STEREOCHEMISTRY OF HEXENYL RADICAL CYCLIZATIONS WITH *TERT*-BUTYL AND RELATED LARGE GROUPS: SUBSTITUENT AND TEMPERATURE EFFECTS

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The long held notion that hexenyl radicals bearing large substituents on the radical carbon cyclize to give 1,2-*trans*-substituted cyclopentanes is experimentally disproved by study of the radical cyclization of an assortment of simple and complex substrates coupled with careful product analysis and rigorous assignment of configurations. X-ray studies and syntheses of authentic samples establish that the published assignments for *cis*- and *trans*-1-*tert*-butyl-2-methylcyclopentane must be reversed. The original assignment based on catalytic hydrogenation of 1-*tert*-butyl-2-methylenecyclopentane was compromised by migration of the double bond prior to hydrogenation. The cyclization of 1-*tert*-butylhexenyl radical is moderately *cis* selective, and the selectivity is increased by geminal substitution on carbon 3. This selectivity trend is general and extends to relatively complex substrates. It has allowed Ihara to reduce the complexity of an important class of round trip radical cyclizations to make linear triquinanes to the point where two tricyclic products, *cis-syn-cis* and *cis-anti-cis*, account for about 80% of the products. However, the further increase in selectivity that was proposed by lowering the temperature is shown to be an artifact of the analysis methods and is not correct. This work solidifies “1,2-*cis* selectivity” in cyclizations of 1-subsituted hexenyl radicals as one of the most general stereochemical trends in radical cyclizations.

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LIST OF ABBREVIATIONS

Ac	acetyl
AIBN	azobisisobutyronitrile
APCI	atmospheric pressure chemical ionization mass spectrometry
Bu	butyl
Bn	benzyl
COSY	correlation spectroscopy
DCC	*N, N′*-dicyclohexylcarbodiimide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	4-dimethylaminopyridine
DMSO	dimethylsulfoxide
DIBAL-H	di-isobutylaluminum hydride
E	methyl ester (CO_2Me)
equiv	equivalent
Et	ethyl
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
HAT	hydrogen atom transfer
HMPA	hexamethyl phosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IR	infrared spectrometry
J	coupling constant (Hz)
LDA	lithium diisopropylamide
M	molar
***m*-CPBA**	*meta*-chloroperoxybenzoic acid
Me	methyl

MeO	methoxy
MS	low resolution mass spectrometry
NaHMDS	sodium hexamethyldisilazide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Ph	phenyl
ppm	parts per million
Pr	propyl
$\mathbf{R_f}$	retention factor
$\mathbf{R_t}$	retention time
rt	room temperature
t	tert
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
UV	ultraviolet

PREFACE

I would like to take this opportunity to thank a number of people who have helped and supported my throughout my five years at the University of Pittsburgh. First and foremost I would like to thank Dr. Curran for allowing me to work under his guidance and benefit from his teaching. I have learned so much from him not only about chemistry, but also on how to conduct myself professionally as a scientist and a person. I have always appreciated the freedom that he has given me to explore my own ideas and the respect that he has shown me. I would especially like to thank him for his help and patience in preparing this and my proposal documents. In addition I would like to thank all of the Curran group members past and present for their friendship, helpfulness and many good times. Special thanks go out to Andre Lapierre and Tiffany Turner for their support not only on the academic front, but also on the personal front which in many ways has been equally challenging.

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To all of my friends and family that I have not mentioned, you have certainly not been forgotten. I cherish your love, friendship and support over the years tremendously. Each and every one of you has contributed in a special way to me reaching this milestone in my life. Thank you all so much.

Chapter 1 Introduction

In the eighteenth century, Lavoisier was the first chemist to use the word “radical” to describe the portion of a molecule that remains unchanged during a chemical reaction. The modern definition of a radical reaction is a chemical process that involves molecules having unpaired electrons. This new definition was born in 1900 when Professor M. Gomberg mixed triphenylchloride and mercury to get the triphenylmethyl radical.[1,2] Gomberg’s experiment challenged the “fact” that carbon could only be tetravalent and so was met with due skepticism. Gomberg, however, was quite correct that his experiment had produced, albeit briefly, a trivalent carbon atom with an unpaired electron.

Between 1900 and about 1980, radicals were perceived as interesting reactive intermediates with limited synthetic potential. In no small part, this was due to the notion that something so reactive could not possibly be selective, and selectivity is after all the key to a high yielding process. Fortunately the physical organic chemists persevered and forged a great understanding of the structure and reactivity of radicals.[3] Based on their work, synthetic organic chemists realized the enormous potential of radical chemistry. It is this realization that has led to the widespread use of radical reactions in synthesis throughout the 1980’s and into the present day.[4]

Radical reactions are ordinarily initiated by a homolytic bond cleavage, Figure 1-1, where atoms A and B each receive one of the electrons from the broken bond. The two products of this homolytic bond cleavage are electronically neutral, but at the same time they are reactive because of the unpaired electron. Ionic reactions on the other hand involve a heterolytic bond dissociation where one atom gets both of the electrons to give reactive cation and anion products.

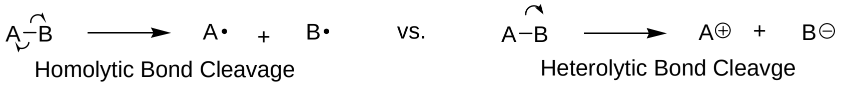


Figure 1-1: Homolytic versus heterolytic bond dissociation of a molecule A-B.

The fact that most radicals are neutral provides them with some nice advantages over their ionic counterparts. For instance, because of this neutrality, radical reactions occur under mild conditions resulting in high functional group tolerance. The elaborate protecting group chemistry often seen in ionic reactions is therefore not necessary. Fortunately, nearly all of the popular classes of protecting groups are tolerated by radical reactions should they be necessary for other steps in the synthetic sequence. Another advantage of radical over ionic chemistry is that a much wider variety of solvents, including water, can be used to carry out transformations. Furthermore radicals are less sensitive to steric encumbrance than ions are. This means that radicals can be used for transformations that are otherwise difficult to accomplish.[5] For the reasons mentioned above and many others, radicals have found widespread use in the deoxygenation of alcohols, ketones and aldehydes, as well as desulfurization, deamination, decarboxylation, dehalogenation and carbon-carbon bond forming reactions.

The reactive nature of radicals means that they often react in chains, because the product of one radical reaction is another radical. This radical product then serves as the starting material for another reaction and so on.[3b] The chain ends with a termination step when two radicals react together to give non-radical products. This work focuses on the chemistry of carbon centered radicals and their involvement in carbon-carbon bond forming reactions.

1.1 Chain Mechanisms for the Generation of Carbon Centered Radicals

Direct formation of the desired carbon centered radical C• from a C-X precursor, would require the homolytic cleavage of the C-X bond. Effecting this cleavage under reasonable conditions is not a trivial task because homolytic bond dissociation energies are high. For instance, the homolytic bond dissociation energy for the carbon-carbon bond in ethane[6] is 88 kcal mol^{-1}, whereas the "weaker" carbon iodine bond of iodomethane is still 56 kcal mol^{-1}. For this reason, carbon-centered radicals are frequently generated through chain mechanisms that consist of initiation, propagation and termination steps. The initial radical in a chain mechanism is formed by the homolytic cleavage of a weak bond and then transferred by a series of propagation steps to the carbon atom of interest.

1.1.1 Chain Initiation

The compound containing the requisite weak bond to start the chain is known as a radical initiator, and some of the most common initiators are shown in Figure 1-2. When 2,2-azobisisobutyonitrile (AIBN)[7] **1.1** is heated or irradiated, a molecule of N_2 is extruded giving tertiary radical **1.2**. Unfortunately, the need for heat or light in AIBN initiation precludes its use with some substrates or functional groups. Triethylborane[8] **1.3** addresses this compatibility problem by readily reacting with molecular oxygen to give peroxy radical **1.4** and an ethyl radical **1.5** at temperatures as low as −78 °C. Finally, another popular radical initiator is benzoyl peroxide **1.6**. Upon heating, peroxy compound **1.6** decomposes to give two benzoyl radicals **1.7**. The benzoyl radicals **1.7** can initiate chains directly or decompose further to give two phenyl radicals **1.8** and two molecules of carbon dioxide.

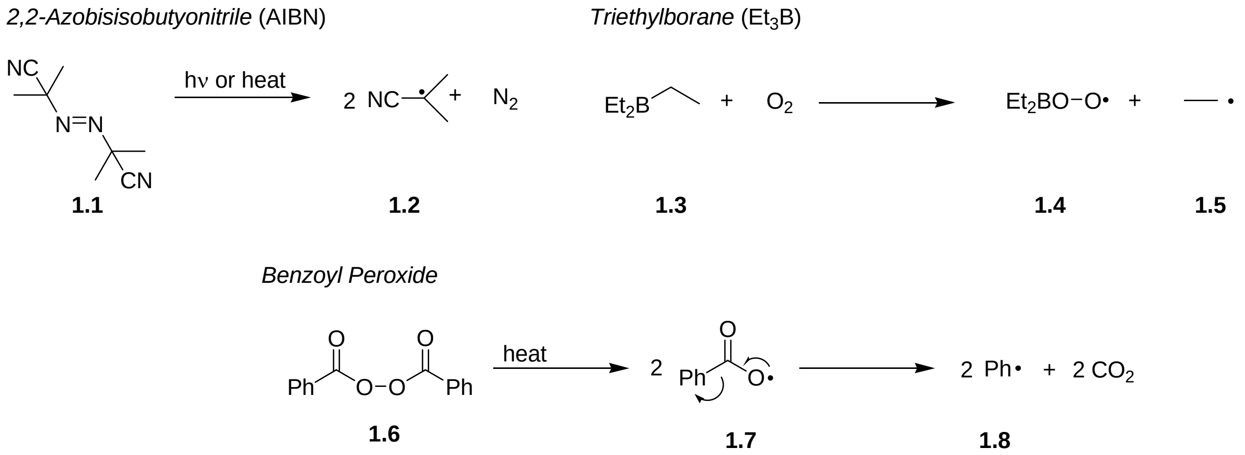
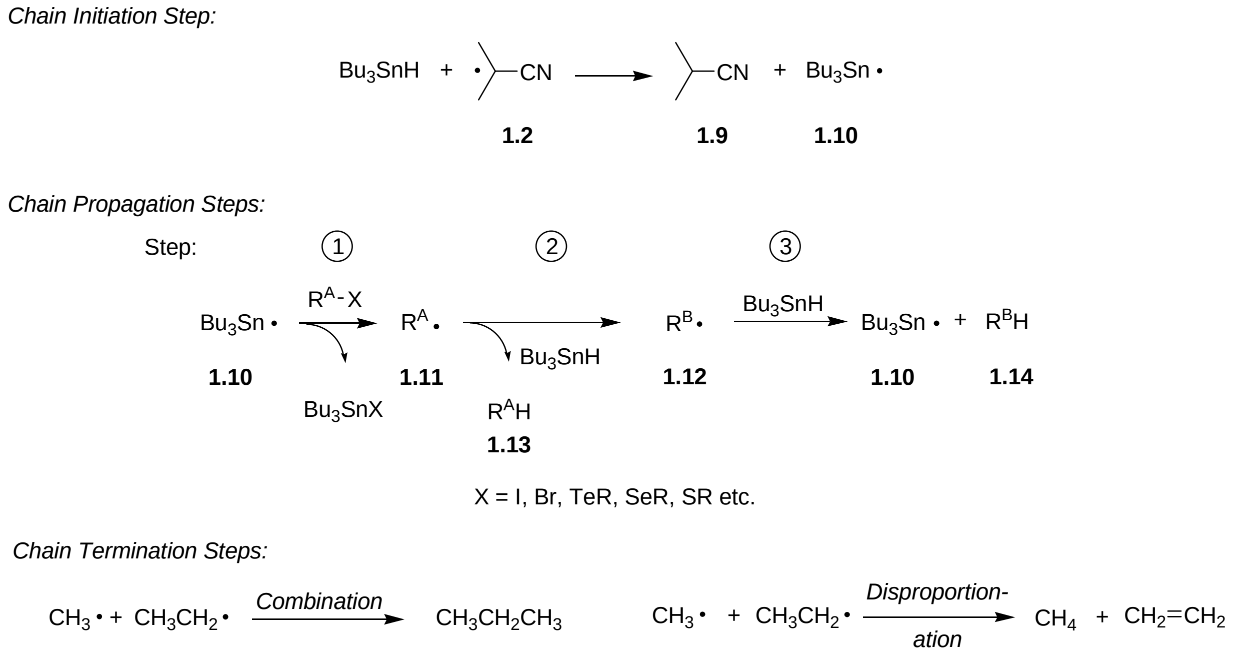


Figure 1-2: Common radical initiators and their derived radicals.

1.1.2 Chain Propagation and Termination

In the propagation steps of a chain mechanism, the desired radical $R^A\bullet$ **1.11** is formed by the homolytic cleavage of the R^A-X bond, Scheme 1-1. R^A-X is called a radical precursor and X can be a number of different atoms or groups, some of which are shown in Scheme 1-1. The key to propagation is that one radical is consumed and another one is formed that is used in a subsequent step. The propagation steps are often mediated by a reducing agent such as Bu_3SnH, Ph_3SnH or $(TMS)_3SiH$. In Scheme 1-1, typical propagation steps are summarized using radical **1.2** from AIBN initiation and Bu_3SnH as the reducing agent.

Following from the initiation reaction, radical **1.2** reacts with the Bu_3SnH to give stannyl radical **1.10** and 2-cyanopropane **1.9**. In the first propagation step, the stannyl radical reacts with the radical precursor R^A-X to give the desired radical $R^A\bullet$ **1.11** and Bu_3SnX. Compound **1.11** then undergoes the desired reaction in step 2, be it intra- or intermolecular, to give radical $R^B\bullet$ **1.12**. Finally, in step 3, **1.12** abstracts a hydrogen from Bu_3SnH to give the desired product R^BH **1.14** and the stannyl radical **1.10**. The stannyl radical produced in step 3 then re-enters the chain at step 1.[9] The regeneration of the stannyl radical in the final step means that the initiator can be used in substoichiometric amounts. An undesirable side reaction is where radical $R^A\bullet$ **1.11** abstracts a hydrogen from the reducing agent to give product R^AH **1.13** before the desired reaction can occur.


Chain Initiation Step:
Bu3SnH + •—CN → —CN + Bu3Sn•
1.2
1.9
1.10
Chain Propagation Steps:
Step: ① ② ③
Bu3Sn•
RA-X
Bu3SnX
RA•
Bu3SnH
RAH
RB•
Bu3SnH
Bu3Sn• + RBH
1.10
1.11
1.13
1.12
1.10
1.14
X = I, Br, TeR, SeR, SR etc.
Chain Termination Steps:
CH3• + CH3CH2• Combination → CH3CH2CH3
CH3• + CH3CH2• Disproportion-ation → CH4 + CH2=CH2

Scheme 1-1: Propagation and termination steps in a radical chain mechanism.

The chain mechanism can be interrupted when two radicals react together to give non-radical products. This interruption can occur through either a combination or a disproportionation reaction, Scheme 1-1. An example of a combination reaction is where a methyl and an ethyl radical produce a molecule of propane. A disproportionation reaction is where these same two radicals give a molecule of methane and ethene. Such reactions are called termination steps.

1.2 General Considerations for Running Radical Reactions

Radicals are highly reactive species and they will react with each other by combination or disproportionation at rates approaching the diffusion controlled limit (about 10^9-10^{10} M^{-1} sec^{-1}). Therefore, low concentrations of radical species are generally desirable and can be achieved by controlling the rates of initiation and termination. Furthermore, low concentrations of the reducing agent are desirable to minimize the reduction of radical $R^A\bullet$ before it undergoes the conversion to $R^B\bullet$.

The easiest way to minimize the undesired side reactions is to use a dilute solution of Bu_3SnH and substrate R-X. This however requires a large volume of solvent that is not easy to handle on larger scale. Another way to keep reducing agent concentrations low is to add it to the reaction mixture by syringe pump over a long period of time.[9,10] It is also possible to regenerate the Bu_3SnH from the Bu_3SnX by using sodium cyanoborohydride[11] or sodium borohydride.[12] This allows sub-stoichiometric amounts of reducing agent to be used ensuring that concentrations remain low during the reaction.

While a dilute reaction medium helps in the formation of the desired product R^BH, it is possible for the reducing agent to be too dilute. In order for the chain to propagate, radical **1.12** must abstract a hydrogen from Bu_3SnH to generate **1.10** so that it can re-enter the cycle. Due to the limited lifetime of radicals, $R^B\bullet$ **1.12** could undergo termination or an undesirable reaction instead of abstracting a hydrogen. For example, a common solvent for radical reactions is benzene and the rate constant for radical additions to this solvent is about 10^2 M^{-1} sec^{-1}. Therefore, if the concentration of Bu_3SnH is low enough, this undesired addition to benzene can compete with hydrogen abstraction from the reducing agent.

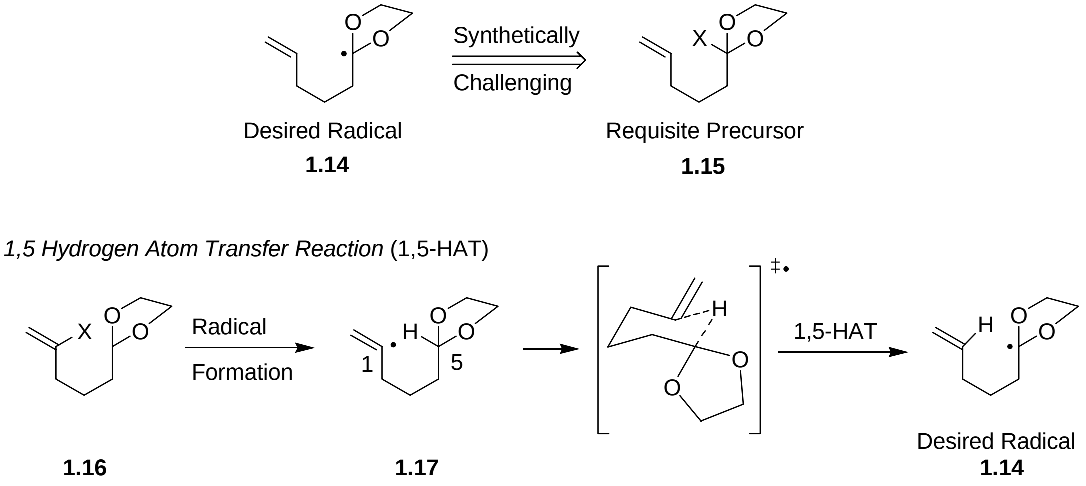
1.3 Common Types of Radical Reactions

There are a vast number of reactions that are known to proceed through a radical mechanism, but three are of particular relevance to this work, namely the 1,5 hydrogen atom transfer process (1,5 HAT), the Barton decarboxylation and the 5-*exo* cyclization of a hexenyl radical. After a brief overview of the 1,5 HAT process and the Barton decarboxylation reaction, the 5-*exo* cyclization of a hexenyl radical will be discussed in more detail.

1.3.1 1,5 Hydrogen Atom Transfer Reactions

The tin hydride method for generating radicals by homolysis of C-X bonds (X = I, Br, Cl, SePh, etc) continues to be one of the most convenient and widely used procedures. In certain instances, however, the desired radical may result from the homolysis of a C-H bond, but this brings with it a number of challenges. The first problem is the thermodynamics of homolytic C-H bond cleavage. With homolytic dissociation energies around 95 kcal mol^{-1}, C-H bonds are rather strong in comparison to Sn-H bonds that have bond dissociation energies[13] around 74 kcal mol^{-1}. The result is that a carbon-centered radical can abstract hydrogen from a Sn-H bond, but the reverse process of a tin radical abstracting hydrogen from C-H bond is thermodynamically unfavorable. A second hurdle is that the C-H bond is the most common bond in organic molecules and so abstraction of a specific hydrogen poses significant challenges.

Nevertheless, using the C-H bond as a radical precursor is desirable because synthesis of a C-X precursor can be challenging, especially when the carbon atom has heteroatomic substituents. A convenient strategy to use the C-H bond as a precursor is to generate the radical at a remote site and then translocate it to the desired position through a 1,5 hydrogen atom transfer (1,5 HAT) process. Generating new carbon-centered radicals from heteroatomic radicals (oxygen or nitrogen) by a 1,5 HAT process is well known and forms the basis for the Barton,[14] Hoffman-Löffler-Freytag[15] and the Fraser-Reid[16] reactions. As a nice complement to the heteroatomic variants, Curran and Shen[17] developed a process where both of the radicals in the 1,5 HAT process are carbon-centered as shown in Scheme 1-2. For example, if the desired radical is acetal **1.14**, then compound **1.15** would serve as the requisite precursor. However, formation of the necessary C-X bond in **1.15** on the same carbon as the acetal functionality may be synthetically challenging. The bottom half of Scheme 1-2 shows radical **1.14** can still be reached from precursor **1.16**. Homolytic cleavage of the C-X bond in **1.16** gives **1.17** with the radical in the 1 position and a hydrogen atom in the 5 position. This hydrogen atom can be readily transferred to give the desired radical **1.14** as shown in Scheme 1-2.

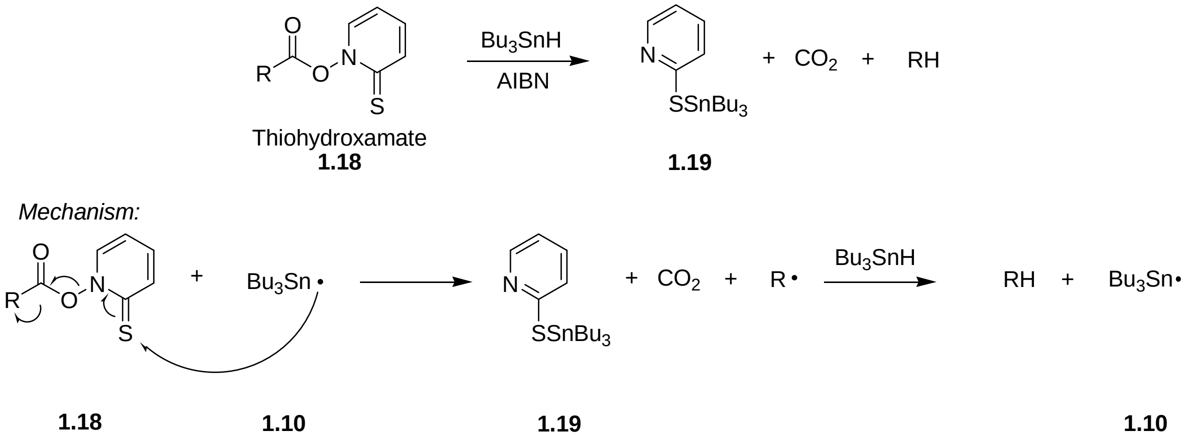


Scheme 1-2: 1,5 Hydrogen atom transfer reaction.

The process of 1,5-HAT is also favorable because it goes through a chair-like transition state,[18] Scheme 1-2, that has minimal strain. While 1,4-, 1,6-, and 1,7-HAT processes are known,[19] it is difficult for them to compete with the 1,5 process. In the case of a 1,4-HAT the chain is too short to allow for the proper alignment of the hydrogen and the radical. For the 1,6- and 1,7-HAT process the entropic cost of reaching the necessary 7 and 8 membered transition states is significantly higher than the 6-membered transition state needed for the 1,5 process. Clearly, the 1,5-HAT method of obtaining carbon centered radicals is an extremely useful and powerful tool in radical chemistry.

1.3.2 The Barton Decarboxylation Reaction

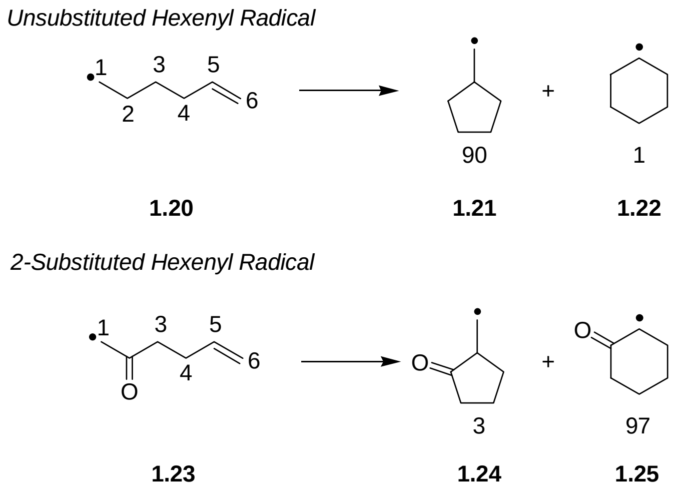
The Barton decarboxylation reaction uses a thiohydroxamate as a radical precursor. In a typical reductive decarboxylation, thiohydroxamate **1.18** is treated with Bu_3SnH to give thiopyridyl compound **1.19**, CO_2, and the reduced product RH as shown in Scheme 1-3. The fragmentation of the R-C(O) and the N-O bond is initiated by addition of the Bu_3Sn• radical **1.10** into the C-S double bond also shown in Scheme 1-3. This fragmentation process is driven by the aromatization of the thiohydroxamate to give thiopyridine **1.19** and the formation of the stable molecule CO_2. The resulting radical R• then abstracts a hydrogen from Bu_3SnH to give the reduced product RH and the stannyl radical starting material, thereby propagating the chain. While the Barton decarboxylation is frequently used to remove carboxyl groups from molecules to give the corresponding alkane, the intermediate radical R• can also be trapped in either an inter- or an intramolecular process.[20]


O
R
O
N
S
Thiohydroxamate
1.18
Bu3SnH
AIBN
N
SSnBu3
1.19
+ CO2 + RH
Mechanism:
Bu3Sn•
+ CO2 + R•
Bu3SnH
RH + Bu3Sn•
1.18
1.10
1.19
1.10

Scheme 1-3: Mechanism for a Barton decarboxylation reaction.

1.3.3 5-*Exo* Cyclizations of Hexenyl Radicals

Arguably the most well studied of all radical reactions is the cyclization of a 5-hexenyl radical **1.20**. This radical can cyclize either through a 5-*exo* pathway to give the methyl cyclopentyl radical **1.21**, or in a 6-*endo* manner to give the cyclohexyl radical **1.22** as shown in Scheme 1-4. Stereoelectronic effects dictate that this cyclization favors the 5-*exo* pathway and indeed the 5-*exo* and 6-*endo* products are obtained in a 90/1 ratio.[21] Substitution of the hexenyl radical normally does not affect the 5-*exo* selectivity of the cyclization. However, with certain substituents the selectivity can be overturned. For instance, placement of a carbonyl group in the 2 position, compound **1.23**, provides the 5-*exo* product **1.24** and the 6-*endo* product **1.25** in a 3/97 ratio.[22]


Unsubstituted Hexenyl Radical
1
2
3
4
5
6
90
1
1.20
1.21
1.22
2-Substituted Hexenyl Radical
1
3
4
5
6
O
O
O
3
97
1.23
1.24
1.25

Scheme 1-4: Selectivity in an unsubstituted and 2-substituted hexenyl radical cyclization.

While it is evident that hexenyl radical cyclizations can be regioselective, their widespread use in synthesis also depends on the levels of stereoselectivity that can be obtained. In an effort to understand the factors that affect the stereoselectivity of the cyclization, the Beckwith-Houk transition state model was developed.[23] This model provides a convenient way to predict and rationalize the stereoselectivity of the 5-*exo* hexenyl radical cyclization by providing a clear picture of the transition state. In the addition of a radical to an alkene, a tetrahedral-like approach is preferred and this can be accommodated by either a "chair"[23a,b] or a "boat"[23d] transition state, as shown in Figure 1-1. The names of the transition states are derived from the two analogous conformations of cyclohexane.

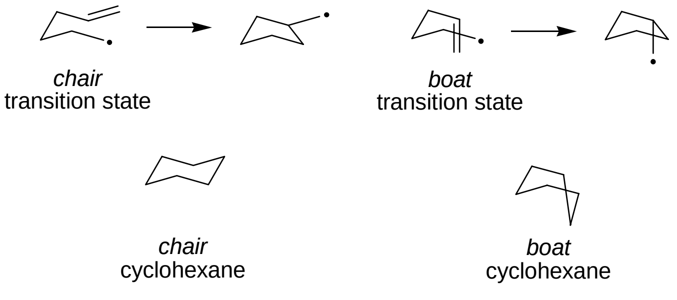

chair
transition state
boat
transition state
chair
cyclohexane
boat
cyclohexane

Figure 1-3: Transition state structures for hexenyl radical cyclizations.

Once the various transition states for the radical cyclization have been located, either computationally or conceptually, they can be evaluated using many of the same principles of cyclohexane conformational analysis. For instance, similar to cyclohexane, substituents in the radical cyclization transition states prefer to adopt an equatorial as opposed to an axial orientation. In this manner, it is possible to decide which of the competing transition states is lowest in energy and thereby most favored. However the analogy does have limits. The boat conformation of cyclohexane is 6.4 kcal mol^{-1} higher[24] in energy than that of the chair, but the boat transition state for a hexenyl radical is only about 1.0 kcal mol^{-1} higher[23d] in energy than the hexenyl radical chair. Therefore in the transition state analysis of hexenyl radical cyclizations, a boat is often invoked, whereas the boat conformation of cyclohexane is rarely considered in reactions.[25]

Adding a substituent to the hexenyl radical in the 2, 3, or 4 position introduces a stereocenter and results in four possible transition states: *chair-equatorial*, *chair-axial*, *boat-equatorial* and *boat-axial*. As an example, the four possible transition states for a 3-substituted hexenyl radical are shown in Figure 1-4. In this case, the *chair-equatorial* and the *boat-axial* transition states lead to the *cis* cyclopentyl radical whereas the *chair-axial* and the *boat-equatorial* both proceed to the *trans* product. It is possible to predict the major product of a cyclization by determining which transition state has the lowest energy. For this reaction, the *cis* product is predicted to be the major isomer, because the *chair-equatorial* transition state is void of axial substituents and therefore the lowest in energy. The *chair-axial* and *boat-equatorial* transition states are destabilized by the axial placement of the R group or the alkene respectively. Although the *boat-axial* transition state also leads to the major product, it is not a major contributor because with two axial substituents it is too high in energy and is thus often ignored.[26]

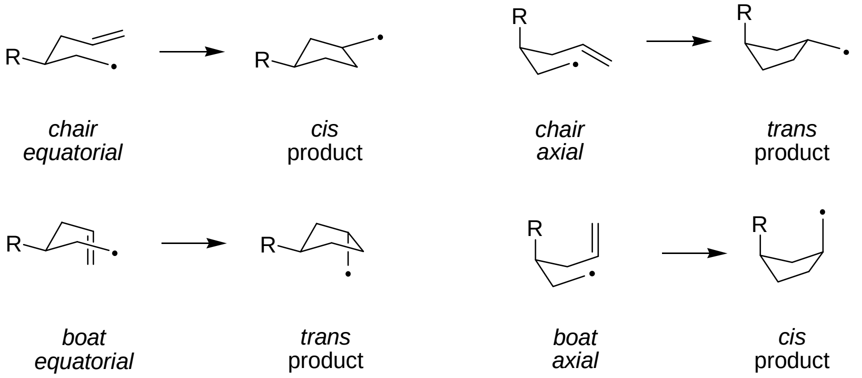


Figure 1-4: Transition states for a 3 substituted hexenyl radical.

1.4 Synthesis of Linear Triquinanes by Tandem Radical 5-*Exo* Cyclization Reactions

Some of the most powerful reactions in organic synthesis are those where several bond forming steps occur in a single synthetic operation. Such processes are known as tandem reactions. Tietze concisely defined a tandem reaction as a process that involves two or more bond-forming transformations, which take place under the same reaction conditions without additional reagents or catalysts and in which the subsequent reaction is the direct result of the functionality formed in the previous step.[27] Tandem reactions are particularly useful because they can quickly build up molecular complexity from relatively simple starting materials. Employing sequential 5-*exo* hexenyl radical cyclizations in a tandem sequence makes polycyclopentanoid molecules or polyquinanes ideal targets.[4,5b,28]

A number of triquinane natural products, compounds with three cyclopentane rings, have been isolated with a variety of geometries as shown in Figure 1-5. Modhephene contains a propellane geometry in which all three rings have two carbon atoms in common. Silphiperfol-6-ene has an angular triquinane geometry where all three rings share a central carbon atom. Finally hirsutene contains a linear triquinane in which two of the cyclopentane rings surround a central ring. Additionally, a particularly interesting natural product is crinipellin A that contains both a linear and an angular triquinane. For the synthesis of crinipellin A, a tandem radical cyclization approach is ideal and efforts towards constructing the angular triquinane portion by a tandem cyclization sequence have been reported.[4b,29] As a different approach, we wanted to explore the construction of the linear triquinane portion of crinipellin A using a tandem radical cyclization.

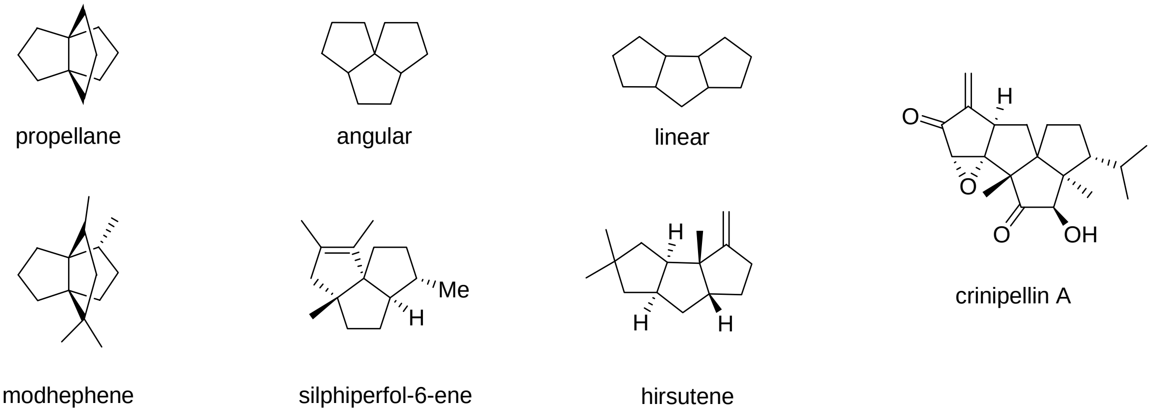
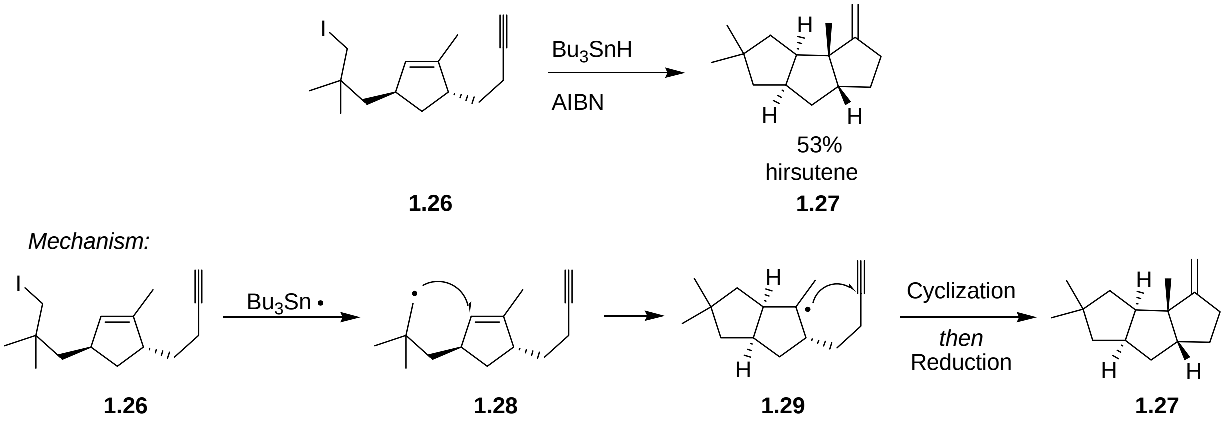


Figure 1-5: Triquinane geometries and natural products.

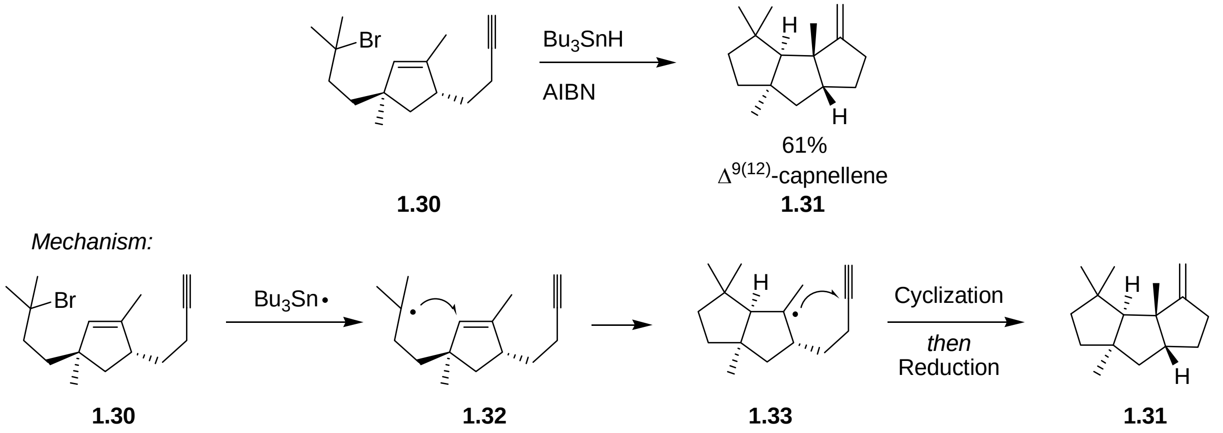
1.4.1 Total Synthesis of Linear Triquinane Natural Products

Tandem radical cyclizations have been employed in the synthesis of several linear triquinane natural products. The synthesis of (±)-hirsutene[30] by Curran and Rakiewicz was the first report of a total synthesis using this approach, and is shown in Scheme 1-5. The radical precursor in this case is iodide **1.26** and upon treatment with AIBN and Bu_3SnH gives (±)-hirsutene **1.27** in 53% yield. The cascade cyclization is initiated by a stannyl radical abstracting iodine from precursor **1.26** to give primary radical **1.28**. This radical then undergoes a 5-*exo trig* cyclization to give tertiary radical **1.29**. Intermediate **1.29** is now perfectly arranged to undergo a 5-*exo dig* cyclization with the pendant alkyne to give (±)-hirsutene **1.27** upon reduction.



Scheme 1-5: Total synthesis of hirsutene.

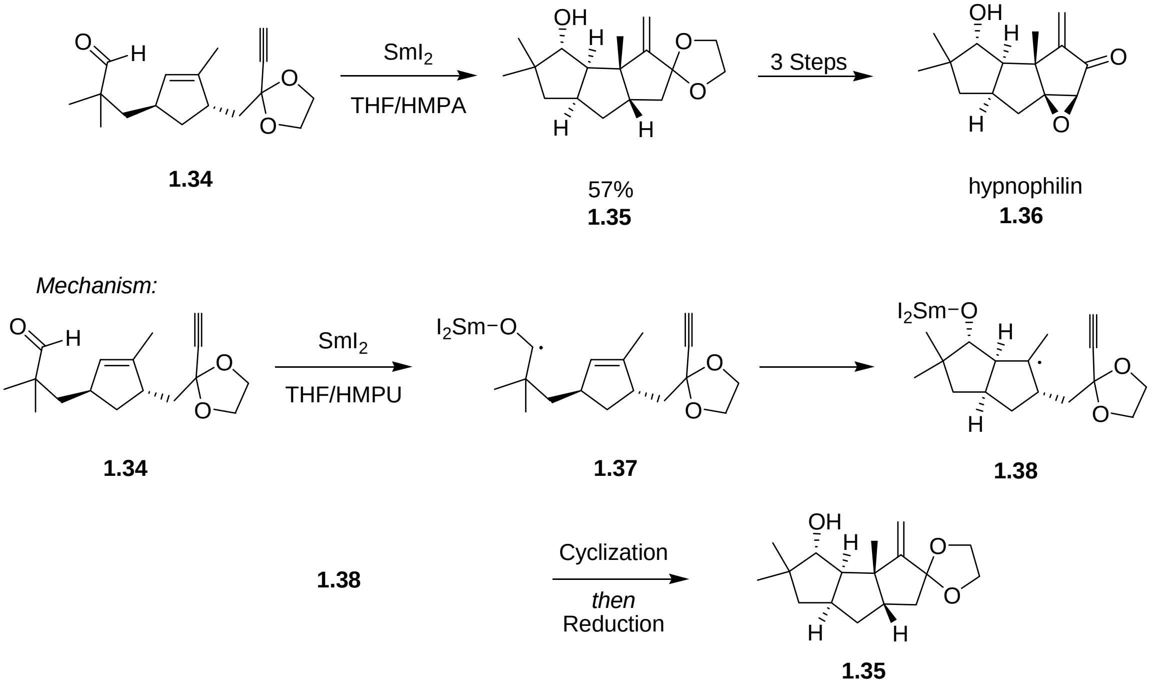
A similar strategy was used in the total synthesis of $\Delta^{9(12)}$-capnellene[31] starting from bromide **1.30**, Scheme 1-6. Treatment of radical precursor **1.30** with Bu_3SnH and AIBN furnishes $\Delta^{9(12)}$-capnellene **1.31** in 61% yield. The first step in the cascade is abstraction of the bromide from **1.30** by a stannyl radical to give tertiary radical **1.32**. Radical **1.32** then cyclizes in a 5-*exo trig* fashion to give bicyclic radical **1.33**, that undergoes a 5-*exo dig* cyclization to give $\Delta^{9(12)}$-capnellene upon reduction. These two total syntheses are good examples of how tandem radical cyclizations can rapidly build up molecular complexity from relatively simple starting materials.



Br
Bu3SnH
AIBN
H
H
61%
Δ9(12)-capnellene
1.30
1.31
Mechanism:
Br
Bu3Sn•
H
Cyclization
then
Reduction
H
H
1.30
1.32
1.33
1.31

Scheme 1-6: Total synthesis of hirsutene and $\Delta^{9\,(12)}$ capnellene.

The total synthesis of hypnophilin,[32] a more oxygenated member of the hirsutene family, has also been accomplished using a tandem radical cyclization, Scheme 1-7. In this synthesis treatment of radical precursor **1.34** with SmI_2 in a THF/HMPA solvent mixture yields linear triquinane **1.35** in 57% yield. From compound **1.35**, the total synthesis of hypnophilin **1.36** is completed in three steps. The cascade cyclization is initiated by treatment of aldehyde **1.34** with SmI_2 to give ketyl radical **1.37**. Radical cyclization of **1.37** gives compound **1.38** that undergoes a 5-*exo dig* cyclization with the alkyne to give acetal **1.35** after reduction. This synthesis nicely demonstrates how the mild reaction conditions of radical cyclizations can tolerate dense oxygenation and the sensitive acetal functionality. This functional group tolerance is important to consider because crinipellin A is also densely oxygenated.



Scheme 1-7: Total synthesis of hypnophilin.

1.4.2 Synthesis of Linear Triquinanes from Acyclic Precursors

It is clear that a tandem radical cyclization approach to linear triquinane synthesis is efficient. In the three examples presented above, the diastereoselectivity of the cyclization is dictated by the stereochemistry of the cyclopentene ring present in the radical precursor. While using the pre-existing ring as a stereochemical template is successful, it can make the synthesis of the precursors somewhat tedious. An attractive and more direct approach to linear triquinanes would be to use a tandem radical cyclization approach starting from an acyclic precursor.

A number of strategies have been developed for the synthesis of linear triquinanes from acyclic precursors, some of which are summarized in Figure 1-6.[29d, 33] In the zipper strategy, the radical is generated in the middle of the chain and the cascade then brings the two ends together. In a macrocyclization, strategy the radical is generated at one end of the chain and the first cyclization forms a large ring which then closes down to make the linear triquinane. Finally, a round-trip approach is unique in that the site of the last radical attack is also the carbon where the radical was initially generated. The round-trip strategy further distinguishes itself by being the only one where the formation of geminal bonds is possible.

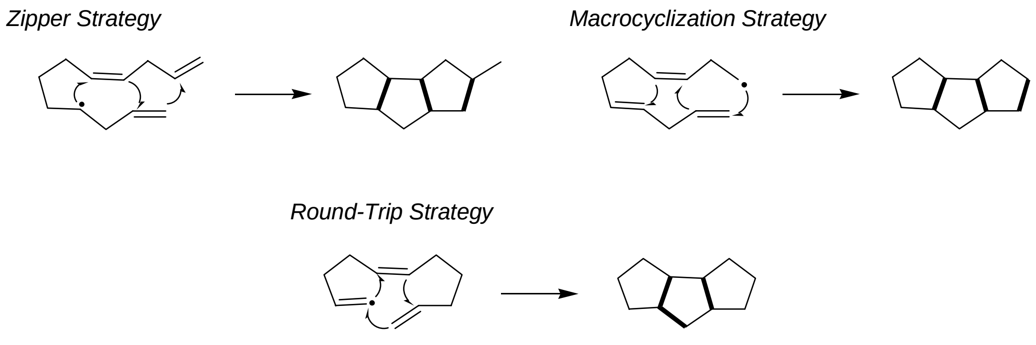
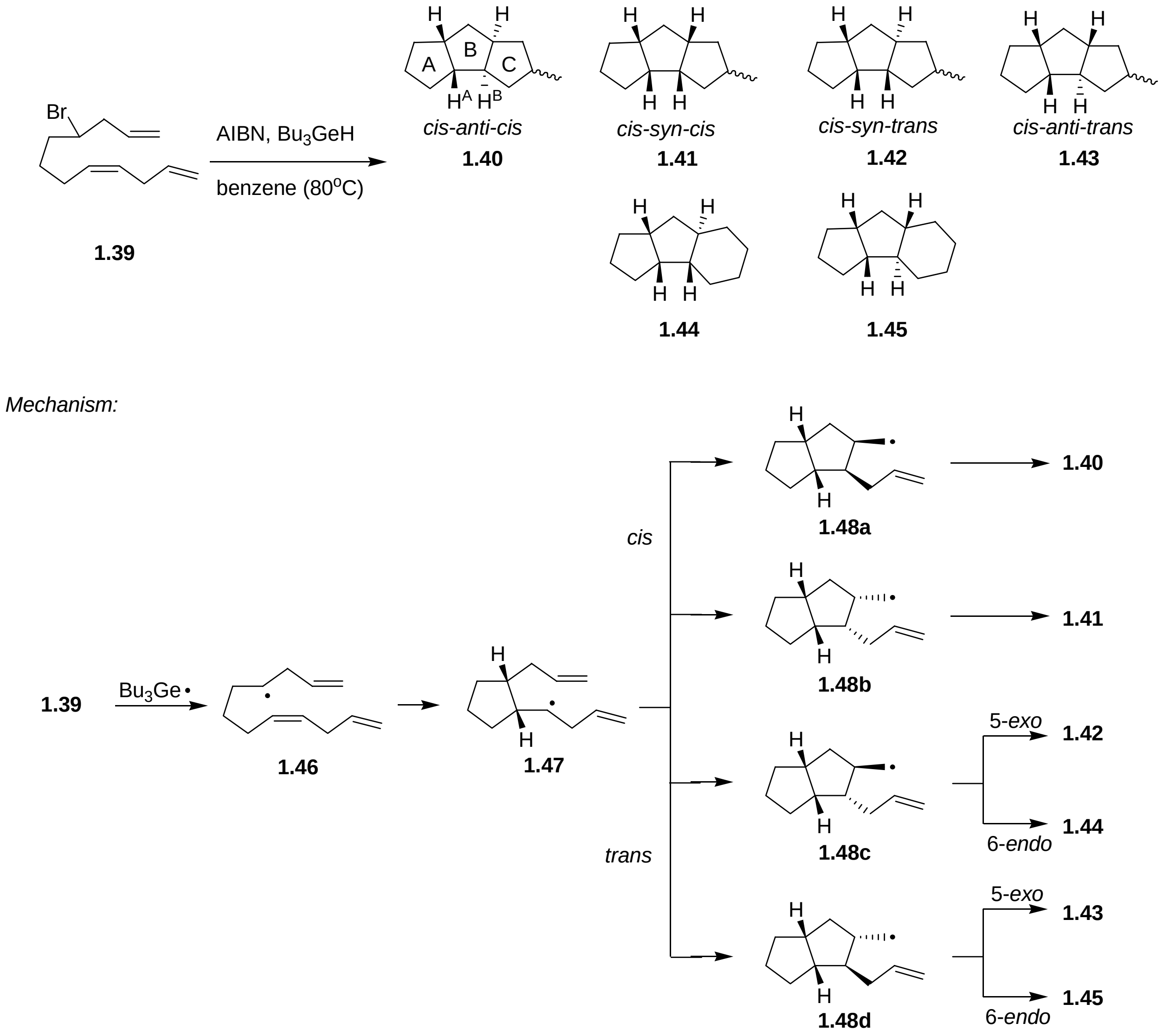


Figure 1-6: Strategies for the synthesis of linear triquinanes from acyclic precursors. Bolded bonds indicate those that are formed during the cascade.

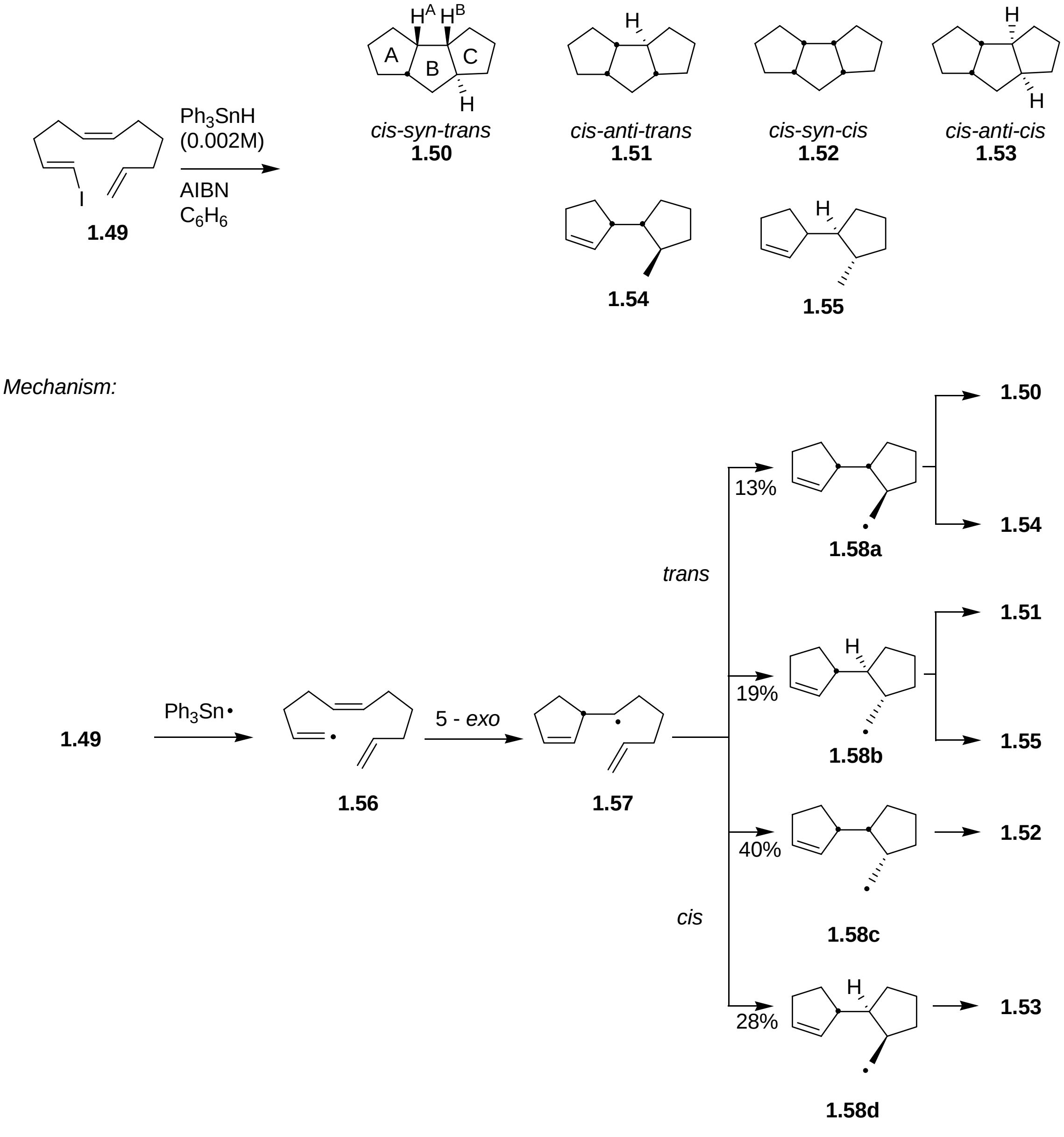
In early work, Beckwith and co-workers[34] demonstrated both the power and problems of synthesizing linear triquinanes from an acyclic precursor through a tandem radical cyclization, as shown in Scheme 1-8. They employed a zipper strategy starting from bromide **1.39**. Reduction of radical precursor **1.39** with AIBN and Bu_3GeH gave a complex mixture of linear triquinanes **1.40-1.43** and two cyclohexane containing products **1.44** and **1.45**. The nomenclature of the linear triquinane products is either *cis* or *trans* based on the ring fusion of the A and B rings and then *syn* or *anti* based on the relationship of protons H^A and H^B shown in **1.40**. The final *cis* or *trans* depends on the ring fusion between the B and C rings.

The cascade cyclization is initiated with abstraction of the bromide in precursor **1.39** by a Bu_3Ge• to give acyclic radical **1.46**. Radical **1.46** then cyclizes selectively to give *cis* substituted cyclopentane **1.47**. The problems in this cascade arise in the second cyclization because radical **1.47** can cyclize in a *cis* fashion to give radical **1.48a** or **1.48b**. However **1.47** can also cyclize in a *trans* fashion to give products **1.48c** or **1.48d**. Finally, each diastereomer of **1.48** cyclizes to give a single linear triquinane **1.40** through **1.43** upon reduction. Furthermore the final 5-*exo* cyclization of the two *trans* substituted products **1.48c** and **1.48d** is slow allowing the 6 *endo* pathway to compete giving cyclohexanes **1.44** and **1.45**.


Br
AIBN, Bu3GeH
benzene (80°C)
1.39
A
B
C
H
H
H^A H^B
cis-anti-cis
1.40
cis-syn-cis
1.41
cis-syn-trans
1.42
cis-anti-trans
1.43
1.44
1.45
Mechanism:
1.39
Bu3Ge•
1.46
1.47
cis
trans
1.48a
1.48b
1.48c
1.48d
1.40
1.41
5-exo
1.42
6-endo
1.44
5-exo
1.43
6-endo
1.45

Scheme 1-8: Beckwith's synthesis of linear triquinanes from an acyclic precursor.

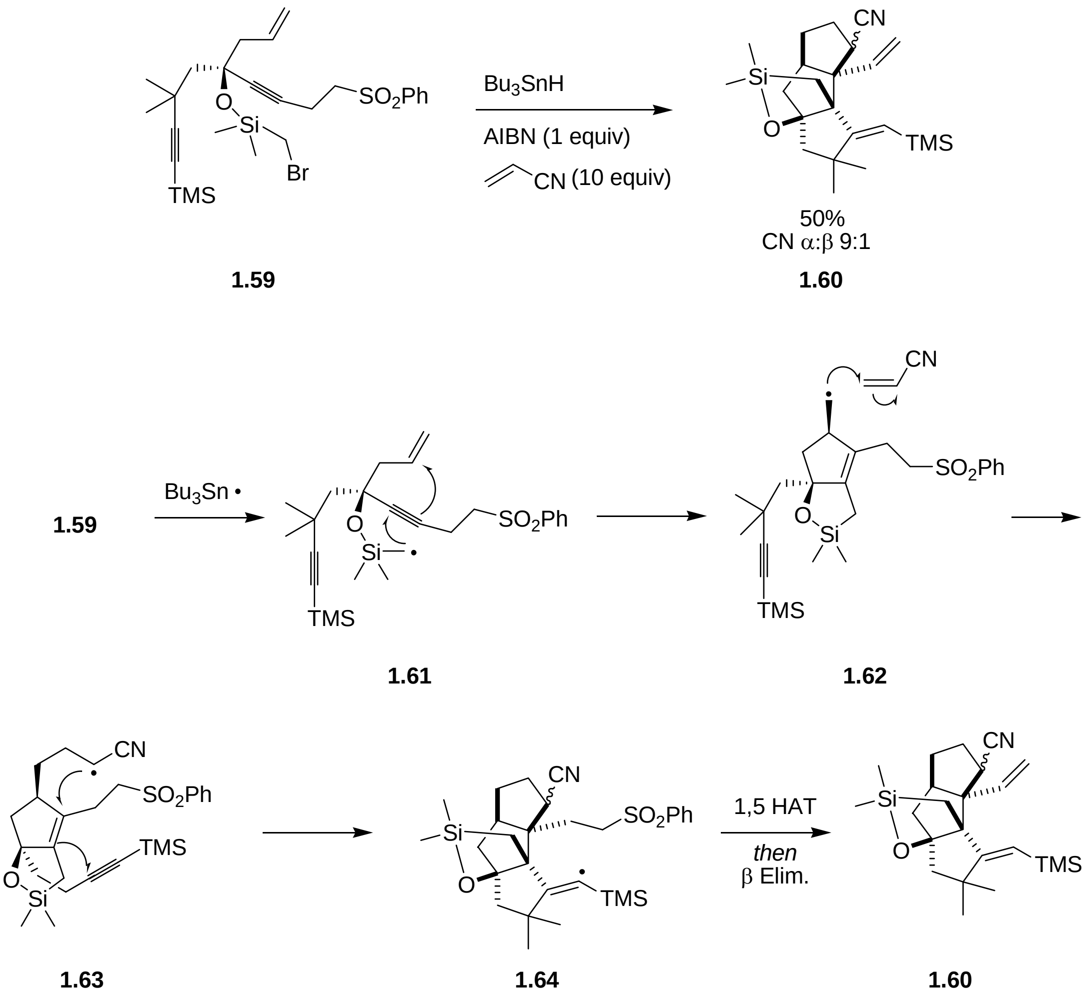
Curran and Sun reported[35] a round-trip radical cyclization approach to linear triquinanes from an acyclic precursor as shown in Scheme 1-9. Treatment of triene **1.49** with Ph_3SnH and AIBN gives rise to four triquinane products **1.50-1.53** and two bicyclic products **1.54** and **1.55**. The cascade starts when a Ph_3Sn• radical abstracts an iodine from precursor **1.49** to give vinyl radical **1.56**. Acyclic radical **1.56** then quickly cyclizes to give monocycle **1.57**. Radical **1.57** can then cyclize in a *trans* fashion to give products **1.58a** or **1.58b** or in a *cis* fashion to give bicycles **1.58c** or **1.58d**. The final cyclization in the cascade is forming a 5,5 fused bicyclic system that is known[36] to give exclusively the *cis* product. For this reason, each bicyclic radical **1.58a-1.58d** cyclizes to give a single triquinane product **1.50-1.53**. In the case of the *trans* bicyclic radicals, **1.58a** and **1.58b** the final cyclization is slow because it is forming the more strained *trans* triquinanes. This slow cyclization allows reduction by Ph_3SnH to compete giving rise to the bicyclic products **1.54** and **1.55**. Similar to Beckwith's work with precursor **1.39**, the diastereodiversity in the cyclization of **1.49** can be attributed to a lack of selectivity in the second of the three cyclizations.


Ph3SnH
(0.002M)
AIBN
C6H6
1.49
HA HB
A
B
C
H
cis-syn-trans
1.50
H
cis-anti-trans
1.51
cis-syn-cis
1.52
H
H
cis-anti-cis
1.53
1.54
H
1.55
Mechanism:
1.49
Ph3Sn•
1.56
5 - exo
1.57
trans
cis
13%
1.58a
1.50
1.54
19%
H
1.58b
1.51
1.55
40%
1.58c
1.52
28%
H
1.58d
1.53

Scheme 1-9: Synthesis of linear triquinanes using a round-trip radical cyclization strategy.

Diastereoselectivity is clearly the main obstacle for the synthesis of triquinanes from acyclic precursors. Malacria and co-workers,[37] however, have had success as shown in Scheme 1-10. Treatment of bromide **1.59** with Bu_3SnH, AIBN and acrylonitrile provides tetracyclic compound **1.60** in 50% yield. This is an impressive result because the triquinane portion of compound **1.50** is obtained diastereomerically pure. They do, however, obtain a 9/1 mixture of epimers at the cyano stereocenter.

The cascade cyclization starts with the abstraction of bromide by $Bu_3Sn\bullet$ from **1.59** to give radical **1.61**. This radical then undergoes a 5-*exo dig* followed by a 5-*exo trig* cyclization to give bicycle **1.62**. Homoallylic radical **1.62** then reacts intermolecularly with acrylonitrile to give stabilized radical **1.63**. The cascade continues with a 5-*exo trig* followed by a 5-*exo dig* cyclization onto the pendant alkyne to give tetracyclic compound **1.64**. The sequence is completed by a 1,5-hydrogen atom transfer and subsequent β elimination of the sulfone to give a single *cis-anti-cis* triquinane **1.60**. The diastereoselectivity of this cascade is controlled by the formation of the oxasilolane ring in the first cyclization. While the selectivity in this cascade is impressive, the synthesis of precursor **1.59** is somewhat lengthy.

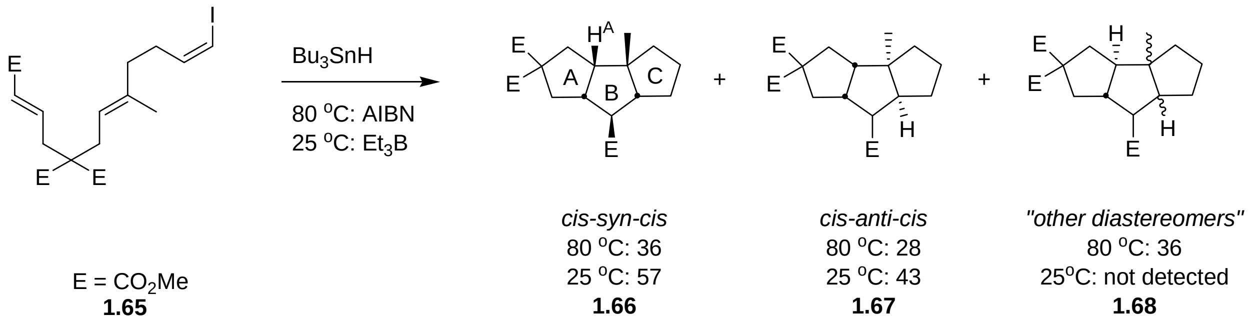

TMS
SO2Ph
Br
Bu3SnH
AIBN (1 equiv)
CN (10 equiv)
CN
TMS
50%
CN α:β 9:1
1.59
1.60
1.59
Bu3Sn •
SO2Ph
TMS
CN
SO2Ph
TMS
1.61
1.62
CN
SO2Ph
TMS
CN
SO2Ph
TMS
1,5 HAT
then
β Elim.
CN
TMS
1.63
1.64
1.60

Scheme 1-10: Malacria's diastereoselective synthesis of a *cis-anti-cis* triquinane.

1.4.3 Temperature Effects in the Synthesis of Linear Triquinanes

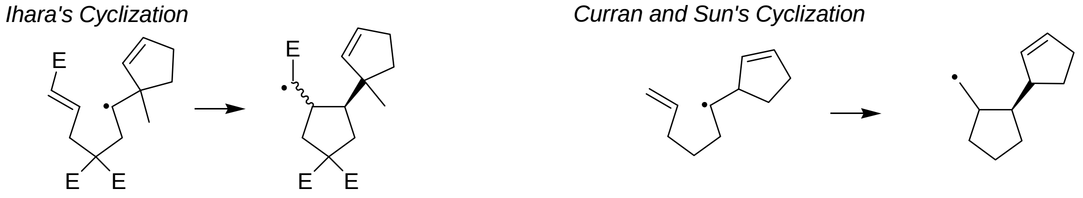
The examples presented above expose the crux of linear triquinane synthesis from acyclic precursors. If the precursor is easy to synthesize, then it does not cyclize diastereoselectively. On the other hand, if the cyclization is diastereoselective then the precursor is difficult to prepare. Controlling the diastereoselectivity of simple acyclic precursors is therefore particularly attractive, but also challenging because the stereochemical issues must be addressed by control of the reaction conditions.

In 2001, Ihara and co-workers[38] reported that reaction temperature had a dramatic effect on the diastereoselectivity of a round-trip cascade radical cyclization as shown in Scheme 1-11. Cyclization of vinyl iodide **1.65** under standard AIBN and Bu_3SnH conditions at 80 °C resulted in a mixture of the *cis-syn-cis* tricycle **1.66**, the *cis-anti-cis* tricycle **1.67**, and “other diastereomers” in a ratio of 36/28/36. Intriguingly, when the reaction was run at 25 °C using Et_3B/O_2 as the initiator, the “other diastereomers” **1.68** were not detected and the cyclization only provided tricycles **1.66** and **1.67** in a 57/43 ratio. The nomenclature of these isomers is either *cis* or *trans* depending on the A/B ring fusion and *syn* or *anti* based on the relationship between the methyl group and H^A. The final *cis* or *trans* is determined by the geometry of the of the B/C ring fusion.



Scheme 1-11: Temperature dependent cyclization of vinyl iodide **1.65.**

In this report, the structure of the *cis-syn-cis* isomer was fully assigned, but the configuration of the ester-bearing stereocenter in triquinane **1.67** was not. There was also no discussion of the identity of the “other diastereomers” **1.68**. We considered two possibilities for the “other diastereomers.” They might be the epimers at the ester stereocenter of tricycles **1.66** and **1.67** or by analogy to the cyclization of iodide **1.49**, they could be the *trans* isomers at the A/B ring junction as shown for **1.68**. These *trans* isomers would arise in the second of the three cyclizations and the corresponding hexenyl radical is shown in Figure 1-7. If the other diastereomers are indeed the *trans* cyclization products, this report implies that radical **1.69** cyclizes with a 64/37 *cis/trans* selectivity at 80 °C. This selectivity, however, improves to 100/0 when the cyclization is carried out at 25 °C as shown in Figure 1-7. To better understand this selectivity we compared the cyclization of Ihara’s hexenyl radical **1.69** to the second hexenyl radical **1.51** from Curran and Sun’s round-trip cyclization of iodide **1.49**. The cyclization of **1.49** was never run at 25 °C, but we see that the selectivity for both of these cyclizations at 80 °C is about 68/32 *cis*/*trans*.



1.69

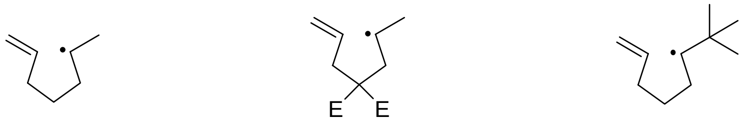
cis/trans
80 °C:64/36
25 °C: 100/0
1.70

1.51

cis/trans
80 °C: 68/32
1.52a-1.52d

Figure 1-7: Comparison of the key hexenyl radicals from the second cyclization.

Direct comparison of these two results is difficult because the hexenyl radicals **1.51** and **1.69** are materially different in three ways, all of which could affect the selectivity of the key second cyclization. First, the 1-substituent of radical **1.69** is tertiary whereas in radical **1.51**, it is secondary. Second, hexenyl radical **1.69** has a geminal ester substitution in the 3 position where **1.51** only has two hydrogens. Third, the acceptor olefin in **1.69** is an α,β-unsaturated ester whereas in **1.51** it is terminal. While the combined effects of all of these differences is hard to predict, there are a number of literature benchmarks that provide some indication as to what the individual effects might be, as shown in Figure 1-8.



cis/trans
65 °C: 70/30
1.71

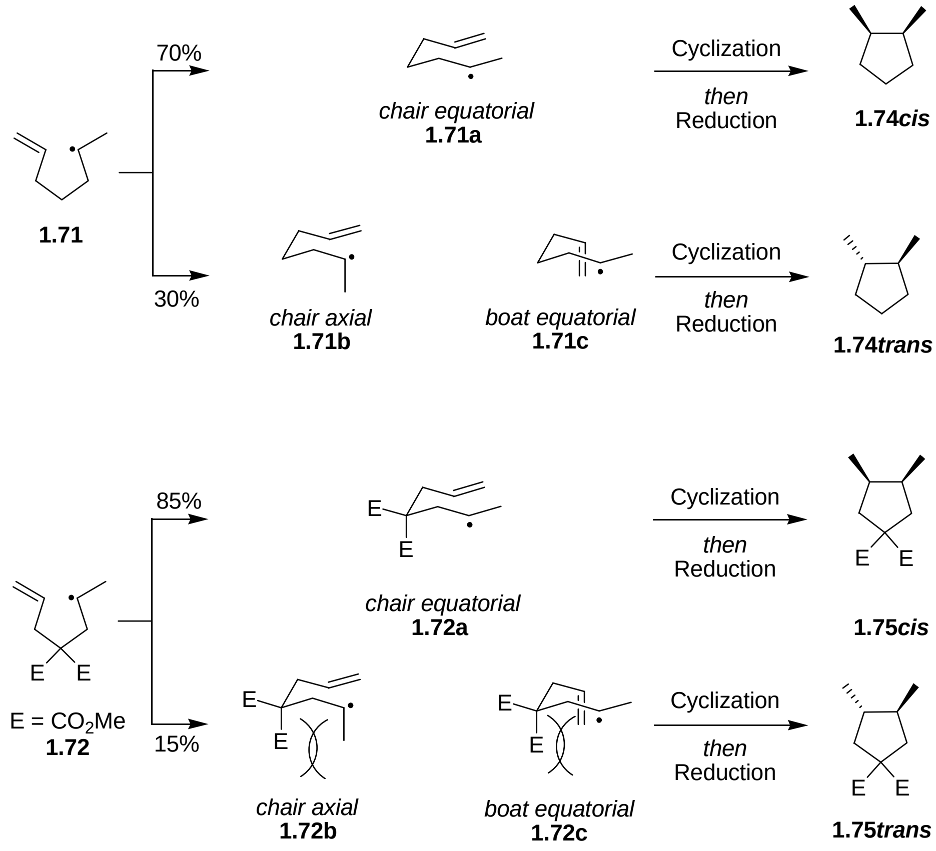
cis/trans
83 °C: 85/15
1.72

cis/trans
80 °C: 44/56
25 °C: 25/75
1.73

Figure 1-8: Literature benchmarks for related hexenyl radical cyclizations.

The results from the cyclization of **1.71** and **1.72** show that by placing a geminal ester group in the 3 position of the hexenyl radical the *cis* selectivity improves from 70/30 to 85/15 *cis/trans*. In hexenyl radical cyclizations, malonates are well known to not only accelerate the reaction by virtue of the Thorpe-Ingold effect,[39] but also to improve the *cis* selectivity.[40] The improvement to the selectivity can be nicely understood using the Beckwith-Houk transition state model, as shown in Scheme 1-12. Radical **1.71** can adopt three transition states: *chair-equatorial* **1.71a**, *chair-axial* **1.71b**, and *boat-equatorial* **1.71c**. A fourth *boat-axial* transition state (not shown) is also possible, but will be ignored because it is too high in energy to be a significant contributor. If the cyclization goes through transition state **1.71a**, then the *cis* product **1.74*cis*** is formed upon reduction of the radical. If, however, the cyclization goes through transition states **1.71b** or **1.71c**, then the product **1.74*trans*** results upon reduction. For the cyclization of **1.71**, a 70/30 *cis* preference was observed, showing that transition state **1.71a** was favored over **1.71b** and **1.71c**.

For the cyclization of **1.72**, three analogous transition states are possible, **1.72a-c**, with **1.72a** leading to the *cis* product **1.75*cis*** and **1.72b/c** proceeding to **1.75*trans*.** The latter two transition states, however, are disfavored over **1.72a** because of the indicated diaxial interaction between the methyl group or the olefin and one of the esters in the 3 position. The 1,3 diaxial interactions that are caused by the introduction of the malonate group explains why the *cis* selectivity improves from 70/30 to 85/15 when comparing the cyclizations of **1.71** and **1.72**.


70%
chair equatorial
1.71a
Cyclization
then
Reduction
1.74cis
1.71
30%
chair axial
1.71b
boat equatorial
1.71c
Cyclization
then
Reduction
1.74trans
85%
E
E
chair equatorial
1.72a
Cyclization
then
Reduction
E E
1.75cis
E E
E = CO2Me
1.72
15%
E
E
chair axial
1.72b
E
E
boat equatorial
1.72c
Cyclization
then
Reduction
E E
1.75trans

Scheme 1-12: Top: Transition state analysis for the cyclization of **1.71**. Bottom: Transition state analysis for the cyclization of **1.72**.

The cyclization of hexenyl radical **1.73** reported by Beckwith[41] is an important benchmark because of the *t*-butyl group in the 1 position. The *t*-butyl group in **1.73** is comparable in size to the 1-(1-methylcyclopent-2-enyl) group from radical **1.69**. However, this benchmark hexenyl radical cyclizes with a *trans* preference. This is an exception to the rule because the *cis* selectivity of 1-substituted hexenyl radicals is one of the firmest stereochemical trends in radical cyclization reactions. Interestingly, the stereoselectivity for the cyclization of radical **1.73** also exhibits a dramatic temperature effect improving from 44/56 *cis*/*trans* at 80 °C to 24/76 at 25 °C. So Ihara and Beckwith's cyclizations both exhibit a dramatic temperature effect, but for the opposite stereoisomer! Given the presence of the malonate in Ihara's hexenyl radical, this result is not entirely inconceivable. Still it is striking that the selectivity in the cyclization of **1.73** could be completely overturned from *trans* to *cis* by the placement of the malonate group in the 3 position.

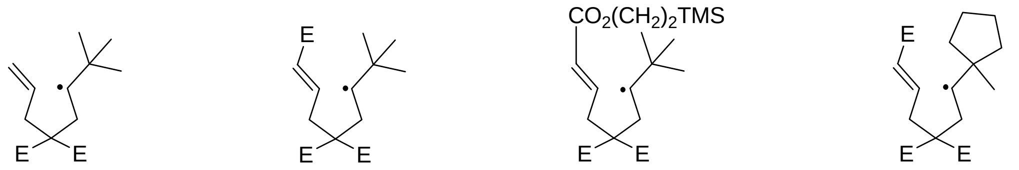
Finally, the α,β-unsaturated ester that is present in radical **1.69** will accelerate the rate of the cyclization,[36a] but is not expected to affect the stereochemical outcome. This acceleration is due to the electron withdrawing effect of the ester making the olefin more electrophilic towards the radical.

1.5 Goals

In an attempt to unravel these puzzling temperature and substituent effects, we wanted to extend the number of benchmark substrates to more accurately represent the hexenyl radical for the second cyclization in Ihara's cascade. We also wanted to gain more insight into Ihara's cyclization by getting a better idea of what the "other diastereomers" are. These endeavors are intended to provide a more comprehensive understanding of how very large substituents in the 1 position affect the stereoselectivity in hexenyl radical cyclizations, both alone and in combination with other substituents.

Chapter 2 Stereochemistry of Hexenyl Radical Cyclizations with *tert*-Butyl and Related Large Groups in the 1 Position

To assess the stereochemical outcome of a 3,3 geminally di-substituted hexenyl radical cyclization with a large group in the 1 position, we choose to study the four radicals shown in Figure 2-1. These four radicals serve to extend the number of benchmarks needed to better understand Ihara's cyclization results. Hexenyl radicals **2.1** and **2.2a**, are benchmarks to determine the effect of an α,β-unsaturated ester on the cyclization and radical **2.2b** serves as a relay between the products of the previous two cyclizations for a rigorous assignment of configuration. Radical **2.3** is structurally very close to Ihara's system; it only lacks an olefin in the cyclopentane ring, preventing the round-trip cascade from being completed. However, this modification greatly simplifies product analysis because only two products, *cis* and *trans* cyclopentane isomers, are now possible.



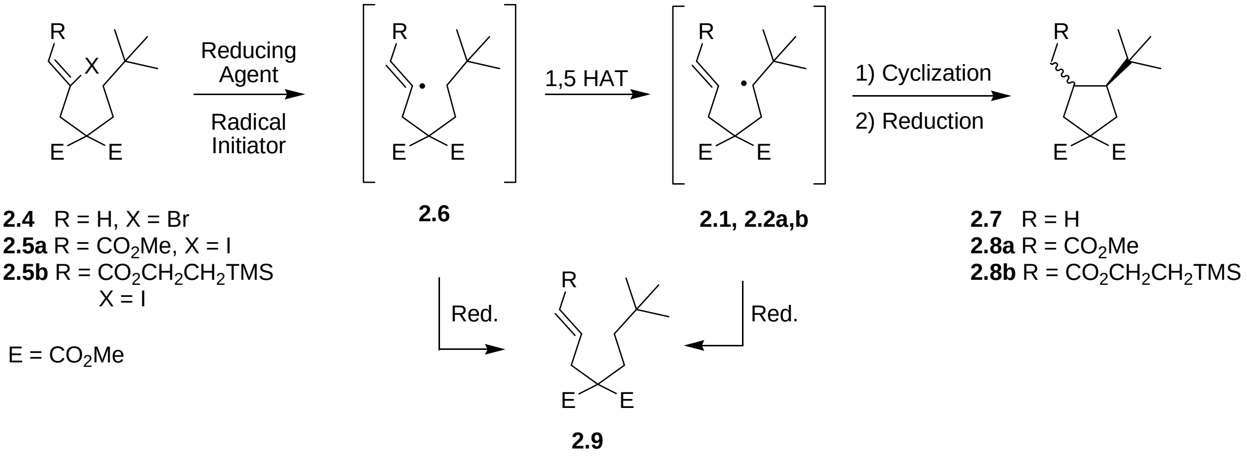
2.1 **2.2a** **2.2b** **2.3**

E = CO$_2$Me

Figure 2-1: New cyclization benchmarks.

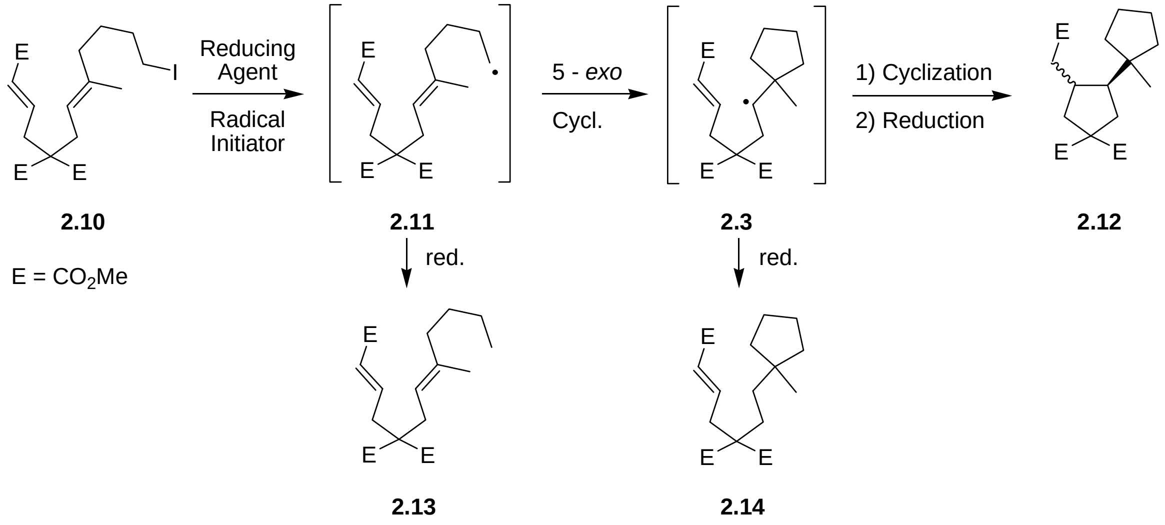
2.1 Substrate Design and Synthesis

For convenience of precursor synthesis, we decided to generate radicals **2.1** and **2.2a**,**b** by a 1,5 hydrogen atom transfer (1,5 HAT), as shown in Scheme 2-1. Treatment of vinyl halides **2.4** and **2.5a**,**b** with a suitable reducing agent and radical initiator gives vinyl radicals **2.6**, which undergo a 1,5 HAT to give the hexenyl radicals of interest **2.1** and **2.2a**,**b.** These radicals, after cyclization and reduction, give cyclopentanes **2.7** and **2.8a**,**b** as mixtures of the *cis* and *trans* isomers. A potential side reaction for this cascade is the direct reduction of **2.1**, **2.2a**,**b**, or **2.6** to give **2.9**.


Reducing Agent
Radical Initiator
1,5 HAT
1) Cyclization
2) Reduction
Red.
Red.
R
X
E
2.4 R = H, X = Br
2.5a R = CO2Me, X = I
2.5b R = CO2CH2CH2TMS X = I
E = CO2Me
2.6
2.1, 2.2a,b
2.7 R = H
2.8a R = CO2Me
2.8b R = CO2CH2CH2TMS
2.9

Scheme 2-1: Cyclization precursors and pathways for generation of radicals **2.1** and **2.2 a**,**b**.

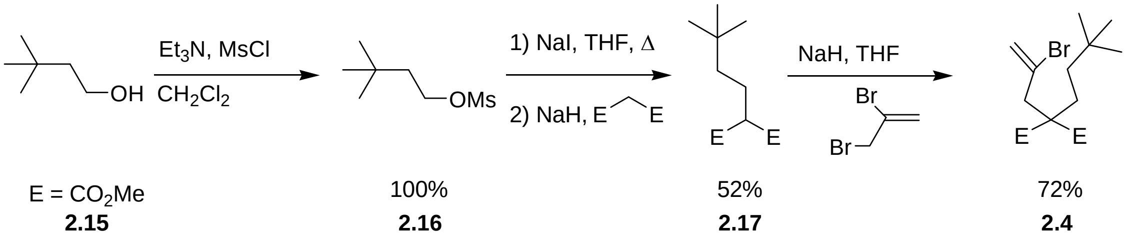
For generation of hexenyl radical **2.3**, we relied on a cascade sequence starting from alkyl iodide **2.10**, as shown in Scheme 2-2. Radical **2.11**, formed by abstraction of iodine from **2.10**, cyclizes in a 5-*exo* fashion to give the desired hexenyl radical **2.3**. After cyclization and reduction, adduct **2.12** is formed as a mixture of *cis* and *trans* isomers. For this cascade, the prematurely reduced products are **2.13** and **2.14** arising from the reduction of **2.11** and **2.3**, respectively.


Reducing Agent
Radical Initiator
5 - exo Cycl.
1) Cyclization
2) Reduction
red.
red.
E
I
2.10
E = CO2Me
2.11
2.3
2.12
2.13
2.14

Scheme 2-2: Cyclization precursor and pathway for the generation of radical **2.3**.

2.1.1 Synthesis of Cyclization Precursor 2.4

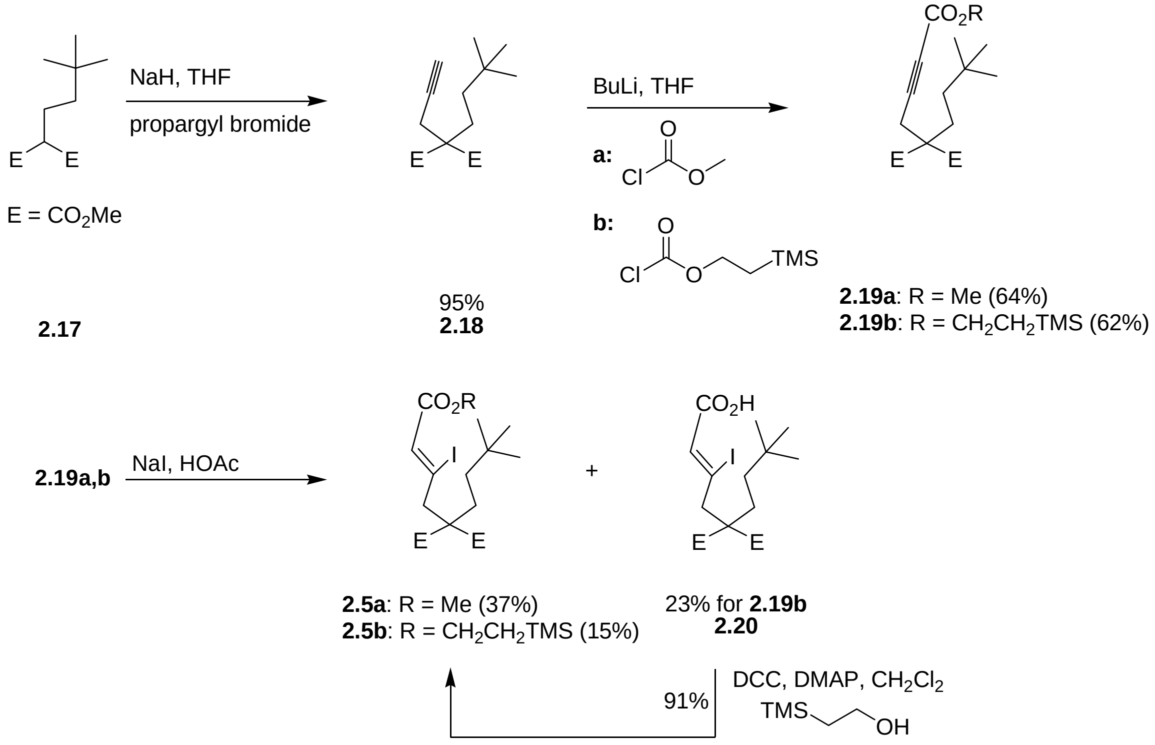
The synthesis of cyclization precursor **2.4** is outlined in Scheme 2-3. Treatment of 3,3-dimethylbutanol **2.15** with triethylamine and mesyl chloride gave mesylate **2.16** in quantitative yield.[42] Treatment of the crude mesylate with NaI in refluxing THF for 16 h gave the corresponding iodide.[43] This was not isolated, but used directly in the alkylation of the dimethylmalonate anion generated from treatment of dimethylmalonate with NaH in THF. Refluxing this mixture gave substituted malonate **2.17** in 52% yield.[44] Treatment of **2.17** with NaH and alkylation of the subsequent anion with 2,3-dibromopropene gave *bis*-substituted malonate **2.4** in 72% yield.



Scheme 2-3: Synthesis of cyclization precursor **2.4**.

2.1.2 Synthesis of Cyclization Precursors 2.5a,b

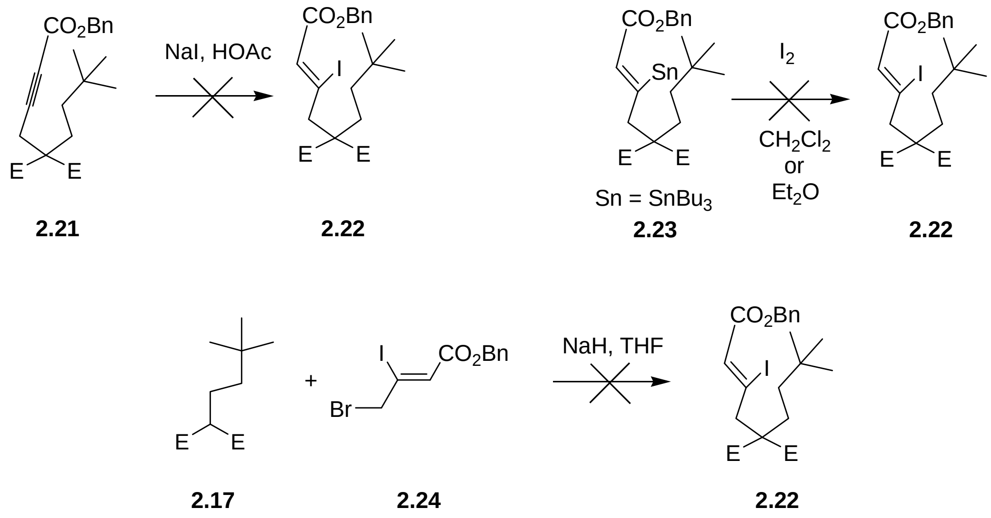
The general synthesis of the α,β-unsaturated ester cyclization precursors **2.5a**,**b** is outlined in Scheme 2-4, with the synthesis of **2.5a** being representative. Treatment of malonate **2.17** with NaH and quenching of the resulting anion with propargyl bromide gave *bis*-substituted malonate **2.18** in 95% yield. Deprotonation of the alkynyl proton using BuLi and addition of methyl chloroformate to the anion gave alkynyl malonate **2.19a** in 64% yield.[45] Treatment of the internal alkyne with NaI in acetic acid gave vinyl iodide **2.5a** as a single regio- and stereoisomer in 37% yield.[46]


NaH, THF
propargyl bromide
E = CO2Me
2.17
95%
2.18
BuLi, THF
a:
b:
TMS
Cl
O
CO2R
2.19a: R = Me (64%)
2.19b: R = CH2CH2TMS (62%)
2.19a,b
NaI, HOAc
CO2H
I
+
2.5a: R = Me (37%)
2.5b: R = CH2CH2TMS (15%)
23% for 2.19b
2.20
91%
DCC, DMAP, CH2Cl2
TMS
OH
E

Scheme 2-4: Synthesis of cyclization precursors **2.5a**,**b**.

The low yield in the hydroiodination of alkyne **2.19b** to give **2.5b** is attributed to hydrolysis of the ethyl TMS ester functionality to give the corresponding acid **2.20**, which accounted for 23% of the material. Acid **2.20** could be isolated and recycled in a DCC-mediated coupling with 2-trimethylsilylethanol to give back **2.5b** in 91% yield.[47] The *Z*-stereochemistry of the final vinyl iodides was assigned based on literature precedent.[48] Regardless, the *Z* and *E* isomers give the same rapidly interconverting vinyl radical **2.6** upon treatment with AIBN and Bu_3SnH.[49]

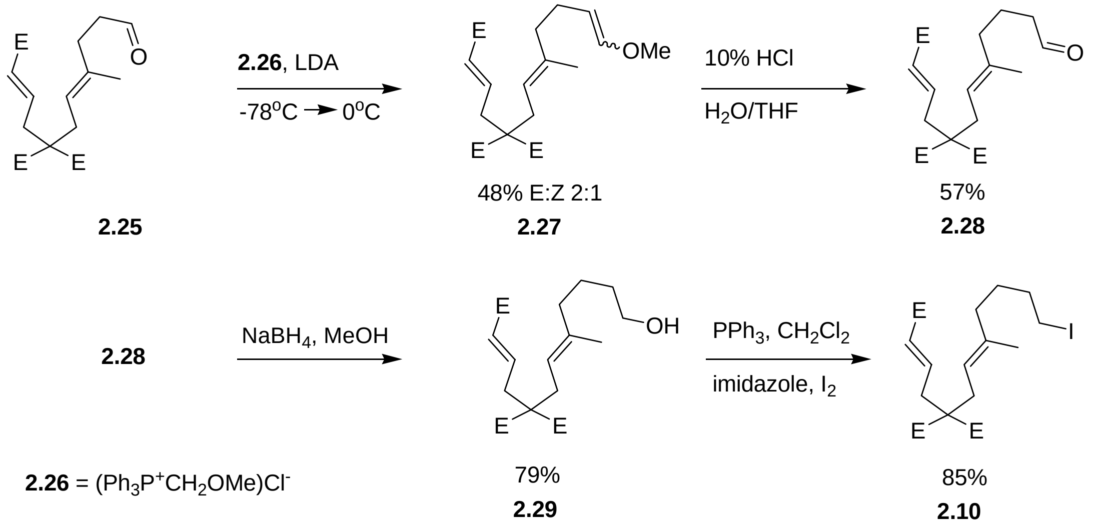
Initially we envisioned using a benzyl ester **2.22** instead of the ethyl TMS ester for the structural relay substrate. However, the synthesis of this precursor was unsuccessful despite a variety of approaches as shown in Scheme 2-5. Hydroiodination of alkyne **2.21** simply led to decomposition, presumably due to iodination at the benzylic position. Surprisingly the iododestannylation of **2.23** in either CH_2Cl_2 or Et_2O also failed, probably for the same reason. As a final approach, an alkylation of malonate **2.17** was attempted with allylic bromide **2.24**, but no desired compound **2.22** could be isolated. The most likely reason for the failure of this reaction is that either NaH or the malonate anion deprotonated one of the activated allylic protons of **2.24** before an S_N2 displacement of the bromide could occur.


CO2Bn
E
E
2.21
NaI, HOAc
CO2Bn
I
E
E
2.22
CO2Bn
Sn
E
E
Sn = SnBu3
2.23
I2
CH2Cl2
or
Et2O
CO2Bn
I
E
E
2.22
E
E
2.17
+
I
CO2Bn
Br
2.24
NaH, THF
CO2Bn
I
E
E
2.22

Scheme 2-5: Attempted approaches towards relay precursor **2.22**.

2.1.3 Synthesis of Cyclization Precursor 2.10

The synthesis of cyclization precursor **2.10** is outlined in Scheme 2-6. Treatment of aldehyde **2.25**, the synthesis of which is discussed in Chapter 3, with LDA and Wittig salt **2.26**[50] gave a 2:1 *E*:*Z* mixture of enol ether **2.27** in 48% yield. Stirring this enol ether in dilute hydrochloric acid quickly converted it to the homologated aldehyde **2.28** in 57% yield. Sodium borohydride reduction[51] of aldehyde **2.28** gave alcohol **2.29** in 79% yield. Alcohol **2.29** was then converted to the corresponding iodide **2.10** in 85% yield by treating it with PPh_3, imidazole and I_2.[52]



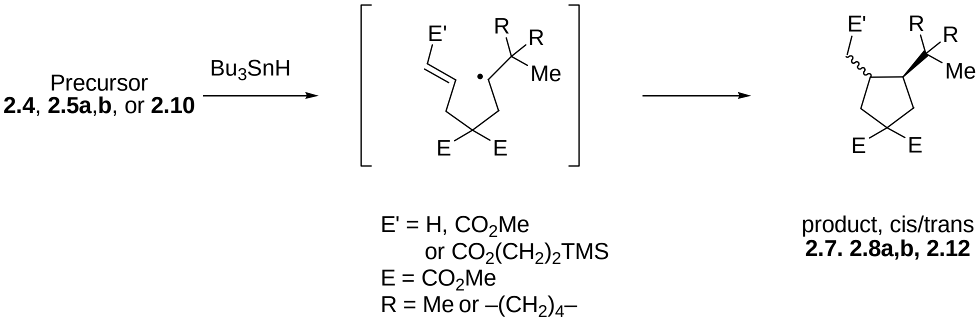
Scheme 2-6: Synthesis of iodide **2.10**.

2.2 Cyclization Results

The cyclizations of the benchmark substrates were all carried out under similar conditions and the results are summarized in Table 2-1. For reactions at 80 °C, the precursor (0.1 mmol) was dissolved in benzene (50 mL, 2 mM with respect to the precursor) and then AIBN (0.05 mmol) and Bu_3SnH (0.12 mmol) were added sequentially. The resulting solution was then refluxed for 4 h, cooled to room temperature and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel to remove the tin by-products and obtain an isolated yield. The mixture was then analyzed by NMR spectroscopy and GC to determine the ratio of *cis* and *trans* products. Both techniques gave very similar results, so only the GC ratio is recorded in the table. For the reactions run at 25 °C, the procedure was similar to the one described above, but the radical initiator was changed from AIBN to Et_3B/O_2. Furthermore, the initiator was the last component to be added to the reaction mixture.

The data in Table 2-1 show that, all four of the precursors exhibit a modest *cis* preference (78/22) when cyclized at 80 °C (entries 2, 4, 6 and 8). The *cis* preference of the cyclization improves marginally to 81/19 when the reaction temperature is lowered to 25 °C (entries 3, 5 and 7). In the reaction of vinyl bromide **2.4** at room temperature, entry 1, all of the starting material was recovered indicating that chain propagation failed under these conditions.

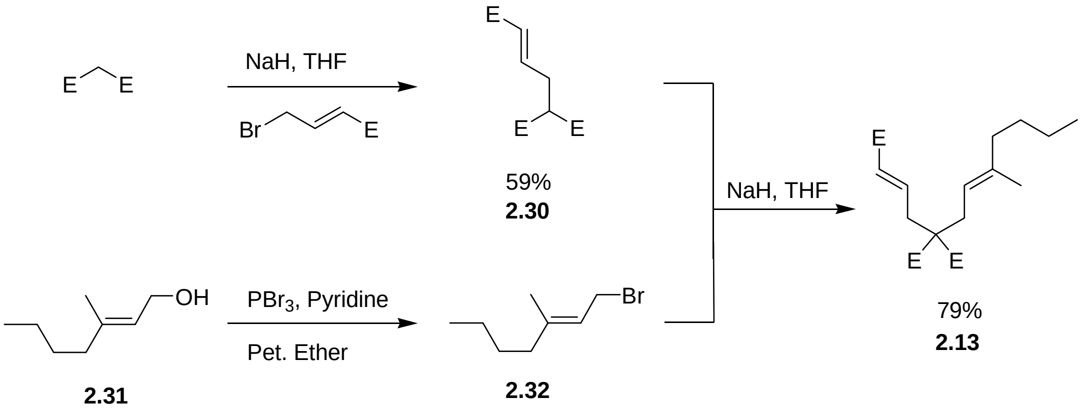
Table 2-1: Cyclization data for precursors **2.4**, **2.5a**,**b** and **2.9**.



Entry	Precursor	R	E′	Cyclization Method[a]	T (°C)	Product	Selectivity *cis/trans*[b]	Yield[c] (%)
1	**2.4**	Me	H	A	25	**2.7**	-	-
2	**2.4**	Me	H	B	80	**2.7**	75/25	50%
3	**2.5a**	Me	CO_2Me	A	25	**2.8a**	83/17	45%
4	**2.5a**	Me	CO_2Me	B	80	**2.8a**	78/22	52%
5	**2.5b**	Me	$CO_2(CH_2)_2TMS$	A	25	**2.8b**	79/21	35%
6	**2.5b**	Me	$CO_2(CH_2)_2TMS$	B	80	**2.8b**	77/23	67%
7	**2.9**	$(CH_2)_4$	CO_2Me	A	25	**2.12**	81/19	62%
8	**2.9**	$(CH_2)_4$	CO_2Me	B	80	**2.12**	80/20	60%

[a] Initiation at 80 ºC with AIBN and at 25 ºC with Et_3B/O_2 see chapter 5 for details.
[b] Raw GC ratio
[c] Isolated yield of a *cis/trans* mixture after flash chromatography

In all of the cyclizations with precursors **2.4** and **2.5a,b**, entries 2-6, prematurely reduced product **2.9** was not observed by GC or NMR. However, in the cyclization of iodide **2.10** about 5% of the crude reaction mixture was directly reduced product **2.13.** This was verified by an independent synthesis of compound **2.13**, as shown in Scheme 2-7, and subsequent GC co-injection with the crude cyclization mixture. Synthesis of the authentic sample of **2.13** started with the deprotonation of dimethyl malonate with sodium hydride and alkylation of the resulting anion with *E*-methyl-4-bromocrotonate to give malonate **2.30** in 59% yield. The next step was to treat known allylic alcohol **2.31**[53] with PBr_3 to give allylic bromide **2.32**.[54] The final step was deprotonation of malonate **2.30** with NaH in THF and quenching of the anion with bromide **2.32**, to give malonate **2.13** in 79% yield.



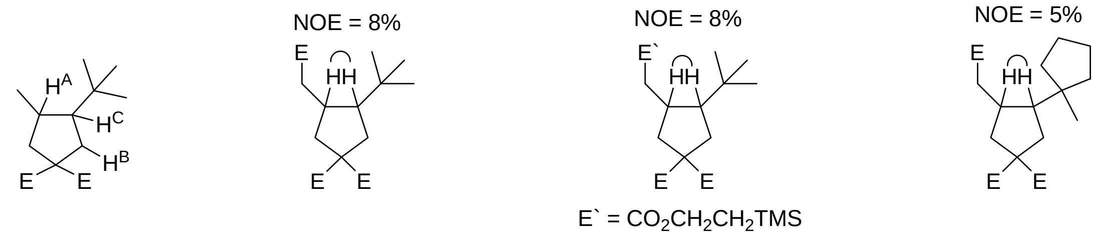
Scheme 2-7: Independent synthesis of directly reduced product **2.13**.

2.3 Configuration Assignment of the Cyclization Products 2.7, 2.8a,b and 2.12

A key aspect of this work is to unequivocally establish the configuration of the cycloadducts. Unfortunately, we were not able to preparatively separate any of the *cis* and *trans* isomers of **2.7**, **2.8a**,**b** or **2.12** by column chromatography or HPLC. This led us to pursue a threefold approach to assigning the configuration of the cyclopentanes: 1) 1D NOE analysis of the cyclization mixtures, 2) synthesis of an authentic sample of **2.7*trans***, and 3) rigorous assignment of configuration by x-ray diffraction analysis.

2.3.1 1D NOE Analysis Approach to Configurational Assignment

After extensive 1D and 2D NMR analysis of each product mixture **2.7**, **2.8a**,**b** and **2.12,** it was possible to assign all of the resonances for the major isomer in the ^{1}H NMR spectrum. With these assignments, a series of 1D NOE experiments were carried out and the key enhancements indicated in Figure 2-2 were observed. For product mixtures **2.8a**,**b** and **2.12**, the NOE enhancement between the two methine protons led us to tentatively assign the major product from each mixture as the *cis* isomer. Unfortunately, for product **2.7** protons H^A and H^B are accidentally chemical shift equivalent, making NOE analysis impossible. Additionally, in product **2.7** we observed an NOE enhancement between the methyl group and proton H^C. This was unexpected for the *cis* isomer, leading us to conclude that NOE analysis was not a reliable method for assigning the configuration of such compounds anyway.


NOE = 8%
NOE = 8%
NOE = 5%
H^A
H^C
H^B
E
HH
E`
E` = CO2CH2CH2TMS

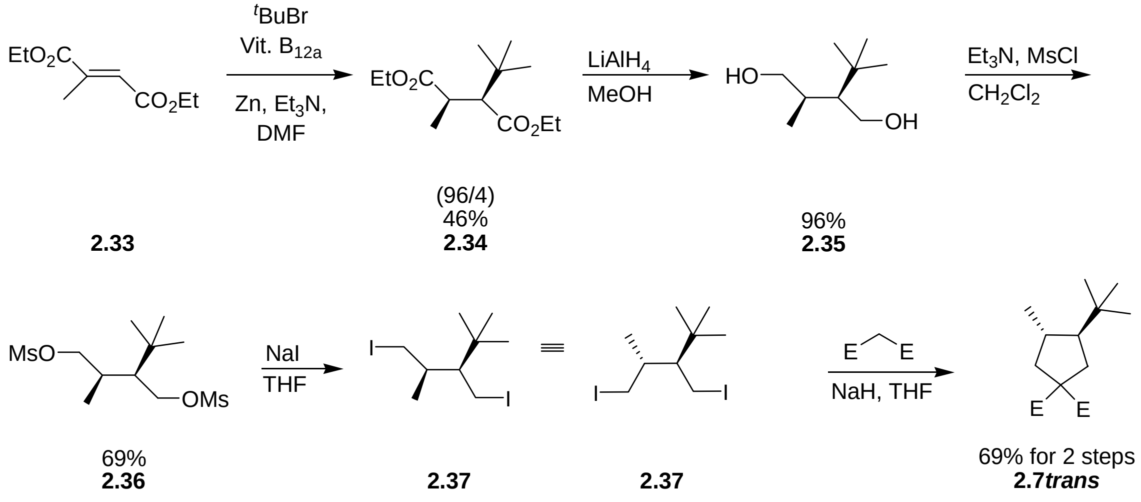
2.7 **2.8a** **2.8b** **2.12**

E = CO_2Me

Figure 2-2: NOE analysis of the four product mixtures **2.7, 2.8a**,**b** and **2.12**,

2.3.2 Configuration Assignment by Synthesis of an Authentic Sample

For rigorous structural assignment, we synthesized an authentic sample of **2.7*trans*** by the pathway shown in Scheme 2-8. Starting from diethyl mesaconoate **2.33**,[55] a vitamin B_{12a} mediated reduction gave *tert*-butyl compound **2.34** as a 96/4 *syn*/*anti* mixture of diastereomers in 46% yield.[56] Subsequent $LiAlH_4$ reduction of the diester gave diol **2.35** in 96% yield as a single diastereomer after chromatography.[57] Mesylation of the diol gave *bis*-mesylated compound **2.36** in 69% yield. By treatment of the *bis*-mesylate with NaI, the *bis*-iodide **2.37** was obtained. This was used immediately in the alkylation of the dimethylmalonate anion to give **2.7*trans*** in 69% yield as a single isomer, free of any **2.7*cis***.[58]


EtO2C
CO2Et
tBuBr
Vit. B12a
Zn, Et3N,
DMF
EtO2C
CO2Et
LiAlH4
MeOH
HO
OH
Et3N, MsCl
CH2Cl2
(96/4)
46%
2.33
2.34
96%
2.35
MsO
OMs
NaI
THF
I
I
E
E
NaH, THF
E
E
69%
2.36
2.37
2.37
69% for 2 steps
2.7trans

Scheme 2-8: Synthesis of **2.7*trans***.

With authentic **2.7*trans*** in hand, we were able to verify that the major product from the cyclization of **2.4** has the *cis* configuration by a series of GC injections. Figure 2-3a shows the GC trace when **2.7*trans*** is injected in pure form. Figure 2-3b is the trace obtained when the cyclization mixture **2.7** is injected, and finally Figure 2-3c is a co-injection of **2.7*trans*** and mixture **2.7**. These results show that the *trans* isomer is indeed the minor component of the cyclization.

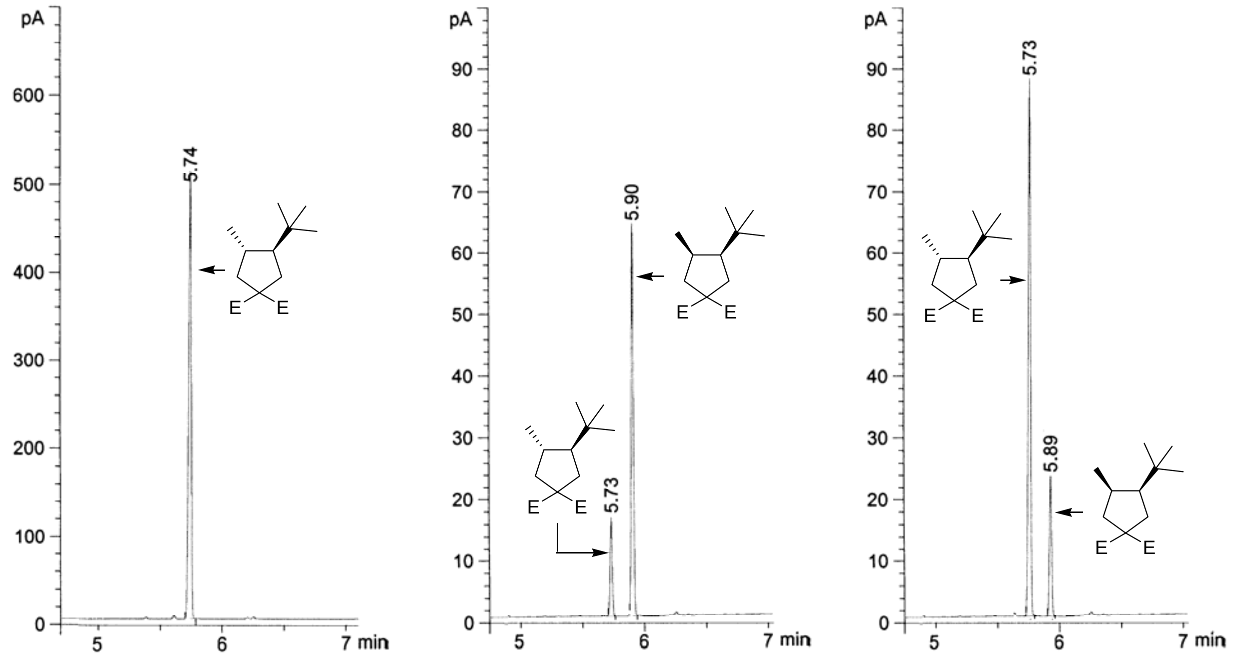
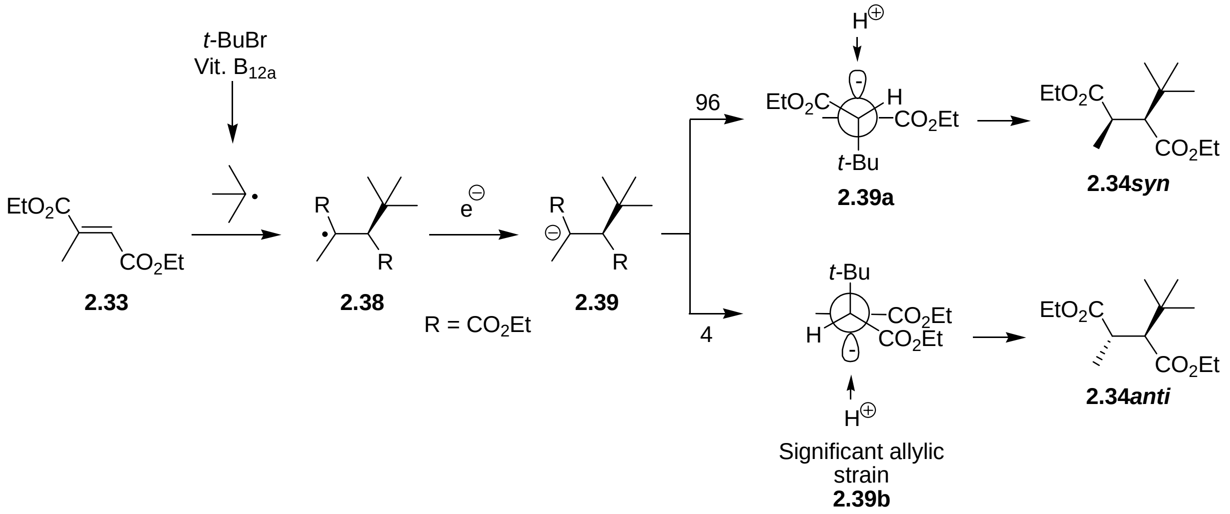


Figure 2-3: a) Left: injection of authentic **2.7*trans***, b) Middle: injection of **2.7** from the cyclization of **2.4** and c) Right: co-injection of the two. All three GC injections were performed on an Agilent 6850 gas chromatograph equipped with an HP-1 column: dimethylpolysiloxane, 30m x 0.32mm, and a 0.25 µm film thickness. The initial temperature of 100 °C was then increased by 10 °C/min to 250 °C and then by 15 °C/min to 315 °C.

The stereoselectivity in the addition of *tert*-butyl bromide to diethyl mesaconoate **2.33** in the synthesis of compound **2.34** is dictated by the minimization of $A^{1,3}$ strain as shown in Scheme 2-9. A *tert*-butyl radical, generated from *tert*-butyl bromide and vitamin $B12_a$, adds into diethylmesaconaoate **2.33** at the less substituted carbon to give radical **2.38**. Radical **2.38** is then reduced by the zinc metal to give anion **2.39**. Upon aqueous workup, the protonation of anion **2.39** must occur from the face opposite to the large *tert*-butyl group, which can be achieved by the two conformations shown in either **2.39a** or **2.39b**. If configuration **2.39a** is favored then the *syn* diester **2.34*syn*** is formed upon protonation. If however, the protonation occurs to anion

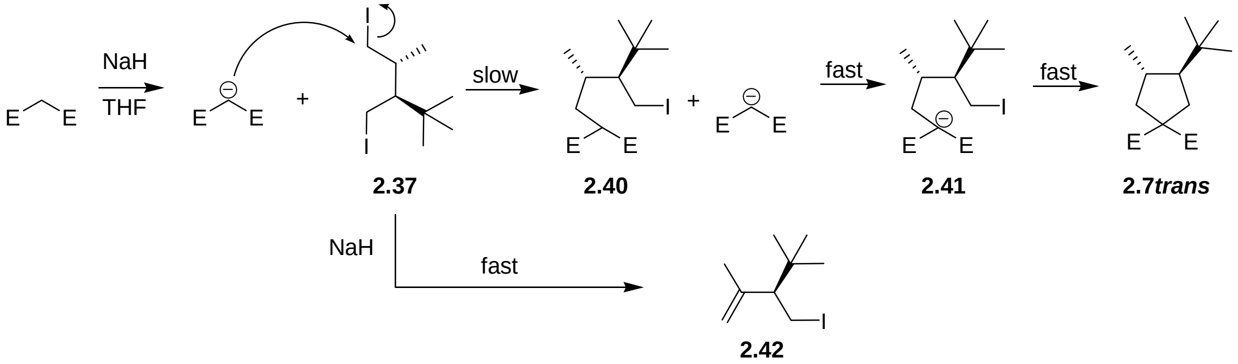
2.39b, the *anti* diester **2.34*anti*** results. The orientation depicted in **2.39b**, however, is greatly disfavored because of the allylic strain that is introduced between the two ester groups. In **2.39a** this allylic strain is not present. This difference in strain between **2.39a** and **2.39b** explains the observed 96/4 ratio of *syn*/*anti* adducts.



Scheme 2-9: Stereoselectivity in the radical addition of *tert*-butylbromide to diethylmesaconoate **2.33**.

The *bis*-alkylation of dimethyl malonate with *bis*-iodide **2.37** was an interesting reaction because of an unexpected observation. When dimethylmalonate was treated with 1 equiv of NaH followed by the addition of *bis*-iodide **2.37** and the resulting mixture was stirred, we observed a 1/1 mixture of starting iodide **2.37** and product malonate **2.7*trans***. Adding more NaH at this point simply lead to the decomposition of iodo compound **2.37** without producing any additional product **2.7*trans***. However, if more dimethylmalonate anion was added, the iodide was smoothly consumed, pushing the reaction to completion.

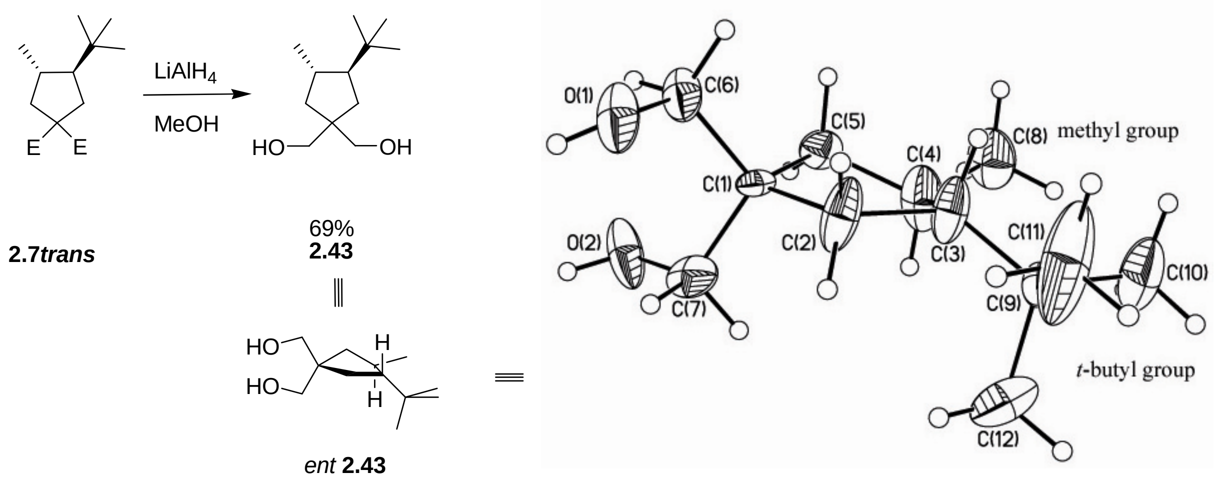
Based on these observations, we propose a mechanism for this double alkylation reaction shown in Scheme 2-10. The first alkylation of dimethylmalonate anion by iodide **2.37** to give malonate **2.40** is the rate determining step. Once intermediate **2.40** has been formed, it reacts with another equivalent of dimethylmalonate anion to give intermediate **2.41**. Anion **2.41** rapidly undergoes the second alkylation step to give **2.7*trans***. By invoking the malonate anion as the base in the second deprotonation, we can explain why a 1/1 mixture of starting material to product was initially observed even though only 1 equiv of NaH had been added. Using the malonate base for the second deprotonation is further supported by the observation that more malonate anion drives the reaction to completion. That additional NaH is detrimental to the reaction is explained by the elimination of HI from **2.37** to give **2.42** being faster than the first alkylation of the anion. Fortunately the malonate anion is not a strong enough base to effect this elimination.



Scheme 2-10: Proposed mechanism for the bis alkylation reaction of dimethyl malonate.

2.3.3 Configuration Assignment by X-Ray Crystallography

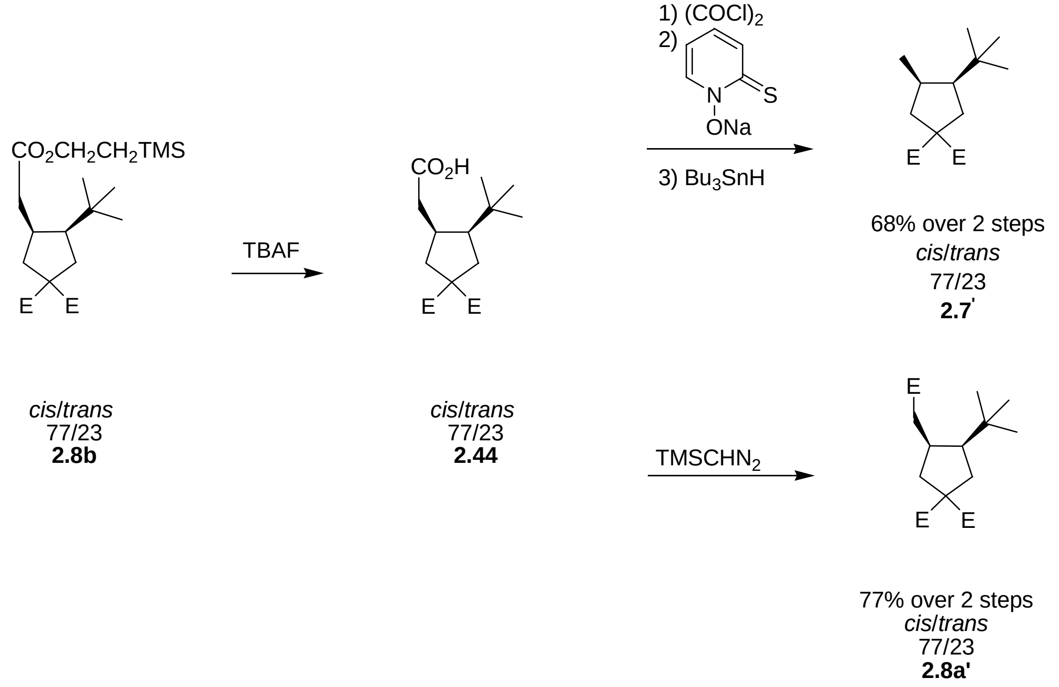
The GC analysis in Chapter 2.3.2 relies on the product of the vitamin $B12_a$ mediated reduction being compound **2.34*syn***, Scheme 2-8. So as definitive proof that the minor component in the cyclization of **2.4** is indeed cyclopentane **2.7*trans***, we treated pure **2.7*trans*** with $LiAlH_4$ to give diol **2.36** in 69% yield as a white solid. By slow vapor phase diffusion of hexanes into a solution of diol **2.43** in ethyl acetate, a single crystal was grown and the x-ray structure solved as shown in Scheme 2-11. With this crystal structure, we are able to unambiguously assign the stereochemical preference for the cyclization of **2.1** as *cis*.



Scheme 2-11: Synthesis and ORTEP diagram of diol **2.43**.

2.4 Stereochemical Relay from Product Mixture 2.7 to 2.8a and 2.8b

With the major product of mixture **2.7** firmly assigned as *cis*, we relayed this assignment to the methyl ester product mixture **2.8a** through the TMS ethyl ester mixture **2.8b** as shown in Scheme 2-12. Desilylation[59] of a 77/23 *cis*/*trans* mixture of **2.8b** with TBAF gave acid **2.44**. The acid was then split with a portion being treated with oxallyl chloride to give the corresponding acid chloride. The crude acid chloride was treated with 2-mercaptopyridine N-oxide sodium salt to provide the corresponding Barton ester. Finally a Bu_3SnH mediated Barton decarboxylation gave a 77/23 *cis*/*trans* mixture of **2.7′** in 68% yield from **2.8b**. The other portion of acid **2.44** was treated with (trimethylsilyl)diazomethane[60] to give a 77/23 *cis*/*trans* mixture of **2.8a′** in 77% yield over the two steps. Comparative GC analysis of **2.7** with **2.7′**, Figure 2-4a and b, and **2.8a** with **2.8a′**, Figure 2-4c and d, showed that in each case the major and the minor products had identical retention times. This proves that precursors **2.4** and **2.5a**,**b** all cyclize to give the *cis* adducts as the major products. By analogy, we concluded that the bicyclic system **2.3** also cyclizes with a *cis* preference.


1) (COCl)$_2$
2)
N
S
ONa
3) Bu$_3$SnH
TBAF
TMSCHN$_2$
CO$_2$CH$_2$CH$_2$TMS
CO$_2$H
E
E
cis/trans
77/23
2.8b
cis/trans
77/23
2.44
68% over 2 steps
cis/trans
77/23
2.7'
77% over 2 steps
cis/trans
77/23
2.8a'

Scheme 2-12: Stereochemical relay between the three cyclization mixtures.

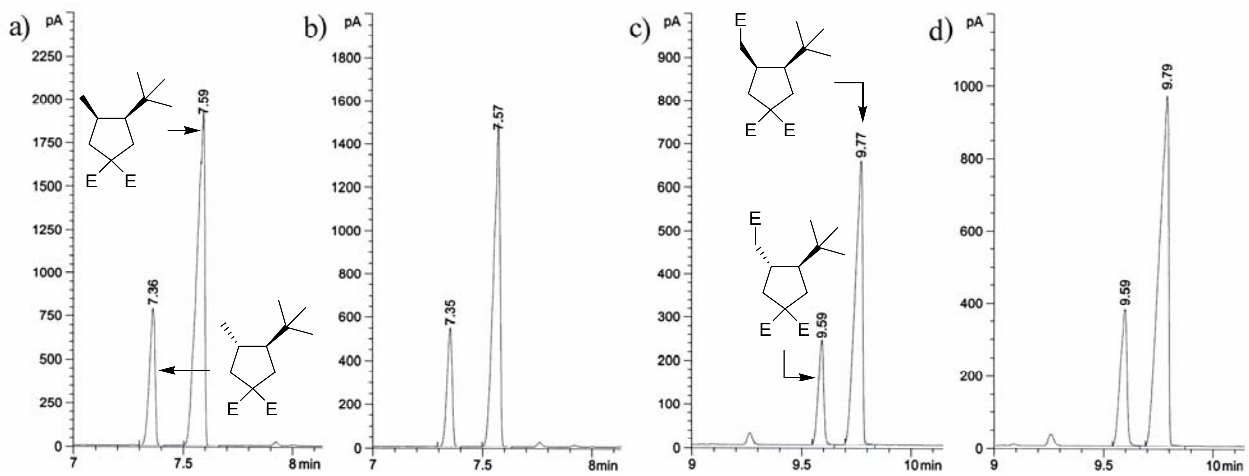
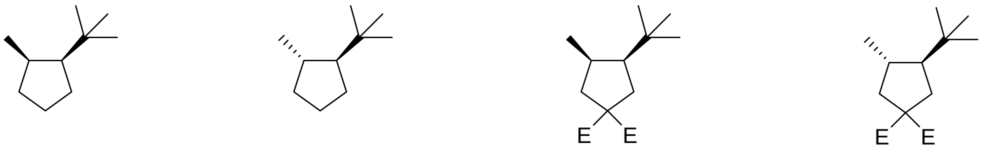


Figure 2-4: a) GC chromatogram of the decarboxylation products **2.7′**, b) GC chromatogram from a co-injection of the cyclization mixture of **2.7** and the decarboxylated products **2.7′**, c) GC chromatogram of the transesterfied products **2.8a′**, and d) GC chromatogram from a co-injection of the cyclization mixture **2.8a** and the transesterified products **2.8a′**. All four of the GC injections were performed under the same conditions as described for Figure 2-3.

2.5 Structural Correlation to Beckwith's Work

Comparing the results from the cyclization of **2.4** (*cis* selective) to those of the parent 1-*t*-butyl hexenyl radical **2.48** (*trans* selective), Figure 1-8 and Scheme 2-13, suggests that the malonate group in the 3 position reverses the stereochemistry of the cyclization. This in itself is not inconsistent with the literature because malonates in the 3 position of a hexenyl radical are known to favor *cis* cyclization. However, a comparison of our spectral data to that of the products from the original cyclization of **1.73**, Figure 2-5, was disconcerting because the resonances assigned to **2.45*cis*** correlated with those of **2.7*trans*** and the data for **2.45*trans*** matched that of compound **2.7*cis***. This lack of pattern matching forced us to consider that Beckwith's assignments for cyclopentanes **2.45** may be reversed.

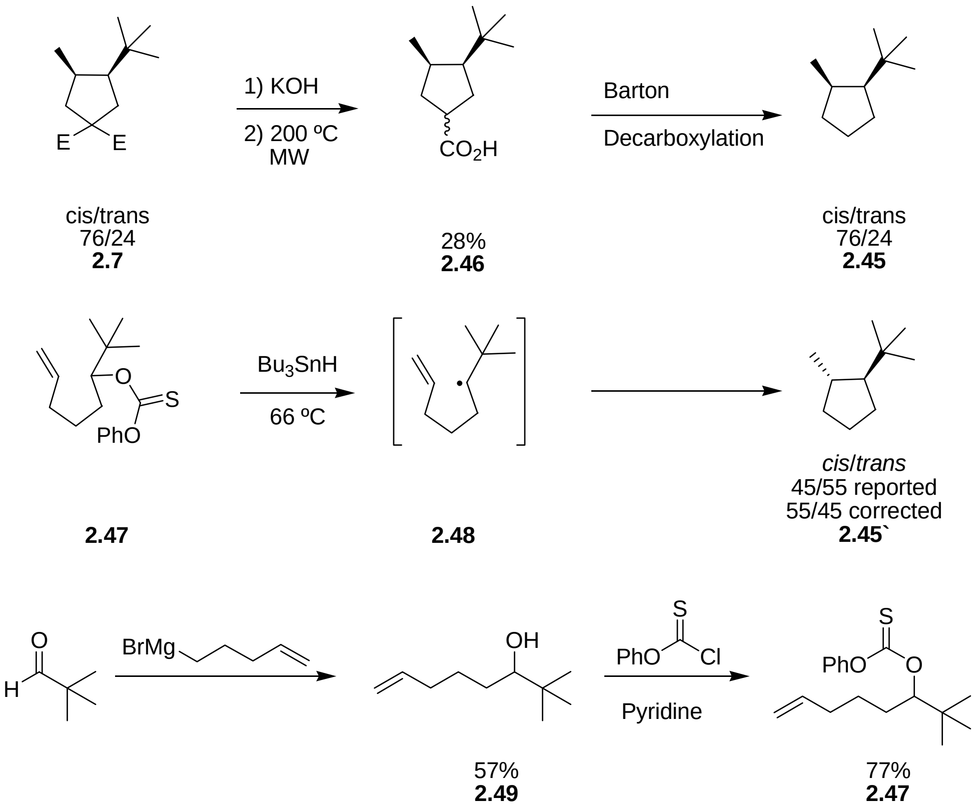


	2.45*cis*	**2.45*trans***	**2.7*cis***	**2.7*trans***
Beckwith's Original Assignments:	0.97 (d, 3H, *J* = 6.8 Hz) 0.84 (s, 9H)	0.93 (s, 9H) 0.85 (d, 3H *J* = 7.1 Hz)	0.96 (s, 9H) 0.91 (d, 3H *J* = 7.2 Hz)	1.00 (d, 3H, *J* = 7.0 Hz) 0.88 (s, 9H)
Corrected Assignments:	0.93 (s, 9H) 0.85 (d, 3H *J* = 7.1 Hz)	0.97 (d, 3H, *J* = 6.8 Hz) 0.84 (s, 9H)		

Figure 2-5: Comparison of selected ^{1}H NMR spectral data for **2.45** and **2.7**.

To resolve this discrepancy, we converted product mixture **2.7** to mixture **2.45** by the sequence outlined in Scheme 2-13. Treatment of a 76/24 *cis*/*trans* mixture of malonate **2.7** in refluxing potassium hydroxide hydrolyzed the malonic ester to a malonic acid (not shown).[61] The malonic acid was subjected to a microwave mediated decarboxylation[62] to give mono acid **2.46** in 28% isolated yield over the two steps. This mixture of products was then fully decarboxylated by using a Barton decarboxylation to give a 76/24 *cis*/*trans* mixture of cyclopentane **2.45**, which was not isolated due to its volatility. For direct comparison, we simultaneously synthesized known compound **2.47**, which upon treatment with AIBN and Bu_3SnH gives hexenyl radical **2.48**. This radical, then cyclizes to give a 45/55 *cis*/*trans* mixture of cyclopentanes **2.45′**.

The synthesis of cyclization precursor **2.47** is also shown in Scheme 2-13 and starts with the addition of 4-pentenylmagnesium bromide to pivaldehyde to give alcohol **2.49** in 57% yield. The alcohol is then treated with pyridine and phenylchlorothionocarbonate to give precursor **2.47** in 77% yield.


E
E
cis/trans
76/24
2.7
1) KOH
2) 200 ºC
MW
CO₂H
28%
2.46
Barton
Decarboxylation
cis/trans
76/24
2.45
O
S
PhO
2.47
Bu₃SnH
66 ºC
2.48
cis/trans
45/55 reported
55/45 corrected
2.45`
O
H
BrMg
OH
57%
2.49
S
PhO
Cl
Pyridine
S
PhO
O
77%
2.47

Scheme 2-13: Direct comparison of our cyclization mixture with that of Beckwith's cyclization and synthesis of precursor **2.47**.

If Beckwith's assignments are correct, then the major product of **2.45** should be the minor product of **2.45′** and vice versa. Unfortunately, as shown by the GC chromatograms in Figure 2-6, this was not the case. The major and the minor products from the decarboxylation of **2.46** and the cyclization of **2.47** match with retention times of 6.10 and 6.71 min, respectively. This means that Beckwith's assignments for *cis* and *trans* **2.45** are backwards because the crystal structure confirms that our assignments are correct. How though could Beckwith have mis-assigned the *cis* and *trans* isomers?

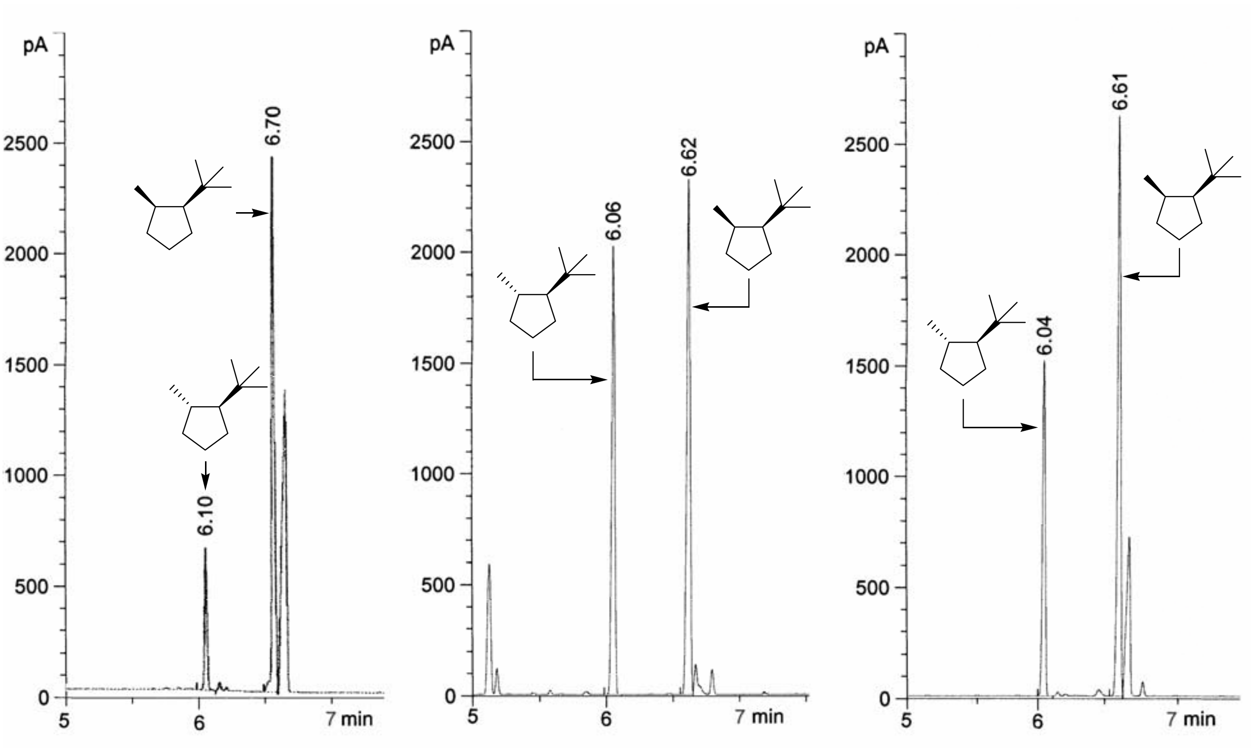


Figure 2-6: a) Left: GC injection of the decarboxylation mixture **2.45** and b) Middle: GC injection of the cyclization mixture **2.45′** and c) Right: co-injection of the two. All three GC injections were performed on an Agilent 6850 gas chromatograph equipped with an HP-1 column: dimethylpolysiloxane, 30m x 0.32mm, and a 0.25 µm film thickness. The temperature profile of the injection has an initial temperature of 30 °C which then increases by 10 °C/min to a final temperature of 315 °C.

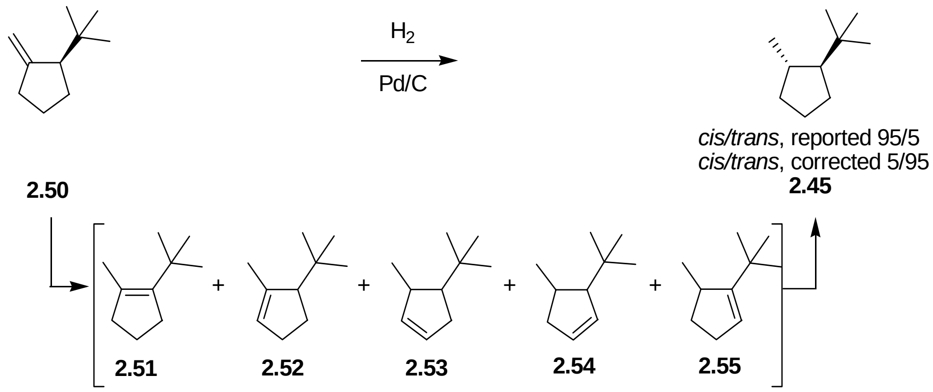
2.6 Revisiting Beckwith's Analysis

Beckwith assigned the *cis* and *trans* isomers of **2.45** by carrying out a palladium mediated catalytic hydrogenation of *exo*-methylene compound **2.50**, shown in Scheme 2-14. GC analysis of this reaction after 3 h revealed consumption of the starting material and the formation of two products in a 95/5 ratio. Beckwith assumed that hydrogenation occurred opposite to the bulky *tert*-butyl group giving the *cis* substituted cyclopentane as the major product. Molander and Winterfeld have also posited *cis* selectivities in related systems.[63] Beckwith was then able to separate the two products from the hydrogenation reaction by a preparative GC experiment. NOE analysis of the major product of the hydrogenation reaction showed a 10% enhancement of the *tert*-butyl singlet when the methyl doublet was irradiated. Beckwith took this enhancement as evidence that the major product was indeed the *cis* isomer of **2.45**. There was no discussion of an NOE analysis for the minor isomer. A likely reason for this is that the small chemical shift difference of 0.08 ppm between the methyl doublet and the *tert*-butyl singlet of the minor product makes accurate NOE determinations difficult.

We know that Beckwith's assignments are backwards and so how is it that hydrogenation of compound **2.50** gives cyclopentane **2.45*trans*** as the major product? Also, how is it possible for compound **2.45*trans*** to exhibit such a large NOE enhancement? To answer these two questions, we repeated Beckwith's hydrogenation experiments on olefin **2.50**.

2.6.1 Hydrogenation Experiments

In the palladium on carbon mediated hydrogenation of compound **2.50**, we also observed the 5/95 ratio of products. So the literature ratio for the hydrogenation is correct, but the assumption of *cis* selectivity is not. When we closely monitored the hydrogenation reaction by GC, we observed rapid consumption of alkene **2.50** and the appearance of three product peaks. As will be shown later, these three peaks actually correspond to four products where two products accidentally have the same retention time. A representative GC chromatogram of the four product mixture is shown in Figure 2-7. Two of these products were immediately identified as the *cis* and *trans* isomers of **2.45**. The other two products were tentatively assigned as isomerized products **2.51** and **2.52**, because hindered double bonds are known to undergo palladium catalyzed isomerizations.[64] Upon continued hydrogenation, the two additional peaks disappeared and the 5/95 ratio of **2.45*cis/trans*** resulted, as shown in the second GC chromatogram in Figure 2-7.



Scheme 2-14: Isomerization of exo-methylene compound **2.50** under the hydrogenation conditions.

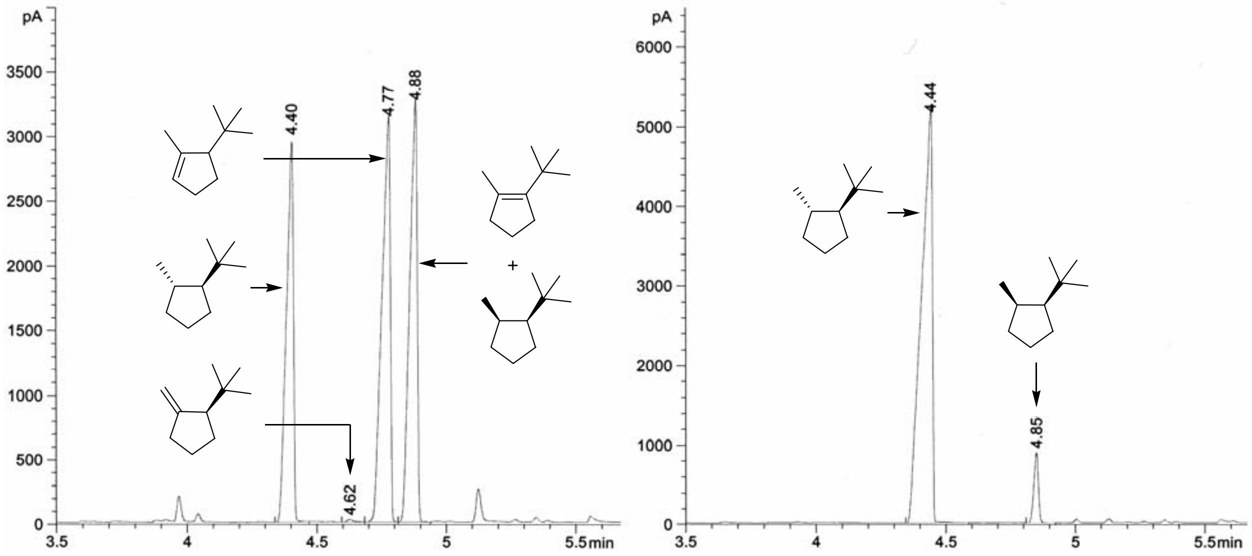
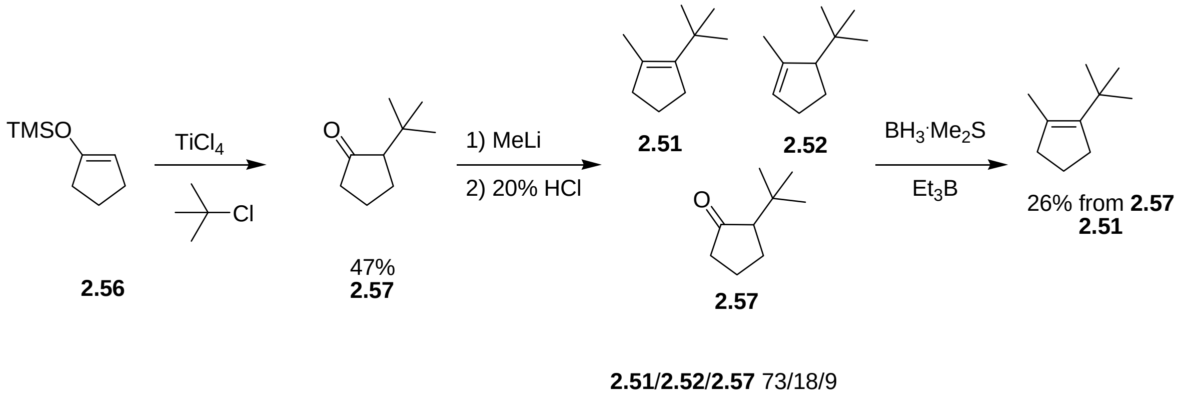


Figure 2-7: a) Left: GC chromatogram of the hydrogenation of **2.42** after 1 h and b) Right: GC chromatogram of the same hydrogenation after 3 h. Both of the GC injections were carried out under the same conditions as described for Figure 2-6.

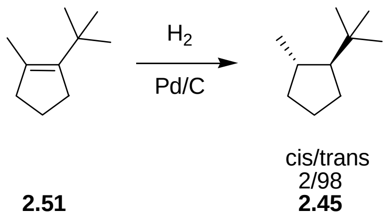
We were able to independently synthesize tetrasubstituted alkene **2.51** by the synthetic sequence shown in Scheme 2-15. The synthesis of **2.51** starts with the commercially available silyl enol ether **2.56**, that is treated with $TiCl_4$ and *tert*-butyl chloride to give ketone **2.57** in 47% yield.[65] The addition of MeLi to ketone **2.57** gives a tertiary alcohol (not shown). The alcohol is then eliminated using a 20% aqueous solution of HCl to give an inseparable 73/18/9 mixture of **2.51**, **2.52**, and **2.57**. Treatment of this mixture with $BH_3 \cdot Me_2S$ and Et_3B provided alkene **2.57** as a single product in 26% yield from ketone **2.57**.[66]

Upon GC co-injection of the four compound mixture from the hydrogenation with authentically prepared alkene **2.51** we learned that the peak with a retention time of 4.88 min is compound **2.51**. Unfortunately, the retention times of alkene **2.51** and product **2.45*cis*** are accidentally identical. By co-injecting the mixture containing **2.51**, **2.52**, and **2.57** with the four compound hydrogenation mixture, we were able to identify the peak at 4.77 min as coming from alkene **2.52** by a process of elimination.



Scheme 2-15: Synthesis of alkene **2.51**.

Interestingly, independent hydrogenation of **2.51**, Scheme 2-16, resulted in a 2/98 *cis*/*trans* mixture of **2.45**. Direct hydrogenation of cyclopentene **2.51** cannot possibly give **2.45*trans*** because such hydrogenations are well-known to be stereospecific for the *cis* isomer.[67] Taken together, all of the hydrogenation results suggest that **2.50** (exclusively), **2.51** (to a large extent) and possibly also **2.52** isomerize prior to hydrogenation and that the isomerization process determines the final *cis*/*trans* ratio. We speculate that disubstituted olefins **2.53** and **2.54**, resulting from further isomerizations of **2.51** and **2.52**, are the species actually undergoing the hydrogenation and that the *trans* selectivity is the result of a thermodynamically controlled isomerization. Regardless, compound **2.50** is not directly hydrogenated and so any assumptions about its *cis* hydrogenation selectivity, although probably correct, are certainly not relevant given the isomerization problem.



Scheme 2-16: Hydrogenation of tetrasubstituted alkene **2.45**.

We attempted to show that Beckwith's assumption of hydrogenation opposite to the *tert*-butyl group was actually correct. We screened a number of conditions that should not isomerize the *exo*-methylene compound **2.50** prior to hydrogenation and the results are summarized in

Table 2-2. Raney Nickel, entry 1, is reported[68] to isomerize olefins less than palladium, but significant isomerization products were observed in the GC chromatogram, all of which eventually disappeared to give a 4/96 *cis*/*trans* mixture of **2.45**. Hydrogenation over platinum, entry 3, is also reported[69] to significantly reduce the amount of isomerization and although we observed clean conversion of the starting material to the product, we still ended up with a 56/44 *cis*/*trans* mixture of the products. Finally a diimide reduction was attempted, entry 4, and while again no isomerization was observed an 84/16 *cis*/*trans* mixture was obtained.[70]

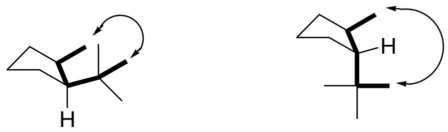
Table 2-2: Reduction of **2.50** under various conditions.

Entry	Reducing Conditions	Selectivity (*cis/trans)*	Isomerization Intermediates in the GC?
1	Raney Nickel under H_2	4/96	Yes
2	Pd/C under H_2	5/95	Yes
3	Pt/C under H_2	56/44	No
4	Hydrazine/$CuSO_4$	84/16	No

The results from the platinum and the diimide reductions, entries 3 and 4, prove that the *trans* isomer can be obtained without the exocyclic olefin isomerizing into the ring. This indicates that both faces of the olefin in compound **2.50** are accessible enough to be hydrogenated. Furthermore the results from these two experiments support Beckwith's assumption that the *tert*-butyl group directs the hydrogenation to the opposite face because the *cis* isomer of **2.45** is the major product in these cases.

2.6.2 Explaining the NOE Analysis Results

The envelope conformations of compounds **2.45*cis*** and **2.45*trans*** are shown in Figure 2-8. These representations show that both the *cis* and the *trans* isomer have nominal syn pentane interactions that are known to give strong NOE enhancements.[71] This explains why Beckwith observed the 10% NOE enhancement in the *tert*-butyl singlet when the methyl doublet was irradiated even though he was analyzing the *trans* isomer of **2.45**.

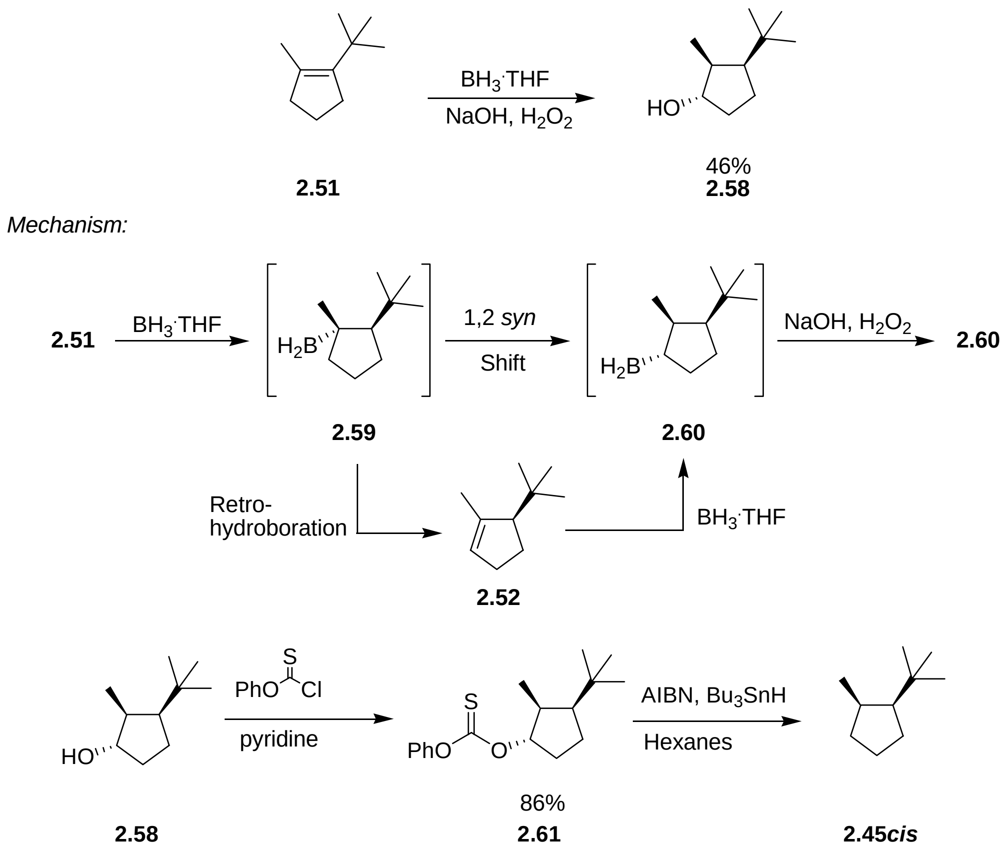


2.45*cis* **2.45*trans***

Figure 2-8: Nominal syn pentane interactions in **2.45*cis*** and ***trans***.

2.7 Additional Verification of the Reversed *Cis*/*Trans* Assignment of 2.45

As another way to show that Beckwith's assignments for the *cis* and *trans* isomers of **2.45** were backwards, alkene **2.51** was hydroborated to give alcohol **2.58** in 46% yield upon reductive workup, Scheme 2-19. Mechanistically, hydroboration of alkene **2.51** provides borane **2.59**. The regioselectivity of this addition is determined by the large *tert*-butyl group that drives the boron towards the less hindered carbon. Borane **2.59** then undergoes a 1,2 *syn* shift to give compound **2.60**. It is conceivable that borane **2.60** is not formed by this 1,2 *syn* shift, but rather that **2.59** undergoes a retro-hydroboration to give alkene **2.52** which is then hydroborated to give borane **2.59**. In any event intermediate **2.60** gives known alcohol **2.50** upon reductive workup with sodium hydroxide and hydrogen peroxide**.** We then converted alcohol **2.58** to thionoformate **2.61** in 86% yield. Barton-McCombie deoxygenation[72] of **2.61** provides **2.45*cis*** as a single isomer. GC injection of a pure sample of **2.45*cis*** provides the GC trace shown in Figure 2-9a. Figure 2-9b shows the GC trace from the cyclization mixture **2.48** and finally Figure 2-9c is the GC trace from a co-injection of **2.45*cis*** from the deoxygenation reaction with the cyclization mixture from **2.47.** This series of injections proves that the major isomer in Beckwith's cyclization of **2.47** is indeed compound **2.45*cis*** and confirms that the original configurational assignments are reversed.


BH$_3$·THF
NaOH, H$_2$O$_2$
HO
46%
2.51
2.58
Mechanism:
2.51
BH$_3$·THF
H$_2$B
1,2 *syn*
Shift
H$_2$B
NaOH, H$_2$O$_2$
2.60
2.59
2.60
Retro-
hydroboration
BH$_3$·THF
2.52
HO
S
PhO Cl
pyridine
S
PhO O
AIBN, Bu$_3$SnH
Hexanes
86%
2.58
2.61
2.45*cis*

Scheme 2-17: Confirmation of Beckwith's reversed assignments.

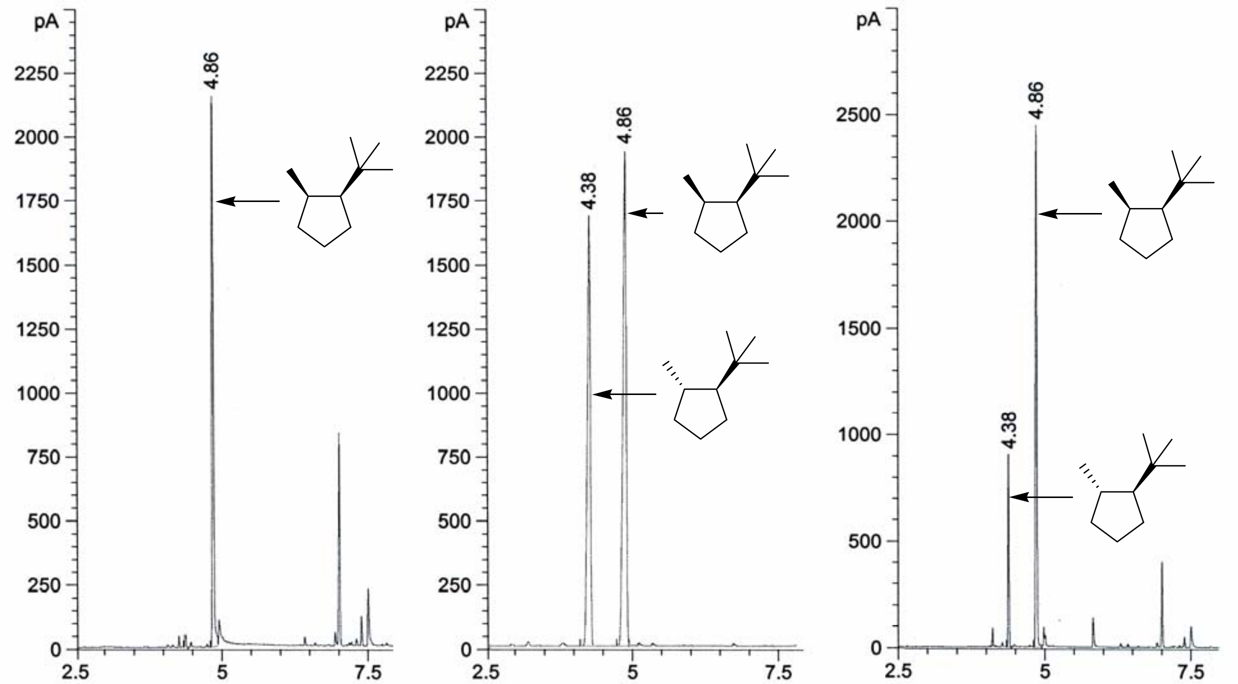
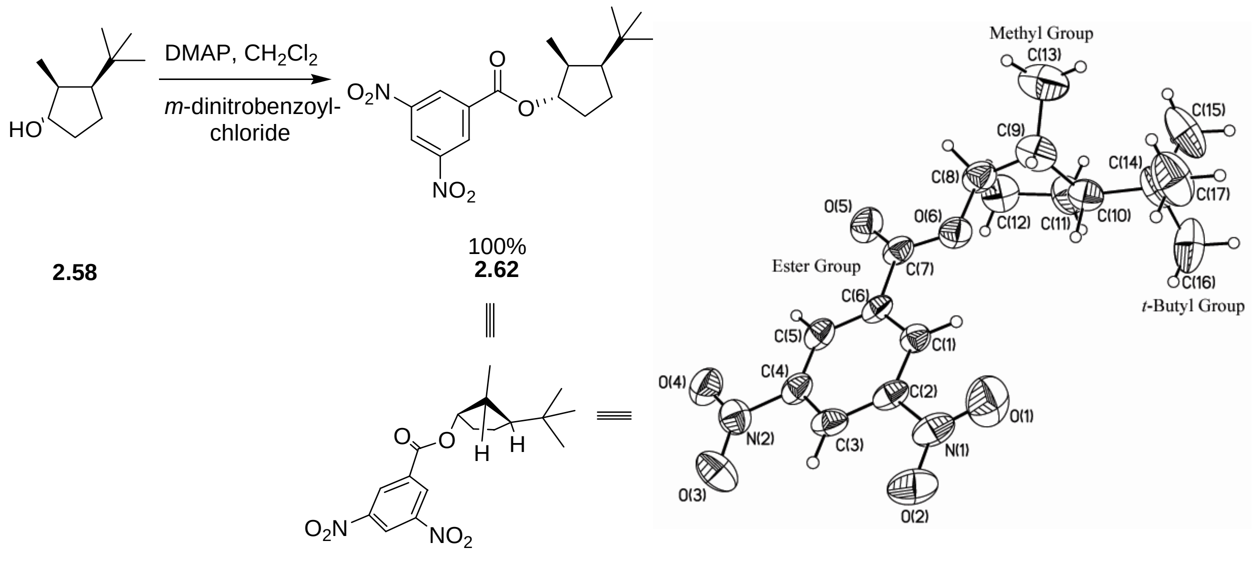


Figure 2-9: a) Left: **2.45** from the deoxygenation of **2.60**, b) Middle: Radical cyclization mixture **2.45** and c) Right: co-injection of a and b. All three of the GC injections were carried out under the same conditions as described for Figure 2-6.

The above proof relies on Knochel's stereochemical assignment of **2.58**, which was made based on 1 and 2D NMR experiments. To verify the assignment of **2.58**, we derivatized the alcohol with *meta*-di-nitrobenzoyl chloride to give ester **2.62** in 100% yield, Scheme 2-18. A single crystal of **2.62** was grown by slow evaporation of a methanol solution and the x-ray diffraction pattern was solved to provide the ORTEP diagram shown in Scheme 2-18.


DMAP, CH2Cl2
m-dinitrobenzoyl-chloride
O2N
NO2
HO
O
100%
H
H
Methyl Group
Ester Group
t-Butyl Group
C(1)
C(2)
C(3)
C(4)
C(5)
C(6)
C(7)
C(8)
C(9)
C(10)
C(11)
C(12)
C(13)
C(14)
C(15)
C(16)
C(17)
O(1)
O(2)
O(3)
O(4)
O(5)
O(6)
N(1)
N(2)

2.58

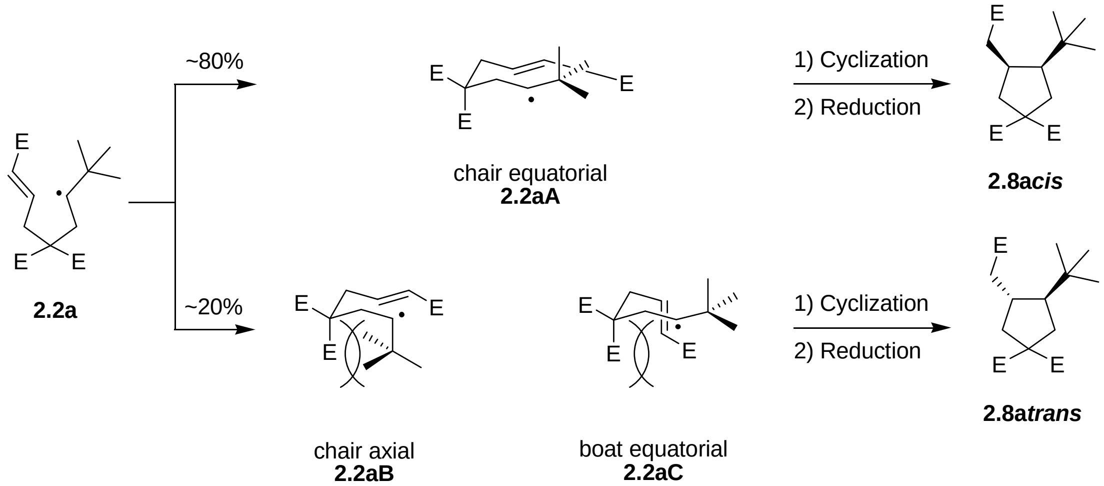
2.62

2.62

Scheme 2-18: Derivatization of alcohol **2.58** and ORTEP of cyclopentane **2.62**.

2.8 Transition State Analysis for the Cyclization of 2.2a

We have shown that hexenyl radicals with a large group in the 1 position and a geminal ester substitution in the 3 position cyclize with *cis* selectivity. This result can be nicely rationalized using a Beckwith/Houk transition state analysis as shown in Scheme 2-19. The analysis for radical **2.2a** is representative for all of the cyclizations examined in this work. Radical **2.2a** can adopt three low energy transition states, Scheme 2-19, namely *chair-equatorial* **2.2aA**, *chair-axial* **2.2aB**, and *boat-equatorial* **2.2aC**. A fourth *boat-axial* transition state (not shown) is also possible, but will be ignored because it is too high in energy to be a significant contributor. If radical **2.2a** adopts the *chair-equatorial* transition state, then it will cyclize to give product **2.8a*cis*** upon reduction**.** However, if radical **2.2a** cyclized through the *chair-axial* or *boat-equatorial* transition states, then **2.8a*trans*** results upon reduction. The *chair-axial* **2.2aB** and boat equatorial **2.2aC** transition states are disfavored in comparison to the *chair-equatorial* arrangement **2.2aA** due to the diaxial interactions indicated in Scheme 2-19. These interactions explain the approximate 80/20 partitioning of the *cis/trans* products that we observe.



Scheme 2-19: Beckwith Houk transition state analysis for the cyclization of **2.2a**.

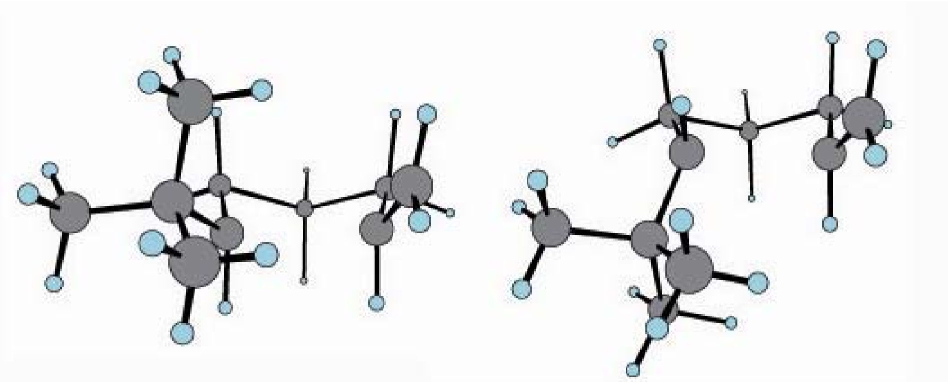
2.9 Calculations

In the original publication, Beckwith discusses two sets of force field calculations that were carried out by Houk/Spellmeyer and by Beckwith/Schiesser. Both sets of calculations independently found that a *chair axial* type of transition was the lowest in energy. This lead them both to predict that **2.45*trans*** would be the major isomer from the cyclization mixture of precursor **2.47**. These calculations nicely supported the experimental results that were obtained at the time. The important caveat with force field calculations is that they only consider the steric and not the electronic interactions of a compound.

Now that we have corrected the *cis* and *trans* assignments from the experimental work, the calculations carried out in 1992 no longer predict the correct stereochemistry for the cyclization of **2.47**. Moreover, these calculations will likely also fail for other hexenyl radicals with bulky substituents in the 1 position. Clearly taking sterics alone into consideration, as the force field calculations did, is inadequate for such radicals. For this reason the calculations were revisited by Professor Carl Schiesser, using *ab initio* and density functional quantum techniques. These techniques consider both the sterics and electronics of a molecule when calculating the potential energy surface.

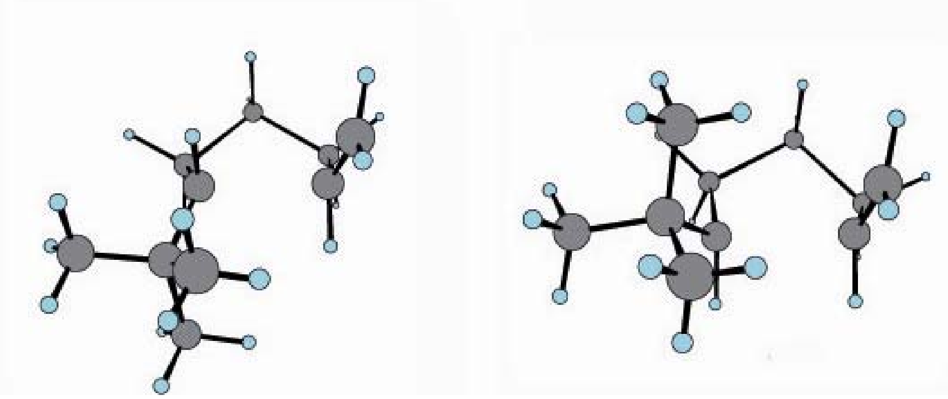
Upon examining this potential energy surface for radical **2.48**, $C_{10}H_{19}$, at various levels of theory,[73] four transition states were located: *chair-equatorial* **2.63,** *chair-axial* **2.64**, *boat-equatorial* **2.65** and *boat-axial* **2.66,** shown in Table 2-3. These are the same four transition states that were found in the original force field calculations. If radical **2.48** proceeds through transition states **2.63** or **2.66** then it will cyclize to give **2.45*cis***. If on the other hand radical **2.48** adopts transition state **2.64** or **2.65**, then **2.45*trans*** results upon cyclization. The relative energies of these four transition states, in KJ/mol, were determined using ten different theory data sets and are tabulated Table 2-3.

Table 2-3: Transition States and Relative Energies for the Cyclization of Radical **2.48**.



chair-equatorial
2.63

chair-axial
2.64



boat-equatorial
2.65

boat-axial
2.66

		Relative Energy (KJ mol^{-1})			
Entry	Calculation Method	*chair equatorial* **2.63**	*chair axial* **2.64**	*boat equatorial* **2.65**	*boat axial* **2.66**
1	(UHF/6-31G*)	0	1.1	2.1	12.6
2	(UHF/6-31G* + ZPE)	0	0.8	1.0	12.5
3	(UHF/6-311G**)	0	0.5	1.3	12.6
4	(UHF/6-311G** + ZPE)	0	0.3	0.3	12.4
5	(BHandHLYP/6-311G**)	0	2.2	4.5	12.5
6	(BHandHLYP/6-311G** + ZPE)	0	2.5	3.8	12.8
7	(MP2/6-311G**)	0	1.1	4.6	9.0
8	(BHandHLYP/cc-pVDZ	0	2.7	5.0	13.4
9	(BHandHLYP/cc-pVDZ + ZPE)	0	3.0	4.3	13.5
10	(BHandHLYP/aug-cc-pVDZ)	0	1.5	4.2	12.6

The above results show that the higher quantum level calculations do indeed predict the correct stereochemical outcome for the cyclization of **2.48**. At all levels of theory, the *chair-equatorial* transition state is the lowest in energy by about 1.2 KJ mol^{-1}. These calculations thereby predict that the *cis* product will be the major isomer of the cyclization. This supports the findings for all of our experiments. These results also indicate that hexenyl radical cyclizations with bulky substituents in the 1 position are strongly influenced by electronic phenomena because quantum mechanical calculations were necessary to correctly predict the experimental outcome. The data also justifies us ignoring the *boat-axial* transition state in the analysis because at all levels of theory it is about 12.4 KJ mol^{-1} higher in energy than the *chair-equatorial* transition state.

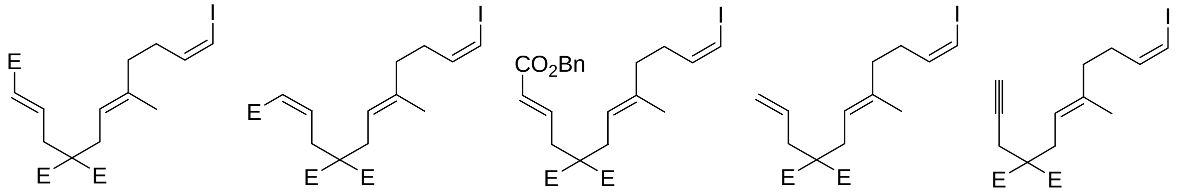
2.10 Conclusions

We have definitively shown that hexenyl radical cyclizations with a large group in the 1 position and a geminal ester substitution in the 3 position cyclize with a modest 80/20 *cis* preference. We have also shown that carrying out the reaction at 25 °C instead of 80 °C gives a small improvement in the *cis* selectivity for this type of hexenyl radical cyclization. In addition, we have investigated the effect that an α,β-unsaturated ester group has on the cyclization of these types of radicals and shown that it has little to no bearing on the outcome of the reaction.

During the course of our investigations, we uncovered an error with the *cis* and *trans* assignments of a key literature benchmark and shown that they are actually reversed. There are very few exceptions to the rule 1 substituted hexenyl radicals cyclize with a *cis* preference, but now there is even one fewer.

Chapter 3 Round-Trip Radical Cyclizations

Having shown that hexenyl radicals with a large *tert*-butyl or other tertiary groups in the 1 position cyclize with a *cis* preference regardless of temperature or additional substitutions at position 3, we turned our attention to Ihara's temperature effect.[38] We initially wanted to see whether the temperature effect was reproducible and whether it was substrate dependent. To answer these questions, five tricyclization substrates were chosen all shown in Figure 3-1.



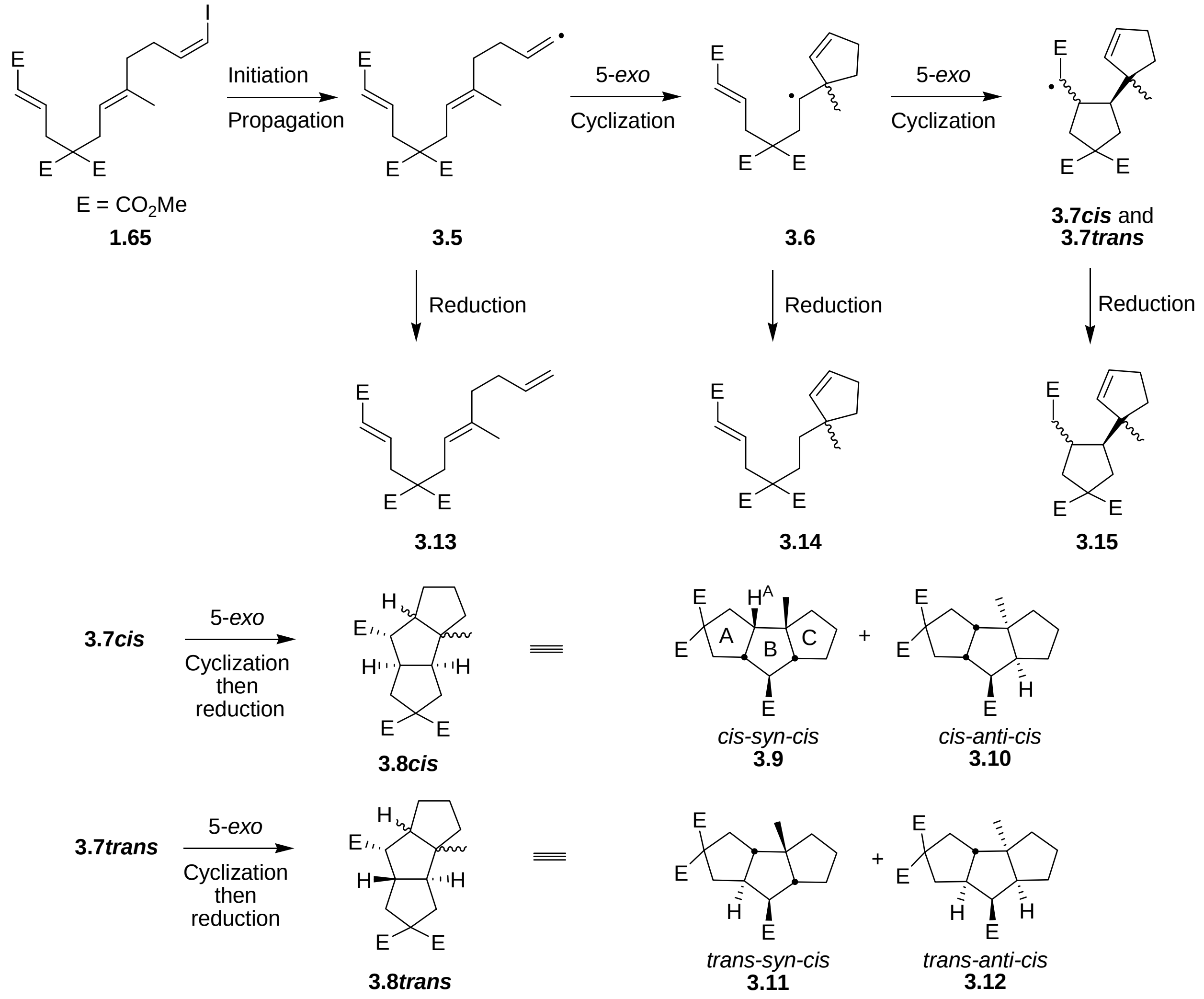
1.65 **3.1** **3.2** **3.3** **3.4**

Figure 3-1: Tandem round-trip radical cyclization substrates.

3.1 Substrate Design and Rationale

Vinyl iodide **1.65** is Ihara's cyclization substrate. To assess the effect of the unsaturated ester geometry on the cyclization selectivity, we selected substrate **3.1**, the *Z* isomer of **1.65**, because *Z* unsaturated esters are reported[26,74] to give higher stereoselectivities in radical cyclizations. Substrate **3.2**, which is the benzyl ester analogue of **1.65**, will serve as the structural relay substrate in this series, like the TMS ethyl ester did previously. Malonate **3.3** lacks the ester in the radical acceptor of the second cyclization and will serve to assess what effect this functionality has on the selectivity. Finally, in vinyl iodide **3.4**, the α,β-unsaturated ester of **1.65** has been replaced with a terminal alkyne, making the second cyclization a 5-*exo dig* instead of a 5-*exo trig* process.

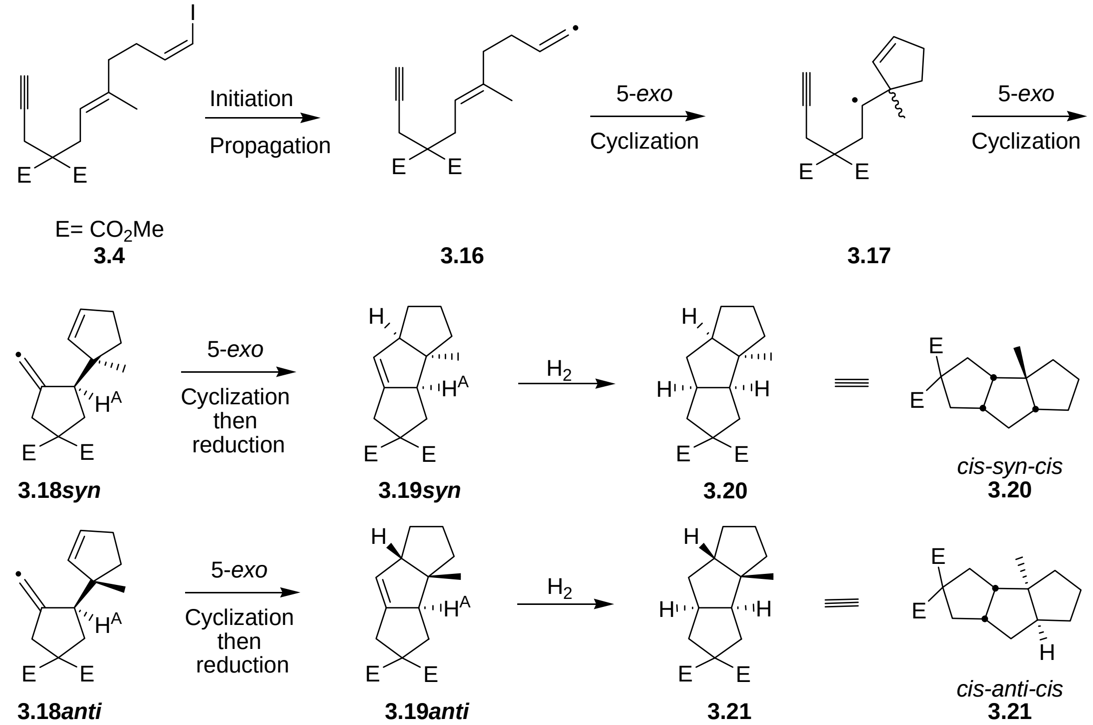
The mechanism for the round-trip radical cyclization of **1.65** is shown in Scheme 3-1 and it is identical to that for precursors **3.1-3.3**. Treatment of vinyl iodide **1.65** with a suitable initiator (AIBN at 80 °C or Et_3B/O_2 at 25 °C) and a reducing agent gives vinyl radical **3.5**. Radical **3.5** cyclizes in a 5-*exo* fashion to give monocyclic radical **3.6**. Hexenyl radical **3.6** then cyclizes again in either a *cis* or *trans* fashion to give **3.7** as a mixture of four diastereomers. Hexenyl radical **3.6** is similar to the systems studied in Chapter 2, and so we expect it to cyclize with an 80/20 *cis* preference. Radicals **3.7*cis*** then cyclize a third time to give tricycles **3.8*cis*** upon reduction, as a mixture of the *cis-syn-cis* **3.9** and the *cis-anti-cis* **3.10** linear triquinane. Likewise, radicals **3.7*trans*** cyclize to give products **3.8*trans***, which are the *trans-syn-cis* **3.11** and the *trans-anti-cis* **3.12** tricyclic isomers. Fortunately each radical in **3.7** cyclizes to give a single triquinane because the formation of a 5,5 fused system gives exclusively the *cis* product.[36] The complete cascade can be interrupted by reduction of radicals **3.5**, **3.6**, or **3.7** to give prematurely reduced products **3.13**, **3.14**, and **3.15** respectively. The nomenclature of the linear triquinanes is either *cis* or *trans* depending on the ring fusion of the A/B rings as denoted in **3.9**. The name is then either *syn* or *anti* depending on the relationship between H^A and the methyl group and finally it is either *cis* or *trans* depending on the geometry of the B/C ring fusion.



E = CO₂Me
1.65
Initiation
Propagation
3.5
5-exo
Cyclization
3.6
5-exo
Cyclization
3.7cis and
3.7trans
Reduction
Reduction
Reduction
3.13
3.14
3.15
3.7cis
5-exo
Cyclization then reduction
3.8cis
Hᴬ
A
B
C
cis-syn-cis
3.9
cis-anti-cis
3.10
3.7trans
5-exo
Cyclization then reduction
3.8trans
trans-syn-cis
3.11
trans-anti-cis
3.12

Scheme 3-1: Mechanism for the round-trip radical cyclization reaction.

From an analysis perspective, the cyclization of substrates **1.65** and **3.1**-**3.3** is going to be complicated by the formation of four tricyclic products and potentially some prematurely reduced products. In order to simplify this analysis and rigorously assign configurations, we designed substrate **3.4**, which cyclizes by the mechanism shown in Scheme 3-2. Upon initiation and propagation, iodide **3.4** forms vinyl radical **3.16**. Radical **3.16** undergoes a 5-*exo* cyclization to give compound **3.17**. Radical **3.17** cyclizes again to give radical **3.18**, but unlike the other round-trip substrates where four products were possible in the second cyclization, now only two products **3.18*syn*/*anti*** are possible because of the olefin that remains in the central ring after the 5-*exo dig* cyclization. The *syn* and *anti* nomenclature comes from the relationship between the methyl group and the adjacent proton H^A. Subsequent cyclization and reduction of **3.18** gives either **3.19*syn*** or **3.19*anti*** as the only possible products from the tandem cyclization. Subsequent hydrogenation of **3.19*syn*** and **3.19*anti*** will give the fully saturated analogues either **3.20** or **3.21**. These two products can then be compared to those of the round-trip substrate **3.3**. Assuming that the hydrogenation of **3.19** occurs exclusively from the more accessible face, *syn* to H^A, **3.19*syn*** will give the *cis-syn-cis* isomer **3.20** and **3.19*anti*** will give the *cis-anti-cis* isomer **3.21**.


I
Initiation
Propagation
5-exo
Cyclization
5-exo
Cyclization
E
E
E= CO2Me
3.4
3.16
3.17
H
HA
5-exo
Cyclization
then
reduction
H2
H
E
cis-syn-cis
3.20
3.18syn
3.19syn
3.20
3.18anti
3.19anti
3.21
cis-anti-cis
3.21

Scheme 3-2: Mechanism for the cyclization of **3.4** and subsequent hydrogenation of the cyclization products **3.19**.

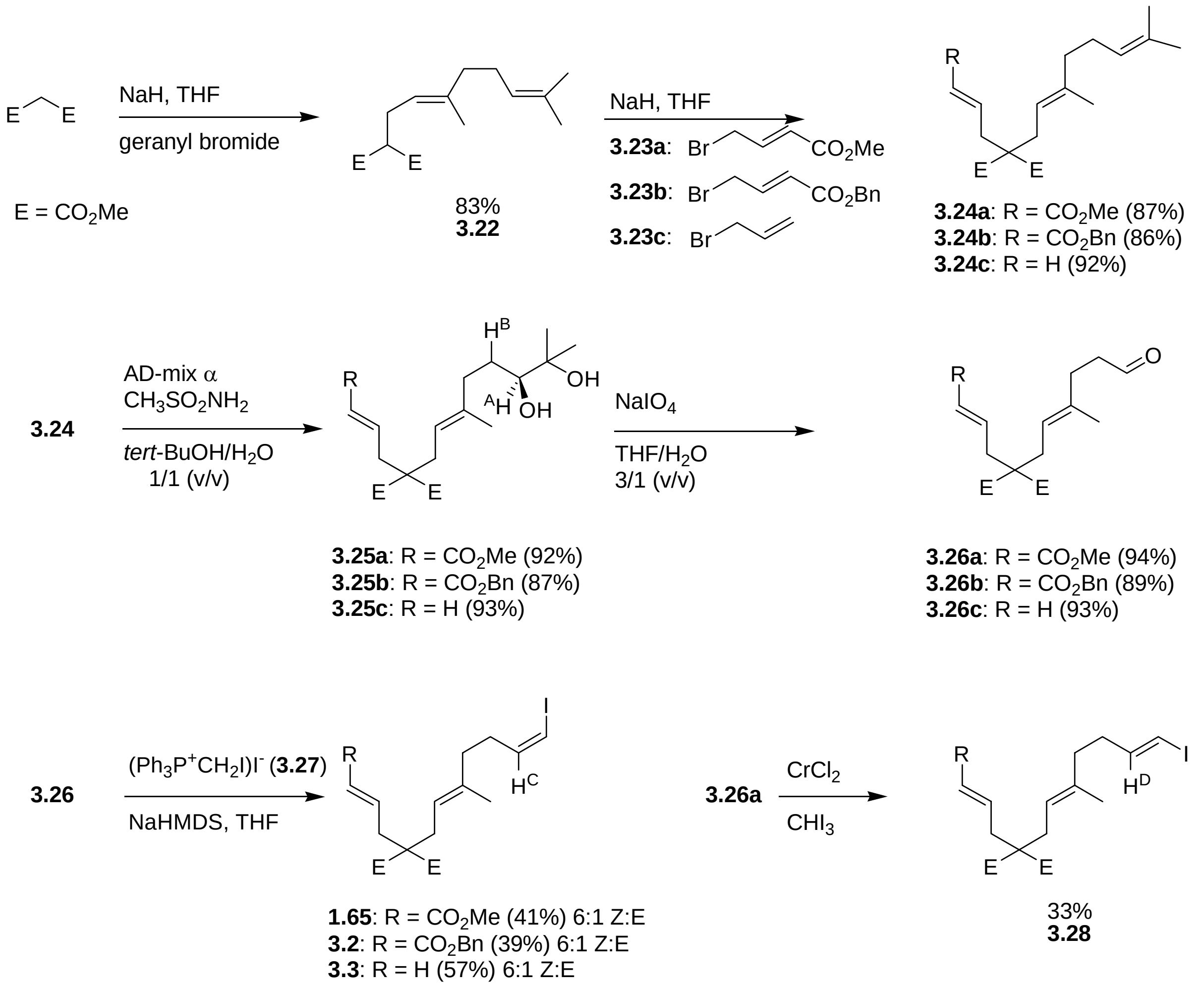
3.2 Substrate Synthesis

The synthesis of all five precursors was readily accomplished through straightforward malonate alkylations. The synthesis of **1.65**, **3.2**, and **3.3** closely followed Ihara's five step synthesis,[38] and the synthesis of **3.1** and **3.4** required only appropriate deviations from this.

3.2.1 Synthesis of 1.65, 3.2 and 3.3

The general synthesis of the triene cyclization precursors is outlined in Scheme 3-3. The synthesis of **1.65** is representative for all three substrates and the first step is the deprotonation of dimethyl malonate with sodium hydride. Subsequent alkylation of the anion with geranyl bromide gave alkylated malonate **3.22** in 83% yield.[44] A second alkylation step with methyl-4-bromocrotonate **3.23a** afforded *bis*-alkylated malonate **3.24a** in 87% yield.[44]

For the dihydroxylation step, Ihara successfully used catalytic OsO_4 with NMO as the oxidant, but in the synthesis of **3.3**, we worried that OsO_4 would preferentially dihydroxylate the mono- over the desired tri-substituted olefin. We chose to use a Sharpless dihydroxylation instead because the addition of $CH_3SO_2NH_2$ shuts down the reaction for terminal olefins.[75] Treating triene **3.24a** with AD-mix α and $CH_3SO_2NH_2$ in *tert*-BuOH/H_2O (1/1) afforded diol **3.25a** in 92% yield. The regioselectivity of this reaction was determined by ^{1}H-^{1}H COSY analysis of diol product **3.25a**, which showed a cross peak between H^A (δ 3.27 ppm, dd, $J = 2.0$, 10.2 Hz) and H^B (δ 1.39−1.34 ppm, m). This proves that the correct olefin was dihydroxylated. The Sharpless' mnemonic[75] predicts that AD-Mix α dihydroxylation of the desired olefin will give the *S* enantiomer as shown in **3.25a**, but this was not verified because the stereocenter was destroyed in the subsequent step.


E = CO2Me
NaH, THF
geranyl bromide
83%
3.22
NaH, THF
3.23a: Br CO2Me
3.23b: Br CO2Bn
3.23c: Br
3.24a: R = CO2Me (87%)
3.24b: R = CO2Bn (86%)
3.24c: R = H (92%)
3.24
AD-mix α
CH3SO2NH2
tert-BuOH/H2O
1/1 (v/v)
HB
AH OH
OH
3.25a: R = CO2Me (92%)
3.25b: R = CO2Bn (87%)
3.25c: R = H (93%)
NaIO4
THF/H2O
3/1 (v/v)
3.26a: R = CO2Me (94%)
3.26b: R = CO2Bn (89%)
3.26c: R = H (93%)
3.26
(Ph3P+CH2I)I- (3.27)
NaHMDS, THF
HC
1.65: R = CO2Me (41%) 6:1 Z:E
3.2: R = CO2Bn (39%) 6:1 Z:E
3.3: R = H (57%) 6:1 Z:E
3.26a
CrCl2
CHI3
HD
33%
3.28

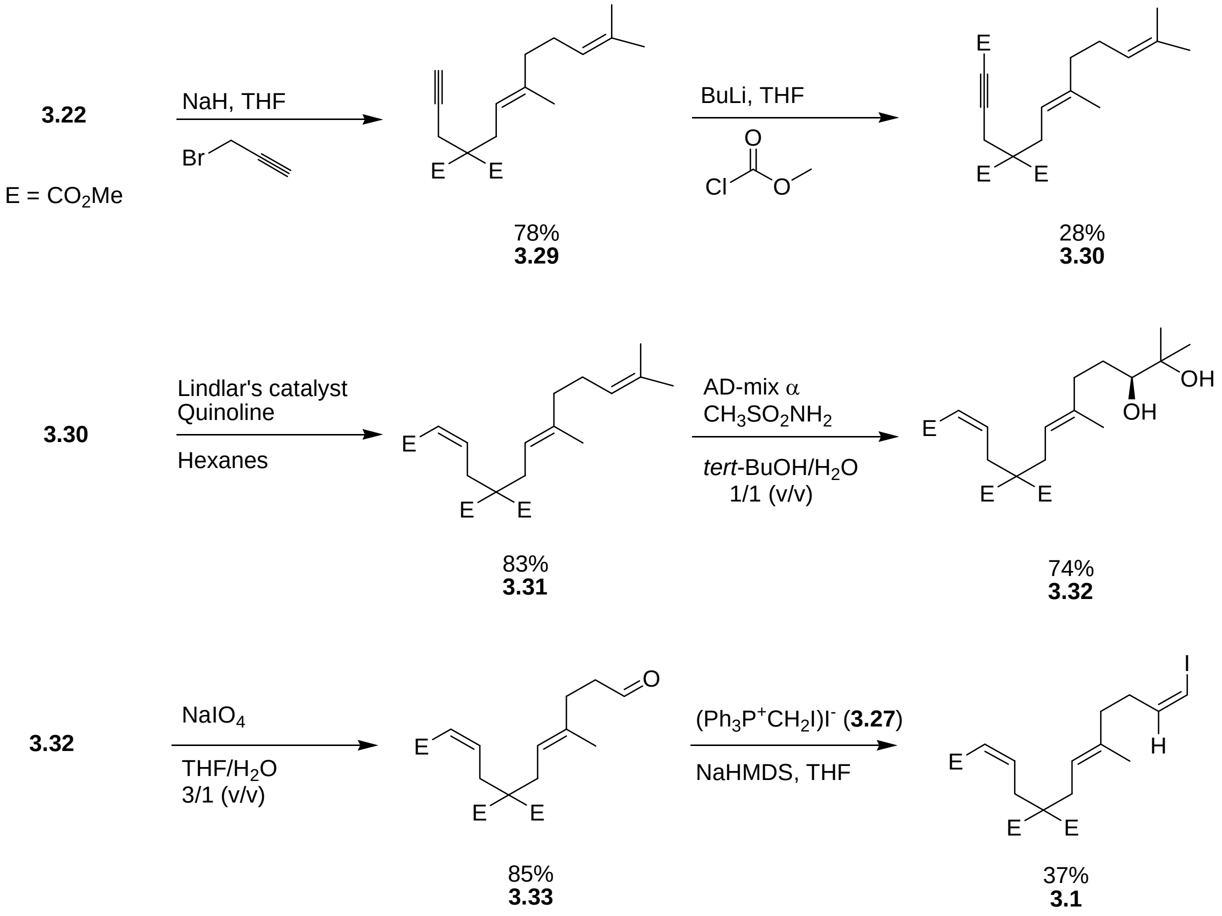
Scheme 3-3: Synthesis of cyclization precursors **1.65**, **3.2** and **3.3**.

Cleavage of diol **3.25a** with $NaIO_4$ in THF/H_2O yielded aldehyde **3.26a** in 94% yield.[76] Wittig olefination using $(Ph_3P^+CH_2I)I^-$ **3.27**,[77] NaHMDS and aldehyde **3.20a** gave vinyl iodide **1.65** in 57% yield as a 6/1 *Z*:*E* ratio.[78] The overall yield of this sequence was 31 % starting from malonate **3.22**. An authentic sample of the *E* isomer was prepared by subjecting aldehyde **3.26a** to a Takai reaction to give iodide **3.28** in 33% yield as a single stereoisomer.[79] Subsequent integration of the diagnostic H^C and H^D protons in the ^1H NMR spectrum of the mixture provided the reported ratio. The key proton H^C in the *Z* isomer appeared as a doublet of triplets, at δ 6.04 ppm with *J* values of 6.4 and 7.2 Hz. For the *E* isomer, H^D appeared as a doublet of triplets at δ 6.46 ppm with *J* values of 6.2 and 14.4 Hz. Although chromatographically separable, the *E* and *Z* isomers were collected together for cyclization purposes. This can be done because the homolysis of the carbon-iodine bond in either the *E* or the *Z* isomer gives the same rapidly interconverting vinyl radical.[49] Substrates **3.2** and **3.3** were prepared in 26% and 45% overall yield, respectively, starting from **3.22** following the same synthetic sequence as for **1.65**.

3.2.2 Synthesis of *Z*-Unsaturated Ester Cyclization Substrate 3.1

We synthesized cyclization precursor **3.1** by the sequence of reactions laid out in Scheme 3-4. Deprotonation of malonate **3.22** with sodium hydride and quenching the subsequent anion with propargyl bromide gave alkyne **3.29** in 78% yield.[44] Treatment of malonate **3.29** with BuLi and subsequent addition of methyl chloroformate furnished trimethyl ester **3.30** in 28% yield.[45] This reaction, although low yielding, was very clean and the starting material could be recovered and resubjected to give more of the desired product. Interestingly, the reaction stalled after about 2 h and adding more BuLi and methyl chloroformate did not complete the conversion.

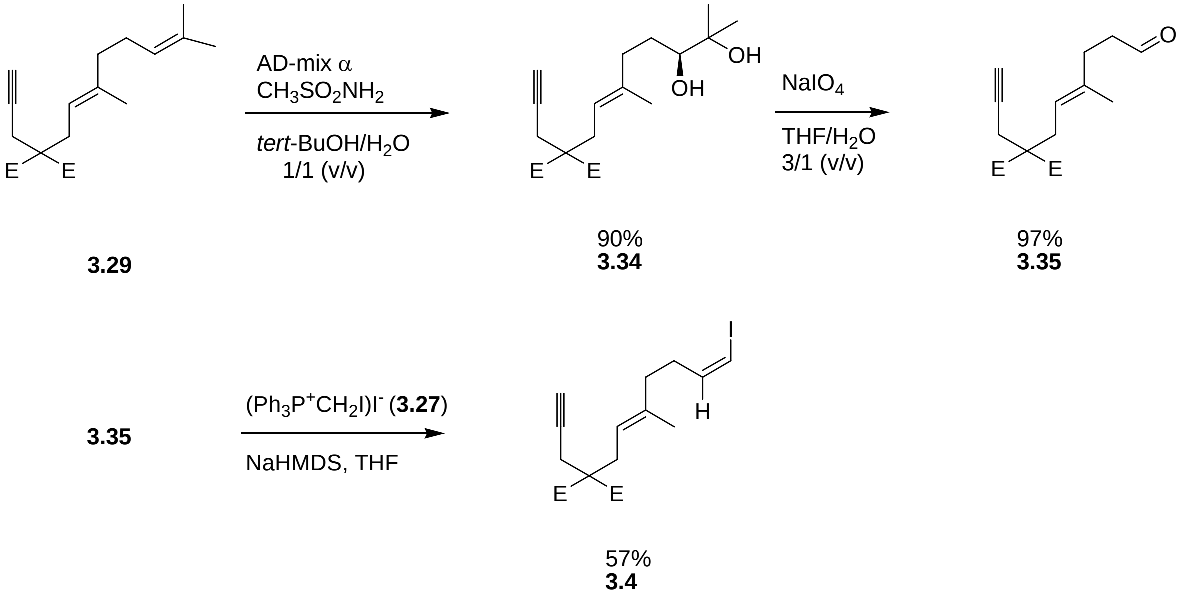
Hydrogenation of malonate **3.30** with Lindlar's catalyst gave the *Z*-olefin **3.31** in 83% yield.[80] Treatment of alkene **3.31** with AD-Mix α and $CH_3SO_2NH_2$ gave diol **3.32** in 74% yield.[75] Cleavage of diol **3.32** with $NaIO_4$ provided aldehyde **3.33** in 85% yield.[76] Wittig olefination of aldehyde **3.33** with the phosphorous ylide derived from salt **3.28** furnished *Z*-vinyl iodide **3.1** in 37% yield.[78] Although our previous experience with this Wittig reaction in the synthesis of **1.65** provided the final vinyl iodide as a 6/1 *Z*/*E* mixture, the same reaction with aldehyde **3.33**, furnished only the *Z* isomer as observed by TLC or crude NMR analysis.


3.22
E = CO2Me
NaH, THF
Br
78%
3.29
BuLi, THF
O
Cl
O
E
28%
3.30
3.30
Lindlar's catalyst
Quinoline
Hexanes
83%
3.31
AD-mix α
CH3SO2NH2
tert-BuOH/H2O
1/1 (v/v)
OH
OH
74%
3.32
3.32
NaIO4
THF/H2O
3/1 (v/v)
O
85%
3.33
(Ph3P+CH2I)I- (3.27)
NaHMDS, THF
I
H
37%
3.1
E

Scheme 3-4: Synthesis of cyclization precursor **3.1**.

3.2.3 Synthesis of the Alkyne Cyclization Substrate 3.4

The synthesis of cyclization precursor **3.4** is outlined in Scheme 3-5 and starts by a dihydroxylation of compound **3.22** with AD-mix α and $CH_3SO_2NH_2$ to give diol **3.27** in 90% yield.[75] Subsequent cleavage of the diol with $NaIO_4$ gave aldehyde **3.28** in 97% yield.[76] Wittig olefination of aldehyde **3.28** with salt **3.27** gave vinyl iodide **3.4** in 57% yield as a single Z-stereoisomer.[78]



Scheme 3-5: Synthesis of alkynyl precursor **3.4**.

3.3 Cyclization Results

With the cyclization precursors in hand, we studied the cascade reactions at different temperatures and with a number of reducing agents. The results from the cyclizations of **1.65**, **3.1** and **3.2** are summarized in Table 3-1, while the results from the cyclization of **3.3** and **3.4** are given in Table 3-2 and Table 3-3, respectively.

3.3.1 Cyclization of Vinyl Iodide 1.65

In a repetition of one of Ihara's key experiments, we reduced **1.65** (0.10 mmol) with Bu_3SnH (0.12 mmol) and AIBN (0.05 mmol) in benzene (55 mL, 2 mM with respect to the reducing agent) at 80 °C, Figure 3-2 and Table 3-1 Entry 2. A relatively complex mixture resulted from this cyclization and column chromatography or HPLC was not helpful for seperating out any of the components. Once again, GC analysis proved to be a useful tool. After subjecting the crude reaction mixture to a DBU workup[81] to remove most of the tin containing by-products, the mixture was analyzed by GC to provide the chromatogram shown in Figure 3-2a. In addition to the major peaks at 8.10 min and 8.39 min (44% and 34% of the mixture respectively), there were at least 4 minor peaks. The minor peak with a retention time of 7.66

min was readily identified as directly reduced product **3.13** (Figure 3-3). This was accomplished by an independent synthesis of **3.13** by a Wittig reaction between aldehyde **3.26a** and methyl triphenylphosphonium bromide[82] to give the triene in 58% yield. GC co-injection of authentically prepared **3.13** and the crude reaction mixture enabled us to identify the peak at 7.66 min as the directly reduced product.

We tentatively assigned the major products of the cyclization as the *cis*-*syn*-*cis* isomer **3.9** and the *cis*-*anti*-*cis* isomer **3.10** on the basis of Ihara's work.[38] We later confirmed this assignment and were able to show that the peak with the shorter retention time corresponded to the *cis*-*syn*-*cis* isomer **3.9**. ^{1}H NMR spectra of the crude cyclization mixture showed small resonances in the alkene region (δ 4.5-6.0 ppm) in addition to those assigned to triene **3.13**. We tentatively assigned those resonances as coming from the mono-cyclized product **3.14** and the *trans* substituted bicyclic product **3.15*trans*** where the round-trip cyclization was interupted by reduction with Bu_3SnH. Although it is possible that some of the resonances can be attributed to *cis* bicycles **3.15*cis***, it is unlikely that they are present because the corresponding radical **3.7*cis*** is known to cyclize rapidly to give the linear triquinane.[35]

To remove the minor alkene containing products from the alkene free tricyclic products, we treated the product mixture with *m*-CPBA with the expectation that the alkene containing products would be epoxidized and thereby rendered more polar. Indeed TLC analysis of the reaction mixture revealed two spots; one with the same R_f as before and a new more polar spot. Flash chromatography of the resulting mixture allowed for isolation of the less polar fraction whose ^{1}H NMR spectra showed no epoxide or alkene resonances. The GC chromatogram of this purified mixture is shown in Figure 3-2b. The peak from triene **3.13** and several of the other minor peaks have been removed, leaving four products, two major and two minor. In a GC-MS experiment, all four peaks exhibited almost identical fragmentation patterns strongly suggesting that they are all tricyclic and isomeric.

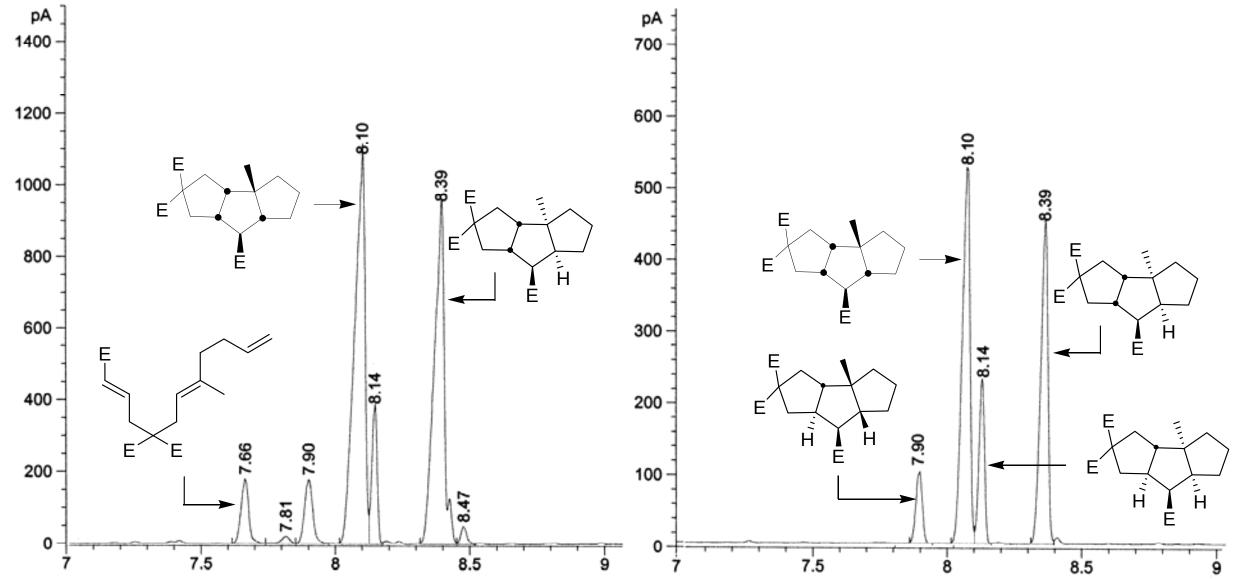


Figure 3-2: a) Left: GC chromatogram of the cyclization reaction of **1.65** after a DBU workup. b) Right: GC chromatogram of the cyclization of **1.65** after DBU workup and m-CPBA treatment of the reaction mixture. Both GC injections were performed on an Agilent 6850 gas chromatograph equipped with an HP-1 column: dimethylpolysiloxane, 30m x 0.32mm, and a 0.25 µm film thickness. The temperature profile of the injection has an initial temperature of 150 °C which then increases by 10 °C/min to a final temperature of 315 °C.

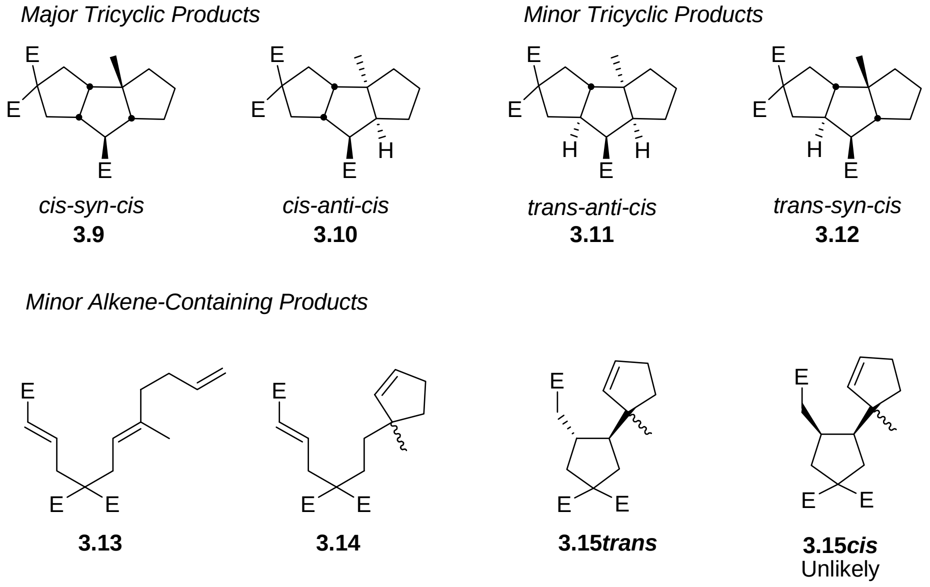
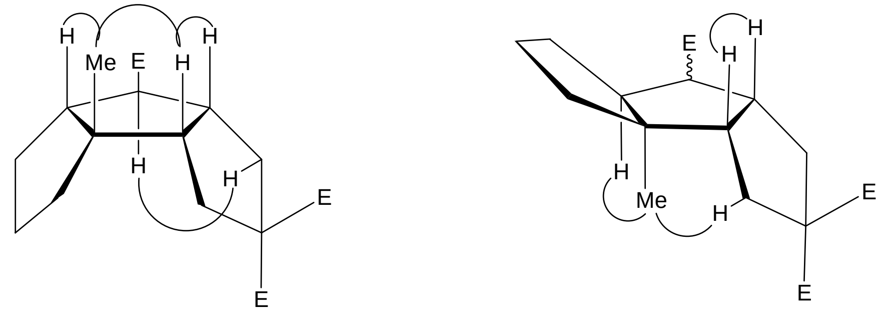

Major Tricyclic Products
Minor Tricyclic Products
cis-syn-cis
3.9
cis-anti-cis
3.10
trans-anti-cis
3.11
trans-syn-cis
3.12
Minor Alkene-Containing Products
3.13
3.14
3.15trans
3.15cis
Unlikely
E
H

Figure 3-3: Potential products from the cyclization of **1.65**.

Having developed a way to isolate only the tricyclic products of this cyclization, we proceeded to more rigorously assign which peak in the GC chromatogram arose from which tricycle. Although Ihara reports that compound **3.9** was separated from the other components of the mixture by flash chromatography, we were unable to do this even when using a Biotage™ purification system. Fortunately, we were able to obtain a 93% enriched sample of **3.9**, with **3.10** being the sole contaminant, through a preparative GC experiment carried out by Prof. M. Newcomb and R. E. P. Chandrasena at the University of Illinois at Chicago. Likewise we obtained a 75% enriched sample of **3.10** with **3.9** as the contaminant. This enabled us to fully assign all of the ^{1}H NMR resonances for both compounds and acquire NOSEY spectra. From the NOSEY spectra, we assigned the configuration of the second eluting compound as the *cis-syn-cis* isomer and the fourth eluting compound as the *cis-anti-cis* isomer based on the correlations shown in Figure 3-4. Unfortunately, we were unable to assign the configuration of the ester stereocenter in tricycle **3.10**.



3.9

3.10

Figure 3-4: a) Left: NOSEY correlations observed for the *cis-syn-cis* isomer **3.9** and b) Right: NOSEY correlations for the *cis-anti-cis* isomer **3.10**.

We assume that the minor peaks in the GC after *m*-CPBA treatment are the *trans* tricyclic products **3.11** and **3.12**. We assigned the peak at 8.14 min as the *trans-anti-cis* isomer **3.11** and the peak at 7.90 min as the *trans-syn-cis* isomer **3.12**. These assignments were made by analogy to the cyclization of **1.49** where the minor *trans* product was the *trans-syn-cis* isomer. However, these assignments are tentative because we could not obtain the compounds in pure enough form for detailed characterization. We considered the possibility that the minor products might be epimers of **3.33** and **3.34** at the ester bearing stereocenter. However, our relay experiments with **3.2**, Chapter 3.4, suggest that this is not the case because the cyclization of **3.3**, without this ester, also gives four tricyclic products.

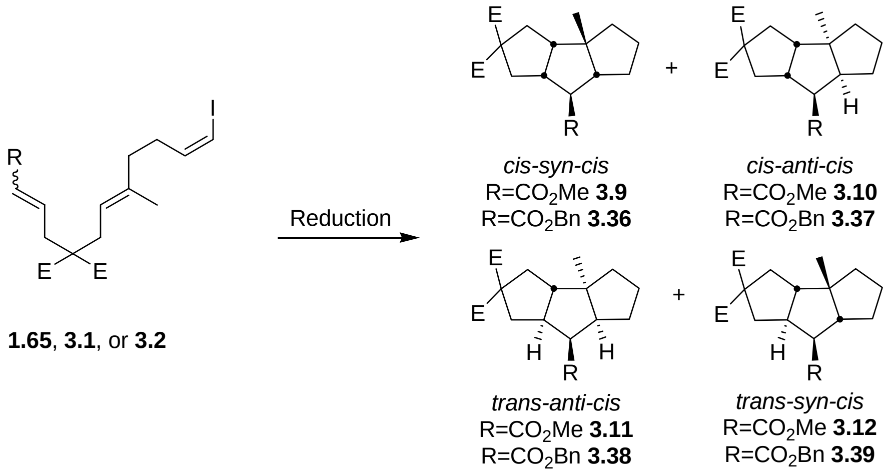
We have now identified which peaks in the GC chromatogram correspond to the tricyclic products, and we have firmly assigned the configuration of the two major products. Additionally the above analysis for the cyclization of **1.65** allowed us to assign the configuration of the tricycles from the cyclization of *Z*-unsaturated ester **3.1** (see below) because it gives the same set of products.

3.3.2 Cyclization Results for Substrates 1.65, 3.1 and 3.2

With a good analysis method in hand, we conducted a series of cyclizations with substrate **1.65** with Bu_3SnH and Ph_3SnH at 80 °C and 25 °C, Table 3-1 entries 1-4. We also varied the reducing agent concentration by adding a 24 mM solution of Bu_3SnH in benzene to the reaction by syringe pump over 3 h, entries 11 and 12. Each reaction was treated with *m*-CPBA and chromatographed to remove any alkene containing products and then subjected to GC analysis to determine the cyclization selectivity reported in Table 3-1. The same analysis procedure was carried out for the two cyclizations of the *Z*-unsaturated ester **3.1**, where we ran one cyclization at 80 °C and the other at 25 °C, Table 3-1 entries 5 and 6. Finally we also performed the cyclization of the benzyl ester substrate **3.2** at 25 °C and 80 °C using Bu_3SnH and Ph_3SnH as the reducing agent entries 7-10.

For the cyclization of vinyl iodide **1.65,** entries 1-4, 11 and 12, the ratio of the four tricyclic products hardly varied at all as shown in Table 3-1 Of special interest is the *cis*/*trans* selectivity of the second 5-*exo* cyclization. This selectivity was calculated by dividing the sum of the major two cis/cis products **3.9** and **3.10** by the sum of the minor two *trans*/*cis* isomers **3.11** and **3.12**. The temperature dependance of selectivities in the second cylization are very consistent with those obtained for the benchmark substrates in Chapter 2, but inconsistent with the results reported by Ihara. We only observe a minor improvement in the selectivity from about 77/23 *cis*/*trans* at 80 °C to 84/16 at 25 °C. The *cis*/*trans* ratios may be slightly overstated because the minor products removed in the *m*-CPBA treatment are likely to result predominantly from *trans* cyclization in the second step. However, we believe that this error is small because the selectivities in the tricyclization reactions are very similar to those found for the benchmark substrates.

Table 3-1: Cyclization data for the cyclization of substrates **1.65**, **3.1** and **3.2**.



1.65, **3.1**, or **3.2**

cis-syn-cis
R=CO_2Me **3.9**
R=CO_2Bn **3.36**

cis-anti-cis
R=CO_2Me **3.10**
R=CO_2Bn **3.37**

trans-anti-cis
R=CO_2Me **3.11**
R=CO_2Bn **3.38**

trans-syn-cis
R=CO_2Me **3.12**
R=CO_2Bn **3.39**

						% Composition					
Entry	Substrate	R	Olefin Geometry	Red. Agent[b]	T (°C)	**3.9** -or- **3.36**	**3.10** -or- **3.37**	**3.11** -or- **3.38**	**3.12** -or- **3.39**	Selectivity (*cis*/*trans*)[c]	Yield (%)
	2 mM fixed reducing agent concentration										
1	**1.65**	CO_2Me	*E*	Bu_3SnH	25	47	39	8	6	86/14	52, 69[e]
2	**1.65**	CO_2Me	*E*	Bu_3SnH	80	44	34	9	13	78/22	50, 70[e]
3	**1.65**	CO_2Me	*E*	Ph_3SnH	25	44	35	7	14	79/21	48
4	**1.65**	CO_2Me	*E*	Ph_3SnH	80	47	37	9	7	77/23	46
5	**3.1**	CO_2Me	*Z*	Bu_3SnH	25	51	40	8	1	91/09	62
6	**3.1**	CO_2Me	*Z*	Bu_3SnH	80	48	40	5	7	88/12	N.D.[d]
7	**3.2**	CO_2Bn	*E*	Bu_3SnH	25	47	40	6	7	87/13	50
8	**3.2**	CO_2Bn	*E*	Bu_3SnH	80	47	37	7	8	84/16	50
9	**3.2**	CO_2Bn	*E*	Ph_3SnH	25	44	39	10	7	83/17	44
10	**3.2**	CO_2Bn	*E*	Ph_3SnH	80	42	35	15	8	77/23	35
	Reducing agent added by syringe pump										
11[a]	**1.65**	CO_2Me	*E*	Bu_3SnH	25	48	38	8	6	86/14	N.D.[d]
12[a]	**1.65**	CO_2Me	*E*	Bu_3SnH	80	42	35	9	14	77/23	N.D.[d]

[a] Ihara's protocol

[b] Cyclization procedures are detailed in Chapter 5

[c] Refers to the selectivity of the second 5-*exo* radical cyclization

[d] N.D.: isolated yield not determined; the selectivity was determined from a GC of the crude reaction mixture

[e] Yield determined using octadecane as an internal GC standard

We noted the moderate (42-50%) isolated yields of our cyclization reactions and worried that we may be selectively removing some products during purification. To see if this was the case, we used octadecane as an internal standard in the reaction, entries 1 and 2, and were able to show that the chemical yield of the cyclization is about 20% higher than the isolated yield. The use of the internal standard, along with the observation that the tricyclic product ratios were the same before and after purifcation, assures us that the ratios reported in Table 3-1 are accurate measures of the selectivity.

The cyclization of the *Z*-unsaturated ester **3.1**, entries 5 and 6, shows an improved selectivity in the second cyclization of 90/10 *cis*/*trans* in comparison to the 80/20 obtained for the *E*-unsaturated ester. The selectivities of the cyclization were also consistent at about 90/10 when the reaction was run at either 80 °C or 25 °C.

Finally, the cyclization of the benzyl ester substrate **3.2** entries 7-10, gave results very similar to those obtained for the methyl ester cyclizations. The product ratios and selectivities were very similar to each other and also showed no temperature dependence. GC chromatograms for a cyclization of substrate **3.2** before (left) and after (right) *m*-CPBA treatment are shown in Figure 3-5. Similar to the cyclization of **1.65**, substrate **3.2** gave a relatively complex mixture of products with two major product peaks at 10.78 min and 11.11 min. We were able to readily identify the directly reduced product **3.40**, Figure 3-6, as the peak at 10.57 min by an independent synthesis and GC co-injection. We once again tentatively assigned the major products as the *cis-syn-cis* isomer **3.36** and the *cis-anti-cis* triquinane **3.37**. Treatment of the cyclization mixture with *m*-CPBA and isolation of the less polar fraction provided a mixture whose ^{1}H NMR spectra was void of alkene resonances. Analysis of this mixture by GC provided the chromatogram shown in Figure 3-5b that clearly shows four products. All four of these products displayed similar fragmentation patterns in a GC-MS experiment. This indicates that they are all tricyclic and isomeric and so we tentatively assigned the peak at 10.59 min as the *trans-anti-cis* isomer **3.38** and the peak at 10.84 min as the *trans-syn-cis* isomer **3.39**.

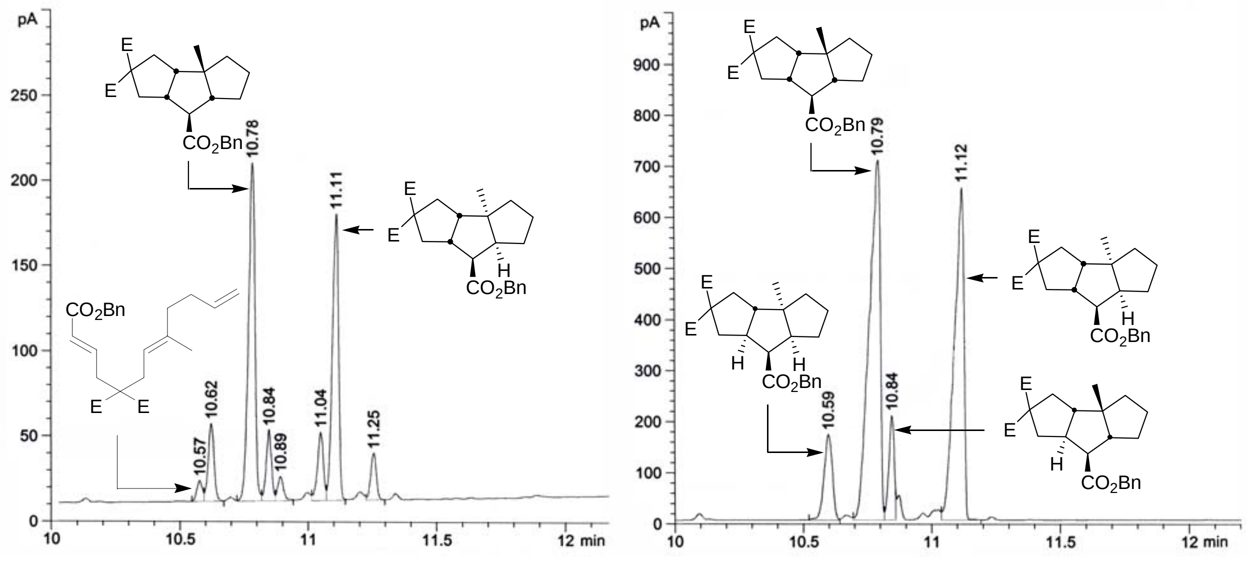


Figure 3-5: a) Left: GC chromatogram of the cyclization reaction of 3.2 after a DBU workup. b) Right: GC chromatogram of the cyclization of 3.2 after DBU workup and m-CPBA treatment of the reaction mixture. Both of the GC injections were carried out under the same conditions as described for Figure 3-2.

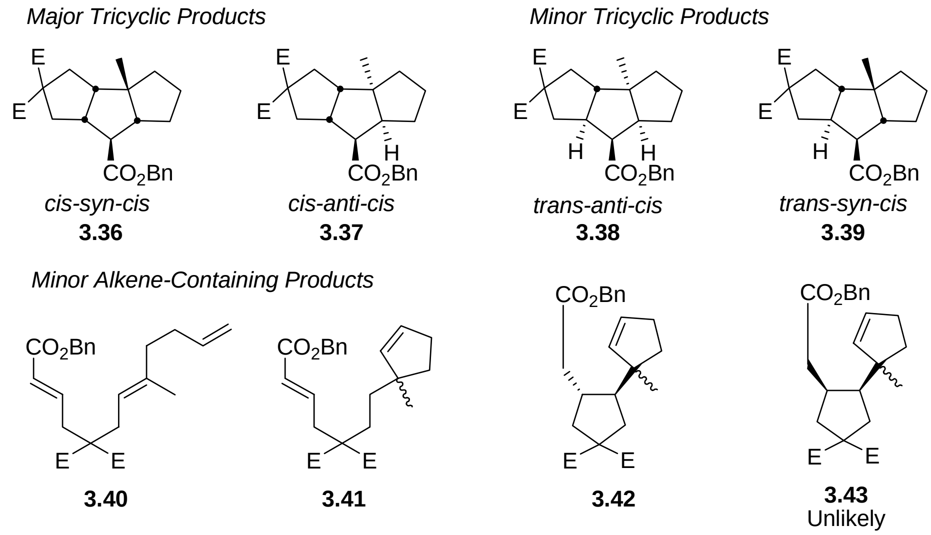

Major Tricyclic Products
Minor Tricyclic Products
E
E
H
CO2Bn
cis-syn-cis
3.36
cis-anti-cis
3.37
trans-anti-cis
3.38
trans-syn-cis
3.39
Minor Alkene-Containing Products
3.40
3.41
3.42
3.43
Unlikely

Figure 3-6: Potential products from the cyclization of **3.2**.

3.3.3 Cyclization of Allyl Precursor 3.3

We next turned our attention to the cyclization of precursor **3.3** to study the effect of the ester on the radical acceptor of the second cyclization. We conducted a series of cyclizations in a manner similar to that for precursors **1.65**, **3.1** and **3.2**. As before, when we reduced **3.3** with Bu_3SnH at 80 °C, a relatively complex mixture resulted with two major and a number of minor products. GC analysis of this mixture after DBU workup provided the left chromatogram shown in Figure 3-7. We readily identified the peak with a retention time of 5.16 min as coming form the directly reduced product **3.48**, Figure 3-8, and tentatively assigned the peak at 5.74 min as the *cis-syn-cis* triquinane **3.44** and the peak at 5.95 min as the *cis-anti-cis* triquinane **3.45**. After treating the crude cyclization mixture with *m*-CPBA and removing the more polar products by column chromatography, we obtained a mixture that upon GC analysis gave the chromatogram shown in Figure 3-7b. Several of the minor products were removed and we were left with a mixture containing two major and two minor products. All four of the products exhibited similar fragmentation patterns suggesting that they are all tricyclic compounds. We then assigned the peak at 5.51 min as the *trans-anti-cis* isomer **3.46** and the peak at 5.64 min as *trans-syn-cis* isomer **3.47**, but these assignments are tentative.

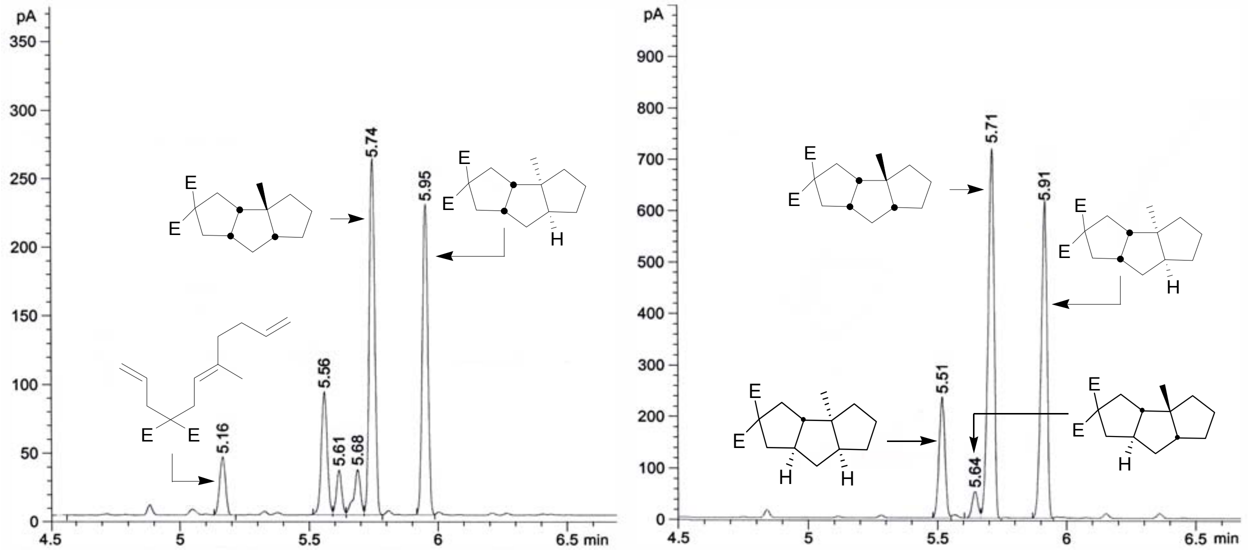


Figure 3-7: a) Left: GC chromatogram of the cyclization reaction of **3.3** after a DBU workup. b) Right: GC chromatogram of the cyclization of **3.3** after DBU workup and m-CPBA treatment of the reaction mixture. Both of the GC injections were carried out under the same conditions as described for Figure 3-2.

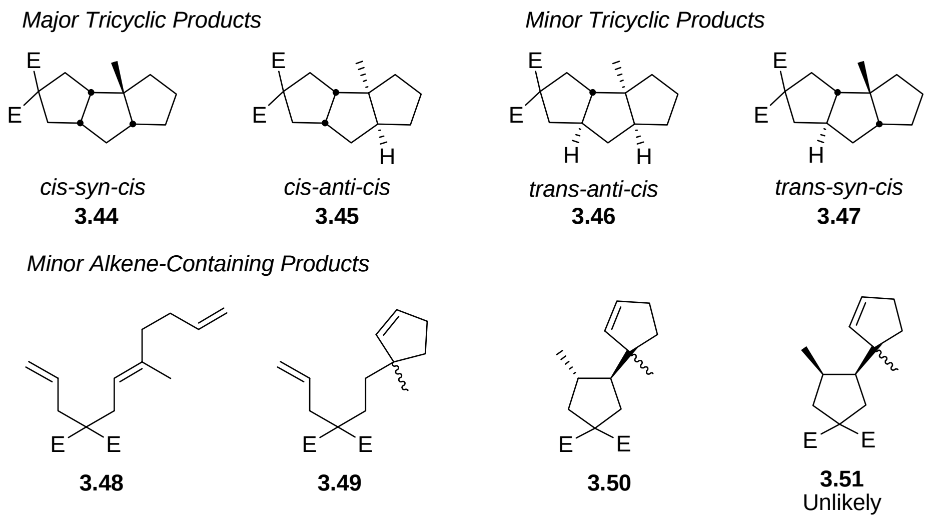
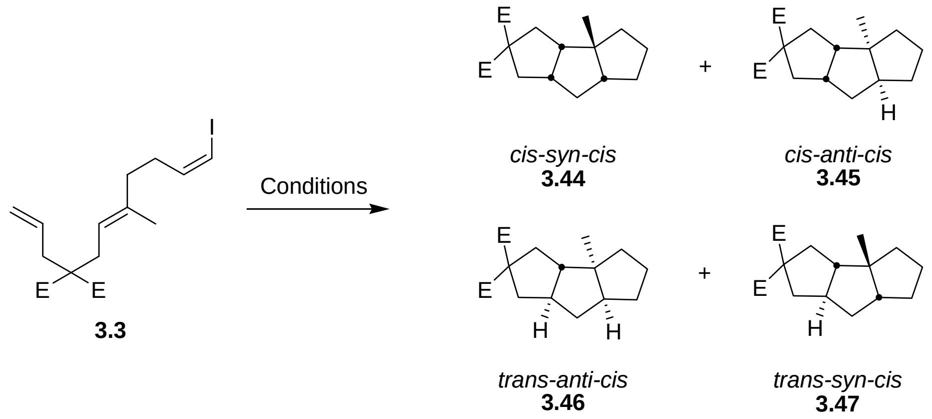

Major Tricyclic Products
Minor Tricyclic Products
E
E
H
cis-syn-cis
3.44
cis-anti-cis
3.45
trans-anti-cis
3.46
trans-syn-cis
3.47
Minor Alkene-Containing Products
3.48
3.49
3.50
3.51
Unlikely

Figure 3-8: Potential products from the cyclization of **3.3**.

Having identified the GC retention times of the four tricyclic products, the cyclization conditions for **3.3** were varied extensively and the results are all summarized in Table 3-2. In total 10 cyclizations were caried out where the reducing agent was changed from Bu_3SnH (entries 1, 2, 7, and 8) to Ph_3SnH (entries 5, 6, 9, and 10) and also $(TMS)_3SiH$ (entries 3 and 4). The cyclizations were also performed at either 25 °C (entries 1, 3, 5, 7, and 9) or 80 °C (enties 2, 4, 6, 8, and 10) and finally the concentration of the reducing agent was varied between a 2 mM fixed concentration, entries 1-6, and slow addition of the reducing agent by syringe pump over 3 h (entries 7-10).

The results in Table 3-2 show that despite variation of the reaction conditions, the tricyclic product ratios and selectivities in the second cyclization remain virtually unchanged. The selectivty of the second cyclization is once again about 80/20 *cis*/*trans* regardless of the reaction conditions. Furthermore the ratios of the tricyclic products are also close to those obtained for the cyclizations of precursors **1.65** and **3.2**, proving the the α,β-unsaturated ester has very little bearing on the course of this reaction. The selectivity in the second cyclization is not only close to that of the other tricyclization substrates, but also close to the selectivities observed in the cyclization of all of the benchmark cyclizations. Taken together, the results from this substrate and those found previously question whether the temperature effect exists.

Table 3-2: Cyclization data for the cyclization of substrate **3.3**



Entry	Cyclization Method[a]	Reducing Agent	T (ºC)	%Composition				Selectivity[d] (*cis/trans*)	Yield[e] (%)
				3.44	**3.45**	**3.46**	**3.47**		
	2 mM fixed reducing agent concentration								
1	A[b]	Bu_3SnH	25	40	42	13	5	82/18	N.D.
2	B	Bu_3SnH	80	40	37	19	4	77/23	N.D.
3	A	$(TMS)_3SiH$	25	43	38	12	7	81/19	N.D.
4	B	$(TMS)_3SiH$	80	41	41	11	7	82/18	N.D.
5	A	Ph_3SnH	25	47	36	13	4	83/17	N.D.
6	B	Ph_3SnH	80	45	38	14	3	83/17	N.D.
	Reducing agent added by syringe pump								
7	C[b,c]	Bu_3SnH	25	44	39	11	6	83/17	51
8	D[c]	Bu_3SnH	80	42	38	14	6	80/20	52
9	C[b,c]	Ph_3SnH	25	43	39	15	3	82/18	N.D.
10	D[b,c]	Ph_3SnH	80	40	36	19	5	76/24	N.D.

[a] See chapter 5 for details on the experimental procedure.
[b] Required the addition of 1 equiv of PPh_3 to avoid exclusive formation of a directly reduced product **3.48**.
[c] Ihara's protocol.
[d] Refers to the selectivity of the second 5-*exo* radical cyclization.
[e] N.D.: not determined; The selectivity was determined from a GC of the crude reaction mixture.

3.3.4 Cyclization of the Alkynyl Precursor 3.4

We conducted the cyclization of substrate **3.4** using our standard reducing conditions of Bu_3SnH, AIBN in refluxing benzene (2 mM). The crude reaction mixture was purified by column chromatography to remove any tin by-products and then analyzed by GC and ^1H NMR spectroscopy. The ^1H NMR spectrum of this mixture showed no evidence of any tin containing impurities and all the necessary resonances for tricycles **3.19** were present. Most notably this mixture showed two resonances with chemical shifts of 5.17 and 4.99 ppm as shown in Figure 3-9. We attributed one of these resonances to the olefinic proton in compound **3.19*syn*** and the other to the olefinic proton in tricycle **3.19*anti***. By integration, the ratio of these two peaks was

33/67 respectively. Interestingly GC analysis of the same mixture showed only a single peak with a retention time of 5.59 min, Figure 3-9, despite trying a number of different GC temperature profiles. Based on the NMR and the GC analysis we concluded that there were two products in this mixture in a 33/67 ratio that coincidentally eluted on the GC. At this point we were unable to definitively determine if ***3.19syn*** or ***3.19anti*** was the major isomer.

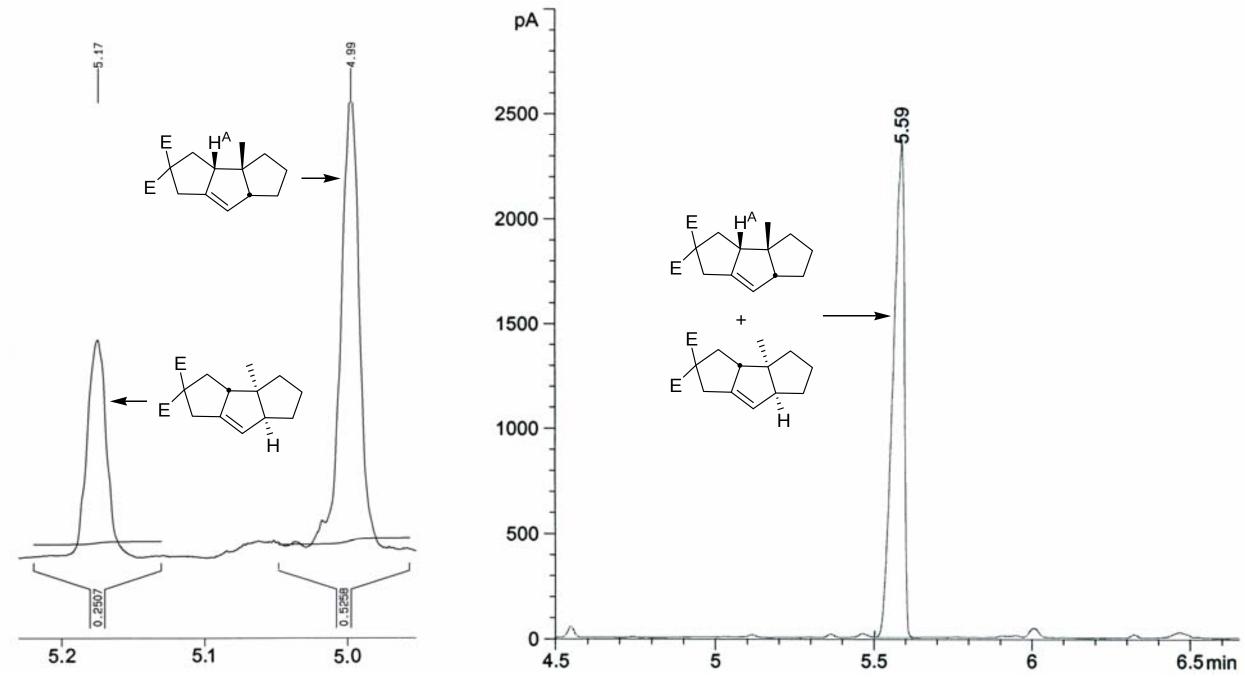


Figure 3-9: a) Left: Expansion of the olefinic region of the ^{1}H NMR spectrum of the cyclization mixture of precursor **3.4**. b) Right: GC chromatogram of the cyclization mixture of **3.4**. The GC injection was carried out under the same conditions as described for Figure 3-2.

We then subjected the cyclization mixture to a palladium-mediated hydrogenation in ethanol.[41] GC analysis of the hydrogenation reaction showed rapid disappearance of the mixture peak at 5.59 min and appearance of two products with retention times of 5.73 and 5.92 min in a 67/33 ratio respectively, Figure 3-10. Purification of this mixture by filtration through Celite and concentration of the filtrate gave the two component mixture in 67% yield over both the cyclization and the hydrogenation step. Comparison of the retention times of these two products to the retention times of the four tricyclic products from the cyclization of the allyl precursor **3.3** showed that the major peak of the hydrogenation corresponded to the *cis-syn-cis* isomer **3.44** and that the minor peak corresponded to the *cis-anti-cis* isomer **3.45**.

We also performed the cyclization of **3.4** at 25 °C, Table 3-3 entry 2, which gave a 60/40 mixture of **3.19*syn*** and **3.19*anti*.** As expected, hydrogenation of this 60/40 mixture over palladium gave a 60/40 mixture of the *cis-syn-cis* triquinane **3.44** and the *cis-anti-cis* triquinane **3.45** in 65% yield over the two steps.

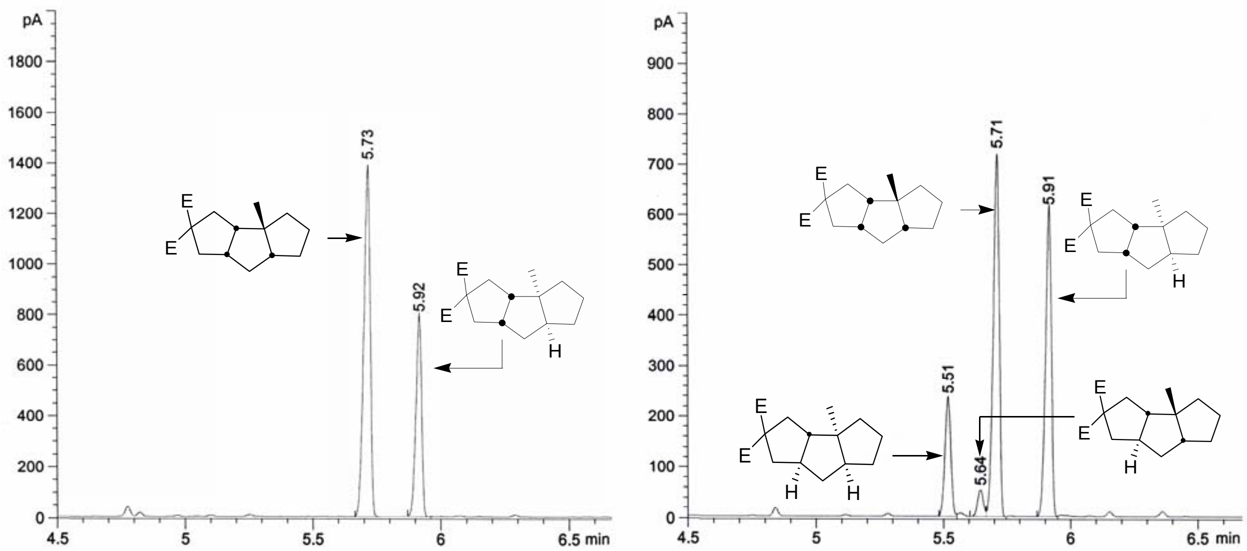
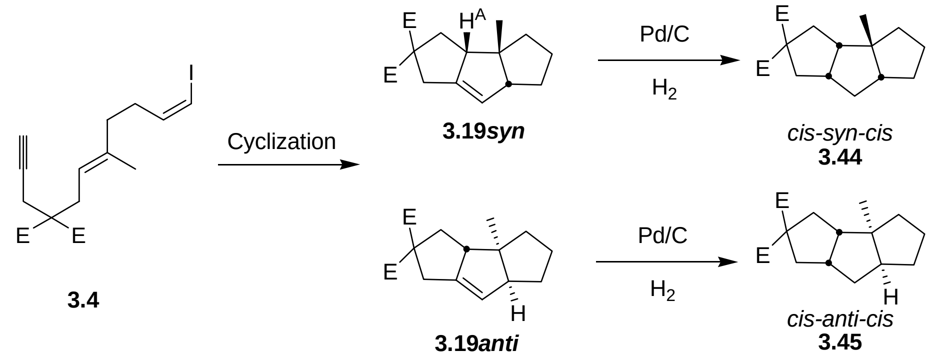


Figure 3-10: a) Left: GC chromatogram of the hydrogenation mixture and b) Right: GC chromatogram of the triquinane mixture from the cyclization of **3.3**. Both GC injections were carried out under the same conditions as described for Figure 3-2.

Table 3-3: Cyclization data for **3.4** and subsequent hydrogenation



				Cyclization % Composition by NMR		Hydrogenation % Composition by GC		
Entry	Cyclization Method[a]	Reducing Agent	T (°C)	**3.19*syn***	**3.19*anti***	**3.44**	**3.45**	Yield (%)[b]
1	A	Bu_3SnH	25	60	40	60	40	65
2	B	Bu_3SnH	80	66	34	66	34	67

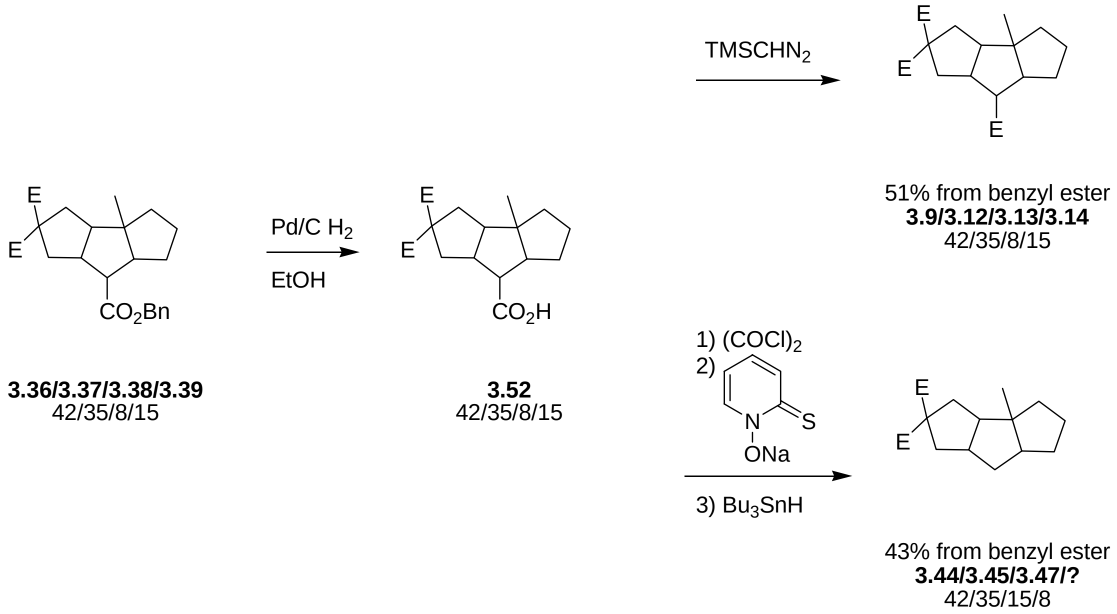
[a] See Chapter 5 for experimental procedures.

[b] Refers to yield over both steps.

The cyclization of substrate **3.4** also showed very little variation in selectivity when carried out at different temperatures, but the clean hydrogenation reaction enabled us to make two conclusions. First, the major product of the radical cyclization of **3.4** is compound **3.19*syn*** because we could establish that triquinane **3.44** was the major product of the hydrogenation. Second the hydrogenation of compound **3.19** occurs exclusively from the same face as H^A indicated in **3.19*syn***. If hydrogenation had occurred from the opposite face, then the *trans* substituted triquinanes **3.46** and **3.47** would have been formed, and these are not visible in the GC chromatogram from the hydrogenation reaction shown in Figure 3-10.

3.4 Stereochemical Relay Between Systems 1.65, 3.2 and 3.3

With the two major products in the cyclization of **1.65** firmly assigned and the minor products tentatively assigned, we relayed the assignments to the products of the cyclizations of **3.2** and **3.3**. This was accomplished by using the benzyl ester in triquinanes **3.36-3.39** as a handle as shown in Scheme 3-6. Treatment of a 42/35/8/15 mixture of benzyl triquinanes **3.36-3.39** with Pd/C under a hydrogen atmosphere in ethanol[83] gave the corresponding acids **3.52** as a mixture of four products, which was used without further purification. The acid mixture was then then split into two portions, and one half was treated with $TMSCHN_2$ to give a mixture of products **3.9-3.12** in 51% yield from the benzyl triquinanes.[60] The other half was decarboxylated by using Barton's method[20] to give a mixture of tricycles **3.44-3.47** in 43% yield from tricycles **3.36-3.39**.



3.36/3.37/3.38/3.39
42/35/8/15

3.52
42/35/8/15

51% from benzyl ester
3.9/3.12/3.13/3.14
42/35/8/15

43% from benzyl ester
3.44/3.45/3.47/?
42/35/15/8

Scheme 3-6: Stereochemical relay experiments.

The transesterified mixture of triquinanes **3.9-3.12** exhibits 4 peaks upon GC analysis as shown in Figure 3-11. A GC co-injection of the transesterified triquinane mixture with the cyclization mixture obtained directly from **1.65** showed that the retention times of the four products in both mixtures were identical, Figure 3-11. This result confirms our initial assignments for the benzyl triquinanes **3.36-3.44**, because we were able to directly compare our firm assignments for **3.9** and **3.10** to the products arising from the cyclization of the benzyl ester precursor **3.2**.

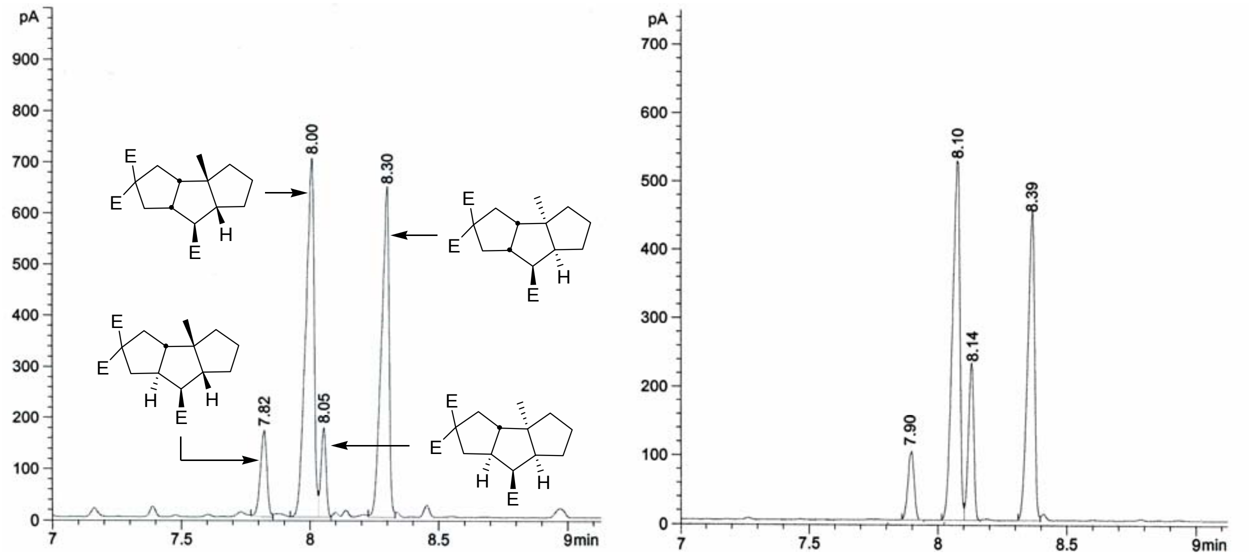


Figure 3-11: a) Left:GC chromatogram of the transesterified mixture **3.9**-**3.12** and b) Right: Co-injection of the transesterified mixture with the purified cyclization mixture of **1.65**. Both GC injections were carried out under the same conditions as described for Figure 3-2.

The mixture of tricycles from the decarboxylation experiment also showed 4 peaks upon GC analysis, Figure 3-12a. However a co-injection of the decrboxylation mixture with the original cyclization mixture from **3.4**, Figure 3-12b, showed a new product with a retention time of 4.02 min. So this experiment allowed us to confirm the assignments of the two major peaks as the *cis-syn-cis* and the *cis-anti-cis* triquinanes by direct comparison to our firm assignments of **3.9** and **3.10**. However, it only allows us to relay the assignment of *trans-anti-cis* compound **3.46**, because the other minor peak's retention time did not match to that of the cyclization mixture from **3.3**. We considered the possibility that the *trans-syn-cis* **3.39** isomer had epimerized under the decarboxylation conditions to give the new product. However we decided not to pursue this any further because our assignments for the minor products were only tentative and the new product was only present in small amounts (<10%).

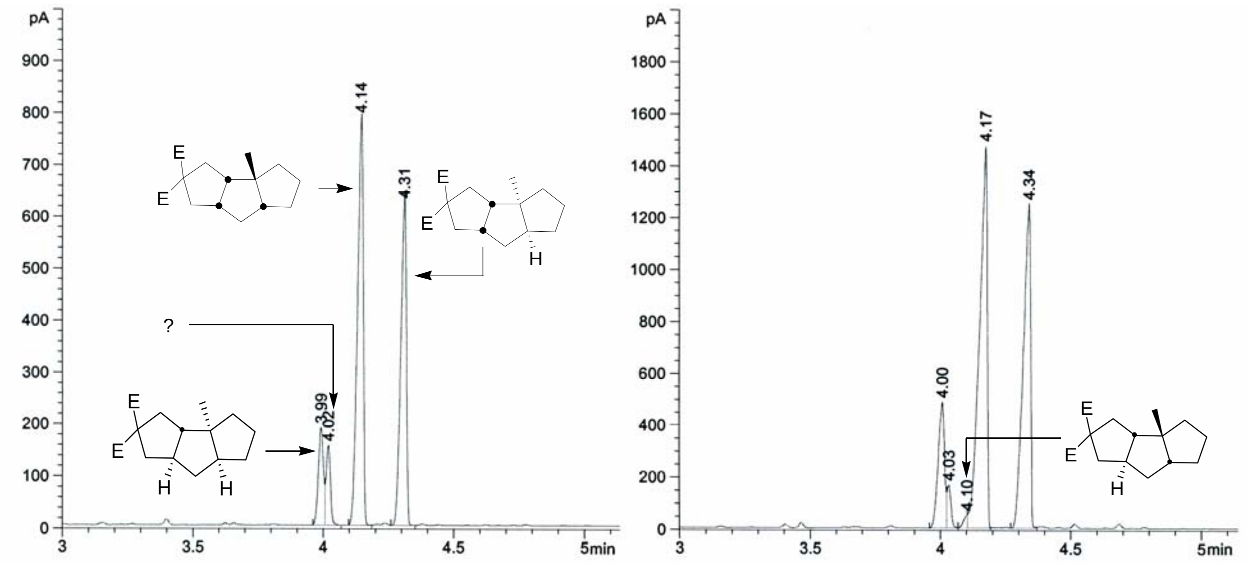


Figure 3-12: a) Left:GC chromatogram of the decarboxylated tricycle mixture and b) Right: Co-injection of the decarboxylated mixture with the purified cyclization mixture of **3.3**. Both GC injections were carried out under the same conditions as described for Figure 3-2.

In addition to relaying our structural assignments, the decarboxylation experiments allowed us to confirm that the minor products in the cyclization of **1.65** were not epimers at the ester bearing stereocenter; if they were, then removal of the ester group would have given two products where four were clearly observed in the GC chromatogram in Figure 3-12. This observation also supports our conclusion that the minor products in the round trip cascade result from *trans* closure in the second cyclization.

3.5 Uncovering the Origin of the Temperature Effect

We were unable to reproduce the temperature effect that Ihara reports. Even in an exact repeat of his experiments, Table 3-1 entries 11 and 12, the selectivity only improves modestly to 86/14 from 77/23 *cis*/*trans* when running the reaction at 25 °C instead of 80 °C. This change in temperature however is reported to improve the ratio from 64/36 to 100/0.[38] We considered the possibility that this discrepenecy did not arise from the way that the experiments were carried out, but in how the amounts of "other diastereomers" were quantified? The process of determining the product ratios was not detailed in the original publication, but Professor Ihara kindly explained his analysis and provided helpful additional data.

The top half of Figure 3-13 shows expansions of the methyl ester region of two separate ^{1}H NMR spectra that Ihara provided us. Figure 3-13a shows this region when the cyclization was conducted at 80 °C while Figure 3-13b is representative of a ^{1}H NMR from a cyclization run at 25°C. Ihara assigned the singlet at 3.67 ppm to the *cis-cyn-cis* isomer **3.9** and the singlet at 3.66 ppm to the *cis-anti-cis* isomer **3.10**. We confirmed these assignments by using our enriched samples from the preparative GC experiments. Ihara then assigned the resonances around 3.68 ppm, highlighted by the boxes in Figure 3-13, as the other diastereomers and the reported product ratios then follow from integration. In comparing the NMR spectra in Figure 3-13a and Figure 3-13b, it is clear how Ihara concluded that this radical cascade cyclization was temperature dependent. However, it turns out that Ihara did not have all of the pieces needed to solve the assignment puzzle.

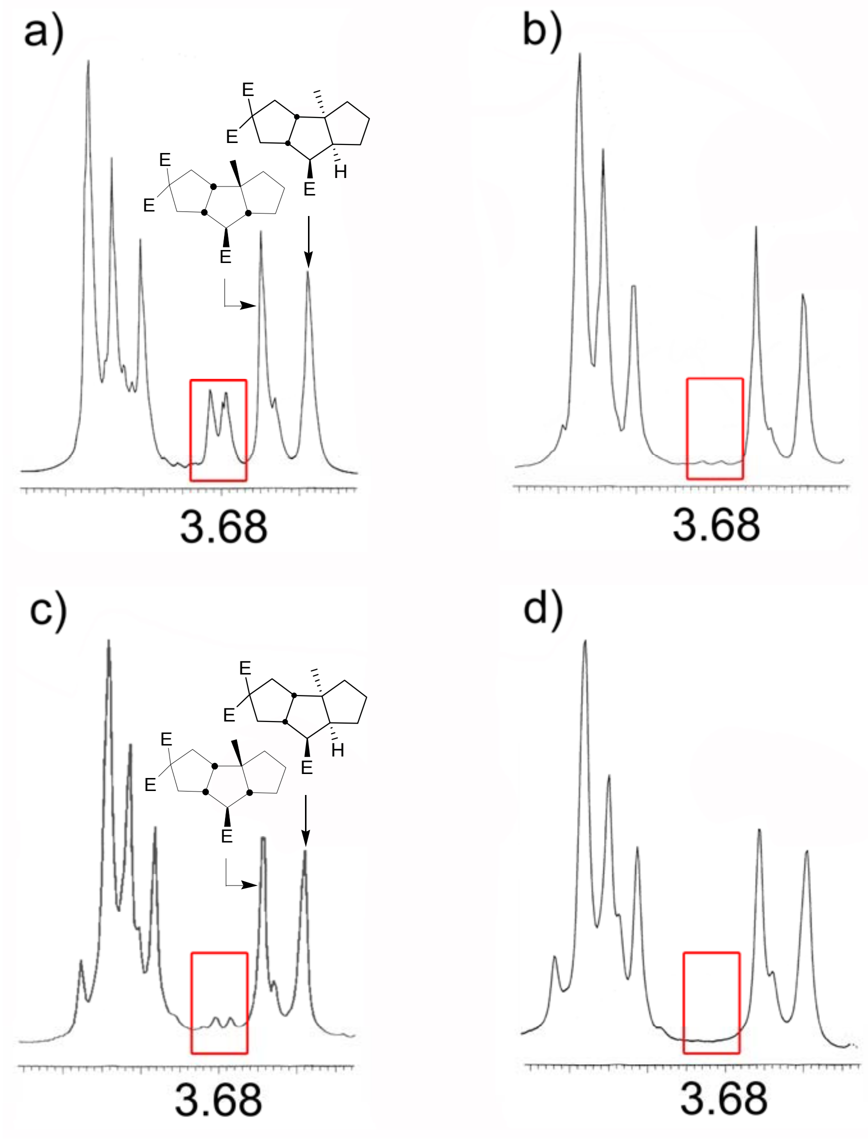


Figure 3-13: Comparison of methyl group resonances in ^{1}H NMR spectra ($CDCl_3$) of the reaction products of the cyclization of **1.65**. a) Ihara's spectrum, Bu_3SnH 80 °C; b) Ihara's spectrum, Bu_3SnH 25 °C; c) Our spectrum, Bu_3SnH 80 °C, before *m*-CPBA treatment; d) Our spectrum, Bu_3SnH 80 °C, after *m*-CPBA treatment; Spectra very similar to those shown in c) and d) were obtained when the cyclization was run at 25 °C.

When carrying out the same NMR analysis but on samples from our 80 °C and 25 °C experiments, we observed about the same amount of resonances at 3.68 ppm in both cases as expected from the results of our GC analysis. However, if we examined the methyl ester region of our cyclization mixture before *m*-CPBA treatment, Figure 3-13c, and then again afterwards, Figure 3-13d, we noticed that the resonances at 3.68 ppm had disappeared. Accordingly, we conclude that the peaks at 3.68 ppm do not belong to other triquinane diastereomers, but rather to alkene-containing, prematurely reduced products that are removed by the *m*-CPBA oxidation.

Integration of the resonances at 3.68 ppm in Figure 3-10c also approximately matches the integration of the minor peaks in the GC chromatogram that are removed upon treatment with *m*-CPBA.

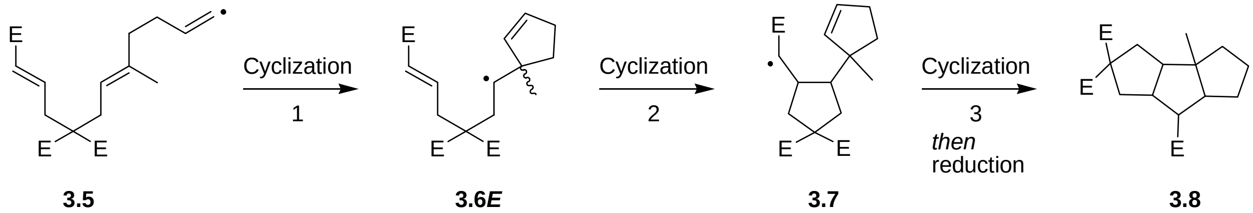
Having corrected the discrepencies in the analysis, we concluded that Ihara had not observed an improvement in the diastereoselctivity of the cyclization, but rather a decrease in the amount of premature reduction when the reaction was run at 25 °C instead of at 80 °C. However, our experiments consistently show that about the same amount of alkene-containing products are formed. At present it is unclear why the amount of prematurely reduced products differ in Ihara and our experiments. Nevertheless, the disappearance of the minor peaks in the GC and the NMR upon *m*-CPBA treatment support our conclusion that the resonances at 3.68 ppm are indeed from alkene containing products. While we have only tentatively assigned structures to the minor products, we have definitely shown that the "other diastereomers" do not have resonances at 3.68 ppm. The problem with using NMR integrations to determine the selectivity is that in the cyclization mixture of **1.65** there are two major products and at least five minor products, all of which have three non-equivalent methyl ester groups. This makes rigorous assignments in the OMe region of the ^{1}H NMR spectrum difficult. While the GC analysis is not complete, it is more accurate than the NMR analysis because we are able to classify each peak as tricyclic or not, and individually integrate it.

3.6 Transition State Analysis for 1.65 and 3.3

We have demonstrated that the round-trip radical cyclization of substrates **1.65** and **3.1**-**3.3** gives two major triquinanes, the *cis-syn-cis* and the *cis-anti-cis* isomer, and two minor triquinanes namely the *trans-anti-cis* and the *trans-syn-cis* isomers. That the *cis* mode of cyclization accounts for 80% of the products in the second cyclization can be nicely rationalized using a Beckwith/Houk transition state analysis. This same model can also be used to explain why changing the geometry of the α,β-unsaturated ester from *E* (**1.65**) to *Z* (**3.1**) improves the selectivity of the second cyclization. While only the cyclization of compound **1.65** will be discussed, the same analysis applies analogously for the other two *E*-geometry α,β-unsaturated ester substrates **3.2** and **3.3**.

3.6.1 Transition State Analysis for the Cyclization of 1.65

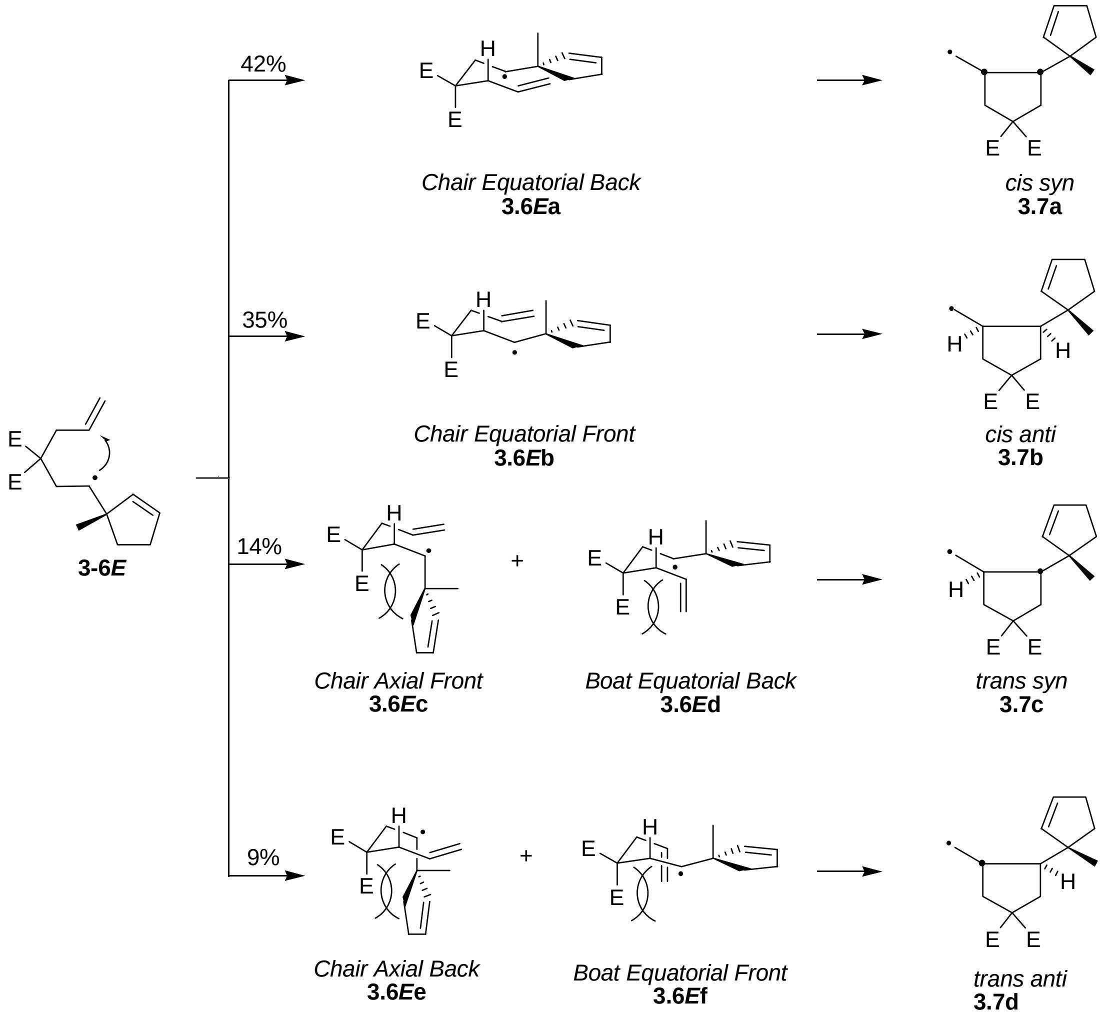
The transition state analysis for substrate **1.65** will be divided into two sections that will cover the second and third cyclizations in the cascade. The first cyclization merely gives a racemic mixture of compounds. The cascade cyclization is summarized in Scheme 3-7 starting with radical **3.5**, which cyclizes in a 5-*exo* fashion to give radical **3.6*E*.** A second 5-*exo* cyclization event gives radical **3.7** which then undergoes the third and final cyclization to give triquinanes **3.8** upon reduction.



Scheme 3-7: Summary of the round-trip radical cyclization.

In the second cyclization, radical **3.6*E*** cyclizes to give four bicyclic radicals **3.7*E*a-d** as shown in Scheme 3-8. Four products arise because the adjacent stereocenter from the first cyclization makes 1,2 stereo-induction possible and two new stereocenters are established during the cyclization by placing the substituents either *cis* or *trans* to each other. The four product radicals are labeled either *cis* or *trans* based on the relationship of the ring substituents in the A ring and *syn* or *anti* based on the relationship between the methyl group and proton H^A, as shown in **3.7a**, Scheme 3-8.

These four products arise from eight transition states, but the two *axial boat* transition states will be ignored, leaving six to consider. Four of these transition states are chairs and the remaining two are boats. All six transition states are shown in Scheme 3-8 and are labeled either *chair* or *boat* depending on their conformation, *equatorial* or *axial* depending on the orientation of the group in the 1 position and *front* or *back* depending on the face of the olefin being attacked by the radical. As an example, transition state **3.6*E*a** is named *chair-equatorial back* and inclusion of the *E* in the numbering is necessary to distinguish these transition states from the *Z*-unsaturated ester analogues to be discussed later.


42%
35%
14%
9%
E
E
3-6*E*
H
Chair Equatorial Back
3.6*E*a
cis syn
3.7a
Chair Equatorial Front
3.6*E*b
cis anti
3.7b
+
Chair Axial Front
3.6*E*c
Boat Equatorial Back
3.6*E*d
trans syn
3.7c
+
Chair Axial Back
3.6*E*e
Boat Equatorial Front
3.6*E*f
trans anti
3.7d

Scheme 3-8: Transition states and products for the cyclization of radical **3.6*E***.

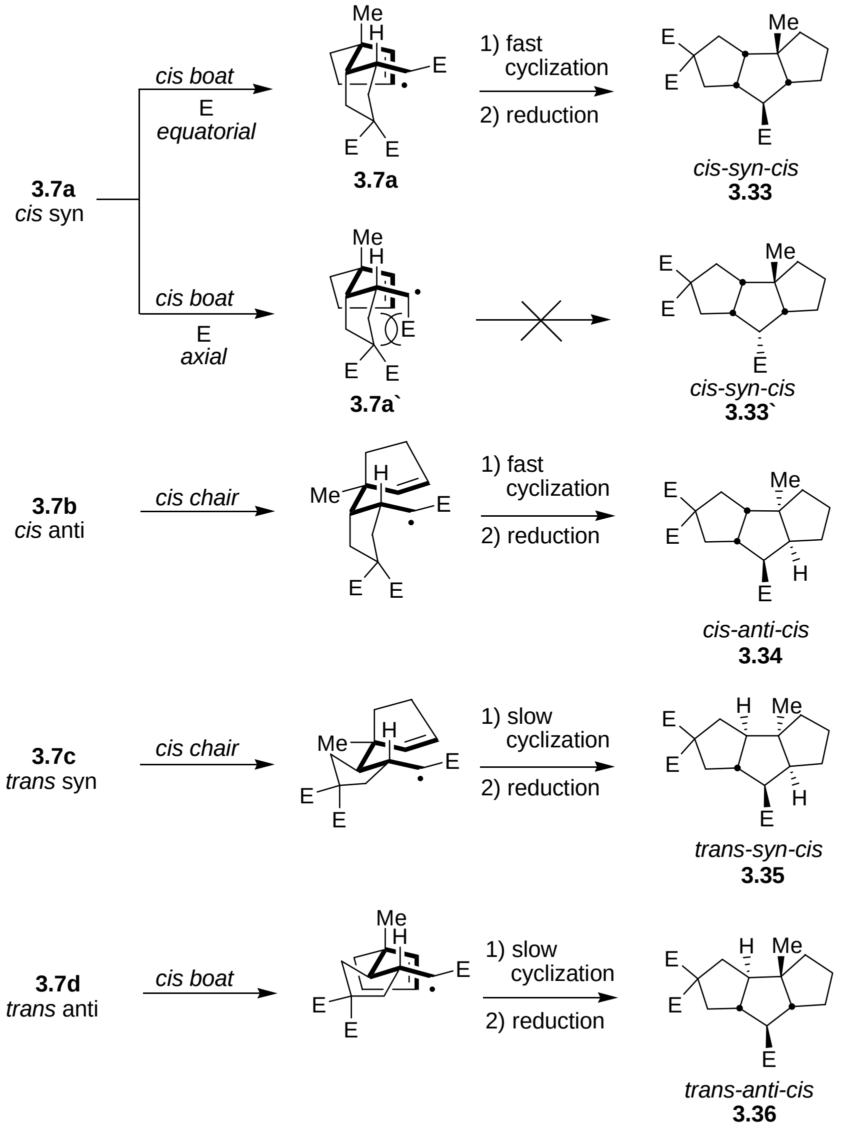
When radical **3.6*E*** adopts a *chair-equatorial* conformation with the olefin approaching the front face of the radical, transition state **3.6*E*a** results and the ensuing 5-*exo* cyclization proceeds to give the *cis syn* product **3.7a**. Transition state **3.6*E*b** also has a *chair-equatorial* conformation, but the olefin approaches the back face of the radical and so the cyclization gives the *cis anti* product **3.7b**. The *trans syn* product **3.7c** comes from transition states **3.6*E*c** and **3.6*E*d**. Likewise the final two transition states **3.6*E*e** and **3.6*E*f** both lead to the *trans anti* product radical **3.7d**. Four of these six transition states, **3.6*E*c-f**, are disfavored by the 1,3 diaxial interactions that are indicated in Scheme 3-8. These interactions result in products **3.7c** and **3.7d** only making up 14% and 9% of the final cyclization mixture, respectively. Transition states

3.6*E*a and **3.6*E*b** have no axial like interactions and are therefore more favored. For this reason, products **3.7a** and **3.7b** make up 42% and 35% of the mixture of bicyclic radicals, respectively.

The cascade reaction is now poised to undergo the third and final 5-*exo* radical cyclization. This final cyclization, however, proceeds to give exclusively *cis* products because it forms a fused 5,5 ring system.[36] This greatly simplifies the analysis because there is only one possible transition state for each of the four radicals **3.7** that can give the 5,5 *cis* fused geometry as shown in Scheme 3-9.[26] In this final cyclization, the configuration of the ester stereocenter is also set and so in the transition state the ester group can be placed either equatorial or axial as shown in structures **3.7a** and **3.7a′**. Placing the ester group in the axial position induces a high energy 1,2 interaction with the adjacent ring and there is literature precedent that 1,2 substituted radicals give only a single product.[84] We assume that each bicyclic radical gives a single ester epimer and will therefore ignore the transition states with an axial ester group for the radicals **3.7b-d**.

In order to furnish a 5,5 *cis* fusion, *cis syn* radical **3.7a** must adopt a *cis boat* transition state which gives the *cis-syn-cis* tricycle **3.33** when the hexenyl radical cyclizes and is reduced. The *cis anti* radical **3.7b** must adopt a *cis chair* transition state in order to give the *cis* fusion, leading to the *cis-anti-cis* product **3.34** upon closure and reduction of the radical. Similarly, radicals **3.7c** and **3.7d** cyclize through a *cis chair* and a *cis boat* transition state, respectively, to give the *trans-syn-cis* **3.35** and the *trans-anti-cis* **3.36** tricycles.

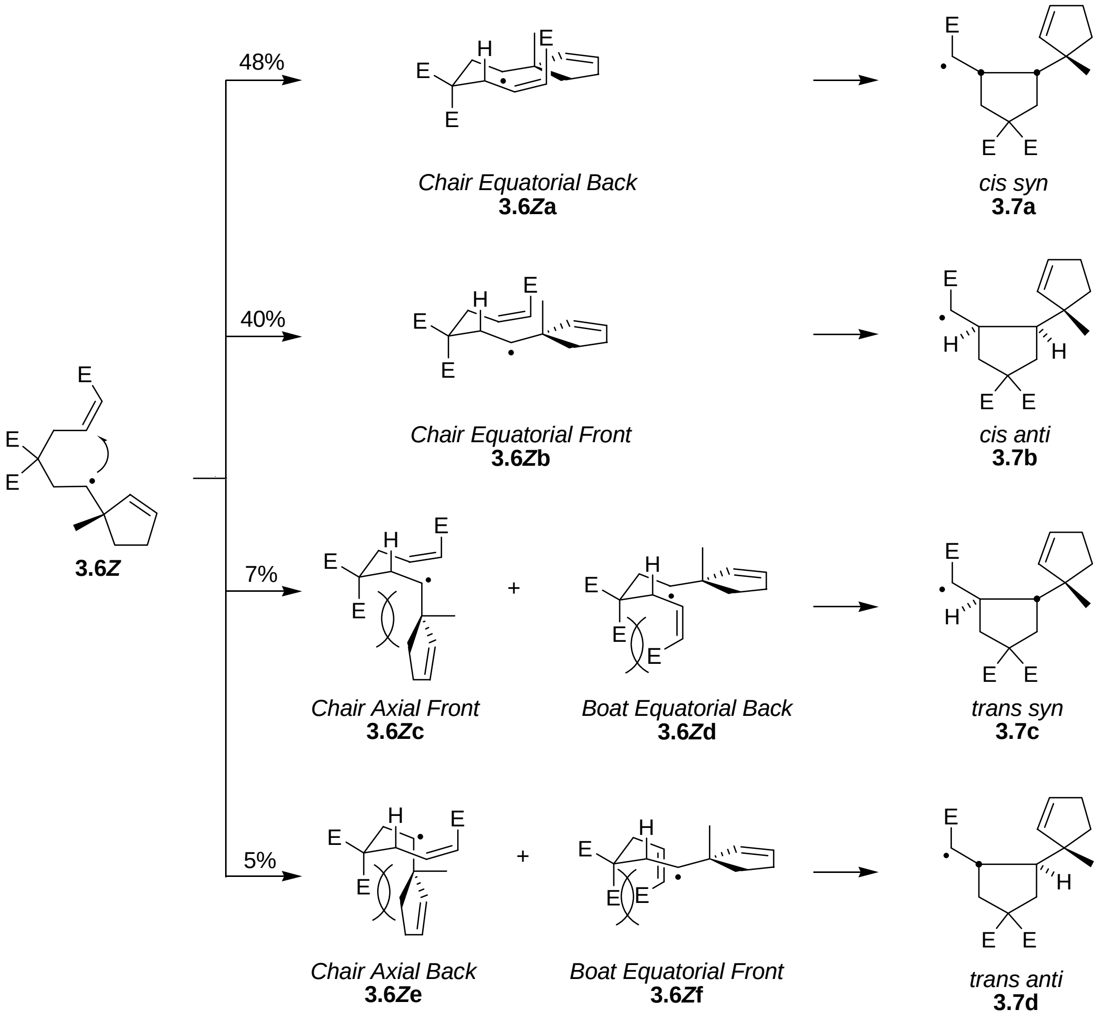
The rate of the final cyclization is strongly influenced by the strain contained in the final product. The more strained the linear triquinane product is, the slower this final cyclization will be.[35] Therefore, the *cis* products from the second cyclization, radicals **3.7a** and **3.7b,** close faster to give the respective products whereas radicals **3.7c** and **3.7d** cyclize slower to give the more strained *trans* substituted triquinanes. This slow final step allows for a greater competition between cyclization and premature reduction to give bicyclic products. For that reason the *cis*/*trans* ratios that we report may be overstated in favor of *cis* selectivity because the bicyclic products that are removed during the *m*-CPBA workup will predominantly be from the *trans* closure in the second cyclization.


3.7a
cis syn
cis boat
E
equatorial
Me
H
E
E E
3.7a
1) fast
cyclization
2) reduction
E
E
Me
E
cis-syn-cis
3.33
cis boat
E
axial
Me
H
E
E E
3.7a`
E
E
Me
E
cis-syn-cis
3.33`
3.7b
cis anti
cis chair
H
Me
E
E E
1) fast
cyclization
2) reduction
E
E
Me
H
E
cis-anti-cis
3.34
3.7c
trans syn
cis chair
Me
H
E
E
E
1) slow
cyclization
2) reduction
E
E
H Me
H
E
trans-syn-cis
3.35
3.7d
trans anti
cis boat
Me
H
E
E
E
1) slow
cyclization
2) reduction
E
E
H Me
E
trans-anti-cis
3.36

Scheme 3-9: Transition states and products for the cyclization of radical **3.6**.

3.6.2 Transition State Analysis for the Cyclization of 3.1

From Table 3-1 Entries 2 and 6, we show that the we can improve the selectivity for the second cyclization from 78/22 to 88/12 *cis*/*trans* by using the *Z* α,β-unsaturated ester cyclization precursor **3.1** instead of the *E* unsaturated ester precursor **1.65**. This improvement can be explained by revisiting the transition states for the second cyclization with the different geometry as shown in Scheme 3-10.[74] Similar to the analysis of substrate **1.65**, upon initiation and propagation vinyl iodide **3.1** is converted into a vinyl radical (not shown). This radical cyclizes to give cyclopenteneyl radical **3.6Z**. Radical **3.6Z** can adopt six different transition states and they are all shown in Scheme 3-10, again the two *boat axial* transition states are ignored. If the radical adopts a *chair equatorial* configuration with the radical approaching the back face of the olefin, transition state **3.6Za** results; this hexenyl radical then cyclizes to give *cis syn* product **3.7a**. Similarly the *cis anti* product **3.7b** arises from the *chair equatorial front* **3.6Zb** transition state. The *trans syn* product **3.7c** is produced when the hexenyl radical adopts either the *chair axial front* **3.6Zc** or the *boat equatorial back* **3.6Zd** transition state. Finally the *trans anti* product **3.7d** comes from transition states **3.6Ze** and **3.6Zf**.



3.6*Z*
48%
Chair Equatorial Back
3.6*Z*a
cis syn
3.7a
40%
Chair Equatorial Front
3.6*Z*b
cis anti
3.7b
7%
Chair Axial Front
3.6*Z*c
Boat Equatorial Back
3.6*Z*d
trans syn
3.7c
5%
Chair Axial Back
3.6*Z*e
Boat Equatorial Front
3.6*Z*f
trans anti
3.7d

Scheme 3-10: Transition state analysis for the second radical cyclization of vinyl iodide **3.1**.

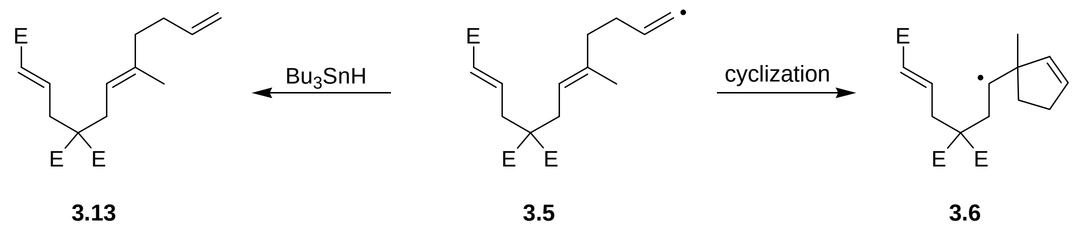
The improved selectivity in the cyclization can be attributed to the additional destabilizing interactions that the *Z*-unsaturated ester introduces into transition states **3.6Zd** and

3.6Zf. In comparison to the *E* analogues, the *Z* vinyl ester is forced back under the forming ring resulting in a collision with the malonate ester at position 3. This interaction significantly raises the energetic cost of accessing the boat transition states. The increased energetic cost causes a shift in the partitioning of the products towards **3.6Za** and **3.6Zb** and away from **3.6Zd** and **3.6Zf**. This new partitioning accounts for the 48/40/7/5 ratio of cyclization products **3.7a/b/c/d** that we observe in this cyclization as opposed to the 42/35/14/9 ratio that we found in the case of the *E* unsaturated ester cyclization. The products of the second cyclization are the same for the *Z* and the *E* olefin, so the transition state analysis for the third cyclization is the same as that shown in Scheme 3-9.

3.7 Kinetics of Cyclization

Under the standard cyclization conditions, the concentration of vinyl iodide **1.65** was 2 mM in benzene. If we increased this concentration to 10, 50 and 250 mM, we noticed that the amount of directly reduced product **3.13** increased at the expense of the tricycles. This indicates that the first cyclization of vinyl radical **3.5** to give radical **3.6** is the rate determining step of the entire cascade. Given that we can measure the amount of directly reduced product that is formed at the different reaction concentrations, we can estimate the rate constant of the first cyclization by using competition kinetics.[85]

The competition in this case is between the reduction of **3.5** by Bu_3SnH to give **3.13** or intramolecular rearrangement (cyclization) to give radical **3.6** as shown in Scheme 3-11. Once the first cyclization occurs, the cascade proceeds rapidly through the remaining two cyclizations and reduction to give the tricyclic products. Plotting the ratio of the cyclized products (**3.9-3.12**) to directly reduced product **3.13** against the concentration of Bu_3SnH should give a straight line. The slope of this line is the ratio of the rate constants for reduction and rearrangement. The rate constants for the reduction of many types of radicals by Bu_3SnH are known.[86] Therefore we can readily calculate the rate of cyclization from the slope of the trend line.



Scheme 3-11: Rate determining step in the cyclization of **1.65**.

To determine the rate constant for the first cyclization at 25 °C, we performed four cyclizations at concentrations of 2, 10, 50, and 250 mM with respect to the cyclization precursor. This was done by dissolving vinyl iodide **1.65** (0.10 mmol), Et_3B (0.05 mmol), and Bu_3SnH (0.12 mmol) in the appropriate amount of benzene (2 mM = 50 mL, 10 mM = 10 mL, 50 mM = 2 mL and 250 mM = 0.4 mL). The reactions were stirred for 4 h, concentrated *in vacuo*, and subjected to a DBU workup to remove the tin by-products. Each reaction mixture was then analyzed by GC. The ratio of the reduced product to the cyclized products was determined by dividing the area of the peak known to come from **3.13** by the sum of the areas of the four tricyclic peaks **3.9-3.12.** This data is summarized in Table 3-4. In these experiments, the concentration of the reducing agent changes throughout the course of the reaction. For rate calculations, a good approximation of the reducing agent concentration is to use the amount of reaction solvent and the moles of reducing agent when 50% of the cyclization precursor has been consumed. Because we used 1.2 equiv of Bu_3SnH to 1.0 equiv of precursor, we used 0.7 equiv of reducing agent to calculate the concentration for a particular cyclization.

Table 3-4: Data for the cyclization of **1.65** at 25 °C at four different concentrations of reducing agent.

Concentration	Volume of Benzene (mL)	% of Reduced Product **3.13**	% of Cyclized Products	Cyclized/Reduced	Concentration of Bu_3SnH
2	50	5	95	0.0526	0.0014
10	10	9	91	0.0989	0.0070
50	2	28	72	0.3889	0.0350
250	0.4	58	42	1.3809	0.1750

From this data, we plotted the cyclized/reduced ratio against the Bu_3SnH concentration to generate the plot shown in Figure 3-14. Linear regression analysis of these four data points generated a trend line that is also shown in Figure 3-14. The slope of this line is 7.6 and is equal to k_{red}/k_{cycl}. The rate of reduction (k_{red}) for a vinyl radical by Bu_3SnH at 25 ºC has been reported as $3.2 \cdot 10^8$ $M^{-1}s^{-1}$. This rate constant was measured by laser flash photolysis and from this data the Arrhenius parameters were calculated.[87] Unfortunately, the rate measurements were carried out in pentane on a 1,1 substituted vinyl radical where our experiments involve a mono substituted vinyl radical in benzene, but we do not anticipate that either of these differences will affect the outcome of the calculations significantly. The rate constant calculation for the cyclization of **1.65** at 25 ºC is shown in equation 1 and was found to be $4.2 \cdot 10^7$ s^{-1}. This rate is reasonable because radical cyclizations often occur with rate constants on the order of 10^8 s^{-1}.

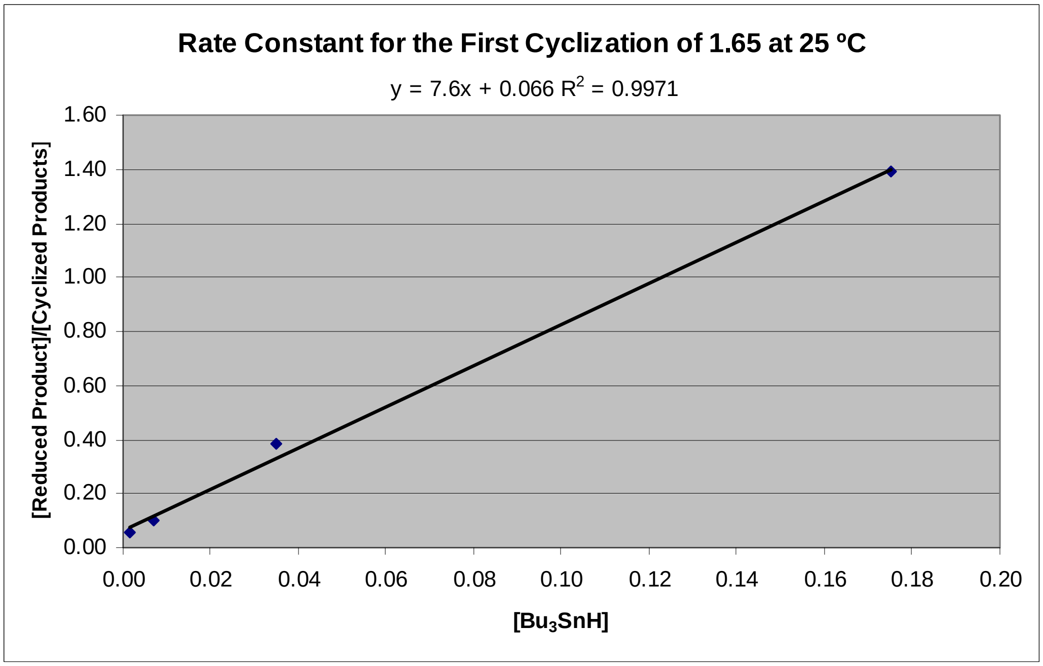


Figure 3-14: Plot used for determining the rate constant for the cyclization of **1.65** at 25 ºC.

$$k_{cyclization,25^{\circ}\mathrm{C}} = \frac{3.2 \cdot 10^8}{7.6} = 4.2 \cdot 10^7 s^{-1} \qquad \text{(eq. 1)}$$

We then wanted to determine the rate constant for this cyclization at 80 ºC and so repeated the cyclization experiments with **1.65**, but in refluxing benzene and with AIBN instead of Et_3B as the radical initiator. As before the four reactions we analyzed by GC and provided us with the necessary data shown in Table 3-5. Using this data we generated the plot shown in Figure 3-15 along with the calculated trend line.

Table 3-5: Data for the cyclization of **1.65** at 80 °C at four different concentrations of reducing agent.

Concentration	Volume of Benzene (mL)	% of Reduced Product **3.13**	% of Cyclized Products	Cyclized/Reduced	Concentration of Bu_3SnH
2	50	7	93	0.0753	0.0014
10	10	6	94	0.0638	0.0070
50	2	14	86	0.1628	0.0350
250	0.4	31	69	0.4493	0.1750

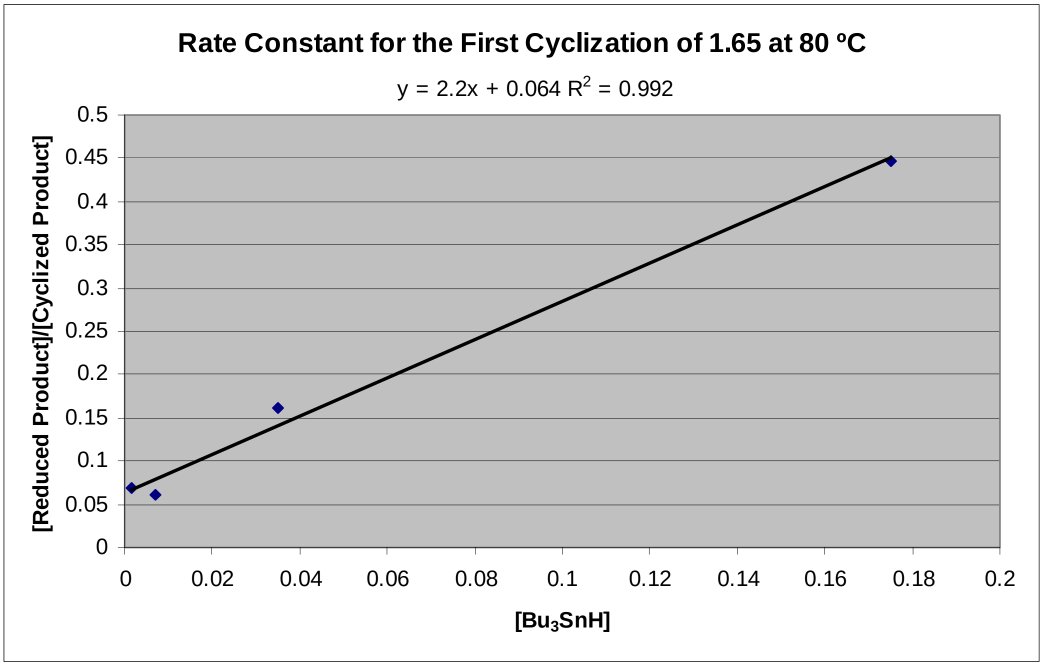


Figure 3-15: Plot used for determining the rate constant for the cyclization of **1.65** at 80 ºC.

Using the reported Arrhenius parameters[87] we calculated the rate constant for the reduction of a vinyl radical by Bu_3SnH to be $5.1 \cdot 10^8$ M^{-1} s^{-1}. With the slope of the trend line and this rate constant we could calculate the rate constant for the radical cyclization at 80 ºC as shown in equation 2.

$$k_{cyclization,80°C} = \frac{5.1 \cdot 10^8}{2.2} = 2.3 \cdot 10^8 s^{-1} \qquad \text{(eq. 2)}$$

As expected, the cyclization at elevated temperatures is faster than it is at ambient temperature. However, the rate constant only increased by a factor of 5.5 even though the temperature increased by 60 ºC. Using the normal rule of thumb that an increase of 10 ºC doubles the rate of a reaction one expects an increase in rate constant of 64 times. Radical reactions are less sensitive than ionic reactions to temperature and an increase of 5.5 times over 60 ºC is in line with other cyclizations.[41]

3.8 Conclusions

The results presented in this chapter build upon the work presented in Chapter 2, where we showed that hexenyl radicals with large groups in the 1 position cyclize with an 80/20 *cis* preference. We have shown that this trend extends to relatively complex substrates such as **1.65, 3.1**, **3.2**, and **3.3** with these cyclizations also proceeding with an 80/20 *cis* preference. This trend allowed Ihara to reduce the complexity of a round-trip radical cyclization to the point that two tricyclic products the *cis-syn-cis* and the *cis-anti-cis* isomer account for 80% of the products. We further increased the amount of these two products to 90% by changing the geometry of α,β-unsaturated ester from *E* to *Z*. Additionally we have shown that any increase in selectivity proposed by lowering the temperature is in fact an artifact of the analysis method.

Chapter 4 Conclusions

In this work we have presented a consistent picture of the stereoselectivity of hexenyl radical cyclizations with tertiary groups in the 1 position and a geminal malonate substitution in the 3 position. It has been demonstrated that such cyclizations proceed with moderate *cis* selectivity and that this selectivity is not affected by the nature of tertiary group, the presence of an ester on the radical acceptor or reaction temperature. Fortunately we have also shown that this stereochemical trend not only holds for simple substrates such as **2.4**, but also extends to relatively complex cascade cyclization precursors such as **1.65** and **2.10**.

The research presented and discussed in this thesis was in part initiated by a publication that reported a dramatic temperature effect for hexenyl radical cyclizations. This work though clearly shows that the reported temperature effect is an analytical oversight. None the less it is important to understand why these reactions do not exhibit a change in their selectivity upon changing the reaction temperature.

By examining a reaction coordinate diagram of the radical cyclizations, it is possible to find an underlying reason for the observed lack of a temperature effect. Using the cyclization of radical **2.2a** as an example, the Gibbs free energy diagram shown in Figure 4-1 can be drawn. Starting in the middle with hexenyl radical **2.2a** and heading to the left, the conformation approaches a local maximum at transition state **2.2aA**. By proceeding further to the left, radical **2.2aA** cyclizes and approaches the local minima of radical **4.1*cis***. Once again starting in the middle and proceeding to the right a local maxima is reached corresponding to **2.2aB** and **2.2aC**. Both of these radicals then cyclize to give **4.1*trans*** shown in the resulting local minima.

In this analysis we are assuming, not unreasonably, that either cyclization is irreversible. This means that the product distribution is not going to depend on the free energy difference between the two product radicals **4.1*cis*** and **4.1*trans***, but on the free energy difference of the respective transition states **2.2aA** and **2.2aB**, **2.2aC**. The energy difference in the transition state energies is represented by $\Delta\Delta G^{\ddagger}$.

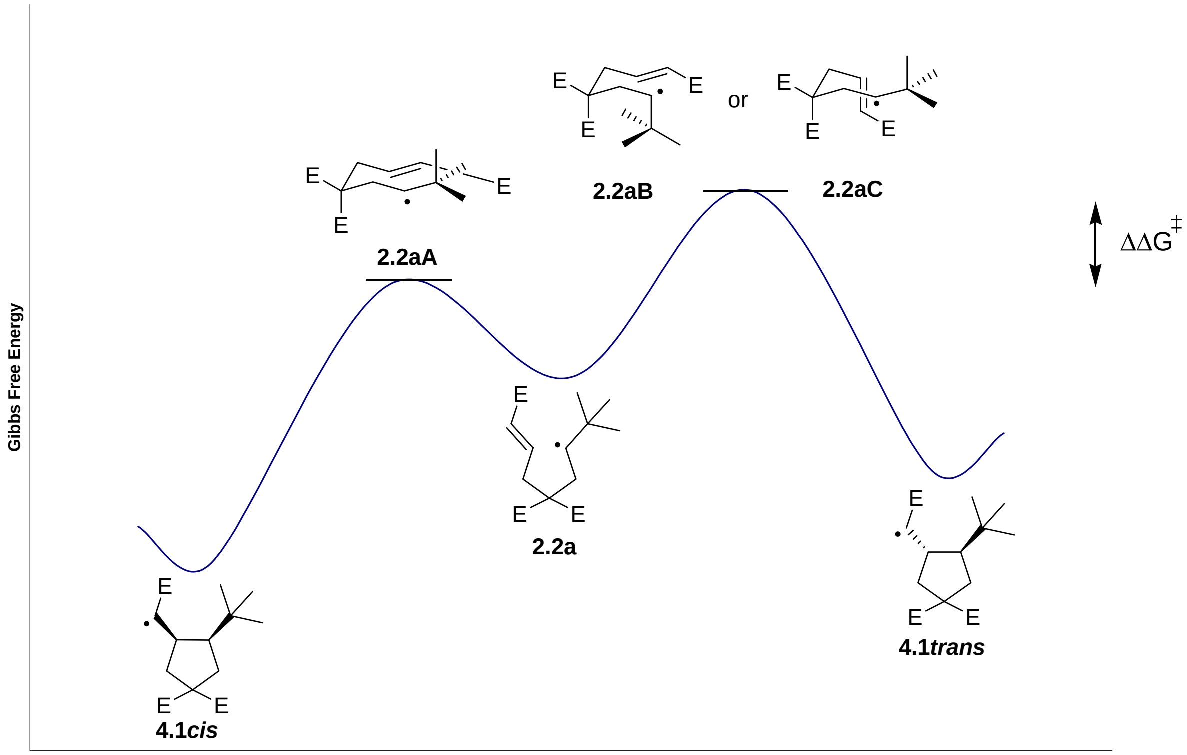


Figure 4-1: Reaction coordinate diagram for the cyclization of hexenyl radical **2.2a**.

Following from the Gibbs free energy equation, we can derive the following equation for ΔΔG‡:

$$\Delta\Delta G^{\ddagger} = \Delta\Delta H^{\ddagger} - T\Delta\Delta S^{\ddagger}$$

The small temperature effect that is observed in all of the cyclizations indicates that the contribution from the $T\Delta\Delta S^{\ddagger}$ term to $\Delta\Delta G^{\ddagger}$ is very small. With the $T\Delta\Delta S^{\ddagger}$ term being very small, the free energy equation for the cyclization can be simplified to the following:

$$\Delta\Delta G^{\ddagger} = \Delta\Delta H^{\ddagger}$$

As the above equation indicates, the ratio of the final products depends only on the $\Delta\Delta H^{\ddagger}$ of the reaction. The $\Delta\Delta H^{\ddagger}$ of the cyclization is not entirely independent of the reaction temperature, but the relationship between the two is complicated and therefore not outright expressed in the equation. However the temperature dependence of $\Delta\Delta H^{\ddagger}$ is responsible for the minor temperature selectivity that was observed in the cyclization experiments.

This simplified free energy equation relies on $\Delta\Delta S^{\ddagger}$ being small and there are two situations that can allow for this 1) both $\Delta S^{\ddagger}$ terms for the separate cyclizations are zero or 2) both $\Delta S^{\ddagger}$ values are very close in value and thus the difference of the two is small The more likely cause for the $\Delta\Delta S^{\ddagger}$ term being small is that the two individual values of $\Delta S^{\ddagger}$ are close. This is reasonable because in order to reach the two transition states about the same amount of bond rotation is necessary making the value of $\Delta S^{\ddagger}$ in both cases very close.

Additionally during the course of this work it was discovered that the *cis* and *trans* assignments for a key stereochemical literature benchmark were reversed. This is an important discovery that may have some crucial consequences in the planning of cascade cyclizations in the future. With this finding, however, we have further solidified the "1,2-cis selectivity" in cyclizations of 1-subsituted hexenyl radicals as one of the most general stereochemical trends in radical cyclizations.

Chapter 5 Experimental Procedures

The experimental procedures chapter is broken up into four sections. Chapter 5.1 contains all of the general procedures that were used for all of the experiments reported here. Chapter 5.2 is a general description of how the various radical cyclization reactions were carried out. Chapter 5.3 and Chapter 5.4 cover the experimental procedures and compound characterization data for the chemistry discussed in chapters 2 and 3, respectively.

5.1 General Experimental

All reactions were performed under an atmosphere of argon unless the reaction solvent contained water. The reaction times reported were dictated by TLC analysis of the reaction mixture in comparison to the starting material. Reaction solvents were freshly dried either by distillation or passing through an activated alumina column. Methylene chloride was distilled from CaH_2 and toluene, benzene, diethyl ether and THF were distilled from Na/benzophenone. Solvents dried by activated alumina were done according to Pangborn, A.B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996** *15*, 1518-1520.

^{1}H and ^{13}C NMR spectra were taken on a Bruker models Avance DPX 300 (300 MHz), Avance 300 (300 MHz), Avance DRX 500 (500 MHz), or an Avance 600 (600 MHz) NMR spectrometer. Chemical shifts are reported in parts per million (ppm) downfield relative to TMS using the residual solvent proton resonance of $CDCl_3$ (7.27 ppm) or central $CDCl_3$ carbon peak (77.0 ppm) as an internal standard. In reporting spectral data the format (δ) chemical shift (multiplicity, *J* values in Hz, integration) was used with the following abbreviations: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = complex multiplet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, dm = doublet of multiplets, tt = triplet of triplets, tm = triplet of multiplets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets.

Infrared spectra were taken on a Mattson Genesis Series FTIR using thin film or neat deposition on NaCl plates. Peaks are reported in wavenumbers (cm^{-1}). Low and high resolution electronic impact mass spectra were obtained on a Micromass Inc, Autospec with an E-B-E geometry. Chemical ionization spectra were taken on the same instrument using methane as the carrier gas. All peaks reported are in units of *m/e*.

Gas chromatograms (GC) were run on an Agilent 6850 gas chromatograph equipped with HPCHEM enhanced integrator software. An HP–1 capillary methyl siloxane column of 30 m in length and 0.32 mm in diameter with a 0.25 μm film was used for all runs. GC data is reported with a retention time and % area of the total integrated area.

Thin layer chromatography was performed on silica gel 60 F_{254} glass backed plates with a layer thickness of 0.25 mm manufactured by E. Merck. TLC visualization was performed by illumination with a 254 nm UV lamp or by staining with phosphomolybdic acid or permangenate solution and subsequent heating. Flash chromatography was performed on silica gel (230–400 mesh ASTM) purchased from Sorbtech or Bodman.

5.2 General Cyclization Procedures

Method A: General procedure for the radical cyclization reactions at fixed reducing agent concentrations at 25 °C temperature: To the cyclization precursor (0.1 mmol) in benzene (45 mL) was added the reducing agent (0.12 mmol) drop wise as a solution in benzene (5 mL). The reaction mixture was stirred and Et_3B (1.0M in hexanes, 0.05 mL, 0.05 mmol) was added. The mixture was stirred until GC analysis showed consumption of the starting material at which point the solvent was removed *in vacuo* to give the crude cyclization mixture.

Method B: Radical cyclization reactions at fixed reducing agent concentrations at 80 °C: To the cyclization precursor (0.1 mmol) in benzene (40 mL) was added AIBN (8.2 mg, 0.05 mmol) in benzene (5 mL). The reaction mixture was stirred and the reducing agent (0.12 mmol) was added drop wise as a solution in benzene (5 mL). The mixture was brought to reflux until GC analysis confirmed consumption of the starting material. The reaction was cooled to room temperature and the solvent was removed *in vacuo* to give the crude cyclization mixture.

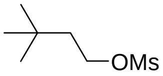
Method C: Radical cyclization reactions with syringe pump addition of the reducing agent at 25 °C: To the cyclization precursor (0.1 mmol) in benzene (50 mL) was added Et_3B (1.0M soln in hexanes, 0.05 mL, 0.05 mmol). The reaction mixture was stirred vigorously and the reducing agent (0.12 mmol in 5 mL of benzene) was added via syringe pump over 3 h. The reaction mixture was stirred until GC analysis confirmed consumption of the starting material.

The benzene was then removed by rotary evaporation *in vacuo* to yield the crude cyclization mixture.

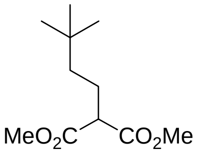
Method D: Radical cyclization reaction with syringe pump addition of the reducing agent at 80 °C: To the cyclization precursor (0.1 mmol) in benzene (45 mL) was added AIBN (8.2 mg, 0.05 mmol) as a solution in benzene (5 mL). The reaction mixture was stirred, brought to reflux and the reducing agent (0.12 mmol in 5 mL of benzene) was added via syringe pump through the condenser over 3 h. The reaction mixture was stirred until GC analysis confirmed consumption of the starting material. The reaction was allowed to cool to room temperature and the benzene was then removed by rotary evaporation *in vacuo* to yield the crude cyclization mixture.

5.3 Experimental Procedures and Characterization Data for Chapter 2

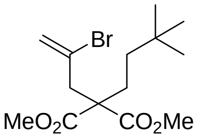
5.3.1 Synthesis of Cyclization Precursor 2.4



Methanesulfonic acid 3,3-dimethylbutyl ester (2.16): To a stirred solution of 3,3-dimethylbutanol (10.0 g, 97.9 mmol) in CH_2Cl_2 (500 mL) was added NEt_3 (28.3 mL, 202.7 mmol) and mesyl chloride (8.7 mL, 111.9 mmol) at room temperature. The resulting solution was stirred for 3 h and then diluted with water (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were washed with a satd aqueous solution of $NaHCO_3$ (200 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 17.6 g of mesylate **2.16** (100%) as a dark brown oil that solidified upon cooling to −20 °C. The mesylate could be used in subsequent reactions without further purification: IR (thin film, CH_2Cl_2) 3059, 2985, 2962, 1423, 1357, 1335, 1259, 1174, 950 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.28 (t, *J* = 7.6 Hz, 2H), 3.00 (s, 3H), 1.69 (t, *J* = 7.4 Hz, 2H), 0.96 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.7, 42.1, 37.4, 29.7 29.4 (3C); MS *m/e* 181, 135, 133, 125, 124, 97, 85, 84, 69, 57; HRMS exact mass calcd for $C_7H_{17}O_3S$: 181.0898, found: 181.0906.

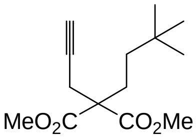


2-(3,3-Dimethylbutyl)malonic acid dimethyl ester (2.17): Mesylate **2.16** (18.4 g, 102.2 mmol) was dissolved in THF (250 mL) and then quickly poured into a stirred suspension of NaI (15.3 g, 102.2 mmol) in THF (500 mL). The reaction mixture was heated at reflux for 16 h at which point ^{1}H NMR analysis showed complete consumption of the mesylate and the reaction mixture was allowed to cool to room temperature. In a separate flask, dimethyl malonate (20.2 g, 153.3 mmol) was added drop wise to a suspension of NaH (95 % dry, 3.7 g, 153.3 mmol) in THF (350 mL) at 0 °C. Upon complete addition of the dimethyl malonate, the THF solution of 1-Iodo-3,3-dimethylbutane was cannulated into the reaction mixture. The resultant mixture was heated at reflux for 8 h, cooled to room temperature, quenched with water (300 mL) and extracted with ethyl acetate (3 x 250 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound. Purification over silica gel eluting with hexanes/ethyl acetate (15/1) gave 11.4 g of **2.17** (52%) as a clear, pale yellow oil: IR (film, CH_2Cl_2) 2956, 1733, 1436, 1272, 1248, 1147 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 6H), 3.25 (t, *J* = 7.5 Hz, 1H), 1.88−1.79 (m, 2H), 1.16−1.10 (m, 2H), 0.85 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8 (2C), 52.3 (2C), 52.2, 41.3, 30.2, 29.0 (3C), 24.2; MS *m/e* 217 (M^+ + H), 201, 185, 159, 132, 57; HRMS exact mass calcd for $C_{11}H_{21}O_4$ $(M + H)^+$ 217.1439, found 217.1444.



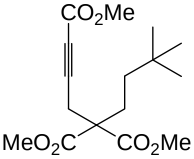
2-(2-Bromoallyl)-2-(3,3-dimethylbutyl)malonic acid dimethyl ester (2.4): To a stirred suspension of NaH (95% dry, 31 mg, 1.27 mmol) in THF (25 mL) cooled to 0 °C was added malonate **2.17** (250 mg, 1.16 mmol) drop wise. Upon complete addition of the malonate, 2,3-dibromopropene (Acros technical grade is 80% pure, 0.15 mL, 1.27 mmol) was added and the resulting mixture was stirred at room temperature for 16 h. The mixture was quenched with water (5 mL) and then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound. Purification over silica gel eluting with hexanes/ethyl acetate (10/1) yielded 281 mg of malonate **2.4** (72%) as a brown solid: mp 50–51 °C; IR (film, CH_2Cl_2) 3050, 2986, 2957, 1733, 1422, 1272, 1254, 1172, 1152, 896 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.66 (dt, *J* = 0.8, 1.6 Hz, 1H), 5.59 (d, *J* = 1.7 Hz, 1H), 3.74 (s, 6H), 3.15 (d, *J* = 0.8 Hz, 2H), 2.03–1.97 (m, 2H), 1.05–0.99 (m, 2H), 0.89 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1 (2C), 127.2, 121.7, 57.0, 52.6 (2C), 42.7, 37.5, 30.2, 29.2 (3C), 26.5; MS *m/e* 321 (M ^{81}Br − Me)$^+$, 319 (M ^{79}Br − Me)$^+$, 305, 303, 279, 277, 255, 195, 171, 139, 69, 57; HRMS exact mass calcd for $C_{11}H_{20}{}^{79}BrO_4$ (M − Me)$^+$ 319.0545, found 319.0558.

5.3.2 Synthesis of Cyclization Precursors 2.5a and 2.5b

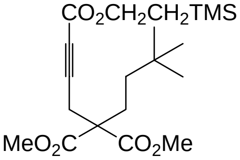


2-(3,3-Dimethylbutyl)-2-prop-2-ynylmalonic acid dimethyl ester (2.18): To a stirred suspension of NaH (95% dry, 1.22 g, 50.9 mmol) in THF (400 mL) cooled to 0 °C was added malonate **2.17** (10.0 g, 46.3 mmol) drop wise. Upon complete addition, propargyl bromide (80% solution in toluene, 7.6 mL, 50.9 mmol) was added and the resulting mixture was stirred at room temperature for 6 h. The reaction was quenched with water (50 mL) and then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound. Purification over silica gel eluting with hexanes/ethyl acetate (15/1) yielded 11.8 g of malonate **2.18** (95%) as a pale brown oil: IR (film, CH_2Cl_2) 3304, 2957, 1735, 1437, 1291, 1204 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.72 (s, 6H), 2.79 (d, *J* = 2.6 Hz, 2H), 2.05–1.98 (m, 3H), 1.03–0.97 (m, 2H), 0.87 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7 (2C), 78.7, 71.2, 56.8, 52.6 (2C), 37.4, 30.1, 29.0 (3C), 27.0, 22.5; MS *m/e* 254, 239, 223, 197, 170, 139, 110, 69, 57; HRMS exact mass calcd for $C_{13}H_{19}O_4$ (M − Me)$^+$ 239.1283, found 239.1282.

General Procedure for the synthesis of alkynes 2.19: To a stirred solution of malonate **2.18** in THF (2 mL/mmol of malonate) cooled to −78 °C was added BuLi (1.6 M in hexanes, 1.2 equiv to the malonate) drop wise. The resulting solution was stirred at −78 °C for 2 h, at which point the respective chloroformate was added (2.0 equiv) and stirring was continued for an additional 2 h. The mixture was warmed to room temperature and stirred for 15 h, then the reaction was quenched with a satd aqueous solution of NH_4Cl (1 mL/mmol). After the addition of ethyl actetate (1 mL/mmol), the layers were separated and the aqueous phase was extracted with additional ethyl acetate (2 x 1 mL/mmol). The combined organic layers were washed with water (2 mL/mmol) and brine (2 mL/mmol), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude compound. Purification over silica gel yielded the respective alkyne **2.19**.



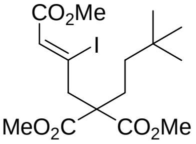
5-(3,3-Dimethylbutyl)-5-methoxycarbonylhex-2-ynedioic acid dimethyl ester (2.19a): Using alkyne **2.18** (2.0 g, 7.9 mmol), methyl chloroformate (1.21 mL, 15.7 mmol) and eluting the column with hexanes/ethyl acetate (15/1) yielded 1.6 g (64%) of the title compound **2.19a** as a clear pale yellow oil: IR (thin film, CH_2Cl_2) cm^{-1} 2957, 1736, 1715, 1435, 1275, 1174; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 6H), 3.68 (s, 3H), 2.91 (s, 2H), 2.01−1.95 (m, 2H), 1.0−0.94 (m, 2H), 0.84 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1 (2C), 153.5, 83.5, 75.0, 56.5, 52.7 (2C), 52.4, 37.3, 30.0, 28.9 (3C), 27.3, 22.6; MS *m/e* 297 $(M - Me)^+$, 281, 255, 228, 221, 205, 196, 165, 164, 137; HRMS exact mass calcd for $C_{15}H_{21}O_6$ $(M - Me)^+$ 297.1338, found 297.1341.



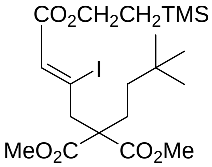
5-(3,3-Dimethyl-butyl)-5-methoxycarbonylhex-2-ynedioic acid 6-methyl ester 1-(2-trimethylsilanylethyl) ester (2.19b): Using alkyne **2.18** (1.0 g, 3.9 mmol) and 2-(trimethylsilyl)ethyl chloroformate (1.4 g, 7.9 mmol), which was prepared immediately prior to use from 2-trimethylsilylethanol and phosgene.[88] The column was eluted with hexanes/ethyl acetate (15/1) to yield 0.97 g (62%) of the title compound **2.19b** as a clear yellow oil: IR (film, CH_2Cl_2) 2957, 1736, 1707, 1251, 1174, 734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.23–4.18 (m,

2H), 3.73 (s, 6H), 2.94 (s, 2H), 2.05–1.99 (m, 2H), 1.08–0.96 (m, 4H), 0.88 (s, 9H), 0.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2 (2C), 153.3, 82.8, 75.6, 64.2, 56.6, 52.8 (2C), 37.4, 30.1, 29.0 (3C), 27.3, 22.7, 17.0, −1.6 (3C); MS *m/e* 383 $(M - Me)^+$, 355, 229, 221, 205, 165, 89, 73, 57; HRMS exact mass calcd for $C_{19}H_{31}O_6Si$ $(M - Me)^+$ 383.1890, found 383.1885.

General Procedure for the hydroiodination of α,β-unsaturated esters 2.5: To alkyne **2.19** was added oven dried NaI (3.2 equiv) and glacial acetic acid (6.4 equiv). The resulting mixture was stirred at 115 °C until GC analysis revealed consumption of the starting material. The mixture was diluted with water (15 mL/mmol of alkyne) and ether (15 mL/mmol) and then K_2CO_3 was added until the formation of gas ceased. The layers were separated and the aqueous layer was extracted with ether (3 x 15 mL/mmol). The combined organic layers were washed with a 10% aqueous solution of $Na_2S_2O_3$ (10 mL/mmol) and water (10 mL/mmol), dried over $MgSO_4$, filtered and concentrated by rotary evaporation *in vacuo* to give the desired compound. Purification over silica eluting with hexanes/ethyl acetate gave the respective vinyl iodide **2.5**.

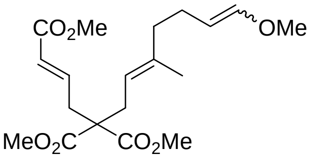


5-(3,3-Dimethylbutyl)-3-iodo-5-methoxycarbonylhex-2-enedioic acid dimethyl ester (2.5a): Using alkyne **2.19a** (1.0 g, 3.2 mmol) and eluting the column with hexanes/ethyl acetate (15/1) yielded 0.52 g (37%) of the title compound as a pale yellow oil that solidified on cooling to −20 °C and liquefied again on warming to room temperature: IR (thin film, CH_2Cl_2) 3054, 2987, 1733, 1435, 1422, 1262, 1175, 896 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42 (s, 1H), 3.80 (s, 6H), 3.75 (s, 3H), 3.47 (s, 2H), 2.00–1.95 (m, 2H), 1.08–1.02 (m, 2H), 0.89 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7 (2C), 164.5, 128.8, 110.7, 57.8, 52.6 (2C), 51.7, 48.2, 37.5, 30.2, 29.1 (3C), 26.8; MS *m/e* 425 $(M - Me)^+$, 409, 393, 383, 377, 361, 349, 325, 313, 253; HRMS exact mass calcd for $C_{15}H_{22}O_5I$ $(M - OMe)^+$ 409.0512, found 409.0523.

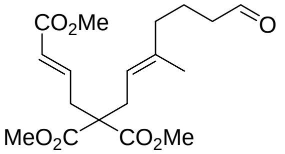


5-(3,3-Dimethylbutyl)-3-iodo-5-methoxycarbonylhex-2-enedioic acid 6-methyl ester 1-(2-trimethylsilanylethyl) ester (2.5b): Using alkyne **2.19b** (1.3 g, 3.3 mmol) and eluting the column with hexanes/ethyl acetate (15/1) yielded 0.26 g (15%) of the title iodide as a dark yellow oil: IR (thin film, CH_2Cl_2) 2957, 1734, 1250, 1172, 861 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.37 (s, 1H), 4.27–4.20 (m, 2H), 3.75 (s, 6H), 3.46 (s, 2H), 2.00–1.94 (m, 2H), 1.07–0.99 (m, 4H), 0.88 (s, 9H), 0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8 (2C), 164.3, 129.4, 110.0, 63.0, 57.8, 52.7 (2C), 48.2, 37.6, 30.3, 29.2 (3C), 26.8, 17.2, −1.5 (3C); MS *m/e* 399 (M − I)$^+$, 399, 73; HRMS exact mass calcd for $C_{20}H_{35}O_6Si$ (M − I)$^+$ 399.2203, found 399.2203. Acidification of the aqueous layer with 2N HCl and extraction with ethyl acetate yielded 0.32 g (23%) of 5-(3,3-dimethylbutyl)-3-iodo-5-methoxycarbonylhex-2-enedioic acid 6-methyl ester **2.20**. This acid could be used as such in a DCC mediated coupling with 2-trimethylsilanylethanol to prepare more of precursor **2.5b**.

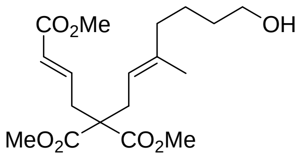
5.3.3 Synthesis of Cyclization Precursor 2.10



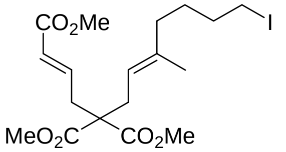
5-Methoxycarbonyl-5-(7-methoxy-3-methylhepta-2*E*,6*E*-dienyl)hex-2*E*-enedioic acid dimethyl ester (2.27): To stirred THF (213 mL) cooled to –78 °C was added diisopropylamine (3.11 mL, 17.9 mmol) and BuLi (1.6 M solution in hexanes, 11.54 mL, 18.5 mmol) and stirring was continued for 30 min. The resulting LDA solution was cannulated into a stirred suspension of methoxymethyl triphenylphosphonium chloride **2.26** (6.32 g, 18.5 mmol) in THF (213 mL) cooled to 0 °C. The dark red solution was stirred for 30 min, then aldehyde **3.26a** (3.0 g, 8.8 mmol) was cannulated in as a solution in THF (213 mL). The final suspension was stirred for 30 min at 0 °C, poured into a satd brine solution (750 mL) and extracted with methylene chloride (2 x 1200 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound. Purification over silica gel eluting with hexanes/ethyl acetate (5/1) gave 1.6 g a 2:1 mixture of *E*:*Z* isomers of **2.27** (48%) as a clear, pale yellow oil. This compound was characterized as a mixture of both isomers: IR (thin film, CH_2Cl_2) 3049, 2985, 1731, 1423, 1280, 1249, 894 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) Resonances attributed to the *E*-isomer: δ 5.85 (dt, *J* = 1.2, 15.5 Hz, 1H), 4.67 (dm, *J* = 12.6, 1H), 3.50 (s, 3H); Resonances attributed to the *Z*-isomer: δ 5.84 (dt, *J* = 1.2, 9.3 Hz, 1H), 4.27 (q, *J* = 7.0 Hz, 1H), 3.58 (s, 3H); Overlapping resonances: δ 6.79 (dt, *J* = 7.7, 15.5 Hz, 1H), 6.29 (d, *J* = 12.6 Hz, 1H), 4.95 (t, *J* = 7.4 Hz, 1H), 3.73 (s, 6H), 3.72 (s, 3H), 2.76 (dt, *J* = 1.2, 7.7 Hz, 2H), 2.63 (d, *J* = 7.5 Hz, 2H), 2.05−2.00 (m, 4H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) Resonances attributed to the *E*-isomer: 146.9, 142.7, 139.0, 117.2, 101.6, 55.2, 40.7, 25.8, 15.8; Resonances attributed to the *Z* isomer: 145.9, 142.8, 139.4, 116.7, 105.4, 59.0, 39.4, 21.8, 15.7; Overlapping Resonances: δ 170.5 (2C), 165.8, 124.1, 57.2, 52.1 (2C), 51.0, 35.0, 31.1; MS *m/e* 368, 337, 336, 308, 304, 297, 71; HRMS exact mass calcd for $C_{19}H_{28}O_7$: 368.1835, found: 368.1836.



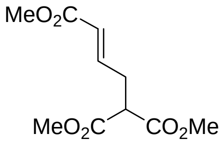
5-Methoxycarbonyl-5-(3-methyl-7-oxohept-2*E*-enyl)hex-2*E*-enedioic acid dimethyl ester (2.28): Enol ether **2.27** (1.9 g, 5.2 mmol) was dissolved in THF (220 mL) and a 9/1 (v/v) mixture of water and HCl (220 mL) was added. The resulting mixture was stirred at room temperature for 2 h, poured into a satd $NaHCO_3$ solution (600 mL) and extracted with CH_2Cl_2 (3 x 600 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound. Purification over silica gel eluting with hexanes/ethyl acetate (5/1) gave 1.10 g of **2.28** (57%) as a clear, colorless oil: IR (thin film, CH_2Cl_2) 3057, 2986, 2952, 2845, 2727, 1726, 1660, 1441, 1288, 1205, 1040, 984 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (t, *J* = 1.6 Hz, 1H), 6.74 (dt, *J* = 7.7, 15.5 Hz, 1H), 5.82 (dt, *J* = 1.3, 15.5 Hz, 1H), 4.94 (tq, *J* = 1.1, 7.5 Hz, 1H), 3.69 (s, 6H), 3.68 (s, 3H), 2.72 (dd, *J* = 1.3, 7.7 Hz, 2H), 2.59 (d, *J* = 7.4 Hz, 2H), 2.35 (td, *J* = 1.6, 7.3 Hz, 2H), 1.99 (t, *J* = 7.4 Hz, 2H), 1.68 (p, *J* = 7.4 Hz, 2H), 1.56 (d, *J* = 1.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 170.7 (2C), 166.1, 142.8, 138.9, 124.5, 118.0, 57.4, 52.5 (2C), 51.4, 42.9, 38.9, 35.3, 31.3, 20.0, 15.9; APCI: Mass calcd for $C_{18}H_{26}O_7Na$ (M + Na)$^+$: 377.2, found 377.1; Mass calcd for $C_{18}H_{28}0_7K$ (M + K)$^+$: 393.1, found 393.0.



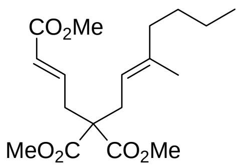
5-(7-Hydroxy-3-methyl-hept-2*E*-enyl)-5-methoxycarbonylhex-2*E*-enedioic acid dimethyl ester (2.29): Aldehyde **2.28** (0.041 g, 0.1 mmol) was dissolved in absolute methanol (10 mL) and cooled to 0 °C. Sodium borohydride powder (0.017 g, 0.5 mmol) was added to the stirred solution and the flask was stoppered. After 14 h the reaction mixture was poured into distilled water (30 mL), acidified with 1M hydrochloric acid (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound. Purification over silica gel eluting with hexanes/ethyl acetate (2/1) gave 0.032 g of **2.29** (79%) as a clear, colorless oil: IR (thin film, CH_2Cl_2) 3612, 3063, 2953, 2863, 1722, 1660, 1439, 1287, 1197, 1060, 1038, 984 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (dt, *J* = 7.8, 15.5 Hz, 1H), 5.79 (dt, *J* = 1.2, 15.5 Hz, 1H), 4.90 (tq, *J* = 1.0, 7.5 Hz, 1H), 3.67 (s, 6H), 3.66 (s, 3H), 3.56 (t, *J* = 6.2 Hz, 2H), 2.69 (dd, *J* = 1.2, 7.7 Hz, 2H), 2.57 (d, *J* = 7.4, 2H), 2.17 (br s, 1H), 1.95 (t, *J* = 6.6 Hz, 2H), 1.53 (d, *J* = 1.0 Hz, 3H), 1.47−1.35 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8 (2C), 166.2, 142.9, 139.8, 124.4, 116.9, 62.4, 57.4, 52.3 (2C), 51.4, 39.4, 35.2, 31.9, 31.2, 23.7, 15.9; APCI: Mass calculated for $C_{18}H_{28}O_7Na$ (M + Na)$^+$: 379.2, found: 379.1; Mass calculated for $C_{18}H_{28}O_7K$ (M + K)$^+$: 395.2, found: 395.1.



5-(7-Iodo-3-methylhept-2*E*-enyl)-5-methoxycarbonylhex-2*E*-enedioic acid dimethyl ester (2.10): Triphenylphosphine (0.147 g, 0.6 mmol) and imidazole (0.030 g, 0.4 mmol) were added to CH_2Cl_2 (5 mL) and the solution was stirred. The mixture was cooled to 0 °C and then iodine (0.111 g, 0.4 mmol) was added. The resulting mixture was stirred for 15 min and alcohol **2.29** (0.10 g, 0.3 mmol) was added. The reaction mixture was stirred for 1h, poured into a satd aqueous solution of $Na_2S_2O_3$ (3 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound. Purification over silica gel eluting with hexanes/ethyl acetate (5/1) gave 0.111 g of iodide **2.10** (85%) as a clear, brown oil: IR (thin film, CH_2Cl_2) 3058, 2985, 2953, 1730, 1437, 1281, 1250, 1173, 894 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.76 (dt, *J* = 7.6, 15.6 Hz, 1H), 5.83 (d, *J* = 15.5 Hz, 1H), 4.93 (t, *J* = 7.4 Hz, 1H), 3.70 (s, 6H), 3.69 (s, 3H), 3.16 (t, *J* = 6.9 Hz, 2H), 2.73 (d, *J* = 7.7 Hz, 2H), 2.60 (d, *J* = 7.4 Hz, 2H), 1.98 (t, *J* = 7.4 Hz, 2H), 1.74 (tt, *J* = 6.9, 7.5 Hz, 2H), 1.57 (s, 3H), 1.46 (tt, *J* = 7.1, 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8 (2C), 166.1, 142.9, 139.3, 124.5, 117.4, 57.4, 52.5 (2C), 51.5, 38.6, 35.3, 32.7, 31.3, 28.5, 16.0, 6.7; MS *m/e* 466, 435, 434, 406, 374, 335, 303, 230, 198, 166, 145, 109, 67, 59, 54; HRMS exact mass calcd for $C_{18}H_{27}IO_6$ 466.0852, found: 466.0875.



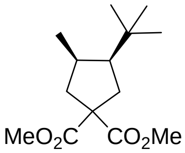
(*E*)-trimethylbut-3-ene-1,1,4-tricarboxylate (2.30): Dimethyl malonate (0.95 mL, 7.5 mmol) was added drop wise to a stirred suspension of NaH (95 % dry, 0.18 g, 7.5 mmol) in anhydrous THF (30 mL) at 0 °C. After complete addition, (*E*)-methyl-4-crotonate **3.23a** (0.69 mL, 5.0 mmol) was added to the mixture drop wise. After 16 h the resulting mixture was poured into a mixture of H_2O (10 mL) and ethyl acetate (100 mL). After separation of the layers, the aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic layers were dried over anhydrous $MgSO_4$. Filtration and solvent evaporation *in vacuo* gave the title compound. Purification by flash chromatography on silica gel eluting with hexanes/ethyl acetate (8/1) gave 0.68 g of **2.30** (59%) as a clear, pale yellow oil: IR (film, $CHCl_3$) 2955, 2925, 2855, 1735, 1731, 1438, 1378, 1341, 1274, 1243, 1216, 1156, 1094, 1041, 929, 909, 888 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.81 (dt, *J* = 7.1, 15.6 Hz, 1H), 5.83 (dt, *J* = 1.5, 15.6 Hz, 1H), 3.68 (s, 6H). 3.65 (s, 3H), 3.47 (t, *J* = 7.4 Hz, 1H), 2.72 (app dt, *J* = 1.5, 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5 (2C), 166.1, 143.7, 123.4, 52.5 (2C), 51.3, 50.2, 30.9; MS *m/e* 230, 215, 199, 198, 167, 166, 139, 111, 59 HRMS exact mass calcd for $C_{10}H_{14}O_6$ 230.0790, found 230.0800.



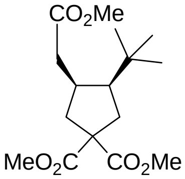
5-Methoxycarbonyl-5-(3-methylhept-2*E*-enyl)hex-2*E*-enedioic acid dimethyl ester (2.13): To a solution of PBr_3 (0.03 mL, 0.33 mmol) and pyridine (0.01 mL) in petroleum ether (2.6 mL) at −10 ºC, was added, drop wise, a solution of alcohol **2.31** (0.10 g, 0.78 mmol) in petroleum ether (0.4 mL). The resulting reaction mixture was stirred at 0 ºC for 1.5 h. The reaction was then quenched with an ice/water mixture (2 mL) and the layers were separated. The aqueous layer was extracted with ether (3 x 10 mL) and the combined organic layers were washed with 2 N HCl (3 mL), satd $NaHCO_3$ (2 x 5 mL), brine (5 mL) and dried over $MgSO_4$. The organic layer was filtered and carefully concentrated *in vacuo*. The resulting allyl bromide was used without further purification in the alklylation of malonate **2.30**.

To a stirred suspension of NaH (95% dry, 0.011 g, 0.48 mmol) in THF (3 mL) was added, drop wise malonate **2.30** (0.100 g, 0.43 mmol) over 5 min. To this was added allyl bromide 110 (0.083 g, 0.43 mmol) and the reaction mixture was stirred for 16 h. The mixture was then poured into a mixture of water (2 mL) and ethyl acetate (2 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound. Purification over silica gel eluting with hexanes/ethyl acetate (5/1) yielded 0.115 g of malonate **2.13** as a clear pale yellow oil (79%): IR (film, CH_2Cl_2) 3057, 2987, 1731, 1422, 1280, 1248, 1172, 894 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 6.75 (dt, *J* = 7.8, 15.5 Hz, 1H), 5.81 (dt, *J* = 1.1, 15.5 Hz, 1H), 4.90 (dt, *J* = 1.0, 7.4 Hz, 1H), 3.69 (s, 6H), 3.68 (s, 3H), 2.72 (dd, *J* = 1.1, 7.8 Hz, 2H), 2.58 (d, *J* = 7.4 Hz, 2H), 1.93 (t, *J* = 7.5 Hz, 2H), 1.54 (d, *J* = 1.0 Hz, 3H), 1.35–1.16 (m, 4H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9 (2C), 166.2, 143.0, 140.3, 124.4, 116.6, 57.5, 52.4 (2C), 51.4, 39.5, 35.3, 31.4, 30.0, 22.2, 16.1, 13.8; MS *m/e* 340, 309, 280, 248, 230, 209, 198, 177, 166, 145, 135, 121, 111, 79, 69; HRMS exact mass calcd for $C_{18}H_{28}O_6$: 340.1886, found: 340.1889.

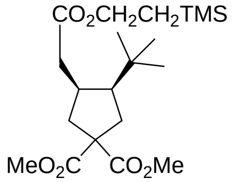
5.3.4 Cyclization Reactions of Precursors 2.4, 2.5a,b and 2.10



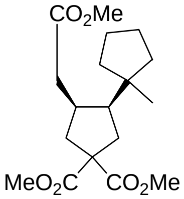
3-*tert*-Butyl-4-methylcyclopentane-1,1-dicarboxylic acid dimethyl ester (2.7): Subjecting precursor **2.4** (33 mg, 0.1 mmol) to the cyclization conditions described for method B for 3 h and purification of the crude reaction mixture by column chromatography eluting with hexanes/ethyl acetate (10/1) after eluting with five column volumes of hexanes, yielded 14 mg (50 %) of a 75/25 *cis*/*trans* mixture of the title compound **2.7**. The NMR data reported is that of the major *cis* isomer, the minor *trans* isomer was independently synthesized and the data is reported subsequently: IR (film, CH_2Cl_2) 2956, 1730, 1276, 1246, 1201 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.72 (s, 3H), 2.40 (dd, *J* = 7.2, 13.8 Hz, 1H), 2.28 (m, 2H), 2.16 (t, *J* = 13.4 Hz, 1H), 2.06 (d, *J* = 13.8 Hz, 1H), 1.74 (dt, *J* = 6.2, 13.5 Hz, 1H), 0.96 (s, 9H), 0.91 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 173.8, 57.7, 53.5, 52.7 (2C), 42.6, 35.6, 33.0, 31.8, 29.1 (3C), 17.1; MS *m*/e 257 $(M + H)^+$, 241, 225, 201, 181, 169, 145, 113, 57; HRMS exact mass calcd for $C_{14}H_{24}O_4$ 256.1675, found 256.1668.



3-*tert*-Butyl-4-methoxycarbonylmethyl-cyclopentane-1,1-dicarboxylic acid dimethyl ester (2.8a): Subjecting precursor **2.5a** (44 mg, 0.1 mmol) to the cyclization conditions outlined in method B for 1.5 h and purification of the crude reaction mixture by column chromatography eluting with hexanes/ethyl acetate (15/1) after five column volumes of hexanes, yielded 16 mg (52%) of a 78/22 *cis*/*trans* isomeric mixture of the title compound **2.8a**. These two products were inseparable and so characterization was performed on the mixture: IR (film, CH_2Cl_2) 3054, 2987, 1730, 1439, 1262, 1175, 896 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) resonances assigned to the *cis* isomer δ 3.74 (s, 3H), 3.72 (s, 3H), 3.68 (s, 3H), 2.64–2.60 (m, 1H), 2.52 (dd, *J* = 3.6, 15.2 Hz, 1H), 2.38 (dd, *J* = 6.9, 14.3 Hz, 1H), 2.34 (dd, *J* = 6.6, 13.4 Hz, 1H), 2.21 (d, *J* = 14.7 Hz, 2H), 2.10 (t, $J = 13.5$ Hz, 1H), 1.83 (dt, $J = 6.1$, 13.7 Hz, 1H), 0.97 (s, 9H); resonances assigned to the *trans* isomer δ 3.74 (s, 3H), 3.71 (s, 3H), 3.67 (s, 3H), 1.92 (dd, $J = 10.9$, 13.3 Hz, 1H), 0.90 (s, 9H), the remaining resonances are insufficiently resolved from those of the *cis* isomer to be reported. ^{13}C NMR (125 MHz, $CDCl_3$) resonances assigned to the *cis* isomer δ 173.5, 173.4, 173.3, 57.5, 53.3, 52.7 (2C), 51.5, 39.4, 37.8, 34.6, 33.6, 31.6, 29.1 (3C); resonances assigned to the *trans* isomer 54.4, 52.6, 41.5, 40.1, 36.6, 35.9, 32.7, 27.8 (3C), 25.1, the remaining resonances are insufficiently resolved from those of the *cis* isomer to be reported. MS *m/e* 283 $(M - MeO)^+$; HRMS exact mass calcd for $C_{15}H_{23}O_5$ $(M - MeO)^+$ 283.1545, found 283.1559.

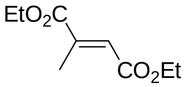


3-*tert*-Butyl-4-(2-trimethylsilanylethoxycarbonylmethyl)cyclopentane-1,1-dicarboxylic acid dimethyl ester (2.5b): Subjecting precursor **2.5b** (53 mg, 0.1 mmol) to the cyclization conditions outlined in method B for 1.5 h and purification of the crude reaction mixture by column chromatography eluting with hexanes/ethyl acetate (15/1) after five column volumes of hexanes yielded 27 mg (67 %) of a 77/23 *cis*/*trans* isomeric mixture of the title compound **2.8b**. These two products were inseparable and so characterization was performed on the mixture: IR (film, CH_2Cl_2) 2972, 1734, 1250, 1172, 861 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) resonances assigned to the *cis* isomer δ 4.20–4.15 (m, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 2.64–2.62 (m, 1H), 2.50 (dd, $J = 3.4$, 15.0 Hz, 1H), 2.41 (dd, $J = 6.6$, 14.6 Hz, 1H), 2.33 (dd, $J = 6.5$, 13.4 Hz, 1H), 2.23 (d, $J = 14.6$ Hz, 1H), 2.19–2.08 (m, 2H), 1.83 (dt, $J = 6.2$, 13.6 Hz, 1H), 1.02–0.94 (m, 11 H), 0.06 (s, 9H); resonances assigned to the *trans* isomer: δ 3.76 (s, 3H), 3.72 (s, 3H), 1.92 (dd, $J = 11.0$, 12.1 Hz, 1H), 0.90−0.87 (m, 11H), the remaining resonances are insufficiently resolved from those of the *cis* isomer to be reported; ^{13}C NMR (125 MHz, $CDCl_3$) resonances assigned to the *cis* isomer δ 173.5, 173.4, 173.1, 62.5, 57.5, 53.2, 52.8 (2C), 39.3, 37.7, 35.0, 33.6, 31.6, 29.1 (3C), 17.4, −1.6 (3C); resonances assigned to the *trans* isomer δ 62.4, 52.6, 52.5, 42.4, 40.0, 32.6, 27.5 (3C), the remaining resonances are insufficiently resolved from those of the *cis* isomer to be reported; MS *m/e* 400, 343, 241, 185, 73, 57; HRMS exact mass calcd for $C_{20}H_{35}O_6Si$ $(M - H)^+$ 399.2203, found 399.2224.

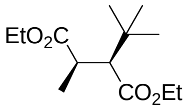


5-Methoxycarbonylmethyl-1'-methyl-bicyclopentyl-3,3-dicarboxylic acid dimethyl ester (2.12): Subjecting precursor **2.10** (0.28 g, 0.6 mmol) to the cyclization conditions outlined in method B for 4 h and purification of the crude reaction mixture by column chromatography eluting with hexanes/ethyl acetate (8/1) after five column volumes of hexanes, yielded 0.12 g (60 %) of a 80/20 *cis*/*trans* isomeric mixture of the title compound **2.12** as a pale opaque yellow oil. These two products were inseparable and so characterization was performed on the mixture: IR (thin film, CH_2Cl_2) 3058, 2987, 2958, 1732, 1437, 1279, 1254, 1173, 894 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) resonances assigned to the *cis* isomer δ 3.72 (s, 3H), 3.70 (s, 3H), 3.66 (s, 3H), 2.61−2.58 (m, 1H), 2.40 (dd, *J* = 7.1, 14.4 Hz, 1H), 2.40 (dd, *J* = 2.7, 15.0 Hz, 1H), 2.31 (dd, *J* = 6.1, 12.9 Hz, 1H), 2.19 (dd, *J* = 12.5, 15.3 Hz, 1H), 2.19 (dd, *J* = 2.7, 15.0 Hz, 1H), 2.08 (t, *J* = 13.3 Hz, 1H), 2.02 (ddd, *J* = 6.2, 6.2, 13.4 Hz, 1H), 1.64–1.54 (m, 4H), 1.37–1.31 (m, 2H), 1.27–1.22 (m, 2H), 0.97 (s, 3H); resonances assigned to the *trans* isomer δ 1.91–1.85 (m, 1H), 1.73–1.68 (m, 4H), 0.80 (s, 3H), the remaining resonances are insufficiently resolved from those of the *cis* isomer to be reported**;** ^{13}C NMR (125 MHz, CD_3OD) resonances assigned to the *cis* isomer δ 175.2, 174.8, 174.6, 59.0, 53.9, 53.3 (2C), 52.0, 43.8, 41.4, 40.1, 39.1, 37.7, 35.7, 34.9, 27.0, 26.6, 25.3; *trans* isomer δ 59.8, 53.3 (2C), 41.3, 41.2, 39.8, 38.3, 25.2, the remaining resonances are insufficiently resolved from those of the *cis* isomer to be reported; MS *m/e* 340, 309, 267, 248, 207, 185, 145, 83; HRMS exact mass calcd for $C_{18}H_{28}O_6$ 340.1886, found 340.1894.

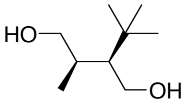
5.3.5 Synthesis of 2.7*trans*



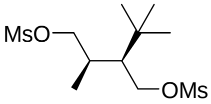
***(E)*-2-Methyl-but-2-enedioic acid diethyl ester (2.33):** To mesaconic acid (5.20 g, 40 mmol) was added ethanol (40 mL) and concentrated H_2SO_4 (0.5 mL). The resulting mixture was stirred and slowly brought to reflux and maintained there for 16 h. After cooling, the reaction mixture was concentrated by *in vacuo* and the residue was taken up in water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water (20 mL), 2M NaOH (20 mL) and then dried over $MgSO_4$. The organic layers were filtered and concentrated *in vacuo* to give 6.0 g of the title compound **2.33** (81%) as a pale yellow oil. The product was analytically pure and used without further purification: IR (film, CH_2Cl_2) 2984, 1721, 1650, 1447, 1367, 1260, 1112, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (q, *J* = 1.5 Hz, 1H), 4.27–4.17 (m, 4H), 2.27 (d, *J* = 1.4 Hz, 3H), 1.33–1.27 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 165.9, 143.7, 126.6, 61.5, 60.5, 14.2, 14.1, 14.0; MS *m/e* 186, 141, 140, 113, 112, 84, 68; HRMS exact mass calcd for $C_9H_{14}O_4$ 186.0892, found 186.0884.



2-*tert*-Butyl-3-methylsuccinic acid diethyl ester (2.34): To a suspension of vitamin B_{12a} (0.50 g, 0.36 mmol) in DMF (48 mL) was added activated zinc (5.33 g, 81.6 mmol) and the resulting mixture was stirred vigorously under argon. Zinc activation was carried out by washing the zinc powder with 2N HCl (2 x 30 mL), water (2 x 30 mL), EtOH (2 x 30 mL), Et_2O (2 x 30 mL) and finally drying the solid *in vacuo*. After 15 min, a degassed solution of *t*-BuBr (8.30 mL, 72.0 mmol), alkene **2.33** (1.33 g, 7.2 mmol) and Et_3N (14.9 mL, 103.2 mmol) in DMF (24 mL) was added. The resulting suspension was stirred for 12 h at room temperature during which the reaction turned from dark red to dark green accompanied by the evolution of a large amount of heat. After consumption of the alkene, the reaction was quenched with water (90 mL). This suspension was filtered and 2N HCl (30 mL) was added. The reaction mixture was then extracted with Et_2O (3 x 300 mL) and the combined organic layers were washed with water (60 mL) and dried over $MgSO_4$. The organic layers were filtered and concentrated *in vacuo* to give the title compound. Purification over silica gel eluting with hexanes/ethyl acetate (15/1) gave 0.805 g of diester **2.34** (46%) as a clear, colorless oil: IR (thin film, CH_2Cl_2) 2978, 1736, 1466, 1370, 1151, 1030 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03–3.96 (m, 4H), 2.78 (app quint, *J* = 7.2 Hz, 1H), 2.30 (d, *J* = 7.6 Hz, 1H), 1.22 (d, *J* = 7.1 Hz, 3H), 1.18–1.12 (m, 6H), 0.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 173.6, 60.2, 59.7, 58.2, 39.7, 33.0, 28.5 (3C), 19.0, 14.0, 13.8; MS *m/e* 199 $(M - OEt)^+$, 188, 142, 115, 83, 69, 57; HRMS exact mass calcd for $C_{11}H_{19}O_3$ $(M - OEt)^+$ 199.1334, found: 199.1340.

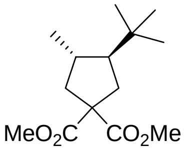


2-*tert*-Butyl-3-methylbutane-1,4-diol (2.35): To a stirred solution of diester **2.34** (0.71 g, 2.91 mmol) in THF (40 mL) was added $LiAlH_4$ (0.40 g, 10.6 mmol) in small portions over 10 min. The suspension was stirred at room temperature for 12 h at which point ethyl acetate (10 mL) was added slowly followed by 1M H_2SO_4 to decompose the excess hydride. Ether (20 mL) was added to the reaction mixture and after separation of the two phases, the aqueous layer was extracted with ether (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound. Purification over silica gel eluting with hexanes/ethyl acetate (1/1) gave 0.45 g of diol **2.35** (96%) as a clear colorless oil: IR (thin film, neat) 3299, 2960, 1471, 1396, 1367, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.93–3.81 (m, 3H), 3.69 (dd, J = 5.0, 11.3 Hz, 1H), 2.84 (br s, 2H), 2.08–1.99 (m, 1H), 1.32–1.27 (m, 1H), 1.13 (d, J = 7.2 Hz, 3H), 0.97 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 64.4, 60.4, 54.3, 33.8, 33.4, 28.5 (3C), 20.3; MS *m/e* 142 $(M - H_2O)^+$, 112, 109, 97, 73, 61, 57; HRMS exact mass calcd for $C_9H_{18}O$ $(M - H_2O)^+$: 142.1357, found: 142.1360.



Methanesulfonic acid 3-methanesulfonyloxymethyl-2,4,4-trimethyl-pentyl ester (2.35): To a stirred solution of diol **2.35** (0.45 g, 2.79 mmol) in CH_2Cl_2 (30 mL) was added Et_3N (1.61 mL, 11.56 mmol) and mesyl chloride (0.49 mL, 6.37 mmol). The reaction was stirred for 20 h at which point the reaction was diluted with CH_2Cl_2 and washed with water (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layer were washed with satd $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated to give the title compound. Purification over silica gel eluting with hexanes/ethyl acetate (3/2) gave 0.61 g of *bis*-mesylate **2.36** (69%) as flaky white solid: mp 71–74 °C, IR (thin film, neat) 3027, 2967, 1475, 1334, 1171, 944, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.39–4.33 (m, 2H), 4.24

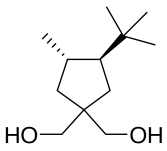
(dd, J = 7.7, 10.2 Hz, 1H), 4.06 (dd, J = 8.5, 9.0 Hz, 1H), 2.99 (s, 3H), 2.97 (s, 3H), 2.41–2.30 (m, 1H), 1.57–1.54 (m, 1H), 1.07 (d, J = 7.1 Hz, 3H), 0.97 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 72.4, 67.8, 51.5, 37.4, 37.2, 33.7, 32.3, 28.5 (3C), 19.4; MS *m/e* 221 (M – OMs)$^+$, 205, 193, 175, 164, 109, 79, 68, 57; HRMS exact mass calcd for $C_{10}H_{21}O_3S$ (M − OMs)$^+$ 221.1211, found: 221.1206.



***trans*-3-*tert*-Butyl-4-methylcyclopentane-1,1-dicarboxylic acid dimethyl ester (2.7*trans*):** To a solution of *bis*-mesylate **2.36** (0.173 g, 0.55 mmol) in acetone (2.7 mL) was added oven dried NaI (0.414 g, 2.76 mmol). The resulting solution was stirred and refluxed for 16 h at which point silica gel was added to the reaction and concentrated *in vacuo*. The solid was loaded onto a short column of silica gel and eluted with hexanes/ethyl acetate (5/1). The first eluting fraction was the *bis*-iodide **2.37** which was used as such in the following step.

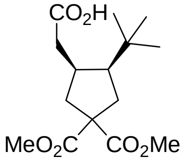
To a suspension of NaH (95%, 0.074 g, 3.1 mmol) in THF (20 mL) was added dimethyl malonate (0.44 mg, 3.3 mmol) drop wise as a solution in THF (20 mL). The resulting solution was stirred for 1 h at which point the *bis*-iodide **2.37** was added as a solution in THF (1 mL). The resulting mixture was refluxed for 10 h during which time a fine white precipitate formed. Additional dimethyl malonate anion (10 equiv at a time, 43.3 mmol total) were added until complete consumption of the alkylating agent was observed. The reaction was quenched by the addition of water (10 mL) and after separation of the layers, the aqueous layers were extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound. Purification over silica gel eluting with hexanes/ethyl acetate (15/1) gave 0.059 g of malonate **2.7*trans*** (69%, based on the mesylate **2.35**) as a clear pale yellow oil: IR (thin film, CH_2Cl_2) 2958, 2931, 1730, 1257 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.71 (s, 3H), 2.47 (dd, J = 8.2, 13.5 Hz, 1H), 2.42 (dd, J = 8.2, 13.0 Hz, 1H), 1.99–1.85 (m, 3H), 1.51 (app q, J = 8.3 Hz, 1H), 1.00 (d, J = 6.6 Hz, 3H), 0.88 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 173.0, 58.7, 56.4, 52.6 (2C), 43.3, 37.3, 34.6, 32.5, 28.0 (3C), 22.3; MS *m/e* 257, 241, 225, 145, 57; HRMS exact mass calcd for $C_{14}H_{24}O_4$: 256.1675, found: 256.1668.

5.3.6 Synthesis of Diol 2.43

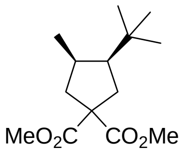


(3-*tert*-Butyl-1-hydroxymethyl-4-methylcyclopentyl)methanol (2.43): To a solution of malonate **2.7*trans*** (0.059 g, 0.23 mmol) in THF (3.0 mL) was added, in small portions, $LiAlH_4$ (0.032 g, 0.83 mmol). The resulting suspension was stirred for 6 h at which point ethyl acetate (1 mL) and 1M H_2SO_4 was added to quench any excess hydride. The reaction mixture was extracted with ether (3 x 10 mL), the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound. Purification over silica gel eluting with hexanes/ethyl acetate (1/5 followed by 1/1) gave 0.32 g of diol **2.43** (69%) as a crystalline white solid. Crystals suitable for x-ray diffraction analysis were grown by slow diffusion of hexanes into a solution of diol **2.43** in ethyl acetate: mp 87–89 °C, IR (thin film, CH_2Cl_2) 3354, 2940 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.65–3.53 (m, 4H), 2.91 (br s, 2H), 1.88–1.79 (m, 1H), 1.71 (dd, J = 8.0, 13.1 Hz, 1H), 1.64 (dd, J = 8.0, 13.3 Hz, 1H), 1.40 (app q, J = 9.7 Hz, 1H), 1.27–1.18 (m, 1H), 1.10 (dd, J = 9.1, 13.1 Hz, 1H), 1.06 (d, J = 6.6 Hz, 3H), 0.90 (s, 9H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 71.0, 70.9, 56.0, 45.5, 42.0, 35.1, 34.6, 32.3, 28.3 (3C), 22.3; ESI 223 $(M + Na)^+$; HRMS ESI exact mass calcd for $C_{12}H_{24}O_2Na$ $(M + Na)^+$: 223.1674 , found: 223.1692.

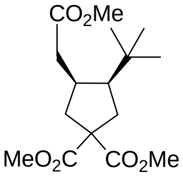
5.3.7 Monocyclic Relay Experiments



3-*tert*-Butyl-4-carboxymethylcyclopentane-1,1-dicarboxylic acid dimethyl ester (2.44): To a 77/23 *cis*/*trans* mixture of **2.8b** (23 mg, 0.057 mmol) in THF (1.0 mL), was added a solution of *p*-toluenesulfonic acid (24 mg, 0.13 mmol) and TBAF (1.0M solution in THF, 0.40 mL, 0.40 mmol). The resulting mixture was stirred for 12 h at room temperature at which point the reaction was diluted with ethyl acetate (5 mL) and washed with water (5 x 2 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give 16 mg the title acid **2.44** (94%). ^{1}H NMR analysis showed complete loss of the ethyl TMS group and the acid was used as such without further purification or characterization.



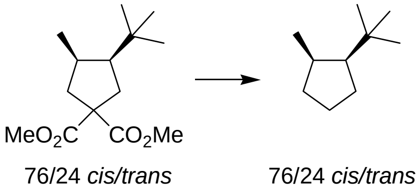
3-*tert*-Butyl-4-methylcyclopentane-1,1-dicarboxylic acid dimethyl ester (2.7′): A 77/23 *cis*/*trans* mixture of acid **2.44** (16 mg, 0.06 mmol) was taken up in benzene (0.3 mL) and treated with oxallyl chloride (0.05 mL, 0.57 mmol) and DMF (1 drop). The resulting solution was stirred at room temperature for 2 h and then concentrated *in vacuo*. The crude reaction mixture was re-dissolved in benzene and concentrated *in vacuo* again. The crude acid chloride was taken up in benzene (0.3 mL) and added to a suspension of 2-mercaptopyridine-1-oxide sodium salt (11 mg, 0.07 mmol) and DMAP (2 mg, 0.01 mmol) in benzene (0.6 mL). The reaction was heated at reflux for 20 min. The heat source was removed and a solution of AIBN (10 mg, 0.06 mmol) and Bu_3SnH (0.05 mL, 0.18 mmol) in benzene (0.3 mL) was added. The reaction was once again brought to reflux for 15 h, cooled, concentrated *in vacuo* and directly purified by column chromatography over silica gel eluting with hexanes/ethyl acetate (20/1) after four column volumes of hexanes to yield 11 mg (68 % from **2.8b**) of a 77/23 *cis*/*trans* mixture of the title malonate **2.7′** as a pale yellow oil. Spectral data for this mixture were identical to that previously synthesized.



3-*tert*-Butyl-4-methoxycarbonylmethylcyclopentane-1,1-dicarboxylic acid dimethyl ester (2.8a′): To a 77/23 *cis*/*trans* mixture of acid **2.44** (5 mg, 0.020 mmol) in benzene (0.1 mL) and methanol (0.03 mL) was added TMS diazomethane (2.0M solution in hexanes, 0.02 mL, 0.04 mmol). The resulting solution was stirred for 1 h, concentrated *in vacuo* and purified by column chromatography over silica gel eluting with hexanes/ethyl acetate (15/1) to give 4 mg (77% from

2.8b) of a 77/23 cis/trans mixture of malonate **2.8a′** as a pale yellow oil. Spectral data for this mixture was identical to that previously synthesized

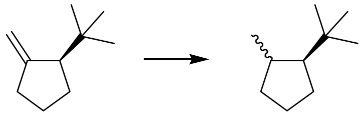
5.3.8 Full Decarboxylation Experiments



1-*tert*-Butyl-2-methyl-cyclopentane 2.45: To a 76/24 *cis/trans* mixture of malonate **2.7** (61 mg, 0.24 mmol) in MeOH (1 mL) and H_2O (1 mL) was added solid KOH (6 mg, 1.11 mmol) and the resulting mixture was stirred at room temperature for 16 h. The mixture was diluted with water and acidified to pH 1 with 2M HCl. The aqueous layer was then extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to yield the corresponding malonic acid as a white solid which was used as such. The crude malonic acid was taken up in water (5 mL) and subjected to microwave irradiation at 200 °C for 20 min. The reaction vessel was allowed to cool and the reaction mixture was acidified to pH 1, extracted with CH_2Cl_2 (3 x 5 mL) and dried over Na_2SO_4. Filtration and concentration *in vacuo*, gave 12 mg of a mono-acid **2.46** (28 %) as a colorless oil. Acid **2.46** is a mixture of diastereomers, and so it was not characterized and used as such in the following reaction.

A mixture of the acids **2.46** (12 mg, 0.06 mmol) was taken up in C_6D_6 (0.3 mL) and treated with oxallyl chloride (0.05 mL, 0.57 mmol) and DMF (1 drop). The resulting solution was stirred at room temperature for 2 h and then concentrated *in vacuo*. The crude reaction mixture was then re-dissolved in C_6D_6 and concentrated *in vacuo* again. The crude acid chloride was taken up in C_6D_6 (0.3 mL) and added to a suspension of 2-mercaptopyridine-1-oxide sodium salt (11 mg, 0.07 mmol) and DMAP (2 mg, 0.01 mmol) in C_6D_6 (1.0 mL). The reaction was then brought to reflux and allowed to do so for 20 min. The heat source was then removed and a solution of AIBN (10 mg, 0.06 mmol) and Ph_3SnH (63 mg, 0.18 mmol) in C_6D_6 (0.3 mL) was added. The reaction was once again brought to reflux for 15 h and then cooled. Due to the volatility of the products **2.45**, the GC and NMR analyses were carried out as this crude solution in C_6D_6.

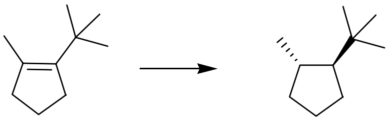
5.3.9 Hydrogenation Experiments



1-*tert*-Butyl-2-methylcyclopentane 2.45

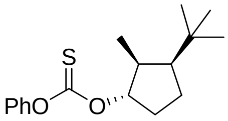
General Procedure for the hydrogenation of olefin **2.50** *using a metal hydrogenation catalyst:*
To a solution of alkene **2.50** (50 mg, 0.36 mmol) in ethanol (1.0 mL) was added the metal catalyst (0.036 mmol, either Pd/C, Pt/C, or Raney Nickel in water). The flask was fitted with a three way stopcock with one outlet to a hydrogen balloon and the other to an aspirator vacuum. The mixture was stirred vigorously and evacuated until the suspension bubbled at which point it was released to the hydrogen balloon. The purging of the reaction mixture with hydrogen was repeated an additional two times. After stirring for 12 h under the hydrogen atmosphere, the mixture was filtered through a 2 μm filter. Due to the volatility of the products **2.45**, the GC analysis was carried out on this crude mixture as a solution in ethanol.

Procedure for the hydrogenation of **2.50** *using diimide as the reducing agent:*
To solution of alkene **2.50** (10 mg, 0.07 mmol) in absolute ethanol (0.5 mL) was added anhydrous hydrazine (0.22 mL, 7.0 mmol) and anhydrous copper sulfate (11 mg, 0.7 mmol). The flask was fitted with a cold finger and the suspensions was stirred for 15 min at room temperature and then at 70 °C for 16 h. Additional hydrazine and copper sulfate was added as needed until complete consumption of the starting material was observed by GC. The mixture was filtered through a 2 μm filter and analyzed by GC without further purification as a solution in ethanol.

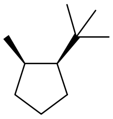


trans-1-_tert_-Butyl-2-methylcyclopentane (2.45): To a solution of alkene **2.51** (50 mg, 0.36 mmol) in ethyl acetate (0.75 mL) was added Pd/C (10% by weight, 12 mg). The flask was fitted with a three way stopcock with one outlet to a hydrogen balloon and the other to an aspirator vacuum. The mixture was stirred vigorously and evacuated until the suspension bubbled at which point it was released to the hydrogen balloon. The purging of the reaction mixture with hydrogen was repeated an additional two times. After stirring for 12 h under the hydrogen atmosphere, the mixture was filtered through a 2 μm filter. Due to the volatility of the products **2.45**, the GC analysis was carried out on this crude mixture as a solution in ethyl acetate.

5.3.10 Deoxygenation Experiments

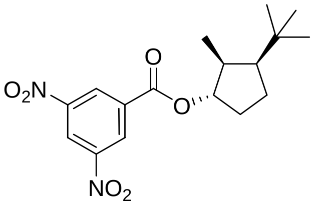


Thiocarbonic acid _O_-(3-_tert_-butyl-2-methylcyclopentyl) ester _O_-phenyl ester (S20): Cyclopentanol **2.58** (0.050 g, 0.32 mmol) was dissolved in CH_2Cl_2 (1.5 mL) to which was added phenylchlorothionoformate (0.05 mL, 0.35 mmol) and pyridine (0.10 mL, 1.18 mmol). The resulting mixture was stirred for 16 h at which point it was poured into water and extracted with ethyl acetate (2 x 15 mL). The combined organic layers were washed with 10 % HCl (4 x 2 mL) and satd $NaHCO_3$ (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound. Purification by column chromatography over silica gel eluting with hexanes/ethyl acetate (25/1) gave 0.080 g of thionoformate **2.61** (86%) as a clear colorless oil: IR (thin film, CH_2Cl_2) 2975, 1180, 1040, 960 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59–7.53 (m, 2H), 7.45–7.43 (m, 1H), 7.29–7.25 (m, 2H), 5.36 (dm, *J* = 6.3 Hz, 1H), 2.60–2.56 (m, 1H), 2.44–2.38 (m, 1H), 2.20–1.90 (m, 2H), 1.84–1.69 (m, 2H), 1.14–1.10 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 153.4, 129.4 (2C), 126.4, 122.0 (2C), 94.0, 51.2, 41.9, 31.8, 29.2 (3C), 29.1, 22.1, 13.7; MS *m/e* 139 (M − PhOC(S)O)$^+$,138, 123, 94, 81, 69, 57 ; HRMS exact mass calcd for $C_{10}H_{19}$ (M − PhOC(S)O)$^+$ 139.1487, found 139.1487.



***cis*-1-*tert*-Butyl-2-methylcyclopentane (2.45):** To a solution of thionoformate **2.61** (50 mg, 0.17 mmol) in hexanes (2 mL) was added a solution of AIBN (3 mg, 0.03 mmol) and Bu_3SnH (0.05 mL, 0.19 mmol) in hexanes (1.3 mL). The resulting solution was refluxed for 16 h and the reaction was cooled. Due to the volatility of the products **2.45**, the GC analysis was carried out on this crude mixture as a solution in hexanes.

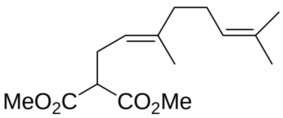
5.3.11 Synthesis of 2.62



(1R,2R,3R)-3-*tert*-Butyl-2-methylcyclopentyl-3,5-dinitrobenzoate (2.62): Cyclopentanol **2.58** (52 mg, 0.33 mmol) was diluted with CH_2Cl_2 (2 mL) and to this solution was added *m*-dinitrobenzoyl chloride (114 mg, 0.50 mmol). The stirred solution was then cooled to 0 °C and DMAP (60 mg, 0.50 mmol) was added drop wise as a solution in CH_2Cl_2 (1 mL). The reaction temperature was maintained at 0 °C for 1.5 h and then warmed to room temperature for an additional 1.5 h. The mixture was then diluted with CH_2Cl_2 (5 mL) and washed with 1M HCl (5 mL) and water (5 mL). The organic layers was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound. Purification over silica gel eluting with hexanes/ethyl acetate (1/7) gave 116 mg of ester **2.62** (99%) as a crystalline white solid. Crystals suitable for x-ray diffraction analysis were grown by slow evaporation of methanol from a solution of title compound: mp 54–56 °C, IR (thin film, CH_2Cl_2) 2940, 1720, 1310, 895, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.22–9.20 (m, 1H), 9.12−9.11 (m, 2H), 5.08 (br d, *J* = 6.5 Hz, 1H), 2.37−2.27 (m, 2H), 2.05−1.96 (m, 1H), 1.89−1.78 (m, 2H), 1.72−1.57 (m, 1H), 1.01 (d, *J* = 6.9 Hz, 3H), 1.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2, 148.7, 134.6, 129.3 (2C), 122.1(2C), 86.6, 51.6, 42.4, 31.8, 29.4 (3C), 29.3, 22.3, 14.1; MS *m/e* 350, 293, 278, 212, 195, 149, 123, 81, 57; HRMS exact mass calcd for $C_{17}H_{22}N_2O_6$ 350.1478, found 350.1485.

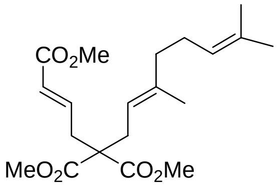
5.4 Experimental Procedures and Characterization Data for Chapter 3

5.4.1 Synthesis of Cyclization Precursors 1.65, 3.2 and 3.3

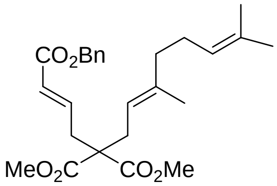


2-(3,7-Dimethylocta-2*E*,6-dienyl)malonic acid dimethyl ester (3.22): Dimethyl malonate (21.1 mL, 184 mmol) was added via syringe pump over 30 min to a stirred suspension of NaH (95 % dry, 4.4 g, 184 mmol) in anhydrous THF (500 mL) at 0 °C. After addition, the flask was protected from light with aluminum foil and geranyl bromide (24.4 mL, 122 mmol) was added via syringe pump over 1 h to the mixture. After 16 h the resulting mixture was poured into a mixture of water (250 mL) and ethyl acetate (250 mL). After separation of the layers, the aqueous layer was extracted with ethyl acetate (3 x 250 mL) and the combined organic layers were dried over anhydrous $MgSO_4$. Filtration and solvent evaporation *in vacuo* gave the title compound. Purification by flash chromatography on silica gel eluting with hexanes/ethyl acetate (15/1) gave 27.5 g of **3.22** (83%) as a clear, pale yellow oil: IR (film, CH_2Cl_2) 2955, 2925, 2855, 1731, 1438, 1378, 1341, 1274, 1243, 1216, 1156, 1094, 1041, 929, 909, 888 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.09−5.06 (m, 2H), 3.74 (s, 6H), 3.39 (t, $J = 7.7$ Hz, 1H), 2.63 (t, $J = 7.4$ Hz, 2H), 2.07−2.02 (m, 4H), 1.70 (s, 3H), 1.66 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4 (2C), 138.5, 131.3, 123.8, 119.3, 52.3 (2C), 51.7, 39.5, 27.4, 26.4, 25.5, 17.5, 15.8; MS *m/e* 268, 225, 199, 139, 121, 107, 93, 79, 69, 59; HRMS exact mass calcd for $C_{15}H_{24}O_4$ 268.1675, found 268.1683.

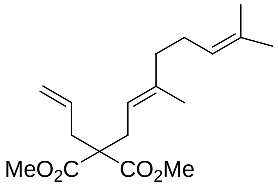
General Procedure for the Alkylation of 3.22: Alkylated malonate **3.22** was added via syringe pump over 30 min to a stirred suspension of NaH (95% dry, 1.1 equiv) in anhydrous THF (150 mL per gram of NaH) at 0 °C. Upon complete addition, the respective alkylating agent, **3.23**, was added via syringe pump over 1 h to the mixture. After 16 h the mixture was poured into a mixture of water (150 mL per gram of NaH) and ethyl acetate (50 mL per gram of NaH). After separation of the layers, the aqueous layer was extracted with ethyl acetate (3 x 130 mL per gram NaH) and the combined organic layers were dried over anhydrous $MgSO_4$. Filtration and solvent evaporation *in vacuo* gave the bis-alkylated product. Purification by flash chromatography on silica gel yielded the title compound.



5-(3,7-Dimethylocta-2*E*,6-dienyl)-5-methoxycarbonylhex-2*E*-enedioic acid dimethyl ester (3.24a): Alkylating **3.22** (23.0 g, 85.7 mmol) with (*E*)-methyl-4-bromocrotonate **3.23a** (11.9 mL, 100.8 mmol, sample available from Aldrich is only 85 % pure and so this represents 1.0 equiv of the crotonate) and eluting the column with hexanes/ethyl acetate (5/1) yielded 27.3 g of **3.24a** (87%) as a clear, pale yellow oil: IR (thin film, $CHCl_3$) 2954, 2925, 2853, 1732, 1659, 1438, 1377, 1342, 1283, 1214, 1175, 1101, 1062, 1041 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.79 (dt, $J = 7.7, 15.5$ Hz, 1H), 5.85 (dt, $J = 1.4, 15.5$ Hz, 1H), 5.07−5.03 (m, 1H), 4.94 (dt, $J = 1.2, 7.5$ Hz, 1H), 3.73 (s, 6H), 3.71 (s, 3H) 2.76 (dd, $J = 1.4, 7.7$ Hz, 2H), 2.63 (d, $J = 7.4$ Hz, 2H), 2.07−1.99 (m, 4H), 1.69 (d, $J = 1.0$ Hz, 3H), 1.60 (br s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9 (2C), 166.2, 143.1, 139.9, 131.6, 124.5, 123.9, 117.0, 57.6, 52.5 (2C), 51.5, 39.9, 35.3, 31.4, 26.4, 25.6, 17.6, 16.2; MS *m/e* 367 $(M + H)^+$, 334, 319, 306, 284, 265, 246, 237, 205, 177, 166, 145, 135, 117, 109, 91, 82, 69, 59; HRMS exact mass calcd for $C_{20}H_{31}O_6$ $(M + H)^+$: 367.2121, found 367.2134.

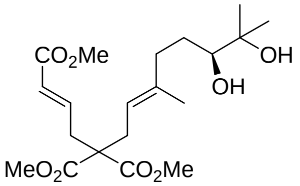


5-(3,7-Dimethylocta-2*E*,6-dienyl)-5-methoxycarbonylhex-2*E*-enedioic acid 1-benzyl ester 6-dimethyl ester (3.24b): Alkylating **3.22** (2.8 g, 10.3 mmol) with 4-bromobut-2*E*-enoic acid benzyl ester **3.23b**[89] (2.6 g, 10.3 mmol) and eluting the column with hexanes/ethyl acetate (10/1) yielded 3.9 g of **3.24b** (86%) as a clear, pale, brown oil: IR (neat) 2952, 2852, 1730, 1657, 1436, 1378, 1277, 1212, 1164, 983, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.31 (m, 5H), 6.85 (dt, $J = 7.7, 15.5$ Hz, 1H), 5.90 (dt, $J = 1.3, 15.5$ Hz, 1H), 5.18 (s, 2H), 5.07−5.03 (m, 1H), 4.94 (tq, $J = 1.1, 7.4$ Hz, 1H), 3.73 (s, 6H), 2.77 (dd, $J = 1.3, 7.7$ Hz, 2H), 2.64 (d, $J = 7.4$ Hz, 2H), 2.07−1.99 (m, 4H), 1.68 (d, *J* = 1.0 Hz, 3H), 1.59 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9 (2C), 165.6, 143.5, 139.9, 136.0, 131.6, 128.5 (2C), 128.1 (3C), 124.5, 123.9, 117.0, 66.1, 57.6, 52.5 (2C), 39.8, 35.3, 31.4, 26.4, 25.6, 17.7, 16.2; MS *m/e* 443 $(M + H)^+$, 351, 157, 135, 109, 91, 69; HRMS exact mass calcd for $C_{26}H_{34}O_6$: 442.2355, found: 442.2348.

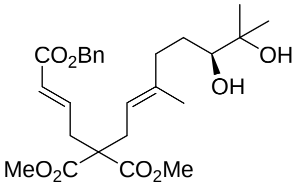


2-Allyl-2-(3,7-dimethylocta-2*E*,6-dienyl)malonic acid dimethyl ester (3.24c): Alkylating **3.22** (4.0 g, 14.9 mmol) with allyl bromide **3.23c** (1.3 mL, 15.0 mmol) and eluting the column with hexanes/ethyl acetate (15/1) yielded 4.2 g of **3.24c** (92%) as a clear pale, yellow oil: IR (thin film, CH_2Cl_2) 3056, 2985, 1731, 1435, 1273, 1249, 1225 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68−5.54 (m, 1H), 5.06−5.00 (m, 3H), 4.92 (dq, *J* = 1.3, 7.5 Hz, 1H), 3.66 (s, 6H), 2.58 (dm, *J* = 7.4 Hz, 4H), 2.03−1.94 (m, 4H), 1.64 (d, *J* = 1.4 Hz, 3H), 1.58−1.55 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4 (2C), 139.1, 132.6, 131.3, 123.9, 118.7, 117.5, 57.8, 52.1 (2C), 39.8, 36.8, 30.9, 26.4, 25.5, 17.5, 16.0; MS *m/e* 308, 293, 277, 179, 147, 119, 105, 91, 79, 69, 59; HRMS exact mass calcd for $C_{18}H_{28}O_4$: 308.1988, found 308.1991.

General Procedure for the Selective Dihydroxylation of the bis-Alkylated Malonates 3.25: To a mixture of *t*-BuOH (5 mL per mmol of olefin) and water (5 mL per mmol of olefin), was added AD-Mix α (1.4 g per mmol of olefin). The mixture was stirred vigorously and $CH_3SO_2NH_2$ (0.095 g per mmol of olefin) was added. The entire mixture was cooled to 0 °C and the *bis*-alkylated malonate **3.24**, was added. The mixture was vigorously stirred for 14 h. Sodium sulfite (1.5 g per mmol of olefin) was added and the mixture was warmed to room temperature and stirred for 1 h. Ethyl acetate (10 mL per mmol of olefin) was added to the mixture and after separation of the layers, the aqueous layer was extracted with ethyl acetate (3 x 5 mL per mmol of olefin). The combined organic layers were then washed with 2N KOH (5 mL per mmol of olefin) and dried over anhydrous $MgSO_4$. Filtration and solvent evaporation *in vacuo* yielded the respective diol. Purification was carried out by flash chromatography on silica gel eluting with hexanes/ethyl acetate to recover any unreacted alkene starting material and then pure ethyl acetate to obtain the product.

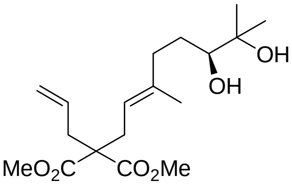


5-(6,7-Dihydroxy-3,7-dimethyloct-2*E*-enyl)-5-methoxycarbonylhex-2*E*-enedioic acid dimethyl ester (3.25a): Using malonate **3.24a** (19.5 g, 53.2 mmol), and eluting the column with hexanes/ethyl acetate (3/1) yielded 19.7 g (92%) of the title diol **3.25a** as a thick pale yellow oil: IR (thin film, $CHCl_3$) 3553, 2985, 2955, 1743, 1659, 1439, 1374, 1261, 1044, 984 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (dt, *J* = 7.6, 15.5 Hz, 1H), 5.87 (dt, *J* = 1.4, 15.5 Hz, 1H), 5.05 (t, *J* = 7.3 Hz, 1H), 3.74 (s, 6H), 3.73 (s, 3H), 3.31 (dd, *J* = 2.0, 10.4 Hz, 1H), 3.00 (br s, 1H), 2.69 (br s, 1H), 2.77 (dd, *J* = 1.6, 6.5 Hz, 2H), 2.64 (d, *J* = 7.4 Hz, 2H), 2.30−2.22 (m, 1H), 2.14−2.06 (m, 1H), 1.62 (s, 3H), 1.62−1.56 (m, 1H) 1.42−1.27 (m, 1H), 1.26 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8 (2C), 166.2, 142.9, 139.8, 124.3, 117.3, 77.2, 72.7, 57.4, 52.4 (2C), 51.3, 36.7, 35.2, 31.3, 29.4, 26.1, 23.1, 15.9; MS *m/e* 382 $(M - H_2O)^+$, 351, 299, 291, 277, 267, 265, 264, 263, 259, 219, 198, 166, 93, 81, 71, 59; HRMS exact mass calcd for $C_{20}H_{30}O_7$: $(M - H_2O)^+$ 382.1992, found: 382.1997.



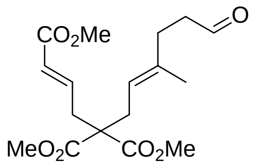
5-(6,7-Dihydroxy-3,7-dimethyloct-2*E*-enyl)-5-methoxycarbonylhex-2*E*-enedioic acid 1-benzyl ester 6-methyl ester (3.25b): Using malonate **3.24b** (3.85 g, 8.7 mmol), and eluting the column with hexanes/ethyl acetate (5/1) yielded 3.6 g (87%) of diol **3.25b** as a thick yellow oil: IR (neat) 3472, 2955, 1730, 1657, 1438, 1379, 1274, 1168, 1075, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.32 (m, 5H), 6.84 (dt, *J* = 7.7, 15.5 Hz, 1H), 5.91 (dt, *J* = 1.2, 15.5 Hz, 1H), 5.17 (s, 2H), 5.05 (tq, *J* = 1.0, 7.5 Hz, 1H), 3.73 (s, 6H), 3.30 (dd, *J* = 2.0, 10.3 Hz, 1H), 2.78 (dd, *J* = 1.2, 7.7 Hz, 2H), 2.64 (d, *J* = 7.4 Hz, 2H), 2.28−2.21 (m, 1H), 2.22 (br s, 1H), 2.15−2.07 (m, 1H), 1.99 (br s, 1H), 1.61 (d, *J* = 1.0 Hz, 3H), 1.45−1.32 (m, 2H), 1.20 (s, 3H), 1.16 (s, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 170.9 (2C), 165.6, 143.4, 139.6, 135.9, 128.4 (2C), 128.1 (3C), 124.5, 117.6, 77.6, 72.9, 66.1, 57.5, 52.5 (2C), 36.8, 35.4, 31.5, 29.4, 26.2, 23.3, 16.1; MS *m/e* 458 (M − H_2O)$^+$, 430, 375, 215, 191, 121, 91, 71 59; HRMS exact mass calcd for $C_{26}H_{34}O_7$ (M − H_2O)$^+$ 458.2305, found 458.2316.

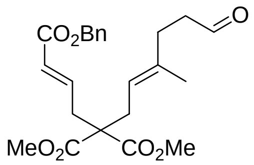


2-Allyl-2-(6,7-dihydroxy-3,7-dimethyloct-2*E*-enyl)malonic acid dimethyl ester (3.25c): Using malonate **3.24c** (2.0 g, 6.5 mmol), and eluting the column with hexanes/ethyl acetate (3/1) yielded 2.1 g (93%) of the **3.25c** as a dark yellow oil: IR (thin film, neat) 3445, 2954, 1729, 1439, 1384, 1291, 1228, 1146, 1075, 921, 735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69−5.55 (m, 1H), 5.09−4.99 (m, 3H), 3.68 (s, 6H), 3.27 (d, *J* = 10.2 Hz, 1H), 2.59 (d, *J* = 7.0 Hz, 4H), 2.59 (br s, 1H), 2.42 (br s, 1H), 2.26−2.16 (m, 1H), 2.11−2.01 (m, 1H), 1.59 (s, 3H), 1.59−1.49 (m, 1H), 1.39−1.34 (m, 1H), 1.17 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5 (2C), 139.0, 132.3, 119.0, 117.9, 77.5, 72.9, 57.8, 52.3 (2C), 36.8 (2C), 30.8, 29.4, 26.1, 23.2, 16.0; MS *m/e* 324 (M − H_2O)$^+$, 251, 241, 219, 179, 172, 161, 153, 141, 140, 108, 93, 81, 71, 67, 59; HRMS exact mass calcd for $C_{18}H_{28}O_5$ (M − H_2O)$^+$ 324.1937, found 324.1942.

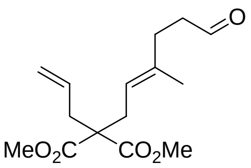
General Procedure for the Diol Cleavage of 3.25: A 3/1 (v/v) mixture of THF and water (5 mL per mmol of diol) was added to the diol **3.25** and the resulting mixture was stirred vigorously until the solution was homogeneous. $NaIO_4$ (1.0 equiv) was added in small portions over 30 min. The flask was stoppered and the mixture was stirred for 17 h during which time a white solid precipitated. The reaction mixture was poured into water (6 mL per mmol of diol) and Et_2O (6 mL per mmol of diol). After separation of the layers, the aqueous layer was extracted with Et_2O (3 x 7 mL per mmol of diol) and the combined organic layers were dried over anhydrous $MgSO_4$. Filtration and solvent evaporation *in vacuo* followed by purification by flash chromatography on silica gel.



5-Methoxycarbonyl-5-(3-methyl-6-oxohex-2*E*-enyl)hex-2*E*-enedioic acid dimethyl ester (3.26a): Using diol **3.25a** (19.7 g, 49 mmol) and eluting the column with hexanes/ethyl actetate (3/1) yielded 15.7 g (94%) of the title aldehyde **3.25a** as a clear, pale yellow oil: IR (thin film, CH_2Cl_2) 2996, 2954, 2845, 2729, 1731, 1659, 1437, 1278, 1171, 1068, 1043, 986 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.7 Hz, 1H), 6.77 (dt, *J* = 7.6, 15.5 Hz, 1H), 5.85 (dt, *J* = 1.4, 15.5 Hz, 1H), 5.01 (t, *J* = 7.4 Hz, 1H), 3.73 (s, 6H), 3.72 (s, 3H), 2.74 (dd, *J* = 1.4, 7.7 Hz, 2H), 2.62 (d, *J* = 7.4 Hz, 2H), 2.53 (tm, *J* = 7.2 Hz, 2H), 2.34 (t, *J* = 7.2 Hz, 2H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 170.6 (2C), 166.0, 142.6, 137.8, 124.4, 118.0, 57.2, 52.4 (2C), 51.3, 41.8, 35.2, 31.7, 31.2, 16.1; MS *m/e* 341 (M + H)$^+$, 291, 263, 249, 241, 177, 166, 111, 107, 93, 81, 59; HRMS exact mass calcd for $C_{17}H_{24}O_7$: 340.1522, found: 340.1535.



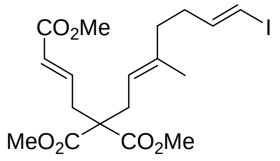
5-Methoxycarbonyl-5-(3-methyl-6-oxo-hex-2*E*-enyl)hex-2*E*-enedioic acid 1-benzyl ester 6-methyl ester (3.26b): Using diol **3.25b** (3.6 g, 7.5 mmol) and eluting the column with hexanes/ethyl acetate (3/1) yielded 2.8 g (89%) of the title aldehyde **3.26b** as a clear dark yellow oil: IR (thin film, CH_2Cl_2) 3057, 2986, 1730, 1436, 1423, 1281, 1250, 1170 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (t, *J* = 1.5 Hz, 1H), 7.29−7.32 (m, 5H), 6.78 (dt, *J* = 7.7, 15.5 Hz, 1H), 5.86 (dt, *J* = 1.3, 15.5 Hz, 1H), 5.12 (s, 2H), 4.97 (dq, *J* = 1.3, 7.5 Hz, 1H), 3.67 (s, 6H), 2.71 (dd, *J* = 1.3, 7.8 Hz, 2H), 2.58 (d, *J* = 7.5 Hz, 2H), 2.45 (dt, *J* = 1.5, 7.5 Hz, 2H), 2.27 (t, *J* = 7.5 Hz, 2H), 1.56 (d, *J* = 1.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 170.5 (2C), 165.3, 143.1, 137.7, 135.7, 128.3 (2C), 128.0, 127.9 (2C), 124.4, 117.9, 65.9, 57.2, 52.4 (2C), 41.8, 35.2, 31.7, 31.2, 16.1; APCI: Mass calcd for $C_{23}H_{28}O_7Na$ (M + Na)$^+$: 439.2, found 439.1; Mass calcd for $C_{23}H_{28}O_7K$ (M + K)$^+$: 455.2, found: 455.1.



2-Allyl-2-(3-methyl-6-oxohex-2-enyl)malonic acid dimethyl ester (3.26c): Using diol **3.25c** (3.9 g, 11.3 mmol) and eluting the column with hexanes/ethyl acetate (3/1) yielded 2.8 g (93%) of the title aldehyde **3.26c** as a clear, pale yellow oil: IR (thin film, CH_2Cl_2) 3057, 2986, 2954, 2859, 1729, 1437, 1274, 1223 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (t, *J* = 1.8 Hz, 1H), 5.69−5.56 (m, 1H), 5.10−4.99 (m, 3H), 3.70 (s, 6H), 2.60 (dm, *J* = 7.4 Hz, 4H), 2.49 (tm, *J* = 7.8 Hz, 2H), 2.32 (t, *J* = 7.7 Hz, 2H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 171.3 (2C), 137.3, 132.4, 119.0, 118.7, 57.7, 52.3 (2C), 42.1, 38.7, 37.0, 32.0, 30.9, 16.2; MS *m/e* 241 $(M - C_3H_5)^+$, 209, 179, 177, 165, 139, 119, 108, 93, 81, 77, 59; HRMS exact mass calcd for $C_{12}H_{17}O_5$ $(M - C_3H_7)^+$: 241.1076, found: 241.1076.

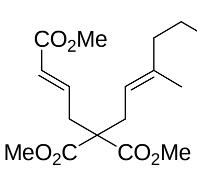
General Procedure for the Synthesis of the Vinyl Iodides From Aldehydes 3.26: To a stirred suspension of (iodomethyl)triphenylphosphonium iodide **3.27** (2.0 equiv) in THF (2.0 mL per mmol of Wittig salt) was added NaHMDS (2.0 equiv of a 1M solution in THF). The resulting suspension was stirred at room temperature for 30 min during which time it turned to a clear dark red solution. The mixture was cooled to –78 °C and to this was added the aldehyde (1.0 equiv) in THF (2.0 mL per mmol of aldehyde). The reaction was removed from the cold bath and warmed to room temperature and stirred for 1 h. The crude reaction mixture was then filtered through a short column of silica gel eluting with ether. Solvent evaporation and purification over silica gel yielded the respective vinyl iodide in a 6/1 *Z*/*E* ratio.

5-(7-Iodo-3-methylhepta-2*E*,6*Z*-dienyl)-5-methoxycarbonylhex-2*E*-enedioic acid dimethyl ester (1.65): Using aldehyde **3.26a** (10.0 g, 29.4 mmol) and eluting the column with hexanes/ethyl acetate (10/1) yielded 5.5 g (41%) of iodide **1.65** as a light brown oil. On a small scale, the *E* and the *Z* were separated with the *E*-isomer eluting first:



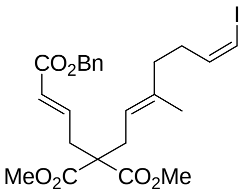
E-isomer

IR (thin film, CH_2Cl_2) 3055, 2986, 1422, 1731, 1422, 1267, 896 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (dt, *J* = 7.7, 15.5 Hz, 1H), 6.45 (dt, *J* = 7.1, 14.4 Hz, 1H), 6.00 (dt, *J* = 1.3, 14.4 Hz, 1H), 5.84 (dt, *J* = 1.2, 15.5 Hz, 1H), 4.96 (tq, 1.2, 7.5 Hz, 1H), 3.73 (s, 6H), 3.71 (s, 3H), 2.75 (dd, *J* = 1.2, 7.7 Hz, 2H), 2.62 (d, *J* = 7.3 Hz, 2H), 2.24−2.07 (m, 4H), 1.58 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9 (2C), 166.2, 145.7, 142.9, 138.5, 124.6, 118.1, 74.9, 57.4, 52.6 (2C), 51.5, 38.5, 35.3, 34.3, 31.4, 16.2; MS *m/e* 464, 433, 404, 365, 333, 277, 245, 205, 198, 167, 145, 107, 91, 79, 59; HRMS exact mass calcd for $C_{18}H_{26}IO_6$ $(M + H)^+$ 465.0774, found 465.0766.

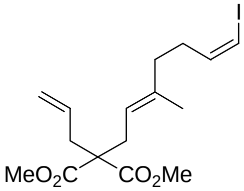


Z-isomer

IR (thin film, CH_2Cl_2) 3048, 2964, 2928, 2860, 1732, 1437, 1280, 1252 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (dt, *J* = 7.7, 15.5 Hz, 1H), 6.21 (dt, *J* = 1.2, 7.3 Hz, 1H), 6.11 (dt, *J* = 6.4, 7.2 Hz, 1H), 5.86 (dt, *J* = 1.2, 15.5 Hz, 1H), 4.99 (tq, 1.4, 7.4 Hz, 1H), 3.74 (s, 6H), 3.73 (s, 3H), 2.76 (dd, *J* = 1.2, 7.7 Hz, 2H), 2.64 (d, *J* = 7.4 Hz, 2H), 2.24 (ddt, *J* = 1.2, 6.7, 6.7 Hz, 2H), 2.12 (t, *J* = 6.7 Hz 2H), 1.64 (d, *J* = 1.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8 (2C), 166.2, 142.9, 140.5, 138.8, 124.6, 117.9, 82.7, 57.5, 52.6 (2C), 51.5, 37.8, 35.4, 33.0, 31.4, 16.2; MS *m/e* 464, 432, 400, 365, 333, 305, 277, 237, 217, 205, 177, 166, 145, 107, 91, 79, 59; HRMS exact mass calcd for $C_{18}H_{26}IO_6$ $(M + H)^+$ 465.0774, found 465.0762.

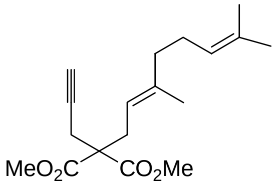


5-(7-Iodo-3-methyl-hepta-2*E*,6*Z*-dienyl)-5-methoxycarbonylhex-2*E*-enedioic acid 1-benzyl ester 6-methyl ester (3.2): Using aldehyde **3.26b** (0.015 g, 0.36 mmol) and eluting the column with hexanes/ethyl acetate (10/1) yielded 0.073 g (39%) of the title iodide **3.2** as a clear, light brown oil: IR (thin film, CH_2Cl_2) 3057, 2986, 1732, 1422, 1278, 1249, 895 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.31 (m, 5H), 6.83 (dt, *J* = 7.7, 15.5 Hz, 1H), 6.20 (dm, *J* = 7.3 Hz, 1H), 6.10 (dt, *J* = 6.7, 7.1 Hz, 1H), 5.91 (dm, *J* = 15.5 Hz, 1H), 5.17 (s, 2H), 4.97 (dq, *J* = 1.2, 7.4 Hz, 1H), 3.72 (s, 6H), 2.76 (d, *J* = 7.7 Hz, 2H), 2.63 (d, *J* = 7.4 Hz, 2H), 2.21 (dt, *J* = 6.5, 7.1 Hz, 2H), 2.11 (t, *J* = 7.1 Hz, 2H), 1.62 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8 (2C), 165.6, 143.3, 140.5, 138.8, 135.9, 128.5 (2C), 128.2, 128.1 (2C), 124.6, 117.8, 82.7, 66.1, 57.4, 52.6 (2C), 37.8, 35.3, 33.0, 31.4, 16.1; MS *m/e* 509 (M − MeOH)$^+$, 481, 449, 431, 403, 333, 233 167, 91; HRMS exact mass calcd for $C_{23}H_{26}IO_5$ (M − MeOH)$^+$ 509.0825, found 509.0831.



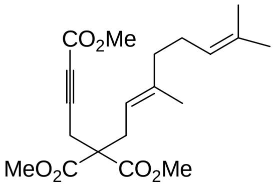
2-Allyl-2-(7-iodo-3-methylhepta-2*E*,6*Z*-dienyl)malonic acid dimethyl ester (3.3): Using aldehyde **3.26c** (2.8 g, 9.8 mmol) and eluting the column with hexanes/ethyl acetate (20/1) yielded 2.3 g (57%) of the title iodide **18** as a dark yellow oil: IR (thin film, CH_2Cl_2) 3058, 2975, 2933, 2869, 1732, 1438, 1276, 1224 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.18 (dt, *J* = 1.3, 7.3 Hz, 1H), 6.09, (dt, *J* =6.5, 7.3 Hz, 1H), 5.70−5.56 (m, 1H), 5.07 (dm, *J* = 14.1 Hz, 2H), 4.98 (dq, *J* = 1.1, 7.5 Hz, 1H), 3.71 (s, 6H), 2.61 (d, *J* = 7.4 Hz, 4H), 2.22 (ddt, *J* = 6.8, 6.8, 1.1 Hz, 2H), 2.11 (t, *J* = 6.9, 2H), 1.63 (d, *J* = 1.1, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3 (2C), 140.5, 138.1, 132.4, 119.0, 118.4, 82.6, 57.7, 52.3 (2C), 37.8, 36.8, 33.0, 30.9, 16.0; ^{13}C NMR resonances attributed to the *E* isomer: 152.3, 145.7, 137.8, 137.5, 74.8, 38.4, 38.4, 34.4, 31.5, 22.6, 14.1 MS *m/e* 406, 375, 365, 333, 179, 167, 119, 107, 91, 79, 59; HRMS exact mass calcd for $C_{16}H_{23}IO_4$: 406.0641, found 406.0645.

5.4.2 Synthesis of Cyclization Precursor 3.1

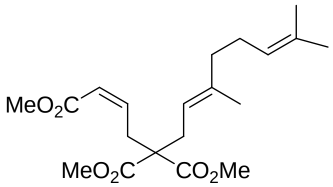


2-(3,7-Dimethylocta-2*E*,6-dienyl)-2-(prop-2-ynyl)malonate (3.29):

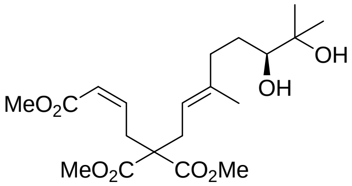
Malonate **3.22** was added via syringe pump over 30 min to a stirred suspension of NaH (95% dry, 0.095g, 3.52 mmol) in anhydrous THF (28 mL) at 0 °C. Upon complete addition, propargyl bromide (80% solution in toluene, 0.43 mL, 3.9 mmol) was added drop wise to the mixture. After 16 h the reaction mixture was poured into water (10 mL) and ethyl acetate (10 mL). After separation of the layers, the aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtration and solvent evaporation *in vacuo* gave the title compound. Purification by flash chromatography on silica gel eluting the column with hexanes/ethyl acetate (5/1) yielded 0.84 g of **3.29** (78%) as a clear, pale, brown oil: IR (neat) 3292, 2954, 2926, 2856, 1740, 1437, 1291, 1223, 1056, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.03−4.99 (m, 1H), 4.87 (t, *J* = 7.4 Hz, 1H), 3.75 (s, 6H), 2.78−2.74 (m, 4H), 2.04−1.98 (m, 5H), 1.66 (s, 3H), 1.62 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2 (2C), 140.3, 131.4, 123.9, 117.0, 79.2, 71.1, 57.1, 52.5 (2C), 39.8, 30.5, 26.3, 25.5, 22.3, 17.5, 16.0; MS *m/e* 306, 291, 275, 237, 203, 177, 145, 117, 69; HRMS exact mass calcd for $C_{18}H_{26}O_4$: 306.1831, found: 306.1817.



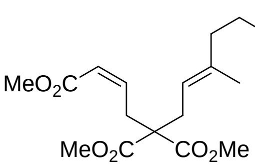
Trimethyl 7,11-dimethyldodeca-6*E*,10-dien-1-yne-1,4,4-tricarboxylate (3.30): To a stirred solution of malonate **3.29** (0.84 g, 2.8 mmol) in THF (6 mL) cooled to −78 °C was added BuLi (1.6M soln in hexanes, 2.6 mL, 3.30 mmol) drop wise. The resulting solution was stirred at −78 °C for 2 h, at which point methyl chloroformate (0.42 mL, 5.5 mmol) was added and stirring was continued for an additional 2 h. The mixture was warmed to room temperature and stirred for 15 h, then the reaction was quenched with a saturated aqueous solution of NH_4Cl (3 mL). After the addition of ethyl actetate (3 mL), the layers were separated and the aqueous layer was extracted with additional ethyl acetate (2 x 3 mL). The combined organic layers were washed with water (6 mL) and brine (6 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude compound. Purification over silica gel eluting the column with hexanes/ethyl acetate (15/1) to recover the starting material and changing to hexanes/ethyl acetate (10/1) to isolate the product yielded 0.36 g of alkyne **3.30** (28%) as a pale yellow oil: IR (neat) 2955, 2917**,** 1740, 1720, 1436, 1322, 1257, 1222, 1079 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.05−5.01 (m, 1H), 4.88 (t, *J* = 7.7 Hz, 1H), 3.75 (s, 9H), 2.93 (s, 2H), 2.80 (d, *J* = 7.6 Hz, 2H), 2.07−2.01 (m, 4H), 1.69 (s, 3H), 1.65 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7 (2C), 153.4, 140.7, 131.4, 123.7, 116.5, 83.5, 74.9, 56.6, 52.6 (2C), 52.3, 39.7, 30.7, 26.1, 25.4, 22.4, 17.4, 15.9; MS *m/e* 332 $(M - MeOH)^+$, 317, 304, 289, 273, 203, 175, 145, 109, 69; HRMS exact mass calcd for $C_{19}H_{24}O_5$ $(M - MeOH)^+$: 332.1623, found: 332.1609.



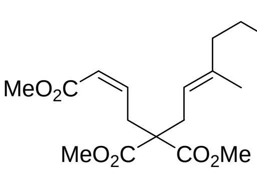
5-(3,7-Dimethylocta-2*E*,6-dienyl)-5-methoxycarbonylhex-2*Z*-enedioic acid dimethyl ester (3.31): To a solution of alkyne **3.30** (0.34 g, 0.92 mmol) and quinoline (0.34 mL, 2.85 mmol) in hexanes (26 mL) was added Lindlar's catalyst (0.17 g). The suspension was stirred and the flask was fitted with a three way stopcock with one outlet to a hydrogen balloon and the other to a vacuum pump. The mixture was stirred vigorously and evacuated until the suspension bubbled at which point it was released to the hydrogen balloon. The purging of the reaction mixture with hydrogen was repeated an additional two times. After stirring for 12 h under the hydrogen atmosphere, the mixture was filtered through celite, washing with an additional hexanes (15 mL). The filtrate was concentrated *in vacuo* to give the title compound and purified over silica gel eluting the column with hexanes/ethyl acetate (10/1) to give 0.28 g of *Z*-alkene **3.31** (83%) as a clear pale yellow oil: IR (neat) 2953, 2923, 2856, 1736, 1649, 1438, 1288, 1206, 1174, 1078 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.20 (dt, *J* = 7.2, 11.6 Hz, 1H), 5.86 (dt, *J* = 1.8, 11.6 Hz, 1H), 5.02−4.94 (m, 2H), 3.68 (s, 3H), 3.67 (s, 6H), 3.22 (dd, *J* = 1.7, 7.2 Hz, 2H), 2.61 (d, *J* = 7.5 Hz, 2H), 2.02−1.95 (m, 4H), 1.64 (s, 3H), 1.56 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2 (2C), 166.2, 144.0, 139.6, 131.4, 123.9, 121.5, 117.3, 57.5, 52.3 (2C), 51.0, 39.8, 32.1 (2C), 26.4, 25.5, 17.5, 16.1; MS *m/e* 389 $(M + Na)^+$, 276; HRMS exact mass calcd for $C_{20}H_{30}O_6Na$ $(M + Na)^+$: 389.1940, found: 389.1924.



5-(6,7-Dihydroxy-3,7-dimethyloct-2*E*-enyl)-5-methoxycarbonylhex-2*Z*-enedioic acid dimethyl ester (3.31): To a mixture of *t*-BuOH (3.8 mL) and water (3.8 mL), was added AD-Mix α (1.06 g). The mixture was stirred vigorously and $CH_3SO_2NH_2$ (0.072 g, 0.76 mmol) was added. The entire mixture was cooled to 0 °C and malonate **3.31** (0.28 g, 0.76 mmol) was added and the mixture was vigorously stirred for 14 h. Sodium sulfite (1.14 g) was added and the mixture was warmed to room temperature and stirred for 1 h. Ethyl acetate (1 mL) was added to the mixture and after separation of the layers, the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were then washed with 2N KOH (5 mL) and dried over anhydrous $MgSO_4$. Filtration and solvent evaporation *in vacuo* yielded the title compound. Purification was carried out by flash chromatography on silica gel eluting with hexanes/ethyl acetate (10/1) yielded 0.27 g (89%) of diol **3.32** as a thick yellow oil: IR (neat) 3530, 2954, 1735, 1720, 1648, 1438, 1325, 1290, 1209, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.17 (dt, *J* = 7.4, 11.6 Hz, 1H), 5.89 (dt, *J* = 1.9, 11.6 Hz, 1H), 5.07 (t, *J* = 7.2 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 6H), 3.37 (dd, *J* = 1.6, 7.6 Hz, 2H), 3.20 (dd, *J* = 1.8, 6.6 Hz, 1H), 2.64 (d, *J* = 7.7 Hz, 2H), 2.53 (br d, *J* = 7.7 Hz, 1H), 2.26 (br s, 1H), 2.19−2.14 (m, 2H), 1.66−1.56 (m, 1H), 1.59 (s, 3H), 1.47−1.34 (m, 1H), 1.20 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3 (2C), 166.4, 144.1, 139.3, 121.4, 117.9, 76.9, 72.8, 57.4, 52.4 (2C), 51.1, 36.4, 32.0, 31.9, 28.9, 25.7, 23.4, 15.8; MS *m/e* 423 $(M + Na)^+$; HRMS exact mass calcd for $C_{20}H_{32}O_8Na$ $(M + Na)^+$ 423.1995, found 423.1992.

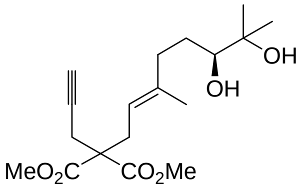


5-Methoxycarbonyl-5-(3-methyl-6-oxohex-2*E*-enyl)hex-2*Z*-enedioic acid dimethyl ester (3.33): THF (3mL) and water (1 mL) was added to the diol **3.32** (0.27 g, 0.69 mmol) and the resulting mixture was stirred vigorously until the solution was homogeneous. $NaIO_4$ (0.15 g, 0.69 mmol) was added in small portions over 30 min. The flask was stoppered and the mixture was stirred for 17 h during which time a white solid precipitated. The reaction mixture was poured into water (5 mL) and Et_2O (5 mL). After separation of the layers, the aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organic layers were dried over anhydrous $MgSO_4$. Filtration and solvent evaporation *in vacuo* provided the title compound. Purification over silica gel eluting with hexanes/ethyl actetate (3/1) yielded 0.20 g (85%) of aldehyde **3.33** as a clear, pale yellow oil: IR (neat) 2954, 1732, 1650, 1438, 1412, 1289, 1207, 816 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.27 (t, *J* = 1.6 Hz, 1H), 6.16 (dt, *J* = 7.2, 11.6 Hz, 1H), 5.87 (dt, *J* = 1.7, 11.6 Hz, 1H), 5.07 (t, *J* = 7.6 Hz, 1H), 3.72 (s, 9H), 3.25 (dd, *J* = 1.8, 7.2 Hz, 2H), 2.63 (d, *J* = 7.4 Hz, 2H), 2.51 (td, *J* = 1.4, 7.7 Hz, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 1.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 171.0 (2C), 166.1, 143.6, 137.6, 121.6, 118.4, 57.3, 52.3 (2C), 50.9, 41.9, 32.0, 31.9, 31.7, 16.1; MS *m/e* 363 $(M + Na)^+$; HRMS exact mass calcd for $C_{17}H_{24}O_7Na$: 363.1420, found: 363.1413.

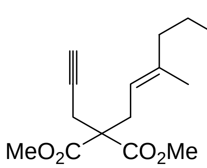


5-(7-Iodo-3-methylhepta-2*E*,6*Z*-dienyl)-5-methoxycarbonylhex-2*Z*-enedioic acid dimethyl ester (3.1): To a stirred suspension of (iodomethyl)triphenylphosphonium iodide **3.27** (0.63 g, 1.18 mmol) in THF (2.5 mL) was added NaHMDS (1M solution in THF, 1.18 mL, 1.18 mmol). The resulting suspension was stirred at room temperature for 30 min during which time it turned to a clear dark red solution. The mixture was cooled to –78 °C and to this was added the aldehyde **3.33** (0.20 g, 0.59 mmol) in THF (1 mL). The reaction was removed from the cold bath, warmed to room temperature and stirred for 1 h. The crude reaction mixture was then filtered through a short column of silica gel eluting with ether. Solvent evaporation and purification over silica gel eluting with hexanes/ethyl acetate (8/1 to 6/1) yielded 0.10 g (37%) of iodide **3.1** as a clear, light brown oil: IR (neat) 2951, 1732, 1650, 1438, 1287, 1207, 1174; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23−6.08 (m, 3H), 5.87 (dt, *J* = 1.7, 11.7 Hz, 1H), 5.04 (t, *J* = 7.6 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 6H), 3.27 (dd, *J* = 1.7, 7.1 Hz, 2H), 2.66 (d, *J* = 7.6 Hz, 2H), 2.26−2.19 (m, 2H), 2.11 (t, *J* = 7.1 Hz, 2H), 1.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2 (2C), 166.2, 143.9, 140.5, 138.5, 121.7, 118.3, 82.5, 57.5, 52.4 (2C), 51.1, 37.9, 33.0, 32.2 (2C), 16.1; MS *m/e* 433 $(M - MeO)^+$, 404, 373, 365, 333, 205, 173, 167, 145, 117, 91, 79, 59 ; HRMS exact mass calcd for $C_{17}H_{22}IO_5$ $(M^+ - MeO)^+$ 433.0512, found 433.0492.

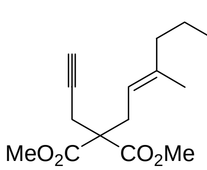
5.4.3 Synthesis of Precursor 3.4.



2-(6*S*,7-Dihydroxy-3,7-dimethyloct-2*E*-enyl)-2-prop-2-ynylmalonic acid dimethyl ester (3.34): To a mixture of *t*-BuOH (20 mL) and water (20 mL), was added AD-Mix α (5.64 g). The mixture was stirred vigorously and $CH_3SO_2NH_2$ (0.38 g, 4.03 mmol) was added. The entire mixture was cooled to 0 °C and malonate **3.31** (1.23g, 4.03 mmol) was added and the mixture was vigorously stirred for 14 h. Sodium sulfite (6.05 g) was added and the mixture was warmed to room temperature and stirred for 1 h. Ethyl acetate (10 mL) was added to the mixture and after separation of the layers, the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were then washed with 2N KOH (10 mL) and dried over anhydrous $MgSO_4$. Filtration and solvent evaporation *in vacuo* yielded the title compound. Purification was carried out by flash chromatography on silica gel eluting with hexanes/ethyl acetate (15/1 to 1/1 to 2/1) yielded 1.24 g (90%) of diol **3.34** as a clear pale yellow oil: IR (thin film) 3434, 3291, 2955, 1732, 1436, 1385, 1294, 1225, 1072 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.93 (t, *J* = 7.6 Hz, 1H), 3.68 (s, 6H), 3.23 (br d, *J* = 9.9 Hz, 1H), 2.73 (d, *J* = 8.7 Hz, 2H), 2.71 (d, *J* = 2.6 Hz, 2H), 2.21−2.15 (m, 1H), 2.07−2.01 (m, 1H), 1.98 (t, *J* = 2.4 Hz, 1H), 1.60 (s, 3H), 1.55−1.45 (m, 1H), 1.39−1.29 (m, 1H), 1.13 (s, 3H), 1,09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4 (2C), 140.2, 117.3, 78.9, 77.5, 72.9, 71.3, 57.0, 52.6 (2C), 36.8. 30.5, 29.4, 26.1, 23.1, 22.4, 15.9; MS *m/e* 363 $(M + Na)^+$; HRMS exact mass calcd for $C_{18}H_{28}O_6Na$ $(M + Na)^+$ 363.1784, found 363.1762.



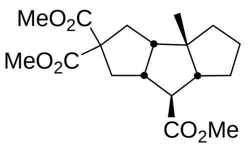
2-(3-Methyl-6-oxohex-2*E*-enyl)-2-prop-2-ynylmalonic acid dimethyl ester (3.35): THF (15 mL) and water (5 mL) was added to the diol **3.33** (1.11g, 3.27 mmol) and the resulting mixture was stirred vigorously until the solution was homogeneous. $NaIO_4$ (0.77 g, 3.6 mmol) was added in small portions over 30 min. The flask was stoppered and the mixture was stirred for 17 h during which time a white solid precipitated. The reaction mixture was poured into water (15 mL) and Et_2O (15 mL). After separation of the layers, the aqueous layer was extracted with Et_2O (3 x 15 mL) and the combined organic layers were dried over anhydrous $MgSO_4$. Filtration and solvent evaporation *in vacuo* provided the title compound. Purification over silica gel eluting with hexanes/ethyl actetate (3/1) yielded 0.90 g (97%) of aldehyde **3.35** as a clear, colorless oil: IR (thin film) 3282, 2955, 2817, 1736, 1436, 1322, 1291, 120, 1057 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ; 9.69 (s, 1H), 4.93 (t, *J* = 7.5 Hz, 1H), 3.69 (s, 6H), 2.74 (d, *J* = 8.0 Hz, 2H), 2.71 (d, *J* = 2.2 Hz, 2H), 2.47 (t, *J* = 7.1 Hz, 2H), 2.28 (t, *J* = 7.3 Hz, 2H), 1.98 (t, *J* = 2.5 Hz, 1H), 1.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 170.1, 138.4, 118.1, 78.9, 71.3, 56.9, 52.6 (2C), 41.9, 31.9, 30.5, 22.5, 16.2; MS *m/e* 303 $(M + Na)^+$; HRMS exact mass calcd for $C_{15}H_{20}O_5Na$ $(M + Na)^+$ 303.1193, found 303.1208.



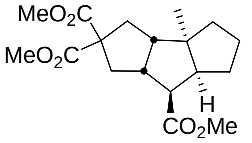
2-(7-Iodo-3-methylhepta-2*E*,6*Z*-dienyl)-2-prop-2-ynylmalonic acid dimethyl ester (3.4): To a stirred suspension of (iodomethyl)triphenylphosphonium iodide **3.27** (1.70 g, 1.60 mmol) in THF (7 mL) was added NaHMDS (1M solution in THF, 3.20 mL, 3.20 mmol). The resulting suspension was stirred at room temperature for 30 min during which time it turned to a clear dark red solution. The mixture was cooled to –78 °C and to this was added aldehyde **3.35** (0.44 g, 1.60 mmol) in THF (1 mL). The reaction was removed from the cold bath, warmed to room temperature and stirred for 1 h. The crude reaction mixture was then filtered through a short column of silica gel eluting with ether. Solvent evaporation and purification over silica gel eluting the column with hexanes/ethyl acetate (15/1) provided 0.37g , after recycling the mixed fractions once, of vinyl iodide **3.4** (57%) as a dark brown oil: IR (thin film) 3295, 2995, 2951, 2849, 1737, 1435, 1321, 1290, 1202, 1056 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.21 (dt, *J* = 1.2, 7.3 Hz, 1H), 6.11 (dt, *J* = 6.7, 7.1 Hz, 1H), 4.95 (tq, J = 1.2, 7.7 Hz, 1H), 3.76 (s, 6H), 2.81 (d, *J* = 8.0 Hz, 2H), 2.79 (d, *J* = 2.7 Hz, 2H), 2.24 (ddt, *J* = 1.4, 6.1, 7.7 Hz, 2H), 2.12 (t, *J* = 6.9 Hz, 2H), 2.02 (t, *J* = 2.6 Hz, 1H), 1.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2 (2C), 140.4, 139.2, 117.8, 82.6, 79.0, 71.3, 56.9, 52.6 (2C), 37.8, 32.9, 30.5, 22.4, 16.0; MS *m/e* 427 $(M + Na)^+$; HRMS exact mass calcd for $C_{16}H_{21}O_4INa$ $(M + Na)^+$ 427.0382, found 427.0370.

5.4.4 Cyclization Reactions with Precursors 1.65, 3.1, 3.3 and 3.4

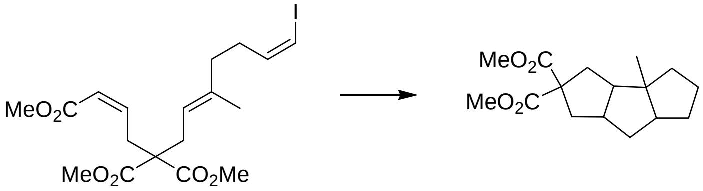
3β-Methyldecahydrocyclopenta[α]pentalene-2,2,7-tricarboxylic acid trimethyl ester (3.9 and 3.10): Cyclization of precursor **1.65** (0.05 g, 0.1 mmol) was carried according to method B. The reducing agent used was Bu_3SnH and the mixture was refluxed for 4 h. The crude reaction mixture which was subjected to a DBU[81] workup and subsequent column chromatography over silica gel eluting with hexanes/ethyl acetate (15/1) after 6 column volumes of hexanes to give 24 mg of a tin free cyclization mixture. This mixture was taken up in CH_2Cl_2 (15 mL) and cooled to 0 °C. The mixture was then vigorously stirred and *m*-CPBA (0.017 g, 0.1 mmol) was added. The reaction was stirred for 14 h and quenched with $NaHCO_3$ (15 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* The resulting oil was purified by column chromatography eluting with hexanes/ethyl acetate (15/1) to yield 0.018 g (52%) of a mixture of four isomeric tricyclic products **3.9/3.10/3.11/3.12** in a 47/39/6/8 ratio as determined by GC analysis. This mixture was then further purified by preparative GC which isolated the two major tricycles from the cyclization as pale yellow oils:



1st eluting on the GC *cis-syn-cis* isomer **3.9**: IR (film, CH_2Cl_2) 3054, 2964, 2928, 2860, 1728, 1440, 1275, 1256 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.73 (s, 3H), 3.68 (s, 3H), 2.89–2.86 (m, 1H), 2.57 (dd, J = 8.2, 14.0 Hz, 1H), 2.43–2.32 (m, 3H), 2.27 (t, J = 10.1 Hz, 1H), 2.05 (dd, J = 5.6, 14.0 Hz, 1H), 2.00 (t, J = 10.7 Hz, 1H), 1.77–1.68 (m, 4H), 1.21–1.26 (m, 2H) 1.09 (s, 3H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.8, 172.6, 172.5, 62.7, 59.8, 56.7, 54.8, 52.8, 52.7, 51.7 (2C), 48.4, 38.8, 36.3, 36.1, 30.0, 29.7 26.0; MS *m/e* 338, 320, 306, 278, 246, 218, 145, 67, 59 ; HRMS exact mass calcd for $C_{18}H_{26}O_6$ 338.1729, found 338.1713.

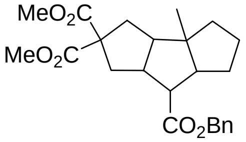


2nd eluting on the GC *cis-anti-cis* isomer **3.10***:* IR (film, CH_2Cl_2) 3055, 2968, 2930, 2858, 1730, 1440, 1275, 1256 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.72 (s, 3H), 3.67 (s, 3H), 2.97–2.91 (m, 1H), 2.82 (dd, J = 8.4, 11.2 Hz, 1H), 2.64 (dd, J = 7.9, 14.5 Hz, 1H), 2.34–2.29 (m, 2H), 2.24 (dt, J = 7.5, 12.5 Hz, 1H), 2.05–2.00 (m, 2H) 1.77−1.74 (m, 4H), 1.26–1.24 (m, 2H), 1.09 (s, 3H); MS *m/e* 338, 320, 306, 278, 246, 218, 145, 67, 59 ; HRMS exact mass calcd for $C_{18}H_{26}O_6$ 338.1729, found 338.1713.

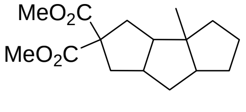


3β-Methyldecahydrocyclopenta[α]pentalene-2,2,7-tricarboxylic acid trimethyl ester 3.44/3.45/3.46.3.47: Cyclization of precursor **3.1** (0.05 g, 0.1 mmol) according to method B using Bu_3SnH as the reducing agent for 4 h gave a crude reaction mixture. Column chromatography over silica gel eluting with hexanes/ethyl acetate (15/1) after 6 column volumes of hexanes to give 29 mg of a tin free cyclization mixture. This mixture was taken up in CH_2Cl_2 (15 mL) and cooled to 0 °C. The mixture was then vigorously stirred and *m*-CPBA (0.021 g, 0.09 mmol) was added. The reaction was stirred for 14 h and quenched with $NaHCO_3$ (15 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* The resulting oil was purified by column chromatography eluting with hexanes/ethyl acetate (15/1) to yield 0.021 g (62%) of a mixture of four isomeric tricyclic products **3.9/3.10/3.11/3.12** in a 51/40/8/1 ratio as determined by GC analysis.

3β-Methyldecahydrocyclopenta[α]pentalene-2,2,7-tricarboxylic acid trimethyl ester

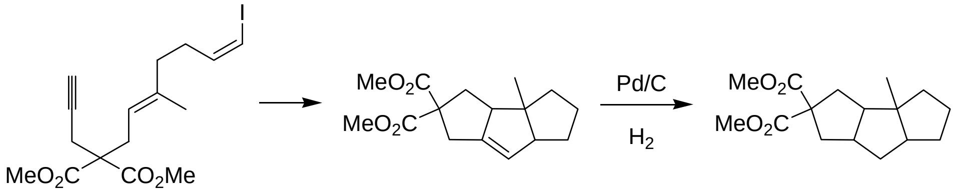


3β-Methyldecahydrocyclopenta[α]pentalene-2,2,7-tricarboxylic acid 7-benzyl ester 2,2-dimethyl ester (3.36/3.37/3.38/3.39): Cyclization of precursor **3.2** (66 mg, 0.12 mmol) was carried out according to method B. Bu_3SnH was used as the reducing agent in benzene (60 mL). The solution was refluxed for 4 h and the crude reaction mixture which was subjected to a DBU workup. Subsequent column chromatography over silica gel eluting with hexanes/ethyl acetate (15/1) after 6 column volumes of hexanes gave 35 mg of a tin-free cyclization mixture. This mixture was then taken up in CH_2Cl_2 (15 mL) and cooled to 0 °C. The reaction was then vigorously stirred and *m*-CPBA (0.017 g, 0.1 mmol) was added. The reaction was stirred for 14 h and quenched with $NaHCO_3$ (15 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* The resulting oil was purified by column chromatography eluting with hexanes/ethyl acetate (15/1) to yield 25 mg (50% from **3.2**) of a mixture of four isomeric tricyclic products **3.36/3.37/3.38/3.39** in a 47/37/7/8 ratio as determined by GC.



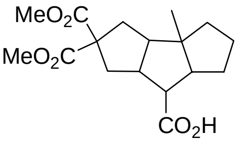
3β-Methyldecahydrocyclopenta[α]pentalene-2,2-dicarboxylic acid dimethyl ester (3.44/3.45/3.46/3.47): Cyclization of precursor **3.3** (50 mg, 0.12 mmol) was carried out according to method D using Bu_3SnH as the reducing agent with a total of 60 mL of benzene.

The reaction was refluxed for 4 h and the crude reaction mixture which was subjected to a DBU workup. Subsequent column chromatography over silica gel eluting with hexanes/ethyl acetate (20/1) after 6 column volumes hexanes to give a tin-free cyclization mixture. This mixture was then taken up in CH_2Cl_2 (15 mL) and cooled to 0 °C. The reaction was then vigorously stirred and *m*-CPBA (0.017g, 0.1 mmol) was added. The reaction was stirred for 14 h and quenched with $NaHCO_3$ (15 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* The resulting oil was purified by column chromatography eluting with hexanes/ethyl acetate (20/1) to yield 17 mg (52% from **3.3**) of a mixture of four isomeric tricyclic products **3.44/3.45/3.46/3.47** in a 42/38/14/6 ratio as determined by GC analysis.

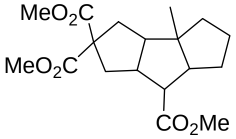


3β-Methyldecahydrocyclopenta[α]pentalene-2,2-dicarboxylic acid dimethyl ester (3.44/3.45): Cyclization of precursor **3.4** (40 mg, 0.10 mmol) was carried out according to method B using Bu_3SnH as the reducing agent with a total of 50 mL of benzene. The resulting solution was refluxed for 4 h. The crude reaction mixture was subjected to a DBU workup. Subsequent column chromatography over silica gel eluting with hexanes/ethyl acetate (20/1) after 6 column volumes hexanes to give 19 mg (70%) of a tin-free cyclization mixture. This mixture was then taken up in ethanol (1.0 mL) and to this solution was added Pd/C (10% by weight, 15 mg). The flask was fitted with a three way stopcock with one outlet to a hydrogen balloon and the other to an aspirator vacuum. The mixture was stirred vigorously and evacuated until the suspension bubbled at which point it was released to the hydrogen balloon. The purging of the reaction mixture with hydrogen was repeated an additional two times. After stirring for 12 h under the hydrogen atmosphere, the mixture was concentrated *in vacuo*. The resulting oil was purified by column chromatography over silica gel eluting with hexanes/ethyl acetate (20/1) to give 18 mg (93%) of a 67/34 mixture of tricycles **3.44** and **3.45**.

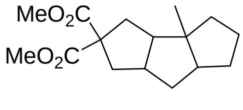
5.4.5 Tricyclic Relay Experiments



3β-Methyldecahydrocyclopenta[α]pentalene-2,2,7-tricarboxylic acid dimethyl ester (3.52): To a 42/35/8/15 mixture of **3.36/3.37/3.38/3.39** (25 mg, 0.06 mmol) in ethyl acetate (5 mL) was added Pd/C (10 wt% on carbon, 20 mg). The flask was fitted with a three way stopcock with one outlet to a hydrogen balloon and the other to an aspirator vacuum. The mixture was stirred vigorously and evacuated until the suspension bubbled at which point it was released to the hydrogen balloon. The purging of the reaction mixture with hydrogen was repeated an additional two times. After stirring for 12 h under the hydrogen atmosphere, the mixture was filtered through celite, washing with an additional 15 mL of ethyl acetate. The solvent was removed *in vacuo* to give 19 mg (99%) of the title acid which was used as such in the following reaction.

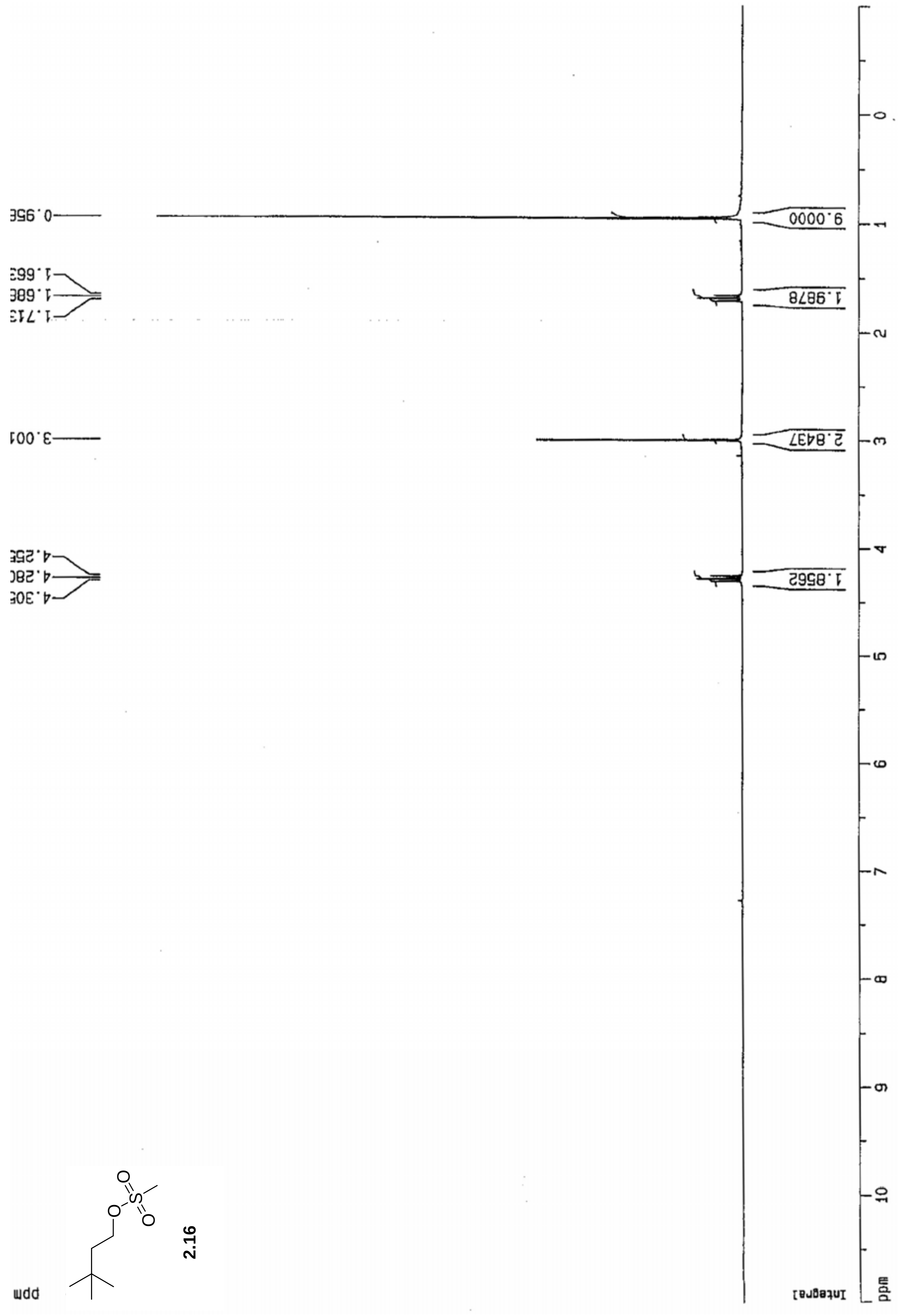


3β-Methyl-decahydro-cyclopenta[α]pentalene-2,2,7-tricarboxylic acid trimethyl ester: To a 42/35/6/15 diasteromeric mixture of acid **3.52** (10 mg, 0.030 mmol) in benzene (0.2 mL) and methanol (0.06 mL) was added TMSCHN$_2$ (0.02 mL, 2.0 M solution in hexanes, 0.04 mmol). The resulting solution was stirred for 1 h, concentrated *in vacuo* and purified by column chromatography over silica gel eluting with hexanes/ethyl acetate (15/1) to give 13 mg of the title tricycles **3.9/3.10/3.11/3.12** (51% from the benzyl ester mixture **3.36/3.37/3.38/3.39**) as a pale yellow oil. Spectral data for this mixture was identical to that previously synthesized.



3β-Methyldecahydrocyclopenta[α]pentalene-2,2-dicarboxylic acid dimethyl ester 3.44/3.45/3.47/?: A 42/35/6/15 diastereomeric mixture of acid **S19** (19 mg, 0.06 mmol) was taken up in benzene (0.4 mL) and treated with oxallyl chloride (0.06 mL, 0.69 mmol) and DMF (1 drop). The resulting solution was stirred at room temperature for 2 h and then concentrated *in vacuo*. The crude reaction mixture was then re-dissolved in benzene and concentrated *in vacuo* again. The crude acid chloride was taken up in benzene (0.3 mL) and added to a suspension of 2-mercaptopyridine-1-oxide sodium salt (11 mg, 0.07 mmol) and DMAP (2 mg, 0.01 mmol) in benzene (0.6 mL). The reaction was brought to reflux and allowed to do so for 20 min. The heat source was removed and a solution of AIBN (10 mg, 0.06 mmol) and Bu_3SnH (0.05 mL, 0.18 mmol) in benzene (0.3 mL) was added. The reaction was once again brought to reflux and kept there for 15 h, cooled, concentrated *in vacuo* and directly purified by column chromatography over silica gel eluting with hexanes/ethyl acetate (20/1) after five column volumes of hexanes to yield 7 mg of the title tricycles **3.44/3.45/3.47/?** (43% from the benzyl ester mixture **3.36/3.37/3.38/3.39**) as a pale yellow oil. It was only possible to match the retention times of three of the four products upon comparison to the authentically cyclized material. Unfortunately the identity of the fourth product in the decarboxylation remains unknown.

APPENDIX A: Spectra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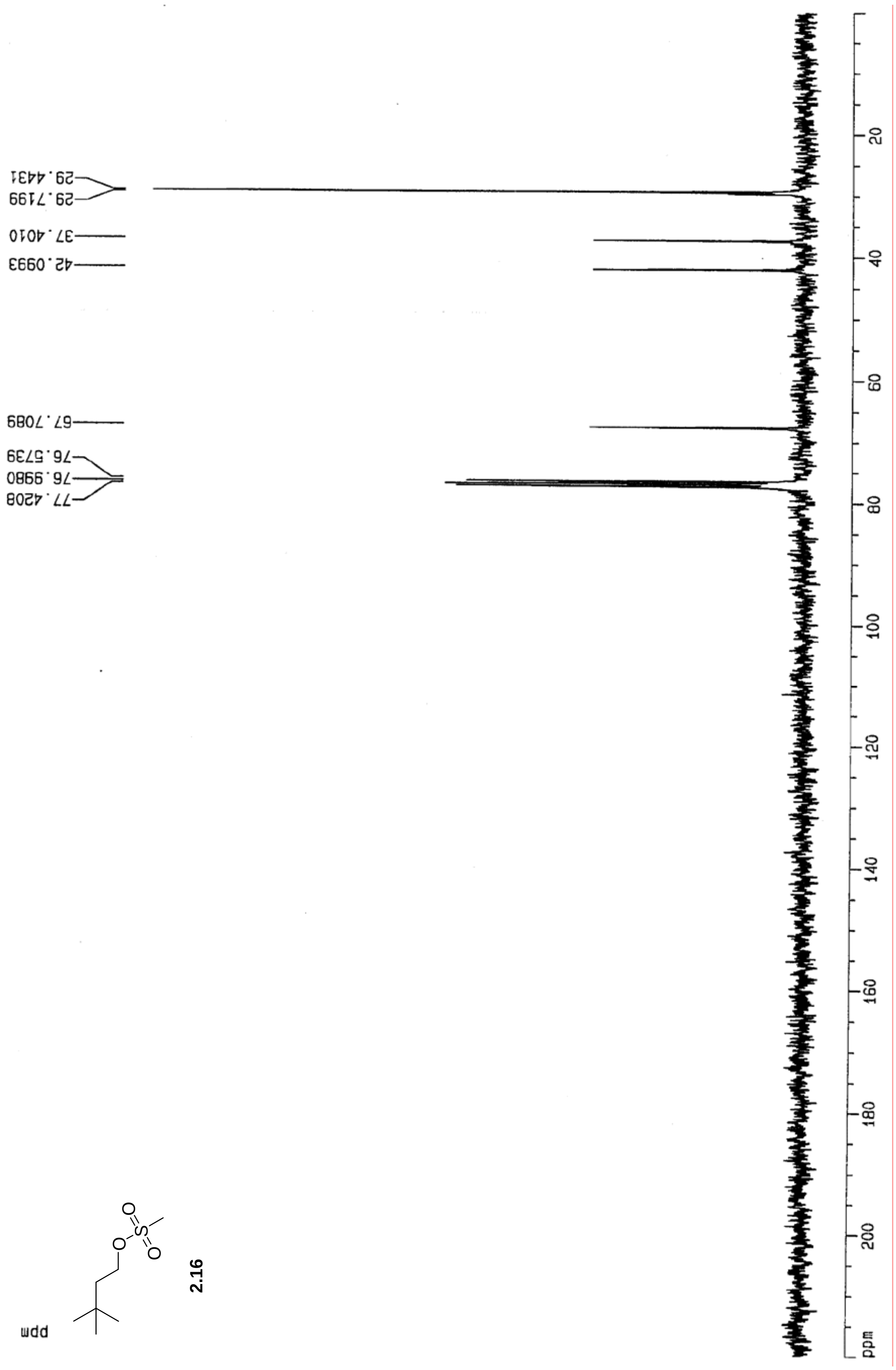
1.68
1.71
3.00
4.25
4.28
4.30
9.0000
1.9878
2.8437
1.8562
Integral
ppm
0
1
2
3
4
5
6
7
8
9
10
ppm
O
S
O
O

2.16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37.4010
42.0993
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76.5739
76.9980
77.4208
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20
40
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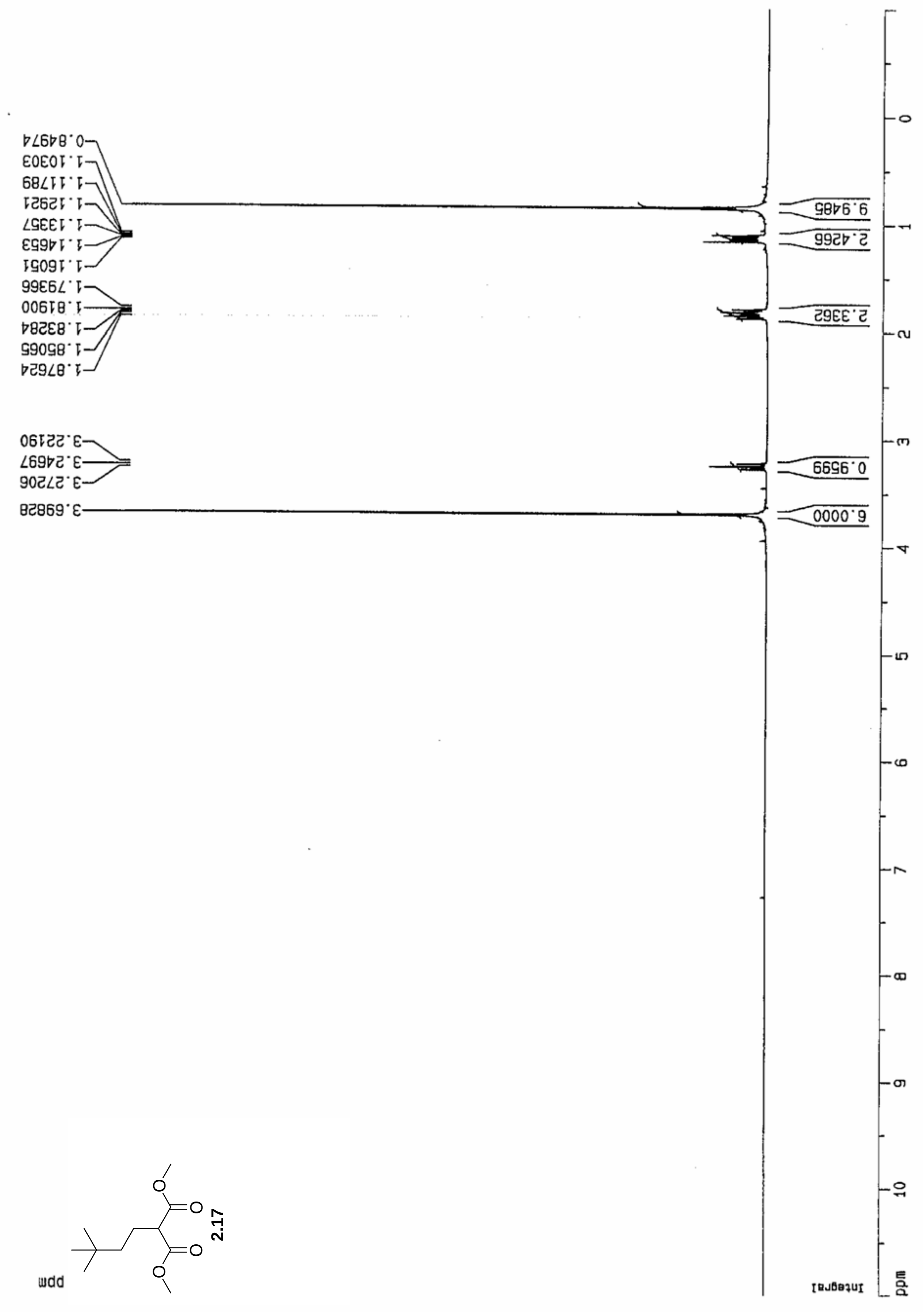
ppm
O
S
O
O

2.16



2.17

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1.10303
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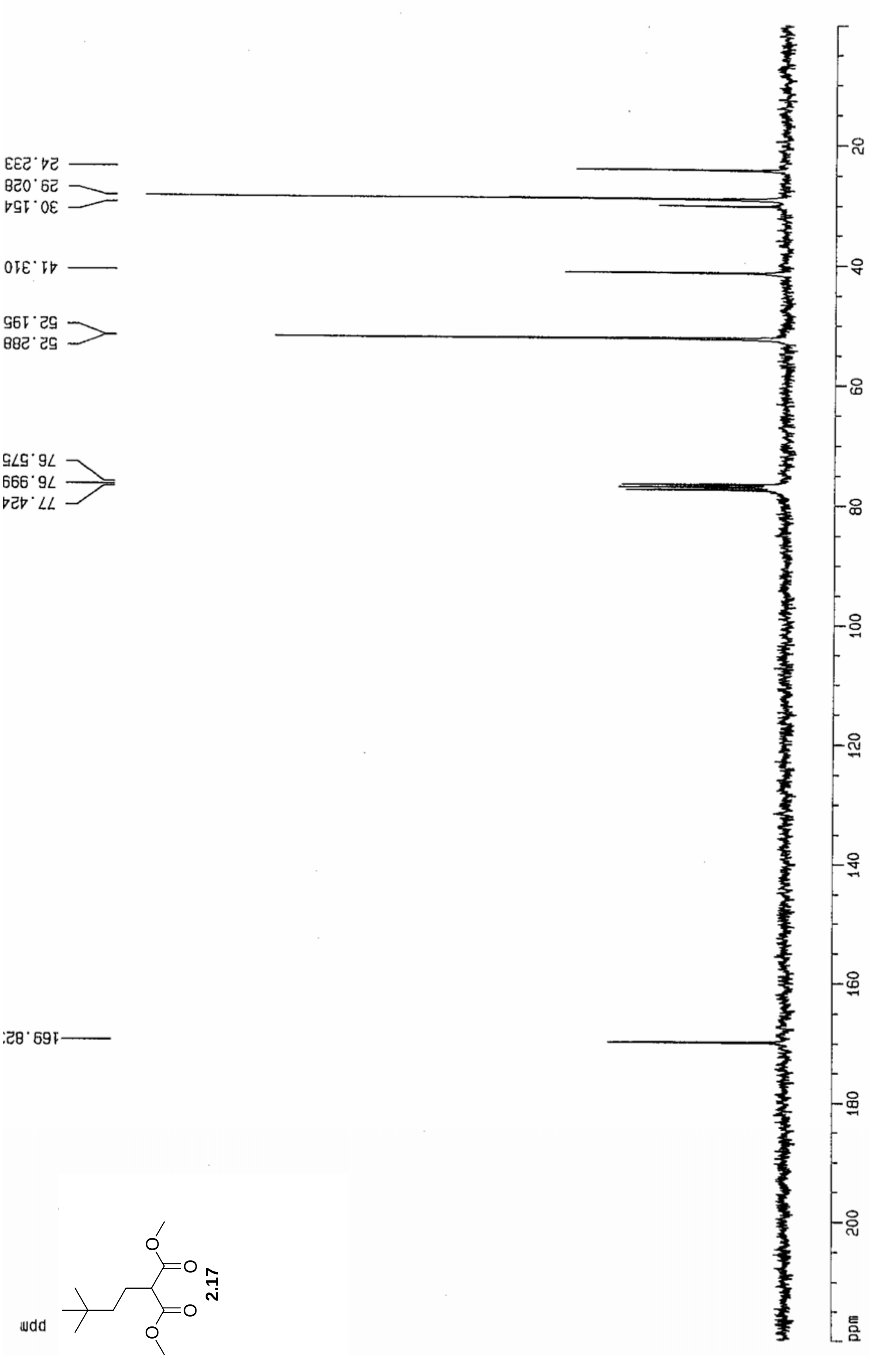
1.12921
1.13357
1.14653
1.16051
1.79366
1.81900
1.83284
1.85065
1.87624
3.22190
3.24697
3.27206
3.69828
9.9485
2.4266
2.3362
0.9599
6.0000
Integral
ppm
0
1
2
3
4
5
6
7
8
9
10
ppm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29.028
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41.310
52.195
52.288
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76.999
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169.82
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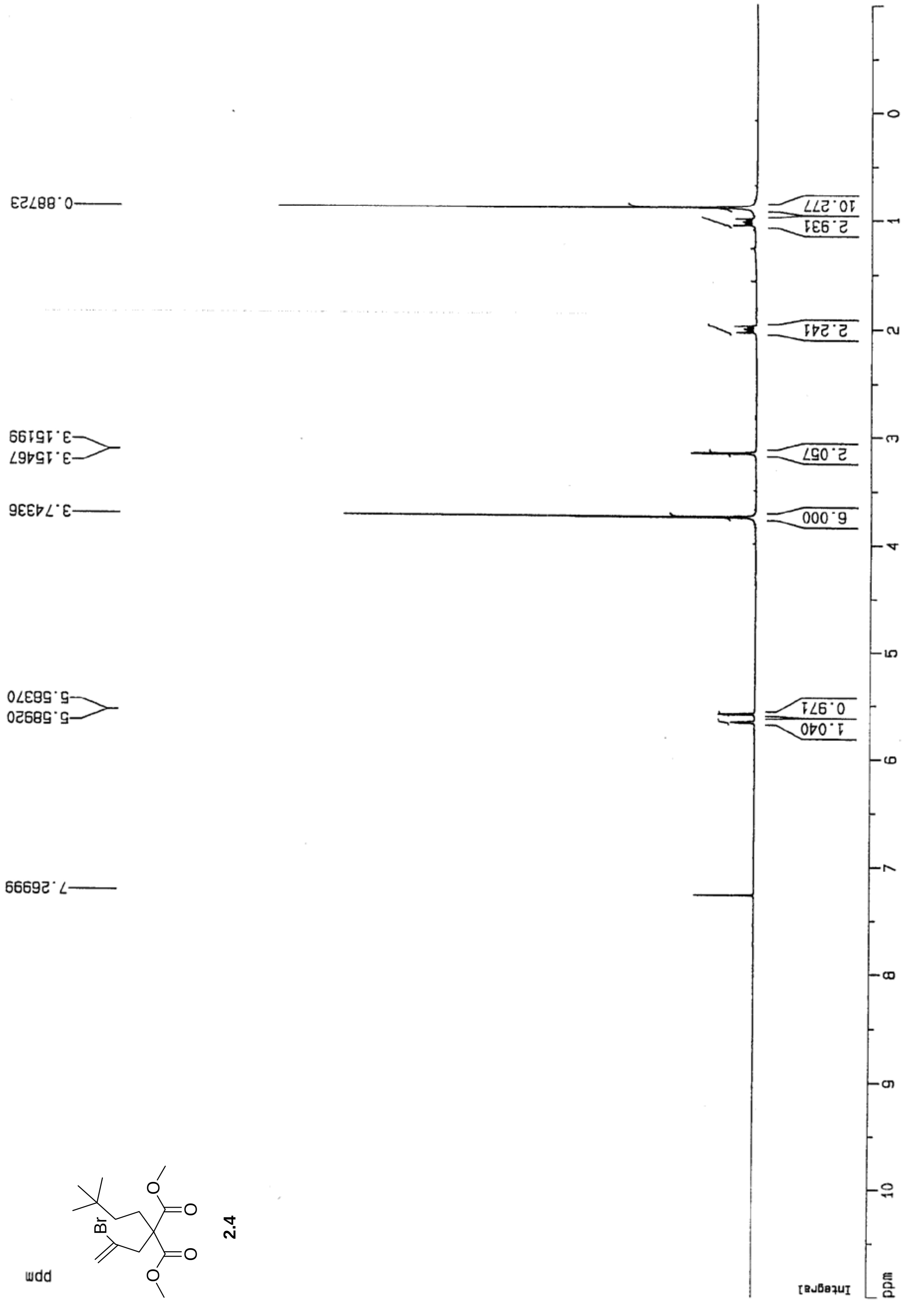
40
60
80
100
120
140
160
180
200
ppm
ppm

2.17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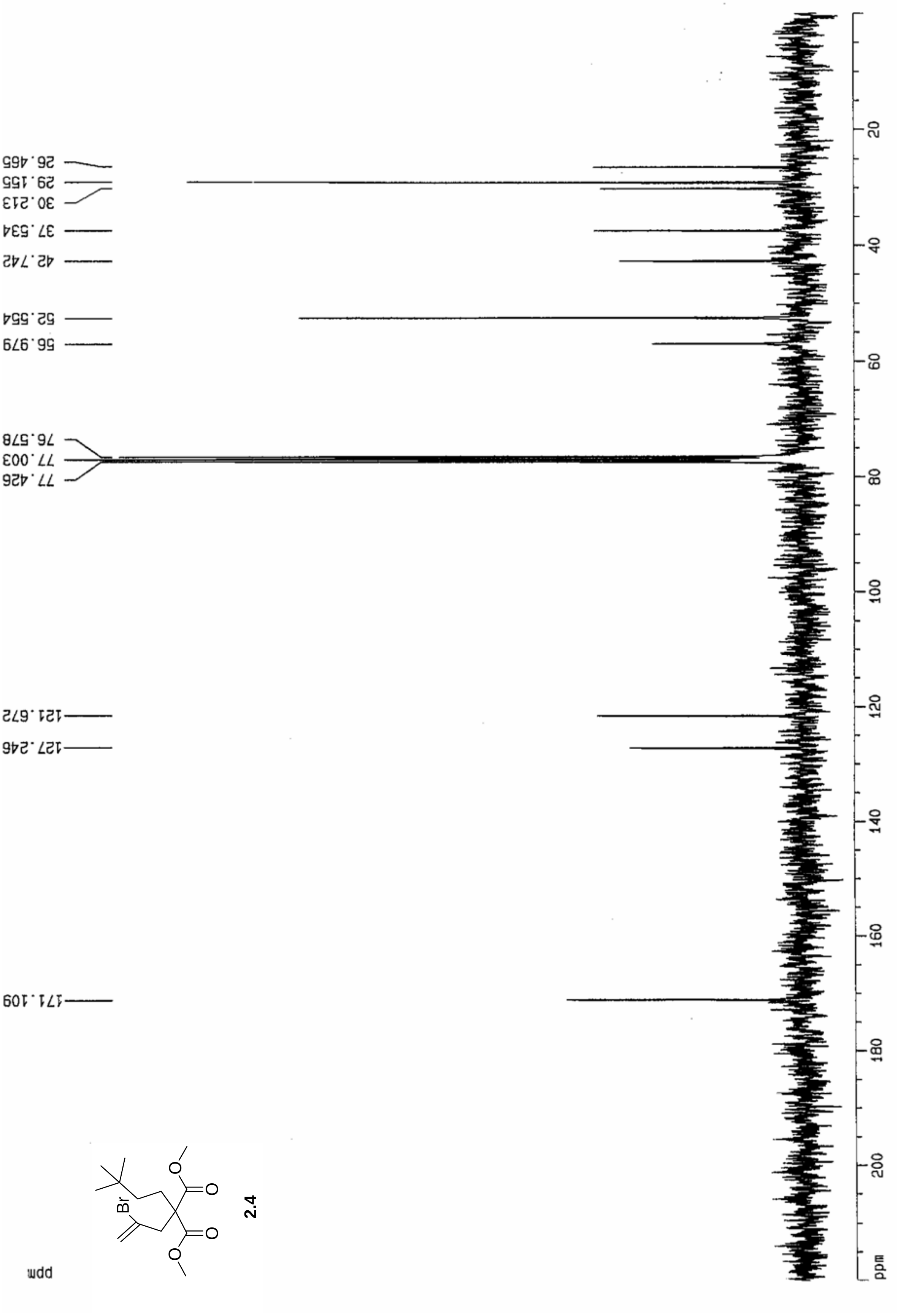
3.15199
3.15467
3.74336
5.58370
5.58920
7.26999
10.277
2.931
2.241
2.057
6.000
0.971
1.040
Integral
ppm
0
1
2
3
4
5
6
7
8
9
10
ppm
Br

2.4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52.554
56.979
76.578
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127.246
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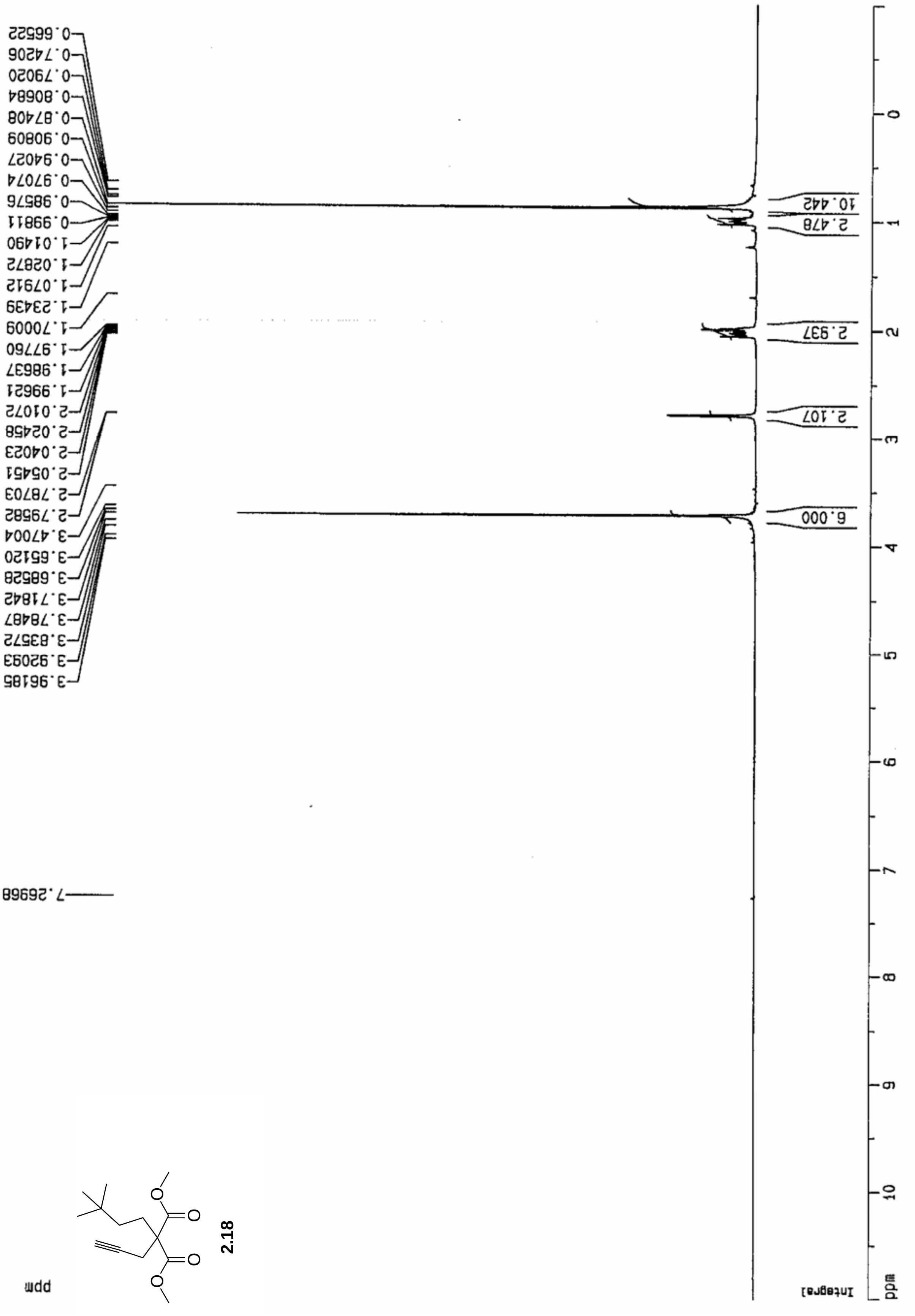
O
O
O
O
20
40
60
80
100
120
140
160
180
200
ppm

2.4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0.99811
1.01490
1.02872
1.07912
1.23439
1.70009
1.97760
1.98637
1.99621
2.01072
2.02458
2.04023
2.05451
2.78703
2.79582
3.47004
3.65120
3.68528
3.71842
3.78487
3.83572
3.92093
3.96185
7.26968
10.442
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2.937
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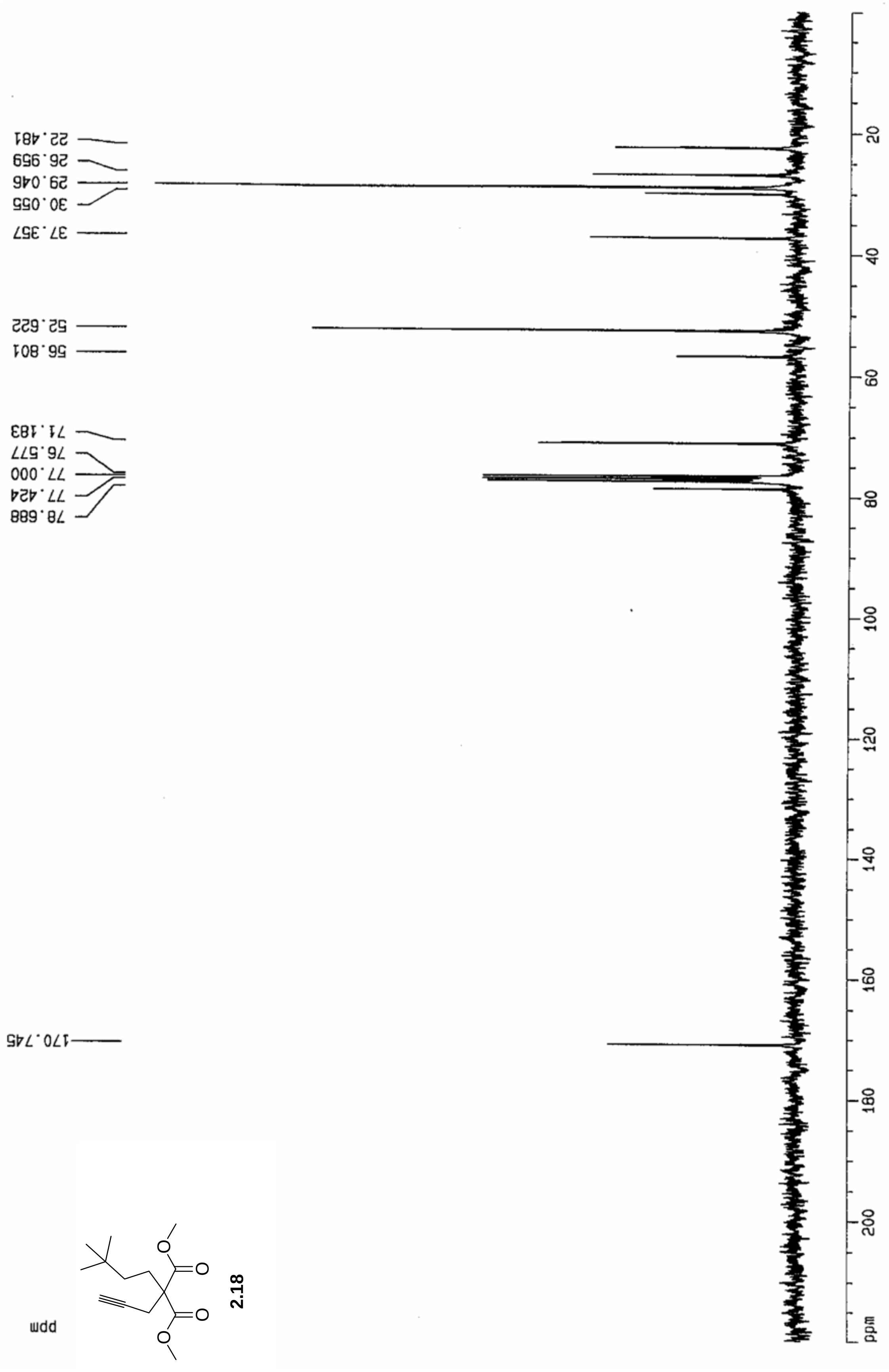
6.000
Integral
ppm
0
1
2
3
4
5
6
7
8
9
10
ppm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26.959
29.046
30.055
37.357
52.622
56.801
71.183
76.577
77.000
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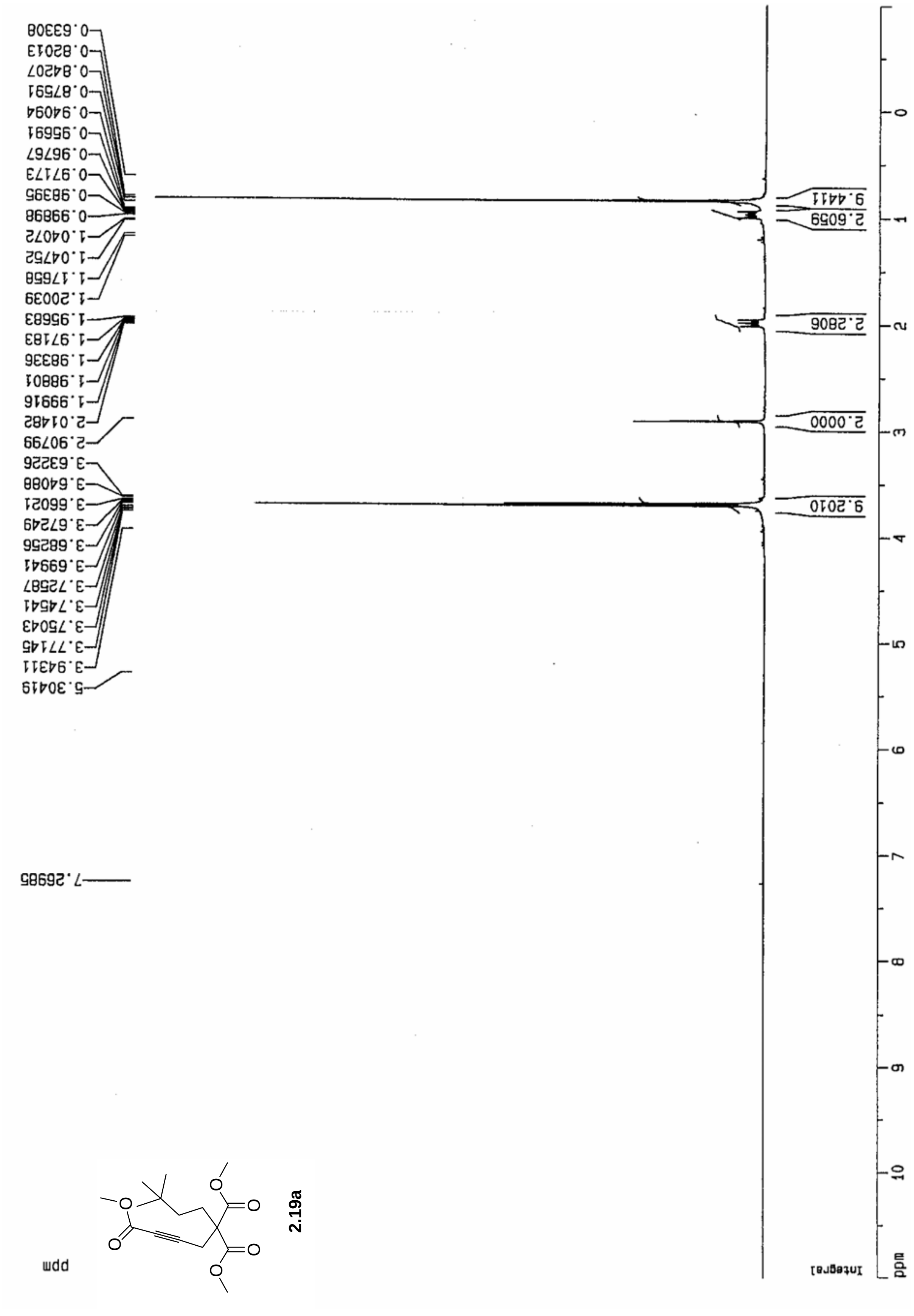
ppm
20
40
60
80
100
120
140
160
180
200
ppm

2.18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0.84207
0.87591
0.94094
0.95691
0.96767
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1.04072
1.04752
1.17658
1.20039
1.95683
1.97183
1.98336
1.98801
1.99916
2.01482
2.90799
3.63226
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3.77145
3.94311
5.30419
7.26985
ppm
9.4411
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Integral
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2
3
4
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6
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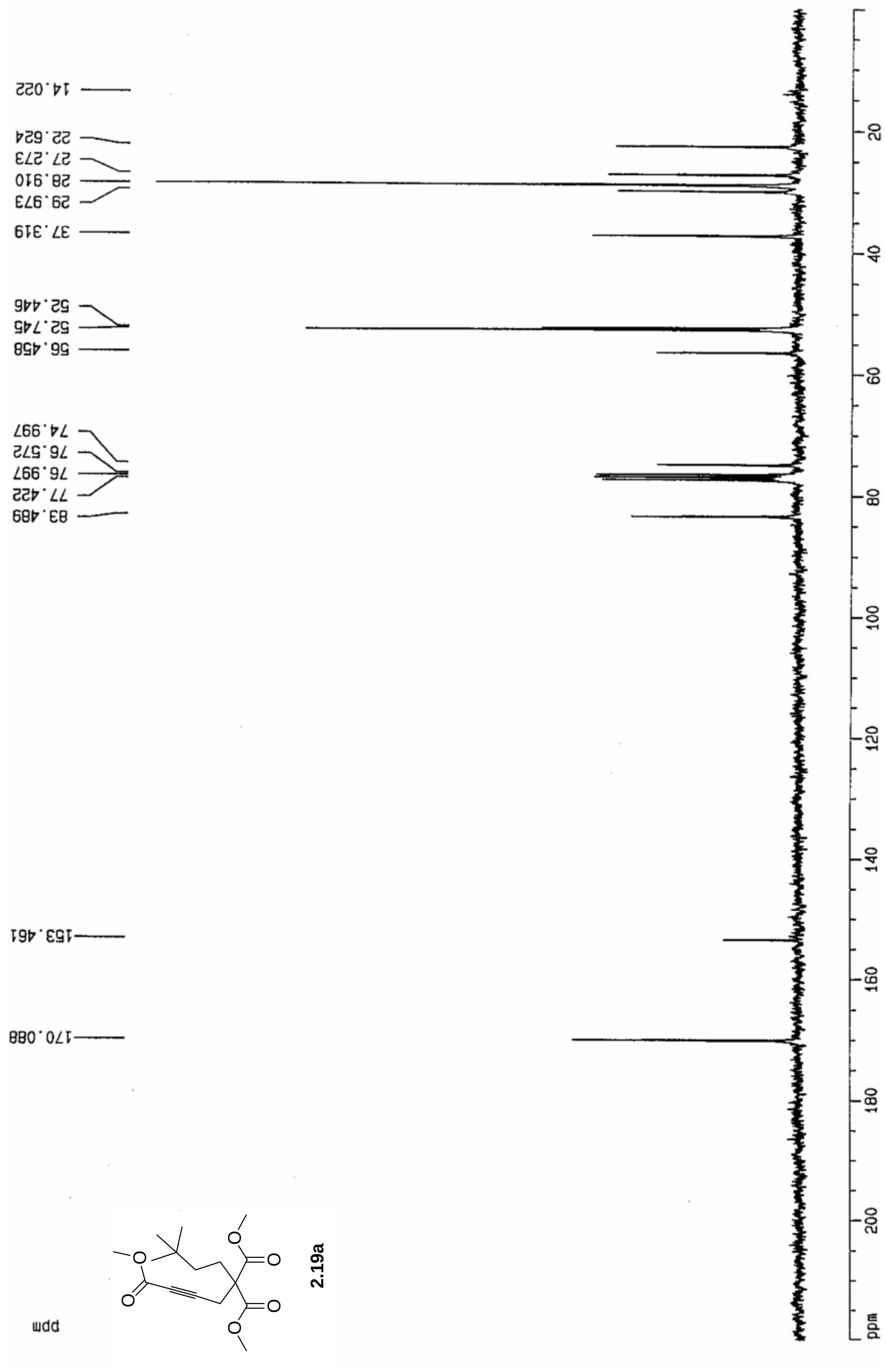
8
9
10
ppm

2.19a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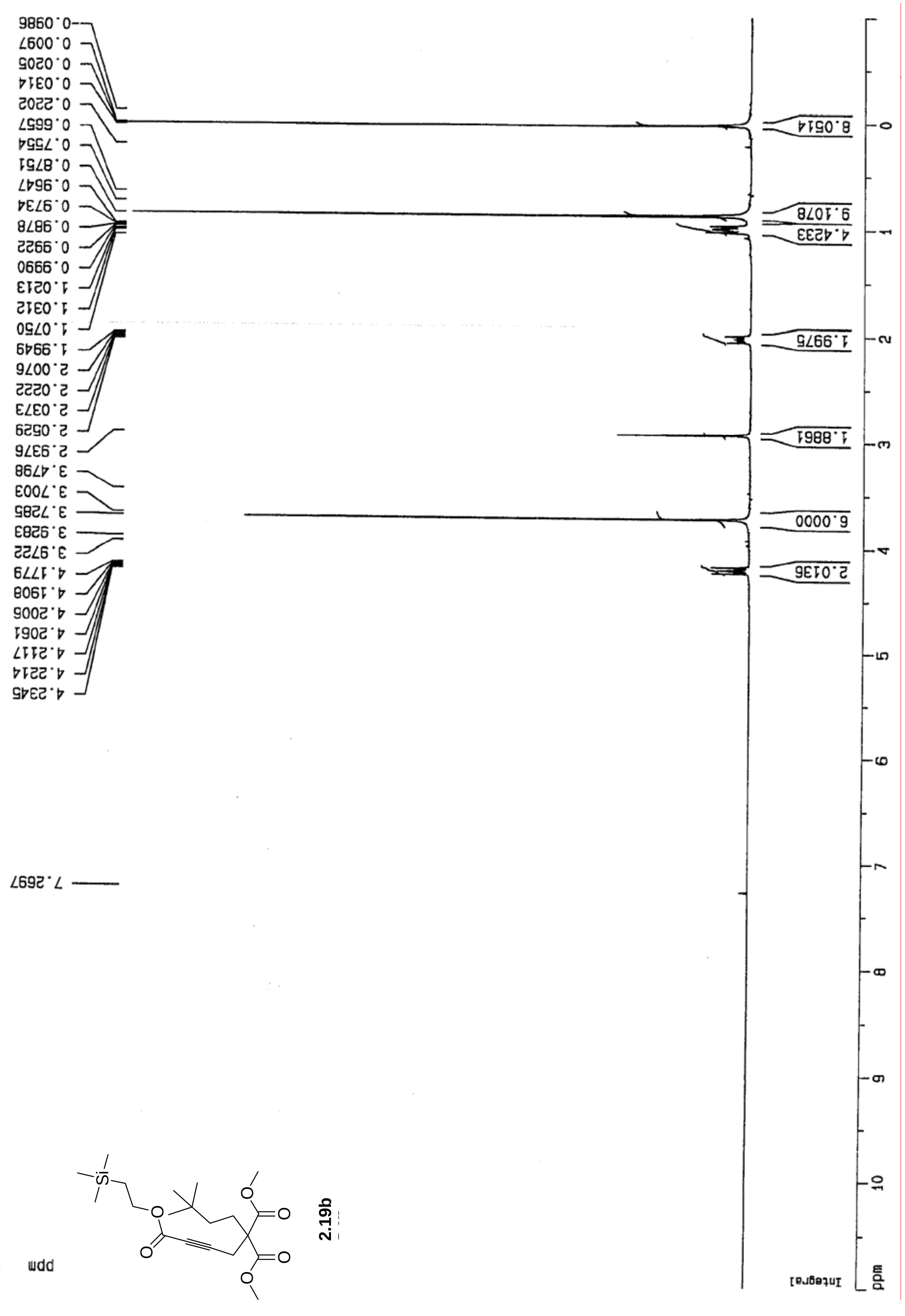
83.489
153.461
170.088
ppm
20
40
60
80
100
120
140
160
180
200
ppm

2.19a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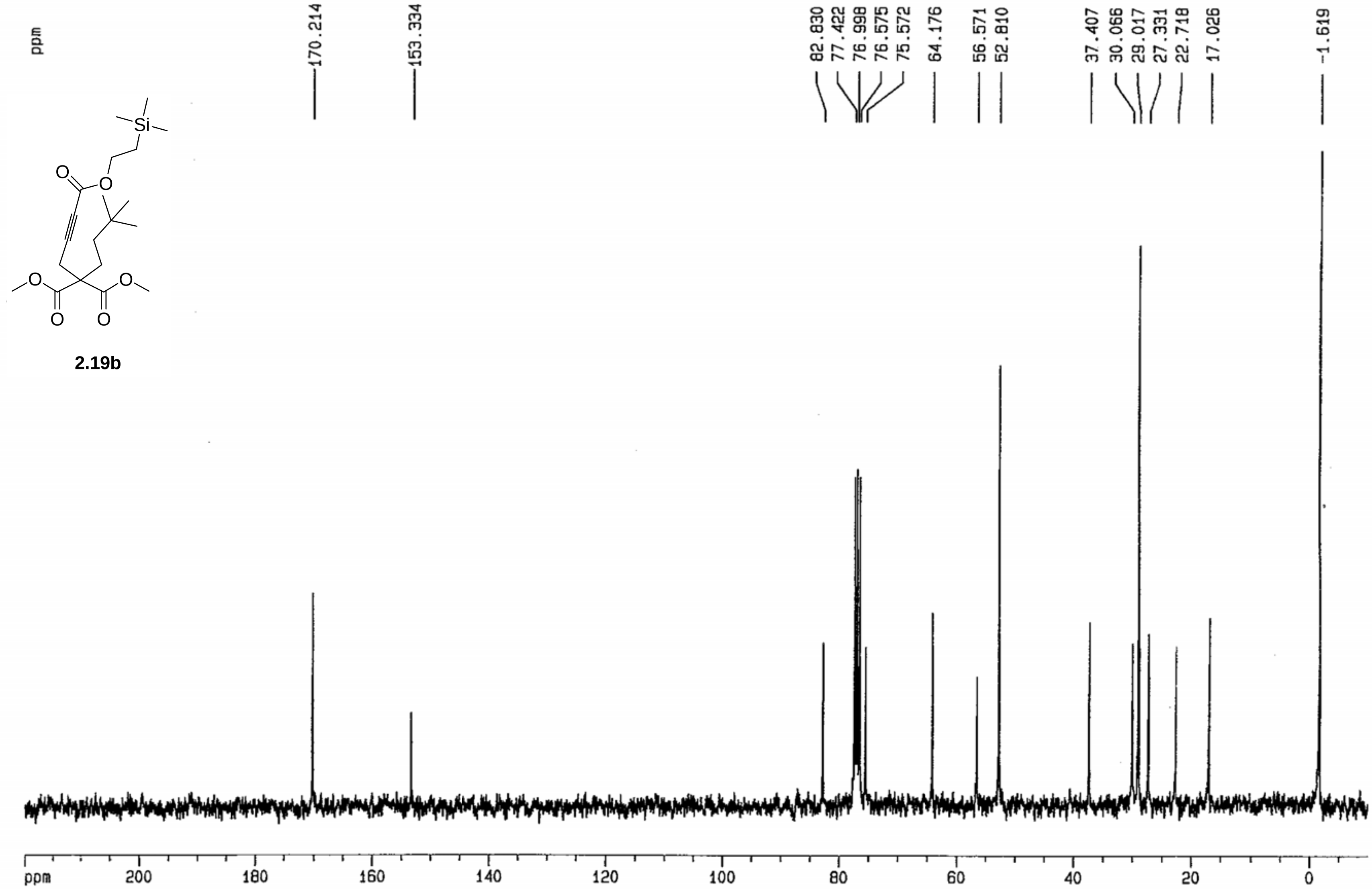
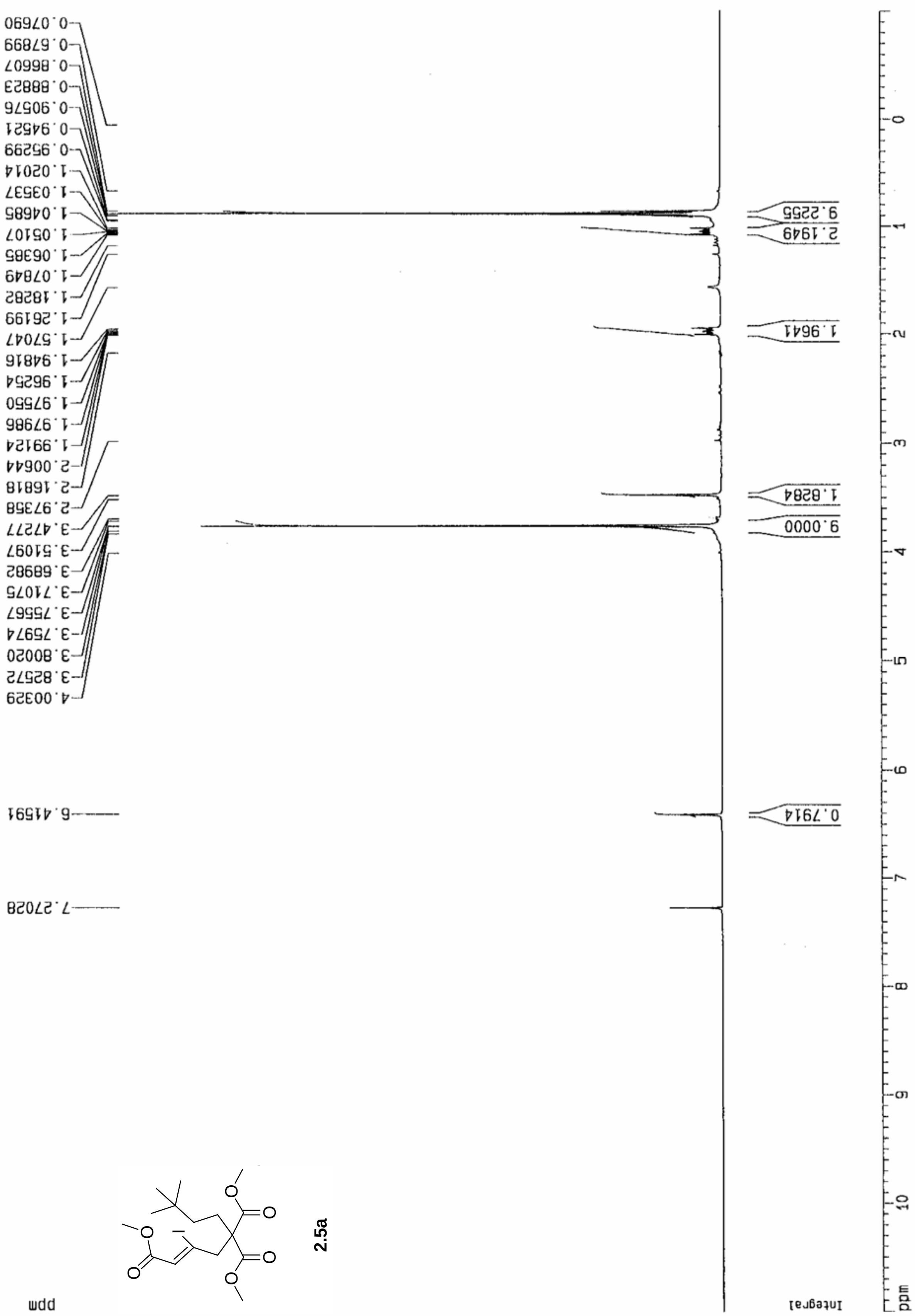
0.0097
0.0205
0.0314
0.2202
0.6657
0.7554
0.8751
0.9647
0.9734
0.9878
0.9922
0.9990
1.0213
1.0312
1.0750
1.9949
2.0076
2.0222
2.0373
2.0529
2.9376
3.4798
3.7003
3.7285
3.9283
3.9722
4.1779
4.1908
4.2006
4.2061
4.2117
4.2214
4.2345
7.2697
8.0514
9.1078
4.4233
1.9975
1.8861
6.0000
2.0136
Integral
ppm
0
1
2
3
4
5
6
7
8
9
10
Si
O
O
O
O
O
O

2.19b



2.19b

170.214
153.334
82.830
77.422
76.998
76.575
75.572
64.176
56.571
52.810
37.407
30.066
29.017
27.331
22.718
17.026
-1.619
ppm
200
180
160
140
120
100
80
60
40
20
0
Si
O


0.07690
0.67899
0.86607
0.88823
0.90576
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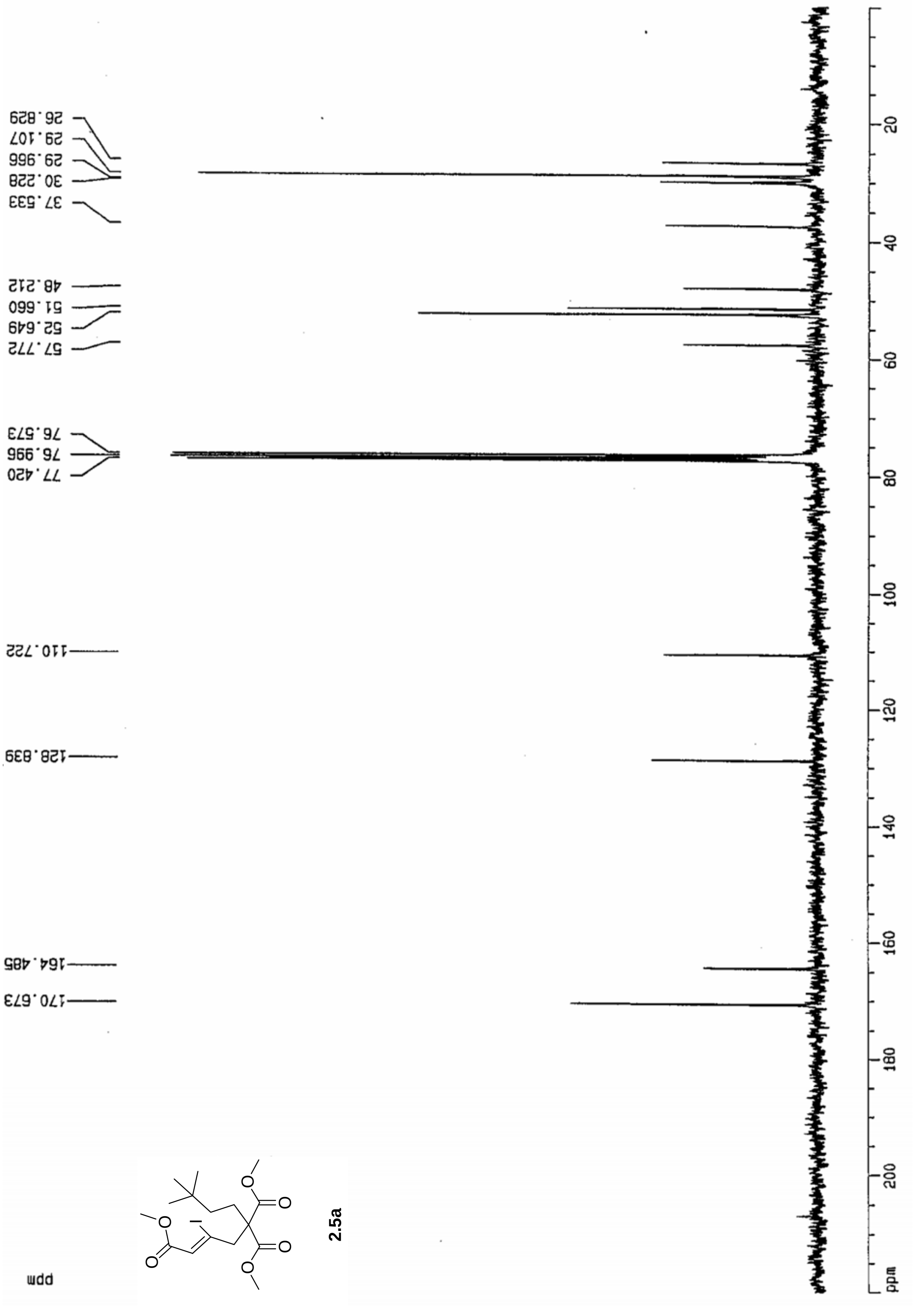
0.95299
1.02014
1.03537
1.04685
1.05107
1.06385
1.07849
1.18282
1.26199
1.57047
1.94816
1.96254
1.97550
1.97986
1.99124
2.00644
2.16818
2.97358
3.47277
3.51097
3.68982
3.71075
3.75567
3.75974
3.80020
3.82572
4.00329
6.41591
7.27028
9.2255
2.1949
1.9641
1.8284
9.0000
0.7914
Integral
ppm
0
1
2
3
4
5
6
7
8
9
10
ppm

2.5a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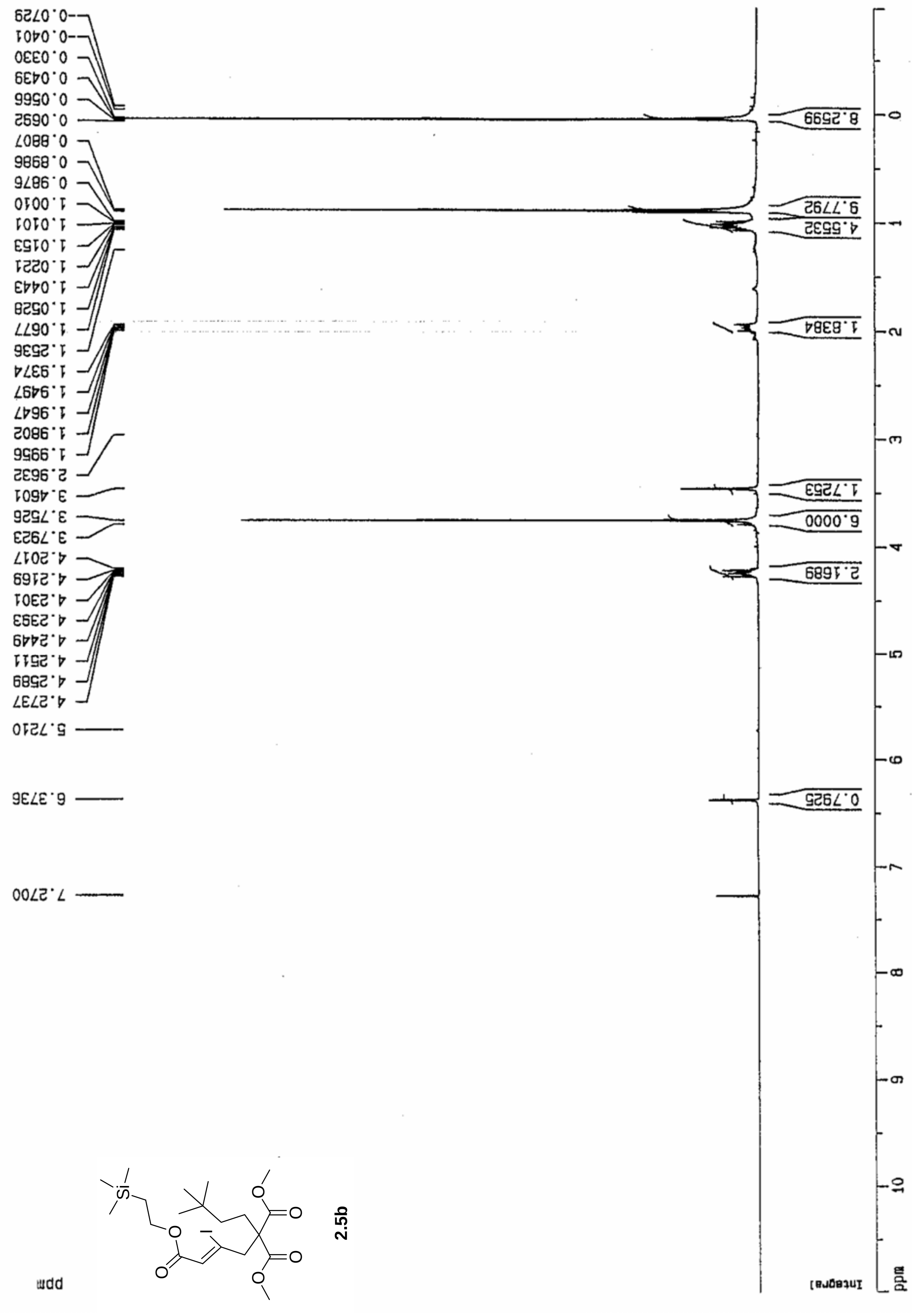
29.107
29.966
30.228
37.533
48.212
51.660
52.649
57.772
76.573
76.995
77.420
110.722
128.839
164.485
170.673
ppm
2.5a
20
40
60
80
100
120
140
160
180
200
ppm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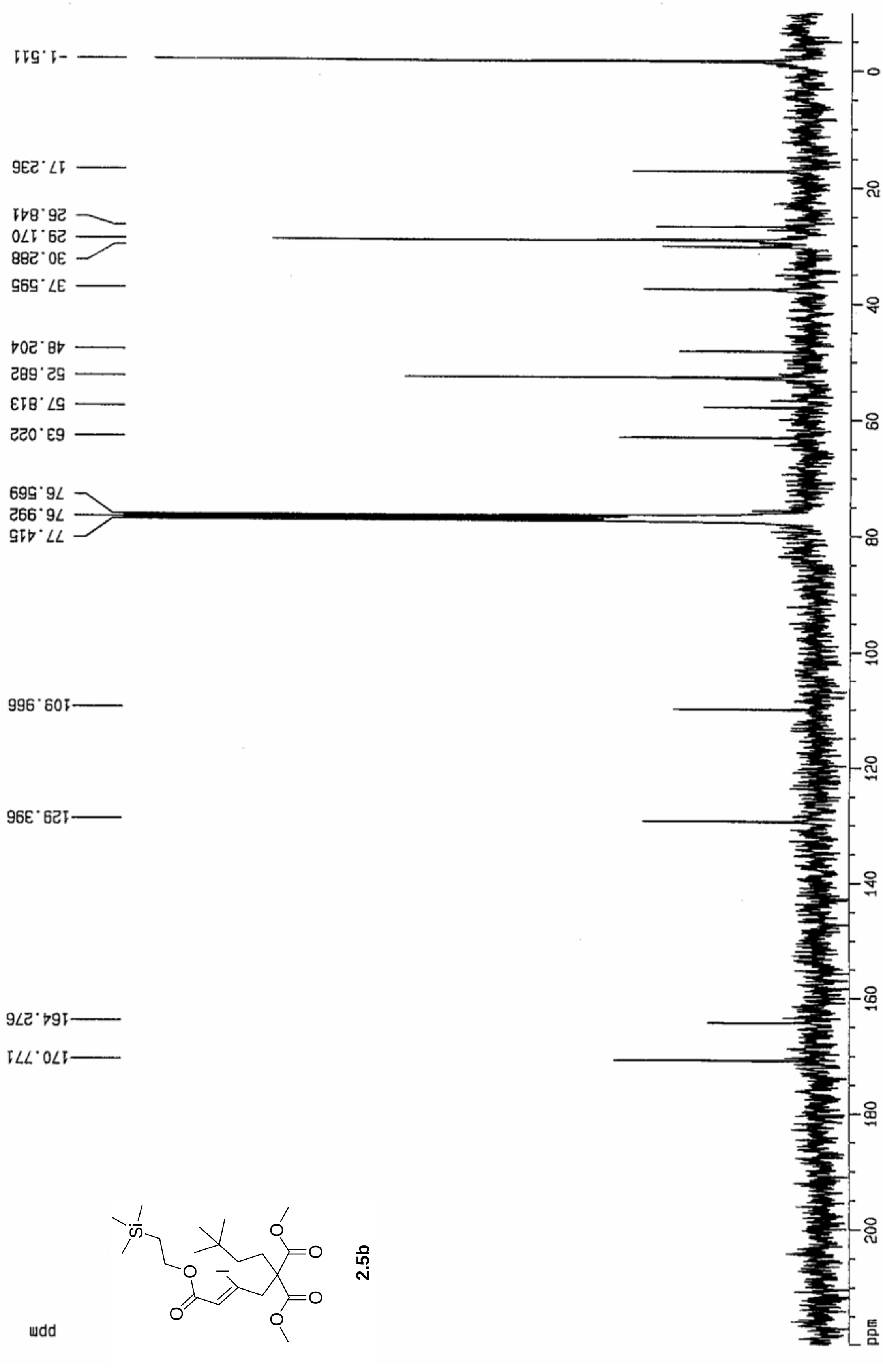
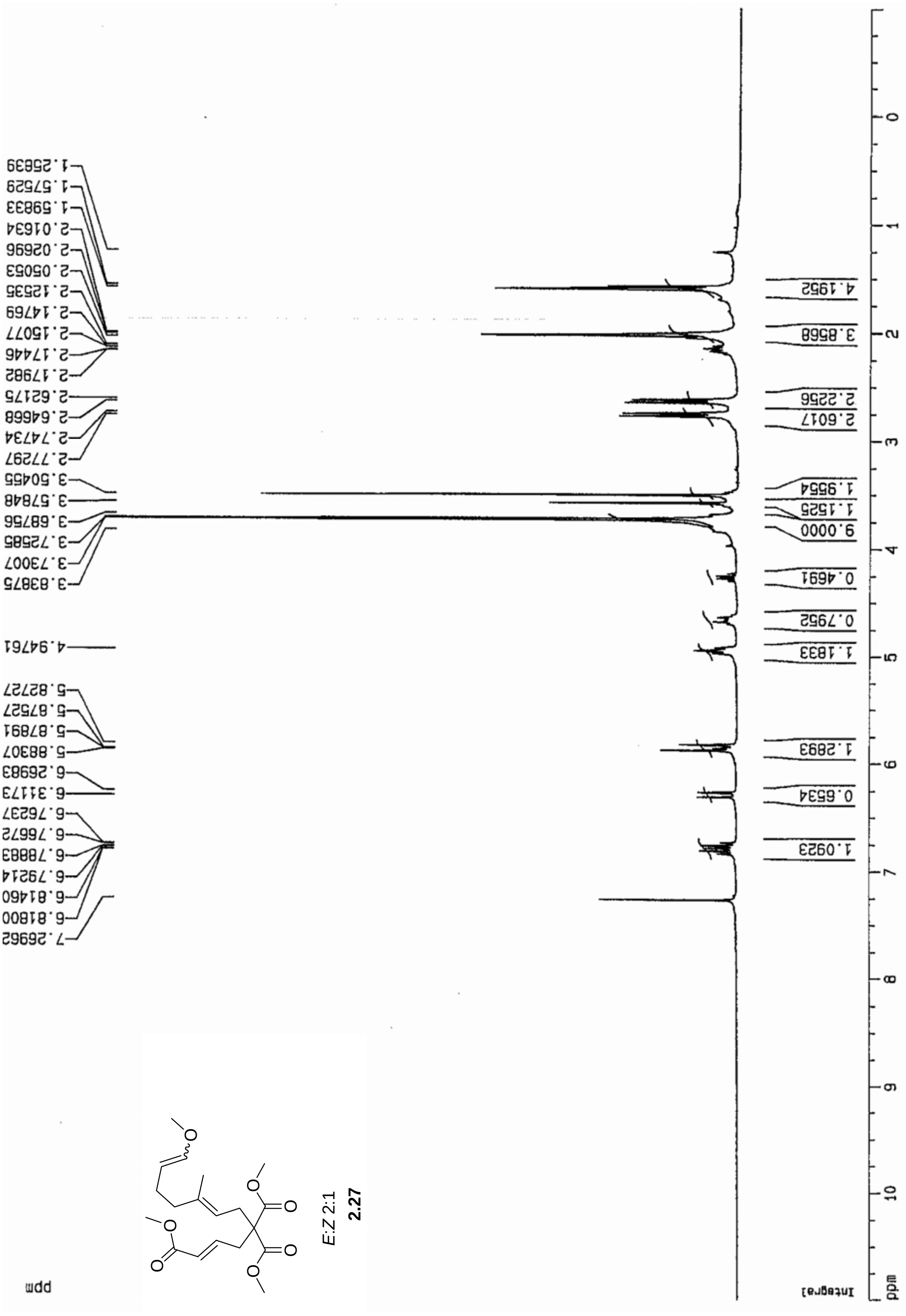
-0.0401
0.0330
0.0439
0.0566
0.0692
0.8807
0.8986
0.9876
1.0010
1.0101
1.0153
1.0221
1.0443
1.0528
1.0677
1.2536
1.9374
1.9497
1.9647
1.9802
1.9956
2.9632
3.4601
3.7526
3.7923
4.2017
4.2169
4.2301
4.2393
4.2449
4.2511
4.2589
4.2737
5.7210
6.3736
7.2700
ppm
8.2599
9.7792
4.5532
1.8384
1.7253
6.0000
2.1689
0.7925
Integral
0
1
2
3
4
5
6
7
8
9
10
ppm
Si
O
O
O
O
O
O
I

2.5b


-1.511
17.236
26.841
29.170
30.288
37.595
48.204
52.682
57.813
63.022
76.569
76.992
77.415
109.966
129.396
164.276
170.771
ppm
0
20
40
60
80
100
120
140
160
180
200
ppm
Si
O
O
O
O
O
O
I

2.5b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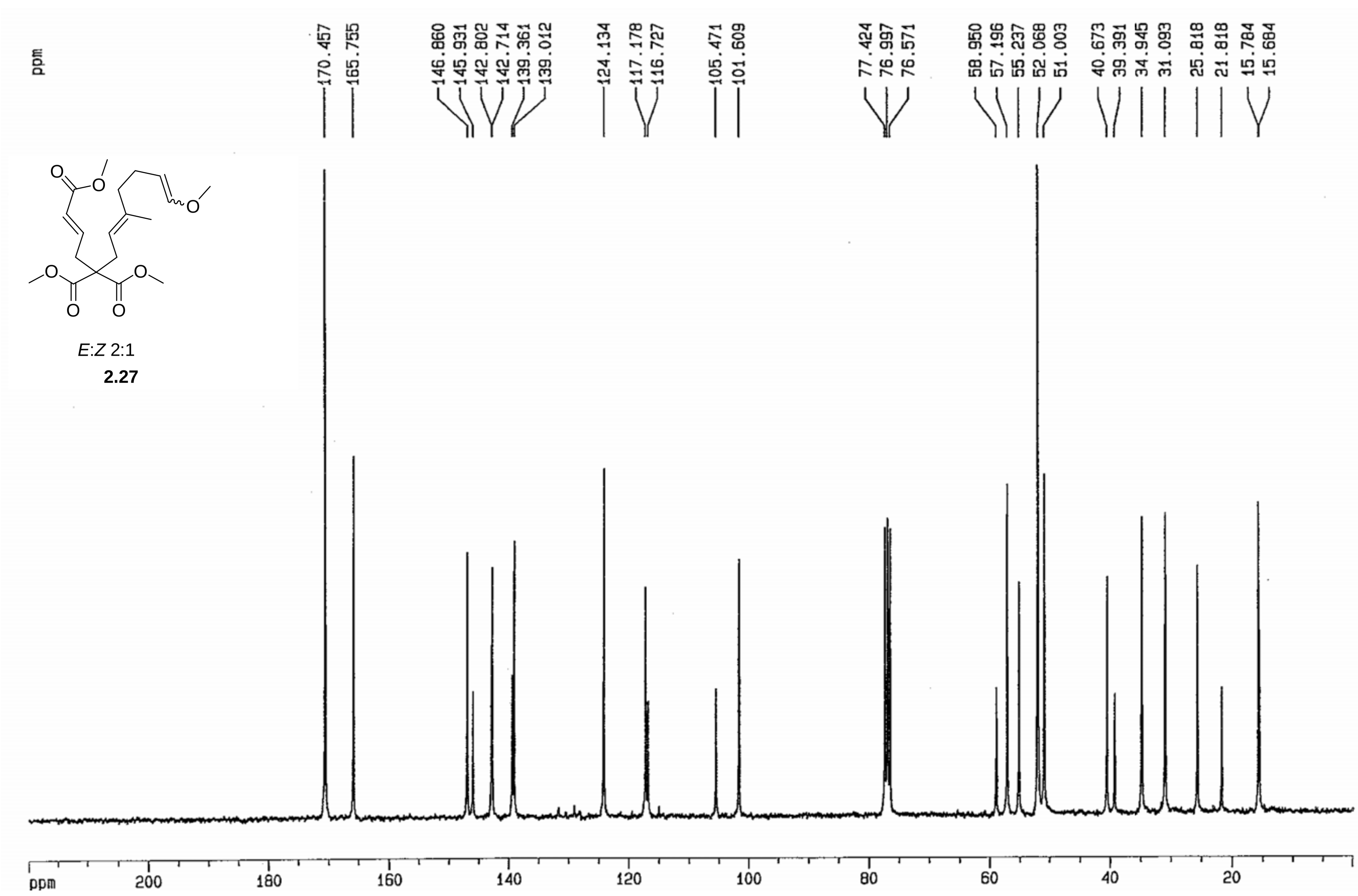
1.59833
2.01634
2.02696
2.05053
2.12535
2.14769
2.15077
2.17446
2.17982
2.62175
2.64668
2.74734
2.77297
3.50455
3.57848
3.68756
3.72585
3.73007
3.83875
4.94761
5.82727
5.87527
5.87891
5.88307
6.26983
6.31173
6.76237
6.76672
6.78883
6.79214
6.81460
6.81800
7.26962
4.1952
3.8568
2.2256
2.6017
1.9554
1.1525
9.0000
0.4691
0.7952
1.1833
1.2893
0.6534
1.0923
Integral
ppm
0
1
2
3
4
5
6
7
8
9
10
ppm

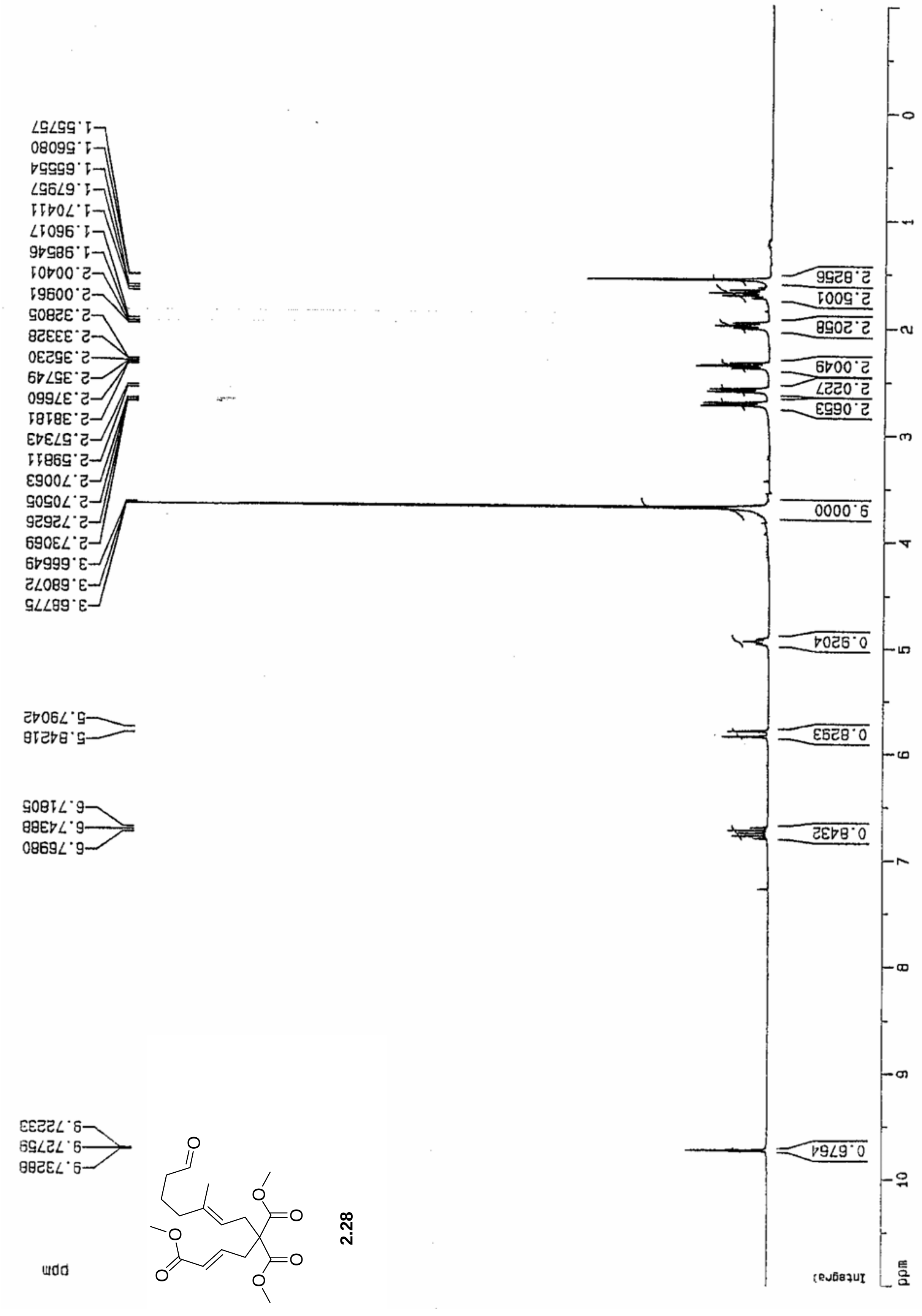
E:*Z* 2:1

2.27

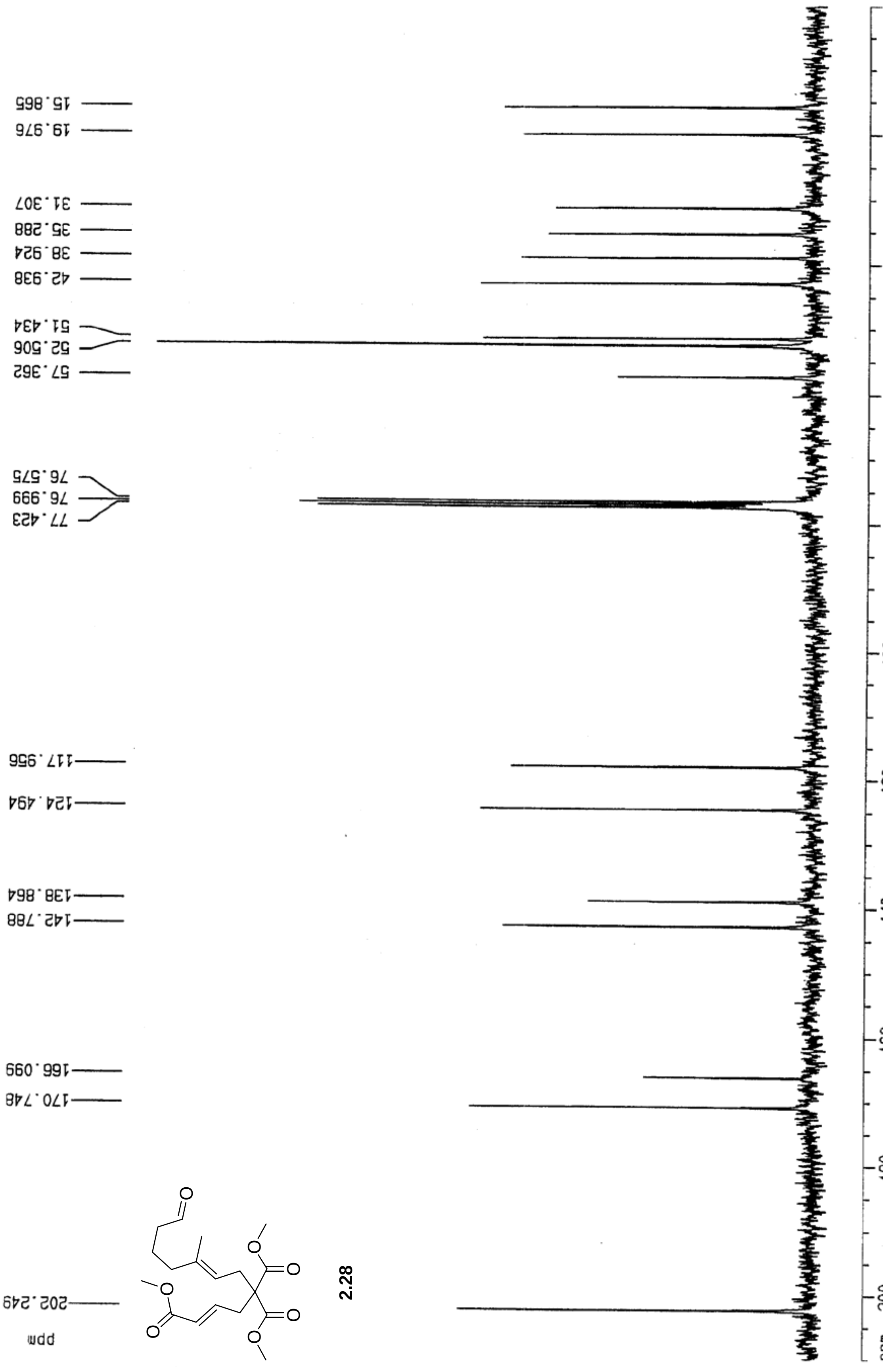

ppm
170.457
165.755
146.860
145.931
142.802
142.714
139.361
139.012
124.134
117.178
116.727
105.471
101.609
77.424
76.997
76.571
58.950
57.196
55.237
52.068
51.003
40.673
39.391
34.945
31.093
25.818
21.818
15.784
15.684
ppm
200
180
160
140
120
100
80
60
40
20
O
O
O
O
O
O
O

E:*Z* 2:1

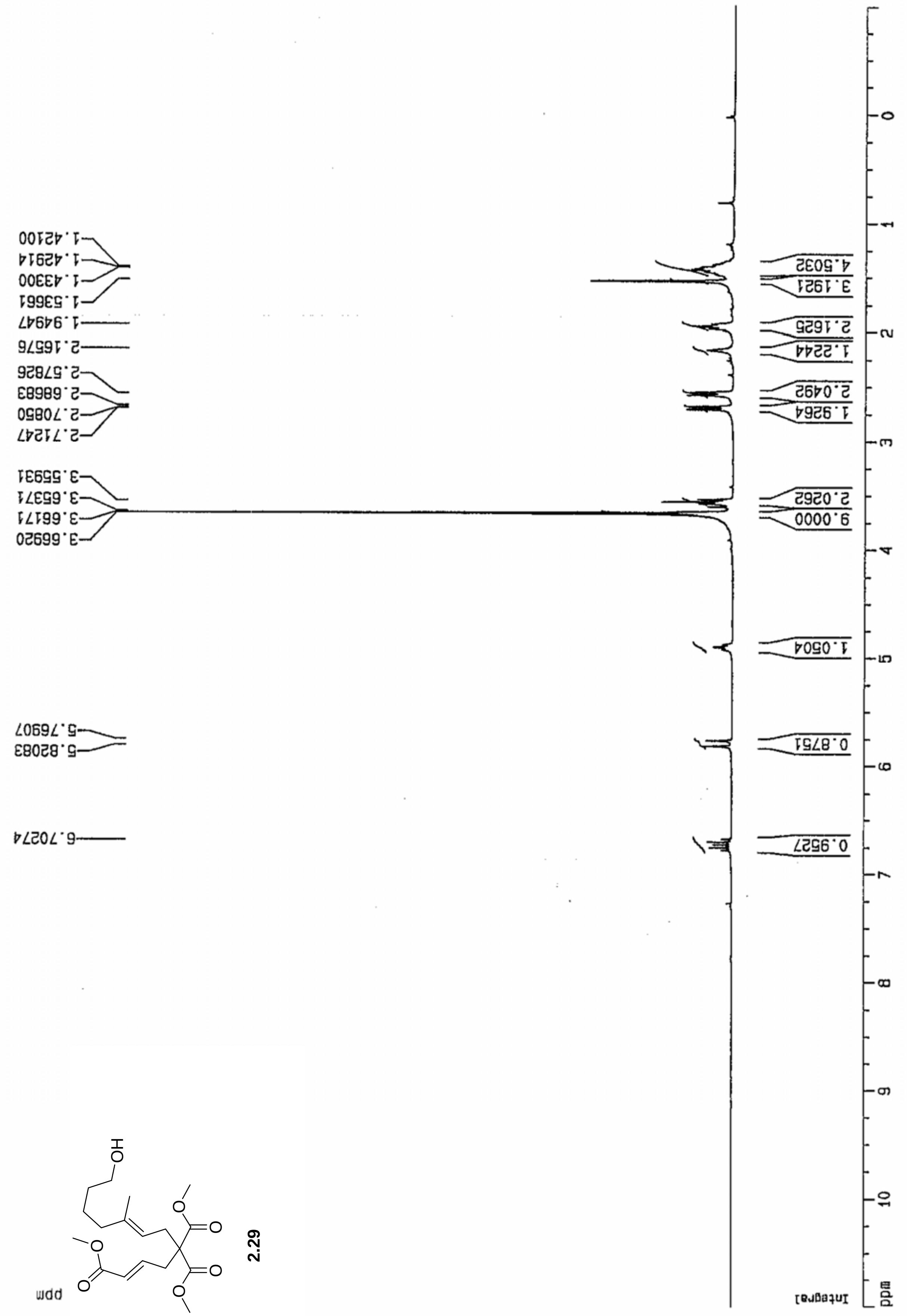
2.27


1.55757
1.56080
1.65554
1.67957
1.70411
1.96017
1.98546
2.00401
2.00961
2.32805
2.33328
2.35230
2.35749
2.37660
2.38181
2.57343
2.59811
2.70063
2.70505
2.72626
2.73069
3.66649
3.68072
3.68775
5.79042
5.84218
6.71805
6.74388
6.76980
9.72233
9.72759
9.73288
ppm
2.8256
2.5001
2.2058
2.0049
2.0227
2.0653
9.0000
0.9204
0.8293
0.8432
0.6764
Integral
ppm
0
1
2
3
4
5
6
7
8
9
10

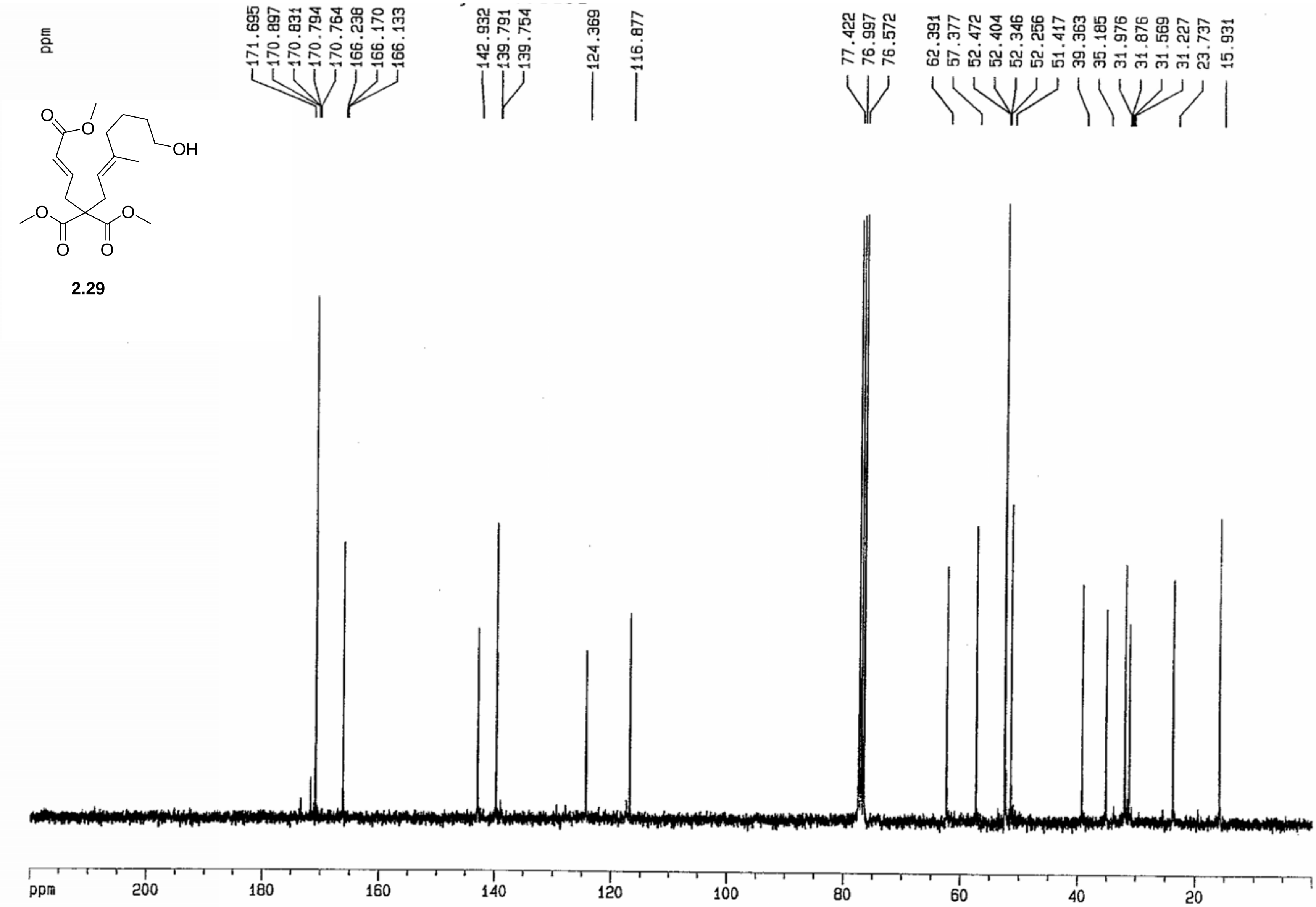
2.28

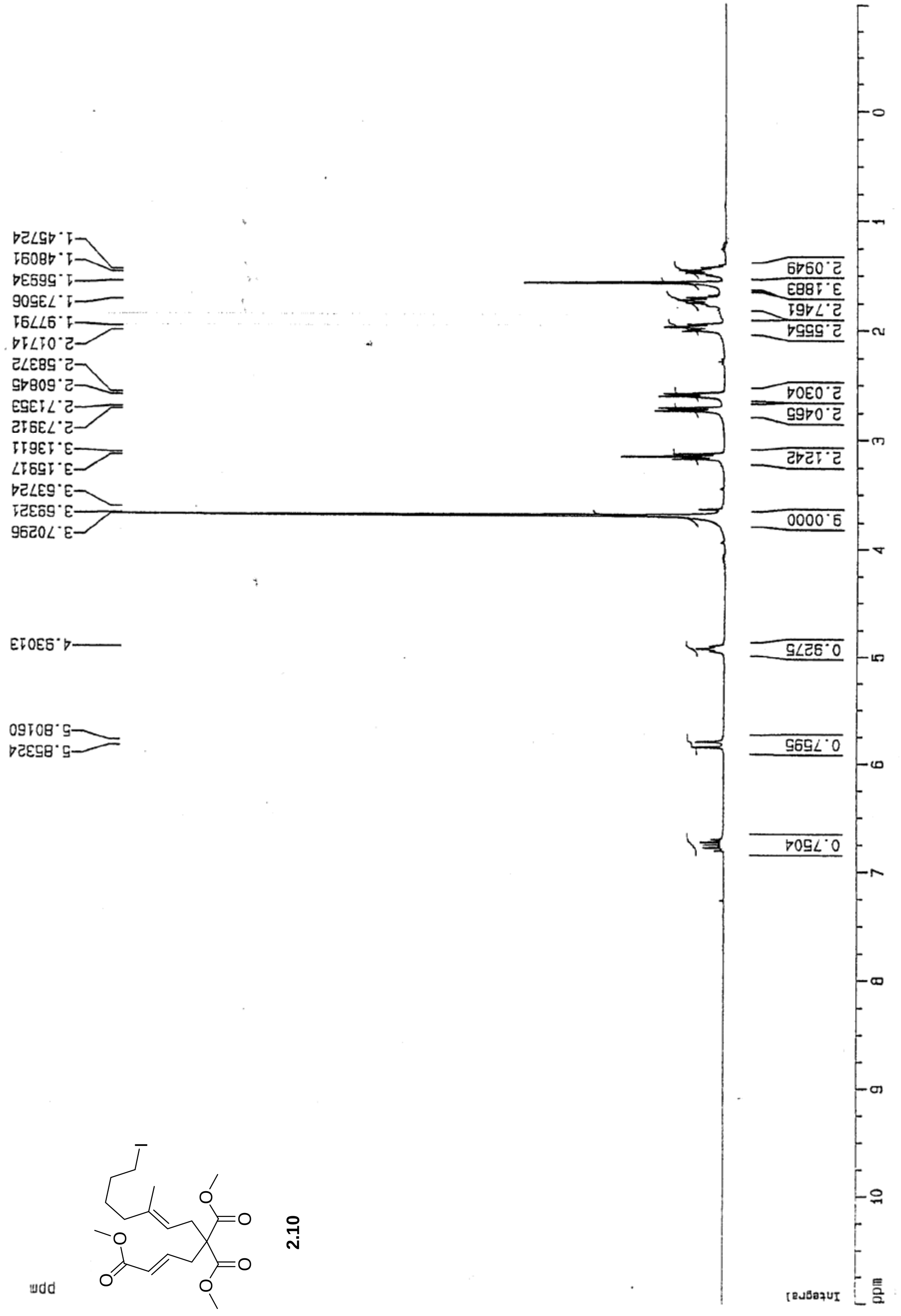

15.865
19.976
31.307
35.288
38.924
42.938
51.434
52.506
57.362
76.575
76.999
77.423
117.956
124.494
138.864
142.788
166.099
170.748
202.249
ppm
20
40
60
80
100
120
140
160
180
200
ppm

2.28

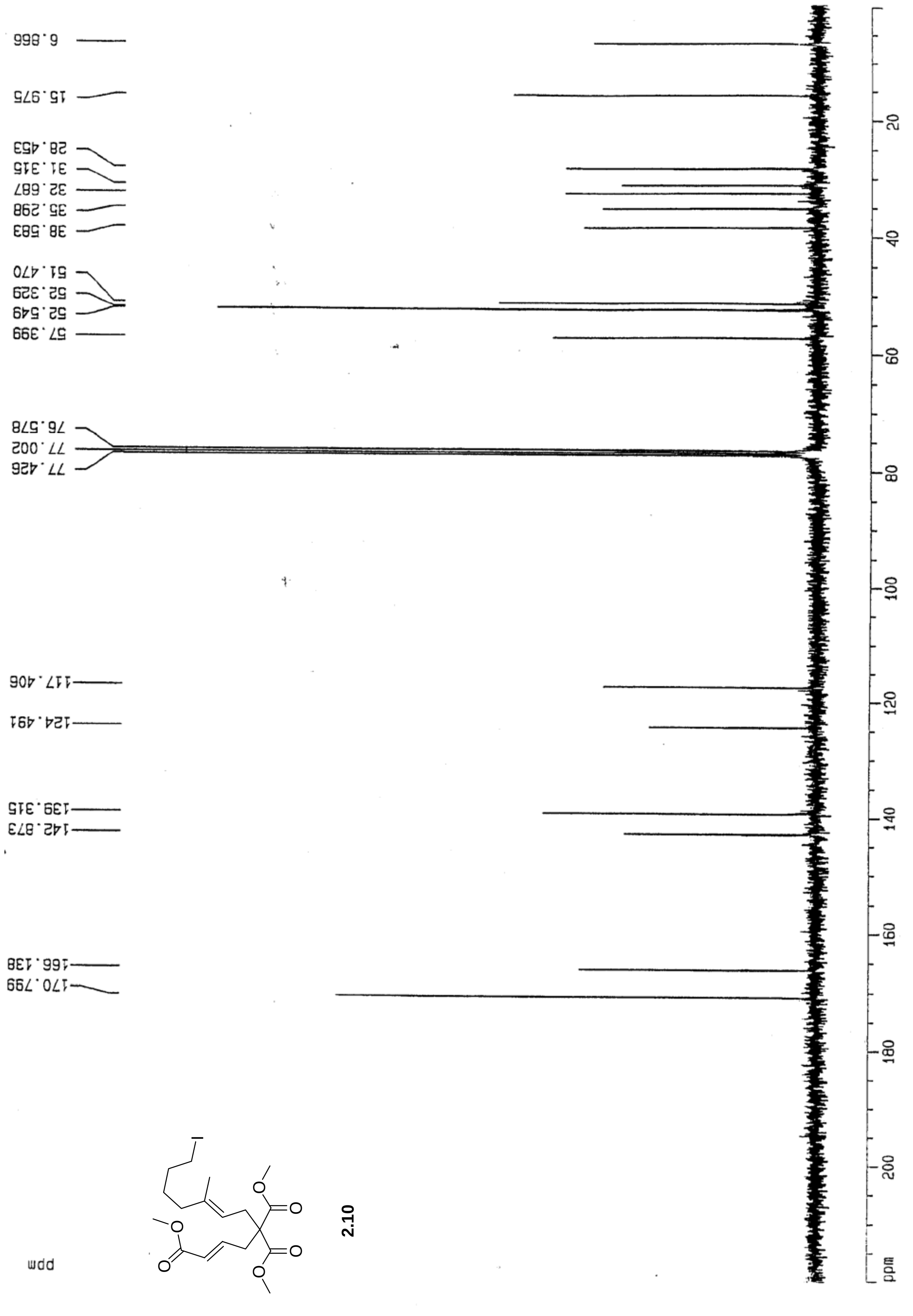

1.42100
1.42914
1.43300
1.53661
1.94947
2.16576
2.57826
2.68683
2.70850
2.71247
3.55931
3.65371
3.66171
3.66920
5.76907
5.82083
6.70274
4.5032
3.1921
2.1625
1.2244
2.0492
1.9264
2.0262
9.0000
1.0504
0.8751
0.9527
Integral
ppm
0
1
2
3
4
5
6
7
8
9
10
ppm
OH

2.29

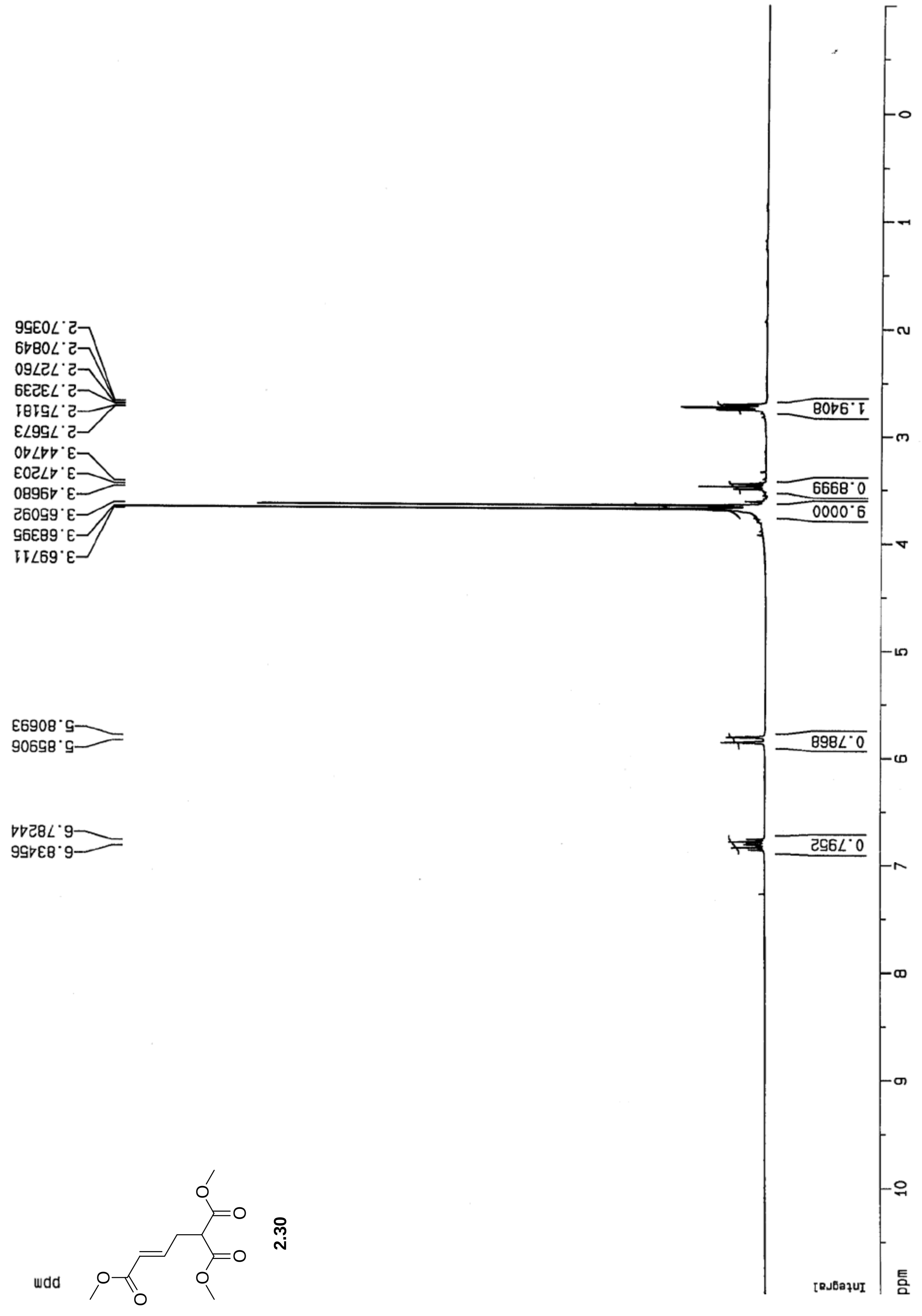

2.29
ppm
171.695
170.897
170.831
170.794
170.764
166.238
166.170
166.133
142.932
139.791
139.754
124.369
116.877
77.422
76.997
76.572
62.391
57.377
52.472
52.404
52.346
52.256
51.417
39.363
35.185
31.976
31.876
31.569
31.227
23.737
15.931
OH
O
ppm
200
180
160
140
120
100
80
60
40
20


1.45724
1.48091
1.56634
1.73506
1.97791
2.01714
2.58372
2.60845
2.71353
2.73912
3.13611
3.15917
3.63724
3.69321
3.70296
4.93013
5.80160
5.85324
ppm
2.0949
3.1883
2.7461
2.5554
2.0304
2.0465
2.1242
9.0000
0.9275
0.7595
0.7504
Integral
0
1
2
3
4
5
6
7
8
9
10
ppm

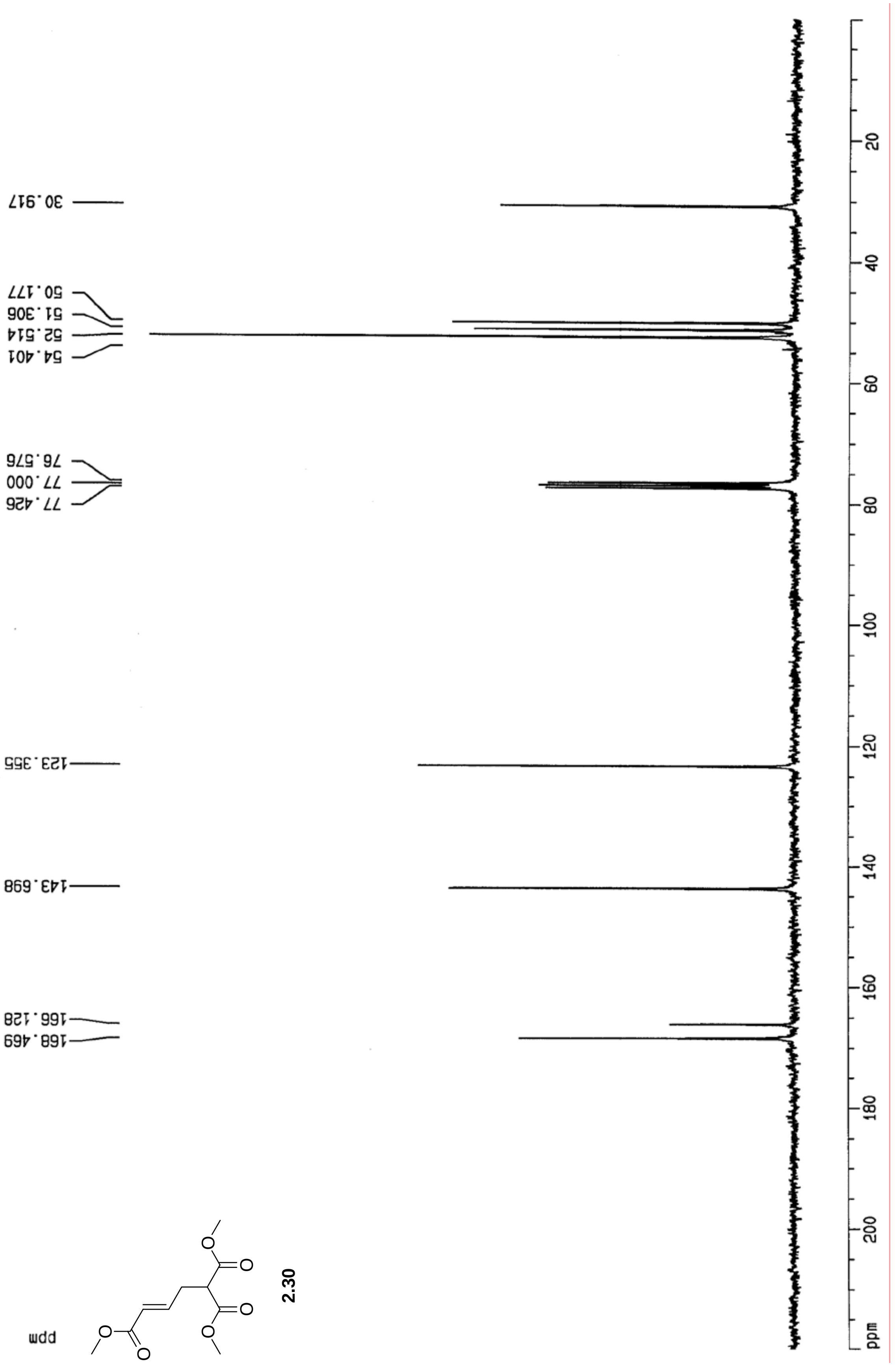
2.10


6.866
15.975
28.453
31.315
32.687
35.298
38.583
51.470
52.329
52.549
57.399
76.578
77.002
77.426
117.406
124.491
139.315
142.873
166.138
170.799
ppm
20
40
60
80
100
120
140
160
180
200
ppm
O
I

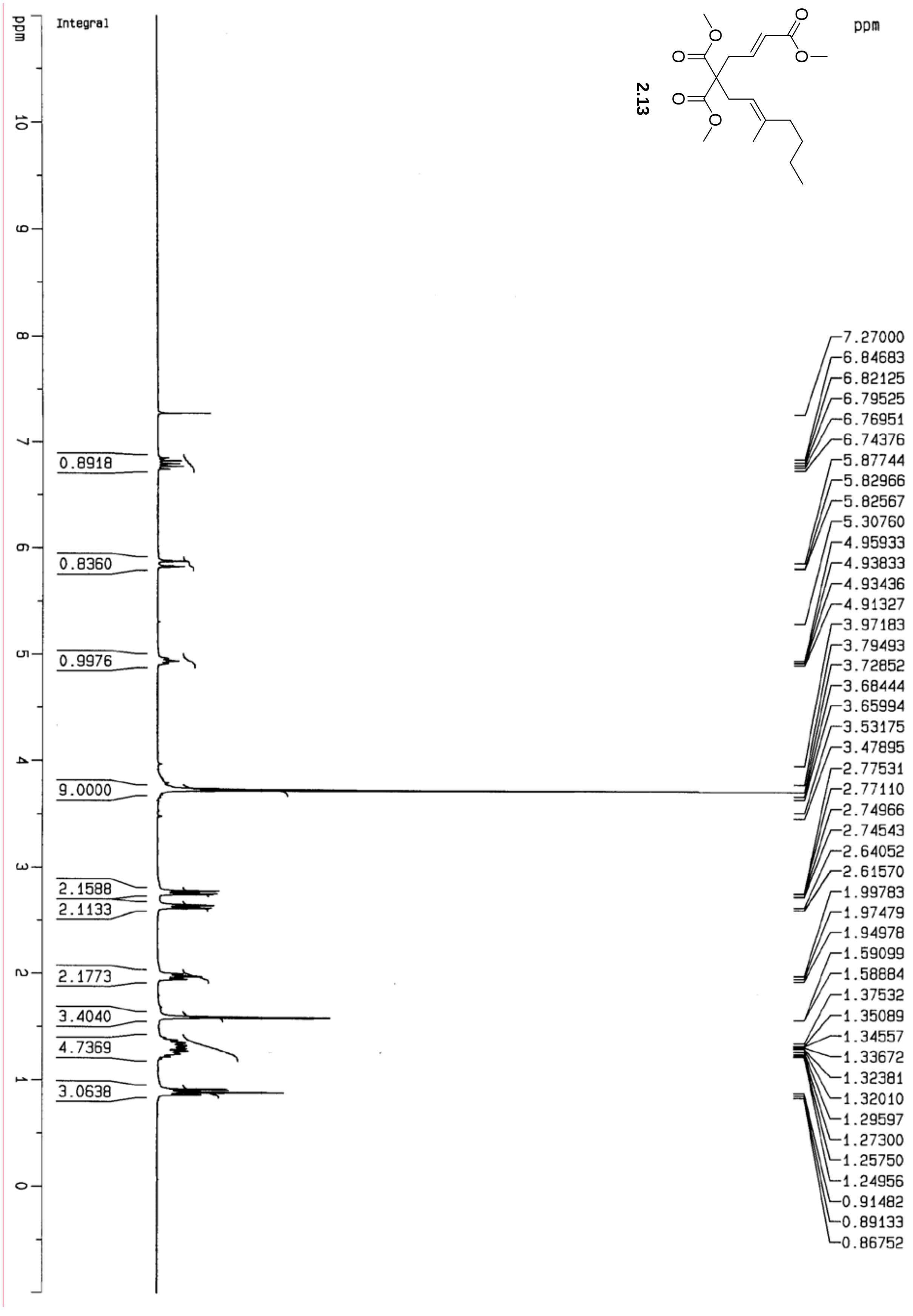
2.10

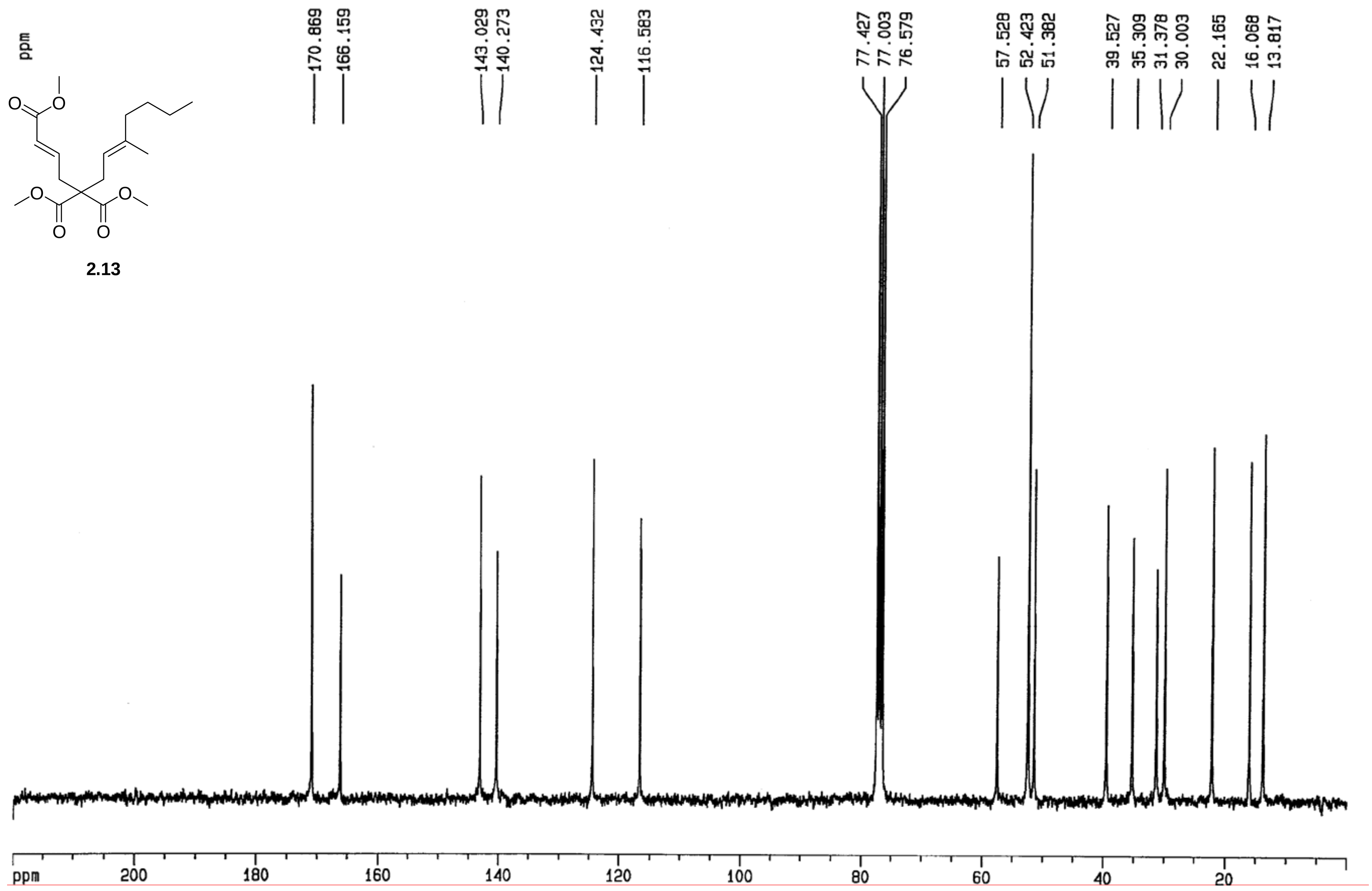

2.70356
2.70849
2.72760
2.73239
2.75181
2.75673
3.44740
3.47203
3.49680
3.65092
3.68395
3.69711
5.80693
5.85906
6.78244
6.83456
1.9408
0.8999
9.0000
0.7868
0.7952
Integral
ppm
0
1
2
3
4
5
6
7
8
9
10
ppm

2.30


30.917
50.177
51.306
52.514
54.401
76.576
77.000
77.426
123.355
143.698
166.128
168.469
ppm
20
40
60
80
100
120
140
160
180
200
ppm

2.30


2.13
ppm
Integral
0.8918
0.8360
0.9976
9.0000
2.1588
2.1133
2.1773
3.4040
4.7369
3.0638
7.27000
6.84683
6.82125
6.79525
6.76951
6.74376
5.87744
5.82966
5.82567
5.30760
4.95933
4.93833
4.93436
4.91327
3.97183
3.79493
3.72852
3.68444
3.65994
3.53175
3.47895
2.77531
2.77110
2.74966
2.74543
2.64052
2.61570
1.99783
1.97479
1.94978
1.59099
1.58884
1.37532
1.35089
1.34557
1.33672
1.32381
1.32010
1.29597
1.27300
1.25750
1.24956
0.91482
0.89133
0.86752
10
9
8
7
6
5
4
3
2
1
0
ppm


ppm
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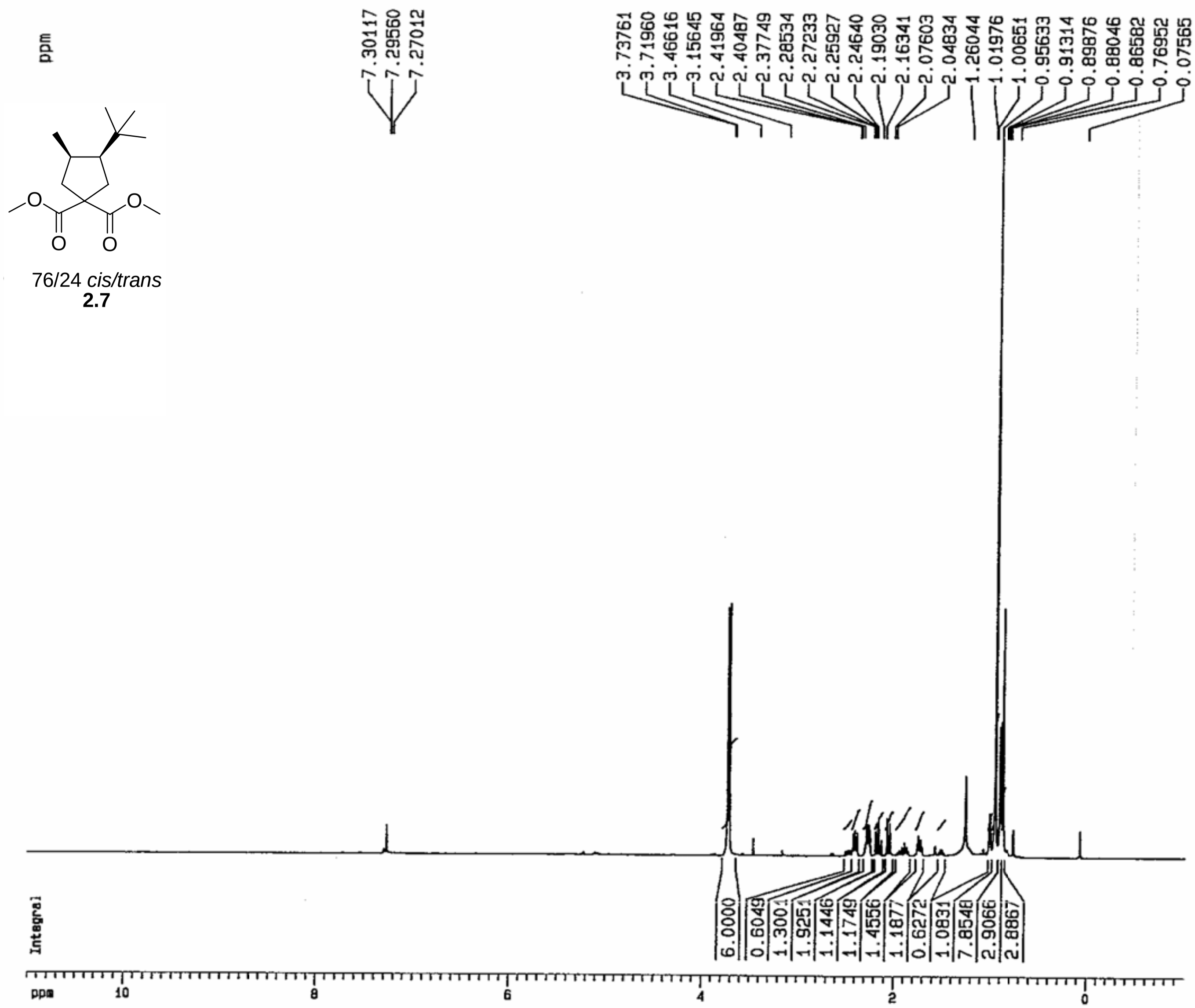
143.029
140.273
124.432
116.583
77.427
77.003
76.579
57.528
52.423
51.382
39.527
35.309
31.378
30.003
22.165
16.068
13.817
ppm
200
180
160
140
120
100
80
60
40
20
O
O
O
O
O
O

2.13



76/24 *cis/trans*

2.7

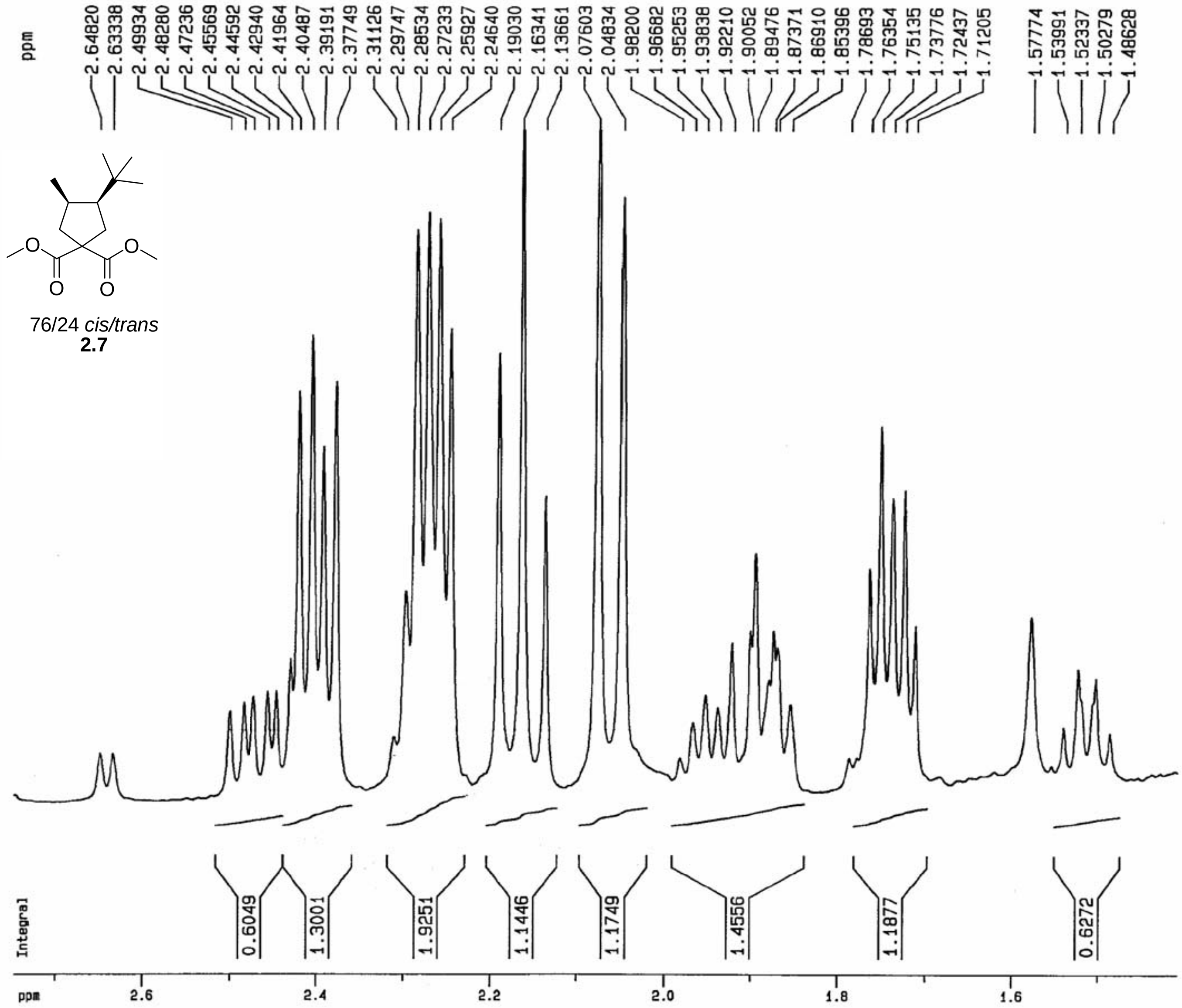
```
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_             500000
Time               12.16
INSTRUM            spect
PROBHD      5 mm TXI 13C
PULPROG               zg
TD                 32768
SOLVENT            CDC13
NS                    16
DS                     0
SWH             7507.507 Hz
FIDRES          0.229111 Hz
AQ             2.1823988 sec
RG                  45.3
DW                66.600 usec
DE                  6.00 usec
TE                 290.0 K
D1            1.00000000 sec
P1                 11.00 usec
DE                  6.00 usec
SFO1         500.1330008 MHz
NUC1                  1H
PL1                 0.00 dB

F2 - Processing parameters
SI                 32768
SF           500.1300233 MHz
WDW                   EM
SSB                    0
LB                  0.40 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX                 20.00 cm
F1P               11.000 ppm
F1               5501.43 Hz
F2P               -1.000 ppm
F2               -500.13 Hz
PPMCM            0.60000 ppm/cm
HZCM           300.07803 Hz/cm
```

76/24 *cis/trans*
2.7



EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

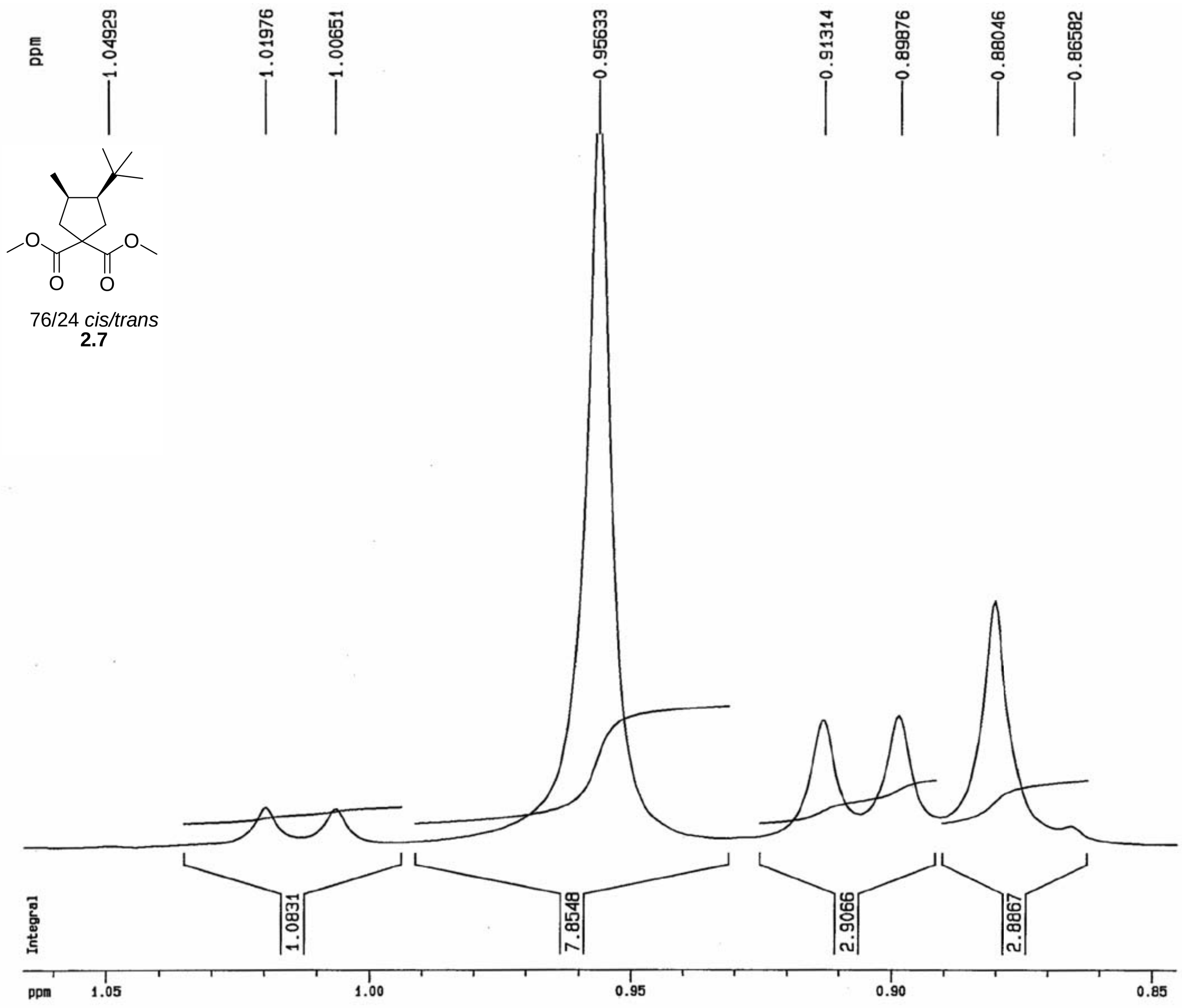
Date_	500000
Time	12.16
INSTRUM	spect
PROBHD	5 mm TXI 13C
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	7507.507 Hz
FIDRES	0.229111 Hz
AQ	2.1823988 sec
RG	45.3
DW	66.600 usec
DE	6.00 usec
TE	290.0 K
D1	1.00000000 sec
P1	11.00 usec
DE	6.00 usec
SFO1	500.1330008 MHz
NUC1	1H
PL1	0.00 dB

F2 - Processing parameters

SI	32768
SF	500.1300233 MHz
WDW	EM
SSB	0
LB	0.40 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	2.748 ppm
F1	1374.47 Hz
F2P	1.409 ppm
F2	704.46 Hz
PPMCM	0.06698 ppm/cm
HZCM	33.50040 Hz/cm



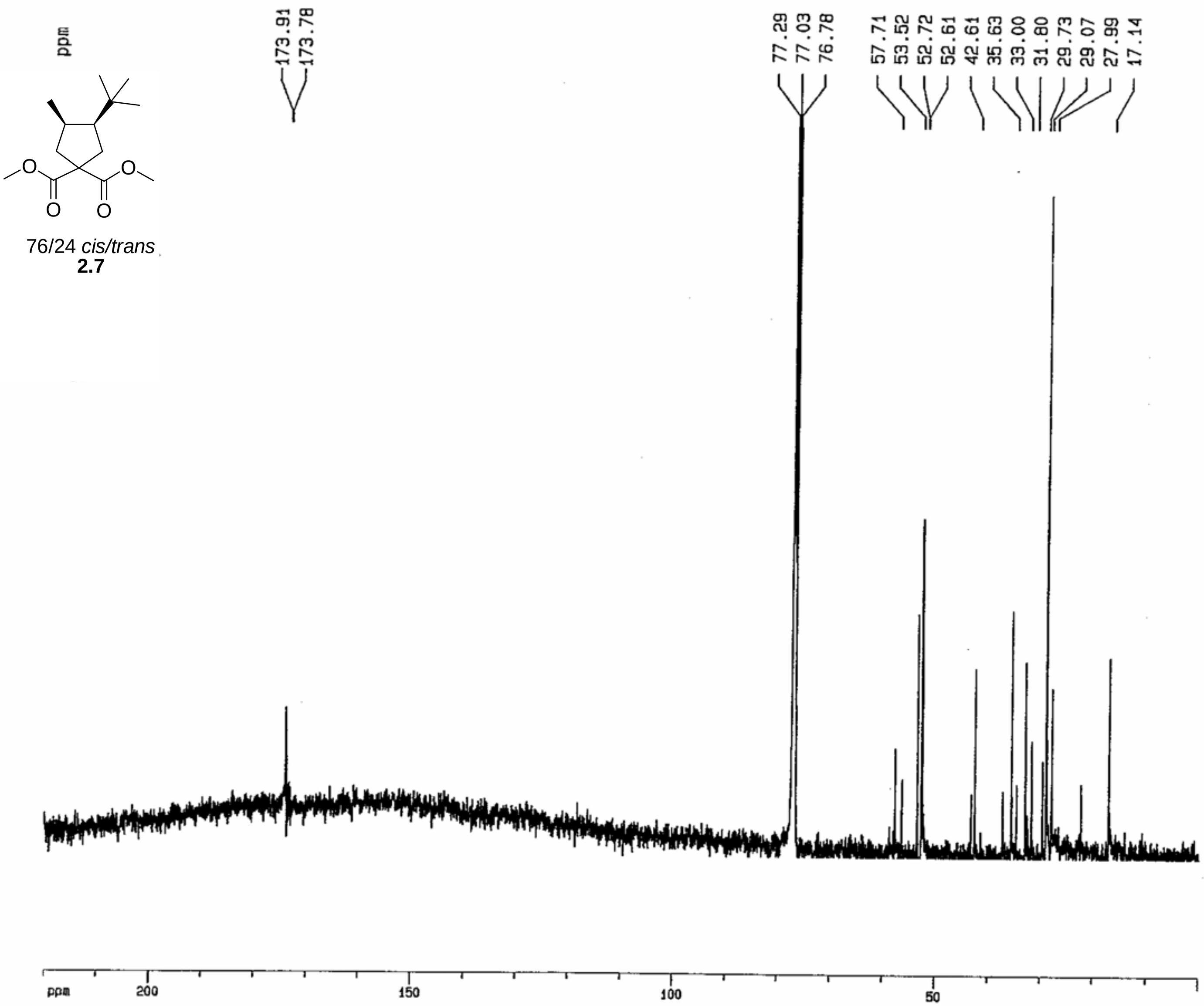
76/24 *cis/trans*
2.7

```
PROCNO                  1

F2 - Acquisition Parameters
Date_              500000
Time                12.16
INSTRUM             spect
PROBHD      5 mm TXI 13C
PULPROG                zg
TD                  32768
SOLVENT             CDC13
NS                     16
DS                      0
SWH              7507.507 Hz
FIDRES           0.229111 Hz
AQ              2.1823988 sec
RG                   45.3
DW                 66.600 usec
DE                   6.00 usec
TE                  290.0 K
D1             1.00000000 sec
P1                  11.00 usec
DE                   6.00 usec
SFO1          500.1330008 MHz
NUC1                   1H
PL1                  0.00 dB

F2 - Processing parameters
SI                  32768
SF            500.1300233 MHz
WDW                    EM
SSB                     0
LB                   0.40 Hz
GB                      0
PC                   1.00

1D NMR plot parameters
CX                  20.00 cm
F1P                 1.066 ppm
F1                 533.00 Hz
F2P                 0.845 ppm
F2                 422.83 Hz
PPMCM             0.01101 ppm/cm
HZCM              5.50861 Hz/cm
```

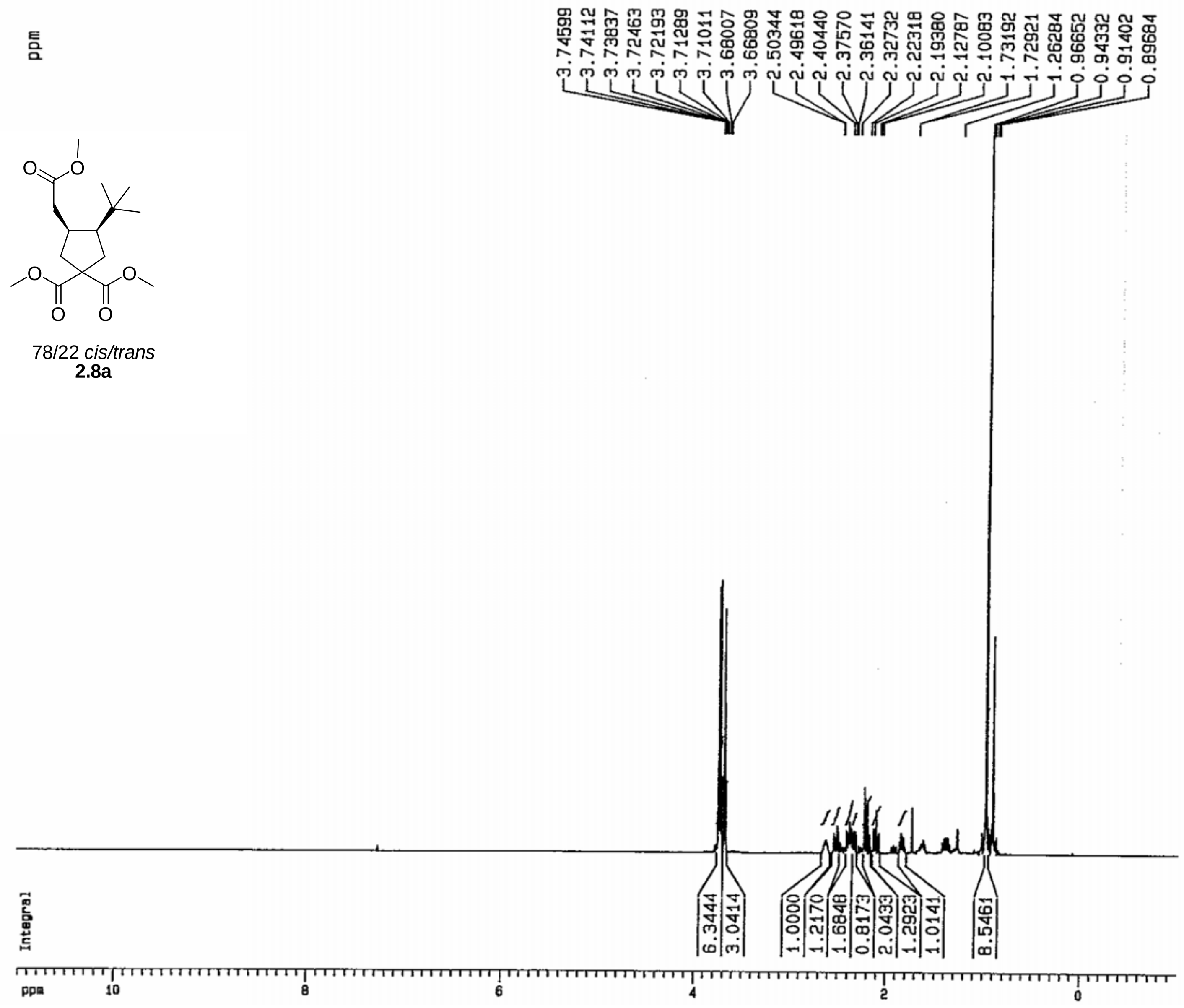


76/24 *cis/trans*
2.7

```
F2 - Acquisition Parameters
Date_              500000
Time                 9.57
INSTRUM             spect
PROBHD      5 mm TXI 13C
PULPROG          c13wonoe
TD                  32768
SOLVENT             CDCl3
NS                   8531
DS                      2
SWH            32679.738 Hz
FIDRES          0.997306 Hz
AQ             0.5014004 sec
RG                  32768
DW                 15.300 usec
DE                   6.00 usec
TE                  290.0 K
D3             0.00100000 sec
PL12                 6.00 dB
D1             6.00000000 sec
CPDPRG2           waltz16
PCPD2              100.00 usec
SFO2         500.1330008 MHz
NUC2                   1H
PL2                120.00 dB
P1                  17.00 usec
DE                   6.00 usec
SFO1         125.7715724 MHz
NUC1                  13C
PL1                  0.00 dB

F2 - Processing parameters
SI                   8192
SF           125.7577921 MHz
WDW                    EM
SSB                     0
LB                   4.00 Hz
GB                      0
PC                   1.00

1D NMR plot parameters
CX                  20.00 cm
F1P               220.000 ppm
F1               27666.71 Hz
F2P                 0.000 ppm
F2                   0.00 Hz
PPMCM         11.00000 ppm/cm
HZCM        1383.33569 Hz/cm
```



78/22 *cis/trans*
2.8a

PROCNO	1

F2 - Acquisition Parameters

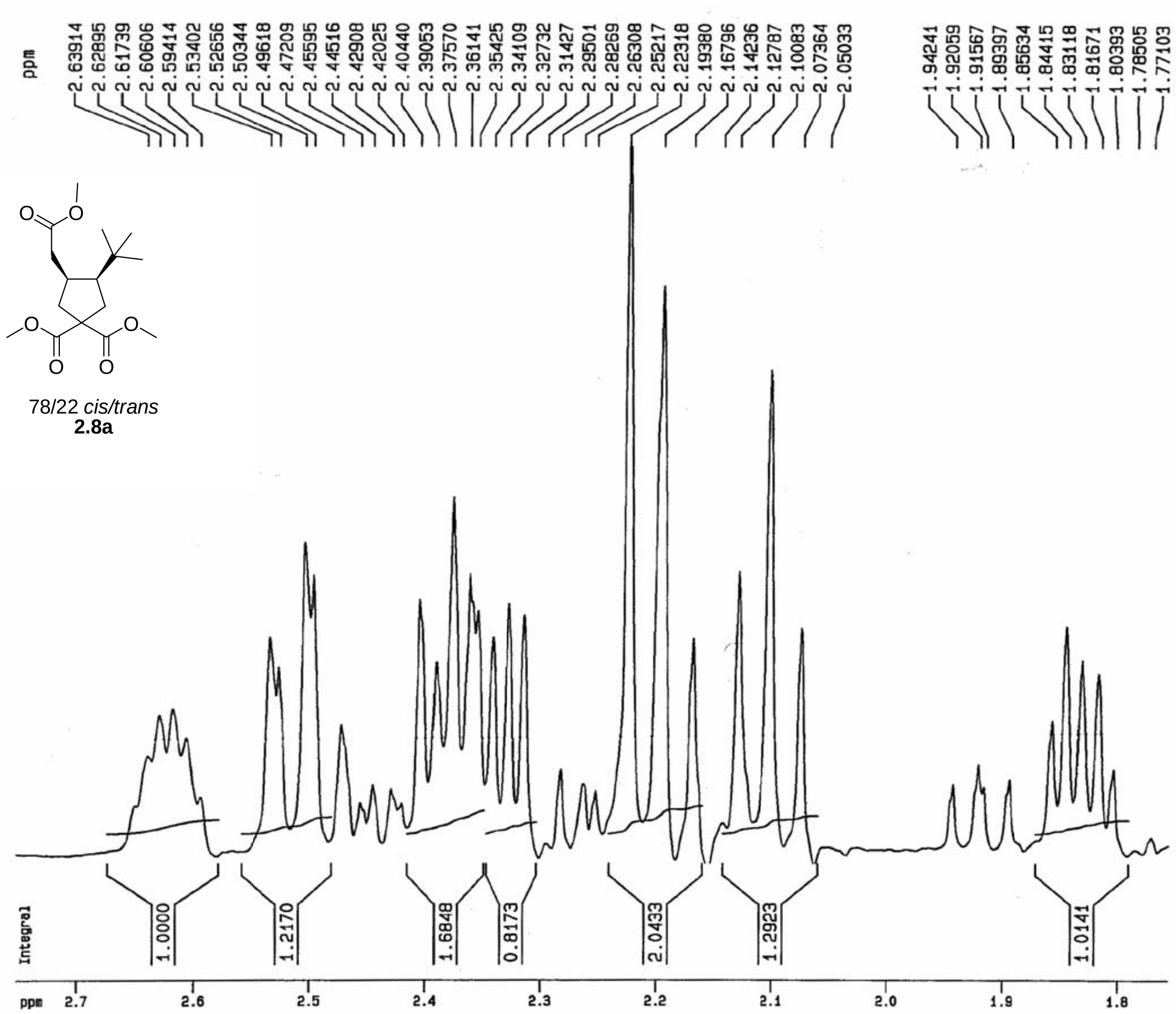
Date_	500000
Time	12.23
INSTRUM	spect
PROBHD	5 mm TXI 13C
PULPROG	zg
TD	32768
SOLVENT	CDC13
NS	16
DS	0
SWH	7507.507 Hz
FIDRES	0.229111 Hz
AQ	2.1823988 sec
RG	35.9
DW	66.600 usec
DE	6.00 usec
TE	290.0 K
D1	1.00000000 sec
P1	10.60 usec
DE	6.00 usec
SFO1	500.1330008 MHz
NUC1	1H
PL1	0.00 dB

F2 - Processing parameters

SI	32768
SF	500.1300222 MHz
WDW	EM
SSB	0
LB	0.40 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	11.000 ppm
F1	5501.43 Hz
F2P	-1.000 ppm
F2	-500.13 Hz
PPMCM	0.60000 ppm/cm
HZCM	300.07803 Hz/cm



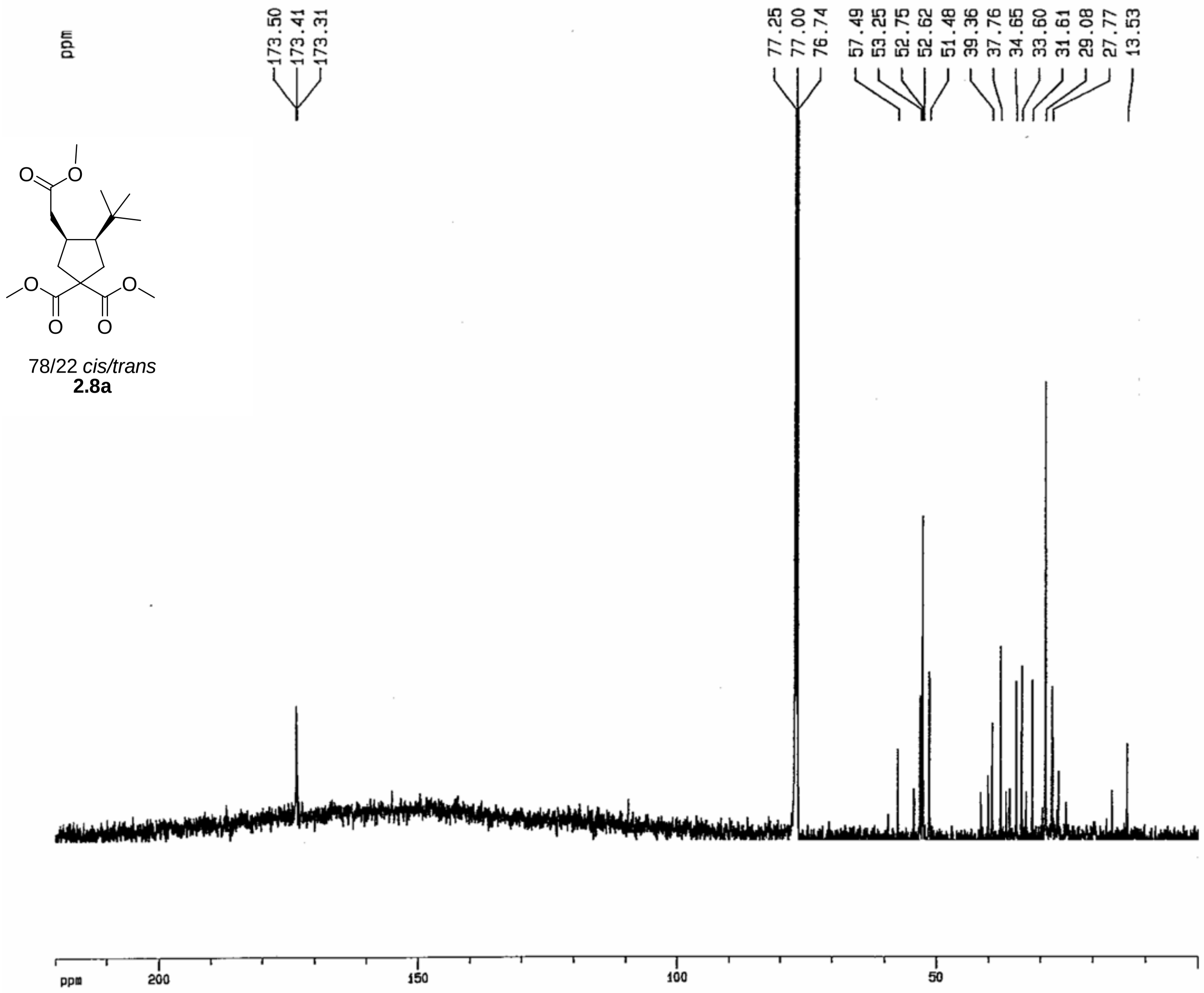
78/22 *cis/trans*
2.8a

```
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_             500000
Time               12.23
INSTRUM            spect
PROBHD      5 mm TXI 13C
PULPROG               zg
TD                 32768
SOLVENT            CDC13
NS                    16
DS                     0
SWH             7507.507 Hz
FIDRES          0.229111 Hz
AQ             2.1823988 sec
RG                  35.9
DW                66.600 usec
DE                  6.00 usec
TE                 290.0 K
D1            1.00000000 sec
P1                 10.60 usec
DE                  6.00 usec
SFO1      500.1330008 MHz
NUC1                  1H
PL1                 0.00 dB

F2 - Processing parameters
SI                 32768
SF        500.1300222 MHz
WDW                   EM
SSB                    0
LB                  0.40 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX                 20.00 cm
F1P                2.753 ppm
F1               1376.82 Hz
F2P                1.756 ppm
F2                878.15 Hz
PPMCM            0.04985 ppm/cm
HZCM            24.93338 Hz/cm
```

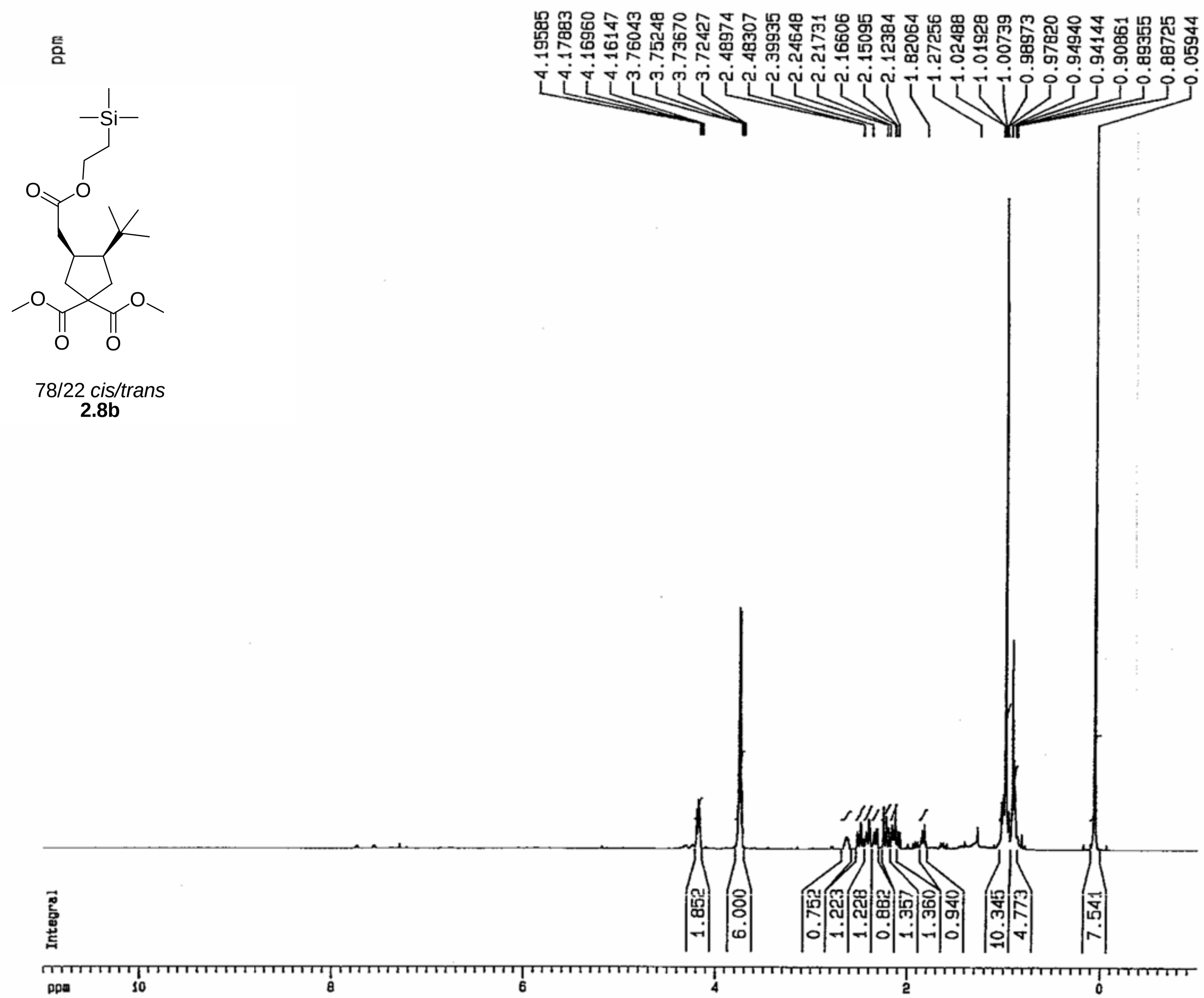


78/22 *cis/trans*
2.8a

```
F2 - Acquisition Parameters
Date_              500000
Time                 8.49
INSTRUM             spect
PROBHD     5 mm TXI 13C
PULPROG          c13wonoe
TD                  32768
SOLVENT               D2O
NS                   3562
DS                      0
SWH             32679.738 Hz
FIDRES           0.997306 Hz
AQ              0.5014004 sec
RG                  32768
DW                 15.300 usec
DE                   6.00 usec
TE                  290.0 K
D3             0.00100000 sec
PL12                 6.00 dB
D1             8.00000000 sec
CPDPRG2           waltz16
PCPD2              100.00 usec
SFO2          500.1330008 MHz
NUC2                   1H
PL2                120.00 dB
P1                  21.60 usec
DE                   6.00 usec
SFO1          125.7715724 MHz
NUC1                  13C
PL1                  0.00 dB

F2 - Processing parameters
SI                   8192
SF            125.7577961 MHz
WDW                    EM
SSB                     0
LB                   4.00 Hz
GB                      0
PC                   1.00

1D NMR plot parameters
CX                  20.00 cm
F1P               220.000 ppm
F1               27666.71 Hz
F2P                 0.000 ppm
F2                   0.00 Hz
PPMCM            11.00000 ppm/cm
HZCM           1383.33582 Hz/cm
```



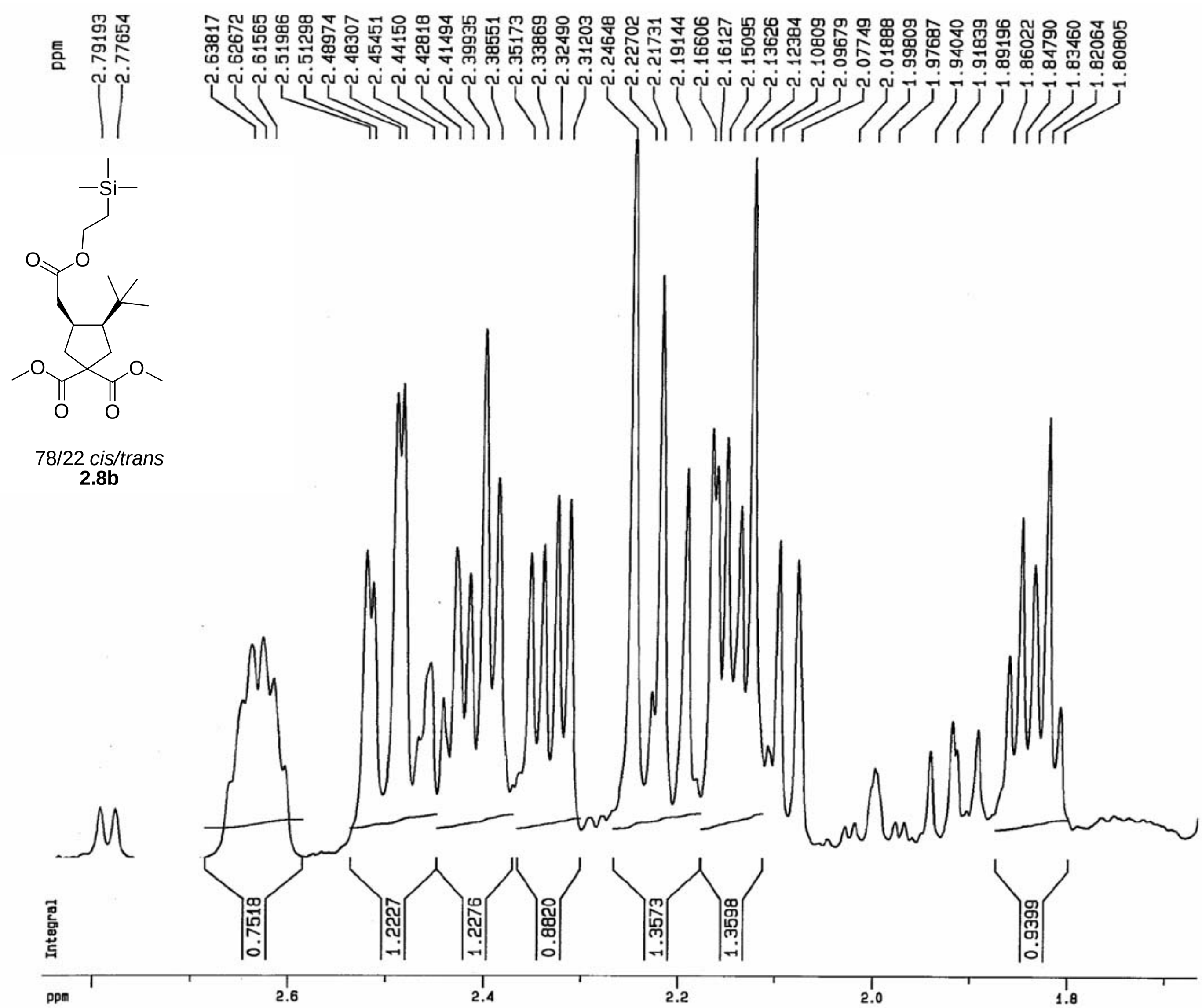
78/22 *cis/trans*
2.8b

```
PROCNO                  1

F2 - Acquisition Parameters
Date_              500000
Time                18.38
INSTRUM             spect
PROBHD     5 mm TXI 13C
PULPROG                zg
TD                  32768
SOLVENT             CDCl3
NS                     16
DS                      0
SWH              7507.507 Hz
FIDRES           0.229111 Hz
AQ              2.1823988 sec
RG                   25.4
DW                 66.600 usec
DE                   6.00 usec
TE                  290.0 K
D1             1.00000000 sec
P1                  10.60 usec
DE                   6.00 usec
SFO1          500.1330008 MHz
NUC1                   1H
PL1                  0.00 dB

F2 - Processing parameters
SI                  32768
SF            500.1300141 MHz
WDW                    EM
SSB                     0
LB                   0.40 Hz
GB                      0
PC                   1.00

1D NMR plot parameters
CX                  20.00 cm
F1P                11.000 ppm
F1                5501.43 Hz
F2P                -1.000 ppm
F2                -500.13 Hz
PPMCM             0.60000 ppm/cm
HZCM            300.07800 Hz/cm
```



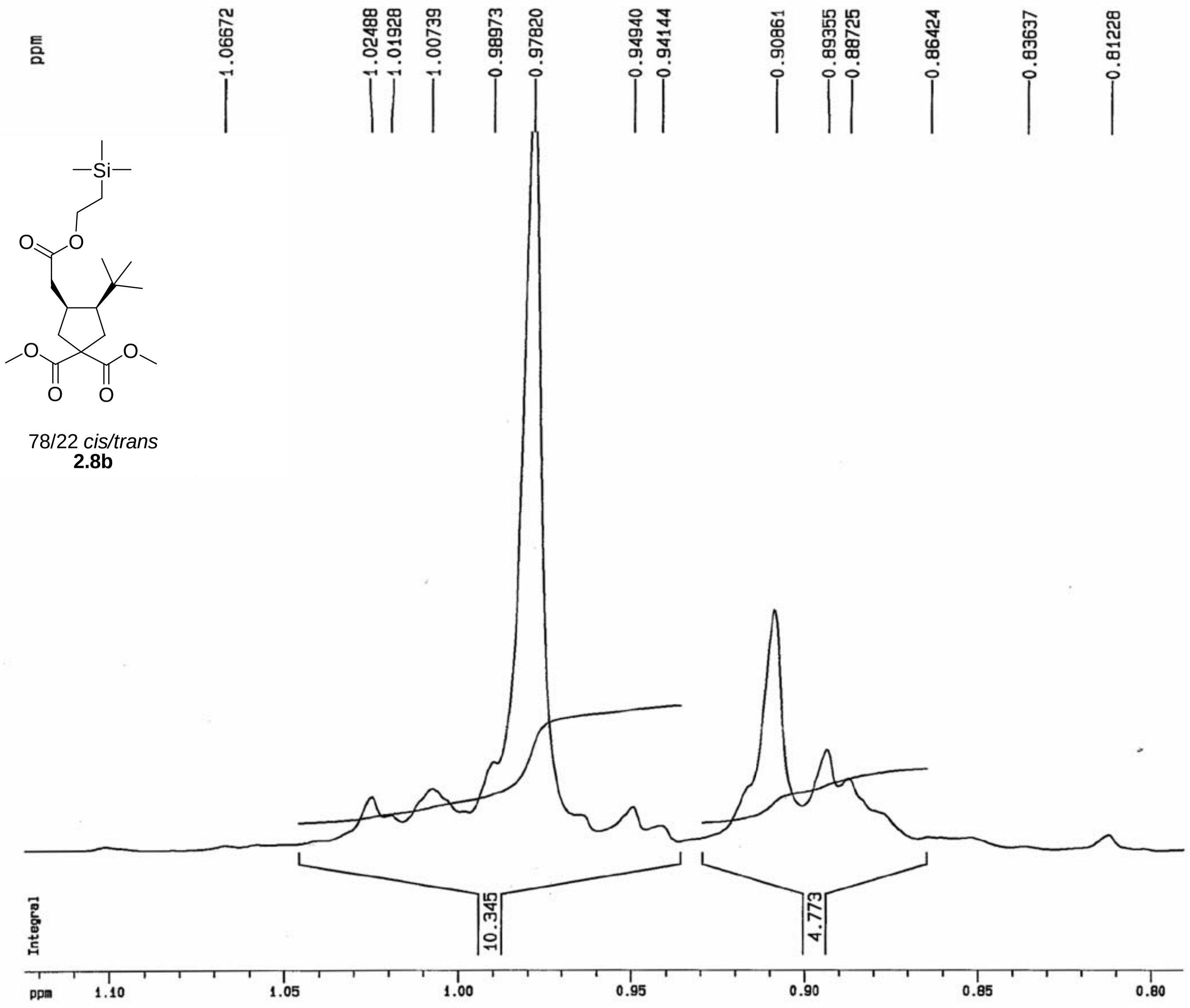
78/22 *cis/trans*
2.8b

```
PROCNO                    1

F2 - Acquisition Parameters
Date_                500000
Time                  18.38
INSTRUM               spect
PROBHD         5 mm TXI 13C
PULPROG                  zg
TD                    32768
SOLVENT               CDC13
NS                       16
DS                        0
SWH              7507.507 Hz
FIDRES           0.229111 Hz
AQ              2.1823988 sec
RG                     25.4
DW                  66.600 usec
DE                    6.00 usec
TE                   290.0 K
D1             1.00000000 sec
P1                   10.60 usec
DE                    6.00 usec
SFO1         500.1330008 MHz
NUC1                     1H
PL1                    0.00 dB

F2 - Processing parameters
SI                    32768
SF           500.1300141 MHz
WDW                      EM
SSB                       0
LB                     0.40 Hz
GB                        0
PC                     1.00

1D NMR plot parameters
CX                    20.00 cm
F1P                   2.851 ppm
F1                  1425.90 Hz
F2P                   1.666 ppm
F2                   833.43 Hz
PPMCM               0.05923 ppm/cm
HZCM               29.62326 Hz/cm
```



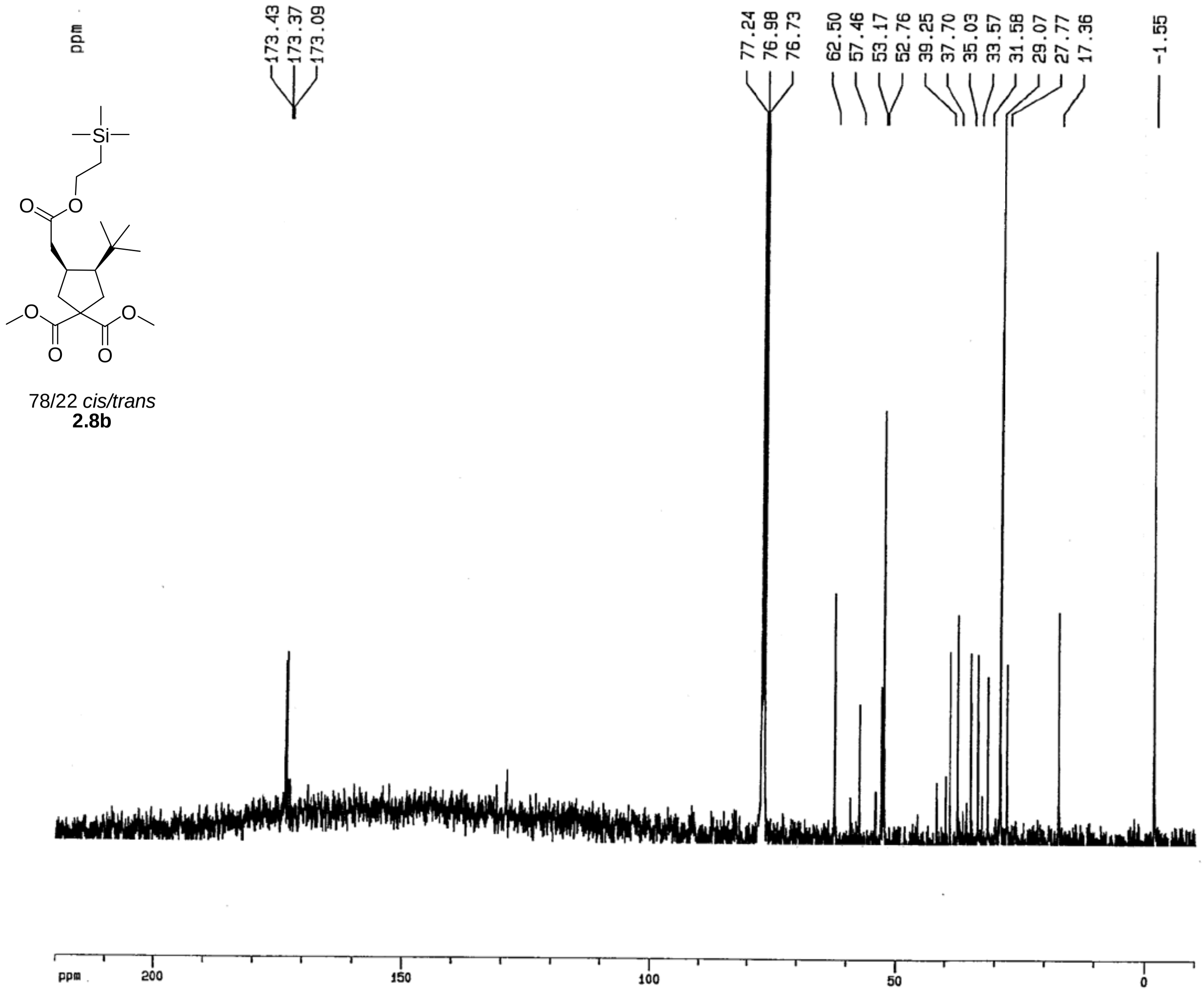
78/22 *cis/trans*
2.8b

```
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_            500000
Time              18.38
INSTRUM           spect
PROBHD      5 mm TXI 13C
PULPROG              zg
TD                32768
SOLVENT           CDC13
NS                   16
DS                    0
SWH            7507.507 Hz
FIDRES         0.229111 Hz
AQ            2.1823988 sec
RG                 25.4
DW               66.600 usec
DE                 6.00 usec
TE                290.0 K
D1           1.00000000 sec
P1                10.60 usec
DE                 6.00 usec
SFO1        500.1330008 MHz
NUC1                 1H
PL1                0.00 dB

F2 - Processing parameters
SI                32768
SF          500.1300141 MHz
WDW                  EM
SSB                   0
LB                 0.40 Hz
GB                    0
PC                 1.00

1D NMR plot parameters
CX                20.00 cm
F1P               1.124 ppm
F1               562.28 Hz
F2P               0.791 ppm
F2               395.40 Hz
PPMCM           0.01668 ppm/cm
HZCM            8.34438 Hz/cm
```

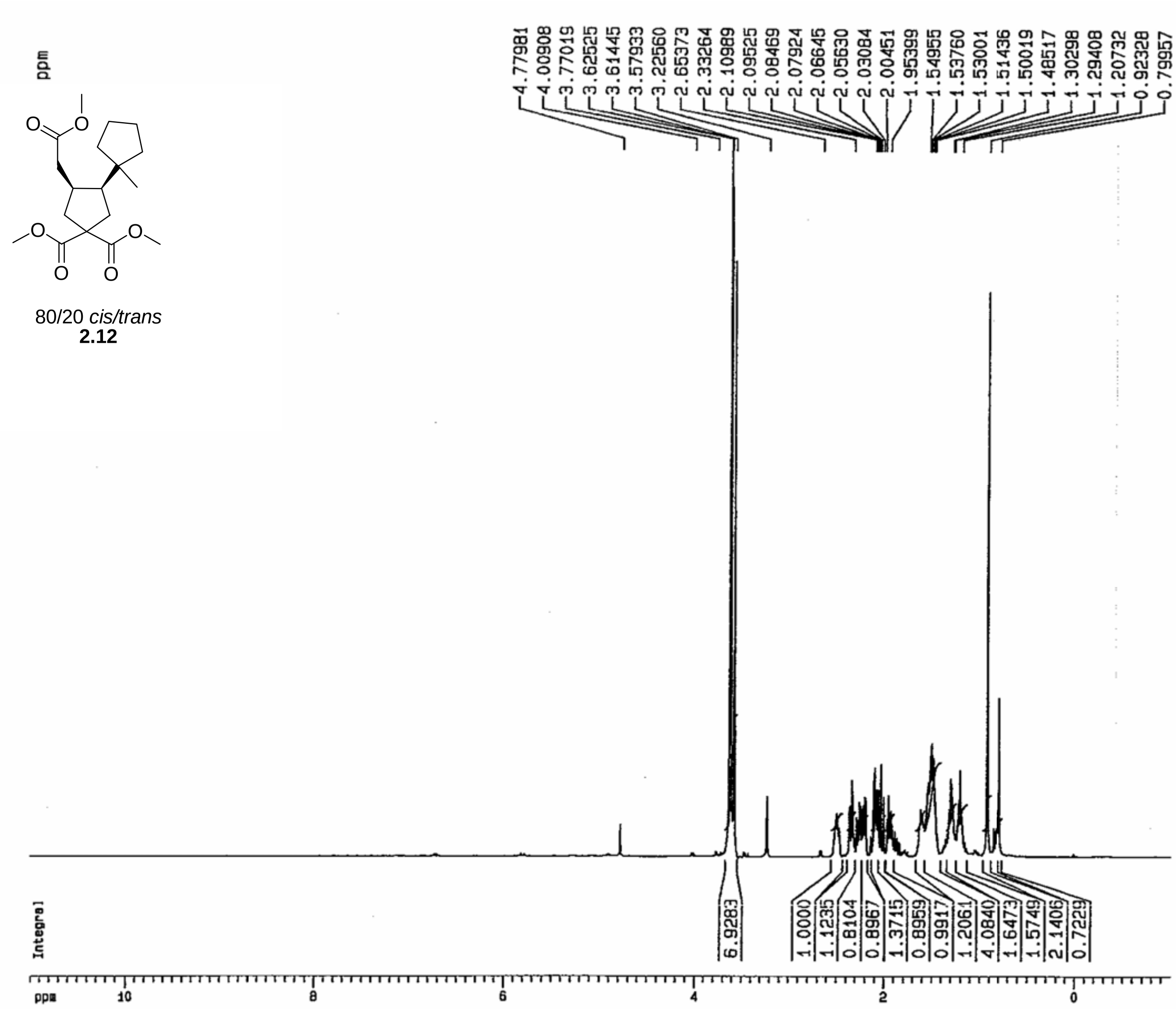


78/22 *cis/trans*
2.8b

```
F2 - Acquisition Parameters
Date_            500000
Time               5.48
INSTRUM           spect
PROBHD     5 mm TXI 13C
PULPROG        c13wonoe
TD                32768
SOLVENT           CDCl3
NS                 1473
DS                    0
SWH           32679.738 Hz
FIDRES         0.997306 Hz
AQ            0.5014004 sec
RG                32768
DW               15.300 usec
DE                 6.00 usec
TE                290.0 K
D3           0.00100000 sec
PL12               6.00 dB
D1           8.00000000 sec
CPDPRG2         waltz16
PCPD2            100.00 usec
SFO2        500.1330008 MHz
NUC2                 1H
PL2              120.00 dB
P1                21.60 usec
DE                 6.00 usec
SFO1        125.7715724 MHz
NUC1                13C
PL1                0.00 dB

F2 - Processing parameters
SI                 8192
SF          125.7578000 MHz
WDW                  EM
SSB                   0
LB                 4.00 Hz
GB                    0
PC                 1.00

1D NMR plot parameters
CX                20.00 cm
F1P             220.000 ppm
F1             27666.71 Hz
F2P             -10.000 ppm
F2             -1257.58 Hz
PPMCM          11.50000 ppm/cm
HZCM         1446.21472 Hz/cm
```



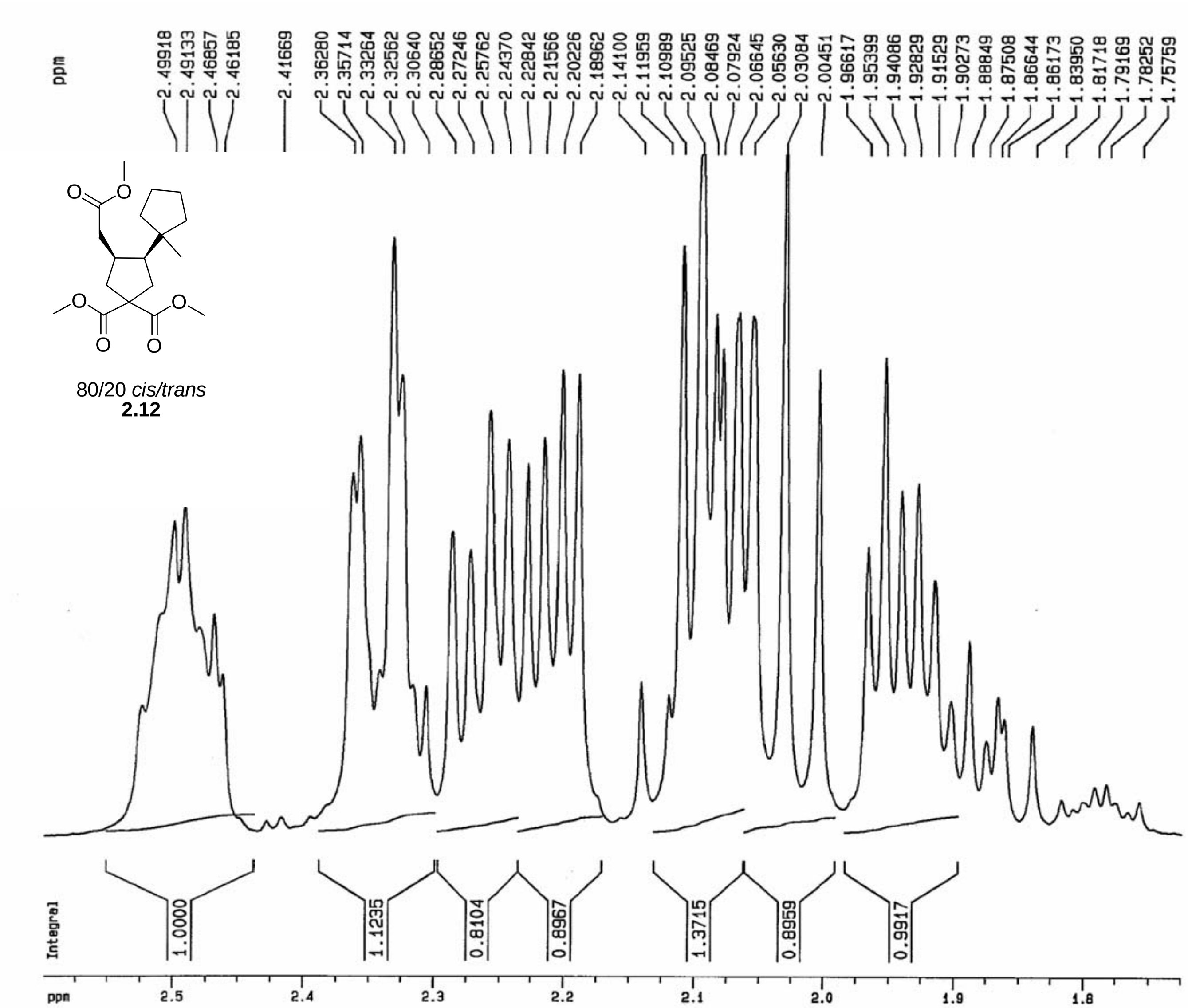
80/20 *cis/trans*
2.12

```
EXPNO                1
PROCNO               1

F2 - Acquisition Parameters
Date_           500000
Time             17.51
INSTRUM          spect
PROBHD   5 mm TXI 13C
PULPROG             zg
TD               32768
SOLVENT           MeOH
NS                  16
DS                   0
SWH           7507.507 Hz
FIDRES        0.229111 Hz
AQ           2.1823988 sec
RG                  16
DW              66.600 usec
DE                6.00 usec
TE               290.0 K
D1          1.00000000 sec
P1               11.00 usec
DE                6.00 usec
SFO1      500.1330008 MHz
NUC1                1H
PL1               0.00 dB

F2 - Processing parameters
SI               32768
SF        500.1300532 MHz
WDW                 EM
SSB                  0
LB                0.40 Hz
GB                   0
PC                1.00

1D NMR plot parameters
CX               20.00 cm
F1P             11.000 ppm
F1             5501.43 Hz
F2P             -1.000 ppm
F2             -500.13 Hz
PPMCM          0.60000 ppm/cm
HZCM         300.07803 Hz/cm
```



80/20 *cis/trans*
2.12

EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

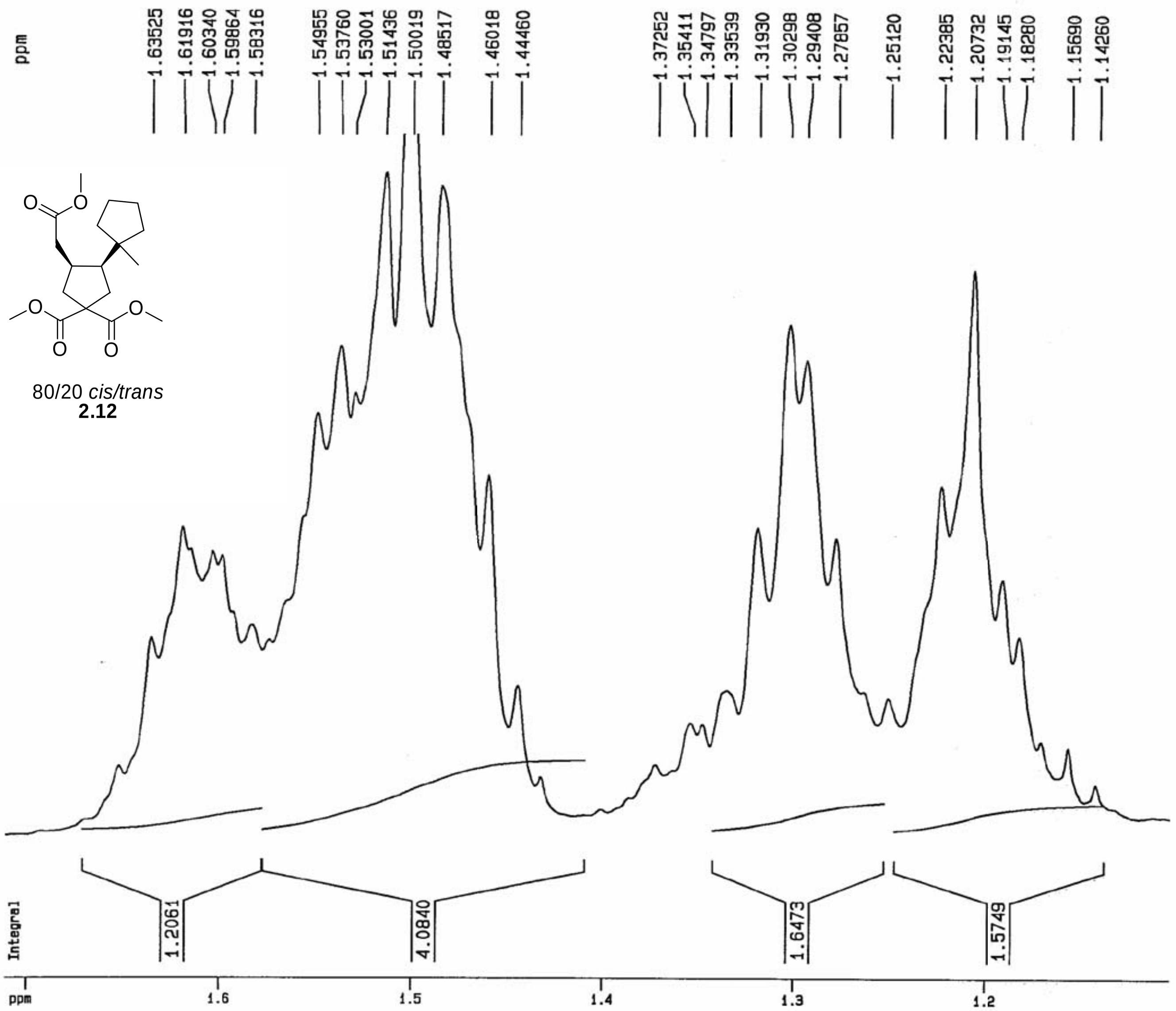
Date_	500000
Time	17.51
INSTRUM	spect
PROBHD	5 mm TXI 13C
PULPROG	zg
TD	32768
SOLVENT	MeOH
NS	16
DS	0
SWH	7507.507 Hz
FIDRES	0.229111 Hz
AQ	2.1823988 sec
RG	16
DW	66.600 usec
DE	6.00 usec
TE	290.0 K
D1	1.00000000 sec
P1	11.00 usec
DE	6.00 usec
SFO1	500.1330008 MHz
NUC1	1H
PL1	0.00 dB

F2 - Processing parameters

SI	32768
SF	500.1300532 MHz
WDW	EM
SSB	0
LB	0.40 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	2.599 ppm
F1	1299.70 Hz
F2P	1.725 ppm
F2	862.51 Hz
PPMCM	0.04371 ppm/cm
HZCM	21.85944 Hz/cm



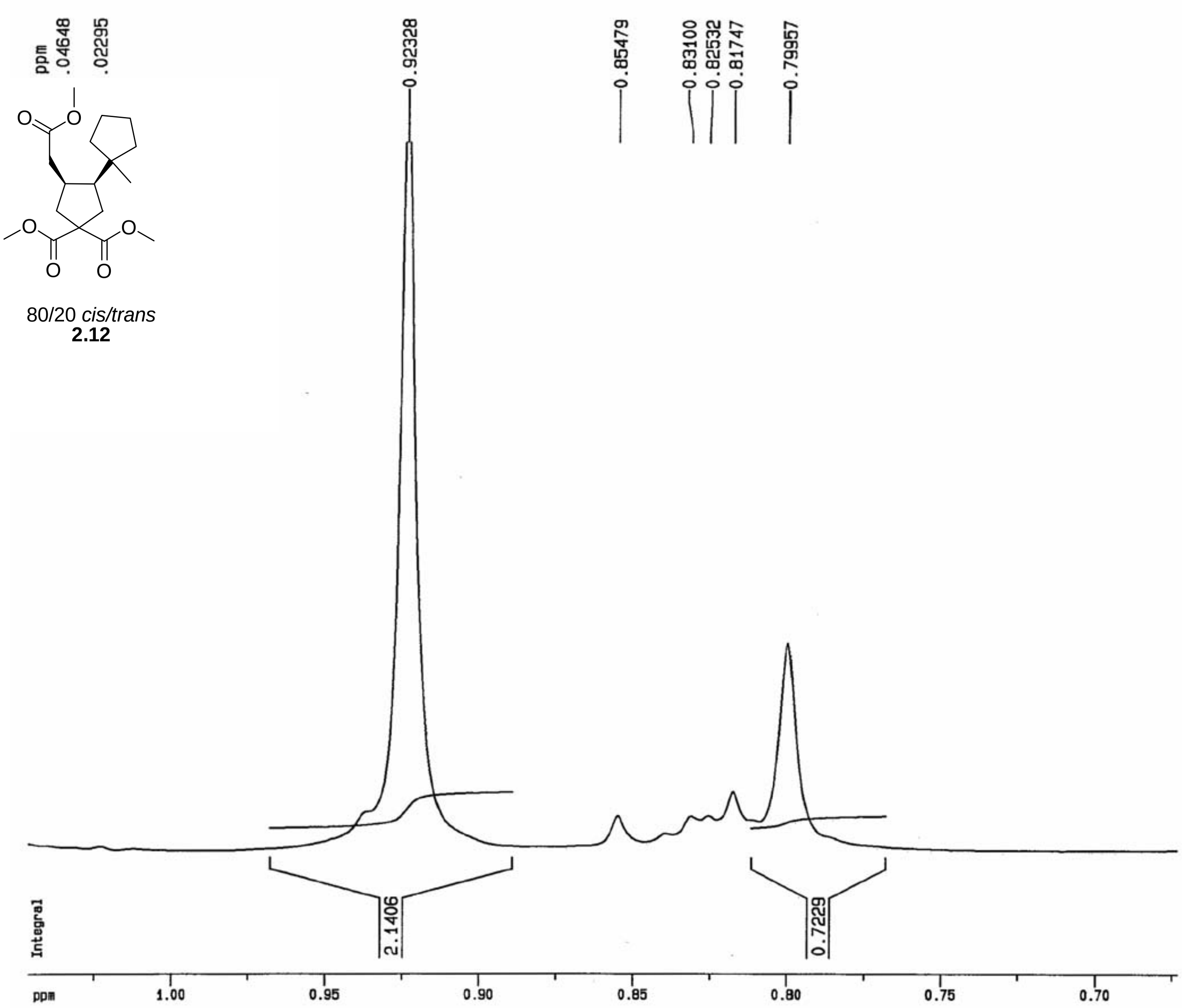
80/20 *cis/trans*
2.12

```
NAME              jt217-2
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_              500000
Time                17.51
INSTRUM             spect
PROBHD       5 mm TXI 13C
PULPROG                zg
TD                  32768
SOLVENT              MeOH
NS                     16
DS                      0
SWH              7507.507 Hz
FIDRES           0.229111 Hz
AQ              2.1823988 sec
RG                     16
DW                 66.600 usec
DE                   6.00 usec
TE                  290.0 K
D1             1.00000000 sec
P1                  11.00 usec
DE                   6.00 usec
SFO1         500.1330008 MHz
NUC1                   1H
PL1                  0.00 dB

F2 - Processing parameters
SI                  32768
SF           500.1300532 MHz
WDW                    EM
SSB                     0
LB                   0.40 Hz
GB                      0
PC                   1.00

1D NMR plot parameters
CX                  20.00 cm
F1P                 1.711 ppm
F1                 855.67 Hz
F2P                 1.104 ppm
F2                 552.02 Hz
PPMCM             0.03036 ppm/cm
HZCM             15.18245 Hz/cm
```



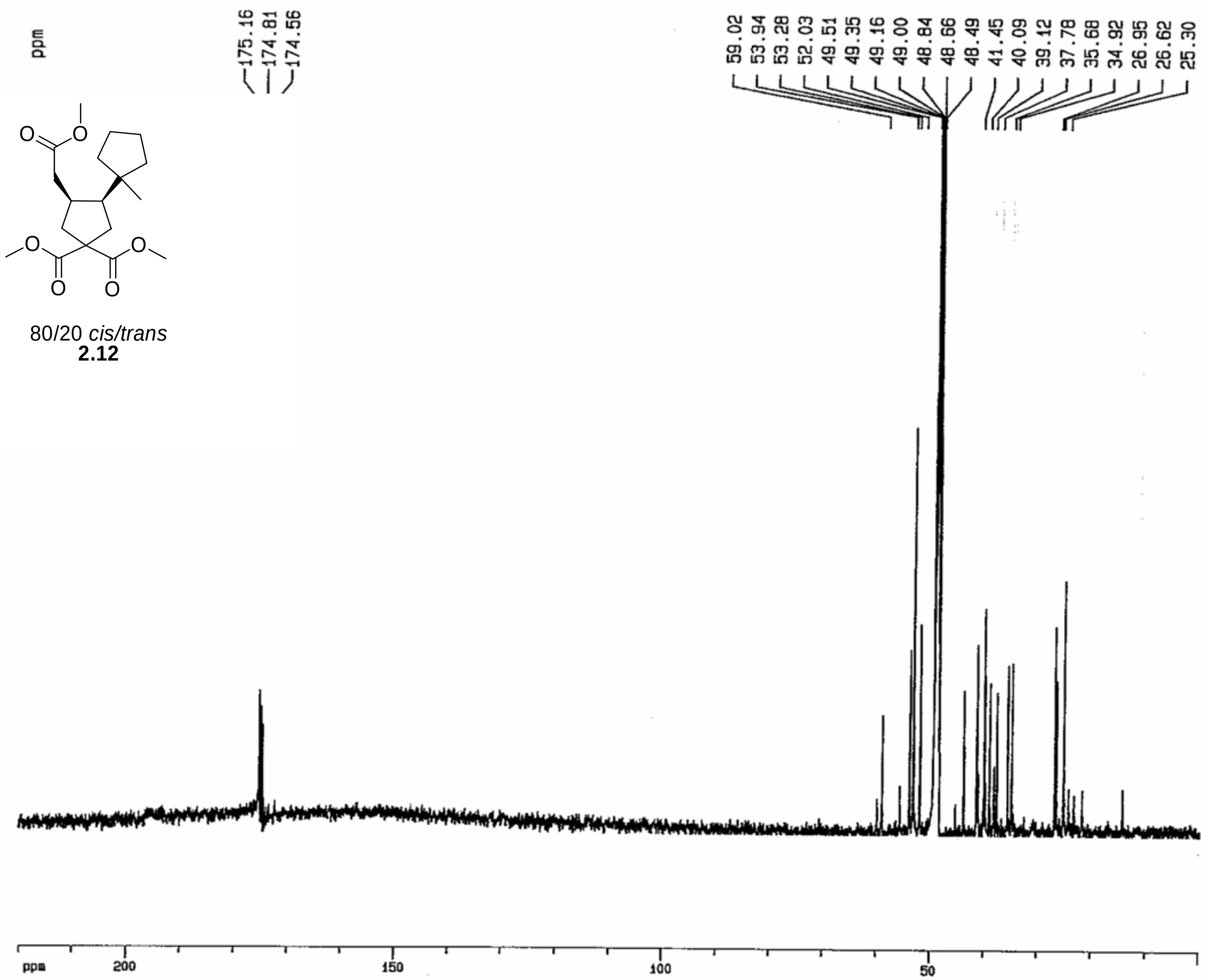
80/20 *cis/trans*
2.12

```
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_            500000
Time              17.51
INSTRUM           spect
PROBHD     5 mm TXI 13C
PULPROG              zg
TD                32768
SOLVENT            MeOH
NS                   16
DS                    0
SWH            7507.507 Hz
FIDRES         0.229111 Hz
AQ            2.1823988 sec
RG                   16
DW               66.600 usec
DE                 6.00 usec
TE                290.0 K
D1           1.00000000 sec
P1                11.00 usec
DE                 6.00 usec
SFO1        500.1330008 MHz
NUC1                 1H
PL1                0.00 dB

F2 - Processing parameters
SI                32768
SF          500.1300532 MHz
WDW                  EM
SSB                   0
LB                 0.40 Hz
GB                    0
PC                 1.00

1D NMR plot parameters
CX                20.00 cm
F1P               1.046 ppm
F1               523.38 Hz
F2P               0.673 ppm
F2               336.66 Hz
PPMCM           0.01867 ppm/cm
HZCM            9.33559 Hz/cm
```



80/20 *cis/trans*
2.12

F2 - Acquisition Parameters

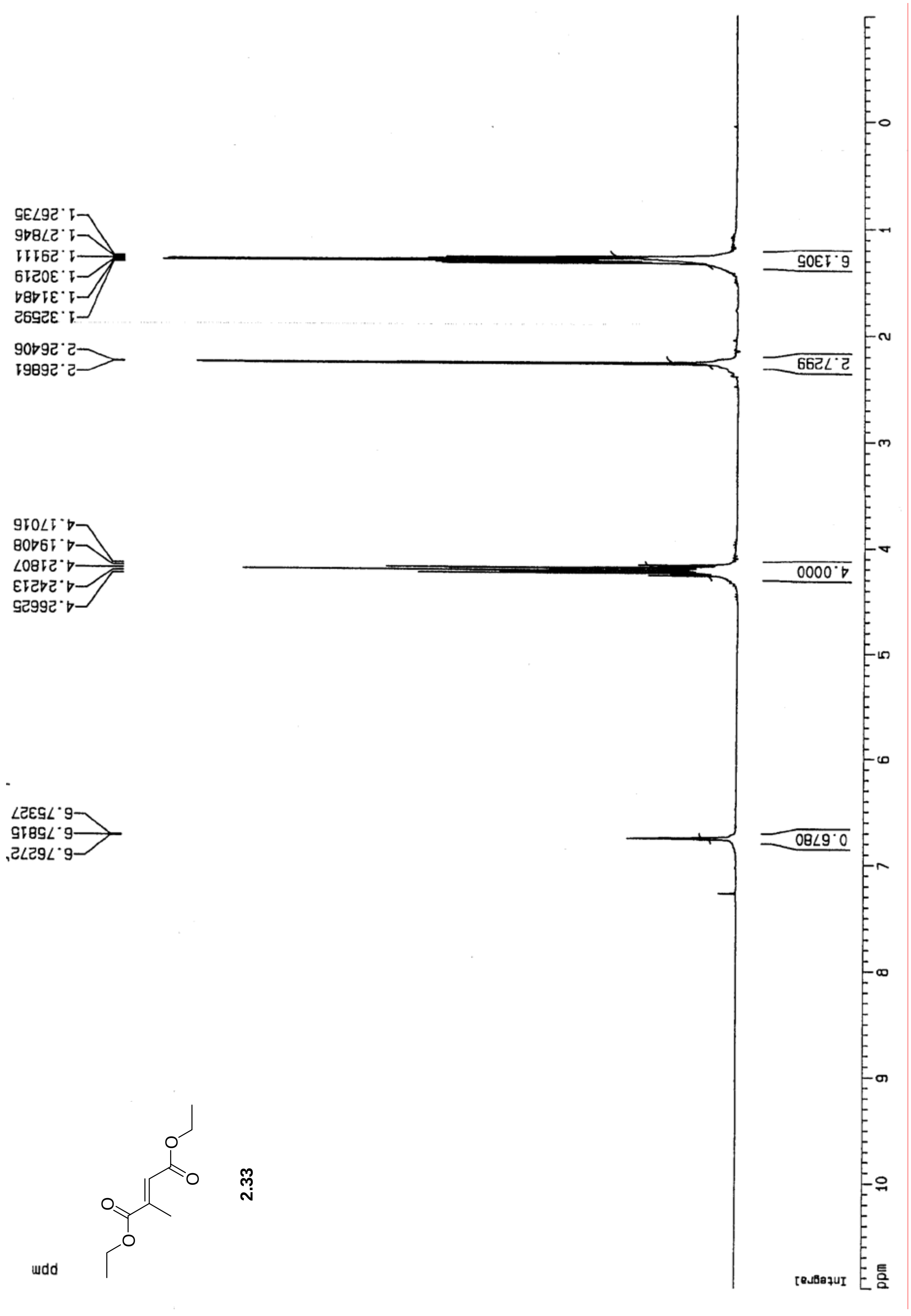
Date_	500000
Time	18.11
INSTRUM	spect
PROBHD	5 mm TXI 13C
PULPROG	c13wonoe
TD	32768
SOLVENT	CDC13
NS	2538
DS	0
SWH	32679.738 Hz
FIDRES	0.997306 Hz
AQ	0.5014004 sec
RG	18390.4
DW	15.300 usec
DE	6.00 usec
TE	290.0 K
D3	0.00100000 sec
PL12	6.00 dB
D1	8.00000000 sec
CPDPRG2	waltz16
PCPD2	100.00 usec
SFO2	500.1330008 MHz
NUC2	1H
PL2	120.00 dB
P1	21.60 usec
DE	6.00 usec
SFO1	125.7715724 MHz
NUC1	13C
PL1	0.00 dB

F2 - Processing parameters

SI	8192
SF	125.7576153 MHz
WDW	EM
SSB	0
LB	4.00 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	220.000 ppm
F1	27666.68 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	11.00000 ppm/cm
HZCM	1383.33374 Hz/cm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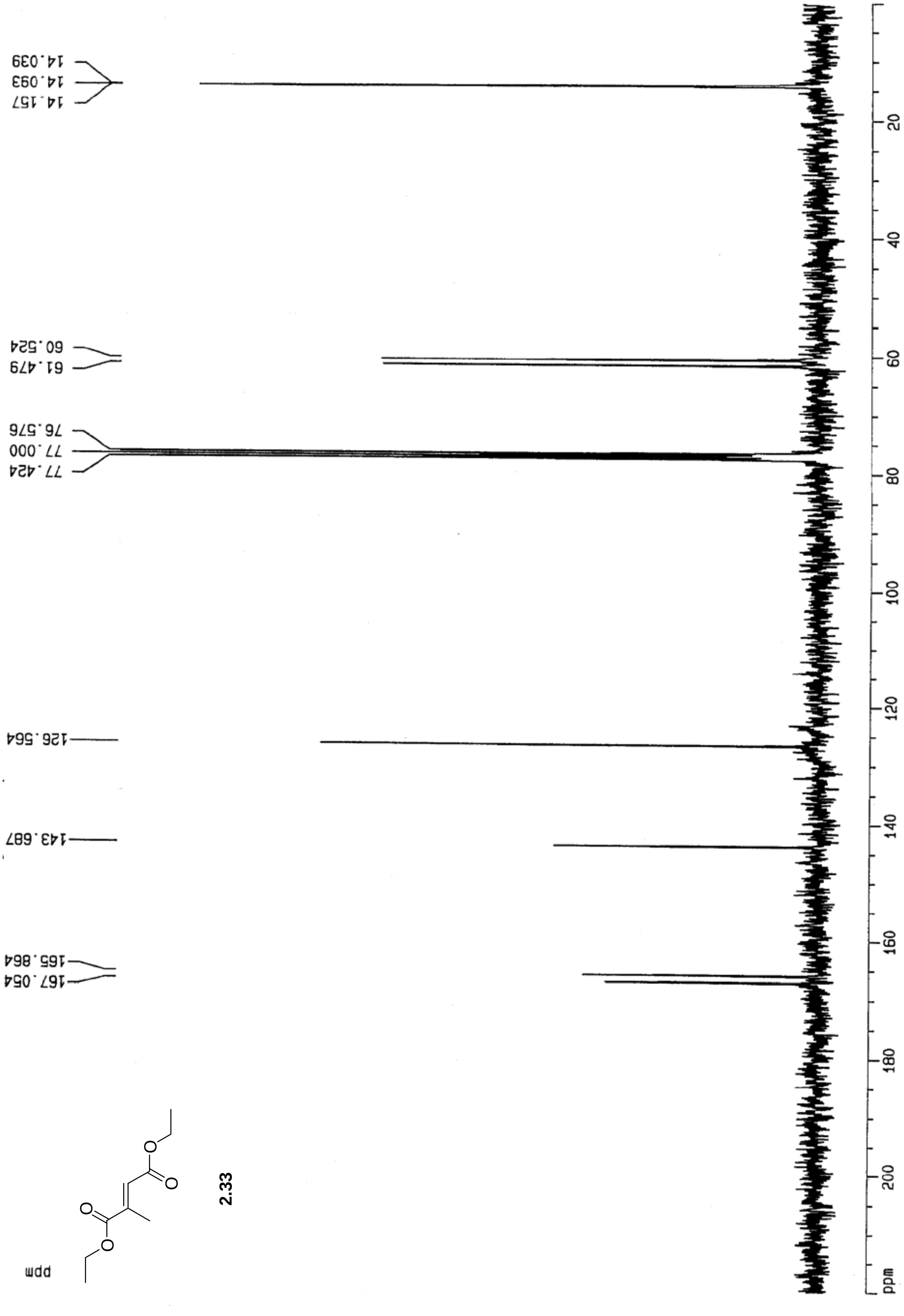
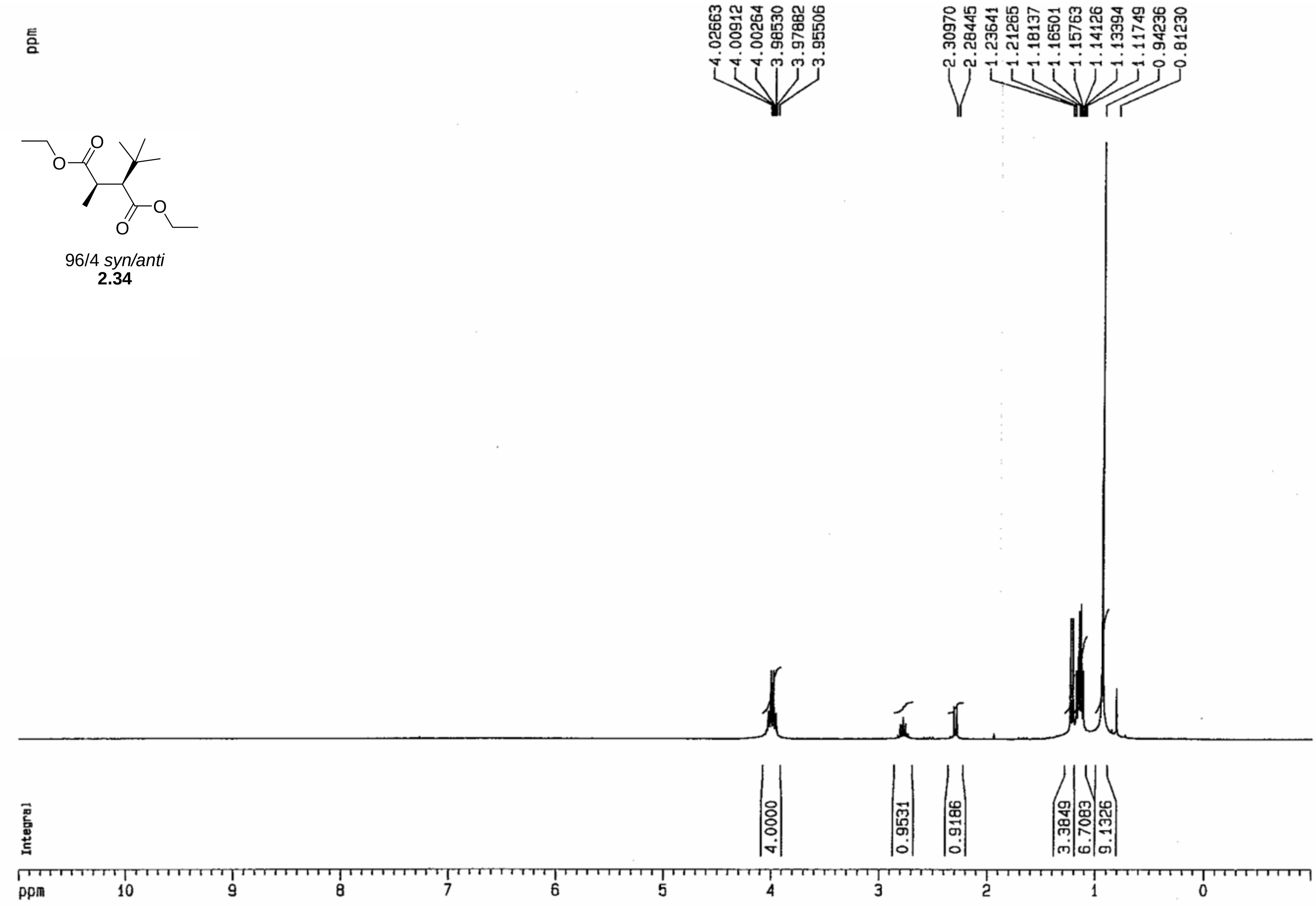
1.29111
1.30219
1.31484
1.32592
2.26406
2.26861
4.17016
4.19408
4.21807
4.24213
4.26625
6.75327
6.75815
6.76272
6.1305
2.7299
4.0000
0.6780
Integral
ppm
0
1
2
3
4
5
6
7
8
9
10
ppm

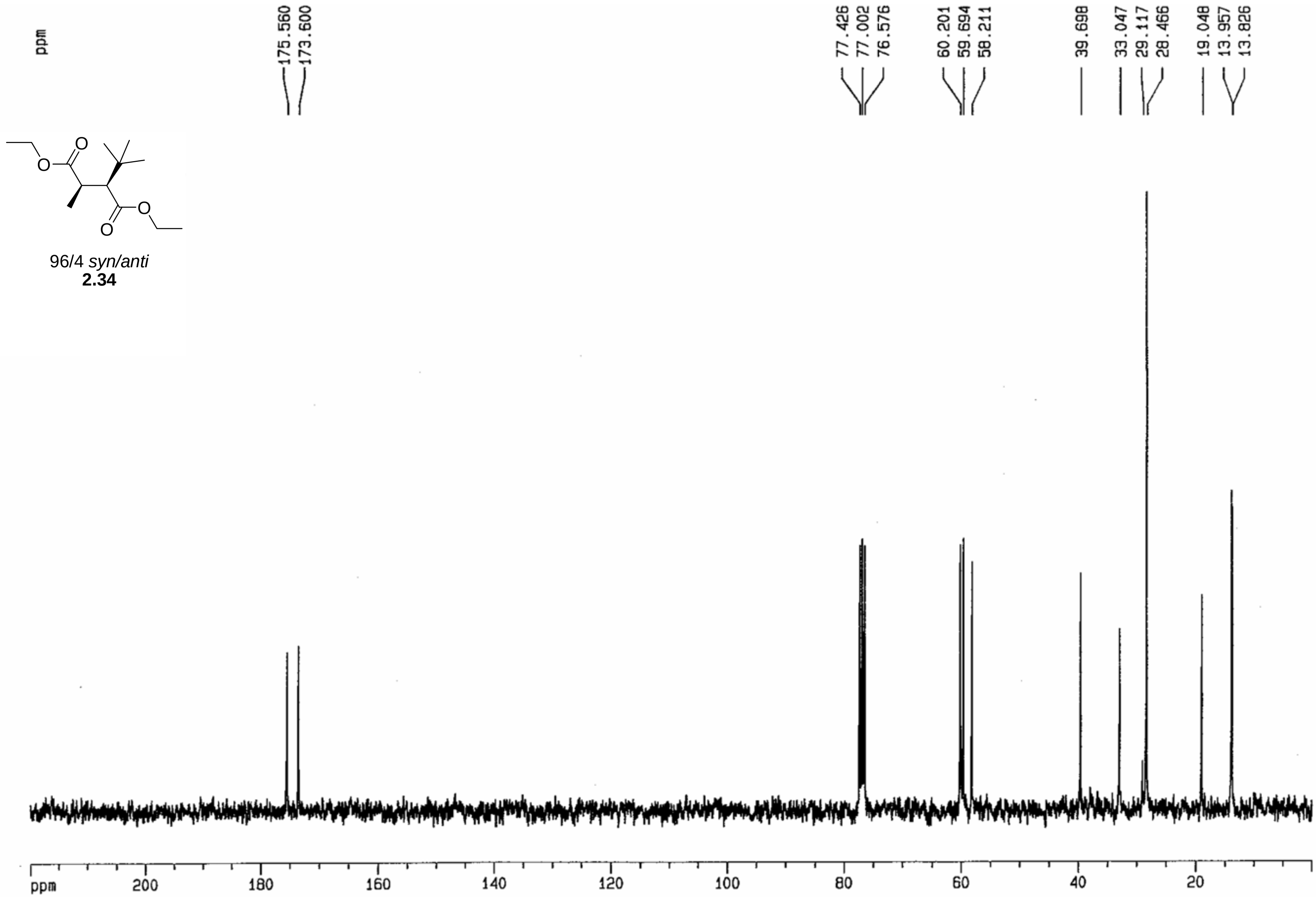
2.33


14.039
14.093
14.157
60.524
61.479
76.576
77.000
77.424
126.564
143.687
165.864
167.054
ppm
20
40
60
80
100
120
140
160
180
200
ppm

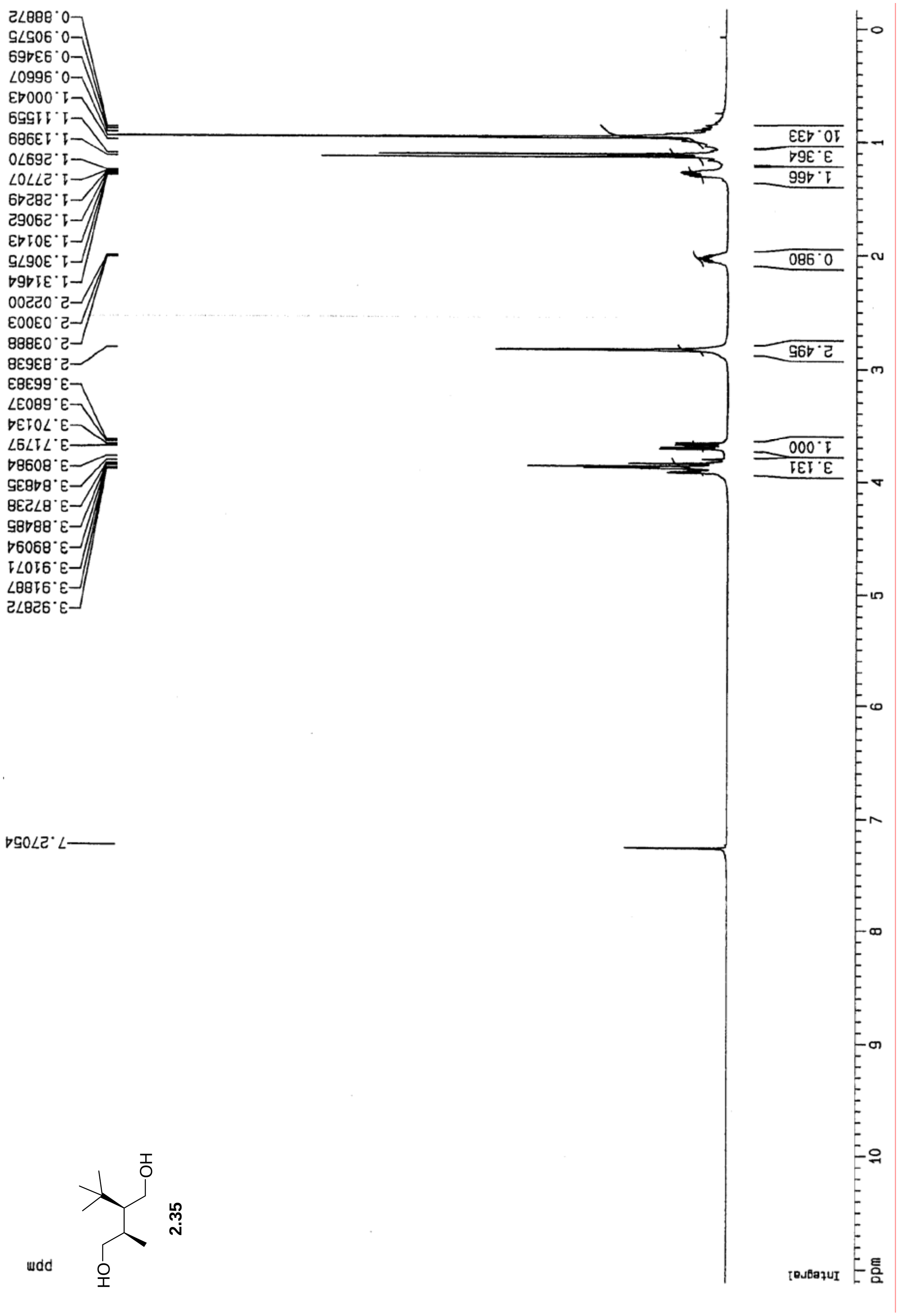
2.33



96/4 *syn/anti*
2.34



96/4 *syn/anti*
2.34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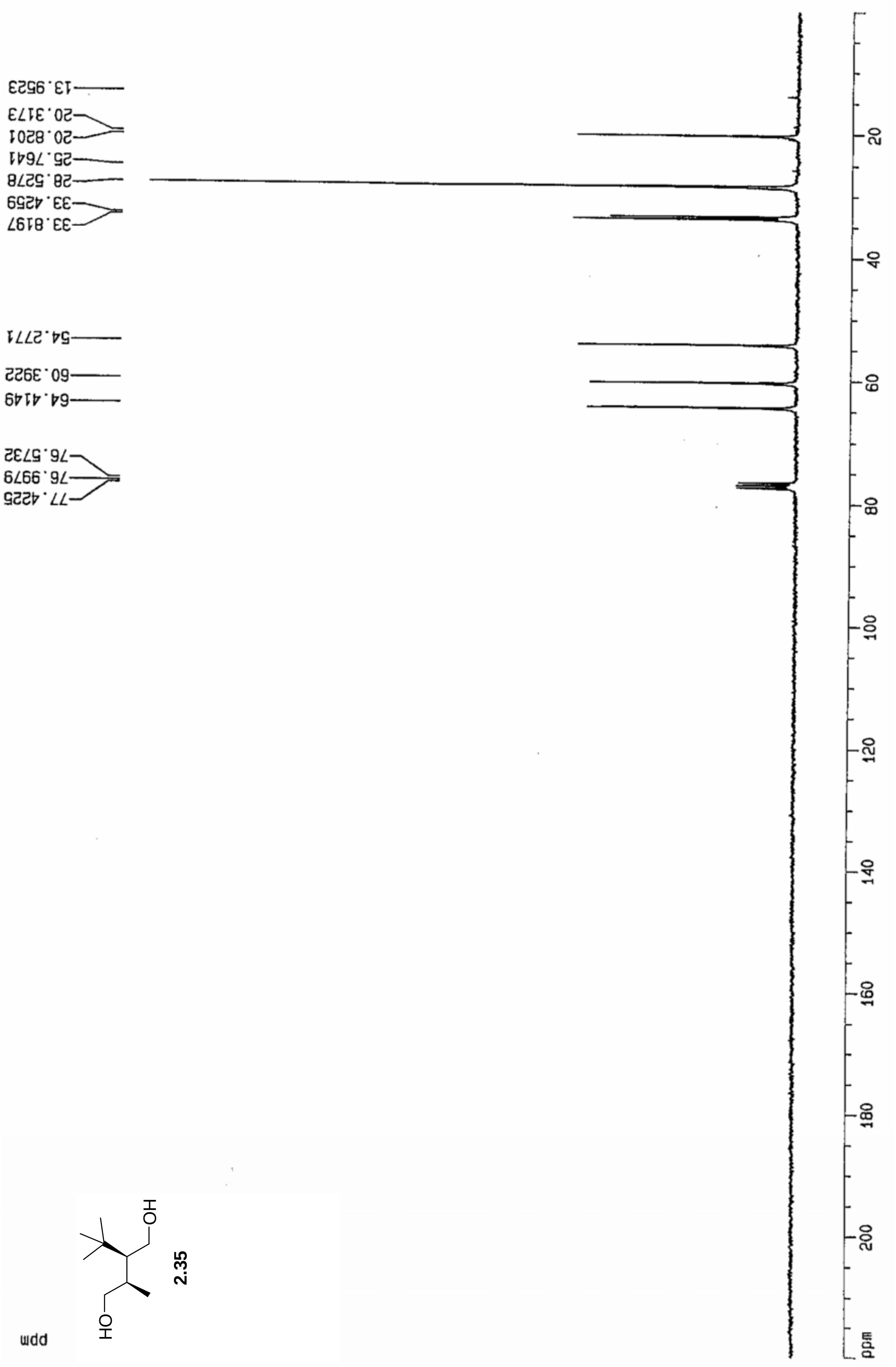
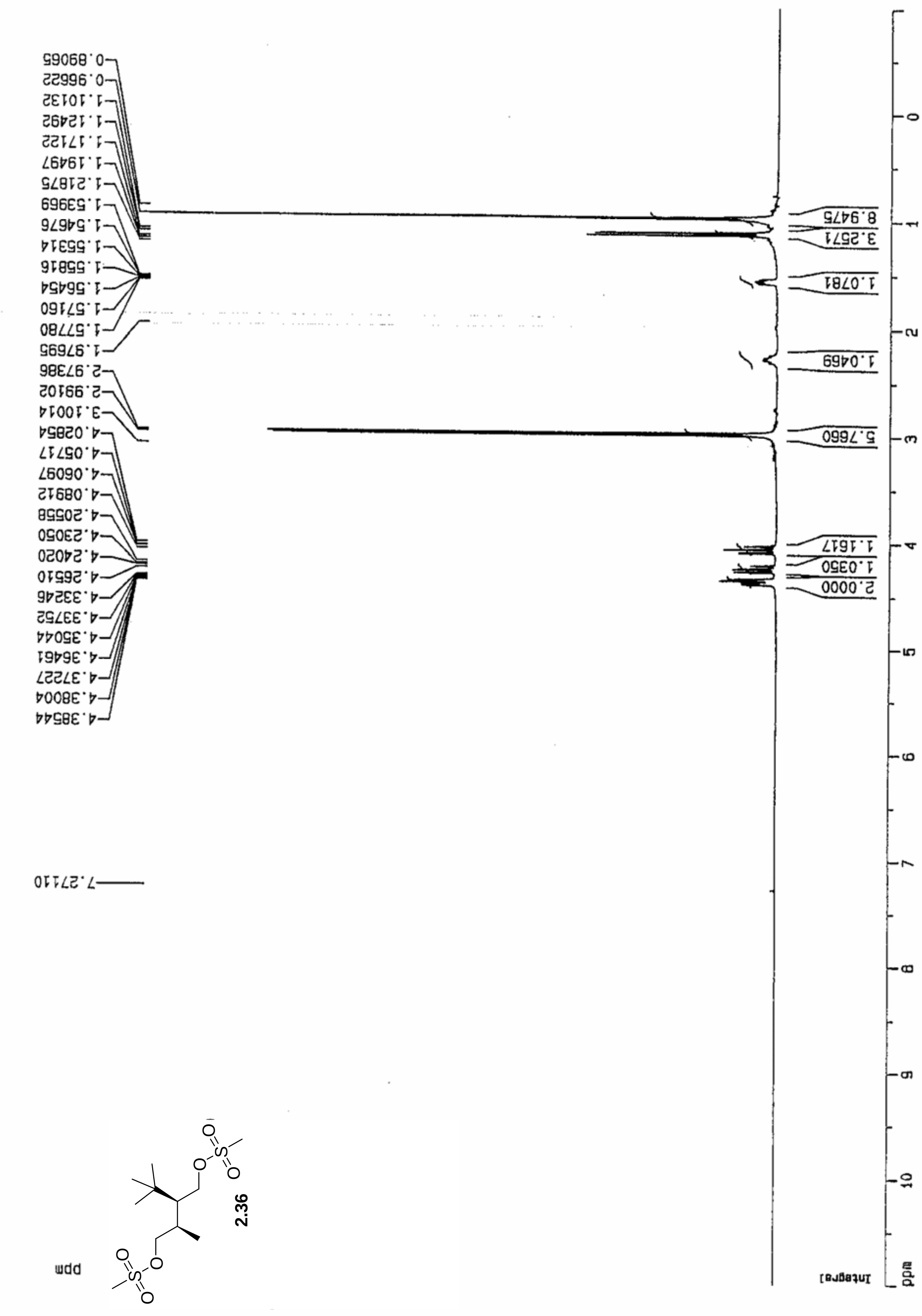
0.93469
0.96607
1.00043
1.11559
1.13989
1.26970
1.27707
1.28249
1.29062
1.30143
1.30675
1.31464
2.02200
2.03003
2.03888
2.83638
3.66383
3.68037
3.70134
3.71797
3.80984
3.84835
3.87238
3.88485
3.89094
3.91071
3.91887
3.92872
7.27054
ppm
HO
OH
10.433
3.364
1.466
0.980
2.495
1.000
3.131
Integral
0
1
2
3
4
5
6
7
8
9
10
ppm

2.35


2.35

13.9523
20.3173
20.8201
25.7641
28.5278
33.4259
33.8197
54.2771
60.3922
64.4149
76.5732
76.9979
77.4225
ppm
HO
OH
20
40
60
80
100
120
140
160
180
200
ppm


2.36

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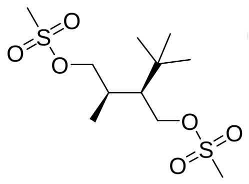
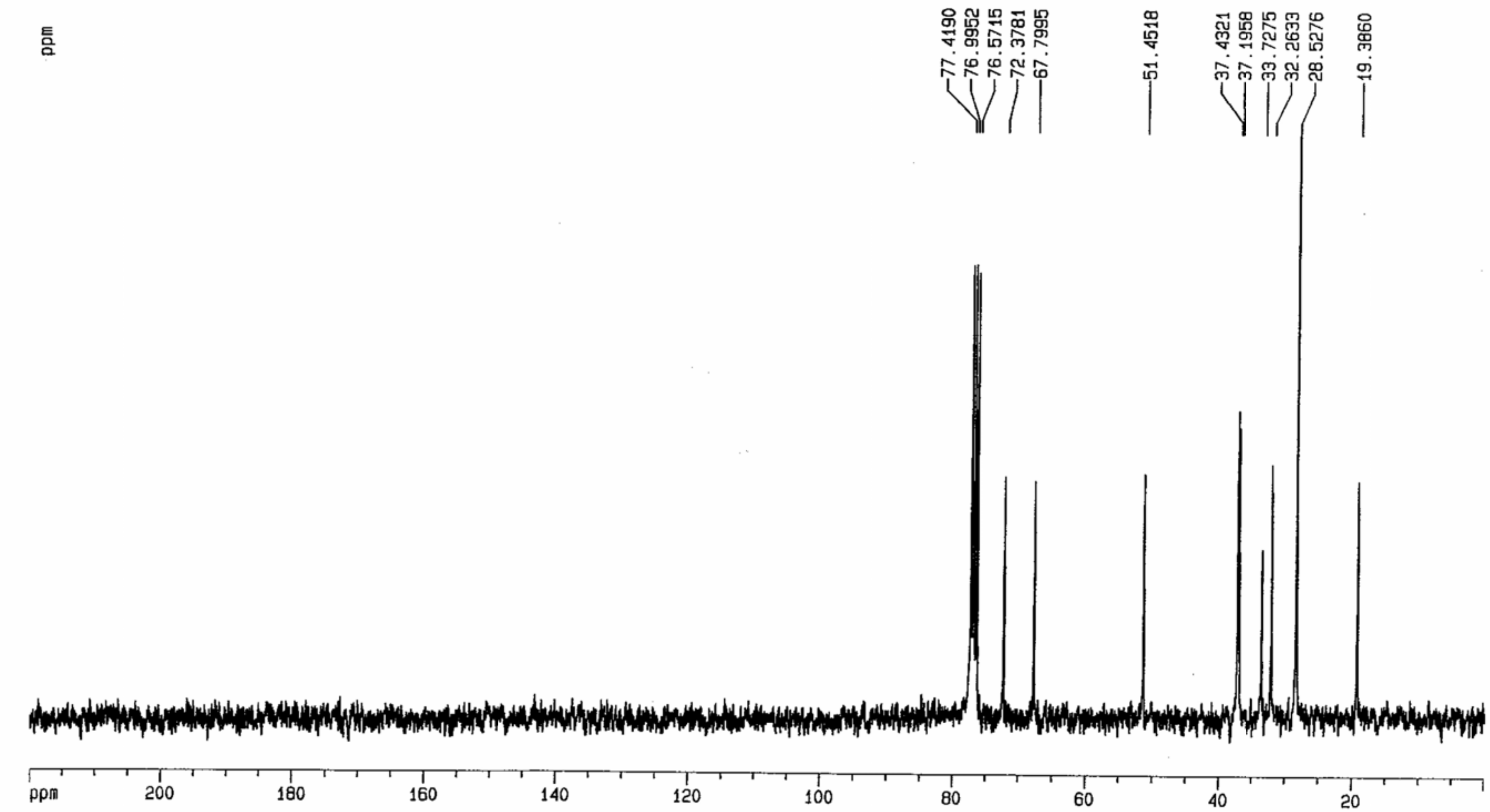
0.96622
1.10132
1.12492
1.17122
1.19497
1.21875
1.53969
1.54676
1.55314
1.55816
1.56454
1.57160
1.57780
1.97695
2.97386
2.99102
3.10014
4.02854
4.05717
4.06097
4.08912
4.20558
4.23050
4.24020
4.26510
4.33246
4.33752
4.35044
4.36461
4.37227
4.38004
4.38544
7.27110
ppm
8.9475
3.2571
1.0781
1.0469
5.7660
1.1617
1.0350
2.0000
Integral
0
1
2
3
4
5
6
7
8
9
10
ppm



2.36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76.5715
72.3781
67.7995
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37.4321
37.1958
33.7275
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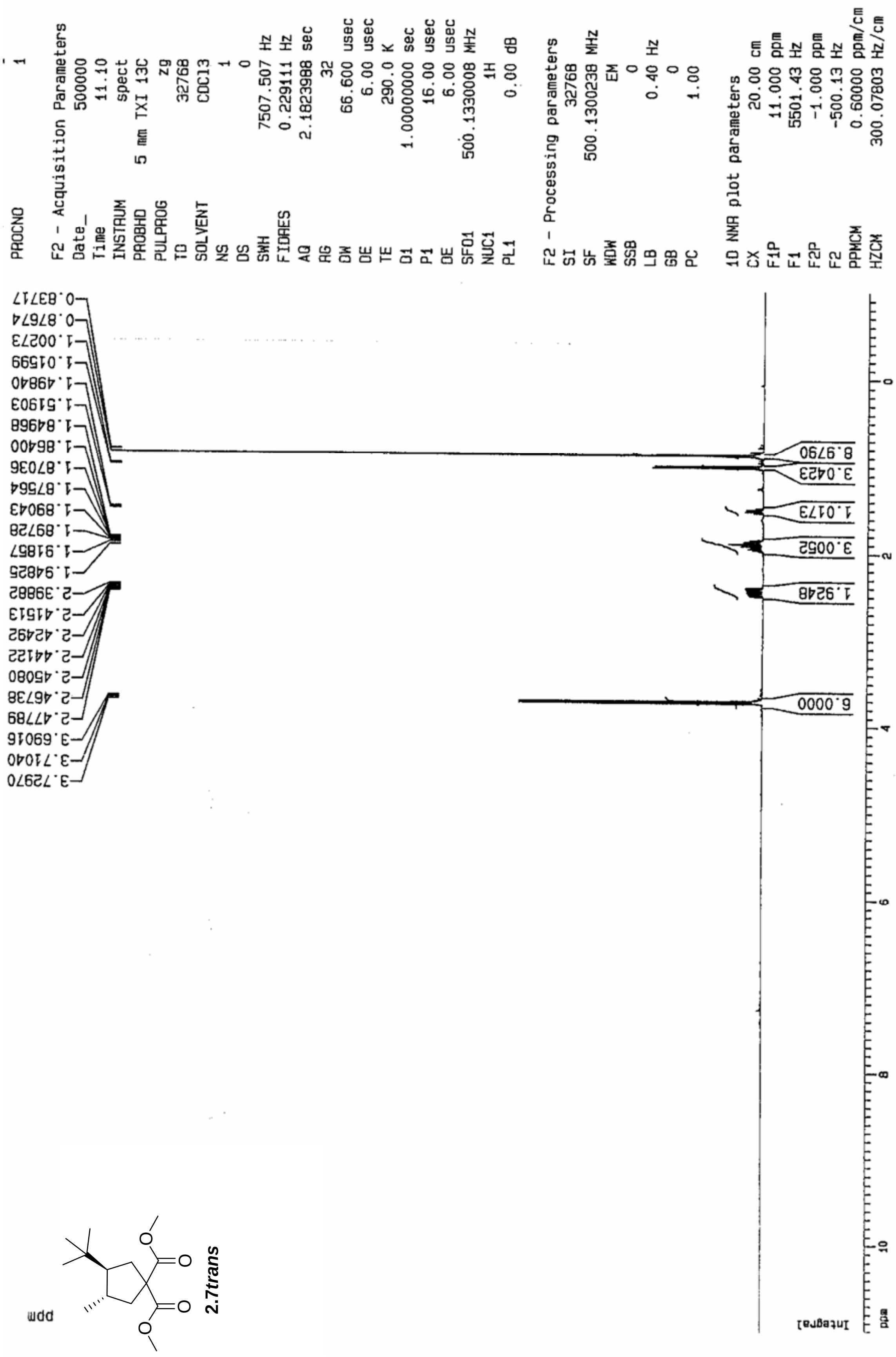
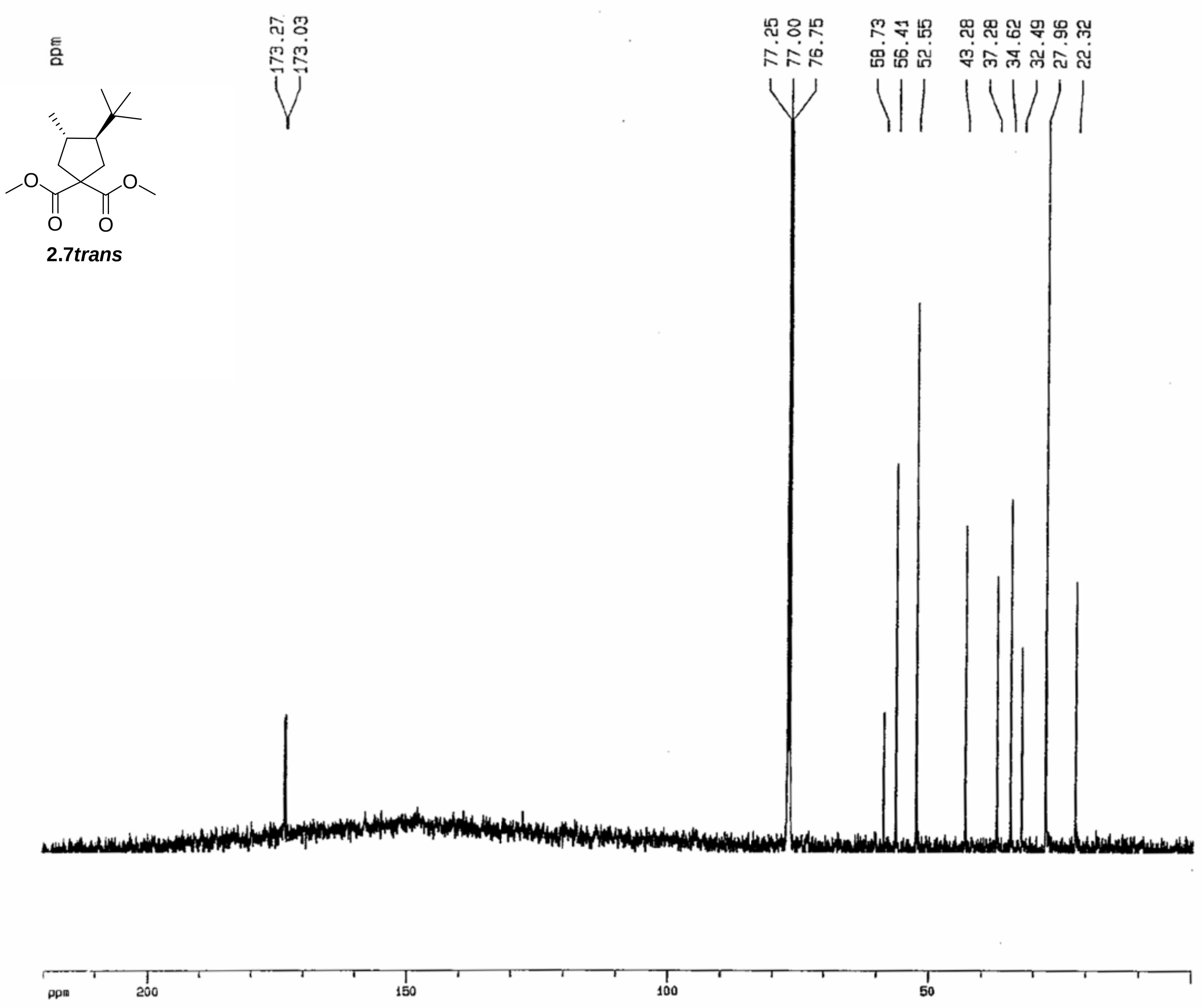
140
120
100
80
60
40
20


2.7trans

0.83717
0.87674
1.00273
1.01599
1.49840
1.51903
1.84968
1.86400
1.87036
1.87564
1.89043
1.89728
1.91857
1.94825
2.39882
2.41513
2.42492
2.44122
2.45080
2.46738
2.47789
3.69016
3.71040
3.72970
8.9790
3.0423
1.0173
3.0052
1.9248
6.0000
Integral
ppm
10
8
6
4
2
0
PROCNO 1
F2 - Acquisition Parameters
Date_ 500000
Time 11.10
INSTRUM spect
PROBHD 5 mm TXI 13C
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 1
DS 0
SWH 7507.507 Hz
FIDRES 0.229111 Hz
AQ 2.1823988 sec
RG 32
DW 66.600 usec
DE 6.00 usec
TE 290.0 K
D1 1.00000000 sec
P1 16.00 usec
DE 6.00 usec
SFO1 500.1330008 MHz
NUC1 1H
PL1 0.00 dB
F2 - Processing parameters
SI 32768
SF 500.1300238 MHz
WDW EM
SSB 0
LB 0.40 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 11.000 ppm
F1 5501.43 Hz
F2P -1.000 ppm
F2 -500.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 300.07803 Hz/cm

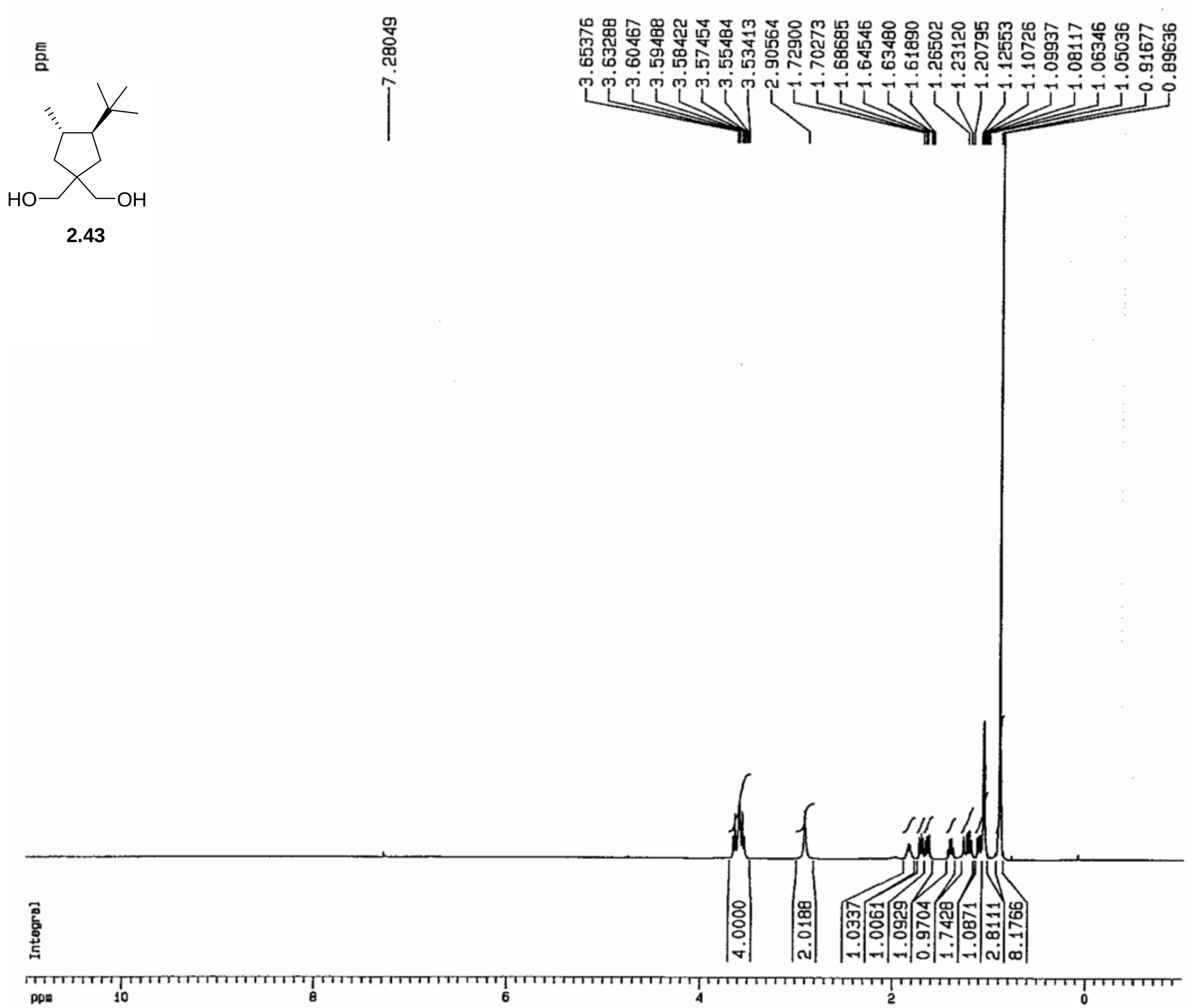


2.7*trans*

```
F2 - Acquisition Parameters
Date_               500000
Time                  0.22
INSTRUM              spect
PROBHD       5 mm TXI 13C
PULPROG           c13wonoe
TD                   32768
SOLVENT              CDCl3
NS                    2874
DS                       0
SWH          32679.738 Hz
FIDRES        0.997306 Hz
AQ           0.5014004 sec
RG                   32768
DW              15.300 usec
DE                6.00 usec
TE               290.0 K
D3          0.00100000 sec
PL12              6.00 dB
D1          8.00000000 sec
CPDPRG2           waltz16
PCPD2           100.00 usec
SF02        500.1330008 MHz
NUC2                    1H
PL2             120.00 dB
P1               21.60 usec
DE                6.00 usec
SF01        125.7715724 MHz
NUC1                   13C
PL1               0.00 dB

F2 - Processing parameters
SI                    8192
SF          125.7577961 MHz
WDW                     EM
SSB                      0
LB                4.00 Hz
GB                       0
PC                    1.00

1D NMR plot parameters
CX               20.00 cm
F1P            220.000 ppm
F1             27666.71 Hz
F2P              0.000 ppm
F2                0.00 Hz
PPMCM        11.00000 ppm/cm
HZCM       1383.33582 Hz/cm
```



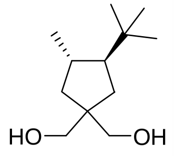
2.43

```
EXPNO                      1
PROCNO                     1

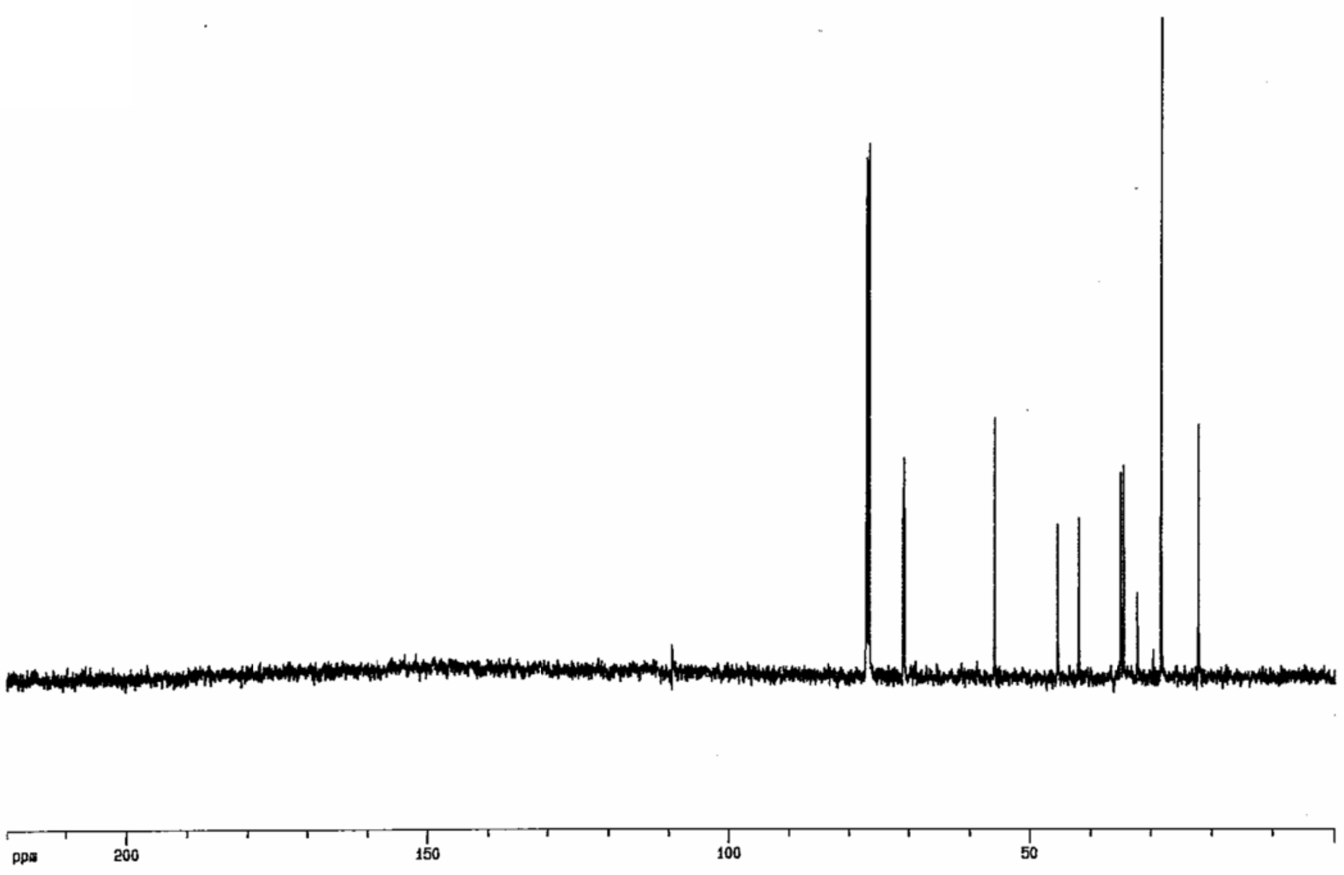
F2 - Acquisition Parameters
Date_                 500000
Time                   16.30
INSTRUM                spect
PROBHD       5 mm TXI 13C
PULPROG                   zg
TD                     32768
SOLVENT                CDCl3
NS                        16
DS                         0
SWH               7507.507 Hz
FIDRES            0.229111 Hz
AQ               2.1823988 sec
RG                      71.8
DW                  66.600 usec
DE                    6.00 usec
TE                   290.0 K
D1              1.00000000 sec
P1                   10.60 usec
DE                    6.00 usec
SFO1           500.1330008 MHz
NUC1                      1H
PL1                   0.00 dB

F2 - Processing parameters
SI                     32768
SF             500.1300185 MHz
WDW                       EM
SSB                        0
LB                    0.40 Hz
GB                         0
PC                      1.00

1D NMR plot parameters
CX                     20.00 cm
F1P                   11.000 ppm
F1                   5501.43 Hz
F2P                   -1.000 ppm
F2                   -500.13 Hz
PPMCM                0.60000 ppm/cm
HZCM               300.07800 Hz/cm
```



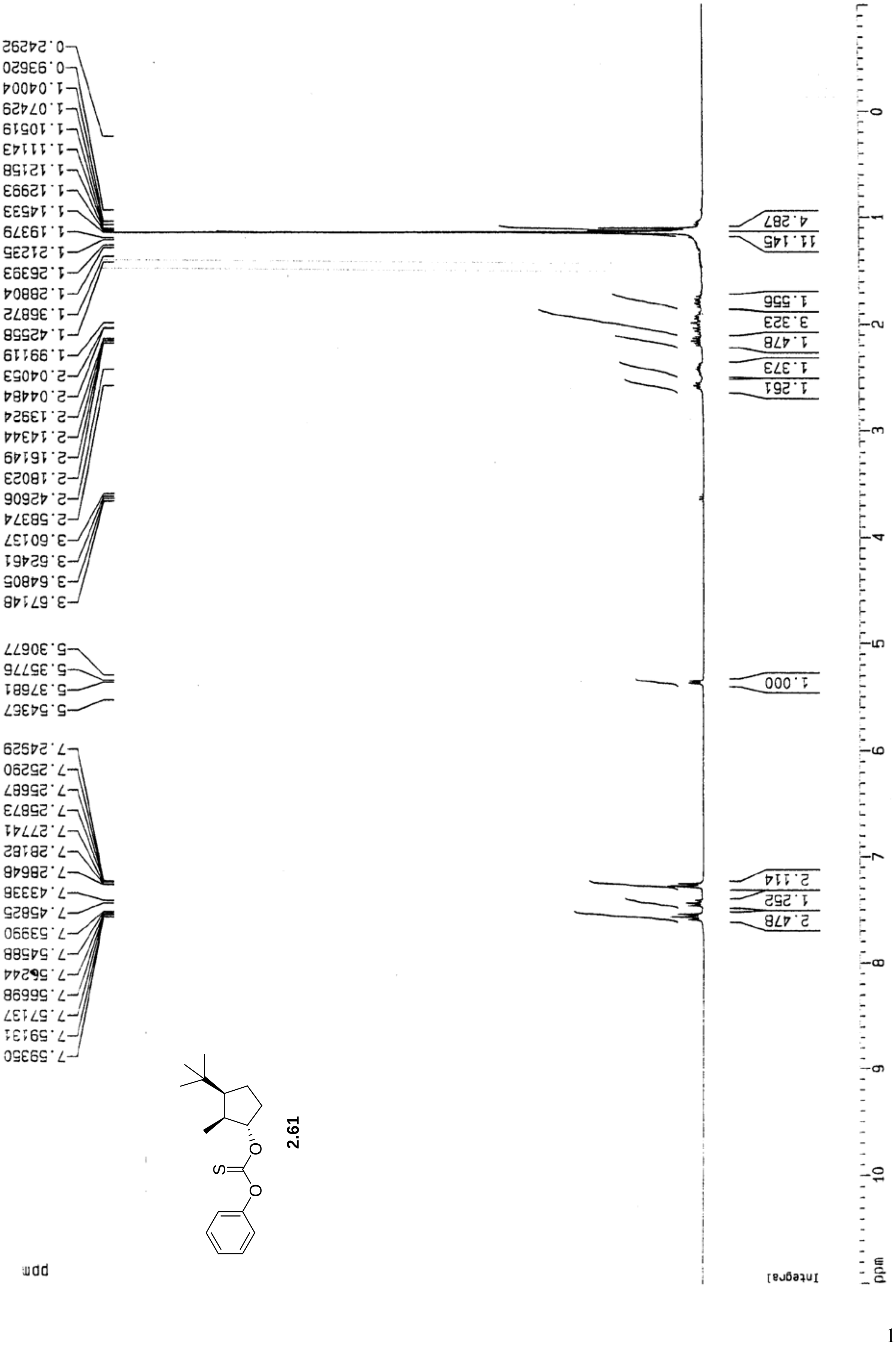
2.43



```
F2 - Acquisition Parameters
Date_             500000
Time               16.36
INSTRUM            spect
PROBHD      5 mm TXI 13C
PULPROG         c13wonoe
TD                 32768
SOLVENT            CDCl3
NS                   551
DS                     0
SWH            32679.738 Hz
FIDRES          0.997306 Hz
AQ             0.5014004 sec
RG                 32768
DW                15.300 usec
DE                  6.00 usec
TE                 290.0 K
D3            0.00100000 sec
PL12                6.00 dB
D1            8.00000000 sec
CPDPRG2          waltz16
PCPD2             100.00 usec
SF02         500.1330008 MHz
NUC2                  1H
PL2               120.00 dB
P1                 21.60 usec
DE                  6.00 usec
SF01         125.7715724 MHz
NUC1                 13C
PL1                 0.00 dB

F2 - Processing parameters
SI                  8192
SF           125.7577961 MHz
WDW                   EM
SSB                    0
LB                  4.00 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX                 20.00 cm
F1P              220.000 ppm
F1              27666.71 Hz
F2P                0.000 ppm
F2                  0.00 Hz
PPMCM           11.00000 ppm/cm
HZCM          1383.33582 Hz/cm
```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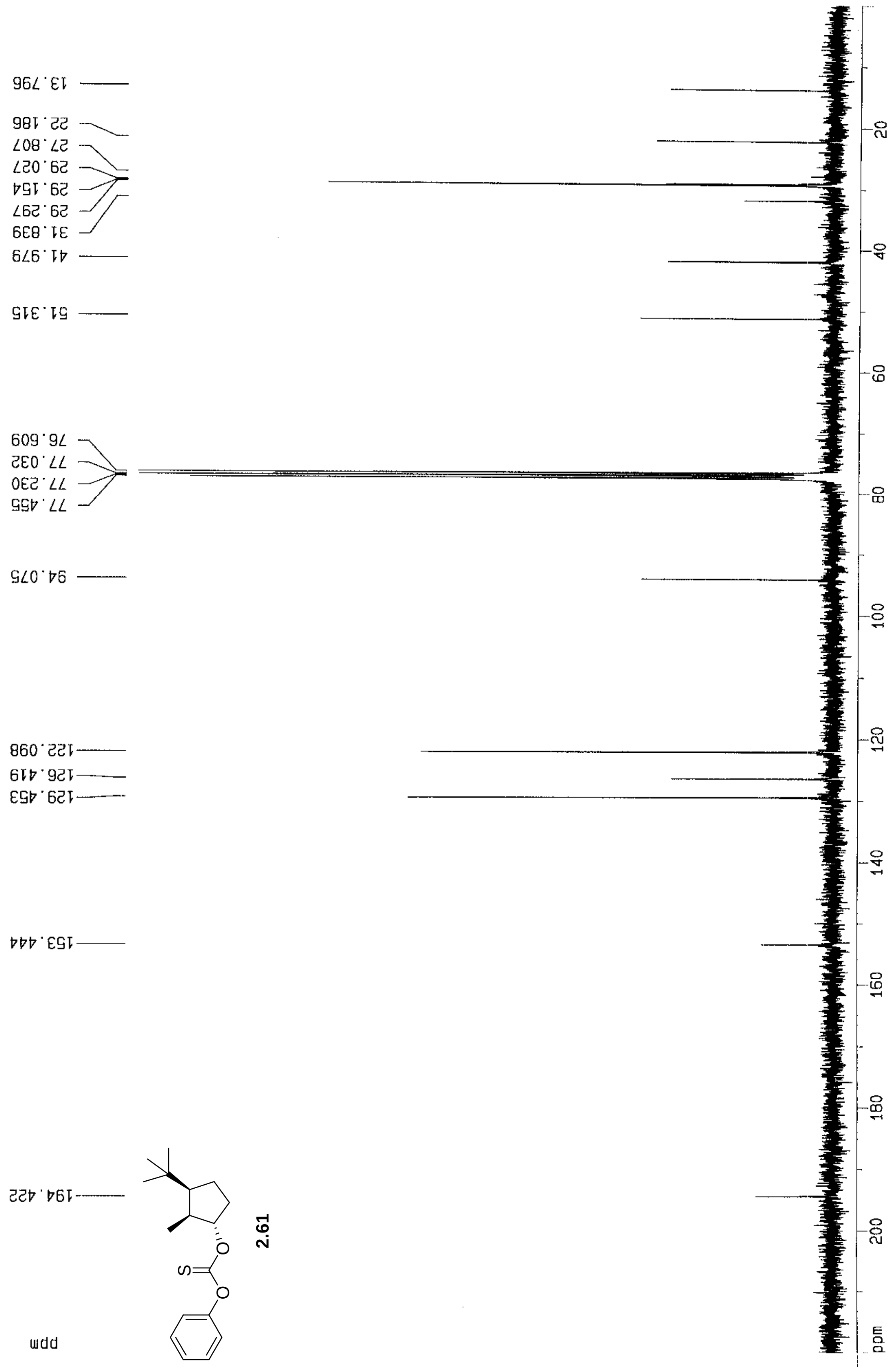
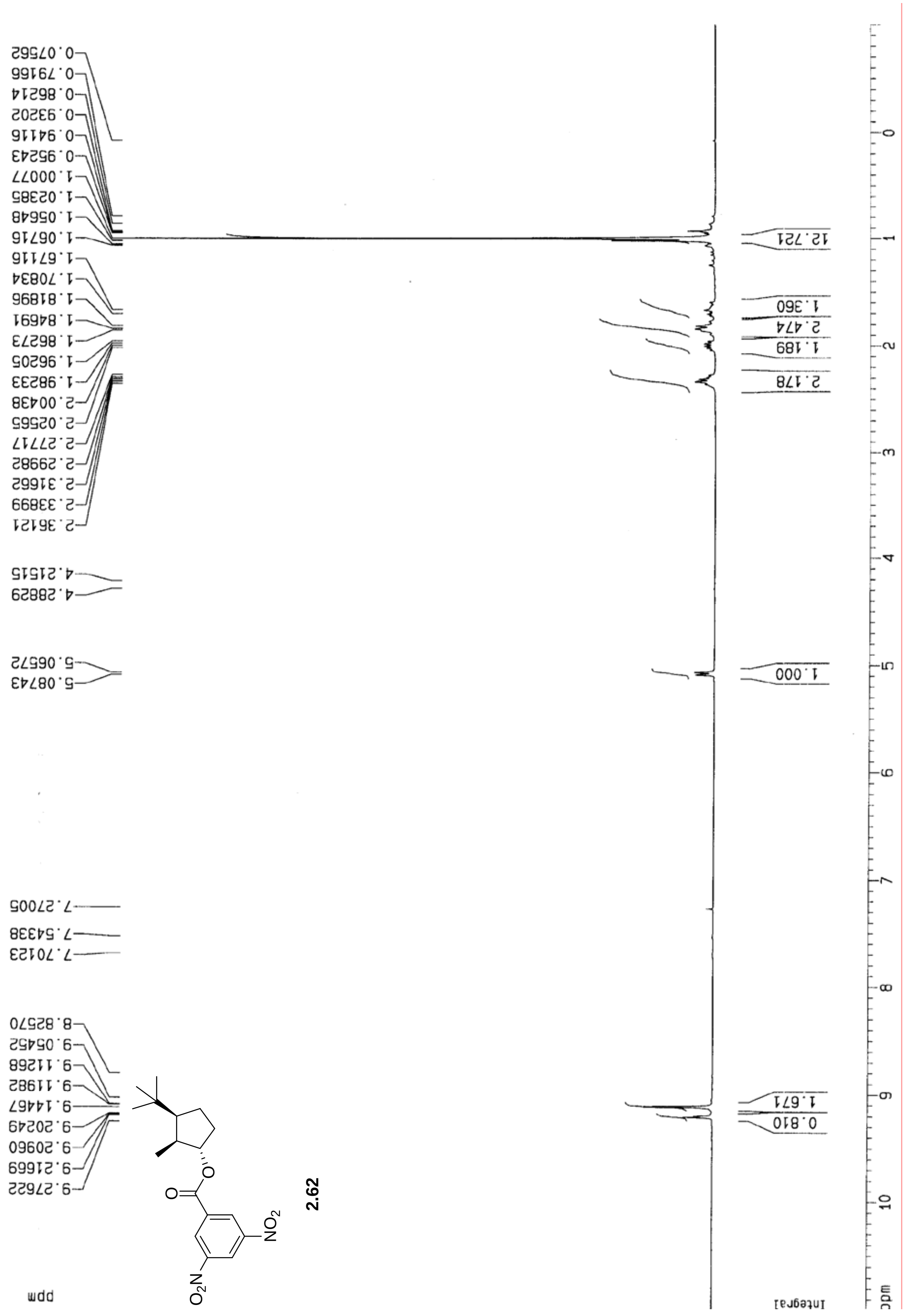
0.93620
1.04004
1.07429
1.10519
1.11143
1.12158
1.12993
1.14533
1.19379
1.21235
1.26393
1.28804
1.36872
1.42558
1.99119
2.04053
2.04484
2.13924
2.14344
2.16149
2.18023
2.42606
2.58374
3.60137
3.62461
3.64805
3.67148
5.30677
5.35776
5.37681
5.54367
7.24529
7.25290
7.25687
7.25873
7.27741
7.28182
7.28648
7.43336
7.45825
7.53990
7.54588
7.56244
7.56698
7.57137
7.59131
7.59350
ppm
4.287
11.145
1.556
3.323
1.478
1.373
1.261
1.000
2.114
1.252
2.478
Integral
0
1
2
3
4
5
6
7
8
9
10
ppm
S
O
O

2.61

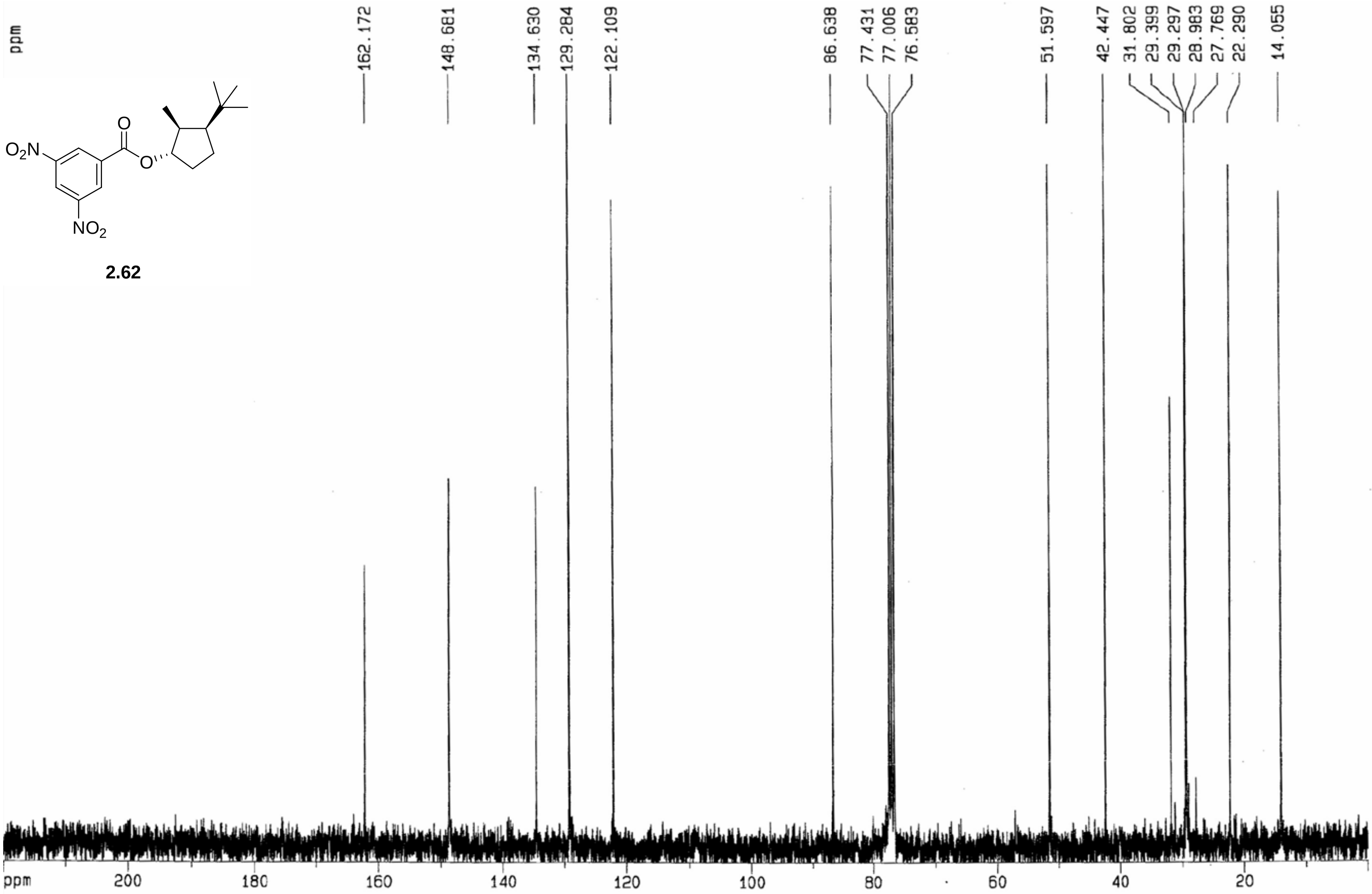

13.796
22.186
27.807
29.027
29.154
29.297
31.839
41.979
51.315
76.609
77.032
77.230
77.455
94.075
122.098
126.419
129.453
153.444
194.422
ppm
O
S
O
20
40
60
80
100
120
140
160
180
200
ppm

2.61

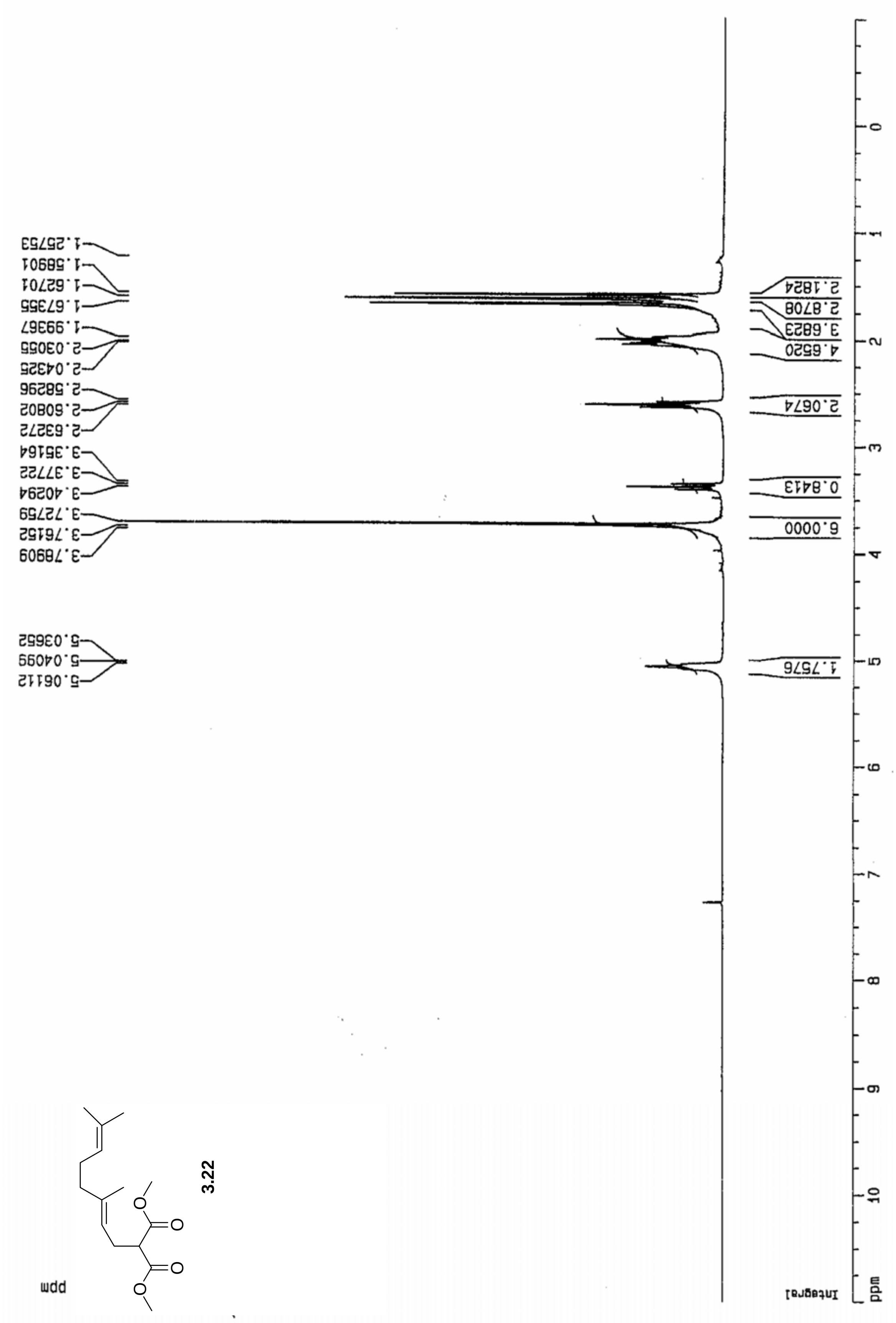


0.07562
0.79166
0.86214
0.93202
0.94116
0.95243
1.00077
1.02385
1.05648
1.06716
1.67116
1.70834
1.81896
1.84691
1.86273
1.96205
1.98233
2.00438
2.02565
2.27717
2.29982
2.31662
2.33899
2.36121
4.21515
4.28829
5.06572
5.08743
7.27005
7.54338
7.70123
8.82570
9.05452
9.11268
9.11982
9.14467
9.20249
9.20960
9.21669
9.27622
12.721
1.360
2.474
1.189
2.178
1.000
1.671
0.810
Integral
ppm
0
1
2
3
4
5
6
7
8
9
10
O
O
NO$_2$
O$_2$N

2.62


2.62

ppm
162.172
148.681
134.630
129.284
122.109
86.638
77.431
77.006
76.583
51.597
42.447
31.802
29.399
29.297
28.983
27.769
22.290
14.055
O_2N
NO_2
O
O
ppm
200
180
160
140
120
100
80
60
40
20


ppm
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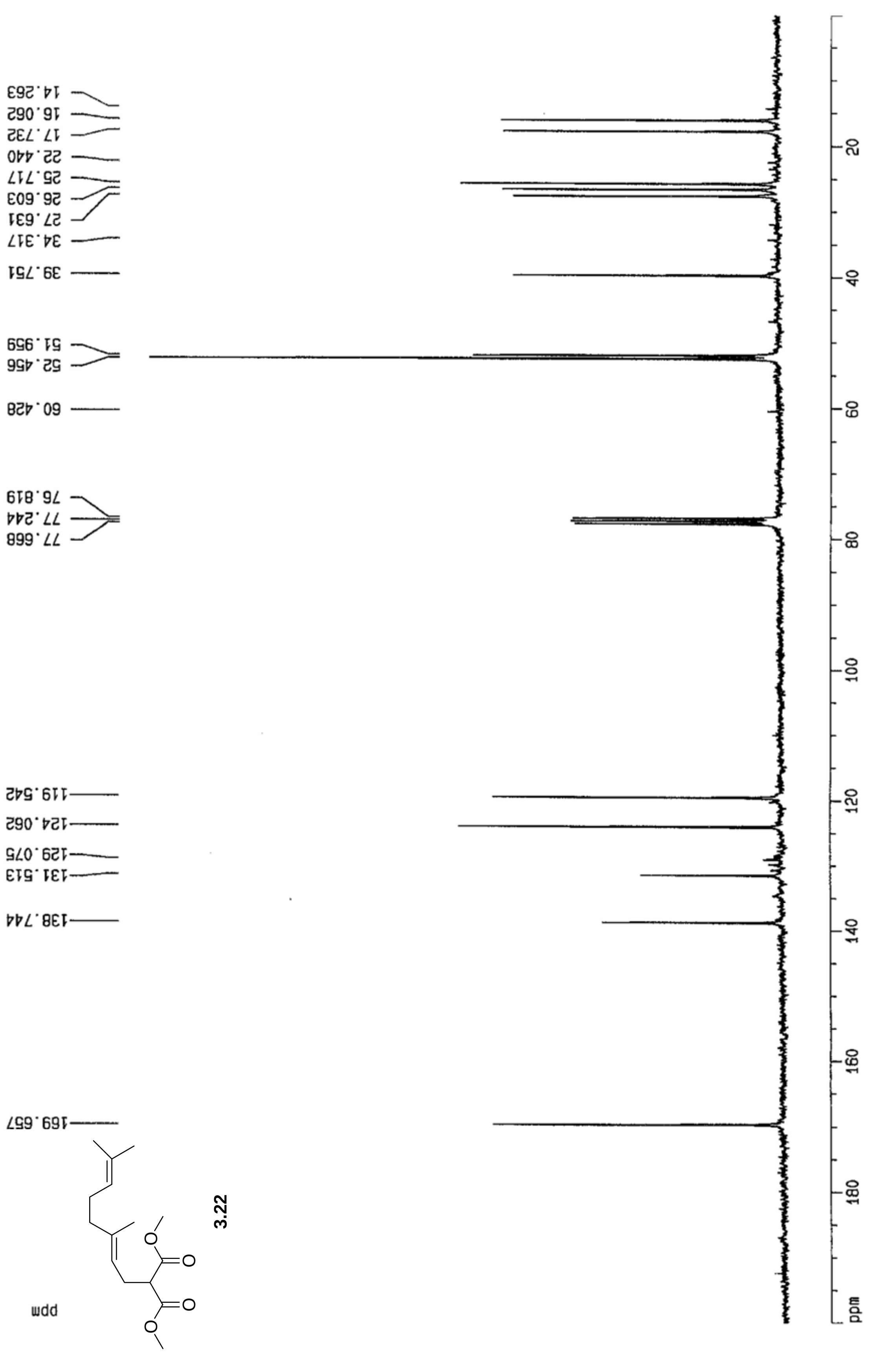
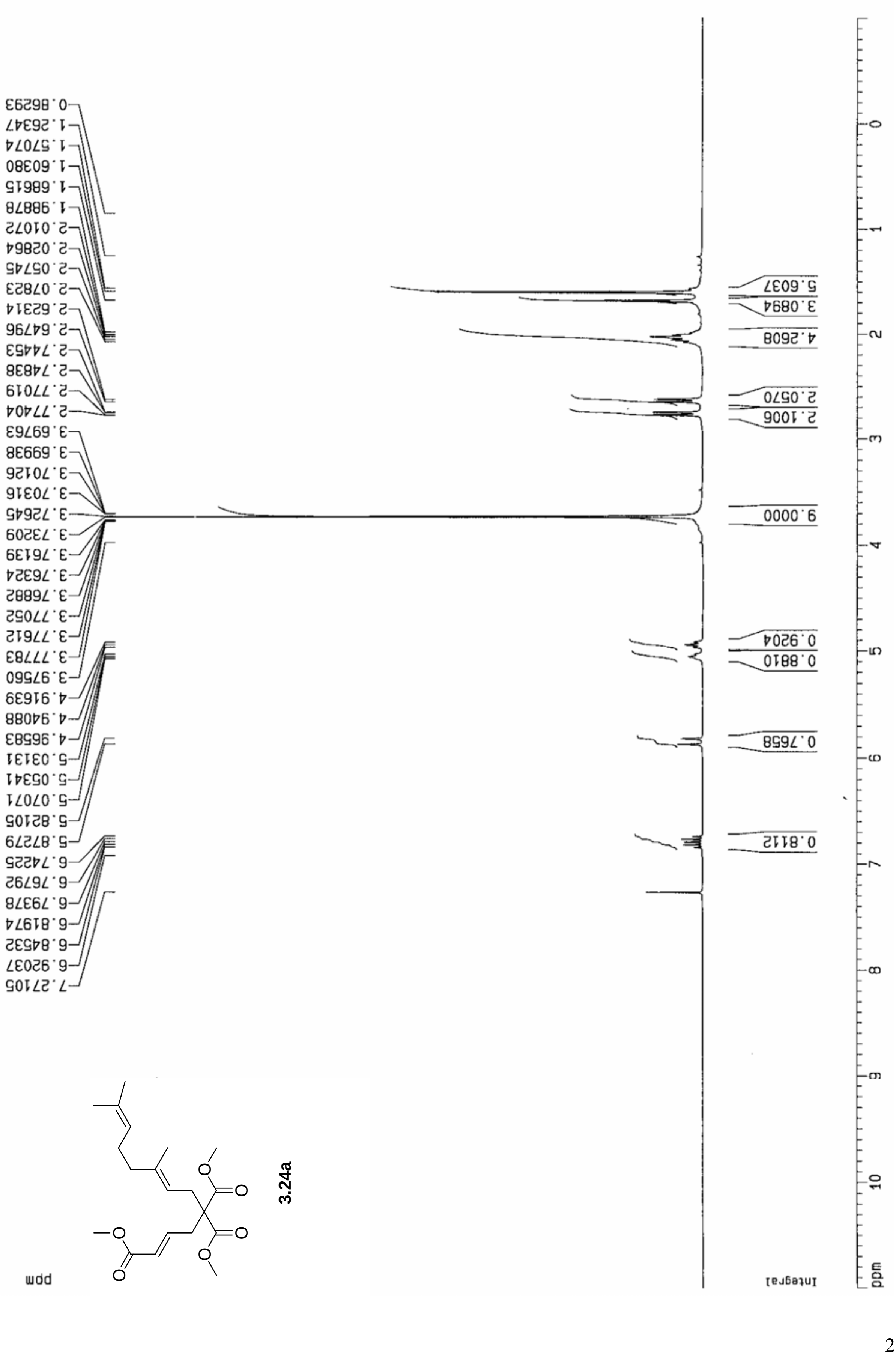
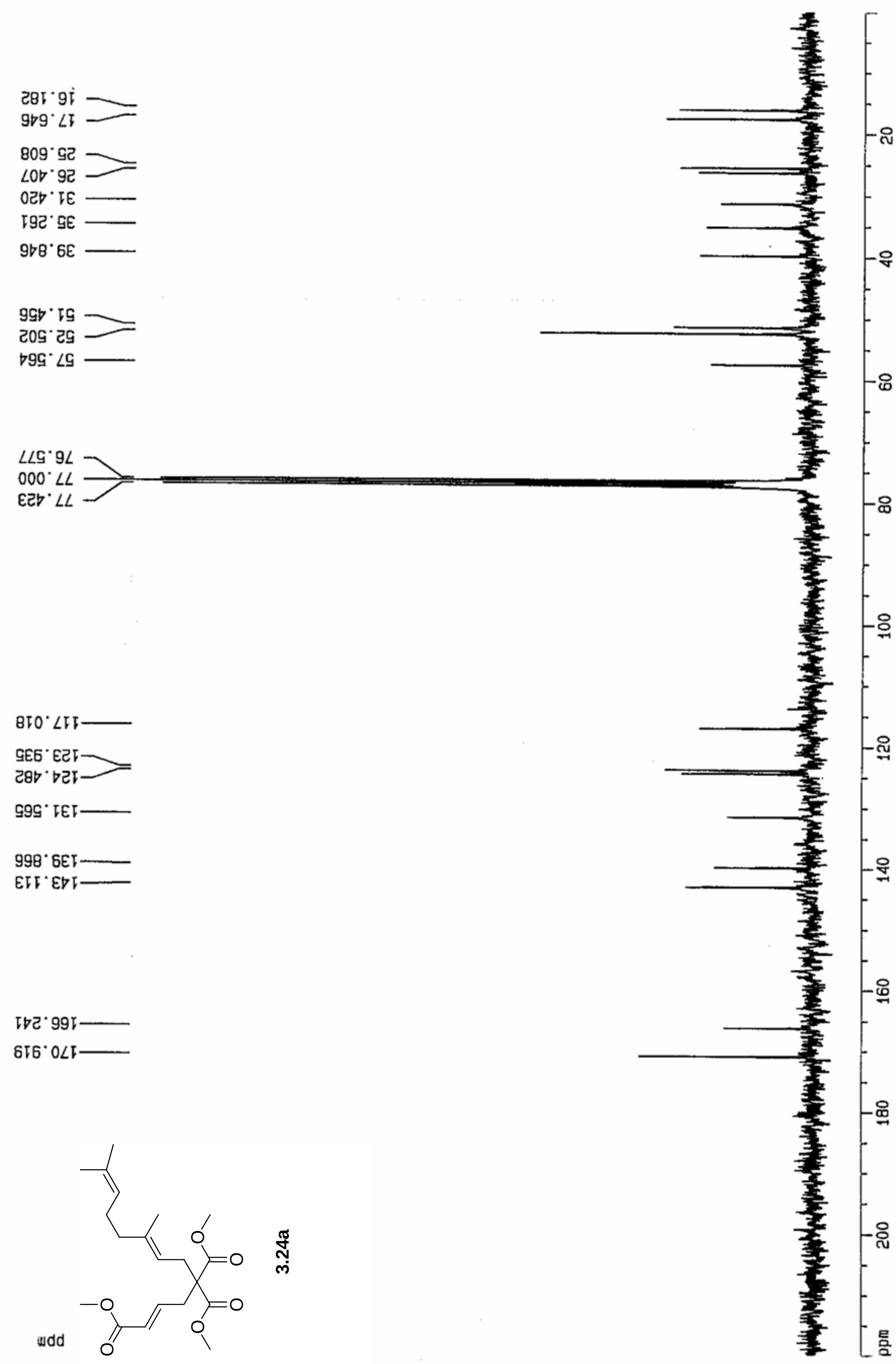
1.58901
1.62701
1.67355
1.99367
2.03055
2.04325
2.58296
2.60802
2.63272
3.35164
3.37722
3.40294
3.72759
3.76152
3.78909
5.03652
5.04099
5.06112
2.1824
2.8708
3.6823
4.6520
2.0674
0.8413
6.0000
1.7576
Integral
0
1
2
3
4
5
6
7
8
9
10
ppm

3.22

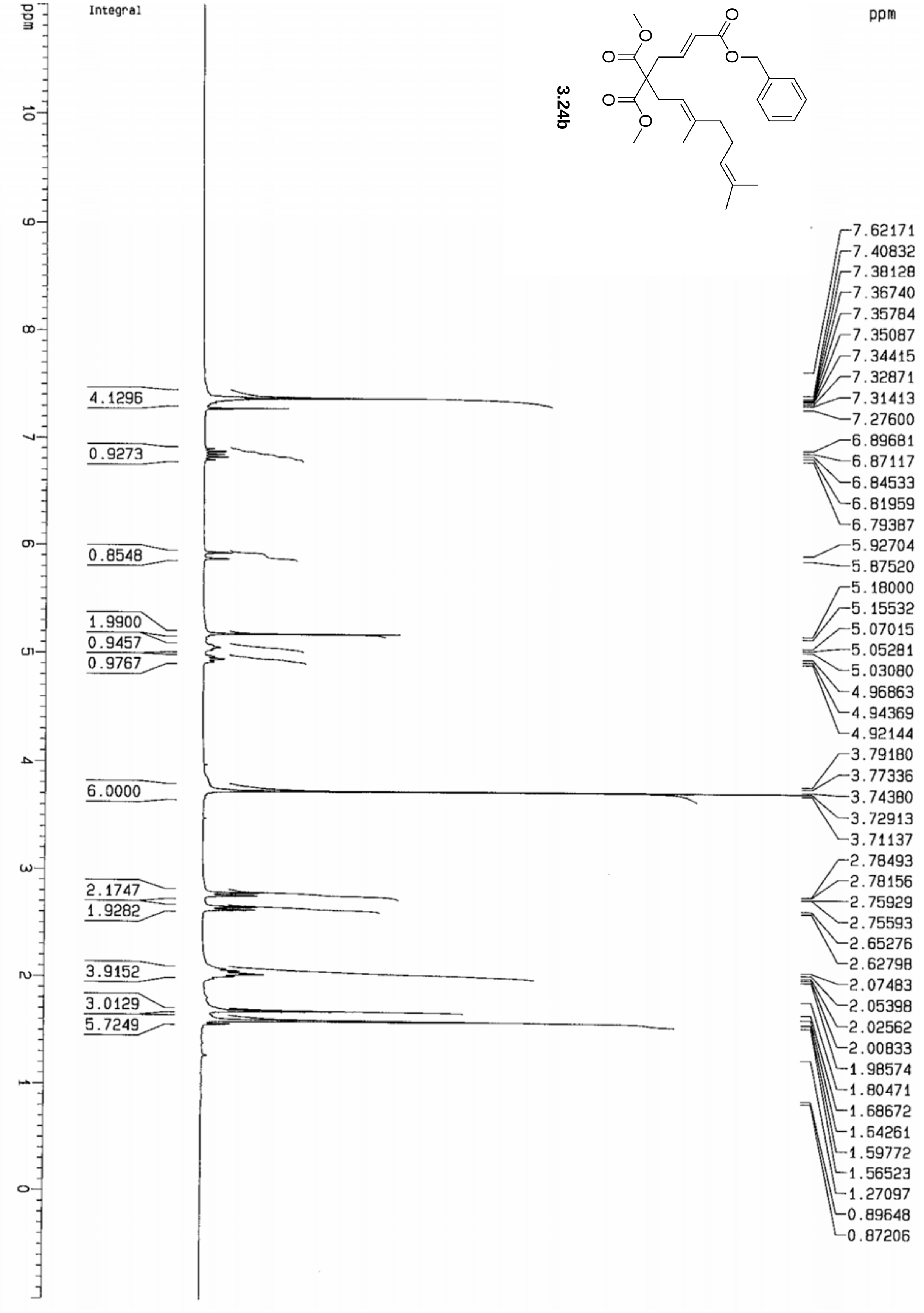

14.263
16.062
17.732
22.440
25.717
26.603
27.631
34.317
39.751
51.959
52.456
60.428
76.819
77.244
77.668
119.542
124.062
129.075
131.513
138.744
169.657
ppm
20
40
60
80
100
120
140
160
180
ppm

3.22

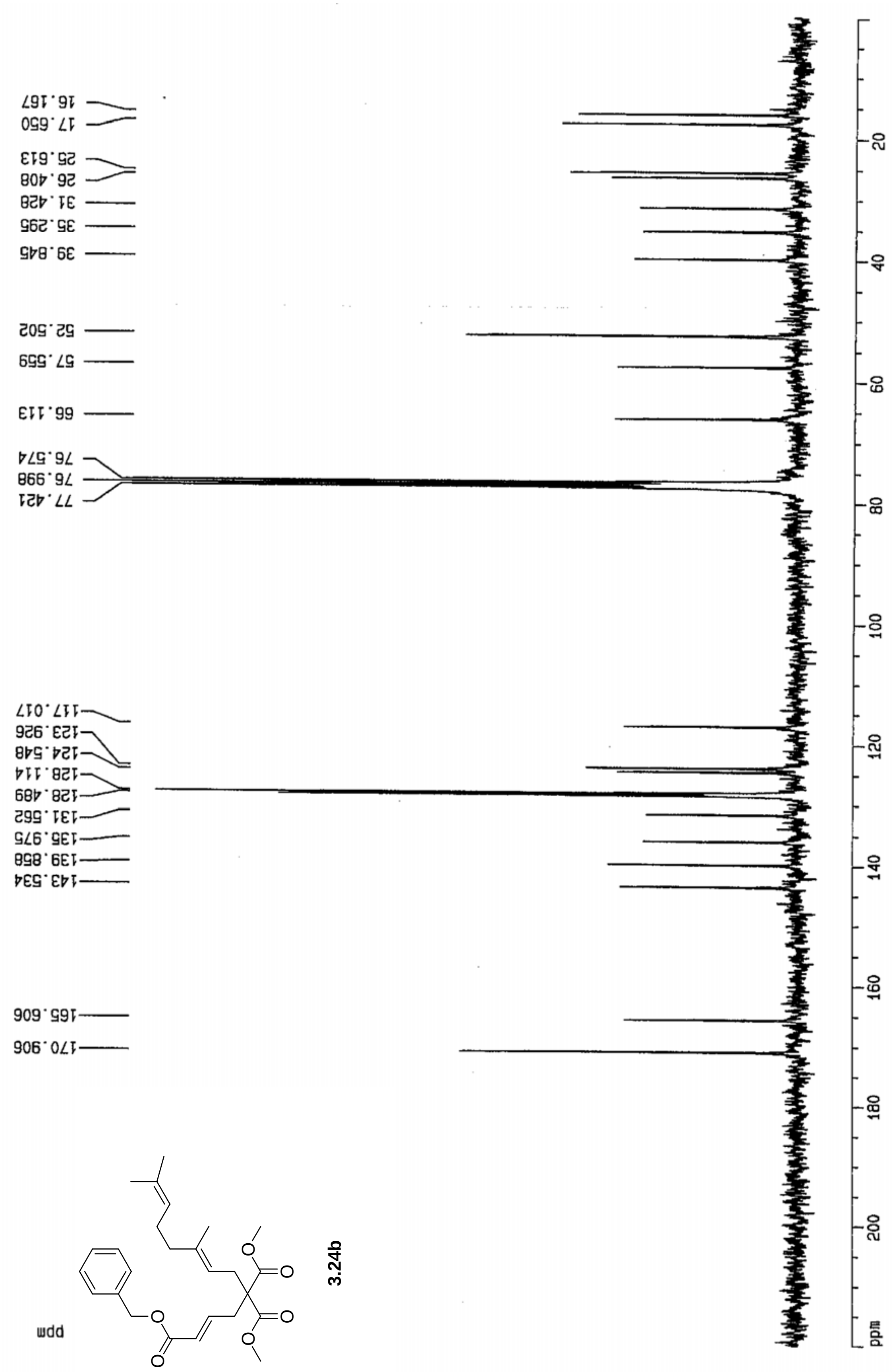

3.24a
0.86293
1.26347
1.57074
1.60380
1.68615
1.98878
2.01072
2.02864
2.05745
2.07823
2.62314
2.64796
2.74453
2.74838
2.77019
2.77404
3.69763
3.69938
3.70126
3.70316
3.72645
3.73209
3.76139
3.76324
3.76882
3.77052
3.77612
3.77783
3.97560
4.91639
4.94088
4.96583
5.03131
5.05341
5.07071
5.82105
5.87279
6.74225
6.76792
6.79378
6.81974
6.84532
6.92037
7.27105
ppm
5.6037
3.0894
4.2608
2.0570
2.1006
9.0000
0.9204
0.8810
0.7658
0.8112
Integral
0
1
2
3
4
5
6
7
8
9
10
ppm


3.24a

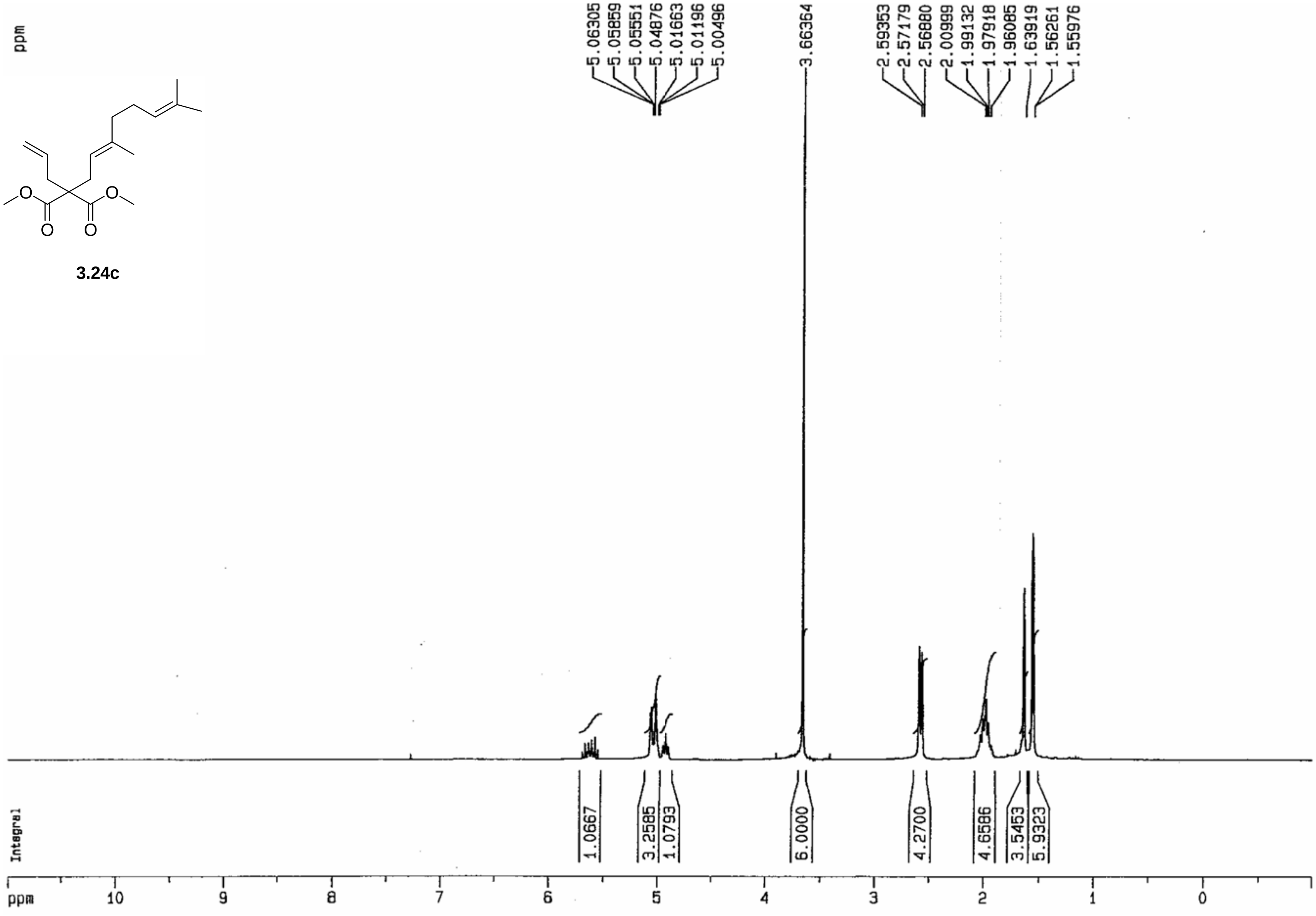
16.182
17.646
25.608
26.407
31.420
35.261
39.846
51.456
52.502
57.564
76.577
77.000
77.423
117.018
123.935
124.482
131.565
139.866
143.113
166.241
170.919
ppm
20
40
60
80
100
120
140
160
180
200
ppm


3.24b

ppm
Integral
7.62171
7.40832
7.38128
7.36740
7.35784
7.35087
7.34415
7.32871
7.31413
7.27600
6.89681
6.87117
6.84533
6.81959
6.79387
5.92704
5.87520
5.18000
5.15532
5.07015
5.05281
5.03080
4.96863
4.94369
4.92144
3.79180
3.77336
3.74380
3.72913
3.71137
2.78493
2.78156
2.75929
2.75593
2.65276
2.62798
2.07483
2.05398
2.02562
2.00833
1.98574
1.80471
1.68672
1.64261
1.59772
1.56523
1.27097
0.89648
0.87206
4.1296
0.9273
0.8548
1.9900
0.9457
0.9767
6.0000
2.1747
1.9282
3.9152
3.0129
5.7249
10
9
8
7
6
5
4
3
2
1
0
ppm


16.167
17.650
25.613
26.408
31.428
35.295
39.845
52.502
57.559
66.113
76.574
76.998
77.421
117.017
123.926
124.548
128.114
128.489
131.562
135.975
139.858
143.534
165.606
170.906
ppm
200
180
160
140
120
100
80
60
40
20
ppm

3.24b


3.24c
ppm
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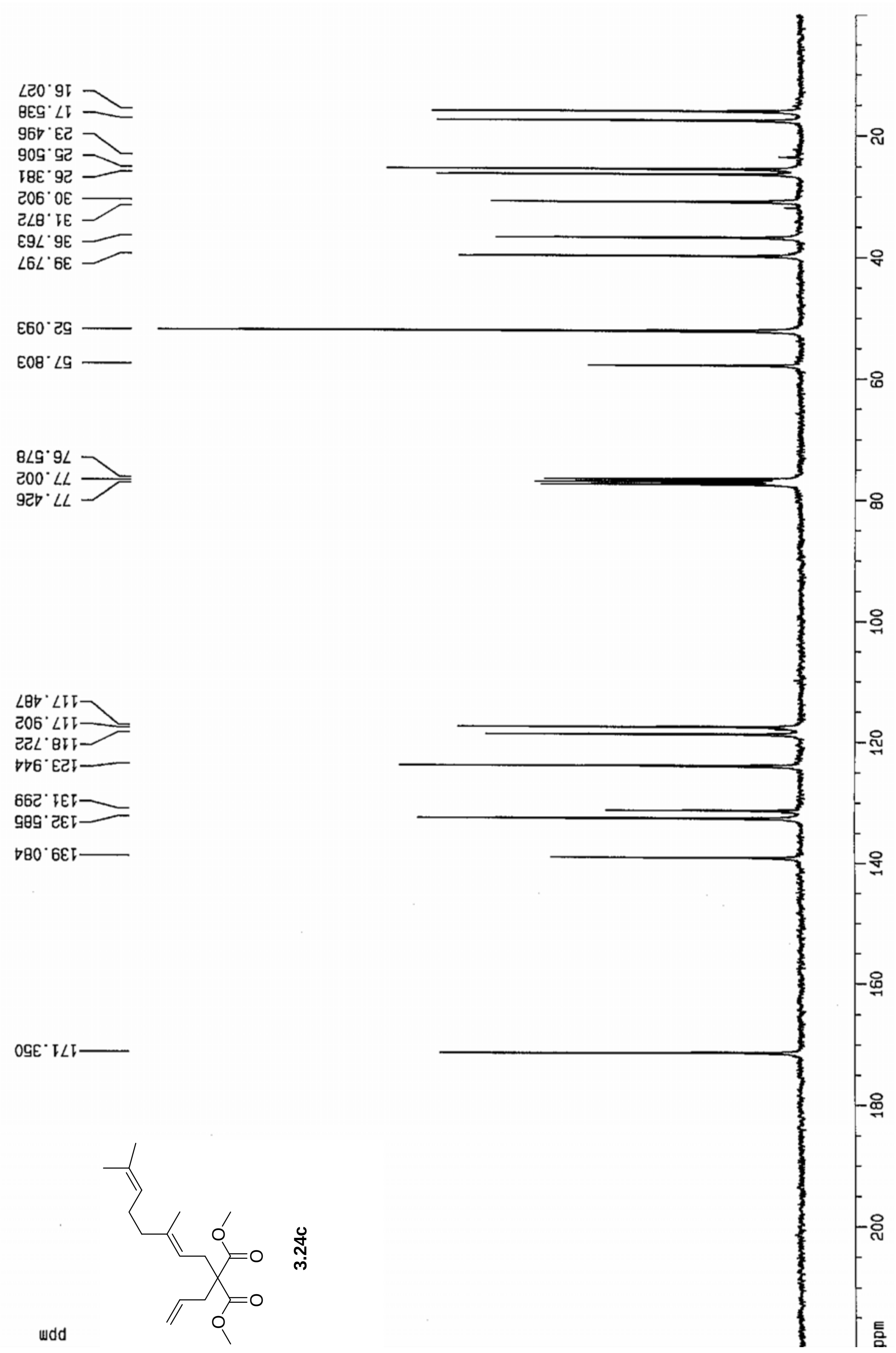
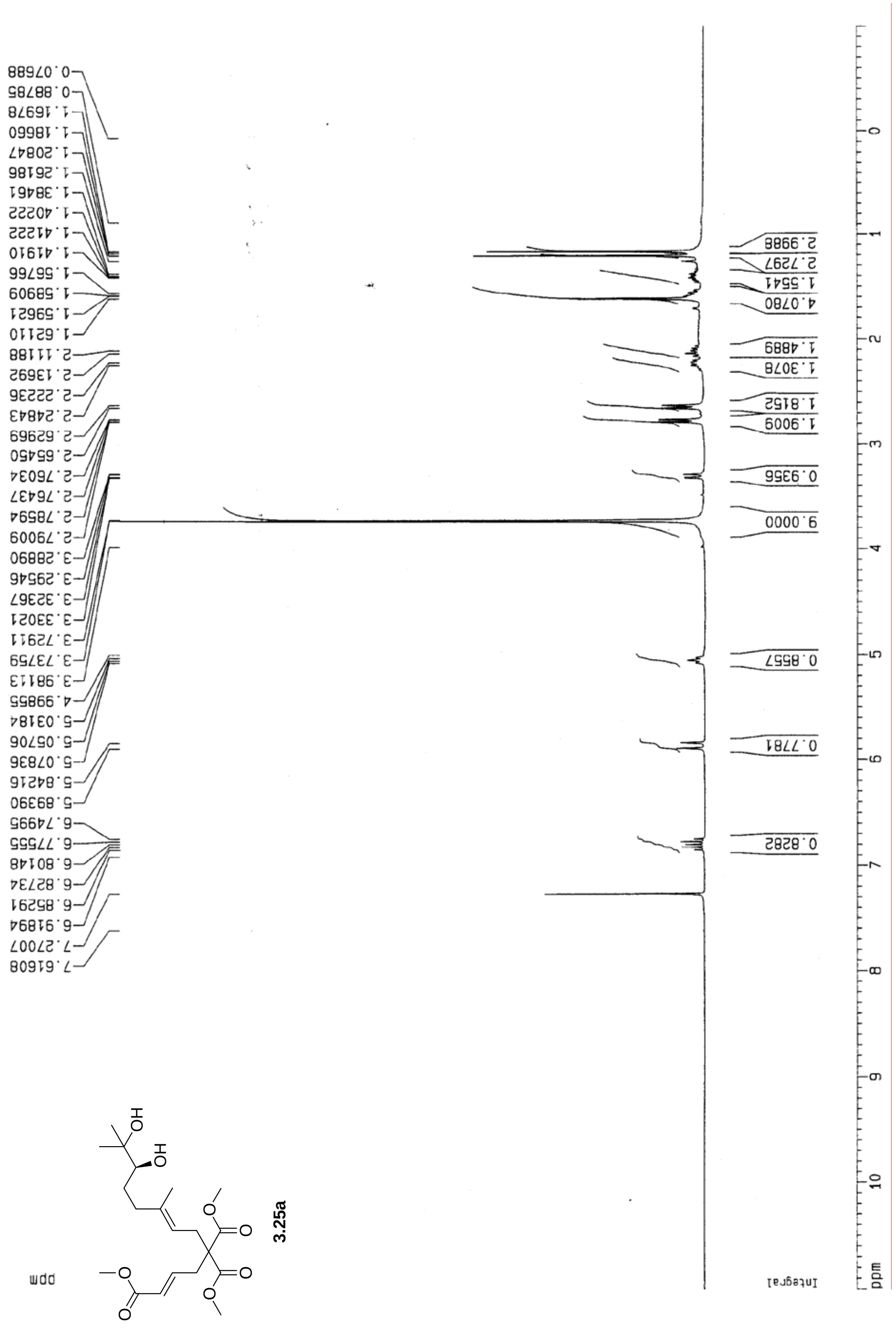
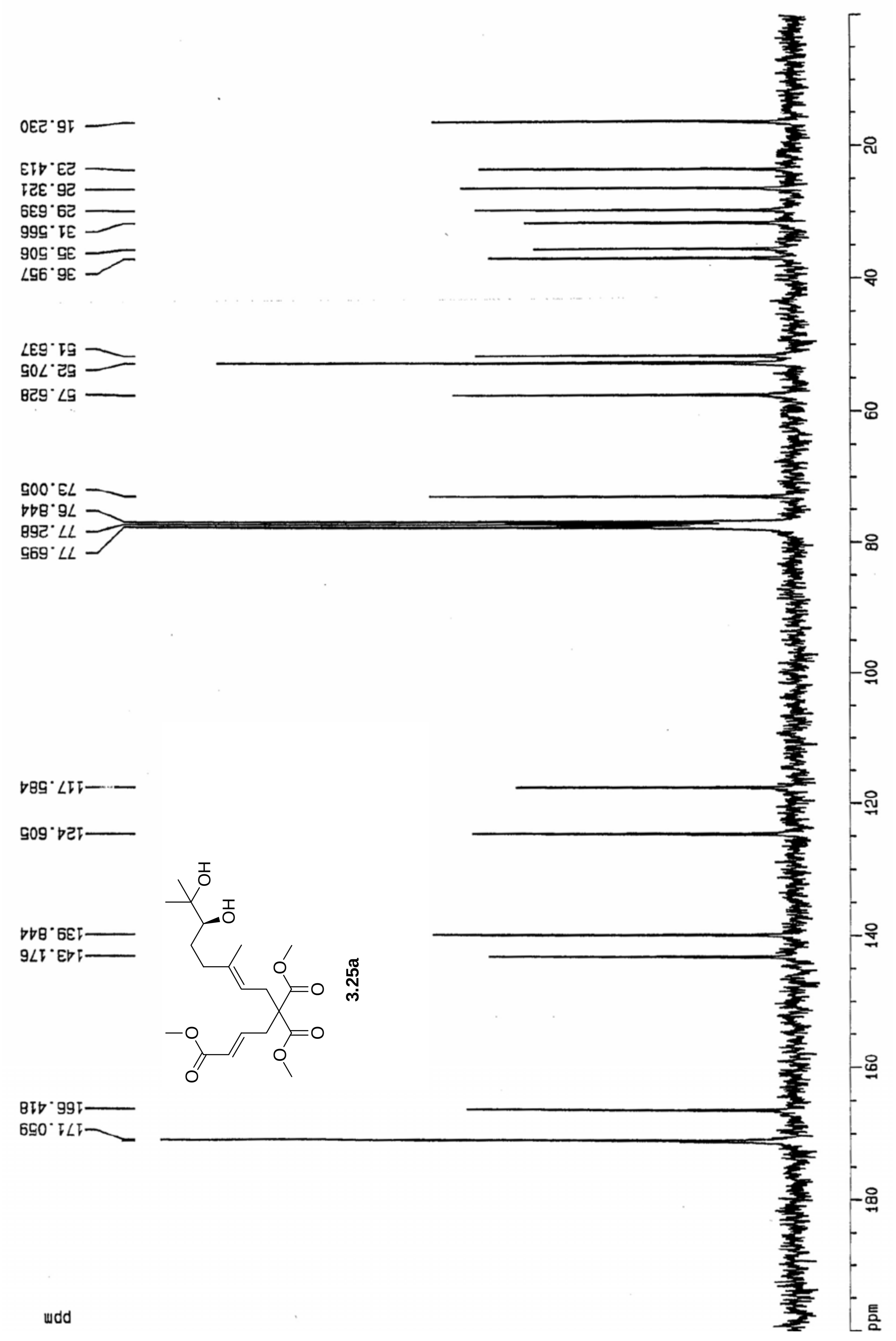
5.05551
5.04876
5.01663
5.01196
5.00496
3.66364
2.59353
2.57179
2.56880
2.00999
1.99132
1.97918
1.96085
1.63919
1.56261
1.55976
Integral
1.0667
3.2585
1.0793
6.0000
4.2700
4.6586
3.5453
5.9323
ppm
10
9
8
7
6
5
4
3
2
1
0
O
O
O
O


16.027
17.538
23.496
25.506
26.381
30.902
31.872
36.763
39.797
52.093
57.803
76.578
77.002
77.426
117.487
117.902
118.722
123.944
131.299
132.585
139.084
171.350
ppm
20
40
60
80
100
120
140
160
180
200
ppm

3.24c


3.25a

ppm
7.61608
7.27007
6.91894
6.85291
6.82734
6.80148
6.77555
6.74995
5.89390
5.84216
5.07836
5.05706
5.03184
4.99855
3.98113
3.73759
3.72911
3.33021
3.32367
3.29546
3.28890
2.79009
2.78594
2.76437
2.76034
2.65450
2.62969
2.24843
2.22236
2.13692
2.11188
1.62110
1.59621
1.58909
1.56766
1.41910
1.41222
1.40222
1.38461
1.26186
1.20847
1.18660
1.16978
0.88785
0.07688
Integral
0.8282
0.7781
0.8557
9.0000
0.9356
1.9009
1.8152
1.3078
1.4889
4.0780
1.5541
2.7297
2.9988
ppm
10
9
8
7
6
5
4
3
2
1
0
OH
OH
O
O
O
O
O
O



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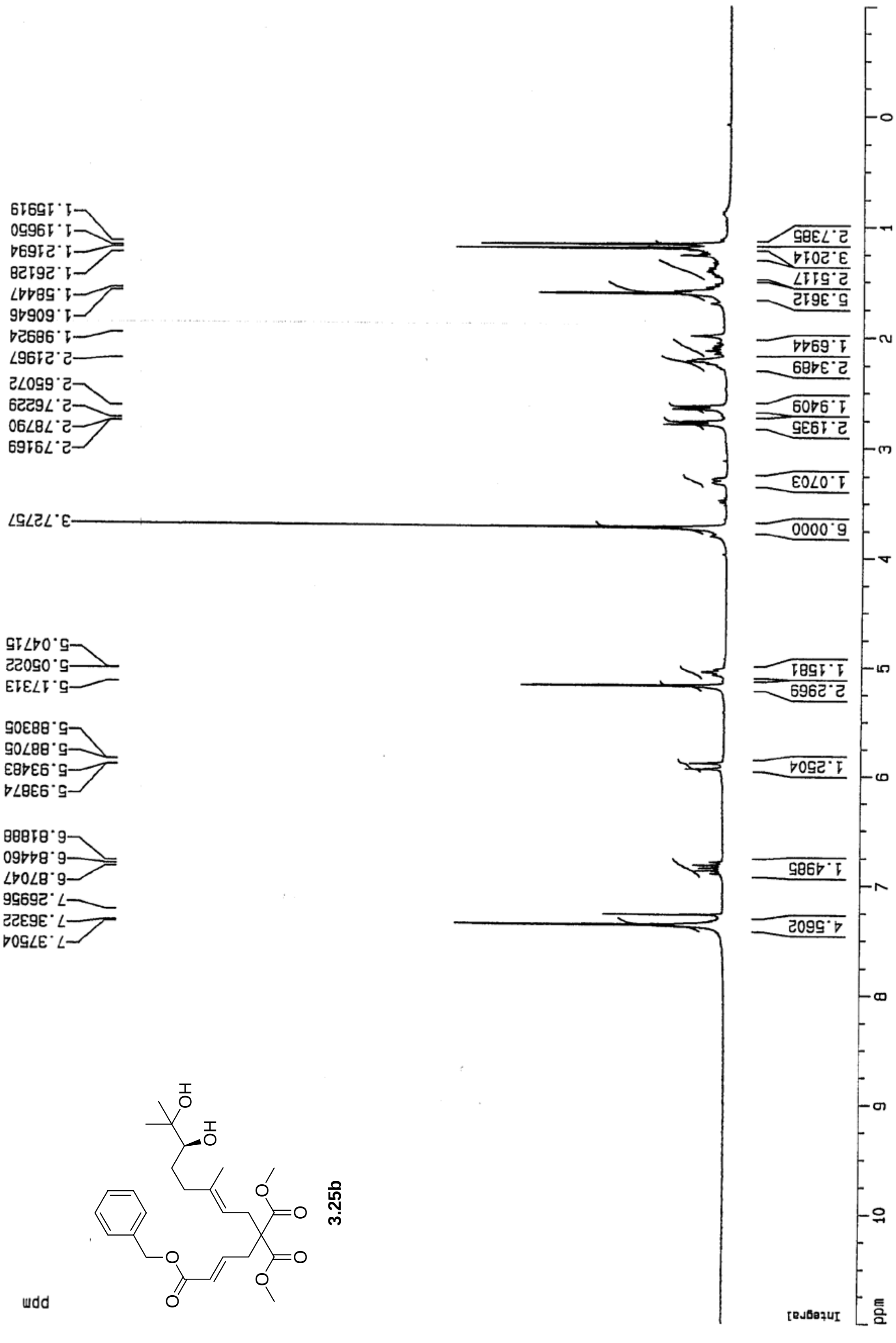
23.413
26.321
29.639
31.566
35.506
36.957
51.637
52.705
57.628
73.005
76.844
77.268
77.695
117.584
124.605
139.844
143.176
166.418
171.059
ppm
20
40
60
80
100
120
140
160
180
ppm
HO
OH
O
O
O
O
O
O

3.25a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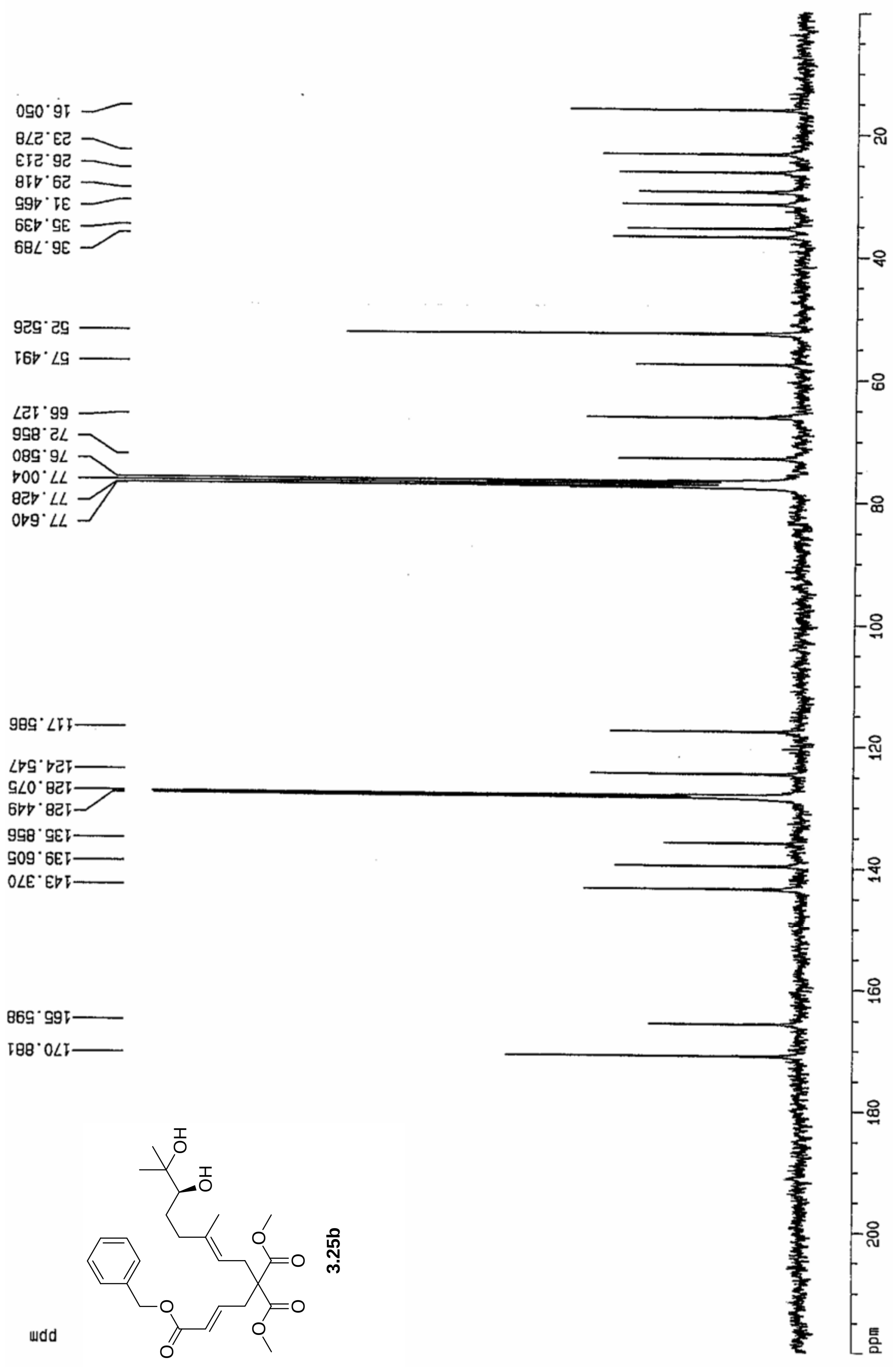
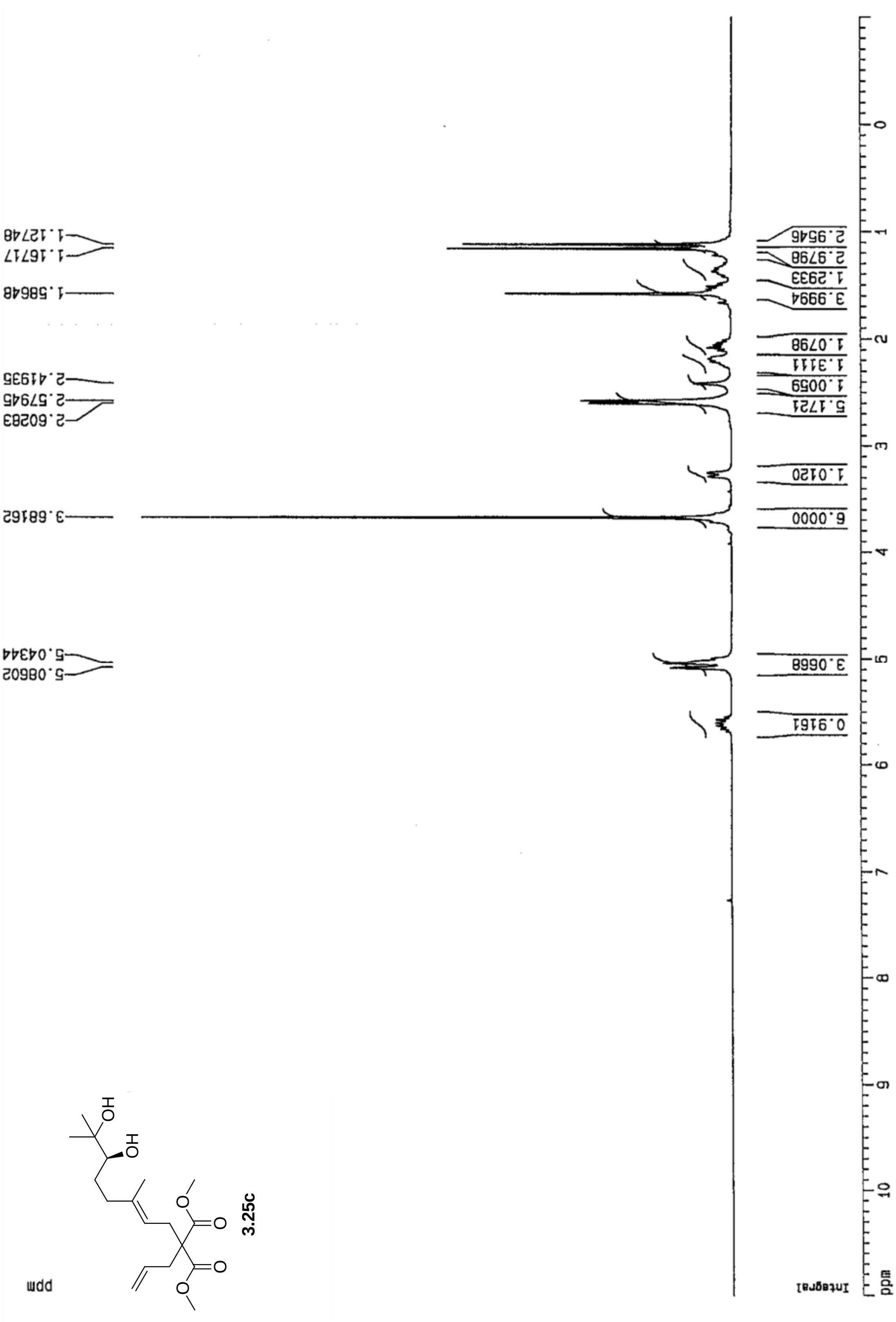
1.58447
1.60646
1.98924
2.21967
2.65072
2.76229
2.78790
2.79169
3.72757
5.04715
5.05022
5.17313
5.88305
5.88705
5.93483
5.93874
6.81888
6.84460
6.87047
7.26956
7.36322
7.37504
2.7385
3.2014
2.5117
5.3612
1.6944
2.3489
1.9409
2.1935
1.0703
6.0000
1.1581
2.2969
1.2504
1.4985
4.5602
Integral
ppm
0
1
2
3
4
5
6
7
8
9
10
ppm
OH
OH
O
O
O
O
O
O

3.25b


3.25b

16.050
23.278
26.213
29.418
31.465
35.439
36.789
52.526
57.491
66.127
72.856
76.580
77.004
77.428
77.640
117.586
124.547
128.075
128.449
135.856
139.605
143.370
165.598
170.881
ppm
20
40
60
80
100
120
140
160
180
200
ppm
HO
OH
O
O
O
O
O
O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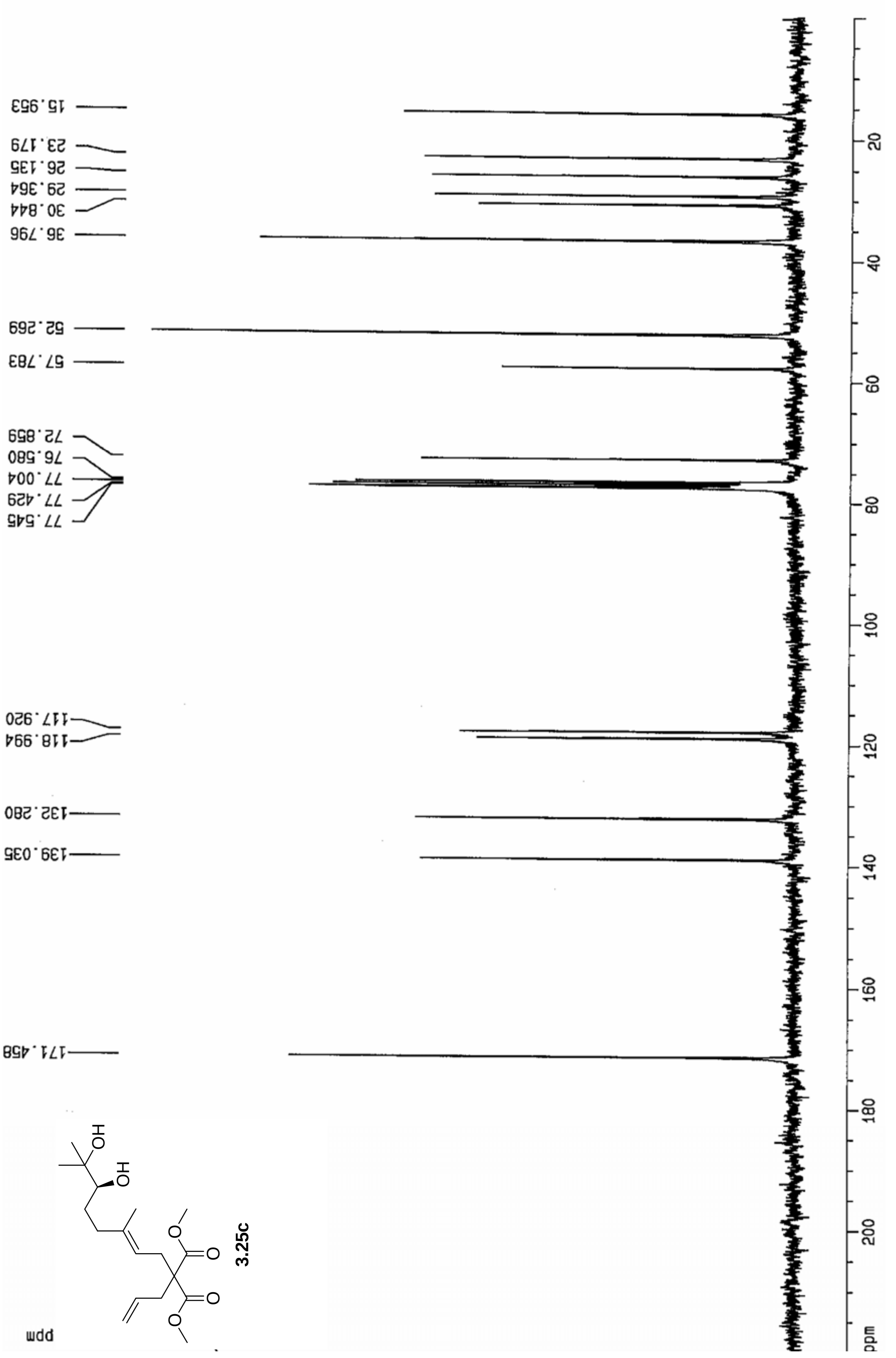
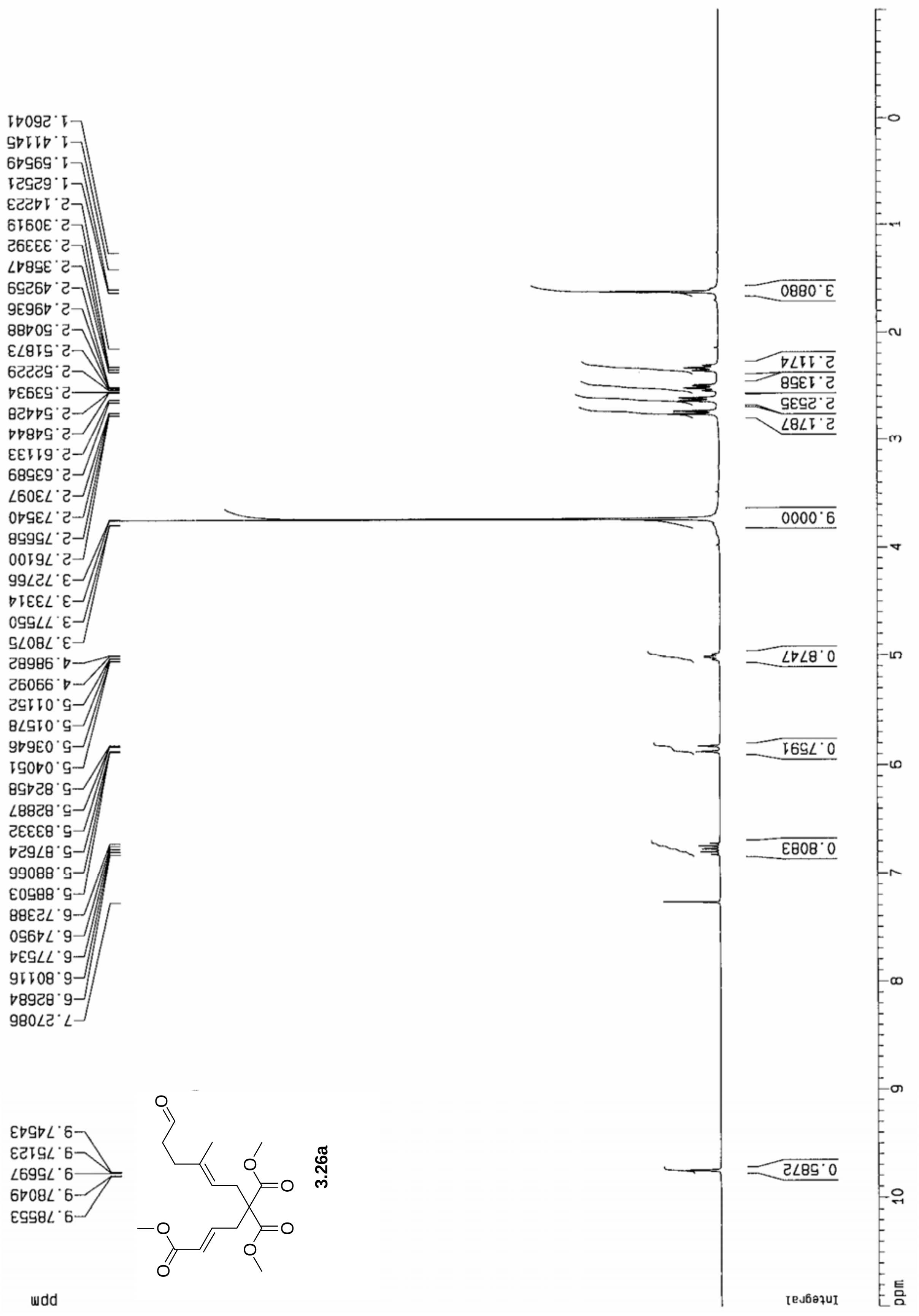
1.16717
1.58648
2.41935
2.57945
2.60283
3.68162
5.04344
5.08602
2.9546
2.9798
1.2933
3.9994
1.0798
1.3111
1.0059
5.1721
1.0120
6.0000
3.0668
0.9161
Integral
ppm
0
1
2
3
4
5
6
7
8
9
10
ppm
HO
OH
O
O
O
O
3.25c


15.953
23.179
26.135
29.364
30.844
36.796
52.269
57.783
72.859
76.580
77.004
77.429
77.545
117.920
118.994
132.280
139.035
171.458
ppm
20
40
60
80
100
120
140
160
180
200
ppm
OH
OH
O
O
O
O

3.25c



9.78553
9.78049
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9.75123
9.74543
7.27086
6.82684
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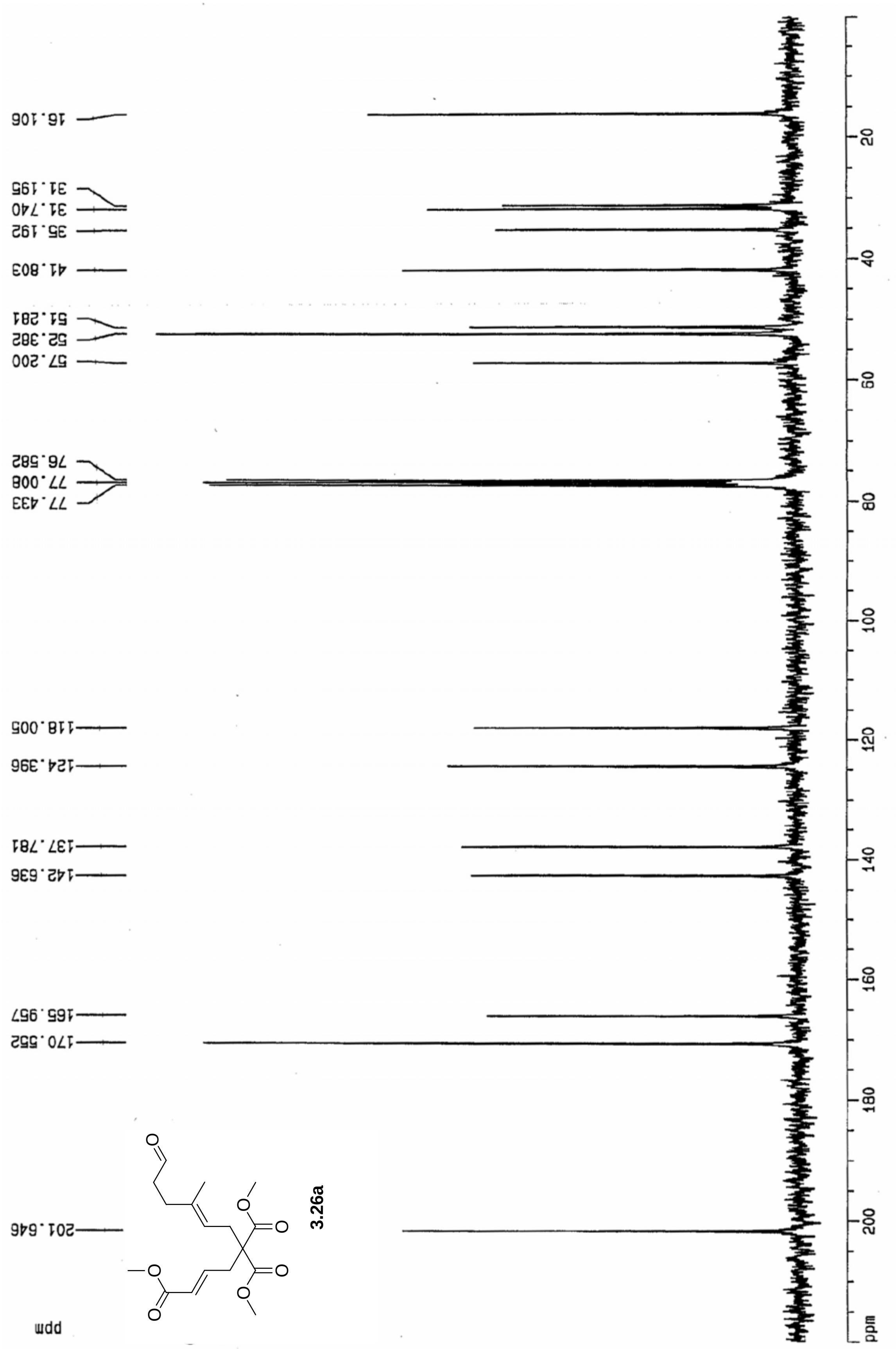
6.77534
6.74950
6.72388
5.88503
5.88066
5.87624
5.83332
5.82887
5.82458
5.04051
5.03646
5.01578
5.01152
4.99092
4.98682
3.78075
3.77550
3.73314
3.72766
2.76100
2.75558
2.73540
2.73097
2.63589
2.61133
2.54844
2.54428
2.53934
2.52229
2.51873
2.50488
2.49636
2.49259
2.35847
2.33392
2.30919
2.14223
1.62521
1.59549
1.41145
1.26041
ppm
0.5872
0.8083
0.7591
0.8747
9.0000
2.1787
2.2535
2.1358
2.1174
3.0880
Integral
10
9
8
7
6
5
4
3
2
1
0
ppm
O
O
O
O
O
O
O

3.26a



16.106
31.195
31.740
35.192
41.803
51.281
52.382
57.200
76.582
77.008
77.433
118.005
124.396
137.781
142.636
165.957
170.552
201.646
ppm
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120
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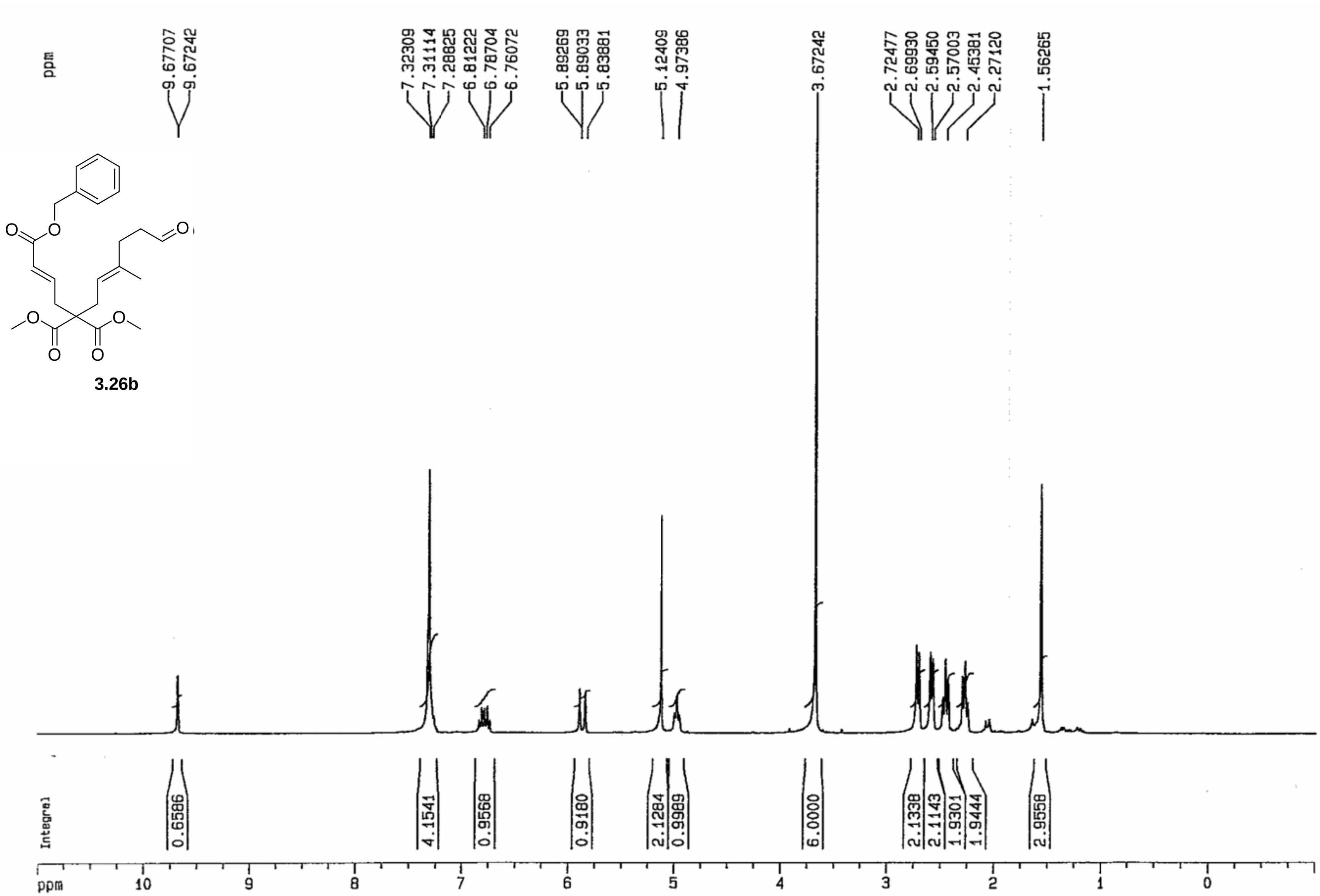
180
200
ppm

3.26a


3.26b

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9.67242
7.32309
7.31114
7.28825
6.81222
6.78704
6.76072
5.89269
5.89033
5.83881
5.12409
4.97386
3.67242
2.72477
2.69930
2.59450
2.57003
2.45381
2.27120
1.56265
Integral
0.6586
4.1541
0.9568
0.9180
2.1284
0.9989
6.0000
2.1338
2.1143
1.9301
1.9444
2.9558
ppm
10
9
8
7
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5
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3
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1
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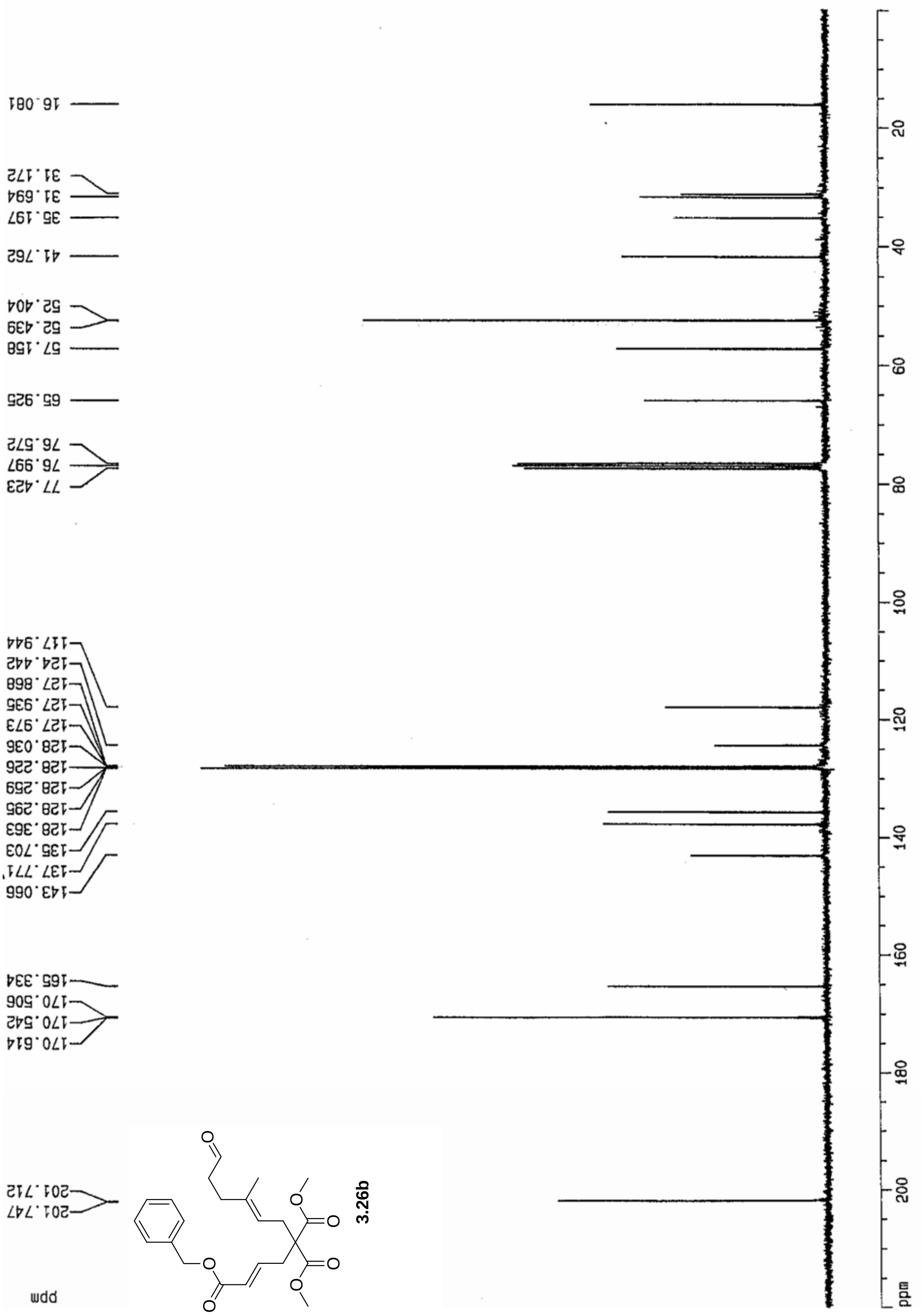

3.26b

16.081
31.172
31.694
35.197
41.762
52.404
52.439
57.158
65.925
76.572
76.997
77.423
117.944
124.442
127.868
127.935
127.973
128.036
128.226
128.259
128.295
128.363
135.703
137.771
143.066
165.334
170.506
170.542
170.614
201.712
201.747
ppm
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80
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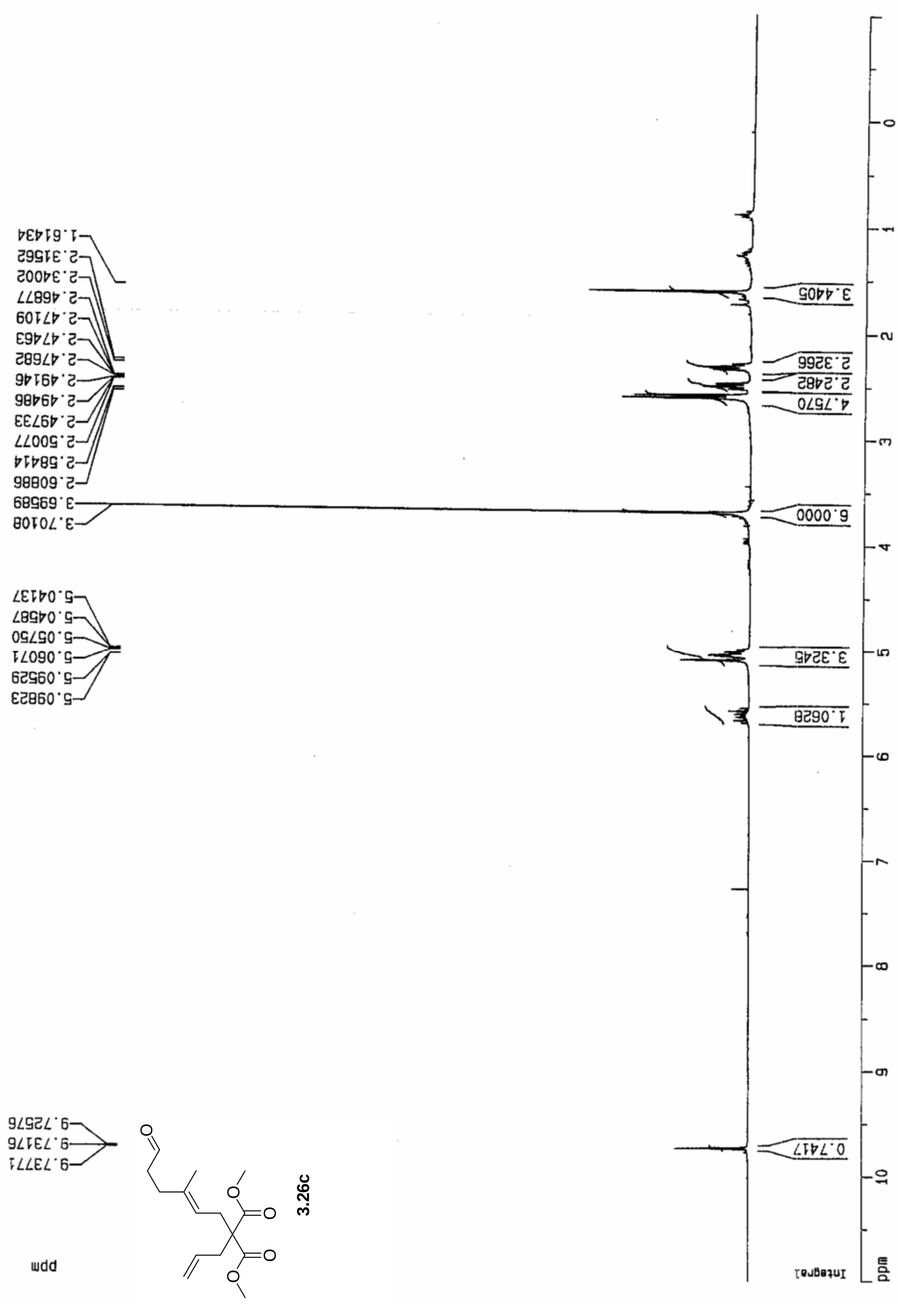
160
180
200
ppm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9.73176
9.72576
5.09823
5.09529
5.06071
5.05750
5.04587
5.04137
3.70108
3.69589
2.60886
2.58414
2.50077
2.49733
2.49486
2.49146
2.47682
2.47463
2.47109
2.46877
2.34002
2.31562
1.61434
ppm
0.7417
1.0628
3.3245
6.0000
4.7570
2.2482
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Integral
10
9
8
7
6
5
4
3
2
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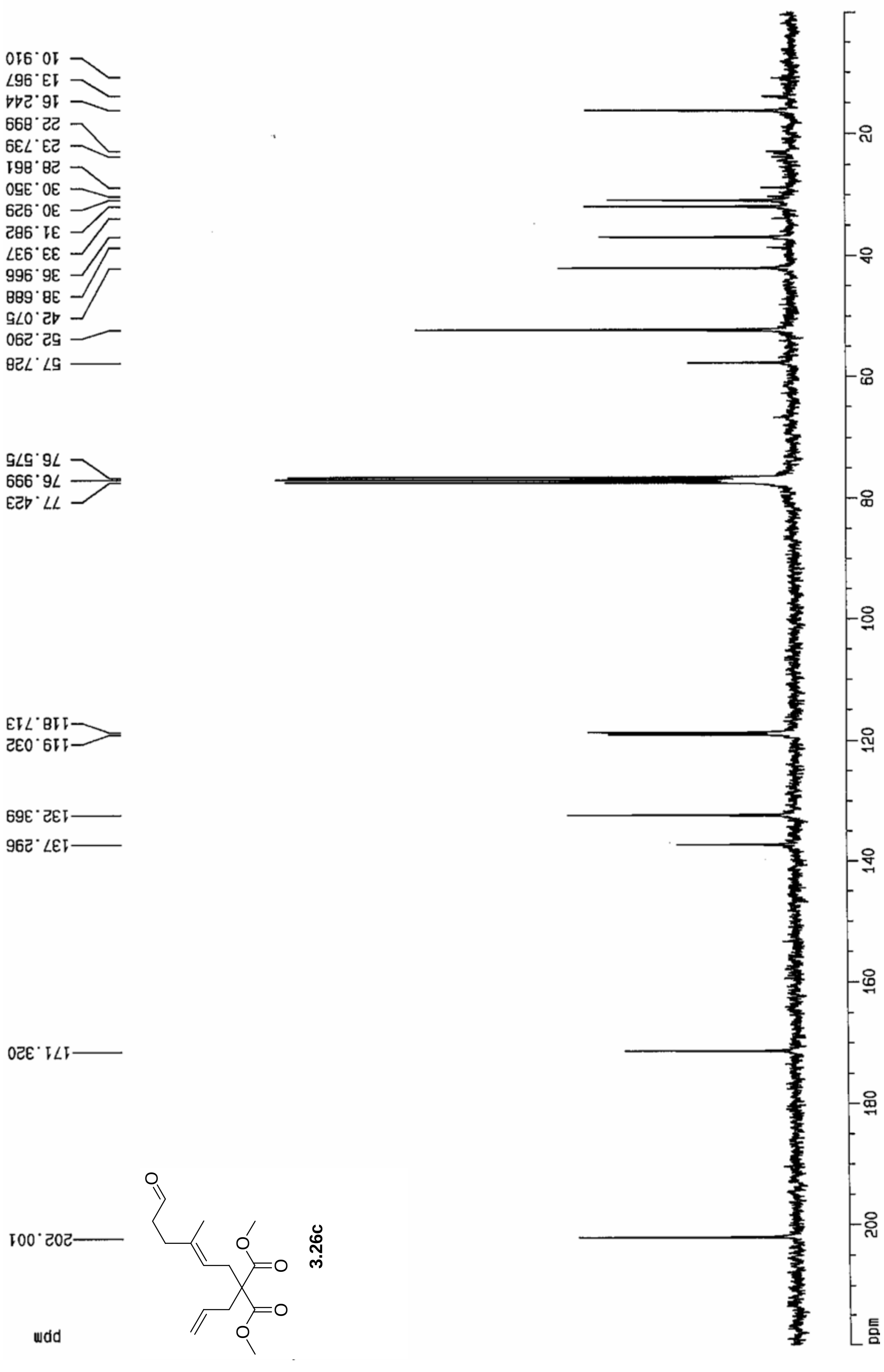
0
ppm

3.26c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13.967
16.244
22.899
23.739
28.861
30.350
30.929
31.982
33.937
36.966
38.688
42.075
52.290
57.728
76.575
76.999
77.423
118.713
119.032
132.369
137.296
171.320
202.001
ppm
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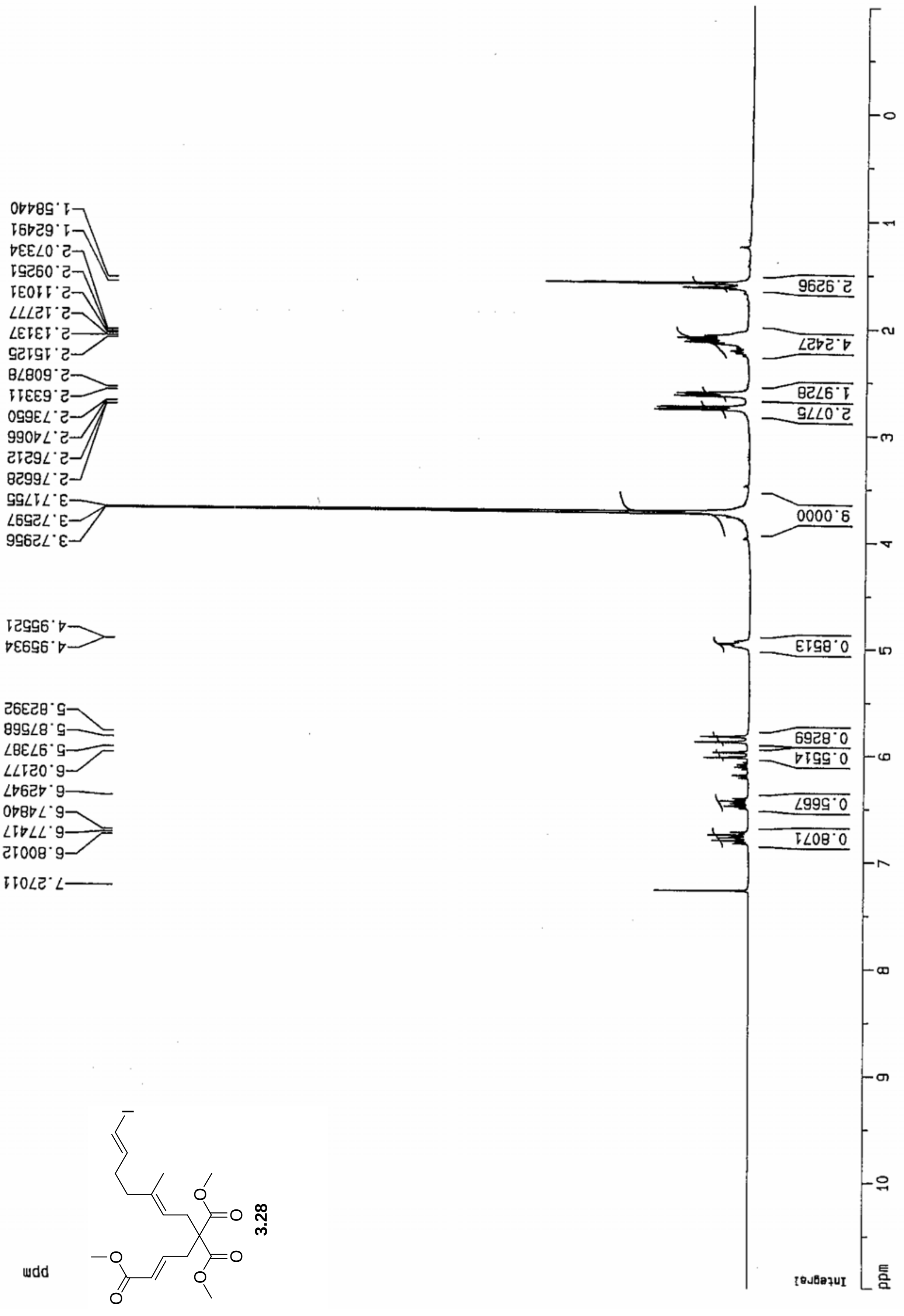
40
60
80
100
120
140
160
180
200
ppm

3.26c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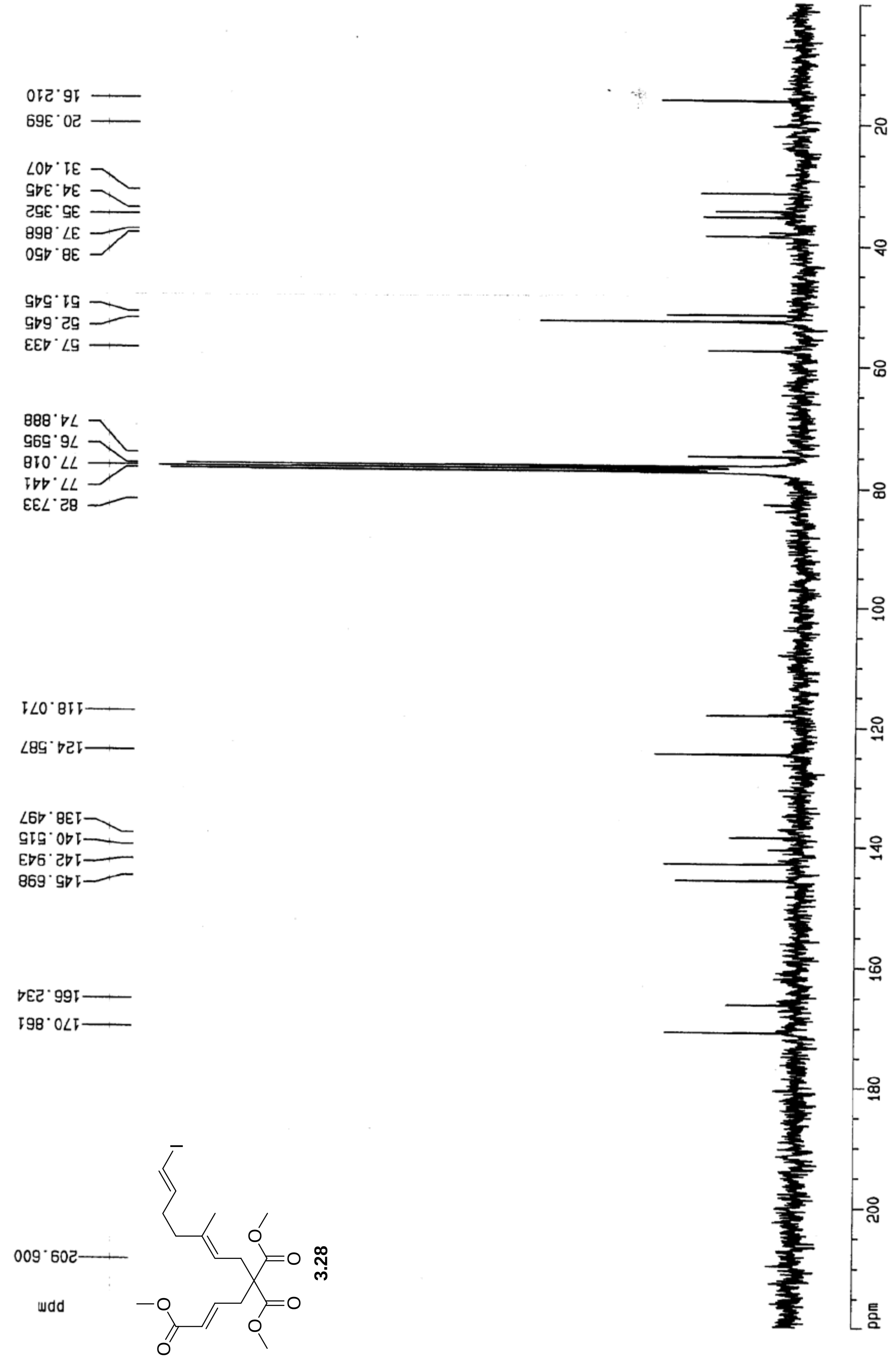
2.07334
2.09251
2.11031
2.12777
2.13137
2.15125
2.60878
2.63311
2.73650
2.74066
2.76212
2.76628
3.71755
3.72597
3.72956
4.95521
4.95934
5.82392
5.87568
5.97387
6.02177
6.42947
6.74840
6.77417
6.80012
7.27011
2.9296
4.2427
1.9728
2.0775
9.0000
0.8513
0.8269
0.5514
0.5667
0.8071
Integral
ppm
0
1
2
3
4
5
6
7
8
9
10
ppm
I

3.28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51.545
52.645
57.433
74.888
76.595
77.018
77.441
82.733
118.071
124.587
138.497
140.515
142.943
145.698
166.234
170.861
209.600
ppm
20
40
60
80
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160
180
200
ppm
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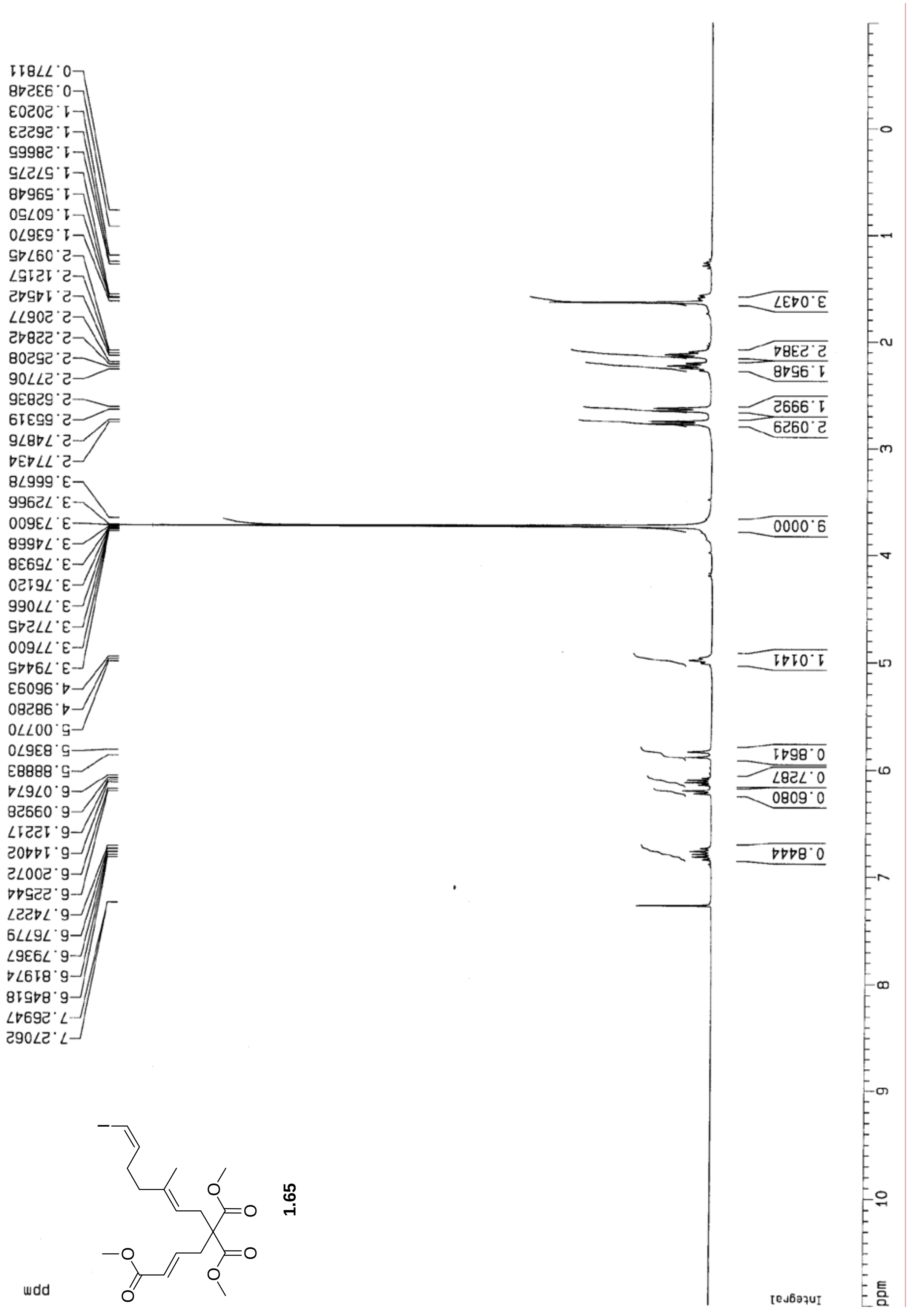
O
O
O
O
O
O
O
I

3.28



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1.59648
1.60750
1.63670
2.09745
2.12157
2.14542
2.20677
2.22842
2.25208
2.27706
2.62836
2.65319
2.74876
2.77434
3.66678
3.72966
3.73600
3.74668
3.75938
3.76120
3.77066
3.77245
3.77600
3.79445
4.96093
4.98280
5.00770
5.83670
5.88883
6.07674
6.09928
6.12217
6.14402
6.20072
6.22544
6.74227
6.76779
6.79367
6.81974
6.84518
7.26947
7.27062
ppm
3.0437
2.3884
1.9548
1.9992
2.0929
9.0000
1.0141
0.8641
0.7287
0.6080
0.8444
Integral
0
1
2
3
4
5
6
7
8
9
10
ppm
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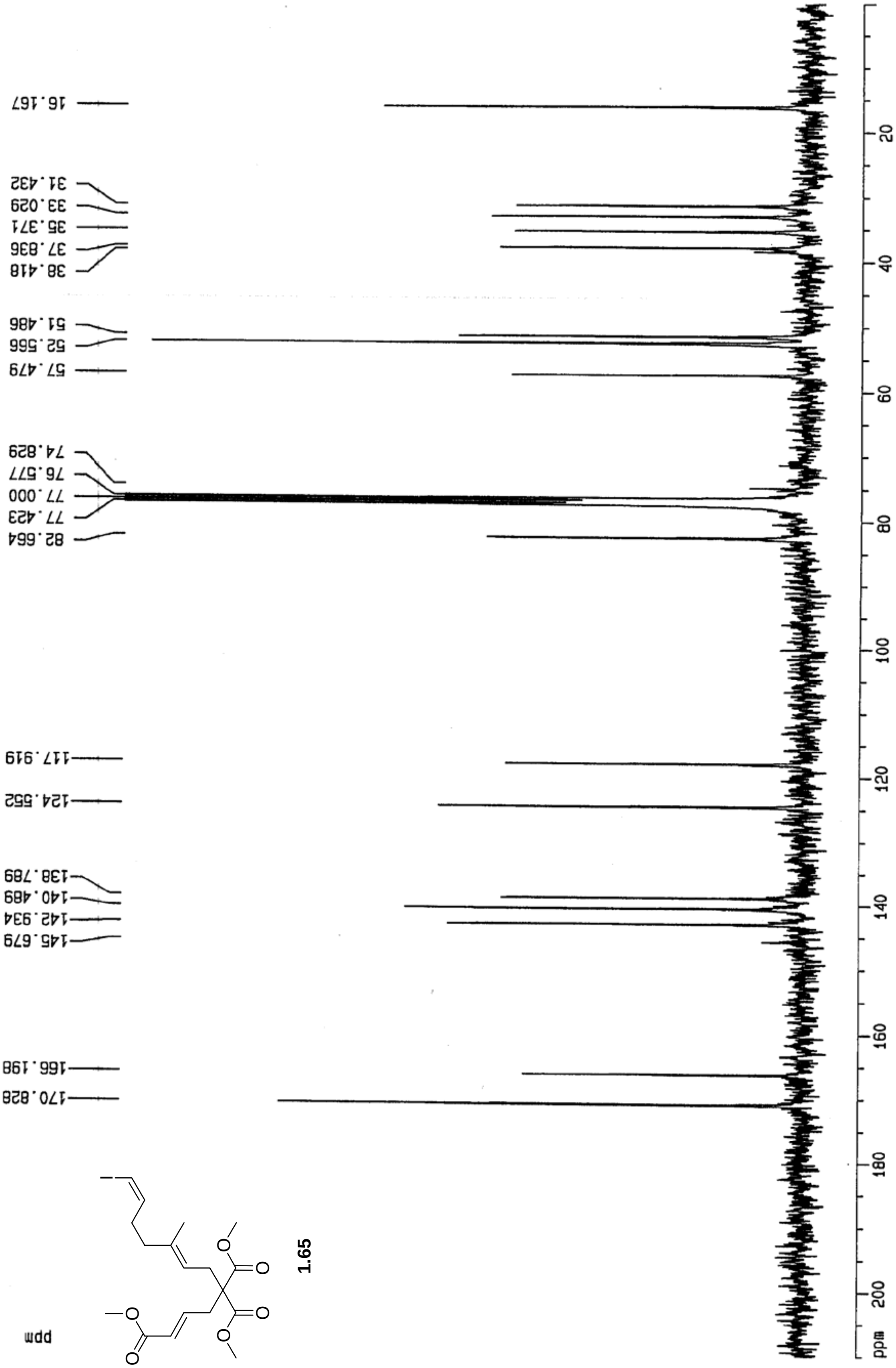
O
O
O
O
O
I

1.65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33.029
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37.836
38.418
51.486
52.566
57.479
74.829
76.577
77.000
77.423
82.664
117.919
124.552
138.789
140.489
142.934
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170.828
ppm
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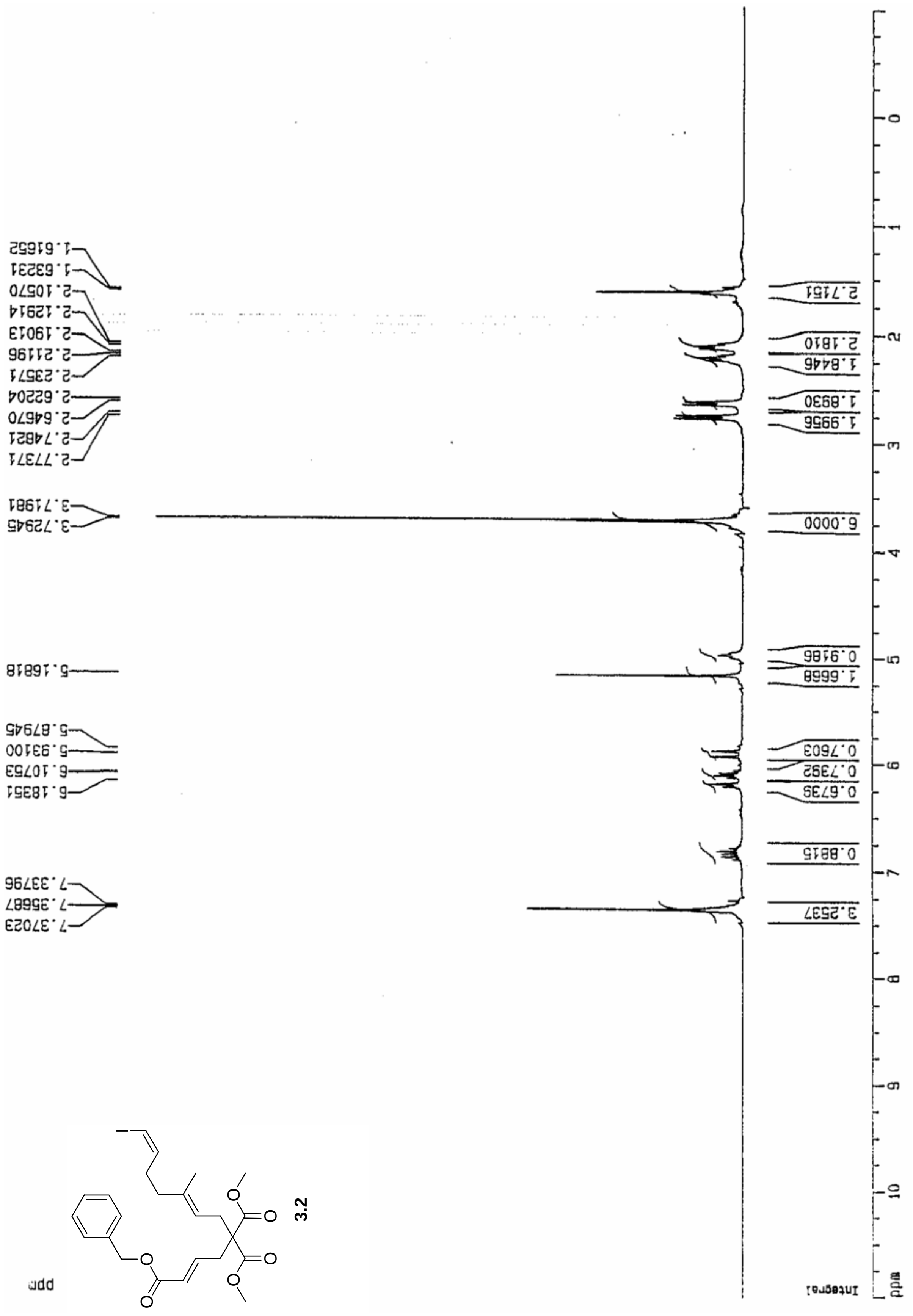
80
100
120
140
160
180
200
ppm

1.65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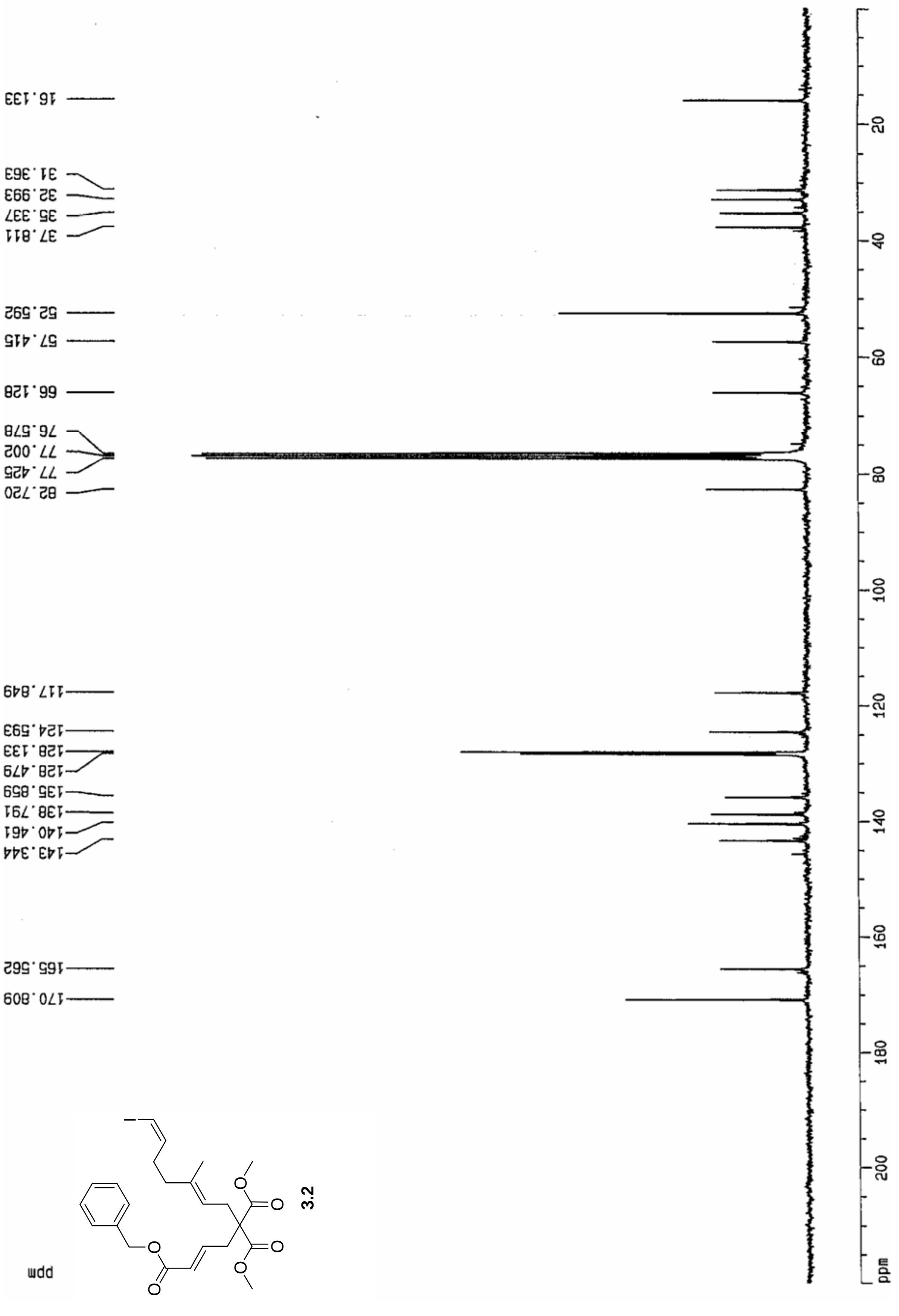
2.10570
2.12914
2.19013
2.21196
2.23571
2.62204
2.64670
2.74821
2.77371
3.71981
3.72945
5.16818
5.87945
5.93100
6.10753
6.18351
7.33796
7.35687
7.37023
2.7151
2.1810
1.8446
1.8930
1.9956
6.0000
0.9186
1.6668
0.7603
0.7392
0.6739
0.8815
3.2537
Integral
0
1
2
3
4
5
6
7
8
9
10
ppm
ppm

3.2



3.2

16.133
31.363
32.993
35.337
37.811
52.592
57.415
66.128
76.578
77.002
77.425
82.720
117.849
124.593
128.133
128.479
135.859
138.791
140.461
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165.562
170.809
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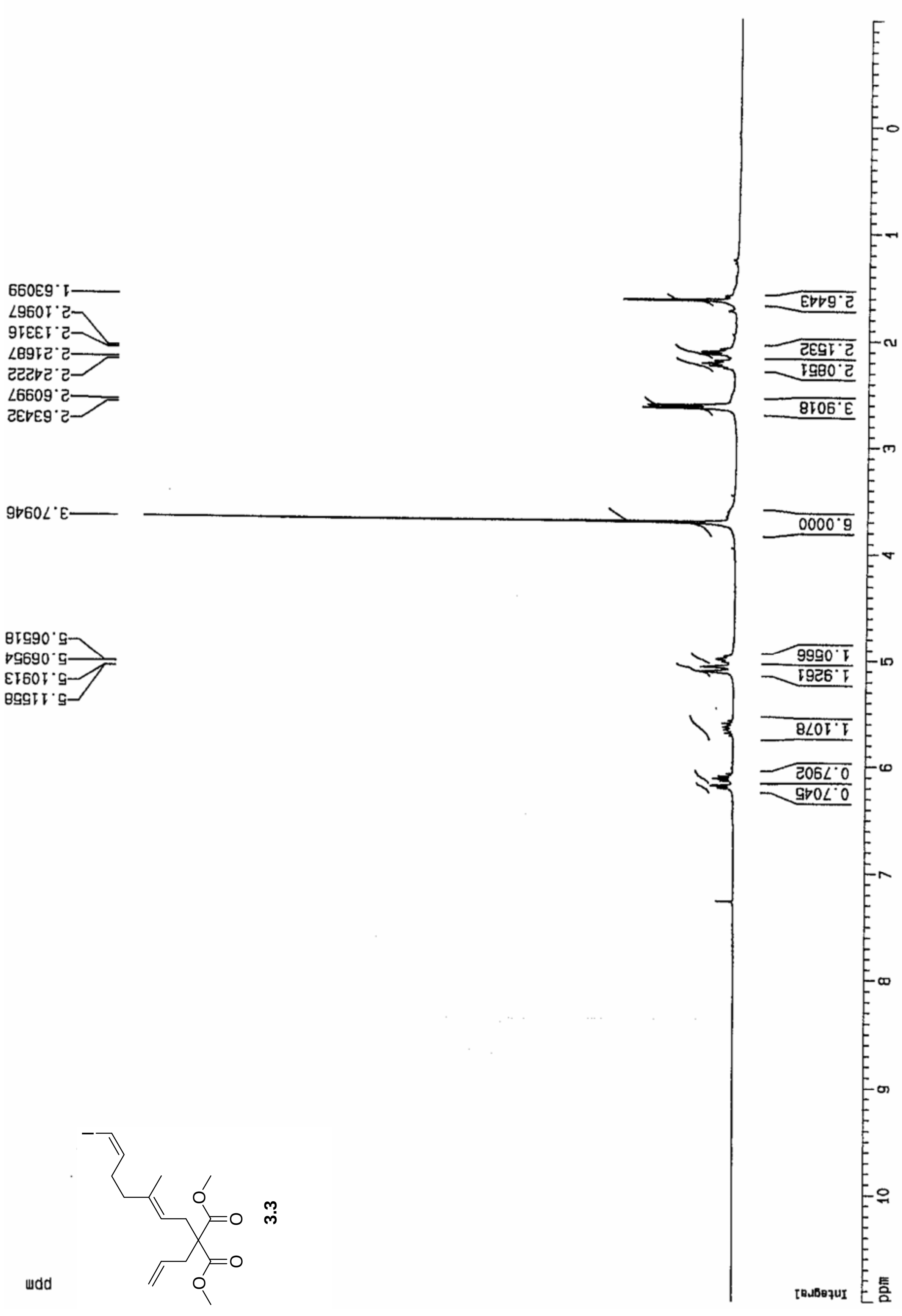
80
100
120
140
160
180
200
ppm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2.13316
2.21687
2.24222
2.60997
2.63432
3.70946
5.06518
5.06954
5.10913
5.11558
2.6443
2.1532
2.0851
3.9018
6.0000
1.0566
1.9261
1.1078
0.7902
0.7045
Integral
ppm
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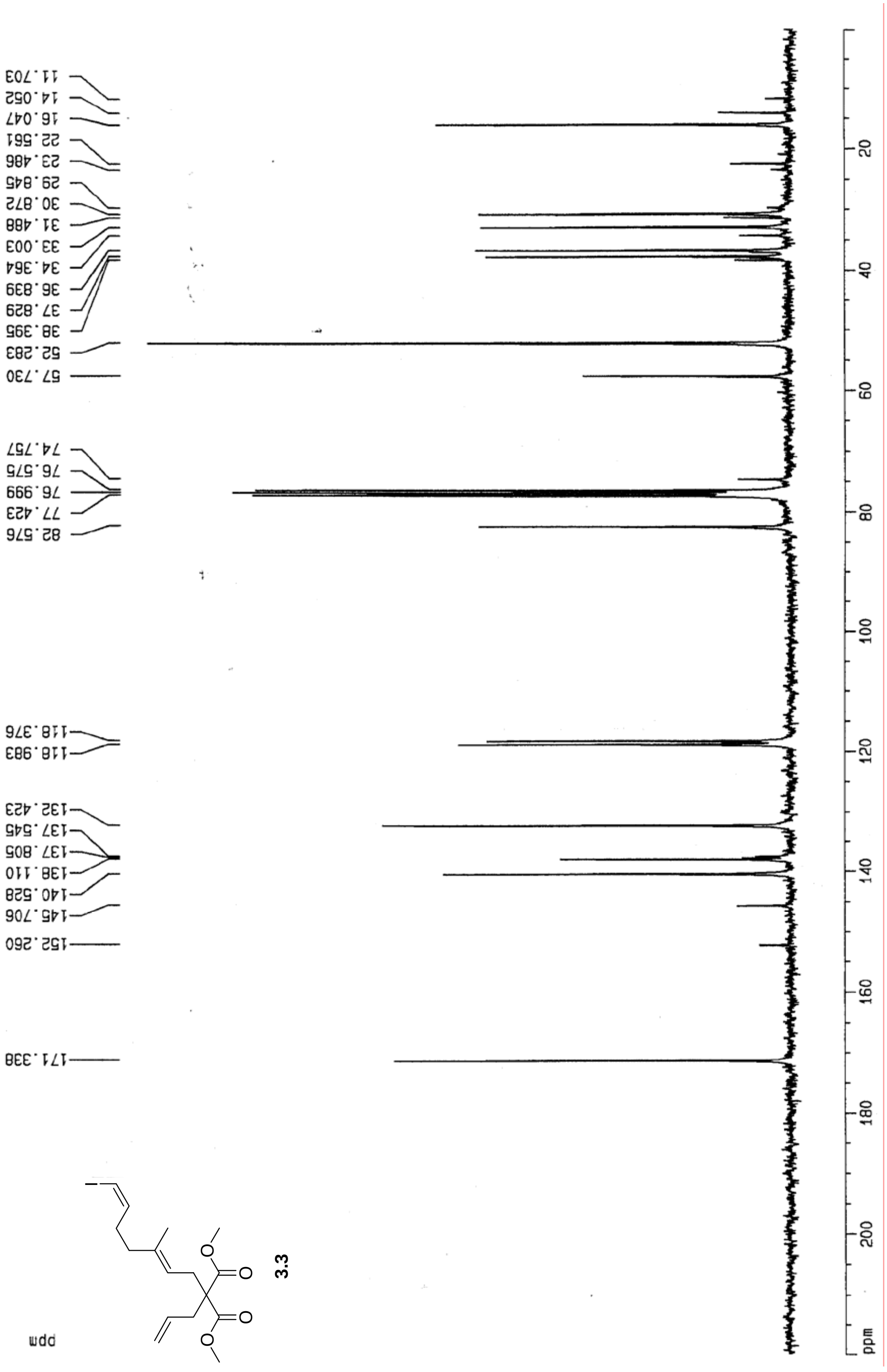
9
8
7
6
5
4
3
2
1
0
ppm
O
O
O
O

3.3


11.703
14.052
16.047
22.561
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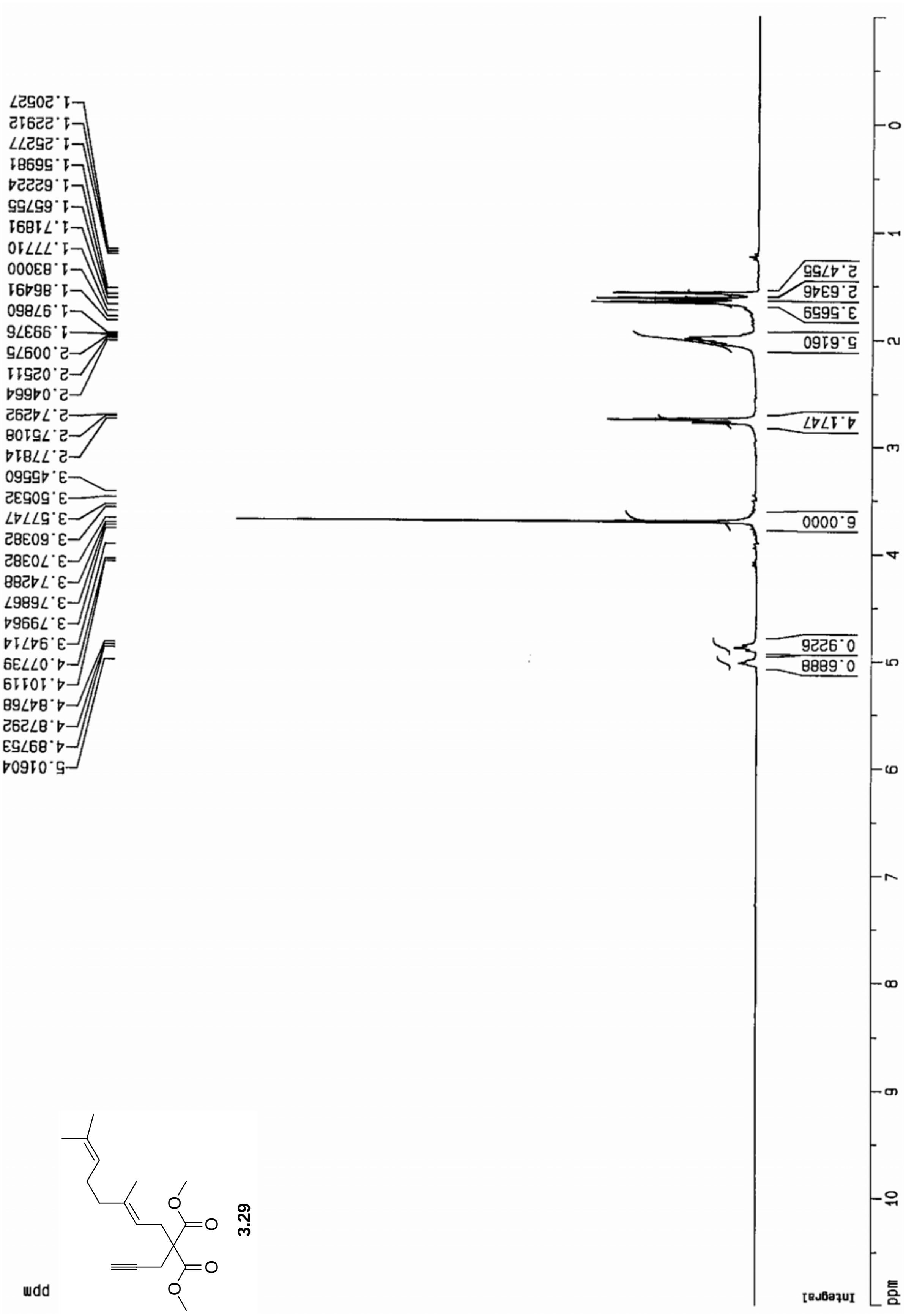
29.845
30.872
31.488
33.003
34.364
36.839
37.829
38.395
52.283
57.730
74.757
76.575
76.999
77.423
82.576
118.376
118.983
132.423
137.545
137.805
138.110
140.528
145.706
152.260
171.338
ppm
20
40
60
80
100
120
140
160
180
200
ppm

3.3



1.20527
1.22912
1.25277
1.56981
1.62224
1.65755
1.71891
1.77710
1.83000
1.86491
1.97860
1.99376
2.00975
2.02511
2.04664
2.74292
2.75108
2.77814
3.45560
3.50532
3.57747
3.60382
3.70382
3.74288
3.76867
3.79964
3.94714
4.07739
4.10119
4.84768
4.87292
4.89753
5.01604
ppm
2.4755
2.6346
3.5659
5.6160
4.1747
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Integral
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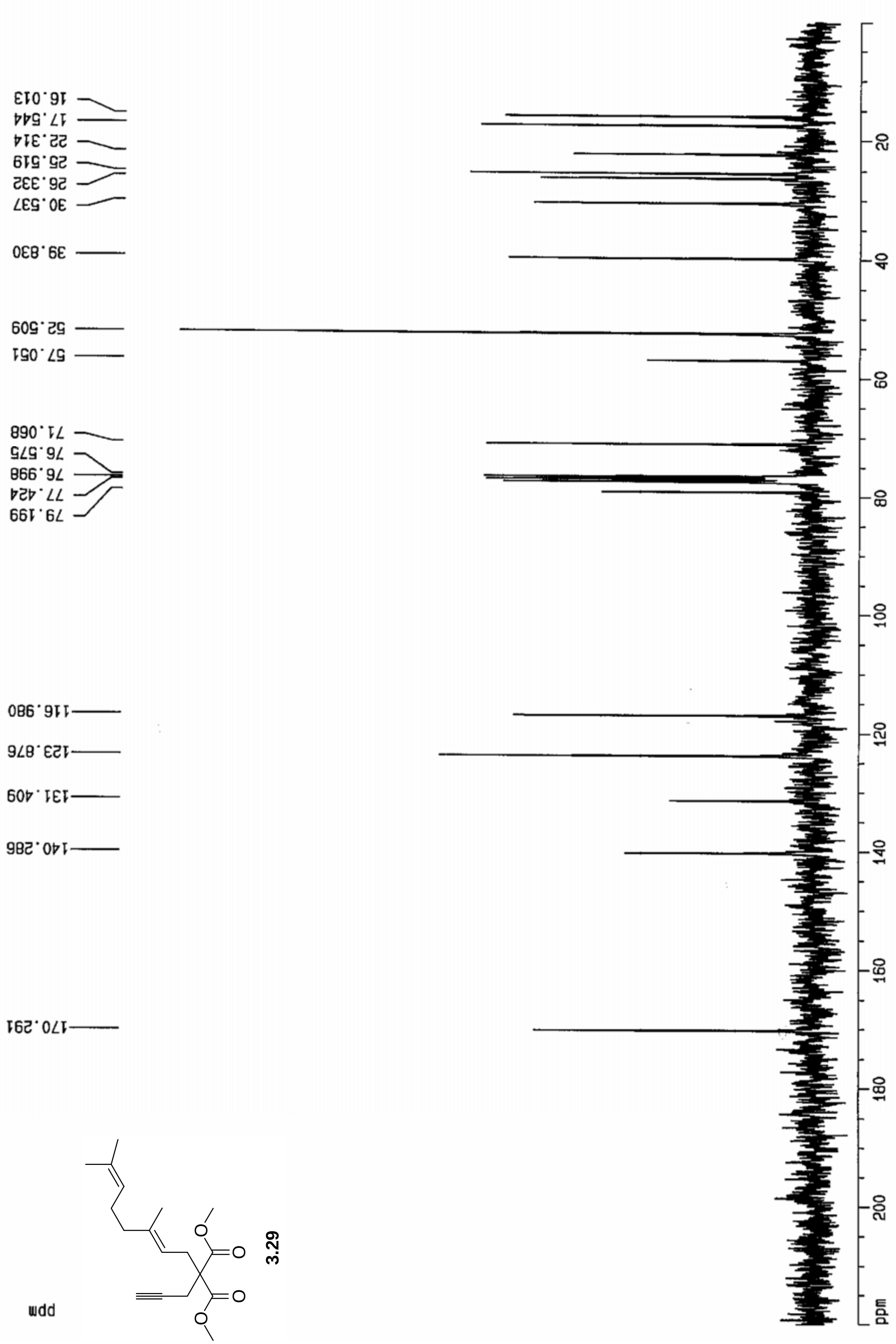
4
5
6
7
8
9
10
ppm

3.29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26.332
30.537
39.830
52.509
57.051
71.068
76.575
76.998
77.424
79.199
116.980
123.876
131.409
140.286
170.291
ppm
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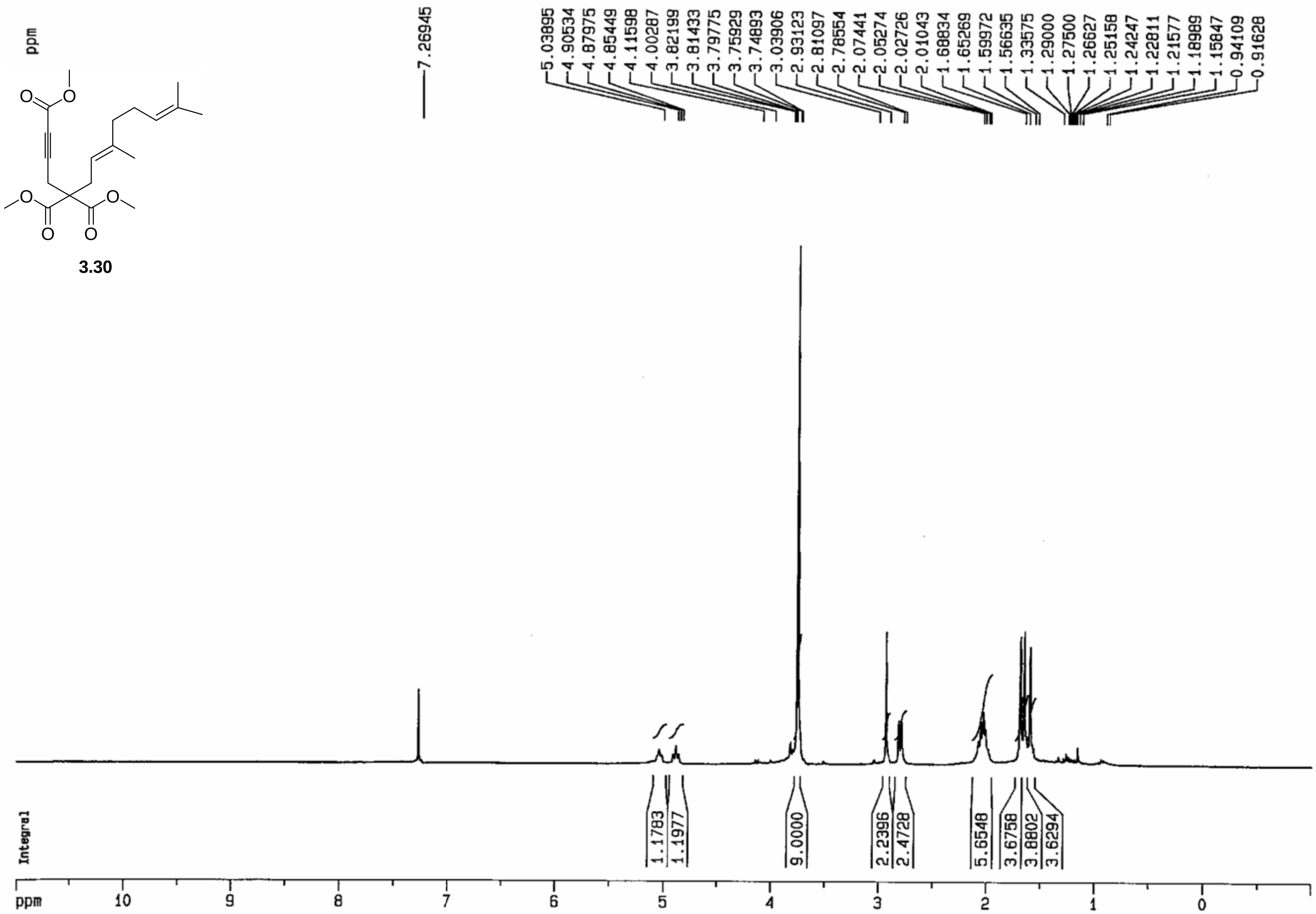
40
60
80
100
120
140
160
180
200
ppm

3.29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4.11598
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3.79775
3.75929
3.74893
3.03906
2.93123
2.81097
2.78554
2.07441
2.05274
2.02726
2.01043
1.68834
1.65269
1.59972
1.56635
1.33575
1.29000
1.27500
1.26627
1.25158
1.24247
1.22811
1.21577
1.18989
1.15847
0.94109
0.91628
Integral
1.1783
1.1977
9.0000
2.2396
2.4728
5.6548
3.6758
3.8802
3.6294
ppm
10
9
8
7
6
5
4
3
2
1
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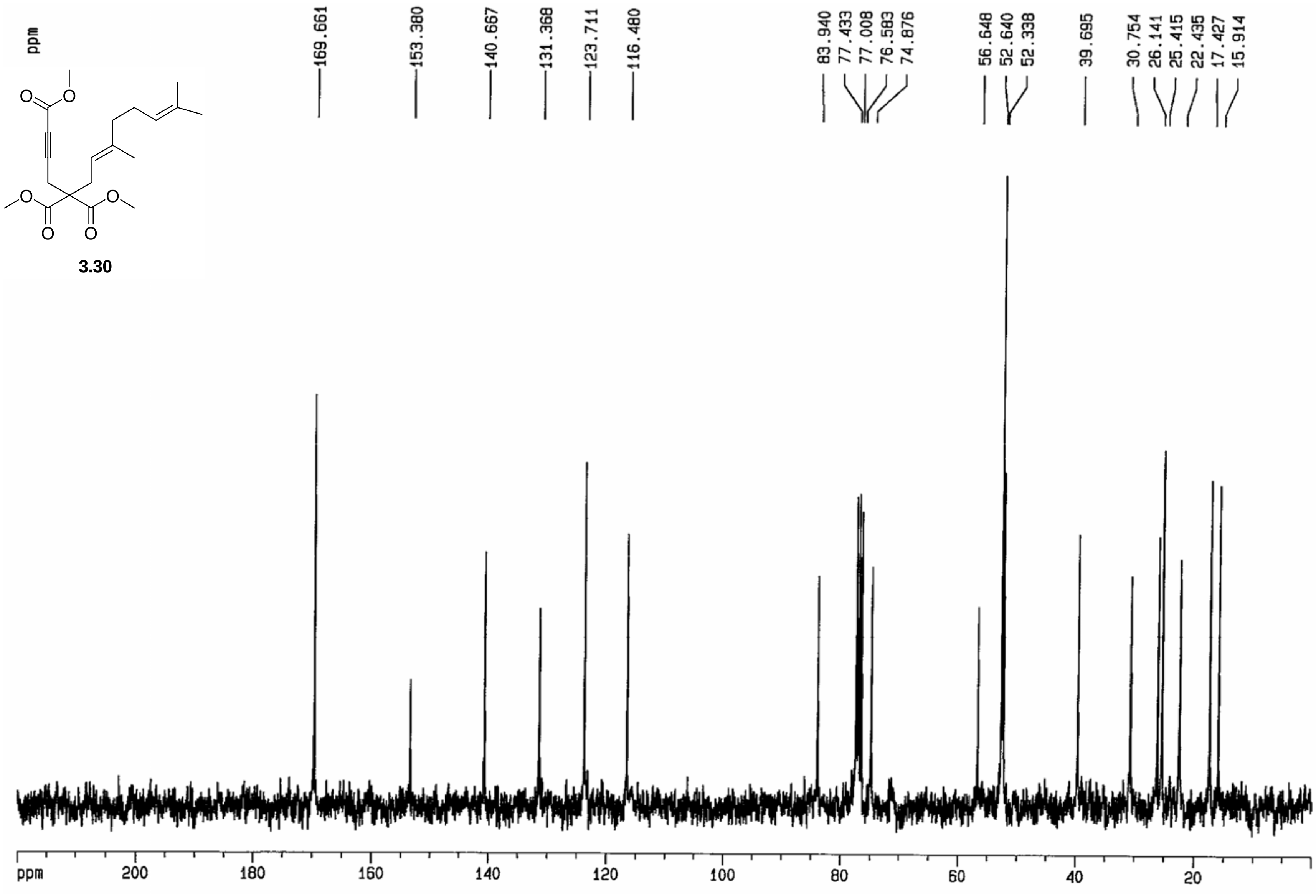
3.30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116.480
83.940
77.433
77.008
76.583
74.876
56.648
52.640
52.338
39.695
30.754
26.141
25.415
22.435
17.427
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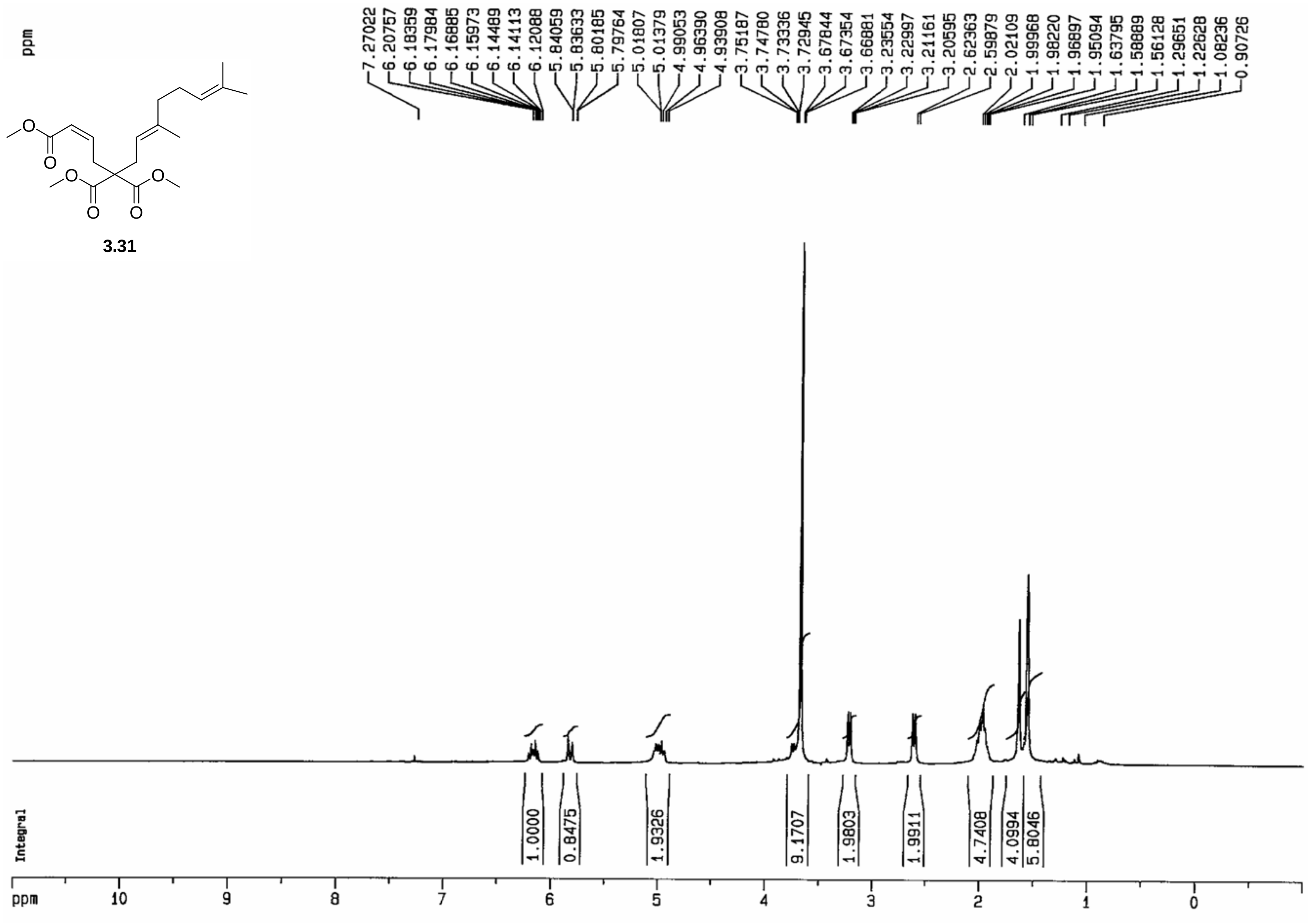
O
O
O
O
O
O
ppm
200
180
160
140
120
100
80
60
40
20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5.83633
5.80185
5.79764
5.01807
5.01379
4.99053
4.96390
4.93908
3.75187
3.74780
3.73336
3.72945
3.67844
3.67354
3.66881
3.23554
3.22997
3.21161
3.20595
2.62363
2.59879
2.02109
1.99968
1.98220
1.96897
1.95094
1.63795
1.58889
1.56128
1.29651
1.22628
1.08236
0.90726
Integral
1.0000
0.8475
1.9326
9.1707
1.9803
1.9911
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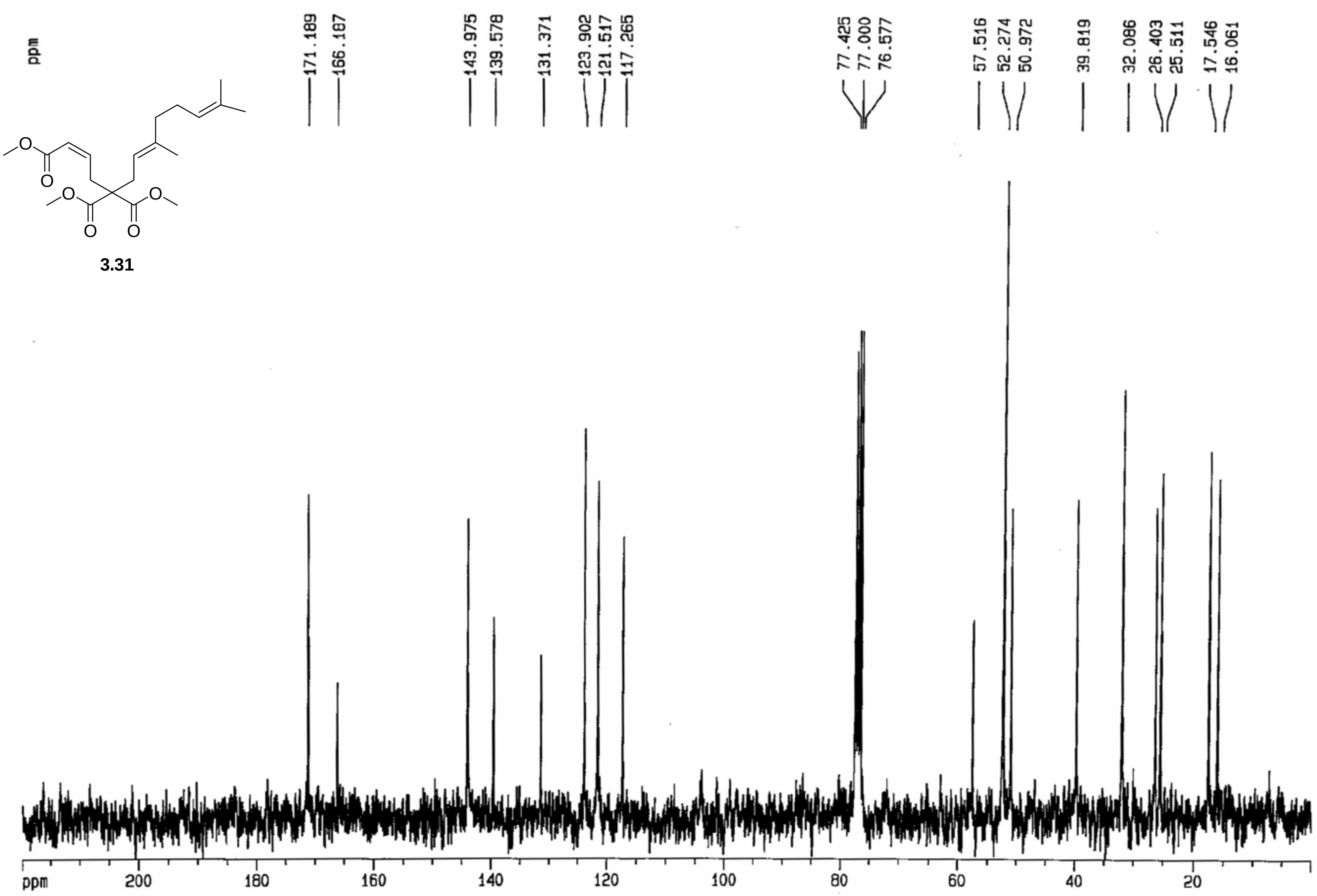
4.0994
5.8046
ppm
10
9
8
7
6
5
4
3
2
1
0

3.31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131.371
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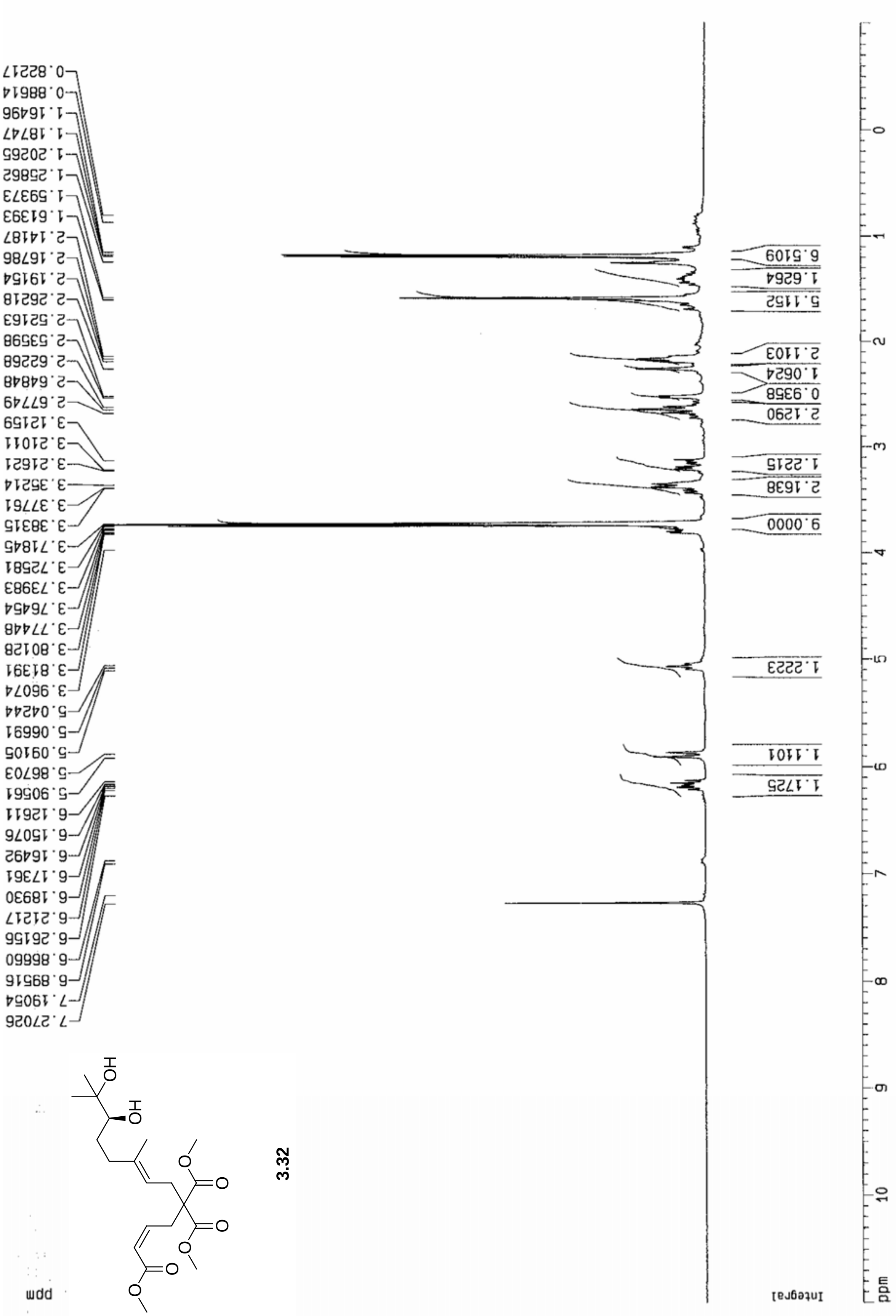
121.517
117.265
77.425
77.000
76.577
57.516
52.274
50.972
39.819
32.086
26.403
25.511
17.546
16.061
O
ppm
200
180
160
140
120
100
80
60
40
20

3.31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2.19154
2.26218
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2.67749
3.12159
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3.38315
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3.72581
3.73983
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3.81391
3.96074
5.04244
5.06691
5.09105
5.86703
5.90561
6.12611
6.15076
6.16492
6.17361
6.18930
6.21217
6.26156
6.86660
6.89516
7.19054
7.27026
ppm
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1.6264
5.1152
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1.0624
0.9358
2.1290
1.2215
2.1638
9.0000
1.2223
1.1101
1.1725
Integral
10
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5
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3
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1
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ppm
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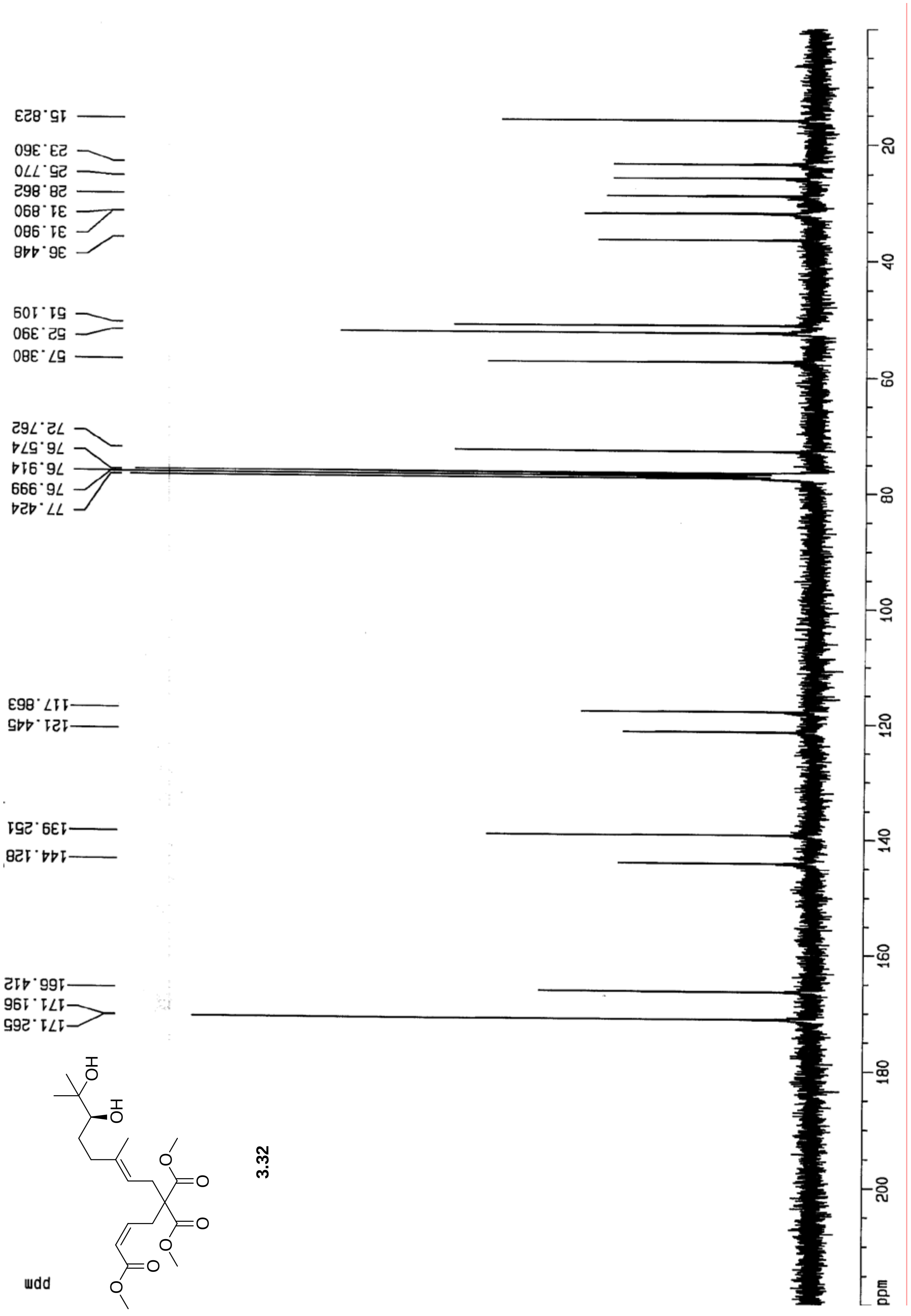
HO
O
O
O
O
O
O

3.32


3.32

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31.980
36.448
51.109
52.390
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72.762
76.574
76.914
76.999
77.424
117.863
121.445
139.251
144.128
166.412
171.196
171.265
ppm
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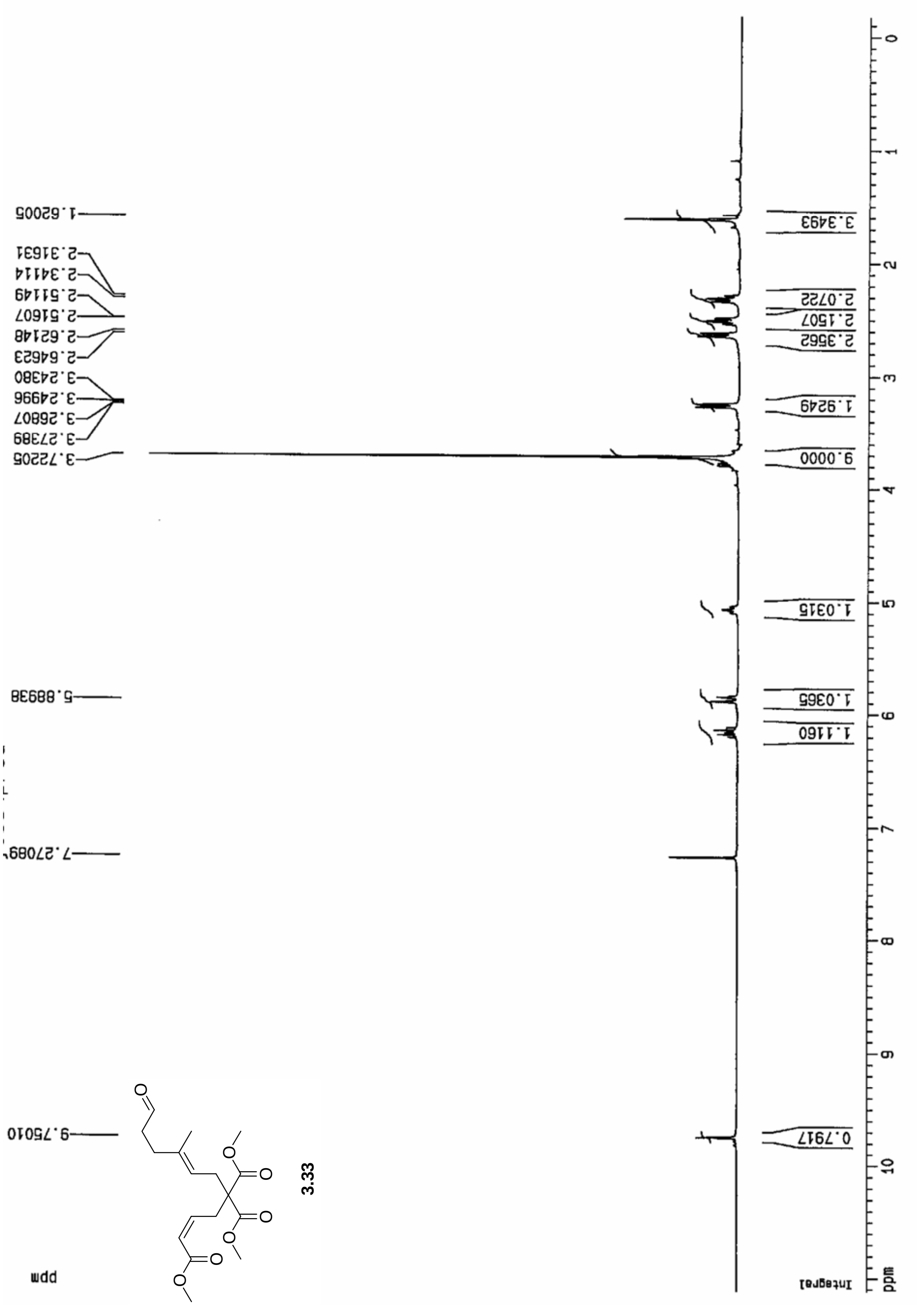
40
60
80
100
120
140
160
180
200
ppm
HO
HO
O
O
O
O
O
O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7.27089
9.75010
ppm
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2.1507
2.3562
1.9249
9.0000
1.0315
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Integral
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1
2
3
4
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6
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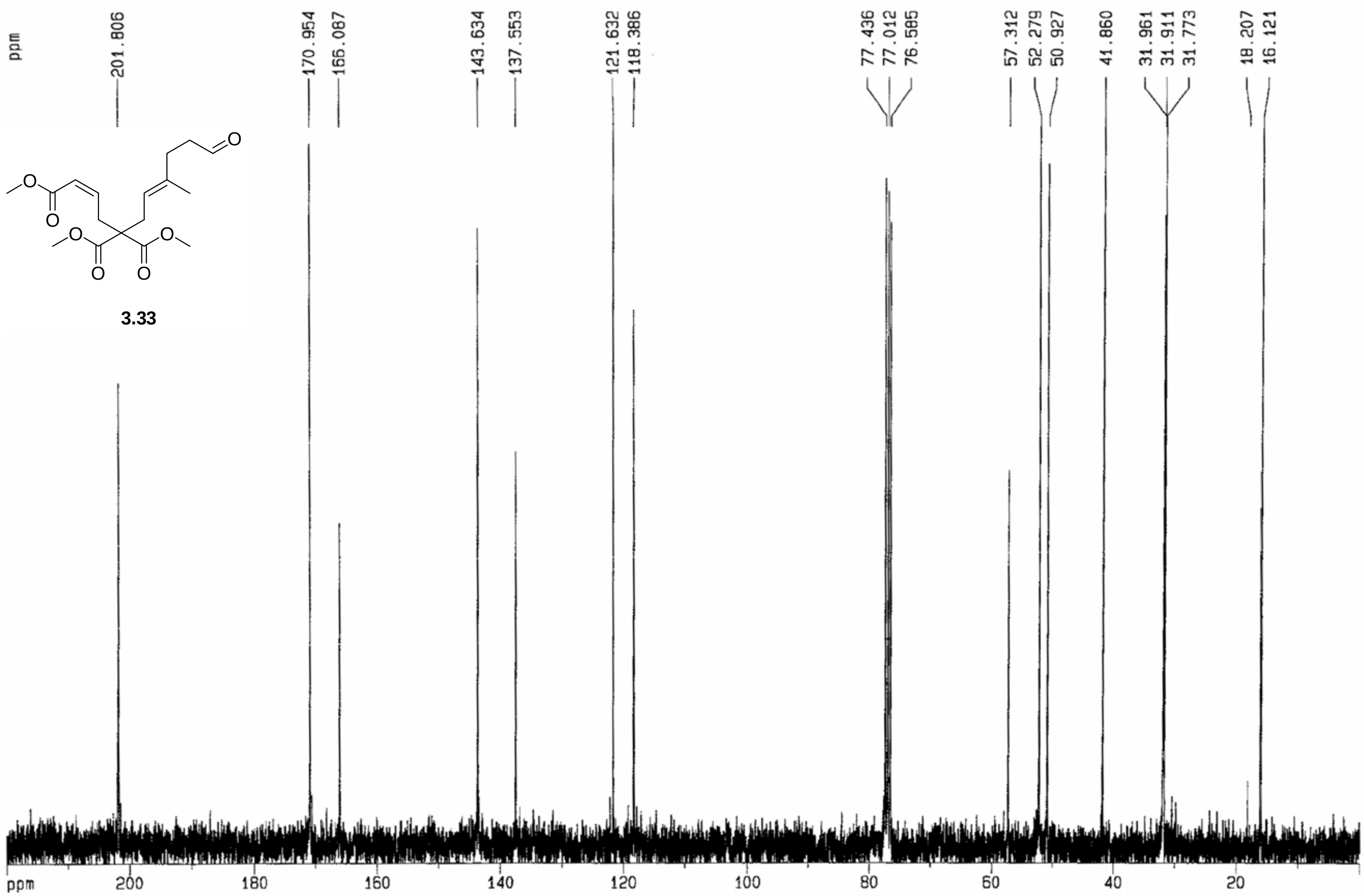
8
9
10
ppm

3.33


3.33

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143.634
137.553
121.632
118.386
77.436
77.012
76.585
57.312
52.279
50.927
41.860
31.961
31.911
31.773
18.207
16.121
O
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O
O
O
O
O
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120
100
80
60
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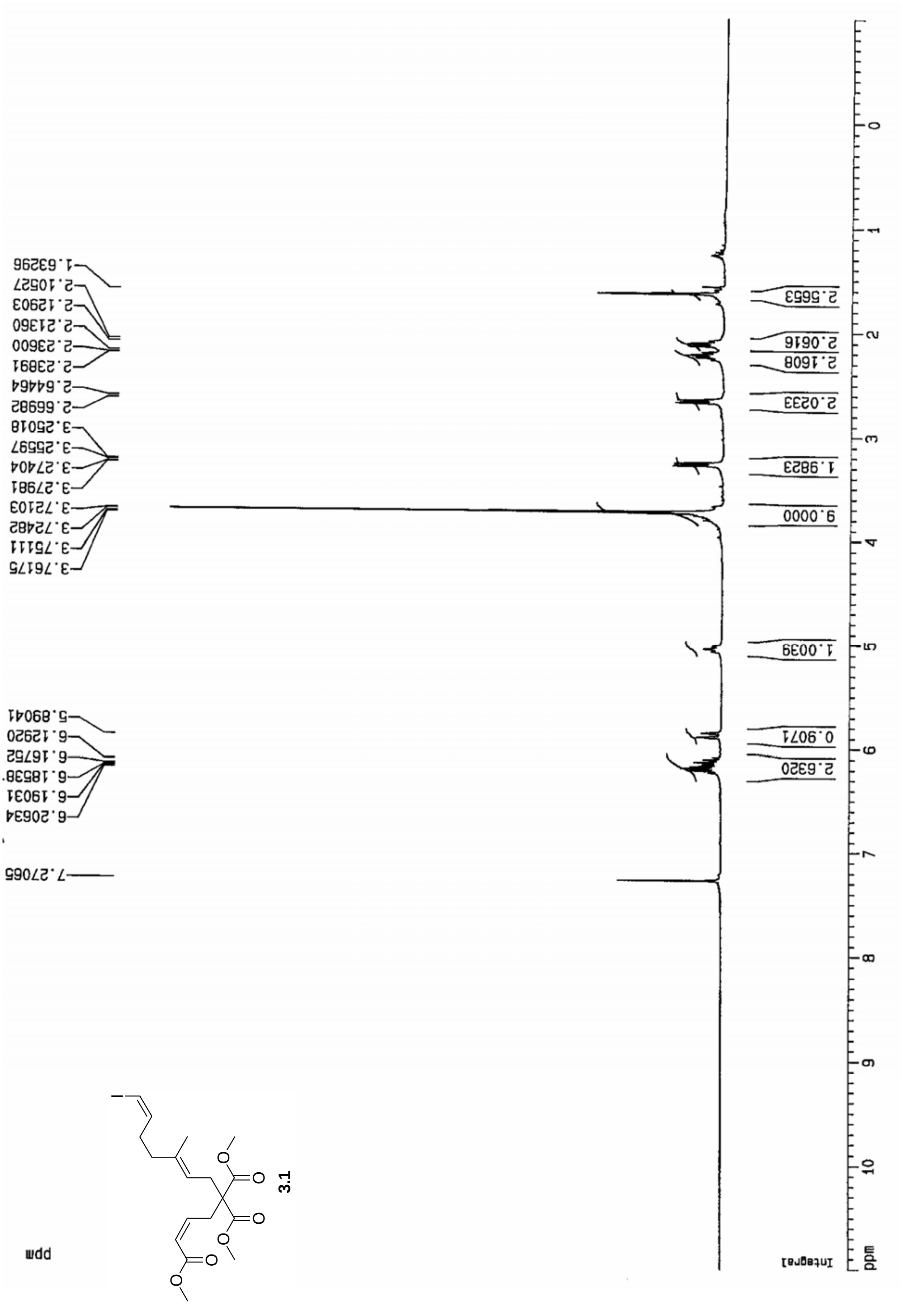
20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3.25597
3.27404
3.27981
3.72103
3.72482
3.75111
3.76175
5.89041
6.12920
6.16752
6.18538
6.19031
6.20634
7.27065
ppm
2.5653
2.0616
2.1608
2.0233
1.9823
9.0000
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Integral
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6
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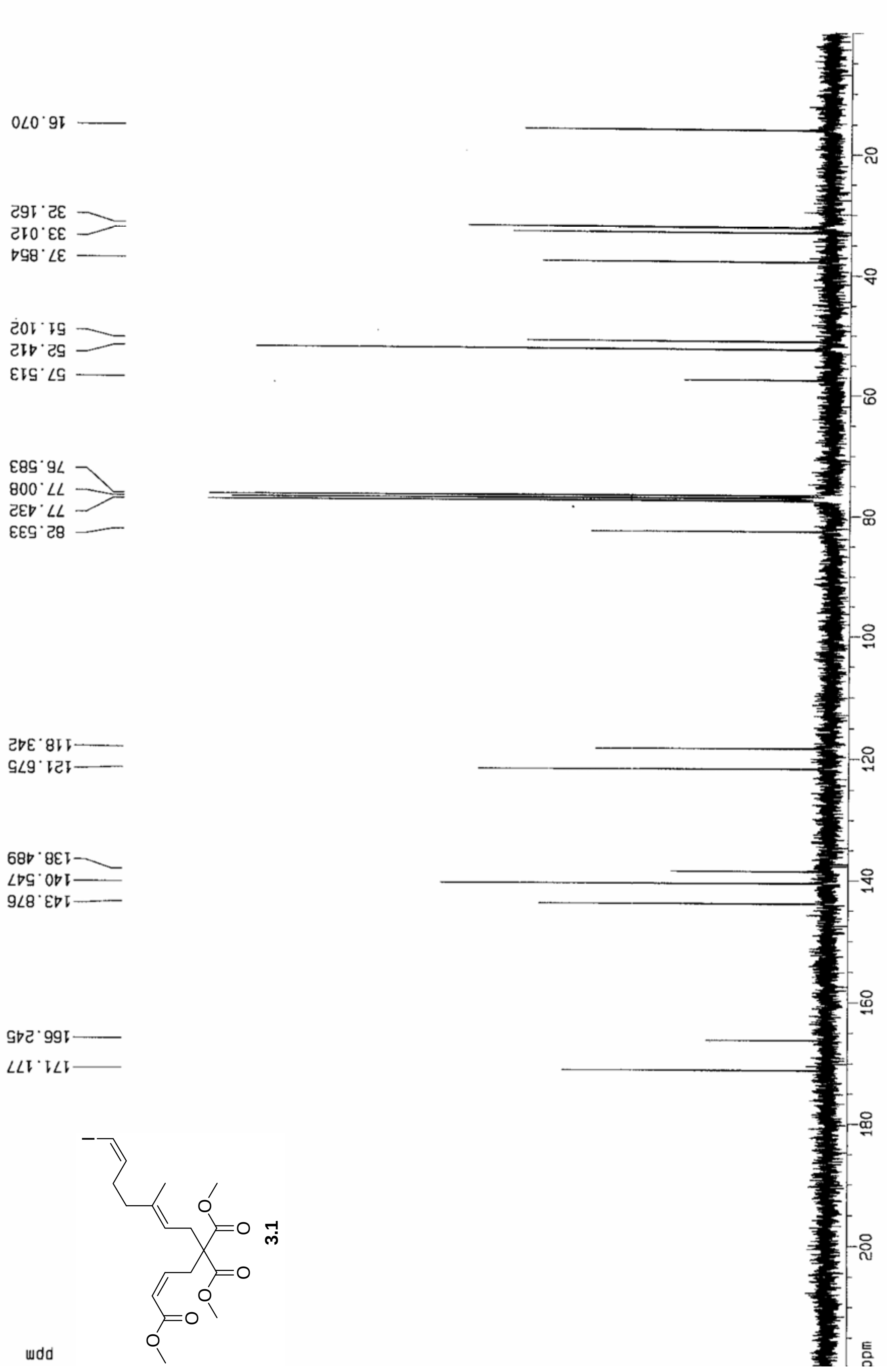
9
10
ppm

3.1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57.513
76.583
77.008
77.432
82.533
118.342
121.675
138.489
140.547
143.876
166.245
171.177
ppm
20
40
60
80
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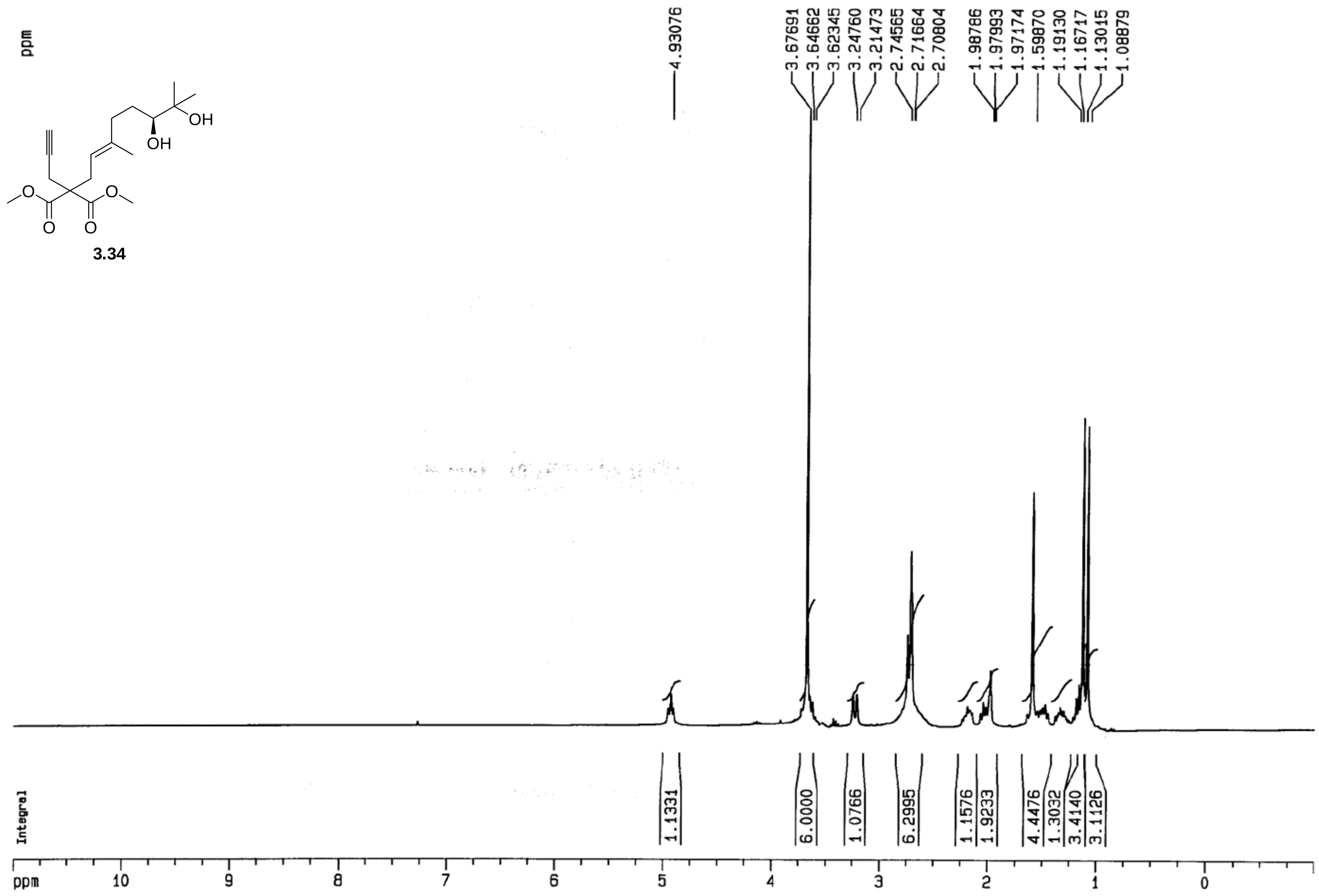

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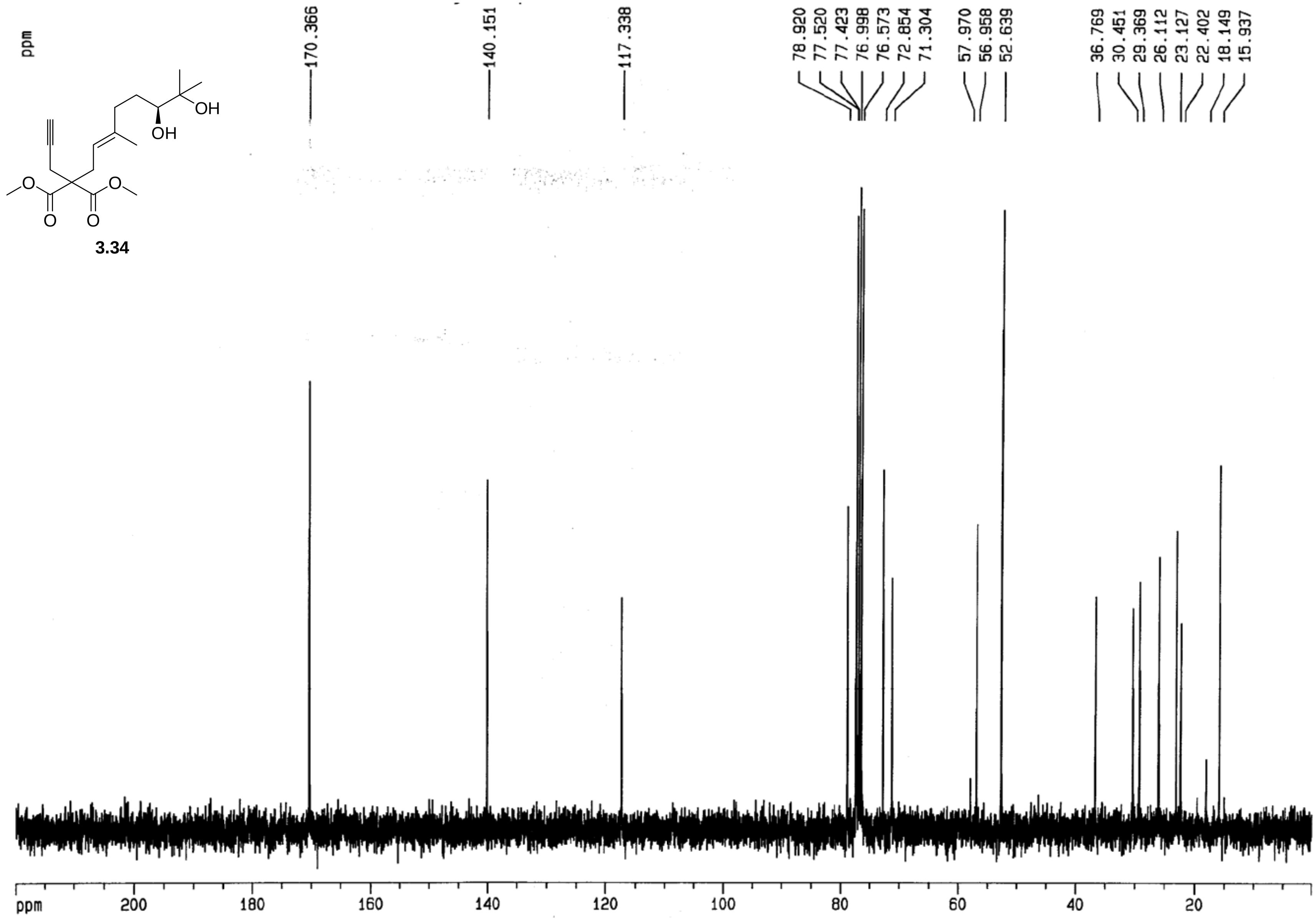
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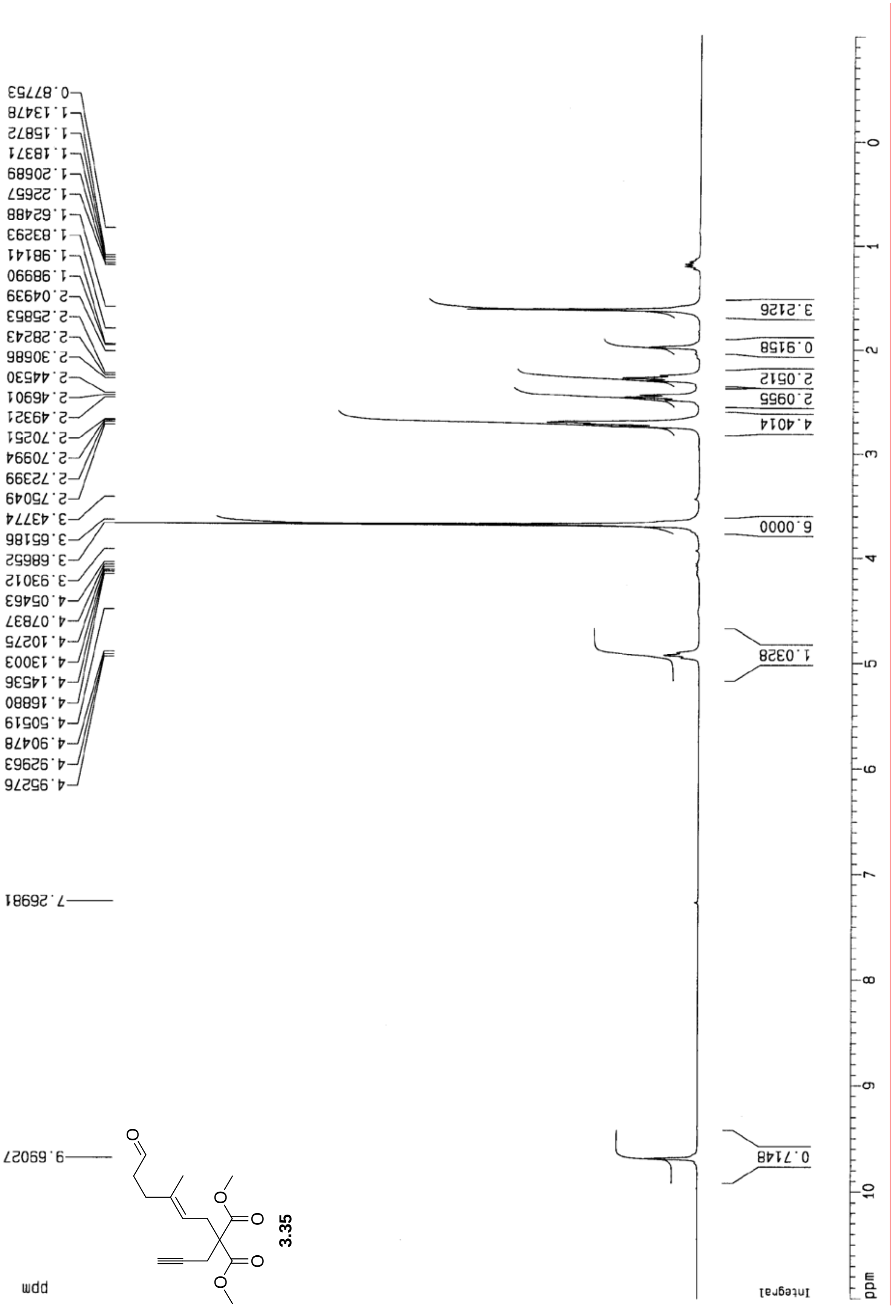
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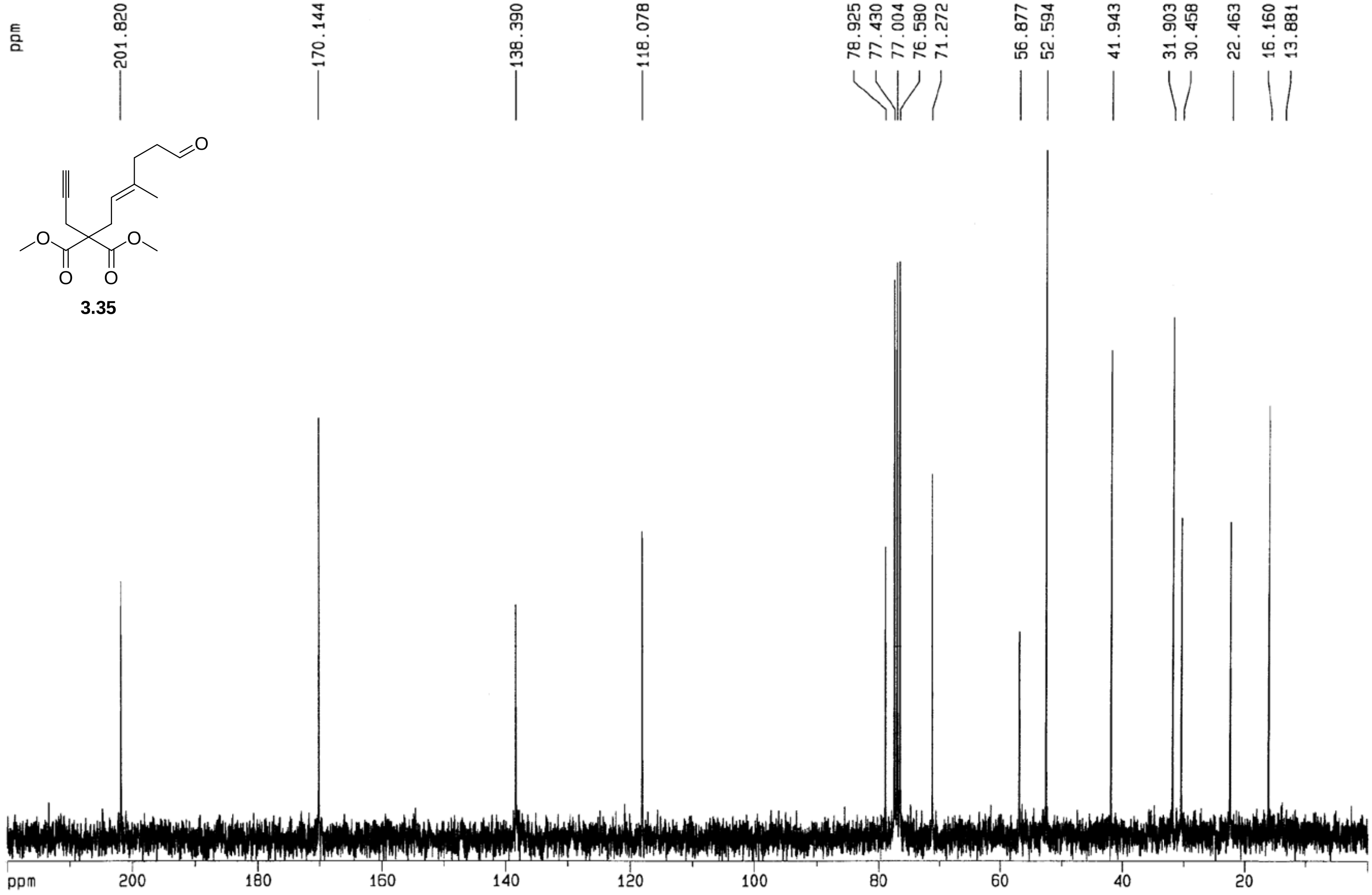
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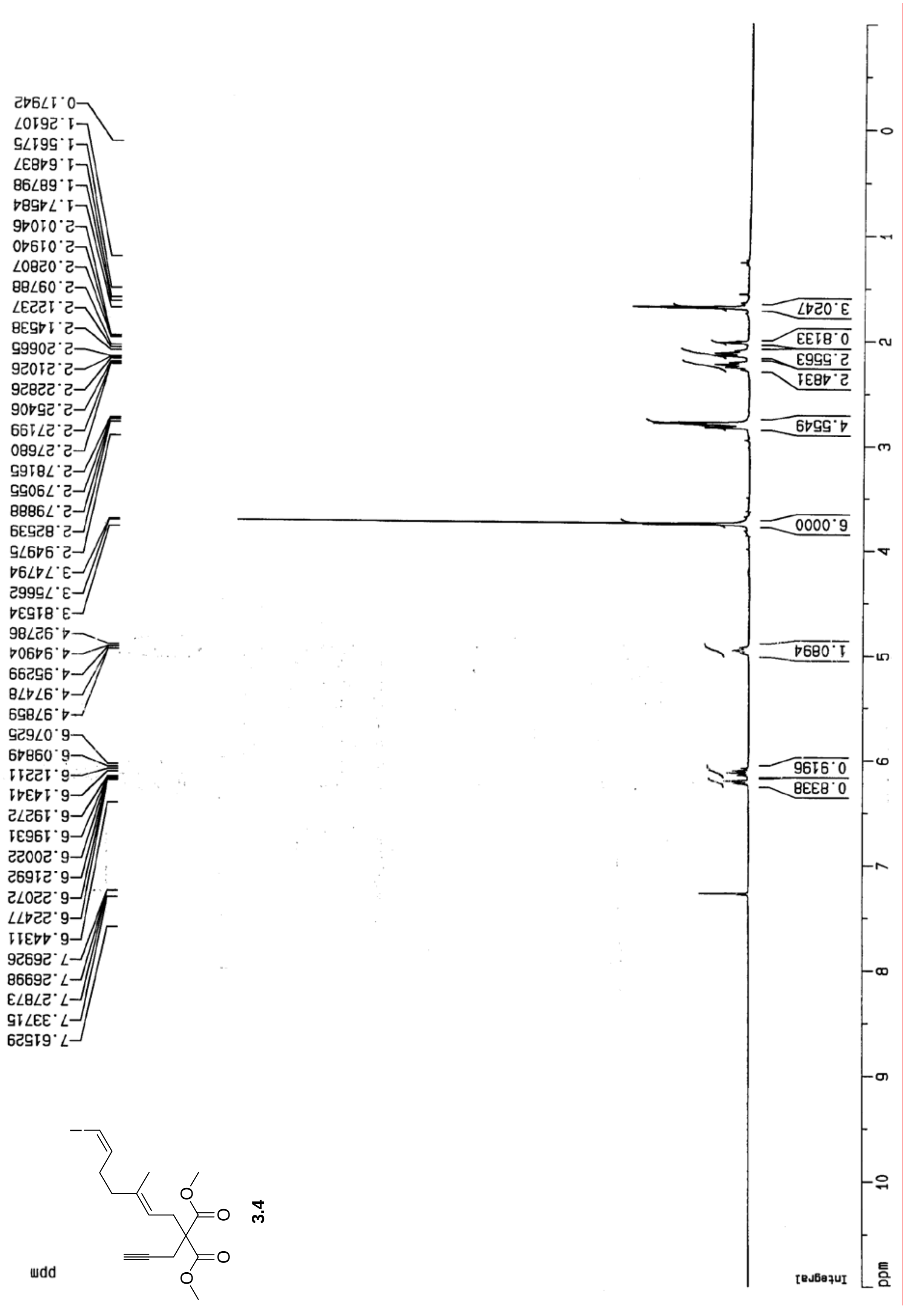
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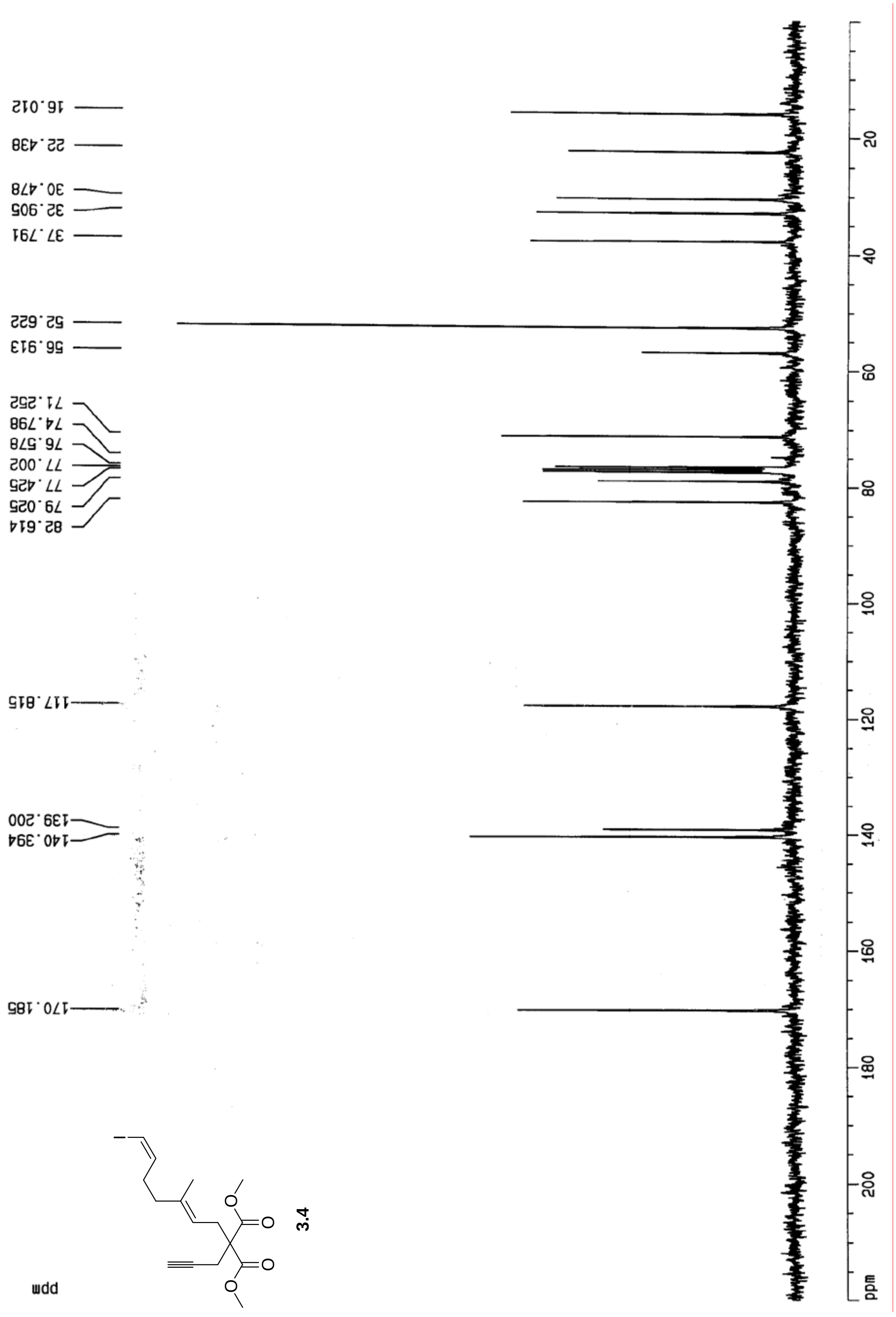
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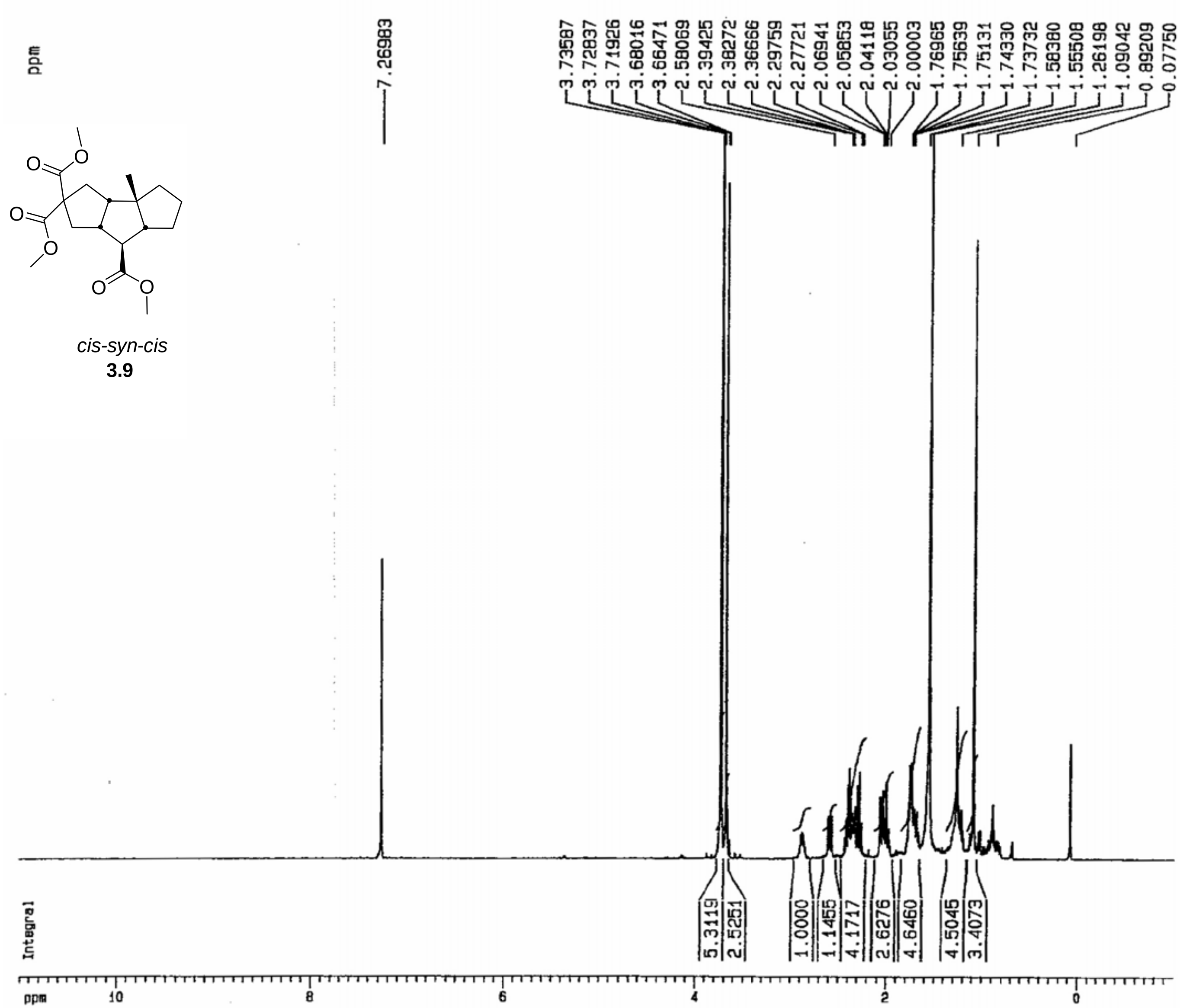

cis-syn-cis
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PROCNO	1

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SOLVENT	CDCl3
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FIDRES	0.229111 Hz
AQ	2.1823988 sec
RG	456.1
DW	66.600 usec
DE	6.00 usec
TE	290.0 K
D1	1.00000000 sec
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NUC1	1H
PL1	0.00 dB

F2 - Processing parameters

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SSB	0
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1D NMR plot parameters

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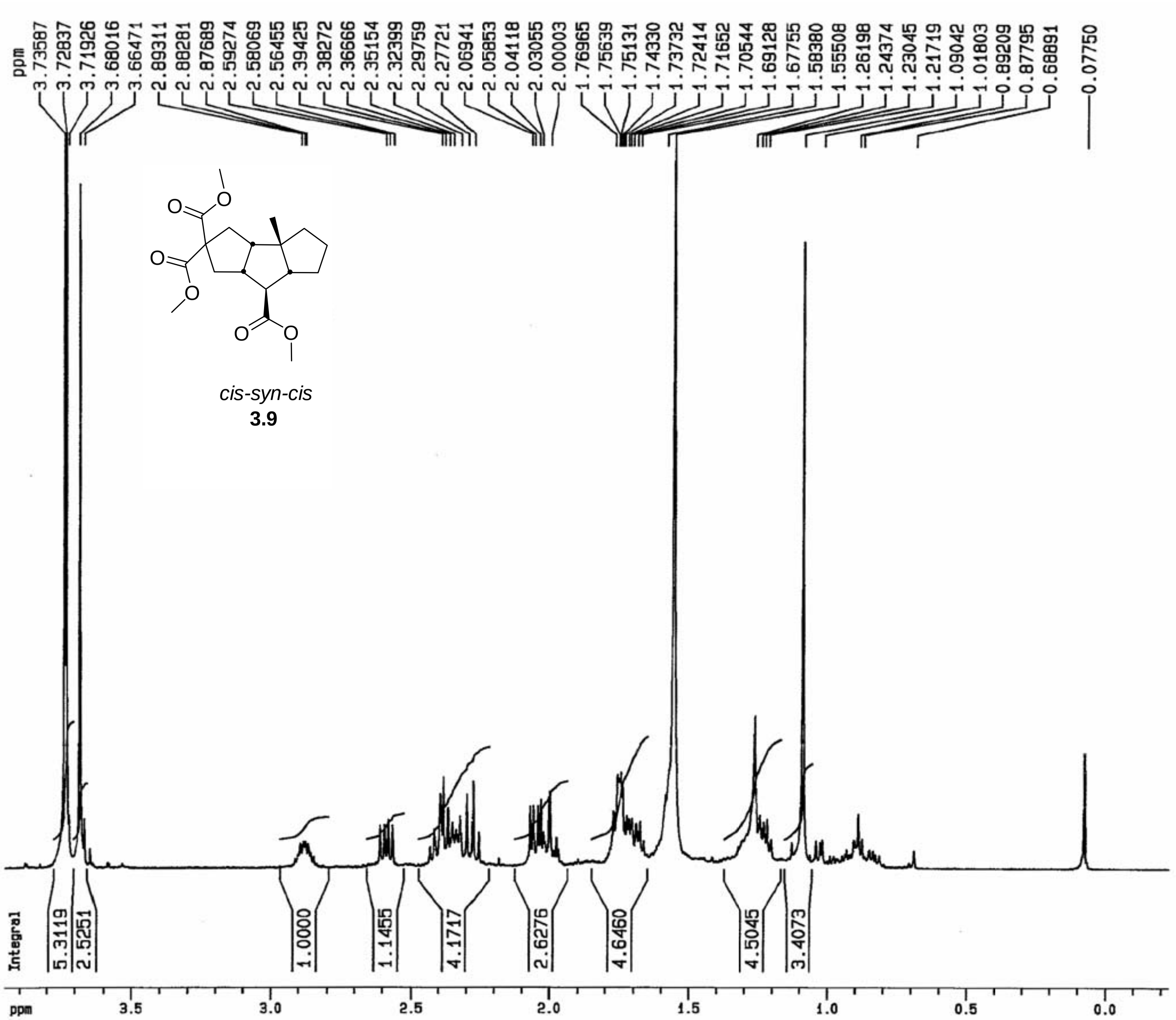

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AQ              2.1823988 sec
RG                   456.1
DW                  66.600 usec
DE                    6.00 usec
TE                   290.0 K
D1             1.00000000 sec
P1                   10.60 usec
DE                    6.00 usec
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NUC1                    1H
PL1                   0.00 dB

F2 - Processing parameters
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LB                    0.40 Hz
GB                       0
PC                    1.00

1D NMR plot parameters
CX                   20.00 cm
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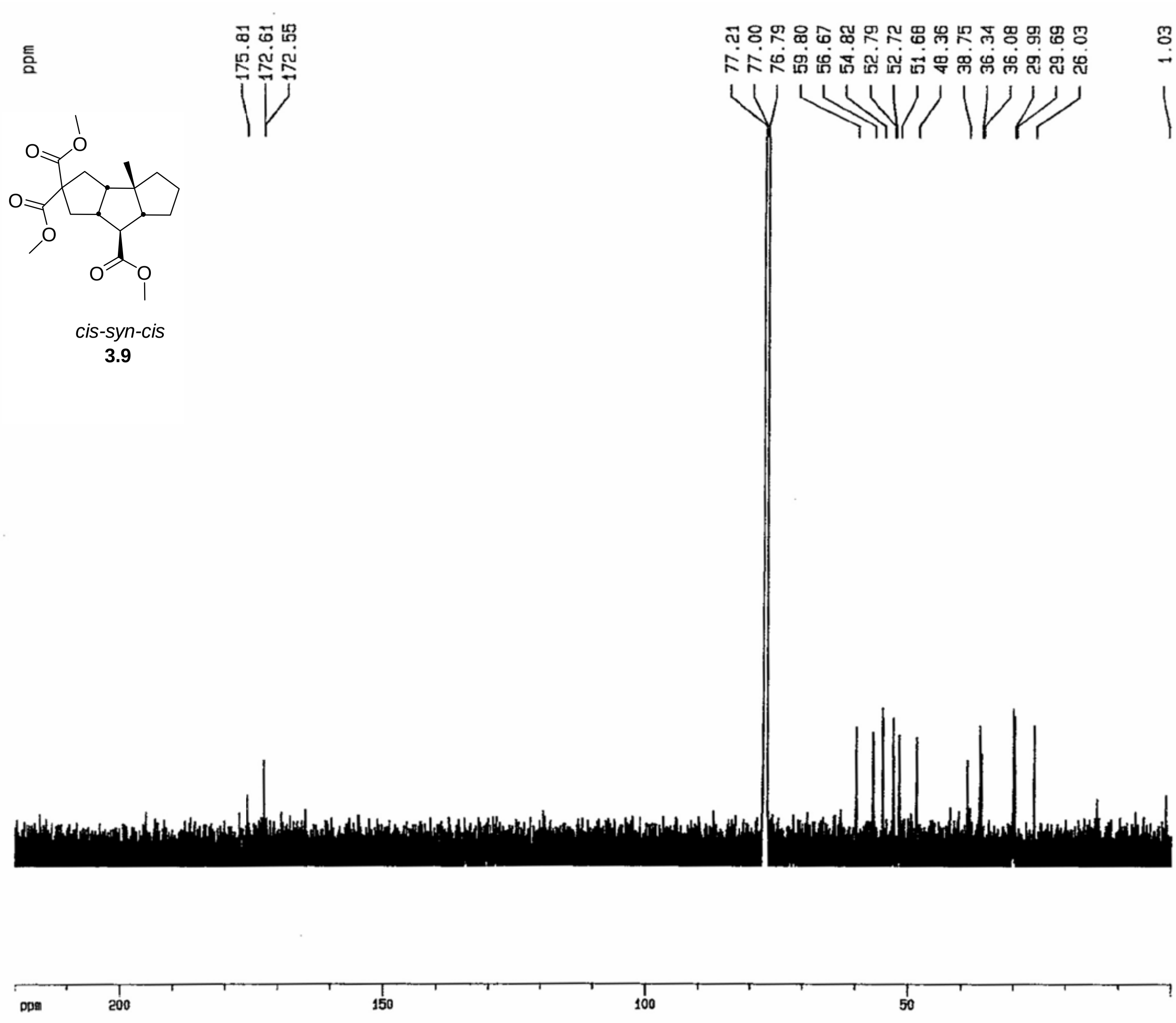

cis-syn-cis
3.9

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FIDRES        0.577984 Hz
AQ           0.8651252 sec
RG                32768
DW               13.200 usec
DE                 6.00 usec
TE                290.0 K
D1          8.00000000 sec
D3          0.00100000 sec

=========== CHANNEL f1 ========
NUC1                13C
P1                13.50 usec
PL1                0.00 dB
SFO1     151.0953827 MHz

=========== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2            100.00 usec
PL2                0.00 dB
PL12              12.00 dB
SFO2     600.8336050 MHz

F2 - Processing parameters
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SF        151.0788327 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.00

1D NMR plot parameters
CX                20.00 cm
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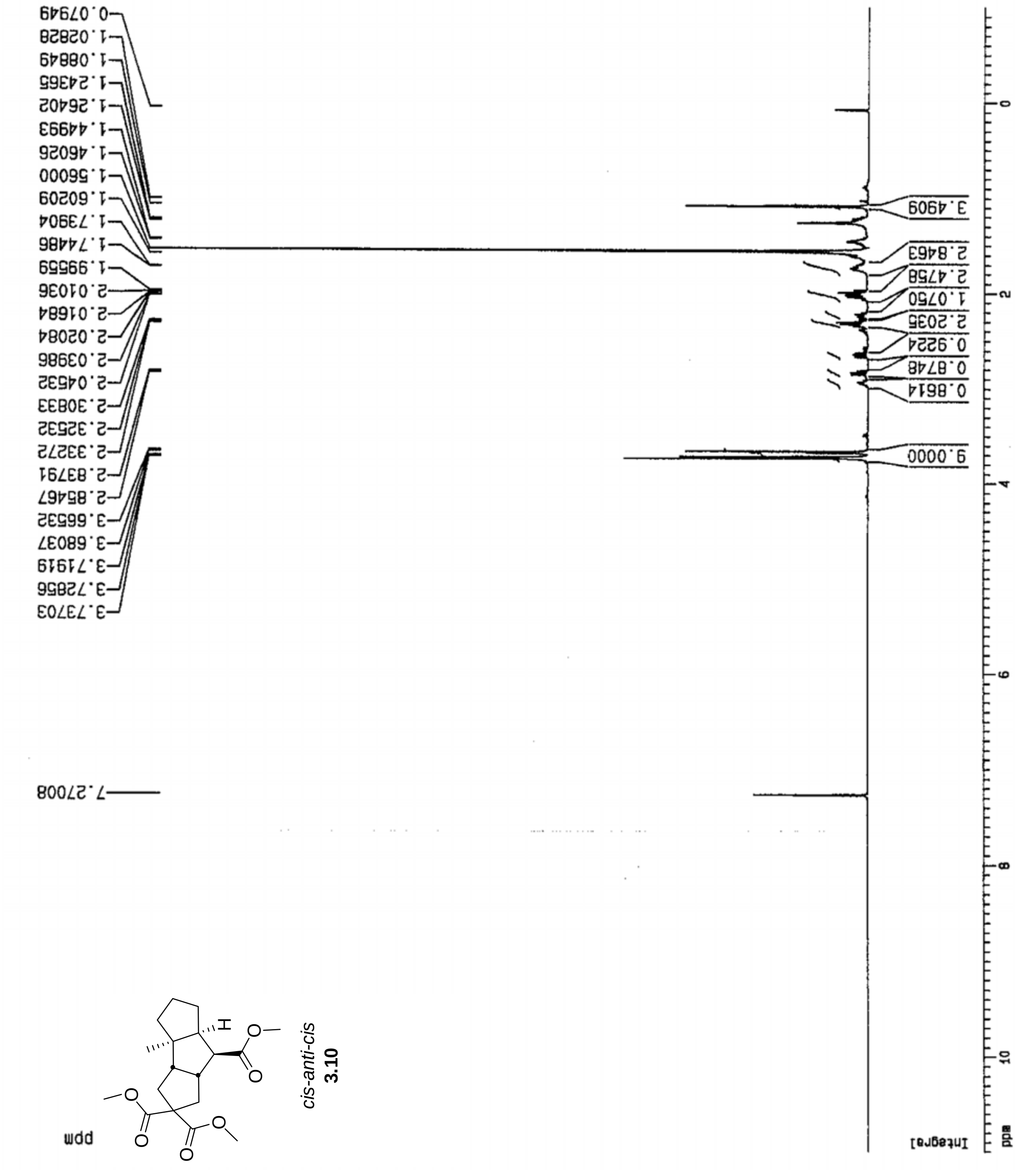
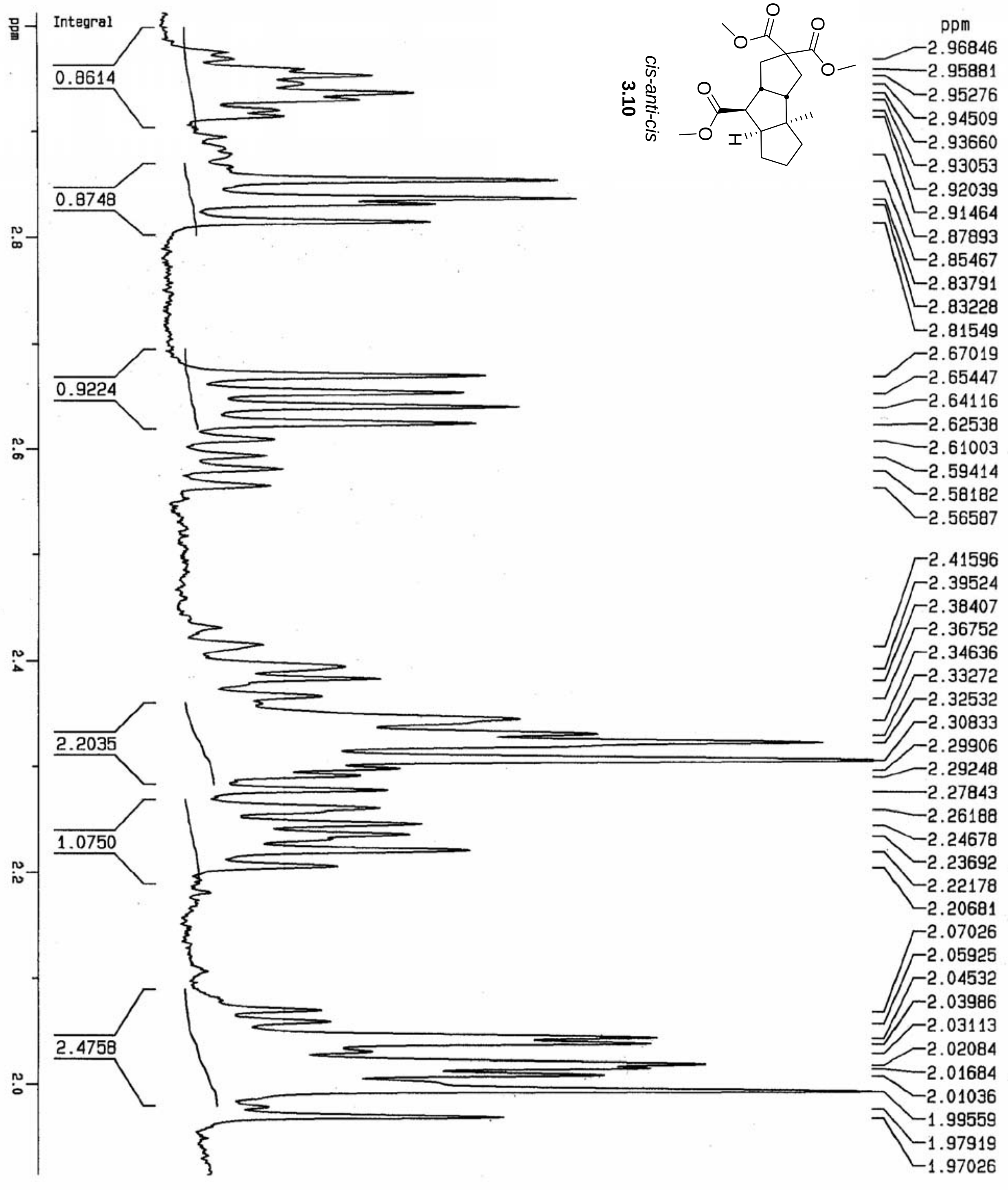


cis-anti-cis

3.10



cis-anti-cis
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APPENDIX B: Crystallographic Data Tables

This information is also available in CIF format from the *J. Am. Chem. Soc*. Webpage at:
http://pubs3.acs.org/acs/journals/supporting_information.page?in_manuscript=ja042595u
Reference: Tripp, J. C.; Schiesser, C. H; Curran, D. P *J. Am. Chem. Soc.* **2005**, *127*, 5518-5527

Crystallographic Tables for Diol 2.43

Table 1. Crystal data and structure refinement for jt0527.

Identification code	jt0527	
Empirical formula	C12 H24 O2	
Formula weight	200.31	
Temperature	295(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 17.543(3) Å	α= 90°.
	b = 6.1234(10) Å	β= 105.708(4)°.
	c = 12.0521(19) Å	γ = 90°.
Volume	1246.3(3) Å^3	
Z	4	
Density (calculated)	1.068 Mg/m^3	
Absorption coefficient	0.070 mm^{-1}	
F(000)	448	
Crystal size	0.03 x 0.03 x 0.18 mm^3	
Theta range for data collection	2.41 to 24.99°.	
Index ranges	-20<=h<=20, -7<=k<=7, -14<=l<=14	
Reflections collected	9457	
Independent reflections	2188 [R(int) = 0.1757]	
Completeness to theta = 24.99°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2188 / 0 / 128	
Goodness-of-fit on F^2	1.127	
Final R indices [I>2sigma(I)]	R1 = 0.1611, wR2 = 0.3250	
R indices (all data)	R1 = 0.2559, wR2 = 0.3685	
Extinction coefficient	0.000(4)	
Largest diff. peak and hole	0.330 and -0.284 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for jt0527. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	3622(4)	3413(10)	10412(5)	31(2)
O(1)	4326(3)	116(8)	11279(5)	69(2)
O(2)	4568(4)	5841(8)	11700(5)	77(2)
C(2)	2805(4)	2332(14)	10242(8)	67(3)
C(3)	2210(4)	3519(14)	9243(8)	61(3)
C(4)	2621(5)	5444(16)	9007(8)	70(3)
C(5)	3488(4)	4975(12)	9386(6)	43(2)
C(6)	4247(5)	1728(12)	10419(7)	55(2)
C(7)	3842(5)	4672(13)	11525(7)	57(2)
C(8)	2373(5)	6624(17)	7872(7)	78(3)
C(9)	1359(4)	3428(11)	9301(6)	37(2)
C(10)	774(5)	4496(19)	8296(9)	96(4)
C(11)	1116(6)	1093(17)	9358(14)	151(7)
C(12)	1269(7)	4610(30)	10362(11)	129(5)

Table 3. Bond lengths [Å] and angles [°] for jt0527.

C(1)-C(6)	1.504(9)
C(1)-C(7)	1.504(10)
C(1)-C(5)	1.531(9)
C(1)-C(2)	1.541(9)
O(1)-C(6)	1.411(9)
O(2)-C(7)	1.425(10)
C(2)-C(3)	1.545(10)
C(3)-C(4)	1.450(11)
C(3)-C(9)	1.514(10)
C(4)-C(5)	1.493(10)
C(4)-C(8)	1.503(11)
C(9)-C(11)	1.498(12)
C(9)-C(10)	1.509(11)
C(9)-C(12)	1.514(13)
C(6)-C(1)-C(7)	109.6(6)
C(6)-C(1)-C(5)	112.6(6)
C(7)-C(1)-C(5)	110.3(6)
C(6)-C(1)-C(2)	110.9(6)
C(7)-C(1)-C(2)	110.1(7)
C(5)-C(1)-C(2)	103.1(5)
C(1)-C(2)-C(3)	108.0(6)
C(4)-C(3)-C(9)	126.0(7)
C(4)-C(3)-C(2)	105.6(6)
C(9)-C(3)-C(2)	114.4(7)
C(3)-C(4)-C(5)	107.6(7)
C(3)-C(4)-C(8)	122.2(8)
C(5)-C(4)-C(8)	113.0(7)
C(4)-C(5)-C(1)	106.8(5)
O(1)-C(6)-C(1)	114.2(7)
O(2)-C(7)-C(1)	113.1(6)
C(11)-C(9)-C(10)	108.1(8)
C(11)-C(9)-C(12)	108.7(10)
C(10)-C(9)-C(12)	105.5(8)

C(11)-C(9)-C(3)	109.5(7)
C(10)-C(9)-C(3)	114.3(7)
C(12)-C(9)-C(3)	110.5(7)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x 10^3$) for jt0527. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	33(4)	30(4)	33(4)	-8(3)	17(3)	3(3)
O(1)	66(4)	30(3)	85(4)	-5(3)	-24(3)	8(3)
O(2)	92(5)	35(3)	70(4)	-1(3)	-40(3)	-2(3)
C(2)	32(4)	63(6)	99(7)	48(5)	3(4)	-3(4)
C(3)	36(5)	57(5)	79(6)	34(5)	-4(4)	3(4)
C(4)	56(6)	85(7)	62(6)	42(5)	2(4)	-13(5)
C(5)	39(4)	47(5)	48(5)	0(4)	21(3)	-10(4)
C(6)	55(5)	33(4)	61(5)	-9(4)	-12(4)	10(4)
C(7)	77(6)	43(5)	57(5)	18(4)	28(5)	33(5)
C(8)	76(7)	90(7)	62(6)	34(6)	11(5)	-3(6)
C(9)	29(4)	33(4)	42(4)	-3(3)	-1(3)	0(3)
C(10)	48(6)	117(9)	110(9)	27(7)	-2(6)	16(6)
C(11)	55(7)	59(7)	290(19)	22(9)	-35(9)	-23(5)
C(12)	80(8)	200(16)	120(10)	-24(10)	50(8)	48(9)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for jt0527.

	x	y	z	U(eq)
H(1A)	4673	481	11854	103
H(2C)	4864	5522	12330	116
H(2A)	2637	2448	10943	81
H(2B)	2833	797	10059	81
H(3A)	2201	2580	8582	74
H(4A)	2541	6523	9566	84
H(5A)	3785	6314	9612	52
H(5B)	3659	4305	8765	52
H(6A)	4122	1018	9672	66
H(6B)	4752	2463	10527	66
H(7A)	3422	5697	11530	68
H(7B)	3887	3665	12161	68
H(8A)	1812	6865	7665	116
H(8B)	2508	5757	7288	116
H(8C)	2642	8002	7937	116
H(10A)	794	3789	7593	144
H(10B)	905	6012	8263	144
H(10C)	250	4367	8391	144
H(11A)	1163	334	8682	226
H(11B)	577	1035	9396	226
H(11C)	1453	416	10031	226
H(12A)	726	4546	10382	194
H(12B)	1426	6104	10338	194
H(12C)	1597	3918	11040	194

Crystallographic Tables for Cyclopentane 2.62

Table 1. Crystal data and structure refinement for trip104.

Identification code	trip104	
Empirical formula	C17 H22 N2 O6	
Formula weight	350.37	
Temperature	295(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 20.881(10) Å	α= 90°.
	b = 8.843(4) Å	β= 92.772(10)°.
	c = 10.102(5) Å	γ = 90°.
Volume	1863.1(15) Å^3	
Z	4	
Density (calculated)	1.249 Mg/m^3	
Absorption coefficient	0.095 mm^{-1}	
F(000)	744	
Crystal size	0.03 x 0 .07 x 0.16 mm^3	
Theta range for data collection	1.95 to 23.99°.	
Index ranges	-23<=h<=23, -10<=k<=10, -11<=l<=11	
Reflections collected	12308	
Independent reflections	2912 [R(int) = 0.0930]	
Completeness to theta = 23.99°	99.7 %	
Absorption correction	Sadabs	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2912 / 0 / 227	
Goodness-of-fit on F^2	1.120	
Final R indices [I>2sigma(I)]	R1 = 0.1581, wR2 = 0.4022	
R indices (all data)	R1 = 0.1802, wR2 = 0.4141	
Extinction coefficient	0.013(5)	
Largest diff. peak and hole	0.357 and -0.365 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for trip104. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	1644(4)	5165(8)	8413(7)	54(2)
N(1)	1838(5)	6527(8)	6348(8)	77(2)
O(1)	2409(4)	6528(11)	6664(8)	122(3)
C(2)	1387(4)	5749(8)	7238(8)	60(2)
N(2)	-330(4)	4716(9)	7243(8)	76(2)
O(2)	1605(4)	7114(9)	5338(7)	103(2)
C(3)	746(5)	5613(8)	6819(8)	65(2)
O(3)	-528(4)	5396(10)	6230(7)	107(3)
C(4)	367(4)	4845(9)	7654(8)	62(2)
O(4)	-676(3)	3953(8)	7945(9)	102(2)
O(5)	1139(3)	2895(8)	11188(6)	86(2)
C(5)	592(4)	4232(9)	8830(8)	64(2)
O(6)	2098(3)	3946(7)	10760(5)	72(2)
C(6)	1231(4)	4388(8)	9221(8)	58(2)
C(7)	1475(4)	3662(9)	10510(8)	62(2)
C(8)	2407(5)	3267(11)	11969(9)	79(3)
C(9)	3135(5)	3324(12)	11800(9)	87(3)
C(10)	3285(4)	4930(11)	12277(8)	74(2)
C(11)	2881(5)	5087(14)	13506(11)	96(3)
C(12)	2267(5)	4182(13)	13163(9)	93(3)
C(13)	3472(7)	2021(16)	12545(13)	128(5)
C(14)	3995(5)	5548(16)	12400(12)	102(4)
C(15)	4368(6)	4970(20)	13656(14)	149(6)
C(16)	3957(7)	7280(20)	12494(19)	164(7)
C(17)	4358(6)	5150(20)	11182(13)	135(5)

Table 3. Bond lengths [Å] and angles [°] for trip104.

C(1)-C(2)	1.378(11)
C(1)-C(6)	1.398(10)
N(1)-O(2)	1.225(10)
N(1)-O(1)	1.220(11)
N(1)-C(2)	1.500(11)
C(2)-C(3)	1.390(12)
N(2)-O(4)	1.237(10)
N(2)-O(3)	1.240(10)
N(2)-C(4)	1.498(11)
C(3)-C(4)	1.366(11)
C(4)-C(5)	1.368(12)
O(5)-C(7)	1.212(9)
C(5)-C(6)	1.381(12)
O(6)-C(7)	1.335(10)
O(6)-C(8)	1.481(10)
C(6)-C(7)	1.518(11)
C(8)-C(12)	1.493(13)
C(8)-C(9)	1.538(14)
C(9)-C(10)	1.528(14)
C(9)-C(13)	1.530(15)
C(10)-C(11)	1.541(13)
C(10)-C(14)	1.579(14)
C(11)-C(12)	1.538(15)
C(14)-C(15)	1.544(17)
C(14)-C(16)	1.54(2)
C(14)-C(17)	1.518(17)
C(2)-C(1)-C(6)	117.5(8)
O(2)-N(1)-O(1)	124.1(8)
O(2)-N(1)-C(2)	117.3(9)
O(1)-N(1)-C(2)	118.5(8)
C(3)-C(2)-C(1)	124.0(7)
C(3)-C(2)-N(1)	118.7(8)
C(1)-C(2)-N(1)	117.3(8)
O(4)-N(2)-O(3)	123.9(9)

O(4)-N(2)-C(4)	117.9(8)
O(3)-N(2)-C(4)	118.2(8)
C(4)-C(3)-C(2)	115.7(8)
C(5)-C(4)-C(3)	123.2(9)
C(5)-C(4)-N(2)	119.9(8)
C(3)-C(4)-N(2)	116.8(8)
C(4)-C(5)-C(6)	119.7(8)
C(7)-O(6)-C(8)	117.5(6)
C(5)-C(6)-C(1)	119.8(7)
C(5)-C(6)-C(7)	118.9(7)
C(1)-C(6)-C(7)	121.2(8)
O(5)-C(7)-O(6)	125.7(8)
O(5)-C(7)-C(6)	122.8(8)
O(6)-C(7)-C(6)	111.5(7)
O(6)-C(8)-C(12)	110.6(8)
O(6)-C(8)-C(9)	106.8(7)
C(12)-C(8)-C(9)	107.8(8)
C(10)-C(9)-C(13)	117.5(9)
C(10)-C(9)-C(8)	100.6(8)
C(13)-C(9)-C(8)	110.8(10)
C(9)-C(10)-C(11)	103.0(8)
C(9)-C(10)-C(14)	121.6(9)
C(11)-C(10)-C(14)	117.0(8)
C(12)-C(11)-C(10)	104.8(8)
C(8)-C(12)-C(11)	105.7(8)
C(15)-C(14)-C(16)	107.8(12)
C(15)-C(14)-C(17)	109.7(10)
C(16)-C(14)-C(17)	108.2(13)
C(15)-C(14)-C(10)	112.6(11)
C(16)-C(14)-C(10)	107.4(9)
C(17)-C(14)-C(10)	111.1(10)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3) for trip104. The anisotropic displacement factor exponent takes the form: $-2\pi^2$[h^2 $a^{*2}U^{11}$ + ... + 2 h k a* b* U^{12}]

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	68(5)	47(4)	47(4)	-2(3)	3(3)	-2(3)
N(1)	106(6)	62(4)	64(5)	15(4)	27(5)	-4(4)
O(1)	105(6)	162(8)	102(6)	26(6)	23(5)	-37(6)
C(2)	91(6)	39(4)	52(4)	-2(3)	18(4)	0(4)
N(2)	77(5)	80(5)	70(5)	-7(4)	-1(4)	-2(4)
O(2)	132(6)	101(5)	78(5)	41(4)	27(4)	1(4)
C(3)	98(7)	42(4)	56(5)	0(4)	3(4)	10(4)
O(3)	104(5)	148(7)	66(4)	5(5)	-14(4)	13(5)
C(4)	86(6)	46(4)	56(5)	-8(4)	8(4)	-9(4)
O(4)	85(5)	80(5)	140(7)	6(5)	1(4)	-20(4)
O(5)	107(5)	88(5)	64(4)	21(3)	2(3)	-31(4)
C(5)	83(6)	49(4)	62(5)	-8(4)	9(4)	-9(4)
O(6)	87(4)	73(4)	54(3)	17(3)	3(3)	-10(3)
C(6)	82(6)	35(4)	59(5)	-3(3)	8(4)	-5(4)
C(7)	88(6)	49(4)	49(4)	4(4)	4(4)	-9(4)
C(8)	103(7)	69(5)	63(5)	11(4)	-2(5)	-8(5)
C(9)	100(7)	102(8)	60(5)	-6(5)	10(5)	19(6)
C(10)	86(6)	83(6)	52(5)	3(4)	1(4)	9(5)
C(11)	76(6)	115(9)	97(8)	-24(7)	4(5)	5(6)
C(12)	106(8)	117(8)	58(5)	10(5)	26(5)	-6(6)
C(13)	158(12)	123(10)	99(9)	-3(8)	-12(8)	48(9)
C(14)	56(6)	142(11)	109(9)	-1(8)	1(5)	8(6)
C(15)	85(8)	238(18)	119(10)	-23(12)	-43(7)	15(10)
C(16)	122(11)	162(15)	207(18)	-22(13)	-20(11)	-71(11)
C(17)	86(8)	222(17)	99(9)	4(10)	14(7)	-3(9)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10 ^{3}) for trip104.

	x	y	z	U(eq)
H(1A)	2077	5285	8658	65
H(3A)	586	6020	6022	78
H(5A)	315	3713	9364	77
H(8A)	2264	2220	12076	95
H(9A)	3218	3248	10856	105
H(10A)	3069	5583	11610	88
H(11A)	3108	4672	14285	115
H(11B)	2782	6140	13671	115
H(12A)	2164	3528	13894	111
H(12B)	1908	4857	12972	111
H(13A)	3924	2070	12419	191
H(13B)	3306	1075	12211	191
H(13C)	3397	2099	13473	191
H(15A)	4415	3889	13604	223
H(15B)	4137	5222	14424	223
H(15C)	4784	5429	13721	223
H(16A)	3732	7674	11716	247
H(16B)	4383	7696	12560	247
H(16C)	3733	7560	13265	247
H(17A)	4386	4067	11103	203
H(17B)	4782	5567	11265	203
H(17C)	4137	5553	10406	203

APPENDIX C: Gaussian Entry Archives

Chair-Equatorial 2.63

MP2/6-311G**

```
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chair\\0,2\C\C,1,cc2\C,2,cc3,1,ccc3\C,2,cc4,3,ccc4,1,dih4,0\C,4,cc5,2,cc
c5,3,dih5,0\C,5,cc6,4,ccc6,2,dih6,0\C,1,cc7,2,ccc7,3,dih7,0\C,7,cc8,1,
ccc8,2,dih8,0\C,7,cc9,1,ccc9,2,dih9,0\C,7,cc10,1,ccc10,2,dih10,0\H,3,h
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BHLYP/6-311G**

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cc5,2,ccc5,3,dih5,0\C,5,cc6,4,ccc6,2,dih6,0\C,1,cc7,2,ccc7,3,dih7,0\C,
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BHLYP/cc-pVDZ**

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BHLYP/aug-cc-pVDZ**

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 ,4,cc5,2,ccc5,3,dih5,0\C,5,cc6,4,ccc6,2,dih6,0\C,1,cc7,2,ccc7,3,dih7,0
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 \H,5,hc16,4,hcc16,2,dih16,0\H,5,hc17,4,hcc17,2,dih17,0\H,6,hc18,5,hcc1
 8,4,dih18,0\H,6,hc19,5,hcc19,4,dih19,0\H,1,hc20,2,hcc20,3,dih20,0\H,8,
 hc21,7,hcc21,1,dih21,0\H,8,hc22,7,hcc22,1,dih22,0\H,8,hc23,7,hcc23,1,d
 ih23,0\H,9,hc24,7,hcc24,1,dih24,0\H,9,hc25,7,hcc25,1,dih25,0\H,9,hc26,
 7,hcc26,1,dih26,0\H,10,hc27,7,hcc27,1,dih27,0\H,10,hc28,7,hcc28,1,dih2
 8,0\H,10,hc29,7,hcc29,1,dih29,0\\cc2=2.2013806\cc3=1.37477796\ccc3=114
 .33475674\cc4=1.50877124\ccc4=121.12138395\dih4=-110.82474415\cc5=1.52
```

```
134789\ccc5=111.17136022\dih5=146.23720626\cc6=1.52206432\ccc6=107.045
04144\dih6=-49.42666386\cc7=1.516194\ccc7=118.67998711\dih7=6.82618093
\cc8=1.52966757\ccc8=109.633904\dih8=62.0969781\cc9=1.52978098\ccc9=11
2.83789334\dih9=-60.04108981\cc10=1.53994435\ccc10=108.00802518\dih10=
179.92619976\hc11=1.08296019\hcc11=121.19192786\dih11=91.63194717\hc12
=1.08121954\hcc12=121.62035651\dih12=-84.1027383\hc13=1.08441534\hcc13
=116.28731858\dih13=100.61376244\hc14=1.09316569\hcc14=108.8802551\dih
14=25.36345068\hc15=1.09310921\hcc15=109.36862097\dih15=-91.04180604\h
c16=1.09408592\hcc16=109.79306619\dih16=69.44265945\hc17=1.09143084\hc
c17=111.49502111\dih17=-172.07614068\hc18=1.09189342\hcc18=109.2299583
3\dih18=-69.1163097\hc19=1.09578226\hcc19=110.65512481\dih19=173.64644
95\hc20=1.08845844\hcc20=93.64224174\dih20=123.85134468\hc21=1.0919831
8\hcc21=110.89999136\dih21=56.67577126\hc22=1.09176131\hcc22=110.65567
714\dih22=176.22055014\hc23=1.08862824\hcc23=111.17612976\dih23=-63.68
808463\hc24=1.09168135\hcc24=109.9938943\dih24=180.20916108\hc25=1.090
25299\hcc25=111.8293364\dih25=-60.65597949\hc26=1.08841849\hcc26=111.0
8047117\dih26=60.48551125\hc27=1.09169648\hcc27=111.14756787\dih27=-57
.25396732\hc28=1.09064023\hcc28=111.41061907\dih28=63.37478045\hc29=1.
0924174\hcc29=110.2939663\dih29=-176.92991653\\Version=x86-Linux-G03Re
vB.04\State=2-A\HF=-392.1932547\S2=0.82603\S2-1=0.\S2A=0.750785\RMSD=9
.356e-09\RMSF=2.754e-05\Dipole=-0.2050929,0.0638116,-0.1851088\PG=C01
[X(C10H19)]\\@
```

Chair-Axial **2.64**

MP2/6-311G**

```
1\1\ CHEMCLUSTER-KNET15\FTS\UMP2-FC\6-311G(d,p)\C10H19(2)\CARLHS\06-Au
g-2004\1\\#MP2/6-311G** OPT=(GRAD,TS,READFC,NOEIGENTEST,NOFREEZE) GEOM
=CHECKPOINT GUESS=READ\\tert-butylhexenyl cyclization TS – trans-chair\\0,2
\C\C,1,r\C,2,cc3,1,ccc3\C,1,cc4,2,ccc4,3,dih4,0\C,1,cc5,2,ccc5,3,dih5,
0\C,2,cc6,3,ccc6,1,dih6,0\C,6,cc7,2,ccc7,3,dih7,0\C,5,cc8,1,ccc8,2,dih
8,0\C,5,cc9,1,ccc9,2,dih9,0\C,5,cc10,1,ccc10,2,dih10,0\H,1,hc11,2,hcc1
1,3,dih11,0\H,2,hc12,3,hcc12,1,dih12,0\H,3,hc13,2,hcc13,1,dih13,0\H,3,
hc14,2,hcc14,1,dih14,0\H,6,hc15,2,hcc15,3,dih15,0\H,6,hc16,2,hcc16,3,d
ih16,0\H,7,hc17,6,hcc17,2,dih17,0\H,7,hc18,6,hcc18,2,dih18,0\H,4,hc19,
1,hcc19,2,dih19,0\H,4,hc20,1,hcc20,2,dih20,0\H,8,hc21,5,hcc21,1,dih21,
0\H,8,hc22,5,hcc22,1,dih22,0\H,8,hc23,5,hcc23,1,dih23,0\H,9,hc24,5,hcc
24,1,dih24,0\H,9,hc25,5,hcc25,1,dih25,0\H,9,hc26,5,hcc26,1,dih26,0\H,1
0,hc27,5,hcc27,1,dih27,0\H,10,hc28,5,hcc28,1,dih28,0\H,10,hc29,5,hcc29
,1,dih29,0\\cc3=1.34890722\ccc3=107.44204204\cc4=1.50996816\ccc4=95.91
557786\dih4=131.94134094\cc5=1.51608875\ccc5=111.01404046\dih5=-101.83
22809\cc6=1.51054744\ccc6=123.01489062\dih6=104.43082934\cc7=1.5267461
7\ccc7=110.80886702\dih7=-144.95793032\cc8=1.53428606\ccc8=109.9521439
8\dih8=56.16543746\cc9=1.54392464\ccc9=107.78320612\dih9=173.78775113\
cc10=1.53334129\ccc10=113.05666197\dih10=-66.49021682\hc11=1.09015652\
hcc11=97.62152633\dih11=15.31506518\hc12=1.08872742\hcc12=118.04415959
\dih12=-98.54617943\hc13=1.08415827\hcc13=121.51824849\dih13=85.664078
76\hc14=1.08594246\hcc14=120.88592585\dih14=-89.11128026\hc15=1.097207
97\hcc15=109.09717063\dih15=-23.58195977\hc16=1.09756839\hcc16=108.825
31497\dih16=93.3183526\hc17=1.09575815\hcc17=109.22088653\dih17=-65.23
710066\hc18=1.09625417\hcc18=111.64520224\dih18=176.0782263\hc19=1.096
64698\hcc19=109.42392035\dih19=-97.29076098\hc20=1.09910825\hcc20=111.
58382689\dih20=144.56886215\hc21=1.09571381\hcc21=110.57425628\dih21=5
3.00794463\hc22=1.09390036\hcc22=111.40895306\dih22=-67.2033059\hc23=1
.09637841\hcc23=110.25311656\dih23=172.71967937\hc24=1.0952939\hcc24=1
10.53929886\dih24=-59.42123919\hc25=1.09713807\hcc25=110.24117161\dih2
5=-179.16838565\hc26=1.09506139\hcc26=111.16087036\dih26=60.95441681\h
c27=1.09448923\hcc27=111.68079023\dih27=62.50337708\hc28=1.09492659\hc
c28=111.55892852\dih28=-58.86538291\hc29=1.09608359\hcc29=109.67914503
\dih29=-178.10544681\r=2.2523784\\Version=x86-Linux-G03RevB.04\State=2
-A\HF=-389.7512035\MP2=-391.2302372\PUHF=-389.7688341\PMP2-0=-391.2453
975\S2=0.986243\S2-1=0.918453\S2A=0.759553\RMSD=5.098e-09\RMSF=1.931e-
05\Dipole=-0.1831039,-0.0624719,-0.1898693\PG=C01 [X(C10H19)]\\@
```

BHLYP/6-311G**

```
 1\1\ CHEMCLUSTER-KNET15\FTS\UBHandHLYP\6-311G(d,p)\C10H19(2)\CARLHS\04
 -Aug-2004\1\\#BHANDHLYP/6-311G**
OPT=(GRAD,TS,READFC,NOEIGENTEST,NOFRE
 EZE) GEOM=CHECKPOINT GUESS=READ\\tert-butylhexenyl cyclization TS – trans-
chair\\0,2\C\C,1,r\C,2,cc3,1,ccc3\C,1,cc4,2,ccc4,3,dih4,0\C,1,cc5,2,ccc
 5,3,dih5,0\C,2,cc6,3,ccc6,1,dih6,0\C,6,cc7,2,ccc7,3,dih7,0\C,5,cc8,1,c
 cc8,2,dih8,0\C,5,cc9,1,ccc9,2,dih9,0\C,5,cc10,1,ccc10,2,dih10,0\H,1,hc
 11,2,hcc11,3,dih11,0\H,2,hc12,3,hcc12,1,dih12,0\H,3,hc13,2,hcc13,1,dih
 13,0\H,3,hc14,2,hcc14,1,dih14,0\H,6,hc15,2,hcc15,3,dih15,0\H,6,hc16,2,
 hcc16,3,dih16,0\H,7,hc17,6,hcc17,2,dih17,0\H,7,hc18,6,hcc18,2,dih18,0\
 H,4,hc19,1,hcc19,2,dih19,0\H,4,hc20,1,hcc20,2,dih20,0\H,8,hc21,5,hcc21
 ,1,dih21,0\H,8,hc22,5,hcc22,1,dih22,0\H,8,hc23,5,hcc23,1,dih23,0\H,9,h
 c24,5,hcc24,1,dih24,0\H,9,hc25,5,hcc25,1,dih25,0\H,9,hc26,5,hcc26,1,di
 h26,0\H,10,hc27,5,hcc27,1,dih27,0\H,10,hc28,5,hcc28,1,dih28,0\H,10,hc2
 9,5,hcc29,1,dih29,0\\cc3=1.36613271\ccc3=108.89181693\cc4=1.50787495\c
 cc4=95.87969317\dih4=131.8357007\cc5=1.51801567\ccc5=112.50212773\dih5
 =-101.13333295\cc6=1.50554646\ccc6=122.254848\dih6=106.661246\cc7=1.51
 932859\ccc7=110.59451562\dih7=-146.25028487\cc8=1.53041295\ccc8=109.93
 04782\dih8=56.7173932\cc9=1.53988732\ccc9=107.86156008\dih9=174.325408
 9\cc10=1.53027571\ccc10=113.08896224\dih10=-65.76957742\hc11=1.0798712
 4\hcc11=97.68550336\dih11=16.07882666\hc12=1.07932476\hcc12=117.017114
 2\dih12=-101.55909409\hc13=1.07589835\hcc13=121.56323232\dih13=85.5814
 0725\hc14=1.07775244\hcc14=121.07990372\dih14=-88.55116729\hc15=1.0885
 3554\hcc15=109.25934102\dih15=-24.91938201\hc16=1.08872729\hcc16=109.4
 0139985\dih16=91.7027809\hc17=1.08755448\hcc17=109.41598213\dih17=-67.
 71970814\hc18=1.08695632\hcc18=111.64949783\dih18=174.0971418\hc19=1.0
```

```
8752148\hcc19=109.23077226\dih19=-98.23447398\hc20=1.08911538\hcc20=11
1.6332388\dih20=144.34570438\hc21=1.08667225\hcc21=110.95094442\dih21=
53.9448954\hc22=1.08491996\hcc22=111.63049554\dih22=-66.31072567\hc23=
1.08709988\hcc23=110.55968766\dih23=173.62034678\hc24=1.08643814\hcc24
=110.93081668\dih24=-59.10728813\hc25=1.08775183\hcc25=110.50965068\di
h25=-178.81063225\hc26=1.0859887\hcc26=111.54188069\dih26=61.30240912\
hc27=1.08547635\hcc27=111.83826201\dih27=62.55552809\hc28=1.08583806\h
cc28=111.78834289\dih28=-58.6849458\hc29=1.086846\hcc29=110.07306514\d
ih29=-177.98493858\r=2.21508175\\Version=x86-Linux-G03RevB.04\State=2-
A\HF=-392.254233\S2=0.827342\S2-1=0.\S2A=0.750801\RMSD=4.128e-09\RMSF=
3.484e-05\Dipole=-0.1604153,-0.0553529,-0.1899717\PG=C01 [X(C10H19)]\\
@
```

BHLYP/cc-pVDZ**

```
 1\1\ CHEMCLUSTER-KNET10\FTS\UBHandHLYP\CC-pVDZ\C10H19(2)\CARLHS\04-Aug
 -2004\1\\#BHANDHLYP/CC-PVDZ
OPT=(GRAD,TS,READFC,NOEIGENTEST,NOFREEZE)
 GEOM=CHECKPOINT GUESS=READ\\tert-butylhexenyl cyclization TS – trans-chair\
 \0,2\C\C,1,r\C,2,cc3,1,ccc3\C,1,cc4,2,ccc4,3,dih4,0\C,1,cc5,2,ccc5,3,d
 ih5,0\C,2,cc6,3,ccc6,1,dih6,0\C,6,cc7,2,ccc7,3,dih7,0\C,5,cc8,1,ccc8,2
 ,dih8,0\C,5,cc9,1,ccc9,2,dih9,0\C,5,cc10,1,ccc10,2,dih10,0\H,1,hc11,2,
 hcc11,3,dih11,0\H,2,hc12,3,hcc12,1,dih12,0\H,3,hc13,2,hcc13,1,dih13,0\
 H,3,hc14,2,hcc14,1,dih14,0\H,6,hc15,2,hcc15,3,dih15,0\H,6,hc16,2,hcc16
 ,3,dih16,0\H,7,hc17,6,hcc17,2,dih17,0\H,7,hc18,6,hcc18,2,dih18,0\H,4,h
 c19,1,hcc19,2,dih19,0\H,4,hc20,1,hcc20,2,dih20,0\H,8,hc21,5,hcc21,1,di
 h21,0\H,8,hc22,5,hcc22,1,dih22,0\H,8,hc23,5,hcc23,1,dih23,0\H,9,hc24,5
 ,hcc24,1,dih24,0\H,9,hc25,5,hcc25,1,dih25,0\H,9,hc26,5,hcc26,1,dih26,0
 \H,10,hc27,5,hcc27,1,dih27,0\H,10,hc28,5,hcc28,1,dih28,0\H,10,hc29,5,h
 cc29,1,dih29,0\\cc3=1.37011297\ccc3=108.90481014\cc4=1.50894533\ccc4=9
 5.64269156\dih4=131.78088718\cc5=1.52048079\ccc5=112.59561408\dih5=-10
 1.18340512\cc6=1.50608757\ccc6=122.38691401\dih6=106.56716002\cc7=1.51
 918326\ccc7=110.63114776\dih7=-146.21654729\cc8=1.53063844\ccc8=109.87
 679375\dih8=56.87647606\cc9=1.53969946\ccc9=107.82342746\dih9=174.4637
 8802\cc10=1.53057445\ccc10=113.13489497\dih10=-65.59599361\hc11=1.0879
 7696\hcc11=97.8824794\dih11=16.05767877\hc12=1.08736003\hcc12=117.0197
 0432\dih12=-101.30511883\hc13=1.08421018\hcc13=121.45743664\dih13=85.4
 3887994\hc14=1.08613109\hcc14=121.0334271\dih14=-88.51926369\hc15=1.09
 632373\hcc15=109.28388404\dih15=-24.77266028\hc16=1.0964919\hcc16=109.
 43286452\dih16=91.77983749\hc17=1.09561897\hcc17=109.38146679\dih17=-6
 7.47420773\hc18=1.09466628\hcc18=111.6871235\dih18=174.5086607\hc19=1.
 09515205\hcc19=109.21553442\dih19=-97.99107741\hc20=1.09684128\hcc20=1
 11.65872133\dih20=144.66529559\hc21=1.09437639\hcc21=111.01818541\dih2
 1=53.8428716\hc22=1.09273085\hcc22=111.67596005\dih22=-66.40122213\hc2
 3=1.09478244\hcc23=110.62049693\dih23=173.53540696\hc24=1.09424508\hcc
 24=111.00145946\dih24=-59.1167499\hc25=1.09554277\hcc25=110.59245726\d
 ih25=-178.84611555\hc26=1.0938461\hcc26=111.57109767\dih26=61.27537281
```

```
\hc27=1.09332199\hcc27=111.89104021\dih27=62.51703983\hc28=1.09360476\
hcc28=111.85697736\dih28=-58.75591281\hc29=1.0946261\hcc29=110.1421353
5\dih29=-178.03493756\r=2.22501266\\Version=x86-Linux-G03RevB.04\State
=2-A\HF=-392.1698217\S2=0.829603\S2-1=0.\S2A=0.750836\RMSD=6.320e-09\R
MSF=3.410e-05\Dipole=-0.1704833,-0.0420482,-0.181867\PG=C01 [X(C10H19)
]\\@
```

BHLYP/aug-cc-pVDZ**

```
1\1\ CHEMCLUSTER-KNET5\FTS\UBHandHLYP\Aug-CC-pVDZ\C10H19(2)\CARLHS\06-
Aug-2004\1\\#BHANDHLYP/AUG-CC-PVDZ
OPT=(GRAD,TS,READFC,NOEIGENTEST,NOF
REEZE) GEOM=CHECKPOINT GUESS=READ\\tert-butylhexenyl cyclization TS – trans-
chair\\0,2\C\C,1,r\C,2,cc3,1,ccc3\C,1,cc4,2,ccc4,3,dih4,0\C,1,cc5,2,c
cc5,3,dih5,0\C,2,cc6,3,ccc6,1,dih6,0\C,6,cc7,2,ccc7,3,dih7,0\C,5,cc8,1
,ccc8,2,dih8,0\C,5,cc9,1,ccc9,2,dih9,0\C,5,cc10,1,ccc10,2,dih10,0\H,1,
hc11,2,hcc11,3,dih11,0\H,2,hc12,3,hcc12,1,dih12,0\H,3,hc13,2,hcc13,1,d
ih13,0\H,3,hc14,2,hcc14,1,dih14,0\H,6,hc15,2,hcc15,3,dih15,0\H,6,hc16,
2,hcc16,3,dih16,0\H,7,hc17,6,hcc17,2,dih17,0\H,7,hc18,6,hcc18,2,dih18,
0\H,4,hc19,1,hcc19,2,dih19,0\H,4,hc20,1,hcc20,2,dih20,0\H,8,hc21,5,hcc
21,1,dih21,0\H,8,hc22,5,hcc22,1,dih22,0\H,8,hc23,5,hcc23,1,dih23,0\H,9
,hc24,5,hcc24,1,dih24,0\H,9,hc25,5,hcc25,1,dih25,0\H,9,hc26,5,hcc26,1,
dih26,0\H,10,hc27,5,hcc27,1,dih27,0\H,10,hc28,5,hcc28,1,dih28,0\H,10,h
c29,5,hcc29,1,dih29,0\\cc3=1.36926002\ccc3=108.78493003\cc4=1.50806779
\ccc4=95.69589617\dih4=131.77754915\cc5=1.51800038\ccc5=112.30480767\d
ih5=-101.3351738\cc6=1.50592155\ccc6=122.45455936\dih6=106.46378541\cc
7=1.52005294\ccc7=110.69558507\dih7=-145.96234949\cc8=1.53038627\ccc8=
109.9235212\dih8=56.76417681\cc9=1.53983682\ccc9=107.76660229\dih9=174
.43979841\cc10=1.53024691\ccc10=113.05374651\dih10=-65.71514296\hc11=1
.08452481\hcc11=97.61802365\dih11=15.91335688\hc12=1.08411142\hcc12=11
7.05786115\dih12=-100.87208373\hc13=1.08150299\hcc13=121.5301691\dih13
=85.35814594\hc14=1.08331115\hcc14=121.13608298\dih14=-89.24397539\hc1
5=1.09328365\hcc15=109.21201812\dih15=-24.57266588\hc16=1.09359872\hcc
16=109.34671053\dih16=92.08048247\hc17=1.09224757\hcc17=109.42435924\d
ih17=-67.69231422\hc18=1.09196606\hcc18=111.53545716\dih18=174.1440086
2\hc19=1.09232928\hcc19=109.22461477\dih19=-98.11135887\hc20=1.0939948
5\hcc20=111.59375837\dih20=144.44337692\hc21=1.09145003\hcc21=110.9515
9273\dih21=53.9242196\hc22=1.08973697\hcc22=111.63057345\dih22=-66.387
07832\hc23=1.09189601\hcc23=110.53007629\dih23=173.59217802\hc24=1.091
3256\hcc24=110.91526032\dih24=-59.01454536\hc25=1.09267773\hcc25=110.5
1854175\dih25=-178.75589541\hc26=1.09088414\hcc26=111.4866036\dih26=61
.3724741\hc27=1.09015977\hcc27=111.83580051\dih27=62.57973545\hc28=1.0
9051654\hcc28=111.76894498\dih28=-58.71854565\hc29=1.09152583\hcc29=11
0.0505674\dih29=-177.97033792\r=2.22744449\\Version=x86-Linux-G03RevB.
04\State=2-A\HF=-392.1926802\S2=0.825479\S2-1=0.\S2A=0.750786\RMSD=2.9
97e-09\RMSF=5.710e-05\Dipole=-0.1907371,-0.0558838,-0.2300665\PG=C01 [
X(C10H19)]\\@
```

***Boat-Equatorial* 2.65**

MP2/6-311G**

```
 1\1\ CHEMCLUSTER-KNET9\FTS\UMP2-FC\6-311G(d,p)\C10H19(2)\CARLHS\16-Aug
 -2004\1\\#MP2/6-311G** OPT=(GRAD,TS,READFC,NOEIGENTEST,NOFREEZE) GEOM=
 CHECKPOINT GUESS=READ\\tert-butylhexenyl cyclization TS – cis-
boat\\0,2\C\C,1,r\C,2,cc3,1,ccc3\C,1,cc4,2,ccc4,3,dih4,0\C,1,cc5,2,cc
 c5,3,dih5,0\C,2,cc6,3,ccc6,1,dih6,0\C,5,cc7,1,ccc7,2,dih7,0\C,5,cc8,1,
 ccc8,2,dih8,0\C,5,cc9,1,ccc9,2,dih9,0\C,6,cc10,2,ccc10,3,dih10,0\H,6,h
 c11,2,hcc11,3,dih11,0\H,6,hc12,2,hcc12,3,dih12,0\H,10,hc13,6,hcc13,2,d
 ih13,0\H,10,hc14,6,hcc14,2,dih14,0\H,4,hc15,1,hcc15,2,dih15,0\H,4,hc16
 ,1,hcc16,2,dih16,0\H,1,hc17,2,hcc17,3,dih17,0\H,2,hc18,3,hcc18,1,dih18
 ,0\H,3,hc19,2,hcc19,1,dih19,0\H,3,hc20,2,hcc20,1,dih20,0\H,7,hc21,5,hc
 c21,1,dih21,0\H,7,hc22,5,hcc22,1,dih22,0\H,7,hc23,5,hcc23,1,dih23,0\H,
 8,hc24,5,hcc24,1,dih24,0\H,8,hc25,5,hcc25,1,dih25,0\H,8,hc26,5,hcc26,1
 ,dih26,0\H,9,hc27,5,hcc27,1,dih27,0\H,9,hc28,5,hcc28,1,dih28,0\H,9,hc2
 9,5,hcc29,1,dih29,0\\cc3=1.35224449\ccc3=112.82513106\cc4=1.5137957\cc
 c4=97.79702417\dih4=104.19953797\cc5=1.51400574\ccc5=115.22867385\dih5
 =-24.72806115\cc6=1.51964755\ccc6=120.63008741\dih6=103.04254185\cc7=1
 .54446267\ccc7=107.90791771\dih7=-174.19918634\cc8=1.53319876\ccc8=109
 .92350379\dih8=-56.57248442\cc9=1.53291426\ccc9=112.47787036\dih9=65.9
 8443815\cc10=1.52840616\ccc10=109.27871294\dih10=-73.54535009\hc11=1.0
 9535201\hcc11=109.75845184\dih11=48.81747254\hc12=1.09666292\hcc12=109
 .81650451\dih12=166.85054758\hc13=1.0960629\hcc13=109.2093382\dih13=58
 .84389973\hc14=1.09640364\hcc14=112.07165962\dih14=-181.78498198\hc15=
 1.09761877\hcc15=109.58663594\dih15=108.0073912\hc16=1.09596684\hcc16=
 111.39472595\dih16=-133.72705595\hc17=1.09294742\hcc17=92.84642316\dih
 17=-140.71270288\hc18=1.08732227\hcc18=117.63478497\dih18=-99.60832256
 \hc19=1.08381046\hcc19=121.77403593\dih19=86.99548197\hc20=1.08618024\
 hcc20=121.14137157\dih20=-90.17283118\hc21=1.09565594\hcc21=110.690701
 12\dih21=58.80023711\hc22=1.09711619\hcc22=110.0452391\dih22=178.47622
 409\hc23=1.09493655\hcc23=111.25405042\dih23=-61.74394249\hc24=1.09638
 607\hcc24=110.50983305\dih24=-56.06455616\hc25=1.09245415\hcc25=110.92
 909428\dih25=64.33522043\hc26=1.09628317\hcc26=110.39783036\dih26=-175
 .51983698\hc27=1.09521915\hcc27=111.52416228\dih27=58.34117305\hc28=1.
 09632043\hcc28=109.7932722\dih28=-182.47192178\hc29=1.0926933\hcc29=11
 0.83810814\dih29=-62.60809855\r=2.2296369\\Version=x86-Linux-G03RevB.0
 4\State=2-A\HF=-389.7462302\MP2=-391.227236\PUHF=-389.7641956\PMP2-0=-
 391.2426793\S2=0.989811\S2-1=0.920841\S2A=0.759828\RMSD=3.592e-09\RMSF
 =6.341e-06\Dipole=-0.1600088,-0.0875349,-0.1531037\PG=C01 [X(C10H19)]\
 \@
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BHLYP/6-311G**

```
 1\1\ CHEMCLUSTER-KNET23\FTS\UBHandHLYP\6-311G(d,p)\C10H19(2)\CARLHS\14
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```
-Aug-2004\1\\#BHANDHLYP/6-311G**
OPT=(GRAD,TS,READFC,NOEIGENTEST,NOFRE
EZE) GEOM=CHECKPOINT GUESS=READ\\tert-butylhexenyl cyclization TS – cis-
boat\\0,2\C\C,1,r\C,2,cc3,1,ccc3\C,1,cc4,2,ccc4,3,dih4,0\C,
1,cc5,2,ccc5,3,dih5,0\C,2,cc6,3,ccc6,1,dih6,0\C,5,cc7,1,ccc7,2,dih7,0\
C,5,cc8,1,ccc8,2,dih8,0\C,5,cc9,1,ccc9,2,dih9,0\C,6,cc10,2,ccc10,3,dih
10,0\H,6,hc11,2,hcc11,3,dih11,0\H,6,hc12,2,hcc12,3,dih12,0\H,10,hc13,6
,hcc13,2,dih13,0\H,10,hc14,6,hcc14,2,dih14,0\H,4,hc15,1,hcc15,2,dih15,
0\H,4,hc16,1,hcc16,2,dih16,0\H,1,hc17,2,hcc17,3,dih17,0\H,2,hc18,3,hcc
18,1,dih18,0\H,3,hc19,2,hcc19,1,dih19,0\H,3,hc20,2,hcc20,1,dih20,0\H,7
,hc21,5,hcc21,1,dih21,0\H,7,hc22,5,hcc22,1,dih22,0\H,7,hc23,5,hcc23,1,
dih23,0\H,8,hc24,5,hcc24,1,dih24,0\H,8,hc25,5,hcc25,1,dih25,0\H,8,hc26
,5,hcc26,1,dih26,0\H,9,hc27,5,hcc27,1,dih27,0\H,9,hc28,5,hcc28,1,dih28
,0\H,9,hc29,5,hcc29,1,dih29,0\\cc3=1.37050066\ccc3=113.79747867\cc4=1.
51147399\ccc4=97.59051265\dih4=107.23177038\cc5=1.51621879\ccc5=116.73
756391\dih5=-22.72996832\cc6=1.51449396\ccc6=120.30145306\dih6=105.991
53168\cc7=1.5405595\ccc7=108.04878479\dih7=-174.31741015\cc8=1.5299008
1\ccc8=109.88729305\dih8=-56.76419143\cc9=1.52952382\ccc9=112.62181692
\dih9=65.66830842\cc10=1.52076443\ccc10=109.55954931\dih10=-78.7725318
4\hc11=1.08661566\hcc11=110.15824871\dih11=43.86330518\hc12=1.08779927
\hcc12=109.65313765\dih12=161.29652493\hc13=1.08783026\hcc13=109.31304
609\dih13=63.13981155\hc14=1.08712428\hcc14=111.88632129\dih14=-178.35
569373\hc15=1.08844896\hcc15=109.3297329\dih15=107.73689409\hc16=1.086
46348\hcc16=111.5147249\dih16=-134.75736282\hc17=1.08221365\hcc17=93.1
0115177\dih17=-138.51464318\hc18=1.07794303\hcc18=116.48418874\dih18=-
102.78558313\hc19=1.07551994\hcc19=121.68693479\dih19=86.16188515\hc20
=1.07779873\hcc20=121.40215317\dih20=-89.92486808\hc21=1.08668446\hcc2
1=111.07822809\dih21=58.69493106\hc22=1.08770368\hcc22=110.30057543\di
h22=178.32426944\hc23=1.08588696\hcc23=111.65457761\dih23=-61.90977263
\hc24=1.08728071\hcc24=110.90195534\dih24=-55.96053876\hc25=1.08366094
\hcc25=111.38921382\dih25=64.50844895\hc26=1.08705995\hcc26=110.610117
27\dih26=-175.38682258\hc27=1.0861201\hcc27=111.73663919\dih27=58.3153
0769\hc28=1.08704358\hcc28=110.17650821\dih28=-182.41556137\hc29=1.083
73001\hcc29=111.11188263\dih29=-62.55137814\r=2.19475749\\Version=x86-
Linux-G03RevB.04\State=2-A\HF=-392.2503205\S2=0.828687\S2-1=0.\S2A=0.7
50823\RMSD=3.986e-09\RMSF=2.527e-05\Dipole=-0.1507661,-0.0734521,-0.15
04174\PG=C01 [X(C10H19)]\\@
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BHLYP/cc-pVDZ**

```
1\1\ CHEMCLUSTER-KNET9\FTS\UBHandHLYP\CC-pVDZ\C10H19(2)\CARLHS\14-Aug-
2004\1\\#BHANDHLYP/CC-PVDZ
OPT=(GRAD,TS,READFC,NOEIGENTEST,NOFREEZE) G
EOM=CHECKPOINT GUESS=READ\\tert-butylhexenyl cyclization TS – cis-
boat\\0,2\C\C,1,r\C,2,cc3,1,ccc3\C,1,cc4,2,ccc4,3,dih4,0\C,1,cc5,
2,ccc5,3,dih5,0\C,2,cc6,3,ccc6,1,dih6,0\C,5,cc7,1,ccc7,2,dih7,0\C,5,cc
8,1,ccc8,2,dih8,0\C,5,cc9,1,ccc9,2,dih9,0\C,6,cc10,2,ccc10,3,dih10,0\H
```

```
,6,hc11,2,hcc11,3,dih11,0\H,6,hc12,2,hcc12,3,dih12,0\H,10,hc13,6,hcc13
,2,dih13,0\H,10,hc14,6,hcc14,2,dih14,0\H,4,hc15,1,hcc15,2,dih15,0\H,4,
hc16,1,hcc16,2,dih16,0\H,1,hc17,2,hcc17,3,dih17,0\H,2,hc18,3,hcc18,1,d
ih18,0\H,3,hc19,2,hcc19,1,dih19,0\H,3,hc20,2,hcc20,1,dih20,0\H,7,hc21,
5,hcc21,1,dih21,0\H,7,hc22,5,hcc22,1,dih22,0\H,7,hc23,5,hcc23,1,dih23,
0\H,8,hc24,5,hcc24,1,dih24,0\H,8,hc25,5,hcc25,1,dih25,0\H,8,hc26,5,hcc
26,1,dih26,0\H,9,hc27,5,hcc27,1,dih27,0\H,9,hc28,5,hcc28,1,dih28,0\H,9
,hc29,5,hcc29,1,dih29,0\\cc3=1.37504145\ccc3=113.99995159\cc4=1.512405
75\ccc4=97.26672238\dih4=108.81591049\cc5=1.5189221\ccc5=116.82900248\
dih5=-20.94780926\cc6=1.51538722\ccc6=120.30788331\dih6=106.33919609\c
c7=1.54039425\ccc7=108.02487332\dih7=-174.64509006\cc8=1.53007499\ccc8
=109.8706231\dih8=-57.12696696\cc9=1.52984816\ccc9=112.60338535\dih9=6
5.3305536\cc10=1.52057858\ccc10=109.64519824\dih10=-79.9432809\hc11=1.
09451229\hcc11=110.19758001\dih11=42.68298921\hc12=1.09548687\hcc12=10
9.68225213\dih12=160.05755546\hc13=1.09602456\hcc13=109.23961493\dih13
=63.04075781\hc14=1.09492693\hcc14=111.93538267\dih14=-178.57217636\hc
15=1.09605324\hcc15=109.34176894\dih15=106.14178138\hc16=1.0943927\hcc
16=111.5554334\dih16=-136.39121725\hc17=1.08997905\hcc17=93.38217985\d
ih17=-136.82521665\hc18=1.08576656\hcc18=116.42013053\dih18=-102.40382
962\hc19=1.08385773\hcc19=121.62353854\dih19=85.47761808\hc20=1.086307
82\hcc20=121.34145178\dih20=-90.22982422\hc21=1.09452289\hcc21=111.149
05291\dih21=58.53891362\hc22=1.09550546\hcc22=110.36490454\dih22=178.1
7641932\hc23=1.09373289\hcc23=111.70944126\dih23=-62.07518803\hc24=1.0
9498852\hcc24=110.95399713\dih24=-56.01855398\hc25=1.0913913\hcc25=111
.46388253\dih25=64.43823227\hc26=1.09475291\hcc26=110.65237217\dih26=-
175.43331138\hc27=1.09397691\hcc27=111.75395743\dih27=58.26993959\hc28
=1.09479787\hcc28=110.25497207\dih28=-182.5001224\hc29=1.09169878\hcc2
9=111.1835274\dih29=-62.60434908\r=2.20496082\\Version=x86-Linux-G03Re
vB.04\State=2-A\HF=-392.1657503\S2=0.831417\S2-1=0.\S2A=0.750864\RMSD=
6.642e-09\RMSF=2.946e-05\Dipole=-0.1464813,-0.0686936,-0.1377149\PG=C0
1 [X(C10H19)]\\@
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BHLYP/aug-cc-pVDZ**

```
1\1\ CHEMCLUSTER-KNET10\FTS\UBHandHLYP\Aug-CC-pVDZ\C10H19(2)\CARLHS\15
-Aug-2004\1\\#BHANDHLYP/AUG-CC-PVDZ
OPT=(GRAD,TS,READFC,NOEIGENTEST,NO
FREEZE) GEOM=CHECKPOINT GUESS=READ\\tert-butylhexenyl cyclization TS – cis-
boat\\0,2\C\C,1,r\C,2,cc3,1,ccc3\C,1,cc4,2,ccc4,3,dih4,0
\C,1,cc5,2,ccc5,3,dih5,0\C,2,cc6,3,ccc6,1,dih6,0\C,5,cc7,1,ccc7,2,dih7
,0\C,5,cc8,1,ccc8,2,dih8,0\C,5,cc9,1,ccc9,2,dih9,0\C,6,cc10,2,ccc10,3,
dih10,0\H,6,hc11,2,hcc11,3,dih11,0\H,6,hc12,2,hcc12,3,dih12,0\H,10,hc1
3,6,hcc13,2,dih13,0\H,10,hc14,6,hcc14,2,dih14,0\H,4,hc15,1,hcc15,2,dih
15,0\H,4,hc16,1,hcc16,2,dih16,0\H,1,hc17,2,hcc17,3,dih17,0\H,2,hc18,3,
hcc18,1,dih18,0\H,3,hc19,2,hcc19,1,dih19,0\H,3,hc20,2,hcc20,1,dih20,0\
H,7,hc21,5,hcc21,1,dih21,0\H,7,hc22,5,hcc22,1,dih22,0\H,7,hc23,5,hcc23
,1,dih23,0\H,8,hc24,5,hcc24,1,dih24,0\H,8,hc25,5,hcc25,1,dih25,0\H,8,h
```

```
c26,5,hcc26,1,dih26,0\H,9,hc27,5,hcc27,1,dih27,0\H,9,hc28,5,hcc28,1,di
h28,0\H,9,hc29,5,hcc29,1,dih29,0\\cc3=1.37402574\ccc3=113.87593374\cc4
=1.51200556\ccc4=97.4340559\dih4=108.13191798\cc5=1.51660469\ccc5=116.
77797056\dih5=-21.67397666\cc6=1.51518919\ccc6=120.42570988\dih6=106.0
8356066\cc7=1.54049882\ccc7=107.94797469\dih7=-174.467631\cc8=1.529849
48\ccc8=109.89686694\dih8=-56.85983159\cc9=1.5294977\ccc9=112.55888049
\dih9=65.59062397\cc10=1.52143108\ccc10=109.68890292\dih10=-79.3383163
7\hc11=1.0915815\hcc11=110.15342938\dih11=43.21339865\hc12=1.0926738\h
cc12=109.60428294\dih12=160.71933429\hc13=1.09251718\hcc13=109.3179016
8\dih13=63.1071743\hc14=1.09198899\hcc14=111.77553826\dih14=-178.36211
703\hc15=1.09312014\hcc15=109.31380967\dih15=106.92134179\hc16=1.09116
735\hcc16=111.49389728\dih16=-135.52413751\hc17=1.08684935\hcc17=93.05
322393\dih17=-137.51806274\hc18=1.0829572\hcc18=116.48135489\dih18=-10
2.17209876\hc19=1.08097812\hcc19=121.67608339\dih19=85.60627095\hc20=1
.0832582\hcc20=121.40046024\dih20=-90.34033869\hc21=1.09149982\hcc21=1
11.04669045\dih21=58.54899804\hc22=1.09252771\hcc22=110.29967039\dih22
=178.19807903\hc23=1.09066293\hcc23=111.61939415\dih23=-62.04246958\hc
24=1.09194341\hcc24=110.8820588\dih24=-56.08261956\hc25=1.0883129\hcc2
5=111.37997526\dih25=64.39441858\hc26=1.09179341\hcc26=110.58904215\di
h26=-175.50034032\hc27=1.09065608\hcc27=111.69803441\dih27=58.42754007
\hc28=1.09162123\hcc28=110.13893422\dih28=-182.37691673\hc29=1.0885025
\hcc29=111.11538765\dih29=-62.52197086\r=2.20455032\\Version=x86-Linux
-G03RevB.04\State=2-A\HF=-392.188454\S2=0.828205\S2-1=0.\S2A=0.750826\
RMSD=4.170e-09\RMSF=2.510e-05\Dipole=-0.163207,-0.0765512,-0.1894014\P
G=C01 [X(C10H19)]\\@
```

***Boat-Axial* 2.66**

MP2/6-311G**

```
1\1\ CHEMCLUSTER-KNET19\FTS\UMP2-FC\6-311G(d,p)\C10H19(2)\CARLHS\02-Au
g-2004\1\\#MP2/6-311G** OPT=(GRAD,TS,READFC,NOEIGENTEST) GEOM=CHECKPOI
NT GUESS=READ\\tert-butylhexenyl cyclization TS – trans-boat\\0
,2\C\C,1,cc2\C,2,cc3,1,ccc3\C,2,cc4,3,ccc4,1,dih4,0\C,4,cc5,2,ccc5,3,d
ih5,0\C,5,cc6,4,ccc6,2,dih6,0\C,1,cc7,2,ccc7,3,dih7,0\C,7,cc8,1,ccc8,2
,dih8,0\C,7,cc9,1,ccc9,2,dih9,0\C,7,cc10,1,ccc10,2,dih10,0\H,2,hc11,3,
hcc11,1,dih11,0\H,4,hc12,2,hcc12,3,dih12,0\H,4,hc13,2,hcc13,3,dih13,0\
H,5,hc14,4,hcc14,2,dih14,0\H,5,hc15,4,hcc15,2,dih15,0\H,6,hc16,5,hcc16
,4,dih16,0\H,6,hc17,5,hcc17,4,dih17,0\H,1,hc18,2,hcc18,3,dih18,0\H,8,h
c19,7,hcc19,1,dih19,0\H,8,hc20,7,hcc20,1,dih20,0\H,8,hc21,7,hcc21,1,di
h21,0\H,9,hc22,7,hcc22,1,dih22,0\H,9,hc23,7,hcc23,1,dih23,0\H,9,hc24,7
,hcc24,1,dih24,0\H,10,hc25,7,hcc25,1,dih25,0\H,10,hc26,7,hcc26,1,dih26
,0\H,10,hc27,7,hcc27,1,dih27,0\H,3,hc28,2,hcc28,1,dih28,0\H,3,hc29,2,h
cc29,1,dih29,0\\cc2=2.25659832\cc3=1.34895166\ccc3=107.02691502\cc4=1.
51901739\ccc4=121.74201524\dih4=103.09788398\cc5=1.53180873\ccc5=110.3
0757685\dih5=-80.42437246\cc6=1.53164837\ccc6=106.83900156\dih6=-55.27
```

```
475912\cc7=1.51449576\ccc7=112.21379516\dih7=-110.67232656\cc8=1.53387
207\ccc8=109.44889912\dih8=62.04628842\cc9=1.54309826\ccc9=108.0547117
2\dih9=180.10144335\cc10=1.53426125\ccc10=112.94154435\dih10=-59.99359
788\hc11=1.08598981\hcc11=117.82563868\dih11=-97.30940377\hc12=1.09522
797\hcc12=109.76858977\dih12=42.15068438\hc13=1.09668314\hcc13=109.483
53496\dih13=159.82388844\hc14=1.09640883\hcc14=111.69604549\dih14=-177
.78009398\hc15=1.09690978\hcc15=109.19746865\dih15=63.08368404\hc16=1.
10044265\hcc16=110.41919634\dih16=173.38703567\hc17=1.09605528\hcc17=1
08.83637527\dih17=-69.1696954\hc18=1.09208274\hcc18=96.63008868\dih18=
7.01010245\hc19=1.09580394\hcc19=110.52375562\dih19=55.15229023\hc20=1
.09450516\hcc20=111.22322794\dih20=-64.88757014\hc21=1.0962669\hcc21=1
10.46044094\dih21=174.91688554\hc22=1.09551581\hcc22=110.61402078\dih2
2=-58.46711747\hc23=1.09727173\hcc23=110.33156589\dih23=-178.32874895\
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BHLYP/cc-pVDZ**

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BHLYP/aug-cc-pVDZ**

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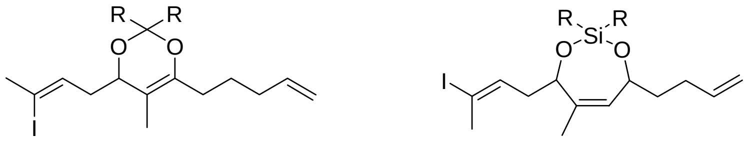
APPENDIX D: The Dioxin and Silicon-Tethered Cyclization Precursor

Appendix D: Other Model Systems

Although we were disappointed that the temperature related improvement reported by Ihara turned out to be non-existant,[38] we still wanted to focus on the synthesis of linear triquinanes by way of a cascade radical cyclization. It is clear from our work and that of others that the lack of selectivity arises in the second of the three cyclizations in the cascade and so our efforts focused on improving the selectivity of this step. With this in mind we designed two general types of cyclization precursor shown in Figure D-1. Both of these substrates are designed to undergo three consecutive 5-*exo* radical cyclizations to give the linear triquinane as before. However the second hexenyl radical is tethered by either the dioxin or the silicon bridge. We reasoned that by installing this removable tether, we may be able to lock the hexenyl radical of the second cyclization into a particular geometry. Hopefully the locking effect of the tether would force the cyclization to proceed more selectively.



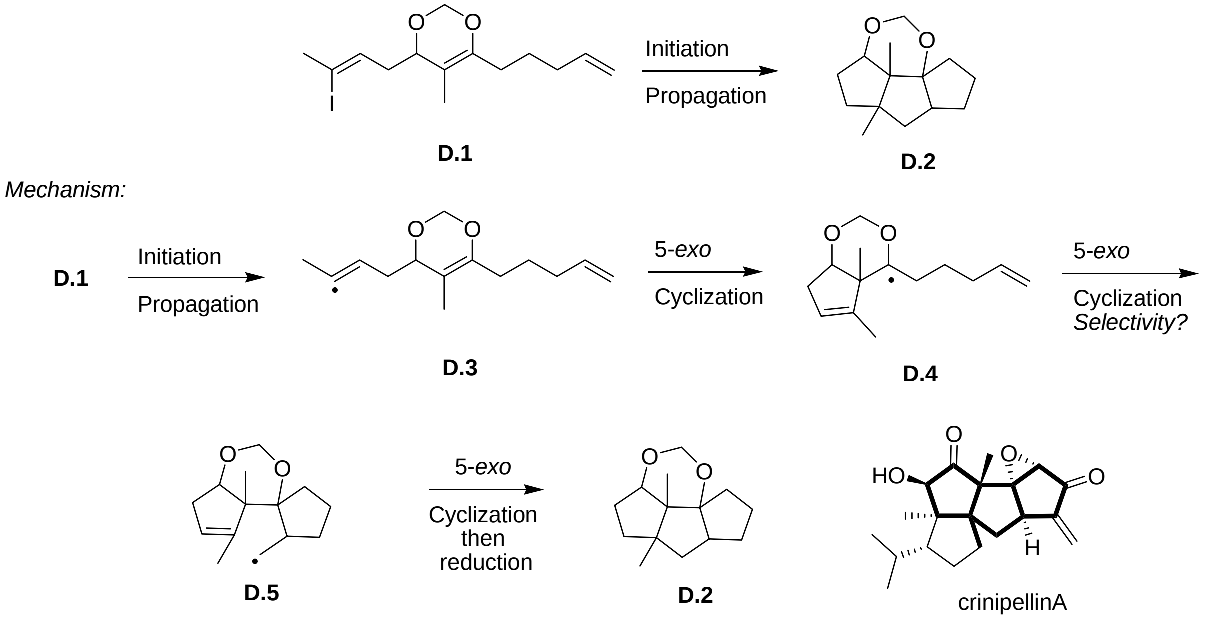
R = H or Me
Dioxin Tethered Precursor

R = ^{i}Pr or ^{t}Bu
Silicon Tethered Precursor

Figure D-1: Two new classes of cyclization precursor.

D.1: Cyclization Mechanisms

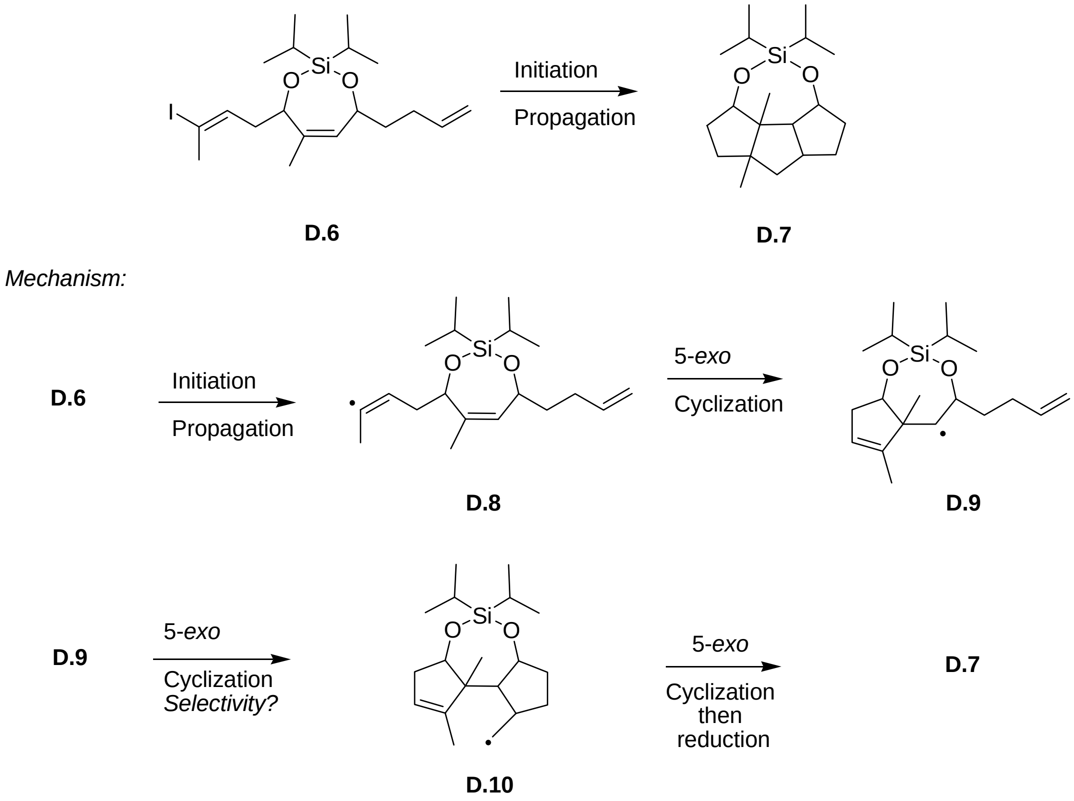
The mechanism for the cascade of the dioxin system is shown in Scheme D-1. In a typical reductive cyclization of iodide **D.1**, the three consecutive cyclizations should give linear triquinanes **D.2**. The cascade cyclization is initiated by iodine abstraction from **D.1** to give vinyl radical **D.3.** Cyclization of **D.3** gives bicyclic radical **D.4**. This key second hexenyl radical is interesting because it not only contains the *t*-butyl like group in the 1 position that we have studied previously, but it also has an oxo substituent in the 1 position. We have shown that the *t*-butyl group should induce *cis* selectivity in the cyclization, but the oxo group is reported to impart *trans* selectivity. Therefore it is fundamentally interesting to see what the result will be of this competition in the cyclization of **D.4** to give radical **D.5**. Finally, compound **D.5** can undergo the third and final radical cyclization to complete the round-trip cyclization and give linear triquinane **D.2** upon reduction. Compound **D.5** should cyclize selectively to give a single linear triquinane because a 5,5 fused system is being formed. When we compare the final triquinane products of the cascade to crinipellin A, linear triquinane portion highlighted, we see some key structural similarities. The two oxygens in **D.2** match the positioning of two of the oxygens in crinipellin A. Furthermore we notice that the two methyl groups in **D.2** nicely match with a methyl group and an alkyl group in crinipellin A. For these reasons, the cyclization of the dioxin precursor could be an efficient approach to the crinipellin skeleton and **D.1** serves as a good model system to study to what extent this is true.



D.1
Initiation
Propagation
D.2
Mechanism:
D.1
Initiation
Propagation
D.3
5-*exo*
Cyclization
D.4
5-*exo*
Cyclization
Selectivity?
D.5
5-*exo*
Cyclization
then
reduction
D.2
HO
H
crinipellinA

Scheme D-1: Mechanism for the cyclization of vinyl iodide **D.1**.

The cyclization cascade for silicon tethered vinyl iodide **D.6** is similar to that of the dioxin tether and is shown in Scheme D-2. The cyclization of iodide **D.6** is expected to give triquinanes **D.7**. In a typical cyclization sequence, abstraction of iodine from **D.6** gives vinyl radical **D.8**. Radical **D.8** can then cyclize to give the key second hexenyl radical **D.9**. Hexenyl radical **D.9** also has a *t*-butyl like group in the 1 position, but in contrast to the dioxin precursor **D.9** has an *oxo* group in the 2 position. It is difficult to assess what affect this *oxo* substitution will have on the selectivity of the cyclization because it is highly dependent on the nature and substitution pattern of the chain.[90] After 5-*exo* cyclization of radical **D.9**, tricyclic radical **D.10** is formed. Reduction of **D.10** gives the desired tricyclic products **D.7**.


Si
O
I
Initiation
Propagation
D.6
D.7
Mechanism:
D.6
Initiation
Propagation
D.8
5-exo
Cyclization
D.9
D.9
5-exo
Cyclization
Selectivity?
D.10
5-exo
Cyclization
then
reduction
D.7

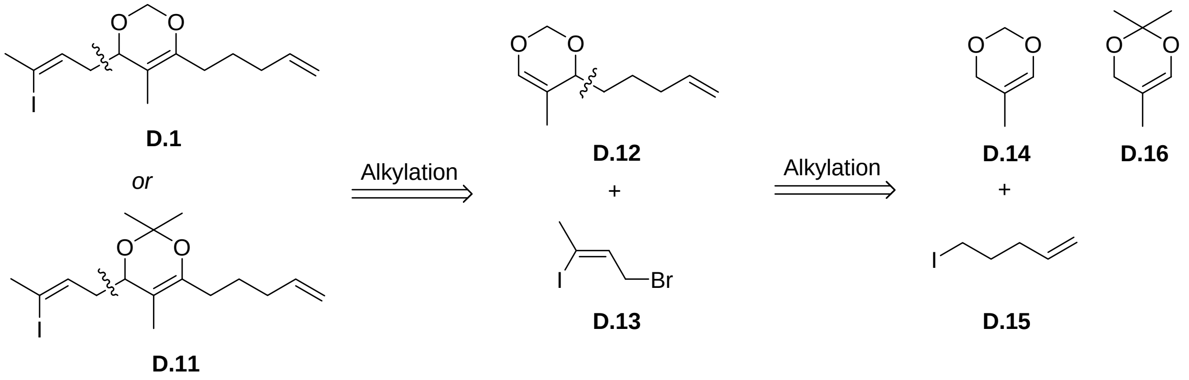
Scheme D-2: Mechanism for the cyclization of vinyl iodide **D.6**.

D.2: Synthesis of the Dioxin Precursor

We approached the synthesis of the dioxin precursor **D.1** in two separate ways. The first approach involved two sequential alkylations of a dioxin ring whereas the second approach employed a methyleneation of a suitably functionalized β-hydroxy acid.

D.2.1: First Retrosynthetic Analysis of Vinyl Iodide D.1

Our first retrosynthesis for precursor **D.1** is shown in Scheme D-3. We reasoned that the requisite vinyl iodide precursor could be synthesized using Funk's conditions[91] for the alkylation of dioxin **D.12** with known allylic bromide **D.13.**[46] Using the same alkylation strategy, **D.11** can be assembled from known dioxin **D.14** and alkyl iodide **D.15**. Should we opt for the dimethyl variant of the precursor **D.11**, then the same retrosynthetic analysis is applicable leading back to dioxin **D.16**.



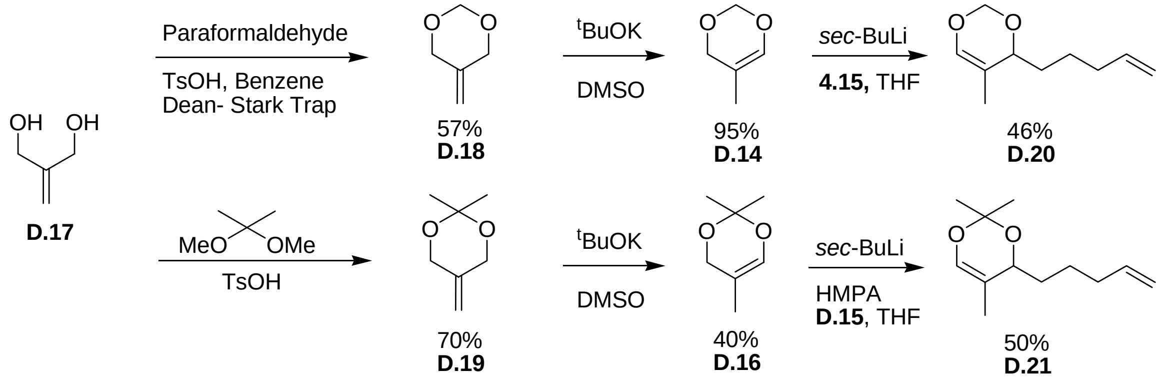
Scheme D-3: Retrosynthetic analysis of cyclization precursors **D.1** or **D.11**.

D.2.2: Progress Towards the Synthesis of D.1 and D.11 by the Alkylation Route

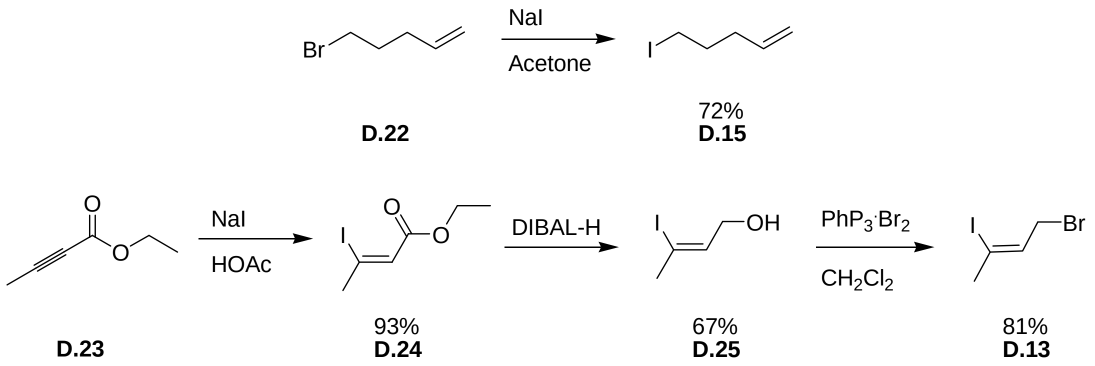
The requisite dioxins were prepared according to known procedures starting from 2 methylene 1,3 propane diol **D.17**.[92] Treatment of this diol with paraformaldhyde and TsOH in benzene readily gave dioxane **D.18** in 57% yield. Similarly treatment of **D.17** with TsOH in neat 2,2-dimethoxypropane gave dimethyl dioxane **D.19** in 70% yield. The *exo*-methylene group in **D.18** and **D.19** was then isomerized to the internal alkene by *t*-BuOK to give the desired dioxins **D.14** and **D.16** in 95% and 40% yield respectively.

The necessary iodopentene alkylating agent **D.15** was synthesized[93] in 72% yield by a Finkelstein reaction on bromide **D.22** with NaI. The allylic bromide was synthesized by the three step procedure outlined in Scheme D-4 starting from alkynoate **D.23**. Treatment of **D.23** with NaI in refluxing acetic acid gave vinyl iodide **D.24** in 93% yield. The ester was then reduced to the allylic alcohol using DIBAL-H in hexanes to give iodoalcohol **D.25** in 67% yield. Finally the alcohol was converted to the corresponding bromide **D.13** using *in situ* generated $Ph_3P{\cdot}Br_2$ complex in 81% yield.

The first alkylation reaction was carried out by treating dioxin **D.14** with 1.2 equiv of *sec*-BuLi at −78 °C. The resulting metalated species was then quenched with iodide **D.15** to give dioxin **D.20** in 46% yield. Using the same conditions for the alkylation of dioxin **D.16** proved to be unsuccessful, but addition of HMPA as a co-solvent during the metalation enabled compound **D.21** to be isolated in 50% yield.


Paraformaldehyde
TsOH, Benzene
Dean- Stark Trap
ᵗBuOK
DMSO
sec-BuLi
4.15, THF
OH OH
D.17
57%
D.18
95%
D.14
46%
D.20
MeO OMe
TsOH
ᵗBuOK
DMSO
sec-BuLi
HMPA
D.15, THF
70%
D.19
40%
D.16
50%
D.21

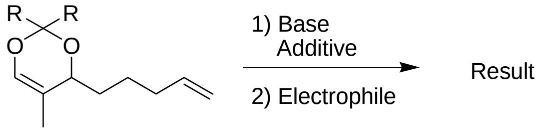
Synthesis of Alkylating Agents


Br
NaI
Acetone
I
D.22
72%
D.15
NaI
HOAc
DIBAL-H
PhP3·Br2
CH2Cl2
OH
Br
D.23
93%
D.24
67%
D.25
81%
D.13

Scheme D-4: Synthesis of alkylated dioxins **D.20** and **D.21**.

Having successfully carried out the first alkylation of the dioxins, we next turned our attention to the second alkylation as shown in Table D-1. Unfortunately the alkylation conditions that were developed for the first alkylation step did work in this case resulting in the recovery of the starting material (Entry 1). Alkylating agent **D.13** is known to be somewhat unstable and so tried the same set of conditions with allyl bromide, entries 3, 4, and 5, with no more success. We further verified that vinyl iodide **4.13** was not the culprit by using it to alkylate dimethyl malonate (not shown). This reaction smoothly afforded the desired product in 75% yield proving that the alkylating agent was not the problem. We then proceeded to vary the base used for the deprotonation to *tert*-BuLi or *tert*-BuOK, entries 4, 5, 7, and 8 without any success. Addition of HMPA as a co-solvent*,* entries 2, 3, and 4, and variation of the reaction temperature, entries 3, 4, 5, and 8 also did not allow any desirable product to be isolated. At this point we suspected that the dioxin was simply not being metalated and tested for this by trying to quench the reactions with D_2O, entries 6 and 9, but we were unable to detect any deuterium incorporation. The two deuterium experiments confirm our suspicions and it is not entirely surprising because vinyl ethers of this type are known to be difficult to metalate.[94] With no encouraging results, we abandoned this approach to the dioxin precursors.

Table D-1: Attempted alkylations of dioxins **D.20** and **D.21**.

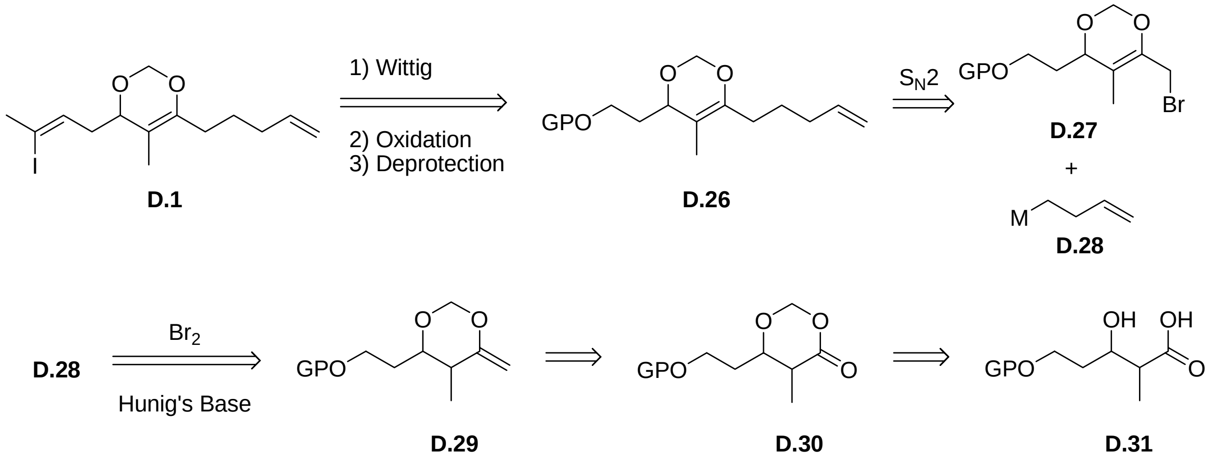


D.20 R = H
D.21 R = Me

Entry	Dioxin	Base	Electrophile	T (°C)	Additive	Result
1	**D.20**	*sec*-BuLi	**D.13**	−78	-	Recovered starting material
2	**D.20**	*sec*-BuLi	**D.13**	−78	HMPA	Recovered starting material
3	**D.20**	*sec*-BuLi	Allyl bromide	−65	HMPA	Recovered starting material
4	**D.20**	*tert*-BuLi	Allyl bromide	−65	HMPA	Decomposition
5	**D.20**	*tert*-BuOK	Allyl bromide	20	-	Recovered starting material
6	**D.20**	*sec*-BuLi	D_2O	−78	-	No D incorporation
7	**D.20**	*tert*-BuLi	**D.13**	−78	-	Recovered starting material
8	**D.21**	*tert*-BuOK	**D.13**	20	-	Recovered starting material
9	**D.21**	*sec*-BuLi	D_2O	−78	-	No D incorporation

D.2.3: Second Retrosynthetic Analysis of Vinyl Iodide D.1

Our second retrosynthetic analysis for the dioxin precursors is outlined in Scheme D-5. We envisioned installing the vinyl iodide through a Wittig olefination in the final step. We unmasked the necessary aldehyde for the Wittig reaction by an oxidation and a deprotection leading back to protected alcohol **D.26**. The other side chain is installed using an S_N2 displacement of allylic bromide **D.27** with a suitably metalated four carbon alkene building block **D.28**. We saw compound **D.27** coming from a bromination of *exo*-methylene compound **D.29**[95] which in turn was synthesized by methyleneation of lactone **D.30**. Finally lactone **D.30** can be formed by treating β-hydroxy acid **D.31** with paraformaldehyde and a number of such acids are known in the literature.

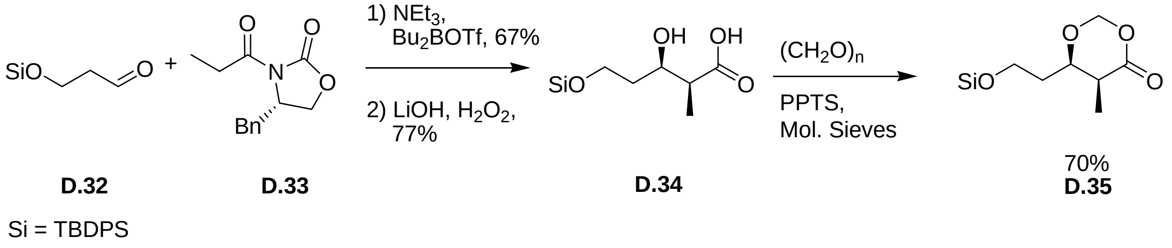


D.1
1) Wittig
2) Oxidation
3) Deprotection
GPO
D.26
S_N2
D.27
Br
+
M
D.28
D.28
Br_2
Hunig's Base
D.29
D.30
D.31
OH OH

Scheme D-5: Second retrosynthetic analysis for dioxin **D.1**.

D.2.4: Progress Towards the Synthesis of D.1 by the β-Hydroxy Acid Route

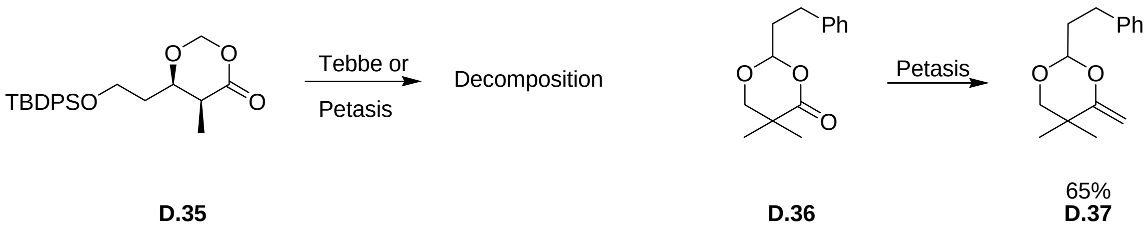
Some of the steps in our retrosynthetic analysis place heavy demands upon the protecting group and so we chose to use a TBDPS group. Therefore we synthesized known β-hydroxy acid **D.34** shown in Scheme 4-6. This acid is a known compound[96] and is readily constructed through an Evans aldol between aldehyde **D.32** and propiolated Evans' auxiliary **D.33** in 67% yield as shown in Scheme D-6**.** Hydrolysis of the chiral auxiliary using LiOOH gave the desired β-hydroxy acid **D.34** in 77% yield. Treatment of the acid with paraformaldehyde and catalytic PPTS provided us with the desired lactone **D.35** in 70% yield.[97]



SiO
1) NEt_3, Bu_2BOTf, 67%
2) LiOH, H_2O_2, 77%
Bn
$(CH_2O)_n$
PPTS, Mol. Sieves
70%
D.32
D.33
D.34
D.35
Si = TBDPS

Scheme D-6: Synthesis of lactone **D.35**.

With the desired lactone in hand we proceeded to examine the methyleneation reaction to form **D.29** shown in Scheme 4-7**.** Unfortunately treatment of lactone **D.35** using either the Tebbe or Petasis reagent resulted in decomposition of the starting material. In a related experiment, we treated known lactone **D.36** with the Petasis reagent and were able to isolate enol ether **D.37** in 65% yield. The success of the methyleneation for lactone **D.36**[96] and its failure for **D.35** indicated to us that our lactone was unstable to the reaction conditions. At this point we decided to focus our efforts on the silicon tethered precursor **D.6.**

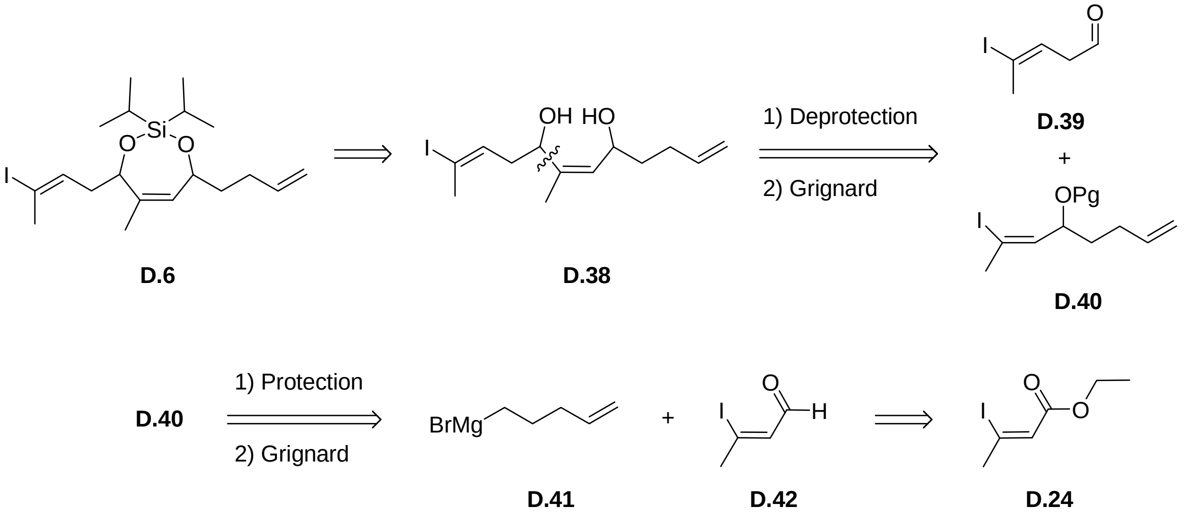


TBDPSO
Tebbe or
Petasis
Decomposition
Ph
Petasis
Ph
65%
D.35
D.36
D.37

Scheme D-7: Methyleneation attempts on lactone **D.35** and methylenation of lactone **D.36**.

D.3: Synthesis of the Silicon Tethered Precursor D.6

Our retrosynthetic analysis for vinyl iodide **D.6** is shown in Scheme **D-8**. Based on some other work that we had done with the diisopropyl silicon tethers we knew that this functionality can be unstable and so we envisioned installing it in the last step which leads back to diol **D.38**. Diol **D.38** can be assembled through a Grignard reaction between known aldehyde **D.39**[98] and vinyl iodide **D.40**. Iodide **D.40** can be synthesized through a coupling reaction between Grignard reagent **D.41** and aldehyde **D.42**.[99] Aldehyde **D.42** was constructed by a DIBAL-H reduction of ester **4.24**.[99]

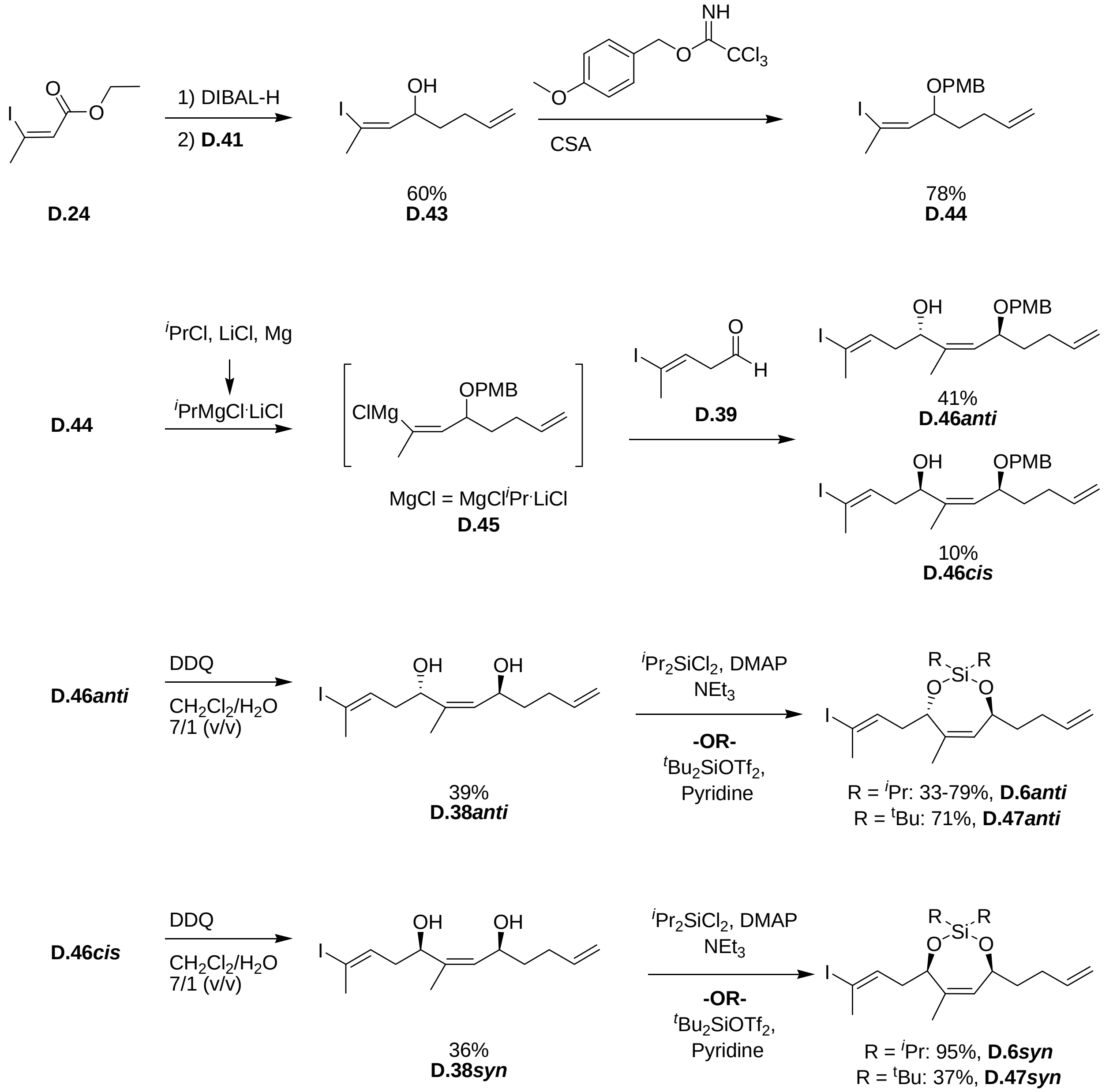


I
Si
O
O
D.6
OH HO
I
D.38
1) Deprotection
2) Grignard
O
I
D.39
+
OPg
I
D.40
D.40
1) Protection
2) Grignard
BrMg
D.41
+
O
I
H
D.42
O
I
O
D.24

Scheme D-8: Retrosynthetic analysis for vinyl iodide **D.6**.

D.3.1: Forward Synthesis of the Silicon Tethered Precursor D.6

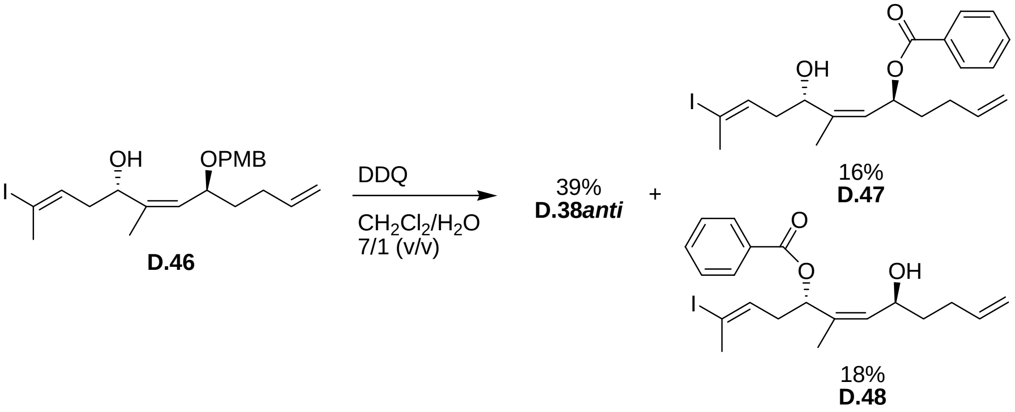
Our synthesis of a silicon tethered vinyl iodide **4.6** and other related precursors is shown in Scheme 4-9. Treatment of iodoester **D.24** with 1 equiv of DIBAL-H gave aldehyde **D.42**, Scheme D-8, which was not isolated, but was immediately treated with butenyl Grignard reagent **D.41** to give alcohol **D.42** in 60% yield. PMB protection of the secondary alcohol with PMB-trichloroacetimidate gave vinyl iodide **D.44**.[100] Conversion of iodide **D.44** to the corresponding Grignard reagent **D.45** was accomplished using Knochel's protocol[101] and then quenched with aldehyde **D.39**. As expected this reaction produced two diastereomers **D.46*anti*** and **D.46*syn*** in 41% and 10% yield respectively. DDQ deprotection of allylic PMB ethers **D.46*anti*** and **D.46*syn*** yielded diols **D.38*anti*** and **D.38*syn*** in 39% and 36% respectively. Finally installation of the silicon tether was accomplished by treating diol **D.38*anti*** with $^{i}Pr_2SiCl_2$, DMAP and Et_3N.[102] The final tethering reaction was very clean, but the yields were quite variable ranging from 33% to 79% with 60% being the most reproducible yield. Inexplicably the tethering reaction of **D.38*syn*** consistently gave a 95% yield under the same reaction conditions. Similarly if diol **D.38*anti*** was treated with $^{t}Bu_2SiOTf_2$ in the presence of pyridine, we could isolate di-*t*-butyl tethered compound **D.47*anti*** in 71% yield. Subjecting diol **D.38*syn*** to the same conditions gave silicon tethered compound **D.47*syn*** albeit in 37% yield, where mono silylated products made up the remainder of the recovered material.


D.24
1) DIBAL-H
2) D.41
60%
D.43
CSA
78%
D.44
D.44
^{i}PrCl, LiCl, Mg
^{i}PrMgCl·LiCl
ClMg
OPMB
MgCl = MgCl^{i}Pr·LiCl
D.45
D.39
41%
D.46anti
10%
D.46cis
D.46anti
DDQ
CH_2Cl_2/H_2O
7/1 (v/v)
39%
D.38anti
^{i}Pr$_2$SiCl$_2$, DMAP
NEt$_3$
-OR-
^{t}Bu$_2$SiOTf$_2$,
Pyridine
R = ^{i}Pr: 33-79%, D.6anti
R = ^{t}Bu: 71%, D.47anti
D.46cis
DDQ
CH_2Cl_2/H_2O
7/1 (v/v)
36%
D.38syn
^{i}Pr$_2$SiCl$_2$, DMAP
NEt$_3$
-OR-
^{t}Bu$_2$SiOTf$_2$,
Pyridine
R = ^{i}Pr: 95%, D.6syn
R = ^{t}Bu: 37%, D.47syn

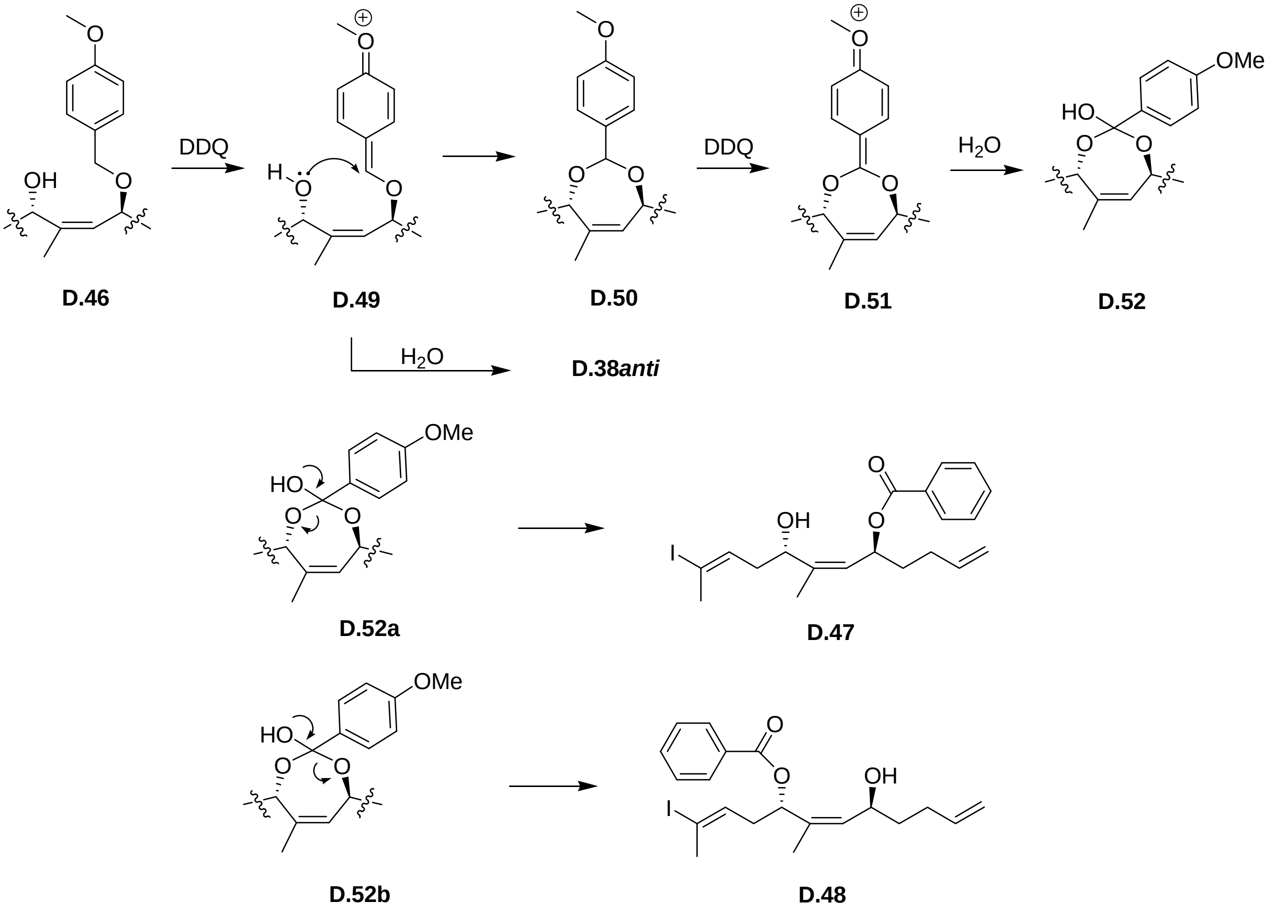
Scheme D-9: Synthesis of silicon tethered precursor **D.6**.

The yield of the DDQ protection of ***D.46anti*/*syn*** to give diols **D.38** suffered from a side reaction as shown in Scheme D-10 in which esters **D.47** and **D.48** were isolated in addition to the desired diol. In Scheme D.11 we propose a mechanism for the formation of **D.47** and **D.48**. Treatment of PMB ether **D.46** with DDQ leads to oxo-carbenium ion **D.49**. Ion **D.49** can then be attacked by water to give the desired diol **D.38*anti***. However the *oxo*-carbenium ion can also be attacked by the free alcohol in the 4 position to give acetal **D.50**. Acetal **D.50** is then oxidized by DDQ to give another *oxo*-carbenium ion **D.51** which is attacked by water to give compound

D.52. Compound **D.52** can then collapse in one of two ways either by the pathway shown in **D.52a** to give ester **D.47** or according to the path in **D.52b** to give the other regio-isomer **D.48**.

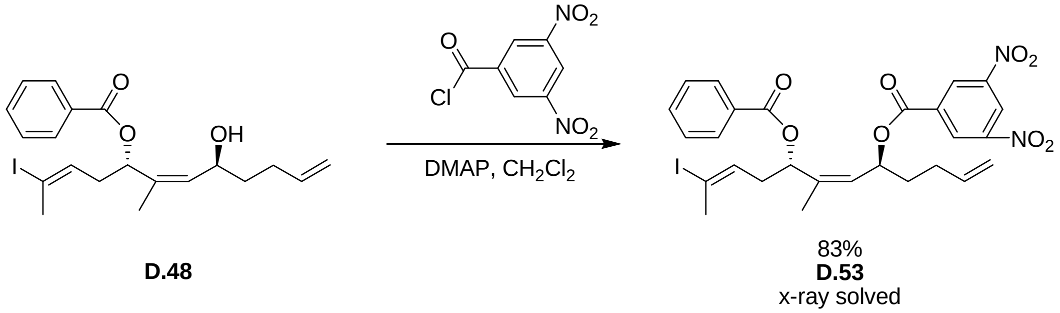

OH
OPMB
I
D.46
DDQ
CH$_2$Cl$_2$/H$_2$O
7/1 (v/v)
39%
D.38*anti*
+
OH
O
O
I
16%
D.47
O
O
OH
I
18%
D.48

Scheme 4-10: Side reaction in the deprotection of PMB ether **D.46**.


OH
O
D.46
DDQ
H
D.49
D.50
DDQ
D.51
H$_2$O
HO
OMe
D.52
H$_2$O
D.38*anti*
OMe
HO
D.52a
OH
D.47
OMe
HO
D.52b
OH
D.48

Scheme 4-11: Mechanism for the formation of esters **D.47** and **D.48**.

To ascertain the major isomer from the Knochel coupling reaction **D.44→D.46**, we derivatized ester **D.48** with *bis* *m*-nitrobenzoylchloride as shown in Scheme D-11 to give ester **D.53**. The solid that resulted from this reaction was taken up in THF and a single crystal, suitable for x-ray diffraction analysis, was grown by slow evaporation of this solution. When the crystal structure was solved we were able to conclude that the major product had the *anti* configuration. This allowed us to rigorously assign the configurations of all of the cyclization precursors.

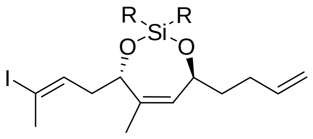


Scheme D-12: Derivatization of alcohol **D.48** in order to obtain an x-ray crystal structure.

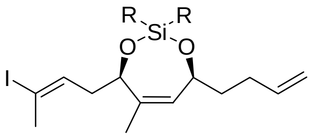
D.4: Cyclization Results of the Silicon Tethered Precursors

With the desired silicon tethered precursors in hand and their relative stereochemistry firmly assigned, we subjected them to various radical cyclization conditions which are summarized in Table D-2. Using our standard conditions, Entry 1 (Bu_3SnH, AIBN, 2mM and 80°C), we observed rapid consumption of the starting material by GC, but the appearance of numerous peaks with no major product(s) being observed. We made similar observations when we ran the same reaction at room temperature with Et_3B as the initiator Entry 2. Changing the hydride source to $(TMS)_3SiH$ also did not alter the outcome of the reaction Entries 3 and 4. We next moved to the **D.6*syn*** isomer, but similarly disappointing results were obtained with either Bu_3SnH entry 5 or $(TMS)_3SiH$ entry 6 as the reducing agent. We also attempted a cyclization with a $Bu_3SnCl/NaCNBH_3$ system entry 7, but to no avail. At this point we thought that maybe the isopropyl tether was unstable to the reaction conditions and so we opted for the more stable di-*t*-butyl silicon tether, entries 8, 9 and 10, but the results were similar to those from other cyclization attempts.

Table 4-2: Cyclization results for precursors **D.6*anti*/*syn*** and **D.47*syn/anti***.



R = ^{i}Pr: **D.6*anti***
R = *t*-Bu: **D.47*anti***

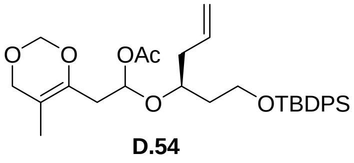


R = ^{i}Pr: **D.6*syn***
R = *t*-Bu: **D.47*syn***

Entry	Precursor	Reducing Agent	T (°C)	Initiator	Concentration (mM)	Results
1	**D.6*anti***	Bu_3SnH	80	AIBN	2	Decomposition
2	**D.6*anti***	Bu_3SnH	25	Et_3B	2	Decomposition
3	**D.6*anti***	$(TMS)_3SiH$	25	Et_3B	2	Decomposition
4	**D.6*anti***	$(TMS)_3SiH$	25	Et_3B	4	Decomposition
5	**D.6*syn***	Bu_3SnH	80	AIBN	2	Decomposition
6	**D.6*syn***	$(TMS)_3SiH$	80	AIBN	2	Decomposition
7	**D.6*syn***	Bu_3SnCl, $NaCNBH_3$	80	AIBN	5	Decomposition
8	**D.47*anti***	Bu_3SnH	80	AIBN	2	Decomposition
9	**D.47*anti***	Bu_3SnH	25	Et_3B	2	Decomposition
10	**D.47*syn***	Bu_3SnH	80	AIBN	2	Decomposition

D.5: Conclusions and Outlook

It is unfortunate that at present our results with either of these precursors are not more encouraging. These two precursor however remain incredibly attractive due to their potential to allow the second cyclization cascade to proceed more selectively. For the dioxin tether, the problems lie with synthesis of the precursor, but recent work by Rychnovsky and Dalgard describes another possible route to this compound. They recently reported[103] the synthesis of compound **D.54**, and suitable modifications should allow for a synthesis of **D.1.**



D.54

The problems with the silicon tethered radical cyclizations rest with finding reductive conditions that are compatible with the substrate. Radical cyclizations with similar silicon tethers have been reported[104] and so the anticipated cascade should be possible. With a facile synthesis of the precursors already developed it should be possible to find suitable conditions to effect the tricyclization and study the effect that tethering has on the second cyclization.

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