A Ring-Expansion Approach to Roseophilin

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A RING EXPANSION APPROACH TO ROSEOPHILIN

By

SAMUEL G. SALAMONE

A Thesis submitted to the
Department of Chemistry and Biochemistry
in partial fulfillment of the
requirements for the degree of
Master of Science

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LIST OF ABBREVIATIONS

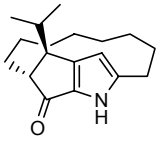
Ac	acetyl
aq	aqueous
atm	atmosphere(s)
Bn	benzyl
BOC	*t*-butoxycarbonyl
br	broad (spectral)
BuLi	*n*-butyl lithium
t-BuOK	potassium *tert*-butoxide
$^{\circ}$C	degrees Celsius
Calc'd	calculated
*m*CPBA	3-chloroperbenzoic acid
CSA	camphorsulfonic acid
d	doublet
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	4-(dimethylamino)pyridine
equiv	equivalent(s)
Et	ethyl
FMO	frontier molecular orbital
g	gram(s)
h	hour(s)
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectroscopy
Hz	Hertz
IR	infrared
J	coupling constant (NMR)
L	liter

LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
m	multiplet (spectral)
M	Molarity of solution (moles per liter)
Me	methyl
MHz	megahertz
min	minute(s)
mL	milliliter
mol	mole(s)
MS	molecular sieves
MVK	methyl vinyl ketone
n	normal (isomer)
NOE	nuclear Overhauser effect
NMR	nuclear magnetic resonance
Ph	phenyl
Ph_3P	triphenylphosphine
ppm	parts per million (NMR)
q	quartet (spectral)
RCM	ring closing metathesis
rt	room temperature
s	singlet (spectral)
SEM	2-(trimethylsilyl)ethoxymethyl
TAMA	N-methylanilinium trifuoroacetate
TBAF	tetrabutylammonium fluoride
TCNE	tetracyanoethylene
TBS	*t*-butyldimethylsilyl
THF	tetrahydrofuran
TMS	tetramethylsilane
TMSCl	chlorotrimethylsilane
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Ts	*p*-toluenesulfonyl

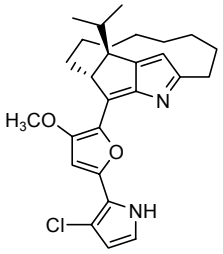
p-TsOH	*p*-toluenesulfonic acid
μ	micro

ABSTRACT

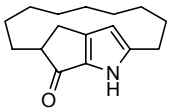
Roseophilin is an *ansa*-bridged potent cytotoxic compound that has generated continual interest from synthetic chemists since its discovery in 1992. As a synthetic target, roseophilin's most difficult challenge is the construction of the eight-carbon *ansa* chain that bridges the azafulvene unit. Such features traditionally have been installed via some form of macrocyclization reaction. Macrocyclization reactions typically require high dilution conditions that limit their utility on a preparative scale. This is especially true of entropically constrained systems such as roseophilin's core.



Tricyclic Core

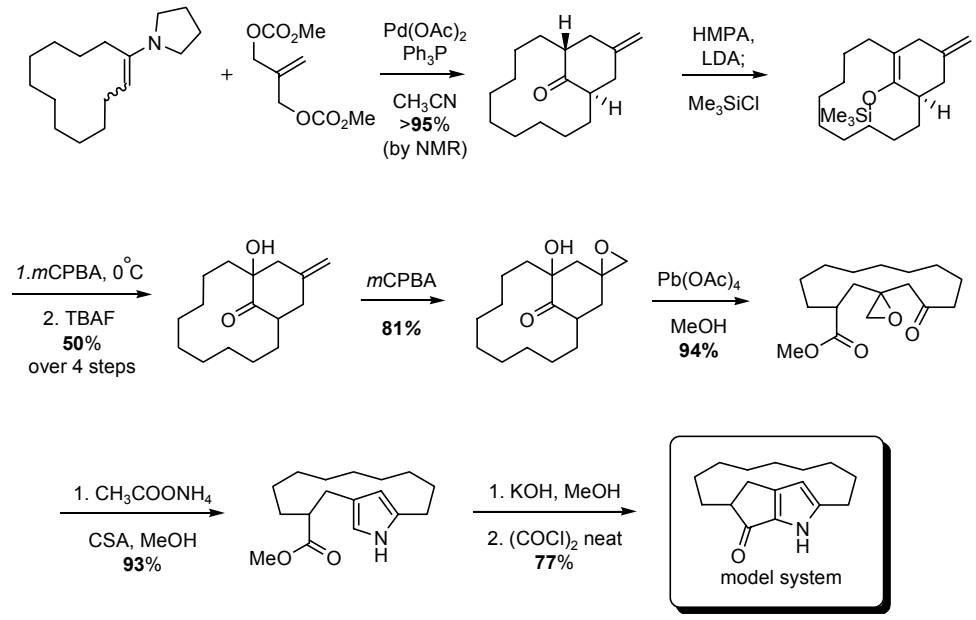


Roseophilin



Model System

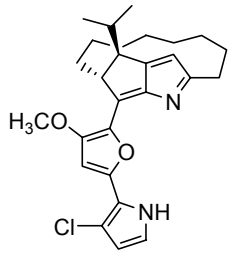
Herein, we report an efficient and potentially scalable synthesis of a cyclopentenone-fused pyrrolophane, which serves as a model for the tricyclic core of roseophilin.



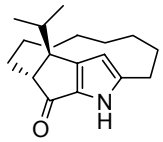
The synthetic scheme features a palladium-catalyzed annulation and oxidative cleavage sequence to provide a macrocyclic keto-ester. Modified Paal-Knorr pyrrole synthesis and Friedel-Crafts acylation complete the pyrrolophane model system. Elaboration of the above scheme, which avoids macrocyclization reactions, may facilitate large-scale prodution of roseophilin and analogs in due course.

CHAPTER I

INTRODUCTION

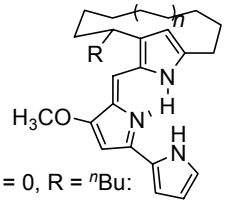


roseophilin (**1**)

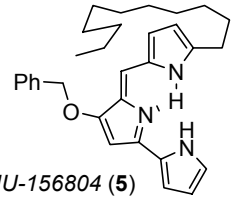


tricyclic core (**2**)

In 1992, Seto et al. revealed the structure of roseophilin (**1**), a novel antitumor antibiotic isolated from the culture broth of an actinomycete identified as *Streptomyces griseoviridis*[1]. This alkaloid possesses a topologically unique pentacyclic skeleton, which was found to consist of a constrained macrocycle incorporated in an *ansa*-bridged azafulvene linked to a conjugated heterocyclic ring system comprising a substituted pyrrolylfuran. The compound shows activity in vitro against K562 human erythroid leukemia cells (IC_{50}, 0.34 μM) and against KB cells, a human nasopharyngeal carcinoma cell line (IC_{50}, 0.88 μM). While the relative stereochemistry of roseophilin was assigned largely by NMR spectroscopy, the absolute stereochemistry was only established by total synthesis of the non-naturally occurring enantiomer.[2]



n = 0, R = ^{n}Bu:
streptorubicin B (**3**)
n = 1, R = Et:
metacycloprodigiosin (**4**)

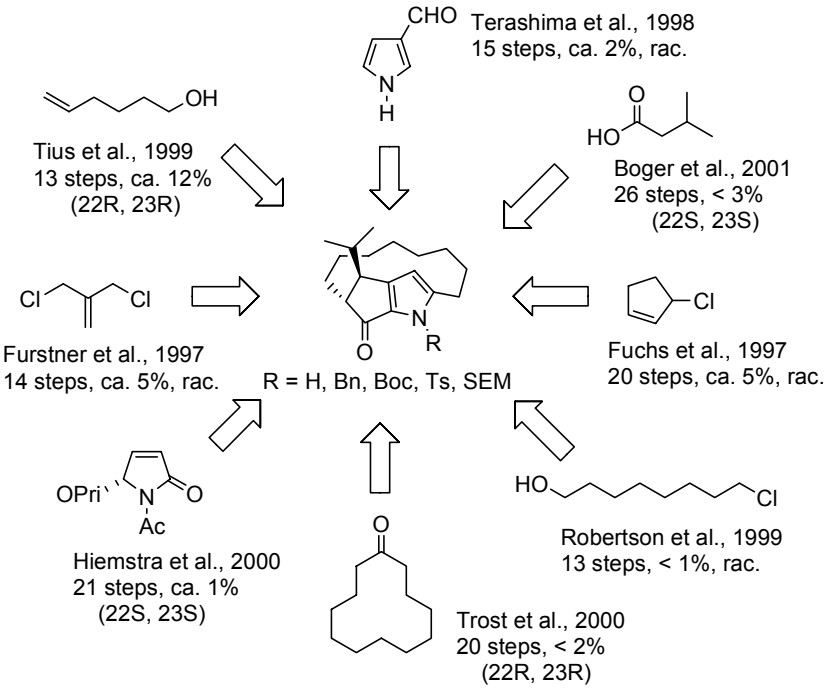


PNU-156804 (**5**)

The closest known structural relatives to roseophilin occurring in nature are the members of the prodigiosin family such as (**3,4**).[3] Like roseophilin, these alkaloids contain an azafulvene motif as well as, in some cases, an *ansa*-bridge. Prodigiosins that

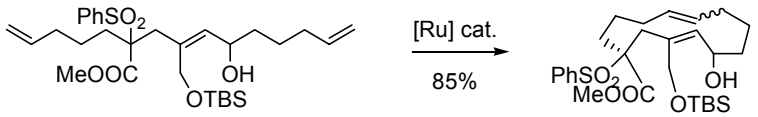
incorporate a methoxypyrrole rather than a methoxyfuran as the central ring into their heterocyclic perimeter show the most promise for pharmaceutical applications. The drug development efforts related to the prodigiosins yielded the synthetic pyrrole PNU-156804 (**5**), a clinical candidate for suppression of heart allograft rejection.[3] Recently, it has been demonstrated that these prodigiosins bind to DNA and produce oxidative strand cleavage if administered in combination with Cu^{II} salts.[4] This biological effect is triggered by the formation of π–radical cations through oxidation of the electron-rich pyrrolylpyrromethene chromophor by the metal cation and may account for the mode of action and cytotoxicity of these alkaloids.[5] In contrast to these alkaloids, the structurally related and highly potent alkaloid, roseophilin, does not damage DNA under oxidative conditions. As a consequence, it must exert its cytotoxic activity by another mechanism. Roseophilin's unusual structure, unknown mode of action, and its promising biological activity have stimulated substantial interest and work from the synthetic community since its discovery in 1992.

Scheme 1. Synthetic Summary[3]



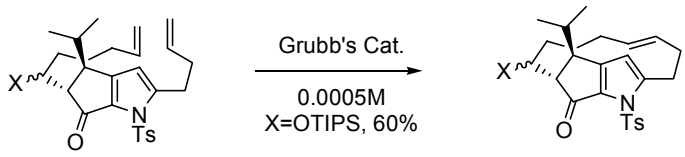
Fürstner, Tius, and Boger have completed the total syntheses of roseophilin, while Fuchs, Terashima, Trost, Heimstra, and Robertson each prepared the tricyclic core **2**.[6] Their synthetic work including yields and steps are summarized in Scheme 1.[3] All of these approaches, except Trost's, utilize macrocyclization reactions to construct the challenging eight-carbon *ansa* chain that bridges the azafulvene unit.

Scheme 2. Fürstner's RCM



In Fürstner's two total syntheses[6a,b] his lab employed an intramolecular allylation reaction in the first generation and a ring-closing metathesis reaction (Scheme 2) to craft the macrocycle in the second. Tius,[6c] Boger,[6d] Fuchs,[6e] and Hiemstra[6h] labs also utilized ring-closing metathesis to complete the cycle. Fuchs was the only one to employ the RCM after the keto-pyrrole unit was intact (Scheme 3).

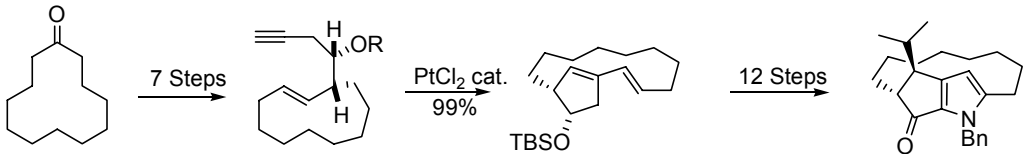
Scheme 3. Fuchs's RCM



Robertson's group[6i] achieved the macrocycle using a 13-*endo* radical cyclization in his formal synthesis. Terashima's formal synthesis[6f] included an intramolecular alkylation to the core. One thing in common to these synthetic methods are high dilution conditions, ranging from 0.005 M to 0.0005 M. For academic purposes, these methods of construction are acceptable, but on a large industrial scale these methods become problematic. High dilution and a large entropic barrier[7] make macrocyclization reactions[8] on roseophilin's core difficult.

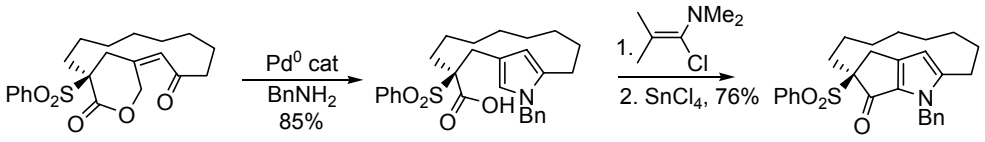
The Trost lab,[6g] to date, has been the only one to approach roseophilin's core without using macrocyclization reactions. They go through a ring contraction of cyclododecanone followed by elaboration of a fused bicycle using enyne metathesis, to obtain the core in 20 steps and less than 2% overall yield (Scheme 4).

Scheme 4. Trost's Approach



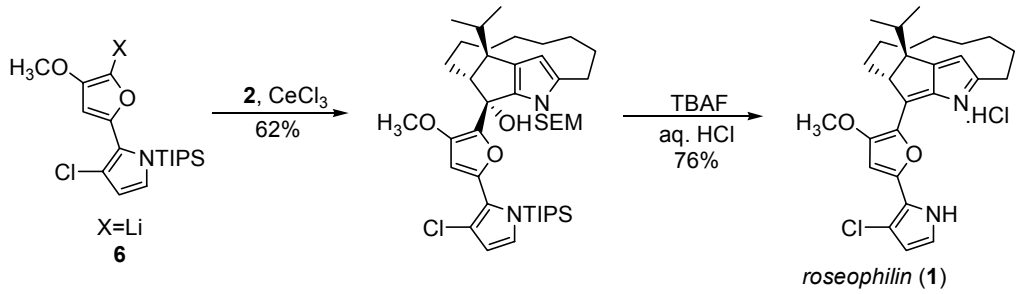
While construction of the macrocyle is a daunting challenge, formation of the keto-pyrrole is also no easy task. In earlier studies, it has been demonstrated that late-stage pyrrole condensation followed by Friedel-Crafts acylation can work. Fürstner exploited this synthetic sequence in his two syntheses[6a,b] using a three-step, two-pot procedure shown in Scheme 5.

Scheme 5. Fürstner's Keto-pyrrole



With the tricyclic core **2** in place, Fürstner developed and Tius refined the attachment of side chain **6** completing the total synthesis of roseophilin (Scheme 6).

Scheme 6. Pyrrolylfuran Coupling

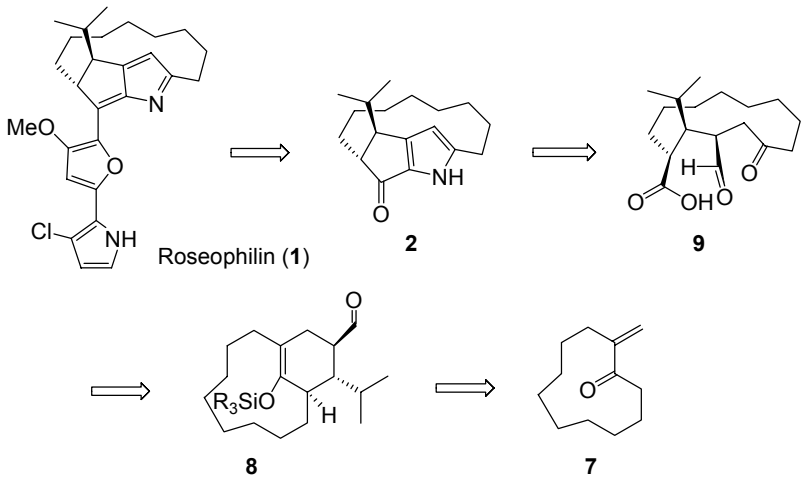


The considerable previous work relating to roseophilin and the prodigiosins provides a good foundation for our unique synthetic route. A large-scale, inexpensive synthesis of the *ansa*-bridged structure, roseophilin, should be attainable with improved strategies that require fewer operations and avoid entropically disfavored macrocyclization reactions. In particular, cleavage of the bridging bond in roseophilin, as a means to reveal the peripheral macrocycle, should be a way to avoid macrocyclization. Bond cleavage approaches are less common in the literature, rightly so, since they are less apparent, and more difficult to design than straight-forward synthetic strategies. Some transformations utilizing bond cleavage approaches include ozonolysis, Rubottom oxidation, Baeyer-Villiger, and Grob-type fragmentations.[9]

Retrosynthetic Analysis

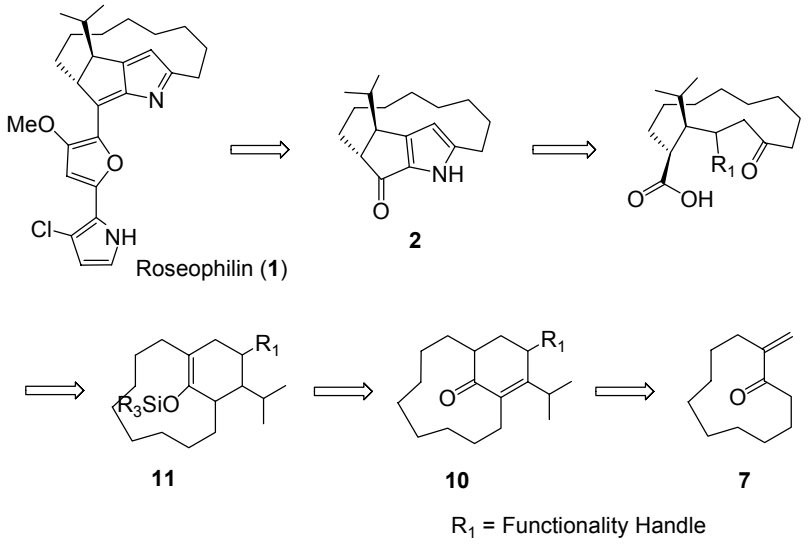
The retrosynthetic analysis to which we were initially attracted involves a stereo- and regio-selective Diels-Alder reaction and an oxidative ring cleavage to afford roseophilin's tricyclic core **2** (Scheme 7).

Scheme 7. Diels-Alder Approach



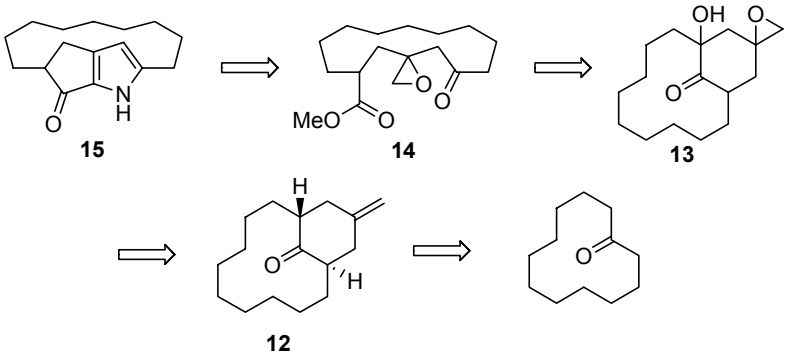
We anticipated that enone **7** could be converted to the *Z*-(O)-siloxy diene, that would set the stage for a key proposed Diels-Alder reaction with MacMillan's dieneophile.[10] Bicycloadduct **8** could then be treated with oxidative conditions (ozone) to afford the ring cleaved macrocycle **9**. Macrocycle **9** could then be converted to the core (**2**) by a Paal-Knorr pyrrole synthesis followed by a Friedel-Crafts acylation.

Scheme 8. Robinson-Annulation Approach



A variation on the same basic strategy relies on a sequence utilizing a Robinson-type annulation reaction[11] to install a functionalized six-membered ring (**10**) needed for our synthesis (Scheme 8). This annulation product could then be converted into bicycloadduct **11**, by reduction and formation of the silyl enol ether. From here out the Diels-Alder approach (Scheme 7) could be followed.

Scheme 9. Bis-allylation/Oxidative Ring Fragmentation Approach



A third, and final, approach we envisioned and completed to a model system **15** of roseophilin and analogs involves a bis-allylation protocol and an oxidative ring fragmentation with lead tetraacetate for key steps in the transformation to model system **15**. Cyclododecanone can be seen to provide exo-methylene bicycloadduct **12** via a bis-allylation palladium protocol, followed by oxidative manipulations (Rubottom oxidation, epoxidation) to provide α–hydroxy ketone **13.** This compound is set for an oxidative ring fragmentation using lead tetraacetate that concludes in macrocycle **14**. A modified Paal-Knorr pyrrole synthesis followed by a Friedel-Crafts acylation provided model tricyclic core **15**. This approach contests even the initial Diels-Alder approach in terms of potential efficiency for accessing analogous tricyclic systems of roseophilin.

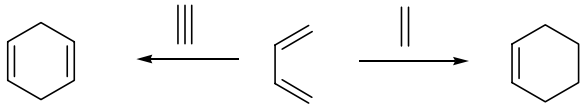
CHAPTER II

DIELS-ALDER APPROACH

Diels-Alder Reaction

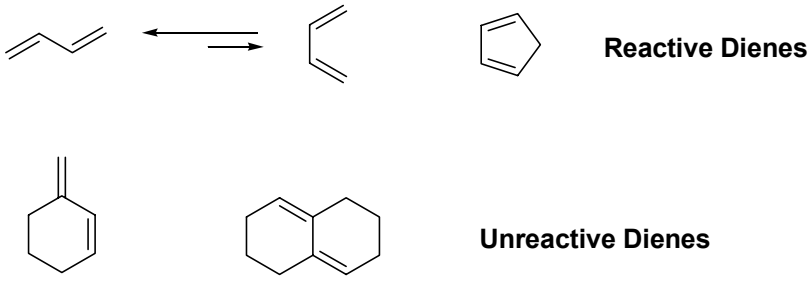
The Diels-Alder is widely used to construct, in a regio- and stereo-controlled way, a six membered ring with up to four stereogenic centers. Since its discovery in 1928,[12] more than 17,000 papers have been published concerning synthetic, mechanistic, and theoretical aspects of the reaction and more than half of these have appeared in the last decade. With the ability of forming carbon-carbon, carbon-heteroatom, and heteroatom-heteroatom bonds, the reaction is a versatile synthetic tool for constructing simple and complex molecules (Scheme 10).[13]

Scheme 10. Diels-Alder Reaction



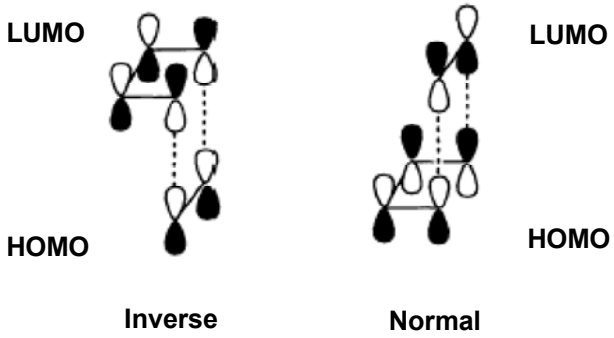
The reaction is classified as a $[{}_{\pi}4_{s} + {}_{\pi}2_{s}]$ cycloaddition; 4 and 2 identify both the number of π electrons involved in the electronic rearrangement and the number of atoms originating the unsaturated six-membered ring. The subscript *s* indicates that the reaction takes place suprafacially on both components. The reaction can be intermolecular or intramolecular and can be carried out under a variety of experimental conditions, such as Lewis acid promoted, thermal, high pressure, sonication, and different reaction media.[14]

Scheme 11. Diene Reactivity



Conjugated dienes may react providing that the two double bonds have or can assume a cisoid geometry. A transoid diene would give an energetically unfavorable six-membered ring having a trans double bond (Scheme 11). Cyclic dienes, in general, are more reactive than open chain ones. The electronic effects of the substituents in the diene influence the ratio of cycloaddition. Electron-donating groups on the diene and electron-withdrawing groups on the dienophile accelerate the reaction coined a normal electron-demand Diels-Alder reaction. The opposite scenario, having the electron-donating group on the dienophile and electron-accepting group on the diene, is termed inverse electron-demand Diels-Alder reaction.[15b]

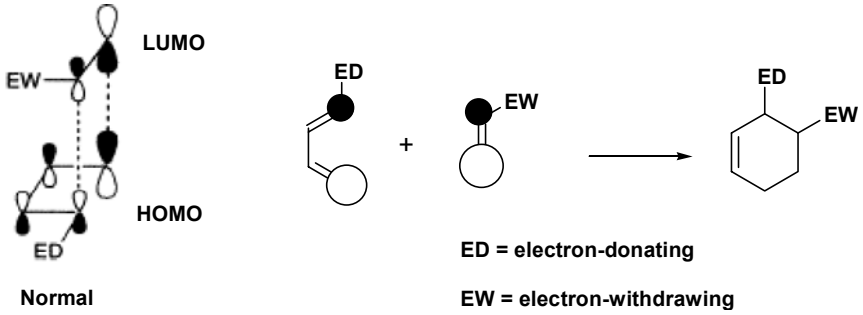
Scheme 12. FMO Theory[15c]



According to frontier molecular orbital (FMO) theory, the reactivity, regiochemistry and stereochemistry of the Diels-Alder reaction are controlled by the suprafacial in phase interaction of the highest occupied molecular orbital (HOMO) of one

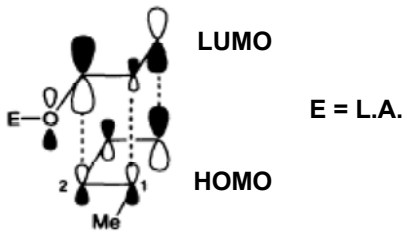
component and the lowest unoccupied molecular orbital (LUMO) of the other. These orbitals are the closest in energy; the two dominant orbital interactions of a symmetry allowed Diels-Alder cycloaddition (Scheme 12).[16] The *ortho-para* rule is explained by FMO theory. The regiochemistry is determined by the overlap of the orbitals that have larger coefficients. The greater the difference between the orbital coefficients of the two end atoms of the diene and two atoms of the dienophile, which form the two σ-bonds, the more regioselective the cycloaddition (Scheme 13).

Scheme 13. Regiochemistry[14]



The FMO theory explains the kinetically favored *endo* approach considering an additional nonbonding interaction. The larger the lobes are of interacting orbitals, the better is the overlap, the stronger is the interaction, and the more favored is the formation of *endo* adduct. Complexation with either a Lewis acid or protonation influences both the energy and coefficients of carbon atoms of the LUMO orbital (Scheme 14).[17] An increase in the carbon orbitals, causes the stability of the secondary orbital interaction to greatly increase, and therefore the *endo* addition is more favored.

Scheme 14. *Endo* Approach[14]

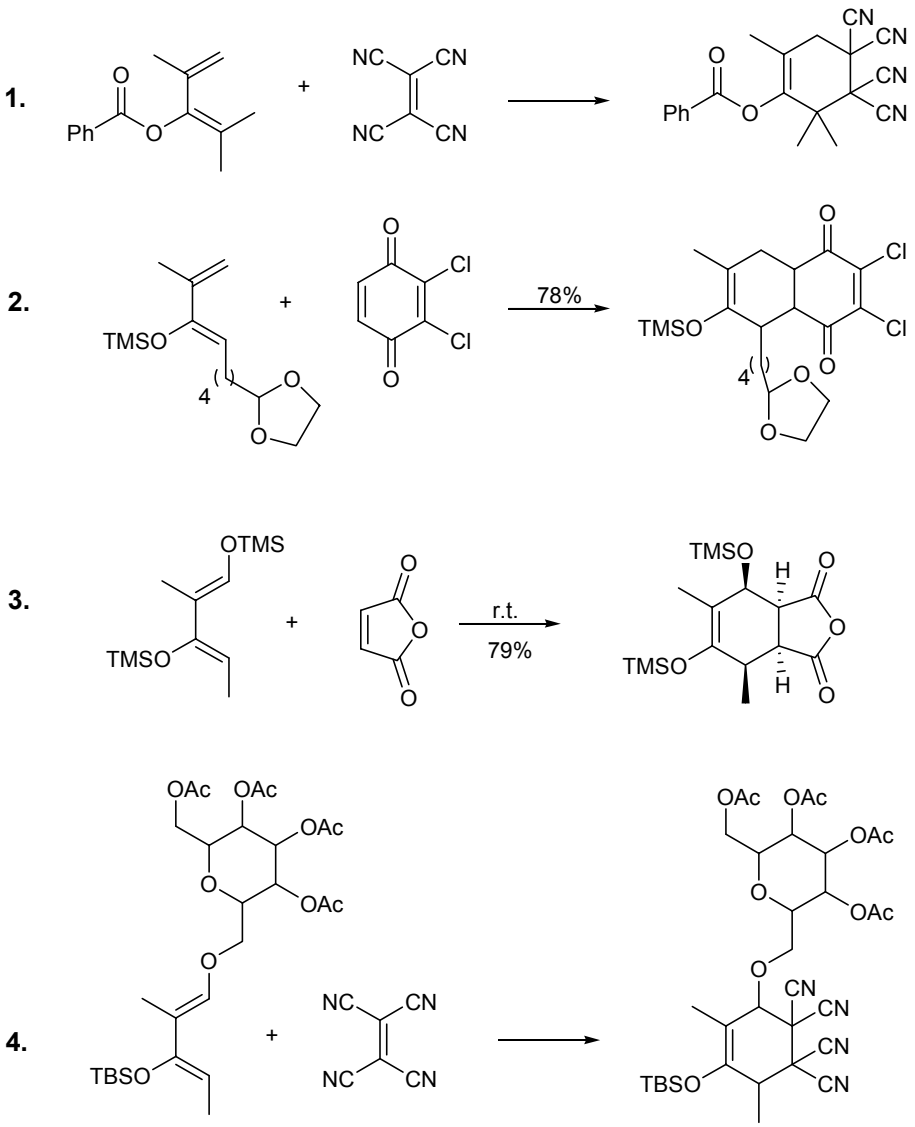


Piperylene and Acrolein

Relevant Diels-Alder Reactions

A current investigation into the ~17,000 publications that involve Diels-Alder reactions reveals that there are only four reported reactions that involve an acyclic diene with an oxygen substituent flanked by alkyl groups (Scheme 15).[18a,b,c,d]

Scheme 15. Acyclic Dienes[18a,b,c,d]

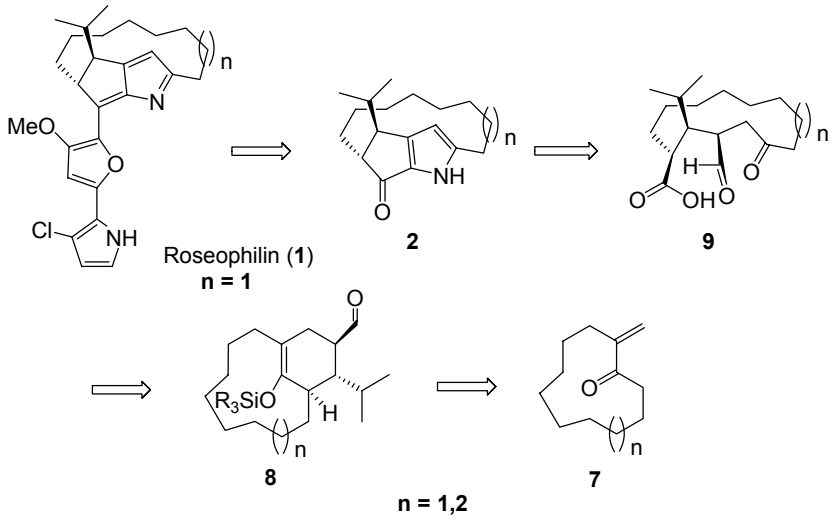


All examples in Scheme 15 utilize rather reactive dienophiles, while examples 3 and 4 also employ a second electron donating group on the diene for greater reactivity.

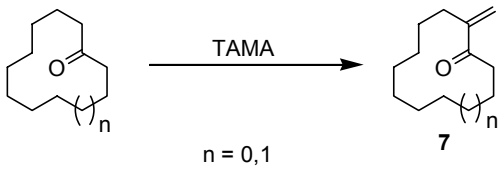
As proposed in our original Diels-Alder retrosynthesis an acyclic diene with an oxygen substituent flanked by a bridging macrocycle would be needed to complete the bicycloadduct (**8**), on the way to the core. Understanding that there are very few examples in the literature and that a bridged macrocycle would be involved made the Diels-Alder approach an initial challenge.

Results and Discussion

A review of the proposed Diels-Alder retrosynthesis:



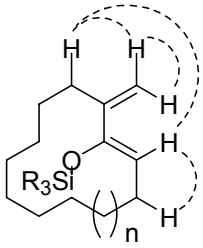
We chose to include cyclododecanone as well as cycloundecanone in our Diels-Alder studies due to the cost of starting materials. Cycloundecanone is $63 for 1 g, while cyclododecanone is $27 for 100g from Aldrich. Cycloundecanone can either be made from cyclododecanone in a three step procedure[19] or commercially purchased. Treating cycloundecanone or cyclododecanone with commercially available *N*-methylanilinium trifluoroacetate (TAMA)[20] using a literature procedure[21] produces enones **7** in good yield.



n = 0,1 **7**

Having enones **7** in hand set the stage for the formation of the silyl enol ethers (**16**). At the outset, we did not know what to expect with regard to the kinetic enolization of enones **7**. Acyclic dienes were known to afford the Z-(O)-enolate;[22] silylation of the Z-(O)-enolate to generate the E-diene would afford the highest probability of success in the Diels-Alder reactions. In fact, we did obtain siloxydienes **16** as single stereoisomers, which were assigned by an extensive NOE cross-peak analysis shown in Scheme 16. The NOE spectra are included in the supporting information section.

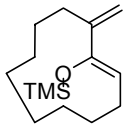
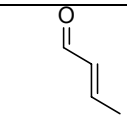
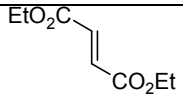
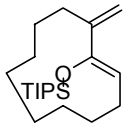
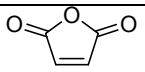
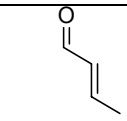
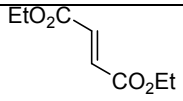
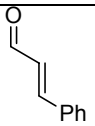
Scheme 16. NOE Cross-peaks



16 n = 0,1

We were unable to obtain encouraging preliminary results in our attempted cycloadditions of dienes **16** with a range of dieneophiles. A list of dienes and dienophiles attempted are shown in Table 1. All reactions resulted in recovery of starting materials, partial polymerization, or recovery of decomposed diene.

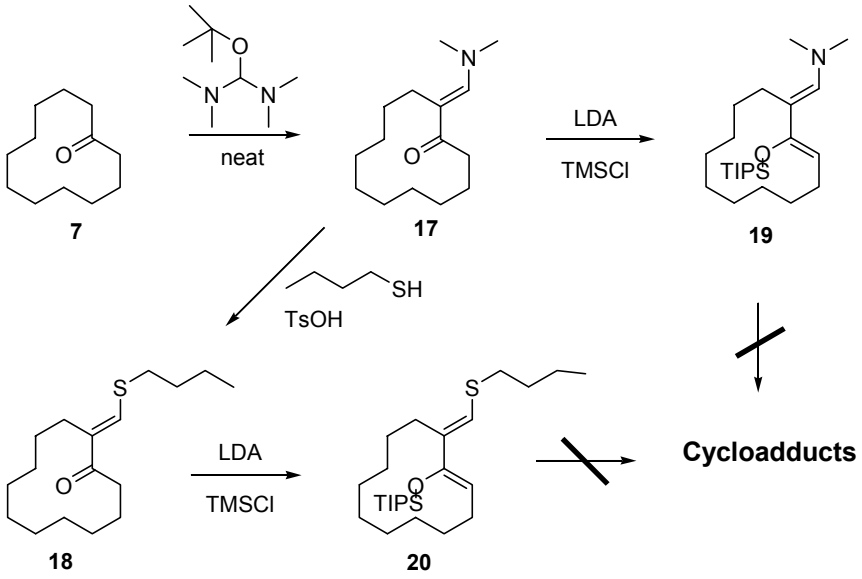
Table 1. Diels-Alder Attempts With Dienes 16

Failed Attempts At Cycloadducts		
Dienes (16)	Dienophile	Conditions
		Thermal & L.A.
		Thermal
		Thermal
		L.A. (multiple)
		Thermal
		Thermal

Having initially failed in the formation of a bicycloadduct for the key step; we sought after a way to make the diene more reactive to overcome this problem. One way to make the siloxydienes **16** more reactive would be to add an electron-donating group to the one-position of the diene. Taking cyclododecanone and treating it with tert-butoxybis(dimethylamino)methane neat afforded dimethylamino enone **17,**[23] which could then be converted to the dimethylamino siloxydiene **19**. Dimethylamino enone **17** could also be transformed into the more stable white crystalline butyl thiane enone **18** in good yield. Treating enone **18** with the same LDA conditions as previous, produced butyl thiane siloxydiene **20** (Scheme 17) as a single stereoisomer, which we assumed to be the *E*-diene by analogy to our previous studies. Having a large quantity of these two substituted dienes (**19,20**), another set of Diels-Alder reactions were attempted with a set of dieneophiles. Attempted cycloadditions with dienes **19,20** were unsuccessful resulting

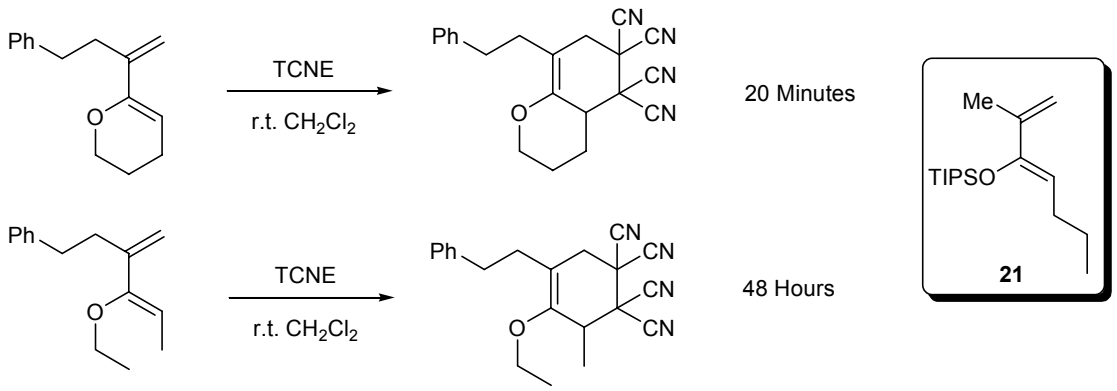
in recovery or decomposition of starting material. Since this approach also added extra steps to the synthetic sequence, it was abandoned before we investigated it fully.

Scheme 17. Substituted Acyclic Dienes



While conducting these experiments and seeing the lack of reactivity of the proposed dienes, we started to formulate a hypothesis. The first major problem that we believe is difficult to overcome is $A_{1,3}$ strain. The two alkyl groups that flank the siloxy oxygen may be so strained that the siloxy oxygen is being pushed out of the orbital overlap with the diene, and essentially deactivating the diene. This issue is currently being further investigated in our lab and the preliminary results are shown in Scheme 18.[24]

Scheme 18. Current $A_{1,3}$ Strain Investigation



Similar acyclic dienes, such as **21** shown in Scheme 18, were investigated for a model system of roseophilin's Diels-Alder. Results were unsuccessful and inconclusive as shown in the experimental section. To get back to the roseophilin system, another challenging factor that cannot be overlooked is the bridging macrocycle. The most stable conformer of the marcocyclic diene may adopt a *s*-trans conformation, with limited flexibility to the needed *s*-cis conformation. It is seen in the NOE analysis (Scheme 16) that the vinyl protons on carbons 2 and 4 do not enhance each other. This leads to the notion that the vinyl protons are essentially perpendicular with respect to each other, putting the diene in a dihedral angle far from coplanar.

These two factors ($A_{1,3}$ strain, and coplanarity) along with the limited stability of the diene systems made us, for the meantime, pursue alternative routes to the core of roseophilin. There are multiple ways of forming six-membered rings, and two of them were invested further in the roseophilin system, described in the next two chapters.

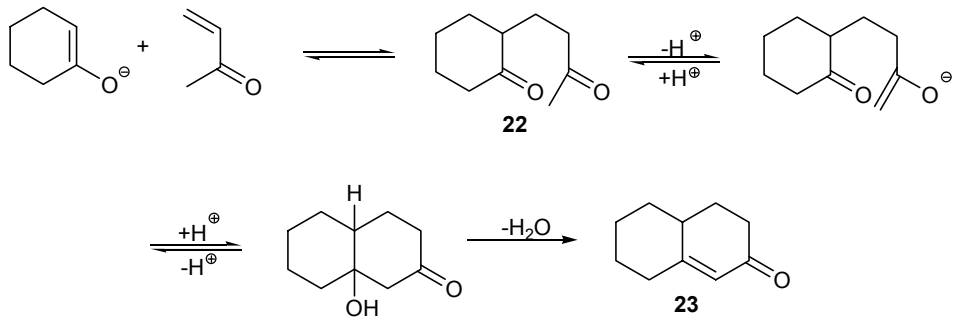
CHAPTER III

ROBINSON-ANNULATION APPROACH

Robinson-Annulation Reaction

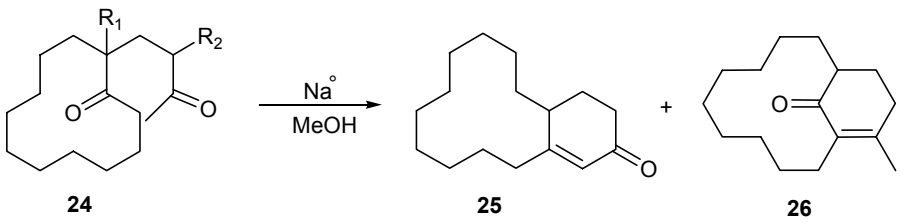
The Robinson-annulation since its discovery in 1935[11] has been a widely used synthetic tool for construction of cyclohexenone systems. The original procedure involved a nucleophilic attack of a ketone or ketoester enolate, in a Michael reaction, on a vinyl ketone to produce the intermediate Michael adduct **22**. Subsequent aldol-type ring closure to the keto-alcohol, followed by dehydration, produced the annulation cyclohexenone product **23** (Scheme 19).[25]

Scheme 19. Robinson-Annulation



Michael adduct **22** can enolize on two separate ketones, allowing for aldol condensation and dehydration to give two different cyclohexenone systems. Studies conducted by Buchanan have shown that the bridged ketones are the product of kinetic control, while the fused enones are the thermodynamically more stable products.[26] With medium sized rings (8 to 12 membered), the steric environment of the intermediate ketols have an important effect on the outcome of the cyclization. In our system (12-membered) it is conceivable to achieve two possible cyclization products (Scheme 20).

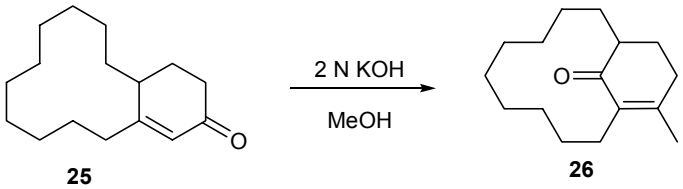
Scheme 20. Possible Robinson-Annulation Products



24 **25** **26**

Cyclohexenone **26** is exclusively formed under basic annulation conditions, due to the difference in *I*-strain[27a] of the fused ketols. All the atoms of the original cycloalkanone ring become sp^3-hybridized during the fused ketol formation leading to **25**, thus increasing the *I*-strain; in contrast, during formation of **26** at least one sp^2-hybridized atom is maintained throughout the reaction and consequently the latter less sterically hindered mode will be the preferred method of cyclization.[27b] In addition, models have shown that the favored 'O-inside' conformation of cyclododecanone will also promote bicyclic ketol formation.[28]

Scheme 21. Enone Conversion



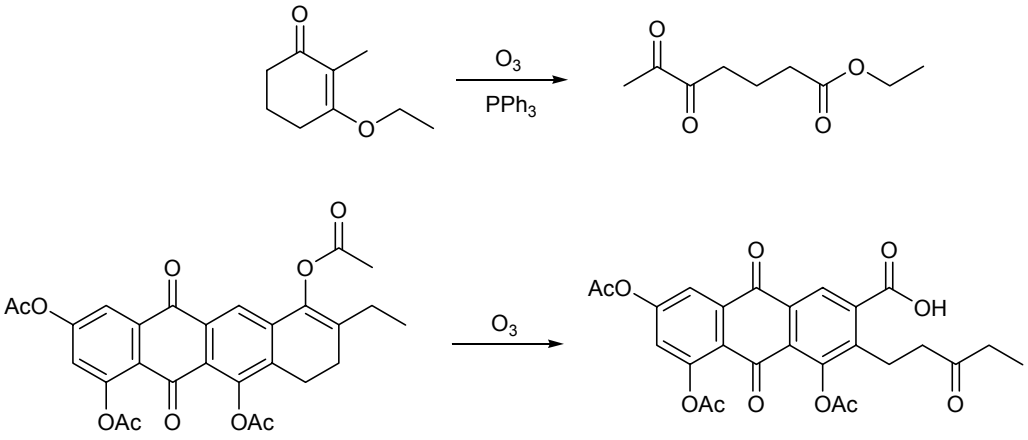
25 **26**

Interestingly, under more vigorous alkaline conditions, it is possible to isomerize the fused enone **25** to the bridged enone **26** (Scheme 21). In the cyclododecane series, the bridged enone appears to be more stable than the fused enone, in complete contrast to the cyclohexane analogues.

Relevant Ozonolysis Reactions

After completion of the bicyclic system **26** and manipulation to a silyl enol ether, the stage will be set to test the key oxidative ring fragmentation using ozone. Two relevant oxidative ring fragmentations using ozone are illustrated in Scheme 22.[29]

Scheme 22. Ozonolysis



The Robinson-type annulation coupled with an oxidative ring fragmentation should be a designed route to get to the core of roseophilin and analogs. The progress obtained using these envisioned schemes are described below.

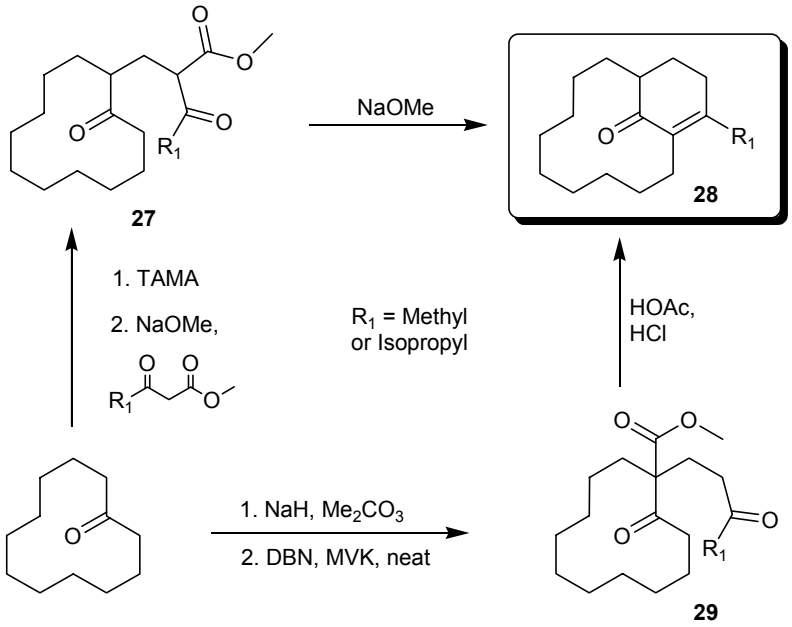
Results and Discussion

Again, like in the Diels-Alder studies, cyclododecanone was used in lieu of cycloundecanone for starting material due to the cost difference. We developed two routes that allowed us to obtain good quantities of the bicyclohexenone adduct **28**.

The first started with formation of 2-methylene cyclododecanone **7** from cyclododecanone followed by Michael addition with methyl isobutyryacetate to give the Robinson-annulation precursor **27**. Treatment of **27** with sodium methoxide provided bicylohexenone **28** in good overall yield. Attempts to prevent decarboxylation using less harsh conditions were unsuccessful. All resulted in either decarboxylation or no

cyclization. The second approach to bicyclohexenone **28** was developed by starting with cyclododecanone and acylating with dimethylcarbonate using sodium hydride. A subsequent alkylation with methyl vinyl ketone using DBN provided the Robinson-annulation precursor **29** in good overall yield. Similar to **27**, precursor **29** when treated with acetic acid and hydrochloric acid provided bicyclohexenone **28** upon decarboxylation (Scheme 23). We concluded that decarboxylation must occur first before cyclization can occur.

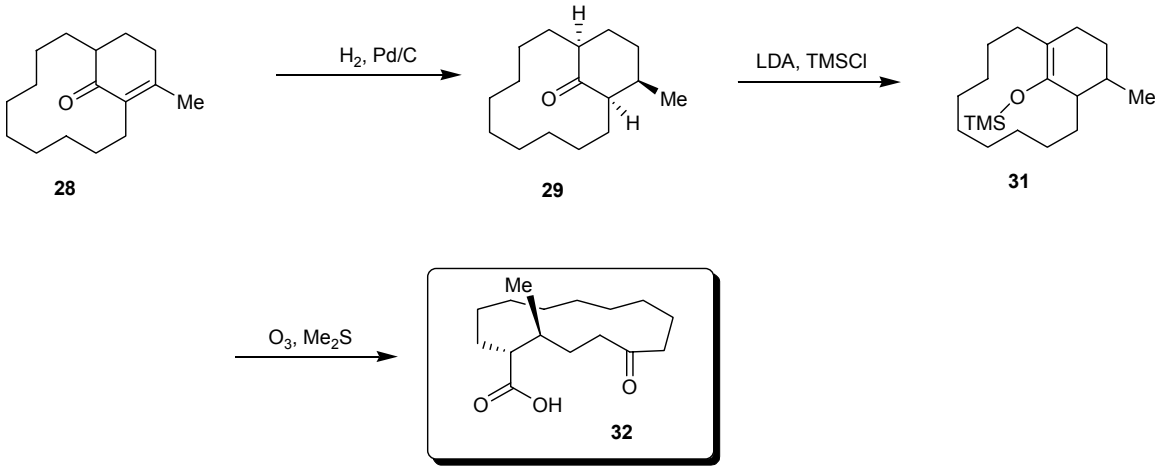
Scheme 23. Bicyclohexenone System



Catalytic hydrogenation of bicyclohexenone **28** (R_1 = Me) proceeded smoothly using 5% Pd/C under 1 atm of hydrogen gas to afford two stereoisomers of methyl bicyclohexanone **30** in good yield in the ratio of 13:87 as deduced from the methyl NMR signal (Scheme 24). The spectrum indicates that both protons α to the carbonyl group are axial, leading to about equally large couplings in the 2.71 ppm signal (J = 12 Hz) and only one in the 2.90 ppm signal (J = 11.4 Hz). One large coupling involves a proton in each of the two methylene groups in the 12-membered ring α to the ring junction with which the torsion angle approaches 180 degrees. The methyl group must also be axial and all substituents are cis in the major product **29**, while the minor product is a

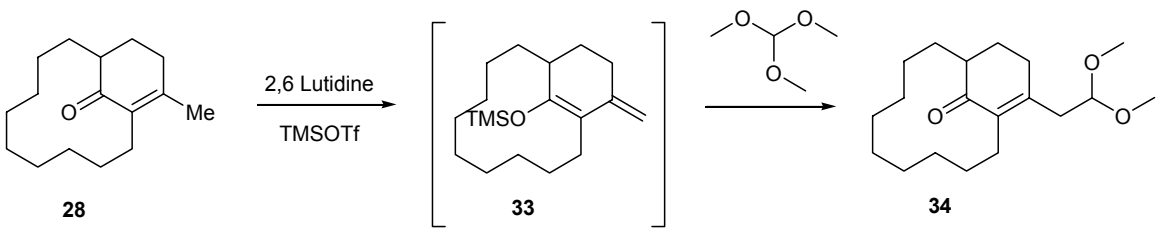
stereoisomer.[27] Treatment of **30** with LDA and trapping with TMSCl afforded silyl enol ether **31** selectively. We speculate that the α-proton closest to the β-methyl group is less acidic than the other α-proton to the carbonyl due to $A_{1,2}$ strain that would develop during enolization. Having silyl enol ether **31**, the stage was now set to test our key oxidative cleavage, which proceeded nicely by treating **31** in a methylene chloride/methanol mixture under ozone for 15 minutes at -78°C to afford keto-ester **32**.

Scheme 24. Keto-Ester Formation



To progress further in the roseophilin model system a handle functionality is needed at the γ-carbon to the ketone. Once functionality is obtained there a pyrrole synthesis followed by Friedel-Crafts acylation can be tested properly. Bicyclohexenone **28** was a place in which we believed functionality could be installed via γ-alkylation with little change to the subsequently developed reactions. The only γ-alkylation of **28** we were able to observe was when **28** was initially treated with 2,6-lutidine and TMSOTf, followed by one-pot alkylation with trimethyl orthoformate to give undesired exocyclic γ-alkylated acetal **34** in excellent yield. The observed product is obtained by a through-conjugated ("thermodynamic") exocyclic isomer **33**.

Scheme 25. γ-Alkylation



Other procedures were attempted to obtain the desired endocyclic isomer over the other two possible regioisomeric dienolates; all of which were unsuccessful. Methods attempted were: DBU and TMSCl (recovery of starting material); *t*-BuOK and TMSCl (< 5% desired enolate); NEt_3, Fe(0), HMPA, and TMSCl (recovery of starting material);[30] and NEt_3/TMSCl (recovery of starting material).

Since γ-alkylation was unsuccessful, another approach to a model system of roseophilin was pursued, and is described in the subsequent chapter. The Robinson-related approach did indicate to us that an addition-cyclization-oxidative cleavage sequence is achievable for the desired roseophilin system and models.

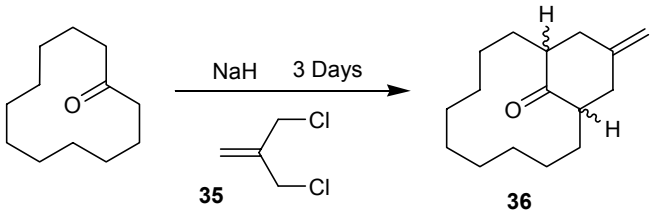
CHAPTER IV

BIS-ALLYLATION/OXIDATIVE RING FRAGMENTATION APPROACH

Bis-Allylation Reaction

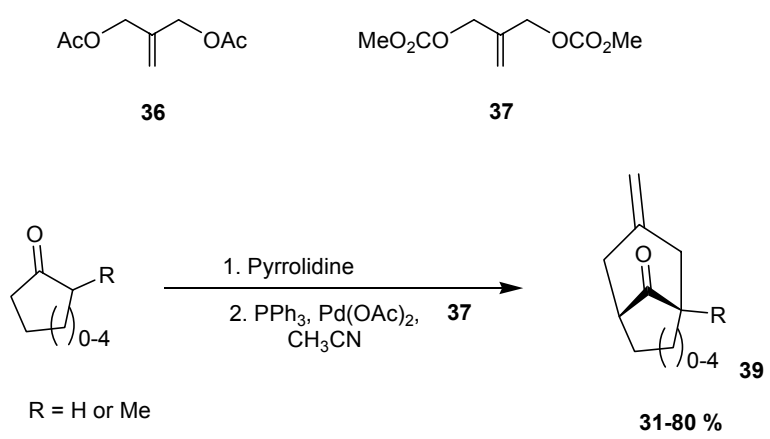
Currently in the literature, methods for forming bicyclo[9.3.1]pentadecanone systems are very limited. Hiyama[31] in the 1970's developed a bis-allylation method using cyclododecanone and 3-chloro-2-chloromethylpropene **35** to afford the exo-methylene ketone **36**. There are many limitations to this reaction, including an irreproducible yield of 34%, a long reaction time of 3 days at reflux, and isolation of a liquid mixture of the cis/trans isomers.

Scheme 26. Hiyama's Bis-Allylation



A second, interesting bicycloannulation of cyclic ketones, which used an enamine as a nucleophile in a π–allylpalladium reaction was first reported by Lu in 1988.[32] The reaction involved a sequential inter- and intramolecular *C,C*-dialkylation and afforded bicyclo[3.n.1]alkanones (n = 3,2) in fairly good yields (Scheme 27). This reaction was refined by Buono in 2000,[33] to increase the size of the bicycloalkanones **39**, lower the reaction temperature, and increase the yields. These improvements were obtained primarily by switching from diacetate **36** to dicarbonate **37,**[34] and changing to acetonitrile for a solvent. The improved results are summarized in Scheme 27.

Scheme 27. Buono's Improvements

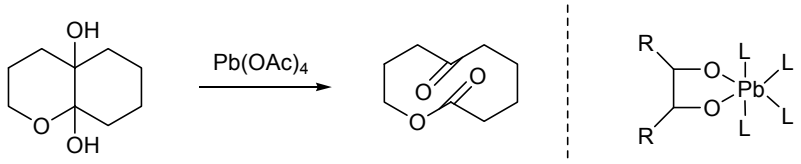


All bicycloannulation reactions resulted in the formation of the *cis*-fused system with moderate to good yields. The bicycloalkanones were obtained in yields that decreased when the ring size increased, while the largest attempted, the basic AB ring system of the taxoids (bicyclo[5.3.1]alkanone) resulted in 31 % yield. We desired a much larger ring system, a bicyclo[9.3.1]alkanone, and we speculated that yields would rebound and improve as the ring size grew beyond the range explored by Buono.

Oxidative Cleavage using $Pb(OAc)_4$

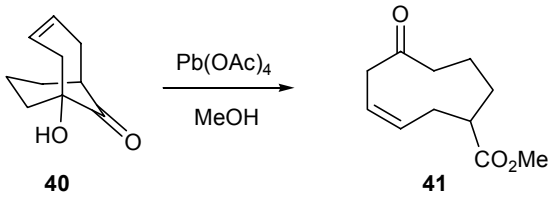
One of the first examples of lead tetraacetate being used as an oxidative cleavage is with a bicyclic diol system (Scheme 28).[35] A cyclic intermediate is suggested for the mechanism by the same kind of stereochemistry-reactivity relationships as for sodium periodate.[36] Unlike periodate, lead tetraacetate can eventually oxidize glycols that cannot form cyclic intermediates. A cyclic transition state appears to be the lowest-energy pathway, although it is not the only possible mechanism.

Scheme 28. $Pb(OAc)_4$ Cleavage



Oxidative cleavage with lead tetraactetate has been modified over the years to also include cleavage of α-hydroxy ketones in an alcohol medium. A recent example of this transformation is shown in Scheme 29. Mascarenas was able to oxidatively cleave the bridge of bicycle **40** to give the desired cyclooctanenone **41** instantaneously in a satisfactory yield of 84 %.[37]

Scheme 29. Cleavage of a α-Hydroxy Ketone

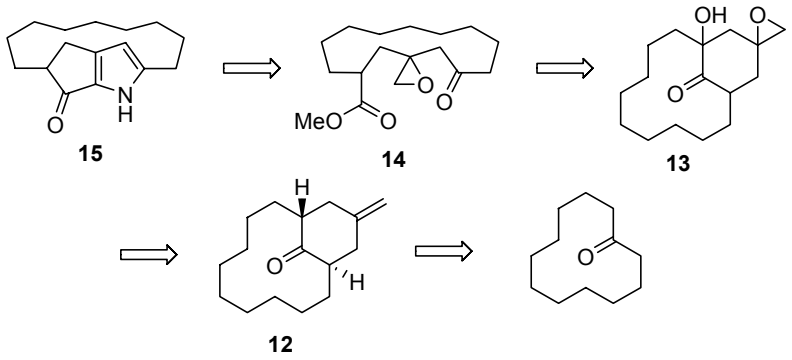


40 **41**

Having strong precedent and straightforward chemistry should allow for this designed route to be efficiently completed for a model system of roseophilin and analogs as well. The bis-allylation coupled with oxidative ring fragmentation is a creative way of obtaining a macrocycle without using a high dilution macrocyclization reaction.

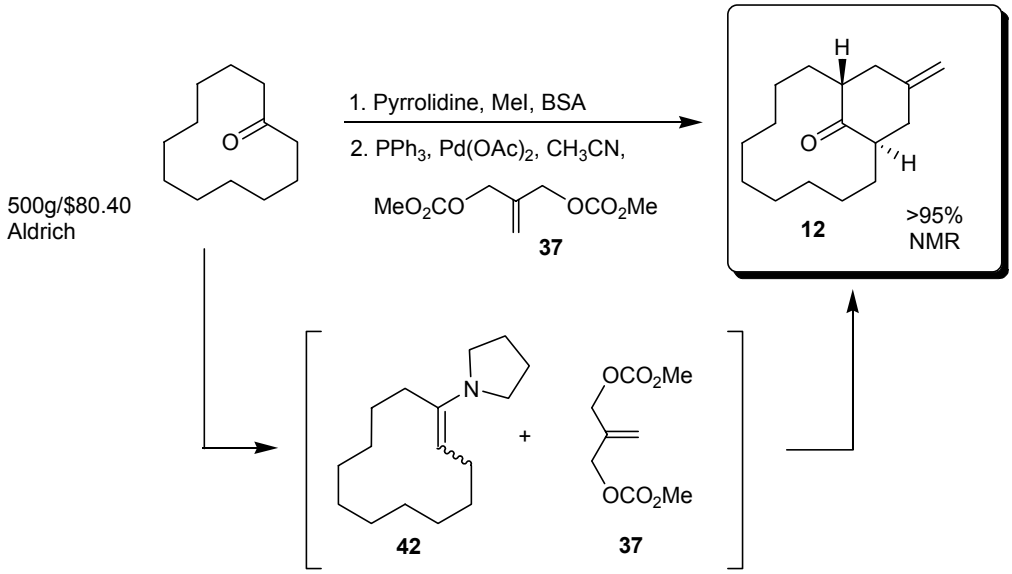
Results and Discussion

A review of the proposed retrosynthesis:



Model system **15** was the initial target compound for a model study of roseophilin. For this investigation, again, we chose to employ cyclododecanone in lieu of cycloundecanone due to cost. This material ultimately provided a homologated analog of roseophilin.

Scheme 30. Bis-Allylation Reaction

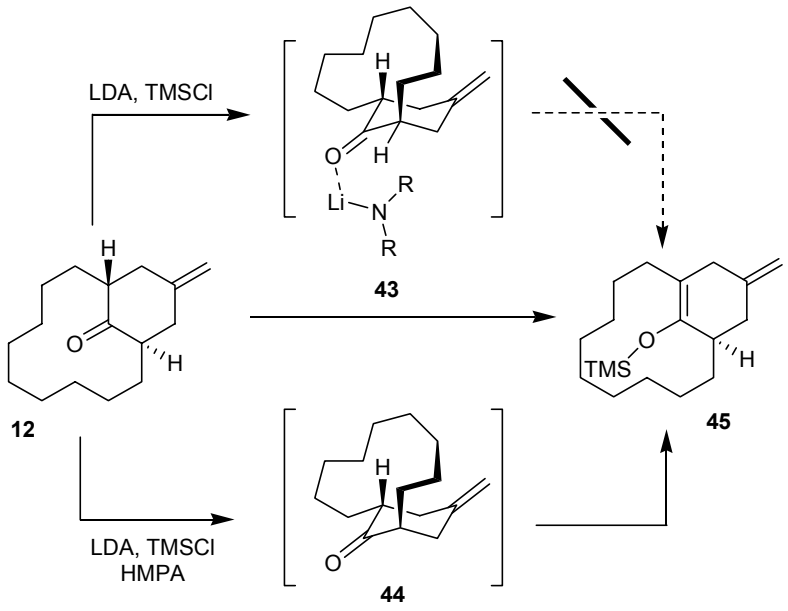


We assembled the requisite bridged bicycle **12**, albeit without the isopropyl substituent, using Buono's enamine bis-allylation protocol.[33] The crude enamine[38] **42** was

formed using pyrrolidine, bis(trimethylsilyl)acetamide, and methyl iodide and reacted with dicarbonate **37** under π-allylpalladium conditions to yield the bicycle **12** (Scheme 30). Interestingly, unlike in all of Buono's systems, the in/out[39] (trans) stereoisomer is obtained almost exclusively. Bicycle **12** can either be purified by chromatography or recrystallized from MeOH, but simple aqueous workup provides material of sufficient purity (>95% NMR) for subsequent reactions. This palladium-catalyzed annulation provides significantly improved access to crystalline **12**, which was obtained previously in a low yield of 34 % as an oily mixture of cis and trans isomers.[31]

Bicycle **12** comprises the full complement of carbon atoms needed for model system **15**, so we now focused on the oxidative manipulations needed to access a more suitable keto-pyrrole precursor.

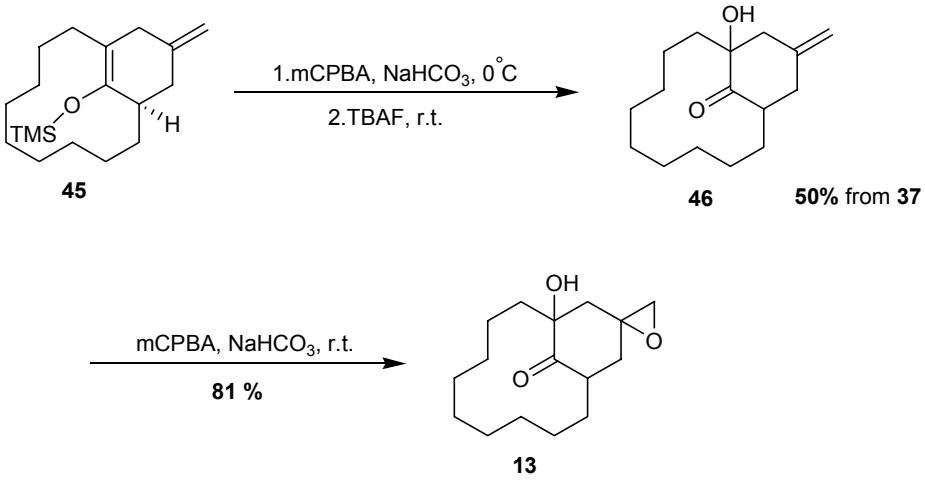
Scheme 31. Closed Vs. Open Transition State



Our initial attempts at forming silyl enol ether **45** were frustrated by poor reactivity of the *ansa*-bridged cyclohexanone (**12**) towards LDA. We assume that at least one of the α-hydrogens occupies an axial position and is electronically activated by the carbonyl, and so we hypothesize that steric congestion is responsible for this sluggish reactivity. Considering a potential closed transition state for deprotonation[40] (**43**), perhaps

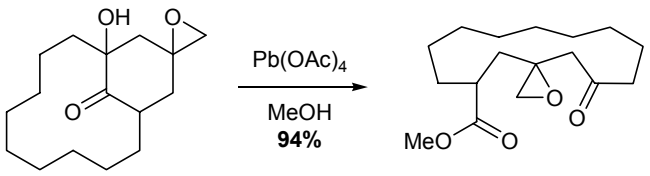
LDA coordinates selectively to the less hindered lone pair of the ketone carbonyl, which happens to be the side of the non-acidic equatorial hydrogen. Addition of HMPA is believed to disrupt the closed transition state leading to **44**, and enolization with LDA in the presence of HMPA proceeded efficiently, giving silyl enol ether **45** in good yield upon trapping with TMSCl (Scheme 31).

Scheme 32. Rubottom Oxidation



Rubottom oxidation[41] of **45** provided α-hydroxy ketone **46** after fluoride workup, which was subsequently epoxidized. Although a one-pot bis-epoxidation using excess *m*CPBA afforded **13**, the two-step approach provided higher yields of **13** with easier purification on a larger scale (Scheme 32). Also the epoxidations were diastereoselective following this route. Although we made no effort to assign the relative stereochemistry of **13**, since it is lost in the pyrrole formation, for a procedural matter it was convenient to be working with a single diastereomer.

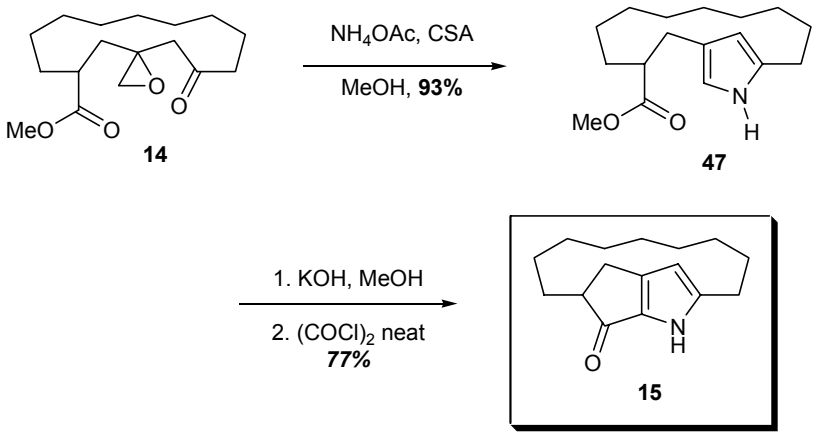
Scheme 33. Key $Pb(OAc)_4$ Fragmentation



13 **14**

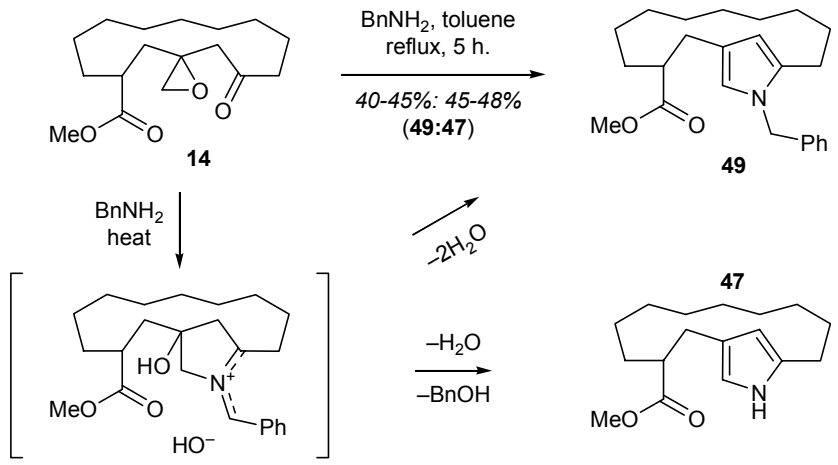
Oxidative cleavage using lead tetraacetate in MeOH at room temperature afforded keto-ester **14** in 94% yield (Scheme 33). This is the key step from a strategic standpoint, and it reduces to practice in a highly satisfactory manner.

Scheme 34. Model System Core



With the epoxidized keto-ester (**14**) in hand, the final stages of the model study required crafting the keto-pyrrole unit. The epoxide of **14** serves as an aldehyde equivalent for the pyrrole condensation. Treatment of **14** with ammonium acetate under Paal-Knorr conditions afforded **47** in high yield. Saponification of the methyl ester and intramolecular Friedel-Crafts acylation completed the assembly of keto-pyrrole **15** (Scheme 34). Note that cyclization (to **15**) occured spontaneously under conditions intended to convert **47** into the corresponding acid chloride. Tricyclic core **15** is an unstable compound in which characterization was conducted on the crude material.

Scheme 35. Debenzylation



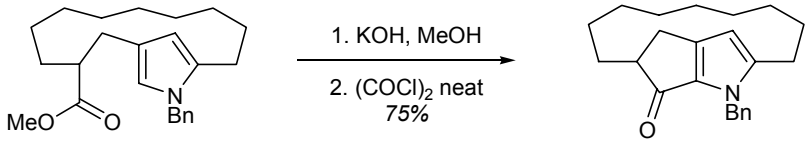
Considering the instability of compound **15** a benzyl-protected pyrrole was expected to be more stable and was therefore synthesized. Taking epoxy keto-ester **14** and treating it with excess benzyl amine, molecular sieves, in toluene at reflux for 5 hours afforded a mixture of two products (Scheme 35). Interestingly, we obtain about a 50:50 ratio of the desired benzyl pyrrole **49** and the debenzylated pyrrole **47**. A proposed mechanism for the debenzylation is shown in Scheme 36. Other reaction conditions were attempted to avoid debenzylation and are in Table 2.

Table 2. Pyrrole Formation

Formation of Benzyl Pyrrole **49** Vs. Debenzylated Pyrrole **47**			
	Crude Ratios (%)		
Conditions	**Pyrrole, 49**	**Pyrrole, 47**	**Unknown Biproducts**
1.1 eq $BnNH_2$, Tol, reflux, 12 hr	25	75	0
2.2 eq $BnNH_2$, Tol, M.S., reflux, 5 hr	60	40	0
$BnNH_2$, neat, 80C, 6 hr	Minor	0	Major
2.2 eq $BnNH_2$, PhH, CSA, r.t., 3 hr	0	>95	0
2.2 eq Bn_2NH, Tol, reflux, 5 hr	0	>95	0

Since we were unable to optimize the reaction conditions for the formation of the benzyl pyrrole, we then attempted benzylating pyrrole **47**. Taking the reaction mixure from entry 1 of Table 2, (75:25 of **47:49**) and treating it with benzyl bromide, tetrabutylammonium bromide, and sodium hydroxide at reflux provided only pyrrole **47**. This was a very interesting reaction, in which, using known benzylating conditions, we were able to debenzylate the pyrrole **49**.

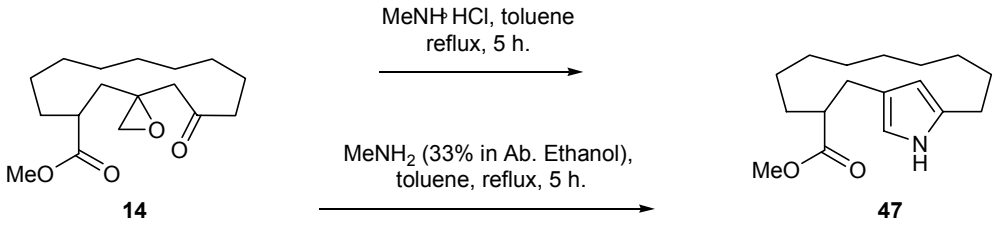
Scheme 36. Tricyclic Benzylated Core



49 **53**

To finish the tricyclic benzylated core **53**, benzyl pyrrole **49** was carried through using the same procedure as the free amine pyrrole **47** to obtain the core (**53**) in good yield. Unfortunately, compound **53** was as unstable as tricyclic core **15**, in which characterization was needed to be conducted on the crude material.

Scheme 37. Methyl Amine Reactions



14 **47**

One last effort was attempted to make a more stable derivative of **15**, in which the pyrrole formation was carried out using methyl amine. Two experiments were conducted; one using methyl amine in absolute ethanol solution, and the other using a hydrochoric

methyl amine salt in toluene, with both resulting in the same only isolable demethylated product **47** (Scheme 37).

Conclusions

With this model study complete, we lay the groundwork for an eventual synthesis of roseophilin, its enantiomer, and a diverse set of analogs. It may be possible to derivatize **15** with the requisite isopropyl group, but our lab is currently interested in revisiting the Diels–Alder reaction and introducing the isopropyl group at an earlier stage.

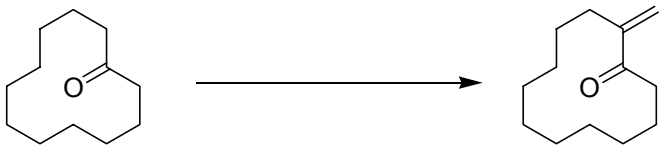
In conclusion, the synthesis of keto-pyrrole **15** described herein provides insight necessary to the development of our ring expansion approach to keto-pyrrole **2**. By avoiding macrocyclization reactions, the stage is set to facilitate large-scale production of synthetic roseophilin and analogs.

CHAPTER V

EXPERIMENTAL

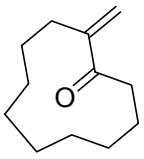
All the ^{1}H and ^{13}C NMR spectra were recorded on a Mercury Varian 300 MHz or Inova Varian 500 MHz spectrometer using $CDCl_3$ as the deuterated solvent unless otherwise stated. The chemical shifts (δ) are reported in parts per million (ppm) relative to the chloroform peak (7.26 ppm for ^{1}H NMR, 77.0 ppm for ^{13}C NMR). The IR spectra were recorded on a Perkin Elmer Paragon 1000 FTIR spectrometer on NaCl discs. Low and high-resolution mass spectra were performed on a JEOL JMS600 apparatus. The melting points were determined on a Köfler melting point apparatus and are uncorrected. Yields refer to isolated material judged to be > 95% pure by ^{1}H NMR spectroscopy following silica gel chromatography, recrystallization, or other purification method.

General Procedures. All reactions were performed in oven-dried glassware with magnetic stirring. All the chemicals were purchased from Aldrich or Acros and were used as received unless otherwise stated. Diethyl ether, THF, toluene, and dichloromethane were dried through a solvent purification system packed with alumina and molecular sieves. The purifications of the compounds were performed on flash chromatography using silica gel F-254 (230-400 mesh particle size).

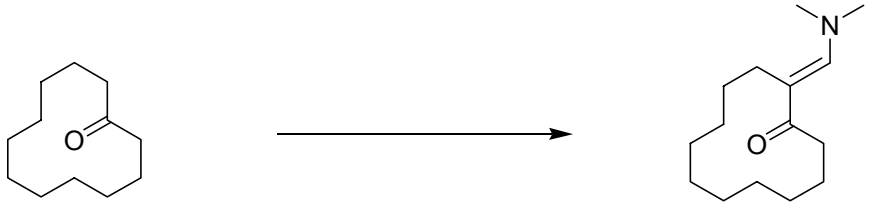


2-Methylene cyclododecanone 7a. A 100-mL, one-neck, round-bottom flask equipped with a condenser under argon was charged with cyclododecanone (5.67 g, 31.1 mmol), N-methylanilinium trifluoroacetate (TAMA[20], 11.0 g, 49.7 mmol), paraformaldehyde (3.94 mg, 13.7 mmol), and dioxane (20 mL). The reaction mixture was

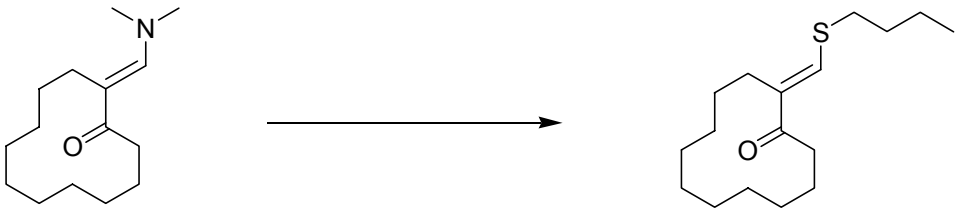
brought to reflux for 4 hr. After bringing to room temperature the mixture was extracted with diethyl ether (2 x 50 mL), the organic layers were combined and washed with water (2 x 40 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography on 100 g of silica gel (elution with hexanes to 10% ethyl acetate in hexanes) provided 6.0 g (99%) of **7a** as a liquid. Characterization matched that reported in the literature;[21] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (s, 1 H), 5.68 (s, 1 H), 2.70 (m, 2H), 2.39 (m, 2 H), 1.76 (m, 2 H), 1.43-1.17 (m, 14 H).



2-Methylene cycloundecanone[42] **7b** was prepared in a similar fashion from cycloundecanone[43]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (s, 1 H), 5.66 (s, 1 H), 2.60 (m, 2 H), 2.32 (m, 2 H), 1.80 (m, 2 H), 1.58-0.93 (m, 12 H).

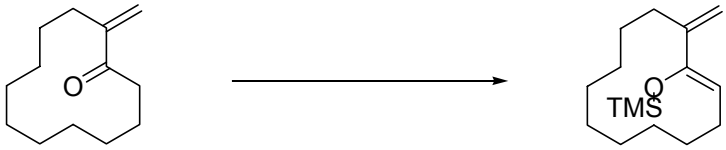


Dimethylamine enone 17. A 10-mL, one-neck, round-bottomed flask was equipped with a septum pierced with an argon inlet needle was charged with cyclododecanone (652 mg, 3.57 mmol) and *tert*-butoxybis(dimethylamino)methane (0.775 mL, 3.75 mmol). The reaction mixture was brought to 55°C for 24 hr, then brought to room temperature and concentrated under reduced pressure to give 810 mg (95%) of **17** as a liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (s, 1 H), 3.05 (s, 6 H), 2.61-2.42 (m, 4 H), 1.63 (m, 2 H), 1.29 (m, 14 H). This data is in accordance with the literature.[23]

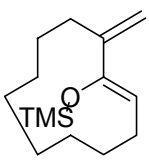


Butylthiane enone 18. A 25-mL, one-neck, round-bottom flask was equipped with a dean-stark trap, a condenser, and a rubber septum pierced with an argon inlet

needle was charged with dimethylamino enone **17** (200mg, 0.838 mmol), butanethiol (5.0 mL), TsOH (10 mg), and benzene (5 mL). The reaction mixture was brought to reflux 16 hr. After reaching room temperature the reaction was diluted with diethyl ether (10 mL), washed with $NaHCO_3$ (5 mL) and brine (5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography on 2 g of silica gel (elution with 5-10% ethyl acetate hexanes) provided 151 mg (75%) of **18** as a white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (s, 1 H), 2.83 (t, J = 7.38 Hz, 2 H), 2.65 (m, 2 H), 2.43 (m, 2 H), 1.68 (m, 4 H), 1.46 (m, 4 H), 1.40-1.12 (m, 12 H), 0.93 (t, J = 7.38 Hz, 3 H).

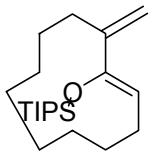


Trimethylsilyl cyclododecanyloxydiene 16a. A 25-mL, one-neck, round-bottom flask equipped with a rubber septum pierced with an argon inlet needle was charged with diisopropylamine (0.36 mL, 2.6 mmol) in THF (10 mL) at -78°C. After dropwise addition of BuLi (1.1M, 2.4 mL, 2.6 mmol), the mixture was stirred for 30 minutes at -78°C. A solution of 2-methylenecyclododecanone[21a] **7a** (200 mg, 1.03 mmol) in THF (5 mL) was added dropwise, stirred for 5 minutes at -78°C, and then TMSCl (0.43 mL, 3.4 mmol) was added. The reaction mixture was stirred for 1 hr at -78°C, quenched with $NaHCO_3$ (10 mL), and brought to room temperature. The organic layer was separated, and the aqueous layer extracted with ethyl acetate (3 x 7 mL). The organic layers were combined, washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography on 6 g of silica gel (elution with hexanes) provided 201 mg (73%) of **16a** as a clear colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (m, 2 H), 4.78 (s, 1 H), 2.20 (t, J = 6.71 Hz, 2 H), 2.09 (m, 2 H), 1.57-1.21 (m, 14 H), 0.17 (s, 9 H).

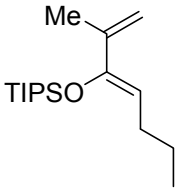


Trimethylsilyl cycloundecanyloxydiene 16b was prepared in a similar fashion from 2-methylene cycloundecanone[42] **7b**; (31 mg, 37%); NOE

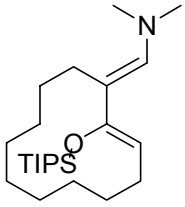
analysis (Scheme 16); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.08 (d, *J* = 2.2 Hz, 1H), 4.98 (t, *J* = 7.4 Hz, 1H), 4.81 (d, *J* = 1.7 Hz, 1H), 2.23 (t, *J* = 6.2 Hz, 2H), 2.07 (q, *J* = 7.2 Hz, 2H), 1.55-1.40 (m, 4H), 1.34-1.20 (m, 8H), 0.19 (s, 9H).



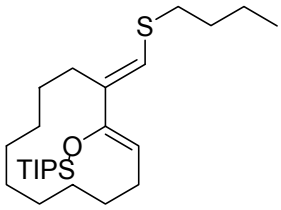
Triisopropylsilyl cycloundecanyloxydiene 16c was prepared in a similar fashion from 2-methylene cycloundecanone[42] **7b**; (360 mg, 70%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.95 (d, *J* = 2.68 Hz, 1 H), 4.79 (m, 1 H), 4.70 (s, 1 H), 2.26-2.16 (m, 2 H), 2.15-2.07 (m, 2 H), 1.77-0.57 (m, 36 H).



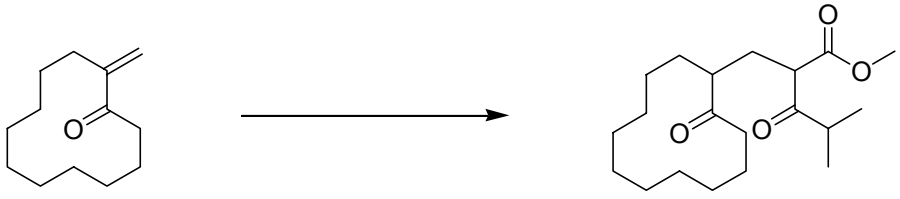
Acyclic diene 21 was prepared in a similar fashion from the acyclic enone[44]**;** (620 mg, 43%) as a liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.22 (s, 1 H), 4.86 (s, 2 H), 2.10 (m, 2 H), 1.86 (s, 3 H), 1.50-1.16 (m, 2 H), 1.13-0.63 (m, 24 H).



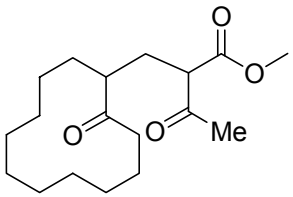
Dimethylamino diene 19 was prepared in a similar fashion from dimethylamine enone **17;** (372 mg, 90%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (s, 1 H), 4.62 (t, *J* = 8.05 Hz, 1 H), 2.52 (s, 6 H), 2.28 (m, 2 H), 2.07 (m, 2 H), 1.50-0.87 (m, 33 H).



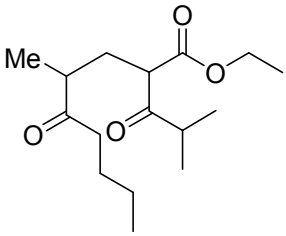
Butyl thinyl diene 20 was prepared in a similar fashion from enone **18;** (173 mg, 70%) as a liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (s, 1 H), 4.73 (t, *J* = 8.05 Hz, 1 H), 3.76-3.62 (m, 1 H), 2.65 (t, *J* = 6.71 Hz, 2 H), 2.30 (m, 2 H), 2.09 (m, 2 H), 1.63-1.00 (m, 38 H), 0.91 (t, *J* = 7.38 Hz, 3 H).



Cyclododecanyl isobutyryacetate ethyl ester 27a. A 50-mL, one-neck, round bottom flask equipped with a rubber septum pierced with an argon inlet needle was charged with methanol (4.3 mL) and sodium metal (11 mg) (0.11 N solution). Methyl isobutyryacetate (0.988 mL, 6.13 mmol) was then added and stirred at room temperature for 15 minutes, following an addition of 2-methylene cyclododecanone **7a** (500 mg, 2.57 mmol) in methanol (3 mL). The reaction mixture was stirred for 15 hr, then neutralized with sat. ammonium chloride (3 mL), and concentrated under reduced pressure. The remaining liquid was extracted with ether (3 x 5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography on 100 g of silica gel (elution with hexanes to 20% ethyl acetate in hexanes) provided 880 mg (97%) of **27a** as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.2 (m, 2 H), 3.6 (m, 1 H), 2.9-2.5 (m, 2 H), 2.4-2.1 (m, 2 H), 2.0-1.4 (m, 6 H), 1.4-1.0 (m, 23 H).

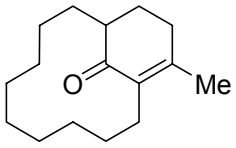


Cyclododecanyl acetate methyl ester 27b was prepared in a similar fashion from cyclododecanone; (1.8 g, 28%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.7 (s, 3 H), 3.4 (m, 1 H), 2.9-2.4 (m, 2 H), 2.3-2.1 (m, 4 H), 2.0-1.4 (m, 4 H), 1.4-1.0 (m, 16 H).

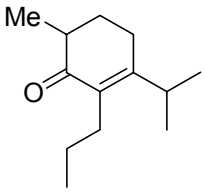


Septanyl isobutyryacetate ethyl ester 27c was prepared in a similar fashion from acyclic enone[44]; (250 mg, 56%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.2 (m, 2 H), 3.6 (m, 1 H), 2.8 (m, 1 H), 2.6-2.3 (m, 3 H), 2.2-2.0 (m, 1 H), 1.8 (m, 1 H), 1.5 (m, 2 H), 1.4-0.8 (m, 14 H).

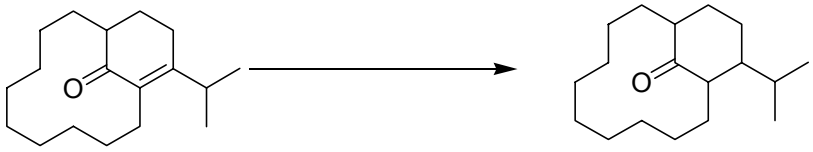
14-Isopropylbicyclo[9.3.1]pentadec-(14)-en-15-one 28a. A 10-mL, one-neck, round bottom flask equipped with a rubber septum pierced with an argon inlet needle was charged with cyclododecanyl isobutyryacetate methyl ester **27a** (270 mg, 0.710 mmol) in methanol (1 mL). Upon addition of aq. NaOH (5N, 0.5 mL), the reaction mixture was then brought to 55°C and left for 4 hr. The reaction was diluted with water (3 mL), concentrated under reduced pressure, extracted with ethyl acetate (2 x 5 mL), and acidified with 5 N HCl (aq) till pH = 6. The suspension was then extracted once more with ethyl acetate (5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography on 5 g of silica gel (elution with 3.5%-20% ethyl acetate in hexanes) provided 14-isopropylbicyclo[9.3.1]pentadec-(14)-en-15-one **28a** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.7-2.5 (m, 3 H), 2.5-2.3 (m, 2 H), 2.0-1.8 (m, 1 H), 1.8-1.5 (m, 4 H), 1.4-1.1 (m, 16 H), 1.1 (dd *J* = 8.4,1.4 Hz, 6 H).



14-Methylbicyclo[9.3.1]pentadec-(14)-en-15-one 28b was prepared in a similar fashion from cyclododecanyl acetate methyl ester **27b**; (17mg, 49%); characterization matched the literature reported values.[27]

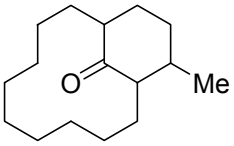


3-Isopropyl cyclohexenone 28c was prepared in a similar fashion from septanyl isobutyryacetate ethyl ester **27c** as a white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.0 (m, 1 H), 2.2-2.3 (m, 4 H), 2.0 (m, 1 H), 1.3 (m, 4 H), 1.1 (d, 3 H), 1.0 (dd, 6 H), 0.9 (t, 3 H).

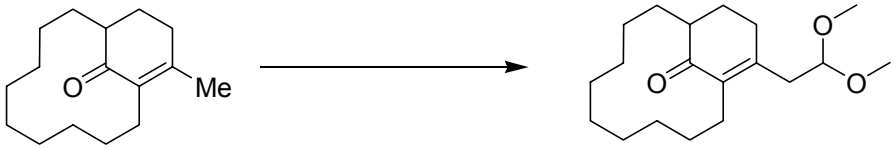


12-Isopropylbicyclo[9.3.1]pentadecan-15-one 29a. A 10-mL, one-neck, round bottom flask equipped with a septum pierced with an argon inlet needle was charged with 14-isopropylbicyclo[9.3.1]pentadec-(14)-en-15-one **28a** (150 mg, 0.580 mmol), 5% palladium over carbon (75 mg), and ethanol (5 mL). A balloon full of hydrogen gas

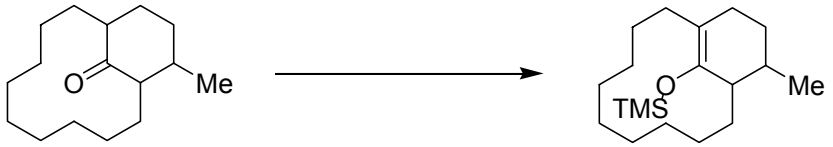
attached to an inlet needle was switched with the argon needle and the flask was flushed and filled three times with hydrogen. Upon the last filling, the reaction mixture was left under hydrogen gas (balloon) with stirring for 24 hr. The mixture was then filtered and rinsed with ethanol (10 mL), and concentrated under reduced pressure. Purification by column chromatography on 5 g of silica gel (elution with hexanes to 5% ethyl acetate in hexanes) provided 135 mg (89%) of **29a** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.9 (m, 1H), 2.7 (m, 1 H), 2.4 (m, 1 H), 2.3-0.9 (m, 21 H), 0.8 (d, 6 H).



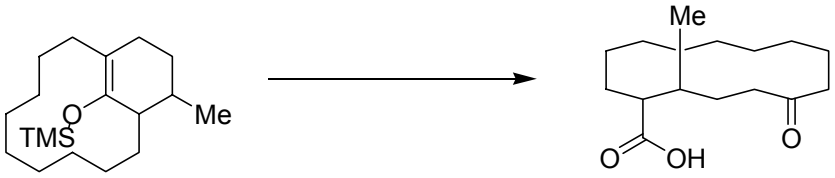
12-Methylbicyclo[9.3.1]pentadecan-15-one 29b was prepared in a similar fashion from 14-methylbicyclo[9.3.1]pentadec-(14)-en-15-one **28b** as a white solid; (130 mg, 86%); characterization matched the literature reported values.[27]



Dimethoxy acetal bicycle 34. A 10-mL, one-neck, round bottom flask equipped with a rubber septum pierced with an argon inlet needle was charged with enone **28b** (50 mg, 0.21 mmol), 2,6-lutidine (0.075 mL, 0.64 mmol), and methylene chloride (3 mL). The mixture was stirred at room temperature for 5 minutes, brought to -78° C, and TMSOTf was added dropwise turning the colorless solution yellow. The reaction mixture was allowed to reach -60° C over 3 hr, then trimethyl orthoformate (77 μL, .70 mmol) was added dropwise. The reaction was quenched after 5 minutes, with methanol (3 mL) and brought to room temperature. The mixture was then extracted with methylene chloride (2 x 5 mL), washed with water (7 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography on 5 g of silica gel (elution with 3.5-20% ethyl acetate in hexanes) provided 52 mg (98%) of **34** as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.4 (m, 1 H), 3.3 (d, 6 H), 2.7 (m, 2 H), 2.6-1.8 (m, 8 H), 1.5-1.0 (m, 15 H).

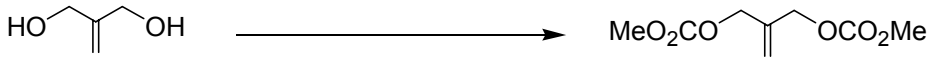


Methyl silyl enol ether 31. A 10-mL, one-neck, round bottom flask equipped with a rubber septum pierced with an argon inlet needle was charged with diisopropylamine (75 μL, .53 mmol) in THF (3 mL) at -30° C. *n*-BuLi (2.6 M, 0.20 mL, 0.53 mmol) was added dropwise over 5 minutes and the mixture was left to stir at -30° C for 15 minutes. The reaction was brought to 0° C for 20 minutes, and then cooled to -78° C. A solution of cyclic ketone **29b** (50 mg, 0.22 mmol) in THF (1 mL) was added dropwise. The reaction was then brought to -30° C for 30 minutes, and TMSCl (80 μL, 0.66 mmol) was added dropwise. After 1 hr the reaction was quenched with $NaHCO_3$ (5 mL), allowed to reach room temperature, and diluted with ethyl acetate (10 mL). The organic layer was washed with sat. brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography on 2 g of silica gel (elution with hexanes to3.5% ethyl acetate in hexanes and 1% triethylamine) provided 42 mg (64%) of **31** as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.6 (m, 1 H), 2.1 (m, 1 H), 2.0-1.8 (m, 3 H), 1.6-1.0 (m, 19 H), 0.9 (d, 3 H), 0.1 (s, 9 H).



Carboxylic acid macrocycle 32. A 25-mL, one-neck, round-bottomed flask was charged with sily enol ether **31** (130 mg, 0.421 mmol), methylene chloride (5 mL), and methanol (2.5 mL). The mixture was then brought to -78°C and ozone was bubbled through the mixture for 15 minutes, until a saturated light blue color persisted. Dimethyl sulfide (0.620 mL, 8.40 mmol) was added and the reaction was brought to room temperature and left to stir for 15 hr. The reaction mixture was diluted with methylene chloride (5 mL), washed with brine (5 mL) and water (5 mL), $MgSO_4$ dried, and concentrated under reduced pressure. Purification by column chromatography on 10 g of

silica gel (elution with 1.0-3.5% ethyl acetate in hexanes) provided 46 mg of **32** as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.8 (m, 1 H), 2.6-2.5 (m, 1 H), 2.5-2.3 (m, 3 H), 1.8-1.1 (m, 18 H), 1.0 (d, 3 H).



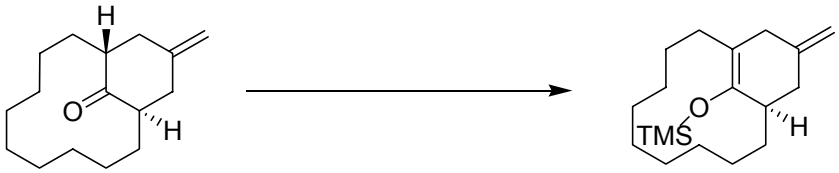
2-{[(Methoxycarbonyl)oxy]methyl}allyl methyl carbonate 37. A 250-mL, three-neck, round-bottom flask equipped with a pressure-equalizing addition funnel, glass stopper, and rubber septum pierced with an argon inlet needle was charged with 2-(hydroxymethyl)allyl alcohol (3.7 mL, 0.045 mol), DMAP (2.2g, 0.18 mol), and pyridine (15 mL, 0.18 mmol) stirring in CH_2Cl_2 (150 mL) at 0°C. Methyl chloroformate (14 mL, 0.18 mol) was added dropwise at 0°C over 30 minutes. The reaction mixture was brought to room temperature and stirred for 24 h. After the reaction was determined to be complete by TLC, the reaction mixture was quenched with sat. aq solution of $CuSO_4$ (60 mL), extracted with diethyl ether (3 x 100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography on 100 g of silica gel (elution with 20% ethyl acetate in hexanes) provided 9.1 g (98%) of **37** as a clear colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30 (s, 2H), 4.65 (s, 4H), 3.75 (s, 6H). This analytical data is in agreement with the literature.[34]

***3*-Methylenebicyclo[9.3.1]cyclopentadecan-15-one 12.** A 150-mL, three-neck, round-bottom flask equipped with a pressure-equalizing addition funnel, condenser, and rubber septum pierced with an argon inlet needle was charged with pyrrolidine (7.7 mL, 0.092 mol), methyl iodide (114 μL, 1.80 mmol), and stirred in benzene (50 mL) at 45°C for 35 minutes. A solution of cyclododecanone (11 g, 0.061 mol) in benzene (10 mL) was added dropwise over 15 minutes, followed by dropwise addition of *N*,*O*-

bis(trimethylsilyl)acetamide (15 mL, 0.061 mol) over 30 minutes. The reaction mixture was brought to 80°C and left to stir for 16 h. After the addition of diethyl ether (70 mL), the reaction mixture was cooled in an ice water bath, then separated by filtration of the precipitated acetamide, and removal of volatile materials under reduced pressure. The crude material (evaluated by ^{1}H NMR, >90:10 pyrrolidine enamine: cyclododecanone) was used without further purification.

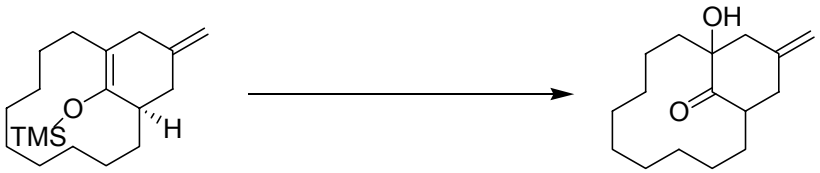
A 250-mL, three-neck, round bottom flask equipped with a pressure-equalizing addition funnel and a rubber septum pierced with an argon inlet needle was charged with $Pd(OAc)_2$ (105mg, 0.470 mmol), PPh_3 (616 mg, 2.35 mmol), and dicarbonate **37** (2.00g, 9.80 mmol), in acetonitrile (40 mL). Crude pyrrolidine enamine **42** (~10.8 mmol) was then added dropwise to the stirred solution and the reaction mixture was brought to 45° C for 1.5 h. Water (80 mL) was added, and the mixture was stirred at 50° C for 3 h and concentrated under reduced pressure. The aqueous layer was extracted with ether (2 x 40 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was used as is without further purification.

For characterization purposes a sample of 3-methylenebicyclo[9.3.1]cyclopentadecan-15-one **12** was purified by column chromatography to provide a white solid: mp 44°C; IR 3076, 2934, 2867, 1709, 1468; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.89 (d, *J* = 1.8 Hz, 1H), 4.83 (d, *J* = 1.8 Hz, 1H), 2.98 (m, 1H), 2.59 (dd, *J* = 7.2, 22.2 Hz, 1H), 2.48 (ddd, *J* = 13.2, 5.4, 3.0 Hz, 1H), 2.41 (m, 1H), 2.34 (d, *J* = 13.2 Hz, 1H), 2.12 (d, *J* = 13.2 Hz, 1H), 2.08-1.94 (m, 1H), 1.88-1.73 (m, 1H), 1.57-0.82 (m, 16H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 217.1, 143.3, 112.4, 52.4, 43.8, 43.6, 42.2, 30.6, 27.5, 26.2, 25.7, 23.2, 22.8, 22.8, 22.5, 22.3. HRMS (EI) Calcd for $C_{16}H_{26}O$ ([M^+]) 234.19837; Found 234.19853.



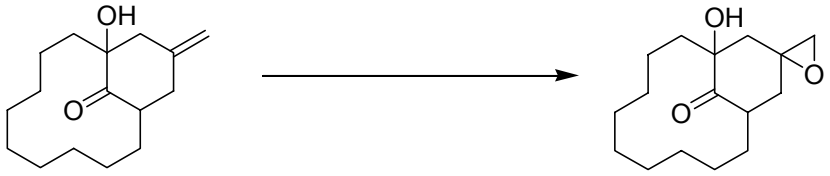
Exomethylene silyl enol ether 45. A 250-mL, one-neck, round bottom flask equipped with a pressure-equalizing addition funnel under argon was charged with diisopropylamine (5.8 mL, 41 mmol) in THF (70 mL) at -30° C. *n*-BuLi (2.2 M, 18.5 mL,

41 mmol) was added dropwise over 10 minutes and the mixture was left to stir at -30° C for 15 minutes. The reaction was brought to 0° C for 30 minutes, and then cooled to -78° C. A solution of crude methylenebicyclo[9.3.1]cyclopentadecan-15-one **12** (20.1 mmol) in THF (30) was added dropwise, stirred for 5 minutes, and then HMPA (3.48 mL, 20.1 mmol) was added. The reaction was then brought to -30° C for 30 minutes, and TMSCl (7.62 mL, 60.3 mmol) was added dropwise. After 15 minutes the reaction was quenched with $NaHCO_3$ (60 mL), allowed to reach room temperature, and diluted with diethyl ether (60 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was used as is without further purification.

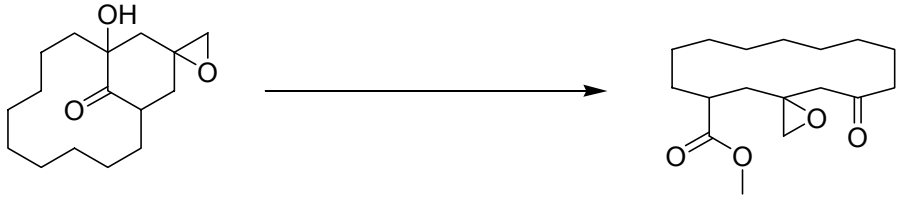


α-Hydroxy ketone 46. A 250-mL, three-neck, round bottom flask equipped with a glass stopper and a rubber septum pierced with an argon inlet needle was charged with crude exomethylene silyl enol ether **45** (20.1 mmol) in CH_2Cl_2 (60 mL) at 0° C. *m*-CPBA (5.8 g, 26 mmol) was added in three portions over 45 minutes and the reaction mixture was stirred at 0° C for 1.5 h. The reaction mixture was then partitioned between CH_2Cl_2 (50 mL) and 1 N $NaHSO_3$ (70 mL). The aqueous layer was extracted with two 40-mL portions of CH_2Cl_2. The combined organic layers were then washed with $NaHCO_3$ (100 mL), then water (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was immediately transferred to a 250-mL, one-neck, round-bottom flask equipped with a pressure-equalizing addition funnel. THF (60 mL) and TBAF (1.0M in THF, 24 mL, 24 mmol) were then added dropwise with stirring at room temperature. After 1 h at room temperature, sat. $NaHCO_3$ (40 mL) was added, and then the mixture was extracted with diethyl ether (40 mL x 2), washed with sat. brine (60 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography on 120 g of silica gel (elution with 3.5-5% ethyl acetate in hexanes) provided 1.22 g (50%, four steps overall from **37**) of **46** as a clear colorless liquid: IR 3486, 2935, 2851, 1708, 1469; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.91 (dd, J = 9.6, 1.8 Hz,

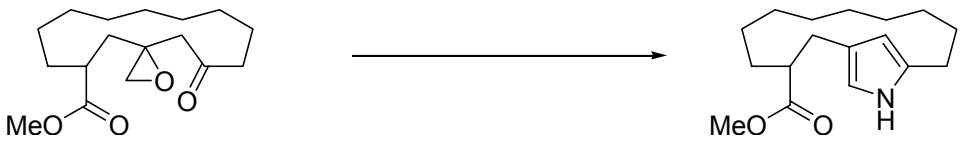
2H), 4.01 (s, 1H), 2.98 (m, 1H), 2.71 (dd, *J* = 16.8, 3.0 Hz, 1H), 2.55 (ddd, *J* = 13.18, 5.99, 2.40 Hz, 1H), 2.36 (dd, *J* = 15, 1.8 Hz, 1H), 2.18-2.04 (m, 2H), 2.00-1.91 (m, 1H), 1.79-1.65 (m, 1H), 1.63-0.80 (m, 15H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 215.9, 142.4, 113.3, 80.4, 51.6, 44.1, 43.5, 35.8, 27.4, 25.9, 25.5, 23.0, 22.9, 22.9, 22.2, 19.9. HRMS (EI) Calcd for $C_{16}H_{26}O_2$ ([M^+]) 250.19328; Found 250.19364.



α-Hydroxy ketone epoxide 13. A 15-mL, two neck, round-bottomed flask equipped with a rubber septum pierced with an argon inlet needle and a glass stopper was charged with **46** (90 mg, 0.36 mmol), CH_2Cl_2 (4 mL), and $NaHCO_3$ (60 mg, 0.72 mmol). *m*-CPBA (77% max, 121 mg, 0.54 mmol) was added in one portion and the resulting mixture was stirred for 15 h at room temperature. The reaction mixture was partitioned between CH_2Cl_2 (10 mL) and 1 N $NaHSO_3$ (7 mL). The aqueous layer was then extracted with two 5-mL portions of CH_2Cl_2. The combined organic layers were washed with water (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography on 9 g of silica gel (gradient elution with 10-30% ethyl acetate in hexanes) provided 76 mg (80%) of **13** as a white solid: mp 81° C; IR 3488, 2933, 2858, 1712, 1468; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01 (s, 1H), 3.18 (m, 1H), 2.91 (dd, *J* = 4.8, 2.4 Hz, 1H), 2.86 (brd, *J* = 4.8 Hz, 1 H) 2.28 (d, *J* = 13.2 Hz, 1H), 2.18-1.98 (m, 3H), 1.88-1.74 (m, 2H), 1.68-.92 (m, 16H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 216.0, 80.5, 56.3, 51.9, 49.4, 42.6, 41.5, 37.0, 27.3, 25.9, 25.6, 22.9, 22.9, 22.7, 22.3, 20.0. HRMS (EI) Calcd for $C_{16}H_{26}O_3$ ([M^+]) 266.18820; Found 266.18827.

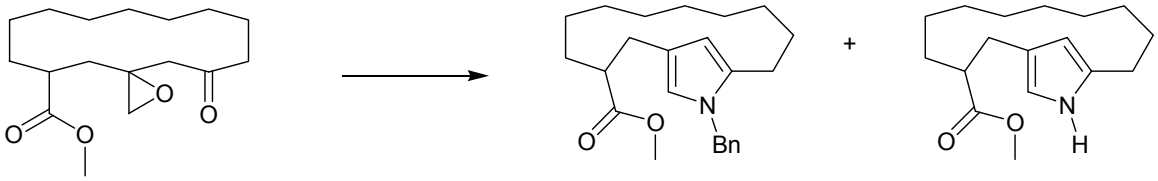


Epoxy-ketoester macrocyle 14. A 10-mL, one-neck, round-bottomed flask equipped with a rubber septum pierced with an argon inlet needle was charged with α-hydroxy ketone **13** (60 mg, 0.22 mmol), and MeOH (3 mL). At room temperature lead tetracetate (130 mg, 0.291 mmol) was added followed after 30 minutes with a second portion of $Pb(OAc)_4$ (80 mg, 0.18 mmol) with continued stirring for 1 hr. The reaction mixture was then concentrated under reduced pressure and partitioned between ethyl acetate (5 mL) and water (3 mL). The aqueous layer was extracted with two 5-mL portions of ethyl acetate. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography on 1 g of silica gel (elution with 30% ethyl acetate in hexanes) provided 60 mg (94%) of **14** as a white solid: mp 62° C; IR 2932, 2863, 1778, 1732, 1714; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.24 (d, J = 18.0 Hz, 1H), 2.71-2.20 (m, 7H), 1.88-1.06 (m, 17 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 208.0, 176.1, 55.2, 51.9, 51.8, 46.7, 41.9, 40.1, 36.2, 30.3, 26.2, 26.0, 25.4, 24.4, 24.4, 23.9, 23.3. HRMS (EI) Calcd for $C_{17}H_{28}O_4$ ([M^+]) 296.19876; Found 296.19853.

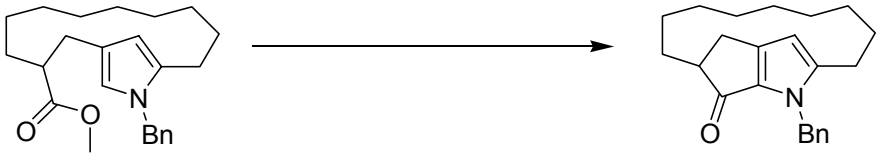


Pyrrole macrocyle 47. A 10-mL, one-neck, round-bottomed flask equipped with a condenser and a rubber septum pierced with an argon inlet needle was charged with epoxy-ketoester macrocyle **14** (15 mg, 0.051 mmol), ammonium acetate (22 mg, 0.30 mmol), camphorsulfonic acid (1 mg, 0.003 mmol), powdered molecular sieves (20 mg), and methanol (0.5 mL). The reaction mixture was brought to 50°C for 3.5 hr. The reaction was cooled to room temperature, and partitioned between diethyl ether (3 mL) and water (2 mL). The aqueous layer was then extracted with diethyl ether (2 x 3 mL); the organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography on 1 g of silica gel (elution with 1.75% ethyl acetate in hexanes) provided 13 mg (93%) of **47** as an orange liquid; IR 2928, 2857, 1737; ^{1}H NMR (300 MHz, $CDCl_3$) 7.13 (s, 1 H), 5.97 (s, 1 H), 3.72 (s, 3 H), 2.81-2.60 (m, 2 H), 2.59-2.33 (m, 3 H), 1.78-0.81 (m, 17 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.9,

157.9, 138.6, 123.5, 106.9, 51.8, 44.3, 27.7, 27.5, 27.5, 26.9, 26.7, 26.4, 26.1, 25.9, 25.7, 25.5.

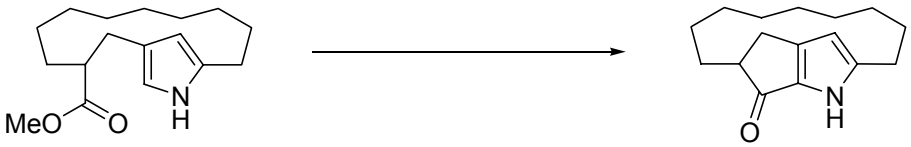


Benzyl pyrrole macrocycle 49. A 10-mL, one-neck, round-bottomed flask equipped with a condenser and a rubber septum pierced with an argon inlet needle was charged with epoxy-ketoester macrocyle **14** (18 mg, 0.06 mmol) and toluene (2.5 mL), followed by direct addition of powdered molecular sieves (50 mg), and benzyl amine (.023 mL, 0.214 mmol). The solution was then brought to reflux under vigorous stirring for 4 hours. The reaction mixture was brought to room temperature and partitioned between $NaHCO_3$ (5 mL) and ether (5 mL). The aqueous layer was extracted with ether (2 x 5 mL). The organic layers were combined, washed with brine (5 mL) then water (5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography on 3.5 g of silica gel (elution with 1.75% ethyl acetate in hexanes) provided 10 mg (45%) of **49** as a yellow liquid and 11 mg (48%) of **47** as a dark orange liquid. Characterization of **49;** IR 2936, 2875, 1741; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4-7.2 (m, 3 H), 7.0 (d, *J* = 6 Hz, 2 H), 6.4 (s, 1H), 5.9 (s, 1 H), 5.0 (s, 2 H), 3.7 (s, 3 H), 2.8 (dd, *J* = 16.2, 2.4 Hz, 1 H), 2.7-2.4 (m, 3 H), 2.4-2.2 (m, 1 H), 1.6-0.8 (m, 16 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 177.6, 138.9, 134.0, 128.8, 128.8, 127.4, 126.7, 126.7, 120.3, 119.6, 106.9, 52.1, 50.4, 44.8, 29.7, 27.3, 27.2, 27.0, 26.5, 26.3, 25.5, 25.3, 25.2, 25.1.



Benzyl tricyclic core 53. A 10-mL, one-neck, round-bottom flask equipped with a condenser and a rubber septum pierced with an argon inlet needle was charged with

benzyl pyrrole macrocycle **49** (13 mg, .04 mmol), methanol (2 mL), water (2 mL), and KOH (22 mg, .38 mmol). The reaction mixture was then brought to reflux for 1 hr. After reaching room temperature, the reaction mixture was diluted with water (2 mL), and acidified with 1 N HCl (pH = 6). The mixture was then extracted with methylene chloride (2 x 4 mL); the organic layers were then combined, dried over $MgSO_4$, and concentrated under reduced pressure to give a crude orange solid. In a dry 10-mL, one-neck, round-bottom flask equipped with a rubber septum pierced with an argon inlet needle was charged with the crude carboxylic acid and .100 mL of oxalyl chloride with stirring. After stirring for 10 minutes at room temperature the reaction mixture was concentrated under reduced pressure. Compound **53** is highly unstable. Characterization was complete on crude material; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4-7.2 (m, 3 H), 6.9 (d, *J* = 7.04 Hz, 2 H), 6.1 (s, 1 H), 5.7 (d, *J* = 16.3 Hz, 1 H), 5.6 (d, *J* = 16.3 Hz, 1 H), 3.3-3.1 (m, 2 H), 2.9-2.8 (m, 1H), 2.7-2.4 (m, 2 H), 1.8-0.7 (m, 16 H).



Model tricyclic core 15. A 10-mL, one-neck, round-bottom flask equipped with a condenser and a rubber septum pierced with an argon inlet needle was charged with pyrrole macrocycle **47** (7 mg, 0.03 mmol), methanol (1 mL), water (1 mL), and KOH (12 mg, 0.22mmol). The reaction mixture was then brought to reflux for 1 hr. After reaching room temperature, the reaction mixture was diluted with water (2 mL), and acidified with 1 N HCl (pH = 6). The mixture was then extracted with methylene chloride (2 x 4 mL); the organic layers were then combined, dried over $MgSO_4$, and concentrated under reduced pressure to give a crude orange solid. A dry 10-mL, one-neck, round-bottom flask equipped with a rubber septum pierced with an argon inlet needle was charged with the crude carboxylic acid and 0.10 mL of oxalyl chloride with stirring. After stirring for 10 minutes at room temperature the reaction mixture was concentrated under reduced pressure to afford crude 5 mg of **15** (77%) as an orange liquid. Compound **15** is highly unstable. Characterization was completed on crude material; IR 2930, 2858, 1788, 1517;

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.39 (s, 1 H), 3.35-2.90 (m, 3 H), 2.89-2.59 (m, 2 H), 1.93-0.77 (m, 17 H); ^{13}C NMR (300 MHz, C_6D_6) δ 175.8, 165.8, 142.2, 140.2, 112.9, 54.7, 28.7, 27.8, 27.7, 26.4, 26.3, 26.0, 26.0, 25.4, 25.4, 24.9.

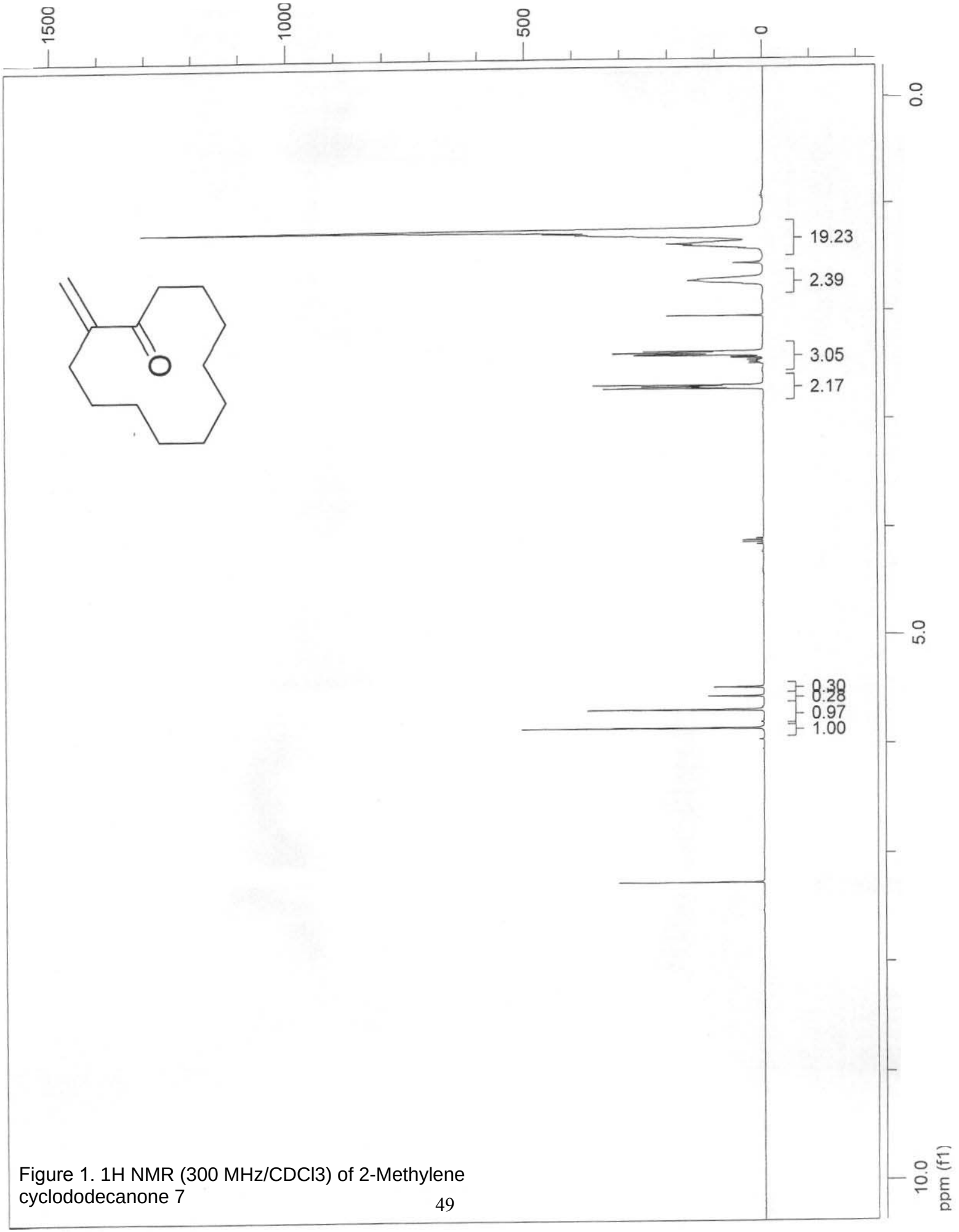


Figure 1. 1H NMR (300 MHz/CDCl3) of 2-Methylene cyclododecanone 7

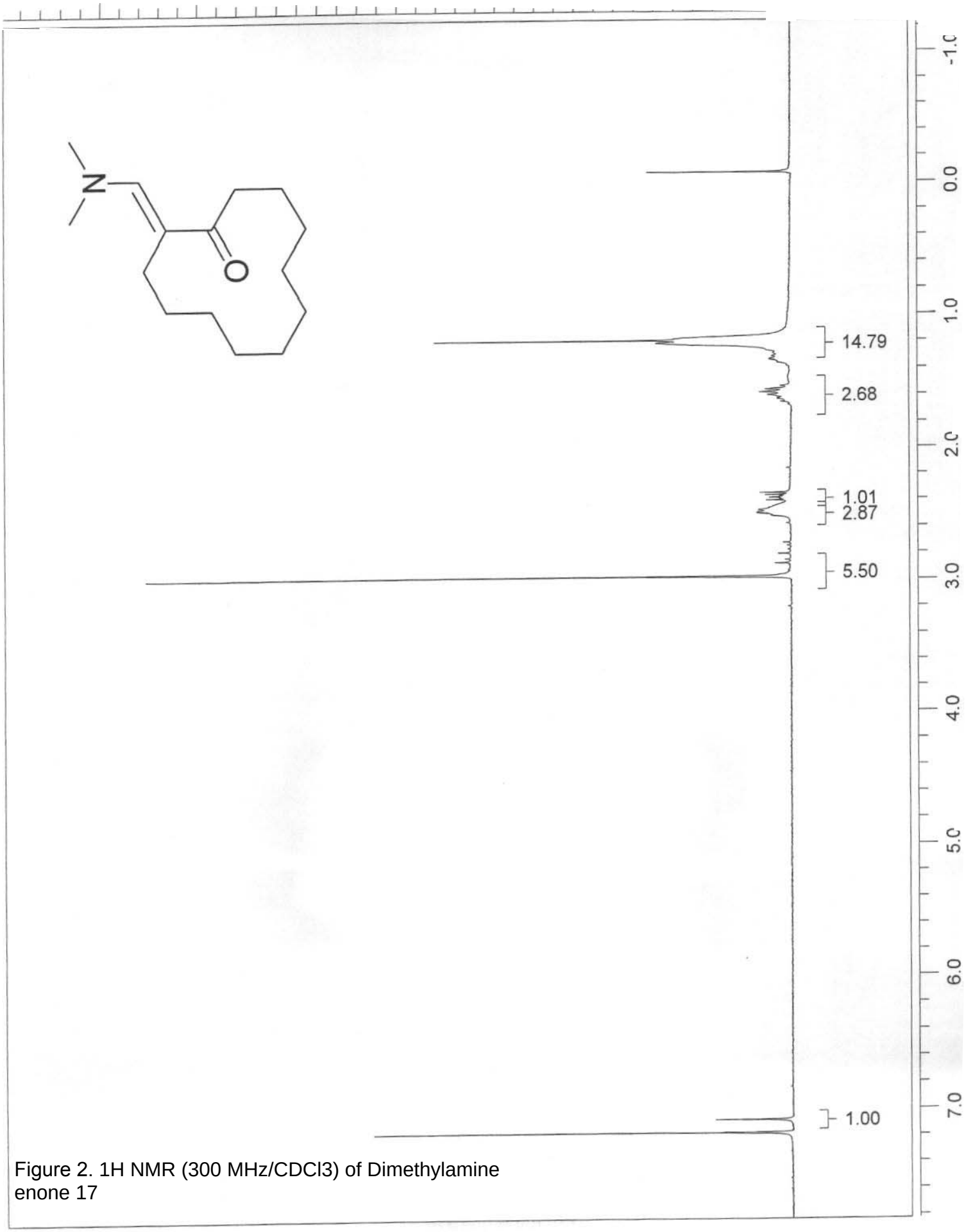


Figure 2. 1H NMR (300 MHz/CDCl3) of Dimethylamine enone 17

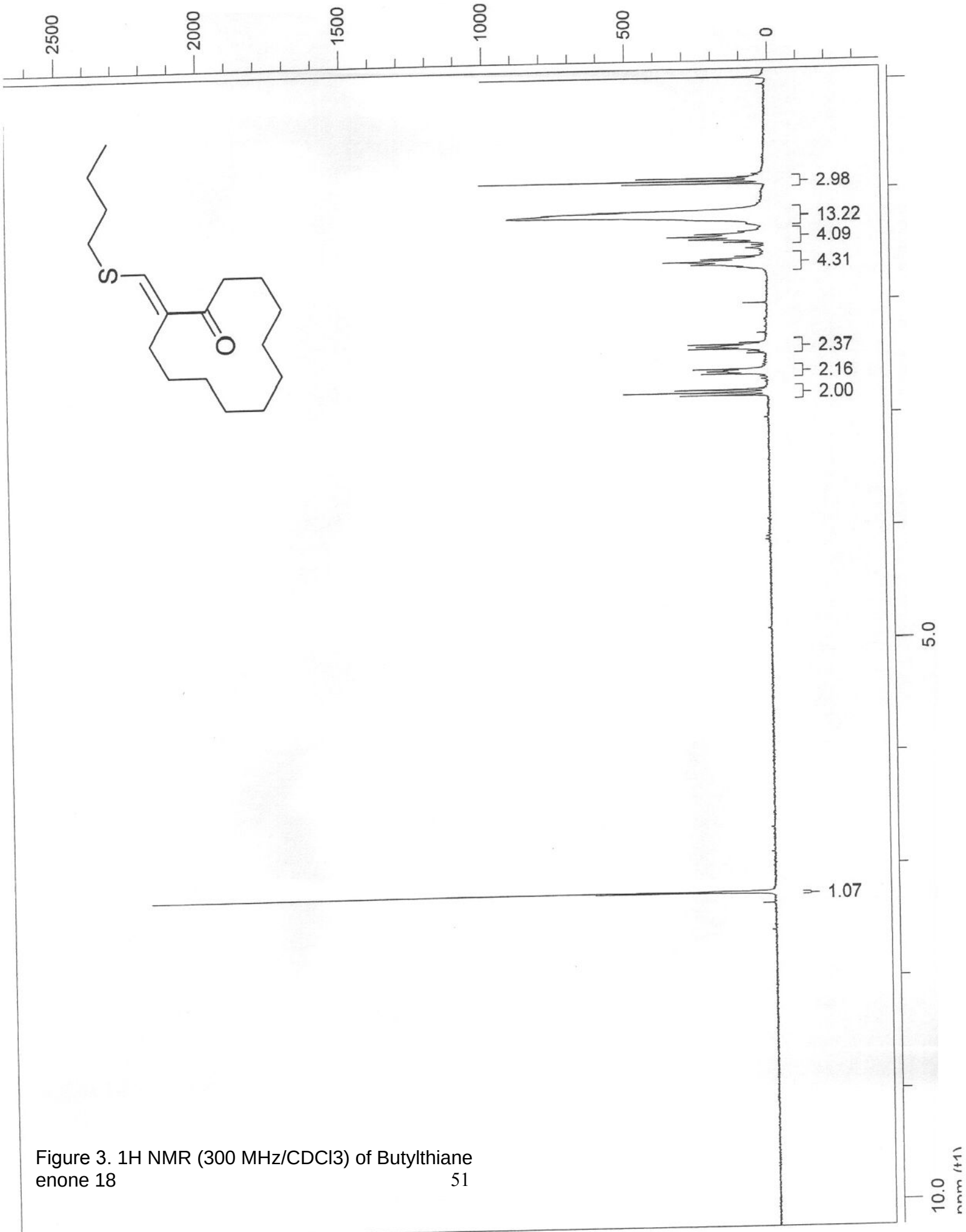


Figure 3. 1H NMR (300 MHz/CDCl3) of Butylthiane enone 18

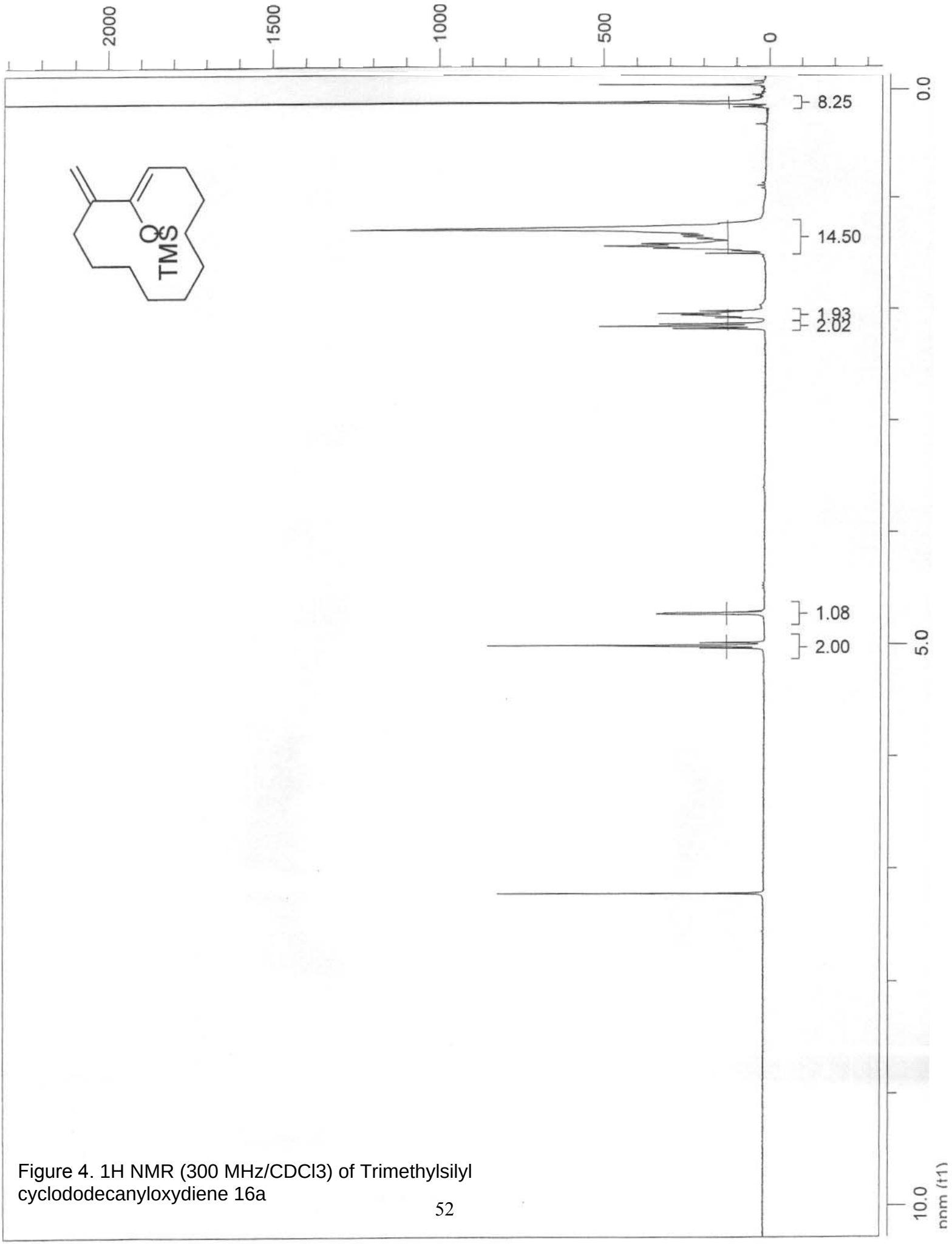


Figure 4. 1H NMR (300 MHz/CDCl3) of Trimethylsilyl cyclododecanyloxydiene 16a

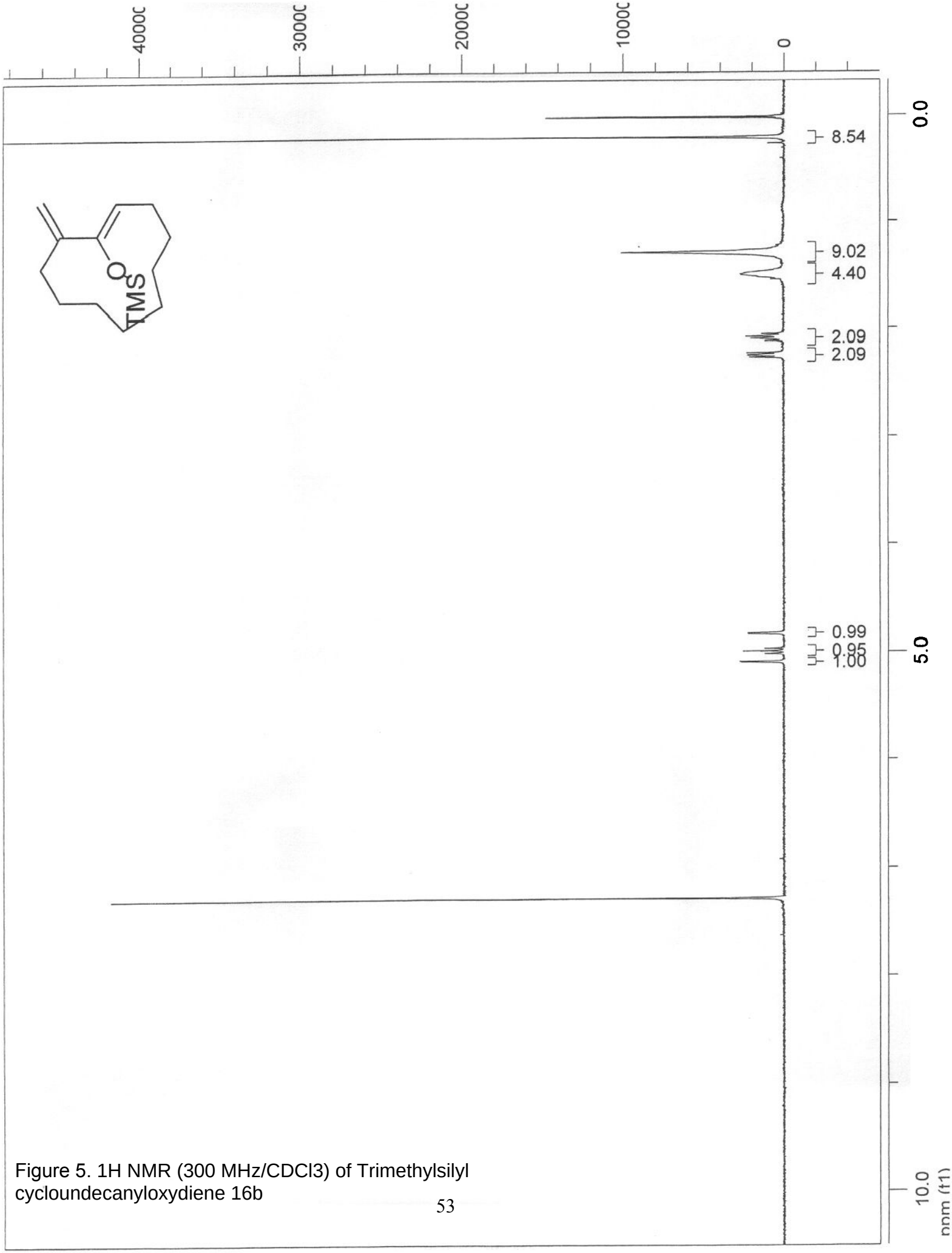


Figure 5. 1H NMR (300 MHz/CDCl3) of Trimethylsilyl cycloundecanyloxydiene 16b

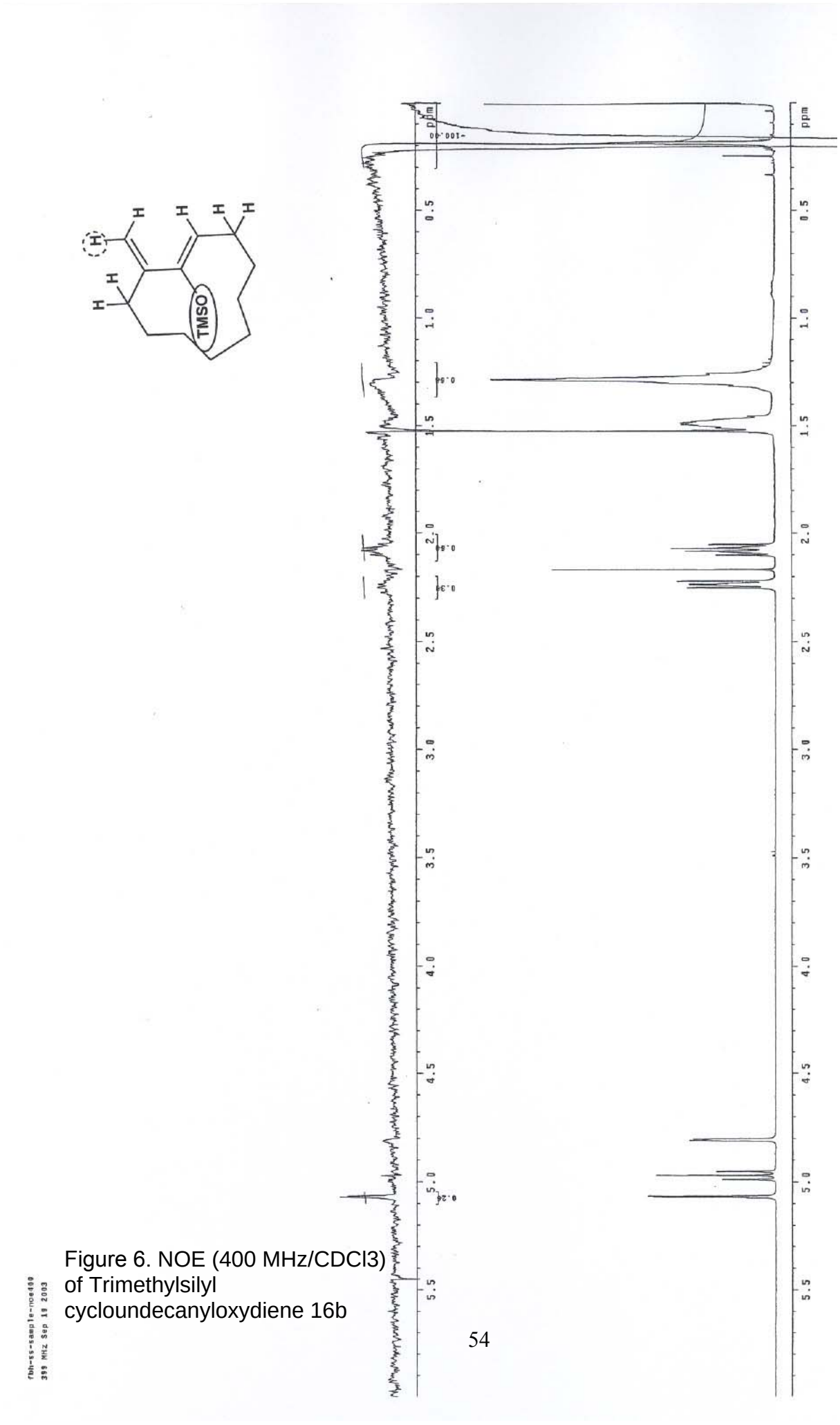


Figure 6. NOE (400 MHz/CDCl3) of Trimethylsilyl cycloundecanyloxydiene 16b

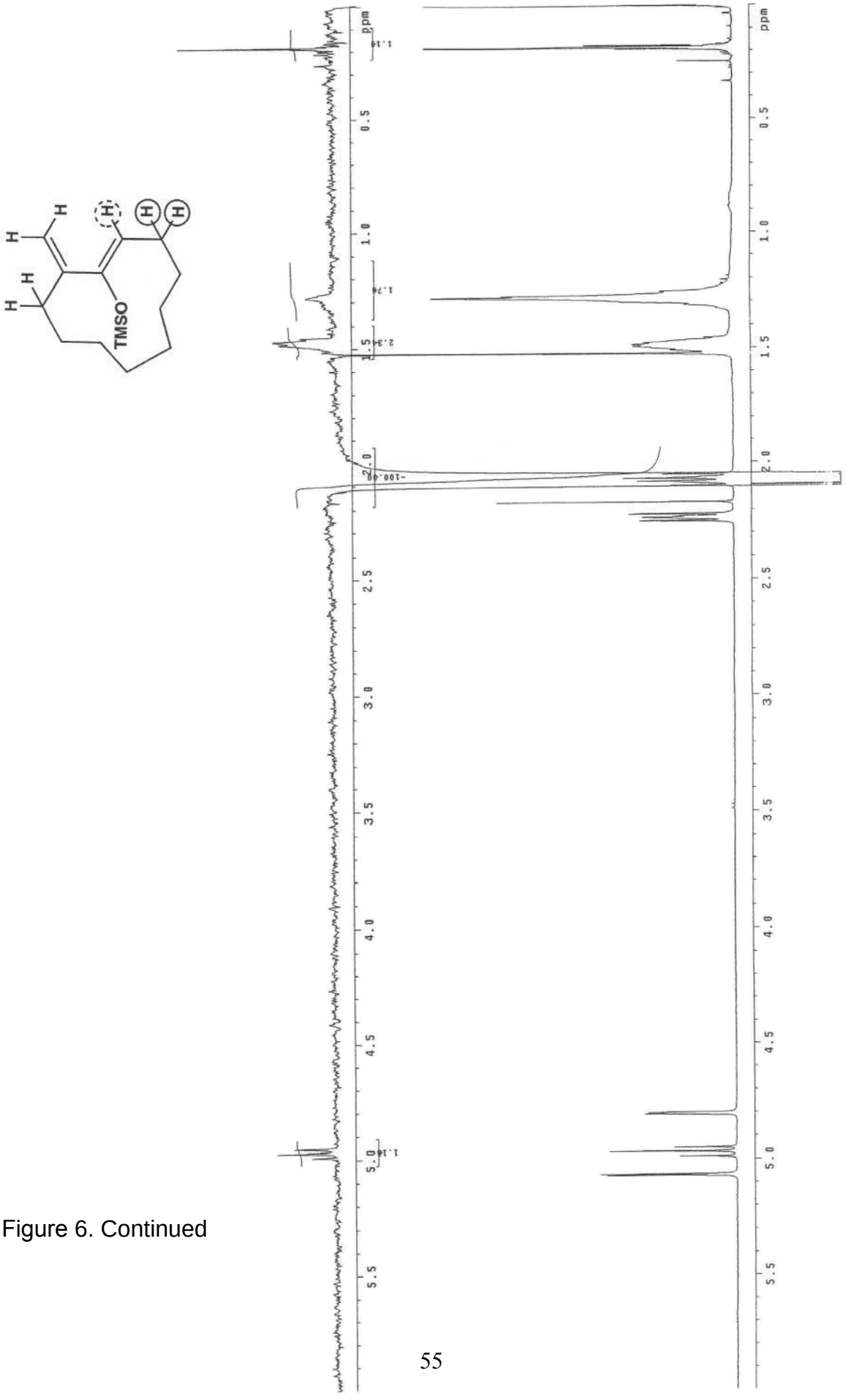


Figure 6. Continued

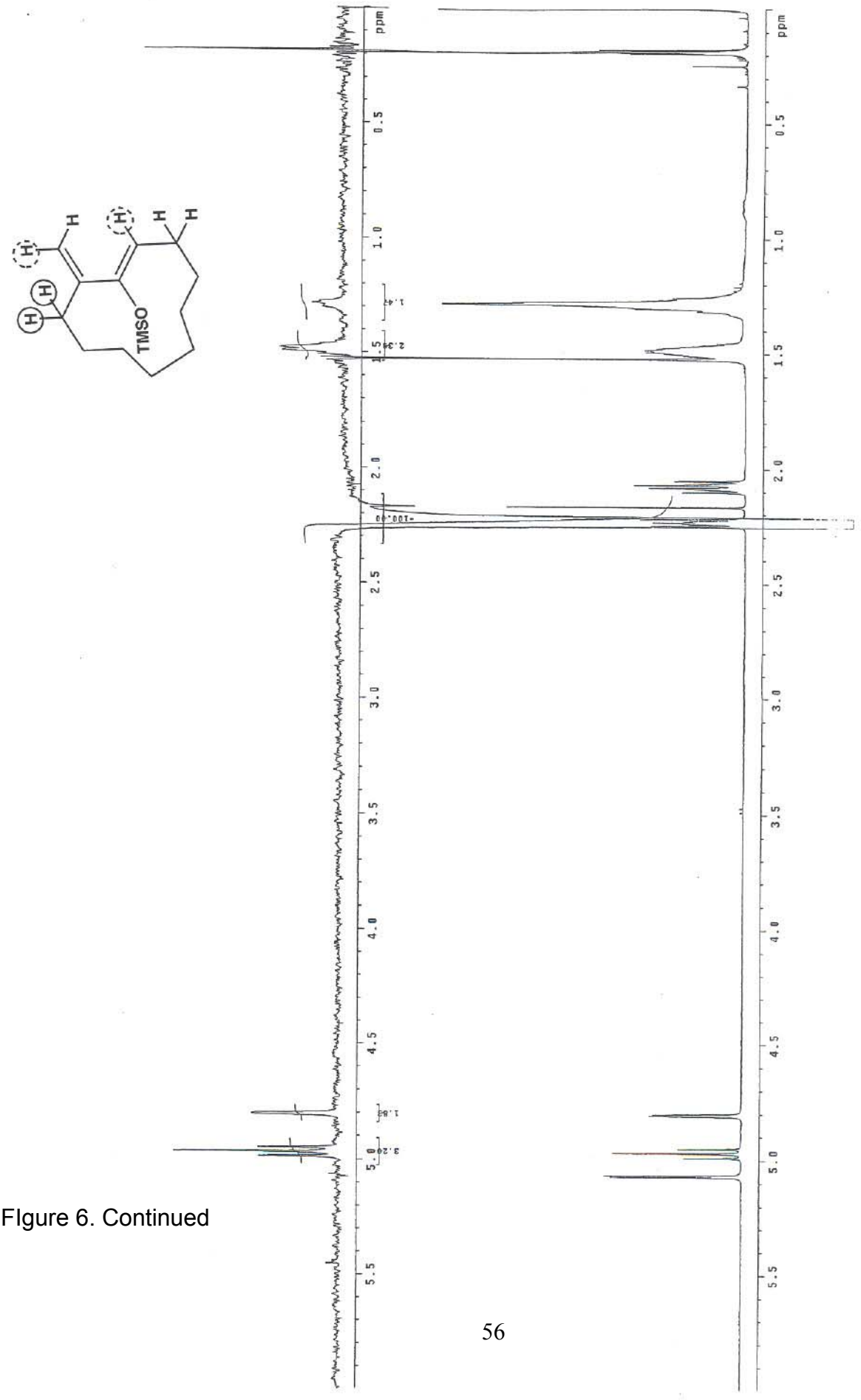


FIgure 6. Continued

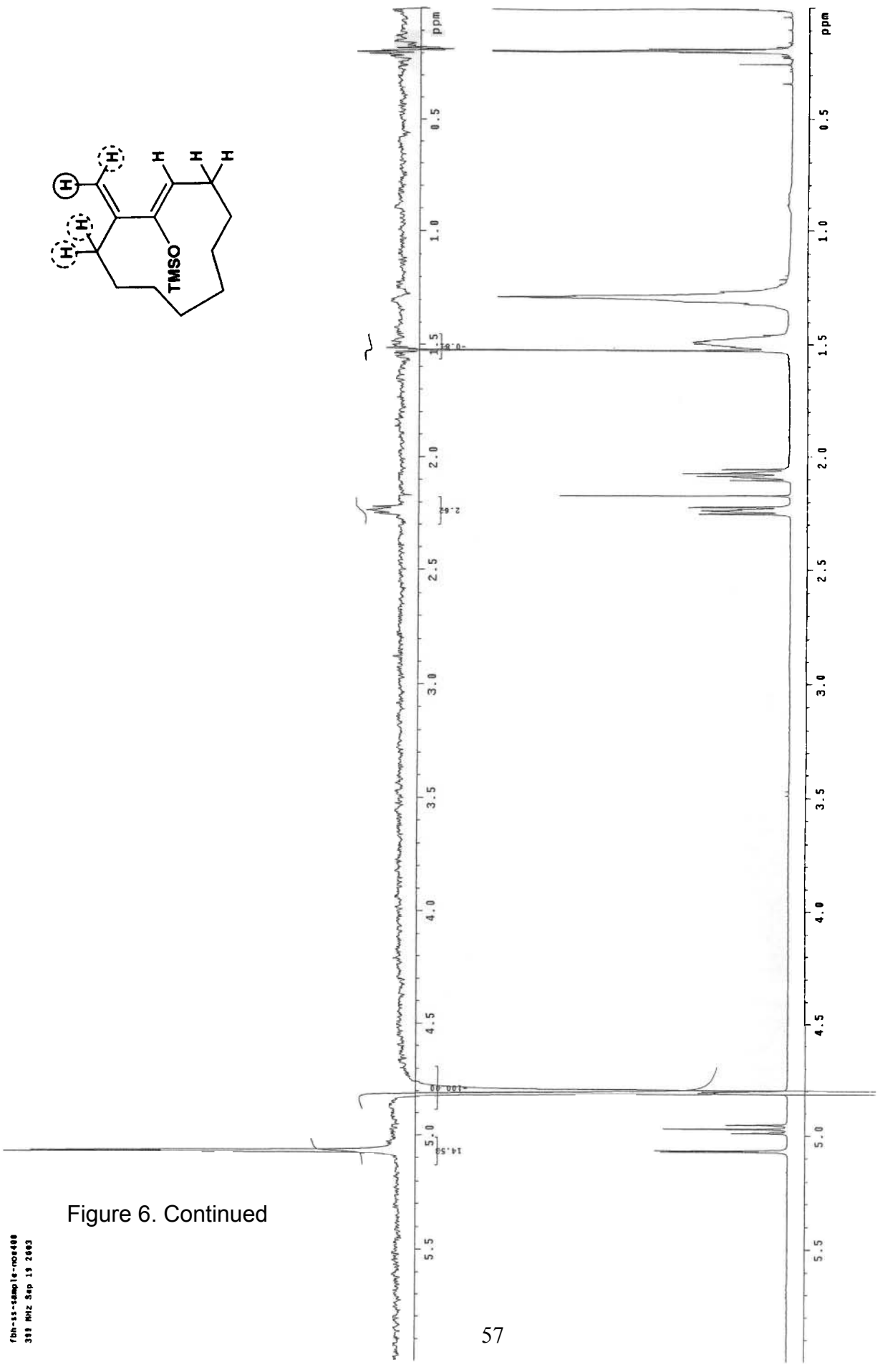
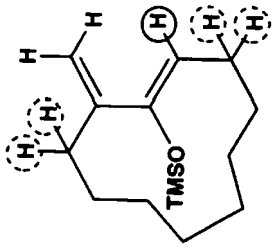


Figure 6. Continued



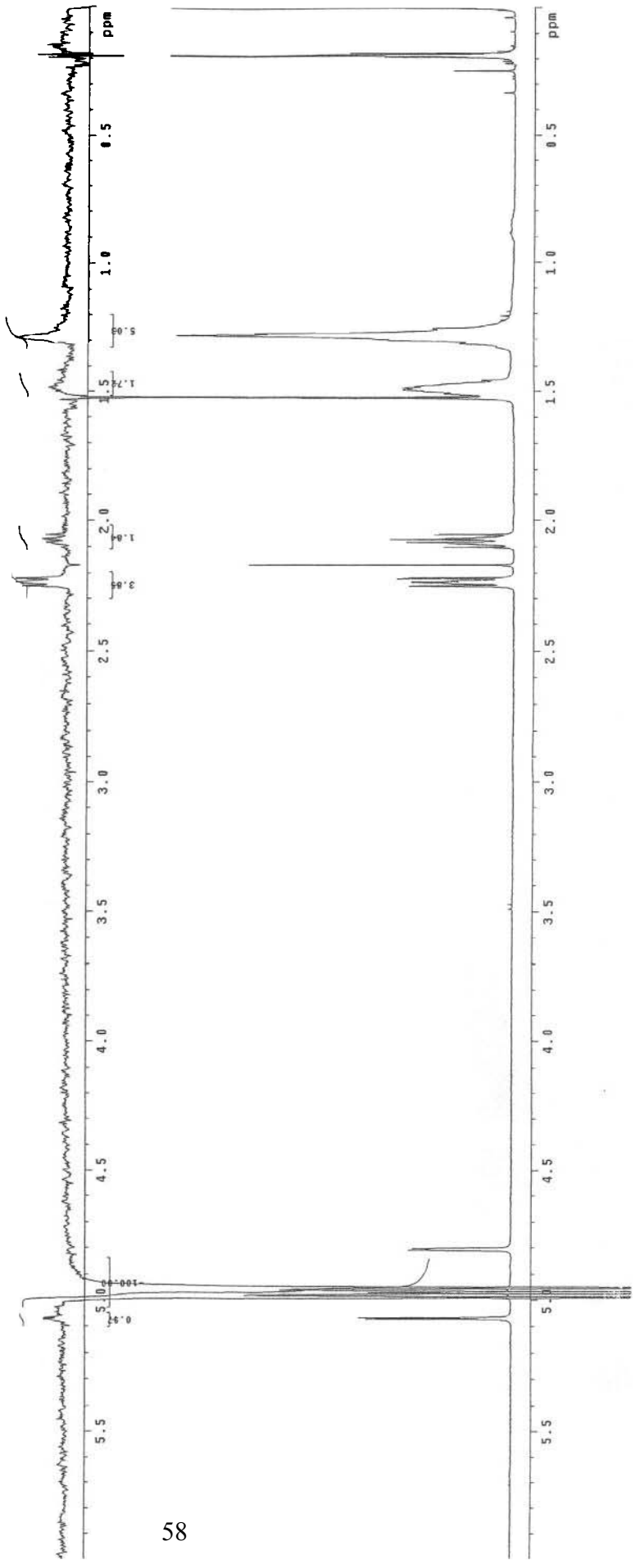
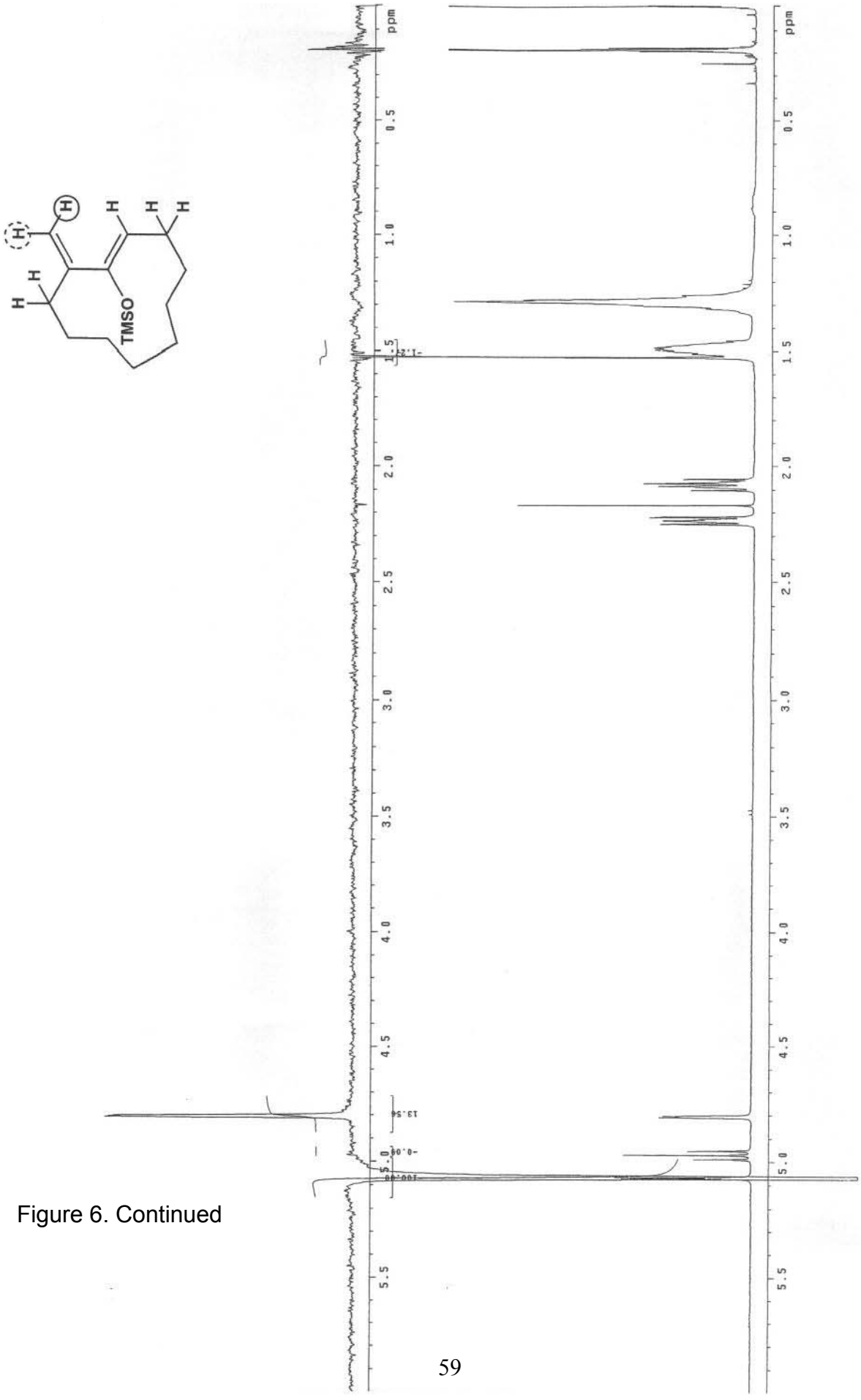


Figure 6. Continued

fbh-ss-sample-mod400
300 MHz Sep 13 2003



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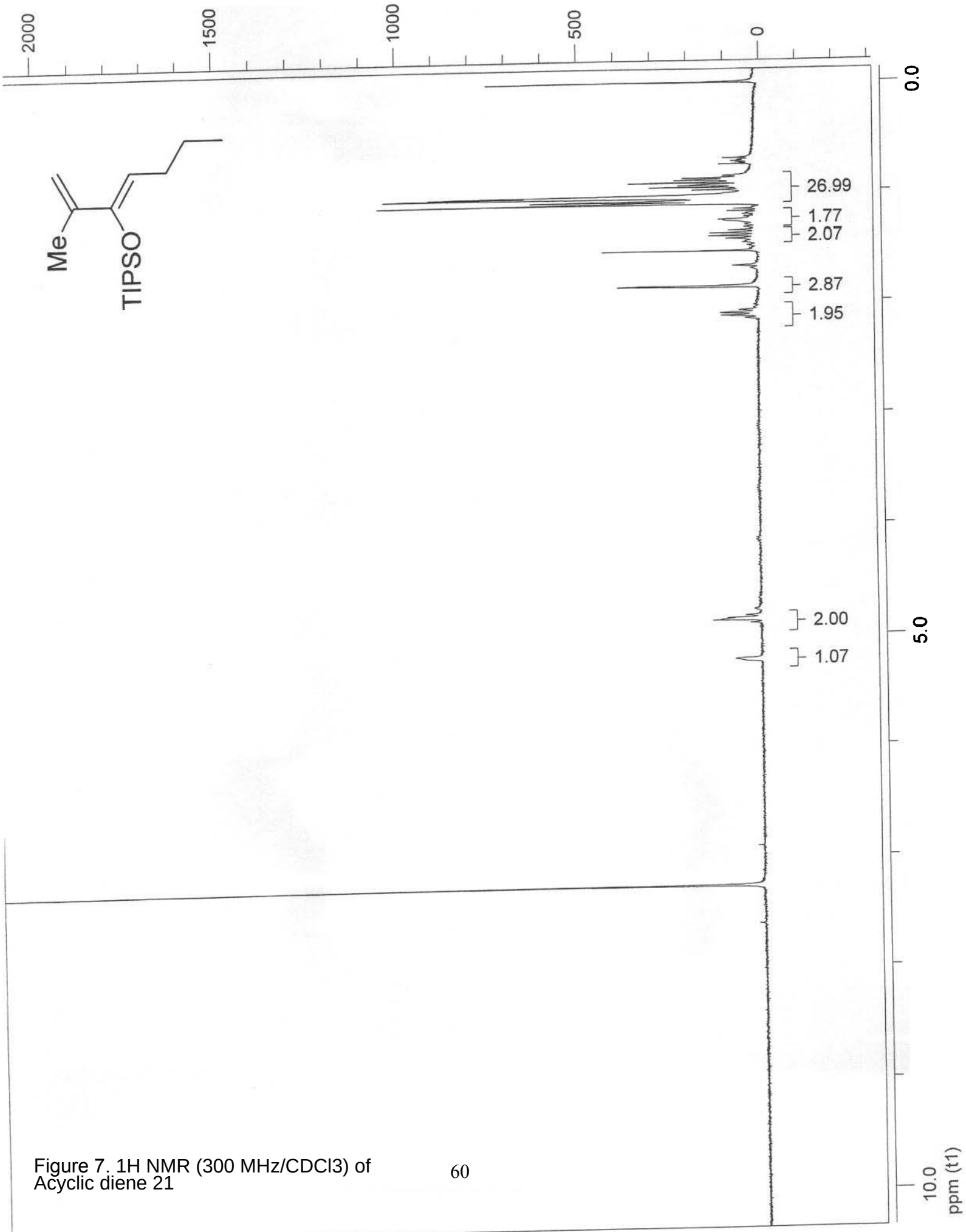


Figure 7. 1H NMR (300 MHz/CDCl3) of Acyclic diene 21

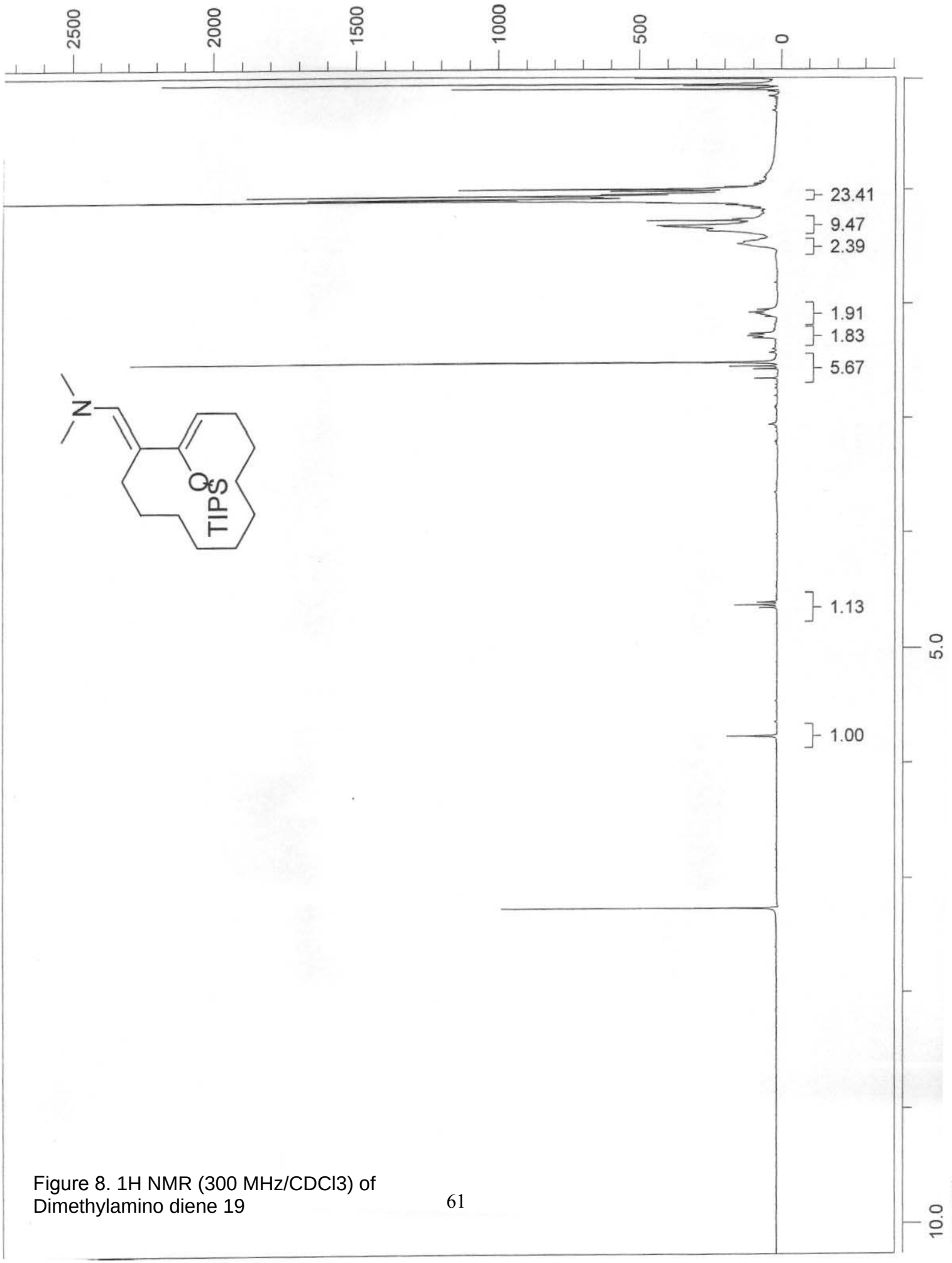


Figure 8. 1H NMR (300 MHz/CDCl3) of Dimethylamino diene 19

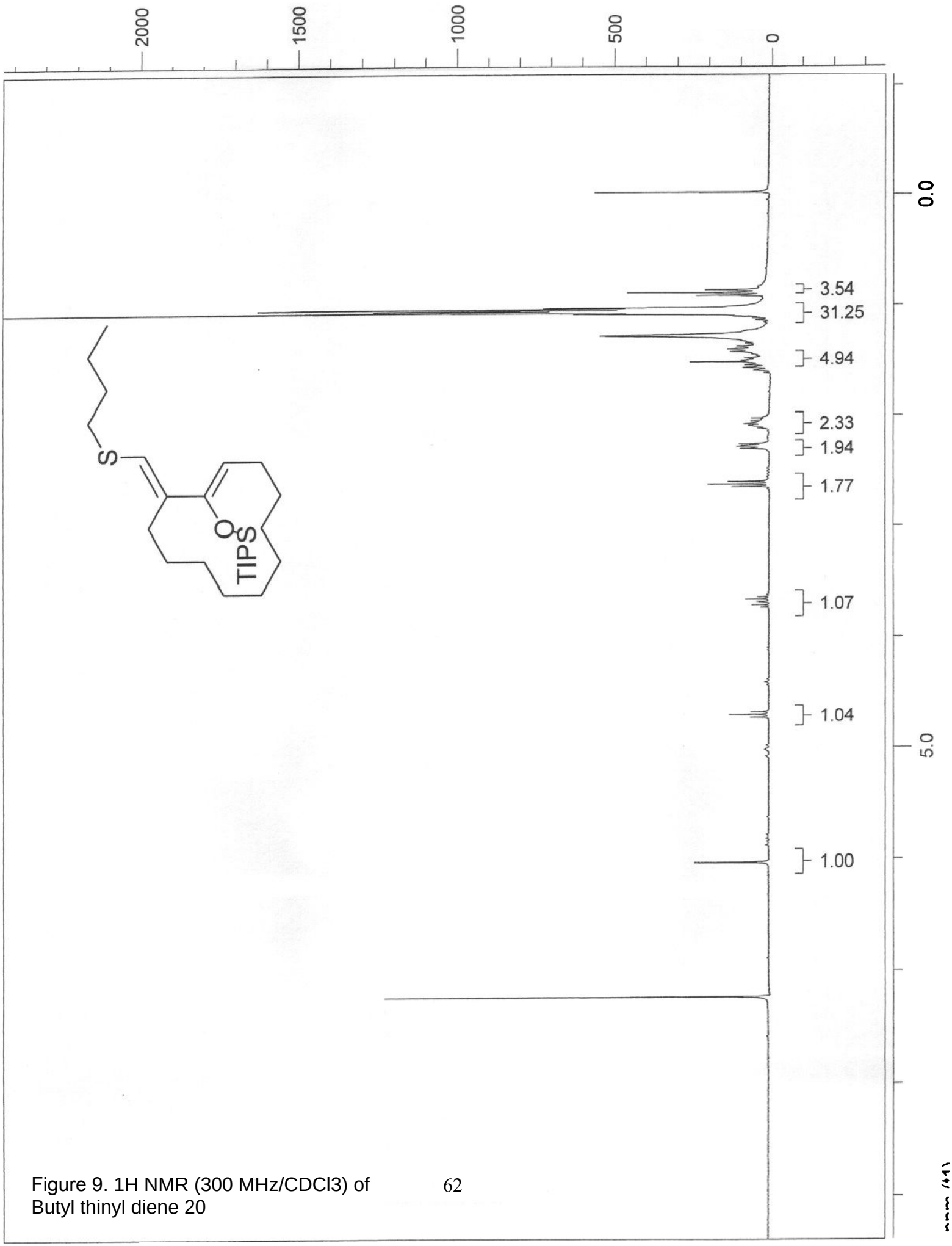


Figure 9. 1H NMR (300 MHz/CDCl3) of Butyl thinyl diene 20

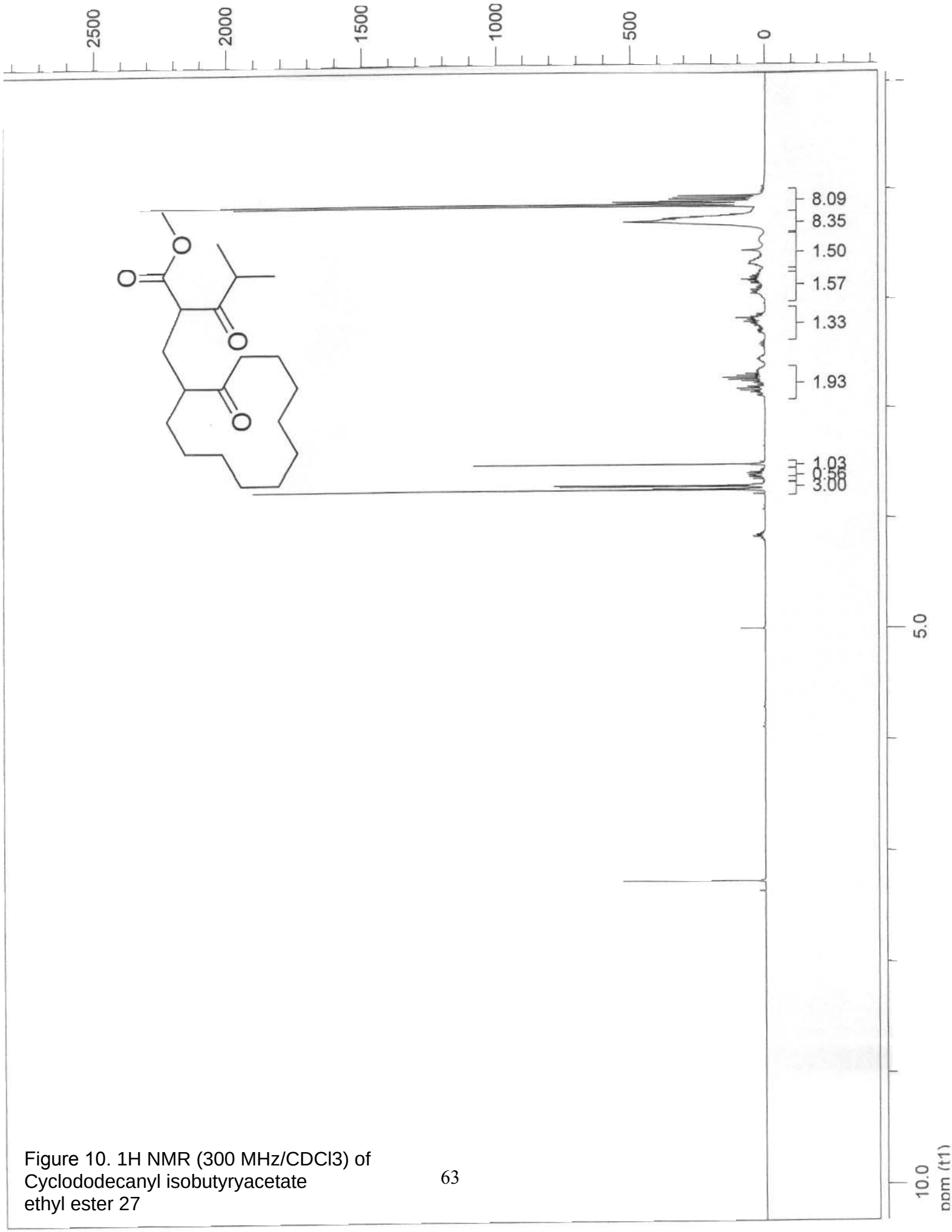


Figure 10. 1H NMR (300 MHz/CDCl3) of Cyclododecanyl isobutyryacetate ethyl ester 27

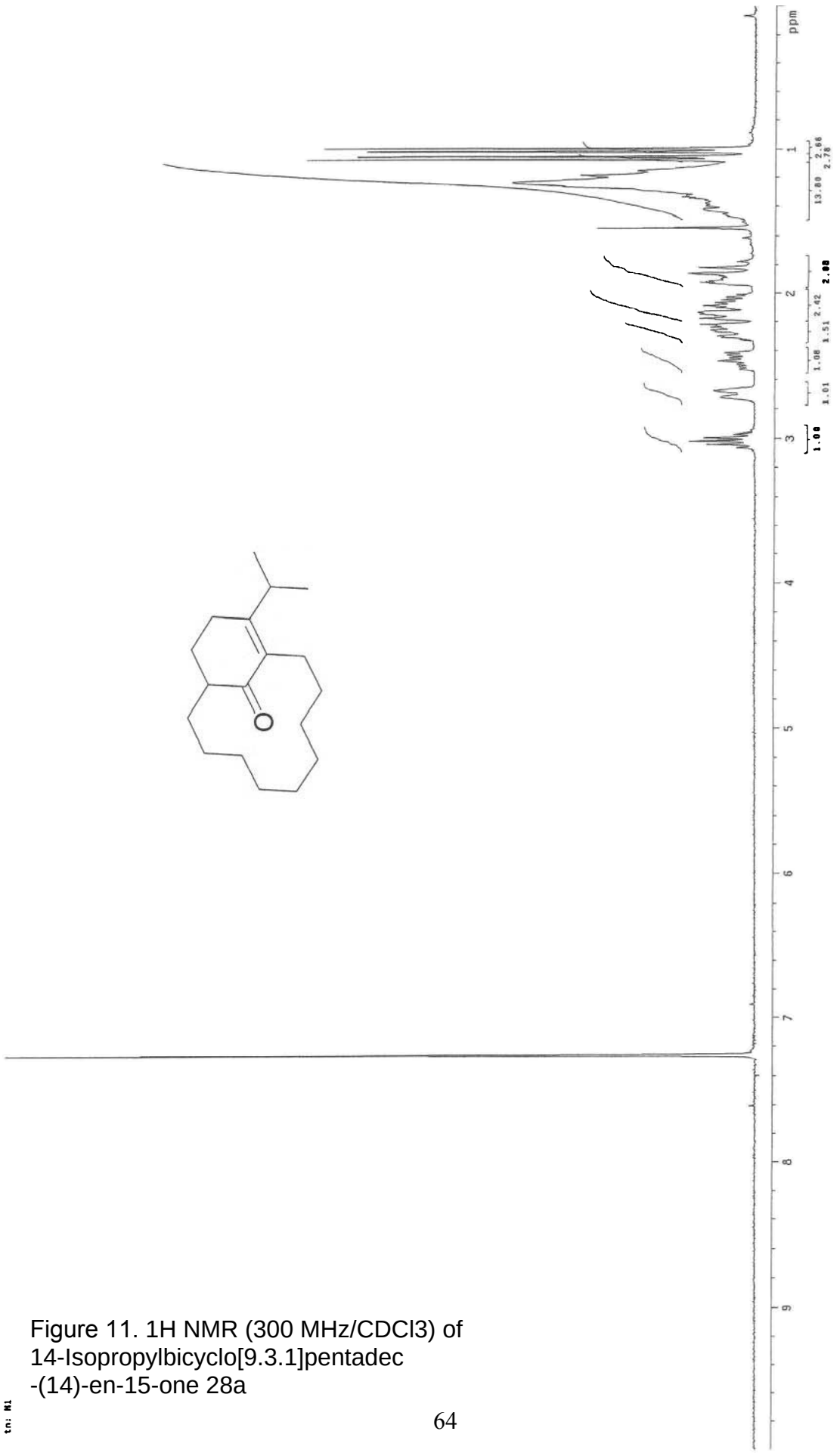


Figure 11. 1H NMR (300 MHz/CDCl3) of 14-Isopropylbicyclo[9.3.1]pentadec -(14)-en-15-one 28a

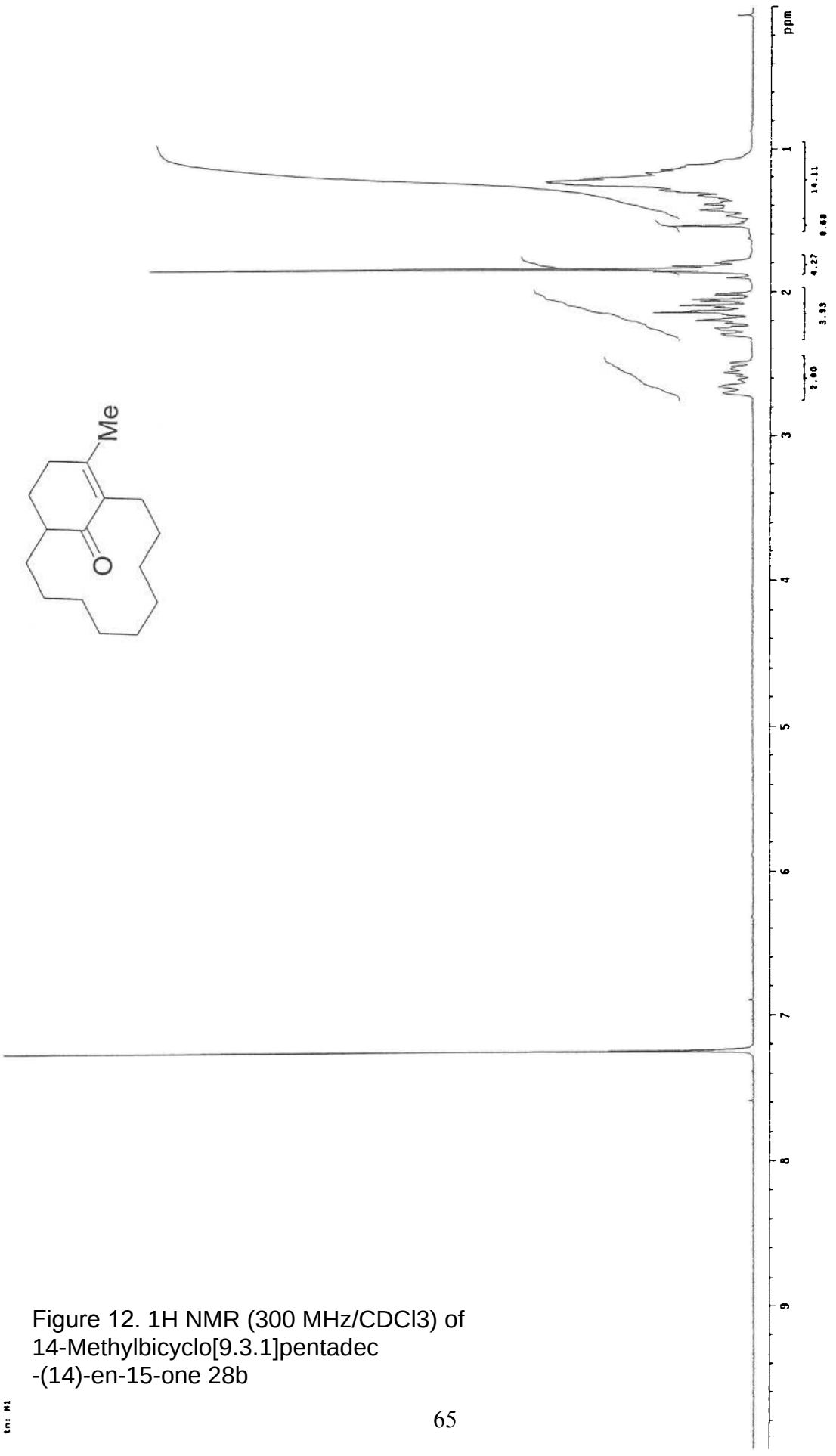


Figure 12. 1H NMR (300 MHz/CDCl3) of 14-Methylbicyclo[9.3.1]pentadec -(14)-en-15-one 28b

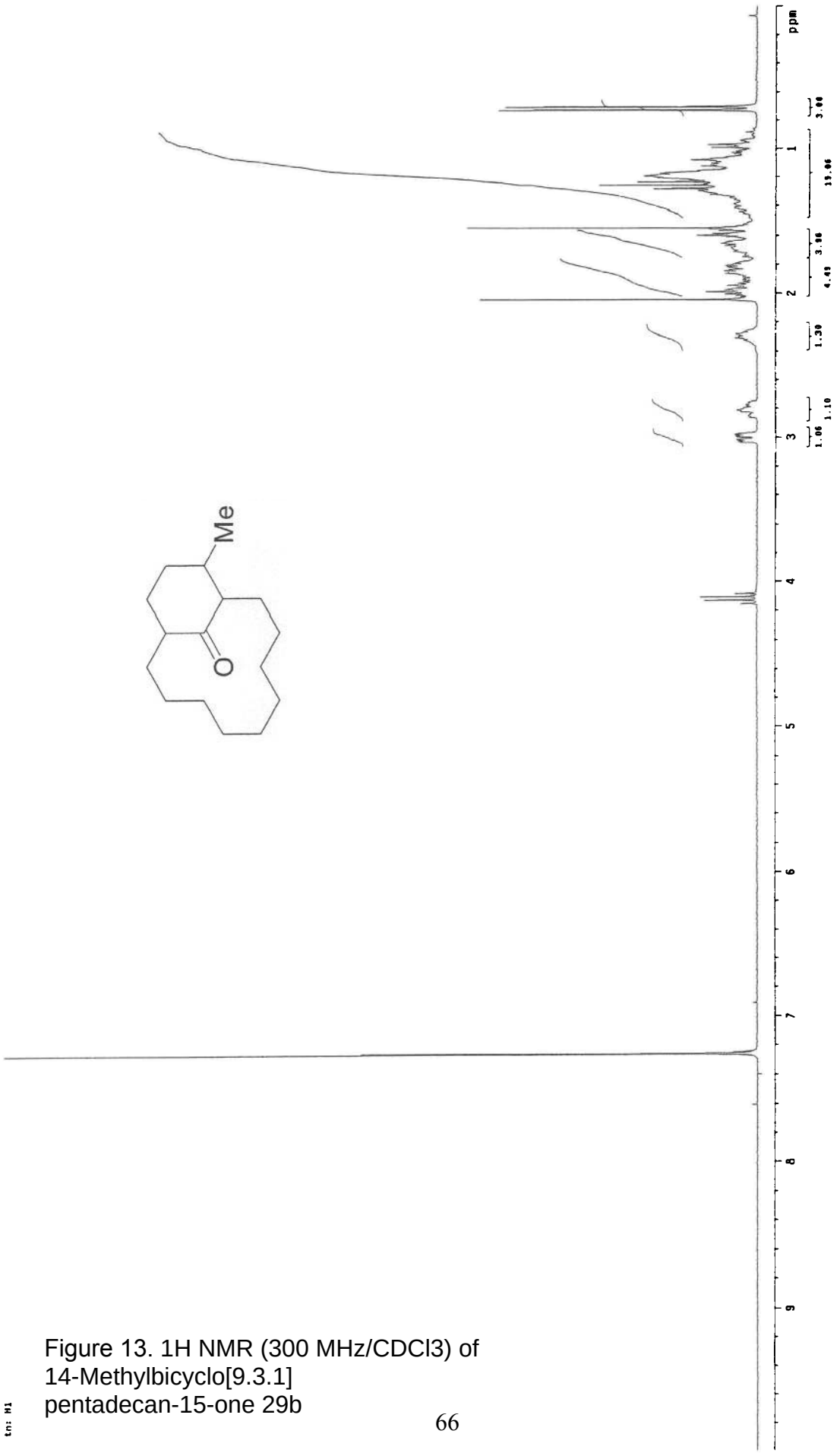


Figure 13. 1H NMR (300 MHz/CDCl3) of 14-Methylbicyclo[9.3.1] pentadecan-15-one 29b

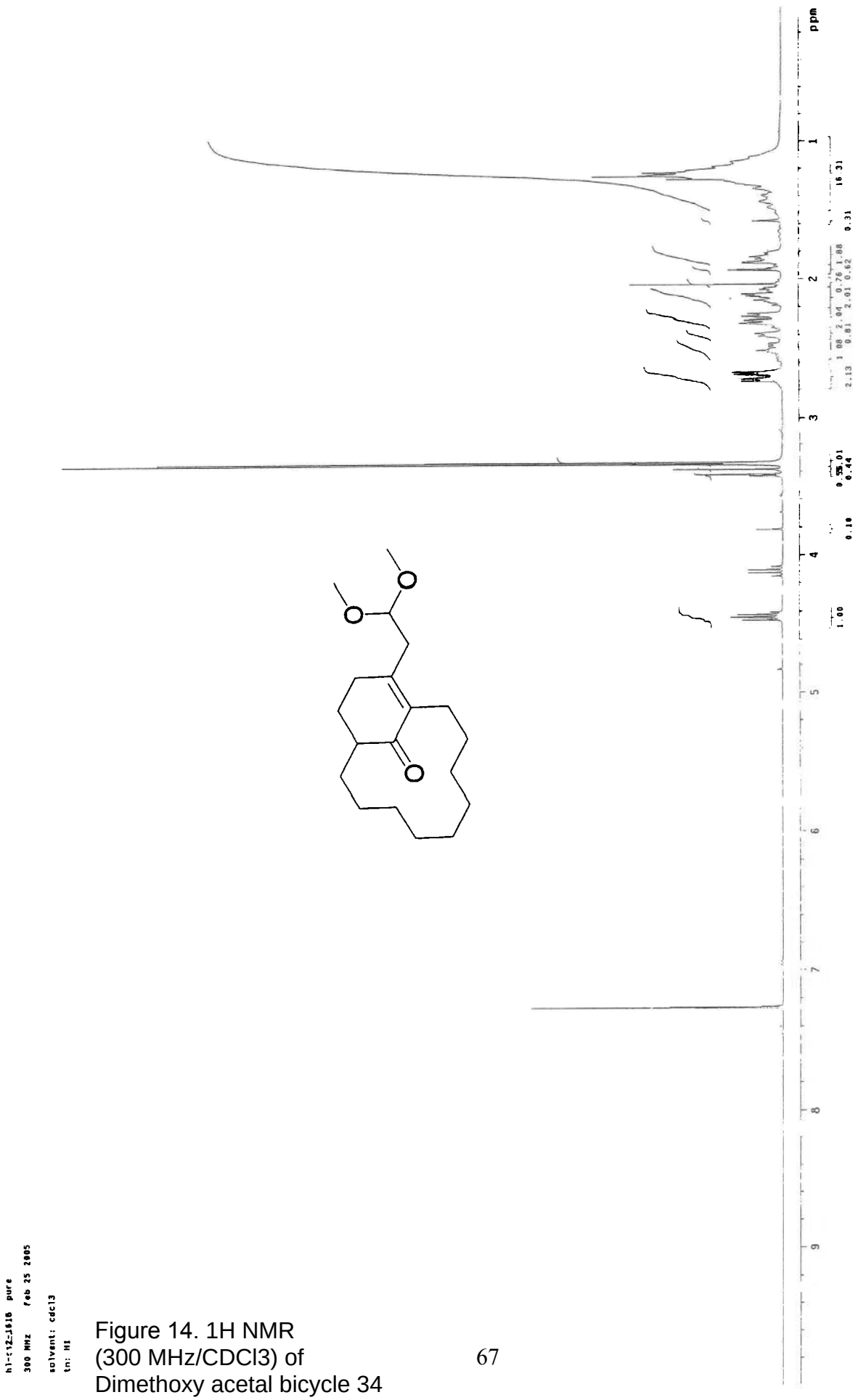


Figure 14. 1H NMR (300 MHz/CDCl3) of Dimethoxy acetal bicycle 34

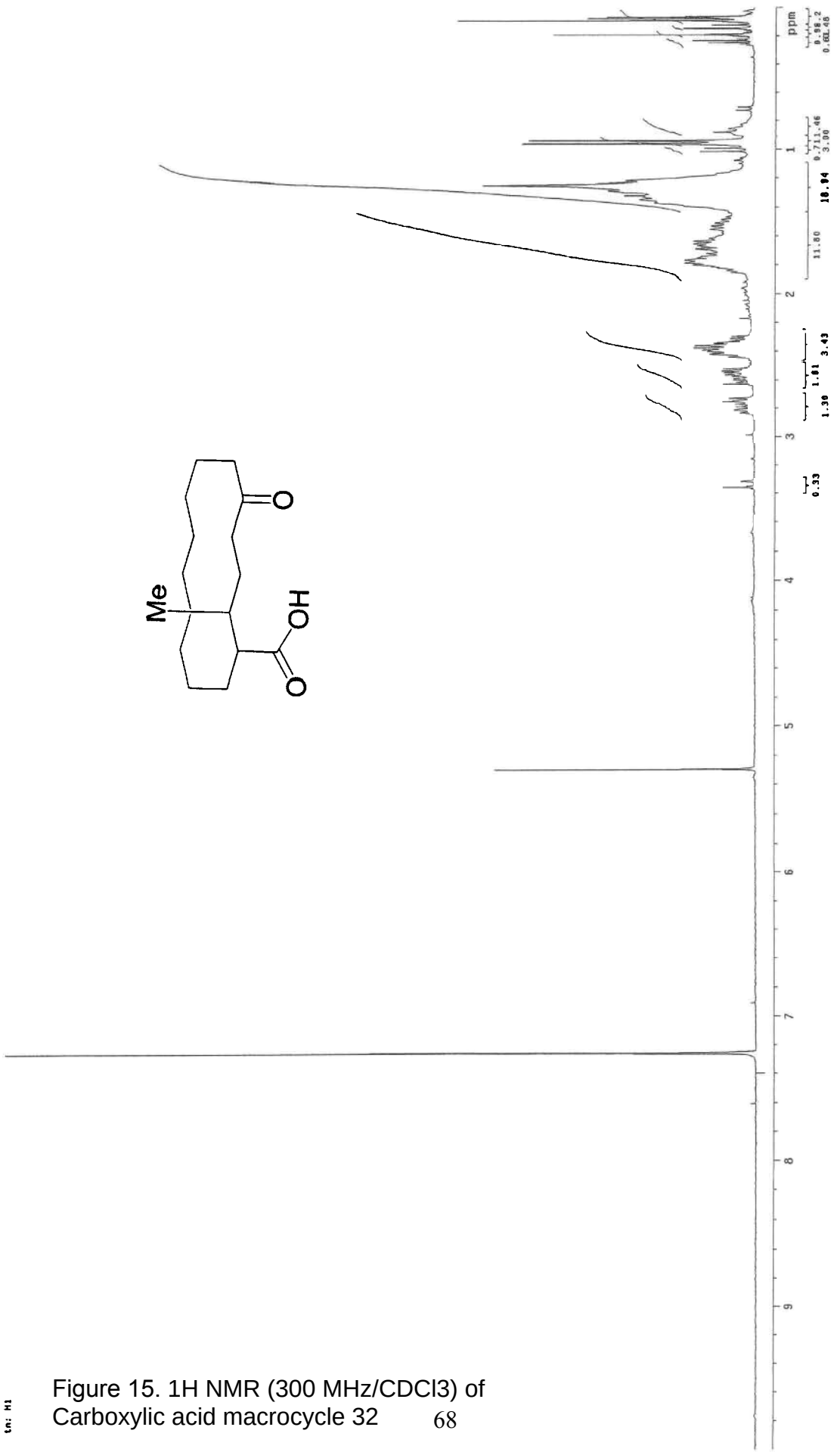


Figure 15. 1H NMR (300 MHz/CDCl3) of Carboxylic acid macrocycle 32

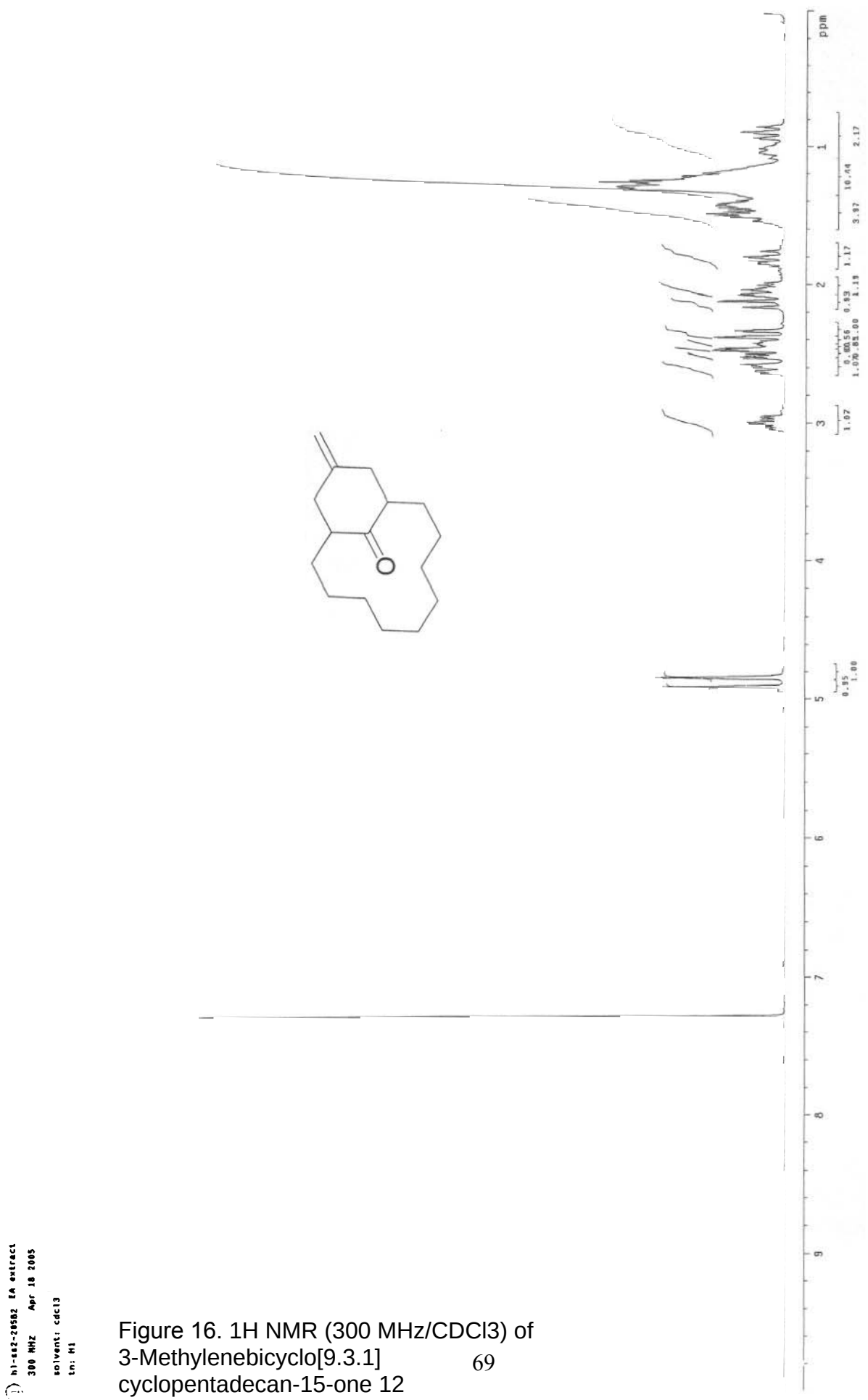
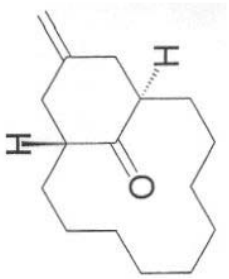
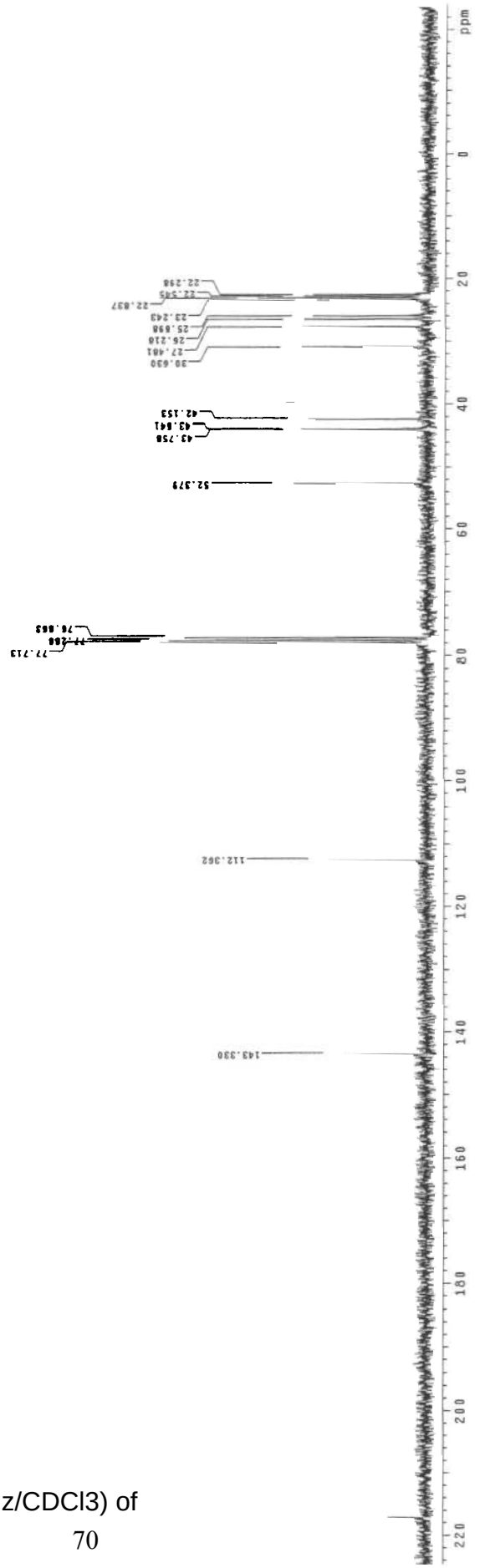


Figure 16. 1H NMR (300 MHz/CDCl3) of 3-Methylenebicyclo[9.3.1] cyclopentadecan-15-one 12





hl-sz-2058 carbon
75 MHz Apr 27 2005
solvent: CDCl3
tn: C13

Figure 17. 13C NMR (75 MHz/CDCl3) of 3-Methylenebicyclo[9.3.1] cyclopentadecan-15-one 12

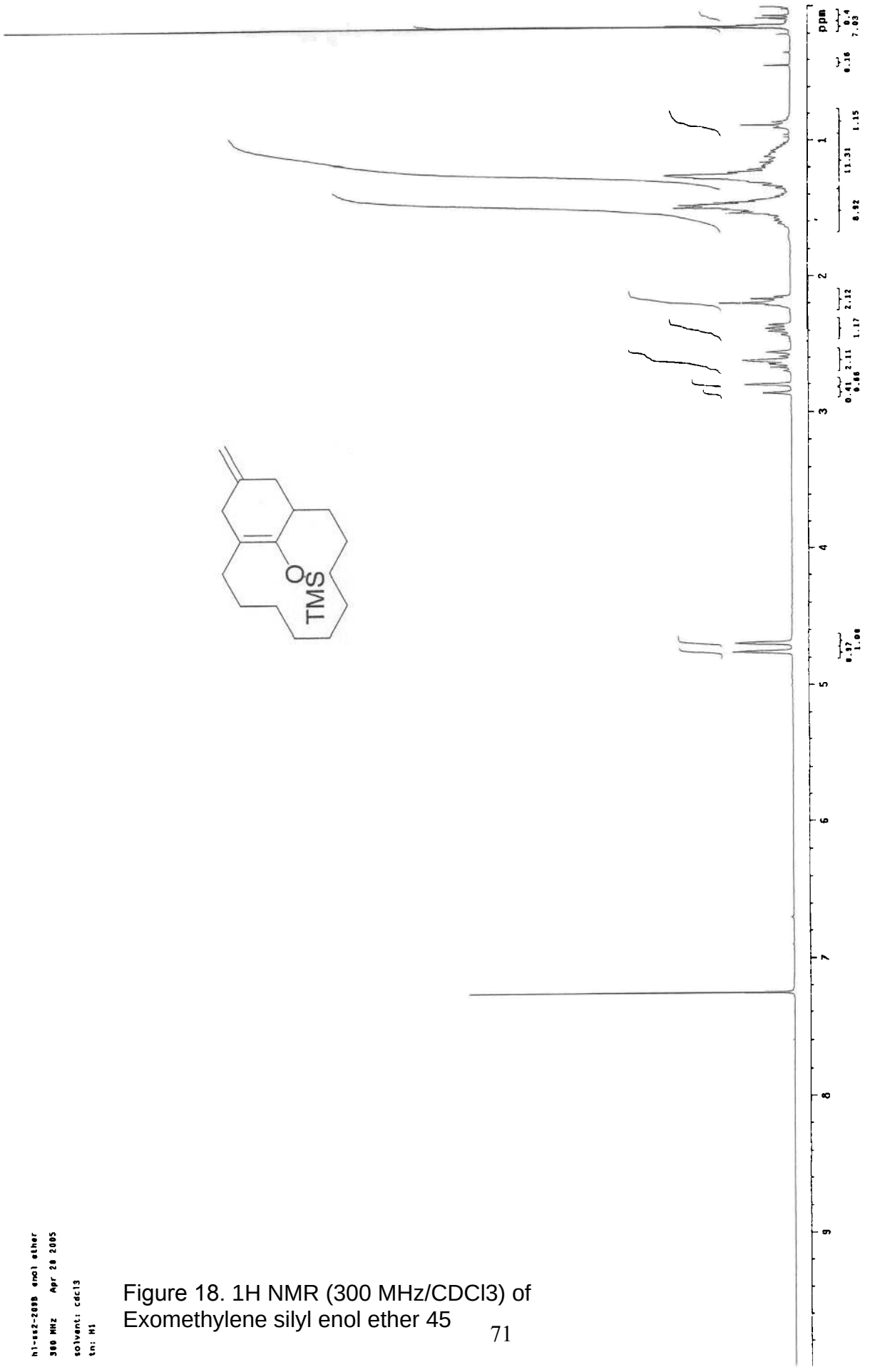


Figure 18. 1H NMR (300 MHz/CDCl3) of Exomethylene silyl enol ether 45

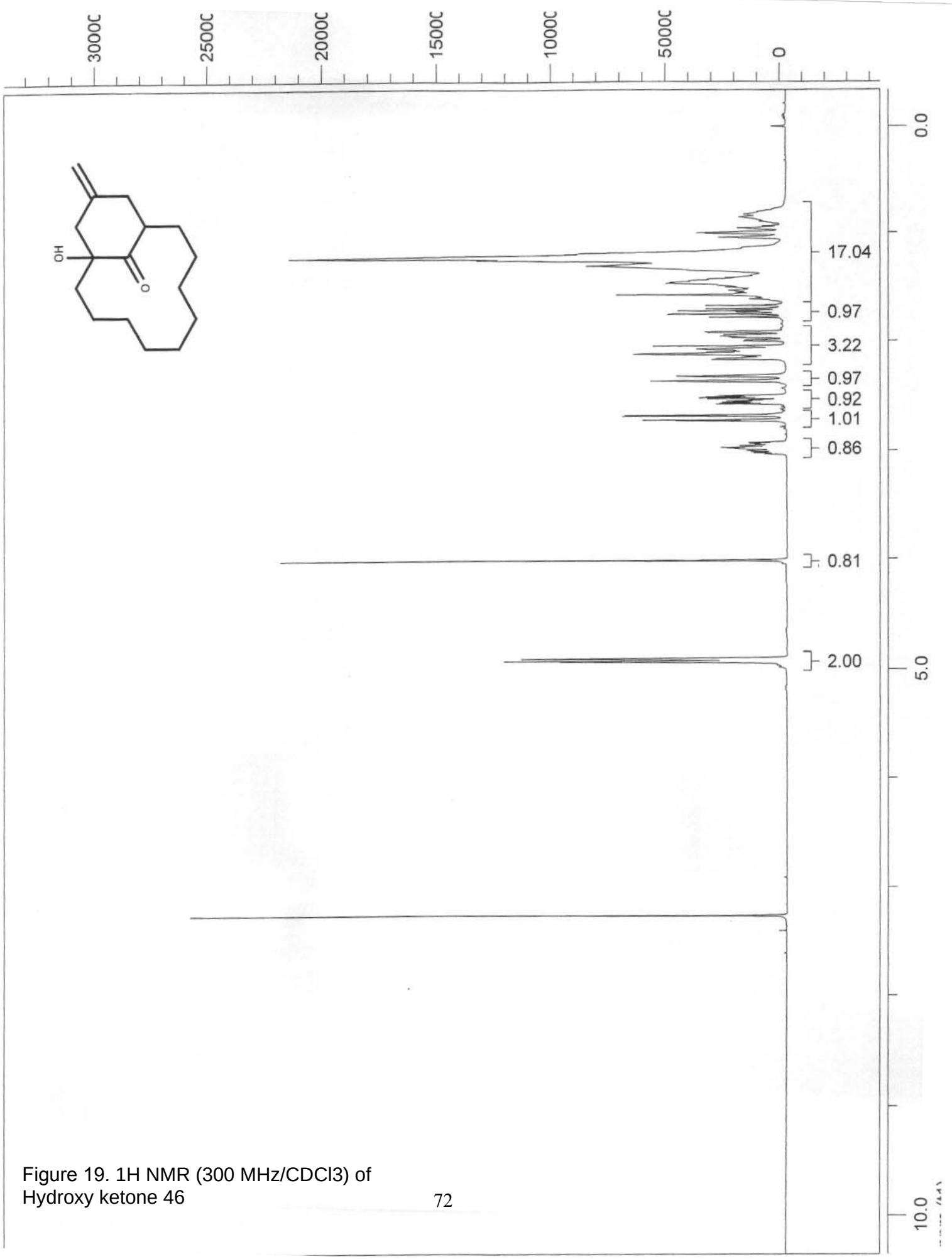


Figure 19. 1H NMR (300 MHz/CDCl3) of Hydroxy ketone 46

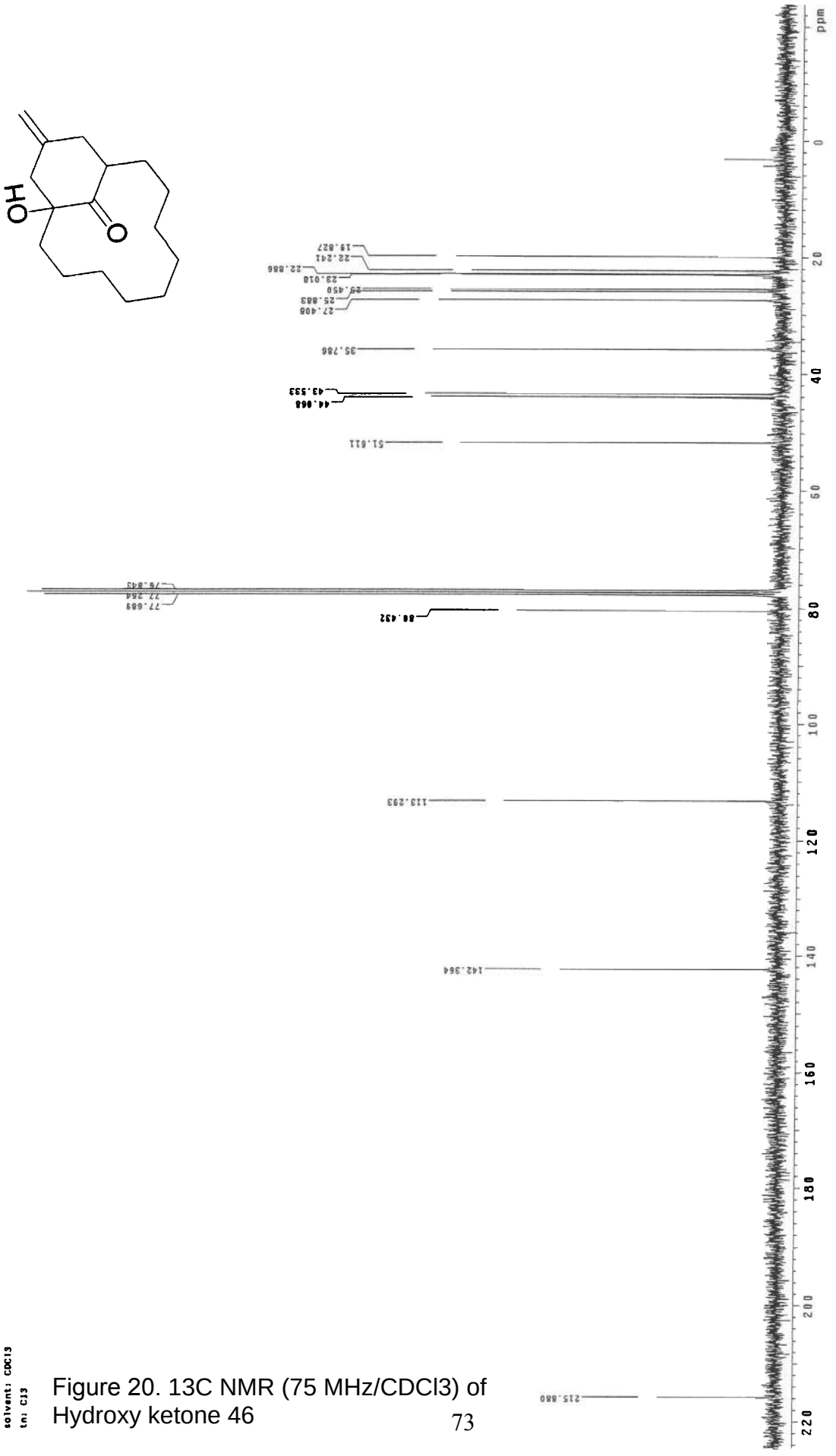


Figure 20. 13C NMR (75 MHz/CDCl3) of Hydroxy ketone 46

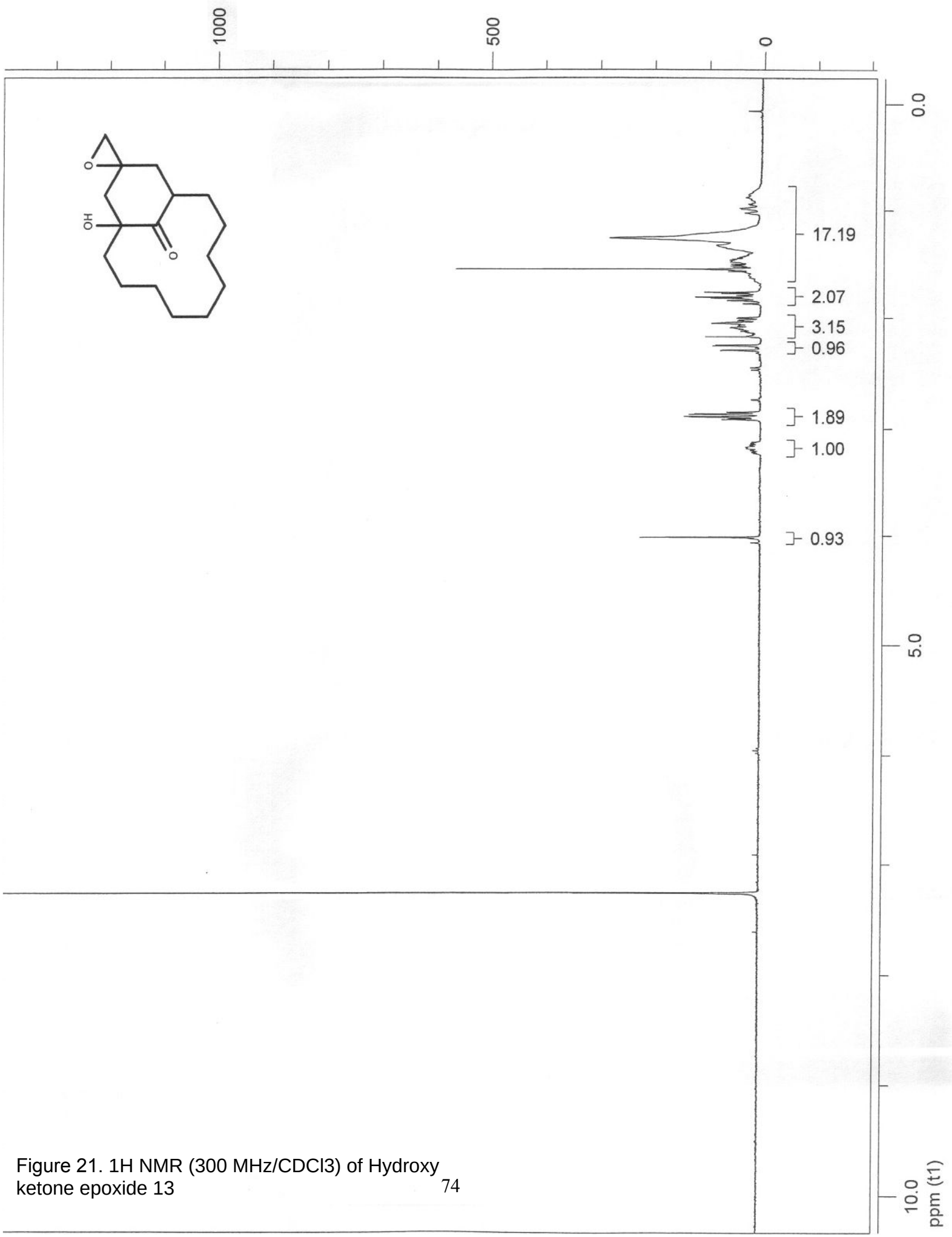


Figure 21. 1H NMR (300 MHz/CDCl3) of Hydroxy ketone epoxide 13

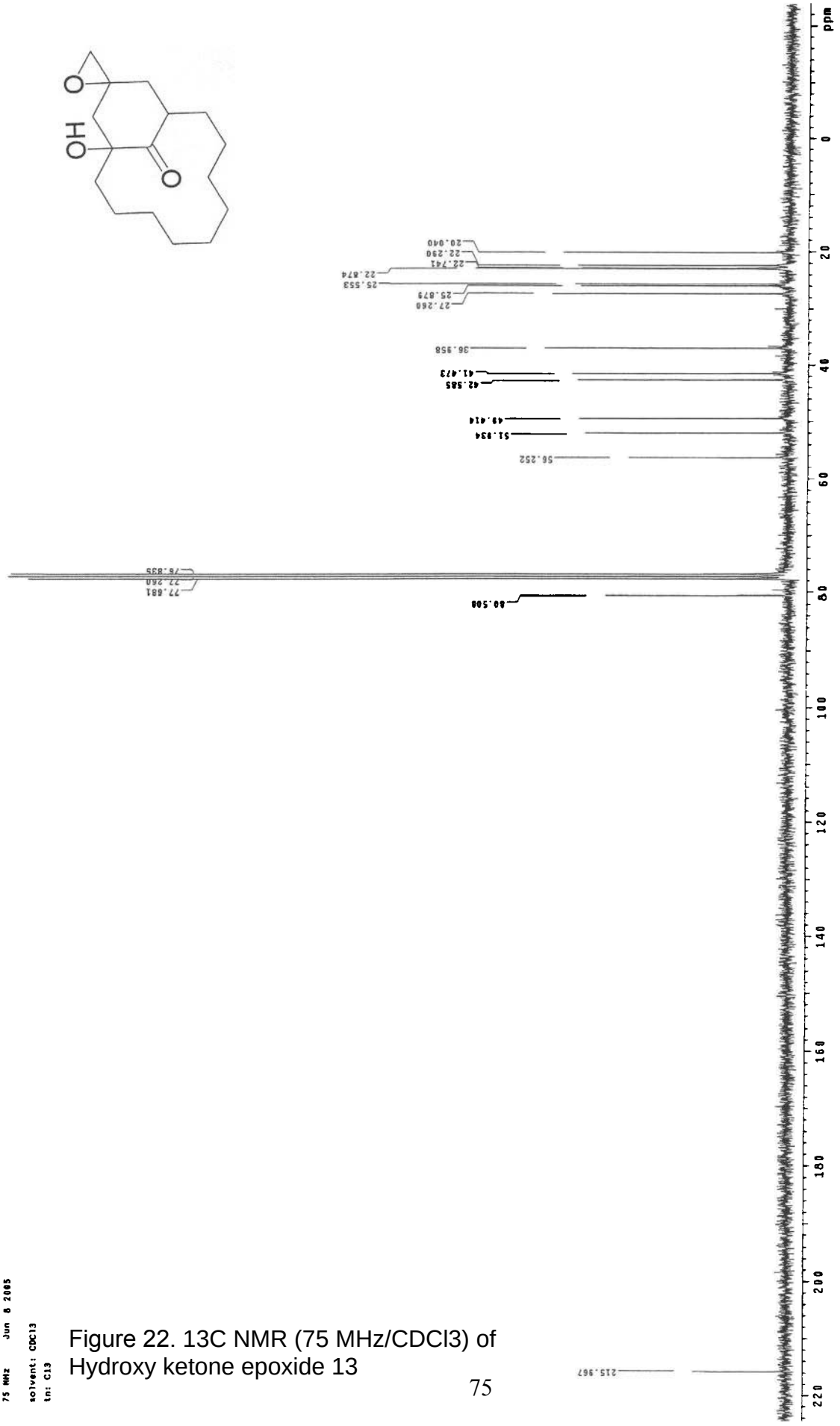


Figure 22. 13C NMR (75 MHz/CDCl3) of Hydroxy ketone epoxide 13

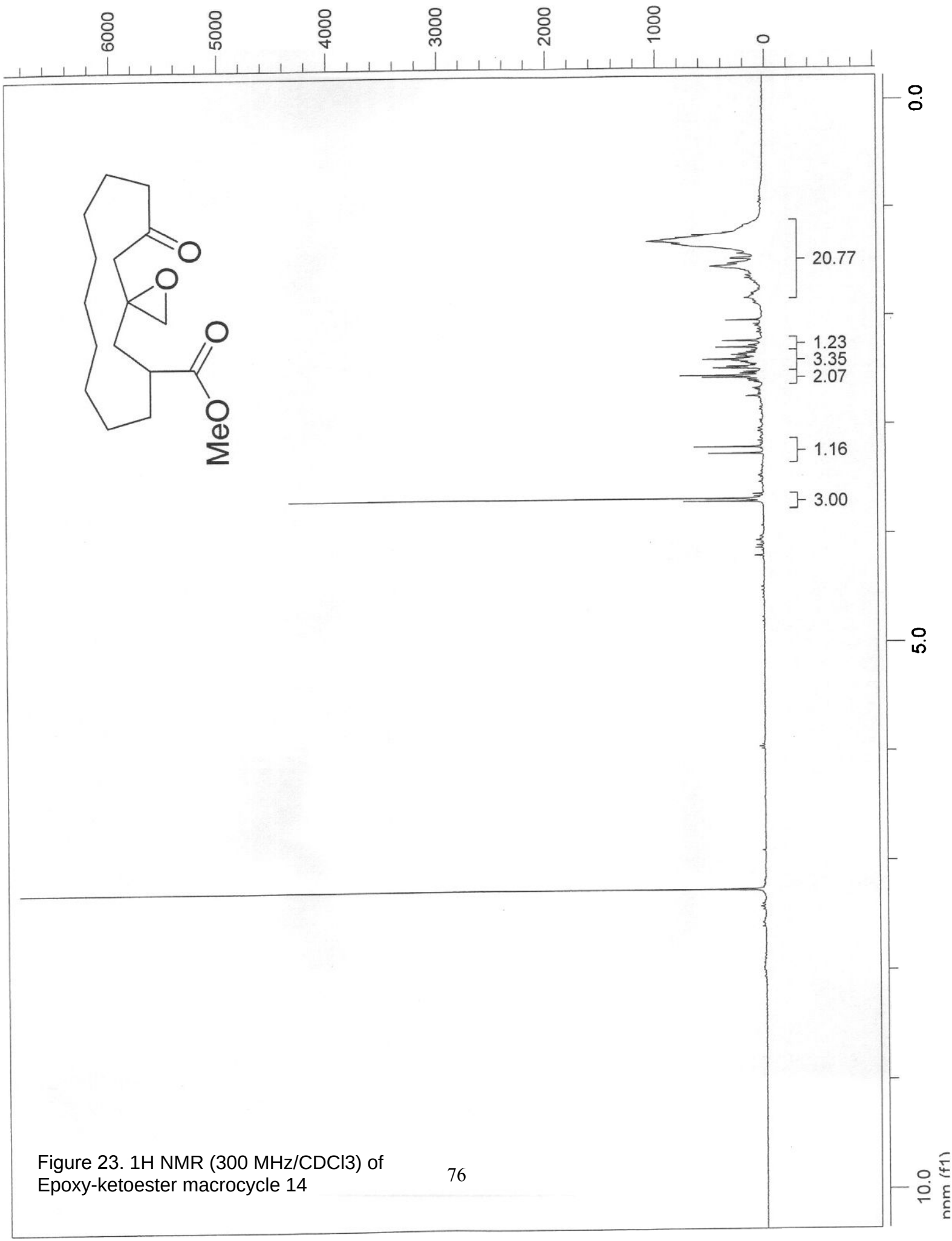


Figure 23. 1H NMR (300 MHz/CDCl3) of Epoxy-ketoester macrocycle 14

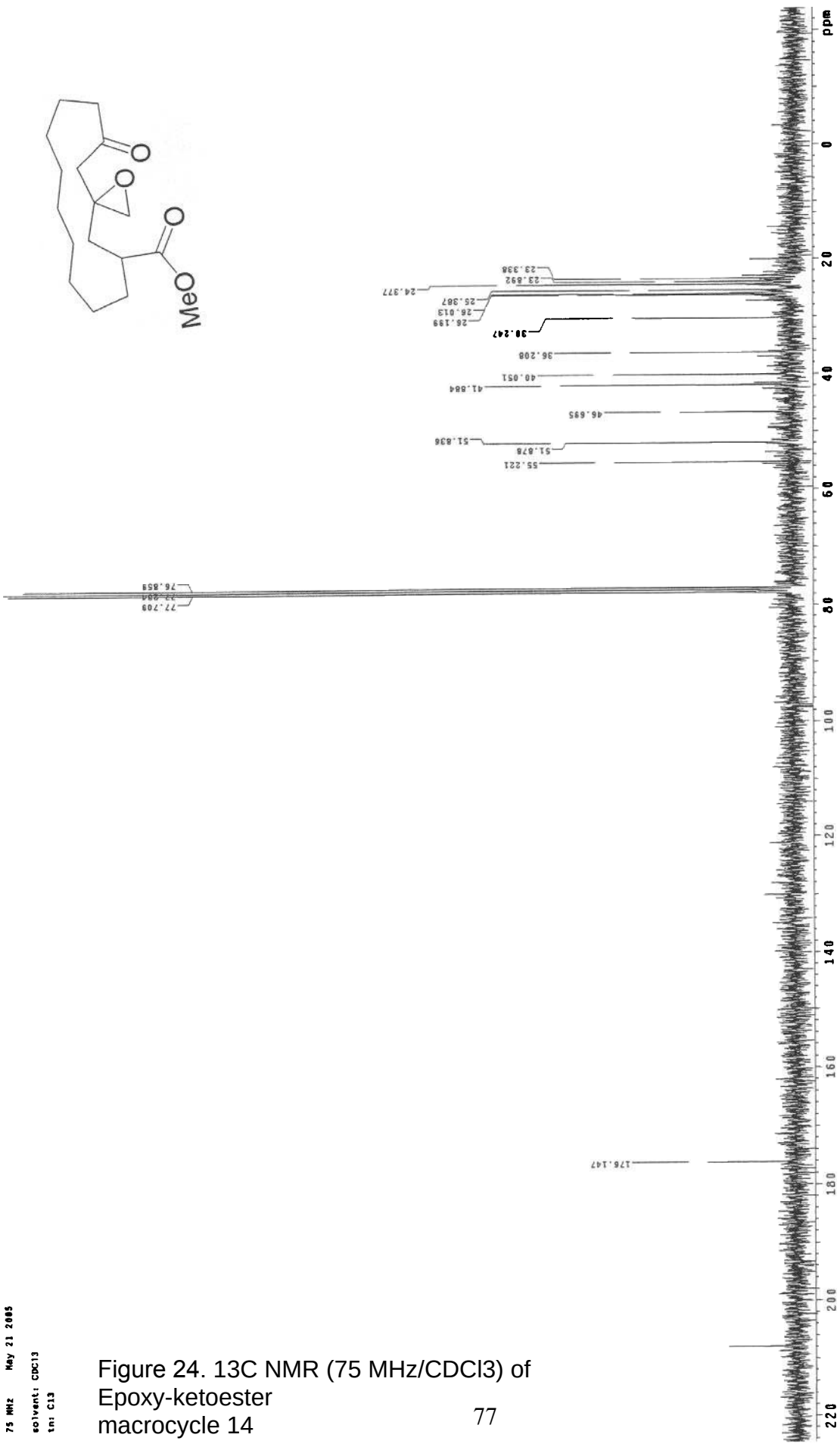


Figure 24. 13C NMR (75 MHz/CDCl3) of Epoxy-ketoester macrocycle 14

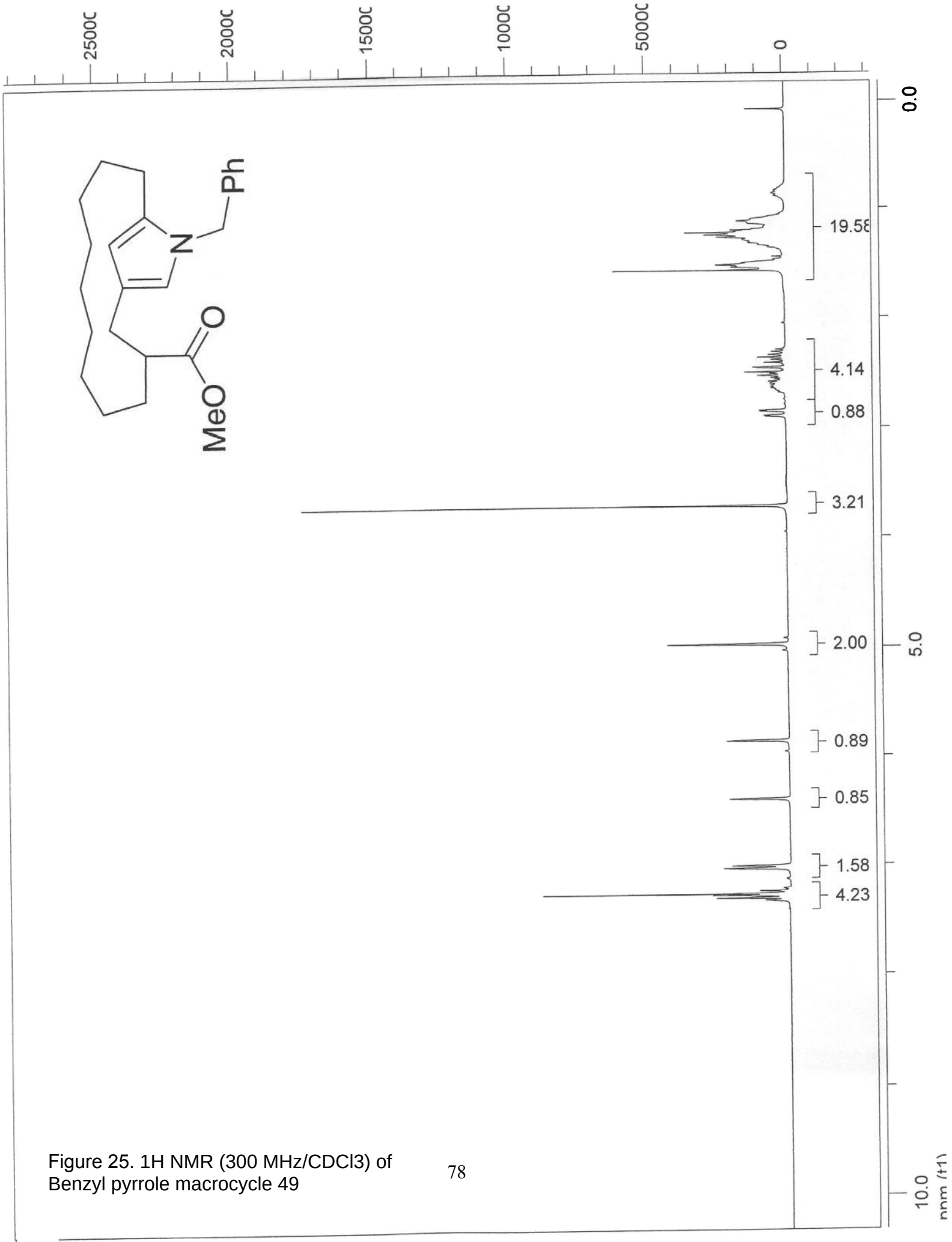


Figure 25. 1H NMR (300 MHz/CDCl3) of Benzyl pyrrole macrocycle 49

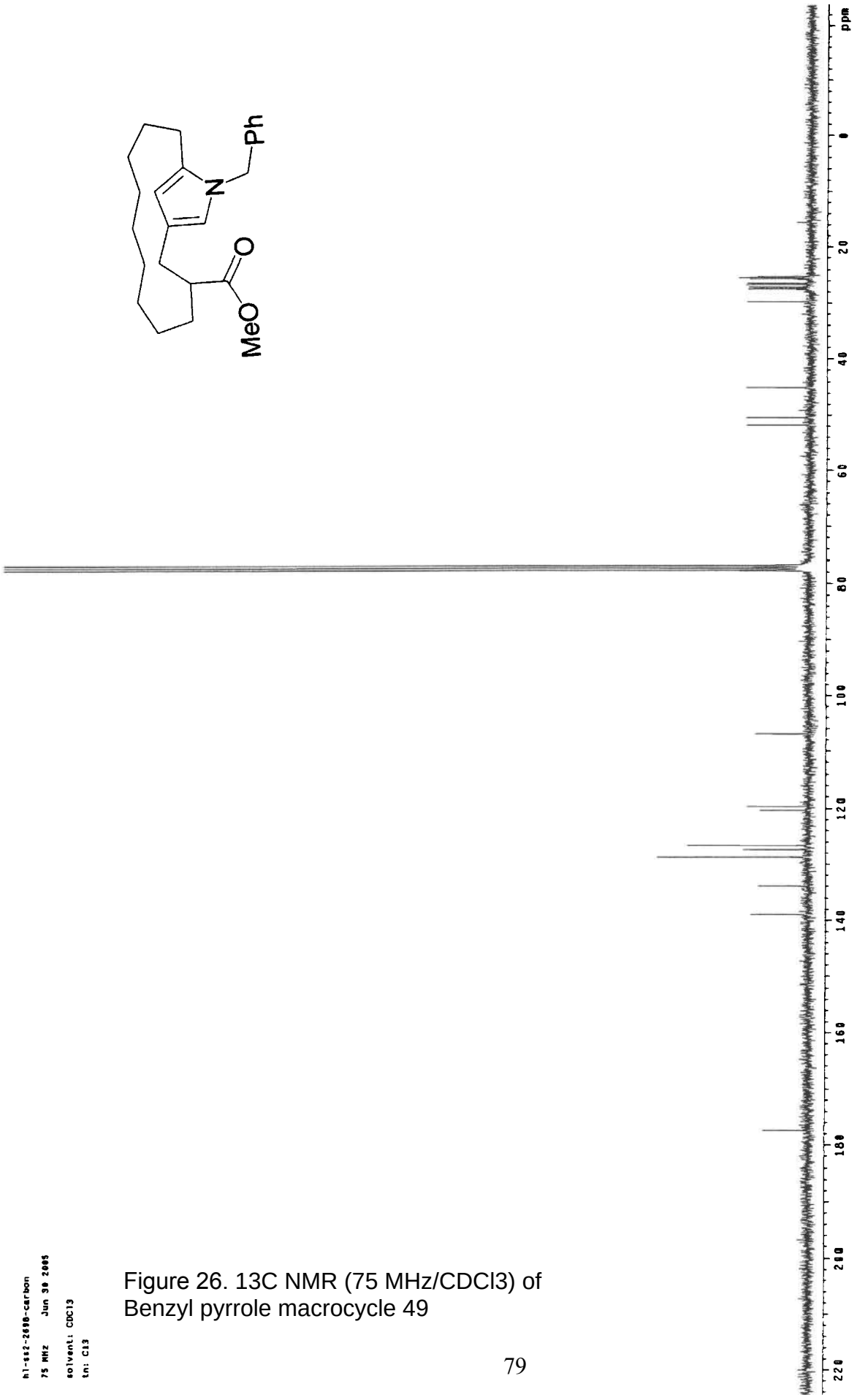


Figure 26. 13C NMR (75 MHz/CDCl3) of Benzyl pyrrole macrocycle 49

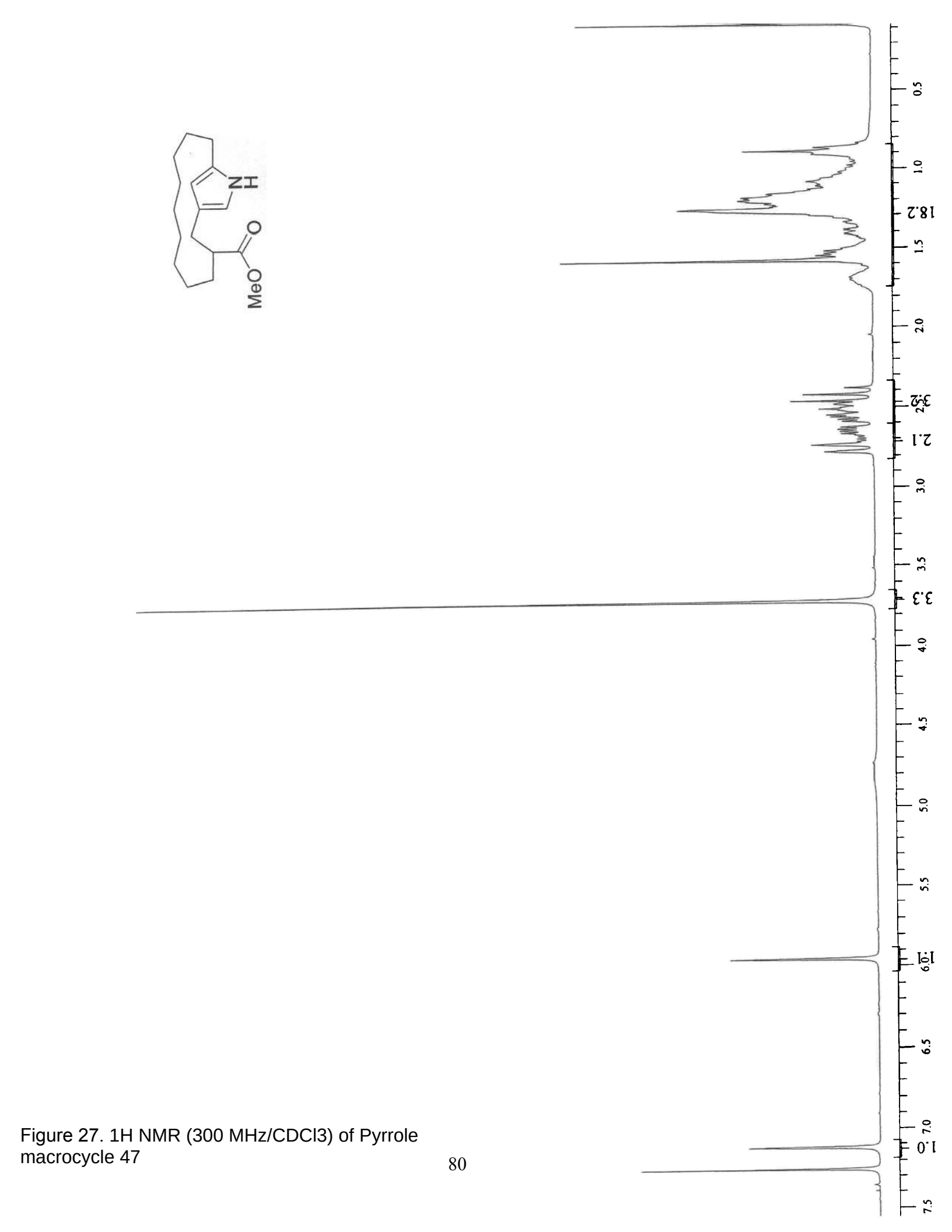


Figure 27. 1H NMR (300 MHz/CDCl3) of Pyrrole macrocycle 47

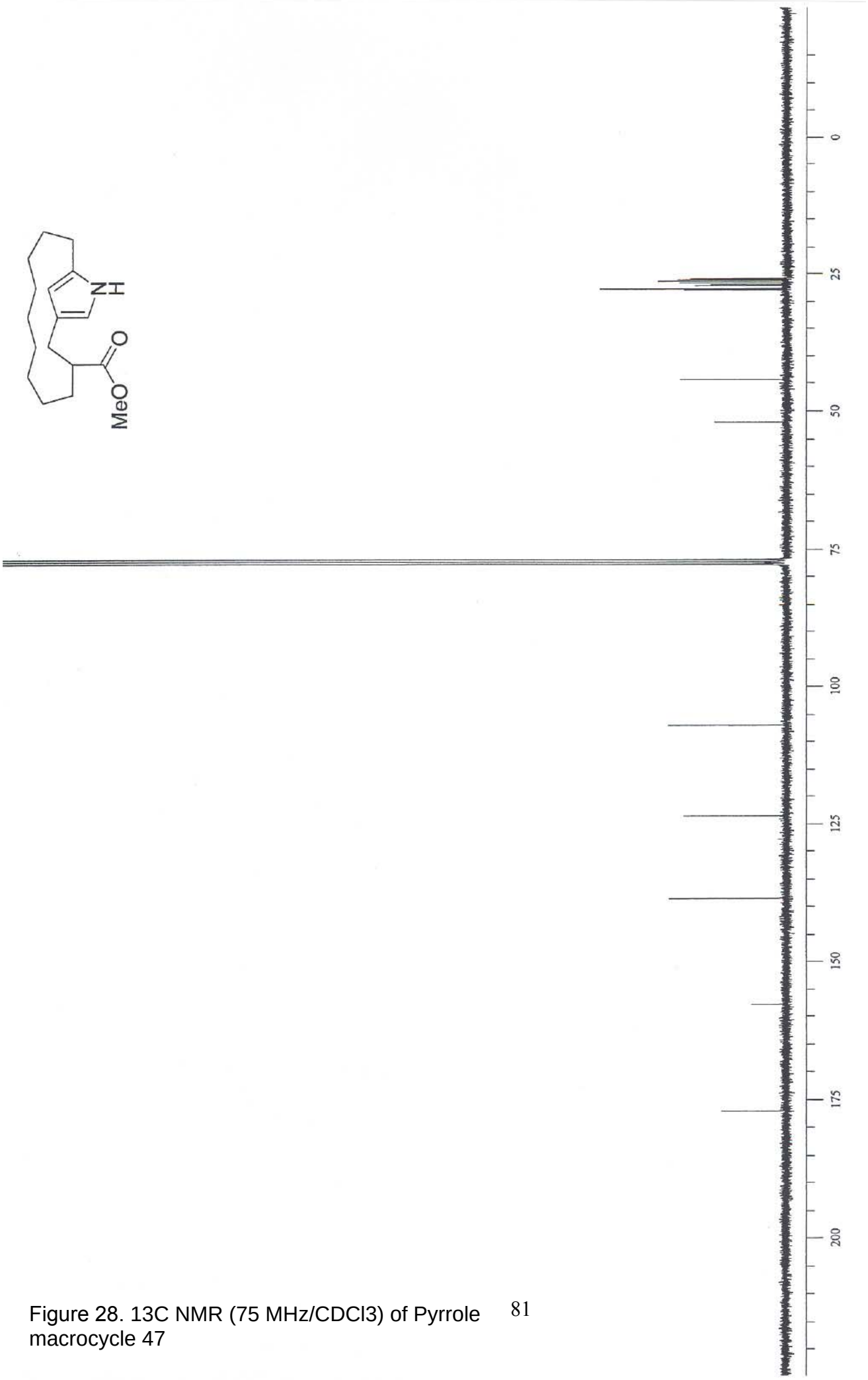
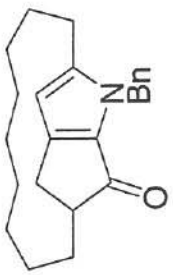


Figure 28. 13C NMR (75 MHz/CDCl3) of Pyrrole macrocycle 47



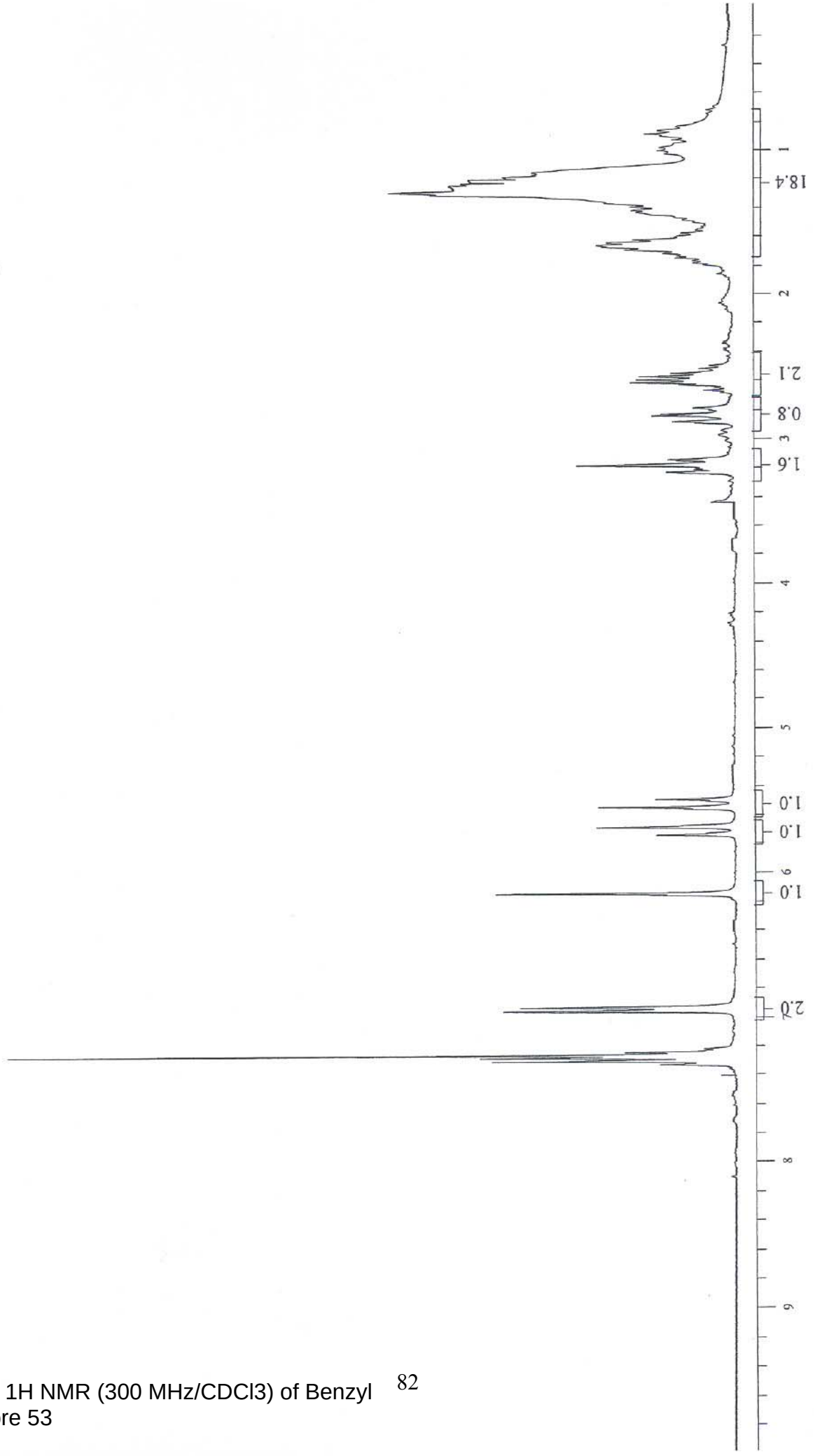
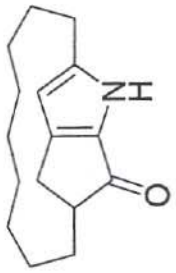


Figure 29. 1H NMR (300 MHz/CDCl3) of Benzyl tricyclic core 53



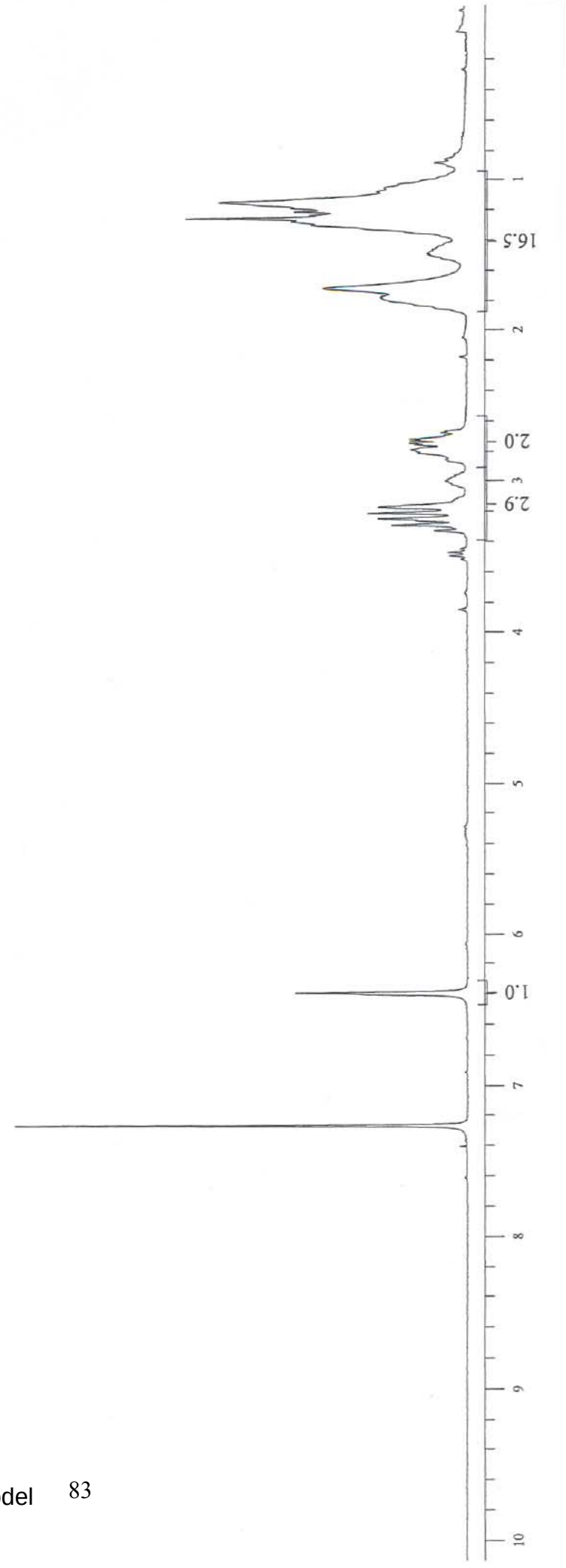


Figure 30. 1H NMR (300 MHz/CDCl3) of Model tricyclic core 15

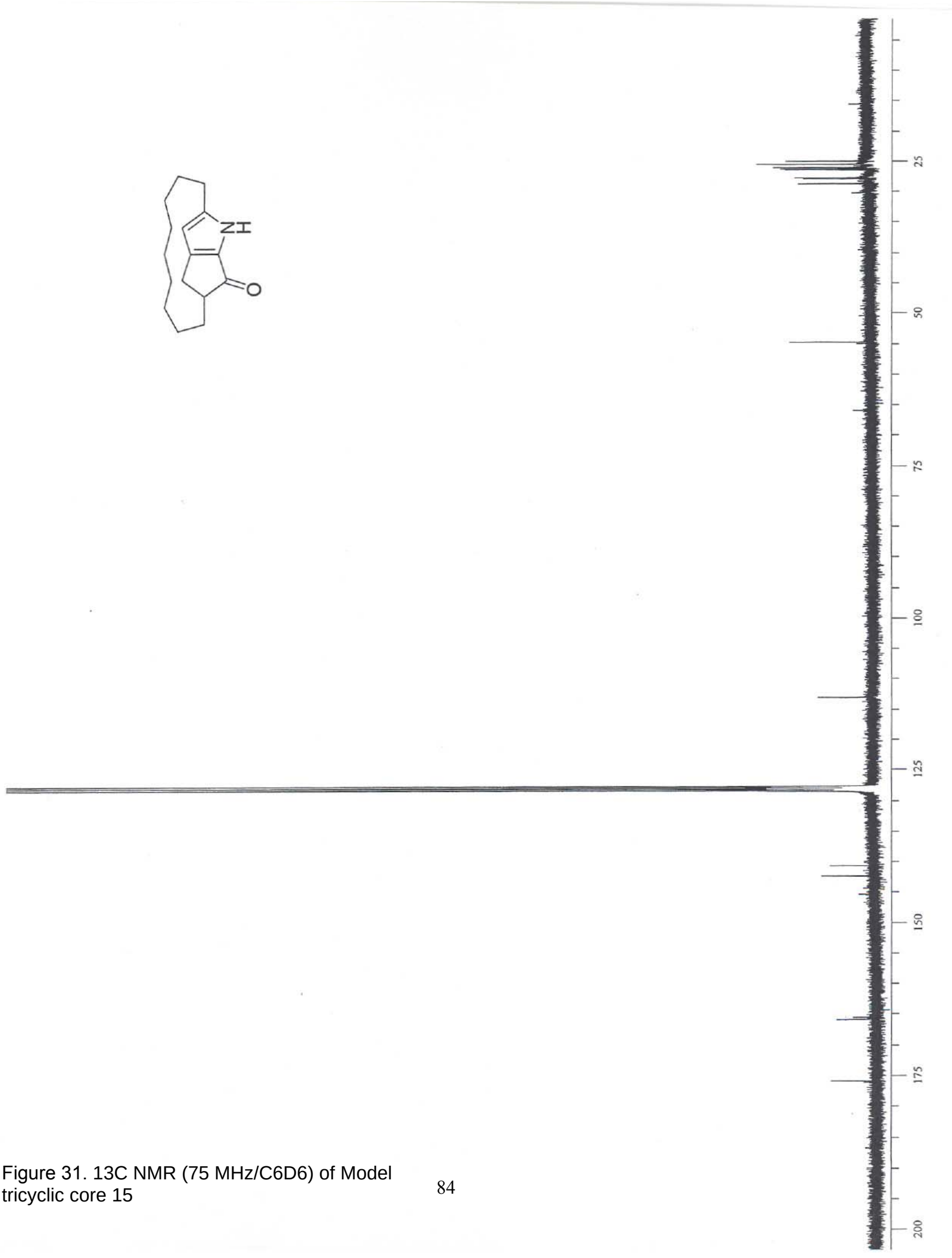


Figure 31. 13C NMR (75 MHz/C6D6) of Model tricyclic core 15

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BIOGRAPHICAL SKETCH

EDUCATION

Florida State University **Tallahassee, FL**

Candidate for **M.S. thesis**
Major: **Organic Chemistry (synthetic)**

Project (Advisor: Dr. Gregory B. Dudley)
- A Ring Expansion Approach to Roseophilin

Courses
- Reactions, Synthesis, Structure, Physical Org Chem, Spec Chem Analysis

Publications/Presentations
- Manuscript submitted (ol051730k, "A Ring Expansion Approach to Roseophilin")
- Manuscript in writing (Procter & Gamble, Org. Lett.)
- Sam Salamone; Stephen Jarboe; Paul Dybas; David Berry; Jared Randall; Catalytic Asymmetric Hydrogenation of Tetra-substituted Olefins: Stereoselective Synthesis of β,β-Disubstituted Glycine Esters. Procter and Gamble 2004 Organic Chemistry CoP Symposium, Sharonville, OH Sept. 29-30, 2004

Merrimack College **North Andover, MA**

B.S. May 2002 *Summa Cum Laude*
Major: Chemistry Minor: Business Administration
Cumulative GPA: **3.6** Major GPA: **3.8**

Honors
- Organic senior of the year (2002), James W. Kennedy Jr. Award (2001), Commonwealth Future Grant (2001-2), McGravey/Werman Analytical Laboratory Scholarship Award (2000), Chemistry student of the year (1999), Dean's List (all semesters)

EXPERIENCE

The Procter and Gamble Pharmaceuticals **Norwich, NY**

Chemical Development Chemist-(Intern) Summer 2004
- Total Synthesis, Methodology Development,

and Project related work

NeoResins (Avecia) **Wilmington, MA**

Applications Coatings Specialist – (Coop) Summer 2001

- Perform Chemistry/Business skills in Coatings Industry

Groundwater Analytical **Buzzards Bay, MA**

Lab Technician/Analyzer –(Coop) Summer 2000

- Perform GC/GC-MS instrumentation in volatile organics

Merrimack College **N. Andover, MA**

Chemistry Demonstration Assistant 2000-2002

- Performed chemistry experiments at local high schools

Math Tutor 1999-2000

- Teach students all types of college math

Microscale Chemistry Lab Assistant 1998-1999

- Assisted in teaching microscale lab techniques under Dr. Singh

CURRENT/FUTURE

Vertex Pharmaceuticals Incorporated **Cambridge, MA**

Senior Scientific Associate

- Work in a process group upon graduation