EXPANDING THE SCOPE OF THE NUCLEOPHILE CATALYZED ALDOL LACTONIZATION (NCAL) PROCESS AND TRANSFORMATIONS OF THE RESULTING β–LACTONES

A Thesis

by

ANDREA SLAVA MATLA

Submitted to the Office of Graduate Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

May 2008

Major Subject: Chemistry

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Approved by:

Chair of Committee,	Daniel Romo
Committee Members,	Brian Connell
	Gil Rosenthal
Head of Department,	David H. Russell

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ABSTRACT

Expanding the Scope of the Nucleophile Catalyzed Aldol Lactonization (NCAL) Process and Transformations of the Resulting β-Lactones. (May 2008)

Andrea Slava Matla, B.S., University of Pittsburgh

Chair of Advisory Committee: Dr. Daniel Romo

Expanding the uses of the NCAL and finding the spectrum of substrates best suited for such a transformation has been the main effort of my research. Previous studies had focused on aldedydes as the requisite functionality that would provide the needed electrophilicity in order to complete the aldol; however, recent advancements have introduced ketones as a viable carbonyl. With an established protocol in hand, I set out to explore various substrates that could yield β-lactones in good to moderate yields such as amino acid derivatives, diones, and large cyclic formations as well as simple, straight chain acids with varying groups α to the ketone. In general, I was able to establish a basic framework of substrates that are highly and/or moderately susceptible towards the NCAL and current studies continue to further expand the scope.

In addition to making β-lactones, I investigated alkyl cuprates as soft nucleophiles to afford addition at the β carbon yielding a variety of acids. Substrates for cuprate additions have been expanded to bulkier and multi-cyclic β-lactones and applied to the synthesis of a Merck IND intermediate. Additions to bi- and tri-chloro β-lactones due to the presence of the resulting moity in natural products are currently being studied.

DEDICATION

To the love of my life: Manly

ACKNOWLEDGEMENTS

First, I would like to thank Dr. Daniel Romo for letting me work in this group on such exciting and interesting projects. I would also like the thank Dr. Brian Connell and Dr. Gil Rosenthal for their time and willingness to serve on my masters committee.

Secondly, I would like to thank my mother, Oksana Matla, for without her help, constant encouragement and reassurance that I am not dying, I would surely have gone insane. Also, I thank my father, Zenon Matla, for without his unfortunate circumstances I may have never had the initial desire to study chemistry. Many thanks to my grandmother, Olga Dymicky (babcha) for her recipes, genuine concern for what I have been eating and taking care of the most loving, cutest, smartest and best dog in the world, Manly. Last, but not least, many thanks to my family: Talia, Shasha, Claudio, Maya-woman, Luca-man, Eva-evushks and Teta Lida for without their stories, care and laughter I would not be where I am today.

I also owe many thanks to every member in the Romo Group for always being there to answer questions, offer help and discuss any topic from science to theology. Although I have not made many good friends here in College Station, there are a few who have provided much influence and encouragement towards the successful completion of my degree: Shaohui Wang, Bartek Mika and Paolo Bottarelli.

Finally, I would like to thank Ukraine for being a constant source of inspiration, passion and pride in my life. I love her past, present and future, her people, traditions and culture; for without knowing where we came from, we cannot know where we are going. 

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CHAPTER I

INTRODUCTION: RECENT ADVANCES IN ORGANOCATALYZED STEREOSELECTIVE ALDOL-LACTONIZATIONS

A. Nucleophile (Lewis Base) Promoted Tandem Aldol-Lactonizations: Introduction and History

Modern day synthetic organic chemistry requires scientists to possess a vast arsenal of chemical tools which allow them to pursue larger, more interesting and more structurally complex compounds and/or natural products. Tools such as catalysts, chiral reagents, established reactions and useful intermediates can greatly improve efficiency and cost when considering strategies toward total syntheses. Cyclic esters, or lactones have been used to accomplish such challenges and have found great utility in this area. Similarly, there have been several advancements made in the synthesis of lactones, making their usefulness and applicability quite broad in chemical endeavors.

There are several methods to make β-lactones. These range from the most basic approaches such as iodolactonization and bromolactonization to more ambitious routes such as Lewis acid promoted [2+2] cycloadditions or asymmetric aldol-lactonizations with chiral catalysts. As the name implies, an aldol-lactonization process merges two of the most useful reactions in organic synthesis. In addition, adding Lewis bases, Lewis acids or organocatalysts improve the efficiency and propels both of these

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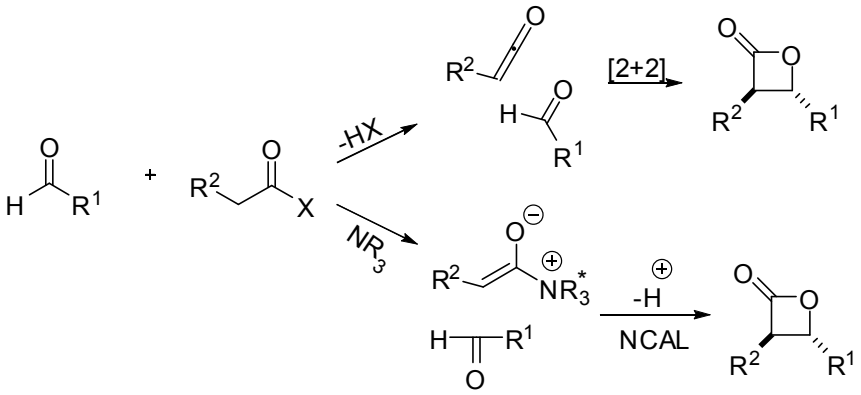
This thesis follows the style of the *Journal of the American Chemical Society.*

transformations into powerful methodologies. Here, we will explore some of the origins, applications and advancements made in organocatalyzed aldol-lactonizations and each of the respective catalyst sub-categories.

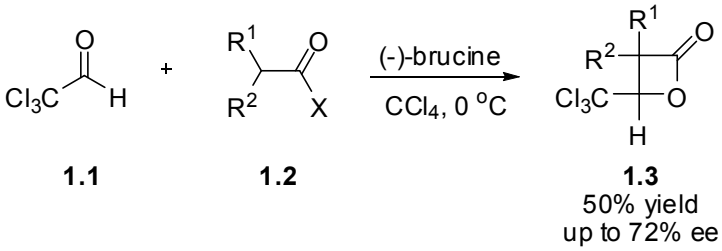
Scheme 1.1

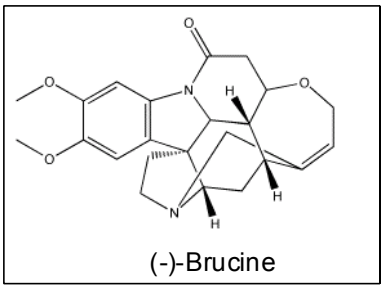


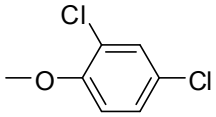
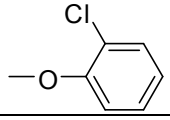
B. Lewis Bases as Chiral Nucleophilic Promoters

In 1966, Borrmann and Wegler[1] first synthesized optically active β-lactones via an aldol-lactonization process consisting of α-chlorinated aldehydes, a chiral Lewis base (nucleophilic promoter) and halogenated ketones in which ketene would be generated *in situ*. The β-lactones were isolated in moderate to good yields with enantioselectivity up to 72% (Table 1).

Table 1. Examples from the work of Borrmann and Wegler.

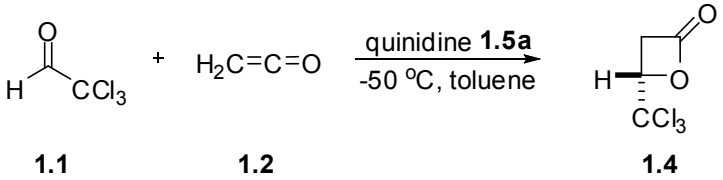




entry	R^1	R^2	yield (%)
1	H	H	69
2	Cl	Cl	39
3	H		63
4	H		45

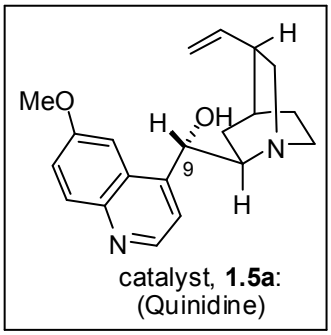
In 1982, Wynberg and Staring[2] building on the precedent of Borrmann and Wegler and reported the use pseudo-enantiomeric cinchona alkaloids, specifically quinidine **1.5a** and quinine **1.5b,** to catalyze the net [2+2] cycloaddition of chloral **1.1** and ketene **1.2** and obtain the β-(trichloromethyl)-β-propiolactone **1.3** in good yields and high enantiomeric excess. Wynberg also noted that with proper choice of catalyst (i.e. pseudo-enantiomer quinine) the enantiomeric β-lactone could be produced (Table 2).

Table 2. Wynberg's seminal studies.

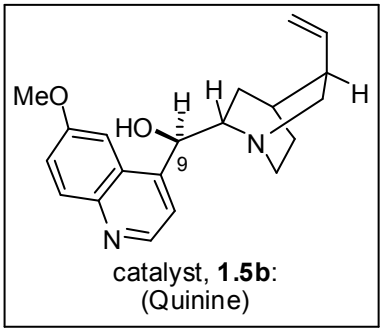


1.1 **1.2** **1.4**

R^1	R^2	% ee quinidine	% ee quinine	yield (%)
CCl_3	H	98	76	89
CCl_2H	H	45		67
CCl_2CH_3	H	91	76	95
$CCl_2CH_2CH_3$	H	89	70	87
$CCl_2C_6H_5$	H	90	68	89
CCl_3	CH_3	94	85	72
CCl_3	C_6H_4Cl-*p*	90	65	68
CCl_3	$C_6H_4NO_2$-*p*	89	65	95



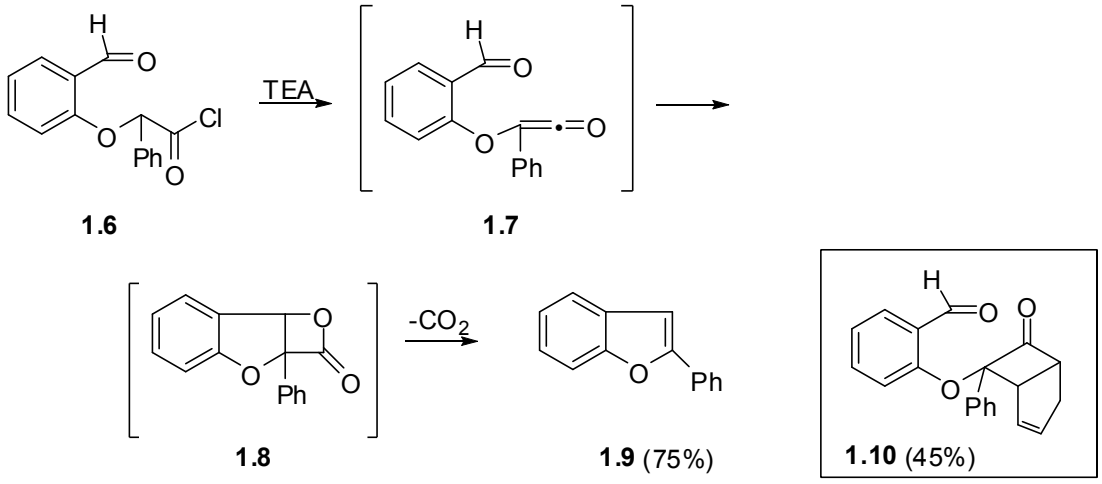
catalyst, **1.5a**: (Quinidine)



catalyst, **1.5b**: (Quinine)

This important advance in the field of catalytic, asymmetric β-lactone synthesis reintroduced them as useful chiral reagents and intermediates for organic synthesis and continues to stand as a benchmark in this area. Although influential, Wynberg's method requires the use of a ketene generator and activated highly electon deficient aldehydes/ketones. Because of these limitations, several other groups[3,4] were prompted to expand upon and improve this promising advancement. Therefore in 1986, Brady employed ketene in a presumed [2+2] cycloaddition to aldehydes and ketones to form substituted benzofurans following decarboxylation of β-lactones (Scheme 1.2).[5]

Scheme 1.2

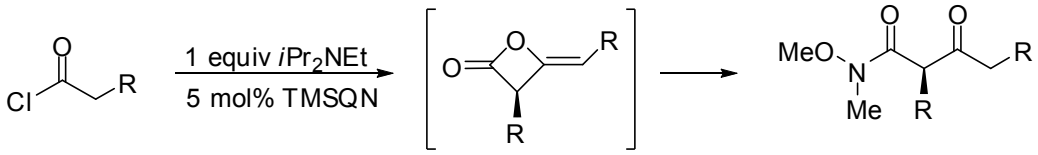


Although Brady presents this as an initial [2+2] cycloaddition, another mechanism may be operative here. The generated ketenes were never identified and excess triethylamine (TEA) could lead to the formation of a possible ammonium enolate intermediate, leading to an aldol-lactonization process to deliver the presumed β-lactone. Although Brady found evidence for a [2+2] cycloaddition from trapping the phenoxyketene **1.6** with cyclopentadine, the product **1.10** was isolated in only 45% yield.

Possibility of a simultaneous generation of an ammonium enolate intermediate cannot be completely disregarded since tertiary amines have been shown to promote aldol-lactonization type pathways via an ammonium enolate (*vide infra*). One such example has been illustrated by Calter *et al*. in 1996 when they used cinchona alkaloid catalysts and their derivatives to catalyze a dimerization reaction of monosubstituted ketenes generated *in situ* to obtain β-lactones with high enantioselectivity. The

intermediate obtained from this transformation has been used as a synthon for polypropionate synthesis.[1c,d]

Scheme 1.3



1.11 **1.12** **1.13**

Also classified as a [2+2] cycloaddition/dimerization, an aldol-lactonization can efficiently operate in forming **1.13** from **1.12**. Continuing with the ketene dimerizations, in 2003 they reported the first examples of catalytic, asymmetric dimerization of *in situ* ketenes generated from acid halides. Cinchona alkaloids were used as the catalysts for these transformations and formation of the acyl ammonium would increase the electrophilicity of the carbonyl, thus facilitating an aldol-lactonization mechanism.

1. Cinchona Alkaloid Catalysts

Cinchona Alkaloids are a family of natural products which are isolated from the bark of cinchona trees which are all indigenous to the slopes of the Andes in South America[6]. Wynberg was the first to use them to catalyze the net [2+2] cycloaddition towards the formation of optically active β-lactones. Although a good foundation, their method was limited to activated carbonyl compounds and use of a ketene generator thus severely limiting the scope.

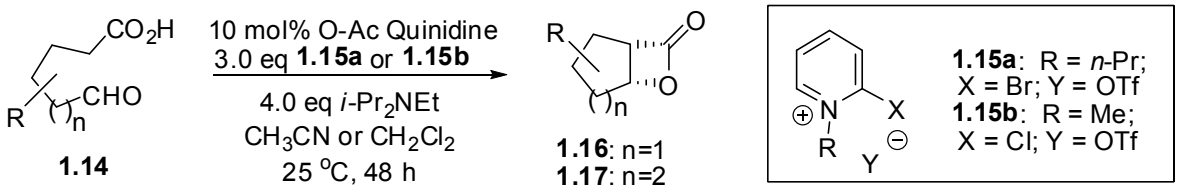
In order to advance the utility of this methodology, the Romo group has been engaged in exploiting these catalysts to access β-lactones in recent years. Noting the drawback in Wynberg's method, conditions were developed which would allow the formation of *in situ* generated ketene via the dehydrochlorination of acid chlorides. In the end, our group was able to extend Wynberg's approach and successfully demonstrated use of activated aldehydes through *in situ* generated ketenes[7] to produce optically active β-lactones (Table 3). In addition, the use of non-activated aldehydes has been exploited in the intramolecular nucleophile catalyzed aldol lactonization (NCAL).[8] Aldehyde acids are used in conjunction with Mukaiyama's reagent as carboxylate activator and cinchona alkaloid derivatives as catalysts to deliver bicyclic β-lactones with high enantiomeric excess (Figure 1).

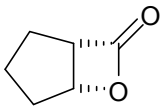
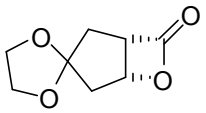
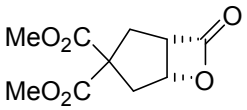
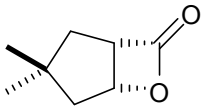
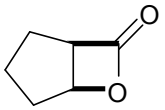
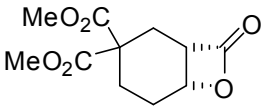
The catalyst used here can be either quinidine or quinine. We then became interested in the catalysts themselves and decided to study their conformations in solution to gain insight into the high enentioselectivity of these reactions. It was determined that although a variety of low energy conformations are operative,[9] only small variations in enantioselectivity were observed for several variations at the C9 position of quinidine.[10] The cinchona alkaloids have proven to be quite effective towards aldehyde-acid conversion to β-lactone, however they are not as useful when applied to the corresponding keto-acid substrates. Currently, our group is expanding studies of the NCAL methodology towards keto-acids and is making good progress (see Chapter III).

2. Cinchona Alkaloid/Lewis Acid Combinations

In addition to using cinchona alkaloids by themselves, Nelson has combined them with Lewis acids in order to induce formation of β-lactones. Although somewhat

Table 3. Catalytic asymmetric intramolecular NCAL reactions leading to bicyclic β-lactones.



entry	β-lactone	cmpd. no.	method[a]	% yield	% ee[b]	config.
1		**1.16a**	**B**	82	92	1*R*, 2*S*[c]
2		**1.16b**	**A**	74	92	3*R*, 4*S*[c]
4		**1.16c**	**A**	74	91	1*R*, 2*S*[d]
5		**1.16d**	**A**	45	90	1*R*, 2*S*[c]
6		**1.16e**	**A**	51	86	1*S*, 2*R*[e]
7		**1.17**	**B**	76	98	1*R*, 2*S*[d]

[a]Method A: Pyridinium salt **1.15a** was employed in CH_2Cl_2 for 48 h. Method B: Pyridinium salt **1.15b** in CH_3CN for 108 h. [b]Enantiomeric excess was determined by chiral GC analysis. [c]Absolute configuration was assigned by reduction to the known diol[1] and comparison of optical rotations. [d]Predicted based on analogy to that determined for β-lactones **1.16a** and **1.16b**. [e]*O*-Ac-Quinine used as the chiral catalyst.

[1] Inoguchi, K.; Fujie, N.; Yoshikawa, K.; Achiwa, K. *Chem. Pharm. Bull.* **1992**, *40*, 2921-2926.

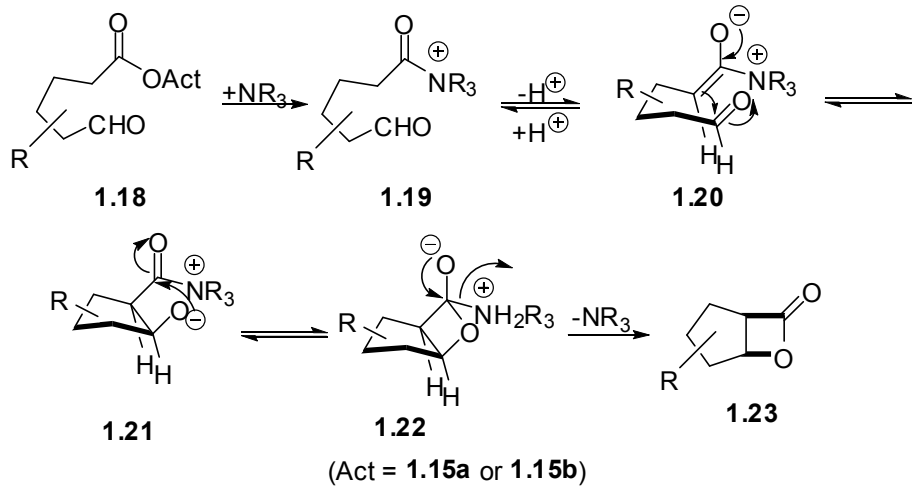
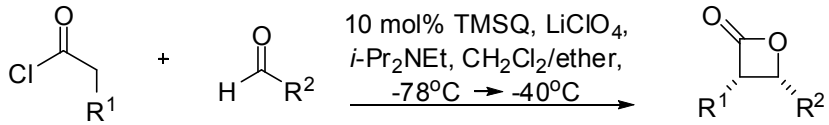


Figure 1. Proposed NCAL mechanism.

mechanistically distinct, in 2004, they used cinchona alkaloids to catalyze acid chloride-aldehyde cyclocondensation (AAC) reactions. They were able to obtain high enantio- and diastereoselection in most cases. They also tested various Lewis acids as cocatalysts in their reactions and lithium perchlorate emerged as particularly effective for commencing the AAC reaction. Additionally, the Nelson group investigated variations at C9 of the alkaloids and found the TMS protected alcohol to be most ideal for both quinidine (TMSQ) and quinine (TMSq).[11] With solvent optimization and Lewis acid stoicheometry modulation, they developed an effective procedure for AAC reactions towards β-lactones (Table 4).

Table 4. Cinchona alkaloid/$LiClO_4$-catalyzed AAC reactions.



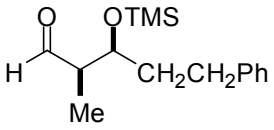
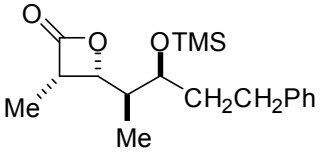
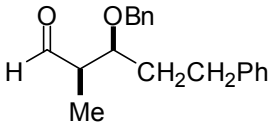
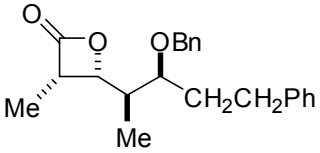
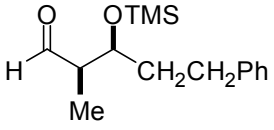
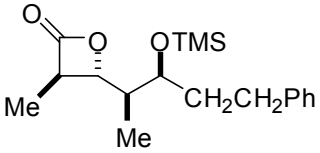
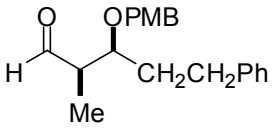
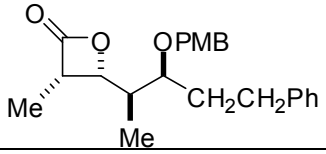
1.24 **1.25** **1.26**

entry	R^1	R^2	%ee[a,b]	%de[c]	yield
1	H	$^cC_6H_{11}$	94[d]	-	85
2	H	CMe_3	96[e]	-	71
3	H	CH_2CH_2Ph	92	-	80
4	Me	$^cC_6H_{11}$	97[f]	>96	74
5	Me	$^oC_6H_4Cl$	>99	96	80

[a] Enantiomer ratios determined by chiral GLC or HPLC. [b] Minor enantiomer not observed for values >99%. [c] Diastereomer ratios determined by ^{1}H NMR of crude product mixtures. [d] 90% ee using TMSq as catalyst. [e] 95% ee using TMSq as catalyst. [f] 96% ee using TMSq as catalyst.

Two years later, Nelson expanded upon his own studies to provide a general methodology applicable towards obtaining optically active *syn*- or *anti*- β-lactones derived from optically active aldehydes. The mechanism is based upon his aforementioned AAC type reactions and provides access to various polypropionate substrates (Table 5).[12]

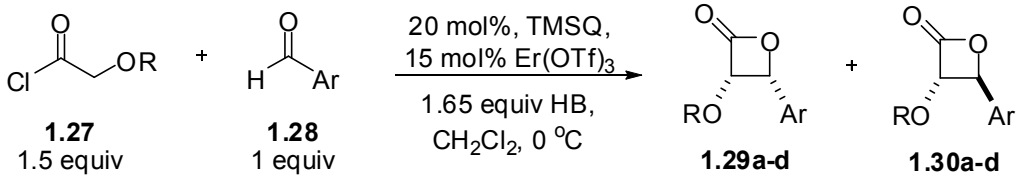
Table 5. Matched and mismatched AAC Reactions.

entry	aldehyde[a]	β-lactone[b]	% de (% yield)[c]
1			≥95 (83)
2			≥95 (78)
3			91 (81)
4			92 (81)

[a] Catalyst (10 mol %) TMS-quinine, entries 1 and 2; TMS-quinidine, entries 3 and 4. [b] Stereochemical asignments based on X-ray structure determinations of derivatives of entry 4's β-lactone and comparison of ^{1}H coupling constants. [c] Diastereomeric ratios determined by HPLC or ^{1}H-NMR analysis of crude reaction mixtures.

Similar to Nelson's studies, Calter has also used a combination of cinchona alkaloids and achiral Lewis acids to catalyze the asymmetric condensation of aromatic aldehydes with acid chlorides. They screened a variety of lanthanide and pseudolanthanide triflates which presumably co-catalyzed the addition of substitued ketenes to unactivated aldehydes (Table 6). In some cases, they were able to obtain the *trans*-β-lactone, which represents the first direct access to such systems with high diastereoselectivity.[13]

Table 6. Yields and selectivities for the formation of β-lactones **1.29a-d**.



1.27 1.5 equiv + **1.28** 1 equiv → **1.29a-d** + **1.30a-d**

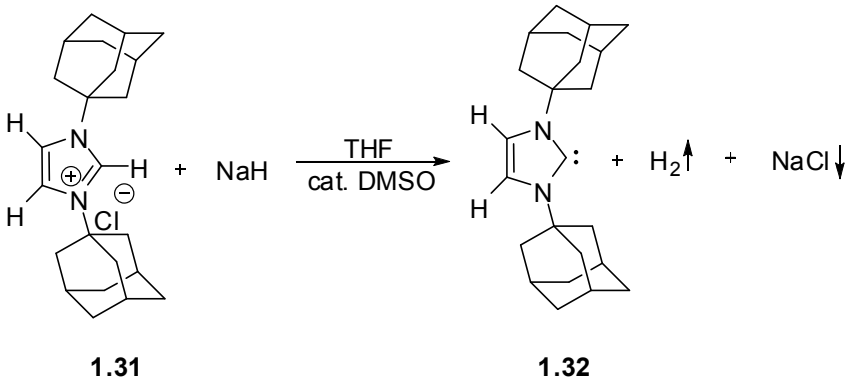
products	**1.29**/**1.30**[a]	% yield of **1.29**[b] (% ee)[c]	% yield of **1.30**[b] (% ee)[c]
a: R = Ph, Ar = Ph	88:12	58 (>99)	nd
b: R = Ph, Ar = 4-bromophenyl	88:12	55 (>99)	nd
c: R = Ph, Ar = 3-chlorophenyl	92:8	88 (>99)	5 (nd)
d: R = Bn, Ar = 4-cyanophenyl	87:13	68 (>99)[d]	nd

[a] Determined by ^{1}H NMR analysis of the unpurified reaction mixture. [b] Yield of puified compound. [c] Determined by HPLC analysis of purified isomer. [d] Reaction performed with TMS-quinine as catalyst; the enantiomer of **1.29d** was the major product.

3. N-Heterocyclic Carbenes (NHC)

Carbenes have been recognized as important reaction intermediates. In 1991, Arduengo reported the first synthesis, structure and characterization of crystalline N-heterocyclic carbene derived from the deprotonation of 1,3-di-1-adamantylimidazolium chloride **1.31** (Scheme 1.5).[14] As a carbene, it is quite reactive however it also enjoys both steric and electronic stability. As a result, these NHC's have enjoyed widespread use and applications as ligands in transition metal catalysis, as nucleophiles and as catalysts for conjugate umpolung chemistry of α,β-unsaturated aldehydes resulting in β- and γ- lactones.[15]

Scheme 1.4



1.31 **1.32**

a. Bicyclic β-Lactones via Aldol-Lactonizations

Currently NHC's are being explored as catalysts in the formation of β-lactones via an aldol-lactonization process. Recently, Glorius found conditions for the formation of β-lactones from ketones and α, β-unsaturated aldehydes using catalytic amounts of IMes*•HCl via a conjugate umpolung (Table 7).[15]

* bis(1,3-(2,4,6-trimethylphenyl)imidazol-2-ylidene).

Scheme 1.5

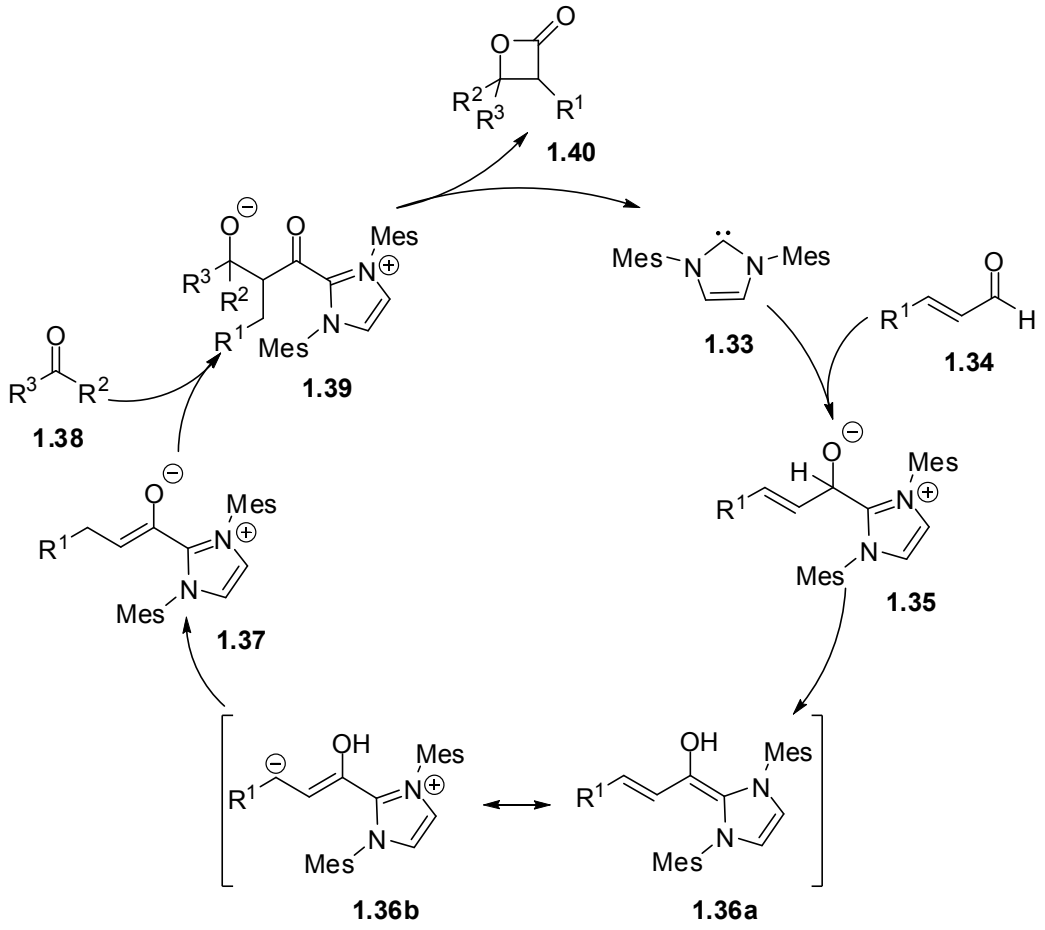


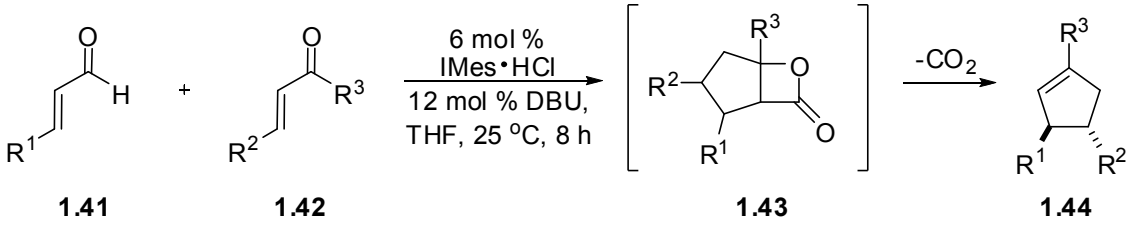
Table 7. β-lactone formation by conjugate umpolung.[a]

entry	R^1	R^2	yield (%)	ratio[b] *l*/*u*
1	Me	CF_3	34	60:40
2	Pr	CF_3	45	55:45
3	*i*-Pr	CF_3	48	62:38
4	Ph	CF_3	30	70:30
5	*i*-Pr	CO_2Me	22[c]	71:29

[a] General reaction conditions: IMes•HCl (0.05 mmol), TEA (2.0 mmol), toluene (2.5 mL), α,β-unsaturated aldehyde (1.0 mmol), ketone (1.0 mmol), 60 °C, 16 h. [b] Determined by GC-MS. [c] IMes•HCl (0.1 mmol), DBU (0.1 mmol).

In 2006, Nair also employed IMes to catalyze the formation of cyclopentenes via an unstable β-lactone which undergoes a retro [2+2] to decarboxylate.[16] Using α,β-unsaturated aldehydes and ketones, they isolate the desired 1,3,4-trisubstitued cyclopentnes in moderate yields. The intermediate β-lactone is proposed to form via an aldol-lactonization process, however it was never isolated, just observed via IR spectroscopy with a time-dependent disappearance of the characteristic β-lactone peak at 1822 cm^{-1}.

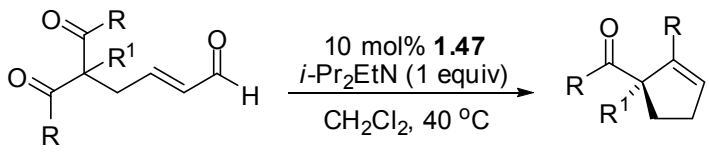
Scheme 1.6



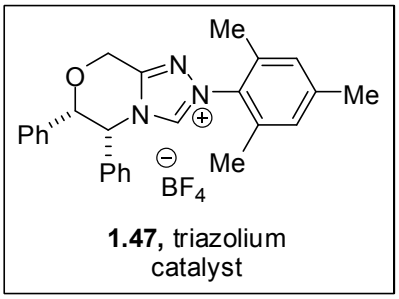
1.41 **1.42** **1.43** **1.44**

Scheidt and co-workers expanded upon this and found that several triazolium salts were also able to catalyze the formation of cyclopentenes and a few optically active β-lactones from aliphatic diketones albeit the latter in moderate yields (Table 8).[17]

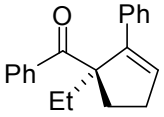
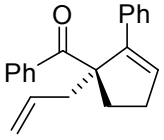
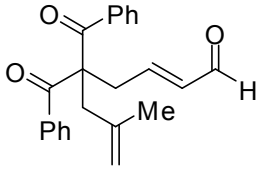
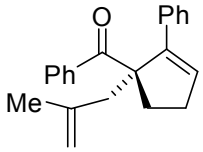
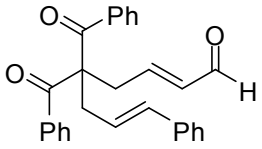
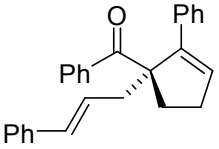
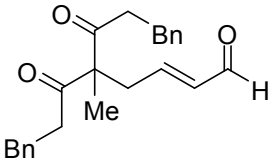
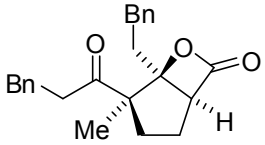
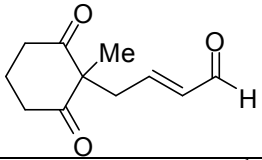
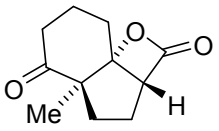
Table 8. Substrate scope.



1.45 **1.46**



1.47, triazolium catalyst

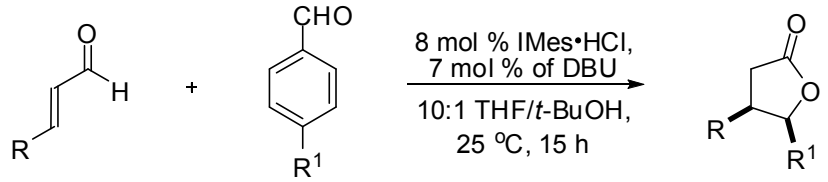
entry	R	R^1	cyclopentene	yield (%)	ee (%)[a]
1	Ph	Et		73	90
2	Ph	allyl		70	83
3				69	83
4[b]				64	82
5[b]				65[c]	93
6[b]				51[c]	96

[a] Determined by HPLC Chiracel AD-H. [b] 20 mol % of the triazolium catalyst. [c] Diastereomeric ratio = 20:1. Relative stereochemistry of β-lactones determined by NOE or X-ray crystallography.

b. Bicyclic γ-Butyrolactones via Aldol-Lactonizations

Similar to the way that IMes catalyzes the stereospecific synthesis of β-lactones, it can catalyze the synthesis of γ-lactones if the base, solvent and temperature are optimized. In 2004, Bode studied the formation of homoenolates derived from α,β-unsaturated aldehydes and the subsequent generation of γ-butyrolactones (Table 9). They also obtained corresponding lactones in moderate yields and diastereoselectivities using a variety of NHC catalysts[18].

Table 9. Direct, catalytic annulations of aldehydes and enals[a].



1.48 **1.49** **1.50**

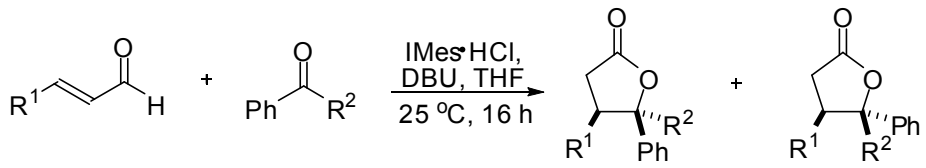
entry	R	R^1	dr[b]	yield (%)[c]
1	Ph	Br	4:1	79
2	Ph	CO_2Me	5:1	87
3	4-$MeOC_6H_4$	Br	4:1	76
4	4-$MeOC_6H_4$	H	4:1	65
5	TIPS—≡—§-	CO_2Me	3:1	41

[a] Reaction conditions: 1.0 mmol enal, 0.5 M in 10:1 THF/ *t*-BuOH at 25 °C for 15 h, 8 mol % IMes•HCl, 7 mol % DBU, 2 equiv of aldehyde. [b] Determined by ^{1}H NMR analysis of unpurified reactions mixtures. [c] Combined yield of both diastereomers after chromatography. [d] Concentration = 0.1 M. [e] Performed with 15 mol % IMes•HCl, 14 mol % DBU. [f] The enal was added over 3 h.

Glorius[15] studied the formation of γ-lactones extensively and found that when activated ketones were used, high yields and moderate diastereomeric ratios were obtained (Table 10). They also studied a variety of substrates that could be subjected to

the conjugate umpolung of α,β-unsaturated aldehydes and established a useful method for the formation of such functionalities.

Table 10. Reaction of alkyl-substituted α,β-unsaturated aldehydes with ketones[a].



1.51 **1.52** **1.53a** **1.53b**

entry	R^1	R^2	yield (%)	ratio (**1.53a**/**1.53b**)[b]
1	Me	CF_3	82	81:19[c]
2	Pr	CF_3	90	84:16[c]
3	*i*-Pr	CF_3	66	93:7[d]
4	Me	CO_2Me	87	68:32[c]
5[e]	Pr	CO_2Me	71	67:33[c]
6[f]	*i*-Pr	CO_2Me	72	65:35[d]

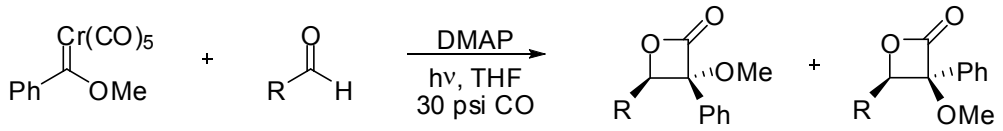
[a] General reaction conditions: IMes•HCl (0.05 mmol), DBU (0.05 mmol), α,β-unsaturated aldehyde (0.5 mmol), ketone (1.0 mmol), THF (2.5 mL), r. t., 16 h. Yield given for the isolated mixture of diastereomers. [b] Determined by GC-MS. [c] **1.53a** = *like*, **1.53b** = *unlike*. [d] **1.53a** = *unlike*, **1.53b** = *like*. [e] DBU (0.25 mmol), 50 °C. [f] DBU (0.25 mmol).

4. Pyridine Derivatives

Recently, there has been more exploration and variation in the synthesis of β-lactones, especially under catalytic conditions. Currently, investigations involve the use of pyridine catalysts and some have reported good to moderate yields and high diastereoselectivites. One such example comes from Merlic and his studies using tertiary amines as catalysts. Electron-rich aldehydes were reacted with ketenes which were derived from chromium carbene complexes to yield the β-lactones and in some

cases, enol ethers from decarboxylation (Table 11). They screened a number of catalysts including cinchona-like alkaloids which have been known to catalyze such reactions with activated aldehydes. Most of the Lewis bases failed except for DBU, DABCO and DMAP*, which delivered the highest yield and best diastereomeric ratio.[19]

Table 11. Results of ketene-aldehyde coupling.



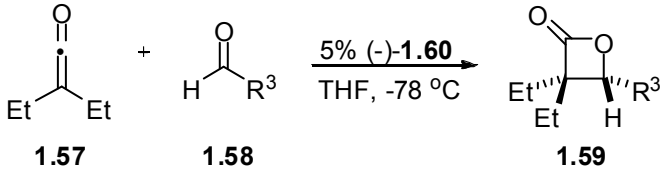
1.54 **1.55** **1.56** (syn) **1.56'** (anti)

entry	aldehyde	product	yield of **1.56** (%) (syn/anti)
1	propionaldehyde	**1.56a/1.56a'**	53 (15/1)
2	acetaldehyde	**1.56b/1.56b'**	55 (8/1)
3	*n*-butyraldehyde	**1.56c/1.56c'**	43 (23/1)
4	isobutyraldehyde	**1.56d/1.56d'**	35 (4/1)
5	benzaldehyde	**1.56e/1.56e'**	33 (15/1)

Fu and co-workers have been exploring the use of planar-chiral derivatives of DMAP as nucleophilic catalysts for enantioselective processes.[20] They then applied this idea towards C-acylation processes and found that several pyridine derivatives catalyze the asymmetric synthesis of β-lactones from disubstituted ketenes. They found that a chiral 4-pyrrolidinopyridine (PPY) derivative **1.60** gave the best enantioselectivity which is the first catalyst to date that has been found most effective for generating α,α-disubstituted β-lactones from disubstitued ketenes (Table 12).[20d]

* DBU: 1,8-diazadicyclo[5.4.0]undec-7-ene. DABCO: 1,4-diazabicyclo[2.2.2]octane. DMAP: *N,N*-4-dimethylaminopyridine.

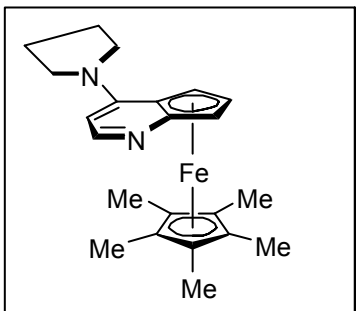
Table 12. Catalytic asymmetric synthesis of β-lactones by cycloadditions of disubstituted ketenes with aldehydes.



1.57 **1.58** **1.59**

entry	R^3	ee (%)[a]	yield (%)[a]
1	Ph	91	92
2	2-naphthyl	89	77
3	4-$(CF_3)C_6H_4$	80	74
4	4-$(MeCO)C_6H_4$	81	76
5	4-MeC_6H_4	89	67

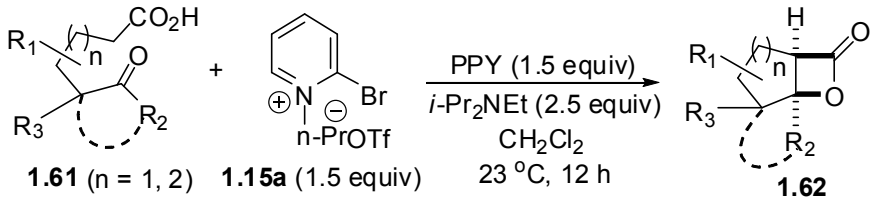
[a] Average of two runs.



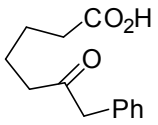
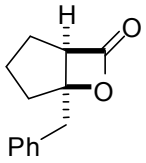
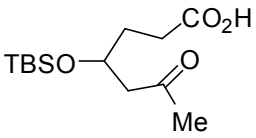
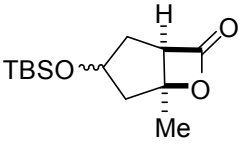
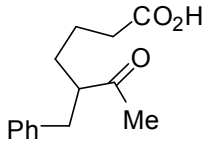
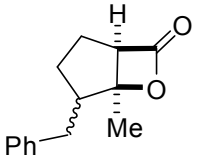
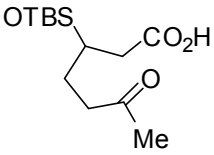
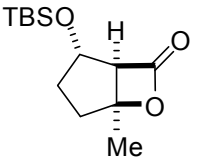
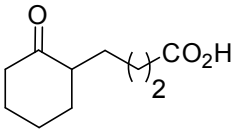
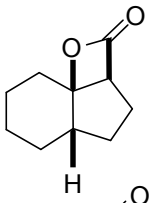
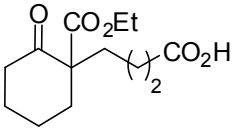
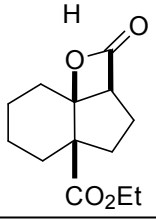
1.60
chiral PPY derivative

Romo and coworkers recently developed a biscyclization method to synthesize bicyclic and tricyclic β-lactones starting with readily available keto-acids.[21] This work expands upon their previous studies with aldehyde acids and nucleophile catalyzed aldol lactonizations. Although this is not an enantioselective process yet, the diastereoselectivity is quite acceptable in most cases. PPY is used as the catalyst as opposed to the cinchona alkaloids which were previously employed for the aldehyde substrates (Table 13).

Table 13. Carbocycle fused β-lactones obtained via the intramolecular NCAL reaction of keto-acid substrates.



1.61 (n = 1, 2) **1.15a** (1.5 equiv) **1.62**

entry	keto acid	b-lactone[a]	% yield[b]	dr[d]
1			58	-
2			51	2:1
3			75c	~1:1
4			67	>19:1
5			61	>19:1
6			70	>19:1

[a] Yields refer to isolated (silica gel), purified product. [b] 1.5 equiv PPY, 1.5 equiv **1.15a**, and 2.5 equiv Hunig's base were employed. [c] Relative stereochemical assignment of bicyclic β-lactones is based on either strain arguments, nOe, x-ray analysis, coupling constant analysis of derivatives or analogy to dihydroplakevulin.

Since PPY is not a chiral catalyst and no enantioselectivity is observed, we can not confirm an aldol-lactonization pathway. We favor an aldol-lactonization route for several reasons. Mainly, we observed high diastereoselectivity with β-substituted keto-acid substrates which is consistent with $A^{1,3}$ strain for an intermediate ammonium enolate.[21] A [2+2] cycloaddition pathway would not have such $A^{1,3}$ strain and thus no diastereoselectivity would be observed (Figure 2). Also, we suggest nucleophile involvement based on improved efficiency with more nucleophilic promoters.

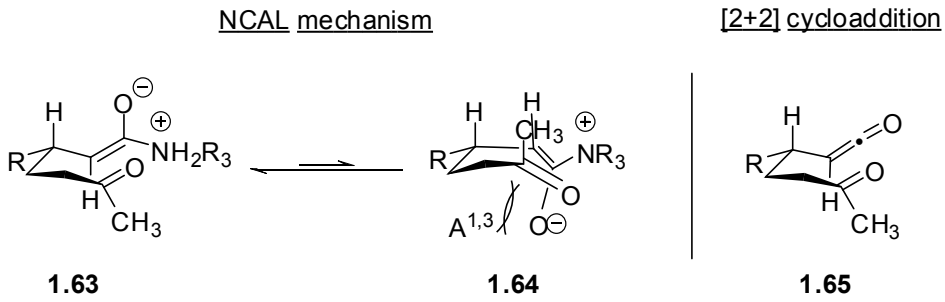


Figure 2. Rational for high diastereoselectivity in β-substituted acids.

Also, identifying discrete ketene intermediates should provide a conclusive result. Although none were observed by *in situ* IR spectroscopy to date, we cannot exclude the existence of such fleeting intermediates. Studies are currently underway to expand this methodology into an asymmetric process under catalytic conditions.

C. Applications

β-lactones are highly versatile; they are represented in natural products as themselves or are used as intermediates towards the synthesis of natural products (Figure 3).[12,22] A few recent examples that utilize an organocatalyzed aldol-lactonization pathway are presented below.

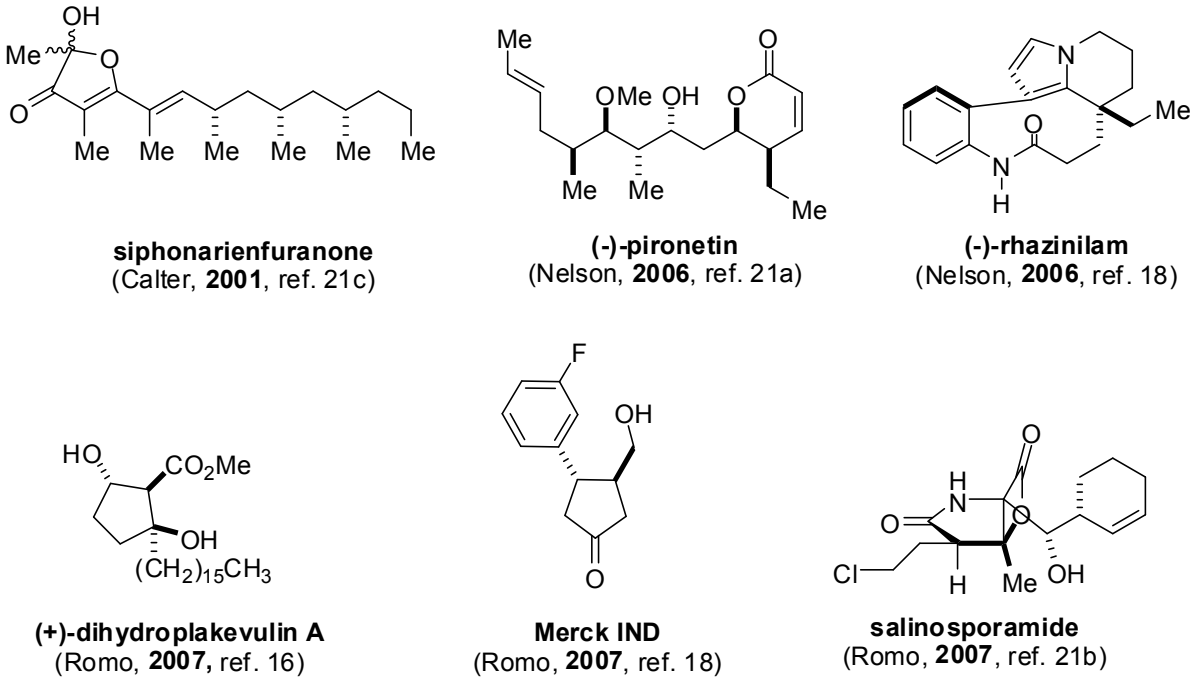


Figure 3. Natural products or intermediates derived from a β-lactone made by an aldol-lactonization type mechanism.

D. Summary

Aldol-lactonizations can be catalyzed in a variety of ways, utilizing different types of catalysts depending on the desired stereochemistry and conditions. Whether it be cinchona alkaloids, pyridine derivatives or the more recent NHCs, methods to

accomplish the aldol-lactonization prove to be diverse and more effective. The synthetic community calls for such variety in methods as our targets become more complicated and the need for choice for methodology more demanding. Whether for the production of intermediates or being targets themselves, β-lactones continue to be highly utilized and possessing a diverse arsenal of chemical reactions to accomplish such transformations is undoubtedly necessary.

CHAPTER II

CUPRATE ADDITIONS TO β-LACTONES

A. Introduction: Dual Electrophilic Character of β-Lactones

β-Lactones are unique, strained, four membered cyclic esters with a bielectrophilic character. The dual reactivity of the β-lactones is derived from their inherent structure in which nucleophilic attack can lead to either acyl C-O cleavage or alkyl C-O cleavage (Figure 3).[23] Appealing to hard/soft acid base theory, the carbonyl carbon is characterized as hard when compared to the β-carbon. As such, if one carefully engineers the reagent, hard nucleophiles will lead to acylation while soft nucelophiles will lead to alkylation (Figure 4).

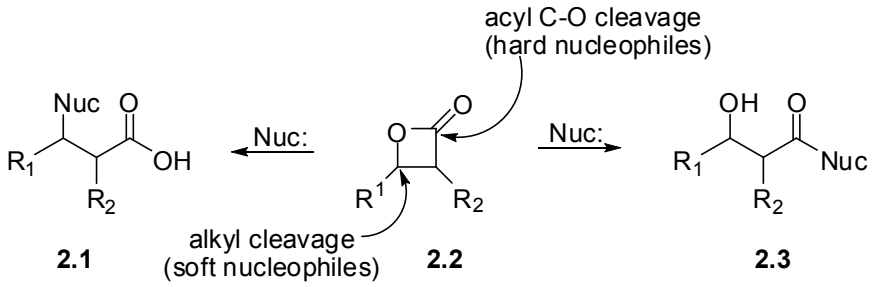


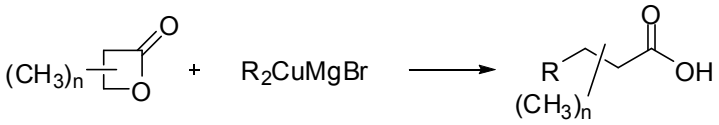
Figure 4. Dual reactivity of β-lactones.

B. Background

1. Previous Cuprate Additions to β-Lactones

Historically, Normant (R_2CuMgX) reagents[24] have been used to react with various β-lactones via C-O cleavage leading to an acid as Fujisawa,[25] Normant[26] and Vederas[27] have shown. The reaction has been successful in converting various methyl substituted β-lactones with decreasing yields as more steric bulk was added to the lactone (Scheme 2.1). A variety of nucleophiles have also been tried, however aryl cuprate addition was often compromised by lower conversion and 1,2-addition.[25f, 28]

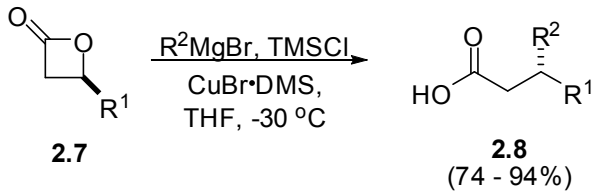
Scheme 2.1



2.4 **2.5** **2.6**

In 2002, Nelson[28a] and co-workers established a general protocol in which they were able to access several acids derived from the requisite β-lactone. They used commercially available Grignard reagents to generate the cuprate *in situ* and isolated enantiomerically enriched β-lactones in good yields (74-94%). They also reported lower yields when using cuprates derived from aryl and vinyl Grignard reagents while larger (isopropyl- or *tert*-butylmagnesium bromide) Grignard reagents required addition of 5 mol% of CuBr•DMS.

Scheme 2.2

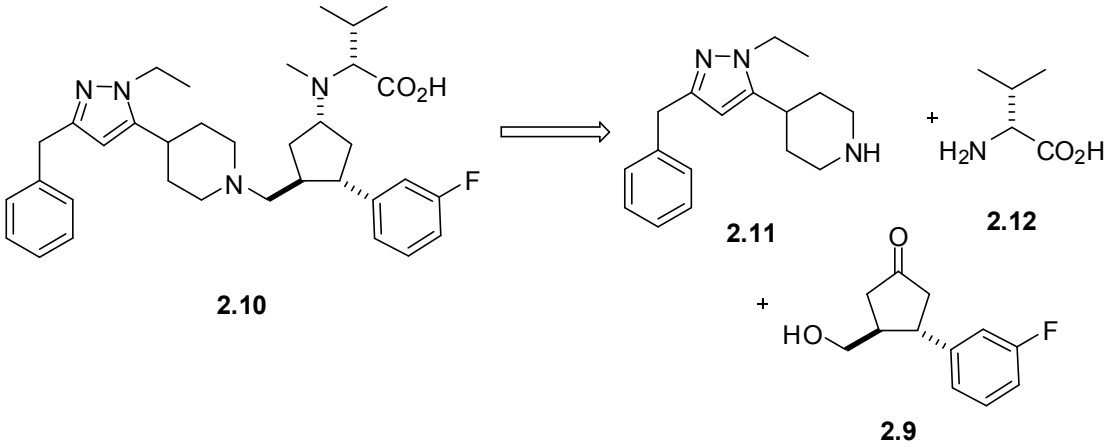


2.7 **2.8** (74 - 94%)

2. Background on the Merck IND and Previous Syntheses

In 2002, scientists at Merck published results detailing their isolation and route towards the asymmetric synthesis of (+)-*trans*-3-hydroxymethyl-4-(3-fluorophenyl)-cyclopentanone **2.9** (Merck IND). The cyclopentanone **2.9** was viewed as an advanced intermediate towards the preparation of a drug, **2.10** that would provide a novel method to treat HIV (Scheme 2.3).[29]

Scheme 2.3

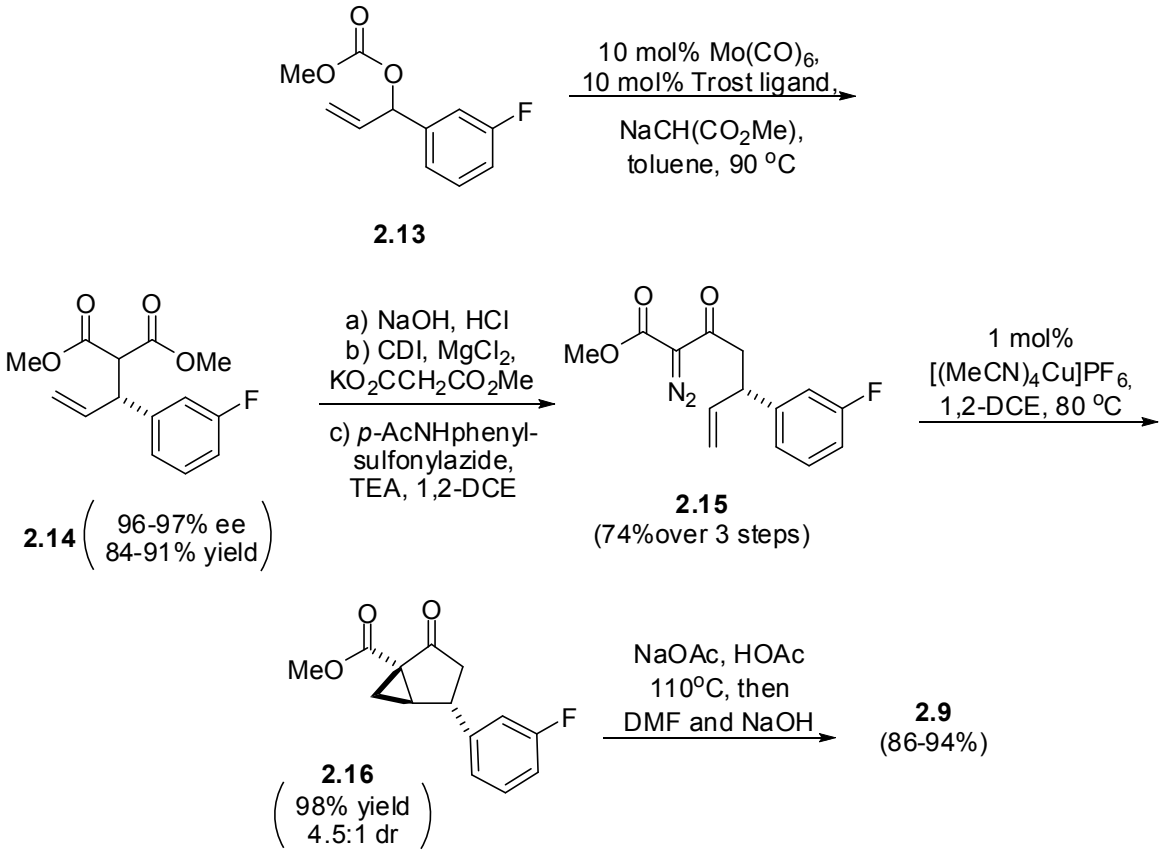


2.10 **2.11** **2.12** **2.9**

Compound **2.10** was found to be a CCR5 antagonist, which will function to block the primary co-receptor that is needed on macrophages, monocytes, and primary T-cells when they are infected by the HIV-1 virus. If this receptor, CCR5 is blocked with its

antagonist, it will prevent infection of host cells by the HIV virus. In an effort to complete **2.10**, medicinal chemists at Merck completed the large scale multistep synthesis of **2.9** in a total of 9 steps. Their asymmetric synthesis was highlighted by a Mo-catalyzed alkylation in order to induce the proper sterochemistry at the first chiral center and then a diastereoslective Cu-catalyzed intramolecular cyclopropanation which allowed them to set the second stereocenter. Lastly, they were able to develop a one-pot ring-opening/deprotection/hydrolysis/decarboxylation sequence which produced the desired IND intermediate in good yield.[30]

Scheme 2.4

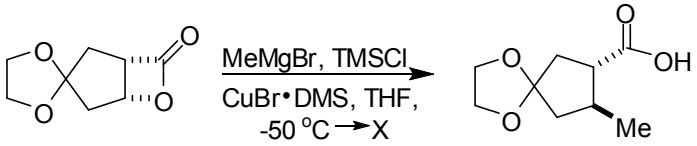


C. Main Strategy and Methods

1. Cuprate Additions to Bicyclic β-Lactones

We began our studies with bicyclic β-lactone **2.17**[31] and screened a variety of cuprates beginning with methyl cuprate using Nelson's established protocol (Table 1). At first, we obtained only poor results and minimal conversion presumably due to the extreme sensitivity of the cuprate to moisture and discrepancies in the titer (concentration) of our Grignard solutions which were used to form the cuprate prior to use. In order to obtain better results, we varied time and temperature in order to determine which combination would lead to conversion (Table 14).

Table 14. Initial trials with methyl cuprate additions.



2.17 **2.18**

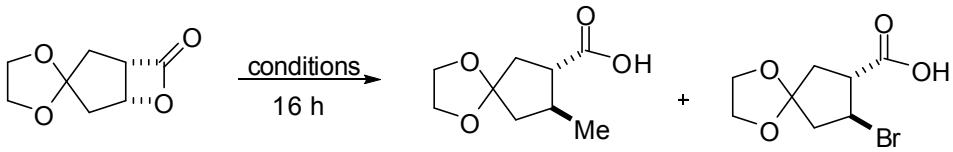
entry	X (°C)	time (h)	result*
1	0	3.5	SM
2	10	4.5	SM
3	20	5	SM
4	25	5.5	SM
5	25	6.25	SM
6	25	17.5	37% product

* result based on crude ^{1}H-NMR.

Next, we set out to find conditions that would optimize our result and produce higher yields. In addition, we saw the appearance of a consistent by-product which was

determined to be the bromide substituted acid **2.19**. In order to maximize our desired yield and minimize the production of the side product, we varied the ethereal solvent, temperature, methyl source and copper reagent (Table 15).

Table 15. Optimization of methyl cuprate addition.



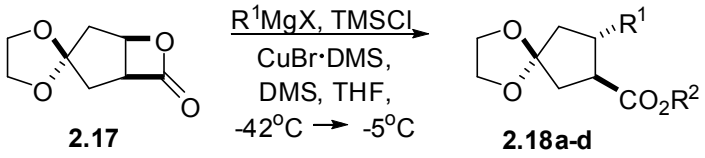
2.17 **2.18a** (product) **2.19** (by-product)

entry	solvent	methyl source	copper source	temperature (^{o}C)	prod : by-product
1	ether	MeMgBr	CuBr•DMS	-42 → 20	0% : 25%
2	DME	MeMgBr	CuBr•DMS	-42 → 20	0% : 65%
3	THF	MeMgBr	CuBr•DMS	-42 →20	55% : 5%
4	THF	MeLi	CuCN	-78 → 0	2% : 0%
5	THF	MeMgBr	CuI	-30 → 0	SM

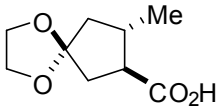
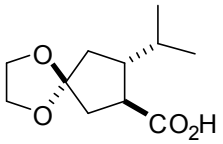
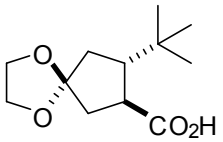
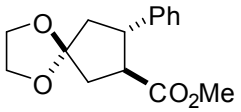
The efficiency of addition was quite sensitive to the stoichiometry of copper reagent and magnesium bromide, as noted by our group[23] and in the literature[28]. After screening various amounts, we determined that 3.0 equivalents of cuprate (via CuBr•DMS complex and MeMgBr) was necessary for optimal conversion. A homogeneous, clear solution was used as an indicator for proper cuprate conversion (as tested against various substrates such as α,β-unsaturated carbonyls). Freshly distilled THF over Na and benzoquinone was found to be an ideal solvent and -42 ^{o}C warming to -5 ^{o}C over 2 hours were determined to be the optimal conditions. After our success in methyl additions, we ventured to explore more bulky alkyl and aryl nucleophiles (Table

16). When the cuprate derived from CuBr•DMS and *i*-PrMgCl was used, the reaction was complete within 0.5 h, whereas the *t*-BuMgBr derived cuprate yielded only modest conversion even when warmed to room temperature. We were specifically excited about the aryl addition since this was the first example of an sp^2 hybridized nucleophile adding successfully with such high yield. (entry 4).

Table 16. Cuprate additons to bicyclic β-lactone **2.17**.



2.17 **2.18a-d**

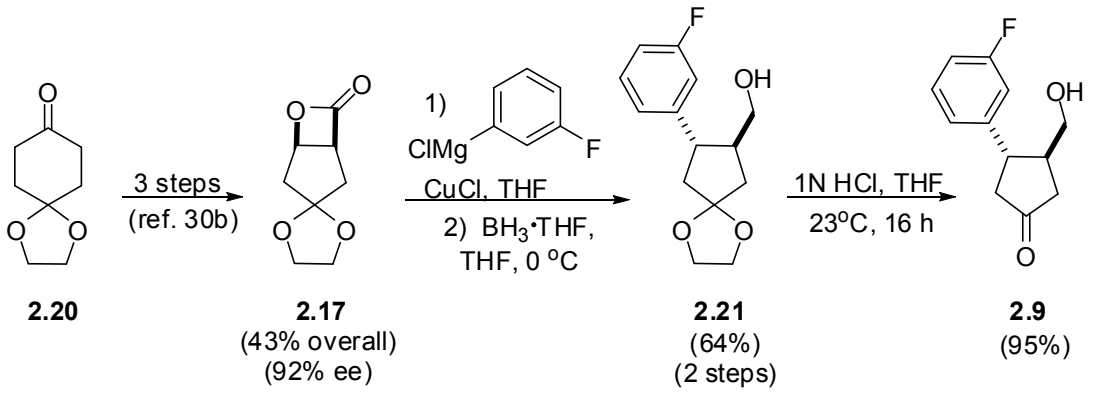
entry	R	product	compound no.	% yield
1	Me		**2.18a**	62
2	*i*-Pr		**2.18b**	56
3	*t*-Bu		**2.18c**	25
4[b]	Ph		**2.18d**	72

[a]Major contributions in this table and above section have been made by Dr. Wei Zhang. [b]Conditions used for aryl addition: 0.02 M, 5.55 equiv of cuprate, 11 equivs of 2.0M PhMgCl in THF, 16.0 equiv of DMS, TMSCl (1.5 equiv), -42 to 10 °C, 6-10 h. Choro-Grignard's must be used.

2. Application to Merck IND

Motivated by the success of the alkyl and aryl cuprate additions to the bicyclic β-lactone, we wanted to attempt the addition of a *meta*-fluorophenyl adduct since this would be a precursor to the same intermediate previously synthesized by Merck, as discussed above. To minimize the production of the bromo-acid by-product, an aryl cuprate derived from (3-fluorophenyl)magnesium chloride and CuCl were used for the addition to the dioxolane substituted bicyclic β-lactone **2.17**. Subsequent reduction via borane-THF complex (64% yield over 2 steps) followed by deprotection with 1N HCl afforded the desired ketone **2.9** in 95% yield (Scheme 2.5).

Scheme 2.5



2.20 | **2.17** (43% overall) (92% ee) | **2.21** (64%) (2 steps) | **2.9** (95%)

D. Summary

Highly diastereoselective, Cu(I)-mediated additions to **2.17** with either alkyl or aryl cuprates proceeded with inversion of stereochemistry to provide access to *trans*-substituted cyclopentanone acids. By optimizing this methodology, we were able to

minimize the formation of the bromo-acid by-product and improve the yields of the alkyl and typically problematic aryl cuprates. The applicability of this process was demonstrated by the short, efficient synthesis of a Merck IND intermediate in 6 steps as opposed to 9 steps (as previously reported). The synthesis produced the cyclopentanone **2.9** from ketone **2.20** in 26% overall yield.

CHAPTER III

THE NUCLEOPHILE PROMOTED BIS-CYCLIZATION AS APPLIED TOWARDS DIONES, AMINO ACID DERIVATIVES AND OTHER α-SUBSTITUTED KETO-ACIDS

A. Background: Keto-acids

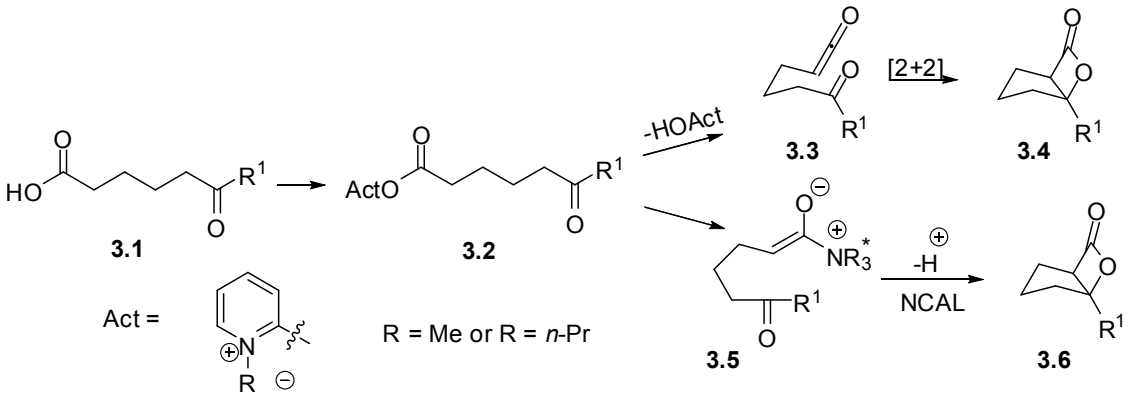
β-lactones are strained four membered rings and offer synthetic chemists considerable flexibility as useful intermediates.[32] The production of optically active β-lactones began in 1982, when Wynberg utilized chiral catalysts to assist in a net [2+2] cycloaddition (aldol-lactonization) reaction between ketene and various activated carbonyl compounds.[2] Wynberg found the use of diastereomeric cinchona alkaloids (quinidine and quinine) to be especially effective in obtaining high enantiomeric excess of β-lactones.[4] (Chapter I). We were able to build upon and optimize this methodology, which greatly increased the applicability of the nucleophile catalyzed aldol-lactonization (NCAL) towards the synthesis of bioactive natural products.

Recently, the scope was expanded by incorporating the use of keto-acids as substrates, which initially gave low yields due to the lower electrophilicity of ketones. However, we explored several tertiary amines and bases that might increase the nucleophilicity of the ammonium enolate thereby promoting the crucial aldol. Such nucleophiles would need to have increased electron density on the heteroatom (nitrogen), and bases such as DMAP and PPY (Figure 5) were obvious choices. To date, PPY has proven to be the best nucleophile and DIPEA remains as the best base.

Figure 5. Nucleophiles DMAP and PPY.

Generally, there are two possibilities for the formation of the lactone from keto-acids: a [2+2] pathway between a ketene and carbonyl or a nucleophile promoted pathway between an ammonium enolate and carbonyl. Our studies seem to favor a rate-determining, nucleophile promoted process based on several factors (see Chapter I) specifically that more nucleophilic substances are more efficient. In addition, the use of only Hunig's base produced no β-lactone and this suggests a nucleophile catalyzed process.[21] Although we have not found evidence of ketenes via *in situ* IR spectroscopy, we cannot exclude the possibility of such a short lived intermediate.[8] Also, as studies proceed, we will be able to gain further insight by using chiral nucleophiles and then confirming our hypothesis based on stereochemical induction of the derived β-lactones.

Scheme 3.1



Thus far, we have been able to take advantage of this process and efforts are currently underway to fully explore and investigate the limits of this methodology. Our group has been successful in establishing a set protocol for aldehyde-acids and keto-acids separately. Although we have investigated the aldehyde-acid substrates quite extensively in the past, several families of keto-acids remain unexplored. Recently, we have been studying these keto-acid substrates and successfully prepared several examples which yield the desired β-lactones in moderate to high yields, with varying degrees of diastereoselectivity (Figure 6).[21]

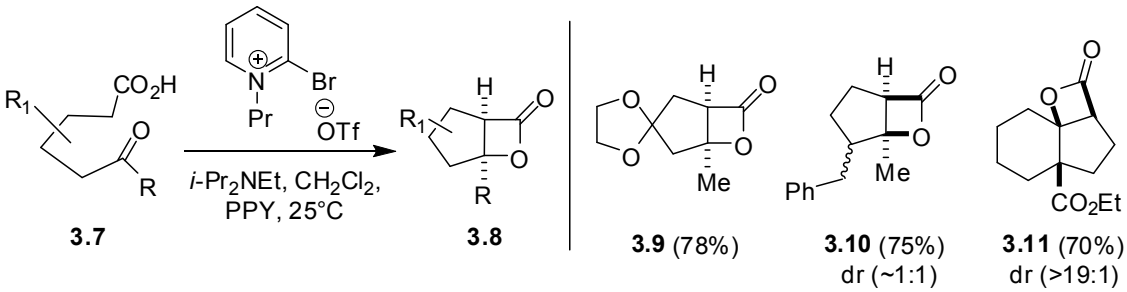


Figure 6. Examples of the NCAL with keto-acids.

After such promising results, it has been a goal to find the limits of this process and fully investigate the diversity of substrates that can be utilized in the intramolecular NCAL process. Specifically, we are interested in studying members of the keto-acid class such as diones, protected amino acids, tricyclics, heterocycles and derivatives. We plan to test which ring sizes can be tolerated by this methodology and investigate the various functionalities that are compatible with the optimized reaction conditions. This will potentially utilize this process in order to effectively and efficiently synthesize natural/unnatural products and/or their intermediates.

B. Various Substrates Studied

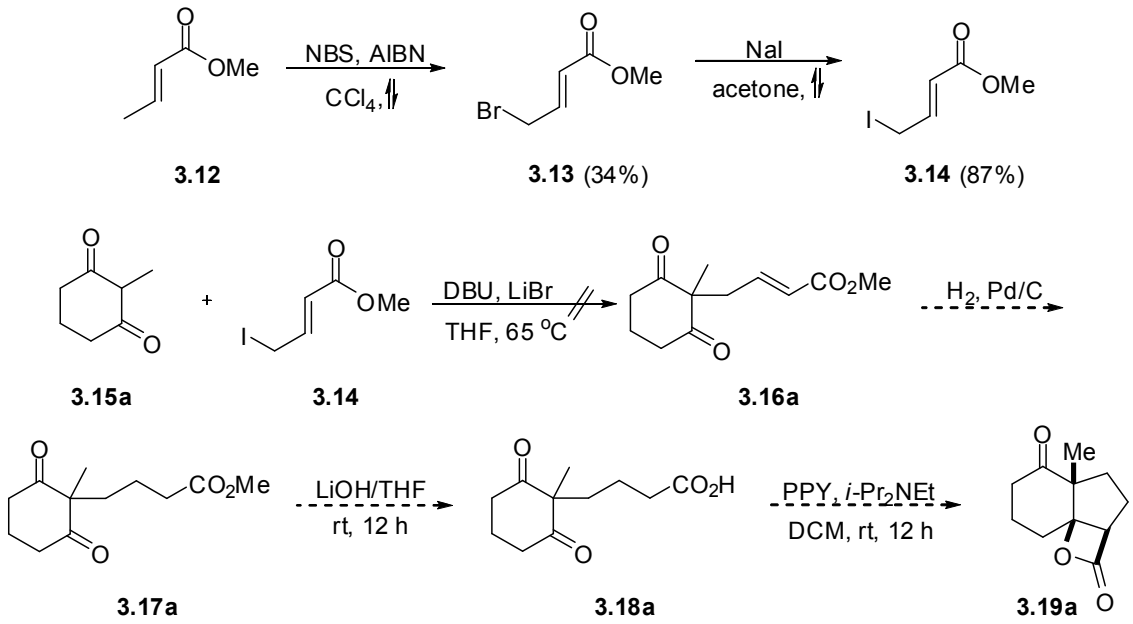
1. Tricyclic β-Lactones

Recently, our group has made several advances in the production of β-lactones in which we have placed different heteroatoms in and around the substrate as well as increasing the complexity of the keto-acid. In terms of complexity, we decided to explore the realm of tricyclics and observe both the efficiency of reaction and conformation of these products.

a. 5- and 6-membered Diones

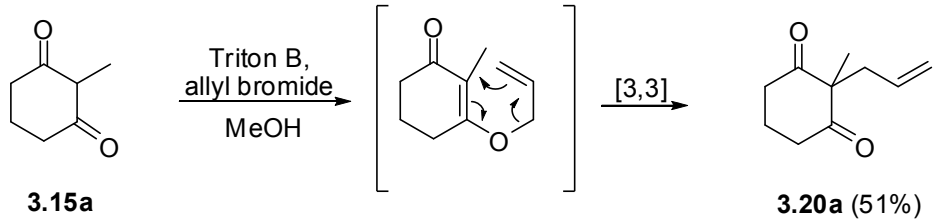
Our efforts towards testing our conditions on various keto-acids substrates begins with 2-methyl substituted 1,3-diones. Five and six-membered diones are commercially available and stable at lower temperatures. Initially, we envisioned a simple approach to directly append the ester side chain onto the dione **3.15a** (Scheme 3.2). Due to other studies in our group, *O*-alkylation was expected to occur and in order to minimize this propensity, a Finkelstein[33] reaction was run on the bromo-ester to convert the halogen into an iodide. This was done in hopes to make the electrophilic carbon more 'soft'. This should favor attack by the "softer" enolate carbon versus the 'hard' enolate oxygen.[34] Several trials and reaction conditions were screened[35] to append on the alkyl-ester chain with little success. Even though precautions were taken, the major product was *O*-alkylation in all cases with only trace amounts of the desired *C*-alkylation product **3.16a**.

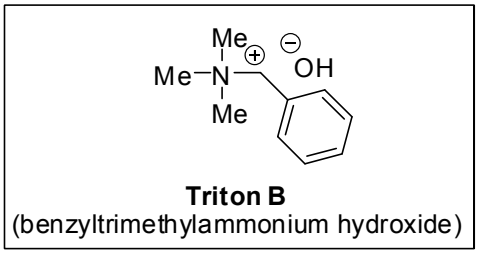
Scheme 3.2



In order to circumvent this *O*-alkylation problem, the procedure of Katoh[36] was studied in which a similar side chain was provided in a two step process. It was then decided to use allyl iodide and allyl bromide as electrophiles. This has a two fold benefit in that allyl halides are not only known to be good electrophiles in enolate chemistry but even if *O*-alkylation were to occur, the Claisen rearrangement would result in the desired product, **3.20a**. (Scheme 3.3). Triton B was chosen as the base and MeOH as the solvent.[37]

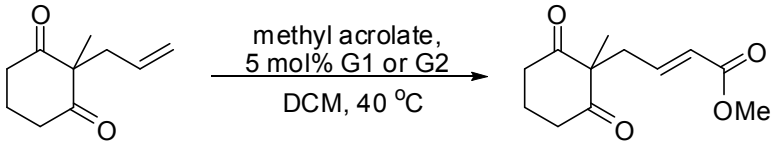
Scheme 3.3





Next, we screened several metathesis catalysts and equivalents of substrate to find the optimal conditions for extending the chain with methyl acrylate. Some homodimerization was observed with this allyl halide as expected,[38] however it was isolated as a minor by-product and was not a major hindrance to the desired reaction pathway. Grubb's 2nd Generation catalyst proved to be the most efficient, generating the desired α,β−unsaturated ester **3.16a** in 69% overall yield (Table 17).

Table 17. Screening Grubbs' catalysts.



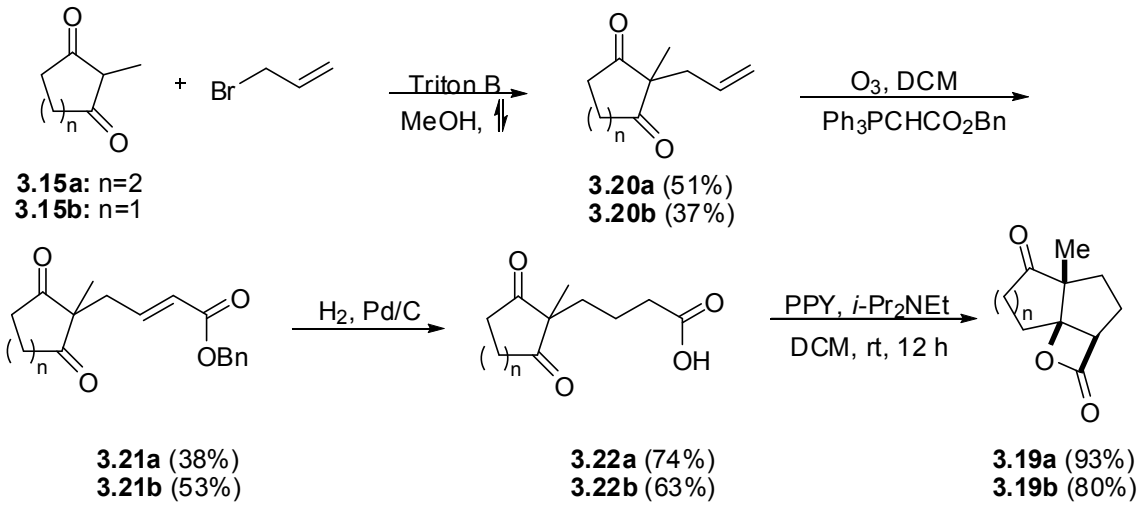
3.20a **3.16a**

entry	acrolate (eq)	G1 or G2	time (hrs)	yield
1	2	G1	8	4 %
2	5	G1	26	trace
3	2	G2	8	69 %

After reduction of the olefin, hydrolysis of the methyl ester **3.16a** to the acid **3.22a** proved to be a difficult task. Several conditions such as LiOH and NaOH were attempted without success so the corresponding benzyl acrylate was utilized and thus eliminated one step from the sequence. NCAL conditions were then applied to the keto-acid, **3.22a** and yielded the desired β-lactone, **3.19a** as a single diastereomer. The overall yield for this 6,5-system was quite high and so the product, **3.19a** lent itself as an attractive starting material for other investigations. This being the case, more material had to be prepared and the entire sequence scaled up. The final procedural modification was to use ozonolysis to convert the olefin to the aldehyde and then directly quenching with 1.3 equivalents of ylide,[39] (commercially available) which proved to be a convenient method to avoid the use of Grubbs 2nd Generation catalyst on large scale (Scheme 3.4). The success of this encouraged us to try a variety of dione ring sizes. Next, we focused on 2-methyl-1,3-cyclopenadione **3.15b** and we followed the exact same route as previously described and obtained comparable yields of β-lactone **3.19b**. The NCAL was also attempted on the 6-membered dione, **3.22a** using conditions found

for aldehyde acids (i.e. modified Mukaiyama's reagent and acetonitrile as solvent) and although the desired β-lactone was isolated, it was in reduced yield (70%).

Scheme 3.4



Previous cyclizations with carbocycle keto-acids have not been as efficient and so we speculate as to why these diones readily cyclize. From our experience, there seem to be two possibilites. Diones are unique since they contain two carbonyls and statistics would dictate that chances of reaction are higher. Secondly, compared to similar compounds, previously synthesized in our group, the only difference is conformation. The second carbonyl makes the system more rigid keeping the acid and ketone closer in space, thus decreasing entropy and increasing reactivity, as dictated by the Thorpe-Ingold effect. We propose this would be kinetically favored, especially for the formation of 5 and 6-membered rings.

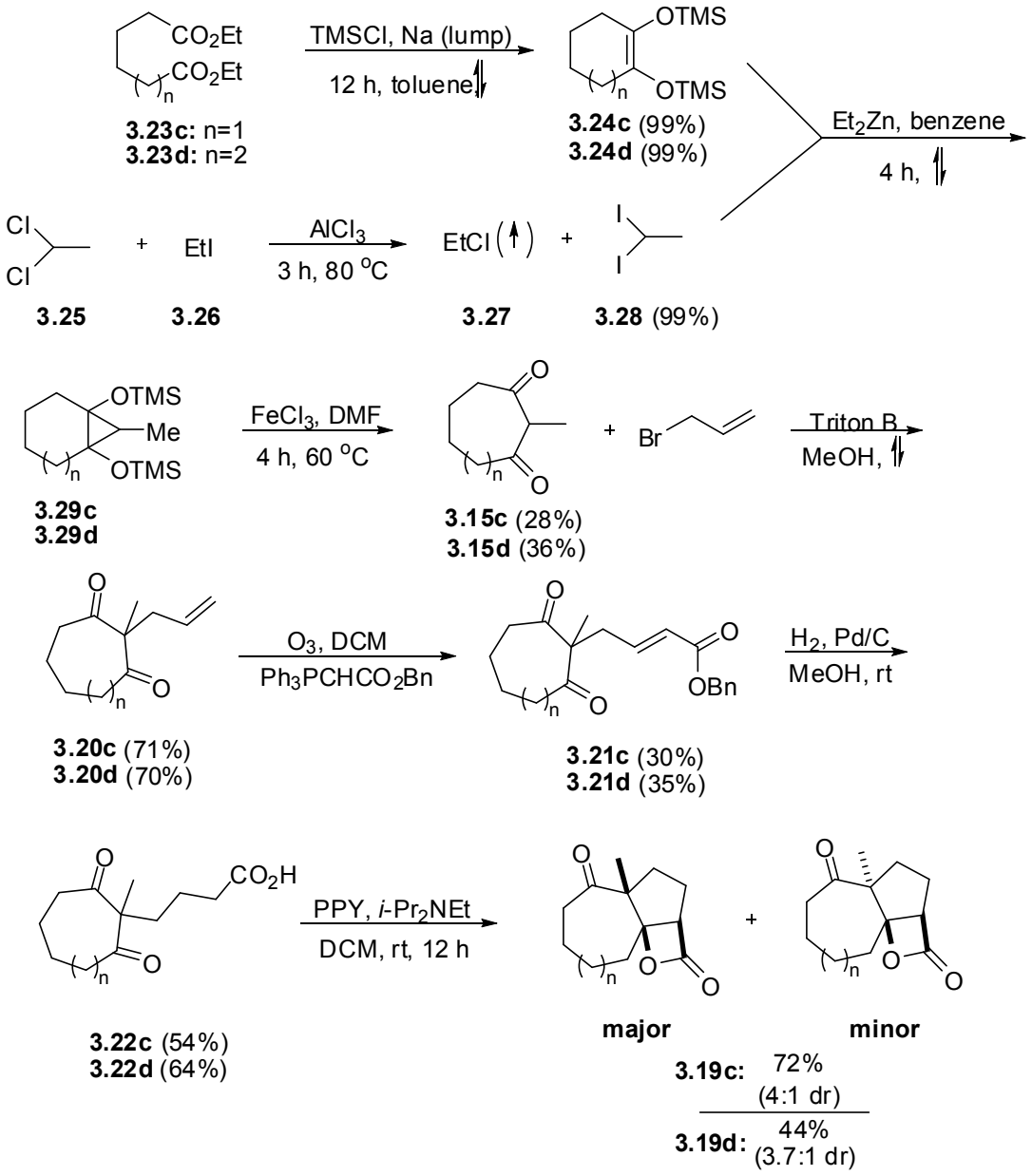
b. 7- and 8-membered Diones

To further investigate the scope of this methodology, we decided to explore the corresponding 7 and 8-membered methyl diones. Although not commercially available, precedents in the literature[40] allowed us to pursue further studies on these substrates. The procedures were followed as they were described with minor modifications in order to form the 7 and 8-membered diones and then the previous route applied to obtain the β-lactones. Major differences included higher yields when allylating and reduced yields for β-lactones **3.19c** and **3.19d**. Both acids, **3.22c** and **3.22d** produced two diastereomers with a 1:4 ratio for the 7,5 system, **3.19c** and a 1:3.7 ratio* for the 8,5 system, **3.19d** (Scheme 3.5).

One possible explanation for the reduced yields is that the conformation prior to cyclization is not as conducive and does not have the reactive groups in such favorable proximity. This would support our previous hypothesis on conformational benefit for other dione systems.

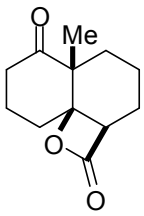
* diastereomeric ratios determined by crude ^{1}H-NMR.

Scheme 3.5


CO2Et
CO2Et
n
3.23c: n=1
3.23d: n=2
TMSCl, Na (lump)
12 h, toluene
OTMS
OTMS
3.24c (99%)
3.24d (99%)
Et2Zn, benzene
4 h,
Cl
Cl
3.25
EtI
3.26
AlCl3
3 h, 80 °C
EtCl
3.27
I
I
3.28 (99%)
OTMS
Me
OTMS
3.29c
3.29d
FeCl3, DMF
4 h, 60 °C
O
O
3.15c (28%)
3.15d (36%)
Br
Triton B
MeOH,
O
O
3.20c (71%)
3.20d (70%)
O3, DCM
Ph3PCHCO2Bn
O
OBn
3.21c (30%)
3.21d (35%)
H2, Pd/C
MeOH, rt
CO2H
3.22c (54%)
3.22d (64%)
PPY, i-Pr2NEt
DCM, rt, 12 h
major
minor
3.19c: 72% (4:1 dr)
3.19d: 44% (3.7:1 dr)

c. Other Diones

Since we had explored several diones with varying sizes of their stationary ring, we wanted to investigate cyclizing other ring sizes. It was previously found by a colleague in our group* that formation of a 6 membered ring during the NCAL protocol yielded only low conversion. This was concluded after his completion of a 6,6 dione ring system, **3.30** with only a 38% yield (Figure 7).



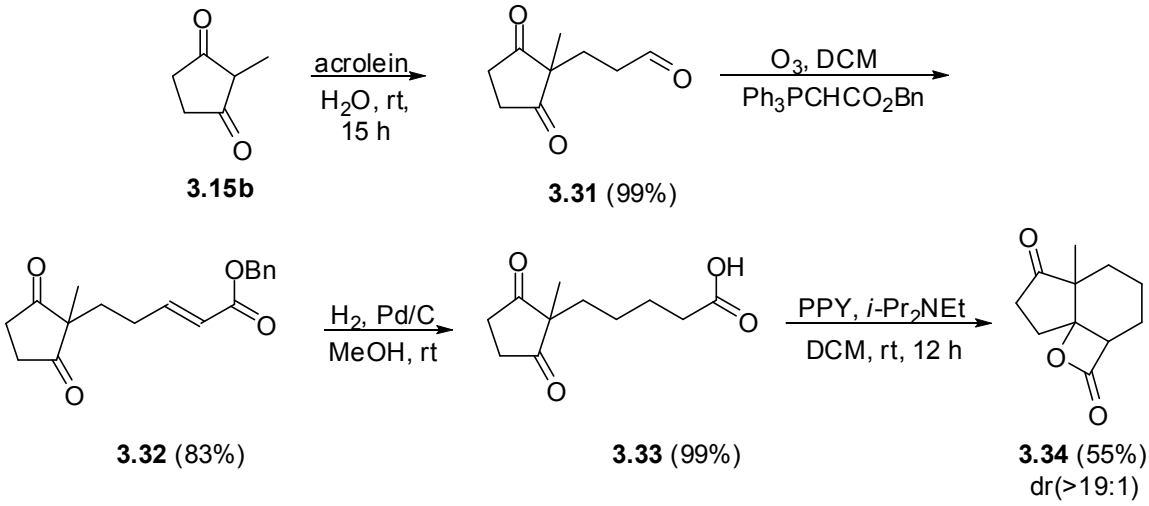
3.30

Figure 7. Tricyclic β-lactone **3.30**.

Nonetheless, we attempted to construct tricyclic β-lactone **3.34** from 2-methyl-1,3-dione **3.15b** (Scheme 3.6). Alkylation with acrolein, according to a procedure by Huddleston[41] delivered **3.31.** The aldehyde was then converted to the benzyl ester **3.32**, which after hydrogenation gave the acid **3.33**. The keto-acid was then subjected to our typical NCAL conditions which yielded the desired β-lactone **3.34** in 55% yield.

* Thanks to Vikram Purohit for the synthesis of the 6,6-β-lactone (**3.30**).

Scheme 3.6



3.15b

3.31 (99%)

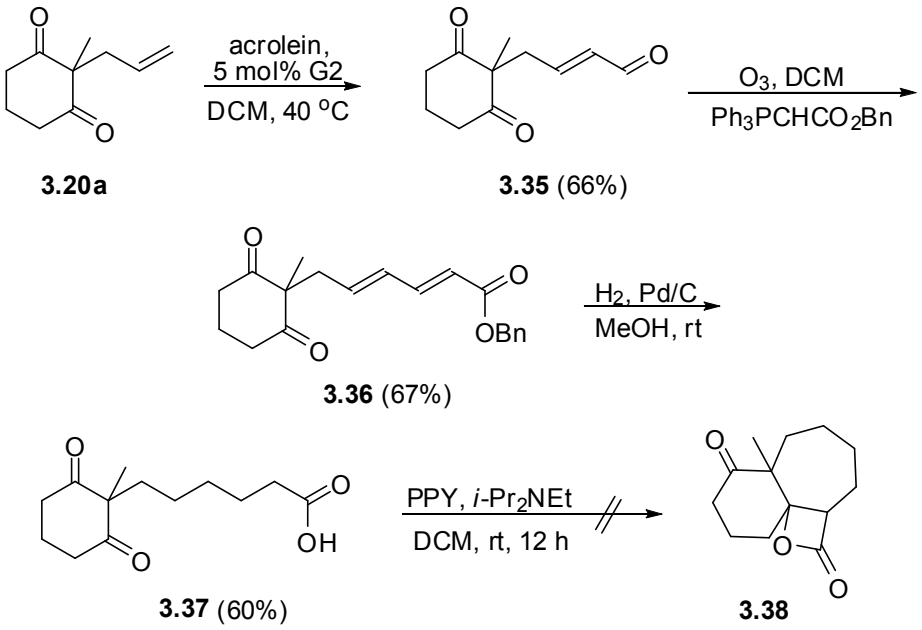
3.32 (83%)

3.33 (99%)

3.34 (55%)
dr(>19:1)

We also envisioned the synthesis of a 6,7 system. Although the cyclization of 7 membered rings is known to be less favorable than 5 or 6, we reasoned that the lower strain energy (H = 7.6 kcal/mol) and entropy (S = 19 carbon/degrees) of 7 membered cyclic systems (as compared to 8,9,10 & 11) was favorable enough to yield our desired product in reasonable yields.[42] Following our previous studies, acid **3.37** was prepared however, upon cyclization no β-lactone **3.38** was found (Scheme 3.7). With these findings, the boundaries of dione cyclizations become more defined.

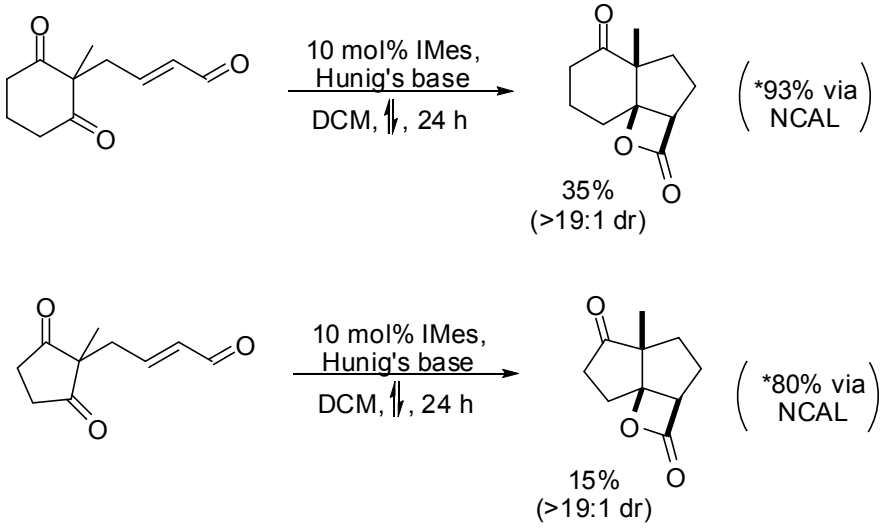
Scheme 3.7



3.20a **3.35** (66%) **3.36** (67%) **3.37** (60%) **3.38**

In addition to our NCAL protocol for the synthesis of tricyclic β-lactones, recent publications have shown N-heterocyclic carbenes being used as catalysts to synthesize both β- and γ-lactones.[15,17] We wanted to explore the possibility of synthesizing our substrates via this method, which led us to study the IMes•HCl catalyst for achieving such transformations. Although the products were isolated in reduced yields, the use of NHC's as a methodology has great potential for the optically active synthesis of lactones.

Scheme 3.8



2. Bicyclic β-Lactones

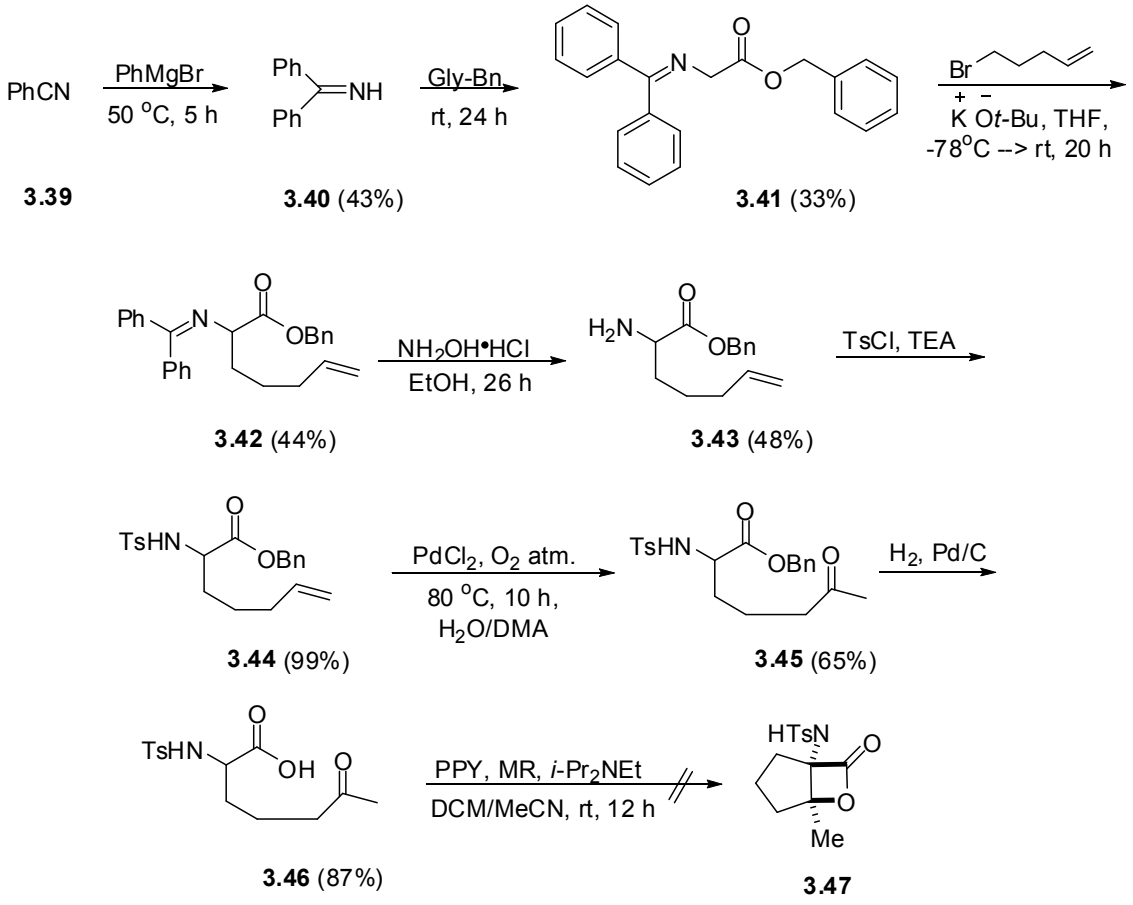
Motivated by our success with the diones and formation of tricyclic β-lactones, we wanted to explore the synthesis of bicyclic β-lactones. Since we have had much success with these substrates in the past and have studied them extensively, we wanted to delve into such constructions with heteroatoms as substituents on the main bicyclic moiety. Although our results were not as exciting as those of the diones, we were able to learn from their failures and set one more boundary in this previously unexplored territory.

a. α-Amino Substituted

We began our investigation into the heteroatomic bicyclic β-lactones with an amino acid inspired substrate. Although the synthesis of the acid substrate was quite time consuming and its completion was rewarding enough, the key transformation (the NCAL) was unsuccessful (Scheme 3.8). We began the route by making a diphenyl

ketimine **3.40** and protecting the benzylated glycine amino acid, based on the precedent of Pickard and O'Donnell.[43] Once the protected amino acid **3.41** was made, we screened several methods in order to alkylate including phase transfer conditions[44] and lithium bases,[45] but finally KO*t*Bu[45] gave the best result yielding **3.42**. The next step was to remove the imide group which was unexpectedly challenging. However after several methods such as 15% citric acid,[46] aqueous HCl[18b,47] and finally with hydroxylamine hydrochloride (NH_2OH•HCl)[48] the desired deprotection was successful. After the free amine **3.43** was in hand, it was protected with tosyl chloride to give ester **3.44**. Wacker oxidation would presumably deliver the methyl ketone **3.45** and as such, several conditions were tried with the final method utilizing $PdCl_2$ in an oxygen atmosphere; the desired ketone **3.45**[49] was isolated. After successful isolation of the Wacker product, the benzyl ester was deprotected via hydrogenation followed directly by the NCAL. Due to the insolubility of the acid **3.46** in methylene chloride, the keto-acid was added in acetonitrile however, no desired β-lactone was isolated. Decomposition of the acid **3.46** was observed presumably because of the acidic amine hydrogen competing with the acid.

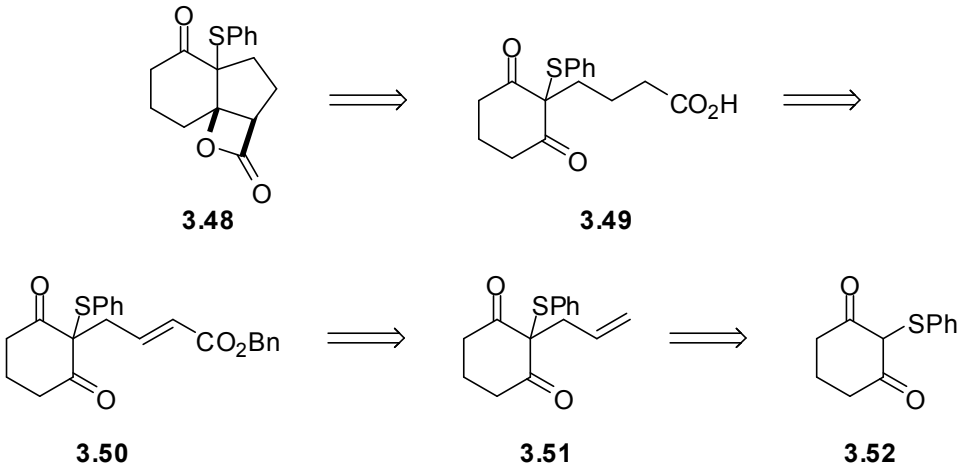
Scheme 3.9



b. Miscellaneous

In conjunction with the previous effort, we then decided to pursue a different type of bicyclic β-lactone. Our initial idea was to test whether a dione could be prepared without a methyl group. Since efforts towards preparing an acid from the corresponding non-methyl substituted dione were unsuccessful, we decided to try a thiophenyl group in place of the methyl.

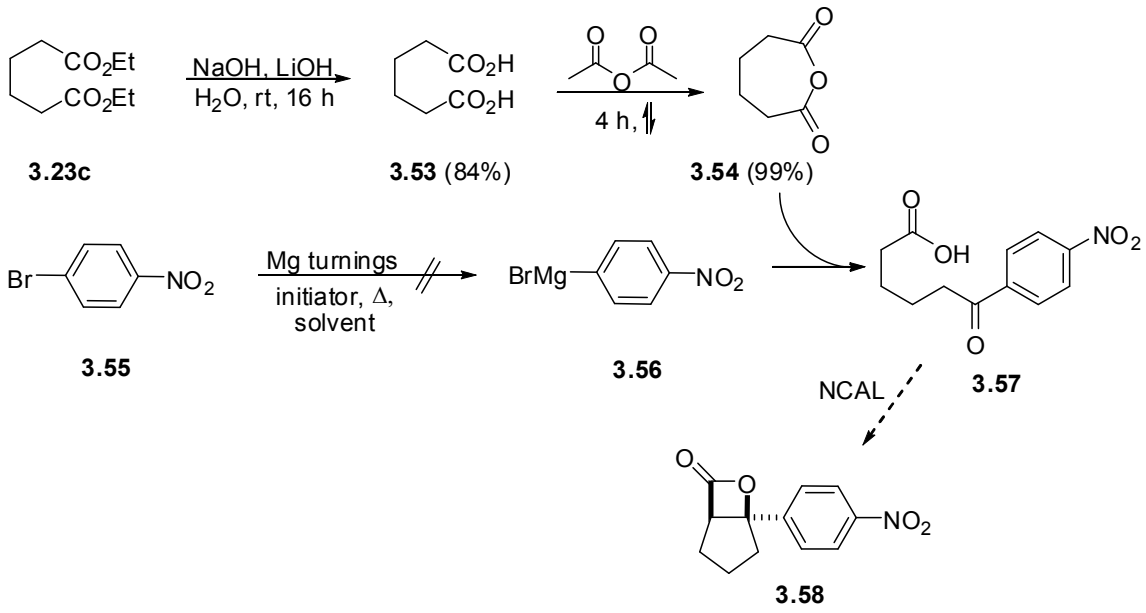
Scheme 3.10



Current studies are underway towards the preparation of this substrate, however initial results are not promising. Preliminary trials have been attempted in order to allylate, however under various conditions such as Triton B in MeOH and LHMDS in THF, only unidentified by-products have been formed.

Another possible target has evolved from our unsuccessful phenyl adduct. A *para*-nitrophenyl substituent is presumed to yield a productive aldol-lactonization due to its electron withdrawing properties. Initial studies have begun towards the substrate, however the Grignard step towards the acid **3.57** has thus far been quite difficult to initiate. The Grignard reaction was attempted both in ether and THF with activated magnesium turnings. Initiators such as iodine, dibromoethane and heat were used with no success. Further studies will be necessary to complete the desired substrate.

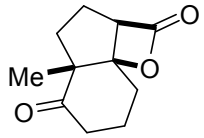
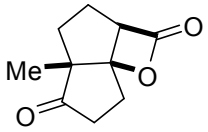
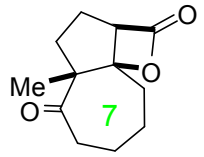
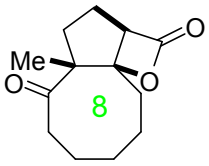
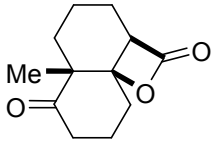
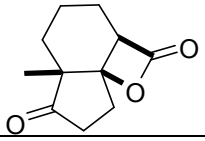
Scheme 3.11



C. Summary

In an effort to expand the repertoire of substrates available to the nucleophile promoted aldol-lactonization, we explored several acids with varying functionality, structure and substituents. The already established protocol for keto-acids was applied toward diones of varying cyclic sizes and high to moderate yields were obtained with high to moderate diastereoselectivity (Table 18). In general, most diones have proven themselves as excellent substrates towards biscyclization via the NCAL . Overall, we are very pleased with the results of these studies and hope to further increase the scope of the NCAL procedure with keto-acids.

Table 18. Tricyclic β-lactones synthesized from diones.

β-lactone	yield	dr[a]
	93	>19:1
	80	>19:1
	82	4:1
	44	3.7:1
	38	>19:1
	55	>19:1

[a] Diastereomeric ratios determined by ^{1}H-NMR of crude product mixtures. Minor diastereomer not observed for values >19:1.

CHAPTER IV

TRICHLORO β-LACTONES AS SUBSTRATES FOR TRICHLOROLEUCINE AND TRICHLOROBUTANOIC ACID

A. Trichloro β-Lactones: Cleavage of the Alkyl C-O Bond

Far from NCAL cyclizations, one of our long term goals involved finding specific conditions for β-lactone **4.1** opening to form (S)-trichloromethyl butanoic acid **4.2**. We wanted to study two distinct approaches: the first was via methylcuprate addition (see chapter II) and the second was via hydride addition. Our interest in β-lactone alkyl C-O bond cleavage is rooted in the fact that β-lactones are extremely useful and versatile intermediates which provide access to several natural and unnatural products (Figure 8). Specifically, the tri-chloro β-lactone **4.2** when opened, leads to a particularly useful moiety.

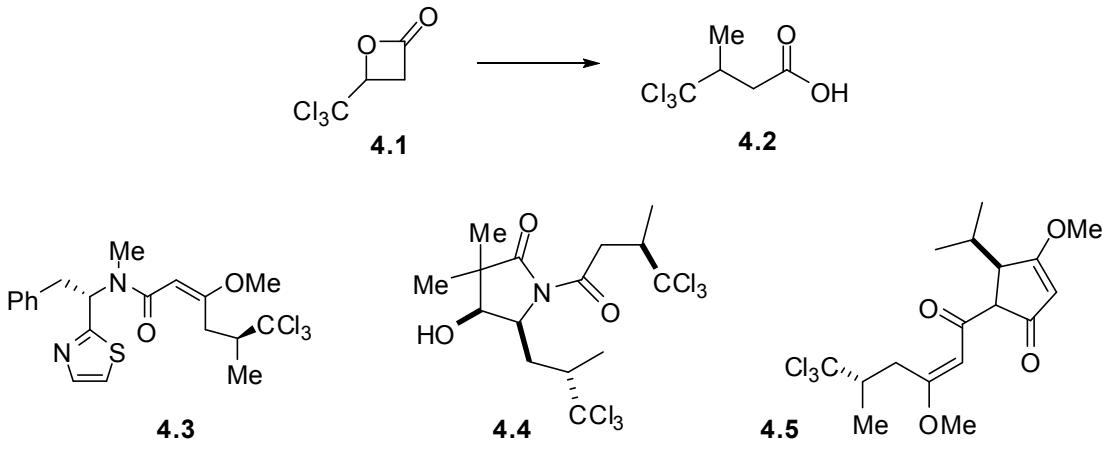
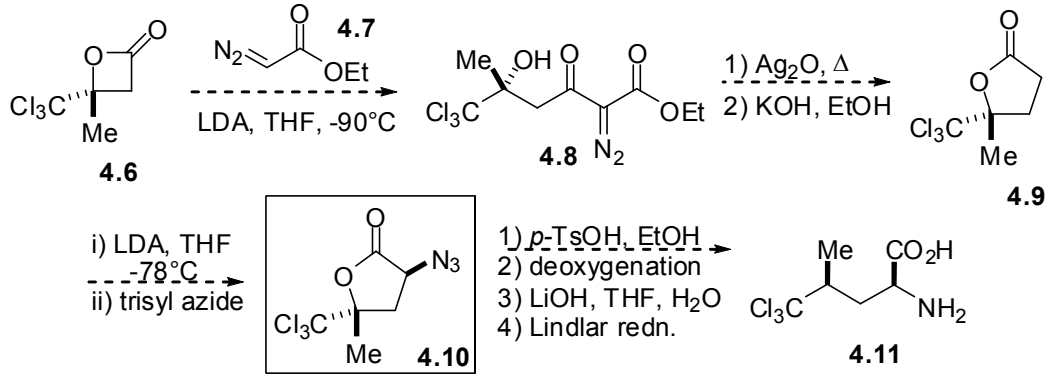


Figure 8. Trichloro β-lactone in natural products.

Our initial goal was to find the best method to open (R)-4-(Trichloromethyl-2-oxetanone **4.1**. Once we established the most efficient way, we could then apply it to acyl bond cleavage of (R)-methyl-trichloromethyl β-lactone **4.6** towards the synthesis of (S,S)-trichloroleucine **4.11.** Our route would be highlighted by addition of the enolate of α-diazoethyl acetate, **4.7**, followed by thermolysis followed by decarboxylation of the (R)-methyl-trichloromethyl β-lactone. The γ-lactone **4.9** will then be subjected to α-azidation with trisyl azide which should give us the correct stereochemistry for **4.10**. Ethanolysis then deoxygenation and hydrolysis followed by azide reduction should provide trichloroleucine (Scheme 4.1).

Scheme 4.1



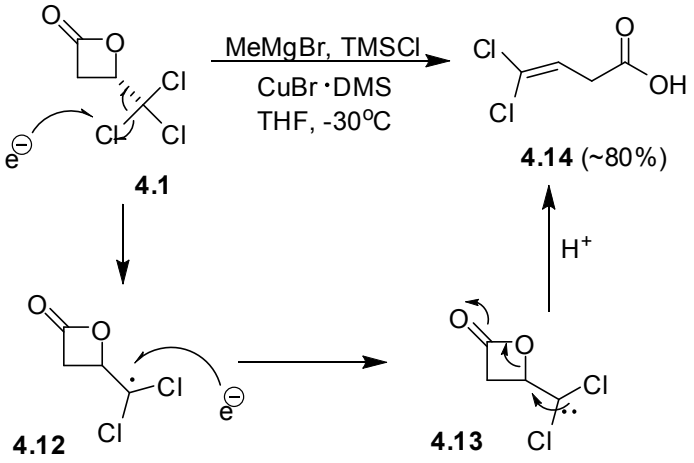
B. Methods

1. Methylcuprate Additions

First, we began efforts towards cleavage of the alkyl C-O bond via methylcuprate addition to the β-lactone **4.2**. Unfortunately results in our laboratory have shown that

this leads to the elimination product, as documented by Ashby.[50] We attempted this reaction using both TMSCl as the Lewis acid and the stronger TIPSOTf at colder temperatures in order to create a more electron deficient environment at the β-carbon on **4.1**. In both cases, the same elimination product was isolated as the major product. We presume a single electron transfer mechanism is operative, thus leading to the undesired by-product (Scheme 4.2).

Scheme 4.2



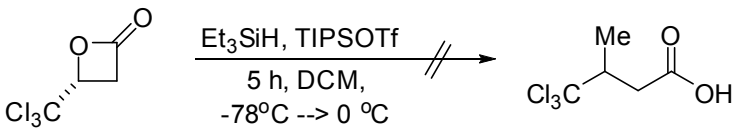
In addition, we wanted to try the same methylcuprate addition onto the 4-dichloromethyl-2-oxetanone. We reasoned that having one less chlorine atom would make a less stable radical, thus hindering the single electron transfer cascade. As such, it did provide the desired product, however only in trace amounts*. On the other hand, no olefin was visible by ^{1}H-NMR.

* Preliminary studies indicate the successful synthesis of this product, however it has not been confirmed.

2. Hydride Additions

Since the methylcuprate pathway does not open the trichloro β-lactone in the desired fashion, we decided to try a hydride addition. Although stereochemistry would be lost in such an addition, we wanted to confirm the feasibility of the reaction in general. We thus used triethylsilane as the hydride source and TIPSOTf as the Lewis acid,[51] however after 5 hours and slowly warming from -78 ^{o}C to 0 ^{o}C, no change was observed by TLC and only starting material was isolated (Scheme 4.3). Another possibility would be to use Stryker's reagent $[Ph_3P(CuH)]_6$ since it has been shown to chemoselectively reduce lactones[52].

Scheme 4.3



4.1 **4.2**

C. Summary

Cuprate additions to β-lactones continue to be highly useful due to the potential versatility of products that can be obtained. However, cuprate additons have historically been quite sensitive to varying reactions conditions and as such our studies in this area are not over. Although our initial studies with methyl cuprate addition to the trichloro β-lactone have not been successful, intriguing results with the dichloro β-lactone have

been obtained and one can speculate that altering some conditions combined with further studies may lead to isolation of the desired acid **4.2**.

CHAPTER V

CONCLUSION

Recent years in our laboratory have yielded an expansion of substrates that are susceptible to the NCAL. Aldehyde and keto-acids can broad and diverse compounds and as such can lend the same attractive attributes to their respective β-lactone product. Providing chemists with a wide array of interchangeable functionality which can still be applicable to the same NCAL protocol is invaluable as a useful methodology. In addition, the β-lactone has also served as a useful intermediate towards natural product synthesis and exploring the methods in which to open it efficiently can also serve as a highly desirable and applicable reaction. Because of this importance, we have been engaged in both the synthesis and manipulation of this functionality.

We have investigated several types of substrates such as diones, large cycles, amino acid derivatives as well as simple, straight chain acids with varying functionality α to the ketone. We then discovered that the greater electrophilicity of the diones has produced high yields and good diastereoselectivity when subjected towards NCAL conditions. The diones, together with the other types of substrates have greatly improved our view into NCAL bis-cyclizations and gave us a basic idea of which substrate features are advantageous when applying this methodology.

In addition to studies towards the formation of β-lactones, we have also investigated cuprate additions to them. Due to the dual reactivity of β-lactones, cuprates have been found to afford soft nucleophilic addition to the b-carbon yielding cleavage of

the acyl C-O bond. We have exploited this fact and have successfully achieved stereochemical invertive ring cleavage of bicyclic b-lactones which lead stereospecifically to b-substituted cyclopentyl and cyclohexyl carboxylic acids. Specifically, we have been able to apply this method to the synthesis of an investigational new drug (IND) intermeidate initially synthesized by scientists at Merck. In addition, we have applied this to the synthesis of several acids. Studies are currently underway in our laboratory to further explore these versatile cuprate additions to polychlorinated β-lactones.

CHAPTER VI

EXPERIMENTAL PROCEDURES

General

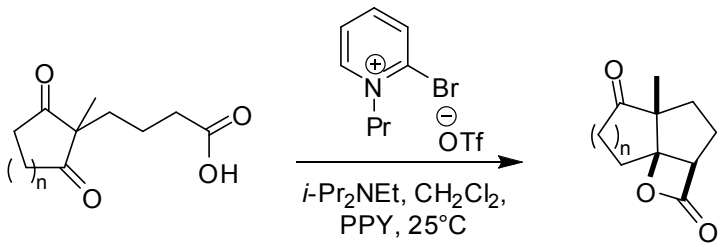
All non-aqueous reactions were carried out with flame dried glassware and under a nitrogen atmosphere. Tetrahydrofuran (THF), methylene chloride (DCM), dimethylformamide (DMF) and toluene were dried and purified by a MBRAUN solvent purification system by passage under 8 psi N_2 through activated molecular sieves. Methanol (MeOH) was distilled from magnesium prior to use. Trimethylsilyl chloride (TMSCl), triethylamine (TEA), Hunig's base (diisopropylethylamine) and benzene were distilled from calcium hydride prior to use. All other solvents and commercially available reagents were used as received. Brine refers to a saturated solution of sodium chloride. Reactions were followed by thin layer chromotography (TLC) on SiliCycle® silica gel 60 Å F_{254} (250 μm). Visualization of the developed plate was accomplished by fluorescence quenching and by staining with potassium permanganate ($KMnO_4$). Chromatographic purification of compounds was accomplished by flash chromatography on SiliCycle® Silia*Flash*® F60, 40-63 μm 60 Å.

Nuclear magnetic resonance (NMR) spectra were acquired on a Varian Inova-500 MHz operating at 500 and 125 MHz for ^{1}H and ^{13}C, respectively and are referenced internally according to residual solvent signals. ^{1}H NMR coupling constants (*J*) are reported in Hertz (Hz) and multiplicity is abbreviated as follows: s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets,

dddd = doublet of doublets of doublets of doublets, t = triplet, dt = doublet of triplets, td = triplet of doublets, m = multiplet. IR spectra were acquired using a Bruker Tensor 27 FTIR spectrophotometer. Vibration frequencies are expressed in cm^{-1}. Mass spectra were obtained at the Laboratory for Biological Mass Spectrometry (LBMS) at Texas A&M University. Melting point data was acquired on a Stanford Research Systems EZ-Melt, automated melting point apparatus. Temperatures are expressed in degrees Celsius.

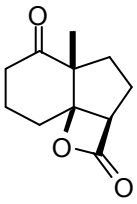
Procedures

Representative Procedure for the Preparation of β-lactones via the NCAL protocol as described for 3.19a-d:



3.22a-d **3.19a-d**

Tricyclic β-lactone 3.19a;(n = 2):

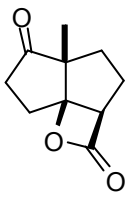


PPY (66.25 mg, 0.447 mmol, 1.5 equiv) and modified Mukiyama's Reagent[2] (156.52 mg, 0.447 mmol, 1.5 equiv) were weighed out in a dry 25 ml round bottom flask and diluted with 3.5 mL DCM (0.05 M) resulting in a white slurry. Hunig's base (0.13 mL, 0.745 mmol, 2.5 equiv) was then

[2] Oh, S. H.; Cortez, G. S.; Romo, D. *J. Org. Chem.* **2005**, *70*, 2835.

added followed by slow addition of the keto-acid **3.22a** (63.2 mg, 0.298 mmol, 1 equiv) in 2 mL DCM over 1 hour via a syringe pump. After the addition of keto-acid **3.22a** was complete, the resulting clear, bright orange solution was stirred for an additional 12 h at 21 ^{o}C. The mixture was then concentrated *in vacuo*, re-dissolved in EtOAc and quenched with saturated NH_4Cl solution. The organics were extracted with EtOAc (x3), washed with sat. NH_4Cl sol. (x3) and brine (x1), dried over $MgSO_4$, filtered and concentrated. The crude product was purified via flash column chromatography with SiO_2 (0-10-20-30% EtOAc/Hex) to yield β-lactone, **3.19a** (78.5 mg, 95%) as a white solid. mp: 64.9-65.3 ^{o}C (recrystallized from EtOAc); IR (thin film): 1826 cm^{-1}, 1711 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.47-3.46 (dd, *J* = 1, 7, 1H), 2.75-2.71 (m, 1H), 2.57-2.50 (dt, *J* = 5.5, 14.5, 1H), 2.37-2.31 (dd, *J* = 4, 14.5, 2H), 2.26-2.22 (td, *J* = 3, 7.5, 1H), 2.11-2.07 (m, 1H), 1.95-1.91 (dd, *J* = 5.5, 12.5, 1H), 1.61-1.48 (m, 2H), 1.44-1.36 (m, 1H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.45, 170.73, 89.68, 59.27, 58.97, 37.38, 32.14, 28.26, 24.82, 19.73, 18.55; LRMS (CI) Calcd for $C_{11}H_{14}O_3$ [M+H]: 195. Found: 195.

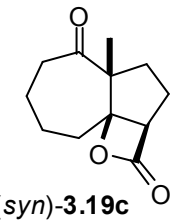
Tricyclic β-lactone 3.19b;(n = 1):



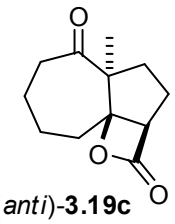
The acid precusor, **3.22b** (123.5 mg, 0.623 mmol) was subjected to the conditions above and upon purfication with flash column chromotography (0-10-20-30-40% EtOAc/Hex) to yield β-lactone **3.19b** (95.2 mg, 85%) as a white solid. mp: 123.9 - 124.8 ^{o}C (recrystallized from EtOAc); IR (thin film): 1821 cm^{-1}, 1735 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.68 (d, *J* = 8, 1H), 2.73-2.67 (ddd, *J* = 2.5, 9, 19.5, 1H), 2.54-2.45 (m, 2H), 2.39-2.35 (dd, *J* = 7, 13.5, 1H),

2.23-2.16 (m, 1H), 2.03-1.99 (dd, *J* = 7.5, 13, 1H), 1.77-1.71 (dt, *J* = 7.5, 13.5, 1H), 1.52-1.43 (m, 1H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.52, 170.03, 91.87, 61.02, 56.97, 36.79, 34.20, 25.57, 24.74, 15.83; LRMS (CI) Calcd for $C_{10}H_{12}O_3$ [M+H]: 181. Found: 181.

Tricyclic β-lactone 3.19c;(n = 3):



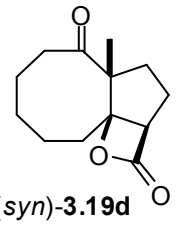
(*syn*)-**3.19c**

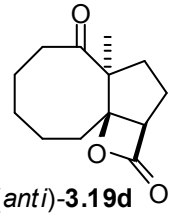


(*anti*)-**3.19c**

The acid precursor, **3.22c** (531.8 mg, 2.35 mmol) was subjected to the representative procedure for the formation of β-lactones and the crude product was purified via flash column chromatography on SiO_2 (10-20-30-40% EtOAc/Hex) and the pure *syn* and *anti* diasteromers were isolated as well as a mix (*syn*: 335 mg, 68%, *anti*: 40.3 mg, 8%, mix: 71.6 mg, 18%, total: 91%) as solids. ***syn*:** IR (thin film): 1824 cm^{-1}, 1699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.64 (d, *J* = 8, 1H), 2.90-2.85 (m, 1H), 2.37-2.27 (m, 2H), 2.22-2.12 (m, 2H), 2.09-2.05 (dd, *J* = 7.5, 14, 1H), 2.02-1.89 (m, 2H), 1.87-1.82 (m, 1H), 1.81-1.75 (m, 1H), 1.67-1.58 (m, 1H), 1.45-1.34 (m, 1H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.11, 171.45, 91.13, 60.39, 59.10, 40.59, 36.44, 31.93, 25.57, 24.90, 23.89, 19.06; LRMS (APCI) Cacld for $C_{12}H_{16}O_3$ [M+H]: 209. Found: 209. ***anti***: IR (thin film): 1824 cm^{-1}, 1693 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.55-3.53 (td, *J* = 0.5, 8, 1H), 2.73-2.67 (ddd, *J* = 1.5, 6, 17.5, 1H), 2.61-2.54 (ddd, *J* = 2.5, 12, 17, 1H), 2.27-2.20 (m, 3H), 2.01-1.95 (m, 3H), 1.93-1.79 (m, 4H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.50, 171.14, 89.89, 61.76, 59.51, 44.67, 35.36, 31.55, 25.50, 23.23, 22.72, 22.02; LRMS (APCI) Cacld for $C_{12}H_{16}O_3$ [M+H]: 209. Found: 209.

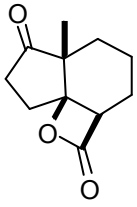
Tricyclic β-lactone 3.19d;(n = 4):


(*syn*)-**3.19d**


(*anti*)-**3.19d**

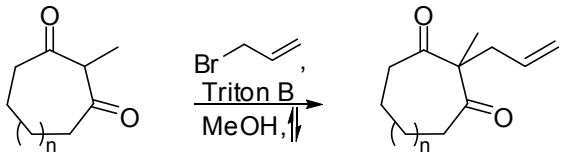
The keto-acid precursor **3.22d** (197.9 mg, 0.82 mmol) was subjected to the conditions and protocol outlined in the representative procedure for the formation of β-lactones. The crude product was purified via flash column chromatography with (20-30-40% EtOAc/Hex) to yield pure *syn* and *anti* diastereomers **3.19d** as solids. (*syn*: 77 mg, 42%, *anti*: 4.1 mg, 2%, total: 44%). ***syn***: mp: 94.2 ^{o}C (recrystallized from benzene); IR (thin film): 1821 cm^{-1}, 1696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.46 (d, *J* = 7.5, 1H), 2.98-2.92 (m, 1H), 2.50-2.46 (dd, *J* = 6.5, 13, 1H), 2.46-2.25 (m, 2H), 2.18-2.13 (m, 1H), 2.12-2.05 (m, 1H), 2.03-1.98 (m, 1H), 1.96-1.88 (m, 1H), 1.67-1.56 (m, 2H), 1.40-1.34 (m, 1H), 1.38 (s, 3H), 0.79-0.38 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.12, 171.59, 91.98, 59.41, 59.05, 37.86, 35.39, 31.85, 28.72, 27.85, 26.19, 22.59, 18.52; LRMS (CI) Cacld for $C_{13}H_{18}O_3$ [M+H]: 223. Found: 223. ***anti***: IR (thin film): 1824 cm^{-1}, 1693 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.55-3.53 (d, *J* = 9.5, 1H), 3.63-3.33 (td, *J* = 3.75, 11, 1H), 2.27-2.2 (m, 2H), 2.18-2.09 (t, *J* = 31.5, 2H), 2.07-2.01(m, 2H), 1.89-1.81 (m, 2H), 1.76-1.69 (m, 2H), 1.61-1.55 (m, 2H), 1.46-1.41 (m, 1H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.43, 171.07, 92.63, 61.52, 56.91, 38.72, 35.65, 32.95, 30.34, 24.74, 24.17, 23.90, 19.21; LRMS (CI) Cacld for $C_{13}H_{18}O_3$ [M+H]: 223. Found: 223.

Tricyclic β-lactone 3.34:



The corresponding precursor acid **3.33** (400 mg, 1.89 mmol) was subjected to the conditions outlined in the representative procedure for the NCAL. The crude product was purified via flash column chromatography (20-30-40% EtOAc/Hex) to yield β-lactone **3.34** (228 mg, 62%) as a yellow, viscous oil. IR (thin film): 1832 cm^{-1}, 1741 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.50-3.47 (dd, *J* = 6.5, 15.5, 1H), 2.64-2.50 (m, 2H), 2.26-2.15 (m, 2H), 1.86-1.79 (m, 3H), 1.57-1.55 (m, 1H), 1.43-1.38 (ddd, *J* = 10, 3, 13, 1H), 1.15-1.06 (m, 1H), 1.08 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.49, 171.27, 83.64, 52.56, 49.98, 36.17, 31.60, 30.61, 22.40, 20.40, 19.19; LRMS (APCI) Cacld for $C_{11}H_{14}O_3$ [M+H]: 195. Found: 195.

Representative Procedure for the allylation of the 7 and 8 membered diones and 1,3-cyclohexanedione as described for 3.20c/d:



3.15c/d **3.20c/d**

Allyl dione 3.20c; (n = 1):

The 2-methyl-1,3-cycloheptandione **3.15c** was prepared according to the procedure outlined by Lewicka-Piekut.[3] The dione (339.6 mg, 2.42 mmol, 1 equiv) in a 15 mL seal tube was diluted with 3.4 mL freshly distilled MeOH to form a brown slurry.

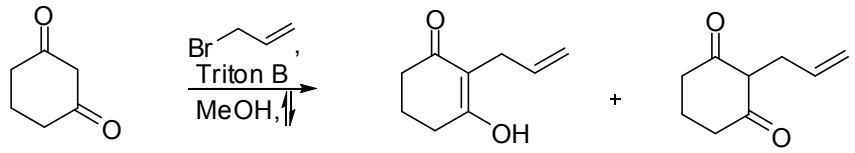
[3] (a) Lewicka-Piekut, S.; Okamura, W.H. *Synth. Comm.*, **1980**, *10*, 415. (b) Brooks, D.W.; Mazdiyasni, H.; Sallay, P. *J. Org. Chem.* **1985**, *50*, 3411. (c) Letsinger, R.L.; Kammeyer, C.W. *J. Am. Chem. Soc.* **1951**, *73*, 4476.

Upon addition of Triton B (1.03 mL, 2.42 mmol, 40% in MeOH) the dione dissolved to result in a clear brown solution. The allyl bromide (0.23 mL, 2.67 mmol, 1.1 equiv) was added at 23 ^{o}C and then the mixture was heated to reflux (60^{o}C) and stirred for 8 h. After cooling, 1M HCl was added to the mixture and allowed to stir vigorously for 10 minutes. The organics were extracted with EtOAc (x3) and washed with brine (x2). Dried over $MgSO_4$, filtered and concentrated. The crude product was purified via flash column chromatography with SiO_2 (30-40-50% EtOAc/Hex) to yield the allylated product **3.20c** (312 mg, 71%). IR (thin film): 2940 cm^{-1}, 1697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.55-5.50 (m, 1H), 4.99-4.96 (m, 2H), 2.47-2.45 (dd, *J* = 7.5, 2H), 2.44-2.36 (m, 4H), 1.84-1.81 (dddd, *J* = 3.5, 3.5, 3.5, 3.5, 4H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.37, 132.63, 119.03, 64.88, 41.66, 38.70, 28.15, 18.58; LRMS (CI) Calcd for $C_{11}H_{16}O_2$ [M+H]: 181. Found: 181.

Allyl dione 3.20d;(n = 2):

The 2-methyl-1,3-cyclooctandione **3.15d** was prepared according the Lewicka-Piekut[3] procedure and then used in the representative procedure outlined above (1.58 g, 10.25 mmol) and the crude product was purified via flash column chromatography on SiO_2 (10-20-30% EtOAc/Hex) and the pure allylated dione **3.20d** (1.39 g, 70%) was isolated as a yellow oil. IR (thin film): 2935 cm^{-1}, 1692 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.47-5.42 (m, 1H), 4.97-4.92 (m, 1H), 2.42 (d, *J* = 7.5), 2.34-2.31 (ddd, *J* = 6, 1.5, 6, 4H), 1.62-1.57 (m, 4H), 1.47-1.45 (m, 2H), 1.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.77, 132.74, 119.09, 65.08, 41.49, 38.57, 27.34, 25.18, 18.51; LRMS (CI) Calcd for $C_{12}H_{18}O_2$ [M+H]: 195. Found: 195.

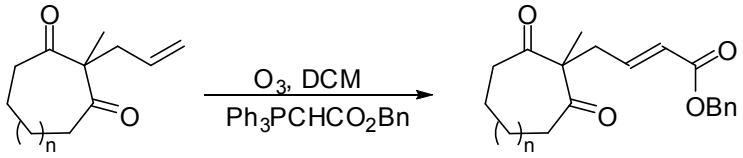
Allyl dione 3.60:



3.59 **3.60**

The allylated dione **3.60** was prepared following the representative procedure above using **3.59** (1 g, 8.90 mmol). The crude product was purified via flash column chromatography on SiO_2 (30-40-50-60-70% EtOAc/Hex) to yield **3.60** (417 mg, 31%) as white solid. IR (thin film): 3350-2200 cm^{-1} (broad), 1600 cm^{-1}, 1550 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.31-10.13 (bs, 1H), 5.82-5.76 (m, 1H), 5.00-4.96 (dddd, *J* = 1.5, 1.5, 1.5, 17, 1H), 4.90-4.87 (dddd, *J* = 1.5, 1.5, 1.5, 10, 1H), 3.04 (d, *J* = 6.5, 2H), 2.46 (t, *J* = 6.5, 4H), 2.42-2.33 (dt, *J* = 6, 32.5, 1H) (partially keto-form), 1.98-1.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.90, 136.90, 114.55, 114.21, 102.43, 102.37, 56.37 (keto-form), 36.88 (keto-form), 33.33, 29.34 (keto-form), 26.50, 21.57 (keto-form), 21.26; LRMS (APCI) Calcd for $C_9H_{12}O_2$ [M+H]: 153. Found: 153.

Representative Procedure for the benzyl ester of the 7 and 8 membered diones:



3.20c/d **3.21c/d**

Benzyl ester 3.21c;(n = 1):

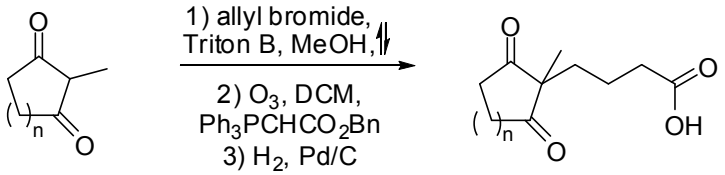
In a 50 mL RBF, the SM **3.20c** was weighed out (301.6 mg, 1.67 mmol, 1 equiv.) and dissolved in 10 mL DCM. The solution was allowed to cool to -78°C and then ozone was bubbled in through a gas dispersion tube until the solution remained a cloudy

blue. This was then followed by bubbling N_2 until the solution returned to a clear light yellow again. The ylide (893.4 mg, 2.18 mmol, 1.3 equiv.) in 5 mL DCM was added and the solution was allowed to stir overnight (~12 h) while warming slowly to rt. The mixture was then concentrated *in vacuo* and purified via flash column chromatography on SiO_2 (0-3-10% EtOAc/DCM) and the pure ester was isolated (158 mg, 30%). IR (thin film): 2946 cm^{-1}, 1720 cm^{-1}, 1691 cm^{-1}, 1655 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29-7.26 (d, *J* = 4, 4H), 7.25-7.22 (dd, *J* = 4.5, 9, 1H), 6.72-6.69 (dddd, *J* = 8, 8, 8, 8, 1H), 5.79 (d, *J* = 16, 1H), 5.21 (s, 2H), 2.56-2.54 (dd, *J* = 1, 7.5, 2H), 2.39-2.35 (m, 4H), 1.82-1.78 (m, 4H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.41, 165.60, 143.44, 136.03, 128.69, 128.36, 128.36, 124.76, 66.32, 34.45, 41.41, 36.78, 28.02, 18.62; LRMS (CI) Calcd for $C_{19}H_{22}O_4$ [M+H]: 315. Found: 315.

Benzyl ester 3.21d;(n = 2):

The starting allylated dione **3.20d** (1.39 g, 7.16 mmol) was subjected to the representative procedure for obtaining the benzyl ester and the crude product **3.21d** was purified via flash column chromatography on SiO_2 (0-5% EtOAc/DCM) and the pure ester (821.8 mg, 35%) was isolated as a yellow oil. IR (thin film): 2940 cm^{-1}, 1697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.32 (m, 5H), 6.79-6.76 (ddd, *J* = 8, 8, 15.5, 1H), 5.93-5.89 (td, *J* = 1.5, 15.5, 1H), 5.15 (s, 2H), 2.69-2.67 (dd, *J* = 1, 7.5, 2H), 2.48-2.43 (m, 4H), 1.73-1.70 (dddd, *J* = 5, 5, 5, 5, 4H), 1.59-1.58 (m, 2H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.14, 165.83, 143.75, 136.17, 128.89, 128.62, 128.58, 125.07, 66.59, 64.96, 41.40, 37.05, 27.33, 25.42, 18.67; LRMS (CI) Calcd for $C_{20}H_{24}O_4$ [M+H]: 329. Found: 329.

Representative Procedure for the preparation of keto-acid substrates:



3.15a/b **3.22a/b**

Keto-acid 3.22a; (n = 2):

The 2-methyl-1,3-cyclohexanedione **3.15a** (5.39g, 42.73 mmol, 1.0 equiv) was diluted with 54 mL of freshly distilled MeOH to create a turbid mixture. Upon addition of 18.2 mL Triton B (40% in MeOH), the solution becomes a clear brown and then allyl bromide (4.04 mL, 47 mmol, 1.1 equiv) is added. The solution was then heated to a gentle reflux (65-70^{o}C) and allowed to stir for 12 h. After cooling, 1M HCl solution was poured into the reactions flask and allowed to stir for 10-15 minutes. The product was extracted with ethyl acetate (x3), washed with brine (x2), dried over $MgSO_4$, filtered and concentrated. The crude mixture was purified by flash column chromatography on SiO_2 (20-30% EtOAc/Hex) to yield the allylated dione, **3.20a**[4] (3.32 g, 47%) as a pale yellow oil.

The allylated dione, **3.20a** (500mg, 3.3mmol, 1.0 equiv) was then dissolved in 17 mL of DCM. This was then cooled to -78^{o}C and allowed to stir at this temperature for 15 minutes. Ozone was then bubbled through the solution through a gas dispersion tube until the mixture was blue. Nitrogen was then bubbled through until the mixture returned to a clear white color. The ylide (1.76 g, 4.3 mmol, 1.3 equiv) in 8.5 mL DCM

[4] (a) Katoh, T.; Mizumoto, S.; Fudesaka, M.; Takeo, M.; Kajimoto, T.; Node, M. *Tetradedron: Asymmetry* **2006**, *17*, 1655. (b) Mori, K.; Fujiwhara, M. *Tetrahedron*, **1988**, *44*, 343.

was added to the mixture slowly, still at -78°C. The mixture was then allowed to stir overnight 16 h while warming to 21°C. The solvent was removed *in vacuo* and purified directly by flash column chromatography on SiO_2 (25-35-50% EtOAc/Hex) to yield the α,β-unsaturated benzyl ester, **3.21a**[5] (433 mg, 44%) as a yellow oil.

The benzyl ester (1.74 g, 5.80 mmol) was then hydrogenated to yield the keto-acid **3.22a** (910.8 mg, 74%) as a white solid: IR (thin film) 3530-2650 cm^{-1}; 1726 cm^{-1}; 1693 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.72-2.60 (m, 4H), 2.32 (t, *J* = 7 Hz, 2H), 2.00-1.97 (m, 1H), 1.90-1.87 (m, 1H), 1.83-1.80 (m, 2H), 1.47-1.42 (m, 2H), 1.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.49, 179.27, 65.70, 38.18. 36.15, 34.09, 20.11, 20.06, 17.91; LRMS (ESI) Cacld for $C_{11}H_{16}O_4$ [M-H]: 211. Found: 211.

Keto-acid 3.22b;(n = 1):

The 2-methyl-1,3-cyclopentadione **3.15b** (1.02 g, 9.10 mmol) was converted to the allylated dione (495.3 mg, 36%) which was subsequently made into the benzyl ester (641.2 mg, 69%) via Grubb's catalyst procedures. The ester was then was converted to the corresponding keto-acid using the representative procedure above to yield acid **3.22b** (281.4 mg, 63%) as a white solid: IR (thin film) 3600-2600 cm^{-1}; 1717 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.80-2.72 (m, 4H), 2.27 (t, *J* = 7.5, 2H), 1.65-1.62 (m, 2H), 1.49-1.44 (m, 2H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.61, 179.05, 56.80, 35.43, 34.53, 34.10, 19.88, 19.45; LRMS (ESI) Calcd for $C_{10}H_{14}O_4$ [M-H]: 197. Found: 197.

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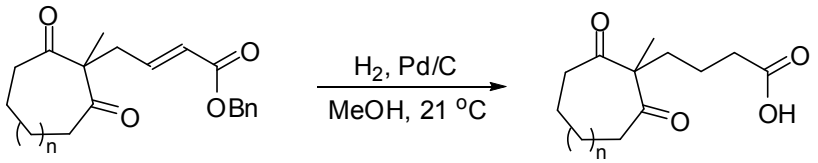
[5] Hon, Y.S.; Lu, L.; Chang, R.C.; Lin, S.W.; Sun, P.P.; Lee, C.F. *Tetrahedron,* **2000**, *56*, 9269

Representative Procedure for the keto-acid of the 7 and 8 membered diones:



3.21c/d **3.22c/d**

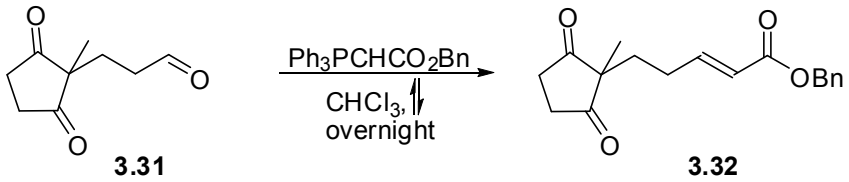
Keto-acid 3.22c;(n = 3):

The benzyl ester **3.21c** (2.14 g, 6.812 mmol) was then hydrogenated under established conditions to yield the keto-acid, **3.22c** (1.2 g, 78%) as a white solid: IR (thin film) 3550-2500 cm^{-1}, 1694 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.44 (app d, *J* = 3.5, 4H), 2.33 (t, *J* = 7, 2H), 1.87-1.85 (qt, 4H), 1.82-1.79 (m, 2H), 1.40-1.37 (m, 2H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.97, 179.48, 64.76, 41.49, 34.24, 33.10, 28.36, 19.17, 18.04; LRMS (ESI) Calcd for $C_{12}H_{18}O_4$ [M-H]: 225. Found: 225.

Keto-acid 3.22d;(n = 4):

The benzyl ester **3.21d** (821.8 mg, 2.50 mmol) was subjected to the representative procedure outlined above to give the keto-acid **3.22d** (393 mg, 65%) as a white solid: IR (thin film): 3570-2750 cm^{-1}, 1688 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.38 (t, *J* = 6, 4H), 2.32 (t, *J* = 7.5, 2H), 1.79-1.75 (m, 2H), 1.66-1.60 (m, 4H), 1.52-1.47 (m, 2H), 1.37-1.30 (m, 2H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.35, 179.35, 65.09, 41.22, 34.14, 32.91, 27.24, 25.31, 19.06, 17.91; LRMS (ESI) Calcd for $C_{13}H_{20}O_4$ [M-H]: 239. Found: 239.

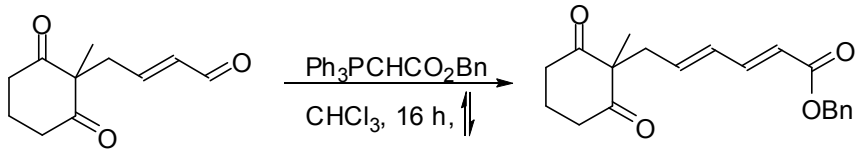
Benzyl ester 3.32:



Procedure was based upon the work done by Huddleston *et. al.*[6]. The aldehyde **3.31** (1 g, 5.95 mmol, 1 equiv.) was dissolved in 40 mL chloroform and to this was added the solid Wittig reagent (4.88 g, 11.899 mmol, 2 equiv.). The solution becomes green and then blue. After stirring overnight (16 h) at reflux, the solution remained a constant clear yellow. The solution was cooled, concentrated and purified via flash column chromatography on SiO_2 (0-5-10% EtOAc/Hex) and the pure ester **3.32** (1.48 g, 83%) was isolated. IR (thin film): 1720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H), 6.87-6.84 (td, *J* = 7, 16, 1H), 5.84-5.81 (d, *J* = 15.5, 1H), 5.17 (s, 2H), 2.84-2.70 (m, 4H), 2.11-2.09 (m, 2H), 1.82-1.79 (m, 2H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.20, 147.95, 136.31, 128.90, 128.56, 128.51, 127.57, 122.31, 66.49, 56.44, 35.36, 32.96, 27.62, 20.27; LRMS (APCI) Calcd for $C_{18}H_{20}O_4$ [M+Li]: 300. Found: 300.

[6] Huddleston, R. R.; Krische, M. J. *Org. Lett*. **2003**, *5*, 1143

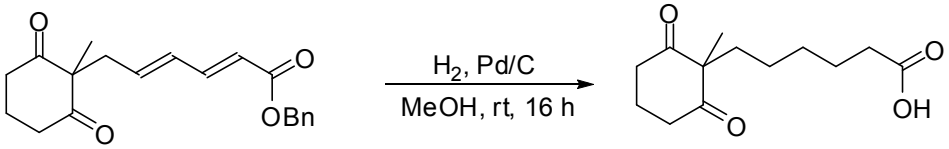
Benzyl ester 3.36:



3.35 **3.36**

The starting dione **3.35** (402.9 mg, 2.40 mmol) was subjected to the procedure above. After stirring overnight, the cooled mixture was concentrated and directly purified via flash column chromatography on SiO_2 (30-40-50-60% EtOAc/Hex) and the pure ester **3.36** (582 mg, 74%) was isolated as a pale yellow oil. IR (thin film): 1696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.33 (m, 5H), 7.22-7.17 (dd, *J* = 11.5, 15.5, 1H), 6.19-6.17 (dd, *J* = 1, 11, 1H), 5.89-5.85 (m, 2H), 5.17 (s, 2H), 2.73-2.56 (m, 6H), 1.96-1.90 (m, 2H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.98, 209.91, 167.06, 144.60, 132.51, 136.38, 138.28, 128.88, 128.52, 120.93, 66.48, 65.30, 39.05, 38.44, 22.15, 17.67; LRMS (ESI) Calcd for $C_{20}H_{22}O_4$ [M+Li]: 333. Found: 333.

Keto-acid 3.37:

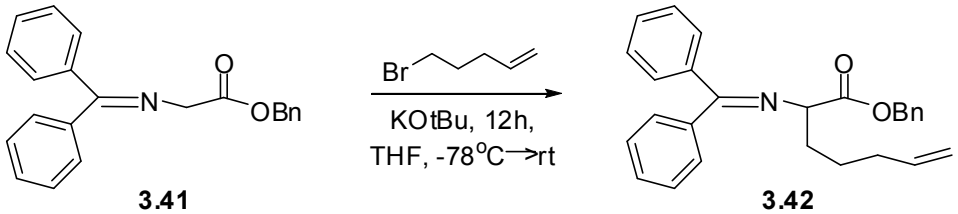


3.36 **3.37**

The benzyl ester **3.36** was subjected to a typical hydrogenation procedure. **3.36** (542.7 mg, 1.66 mmol, 1 equiv.) was weighed out in a 50 mL RBF and dissolved in 16 mL freshly distilled MeOH. Palladium on activated carbon (approx. 40 mg) was added and the flask was purged several times with H_2 and allowed to stir for 16 hours at rt

under H_2 atm. The mixture was poured through celite, concentrated *in vacuo* and then purified via flash column chromatography on SiO_2 (40-50-60% EtOAc/Hex with 1% AcOH) and the pure acid (230.5 mg, 57.8 %) was isolated. IR (thin film): 3464 cm^{-1}, 1723 cm^{-1}, 1690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.67-2.61 (m, 4H), 2.31-2.28 (t, *J* = 7.5, 2H), 2.00-1.96 (m, 1H), 1.88-1.84 (m, 1H), 1.77-1.74 (m, 2H), 1.60-1.54 (m, 2H), 1.31-1.25 (m, 2H), 1.20 (s, 3H), 1.14-1.09 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.85, 180.08, 65.84, 38.25, 37.38, 34.11, 29.47, 24.64, 24.52, 19.63, 17.94; LRMS (ESI) Calcd for $C_{13}H_{20}O_4$ [M-H]: 239. Found: 239.

Imine 3.42:

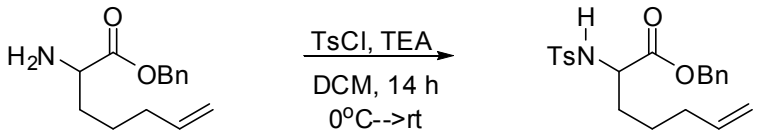


3.41 **3.42**

Potassium tert-butoxide (3 mL, 3 mmol, 1M in THF) and 9 mL of THF were combined in a 10 mL RBF and cooled to -78°C. Upon addition of the imine (987.4 mg, 3 mmol, 1 equiv.) in 3 mL THF, the solution becomes bright yellow. Then the alkyl halide (0.39 mL, 3.3 mmol, 1.1 equiv.) was slowly added and the mixture was let to stir for 12 h while warming to rt. The mixture was then poured into sat. NH_4cl sol, the organics were extracted with EtOAc (x3), washed with sat. NH_4Cl sol. (x3), dried over $MgSO_4$, filtered and concentrated. The crude product was purified via flash column chromatography on SiO_2 (0-5-10% EtOAc/Hex) and the pure alkylated imine **3.42** (517 mg, 43%). IR (thin film): 1741 cm^{-1}, 1664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 1.5, 8.5, 3H), 7.66 (dd, *J* = 1, 8.5, 2H), 7.63-7.59 (tt, *J* = 1.5, 7, 1H), 7.53-7.48

(dt, *J* = 1.5, 7.5, 3H), 7.43-7.38 (m, 4H), 7.37-7.32 (m, 6H), 7.14-7.11 (dd, *J* = 1.5, 7.5, 2H), 5.80-5.71 (m, 1H), 5.24-5.13 (ddd, *J* = 12.5, 12.5, 12.5, 2H), 4.98-4.91 (m, 2H), 4.12 (t, *J* = 6.5, 1H), 2.02-1.95 (dddd, *J* = 8, 8, 8, 8, 4H), 1.47-1.38 (m, 1H0, 1.36-1.26 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.32, 172.68, 171.12, 140.05, 138.97, 138.17, 136.96, 136.55, 132.99, 130.90, 130.63, 129.39-128.39, 115.23, 66.96, 65.89, 33.97, 33.66, 25.80; LRMS (ESI) Calcd for $C_{27}H_{27}NO_2$ [M+H]: 398. Found: 398.

Tosyl amine 3.44:

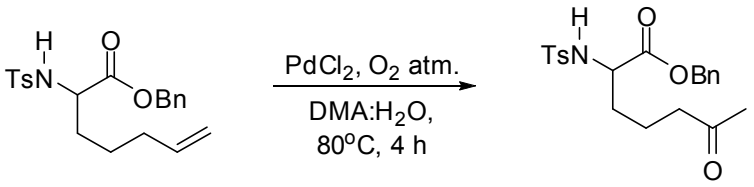


3.43 **3.44**

The starting benzylated amino acid **3.43** (303.8 mg, 0.90 mmol, 1 equiv.) was dissolved in 11 mL DCM in a 25 mL RBF. To this was added tosyl chloride, TsCl (188.73 mg, 0.99 mmol, 1.1 equiv.) in 2 mL DCM and then the solution was cooled to 0°C. TEA (0.14 mL, 1.8 mmol, 2 equiv.) was added and then the solution was let to stir for 14 h while warming to rt. pH 7 buffer was poured into the reaction and was stirred vigorously for about 15 minutes. The organics were then extracted with DCM (x3) and dried over $MgSO_4$, filtered and concentrated. The crude product was purified via flash column chromatography on SiO_2 (10-20-30-40% EtOAc/Hex) and the pure tosylated amine **3.44** (423.8 mg, 99%) was isolated. IR (thin film): 3284 cm^{-1}, 2928 cm^{-1}, 1726 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8, 2H), 7.34-7.31 (dd, *J* = 2,5, 3H), 7.23-7.19 (dd, *J* = 2.5, 7, 4H), 5.70-5.64 (m, 2H), 4.96-4.92 (m, 1H), 4.91 (s, 2H), 4.01-3.97 (m, 1H), 2.38 (s, 3H), 2.03-1.94 (m, 2H), 1.79-1.70 (m, 1H), 1.68-1.59 (m, 1H),

1.46-1.36 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.72, 143.55, 137.84, 137.01, 135.06, 129.69, 128.64, 128.55, 128.26, 127.30, 115.18, 67.24, 55.75, 32.94, 32.75, 24.15, 21.61; LRMS (ESI) Calcd for $C_{21}H_{25}NO_4S$ [M+H]: 388. Found: 388.

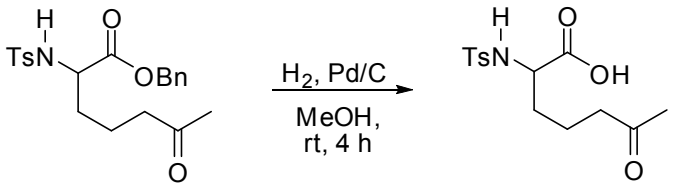
Tosyl amine 3.45:



3.44 **3.45**

The catalyst, $PdCl_2$ (1 mg, 0.0056 mmol, 0.01 equiv.) was weighed in a 25 mL RBF and diluted with 5 mL DMA and 0.3 mL H_2O. The flask was purged with O_2 atm. and was let to stir for 4 h at reflux. The starting material **3.44** (217.5 mg, 0.562 mmol, 1 equiv.) in 1 mL DMA was added and the mixture was stirred vigorously for 6.5 h at 80°C under O_2 atm. After cooling, the reaction was poured into an ether/water mixture and the organics were extracted (x2) with ether, dried over $MgSO_4$, filtered and concentrated. The crude product was purified via flash column chromatography on SiO_2 (20-30-40% EtOAc/Hex) and the pure keto-ester **3.45** (142.3 mg, 63%) was isolated. IR (thin film): 1744 cm^{-1}, 1714 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69-7.67 (d, J = 8, 2H), 7.33-7.30 (dd, J = 2, 4, 2H), 7.22-7.17 (m, 4H), 5.56 (d, J = 9, 1H), 4.89 (d, J = 2, 2H), 3.94-3.91 (m, 1H), 2.40-2.33 (m, 2H), 2.37 (s, 3H), 2.06 (s, 3H), 1.77-1.68 (m, 1H), 1.67-1.56 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.31, 171.58, 143.77, 136.89, 135.02, 129.82, 128.71, 128.42, 127.38, 67.50, 55.70, 55.68, 42.58, 32.62, 30.00, 21.74, 19.29; LRMS (ESI) Calcd for $C_{21}H_{25}NO_5S$ [M+H]: 404 Found: 404.

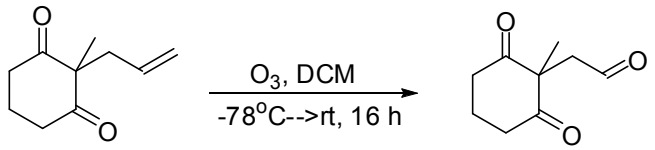
Keto-acid 3.46:



3.45 **3.46**

The starting keto-ester **3.45** (184.9 mg, 0.459 mmol, 1 equiv.) was weighed out in a 25 mL RBF and dissolved in 7 mLs of MeOH. The palladium on activated carbon (approx. 25 mg) was added and then the flask was purged with H_2 atm. and was let to stir for 4 h at rt. The mixture was then passed through celite and then the crude product was purfied via flash column chromatography on SiO_2 (50-60-70-80% EtOAc/Hex) and the pure keto-acid **3.46** (125.6 mg, 87%) was isolated. IR (thin film): 3600-2900 cm^{-1} (broad), 1723 cm^{-1}, 1638 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.76 (d, J = 8.5, 2H), 7.36 (d, J = 8, 2H), 5.00 (bs, 2H), 3.82 (t, J = 4.5, 7.5, 1H), 2.47-2.43 (t, J = 7, 2H), 2.43 (s, 3H), 2.11 (s, 3H), 1.77-1.68 (m, 1H), 1.65-1.54 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.08, 175.51, 145.48, 139.99, 131.41, 129.00, 57.68, 44.00, 33.99, 30.63, 22.33, 21.46; LRMS (ESI) Calcd for $C_{14}H_{19}NO_5S$ [$M-H^+$]: 312 Found: 312.

Aldehyde 3.61:



3.15a **3.61**

The allylated dione **3.61** (310.3 mg, 1.87 mmol, 1 equiv.) was weighed out in a 50 mL RBF and diluted with 8 mL DCM. The solution was cooled thoroughly to -78°C

and then ozone was bubbled in through a gas dispersion tube until the solution was a consistant light blue color. Atmospheric O_2 was then bubbled in until the original pale yellow color returned and then DMS (0.7 mL, 9.34 mmol, 5 equiv.) was added. The reaction was allowed to stir at -78^{o}C while warming to rt over 16 hours. The reaction was quenched with brine and diluted with DCM. The organics were extracted with DCM (x2), washed with brine (x2), dried over $MgSO_4$, filtered and concentrated. The crude product was purified via flash column chromatography on SiO_2 (20-30-40-50% EtOAc/Hex) and the pure aldehyde (71.2 mg, 25%) was isolated. IR (thin film): 3550-3000 cm^{-1} (broad), 1697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (s, 1H), 3.27 (s, 2H), 2.74-2.71 (dd, *J* = 5.5, 7.5, 4H), 2.19-2.13 (m, 1H), 2.12-2.05 (m, 1H), 1.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.22, 199.77, 59.72, 49.97, 37.73, 23.53, 17.64; LRMS (ESI) Calcd for $C_9H_{12}O_3$ [M+Li]: 175. Found: 175.

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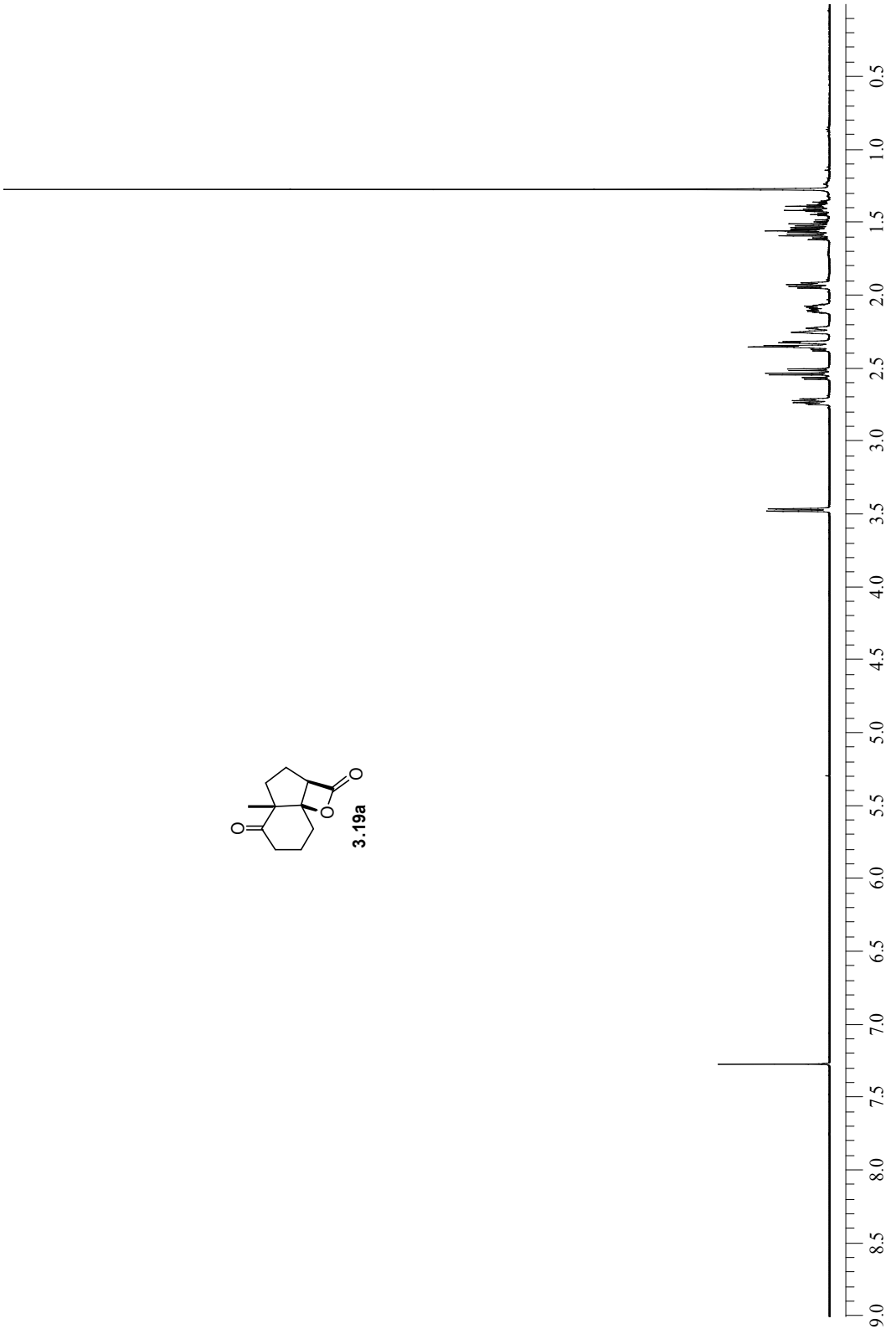
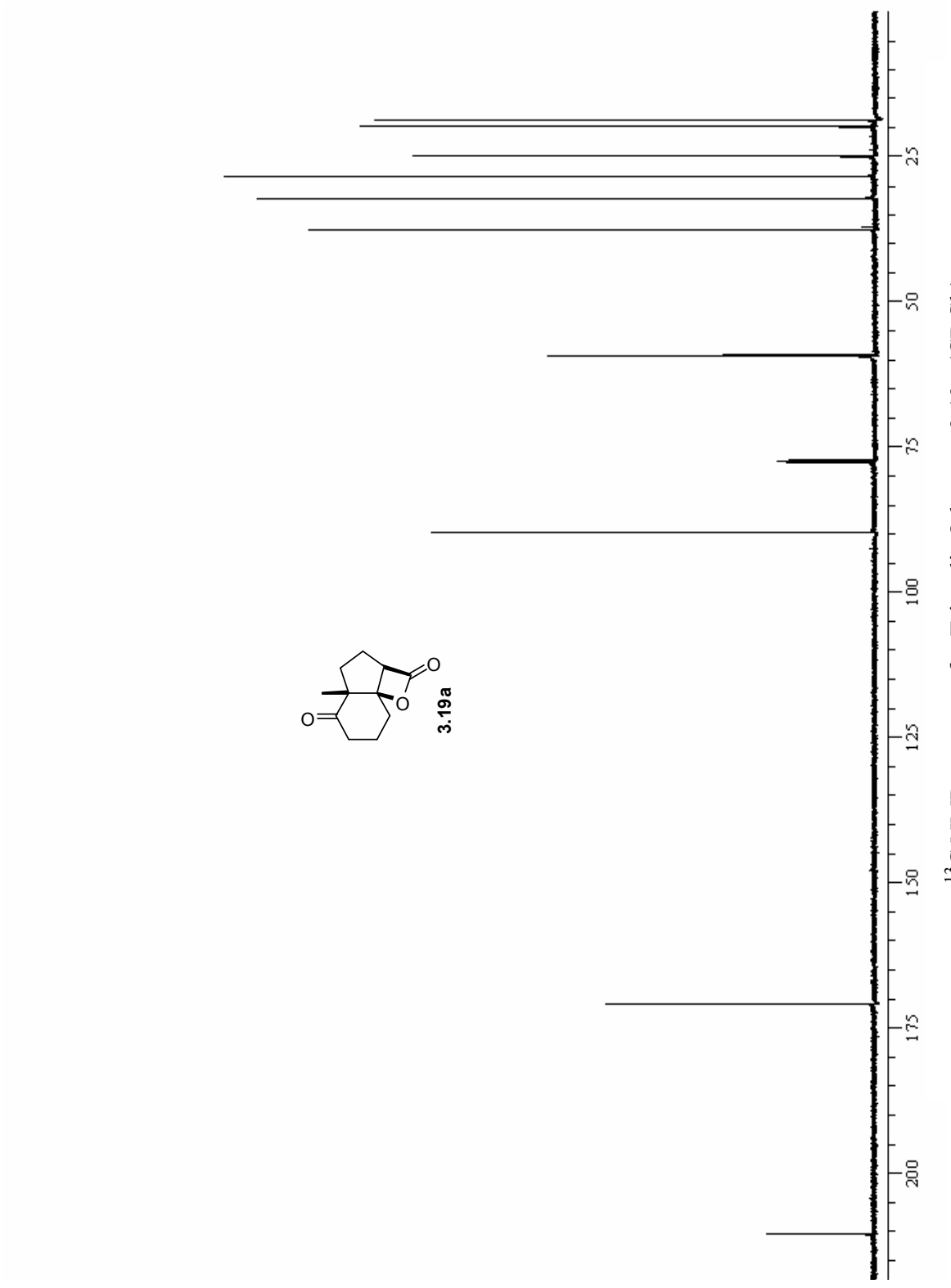
APPENDIX A

SELECTED SPECTRAL DATA



^{1}H NMR spectrum for Tricyclic β-lactone **3.19a** ($CDCl_3$)



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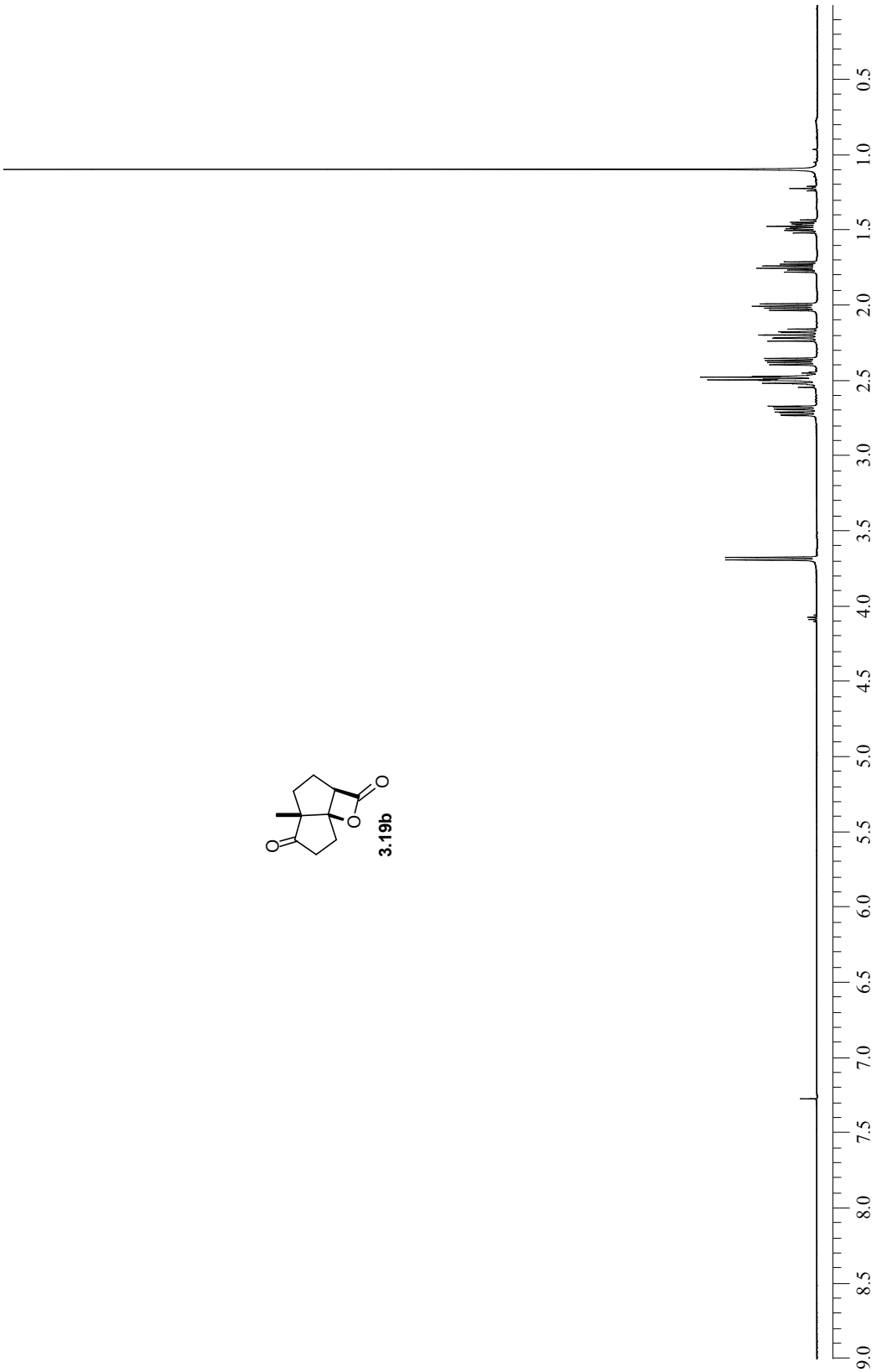
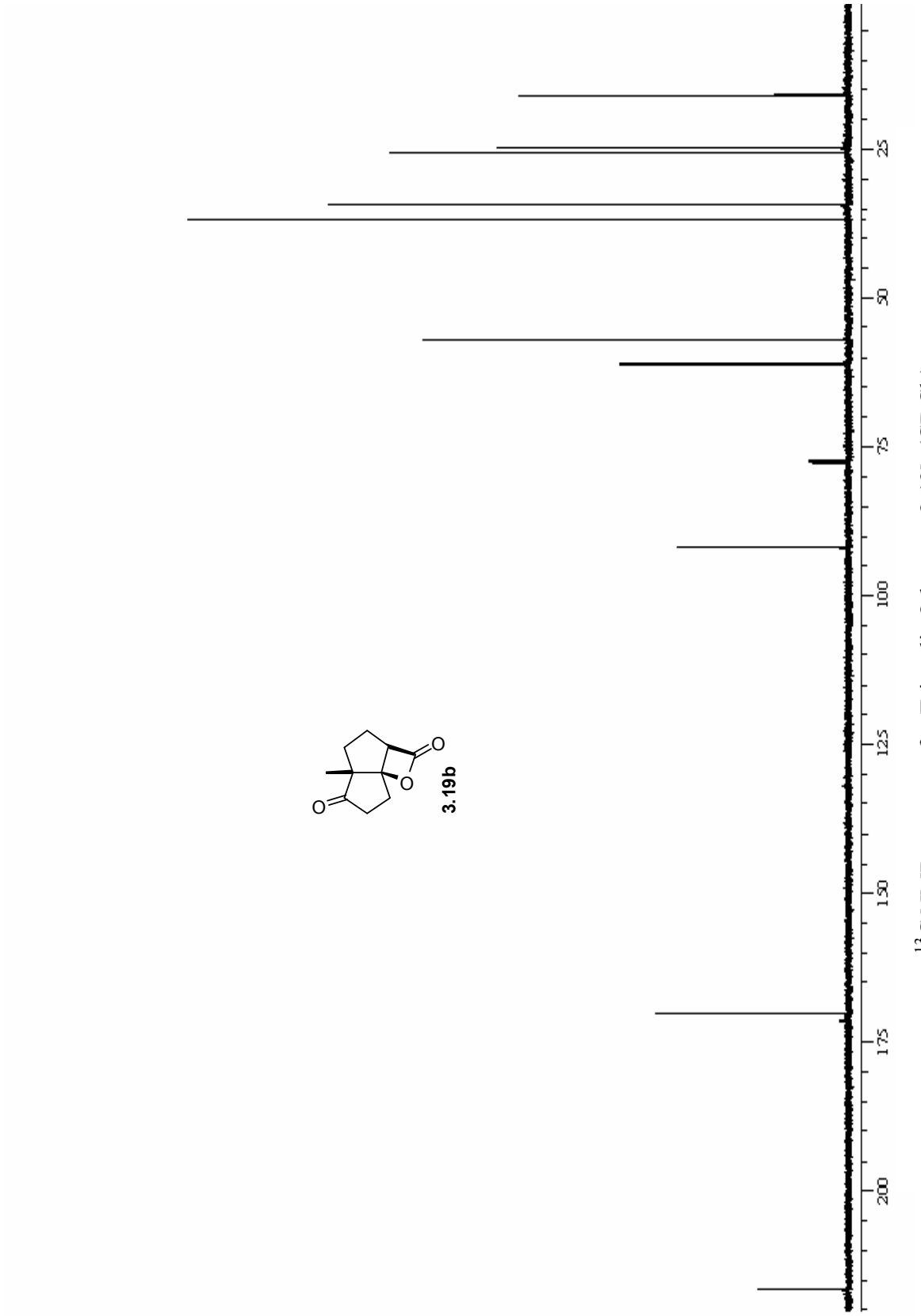
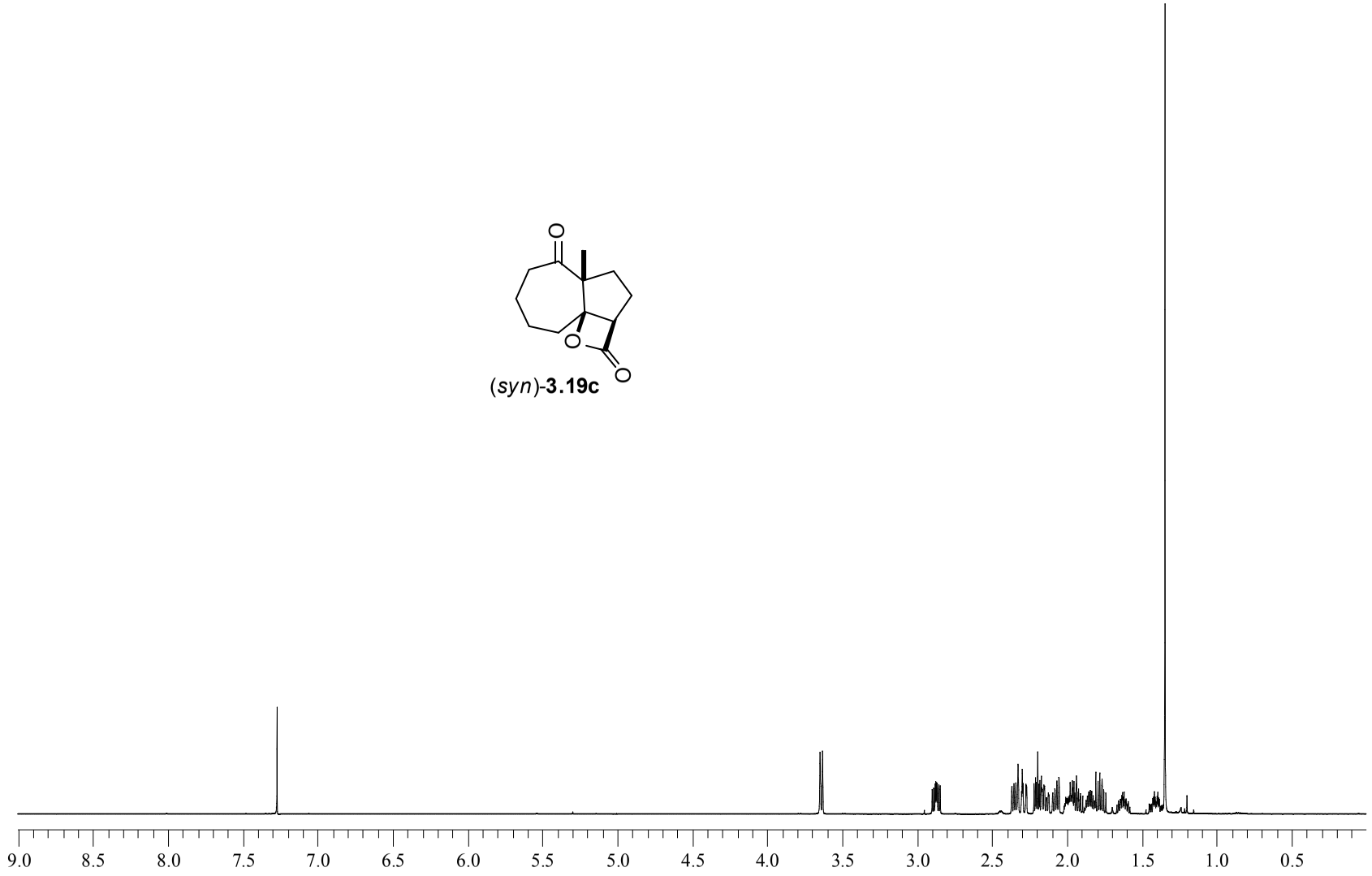


^{1}H NMR spectrum for Tricyclic β-lactone **3.19b** ($CDCl_3$)



^{13}C NMR spectrum for Tricyclic β-lactone **3.19b** ($CDCl_3$)



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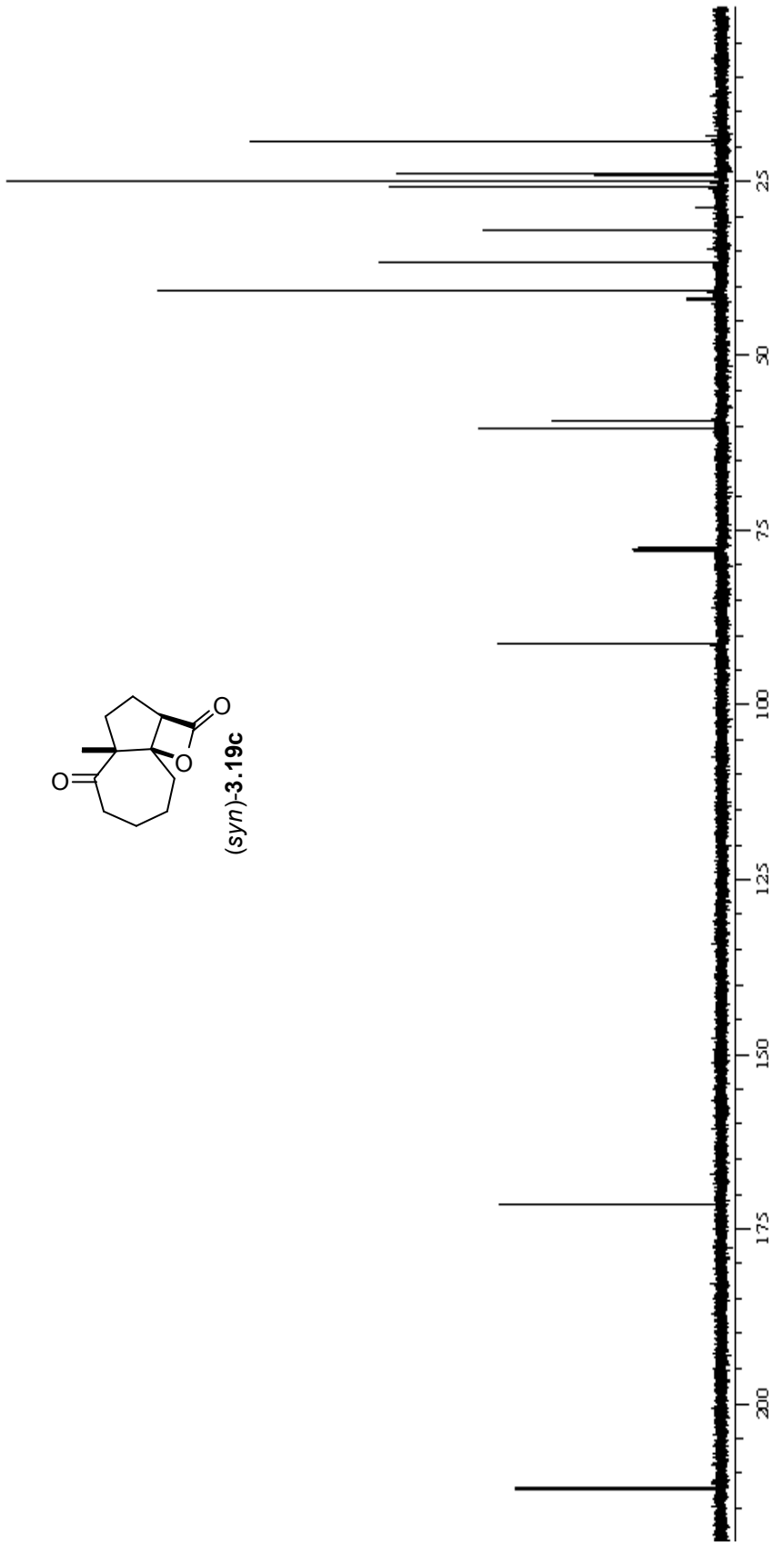

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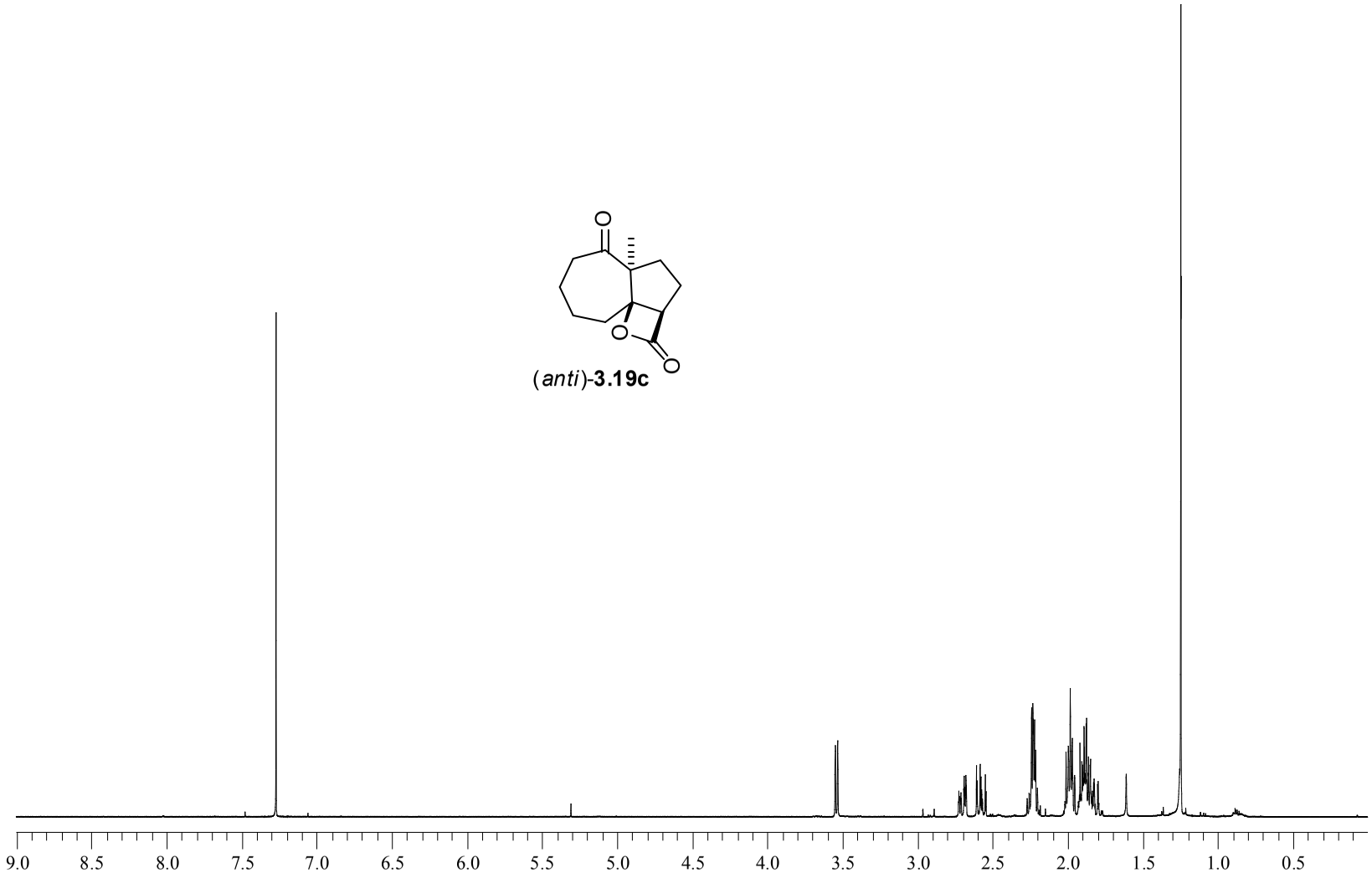

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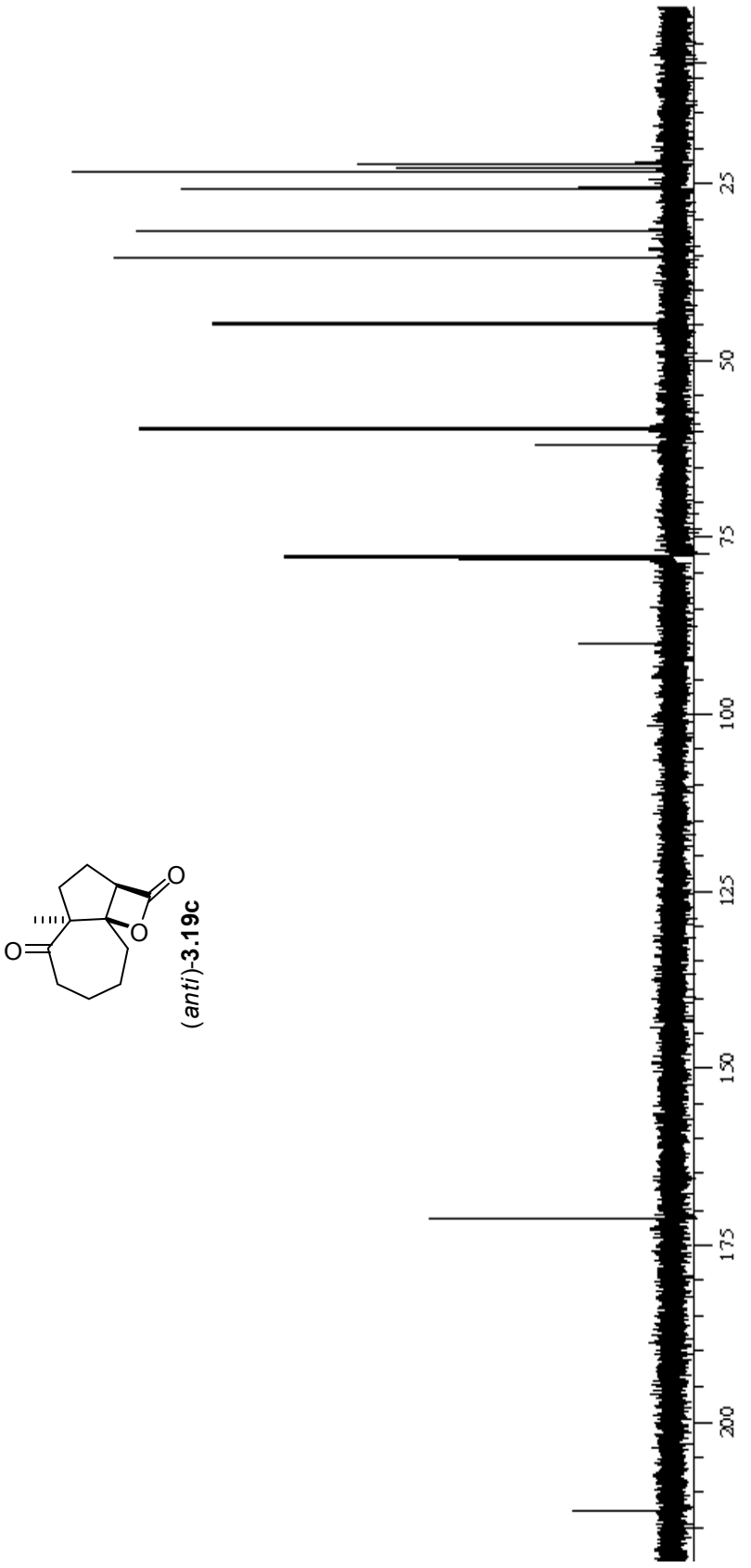

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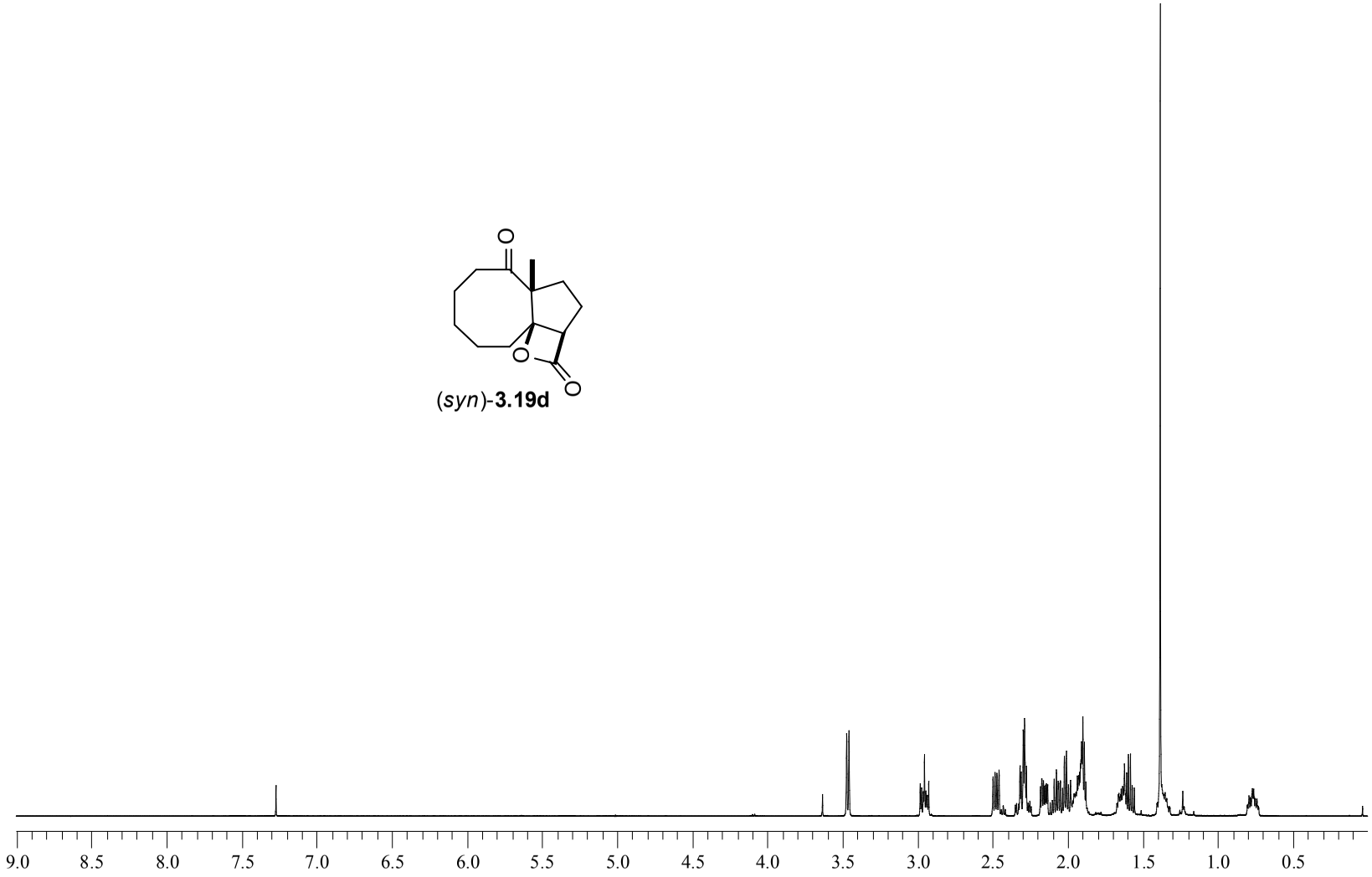

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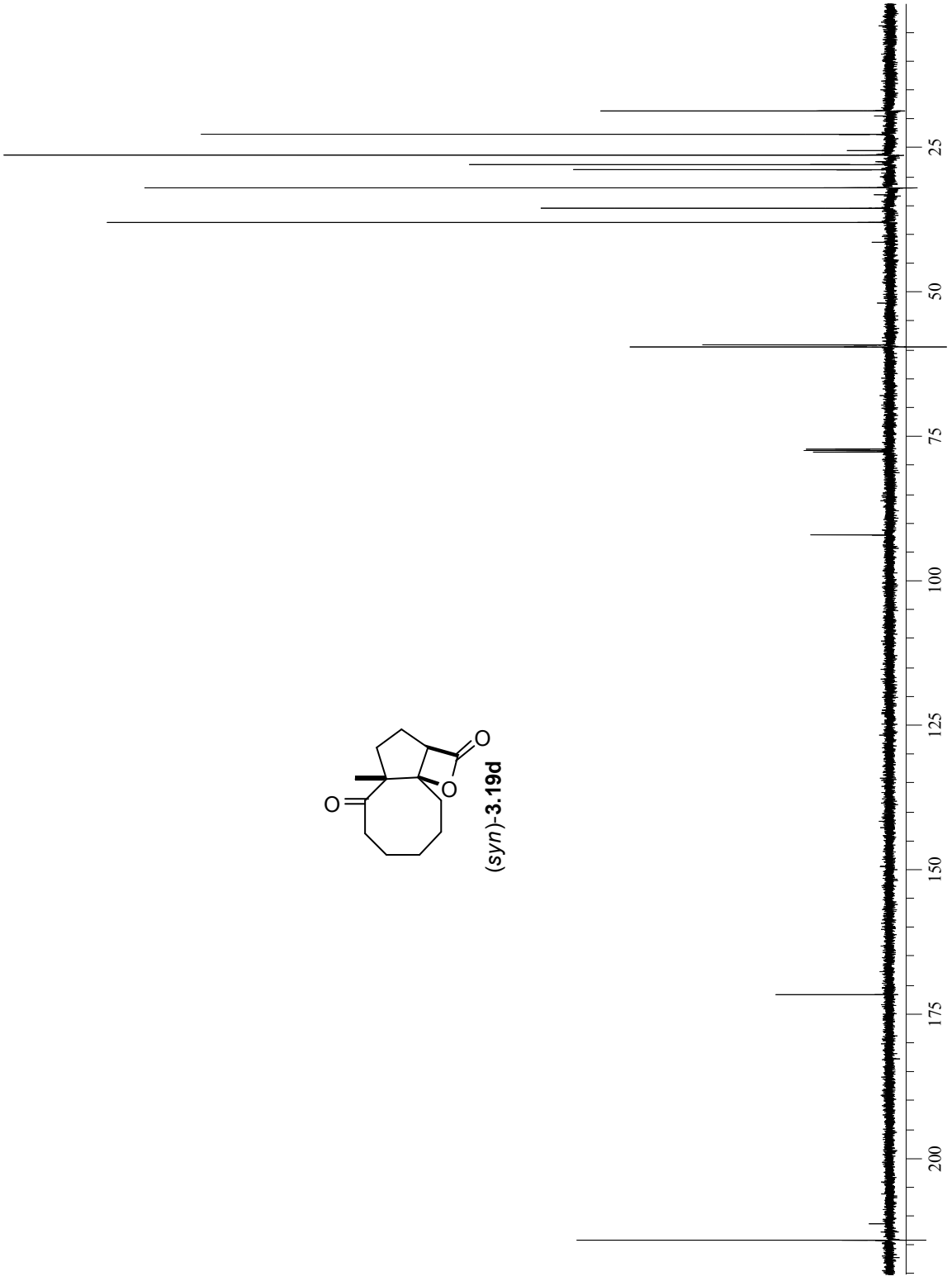

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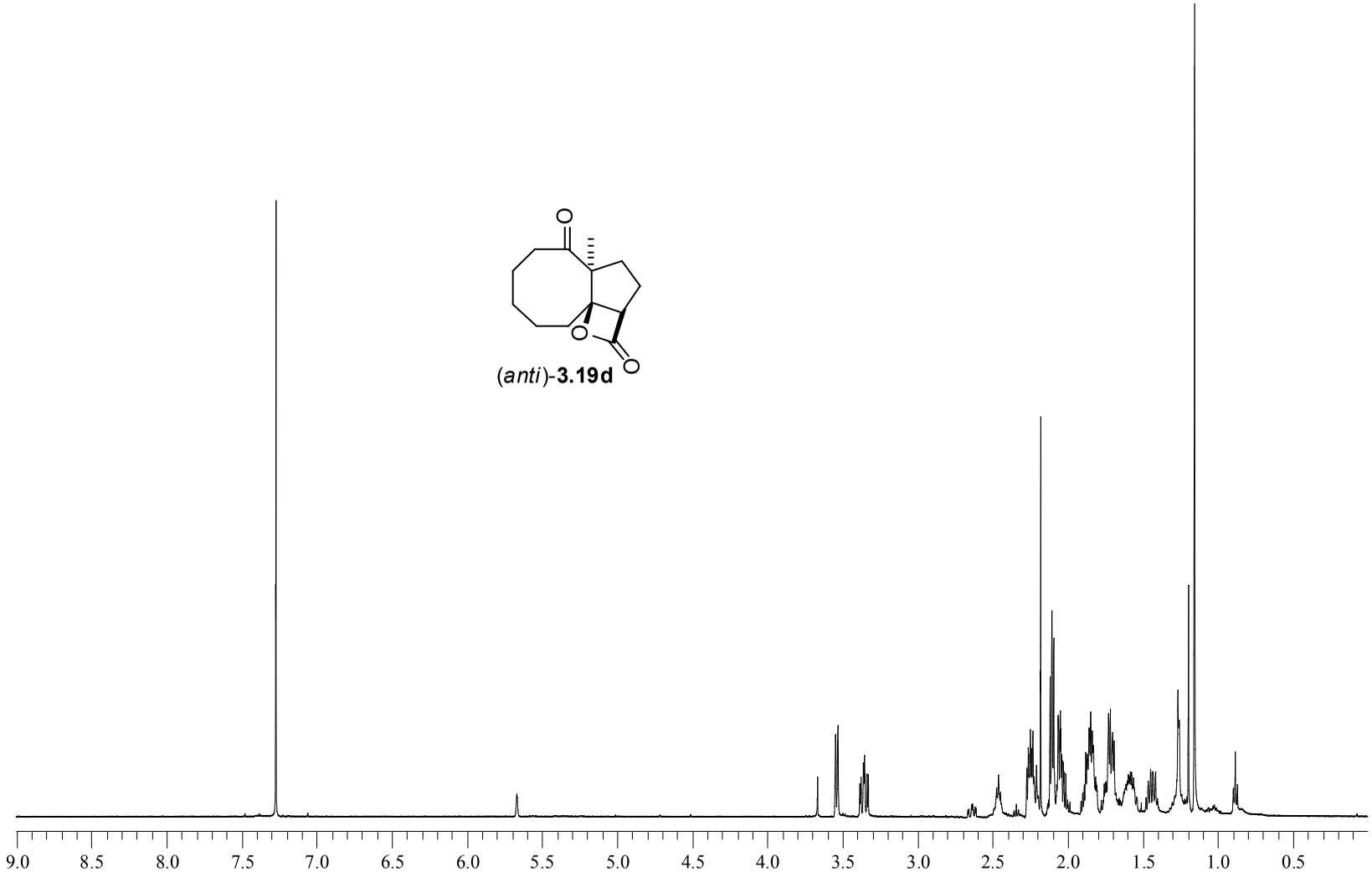

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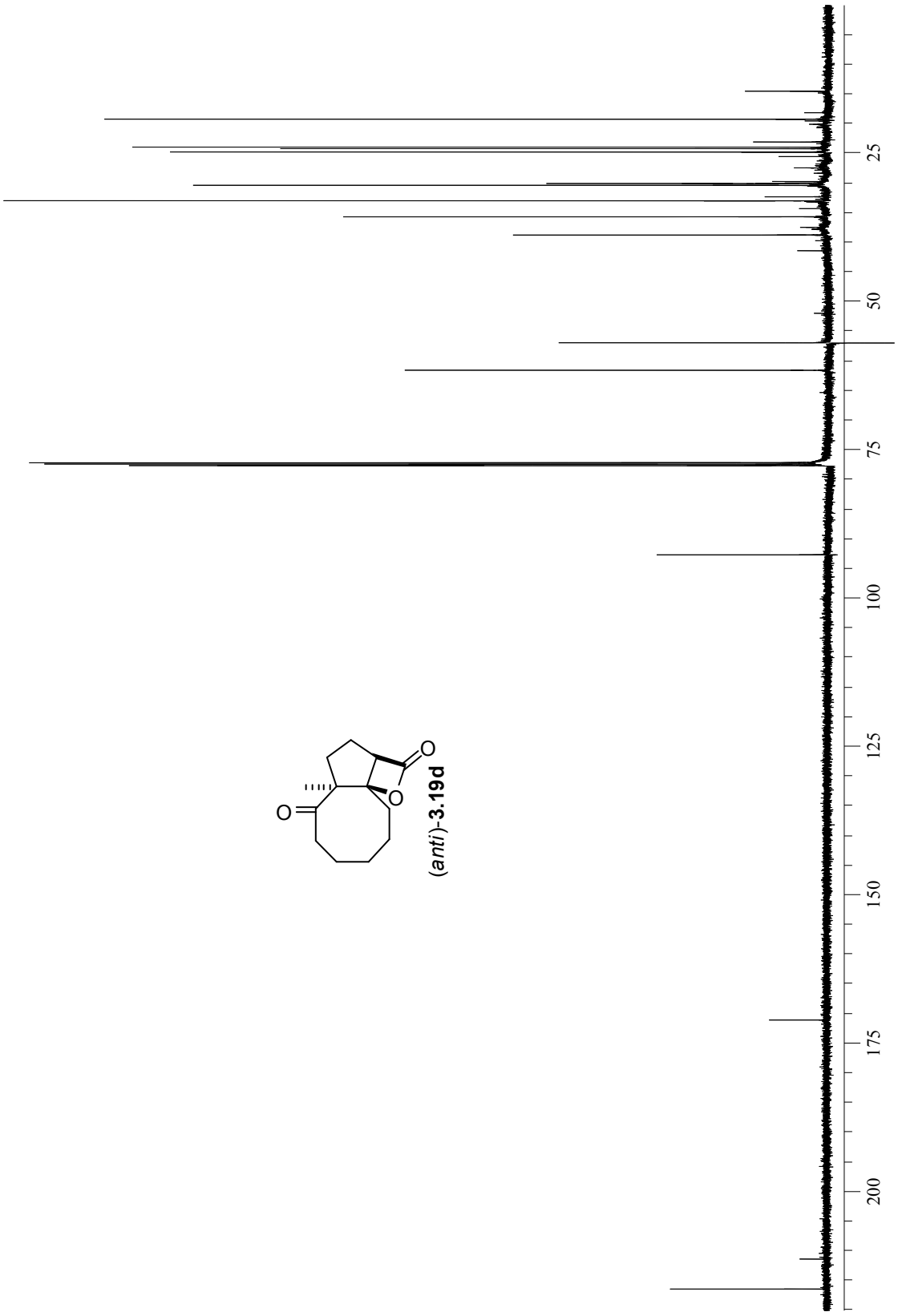

(*anti*)-**3.19d**

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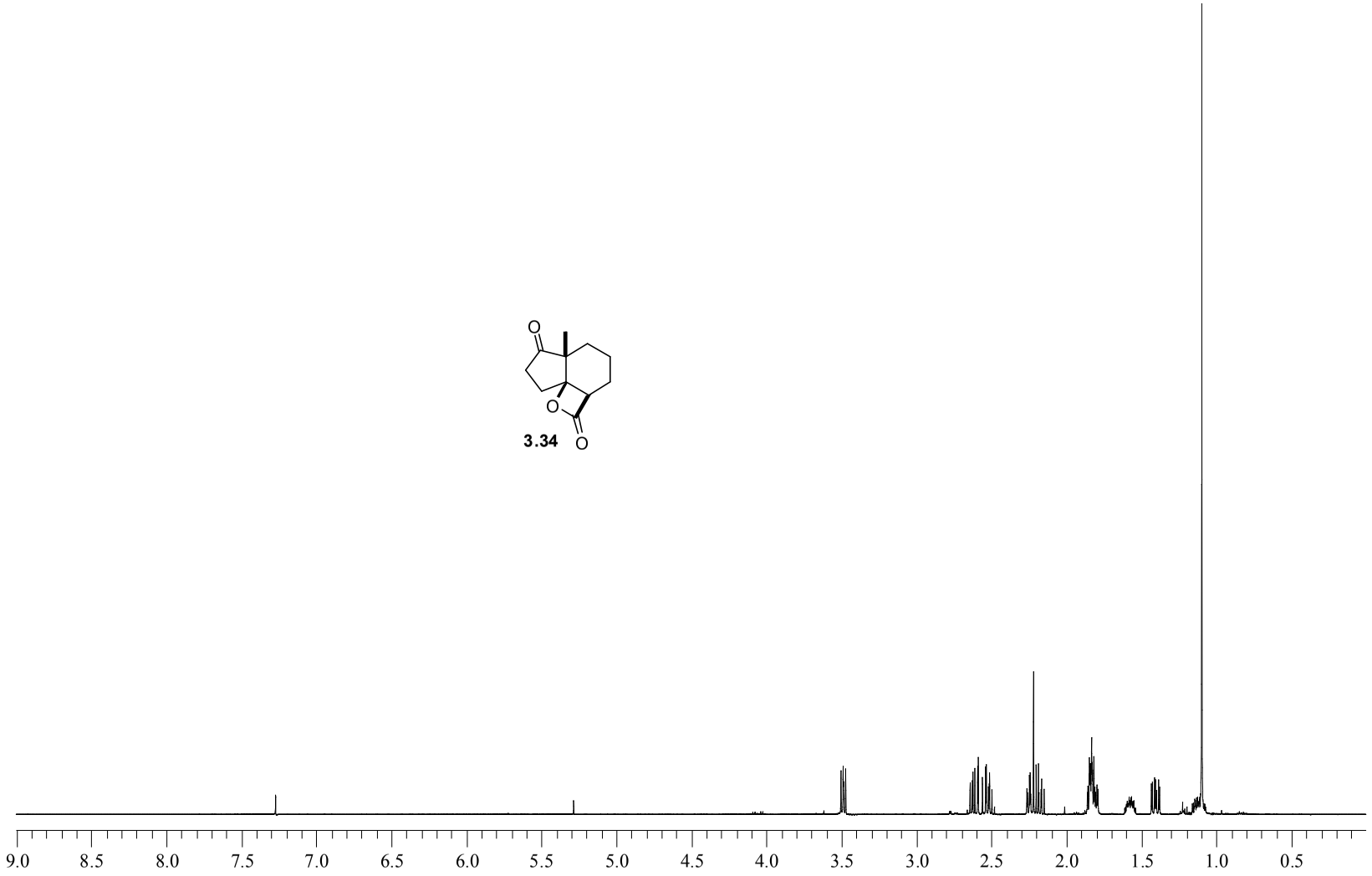
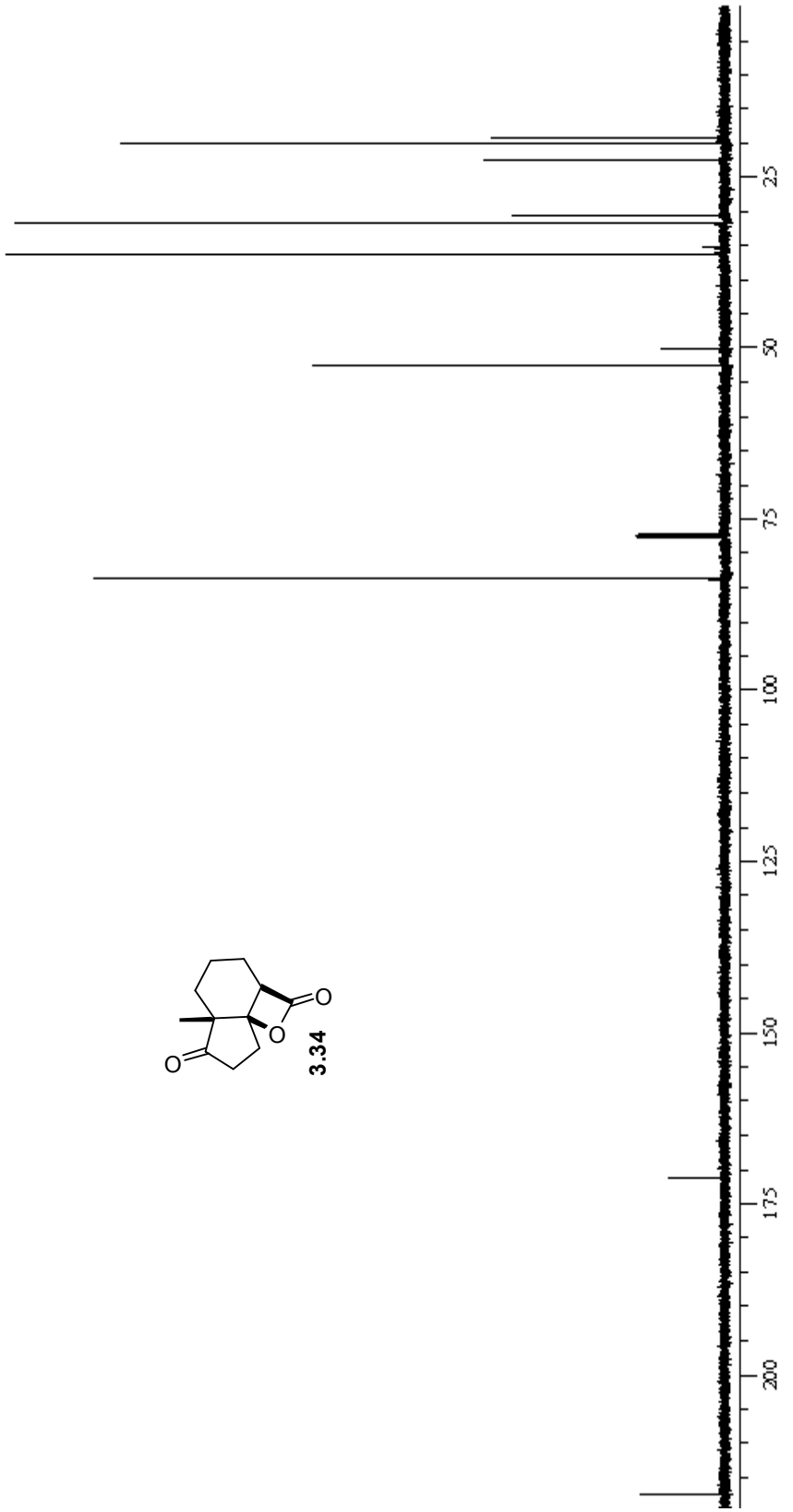


^{1}H NMR spectrum for Tricyclic β-lactone **3.34** ($CDCl_3$)



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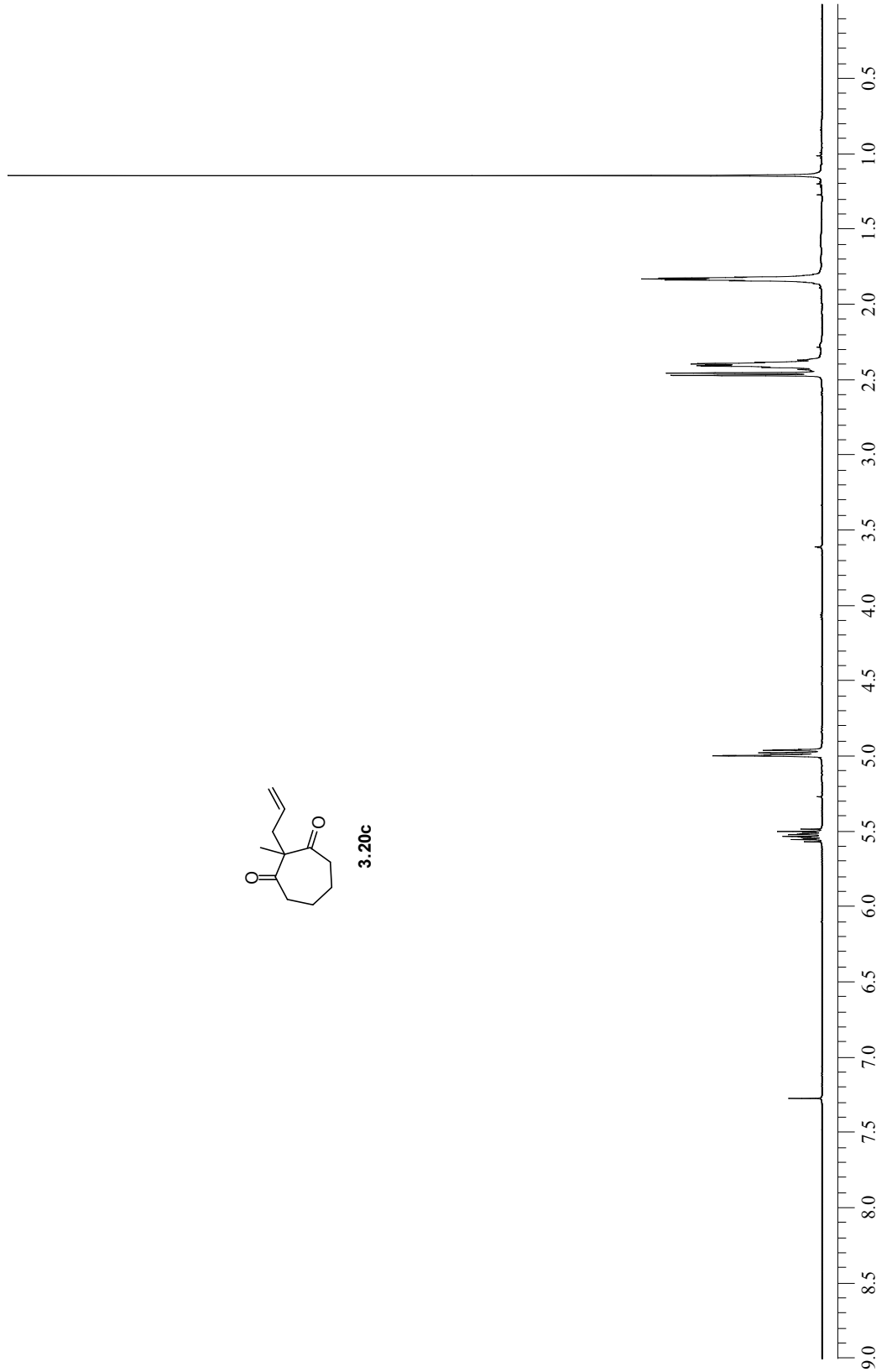

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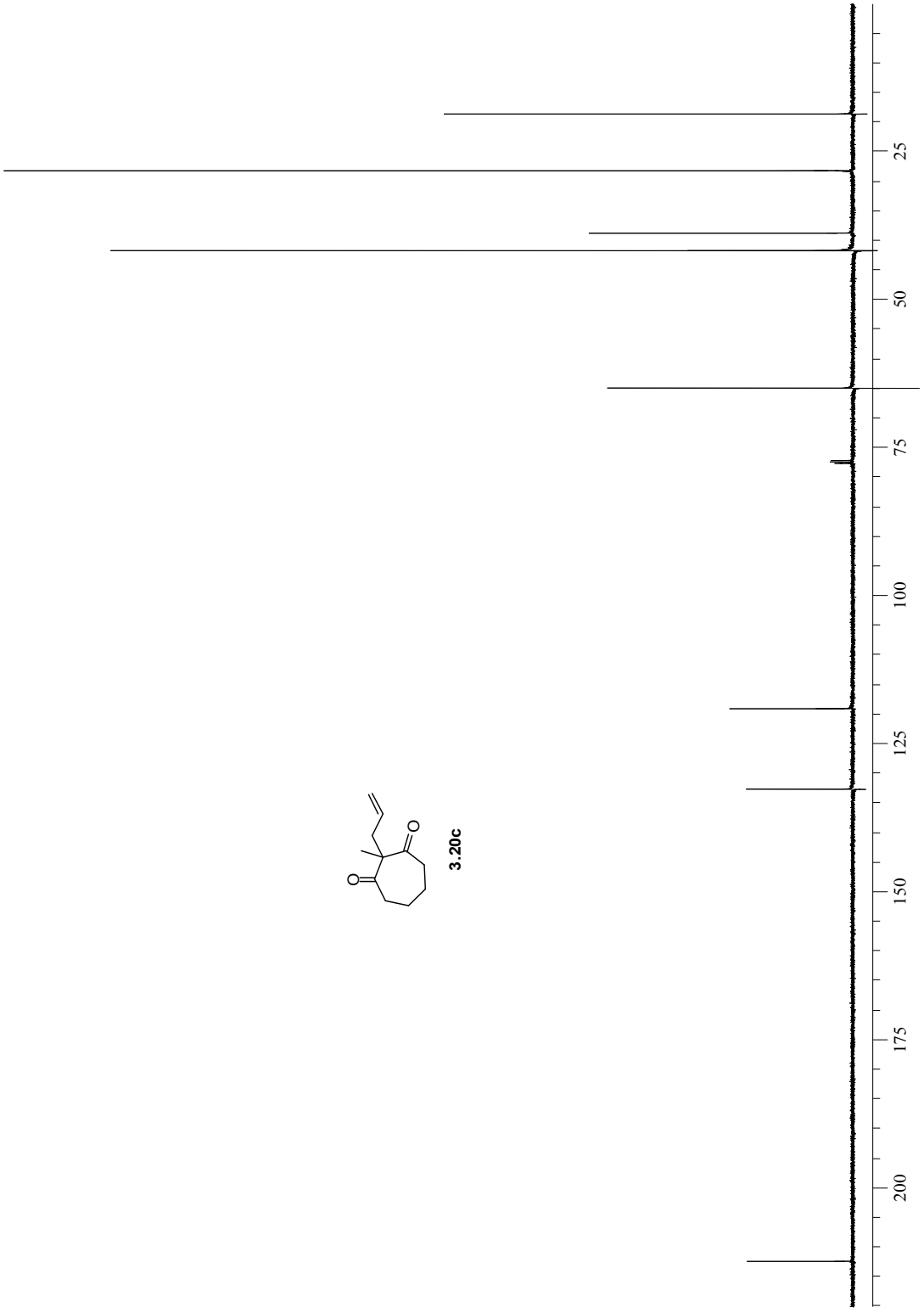

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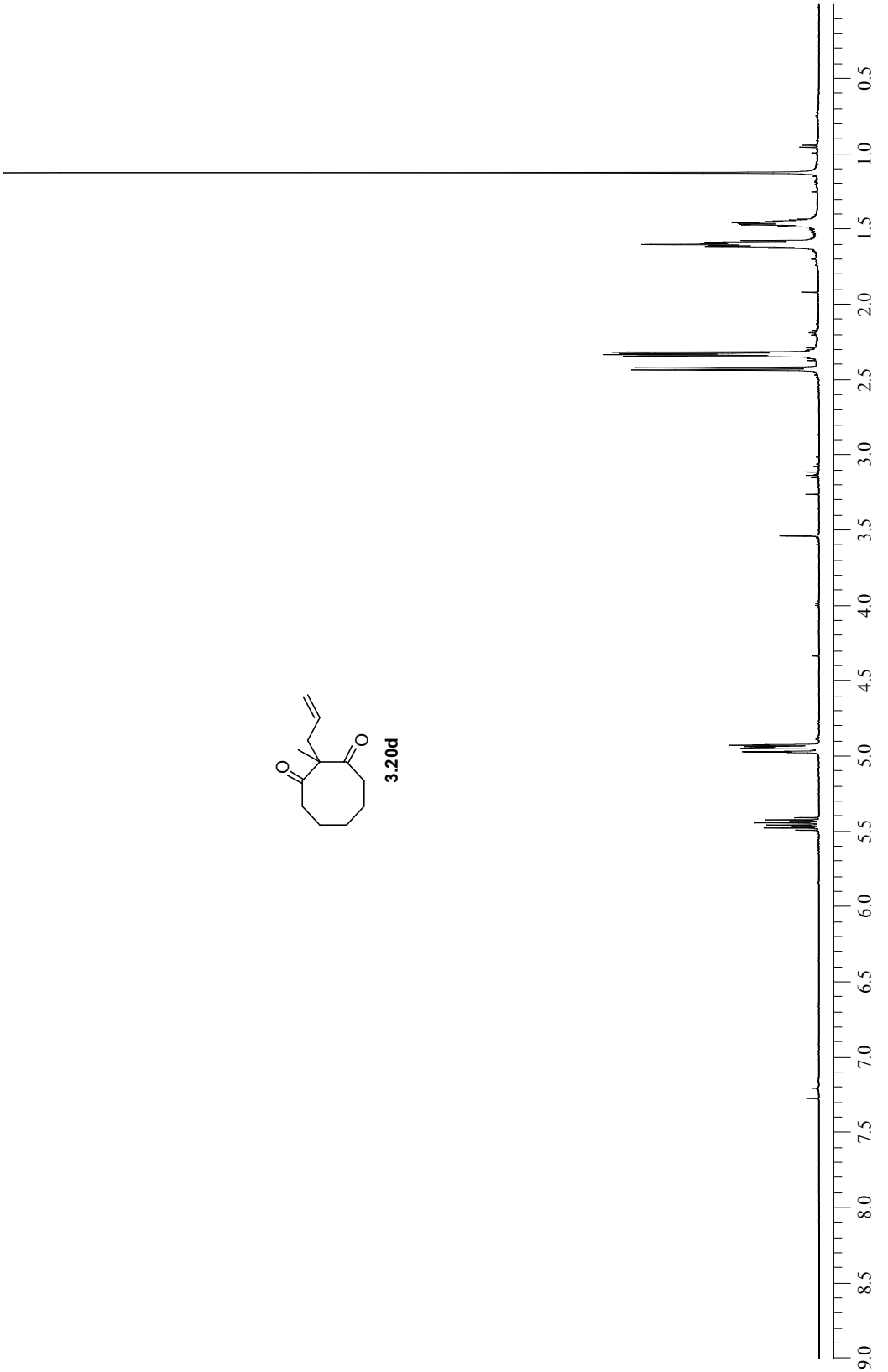

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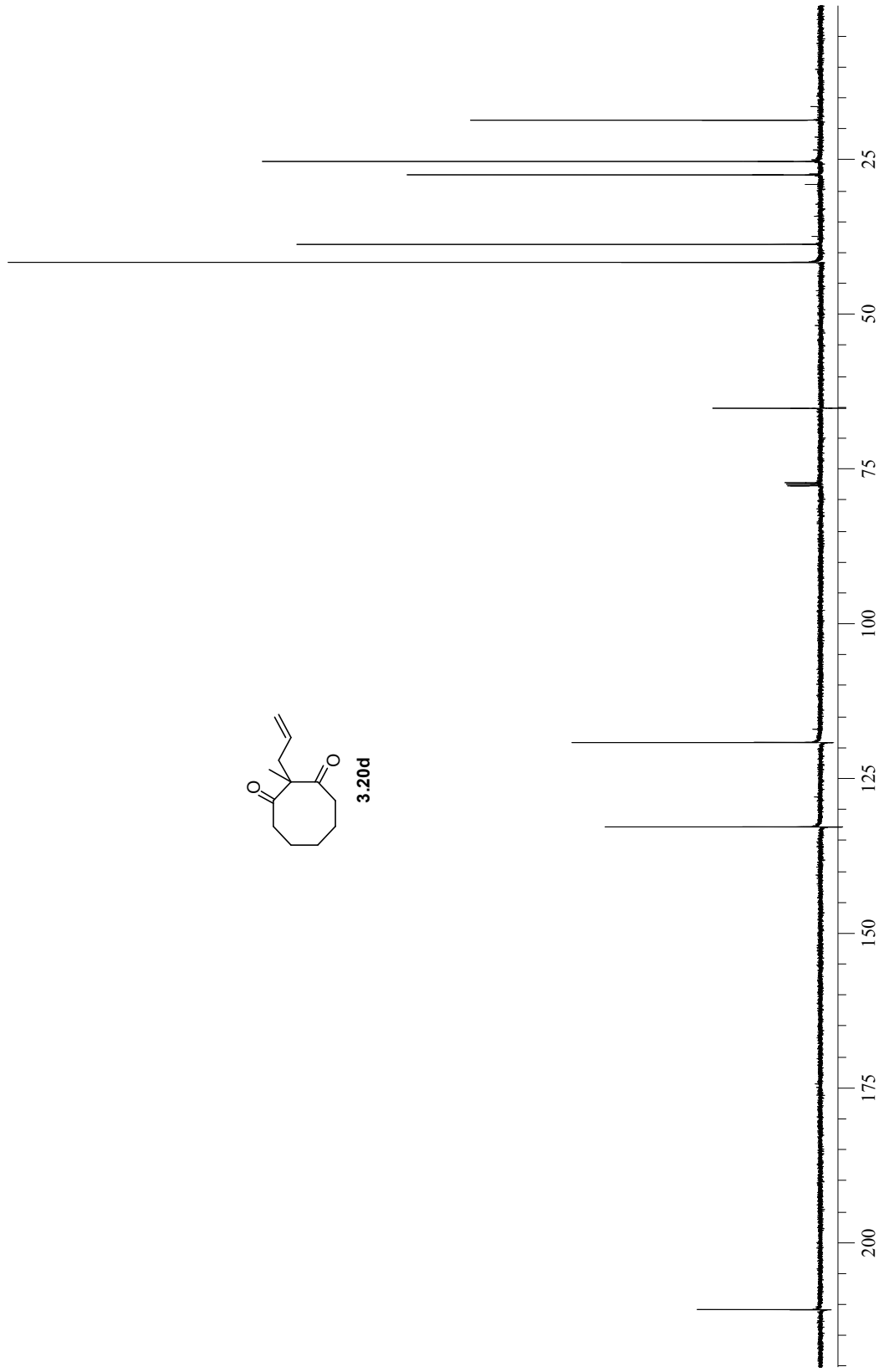

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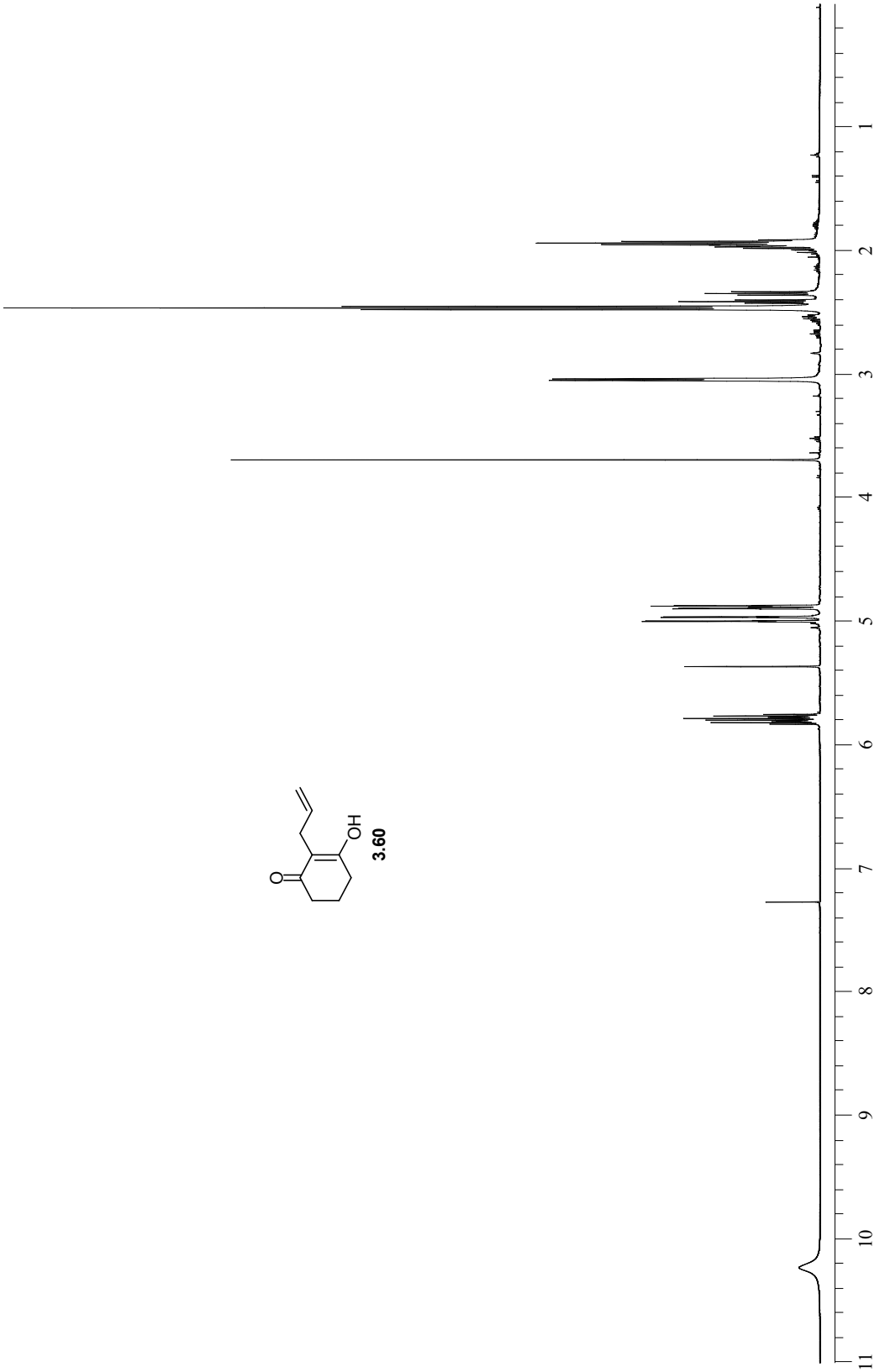
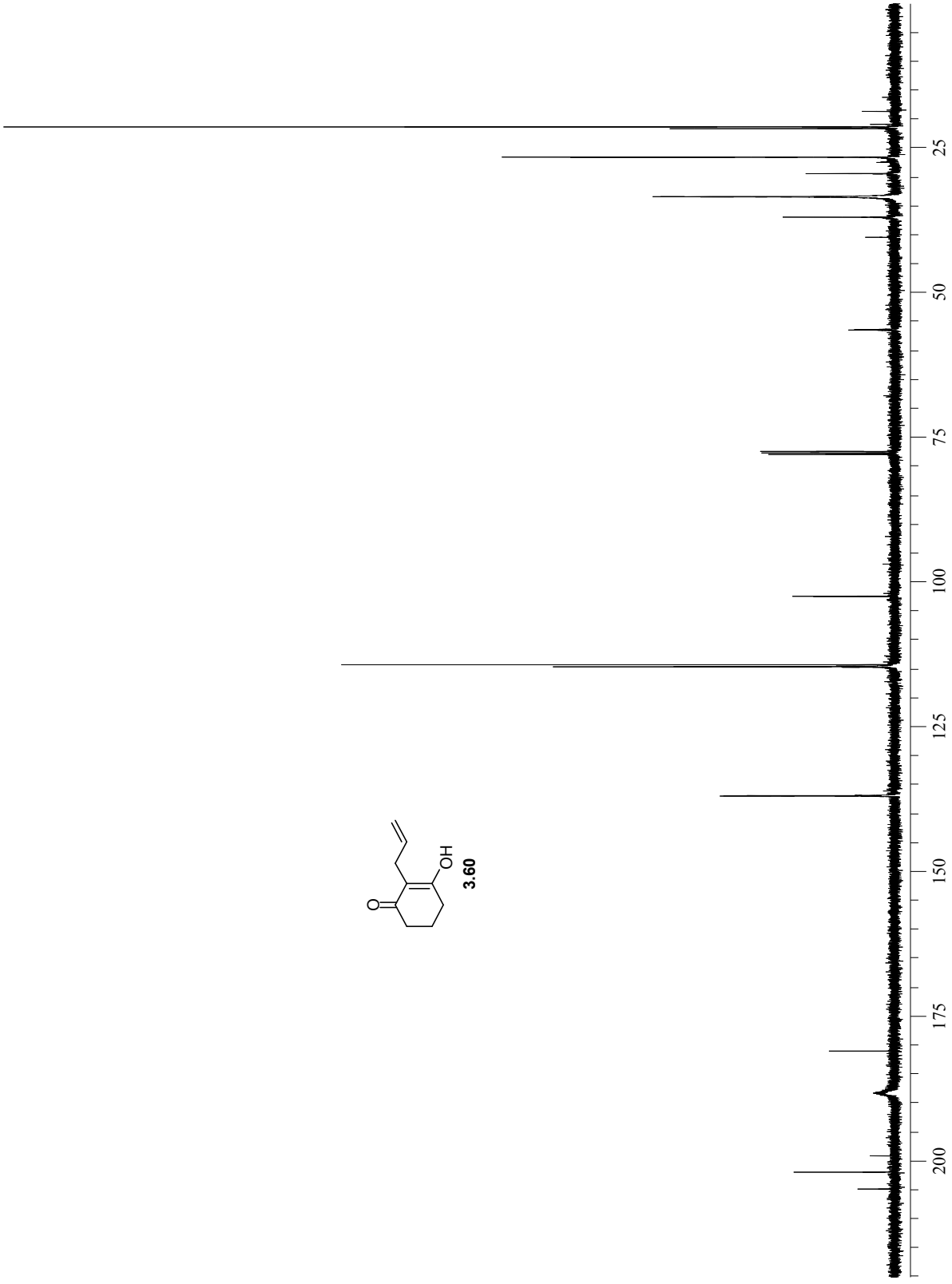
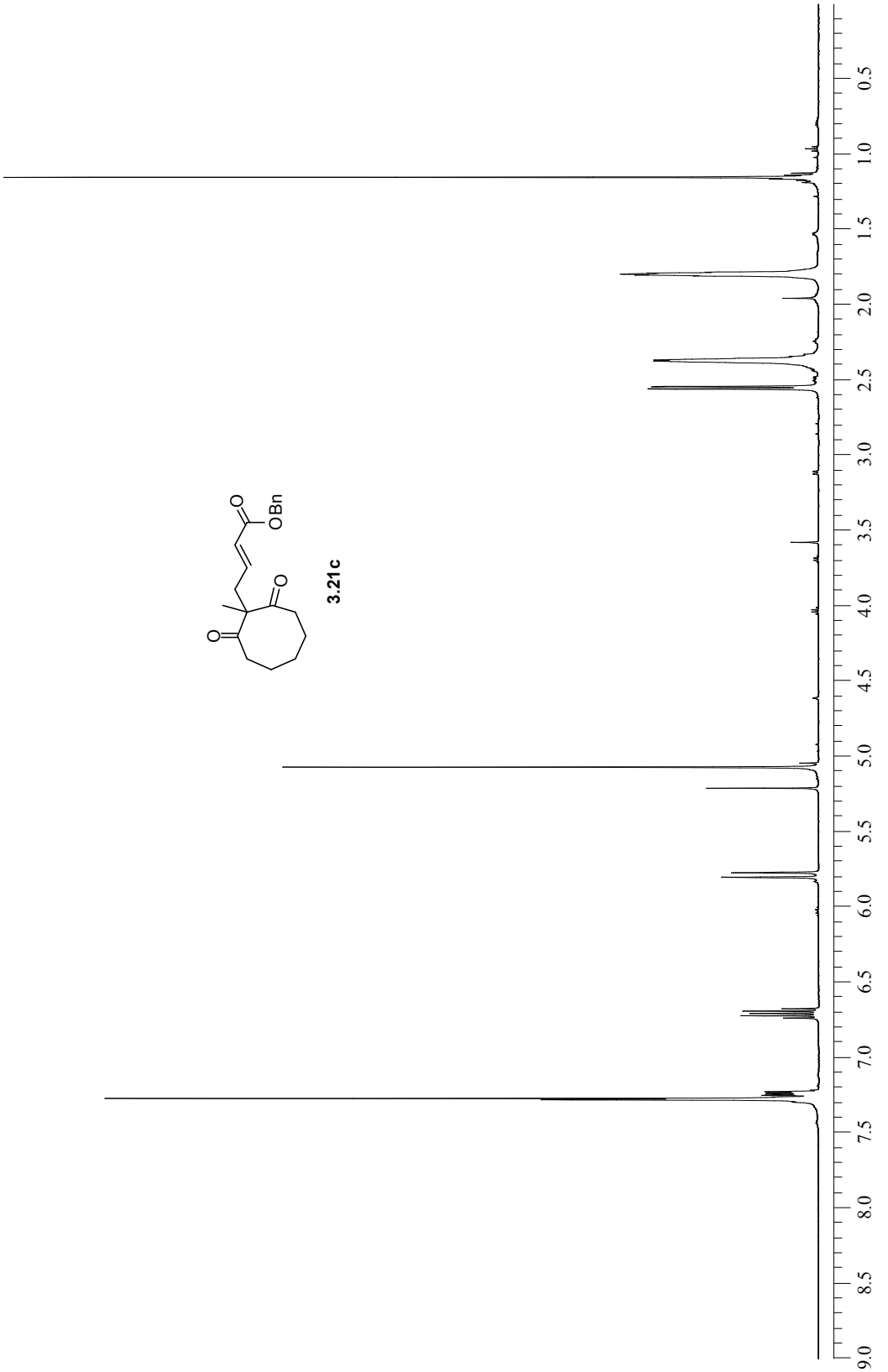


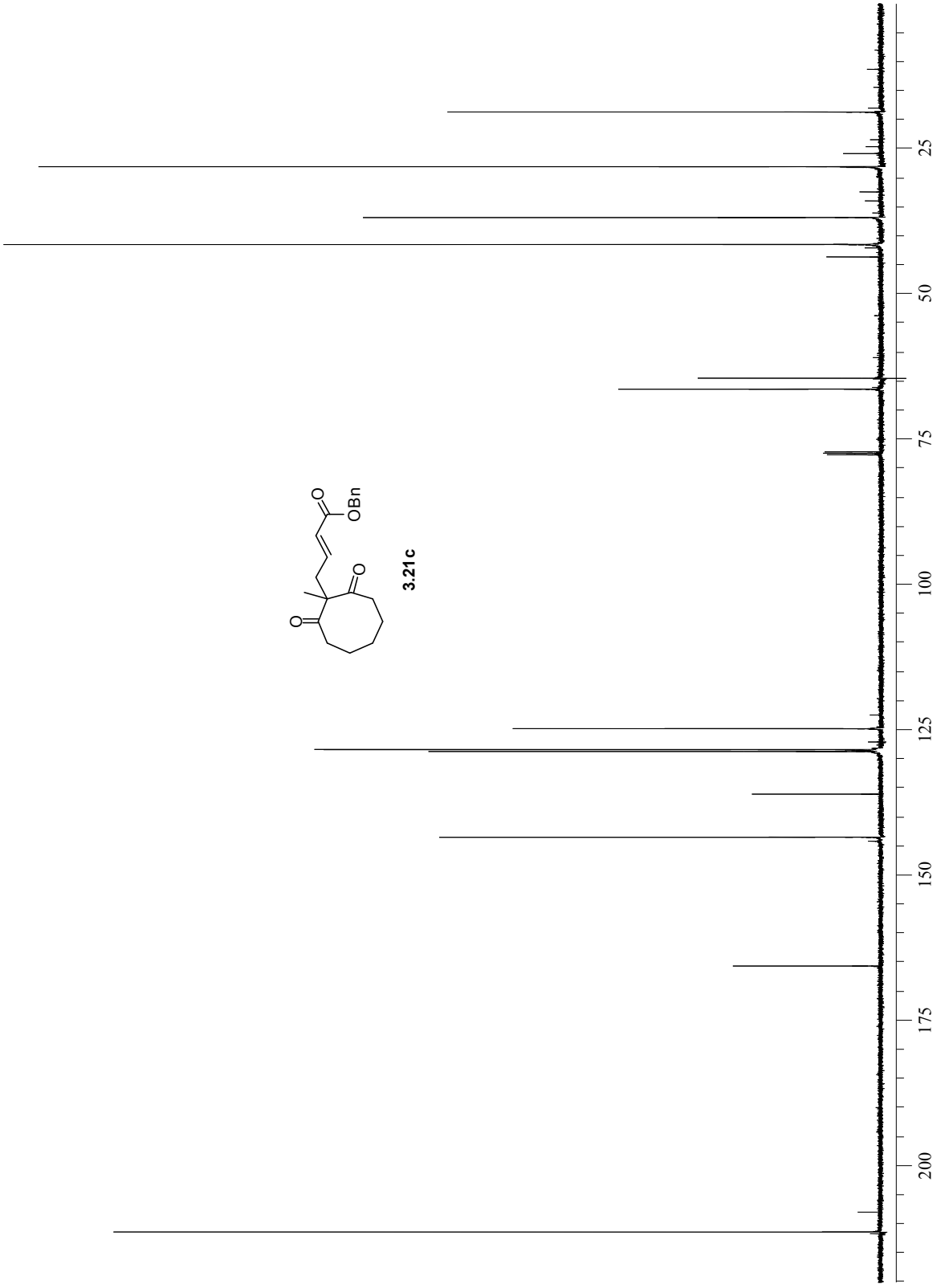
^{1}H NMR spectrum for allyl dione **3.60** ($CDCl_3$)



^{13}C NMR spectrum for allyl dione **3.60** ($CDCl_3$)



^{1}H NMR spectrum for benzyl ester **3.21c** ($CDCl_3$)



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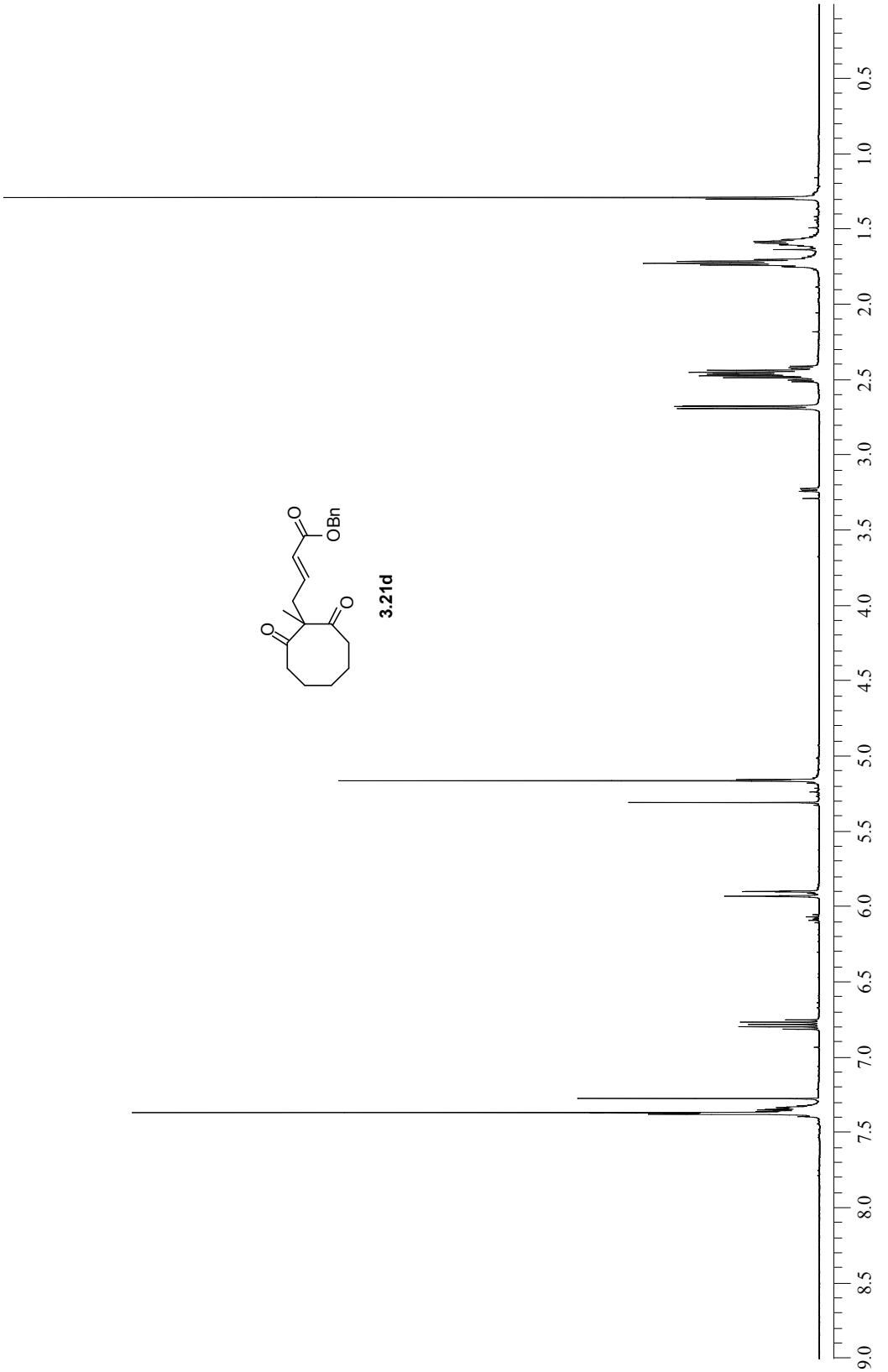

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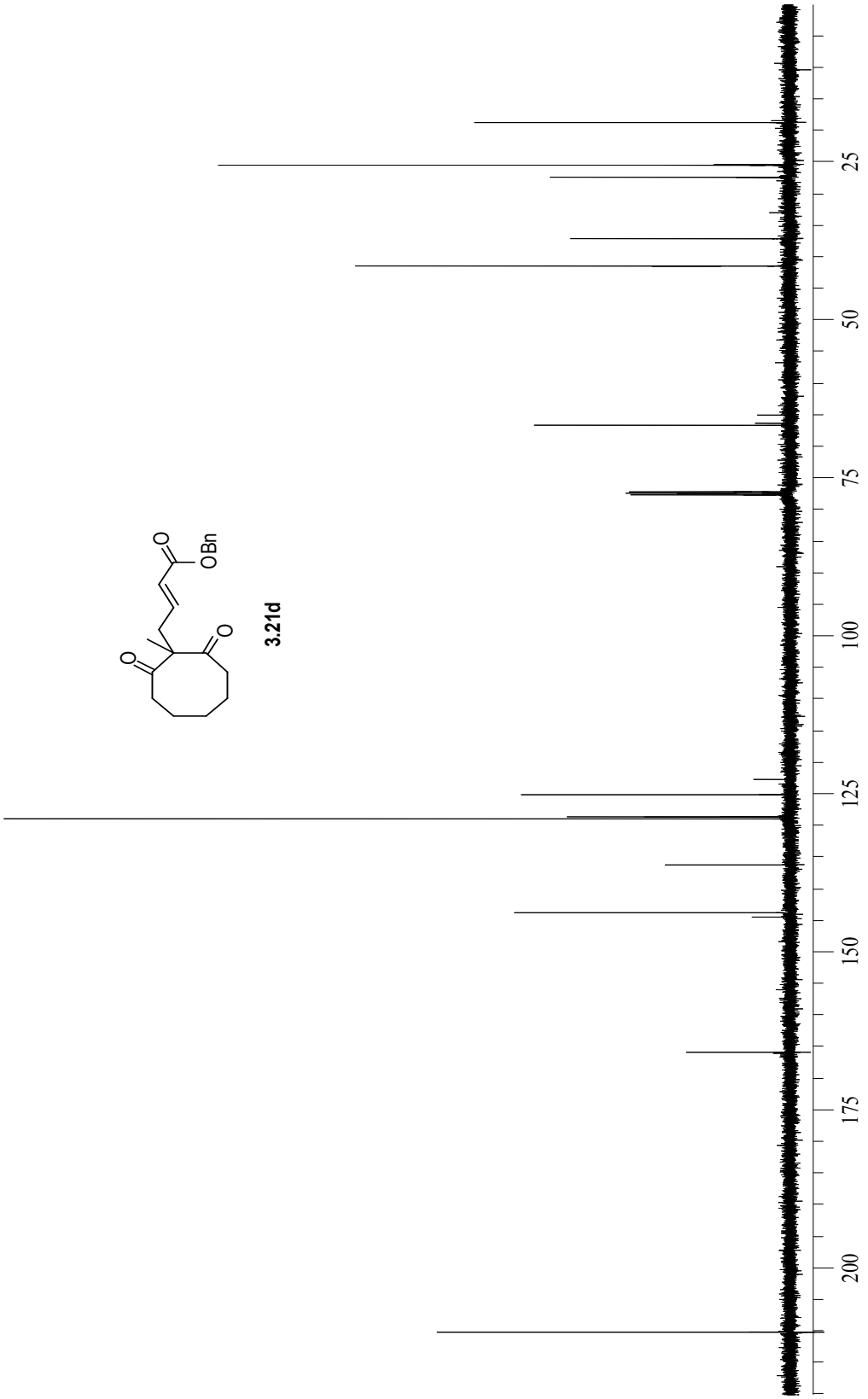

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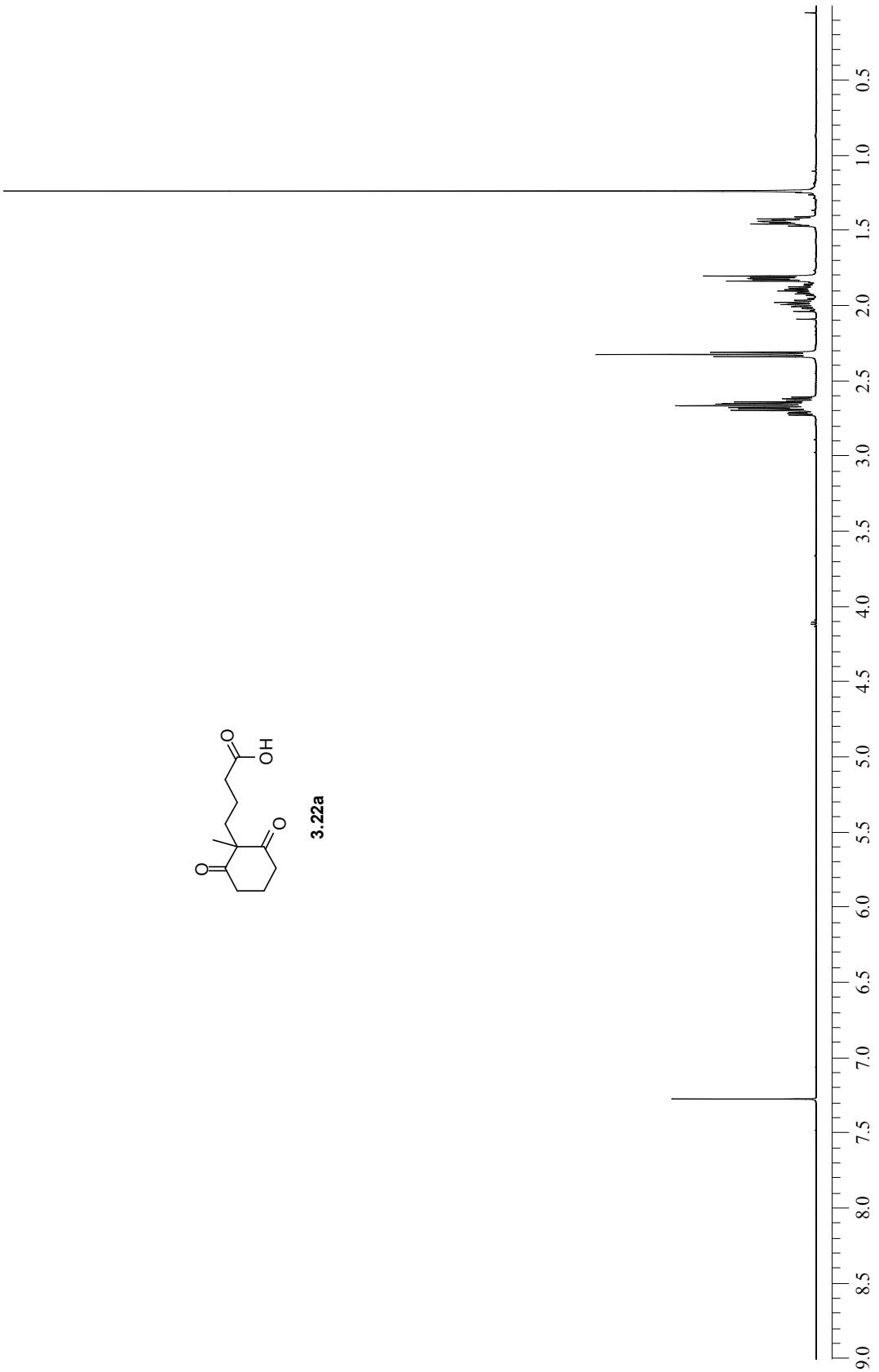

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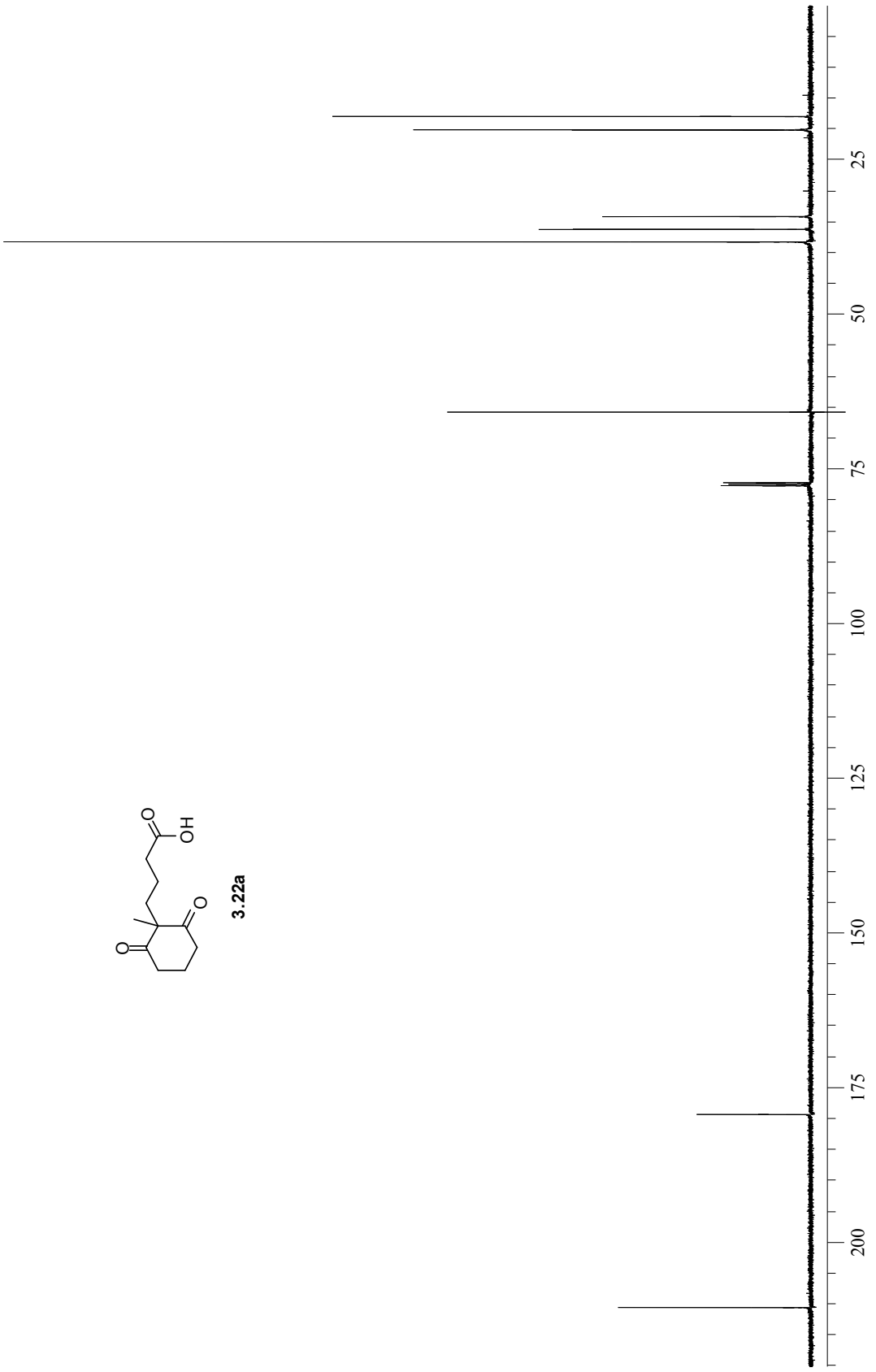

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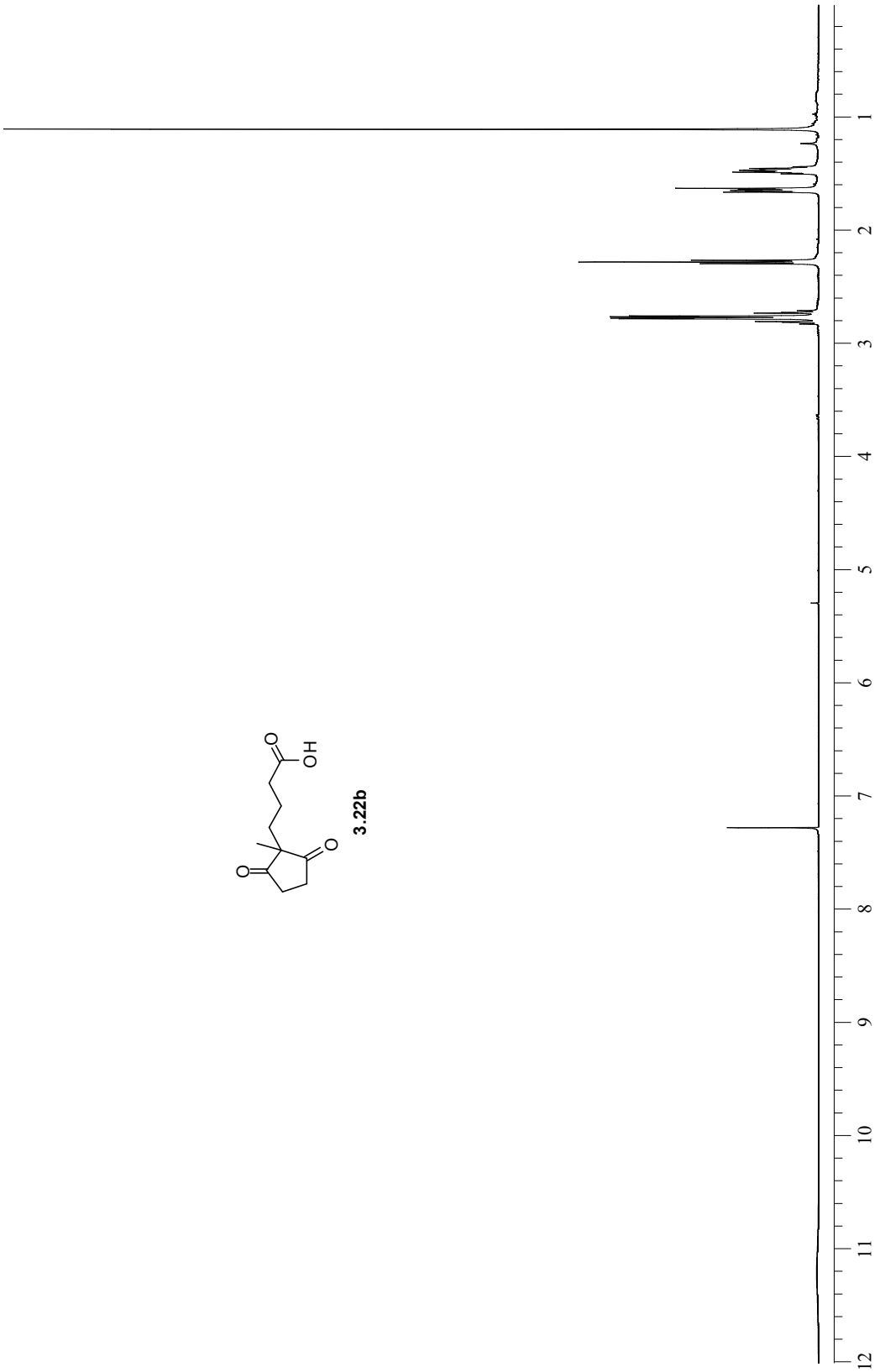

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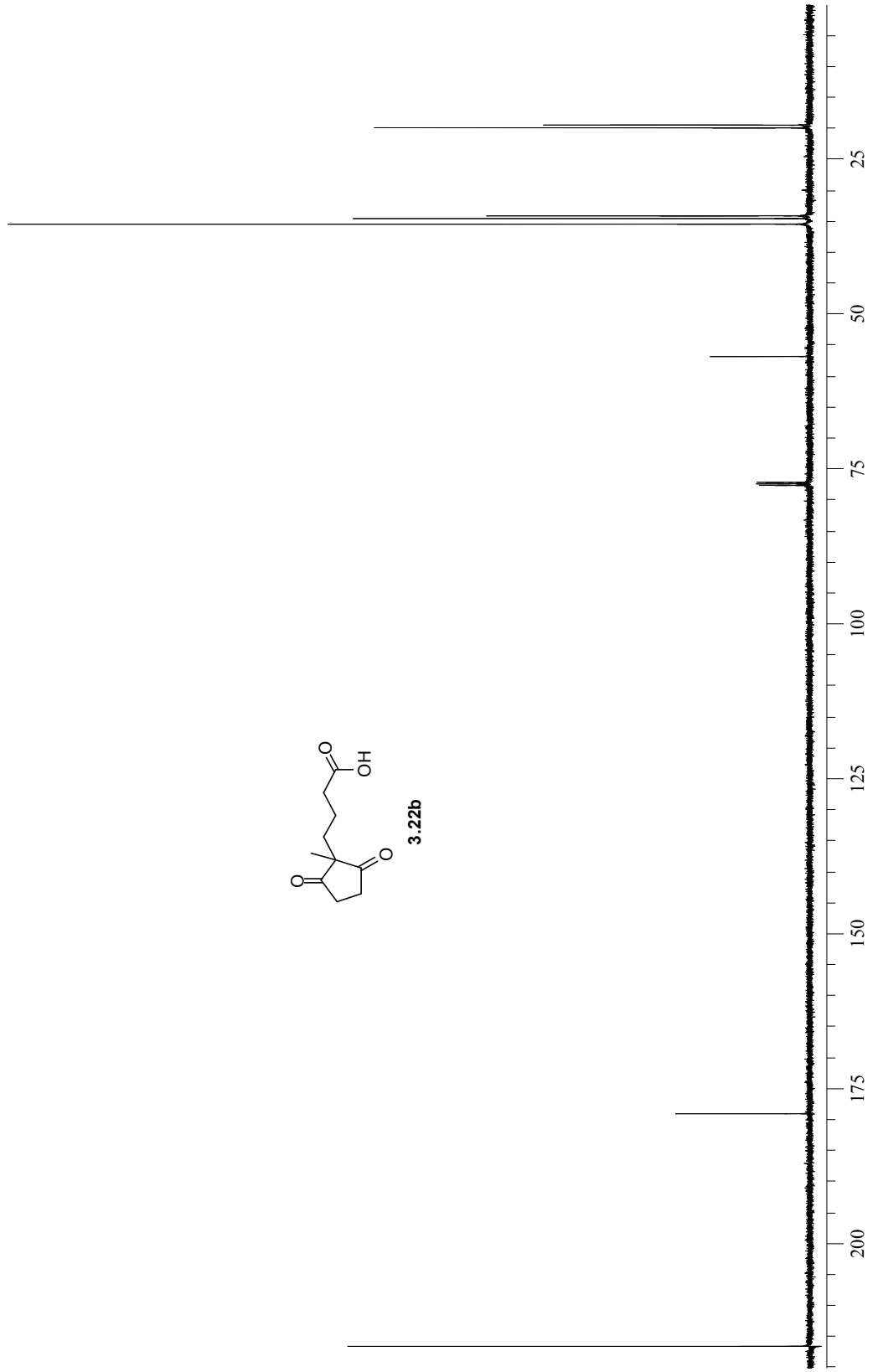

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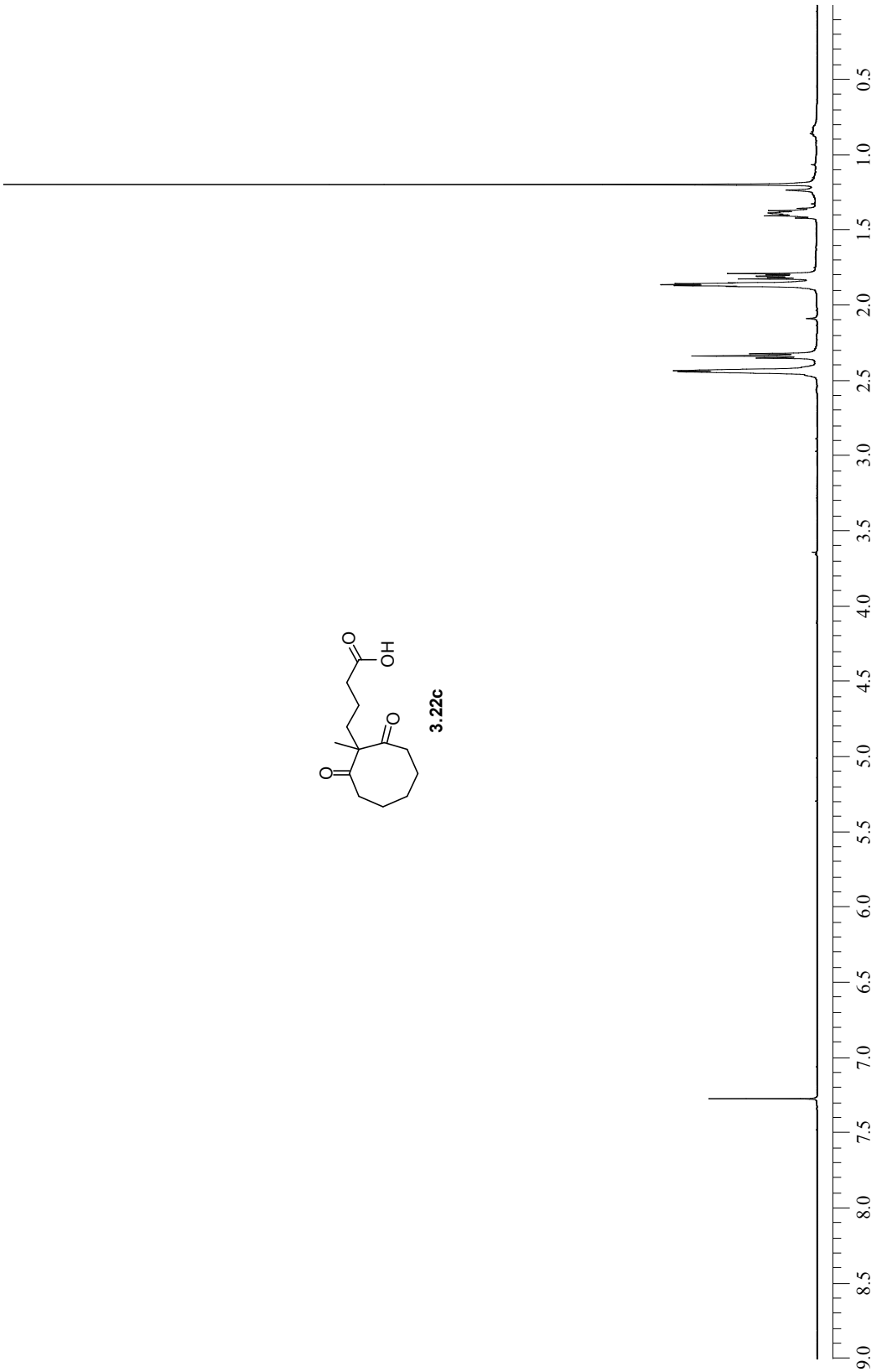

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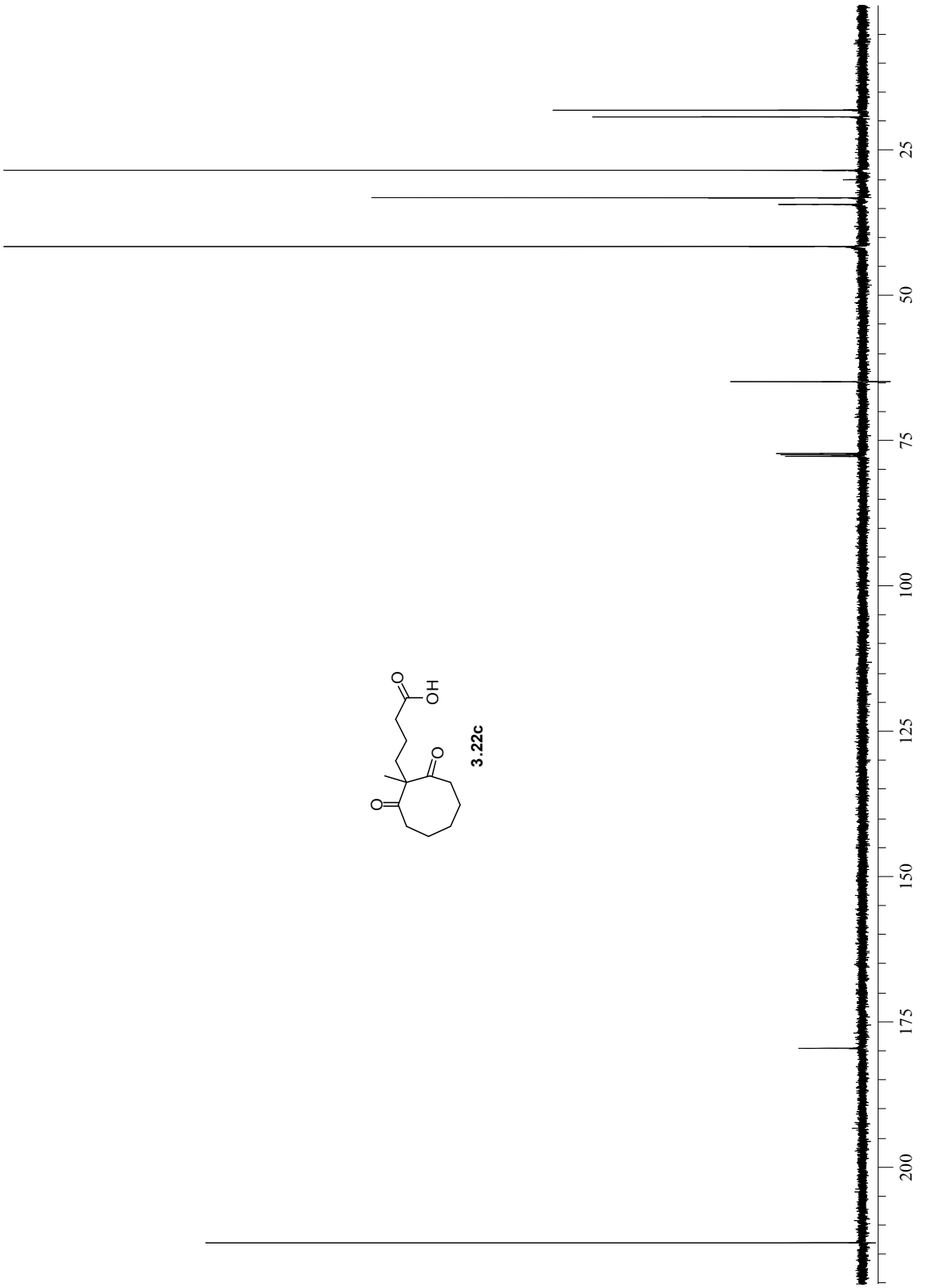

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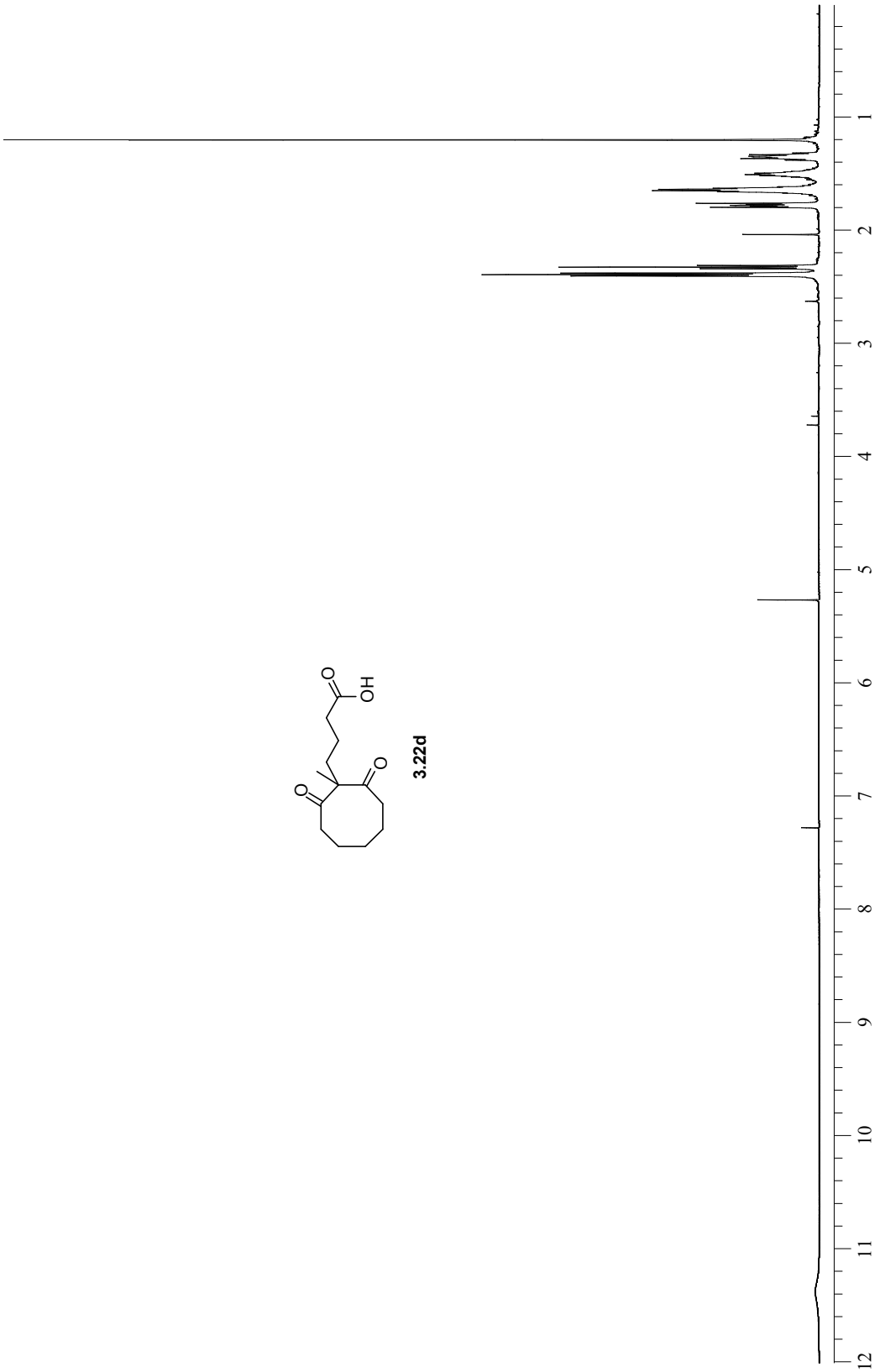

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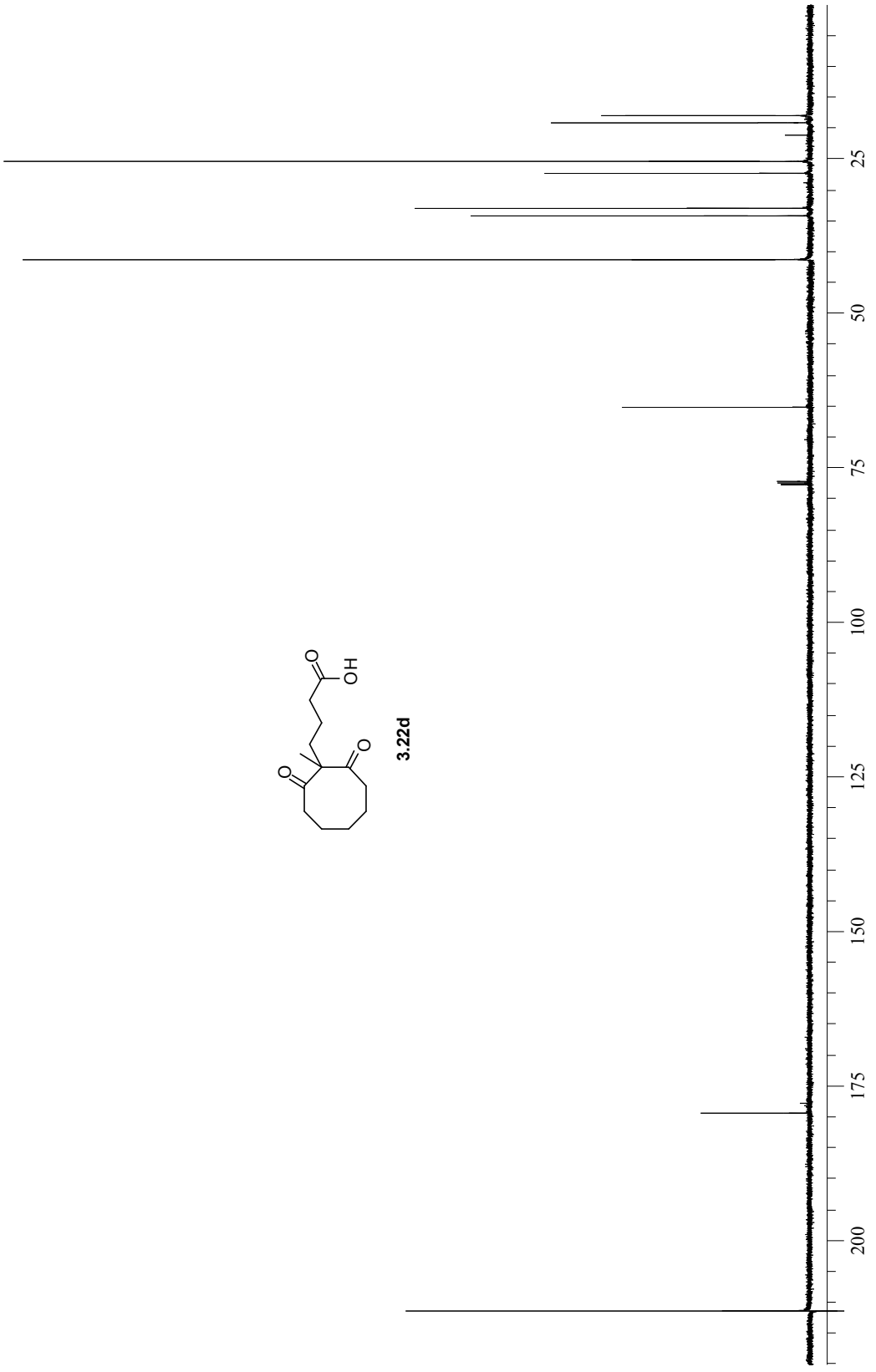

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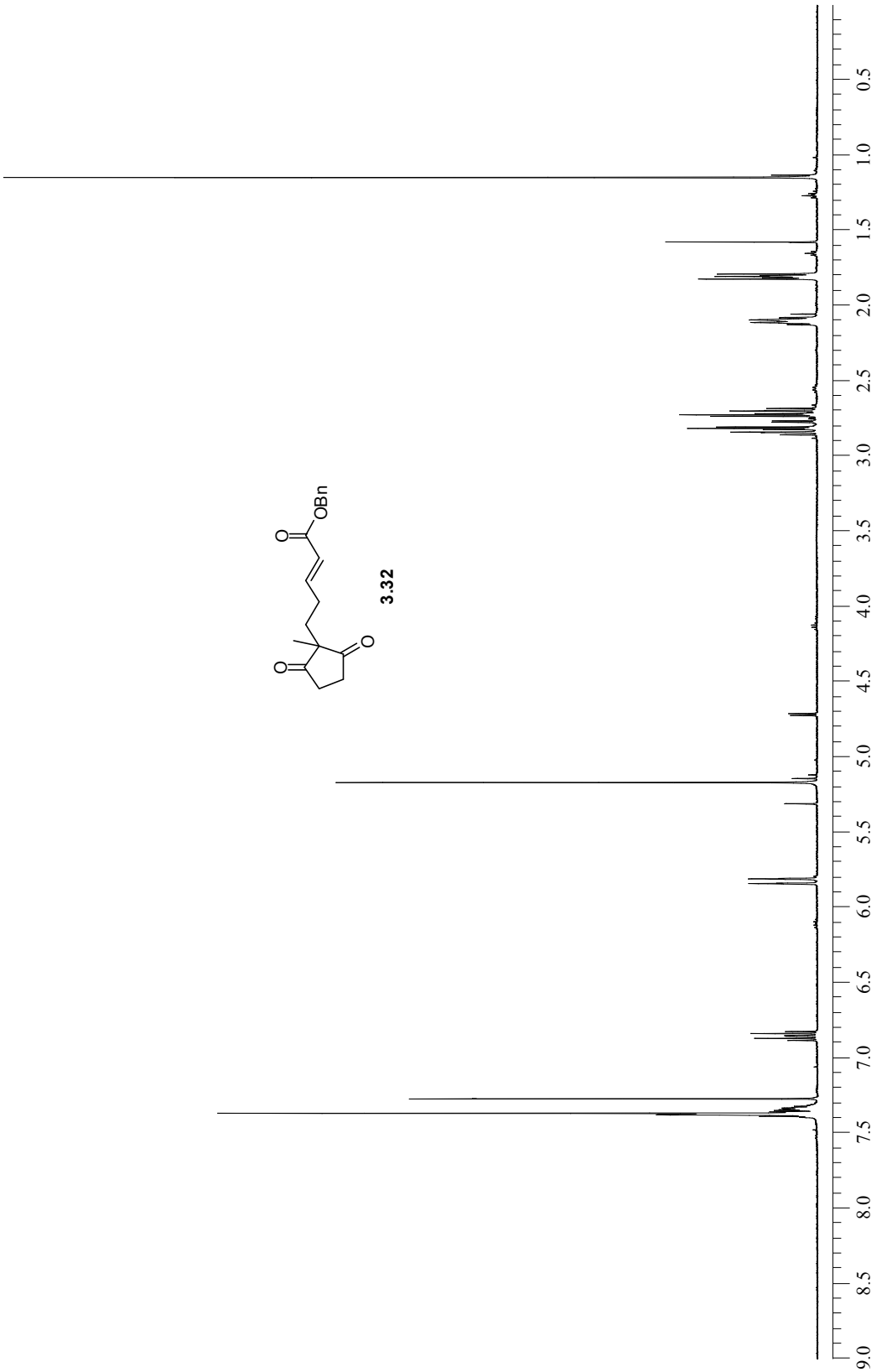

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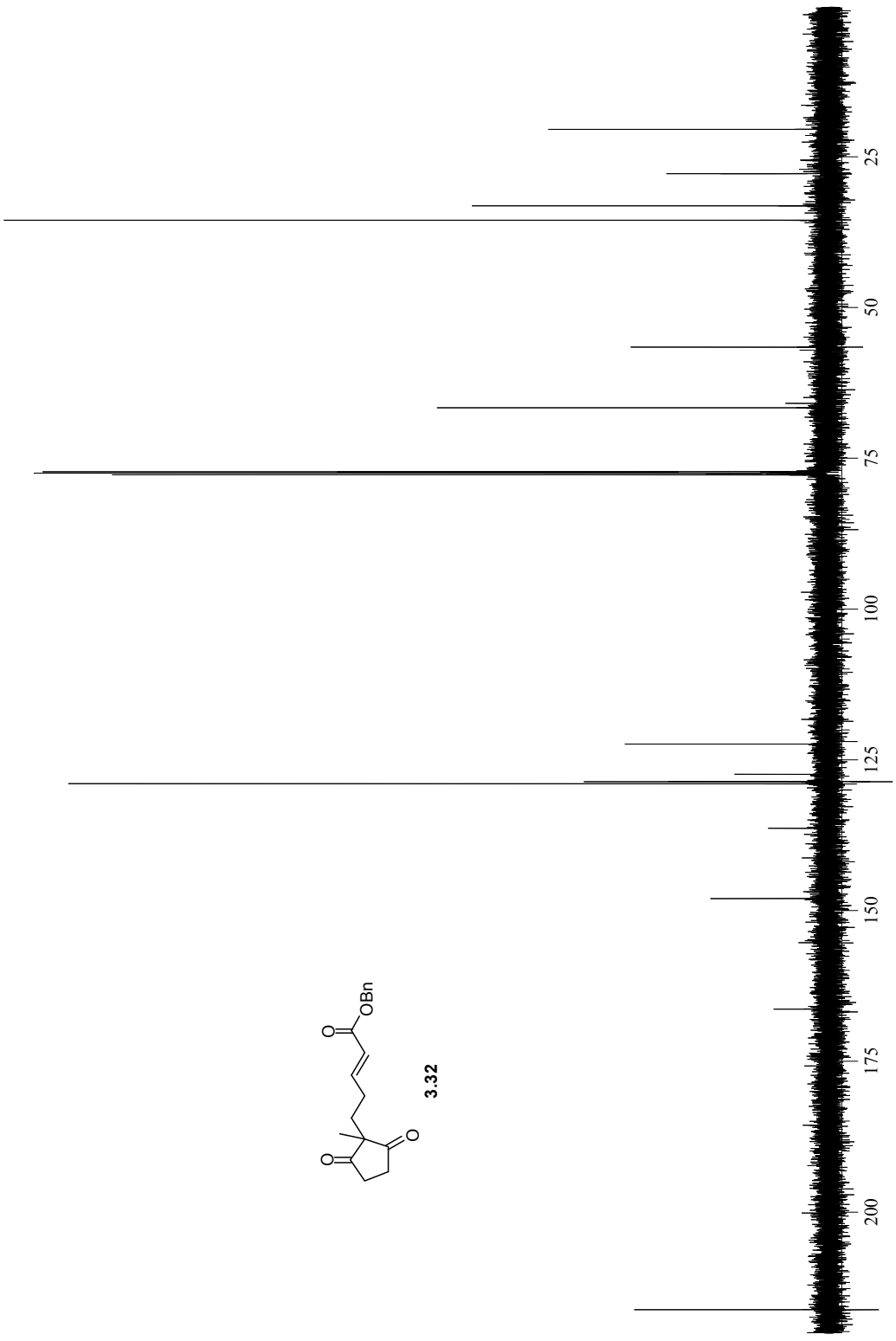

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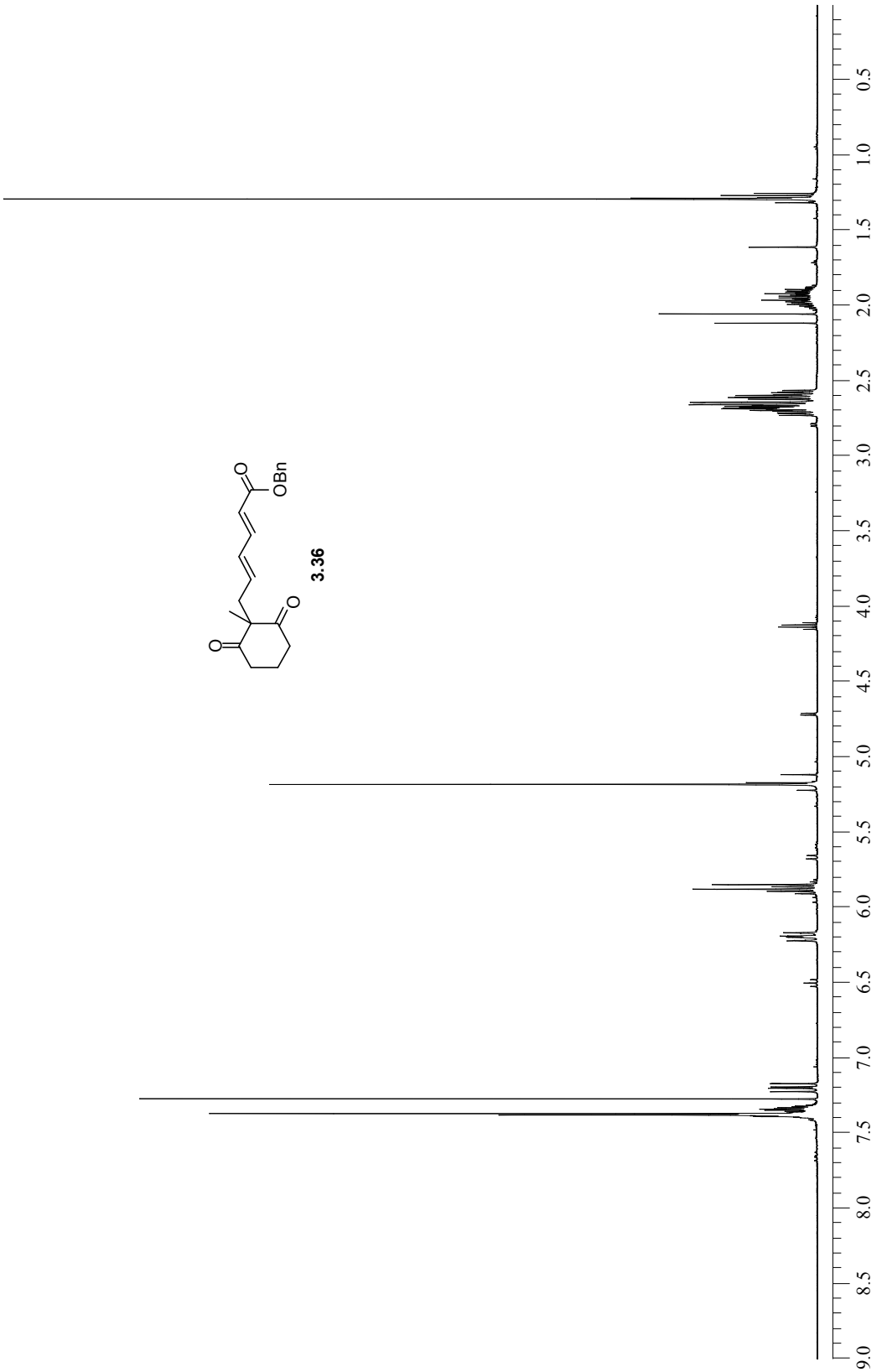

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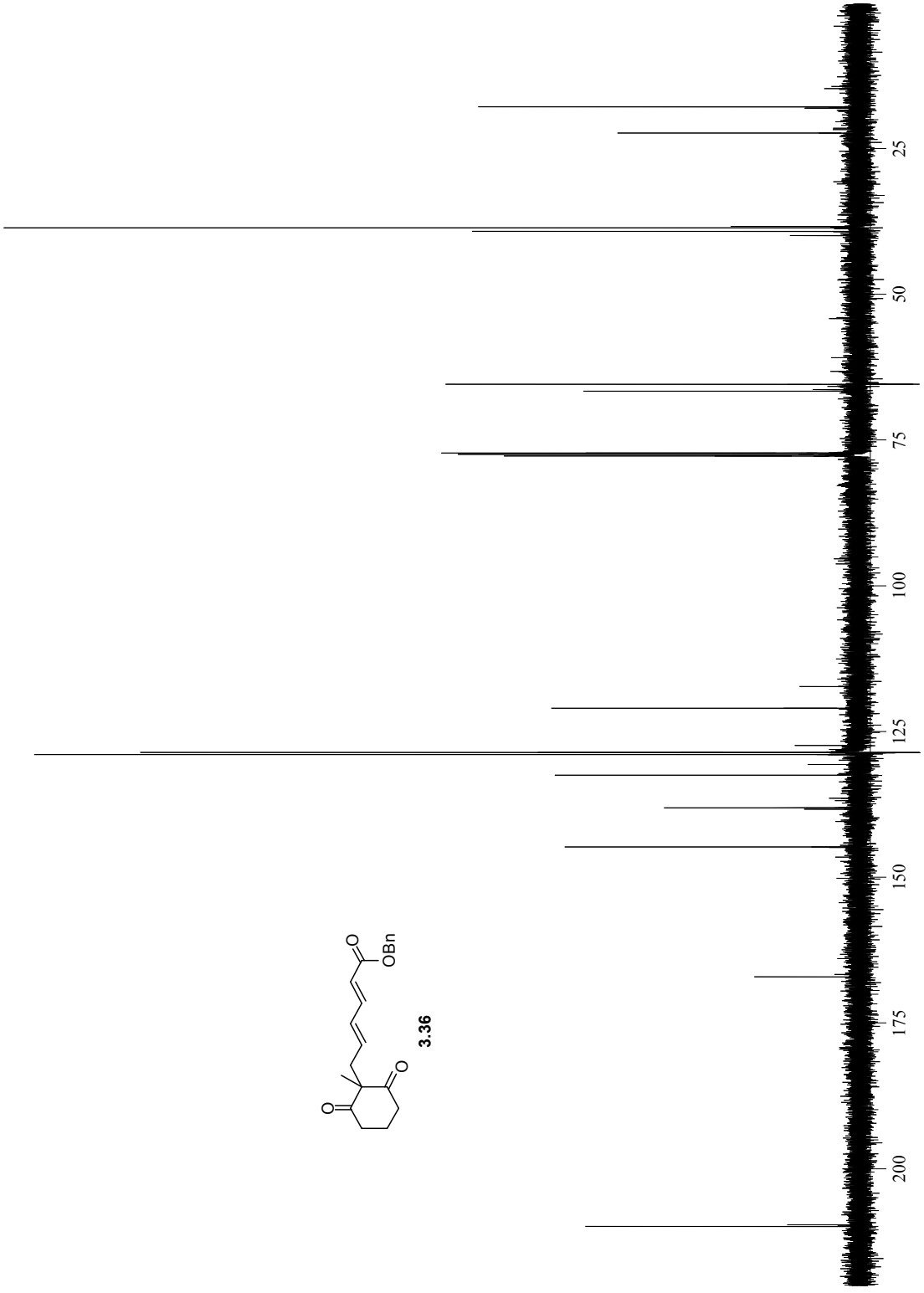

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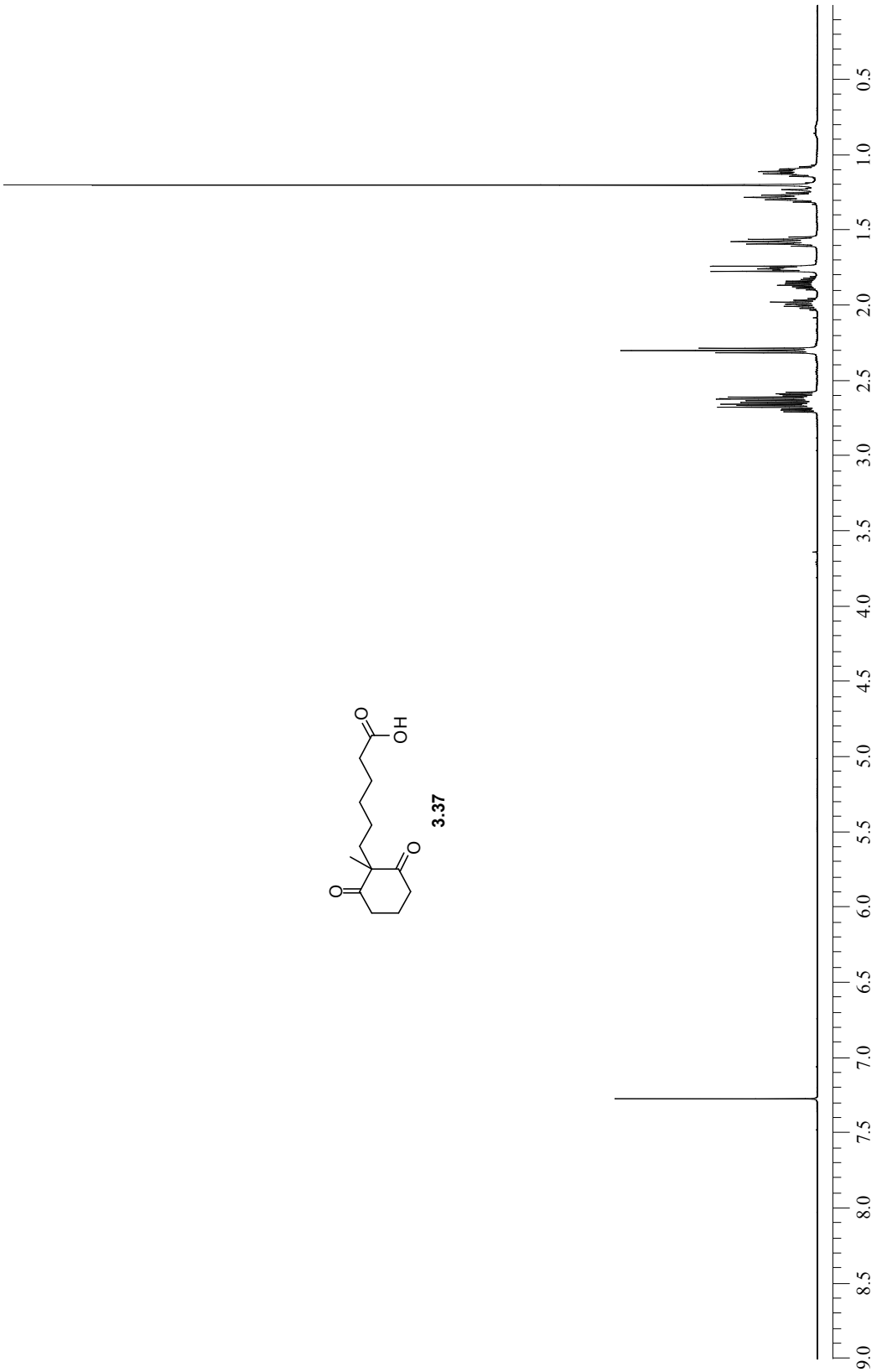
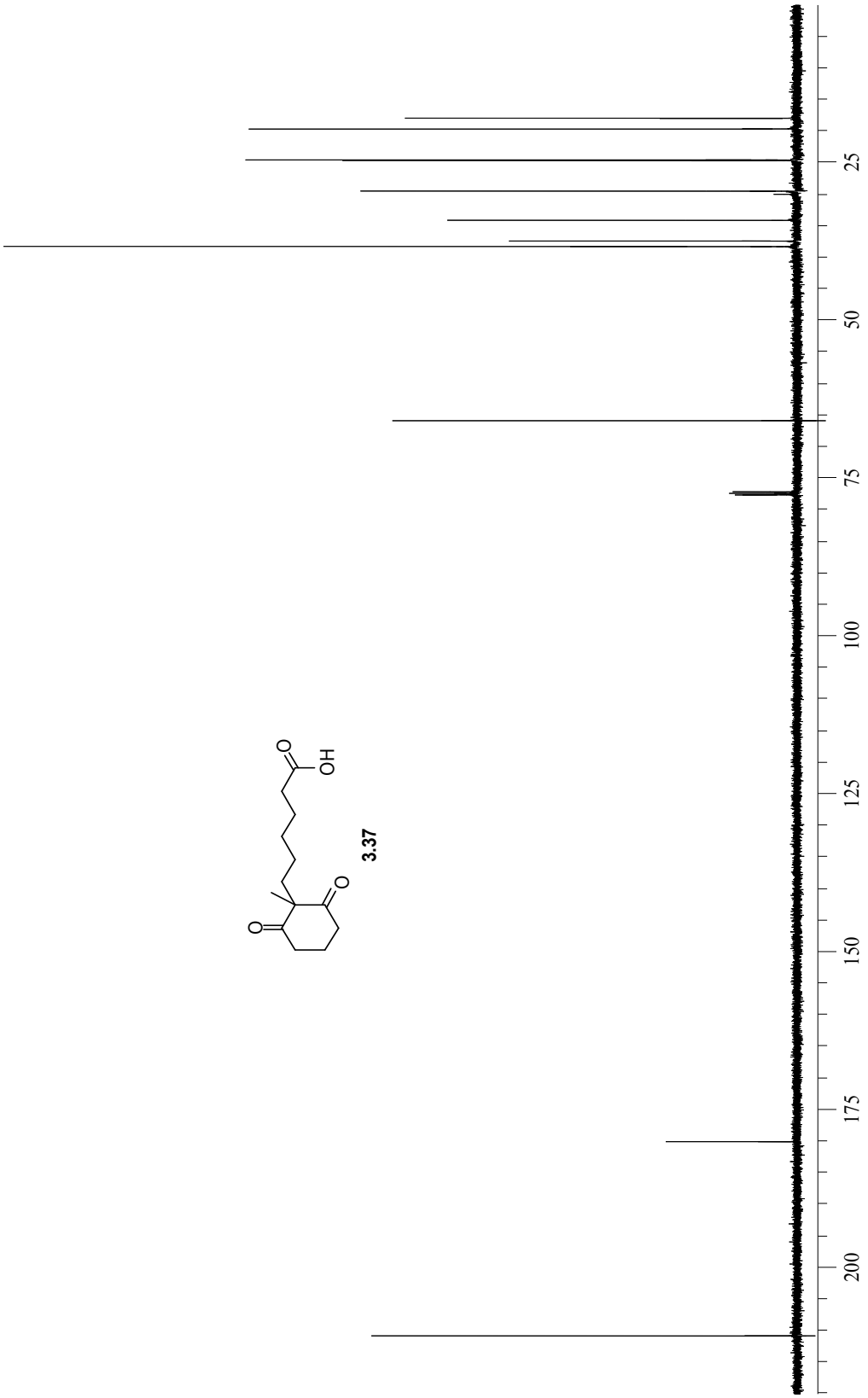


^{1}H NMR spectrum for keto-acid **3.37** ($CDCl_3$)



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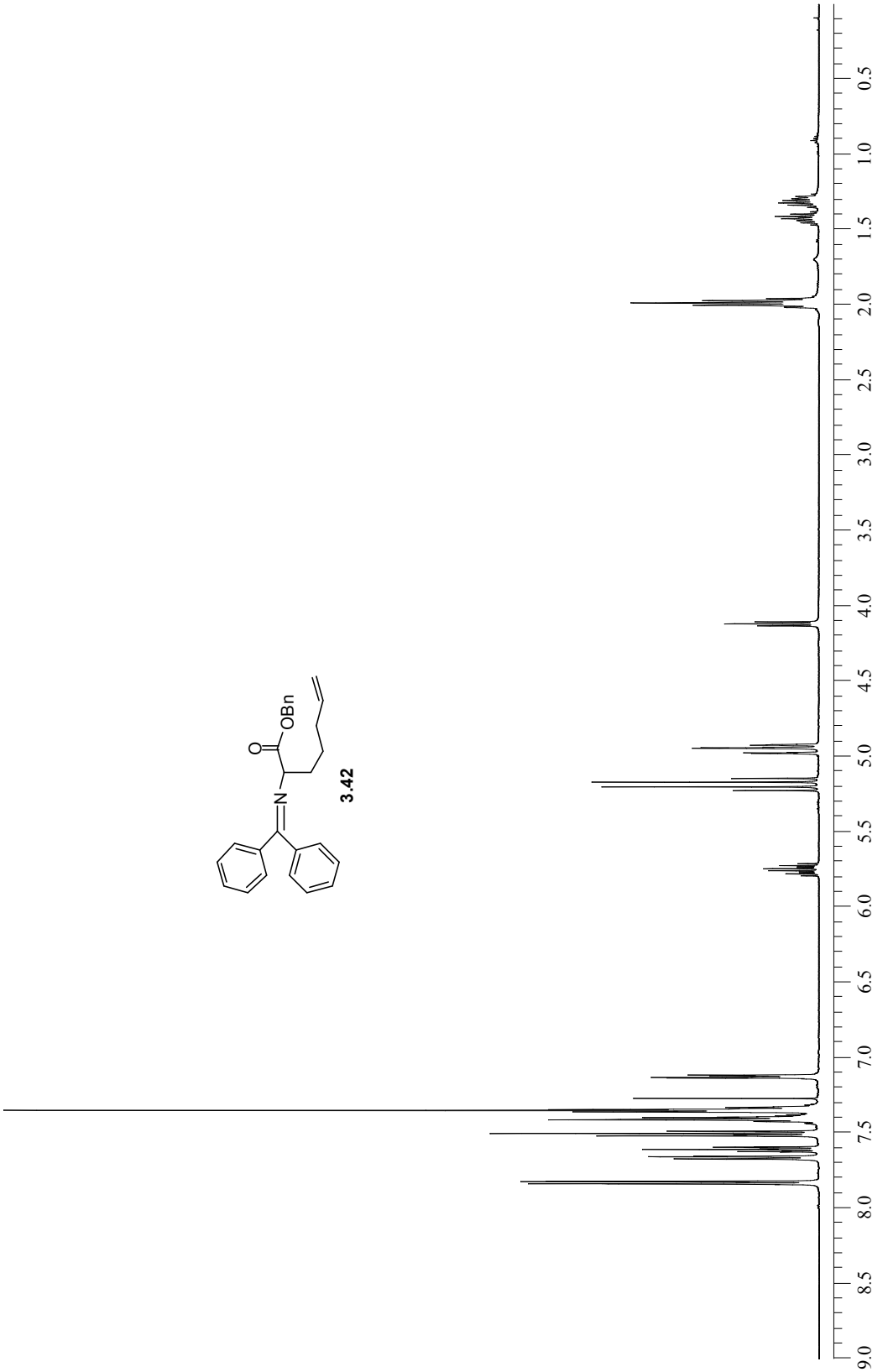
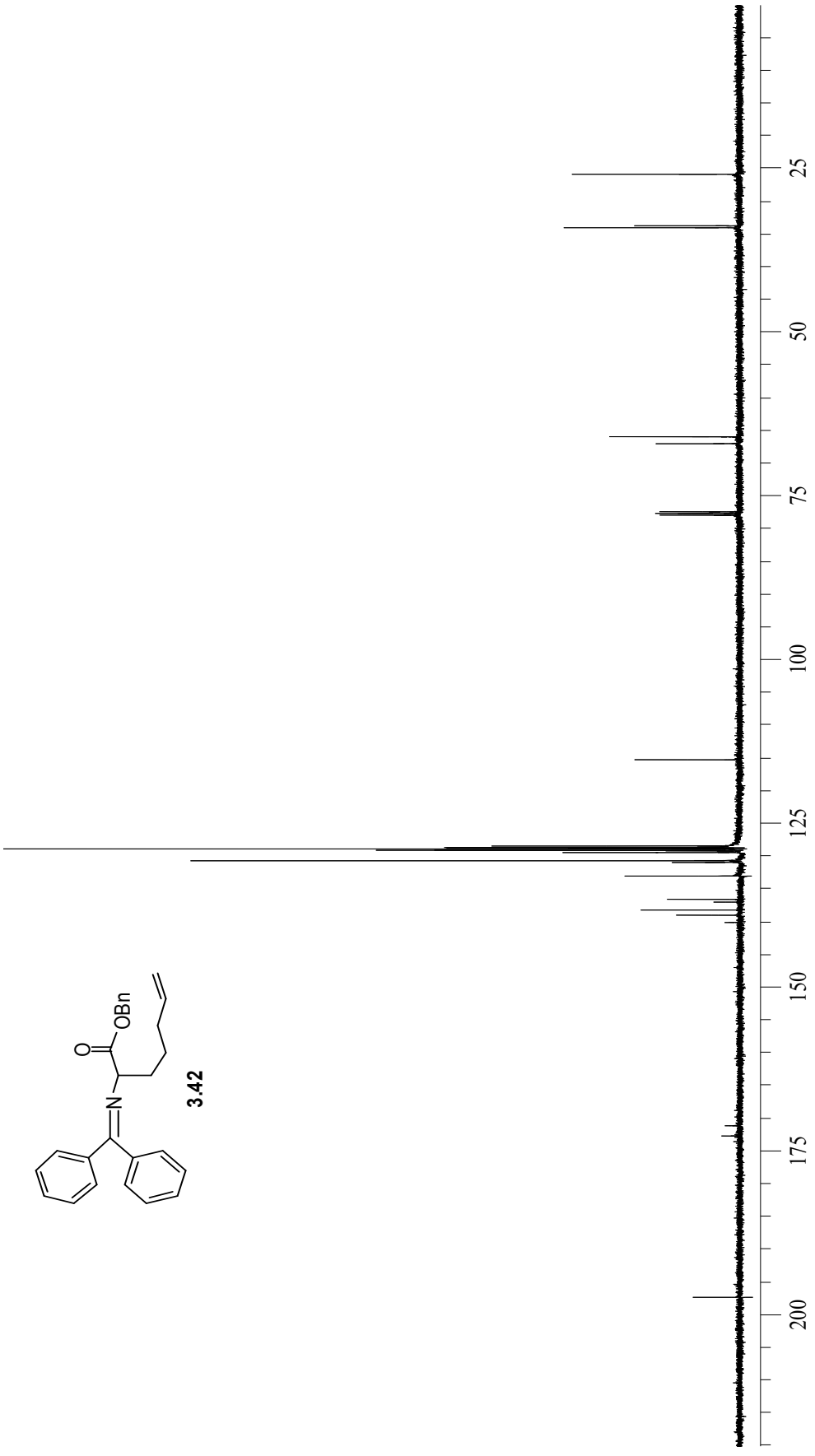
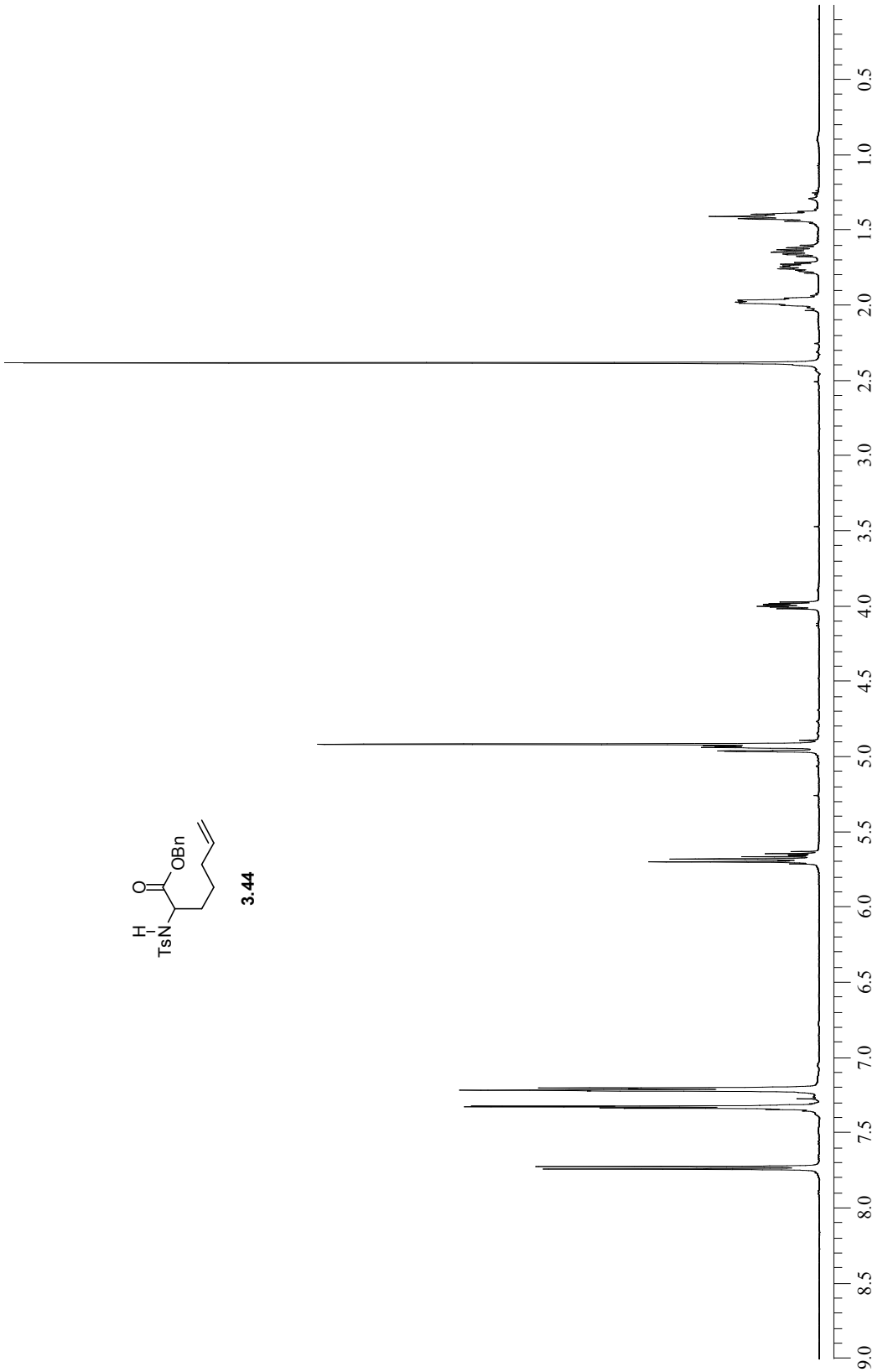


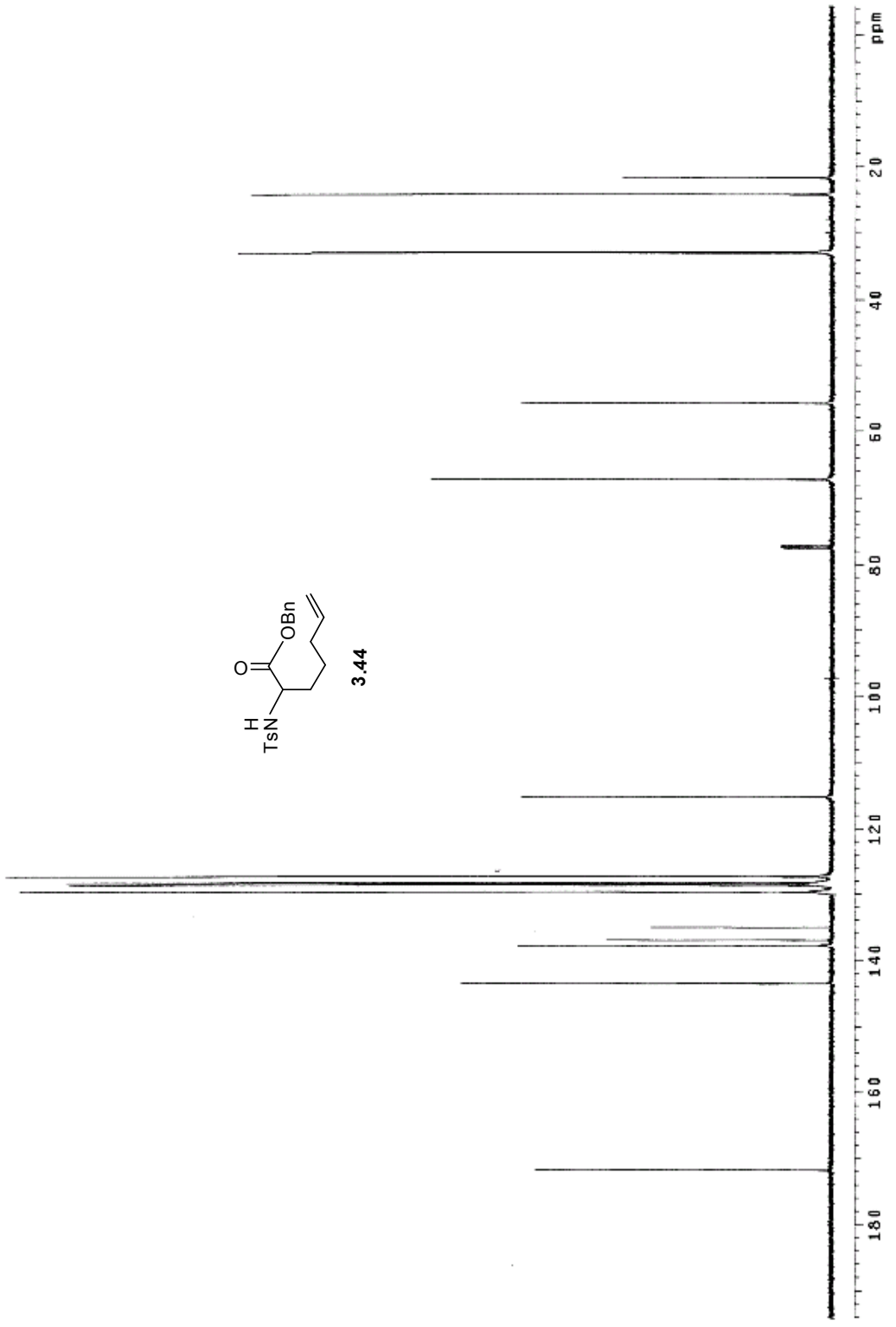
^{1}H NMR spectrum for imine **3.42** ($CDCl_3$)



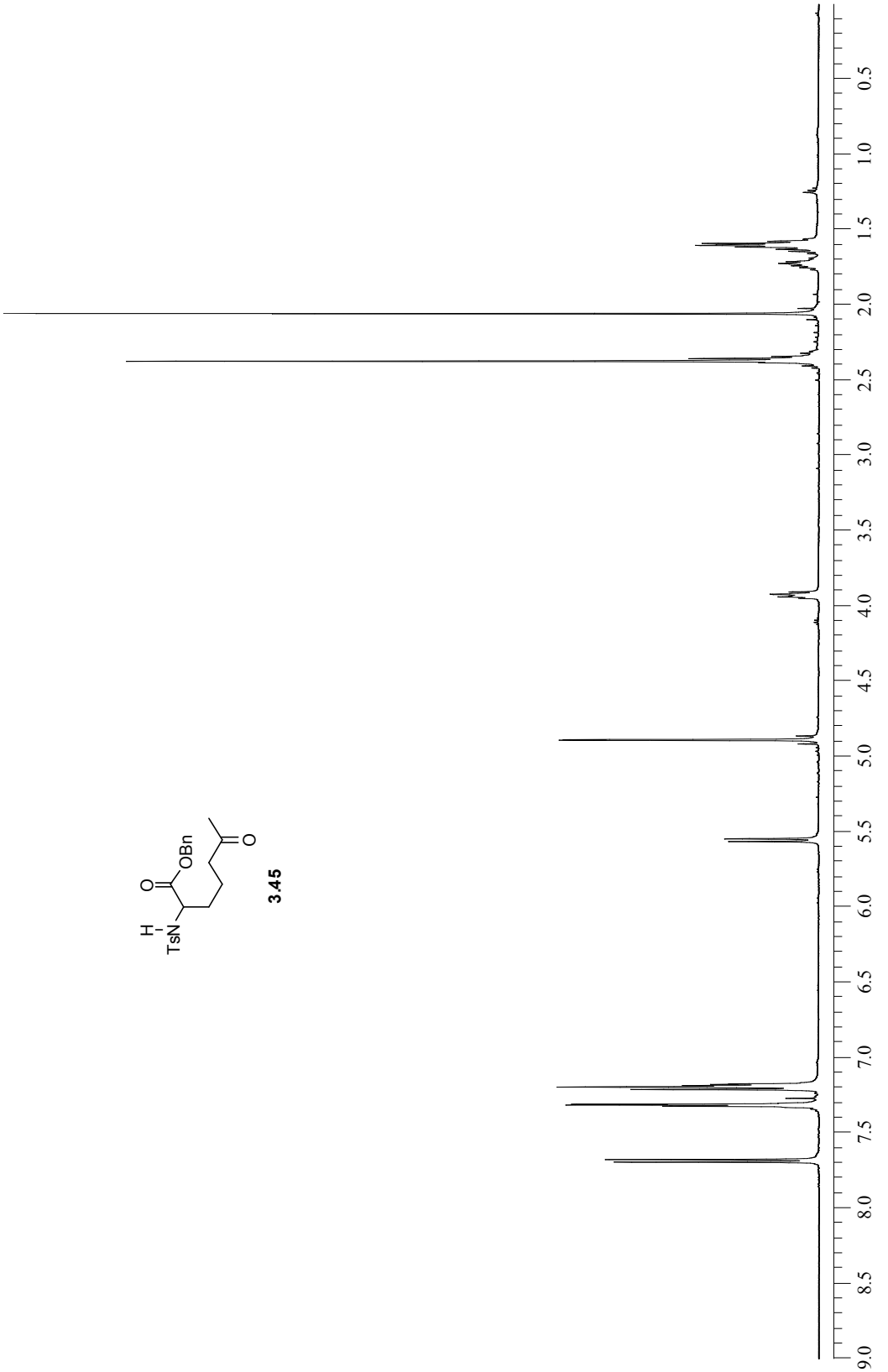
^{13}C NMR spectrum for imine **3.42** ($CDCl_3$)



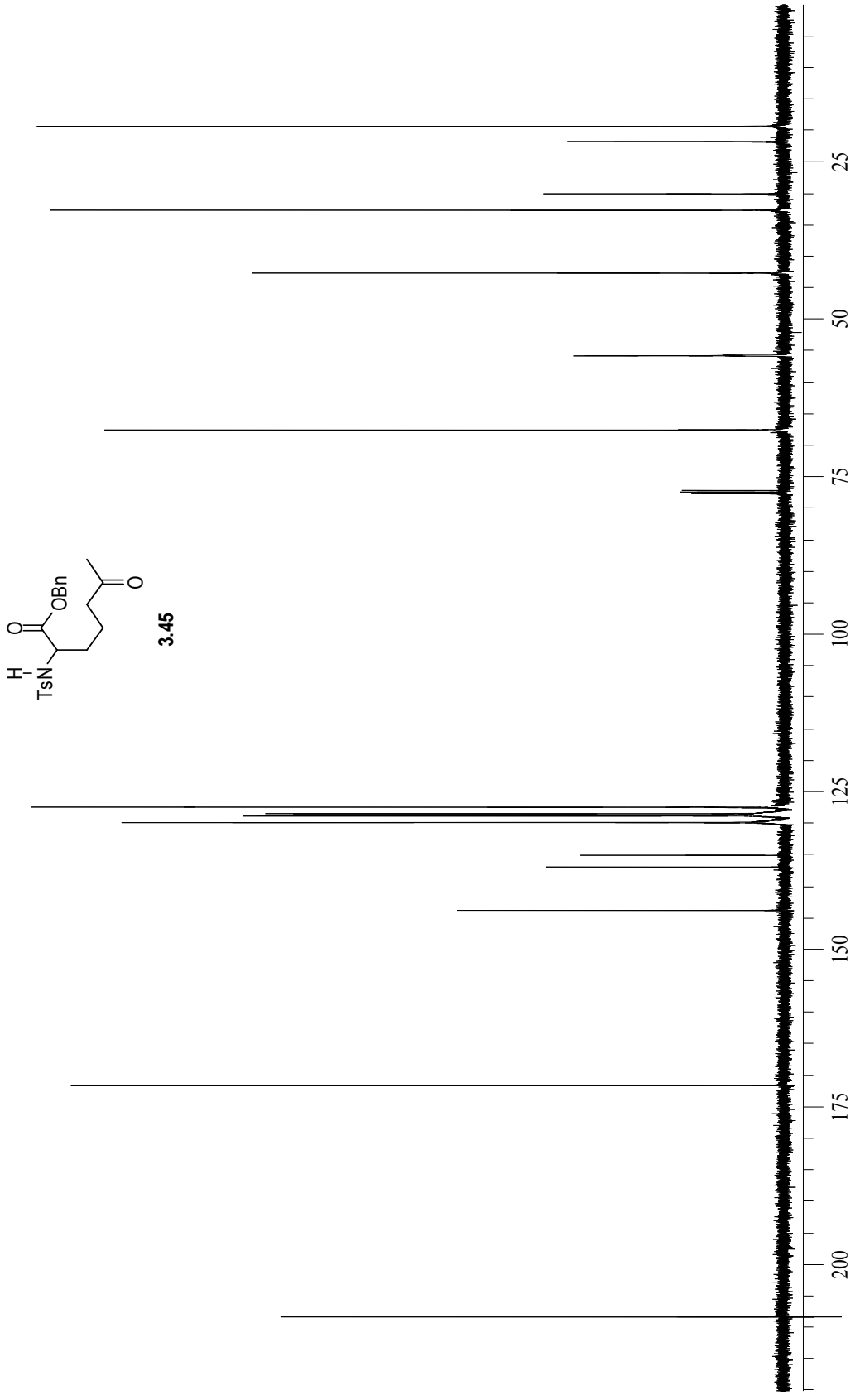
^{1}H NMR spectrum for tosyl amine **3.44** ($CDCl_3$)



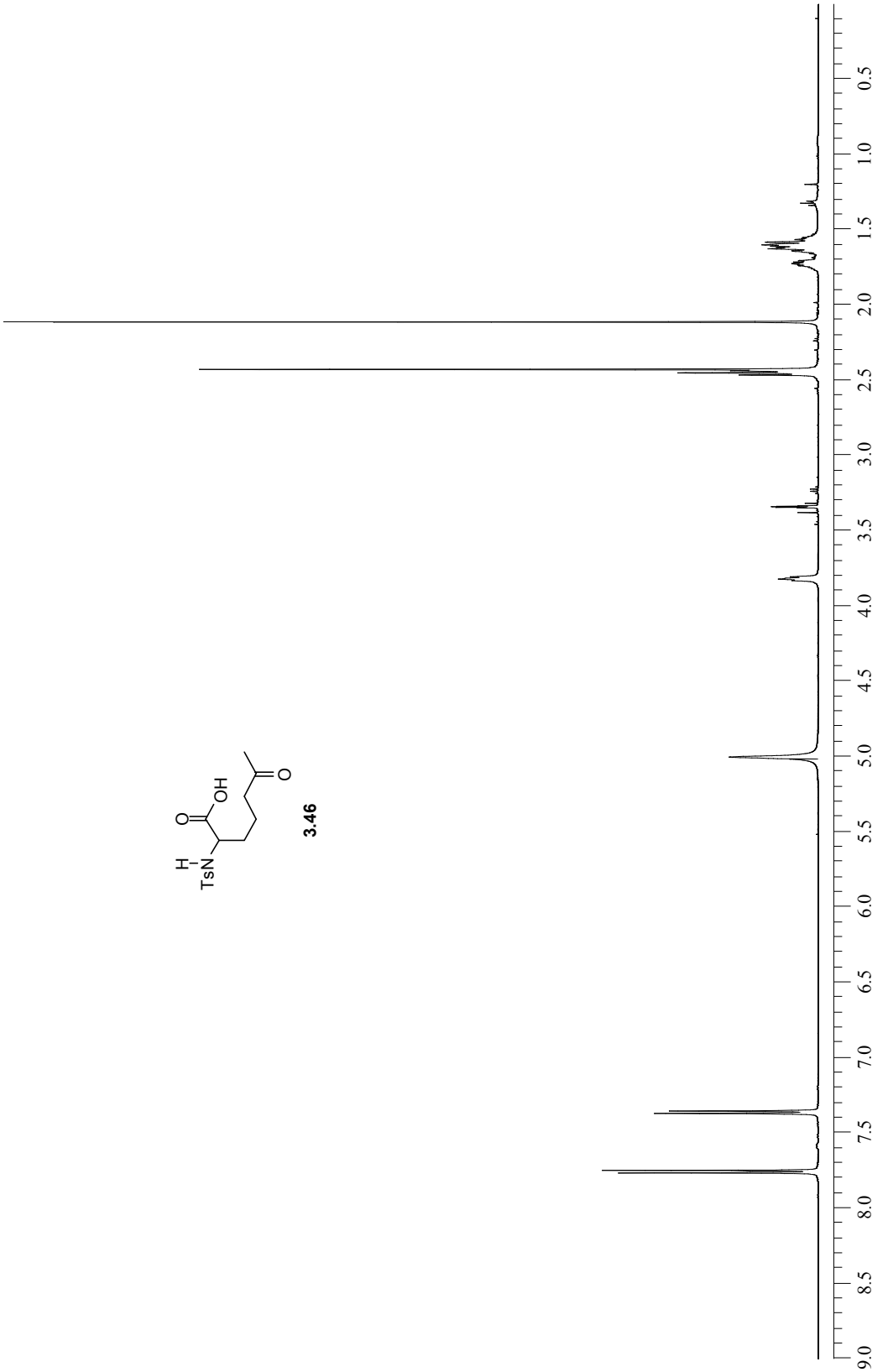
^{13}C NMR spectrum for tosyl amine **3.44** ($CDCl_3$)



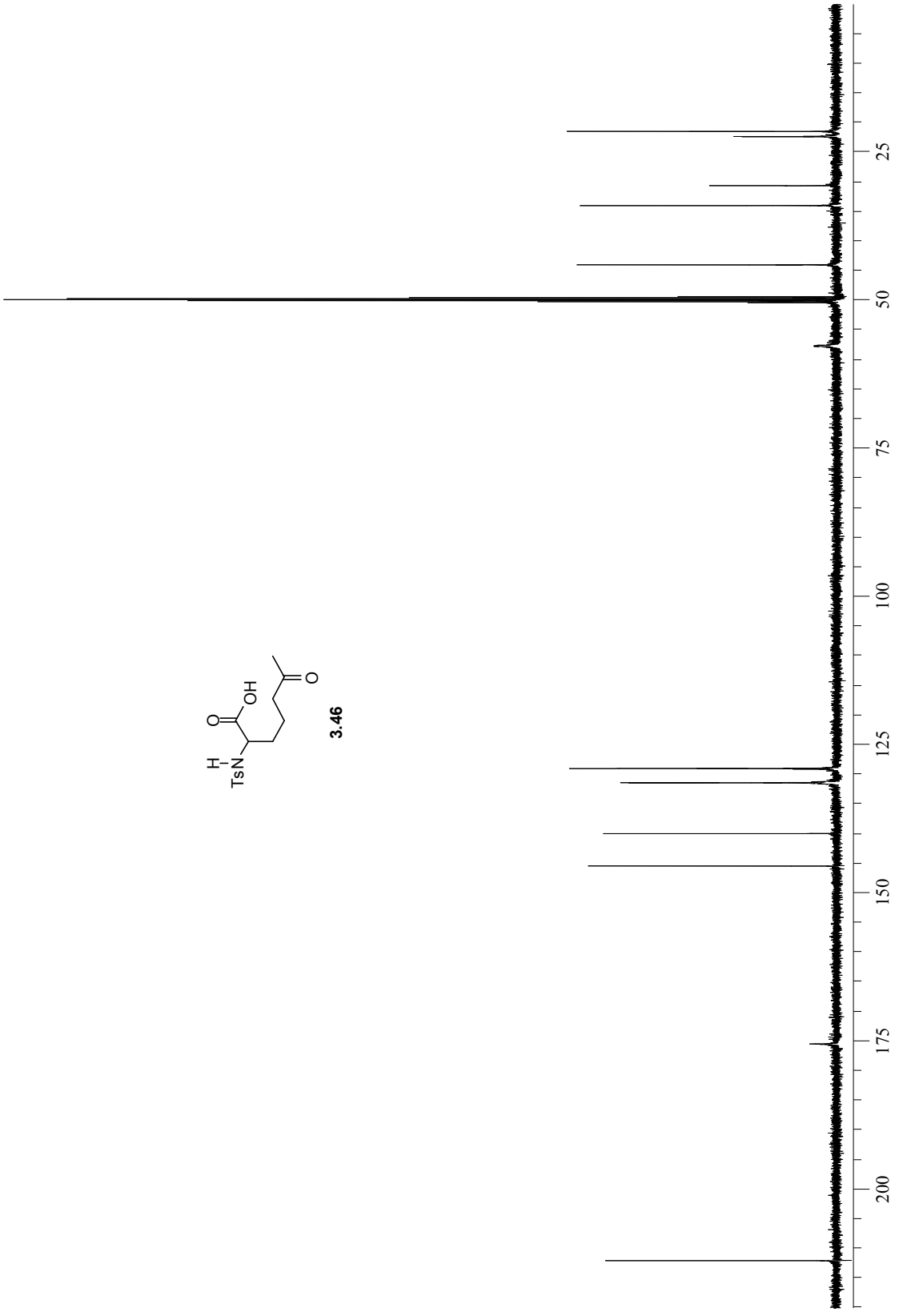
^{1}H NMR spectrum for tosyl amine **3.45** ($CDCl_3$)



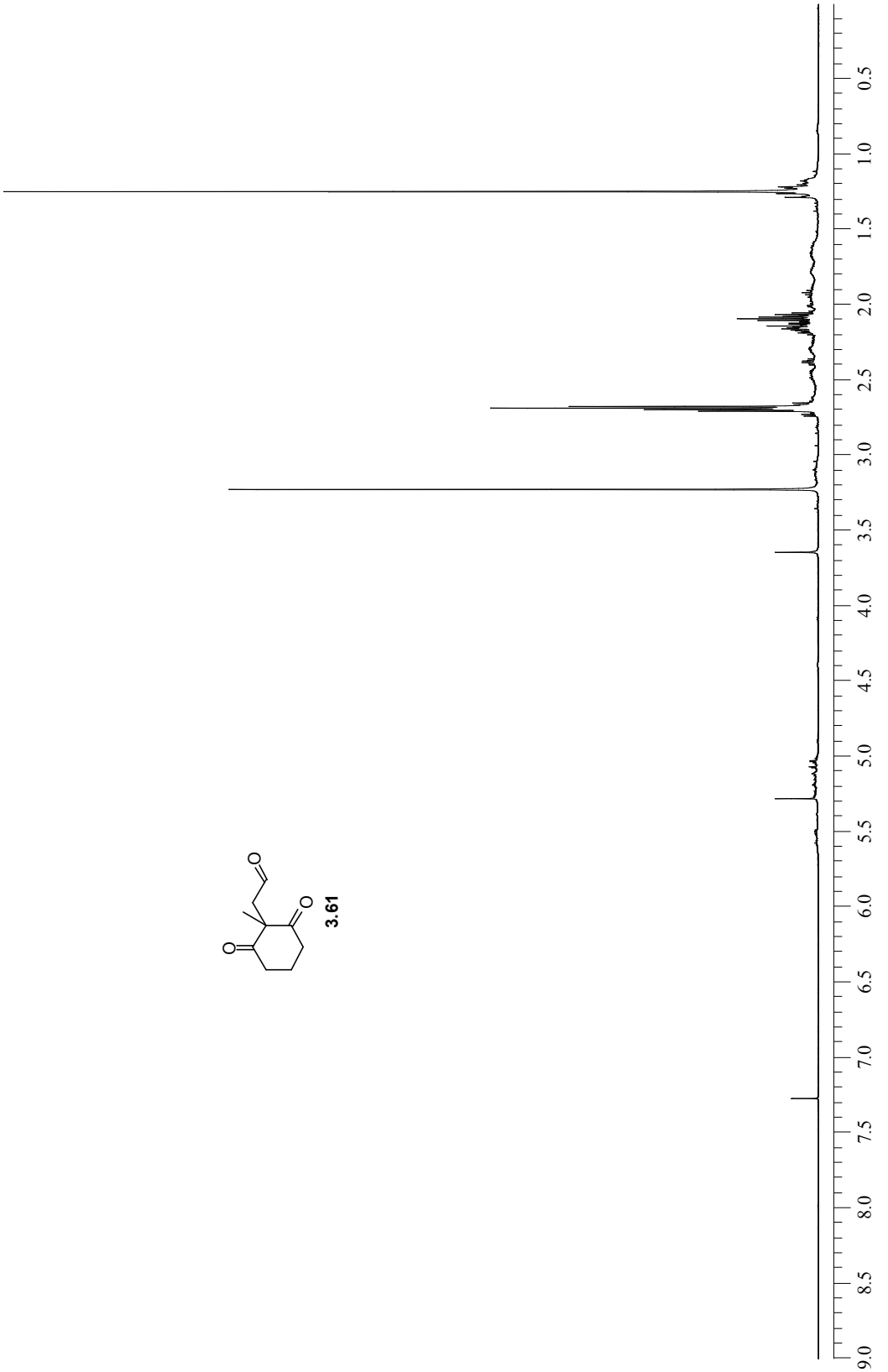
^{13}C NMR spectrum for tosyl amine **3.45** ($CDCl_3$)



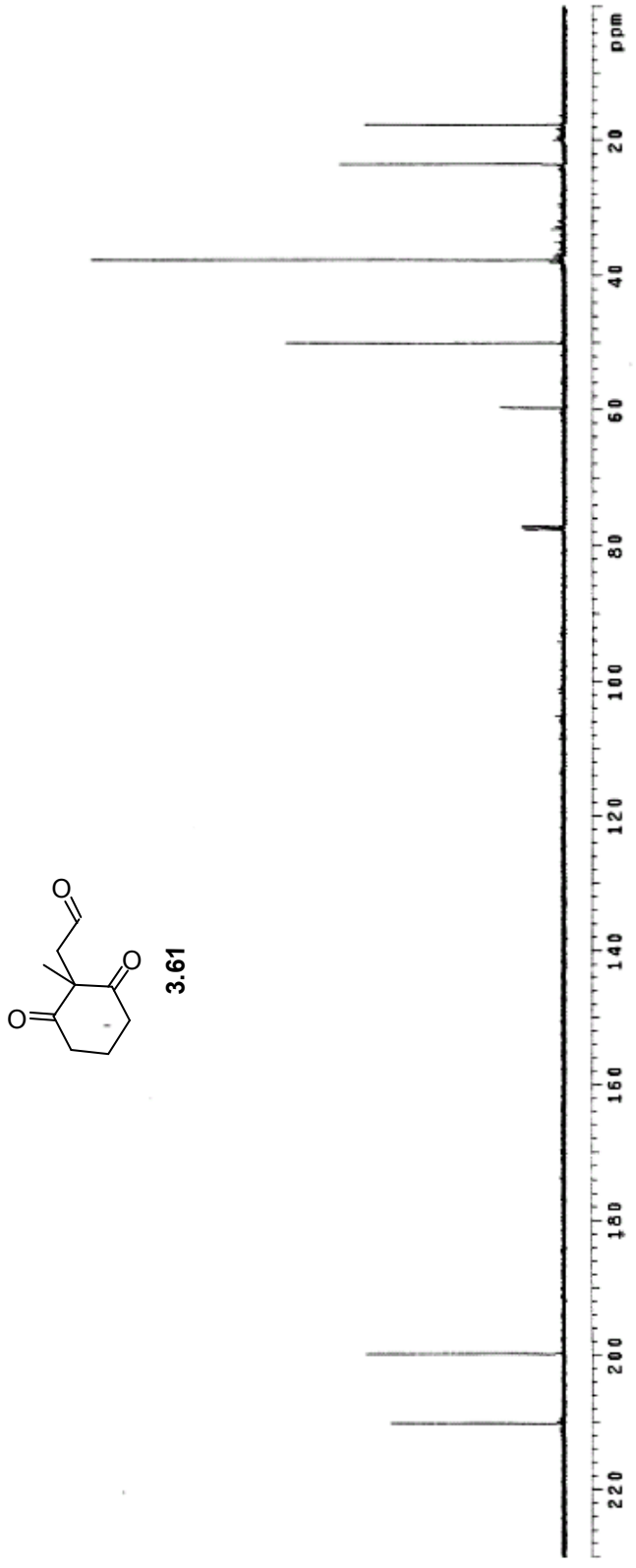
^{1}H NMR spectrum for keto-acid **3.46** (CD_3OD)



^{13}C NMR spectrum for keto-acid **3.46** (CD_3OD)



^{1}H NMR spectrum for aldehyde **3.61** ($CDCl_3$)

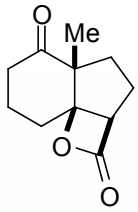


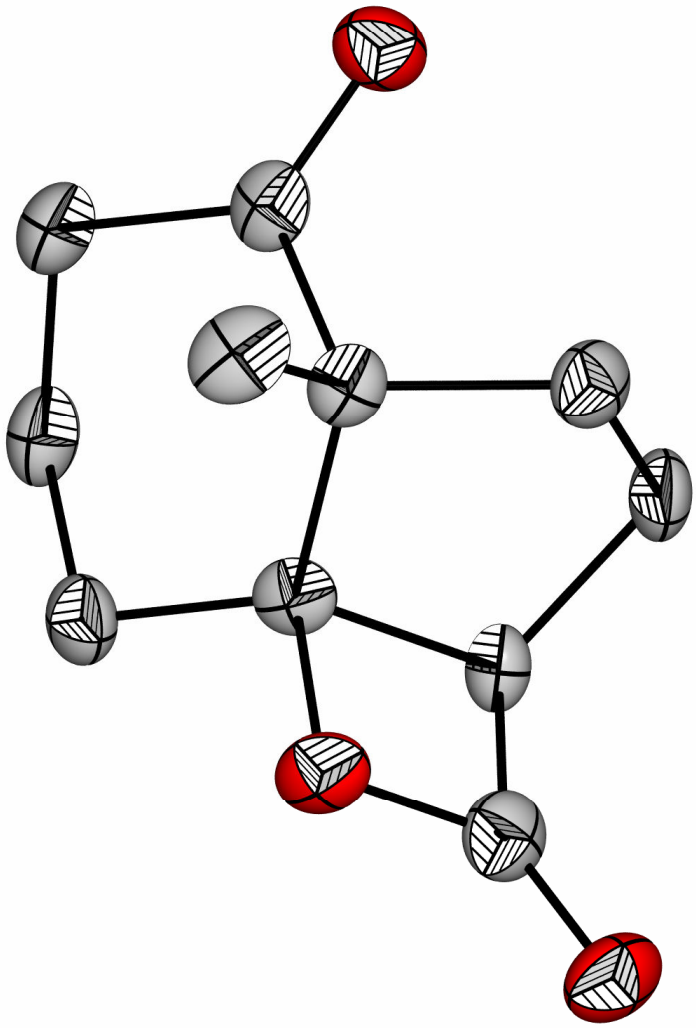
^{13}C NMR spectrum for aldehyde **3.61** ($CDCl_3$)

APPENDIX B

CRYSTALLOGRAPHIC DATA

Crystal Data for tricyclic β-lactone **3.19a**:





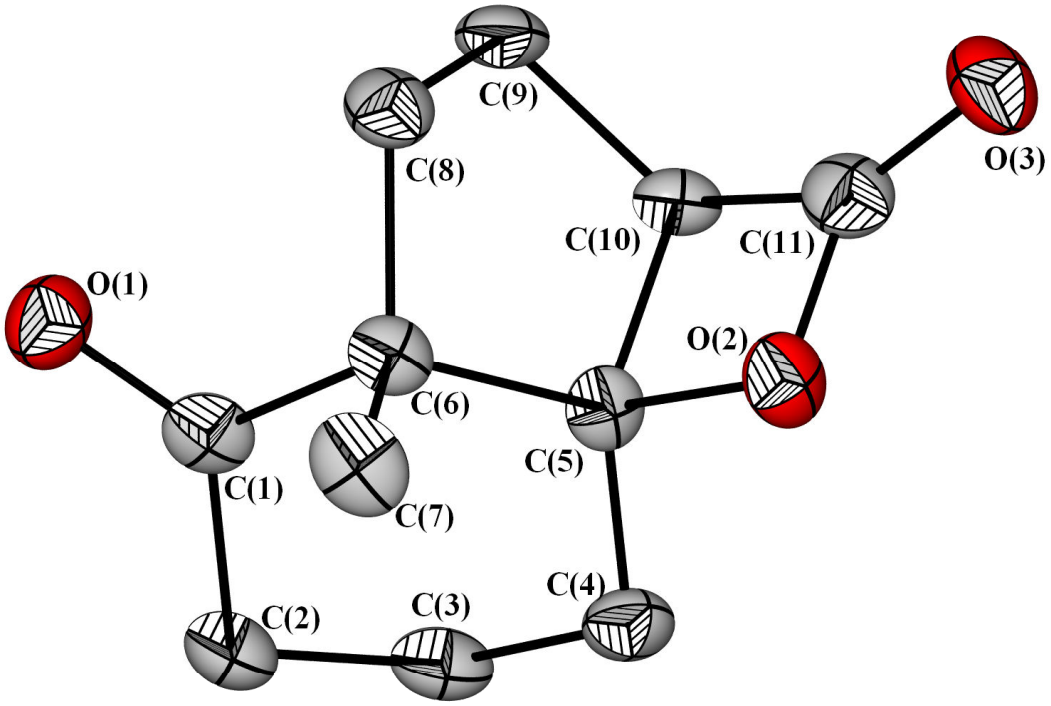
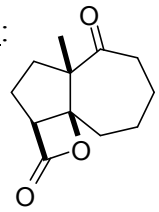
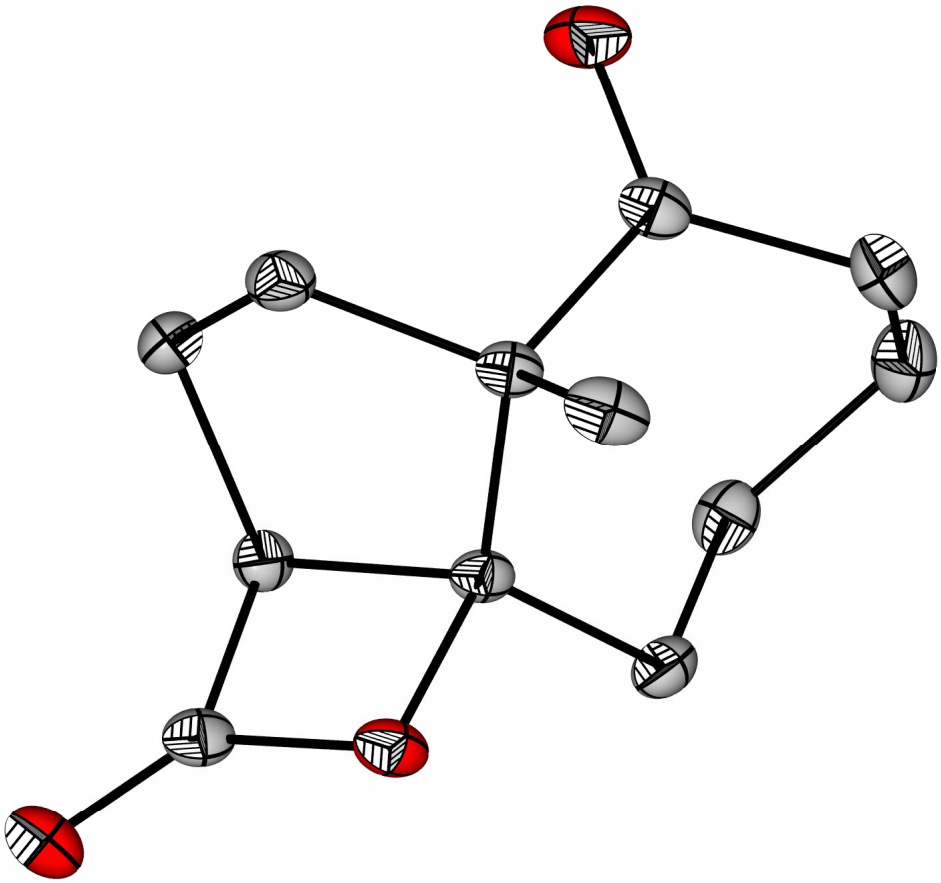

C(9)
O(3)
C(8)
C(10)
C(11)
O(1)
O(2)
C(6)
C(5)
C(1)
C(7)
C(4)
C(2)
C(3)

Table 17. Crystal data and structure refinement for tricyclic β-lactone **3.19a**.

Identification code	p21	
Empirical formula	C11 H14 O3	
Formula weight	194.22	
Temperature	140(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 6.773(3) Å	α= 90°.
	b = 18.993(9) Å	β= 90.046(5)°.
	c = 7.715(4) Å	γ = 90°.
Volume	992.3(8) $Å^3$	
Z	4	
Density (calculated)	1.300 Mg/m^3	
Absorption coefficient	0.094 mm^{-1}	
F(000)	416	
Crystal size	0.19 x 0.05 x 0.05 mm^3	
Theta range for data collection	2.64 to 28.48°.	
Index ranges	-8<=h<=8, -24<=k<=24, -10<=l<=10	
Reflections collected	11258	
Independent reflections	4593 [R(int) = 0.0454]	
Completeness to theta = 28.48°	94.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9953 and 0.9824	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4593 / 1 / 256	
Goodness-of-fit on F^2	1.039	
Final R indices [I>2sigma(I)]	R1 = 0.0479, wR2 = 0.0840	
R indices (all data)	R1 = 0.0667, wR2 = 0.0915	
Absolute structure parameter	0.2(14)	
Largest diff. peak and hole	0.167 and -0.220 $e.Å^{-3}$	

Crystal Data for tricyclic β-lactone (*syn*)-**3.19c**:





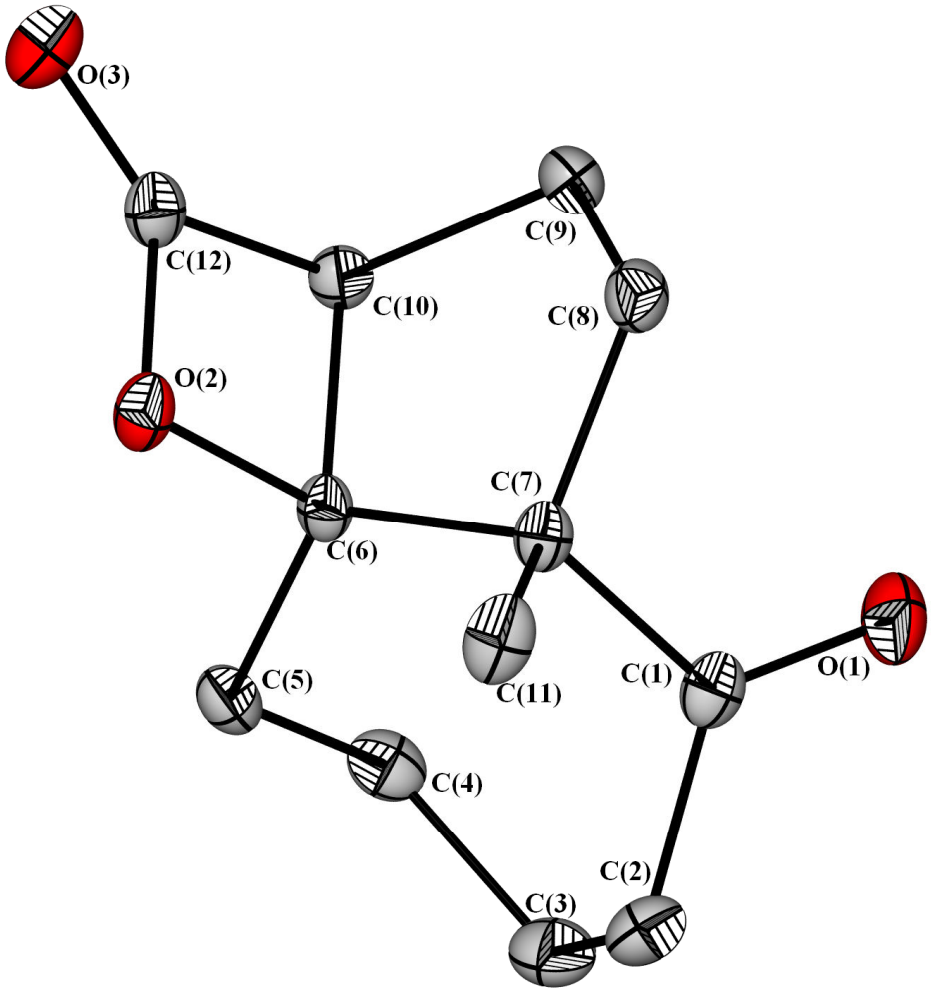
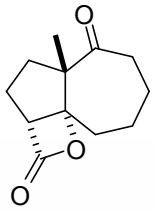
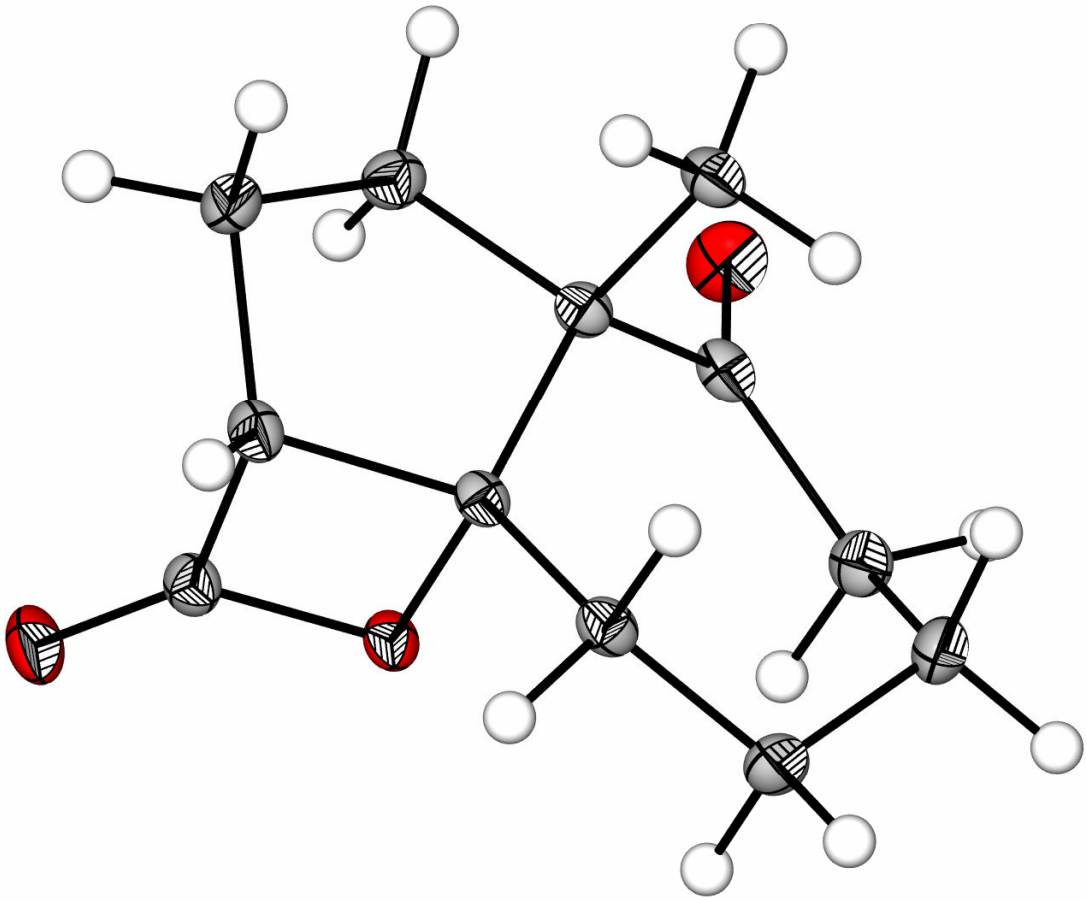

O(3)
C(12)
C(9)
C(10)
C(8)
O(2)
C(7)
C(6)
C(11)
C(1)
O(1)
C(5)
C(4)
C(2)
C(3)

Table 18. Crystal data and structure refinement for tricyclic β-lactone (syn)-**3.19c.**

Identification code	drb0628g	
Empirical formula	C12 H16 O3	
Formula weight	208.25	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 10.8422(9) Å	α= 90°.
	b = 7.1838(6) Å	β= 110.0990(10)°.
	c = 14.0565(12) Å	γ = 90°.
Volume	1028.16(15) $Å^3$	
Z	4	
Density (calculated)	1.345 Mg/m^3	
Absorption coefficient	0.096 mm^{-1}	
F(000)	448	
Crystal size	0.30 x 0.20 x 0.20 mm^3	
Theta range for data collection	2.06 to 27.54°.	
Index ranges	-14<=h<=14, -9<=k<=9, -18<=l<=18	
Reflections collected	11410	
Independent reflections	2374 [R(int) = 0.0332]	
Completeness to theta = 27.54°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9812 and 0.9719	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2374 / 0 / 137	
Goodness-of-fit on F^2	1.104	
Final R indices [I>2sigma(I)]	R1 = 0.0416, wR2 = 0.0960	
R indices (all data)	R1 = 0.0476, wR2 = 0.0991	
Largest diff. peak and hole	0.343 and -0.186 $e.Å^{-3}$	

Crystal Data for tricyclic β-lactone (*anti*)-**3.19c**:





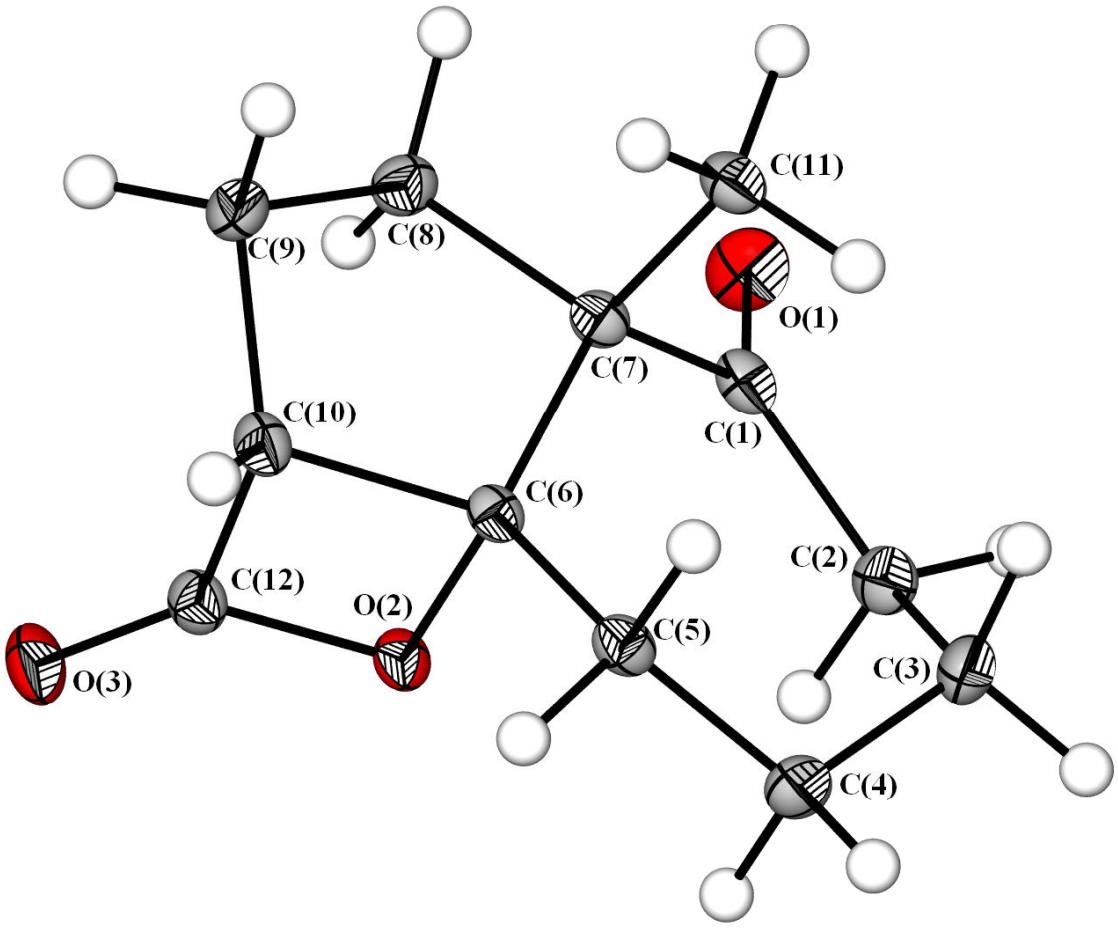
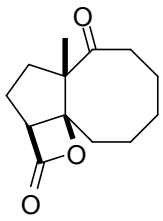
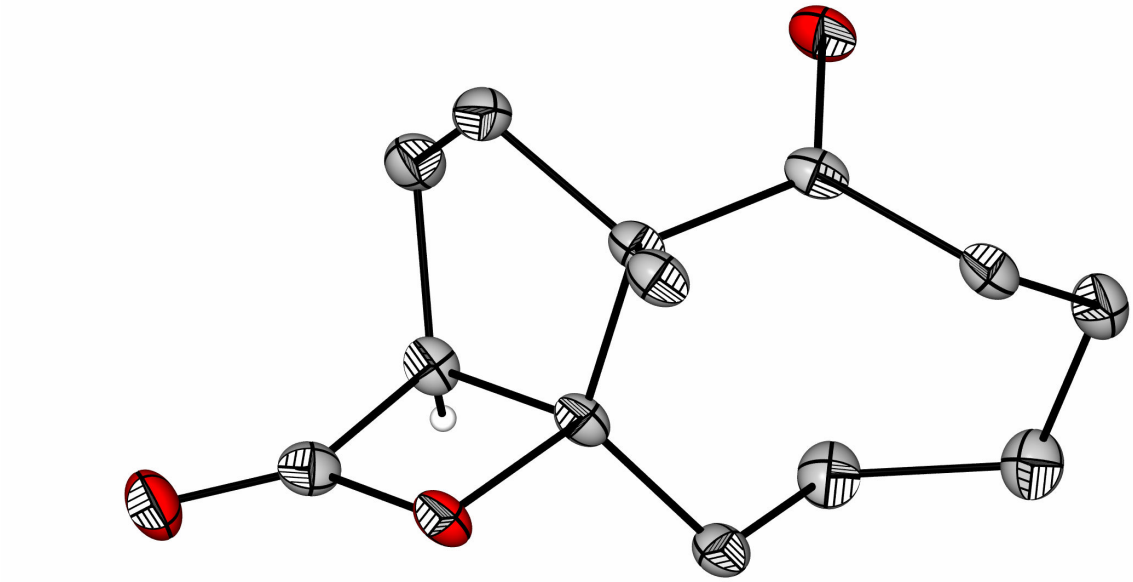

C(11)
C(9)
C(8)
O(1)
C(7)
C(10)
C(1)
C(6)
C(2)
C(12)
O(2)
C(5)
C(3)
O(3)
C(4)

Table 19. Crystal data and structure refinement for (*anti*)-tricyclic β-lactone **3.19c.**

Identification code	drb0626g	
Empirical formula	C12 H16 O3	
Formula weight	208.25	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.751(2) Å	α= 112.543(4)°.
	b = 11.521(3) Å	β= 97.399(5)°.
	c = 11.735(3) Å	γ = 101.084(5)°.
Volume	1045.2(5) $Å^3$	
Z	4	
Density (calculated)	1.323 Mg/m^3	
Absorption coefficient	0.094 mm^{-1}	
F(000)	448	
Crystal size	0.50 x 0.40 x 0.05 mm^3	
Theta range for data collection	1.93 to 27.53°.	
Index ranges	-11<=h<=11, -14<=k<=14, -15<=l<=15	
Reflections collected	12096	
Independent reflections	4730 [R(int) = 0.0328]	
Completeness to theta = 27.53°	98.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9953 and 0.9545	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4730 / 0 / 273	
Goodness-of-fit on F^2	1.036	
Final R indices [I>2sigma(I)]	R1 = 0.0439, wR2 = 0.0950	
R indices (all data)	R1 = 0.0569, wR2 = 0.1006	
Largest diff. peak and hole	0.367 and -0.186 $e.Å^{-3}$	

Crystal Data for tricyclic β-lactone (*syn*)-**3.19d**:





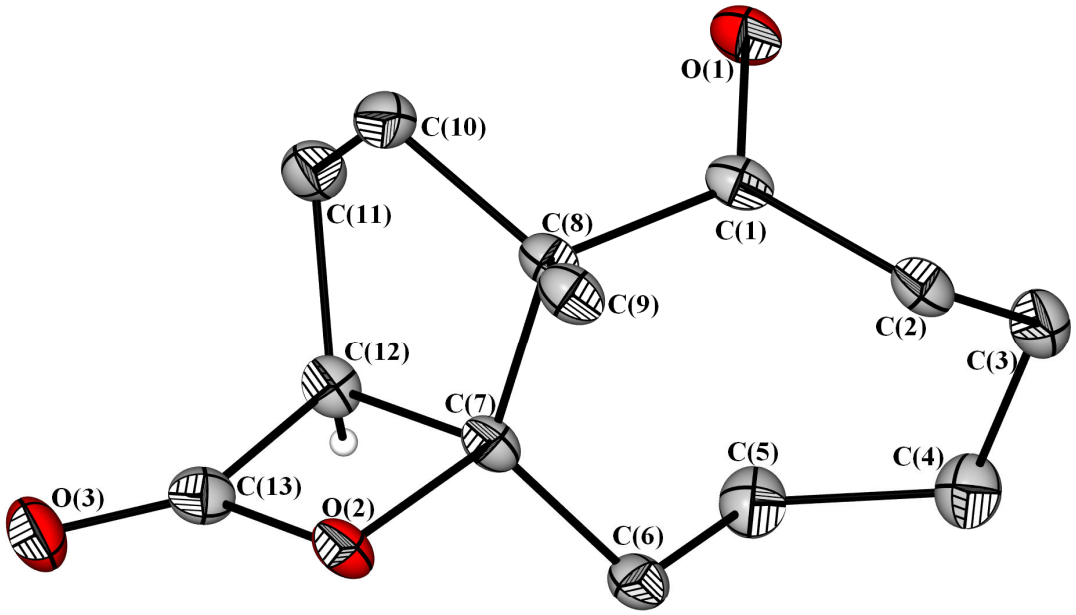

O(1)
C(10)
C(11)
C(8)
C(1)
C(9)
C(2)
C(3)
C(12)
C(7)
C(5)
C(4)
O(3)
C(13)
O(2)
C(6)

Table 20. Crystal data and structure refinement for (*syn*)-tricyclic β-lactone **3.19d**.

Identification code	drb08070g	
Empirical formula	C13 H18 O3	
Formula weight	222.27	
Temperature	110(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.1697(3) Å	α= 90°.
	b = 10.7054(4) Å	β= 90°.
	c = 14.4136(6) Å	γ = 90°.
Volume	1106.31(8) $Å^3$	
Z	4	
Density (calculated)	1.335 Mg/m^3	
Absorption coefficient	0.757 mm^{-1}	
F(000)	480	
Crystal size	0.30 x 0.20 x 0.02 mm^3	
Theta range for data collection	5.15 to 60.85°.	
Index ranges	-8<=h<=7, -12<=k<=12, -16<=l<=16	
Reflections collected	7641	
Independent reflections	1677 [R(int) = 0.0371]	
Completeness to theta = 60.85°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9850 and 0.8048	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1677 / 0 / 147	
Goodness-of-fit on F^2	1.048	
Final R indices [I>2sigma(I)]	R1 = 0.0291, wR2 = 0.0721	
R indices (all data)	R1 = 0.0324, wR2 = 0.0739	
Absolute structure parameter	0.5(2)	
Largest diff. peak and hole	0.141 and -0.159 $e.Å^{-3}$	

VITA

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