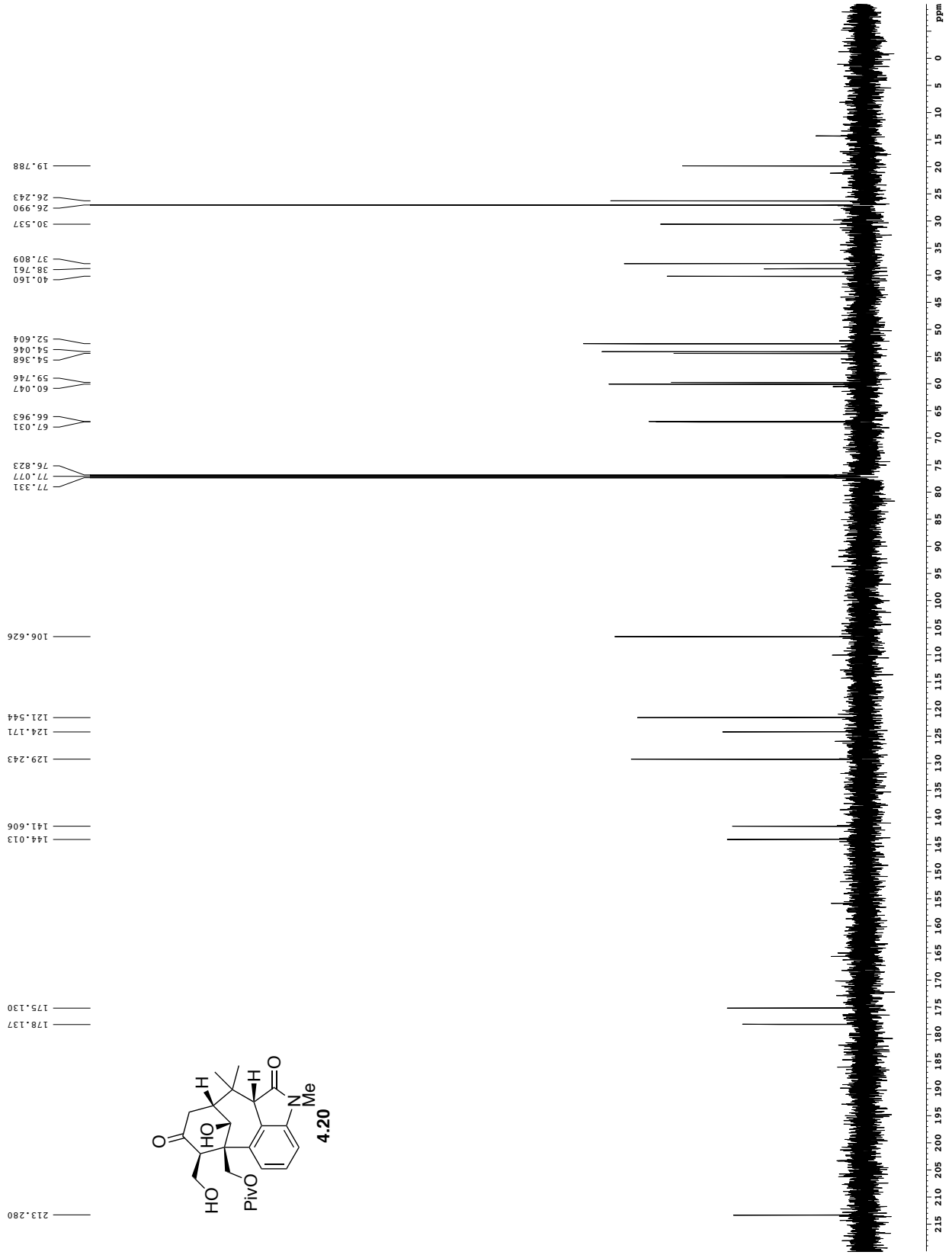
1.000
ppm

O
H
HO
HO
PivO
H
O
N
Me

4.20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175.130
144.013
141.606
129.243
124.171
121.544
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77.331
77.077
76.823
67.031
66.963
60.047
59.746
54.368
54.046
52.604
40.160
38.761
37.809
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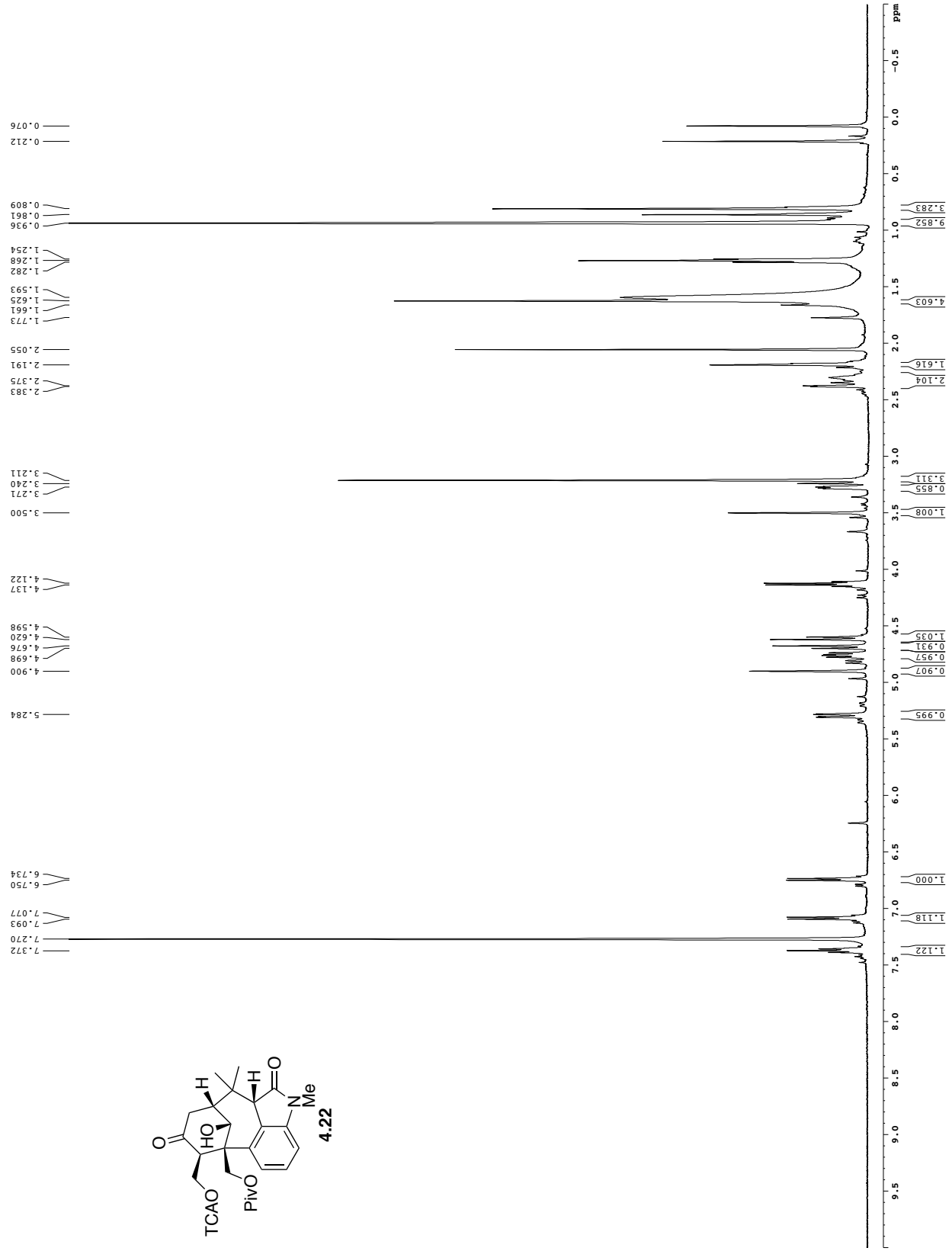
26.243
19.788
ppm
HO
PivO
HO
O
O
H
H
N
Me
4.20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4.137
4.122
3.500
3.271
3.240
3.211
2.383
2.375
2.191
2.055
1.773
1.661
1.625
1.593
1.282
1.268
1.254
0.936
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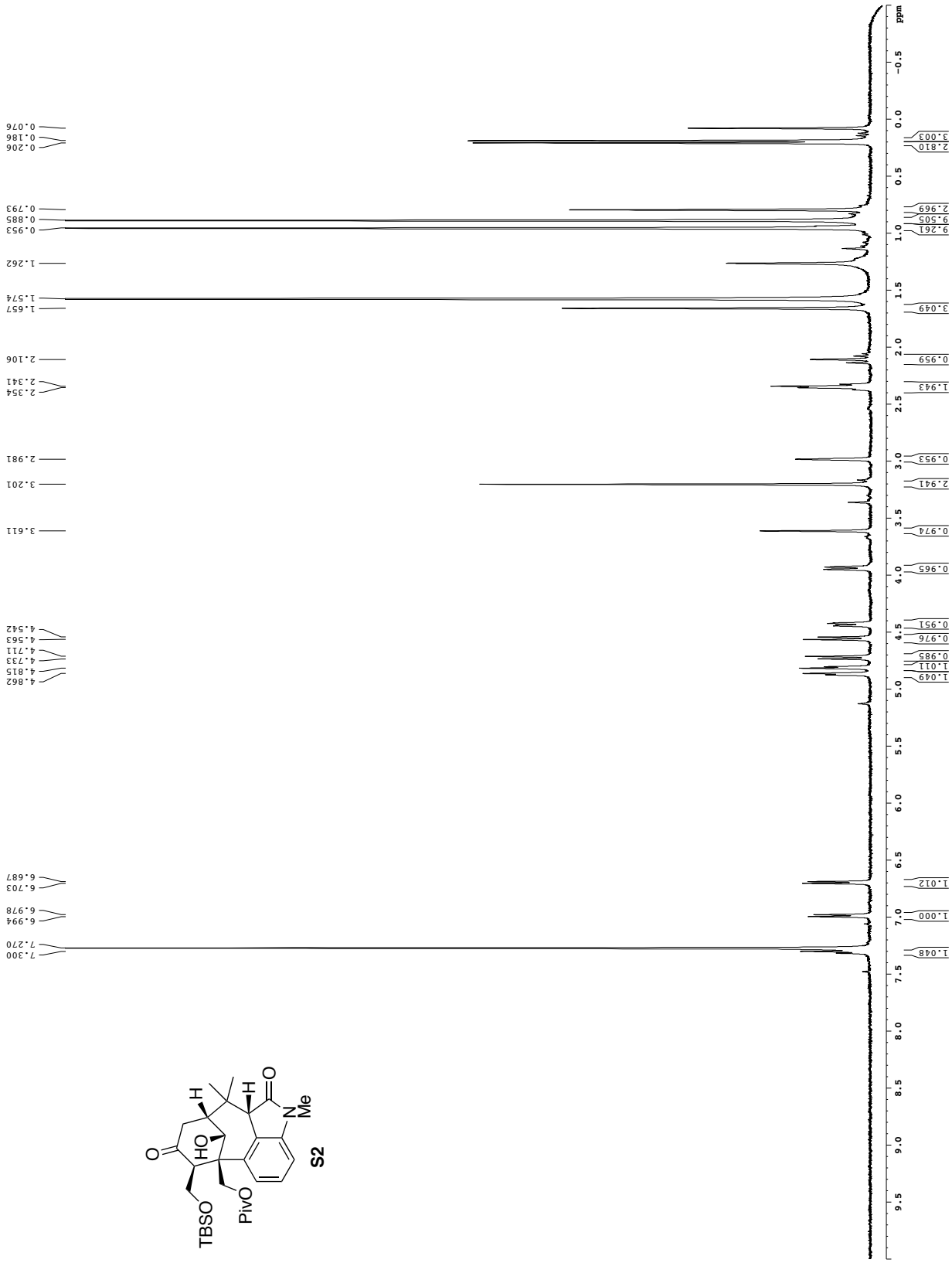
0.809
0.212
0.076
ppm
4.22
TCAO
PivO
HO
Me
N
O
H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2.341
2.354
2.981
3.201
3.611
4.542
4.563
4.711
4.733
4.815
4.862
6.687
6.703
6.978
6.994
7.270
7.300
ppm
1.048
1.000
1.012
1.049
1.011
0.985
0.976
0.951
0.965
0.974
2.941
0.953
1.943
0.959
3.049
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2.969
2.810
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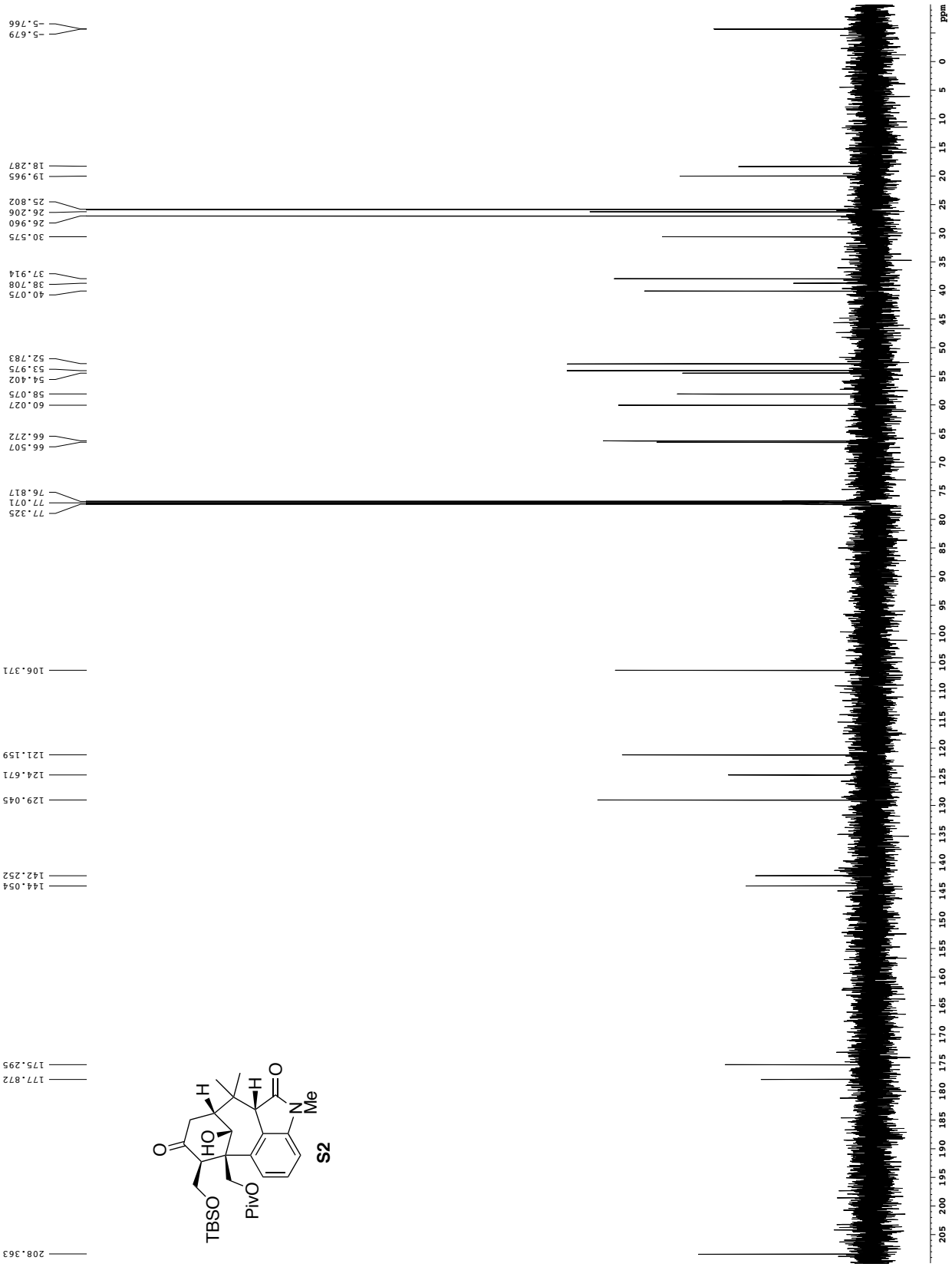
TBSO
PivO
HO
O
H
H
O
N
Me
S2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37.914
38.708
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53.975
54.402
58.075
60.027
66.272
66.507
76.817
77.071
77.325
106.371
121.159
124.671
129.045
142.252
144.054
175.295
177.872
208.363
ppm
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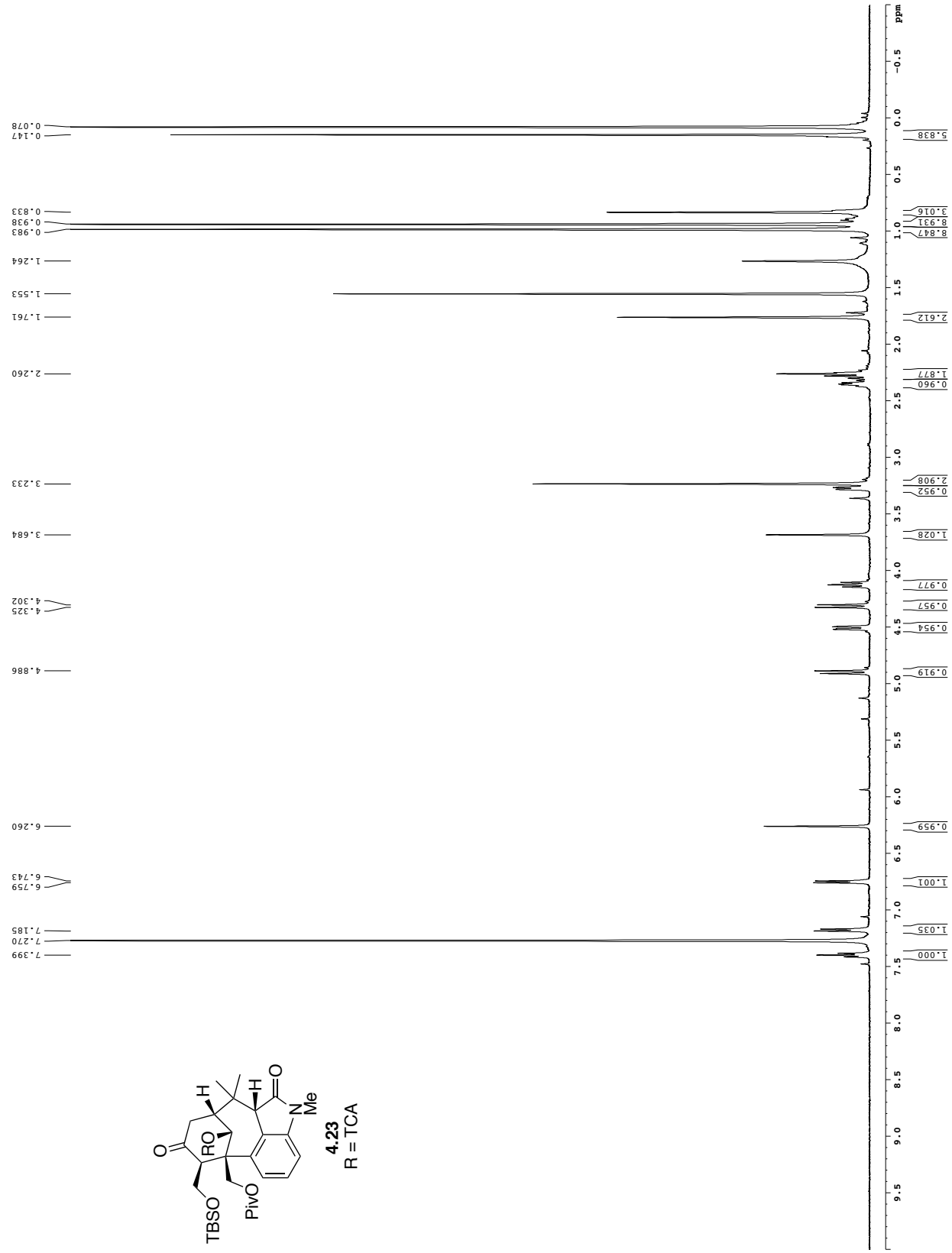
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
140
145
150
155
160
165
170
175
180
185
190
195
200
205
O
H
HO
H
O
N
Me
TBSO
PivO
S2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0.147
0.833
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1.553
1.761
2.260
3.233
3.684
4.302
4.325
4.886
6.260
6.743
6.759
7.185
7.270
7.399
5.838
3.016
8.931
8.847
2.612
1.877
0.960
2.908
0.952
1.028
0.977
0.957
0.954
0.919
0.959
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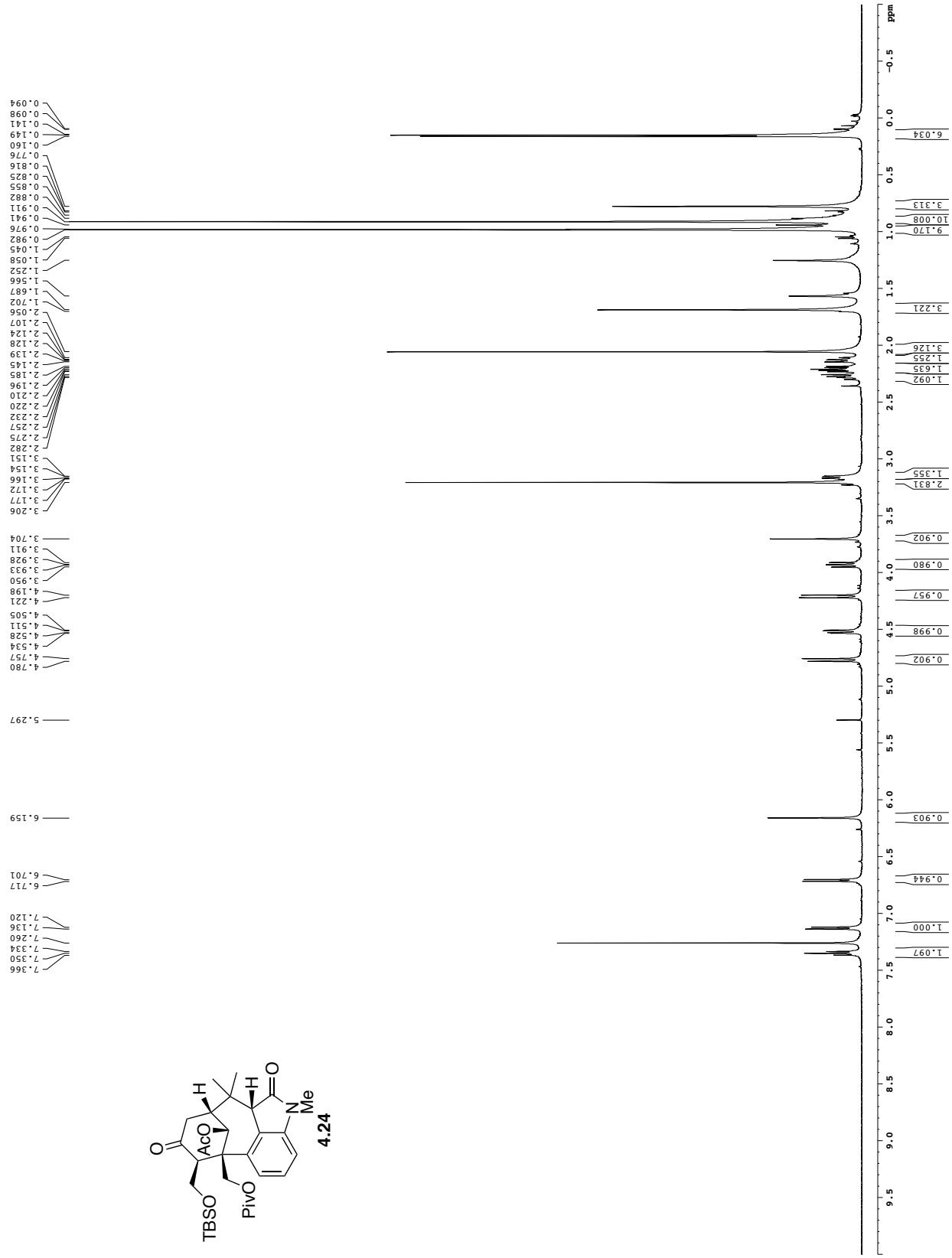
1.035
1.000
ppm
4.23
R = TCA
TBSO
PivO
RO
O
N
Me
H
H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0.825
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0.911
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0.976
0.982
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1.058
1.252
1.566
1.687
1.702
2.056
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2.124
2.128
2.139
2.145
2.185
2.196
2.210
2.220
2.232
2.257
2.275
2.282
3.151
3.154
3.166
3.172
3.177
3.206
3.704
3.911
3.928
3.933
3.950
4.198
4.221
4.505
4.511
4.528
4.534
4.757
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6.159
6.701
6.717
7.120
7.136
7.260
7.334
7.350
7.366
ppm
6.034
3.313
10.008
9.170
3.221
3.126
1.255
1.635
1.092
2.831
1.355
0.902
0.980
0.957
0.998
0.902
0.903
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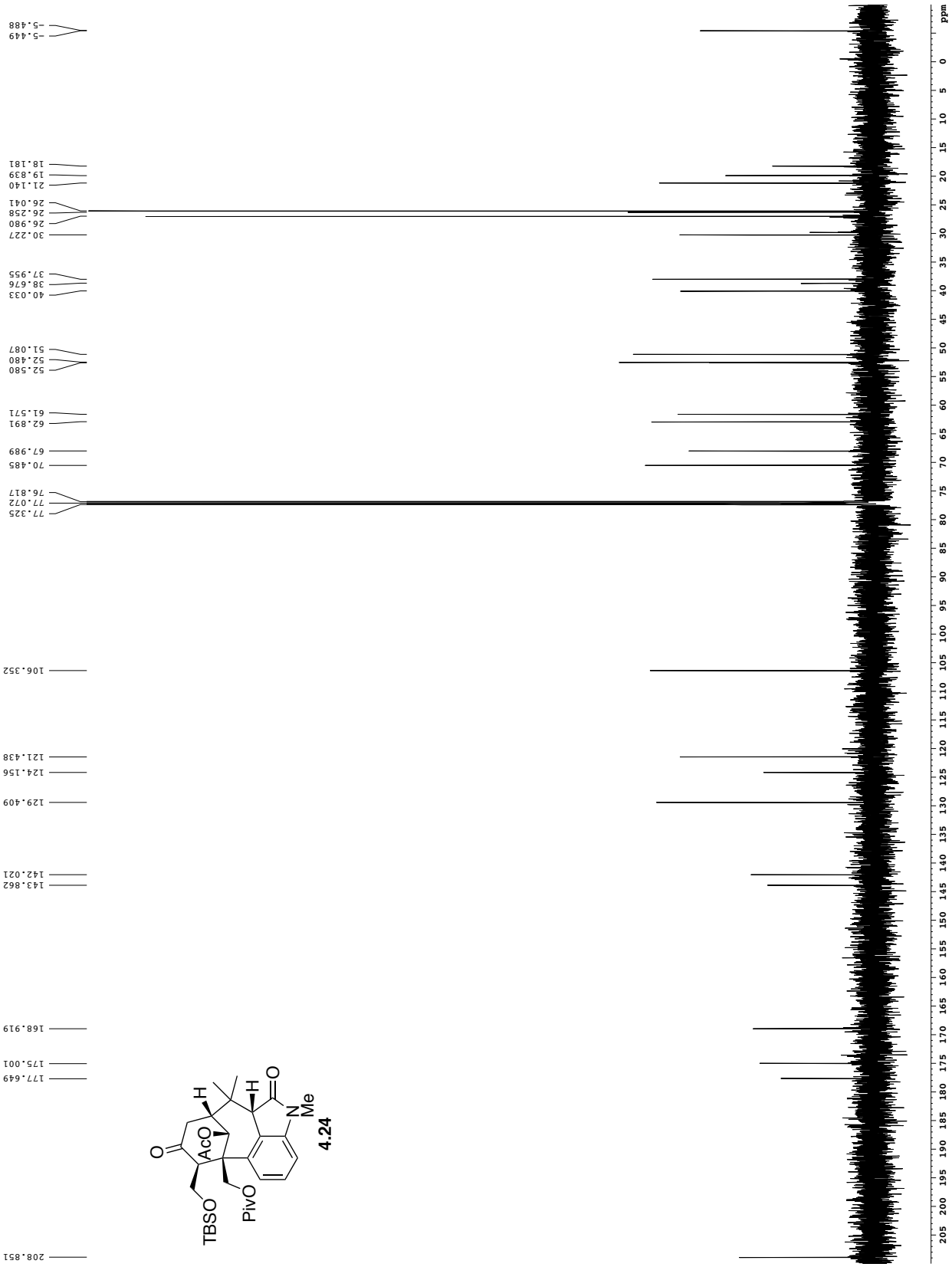
1.000
1.097

O
H
AcO
H
O
N
Me
TBSO
PivO

4.24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38.676
40.033
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52.480
52.580
61.571
62.891
67.989
70.485
76.817
77.072
77.325
106.352
121.438
124.156
129.409
142.021
143.862
168.919
175.001
177.649
208.851
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0
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10
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20
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30
35
40
45
50
55
60
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70
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80
85
90
95
100
105
110
115
120
125
130
135
140
145
150
155
160
165
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175
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200
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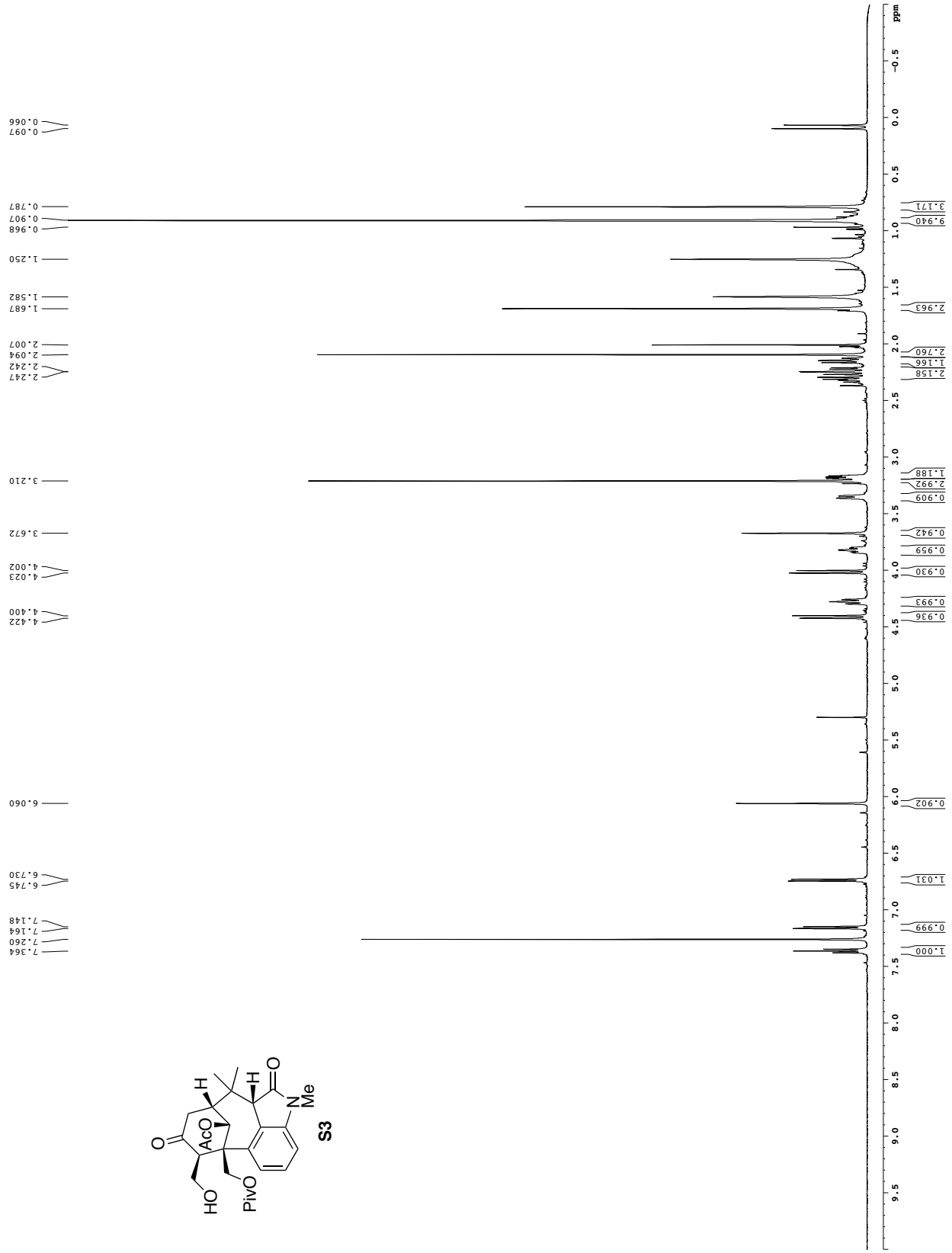
AcO
TBSO
PivO
H
O
N
Me
4.24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4.023
4.002
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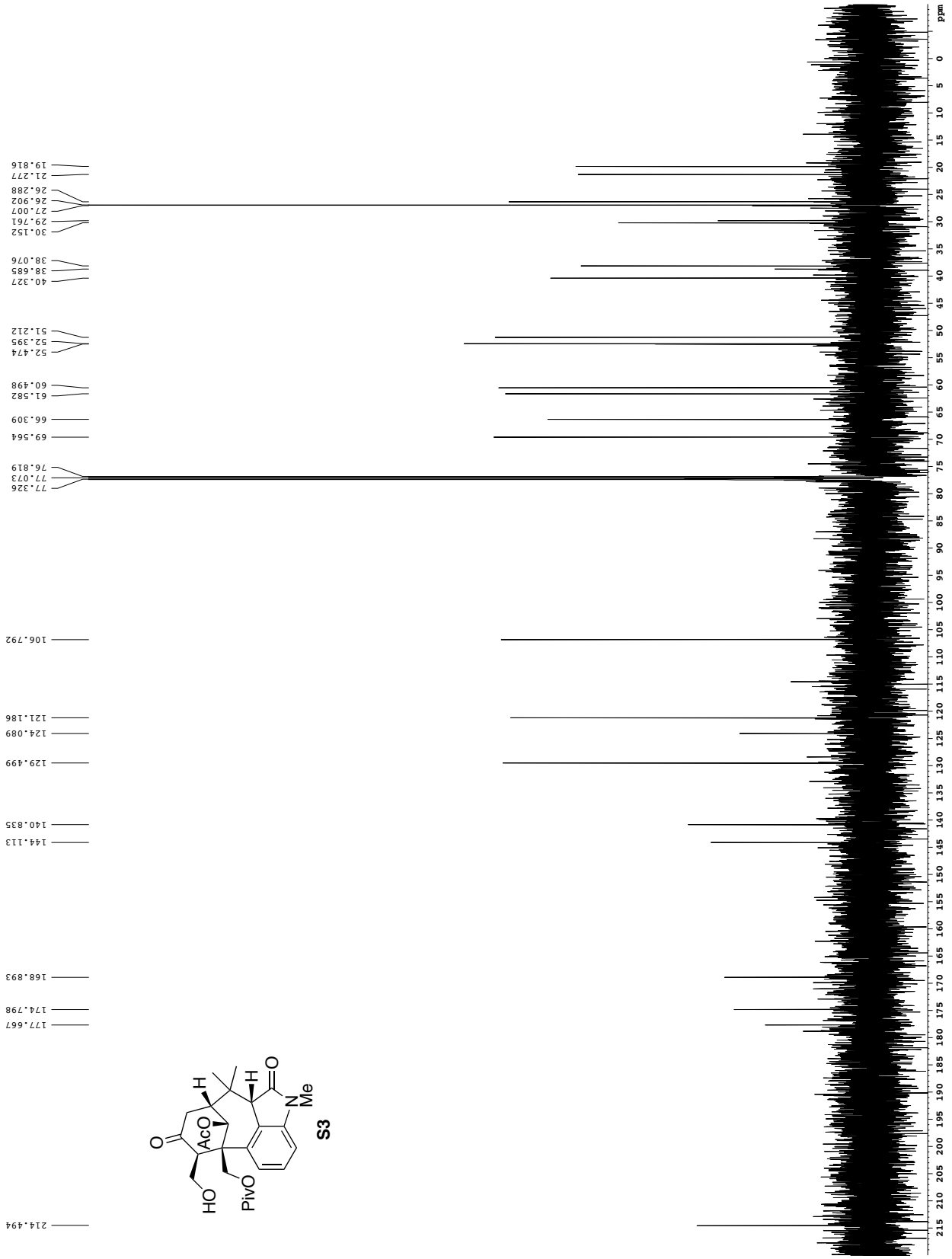
2.247
2.242
2.094
2.007
1.687
1.582
1.250
0.968
0.907
0.787
0.097
0.066
ppm
3.171
9.940
2.963
2.760
1.166
2.158
1.188
2.992
0.909
0.942
0.959
0.930
0.993
0.936
0.902
1.031
0.999
1.000
HO
PivO
AcO
O
H
H
O
N
Me

S3


19.816
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40.327
51.212
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52.474
60.498
61.582
66.309
69.564
76.819
77.073
77.326
106.792
121.186
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140.835
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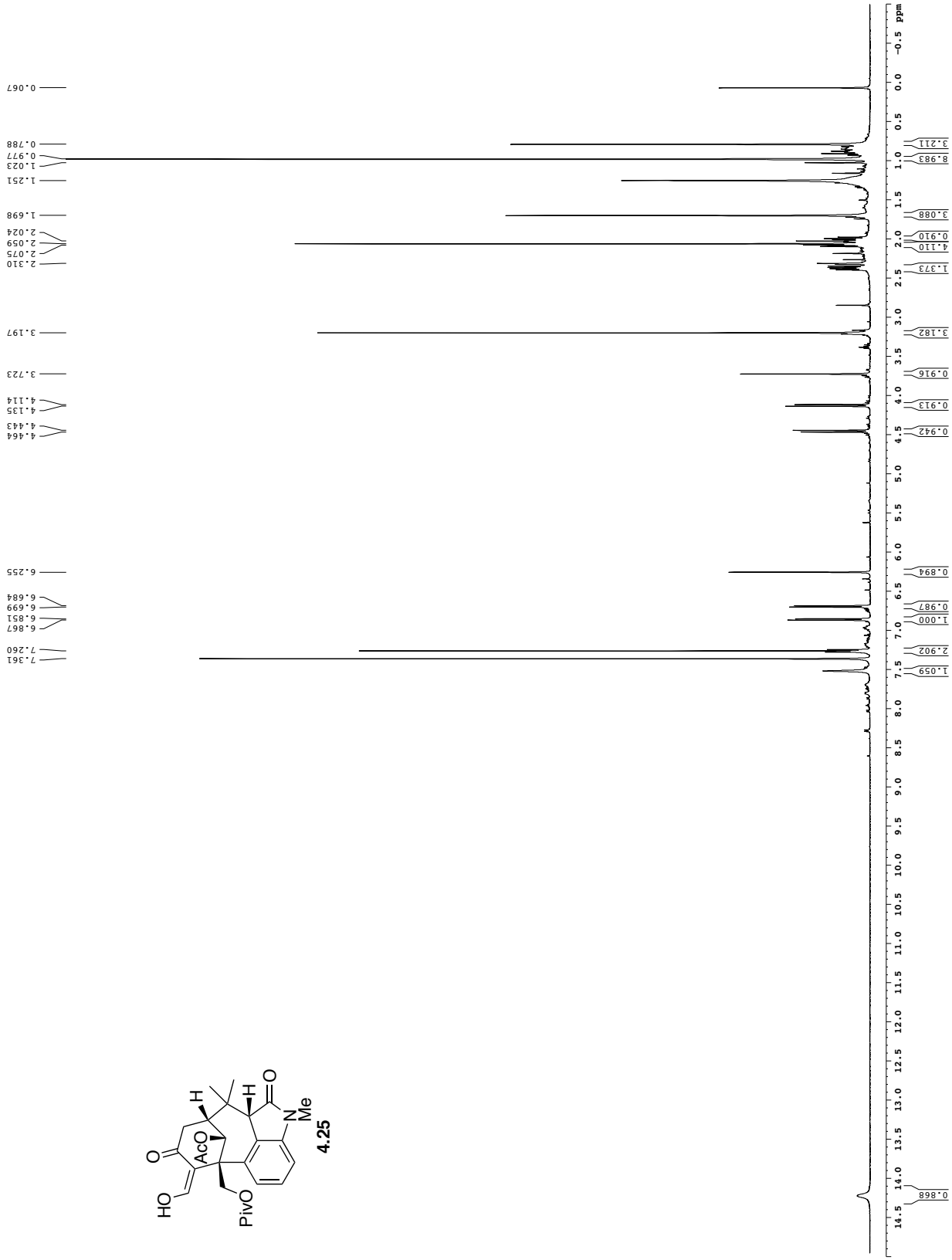
ppm
O
AcO
H
H
O
N
Me
HO
PivO
S3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2.059
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3.723
4.114
4.135
4.443
4.464
6.255
6.684
6.699
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7.361
3.211
8.983
3.088
0.910
4.110
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3.182
0.916
0.913
0.942
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HO
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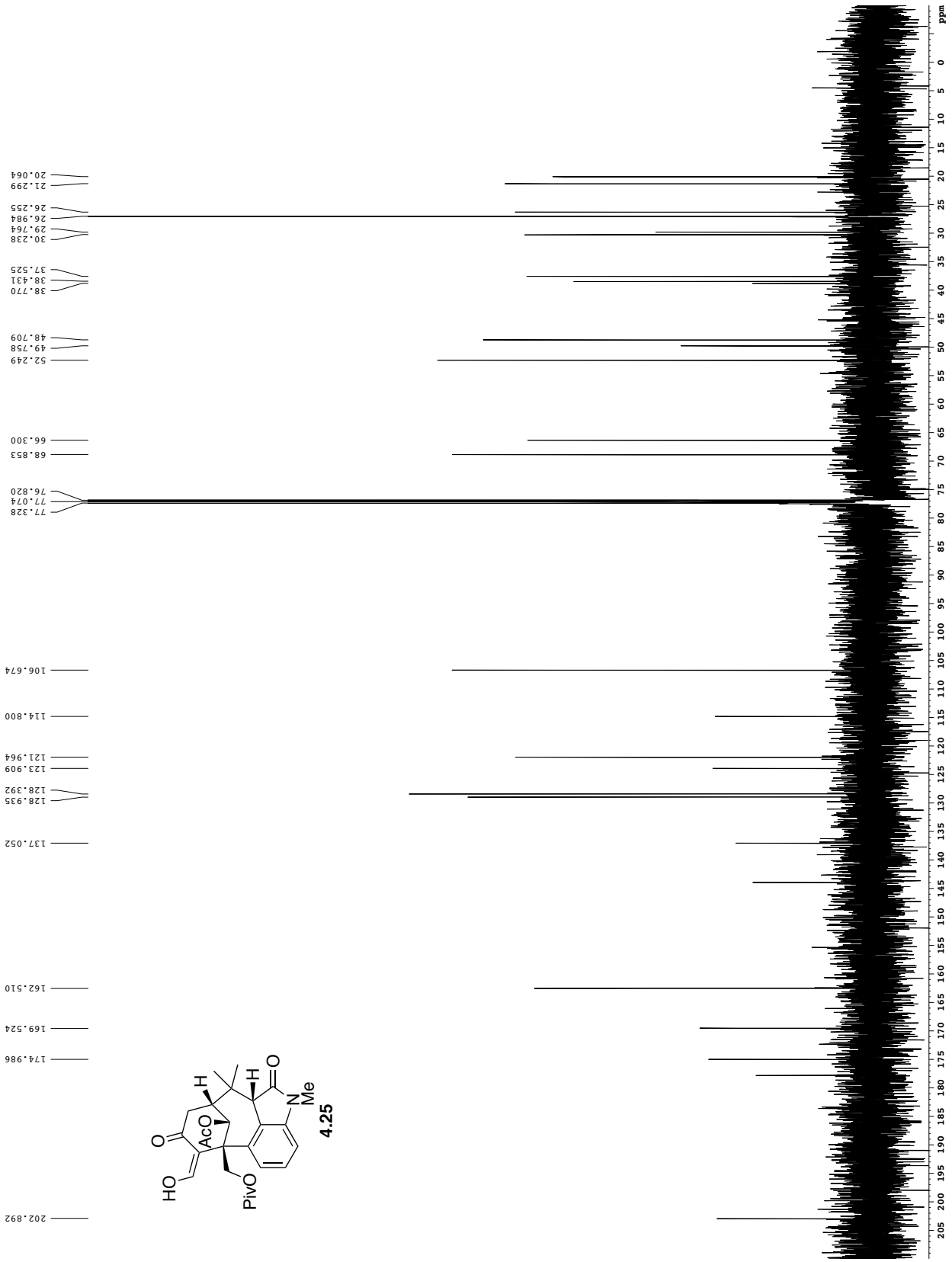
H
H
O
N
Me
PivO
4.25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37.525
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66.300
68.853
76.820
77.074
77.328
106.674
114.800
121.964
123.909
128.392
128.935
137.052
162.510
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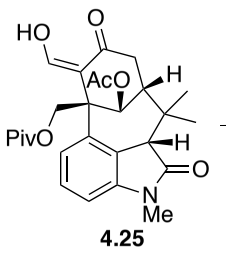
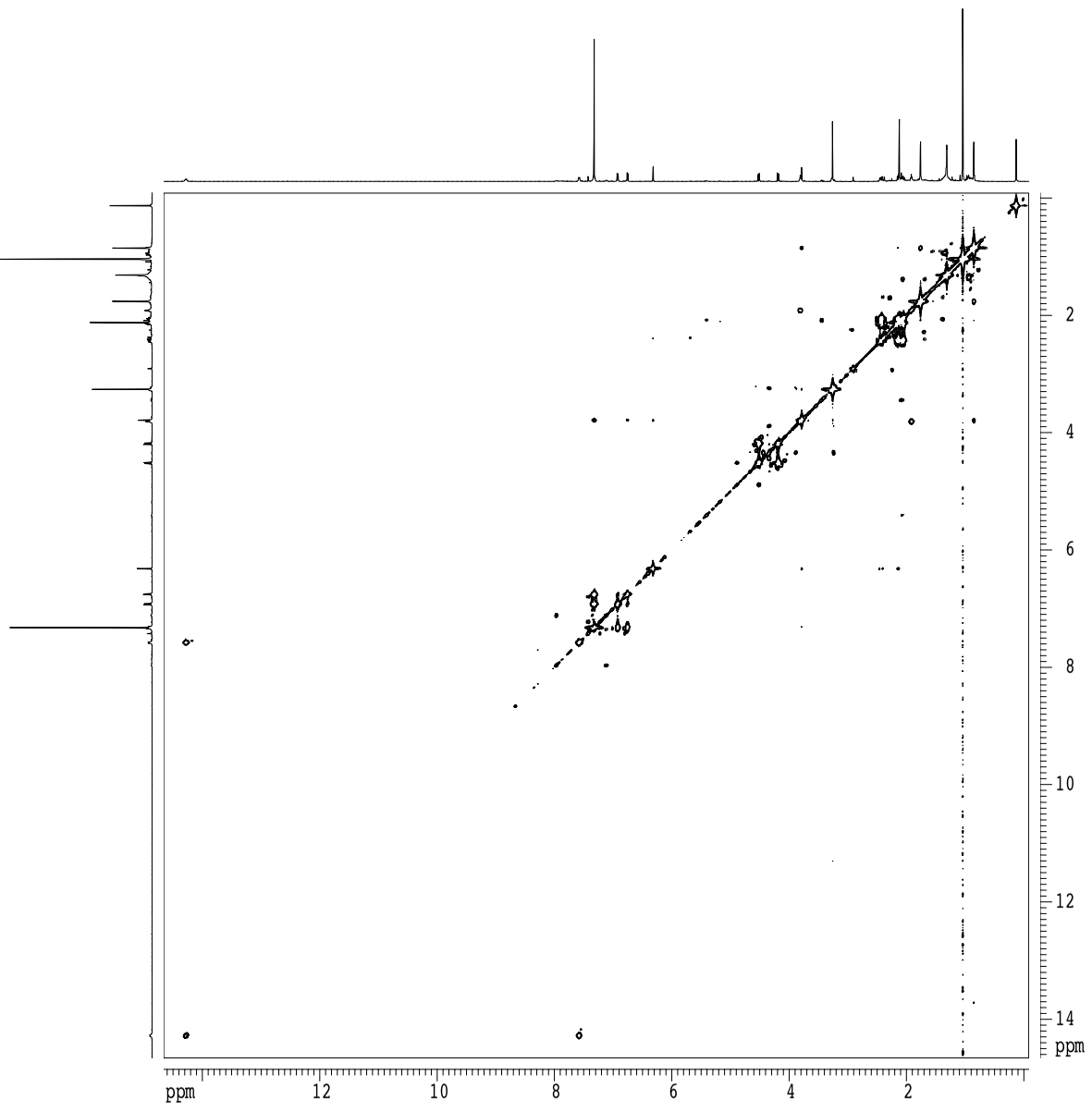
202.892
ppm
AcO
HO
PivO
N
Me
H
H
O
O
4.25

gcosy60



4.25

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NAME              JP06129
EXPNO                   4
PROCNO                  1

      F2 - Acquisition Parameters
Date_           20140925
Time                9.28
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG     cosygp60.prd
TD                   2048
SOLVENT             CDCl3
NS                      2
DS                     16
SWH             7374.631 Hz
FIDRES          3.600894 Hz
AQ              0.1389044 sec
RG                  574.7
DW                 67.800 usec
DE                  6.00 usec
TE                 298.0 K
d0              0.00000300 sec
D1              1.00000000 sec
d13             0.00000300 sec
D16             0.00020000 sec
IN0             0.00013560 sec

     ======== CHANNEL f1 ========
NUC1                   1H
P1                   7.50 usec
PL1                  1.60 dB
SFO1          500.2236452 MHz

     ====== GRADIENT CHANNEL =====
GPNAM1           sine.100
GPNAM2           sine.100
GPX1                 0.00 %
GPX2                 0.00 %
GPY1                 0.00 %
GPY2                 0.00 %
GPZ1                17.00 %
GPZ2                17.00 %
P16               1000.00 usec

      F1 - Acquisition parameters
ND0                     1
TD                    512
SFO1            500.2236 MHz
FIDRES         14.403577 Hz
SW                14.743 ppm
FnMODE          undefined

      F2 - Processing parameters
SI                    1024
SF            500.2200000 MHz
WDW                   SINE
SSB                      0
LB                   0.00 Hz
GB                       0
PC                    2.00

      F1 - Processing parameters
SI                    1024
MC2                     QF
SF            500.2200000 MHz
WDW                   SINE
SSB                      0
LB                   0.00 Hz
GB                       0

        2D NMR plot parameters
CX2                  15.00 cm
CX1                  15.00 cm
F2PLO               14.659 ppm
F2LO              7332.54 Hz
F2PHI               -0.084 ppm
F2HI                -42.09 Hz
F1PLO               14.659 ppm
F1LO              7332.54 Hz
F1PHI               -0.084 ppm
F1HI                -42.09 Hz
F2PPMCM           0.98285 ppm/cm
F2HZCM          491.64209 Hz/cm
F1PPMCM           0.98285 ppm/cm
F1HZCM          491.64209 Hz/cm
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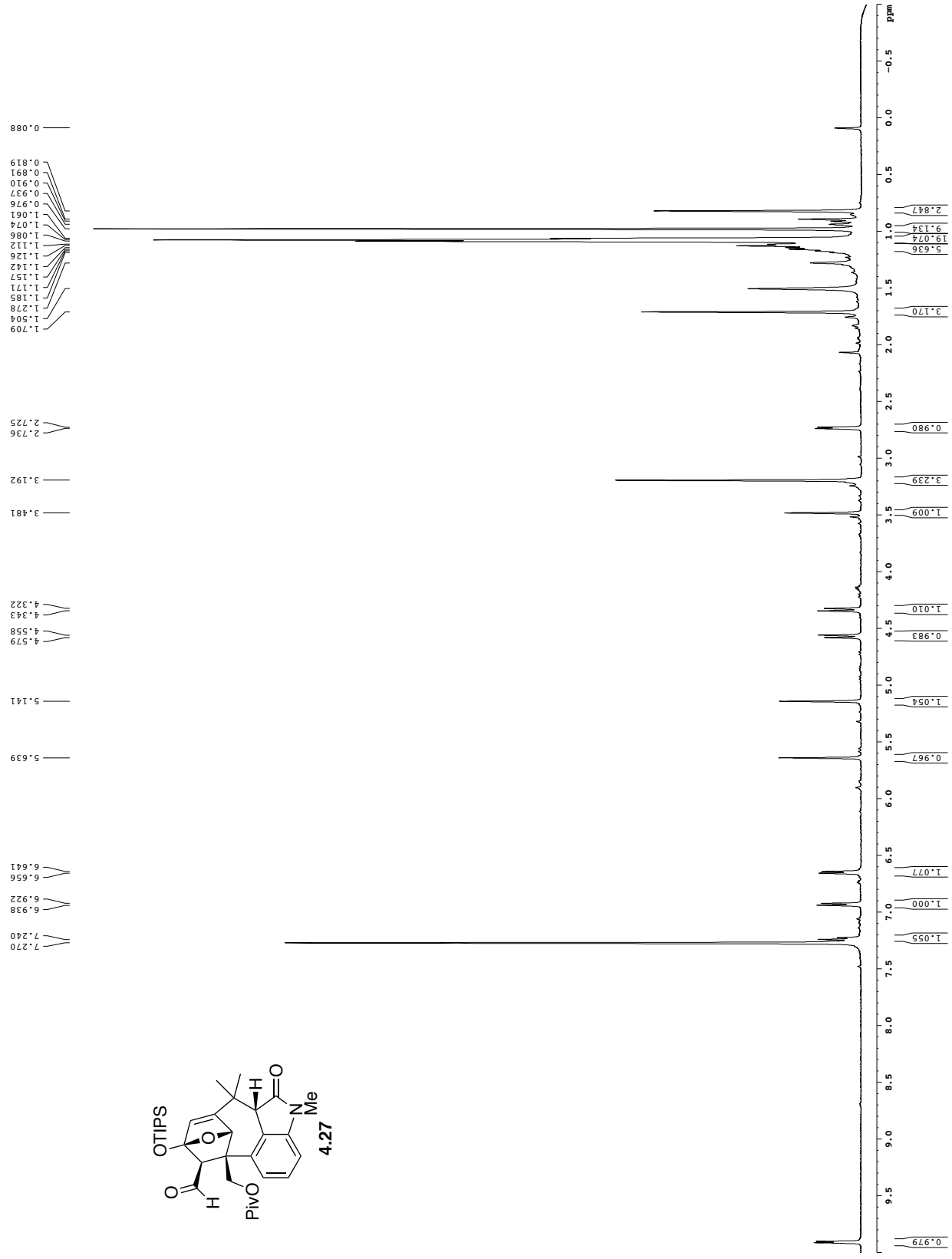
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0.910
0.937
0.976
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1.074
1.086
1.112
1.126
1.142
1.157
1.171
1.185
1.278
1.504
1.709
2.725
2.736
3.192
3.481
4.322
4.343
4.558
4.579
5.141
5.639
6.641
6.656
6.922
6.938
7.240
7.270
0.979
1.055
1.000
1.077
0.967
1.054
0.983
1.010
1.009
3.239
0.980
3.170
5.636
19.074
9.134
2.847
ppm
OTIPS
O
H
O
PivO
O
N
Me
4.27