APPLICATIONS OF β-LACTONES: UTILITY OF SPIROEPOXY-β-LACTONES AND DEVELOPMENT OF A DOUBLE DIASTEREOSELECTIVE NUCLEOPHILE CATALYZED, ALDOL-LACTONIZATION PROCESS LEADING TO β-LACTONE FUSED CARBOCYCLES AND TETRAHYDROFURANS

A Dissertation

by

KAY ANN MORRIS

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

DOCTOR OF PHILOSOPHY

August 2010

Major Subject: Chemistry

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Approved by:

Chair of Committee,	Daniel Romo
Committee Members,	David E. Bergbreiter
	Brian T. Connell
	Charles M. Kenerley
Head of Department,	David H. Russell

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ABSTRACT

Applications of β-Lactones: Utility of Spiroepoxy-β-Lactones and Development of a Double Diastereoselective Nucleophile Catalyzed, Aldol-Lactonization Process Leading to β-Lactone Fused Carbocycles and Tetrahydrofurans.

(August 2010)

Kay Ann Morris, B.S., Cameron University

Chair of Advisory Committee: Dr. Daniel Romo

Natural products continue to inspire synthetic chemists to develop novel methodologies to provide efficient and expedient syntheses of the target molecules. Haterumalide NA aroused our interest and prompted development of four differing methodologies. Three of the strategies pursued involved use of β-lactone scaffolds as intermediates. Extensions of the nucleophile catalyzed, aldol-lactonization (NCAL) reaction were also pursued and targeted toward alternative natural product targets.

The reactivity of the unexpectedly stable strained spirocycle, spiroepoxy-β-lactone, was explored. Spiroepoxy-β-lactones exhibited a wide range of reactivity, but largely rearranged to tetronic acids. The desired reaction manifold remained inaccessible and led to application of the NCAL process to tetrahydrofuran-fused β-lactones. Several tetrahydrofuran-fused β-lactones were prepared, which displayed low diastereoselectivity. The diastereoselectivity could be somewhat improved in a double diastereoselective NCAL process with varied solvent systems, yet the carbocyclic analogues gave much more promising results. The use of carbocycle-fused β-lactones ultimately culminated in a double diastereoselective NCAL process, and overall led to

improvements in diastereoselectivities from 1:1-2 up to >19:1. Further expansion of the substrate scope for the NCAL process was studied for application to bridged tricyclic β-lactones, access to carbocycle-fused γ-lactones, and towards development of a dynamic kinetic resolution NCAL process.

With our interest aimed at haterumalide NA, a modified Negishi cross coupling between zincates and dichloroolefins was also revisited. The stringent anhydrous reaction conditions led to reexamination of initial leads, which provided user-friendly anhydrous conditions by utilizing commercially available anhydrous solvent. However, application was implemented solely to a simplified model system.

DEDICATION

To my loving and supportive parents, John & Marjorie Morris

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I earnestly thank my research advisor, Prof. Daniel Romo, for his enthusiastic commitment to education. I have had the pleasure to pursue several research projects while in his research group during which he allowed independence to follow my own hypotheses and develop more fully into an independent researcher. I also thank his family for providing a sense of community while in graduate school. His contributions to my career as both a student and researcher are invaluable. In fact, I would not still be pursuing my Ph.D. without the encouragement and persistence he has provided, which has empowered me to continually improve as a researcher.

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Richard Duffy, thank you for being willing to serve as my mentors. You both assisted me countless times, and I could never even begin to return the favor. Your insightful discussions and contributions helped me continue to be inspired by chemistry. Much appreciation goes to all others I had the opportunity to share time with in the laboratory including Andy Skauge, Chun-Xiao Xu, Fang Li, Gil Ma, Huda Henry-Riyad, Jing Li, Liang Tang, Mahesh Peddibhotla, Omar Robles, Paul Dransfield, Wei Zhang, Yongang Wang, and Ziad Moussa. I also thank my peers for their encouragement and assistance during our schooling, namely Andrea Matla, Changsuk Lee, Dorianne Castillo, Francisco Franco-Torres, Gang Liu, Henry Nguyen, J.C. Reyes, Ke Kong, Manuel Zancanella, Morgan Shirley, Ravikrishna Vallakati, Seong Ho Oh, Shaohui Wang, Sung Wook Cho, Supakarn Chamni, Vikram Purohit, Yatsandra Oyola, and our most recent coworkers, Alfred Tuley and Mikail Abbasov. It was a joy to enter graduate school with Henry, Manuel, and Yatsandra, who helped me laugh and further grow as a researcher. A special thanks goes to my collaborators, Andy S., Richard, Ravi, and Kevin for laying an excellent foundation for me to merely stand on and for providing supplemental experimentation as needed. It has been a particularly rewarding experience to mentor Kevin. Thank you for catching on so quickly and being diligent in your research. Also, I thank my predecessors, Guillermo Cortez, Reginald Tennyson, and Seong Ho Oh, who initially developed the NCAL process to access bicyclic β-lactones. Finally, it has been a pleasure working with my great friends, Carolyn Leverett and Kevin Arendt, who have motivated and assisted me during the past few years.

There are several other people who played an integral role in preparing me for graduate school. I cannot forget the training and attention I received at Cameron

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learn. My Grandpa John gave me sound advice that I should pursue a Ph.D. in graduate school, which in honoring his request I have developed a passion to encourage and persuade young people to enter chemistry and related science fields.

I also would like thank Cynthia Samples, Ted Brown, Arika Pravitasar, Rachel DeLeon, Laurel Henderson, and Ron & Betsy Dupont for their support. Ethan Montgomery, Jeremy Galindo, Jessica Kyle, Ray Alderete, and Zach Laguire, I cannot thank enough for their friendship and encouragement. I consider them a part of my extended family, and College Station as a place I can call home. Thank you for supporting me in my educational endeavor; you have made helped my last year here be one of the most memorable.

Finally, my greatest appreciation goes to Jesus Christ, the Lord of my life. My strength, my help, and my hope come from Him. My ability and sufficiency do not come from my own accord, but they come from God (II Corinthians 3:5).

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LIST OF ABBREVIATIONS

2,6-lutidine	2,6-dimethylpyridine
Abn	azabicyclononane
Ac	acetyl
Act	activating
β-ICPD	*β*-isocupreidine
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
BOP-Cl	*bis*(2-oxo-3-oxazolidinyl)phosphinic chloride
BTM	benzotetramisole
Bz	benzoyl
Co(III)salen•OAc	1,2-cyclohexanediamino,*N*,*N'*-*bis*(3,5-di-*tert*-butyl salicylidene) cobalt (III) acetate
CSA	camphorsulfonic acid
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DHP	3,4-Dihydro-2*H*-pyran
$(DHQ)_2PHAL$	*bis*(dihydroquinino)phthalazine
$(DHQD)_2PHAL$	*bis*(dihydroquinidino)phthalazine
DIBAl-H	diisobutylaluminum hydride
DKR	dynamic kinetic resolution
DLD-1	colon cancer cell line

DMA	*N*,*N*,-dimethylacetamide
DMAP	*N*,*N*-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dpephos	oxydiphenyl-2,1-phenylene *bis*(diphenylphosphine)
dppb	1,4-*bis*(diphenyphosphino)butane
dr	diastereomeric ratio
ee	enantiomeric excess
equiv	equivalent
HBTM	homobenzotetramisole
HKR	hydrolytic kinetic resolution
HPLC	high performance liquid chromatography
IC_{50}	half maximal inhibitory concentration
Imid.	imidazole
IR	infrared spectroscopy
KR	kinetic resolution
L.A.	Lewis acid
LD_{99}	dosage required to kill 99% of test population
LHMDS	lithium *bis*(trimethylsilyl)amide
m-CPBA	*meta*-chloroperbenzoic acid

MDA-MB-231	breast cancer cell line from M. D. Anderson Cancer Center
Me	methyl
MRC	Mead reductive cyclization
Ms	mesyl (methanesulfonyl)
MTPA	α-methoxy-α-(trifluoromethyl)phenylacetic acid
MW	microwave
NCAL	nucleophile catalyzed, aldol-lactonization
NHK	Nozaki-Hiyama-Kishi
NMP	*N*-methylpyrrolidinone
NMR	nuclear magnetic resonance
Ns	4-nitrobenzenesulfonyl
Nuc	nucleophile
*O*Ac-QD	*O*-acetyl quinidine
*O*Bz-QD	*O*-benzoyl quinidine
ORTEP	Oak Ridge Thermal Ellipsoid Plot
*O*TMS-QD	*O*-trimethylsilyl quinidine
*O*TMS-QN	*O*-trimethylsilyl quinine
P388	murine leukemia cell line
Ph	phenyl
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PMBTCA	*p*-methoxybenzyl trichloroacetimidate
PPTS	pyridinium *p*-toluenesulfonate

PPY	4-pyrrolidinopyridine
Py	pyridine
rds	rate determining step
SPy	thiopyridyl
Sudan Red	*N*-ethyl-1-[[*p*-(phenylazo)phenyl]azo]-2-naphthalenamine
TBACl	tetra-*n*-butylammonium chloride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
TES	triethylsilyl
TESOTf	triethylsilyl trifluoromethanesulfonate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMAL	tandem Mukaiyama aldol-lactonization
TMS	trimethylsilyl
TMSE	2-(trimethylsilyl)ethyl
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
Ts	4-toluenesulfonyl
xantphos	9,9-dimethyl-4,5-*bis*-(diphenylphosphino)xanthene

CHAPTER I

INTRODUCTION: NATURAL PRODUCT INSPIRED METHODOLOGY; TETRAHYDROFURAN SYNTHESIS VIA *β*-LACTONES AND ORGANOMETALLIC COUPLINGS WITH DICHLOROOLEFIN SUBSTRATES*

1.1 The Cytotoxic Marine Agent, Haterumalide NA, as Inspiration for Method Development

The diverse structural complexities and potent biological activities of natural products attract the attention of chemists worldwide. Quantities of natural products are often limited from their producing organisms thus hindering testing and potential applications; however, synthesis can help circumvent this issue. Ideal syntheses have a minimal number of high yielding steps with excellent stereocontrol ultimately aiming for atom economy,[1] few redox transformations,[2,3] and high chemoselectivity[4] thus not requiring masking of intermediate functionalities. Natural product syntheses continue to captivate the efforts of synthetic chemists due to their potential use as pharmaceutical agents[5] and in order to probe the boundaries of existing synthetic methods.[6,7] Difficulties regularly arise when applying known methods in total synthesis efforts and when exploring the boundaries within known methodology,[8] thus improved or new methodologies are conceived and developed as a result of these challenges. Methodology and total synthesis are fields that largely overlap, and thus it is difficult to distinguish the reason for development of new methodology. A few specific examples of method development for natural product syntheses include the four methods of intramolecular ether ring formation towards the synthesis of brevetoxin B,[7] a palladium catalyzed alkyne-alkyne coupling to give the macrocycle of bryostatin 16,[9] and a

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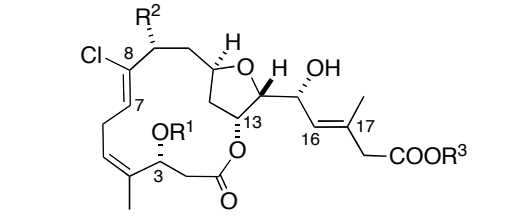
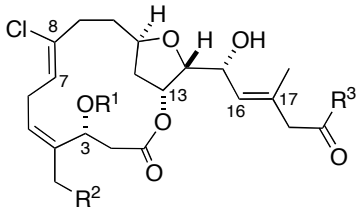
This dissertation follows the style of the *Journal of the American Chemical Society*.

double stereoablative enantioselective alkylation to install two quaternary centers in an enantioselective manner culminating in the synthesis of cyanthiwigin F.[10,11] Therefore, invention and development of new methods are common to total synthesis efforts, however methods development may also be aimed at a particular reoccurring problematic transformation in synthesis rather than a specific target. Methodology such as hydrolytic kinetic resolution (HKR) studied by Jacobsen,[12,13] Sharpless asymmetric epoxidation[14] as well as Sharpless asymmetric dihydroxylation,[15,16] Noyori hydrogenation,[17,18] and Yamaguchi macrocyclization[19] are but a few examples that have been applied in numerous total syntheses, which demonstrate the necessity for continued method advancements.

In efforts toward a total synthesis of haterumalide NA (**1a**), several opportunities arose to explore new *β*-lactone-based methodologies and explore new C-C bond disconnections (Figure 1.1). Haterumalide NA belongs to the haterumalide[20,21] and biselide[22,23] family of macrolactone natural products. Key structural features include a *trans*-trisubstituted tetrahydrofuran ring that can be derived from a *β*-lactone containing subunit, four contiguous stereocenters, and a skipped diene unit possessing an unusual *trans*-substituted chloroolefin.



1a: A/NA; R^1 = Ac, R^2 = H, R^3=H $\Delta^{16,17}$= *E*
1b: NB; R^1 = Ac, R^2 = H, R^3=^{n}Bu $\Delta^{16,17}$= *E*
1c: NC; R^1 = Ac, R^2 = OH, R^3=^{n}Bu $\Delta^{16,17}$= *E*
1d: ND; R^1 = Ac, R^2 = OH, R^3=H $\Delta^{16,17}$= *E*
1e: NE; R^1 = H, R^2 = H, R^3=H $\Delta^{16,17}$= *E*
1f: X; R^1 = Ac, R^2 = H, R^3=H $\Delta^{16,17}$= *Z*
1g: B; R^1 = Ac, R^2 = H, R^3= $\Delta^{16,17}$= *E*
1h: R^1 = Ac, R^2 = H, R^3=Me $\Delta^{16,17}$= *E*



2a: A; R^1 = Ac, R^2 = OAc, R^3 = OH,
2b: B; R^1 = Ac, R^2 = OAc, R^3 = O COCH$_3$
2c: C; R^1 = Ac, R^2 = OH, R^3 = OH,
2d: D; R^1 = Ac, R^2 = H, R^3 = N H SO$_3$H

Figure 1.1. Structure of haterumalides **1a-1h** and biselides **2a-2d**.

Haterumalides NA-NE were initially isolated from a marine sponge of the *Ircinia sp*. off the coast of Hateruma island in Japan,[20] and later from the soil bacteria, *Serratia marcesens* and *S. plymuthica*. (Figure 1.1).[24-26] Haterumalide NA has shown to be cytotoxic against P388 cells with an IC_{50} 0.68 μM and a LD_{99} 0.24 g/kg towards mice. Further studies have shown that it aids in the decrease of lipid droplet formation in adipocyte cells[27-29] presenting the haterumalides as promising candidates in the treatment of hypertriglyceridemia and hyperlipidemia[30] since elevated plasma lipid levels, especially triglyceride levels, are recognized as risks for cardiovascular disease, obesity, diabetes, and hypertension.[27] Other members of this family, namely biselide A (**2a**), exhibited cytotoxicity towards DLD-1, human colon cancer, with an IC_{50} 0.96 μM.[23] More potent cytotoxicity was observed for haterumalide NA, biselide A, and derivatives towards human breast cancer, MDA-MB-231, and lung cancer cell lines compared to the anticancer drug cisplatin.[23]

1.2 Summary of Haterumalide NA Syntheses

The intriguing biological activity of the haterumalides and biselides sparked several syntheses of haterumalide NA (Figure 1.2). The first total synthesis was reported in 2003 by Kigoshi, first generation route, which resulted in revision of the absolute stereochemistry as to that shown in Figure 1.2.[31] A Nozaki-Hiyama-Kishi coupling installed the side chain and has been utilized in all of the subsequent syntheses. Snider published the synthesis of enantiomeric haterumalide NA later that year and demonstrated use of a higher yielding Yamaguchi macrocyclization to deliver the desired macrolactone.[32] Two years later, in 2005, Hoye published the first total synthesis of the correct enantiomer of haterumalide NA and was the first to close the macrolactone in the vicinity of the vinyl chloride through a palladium mediated alkyne haloallylation.[33] Kigoshi, second generation route, and Roulland next published concurrent syntheses utilizing a Suzuki-Miyaura coupling between a borane derived from tetrahydrofurans **8** or **4** and a 1,1-substituted haloalkene component,

respectively.[34,35] Borhan also published a total synthesis of haterumalide NA, which employed a chromium-mediated macrocyclization and a final stage deoxygenation of haterumalide NC.[36] The total synthesis of haterumalide B has also been reported,[37] and the synthetic efforts towards the haterumalides have been recently reviewed.[38,39]

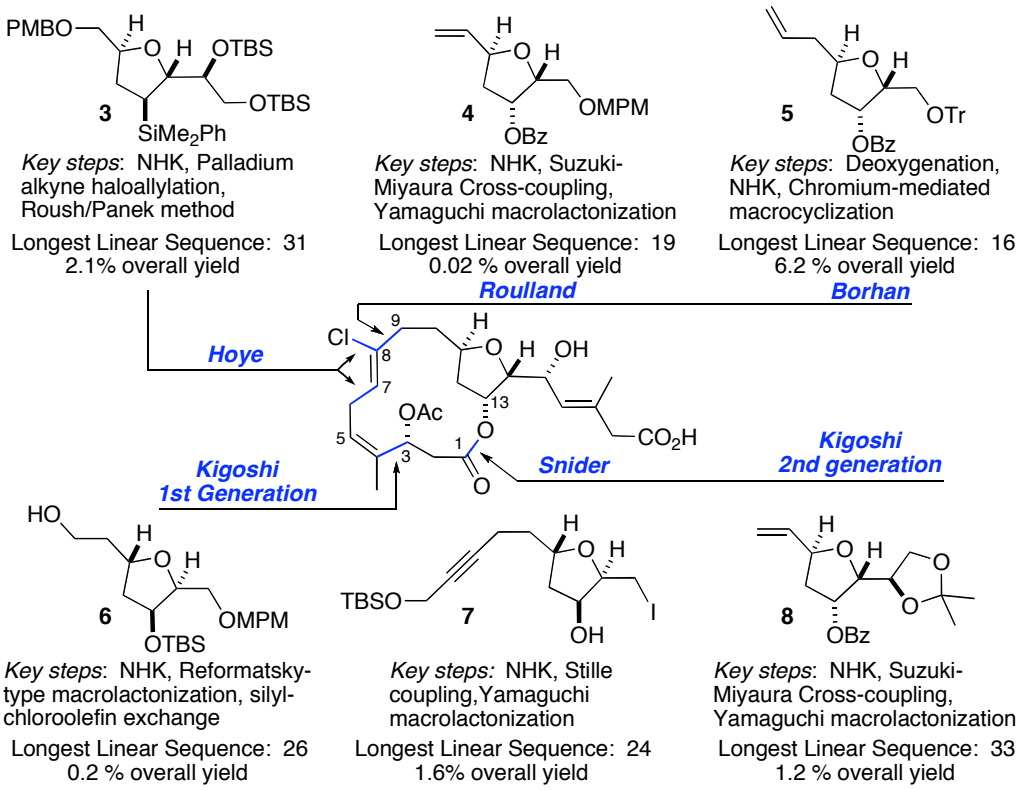


Figure 1.2. Summary of haterumalide NA syntheses.

1.3 Structural Revision of Haterumalide NA

Herein, we provide a full account of several methodology projects that have their genesis and inspiration from our interest in haterumalide NA as a target for total synthesis. In efforts to develop a concise route to the tetrahydrofuran fragment, we extended the utility of the previously developed tandem Mukaiyama aldol-lactonization (TMAL) process that proceeds through a silylated β-lactone intermediate to include a reductive cyclization leading to a one step, multicomponent synthesis of tetrahydrofurans

from a thiopyridyl ketene acetal, a trialkylsilane, and a ketoaldehyde. The discovery of novel, unexpectedly stable spiroepoxy-β-lactones stemmed from our interest in the preparation of such systems to access γ-hydroxy β-lactones required for a reductive cyclization of keto-β-lactones building on work by Mead. In addition, we developed a variant of our nucleophile catalyzed, aldol-lactonization (NCAL) process that enabled access to tetrahydrofuran-fused β-lactones **11** and also explored double diastereoselection for these systems and carbocycle fused β-lactones.[40] Finally, we describe new conditions for Pd-catalyzed coupling reactions of dichloroolefins **12** leading to (*Z*)-trisubstituted chloroolefins related to those found in HatNA.

Our group envisioned two key fragments towards the synthesis of haterumalide NA; a skipped diene possessing a vinyl chloride, and a *trans*-trisubstituted tetrahydrofuran ultimately derived from a β-lactone moiety **9** (Figure 1.3). Cross coupling of a 1,1-dichloroolefin **12** would install the vinyl chloride present in the macrolactone ring, a method which had minimal precedent at the onset of our synthetic efforts.[41] The tetrahydrofuran subunit would be derived from Mead reductive cyclization (MRC) of the corresponding β-lactone **9** prepared by a tandem Mukaiyama aldol-lactonization (TMAL). During our initial studies Kigoshi published a total synthesis establishing that the previously reported stereochemistry was in fact a diastereomer of what was originally assigned for haterumalide NA.[31] The synthesis resulted in a revision of absolute stereochemistry from

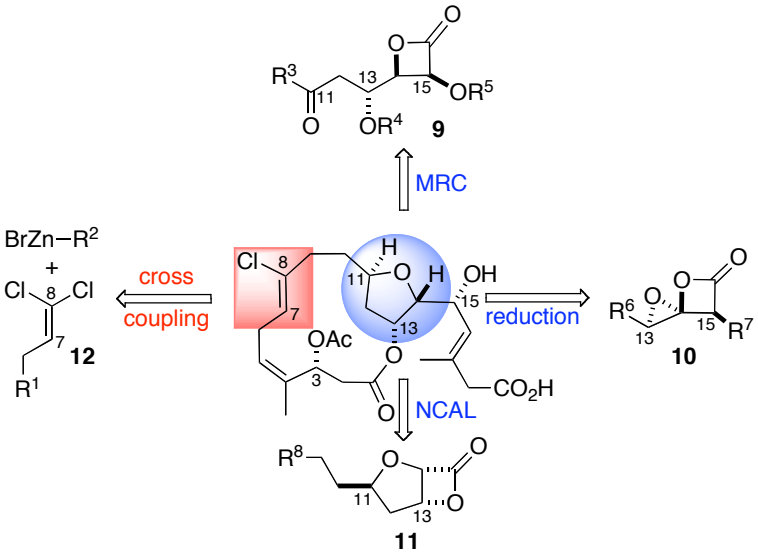


Figure 1.3. Haterumalide NA as inspiration for method development (numbering on intermediates **9-12** reflects haterumalide numbering).

the original 3*S*, 11*S*, 13*S*, 14*S*, 15*R* to 3*R*, 11*R*, 13*R*, 14*R*, 15*R* (Figure 1.3, revised stereochemistry shown). Simultaneously, the revision in stereochemistry also altered the relative stereochemistry of the *β*-lactone to be employed in the MRC reaction from a *trans*-*β*-lactone to a *cis*-*β*-lactone **9**. As a result of substrate limitations in the TMAL process, alternative strategies were investigated including regioselective reduction of spiroepoxy-*β*-lactones **10**, and a nucleophile catalyzed, aldol-lactonization (NCAL) to provide tetrahydrofuran-fused *β*-lactone **11**.

1.4 Tandem Mukaiyama Aldol-Lactonization Strategy

Initially the tetrahydrofuran unit **13** was envisioned as coming from a tandem Mukaiyama[42-45] aldol-lactonization[46,47] process, which as we previously reported allows access to both *cis*[46] and *trans*[47] *β*-lactones (Figure 1.4). The TMAL methodology provides mild reaction conditions and has supported application to total syntheses such as; (–)-panclicin,[48] okinonellin B,[49] brefeldin A,[50] and tetrahydrolipstatin/orlistat.[51] Thus

combination of the TMAL methodology with Mead reductive cyclization[52] could provide substituted tetrahydrofurans in a highly diastereoselective manner. Lewis acid mediated cyclization of keto-β-lactones to tetrahydrofurans is known to proceed by invertive alkyl C-O ring cleavage,[52] and the desired *trans*-substituted tetrahydrofuran was expected following the stereochemical models for nucleophilic addition to oxocarbeniums set forth by Woerpel.[53,54] Utilizing a α-silyloxy aldehyde **14** and a thiopyridyl ketene acetal **15** in the TMAL process was envisioned to afford the *anti, cis*-γ-substituted β-lactone **9**.

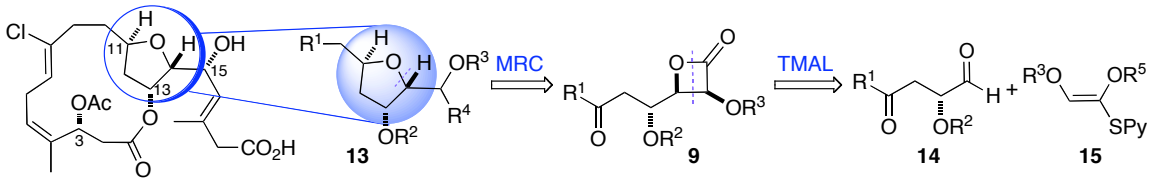
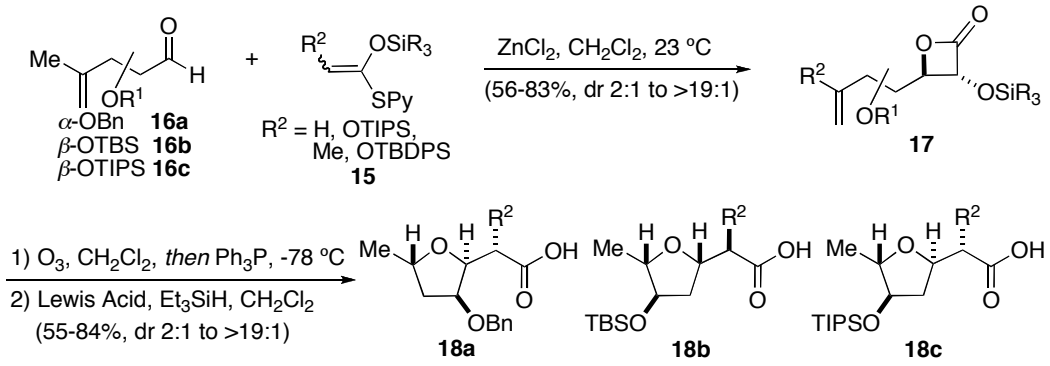


Figure 1.4. Initial strategy to tetrahydrofuran fragment.

Both α- and β-oxygenated aldehydes were supported in the stepwise TMAL-MRC process (Scheme 1.1).[55] High diastereoselectivity was observed with α-benzyloxy aldehydes **16a** based on chelation control. Whereas, β-silyloxy aldehydes **16b-16c** led to moderate diastereoselectivities consistent with Evan's model for addition to β-silyloxy

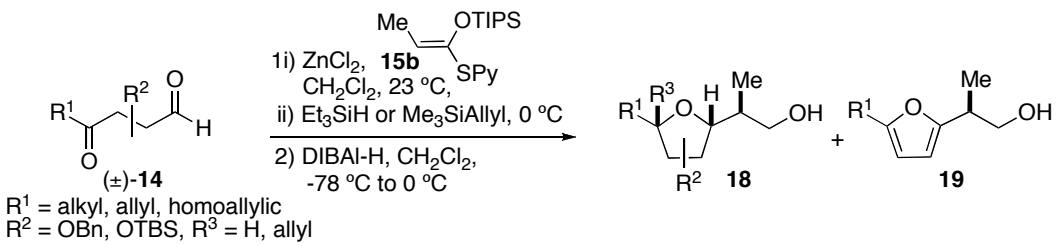
Scheme 1.1. Stepwise TMAL-MRC Process



aldehydes.[56] After ozonolysis, alkenyl-β-lactones **17** underwent Mead reductive cyclization in the presence of TESOTf, BF_3•OEt_2, or $TiCl_4$. Cyclization proceeded through invertive alkyl C-O cleavage, which upon subsequent reduction via "inside attack" of the resulting cyclic oxocarbenium according to Woerpel's model[53,54] gave tetrahydrofurans **18a-18c.**

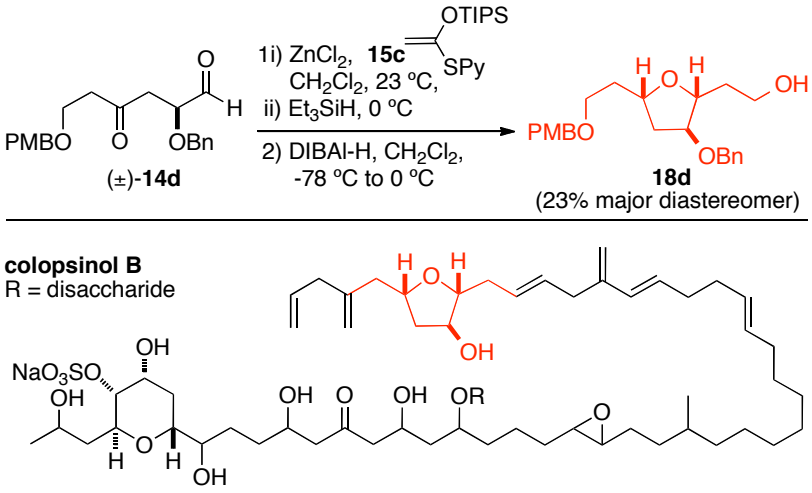
Extension to a cascade TMAL-MRC process was feasible with the advent of the stepwise TMAL-MRC process. The cascade, three-component synthesis of tetrahydrofurans utilizes γ-ketoaldehydes, thiopyridyl ketene acetals, and a silyl-based nucleophile.[57,58] The reaction proceeds through a presumed silylated β-lactone providing further activation for the concomitant cyclization, which allowed use of mild reaction conditions. The $ZnCl_2$ mediated cascade TMAL-MRC process with subsequent reduction to ease purification gave tetrahydrofurans **18** in moderate overall yields (Scheme 1.2). Tetrahydrofuran formation was the major product over competitive furan formation. For ease of purification, the silylester and corresponding acid are directly reduced with DIBAl-H to give tetrahydrofurans **18** in moderate overall yields Combinations of chelation control and stereoelectronic factors governed the diastereoselectivity and are in accord with previous studies.[55,56] The average yield per step is 86% over the four steps for the cascade TMAL-MRC process and subsequent reduction with α-benzyloxy-γ-ketoaldehydes **14**.[57] The reaction also supported use of β-silyloxy-γ-ketoaldehydes **14**, and allylsilane was used as a nucleophile to generate a quaternary center.

Scheme 1.2. Multicomponent Cascade TMAL-MRC Process to Tetrahydrofurans



The cascade TMAL-MRC methodology was applied to the tetrahydrofuran fragment of colopsinol B (Scheme 1.3). Tetrahydrofuran **18d** was formed as a mixture of diastereomers (≅ 3:1:3:1, ≅ 42%). After separation the major diastereomer was obtained in 23 % yield (≅ 70% yield per step over four steps).

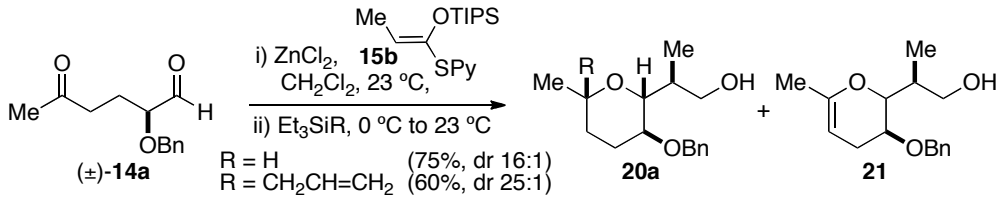
Scheme 1.3. Utility of Cascade TMAL-MRC towards Colopsinol B



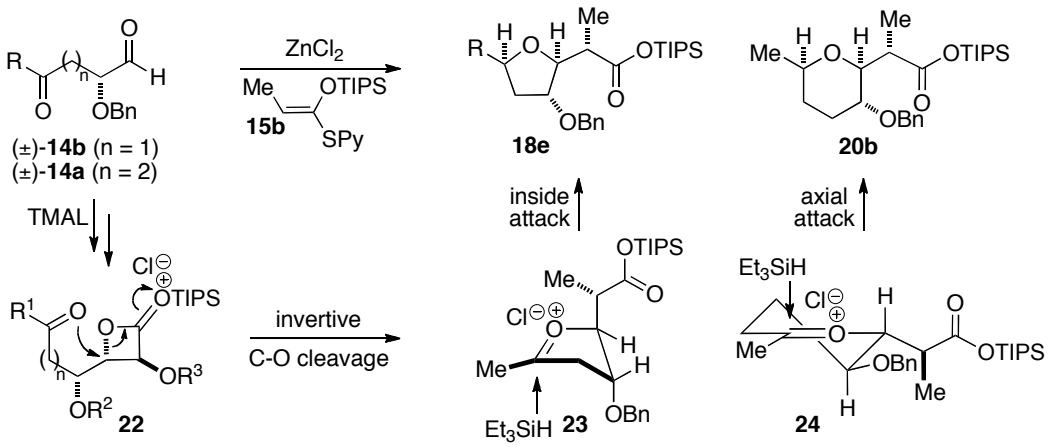
The tandem process proved to be more efficient when applied to tetrahydropyrans **20a** providing yields up to 75% (Scheme 1.4).[58] Triethylsilane and allylsilane added effectively and gave high diastereoselectivity of the resulting tetrahydropyran **20a** in accord with refined models for additions to 6-membered oxocarbeniums.[59] Minor amounts of dihydropyran **21** were also formed through elimination in a similar manner as the tetrahydrofuran systems. The selectivity observed was consistent with both the TMAL process and the models for nucleophilic addition to oxocarbeniums **23/24** proceeding by "inside attack" or "axial attack" for tetrahydrofuran **18e** and tetrahydropyran **20b** systems, respectively (Scheme 1.5). While not applicable to the synthesis of HatNA due to the stereochemical outcome of the initial TMAL process, this cascade TMAL-MRC provides an efficient methodology to generate up to two C-C bonds, one C-O bond, and

three newly formed stereocenters for the synthesis of both tetrahydrofurans and tetrahydropyrans.

Scheme 1.4. Multicomponent Cascade TMAL-MRC to Tetrahydropyrans



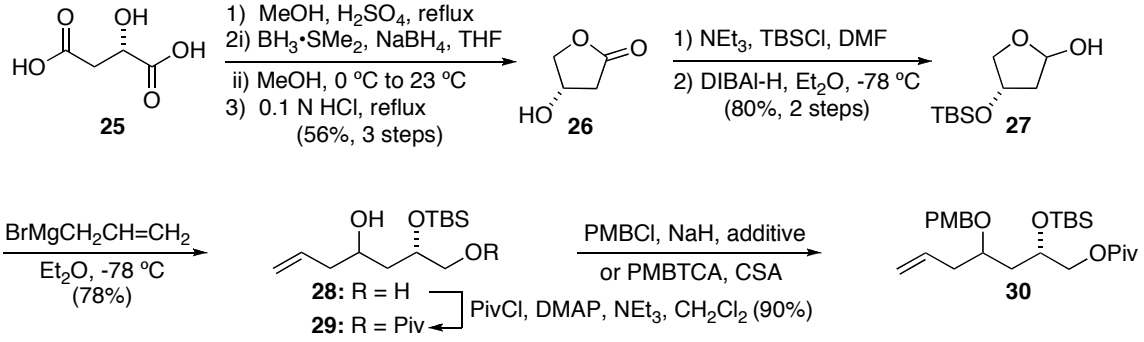
Scheme 1.5. Proposed Mechanism and Stereochemical Rationale for the Three-Component Cascade TMAL-MRC to Tetrahydrofurans and Tetrahydropyrans



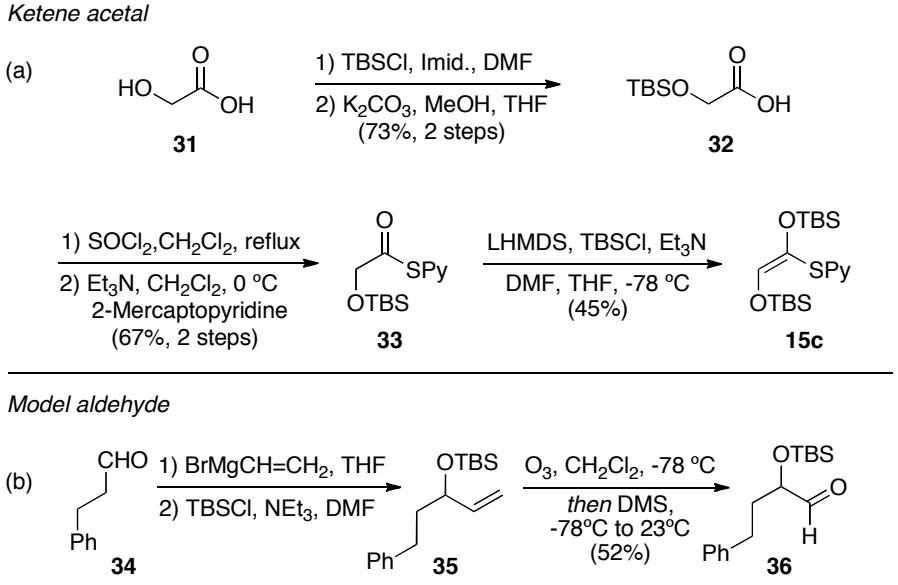
Despite the efficiency and substrate scope of the TMAL process, an *anti, cis*-γ-substituted β-lactone remained elusive. After several futile efforts, our focus was aimed on formation of the requisite keto-β-lactone **9** from L-malic acid (Scheme 1.6). Gram scale quantities of lactone **26** were prepared following known procedures and are outlined below.[54,60,61] Alcohol **26** was protected and subsequent reduction gave lactol **27**.[62] Monoalkylation by Grignard addition provided diol **28**, and the primary hydroxyl was easily protected as the corresponding pivalate **29**. However, protection of the remaining

alcohol under both basic and acidic conditions led to either loss of the pivalate or silyl migration rather than the desired ether **30**.

Scheme 1.6. Attempted Route towards Requisite Ketoaldehyde



Scheme 1.7. Preparation of Precursors for Studies for *Anti*, *Cis*-γ-Substituted β-Lactone

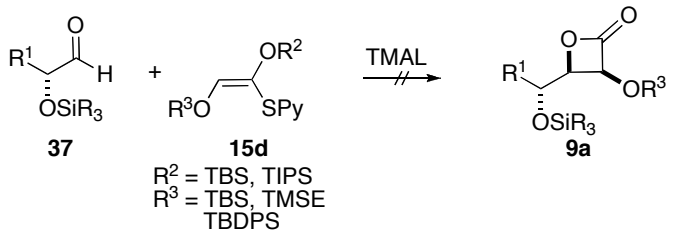


Therefore, model aldehyde **36** and ketene acetal **15c** were prepared for use in the TMAL process. Ketene acetal **15c** was prepared by protection of glycolic acid and hydrolysis to give acid **32**, which after a two-step sequence yielded thiopyridyl ester **33** (Scheme 1.7a).[63-65] Subsequent deprotection and trapping of the enolate led to ketene acetal

15c. Model aldehyde **36** was prepared though Grignard addition and protection followed by ozonolysis (Scheme 1.7b).

Screening known TMAL conditions employing $ZnCl_2$ or $SnCl_4$ were unsuccessful (Scheme 1.8). Alternative reagents (*e.g.* $CeCl_3$, $GaCl_3$, $SmCl_3$, $PrCl_3$, $NdCl_3$, and Cy_2BCl) provided either no reaction or only aldol products.[66-70] After extensive efforts in our group, *anti*, *cis*-γ-substituted β-lactones remain challenging stereochemical arrangements to prepare via the TMAL process.

Scheme 1.8. Attempted TMAL Reactions with α-Silyloxy Aldehydes to Access *Anti*, *Cis*-γ-Substituted β-Lactones



1.5 Dichloroolefin Cross Couplings

1.5.1 Known Methods Prior to Development

Cross coupling of a 1,1-dichloroolefin **12** was envisioned to install the vinyl chloride present in the macrolactone ring of haterumalide NA. Cross coupling with 1,1-dichloroalkenes had only minimal precedent at the onset of our studies (Scheme 1.7a).[41] Although significant advancements have been made toward the stereoselective preparation of trisubstituted alkenes under mild reaction conditions, efforts have been focused on the use of bromo[71] and iodo[72] alkenes. A *trans*-selective cross coupling to provide trisubstituted chlorinated alkenes remained a challenge; however, the presence of these moieties in natural products provoked further method development as we

envisioned a metal catalyzed preparation of vinyl chlorides from a *trans*-selective cross coupling between a 1,1-dichloroolefin and an appropriate nucleophile. Vinyl chloride moieties are present in natural products such as the aurantosides (*e.g.* aurantoside A **38**),[73] pinnaic acid **39**, tauropinnaic acid **40**,[74] halichlorine **41**,[75] haterumalides[20,24] (*e.g.* haterumalide NA/A **1a**, our methodology inspiration), and biselides[22,23] (*e.g.* biselide A **2a**) (Figure 1.5).

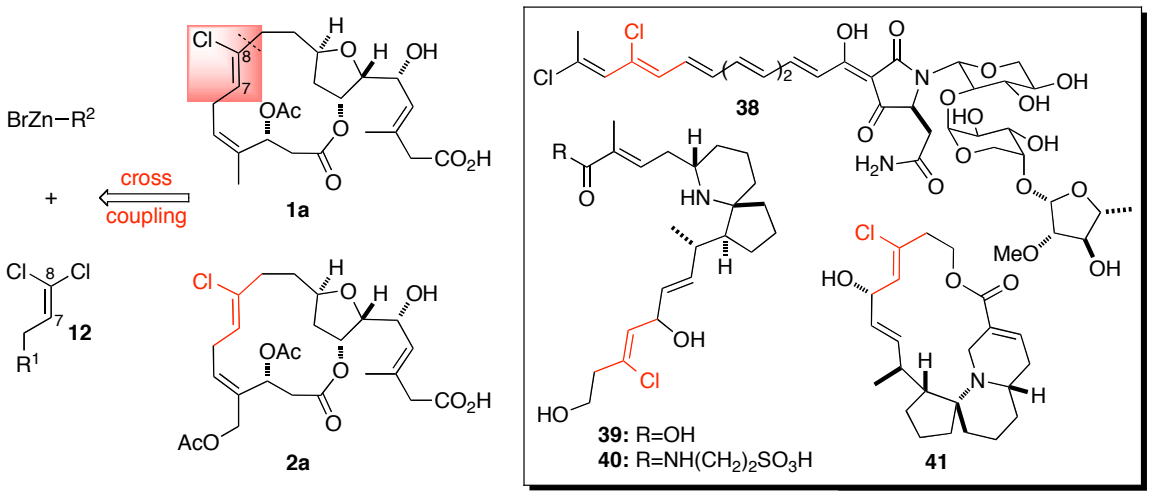


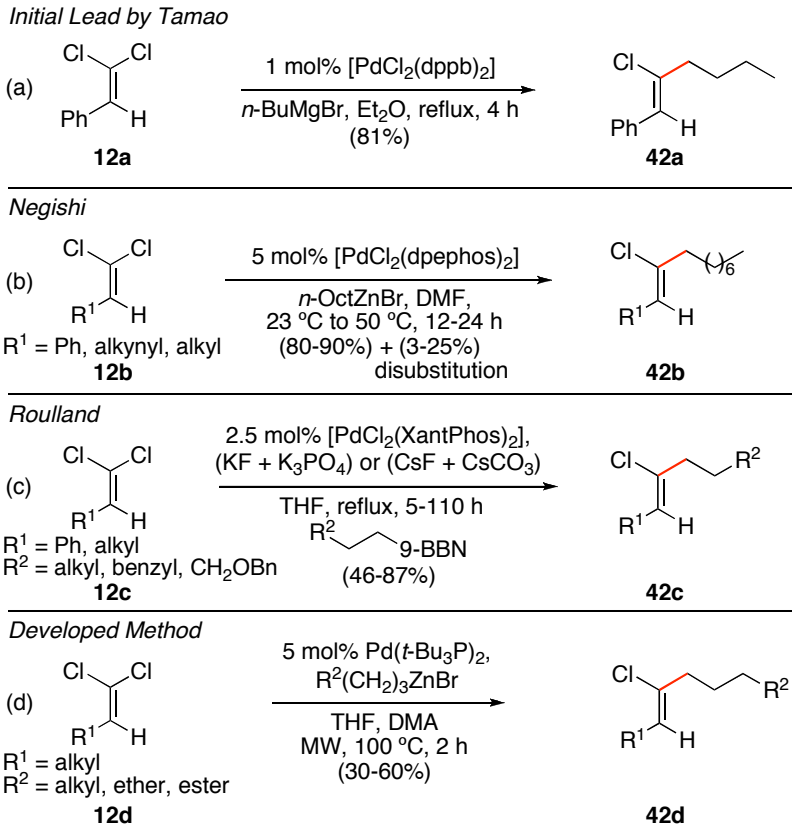
Figure 1.5. Structures of natural products containing a trisubstituted vinyl chloride and synthetic strategy.

1.5.2 Review of Known Methods to Date

Recent advancements in palladium catalysis have enabled applications of cross coupling to a variety of challenging substrates.[76,77] During our initial exploration, Negishi reported his investigations in this area and demonstrated a profound effect of catalyst bite angle and selectivity for monoalkylation **42b** over competitive disubstitution (Scheme 1.9b).[78] The palladium catalyst, $PdCl_2$(dpephos) (dpephos = oxydiphenyl-2,1-phenylene bis(diphenylphosphine), provided good yields of the monosubstituted products **42b** in

conjunction with minor amounts of disubstituted products. Ensuingly, Roulland reported use of a *trans*-selective coupling between 1,1-dichloroalkenes **12c** and alkyl boranes thus expanding the substrate scope to include oxygenated substituents to solely provide monosubstitution **42c**, and this methodology was applied in the complex setting of natural product synthesis (Scheme 1.9c).[35,79] Use of $PdCl_2$(xantphos) (xantphos = 9,9-dimethyl-4,5-bis-(diphenylphosphino)xanthene, possessing an even larger bite angle, suppressed the disubstitution pathway.

Scheme 1.9. Overview of Cross Coupling with 1,1-Dichloroolefins



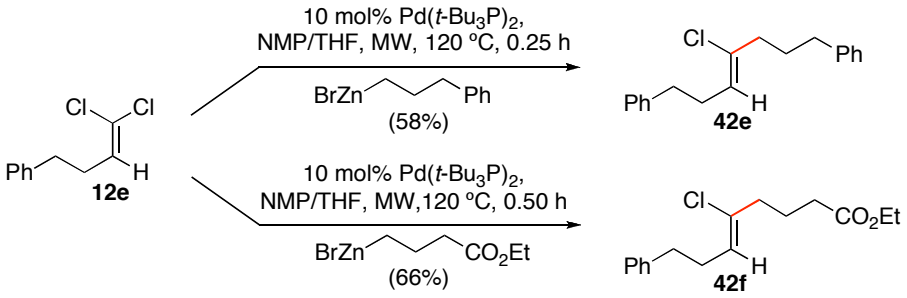
1.5.3 Scope of Modified Negishi Cross Coupling

Herein, we report the stereoselective preparation of (*Z*)-chlorodialkyl alkenes **42d** by a modified Negishi cross coupling of the corresponding 1,1-dichloroolefin **12d** and

respective zincate. Our approach employs a more sterically constrained catalyst, microwave heating to enhance reaction rates, and mild conditions for zincate generation. With the assortment of electron rich and sterically constrained palladium catalysts available, we decided to investigate *trans*-selective cross couplings utilizing *bis*-(tri-*tert*-butylphosphine) palladium.

Initial screening of 1,4-*bis*-(diphenyphosphino)butane-palladium (II) chloride led to no reaction when alkyl Grignard reagents were used as the coupling partner and the use of alkyl zincates gave only disubstituted products. Employing a more sterically encumbered catalyst such as Pd(*t*-$Bu_3P)_2$ (*bis*-(tri-*tert*-butylphosphine) palladium), known to effect the desired tranformation with aryl chloride substrates,[80] provided the desired monosubstituted product.[81] Microwave heating conditions in the presence of *bis*-(tri-*tert*-butylphosphine) palladium with a 1:1 mixture NMP:THF were applicable to both alkyl and ester containing zincates and gave good yields of monosubstituted products **42e-42f**, respectively (Scheme 1.10).

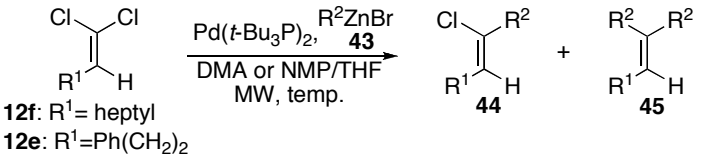
Scheme 1.10. Initial Lead for the Modified Negishi Cross Coupling



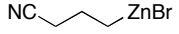
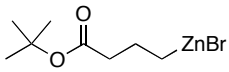
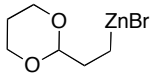
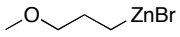
Since the conditions required use of a zincate, a mild preparation for zincate generation was pursued. Mild reaction conditions were reported by Knochel for formation of zincates in the presence of DMA (*N*,*N*-dimethylacetamide) and were thus

explored in subsequent reactions.[82-84] Coupling proceeded in DMA (*N*,*N*-dimethylacetamide) with heteroatom substituted zincates **43a-43d** to deliver only monosubstituted products **44a-44d** in moderate yields (Table 1.1, entries 1-4). However when unfuntionalized zincates or those with large protecting groups (*i.e*. TBDPS) were utilized, the coupling did not proceed, although recovery of the 1,1-dichloroolefin was possible suggestive of the need for intramolecular complexation of the zincate with pendant Lewis basic functional groups. Prior distillation of DMA from BaO was also found to be required since <100 ppm of water led to significantly lowered conversion.[85]

Table 1.1. Modified Negishi Cross Couplings of 1,1-Dichloroolefins in DMA or NMP



12f: R^1= heptyl
12e: R^1=$Ph(CH_2)_2$

entry	R^1	R^2ZnBr	method[a]	**44**:**45**[b]	%yield[c]
1	**12f**	 **43a**	A	>19:1	52
2	**12e**	 **43b**	A	>19:1	60
			B	>19:1	39
3	**12f**	 **43c**	A	>19:1	39
4	**12e**	 **43d**	A	>19:1	40
5	**12e**	$H_{17}C_8-ZnBr$ **43e**	B	>19:1	38[b,d]

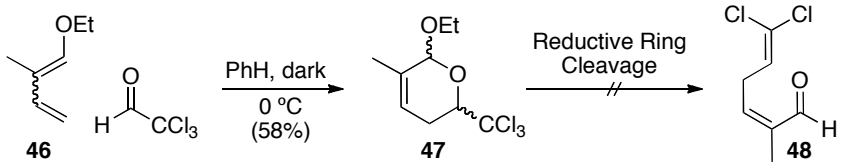
[a] Method A: Reaction conducted in 1:1 DMA/THF under MW irradiation for 5 h at 100 ºC. Method B: Reaction conducted in 1:1 NMP/THF under MW irradiation for 0.5 h at 80 ºC. [b] Ratios were determined by ^{1}H NMR analysis (integration) of the crude reaction mixtures. [c] Refers to isolated yield. [d] Reaction run for 3 h.

The strict anhydrous conditions required for coupling in DMA led us to reexamine some of our initial leads. Coupling reactions conducted in commercially

available anhydrous NMP (1-methyl-2-pyrrolidinone) also afforded the coupled products in moderate yields (Table 1.1, entries 2 and 5).[86] Employing NMP as the solvent significantly decreased the reaction time and temperature, and the optimal reaction conditions required microwave heating at 80°C for 0.5 h. These reaction conditions repeatedly provided the monosubstituted products **44b** and **44e** while also expanded the substrate scope to include unfunctionalized zincates (Table 1.1, entries 2 and 5). Thus providing more practical cross coupling reaction conditions with NMP, which utilized a commercially available catalyst and solvent while maintaining tolerable anhydrous conditions.

As we sought to apply this methodology, we explored synthetic routes toward the skipped diene of haterumalide NA. Our first route to the skipped diene involved a hetero-Diels-Alder reaction between known diene **46** and chloral which proceeded to give the desired dihydropyran **47** as an inconsequential mixture of diastereomers (Scheme 1.11).[87,88] Unfortunately, after extensive efforts only complete isomerization of the alkene was observed.

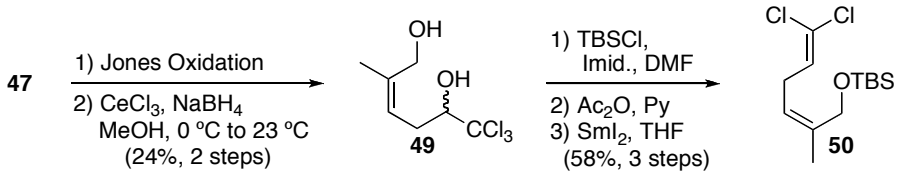
Scheme 1.11. Attempted Synthesis of the Skipped Diene of Haterumalide NA



Due to the difficulties encountered in attempting to prepare 1,1-dichloroolefin **48**, an alternative strategy was pursued.[89,90] After functional group manipulation, diol **49** was obtained (Scheme 1.12).[91,92] Finally, 1,1-dichloroalkene **50** was prepared upon reductive

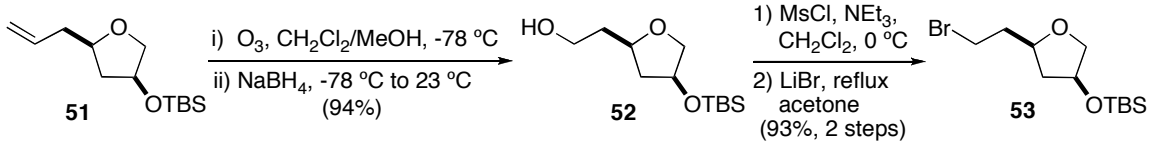
fragmentation after protection and acylation, and a similar proceeding was applied in the context of natural product synthesis.[35]

Scheme 1.12. Synthesis of the Skipped Diene of Haterumalide NA



We then constructed a suitable model-coupling partner. This synthesis began with L-malic acid by initial conversion to known alkene **51** (Scheme 1.13).[54,61,62] Alkene **51** was converted to alcohol **52** via reductive ozonolysis, and the resulting primary alcohol **52** was converted to the corresponding bromide **53** by displacement of the mesylate. This process delivered tetrahydrofuran **53** in excellent yield as a single diastereomer.

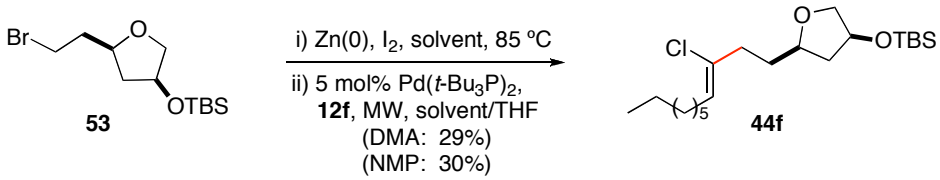
Scheme 1.13. Synthesis of Model Tetrahydrofuran



With both the skipped diene **50** and the model tetrahydrofuran fragment **53** in hand, we initiated tests for more coupling reactions in a more complex setting (Scheme 1.14). Conversion of bromide **53** to the corresponding zincate and subsequent coupling with model dichloroolefin **41e** using our standard protocol in DMA or NMP gave the monosubstituted product **54** in 29% and 30% yield, respectively. Next, the bromide **53** was converted to the zincate and subjected to coupling conditions with skipped diene **50**.

Unfortunately, none of the desired product was obtained. Trace amounts of *β*-eliminated product derived from bromide **53** were observed along with recovered starting material (not shown). This reaction was run on smaller scale, and the high moisture sensitivity also presumably led to diminished yields. Despite use of a large excess of zincate no coupled product was isolated and we concluded that this methodology was not directly applicable to the HatNA synthesis

Scheme 1.14. Model Coupling toward Haterumalide NA



In summary, our modified Negishi cross coupling method offers a strategy for the highly selective palladium catalyzed coupling of 1,1-dichloroalkenes with both heteroatom-substituted and unfunctionalized zincates in moderate yields using commercially available catalyst and solvent. We have also demonstrated a route to the skipped diene of haterumalide NA. Significant progress has recently been made with 1,1-dichloroolefin couplings, but limitations of substrate compatibility remain a challenge with our developed reaction conditions.

1.6 Spiroepoxy-*β*-Lactone Approach

The difficulty in accessing the *anti*, *cis*-*γ*-substituted *β*-lactone **9** with the TMAL process required us to reconsider alternative strategies including regioselective C-O bond cleavage at the desired reaction site of the corresponding spiroepoxy-*cis*-*β*-lactone **10**, a

strained ring system heretofore unknown (Figures 1.6 and 1.7).[93] We envisioned the dioxaspiro[2.3]hexan-5-one ring system (spiroepoxy-*β*-lactone **10**) coming from oxidation of the corresponding optically active ketene dimer **58**, which may undergo regioselective ring opening at the anomeric carbon followed by facially selective reduction to deliver *anti*, *cis*-*γ*-substituted *β*-lactone **9** (Scheme 1.15).[94-97]

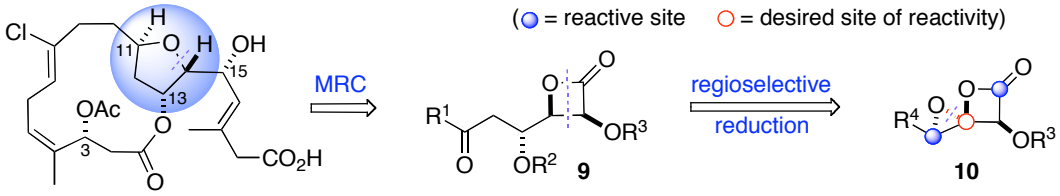


Figure 1.6. Retrosynthetic strategy revealing spiroepoxy-*cis*-*β*-lactones and their reactivity patterns.

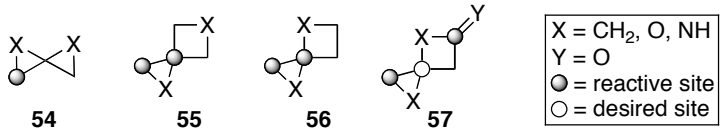
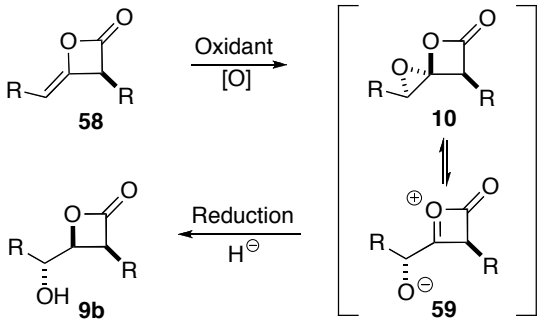


Figure 1.7. Known small, spiroheterocyclic ring systems

Indeed the spiroepoxy-*β*-lactone could be accessed by oxidation of the ketene dimer upon exposure to dimethyldioxirane (DMDO) (Scheme 1.16).[98] A variety of ketene dimers were converted to the corresponding spiroepoxy-*cis*-*β*-lactones **10** in moderate to good yield with excellent diastereoselective control (dr 10:1 to 24:1) as a result of the incoming oxidant adding opposite to the alkene to avoid steric interactions (*cis/trans* refers to the *β*-lactone stereocenters). What was unexpected was the fact that these novel compounds were isolable and in most cases could be purified by typical

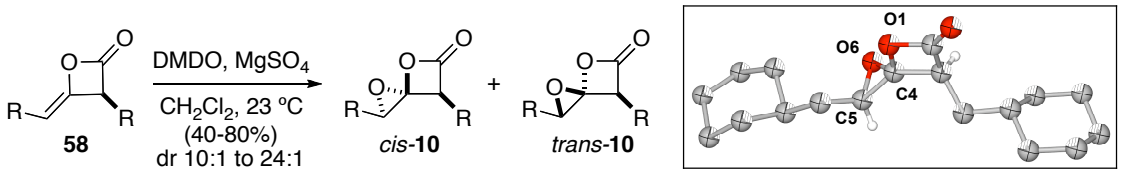
chromatography. However, spiroepoxy-*β*-lactones were typically generated and used within a week, but the shelf life could be extended by proper storage procedures. X-ray analysis was obtained for the cyclohexyl substituted spiroepoxy-*cis*-*β*-lactone **10a**, and displayed unique bond characteristics (Scheme 1.6, ORTEP plot, inset).

Scheme 1.15. Homoketene Dimer Epoxidation and Proposed Oxocarbenium Reduction



Scheme 1.16. Epoxidation of Ketene Dimers to Spiroepoxy-*β*-Lactones

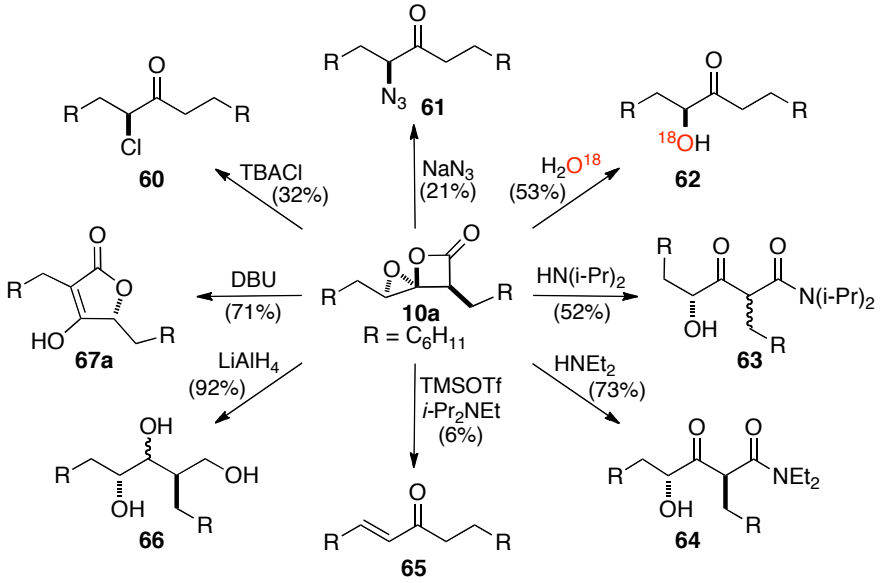
(ORTEP Plot of Spiroepoxy-*Cis*-*β*-Lactone **10a**, inset)



Only two of four possible expected modes of reactivity for the spiroepoxy-*β*-lactone systems were observed in conjuction with products formed from unanticipated reaction pathways. Nucleophilic additions provided *α*-substituted ketones **60-62**, and the proposed addition to the C5-O6 bond was confirmed by a heavy water experiment (Scheme 1.17).[98,99] The strained system **10a** was completely unraveled to amides **63-64** upon exposure to secondary amines, and reduced to triol **66** by lithium aluminum

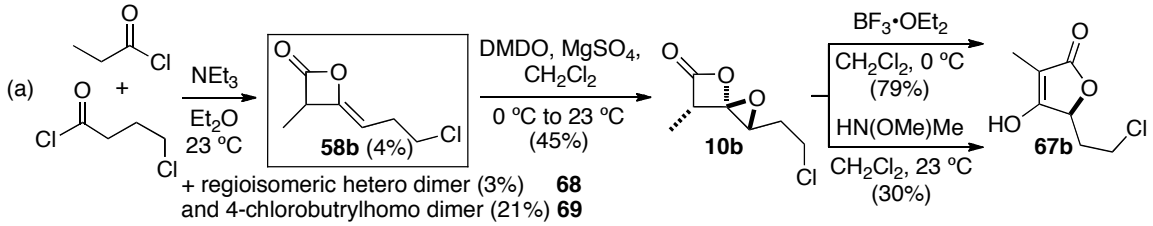
hydride. Reaction with a silyl triflate and base led to minor amounts of enone **65** arising presumably from α-deprotonation of the epoxide. Tetronic acid **67** was surprisingly obtained upon subjection to a less nucleophilic base such as DBU.

Scheme 1.17. Reaction of Spiroepoxy-β-Lactones



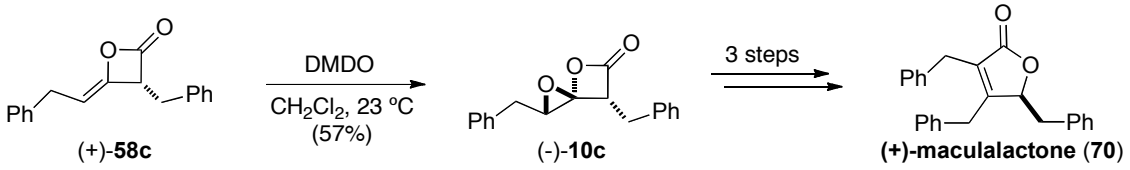
As our interest was in applying a spiroepoxy-*cis*-β-lactone derived from a heteroketene dimer towards the synthesis of haterumalide NA, heteroketene dimerization and epoxidation were briefly explored (Scheme 1.18).[100] Heteroketene dimer **58b** was formed as part of a statistical mixture of dimers formed from a mixture of propionyl chloride and 4-chlorobutyryl chloride, and the heteroketene dimer underwent epoxidation to spiroepoxy-*cis*-β-lactone **10b**. Spiroepoxy-β-lactone **10b** derived from the heteroketene dimer **58b** reacted in a similar fashion to other spiroepoxy-β-lactones. However, spiroepoxy-β-lactones were found to have a high propensity to rearrange to the corresponding tetronic acid derivative. Lewis acids easily effected the rearrangement and gave good yields of tetronic acid **67**.

Scheme 1.18. Rearrangement of Spiroepoxy-β-Lactones to Tetronic Acids



The rearrangement occurred with retention of stereochemistry as confirmed by the total synthesis of (+)-maculalactone A, a natural product with antifouling activity (Scheme 1.19).[99] Ketene dimerization with *O*-TMSQN provided the enantioenriched hydrocinnamyl derived ketene dimer **58c**. Epoxidation gave spiroepoxy-*cis*-β-lactone **10c** in 57% yield as single diastereomer after purification. The tetronic acid was easily formed, and the relative and absolute stereochemistries were determined by X-ray analysis and Mosher ester derivatives, respectively. The synthesis of (+)-maculalactone A (**70**) was completed upon triflate formation and subsequent cuprate addition/elimination.[101]

Scheme 1.19. Total Synthesis of Maculalactone A



Spiroepoxy-β-lactones displayed varying modes of reactivity and have a high propensity to rearrange to tetronic acids. The rearrangement was exploited in a small molecule synthesis. After extensive efforts, the *anti, cis*-γ-substituted β-lactone **9**

remained inaccessible and again redirected our strategy to alternative method development.

1.7 Nucleophile Catalyzed, Aldol Lactonization Strategy

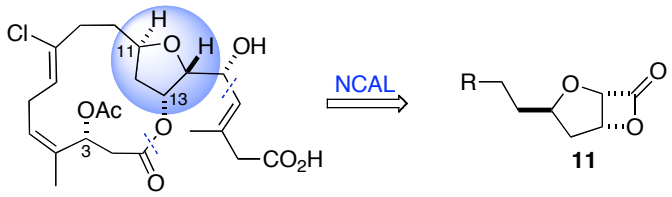
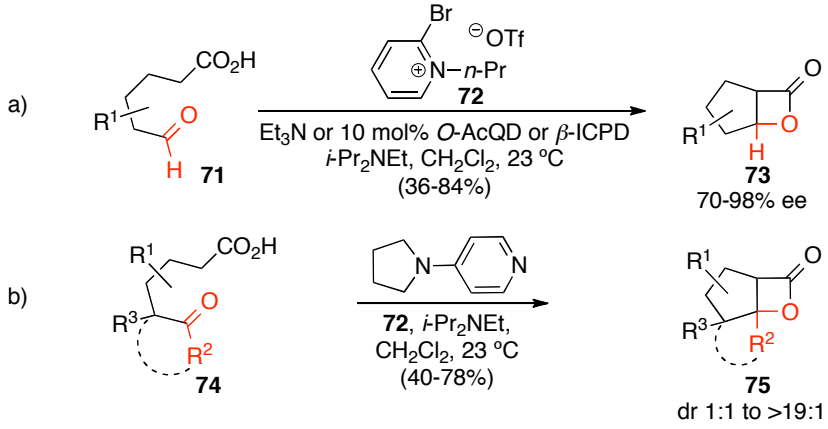


Figure 1.8. Retrosynthetic strategy utilizing tetrahydrofuran-fused *β*-lactones.

Our efforts toward the haterumalides, led us to explore the nucleophile catalyzed, aldol-lactonization (NCAL) process for the synthesis of dioxabicyclo[3.2.0]heptanones (tetrahydrofuran-fused *β*-lactones *e.g.* **11**) to access the tetrahydrofuran found in these natural products and also extend the scope of the NCAL methodology (Figure 1.8). The NCAL process provides convenient access to enantioenriched carbocycle-fused *β*-lactones bearing one two or more stereocenters. [102-104] Use of aldehyde acids **71** in the NCAL provides products with excellent enantioselectivity by employing *cinchona* alkaloid derived catalysts, which have been widely utilized for organ catalysis (Scheme 1.20a).[105] The substrate scope has been expanded to include keto acids **74** with the use of a stronger nucleophilic promoter such as 4-pyrollidinopyridine,[104] and an enantioselective variant was realized with the use of tetramisole (Scheme 1.20b).[106,107] Application to heteroatom containing bicyclic products was achieved in the synthesis of salinosporamide A,[108] yet further extension to tetrahydrofuran-fused *β*-lactones remained undescribed.

At the beginning of our studies, there was a sole report by Crich and Hao documenting formation of isolable tetrahydrofuran-fused *β*-lactones.[109] The NCAL process indeed furnished *anti/syn* tetrahyrofuran-fused *β*-lactones **11a-11f** in modest

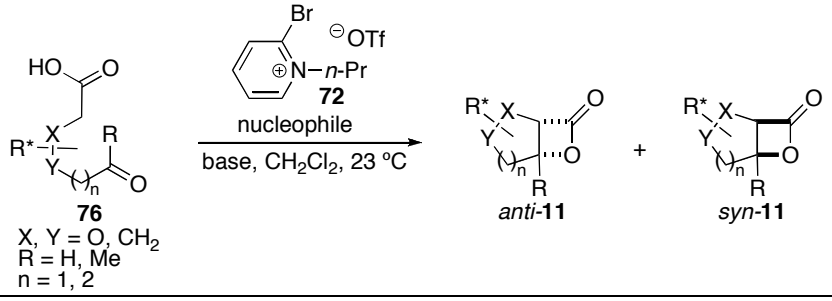
Scheme 1.20. NCAL Process with (a) Aldehyde Acids and (b) Keto Acids

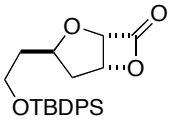
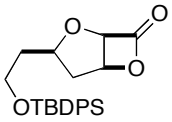
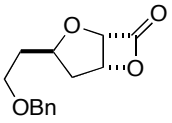
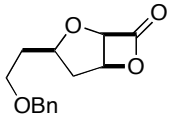
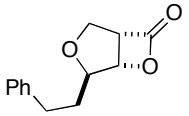
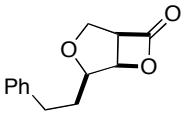
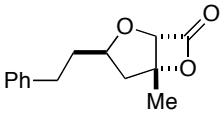
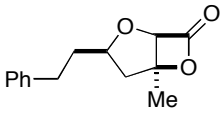
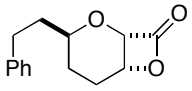
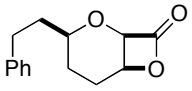
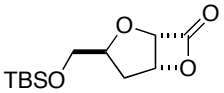
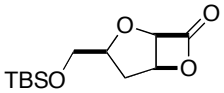


yields with low diastereoselectivities (*anti/syn* refers to the stereogenic relationship of the tetrahydrofuran stereocenters) (Table 1.2).[68] Tetrahyrofuran-fused *β*-lactones **11a-11b** and **11f** were of particular interest in our studies toward the haterumalides and laurefucin, respectively (Table 1.2, entries 1-2, 5).

In order to overcome the inherent low diastereoselectivity exhibited with tetrahyrofuran-fused *β*-lactones, we considered a double asymmetric NCAL approach utilizing both an asymmetric nucleophile and an enantioenriched substrate.[40,110,111] The parent carbocycle-fused *β*-lactone systems delivered much more practical yields and were used for development of double diastereoselective NCAL process. In order to access these systems with greater diastereoselective control, enantioenriched substrates **71** were prepared through Noyori hydrogenation,[18] asymmetric deprotonation of a substituted cyclohexanone,[112] or HKR of a terminal epoxide[13] with subsequent elaboration. After screening a variety of *cinchona* alkaloid derivatives, *O*-TMS quinidine (*O*-TMSQD) and *O*-TMS quinine (*O*-TMSQN) emerged as the most promising nucleophilic catalysts. *β*-lactones **73** containing *β*-substitution with respect to the acid gave high diastereoselective control (dr >19:1, *anti*-*β*-lactone **73**) in accord to our previous findings (*anti/syn* refers to

Table 1.2. Synthesis of Tetrahydrofuran-Fused *β*-Lactones



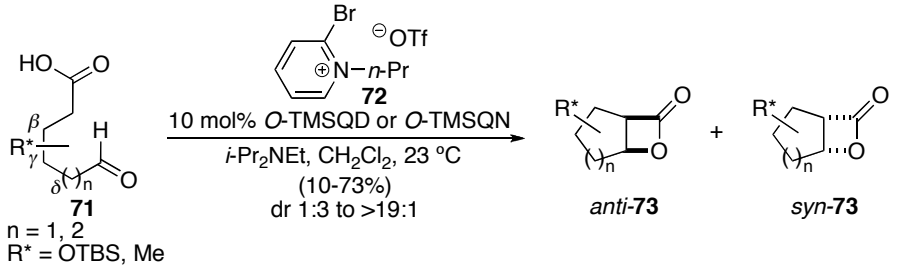
entry	tetrahydrofuran bicyclic *β*-lactones		% yield (dr)[a]
1[b]	 *anti*-**11a**	 *syn*-**11a**	25[c] (1:1)
2[b]	 *anti*-**11b**	 *syn*-**11b**	35[c] (2:1)
3[b]	 *anti*-**11c**	 *syn*-**11c**	31[c] (2:1)
4[b]	 *anti*-**11d**	 *syn*-**11d**	54[d] (1:1)
5	 *anti*-**11e**	 *syn*-**11e**	26[c] (>19:1)
6	 *anti*-**11f**	 *syn*-**11f**	17[c] (4:1)

[a] Diastereomeric ratios were determined by ^{1}H NMR (500 MHz) analysis (integration) of the crude reaction mixtures. [b] Prepared with racemic starting material. [c] Et_3N was used as both the nucleophile and base. [d] PPY was used as the nucleophile and *i*-Pr_2NEt as base.

the stereochemistry of the carbocycle substituent with respect to the *β*-lactone) (Scheme 1.21).[102,113] The inherent substrate bias exhibited by *γ*-substitution in *anti/syn* carbocycle-fused *β*-lactones **73** was overridden with *O*-TMSQD and *O*-TMSQN and improved the diastereoselectivity (dr 1:7 to >19:1). Both the relative and absolute stereochemistries

were confirmed by X-ray analysis. Substrates possessing δ-substituents also gave good diastereoselectivity. Although the *anti/syn* cyclohexane-fused β-lactones were only formed in modest yields, the diastereoselectivity could be completely reversed (dr 1:>19 to >19:1).

Scheme 1.21. Double Asymmetric NCAL Process to Carbocycle-Fused β-Lactones

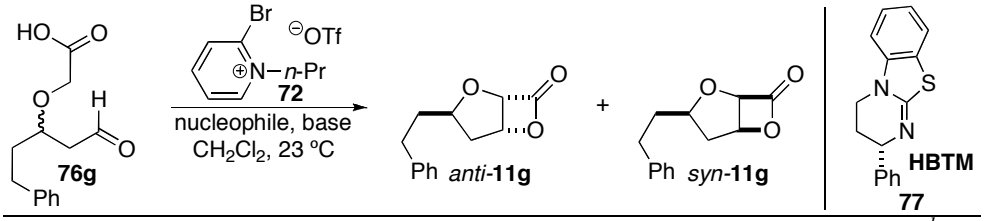


The conditions developed for a double diastereoselective NCAL process with carbocycle-fused β-lactones were not directly applicable to tetrahydrofuran-fused β-lactones (Table 1.3, entry 2). Therefore, racemic aldehyde acid **76g** was used due to greater availability and in order to test the degree of reagent control. The enhanced nucleophilicity of homobenzotetramisole **77** (HBTM), a tetramisole catalyst derivative developed by Birman as an asymmetric acylation catalyst, provided up to 78% enantiomeric excess albeit in modest yield (Table 1.3, entry 3). Although application of enantioenriched **76g** did not lead to a significant improvement in the diastereoselectivity, a marked solvent effect leading to improvement in the diastereoselectivity up to 7:1 (Table 1.3, entry 4). Enhancement in the diastereoselectivity was observed, yet it is plausible that the optimization was performed on the substrate leading to a mismatched case. However, the consistently low yields obtained deterred further investigations.

Double asymmetric synthesis was applied to both carbocycle-fused β-lactones and tetrahydrofuran-fused β-lactones (Scheme 1.22). Carbocycle-fused β-lactone

diastereoselectivities were improved from 1:1-2 to >19:1. Direct application of the asymmetric *cinchona* alkaloid catalysts used for carbocycles was not feasible to tetrahydrofurans. Instead, homobenzotetramisole provided excellent enantioselectivity, and somewhat increased diastereoselectivity was obtained when using toluene as a co-solvent albeit in modest yield. The *cinchona* alkaloids were able override the inherent substrate bias and in some cases reverse the diastereoselectivity of the NCAL process thus affording a double diastereoselective NCAL process.

Table 1.3. Double Asymmetric NCAL Process to Tetrahydrofuran-Fused β-Lactones



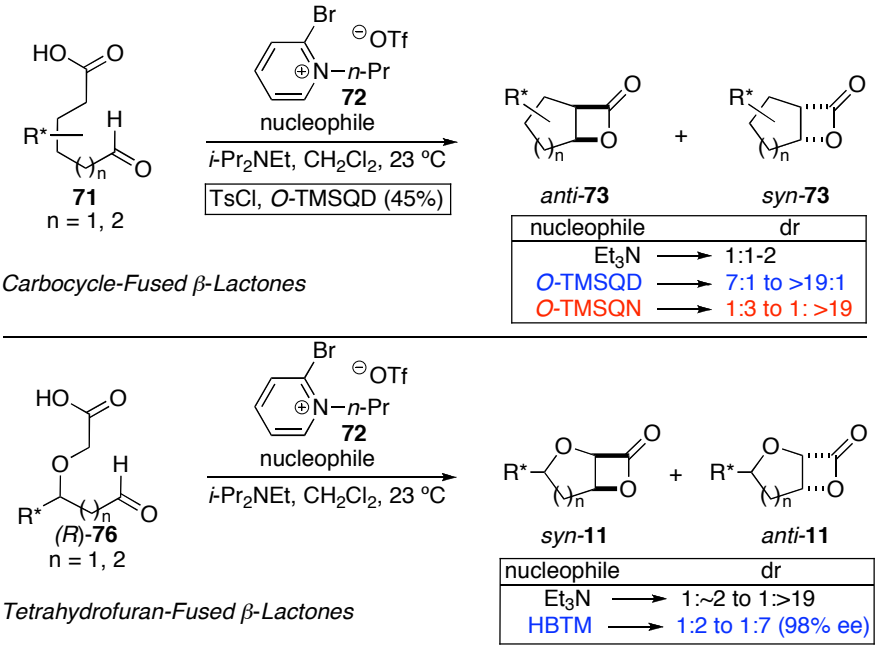
entry	nucleophile[a]	% yield	dr (*anti:syn*)	% ee[b]
1[c]	NEt_3[d]	47	1:1	—
2[c]	HBTM	30	2:1	78
3[e,f]	HBTM	22	7:1	98

[a] Reactions run with *i*-Pr_2NEt as base at 0.5 M. [b] Enantiomeric excess of major diastereomer. [c] (±)-Aldehyde acid was used. [d] Et_3N used as both base and nucleophile. [e] Reaction run with a 1:1 solvent mixture of CH_2Cl_2:toluene. [f] Used enantioenriched **76g**.

1.8 Conclusions

Natural product diversity continues to serve as a rich source for application and inspiration for novel methodology development. The haterumalides captivated our attention, as a muse, which in turn sparked our creativity and culminated in the development of four differing methods. A cascade, three-component TMAL-MRC converts simple ketoaldehydes and ketene acetals to tetrahydrofurans bearing up to four stereogenic centers and even formation of a quaternary carbon center. Reacting 1,1-dichloroolefins in conjunction with a zincate in the modified Negishi cross coupling led

Scheme 1.22. Overview of Double Asymmetric NCAL Process



to *trans*-trisubstituted alkenes containing a chlorine atom, and similar strategies were in fact applied in total syntheses of haterumalide NA. Highly strained spiroepoxy-β-lactones were unexpectedly stable isolable products that displayed varying modes of reactivity. The innate propensity for conversion of spiroepoxy-β-lactones to tetronic acids was utilized in the total synthesis of (+)-maculalactone A. Our interest in the synthesis of tetrahydrofuran-fused β-lactones led to studies of a double diastereoselective NCAL process in order to circumvent the inherent substrate bias exerted upon formation of bicyclic β-lactones, which was found to be highly successful with carbocycle-fused-β-lactones. The rich informational content of natural products continue to captivate chemists as demonstrated herein, and surely these genetically-encoded small molecules will continue to serve as a vast wealth of inspiration for developing novel of synthetic methodology in the future.

CHAPTER II

UTILITY OF SPIROEXPOXY-*β*-LACTONES*

2.1 Retrosynthesis of Haterumalide NA

Our initial route to haterumalide NA utilized a tandem Mukaiyama aldol-lactonization (TMAL)[46,47] process known to provide access to either *cis*[46] or *trans*[47] *β*-lactones and subsequent Mead reductive cyclization (MRC)[52] to the desired tetrahyrofuran moiety.[55,57,58] The revision in the absolute stereochemistry for the target in conjunction with unfruitful efforts toward the preparation of an *anti*, *cis*-*γ*-substituted *β*-lactone **9** with the TMAL process redirected our strategy. Our keen interest in *β*-lactone method development and their synthetic applications focused efforts on formation of the requisite *anti*, *cis*-*γ*-substituted *β*-lactone **9** by a regioselective reduction of the highlighted epoxide C-O bond in spiroepoxy-*cis*-*β*-lactone **10**, which upon subsequent Mead reductive cyclization would deliver the tetrahydrofuran ring of haterumalide NA (Figure 2.1).

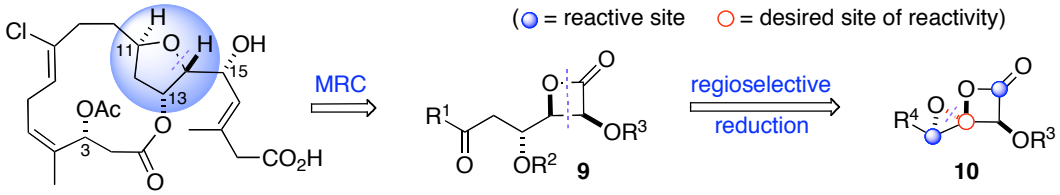


Figure 2.1. Retrosynthetic strategy revealing spiroepoxy-*cis*-*β*-lactones.

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*Part of the data reported in this chapter is reproduced with permission from "Synthesis, Structure, and Reactivity of Unexpectedly Stable Spiroepoxy-*β*-Lactones Obtained by Epoxidation of 4-Alkylidene-2-Oxetanones" by Duffy, R. J.; Morris, K. A.; Romo, D. *J. Am. Chem. Soc.* **2005**, *127*, 16754-16755. Copyright 2005 American Chemical Society and from "Asymmetric Synthesis, Structure, and Reactivity of Unexpectedly Stable Spiroepoxy-***β***-Lactones Including Facile Conversion to Tetronic Acids: Application to (+)-Maculalactone A" by Duffy, R. J.; Morris, K. A.; Vallakati, R.; Zhang, W.; Romo, D. *J. Org. Chem.* **2009**, *74*, 4722-4781. Copyright 2009 American Chemical Society See Appendix D.

2.2 Potential Reactivity

Of four possible predicted modes of reactivity, only two pathways were observed with attack predominating at the ether and ester carbon centers **10d** (Figure 2.2).[98] A detailed review of these systems along with other highly strained spirocycles was recently disclosed.[93] Although extensive screening did not lead to any desired regioselective reductive ring opening, unexpected reaction pathways were discovered.[99]

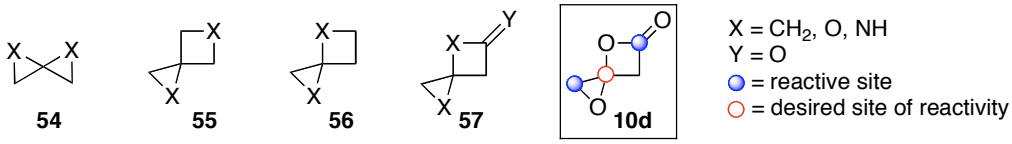
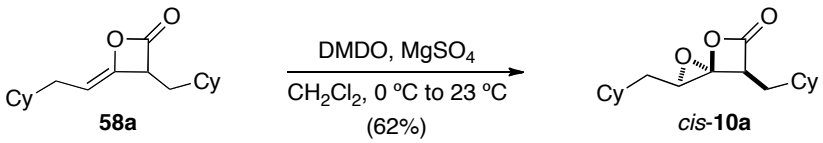


Figure 2.2. Summary of known spirocycles and reactive sites of spiroepoxy-*β*-lactones.

2.3 Discovered Reaction Manifolds

Studies on structure elucidation, preparation and exploration of reactivity patterns set forth by Dr. Richard Duffy for spiroepoxy-*β*-lactones **10** laid the foundation for further studies regarding reactivity and scope for these spirocycles (*vide supra*).[98,99,114] Spiroepoxy-*cis*-*β*-lactone **10a** was prepared from epoxidation of the corresponding ketene dimer **58a** with dimethyldioxirane (DMDO) in accord with procedures developed by Duffy[98] and Calter,[97] respectively (Scheme 2.1).

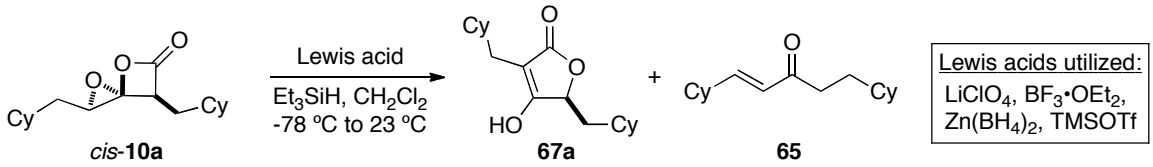
Scheme 2.1. Spiroepoxy-*β*-Lactone Preparation



Extensive efforts made by Duffy to effect the desired regioselective reduction were unsuccessful. Further studies of the spiroepoxy-*cis*-*β*-lactone **10a** with Lewis acids[115-117]

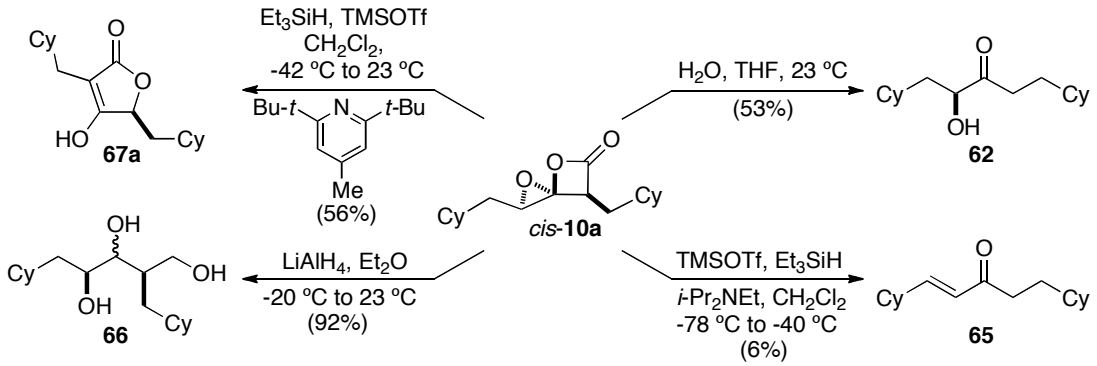
only gave rise to enone **65**, tetronic acid **67a**, or complex mixtures of products (Scheme 2.2). Duffy had previously observed both base and Lewis acid induced formation of tetronic acid **67a** occurring through rearrangement of the spiroepoxy-β-lactone system. However, enone **65** arose from an unanticipated reaction pathway.

Scheme 2.2. Attempted Regioselective Ring Opening



A variety of conditions were explored in order to investigate alternate reactivity of spiroepoxy-*cis*-β-lactone **10a** further (Scheme 2.3). Water incorporated into the spiroepoxy-β-lactone framework to afford α-hydroxy substituted ketone **62**. Enone **65** was produced, albeit in low yield, when TMSOTf was used as a Lewis acid in conjunction *N*,*N*-diisopropylethylamine.[118] Alternatively, TMSOTf and 2,6-di-*tert*-butyl-4-methyl pyridine gave moderate yields of tetronic acid **67a**. Spiroepoxy-*cis*-β-lactone **10a** could, however, be completely reduced by reaction with lithium aluminum hydride.

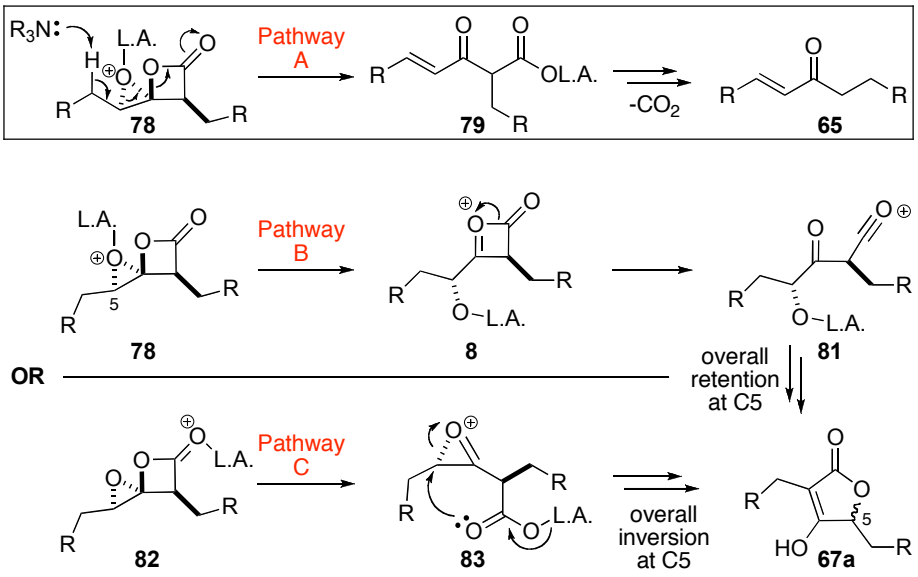
Scheme 2.3. Discovered Modes of Reactivity



Reactions with TMSOTf presumably proceed through a transient silylated epoxide **78** (Pathway A and B) or silylated β-lactone **82** (Pathway C) (Scheme 2.4). Enhanced sterics

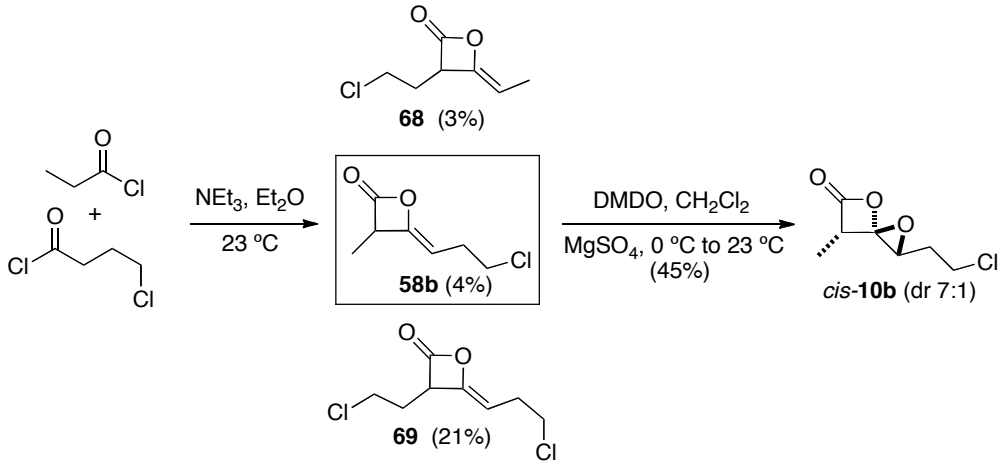
of the base can obviate the deprotonation pathway and subsequent decarboxylation to enone **65** (Pathway A) to give tetronic acid **67a** (Pathway B). The high propensity of the spiroepoxy-β-lactones to rearrange to tetronic acids was utilized in the synthesis of (+)-maculalactone A, which also provided evidence for intermediacy of a silylated epoxide **82** as the rearrangement was found to proceed with retention of stereochemistry at C5.[99]

Scheme 2.4. Possible Reaction Pathways to Enone **65** and Tetronic Acid **67a**



As our efforts were aimed toward the haterumalides, we sought to apply the methodology of spiroepoxy-β-lactones derived from homoketene dimers to those obtained from heteroketene dimers (Scheme 2.5). Partnering with Mr. Ravikrishna Vallakati, we found that heteroketene dimers **58b, 68-69** could be obtained.[99] The heteroketene dimers were obtained as ~7:1:1 mixture (**69**/**68**/**58b**). Heteroketene dimer **58b** was then further oxidized to provide spiroepoxy-*cis*-β-lactone **10b** with good diastereoselectivity (dr 7:1), which exhibited similar reactivity as other spiroepoxy-β-lactones and could easily be converted to the corresponding tetronic acid derivative as demonstrated by Vallakati.

Scheme 2.5. Epoxidation of Heteroketene Dimer to Spiroepoxy-β-Lactone



2.4 Conclusions

Spiroepoxy-β-lactones were prepared in accord with the procedure developed by Duffy. Spiroepoxy-β-lactones obtained from heteroketene dimers were prepared smoothly, and displayed similar reactivity patterns as the spiroepoxy-β-lactones derived from homoketene dimers. However, the desired reaction manifold to open the spiroepoxy-β-lactone ring system to the *anti, cis*-γ-substituted β-lactone for use towards haterumalide NA remained inaccessible after extensive studies. Unanticipated reaction pathways were discovered, namely rearrangement to tetronic acids and formation of enone products. The facile rearrangement of these systems to tetronic acids culminated in the total synthesis of (+)-maculalactone A.

CHAPTER III

NUCLEOPHILE CATALYZED, ALDOL-LACTONIZATIONS (NCAL) TO β-LACTONE FUSED TETRAHYDROFURANS

3.1 Previous NCAL Studies

The development of concise enantioselective routes to β-lactones continues to be an active area of research due to their varied reactivity and applications.[119-127] Our contributions to this area have focused on an intramolecular, nucleophile catalyzed, aldol-lactonization (NCAL) process of aldehyde acids that provide convenient access to bicyclic β-lactones bearing two or more stereogenic centers building on elegant work by Wynberg and coworkers (Scheme 3.1a).[102-104,128] This strategy was previously rendered enantioselective with the use of *O*-acetyl quinidine (*O*-AcQD) or β-isocupreidine (β-ICPD) as chiral nucleophilic promoters (chiral Lewis bases) to obtain enantioenriched β-lactone fused cyclopentanes **73** (Figure 3.1).[102-105] Silylated *cinchona* alkaloids (*O*-TMSQD and *O*-TMSQN) were used in further applications based on Calter's evidence for greater stability and higher enantioselectivities obtained with the silylated derivatives.[129] The NCAL process, initially inspired by γ-lactam fused β-lactone natural products including omuralide and more recently salinosporamide A, was applied to a concise, bioinspired racemic[108] and subsequently enantioselective[130] total synthesis of the latter natural product. More recently, the NCAL process was extended to keto acid **74** substrates with the use of a stronger nucleophilic promoter, 4-pyrrolidinopyridine (PPY) (Scheme 3.1b).[113] A single example of a stoichiometric, enantioselective reaction was

realized making use of tetramisole.[106,107] Tricyclic *β*-lactones produced from the NCAL method featured novel modes of reactivity demonstrating transformations through stereospecific, dyotropic rearrangements involving 1,2-acyl and *δ*-lactone migrations.[106]

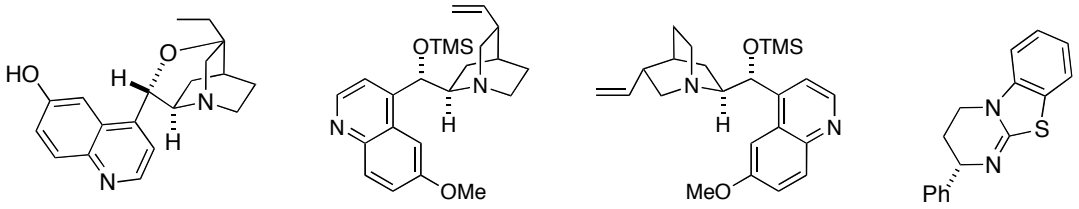
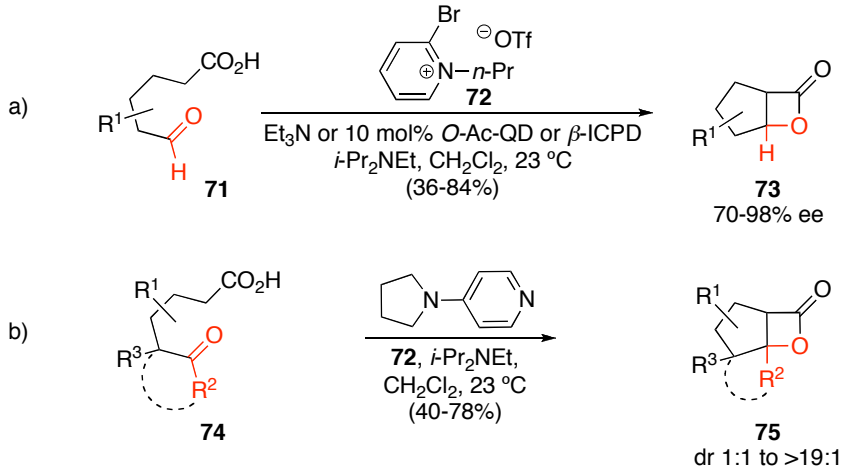


Figure 3.1. Optically active nucleophiles (Lewis bases) employed in NCAL processes.

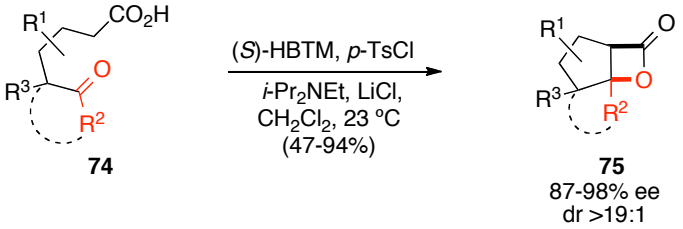
Scheme 3.1. Formation of Bicyclic and Tricyclic β-lactones via the NCAL Process from (a) Aldehyde Acids and (b) Keto Acids



A stronger nucleophilic promoter was required with keto acids **74**, due to the less electrophilic nature of these systems compared to the corresponding aldehyde acid substrates **71** thus initially precluding an enantioselective variant. Most recently

conditions were developed to facilitate a catalytic, asymmetric NCAL process with keto acids **74** (Scheme 3.2).[131] The catalytic, asymmetric NCAL process made use of a commercially available activating agent (*p*-TsCl) and (*S*)-HBTM as a nucleophilic promoter in conjunction with lithium chloride,[132] which presumably promoted the reaction through a cyclic transition state arrangement and ultimately provided a significant increase in yields.[133,134]

Scheme 3.2. Catalytic, Asymmetric NCAL Process with Keto Acids

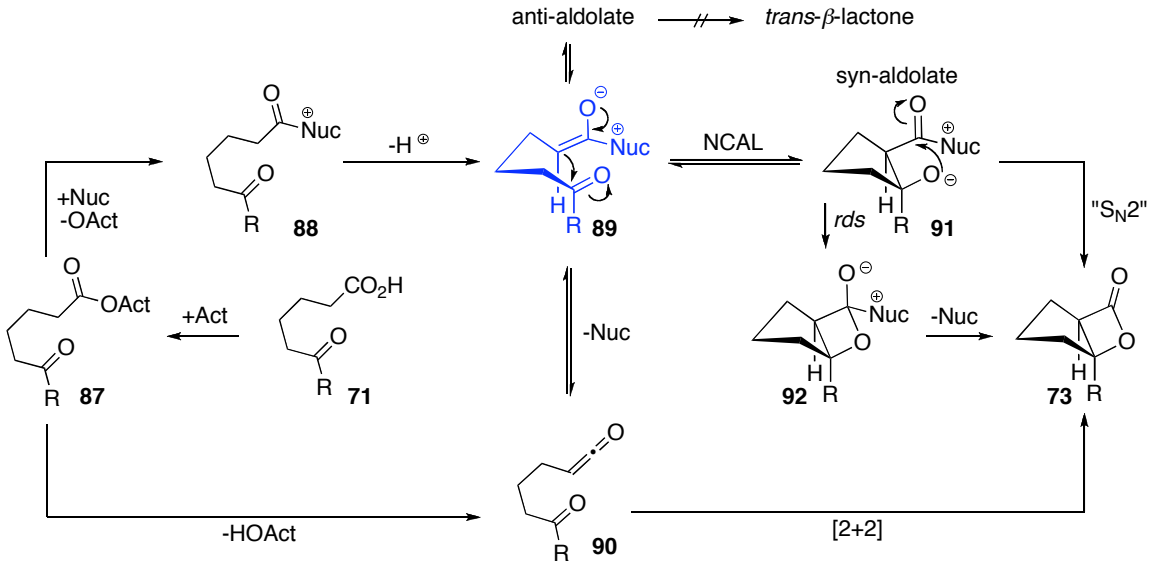


3.2 Proposed Mechanistic Rationale

The NCAL process is thought to proceed by activation of the acid **87** followed by displacement with the nucleophile to provide the corresponding acyl ammonium species **88** (Scheme 3.3).[113] Acylammonium **88** could then undergo deprotonation to give ammonium enolate **89**. The high diastereoselectivity observed for substrates possessing *β*-substituents provided evidence for a NCAL process proceeding through ammonium enolate intermediates based on $A^{1,3}$-strain arguments. Establishment of a rapid thermodynamic equilibration between ammonium enolate **89** and *syn*-aldolate **91** led to ring closure to form zwitterionic intermediate **91**. Subsequent elimination through direct displacement or through a tetrahedral intermediate **92** would deliver *cis*-*β*-lactone **73** in enantioenriched form with the use of an asymmetric nucleophile; however, the *anti*-

aldolate would not proceed to a *trans*-β-lactone due to ring constraints. Alternatively, displacement of the activated acid, acyl ammonium species, or ammonium enolate leads to ketene **90** that can form racemic β-lactones via a [2+2] reaction pathway.

Scheme. 3.3. Working Mechanism for the NCAL Process



3.3 Applications to β-Lactone Fused Tetrahydrofurans

3.3.1 Retrosynthesis of Haterumalide NA

Our initial routes to haterumalide NA focused on formation and utility of an *anti, cis*-γ-substituted β-lactone **9**, which remained elusive from both the TMAL-MRC process as well as from the attempted regioselective reduction of spiroepoxy-β-lactones (*vida supra)*. Our efforts toward the haterumalides, led us to explore the NCAL process for the synthesis of dioxabicyclo[3.2.0]heptanones (tetrahydrofuran-fused β-lactones *e.g.* **11**) to access the required tetrahydrofuran found in these natural products and also extend the scope of the NCAL methodology. Tetrahydrofuran-fused β-lactones were previously reported as isolable products by Crich and Hao via cyclization of the corresponding

hydroxyacid with BOP-Cl to prepare C4'α-carboxylated 2'-deoxynucleoside derivatives.[109] Thus our efforts were redirected toward the preparation and use of tetrahydrofuran-fused β-lactone **11** (Figure 3.2). We envisioned the tetrahydrofuran-fused β-lactone system **11** coming from the NCAL process by subjection of the appropriate aldehyde acid.

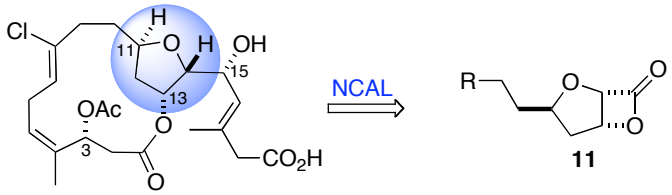
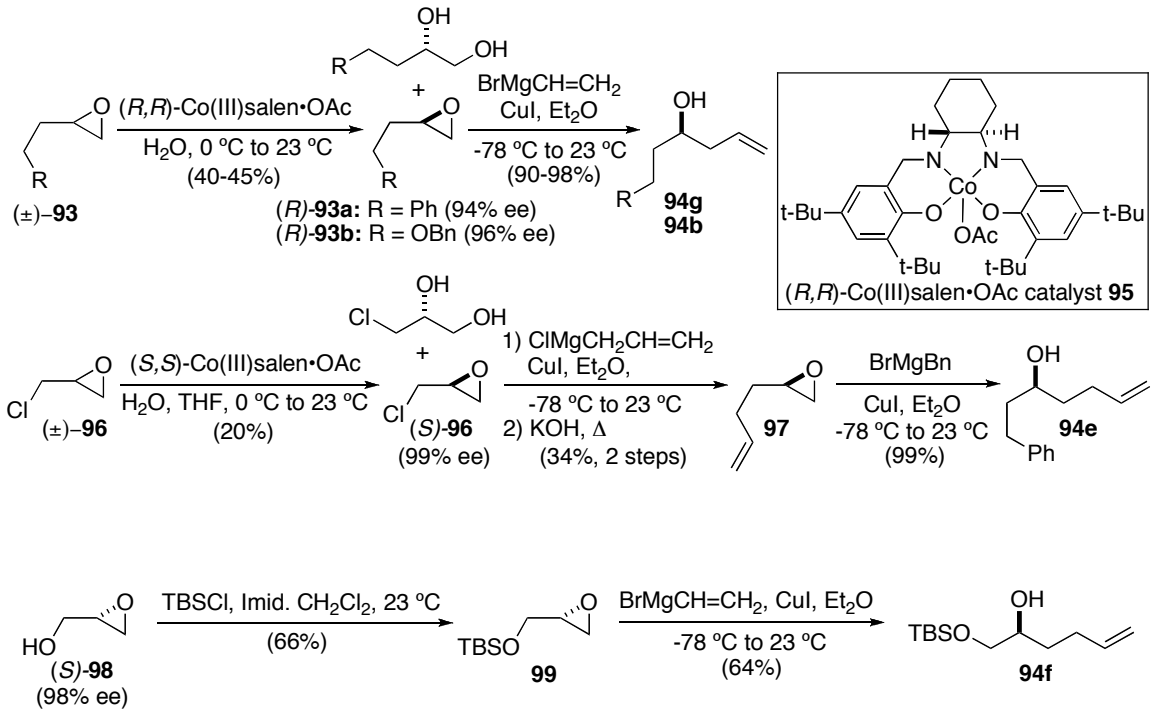


Figure 3.2. Retrosynthetic strategy utilizing tetrahydrofuran-fused β-lactones.

3.3.2 Substrate Preparation

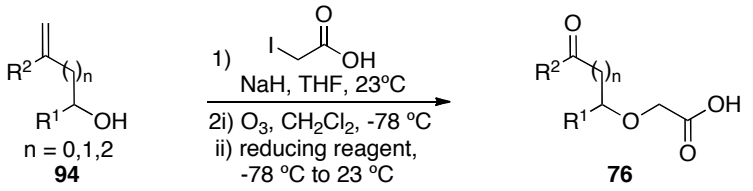
Scheme 3.4. Preparation of Enantioenriched Alcohols



Aldehyde acids **76a-76i** were prepared from the related alcohols **94a-94i** obtained by Grignard addition in the presence of copper iodide to provide the corresponding aldehyde or terminal epoxide (Table 3.1).[135] Alcohols **94b** and **94e-g** were prepared in enantioenriched form either by utilizing hydrolytic kinetic resolution (HKR) as developed by Jacobsen[12,13,136] or from commercially available starting materials (*S*)-**98** (Scheme 3.4). Enantioenriched epoxides underwent further alkylation to give the corresponding alcohols **94b** and **94e-94g**.

Alkylation of alcohols **94a-94i** with iodoacetic acid and subsequent ozonolysis delivered aldehyde acids **76a-76i** for use in further studies of the NCAL process in moderate to good yields over the two steps (Table 3.1).[137] Silylated aldehyde acids **76a** and **76f** were purified by column chromatography. Whereas, alkylated aldehyde acids **76b-76e** and **76g-76i** were purified easily by acid/base extraction rather than tedious and insufficient purification by column chromatography.

Table 3.1. Aldehyde and Keto Acid Preparation for Tetrahydrofuran-Fused *β*-Lactones



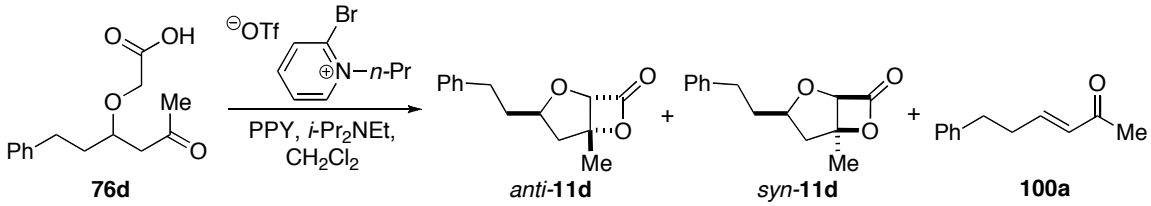
entry	alcohol	R^1	R^2	n	aldehyde acid	% yield[a]
1	**94a**	$TBDPSO(CH_2)_2$	H	1	**76a**[b]	38
2	**94b**	$BnO(CH_2)_2$	H	1	**76b**[c]	69
3[d]	**94c**	$Ph(CH_2)_2$	H	0	**76c**[c]	28[e]
4	**94d**	$Ph(CH_2)_2$	Me	1	**76d**[c]	64
5	**94e**	$Ph(CH_2)_2$	H	2	**76e**[c]	44
6	**94f**	$TBSOCH_2$	H	1	**76f**[b]	41
7	**94g**	$Ph(CH_2)_2$	H	1	**76g**[c]	74
8	**94h**	Ph	H	1	**76h**[c]	30
9	**94i**	$PhCH_2$[f]	H	0	**76i**[c]	74

[a] Yield is calculated for combined alkylation and ozonolysis steps. [b] DMS used as reducing reagent. [c] Ph_3P used as reducing reagent. [d] *tert*-butylacrylate used as alkylating agent instead of iodoacetic acid.[138] [e] Yield for alkylation, hydrolysis, and ozonolysis combined. [f] Secondary alcohol replaced with CH_2OH.

3.3.3 Optimization of Reaction Conditions

Bis-cyclization of keto acid **76d** provided *anti/syn* *β*-lactones **11d** in moderate yields (dr 1:1) (Table 3.2, entry 1). Not unexpectedly, *β*-elimination was observed. The reaction temperature was varied in order to suppress the *β*-elimination pathway and enhance the diastereoselectivity. When the reaction was carried out at -30ºC for keto acid **76d** production of *β*-eliminated product, enone **100a**, was suppressed obtaining *anti/syn* *β*-lactones **11d** in 54% yield (dr 1:1) (Table 3.2, entry 3). A single X-ray crystal structure was obtained for *syn*-*β*-lactone **11d**, which allowed for assignment of relative stereochemistry for the *syn* and *anti* diastereomers (Figure 3.3).

Table 3.2. Time and Temperature Optimization for Tetrahydrofuran-Fused *β*-Lactone **11d**



entry	temp (ºC)	time (h)	% yield **11d**	dr (*anti:syn*)	% yield **100a**
1	23	24	22	1:1	5
2	0 to 23	65	11	1:1	----
3	-30	66	54	1:1	----

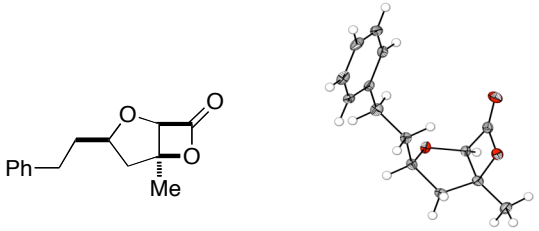
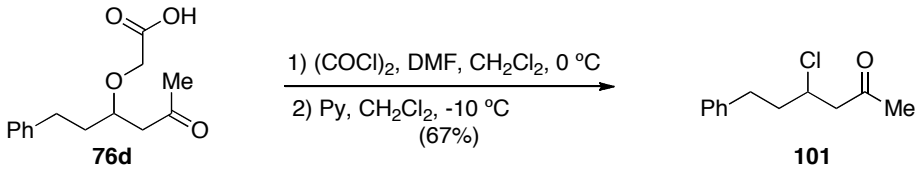


Figure 3.3. Single crystal X-ray structure (ORTEP Representation) of tetrahydrofuran-fused *syn*-*β*-lactone **11d**.

In order to determine if an acid chloride could be utilized to access tetrahydrofuran-fused β-lactone **11d** by way of a ketene, the acid chloride was prepared from keto acid **76d** (Scheme 3.5). The NCAL reaction conditions were found essential in order to access tetrahydrofuran-fused β-lactones, as was evident by formation of β-chloro ketone **101** alone formed by displacement of the glycolic acid fragment after subjecting the acid chloride to pyridine. The highly labile nature of keto acids and aldehyde acids bearing an oxo bridge must be controlled and required the use of mild NCAL conditions in order to provide any of the desired products.

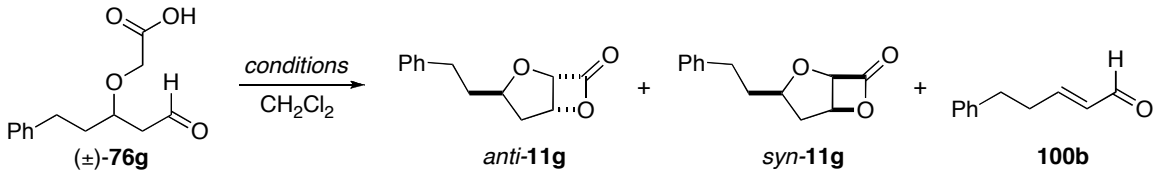
Scheme 3.5. Attempted β-Lactone Formation from an Acid Chloride



Application of the NCAL conditions employing pyridinium salt **62** and triethylamine as both nucleophile and base to aldehyde acid substrates was more challenging compared to the keto acid substrates. Subjection of aldehyde acid **76g** to the standard NCAL conditions gave minor amounts of the desired tetrahydrofuran-fused β-lactone **11g** (Table 3.3, entry 1). Decreasing the reaction time provided moderate yields of *anti*/*syn* β-lactones **11g** (47%) (Table 3.3, entry 2). Tetrahydrofuran-fused β-lactone **11g** was formed in the absence of a nucleophile in 8% yield as a result of ketene formation (Table 3.3, entry 3). Alternative activating agents (*e.g.* NsCl, MsCl, and Tf_2O) were not promising giving rise to reduced yields or predominantly α,β-unsaturated aldehyde **100b** (Table 3.3, entries 4-7). β-lactone **11g** was also prepared by employing PPY as the nucleophilic promoter, albeit in reduced yields (Table 3.3, entries 8 and 9).

Alternate substitution patterns were then studied to explore the substrate scope and the effect on diastereoselectivity (Table 3.4). Tetrahydrofuran-fused β-lactone **11c** was obtained as the minor product along with enol lactone **102** when the reaction was carried out over extended reaction times with aldehyde acid **76c** (Table 3.4, entry 1). However, *anti*/*syn* tetrahydrofuran-fused β-lactones **11c** (dr 2:1) were formed in modest yield, overall resulting in a 19% increase in yield, after lowering the reaction temperature to 0 ºC and reducing the reaction time (Table 3.4, entries 2 and 3).

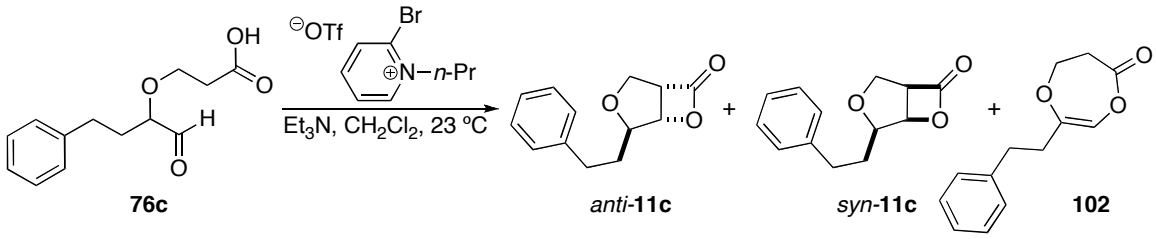
Table 3.3. Reaction Time and Activation Investigations



entry[a]	activating agent	nucleophile (equiv)	base	time (h)	temp (ºC)	% yield **11g**	dr (*anti*:*syn*)	% yield **100b**
1	pyridinium salt **72**	Et_3N (1.0)	Et_3N	33	23	9	2:1	4
2	pyridinium salt **72**	Et_3N (1.0)	Et_3N	2	23	47	2:1	7
3	pyridinium salt **72**	—	*i*-Pr_2NEt	3	23	8	2:1	4
4	NsCl	Et_3N (1.0)	Et_3N	3	23	23	1:1	5
5	Tf_2O	Et_3N (1.0)	Et_3N	9	0→23	< 5%	—	—
6	Tf_2O	PPY (1.0)	*i*-Pr_2NEt	9	0→23	0	—	22
7	MsCl	PPY (0.1)	*i*-Pr_2NEt	9	0→23	0	—	37
8	pyridinium salt **72**	PPY (0.1)	*i*-Pr_2NEt	3	23	35	2:1	6
9	pyridinium salt **72**	PPY (1.0)	*i*-Pr_2NEt	9	0	21	2:1	6

[a] Reactions were run with 2.0 equiv activating agent, 3.0 equiv base at 0.05 M. [b] Diastereomeric ratios were determined by ^{1}H NMR (500 MHz) analysis (integration) of the crude reaction mixtures

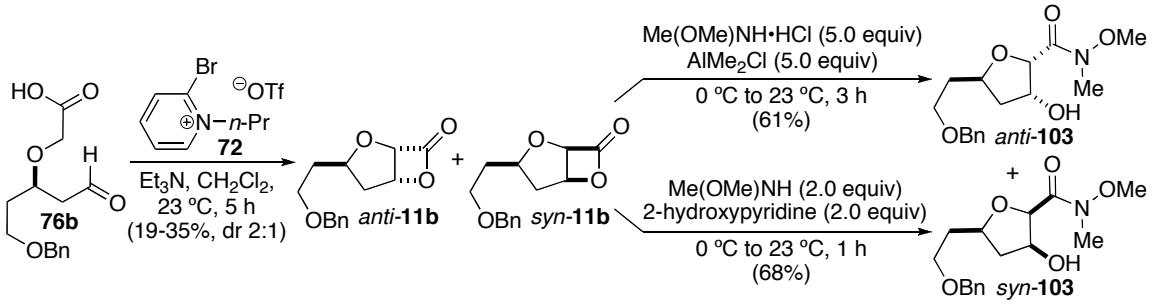
Table 3.4. Optimization of Reaction Conditions for Tetrahydrofuran-Fused *β*-Lactone **11c**



entry	temp (°C)	time (h)	% yield **11c**	dr (*anti:syn*)	% yield **102**
1	23	40	12	3:1	16
2	0	2	25	2:1	11
3	0	5	31	2:1	20

As our efforts were aimed toward the haterumalides, we incorporated a protected alcohol into the aldehyde acid side chain (Scheme 3.6). *Anti*/*syn* tetrahydrofuran-fused *β*-lactones **11b** were formed in modest yield as a 1:1 mixture of diastereomers. Tetrahydrofuran-fused *β*-lactone **11b** was unstable obtaining only 58% mass recovery after purification of a pure sample of tetrahydrofuran-fused *β*-lactone **11b** on silica gel by flash column chromatography. Alternative purification methods (*e.g.* florisil, neutral alumina, or deactivated silica gel) were not promising. Therefore, further conversion of the *anti*/*syn* tetrahydrofuran-fused *β*-lactones **11b** (85% pure) to the corresponding Weinreb amide was pursued (Scheme 3.6). After briefly screening reaction conditions, Weinreb amide **103** was formed in moderate yield.[140,141] The mild reaction conditions

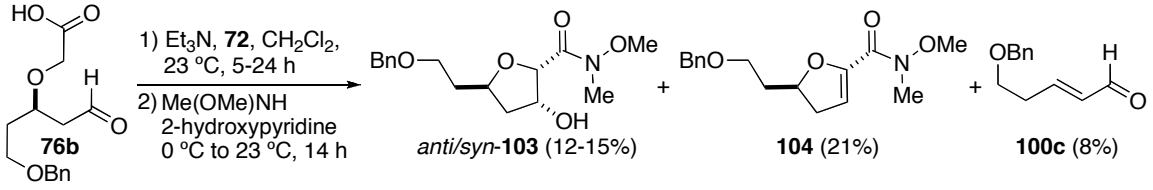
Scheme 3.6. Preparation of Tetrahydrofuran-Fused *β*-Lactone **11b** and Conversion to the Corresponding Weinreb Amide



employing 2-hydroxypyridine were used for subsequent reactions since pyridone byproducts are formed in the NCAL reaction upon reaction of the activating agent thus facilitating a two-step, one pot conversion from an aldehyde acid to the corresponding Weinreb amide.

The NCAL process was followed directly with Weinreb amide formation to provide Weinreb amide **103** in order to circumvent the instability of the tetrahydrofuran-fused β-lactone intermediate **11b** (Scheme 3.7). Intercepting the unstable β-lactone was feasible; however, improvement in the yield was not observed. Multiple products were formed in the reactions including α,β-unsaturated Weinreb amide **104** and β-eliminated product **100c**. The low yields of *in situ* generated Weinreb amide **103** were consistent with a two-step procedure utilizing isolated tetrahydrofuran-fused β-lactone **11b** (Scheme 3.6). Due to formation of multiple products and low yields, alternative tetrahydrofuran-fused β-lactones were explored.

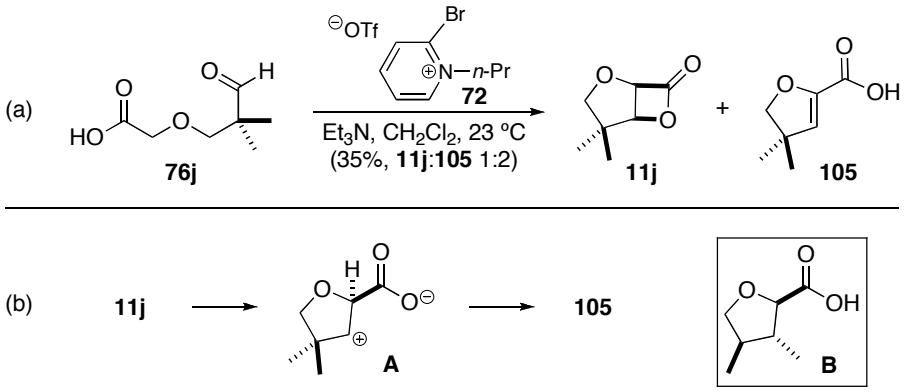
Scheme 3.7. NCAL Optimization and Subsequent Weinreb Amide Formation



In an effort to suppress β-elimination to the α,β-unsaturated aldehydes, a substrate containing *gem*-dimethyl substitution was prepared. Aldehyde acid **76j** was then subjected to the NCAL conditions (Scheme 3.8a). No β-elimination occurred as evidenced by the absence of a α,β-unsaturated aldehyde; however, tetrahydrofuran-fused β-lactone **11j** was highly unstable and readily transformed to α,β-unsaturated acid **105** only allowing isolation as a 1:2 mixture of tetrahydrofuran-fused β-lactone **11j** and α,β-unsaturated acid **105**, respectively. α,β-Unsaturated acid **105** may arise from an aldol condensation pathway or

via β-lactone opening of tetrahydrofuran-fused β-lactone **11j** to a transient carbocation intermediate **A**, which presumably forms α,β-unsaturated acid **105** upon quenching (Scheme 3.8b). If formation of carbocation **A** is indeed occurring, 1,2-methyl migrations may also be observed in acid products **B**.

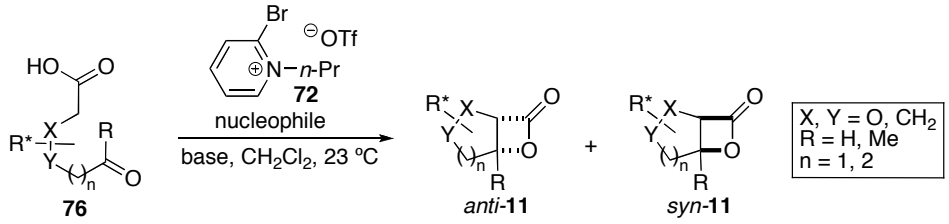
Scheme 3.8. Prevention of β-Elimination Pathway

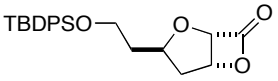
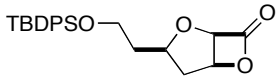
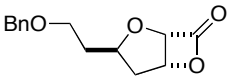
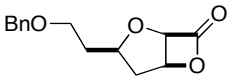
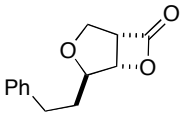
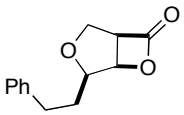
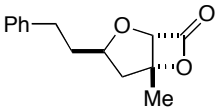
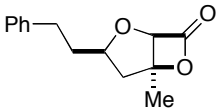
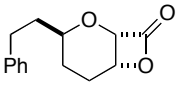
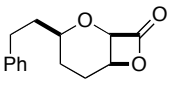
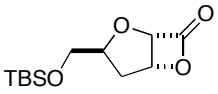
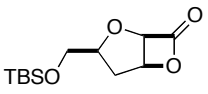
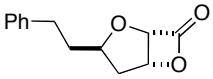
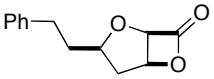
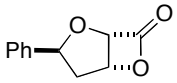
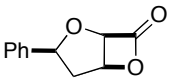
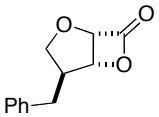
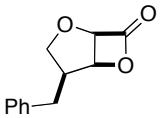


3.3.4 Summary of β-Lactone Fused Tetrahydrofurans with an Achiral Nucleophile

Initially studies toward tetrahydrofuran-fused β-lactones provided access to racemic *anti*/*syn* tetrahydrofuran- and tetrahydropyran-fused β-lactones **11a-11i** (Table 3.5). More tractable keto acid substrates **76d** delivered the highest yields for *anti*/*syn* β-lactones **11d** with 4-pyrrolidinopyridine (PPY) as a nucleophilic promoter (Table 3.5, entry 3). The relative stereochemistry of *syn*-β-lactone **11d** was confirmed by single crystal X-ray analysis (Figure 3.3). In the case of *anti*-tetrahydropyran-fused β-lactone **11e**, high diastereoselectivity was observed (Table 3.5, entry 4). Substrates containing γ- or δ-substituents consistently gave low diastereoselectivities. Major side reactions included formation of the α,β-unsaturated carbonyl **100** formed from competitive β-elimination of the starting material. However, the presence of δ-substitution led to enol lactone **102** with aldehyde acid **76c** and with aldehyde acid **76i** an unexpected

Table 3.5. Synthesis of Tetrahydrofuran-Fused β-Lactones



entry	tetrahydrofuran bicyclic β-lactones		% yield (dr)[a]
1[b]	 *anti*-**11a**	 *syn*-**11a**	25[c,d] (1:1)
2[b]	 *anti*-**11b**	 *syn*-**11b**	35[c] (2:1)
3[b]	 *anti*-**11c**	 *syn*-**11c**	31[c,e,f] (2:1)
4[b]	 *anti*-**11d**	 *syn*-**11d**	54[g,h] (1:1)
5	 *anti*-**11e**	 *syn*-**11e**	26[c] (>19:1)
6	 *anti*-**11f**	 *syn*-**11f**	17[c] (4:1)[i]
7	 *anti*-**11g**	 *syn*-**11g**	47[c,j] (1:1)
8	 *anti*-**11h**	 *syn*-**11h**	16[c,k] (1:1)
9	 *anti*-**11i**	 *syn*-**11i**	25[c,l] (3:1)

[a] dr determined by ^{1}H NMR (500 MHz) analysis of the crude reaction mixtures. [b] (±)-Starting material used. [c] Et_3N used nucleophile and base. [d] α,β-unsaturated aldehyde formed in 19% yield. [e] **102** formed in 20% yield. [f] Run at 0 °C. [g] PPY was used as the nucleophile, and the base was *i*-Pr_2NEt. [h] Run at -30 °C. [i] Significant improvement in the dr was not observed with *O*-TMSQD (dr 6:1). [j] **100b** formed in 7% yield. [k] Cinnamaldehyde formed in 6% yield. [l] Furanone minimized to 1% yield.

furanone,[142] which presumably arose by a Claisen/retro-Claisen sequence (Table 3.5, entries 3 and 8). Although tetrahydrofuran-fused β-lactones can be prepared with the NCAL process, low yields and formation of multiple products limit the scope of this process. However, competitive β-elimination to the corresponding α,β-unsaturated carbonyl can be suppressed, in some cases, by lowered reaction temperatures or shortened reaction times.

3.3.5 Diastereoselectivity of β-Lactone Fused Tetrahydrofurans

High diastereoselectivity (dr >19:1) was observed for the tetrahydropyran-fused β-lactone **11e**. Tetrahydrofuran-fused β-lactones **11a-11d** and **11f-11i** were obtained in low yields with low diastereoselectivities (dr 1:1 to 4:1) when bearing γ- or δ-substituents in analogy to cyclopentyl systems. Thus these positions have little bearing on the diastereoselectivity of the NCAL process, and these results prompted study of double diastereodifferentiation with these systems as well as with carbocyclic systems.

3.4 Conclusions

Tetrahydrofuran-fused β-lactones are accessible with the NCAL process. In many cases β-elimination of the aldehyde acid was competitive with product formation; however, suppression of the α,β-unsaturated carbonyl was feasible with lower reaction temperatures or shortened reaction times. Tetrahydrofuran-fused β-lactones suffer from low yields due to formation of multiple byproducts and low diastereoselectivity as a result of reduced $A^{1,3}$ strain as in accord to the cyclopentyl systems. The combination of these results prompted study of double diastereodifferentiation with both β-lactone fused tetrahydrofurans and the previously described β-lactone fused carbocycles.

CHAPTER IV

DEVELOPMENT OF DOUBLE DIASTEREOSELECTIVE NUCLEOPHILE CATALYZED, ALDOL-LACTONIZATIONS (NCAL) TO β-LACTONE FUSED CARBOCYCLES AND TETRAHYDROFURANS

4.1 Double Diastereodifferentiation

Enzymes interact with molecules with high specificity. Therefore, the pharmaceutical industry requires the preparation of potential drug candidates as single enantiomers in order to avoid unnecessary and unexpected side effects. The necessity for introduction of asymmetry when creating new chiral centers governs organic synthesis, and the continued development of new pharmaceutical drugs is a driving force for the development of novel asymmetric reactions. Asymmetric syntheses are achieved by use of either enantiomerically enriched reagents (reagent control) or enantiomerically enriched substrates (substrate control), which aside from a few scattered examples were the primary tools of asymmetric synthesis until the 1980's. With the development of both reagent and substrate controlled processes it was inevitable to combine both strategies, and ultimately derive the concept of double asymmetric induction synonymous with double diastereodifferentiation.[110,111] The significant utility of double diastereodifferentiation has been demonstrated on numerous occasions in the context of natural product total synthesis, and the importance of this strategy cannot be overstated.[14-16,143,144] Furthermore, the degree to which a chiral reagent can influence stereochemical outcomes by overcoming inherent substrate bias is revealed through the study of double

diastereodifferentiation. The goal of double asymmetric induction is to achieve high diastereoselectivity by combination of both an enantiomerically enriched reagent and an enantiomerically enriched substrate, which also gave rise to the novel concept of matched and mismatched cases as described by Masamune[111] and Sharpless.[110] Matched cases are presented when the sense of stereoinduction of the reagent and substrate are the same and reinforce each other, resulting in an increase in diastereoselectivity. Although in a mismatched case, the sense of stereoinduction of the substrate and reagent are different and thus oppose each other.

4.2 Premise for Development

We previously found that with respect to the acid, β-substituents in aldehyde acid substrates provided bicyclic β-lactones (*i.e.* **73e**) with high diastereoselectivity (Figure 4.1). The high diastereoselectivity observed for these substrates provided evidence for a NCAL process proceeding through ammonium enolate intermediates **106** and **107** based on $A^{1,3}$-strain arguments, since a [2+2] pathway proceeding by a ketene intermediate **108** would be expected to afford low diastereoselectivity. However, substrates bearing substituents at other positions **73f-73g** (*i.e.* γ, δ) gave low diastereoselectivities as would be predicted based on the absence of $A^{1,3}$ strain.[113] This led us to consider double diastereodifferentiation[110,111] with chiral nucleophiles (*e.g.* *O*-TMSQD and *O*-TMSQN)[129] in conjunction with enantioenriched substrates to determine if catalyst control could override the low diastereoeselectivities obtained from substrate control alone.

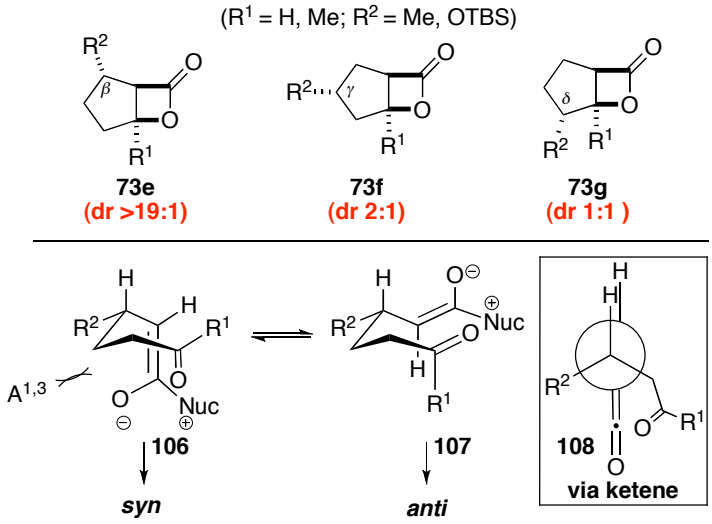


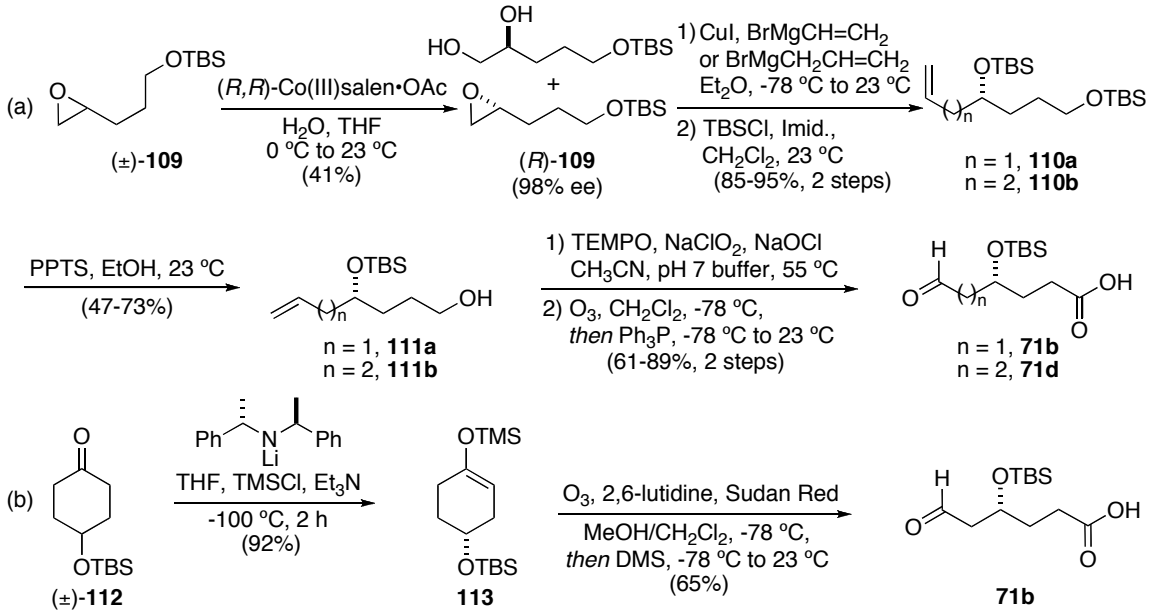
Figure 4.1. Observed diastereoselectivities for NCAL reactions leading to *β*-lactone fused carbocycles and proposed selectivity models.

4.3 Substrate Preparation of Aldehyde Acids for Carbocycles

Enantiomerically enriched aldehyde acids were prepared in order to study a double diastereoselective NCAL process. Racemic epoxide **109** underwent hydrolytic kinetic resolution in the presence of the (*R*,*R*)-Co(III)salen•OAc catalyst **95** to give enantiopure epoxide (*R*)-**109** (98% ee) (Scheme 4.1a).[12,13] Epoxide ring opening with either vinylmagnesium bromide or allylmagnesium bromide and subsequent protection of the resulting alcohol provided silyl ether **110a-110b**.[135] Selective deprotection of the primary silyl group led to alcohol **111a-111b**, which was oxidized under modified Pinnick reaction conditions and later ozonized to obtain aldehyde acid **71b** and **71d**.[145] Since reaction optimization was to be conducted with aldehyde acid **71b**, a more concise synthetic strategy was amenable with the improvements to ozonolysis of cyclic silyl enol ethers established in our group.[146] Aldehyde acid **71b** (87% ee) was obtained after

subjecting cyclohexanone **112** to asymmetric deprotonation[112] conditions and subsequent ozonolysis (Scheme 4.1b).

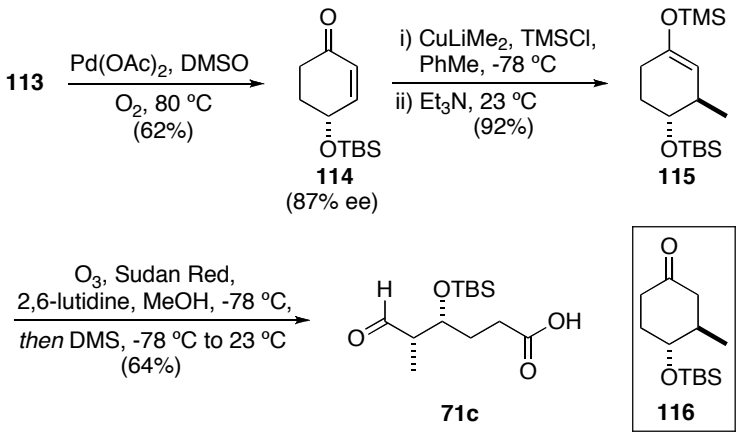
Scheme 4.1. Preparation of Enantiopure Aldehyde Acids **71b** and **71d**



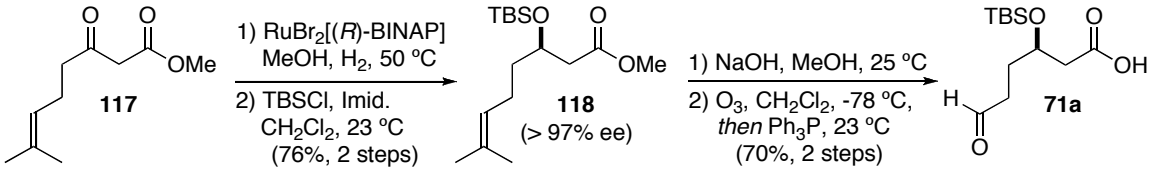
Silyl enol ether **113** underwent Saegusa oxidation to enone **114** (87% ee, chiral HPLC) (Scheme 4.2).[147,148] Cuprate addition and subsequent trapping as silyl enol ether **115** followed by ozonolysis furnished aldehyde acid **71c**. Filtering the cuprate reaction mixture through silica gel prior to ozonolysis proved to be key in order to provide reproducible results leading to increased yields and suppression of ketone **116** formation, which was obtained in up to 84% yield without filtration (Scheme 4.2, inset).

Noyori hydrogenation[18,149] of β-keto ester **117** followed with silyl protection afforded ester **118** in >97% ee (Scheme 4.3).[150] Hydrolysis of ester **118** to the carboxylic acid proceeded smoothly. Ozonolysis of alkene **118** delivered aldehyde acid **71a** in good yield. Enantiomerically enriched aldehyde acids **71a-71d** were utilized in studies towards development of a double diastereoselective NCAL process.

Scheme 4.2. Preparation of Enantiopure Aldehyde Acid **71c**



Scheme 4.3. Preparation of Enantiopure Aldehyde Acid **71a**



4.4 Applications to β-Lactone Fused Carbocycles

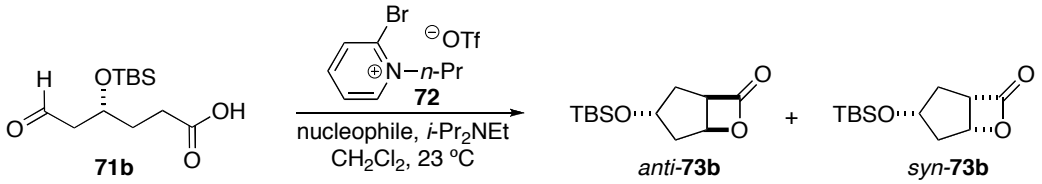
4.4.1 Optimization of Reaction Conditions

Although low diastereoselectivities observed with tetrahydrofuran-fused β-lactones initially prompted studies of double diastereoselective NCAL processes in efforts toward the tetrahydrofuran of the haterumalides (*vide supra*), we initiated double diastereodifferentiation studies with the well-studied carbocyclic substrates.[40] Subjecting enantiomerically enriched γ-substituted aldehyde acid (+)-**71b** (87% ee, based on asymmetric deprotonation) to standard NCAL conditions with Et_3N as the nucleophile resulted in a 2:1 mixture of *anti/syn* β-lactones **73b**, respectively (Table 4.1, entry 1). The low diastereoselectivity observed was in accord to previous findings with the

tetrahydrofuran and carbocycle systems. Combination of low diastereoselectivity and use of *cinchona* alkaloid derivatives, which were previously utilized to induce asymmetry with unsubstituted substrates in the NCAL process,[102-104] allowed for development of a double diastereoselective NCAL process. The inherent substrate bias was overridden with the use of *O*-TMSQD changing the diastereomeric ratio for *anti/syn* β-lactones **73b** from 2:1 to 1:7 (Table 4.1, entry 2). Similarly, *O*-TMSQN provided *anti* β-lactone **73b** as a single diastereomer (Table 4.1, entry 3). These results showed great promise toward the development of a double diastereoselective NCAL process and were used for further optimization of the reaction conditions. Dilute concentrations required use of extended reaction times as was evidenced by reactions run at increased concentration, 0.2 M, providing similar yields over 24 h (Table 4.1, entry 5). Neither catalyst loading nor addition time of the aldehyde acid had a significant effect on the yield (Table 4.1, entries 6 and 7). Hydrolysis of pyridinium salt **72** became a concern since product formation slowed over time, yet no improvement was observed with portion-wise addition, which ensured presence of active pyridinium salt **72** (Table 4.1, entry 7). However, the yields could be further increased by longer reaction times of 48-72 h (Table 4.1, entries 9-12). Reaction conditions using *3 equiv pyridinium salt **72**, 4.0 equiv i-Pr$_2$NEt, and 10 mol% nucleophile for 72 h at 0.20 M were deemed optimal* and used for further development of a double diastereoselective NCAL process towards β-lactone fused carbocycles.

Alternative methods for acid activation were also explored. Pyridinium salt **72** provided moderate yield of the *anti/syn* carbocycle-fused β-lactones **73b** (Table 4.2, entries 1 and 2). Reducing the reaction time from the optimal 72 h to 48 h as well as

Table 4.1. Initial Studies Toward a Double Diastereoselective NCAL Process



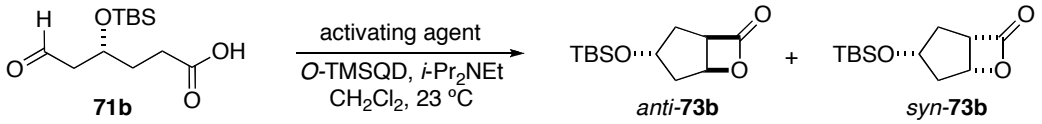
entry[a]	nucleophile	time (h)	conc. (M)	% yield	dr[b] (*anti:syn*)
1[c]	Et_3N	24	0.05	58 (52)[d]	2:1
2	*O*-TMSQD	96	0.05	47	1:7
3	*O*-TMSQN	96	0.05	43	>19:1
4	*O*-TMSQD	24	0.10	45	1:~10
5	*O*-TMSQD	24	0.20	50	1:7
6	*O*-TMSQD[e]	48	0.20	59	1:7
7	*O*-TMSQD	48	0.20	62[f] (64)[g]	1:7
8	*O*-TMSQD	48	0.20	55[h]	1:7
9	*O*-TMSQD	48	0.20	61	1:7
10	*O*-TMSQN	48	0.20	43	>19:1
11	*O*-TMSQD	72	0.20	73	1:7
12	*O*-TMSQN	72	0.20	60	>19:1

[a] Reaction run with 3 equiv **72**, 4.0 equiv *i*-Pr_2NEt, and 10 mol% nucleophile adding aldehyde acid over 1 h. [b] Diastereomeric ratios were determined by ^{1}H NMR (500 MHz) analysis (integration) of the crude reaction mixtures. [c] Reaction was run with 3 equiv **72** and 4.0 equiv triethylamine. [d] Reaction run in acetonitrile. [e] 20-40 mol% nucleophile used. [f] Aldehyde acid added over 12 h. [g] *i*-Pr_2NEt and **72** and added portionwise (3 portions). [h] 1.5 equiv **72** was used.

determining initial yields by ^{1}H NMR upon comparison to an internal standard established a more rapid screening of activating agents. Methanesulfonyl chloride and triflic anhydride gave mainly unreacted starting material **71b** (Table 4.2, entries 3 and 4). Nosyl chloride provided modest yields of the desired carbocycle-fused *β*-lactone **73b**; whereas, tosyl chloride provided similar yields in conjunction with an equal portion of unreacted aldehyde acid **71b** (Table 4.2, entries 5 and 6). Extending the reaction time to the optimal time frame led to improved yield of 45% (Table 4.2, entry 7). However, longer reaction times led to reduced yields presumably due to decomposition of the carbocycle-fused *β*-lactone **73b** product (Table 4.2, entry 8). Tosyl chloride was shown

to be a viable alternative to pyridinium salt **72** for keto acids and use of lithium chloride as a Lewis acid further enhanced yields.[131] A similar trend was not observed with aldehyde acids (Table 4.2, entries 9 and 10). Instead, reduced yields were obtained. Therefore, pyridinium salt **72** remained the activating agent of choice for aldehyde acids leading to *β*-lactone fused carbocycles.

Table 4.2. Alternative Acid Activation for the Double Diastereoselective NCAL Process



entry[a]	activating agent	additive (equiv)	time (h)	% yield **71b**[b]	% yield **73b**[c]
1	pyridinium salt **72**	—	48	—	55
2	pyridinium salt **72**	—	48	0	50[d]
3	MsCl	—	48	62	20[b,e]
4	Tf_2O	—	48	91	0[b,e]
5	NsCl	—	48	28	36[b,g]
6	TsCl	—	48	41	32 (42)[b]
7	TsCl	—	72	—	45[h]
8	TsCl	—	96	—	35 (40)[h]
9	TsCl	LiCl (0.5)	48	—	15 (42)[h]
10	TsCl	LiCl (1.0)	72	—	22[h]

[a] Reaction run with 1.5 equiv activating agent, 3.0 equiv *i*-Pr_2NEt, and 10 mol% *O*-TMSQD at 0.20 M. [b] Yield based on ^{1}H NMR integration compared to 4-bromo-1-nitrobenzene as an internal standard. [c] Isolated yield. [d] 50% enol lactone obtained according to integration. [e] *β*-elimination of aldehyde acid was observed (4-10%). [f] 28% enol lactone obtained according to integration. [g] 17% enol lactone obtained. [i] 3.0 equiv activating agent was used.

4.4.2 Screening of Catalysts

Use of 10 mol% *O*-TMSQD with aldehyde acid **71b** led to an increased level of diastereoselection to 7:1 for *syn*/*anti* *β*-lactones **73b**, and the relative and absolute stereochemistry of the major *syn*-*β*-lactone **73b** was confirmed by X-ray analysis (Figure 4.2 and Table 4.3, entry 1).[151] Diastereomeric *syn*-*β*-lactone **73b** was obtained with high

diastereoselectivity (dr >19:1) employing *O*-TMSQN indicative of the matched case (Table 4.3, entry 2). *O*-Bz-QD and *β*-ICPD provided similar results as *O*-TMSQD and *O*-TMSQN, respectively, albeit in reduced yields (Table 4.3, entries 3 and 4). Commercially available dimeric catalysts, $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$, were also studied and provided similar results as the corresponding monomeric derivatives (Table 4.3, entries 5 and 6). However, enantiopure tetramisole[107] and racemic homobenzotetramisole (HBTM),[152] which proved successful with ketoacid substrates led to low conversions (Table 4.3, entries 7 and 8).[106,131]

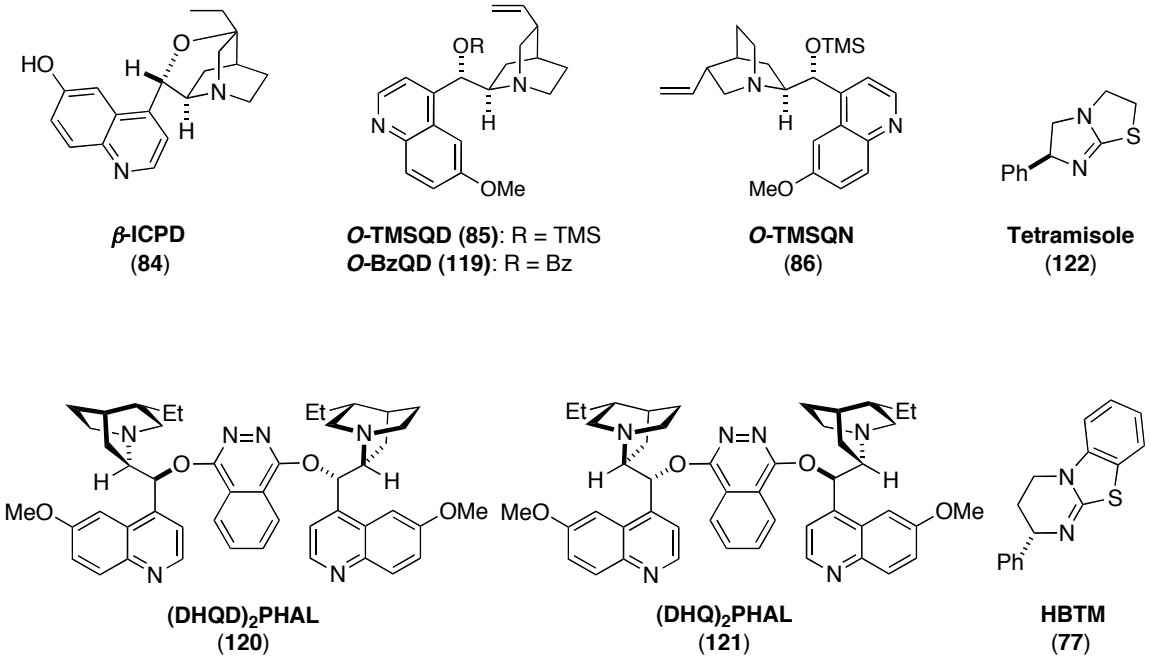
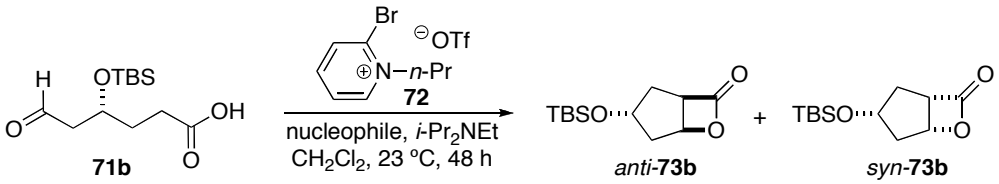


Figure 4.2. Structure of *cinchona* alkaloid and tetramisole based asymmetric catalysts.

4.4.3 Double Diastereoselective NCAL Process with Enantioenriched Aldehyde Acids to *β*-Lactone Fused Carbocycles

As expected, high diastereoselectivity (dr >19:1) was obtained for *anti*-silyloxy *β*-

Table 4.3. Catalyst Screening for a Double Asymmetric NCAL with Aldehyde Acid **71b**



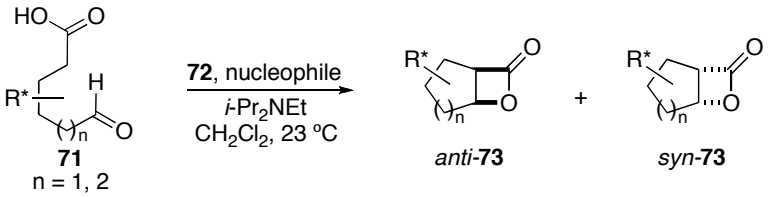
entry[a]	nucleophile (mol%)	% yield	dr[b] (*anti:syn*)
1	*O*-TMSQD **85** (10)	73	1:7
2	*O*-TMSQN **86** (10)	60	>19:1
3[c]	*O*-BzQD **119**(10)	33	1:6
4[c]	*β*-ICPD **84** (10)	23	16-19:1
5	$(DHQD)_2$PHAL **120** (10)	59	1:4
6	$(DHQ)_2$PHAL **121** (10)	53	>19:1
7[d]	Tetramisole **122** (10)	18	>19:1
8	HBTM[e] **77** (10)	34	2:1

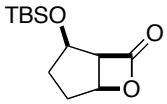
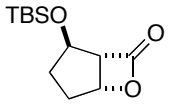
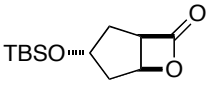
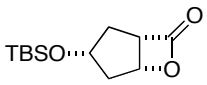
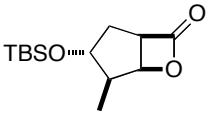
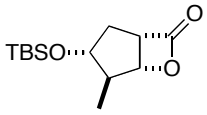
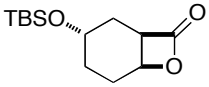
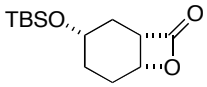
[a] Reaction run with 3 equiv pyridinium salt **72** and 4.0 equiv *i*-Pr_2NEt for 72 h at 0.20 M. [b] Diastereomeric ratios were determined by ^{1}H NMR (500 MHz) analysis (integration) of the crude reaction mixtures. [c] Reaction carried out for 53 h. [d] Reaction run for 24 h. [e] Racemic HBTM used.

lactone **73a** in analogy to previous NCAL reactions with substrates possessing *β*-substituents. This substrate also provided excellent efficiency as previously reported by Oh.[150] However, not surprisingly, diastereoselectivity could not be altered with either *O*-TMSQD or *O*-TMSQN due to the strong conformational bias exerted by allylic 1,3-strain (see Figure 4.1) but rather led only to greatly reduced conversion (Table 4.4, entry 1). Aldehyde acid (+)-**71b** was utilized for both reaction optimization and catalyst screening, which provided a firm foundation (dr 1:7 to >19:1) to further explore the double diastereoselective NCAL process (Table 4.4, entry 2). Since double diastereoselectivity was achieved with *γ*-substituted aldehyde acid substrates **73b**, other enantiomerically enriched substrates with alternate substitution patterns were then studied. Use of Et_3N with *anti*-*γ,δ*-substituted acids **71c** gave low diastereoselectivity leading to a 2:1 mixture of *anti/syn* *β*-lactones **73c** (Table 4.4, entry 3). Reversed selectivity was obtained with

O-TMSQD to provide *syn/anti* β-lactones **73c** as the major diastereomer but gave poor selectivity (dr 3:1). However, use of *O*-TMSQN gave both improved yields and diastereoselectivity (dr 10:1) of *anti/syn* β-lactones **73c** suggestive of a matched case (Table 4.4, entry 3). Double diastereodifferentiation was also possible with *anti/syn* cyclohexyl-fused β-lactones **73d**, which improved a 2:1 diastereomeric ratio obtained

Table 4.4. Summary of Double Diastereoselective NCAL Reactions with Enantioenriched Aldehyde Acids



entry	carbocycle-fused bicyclic β-lactone	Et_3N % yield (dr)[a,b]	*O*-TMSQD % yield (dr)[b,c]	*O*-TMSQN % yield (dr)[b,c]
1	 *anti*-**73a**  *syn*-**73a**	84 (1:>19)	33[d] (1:>19)	23 (1:>19)
2	 *anti*-**73b**  *syn*-**73b**	58 (2:1)	73 (1:7)	60 (>19:1)
3	 *anti*-**73c**  *syn*-**73c**	45 (2:1)	32 (1:3)	55 (10:1)
4	 *anti*-**73d**  *syn*-**73d**	38 (2:1)	31 (1>19)	10 (>19:1)

[a] Reaction run with 3 equiv pyridinium salt **62** and 4 equiv Et_3N for 12-24 h at 0.05 M. [b] Diastereomeric ratios were determined by ^1H NMR (500 MHz) analysis (integration) of the crude reaction mixtures. [c] Reaction run with 3 equiv pyridinium salt **62** and 4 equiv *i*-Pr_2NEt, and 10 mol% nucleophile for 48-72 h at 0.20 M. [d] HBTM gave 17% yield of *anti*-**73b** as a single diastereomer.

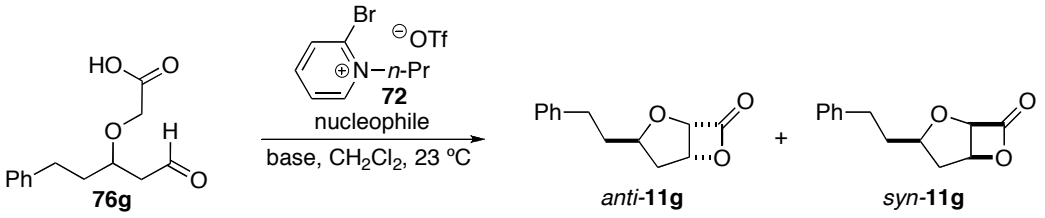
with Et_3N to complete catalyst control with *O*-TMSQN leading to high diastereoselectivity (>19:1); however, conversions were low (Table 4.4, entry 4).

4.5 Applications to β-Lactone Fused Tetrahydrofurans

4.5.1 Initial Studies of a Double Diastereoselective NCAL Process

Our initial interest in a double diastereoselective NCAL stemmed from our preliminary findings with tetrahydrofuran-fused β-lactones that gave low diastereomeric ratios. However, the *cinchona* alkaloid catalysts, which were suitable for the carbocycles, provided poor enantioenrichment when oxygen was incorporated into the aldehyde acid framework (Table 4.5, entry 1). Low diastereoselectivities were also obtained with enantiomerically enriched aldehyde acid **76g** as a result of poor reagent control (Table 4.5, entries 3 and 4).

Table 4.5. Screening of *Cinchona* Alkaloids Toward β-Lactone Fused Tetrahydrofurans



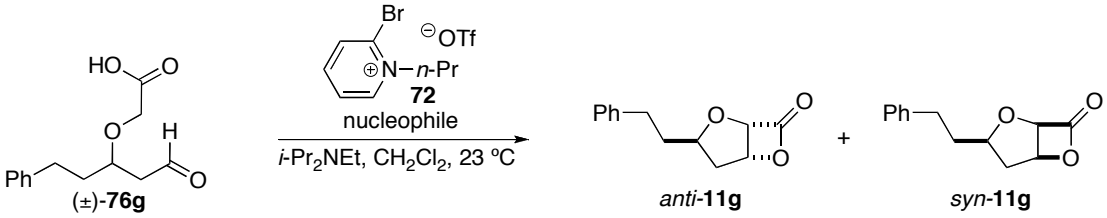
entry[a]	**76g**	nucleophile	time (h)	% yield	dr[b] (*anti:syn*)	% ee (*anti*-**11g**,*syn*-**11g**)
1	±	*O*-TMSQD[d]	24	39[e]	2:1	12,21[f]
2	±	*O*-TMSQN[d]	48	35	2:1	—
3	*R*	*O*-TMSQD	24	13	1:1	100,96
4	*R*	*O*-TMSQN	24	16	1:1	98,98

[a] Reaction run with 3.0 equiv pyridinium salt **72**, 4.0 equiv *i*-Pr_2NEt, and 10 mol% nucleophile at 0.05 M. [b] Diastereomeric ratios were determined by ^1H NMR (500 MHz) analysis (integration) of the crude reaction mixtures. [c] 4.0 equiv of Et_3N was used as both nucleophile and base. [d] Reaction run at 0.20 M. [e] Similar yield was obtained when reaction run for 48 h. [f] Opposite enantiomer is the major product formed.

4.5.2 Screening of Catalysts

Alternative tetramisole derived catalysts have been exploited by Birman[107,152] as highly effective asymmetric acylation catalysts and proved profitable with ketoacid substrates.[106,131] Racemic aldehyde acid **76g** was used due to greater availability and in order to test the degree of reagent control. A variety of these tetramisole-based derivatives were screened due to the poor reagent control exhibited by *cinchona* alkaloid catalysts. Enantiopure tetramisole provided excellent enantioselectivities but with low yield and diastereoselectivity (Table 4.6, entry 2).[17] However, the results obtained with tetramisole were inconsistent and at times irreproducible so alternative catalysts were pursued. Only trace amounts of *anti/syn* tetrahydrofuran-fused *β*-lactones **11g** were provided with benzotetramisole (Table 4.6, entry 3). However, more nucleophilic HBTM[152] provided tetrahydrofuran-fused *β*-lactones **11g** in 78% enantiomeric excess with increased yield (Table 4.6, entry 4). The tetramisole and HBTM catalysts gave enantiomeric products from the NCAL reaction.

Table 4.6. Catalyst Screening for a Double Asymmetric NCAL with Aldehyde Acid **76g**



entry	nucleophile (mol%)	% yield	dr (*anti:syn*)	% ee (*anti*-**11g**,*syn*-**11g**)
1	*O*-TMSQD (10)	13	2:1	12,21[b]
2	Tetramisole (10)	13	2:1	86-92[a]
3	BTM (10)	6	2:1	7[a]
4	HBTM (10)	30	2:1	34,78[b]

[a] Determined enantiomeric excess only for major diastereomer *anti*-**11g**. [b] Opposite enantiomer is the major product formed.

Several catalysts models can rationalize the enantioselectivity and lack thereof as observed with tetrahydrofuran-fused β-lactones **11g** (Figure 4.3). Tetramisole and the related catalyst derivatives presumably form ammonium enolates **119** and **120**, respectively. Attack on the electrophilic aldehyde would then occur from the least hindered face of the ammonium enolates **119** and **120** to give enantiomeric *anti*-β-lactone **11g** and *syn*-β-lactone **11g**, respectively. Loss of reagent control arose when employing BTM as an asymmetric nucleophile resulting from insufficient blockage of one face on the ammonium enolate as exhibited in model **122** compared to that found in tetramisole **121** (Figure 4.3, inset).

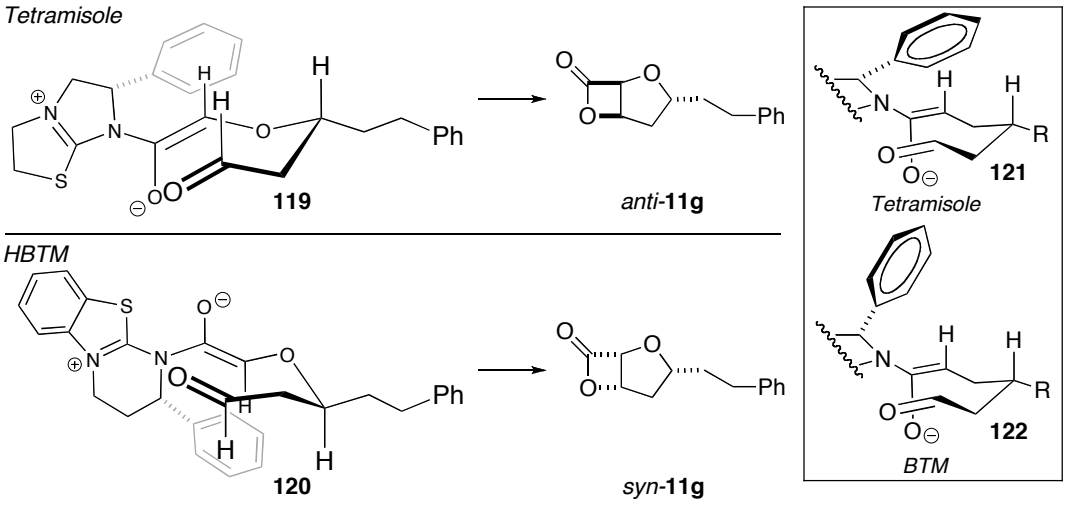


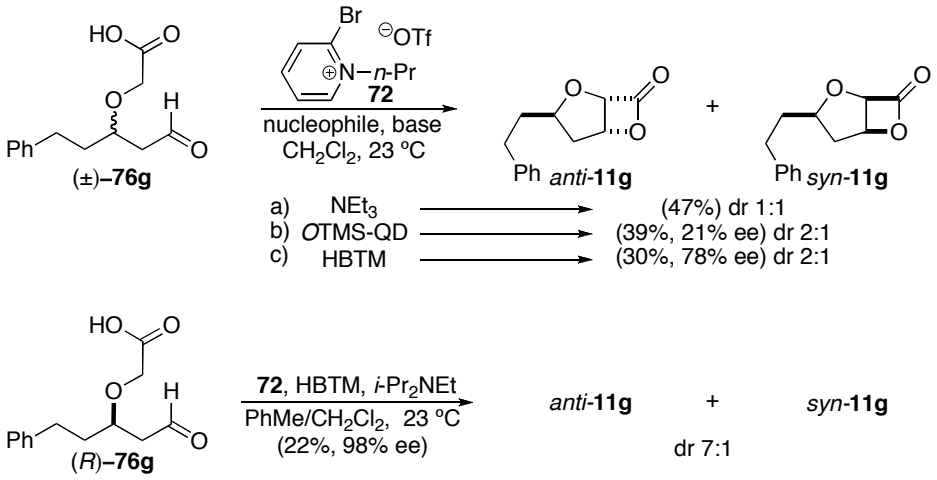
Figure 4.3. Models for tetramisole and related catalyst derivatives.

4.5.3 Double Diastereoselective NCAL Process with Enantioenriched Aldehyde Acids to β-Lactone Fused Tetrahydrofurans

Although the more nucleophilic HBTM catalyst provided *anti/syn* tetrahydrofuran-fused β-lactones **11g** in 78% enantiomeric excess that was much improved compared to

cinchona alkaloid catalysts, no change in the diastereoselectivity was observed (Scheme 4.4b and c). Unfortunately, when testing the feasibility of a double diastereoselective NCAL process with tetrahydrofuran-fused β-lactones **11g** by employing enantioenriched aldehyde acid **76g** in conjunction with an asymmetric catalyst, no enhancement in the diastereoselectivity was observed (not shown). Interestingly, a marked solvent effect led to improvement in diastereoselectivity when the reaction was run in a mixture of CH_2Cl_2/PhMe (dr 7:1). Although enhancement in the diastereoselectivity was observed, it is plausible that the optimization was performed on the substrate leading to a mismatched case, yet the consistently low yields obtained with tetrahydrofuran-fused β-lactones deterred further investigations.

Scheme 4.4. Summary of Double Diastereoselective Synthesis of Tetrahydrofuran-fused β-Lactones



4.6 Other NCAL Variations: Dynamic Kinetic Resolution

4.6.1 Dynamic Kinetic Resolution Process

Advancements have been made to the NCAL process since the initial disclosure[102]

including further development of an asymmetric variant with aldehyde acids,[103,104] extension to keto acids,[113] application of an asymmetric version with keto acids using commercially available activating agents,[131] and development of a double diastereoselective process.[68] Dynamic kinetic resolution (DKR)[153-156] in combination with the NCAL process would further extend the scope of this process (Figure 4.4). Kinetic resolution (KR)[157] occurs when one enantiomer **R** in a racemic mixture reacts more readily than the corresponding enantiomer **S** to form separable products **P-Q** having a maximum of 50% theoretical yield as in the case of hydrolytic kinetic resolution developed by Jacobsen.[13] However, chemists continued search and development of new and efficient methods for the formation of enantiomerically enriched compounds led to a novel procedure in asymmetric synthesis that of dynamic kinetic resolution, which does not have the same limitations in yield. Dynamic kinetic resolution couples kinetic resolution of enantiomers with racemization or equilibration of the substrate, which leads to the selective formation of one product enantiomer in 100% theoretical yield. The importance of dynamic kinetic resolution in industry cannot be undermined as enantiopure pharmaceuticals are required by regulatory agencies and modifications of

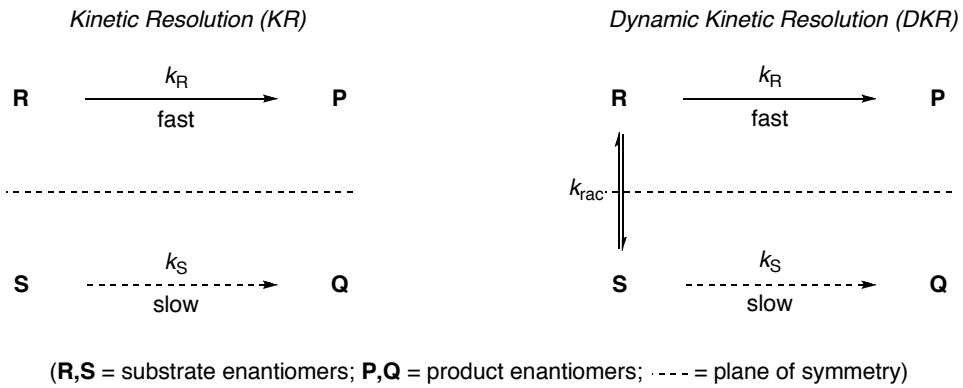


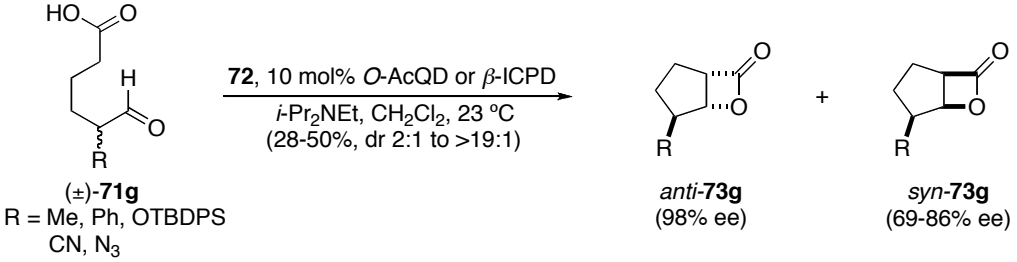
Figure 4.4. Juxtaposition of kinetic resolution and dynamic kinetic resolution processes.

chiral pool starting materials are often lengthy or limited in scope.[158] Use of aldehyde acids bearing a chiral δ-substituent (α-substituents with respect to the aldehyde moiety) could provide epimerizable substrates for studies toward the development of a DKR-NCAL process.

4.6.2 Previous Studies

Cortez began studies towards the development of a DKR-NCAL process in our group shortly after the initial NCAL conditions were discovered (Scheme 4.5).[159] Alkylated δ-substituents gave modest yields and diastereoselectivities with excellent enantioselectivities for *anti/syn* carbocycle-fused β-lactones **73g**. Further study of a δ-substituent containing a heteroatom was investigated in order to increase the acidity and gave up to 50% yield of *anti*-β-lactone **73g** (dr >19:1). δ-Cyano and δ-azido aldehyde acids remained inaccessible due to difficulties encountered in the last step of preparation, hydrolysis of the silylester to the corresponding carboxylic acid. Determination of the absolute stereochemistry of the *anti/syn* carbocycle-fused β-lactones **73g** remained necessary to determine whether the reaction proceeded through a matched/mismatched case as demonstrated with the double diastereoselective NCAL (*vide supra*) or through dynamic kinetic resolution.

Scheme 4.5. Previous Results Using α-Substituted Aldehyde Acids

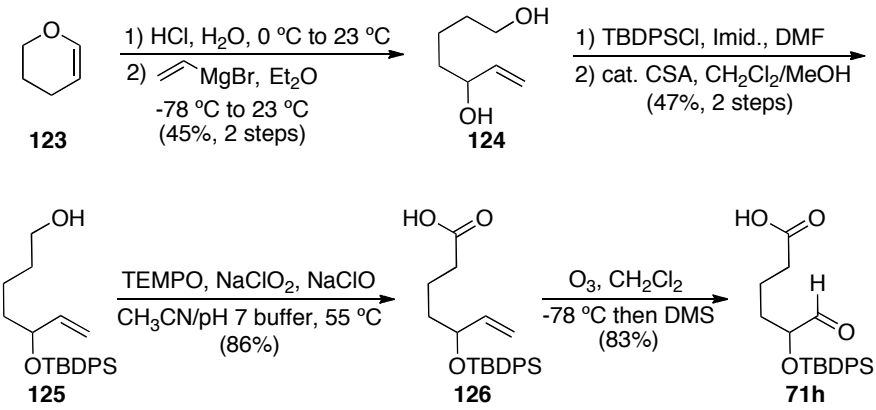


4.6.3 α-Substituted Aldehydes

Aldehyde acid **71h** was prepared by hydrolysis of 3,4-dihydro-2*H*-pyran **123** with subsequent vinylmagnesium bromide addition to the lactol to furnish diol, which after further protecting group manipulation gave alcohol **124** (Scheme 4.6).[160] Modified Pinnick oxidation proceeded to afford acid **126**. Final ozonolysis of alkene acid **126** led to aldehyde acid **71h** (15% overall yield) for studies of a DKR-NCAL process.

If rapid equilibration can be achieved with substrates possessing δ-substituents (α-substituents with respect to the aldehyde moiety) dynamic kinetic resolution could occur, thereby leading to increased yields and diastereoselectivity. Efforts to explore this reaction pathway were conducted with racemic aldehyde acid **71h**, and afforded *anti*-β-

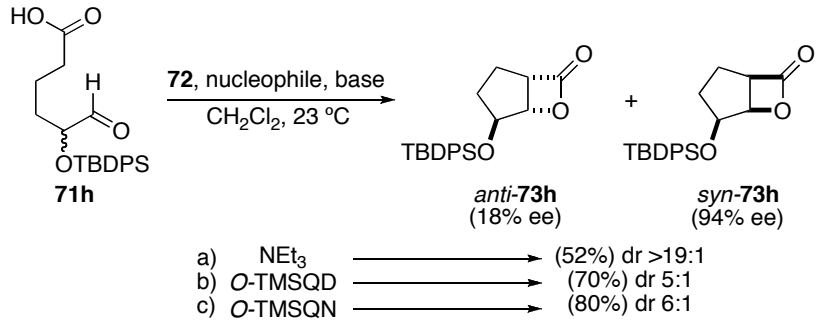
Scheme 4.6. Aldehyde Acid Preparation for Use in Developing a DKR-NCAL Process



lactone **73h** as a single diastereomer in the presence of triethylamine (Scheme 4.7a). However, lower diastereomeric ratios (dr 5-6:1) were observed with *O*-TMSQD and *O*-TMSQN in contrast to the results previously reported (Scheme 4.7b and c).[159] High enantiopurity was obtained only in the minor diastereomer with both asymmetric nucleophiles providing similar levels but reversed enantioenrichment. Employing

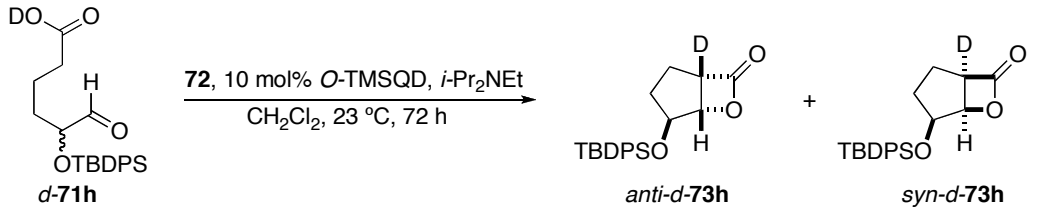
substoichiometric amounts of DBU in attempt to promote racemization led only to reduced yield (31% yield) with consistent product enantiopurities.

Scheme 4.7. Possibility of Dynamic Kinetic Resolution



Attempted deuterium labeling was inconclusive for determining if epimerization was occurring giving rise to deuterium incorporation at the α-position to the acid or multiple products (Scheme 4.8). Subjection of deuterated aldehyde acid *d*-**71h** to the NCAL conditions led to 20% deuterium incorporation at the β-lactone ring juncture providing evidence for ammonium enolate formation (theoretical maximum = 50%). Therefore, epimerization of the δ-substituent remains a challenge towards applying dynamic kinetic resolution in these systems. Although good yields are obtained, the low diastereoselectivities and varied enantioselectivities make it difficult to ascertain which pathway is predominating (matched/mismatched vs. DKR). These pathways could more readily be distinguished by use of an enantiopure δ-substituted aldehyde acid and determination of the absolute stereochemistry for the corresponding products, since any formation of β-lactone with the epimeric δ-substituent would provide direct evidence of a DKR-NCAL process while formation of β-lactones with the same absolute configuration as the starting material would be derived from the matched/mismatched scenario.

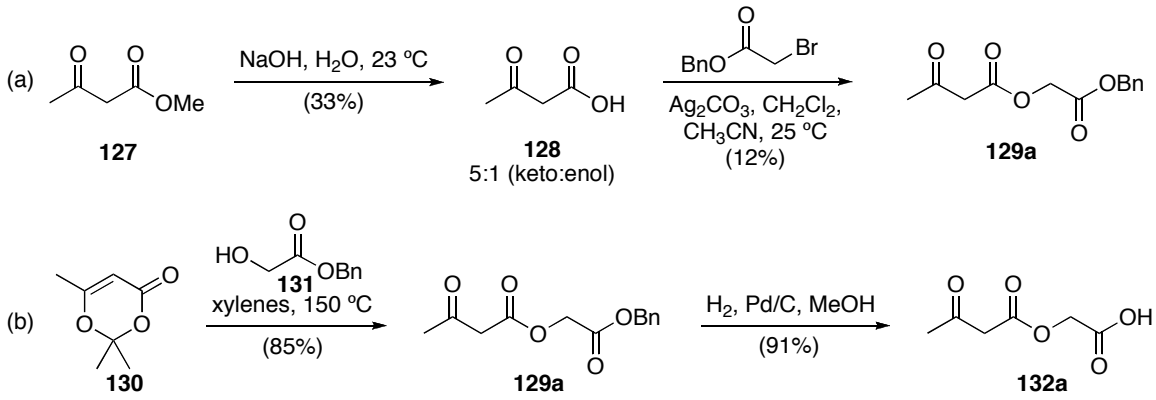
Scheme 4.8. Exploration of Deuterium Incorporation



4.6.4 1,3-Dicarbonyl Containing Aldehydes

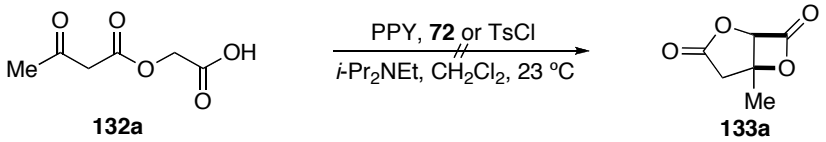
In order to overcome the racemization issues encountered with δ-substituted aldehyde acids, substituted 1,3-dicarbonyl containing aldehyde acids were studied. The increased acidity of the 1,3-dicarbonyl substrates would allow for facile racemization. An unsubstituted β-keto ester **132a** was initially prepared due to its facile preparation (Scheme 4.9a). Methyl acetoacetate was hydrolyzed to provide 3-oxobutanoic acid **128**,[161] which was subsequently alkylated with benzyl-2-bromoacetate in the presence of silver carbonate giving β-keto ester **129a** in low yield.[162] Alkylation of alcohol **131**[163] with dioxinone **130** afforded β-keto ester **129a** with improved yields, which after hydrogenolysis afforded keto acid **132a** along with trace amounts of the corresponding methyl ester (Scheme 4.9b).[164]

Scheme 4.9. Preparation of Unsubstituted β-Keto Acid



When keto acid **132a** was subjected to the standard NCAL conditions, none of the desired product was formed (Scheme 4.10). Even use of tosyl chloride as an activating agent gave none of the desired product. Due to the volatility of both the products (if formed) and side products, an alternative substituted keto acid was pursued.

Scheme 4.10. Reaction Outcome with Unsubstituted Keto Acid

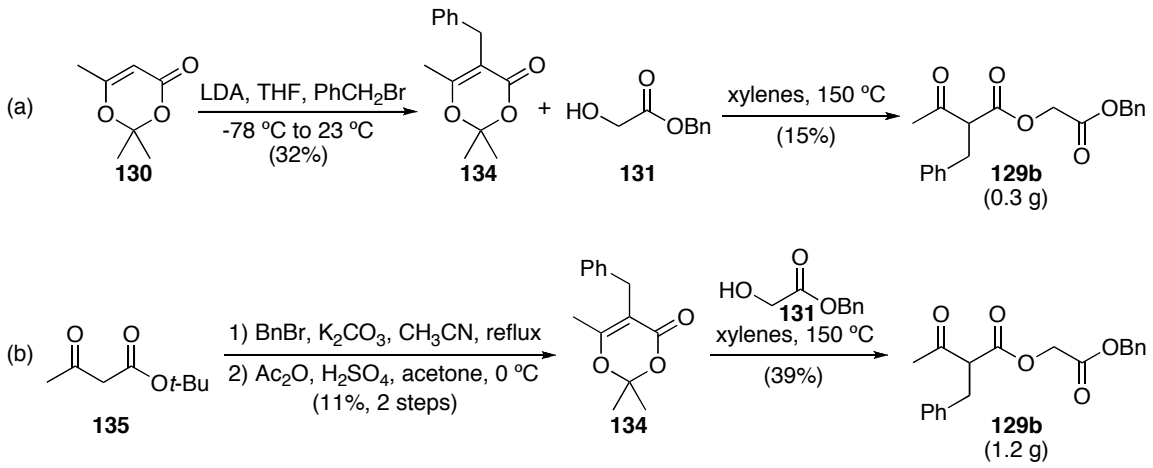


132a **133a**

Dioxinone **130** was alkylated with benzyl bromide to give substituted dioxinone **134**,[165,166] which after reaction with alcohol **131** provided β-keto ester **129b** (Scheme 4.11a).[163] This route suffered from poor selectivity during alkylation to dioxinone **134** as expected (2:1 α-alkylation:γ-alkylation) that ultimately led to reduced yields of β-keto ester **129b**. A more scalable route was pursued by alkylation of *t*-butyl acetoacetate **135** with benzyl bromide and further reaction with acetone provided pure dioxinone **134** after column chromatography (Scheme 4.11b). The two-step sequence avoided alkylation selectivity issues and allowed for greater material throughput. Ketene trapping with alcohol **131** afforded β-keto ester **129b**.

Keto ester **129b** was converted to keto acid **132b** through hydrogenolysis in ethyl acetate in order to avoid trace formation of the methyl ester (Scheme 4.12). Keto acid **132b** was then subjected to the NCAL process with PPY as the nucleophilic promoter. After 48 h, presence of a β-lactone was observed as indicated by an IR frequency of 1815 cm^{-1}. However, further attempts to improve the yield by longer reaction times, addition

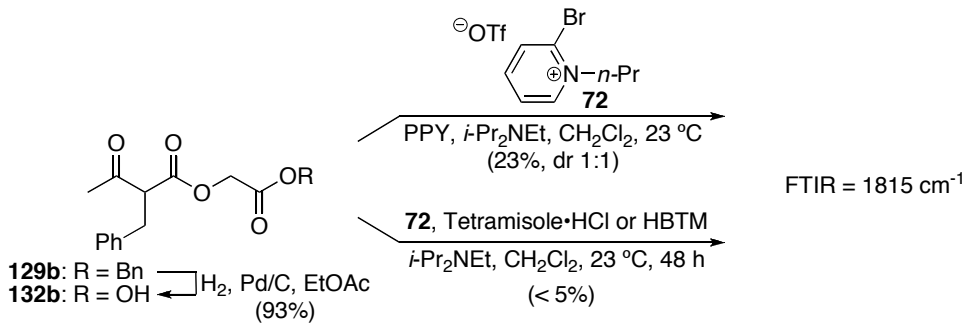
Scheme 4.11. Preparation of Substituted Keto Ester **129b**



of potassium carbonate to act as a shuttle base,[146] or heating due to the sluggish reaction were unsuccessful. The product was unstable and further purification attempts led to product decomposition. Trace amounts of the product were also obtained when tetramisole or HBTM were employed as nucleophiles. Addition of lithium chloride did not lead to any improvement in reaction times or yield.[131] The 1,3-dicarbonyl system is promising, but trace product formation may be a result of the ester preferring to remain in the *s-trans* conformation due to electron donation from the $\sigma \rightarrow \sigma^*$ orbital of the oxygen atom in the C-O bond to the C=O bond that must be overturned to access the *s-cis* conformation in order for cyclization to occur. Also, low yields were observed with tetrahydrofuran-fused β-lactones compared to the carbocyclic analogs, and a similar trend may exist with the β-lactones derived from 1,3-dicarbonyls. Therefore, a carbocyclic 1,3-dicarbonyl analog was pursued.

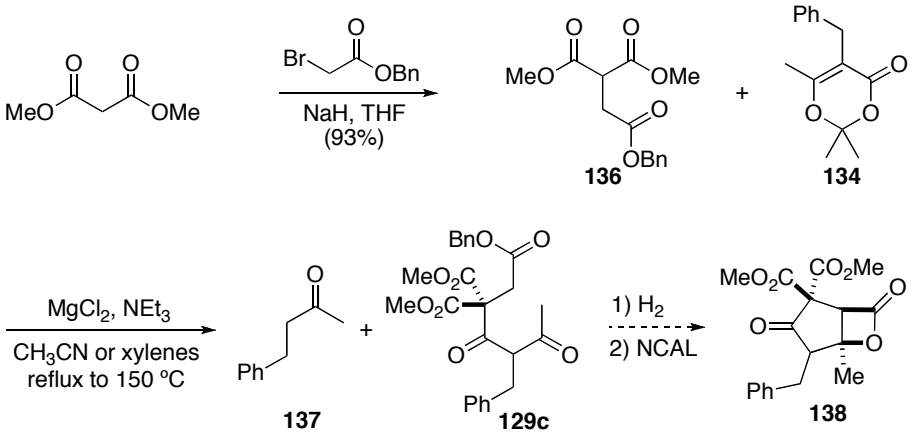
Alkylation of methyl acetoacetate led to triester **136** in excellent yield (Scheme 4.13).[167] Acylation of triester **136** in the presence of magnesium chloride while heating gave 4-phenylbutan-2-one **137** as the major product formed from hydrolysis and

Scheme 4.12. Evidence from the NCAL Process



decarboxylation of dioxinone **134** with only trace amounts of the desired keto ester **129c**.[168] The highly reactive ketene intermediate reacted only sparingly with triester **136**, and thus hindered further testing. Reaction conditions for alkylation of triester **136** need to be developed of which alkylation with the corresponding acid chloride[168,169] or heteroketene dimer may prove useful. Hydrogenolysis of keto ester **129c** would provide the corresponding keto acid in which the Thorpe-Ingold effect may facilitate ring closure. The keto acid could be utilized in further tests towards development of a DKR-NCAL process.

Scheme 4.13. Attempted Preparation of Cyclopentanone-Fused *β*-Lactone



4.7 Conclusions

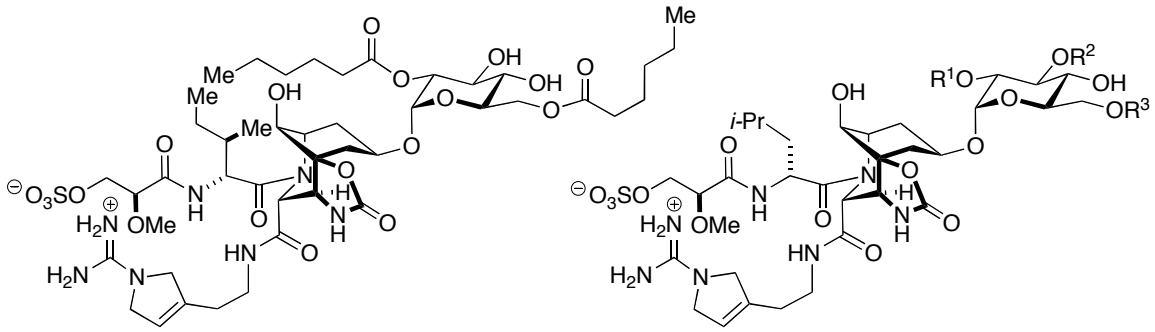
Double diastereodifferentiation with the NCAL process is possible with *cinchona* alkaloid catalysts and enantioenriched aldehyde acids. In particular, carbocycle-fused β-lactones were highly amenable to double diastereodifferentiation leading to improvements in diastereoselectivities from 1:1-2 to >19:1 in several cases. This process thus enables access to highly functionalized carbocycles with existing stereocenters with high diastereoselectivity. While tetrahydrofuran-fused β-lactones were the initial inspiration for this study, only low yields could be obtained with these substrates with some level of double diastereodifferentiation. These studies reveal the exquisite stereochemical control exerted by the *cinchona* alkaloids in the NCAL process given the ability of these catalysts to override the inherent substrate bias and in some cases reverse the diastereoselectivity obtained from substrate control alone. Combination of dynamic kinetic resolution with the NCAL process would provide an influential strategy towards bicyclic β-lactones; however, further studies are needed for development.

CHAPTER V

NUCLEOPHILE CATALYZED, ALDOL-LACTONIZATION (NCAL) FOR BRIDGED TRICYCLIC β-LACTONES

5.1 Suomilide

Potential application of the NCAL process to the synthesis of natural products, such as haterumalide NA, inspired investigations of other natural products, which could be accessed through the NCAL process. Since tricyclic β-lactones have previously been prepared with this methodology,[106,113] another variant of the NCAL process could potentially lead to the formation of bridged β-lactones and ultimately culminate in the synthesis of suomilide (Figure 5.1). Suomilide (**139**) belongs to the aeruginsosin family of natural products,[170-172] and is a complex natural product bearing six stereogenic centers featuring an azabicyclononane core (Abn). Suomilide was isolated in 1997 by Fujii and coworkers and has shown to have potent biological activity



139

140: A; R^1=C(O)C_5H_{11}, R^2=C(O)NH_2, R^3=H
141: B; R^1=H, R^2=H, R^3=C(O)C_5H_{11}

Figure 5.1. Structures of suomilide **139** and banyasides A-B **140-141**.

towards trypsin, thrombin, and plasmin with IC_{50} values of 19.4 μM, 1.8 μM, and 6.5 μM respectively.[173] Pluotno and Carmeli reported the isolation of the structurally analogous banyasides A (**140**) and B (**141**) in 2005.[174] A common 8-10 step strategy to access the Abn core of these natural products was reported by Carreira, which featured a tandem Diels-Alder, Mukaiyama-aldol reaction to a substituted oxonorbornene and subsequent manganese-catalyzed hydration installed the final hydroxyl group on the Abn core.[175]

5.2 Retrosynthesis of Suomilide

Our strategy towards the suomilide Abn core **142** was envisioned from Hofman rearrangement of tricyclic β-lactone **143**, which would be obtained from the NCAL process with the appropriate keto acid **144** (Figure 5.2). Aza-Michael addition between protected aspartic acid derivative **145** and enone **146** would deliver keto acid **144**. However, a simplified carbocyclic model system for the Abn core of suomilide was pursued due to further studies required for the aza-Michael reaction (Scheme 5.1, inset).

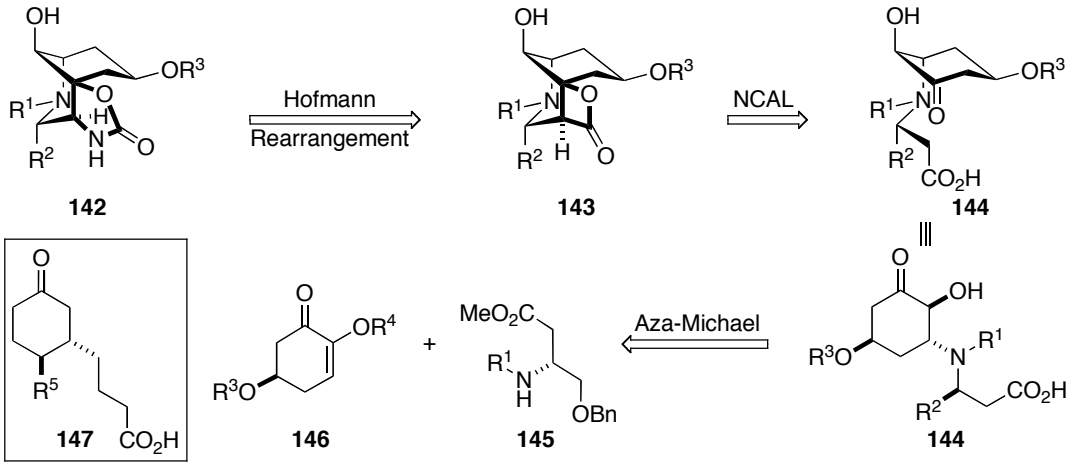
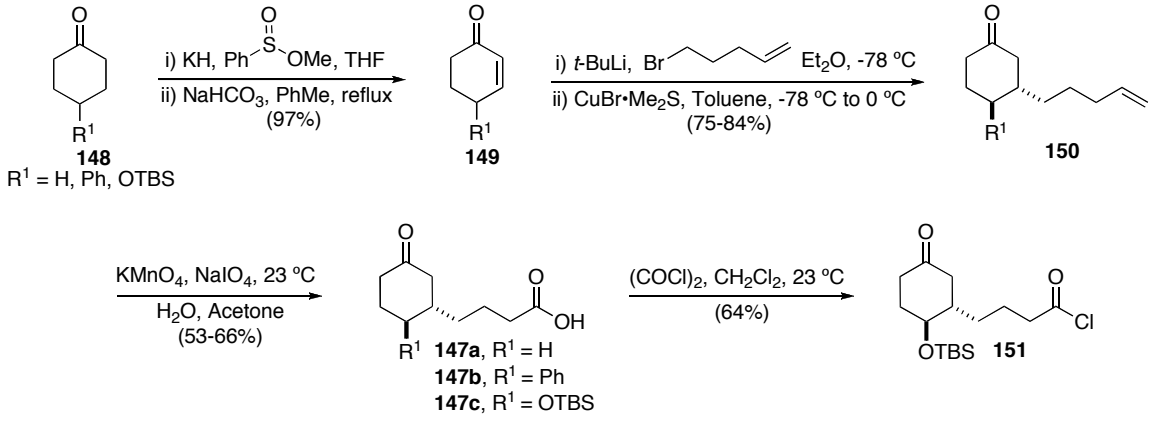


Figure 5.2. Retrosynthetic analysis of suomilide Abn core with the NCAL process.

5.3 Substrate Preparation

Enone **149b-149c** was obtained in good yield after submission of ketone **148** to methyl phenylsulfinate followed by refluxing in toluene (Scheme 5.1).[176] Enones **149a-149c** underwent cuprate addition with 5-bromo-1-pentene in a similar manner to provide alkenes **150a-150c**, which underwent subsequent oxidative cleavage affording keto acids **147a-147c** for use in studies of the NCAL process. Keto acid **147c** was also converted to acid chloride **151** in moderate yield.

Scheme 5.1. Preparation of Keto Acids **147a-147c**

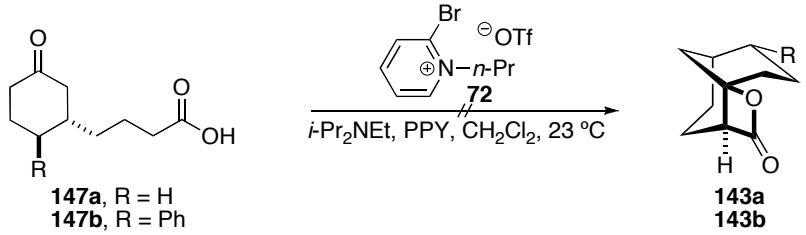


5.4 Synopsis of Results Toward Bridged Tricyclic β-Lactones

Keto acids **147a-147b** were reacted under standard NCAL conditions at room temperature or at elevated temperatures (40 ºC), but only trace reactions were observed (Scheme 5.2). Pyridone was recovered, which hinted at ester activation without subsequent cyclization. A more tractable substrate **147c** was prepared due to the ambiguity of the ^{1}H and ^{13}C NMR when attempting to identify trace products.

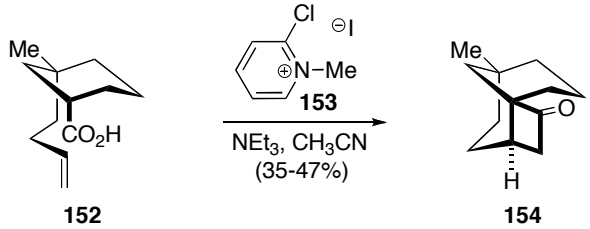
Since the NCAL process did not lead to the desired *β*-lactone **143**, [2+2] cycloaddition conditions were explored. Funk previously reported the preparation of

Scheme 5.2. Initial Attempts to Bridged Tricyclic *β*-Lactone



cyclobutanone **154** in moderate yield via [2+2] cycloaddition of alkene acid **152** (Scheme 5.3).[177] The reaction proceeded through a ketene intermediate, which may offer a viable alternative in the construction of the tricyclic framework of suomilide. Further NCAL reaction conditions could be explored employing alternative nucleophilic promoters and Lewis acids, which were useful in improving yields for keto acid substrates, provided that suitable conditions are found to facilitate the [2+2] cycloaddition to desired *β*-lactone **143** to then serve as a standard.

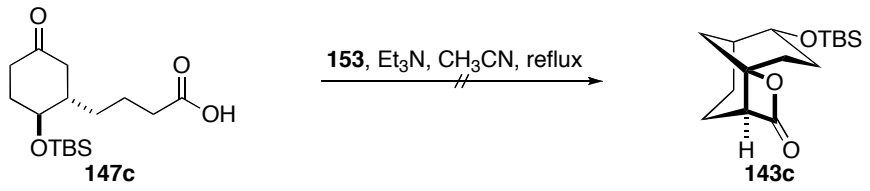
Scheme 5.3. Known Cycloaddition to Bridged Tricyclic Cyclobutanone



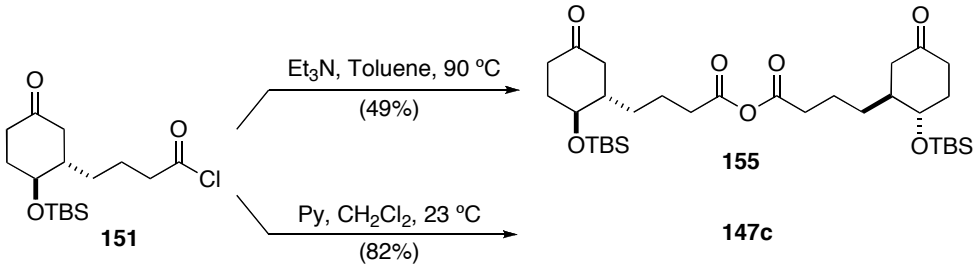
Keto acid **147c** was subjected to pyridinium salt **153** and triethylamine as demonstrated by Funk to provide effective ketene generation; however, no reaction was observed (Scheme 5.4).[178] Keto acid **147c** was then converted to acid chloride **151** and

was submitted to triethylamine while heating in toluene, conditions also known to generate ketene (Scheme 5.5).[179] Unexpectedly, anhydride **155** was obtained in moderate yield. When acid chloride **151** was submitted to pyridine, keto acid **147c** was recovered in good yield due to hydrolysis of the acid chloride.[180] Further studies are needed to overcome the difficulties encountered in the preparation of bridged tricyclic-*β*-lactone **143c**.

Scheme 5.4. Application of Known Cycloaddition Reaction Conditions

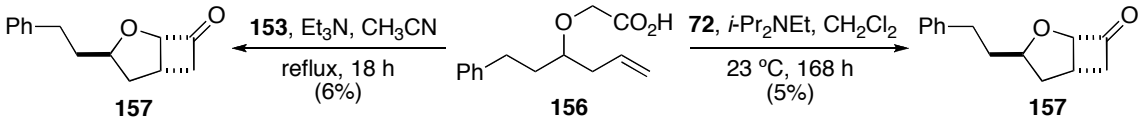


Scheme 5.5. Attempted Formation of Bridged *β*-Lactone from an Acid Chloride



Alkene acid **156** was used to determine if the known [2+2] cycloaddition conditions were reproducible (Scheme 5.6).[179] Indeed, the tetrahydrofuran-fused cyclobutanone **157** was prepared from the known reaction conditions, albeit in low yield. Tetrahydrofuran-fused cyclobutanone **157** could also be prepared in similar yield when subjected to modified pyridinium salt **72** and *i*-Pr_2NEt after extended reaction times.

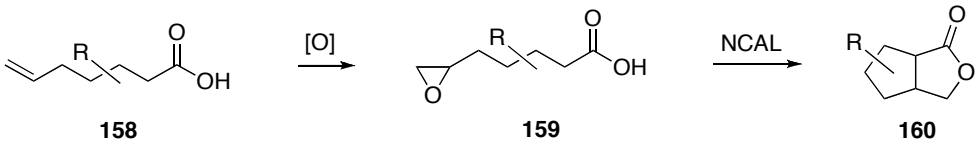
Scheme 5.6. Cycloaddition to Tetrahydrofuran-Fused Cyclobutanone



5.5 Summary of Results with Varied Electrophiles

Variations of the NCAL process have typically investigated substrate scope and asymmetric product formation; however, alteration of the electrophilic component could provide access to varied scaffolds. One variation involved the use of dione containing keto acids, which have provided the highest yields with the NCAL process.[106] Another alternative that was envisioned was the use of epoxy acids **159** as a means to extend the NCAL reaction scope and access γ-lactones rather than β-lactones (Scheme 5.7).

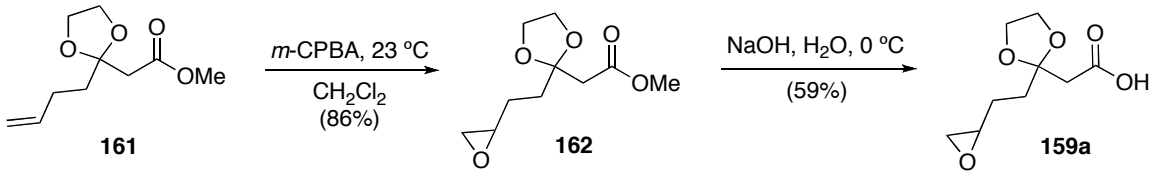
Scheme 5.7. Proposed Access to γ-Lactones from the NCAL Process with Epoxy Acids



Epoxy acid **159a** was desired in order to use NCAL conditions to provide γ-lactone **160a**. Alkene **161** was prepared according to literature procedure by alkylation of methyl acetoacetate with allyl bromide and subsequent dioxolane formation (Scheme 5.8).[181,182] Alkene **161** was epoxidized in the presence of *m*-CPBA providing epoxide **162** of which the ester was hydrolyzed in moderate yield to afford the desired epoxy acid **159a**.[183,184]

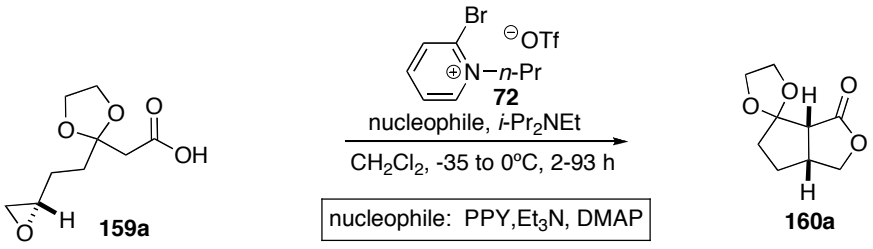
Epoxy acid **159a** was then submitted to the standard NCAL conditions but provided a complex mixture of products at room temperature. The NCAL reaction temperature

Scheme 5.8. Preparation of Epoxy Acid **159a**



was lowered and then run with epoxy acid **159a** with PPY as a nucleophilic promoter, yet multiple products continued to form, which were inseparable by column chromatography (Scheme 5.9). A cleaner reaction resulted from the NCAL reaction of epoxy acid **159a** with triethylamine, but upon work up a ~1:1 mixture of unknown products in addition to starting material were obtained. As in accord to our previous findings, reaction with DMAP as a nucleophile was slow (93 h) and a majority of the starting material remained. Use of a Lewis acid such as lithium chloride may more readily give access to γ-lactones from the NCAL process by further activating the epoxide and thus facilitating ring opening.[131] Another epoxy acid may provide cleaner reactions with higher regioselectivity as well as minimize side reactions with the dioxolane. In addition, hydroxy acid products may be delivered from incomplete cyclization in the NCAL process so a substrate with limited water solubility would be useful for further studies.

Scheme 5.9. NCAL Studies with Epoxy Acids



5.6 Conclusions

Bridged β-lactones remain inaccessible; however, alternative substrates may give more promising results. The NCAL process continually affords 5-membered rings in higher yields in comparison to the formation of 6-membered rings. Thus NCAL reactions to produce 5-membered ring containing bridged tricyclic β-lactones maybe more successful. However, additional [2+2] cycloaddition conditions or NCAL reaction conditions should be explored briefly with keto acid **147c**, as well as be supplemented with computational studies to determine the feasibility for bridged tricyclic-β-lactone formation. Alternate substrates are also needed to make the NCAL process amenable to epoxy acids. Recent applications of the NCAL process employed lithium chloride to increase yields and may assist in epoxide opening to afford γ-lactones.

CHAPTER VI

STEREOSELECTIVE ACCESS TO (*Z*)-CHLORODIALKYL ALKENES THROUGH A MODIFIED NEGISHI CROSS COUPLING OF ZINCATES AND DICHLOROOLEFINS

6.1 Attempted Application to Model System

Our interest in the haterumalides also stimulated the development of a stereoselective cross coupling method to (*Z*)-chlorodialkyl alkenes to construct the *trans*-dialkyl alkene bearing a chlorine atom as found in the natural product (Figure 6.1). A modified Negishi cross coupling between zincates and 1,1-dichloroolefins was further explored based on the reaction conditions found in our group by Dr. Andy Skauge,[81] which were optimized by Dr. Richard Duffy.[114] The known conditions required the use of microwave heating to enhance reaction rates and the sterically encumbered, electron rich, Pd(*t*-$Bu_3P)_2$ (*bis*-(tri-*tert*-butylphosphine) palladium) catalyst (5 mol%).[1] Good yields and excellent selectivity were obtained to provide only monosubstituted (*Z*)-chlorodialkyl alkenes with heteroatom containing zincates (*vide supra*).[81,114] Duffy found that mild preparation of the zincate reagent could be carried out with DMA (*N*,*N*-dimethylacetamide) as reported by Knochel,[82-84] and the DMA zincate preparation was utilized in subsequent reactions.[114]

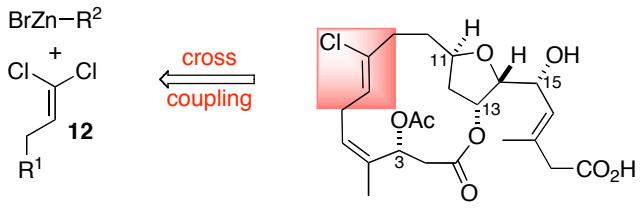
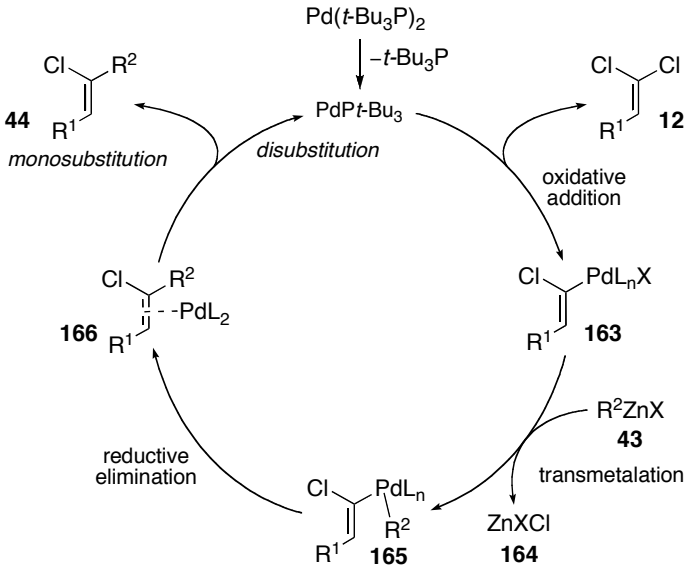


Figure 6.1. Retrosynthetic analysis of haterumalide NA from cross coupling.

The reaction presumably proceeds in a similar manner as the $PdCl_2$(dpephos) catalyst reported by Negishi after displacement of one *t*-Bu_3P ligand, which is known to occcur (Scheme 6.1).[78,185] The reaction then progresses via a palladium(0) catalyst, which undergoes oxidative addition **163** to dichloroolefin **12** followed by transmetalation **165** with the zincate **43**. Reductive elimination delivers the monosubstituted product **44**. Although if the dissociation of the catalyst from the monosubstituted product **44** is slow, disubstituted products **45** would form. The formation of disubstituted products can be readily suppressed by promoting catalyst dissociation with the use more sterically encumbered ligands as demonstrated by Negishi.[78] The electronics of the dichloroolefin also deactivate the initial insertion step, which provides high *trans*-selectivity for the cross coupling products.

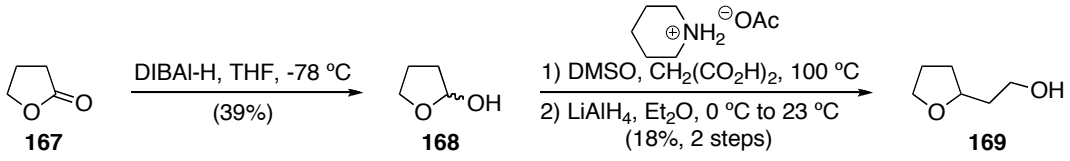
Scheme 6.1. Proposed Mechanism for Modified Negishi Cross Coupling



Duffy proposed the use of a mixture of diastereomeric tetrahydrofurans as a model for cross coupling, and he had demonstrated that strict anhydrous conditions were

necessary for successful cross couplings (DMA < 100 ppm water).[114] The water content of DMA was controlled by distillation from barium oxide, since commercially available DMA contained ≤1000 ppm of water.[85] DMA was dried by stirring with barium oxide at 40 ºC for 12 h followed by subsequent distillation to provide anhydrous DMA (≤150 ppm water).[85] However, intial cross coupling attempts with a dichloroolefin were unsuccessful due to quenching of the zincate (0.83 M in DMA according to iodine titration prior to cross coupling) when DMA was utilized (DMA contained 105 ppm H_2O after two distillations from barium oxide).[85] In attempt to provide a more scalable route to the tetrahydrofuran coupling partner and eliminate formation of product mixtures from the palladium catalyzed *trans*-selective cross coupling, model tetrahydrofuran **169** was prepared (Scheme 6.2).[186] γ-Butyrolactone **167** underwent reduction to lactol **168** was followed by malonic acid addition, decarboxylation, and subsequent reduction to deliver alcohol **169**. However, the volatility of tetrahydrofuran **169** precluded further use.

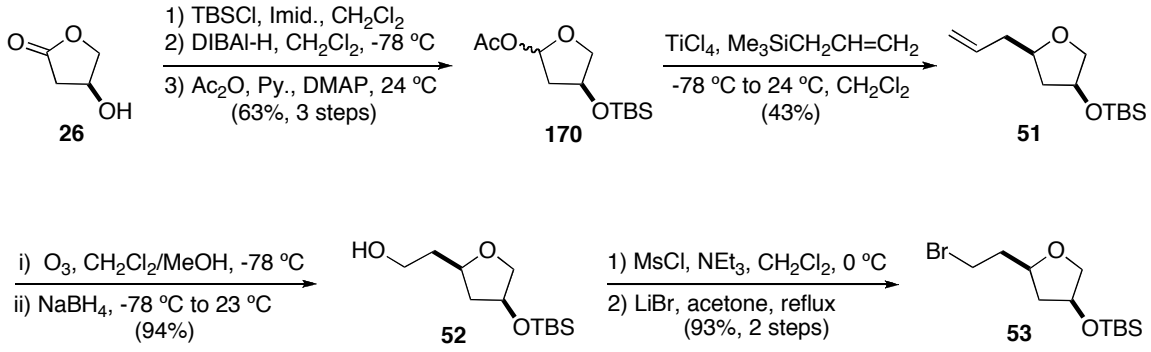
Scheme 6.2. Initial Preparation of Model Tetrahydrofuran



Due to the mixtures of diastereomers and small quantities available for the tetrahydrofuran coupling partners, an alternative model tetrahydrofuran was constructed. The synthesis began with L-malic acid by initial conversion to known alkene **51** by way of lactone **26** (Scheme 6.3).[54,61,62] The alkene was converted to alcohol **52** via reductive ozonolysis, and the resulting primary alcohol **52** was converted to the corresponding bromide **53** by displacement of the corresponding mesylate. This process delivered

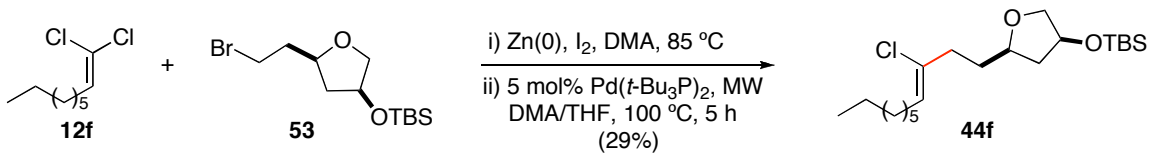
sufficient quantities (12 g) of tetrahydrofuran **53** in excellent yield as a single diastereomer

Scheme 6.3. Scalable Route to Model Tetrahydrofuran



Next, tests were initiated in a more complex setting. Conversion of bromide **53** to the corresponding zincate and subsequent coupling with model dichloroolefin **12f** using our standard protocol in DMA (53 ppm water)[85] gave the monosubstituted product **44f** in 29% yield (Scheme 6.4). The modified Negishi cross coupling provided only the monosubstituted product **44f** and none of the disubstitution products were observed.

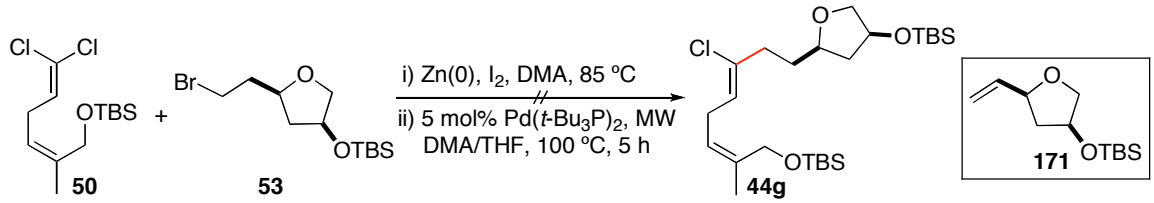
Scheme 6.4. Cross Coupling with Model Tetrahydrofuran



Bromide **53** was then converted to the zincate and subjected to coupling conditions with skipped diene **50**, which was prepared according to the procedure developed by Duffy (Scheme 6.5).[114] Unfortunately, none of the desired product **44g** was obtained. Trace amounts of β-eliminated product **171** (≅6%) were observed along with

67% of recovered starting material **50**. The olefin product **171** presumably arose through a β-elimination pathway. This reaction was run on smaller scale, and the high moisture sensitivity also presumably led to diminished yields. Due to requirements of large excess of zincates, lack of product formation using DMA, and cost concerns, alternative cross coupling methods were explored.

Scheme 6.5. Cross Coupling with Skipped Diene toward Haterumalide NA

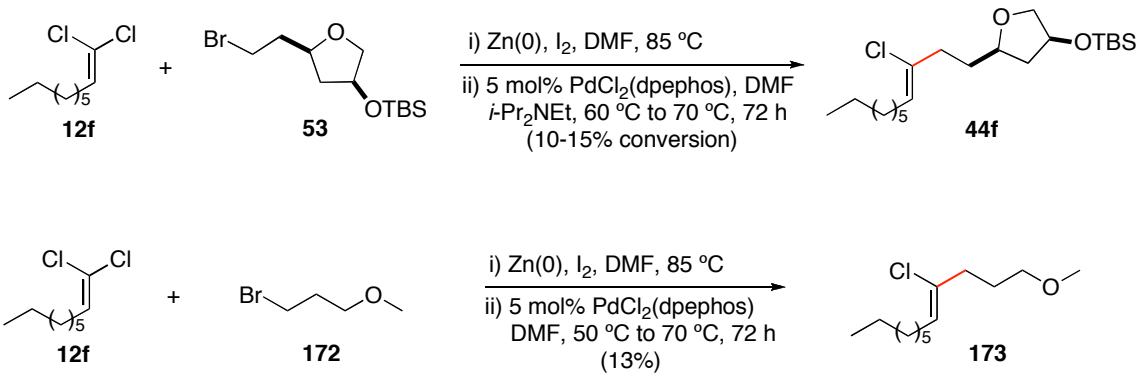


6.2 Alternative Methods for Cross Coupling of Dichloroolefins

During our studies reports by Negishi[78] and Roulland[79] disclosed the development of methods for the stereoselective formation of (*Z*)-dialkyl alkenes from dichloroolefins. Roulland's method required use of fluorine additives, which was later circumvented.[35] Negishi showed that cross couplings occurred in good yield with alkyl zincates in DMF to give predominately monosubstituted products.[11] Thus we sought to apply this methodology towards haterumalide NA. However, use of heteroatom containing zincates led to reduced yields and conversions of dichloroolefin **12f** to monosubstituted product **44f** for the Negishi cross coupling method, which supported use of degassed, commercially available, anhydrous DMF (60-140 ppm water) (Scheme 6.6). Application to a more readily available zincate derived from bromide **172** permitted brief screening of reaction conditions (*e.g.* catalyst loading and zincate equivalents). However, only low yields were obtained. The coordination of the zincate with the heteroatom present within

may affect adversely the reaction rather than coordination effects between the zincate and catalyst since comparable yields were obtained when the reaction was conducted in THF rather than DMF. The low conversions obtained with the use of functionalized zincates with the Negishi protocol in combination with the strict anhydrous conditions required for the microwave mediated cross coupling in DMA led us to reexamine some of our initial leads.

Scheme 6.6. Application of Known Negishi Cross Coupling to Dichloroolefins



6.3 Improvements to the Modified Negishi Cross Coupling

Initial leads for identified by Skauge the stereoselective formation of (*Z*)-chlorodialkyl alkenes employed the sterically encumbered Pd(*t*-$Bu_3P)_2$ catalyst, microwave heating conditions for 0.5 h, and use of a NMP/THF mixed solvent system (*vide supra*).[81] Skauge reported two examples with yields up to 66%, but more mild conditions for zincate generation were necessary for further studies.[81] NMP was then further explored for use in the cross coupling reaction due to the stringent anhydrous conditions, expense when conducting the cross coupling in DMA, and the promising results obtained previously with NMP.

6.3.1 Optimization of Reaction Conditions

Zincate **43b** was then prepared in a similar manner to those fomed in DMA and DMF; however, the solvent was replaced with NMP (commercialy available NMP contained 112 ppm water) (Scheme 6.7). Conversion of bromide **174** to zincate **43b** proceeded with 100% conversion and provided zincate **43b** as a 1.0 M solution in NMP. All subsequent zincates were prepared in a similar fashion.

The results reported by Skauge with commercially available anhydrous NMP (1-methyl-2-pyrrolidinone) were reproducible (Table 6.1, entry 1).[81,86] Complete conversion

Scheme 6.7. Use of NMP during Zincate Generation

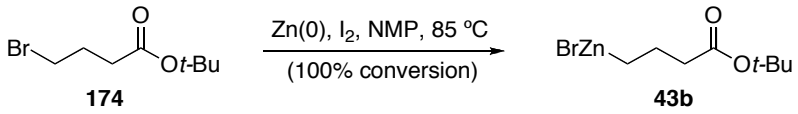
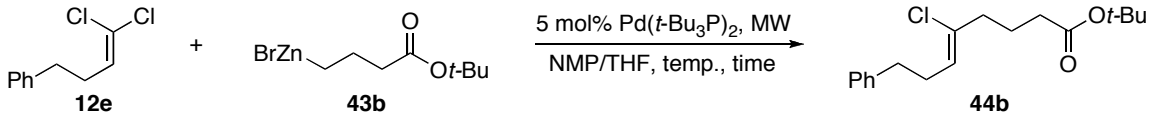


Table 6.1. Optimization of Modified Negishi Cross Coupling in NMP with Functionalized Zincates



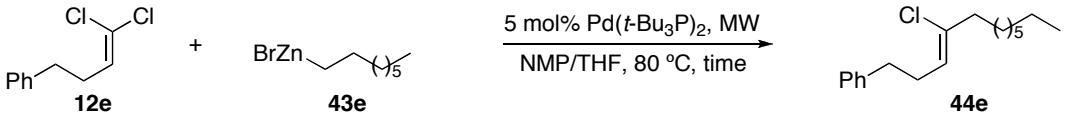
entry	**12e** (equiv)	**43b** (equiv)	time (h)	temp (ºC)	% conversion[a]
1	1	4	0.5	120	100[c]
2	1	3	2	100	100
3	1	3	2	90	100
4	1	3	2	80	100[d]
5	1	3	2	60	67
6	1	3	0.5	80	100[e]
7	1	2	0.5	80	47 (26)[b]
8	1	1.2	0.5	80	13

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Reaction un at 100 ºC. [c] Obtained 45% isolated yield. [d] Obtained 40% isolated yield. [e] Isolated yield was 38%.

to monosubstituted product **44b** was observed when the reaction was run at 80 ºC to 120 ºC (Table 6.1, entries 1-4). Decreasing the reaction time to 0.5 h did not lead to any decrease in product formation (Table 6.1, entry 5). However, the cross coupling conditions required excess zincate **43b**, which was not overridden simply by increased reaction temperatures (Table 6.1, entries 6-8). Employing NMP as the solvent significantly decreased the reaction time and temperature (DMA required 5 h), and afforded the coupled products in moderate yields. *Reaction conditions deemed optimal for functionalized zincates utilized 3 equiv of zincate at 80 ºC for 0.5 h*.

The modified Negishi cross coupling was also extended to include unfunctionalized zincates **43e** (Table 6.2).[81] Unfunctionalized zincates **43e**, previously precluded when using DMA, required extended reaction times (Table 6.2, entries 3 and 5). Thus employing NMP provided more practical cross coupling reaction conditions, which utilized commercially available catalyst and solvent while maintaining tolerable anhydrous conditions.

Table 6.2. Optimization of Modified Negishi Cross Coupling in NMP with Unfunctionalized Zincates



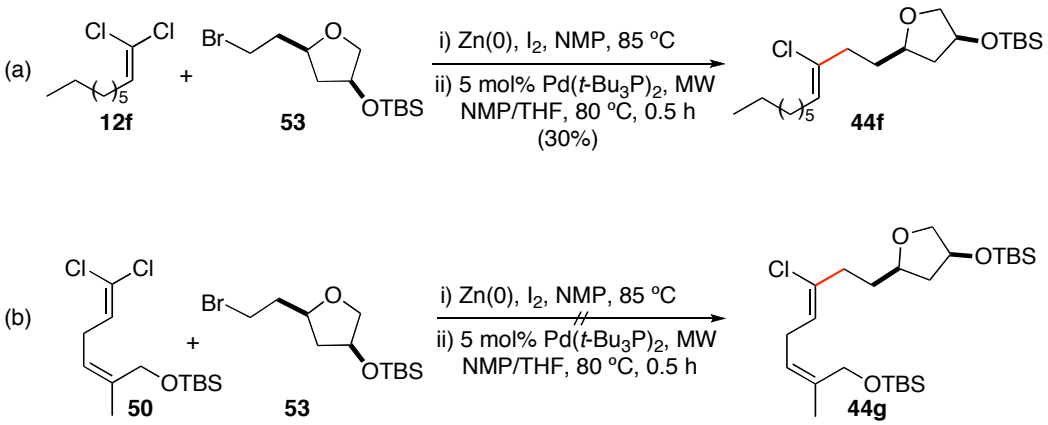
entry	**12e** (equiv)	**43e** (equiv)	time (h)	% conversion[a]
1	1	3	0.5	54
2	1	3	2	74
3	1	3	3	90[b]
4	1	5	0.5	63
5	1	5	2	100

[a] Determined by integration of ^{1}H NMR of crude reaction mixture. [b] Obtained 38% isolated yield.

6.3.2 Application with Model Tetrahydrofuran

Conversion of bromide **53** to the corresponding zincate and subsequent coupling with model dichloroolefin **12f** using in NMP gave the monosubstituted product **44f** in 30% yield (Scheme 6.8a). However, further attempts to apply the cross coupling reaction conditions to the skipped diene were unsuccessful providing unreacted dichloroolefin **50** (Scheme 6.8b). Although due to the limited quantities of the skipped diene **50** that was used, several variables may have affected the reaction outcome. Thus a scalable route to a skipped diene fragment was pursued.

Scheme 6.8. Modified Negishi Cross Coupling with Model Tetrahydrofuran in NMP

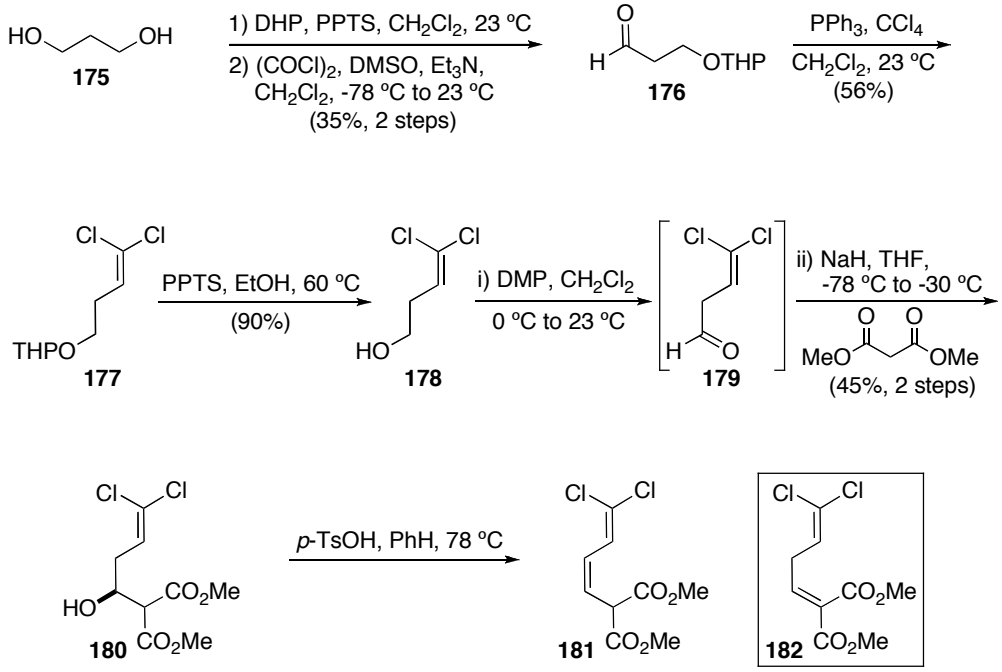


6.3.3 Scalable Route to the Skipped Diene

Facile access to a skipped diene in large quantities was pursued to overcome the drawbacks to the skipped diene fragment previously prepared (*vide supra*).[114] Protection of 1,3-propanediol with subsequent oxidation gave aldehyde **176**, which was easily converted to dichloroolefin **177** under Corey-Fuchs conditions (Scheme 6.9).[187] The free alcohol **178** was revealed upon treatment with PPTS in ethanol while heating.[188] Oxidation of alcohol **178** was accomplished with DMP[189] in order to avoid isomerization

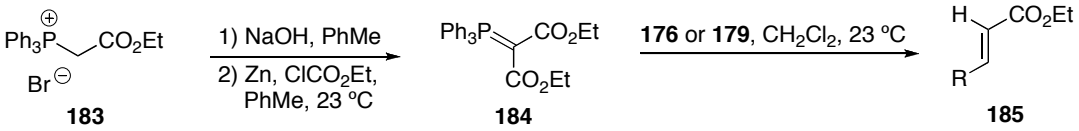
of the aldehyde product **179** that proved facile in the presence of a variety of other oxidation conditions (*e.g.* PCC, Swern, and Moffatt). Isomerization of aldehyde **179** could be avoided during oxidation by the use of DMP with the appropriate work-up procedure, which entailed dilution with Et_2O followed by filtering through a pad of celite. Subsequent addition of dimethyl malonate afforded alcohol **180** in moderate yield. However, attempts to eliminate the alcohol in order to provide the desired skipped diene **182** were unsuccessful and gave no reaction (heating PPTS or piperidinium acetate in PhH/DMSO) or led instead to elimination (*p*-TsOH, PhH, 78 ºC) into conjugation with dichloroolefin **181**.[190] Acidic and buffered conditions were explored since both the aldehyde and the skipped diene were prone to isomerization, yet mild basic conditions may give the desired product. Although, an alternate route was pursued in order utilize more mild conditions during the later stages of skipped diene **182** preparation.

Scheme 6.9. Alternative Scalable Skipped Diene Route



An alternative route was pursued in order to circumvent isomerization and instead install the dichloroalkene moiety at a later stage (Scheme 6.10). However, attempted formation of the diacyl ylide **184** gave the vinyl ester product **185** along with starting material, which demonstrated that the diacyl ylide never formed.[191,192] A scalable route to the skipped diene fragment is plausible, but formation of the sensitive skipped diene remained elusive from either elimination or Wittig olefination routes. Several methods exist for the preparation of ylide **184**, yet several publications of haterumalide syntheses discouraged further pursuit of this methodology.[34-37]

Scheme 6.10. Ylide Preparation and Attempted Application to Skipped Diene



6.4 Conclusions

The modified Negishi cross coupling method offers a strategy for the highly selective palladium catalyzed coupling of 1,1-dichloroalkenes with both heteroatom-substituted and unfunctionalized zincates in moderate yields using commercially available catalyst and solvent. Significant progress has recently been made with 1,1-dichloroolefin couplings. However, limitations of substrate compatibility remain a challenge with our developed reaction conditions.

CHAPTER VII

CONCLUSIONS

The utility of β-lactones as synthetic scaffolds along with natural product targets, haterumalide NA, served as sources of inspiration and prompted studies regarding reactivity of spiroepoxy-β-lactones in conjunction with extensions of the nucleophile catalyzed, aldol-lactonization (NCAL) reaction and improvements to a modified Negishi cross coupling. Spiroepoxy-β-lactones demonstrated several modes of reactivity and could be derived from the corresponding homo- or heteroketene dimers according to known procedures, yet the desired reaction manifold remained elusive. Thus the NCAL process was applied to β-lactone fused tetrahydrofurans. The tetrahydrofuran-fused β-lactones were prepared, albeit in reduced yields, and exhibited some level of double diastereodifferentiation when tetramisole catalyst derivatives were employed. However, development of a double diastereoselective NCAL process was more readily facilitated with the use of β-lactone fused carbocycles. *Cinchona* alkaloids previously rendered the NCAL process enantioselective, and employing enantioenriched substrates led to a double diastereoselective NCAL process. With carbocyclic substrates the inherent substrate bias could be overcome and led to improvements in the diastereoselectivity form 1:1-2 up to >19:1. Further applications of the NCAL process included involvement of dynamic kinetic resolution or access to bridged tricyclic β-lactones aimed at other natural products. Initial studies of a DKR-NCAL process were conducted, and the 1,3-dicarbonyl containing keto acid substrates are promising. Problematic preparation of the

γ-lactone-fused β-lactone system motivated further studies toward cyclopentanone-fused β-lactones, which may expedite development of a DKR-NCAL process. Substrates directed toward bridged tricyclic β-lactones and carbocycle-fused γ-lactones were also studied briefly. Advent of NCAL conditions utilizing both a nucleophile (Lewis base) as well as a Lewis acid (lithium chloride) may also enable access to carbocycle-fused γ-lactone systems via the NCAL process, which warrants further investigations. Initial cross coupling conditions were further optimized and applied with a model tetrahydrofuran fragment towards haterumalide NA. Reacting 1,1-dichoroolefins in conjunction with a functionalized or unfunctionalized zincate in the modified Negishi cross coupling led to *trans*-trisubstituted alkenes containing a chlorine atom, and similar strategies were in fact applied in total syntheses of haterumalide NA. Use of NMP for zincate generation enabled utility of commercially available anhydrous solvent in the modified Negishi cross coupling.

REFERENCES

(1) Trost, B. *Science* **1991**, *254*, 1471-1477.

(2) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem. Int. Ed.* **2009**, *48*, 2854-2867.

(3) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010-3021.

(4) Trost, B. M. *Science* **1983**, *219*, 245-250.

(5) Newman, D. J.; Cragg, G. M.; Snader, K. M. *J. Nat. Prod.* **2003**, *66*, 1022-1037.

(6) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II*; Wiley-VCH: Germany, 2003.

(7) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; 4 ed.; VCH Publishers, Inc.: New York, 1996.

(8) Sierra, M. Á.; Torre, M. C. d. l. *Dead Ends and Detours: Direct Ways to Successful Total Synthesis*; Wiley-VCH: New York, 2004.

(9) Trost, B. M.; Dong, G. *Nature* **2008**, *456*, 485-488.

(10) Enquist Jr, J. A.; Stoltz, B. M. *Nature* **2008**, *453*, 1228-1231.

(11) Mohr, J. T.; Ebner, D. C.; Stoltz, B. M. *Organic & Biomolecular Chemistry* **2007**, *5*, 3571-3576.

(12) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307-1315.

(13) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936-938.

(14) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974-5976.

(15) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263-4265.

(16) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968-1970.

(17) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932-7934.

(18) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856-5858.

(19) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989-93.

(20) Takada, N.; Sato, H.; Suenaga, K.; Arimoto, H.; Yamada, K.; Ueda, K.; Uemura, D. *Tetrahedron Lett.* **1999**, *40*, 6309-6312.

(21) Ueda, K.; Hu, Y. *Tetrahedron Lett.* **1999**, *40*, 6305-6308.

(22) Teruya, T.; Shimogawa, H.; Suenaga, K.; Kigoshi, H. *Chem. Lett.* **2004**, *33*, 1184-1185.

(23) Teruya, T.; Suenaga, K.; Maruyama, S.; Kurotaki, M.; Kigoshi, H. *Tetrahedron* **2005**, *61*, 6561-6567.

(24) Strobel, G.; Li, J.-Y.; Sugawara, F.; Koshino, H.; Harper, J.; Hess, W. M. *Microbiology* **1999**, *145*, 3557-3564.

(25) Thaning, C.; Welch, C. J.; Borowicz, J. J.; Hedman, R.; Gerhardson, B. *Soil Biol. Biochem.* **2001**, *33*, 1817-1826.

(26) Levenfors, J. J.; Hedman, R.; Thaning, C.; Gerhardson, B.; Welch, C. J. *Soil Biol. Biochem.* **2004**, *36*, 677-685.

(27) Kobayashi, M.; Sato, K.; Yoshimura, S.; Yamaoka, M.; Takase, S.; Ohkubo, M.; Fujii, T.; Nakajima, H. *J. Antibiot.* **2005**, *58*, 648-653.

(28) Sato, B.; Nakajima, H.; Fujita, T.; Takase, S.; Yoshimura, S.; Kinoshita, T.; Terano, H. *J. Antibiot.* **2005**, *58*, 634-639.

(29) Yamaoka, M.; Sato, K.; Kobayashi, M.; Nishio, N.; Ohkubo, M.; Fujii, T.; Nakajima, H. *J. Antibiot.* **2005**, *58*, 654-662.

(30) Inami, M.; Kawamura, I.; Tsujimoto, S.; Yasuno, T.; Lacey, E.; Hirosumi, J.; Takakura, S.; Nishigaki, F.; Naoe, Y.; Manda, T.; Mutoh, S. *J. Antibiot.* **2005**, *58*, 640-647.

(31) Kigoshi, H.; Kita, M.; Ogawa, S.; Itoh, M.; Uemura, D. *Org. Lett.* **2003**, *5*, 957-960.

(32) Gu, Y.; Snider, B. B. *Org. Lett.* **2003**, *5*, 4385-4388.

(33) Hoye, T. R.; Wang, J. *J. Am. Chem. Soc.* **2005**, *127*, 6950-6951.

(34) Hayakawa, I.; Ueda, M.; Yamaura, M.; Ikeda, Y.; Suzuki, Y.; Yoshizato, K.; Kigoshi, H. *Org. Lett.* **2008**, *10*, 1859-1862.

(35) Roulland, E. *Angew. Chem. Int. Ed.* **2008**, *47*, 3762-3765.

(36) Schomaker, J. M.; Borhan, B. *J. Am. Chem. Soc.* **2008**, *130*, 12228-12229.

(37) Ueda, M.; Yamaura, M.; Ikeda, Y.; Suzuki, Y.; Yoshizato, K.; Hayakawa, I.; Kigoshi, H. *J. Org. Chem.* **2009**, *74*, 3370-3377.

(38) Kigoshi, H.; Hayakawa, I. *Chem. Rec.* **2007**, *7*, 254-264.

(39) Hiersemann, M. *Nachr. Chem.* **2006**, *54*, 1091-1095.

(40) Morris, K. A.; Arendt, K. M.; Oh, S. H.; Romo, D. **2010**, submitted.

(41) Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257-1258.

(42) Taguchi, T.; Nishi, M.; Watanabe, K.; Mukaiyama, T. *Chem. Lett.* **1973**, 1307-10.

(43) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503-7509.

(44) Mukaiyama, T. *Aldrichimica Acta* **1996**, *29*, 59-76.

(45) Heathcock, C. H. *Science* **1981**, *214*, 395-400.

(46) Wang, Y.; Zhao, C.; Romo, D. *Org. Lett.* **1999**, *1*, 1197-1199.

(47) Yang, H. W.; Romo, D. *J. Org. Chem.* **1997**, *62*, 4-5.

(48) Yang, H. W.; Zhao, C.; Romo, D. *Tetrahedron* **1997**, *53*, 16471-16488.

(49) Schmitz, W. D.; Messerschmidt, N. B.; Romo, D. *J. Org. Chem.* **1998**, *63*, 2058-2059.

(50) Wang, Y.; Romo, D. *Org. Lett.* **2002**, *4*, 3231-3234.

(51) Ma, G.; Zancanella, M.; Oyola, Y.; Richardson, R. D.; Smith, J. W.; Romo, D. *Org. Lett.* **2006**, *8*, 4497-4500.

(52) Mead, K. T.; Pillai, S. K. *Tetrahedron Lett.* **1993**, *34*, 6997-7000.

(53) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10879-10884.

(54) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208-12209.

(55) Mitchell, T. A.; Romo, D. *J. Org. Chem.* **2007**, *72*, 9053-9059.

(56) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322-4343.

(57) Mitchell, T. A.; Zhao, C.; Romo, D. *Angew. Chem. Int. Ed.* **2008**, *47*, 5026-5029.

(58) Mitchell, T. A.; Zhao, C.; Romo, D. *J. Org. Chem.* **2008**, *73*, 9544-9551.

(59) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521-15528.

(60) Tanaka, A.; Yamashita, K. *Synthesis* **1987**, 570-573.

(61) Saito, S.; Hasegawa, T.; Inaba, M.; Nishida, R.; Fujii, T.; Nomizu, S.; Moriwake, T. *Chem. Lett.* **1984**, *13*, 1389-1392.

(62) Rhee, J. U.; Bliss, B. I.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2003**, *125*, 1492-1493.

(63) Kobayashi, S.; Horibe, M.; Saito, Y. *Tetrahedron* **1994**, *50*, 9629-9642.

(64) Wang, Y. Ph.D. Dissertation, Texas A&M University, 2002.

(65) Yang, H. W. Ph.D. Dissertation, Texas A&M University, 1998.

(66) Paterson, I.; Temal-Laïb, T. *Org. Lett.* **2002**, *4*, 2473-2476.

(67) Murga, J.; Falomir, E.; Carda, M.; González, F.; Marco, J. A. *Org. Lett.* **2001**, *3*, 901-904.

(68) Morris, K. A. unpublished results, Texas A&M University, 2004-2010.

(69) Marco, J. A.; Carda, M.; Diaz-Oltra, S.; Murga, J.; Falomir, E.; Roeper, H. *J. Org. Chem.* **2003**, *68*, 8577-8582.

(70) Duffy, R. J. unpublished results, Texas A&M University, 2002-2007.

(71) Roush, W. R.; Moriarty, K. J.; Brown, B. B. *Tetrahedron Lett.* **1990**, *31*, 6509-6512.

(72) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173-2174.

(73) Sata, N. U.; Matsunaga, S.; Fusetani, N.; van Soest, R. W. M. *J. Nat. Prod.* **1999**, *62*, 969-971.

(74) Chou, T.; Kuramoto, M.; Otani, Y.; Shikano, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3871-3874.

(75) Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867-3870.

(76) Netherton, M. R.; Fu, G. C. In *Topics in Organometallic Chemistry* ; Fürstner, A., Ed.; Palladium in Organic Synthesis 14; Springer: New York: 2005, p 85-108.

(77) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442-4489.

(78) Tan, Z.; Negishi, E.-i. *Angew. Chem. Int. Ed.* **2006**, *45*, 762-765.

(79) Liron, F. d. r.; Fosse, C. l.; Pernolet, A.; Roulland, E. *J. Org. Chem.* **2007**, *72*, 2220-2223.

(80) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719-2724.

(81) Skauge, A. Post-Doctoral Research Final Report, Texas A&M University, 2005.

(82) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726-14727.

(83) *Organozinc Reagents*; Knochel, P., Jones, P., Eds.; A Practical Approach Series; Oxford: New York, 1999.

(84) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 4414-4435.

(85) Water content was measured by Karl-Fischer titration.

(86) Reactions were run with >100 ppm of water as determined by Karl-Fischer titration.

(87) Barbot, F.; Miginiac, P. *Helv. Chim. Acta* **1979**, *62*, 1451-1457.

(88) Dale, W. J.; Sisti, A. J. *J. Am. Chem. Soc.* **1954**, *76*, 81-82.

(89) Malanga, C.; Menicagli, R.; Dell'Innocenti, M.; Lardicci, L. *Tetrahedron Lett.* **1987**, *28*, 239-240.

(90) Hale, K. J.; Hummersone, M. G.; Bhatia, G. S. *Org. Lett.* **2000**, *2*, 2189-2192.

(91) The lactone obtained matched the previously reported data by Roulland, see reference 35.

(92) Tiseni, P. S.; Peters, R. *Angew. Chem. Int. Ed.* **2007**, *46*, 5325-5328.

(93) Duffy, R. J.; Morris, K. A.; Romo, D. *Tetrahedron* **2009**, *65*, 5879-5892.

(94) Calter, M. A.; Guo, X. *J. Org. Chem.* **1998**, *63*, 5308-5309.

(95) Calter, M. A.; Guo, X.; Liao, W. *Org. Lett.* **2001**, *3*, 1499-1501.

(96) Calter, M. A.; Liao, W. *J. Am. Chem. Soc.* **2002**, *124*, 13127-13129.

(97) Calter, M. A.; Orr, R. K.; Song, W. *Org. Lett.* **2003**, *5*, 4745-4748.

(98) Duffy, R. J.; Morris, K. A.; Romo, D. *J. Am. Chem. Soc.* **2005**, *127*, 16754-16755.

(99) Duffy, R. J.; Morris, K. A.; Vallakati, R.; Zhang, W.; Romo, D. *J. Org. Chem.* **2009**, *74*, 4772-4781.

(100) Fusetani, N. *Nat. Prod. Rep.* **2004**, *21*, 94-104.

(101) Brown, G. D.; Wong, H.-F. *Tetrahedron* **2004**, *60*, 5439-5451.

(102) Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123*, 7945-7946.

(103) Oh, S. H.; Cortez, G. S.; Romo, D. *J. Org. Chem.* **2005**, *70*, 2835-2838.

(104) Cortez, G. S.; Oh, S. H.; Romo, D. *Synthesis* **2001**, 1731-1736.

(105) For a review of cinchona alkaloids as organocatalysts see; Marcelli, T.; Maarseveen, J. H. v.; Hiemstra, H. *Angew. Chem. Int. Ed.* **2006**, *45*, 7496-7504.

(106) Purohit, V. C.; Matla, A. S.; Romo, D. *J. Am. Chem. Soc.* **2008**, *130*, 10478-10479.

(107) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351-1354.

(108) Ma, G.; Nguyen, H.; Romo, D. *Org. Lett.* **2007**, *9*, 2143-2146.

(109) Crich, D.; Hao, X. *J. Org. Chem.* **1999**, *64*, 4016-4024.

(110) Sharpless, K. B. *Chem. Scr.* **1985**, *25*, 71-77.

(111) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem. Int. Ed.* **1985**, *24*, 1-30.

(112) Parker, K. A.; Dermatakis, A. *J. Org. Chem.* **1997**, *62*, 6692-6696.

(113) Henry-Riyad, H.; Lee, C.; Purohit, V. C.; Romo, D. *Org. Lett.* **2006**, *8*, 4363-4366.

(114) Duffy, R. J. Ph.D. Dissertation, Texas A&M University, 2007.

(115) Narasimhan, S.; Madhavan, S.; Prasad, K. G. *J. Org. Chem.* **1995**, *60*, 5314-5315.

(116) Geetha Saraswathy, V.; Sankararaman, S. *J. Org. Chem.* **1994**, *59*, 4665-4670.

(117) Sudha, R.; Malola Narasimhan, K.; Geetha Saraswathy, V.; Sankararaman, S. *J. Org. Chem.* **1996**, *61*, 1877-1879.

(118) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 2738-2739.

(119) For recent publications not included in these reviews, see references 122 and 125-127.

(120) Orr, R. K.; Calter, M. A. *Tetrahedron* **2003**, *59*, 3545-3565.

(121) Paull, D. H.; Weatherwax, A.; Lectka, T. *Tetrahedron* **2009**, *65*, 6771-6803.

(122) Purohit, V. C.; Matla, A. S.; Romo, D. *Heterocycles* **2008**, *76*, 949-979.

(123) Yang, H. W.; Romo, D. *Tetrahedron* **1999**, *55*, 6403-6434.

(124) For reviews describing enantioselective *β*-lactone synthesis, see references 120-121 and 123.

(125) Chidara, S.; Lin, Y.-M. *Synlett* **2009**, 1675-1679.

(126) Phillips, E. M.; Wadamoto, M.; Scheidt, K. A. *Synthesis* **2009**, *2009*, 687-690.

(127) Wang, X.-N.; Shao, P.-L.; Lv, H.; Ye, S. *Org. Lett.* **2009**, *11*, 4029-4031.

(128) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166-168.

(129) Calter, M. A. *J. Org. Chem.* **1996**, *61*, 8006-8007.

(130) Nguyen, H.; Ma, G.; Romo, D. *Chem. Commun.* **2010**, DOI: 10.1039/C0CC00607F.

(131) Leverett, C.; Romo, D. *Angew. Chem. Int. Ed.* **2010**, manuscript in preparation.

(132) Vicario, J. L.; Badia, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 5801-5807.

(133) Calter, M. A.; Tretyak, O. A.; Flaschenriem, C. *Org. Lett.* **2005**, *7*, 1809-1812.

(134) Zhu, C.; Shen, X.; Nelson, S. G. *J. Am. Chem. Soc.* **2004**, *126*, 5352-5353.

(135) Allais, F.; Cossy, J. *Org. Lett.* **2006**, *8*, 3655-3657.

(136) Bose, D. S.; Fatima, L.; Rajender, S. *Synthesis* **2006**, *11*, 1863-1867.

(137) Gravestock, M. B.; Knight, D. W.; Lovell, J. S.; Thornton, S. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3143-3155.

(138) Simonot, B.; Rousseau, G. *Synth. Commun.* **1993**, *23*, 549-60.

(139) Hartke, K.; Richter, W.; Massa, W.; Baum, G. *Tetrahedron Lett.* **1986**, *27*, 2743-2746.

(140) Goel, O. P.; Krolls, U.; Stier, M.; Kesten, S. *Organic Synthesis* **1989**, *67*, 69-71.

(141) Tunoori, A. R.; White, J. M.; Georg, G. I. *Org. Lett.* **2000**, *2*, 4091-4093.

(142) Crich, D.; Yao, Q. *J. Org. Chem.* **1996**, *61*, 3566-3570.

(143) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925-7926.

(144) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65-75.

(145) Wender, P. A.; Horan, J. C.; Verma, V. A. *Org. Lett.* **2006**, *8*, 5299-5302.

(146) Lui, G. developed procedure, Texas A&M Univesity, 2010.

(147) Larock, R. C.; Hightower, T. R.; Kraus, G. A.; Hahn, P.; Zheng, D. *Tetrahedron Lett.* **1995**, *36*, 2423-2426.

(148) Rodeschini, V.; Van de Weghe, P.; Salomon, E.; Tarnus, C.; Eustache, J. *J. Org. Chem.* **2005**, *70*, 2409-2412.

(149) Marotta, E.; Foresti, E.; Marcelli, T.; Peri, F.; Righi, P.; Scardovi, N.; Rosini, G. *Org. Lett.* **2002**, *4*, 4451-4453.

(150) Oh, S. H. Ph.D. Dissertation, Texas A&M University, 2006.

(151) For details of the X-ray crystal structure see Appendix A.

(152) Birman, V. B.; Li, X. *Org. Lett.* **2008**, *10*, 1115-1118.

(153) Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475-1490.

(154) Pellissier, H. *Tetrahedron* **2003**, *59*, 8291-8327.

(155) Pellissier, H. *Tetrahedron* **2008**, *64*, 1563-1601.

(156) Huerta, F. F.; Minidis, A. B. E.; Backvall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321-331.

(157) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5-26.

(158) Ebbers, E. J.; Ariaans, G. J. A.; Houbiers, J. P. M.; Bruggink, A.; Zwanenburg, B. *Tetrahedron* **1997**, *53*, 9417-9476.

(159) Cortez, G. S., Post-Doctoral Research Final Report, Texas A&M University, 2002.

(160) Murphy, P. J.; Harri Lloyd, W.; Hibbs, D. E.; Hursthouse, M. B.; Abdul Malik, K. M. *Tetrahedron* **1996**, *52*, 8315-8332.

(161) Bradley, P. A.; Dack, K. N.; Johnson, P. S.; Skerratt, S. E. Preparation of pyrazole derivatives as progesterone receptor antagonists. U.S. Patent. US 2006-592574, 2007.

(162) Sarek, J.; Hajduch, M.; Svoboda, M.; Novakova, K.; Spacilova, P.; Kubelka, T.; Biedermann, D. Method of preparation of a soluble formulation of water-insoluble pentacyclic and tetracyclic terpenoids, a soluble formulation of a pentacyclic or tetracyclic terpenoid and a pharmaceutical composition containing this soluble formulation. Patent. WO 2007-CZ88, 2008.

(163) Barrish, J. C.; Lee, H. L.; Mitt, T.; Pizzolato, G.; Baggiolini, E. G.; Uskokovic, M. R. *J. Org. Chem.* **1988**, *53*, 4282-4295.

(164) Marco, J. L.; MartÌn, N.; MartÌnez-Grau, A.; Seoane, C.; Albert, A.; Cano, F. H. *Tetrahedron* **1994**, *50*, 3509-3528.

(165) Graalfs, H.; Frˆhlich, R.; Wolff, C.; Mattay, J. *Eur. J. Org. Chem.* **1999**, *1999*, 1057-1073.

(166) Sato, M.; Ogasawara, H.; Oi, K.; Kato, T. *Chem. Pharm. Bull.* **1983**, *31*, 1896-1901.

(167) Fukuda, T.; Makarova, E. A.; Lukprimeyanets, E. A.; Kobayashi, N. *Chem. Eur. J.* **2004**, *10*, 117-133.

(168) Rathke, M. W.; Cowan, P. J. *J. Org. Chem.* **1985**, *50*, 2622-2624.

(169) Shen, Q.; Huang, W.; Wang, J.; Zhou, X. *Org. Lett.* **2007**, *9*, 4491-4494.

(170) Murakami, M.; Ishida, K.; Okino, T.; Okita, Y.; Matsuda, H.; Yamaguchi, K. *Tetrahedron Lett.* **1995**, *36*, 2785-2788.

(171) Ishida, K.; Okita, Y.; Matsuda, H.; Okino, T.; Murakami, M. *Tetrahedron* **1999**, *55*, 10971-10988.

(172) Ersmark, K.; Del Valle, J. R.; Hanessian, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 1202-1223.

(173) Fujii, K.; Sivonen, K.; Adachi, K.; Noguchi, K.; Shimizu, Y.; Sano, H.; Hirayama, K.; Suzuki, M.; Harada, K.-i. *Tetrahedron Lett.* **1997**, *38*, 5529-5532.

(174) Pluotno, A.; Carmeli, S. *Tetrahedron* **2005**, *61*, 575-583.

(175) Schindler, C. S.; Stephenson, C. R. J.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 8852-8855.

(176) Resek, J. E.; Meyers, A. I. *Tetrahedron Lett.* **1995**, *36*, 7051-7054.

(177) Funk, R. L.; Novak, P. M.; Abelman, M. M. *Tetrahedron Lett.* **1988**, *29*, 1493-1496.

(178) Funk, R. L.; Abelman, M. M.; Jellison, K. M. *Synlett* **1989**, 36-37.

(179) Snider, B. B.; Hui, R. A. H. F. *J. Org. Chem.* **1985**, *50*, 5167-5176.

(180) Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 1717-1719.

(181) Keränen, M. D.; Eilbracht, P. *Organic & Biomolecular Chemistry* **2004**, *2*, 1688-1690.

(182) Funakoshi, K.; Togo, N.; Taura, Y.; Sakai, K. *Chem. Pharm. Bull.* **1989**, *37*, 1776-1779.

(183) Basta, P. V.; Adcock, A. F.; Tallent, C. R.; Fleming, D. N.; Seltzman, H. H.; Whisnant, C. C.; Cook, C. E. *J. Immunological Methods* **2004**, *285*, 181-195.

(184) Appleton, D.; Duguid, A. B.; Lee, S.-K.; Ha, Y.-J.; Ha, H.-J.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 89-101.

(185) Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2003**, *42*, 5749-5752.

(186) Ragoussis, V.; Theodorou, V. *Synthesis* **1993**, 84-85.

(187) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772-3774.

(188) Qiu, Y.; Li, D. *Org. Lett.* **2006**, *8*, 1013-1016.

(189) Mergott, D. J.; Frank, S. A.; Roush, W. R. *Org. Lett.* **2002**, *4*, 3157-3160.

(190) Tietze, L. F.; Beifuss, U.; Ruther, M.; R¸hlmann, A.; Antel, J.; Sheldrick, G. M. *Angew. Chem. Int. Ed.* **1988**, *27*, 1186-1187.

(191) Siebum, A. H. G.; Woo, W. S.; Lugtenburg, J. *Eur. J. Org. Chem.* **2003**, *2003*, 4664-4678.

(192) Meshram, H. M.; Reddy, G. S.; Muralidhar Reddy, M.; Yadav, J. S. *Tetrahedron Lett.* **1998**, *39*, 4107-4110.

(193) Suffert, J. *J. Org. Chem.* **1989**, *54*, 509-510.

(194) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

(195) Purohit, V. C.; Richardson, R. D.; Smith, J. W.; Romo, D. *J. Org. Chem.* **2006**, *71*, 4549-4558.

(196) Murray, R. W.; Singh, M. *Org. Synth.* **1998**, *Coll. Vol. 9*, 288-294.

(197) Caprio, V.; Brimble, M. A.; Furkert, D. P. *Tetrahedron* **2001**, *57*, 4023-4034.

(198) Fujisawa, T.; Igeta, K.; Odake, S.; Morita, Y.; Yasuda, J.; Morikawa, T. *Biorg. Med. Chem.* **2002**, *10*, 2569-2581.

(199) Ochiai, M.; Fujita, E.; Arimoto, M.; Yamaguchi, H. *Chem. Pharm. Bull.* **1985**, *33*, 989-97.

(200) Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2004**, *126*, 2495-2500.

(201) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092-1093.

(202) Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron* **1999**, *55*, 977-988.

(203) Evarts Jr, J. B.; Fuchs, P. L. *Tetrahedron Lett.* **2001**, *42*, 3673-3675.

(204) Greck, C.; Ferreira, F.; GenÍt, J. P. *Tetrahedron Lett.* **1996**, *37*, 2031-2034.

(205) Johannes, J. W.; Wenglowsky, S.; Kishi, Y. *Org. Lett.* **2005**, *7*, 3997-4000.

(206) Xie, C.; Nowak, P.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4427-4429.

(207) Takahata, H.; Kubota, M.; Momose, T. *Tetrahedron: Asymmetry* **1997**, *8*, 2801-2810.

(208) Perepogu, A. K.; Raman, D.; Murty, U. S. N.; Rao, V. J. *Bioorg. Chem.* **2009**, *37*, 46-51.

APPENDIX A

EXPERIMENTAL PROCEDURES

General Procedures

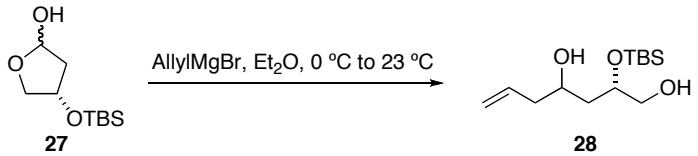
All non-aqueous reactions were carried out under nitrogen atmosphere in oven-dried glassware (120 °C). Acetonitrile (CH_3CN), dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), and toluene were obtained from a MBraun solvent purification system (alumina). Tetrahydrofuran (THF) was distilled from a sodium/benzophenone ketyl still. Methanol was distilled from magnesium prior to use. Triethyl amine (Et_3N), diisopropylamine (*i*-Pr_2NH), and diisopropylethyl amine (*i*-Pr_2NEt) were distilled from calcium hydride immediately prior to use. Anhydrous sodium sulfate (Na_2SO_4) or anhydrous magnesium sulfate ($MgSO_4$) were used in the following procedures. Deuterated solvents were purchased from either Aldrich or Cambridge Isotopes and used as received. Brine refers to a saturated aqueous sodium chloride solution. The molarities indicated for organolithium reagents were established by titration with *N*-Pivaloyl-*o*-toluidine as indicator.[193] All other commercially available reagents were used as received. Flash column chromatography was carried out with silica gel 60Å (230-400 Mesh) as a stationary phase as described by Still.[194] Thin layer chromatography was carried out with silica gel 60Å F254 glass plates (0.25 mm). ^1H NMR spectra were recorded on a 500 or 300 MHz spectrometer and ^{13}C spectra were recorded on a 125 or 75 MHz spectrometer. ^1H NMR chemical shifts are reported as δ values in ppm relative to residual $CHCl_3$ (7.26 ppm) or residual C_6D_5H (7.16 ppm). ^1H NMR coupling constants (*J*) are reported in Hertz (Hz), and multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), app t (apparent triplet), td (triplet of doublets), q (quartet), p (pentet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dddd (doublet of doublet of doublet of doublets), dt (doublet of triplets), ddt (doublet of

doublet of triplets), dq (doublet of quartets), app p (apparent pentet), m (multiplet), bs (broad singlet). Diastereomeric ratios were determined by crude ^{1}H NMR analysis (300 MHz). Deuterobenzene (benzene-d_6) or deuterochloroform ($CDCl_3$) served as internal standards (128.23 ppm, 77.00 ppm, respectively unless otherwise stated) for all ^{13}C spectra. Based on intensity in the ^{13}C spectra, both magnetic and chemical shift equivalent peaks are noted in parentheses. Mass spectra were obtained at the Center for Chemical Characterization and Analysis at Texas A&M University. Infrared spectra were obtained as thin film on NaCl plates on a FTIR spectrometer. Optical rotations were recorded at 589 nm using a 250 μL cell.

Hazard Warning

Ozonides are produced in several procedures described below to generate aldehyde acid and keto acid substrates. To ensure complete reduction of the ozonides, excess quenching agent should be used and stirring should continue for at least 12 h at 25 ºC prior to further handling.

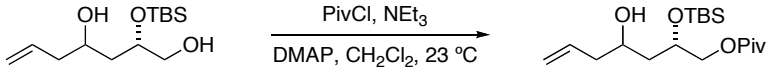
CHAPTER I – INTRODUCTION: NATURAL PRODUCT INSPIRED METHODOLOGY; TETRAHYDROFURAN SYNTHESIS VIA β-LACTONES AND DICHLOROOLEFIN COUPLINGS



27 **28**

(2*S*)-2-(*tert*-butyldimethylsilyloxy)hept-6-ene-1,4-diol (28). To a flask containing lactol **27**[54,60-62] (4.20 g, 19.3 mmol) was added Et_2O (190 mL). The vessel was cooled to 0 ºC and allyl magnesium bromide (7.72 mL of 2.0 M solution in THF, 15.4 mmol) was added down the side of cooled reaction vessel. The reaction was stirred for an additional 10 h at 0 ºC, then warmed to 23ºC for 1 h. The reaction was again cooled to 0 ºC and additional allyl magnesium bromide (11.58 mL of 2.0 M solution in THF, 23.2 mmol) was added. The reaction was stirred for 3 h at 0 ºC. The reaction was then quenched upon addition of saturated NH_4Cl (80 mL). The aqueous layer was separated and acidified with 1 N HCl to pH 3 and then extracted with Et_2O (6 x 20 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:9 to 1:0) to provide diol **28** (3.88 g, 78%) as a white solid. (diastereomer 1) IR (thin film) ν_{max} 3363, 1472, 1255, 1095 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.86-5.76 (m, 1H), 5.15-5.09 (m, 2H), 4.00 (app p, J = 5.5 Hz, 1H), 3.90-3.82 (m, 1H), 3.63 (dd, J = 4.5, 11.0 Hz, 1H), 3.55 (dd, J = 3.5, 11.0 Hz, 1H), 2.39 (bs, 2H), 2.29-2.17 (m, 2H), 1.75 (ddd, J = 2.5, 6.0, 14.5 Hz, 1H), 1.67 (ddd, J = 6.0, 9.5, 14.5 Hz, 1H), 0.90 (s, 9H), 0.101 (s, 3H), 0.099 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.5, 118.1, 71.1, 67.5, 66.0, 42.6, 40.5, 25.8 (3), 18.0, -4.6, -4.8; LRMS (CI) Calcd. for $C_{13}H_{29}O_3Si$ [M+H] 261, found 261. (diastereomer 2) IR (thin film) ν_{max} 3425, 1641,

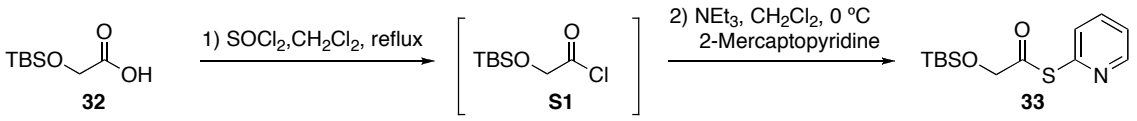
1044 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.87-5.77 (m, 1H), 5.16-5.13 (m, 1H), 5.13-5.11 (m, 1H), 4.05-3.99 (m, 1H), 3.87 (dddd, J = 2.5, 5.5, 7.5, 12.5 Hz, 1H), 3.63 (dd, J = 4.8, 10.0 Hz, 1H), 3.57 (dd, J = 4.5, 10.0 Hz, 1H), 2.30-2.16 (m, 2H), 1.76 (ddd, J = 2.5, 6.5, 14.5 Hz, 1H), 1.59 (ddd, J = 4.5, 10.0, 14.5 Hz, 1H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.5, 118.2, 71.1, 67.5, 66.6, 42.7, 40.5, 25.8 (3), 18.0, -4.6, -4.8 ; LRMS (CI) Calcd. for $C_{13}H_{29}O_3Si$ [M+H] 261, found 261.



28 **29**

(2*S*)-2-(*tert*-butyldimethylsilyloxy)-4-hydroxyhept-6-enyl 2,2-dimethylpropanoate (29). To a solution of diol **28** (3.88 g, 14.9 mmol) in CH_2Cl_2 (72 mL) at 23 ºC was added triethylamine (8.33 mL, 59.8 mmol) followed by dropwise addition of trimethylacetyl chloride (2.02 mL, 16.4 mmol). Vapor evolved upon addition of trimethylacetyl chloride. The solution was stirred for 14 h, and then DMAP (0.206 g, 1.79 mmol) was added. The reaction was stirred for an additional 21 h, and was quenched upon addition saturated Na_2CO_3 (60 mL). The layers were separated, and the organic layer was washed with saturated NH_4Cl (4 x 15 mL). The aqueous layers were combined and extracted with Et_2O (2 x 20 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography with a mixture of Et_2O:hexanes (3:7) to afford alcohol **29** (4.64 g, 90%) as a colorless oil. Diastereomers were inseparable by column chromatography. IR (thin film) ν_{max} 3438, 1731, 1285, 1255, 1163 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.84-5.73 (m, 2H), 5.11-5.04 (m, 4H), 4.19-3.88 (m, 6H), 3.84-3.77 (m, 2H), 2.71 (bs, 2H), 2.21 (app t, J = 6.0 Hz, 4H), 1.73-1.55 (m, 4H), 1.17 (s, 18H), 0.86 (s, 18H), 0.10 (s, 12H); ^{13}C

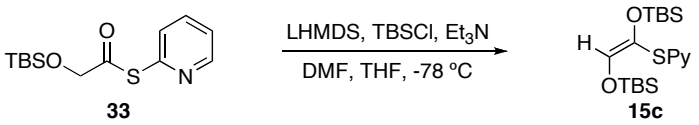
NMR (125 MHz, $CDCl_3$) δ 178.3, 178.2, 134.6, 134.5, 117.8, 117.7, 69.80, 69.97, 68.4, 67.7, 67.2, 67.1, 42.4, 42.1, 40.5, 39.8, 38.71, 38.67, 27.1 (6), 25.7 (3), 25.6 (3), 17.84, 17.79, -4.5, -4.7, -4.9, -5.0; LRMS (CI) Calcd. for $C_{18}H_{37}O_4Si$ [M+H] 345, found 345.



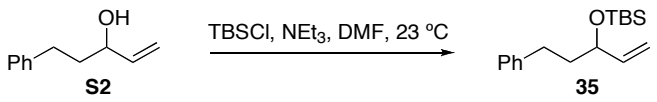
***S*-pyridin-2-yl 2-(*tert*-butyldimethylsilyloxy)ethanethioate (33).** Thionyl chloride (9.80 mL, 146 mmol) was added to a solution of acid **32** (2.77 g, 14.6 mmol) in CH_2Cl_2 (210 mL). The solution was refluxed for 15 min., and then cooled to room temperature and stirred for 12 h. The solution was concentrated by rotary evaporation to give the corresponding acid chloride **S1**. The crude oily residue was taken on without further purification.

A solution of 2-mercaptopyridine (0.978 g, 8.79 mmol) in CH_2Cl_2 (100 mL) was cooled to 0 ºC and triethylamine (1.73 mL, 12.2 mmol) was added. A solution of freshly prepared acid chloride **S1** (1.77 g, 8.48 mmol) in CH_2Cl_2 (20 mL) was subsequently added via syringe pump. The yellow solution was stirred for 2 h and was then concentrated by rotary evaporation. The residue was redissolved in pentane and washed with water and brine, dried (Na_2SO_4) and concentrated. The crude residue was purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:9 to 1:4) to provide thioester **33** (1.89 g, 79%) as a pale yellow solid. R_f 0.44 (1:4 EtOAc:hexanes); IR (thin film) ν_{max} 1706, 1617 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.65 (ddd, J = 0.5, 2.0, 5.0 Hz, 1H), 7.74 (ddd, J = 2.0, 7.5, 9.5 Hz, 1H), 7.60 (dd, J = 1.0, 7.5 Hz, 1H), 7.29 (ddd, J = 1.0, 5.0, 7.5 Hz, 1H), 4.37 (s, 2H), 0.99 (s, 9H), 0.17 (s, 6H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 200.0, 151.5, 150.5, 136.9, 136.4, 130.4, 123.3, 68.8, 25.6 (3), 18.1, -5.7 (2); HRMS (ESI) Calcd. for $C_{13}H_{22}NO_2SSi$ [M+H] 284.1141, found 284.1149.

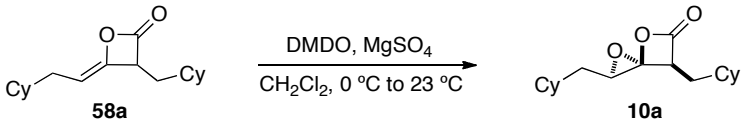


(*Z*)-2-(2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladec-5-en-5-ylthio)pyridine (15c). To a flask containing DMF (0.99 mL, 13.0 mmol) was added LHMDS (4.6 mL of 1.0 M solution in THF, 4.28 mmol). The solution was then cooled to -78 ºC. Triethylamine (0.50 mL, 7.13 mmol) was then added, followed by *t*-butyldimethylsilyl chloride (0.58 g, 7.13 mmol) in THF (1 mL) and thioester **33** (1.04 g, 3.67 mmol) in THF (3 mL), respectively. The reaction was stirred at -78 ºC, and then quenched upon addition of pH 7 buffer (4 mL) and diluted with Et_2O. The solution was warmed to room temperature with vigorous stirring. The layers were separated, and the organic layer was washed with H_2O, brine, dried (Na_2SO_4), and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography with a mixture of pentane:Et_2O:Et_3N (95:5:2) to provide ketene acetal **15c** (0.649 g, 45%) as a white solid. R_f 0.61 (1:4 EtOAc:hexanes); IR (thin film) ν_{max} 1636, 1575, 1561 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.40 (ddd, J = 0.9, 1.8, 4.8 Hz, 1H); 7.51 (ddd, J = 1.8, 7.2, 8.1 Hz, 1H), 7.31 (ddd, J = 0.9, 1.8, 8.1 Hz, 1H), 6.97 (ddd, J = 1.2, 4.8, 7.5 Hz, 1H), 6.69 (s, 1H), 6.39 (s, 1H), 0.88 (s, 9H), 0.85 (s, 9H), 0.13 (s, 6H), 0.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 136.2, 135.5, 133.8, 130.7, 121.7, 119.4, 25.6 (3), 25.5 (3), 18.2, 17.9, -4.8 (2), -5.3 (2); LRMS (ESI) Calcd. for $C_{19}H_{35}NO_2SSi_2$ [M+H] 398, found 398.



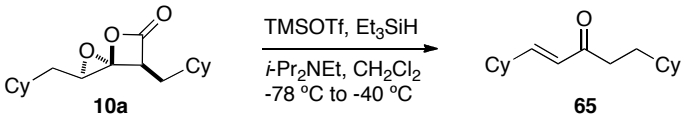
***tert*-butyldimethyl(5-phenylpent-1-en-3-yloxy)silane (35).** To a solution of alcohol **S2** (4.84 g, 29.9 mmol) in DMF (180 mL) at 23 ºC was added *tert*-butyldimethylsilyl chloride (7.07 g, 12.9 mmol) and triethylamine (8.33 mL, 59.8 mmol), respectively. The mixture was stirred for 12 h. The reaction was diluted with EtOAc (100 mL). The organic layer was then washed with brine (5 x 10 mL). The aqueous layers were combined and extracted with Et_2O (2 x 25 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography with only hexanes to provide alkene **35** (5.56 g, 67%) as a viscous, colorless oil. R_f 0.40 (hexanes); IR (thin film) ν_{max} 1472, 1085 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.24 (m, 5H), 5.97 (ddd, J = 6.0, 10.5, 17.0 Hz, 1H), 5.31 (ddd, 2.0, 2.0, 17.0 Hz, 1H), 5.19 (ddd, J = 2.0, 2.0, 10.5 Hz, 1H), 4.27 (q, J = 6.0 Hz, 1H), 2.85-2.71 (m, 2H), 2.01-1.87 (m, 2H), 1.05 (s, 9H), 0.19 (d, 3H), 0.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 141.4, 128.4(2), 128.3(2), 125.7, 113.9, 73.3, 39.8, 31.5, 25.9 (3), 18.3, -4.3, -4.8; LRMS (ESI) Calcd. for $C_{17}H_{28}OSiLi$ [M+Li] 283, found 283.

CHAPTER II – UTILITY OF SPIROEPOXY-*β*-LACTONES



(2*R*,3*S*,6*S*)-2,6-bis(cyclohexylmethyl)-1,4-dioxaspiro[2.3]hexan-5-one (10a). To a flask under nitrogen containing homoketene dimer **58a**[97,195] (0.220 g, 0.803 mmol) and

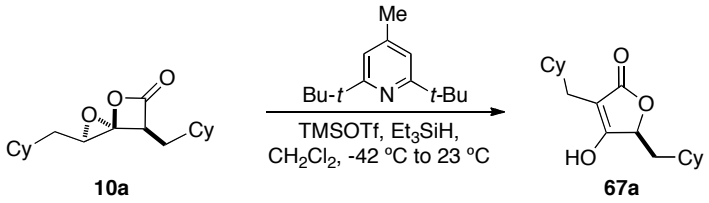
CH_2Cl_2 (80 mL) was added $MgSO_4$ (the tip of a spatula amount) to which DMDO[196] was added at 0 ºC, which was obtained from 300 g of Oxone.® The solution was stirred for 1.5 h, and then as warmed to room temperature and stirred for an additional 3.5 h. The reaction mixture was filtered through $MgSO_4$ and concentrated by rotary evaporation to obtain spiroepoxy-β-lactone **10a** as a colorless oil, which was purified rapidly by flash column chromatography with a mixture of Et_2O:hexanes (1:9) to afford *cis*/*trans* spiroepoxy-β-lactone **10a** (0.168 g, 62%, dr 10:1) as a colorless oil. Store frozen in benzene if not used immediately. R_f 0.45 (1:9 Et_2O:hexanes); IR (thin film) ν_{max} 1852 cm^{-1}; ^1H NMR (300 MHz, benzene-d_6) δ 3.36 (dd, J = 6.6, 8.7 Hz, 1H), 2.94 (dd, J = 5.4, 6.9 Hz, 1H), 0.50-1.64 (m, 31H); ^{13}C NMR (75 MHz, benzene-d_6) δ 167.8, 91.8, 58.3, 52.3, 35.9, 35.7, 33.7, 33.4, 33.3, 33.1, 32.9, 26.8, 26.7, 26.64, 26.57, 26.51, 26.44, 26.42; LRMS (APCI) Calcd. for $C_{18}H_{28}O_3$ [M+H] 293, found 293.



10a **65**

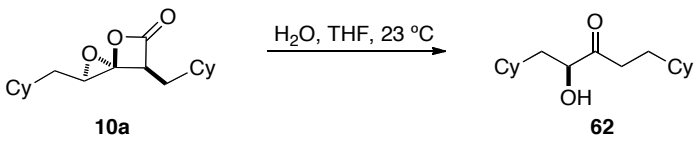
(*E*)-1,5-dicyclohexylpent-1-en-3-one (65). A solution of spiroepoxy-β-lactone **10a** (340 mg, 1.17 mmol) in CH_2Cl_2 (9 mL) was cooled to -96 ºC. To the solution was added *i*-Pr_2NEt (0.59 mL of a 2.0 M in CH_2Cl_2) followed directly by addition of trimethylsilyl triflate (0.45 mL of 2.6 M in CH_2Cl_2). The solution was stirred for 0.5 h, then warmed to -78 ºC for 2 h and then -40 ºC for 2 h. The reaction was quenched at -40 ºC by the addition of saturated $NaHCO_3$ (5 mL). The solution was warmed to 23 ºC and extracted with CH_2Cl_2 (4 x 5 mL), dried ($MgSO_4$), and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography with a gradient mixture of

Et_2O:hexanes (0:1 to 0.5:9.5) to afford enone **65** (18.6 mg, 6%) as a colorless oil. Store frozen in benzene if not used immediately. R_f 0.63 (2:8 Et_2O:hexanes); IR (thin film) ν_{max} 1754, 1721, 1697, 1673, 1628, 1448 cm^{-1}; ^1H NMR (300 MHz, benzene-d_6) δ 6.72 (dd, J = 6.6, 15.9 Hz, 1H), 6.03 (d, J = 15.9 Hz, 1H), 2.35 (t, J = 7.5 Hz, 2H), 1.83-1.48 (m, 21H) 1.32-0.64 (m, 26H); ^{13}C NMR (125 MHz, benzene-d_6) δ 199.4, 150.9, 40.8, 38.2, 37.8, 33.7, 32.2, 32.1, 30.4 (2), 27.1, 26.9 (2), 26.4, 26.2 (2); LRMS (ESI) Calcd. for $C_{17}H_{28}OLi$ [M+Li] 255, found 255.



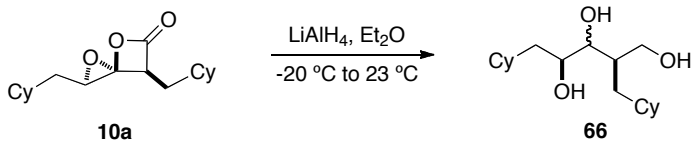
(*S*)-3,5-bis(cyclohexylmethyl)-4-hydroxyfuran-2(5*H*)-one (67a). To a flask at -42 ºC containing TMSOTf (0.305 g, 1.40 mmol), 2,6-ditertbutyl-4-methyl-pyridine (0.281 g, 1.40 mmol), and Et_3SiH (0.160 g, 1.40 mol) under nitrogen was added spiroepoxy-β-lactone **10a** by cannula transfer in solution of CH_2Cl_2 (5 mL). The solution was stirred for 2 h, warmed to 0 ºC and stirred for an additional 3 h. Further TMSOTf (0.204 g, 0.916 mmol), 2,6-ditertbutyl-4-methyl-pyridine (0.188 g, 0.916 mmol), and Et_3SiH (0.107 g, 0.916 mmol) were added again. The solution was warmed to 23°C and stirred for 19 h. A white solid formed which was soluble in CH_2Cl_2. The reaction was quenched upon addition of saturated $NaHCO_3$, which was extracted three times with CH_2Cl_2 (3 x 15 mL). The organic phase was then dried ($MgSO_4$) and concentrated by rotary evaporation to obtain **67a** as a crude mixture. The mixture was filtered, and the

collected precipitate was tetronic acid **67a** (0.078 g, 56%) collected as a white solid. The spectroscopic data matched that found in the literature.[98]



10a **62**

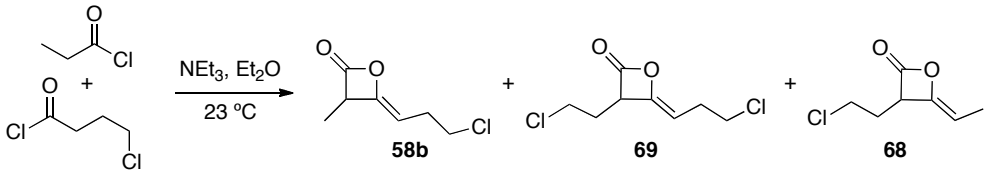
(*S*)-1,5-dicyclohexyl-2-hydroxypentan-3-one (62). To a solution of spiroepoxy-β-lactone **10a** (46.5 mg, 1.59 mmol) in THF (1.45 mL) was added doubly distilled H_2O (0.25 mL, pH = 6.5). The solution was allowed to stir for 19 h at 23 ºC. The reaction was then filtered through Na_2SO_4 and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography with a mixture of Et_2O:hexanes (1:4) to afford α-hydroxy ketone **62** (9.9 mg, 53%) as a colorless oil. R_f 0.48 (1:4 Et_2O:hexanes); IR (thin film) ν_{max} 3475, 1709, 1446 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 4.04 (ddd, J = 3.1, 5.0, 15.5 Hz, 1H), 3.55 (d, J = 5.0 Hz, 1H), 2.14 (ddd, J = 6.5, 26.0 Hz, 1H), 1.98 (ddd, J = 6.5, 26.0 Hz, 1H), 1.95-1.89 (m, 2H), 1.78-1.34 (m, 18H), 1.27-0.98 (m, 11H), 0.93-0.74 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.8, 74.5, 41.6, 37.2, 35.2, 34.40, 33.97, 33.1, 33.0, 32.16, 31.1, 26.49, 26.46, 26.3, 26.2 (2), 26.0; LRMS (ESI) Calcd. for $C_{17}H_{30}O_2Li$ [M+Li] 273, found 273.



10a **66**

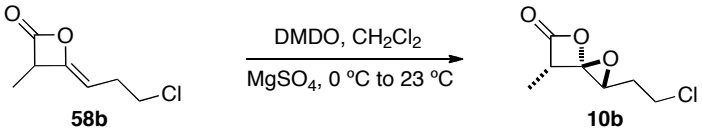
(2*R*,4*S*)-5-cyclohexyl-2-(cyclohexylmethyl)pentane-1,3,4-triol (66). A solution of spiroepoxy-β-lactone **10a** (112 mg, 0.384 mmol) in Et_2O (0.9 mL) was added dropwise to

a suspension of $LiAlH_4$ (18.5 mg, 0.768 mmol) in Et_2O (2.6 mL) at -20 ºC. The reaction mixture was stirred 8 min. and then warmed to 0 ºC for 45 min. Then, the mixture was further warmed to 23 ºC and stirred for 2 h. The reaction was quenched by dilution with Et_2O (4 mL) and slow addition of H_2O (0.02 mL) followed by addition of 15 % NaOH (0.02 mL) and H_2O (0.06 mL). The reaction mixture was stirred vigorously until all the gray color disappeared, and then K_2CO_3 was added. The mixture was stirred for 15 min., filtered through $MgSO_4$ and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography with a mixture of Et_2O:hexanes (1:1) to give triol **66** (106 mg, 92%, dr 3:1) as a milky oil. R_f 0.40 (1:1 Et_2O:hexanes); IR (thin film) ν_{max} 3362, 1447 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.84-3.71 (m, 6H), 3.70-3.60 (m, 2H), 3.42-3.34 (m, 1H), 3.25 (bs, 1H), 2.72 (bs, 1H), 2.02-0.63 (m, 68H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 78.1, 77.5, 70.1, 69.9, 64.6, 63.5, 41.8, 41.0 (2), 39.4, 38.0, 36.8, 35.1, 34.9, 34.7, 34.3, 34.00, 33.97, 33.8, 33.3, 32.7, 32.6, 32.5, 32.1, 29.7, 26.61, 26.55 (2), 26.43 (2), 26.35, 26.30, 26.2 (2) 26.1 (2); LRMS (APCI) Calcd. for $C_{18}H_{35}O_3$ [M+H] 299, found 299.



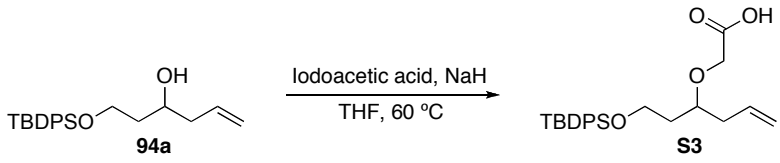
(*Z*)-4-(3-chloropropylidene)-3-methyloxetan-2-one (58b): To a solution of 4-chlorobutyryl chloride (10.0 g, 0.07 mol) and propionyl chloride (8.5 g, 0.09 mol) in Et_2O (106 mL), was added triethylamine (25.0 mL, 0.18 mol) at 23 ºC through a syringe pump over 1.5 h maintaining the reaction at room temperature using water bath. Stirring was

continued for an additional 1.5 h at room temperature. The reaction mixture was diluted with hexane (400 mL), filtered through a pad of silica gel, and then washed with a 1:1 mixture of hexanes and Et_2O (500 mL). The solution was concentrated by rotary evaporation and then purified by flash column chromatography with a mixture of Et_2O:pentane: (0.5:9.5) to give heteroketene dimer **58b** (440 mg, 4%) as a colorless oil. The ketene dimers were obtained as a ~7:1:1 mixture (**69**/**68**/**58b**), which was separable by column chromatorgraphy. **(*Z*)-4-(3-chloropropylidene)-3-methyloxetan-2-one (58b):** R_f 0.33 (1:9 Et_2O:hexanes); IR (thin film) ν_{max} 1880, 1726 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 4.20 (dt, J = 7.0, 1.0 Hz, 1H), 3.10 (dddd, J = 15.5, 7.5, 2.5, 1.0 Hz, 1H), 3.03 (t, J = 6.5 Hz, 2H), 2.27-2.11 (m, 2H), 0.72 (d, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, benzene-d_6) δ 169.0, 149.7, 96.4, 49.3, 44.2, 28.3, 12.0. Mass spectral data could not be obtained. **(*Z*)-3-(2-chloroethyl)-4-ethylideneoxetan-2-one (68):** Dimer **68** (320 mg, 3%) was obtained as a colorless oil. R_f 0.32 (1:9 Et_2O:hexanes); IR (thin film) ν_{max} 1872, 1730, 827 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 4.20 (qd, J = 1.13, 6.93 Hz, 1H), 3.54-3.75 (m, 1H), 3.05 (dt, J = 11.5, 6.5 Hz, 1H), 2.98 (dt, J = 11.5, 6.5 Hz, 1H), 1.57 (app sextet, J = 6.5 Hz, 1H), 1.53-1.43 (m, 4H). ^{13}C NMR (125 MHz, benzene-d_6) δ 168.1, 145.4, 96.6, 51.0, 41.3, 30.3, 9.8. Mass spectral data could not be obtained. **(*Z*)-3-(2-chloroethyl)-4-(3-chloro-propylidene)oxetan-2-one (69):** Dimer **69** (21%) was obtained as a colorless oil. R_f 0.19 (1:9 Et_2O:hexanes); IR (thin film) ν_{max} 1874, 1727 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 3.34 (dt, J = 7.5, 1.5 Hz, 1H), 3.60 (dt, J = 7.5, 1.0 Hz, 1H), 3.21-3.04 (m, 4H), 2.33-2.18 (m, 2H), 1.69-1.52 (m, 2H). ^{13}C NMR (125 MHz, benzene-d_6) δ 167.7, 146.9, 98.0, 51.5, 43.9, 41.3, 30.1, 28.2. Mass spectral data could not be obtained.



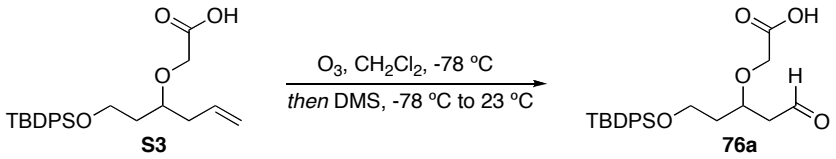
(2*R*,3*S*,6*S*)-2-(2-chloroethyl)-6-methyl-1,4-dioxaspiro[2.3]hexan-5-one (10b): To a solution of heteroketene dimer **58b** (50.0 mg, 0.312 mmol) in CH_2Cl_2 (5 mL) was added a scoopula amount of $MgSO_4$. To the mixture was added the freshly prepared DMDO[196]/acetone mixture (30 mL) at 0 ºC via cannula transfer. After 2 h of stirring at 0 ºC, the mixture was warmed to 23 ºC and stirred for an additional 3 h. The solution was then filtered through $MgSO_4$, concentrated by rotary evaporation, and purified by flash column chromatography eluting with a mixture of Et_2O:hexanes (1.5:8.5). Spiroepoxy-β-lactone **10b** (200 mg, 45%, dr 7:1) was obtained as a colorless oil. (major) R_f 0.40 (2:8 Et_2O:hexanes); IR (thin film) ν_{max} 1857, 1516 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 3.10-2.95 (m, 2H), 3.09 (q, J = 7.5 Hz, 1H), 2.84 (dd, J = 6.5, 5.5 Hz, 1H), 1.69-1.55 (m, 2H), 0.65 (d, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, benzene-d_6) δ 167.2, 91.5, 55.9, 48.8, 40.9, 30.7, 9.3; HRMS (ESI) Calcd. for $C_7H_{10}ClO_3$ [M+H] 177.0318, found 177.0310.

CHAPTER III – NUCLEOPHILE CATALYZED, ALDOL-LACTONIZATIONS (NCAL) TO β-LACTONE FUSED TETRAHYDROFURANS



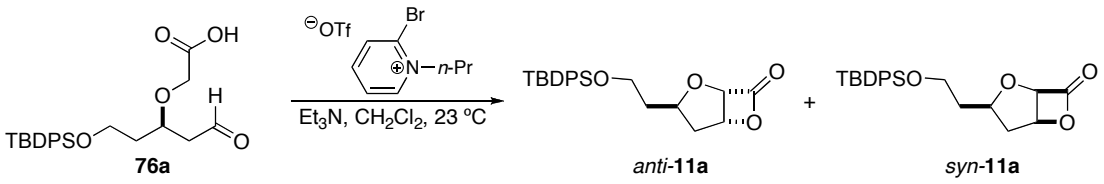
2-(1-(*tert*-butyldiphenylsilyloxy)hex-5-en-3-yloxy)acetic acid (S3). Sodium hydride, 60% suspension in mineral oil (1.35 g, 33.4 mmol) was washed with hexanes (2 x 2 mL). The solid was evaporated to dryness under nitrogen and then suspended in

tetrahydrofuran (3 mL). A solution of iodoacetic acid[137] (1.14 g, 6.14 mmol) in tetrahydrofuran (4 mL) was then added dropwise at 23 ºC. During addition, evolution of hydrogen gas was evident by the mixture bubbling. The mixture was stirred for an additional hour. Alcohol **94a**[197] (2.07 g, 5.85 mmol) was then added as a solution in tetrahydrofuran (6 mL). The mixture was refluxed for 4.5 h and then cooled to room temperature and allowed to stir for 11 h. The reaction was quenched upon partitioning between Et_2O (30 mL) and saturated NH_4Cl (30 mL). The mixture was acidified to pH 1 with 10% H_2SO_4 and the layers were separated. The aqueous layer was extracted with Et_2O (5 x 10 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated. The crude residue was purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (2:5 to 1:0) to provide acid **S3** (1.29 g, 53%) as a colorless oil. R_f 0.57 (1:1 EtOAc:hexanes); IR (thin film) ν_{max} 1733, 1427, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.21 (bs, 1H), 7.75-7.60 (m, 4H), 7.49-7.37 (m, 6H), 5.91-5.74 (m, 1H), 5.17-5.06 (m, 2H), 4.19 (d, J = 16.8 Hz, 1H), 4.09 (d, J = 16.8 Hz, 1H), 3.92-3.69 (m, 3H), 2.38-2.31 (m, 2H), 1.79 (app q, J = 5.7 Hz, 2H), 1.09 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 174.6, 135.44 (2), 135.43 (2), 133.9, 133.5, 133.4, 129.62, 129.61, 127.61 (2), 127.60 (2), 117.7, 77.6, 62.4, 60.3, 38.3, 36.4, 26.8 (3), 19.1; HRMS (ESI) Calcd. for $C_{24}H_{33}O_4Si$ [M+H] 413.2148, found 413.2141.



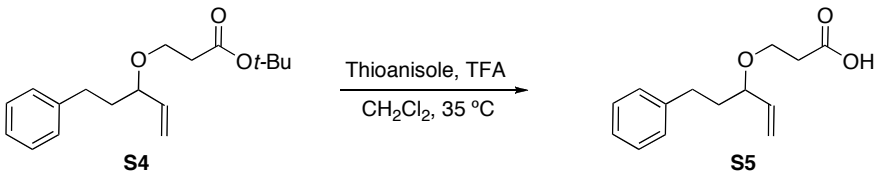
(±)-2-(1-(tert-butyldimethylsilyloxy)-5-oxopentan-3-yloxy)acetic acid (76a). Alkene acid **S3** (250 mg, 0.61 mmol) underwent ozonolysis according to the representative

procedure for ozonolysis of alkene acids. Dimethylsulfide (0.47 mL, 380 mg, 6.00 mmol) was used as reducing reagent. The reaction was worked up with addition of brine (20 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (2 x 20 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated by rotary evaporation. The crude material was purified by flash column chromatography on silica gel (10:2:88 acetone:AcOH:CH_2Cl_2) to yield aldehyde acid **76a** (180 mg, 72%) as a colorless oil. R_f = 0.33 (1:4 EtOAc:Hexanes); IR (thin film) ν_{max} 3071, 1728 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.50 (bs, 1H), 9.80 (s, 1H), 7.78-7.64 (m, 4H), 7.54-7.35 (m, 6H), 4.21 (s, 3H), 3.92-3.71 (m, 2H), 2.77 (dd, J = 17.4, 7.8, 1.5 Hz, 2H), 2.66 (d, J = 17.3, 3.5 Hz, 1H), 1.96-1.69 (m, 2H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, δ $CDCl_3$ at 77.23 ppm) δ 201.9, 175.1, 135.8 (4), 133.6 (2), 130.2 (2), 128.1 (4), 73.5, 66.8, 60.1, 48.7, 36.7, 27.2 (3), 19.4; HRMS (ESI) Calcd. for $C_{23}H_{30}O_5SiLi$ [M+Li] 421.2023, found 421.2020.



Representative Procedure for Nucleophile Catalyzed Aldol Lactonization (NCAL) with achiral nucleophile as described for Tetrahydrofuran-fused β-lactone 11a. Aldehyde acid **76a** was azeotroped with xylenes prior to use. To a flask containing pyridinium salt **72** (33.6 mg, 0.09 mmol) was added 0.50 mL CH_2Cl_2 under nitrogen followed by triethylamine (0.027 mL, 0.19 mmol). The solution turned pale yellow. To the reaction mixture at 23 ºC was added a solution of aldehyde acid **76a** (16.5 mg, 0.05

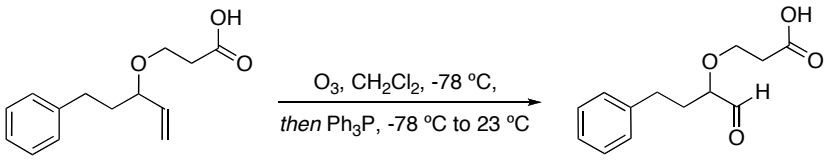
mmol) in CH_2Cl_2 (0.45 mL) via syringe pump over 1 h. The solution turned orange-brown. The reaction was quenched after an additional 11 h of stirring by washing with saturated NH_4Cl, brine, and then dried (Na_2SO_4). The crude residue was purified by flash column chromatography with EtOAc:hexanes (1:9) to provide *anti/syn* tetrahydrofuran-fused β-lactones **11a** (4.0 mg, 25%, dr 1:1) as a colorless oil. The diastereomers were inseparable during column chromatography. **(±)-3-[2-(tert-butyldimethyl-silyloxy)ethyl]-2,6-dioxabicyclo[3.2.0]heptan-7-one (*anti/syn* 11a).** R_f = 0.38 (1:4 EtOAc:Hexanes); IR (thin film) ν_{max} 1836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71-7.65 (m, 5H), 7.45-7.29 (m, 5H), 5.44 (d, J = 3.8 Hz, 1H), 5.40 (d, J = 4.0 Hz, 1H), 5.24 (t, J = 4.0 Hz, 1H), 5.15 (t, J = 3.82 Hz, 1H), 4.98-4.93 (m, 1H), 4.39-4.32 (m, 1H), 3.84-3.73 (m, 2H) 3.83-3.79 (m, 2H), 2.38 (d, J = 1.9 Hz, 2H), 2.33 (d, J = 1.7 Hz, 2H), 2.29-2.24 (m, 2H), 2.24-2.19 (m, 2H), 2.07-1.94 (m 2H), 1.91-1.81 (m, 2H), 1.63-1.58 (m, 2H), 1.57-1.53 (m, 2H), 1.09 (s, 9H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, δ $CDCl_3$ at 77.23 ppm) δ 170.3, 168.8, 135.73 (4), 135.70 (4), 133.7 (2), 133.5 (2), 129.91 (2), 129.90 (2), 127.93 (4), 127.92 (4), 88.2, 88.0, 81.3, 80.0, 78.7, 77.2, 60.8, 60.7, 38.7, 37.0, 36.7, 34.8, 27.03 (3), 27.01 (3), 19.4, 19.3; HRMS (ESI) Calcd. for $C_{23}H_{29}O_4Si$ [M+H] 397.1835, found 397.1830.



S4 **S5**

(±)-3-(5-phenylpent-1-en-3-yloxy)propanoic acid (S5). To a round bottom flask containing CH_2Cl_2 (10 mL) and thioanisole (0.24 mL, 250 mg, 2.01 mmol) at room

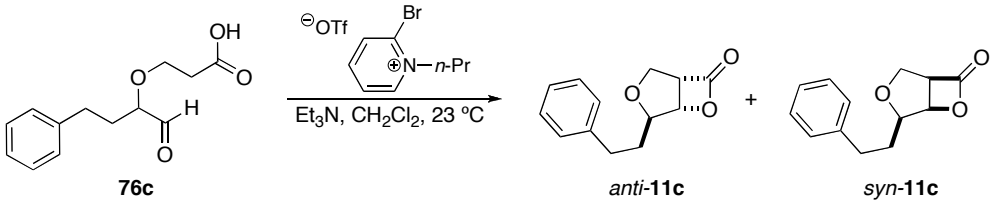
temperature was added *t*-butyl ester **S4** (583 mg, 2.01 mmol).[198] This was followed directly by addition of trifluoroacetic acid (0.77 mL, 1.14 g, 10.0 mmol). A reflux condenser was attached, and the solution was warmed to 35 ºC and stirred for 2.5 h. The dark purple solution was cooled to room temperature and concentrated by rotary evaporation. The crude oily residue was purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:9 to 1:0) to afford acid **S5** (456 mg, 97%) as a colorless oil. R_f 0.17 (1:4 EtOAc:hexanes); IR (thin film) ν_{max} 3171, 1715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.17 (m, 5H), 5.81-5.67 (m, 1H), 5.28-5.19 (m, 2H), 3.81 (dt, J = 6.3, 9.6 Hz, 1H), 3.74-3.64 (m, 1H), 3.57 (dt, J = 6.9, 9.6 Hz, 1H), 2.79-2.62 (m, 4H), 2.02-1.86 (m, 1H), 1.86-1.73 (m, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 177.9, 141.9, 138.4, 128.4 (2), 128.3 (2), 125.7, 117.4, 80.9, 63.4, 36.8, 34.9, 31.4; HRMS (ESI) Calcd. for $C_{14}H_{17}O_3$ [M-H] 233.1178, found 233.1176.



S5 **76c**

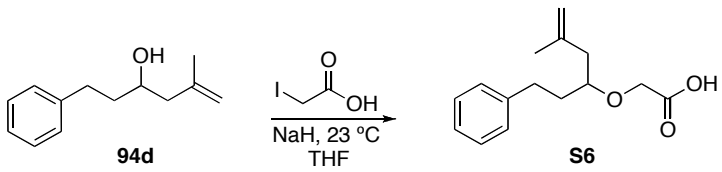
(±)-3-(1-oxo-4-phenylbutan-2-yloxy)propanoic acid (76c). Alkene acid **S5** (232 mg, 0.95 mmol) underwent ozonolysis according to the representative procedure for ozonolysis of alkene acids. Triphenylphosphine (288 mg, 1.10 mmol) was used as the reducing reagent. The crude residue was purified by acid/base extraction by partitioning between CH_2Cl_2 (10 mL) and saturated $NaHCO_3$ (25 mL). The layers were separated, and the aqueous layer was washed subsequently with hexanes (2 x 10 mL), and then acidified with 10% H_2SO_4 to pH 2. The aqueous layer was then extracted with CH_2Cl_2 (5

x 15 mL) and with Et_2O (4 x 15 mL). The extracts obtained after acidification were combined, dried (Na_2SO_4) and concentrated by rotary evaporation to afford aldehyde acid **76c** (174 mg, 74%) as a colorless oil. R_f 0.30 (1:1 EtOAc:hexanes); IR (thin film) ν_{max} 3027, 1729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.63 (d, J = 1.5 Hz, 1H), 7.32-7.17 (m, 5H), 3.88 (dt, J = 6.0, 9.5 Hz, 1H), 3.76-3.65 (m, 2H), 2.81-2.61 (m, 4H), 2.02-1.89 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 203.5, 177.2, 140.6, 128.39 (2), 128.36 (2), 126.0, 83.4, 65.5, 34.8, 31.3, 30.6; LRMS (ESI) Calcd. for $C_{13}H_{15}O_4$ [M-H] 235, found 235.



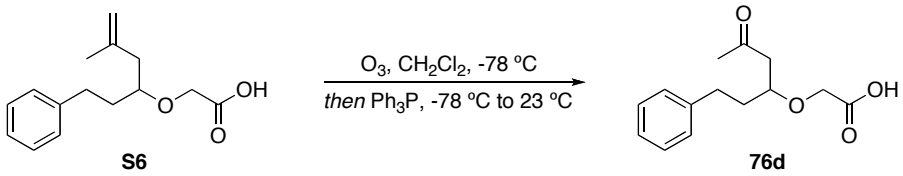
Aldehyde acid **76c** (69.9 mg, 0.30 mmol) underwent cyclization according to the representative procedure for NCAL with achiral nucleophile for tetrahydrofuran-fused β-lactone. The orange solution was stirred at 0 ºC for 5 h total. The crude residue was purified by flash column chromatography with EtOAc:hexanes (1:9) to provide *anti/syn* tetrahydrofuran-fused *β*-lactones **11c** (19.9 mg, 31%, dr 2:1) as a colorless oil. **(±)-4-phenethyl-3,6-dioxabicyclo[3.2.0]heptan-7-one (*anti*-11c)**, (major). R_f 0.21 (1:4 EtOAc:hexanes); IR (thin film) ν_{max} 1833 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.17 (m, 5H), 4.85 (d, J = 4.0 Hz, 1H), 4.38 (d, J = 10.5 Hz, 1H), 4.34 (dd, J = 5.0, 10.0 Hz, 1H), 4.13 (t, J = 5.0 Hz, 1H), 3.78 (dd, J = 6.0, 10.0 Hz, 1H), 2.81 (ddd, J = 5.5, 9.5, 14.5 Hz, 1H), 2.70 (dt, J = 8.0, 14.5 Hz, 1H), 1.75-1.66 (m, 1H), 1.65-1.57 (1H); ^{13}C (75 MHz, $CDCl_3$) δ 168.9, 140.5, 128.6 (2), 128.4 (2), 126.3, 79.3, 77.9, 64.8, 56.8, 31.3, 29.7; HRMS (ESI) Calcd. for $C_{13}H_{14}O_3Li$ [M+Li] 225.1103, found 225.1108. **(±)-4-**

phenethyl-3,6-dioxabicyclo[3.2.0]heptan-7-one (*syn*-**11c**), (minor). R_f 0.14 (1:4 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.19 (m, 5H), 4.87 (dd, J = 2.0, 4.0 Hz, 1H), 4.37 (d, J = 10.5 Hz, 1H), 4.08 (t, J = 5.0 Hz, 1H), 3.58 (dd, J = 5.5, 10.5 Hz, 1H), 3.54 (ddd, J = 2.0, 4.0, 8.0 Hz, 1H), 2.84 (ddd, J = 6.0, 8.5, 14.0 Hz, 1H), 2.76 (dt, J = 8.5, 14.0 Hz, 1H), 2.23-2.14 (m, 1H), 2.09-2.01 (m, 1H); ^{13}C (125 MHz, $CDCl_3$) δ 167.2, 143.4, 141.3, 128.5 (2), 128.4 (2), 126.0, 86.2, 73.3, 36.7, 31.4, 29.7.



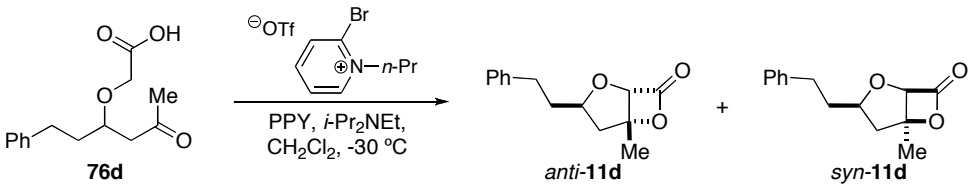
(±)-2-(5-methyl-1-phenylhex-5-en-3-yloxy)ethanoic acid (S6). Sodium hydride, 80% suspension in mineral oil (1.62 g, 0.05 mol) was washed with hexanes (2 x 2 mL). The solid was evaporated to dryness under nitrogen and then suspended in tetrahydrofuran (9 mL). A solution of iodoacetic acid[137] (3.35 g, 0.02 mol) in tetrahydrofuran (6 mL) was then added dropwise at 23 ºC. During addition, evolution of hydrogen gas was evident by the mixture bubbling. The mixture was stirred for an additional 15 min. Alcohol **94d**[199] (1.77 g, 0.01 mol) was then added as a solution in tetrahydrofuran (5 mL). The mixture was allowed to stir for 36 h. The reaction ceased upon dilution with CH_2Cl_2 (50 mL) and saturated NH_4Cl (50 mL). The mixture was then acidified to pH 2 with 10% H_2SO_4 and then extracted with CH_2Cl_2 (3 x 35 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated. The crude residue was purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (2:5 to 4:5) to provide acid **S6** (2.06 g, 89%) as a pale yellow oil. R_f 0.22 (4:6 EtOAc:hexanes); IR (thin film) ν_{max} cm^{-1} 3425, 1733, 1454, 1126; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.16 (m, 5H), 4.92-

4.86 (m, 1H), 4.84-4.78 (m, 1H), 4.14 (d, J = 17.0 Hz, 1H), 4.08 (d, J = 16.0 Hz, 1H), 3.61 (dddd, J = 5.5, 5.5, 11.5, 11.5 Hz, 1H), 2.81-2.65 (m, 2H), 2.38 (ddd, J = 0.5, 7.5, 14.0 Hz, 1H), 2.25 (ddd, J = 1.0, 6.0, 14.0 Hz, 1H), 1.93-1.86 (m, 2H), 1.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 142.1, 141.5, 128.5 (2), 128.3 (2), 126.0, 113.9, 78.9, 66.2, 42.4, 35.4, 31.4, 22.5; HRMS (ESI) Calcd. for $C_{15}H_{20}O_3Li$ [M+Li] 255.1572, found 255.1563.



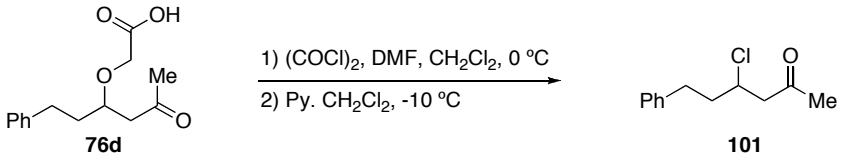
(±)-2-(5-oxo-1-phenylhexan-3-yloxy)ethanoic acid (76d). Alkene acid **S6** (168 mg, 0.68 mmol) underwent ozonolysis according to the representative procedure for ozonolysis of alkene acids. Triphenylphosphine (231 mg, 0.88 mmol) was added as the reducing reagent. The crude residue was purified by acid/base extraction by partitioning between CH_2Cl_2 (15 mL) and saturated $NaHCO_3$ (20 mL). The layers were separated, and the aqueous layer was washed subsequently with hexanes (2 x 15 mL), and then acidified with 10% H_2SO_4 to pH 2. The aqueous layer was then extracted with CH_2Cl_2 (2 x 25 mL) and with Et_2O (4 x 25 mL). The extracts obtained after acidification were combined, dried (Na_2SO_4) and concentrated by rotary evaporation to afford keto acid **76d** (122 mg, 72%) as a pale yellow oil. R_f 0.15 (4:1 EtOAc:hexanes); IR (thin film) ν_{max} 3485, 1712, 1358, 1126 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.30 (bs, 1H), 7.37-7.16 (m, 5H), 4.31 (d, J = 16.8 Hz, 1H), 4.24 (d, J = 17.1 Hz, 1H), 4.08-3.97 (m, 1H), 3.03-2.91 (m, 1H), 2.83-2.872 (m, 3H), 2.32 (s, 3H), 2.12-1.70 (m, 2H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 208.7, 173.8, 141.0, 128.4 (2), 128.0 (2), 126.0, 75.5, 66.3, 47.6, 34.8, 30.8, 30.6; HRMS (ESI) Calcd. for $C_{14}H_{17}O_4$ [M-H] 249.1127, found 249.1135.



To a flask containing 4-pyrrolidinopyridine (650 mg, 0.38 mmol) and pyridinium salt **72** (133 mg, 0.38 mmol) under nitrogen was added CH_2Cl_2 (6 mL) and *i*-Pr_2NEt (0.09 mL, 0.51 mmol), respectively. The reaction mixture turned pale yellow and was then cooled to –30 ºC. A solution of keto acid **76d** (640 mg, 0.26 mmol) in CH_2Cl_2 (4 mL) was added via syringe pump over 2 h. The mixture was allowed to stir for 64 h at -30 °C and then was quenched upon washing twice with saturated NH_4Cl, twice with brine, and dried (Na_2SO_4). The solution was then concentrated and purified by flash column chromatography with EtOAc:hexanes (1:4) to provide *anti/syn* tetrahydrofuran-fused β-lactones **11d** (32.0 mg, 54%, dr 1:1). **(1*S*,3*R*,5*R*)-5-methyl-3-phenethyl-2,6-dioxabicyclo[3.2.0]heptan-7-one (*anti*-11d).** R_f 0.42 (1:4 EtOAc:hexanes); IR (thin film) ν_{max} 1828 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.18 (m, 5H), 4.98 (s, 1H), 4.18-4.14 (m, 1H), 2.82 (ddd, J = 5.2, 9.4, 14.2 Hz, 1H), 2.70 (ddd, J = 6.8, 9.4, 13.8 Hz, 1H), 2.40 (dd, J = 4.5, 14.0 Hz, 1H), 2.11-2.02 (m, 1H), 2.00-1.92 (m, 1H), 1.73 (s, 3H), 1.51 (dd, J = 11.0, 14.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 141.0, 128.5 (2), 128.3 (2), 126.1, 89.8, 88.4, 79.7, 41.9, 35.5, 32.1, 19.9; HRMS (ESI) Calcd. for $C_{14}H_{16}O_3Li$ [M+Li] 239.1259, found 239.1250. **(1*R*,3*R*,5*S*)-5-methyl-3-phenethyl-2,6-dioxabicyclo[3.2.0]heptan-7-one (*syn*-11d).** This diastereomer has been assigned as the

(1*R*,3*R*,5*S*)-diastereomer in accordance with the crystal structure obtained. R_f 0.36 (1:4 EtOAc:hexanes); IR (thin film) ν_{max} 1824 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.14 (m, 5H), 4.91 (s, 1H), 4.57 (dddd, J = 2.1, 5.1, 8.1, 10.2 Hz, 1H), 2.90-2.78 (m, 1H), 2.75-2.62 (m, 1H), 2.29 (dd, J = 2.1, 15.0 Hz, 1H), 2.17 (dd, J = 8.1, 15.0 Hz, 1H), 2.25-2.11 (m, 1H), 1.86-1.71 (m, 1H), 1.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 141.0, 128.6 (2), 128.4 (2), 126.0, 89.9, 89.7, 83.6, 40.1, 37.3, 32.5, 20.7; HRMS (ESI) Calcd. for $C_{14}H_{16}O_3Li$ [M+Li] 239.1259, found 239.1262

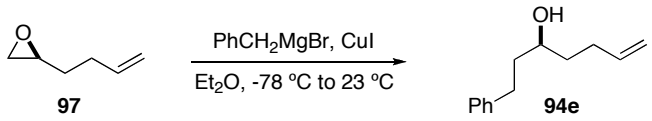


76d **101**

4-chloro-6-phenylhexan-2-one (101). To a solution of keto acid **76d** (312 mg, 0.125 mmol) in CH_2Cl_2 (0.25 mL) at 0 ºC was added DMF (1 drop) followed by oxalyl chloride (0.016 mL, 0.187 mmol). After 10 min., the solution was warmed to room temperature and stirred for 4 h. The solution was quickly filtered through a glass fritted funnel containing a pad of celite and sodium sulfate eluting with CH_2Cl_2. The solution was concentrated to afford a yellow residue and used without further purification.

The residue was dissolved in CH_2Cl_2 (0.25 mL) and cooled to -10 ºC. Pyridine (0.040 mL, 0.499 mmol) was added, and the solution was stirred for 2 h. The solution was diluted with Et_2O (5 mL) and then washed with saturated NH_4Cl, brine, dried (Na_2SO_4), and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography with EtOAc:hexanes (1:9) to provide ketone **101** (17.7 mg, 67%) as a colorless oil. IR (thin film) ν_{max} 1720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.19 (m, 5H), 4.32 (dddd, J = 3.5, 5.0, 9.0, 12.0 Hz, 1H), 3.00 (dd, J = 8.0, 17.0 Hz, 1H), 2.90

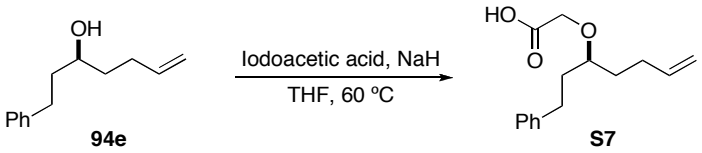
(ddd, J = 5.0, 9.0, 14.0 Hz, 1H), 2.83-2.73 (m, 2H), 2.18 (s, 3H), 2.12-1.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.0, 140.6, 128.50 (2), 128.46 (2), 126.1, 56.5, 51.7, 39.7, 32.5, 30.7; LRMS (ESI) Calcd. for $C_{12}H_{15}ClOLi$ [M+Li] 217, found 217.



97 **94e**

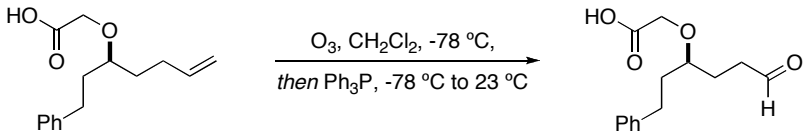
(*S*)-1-phenylhept-6-en-3-ol (94e). To a flask containing CuI (0.39 g, 2.04 mmol) was added Et_2O (75 mL), and the mixture was cooled to -78 °C. Benzylmagnesium bromide (6.64 mL of 2.0 M solution in tetrahydrofuran, 13.3 mmol) was added dropwise, and the mixture was stirred for 0.5 h. The solution was warmed at room temperature until the mixture turned black (~0.5 h) and then was cooled again to -78 ºC. A solution of epoxide **97**[200] (1.00 g, 10.2 mmol) in Et_2O (25 mL) was then added. The mixture was slowly warmed to room temperature over ~ 5 h and continued stirring for a total of 23 h. The reaction was then quenched with saturated NH_4Cl (100 mL). After separating the layers, the aqueous layer was extracted with CH_2Cl_2 (4 x 30 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography EtOAc:hexanes (4:6) to yield alcohol **94e** (1.94 g, 99%) as a pale yellow oil. A single enantiomer was formed (absolute stereochemistry determined by comparison of optical rotations from epichlorohydrin precursor; (*S*)-epichlorohydrin = $[\alpha]^{20}_D$ -33.2 (c = 4.28, MeOH), (*S*)-epichlorohydrin literature value $[\alpha]^{22}_D$ -33.0 (c = 4.22, MeOH).[12] R_f 0.44 (1:4 EtOAc:hexanes); $[\alpha]^{19}_D$ -6.1 (c = 2.01, $CHCl_3$); IR (thin film) ν_{max} 3356, 1640 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.16 (m, 5H), 5.84 (dddd, J = 7.0, 7.0, 10.0, 17.0 Hz, 1H), 5.08-4.95 (m, 2H), 3.71-

3.63 (m, 1H), 2.93 (s, 1H), 2.80 (ddd, J = 5.5, 9.5, 13.5 Hz, 1H), 2.68 (ddd, J = 6.5, 9.5, 13.5 Hz, 1H), 2.26-2.10 (m, 2H), 1.86-1.70 (m, 2H), 1.65-1.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.1, 138.5, 128.4 (4), 125.8, 114.8, 70.9, 39.1, 36.5, 32.0, 30.0; HRMS (ESI) Calcd. for $C_{13}H_{18}OLi$ [M+Li] 197.1518, found 197.1521.



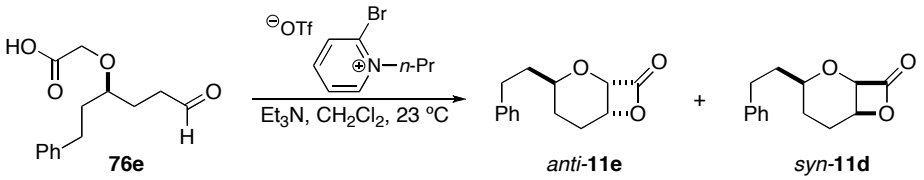
(*S*)-2-(1-phenylhept-6-en-3-yloxy)acetic acid (S7). Sodium hydride, 60% suspension in mineral oil (2.40 g, 58.1 mmol) was washed with hexanes (2 x 5 mL). The solid was dried under nitrogen and then was suspended in tetrahydrofuran (5 mL). A solution of iodoacetic acid[135] (2.05 g, 10.7 mmol) in tetrahydrofuran (10 mL) was then added dropwise at 23 ºC. During addition, evolution of hydrogen gas was evident by the mixture bubbling. The mixture was stirred an additional hour. Alcohol **94e** (1.94 g, 10.2 mmol) was then added as a solution in tetrahydrofuran (10 mL). The mixture was allowed to stir for 48 h. The reaction was quenched upon dilution with CH_2Cl_2 (80 mL) and saturated NH_4Cl (67 mL). The mixture was acidified to pH 2 with 10% H_2SO_4 and the layers were separated. The aqueous layer was extracted with Et_2O (4 x 30 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:1 to 7:3) to provide acid **S7** (1.18 g, 47%) as a pale yellow oil. R_f 0.29 (3:7 EtOAc:hexanes); $[\alpha]^{18}_D$ -5.7 (c = 1.06, $CHCl_3$); IR (thin film) ν_{max} 3165, 1732, 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.15 (m, 5H), 5.80 (ddd, J = 6.9, 6.9, 10.2 Hz, 1H), 5.06-4.94 (m, 2H), 4.12 (s, 2H), 3.47 (p, J = 6.0 Hz, 1H), 2.81-2.61 (m, 2H),

2.15 (dd, J = 6.9, 13.8 Hz, 2H), 1.98-1.79 (m, 2H), 1.79-1.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 141.7, 137.9, 128.4 (2), 128.3 (2), 125.9, 115.0, 79.9, 65.8, 35.1, 32.5, 31.4, 29.3; HRMS (ESI) Calcd. for $C_{15}H_{19}O_3$ [M-H] 247.1334, found 247.1327.

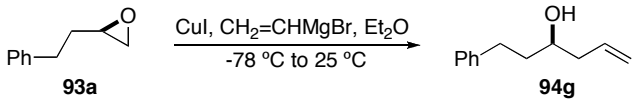


S7 **76e**

(*R*)-2-(6-oxo-1-phenylhexan-3-yloxy)acetic acid (76e). Alkene acid **S7** (210 mg, 0.85 mmol) underwent ozonolysis according to the representative procedure for ozonolysis of alkene acids. Triphenylphosphine (266 mg, 1.01 mmol) was added as the reducing reagent. The crude residue was purified by acid/base extraction by partitioning between CH_2Cl_2 (15 mL) and saturated $NaHCO_3$ (20 mL). The layers were separated, and the aqueous layer was washed subsequently with hexanes (2 x 7 mL), and then acidified with 10% H_2SO_4 to pH 1. The aqueous layer was then extracted with CH_2Cl_2 (2 x 10 mL) and with Et_2O (3 x 10 mL). The extracts obtained after acidification were combined, dried (Na_2SO_4) and concentrated by rotary evaporation to afford aldehyde acid **76e** (198 mg, 94%) as a pale yellow oil. R_f 0.57 (7:3 EtOAc:hexanes); IR (thin film) ν_{max} 2934, 1723 cm^{-1}; ^{1}H NMR (300 MHz, benene-d_6) δ 10.87 (bs, 1H), 9.41 (s, 1H), 7.27-7.01 (m, 5H), 3.81 (d, J = 16.8 Hz, 1H), 3.73 (d, J = 17.1 Hz, 1H), 3.07 (p, J = 6.0 Hz, 1H), 2.51 (t, J = 7.5 Hz, 2H), 2.30-1.94 (m, 2H), 1.74-1.20 (m, 4H); ^{13}C NMR (75 MHz, benzene-d_6) δ 201.9, 176.9, 142.4, 128.9 (2), 128.8 (2), 126.4, 79.2, 65.9, 39.6, 35.5, 31.7, 26.0; HRMS (ESI) Calcd. for $C_{14}H_{17}O_4$ [M-H] 249.1127, found 249.1130.

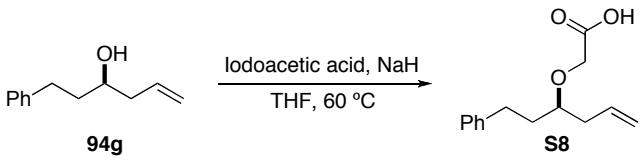


Aldehyde acid **76e** (88.2 mg, 0.35 mmol) underwent cyclization according to the representative procedure for NCAL with achiral nucleophile for tetrahydrofuran-fused *β*-lactone. The crude residue was purified by flash column chromatography with EtOAc:hexanes (1:9) to provide *anti*-tetrahydropyran-fused *β*-lactone **11e** (26.3 mg, 26%, dr >19:1) as a colorless oil. **(1*S*,3*R*,6*R*)-3-phenethyl-2,7-dioxabicyclo[4.2.0]octan-8-one (*anti*-11e).** R_f 0.30 (1:4 EtOAc:hexanes); IR (thin film) ν_{max} 1827 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.16 (m, 5H), 5.08 (d, J = 5.7 Hz, 1H), 4.82 (dddd, J = 0.9, 1.8, 3.6, 5.7 Hz, 1H), 3.83-3.70 (m, 1H), 2.87-2.64 (m, 2H), 2.35-2.24 (m, 1H), 2.09-1.91 (m, 2H), 1.87-1.65 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 141.5, 128.5 (2), 128.3 (2), 125.8, 77.4, 74.5, 72.0, 38.4, 31.2, 24.6, 22.8; HRMS (ESI) Calcd. for $C_{14}H_{16}O_3Li$ [M+Li] 239.1259, found 239.1262.



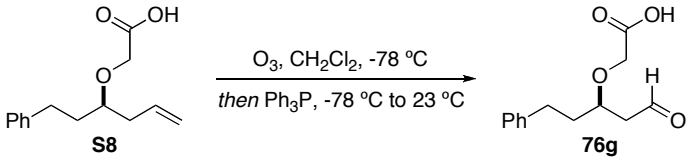
***(R)*-1-Phenylhex-5-en-3-ol (94g).** Epoxide **93a** (absolute stereochemistry assumed to be *R*, since the *R,R*-catalyst was employed)[13] was determined to have an enantiomeric excess = 94% (chiral HPLC, Chiralcel OD, 98:2 hexanes:*i*-PrOH eluent, 1.00 mL/min flow rate and a lamp setting of 210 nm) t_r (major) = 6.960; t_r (minor) = 8.954.) To a flask containing CuI (1.25 g, 6.57 mmol) was added Et_2O (245 mL), and the mixture was cooled to -78 °C. Vinylmagnesium bromide (59.1 mL, 59.1 mmol) was added dropwise, and the mixture was stirred for 30 minutes. The solution was warmed at room

temperature until the mixture turned black and then was cooled again to -78 ºC. A solution of epoxide **93a**[201] (4.87 g, 32.9 mmol) in Et_2O (85 mL) was then slowly added. The mixture was slowly warmed to room temperature over ~ 5 h and continued stirring for a total of 23 h. The reaction was then quenched with saturated NH_4Cl (300 mL). After separating the layers, the aqueous layer was extracted with CH_2Cl_2 (4 x 100 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography EtOAc:hexanes (4:6) to yield alcohol **94g** (5.70 g, 98%) as a pale yellow oil. $[\alpha]^{19}_{D}$ +23.5 (c = 0.17, acetone). The spectroscopic data matched that found in the literature.[202]



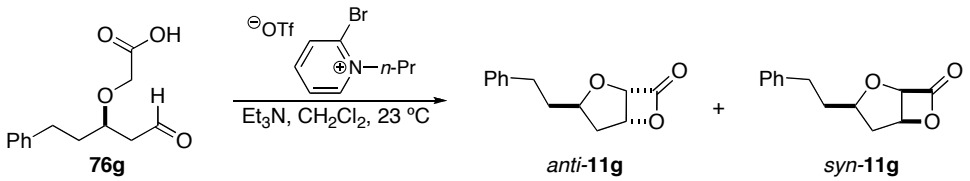
(*R*)-2-(1-phenylhex-5-en-3-yloxy)ethanoic acid (S8). Sodium hydride, 80% suspension in mineral oil (2.15 g, 0.07 mol) was washed with hexanes (2 x 5 mL). The solid was dried under nitrogen and then was suspended in tetrahydrofuran (12 mL). A solution of iodoacetic acid[137] (4.45 g, 0.02 mol) in tetrahydrofuran (10 mL) was then added dropwise at 23 ºC. The mixture was stirred for an additional 15 min. Alcohol **94g** (2.21 g, 0.01 mol) was then added as a solution in tetrahydrofuran (6 mL). The mixture was allowed to stir for 14 h. The reaction was quenched upon dilution with CH_2Cl_2 (250 mL) and saturated NH_4Cl (150 mL). The mixture was extracted with CH_2Cl_2 (3 x 80 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated. The crude residue was purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:1 to 1:0) to provide acid **S8** (2.82 g, 96%) as a white solid. R_f 0.61 (7:3 EtOAc:hexanes);

$[\alpha]^{19}_{D}$ +31.1 (*c* = 1.35, acetone); IR (thin film) ν_{max} 3422, 1731, 1130 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.90 (bs, 1H), 7.33-7.15 (m, 5H), 5.83 (dddd, *J* = 7.0, 7.0, 14.0, 17.0 Hz, 1H), 5.19-5.11 (m, 2H), 4.19 (d, *J* = 16.5 Hz, 1H), 4.14 (d, *J* = 16.5 Hz, 1H), 3.52 (tt, *J* = 5.9, 5.9 Hz, 1H), 2.80 (ddd, *J* = 5.5, 9.5, 14.0 Hz, 1H), 2.71 (ddd, *J* = 6.5, 9.5, 13.5 Hz, 1H), 2.42-2.35 (m, 2H), 1.99-1.79 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 141.6, 133.8, 128.4 (2), 128.3 (2), 125.9, 118.0, 79.8, 66.1, 38.0, 35.2, 31.4; HRMS (ESI) Calcd. for $C_{14}H_{17}O_3$ [M-H] 233.1178, found 233.1180.

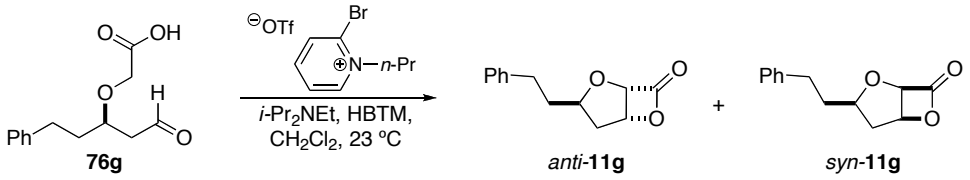


(*R*)-2-(1-oxo-5-phenylpentan-3-yloxy)acetic acid (76g). Alkene acid **S8** (511 mg, 2.18 mmol) was ozonolyzed according to the representative procedure for ozonolysis of alkene acids. Triphenylphosphine (686 mg, 2.61 mmol) was added as the reducing reagent. The crude residue was purified by acid/base extraction by partitioning between CH_2Cl_2 (15 mL) and saturated $NaHCO_3$ (40 mL). The layers were separated, and the aqueous layer was washed subsequently with hexanes (2 x 15 mL), and then acidified with 10% H_2SO_4 to pH 1. The aqueous layer was then extracted with CH_2Cl_2 (2 x 20 mL) and with Et_2O (3 x 20 mL). The extracts obtained after acidification were combined, dried (Na_2SO_4) and concentrated by rotary evaporation to afford aldehyde acid **76g** (432 mg, 84%) as a colorless oil. R_f 0.55 (8:2 EtOAc:hexanes); IR (thin film) ν_{max} 3426, 1729, 1641 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (s, 1H), 9.25 (bs, 1H), 7.34-7.1 (m, 5H), 4.18 (dd, *J* = 17.0, 24.0 Hz, 2H), 4.00-3.94 (m, 1H), 2.80 (ddd, *J* = 2.0; 7.5; 17.5 Hz, 2H), 2.74-2.62 (m, 2H), 2.03-1.82 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.6, 174.5,

140.9, 128.4 (2), 128.2 (2), 126.0, 74.9, 66.2, 47.9, 35.3, 30.9; LRMS (ESI) Calcd. for $C_{13}H_{15}O_4$ [M-H] 235, found 235.

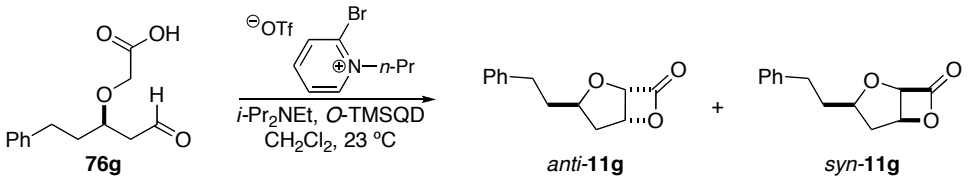


Aldehyde acid **76g** was azeotroped with xylenes prior to use. To a flask containing pyridinium salt **72** (332 mg, 0.94 mmol) was added 6.4 mL CH_2Cl_2 under nitrogen followed by triethylamine (0.26 mL, 1.88 mmol). The solution turned pale yellow. To the reaction mixture at 23 ºC was added a solution of aldehyde acid **76g** (111 mg, 0.47 mmol) in CH_2Cl_2 (2.8 mL) via syringe pump over 1 h. The solution darkened to maroon. The reaction was quenched after an additional hour of stirring by washing twice with saturated NH_4Cl, brine, and dried (Na_2SO_4). The solution was concentrated and purified by flash column chromatography by Et_2O:hexanes (0.6:9.4) to afford *anti/syn* tetrahydrofuran-fused *β*-lactones **11g** (48.2 mg, 47%, dr 1:1) as a colorless oils.

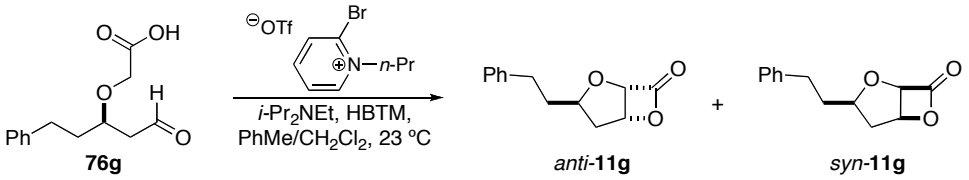


Representative Procedure for Nucleophile Catalyzed Aldol Lactonization (NCAL) with asymmetric nucleophile as described for Tetrahydrofuran-fused *β*-lactone 11g. Aldehyde acid **76g** was azeotroped with xylenes prior to use. To a flask containing pyridinium salt **72** (223 mg, 0.64 mmol) and the asymmetric nucleophile, homobenzotetramisole, (8.4 mg, 0.03 mmol) was added 3.8 mL CH_2Cl_2 under nitrogen

followed by *i*-Pr_2NEt (0.21 mL, 1.28 mmol). The solution turned pale yellow. To the reaction mixture at 23 ºC was added a solution of aldehyde acid **76g** (75.4 mg, 0.32 mmol) in CH_2Cl_2 (2.6 mL) via syringe pump over 1 h. The solution darkened to orange-red. The reaction was concentrated after an additional 18 h of stirring and then purified by flash column chromatography by a gradient mixture of EtOAc:hexanes (1:9 to 1:4) to afford *anti/syn* tetrahydrofuran-fused *β*-lactones **11g** (21.2 mg, 30%, dr 2:1) as a colorless oils. **(1*S*,3*R*,5*R*)-3-phenethyl-2,6-dioxabicyclo[3.2.0]heptan-7-one (*anti*-11g).** R_f 0.30 (1:4 EtOAc:hexanes); $[\alpha]^{19}_D$ +27.6 (*c* = 0.58, $CHCl_3$); IR (thin film) ν_{max} 1824 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.15 (m, 5H), 5.47 (d, *J* = 3.9 Hz, 1H), 5.14 (dd, *J* = 3.9, 4.2 Hz, 1H), 4.21-4.08 (m, 1H), 2.91-2.66 (m, 2H), 2.40 (dd, *J* = 4.5, 14.4 Hz, 1H), 2.16-1.90 (m, 2H), 1.52 (ddd, *J* = 4.2, 10.5, 14.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 141.0, 128.5 (2), 128.3 (2), 126.1, 87.9, 78.7, 78.4, 36.5, 35.4, 32.2; HRMS (ESI) Calcd. for $C_{13}H_{13}O_3$ [M-H] 217.0865, found 217.0859. **(1*R*,3*R*,5*S*)-3-phenethyl-2,6-dioxabicyclo[3.2.0]heptan-7-one (*syn*-11g).** R_f 0.18 (1:4 EtOAc:hexanes); $[\alpha]^{19}_D$ +55.3 (*c* = 1.23, $CHCl_3$); IR (thin film) ν_{max} 1825 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80-7.25 (m, 5H), 5.42 (d, *J* = 4.0 Hz, 1H), 5.21 (ddd, *J* = 1.0, 4.0, 6.0 Hz, 1H), 4.57 (dddd, *J* = 2.5, 5.5, 8.0, 13.0 Hz, 1H), 2.86 (ddd, *J* = 5.0, 9.0, 14.0 Hz, 1H), 2.71 (ddd, *J* = 7.5, 9.0, 14.0 Hz, 1H), 2.23 (dd, *J* = 1.0, 1.5 Hz, 1H), 2.21 (dd, *J* = 5.0, 8.0 Hz, 1H), 2.21-2.09 (m, 1H), 1.82 (dddd, *J* = 5.5, 7.5, 13.0, 15.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 149.9, 128.6 (2), 128.4 (2), 126.0, 88.0, 83.1, 79.5, 37.8, 34.8, 32.5; HRMS (ESI) Calcd. for $C_{13}H_{13}O_3$ [M-H] 217.0865, found 217.0859.

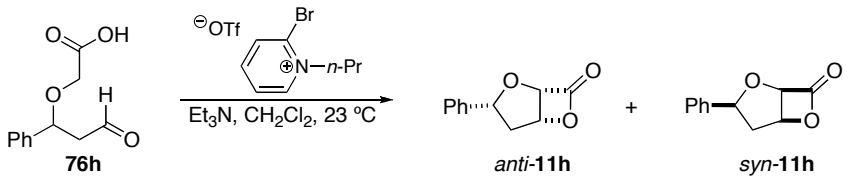


Aldehyde acid **76g** was azeotroped with xylenes prior to use. To a flask containing pyridinium salt **72** (267 mg, 0.76 mmol) and *O*-TMSQD (10.1 mg, 0.03 mmol) was added CH_2Cl_2 (0.77 mL) under nitrogen followed by *i*-Pr_2NEt (0.18 mL, 1.02 mmol). The solution turned pale green-yellow. To the reaction mixture at 23 ºC was added a solution of aldehyde acid **76g** (60.0 mg, 0.25 mmol) in CH_2Cl_2 (0.78 mL) via syringe pump over 1 h. The solution darkened to deep red. The reaction was concentrated after an additional 23 h of stirring and then purified by flash column chromatography with a mixture of EtOAc:hexanes (1:4) to afford *anti/syn* tetrahydrofuran-fused β-lactones **11g** (21.6 mg, 39%, dr 2:1) as a colorless oil.



Aldehyde acid **76g** was azeotroped with xylenes prior to use. To a flask containing pyridinium salt **72** (140 mg, 0.40 mmol) and the asymmetric nucleophile, homobenzotetramisole, (5.3 mg, 0.02 mmol) was added PhMe (4.0 mL) under nitrogen followed by *i*-Pr_2NEt (0.13 mL, 0.80 mmol). The solution turned pale yellow. To the reaction mixture at 23 ºC was added a solution of aldehyde acid **76g** (47.2 mg, 0.20 mmol) in CH_2Cl_2 (1.8 mL) via syringe pump over 1 h. The reaction was concentrated after an additional 18 h of stirring and then purified by flash column chromatography by

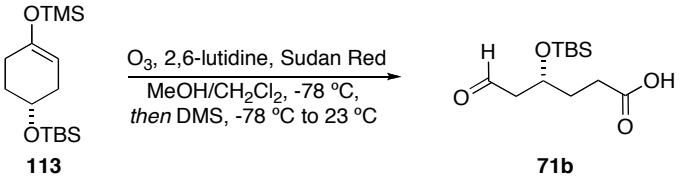
a gradient mixture of EtOAc:hexanes (1:9 to 1:4) to afford *anti/syn* tetrahydrofuran-fused *β*-lactones **11g** (9.4 mg, 22%, dr 7:1) as a colorless oil.



76h *anti*-**11h** *syn*-**11h**

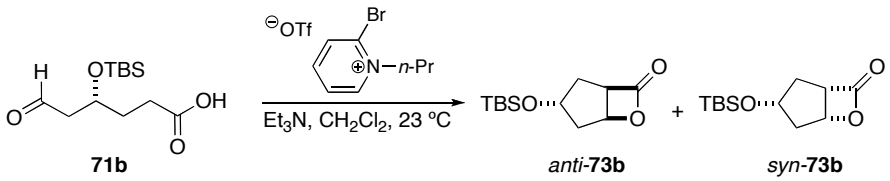
3-phenyl-2,6-dioxabicyclo[3.2.0]heptan-7-one (11h). To a flask containing pyridinium salt **72** (0.353 g, 0.662 mmol) was added CH_2Cl_2 (4.5 mL) and triethylamine (0.19 mL, 1.32 mmol). The solution turned pale yellow and was cooled to -30 ºC. Aldehyde acid **76h** (0.069 g, 0.331 mmol) was added over 3 h via syringe pump as a solution in CH_2Cl_2 (2.2 mL). After 14 h of stirring, the solution was warmed to -5 ºC and stirred for an additional 5 h. The solution was partitioned between Et_2O (60 mL) and saturated NH_4Cl (20 mL). The organic layer was washed with saturated NH_4Cl, twice with brine, filtered (Na_2SO_4), and then concentrated by rotary evaporation. The crude residue was purified by flash column chromatography with a mixture of EtOAc:hexanes (1:4) to give *anti*/*syn* tetrahydrofuran-fused *β*-lactones **11h** (0.010 g, 16%, dr 1.3:1) as a colorless oil. (major) R_f 0.27 (1:4 EtOAc:hexanes); IR (thin film) ν_{max} 1827 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.32 (m, 5H), 5.66 (d, J = 3.6 Hz, 1H), 5.26 (t, 3.6 Hz, 1H), 5.13 (dd, J = 4.8, 10.8 Hz, 1H), 2.74 (dd, J = 4.8, 14.7 Hz, 1H), 1.85 (ddd, J = 4.8, 10.8, 14.7 Hz, 1H); HRMS (ESI) Calcd. for $C_{11}H_{10}O_3$ [M+H] 191.0708, found 191.0699.

CHAPTER IV – DEVELOPMENT OF DOUBLE DIASTEREOSELECTIVE NUCLEOPHILE CATALYZED, ALDOL-LACTONIZATIONS (NCAL) TO *β*-LACTONE FUSED CARBOCYCLES AND TETRAHYDROFURANS

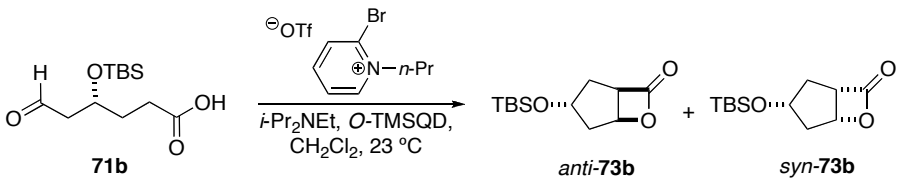


(*R*)-4-(*tert*-butyldimethylsilyloxy)-6-oxohexanoic acid (71b).[146] Silyl enol ether **113** was prepared according to known literature procedure via asymmetric deprotonation in the presence of (–)-bis[(*S*)-1-phenylethyl]amine.[112] Enantiomeric excess = 87% was determined by oxidation of silyl enol ether to enone **114** (*vida infra*), and the absolute stereochemistry was determined by comparison of optical rotations for enone **114** = $[\alpha]^{18}_{D}$ +87.4 (*c* = 1.19, $CHCl_3$), literature value $[\alpha]_D$ +103.8 (*c* = 0.04, $CHCl_3$)[203] and ultimately confirmed by X-ray analysis of *syn*-*β*-lactone **73b**. A solution of silyl enol ether **113** (3.09 g, 10.3 mmol), 2,6-lutidine (1.19 mL, 10.3 mmol), and Sudan Red 7B (< 1.0 mg) in a mixture of methanol (79 mL) and CH_2Cl_2 (79 mL) was cooled to -78 ºC. Ozone was bubbled through the pink solution via a gas sparging tube until solution until the pink color dissipated. This was followed with bubbling of nitrogen (twice the time required for pink color to dissipate). Dimethyl sulfide (3.79 mL, 51.4 mmol) was added and the solution was allowed to warm slowly to room temperature over ~ 10 h. After 3 h of additional stirring at room temperature, the solution was concentrated by rotary evaporation and purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (3:7 to 1:1) to afford aldehyde acid **71b** (1.75 g, 65%) as a colorless oil. Store frozen in benzene if not used immediately. R_f 0.39 (2:3 EtOAc:hexanes); $[\alpha]^{21}_{D}$ +1.3 (*c* = 1.56, $CHCl_3$); IR (thin film) ν_{max} 3044, 2730, 1714 cm^{-1}; ^1H NMR (500 MHz,

$CDCl_3$) δ 9.79 (t, J = 2.0 Hz, 1H), 4.28 (t, J = 6.0 Hz, 1H), 2.56 (ddd, J = 2.0, 5.5, 8.0 Hz, 2H), 2.44 (t, J = 7.5 Hz, 2H), 1.95-1.79 (m, 2H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 201.4, 179.3, 66.7, 50.6, 32.1, 29.4, 25.7 (3), 17.9, -4.68, -4.72; HRMS (ESI) Calcd. for $C_{12}H_{23}O_4Si$ [M-H] 259.1366, found 259.1364.

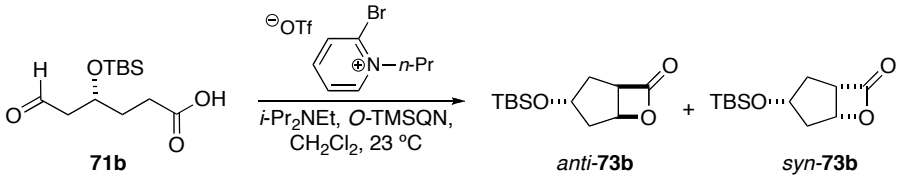


Representative Procedure for Nucleophile Catalyzed Aldol Lactonization (NCAL) with achiral nucleophile as described for Carbocycle 73b. Aldehyde acid **71b** was azeotroped with xylenes in a separate vial prior to use. To a round bottom flask at room temperature containing CH_2Cl_2 (3.0 mL) was added pyridinium salt **72** (369 mg, 1.05 mmol) and triethylamine (0.20 mL, 1.41 mmol). A solution of aldehyde acid **71b** (91.5 mg, 0.35 mmol) in CH_2Cl_2 (4 mL) was added over 1 h via syringe pump. The yellow solution turned dark-red and was stirred for 23 h. The dark red solution was concentrated by rotary evaporation and then portioned between EtOAc (15 mL) and saturated NH_4Cl (15 mL). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated by rotary evaporation. The crude dark brown residue was purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:9 to 3:7) to afford *anti/syn* carbocycle-fused β-lactones **73b** (49.4 mg, 58%, dr 2:1) as a pale yellow oil.

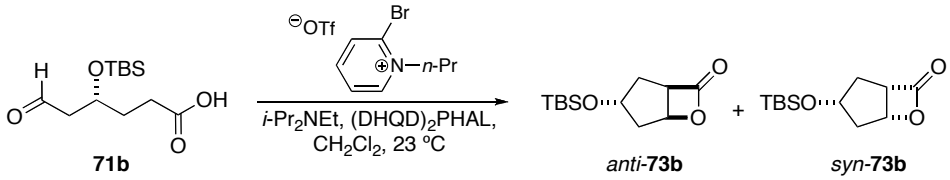


Representative Procedure for Nucleophile Catalyzed Aldol Lactonization (NCAL) with asymmetric nucleophile as described for Carbocycle 73b. Aldehyde acid **71b** was azeotroped with xylenes in a separate vial prior to use. To a vial at room temperature containing CH_2Cl_2 (1.1 mL) was added pyridinium salt **72** (397 mg, 1.13 mmol), asymmetric nucleophile *O*-TMSQD (14.9 mg, 0.04 mmol) and *i*-Pr_2NEt (0.25 mL, 1.51 mmol). The mixture was biphasic, and then a solution of aldehyde acid **71b** (97.2 mg, 0.38 mmol) in CH_2Cl_2 (0.8 mL) was added over 1 h via syringe pump. The yellow-green solution turned dark-red and was stirred for 71 h. The dark brown-red solution was concentrated by rotary evaporation, and the crude dark brown residue was purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:9 to 1:4) to afford *anti/syn* carbocycle-fused *β*-lactones **73b** (66.3 mg, 73%, dr 1:7) as a pale yellow oil. **(1*R*,3*R*,5*S*)-3-(*tert*-butyldimethylsilyloxy)-6-oxabicyclo[3.2.0]heptan-7-one** (*anti*-**73b).** R_f 0.61 (3:7 EtOAc:hexanes); $[\alpha]^{17}_D$ -6.6 (*c* = 1.51, $CHCl_3$); IR (thin film) ν_{max} 1828 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.01 (t, *J* = 4.5 Hz, 1H), 4.53 (t, *J* = 4.0 Hz, 1H), 3.94 (dd, *J* = 4.0, 8.5 Hz, 1H), 2.32-2.23 (m, 2H), 1.83 (ddd, *J* = 4.0, 8.5, 14.5 Hz, 1H), 1.75 (dt, *J* = 4.5, 15.0 Hz, 1H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 171.7, 77.3, 73.5, 55.1, 39.7, 37.3, 25.5 (3), 17.7, -5.0, -5.1; HRMS (ESI) Calcd. for $C_{12}H_{22}O_3SiLi$ [M+Li] 249.1498, found 249.1502. **(1*S*,3*R*,5*R*)-3-(*tert*-butyldimethylsilyloxy)-6-oxabicyclo[3.2.0]heptan-7-one** (*syn*-**73b).** Relative and absolute stereochemistry confirmed by X-ray analysis. R_f 0.36 (3:7 EtOAc:hexanes);

$[\alpha]^{17}_{D}$ +20.0 (*c* = 1.10, $CHCl_3$); IR (thin film) ν_{max} 1833 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.94 (t, *J* = 4.5 Hz, 1H), 4.54-4.44 (m, 1H), 3.91 (dd, *J* = 4.0, 8.5 Hz, 1H), 2.49 (dd, *J* = 6.0, 14.5 Hz, 1H), 2.37 (dd, *J* = 6.0, 13.5 Hz, 1H), 1.71-1.56 (m, 2H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C (125 MHz, $CDCl_3$) δ 171.1, 75.7, 70.9, 53.3, 39.4, 34.6, 25.7 (3), 18.0, -4.91, -4.94; HRMS (ESI) Calcd. for $C_{12}H_{22}O_3SiLi$ [M+Li] 249.1498, found 249.1496.

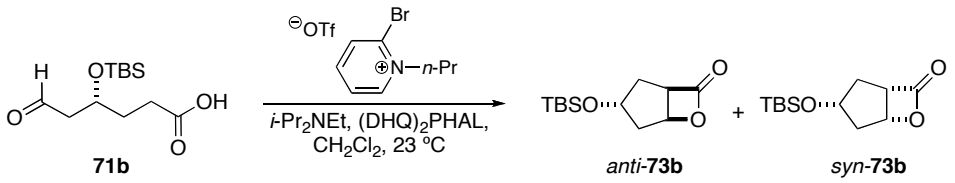


Aldehyde acid **71b** (84.1 mg, 0.32 mmol) underwent cyclization according to the representative procedure for NCAL with asymmetric nucleophile for carbocycles using *O*-TMSQN as the asymmetric nucleophile. The solution was then concentrated by rotary evaporation and purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:9 to 1:4) to provide *anti*-carbocycle-fused β-lactones **73b** (46.9 mg, 60%, dr >19:1) as a colorless oil.

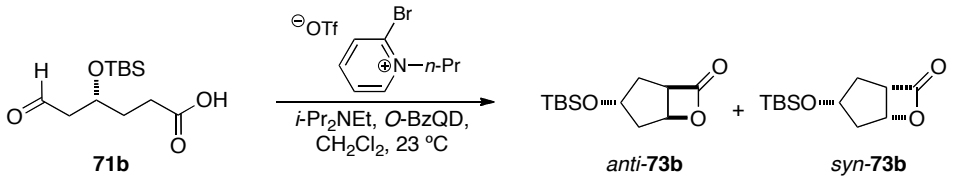


Aldehyde acid **71b** (70.9 mg, 0.27 mmol) underwent cyclization according to the representative procedure for NCAL with asymmetric nucleophile for carbocycles using $(DHQD)_2PHAL$ as the asymmetric nucleophile. The solution was then concentrated by

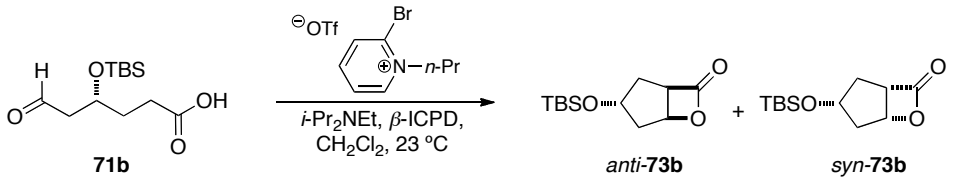
rotary evaporation and purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:9 to 1:4) to provide *anti/syn* carbocycle-fused β-lactones **73b** (39.0 mg, 59%, dr 1:4) as a colorless oil.



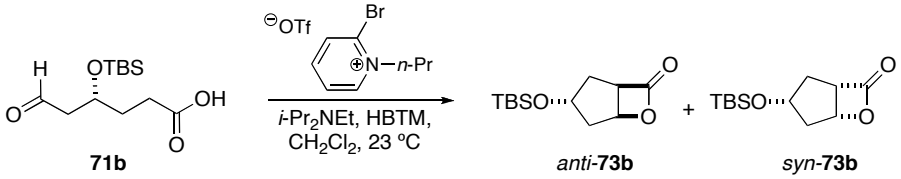
Aldehyde acid **71b** (67.2 mg, 0.26 mmol) underwent cyclization according to the representative procedure for NCAL with asymmetric nucleophile for carbocycles using $(DHQ)_2PHAL$ as the asymmetric nucleophile. The solution was then concentrated by rotary evaporation and purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:9 to 1:4) to provide *anti*-carbocycle-fused β-lactone **73b** (32.9 mg, 53%, dr >19:1) as a colorless oil.



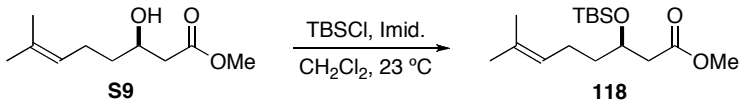
Aldehyde acid **71b** (52.1 mg, 0.20 mmol) underwent cyclization according to the representative procedure for NCAL with asymmetric nucleophile for carbocycles using *O*-BzQD as the asymmetric nucleophile. Reaction stopped after 53 h. The solution was then concentrated by rotary evaporation and purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:9 to 1:4) to provide *anti/syn* carbocycle-fused β-lactones **73b** (15.8 mg, 33%, dr 1:6) as a colorless oil.



Aldehyde acid **71b** (52.1 mg, 0.20 mmol) underwent cyclization according to the representative procedure for NCAL with asymmetric nucleophile for carbocycles using *β*-ICPD as the asymmetric nucleophile. Reaction stopped after 53 h. The solution was then concentrated by rotary evaporation and purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:9 to 1:4) to provide *anti/syn* carbocycle-fused *β*-lactones **73b** (12.0 mg, 23%, dr 16-19:1) as a colorless oil.

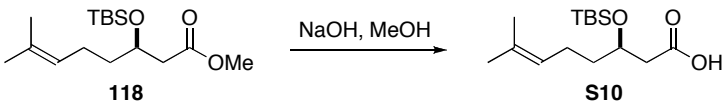


Aldehyde acid **71b** (97.4 mg, 0.37 mmol) underwent cyclization according to the representative procedure for NCAL with asymmetric nucleophile for carbocycles using (±)-HBTM as the achiral nucleophile. The reaction was run for only 48 h. The solution was then concentrated by rotary evaporation and purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:9 to 1:4) to provide *anti/syn* carbocycle-fused *β*-lactones **73b** (30.5 mg, 34%, dr 2:1) as a colorless oil.



(*R*)-methyl 3-(*tert*-butyldimethylsilyloxy)-7-methyloct-6-enoate (118). The enantiomeric excess (>97% ee) and the absolute stereochemistry of alcohol **S9** was

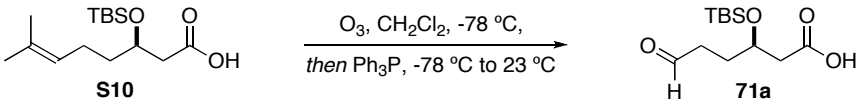
determined by comparison of optical rotations; alcohol **S9** = $[\alpha]^{18}_{D}$ -16.8 (*c* = 1.29, $CHCl_3$), literature value $[\alpha]_D$ -15.7 (*c* = 1.07, $CHCl_3$).[149] To a solution of alcohol **S9**[18,204] (1.51 g, 8.13 mmol) in CH_2Cl_2 (10 mL) was added imidazole (2.21 g, 32.5 mmol) and *tert*-butyldimethylchlorosilane (1.47 g, 9.76 mmol), respectively. The mixture was stirred at 23 ºC for 16 h. The reaction mixture was then quenched upon addition of brine (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated by rotary evaporation. The residue was then purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (0.5:9.5 to 1:9) to provide ester **118** (1.86 g, 76%) as a colorless oil. R_f 0.56 (1:9 EtOAc:hexanes); $[\alpha]^{20}_{D}$ -1.95 (*c* = 2.05, $CHCl_3$). IR (thin film) ν_{max} 1743 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.08 (t, *J* = 7.0 Hz, 1H), 4.13 (p, *J* = 6.0 Hz, 1H), 3.65 (s, 3H), 2.46 (dd, *J* = 7.0, 15.0 Hz, 1H), 2.42 (dd, *J* = 6.0, 14.5 Hz, 1H), 2.07-1.91 (m, 2H), 1.67 (s, 3H), 1.59 (s, 3H), 1.51 (ddd, *J* = 6.0, 8.5, 14.0 Hz, 2H), 0.86 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 131.8, 123.9, 69.2, 51.4, 42.4, 37.6, 25.72 (3), 25.66, 23.6, 17.9, 17.6, -4.6, -4.9; HRMS (ESI) Calcd. for $C_{16}H_{33}O_3Si$ [M+H] 300.2199, found 300.2208.



118 **S10**

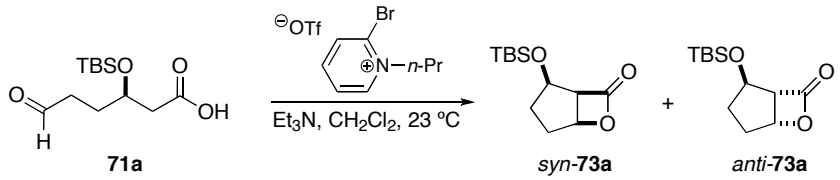
(*R*)-3-(*tert*-butyldimethylsilyloxy)-7-methyloct-6-enoic acid (S10). Ester **118** (1.80 g, 5.99 mmol) dissolved in MeOH (21 mL) was cooled to 0 °C and treated with 1 N NaOH (12.0 mL, 11.97 mmol). After 20 mins, the reaction mixture was warmed to 25 °C and then stirred for 6 h. The reaction mixture was further heated to 40 ºC for 12 h. The

reaction mixture was then cooled to room temperature, and the volatiles were removed under reduced pressure to give a residue that was dissolved in H_2O (30 mL). The crude residue was washed with hexanes (10 mL), and the aqueous layer was acidified with 1% HCl solution. The aqueous layer was extracted with ethyl acetate (3 x 20 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated by rotary evaporation to afford a light yellow residue. The residue was then purified by flash column chromatography with a mixture of EtOAc:hexanes (1:4) to provide acid **S10** (1.01 g, 59%) as a colorless oil. R_f 0.35 (2:3 EtOAc:hexanes); $[\alpha]^{25}_D$ +2.4 (c = 0.01, $CHCl_3$). IR (thin film) ν_{max} 3038, 1717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.11 (tq, J = 6.9, 1.5 Hz, 1H), 4.15 (q, J = 6.0 Hz, 1H), 2.55 (dd, J= 5.7, 2.4 Hz, 2H), 2.04 (q, J = 7.2 Hz, 2H), 1.71 (d, J = 1.5 Hz, 3H), 1.62 (d, J = 1.5 Hz, 3H), 1.60 (dq, J = 7.2, 2.4 Hz, 2H), 1.87 (ddd, J = 7.5, 6.5, 1.0 Hz, 1H), 0.92 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.3, 132.5, 123.7, 77.5, 69.4, 42.0, 37.5, 26.0 (2), 25.9, 24.0, 18.2, 17.9, -4.29, -4.59; HRMS (MALDI) Calcd. for $C_{15}H_{30}O_3SiNa$ [M+Na] 309.1856, found 309.1861.



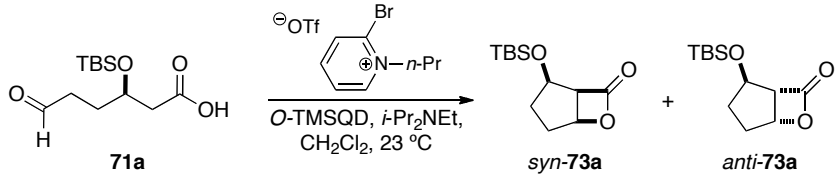
(*R*)-3-(*tert*-Butyldimethylsilyloxy)-6-oxohexanoic acid (71a). A solution of alkene acid **S10** (2.20 g, 7.68 mmol) in dichloromethane (10 mL) was cooled to -78 ºC. Then O_3 was bubbled through solution via a gas sparging tube until solution turned blue (~15 min). This was followed with bubbling of N_2 (twice the time required for solution to turn blue). Reducing reagent, crushed triphenylphosphine (4.03 g, 15.4 mmol), was added. The

solution was allowed to slowly warm to room temperature over ~ 5 h. After 7 h of additional stirring at room temperature, the solution was concentrated by rotary evaporation. The residue was then purified by medium pressure liquid chromatography (MPLC) with a gradient mixture of (EtOAc:hexanes (1:4 to 2:3) to afford aldehyde acid **71a** (1.30 g, 76%) as a colorless oil. R_f 0.25 (2:3 EtOAc:hexanes); $[\alpha]^{25}_D$ +21.9 (*c* = 0.02, MeOH). IR (thin film) ν_{max} 3031, 1712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.82 (t, *J* = 1.5 Hz, 1H), 4.54 (dt, *J* = 6.5, 1.5 Hz, 1H), 2.56 (dt, *J* = 6.5, 1.5 Hz, 1H), 2.53 (dd, *J* = 11.0, 6.0 Hz, 1H), 1.96 (dddd, *J* = 14.5, 12.5, 7.5, 5.0 Hz, 1H), 1.87 (dt, *J* = 7.5, 6.5, 1.0 Hz, 1H), 0.97 (s, 9h), 0.54 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.1, 177.0, 68.2, 42.2, 39.5, 29.4, 26.0 (3), 18.2, -4.39, -4.57; HRMS (ESI) Calcd. for $C_{12}H_{23}O_4Si$ [M-H] 259.1366, found 259.1373.

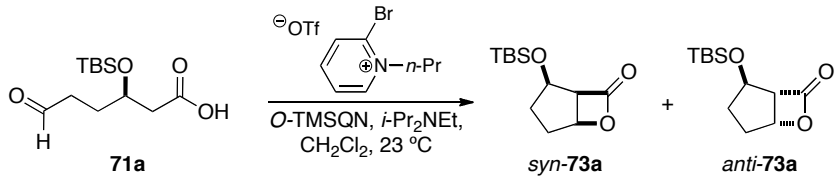


(1*R*,2*R*,5*R*)-2-(*tert*-butyldimethylsilyloxy)-6-oxabicyclo[3.2.0]heptan-7-one (73a). To a solution of pyridinium salt **72** (350 mg, 1.00 mmol) and triethylamine (281 μL, 2.00 mmol) in CH_2Cl_2 (6 mL) was added a solution of aldehyde acid **71a** (130 mg, 0.50 mmol) in CH_2Cl_2 (4 mL) over 1 h via syringe pump. The resulting light red solution was stirred for another 11 h, at which point the volatiles were removed under reduced pressure to give a dark red residue. The crude reaction mixture was then partitioned between ethyl acetate and saturated NH_4Cl solution (50 mL each). The layers were separated, and organic layer was washed with brine (30 mL), dried ($MgSO_4$), and concentrated to afford a light red residue that was purified by flash chromatography with EtOAc:hexanes (1:9,

with 1% triethylamine) to afford *anti*-carbocycle-fused β-lactone **73a** (101 mg, 84%, dr 1: >19) as a light yellow oil. R_f 0.57 (1:4 EtOAc:hexanes); $[\alpha]^{25}_D$ +10.4 (*c* = 0.02, $CHCl_3$). IR (thin film) ν_{max} 1822 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.13 (app t, *J* = 4.0 Hz, 1H), 4.54 (d, *J* = 3.0 Hz, 1H), 3.80 (dd, *J* = 2.0, 4.0 Hz, 1H), 2.19 (m, 1H), 2.02 (m, 3H), 0.89 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 78.9, 72.2, 65.8, 32.4, 28.3, 25.6 (3), 17.9, -4.85, -4.93; HRMS (ESI) Calcd. for $C_{12}H_{22}O_3SiLi$ [M+Li] 249.1498, found 249.1502.

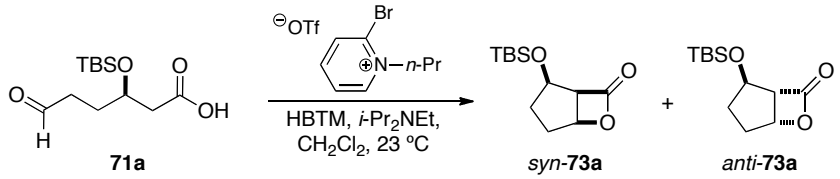


Aldehyde acid **71a** (63.6 mg, 0.24 mmol) underwent cyclization according to the representative procedure for NCAL with asymmetric nucleophile for carbocycles using *O*-TMSQD as the asymmetric nucleophile. The solution was then concentrated by rotary evaporation and purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:9, with 1% triethylamine) to provide *anti*-carbocycle-fused β-lactone **73a** (19.7 mg, 33%, dr >19:1) as a colorless oil.

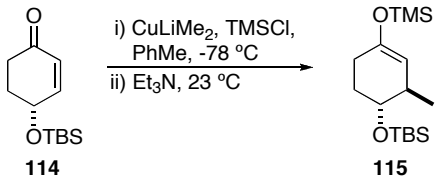


Aldehyde acid **71a** (63.6 mg, 0.24 mmol) underwent cyclization according to the representative procedure for NCAL with asymmetric nucleophile for carbocycles using

O-TMSQN as the asymmetric nucleophile. The solution was then concentrated by rotary evaporation and purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:9, with 1% triethylamine) to provide *anti*-carbocycle-fused β-lactone **73a** (13.5 mg, 23%, dr >19:1) as a colorless oil.

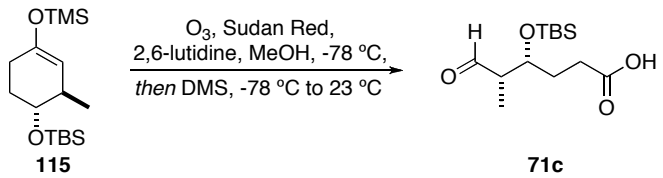


Aldehyde acid **71a** (63.6 mg, 0.24 mmol) underwent cyclization according to the representative procedure for NCAL with asymmetric nucleophile for carbocycles using *O*-TMSQN as the asymmetric nucleophile. The solution was then concentrated by rotary evaporation and purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:9, with 1% triethylamine) to provide *anti*-carbocycle-fused β-lactone **73a** (10.0 mg, 17%, dr >19:1) as a colorless oil.



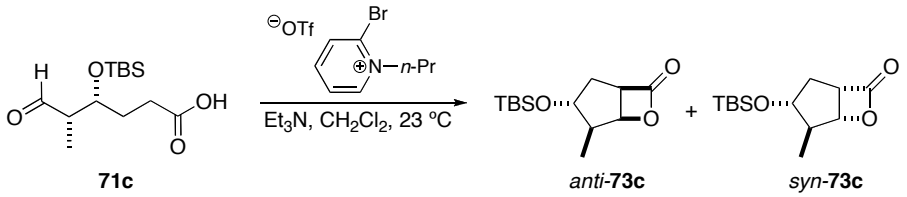
***tert*-butyldimethyl[(1*R*,2*R*)-2-methyl-4-(trimethylsilyloxy)cyclohex-3-enyloxy]silane (115).** Enone **114** was prepared according to known literature procedure by oxidation of the corresponding silyl enol ether **113**.[147,148] Enantiomeric excess = 87% (chiral HPLC, Chiralcel OD, 99:1 hexanes:*i*-PrOH eluent, 1.00 mL/min flow rate and a lamp setting of 222 nm) t_r (minor) = 8.214; t_r (major) = 9.642.) Absolute stereochemistry determined by comparison of optical rotations; enone **114** = $[\alpha]^{18}_D$ +87.4 (*c* = 1.19, $CHCl_3$), literature

value $[\alpha]_D$ +103.8 (c = 0.04, $CHCl_3$).[203] A mixture of CuBr•DMS (300 mg, 1.46 mmol) and toluene (9.5 mL) was cooled to -78 ºC. After 15 min. of stirring, methyl lithium (2.70 mL of 1.15 M in Et_2O, 3.11 mmol) was added slowly. After 45 min., the mixture was warmed to -10 ºC (~30 min.). The colorless, homogenous solution was again cooled to -78 ºC. After subsequent addition of trimethylsilyl chloride (0.25 mL, 1.94 mmol) and enone **114** (220 mg, 0.97 mmol) the solution turned yellow and was stirred for 5 h. Triethylamine (0.47 mL, 3.40 mmol) was then added and the mixture was warmed to room temperature with 4 h of additional stirring over which time the solution became yellow and heterogenous. Additional triethylamine (0.88 mL, 6.31 mmol) was added to reaction mixture. The mixture was filtered through a pad of silica gel (7 g) and celite with pentane (200 mL), which had been eluted with mixture of triethylamine (0.88 mL) and pentane (100 mL) prior to filtration. The solution was concentrated by rotary evaporation and further under high vacuum to afford the desired silyl enol ether **115** (280 mg, 92%) as a colorless oil. R_f 0.84 (1:9 EtOAc:hexanes); IR (thin film) ν_{max} 1667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.62-4.58 (m, 1H), 3.37 (ddd, J = 3.0, 6.3, 9.6 Hz, 1H), 2.22-2.10 (m, 1H), 2.10-2.02 (m, 2H), 1.85-1.58 (m, 2H), 0.97 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.18 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 108.5, 73.8, 37.8, 30.5, 28.4, 25.8 (3), 20.0, 18.0, 0.24 (3), -4.3, -4.7; HRMS (ESI) Calcd. for $C_{16}H_{33}O_2Si_2$ [M-H] 313.2019, found 313.2016.

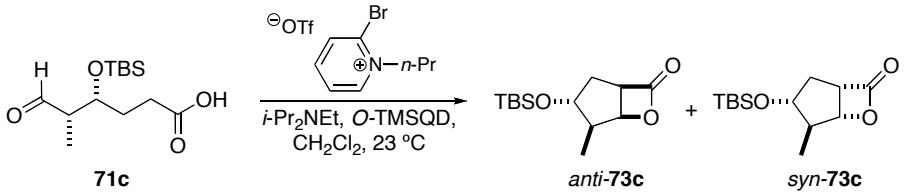


115 **71c**

(4*R*,5*S*)-4-(*tert*-butyldimethylsilyloxy)-5-methyl-6-oxohexanoic acid (71c). A solution of silyl enol ether **115** (155 mg, 0.48 mmol), 2,6-lutidine (0.06 mL, 0.48 mmol), and Sudan red 7B (< 1.0 mg) in methanol (7 mL) was cooled to -78 ºC.[146] Ozone was bubbled through the pink solution via a gas sparging tube until solution until the pink color dissipated. This was followed with bubbling of nitrogen (twice the time required for pink color to dissipate). Dimethyl sulfide (0.18 mL, 2.38 mmol) was added and the solution was allowed to warm slowly to room temperature over ~ 5 h. After 10 h of additional stirring at room temperature, the solution was concentrated by rotary evaporation and purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:9 to 3:7) to afford aldehyde acid **71c** (86 mg, 64%) as a colorless oil. Store frozen in benzene if not used immediately. R_f 0.52 (2:3 EtOAc:hexanes); IR (thin film) ν_{max} 3120, 1714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.80 (d, J = 0.9 Hz, 1H), 4.13 (ddd, J = 4.2, 5.1, 9.0 Hz, 1H), 2.56-2.32 (m, 3H), 1.96-1.70 (m, 2H), 1.09 (d, J = 7.2 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 204.7, 178.1, 71.1, 51.4, 29.9, 29.1, 25.7 (3), 17.9, 8.3, -4.50, -4.55; HRMS (ESI) Calcd. for $C_{13}H_{25}O_4Si$ [M-H] 273.1522, found 273.1520.

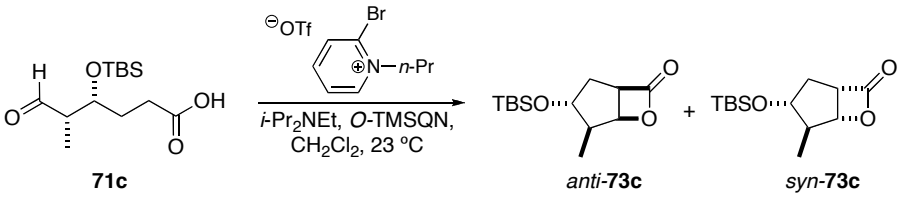


Aldehyde acid **71c** (44.7 mg, 0.16 mmol) underwent cyclization according to the representative procedure for NCAL with achiral nucleophile for carbocycles. The crude residue was concentrated by rotary evaporation and purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (0.5:9.5 to 1:4) to provide *anti/syn* carbocycle-fused *β*-lactones **73c** (18.6 mg, 45%, dr 2:1) as a colorless oil.

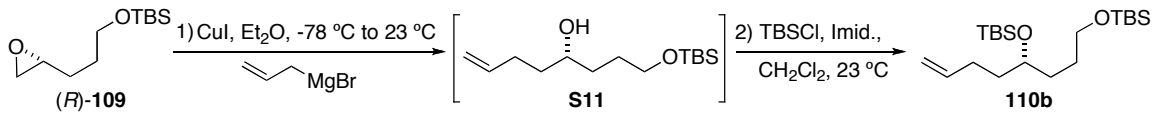


Aldehyde acid **71c** (26.5 mg, 0.10 mmol) underwent cyclization according to the representative procedure for NCAL with asymmetric nucleophile for carbocycles using *O*-TMSQD as the asymmetric nucleophile. The solution was then concentrated by rotary evaporation and purified by flash column chromatography with a gradient mixture of Et_2O:hexanes (0.5:9.5 to 1:4) to provide *anti/syn* carbocycle-fused *β*-lactones **73c** (8.1 mg, 32%, dr 1:3) as a pale yellow oil. **(1*R*,3*R*,4*R*,5*S*)-3-(*tert*-butyldimethylsilyloxy)-4-methyl-6-oxabicyclo[3.2.0]heptan-7-one** (*anti*-**73c**). R_f 0.68 (1:4 EtOAc:hexanes); $[\alpha]^{18}_{D}$ -66.7 (*c* = 0.03, $CHCl_3$); IR (thin film) ν_{max} 1831 cm^{-1}; ^1H NMR (300 MHz, benzene-d_6) δ 3.88 (t, *J* = 4.0 Hz, 1H), 3.82 (ddd, *J* = 6.5, 9.5, 16.0 Hz, 1H), 2.97 (dd, *J* = 4.5, 9.5 Hz, 1H), 2.05 (dd, *J* = 6.5, 12.5 Hz, 1H), 1.26-1.19 (m, 1H), 1.16-1.08 (m, 1H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.88 (s, 9H); -0.10 (s, 3H), -0.12 (s, 3H); ^{13}C (75 MHz, benzene-

d_6) δ 165.5, 77.6, 76.1, 52.2, 45.1, 34.4, 26.0 (4), 11.1, -4.5, -4.8; HRMS (ESI) Calcd. for $C_{13}H_{25}O_3Si$ [M+H] 257.1573, found 257.1558. **(1*S*,3*R*,4*R*,5*R*)-3-(*tert*-butyldimethylsilyloxy)-4-methyl-6-oxabicyclo[3.2.0]heptan-7-one** (*syn*-**73c**). R_f 0.55 (1:4 EtOAc:hexanes); $[\alpha]^{18}_D$ -3.9 (*c* = 0.67, $CHCl_3$); IR (thin film) ν_{max} 1830 cm^{-1}; ^1H NMR (300 MHz, benzene-d_6) δ 3.85 (dd, *J* = 1.2, 4.5 Hz, 1H), 3.68 (d, *J* = 4.5 Hz, 1H), 3.17 (dd, *J* = 4.2, 8.4 Hz, 1H), 2.16 (q, *J* = 7.8 Hz, 1H), 1.90 (d, *J* = 14.4 Hz, 1H), 1.24 (ddd, *J* = 4.5, 8.4, 14.4 Hz, 1H), 1.01 (s, 9H), 0.13 (d, *J* = 7.8 Hz, 3H); 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C (75 MHz, benzene-d_6) δ 170.7, 80.9, 80.2, 55.1, 45.4, 35.2, 25.9 (3), 18.3, 14.3, -4.66, -4.71; HRMS (ESI) Calcd. for $C_{13}H_{24}O_3SiLi$ [M+Li] 263.1655, found 263.1652.



Aldehyde acid **71c** (28.5 mg, 0.10 mmol) underwent cyclization according to the representative procedure for NCAL with asymmetric nucleophile for carbocycles using *O*-TMSQN as the asymmetric nucleophile. The solution was then concentrated by rotary evaporation and purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (0.5:9.5 to 1:4) to provide *anti*-carbocycle-fused β-lactone **73c** (14.8 mg, 55%, dr >19:1) as a colorless oil.

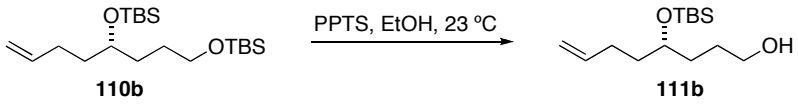


(*R*)-**109** **S11** **110b**

(*S*)-5-(but-3-enyl)-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodecane (110b). Epoxide (*R*)-**109** was prepared according to the known literature procedure, and the spectroscopic data matched that found in the literature.[13,205,206] The enantiomeric excess = 98% (determined by exchange of the TBS to the TBDPS protecting group that was then analyzed with chiral HPLC, Chiralcel OD, 99.7:0.3 hexanes:*i*-PrOH eluent, 1.00 mL/min flow rate and a lamp setting of 230 nm) t_r (minor) = 10.931; t_r (major) = 11.999), and the absolute stereochemistry were determined by comparison of optical rotations; epoxide (*R*)-**109** = $[\alpha]^{20}_D$ +5.8 (*c* = 2.06, $CHCl_3$), literature value $[\alpha]_D$ +5.1 (*c* = 1.28, $CHCl_3$).[207] A flask containing copper iodide (1.06 g, 5.57 mmol), and Et_2O (210 mL) was cooled to -78 ºC.[135] Vinylmagnesium bromide (25.1 mL of 2.0 M solution in THF, 50.2 mmol) was then added. After 0.5 h, the mixture was warmed at room temperature until it turned black. The mixture was directly cooled again to -78 ºC, and a solution of epoxide (*R*)-**109** (6.03 g, 27.9 mmol) in Et_2O (69 mL) was added. The mixture was slowly warmed to room temperature over ~ 5 h. The reaction was quenched after an additional 3 h of stirring upon addition of saturated NH_4Cl (180 mL). The aqueous layer was then extracted with CH_2Cl_2 (4 x 80 mL). The combined organics were dried ($MgSO_4$) and concentrated by rotary evaporation. The desired product, crude alcohol **S11**, was obtained as a colorless oil.

t-Butylchlorodimethylsilane (5.05 g, 33.4 mmol), imidazole (7.60 g, 111.4 mmol), and CH_2Cl_2 (28 mL) were added to a flask containing crude alcohol **S11** (7.20 g, 27.9 mmol).

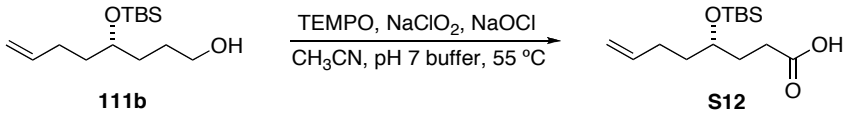
The solution was stirred at room temperature for 48 h. The reaction was then quenched upon addition of saturated NH_4Cl (30 mL). The organic layer was washed with water (15 mL) and brine (15 mL), respectively. The organics were then dried (Na_2SO_4) and concentrated by rotary evaporation and purified by flash column chromatography eluting with a mixture of Et_2O:hexanes (0.5:9.5) to provide the bisprotected product **110b** (8.82 g, 85%, 2 steps) as a colorless oil. R_f 0.79 (1:9 EtOAc:hexanes); $[\alpha]^{18}_D$ -4.6 (*c* = 0.59, $CHCl_3$); IR (thin film) ν_{max} 1642 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.16 (dddd, *J* = 6.9, 6.9, 10.2, 16.8 Hz, 1H), 5.40-5.23 (m, 2H), 4.03 (p, *J* = 5.7 Hz, 1H), 3.94 (t, *J* = 6.3 Hz, 2H), 2.49-2.31 (m, 2H), 2.01-1.68 (m, 6H), 1.23 (s, 9H), 1.22 (s, 9H), 0.38 (s, 12H); ^{13}C (75 MHz, $CDCl_3$) δ 138.9, 114.2, 71.6, 63.4, 36.2, 33.2, 29.6, 28.5, 26.0 (3), 25.9 (3), 18.3, 18.1, -4.4, -4.5, -5.3 (2); HRMS (ESI) Calcd. for $C_{20}H_{44}O_2Si_2$ [M+Li] 379.3040, found 379.3048.



110b **111b**

(*S*)-4-(*tert*-butyldimethylsilyloxy)oct-7-en-1-ol (111b). To a flask containing bisprotected ether **110b** (8.82 g, 23.7 mmol) was added pyridinium *para*-toluenesulfonate (10.41 g, 41.4 mmol) and ethanol (390 mL). The solution was stirred at room temperature for 4 h and then quenched upon addition of brine (200 mL) and saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted (4 x 60 mL) with EtOAc. The combined organics were dried ($MgSO_4$) and concentrated by rotary evaporation and purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:4 to 3:7) to afford alcohol **111b** (2.96 g, 47%) as a colorless oil. R_f 0.58 (3:7

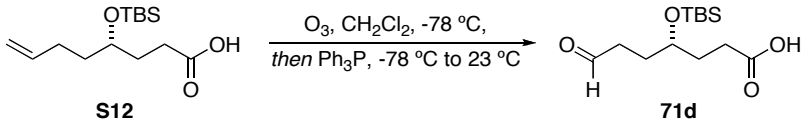
EtOAc:hexanes); $[\alpha]^{17}_{D}$ -10.0 (c = 0.60, $CHCl_3$); IR (thin film) ν_{max} 3331, 1642 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.81 (dddd, J = 6.6, 6.6, 10.2, 16.8 Hz, 1H), 5.06-4.91 (m, 2H), 3.75 (p, J = 6.0 Hz, 1H), 3.70-3.53 (m, 2H), 2.13-2.02 (m, 2H), 2.00 (bs, 1H), 1.69-1.48 (m, 6H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 138.7, 114.4, 71.5, 63.2, 35.7, 33.3, 29.7, 28.1, 25.9 (3), 18.1, -4.46, -4.51; HRMS (ESI) Calcd. for $C_{14}H_{30}O_2SiLi$ [M+Li] 265.2175, found 265.2179.



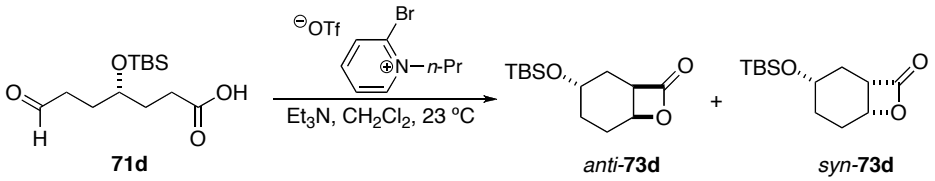
111b **S12**

(*S*)-4-(*tert*-butyldimethylsilyloxy)oct-7-enoic acid (S12). A mixture of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy free radical) (537 mg, 3.44 mmol), $NaClO_2$ (8.29 g, 91.6 mmol), and NaClO (29 mL, 5% in water) was added to a solution of alcohol **111b** (2.96 g, 11.5 mmol) dissolved in CH_3CN (319 mL) and pH 7 buffer (229 mL).[145] The solution turned dark purple and was stirred at 55 ºC for 12 h over which time the color faded to yellow. The solution was cooled to room temperature. The reaction was quenched upon addition of brine (400 mL) and then extracted (4 x 100 mL) with Et_2O. The combined organics were dried ($MgSO_4$) and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:4 to 3:7) to afford alkene acid **S12** (2.16 g, 69%) as a colorless oil. R_f 0.24 (1:4 EtOAc:hexanes); IR (thin film) ν_{max} 1712, 1415 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 11.26 (bs, 1H), 5.89-5.71 (m, 1H), 5.05-4.90 (m, 2H), 3.75 (p, J = 6.0 Hz, 1H), 2.42 (t, J = 7.5 Hz, 2H), 2.15-2.00 (m, 2H), 1.92-1.65 (m, 2H), 1.65-1.48 (m, 2H), 0.09 (s, 9H), 0.06 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 180.1, 138.4, 114.4, 70.4, 35.9, 31.2, 29.7,

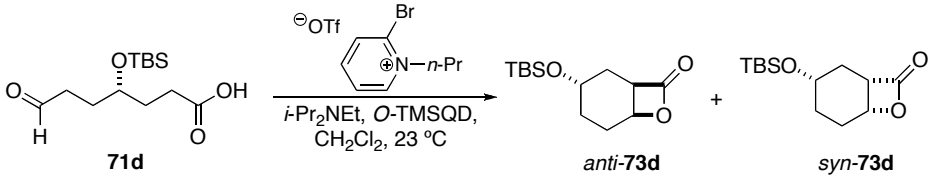
29.3, 25.7 (3), 17.9, -4.6, -4.7; HRMS (ESI) Calcd. for $C_{14}H_{27}O_3Si$ [M-H] 271.1729, found 271.1727.



Representative Procedure for Ozonolysis of Alkene Acids as described for Aldehyde Acid 71d. A solution of alkene acid **S12** (502 mg, 1.84 mmol) in dichloromethane (10 mL) was cooled to -78 ºC. Then O_3 was bubbled through solution via a gas sparging tube until solution turned blue. This was followed with bubbling of O_2 (twice the time required for solution to turn blue). Reducing reagent, crushed triphenylphosphine (580 mg, 2.21 mmol), was added. The solution was allowed to slowly warm to room temperature over ~ 5 h. After 7 h of additional stirring at room temperature, the solution was concentrated by rotary evaporation. The residue was purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:9 to 4:6) to afford aldehyde acid **71d** (445 mg, 88%) as a colorless oil. Store frozen in benzene if not used immediately. **(*S*)-4-(*tert*-butyldimethylsilyloxy)-7-oxoheptanoic acid (71d).** R_f 0.39 (4:6 EtOAc:hexanes); IR (thin film) ν_{max} 3040, 2858, 1711 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.79 (t, J = 1.5 Hz, 0.1H), 3.80 (p, J = 6.0 Hz, 1H), 2.50 (dt, J = 1.0, 7.5 Hz, 1H), 2.42 (app t, J = 7.5 Hz, 3H), 1.90-1.68 (m, 4H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C (125 MHz, $CDCl_3$) δ 202.3, 180.1, 69.7, 39.4, 31.2, 29.6, 28.6, 25.6 (3), 17.9, -4.7 (2); HRMS (ESI) Calcd. for $C_{13}H_{25}O_4Si$ [M-H] 273.1522, found 273.1519.

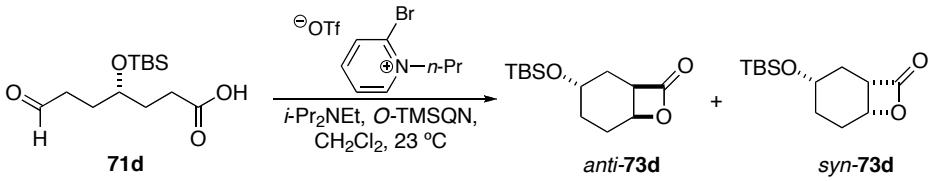


Aldehyde acid **71d** (109 mg, 0.40 mmol) underwent cyclization according to the representative procedure for NCAL with achiral nucleophile for carbocycles. The crude residue was concentrated by rotary evaporation and purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:9 to 1:4) to provide *anti/syn* carbocycle-fused *β*-lactones **73d** (38.4 mg, 38%, dr 2:1) as a colorless oil.

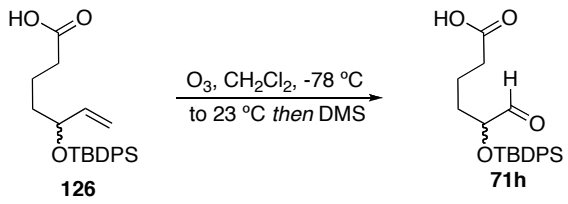


Aldehyde acid **71d** (104 mg, 0.40 mmol) underwent cyclization according to the representative procedure for NCAL with asymmetric nucleophile for carbocycles using *O*-TMSQD as the asymmetric nucleophile. The crude residue was filtered though a short pad of silica gel eluting with Et_2O. The solution was then concentrated by rotary evaporation and purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:9 to 1:4) to provide *syn*-carbocycle-fused *β*-lactone **73d** (29.9 mg, 31%, dr 1:>19) as a colorless oil. **(1*S*,3*S*,6*R*)-3-(*tert*-butyldimethylsilyloxy)-7-oxabicyclo[4.2.0]octan-8-one** (*syn*-**73d**). R_f 0.43 (1:4 EtOAc:hexanes); $[\alpha]^{17}_D$ -1.7 (*c* = 1.20, $CHCl_3$); IR (thin film) ν_{max} 1824 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.71 (ddd, *J* = 3.3, 6.9, 9.9 Hz, 1H), 4.02-3.93 (m, 1H), 3.65 (ddd, *J* = 2.7, 6.6, 9.9 Hz, 1H), 2.29 (dddd, *J* = 3.3, 5.7, 9.6, 18.3 Hz, 1H), 2.09-1.91 (m, 2H), 1.90-1.67 (m, 2H), 1.65-1.51 (m, 1H),

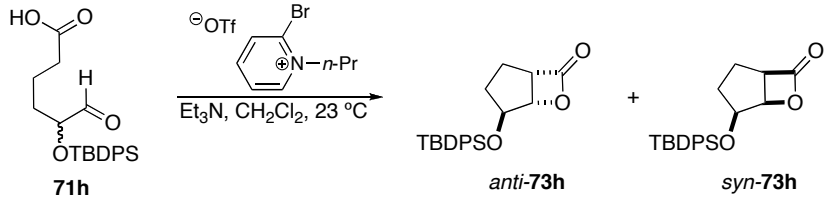
0.88 (s, 9H); 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 172.4, 68.9, 65.5, 45.3, 29.9, 27.9, 25.6 (3), 23.8, 17.9, -5.0 (2); HRMS (ESI) Calcd. for $C_{13}H_{24}O_3SiLi$ [M+Li] 263.1655, found 263.1657.



Aldehyde acid **71d** (123 mg, 0.45 mmol) underwent cyclization according to the representative procedure for NCAL with asymmetric nucleophile for carbocycles using *O*-TMSQN as the asymmetric nucleophile. The crude residue was filtered though a short pad of silica gel eluting with Et_2O. The solution was then concentrated by rotary evaporation and purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:9 to 4:6) to provide *anti*-carbocycle-fused β-lactone **73d** (11.0 mg, 10%, dr >19:1) as a colorless oil. **(1*R*,3*S*,6*S*)-3-(*tert*-butyldimethylsilyloxy)-7-oxabicyclo[4.2.0]octan-8-one (*anti*-73d).** R_f 0.59 (1:4 EtOAc:hexanes); $[\alpha]^{17}_D$ -10.3 (*c* = 0.39, $CHCl_3$); IR (thin film) ν_{max} 1824 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.76 (ddd, *J* = 2.4, 4.8, 7.2 Hz, 1H), 4.08 (p, *J* = 5.4 Hz, 1H), 3.76-3.67 (m, 1H), 2.27-2.07 (m, 2H), 2.04-1.94 (m, 1H), 1.88-1.73 (m, 3H), 0.87 (s, 9H), 0.05 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 172.8, 70.1, 63.9, 45.4, 29.3, 26.5, 25.7 (3), 22.1, 18.0, -4.9 (2); HRMS (ESI) Calcd. for $C_{13}H_{24}O_3SiLi$ [M+Li] 263.1655, found 263.1652.

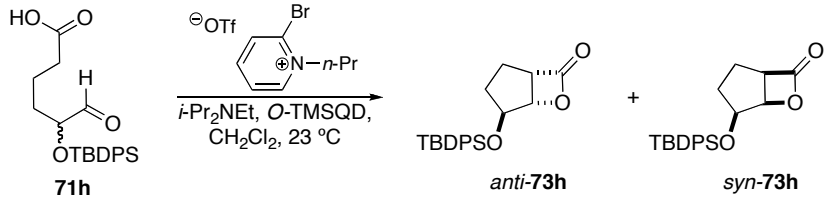


5-(*tert*-butyldiphenylsilyloxy)-6-oxohexanoic acid (71h). Alkene acid **126**[208] (477 mg, 1.25 mmol) was ozonolyzed according to the representative procedure for ozonolysis of alkene acids. Dimethyl sulfide (0.92 mL, 12.5 mmol) was used as the quenching reagent. The crude residue was purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (2:3 to 3:2) to afford aldehyde acid **71h** (399 mg, 83%) as a colorless oil. R_f 0.52 (2:3 EtOAc:hexanes); IR (thin film) ν_{max} 3429, 1733, 1710 cm^{-1}; ^1H NMR (300 MHz, benzene-d_6) δ 9.39 (d, J = 1.5 Hz, 1H), 7.73-7.64 (m, 4H), 7.28-7.15 (m, 6H), 3.91 (dt, J = 1.2, 5.4 Hz, 1H), 1.89-1.81 (m, 2H), 1.64-1.32 (m, 4H), 1.16 (s, 9H); ^{13}C (75 MHz, benzene-d_6) δ 201.9, 179.9, 136.4 (2), 136.3 (2), 133.7, 133.6, 130.5 (2), 128.4 (4), 78.1, 33.7, 32.1, 27.3 (3), 27.2, 19.7; HRMS (ESI) Calcd. for $C_{22}H_{27}O_4Si$ [M-H] 383.1679, found 383.1665.



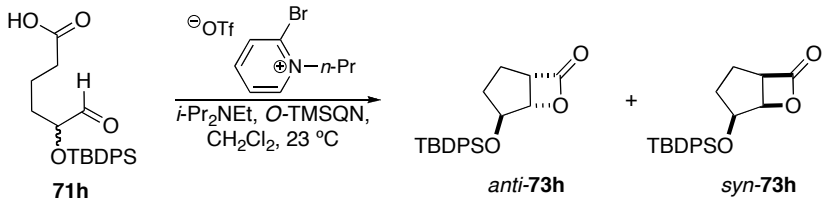
Aldehyde acid **71h** (81.9 mg, 0.21 mmol) underwent cyclization according to the representative procedure for NCAL with achiral nucleophile for carbocycles. The reaction mixture was concentrated by rotary evaporation and purified by flash column chromatography with EtOAc:hexanes (1:9) to provide *anti*-carbocycle-fused β-lactone **73h** (40.4 mg, 52%, dr >19:1) as a colorless oil. **Chiral HPLC analysis method: β-**

lactone 73h: (Chiralcel OD, 95.5:0.5 hexanes:*i*-PrOH eluent, 1.00 mL/min flow rate and a lamp setting of 210 nm) t_r [*syn*-**73h**] = 3.581; t_r [*syn*-**73h**] = 5.317; t_r [*anti*-**73h**] = 9.260; and t_r [*anti*-**73h**] = 10.283.

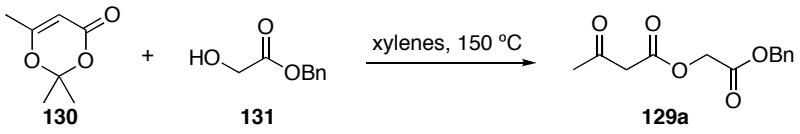


Aldehyde acid **71h** (51.6 mg, 0.13 mmol) underwent cyclization according to the representative procedure for NCAL with asymmetric nucleophile for carbocycles using *O*-TMSQD as the asymmetric nucleophile. The solution was then concentrated by rotary evaporation and purified by flash column chromatography with a mixture of EtOAc:hexanes (0.5:9.5) to provide *anti/syn* carbocycle-fused *β*-lactones **73h** (34.6 mg, 70%, dr 5:1) as a colorless oil. **(1*S*,4*S*,5*S*)-4-(*tert*-butyldiphenylsilyloxy)-6-oxabicyclo[3.2.0]heptan-7-one (*anti*-73h).** R_f 0.57 (1:9 EtOAc:hexanes); IR (thin film) ν_{max} 1835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73-7.58 (m, 5H), 7.51-7.36 (m, 5H), 4.61 (d, J = 3.6 Hz, 1H), 4.42 (d, J = 3.6 Hz, 1H), 3.97 (dd, J = 3.6, 7.5 Hz, 1H), 2.25-2.03 (m, 2H), 1.92 (dd, J = 6.3, 13.8 Hz, 1H), 1.79 (dddd, J = 3.6, 7.2, 13.8, 20.7 Hz, 1H), 1.07 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 171.0, 135.6 (2), 135.5 (2), 133.2, 133.1, 130.1, 130.0, 127.9 (2), 127.8 (2), 78.6, 73.8, 55.5, 31.4, 26.8 (3), 24.2, 19.1; HRMS (MALDI) Calcd. for $C_{22}H_{27}O_3Si$ [M+H] 367.1724, found 367.1713. **(1*R*,4*S*,5*R*)-4-(*tert*-butyldiphenylsilyloxy)-6-oxabicyclo[3.2.0]heptan-7-one (*syn*-73h).** R_f 0.34 (1:9 EtOAc:hexanes); $[\alpha]^{19}_D$ -78.0 (c = 0.13, $CHCl_3$); IR (thin film) ν_{max} 1830 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74-7.64 (m, 4H), 7.46-7.36 (m, 6H), 4.38 (t, J = 4.0 Hz, 1H), 3.98

(ddd, J = 4.0, 7.5, 9.5 Hz, 1H), 3.63 (dd, J = 4.0, 8.5 Hz, 1H), 1.98-1.90 (m, 3H), 1.50-1.36 (m, 1H), 1.07 (s, 9H); ^{13}C (125 MHz, $CDCl_3$) δ 171.2, 135.7 (2), 135.6 (2), 133.4, 133.3, 130.0, 129.9, 127.81 (2), 127.78 (2), 75.3, 74.3, 53.4, 28.7, 26.7 (3), 21.1, 19.1; HRMS (MALDI) Calcd. for $C_{22}H_{27}O_3Si$ [M+H] 367.1724, found 367.1739.

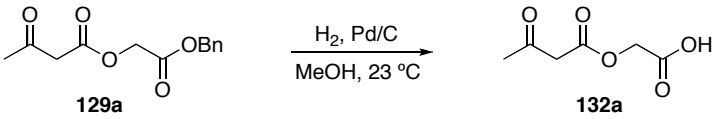


Aldehyde acid **71h** (64.9 mg, 0.17 mmol) underwent cyclization according to the representative procedure for NCAL with asymmetric nucleophile for carbocycles using *O*-TMSQN as the asymmetric nucleophile. The solution was then concentrated by rotary evaporation and purified by flash column chromatography with a mixture of EtOAc:hexanes (0.5:9.5) to provide *anti/syn* carbocycle-fused β-lactones **73h** (49.4 mg, 80%, dr 6:1) as a colorless oil.



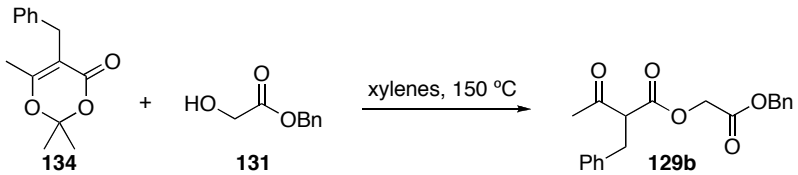
2-(benzyloxy)-2-oxoethyl 3-oxobutanoate (129a). A solution of dioxinone **130** (2.57 g, 18.1 mmol) and alcohol **131** (3.00 g, 18.1 mmol) in xylenes (10.6 mL) was heated in a previously heated oil bath at 150 ºC while stirring vigorously.[164] Evolution of acetone became apparent within several minutes. After 4 h, the mixture was cooled to room temperature and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:4 to 2:3) to

give β-keto ester **129a** (3.85 g, 85%, keto:enol 7:1) as a colorless oil. (major) R_f 0.30 (3:7 EtOAc:hexanes); IR (thin film) ν_{max} 1752, 1720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.28 (m, 5H), 5.17 (s, 2H), 4.68 (s, 2H), 3.52 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.7, 167.0, 166.3, 134.7, 128.45 (2), 128.40, 128.2 (2), 67.0, 61.0, 49.3, 29.8; HRMS (ESI) Calcd. for $C_{13}H_{14}O_5Li$ [M+Li] 257.1001, found 257.1008.



129a 132a

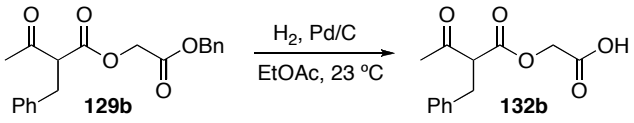
2-(3-oxobutanoyloxy)acetic acid (132a). To a solution of β-keto ester **129a** (1.00 g, 4.00 mmol) in methanol (27 mL) was added 10% palladium on carbon (wet) (0.500 g, 0.467 mmol). Hydrogen was bubbled through the solution for 1 min., and then a balloon of hydrogen was affixed. The mixture stirred at room temperature under hydrogen for 48 h. The black mixture was then filtered through a pad of silica gel and celite eluting with acetone. The solution was concentrated by rotary evaporation to afford keto acid **132a** (0.586 g, 91%, keto:enol 7:1) as a colorless oil. (major) R_f 0.40 (1:1 acetone:CH_2Cl_2); IR (thin film) ν_{max} 3208, 1744, 1716 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.70 (s, 2H), 3.57 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 171.6, 166.5, 60.8, 49.3, 30.0; HRMS (ESI) Calcd. for $C_6H_8O_5Li$ [M+Li] 167.0539, found 167.0528.



134 131 129b

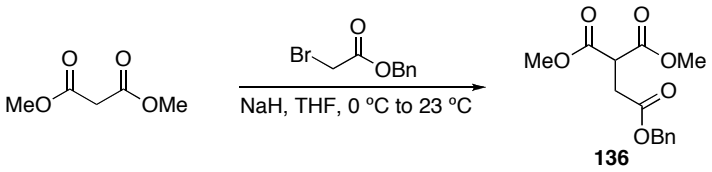
2-(benzyloxy)-2-oxoethyl 2-benzyl-3-oxobutanoate (129b). A solution of dioxinone **134** (2.04 g, 8.61 mmol) and alcohol **131** (1.43 g, 8.61 mmol) in xylenes (9.0 mL) was

heated in a previously heated oil bath at 150 ºC while stirring vigorously.[164] Evolution of acetone became apparent within several minutes. After 10 h, the mixture was cooled to room temperature and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1:4 to 3:7) to give β-keto ester **129b** (1.17 g, 39%) as a pale yellow oil. R_f 0.27 (1:4 EtOAc:hexanes); IR (thin film) ν_{max} 1750, 1719 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46-7.14 (m, 10H), 5.18 (s, 2H), 4.70 (d, J = 16.0 Hz, 1H), 4.61 (d, J = 16.0 Hz, 1H), 3.88 (t, J = 7.5 Hz, 1H), 3.25-3.12 (m, 2H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 168.5, 167.1, 137.9, 134.8, 128.8 (2), 128.68 (2), 128.65 (2), 128.51 (2), 128.50, 126.8, 67.3, 61.2, 60.7, 33.9, 29.7; HRMS (ESI) Calcd. for $C_{20}H_{20}O_5Li$ [M+Li] 347.1471, found 347.1459.



2-(2-benzyl-3-oxobutanoyloxy)acetic acid (132b). To a solution of β-keto ester **129b** (1.17 g, 3.45 mmol) in EtOAc (68 mL) was added 10% palladium on carbon (wet) (0.440 g, 0.414 mmol). Hydrogen was bubbled through the solution for 1 min., and then a balloon of hydrogen was affixed. The mixture stirred at room temperature under hydrogen for 12 h. The black mixture was then filtered through a pad of silica gel and celite eluting with acetone. The solution was concentrated by rotary evaporation to afford keto acid **132b** (0.803 g, 93%) as a colorless oil. R_f 0.24 (1:2 EtOAc:hexanes); IR (thin film) ν_{max} 3178, 1749, 1718 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.17 (m, 5H), 4.71 (d, J = 16.5 Hz, 1H), 4.64 (d, J = 16.5 Hz, 1H), 3.93 (t, J = 7.5 Hz, 1H), 3.26-3.17

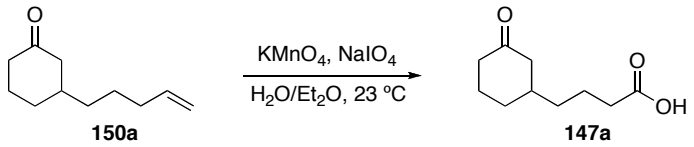
(m, 2H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.1, 172.3, 168.5, 137.6, 128.7 (2), 128.6 (2), 126.8, 60.7, 33.8, 30.9, 29.7; HRMS (ESI) Calcd. for $C_{13}H_{15}O_5$ [M+H] 251.0919, found 251.0910.



136

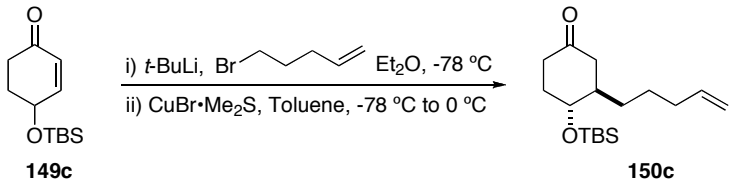
2-benzyl 1,1-dimethyl ethane-1,1,2-tricarboxylate (136). A solution of dimethyl malonate (5.00 g, 31.2 mmol) in THF (47 mL) was stirred at 0 ºC. 60% sodium hydride (1.34 g, 34.3 mmol) was added in three portions, and the resulting mixture was stirred for 1 h. A solution of benzyl 2-bromoacetate (7.87 g, 34.3 mmol) in THF (46 mL) was added over ~5 min. The reaction continued to stir while slowly warming to room temperature overnight (stirring for a total of 18 h). The reaction was quenched upon addition of saturated NH_4Cl (60 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (1.5:8.5 to 3:7) to give triester **136** (8.11 g, 93%) as a colorless oil. R_f 0.44 (3:7 EtOAc:hexanes); IR (thin film) ν_{max} 1737 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.29 (m, 5H), 5.14 (s, 2H), 3.88 (t, J = 7.5 Hz, 1H), 3.74 (s, 6H), 3.00 (d, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 168.6 (2), 135.4, 128.5 (2), 128.3, 128.2 (2), 66.8, 52.8 (2), 47.3, 33.1; HRMS (ESI) Calcd. for $C_{14}H_{17}O_6$ [M+H] 281.1025, found 281.1023.

CHAPTER V – NUCLEOPHILE CATALYZED, ALDOL-LACTONIZATION (NCAL) FOR BRIDGED BICYCLIC β-LACTONES



150a **147a**

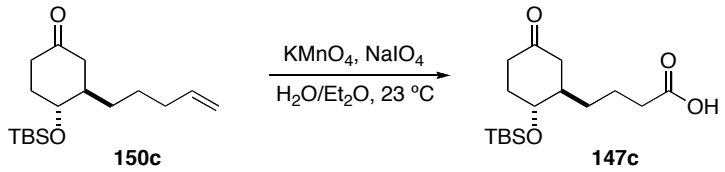
4-(3-oxocyclohexyl)butanoic acid (147a). To a flask containing alkene **150a** (0.602 g, 3.60 mmol) at 23 ºC was added deionized water (115 mL), potassium permanganate (0.103 g, 0.650 mmol), and sodium periodate (4.64 g, 21.7 mmol), respectively. The biphasic purple mixture was stirred 20 h at 23 ºC and then extracted with Et_2O (7 x 100 mL). The organic layers were combined, filtered (Na_2SO_4), and concentrated by rotary evaporation. The crude residue was purified by acid/base extraction by partitioning between CH_2Cl_2 (12 mL) and saturated $NaHCO_3$ (20 mL). The layers were separated, and the aqueous layer was washed subsequently with hexanes (20 mL), and then acidified with 10% H_2SO_4 to pH 3. The aqueous mixture was extracted with Et_2O (4 x 20 mL) followed by CH_2Cl_2 (2 x 20 mL). The organic layers obtained after acidification were combined, dried (Na_2SO_4), and concentrated by rotary evaporation to afford keto acid **147a** (0.356 g, 53%) as a colorless oil. IR (thin film) ν_{max} 3451, 1708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.50-10.90 (bs, 1H), 1.00-2.50 (m, 17H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.3, 178.7, 47.6, 41.0, 38.5, 35.5, 33.6, 30.7, 24.8, 21.5; LRMS (ESI) Calcd. for $C_{10}H_{16}O_3$ [M-H] 183, found 183.



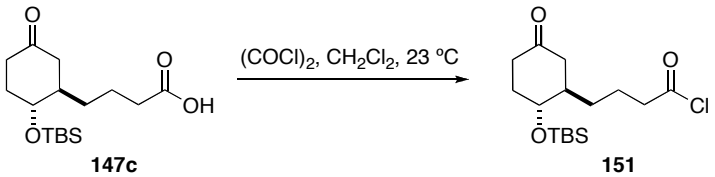
149c **150c**

4-(*tert*-butyldimethylsilyloxy)-3-(pent-4-enyl)cyclohexanone (150c). A solution of 5-bromo-1-pentene (2.53 mL, 21.3 mmol) in Et_2O (42 mL) was cooled to -78 ºC and stirred 10 min. to which a solution of *t*-BuLi (17.0 mL, 25.6 mmol of 1.5 M solution) was added. The mixture was stirred for 4 h at -78 ºC, and then the colorless solution was cannula transferred to a flask containing CuBr•dimethyl sulfide (2.09 g, 10.2 mmol) and degassed toluene (86 mL). After 20 min., the mixture was warmed until it turned black (~20 min.). The mixture was again cooled to -78 ºC, and enone **149c** (2.12 g, 9.28 mmol) was added as a solution toluene (4 mL). The mixture was warmed to -42 ºC and stirred 4 h. The reaction was quenched upon addition of saturated NH_4Cl (50 mL) and then allowed to warm to room temperature while stirring vigorously. The mixture turned blue. The aqueous mixture was partitioned between saturated NH_4Cl (50 mL) and CH_2Cl_2 (100 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography with a mixture of Et_2O:hexanes (1:9) to give alkene **150c** (2.08 g, 75%) as a colorless oil. R_f 0.33 (1:9 Et_2O:hexanes); IR (thin film) ν_{max} 1717, 1253, 1100 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.71 (ddt, J = 6.5, 10.5, 17.0 Hz, 1H), 4.96-4.86 (m, 2H), 3.74 (td, J = 3.0 5.5 Hz, 1H), 2.68 (ddd, J = 1.5, 5.5, 14.0 Hz, 1H), 2.57-2.47 (m, 1H), 2.20-2.12 (m, 1H), 2.05-1.86 (m, 5H), 1.82-1.73 (m, 1H), 1.46-1.32 (m, 2H), 1.31-1.21 (m, 1H), 1.13-1.03 (m, 1H), 0.86 (s, 9H), 0.05 (s, 6H); ^{13}C (125 MHz, $CDCl_3$) δ 211.2, 138.1, 114.6, 70.2,

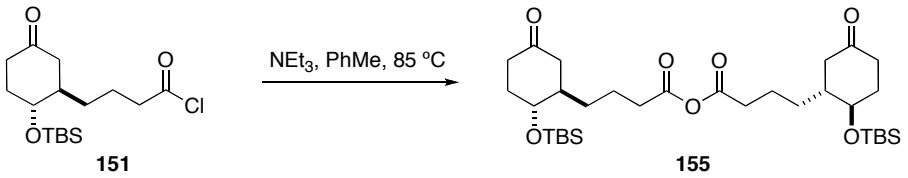
44.4, 42.1, 37.1, 33.6, 31.7, 31.1, 25.9, 25.6 (3), 17.8, -4.7, -5.0; HRMS (ESI) Calcd. for $C_{17}H_{32}O_2SiLi$ [M+Li] 297.2250, found 297.2252.



4-(2-(*tert*-butyldimethylsilyloxy)-5-oxocyclohexyl)butanoic acid (147c). To a flask containing alkene **150c** (0.922 g, 3.11 mmol) at 23 ºC was added deionized water (75 mL), potassium permanganate (0.079 g, 0.50 mmol), and sodium periodate (3.99 g, 18.67 mmol), respectively. The biphasic purple mixture was stirred 12 h at 23 ºC, and then acetone (30 mL) was added to aid with solubility and the mixture was stirred an additional 15 h. The aqueous mixture was extracted with Et_2O (7 x 80 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (3:7 to 1:0) to afford keto acid **147c** (0.648 g, 66%) as a colorless oil. R_f 0.60 (1:1 EtOAc:hexanes); IR (thin film) ν_{max} 3081, 1712 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.79 (td, J = 3.0, 5.7 Hz, 1H), 2.74 (ddd, J = 1.5, 5.1, 14.1 Hz, 1H), 2.65-2.53 (m, 1H), 2.33 (t, J = 7.5 Hz, 2H), 2.28-2.16 (m, 1H), 2.10-1.92 (m, 2H), 1.88-1.10 (m, 4H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 211.4, 178.1, 69.9, 44.1, 41.7, 36.8, 33.5, 31.4, 30.9, 25.7 (3), 21.5, 17.6, -4.9, -5.3; HRMS (ESI) Calcd. for $C_{16}H_{29}O_4Si$ [M-H] 313.1835, found 313.1840.

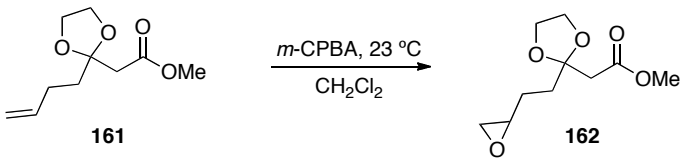


4-(2-(*tert*-butyldimethylsilyloxy)-5-oxocyclohexyl)butanoyl chloride (151). A solution of keto acid **147c** (215 mg, 0.68 mmol) in CH_2Cl_2 (2.0 mL) was stirred at 23 ºC. Oxalyl chloride (130 mg, 1.03 mmol) was added to the colorless solution. Bubbling of solution became apparent. After 4.3 h bubbling ceased, and the solution turned pale yellow. The solution was concentrated *in vacuo* to give acid chloride **151** (146 mg, 64%) as a colorless oil. The crude residue was used immediately in further reactions without purification. Reaction monitored by ^{1}H NMR. IR (thin film) ν_{max} 1799, 1718 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (td, J = 3.3, 6.0 Hz, 1H), 2.89 (t, J = 7.4 Hz, 2H), 2.74 (ddd, J = 1.5, 5.1, 14.1 Hz, 1H), 2.65-2.52 (m, 1H), 2.26 (dddd, J = 1.5, 5.4, 7.2, 14.4 Hz, 1H), 2.13-1.45 (m, 8H), 1.27-1.12 (m, 1H), 0.93 (s, 9H), 0.12 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 211.4, 168.9, 70.2, 44.5, 42.1, 37.3, 35.1, 31.7, 31.5, 31.2, 25.7 (3), 21.4, -4.6, -4.9.



4-((1*R*,2*R*)-2-(*tert*-butyldimethylsilyloxy)-5-oxocyclohexyl)butanoic anhydride (155). To a solution of triethylamine (20.0 mg, 0.210 mmol) and toluene (2.0 mL) was added acid chloride **151** (50.0 mg, 0.150 mmol) as a solution in toluene (1 mL) over 8 h via syringe pump. The mixture was stirred and additional solvent was added (toluene = 1.0

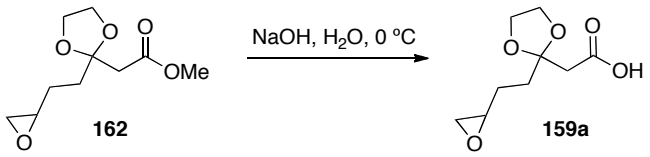
mL; acetonitrile = 1.0 mL). The solution stirred for 99 h. The residue was filtered through a glass fritted funnel and washed with anhydrous toluene. The solution was concentrated by rotary evaporation, filtered through a plug of silica gel eluting with EtOAc:hexanes (1:9 to 3:7) to provide anhydride **155** (22.3 mg, 49%) as a colorless oil. R_f 0.26 (1:0 EtOAc:hexanes); IR (thin film) ν_{max} 1817, 1735, 1716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.79 (td, J = 3.0, 5.7 Hz, 1H), 2.82-1.10 (m, 44H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 211.7 (2), 179.1 (2), 70.2 (2), 44.5 (2), 42.2 (2), 37.3 (2), 33.9 (2), 31.7 (2), 31.2 (2), 25.7 (6), 21.9 (2), 18.0 (2), -4.6 (2), -4.9 (2); LRMS (ESI) Calcd. for $C_{32}H_{58}O_7Si_2$ [M+H] 611, found 611.



161 162

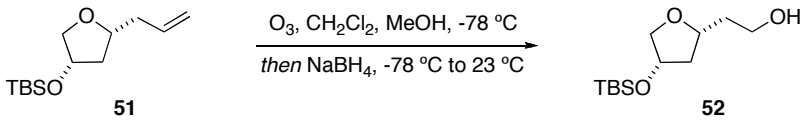
Methyl 2-(2-(2-(oxiran-2-yl)ethyl)-1,3-dioxolan-2-yl)acetate (162). A mixture of 70-75% wt. *m*-CPBA (6.90 g, 28.0 mmol) and alkene **161** (4.67 g, 23.3 mmol) in CH_2Cl_2 (28 mL) was stirred at 23 ºC for 5 h. The white mixture was then cooled to -25 ºC and filtered and eluted with cold CH_2Cl_2 to remove the excess 3-chlorobenzoic acid byproduct. The solution was concentrated by rotary evaporation. The crude residue was purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (3:7 to 1:1) to afford epoxide **162** (4.31 g, 86%) as a colorless oil. R_f 0.39 (2:3 EtOAc:hexanes); IR (thin film) ν_{max} 1737, 1625, 1438 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.06-3.94 (m, 4H), 3.71 (s, 3H), 2.99-2.93 (m, 1H), 2.76 (dd, J = 4.0, 4.9 Hz, 1H), 2.68 (s, 2H), 2.50 (dd, J = 2.7, 4.9 Hz, 1H), 2.09-1.92 (m, 2H), 1.70-1.63 (m, 2H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 169.5, 108.5, 64.9 (2), 51.7, 51.5, 46.9, 42.2, 33.3, 26.3; HRMS (ESI) Calcd. for $C_{10}H_{17}O_5$ [M+H] 217.1076, found 217.1082.

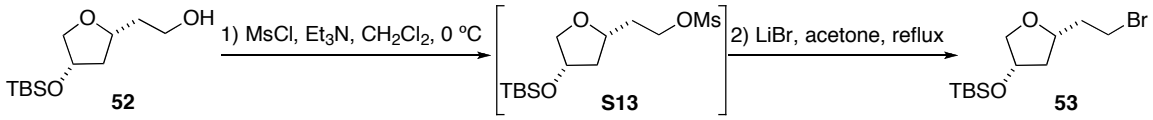


2-(2-(2-(oxiran-2-yl)ethyl)-1,3-dioxolan-2-yl)acetic acid (159a). A mixture of epoxide **162** (1.22 g, 5.55 mmol) in water (3.1 mL) was stirred at 0 ºC for 10 min. Then aqueous NaOH (3.10 mL, 1.80 M) was added dropwise. The colorless solution was stirred for 2 h and then additional NaOH (1.00 mL, 1.80 M) was added. The solution stirred for an additional 0.75 h. The reaction mixture was then partitioned between Et_2O (60 mL) and saturated NH_4Cl (40 mL). The mixture was acidified to pH 4 with 1.0 M HCl. The aqueous layer was then extracted with Et_2O (5 x 40 mL). The combined organics were dried (Na_2SO_4), filtered, and subsequently concentrated by rotary evaporation. The crude residue was purified by flash column chromatography with a gradient mixture of EtOAc:hexanes (2:3 to 1:0) to afford epoxy acid **159a** (0.68 g, 59%) as a pale yellow oil. R_f 0.42 (EtOAc); IR (thin film) ν_{max} 1724 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (bs, 1H), 3.94-3.83 (m, 4H), 2.89-2.83 (m, 1H), 2.66 (dd, J = 4.2, 5.1 Hz, 1H), 2.56 (s, 2H), 2.39 (dd, J = 2.7, 5.1 Hz, 1H), 1.92-1.85 (m, 2H), 1.57-1.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 108.3, 64.8 (2), 51.9, 49.9, 42.0, 33.1, 26.1.

CHAPTER VI - STEREOSELECTIVE ACCESS TO (*Z*)-CHLORODIALKYL ALKENES THROUGH A MODIFIED NEGISHI CROSS-COUPLING OF ZINCATES AND DICHLOROOLEFINS

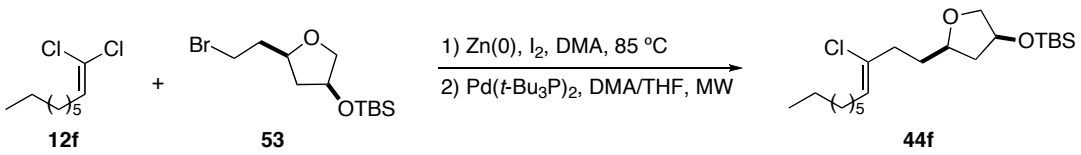


2-((2*R*,4*S*)-4-(*tert*-butyldimethylsilyloxy) tetrahydrofuran-2-yl)ethanol (52). A solution of alkene **51** (2.91 g, 12.0 mmol) in mixture of methanol (60 mL) and CH_2Cl_2 (60 mL) was cooled to -78 ºC. Then O_3 was bubbled through solution via a gas sparging tube until solution turned blue. This was followed with bubbling of O_2 (twice the time required for solution to turn blue). Reducing reagent, sodium borohydride (2.73 g, 72.0 mmol), was added. The solution was allowed to slowly warm to room temperature over ~ 5 h. After 9 h of additional stirring at room temperature, the solution was concentrated by rotary evaporation. Then CH_2Cl_2 (24 mL) was added. The organic layer was washed with saturated NH_4Cl, water, brine, and dried (Na_2SO_4). The solution was concentrated by rotary evaporation. The crude residue was purified by flash column chromatography with a gradient mixture of Et_2O:hexanes (3:5) to afford alcohol **52** (2.79 g, 94%, dr >19:1) as a colorless oil. R_f 0.37 (2:5 EtOAc:hexanes); $[\alpha]_D^{20}$ +7.1 (*c* = 1.13, $CHCl_3$); IR (thin film) ν_{max} 3409, 1114, 1039 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.48-4.38 (m, 1H), 4.09 (dq, *J* = 3.7, 7.6 Hz, 1H), 3.79 (q, *J* = 5.5 Hz, 2H), 3.77-3.69 (m, 2H), 2.75 (t, *J* = 5.5 Hz, 1H), 2.30-2.21 (m, 1H), 1.99-1.89 (m, 1H), 1.86-1.77 (m, 1H), 1.64 (ddd, *J* = 4.0, 7.0, 13.0, 1H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 78.5, 75.4, 72.5, 61.1, 41.3, 37.2, 25.7 (3), 18.0, -4.85, -4.87; HRMS (ESI) Calcd. for $C_{12}H_{27}O_3Si$ [M+H] 253.1729, found 253.1723.



((3*S*,5*S*)-5-(2-bromoethyl)tetrahydrofuran-3-yloxy)(*tert*-butyl)dimethylsilane (53). To a solution of alcohol **52** (1.44 g, 5.85 mmol) in CH_2Cl_2 (38 mL) was added triethylamine (4.11 mL, 29.2 mmol). The solution was cooled to 0 ºC and methanesulfonyl chloride (0.68 mL, 8.78 mmol) was added. The solution was stirred for 2 h, and then quenched upon addition of pH 7 buffer (60 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried (Na_2SO_4) and concentrated by rotary evaporation to provide mesylate **S13**. The mesylate was taken on without further purification.

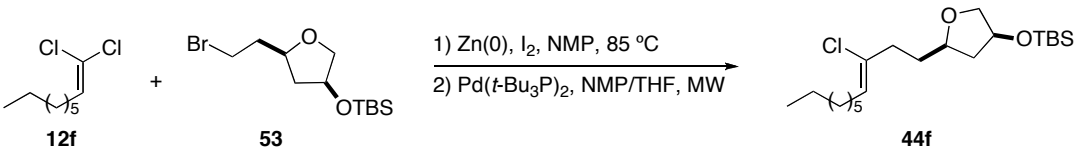
To a solution of mesylate **S13** in acetone (32 mL) was added lithium bromide (3.37 g, 38.8 mmol). The mixture was refluxed for 3 h and then cooled to room temperature and stirred 11 h. The reaction was then quenched upon addition of water (49 mL). The aqueous layer was extracted with Et_2O (4 x 20 mL). The combined organics dried (Na_2SO_4) and concentrated by rotary evaporation to provide bromide **53** (1.79 g, 99%). R_f 0.65 (1:1 EtOAc:hexanes); $[\alpha]_D^{19}$ +23.2 (*c* = 2.67, $CHCl_3$); IR (thin film) ν_{max} 1110, 909, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.46-4.40 (m, 1H), 4.12-4.06 (m, 1H), 3.76 (dd, *J* = 4.5, 9.0 Hz, 1H), 3.70 (ddd, *J* = 1.0, 2.5, 9.0 Hz, 1H), 3.55-3.47 (m, 2H), 2.32-2.22 (m, 2H), 2.08-1.98 (m, 1H), 1.61-1.53 (m, 1H), 0.88 (s, 9H), 0.054 (s, 3H), 0.049 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 76.4, 75.2, 72.5, 40.9, 38.9, 30.4, 25.7 (3), 17.9, -4.88, -4.94; HRMS (ESI) Calcd. for $C_{12}H_{26}BrO_2Si$ [M+H] 309.0885, found 309.0896.



***tert*-butyl((3*S*,5*R*)-5-((*Z*)-3-chloroundec-3-enyl)tetrahydrofuran-3-yloxy)dimethyl-silane (44f).** To a flask containing zinc powder (419 mg, 6.46 mmol) was added DMA (3.2 mL) and iodine (81.4 mg, 0.323 mmol). DMA was distilled from barium oxide prior to use and contained 10 ppm of water as determined by Karl-Fisher titration. This slurry was stirred at 60 ºC until the brown color of the iodine had disappeared. The alkyl bromide **53** (99.9 mg, 3.23 mmol) was then added to this slurry and heated to 85 ºC for 20 h. The disappearance of the starting material was monitored by TLC and ^{1}H NMR. The mixture was cooled to room temperature for 2 h, and the yellow supernatant liquid, zincate, was used immediately in subsequent reactions.

1,1-dichloroalkene **12f** was purified over neutral alumina eluting with hexanes prior to use. To a 10 mL microwave tube was added *bis*(tri-*tert*-butylphosphine)palladium (0) (6.50 mg, 0.013 mmol) in a glove box. A microwave cap was affixed to the tube. This was followed by 1,1-dichloroalkene **12f** (49.5 mg, 0.253 mmol) as a solution in THF (1.3 mL). The zincate (1 M in DMA, 1.3 mL) derived from bromide **53** was added to resulting in a dark purple-brown solution. Argon was bubbled through the solution to degass for 10 min. The tube was then heated with MW irradiation for 5 h at 100 ºC. After cooling the solution was then quenched with saturated NH_4Cl (2 mL) and extracted with Et_2O (3 x 2 mL). The combined organics were then washed with brine (3 x 1 mL). Finally, the organics were combined, dried (Na_2SO_4), and concentrated by rotary evaporation. The golden residue was then purified by flash column chromatography with a gradient mixture of Et_2O:hexanes (3:97) to afford vinyl chloride **44f** (58.1 mg, 29%) as

a colorless oil. R_f 0.67 (1:10 EtOAc:hexanes); $[\alpha]_D^{20}$ +6.0 (c = 1.33, $CHCl_3$); IR (thin film) ν_{max} 1114, 1044, 836, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.47 (t, J = 7.5 Hz, 1H), 4.47-4.37 (m, 1H), 3.84 (ddd, J = 5.5, 7.5, 15.0 Hz, 1H), 3.73 (dd, J = 4.5, 9.0 Hz, 1H), 3.69 (dd, J = 4.5, 9.0 Hz, 1H), 2.52-2.30 (m, 2H), 2.21 (dt, J = 7.0 12.5 Hz, 1H), 2.14 (q, J = 7.0 Hz, 2H), 1.96-1.74 (m, 2H), 1.54 (ddd, J = 0.5, 4.0, 7.0 Hz, 1H), 1.45-1.17 (m, 10H), 0.88 (s, 12H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.1, 126.0, 77.8, 75.2, 72.8, 41.4, 36.4, 33.9, 32.0, 29.30, 29.26, 28.8, 28.6, 25.9 (3), 22.8, 18.2, 14.3, -4.6, -4.7; HRMS (ESI) Calcd. for $C_{21}H_{42}ClO_2Si$ [M+H] 389.2643, found 389.2603.

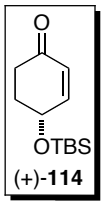


To a flask containing zinc powder (654 mg, 10.0 mmol) was added NMP (2.5 mL) and iodine (25.4 mg, 0.999 mmol). Anhydrous NMP was used directly from commercial source. This slurry was stirred at 60 ºC until the brown color of the iodine had disappeared. The alkyl bromide **53** (1.55 g, 5.00 mmol) was then added to this slurry and heated to 85 ºC for 24 h. The disappearance of the starting material was monitored by TLC and ^1H NMR. The mixture was cooled to room temperature for 2 h, and the supernatant liquid, zincate, was used immediately in subsequent reactions.

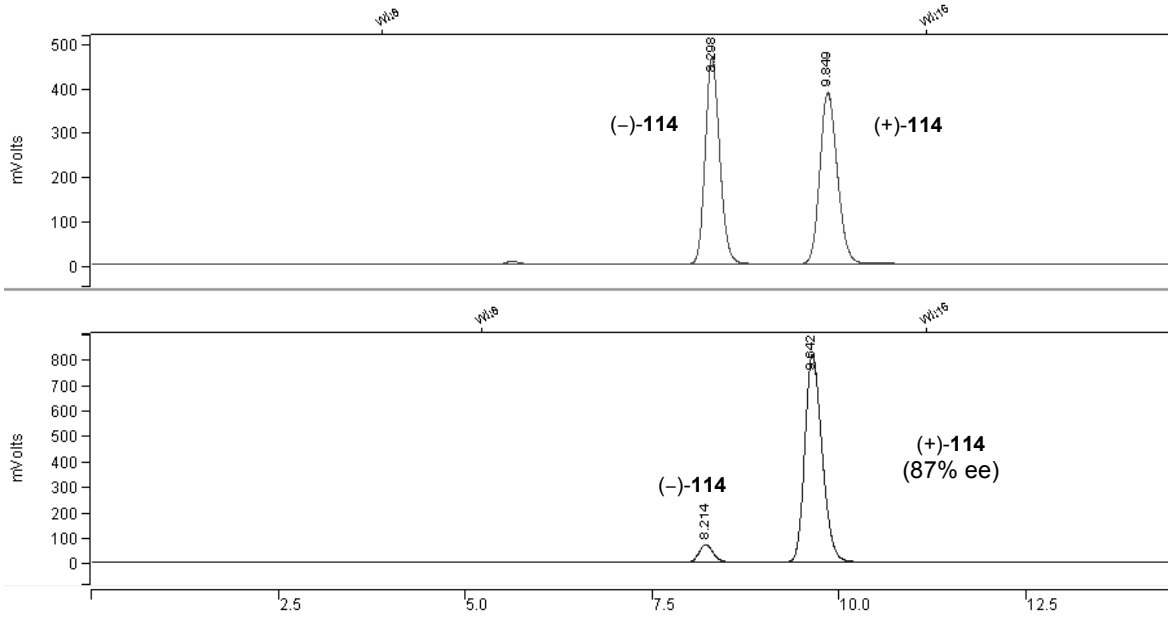
1,1-dichloroalkene **12f** was purified over neutral alumina eluting with hexanes prior to use. To a 10 mL microwave tube was added *bis*(tri-*tert*-butylphosphine)palladium (0) (13.9 mg, 0.027 mmol) in a glove box. A microwave cap was affixed to the tube. This was followed by 1,1-dichloroalkene **12f** (106 mg, 0.542 mmol) as a solution in THF (0.96

mL). The zincate (1.69 M in NMP, 0.96 mL) derived from bromide **53** was added to resulting in a dark purple-brown solution. Argon was bubbled through the solution to degass for 10 min. The tube was then heated with MW irradiation for 0.5 h at 80 ºC. After cooling the solution was then quenched with saturated NH_4Cl (2 mL). The mixture was filtered through a pad of celite eluting with Et_2O. The mixture was then extracted with Et_2O (3 x 2 mL). The combined organics were then washed with brine (2 x 1 mL). Finally, the organics were combined, dried ($MgSO_4$), and concentrated by rotary evaporation. The crude residue was then purified by flash column chromatography with a gradient mixture of Et_2O:hexanes (3:97) to afford vinyl chloride **44f** (65.9 mg, 31%) as a colorless oil.

Determination of enantiomeric excess of via chiral HPLC: Enone 114



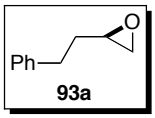
Analysis of (+)-enone 114: (Chiralcel OD, 99:1 hexanes:*i*-PrOH eluent, 1.00 mL/min flow rate and a lamp setting of 222 nm) t_r (minor) = 8.214; t_r (major) = 9.642.



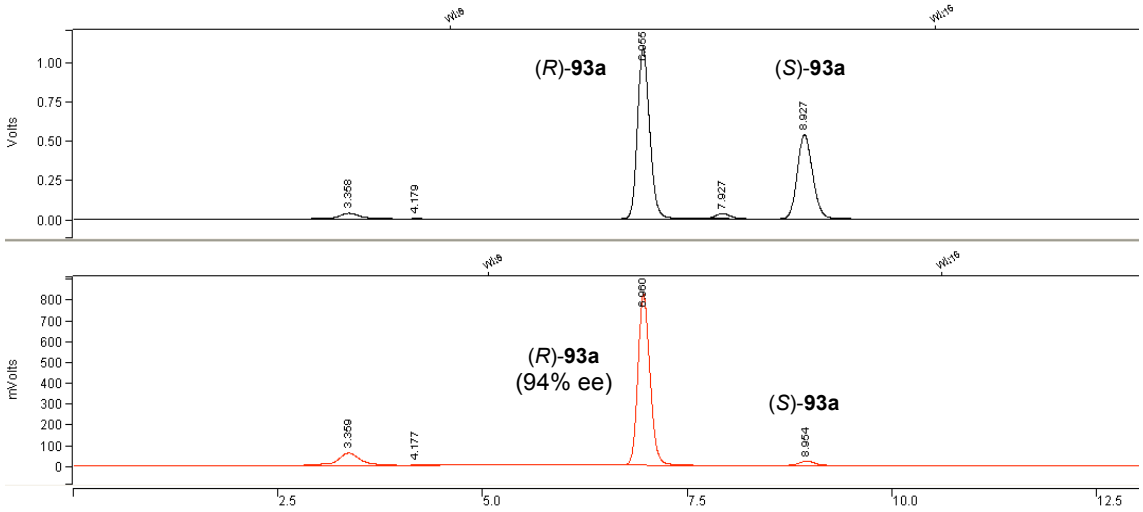
Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)
1		6.5062	8.214	0.000	921981
2		93.4938	9.642	0.000	13248786
	Totals:	100.0000		0.000	14170767

Total Unidentified Counts : 14170767 counts

Determination of enantiomeric excess of via chiral HPLC: Epoxide 93a



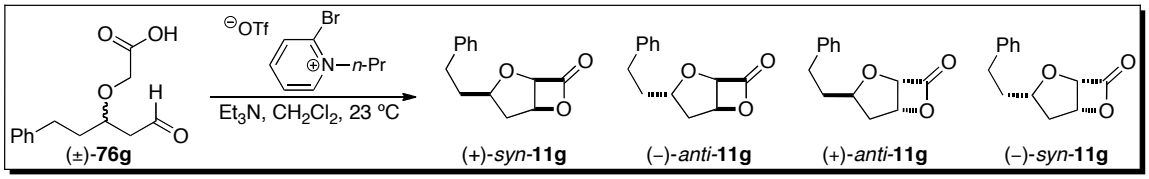
Analysis of (*R*)-epoxide 93a: (Chiralcel OD, 98:2 hexanes:*i*-PrOH eluent, 1.00 mL/min flow rate and a lamp setting of 210 nm) t_r (major) = 6.960; t_r (minor) = 8.954



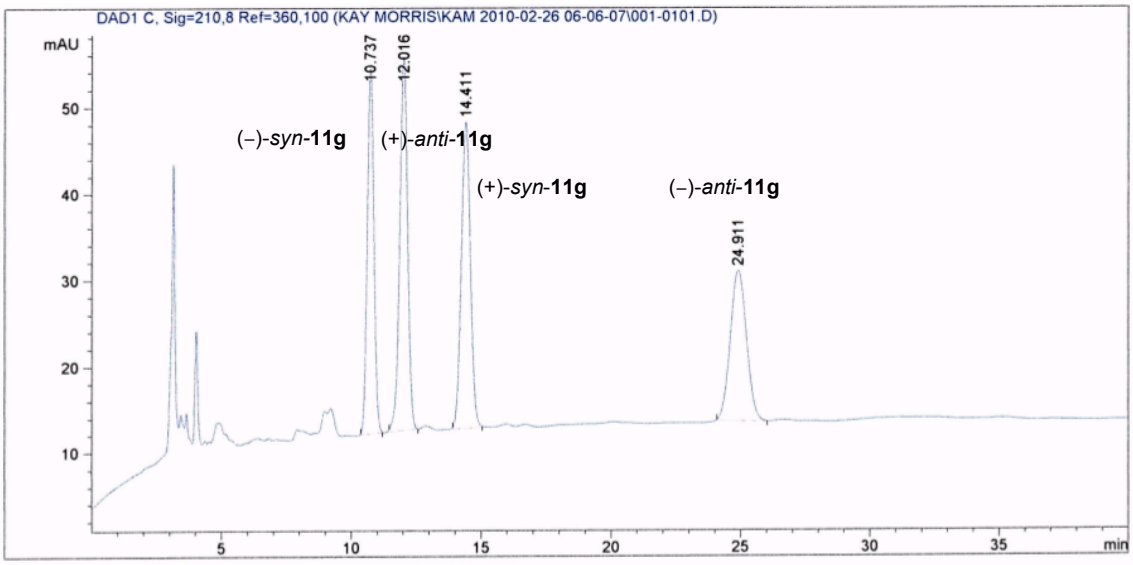
Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)
1		12.3152	3.359	0.000	1225710
2		84.9908	6.960	0.000	8459016
3		2.6940	8.954	0.000	268132
	Totals:	100.0000		0.000	9952858

Total Unidentified Counts : 9952858 counts

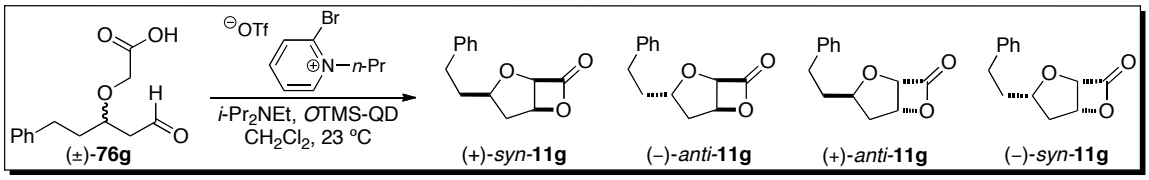
Determination of enantiomeric excess of via chiral HPLC: β-lactone 11g



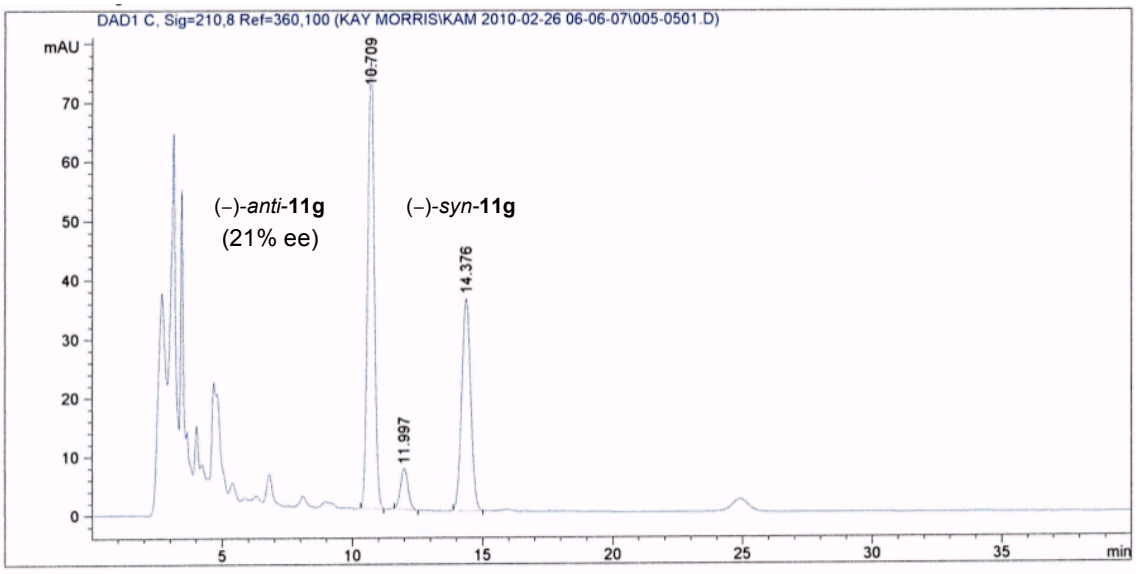
Analysis of (±)-Tetrahydrofuran-fused β-Lactone 11g: (Chiralcel OD, 85:15 hexanes:*i*-PrOH eluent, 1.00 mL/min flow rate and a lamp setting of 210 nm) t_r [(–)-*syn*-**11g**] = 10.737; t_r [(+)-*anti*-**11g**] = 12.016; t_r [(+)-*syn*-**11g**] = 14.411; and t_r [(–)-*anti*-**11g**] = 24.911.



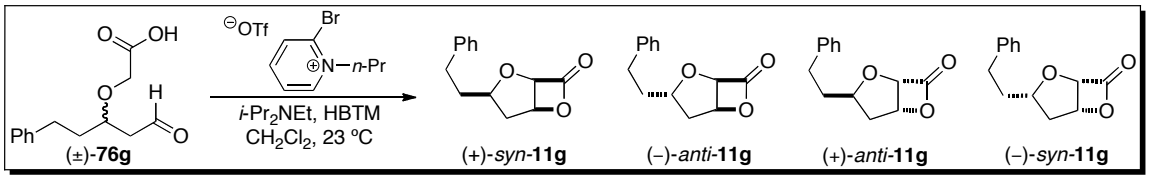
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.737	BB	0.2744	748.82648	42.32589	22.8770
2	12.016	BB	0.3235	908.69922	43.17534	27.7612
3	14.411	BB	0.3794	861.29413	35.45998	26.3129
4	24.911	BB	0.6742	754.45587	17.38839	23.0490
Totals :				3273.27570	138.34961	



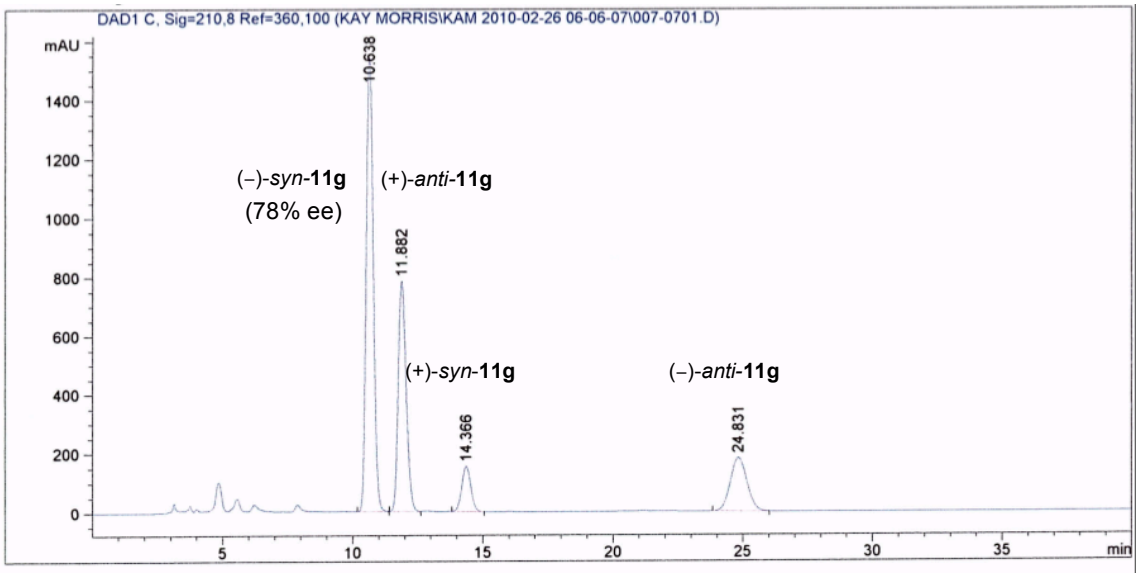
After separation of diastereomers by flash column chromatography. (Chiralcel OD, 85:15 hexanes:*i*-PrOH eluent, 1.00 mL/min flow rate and a lamp setting of 210 nm) t_r [(–)-*syn*-**11g**$_{major}$] = 10.709 and t_r [(+)-*syn*-**11g**] = 14.376.



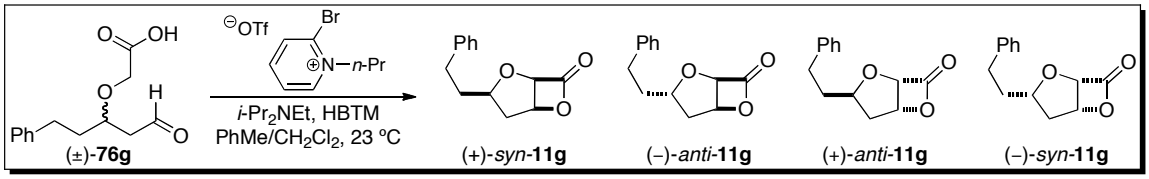
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.709	BB	0.2761	1343.81372	76.06634	56.9968
2	11.997	BB	0.3166	143.02011	6.99357	6.0661
3	14.376	BB	0.3758	870.86810	36.05807	36.9372
Totals :				2357.70193	119.11798	



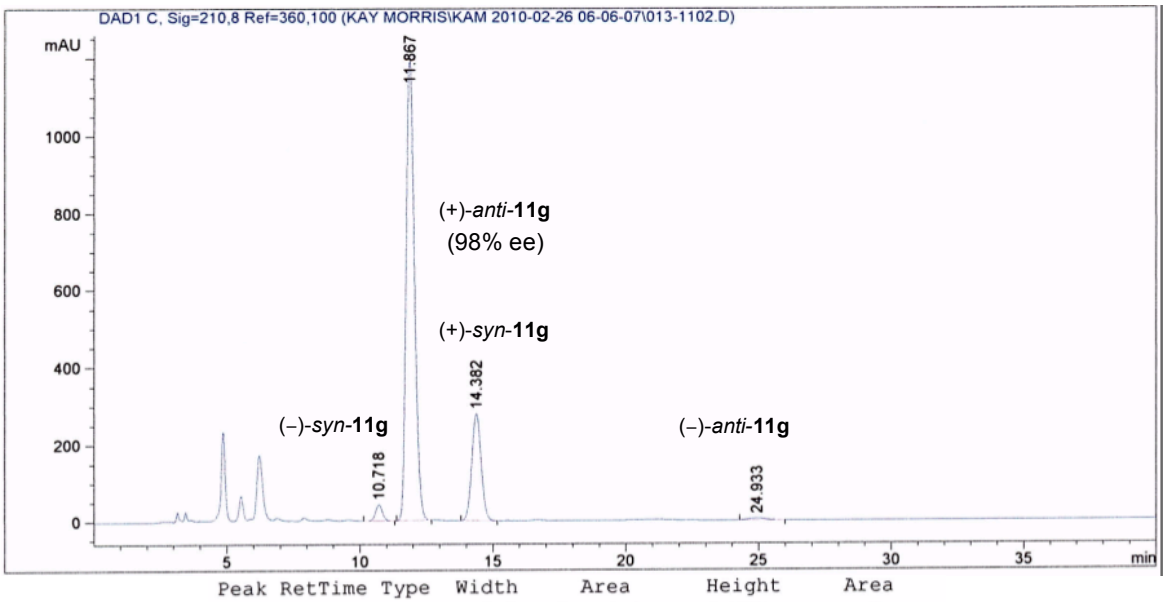
(Chiralcel OD, 85:15 hexanes:*i*-PrOH eluent, 1.00 mL/min flow rate and a lamp setting of 210 nm) t_r [(–)-*syn*-**11g** $_{major}$] = 10.638; t_r [(+)-*anti*-**11g**] = 11.882; t_r [(+)-*syn*-**11g**] = 14.366; and t_r [(–)-*anti*-**11g**] = 24.831.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.638	BB	0.2976	2.92332e4	1538.77747	50.7272
2	11.882	BB	0.3292	1.65822e4	782.51038	28.7744
3	14.366	BB	0.3791	3713.37646	153.00700	6.4437
4	24.831	BB	0.6965	8099.51904	181.53354	14.0547
Totals :				5.76284e4	2655.82838	



(Chiralcel OD, 85:15 hexanes:*i*-PrOH eluent, 1.00 mL/min flow rate and a lamp setting of 210 nm) t_r [(–)-*syn*-**11g**] = 10.718; t_r [(+)-*anti*-**11g** $_{major}$] = 11.867; t_r [(+)-*syn*-**11g**] = 14.382; and t_r [(–)-*anti*-**11g**] = 24.933.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.718	VB	0.2721	734.52161	41.98174	2.1734
2	11.867	BB	0.3378	2.60360e4	1196.62549	77.0382
3	14.382	BB	0.3807	6795.13184	278.47427	20.1062
4	24.933	BB	0.6525	230.56404	5.41798	0.6822
Totals :				3.37962e4	1522.49948	

APPENDIX B

SINGLE CRYSTAL X-RAY ANALYSIS

Crystal and Molecular Structure Determination for *Syn*-Tetrahydrofuran-Fused *β*-Lactone 11d.

X-ray Diffraction Laboratory
Department of Chemistry
Texas A&M University

Report: June 05, 2006
Structure: DR_060206 (GADDS)
Nattamai Bhuvanesh (Sample from Kay Morris)

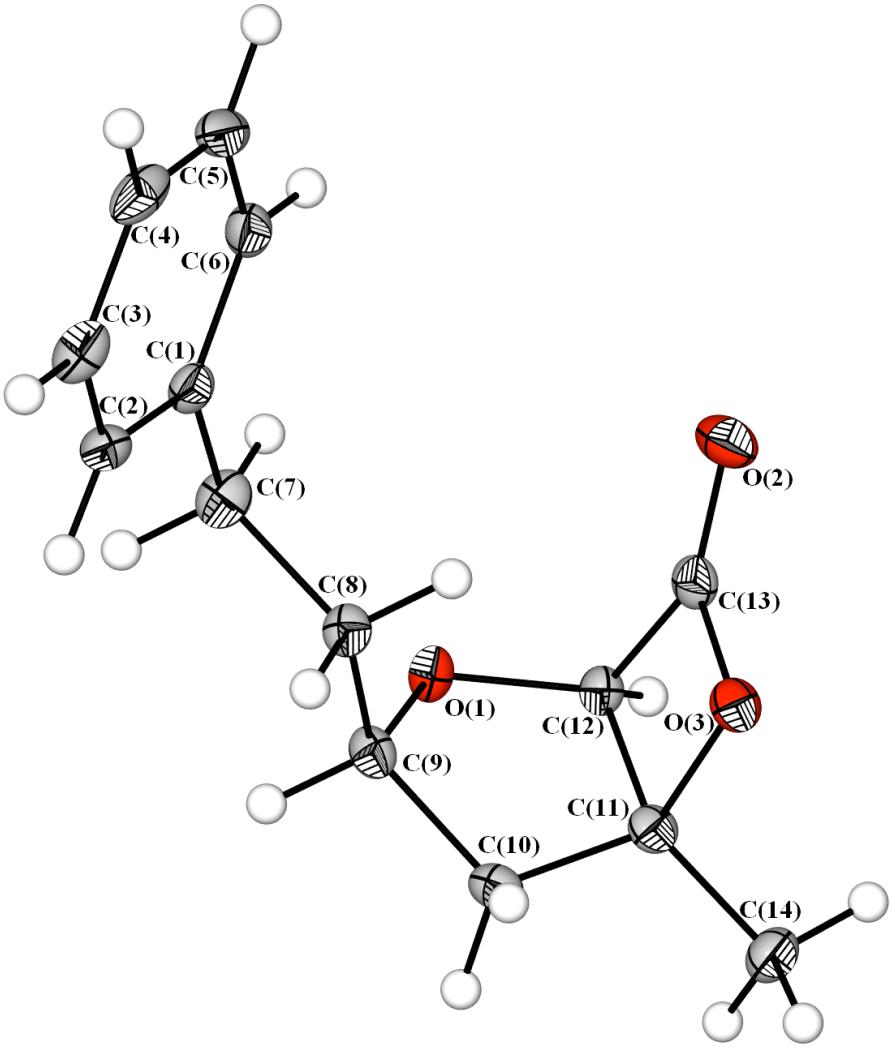


Table B1. Crystal data and structure refinement for DR_060206.

Identification code	dr	
Empirical formula	C14 H16 O3	
Formula weight	232.27	
Temperature	110(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 11.407(4) Å	α= 90°.
	b = 8.586(3) Å	β= 90.501(9)°.
	c = 12.661(4) Å	γ = 90°.
Volume	1240.0(7) $Å^3$	
Z	4	
Density (calculated)	1.244 Mg/m^3	
Absorption coefficient	0.704 mm^{-1}	
F(000)	496	
Crystal size	0.22 x 0.21 x 0.14 mm^3	
Theta range for data collection	5.20 to 60.59°.	
Index ranges	-12<=h<=12, -9<=k<=9, -14<=l<=13	
Reflections collected	7435	
Independent reflections	1791 [R(int) = 0.0439]	
Completeness to theta = 60.59°	95.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9085 and 0.8606	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1791 / 0 / 155	
Goodness-of-fit on F^2	1.020	
Final R indices [I>2sigma(I)]	R1 = 0.0378, wR2 = 0.0988	
R indices (all data)	R1 = 0.0443, wR2 = 0.1067	
Largest diff. peak and hole	0.179 and -0.229 $e.Å^{-3}$	

Table B2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DR_060206. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	1409(1)	1380(2)	3143(1)	21(1)
C(2)	2085(1)	2047(2)	2342(1)	23(1)
C(3)	1973(2)	1555(2)	1292(1)	28(1)
C(4)	1164(2)	403(2)	1037(1)	29(1)
C(5)	473(2)	-253(2)	1818(2)	29(1)
C(6)	604(1)	229(2)	2865(1)	25(1)
C(7)	1605(2)	1883(2)	4283(1)	26(1)
C(8)	2785(1)	1298(2)	4716(1)	21(1)
C(9)	3059(1)	1892(2)	5836(1)	21(1)
C(10)	4233(2)	1335(2)	6311(1)	22(1)
C(11)	3929(1)	-65(2)	6991(1)	21(1)
C(12)	2585(1)	43(2)	7125(1)	20(1)
C(13)	2553(2)	-1453(2)	6459(1)	22(1)
C(14)	4719(2)	-427(2)	7922(1)	27(1)
O(1)	2170(1)	1400(1)	6598(1)	21(1)
O(2)	1837(1)	-2342(1)	6100(1)	30(1)
O(3)	3744(1)	-1510(1)	6313(1)	24(1)

Table B3. Bond lengths [Å] and angles [°] for DR_060206.

C(1)-C(6)	1.393(3)
C(1)-C(2)	1.402(2)
C(1)-C(7)	1.521(2)
C(2)-C(3)	1.399(3)
C(3)-C(4)	1.389(3)
C(4)-C(5)	1.389(3)
C(5)-C(6)	1.396(3)
C(7)-C(8)	1.534(2)
C(8)-C(9)	1.537(2)
C(9)-O(1)	1.469(2)
C(9)-C(10)	1.539(2)
C(10)-C(11)	1.520(2)
C(11)-C(14)	1.510(2)
C(11)-O(3)	1.522(2)
C(11)-C(12)	1.546(2)
C(12)-O(1)	1.4215(19)
C(12)-C(13)	1.537(2)
C(13)-O(2)	1.204(2)
C(13)-O(3)	1.373(2)
C(6)-C(1)-C(2)	118.24(15)
C(6)-C(1)-C(7)	122.14(15)
C(2)-C(1)-C(7)	119.59(16)
C(3)-C(2)-C(1)	121.17(17)
C(4)-C(3)-C(2)	119.42(16)
C(3)-C(4)-C(5)	120.19(15)
C(4)-C(5)-C(6)	119.98(16)
C(1)-C(6)-C(5)	120.98(16)
C(1)-C(7)-C(8)	111.57(14)
C(7)-C(8)-C(9)	113.12(14)
O(1)-C(9)-C(8)	111.97(13)
O(1)-C(9)-C(10)	104.92(12)
C(8)-C(9)-C(10)	115.28(14)
C(11)-C(10)-C(9)	105.38(13)

C(14)-C(11)-C(10)	117.85(14)
C(14)-C(11)-O(3)	110.57(13)
C(10)-C(11)-O(3)	110.90(12)
C(14)-C(11)-C(12)	120.80(14)
C(10)-C(11)-C(12)	104.23(13)
O(3)-C(11)-C(12)	88.74(11)
O(1)-C(12)-C(13)	114.91(13)
O(1)-C(12)-C(11)	108.95(13)
C(13)-C(12)-C(11)	84.76(12)
O(2)-C(13)-O(3)	126.58(15)
O(2)-C(13)-C(12)	138.56(16)
O(3)-C(13)-C(12)	94.82(12)
C(12)-O(1)-C(9)	108.31(12)
C(13)-O(3)-C(11)	91.62(11)

Table B4. Anisotropic displacement parameters ($Å^2$x 10^3) for DR_060206. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	18(1)	21(1)	23(1)	2(1)	-1(1)	4(1)
C(2)	19(1)	24(1)	25(1)	2(1)	-4(1)	-1(1)
C(3)	25(1)	37(1)	23(1)	3(1)	0(1)	7(1)
C(4)	29(1)	33(1)	26(1)	-11(1)	-9(1)	15(1)
C(5)	24(1)	20(1)	45(1)	-7(1)	-10(1)	3(1)
C(6)	20(1)	22(1)	33(1)	7(1)	-1(1)	1(1)
C(7)	26(1)	30(1)	22(1)	0(1)	1(1)	3(1)
C(8)	24(1)	21(1)	18(1)	0(1)	1(1)	1(1)
C(9)	25(1)	18(1)	20(1)	1(1)	2(1)	-1(1)
C(10)	21(1)	22(1)	23(1)	-1(1)	0(1)	-5(1)
C(11)	23(1)	17(1)	22(1)	-4(1)	-1(1)	1(1)
C(12)	21(1)	19(1)	20(1)	3(1)	-1(1)	0(1)
C(13)	26(1)	21(1)	20(1)	5(1)	0(1)	-2(1)
C(14)	26(1)	28(1)	28(1)	1(1)	-5(1)	4(1)
O(1)	22(1)	22(1)	20(1)	3(1)	2(1)	4(1)
O(2)	37(1)	27(1)	26(1)	0(1)	-3(1)	-11(1)
O(3)	26(1)	19(1)	26(1)	-4(1)	0(1)	2(1)

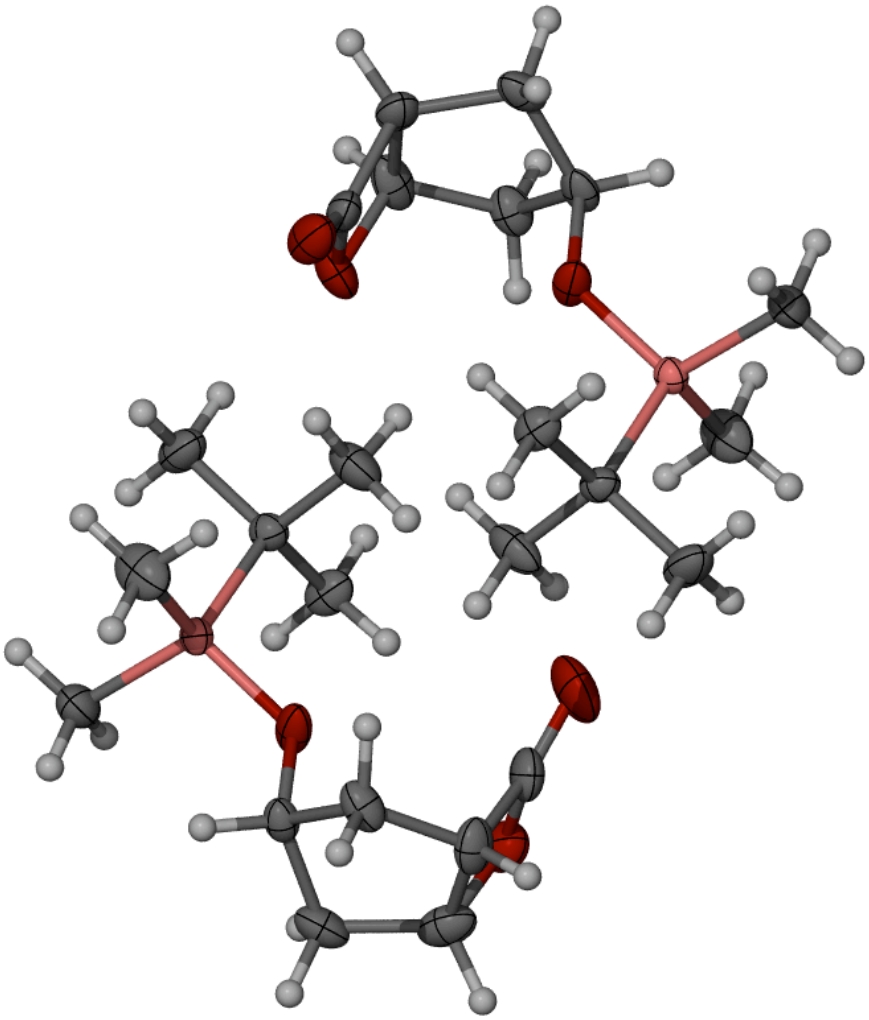
Table B5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for DR_060206.

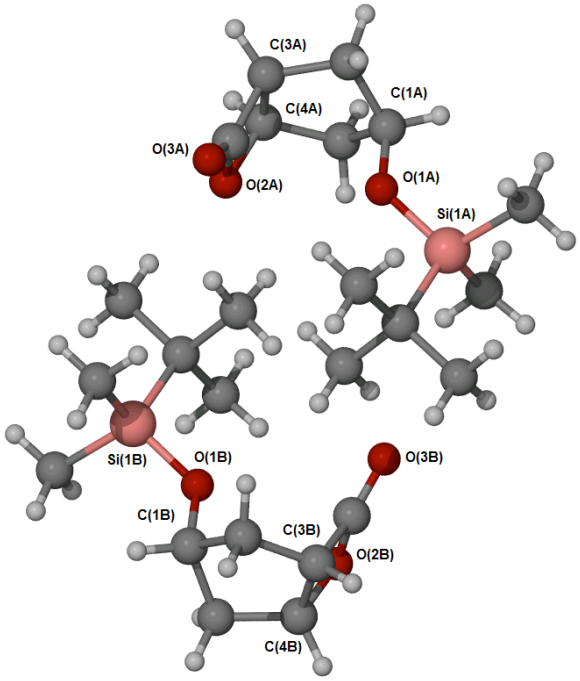
	x	y	z	U(eq)
H(2)	2628	2848	2514	27
H(3)	2446	2005	759	34
H(4)	1083	62	326	35
H(5)	-88	-1030	1639	35
H(6)	135	-235	3396	30
H(7A)	964	1469	4724	31
H(7B)	1582	3034	4325	31
H(8A)	3416	1637	4236	25
H(8B)	2779	145	4723	25
H(9)	3068	3056	5817	25
H(10A)	4783	1035	5746	27
H(10B)	4598	2166	6745	27
H(12)	2307	-81	7866	24
H(14A)	4434	-1362	8281	40
H(14B)	4716	454	8415	40
H(14C)	5519	-606	7674	40

Crystal and Molecular Structure Determination for *Syn*-Carbocycle-Fused *β*-Lactone 73b.

X-ray Diffraction Laboratory
Department of Chemistry
Texas A&M University

Report: May 28, 2009
Structure: DR70
Joe Reibenspies (Sample from Kay Morris)




C(3A)
C(1A)
C(4A)
O(3A)
O(2A)
O(1A)
Si(1A)
Si(1B)
O(1B)
O(3B)
C(1B)
C(3B)
O(2B)
C(4B)

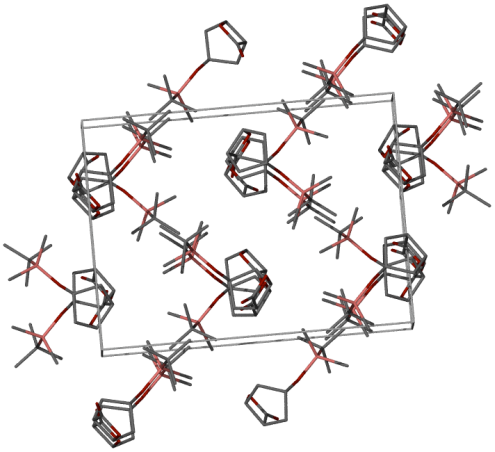


Table B6. Crystal data and structure refinement for DR70.

Identification code	dr70	
Empirical formula	C12 H22 O3 Si	
Formula weight	242.39	
Temperature	70(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 12.2353(8) Å	α= 90°.
	b = 13.6398(9) Å	β= 90°.
	c = 16.6225(12) Å	γ = 90°.
Volume	2774.1(3) $Å^3$	
Z	8	
Density (calculated)	1.161 Mg/m^3	
Absorption coefficient	0.161 mm^{-1}	
F(000)	1056	
Crystal size	0.30 x 0.30 x 0.10 mm^3	
Theta range for data collection	1.93 to 25.00°.	
Index ranges	-14<=h<=14, -16<=k<=16, -19<=l<=19	
Reflections collected	36585	
Independent reflections	4857 [R(int) = 0.0504]	
Completeness to theta = 25.00°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9841 and 0.9532	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4857 / 0 / 299	
Goodness-of-fit on F^2	1.005	
Final R indices [I>2sigma(I)]	R1 = 0.0414, wR2 = 0.0982	
R indices (all data)	R1 = 0.0544, wR2 = 0.1073	
Absolute structure parameter	-0.07(17)	
Largest diff. peak and hole	0.332 and -0.210 $e.Å^{-3}$	

Table B7. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DR70. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Si(1A)	3988(1)	6244(1)	1846(1)	23(1)
O(1A)	3022(2)	6184(1)	1159(1)	34(1)
O(2A)	2567(2)	5249(1)	-425(1)	42(1)
O(3A)	1484(2)	4346(1)	408(1)	44(1)
C(1A)	2554(2)	6995(2)	737(2)	30(1)
C(2A)	1334(2)	6809(2)	672(2)	37(1)
C(3A)	1231(2)	6104(2)	-36(2)	36(1)
C(4A)	2229(3)	6289(2)	-564(2)	41(1)
C(5A)	2937(3)	7011(2)	-128(2)	36(1)
C(6A)	1702(2)	5091(2)	68(2)	33(1)
C(7A)	4356(2)	4930(2)	2044(2)	27(1)
C(8A)	3321(2)	4337(2)	2206(2)	33(1)
C(9A)	4930(3)	4499(2)	1311(2)	44(1)
C(10A)	5110(3)	4869(2)	2783(2)	47(1)
C(11A)	3446(3)	6851(2)	2774(2)	40(1)
C(12A)	5182(3)	6955(2)	1465(2)	45(1)
Si(1B)	5993(1)	3796(1)	-1848(1)	24(1)
O(1B)	6945(2)	3832(1)	-1156(1)	38(1)
O(2B)	8752(2)	4796(2)	-304(1)	45(1)
O(3B)	7333(2)	5533(2)	322(2)	61(1)
C(1B)	7384(2)	3001(2)	-748(2)	29(1)
C(2B)	7119(3)	3068(2)	146(2)	35(1)
C(3B)	7966(3)	3779(2)	466(2)	40(1)
C(4B)	8938(3)	3738(2)	-103(2)	45(1)
C(5B)	8629(2)	3051(2)	-770(2)	41(1)
C(6B)	7879(3)	4838(2)	195(2)	38(1)
C(7B)	5689(2)	5121(2)	-2063(2)	27(1)
C(8B)	5120(3)	5585(2)	-1337(2)	46(1)
C(9B)	6753(2)	5672(2)	-2224(2)	36(1)
C(10B)	4940(3)	5198(2)	-2804(2)	44(1)
C(11B)	6522(3)	3147(2)	-2750(2)	40(1)
C(12B)	4777(3)	3127(2)	-1472(2)	50(1)

Table B8. Bond lengths [Å] and angles [°] for DR70.

Si(1A)-O(1A)	1.6445(19)
Si(1A)-C(12A)	1.865(3)
Si(1A)-C(11A)	1.872(3)
Si(1A)-C(7A)	1.878(3)
O(1A)-C(1A)	1.430(3)
O(2A)-C(6A)	1.356(4)
O(2A)-C(4A)	1.496(3)
O(3A)-C(6A)	1.193(3)
C(1A)-C(5A)	1.512(4)
C(1A)-C(2A)	1.519(4)
C(1A)-H(1A)	1.0000
C(2A)-C(3A)	1.525(4)
C(2A)-H(2A1)	0.9900
C(2A)-H(2A2)	0.9900
C(3A)-C(6A)	1.507(4)
C(3A)-C(4A)	1.525(4)
C(3A)-H(3A)	1.0000
C(4A)-C(5A)	1.498(4)
C(4A)-H(4A)	1.0000
C(5A)-H(5A1)	0.9900
C(5A)-H(5A2)	0.9900
C(7A)-C(9A)	1.524(4)
C(7A)-C(8A)	1.527(4)
C(7A)-C(10A)	1.538(4)
C(8A)-H(8A1)	0.9800
C(8A)-H(8A2)	0.9800
C(8A)-H(8A3)	0.9800
C(9A)-H(9A1)	0.9800
C(9A)-H(9A2)	0.9800
C(9A)-H(9A3)	0.9800
C(10A)-H(10A)	0.9800
C(10A)-H(10B)	0.9800
C(10A)-H(10C)	0.9800
C(11A)-H(11A)	0.9800

C(11A)-H(11B)	0.9800
C(11A)-H(11C)	0.9800
C(12A)-H(12A)	0.9800
C(12A)-H(12B)	0.9800
C(12A)-H(12C)	0.9800
Si(1B)-O(1B)	1.639(2)
Si(1B)-C(12B)	1.854(3)
Si(1B)-C(11B)	1.858(3)
Si(1B)-C(7B)	1.879(3)
O(1B)-C(1B)	1.425(3)
O(2B)-C(6B)	1.354(4)
O(2B)-C(4B)	1.498(3)
O(3B)-C(6B)	1.178(4)
C(1B)-C(2B)	1.524(4)
C(1B)-C(5B)	1.525(4)
C(1B)-H(1B)	1.0000
C(2B)-C(3B)	1.516(4)
C(2B)-H(2B1)	0.9900
C(2B)-H(2B2)	0.9900
C(3B)-C(6B)	1.518(4)
C(3B)-C(4B)	1.521(4)
C(3B)-H(3B)	1.0000
C(4B)-C(5B)	1.500(4)
C(4B)-H(4B)	1.0000
C(5B)-H(5B1)	0.9900
C(5B)-H(5B2)	0.9900
C(7B)-C(9B)	1.527(4)
C(7B)-C(8B)	1.531(4)
C(7B)-C(10B)	1.538(4)
C(8B)-H(8B1)	0.9800
C(8B)-H(8B2)	0.9800
C(8B)-H(8B3)	0.9800
C(9B)-H(9B1)	0.9800
C(9B)-H(9B2)	0.9800
C(9B)-H(9B3)	0.9800
C(10B)-H(10D)	0.9800

C(10B)-H(10E)	0.9800
C(10B)-H(10F)	0.9800
C(11B)-H(11D)	0.9800
C(11B)-H(11E)	0.9800
C(11B)-H(11F)	0.9800
C(12B)-H(12D)	0.9800
C(12B)-H(12E)	0.9800
C(12B)-H(12F)	0.9800

O(1A)-Si(1A)-C(12A)	110.72(13)
O(1A)-Si(1A)-C(11A)	109.86(12)
C(12A)-Si(1A)-C(11A)	109.08(16)
O(1A)-Si(1A)-C(7A)	104.30(11)
C(12A)-Si(1A)-C(7A)	111.58(14)
C(11A)-Si(1A)-C(7A)	111.24(14)
C(1A)-O(1A)-Si(1A)	126.11(17)
C(6A)-O(2A)-C(4A)	91.6(2)
O(1A)-C(1A)-C(5A)	110.7(2)
O(1A)-C(1A)-C(2A)	107.4(2)
C(5A)-C(1A)-C(2A)	103.8(2)
O(1A)-C(1A)-H(1A)	111.5
C(5A)-C(1A)-H(1A)	111.5
C(2A)-C(1A)-H(1A)	111.5
C(1A)-C(2A)-C(3A)	104.0(2)
C(1A)-C(2A)-H(2A1)	111.0
C(3A)-C(2A)-H(2A1)	111.0
C(1A)-C(2A)-H(2A2)	111.0
C(3A)-C(2A)-H(2A2)	111.0
H(2A1)-C(2A)-H(2A2)	109.0
C(6A)-C(3A)-C(2A)	117.2(2)
C(6A)-C(3A)-C(4A)	84.9(2)
C(2A)-C(3A)-C(4A)	105.9(2)
C(6A)-C(3A)-H(3A)	114.9
C(2A)-C(3A)-H(3A)	114.9
C(4A)-C(3A)-H(3A)	114.9
O(2A)-C(4A)-C(5A)	112.9(3)

O(2A)-C(4A)-C(3A)	88.6(2)
C(5A)-C(4A)-C(3A)	107.0(2)
O(2A)-C(4A)-H(4A)	115.1
C(5A)-C(4A)-H(4A)	115.1
C(3A)-C(4A)-H(4A)	115.1
C(4A)-C(5A)-C(1A)	105.8(3)
C(4A)-C(5A)-H(5A1)	110.6
C(1A)-C(5A)-H(5A1)	110.6
C(4A)-C(5A)-H(5A2)	110.6
C(1A)-C(5A)-H(5A2)	110.6
H(5A1)-C(5A)-H(5A2)	108.7
O(3A)-C(6A)-O(2A)	126.5(3)
O(3A)-C(6A)-C(3A)	138.6(3)
O(2A)-C(6A)-C(3A)	94.8(2)
C(9A)-C(7A)-C(8A)	108.6(2)
C(9A)-C(7A)-C(10A)	109.9(2)
C(8A)-C(7A)-C(10A)	109.2(2)
C(9A)-C(7A)-Si(1A)	109.77(19)
C(8A)-C(7A)-Si(1A)	109.73(18)
C(10A)-C(7A)-Si(1A)	109.61(19)
C(7A)-C(8A)-H(8A1)	109.5
C(7A)-C(8A)-H(8A2)	109.5
H(8A1)-C(8A)-H(8A2)	109.5
C(7A)-C(8A)-H(8A3)	109.5
H(8A1)-C(8A)-H(8A3)	109.5
H(8A2)-C(8A)-H(8A3)	109.5
C(7A)-C(9A)-H(9A1)	109.5
C(7A)-C(9A)-H(9A2)	109.5
H(9A1)-C(9A)-H(9A2)	109.5
C(7A)-C(9A)-H(9A3)	109.5
H(9A1)-C(9A)-H(9A3)	109.5
H(9A2)-C(9A)-H(9A3)	109.5
C(7A)-C(10A)-H(10A)	109.5
C(7A)-C(10A)-H(10B)	109.5
H(10A)-C(10A)-H(10B)	109.5
C(7A)-C(10A)-H(10C)	109.5

H(10A)-C(10A)-H(10C)	109.5
H(10B)-C(10A)-H(10C)	109.5
Si(1A)-C(11A)-H(11A)	109.5
Si(1A)-C(11A)-H(11B)	109.5
H(11A)-C(11A)-H(11B)	109.5
Si(1A)-C(11A)-H(11C)	109.5
H(11A)-C(11A)-H(11C)	109.5
H(11B)-C(11A)-H(11C)	109.5
Si(1A)-C(12A)-H(12A)	109.5
Si(1A)-C(12A)-H(12B)	109.5
H(12A)-C(12A)-H(12B)	109.5
Si(1A)-C(12A)-H(12C)	109.5
H(12A)-C(12A)-H(12C)	109.5
H(12B)-C(12A)-H(12C)	109.5
O(1B)-Si(1B)-C(12B)	110.41(14)
O(1B)-Si(1B)-C(11B)	109.46(13)
C(12B)-Si(1B)-C(11B)	108.48(16)
O(1B)-Si(1B)-C(7B)	104.23(11)
C(12B)-Si(1B)-C(7B)	112.25(15)
C(11B)-Si(1B)-C(7B)	111.96(14)
C(1B)-O(1B)-Si(1B)	125.31(17)
C(6B)-O(2B)-C(4B)	91.4(2)
O(1B)-C(1B)-C(2B)	109.6(2)
O(1B)-C(1B)-C(5B)	109.2(2)
C(2B)-C(1B)-C(5B)	103.5(3)
O(1B)-C(1B)-H(1B)	111.4
C(2B)-C(1B)-H(1B)	111.4
C(5B)-C(1B)-H(1B)	111.4
C(3B)-C(2B)-C(1B)	103.6(2)
C(3B)-C(2B)-H(2B1)	111.0
C(1B)-C(2B)-H(2B1)	111.0
C(3B)-C(2B)-H(2B2)	111.0
C(1B)-C(2B)-H(2B2)	111.0
H(2B1)-C(2B)-H(2B2)	109.0
C(2B)-C(3B)-C(6B)	117.1(3)
C(2B)-C(3B)-C(4B)	107.0(2)

C(6B)-C(3B)-C(4B)	84.5(2)
C(2B)-C(3B)-H(3B)	114.7
C(6B)-C(3B)-H(3B)	114.7
C(4B)-C(3B)-H(3B)	114.7
O(2B)-C(4B)-C(5B)	113.5(2)
O(2B)-C(4B)-C(3B)	89.2(2)
C(5B)-C(4B)-C(3B)	106.6(2)
O(2B)-C(4B)-H(4B)	114.9
C(5B)-C(4B)-H(4B)	114.9
C(3B)-C(4B)-H(4B)	114.9
C(4B)-C(5B)-C(1B)	105.2(2)
C(4B)-C(5B)-H(5B1)	110.7
C(1B)-C(5B)-H(5B1)	110.7
C(4B)-C(5B)-H(5B2)	110.7
C(1B)-C(5B)-H(5B2)	110.7
H(5B1)-C(5B)-H(5B2)	108.8
O(3B)-C(6B)-O(2B)	126.3(3)
O(3B)-C(6B)-C(3B)	138.8(3)
O(2B)-C(6B)-C(3B)	94.9(3)
C(9B)-C(7B)-C(8B)	108.8(2)
C(9B)-C(7B)-C(10B)	109.5(2)
C(8B)-C(7B)-C(10B)	109.4(2)
C(9B)-C(7B)-Si(1B)	109.74(19)
C(8B)-C(7B)-Si(1B)	109.75(19)
C(10B)-C(7B)-Si(1B)	109.65(19)
C(7B)-C(8B)-H(8B1)	109.5
C(7B)-C(8B)-H(8B2)	109.5
H(8B1)-C(8B)-H(8B2)	109.5
C(7B)-C(8B)-H(8B3)	109.5
H(8B1)-C(8B)-H(8B3)	109.5
H(8B2)-C(8B)-H(8B3)	109.5
C(7B)-C(9B)-H(9B1)	109.5
C(7B)-C(9B)-H(9B2)	109.5
H(9B1)-C(9B)-H(9B2)	109.5
C(7B)-C(9B)-H(9B3)	109.5
H(9B1)-C(9B)-H(9B3)	109.5

H(9B2)-C(9B)-H(9B3)	109.5
C(7B)-C(10B)-H(10D)	109.5
C(7B)-C(10B)-H(10E)	109.5
H(10D)-C(10B)-H(10E)	109.5
C(7B)-C(10B)-H(10F)	109.5
H(10D)-C(10B)-H(10F)	109.5
H(10E)-C(10B)-H(10F)	109.5
Si(1B)-C(11B)-H(11D)	109.5
Si(1B)-C(11B)-H(11E)	109.5
H(11D)-C(11B)-H(11E)	109.5
Si(1B)-C(11B)-H(11F)	109.5
H(11D)-C(11B)-H(11F)	109.5
H(11E)-C(11B)-H(11F)	109.5
Si(1B)-C(12B)-H(12D)	109.5
Si(1B)-C(12B)-H(12E)	109.5
H(12D)-C(12B)-H(12E)	109.5
Si(1B)-C(12B)-H(12F)	109.5
H(12D)-C(12B)-H(12F)	109.5
H(12E)-C(12B)-H(12F)	109.5

Symmetry transformations used to generate equivalent atoms:

Table B9. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for DR70. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si(1A)	25(1)	19(1)	26(1)	-1(1)	0(1)	-1(1)
O(1A)	47(1)	20(1)	34(1)	4(1)	-16(1)	0(1)
O(2A)	57(1)	28(1)	42(1)	-9(1)	7(1)	4(1)
O(3A)	47(1)	27(1)	59(1)	6(1)	-15(1)	-6(1)
C(1A)	46(2)	15(1)	30(2)	2(1)	-4(1)	6(1)
C(2A)	45(2)	30(2)	36(2)	2(1)	2(1)	14(1)
C(3A)	37(2)	31(2)	40(2)	2(1)	-15(1)	6(1)
C(4A)	66(2)	30(2)	25(1)	0(1)	1(2)	5(2)
C(5A)	49(2)	27(2)	31(2)	2(1)	4(2)	-1(1)
C(6A)	34(2)	28(2)	39(2)	-6(1)	-14(1)	-1(1)
C(7A)	24(1)	23(1)	34(2)	3(1)	-3(1)	1(1)
C(8A)	33(2)	27(2)	38(2)	10(1)	-3(1)	-6(1)
C(9A)	46(2)	22(1)	62(2)	-4(2)	19(2)	1(1)
C(10A)	43(2)	35(2)	63(2)	4(2)	-24(2)	4(2)
C(11A)	38(2)	42(2)	39(2)	-12(2)	-1(1)	9(2)
C(12A)	44(2)	29(2)	62(2)	1(2)	13(2)	-10(2)
Si(1B)	24(1)	19(1)	29(1)	-2(1)	-2(1)	-3(1)
O(1B)	56(1)	18(1)	40(1)	0(1)	-20(1)	-2(1)
O(2B)	39(1)	38(1)	58(1)	4(1)	-3(1)	-10(1)
O(3B)	78(2)	31(1)	74(2)	-18(1)	16(1)	-9(1)
C(1B)	40(2)	21(1)	24(2)	0(1)	-4(1)	0(1)
C(2B)	50(2)	24(2)	31(2)	2(1)	11(2)	-1(1)
C(3B)	58(2)	37(2)	24(1)	0(1)	-9(1)	-8(2)
C(4B)	34(2)	41(2)	60(2)	16(2)	-9(2)	1(2)
C(5B)	44(2)	33(2)	46(2)	3(1)	11(2)	13(1)
C(6B)	45(2)	31(2)	40(2)	-9(1)	-4(2)	-12(2)
C(7B)	27(1)	21(1)	33(2)	1(1)	-1(1)	0(1)
C(8B)	49(2)	32(2)	58(2)	-6(2)	11(2)	7(2)
C(9B)	36(2)	28(2)	46(2)	11(2)	-7(2)	-7(1)
C(10B)	39(2)	34(2)	58(2)	2(2)	-19(2)	0(2)
C(11B)	43(2)	38(2)	39(2)	-7(2)	-3(2)	9(2)

C(12B)	46(2)	35(2)	70(2)	1(2)	16(2)	-13(2)

Table B10. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for DR70.

	x	y	z	U(eq)
H(1A)	2712	7630	1014	36
H(2A1)	932	7426	566	44
H(2A2)	1047	6508	1172	44
H(3A)	514	6129	-325	43
H(4A)	2064	6459	-1137	49
H(5A1)	2852	7674	-361	43
H(5A2)	3715	6817	-164	43
H(8A1)	3517	3651	2309	49
H(8A2)	2839	4371	1736	49
H(8A3)	2943	4606	2676	49
H(9A1)	4447	4543	843	65
H(9A2)	5109	3810	1414	65
H(9A3)	5603	4866	1206	65
H(10A)	5767	5263	2687	70
H(10B)	5319	4185	2876	70
H(10C)	4724	5121	3256	70
H(11A)	2863	6448	3005	59
H(11B)	3155	7498	2635	59
H(11C)	4038	6924	3167	59
H(12A)	4941	7608	1296	68
H(12B)	5507	6611	1005	68
H(12C)	5728	7019	1894	68
H(1B)	7109	2375	-986	34
H(2B1)	6370	3321	232	42
H(2B2)	7187	2419	408	42
H(3B)	8153	3690	1048	48
H(4B)	9655	3593	160	54
H(5B1)	8951	2395	-681	49
H(5B2)	8885	3305	-1295	49
H(8B1)	4402	5280	-1261	70

H(8B2)	5027	6290	-1430	70
H(8B3)	5566	5483	-854	70
H(9B1)	7217	5646	-1744	55
H(9B2)	6589	6356	-2355	55
H(9B3)	7137	5366	-2677	55
H(10D)	4766	5888	-2905	65
H(10E)	4264	4833	-2704	65
H(10F)	5314	4922	-3273	65
H(11D)	6772	2491	-2596	60
H(11E)	7134	3517	-2979	60
H(11F)	5938	3090	-3151	60
H(12D)	4480	3468	-1001	76
H(12E)	4987	2459	-1321	76
H(12F)	4220	3102	-1896	76

Data Collection:

A Leica Z microscope was used to identify a suitable colorless parallelpiped 0.3mm x 0.3mm x 0.1mm from a representative sample of crystals of the same habit. The crystal was coated in a cryogenic protectant (paratone), and was then fixed to a loop, which in turn was fashioned to a copper mounting pin. The mounted crystal was then placed in a cold nitrogen stream (Oxford) maintained at 110 K.

A BRUKER SMART SMART100 X-ray three-circle diffractometer was employed for crystal screening, unit cell determination and data collection. The goniometer was controlled using the SMART software suite (Microsoft operating system). The sample was optically centered with the aid of a video camera such that no translations were observed as the crystal was rotated through all positions. The detector was set at 5.0 cm from the crystal sample (CCD-, 512x512 pixel). The X-ray radiation employed was generated from a Mo sealed X-ray tube (K_α = 0.70173Å with a potential of 50 kV and a current of 40 mA) and filtered with a graphite monochromator in the parallel mode (175 mm collimator with 0.8 mm pinholes).

Dark currents were obtained for the appropriate exposure time 10 sec and a rotation exposure was taken to determine crystal quality and the X-ray beam intersection with the detector. The beam intersection coordinates were compared to the configured coordinates and changes were made accordingly. The rotation exposure indicated acceptable crystal quality and the unit cell determination was undertaken. Forty data frames were taken at widths of 0.5° with an exposure time of 10 seconds. Over 200 reflections were centered and their positions were determined. These reflections were used in the auto-indexing procedure to determine the unit cell. A suitable cell was found and refined by nonlinear least squares and Bravais lattice procedures and reported. The unit cell was verified by examination of the hkl overlays on several frames of data, including zone photographs. No super-cell or erroneous reflections were observed.

After careful examination of the unit cell, a standard data collection procedure was initiated. This procedure consists of collection of one hemisphere of data collected using omega scans, involving the collection over 3600 0.5° frames at fixed angles for ϕ, 2θ, and χ (2θ = -28°, χ = 54.73°), while varying omega. Each frame was exposed for 20 sec and contrasted against a 20 sec. dark current exposure. The total data collection was

performed for duration of approximately 24 hours at 110 K. No significant intensity fluctuations of equivalent reflections were observed. After data collection, the crystal was measured carefully for size, morphology and color.

Crystal and Molecular Structure Determination for *Anti*-Carbocycle-Fused β-Lactone 73h.

X-ray Diffraction Laboratory
Department of Chemistry
Texas A&M University

Report:	October 14, 2009
Structure:	DR74
Joe Reibenspies	(Sample from Kay Morris)

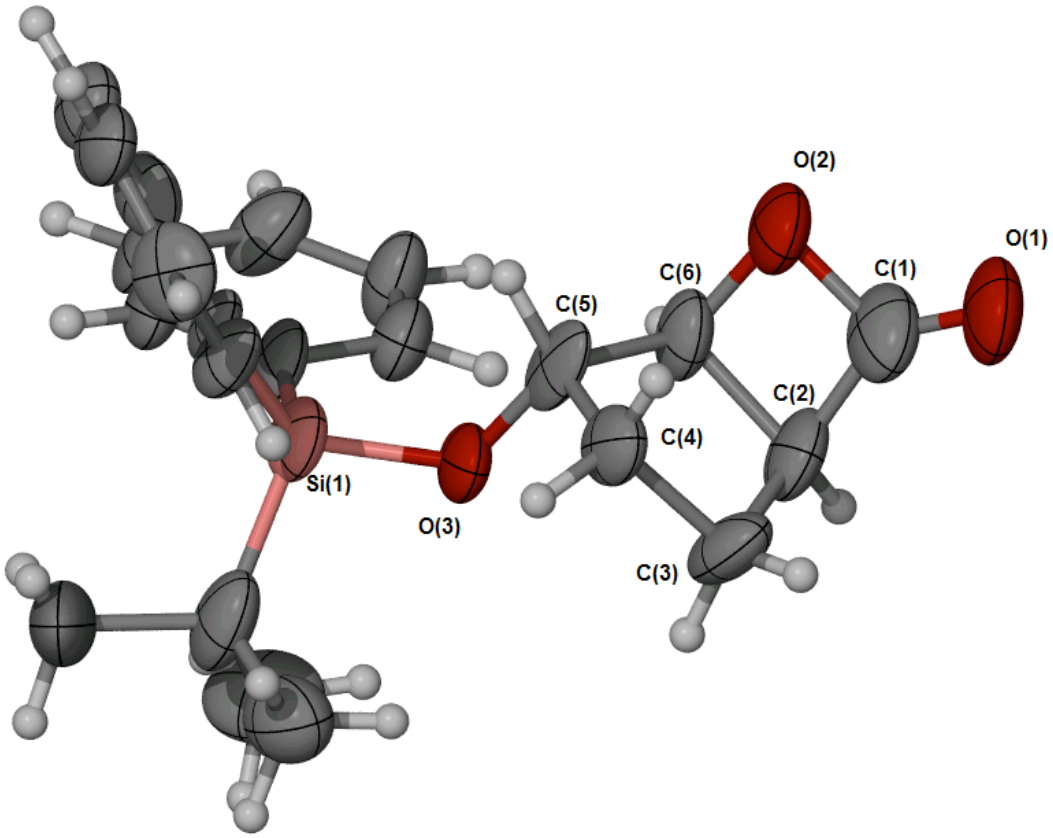

O(2)
O(1)
C(6)
C(1)
C(5)
C(2)
C(4)
Si(1)
O(3)
C(3)

Table B11. Crystal data and structure refinement for DR74M.

Identification code	dr74m	
Empirical formula	C22 H26 O3 Si	
Formula weight	366.52	
Temperature	110(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 14.553(4) Å	α= 90°.
	b = 8.483(3) Å	β= 110.019(12)°.
	c = 17.092(6) Å	γ = 90°.
Volume	1982.6(11) $Å^3$	
Z	4	
Density (calculated)	1.228 Mg/m^3	
Absorption coefficient	1.186 mm^{-1}	
F(000)	784	
Crystal size	0.10 x 0.03 x 0.01 mm^3	
Theta range for data collection	7.17 to 59.99°.	
Index ranges	-16<=h<=16, -9<=k<=9, -19<=l<=19	
Reflections collected	11915	
Independent reflections	2752 [R(int) = 0.3605]	
Completeness to theta = 59.99°	93.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9882 and 0.8906	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2752 / 0 / 238	
Goodness-of-fit on F^2	1.006	
Final R indices [I>2sigma(I)]	R1 = 0.0762, wR2 = 0.1055	
R indices (all data)	R1 = 0.2237, wR2 = 0.1488	
Largest diff. peak and hole	0.202 and -0.260 $e.Å^{-3}$	

Table B12. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DR74M. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Si(1)	14862(1)	-3893(3)	7088(1)	58(1)
O(1)	11512(3)	1414(6)	4615(2)	84(2)
O(2)	11957(3)	-357(6)	5734(2)	68(1)
O(3)	14233(3)	-2809(6)	6291(2)	57(1)
C(1)	11948(6)	273(11)	4953(4)	80(3)
C(2)	12645(5)	-976(9)	4844(3)	68(2)
C(3)	13685(4)	-332(9)	4991(3)	76(3)
C(4)	14070(4)	-48(9)	5963(3)	63(2)
C(5)	13673(4)	-1329(10)	6324(3)	68(2)
C(6)	12623(4)	-1651(9)	5711(3)	62(2)
C(7)	15895(5)	-4611(10)	6792(4)	78(2)
C(8)	15544(6)	-6004(9)	6148(4)	108(3)
C(9)	16310(5)	-3374(10)	6324(4)	88(3)
C(10)	16737(6)	-5287(12)	7532(4)	169(5)
C(11)	15284(4)	-2647(8)	8055(3)	52(2)
C(12)	15032(4)	-3017(8)	8762(3)	58(2)
C(13)	15318(4)	-2090(9)	9493(3)	66(2)
C(14)	15813(4)	-687(9)	9477(3)	66(2)
C(15)	16063(4)	-265(9)	8777(4)	71(2)
C(16)	15799(4)	-1227(8)	8092(3)	56(2)
C(17)	14094(4)	-5545(8)	7190(3)	58(2)
C(18)	13153(4)	-5798(8)	6585(3)	60(2)
C(19)	12542(5)	-7028(8)	6634(4)	69(2)
C(20)	12822(5)	-8051(9)	7304(3)	73(2)
C(21)	13750(4)	-7873(9)	7920(3)	66(2)
C(22)	14359(4)	-6662(8)	7861(3)	60(2)

Table B13. Bond lengths [Å] and angles [°] for DR74M.

Si(1)-O(3)	1.639(4)
Si(1)-C(17)	1.837(7)
Si(1)-C(7)	1.847(7)
Si(1)-C(11)	1.879(6)
O(1)-C(1)	1.193(8)
O(2)-C(1)	1.435(8)
O(2)-C(6)	1.474(7)
O(3)-C(5)	1.508(8)
C(1)-C(2)	1.521(9)
C(2)-C(3)	1.547(8)
C(2)-C(6)	1.598(7)
C(3)-C(4)	1.579(6)
C(4)-C(5)	1.463(8)
C(5)-C(6)	1.553(7)
C(7)-C(10)	1.540(9)
C(7)-C(9)	1.560(9)
C(7)-C(8)	1.575(9)
C(11)-C(16)	1.409(7)
C(11)-C(12)	1.413(8)
C(12)-C(13)	1.412(7)
C(13)-C(14)	1.397(8)
C(14)-C(15)	1.410(7)
C(15)-C(16)	1.370(8)
C(17)-C(18)	1.422(7)
C(17)-C(22)	1.435(8)
C(18)-C(19)	1.392(8)
C(19)-C(20)	1.382(8)
C(20)-C(21)	1.408(7)
C(21)-C(22)	1.384(8)
O(3)-Si(1)-C(17)	108.8(2)
O(3)-Si(1)-C(7)	103.4(2)
C(17)-Si(1)-C(7)	110.7(3)
O(3)-Si(1)-C(11)	109.7(3)

C(17)-Si(1)-C(11)	111.9(3)
C(7)-Si(1)-C(11)	112.0(3)
C(1)-O(2)-C(6)	92.8(5)
C(5)-O(3)-Si(1)	126.3(3)
O(1)-C(1)-O(2)	125.9(7)
O(1)-C(1)-C(2)	140.6(7)
O(2)-C(1)-C(2)	93.5(6)
C(1)-C(2)-C(3)	113.0(6)
C(1)-C(2)-C(6)	84.9(5)
C(3)-C(2)-C(6)	107.8(4)
C(2)-C(3)-C(4)	101.5(4)
C(5)-C(4)-C(3)	106.4(5)
C(4)-C(5)-O(3)	107.8(5)
C(4)-C(5)-C(6)	106.5(5)
O(3)-C(5)-C(6)	104.4(6)
O(2)-C(6)-C(5)	110.8(6)
O(2)-C(6)-C(2)	88.9(5)
C(5)-C(6)-C(2)	103.6(5)
C(10)-C(7)-C(9)	109.5(6)
C(10)-C(7)-C(8)	105.7(7)
C(9)-C(7)-C(8)	103.7(5)
C(10)-C(7)-Si(1)	113.0(5)
C(9)-C(7)-Si(1)	114.4(6)
C(8)-C(7)-Si(1)	109.8(4)
C(16)-C(11)-C(12)	116.2(5)
C(16)-C(11)-Si(1)	122.0(4)
C(12)-C(11)-Si(1)	121.7(5)
C(13)-C(12)-C(11)	123.3(6)
C(14)-C(13)-C(12)	117.1(6)
C(13)-C(14)-C(15)	121.2(6)
C(16)-C(15)-C(14)	119.7(7)
C(15)-C(16)-C(11)	122.5(6)
C(18)-C(17)-C(22)	114.2(6)
C(18)-C(17)-Si(1)	120.8(5)
C(22)-C(17)-Si(1)	125.0(4)
C(19)-C(18)-C(17)	123.0(6)

C(20)-C(19)-C(18)	120.5(6)
C(19)-C(20)-C(21)	119.2(6)
C(22)-C(21)-C(20)	120.0(6)
C(21)-C(22)-C(17)	123.0(5)

Symmetry transformations used to generate equivalent atoms:

Table B14. Anisotropic displacement parameters ($Å^2$x 10^3) for DR74M. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

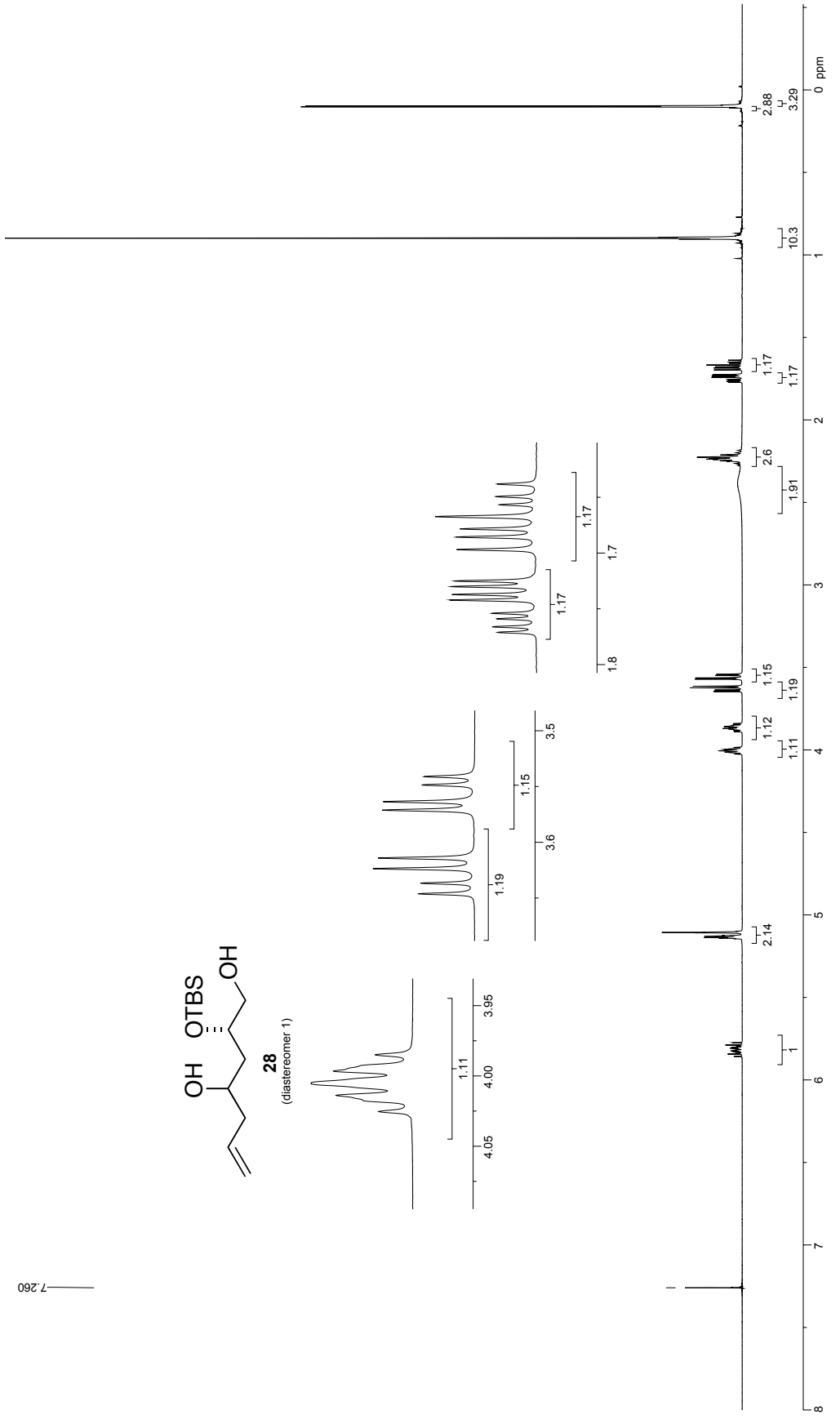
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si(1)	49(1)	79(2)	31(1)	-1(1)	-6(1)	-4(1)
O(1)	76(3)	101(5)	48(2)	5(3)	-16(2)	17(3)
O(2)	63(3)	86(4)	36(2)	0(2)	-6(2)	6(3)
O(3)	47(3)	81(4)	29(2)	2(2)	-5(2)	10(2)
C(1)	76(6)	95(8)	47(4)	-13(5)	-8(4)	9(5)
C(2)	74(5)	84(6)	29(3)	2(4)	-4(3)	-1(5)
C(3)	60(4)	135(8)	33(3)	-3(4)	17(3)	-16(4)
C(4)	38(3)	98(7)	39(3)	-4(4)	-3(3)	-3(4)
C(5)	40(4)	121(8)	26(3)	6(4)	-12(3)	-26(5)
C(6)	47(4)	83(6)	39(3)	9(4)	-8(3)	-4(4)
C(7)	67(5)	110(7)	39(3)	12(4)	-6(3)	-16(4)
C(8)	113(6)	121(9)	92(5)	-57(6)	39(5)	-21(6)
C(9)	66(5)	120(8)	75(4)	-10(5)	19(4)	2(5)
C(10)	138(8)	304(15)	77(5)	82(8)	52(6)	148(9)
C(11)	32(3)	94(6)	21(3)	10(3)	-2(2)	-8(4)
C(12)	36(3)	71(6)	51(3)	-16(4)	-5(3)	-2(3)
C(13)	51(4)	90(7)	41(3)	1(4)	-3(3)	-3(4)
C(14)	47(4)	101(8)	38(3)	2(4)	-1(3)	7(4)
C(15)	50(4)	75(6)	72(5)	-17(4)	-1(4)	-24(4)
C(16)	50(4)	80(6)	29(3)	-4(4)	1(3)	-13(4)
C(17)	58(4)	77(6)	21(3)	-7(3)	-8(3)	13(4)
C(18)	63(4)	73(6)	36(3)	8(4)	5(3)	6(4)
C(19)	63(4)	86(7)	44(3)	19(4)	0(3)	-13(4)
C(20)	76(5)	94(7)	45(3)	-1(4)	15(3)	-26(4)
C(21)	66(4)	95(7)	24(3)	10(4)	0(3)	-11(4)
C(22)	55(4)	85(6)	31(3)	5(4)	2(3)	15(4)

Table B15. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for DR74M.

	x	y	z	U(eq)
H(2)	12372	-1688	4353	82
H(3A)	13666	661	4682	91
H(3B)	14093	-1113	4829	91
H(4A)	14793	-64	6185	75
H(4B)	13842	984	6095	75
H(5)	13685	-1082	6900	82
H(6)	12367	-2747	5704	75
H(8A)	16043	-6218	5896	162
H(8B)	14930	-5710	5713	162
H(8C)	15440	-6950	6436	162
H(9A)	16596	-2491	6697	132
H(9B)	15780	-2986	5835	132
H(9C)	16815	-3869	6146	132
H(10A)	16489	-6147	7788	254
H(10B)	17006	-4455	7945	254
H(10C)	17251	-5689	7336	254
H(12)	14652	-3935	8745	69
H(13)	15179	-2408	9974	79
H(14)	15984	-5	9946	79
H(15)	16412	683	8781	86
H(16)	15970	-925	7625	68
H(18)	12930	-5095	6125	72
H(19)	11928	-7165	6204	83
H(20)	12393	-8864	7348	88
H(21)	13957	-8584	8376	79
H(22)	14982	-6566	8284	72

APPENDIX C

SELECTED SPECTRAL DATA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OH
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7.260
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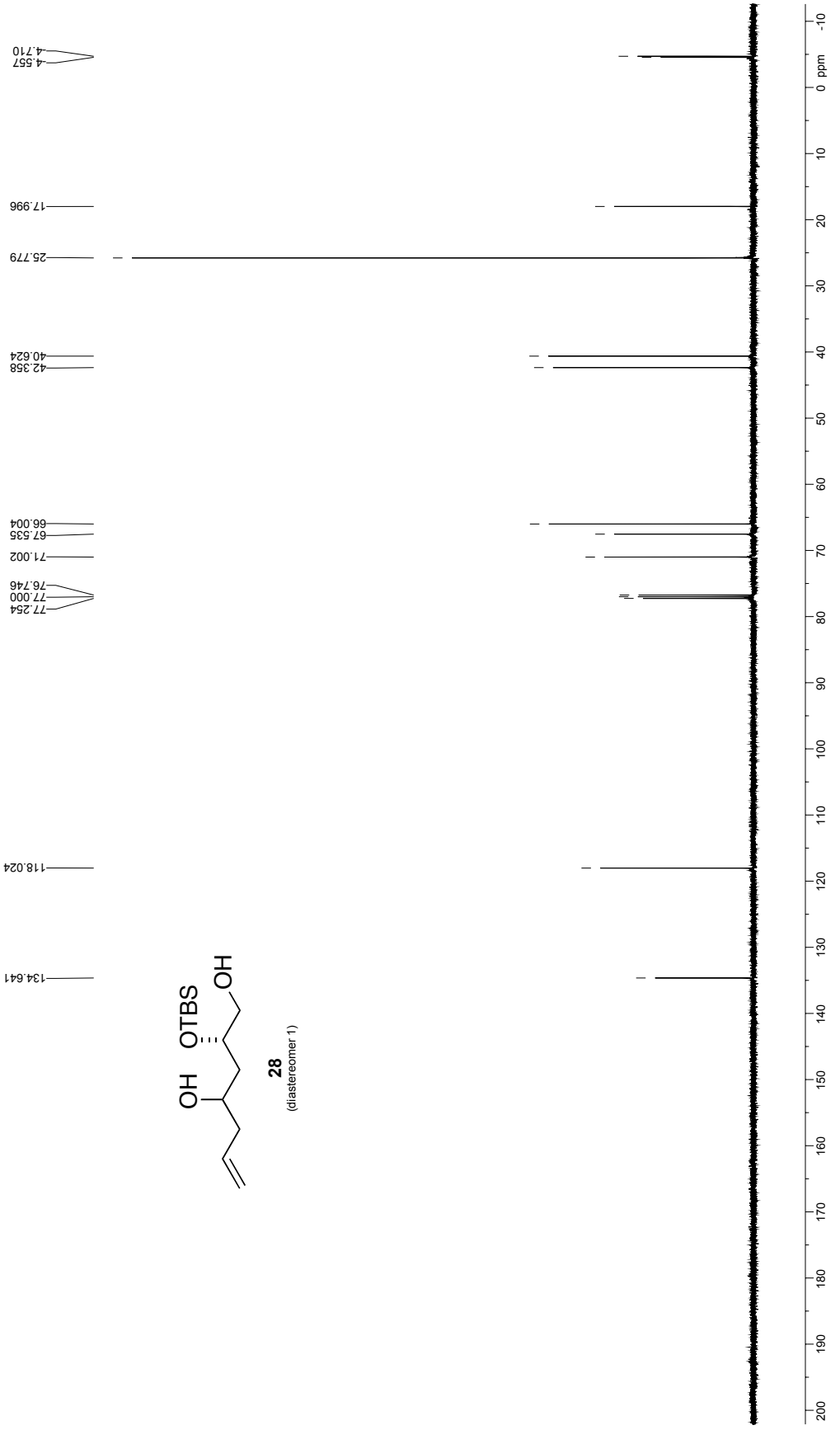
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4.710
17.996
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42.358
66.004
67.535
71.002
76.746
77.000
77.254
118.024
134.641
OH
OTBS
OH
28
(diastereomer 1)
-10
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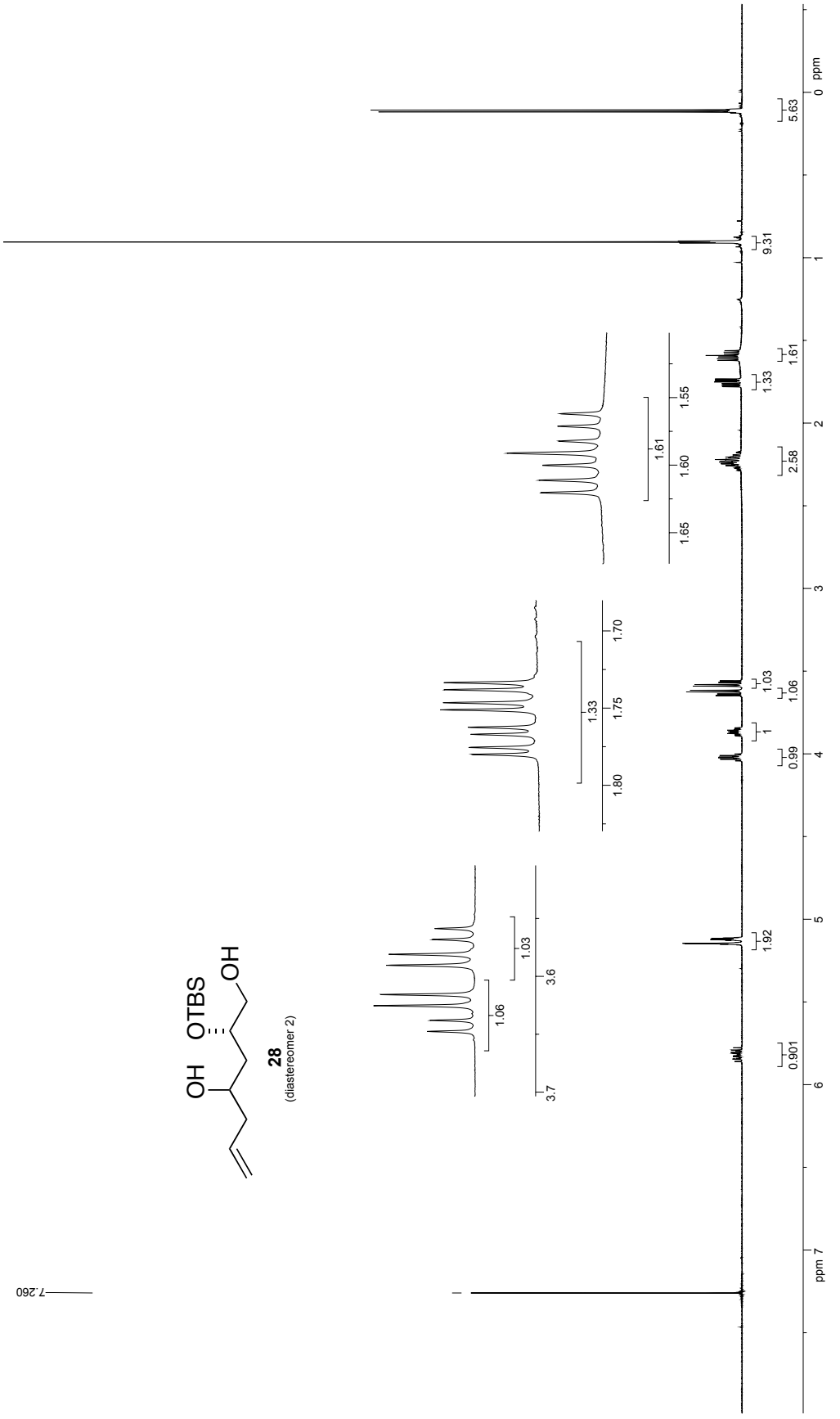
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
ppm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5
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2
1
0 ppm
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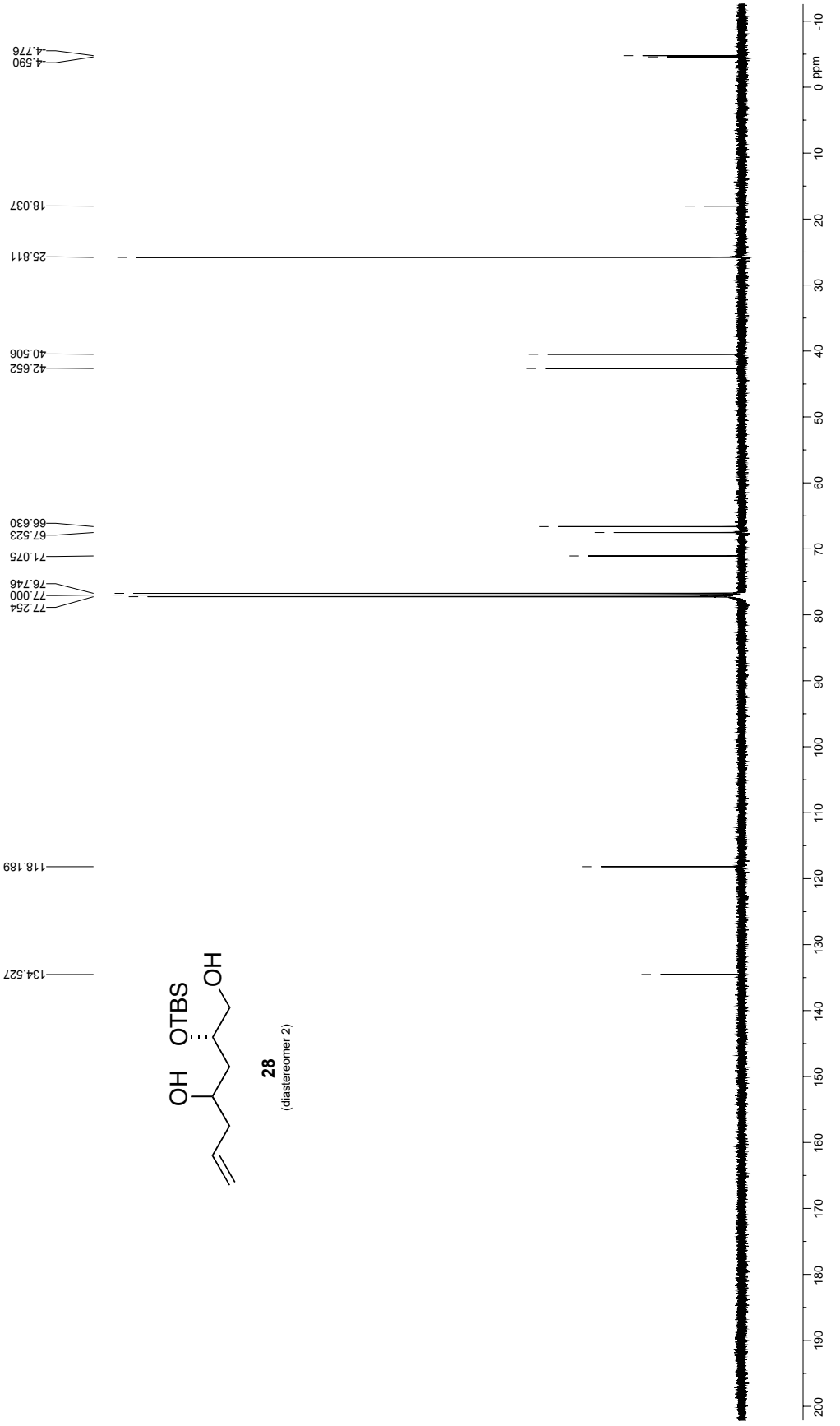
1.92
1.06
1.03
3.7
3.6
0.99
1
1.03
1.06
1.33
1.75
1.70
1.80
1.61
1.60
1.55
1.65
2.58
1.33
1.61
9.31
5.63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OTBS
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76.746
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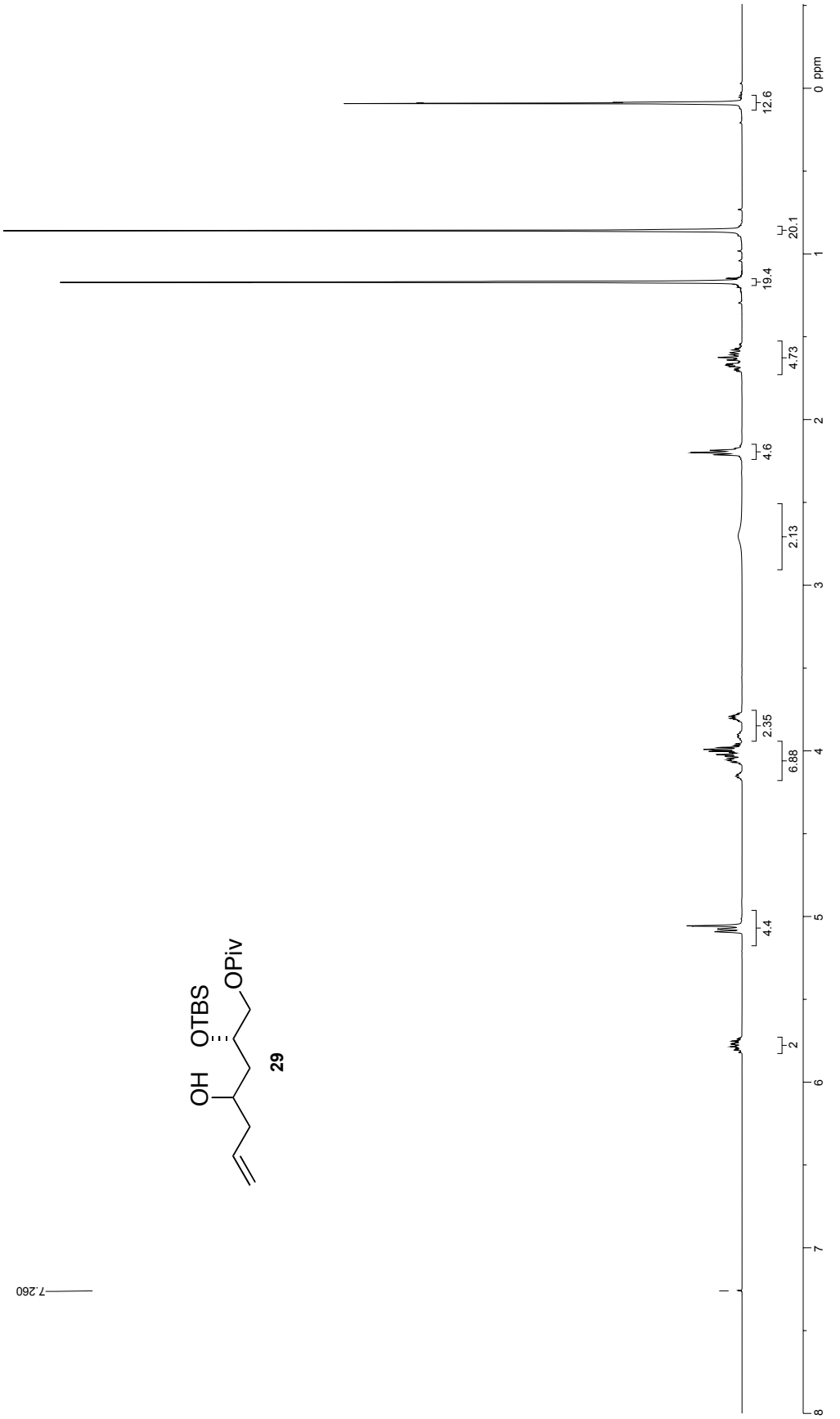
67.523
66.630
42.652
40.506
25.811
18.037
4.590
4.776
0 ppm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7.260
12.6
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19.4
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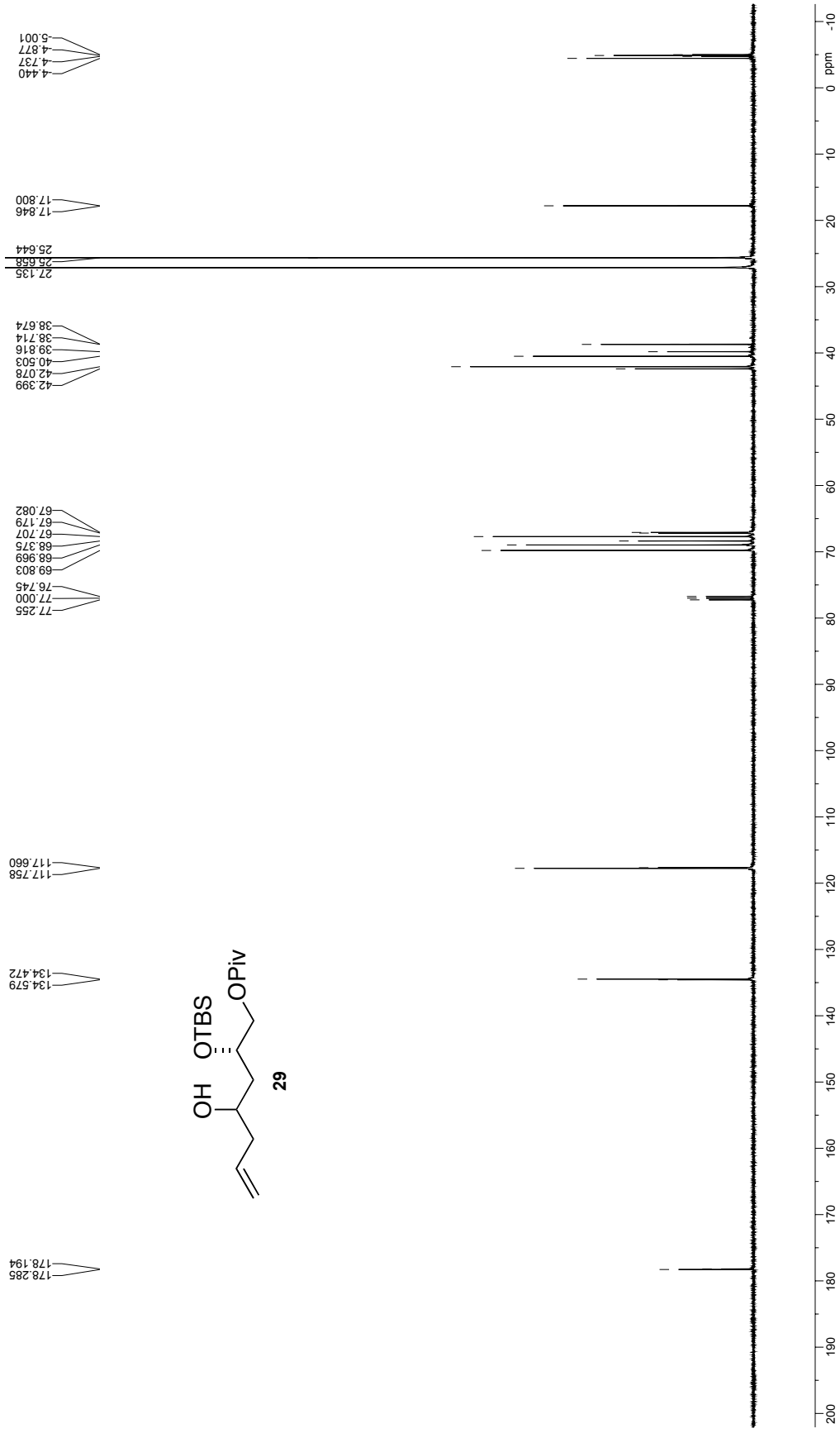
4.6
2.13
2.35
6.88
4.4
2
0 ppm


OH
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OPiv
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17.846
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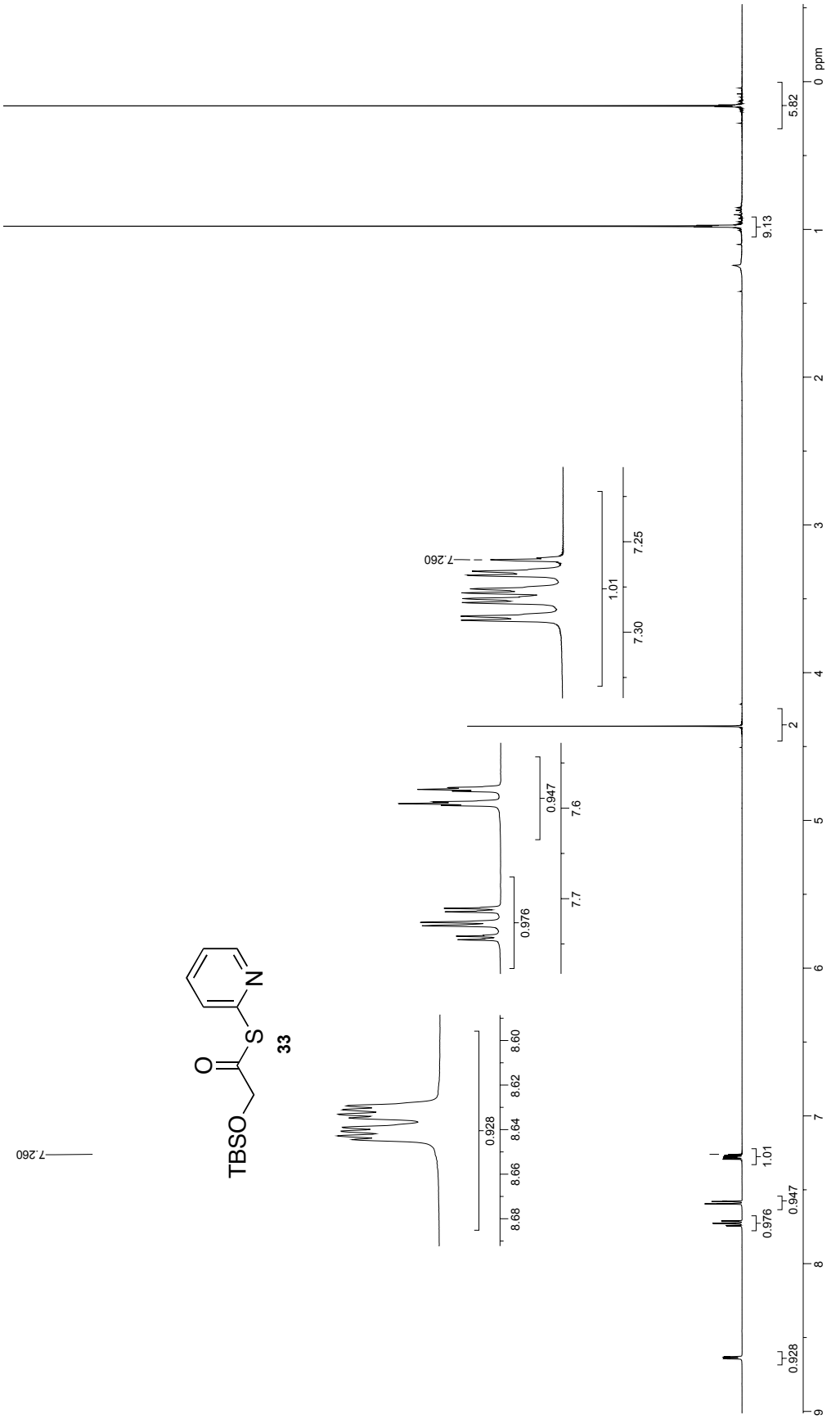
25.658
27.135
38.674
38.714
39.816
40.503
42.078
42.399
67.082
67.179
67.707
68.375
68.969
69.803
76.745
77.000
77.255
117.660
117.758
134.472
134.579
178.194
178.285
ppm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O
S
N
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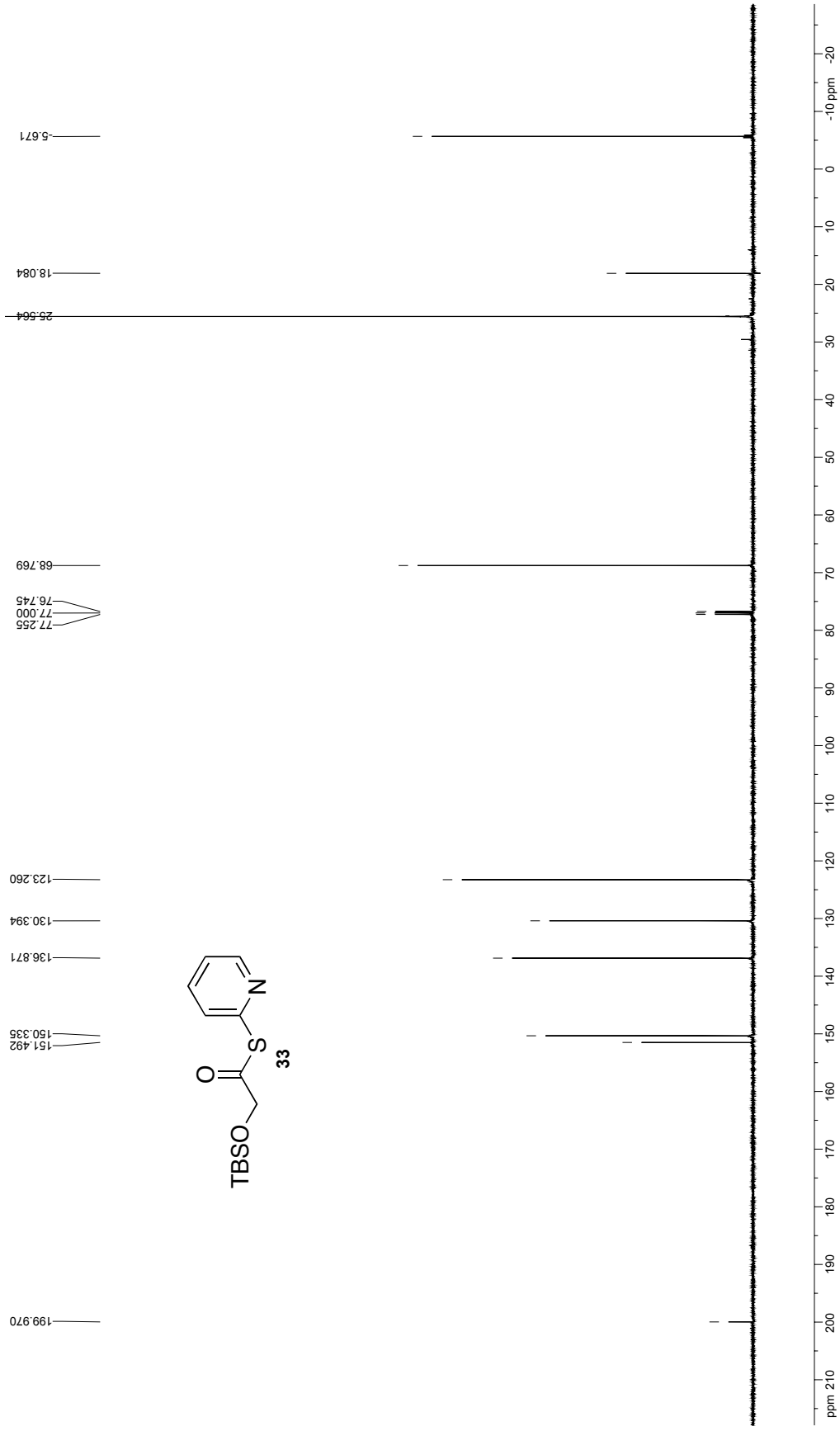
8.66
8.64
8.62
8.60
0.928
0.976
7.7
7.6
0.947
7.260
7.30
7.25
1.01
2
9.13
5.82
0.928
0.976
0.947
1.01
0 ppm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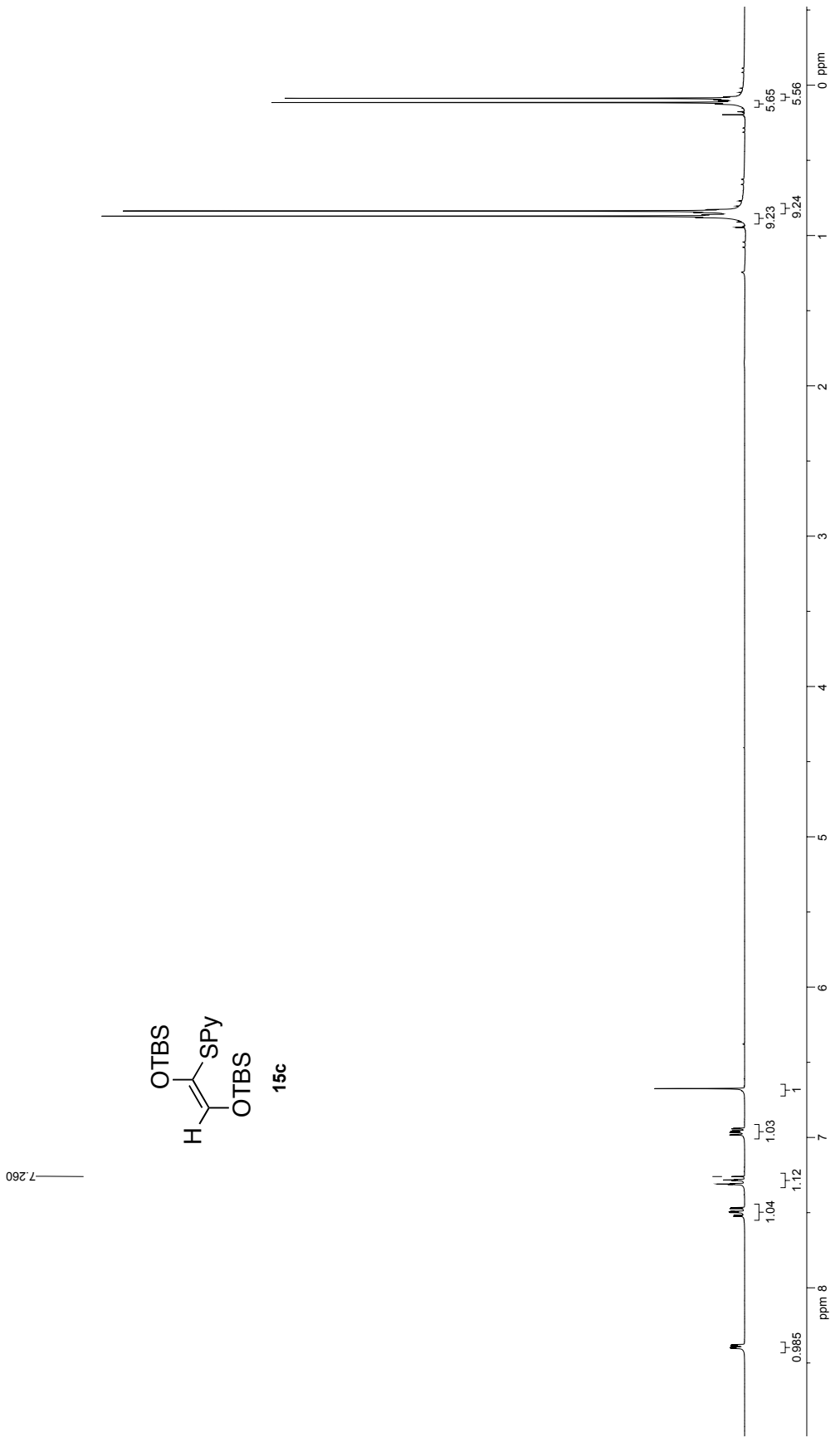
136.871
130.394
123.260
77.255
77.000
76.745
68.769
25.564
18.084
-5.671
TBSO
O
S
N
33
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10 ppm
-20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SPy
H
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9.24
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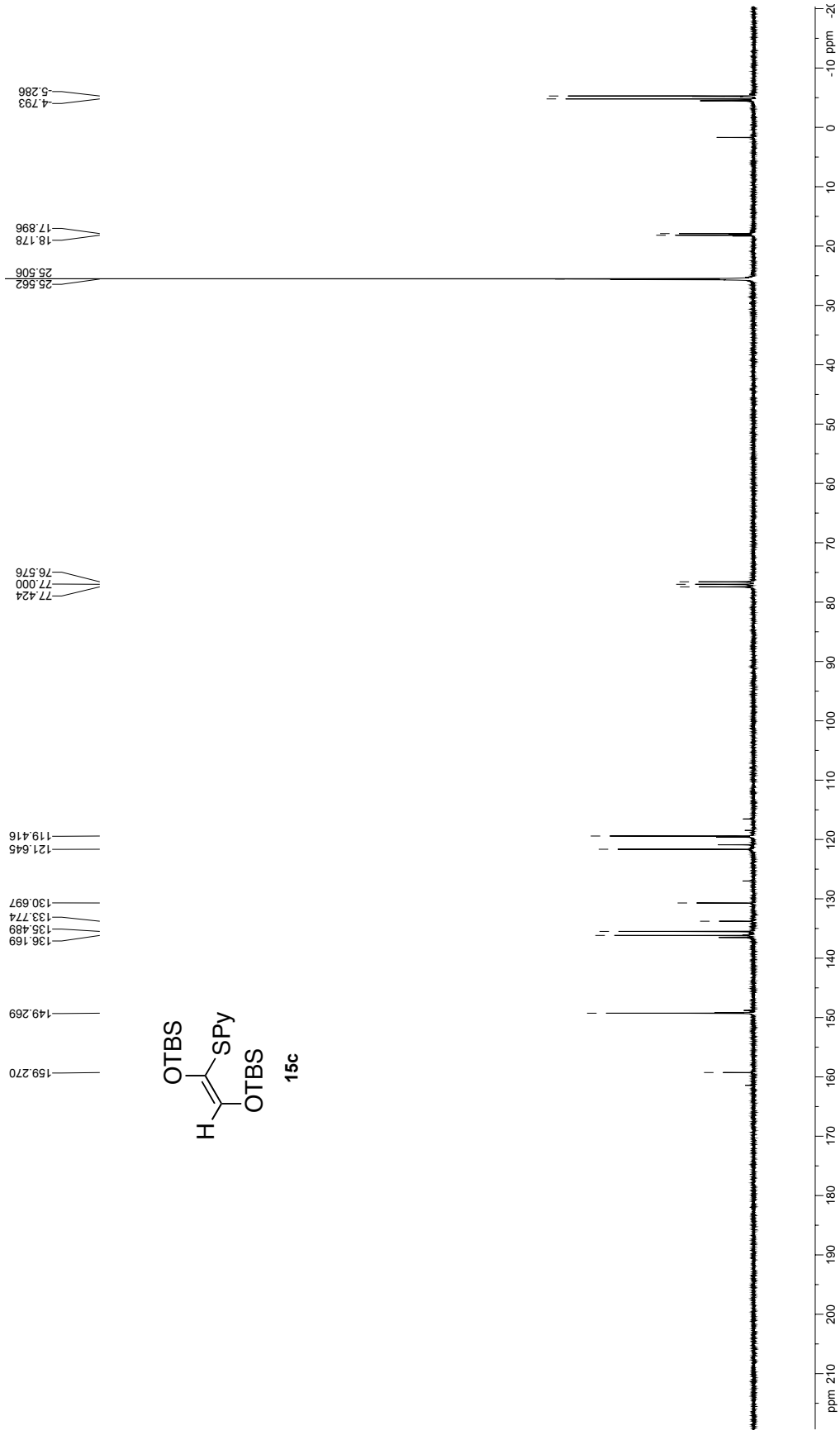
5.56
ppm 8
0 ppm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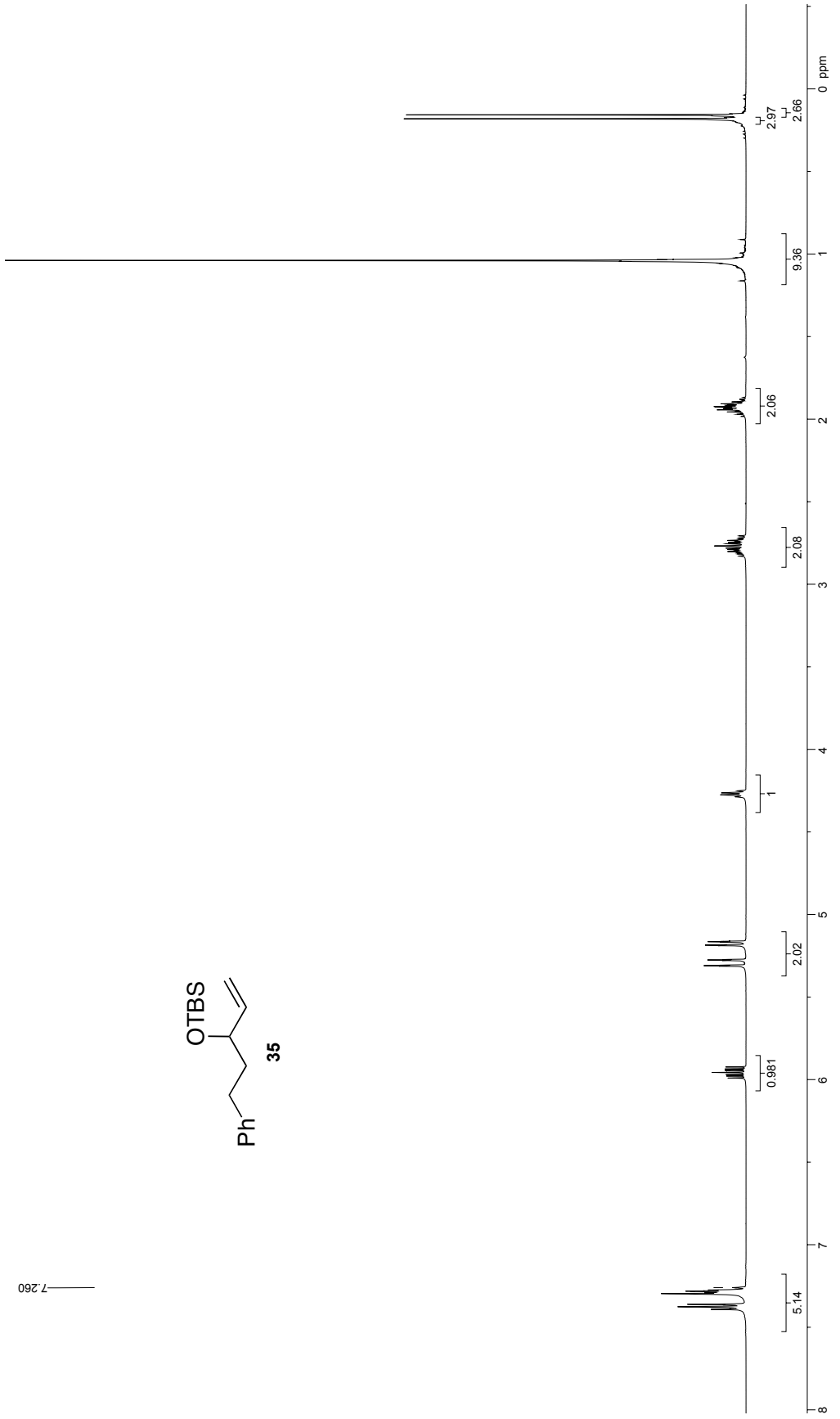
133.774
135.489
136.169
149.269
159.270
OTBS
SPy
OTBS
H
15c
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10 ppm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Ph
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2.08
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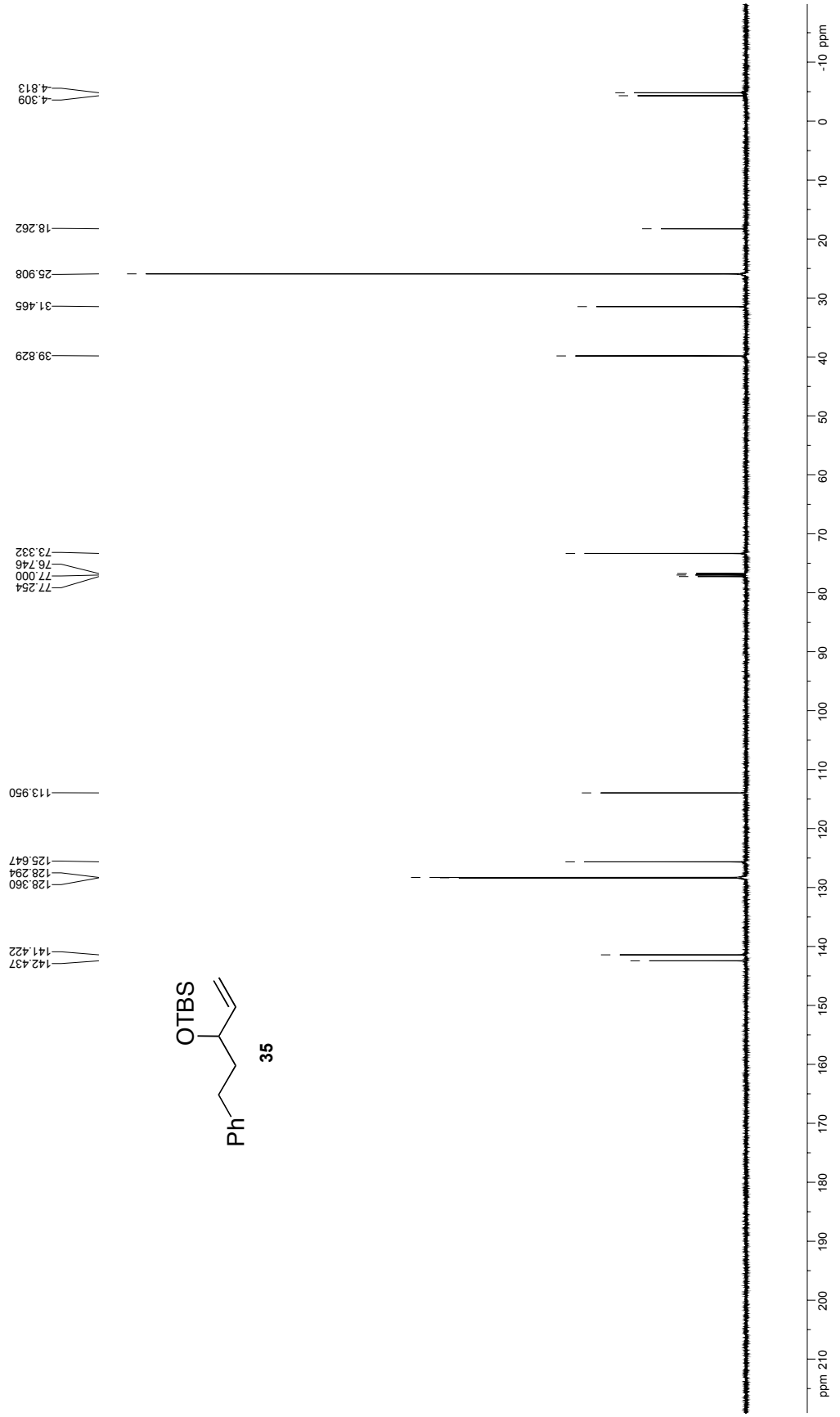
2.97
2.66
0 ppm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39.829
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76.746
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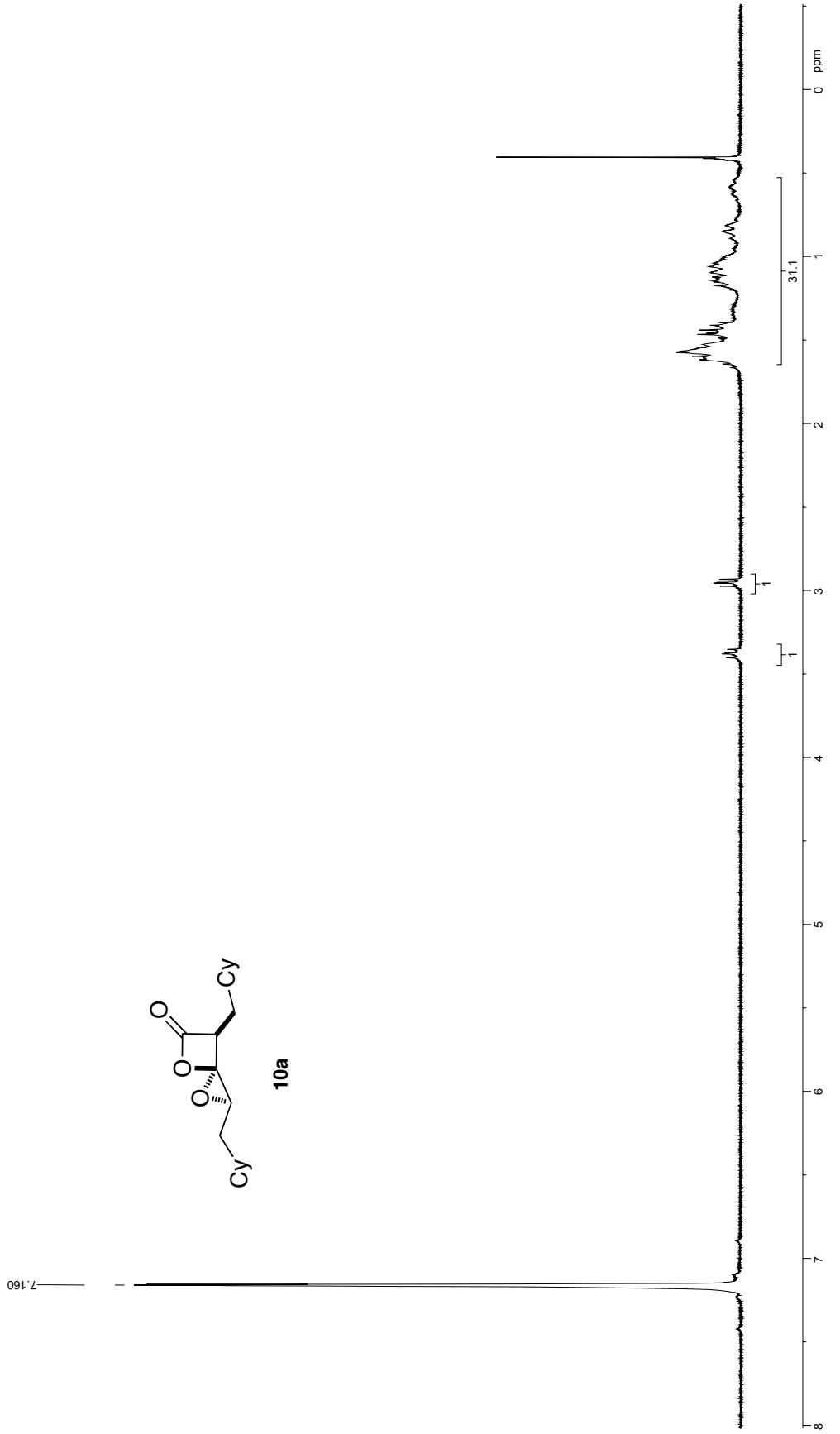
77.254
113.950
125.647
128.360
128.294
141.422
142.437
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10 ppm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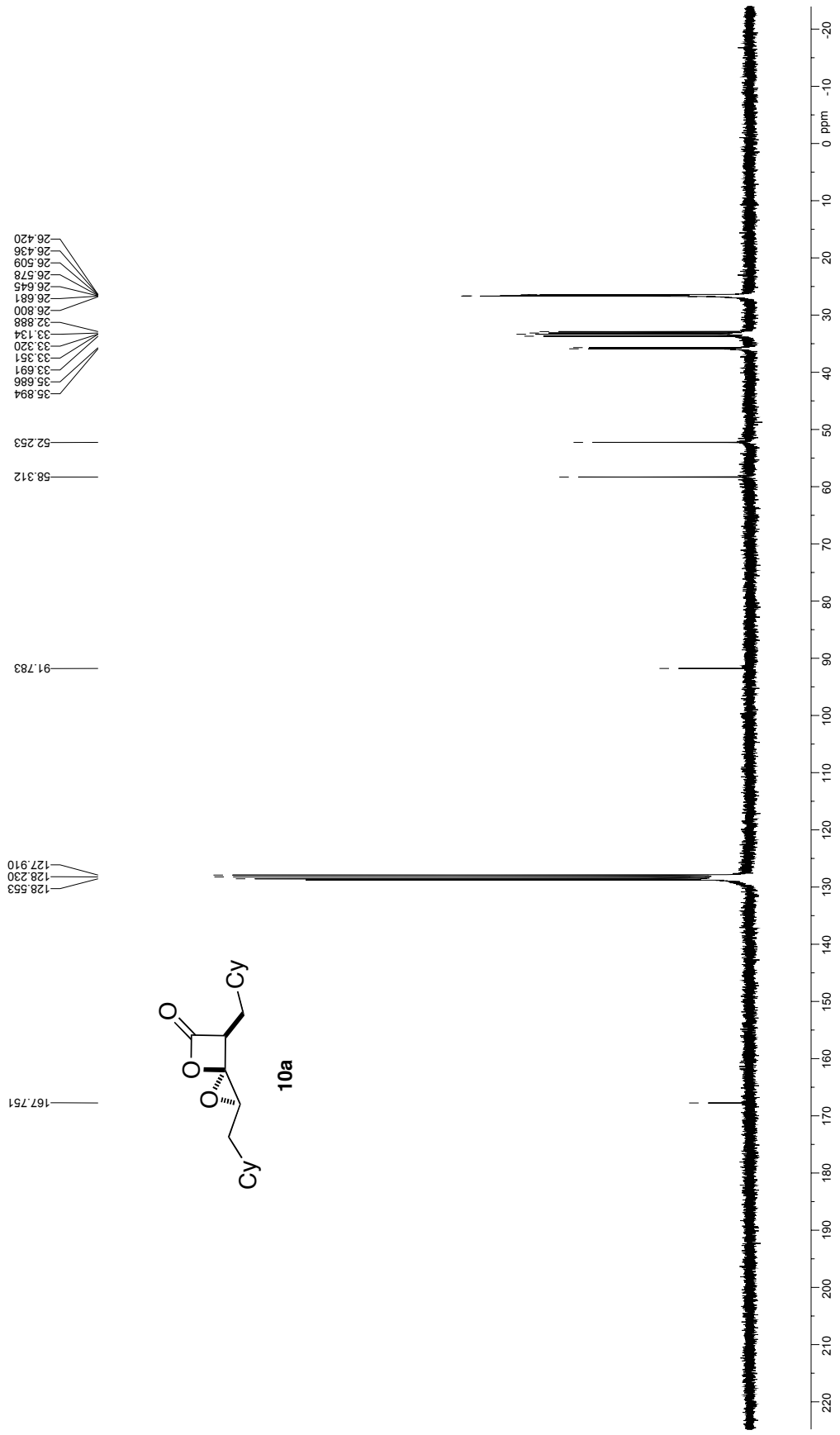
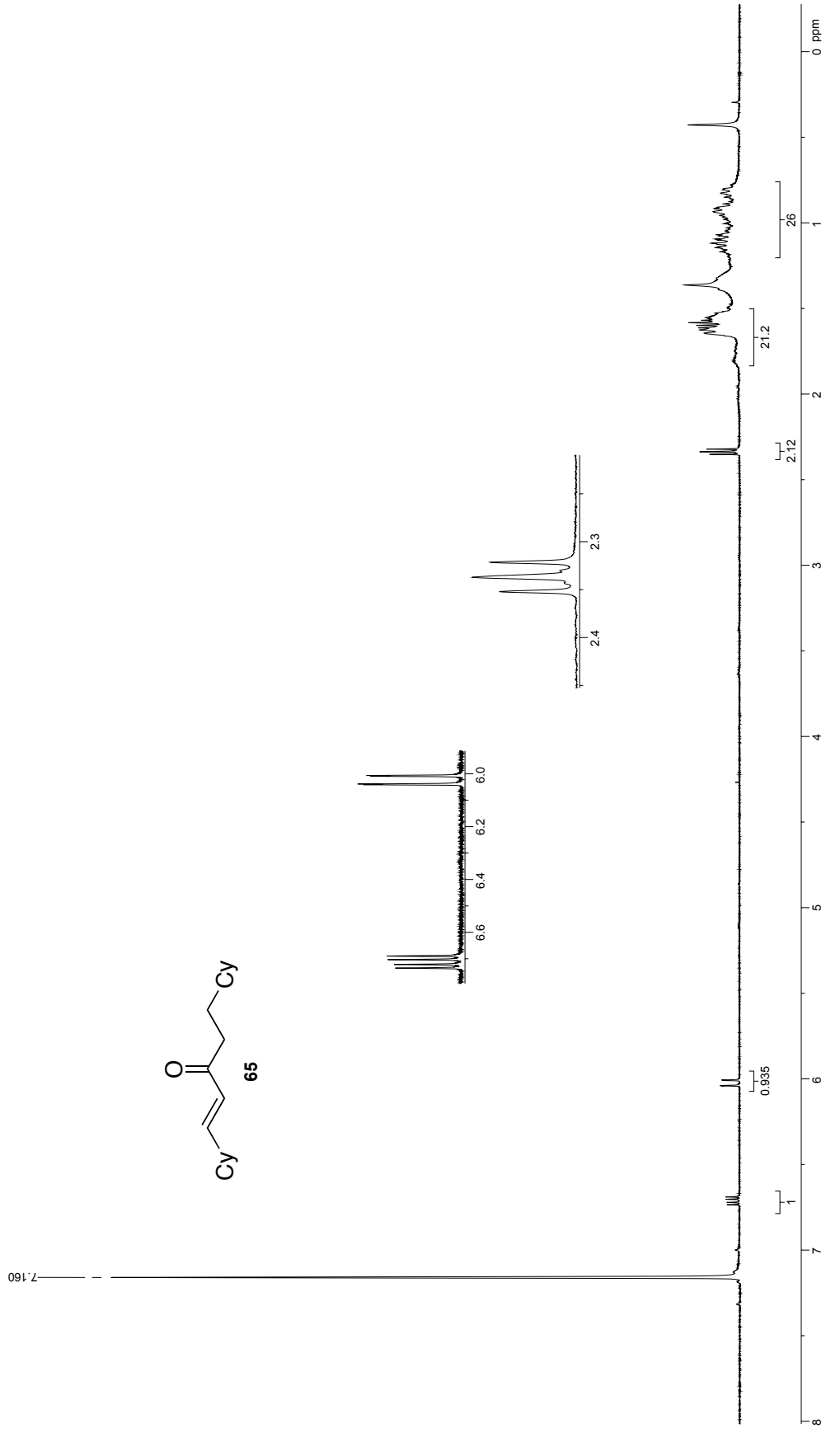
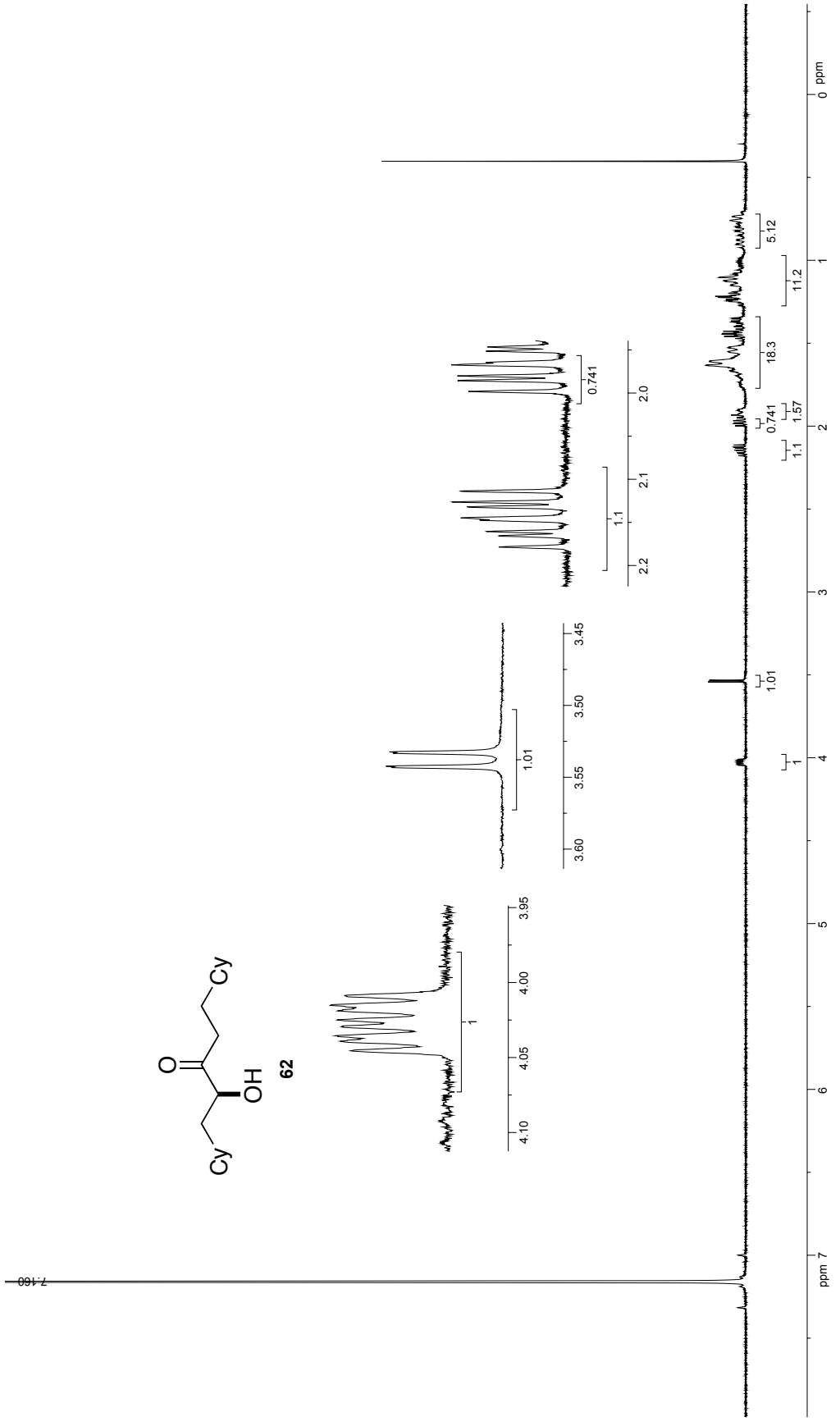
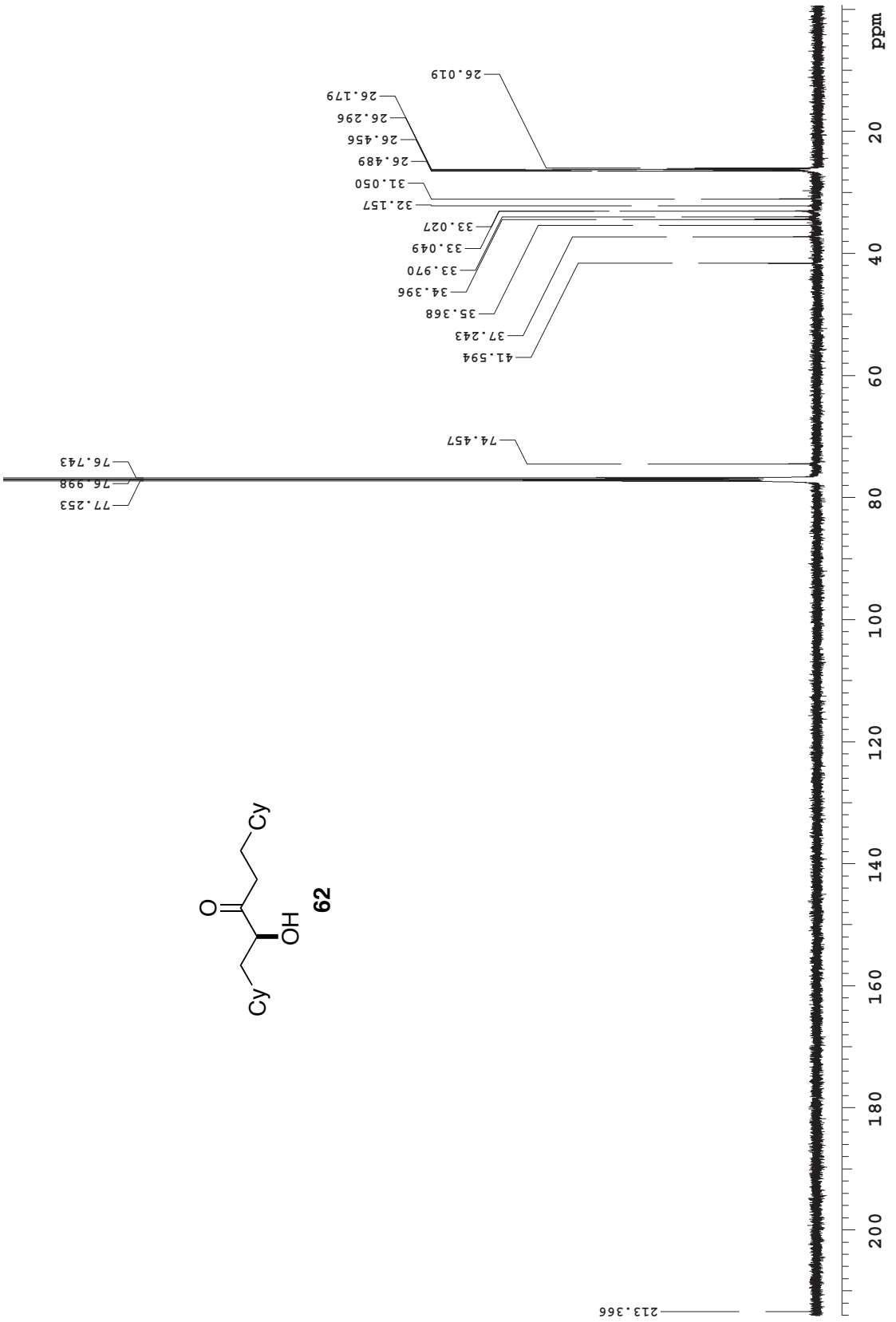
1
2
3
4
5
6
7
8
O
O
O
Cy
Cy
10a


167.751
128.553
128.230
127.910
91.783
58.312
52.263
35.894
35.686
33.691
33.351
33.320
33.134
32.888
26.800
26.681
26.645
26.578
26.509
26.436
26.420
Cy
Cy
O
O
O
10a
0 ppm

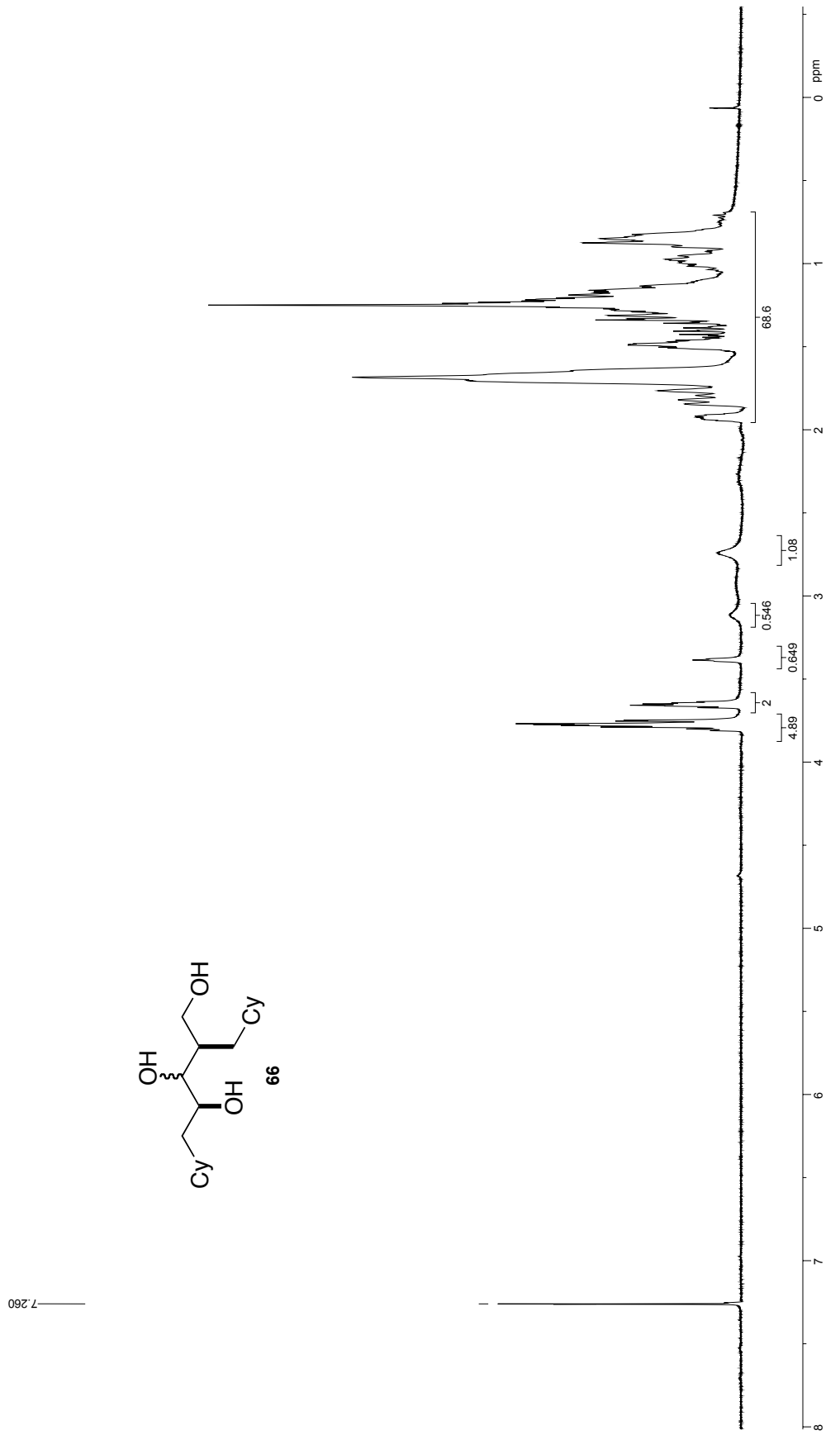

7.160
Cy
O
Cy
65
6.6
6.4
6.2
6.0
2.4
2.3
1
0.935
6
21.2
2.12
26
1
2
3
4
5
6
7
8
0 ppm

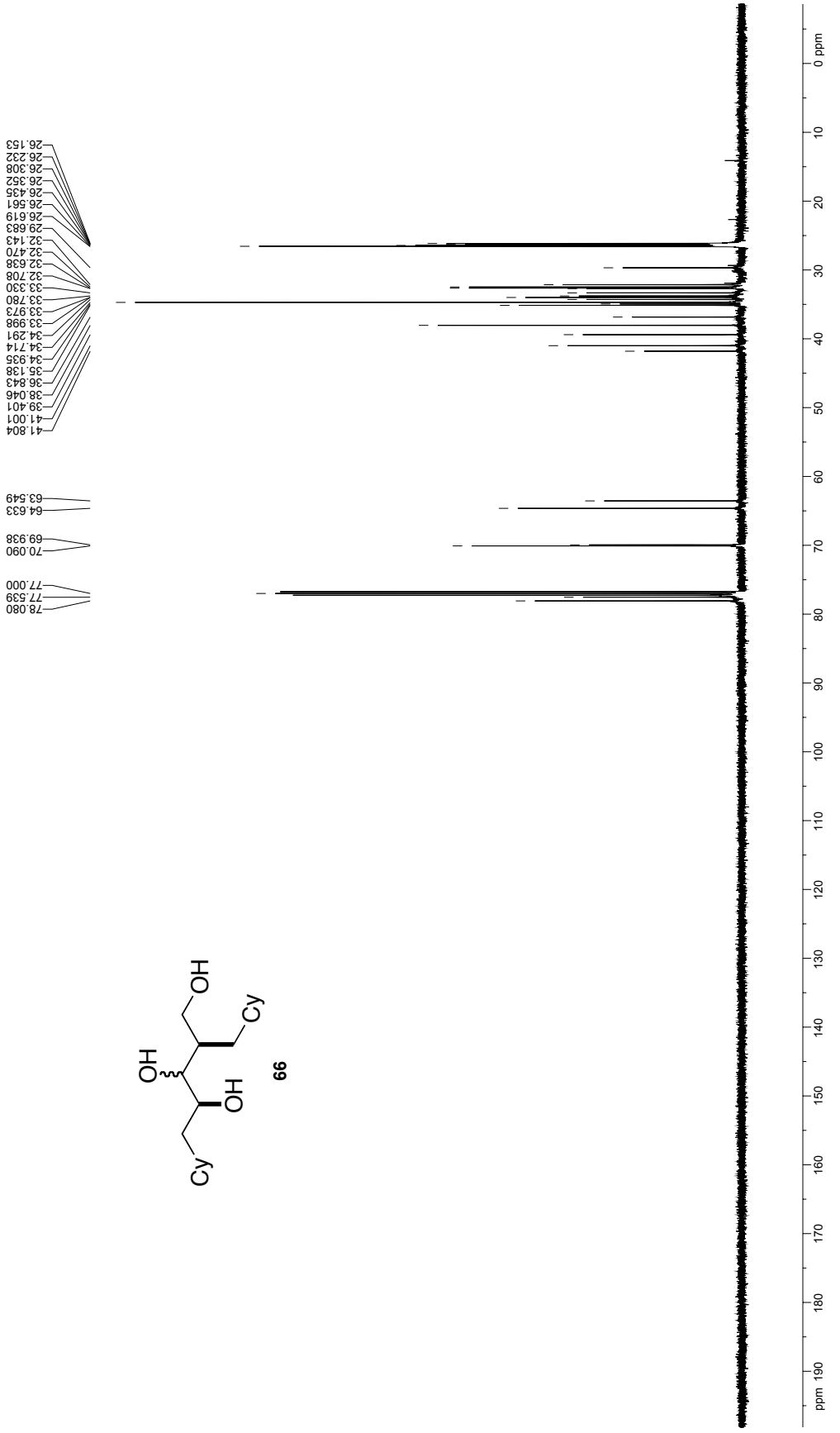

199.380
150.893
128.230
128.076
40.816
38.209
37.797
33.651
32.184
32.109
30.417
27.116
26.851
26.366
26.172
Cy
Cy
O
65
0 ppm

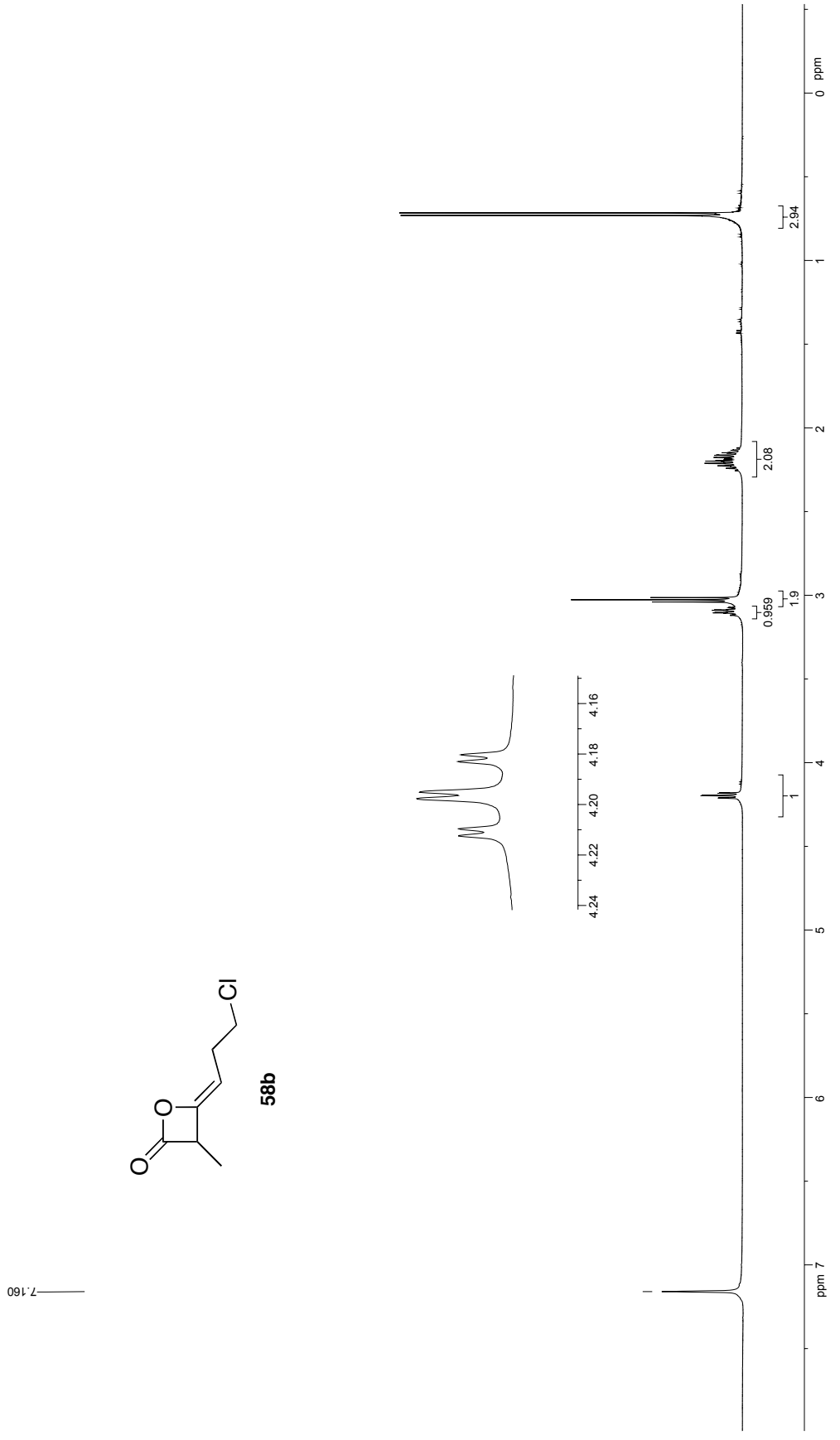

7.160
O
OH
Cy
Cy
62
ppm 7
6
5
4
3
2
1
0 ppm
1
1.01
1.1
0.741
1.57
18.3
11.2
5.12
4.10
4.05
4.00
3.95
3.60
3.55
3.50
3.45
2.2
2.1
2.0

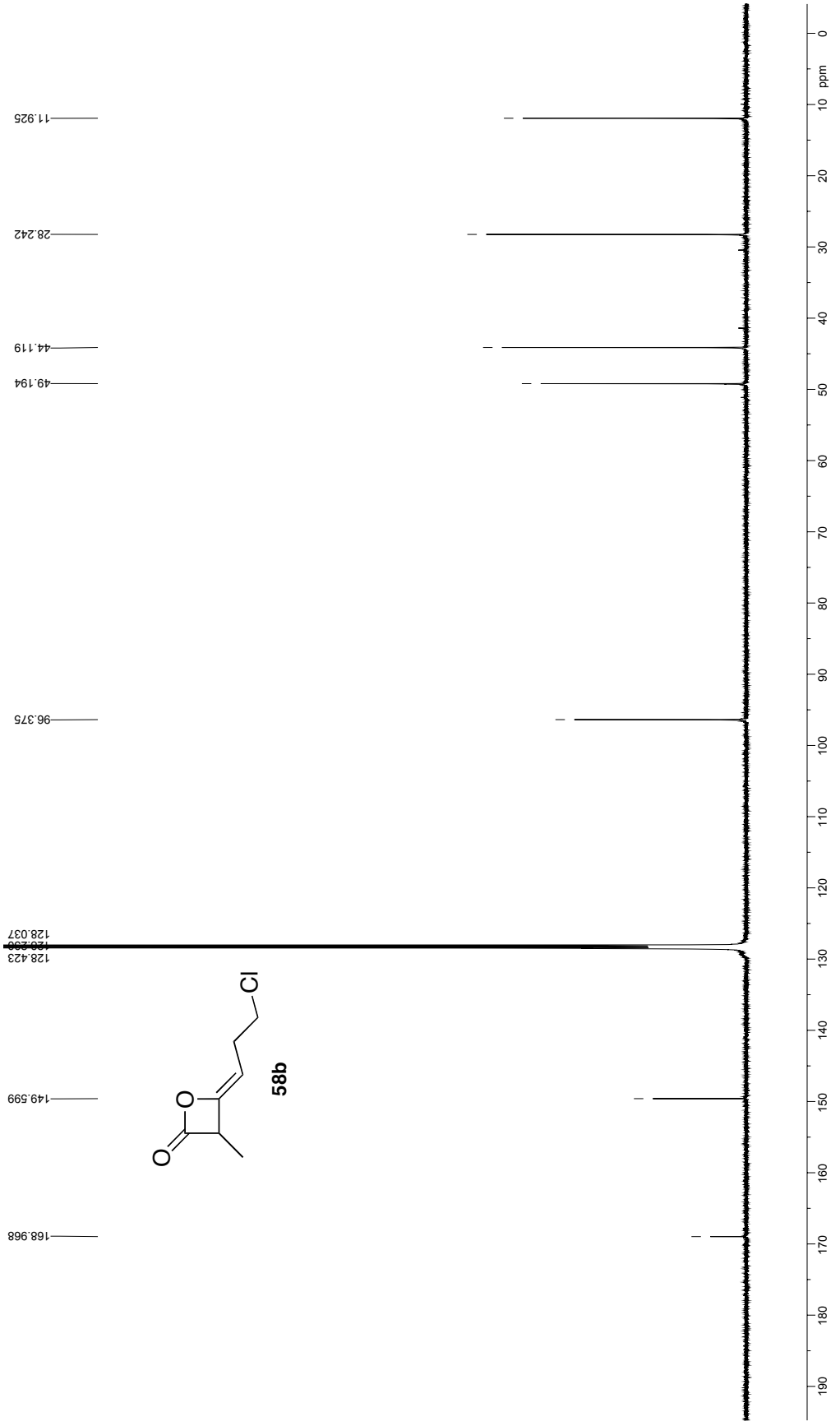

213.366
77.253
76.998
76.743
74.457
41.594
37.243
35.368
34.396
33.970
33.049
33.027
32.157
31.050
26.489
26.456
26.296
26.179
26.019
ppm
200
180
160
140
120
100
80
60
40
20
O
OH
Cy
Cy

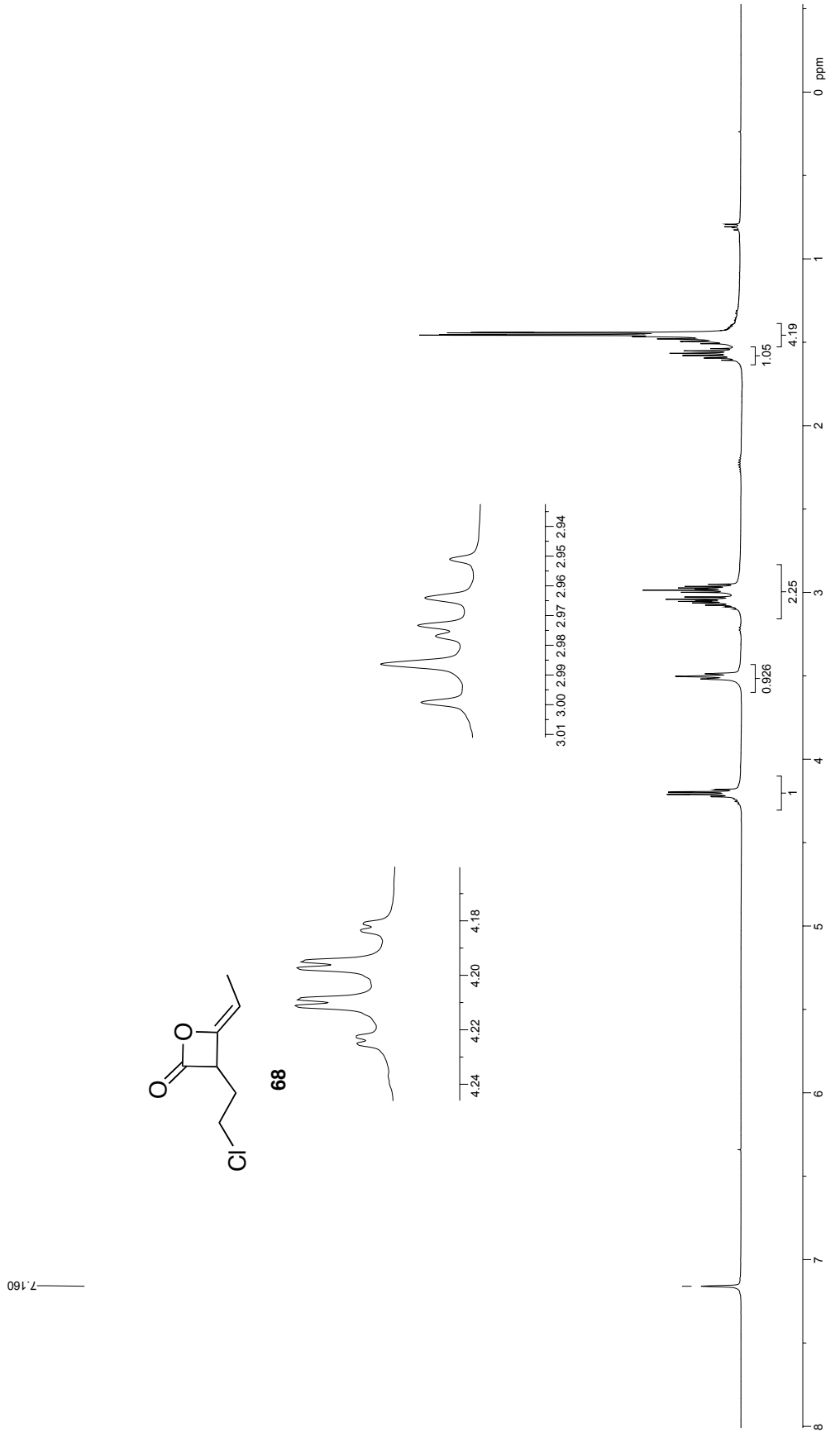
62

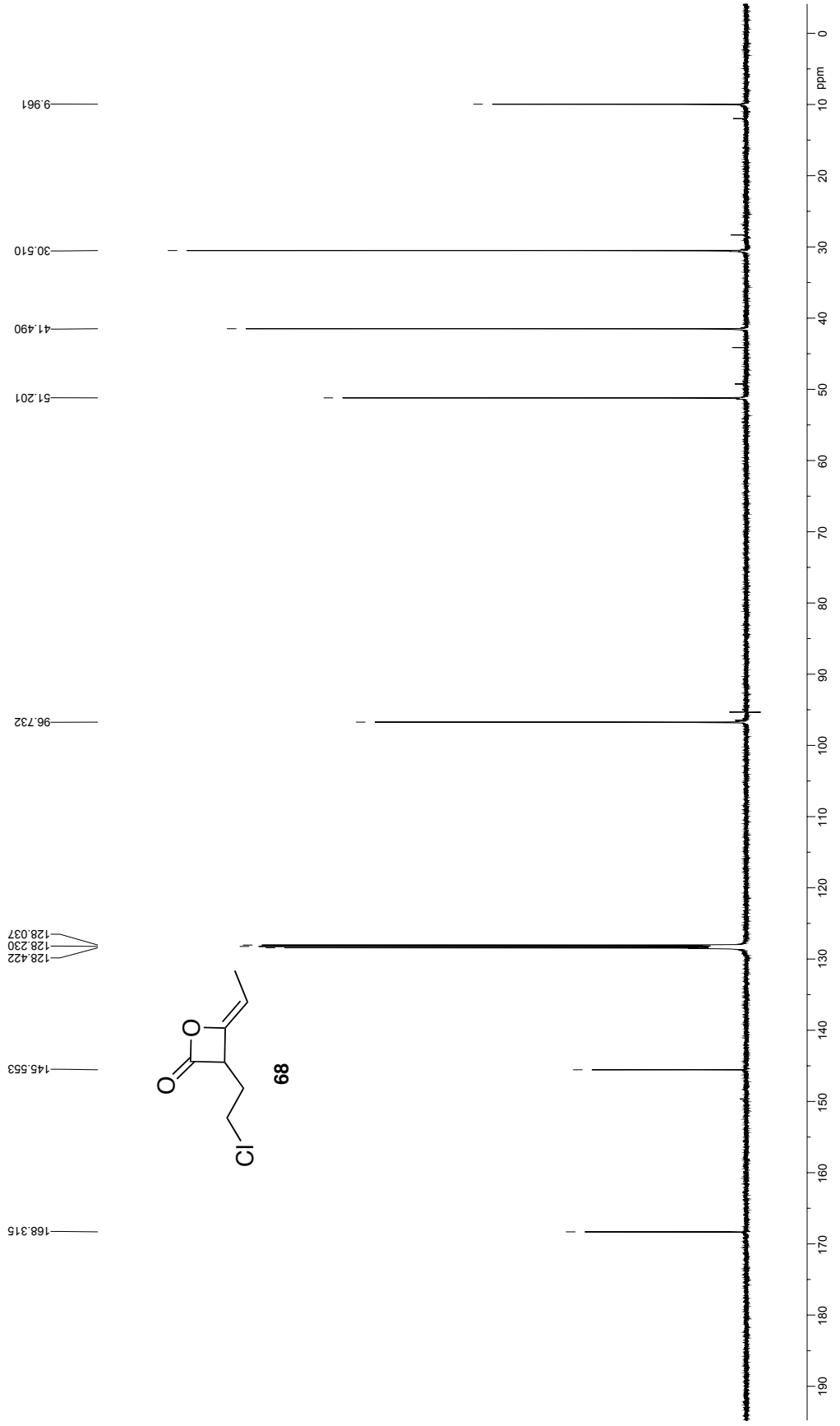

7.260
OH
OH
Cy
Cy
66
68.6
1.08
0.546
0.649
2
4.89
0 ppm
1
2
3
4
5
6
7
8

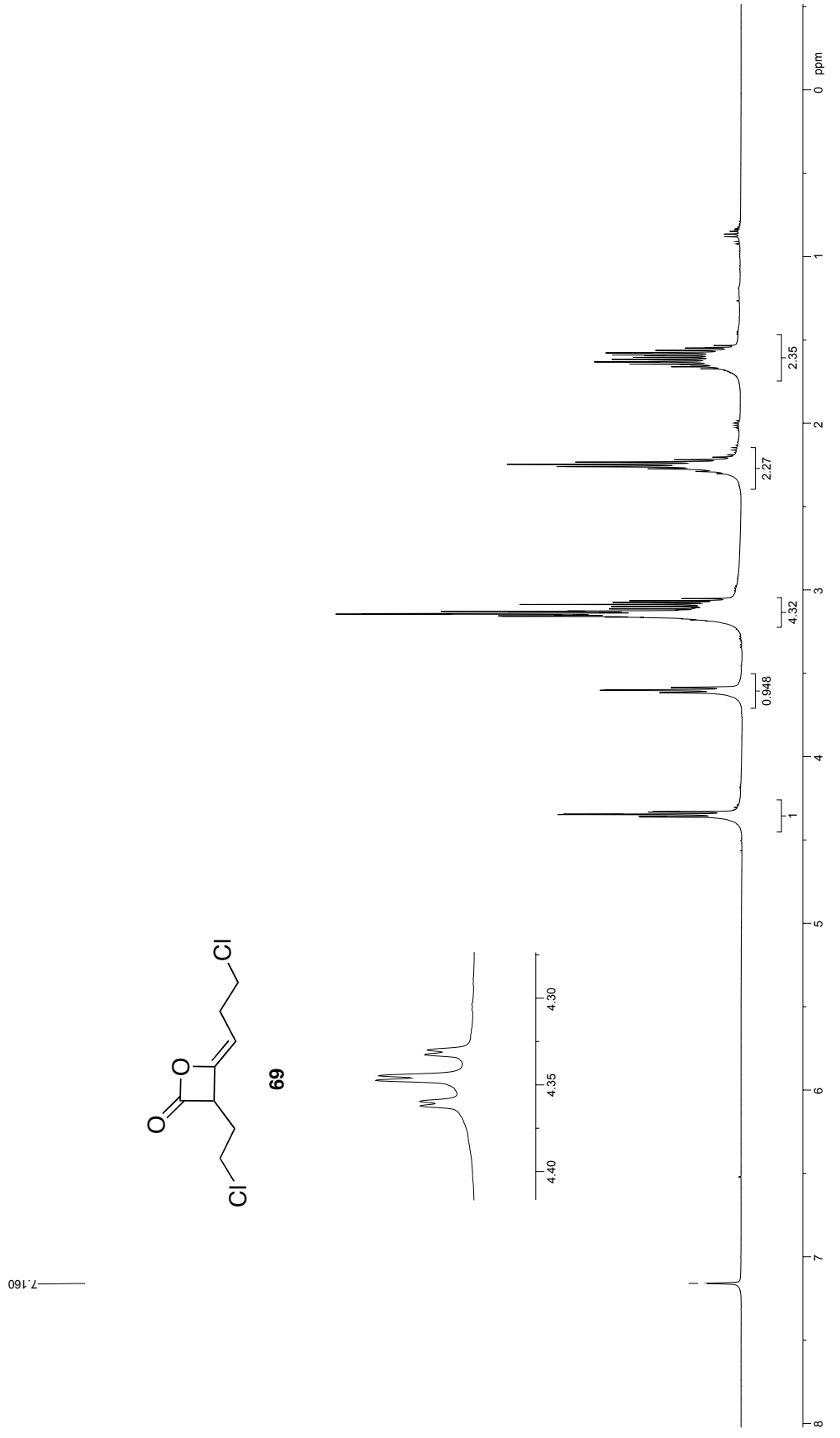

26.153
26.232
26.308
26.352
26.435
26.561
26.619
29.683
32.143
32.470
32.638
32.708
33.330
33.780
33.973
33.998
34.291
34.714
34.935
35.138
36.843
38.046
39.401
41.001
41.804
63.549
64.633
69.938
70.090
77.000
77.539
78.080
OH
OH
Cy
Cy
66
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
ppm

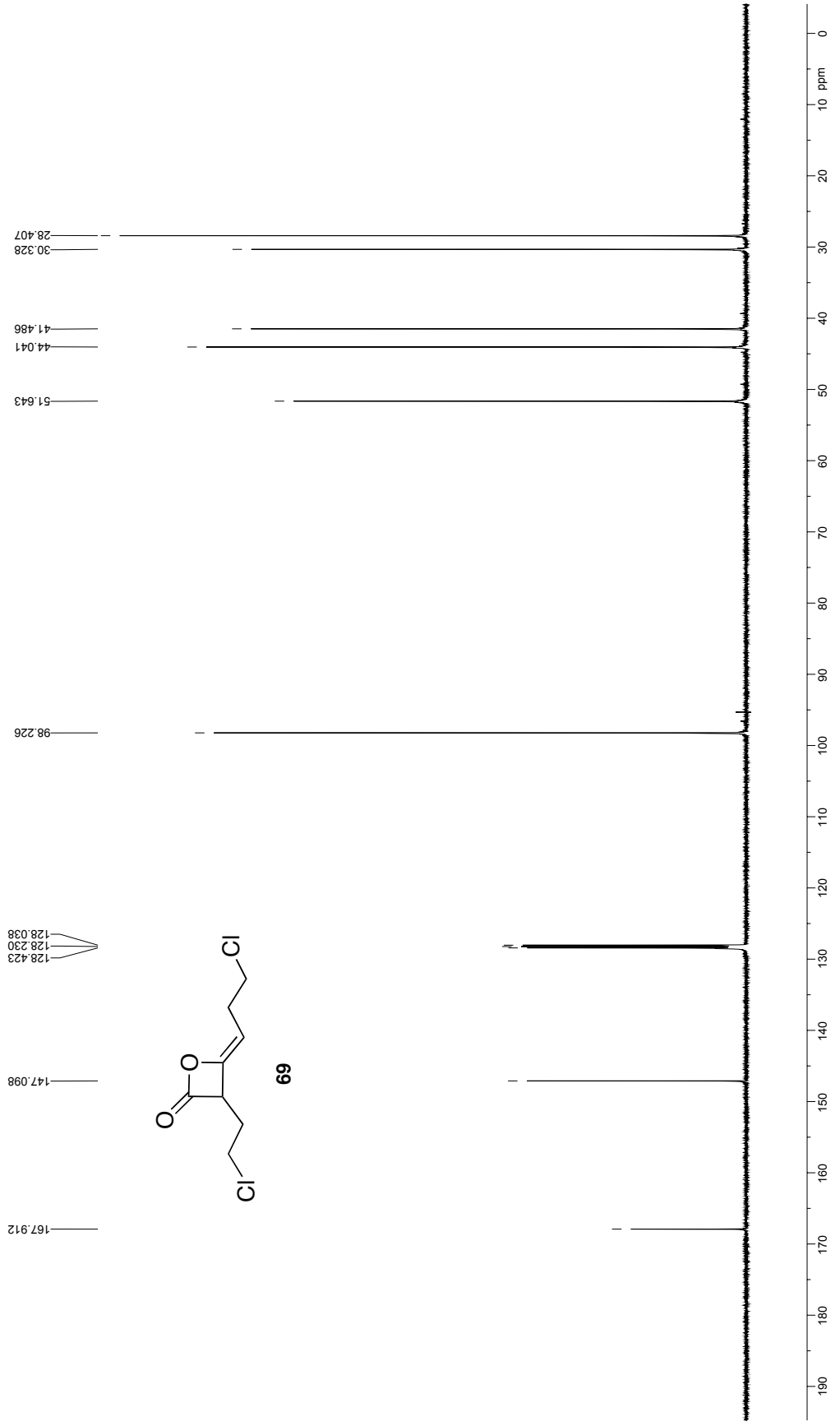

7.160
Cl
O
O
58b
4.24
4.22
4.20
4.18
4.16
0.959
1.9
2.08
1
2.94
ppm 7
6
5
4
3
2
1
0 ppm

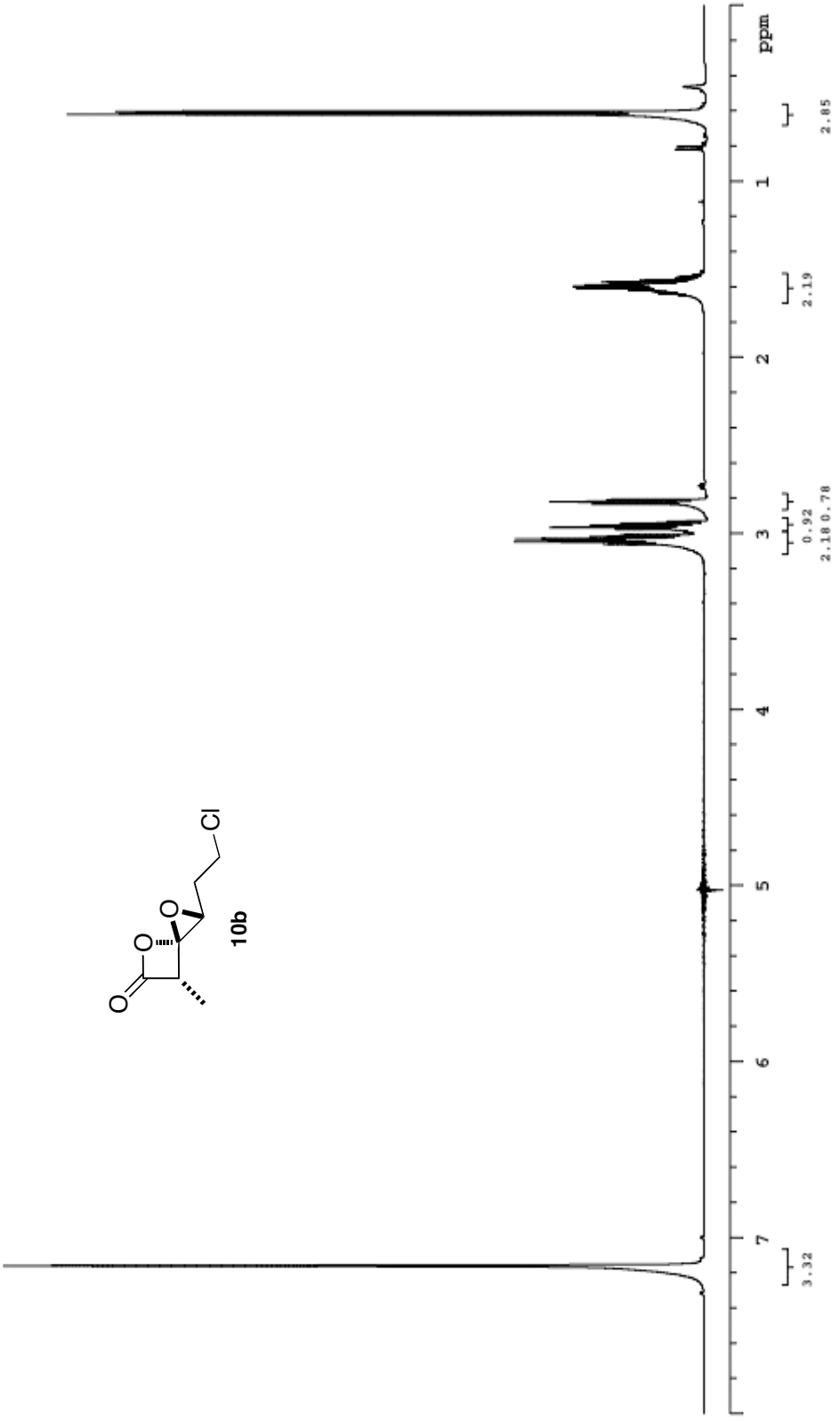

11.925
28.242
44.119
49.194
96.375
128.037
128.230
128.423
149.599
168.968
Cl
O
O
58b
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
ppm

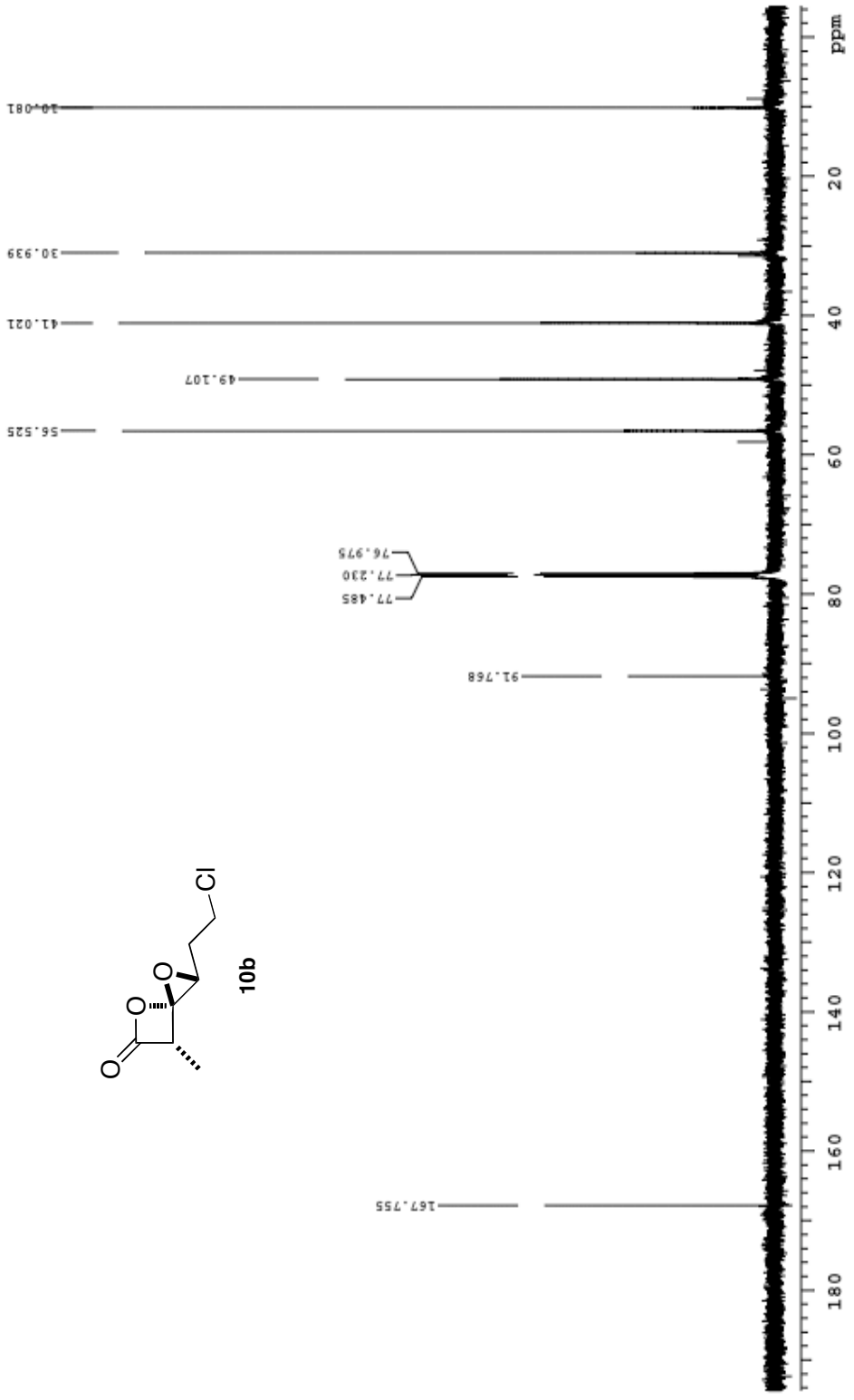

7.160
O
O
Cl
68
4.24
4.22
4.20
4.18
3.01
3.00
2.99
2.98
2.97
2.96
2.95
2.94
1
0.926
2.25
1.05
4.19
8
7
6
5
4
3
2
1
0 ppm

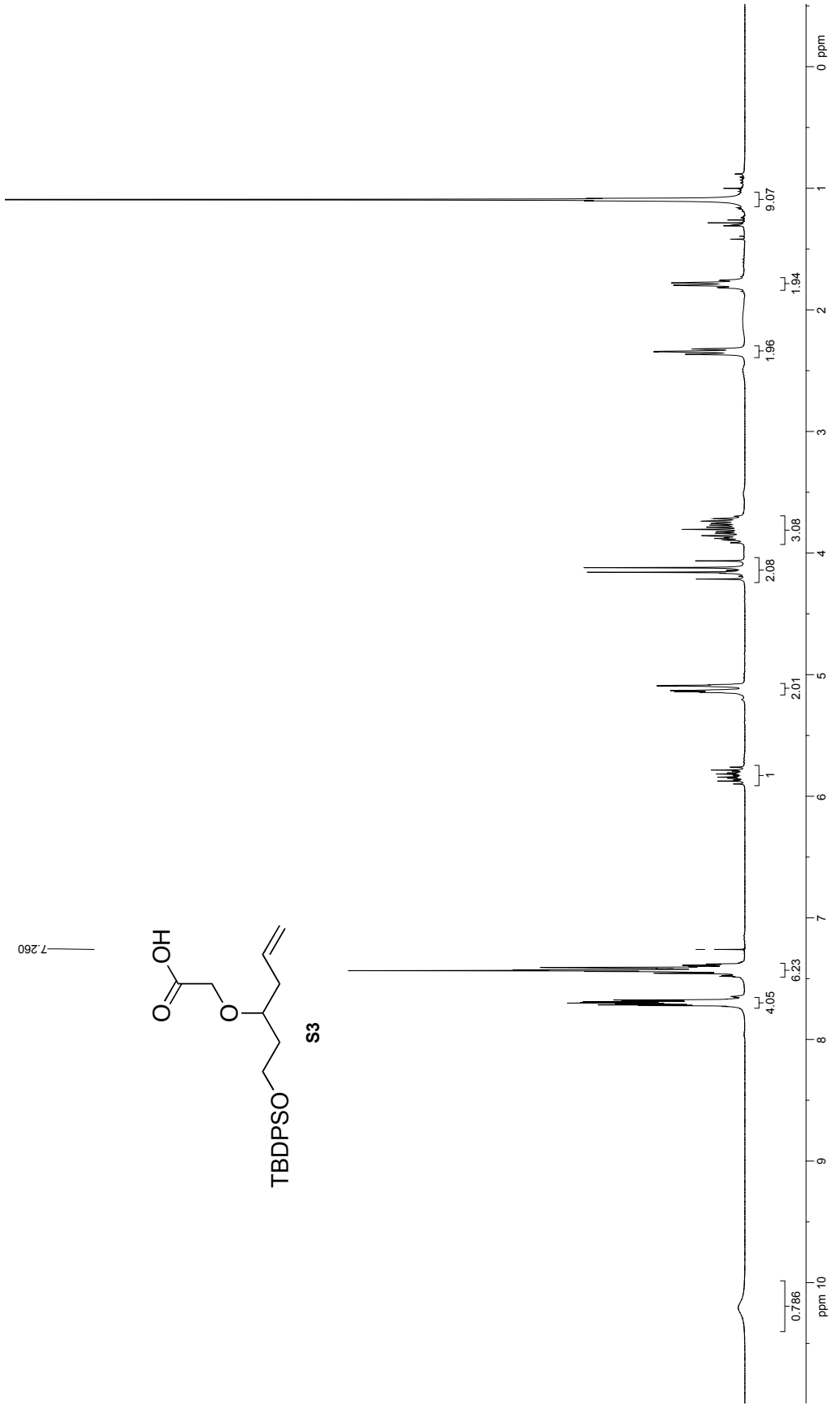

9.961
30.510
41.490
51.201
96.732
128.037
128.230
128.422
145.553
168.315
O
O
Cl
68
ppm

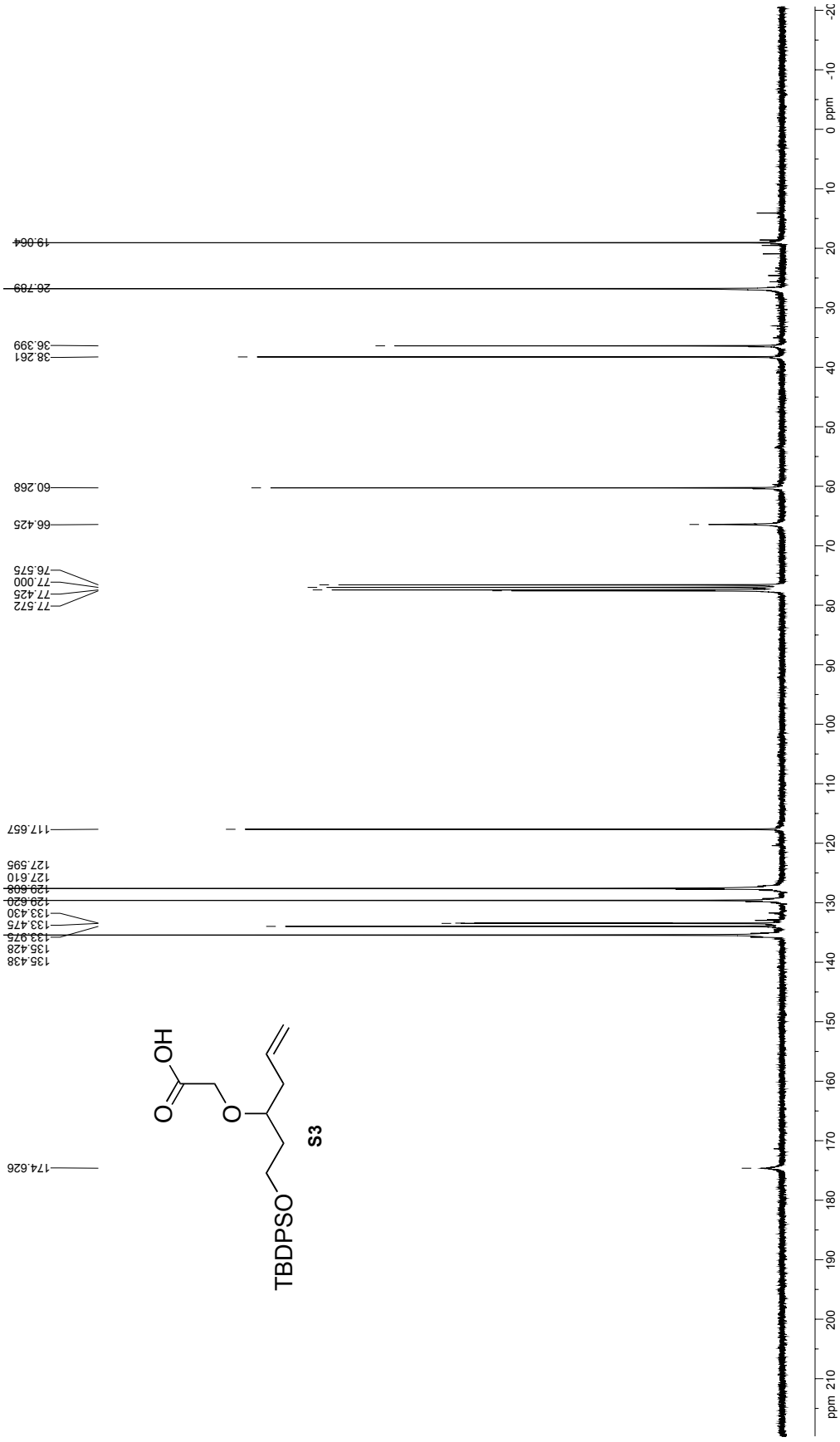

7.160
Cl
O
O
Cl
69
4.30
4.35
4.40
1
0.948
4.32
2.27
2.35
0
ppm
1
2
3
4
5
6
7
8


28.407
30.328
41.486
44.041
51.643
98.226
128.038
128.230
128.423
147.098
167.912
Cl
O
O
Cl
69
0
10 ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

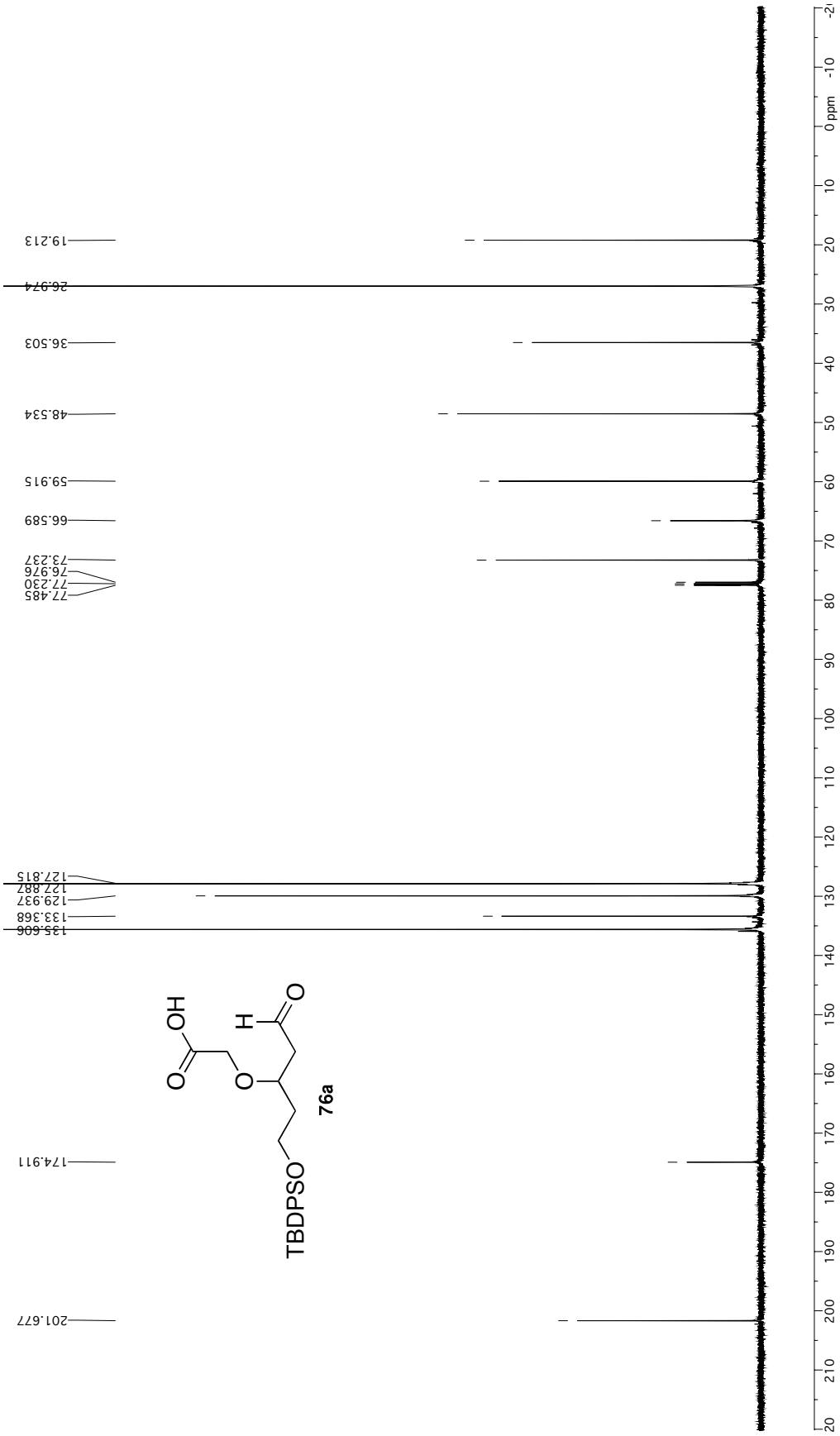

ppm
1
2
3
4
5
6
7
2.65
2.19
0.92
2.18
0.78
3.32
Cl
O
O
O
10b

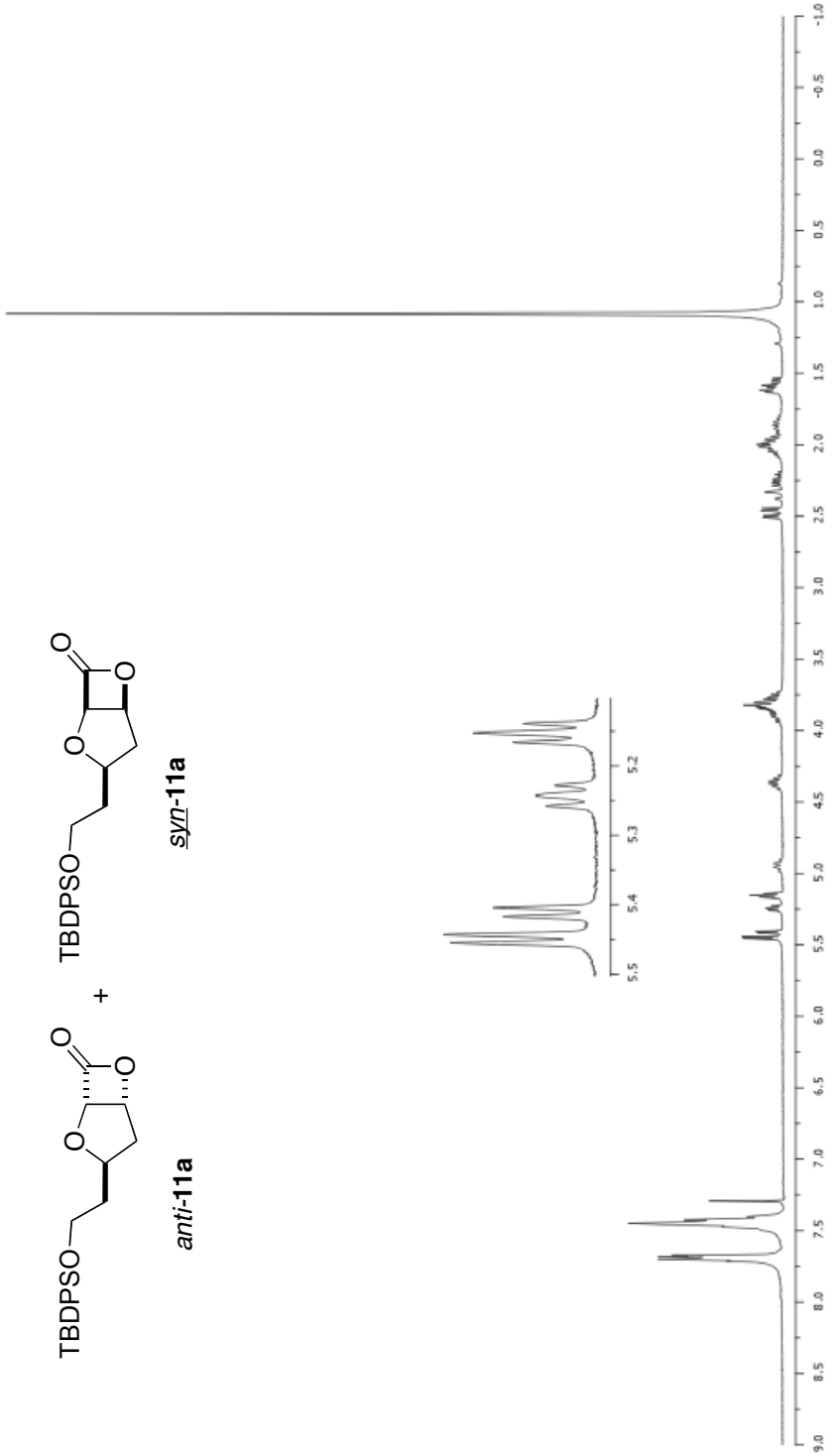

ppm
20
40
60
80
100
120
140
160
180
167.755
91.768
77.485
77.230
76.975
56.525
49.107
41.021
30.939
30.081
Cl
O
O
O
10b

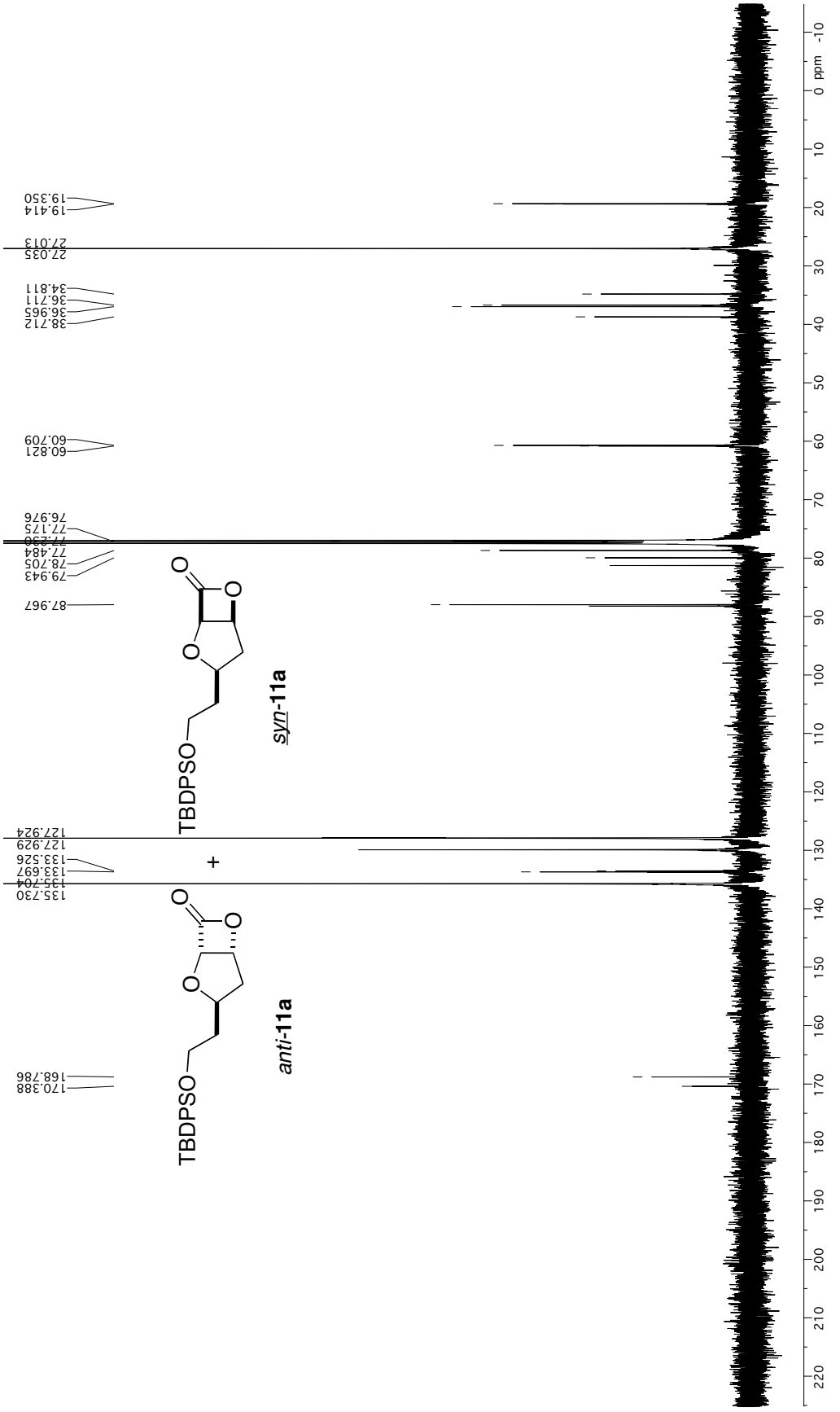

7.260
OH
O
O
TBDPSO
S3
0.786
4.05
6.23
1
2.01
2.08
3.08
1.96
1.94
9.07
ppm 10
9
8
7
6
5
4
3
2
1
0 ppm

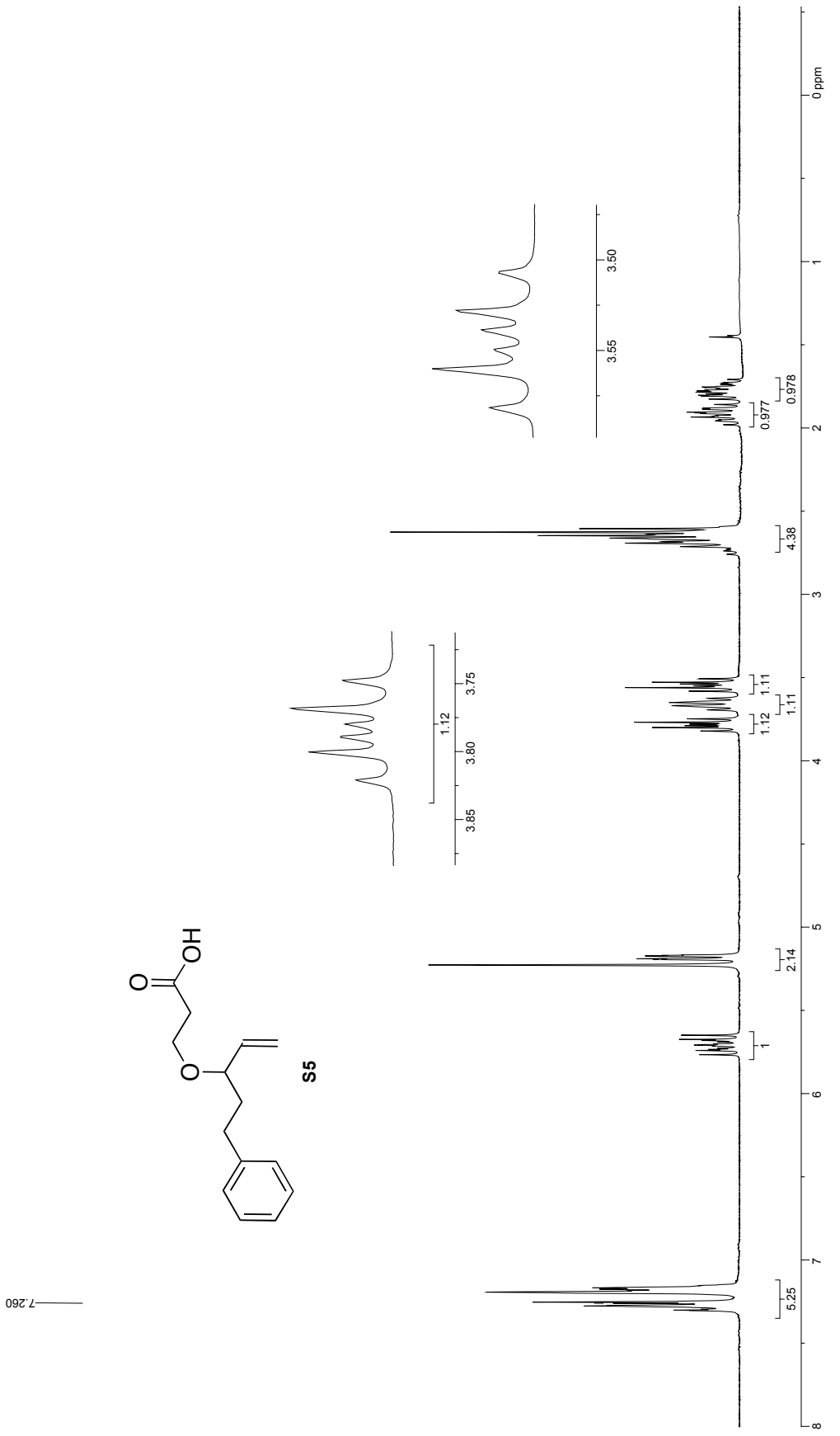

19.064
26.709
36.399
38.261
60.268
66.425
76.575
77.000
77.425
77.572
117.657
127.595
127.610
128.608
128.620
133.430
133.475
133.975
135.428
135.438
174.626
TBDPSO
O
O
OH
S3
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm
-10
-20

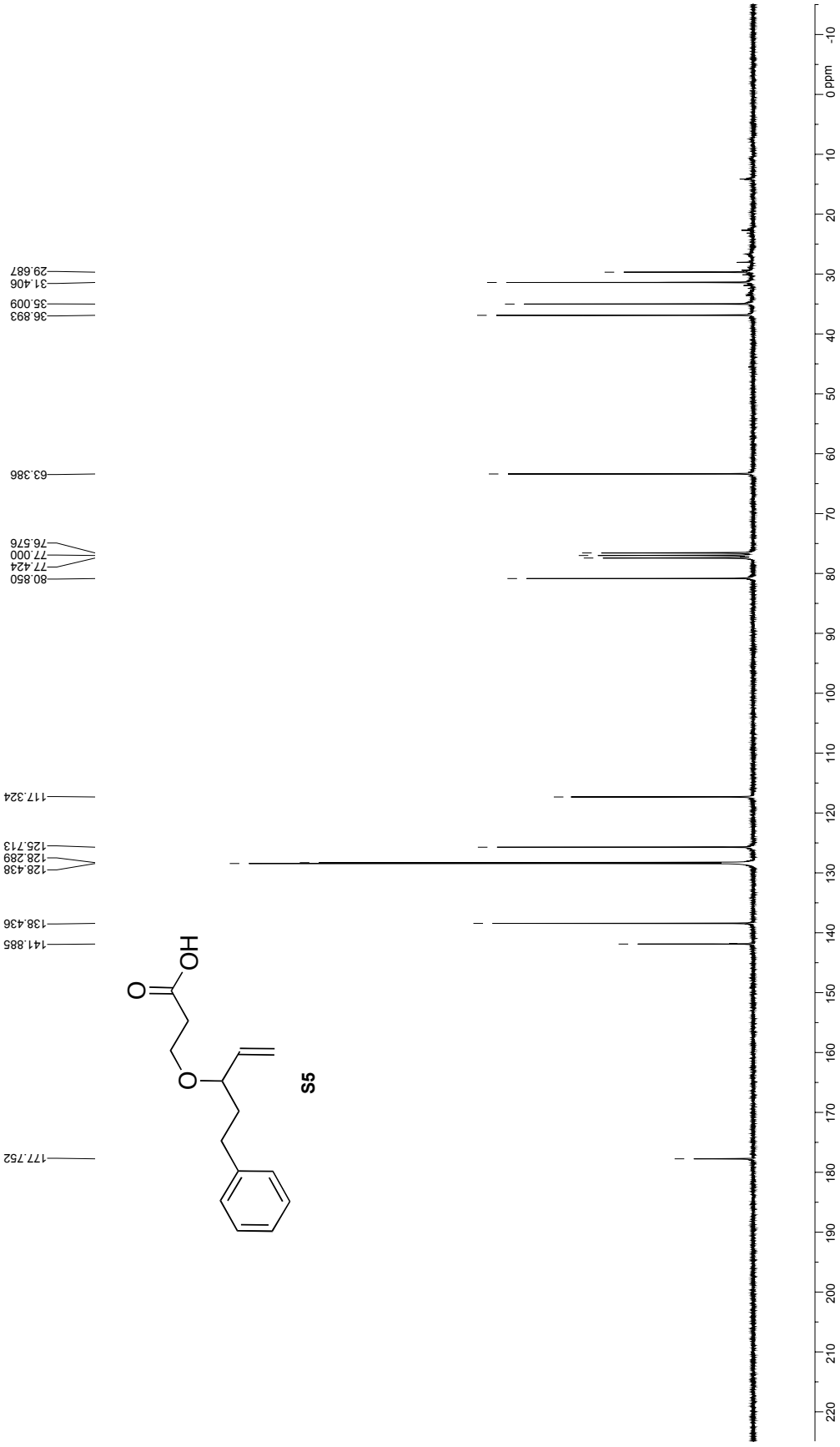

1.096
7.260
9.4
2.46
1.04
2.41
3.23
6.61
4.58
0.97
0.862
ppm 11
10
9
8
7
6
5
4
3
2
1
0 ppm
TBDPSO
O
O
O
OH
H
O
76a

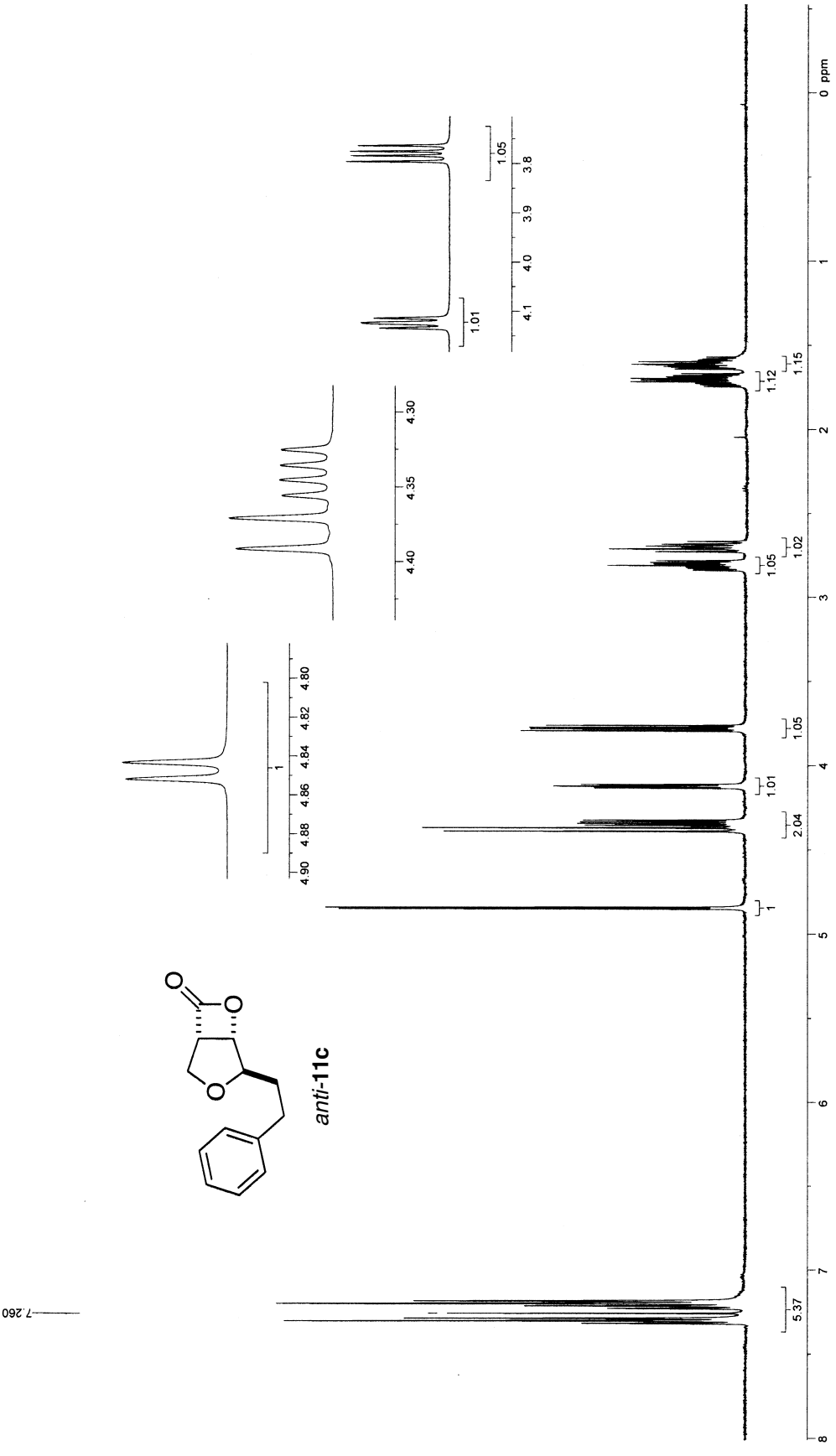

201.677
174.911
135.606
133.368
129.937
127.887
127.815
77.485
77.230
76.976
73.237
66.589
59.915
48.534
36.503
26.974
19.213
TBDPSO
O
O
O
H
OH
76a
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm
-10

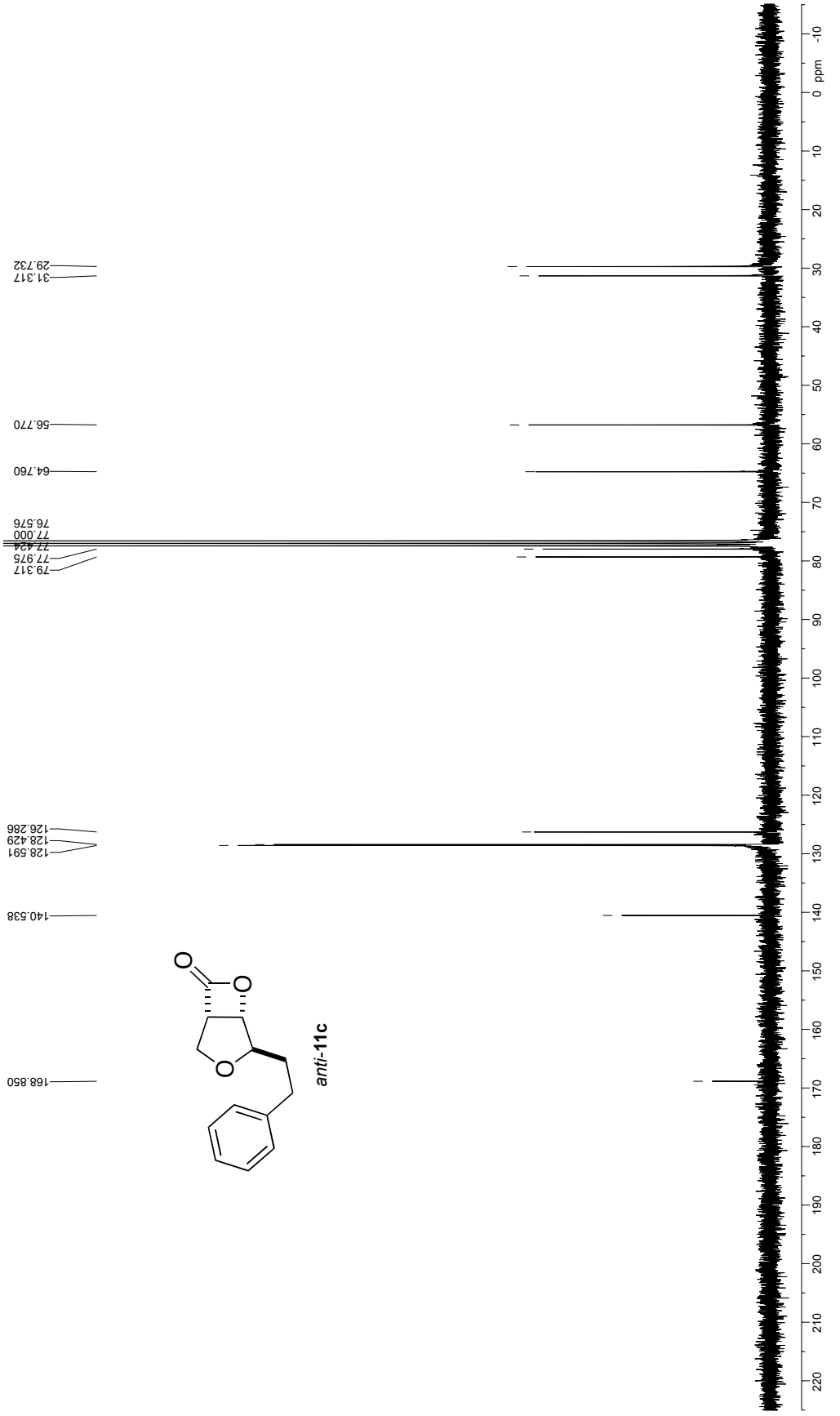

TBDPSO
O
O
O
syn-11a
+
TBDPSO
O
O
O
anti-11a

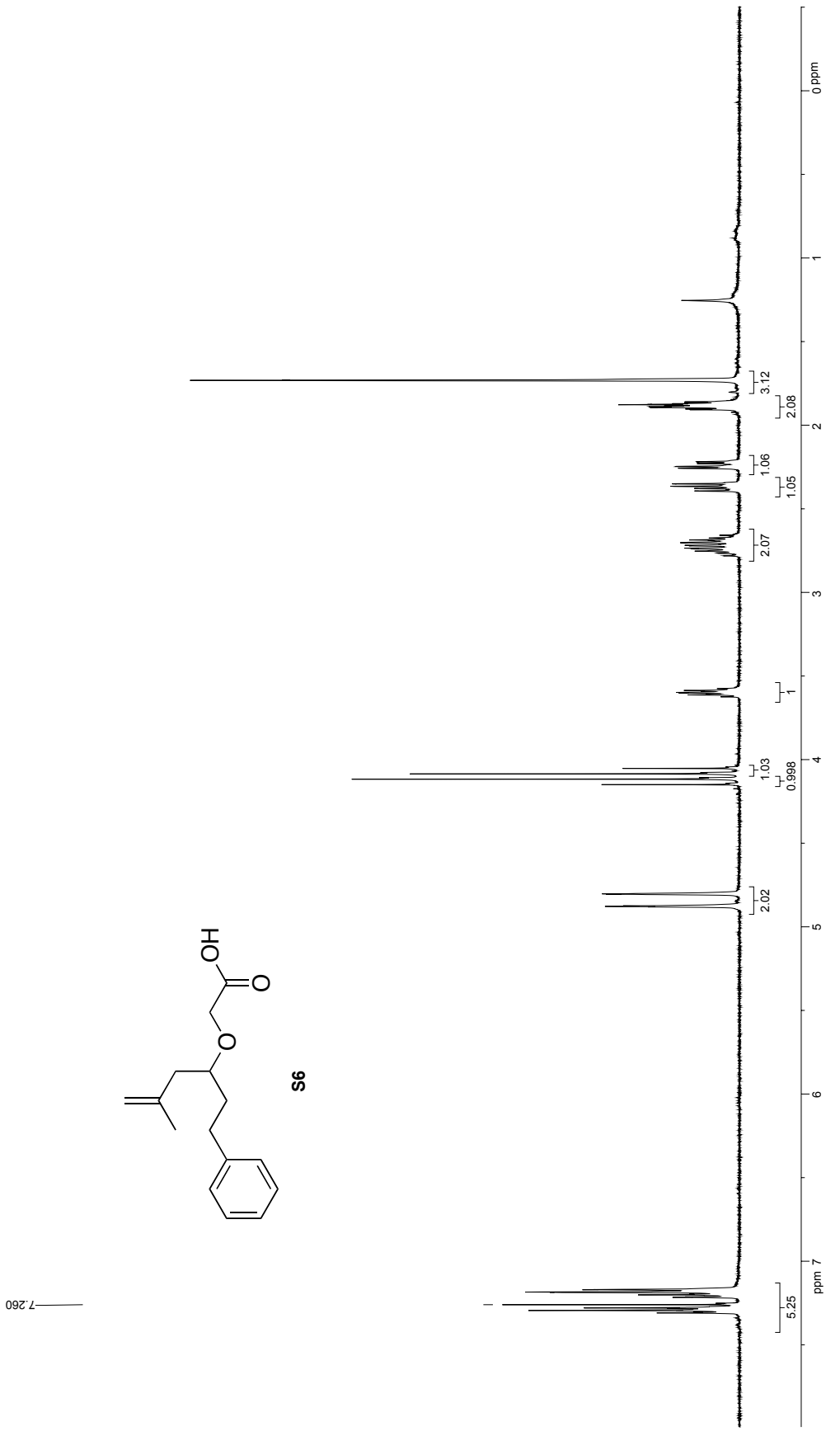

TBDPSO
anti-11a
+
TBDPSO
syn-11a
170.388
168.786
135.730
135.704
133.697
133.526
127.929
127.924
87.967
79.943
78.705
77.484
77.230
77.175
76.976
60.821
60.709
38.712
36.965
36.711
34.811
27.035
27.013
19.414
19.350
0 ppm

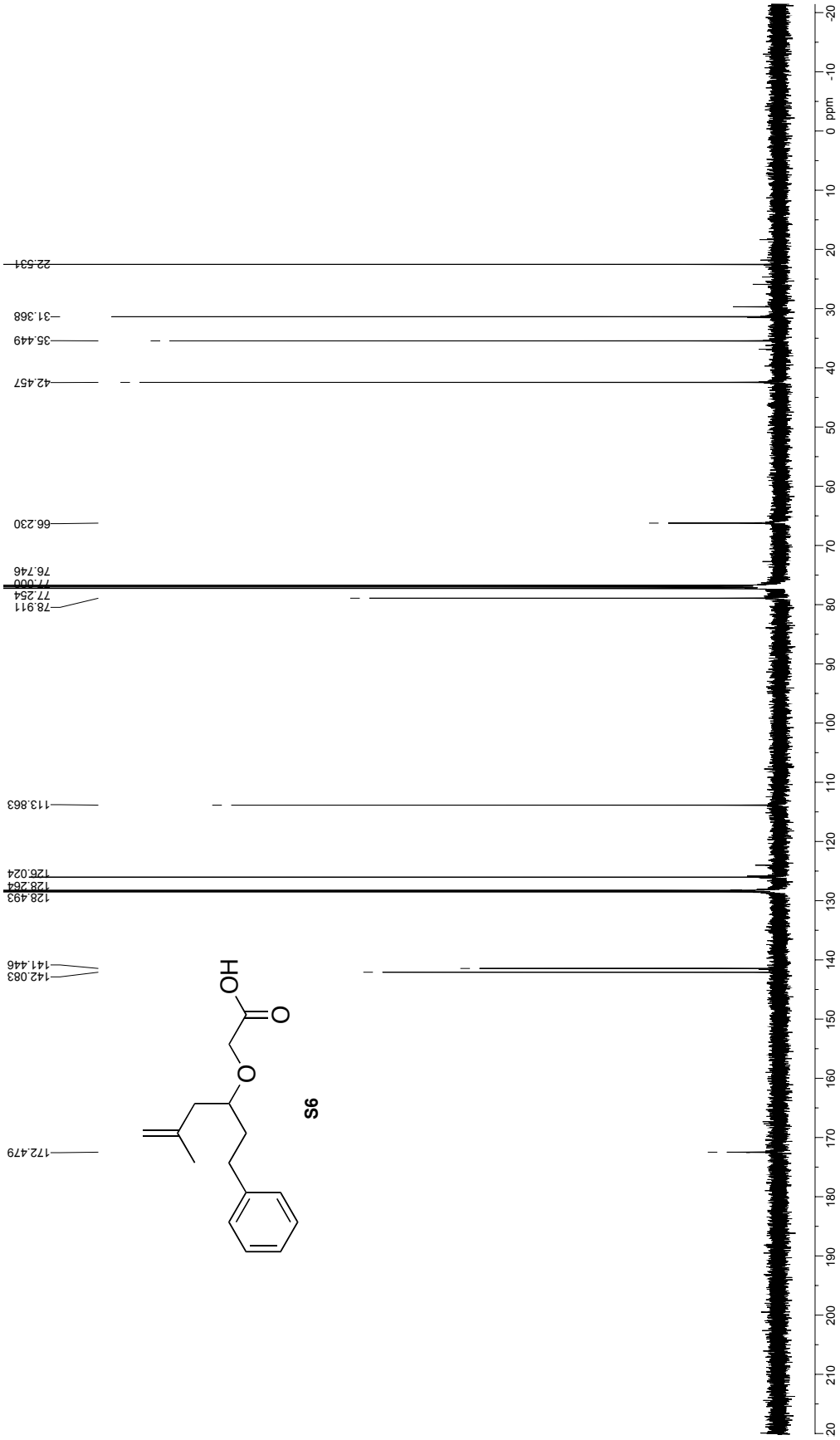

7.260
O
OH
O
S5
5.25
1
2.14
1.12
1.11
1.11
4.38
0.977
0.978
1.12
3.85
3.80
3.75
3.55
3.50
8
7
6
5
4
3
2
1
0 ppm

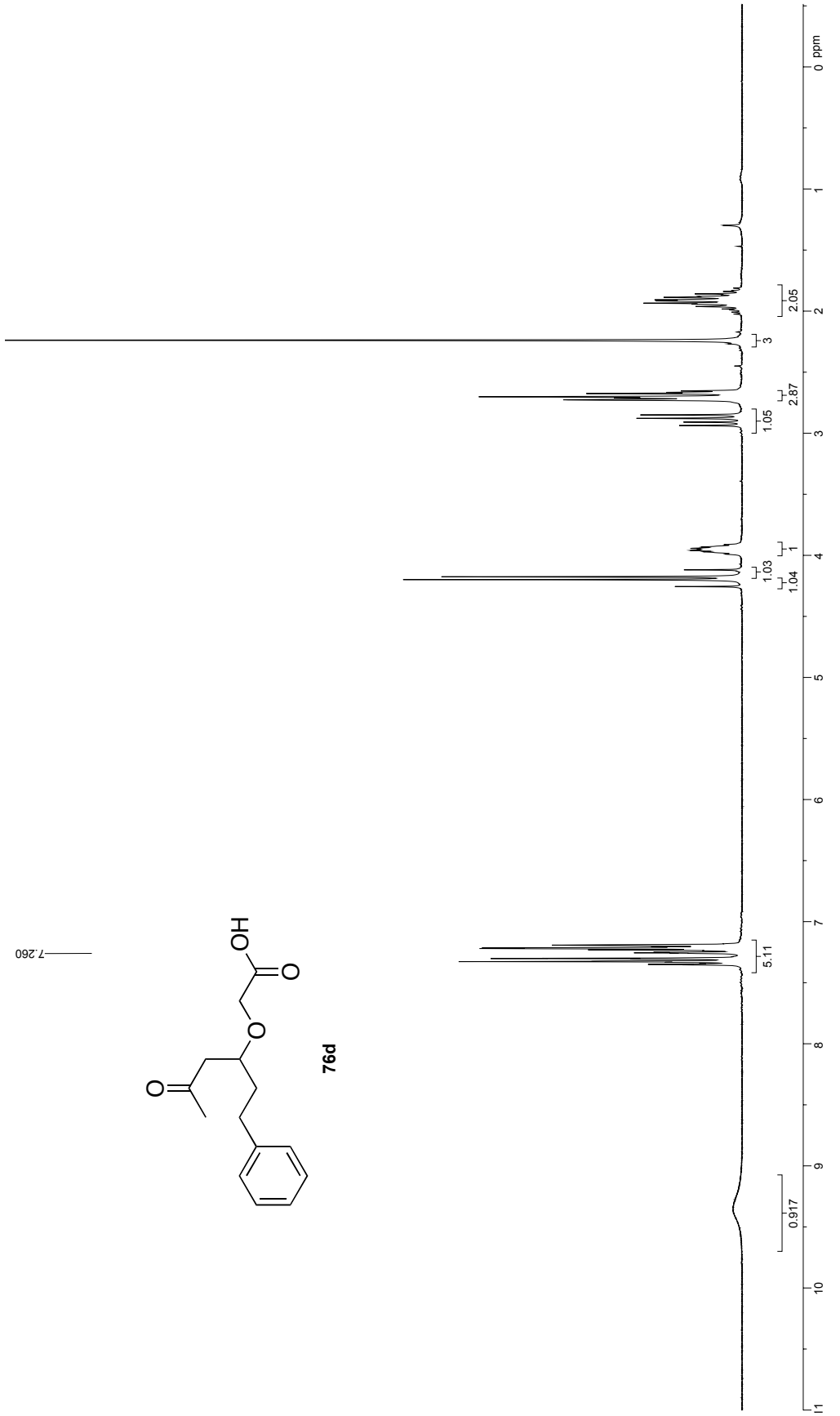

177.752
141.885
138.436
128.438
128.289
125.713
117.324
80.850
77.424
77.000
76.576
63.386
36.893
35.009
31.406
29.687
S5
O
OH
O
ppm

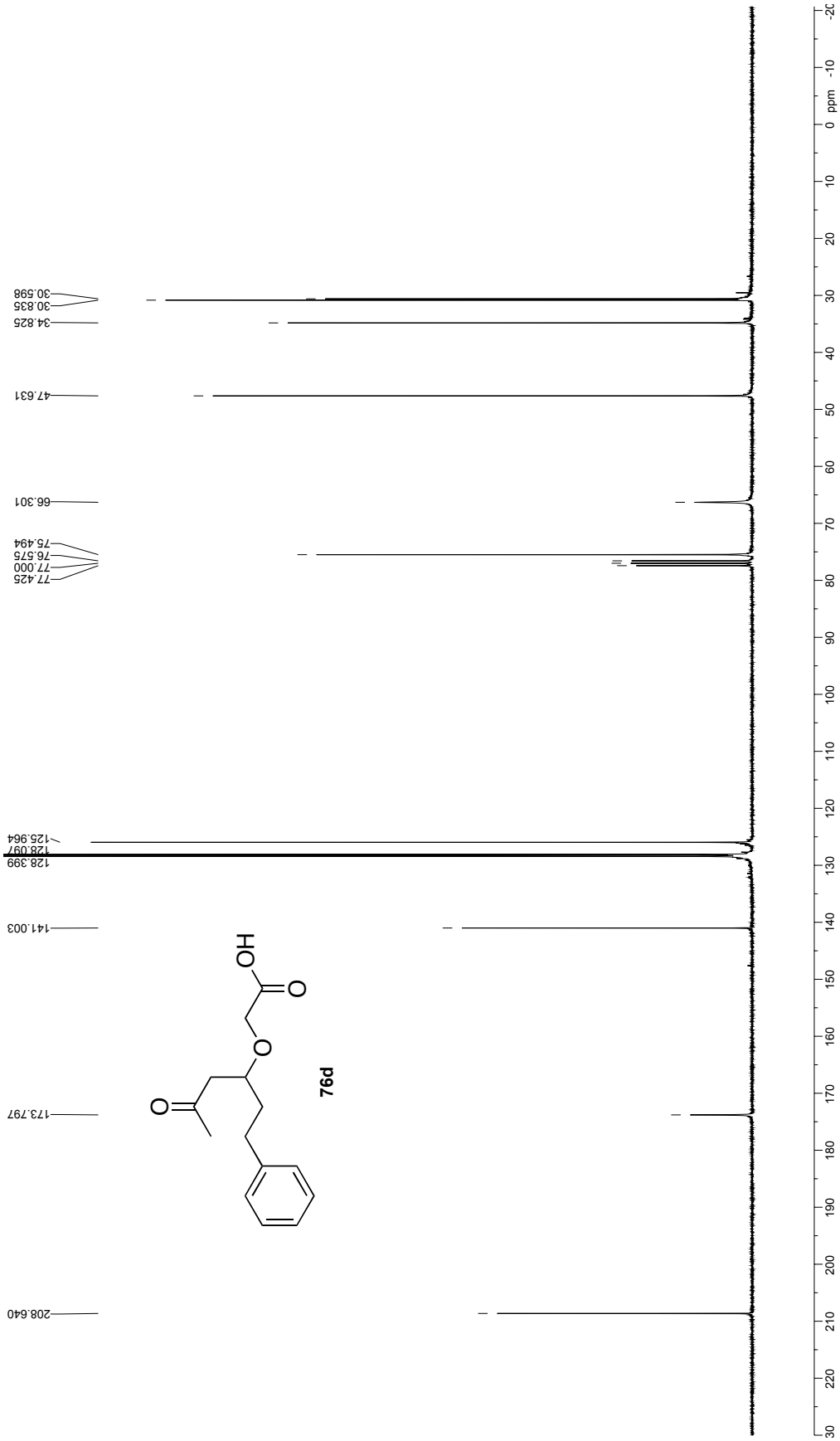

anti-11c
7.260
5.37
1
2.04
1.01
1.05
1.05
1.02
1.12
1.15
1.01
1.05
1
4.90 4.88 4.86 4.84 4.82 4.80
4.40 4.35 4.30
4.1 4.0 3.9 3.8
0 ppm

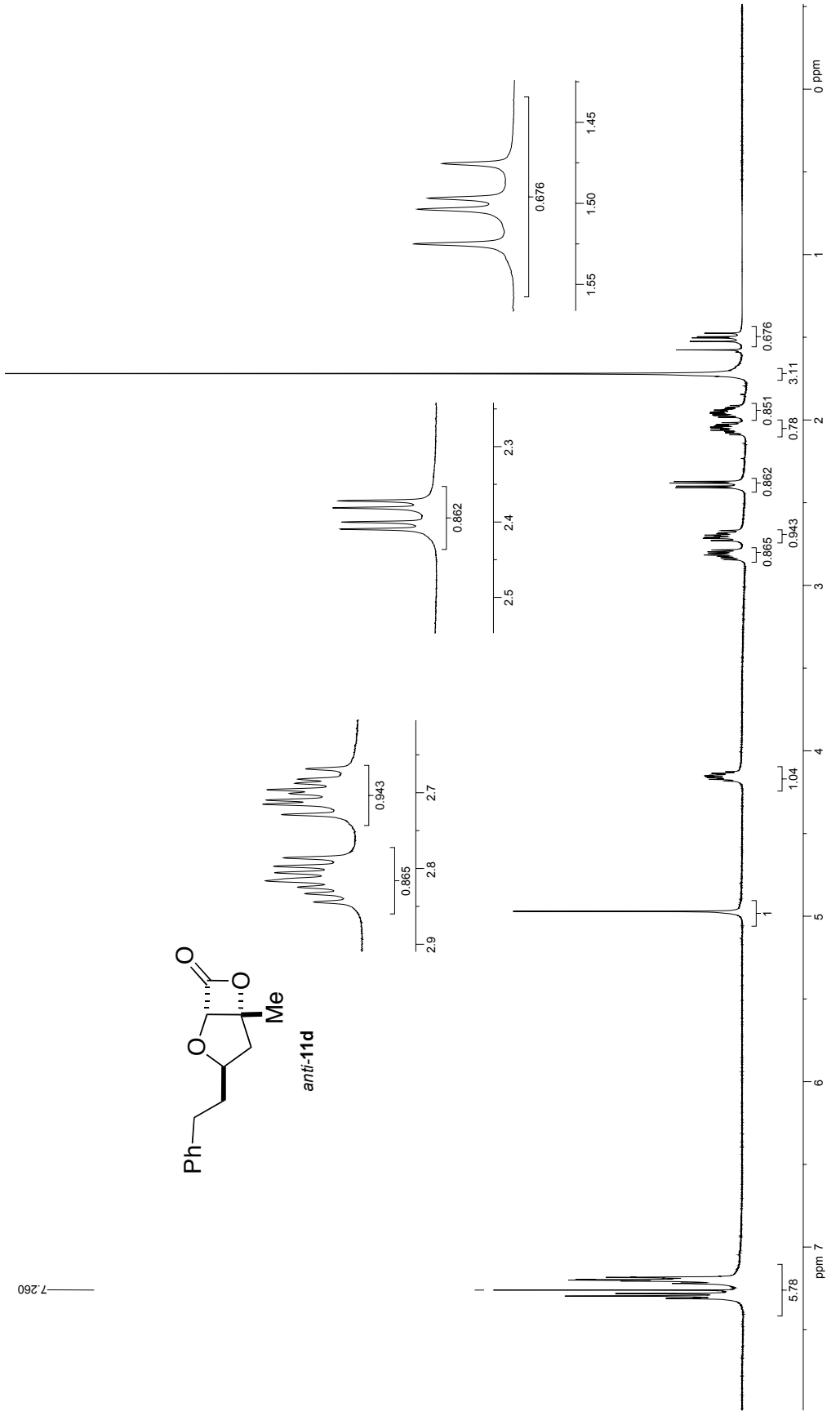

29.732
31.317
56.770
64.760
76.576
77.000
77.424
77.975
79.317
126.286
128.429
128.591
140.538
168.850
anti-11c
0 ppm

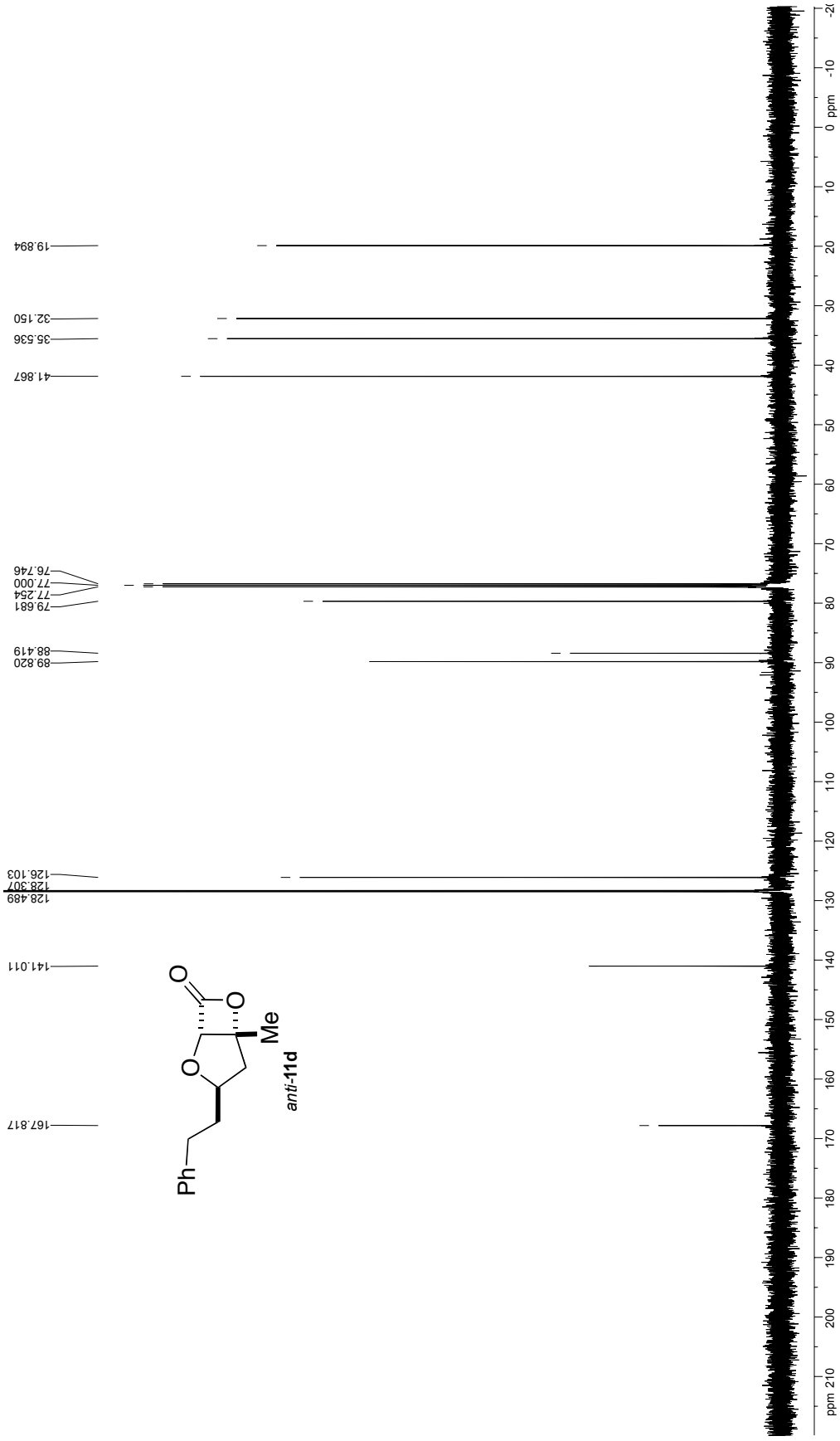

7.260
S6
OH
O
O
5.25
2.02
1.03
0.998
1
2.07
1.06
1.05
3.12
2.08
ppm 7
6
5
4
3
2
1
0 ppm

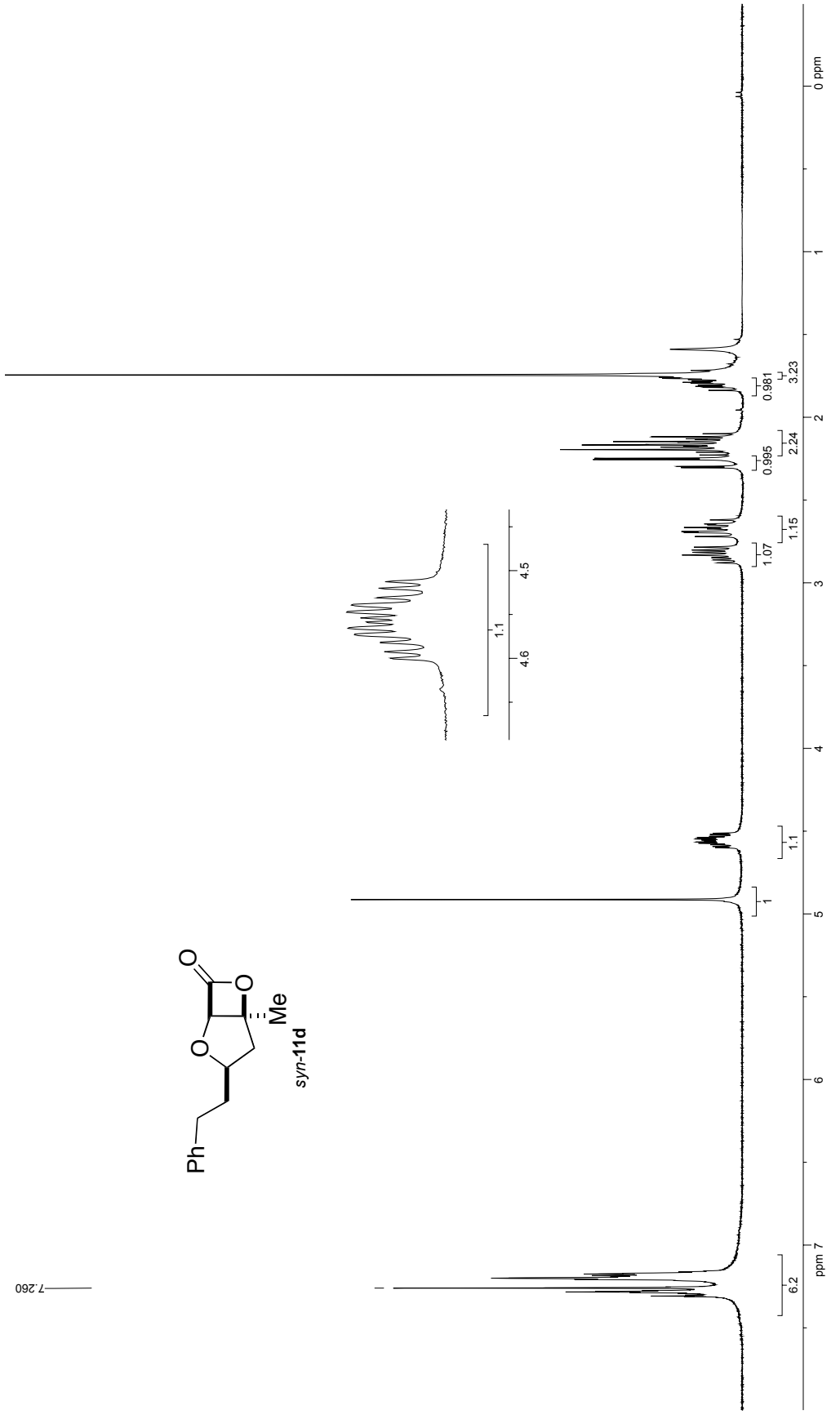

22.531
31.368
35.449
42.457
66.230
76.746
77.000
77.254
78.911
113.863
125.024
128.264
128.493
141.446
142.083
172.479
HO
O
O
S6
20
10
0
-10
-20
ppm

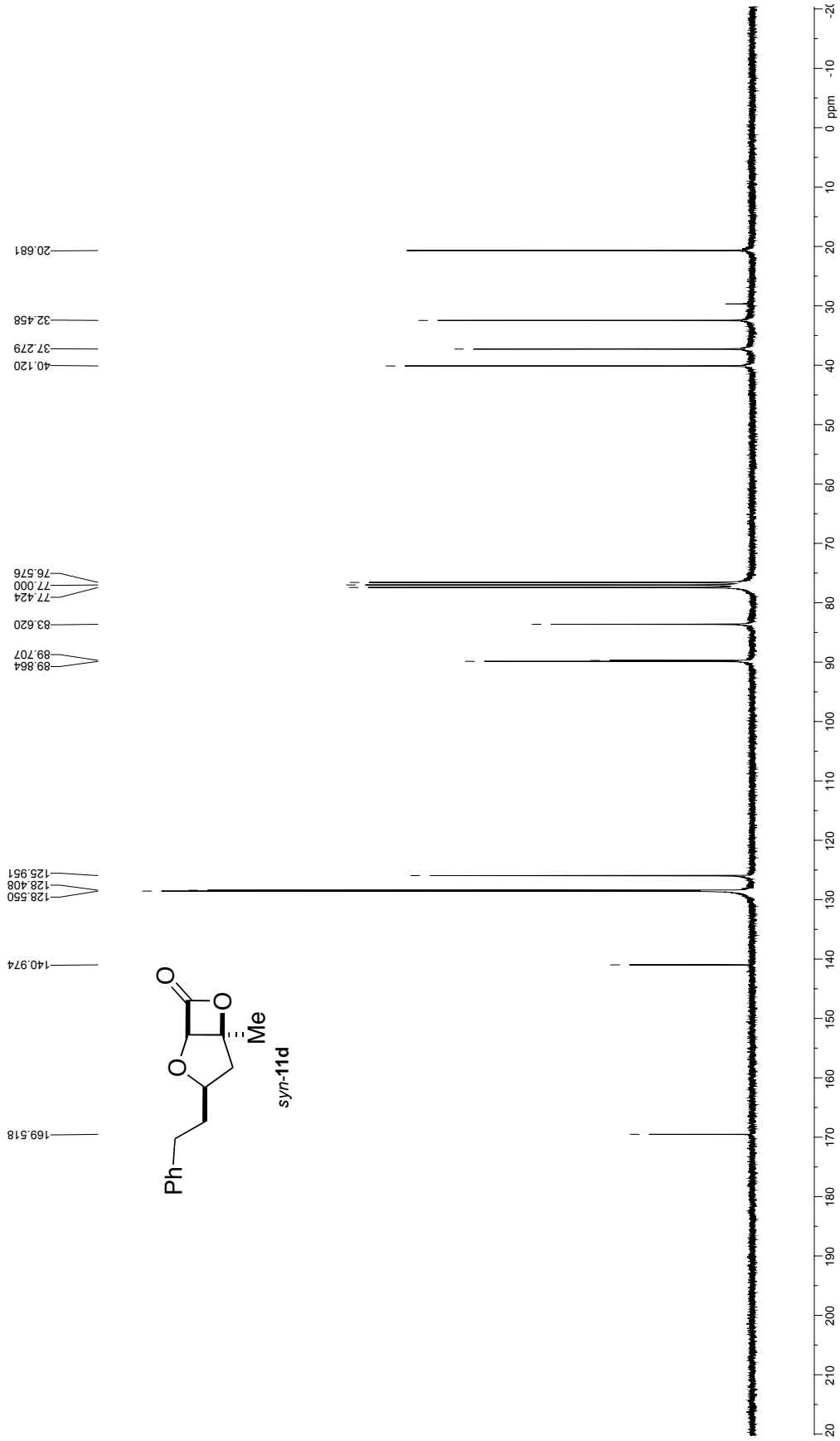

7.260
OH
O
O
O
76d
0.917
5.11
1.04
1.03
1
1.05
2.87
3
2.05
0 ppm

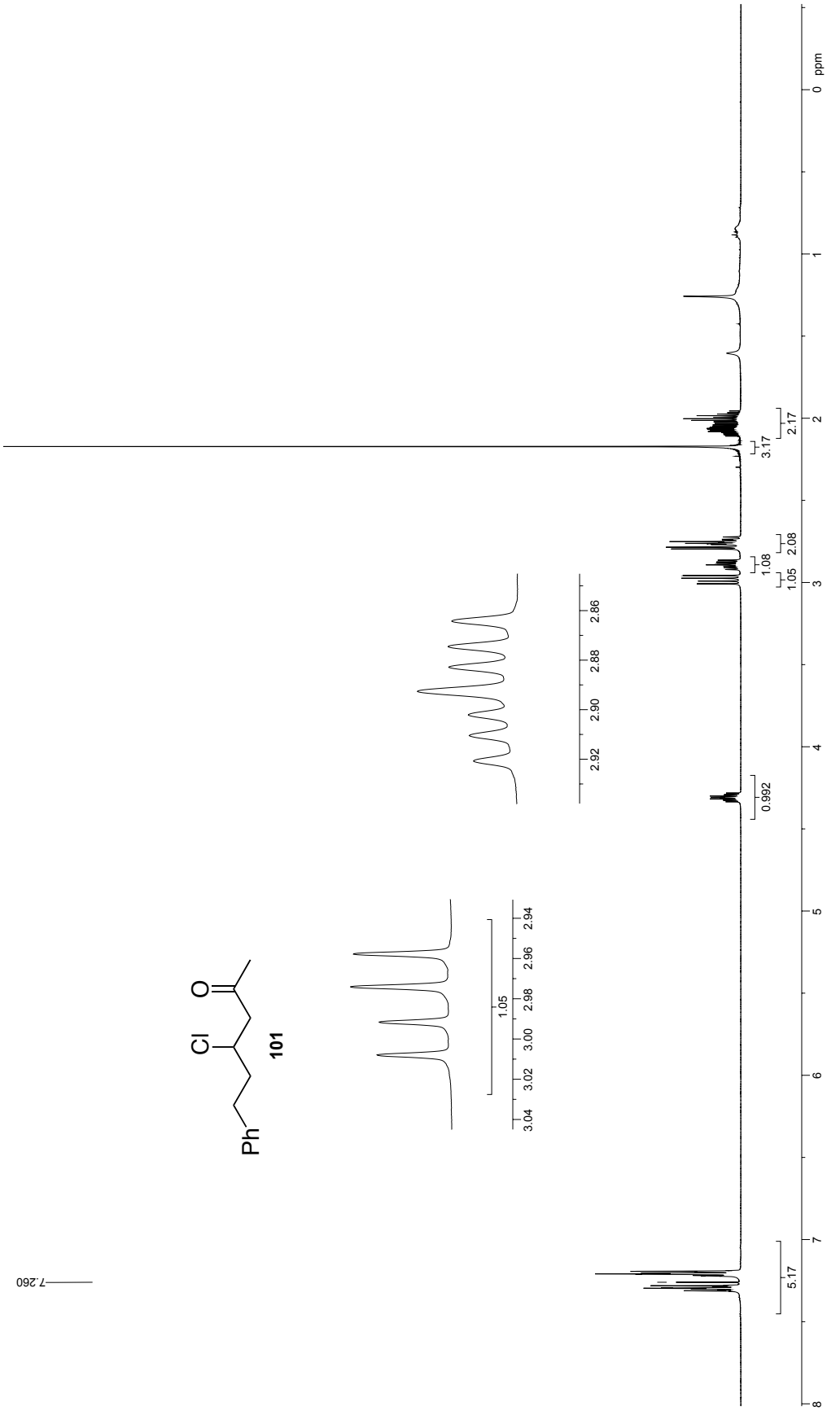

208.640
173.797
141.003
128.399
128.097
125.964
77.425
77.000
76.575
75.494
66.301
47.631
34.825
30.835
30.598
OH
O
O
O
76d
ppm

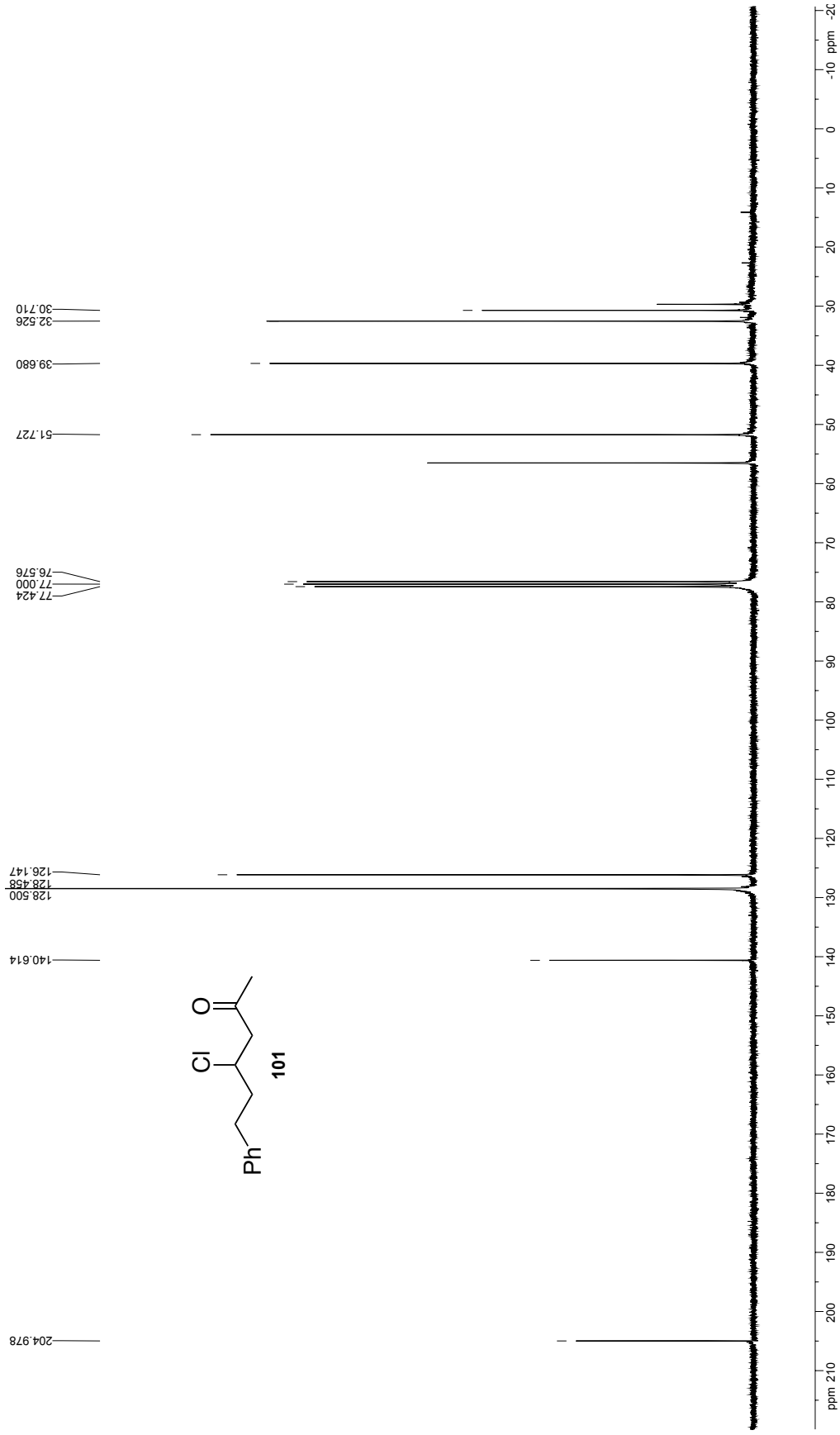

7.260
ppm 7
6
5
4
3
2
1
0 ppm
5.78
1
1.04
0.943
0.865
0.862
0.851
0.78
3.11
0.676
2.9
2.8
2.7
2.5
2.4
2.3
1.55
1.50
1.45
Ph
O
O
O
Me
anti-11d

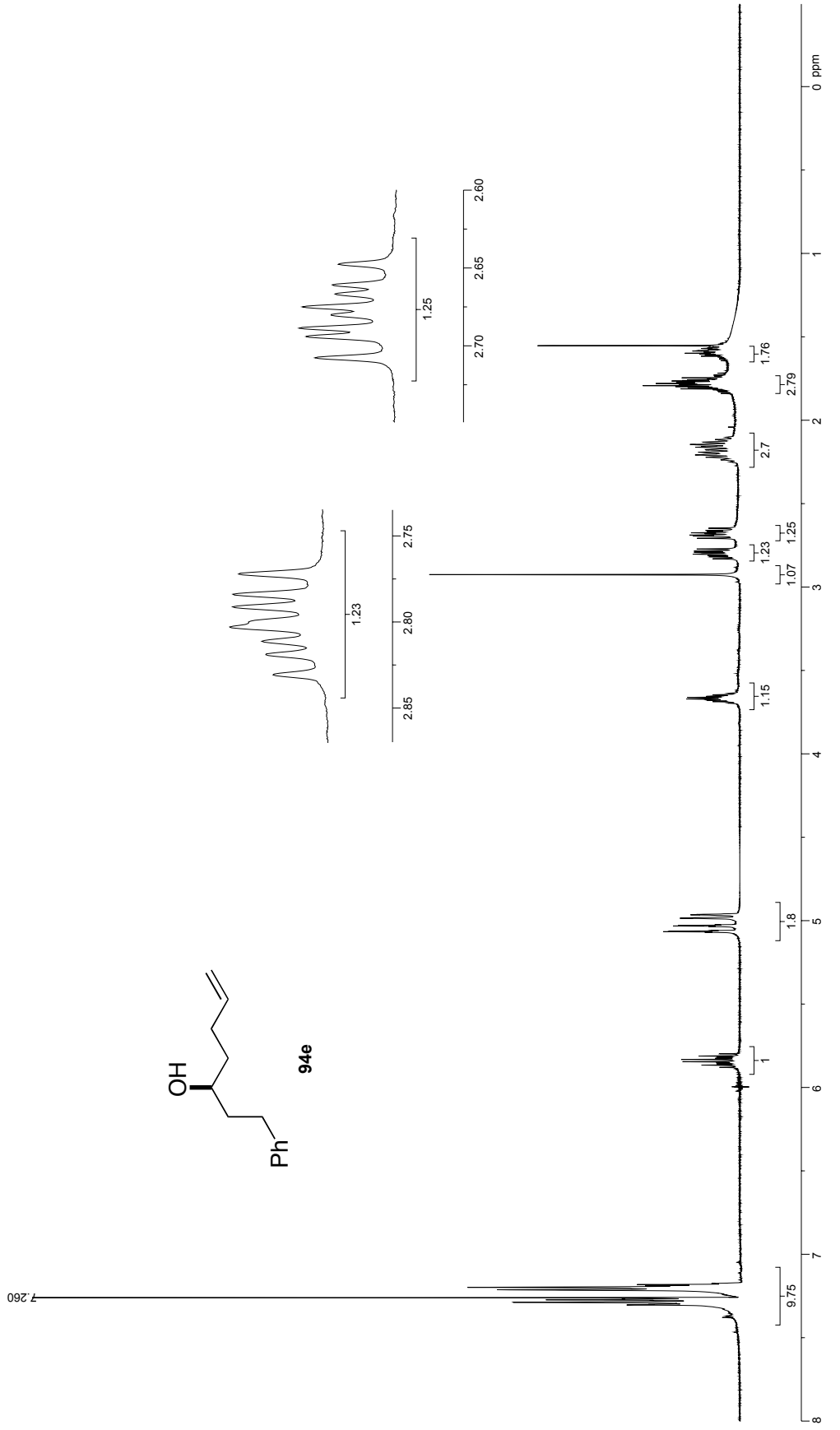

19.894
32.150
35.536
41.867
76.746
77.000
77.254
79.681
88.419
89.820
126.103
128.307
128.489
141.011
167.817
O
O
O
Me
Ph
anti-11d
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm
-10

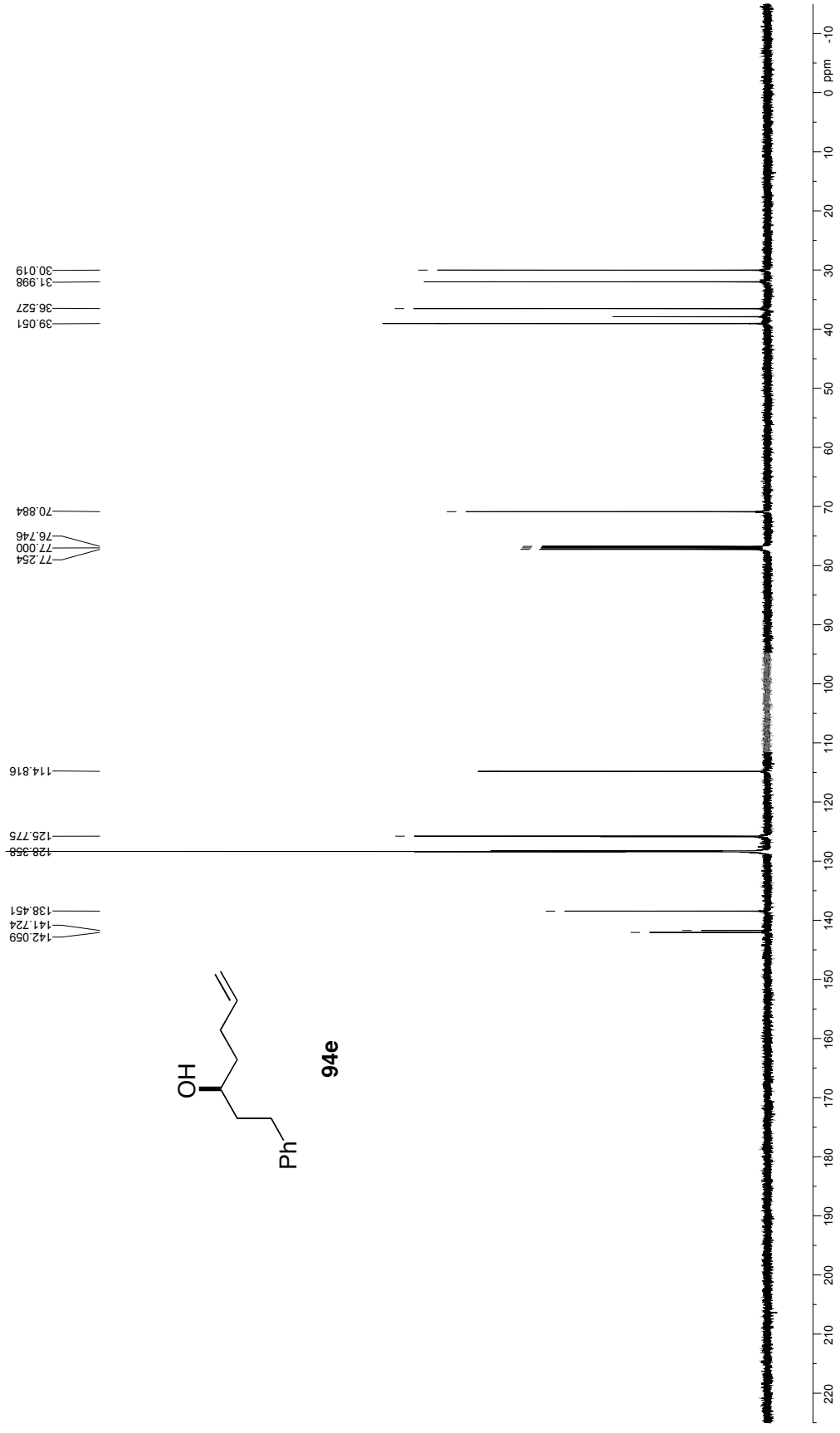

7.260
ppm 7
6
5
4
3
2
1
0 ppm
6.2
1
1.1
1.07
1.15
0.995
2.24
0.981
3.23
4.6
1.1
4.5
O
O
O
Me
Ph
syn-11d

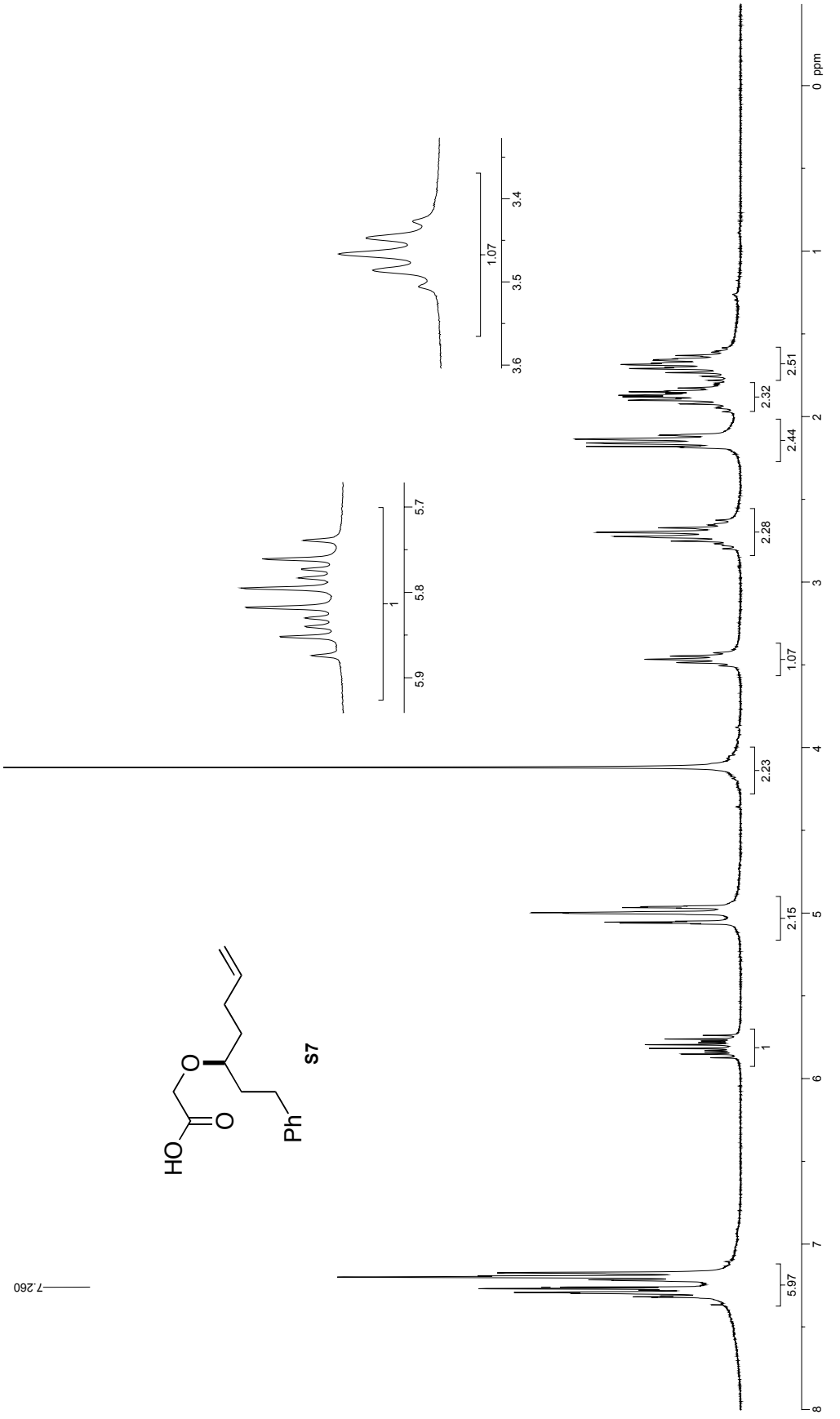

20.681
32.458
37.279
40.120
76.576
77.000
77.424
83.620
89.707
89.864
125.951
128.408
128.550
140.974
169.518
Ph
O
O
O
Me
syn-11d
0 ppm

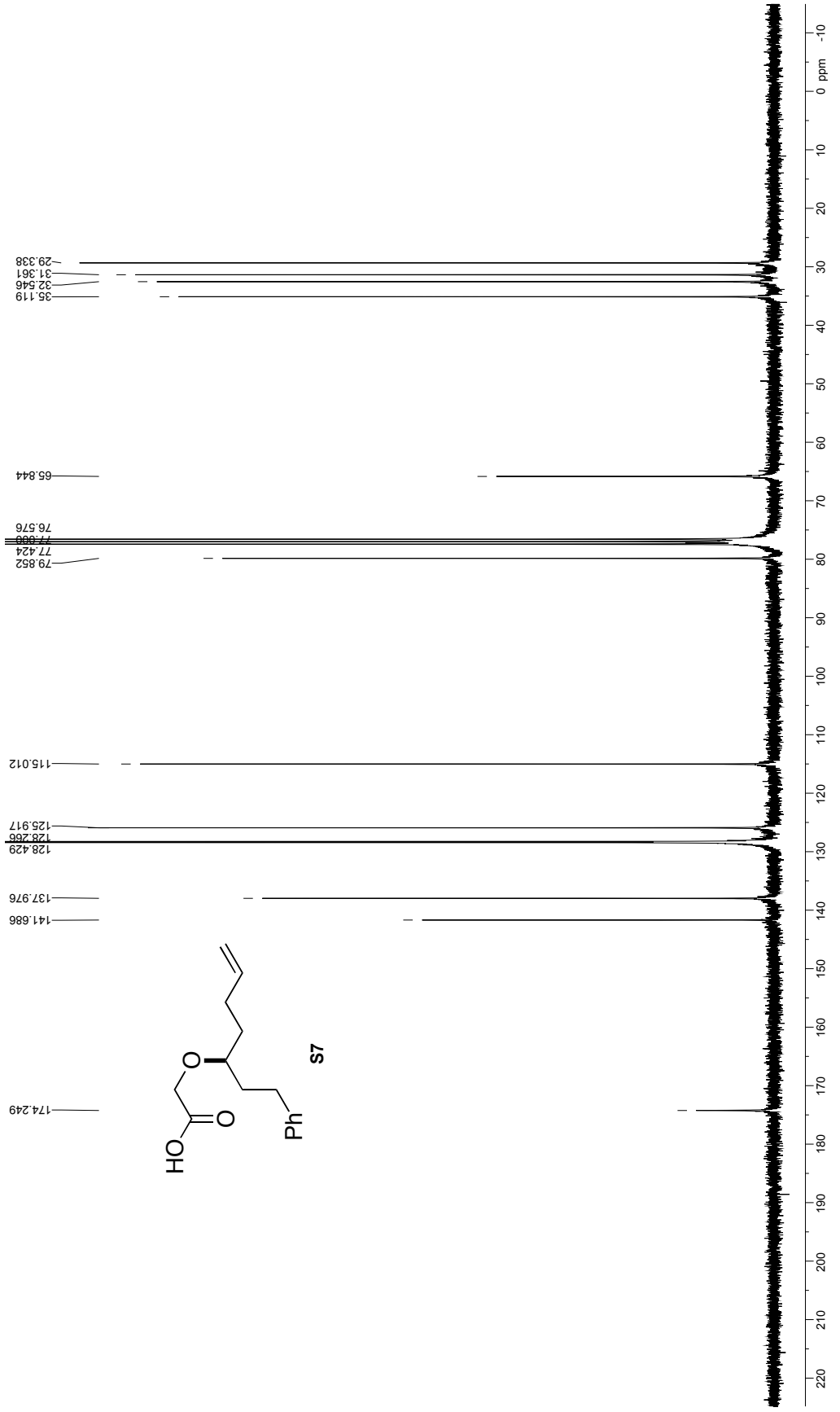

7.260
Cl
O
Ph
101
1.05
3.04
3.02
3.00
2.98
2.96
2.94
2.92
2.90
2.88
2.86
0.992
1.08
1.05
2.08
3.17
2.17
5.17
0
ppm
1
2
3
4
5
6
7
8

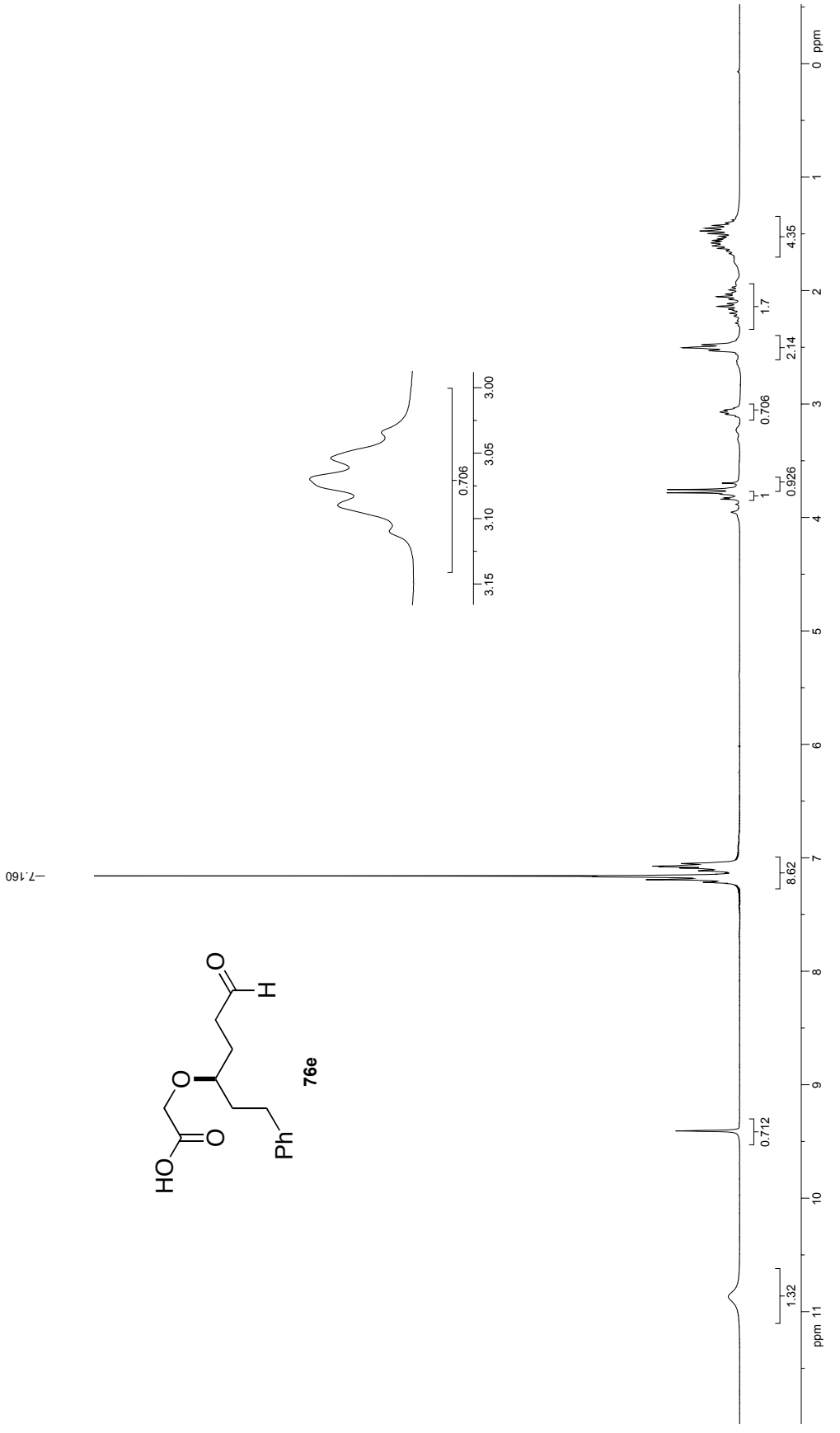

204.978
140.614
128.500
128.458
126.147
77.424
77.000
76.576
51.727
39.680
32.526
30.710
Cl
O
Ph
101
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10 ppm -20

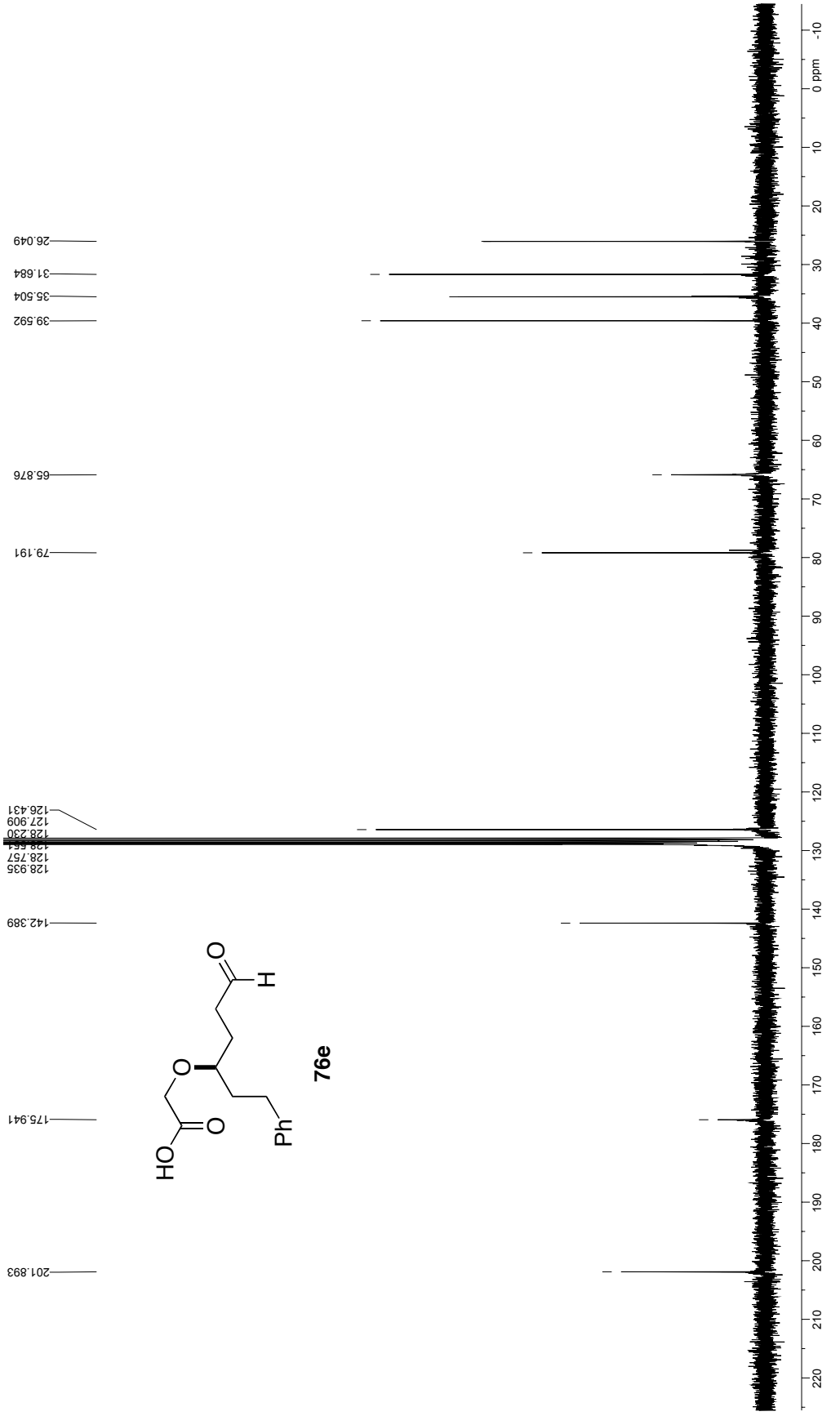

OH
Ph
94e
7.260
9.75
1
1.8
1.15
1.23
1.07
1.25
2.7
1.76
2.79
1.23
2.85
2.80
2.75
1.25
2.70
2.65
2.60
0 ppm

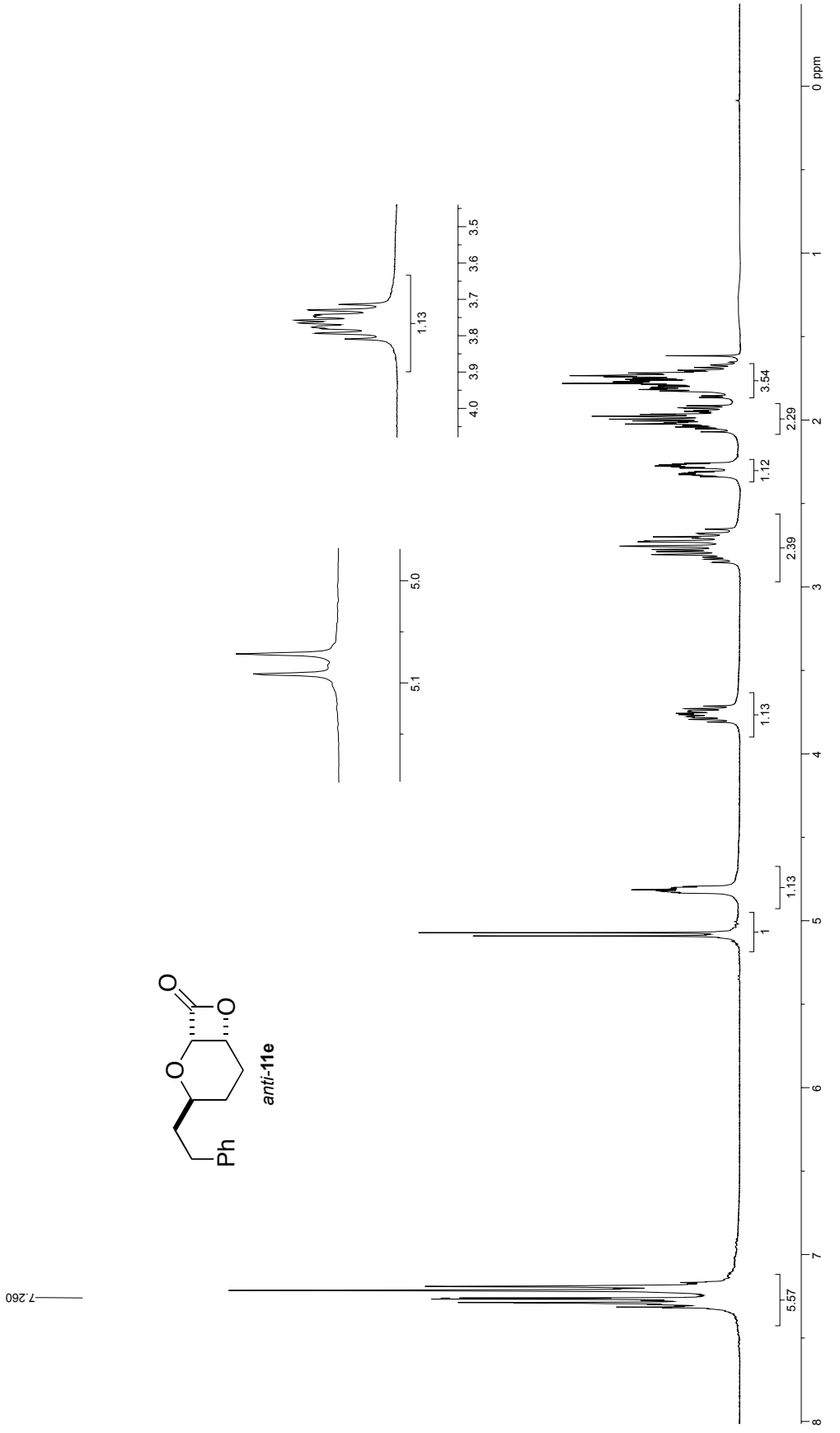

142.059
141.724
138.451
128.358
125.775
114.816
77.254
77.000
76.746
70.884
39.051
36.527
31.998
30.019
OH
Ph
94e
ppm

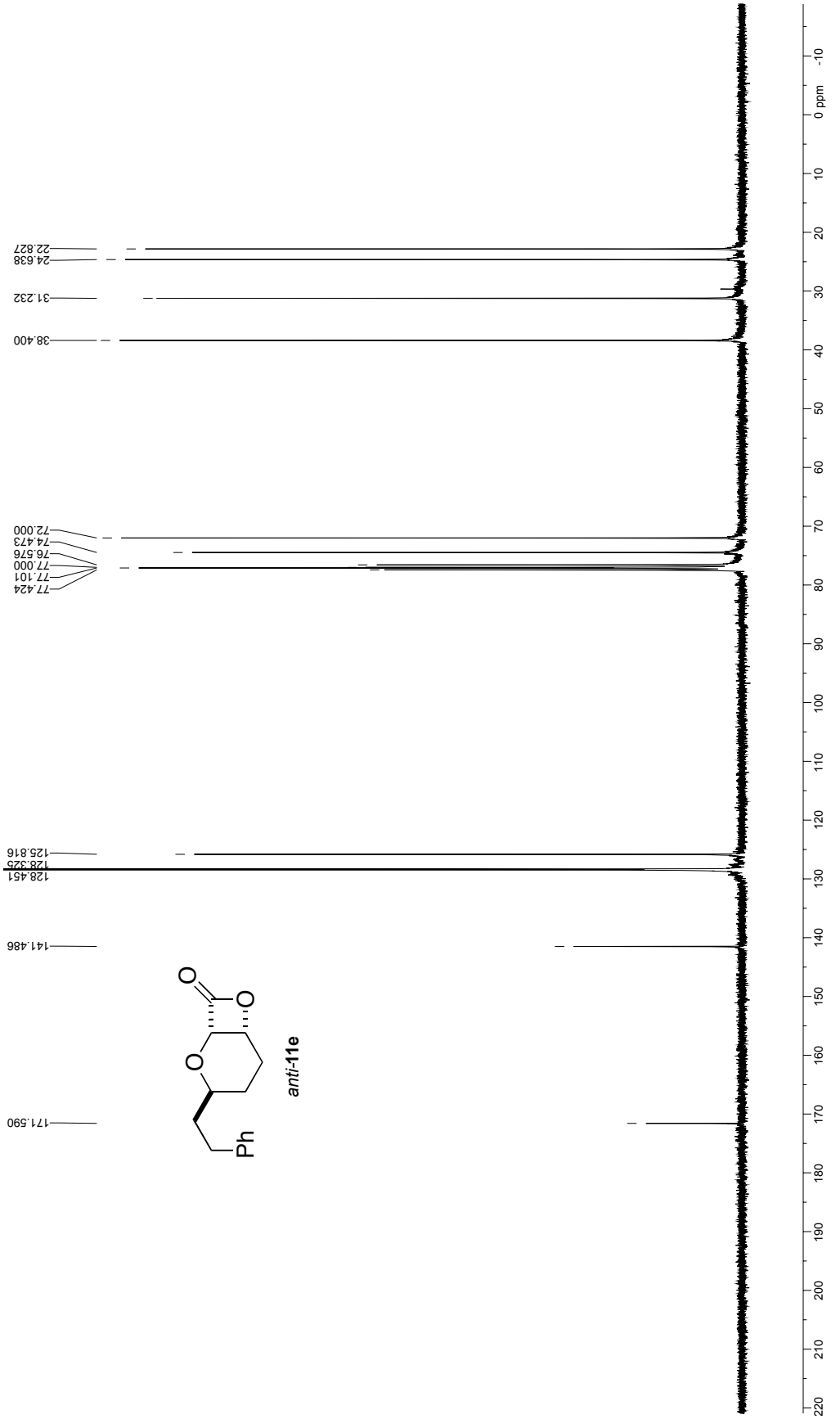

7.260
HO
O
O
Ph
S7
5.97
1
2.15
2.23
1
2.28
1.07
2.44
2.32
2.51
0 ppm

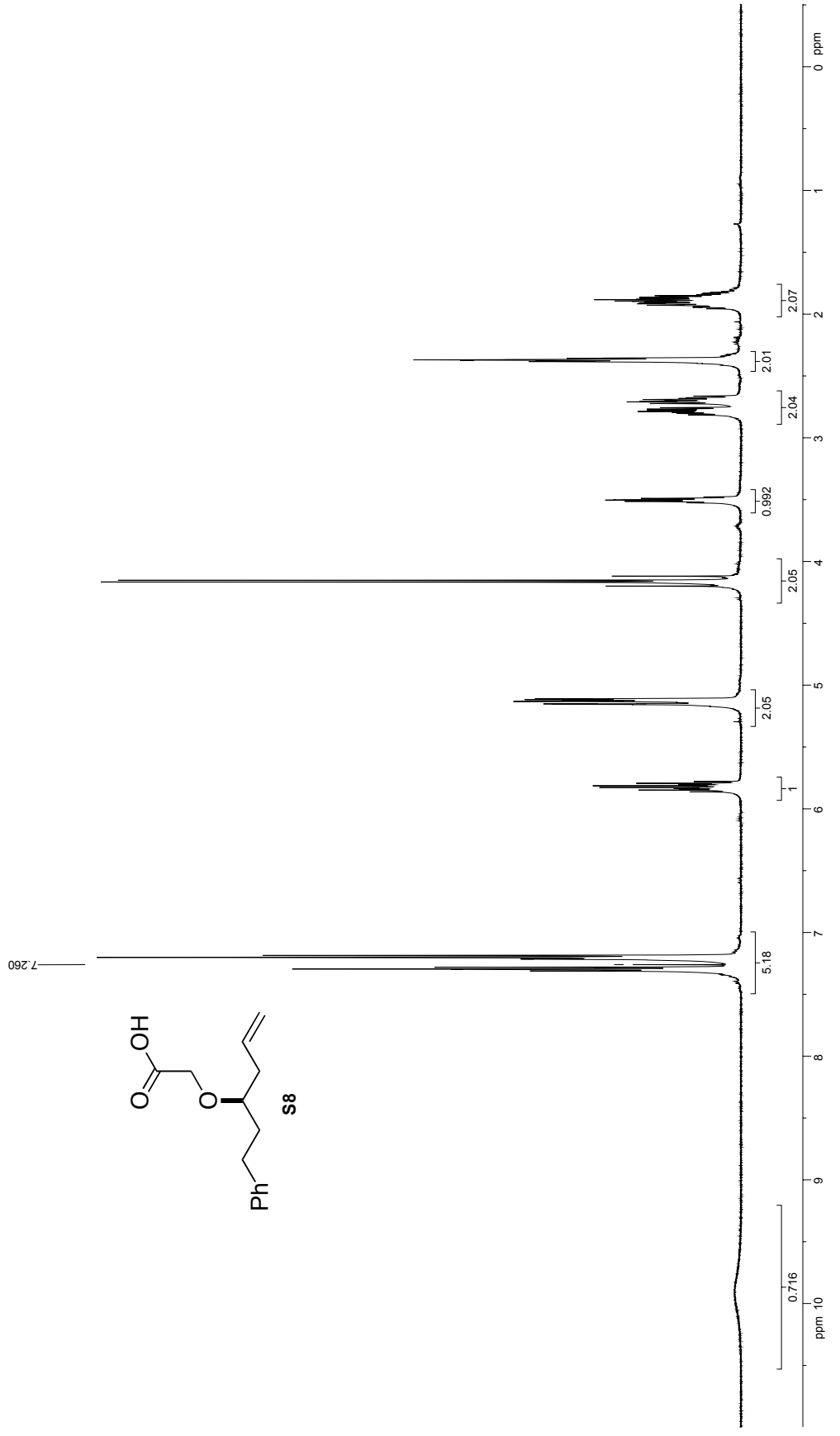

174.249
141.686
137.976
128.429
128.266
125.917
115.012
79.852
77.424
77.000
76.576
65.844
35.119
32.546
31.361
29.338
HO
O
O
Ph
S7
0 ppm

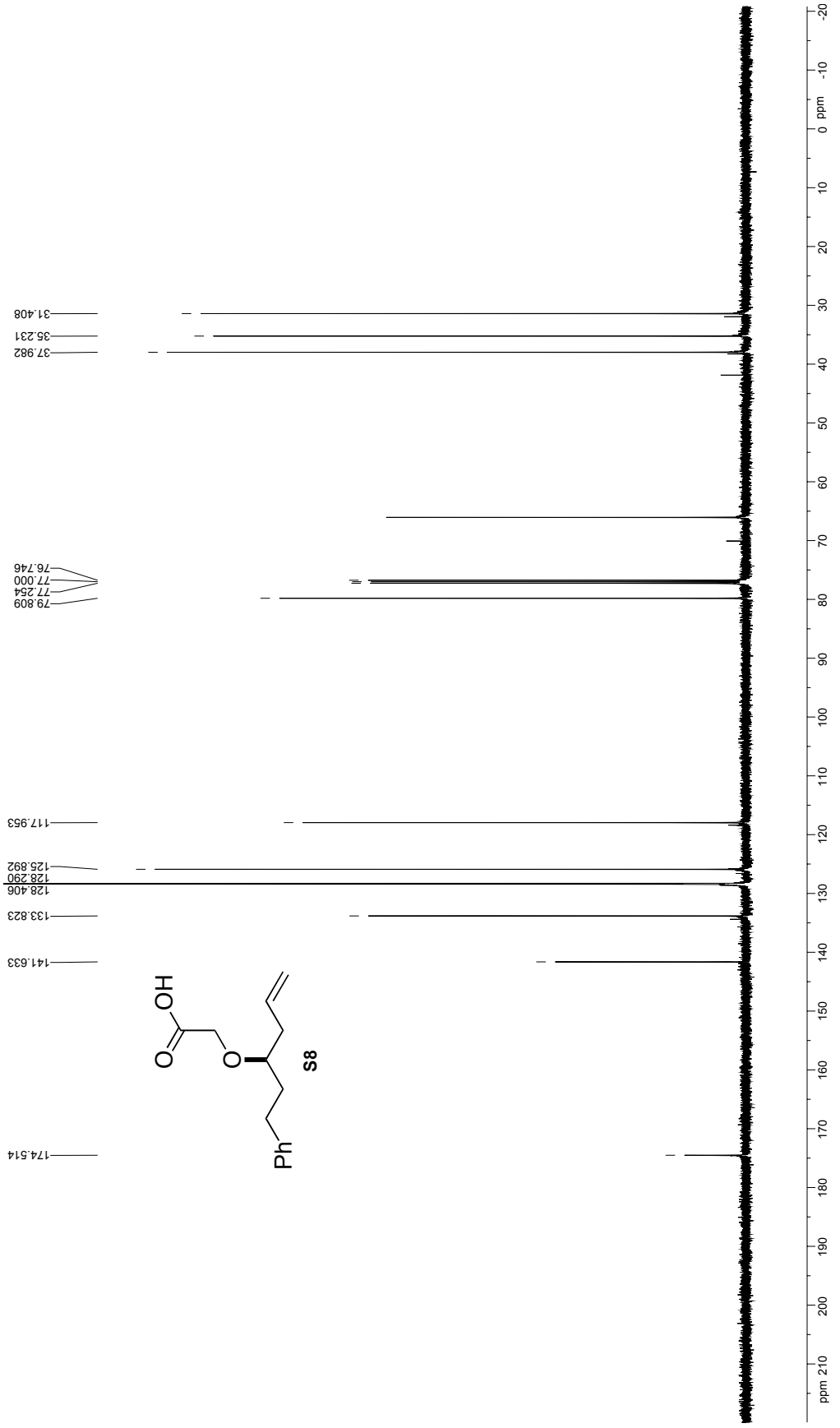

7.160
0.706
3.15
3.10
3.05
3.00
1.32
0.712
8.62
1
0.926
0.706
2.14
1.7
4.35
ppm
11
10
9
8
7
6
5
4
3
2
1
0
HO
O
O
O
O
H
Ph
76e

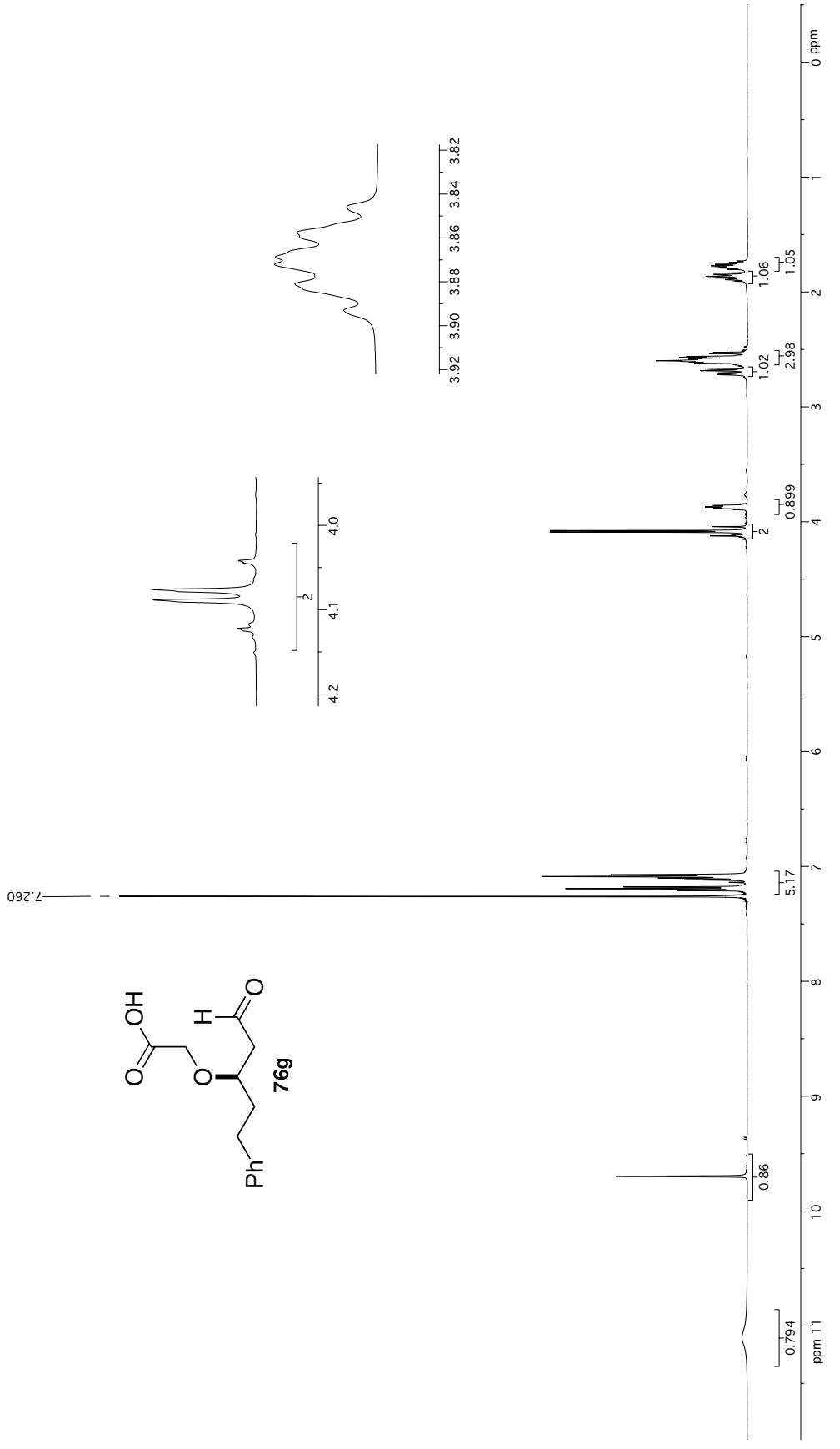

201.893
175.941
142.389
128.935
128.757
128.661
128.230
127.909
126.431
79.191
65.876
39.592
35.504
31.684
26.049
0 ppm
HO
O
O
O
O
H
Ph
76e

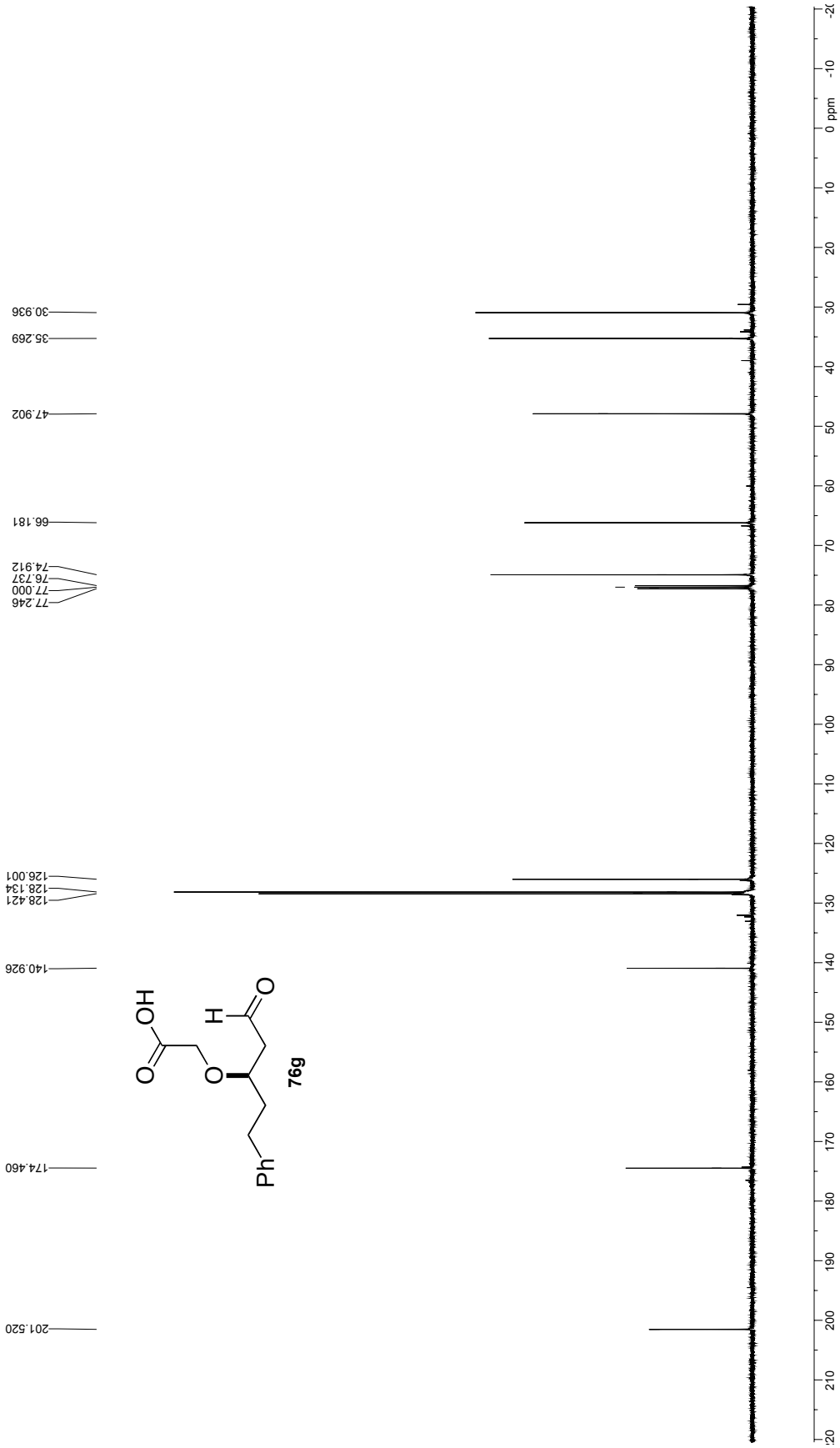

7.260
O
O
O
Ph
anti-11e
5.57
1
1.13
1.13
2.39
1.12
2.29
3.54
5.1
5.0
1.13
4.0
3.9
3.8
3.7
3.6
3.5
8
7
6
5
4
3
2
1
0 ppm

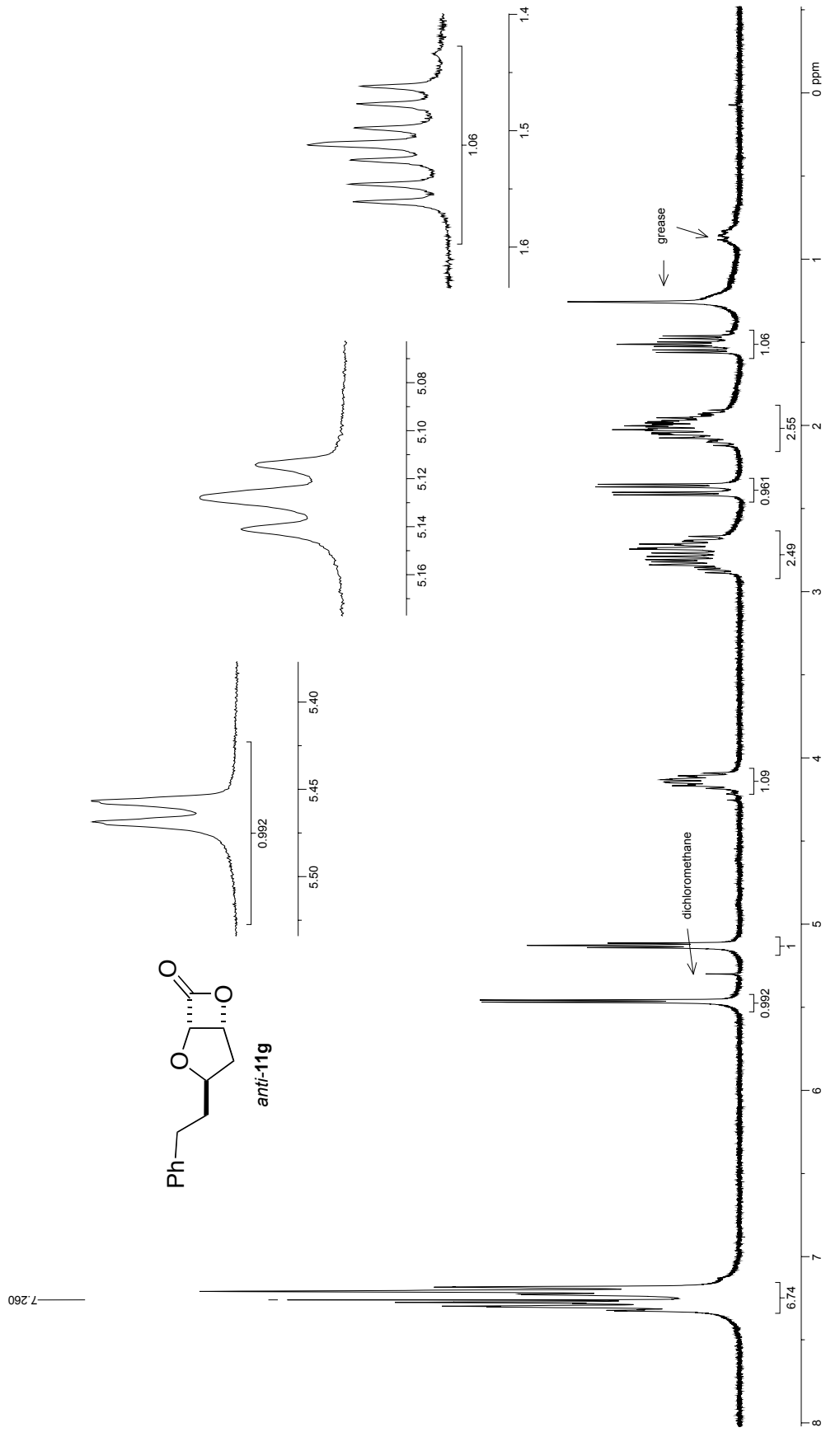

22.827
24.638
31.232
38.400
72.000
74.473
76.576
77.000
77.101
77.424
125.816
128.325
128.451
141.486
171.590
O
O
O
Ph
anti-11e
0 ppm

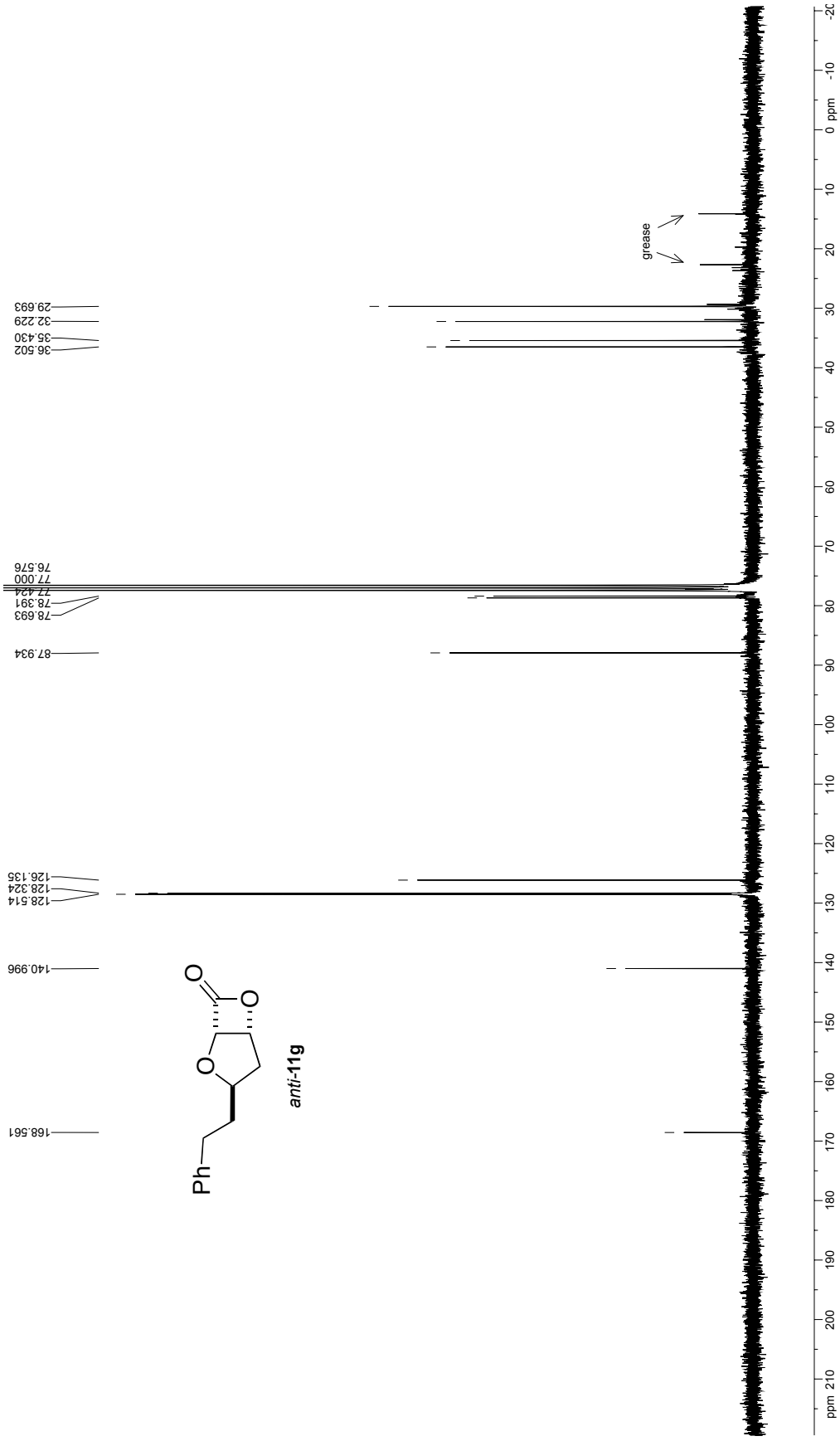

7.260
5.18
1
2.05
0.992
2.05
2.04
2.01
2.07
0.716
ppm
OH
O
O
Ph
S8

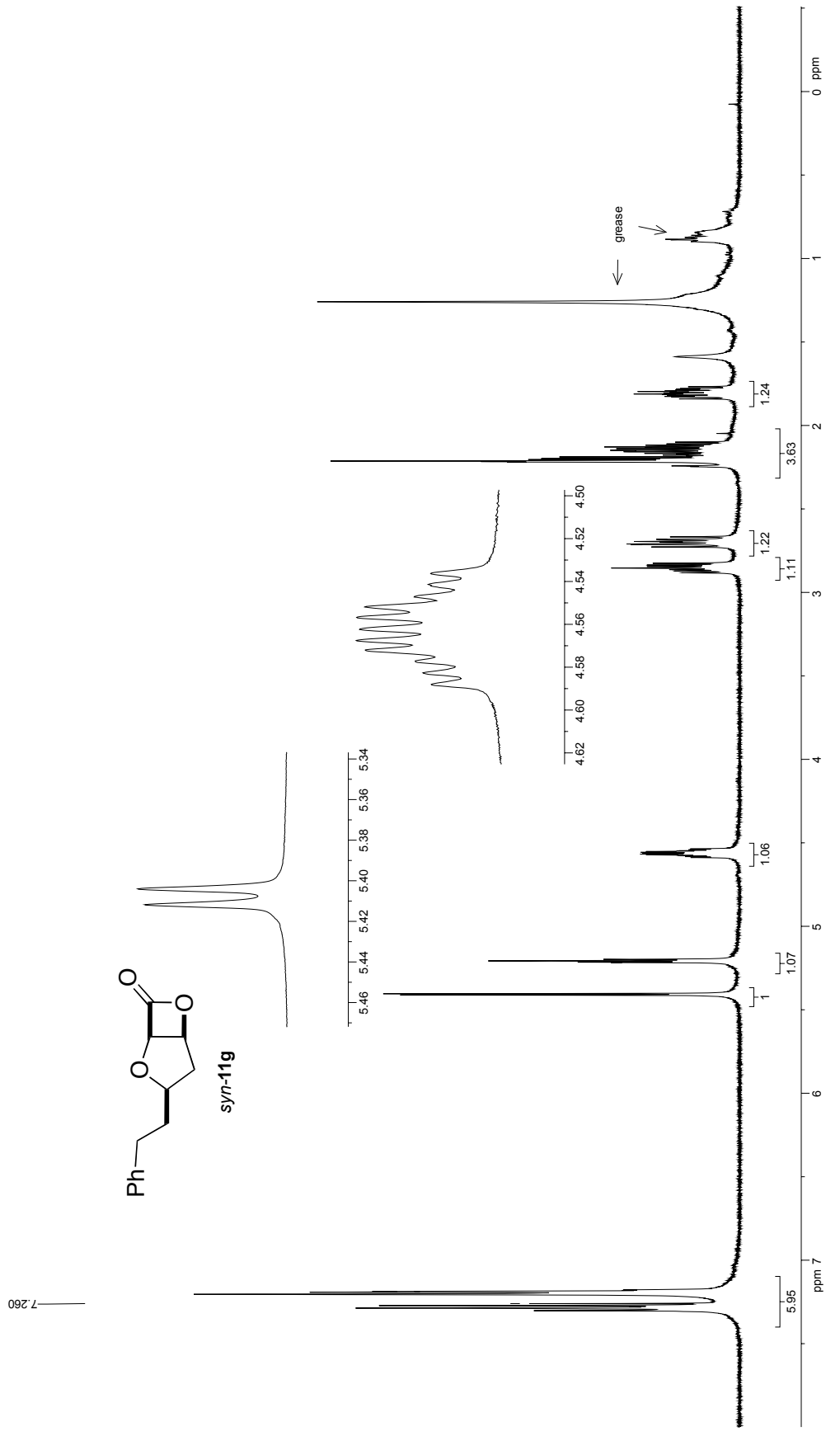

31.408
35.231
37.982
76.746
77.000
77.254
79.809
117.953
125.892
128.290
128.406
133.823
141.633
174.514
OH
O
O
Ph
S8
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm
-10
-20

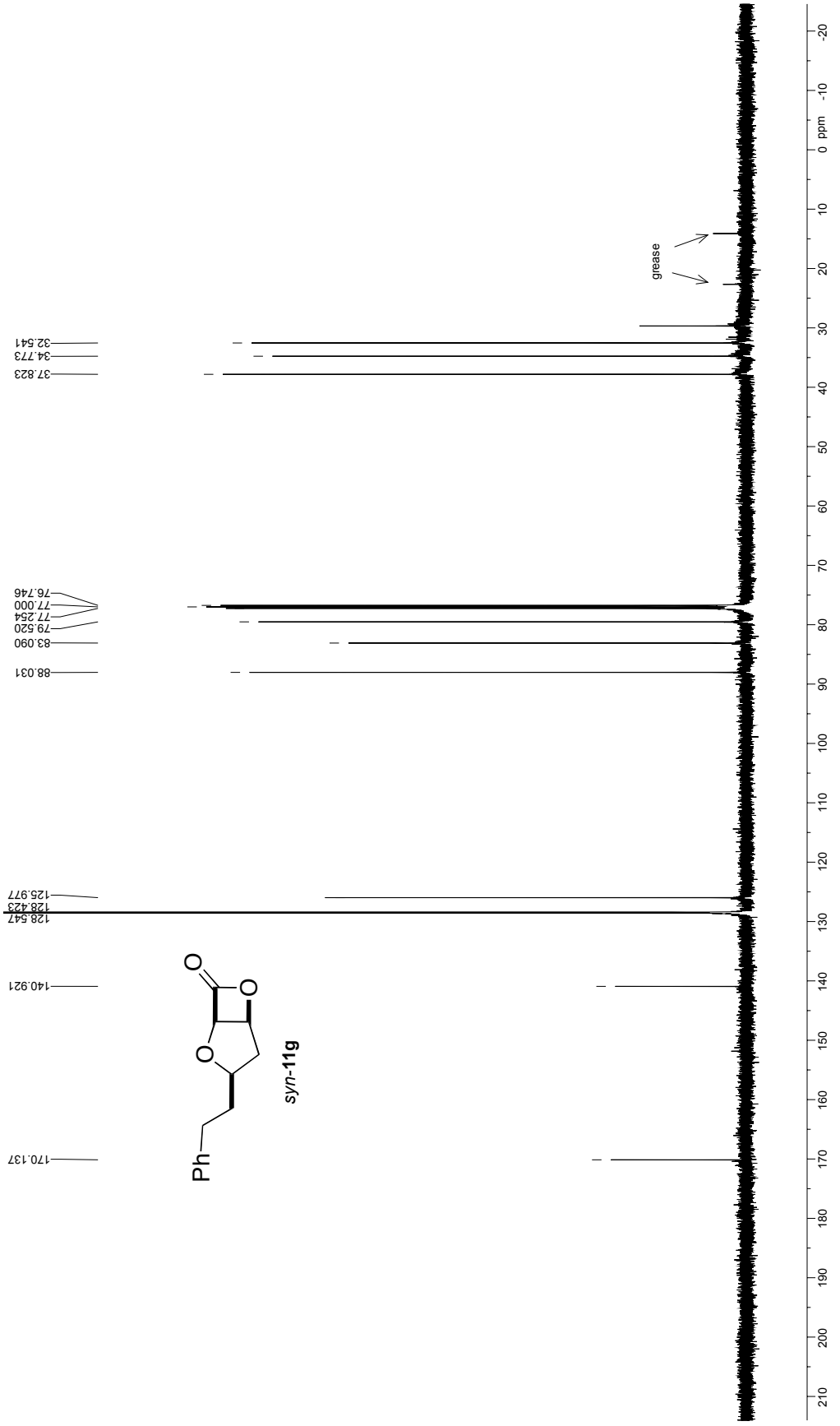

7.260
0.794
0.86
5.17
2
0.899
1.02
2.98
1.06
1.05
ppm 11
0 ppm
76g

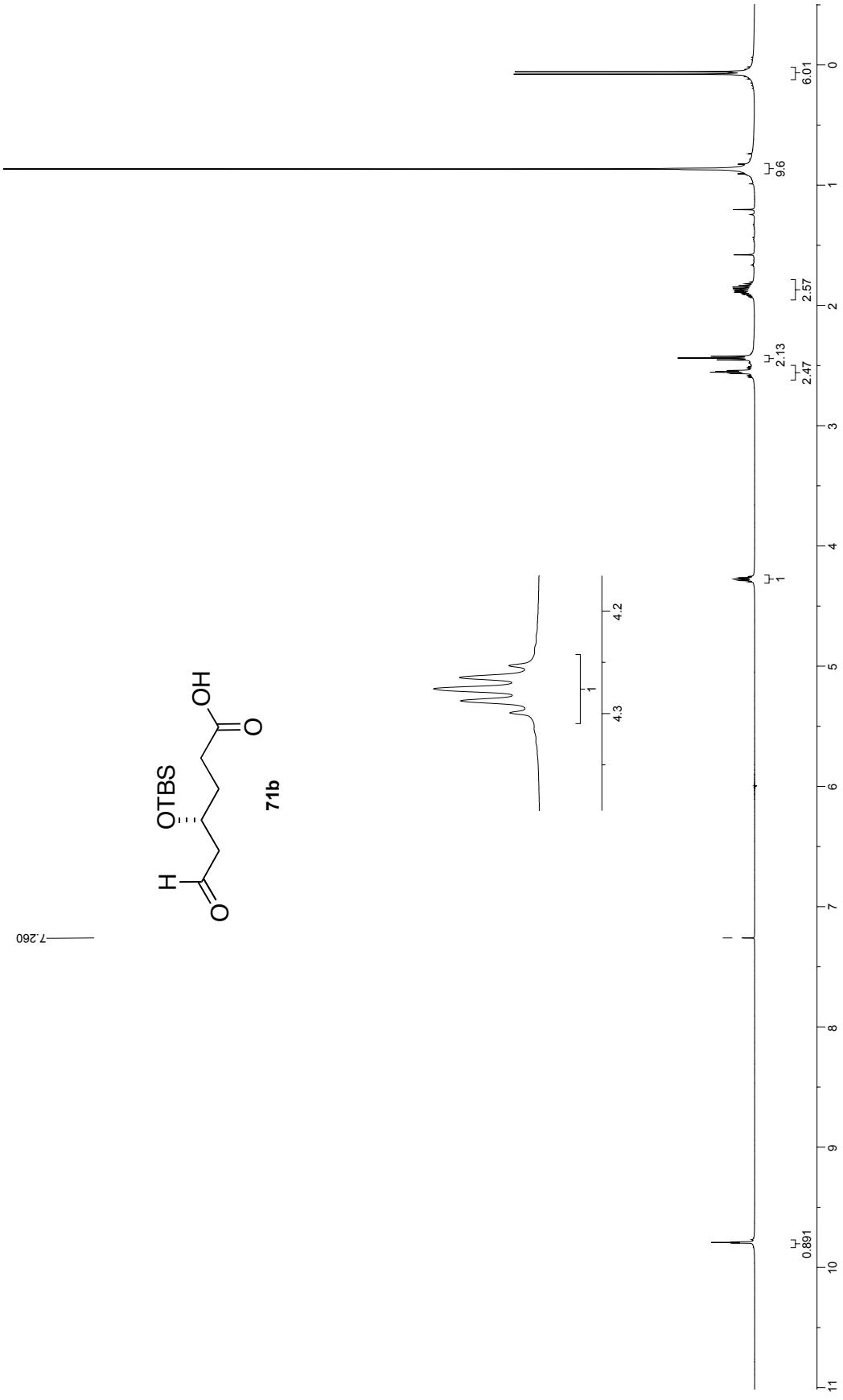

30.936
35.269
47.902
66.181
74.972
76.737
77.000
77.246
128.421
128.134
126.001
140.926
174.460
201.520
O
OH
O
H
Ph
76g
0 ppm

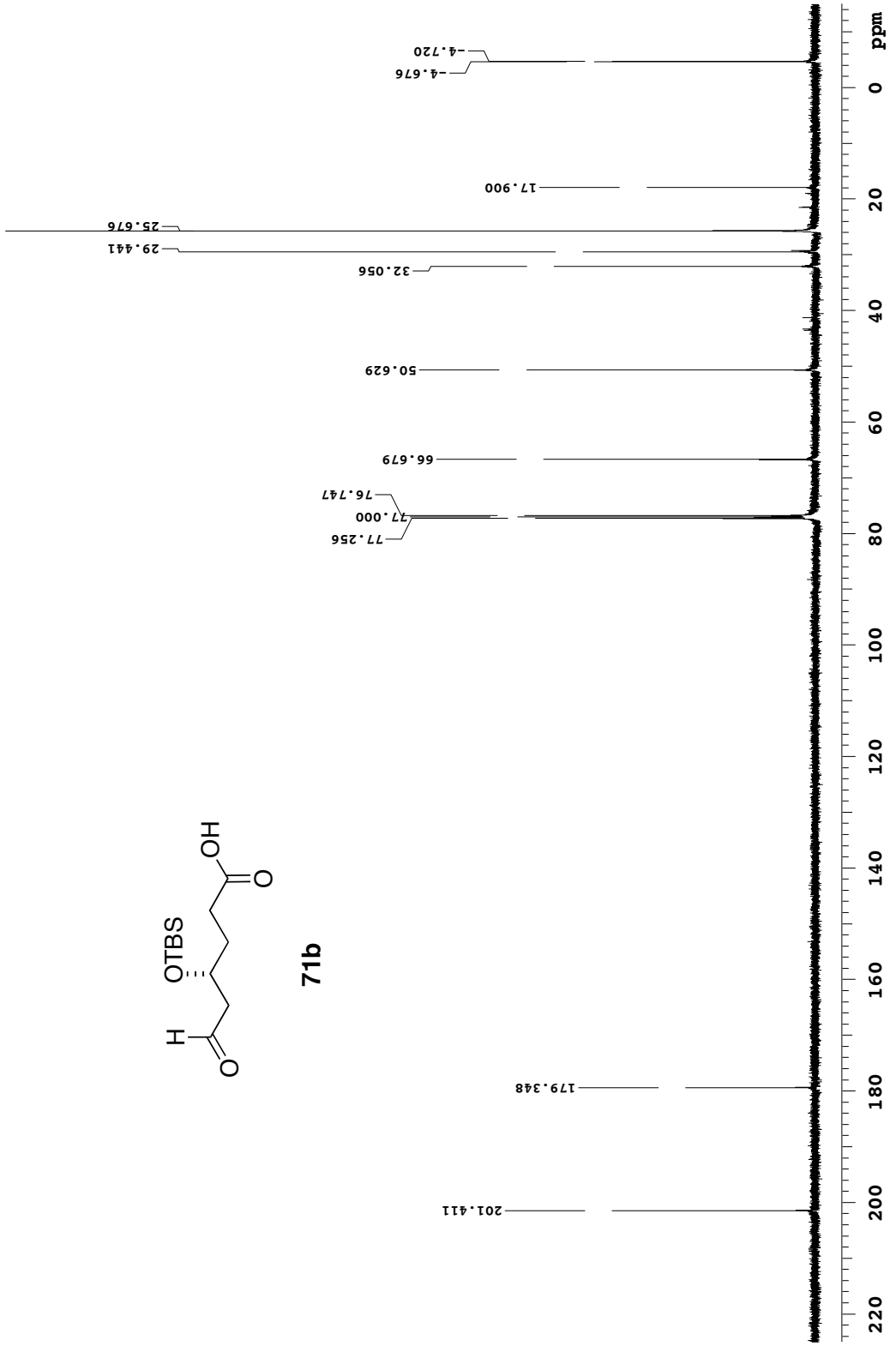

7.260
Ph
O
O
O
anti-11g
0.992
5.50
5.45
5.40
5.16
5.14
5.12
5.10
5.08
1.06
1.6
1.5
1.4
dichloromethane
grease
6.74
0.992
1
1.09
2.49
0.961
2.55
1.06
8
7
6
5
4
3
2
1
0 ppm

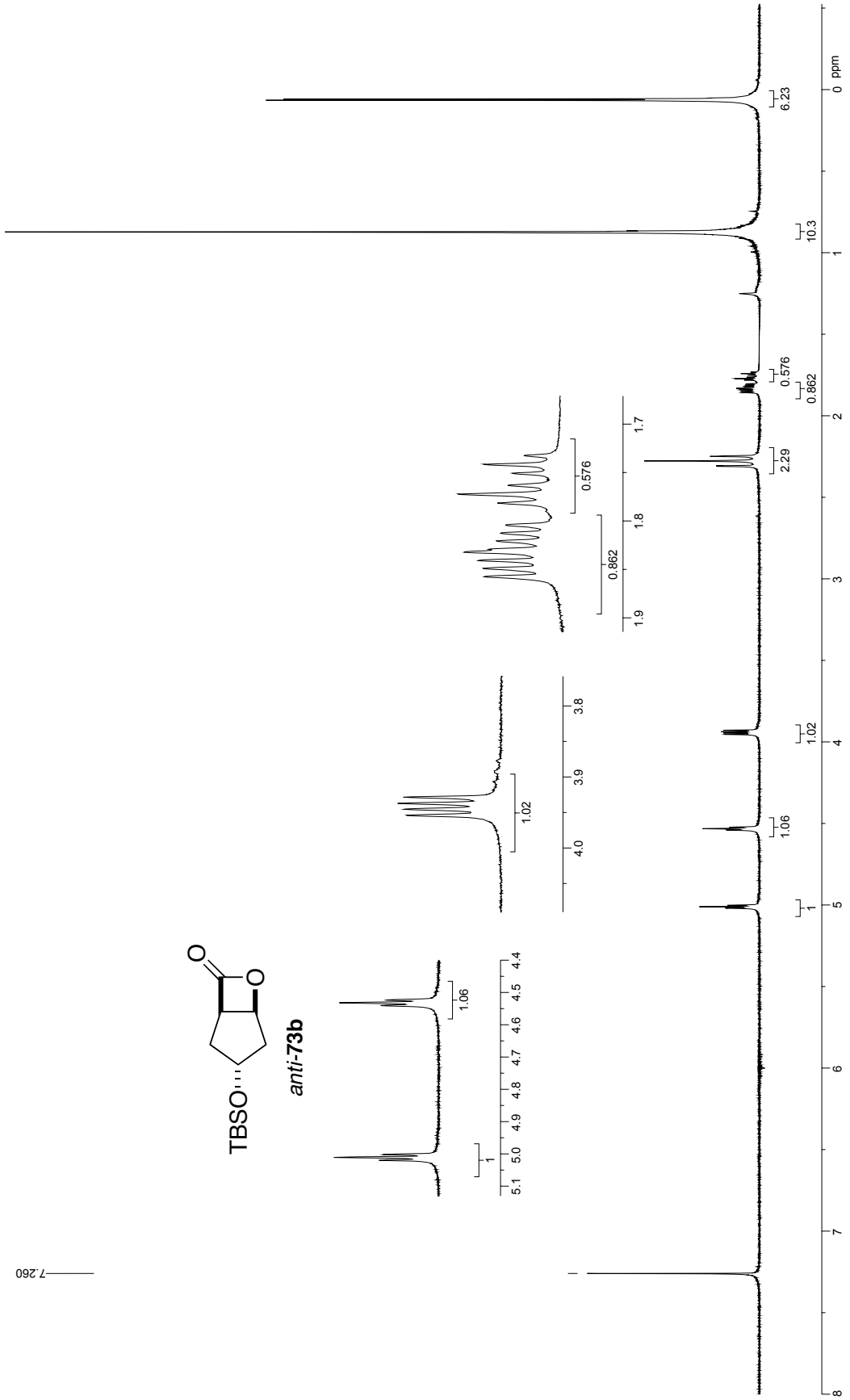

168.561
140.996
128.514
128.324
126.135
87.934
78.693
78.391
77.424
77.000
76.576
36.502
35.430
32.229
29.693
grease
Ph
anti-11g
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm
-10
-20

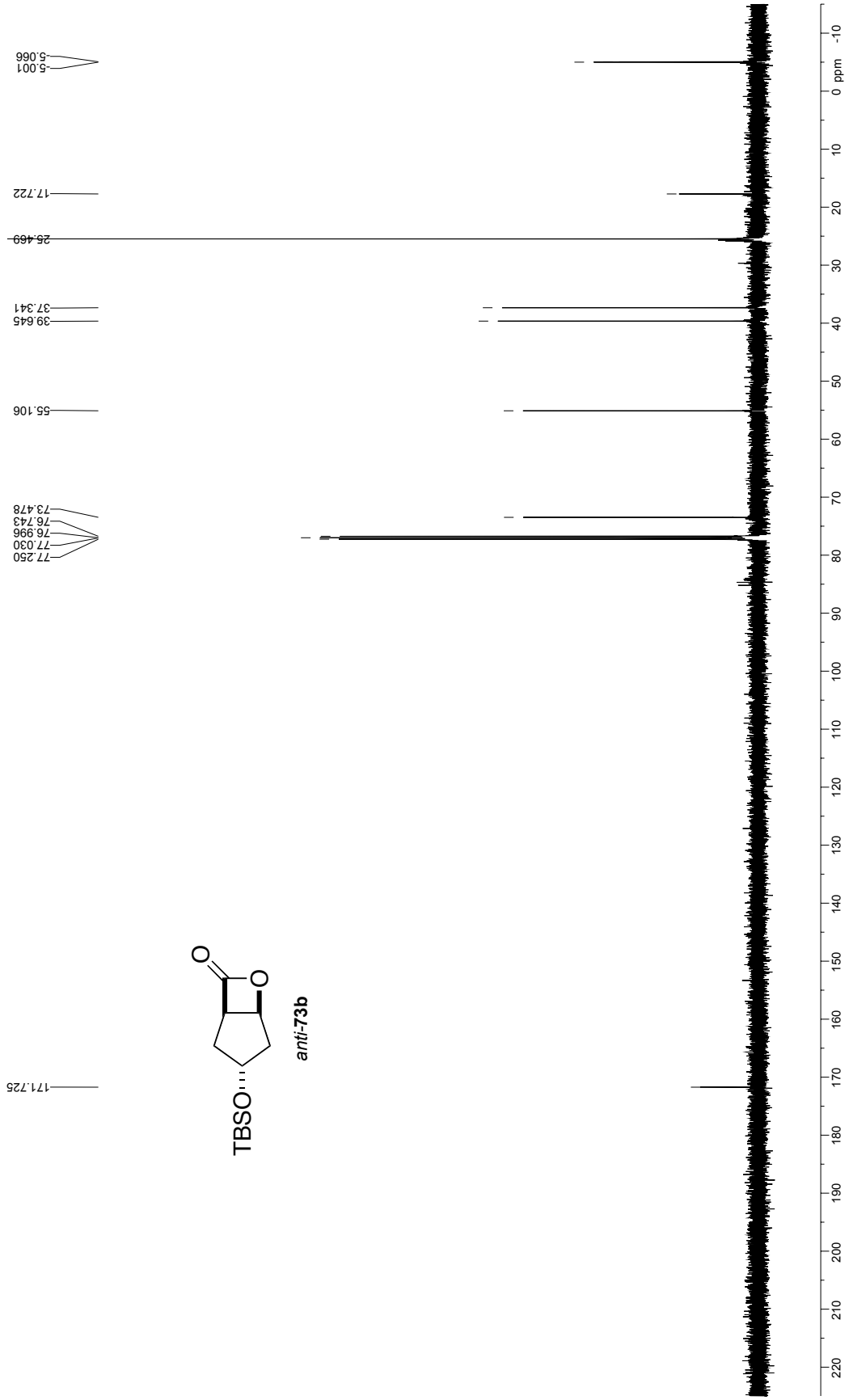

7.260
Ph
O
O
O
syn-11g
grease
ppm 7
6
5
4
3
2
1
0 ppm
5.95
1
1.07
1.06
1.22
1.11
3.63
1.24
5.46
5.44
5.42
5.40
5.38
5.36
5.34
4.62
4.60
4.58
4.56
4.54
4.52
4.50

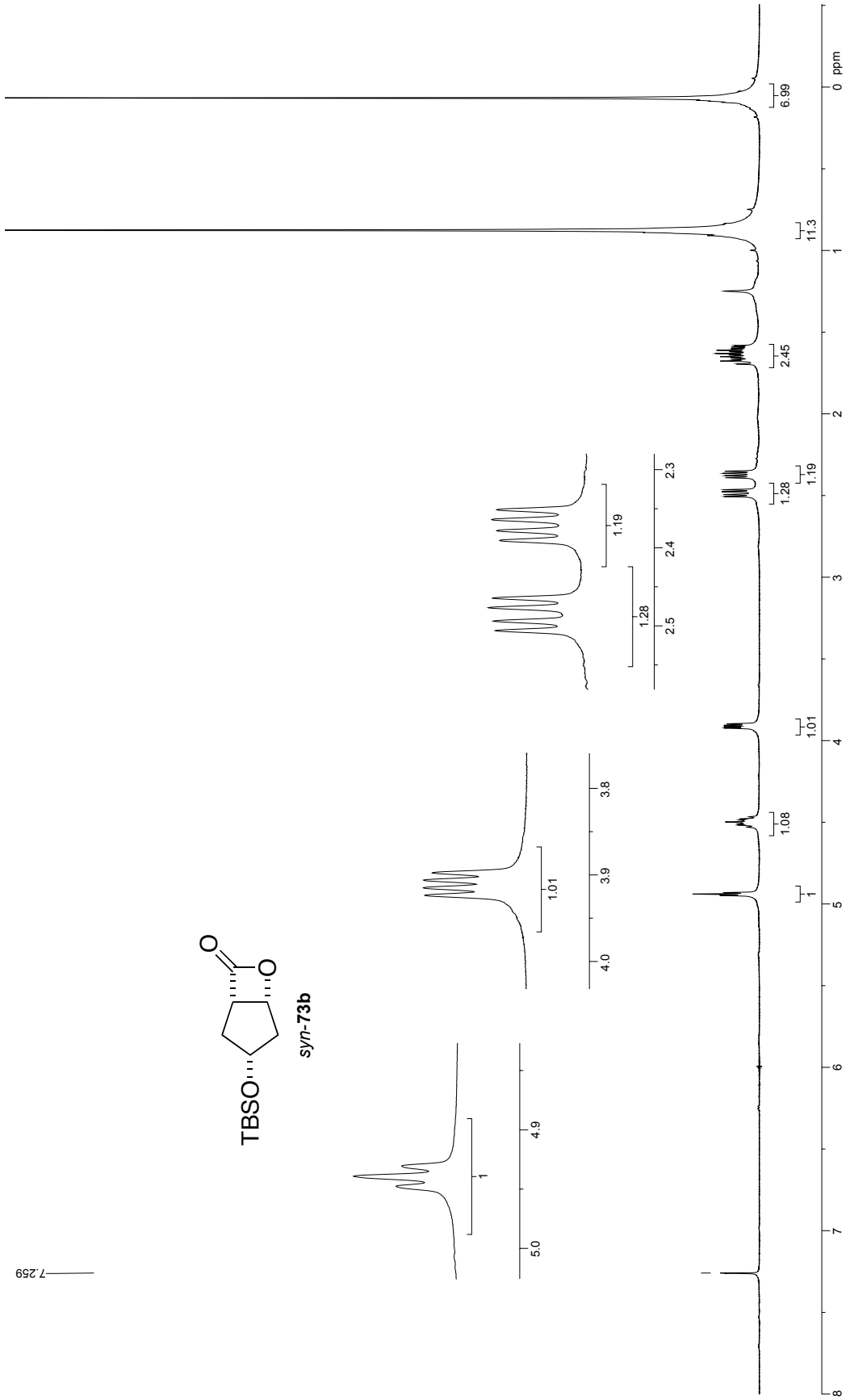

170.137
140.921
128.547
128.423
125.977
88.031
83.090
79.520
77.264
77.000
76.746
37.823
34.773
32.541
grease
Ph
O
O
O
syn-11g
0 ppm

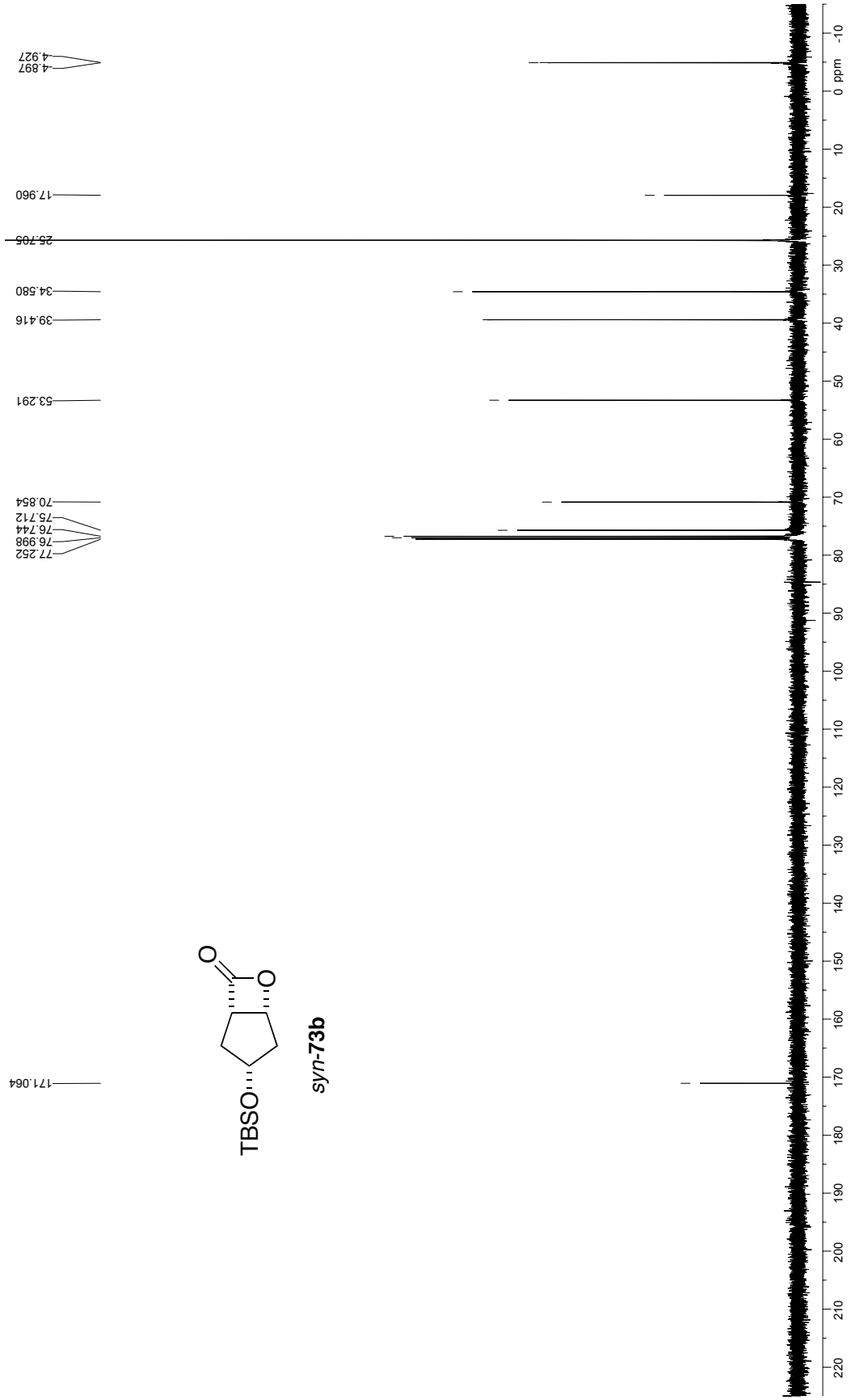

7.260
OTBS
OH
O
H
O
71b
4.2
4.3
1
6.01
9.6
2.57
2.13
2.47
1
0.891
0
1
2
3
4
5
6
7
8
9
10
11

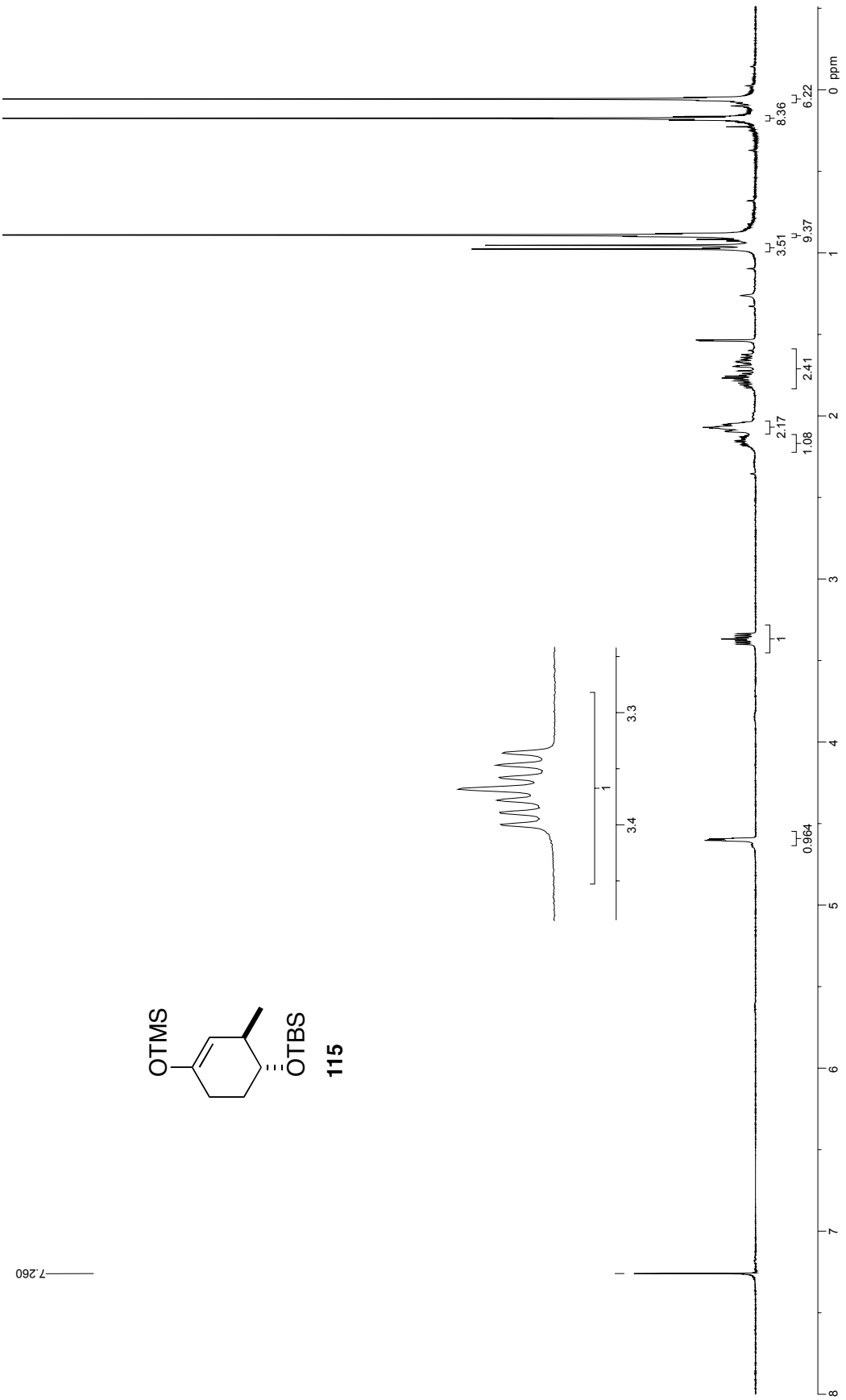

71b
OTBS
H
O
OH
O
201.411
179.348
77.256
77.000
76.747
66.679
50.629
32.056
29.441
25.676
17.900
-4.676
-4.720
ppm

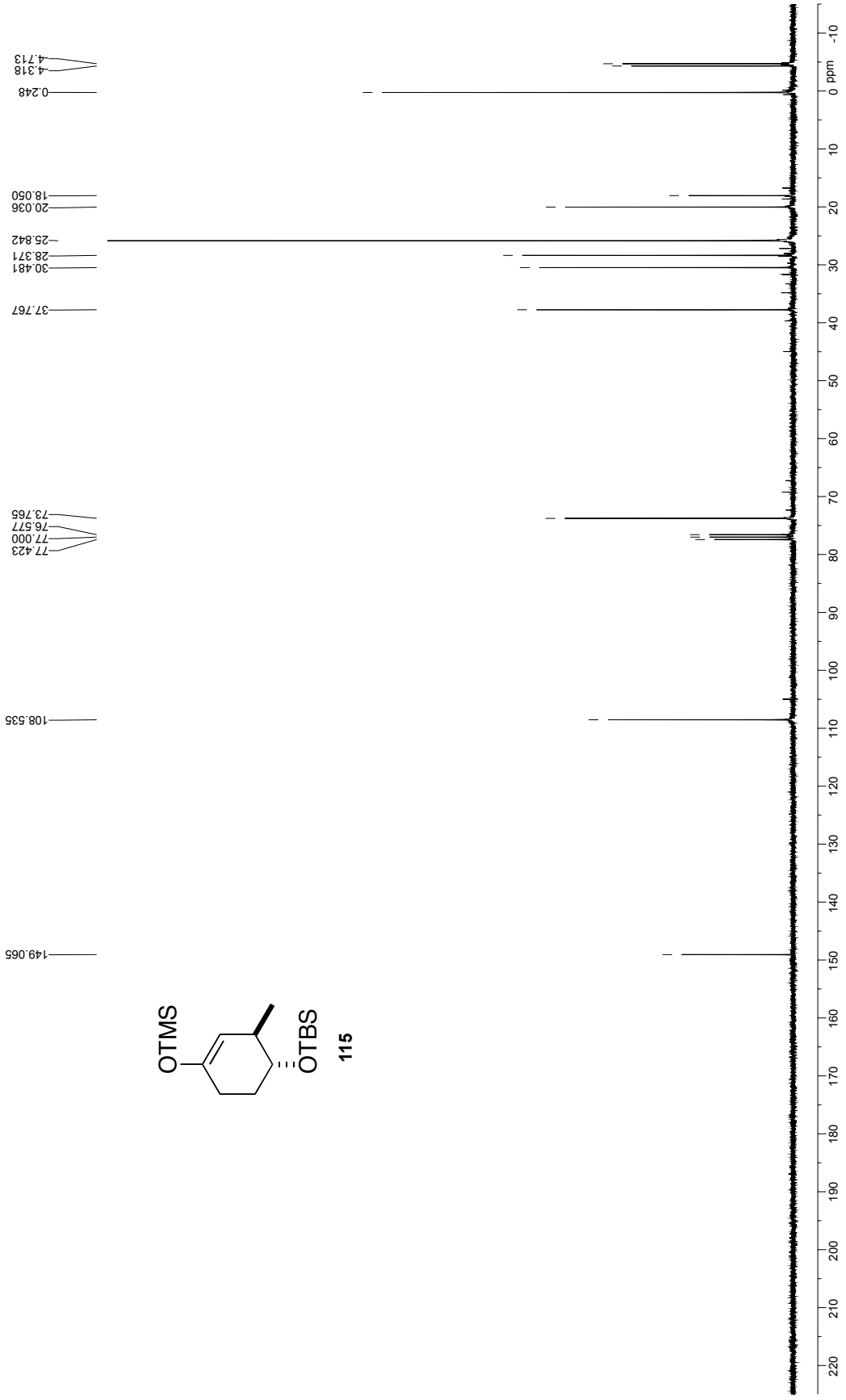

TBSO
anti-73b
7.260
0 ppm

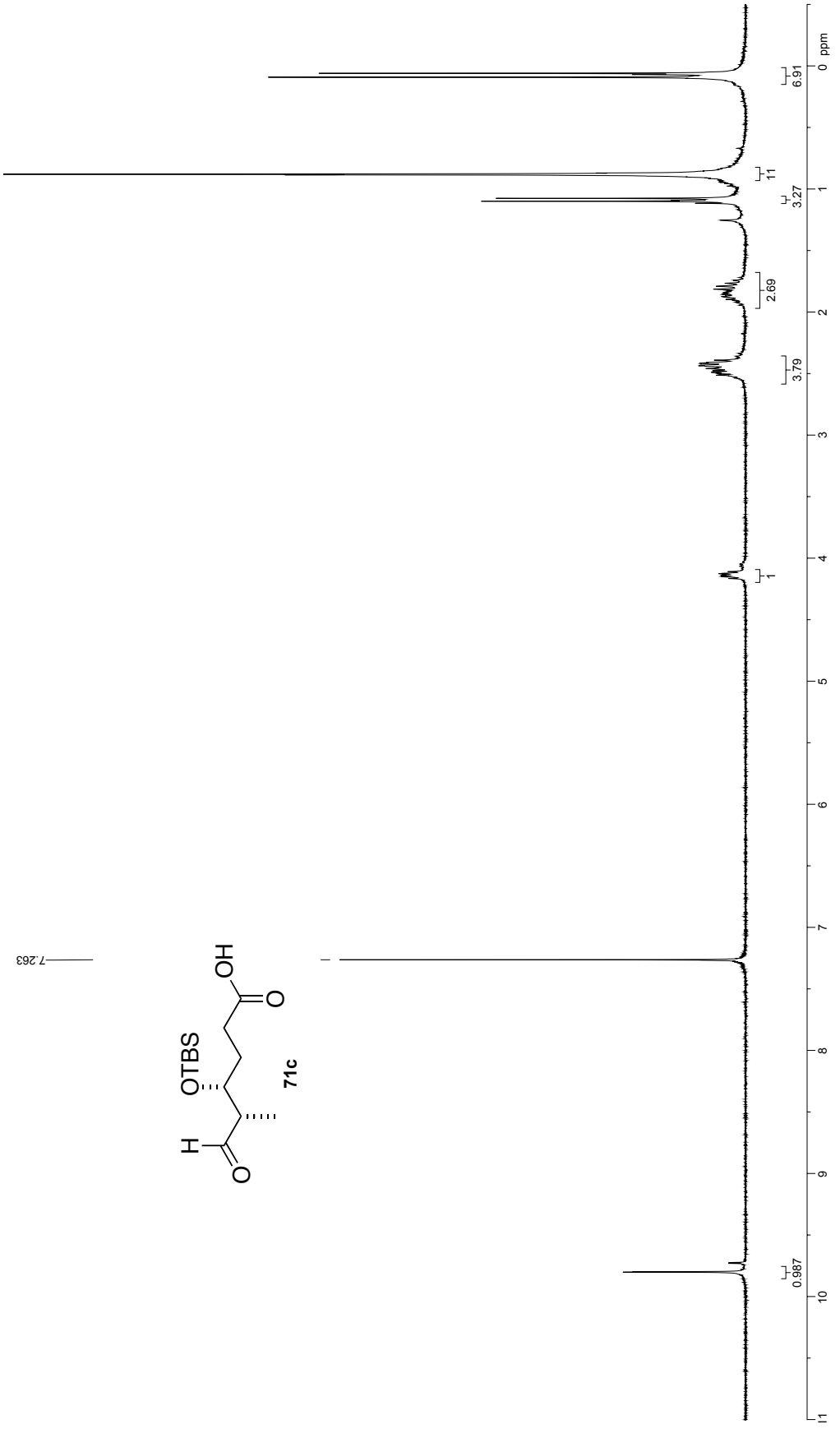

-5.066
-5.001
17.722
25.469
37.341
39.645
55.106
73.478
76.743
76.996
77.030
77.250
171.725
TBSO
O
O
anti-73b
0 ppm

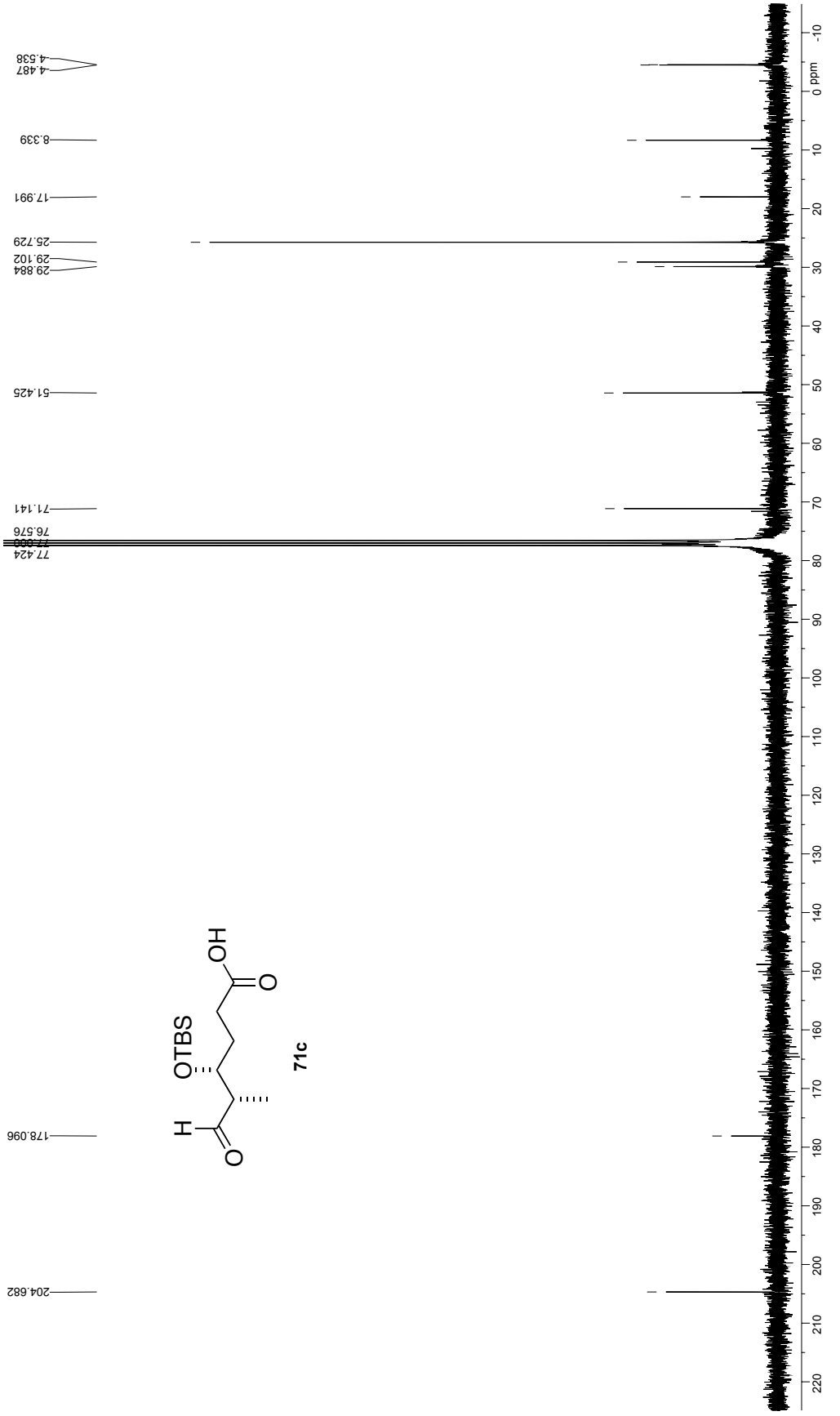

TBSO
O
O
syn-73b
7.259
ppm

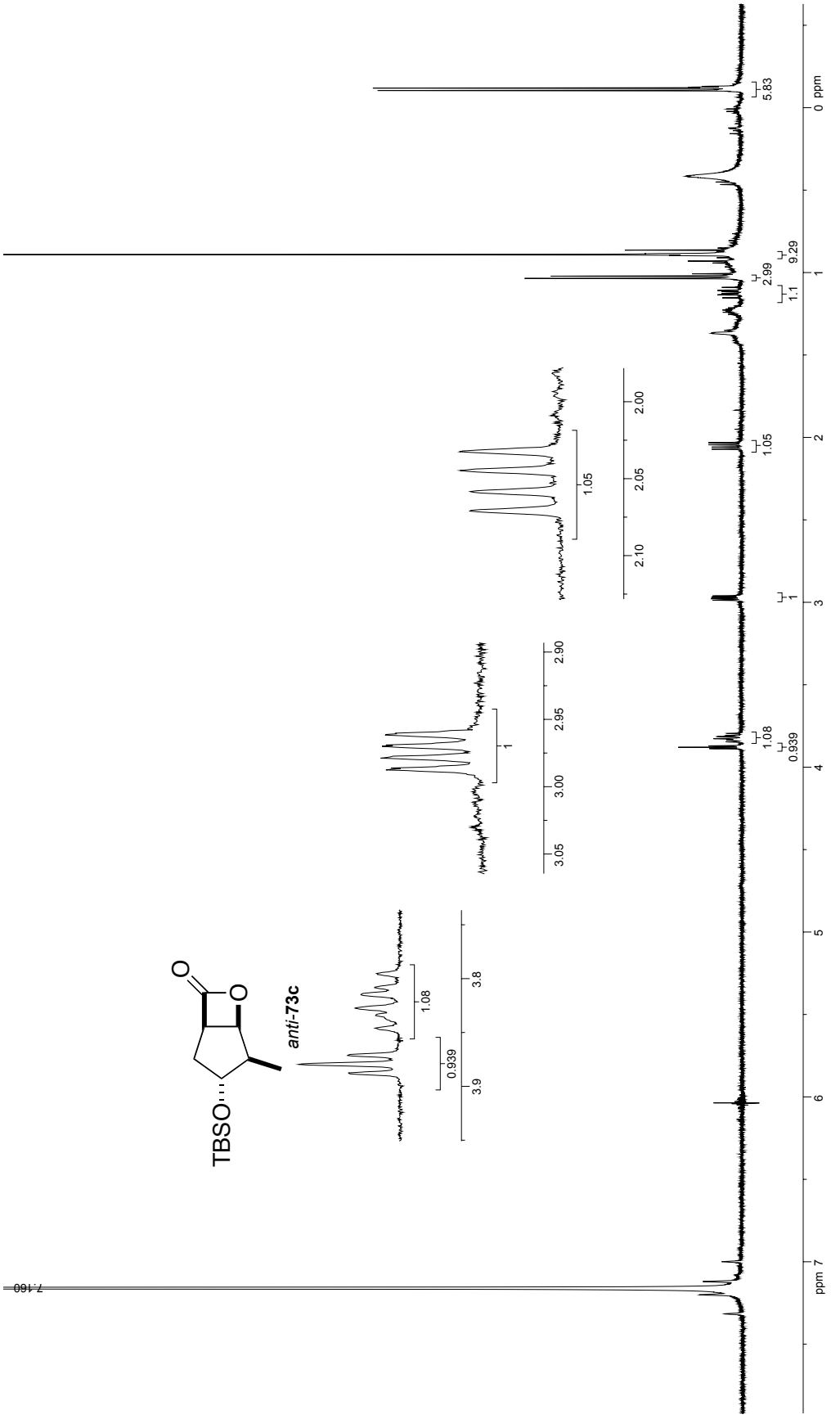

171.064
77.252
76.998
76.744
75.712
70.854
53.291
39.416
34.580
25.705
17.960
4.897
4.927
TBSO
O
O
syn-73b
0 ppm

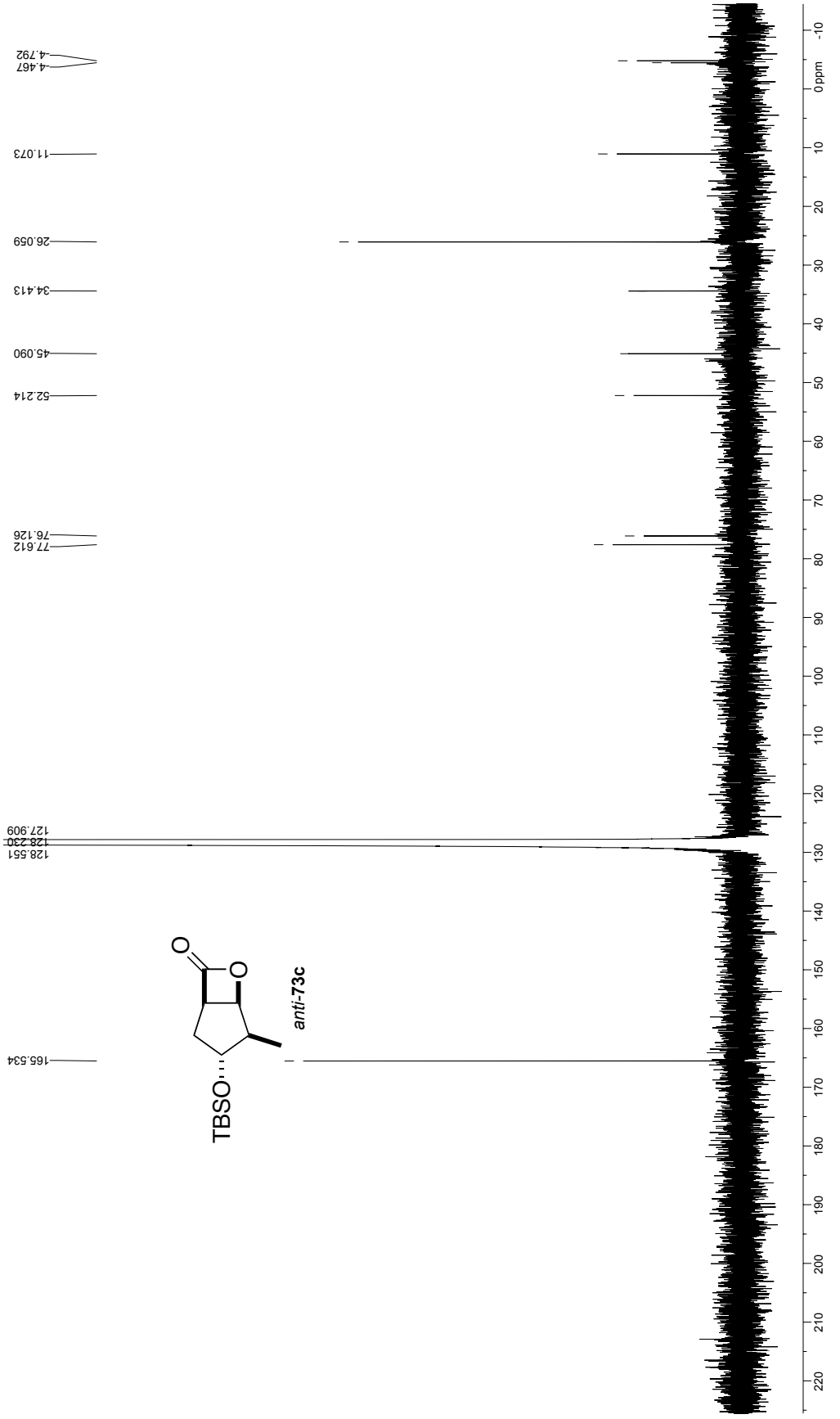

OTMS
OTBS
115
7.260
0.964
3.4
1
3.3
1
2.17
1.08
2.41
3.51
9.37
8.36
6.22
1
0 ppm

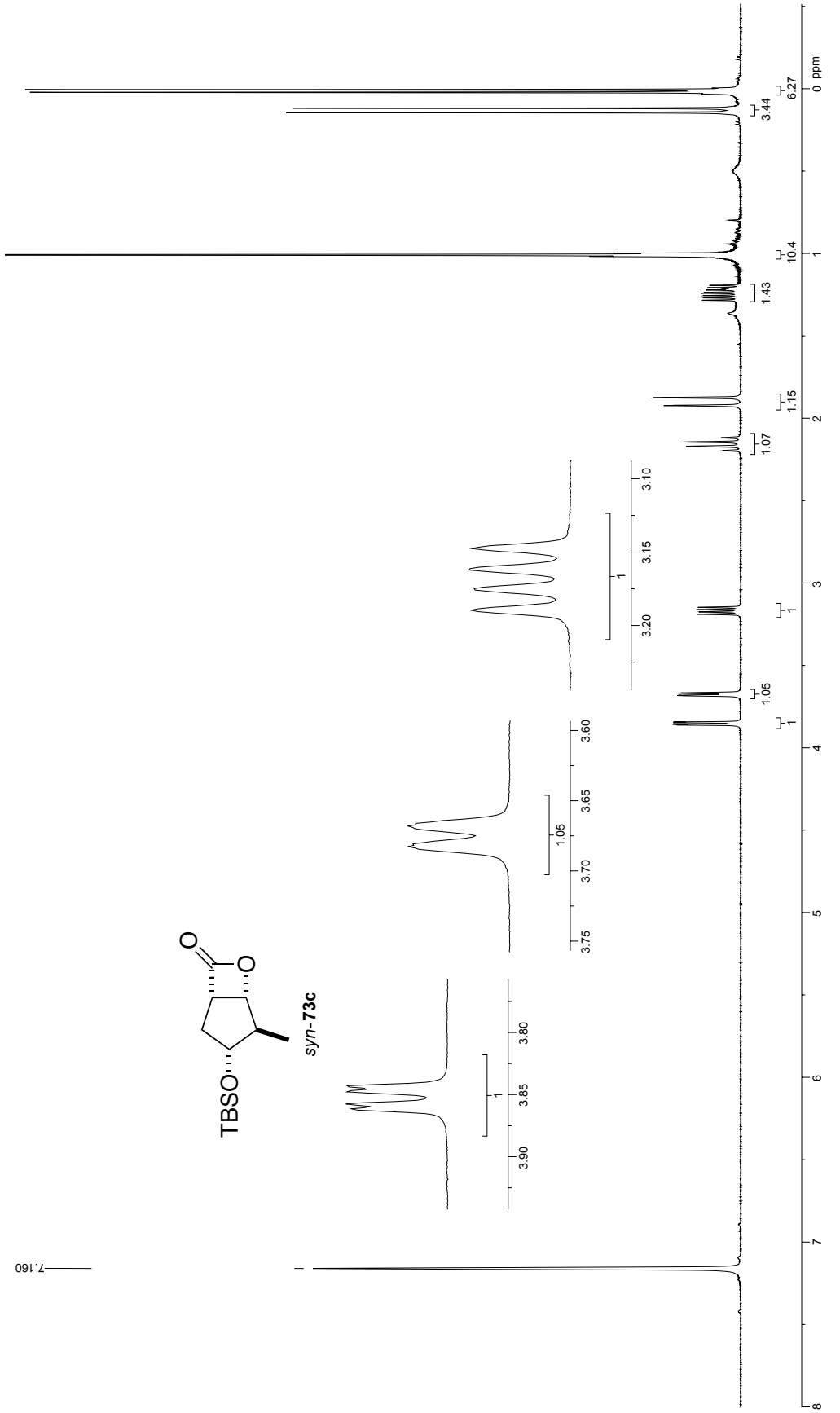

-4.713
-4.318
0.248
18.050
20.036
25.842
28.371
30.481
37.767
73.765
76.577
77.000
77.423
108.535
149.065
OTMS
OTBS
115
0 ppm

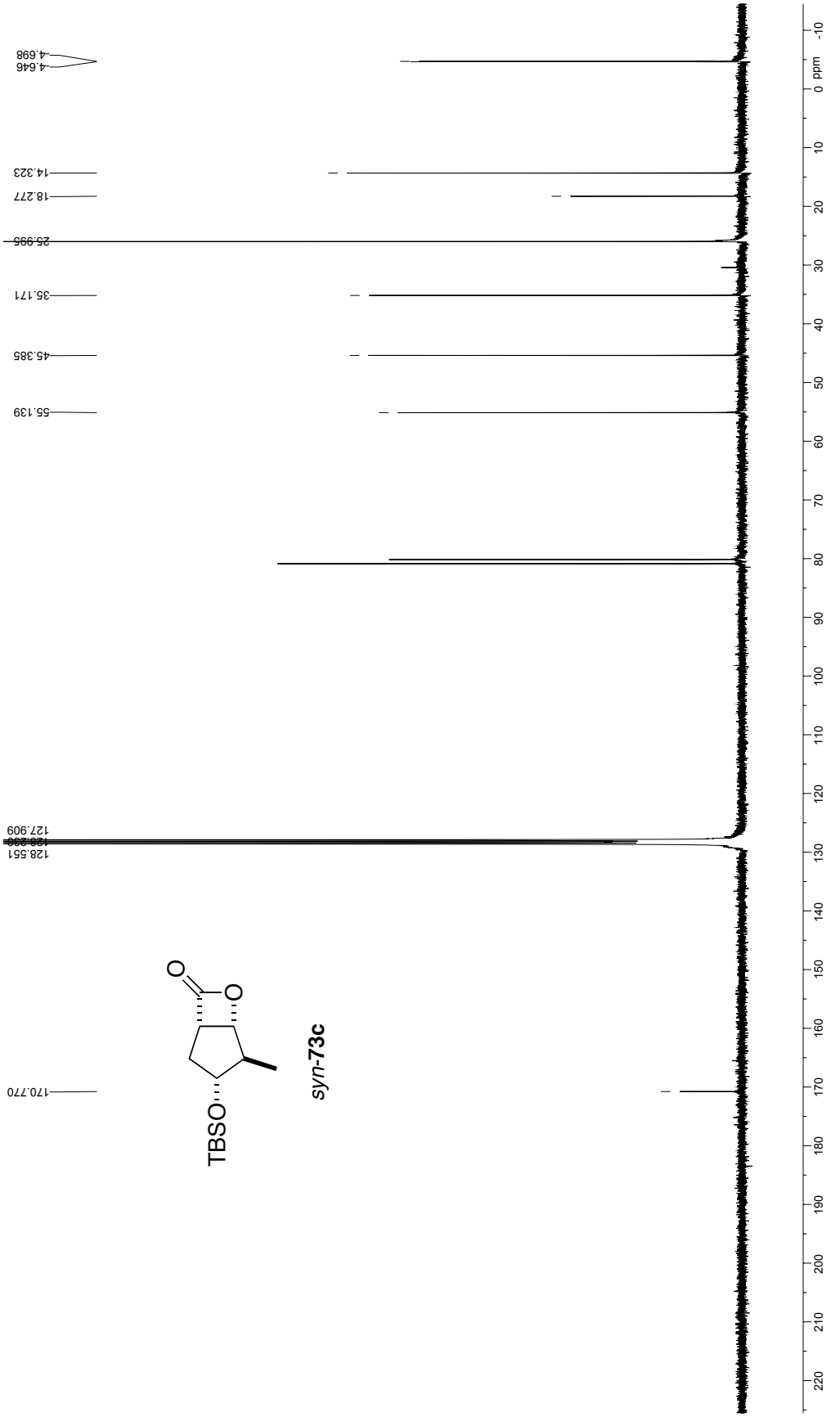

7.263
OH
O
OTBS
H
O
71c
0.987
1
11
3.27
2.69
3.79
6.91
ppm

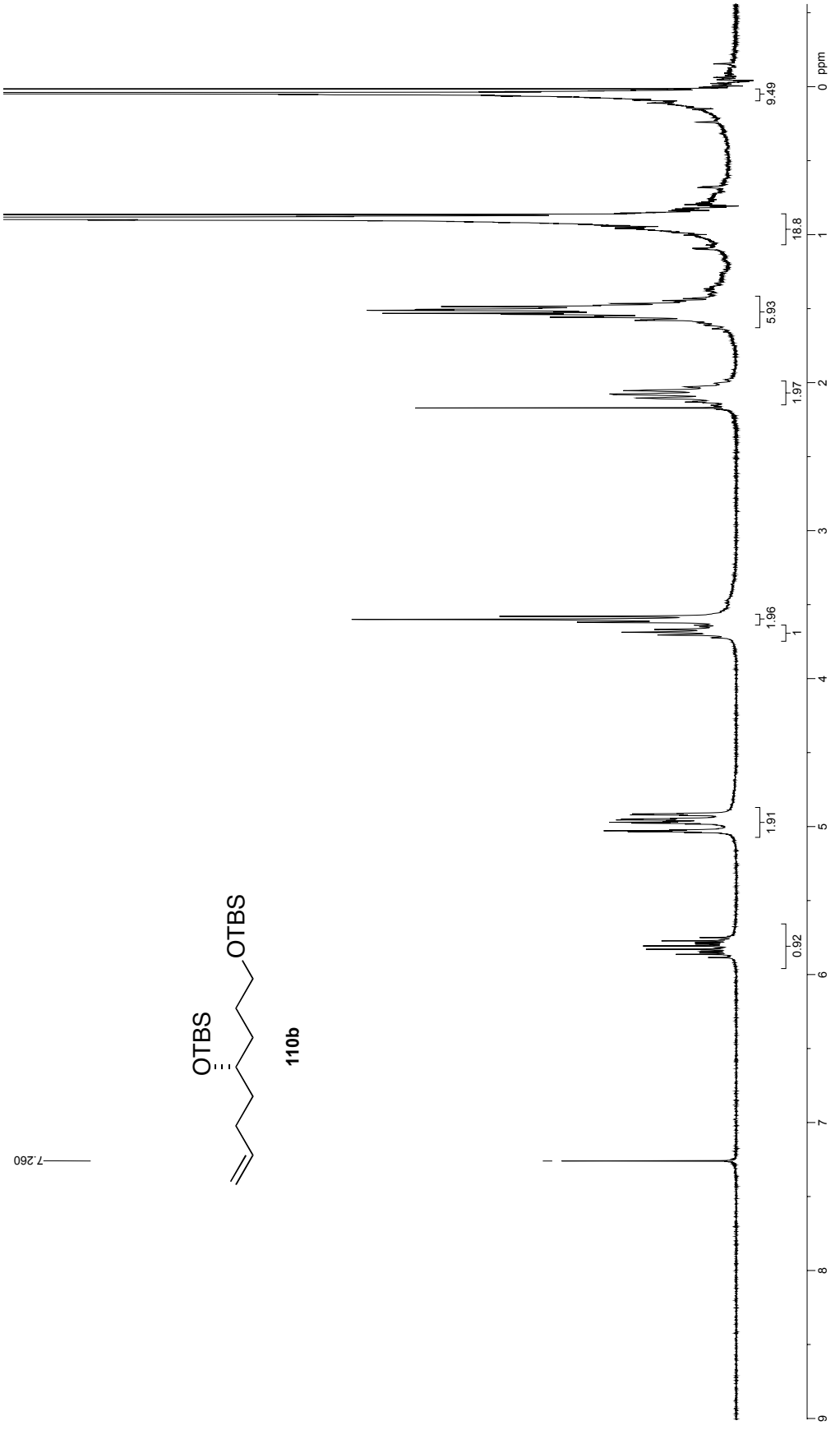

4.538
4.487
8.339
17.991
25.729
29.102
29.884
51.425
71.141
76.576
77.424
178.096
204.682
OTBS
OH
O
H
O
71c
0 ppm

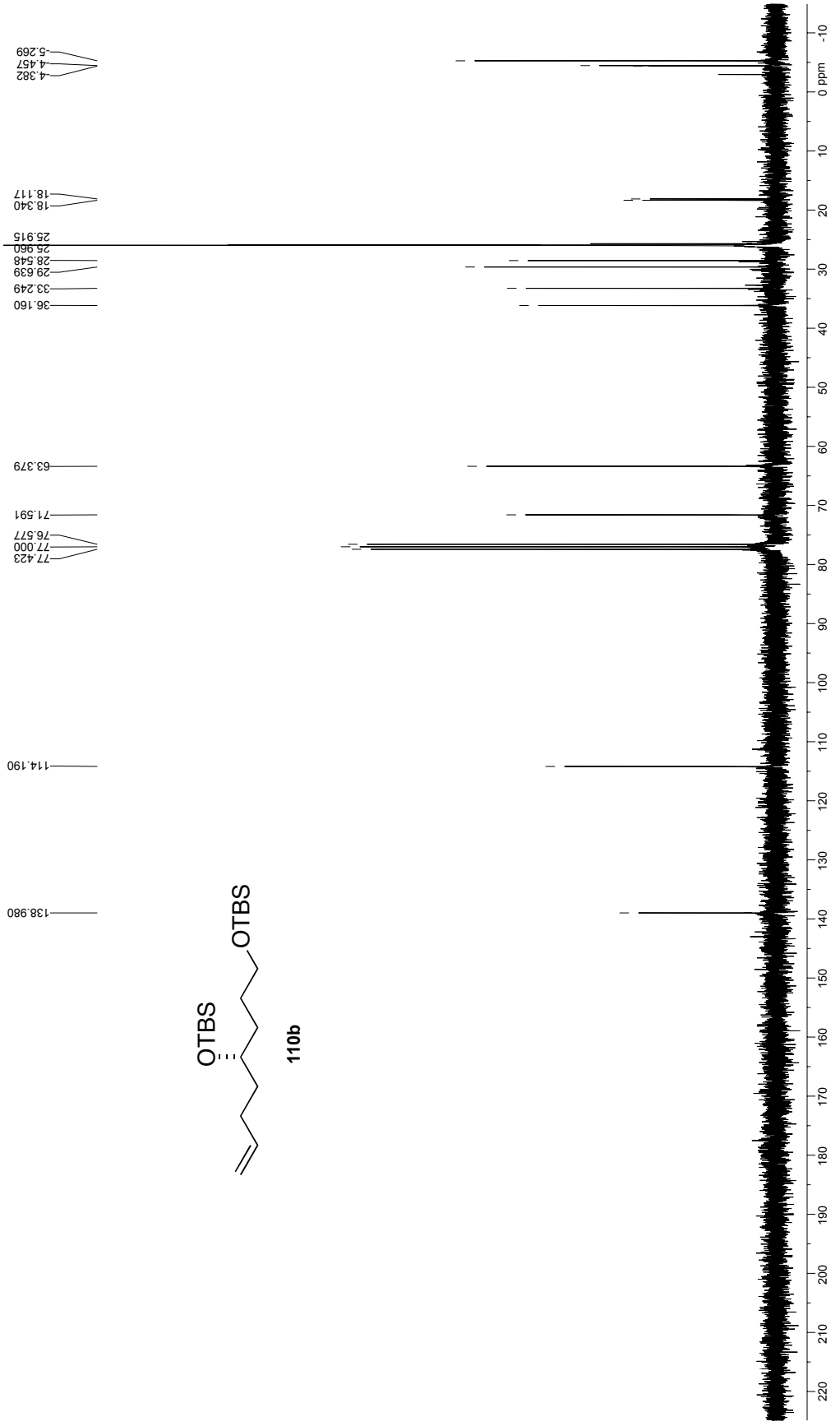

TBSO
anti-73c
7.160
ppm 7
6
5
4
3
2
1
0 ppm
1.08
0.939
1
1.05
2.99
1.1
9.29
5.83
3.9
3.8
3.05
3.00
2.95
2.90
2.10
2.05
2.00

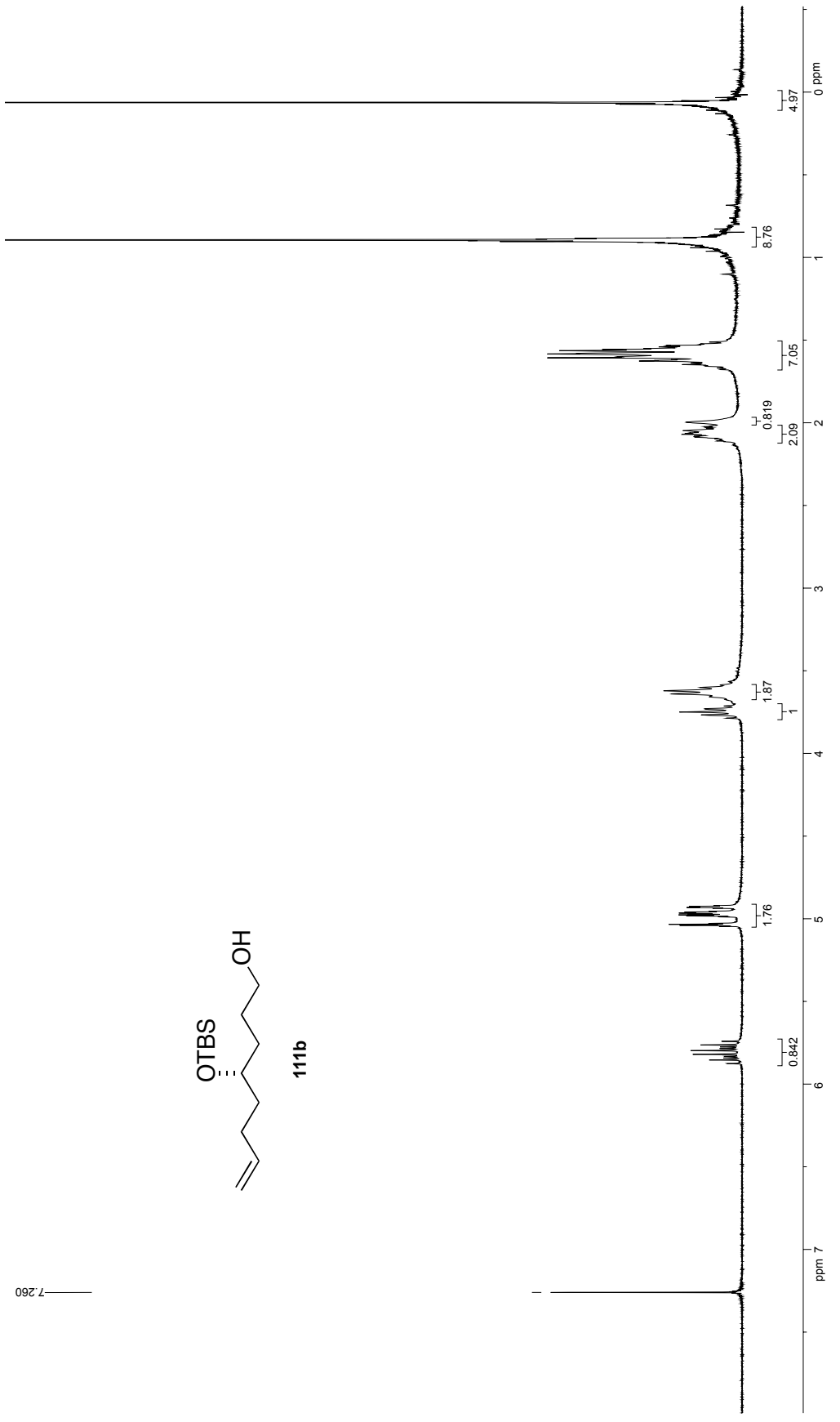

-4.792
-4.467
11.073
26.059
34.413
45.090
52.214
76.126
77.612
127.909
128.230
128.551
165.534
TBSO
O
O
anti-73c
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
ppm

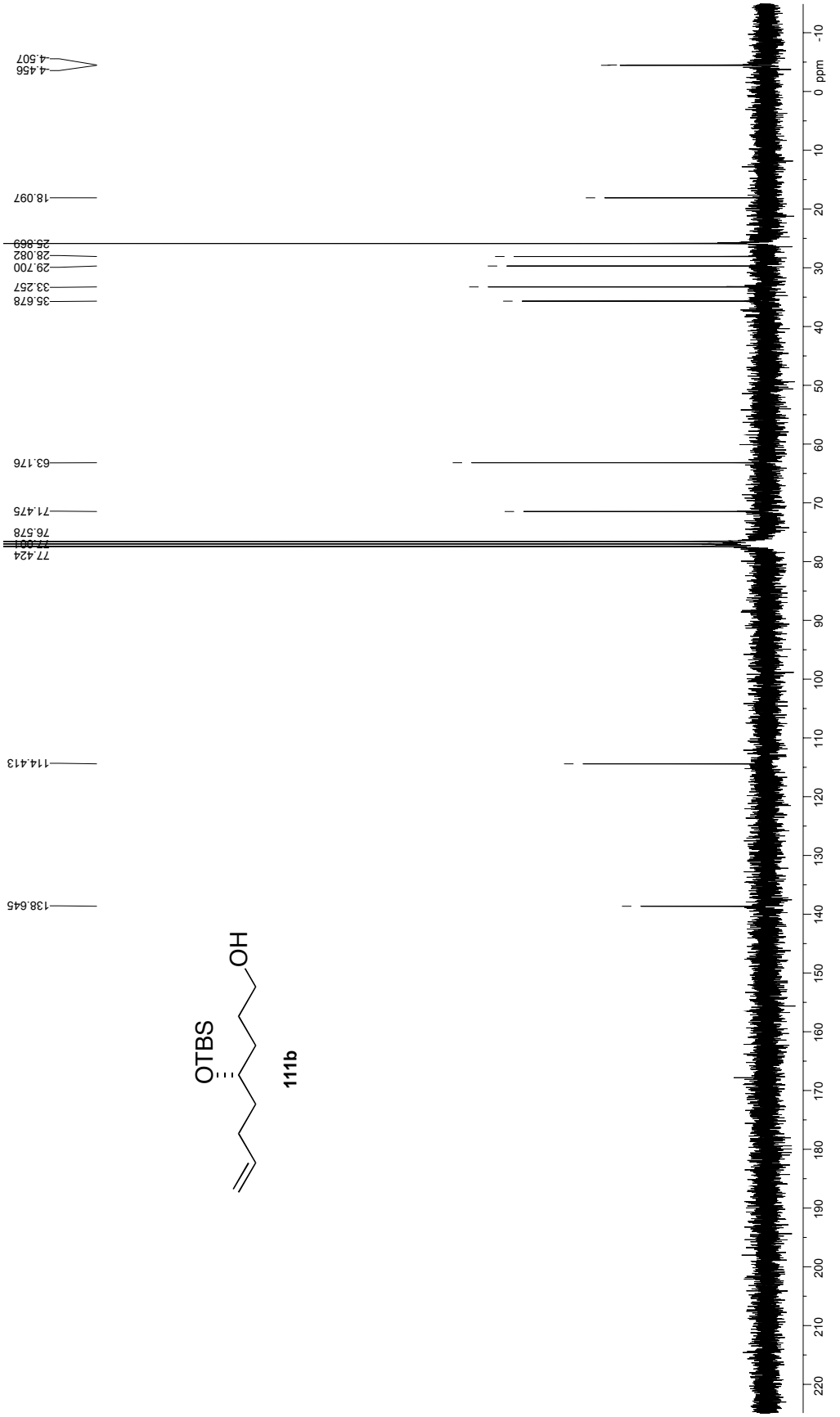

TBSO
O
O
syn-73c
7.160
3.90
3.85
3.80
1
3.75
3.70
3.65
3.60
1.05
3.20
3.15
3.10
1
1.05
1
1
1.07
1.15
2
1.43
10.4
1
3.44
6.27
0 ppm
8
7
6
5
4
3
2
1

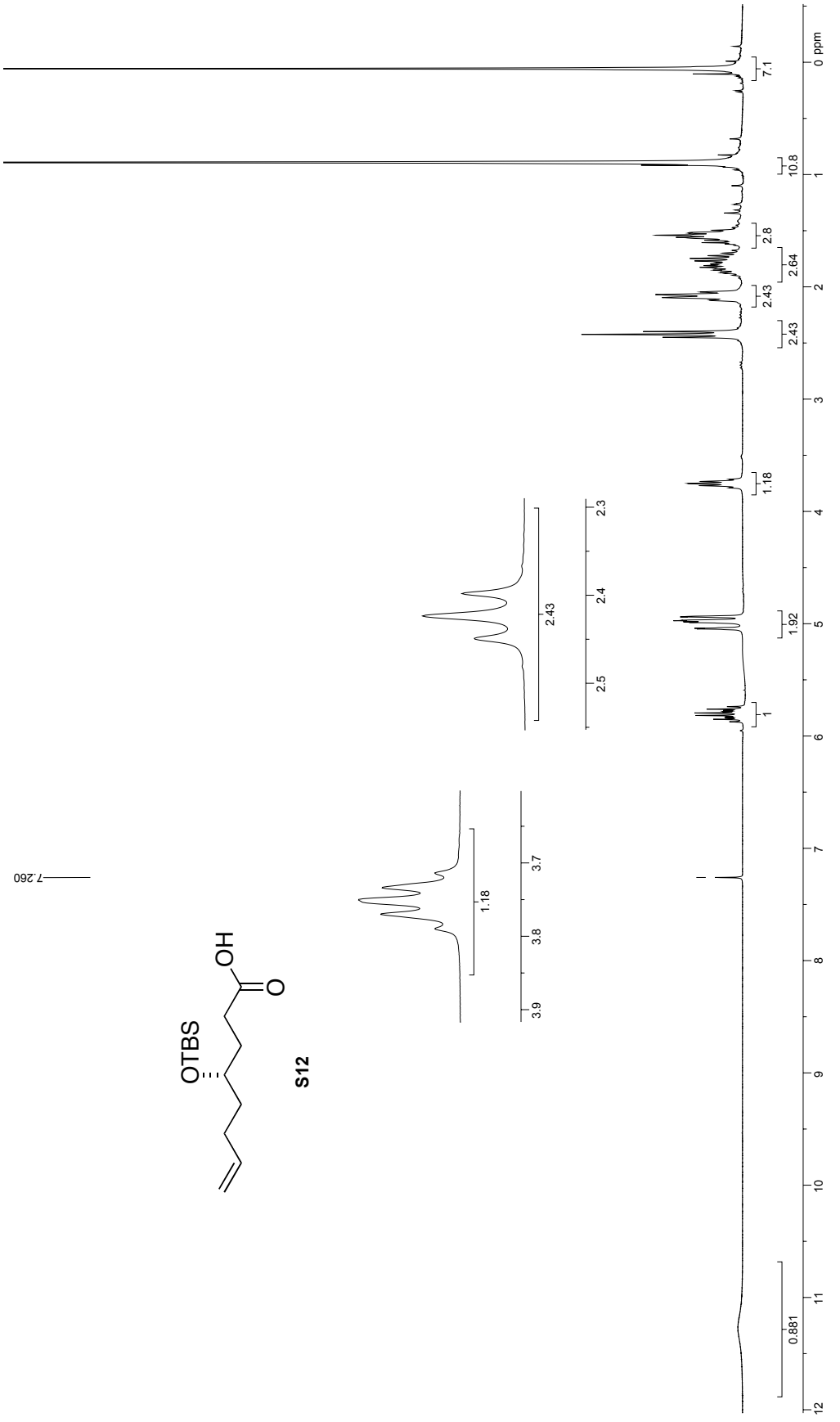

4.698
4.646
14.323
18.277
25.995
35.171
45.385
55.139
127.909
128.399
128.561
170.770
TBSO
O
O
syn-73c
0 ppm

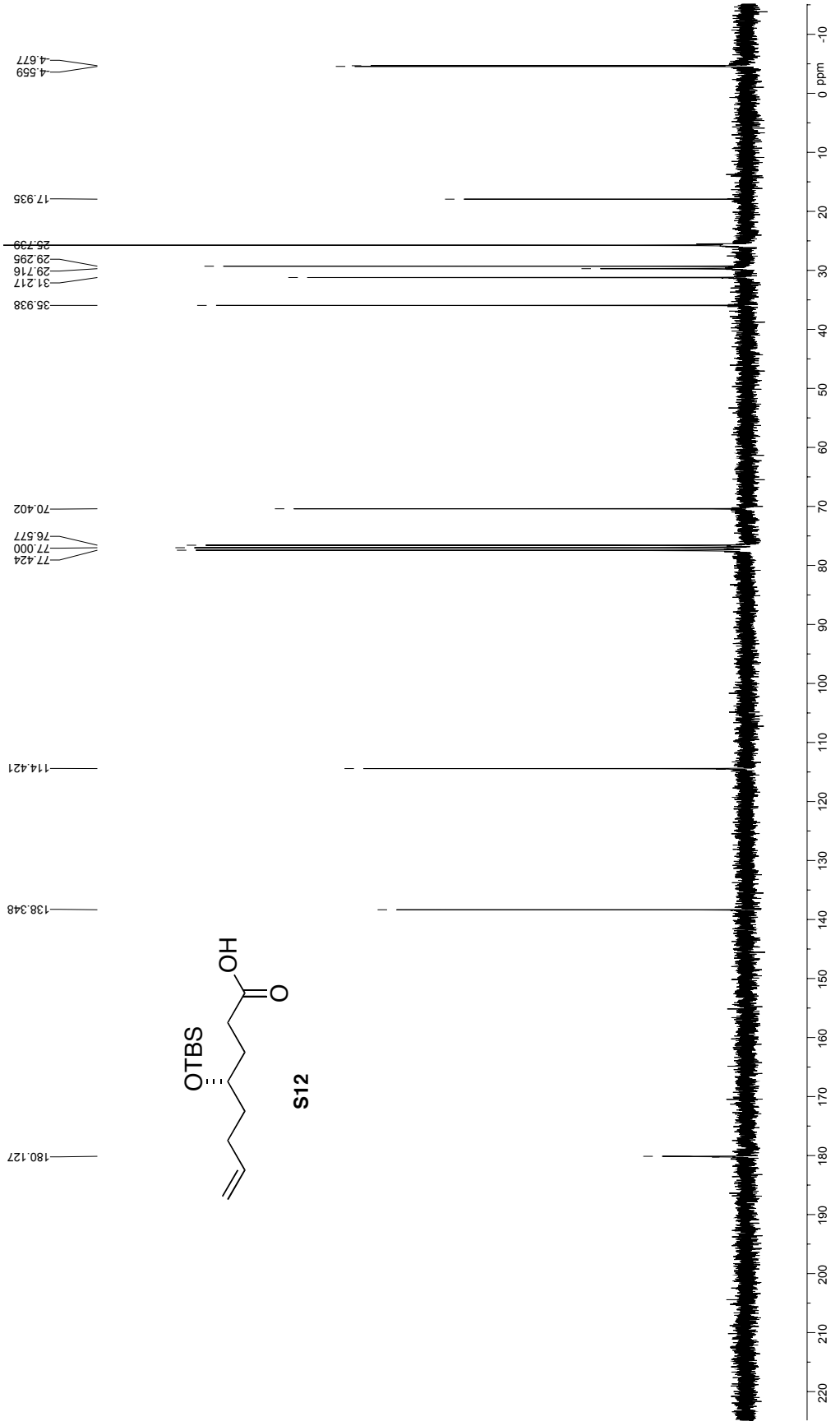

OTBS
OTBS
110b
7.260
9.49
18.8
5.93
1.97
1.96
1
1.91
0.92
0 ppm
1
2
3
4
5
6
7
8
9

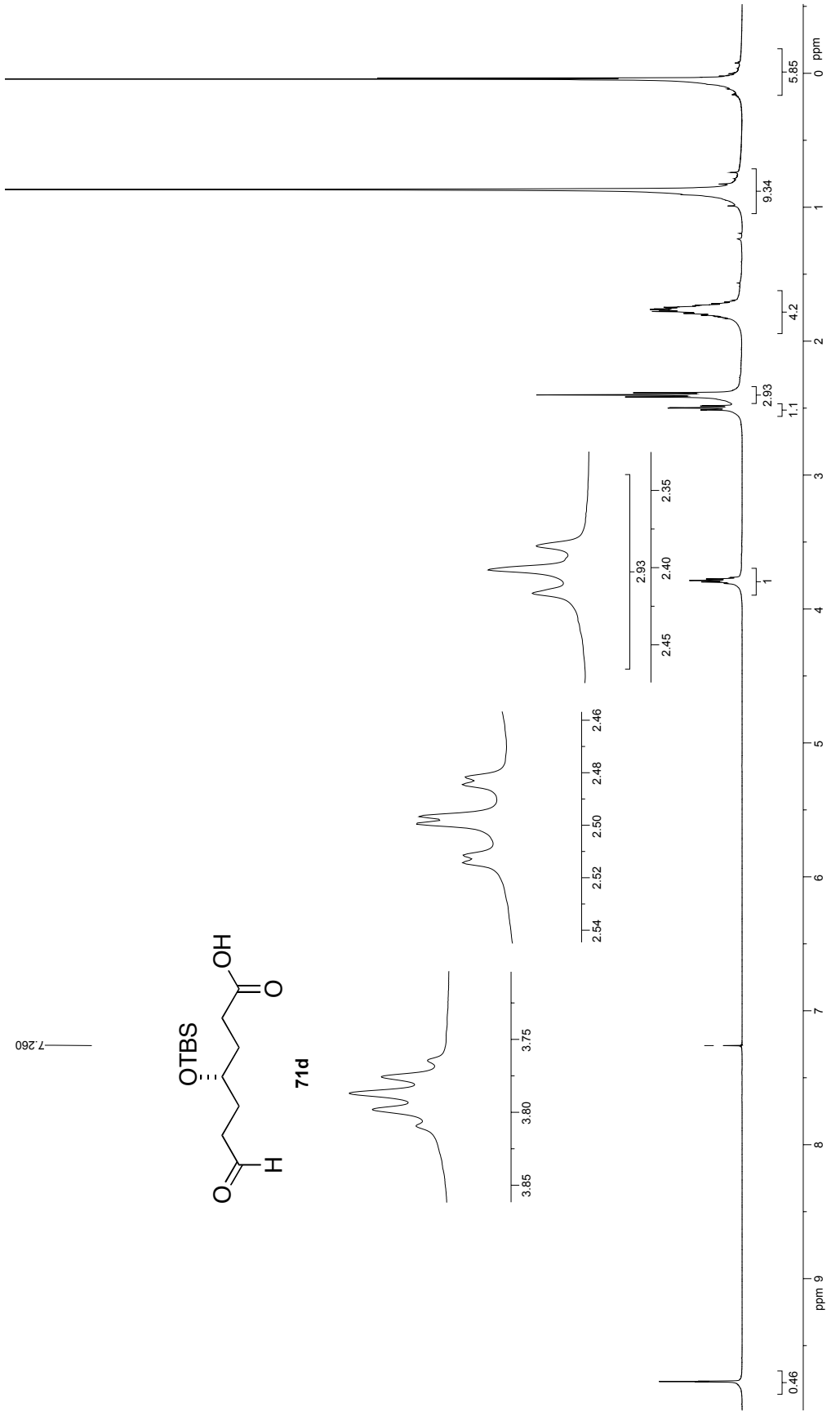

OTBS
OTBS
110b
138.980
114.190
77.423
77.000
76.577
71.591
63.379
36.160
33.249
29.639
28.548
25.960
25.915
18.340
18.117
4.457
4.382
-5.269
0 ppm

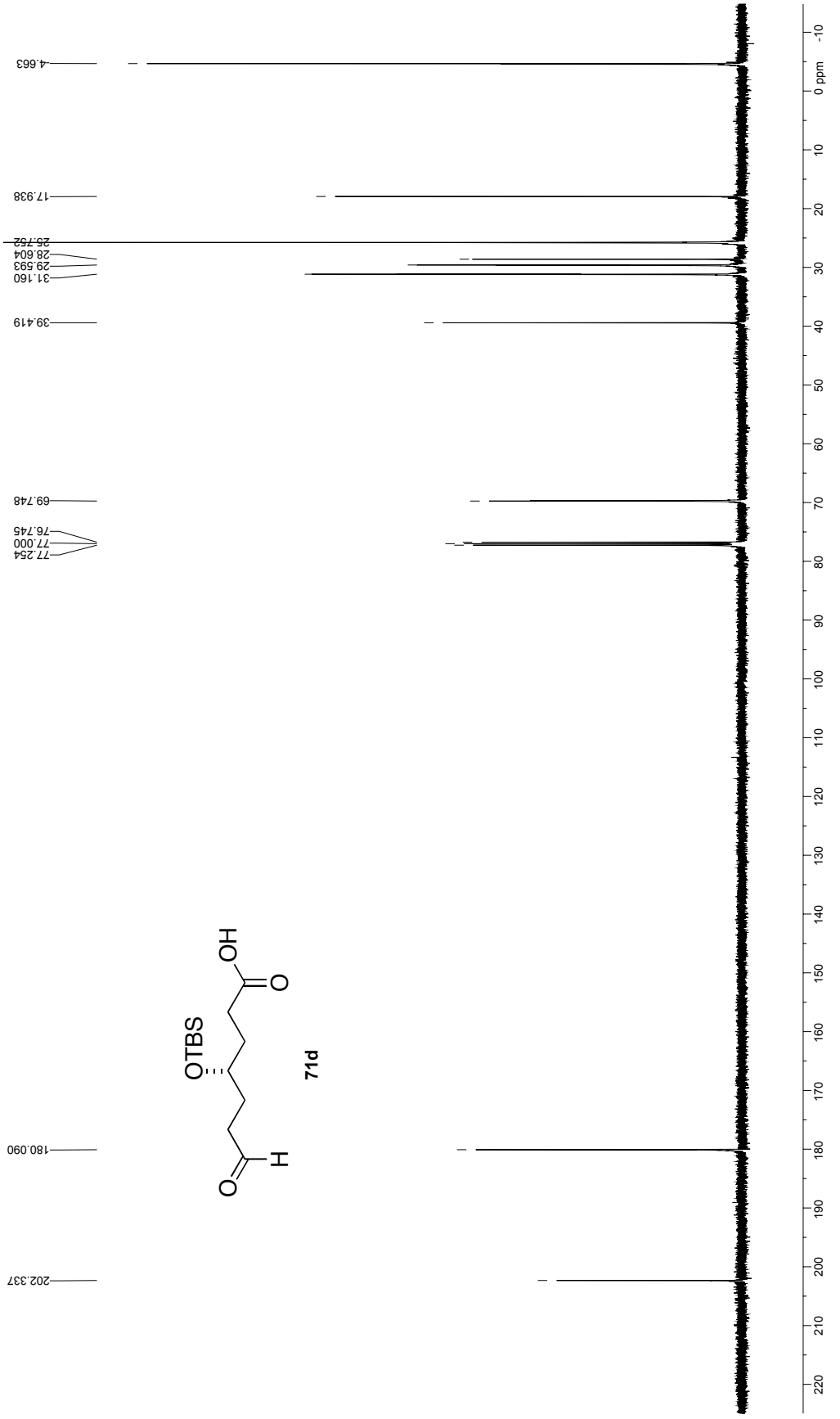

OTBS
OH
111b
7.260
ppm 7
6
5
4
3
2
1
0 ppm
0.842
1.76
1
1.87
0.819
2.09
7.05
8.76
4.97

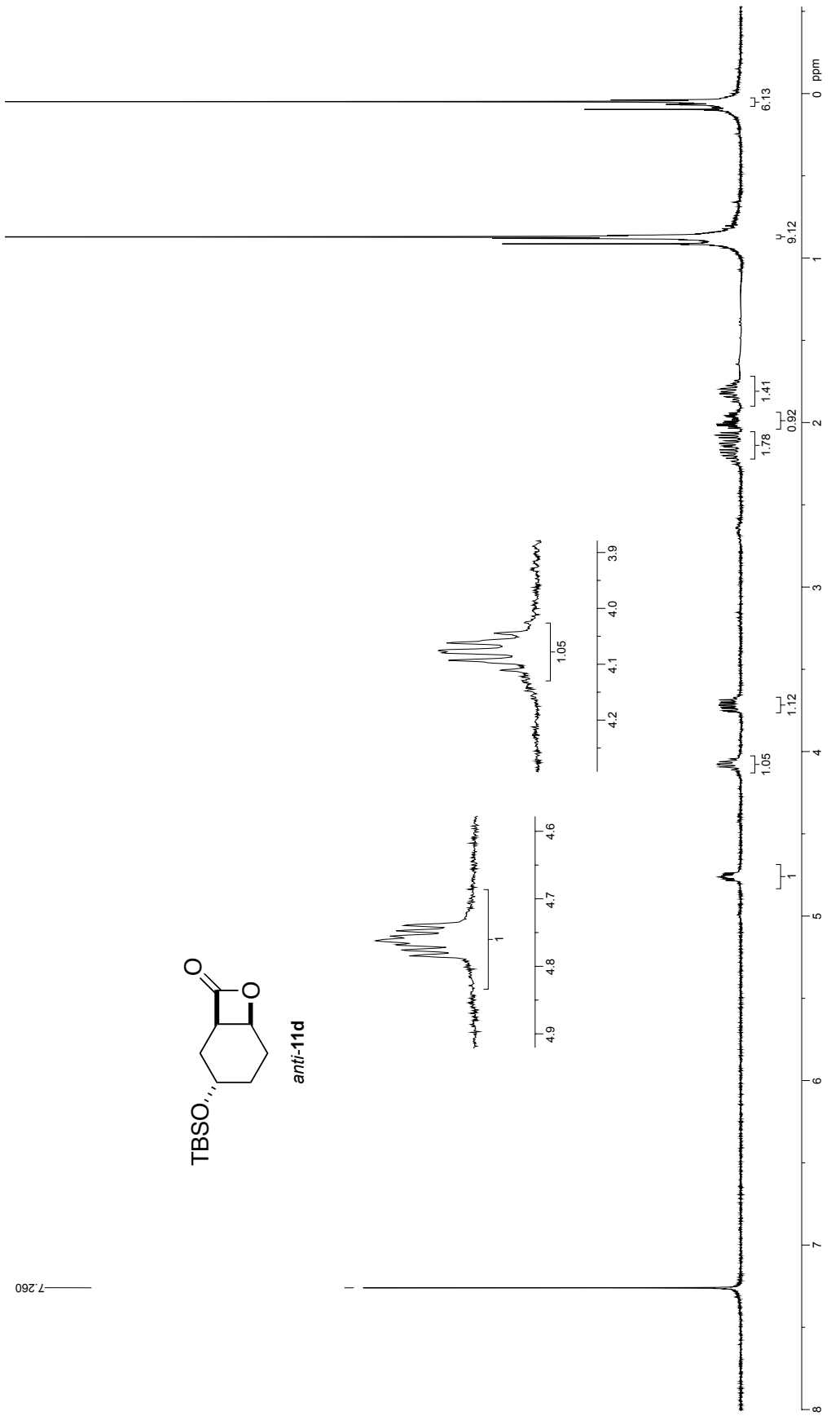

OTBS
OH
111b
138.645
114.413
77.424
76.578
71.475
63.176
35.678
33.257
29.700
28.082
25.869
18.097
4.507
4.456
0 ppm

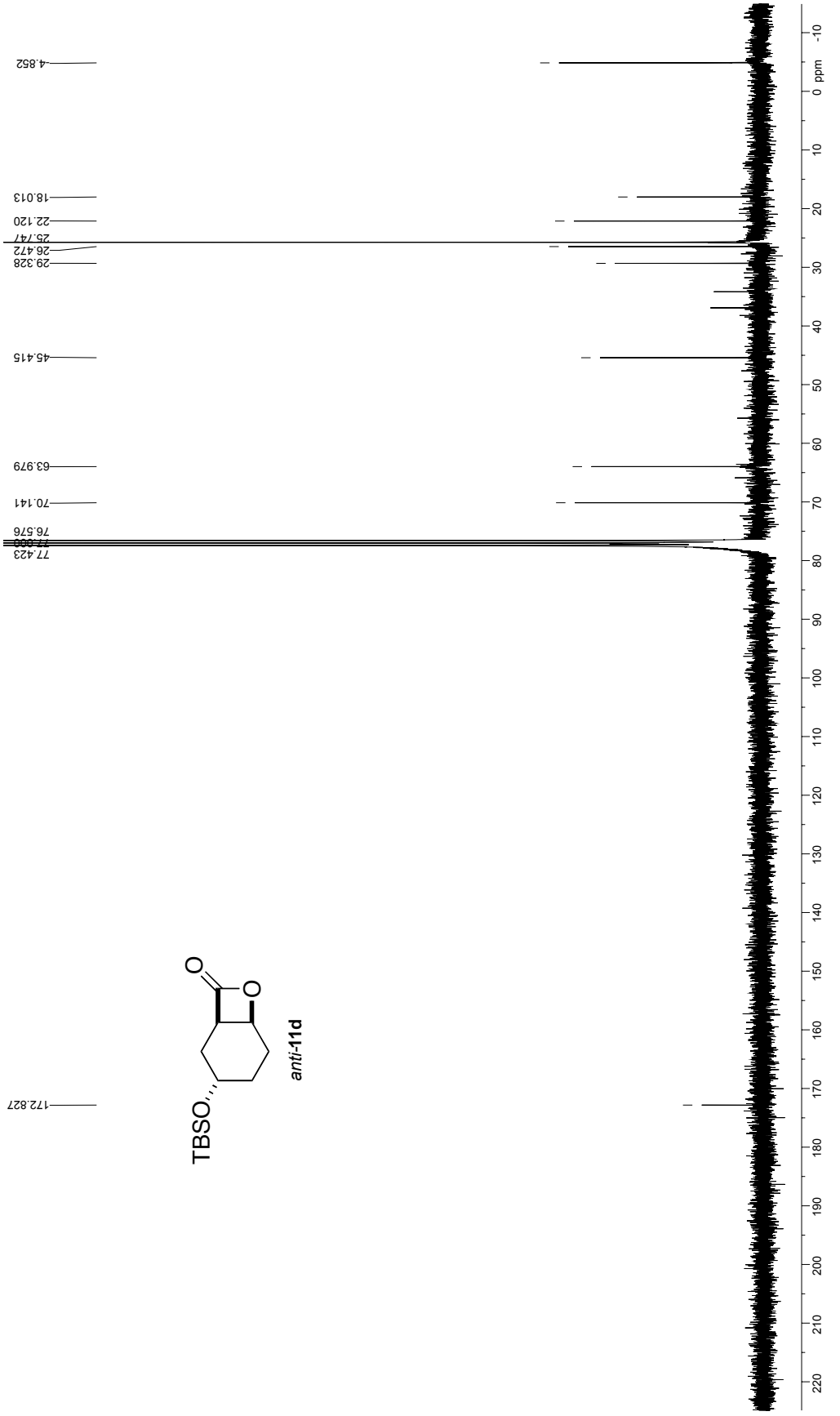

OTBS
OH
O
S12
7.260
0.881
1.18
1.92
2.43
2.8
2.64
2.43
1.18
2.43
1.18
7.1
10.8
0 ppm

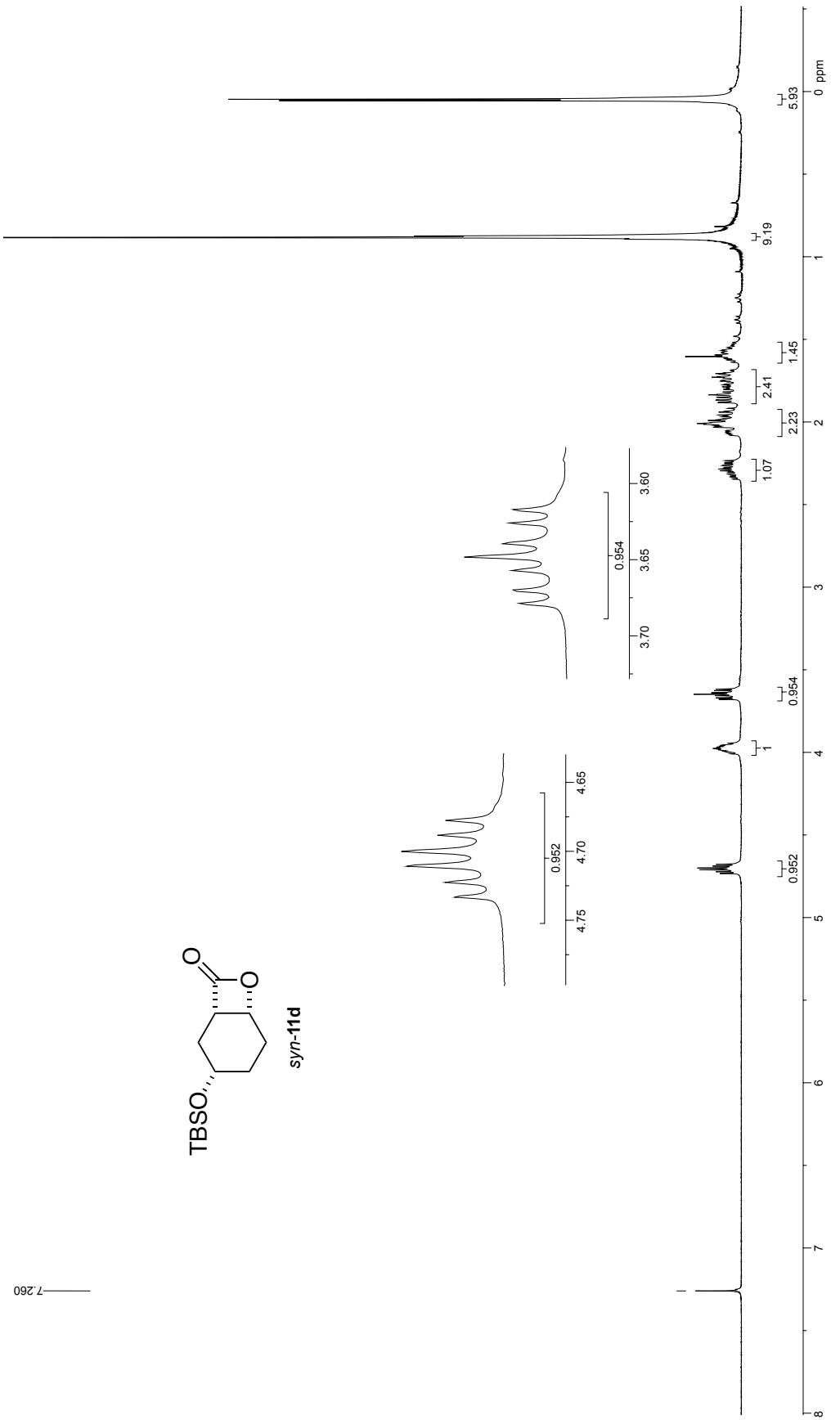

OTBS
OH
O
S12
180.127
138.348
114.421
77.424
77.000
76.577
70.402
35.938
31.217
29.716
29.295
25.739
17.935
4.677
4.559
0 ppm

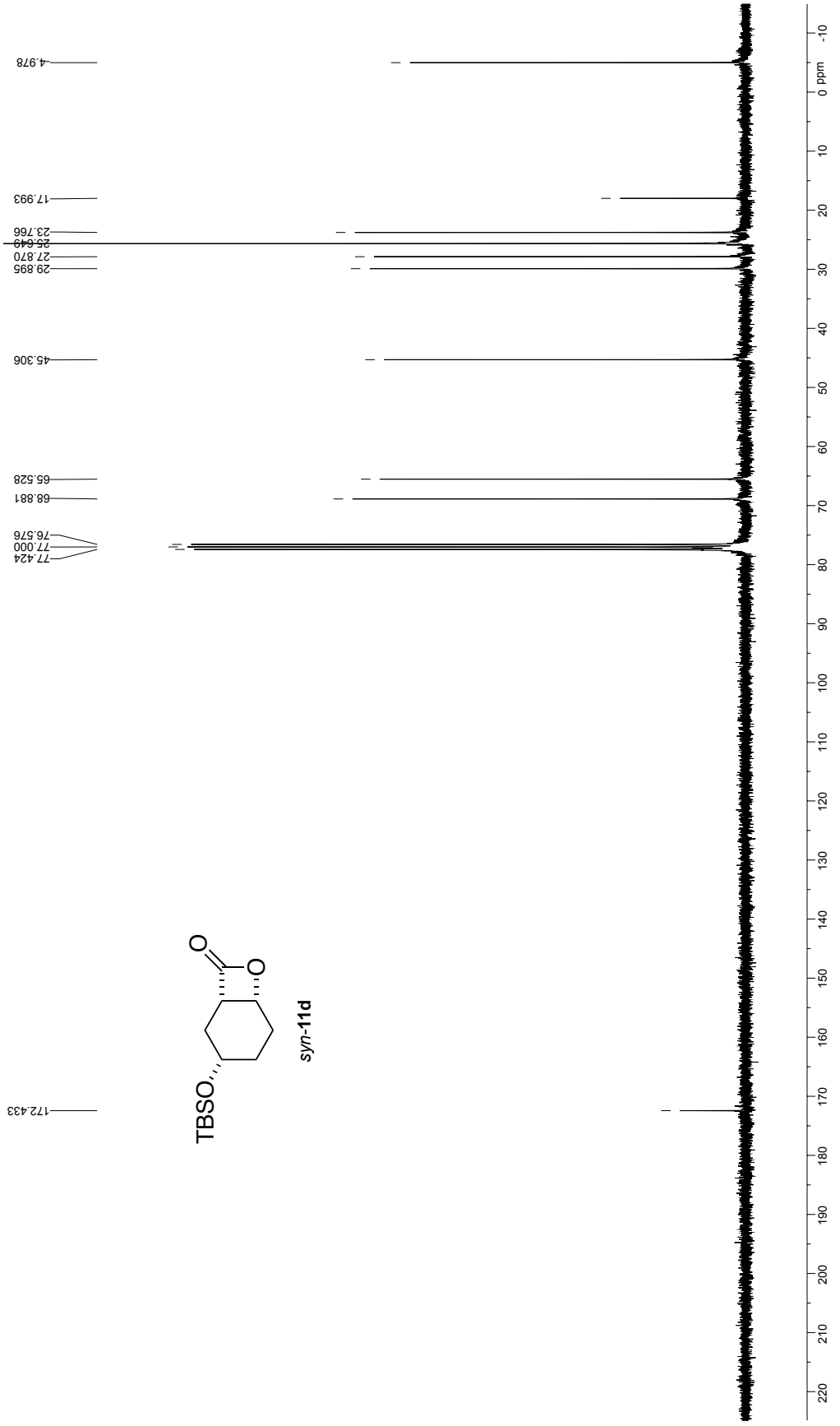

7.260
OTBS
OH
O
O
H
71d
3.85
3.80
3.75
2.54
2.52
2.50
2.48
2.46
2.45
2.40
2.35
2.93
1
2.93
1.1
4.2
9.34
5.85
0.46
ppm 9
8
7
6
5
4
3
2
1
0 ppm

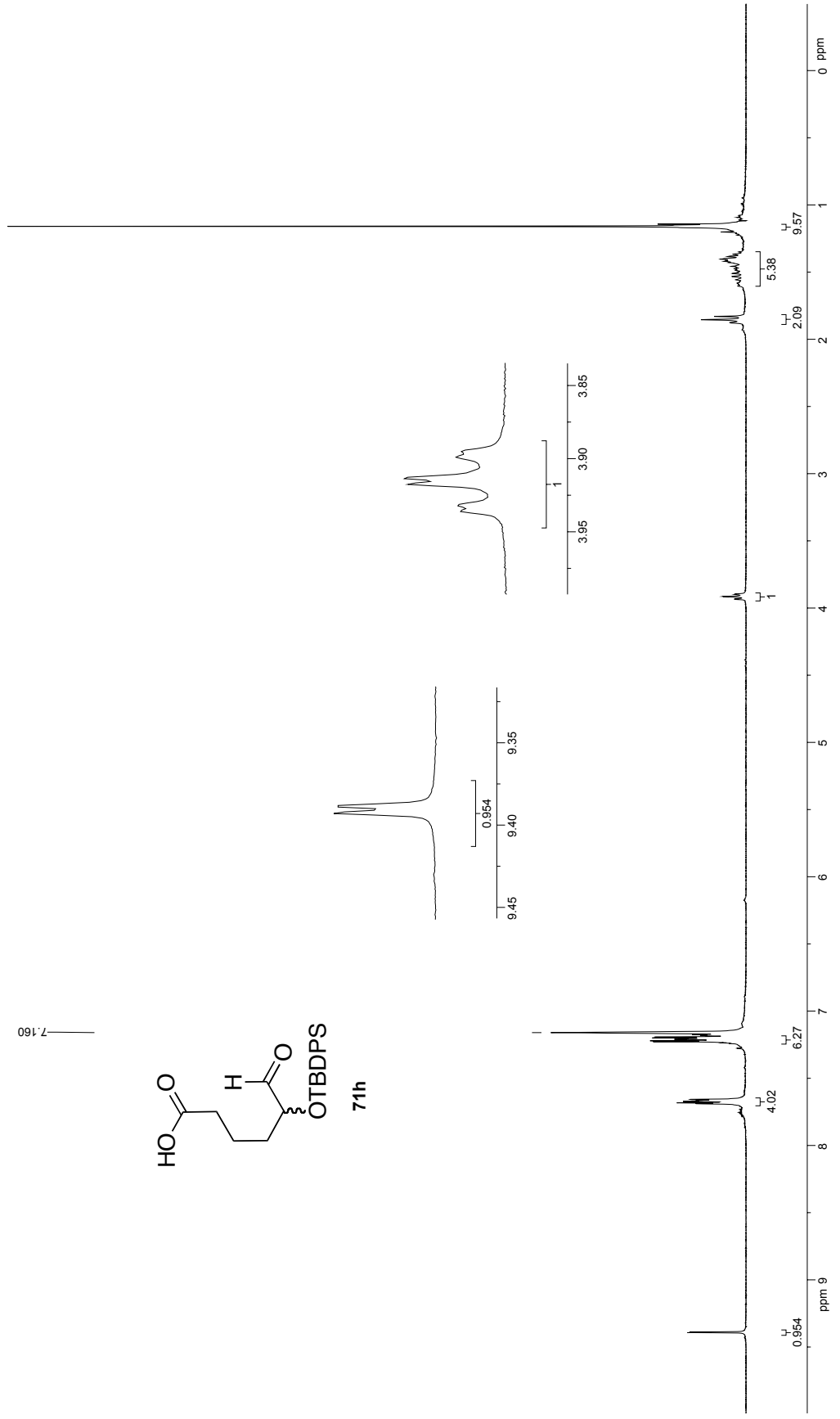

4.663
17.938
25.752
28.604
29.593
31.160
39.419
69.748
76.745
77.000
77.254
180.090
202.337
OTBS
OH
O
O
H
71d
0 ppm

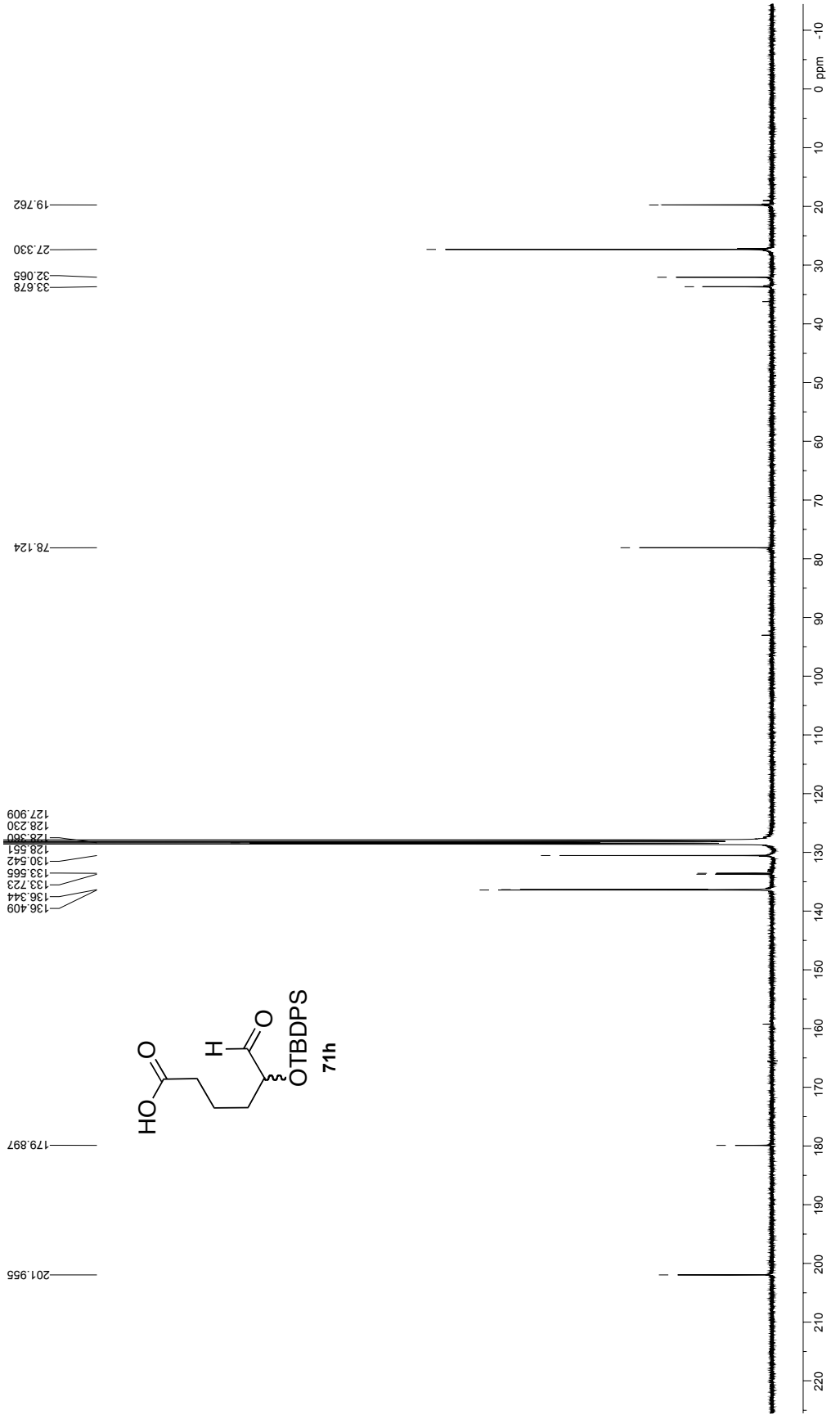

TBSO
O
O
anti-11d
7.260
9.12
6.13
1.78
1.41
0.92
1.12
1.05
1.05
1
1
4.9
4.8
4.7
4.6
4.2
4.1
4.0
3.9
ppm

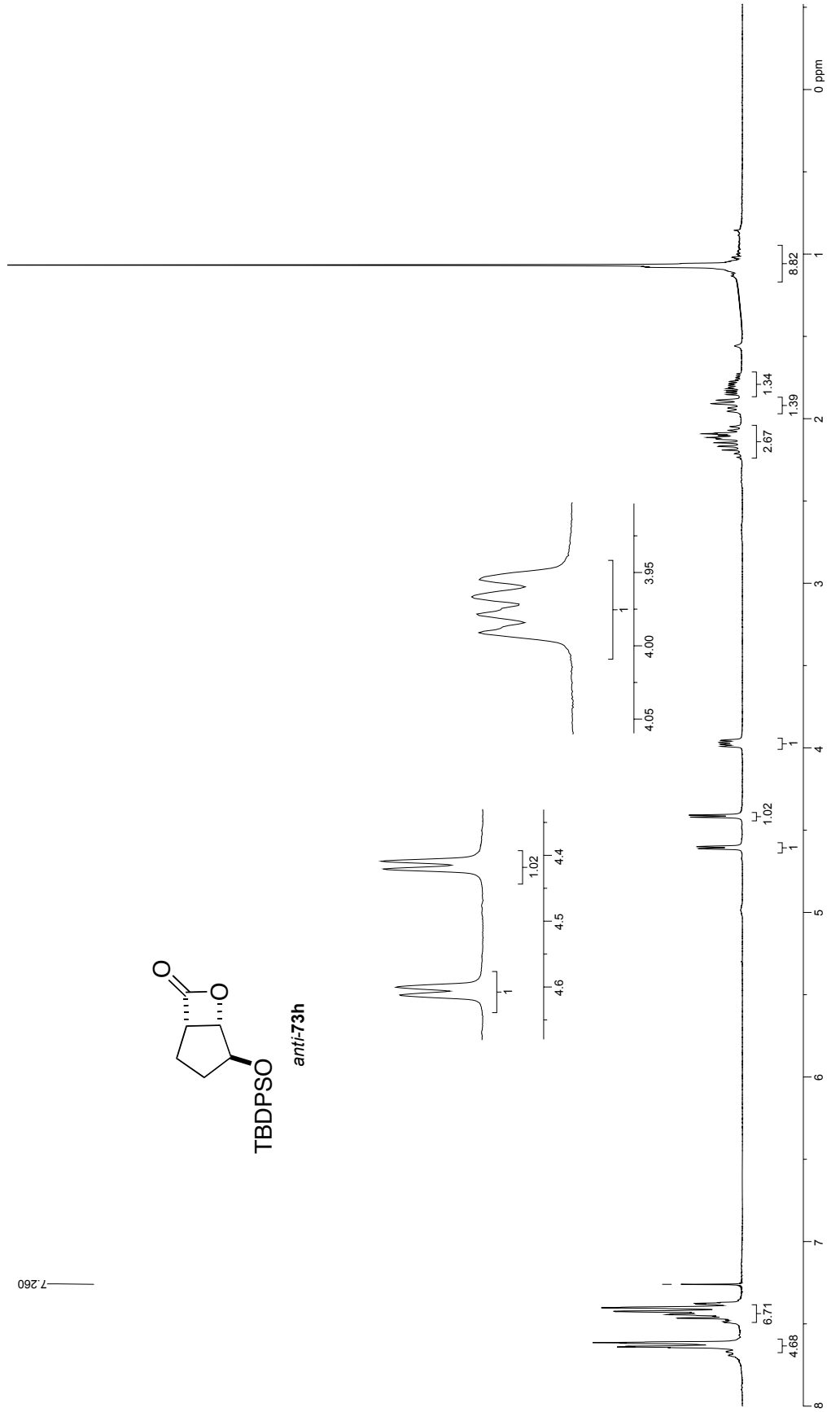

-4.852
18.013
22.120
25.747
26.472
29.328
45.415
63.979
70.141
76.576
77.423
172.827
TBSO
O
O
anti-11d
-10
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

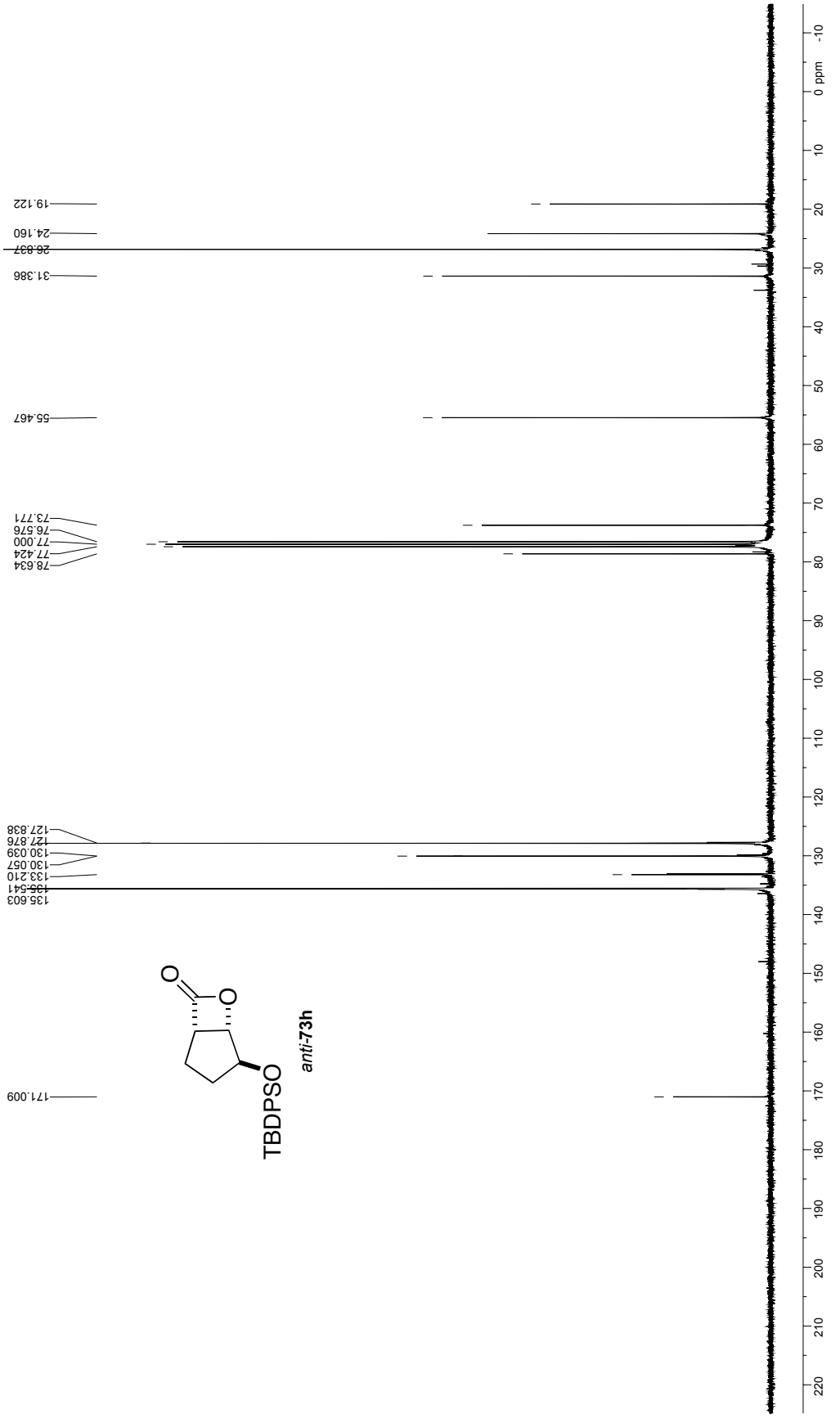

TBSO
O
O
syn-11d
7.260
0.952
4.65
4.70
4.75
0.954
3.60
3.65
3.70
1
0.954
0.962
1.07
2.23
2.41
1.45
9.19
5.93
0 ppm

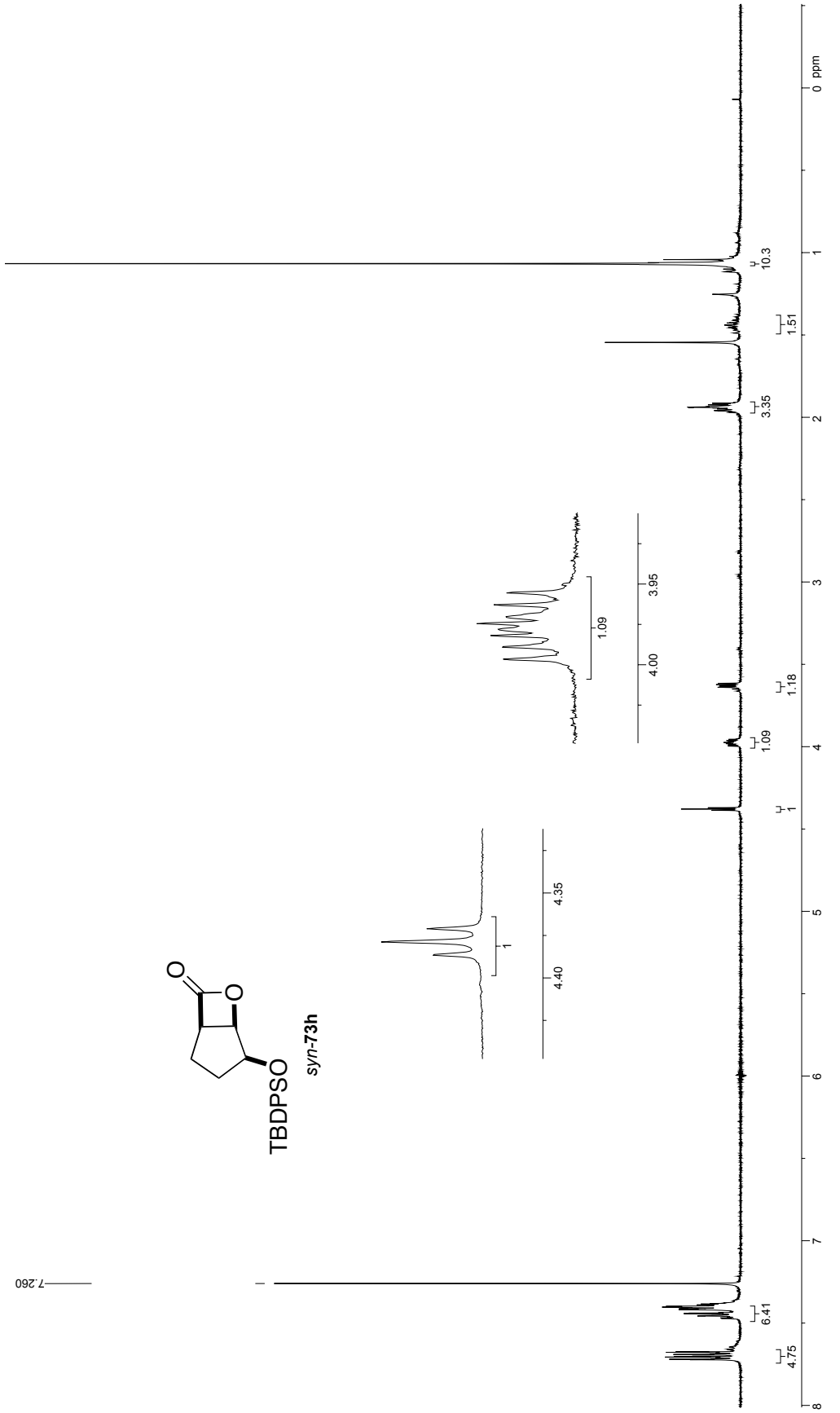

172.433
77.424
77.000
76.576
68.881
65.528
45.306
29.895
27.870
25.649
23.766
17.993
-4.978
TBSO
O
O
syn-11d
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm
-10

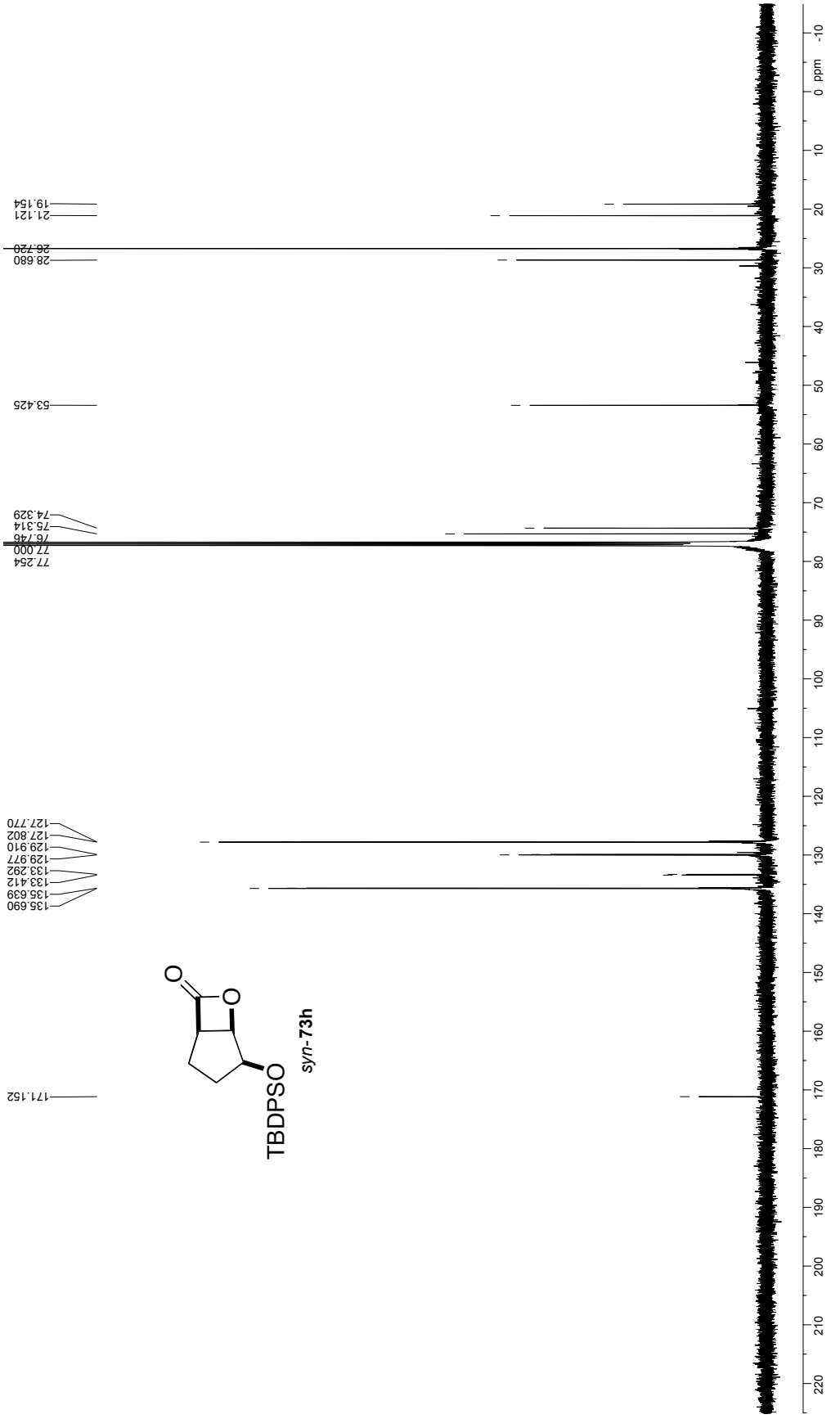

7.160
HO
O
H
O
OTBDPS
71h
0.954
9.40
9.35
9.45
1
3.90
3.85
3.95
1
6.27
4.02
2.09
5.38
9.57
ppm 9
0 ppm

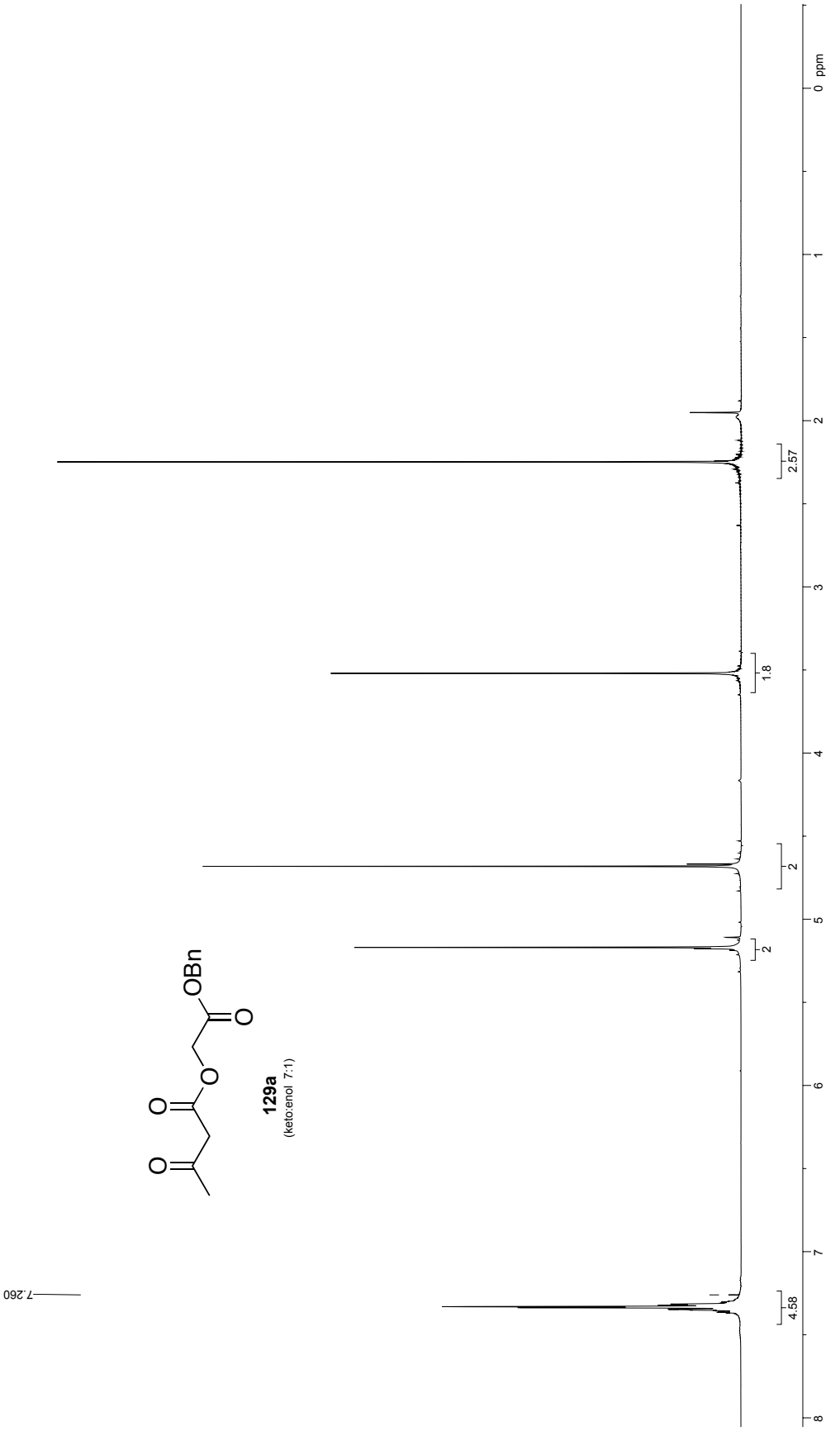

19.762
27.330
32.065
33.678
78.124
127.909
128.230
128.360
128.551
130.542
133.565
133.723
136.344
136.409
179.897
201.955
HO
O
H
O
OTBDPS
71h
0 ppm

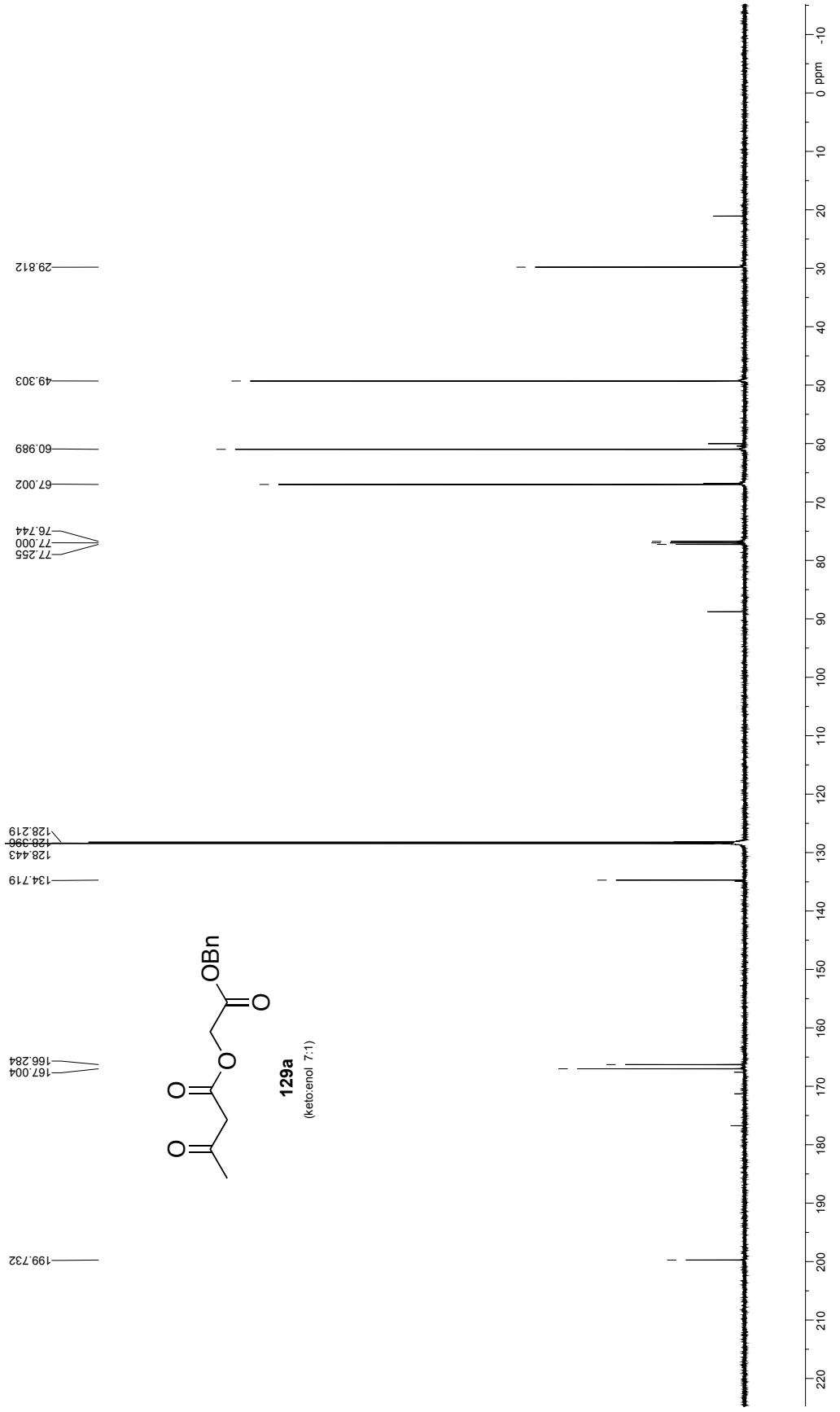

7.260
TBDPSO
anti-73h
0 ppm

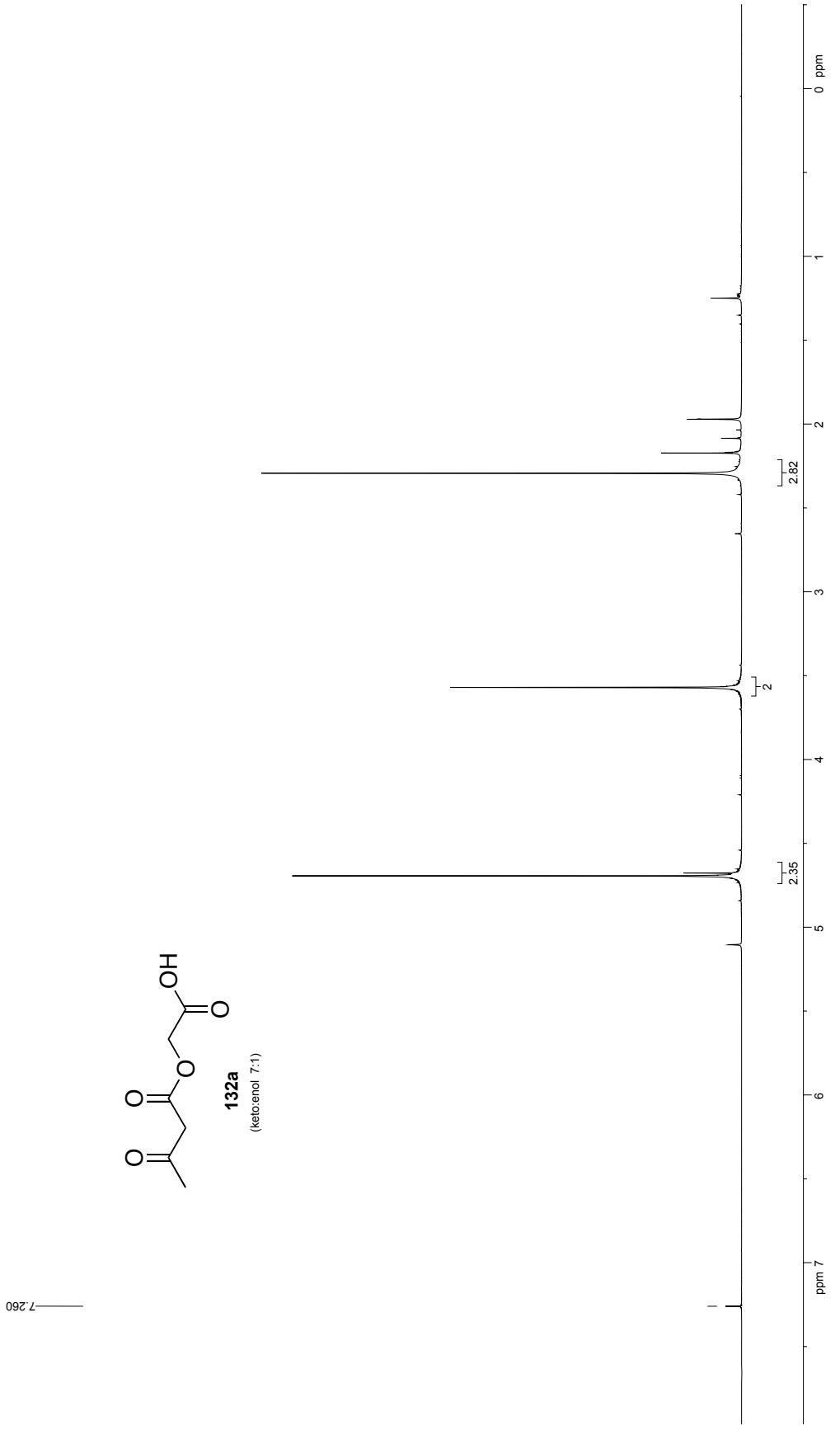

19.122
24.160
26.837
31.386
55.467
73.771
76.576
77.000
77.424
78.634
127.838
127.876
130.039
130.057
133.210
135.541
135.603
171.009
TBDPSO
anti-73h
0 ppm

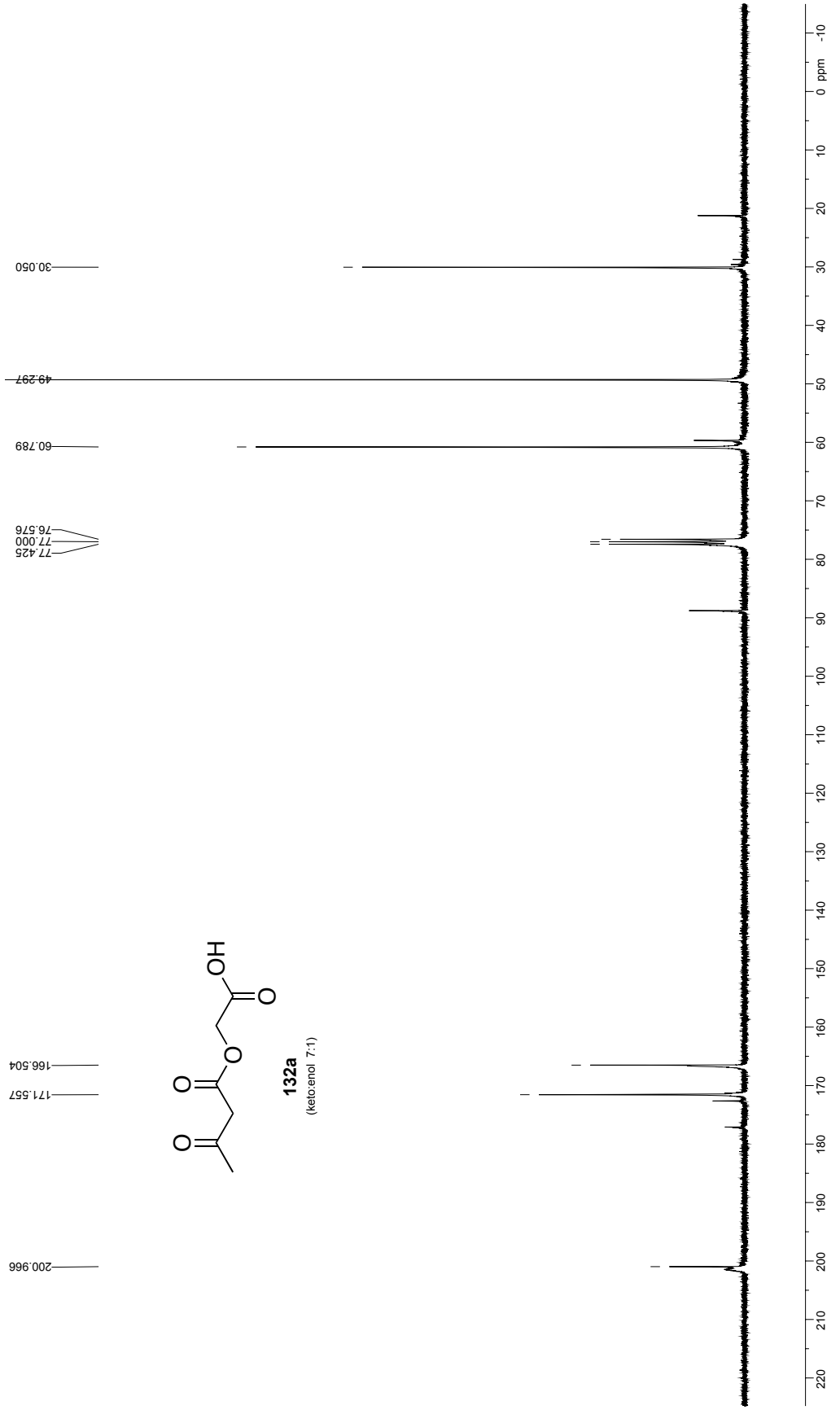

TBDPSO
syn-73h
7.260
6.41
4.75
1.09
1
1.18
4.00
3.95
1.09
4.40
4.35
1
3.35
1.51
10.3
0 ppm

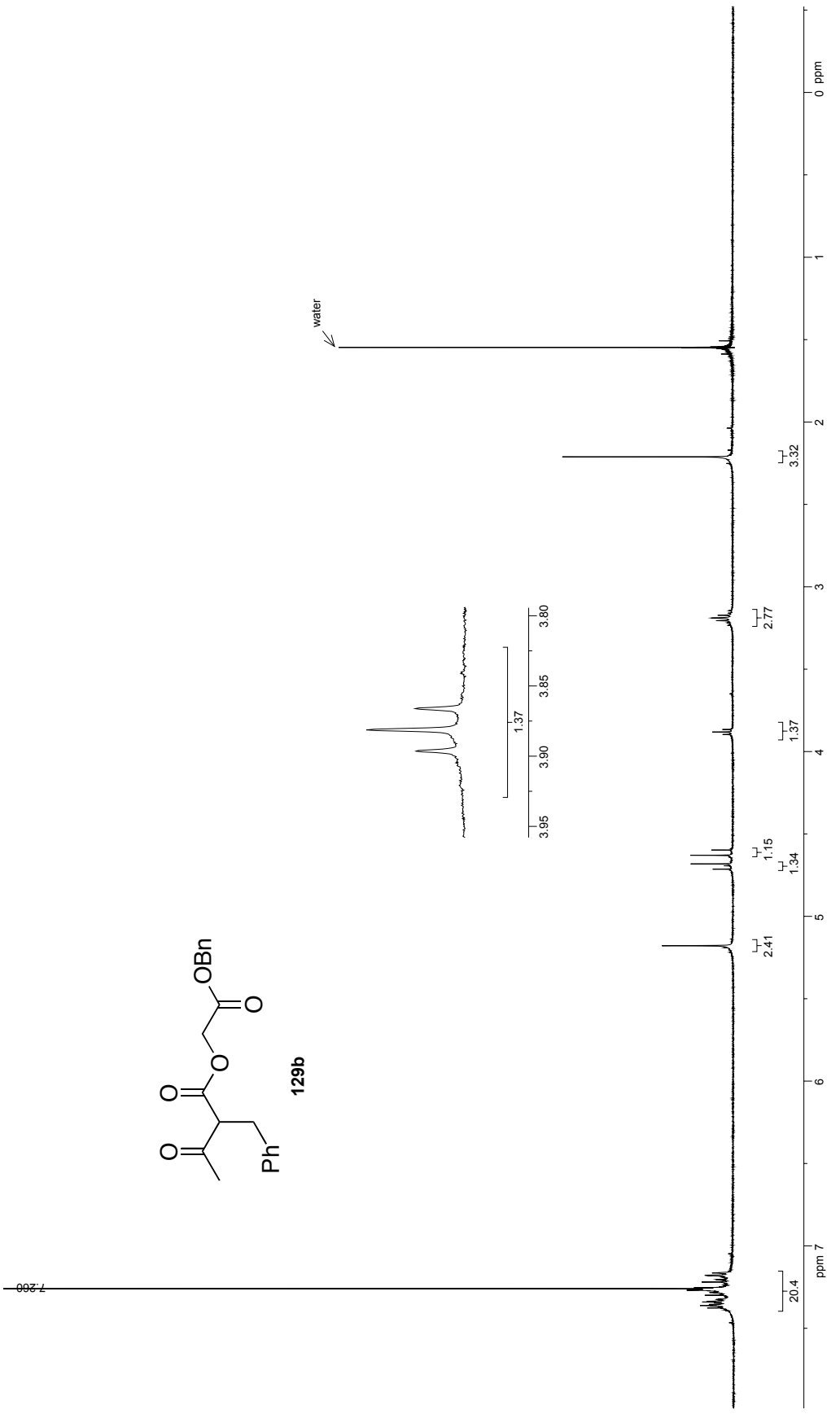

171.152
135.690
135.639
133.412
133.292
129.977
129.910
127.802
127.770
77.254
77.000
76.746
75.314
74.329
53.425
28.680
26.720
21.121
19.154
TBDPSO
syn-73h
0 ppm

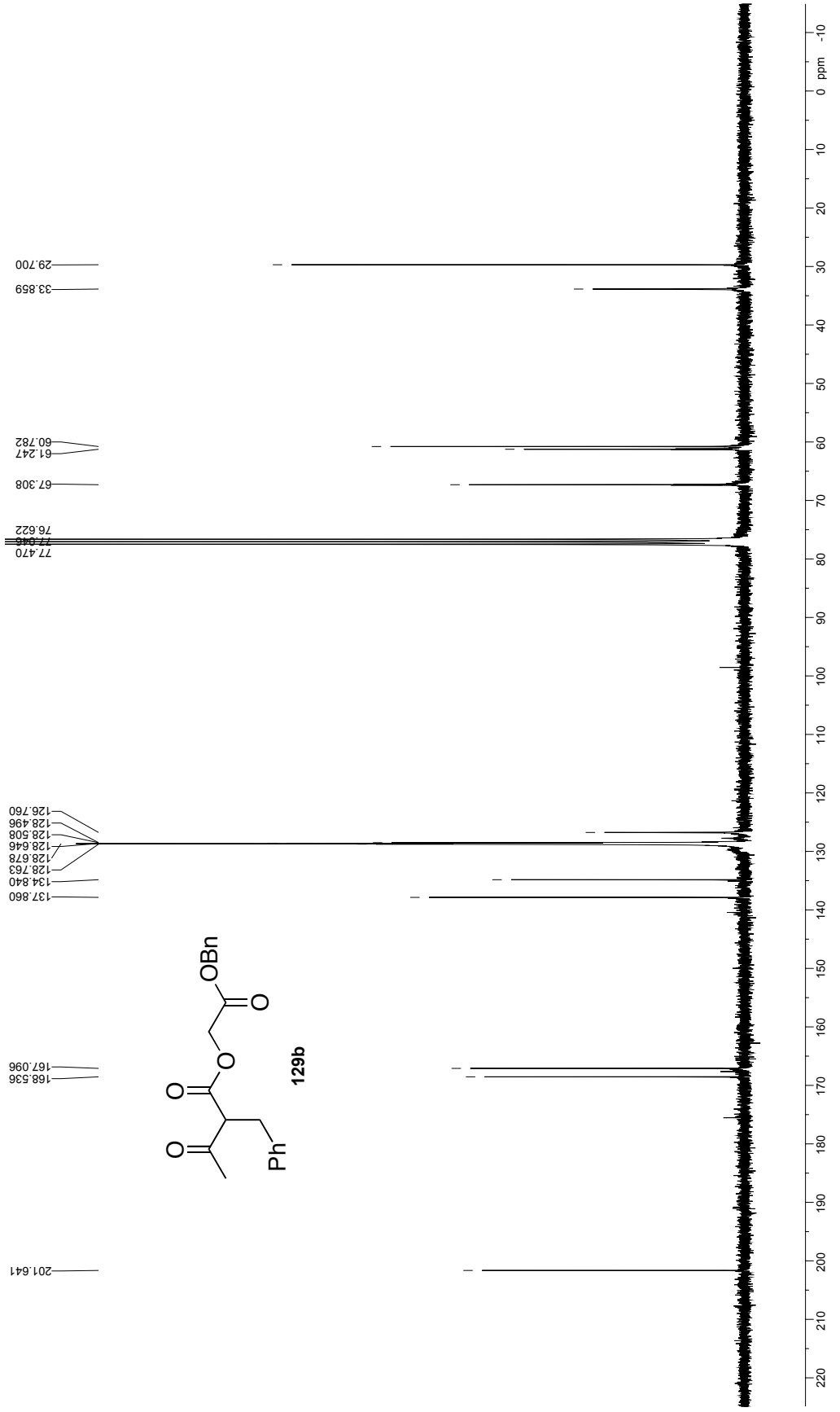

7.260
OBn
O
O
O
O
129a
(keto:enol 7:1)
4.58
2
2
1.8
2.57
0 ppm

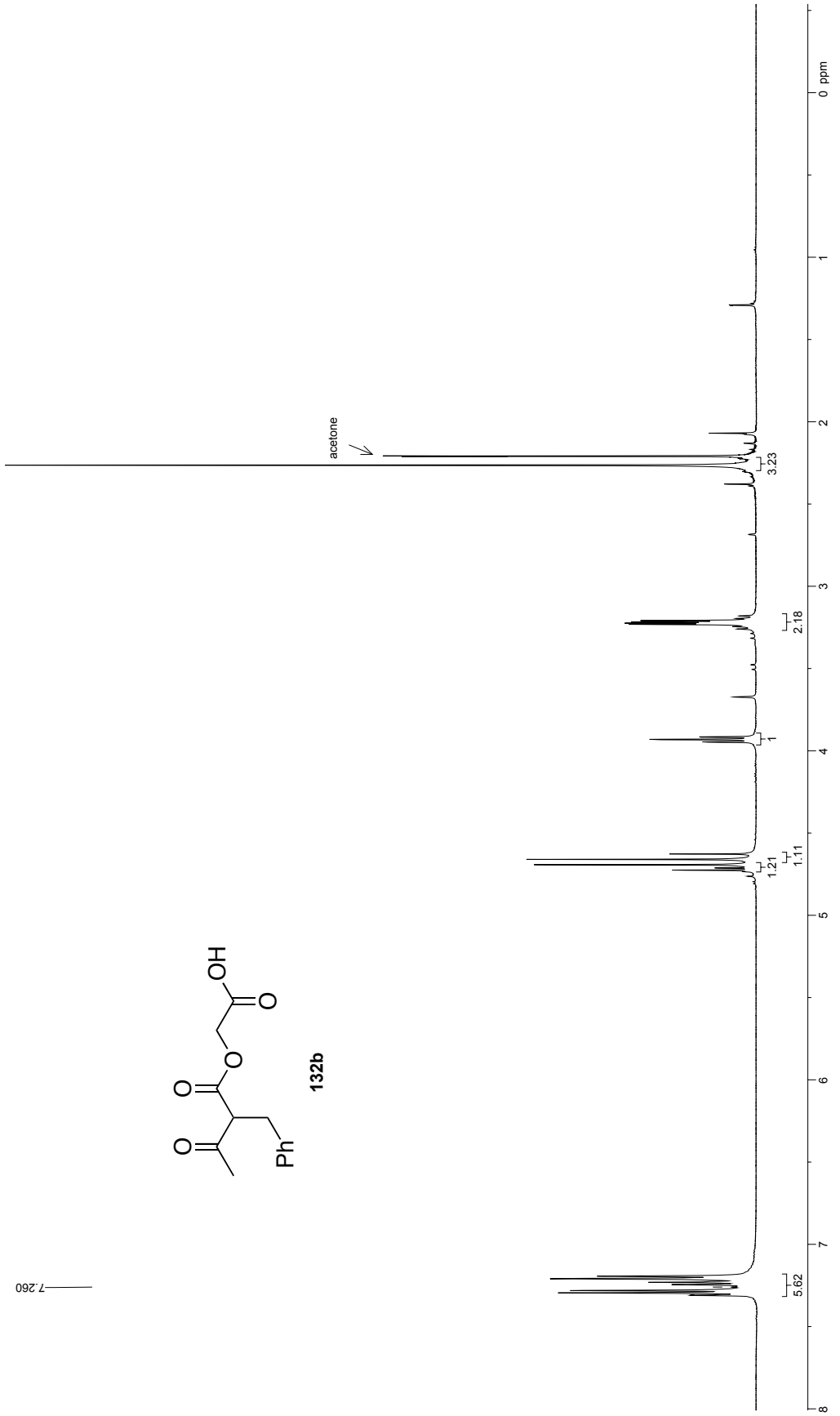

199.732
166.284
167.004
134.719
128.443
128.396
128.219
77.255
77.000
76.744
67.002
60.989
49.303
29.812
OBn
O
O
O
O
129a
(keto:enol 7:1)
0 ppm


7.260
ppm 7
6
5
4
3
2
1
0 ppm
2.35
2
2.82
O
O
O
O
O
OH
132a
(keto:enol 7:1)

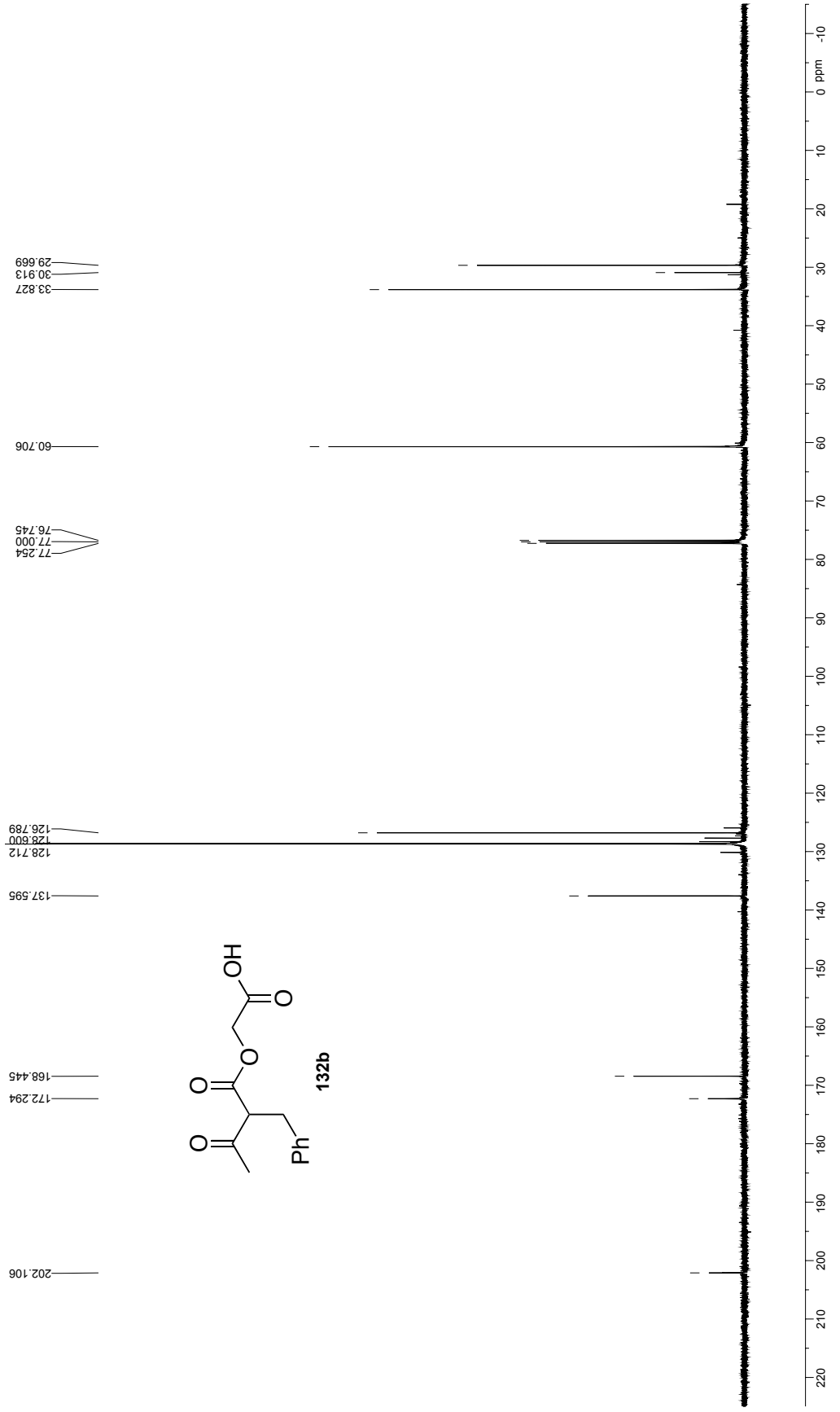

200.966
171.557
166.504
77.425
77.000
76.576
60.789
49.297
30.050
132a
(keto:enol 7:1)
OH
O
O
O
O
0 ppm

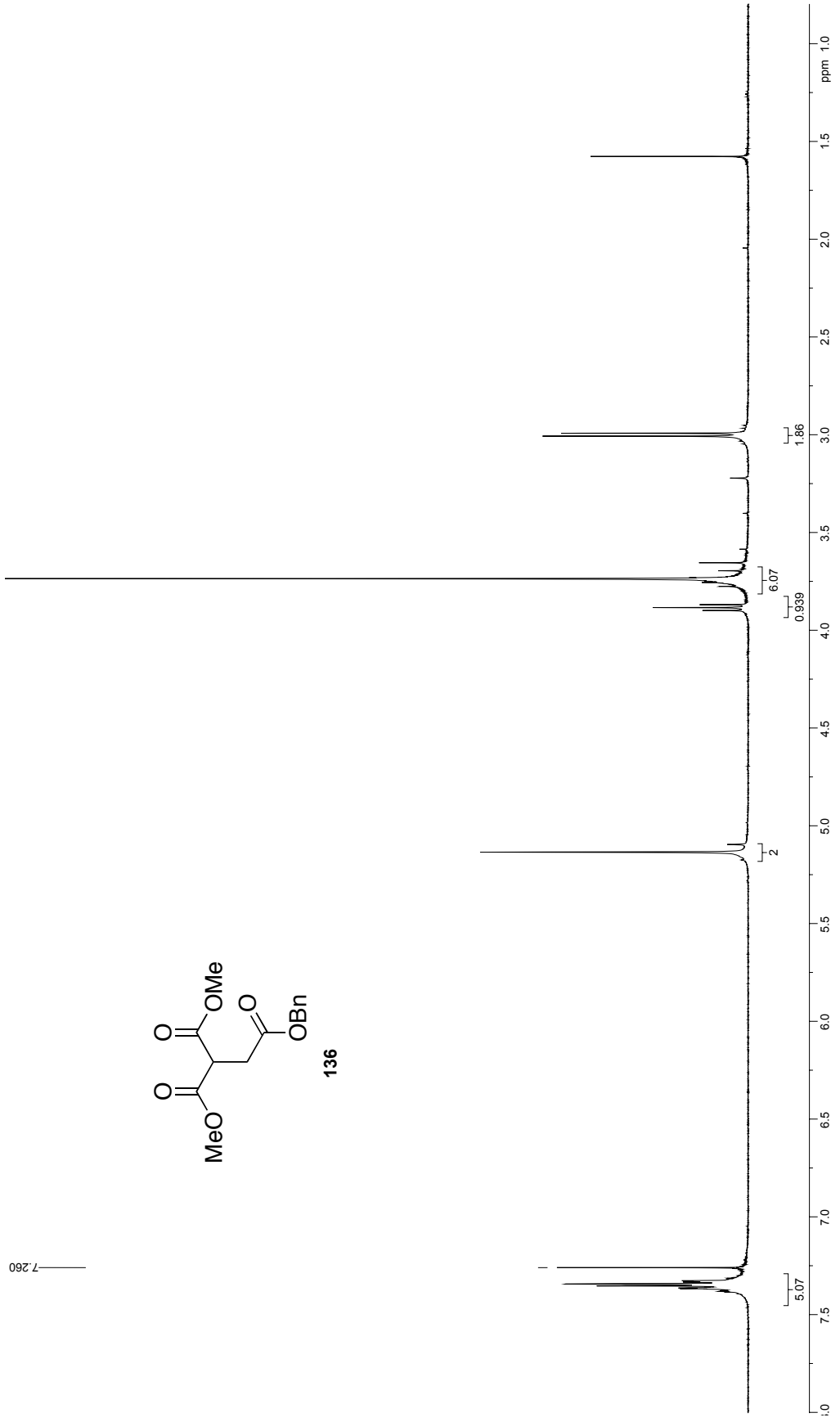

OBn
O
O
O
O
Ph
129b
water
7.260
20.4
2.41
1.34
1.15
1.37
2.77
1.37
3.32
3.95
3.90
3.85
3.80
ppm 7
6
5
4
3
2
1
0 ppm

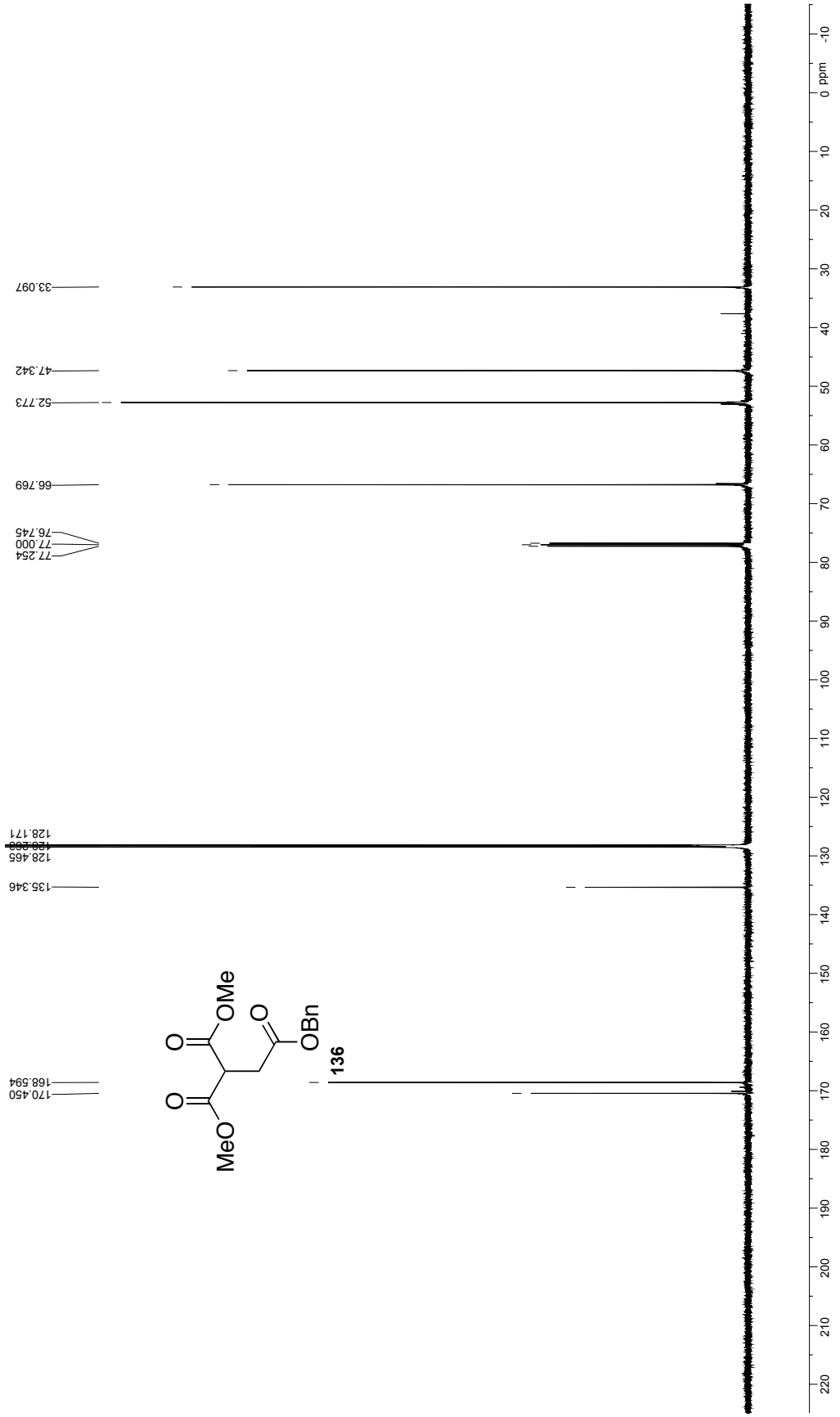

201.641
168.536
167.096
137.860
134.840
128.763
128.678
128.646
128.508
128.496
126.760
77.470
76.622
67.308
61.247
60.782
33.859
29.700
OBn
O
O
O
O
Ph
129b
0 ppm

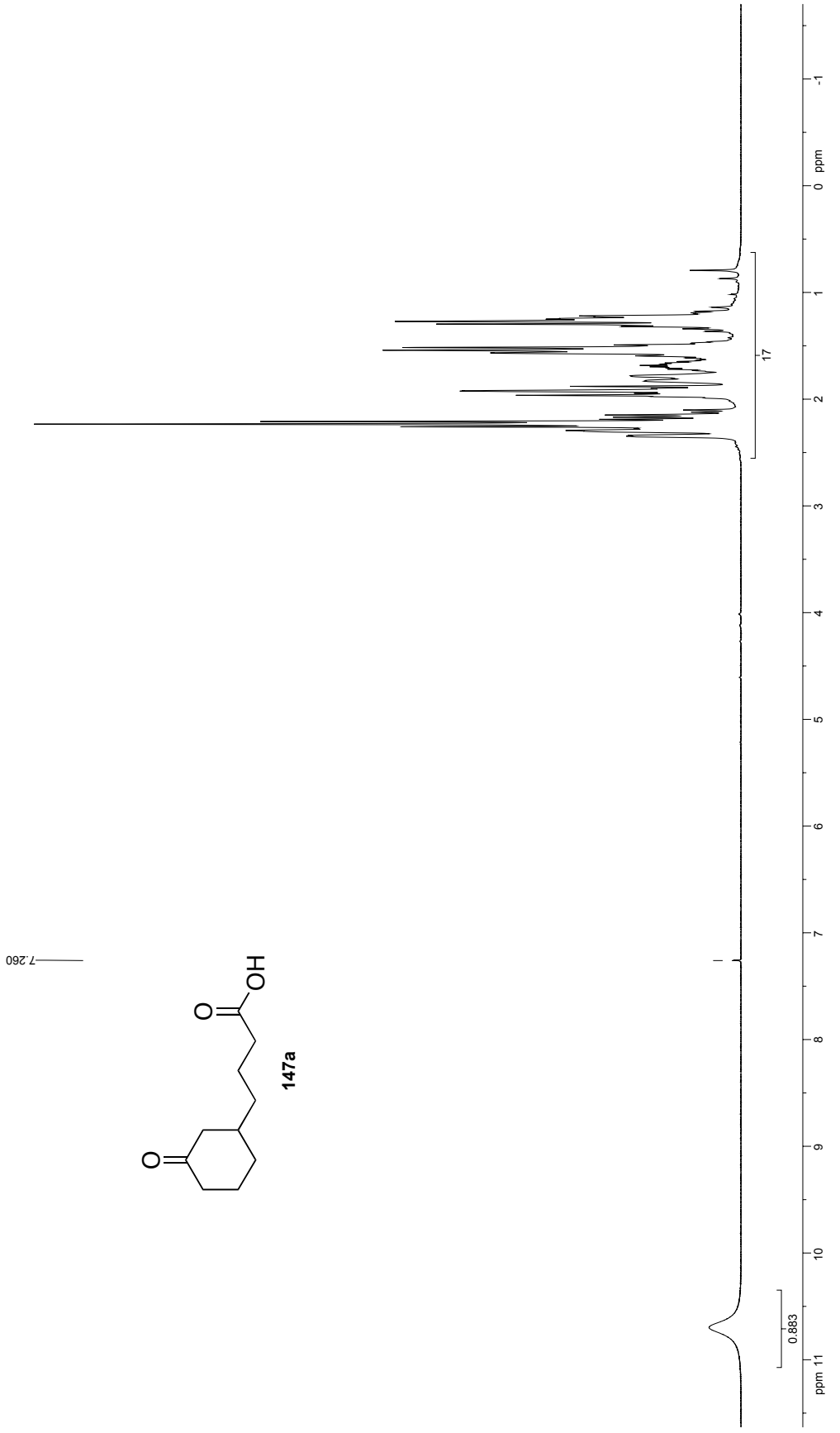


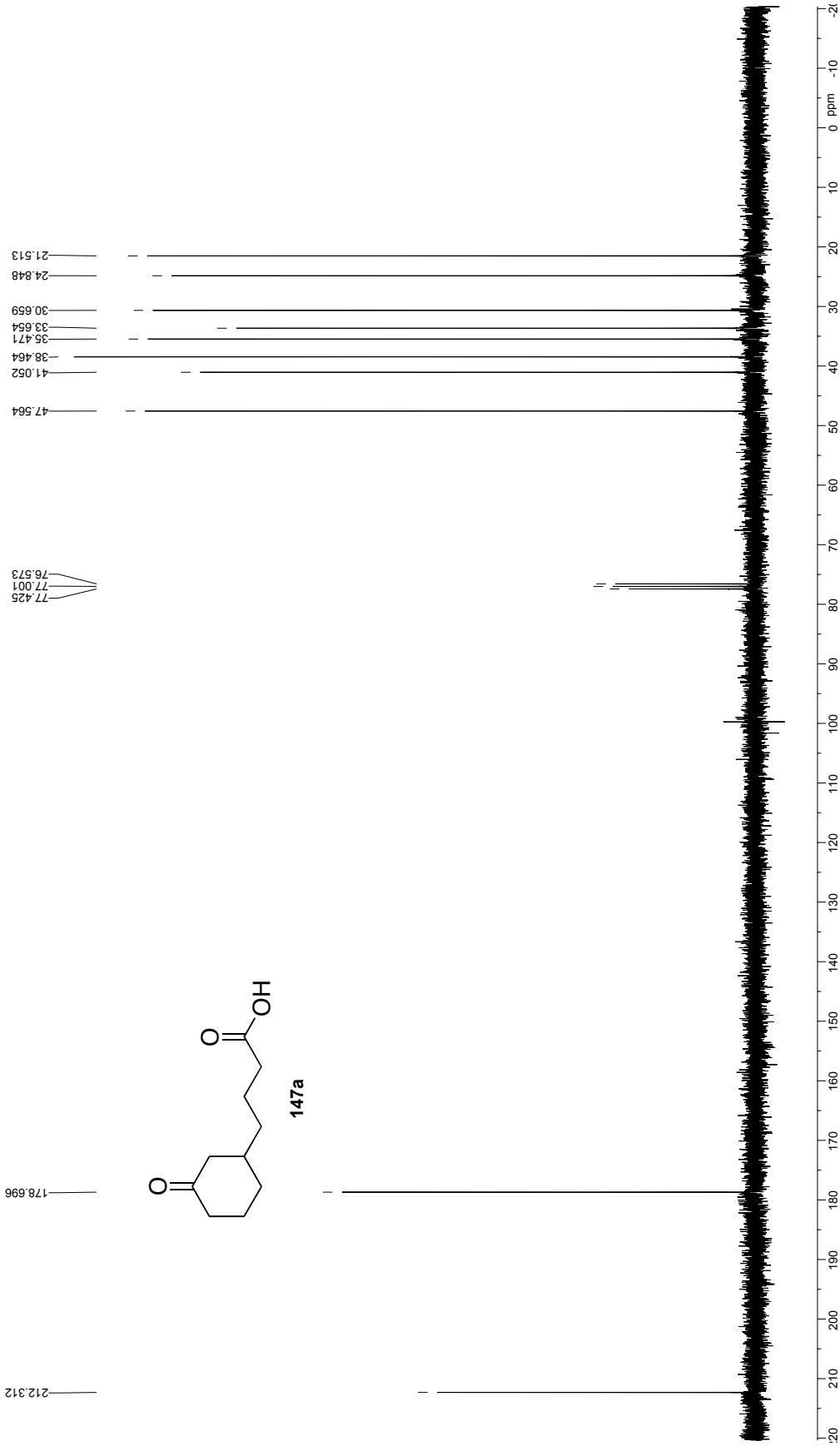
132b


29.669
30.913
33.827
60.706
76.745
77.000
77.254
126.789
128.600
128.712
137.595
168.445
172.294
202.106
OH
O
O
O
O
Ph
132b
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
ppm


OMe
O
O
OBn
O
MeO
136
7.260
5.07
2
6.07
0.939
1.86
ppm 1.0


33.097
47.342
52.773
66.769
76.745
77.000
77.254
128.171
128.280
128.465
135.346
168.594
170.450
MeO
OMe
O
O
O
OBn
136
0 ppm


7.260
O
OH
O
147a
17
0.883
ppm 11
10
9
8
7
6
5
4
3
2
1
0 ppm
-1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178.696
77.425
77.001
76.573
47.564
41.052
38.464
35.471
33.654
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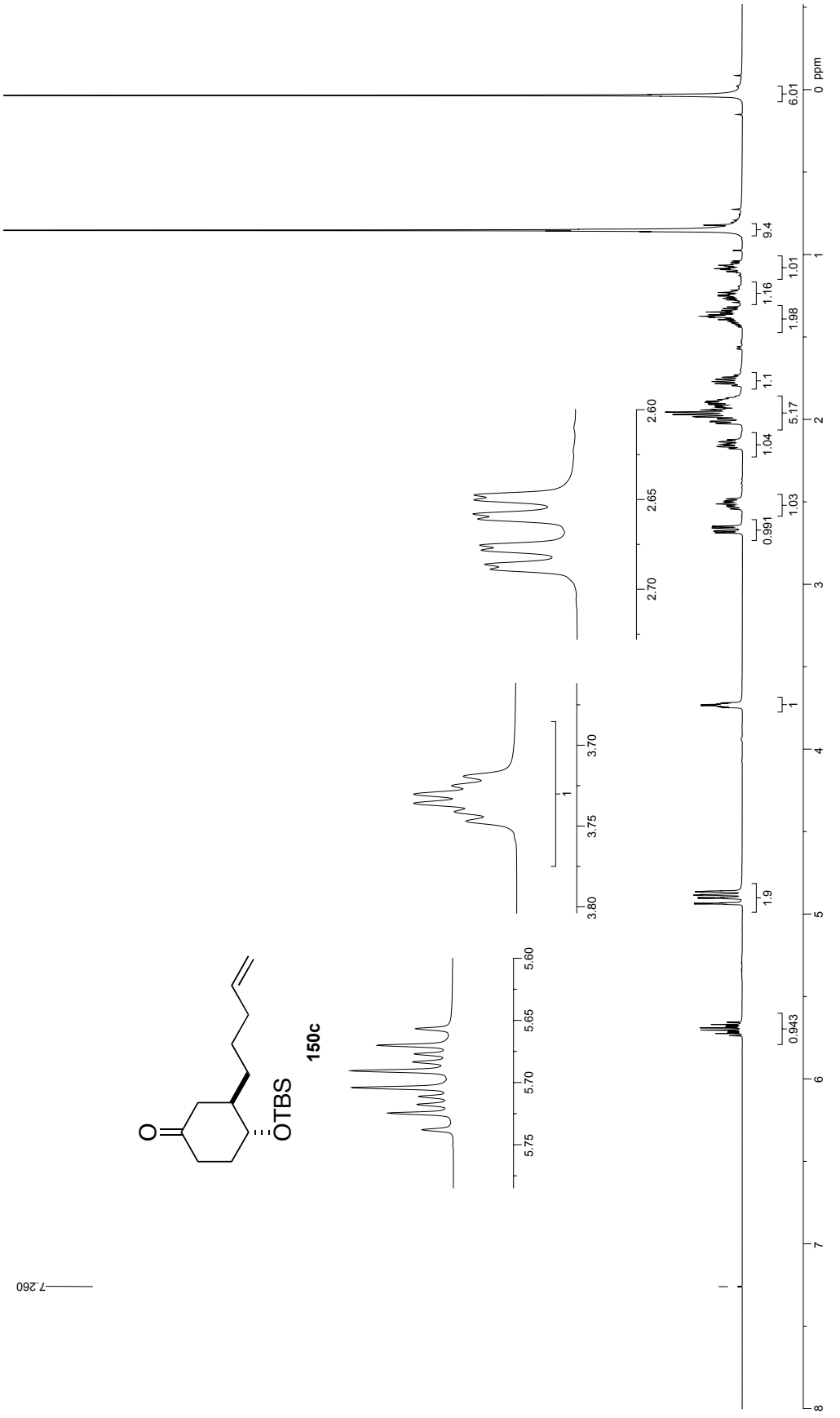
21.513
147a
O
OH
O
0 ppm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OTBS
O
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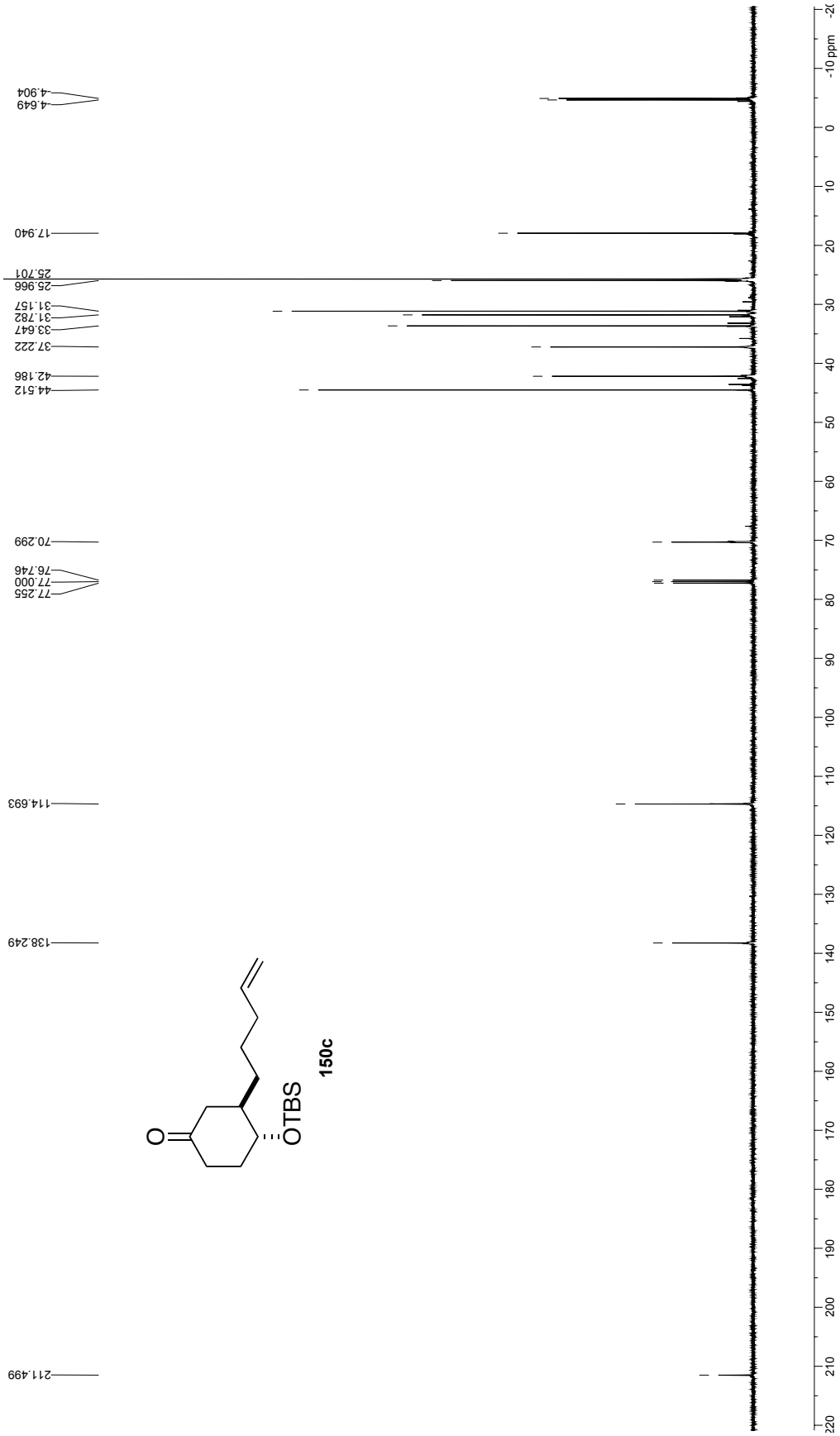
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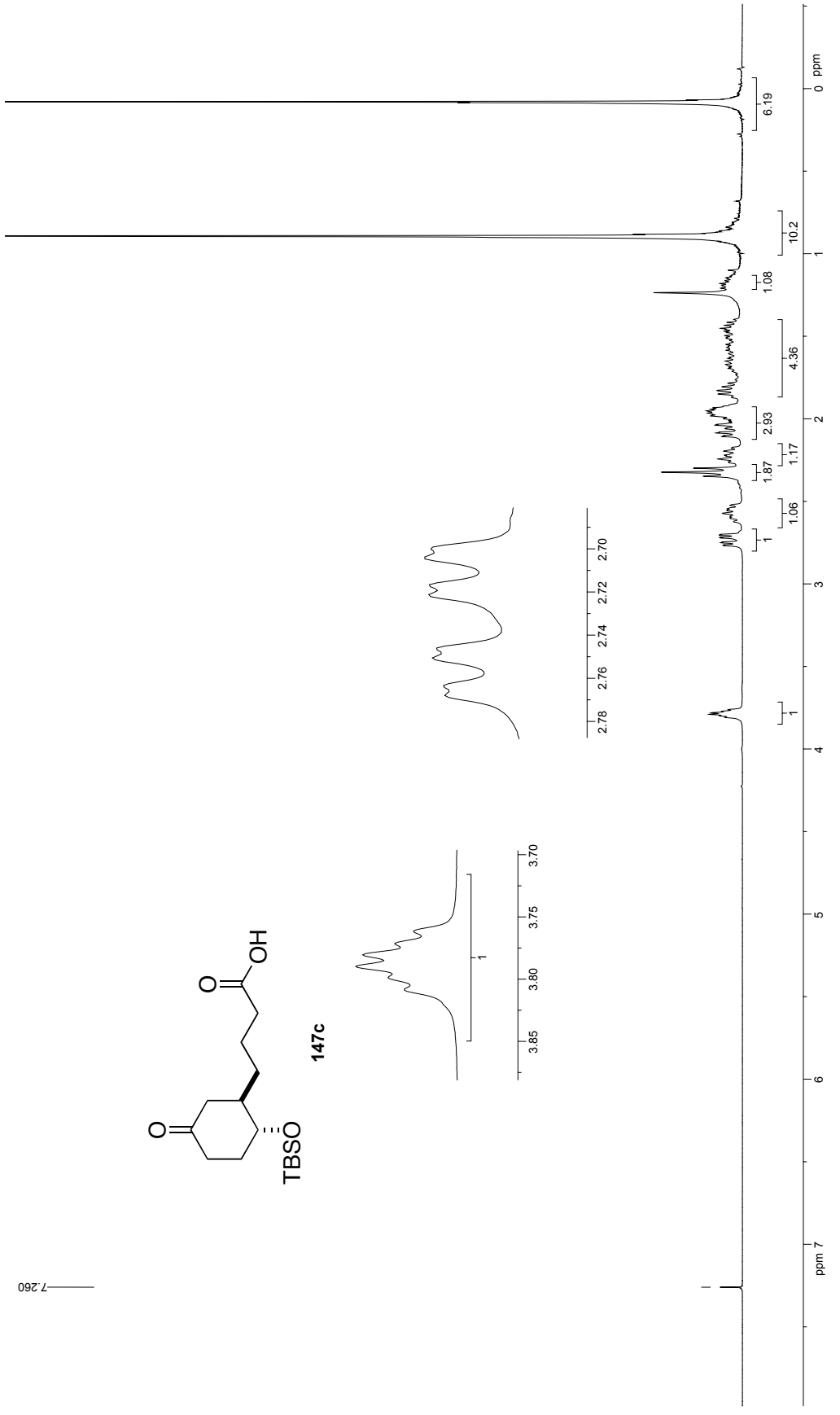
17.940
25.701
25.966
31.157
31.782
33.647
37.222
42.186
44.512
70.299
76.746
77.000
77.255
114.693
138.249
211.499
-10 ppm
OTBS
O
150c


7.260
O
O
OH
TBSO
147c
3.85
3.80
3.75
3.70
1
2.78
2.76
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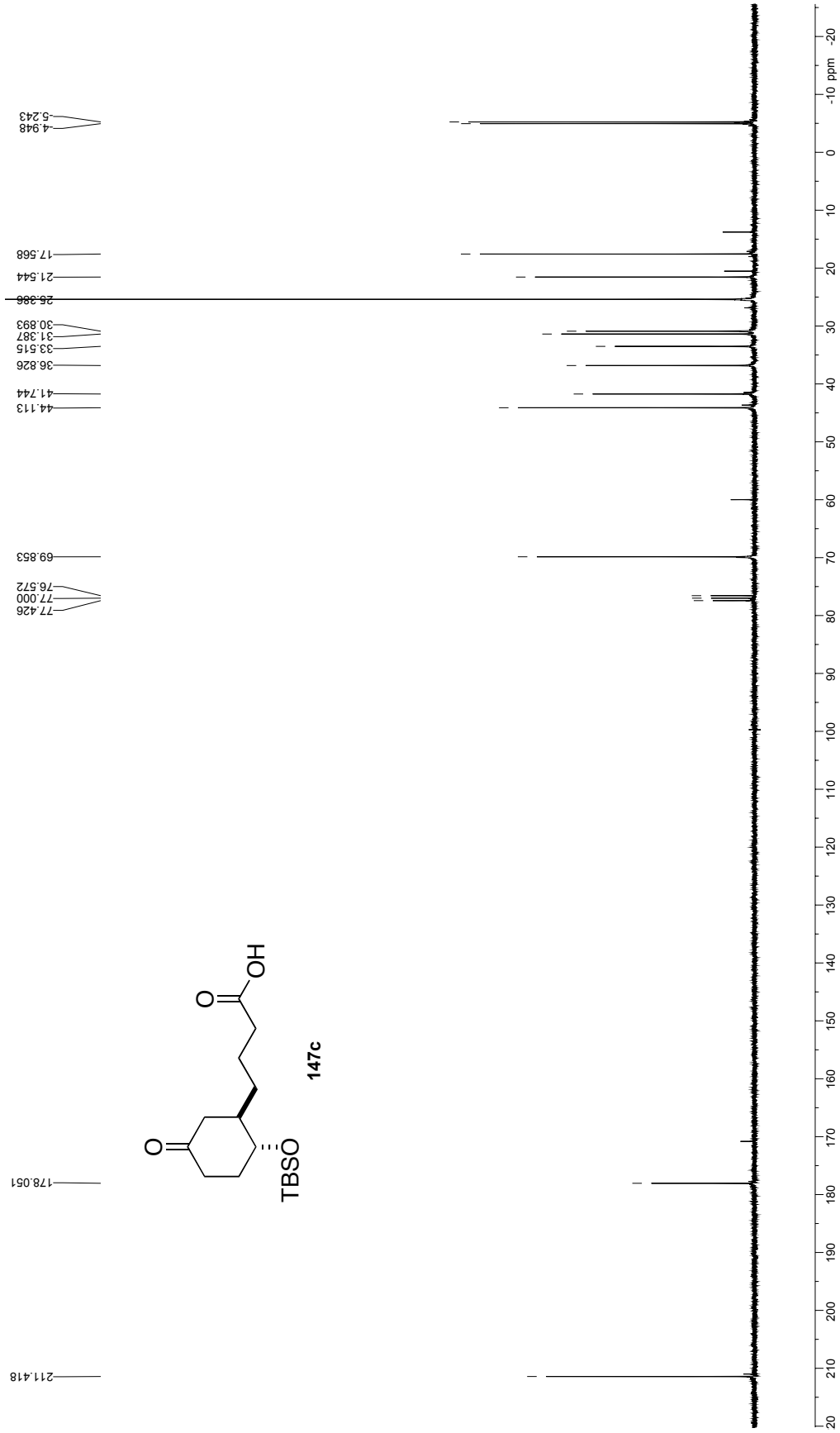
2.72
2.70
1
1.06
1.87
1.17
2.93
4.36
1.08
10.2
6.19
ppm 7
6
5
4
3
2
1
0 ppm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21.544
25.386
30.893
31.387
33.515
36.826
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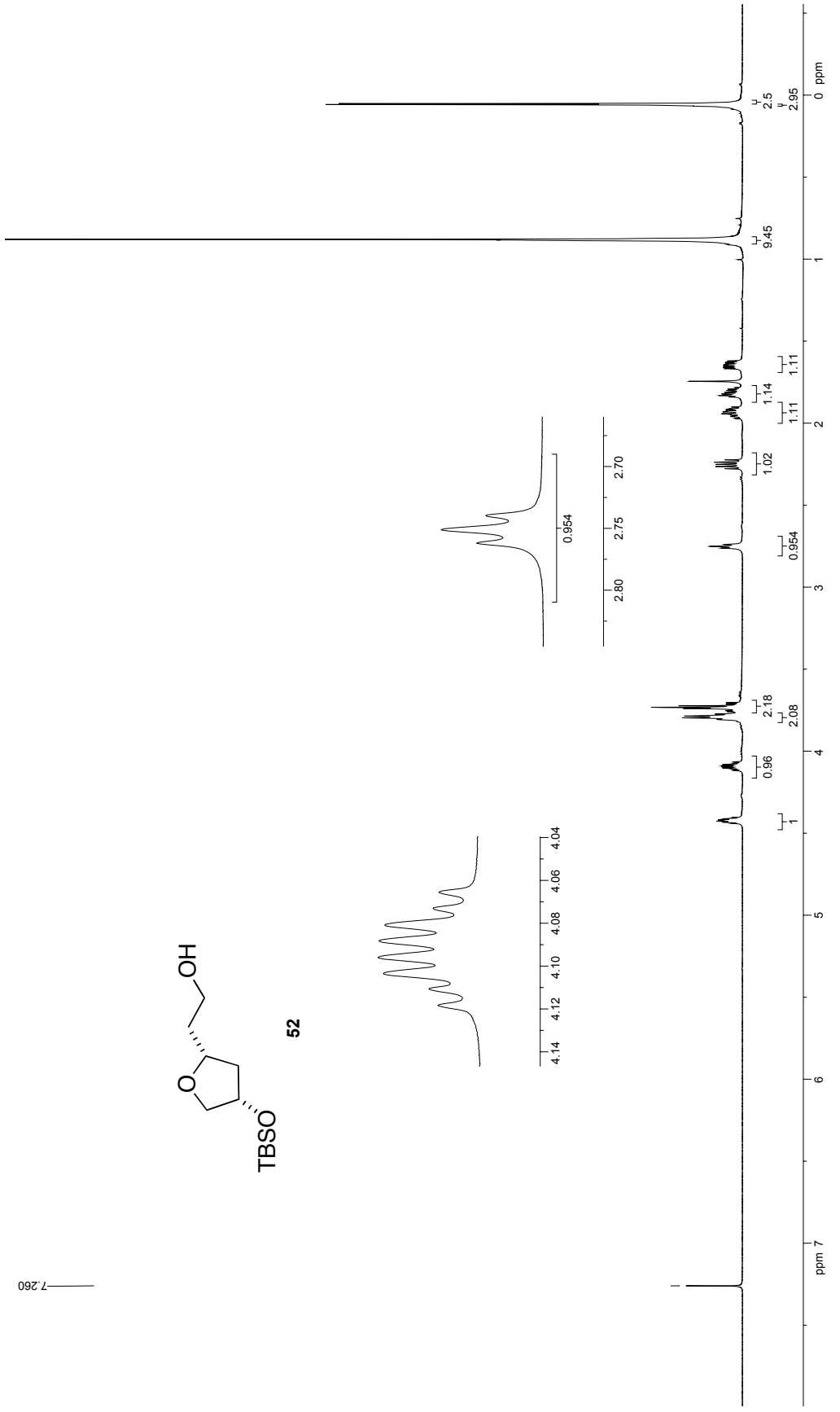
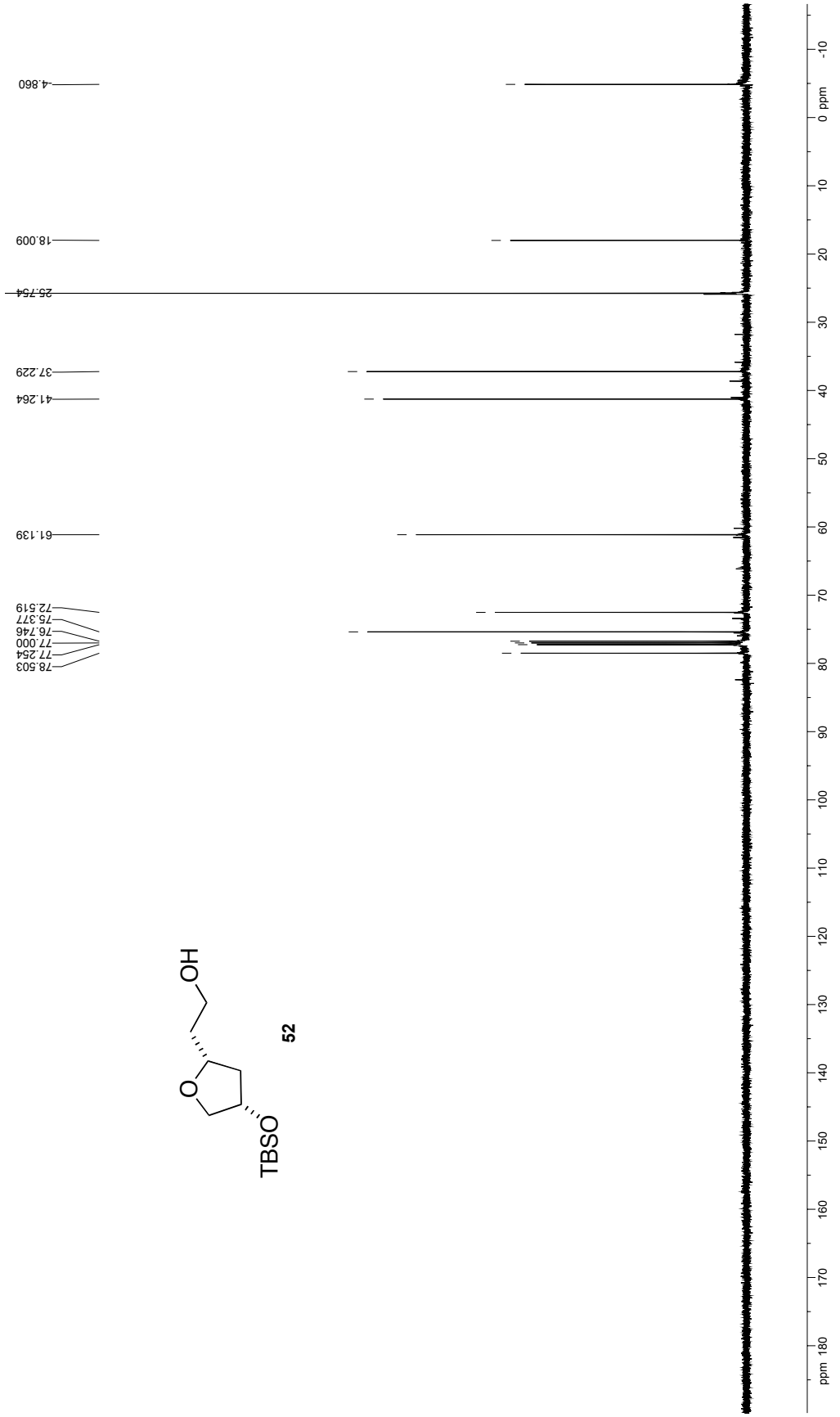
76.572
77.000
77.426
178.051
211.418
-10 ppm
TBSO
O
OH
147c


OH
O
TBSO
52
7.260
ppm 7
6
5
4
3
2
1
0 ppm
1
0.96
2.18
2.08
0.954
1.02
1.11
1.14
1.11
9.45
2.5
2.95
4.14
4.12
4.10
4.08
4.06
4.04
0.954
2.80
2.75
2.70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18.009
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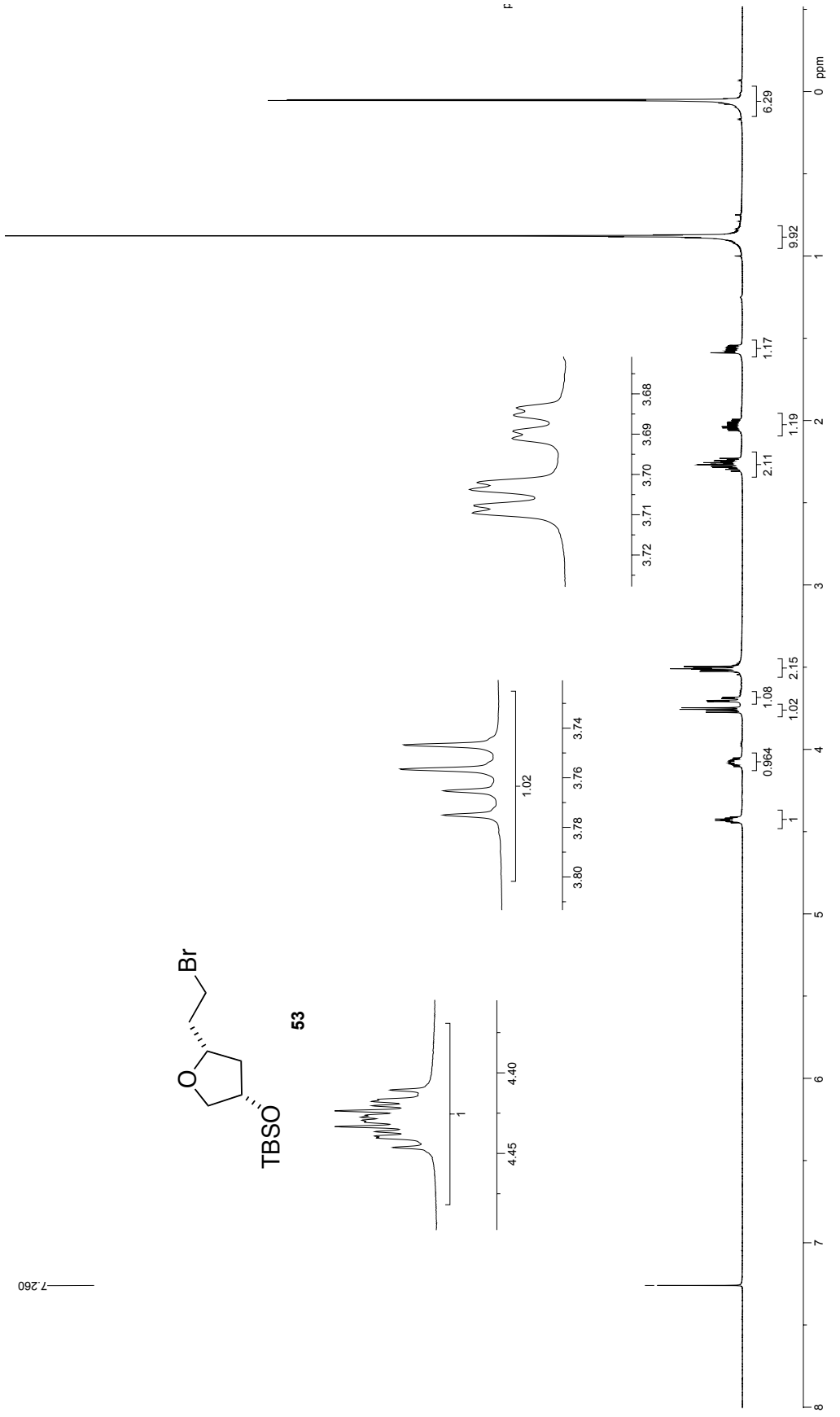
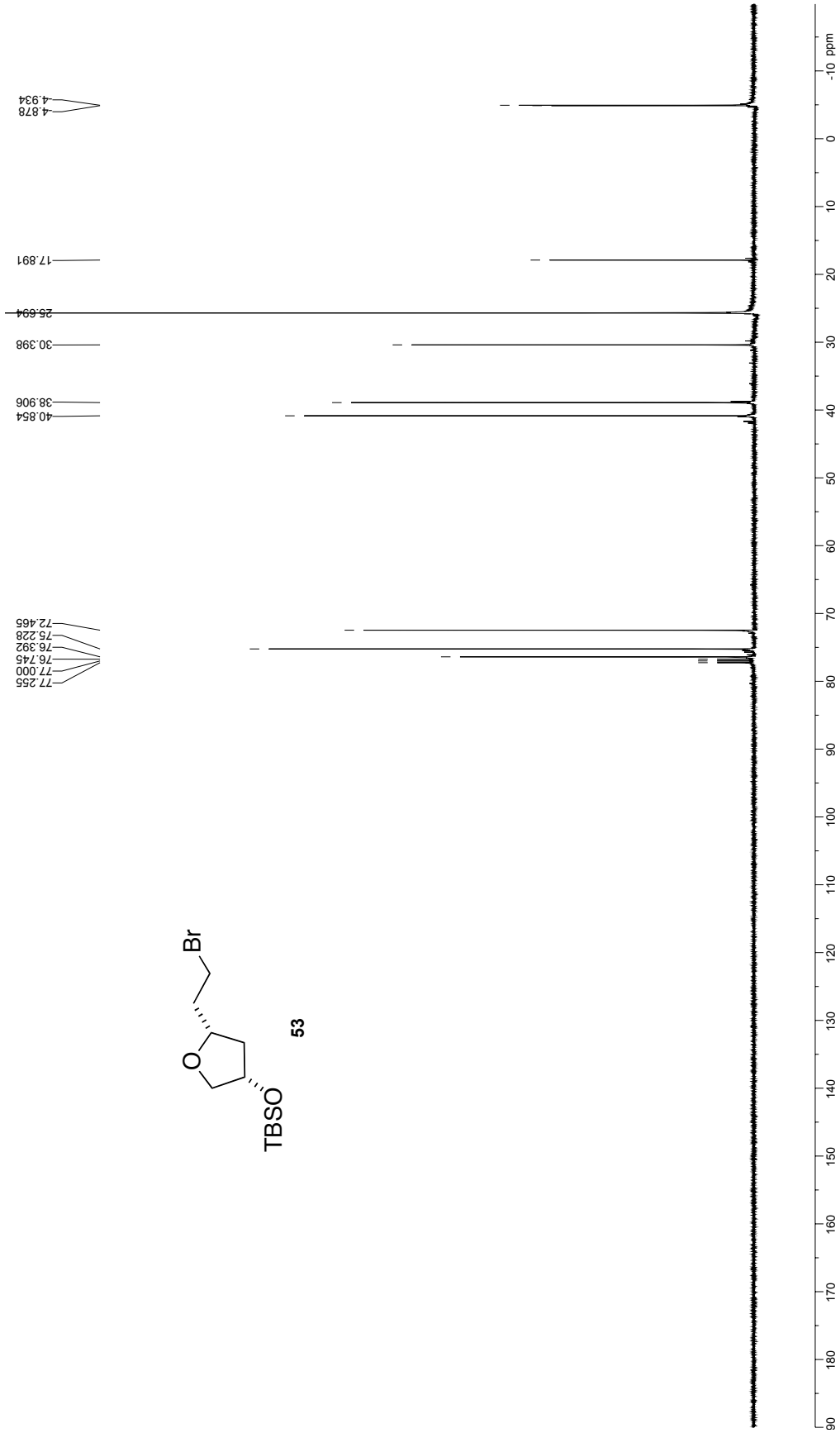
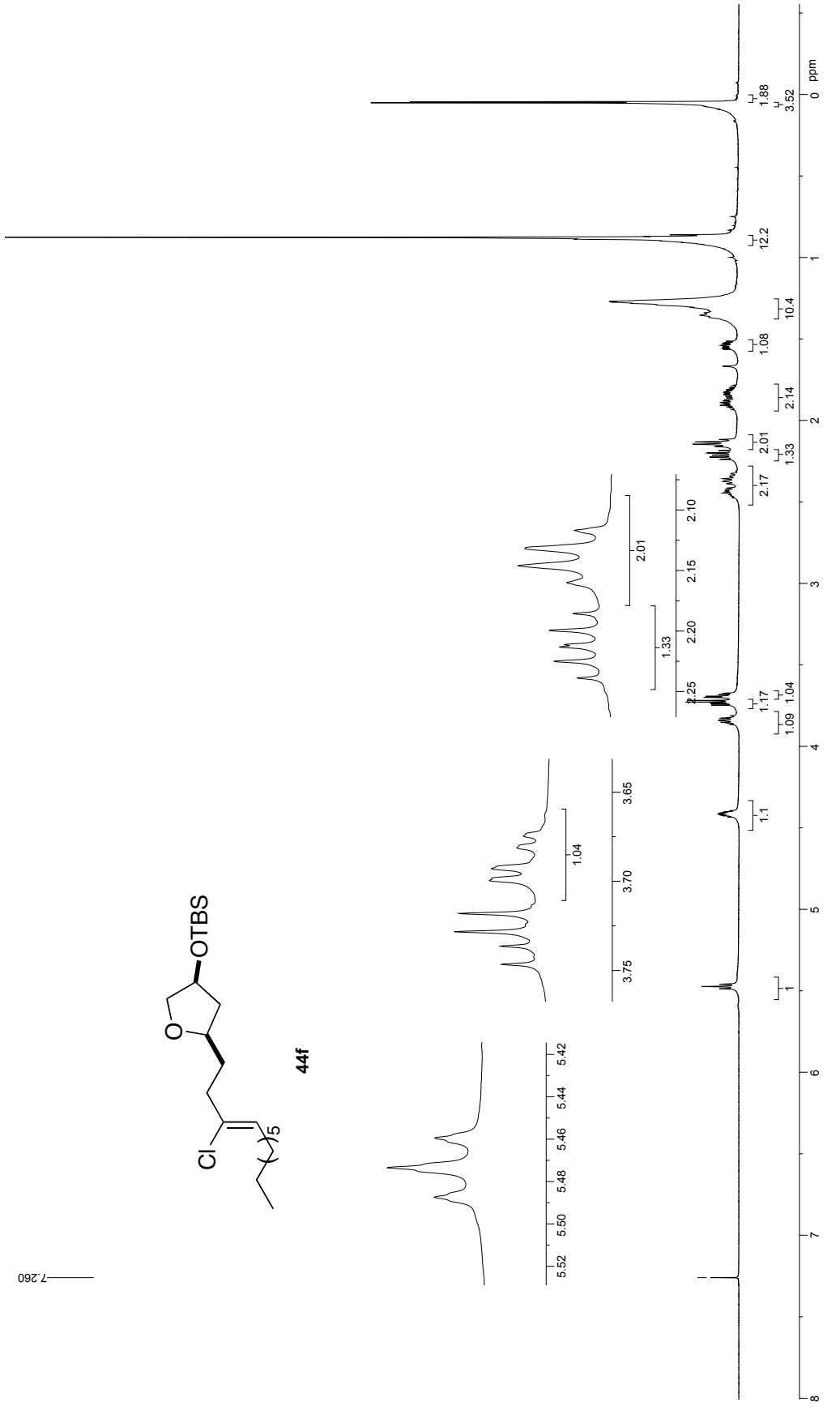
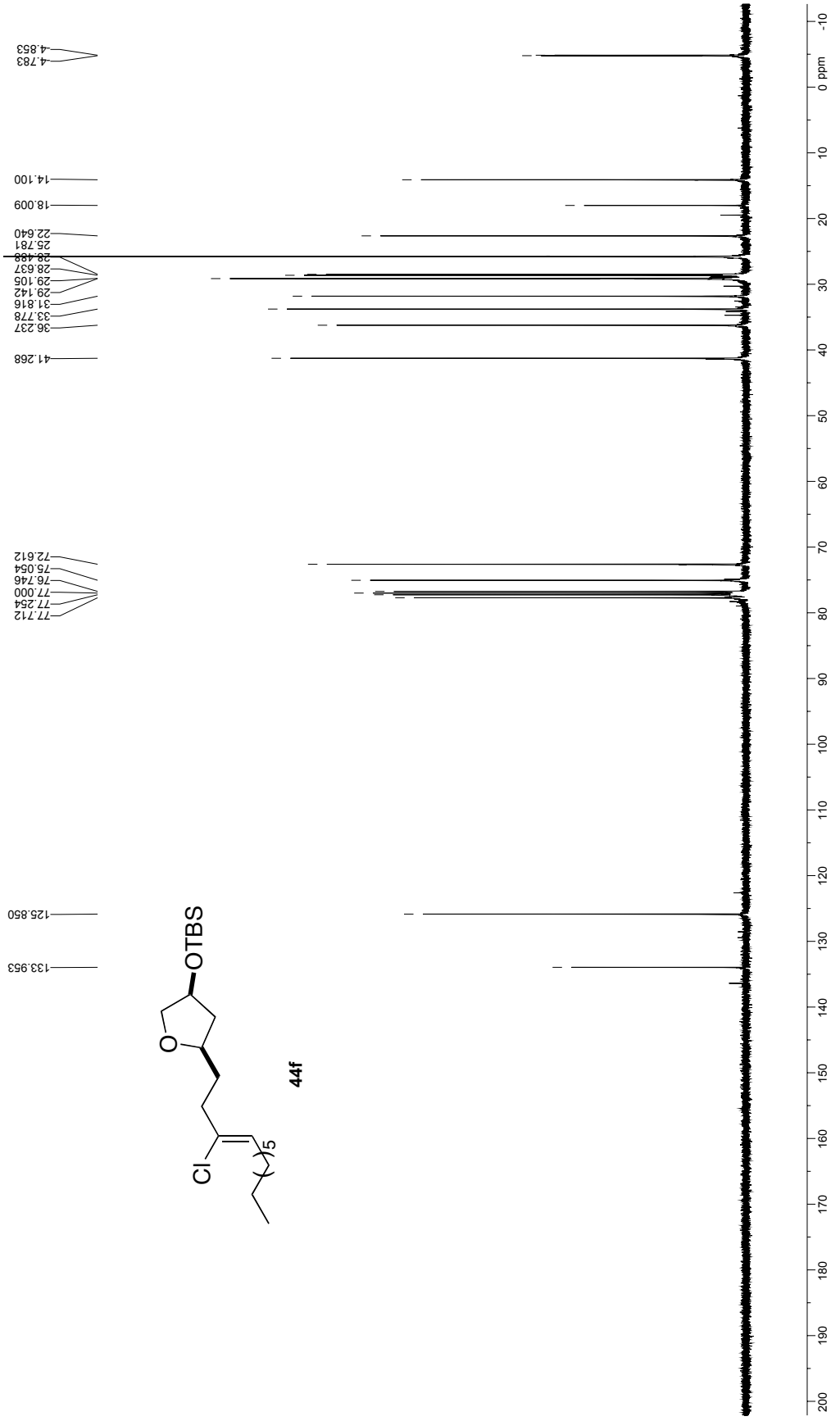
37.229
41.264
61.139
72.519
75.377
76.746
77.000
77.254
78.503
ppm 180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm
-10
OH
O
TBSO

52


Br
O
TBSO
53
7.260
4.45
4.40
1
1.02
3.80
3.78
3.76
3.74
3.72
3.71
3.70
3.69
3.68
1
0.964
1.02
1.08
2.15
2.11
1.19
1.17
9.92
6.29
0 ppm


Br
O
TBSO
53
4.878
4.934
17.891
25.694
30.398
38.906
40.854
72.465
75.228
76.392
76.745
77.000
77.255
-10 ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
90


OTBS
O
Cl
5
44f
7.260
5.52 5.50 5.48 5.46 5.44 5.42
1.04
3.75 3.70 3.65
2.01
1.33
2.25 2.20 2.15 2.10
1.1
1.09 1.04 1.17
2.17 1.33 2.01 2.14 1.08 10.4 12.2 1.88 3.52
1 2 3 4 5 6 7 8 ppm


4.783
4.853
14.100
18.009
22.640
25.781
28.488
28.637
29.105
29.142
31.816
33.778
36.237
41.268
72.612
75.054
76.746
77.000
77.254
77.712
125.850
133.953
OTBS
O
Cl
5
44f
-10
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

APPENDIX D

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Duffy, R. J.; Morris, K. A.; Romo, D. "Synthesis of Unusually Strained Spiroheterocyclic Ring Systems and Their Exploits in Synthesis" *Tetrahedron* **2009**, *65*, 5879-5892

Duffy, R. J.; Morris, K. A.; Vallakati, R.; Zhang, W.; Romo, D. "Asymmetric Synthesis, Structure, and Reactivity of Unexpectedly Stable Spiroepoxy-β-Lactones Including Facile Conversion to Tetronic Acids: Application to (+)-Maculalactone A" *J. Org. Chem.* **2009**, *74*, 4772-4781.

Duffy, R. J.; Morris, K. A.; Romo, D. "Synthesis, Structure, and Reactivity of Unexpectedly Stable Spiroepoxy-β-Lactones Obtained by Epoxidation of 4-Alkylidene-2-Oxetanones" *J. Am. Chem. Soc.* **2005**, *127*, 16754-16755.

Bhaket, P.; Morris, K.; Stauffer, C. S.; Datta, A. "Total Synthesis of Cytotoxic Anhydrophytosphingosine Pachastrissamine (Jaspine B)" *Org. Lett.* **2005**, *7*, 875-876.

Honors: Cameron University Alumni Association Outstanding Young Alumni Award (2010)

Bristol-Myers Squibb Minority Chemist Graduate Fellowship (2008-2009)

American Chemical Society Division of Organic Chemistry Graduate Fellowship, sponsor: Eli Lilly (2007-2008)

Diversity Fellowship, Texas A&M University (2004-2007)