UNIVERSITY OF CALIFORNIA

Santa Barbara

The Development of Efficient Synthetic Routes for Accessing the Structures of Bioactive Natural Products

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Chemistry

by

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June 2022

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June 2022

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ACKNOWLEDGEMENTS

I would like to first thank Professor Armen Zakarian for his excellent guidance and the motivation, encouragement, and support that he provided during my time in his laboratory. I can't express enough how much I appreciate the time spent keeping me focused on my goals, as well as, the resources that were afforded to me.

I also would like to thank my committee; Professors Trevor Hayton, Javier Read de Alaniz, and Liming Zhang for their guidance and excellent discussions of organic chemistry during my PhD effort. I would also like to thank Professor Tom Pettus for our synthetic strategy discussions and for acting as a sounding board for some of my ideas.

Thank you to Dr. Hongjun Zhou for excellent upkeep of the NMR facilities and for helping to perform and interpret NMR experiments. Thank you to Dr. Guang Wu for maintaining the wonderful X-ray crystallography facilities and for help with data interpretation.

I want to thank Dr. Morgan Gainer for being such an excellent supervisor during my time as a teaching assistant. Thank you to the all the staff in the undergraduate laboratory, the chemistry department administrative staff, and the chemistry building maintenance crew.

I want to thank both current and former members of the Zakarian lab for their support during my time there. Very special thanks to Dr. Artur Mailyan for imparting his chemical wisdom to me when I first got to the lab, as well as, Jacob Levin for his insight and supporting me in the final stretch. I also want to thank members of other groups for cooperative sharing of chemicals and resources.

I need to especially thank my parents, Ellen and Tom Reid for their unwavering support, encouragement, and love during my time in the PhD program.

Curriculum Vitae

BRADLEY THOMAS REID

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EDUCATION

Ph.D in Chemistry
University of California, Santa Barbara (UCSB) June 2016–June 2022 (planned)

B.S. Chemistry, "with distinction" and Cum Laude
University of Colorado – Denver (UCD) June 2012–May 2016

B.S. Construction Engineering
Iowa State University, Ames (ISU) Jan 2016–Aug 2009

RESEARCH EXPERIENCE

Graduate Research Assistant | Department of Chemistry, UCSB June 2016–Jan 2022
Primary research advisor: Dr. Armen Zakarian

Stereoselective Synthesis of Cyclic Guanidines by Directed Diamination of Unactivated Alkenes

Developed methodology for the diastereoselective delivery of guanidine to monosubstituted alkenes. Included using optimized reaction conditions on a number of different substrates to demonstrate broad applicability of the reaction. Gained experience in working with molecules that are notoriously difficult to isolate by conventional methods.

Total Synthesis Of (+)-Guadinomic Acid via Hydroxyl-Directed Guanidylation

Developed the shortest synthesis of (+)-guadinomic acid to date. Utilized guanidylation methodology that I helped develop in order to make the synthesis more efficient. Required performing an enantioselective allylation and isolation of the final zwitterionic product by reverse-phase column chromatography. Solved a problem of regioselectivity during installation of urea functionality on cyclic guanidine.

Divergent Synthesis of Spongian Diterpenes (ongoing work)

Designed and implemented a robust approach to an intermediate which can be used to synthesize a number of members of the spongian family of diterpenes. Developed a number of novel methods to access structures which have a limited precedence in literature.

Undergraduate research | Department of Chemistry, UCD Sept 2015–May 2016
Primary research advisor: Dr. Scott Reed

- Organic synthesis and nanoparticle preparation
- Using nanoparticles as a platform for modeling cell membranes
- Using nanoparticles as a means of drug delivery

RESEARCH PUBLICATIONS

1. **Reid, B.** Divergent Total Synthesis For Access To Members Of Spongian Family Containing The 1,3,3 - Trimethylcyclohexyl Subunit. Currently in Progress.
2. **Reid, B.**; Mailyan, A.; Zakarian, A. Total Synthesis Of (+)-Guadinomic Acid via Hydroxyl-Directed Guanidylation. *J. Org. Chem.* **2018**, 83, 16, 9492-9496.
3. Mailyan, A.; Young, K.; Chen, J.; **Reid, B.**; Zakarian, A. Stereoselective Synthesis of Cyclic Guanidines by Directed Diamination of Unactivated Alkenes. *Org. Lett.* **2016**, 18, 5532-5535.
4. **Reid, B.**; Reed, S. M. Improved Methods for Evaluating the Environmental Impact of Nanoarticle Synthesis. *Green Chem.*, **2016**, *18* , 4263-4269.

PRESENTATIONS

1. Poster, **Brad Reid**, "Applying Organic Reaction Efficiency Metrics to Preparations of Gold Nanoparticles" presented at the Research and Creative Activities Symposium at the University of Colorado –Denver on April 17, 2015.
2. Scott M. Reed and **Brad Reid**, "Adapting Green Chemistry Metrics for Nanoparticle Synthesis" presented at the 249th American Chemical Society National Meeting and Exposition in Denver, Colorado on March 25, 2015.
3. Poster, **Brad Reid**, "Applying Organic Reaction Efficiency Metrics to Preparations of Gold Nanoparticles" at the Front Range Symposium on Photonic Applications of Gold Nanomaterials at the University of Colorado – Denver on November 14, 2014.

TEACHING EXPERIENCE

Graduate Research Mentor | UCSB 2016–Present

- Trained 1st year grad students in Mass Spectrometer use.
- Mentored and produced research activities for a 1st year graduate student.

Organic Chemistry Lab I/II/III, Lab Teaching Assistant | UCSB 2016–2020

- Taught chemical instrumentation (NMR, FTIR, etc.) as well as organic laboratory techniques (chromatography, recrystallization, distillation, extractions, sublimations, etc.) twice a week to undergraduate students while enforcing laboratory safety.

Inorganic Chemistry Lab I, Lab Teaching Assistant | UCSB 2016

- Taught inorganic laboratory techniques (e.g. titrations) twice a week to undergraduate students while enforcing laboratory safety.

Organic Chemistry I/II/Honors, Lab & Lecture TA | UCD Fall 2014–Spring 2016

- Attended lecture and help students work through in-class problem sets, as well as, answer any questions about the theory that was presented. Presented chemistry theories and laboratory techniques, with emphasis on safety, to students in undergraduate chemistry lab.

HONORS AND AWARDS

- Bruce Rickborn-Ross Johnson Graduate Fellow (UCSB) 2016–2017
- Outstanding Service to the Department Award (UCSB) 2017
- Outstanding Graduate Award (UCD) 2016

ABSTRACT

The Development of Efficient Synthetic Routes for Accessing the Structures of Bioactive Natural Products

by

Bradley Thomas Reid

The development of efficient strategies for the synthesis of complex organic molecular architectures is a fundamentally important aspect in both the process of the total synthesis of natural products and the manufacture of pharmaceuticals. The necessity for the rapid construction of these complicated structures is often inspiration for the development of new methods for forming chemical bonds and for the creative implementation of previously known reactivity. The content of this dissertation focuses on the development of efficient and stereocontrolled total syntheses of natural products and the necessary methodology for their completion.

The first chapter of the dissertation outlines a straight-forward synthetic route to a common intermediate which can be used to access multiple members of the rearranged spongian diterpene family. The key intermediate is then used to complete the first total synthesis of (±)-cadlinolide A and the unnatural derivative (±)-desmethylcadlinolide A. A model study was conducted to establish the potential for the intermediates' use in the total synthesis of (+)-darwinolide; a spongian diterpene bearing a 7-membered ring as opposed to the more common 6-membered ring. The initial results demonstrate a strong support for its

use in the total synthesis of this natural product and efforts to complete the construction of this biologically active scaffold are currently underway.

The second chapter of this dissertation will focus on the development of methodology for the diastereoselective installation of cyclic guanidines. We demonstrated that a guanidine carbamate, synthesized from a homoallylic alcohol and guanidine hydrochloride, can be used to direct the cyclization of guanidine onto an unactivated, terminal alkene with excellent diastereoselectivity. This method for guanidine installation is more efficient than conventional methods as it allows for the use of a complete, intact guanidine unit.

In the third chapter, we demonstrate the utility of this methodology in the total synthesis of (+)-guadinomic acid. (+)-Guadinomic acid is part of a cyclic-guanidine-containing family called the guadinomines; a family possessing potent anti-proliferation properties towards gram-negative bacteria. The synthesis of guadinomic acid that we developed was a considerably shorter pathway than the pathways developed previously, which we attribute to the use of our methodology.

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List of Abbreviations

Ac	acetate
aq.	aqueous
Ar	generic aryl group
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
Bu	butyl
Bz	benzoyl
c	concentration
calcd	calculated
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CDI	1,1'-carbonyldiimidazole
°C	degrees Celsius
d	doublet
DET	diethyl tartrate
DIAD	diisopropyl azodicarboxylate
DIPEA	*N*,*N*-diisopropyl-*N*-ethylamine
DMAP	*N*,*N*-4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide

dr	diastereomeric ratio
δ	chemical shift(s)
E	entgegen
EDC	1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide
ee	enantiomeric excess
EI	electron impact
EPEC	enteropathogenic *Escherichia coli*
equiv.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
g	gram(s)
Grubbs II	Grubbs catalyst, 2nd generation
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
hr	hour (s)
HRMS	high resolution mass spectrometry
i	iso
IC_{50}	half maximal inhibitory concentration
ImH	imidazole
J	coupling constant
L	liter(s)
LDA	lithium diisopropylamide

m	multiplet
M	molarity
m/z	mass/charge
Mbs	*para*-methoxybenzenesulfonyl
Me	methyl
mg	milligram(s)
MHz	megahertz
MIC	minimum inhibitory concentration
min	minute(s)
mL	milliliter(s)
mmol	millimole(s)
MRSA	methicillin-resistant *Staphylococcus aureus*
MS	mass spectrometry
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
nM	nanomolar
µL	microliter(s)
µM	micromolar
[M+H]	molecular mass + hydrogen
[M+Na]	molecular mass + sodium
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect

Nuc	nucleophile
p	para
Ph	phenyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
Pr	propyl
Py	pyridine
R	generic functional group
s	singlet
SAR	structure-activity relationship
SKA	silyl ketene acetal
spp.	species pluralis
t	tert/tertiary
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	4-toluenesulfonyl

TTSS	Type-III secretion system
Z	zusammen

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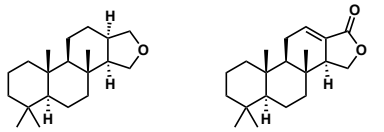
Chapter 1

Divergent Synthesis of Spongian Diterpenes: Total Synthesis of (±)-Desmethyl Cadlinolide A and (±)-Cadlinolide A

1.1 Introduction

1.1.1. Spongian Diterpenes

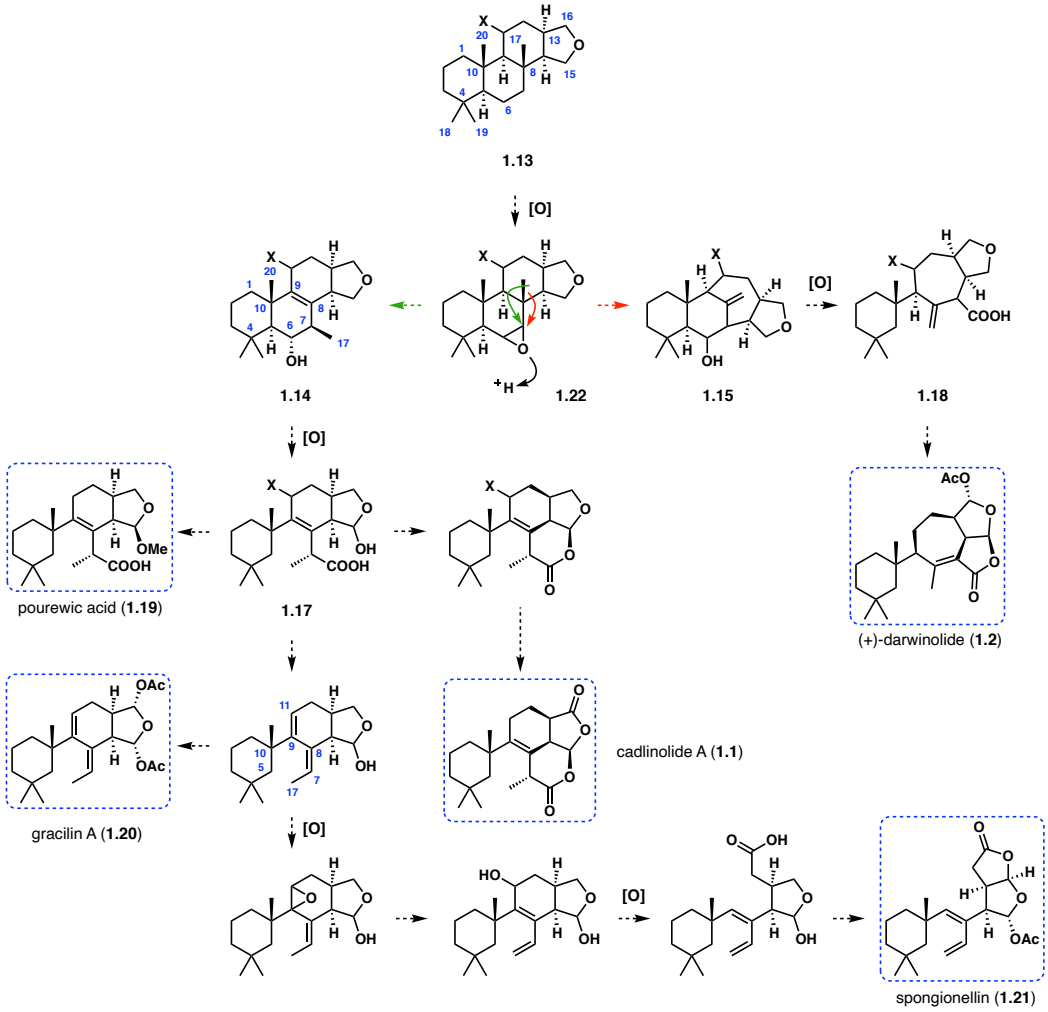


General Spongian Skeleton (**1.13**) isoagatholactone (**1.11**)

Figure 1. Structure of general spongian skeleton, and the first isolated spongian diterpene, isoagothalactone

Spongian diterpenes are an enormous, structurally-diverse class of natural products isolated from marine sponges and the opisthobranch mollusks (nudibranchs) that prey upon them.[1] The use of the name "spongian" reflects the origin of early isolated samples of this class of diterpene in the dictyoceratid sponge genus, *Spongia*. "Spongian diterpene" was first used by Murphy and co-workers in 1979, and has been used consistently in literature over the last 40 years to describe compounds whose structure is derived from the general skeleton **1.13**.[2] The first reported member of this family was isoagatholactone **1.11**; isolated by Cimino *et. al.* in 1973 from a Mediterranean sample of *Spongia officianali*.[3]

Scheme 1. Proposed biosynthetic pathway for formation of several rearranged spongian diterpene classes



Since the initial isolation of isoagatholactone **1.11**, a large number of spongian diterpenes have been isolated from a variety of sponge species, differing in the pattern of oxidation around the general spongian skeleton. The largest group of spongian diterpenes are those whose carbon skeleton is thought to be the result of some form of a rearrangement of **1.13**. This class of compounds is known as the "rearranged spongian diterpenes." An oxidized form of the common spongian intermediate **1.22** can rearrange to form **1.14** through a Wagner-Meerwein shift of the C-17 methyl group, or lead to **1.15** *via* a ring-expansion by migration

of the secondary C-14 carbon. This initial rearrangement is followed by oxidative cleavage of the bond between C-5 and C-6 to give a carboxylic acid. If lactonization of the carboxylic moiety and the C-15 hemiacetal hydroxyl group occurs after rearrangement, this leads to the cadlinolide **1.1** class or the darwinolide **1.2** class of diterpenes. Further decarboxylation of the resulting carboxylic acid moiety produces the skeleton observed in the gracillin **1.20** class of diterpenes. Several subsequent oxidations of the gracillin-type skeleton are thought to give rise to the highly-altered skeleton of the spongionellin **1.21** class of diterpenes.[4,5,6] The proposed biosynthesis exhibited in Scheme 1, covers only a small subset of the extraordinary number of rearranged spongian scaffolds that have been discovered to date.

Historically, the phylogeny of marine sponges has relied heavily on the external features of the organism; namely the size, shape, color and especially the distribution of mineral spicules within the sponge skeleton. These morphological features are often supplemented with other characteristics of the sponge including reproductive, histological, and genetic characteristics. The short-comings of this morphological approach to sponge taxonomy becomes readily apparent during classification of keratose sponges, which lack a spicule skeleton and rely on callogenous fibers as the primary means of structural reinforcement.[7,8]

Table 1. Taxonomic relationships within the Dictyoceratid and Dendroceratid Orders. Genera highlighted in blue have been found to contain spongian diterpenes.

Order	Dicytoceratida			Dendroceratida	
Family	Spongiidae	Thorectidae	Dysideidae	Darwinellidae	Dictyodendrillidae
Genus	*Coscinoderma*	*Aplysinopsis*	*Citronia*	*Aplysilla*	*Acanthodendrilla*
	Hippospongia	*Cacospongia*	*Dysidea*	*Chelonaplysilla*	*Dictyodendrilla*
	Hyattella	*Collospongia*	*Euryspongia*	*Darwinella*	*Igernella*
	Leiosella	*Dactylospongia*	*Lamellodysidea*	*Dendrilla*	*Spongionella*
	Rhopaloeides	*Fascaplysinopsis*	*Pleraplysilla*		
	Spongia	*Fenestraspongia*			
		Hytios			
		Luffariella			
		Narrabeena			
		Petrosaspongia			
		Scalarispongia			
		Semitaspongia			
		Smenospongia			
		Taonura			
		Thorecta			
		Thorectandra			
		Thorectaxia			

Chemotaxonomy, on the other hand, has played a significant role in the identification of sponges by taxonomists. For instance, the production of tyrosine-derived, brominated indole metabolites by sponges in the order verongid, has become a key factor in the assignment of sponges within this order.[22,9] Likewise, the isolation and identification of spongian diterpenoids from keratose sponges made an important contribution to a revision of the classification of certain sponges within the order of Dendroceratida.[10] The propensity for certain sponge genera to produce a unique fingerprint of spongian diterpenes suggests that these biosynthetic pathways are specific to a given genus. To date, there has never been a reported study on the characterization of these biosynthetic sequences.

1.1.2. Bioactivity of Some Spongian Members

Sponges have evolved chemical defense systems in order to combat their natural predators, especially nudibranchs. Nudibranchs prey on a number of sponges and are capable of sequestering sponge metabolites and transforming them for their own defensive purposes. Sponges and nudibranchs are excellent sources of bioactive natural products, particularly spongian diterpenes. This class of natural products displays a wide variety of bioactivities including (but not limited to) antimicrobial, antifeedant, antitumor, and anti-inflammatory. The following discussion on the biological activity of these natural products will cover some select members of rearranged spongian diterpenes which have bioactivity that has been reported on recently.

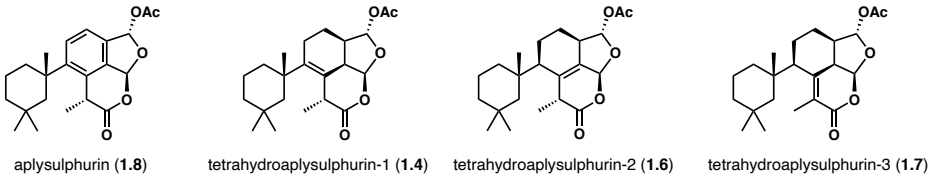
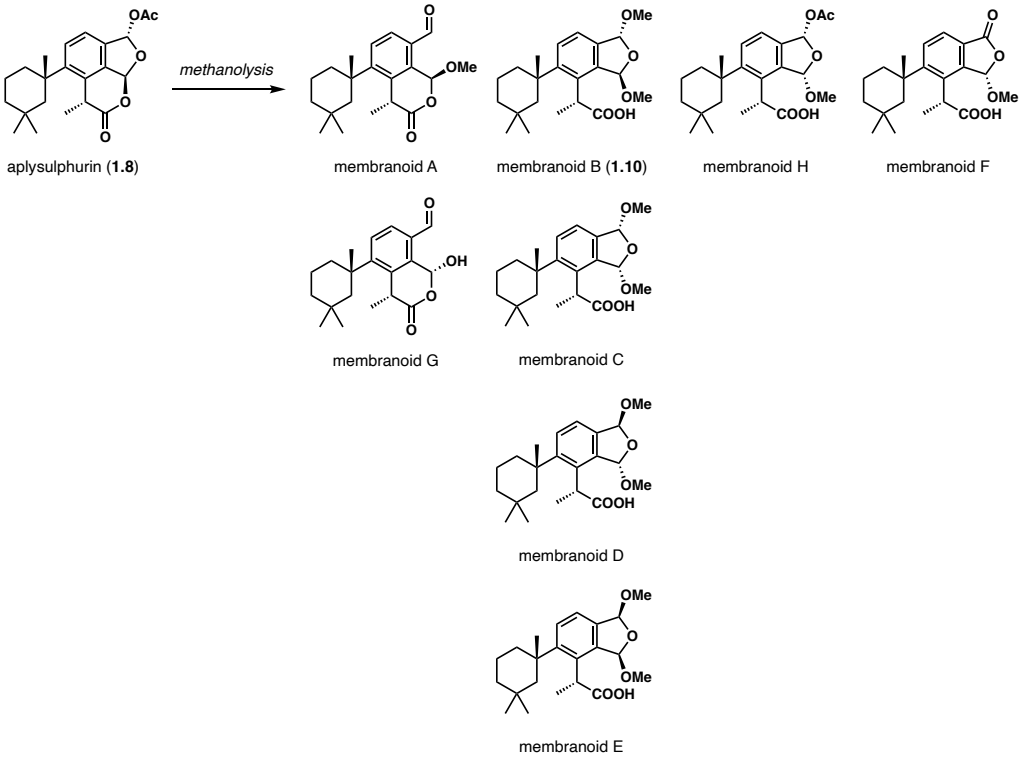


Figure 2. Structure of aplysulphurin and known isomers of tetrahydroaplysulphurin

Extracts from the sponge *Darwinella* sp. (originally misidentified as *Aplysilla rosea*) collected off the coast of New Zealand were reported (ca. 1986) to contain the known diterpene, aplysulphurin **1.8**, as well as, a new diterpene; tetrahydroaplysulphurin-1 **1.4** as the major constituent (0.58%).[11] Initial characterization of **1.4** included analysis by ^{1}HNMR, ^{13}CNMR, HRMS, and elemental analysis, however in a follow up study, it was unambiguously characterized by X-ray crystallography.[12] A recent study by the Baker group revealed that

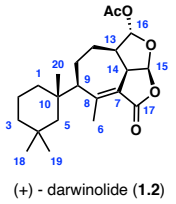
tetrahydroaplysulphurin-1 **1.4** has low micromolar inhibitory activity (3.5 μM) against the parasite *Leishmania donovani.*[13] *L. donovani* is a parasite which is often spread by sand flies and causes Leishmaniasis. This disease affects millions of individuals every year and can be fatal if left untreated.[14] The inhibitory activity of **1.4** was also coupled with poor cytotoxicity against J774A.1 cell line (>133 μM), highlighting the selectivity of the bioactivity. Aplysulphurin **1.8** was also found to have low micromolar inhibitory activity against the parasite (3.1 μM), however this activity was coupled with a much higher cytotoxicity against the J774A.1 cell line (12.3 μM). The most potent inhibitor against *L. donovani* was membranoid B, whose structure was the result of the methanolysis of parent natural product aplysulphurin **1.8**. It was found to have inhibitory activity against *L. donovani* at 0.8 μM with cytotoxicity of J774A.1 greater than 133 μM. The activity of both the natural products and three of the unnatural derivatives prepared through methanolysis (membranoids), showed more potent inhibition against *L. donovani* than miltefosine, a medication currently used to treat Leishmaniasis. Miltefosine has been on the World Health Organization's List of Essential Medicines.[15]

Scheme 2. Structure of the eight membranoids isolated from methanolysis of aplysulphurin



The extracts of *Dendrilla antarctica,* a sponge species closely related to *Dendrilla membranosa*, have yielded a number of rearranged spongian diterpenes including previously isolated aplysulphurin **1.8** and tetrahydroaplysulphurin-1 **1.4**. In 2016, the Baker group reported on the isolation of a new, rearranged spongian skeleton isolated from the dichloromethane extracts of *Dendrilla antarctica* collected near Palmer Station, Antactica.[6] The new compound, (+)-darwinolide **1.2**, is unique to all previously isolated members in that it contains a 7,5,5-fused tricyclic acetal structure instead of the more common 6,6,5 pattern (aplysulphurin **1.8** and tetrahydroaplysulphurin **1.4**). The structure of darwinolide was elucidated (unambiguously) using a number of NMR experiments, as well as, X-ray crystallography. Aside from its interesting structure, darwinolide has shown unique inhibitory activity toward methicillin-resistant *Staphylococcus aureus* (MRSA). A broth dilution assay

revealed that the MIC for darwinolide against MRSA is 132.9 μM; a subsequent growth recovery experiment demonstrated that darwinolide is cytotoxic rather than cytostatic, as only 1.6% of the bacterial culture were able to recover and grow. Darwinolide was found to have no significant toxicity toward mammalian cells (J774 macrophage cell line, IC_{50} = 73.4 μM). The inhibitory activity of darwinolide was also tested against an MRSA biofilm culture, and it was found to possess an IC_{50} value of 33.2 μM. A number of other compounds show more potent activity against MRSA biofilms. However, all of them demonstrate more inhibition against cultures in the broth phase rather than the biofilm phase.[16] This is an important finding, as it is estimated that the source of approximately 80% of all bacterial infections are the result of biofilms.[17] These results suggest that structure of (+)-darwinolide **1.2** could serve as the starting point for the development of biofilm-specific antibiotics to combat the growing problem of antibiotic resistance.



(+) - darwinolide (**1.2**)

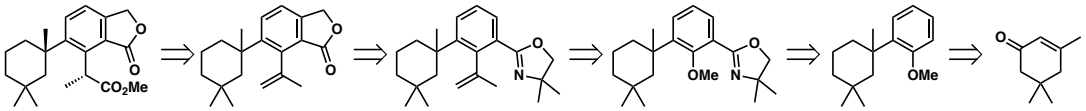
Figure 3. Structure of (+)-darwinolide

1.1.3. Selected Syntheses of Rearranged Spongian Diterpenes

There have been a large number of total syntheses of both spongian and rearranged spongian diterpenes reported in literature since their initial isolation. The examples included in the following section will focus on the syntheses of rearranged spongian diterpenes bearing a pendant 1,3,3-trimethylcyclohexyl subunit.

One of the first synthetic routes for a rearranged spongian diterpene was developed by Sung-eun Yoo and Kyu Yang Yi, for the total synthesis of (±)-membranolide.[18] (±)-Membranolide was isolated from the extracts of *Dendrilla membranosa* and found to inhibit the growth of *Bacillus subtilis* and *Staphylococcus aureus*.[19] The successful general strategy for the racemic synthesis is shown in Scheme 3 below.

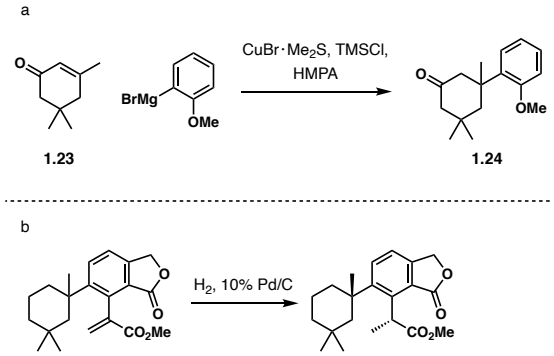
Scheme 3. Yoo and Yi's successful strategy for the total synthesis of racemic membranolide



membranolide (**1.9**) **1.25** **1.24** isophorone (**1.23**)

This route gave the structure of membranolide **1.9** in 12 steps. Installation of the 1,3,3-trimethylcyclohexyl group was accomplished through the use of an organocuprate, conjugate addition to isophorone **1.23** to give intermediate **1.24** (scheme 20a).

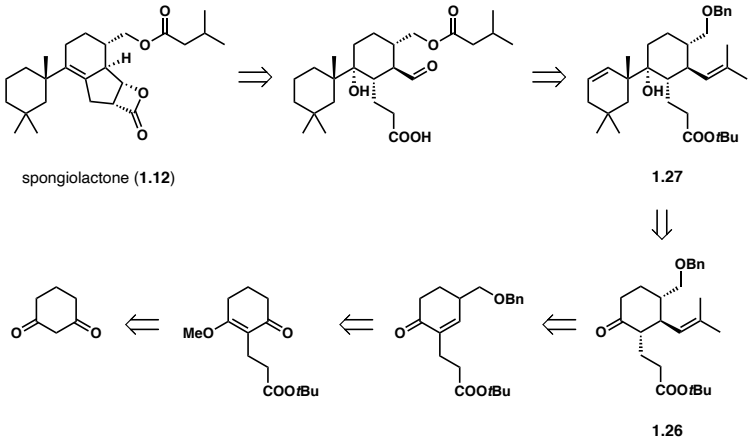
Scheme 4. Key synthetic steps in the total synthesis of membranolide



The final step of the synthesis was the reduction of the olefin in the styrene intermediate **1.25** to form the stereocenter alpha to the methyl ester (scheme 4b). This hydrogenation demonstrated modest diastereoselectivity, suggesting that the configuration of the stereocenter in the trimethylcyclohexyl subunit can favorably influence the configuration of the stereocenter alpha to the methyl ester in certain cases.

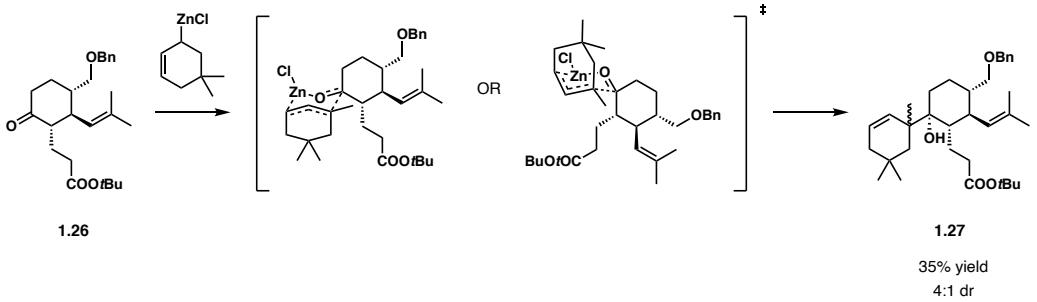
The Romo group has demonstrated another intermolecular method for the installation of the 1,3,3-trimethylcylohexyl subunit in the total synthesis of spongiolactone **1.12**[20] and the synthesis of several unnatural derivatives of gracilin A **1.20** (scheme 7a).[21] The successful retrosynthetic plan for the racemic synthesis of spongiolactone is shown in Scheme 5.

Scheme 5. Retrosynthesis for the racemic synthesis of spongiolactone



For the installation of the 1,3,3-trimethylcyclohexyl moiety, the Romo group employed the 1,2-addition of an organo-zinc reagent to cyclohexanone intermediate **1.26** to give tertiary alcohol intermediate **1.27**. The diastereoselectivity (4:1 favoring *S*-configuration in trimethylcyclohexane ring) and excellent regioselectivity of the reaction is suggested to be the result of a chair-like transition state proposed by Knochel *et al* (Scheme 6).[22]

Scheme 6. Installation of the 1,3,3-trimethylcyclohexyl subunit of spongiolactone

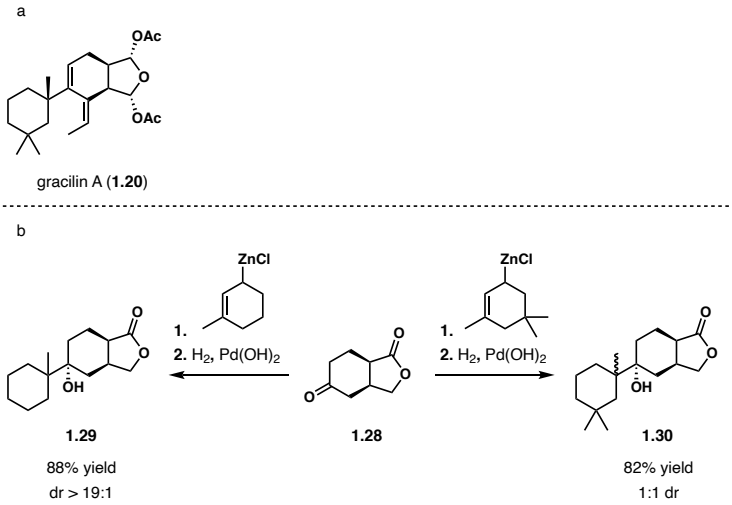


1.26 **1.27**

35% yield
4:1 dr

This methodology was then extended to the synthesis of several analogs of gracilin A **1.20** for an SAR study and a demonstration of pharmacaphore-directed retrosynthesis (PDR) by the same group.[35]

Scheme 7. Structure of gracilin A and the Romo group strategy for installation of 1,3,3-trimethylcyclohexyl group to gracilin A derivatives

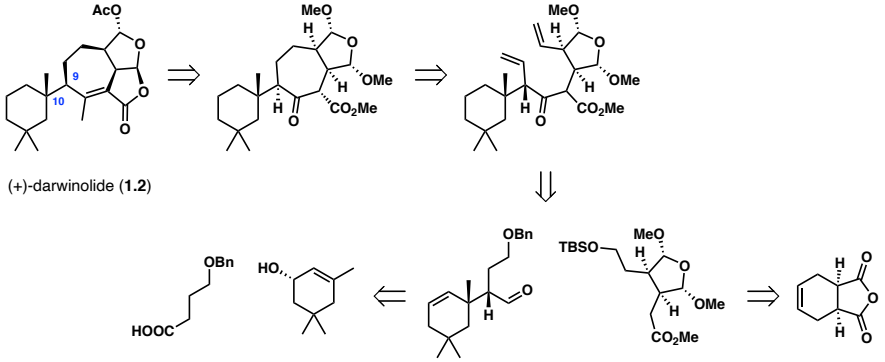


The facial-selectivity in the addition of the cyclic allyl-zinc species to the bicyclic ketone **1.28** was excellent in both examples. However, in the case of the allyl-zinc reagent bearing

the geminal dimethyl group, no diastereoselectivity was observed for the formation of two new stereocenters in structure **1.30**. A pair of epimers were isolated differing in the configuration of the stereocenter in the 1,3,3-trimethylcyclohexyl ring. The Romo group advanced these two intermediates (**1.29**, **1.30**, and stereoisomers) through a demonstration of their PDR strategy and evaluated them according to the neuroprotective and immunosuppressive activity observed in the natural product.[23,24,25,26,27,28] They found that many of these more structurally simple congeners displayed potent neuroprotective and immunosuppressive activity, despite having a structure which is much less complex than that of the natural product, gracilin A **1.20**.

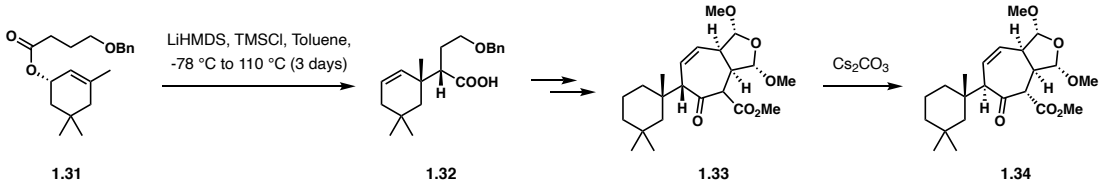
In contrast to the previous two intermolecular methods, the Christmann group utilized an intramolecular strategy for a highly diastereoselective installation of the 1,3,3-trimethylcyclohexyl ring in (+)-darwinolide.[29] The successful strategy they employed for the development of the 21-step synthetic route is shown in Scheme 8.

Scheme 8. Christmann's retrosynthetic plan of (+)-darwinolide



The configuration of the congested, vicinal stereocenters at C9 and C10 were established using an Ireland-Claisen rearrangement of ester **1.31** (Scheme 9).

Scheme 9. Ireland-Claisen rearrangement and subsequent epimerization of C9 of (+)-darwinolide

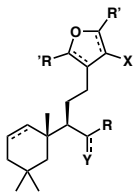


Interestingly, the Christmann group reported on Ireland-Claisen rearrangement conditions that gave, as the major diastereomer (**1.32**), the configuration at C9 which is opposite of that in the natural product. It was stated that this outcome was desirable, as the minor diastereomer was unreactive in an aldol addition later on in the synthesis. In order to obtain the relative stereochemistry present in the natural product, the C9 stereocenter was epimerized to the desired configuration in a subsequent step (Scheme 9, **1.33** to **1.34**). There is little discussion of the details of the rearrangement in the paper. However, it was clearly demonstrated that this strategy could be used to invoke a high level of diastereoselectivity in the formation of the two stereocenters.

The preceding examples of methods used to install the (deceptively complicated) 1,3,3-trimethylcyclohexyl subunit demonstrate that a variety of methods have been used. While the convergent strategy of intermolecular coupling of the two ring systems is highly efficient from a step-count standpoint, it suffers from a lack of diastereoselectivity, which is absent in the intramolecular (sigmatropic rearrangement) strategy.

1.2. Development of a Common Intermediate for the Synthesis of Spongian Diterpenes

The wide variety of bioactivities that the family of spongian diterpenes bearing the 1,3,3-trimethylcyclohexyl subunit have demonstrated, suggest that further investigation into the specific pharmacophore, and its mechanism of action is warranted. We felt that the development of a synthetic intermediate that could act as a point of divergence in order to access several members of this family of rearranged spongian diterpenoids would be of value in potential SAR studies. We envisioned the structure of this intermediate possessing the general functionality of **1.35**.



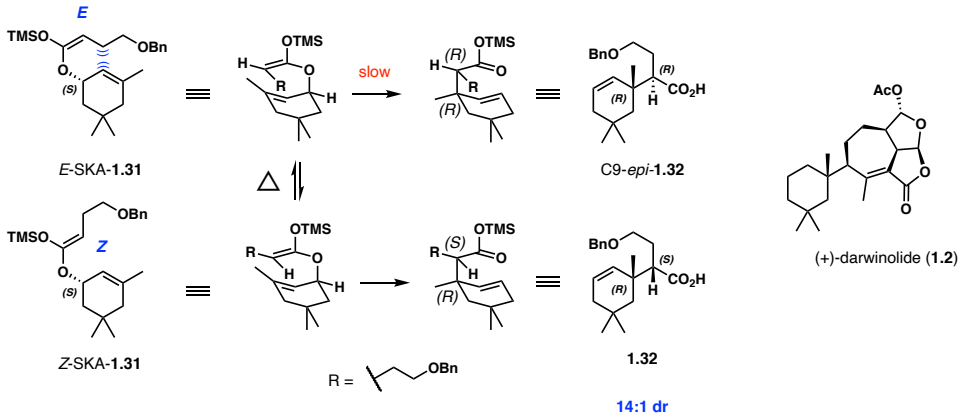
1.35

Figure 4. General, theoretical structure of common intermediate for access to family of spongian diterpenes

For the diastereoselective installation of the 1,3,3-trimethylcyclohexane structure, we wished to build on the strategy utilized by Christmann and coworkers in their total synthesis of (+)-darwinolide **1.2**. As a reminder, the Christmann group invoked a highly diastereoselective Ireland-Claisen rearrangement in order to set the configuration at the C9 and C10 stereocenters of the natural product. Their rearrangement conditions, however, gave a major diastereomer that differed in the relative stereochemistry of that in the final structure of the natural product. The stereochemical outcome of a given Ireland-Claisen rearrangement can *usually* be controlled by a simple change in the reaction conditions, making it possible to obtain either diastereomer as the major product. This suggests that only one diastereomer

could be obtained in excess, regardless of any change to the reaction conditions. One possible explanation for this outcome is that only one *E*/*Z* isomer of the intermediate silyl ketene acetal could be obtained in large excess over the other isomer. Another possible scenario to explain why only one diastereomer could be obtained in this transformation is outlined in Scheme 10.

Scheme 10. Proposed rational for diastereoselectivity observed in the Ireland-Claisen rearrangement utilized in the total synthesis of (+)-darwinolide

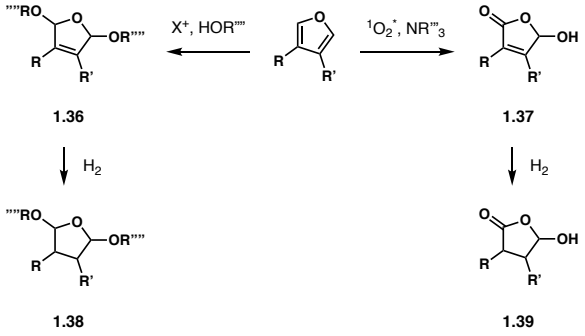


Simply put, it may have been the case that the temperature required to affect the rearrangement of the allylic ester **1.31** derived from isophorol was at or above the temperature at which the silyl-ketene acetal SKA-**1.31** can isomerize (*E*/*Z*). The configuration of the starting silyl ketene acetal may have been inconsequential, as the speed of the rearrangement of the *Z*-isomer (*Z*-SKA-**1.31)** was far greater than that of the *E* (*E*-SKA-**1.31**). This effect has been documented previously by Kishi and coworkers in their attempts to improve the diastereoselectivity of an Ireland-Claisen rearrangement of an ester derived from a cyclic allylic alcohol.[30] We have noted previously in our group that vicinal, congested stereocenters can be installed with the Ireland-Claisen rearrangement of esters derived from acyclic allylic alcohols with high diastereoselectivity.[31,32] The use of an ester derived from an acyclic allylic

alcohol for the Ireland-Claisen substrate, should allow the rearrangement to occur at a temperature below that required for isomerization of the silyl-ketene acetal, and provide some degree of flexibility in obtaining either diastereomer as the major product.

The construction of the wide variety of oxygenation patterns exhibited by this family of spongian diterpenes on the fused acetal (acylal in some cases) portion of a given member, will require early installation of structure which can be flexibly transformed into any one of the oxygenated motifs at a later stage. Furans can be oxidized at the 2 and 5-positions using a number of conditions to give 2,5-dialkoxy-dihydrofuran or hydroxybutenolides (Scheme 11), while remaining unreactive strongly basic or mildly acidic conditions.

Scheme 11. Oxidation of furan at the 2 and 5-position

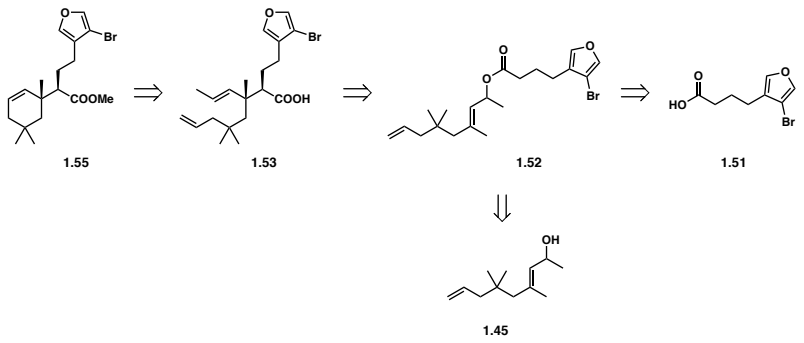


In the presence of alcohols (or carboxylic acids) and a source of electrophilic bromine, furans are known to undergo oxidation to form 2,5-dialkoxy-dihydrofuran **1.36**.[33] The original examples using this reaction rely on molecular bromine as the electrophile. However, several newer methods have been established using *N*-bromosuccinimide and also electrochemical means.[34,35] In the presence of singlet oxygen and a trialkylamine, furans are oxidized to the corresponding hydroxy-butenolides **1.37**. This method has been used successfully numerous times for the installation of hydroxy-butenolides in the structure of a natural product (or

intermediates en route). Subsequent hydrogenation of the olefin remaining after the oxidation of the furan would furnish the fused tetrahydrofuran (**1.38** and **1.39**) motif that is present in many members of this diterpenoid family.

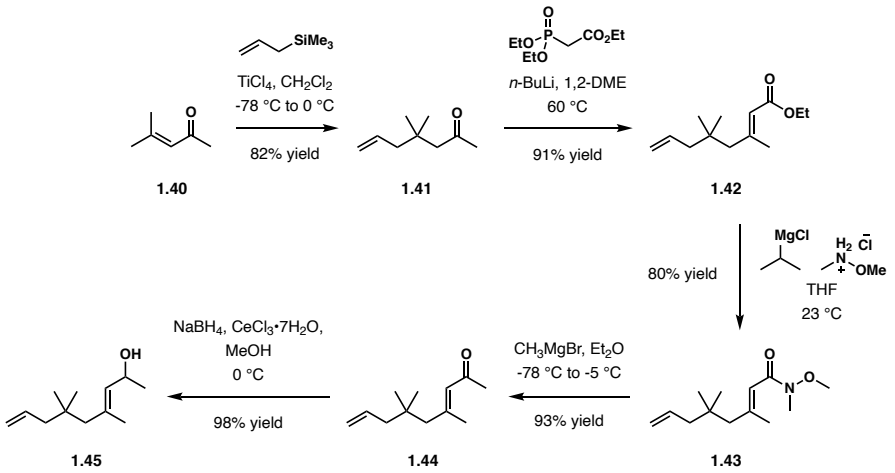
The retrosynthetic plan which relies on the use of the two described (above) synthetic strategies to access the common intermediate is outlined in Scheme 12.

Scheme 12. Synthetic plan to access common intermediate



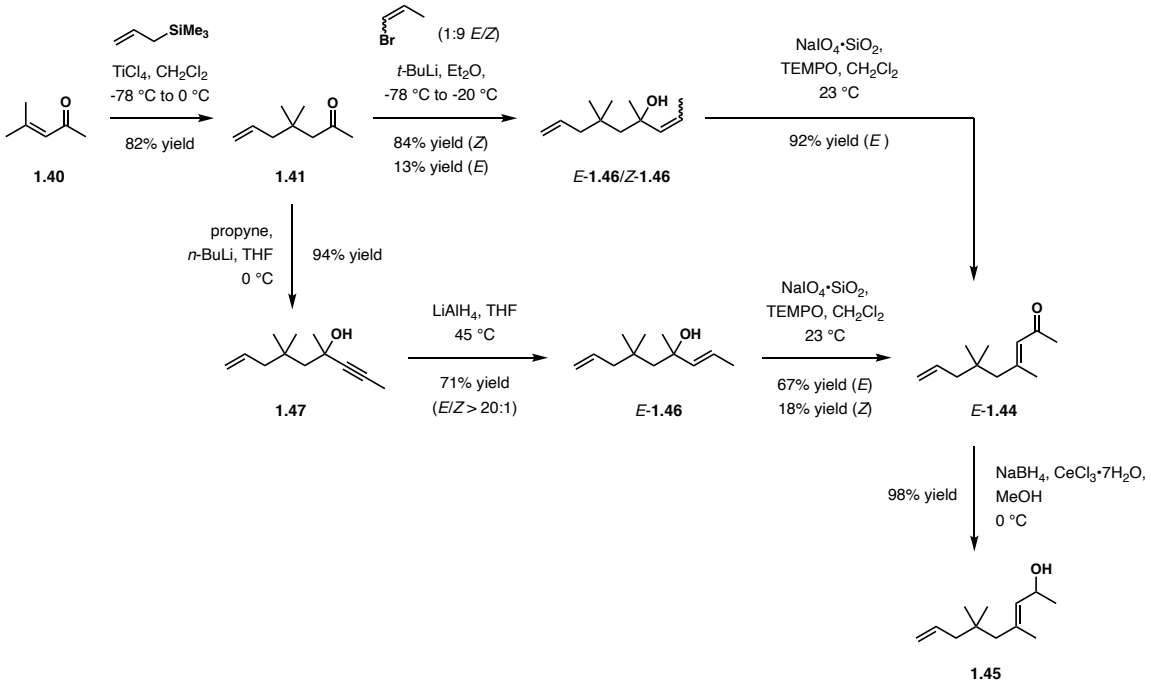
The ultimate formation of the 1,3,3-trimethylcyclohexene is the result of ring closing metathesis after methyl esterification of diene **1.53**. The configuration of the two stereocenters will be established using an Ireland-Claisen rearrangement of acyclic allylic ester **1.52**. The formation of the ester can be traced back to the coupling of furylbutanoic acid **1.53** and allylic alcohol **1.45**. The bromine and methyl ester in the common intermediate were chosen as a starting point for flexible functionality that can be used as handles for cyclization or further transformation.

Scheme 13. Initial route developed for the synthesis of allylic alcohol



The initial synthetic route to access the requisite allylic alcohol **1.52** involved Sakurai addition of allyltrimethylsilane to mesityl oxide **1.40**, which gave the volatile enone **1.41** in 98% yield. Horner-Wadsworth-Emmons homologation of **1.41** using lithiated triethylphosphonoacetate in 1,2-dimethoxyethane at elevated temperature for 4 days afforded **1.42** as a 9:1 (inseparable) mixture of alkene isomers in 91% yield. The ethyl ester **1.42** was smoothly transformed to the Weinreb amide **1.43** furnishing a single alkene diastereomer in 80% yield after silica gel chromatography. Addition of methyl magnesium bromide to the Weinreb amide **1.43** gave the methyl vinyl ketone **1.44** as the sole product in 93% yield. The allylic alcohol **1.45** was obtained after exposure of the ketone **1.44** to sodium borohydride in the presence of cerium trichloride in methanol. This route was high yielding and straightforward, requiring minimal optimization of reaction conditions. However, the step-count of this route was a little lengthy, reagents were expensive, and the homologation step required 4 days to go to completion. As a result, we developed a second route which was more amenable to scale-up and time constraints.

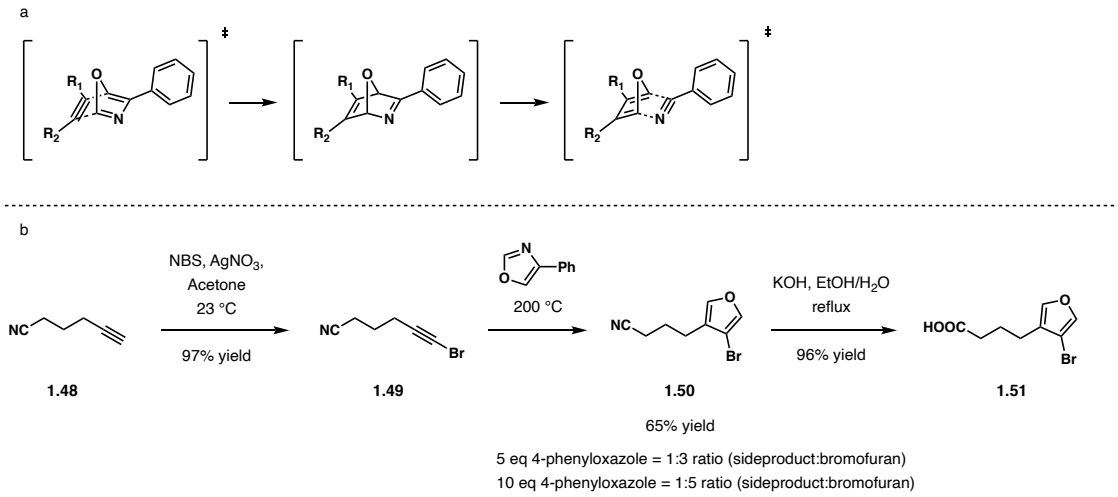
Scheme 14. Revised synthesis of allylic alcohol



Lithium-halogen exchange of 1-bromo-1-propene (1:9 *E*/*Z*) followed by addition of ketone **1.41** gave tertiary allylic alcohols *Z*-**1.46** (84% yield) and *E*-**1.46** (13% yield). Oxidative transposition of the mixture of allylic alcohols *E*/*Z*-**1.46** gave the methyl vinyl ketone *E*-**1.44** in 92% yield. The *E* tertiary allylic alcohol *E*-**1.46** could be obtained as the major isomer in a two-step process; lithiated propyne addition to ketone **1.41** followed by reduction using lithium aluminum hydride. Interestingly, oxidative transposition of *E* tertiary allylic alcohol *E*-**1.46** using the same conditions gave the ketone *E*-**1.44** in much poorer yield (67%).

With the requisite allylic alcohol **1.45** in hand, attention was turned to the synthesis of the butanoic acid containing the 3,4-disubstituted furan.

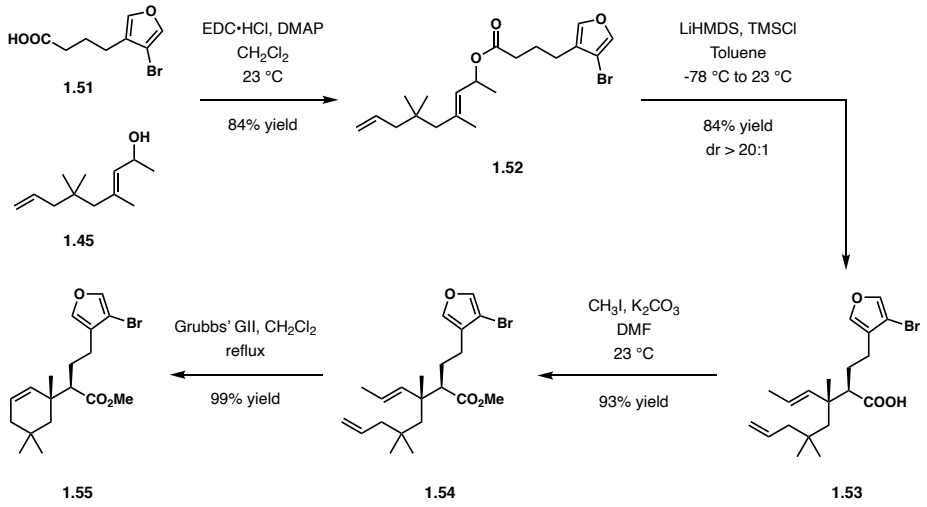
Scheme 15. Mechanism of cycloaddition/cycloreversion for 3,4-disubstituted furan formation (a) and the synthetic route for access to the furylbutanoic acid **1.51** (b)



The methods for the synthesis of furans with almost any varying substitution pattern are extensive, however, direct methods for the synthesis of 3,4-disubstituted furans are extremely limited. One method that is particularly attractive, is the reaction between a substituted alkyne and 4-phenyloxazole *via* a cycloaddition-cycloreversion mechanism (Scheme 15a).[36,37] An initial cycloadduct is formed between the alkyne and the oxazole, followed by elimination of benzonitrile. This methodology facilitates the construction of 3,4-disubstituted furans in a highly direct manner. No solvent is used in the reaction and the temperature required for efficient conversion is usually between 250-300 °C. We questioned whether this reaction could be extended to the synthesis of 3-bromo-4-alkyl furans to create a handle for directed substitution on the furan in a later stage of a synthesis. We were happy to see that the 3-bromofuran **1.50** could be isolated in 65% yield using 5 equivalents of 4-phenyloxazole (Scheme 15b). The desired product was accompanied by an unidentified side-product which we could not assign a definite structure to. Spectroscopically, the ^{1}HNMR and ^{13}CNMR spectra of the side-product resembles those of the bromoalkyne, however there is a new singlet

at approximately 6 ppm in the ^{1}HNMR spectrum. The amount of this side-product could be reduced by increasing the amount of 4-phenyloxazole used in the reaction. Extending reaction time and submitting the side-product to reaction conditions in the absence of bromoalkyne **1.49** gave none of the 3,4-disubstituted furan. Additionally, heating a mixture of the bromoalkyne and bromofuran to 200 °C yielded none of the unidentified side-product. Routine hydrolysis of the nitrile gave the requisite butanoic acid **1.51**, setting the stage for coupling with the allylic alcohol.

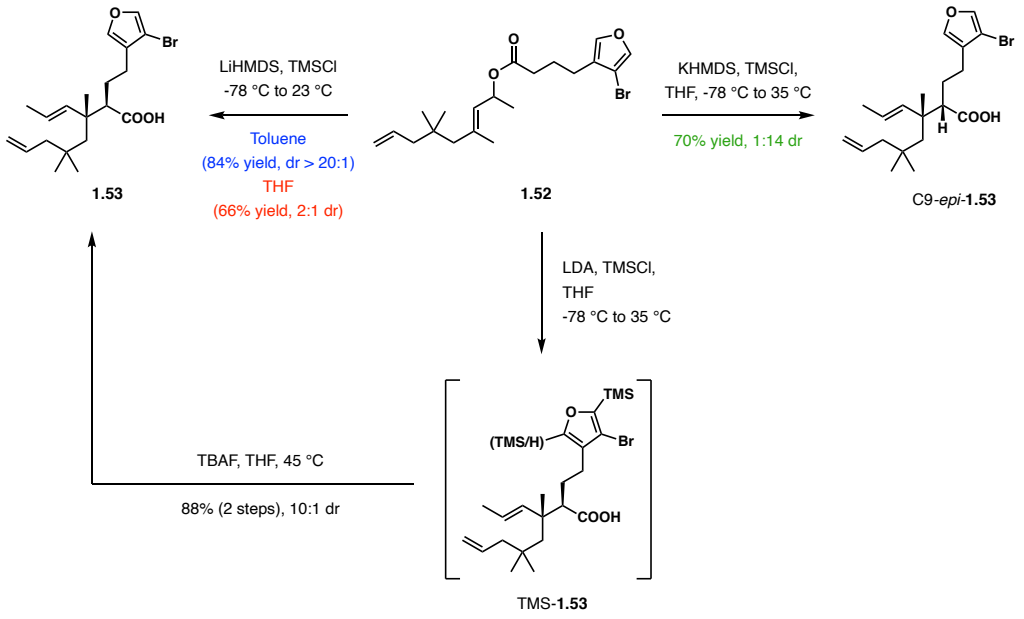
Scheme 16. Successful route to the common intermediate



Carbodiimide esterification of the allylic alcohol **145** with furylbutanoic acid **151** provided the substrate for the Ireland-Claisen rearrangement **152** in 84% yield. A series of different conditions were tested in the rearrangement; the same number of equivalents of base and silylating agent were used in all cases (Scheme 17). The use of LiHMDS (in toluene) and KHMDS (in THF) gave the highest diastereoselectivity; the structure of the major diastereomer using LiHMDS (**1.53**) was the minor diastereomer in conditions using KHMDS

(C9-*epi*-**1.53**). An attempt was made to determine the relative stereochemistry of each diastereomer by identification of key NOE's in a derivative of each diastereomer, however, no definitive conclusions could be drawn from the data. The relative stereochemistry at C9 and C10 was later elucidated by X-ray crystal analysis of an advanced intermediate described in the next section (Figure 6).

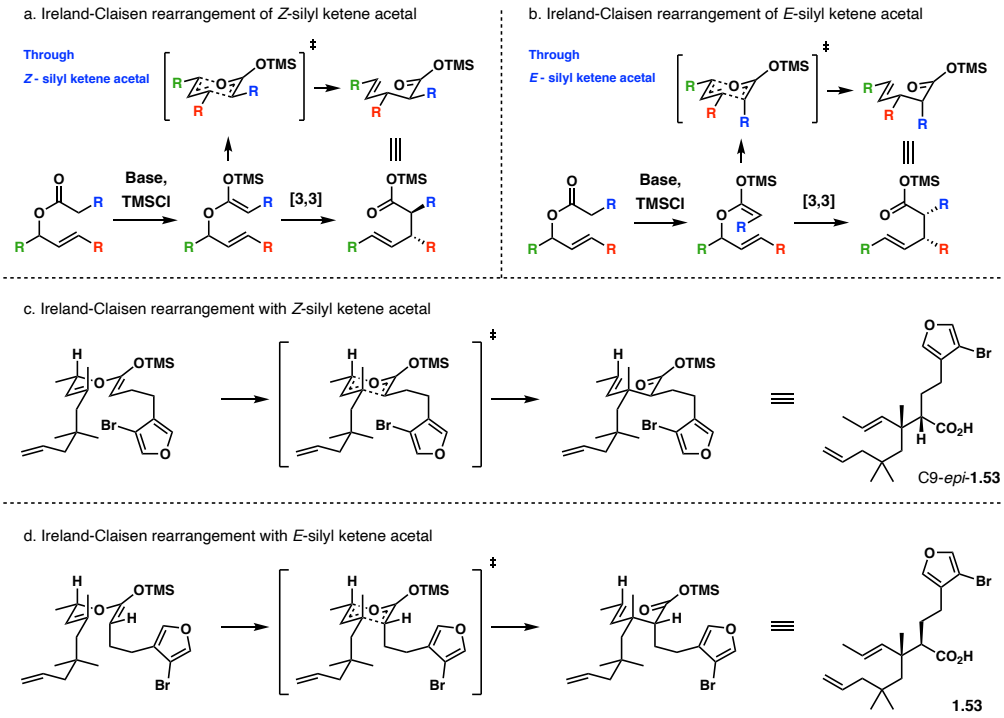
Scheme 17. Identification of optimized conditions for the Ireland-Claisen rearrangement



Interestingly, the use of LDA (in THF) led to a side-reaction which was not observed with the weaker bases. Namely, the use of LDA resulted in the formation (presumably) of the silyl ketene acetal, but also caused silylation of the furan leading to a mixture of mono-(mixture of regioisomers) and di-silylated species (TMS-**1.53**). The silyl groups could be removed by heating with 4 equivalents of TBAF in THF, after the completion of the rearrangement. The results of the Ireland-Claisen rearrangement were exciting, in that we demonstrated that either diastereomer could be obtained as the major product simply by changing reaction conditions.

This flexibility instilled a high level of confidence in our synthetic route to the common intermediate, and as a starting point we moved forward with the rearranged product resulting from the use of LiHMDS in toluene.

Scheme 18. General stereochemical outcomes of the Ireland-Claisen rearrangement (a,b) and during rearrangement of silyl ketene acetal (c,d) of the spongian intermediate



Generally speaking, the high level of diastereoselectivity observed during the Ireland-Claisen rearrangement is the result of two main mechanistic constraints.[38,39] In order for the efficient transmission of stereochemical information of the allylic ester to the product acid (or silyl ester), the initial formation of the silyl ketene acetal must be highly selective for either the *E* or the *Z* isomer. The second constraint, is that the rearrangement must occur as a concerted process in a 6-membered transition state, and that this ring must have a consistent preference for either a boat or a chair conformation. Most of the research in developing highly

diastereoselective Ireland-Claisen rearrangements has focused on changing reaction conditions to control *E/Z* – selectivity of the silyl-ketene acetal. Changes to the base, solvent, and silylating agent can lead to drastically different preference for one isomer of the silyl ketene acetal over the other.

The rearranged acid **1.53** was methylated using methyl iodide and potassium carbonate to give the methyl ester **1.54** in 93% yield. The ring-closing metathesis of the methyl ester **1.54** was routine using Grubbs' 2nd generation catalyst, resulting in the isolation of the common intermediate **1.55** in near quantitative yield.

Having completed the construction of this key intermediate, we wished to demonstrate its utility in accessing a member of the spongian family. In the next section, I detail the development of a synthetic route towards (±)-cadlinolide A **1.1**, a rare member of the spongian family, using this intermediate **1.55**.

1.3. Total Synthesis of (±)-Desmethyl Cadlinolide A and (±)-Cadlinolide A

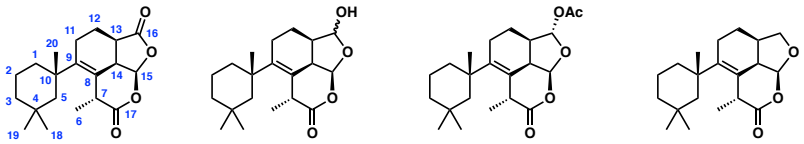
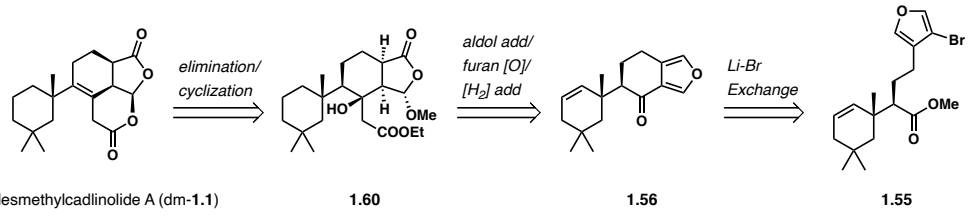


Figure 5. Family of cadlinolides

Cadlinolide A **1.1** was isolated along with cadlinolide B **1.3** and tetrahydroaplysulphurin-1 **1.4** from extracts of the dorid nudibranch *Cadlina luteomarginata* in the vicinity of Sandford Island, British Columbia. Extracts from the encrusting sponge on which *C. luteomarginata*

feeds, *Aplysilla glacialis*, yielded both cadlinolide A and cadlinolide B, but interestingly no tetrahydroaplysulphurin-1.[40,41] In spite of the discovery of these cadlinolide structures over 30 years ago, there has been only one report on their bioactivity. Cadlinolide C, showed moderate anti-inflammatory activity and modest activity against MRSA biofilms.[42,43] The presence of biological information on cadlinolides A and B is surprisingly absent, despite the bioactivity previously demonstrated by structurally similar members of the spongian family. The fused, cyclic acylal structure of cadlinolide A is unique among rearranged spongian diterpenes. To our knowledge, there have been no attempts to synthesize any of the cadlinolide derivatives.

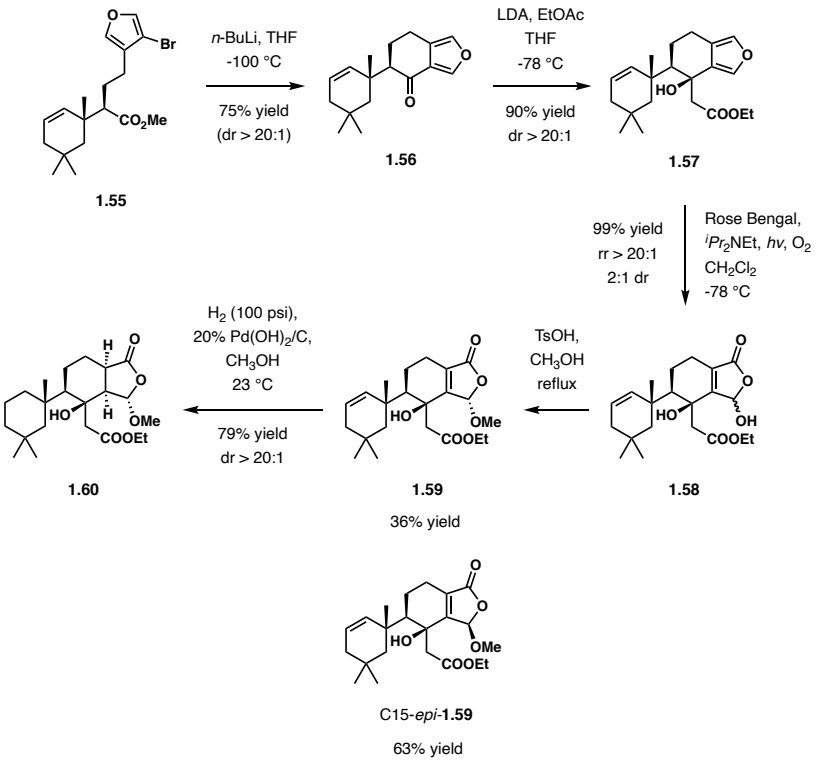
Scheme 19. Retrosynthetic plan to access racemic desmethylcadlinolide A



As an initial target, we chose to develop a synthesis of racemic desmethylcadlinolide A dm-**1.1**. We felt this would serve as a slightly simpler target on which to test out chemistry needed for the pathway, and serve as a unique structure for possible SAR studies. The synthetic plan to access desmethylcadlinolide A dm-**1.1** is outlined in the retrosynthesis in Scheme 19. The final structure of the desmethyl derivative could be furnished after elimination and cyclization of intermediate **1.60**. Intermediate **1.60** could be accessed after aldol addition to furyl ketone **1.56**, followed by oxidation of the fused furan and hydrogenation of the alkene functionality. Formation of the cyclic furyl ketone **1.56** would be realized after

lithium-halogen exchange of the bromide and cyclization onto the methyl ester **1.55**. The value of this total synthesis strategy lies in the transfer of stereochemical information starting from the allylic alcohol and moving toward the highly oxygenated portion of the molecule. The configuration of the 4 stereocenters in the molecule are the result of only one enantioselective step. This is in contrast to previous strategies which rely on more than one enantioselective step.

Scheme 20. Synthetic Route to Intermediate **1.60**



Lithium-bromine exchange of bromofuran followed by cyclization onto the methyl ester gave the fused-furyl ketone **1.56** in 75% yield as a single diastereomer. We were excited to find that tertiary alcohol **1.57** was obtained as a single diastereomer in great yield by addition of the furyl ketone **1.56** to a solution of the lithium enolate of ethyl acetate. The rational for

the excellent diastereoselectivity in the aldol addition reaction was not immediately clear. However, an X-ray crystal structure (Figure 6) obtained later in the investigation suggests that the sterically bulky trimethylcyclohexene substituent is primarily in an axial position in this fused furyl ketone structure, effectively blocking the entire face of the ring system. Oxidation of the furan **1.57** was a facile process using singlet oxygen in the presence of Hünig's base, and gave the hydroxy butenolide **1.58** in great yield and excellent regioselectivity. The formation of the methoxy butenolide **1.59** was accomplished by refluxing **1.58** in methanol with *p*-toluenesulfonic acid, to give a mixture of epimers (**1.59** and C15-*epi*-**1.59**) in excellent yield. Each epimer was submitted separately to hydrogenation conditions. The reduction proved to be highly diastereoselective and resulted in the formation of only one isomer for hydrogenation of each epimer. An X-ray crystal structure was obtained for the reduction product of the minor methoxy butenolide **1.59** formed during the acetal formation conditions.

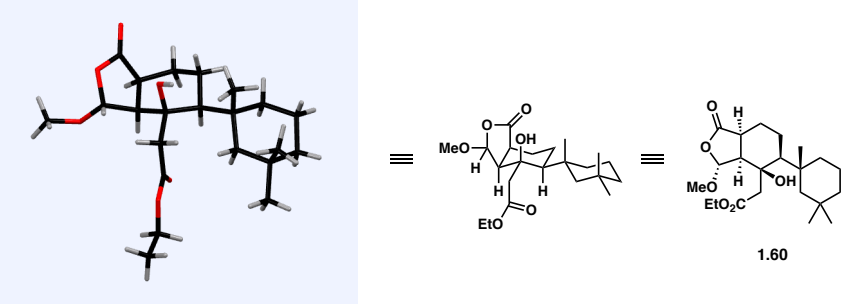
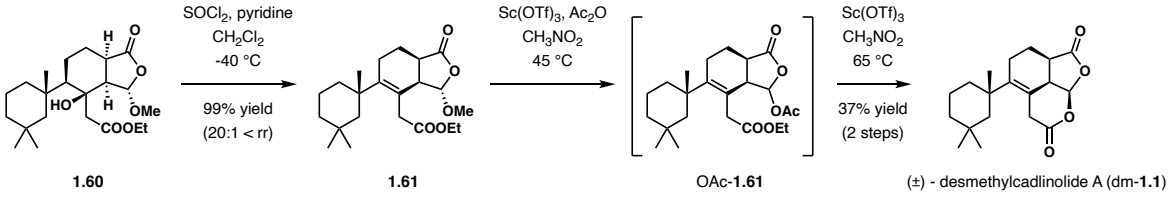


Figure 6. X-ray crystal structure of intermediate **1.60** formed after hydrogenation

The crystal structure of intermediate **1.60** (Figure 6) gave confirmation of the relative stereochemistry resulting from the Ireland-Claisen rearrangement and that this stereochemical information had been successfully transferred during reduction of the butenolide olefin. This

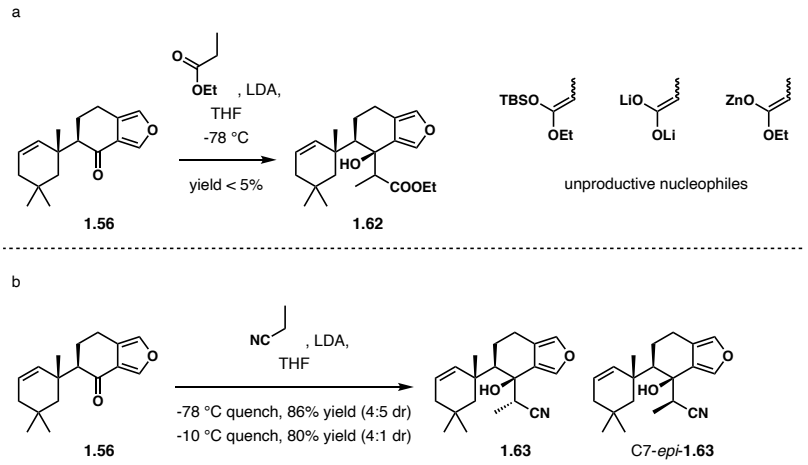
was a clear indication of the potential success of this synthetic route. With this knowledge, we explored conditions for the elimination of the tertiary alcohol.

Scheme 21. Completion of racemic desmethylcadlinolide A



Conveniently, the use of thionyl chloride in the presence of pyridine in methylene chloride at -30 °C, gave the intermediate **1.61** in quantitative yield as a single regioisomer. In developing a strategy for the final cyclization to form the tricyclic, acylal structure of cadlinolide, we searched for conditions that would allow for both exchange of acetal (acylal) and transesterification. It has been known for some time that Group III transition metals act as highly oxophilic lewis acids which catalyze the hydrolysis of acetals.[44,45] Scandium (III) triflate specifically has been shown to facilitate acetal exchange,[46] the esterification of acetic anhydride with alcohols,[47] and transesterification;[48] it was also shown to facilitate the formation of acylals from aldehydes.[49] Mild heating of a nitromethane solution of the mixed acetal/acylal **1.61** with acetic anhydride and scandium triflate provided acylal OAc-**1.61** in full conversion. Heating the acetic acid acylal in nitromethane with scandium triflate in the absence of acetic anhydride provided the structure of racemic desmethylcadlinolide A dm-**1.1** in 37% yield.

Scheme 22. Unproductive nucleophiles in the aldol addition to furyl ketone (a) and successful and diastereoselective addition of propionitrile to furyl ketone (b)



Having successfully completed the racemic synthesis of the unnatural derivative, desmethylcadlinolide A, we turned our attention to the synthesis of the natural product, cadlinolide A (**1.1**). The main deviation from the pathway used to produce the desmethyl derivative, was to change the structure of the nucleophile in the aldol addition to the fused furyl ketone **1.56**. Addition of the ketone to a solution of the lithium enolate of ethyl propionate produced less than 5% of the aldol product **1.62**. The lithium ene-diolate of propionic acid, the zinc enolate of ethyl propionate, and the TBS-silyl ketene acetal of ethyl propionate under acidic conditions were all unproductive in the addition reaction. During the addition of the lithium enolate of ethyl acetate to the furyl ketone **1.56**, we noticed a significant reduction in the yield of the reaction when quenching at 0 °C compared to quenching at -78 °C. This suggested that the addition is reversable and thermodynamically disfavored at warmer temperatures. In the case of the other two lithium nucleophiles that were tried, the speed of addition to the ketone at colder temperatures is much too slow for a productive reaction, and warming of the reaction led only to decomposition of the substrate. As a means

of increasing the rate of addition to the ketone at -78 °C, we tried reducing the steric bulk of the substrate. The rate of addition of lithiated propionitrile to the furyl ketone **1.56** was exceptionally fast. Quenching the reaction after only 10 minutes at -78 °C led to the isolation of 4:5 mixture of epimers in high yield, favoring C7-*epi*-**1.63**. If the reaction was allowed to warm to -10 °C, a reversal in diastereoselectivity was observed; a 4:1 mixture of epimers was isolated favoring the opposite isomer, **1.63**. The two nitrile epimers were easily separated and hydrolyzed under mild conditions to give the amide. A crystal structure of the amide **1.64** derived from the major nitrile epimer isolated after quenching the reaction at -10 °C, is shown in Figure 7.

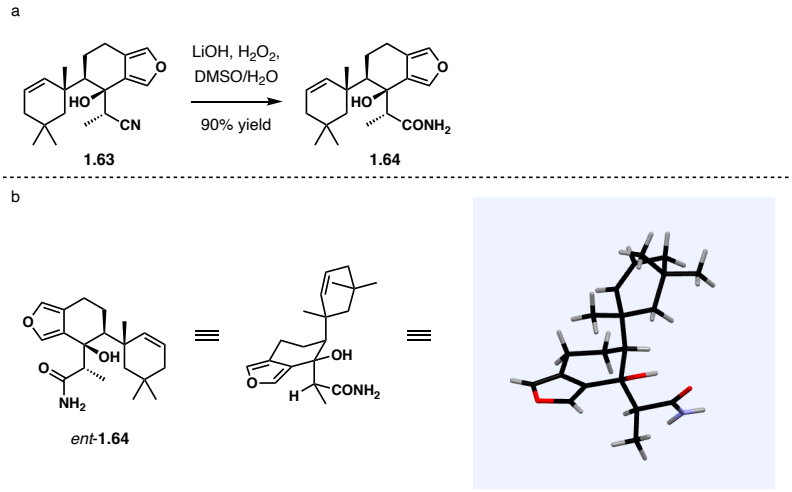
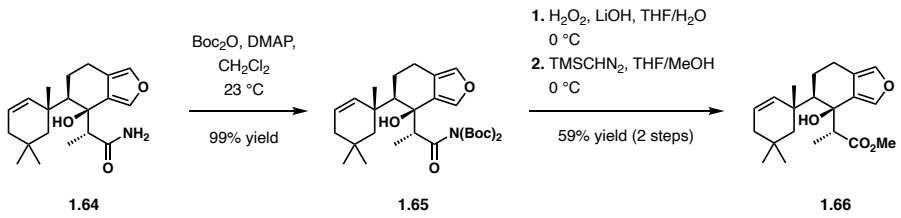


Figure 7. conditions for hydrolysis of nitrile (a) and X-ray crystal structure of the major isomer in the aldol addition (b)

The results of the X-ray crystal structure show that the major epimer obtained from the aldol addition when quenching the reaction at -10 °C has the requisite stereochemistry present in the natural product. The product of aldol addition was found to be sensitive to both acidic and basic conditions, therefore we needed to find mild conditions for the transformation of

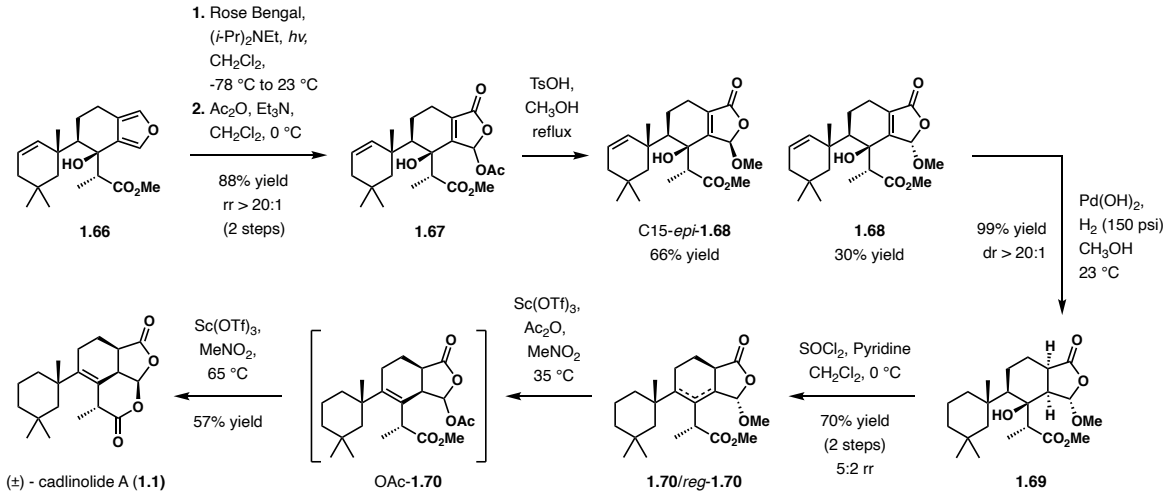
the amide to an ester. The mild, albeit, rather lengthy synthetic route to the ester is outlined in Scheme 23.

Scheme 23. Successful, mild transformation of amide to methyl ester



Formation of the *N,N*-diBoc amide **1.65** was routine using Boc anhydride in the presence of DMAP. Hydrolysis of this intermediate using lithium hydrogen peroxide led to the carboxylic acid which was methylated, using TMS diazomethane giving the methyl ester **1.66** in 59% yield over 2 steps.

Scheme 24. Successful route for completion of racemic cadlinolide A



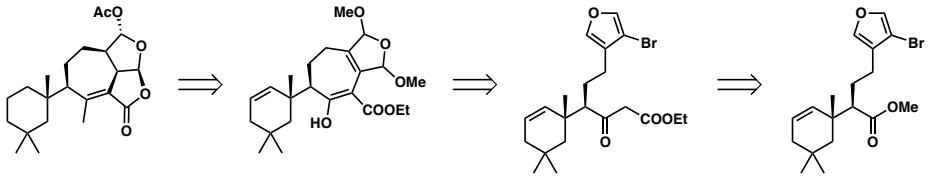
Oxidation of the furan **1.66** was successfully accomplished using the same conditions as the desmethyl derivative, and was immediately acetylated to give the carboxy butenolide **1.67** in 88% yield as a single regioisomer and epimer (unknown configuration at C15). This intermediate was subjected to conditions found previously for the synthesis of methoxy butenolide (acidic methanol) which gave a pair of epimers in 66% (C15-*epi*-**1.68**) and 30% yield (**1.68**). Subjecting the minor diastereomer to hydrogenation conditions gave intermediate **1.69** in full conversion. We were unable to achieve full hydrogenation of the major methoxybutenolide epimer C15-*epi*-**1.68**. The tertiary alcohol **1.69** was eliminated using thionyl chloride and pyridine at 0 °C to give a 2:5 mixture of regioisomers **1.70** (both endocyclic alkenes), which was later found to be inconsequential. Exchange of mixed acetal **1.70** to acylal was accomplished with scandium triflate and acetic anhydride in nitromethane, which also caused isomerization of the alkene to the requisite position, giving OAc-**1.70**. Submitting this acylal to scandium triflate in nitromethane gave the structure of racemic cadlinolide A **1.1**. The spectral data of the sample of **1.1** we prepared, matched very well to that of the sample isolated from the natural source (Table 3 and 4).[40,41] The completion of this total synthesis indicated that this intermediate can be useful for the synthesis of rearranged spongian diterpenes containing the 6,6,5-tricyclic skeleton. In the next section, the versatility of the common intermediate is demonstrated in efforts to access the carbon skeleton of (+)-darwinolide **1.2**.

1.4. Efforts Toward the Total Synthesis of (+)-Darwinolide

The completion of the total synthesis of racemic cadlinolide A 1.1 and its unnatural derivative dm-1.1 was an exciting step in the process of developing a common intermediate

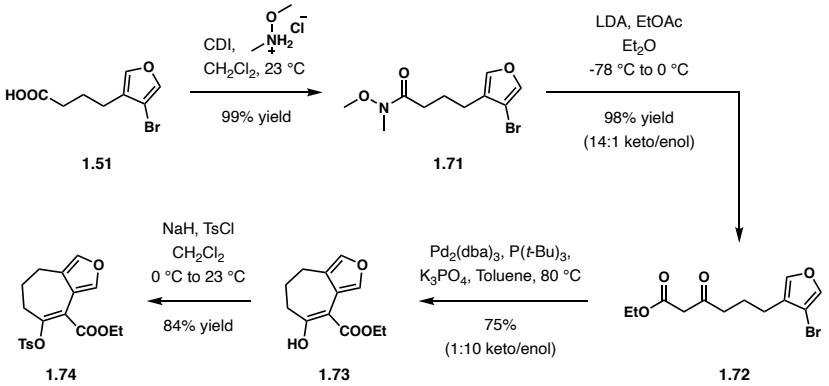
that could be used to synthesize multiple members of the rearranged spongian diterpene family. We envisioned the total synthesis of (+)-darwinolide, a rearranged diterpene bearing a 7-membered ring, as a way to further demonstrate the utility of this intermediate. The general plan for accessing darwinolide is outlined in Scheme 42.

Scheme 25. General strategy for the synthesis of (+)-darwinolide



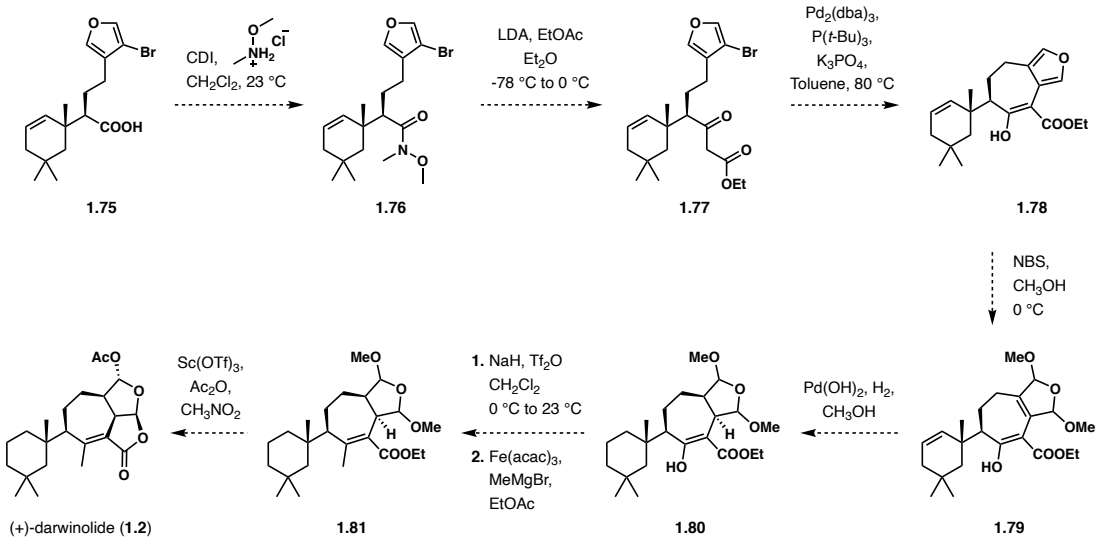
The final structure of (+)-darwinolide can be achieved via the oxidation/reduction strategy of the fused furan which was used in the total synthesis of racemic cadlinolide A. The 7-membered ring can be formed through intramolecular alpha-arylation of a beta-keto ester which is constructed from the carboxylic acid moiety in the common intermediate. In order to test this general strategy, the formation of the 7-membered ring was explored on a simpler structure; acid 1.51.

Scheme 26. Synthetic route for the formation of the 7-membered ring of darwinolide



The route commences with Weinreb amide formation **1.71** from the carboxylic acid **1.51**. The acid was converted first to the imidazolyl amide, followed by addition of *N,O*-dimethyl hydroxylamine hydrochloride which gave the desired amide in excellent yield. Addition of lithiated ethyl acetate into the Weinreb amide **1.71** smoothly furnished the beta-keto ester **1.72**, setting the stage for the alpha-arylation. To our knowledge, there have been no reported intermolecular or intramolecular alpha-arylations of beta-keto esters using a bromo-substituted furan. As a starting point, we chose to first explore conditions developed by the Hartwig group for the alpha-arylation of esters and malonates.[50] To our delight, these conditions worked very well for our substrate, providing the 7-membered ring **1.73** in good yield. Interestingly, the product exists primarily in the enol form rather than the keto form. In order to install the methyl group beta to the ester, our initial plan was to sulfonylate the enol oxygen, and perform a substitution at the beta position of the ethyl ester using a Kumada-like cross-coupling. Sulfonylation proceeded extremely well using sodium hydride and toluenesulfonic anhydride, giving structure **1.74** in 84% yield. Initial attempts to substitute at the sulfonylate using $Fe(acac)_3$ and MeMgBr have so far been unsuccessful. However, further effort is underway.

Scheme 27. Future work in the total synthesis of darwinolide



Future work on this synthesis is depicted in Scheme 27. The initial plan is to apply the reaction sequence developed in the simplified model to the common intermediate. It may be necessary, however, to change out the toluenesulfonylated enol for the trifluoromethylsulfonylated enol during this run. Sulfonylation using the tosylated enol was useful for determining general conditions for sulfonylation, however, substitution using a triflated enol is supported by far more literature precedence. Substitution of the triflate, followed by hydrogenation of the cyclohexene will set the stage for the furan oxidation/reduction sequence.

1.5. Conclusion

In summary, we developed a synthetic route to a common intermediate that can access multiple natural products in the rearranged spongian diterpene family. The utility of this intermediate was demonstrated in the first total synthesis of (±)-cadlinolide A and its unnatural

derivative, (±)-desmethylcadlinolide A. The general strategy employed a convergent route to this common intermediate which can be derivatized in a highly flexible manner to synthesize structures of different ring sizes and oxidation patterns. The synthetic route to the cadlinolide family includes an Ireland-Claisen rearrangement to set the configuration of stereocenters at C9 and C10. The configuration of these two stereocenters were then used to influence the diastereoselectivity during the formation of the remaining stereocenters in the final structure. The use of a furan oxidation/reduction sequence was used to construct the highly oxidized acylal moiety in cadlinolide A; a structure which is rare in the realm of spongian natural products.

The utility of this synthetic route was further demonstrated during a model study for the construction of the 7-membered ring in the carbon skeleton of darwinolide. This strategy represents a unique, and potentially far more rapid approach when compared to the previous synthesis of this bioactive natural product, as well as, other spongian natural products. Future work on this synthesis will involve the extension of the knowledge learned in the model study to a substrate bearing the 1,3,3-trimethyl cyclohexyl group, followed by use of the oxidation/reduction sequence of the furan. We believe that this work will lead to efficient strategies for the synthesis of other spongian diterpenoid members, and lead to a better understanding of the mechanisms of their bioactivity.

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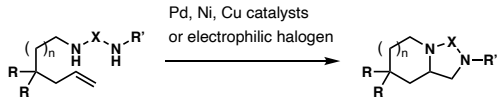
Chapter 2

Stereoselective Synthesis of Cyclic Guanidines by Directed Diamination of Unactivated Alkenes

2.1. Introduction[i]

The total synthesis of natural products containing guanidine functionality can prove to be a difficult undertaking. This is true, even in comparison to the challenge of synthesizing compounds with more conventional nitrogen functional groups.[51] The standard methods for the introduction of the guanidyl group into complex structures are limited**,** and typically involve manipulation of a previously installed amino group. Classical methods include coupling of primary amines with cyanamide,[52] pyrazolylcarboxamidines,[53] *S*-alkylisothiourea reagents,[54] or Goodman reagents (trifluoromethanesulfonyl guanidine reagents).[55] The use of these strategies in the synthesis of complex guanidine-containing natural products typically results in extended synthetic routes and an overall reduction in the efficiency of a synthesis.

Scheme 28. Previously reported general strategy for vicinal diamination of alkenes.



More recently developed methods for the vicinal diamination of alkenes suggest an intriguing alternative for the stereoselective installation of functionalized guanidines, especially cyclic guanidines.[56] Several inter- and intramolecular diaminations of alkenes with ureas, sulfamides, and guanidines have been demonstrated by the utilization of a variety of metal complexes[57,58,59,60] or halogenating reagents.[61] These precedents (Scheme 28), while promising, were lacking in broad substrate scope and applicability for the stereoselective synthesis of cyclic guanidines with desired functionalization. Our interest in the development

[i]Significant portions of this chapter were published in the journal *Organic Letters*.[63]

of efficient strategies for the synthesis of several guanidine alkaloids shown in Figure 8, prompted us to develop a method for the stereoselective delivery of guanidine group to an unactivated alkene, directed by a hydroxyl group, and using guanidine hydrochloride as the source of the guanidine. The method is operationally simple and allows for further functionalization of the installed guanidine.

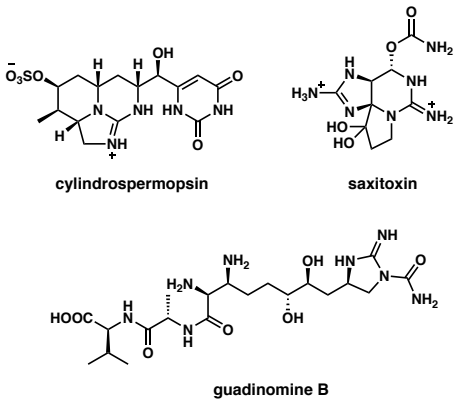
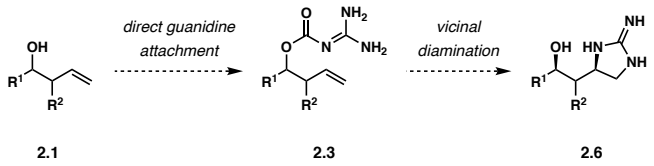


Figure 8. Natural products containing cyclic guanidine.

2.2. Substrate Scope

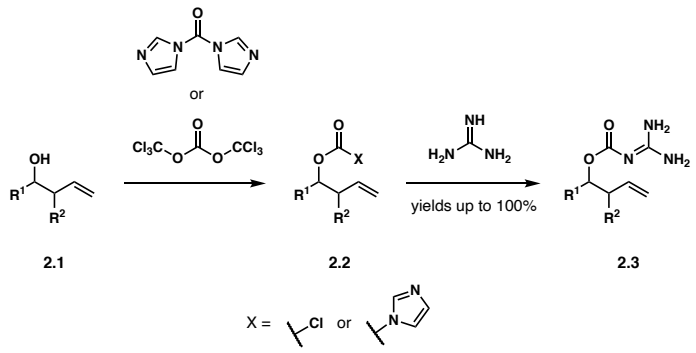
2.2.1. Reaction Optimization

Scheme 29. General strategy for method development.



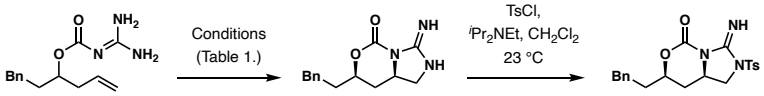
Our general reaction design is depicted in Scheme 29, and first requires attachment of guanidine to a hydroxy group through a carbamate linkage. This is then followed by electrophilic cyclization onto the alkene. Initially, the goal was to develop a straight-forward method for the attachment of guanidine to a homoallylic alcohol using readily available guanidine hydrochloride. The installation of several different prospective tethers were considered, including silyl, sulfonyl, and methylene. The majority of attempted transformations proved unfruitful, largely due to the instability of the intermediates and products. We found that guanidine carbamates, however, could be prepared in two simple steps from alcohols via conversion to chloroformates using triphosgene or (1-imidazolyl)formats with 1,1'-carbonyldiimidazole (CDI), followed by treatment with free guanidine. Both methods afforded the desired product of similar purity and yields; however, CDI was a more benign and user-friendly reagent due to considerably lower toxicity and volatility compared to triphosgene. In addition, when R^1 = Ar, CDI enabled a cleaner conversion to **2.3** without formation of carbonate side-products observed with triphosgene. Therefore, CDI was used to access the guanidine carbamate for intramolecular delivery of guanidine to the double bond.

Scheme 30. Installation of guanidine tether



With an effective method for the preparation of guanidine carbamates established, we next turned our attention to determining optimal conditions for cycloguanidilation. We initially employed reaction conditions reported on previously for successful diamination of unactivated alkenes. Only low conversions were observed with the use of metal catalysts such as $Pd(OAc)_2$, $NiCl_2$, or CuI (Table 2, entries 1-5).

Table 2. Identification of Optimal Conditions for Cycloguanidylation.



2.3a 2.4a 2.5a

entry	reaction conditions	conversion (%)	yield (%)
1	10 mol% $Pd(OAc)_2$, CuI, K_2CO_3, DMF, 23 °C, 24 hr	0	0
2	25 mol% $Pd(OAc)_2$, $PhI(OAc)_2$, CH_2Cl_2, 23 °C, 24 hr	15	0
3	5 mol% $Pd(OAc)_2$, $PhI(OAc)_2$, NMe_4Cl, NaOAc, CH_2Cl_2, 23 °C, 24 hr	30	0
4	10 mol% $NiCl_2$, $PhI(OAc)_2$, NaOAc, DMF, 23 °C, 24 hr	0	0
5	10 mol% CuI, K_2CO_3, 10 mol% 2,2'-bipyridine, O_2, DMF, 60 °C, 24 hr	0	0
6	3 equiv of *t*-BuOCl, CH_2Cl_2, 0 °C, 20 min	100	0
7	Py_2IBF_4, toluene, 23 °C or reflux, 24 hr	65	0
8	2.1 equiv of I_2, $NaHCO_3$, CH_2Cl_2, 23 °C, 6 hr	15	0
9	2.1 equiv of NIS, $NaHCO_3$, CH_2Cl_2, 23 °C, 1 hr	100	62
10	2.1 equiv of NIS, $NaHCO_3$, CH_3CN, 0 °C, 5 hr	100	84

We next examined electrophilic halogen reagents. Although conversion with iodine was still low (entry 8), it was substantially improved with the use of *tert*-butylhypochlorite and dipyridineiodonium tetafluoroborate (entries 6 and 7). *tert*-butylhypochlorite effected *N*-chlorination only, affording a fairly unreactive dichloroguanidine product. The optimal reagent was found to be *N*-iodosuccinimide (NIS), which under optimal conditions ($NaHCO_3$,

CH_3CN, 0 °C) enabled 100% conversion and furnished the cyclic guanidine carbamate in 84% isolated yield (entry 10). Importantly, the guanidine was delivered to the terminal alkene with *complete diastereoselectivity*. This result exceeded our expectations for the stereoselective installation of guanidine to terminal olefins.

2.2.2. Application of Optimized Conditions to Various Substrates

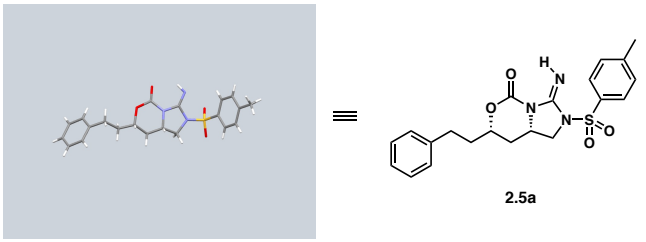


Figure 9. X-ray crystal structure for elucidation of regioselectivity during sulfonylation

With the optimized conditions in hand, the reaction scope was examined with a variety of aryl and alkyl substituted substrates derived from homoallylic alcohols (Figure 10). The substrate scope was designed to test compatibility with a range of reactive functional groups suitable for applications in medicinal chemistry and natural products synthesis. All products were isolated after the sulfonylation of the cyclic guanidine carbamate for ease of purification. We first wanted to establish that *N*-nosylation, *N*-tosylation, and *N*-(4-methoxyphenyl)sulfonylation would afford sulfonylated cyclic guanidines in comparable yields (products **2.5a-c**), and for convenience and consistency we proceeded with tosylation for the remainder of the scope investigation. We also wished to determine the regioselectivity of the sulfonylation as spectroscopic studies failed to yield definitive results, and literature on

the reactivity of cyclic guanidine carbamates with electrophiles is extremely limited.[62] While the exact location of the nitrogen-sulfur bond was unknown, it was clear from the spectroscopic data that the reaction was highly regioselective. We obtained an X-ray crystal structure of the *N*-tosyl cyclic guanidine carbamate (**2.5a**), and found that sulfonyl chlorides react preferentially at the endocyclic nitrogen of the cyclic guanidine as opposed to the exocyclic nitrogen under the conditions employed. Having studied the sulfonylation, we began to demonstrate our diamination method on a variety of different linear and branched alkyl substituents. These compounds readily undergo cyclization, producing expected guanidines **2.5d-f** in high-yields as single diastereomers. The introduction of benzyl or silyl ethers as well as ester groups in the substrate side chain does not hamper the overall efficiency of guanidylation, affording compounds **2.5g-j** after tosylation.

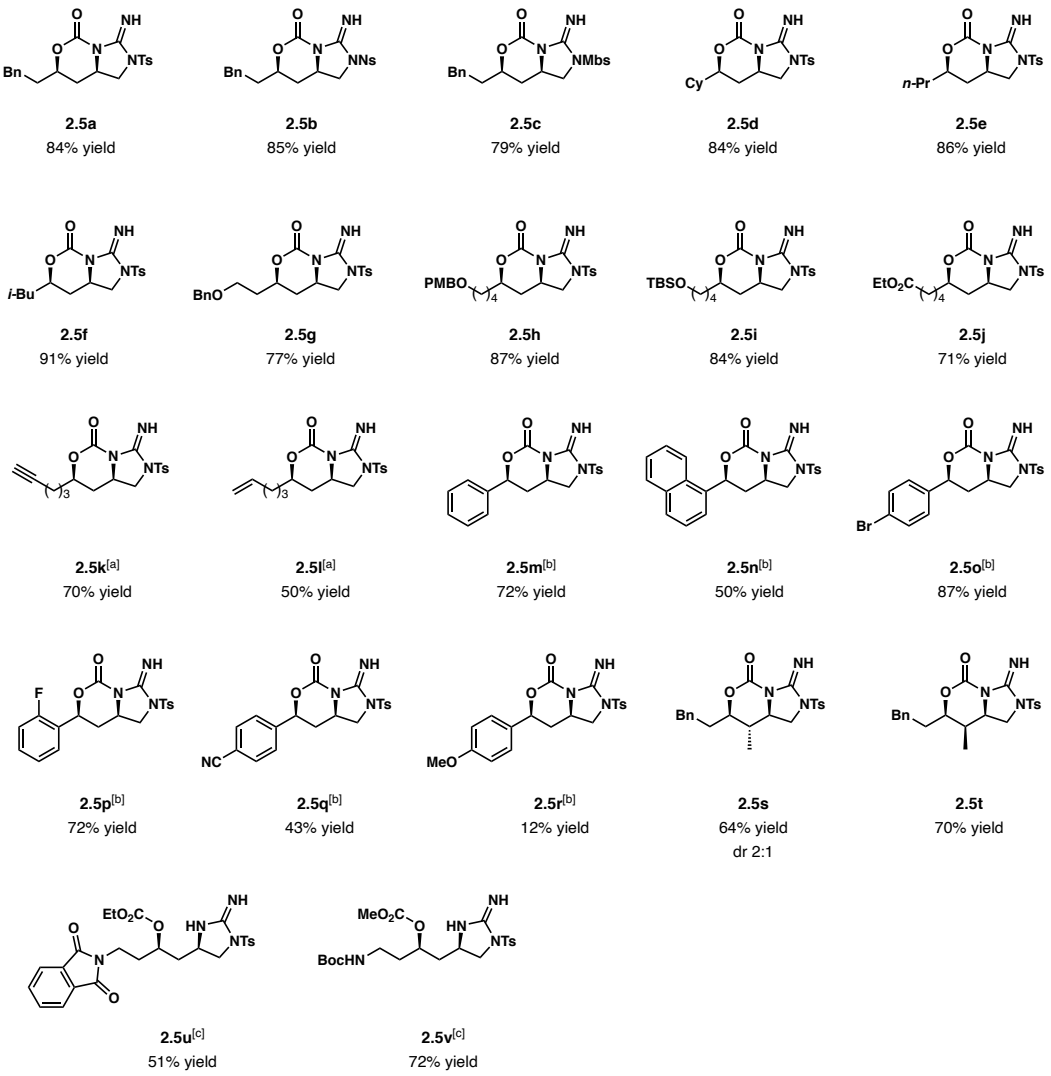


Figure 10. Substrate scope for the cycloguanidylation reaction.

[a]The reaction was performed at 0 °C for 2 hr. [b]The reaction was performed at 0 °C for 5 hr and then at 23 °C for another 5 hr. [c]Products were isolated after methanolysis.

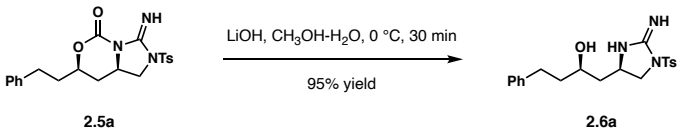
For further exploration of the chemoselectivity of the cycloguanidylation method, substrates bearing a distant terminal alkyne and olefin moiety were examined. In both cases, application of standard reaction conditions resulted in reduced yields of cyclic guanidine products. However, decreasing the reaction time to 2 hr allowed the isolation of **2.5k** and **2.5l** improved yields (70% and 50%, respectively). Substrates derived from substituted benzyl

alcohols were found to be less reactive in comparison to their aliphatic counterparts and required extended reaction times to reach full conversion. Nevertheless, these substrates were successfully isolated after sulfonylation in practical yields and excellent diastereoselectivity. Cyclization of the guanidine carbamate containing 4-methoxyphenyl group afforded compound **2.5r** in only 12% yield. This reaction was accompanied by significant amounts of decomposition products, presumably arising via a carbocationic pathway.

The cyclization of substrates derived from both *syn*- and *anti*-3-methyl -1-alkene-4-ols was also investigated. In the case of the *syn*-isomer, the cyclized guanidine carbamate was isolated in 70% yield as a single isomer (**2.5t**). Interestingly, erosion of diastereoselectivity was observed with the *anti*-isomer and the reaction conditions afforded cyclic product **2.5s** in 64% yield as a 2:1 mixture of diastereomers.

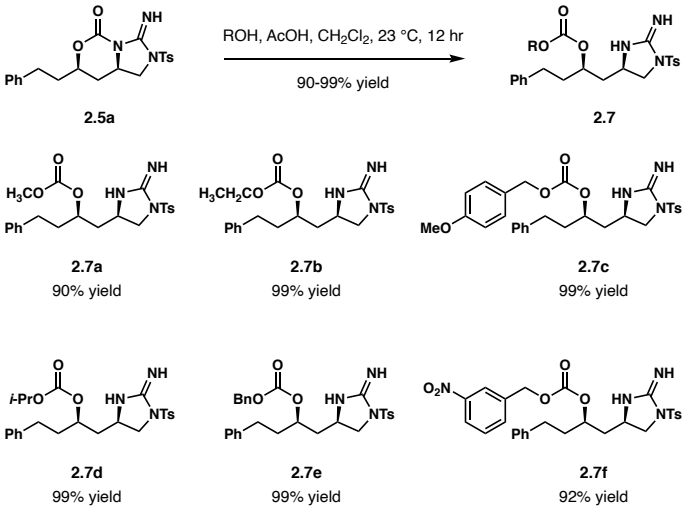
Structures incorporating acylated primary amines were shown to undergo the cyclization under standard conditions; however, separating the cyclized products from succinimide was troublesome. We were able to cleanly separate the guanidine cycle from succinimide by submitting the mixtures to methanolysis (Scheme 5). The products of methanolysis were isolated as the corresponding methyl carbonates **2.5u** and **2.5v**.

Scheme 31. Conditions for hydrolysis of cyclic guanidine carbamate



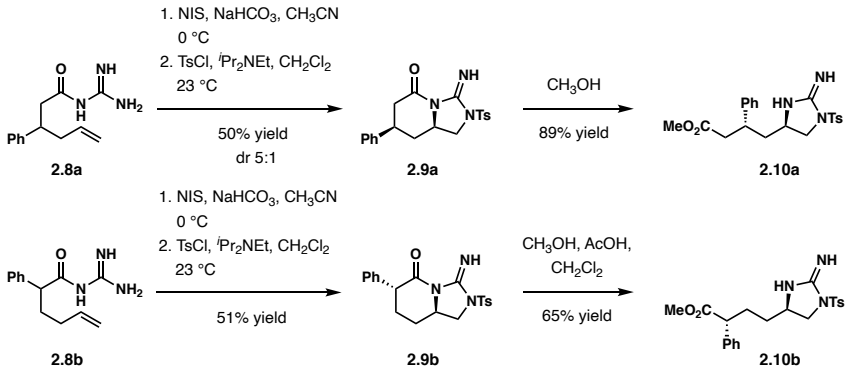
2.5a **2.6a**

Scheme 32. Conditions for alcoholysis of cyclic guanidine carbamates



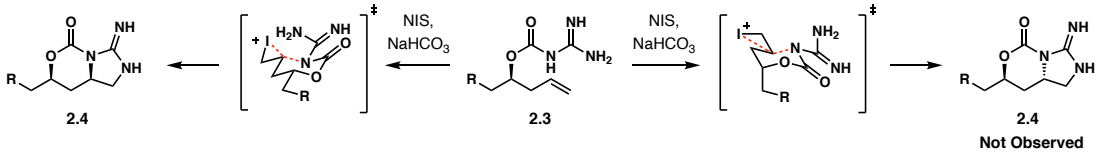
Having explored the chemoselectivity of the cyclization, we wished to investigate manipulations of the cyclized guanidine carbamate. We pursued two strategies for modifications of the carbonyl tether. Hydrolysis of compound **2.5a** was mediated by aqueous lithium hydroxide and afforded alcohol **2.6a** in 95% yield (Scheme 31). In addition to hydrolysis, we discovered that the cyclic guanidine-derived carbamates reacted under exceptionally mild conditions with different alcohols resulting in regioslective ring-opening of the carbamate to give the corresponding carbonates **2.7**. This reaction does not require any additives, but is accelerated in the presence of acetic acid. A range of simple aliphatic and aromatic alcohols can be utilized for this transformation providing compounds **2.7a-f** in excellent yields. *t*-BuOH was found to be the only unreactive alcohol.

Scheme 33. Use of carboxylate at directing group for delivery of guanidine to alkenes.



We were pleased at the successful cyclization of this large number of unique guanidine carbamate substrates, and we were curious if carboxylic acids could serve as a directing group for the cyclization reaction. 2-Phenyl and 3-phenylhexenoic acids were converted to acylguanidine substrates **2.9a** and **2.9b** by exposure to the optimized reaction conditions. Under the standard conditions, these carboxylic acid substrates underwent clean cyclization; however, attempts to isolate the product prior to sulfonylation led to rapid polymerization of the material. Successful isolation was realized by treatment of the reaction mixture with *p*-toluensulfonyl chloride. This allowed isolation of cyclic guanidines **2.10a** and **2.10b** in good yields.

Scheme 34. Possible mechanism to rationalize high diastereoselectivity of diamination method



The mechanistic rational for the diastereoselectivity of the first C-N bond-forming event during cyclization of guanidine onto unactivated alkenes in this methodology is unclear.

However, we hypothesize that the stereochemical outcome is governed by the minimization of transannular interactions in the developing six-membered ring.

2.3. Conclusion

In conclusion, we developed a method for the directed stereoselective guanidylation of alkenes.[63] Free guanidine can be delivered as an intact unit by a hydroxy or carboxy group, usually with high diastereoselectivity. The cyclic guanidine carbamate will react with sulfonyl chlorides in a highly regioselective manner for the purpose of facile isolation or protection for subsequent conditions in a synthetic sequence. We demonstrated that, after guanidine delivery, the directing group can be cleaved under exceptionally mild conditions; either by alcoholysis in the presence of acetic acid or hydrolysis with lithium hydroxide. We also demonstrated that the general conditions for cycloguanidylation and tether modification have broad functional group tolerance which suggests that it could be used in a medicinal chemistry or total synthesis of natural products setting. In the next chapter, we demonstrate the utility of this methodology in the total synthesis of (+)-guadinomic acid.

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Chapter 3

Total Synthesis of (+)-Guadinomic Acid via Hydroxyl-Directed Guanidylation

3.1 Introduction[ii]

3.1.1. Isolation and Biological Activity

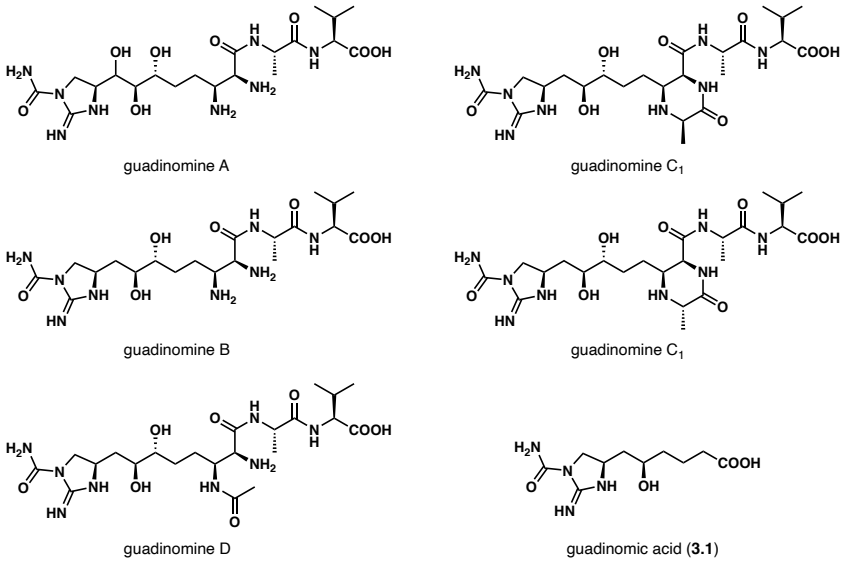


Figure 11. Structures of guadinomines and guadinomic acid

(+)-Guadinomic acid and five structurally similar guadinomines A-D (Figure 11) were isolated as Type-III Secretion system (TTSS) inhibitors from a culture broth of *Streptomyces* sp. K01-0509 by Omura and co-workers during a search for new anti-infective agents.[64] The TTSS is a virulence system common to several types of gram-negative bacteria, including *Salmonella* spp., enterohemorragic *E. coli*, and *Chlamydia* spp.[65] Gram-negative bacteria use the TTSS as a means to deliver effector proteins into the cytosol of a eukaryotic host cell and rely on this system to invade the host, resist phagocytosis, proliferate in deep-tissue, and cause disease.[66] Despite its importance in the infection process, recent studies suggest that the TTSS is not essential for the survival of a bacterium, and is rarely found in non-pathogenic bacteria.

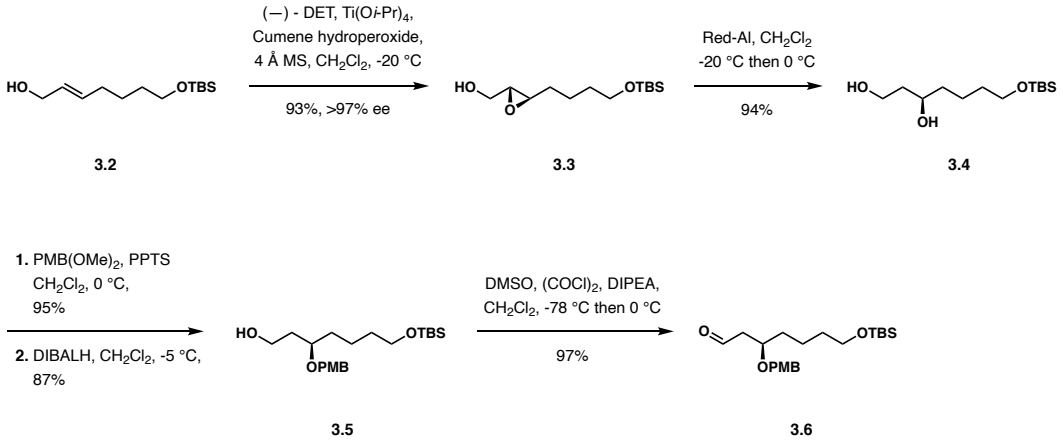
[ii] A significant portion of this chapter was published in the journal *The Journal of Organic Chemistry*.[70]

Because the TTSS is not essential for the survival of pathogenic, gram-negative bacteria, Omura suggests that a specific inhibitor of the TTSS would be expected to attenuate the infection process without killing the pathogen and affecting normal bacterial flora. Such an agent would only target the mechanism of infection; thus, there would be very little selection pressure for viability, and a substantial reduction in the development of antibiotic resistance.

The Omura group found that guadinomines A, B, and D exhibited dose-dependent inhibition of EPEC-induced hemolysis, suggesting that these compounds inhibited the TTSS. Guadinomine B was the most potent among the three compounds with an IC_{50} value of 0.007 µg/ml; followed by guadinomine A (IC_{50}: 0.02 µg/ml). Guadinomine D showed only moderate inhibition with an IC_{50} value of 8.5 µg/ml. Thus, guadinomines are the first microbial metabolites found to inhibit the TTSS, and guadinomines A and B appear to be among the most potent TTSS inhibitors to date.[12] Guadinomines C_1, C_2, and guadinomic acid showed no significant inhibition of the TTSS under the described assay, suggesting that the carbamoylated, cyclic-guanidine moiety alone is not sufficient for inhibitory activity.

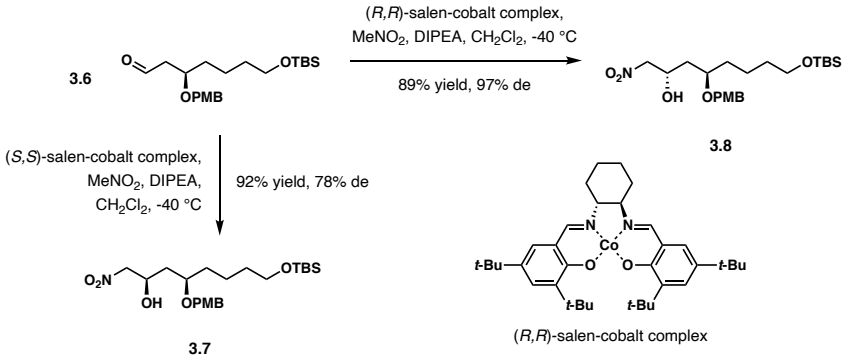
3.1.2. Previous Syntheses of Guadinomic Acid

Scheme 35. Omura preparation of aldehyde for asymmetric Henry reaction



After isolation and preliminary structural elucidation of the guadinomines, the relative and absolute configuration of the stereocenters within the common structural core of this family remained undefined; largely, due to insufficient quantities of these natural products. Furthermore, the exact location of the carbamoyl groups on the cyclic guanidine moiety had yet to be determined. In order to answer these key structural questions, the Omura group pursued a flexible total synthesis route which would allow them to access all possible stereoisomers of guadinomic acid, and complete their stereochemical elucidation.[67]

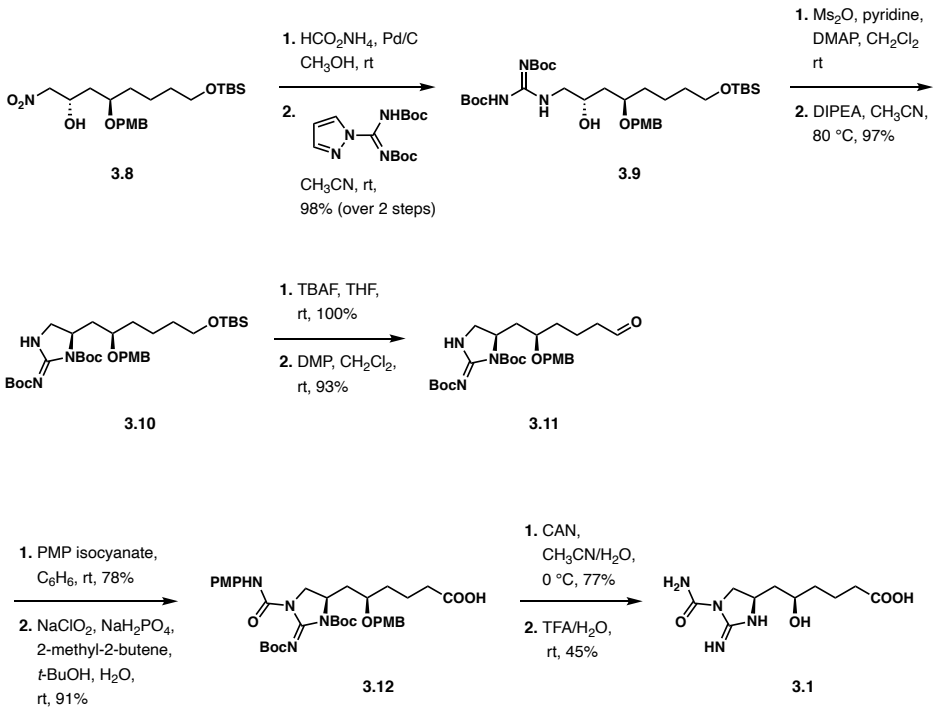
Scheme 36. Asymmetric Henry reaction allowing access to both diastereomers



The Omura synthesis route commences (Scheme 35) with a Sharpless asymmetric epoxidation of allylic alcohol **3.2**, followed by reduction of hydroxy epoxide to give enantio-enriched 1,3-diol **3.4**. PMB-protection of the secondary alcohol followed by oxidation of the primary alcohol gives aldehyde **3.6**, which sets the stage for the asymmetric henry reaction. The Omura group then demonstrates the ability to selectively form each diastereomer through the use of an asymmetric henry reaction (Scheme 36). Optimized conditions for the substrate using the (*R,R*) salen-cobalt-complex gave the *anti*-diastereomer **3.8** in high yield and excellent selectivity (89% yield, 97% de). Optimized conditions using the (*S,S*) salen-cobalt-

complex gave the *syn*-diastereomer **3.7** in high yield and good selectivity (92% yield, 78% de).

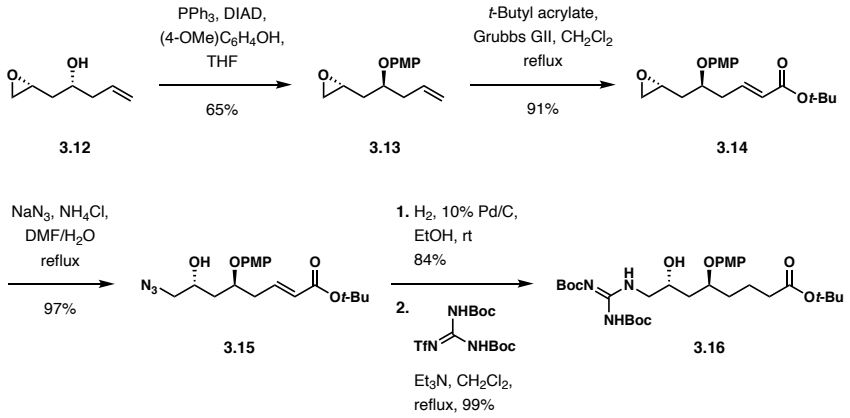
Scheme 37. Completion of Omura's synthesis of (+)-guadinomic acid



Reduction of the nitro-group of **3.8** by means of transfer hydrogenation, followed by guanylation of the resulting primary amine with a diBoc pyrazolylcarboxamidine, furnished **3.9** in nearly quantitative yield. The guanidine ring was installed by intramolecular, nucleophilic displacement of secondary alcohol with perfect inversion using a two-step sequence to give **3.10**. The cyclization was followed by a four-step sequence which results in oxidation of the TBS-protected alcohol to the requisite carboxylic acid and carbamoylation of the remaining free guanidine nitrogen. A further two steps were then required for complete deprotection, and successful completion of the total synthesis of (+)-guadinomic acid **3.1**. This

pioneering synthesis allowed for the complete determination of absolute and relative stereochemistry of guadinomic acid and possibly the entire family of isolated guadinomines.

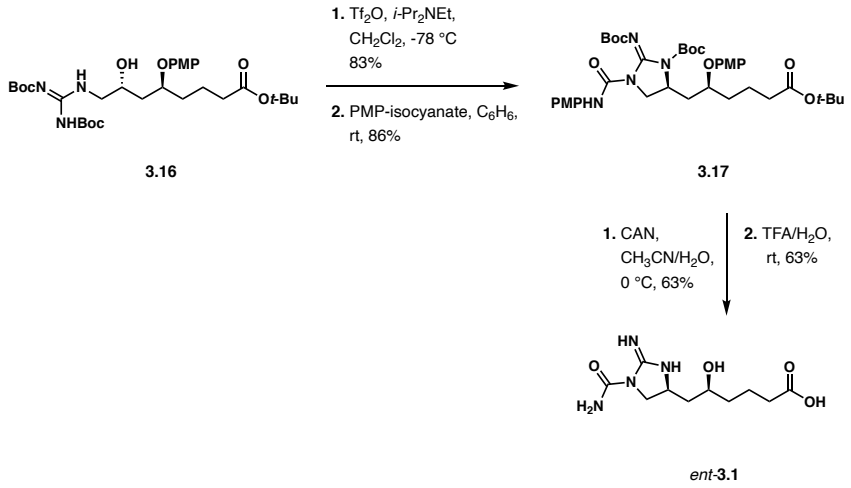
Scheme 38. Tae's synthesis of the diBoc guanidine intermediate prior to cyclization.



A second synthesis of guadinomic acid was reported by the Tae group.[68] The Tae group carried out the total synthesis of the unnatural enantiomer of guadinomic acid, in order to demonstrate the synthetic utility of enantioenriched epoxy alkenol **3.12**. This starting material was readily resolved by Jacobsen's hydrolytic kinetic resolution method. The configuration of the secondary alcohol was inverted under mitsunobu conditions with 4-methoxyphenol, followed by cross-metathesis with tert-butyl acrylate to give **3.14**. The terminal epoxide was then opened by exposure to sodium azide in refluxing DMF/H_2O to furnish the primary azide in excellent yield. Catalytic hydrogenation with Pd/C affected the reduction of both the azide and olefin functionalities in the same flask. Exposure of primary amine to diBoc trifyl guanidine afforded the protected guanidine **3.16**. Following the strategy employed by the Omura group in the first total synthesis of guadinomic acid, the guanidine was cyclized by displacement of unprotected, secondary alcohol through inversion of configuration. The unprotected nitrogen on the guanidine ring was then carbamoylated using PMP-isocyanate to

give intermediate **3.17**. In the final two steps of the synthesis, the PMP groups were removed under oxidative conditions, and the tert-butoxy groups were removed by exposure to aqueous TFA to give *ent*-guadinomic acid.

Scheme 39. Completion of the Tae synthesis of *ent*-guadinomic acid

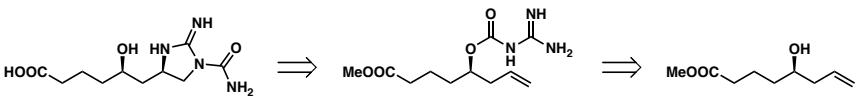


The Omura synthesis of guadinomic acid was designed to aid in the determination of the absolute and relative configuration in the natural form of guadinomic acid. This synthesis was flexible so as to produce all of the possible diastereomers in the hydroxy-cycloguanidine portion of the molecule. This strategy required the use of two separate enantioselective steps in the synthesis. The Tae group improved upon the efficiency of this first synthesis by beginning with enantiomerically resolved material which contained all requisite stereocenters and did not require a second asymmetric step. A key strategy used in both synthetic pathways was the reaction of a pre-installed primary amine with an electrophilic guanylation reagent, followed by intramolecular cyclization to displace a hydroxyl group. Both synthetic pathways demonstrated a high degree of stereocontrol. However, we felt that the laborious multistep

protocol used in the previous two syntheses for the installation of the hydroxyl-cycloguanidine structure, diminished the overall efficiency of these routes.

3.2. Total Synthesis of (+)-Guadinomic Acid

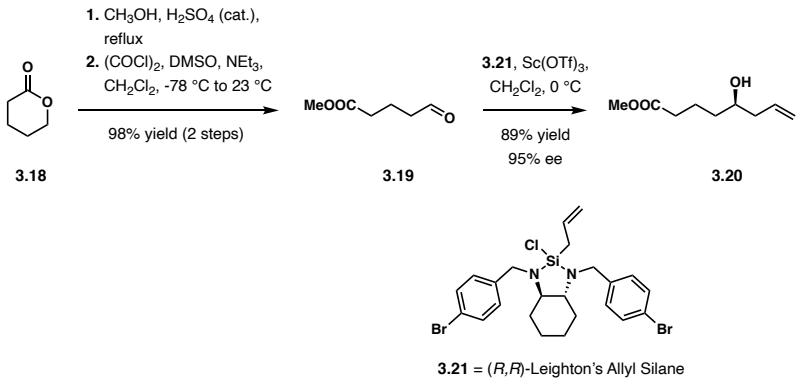
Scheme 40. Retrosynthetic strategy for the synthesis of (+)-guadinomic acid



(+) - guadinomic acid **(3.1)** **3.22** **3.20**

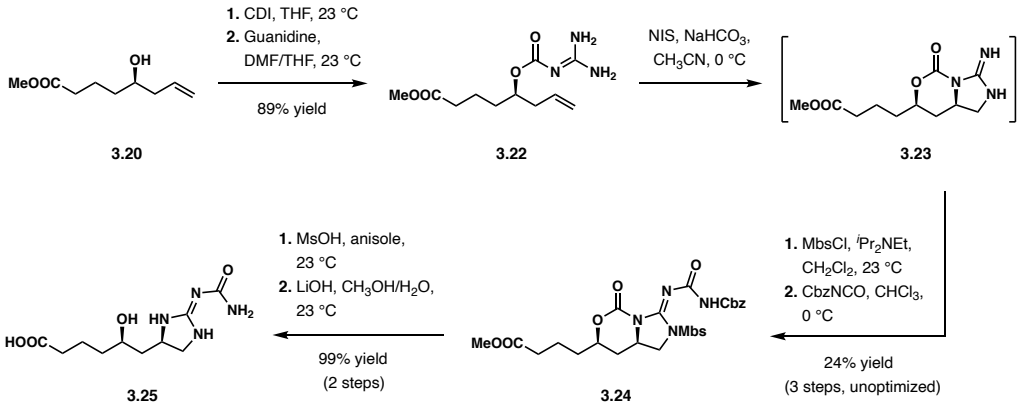
The potent bioactivity demonstrated by the family of guadinomines isolated by Omura, coupled with the opportunity to improve on the first two synthetic routes for accessing guadinomic acid, stimulated our interest in developing our own de novo approach to the total synthesis of (+)-guadinomic acid. We saw this as a perfect opportunity for the utilization of our recently developed method for the stereoselective synthesis of cyclic guanidines by directed diamination of unactivated alkenes. With this in mind, we envisioned accessing the hydroxyl cycloguanidine structure of guadinomic acid according to the retrosynthesis shown in Scheme 40. From the enantioenriched homoallylic alcohol **3.20**, installation of the guanidine carbamate tether, followed by electrophilic cyclization onto the terminal double bond, would furnish the 5-membered guanidine ring with the requisite stereochemistry.

Scheme 41. Access to enantio-enriched homoallylic alcohol



The synthesis commenced with transesterification of delta-valero lactone **3.18** in methanol followed by swern oxidation of the primary alcohol to give aldehyde **3.19**. The enantioenriched homoallylic alcohol was accessed by asymmetric allylation of the aldehyde using Leighton's (*R,R*)-configured allylsilane reagent **3.1**.[69] This reagent delivered the expected alcohol **3.20** in high yield and excellent enantiopurity (89% yield, 95% ee determined after benzoylation of the hydroxy group). We then set out to explore the stereoselective construction of the five-membered cyclic guanidine unit. The reaction between alcohol **3.20** and 1,1' – carbonyldiimidazole followed by in-situ treatment of the intermediate (1-imidazolyl)formate with a solution of free-guanidine in DMF furnished carbamate **3.22**.

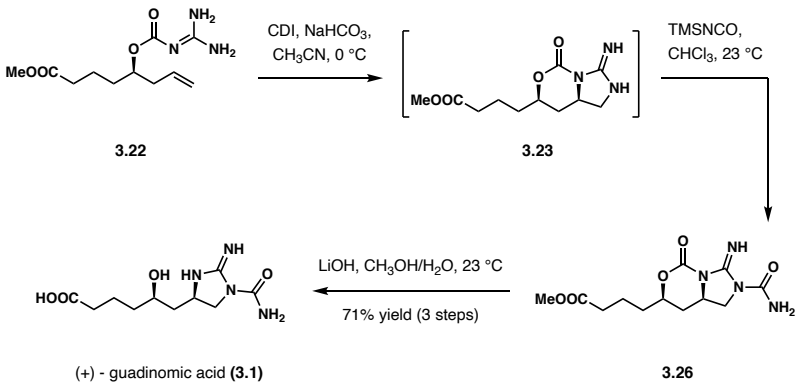
Scheme 42. Synthesis of the regioisomer of (+)-guadinomic acid



With guanidine carbamate **3.22** in hand, we focused our efforts on the installation of the guanidine cycle by intramolecular diamination of the olefin. Treatment of **3.22** with *N*-iodosuccinimide and sodium bicarbonate in acetonitrile at 0 °C furnished a highly polar bicyclic guanidine **3.23** as a single diastereomer. Prior to having knowledge of the regioselectivity in the reaction of the cyclic guanidine carbamate with electrophiles, we explored first the sulfonylation of the bicyclic intermediate according to our published method. Initial derivatization of this intermediate involved sulfonylation with *para*-methoxybenzene sulfonyl chloride and Hünig's base, followed by carbamoylation with carboxybenzyl isocyanate to give **3.24**. Desulfonylation using methanesulfonic acid in anisole was accompanied by removal of the carboxybenzyl group of the guanidine cycle. The cyclic carbamate and methyl ester were then hydrolyzed in the same pot by lithium hydroxide in aqueous methanol to afford a structure having the same molecular weight as guadinomic acid, but did not match spectroscopically with the natural product. We presumed this compound was regioisomer **3.25** of the natural product; differing in the position of the urea functionality. The ^{1}HNMR and ^{13}CNMR of this structure had the same number of signals as the spectra of the natural product, however, the differences in the shifts of the signals during comparison

were different enough that it could be attributed to a completely different structure. We reasoned that if this were indeed a regioisomer of the natural product, then sulfonylation must have taken place at the endocyclic nitrogen of the guanidine ring, and carbamoylation occurred at the exocyclic nitrogen. This suggests that carbamoylation directly following diamination of the terminal alkene would allow the isolation of the natural regioisomer. Feeling confident in our theory, we performed carbamoylation of the bicyclic intermediate using trimethylsilyl isocyanate which afforded a single regioisomer in quantitative conversion, without over-carbamoylation (Scheme 43). Trimethylsilyl isocyanate was used instead of the carboxybenzyl isocyanate due to reproducibility issues using the latter reagent. After global hydrolysis of the carbamoylated intermediate, we were able to isolate the desired (+)-guadinomic acid in 71% yield over three steps, following reverse-phase chromatographic purification.

Scheme 43. Completion of (+)-guadinomic acid



3.3. Conclusion

In conclusion, we developed a concise, protecting-group-free synthesis of the carbamoylated, guanidine alkaloid (+)-guadinomic acid that can be completed in 7 steps with an overall yield of 55%, starting from commercially available delta-valerolactone.[70] The synthetic route was a considerable improvement over previous developed routes from the Omura group (>16 steps) and Tae group (>9 steps). The efficiency of our route hinges upon methodology developed in our group, which demonstrates the synthesis of a guanidine carbamate tether from a homoallylic alcohol, and diastereoselective delivery of this guanidine to a terminal alkene to form a bicyclic 2-iminoimidazolidine unit. This methodology allows for the use of guanidine hydrochloride as a guanidine source rather than an electrophilic guanidine reagent, and requires the installation of only one stereocenter prior to its utilization. While (+)-guadinomic acid has no bioactivity against the TTSS, portions of the synthetic route we have developed could theoretically be used in the synthesis of the guadinomine family, specifically, guadinomine B which is a potent inhibitor of this biological system.

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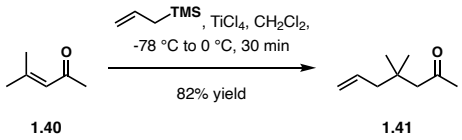
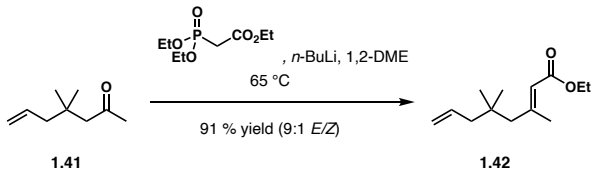
Experimental Procedures

General Information: All reactions were carried out with oven or flame-dried glassware, unless the reaction procedure states otherwise. Tetrahydrofuran (THF) was distilled from sodium-benzophenone in a continuous still under an atmosphere of argon. Dichloromethane (DCM) and acetonitrile were distilled from calcium hydride in a continuous still under and atmosphere of argon. Reaction temperatures were controlled by IKA ETS-D4 fuzzy thermo couples. Analytical thin-layer chromatography (TLC) was performed using pre-coated TLC plates with Silica Gel 60 F_{254} (EMD no. 5715-7) and visualized using combinations of UV, anisaldehyde, ceric ammonium molybdate (CAM), potassium permanganate, and iodine staining. Flash column chromatography was preformed using 40-63 μm silica gel (EMD, Geduran, no. 1.11567.9026) as the stationary phase. Proton nuclear magnetic resonance spectra were recorded at 500 MHz and 600 MHz on Varian Unity Inova spectrometers. Carbon nuclear magnetic resonance spectra were recorded at 126 MHz and 151 MHz on Varian Unity Inova spectrometers. All chemical shifts were reported in δ units relative to tetramethylsilane. Optical rotations were measured on a Rudolph Autopol III polarimeter. High resolution mass spectral data were obtained by the Mass spectrometry laboratory at the University of California, Santa Barbara.



4,4-dimethylhept-6-en-2-one (1.41): An oven-dried, two-neck round-bottom flask equipped with a thermometer, addition funnel, and drying tube was charged with mesityl oxide **1.40** (10 g, 102 mmol) dissolved in dichloromethane (170 mL). The flask was cooled to -78 °C and $TiCl_4$ (11.7 mL, 107 mmol) was added dropwise. The flask was then warmed to 0 °C. An addition funnel was charged with allyl trimethyl silane (15.1 g, 133 mmol) dissolved in 170 mL of dichloromethane and added at a rate slow enough for a stable temperature to be maintained. The flask was warmed to room temperature after the addition of the allyl trimethyl silane was complete. The reaction was quenched after 30 minutes with H_2O (350 mL) and diluted with ether. The mixture was extracted with ether (3x 100 mL), washed with sodium bicarbonate (100 mL), and brine (100 mL). The organic layers were dried over sodium sulfate and concentrated under reduced pressure at 0°C. The crude residue was purified via silica gel chromatography (1% Ether/Pentane) to afford the ketone **1.41** (11.6 g, 82% yield, 82.7 mmol) as a colorless oil. For best results, the ether in the collected fractions was removed via simple distillation.

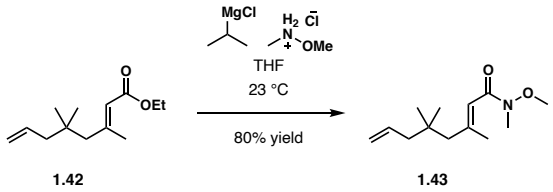
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, J = 16.9, 10.2, 7.5 Hz, 1H), 5.07 – 4.98 (m, 2H), 2.32 (s, 2H), 2.12 (s, 3H), 2.09 (d, J = 7.5 Hz, 2H), 1.00 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.8, 134.9, 117.5, 53.3, 46.4, 33.5, 32.4, 27.1.



1.41 1.42

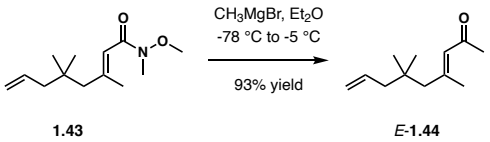
ethyl (*E*)-3,5,5-trimethylocta-2,7-dienoate (1.42): Triethyl phosphonoacetate (6.98 g, 31.1 mmol was dissolved in 1,2-DME (23 mL) under an argon atmosphere and the flask was cooled to 0 °C. *n*-Butyllithium (2.5 M in hexanes, 11.6 mL, 29.1 mmol) was added dropwise to the cooled solution and the reaction was stirred for 10 minutes at 0 °C. The reaction was warmed up to room temperature, and a solution of ketone **1.41** (2.91 g, 20.75 mmol) in 1,2-DME (6 mL) was added to the flask. The reaction was heated to 65 °C for 3 days. 1,2-DME was distilled away from the reaction flask under vacuum. The remaining crude mixture was diluted with ether, quenched with ammonium chloride, and extracted with pentanes (3x 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude oil was purified via silica gel chromatography (1% ether/pentanes) to afford the vinyl ester **1.42** as an inseparable mixture of diastereomers (3.96g, 91% yield, 9:1 *E:Z,* 18.8 mmol)

(*E*-isomer): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 – 5.76 (m, 1H), 5.61 (d, J = 1.2 Hz, 1H), 5.09 – 4.98 (m, 2H), 4.14 (q, J = 7.1 Hz, 2H), 2.19 (d, J = 1.3 Hz, 3H), 2.06 (s, 2H), 1.99 (d, J = 7.5 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H), 0.92 (d, J = 7.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 158.0, 135.0, 118.9, 117.4, 59.4, 52.8, 47.4, 27.1, 21.9, 14.3.



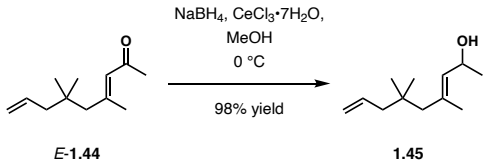
(*E*)-*N*-methoxy-*N*,3,5,5-tetramethylocta-2,7-dienamide (1.43): *N*,*O*-Dimethyl hydroxylamine hydrogen chloride (9.9 g, 101 mmol) and vinyl ester **1.42** (10.7 g, 51 mmol) were dissolved in THF (137 mL) under an argon atmosphere and the solution was cooled to 0 °C. Isopropyl magnesium chloride (2M in diethyl ether, 99 mL, 197 mmol) was added dropwise over 10 minutes. The reaction was then warmed to room temperature. After 45 minutes, the reaction was quenched with ammonium chloride and extracted with ethyl acetate (3x 100 mL). The mixture was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude oil was purified and isolated as a single diastereomer via silica gel chromatography (10% ethyl acetate/hexanes) to afford the vinyl amide **1.43** (9.17 g, 80% yield, 40.7 mmol) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06 (s, 1H), 5.83 (ddt, J = 17.4, 10.2, 7.4 Hz, 1H), 5.08 – 4.97 (m, 2H), 3.66 (s, 3H), 3.20 (s, 3H), 2.16 (d, J = 1.4 Hz, 3H), 2.08 (s, 2H), 2.01 (d, J = 7.5 Hz, 2H), 0.92 (s, 6H).^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 154.5, 135.3, 117.4, 61.5, 53.0, 47.4, 34.9, 27.3, 21.9.



(*E*)-4,6,6-trimethylnona-3,8-dien-2-one (*E*-1.44): Vinyl amide **1.43** (5.72 g, 25.4 mmol) was dissolved in ether (85 mL) under an argon atmosphere and the solution was cooled to -30 °C. Methyl magnesium bromide (3.0 M in diethyl ether, 25.4 mL, 76.2 mmol) was added dropwise to the reaction flask and the mixture was warmed to -5 °C. After 1 hour, the reaction was quenched with saturated ammonium chloride, diluted with ether, and extracted with 1:1 ether:hexanes (3 x 50 mL). The mixture was washed with brine, dried over sodium sulfate, and concentrated. The crude oil was purified via silica gel chromatography (5% ether/pentanes) to afford the enone *E*-**1.44** (4.25 g, 93% yield, 23.6 mmol) as a colorless oil.

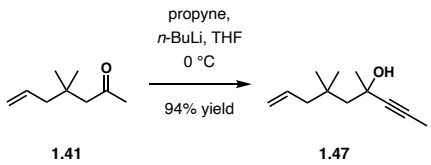
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (s, 1H), 5.82 (ddt, *J* = 17.0, 10.2, 7.4 Hz, 1H), 5.10 – 4.96 (m, 2H), 2.17 (s, 3H), 2.16 (d, *J* = 1.3 Hz, 3H), 2.05 (d, *J* = 0.8 Hz, 2H), 1.99 (d, *J* = 7.4 Hz, 2H), 0.91 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.3, 156.7, 135.0, 126.8, 117.4, 53.1, 47.4, 34.8, 31.9, 27.1, 22.5.



(*E*)-4,6,6-trimethylnona-3,8-dien-2-ol (1.45): Enone *E*-**1.44** (5.00 g, 27.9 mmol) was dissolved in methanol (70.0 mL) and cooled to 0 °C. Cerium trichloride heptahydrate (10.4 g, 27.9 mmol) was added and stirred until fully dissolved. Sodium borohydride (1.06 g, 27.9 mmol) was added portions to minimize effervescence. After 10 minutes, the reaction was quenched with saturated ammonium chloride and extracted with ethyl acetate (3x 50 mL). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over sodium sulfate, and concentrated under vacuum. The reaction was purified by silica gel

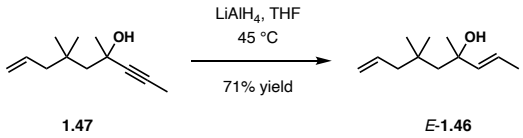
chromatography (10% ethyl acetate/hexanes) to afford the allylic alcohol **1.45** (5.01 g, 98% yield, 27.4 mmol), as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 – 5.78 (m, 1H), 5.21 – 5.15 (m, 1H), 5.04 – 4.95 (m, 2H), 4.61 – 4.51 (m, 1H), 1.97 – 1.88 (m, 4H), 1.72 (s, 3H), 1.48 (s, 1H), 1.23 (d, *J* = 6.3 Hz, 3H), 0.86 (d, *J* = 2.8 Hz, 6H).^{13}C NMR (126 MHz, $CDCl_3$) δ 135.5, 134.9, 133.4, 64.8, 51.3, 47.3, 34.3, 27.2, 27.1, 23.5, 19.1.



4,6,6-trimethylnon-8-en-2-yn-4-ol (1.47): *n*-Butyllithium (2.5 M in hexane, 71 mL, 178 mmol) was added to THF (110 mL) at -78° C under argon. A stream of propyne gas was blown over the surface of the solution for 10 minutes at a rate such that the indentation of the gas hitting the surface is observed (yellow color of the *n*-BuLi solution fades and solution becomes cloudy). Addition of the gas was then stopped and the solution was stirred at the same temperature for a further 20 minutes. A solution of ketone **1.41** (10 g, 71.3 mmol) in THF (30 mL) was added dropwise to the solution at -78 °C. After 20 minutes, the mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction was quenched with saturated ammonium chloride, diluted with ether, and extracted with 1:1 ether:hexanes (3x 100 mL). The mixture was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude oil was purified via silica gel chromatography (10% ether/pentanes) to afford the propargylic alcohol **1.47** as a colorless oil (12.1 g, 94% yield, 67.1 mmol).

^{1}H NMR (500 MHz, CDCl 3) δ 5.86 (ddt, J = 16.8, 10.2, 7.4 Hz, 1H), 5.07 – 4.97 (m, 2H), 2.15 (ddt, J = 7.5, 6.4, 1.2 Hz, 2H), 1.83 (s, 1H), 1.82 (s, 3H), 1.63 (d, J = 1.5 Hz, 2H), 1.48 (s, 3H), 1.08 (s, 3H), 1.07 (s, 3H). 13 C NMR (126 MHz, $CDCl_3$) δ 135.8, 116.9, 83.9, 80.3, 67.5, 52.7, 48.0, 33.9, 28.1, 28.0, 3.5.

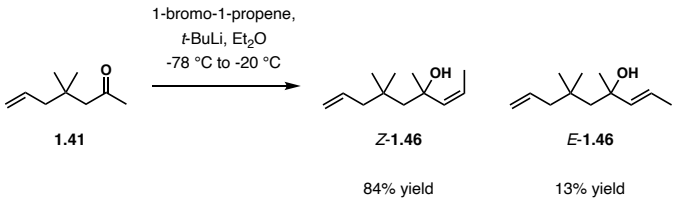


1.47 *E*-**1.46**

(*E*)-4,6,6-trimethylnona-2,8-dien-4-ol (*E*-1.46): A solution of the propargylic alcohol **1.47** (11.2 g, 61.9 mmol) in THF (40 mL) was added to a suspension of lithium aluminum hydride (2.3 g, 61.9 mmol) in THF (80 mL) at 0 °C, at such a rate to control effervescence. The ice water bath was removed and the reaction mixture was warmed naturally to room temperature. The reaction mixture was then heated to 45 °C for 16 hours. The reaction was cooled to 0°C, and diluted with ether (200 mL). Water (2.3 mL) was slowly added, followed by 3 M NaOH (2.3 mL), and again with water (6.9 mL) (careful, violent release of gas and exotherm). The flask was warmed to room temperature and stirred for 15 minutes. Magnesium sulfate was then added, and the flask was stirred for an additional 15 minutes. The resulting solids were filtered, washed with diethyl ether, and the filtrate was concentrated under vacuum. The crude oil was purified via column chromatography (10% diethyl ether/hexanes to 20% diethyl ether/hexanes) to afford the tertiary allylic alcohol *E*-**1.46** as a colorless oil (7.9 g, 71% yield, *E/Z* > 20:1, 43.8 mmol).

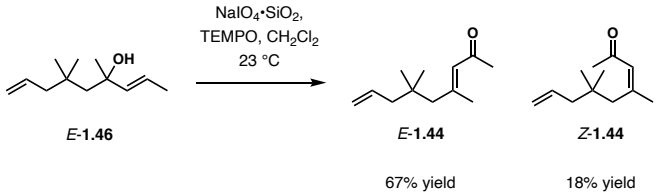
^{1}H NMR (500 MHz, CDCl 3) δ 5.83 (ddt, J = 17.4, 10.2, 7.4 Hz, 1H), 5.63 – 5.53 (m, 2H), 5.05 – 4.95 (m, 2H), 2.06 – 2.01 (m, 2H), 1.70 (d, J = 4.8 Hz, 3H), 1.59 – 1.51 (m, 2H),

1.40 (s, 1H), 1.28 (s, 3H), 0.96 (d, J = 1.4 Hz, 6H). 13 C NMR (126 MHz, CDCl 3) δ 139.4, 135.9, 120.7, 116.8, 73.9, 52.7, 48.4, 34.1, 31.6, 28.5, 28.4, 17.5.



(Z)-4,6,6-trimethylnona-2,8-dien-4-ol (*Z*-1.46): *t*-BuLi (1.5 M in pentanes, 17.1 mL, 25.7 mmol) was added slowly to a solution of 1-bromo-1 propene (9:1 *Z:E* mixture of isomers,1.10 mL, 12.8 mmol) in diethyl ether (16 mL) at -78 °C. After 2 hours, the solution was warmed to 0 °C. After 30 minutes, the solution was cooled to -78 °C, and ketone **1.41** (1.00 g, 7.13 mmol) was added dropwise. After 2 hours, the solution was warmed to -20 °C. After an hour, the solution was quenched with saturated sodium bicarbonate (30 mL), diluted with 1:1 hexanes:ether (30 mL), and extracted with 1:1 ether:hexanes (3x 30 mL). The mixture was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude oil was purified via silica gel chromatography (3% ether/hexanes) to afford a pair of diastereomers: *Z*-**1.46** (1.09 g, 84% yield 5.98 mmol), *E*-**1.46** (0.17 g, 13% yield, 0.93 mmol).

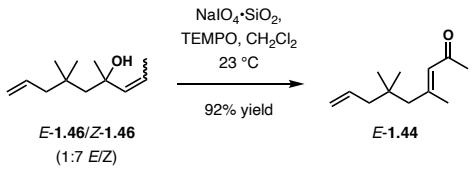
Z-**1.46**: ^{1}H NMR (500 MHz, CDCl3) δ 5.84 (ddt, J = 17.4, 10.2, 7.4 Hz, 1H), 5.47 (dd, J = 11.9, 1.8 Hz, 1H), 5.36 (dq, J = 11.9, 7.1 Hz, 1H), 5.05 – 4.97 (m, 2H), 2.08 (h, J = 6.8 Hz, 2H), 1.84 (dd, J = 7.2, 1.7 Hz, 3H), 1.68 – 1.56 (m, 2H), 1.36 (s, 3H), 1.01 (d, J = 5.2 Hz, 6H).^{13}C NMR (126 MHz, CDCl3) δ 138.2, 136.0, 123.2, 116.9, 75.7, 53.2, 48.7, 34.2, 32.3, 28.6, 28.6, 14.0.



(*E*)-4,6,6-trimethylnona-3,8-dien-2-one (*E*-1.44): $NaIO_4$-SiO_2 (1.53g/mmol, 193 g, 126 mmol) was added to a stirring solution of the alcohol *E*-**1.46** (5.92 g, 32.5 mmol) in dichloromethane (325 mL) followed by TEMPO (0.51 g, 3.25 mmol) and the resulting slurry was stirred vigorously for 48 hr. The solids were filtered off and washed thoroughly with diethyl ether, and the filtrate was concentrated. The crude oil contained a mixture diastereomers (4:1 *E*/Z) which were isolated via silica gel chromatography (2% ether/hexanes) to give the *E*-isomer *E*-**1.44** (3.91 g, 67% yield, 21.7 mmol) and the *Z*-isomer *Z*-**1.44** (1.036 g, 18% yield, 5.75 mmol).

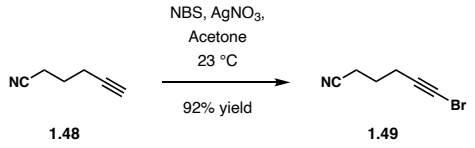
(*E*)-4,6,6-trimethylnona-3,8-dien-2-one *E*-**1.44:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (s, 1H), 5.82 (ddt, *J* = 17.0, 10.2, 7.4 Hz, 1H), 5.10 – 4.96 (m, 2H), 2.17 (s, 3H), 2.16 (d, *J* = 1.3 Hz, 3H), 2.05 (d, *J* = 0.8 Hz, 2H), 1.99 (d, *J* = 7.4 Hz, 2H), 0.91 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.3, 156.7, 135.0, 126.8, 117.4, 53.1, 47.4, 34.8, 31.9, 27.1, 22.5.

(*Z*)-4,6,6-trimethylnona-3,8-dien-2-one *Z*-**1.44:** ^{1}H NMR (500 MHz, $CDCl_3$) 6.95 (ddt, *J* = 17.4, 10.2, 7.4 Hz, 1H), 6.15 – 6.07 (m, 2H), 3.73 (s, 2H), 3.23 (s, 3H), 3.13 (d, *J* = 7.4 Hz, 2H), 3.00 (s, 3H), 2.00 (s, 6H).^{13}C NMR (126 MHz, $CDCl_3$) δ 198.3, 156.6, 135.5, 126.7, 117.1, 48.2, 43.7, 35.6, 32.1, 28.1, 27.3



(*E*)-4,6,6-trimethylnona-3,8-dien-2-one (*E*-1.44): $NaIO_4$-SiO_2 (1.53g/mmol, 36.6 g, 23.99 mmol) was added to a stirring solution of the *Z*-tertiary allylic alcohol **1.46** (1.09 g, 5.98 mmol, 1:7 mixture *E*/*Z*) in dichloromethane (51.0 mL) followed by TEMPO (0.0930 g, 0.598 mmol) and the resulting slurry was stirred vigorously for 48 hr. The solids were filtered off and washed thoroughly with diethyl ether, and the filtrate was concentrated. The crude oil contained a mixture of diastereomers (15:1 *E*/*Z*), and the *E*-isomer was isolated via silica gel chromatography (2% ether/hexanes) to give ketone *E*-**1.44** (0.992 g, 92% yield, 5.50 mmol).

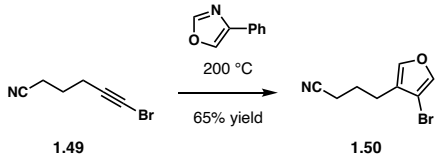
E-**1.44:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (s, 1H), 5.82 (ddt, *J* = 17.0, 10.2, 7.4 Hz, 1H), 5.10 – 4.96 (m, 2H), 2.17 (s, 3H), 2.16 (d, *J* = 1.3 Hz, 3H), 2.05 (d, *J* = 0.8 Hz, 2H), 1.99 (d, *J* = 7.4 Hz, 2H), 0.91 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.3, 156.7, 135.0, 126.8, 117.4, 53.1, 47.4, 34.8, 31.9, 27.1, 22.5.



6-bromohex-5-ynenitrile (1.49): *N*-bromosuccinimide (19.3 g, 108.24 mmol) was added to a stirring solution of hex-5-ynenitrile **1.48** (8.4 g, 90.2 mmol) in acetone (104 mL) at 23 °C. Silver nitrate (1.53 g, 9.02 mmol) was added and the reaction was stirred for 2 hours. The reaction was concentrated to half of the original volume and filtered over celite washing

with diethyl ether. The resulting solution was concentrated completely, then redissolved in 1:1 ether:hexanes (3x 100 mL). The mixture was washed brine (100 mL), dried over sodium sulfate, and concentrated under vacuum. The reaction was purified via silica gel chromatography (15% ethyl acetate/hexanes) to afford the brominated cyano alkyne **1.49** (14.2 g, 92% yield, 82.5 mmol) as a light yellow oil.

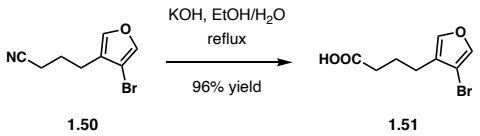
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (t, *J* = 7.1 Hz, 2H), 2.41 (t, *J* = 6.7 Hz, 2H), 1.88 (p, *J* = 6.9 Hz, 2H).^{13}C NMR (126 MHz, CDCl3) δ 118.8, 77.4, 40.2, 24.1, 18.7, 16.0.



1.49 **1.50**

4-(4-bromofuran-3-yl)butanenitrile (1.50): A mixture of bromo-alkyne **1.49** (3.50 g, 20.4 mmol), 4-phenyl oxazole (13.3 mL, 102 mmol), and hydroquinone (0.230 mg, 2.00 mmol) were combined in a microwave vial and the mixture was sparged with argon for 20 minutes then sealed. The vial was wrapped with a thin layer of aluminum foil to protect from light and heated in the dark at 220 ºC for 3 hours. Once cooled, the resulting black oil was purified via silica gel chromatography (0.5% ethyl acetate/hexanes) to afford the brominated furan **1.50** (2.87 g, 65% yield, 13.4 mmol) as a colorless oil.

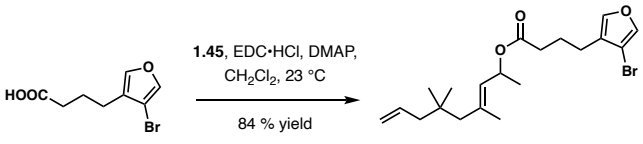
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 1.7 Hz, 1H), 7.26 – 7.25 (m, 1H), 2.61 – 2.55 (m, 2H), 2.37 (t, *J* = 7.1 Hz, 2H), 1.95 (p, *J* = 7.2 Hz, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 141.4, 140.0, 122.8, 119.1, 102.1, 24.5, 22.5, 16.3.



1.50 1.51

4-(4-bromofuran-3-yl)butanoic acid (1.51): KOH (6.30 g, 112 mmol) was added to a solution of Furan **1.50** (4.00 g, 18.6 mmol) in EtOH/H_2O (94 mL, 1:1 v/v) and the reaction was heated to reflux for 20 hours. The mixture was then cooled to room temperature and extracted with ether (3x 100 mL). The aqueous layer was cooled to 0 °C and concentrated HCl was added slowly until a pH of 2. The solution was extracted with ethyl acetate (4x 100 mL), washed with brine (1x 100 mL), dried over sodium sulfate, and concentrated. The crude product was purified via silica gel chromatography (1% AcOH/20% EtOAc/hexanes) to give acid (4.15 g, 96% yield, 17.8 mmol) as a white crystalline solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 11.91 (bs, 1H), 7.40 (d, *J* = 1.7 Hz, 1H), 7.21 (d, *J* = 1.6 Hz, 1H), 2.47 (t, *J* = 7.6 Hz, 2H), 2.41 (t, *J* = 7.4 Hz, 2H), 1.93 (p, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 179.6, 141.0, 139.7, 124.1, 102.4, 33.1, 23.8, 22.9. LRMS (ESI) calcd for $C_8H_8BrO_3$ $[M-H]^-$ 230.97, found 230.8

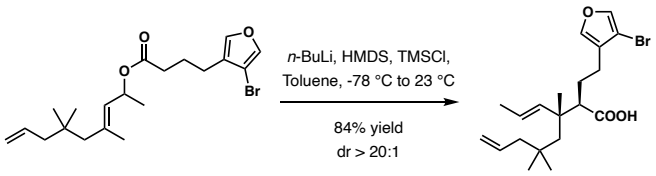


1.51 1.52

Allylic ester 1.52. *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (8.82 g, 46 mmol) was added to a stirring solution of Acid **1.51** (5.36 g, 23 mmol) in CH_2Cl_2 (75 mL) at 23 °C. A solution of allylic alcohol **1.45** (4.97 g, 27.26 mmol) in CH_2Cl_2 (75 mL) was

added to the flask, followed by DMAP (0.843 g , 6.9 mmol) and the reaction mixture was stirred under a drying tube for 18 hr at 23 °C. The reaction was quenched with water and extracted with Et_2O/Hexanes (1:1 v/v, 3x 50 mL). The mixture was washed with water (50 mL), and brine (50 mL), dried over sodium sulfate, and concentrated under vacuum. The crude oil was purified via silica gel chromatography (5% ethyl acetate/hexanes) to afford the ester **1.52** (7.68 g, 84% yield, 19.3 mmol) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 1.7 Hz, 1H), 7.18 (d, *J* = 1.7 Hz, 1H), 5.82 (ddt, *J* = 16.9, 10.2, 7.4 Hz, 1H), 5.59 (dq, *J* = 8.9, 6.4 Hz, 1H), 5.14 – 5.10 (m, 1H), 5.05 – 4.96 (m, 2H), 2.44 – 2.40 (m, 2H), 2.31 (t, *J* = 7.4 Hz, 2H), 1.95 (dt, *J* = 7.5, 1.2 Hz, 2H), 1.93 – 1.90 (m, 2H), 1.88 (t, *J* = 7.5 Hz, 2H), 1.76 (d, *J* = 1.4 Hz, 3H), 1.27 (d, *J* = 6.4 Hz, 3H), 0.85 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 140.9, 139.7, 137.0, 135.6, 128.8, 124.4, 117.0, 102.5, 68.2, 51.3, 47.3, 34.4, 33.8, 27.2, 27.2, 24.2, 23.0, 20.8, 19.4.



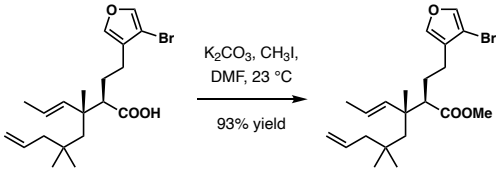
1.52 1.53

Acid 1.53. *n*-BuLi (2.6 M in hexane, 8.60 mL, 22.5 mmol) was added dropwise to a solution of HMDS (4.9 mL, 23.2 mmol) in toluene (60.0 mL) at 0 °C and stirred at the same temperature for 10 min before cooling the mixture to -78 °C. A solution of ester **1.52** (2.976 g, 7.490 mmol) in toluene (15.0 mL) was added dropwise to the solution of LiHMDS over 10 min at -78 °C and stirred at this temperature for 0.5 hr. TMSCl (2.90 mL, 22.5 mmol) was added to the reaction mixture over 5 min at -78 °C and stirred for a further 0.5 hr at the same

temperature. The reaction mixture was then warmed to 0 °C and stirred for 1 hr, then warmed to 23 °C and stirred for a further 1 hr. The reaction was diluted with diethyl ether (75.0 mL) and quenched with sat. aq. $NaHCO_3$ (75.0 mL). The pH of the aqueous layer was adjusted to pH = 2, and extracted with ethyl acetate (3x 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude mixture was purified by silica gel chromatography (5% EtOAc/Hex to 0.1% AcOH/10% EtOAc/Hex) to afford acid **1.53** (2.497 g, 84% yield, 6.284 mmol) as a > 20:1 ratio of diastereomers.

^{1}H NMR (500 MHz, CDCl3) δ 7.38 (d, J = 1.8 Hz, 1H), 7.18 (d, J = 1.7 Hz, 1H), 5.78 (ddt, J = 17.4, 10.2, 7.4 Hz, 1H), 5.35 (dq, J = 15.7, 6.2 Hz, 1H), 5.23 (dd, J = 15.6, 1.7 Hz, 1H), 5.04 – 4.91 (m, 2H), 2.42 (ddd, J = 14.5, 8.4, 5.7 Hz, 1H), 2.25 (dt, J = 15.2, 8.1 Hz, 1H), 2.15 (dd, J = 9.9, 4.0 Hz, 1H), 1.96 (d, J = 7.5 Hz, 2H), 1.80 – 1.67 (m, 2H), 1.70 (d, J = 6.2 Hz, 1H), 1.54 (d, J = 14.5 Hz, 1H), 1.36 (d, J = 14.3 Hz, 1H), 1.20 (s, 3H), 0.89 (s, 6H).

^{13}C NMR (126 MHz, CDCl3) δ 180.94, 180.93, 141.15, 140.09, 138.74, 135.87, 124.31, 123.51, 117.14, 102.59, 56.63, 50.84, 49.42, 42.90, 35.18, 28.98, 28.92, 26.71, 22.56, 19.26, 18.24.

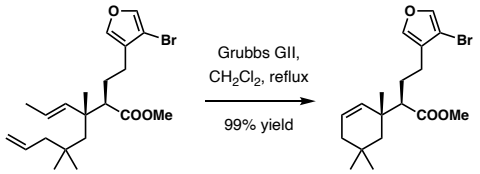


1.53 1.54

Diene 1.54. Acid **1.53** (0.800 g, 2.00 mmol) was dissolved in DMF (20.0 mL) at room temperature with a drying tube attached. Potassium Carbonate (0.280 g, 2.00 mmol) was then added to the solution. Methyl Iodide (0.150 mL, 2.40 mmol) was then added dropwise. The

solution was the stirred for 3 hours and monitored by TLC. Upon completion of the reaction, the solution was diluted with hexane (30.0 mL), water (30.0 mL), and extracted with hexanes (3x 30.0 mL). The mixture was washed with water and brine, dried with sodium sulfate, and concentrated under vacuum. The crude oil was purified via silica gel chromatography (5% ethyl acetate/hexanes) to afford the ester **1.54** (0.768 g, 93% yield, 1.87 mmol) as a colorless oil.

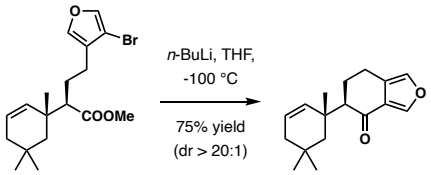
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 1.8 Hz, 1H), 7.14 (d, *J* = 1.6 Hz, 1H), 5.77 (ddt, *J* = 17.4, 10.2, 7.4 Hz, 1H), 5.33 (dq, *J* = 15.7, 6.3 Hz, 1H), 5.21 (dq, *J* = 15.4, 1.5 Hz, 1H), 5.03 – 4.91 (m, 2H), 3.67 (s, 3H), 2.34 – 2.27 (m, 1H), 2.20 – 2.11 (m, 2H), 1.93 (dt, *J* = 7.4, 1.2 Hz, 2H), 1.81 – 1.65 (m, 2H), 1.69 (m, 3H), 1.46 (d, *J* = 14.5 Hz, 1H), 1.20 (d, *J* = 14.4 Hz, 1H), 1.16 (s, 3H), 0.88 (s, 6H). 13C NMR (126 MHz, CDCl3) δ 175.67, 141.07, 139.96, 139.01, 135.97, 124.45, 123.16, 116.99, 102.64, 56.71, 51.22, 50.80, 49.69, 43.12, 35.10, 28.97, 28.88, 26.73, 22.61, 19.15, 18.22.



1.54 **1.55**

Methyl ester 1.55. Ester **1.54** (1.34g, 3.26 mmol) was dissolved in CH_2Cl_2 (130.0 mL) and argon was bubbled through the solution for 1 hr. Grubbs GII (0.135 g, 0.163 mmol) was then added and the solution was stirred at reflux for 2 hours. The solution was then concentrated and purified via silica gel chromatography (1% ethyl acetate/hexanes) to afford the ester **1.55** (1.20g, 99% yield, 3.26 mmol) as a colorless oil.

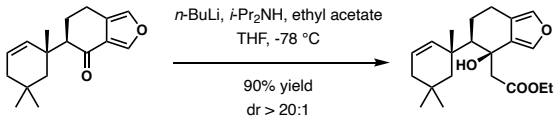
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 1.8 Hz, 1H), 7.17 (s, 0H), 5.62 (ddd, *J* = 10.2, 5.8, 2.2 Hz, 1H), 5.57 – 5.50 (m, 1H), 3.64 (s, 3H), 2.39 – 2.29 (m, 1H), 2.26 – 2.16 (m, 2H), 1.90 (dddd, *J* = 13.8, 11.6, 9.0, 5.1 Hz, 1H), 1.76 (ddt, *J* = 6.8, 4.2, 2.7 Hz, 1H), 1.73 – 1.61 (m, 2H), 1.15 (ddd, *J* = 13.8, 2.4, 1.2 Hz, 1H), 1.07 (s, 3H), 0.94 (s, 7H). ^{13}C NMR (126 MHz, CDCl3) δ 175.17, 140.96, 139.81, 132.25, 125.24, 124.28, 102.41, 56.64, 50.97, 44.66, 38.12, 37.74, 32.65, 29.89, 27.89, 26.52, 25.81, 22.62.



1.55 1.56

Ketone 1.56. *n*-BuLi (2.5 M in hexane, 1.45 mL, 3.63 mmol) was added dropwise to a solution of ester **1.55** (0.659g, 1.78 mmol) in THF (120 mL) over 20 min while maintaining the internal temperature of the solution between -90 °C and -100 °C. After stirring the solution for 30 min at -100 °C, the reaction mixture was warmed to -80 °C and quenched with acetic acid (0.107 mL, 1.78 mmol). The mixture was warmed to 23 °C and saturated aqueous sodium bicarbonate (50 mL) was added. The aqueous layer was extracted with ethyl acetate (3x50 mL) and the organic layers were washed with brine, dried over sodium sulfate and concentrated. The crude product was purified by silica gel chromatography (0.5% EtOAc/Hex to 5% EtOAc/Hex) to give ketone **1.55** (0.346 g, 75% yield, 1.34 mmol) as a single diastereomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (d, J = 1.5 Hz, 1H), 7.21 (m, 1H), 5.65 (ddd, J = 10.1, 5.3, 2.7 Hz, 1H), 5.57 (ddt, J = 10.2, 2.5, 1.1 Hz, 1H), 2.86 (dt, J = 15.9, 4.8 Hz, 1H), 2.59 (dddd, J = 15.8, 10.7, 4.8, 1.8 Hz, 1H), 2.39 (dd, J = 10.7, 3.7 Hz, 1H), 2.27 (dtd, J =

13.5, 4.9, 3.7 Hz, 1H), 1.97 (dtd, J = 13.4, 10.6, 4.4 Hz, 1H), 1.86 (dt, J = 16.8, 2.8 Hz, 1H), 1.80 (d, J = 14.0 Hz, 1H), 1.76 – 1.70 (m, 1H), 1.59 (ddd, J = 14.0, 2.0, 1.0 Hz, 1H), 1.14 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H). LRMS (ESI) calcd for $C_{17}H_{23}O_2$ $[M+H]^+$ 259.17, found 250.0

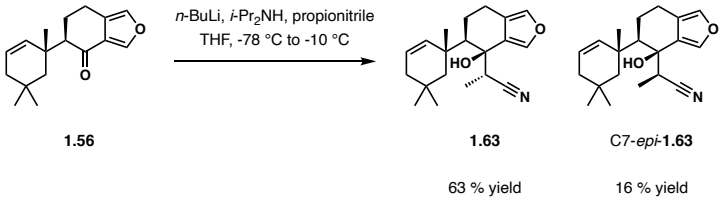


1.56 1.57

Ethyl ester 1.57. *n*-BuLi (2.5 M in hexane, 3.7 mL, 9.35 mmol) was added to a stirring solution of diisopropylamine (1.32 mL, 9.35 mmol) in THF (40 mL) at 0 °C and stirred for 10 min before cooling the mixture to -78 °C. Ethyl acetate (0.913 mL) was added dropwise to the solution of LDA at -78 °C and stirred for 0.5 hr. A solution of ketone **1.56** (0.345 g, 1.335 mmol) in THF (10.0 mL) was added to the lithiated ethyl acetate at -78 °C and stirred for 4 hr. The reaction mixture was quenched with AcOH (1.10 mL, 18.7 mmol) at -78 °C. Water was added (40 mL) and the mixture was extracted with EtOAc (3x30 mL). The organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over sodium sulfate and concentrated. The crude product was purified by silica gel chromatography (1% EtOAc/Hex to 10% EtOAc/Hex) to give ethyl ester **1.57** (416.0 mg, 90% yield, 0.120 mmol) as a single diastereomer.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (d, J = 1.5 Hz, 1H), 7.09 (d, J = 1.5 Hz, 1H), 5.73 (dd, J = 10.2, 2.8 Hz, 1H), 5.68 (ddd, J = 10.1, 5.9, 2.1 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.69 (s, 1H), 3.00 (d, J = 15.5 Hz, 1H), 2.89 (d, J = 15.5 Hz, 1H), 2.67 – 2.58 (m, 1H), 2.40 (dddd, J = 15.8, 7.3, 5.2, 1.6 Hz, 1H), 2.09 (d, J = 13.9 Hz, 1H), 2.00 – 1.92 (m, 2H), 1.87 – 1.79 (m,

2H), 1.68 (ddd, J = 16.7, 6.0, 2.3 Hz, 1H), 1.22 (t, J = 7.1 Hz, 4H), 1.17 (s, 3H), 0.94 (s, 3H), 0.87 (s, 3H). LRMS (ESI) calcd for $C_{21}H_{30}O_4Na$ $[M+Na]^+$ 369.20, found 369.2



1.56 **1.63** C7-*epi*-**1.63**

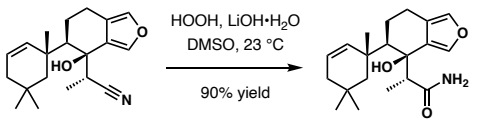
63 % yield 16 % yield

Nitriles 1.63 and C7-*epi*-1.63. *n*-BuLi (2.5 M in hexane, 1.50 mL, 3.87 mmol) was added to a stirring solution of diisopropylamine (0.550 mL, 3.87 mmol) in THF (34 mL) at 0 °C and stirred for 10 min before cooling the mixture to -78 °C. Propionitrile (0.270 mL) was added dropwise to the solution of LDA at -78 °C and stirred for 0.5 hr. A solution of ketone **1.56** (0.200 g, 0.774 mmol) in THF (6.0 mL) was added to the lithiated propionitrile at -78 °C and stirred for 10 min. The reaction mixture was warmed to -10 °C and quenched with AcOH (0.45 mL, 7.74 mmol). Water was added and the mixture was extracted with EtOAc (3x20 mL). The organic layers were washed with brine, dried over sodium sulfate and concentrated. The crude product contained a 4:1 mixture of diastereomers which were separated and purified by silica gel chromatography (3% EtOAc/Hex to 5% EtOAc/Hex) to give nitrile **1.63** (153.0 mg, 63% yield, 0.488 mmol) and nitrile C7-*epi*-**1.63** (40.0 mg, 16% yield, 0.127 mmol)

Nitrile **1.63**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (d, J = 1.5 Hz, 1H), 7.15 (d, J = 1.4 Hz, 1H), 5.85 (ddd, J = 10.2, 6.2, 1.9 Hz, 1H), 5.79 (ddd, J = 10.2, 3.0, 1.3 Hz, 1H), 3.60 (s, 1H), 3.19 (q, J = 7.1 Hz, 1H), 2.67 – 2.59 (m, 1H), 2.35 (dddd, J = 15.9, 7.2, 5.5, 1.5 Hz, 1H), 2.05 (dd, J = 7.2, 4.5 Hz, 1H), 2.01 – 1.88 (m, 3H), 1.85 (d, J = 17.1 Hz, 1H), 1.74 (ddd, J = 17.1,

6.3, 2.5 Hz, 1H), 1.22 (m, 6H), 1.14 (dt, J = 13.9, 1.9 Hz, 1H), 0.93 (s, 3H), 0.83 (s, 3H). LRMS (ESI) calcd for $C_{20}H_{27}NO_2Na$ $[M+Na]^+$ 336.19, found 336.3

Nitrile C7-*epi*-**1.63**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 1.5 Hz, 1H), 7.18 – 7.15 (m, 1H), 5.86 (ddd, J = 10.1, 5.7, 2.2 Hz, 1H), 5.81 (dt, J = 10.2, 1.5 Hz, 1H), 3.34 (s, 1H), 3.15 (q, J = 7.0 Hz, 1H), 2.66 (ddd, J = 15.5, 6.9, 4.4 Hz, 1H), 2.47 (dddd, J = 15.4, 9.3, 4.5, 1.6 Hz, 1H), 2.10 – 2.00 (m, 2H), 1.93 (ddt, J = 14.0, 6.9, 4.3 Hz, 1H), 1.78 (m, 3H), 1.37 (d, J = 7.0 Hz, 3H), 1.27 (s, 3H), 1.22 – 1.18 (m, 1H), 0.94 (s, 3H), 0.88 (s, 3H). LRMS (ESI) calcd for $C_{20}H_{27}NO_2Na$ $[M+Na]^+$ 336.19, found 336.3

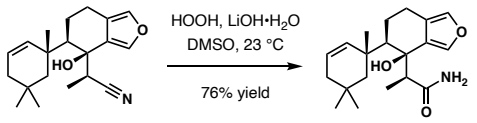


1.63 1.64

Amide 1.64. LiOH•H_2O (0.109 g, 2.60 mmol) was added to an aqueous solution of hydrogen peroxide (30% $H_2O_{2\,(aq)}$ 5.5 mL, 48.5 mmol) at 23 °C and stirred for 5 min. A solution of nitrile **1.63** (153 mg, 0.488 mmol) in DMSO (50.0 mL) was added dropwise while stirring to the basic solution of hydrogen peroxide at 23 °C and stirred for a further 30 min. The reaction was then diluted with EtOAc (50 mL) and H_2O (200 mL). The aqueous layer was extracted with EtOAc (3x50 mL) and the organic layers were washed with brine, dried over sodium sulfate and concentrated. The crude residue was purified by silica gel chromatography (30% EtOAc/Hex) to give amide **1.64** (145 mg, 90% yield, 0.438 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, J = 1.6 Hz, 1H), 7.13 (d, J = 1.5 Hz, 1H), 6.18 (bs, 1H), 5.65 (m, 2H), 5.31 (bs, 1H), 4.17 (s, 1H), 2.67 (q, J = 7.1 Hz, 1H), 2.61 – 2.48 (m, 2H), 2.16 (ddt, J = 15.1, 6.6, 3.4 Hz, 1H), 2.07 – 2.03 (m, 1H), 1.98 (dtd, J = 15.0, 7.3, 3.7 Hz, 1H),

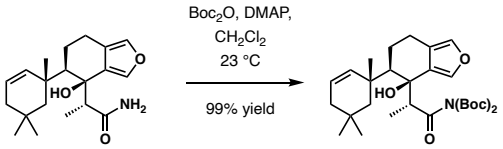
1.83 (d, J = 14.0 Hz, 1H), 1.75 (d, J = 16.9 Hz, 1H), 1.71 – 1.65 (m, 1H), 1.23 – 1.19 (m, 4H), 1.12 (s, 3H), 0.92 (s, 3H), 0.78 (s, 3H). LRMS (ESI) calcd for $C_{20}H_{29}NO_3Na$ $[M+Na]^+$ 354.20, found 354.4



C7-*epi*-**1.63** **S1.64**

Amide S1.64. Amide **S1.64** was obtained by following the same procedure used to prepare amide **1.64**; using C7-*epi*-**1.63** (10.0 mg, 0.0319 mmol) to afford **S1.64** (8.0 mg, 76% yield, 0.0241 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, J = 1.6 Hz, 1H), 7.10 (d, J = 1.5 Hz, 1H), 6.02 (bs, 1H), 5.75 (m, 2H), 5.13 (bs, 1H), 4.47 (s, 1H), 2.72 (q, J = 7.0 Hz, 1H), 2.58 (ddd, J = 16.6, 11.0, 5.8 Hz, 1H), 2.46 (dt, J = 16.3, 5.3 Hz, 1H), 2.11 (t, J = 4.9 Hz, 1H), 2.08 – 1.96 (m, 2H), 1.86 – 1.69 (m, 3H), 1.30 (d, J = 7.1 Hz, 3H), 1.26 – 1.20 (m, 1H), 1.13 (s, 3H), 0.93 (s, 3H), 0.85 (s, 3H). LRMS (ESI) calcd for $C_{20}H_{29}NO_3Na$ $[M+Na]^+$ 354.20, found 354.4

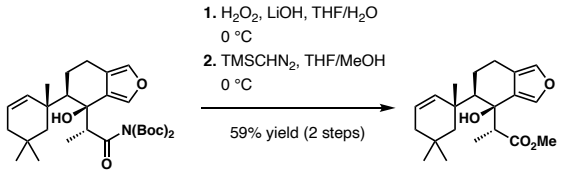


1.64 **1.65**

***N,N*-bisBoc amide 1.65.** DMAP (28.0 mg, 0.230 mmol) was added to a stirring solution of amide **1.64** (70.0 mg, 0.209 mmol) and Boc_2O (100.0 mg, 0.460 mmol) in CH_2Cl_2 (10.0 mL) at 23 °C and stirred for 30 min. Additional Boc_2O (100.0 mg, 0.460 mmol) and DMAP

(28.0 mg, 0.230 mmol) were added and the solution was stirred for an additional 2 hr. The mixture was then concentrated and purified by silica gel chromatography (1% EtOAc/Hexane to 5% EtOAc/Hexane) to give *N,N*-bisBoc amide **1.65** (114.0 mg, 99% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (d, J = 1.6 Hz, 1H), 7.12 (d, J = 1.5 Hz, 1H), 5.57 (ddd, J = 10.1, 5.6, 2.2 Hz, 1H), 5.53 (dd, J = 10.0, 2.6 Hz, 1H), 4.03 (s, 1H), 3.82 (q, J = 6.9 Hz, 1H), 2.60 – 2.53 (m, 1H), 2.49 (dt, J = 11.8, 5.6 Hz, 1H), 2.09 (dq, J = 14.2, 4.6 Hz, 1H), 1.94 (t, J = 4.5 Hz, 1H), 1.90 – 1.80 (m, 3H), 1.64 – 1.58 (m, 1H), 1.53 (s, 18H), 1.24 (m, 4H), 1.05 (s, 3H), 0.91 (s, 3H), 0.81 (s, 3H). LRMS (ESI) calcd for $C_{20}H_{45}NO_7Na$ $[M+Na]^+$ 554.31, found 554.1

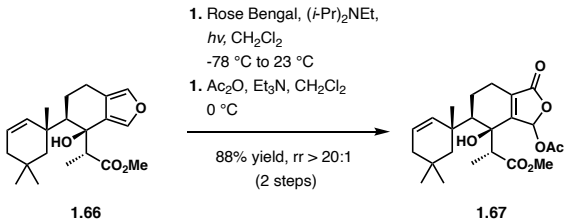


1.65 1.66

Methyl ester 1.66. $LiOH•H_2O$ (5.0 mg, 0.119 mmol) was added to an aqueous solution of hydrogen peroxide (30% $H_2O_{2\,(aq)}$ 0.28 mL, 2.47 mmol). This solution of basic hydrogen peroxide was added to a solution of *N,N*-bisBoc amide **1.65** (13.0 mg, 0.0245 mmol) in THF (2.5 mL) at 0 °C and stirred for 1 hr. After 1 hr, the same amount of the basic hydrogen peroxide solution (containing the same amount of $LiOH•H_2O$ and hydrogen peroxide) was added to the reaction mixture at 0 °C and stirred for an additional hour. The reaction mixture was then diluted with ethyl acetate (3 mL) and aqueous $NaHSO_4$ (pH = 3, 5 mL). The aqueous layer was extracted with ethyl acetate (3x3 mL) and the organic layers were washed with brine and used immediately in the next step.

Methanol (1 mL) was added to the crude, unconcentrated organic layers from the previous reaction at 23 °C. $TMSCHN_2$ (2M in Et_2O, 50 μL, 0.1 mmol) was added to the organic layers and stirred at 23 °C for 1 hr. The reaction mixture was then concentrated and purified by silica gel chromatography (1% EtOAc/Hex to 5% EtOAc/Hex to 10% EtOAc/Hex) to give methyl ester **1.66** (5 mg, 59% yield, 0.0144 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, J = 1.6 Hz, 1H), 7.13 (d, J = 1.5 Hz, 1H), 5.64 (ddd, J = 10.1, 5.8, 2.5 Hz, 1H), 5.57 – 5.52 (m, 1H), 3.78 (s, 1H), 3.74 (s, 3H), 2.91 (q, J = 7.0 Hz, 1H), 2.58 (dddd, J = 16.4, 10.9, 5.6, 1.5 Hz, 1H), 2.44 (dddd, J = 16.1, 6.1, 4.7, 1.4 Hz, 1H), 2.03 (dq, J = 14.7, 5.3 Hz, 1H), 1.95 (d, J = 13.8 Hz, 1H), 1.88 (dddd, J = 15.0, 10.7, 6.0, 4.4 Hz, 1H), 1.82 (dt, J = 16.7, 2.7 Hz, 1H), 1.78 (dd, J = 5.5, 4.4 Hz, 1H), 1.64 (dddd, J = 16.5, 5.8, 2.1, 0.9 Hz, 1H), 1.19 (ddd, J = 13.7, 2.2, 1.1 Hz, 1H), 1.14 (d, J = 7.0 Hz, 3H), 1.07 (s, 3H), 0.91 (s, 3H), 0.82 (s, 3H). LRMS (ESI) calcd for $C_{20}H_{30}O_4Na$ $[M+Na]^+$ 369.20, found 369.3



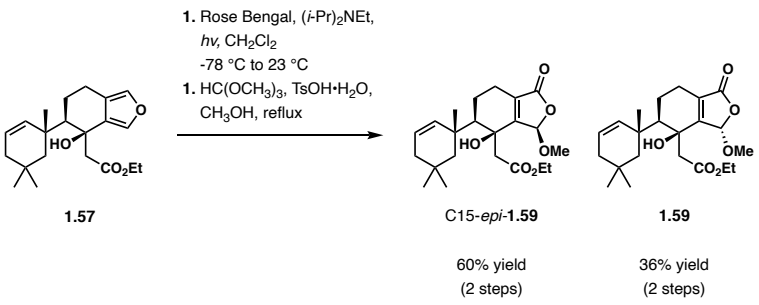
1.66 1.67

γ-Acetoxy butenolide 1.67. Rose Bengal (6.0 mg, 0.00650 mmol) was added to a solution of furan **1.66** (45.0 mg, 0.130 mmol) in CH_2Cl_2 (13.0 ml) followed by *i*-Pr_2NEt (0.230 mL, 1.30 mmol) and the suspension was cooled to -78 °C. Oxygen was bubbled through the solution for 5 min, then the suspension was irradiated (Kessil® Lamp, model: A160WE TUNA BLUE, settings: 100% white light/100% intensity) for 20 min while continuing to bubble

oxygen through the solution. Oxygen delivery and irradiation were halted and the solution was allowed to warm to 23 °C and stir for 20 min at this temperature. Aqueous $NaHSO_4$ (2 M, 13 mL) was added followed by EtOAc (30 mL). The layers were separated and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated.

The crude residue from the previous reaction was resuspended in CH_2Cl_2 (13.0 mL). Ac_2O (26 μL, 0.276 mmol) was added to the CH_2Cl_2 solution followed by *i*-Pr_2NEt (65 μL, 0.374 mmol) and the solution was stirred at 23 °C for 1 hr. The reaction mixture was then diluted with EtOAc (13 mL) and washed with aqueous $NaHSO_4$ (pH = 3), brine, dried over Na_2SO_4 and concentrated. The product was then isolated by silica gel chromatography (5% EtOAc/Hex to 10% EtOAc/Hex to 20% EtOAc/Hex) to give γ-acetoxy butenolide **1.67** (48.0 mg, 88% yield, 0.114 mmol) as a single regioisomer and epimer of unknown configuration at C15.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 (dd, J = 2.3, 1.2 Hz, 1H), 5.68 (ddd, J = 10.1, 6.1, 2.3 Hz, 1H), 5.52 (dd, J = 10.1, 2.9 Hz, 1H), 4.15 (s, 1H), 3.71 (s, 3H), 3.19 (q, J = 7.1 Hz, 1H), 2.36 – 2.28 (m, 1H), 2.23 – 2.17 (m, 1H), 2.15 – 2.06 (m, 5H), 1.92 – 1.78 (m, 3H), 1.69 (ddd, J = 16.3, 6.1, 2.0 Hz, 1H), 1.23 (d, J = 7.2 Hz, 3H), 1.17 (m, 4H), 0.94 (s, 3H), 0.93 (s, 3H). LRMS (ESI) calcd for $C_{23}H_{32}O_7Cl$ $[M+Cl]^-$ 455.18, found 455.1



1.57 C15-*epi*-**1.59** **1.59**

60% yield (2 steps) 36% yield (2 steps)

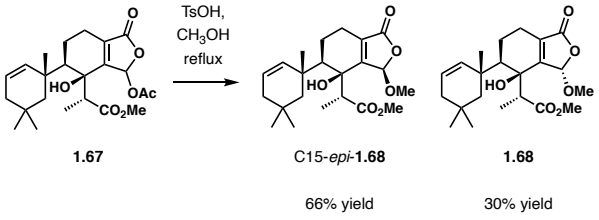
γ-Methoxy butenolides C15-*epi*-1.59 and 1.59. Rose Bengal (7.0 mg, 0.00720 mmol) was added to a solution of ethyl ester **1.57** (50.0 mg, 0.144 mmol) in CH_2Cl_2 (15.0 ml) followed by *i*-Pr_2NEt (0.250 mL, 1.44 mmol) and the suspension was cooled to -78 °C. Oxygen was bubbled through the solution for 5 min, then the suspension was irradiated (Kessil® Lamp, model: A160WE TUNA BLUE, settings: 100% white light/100% intensity) for 20 min while continuing to bubble oxygen through the solution. Oxygen delivery and irradiation were halted and the solution was allowed to warm to 23 °C and stir for 20 min at this temperature. Aqueous $NaHSO_4$ (2 M, 15 mL) was added followed by EtOAc (30 mL). The layers were separated and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude residue was purified by silica gel chromatography (40% EtOAc/Hex) to give an inseparable, 2:1 mixture of γ-hydroxy butenolide **1.58** epimers (54.0 mg, 99% yield, 0.143 mmol).

A solution of γ-hydroxy butenolide **1.58** (54.0 mg, 0.143 mmol), $TsOH•H_2O$ (27.0 mg, 0.143 mmol), and trimethyl orthoformate (34 μL, 0.315 mmol) in CH_3OH (14.0 mL) was heated to reflux for 4 hr. The reaction mixture was cooled to 23 °C then concentrated and resuspended in EtOAc (20 mL). The organic solution was washed with sat. aq. $NaHCO_3$ (2x20 mL), brine, dried over Na_2SO_4 and concentrated. The crude residue contained a 3:2 mixture of epimers which were separated and purified by silica gel chromatography to give γ-methoxy butenolide C15-*epi*-**1.59** (34.0 mg, 60% yield, 0.0866 mmol) and γ-methoxy butenolide **1.59** (20.0 mg, 36% yield, 0.0510 mmol).

γ-Methoxy butenolide C15-*epi*-**1.59:** ^1H NMR (500 MHz, $CDCl_3$) δ 5.93 (d, J = 2.4 Hz, 1H), 5.84 – 5.79 (m, 1H), 5.72 – 5.64 (m, 1H), 4.16 – 4.05 (m, 2H), 3.71 (d, J = 14.9 Hz, 1H), 3.64 (s, 3H), 2.88 (d, J = 1.2 Hz, 1H), 2.63 (d, J = 14.9 Hz, 1H), 2.46 – 2.39 (m, 1H), 2.17 (d,

J = 13.9 Hz, 2H), 2.06 – 1.96 (m, 1H), 1.94 – 1.87 (m, 1H), 1.83 (d, J = 17.3 Hz, 1H), 1.79 – 1.65 (m, 2H), 1.61 (d, J = 11.4 Hz, 1H), 1.25 – 1.21 (m, 5H), 1.15 (d, J = 12.1 Hz, 1H), 0.95 (s, 3H), 0.93 (s, 3H). LRMS (ESI) calcd for $C_{22}H_{32}O_6Na$ $[M+Na]^+$ 415.21, found 415.3

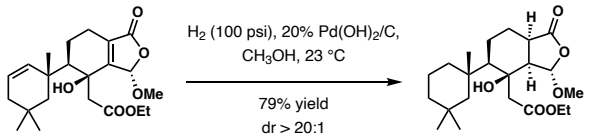
γ-Methoxy butenolide 1.59: ^1H NMR (500 MHz, $CDCl_3$) δ 5.90 – 5.83 (m, 1H), 5.67 (td, J = 7.2, 3.5 Hz, 1H), 5.59 (d, J = 10.2 Hz, 1H), 4.37 (s, 1H), 4.21 – 4.15 (m, 2H), 3.63 (s, 3H), 3.09 (d, J = 16.7 Hz, 1H), 2.78 (d, J = 16.7 Hz, 1H), 2.31 – 2.14 (m, 3H), 1.99 (t, J = 4.4 Hz, 1H), 1.91 (d, J = 13.6 Hz, 1H), 1.85 – 1.75 (m, 2H), 1.68 (dd, J = 16.7, 5.9 Hz, 1H), 1.32 – 1.20 (m, 1H), 1.30 (t, J = 6.9, 3H), 1.13 (s, 3H), 0.94 (s, 3H), 0.88 (s, 3H). LRMS (ESI) calcd for $C_{22}H_{32}O_6Na$ $[M+Na]^+$ 415.21, found 415.3



γ-Methoxy butenolides 1.68 and C15-*epi*-1.68. A solution of γ-acetoxy butenolide **1.67** (47.0 mg, 0.112 mmol) and $TsOH•H_2O$ (70.0 mg, 0.367 mmol) in CH_3OH (22.0 mL) was heated to reflux for 4 hr. The reaction mixture was cooled to 23 °C then concentrated and resuspended in EtOAc (20 mL). The organic solution was washed with sat. aq. $NaHCO_3$ (2x20 mL), brine, dried over Na_2SO_4 and concentrated. The crude residue contained a 2:1 mixture of epimers which were separated and purified by silica gel chromatography to give γ-methoxy butenolide C15-*epi*-**1.68** (29.0 mg, 66% yield, 0.0739 mmol) and γ-methoxy butenolide **1.68** (13.0 mg, 30% yield, 0.0331 mmol).

γ-Methoxy butenolide C15-*epi*-**1.68:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.11 – 6.05 (m, 1H), 5.67 (d, J = 3.6 Hz, 2H), 3.82 (d, J = 0.7 Hz, 1H), 3.73 (s, 3H), 3.63 (t, J = 7.2 Hz, 1H), 3.59 (s, 3H), 2.41 (dt, J = 17.7, 4.6 Hz, 1H), 2.10 (d, J = 13.8 Hz, 1H), 1.98 (dddd, J = 17.6, 9.9, 5.0, 2.4 Hz, 1H), 1.90 – 1.82 (m, 2H), 1.76 (dtd, J = 14.4, 10.0, 4.6 Hz, 1H), 1.70 – 1.64 (m, 1H), 1.59 (dd, J = 10.1, 3.3 Hz, 1H), 1.27 (s, 3H), 1.20 – 1.14 (m, 1H), 1.05 (d, J = 7.2 Hz, 3H), 0.95 (s, 3H), 0.92 (s, 3H). LRMS (ESI) calcd for $C_{22}H_{32}O_6$ $[M+Na]^+$ 415.21, found 415.3

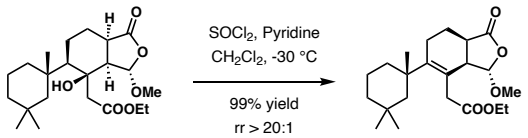
γ-Methoxy butenolide 1.68: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 – 5.70 (m, 1H), 5.70 – 5.65 (m, 1H), 5.64 (s, 1H), 5.59 (dd, J = 10.0, 2.7 Hz, 1H), 3.73 (s, 3H), 3.66 (q, J = 7.1 Hz, 1H), 3.51 (s, 3H), 2.39 – 2.32 (m, 1H), 2.16 (d, J = 13.7 Hz, 1H), 2.09 – 2.01 (m, 1H), 1.91 – 1.82 (m, 3H), 1.73 – 1.64 (m, 2H), 1.22 – 1.16 (m, 6H), 1.13 (dd, J = 13.5, 2.2 Hz, 1H), 0.92 (d, J = 6.8 Hz, 6H). LRMS (ESI) calcd for $C_{22}H_{32}O_6Na$ $[M+Na]^+$ 415.21, found 415.3



1.59 1.60

Tertiary alcohol 1.60. A suspension of γ-methoxy butenolide **1.59** (20.0 mg, 0.0510 mmol) and 20% $Pd(OH)_2/C$ (20.0 mg, 100 wt%) in CH_3OH (1.7 mL) was placed under an atmosphere of H_2 (100 psi) and stirred vigorously at 23 °C for 48 hr. The solid was separated from the solution by filtration with a syringe PTFE filter and the filtrate was concentrated to give a clean sample of tertiary alcohol **1.60** (16.0 mg, 79% yield, 0.0404 mmol) as a single diastereomer which was used without further purification.

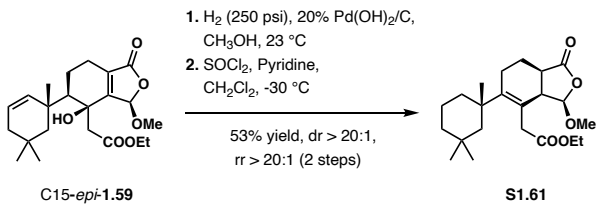
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37 (d, J = 2.4 Hz, 1H), 4.26 – 4.10 (m, 2H), 3.48 (s, 3H), 3.21 (s, 1H), 2.89 (d, J = 17.4 Hz, 1H), 2.86 – 2.80 (m, 1H), 2.75 (d, J = 17.4 Hz, 1H), 2.72 – 2.67 (m, 1H), 2.14 (dt, J = 13.5, 4.5 Hz, 1H), 1.72 (m, 2H), 1.63 (m, 1H), 1.57 (m, 2H), 1.49 – 1.38 (m, 2H), 1.37 – 1.27 (m, 5H), 1.17 (d, J = 13.3 Hz, 1H), 1.09 (s, 3H), 1.01 (m, 2H), 0.96 (s, 3H), 0.85 (s, 3H). LRMS (ESI) calcd for $C_{22}H_{36}O_6Na$ $[M+Na]^+$ 419.51, found 419.3



1.60 1.61

Methoxylactone 1.61. Thionyl chloride (73.0 μL, 1.010 mmol) was added dropwise to a stirring solution of pyridine (0.330 mL, 4.04 mmol) and tertiary alcohol **1.60** (16.0 mg, 0.404 mmol) in CH_2Cl_2 (4.0 mL) at -30 °C and stirred for 2 hr at the same temperature. The reaction was quenched with methanol (41.0 μL, 1.01 mmol) and diluted with hexane (20 mL). The solution was washed with aqueous $NaHSO_4$ (pH = 3, 2x10 mL), brine, dried over Na_2SO_4 and concentrated. The crude material was purified by silica gel chromatography (5% EtOAc/Hex to 7% EtOAc/Hex) to give methoxylactone **1.60** (15.0 mg, 98% yield, 0.0396 mmol) as a single regioisomer.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.03 (d, J = 1.9 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.70 (d, J = 16.8 Hz, 1H), 3.49 (s, 3H), 3.02 (m, 1H), 2.98 (m, 1H), 2.93 (d, J = 16.6 Hz, 1H), 2.24 – 2.12 (m, 2H), 2.07 (dq, J = 12.4, 4.0 Hz, 1H), 1.84 – 1.74 (m, 2H), 1.61 – 1.42 (m, 3H), 1.32 – 1.24 (m, 4H), 1.21 – 1.15 (m, 2H), 1.00 (s, 3H), 0.99 (d, J = 16.6, 1H), 0.85 (s, 3H), 0.78 (s, 3H). LRMS (ESI) calcd for $C_{22}H_{34}O_5Na$ $[M+Na]^+$ 401.23, found 401.3



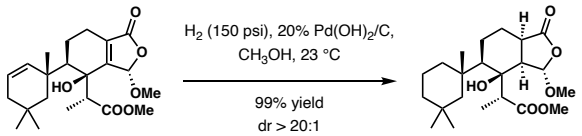
C15-*epi*-**1.59** **S1.61**

Methoxylactone S1.61. A suspension of γ-methoxy butenolide C15-*epi*-**1.59** (32.0 mg, 0.0815 mmol) and 20% $Pd(OH)_2/C$ (32.0 mg, 100 wt%) in CH_3OH (2.5 mL) was placed under an atmosphere of H_2 (250 psi) and stirred vigorously at 23 °C for 48 hr. The solid was separated from the solution by filtration with a syringe PTFE filter and the filtrate was concentrated to give a crude sample of tertiary alcohol as a single diastereomer which was used without further purification.

Thionyl chloride (140.0 µL, 1.96 mmol) was added dropwise to a stirring solution of pyridine (0.630 mL, 7.82 mmol) and the tertiary alcohol from the previous step in CH_2Cl_2 (8.0 mL) at -30 °C and stirred for 2 hr at the same temperature. The reaction was quenched with methanol (80.0 µL, 1.96 mmol) and diluted with hexane (20 mL). The solution was washed with aqueous $NaHSO_4$ (pH = 3, 2x10 mL), brine, dried over Na_2SO_4 and concentrated. The crude material was purified by silica gel chromatography (10% EtOAc/Hex) to give methoxylactone **S1.61** (18.0 mg, 55% yield, 0.0476 mmol) as a single regioisomer and diastereomer over two steps.

^{1}H NMR (600 MHz, cdcl$_3$) δ 5.49 (d, *J* = 6.0 Hz, 1H), 4.19 – 4.14 (q, *J* = 8.0 Hz, 2H), 3.82 (d, *J* = 16.7 Hz, 1H), 3.45 (d, *J* = 0.9 Hz, 3H), 3.31 (dd, *J* = 8.8, 6.3 Hz, 1H), 2.75 (d, *J* = 16.8 Hz, 1H), 2.53 (ddd, *J* = 11.7, 9.0, 5.3 Hz, 1H), 2.32 (dt, *J* = 16.9, 4.5 Hz, 1H), 2.16 – 2.08 (m, 1H), 2.01 – 1.92 (m, 2H), 1.88 (d, *J* = 14.0 Hz, 1H), 1.72 (qd, *J* = 11.9, 4.4 Hz, 1H),

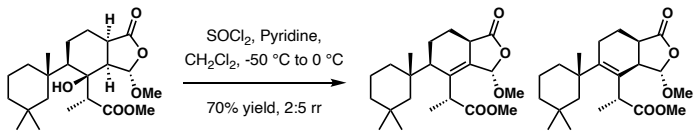
1.52 (dp, J = 9.4, 4.3 Hz, 2H), 1.29 (t, J = 8.0 Hz, 3 H), 1.31 – 1.19 (m, 4H), 1.09 (s, 3H), 0.89 (s, 3H), 0.80 (s, 3H). LRMS (ESI) calcd for $C_{22}H_{34}O_5Na$ $[M+Na]^+$ 401.23, found 401.3



1.68 **1.69**

Tertiary alcohol 1.69. A suspension of γ-methoxy butenolide **1.68** (6.0 mg, 0.0513 mmol) and 20% $Pd(OH)_2/C$ (24.0 mg, 400 wt%) in CH_3OH (2.0 mL) was placed under an atmosphere of H_2 (150 psi) and stirred vigorously at 23 °C for 48 hr. The solid was separated from the solution by filtration with a syringe PTFE filter and the filtrate was concentrated to give a clean sample of tertiary alcohol **1.69** (6.0 mg, 99% yield, 0.0153 mmol) as a single diastereomer which was used without further purification.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.42 (d, J = 4.5 Hz, 1H), 3.81 (s, 1H), 3.76 (s, 3H), 3.52 (s, 3H), 3.15 (q, J = 7.3 Hz, 1H), 2.85 – 2.76 (m, 2H), 2.04 (ddt, J = 14.2, 6.0, 3.2 Hz, 1H), 1.79 – 1.71 (m, 2H), 1.68 – 1.59 (m, 2H), 1.53 – 1.42 (m, 2H), 1.35 – 1.22 (m, 4H), 1.23 (d, J = 8.9 Hz, 3H), 1.17 (s, 3H), 1.15 (m, 1H), 1.07 – 0.97 (m, 1H), 0.98 (s, 3H), 0.88 (s, 3H). LRMS (ESI) calcd for $C_{22}H_{36}O_6Na$ $[M+Na]^+$ 419.24, found 419.

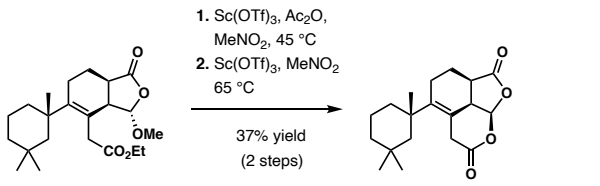


1.69 *reg*-**1.70** **1.70**

Methoxylactones 1.70 and *reg*-1.70. Thionyl chloride (100.0 µL, 1.378 mmol) was added dropwise to a stirring solution of pyridine (0.450 mL, 5.514 mmol) and the tertiary alcohol **1.69** (6.0 mg, 0.0151 mmol) in CH_2Cl_2 (5.0 mL) at -50 °C and stirred for 1 hr at the same temperature. The reaction was then warmed to 0 °C and stirred for 1 hr. The reaction was quenched with methanol (56.0 µL, 1.38 mmol) and diluted with 1:1 EtOAc/hexane (20 mL). The solution was washed with aqueous $NaHSO_4$ (pH = 3, 2x10 mL), brine, dried over Na_2SO_4 and concentrated. The crude material was purified by silica gel chromatography (5% EtOAc/Hex to 10% EtOAc/Hex) to give methoxylactones **1.70** and *reg*-**1.70** (4.0 mg, 70% yield, 0.0106 mmol) as a 5:2 mixture of regioisomers, favoring **1.70**.

Methoxylactone *reg*-**1.70** (selected signals): ^{1}HNMR (600 MHz, $CDCl_3$) δ 5.75 (m, 1H), 3.76 (s, 3H), 3.43 (s, 3H), 3.27 (q, J = 7.5 Hz, 1H), 1.31 (d, J = 7.4 Hz, 3H), 1.04 (s, 3H), 0.96 (s, 3H), 0.87 (s, 3H). LRMS (ESI) calcd for $C_{22}H_{34}O_5Na$ $[M+Na]^+$ 401.23, found 401.2.

Methoxylactone 1.70 (selected signals): ^{1}HNMR (600 MHz, $CDCl_3$) δ 5.01 (d, J = 3.5 Hz, 1H), 4.27 (q, J = 7.4 Hz, 1H), 3.70 (s, 1H), 3.42 (s, 1H), 2.97 (dd, J = 3.5 Hz, 10.0 Hz, 1H), 2.89 (dddd, J = 10.0, 7.3, 2.6, 1.3 Hz, 1H), 1.20 (d, J = 7.4 Hz, 3H), 1.06 (s, 3H), 0.88 (s, 3H), 0.88 (s, 3H). LRMS (ESI) calcd for $C_{22}H_{34}O_5Na$ $[M+Na]^+$ 401.23, found 401.2.



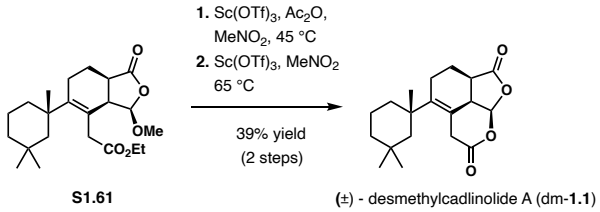
1.61 (±) - desmethylcadlinolide A (dm-**1.1**)

(±)-Desmethylcadlinolide A (dm-1.1): $Sc(OTf)_3$ (33.0 mg, 0.0677 mmol) was added to a stirring solution of methoxylactone **1.61** (16.0 mg, 0.0423 mmol) and Ac_2O (0.20 mL, 2.12

mmol) in nitromethane (5.3 mL) at 23 °C. The reaction mixture was warmed to 45 °C and stirred for 1.5 hr. The mixture was cooled to 23 °C and concentrated. The crude residue was redissolved in EtOAc/Hexane (3:7 v/v, 10 mL) and washed with H_2O (2x 10 mL), brine, dried over Na_2SO_4 and concentrated.

The crude product was redissolved in nitromethane (5.3 mL) and $Sc(OTf)_3$ (33.0 mg, 0.0677 mmol) was added. The reaction mixture was heated to 65 °C for 3 hr. The mixture was cooled to 23 °C and concentrated. The crude product was isolated by silica gel chromatography to give (±)-desmethylcadlinolide A dm-**1.1** (5.0 mg, 37% yield, 0.0157 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.12 (d, J = 5.2 Hz, 1H), 4.17 (d, J = 17.1 Hz, 1H), 3.20 (dp, J = 7.3, 1.9 Hz, 1H), 3.08 (dt, J = 7.1, 4.4 Hz, 1H), 2.92 (dtd, J = 17.1, 2.8, 1.4 Hz, 1H), 2.39 – 2.31 (m, 1H), 2.23 – 2.11 (m, 2H), 1.87 (dt, J = 9.0, 5.1 Hz, 1H), 1.75 (d, J = 14.0 Hz, 1H), 1.72 – 1.66 (m, 1H), 1.61 – 1.45 (m, 2H), 1.34 – 1.16 (m, 4H), 1.14 (s, 3H), 0.92 (s, 3H), 0.77 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.11, 166.31, 148.50, 114.02, 99.78, 50.01, 41.03, 40.25, 39.64, 39.31, 38.16, 37.86, 31.57, 31.54, 30.89, 28.88, 23.43, 20.49, 20.27. LRMS (ESI) calcd for $C_{19}H_{25}O_4$ $[M-H]^-$ 317.18 and $C_{20}H_{30}NaO_5$ $[M+CH_3OH+Na]^+$ 373.2, found 317.3 and 373.3.

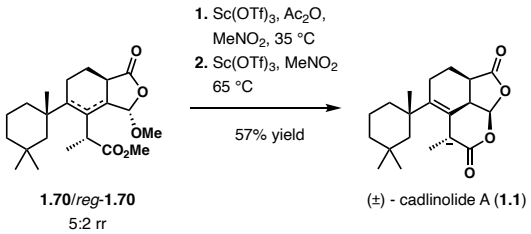


S1.61 (±) - desmethylcadlinolide A (dm-**1.1**)

(±)-Desmethylcadlinolide A (dm-1.1): $Sc(OTf)_3$ (5.0 mg, 0.00102 mmol) was added to a stirring solution of methoxylactone **S1.61** (3.0 mg, 0.0080 mmol) and Ac_2O (15.0 µL, 0.15 mmol) in nitromethane (1.0 mL) at 23 °C. The reaction mixture was warmed to 45 °C and stirred for 1.5 hr. The mixture was cooled to 23 °C and diluted with EtOAc (20 mL) and washed with H_2O (2x 10 mL), brine, dried over Na_2SO_4 and concentrated.

The crude product was redissolved in nitromethane (1.0 mL) and $Sc(OTf)_3$ (5.0 mg, 0.0102 mmol) was added. The reaction mixture was heated to 45 °C for 1 hr, then 65 °C for 3 hr. The mixture was cooled to 23 °C and concentrated. The crude product was isolated by silica gel chromatography to give (±)-desmethylcadlinolide A dm-**1.1**(1.0 mg, 39% yield, 0.00314 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.12 (d, J = 5.2 Hz, 1H), 4.17 (d, J = 17.1 Hz, 1H), 3.20 (dp, J = 7.3, 1.9 Hz, 1H), 3.08 (dt, J = 7.1, 4.4 Hz, 1H), 2.92 (dtd, J = 17.1, 2.8, 1.4 Hz, 1H), 2.39 – 2.31 (m, 1H), 2.23 – 2.11 (m, 2H), 1.87 (dt, J = 9.0, 5.1 Hz, 1H), 1.75 (d, J = 14.0 Hz, 1H), 1.72 – 1.66 (m, 1H), 1.61 – 1.45 (m, 2H), 1.34 – 1.16 (m, 4H), 1.14 (s, 3H), 0.92 (s, 3H), 0.77 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.11, 166.31, 148.50, 114.02, 99.78, 50.01, 41.03, 40.25, 39.64, 39.31, 38.16, 37.86, 31.57, 31.54, 30.89, 28.88, 23.43, 20.49, 20.27. LRMS (ESI) calcd for $C_{19}H_{25}O_4$ $[M-H]^-$ 317.18 and $C_{20}H_{30}NaO_5$ $[M+CH_3OH+Na]^+$ 373.2, found 317.3 and 373.3.

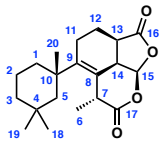


(±)-cadlinolide A (1.1): Ac_2O (0.38 mL, 3.98 mmol) was added to a stirring solution of acetals **1.70**/*reg*-**1.70** (4.0 mg, 0.0106 mmol) and $Sc(OTf)_3$ (26 mg, 0.0530 mmol) in nitromethane (2.0 mL) and heated to 35°C for 3 hr. The reaction mixture was then cooled to 23 °C and diluted with EtOAc/Hex (1:1 v/v, 10 mL). The organic mixture was washed with water (2x 5 mL), brine, dried over Na_2SO_4 and concentrated.

The crude mixture was resuspended in nitromethane (2.0 mL). $Sc(OTf)_3$ (26 mg, 0.0530 mmol) was added to the solution and it was heated to 65°C for 20 min. The reaction mixture was then concentrated and the title product was isolated by silica gel chromatography (20% EtOAc/Hexane to 30% EtOAc/Hexane) to give (±)-cadlinolide A **1.1** (2.0 mg, 57% yield, 0.006 mmol)

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.13 (d, J = 5.2 Hz, 1H), 4.31 (q, J = 7.4 Hz, 1H), 3.43 (td, J = 5.5, 2.7 Hz, 1H), 3.08 (dt, J = 8.4, 4.6 Hz, 1H), 2.36 (d, J = 17.9 Hz, 1H), 2.26 – 2.18 (m, 1H), 2.12 (dq, J = 13.6, 4.9 Hz, 1H), 1.88 (d, J = 14.4 Hz, 1H), 1.75 (d, J = 14.6 Hz, 1H), 1.70 (m, 1H), 1.61 – 1.50 (m, 2H), 1.49 (d, J = 7.4 Hz, 3H), 1.31 – 1.14 (m, 4H), 1.14 (s, 3H), 0.92 (s, 3H), 0.77 (s, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 173.27, 170.12, 148.14, 118.87, 99.58, 50.50, 40.21, 40.13, 39.49, 39.40, 38.49, 35.49, 32.09, 31.64, 29.86, 28.56, 23.55, 20.87, 20.27, 17.13. LRMS (ESI) calcd for $C_{20}H_{27}O_4$ $[M-H]^-$ 331.19 and $C_{20}H_{28}ClO_4$ $[M+Cl]^-$ 367.17 and $C_{22}H_{31}NNaO_4$ $[M+CH_3CN+Na]^+$ 396.22, found 331.1 and 367.1 and 396.0

Table 3. Comparison of ^{1}HNMR data of natural and synthetic cadlinolide A **1.1**

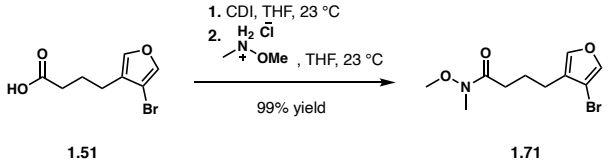


cadlinolide A (**1.1**)

	Natural 1.1 (400 MHz)[71]		Synthetic 1.1 (600 MHz)	
proton	**δ, m, J**	**NOE**	**δ, m, J**	**NOE**
H5	1.72		1.75	
H5'	1.78		1.88	
Me6	1.48, d, *J* = 7.4 Hz	H7, H14, H15	1.49, d, *J* = 7.4 Hz	H7, H14, H15
H7	4.28, q, *J* = 7.4 Hz		4.31, q, *J* = 7.4 Hz	Me20
H11	2.35, bd, *J* = 7.9 Hz		2.36, d, *J* = 17.9 Hz	
H11'	2.19, m		2.20, m	
H12	2.06, m		2.12, m	
H12'	1.69, m		1.70, m	
H13	3.12, dt, *J* = 7.9, 4.6 Hz	H14, H15	3.08 dt, *J* = 8.4, 4.6 Hz	H14, H15,
H14	3.48, m	H13, H15, Me6	3.43, m	H13, H15, Me6
H15	6.16, d, *J* = 5.3 Hz	H13, H14	6.13, d, *J* = 5.2 Hz	H13, H14
H18	0.77, s		0.77, s	
H19	0.92, s		0.92, s	
H20	1.13, s		1.14, s	

Table 4. Comparison of ^{13}CNMR data of natural and synthetic cadlinolide A **1.1**

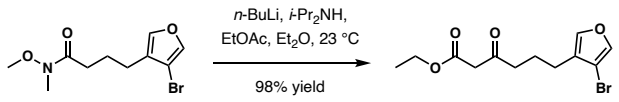
Natural 1.1 (75 MHz)[40]	Synthetic 1.1 (125 MHz)	Difference
16.68	17.13	-0.45
19.94	20.27	-0.33
20.57	20.87	-0.3
23.25	23.55	-0.3
28.14	28.56	-0.42
31.31	29.86	1.45
31.38	31.64	-0.26
31.89	32.09	-0.2
35.07	35.49	-0.42
38.2	38.49	-0.29
38.9	39.4	-0.5
-	39.49	-
39.19	40.13	-0.94
39.9	40.21	-0.31
50.15	50.5	-0.35
99.43	99.58	-0.15
118.85	118.87	-0.02
147.29	148.14	-0.85
169.89	170.12	-0.23
173.26	173.27	-0.01



1.51 1.71

Weinreb Amide 1.71. 1,1'-carbonyl diimidazole (0.904 g, 5.58 mmol) was added in one portion to a solution of **1.51** (1.000 g, 4.291 mmol) in CH_2Cl_2 (11 mL). After 1 hour, *N*,*O*-dimethyl hydroxylamine hydrochloride (0.837 g, 8.58 mmol) was added in one portion. The solution was stirred overnight and quenched at 0 ºC with 1 M HCl (40.0 mL) and stirred for 20 minutes. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x

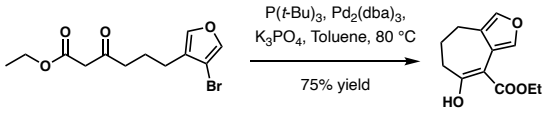
30.0 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by silica gel chromatography (40% ethyl acetate/ hexanes) to afford the Weinreb amide **1.71** (1.181 g, 99% yield, 4.277 mmol) as a colorless oil. ^{1}H NMR (500 MHz, CDCl3) δ 7.38 (d, J = 1.7 Hz, 1H), 7.21 (s, 1H), 3.65 (s, 3H), 3.17 (s, 3H), 2.44 (m, 4H), 1.91 (m, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 174.1, 140.9, 139.7, 124.7, 102.6, 61.2, 32.1, 31.1, 23.7, 23.3.



1.71 1.72

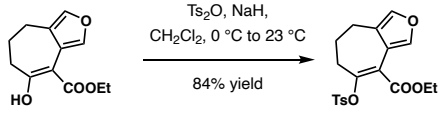
Beta-keto Ester 1.72. *n*-BuLi (2.5 M, 2.71 mL, 6.78 mmol) was added dropwise to a stirring solution of diisopropylamine (1.00 mL, 7.05 mmol) in diethyl ether (22.0 mL) at -10 ºC. After 20 minutes, the solution was cooled to -78 ºC and ethyl acetate (0.690 mL, 7.05 mmol) was added dropwise over 10 minutes and stirred for a further 30 minutes at this temperature. A solution of **1.71** (0.748 g, 2.71 mmol) in diethyl ether (6.0 mL) was added dropwise to the reaction mixture at -78 ºC and stirred for 1 hour at this temperature. The solution was warmed to 0 ºC and stirred for 1 hour. The solution was quenched at 0 ºC with saturated aqueous ammonium chloride (15.0 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by silica gel chromatography (10% EtOAc/hexanes) to afford the beta keto ester **1.72** (0.802 g, 98% yield, 2.64 mmol, 14:1 keto:enol) as a colorless oil.

Beta-keto ester 1.72 (keto form): ^{1}H NMR (500 MHz, CDCl3) δ 7.38 (d, J = 1.8 Hz, 1H), 7.19 (s, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.42 (s, 2H), 2.58 (t, J = 7.2 Hz, 2H), 2.43 – 2.38 (m, 2H), 1.88 (p, J = 7.3 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 202.3, 167.1, 141.0, 139.7, 124.3, 102.5, 61.4, 49.3, 42.0, 22.8, 22.5, 14.1.



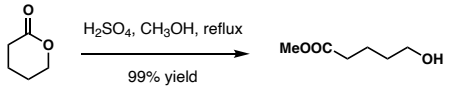
1.72 1.73

Cycle 1.73. $Pd_2(dba)_3$•$CHCl_3$ (8.6 mg, 0.0083 mmol), P(*t*-Bu)$_3$ (14.0 mg, 0.066 mmol), and K_3PO_4 (210.0 mg, 0.991 mmol) were combined under an inert atmosphere and a solution of **1.72** (100.0 mg, 0.330 mmol) in toluene (5.0 mL, degassed by freeze-pump-thaw) was added to the vial. The vial was sealed and heated to 80 °C for 4 hours. The suspension was cooled to room temperature, diluted with ether (5.0 mL), and 1.00 mL of 1M aqueous HCl was added. The solution was extracted with ether (3 x 3 mL), dried over sodium sulfate, and concentrated. The crude oil was purified via silica gel chromatography (5% ethyl acetate/hexanes) to afford **1.73** (54 mg, 75% yield, 0.24 mmol) as a 1:10 (keto:enol) mixture of tautomers. ^{1}H NMR (500 MHz, CDCl3) δ 12.95 (s, 1H), 7.40 (d, J = 1.6 Hz, 1H), 7.21 (d, J = 0.8 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 2.58 – 2.51 (m, 2H), 2.39 (td, J = 7.0, 0.9 Hz, 2H), 2.08 (p, J = 7.2 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 140.4, 137.3, 123.3, 119.1, 95.2, 60.8, 32.2, 27.1, 20.3, 14.2.



1.73 1.74

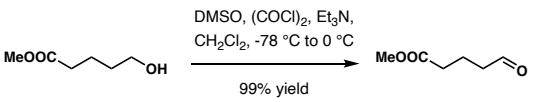
Sulfonate 1.74. Sodium hydride (60% wt in mineral oil, 7.0 mg, 0.175 mmol) was added to a solution of **1.73** (12.0 mg, 0.054 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C. After 30 minutes, Ts_2O (57.0 mg, 0.175 mmol) was added. The suspension was stirred for 30 minutes and quenched with saturated aqueous ammonium chloride (2.0 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by silica gel chromatography (10% EtOAc/hexanes) to afford the enol tosylate **1.74** (16 mg, 84% yield, 0.0425 mmol) as a white solid. ^{1}H NMR (500 MHz, CDCl3) δ 7.84 (d, J = 8.4 Hz, 2H), 7.35 (m, 3H), 7.16 (d, J = 1.5 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 2.76 – 2.70 (m, 2H), 2.67 – 2.61 (m, 2H), 2.46 (s, 3H), 1.90 (p, J = 6.1 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 165.8, 147.8, 145.2, 142.6, 139.1, 134.2, 129.7, 128.0, 123.7, 120.1, 117.5, 61.6, 35.2, 23.8, 23.5, 21.7, 13.9.



3.18 S3.19

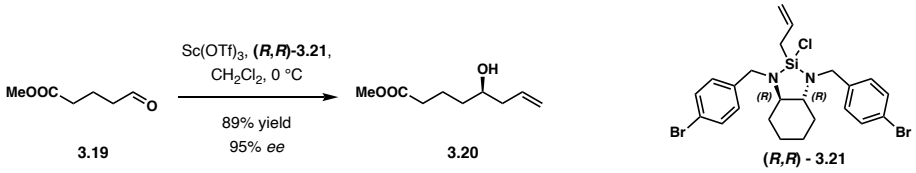
Methyl 5-hydroxypentanoate (S3.19): δ-Valerolactone (2.15 g, 21.6 mmol) was dissolved in methanol (43.0 mL) and sulfuric acid (0.13 mL, 2.37 mmol) and heated at reflux for 12 h. The reaction mixture was then removed from heat and allowed to cool to room temperature. Solid sodium bicarbonate (0.50 g, 5.95 mmol) was added and the mixture was stirred for 10 minutes. Solids were removed by filtration. After the filtrate was concentrated to half of the original volume it was diluted with ethyl acetate (50 mL) and washed with water (25 mL). The organic phase was separated and the aqueous solution was extracted with ethyl acetate (3×25 mL). The combined organic phase was washed with water (2×30 mL), dried over Na_2SO_4 and concentrated to dryness to produce methyl 5-hydroxypentanoate **S3.19** as a colorless oil (2.82 g, 21.4 mmol, 99% yield) which was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.68 (s, 3H), 3.66 (t, J = 6.5 Hz, 2H), 2.36 (t, J = 7.5 Hz, 2H), 1.73 (m, 2H), 1.60 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 174.13, 62.23, 51.53, 33.63, 32.03, 21.06. LRMS-APCI (m/z): $[M+H]^+$ calcd for $C_6H_{13}O_3^+$, 133.1; found, 133.2.



S3.19 3.19

Methyl 5-oxopentanoate (3.19): Dimethyl sulfoxide (1.90 mL, 26.0 mmol) was added dropwise to a solution of oxalyl chloride (1.10 mL, 12.8 mmol) in dichloromethane (60 mL) at -78 °C over 30 min. The resulting mixture was stirred for 20 min before a solution of methyl 5-hydroxypentanoate **S3.19** (1.28 g, 9.70 mmol) in dichloromethane (9.0 mL) was added dropwise over 20 min at -78 °C. The mixture was stirred for an additional 20 min and triethylamine (5.6 mL, 40.0 mmol) was added dropwise over 15 min. After 10 min the reaction mixture was transferred to an ice bath and stirred at 0 °C until complete conversion was observed by TLC. The reaction mixture was then poured into water (60 mL), the organic phase was separated and the aqueous solution was extracted with dichloromethane (4×40 mL). The combined organic phase was washed with water (2×80 mL) and brine (2×80 mL), dried over Na_2SO_4 and concentrated to dryness to give a pale-yellow oil **3.19** (1.25 g, 9.60 mmol, 99% yield) which was used immediately without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.77 (t, J = 1.5 Hz, 1H), 3.67 (s, 3H), 2.53 (dt, J = 1.5, 7 Hz, 2H), 2.37 (t, J = 7 Hz, 2H), 1.95 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 201.39, 173.26, 51.56, 42.85, 32.87, 17.28. HRMS-EI (m/z): $[M+H]^+$ calcd for $C_6H_{11}O_3$, 131.0708; found, 131.0726.



(+)-Methyl (5*R*)-5-hydroxyoct-7-enoate (3.20): A solution of Leighton's allylsilane[72] **3.21** (0.961 g, 1.7 mmol) in dichloromethane (2.4 mL) was added dropwise to a stirring solution of methyl 5-oxopentanoate **3.19** (128 mg, 0.98 mmol) in dichloromethane (14.4 mL) at 0 °C. Scandium (III) triflate (355 mg, 0.72 mmol) was then added to the stirring reaction

mixture in one portion. After stirring for 1 hour at ambient temperature complete disappearance of starting material was observed by TLC, and the reaction was quenched by addition of tetrabutylammonium fluoride (75 mg, 2.88 mmol) solution in tetrahydrofuran (2.88 mL). Then the reaction mixture was stirred for 1 h followed by direct purification by column chromatography (30% EtOAc in hexanes) to produce the product as a colorless oil **3.20** (150 mg, 0.872 mmol, 89% yield). $[\alpha]_D^{21}$ +2.3 (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.79 (m, 1H), 5.10 (m, 2H), 3.64 (s, 3H), 3.62 (m, 1H), 2.32 (t, *J* = 7 Hz, 2H), 2.26 (m, 1H), 2.13 (m, 1H), 1.90 (d, *J* = 5 Hz, 1H), 1.77 (m, 1H), 1.68 (m, 1H), 1.47 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm): 174.07, 134.62, 118.07, 70.11, 51.47, 41.89, 35.99, 33.79, 20.98. HRMS-EI (m/z): $[M+H]^+$ calcd for $C_9H_{17}O_3$, 173.1178; found, 173.1165.

In order to determine the enantiopurity of (+)-methyl (5R)-5-hydroxyoct-7-enoate **3.20** by HPLC/UV, benzoyl chloride (30 μL, 0.26 mmol) was added dropwise to a solution of alcohol **3.20** (30 mg, 0.18 mmol) and pyridine (30 μL, 0.37 mmol) in dichloromethane (0.6 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and an additional hour at room temperature. After TLC showed complete consumption of the starting material, the reaction mixture was diluted with dichloromethane (10 mL) and washed with 1 M HCl (10 mL). The organic layer was separated and the aqueous solution was extracted with dichloromethane (3×7 mL). The combined organic phase was washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated to dryness. The crude product was purified by column chromatography (10% EtOAc in hexanes) to give corresponding benzoate **S3.20** of alcohol **3.20** as a pale-yellow oil (30.0 mg, 60% yield, 0.11 mmol). $[\alpha]_D^{21}$ +21.3 (*c* 0.20, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.03 (d, *J* = 6 Hz, 2H), 7.55 (t, *J* = 6 Hz, 1H), 7.43 (t, *J* = 6 Hz, 2H), 5.81 (dddd, *J* = 7, 7, 10, 17 Hz, 1H), 5.18 (m, 1H), 5.11 (m, 1H), 5.07 (m, 1H),

3.65 (m, 3H), 2.46 (t, J = 6.5 Hz, 2H), 2.35 (dd, J = 5, 7.5 Hz, 2H), 7.73 (m, 4H) . ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 173.64, 166.09, 133.33, 132.80, 130.48, 129.51, 128.28, 117.98, 73.37, 51.47, 38.54, 33.66, 32.94, 20.70. The enantiopurity of the material was determined by HPLC analysis. [Chiralcel ® AD-H; 1% *i*-PrOH- Hexanes; flow rate = 1 mL/ min; detection at 215 nm; t_1 = 23.36 min. (major), t_2 = 21.81 min. (minor)].

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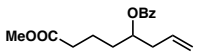

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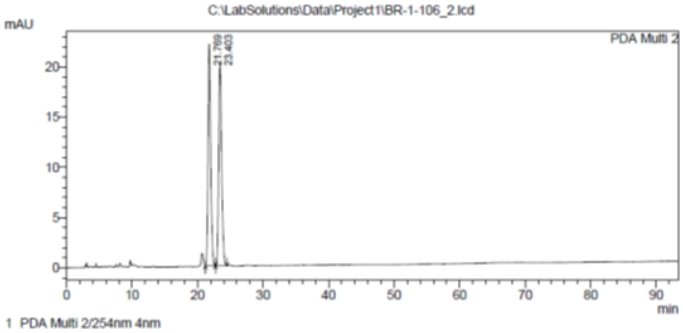

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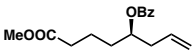

S3.20

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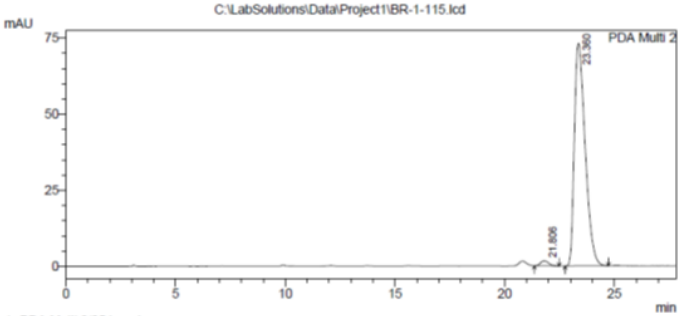

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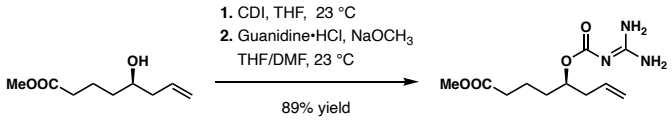
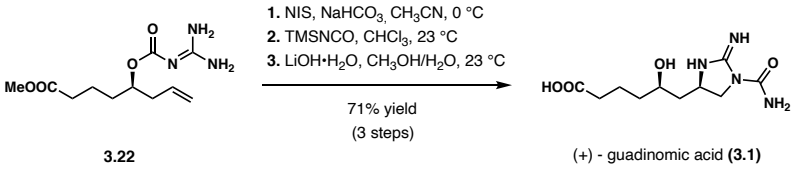


3.20 3.22

(+)-Methyl (5*R*)-5-(((diaminomethylene)carbamoyl)oxy)oct-7-enoate) (3.22): To a solution of methyl (5*R*)-5-hydroxyoct-7-enoate **3.20** (200 mg, 1.16 mmol) in tetrahydrofuran (4.0 mL), 1,1'-carbonyldiimidazole (227 mg, 1.40 mmol) was added at ambient temperature and the reaction was stirred overnight to prepare corresponding N-alkoxycarbonyl imidazole derivative. Guanidine hydrochloride (0.46 g, 4.8 mmol) was added to a freshly prepared solution of sodium methoxide obtained by dissolving 110 mg (4.8 mmol) of sodium in dry methanol (3.6 mL). The reaction mixture was stirred for 10 min and concentrated to dryness under reduced pressure. The material was dried under vacuum for 10 min and dissolved in 8.2 mL of DMF. The crude solution of N-alkoxycarbonyl imidazole in THF obtained in the first step was added dropwise over 10 min to the solution of guanidine in DMF. The reaction was stirred for an additional 10 min and poured into 60 mL of water. The product was extracted with EtOAc (4×30 mL). The combined organic phase was sequentially washed with water (2×60 mL), saturated aqueous ammonium chloride (2×60 mL) and brine (60 mL), then dried over Na_2SO_4 and the organic solvent was removed under reduced pressure. The crude product was subjected to column chromatography (5% MeOH in dichloromethane → 10% MeOH in dichloromethane) to deliver the product **3.22** (267 mg, 1.04 mmol, 89% yield) as a colorless oil. $[\alpha]_D^{22}$ +11.4 (*c* 0.43, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.74 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H), 5.06 (m, 1H), 5.03 (m, 1H), 4.73 (m, 1H), 3.65 (s, 3 H), 2.32 (m, 4 H), 1.69 (m, 1H), 1.60 (m, 1H), 1.55 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 174.3, 161.8,

161.7, 133.6, 117.7, 73.3, 51.6, 38.7, 33.5, 33.0, 20.6. HRMS-EI (m/z): $[M+H]^+$ calcd for $C_{11}H_{20}N_3O_4$, 258.1454; found, 258.1473.



(+)-Guadinomic acid (3.1). A solution of compound **3.22** (48 mg, 0.187 mmol) in 3.7 mL of acetonitrile was added to a 10 mL round bottom flask equipped with a magnetic stirring bar and an argon inlet adapter. Sodium bicarbonate (157 mg, 1.90 mmol) was added and the mixture was cooled to 0 °C before freshly recrystallized N-iodosuccinimide (88 mg, 0.39 mmol) was added in one portion. The heterogeneous mixture was vigorously stirred for 5 h followed by quench with 10% aqueous sodium sulfite (300.0 mL). The crude product was extracted with EtOAc (30 mL). The organic layer was separated and concentrated to dryness under reduced pressure. The residue was dissolved in ethyl acetate (30 mL) and washed with the same sodium sulfite solution used previously. The organic layer was separated and aqueous phase was additionally extracted with ethyl acetate (3×15 mL). The combined organic phase was dried over Na_2SO_4 and concentrated to dryness under reduced pressure to give the crude product as a yellow solid that was used in the next step without further purification.

The material obtained in the previous step (**3.23**) was dissolved in dry $CDCl_3$ (2.0 mL) and trimethylsilyl isocyanate (24.0 μL, 0.19 mmol) was titrated into the solution in 6 μL increments and monitored by ^1H NMR. This process typically took 3 hours and required a total of 1 equivalent of isocyanate. When complete disappearance of starting material was

observed by ^{1}H NMR, a saturated solution of brine (2 mL) was added and the mixture was stirred for 15 minutes. The product was extracted with dichloromethane (2×10 mL). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated to dryness under reduced pressure to give a crude product **3.26** as a white solid which was submitted to hydrolysis without purification.

A solution of lithium hydroxide monohydrate (12.0 mg, 0.29 mmol) was added in the solution of compound **3.26** in a mixture of methanol/water (0.5 mL, 1:1, v/v). The reaction mixture was stirred vigorously for 2 hours at room temperature. The basic solution was then neutralized with trifluoroacetic acid, and the product was directly isolated by column chromatography on C18 reverse-phase silica gel (100% H_2O) to provide (+)-guadinomic acid **3.1** as a white solid (35.0 mg, 71% yield, 0.14 mmol). ^{1}H and ^{13}C NMR data for obtained (+)-guadinomic acid **3.1** are in full accordance with those reported in the literature.[73]

$[\alpha]_D^{23}$ +24.3 (*c* 0.2, CH_3OH). ^{1}H NMR (500 MHz, D_2O) δ (ppm): 4.25 (m, 2H), 3.78 (m, 2H), 2.26 (t, *J* = 7 Hz, 2H), 1.83 (m, 2H), 1.68 (m, 1H), 1.58 (m, 1H), 1.49 (m, 2H). ^{13}C NMR (126 MHz, D_2O) δ (ppm): 177.5, 171.9, 149.5, 135.8, 129.4, 128.9, 128.8, 128.1, 124.4, 123.1, 122.4, 121.0, 119.3, 115.2, 83.6, 56.1, 51.4, 37.8, 35.3, 28.2. HRMS-EI (m/z): $[M+H]^+$ calcd for $C_{10}H_{19}N_4O_4$, 259.1406; found, 259.1428.

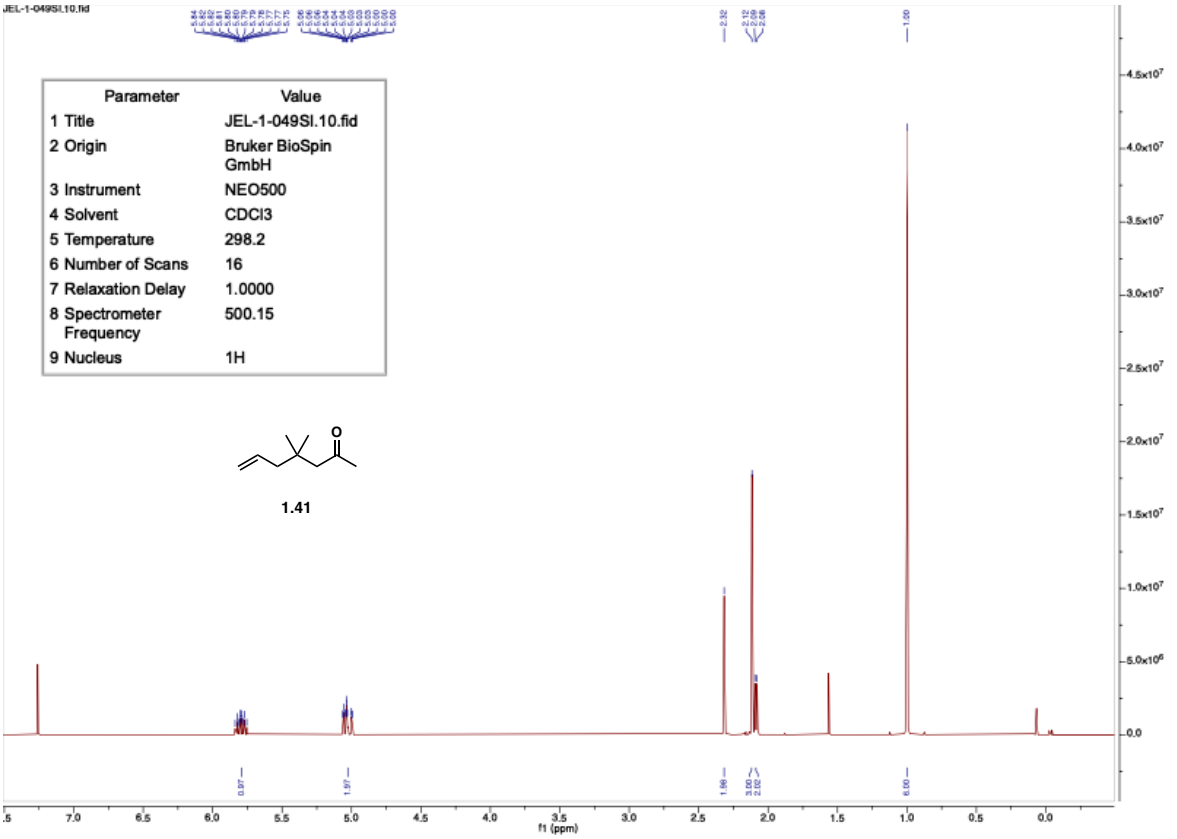
References

[71] (a) Tischler, M.; Andersen, R. J. *J. Org. Chem.* **1991**, *56*, 42-47. (b) Tischler, M. Terpenoids. From the marine sponge Aplysilla glacialis and the nudibranch Cadlina luteomarginata. M.Sc. Thesis, University of British Columbia, December 1989.

[72] Kim, H.; Ho, S.; Leighton, J. L. *J. Am. Chem. Soc.* **2011**, *133*, 6517-6520.

[73] Tsuchiya, S.; Sunazuka, T.; Hirose, T.; Mori, R.; Tanaka, T.; Iwatsuki, M.; Omura, S. *Org. Lett.* **2006,** *8*, 5577-5580.

^{1}H NMR and ^{13}C NMR Spectra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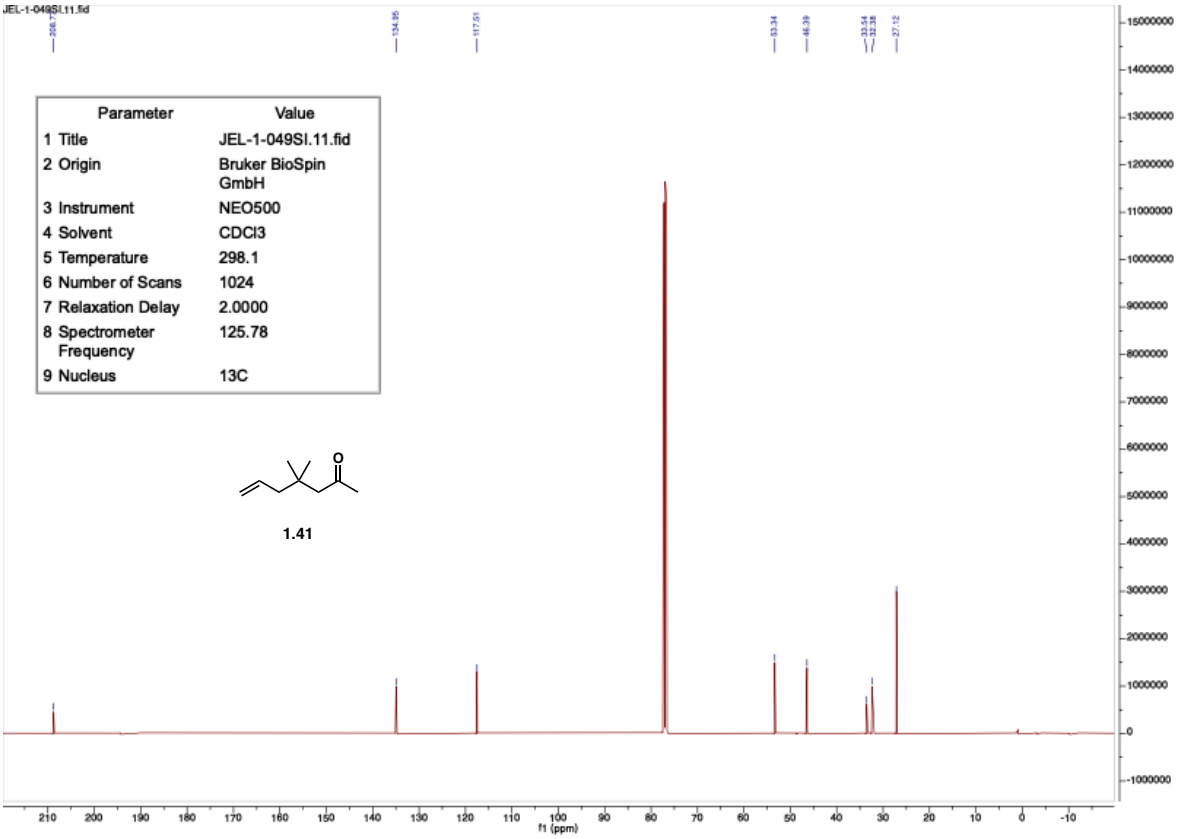
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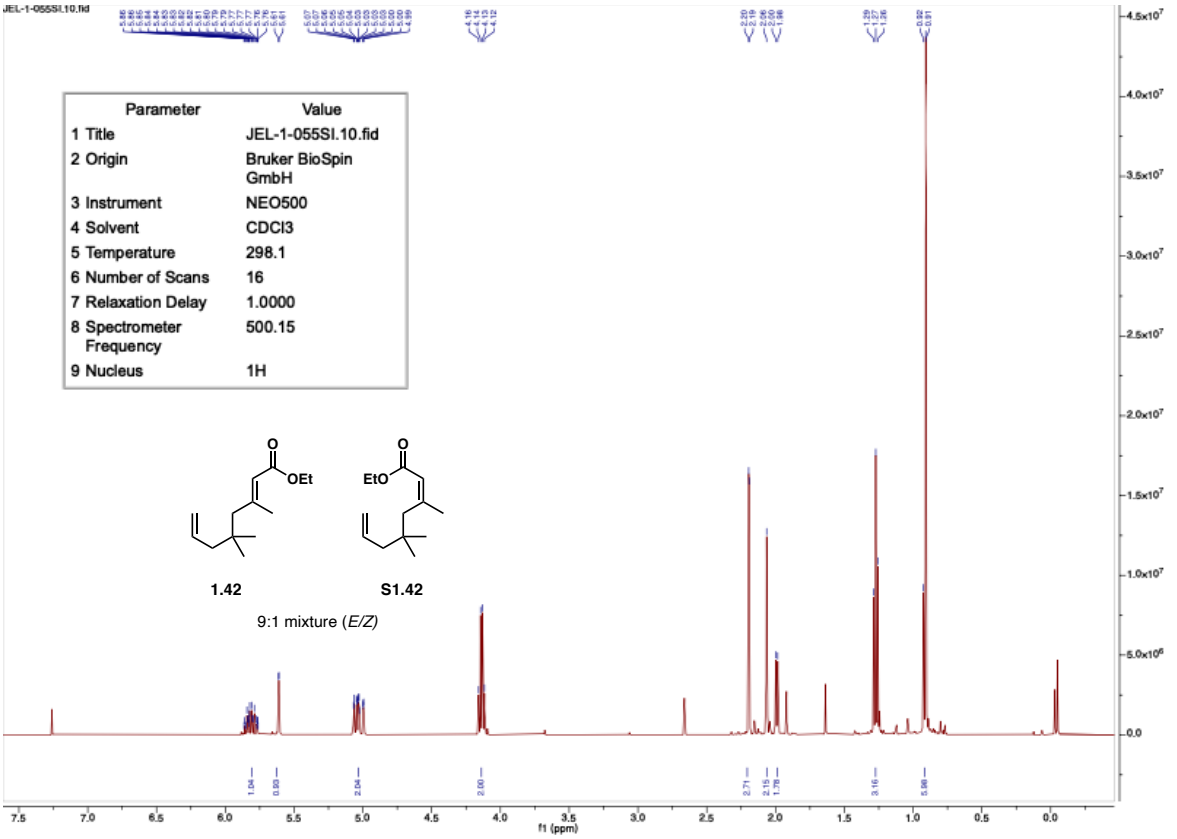
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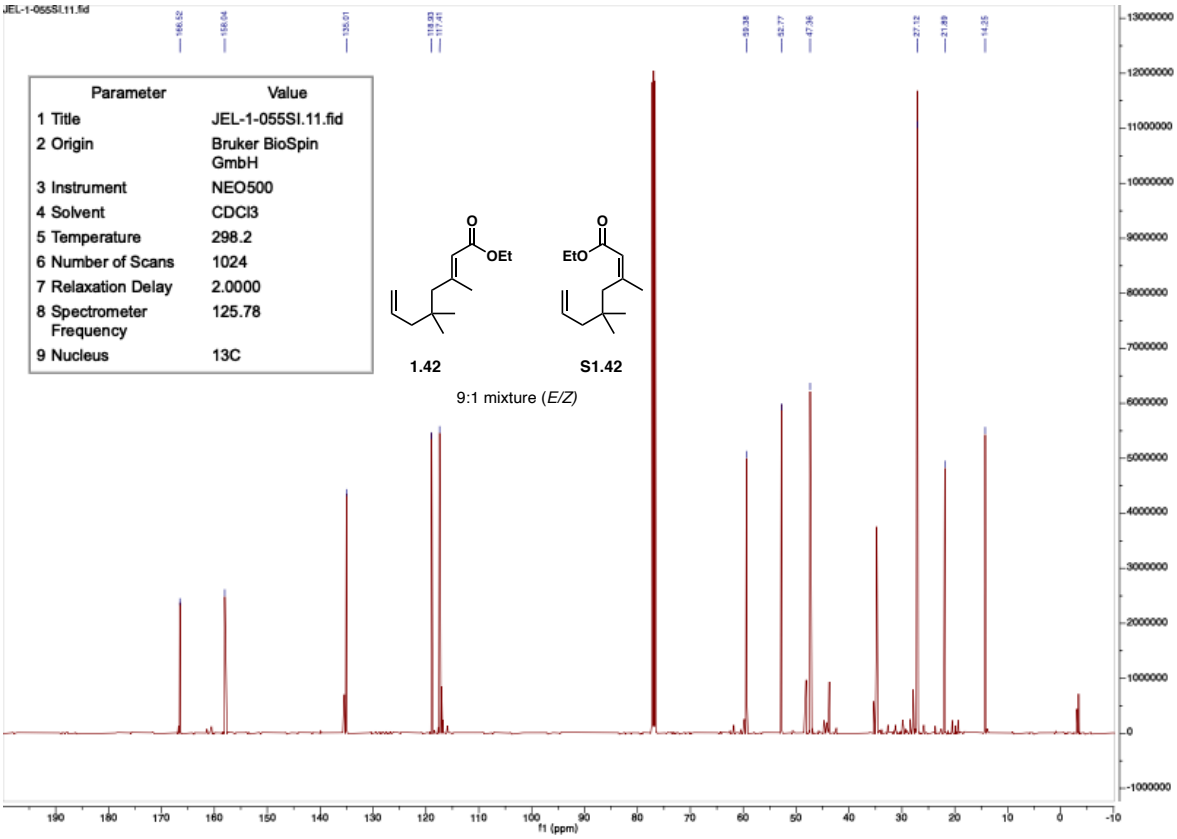
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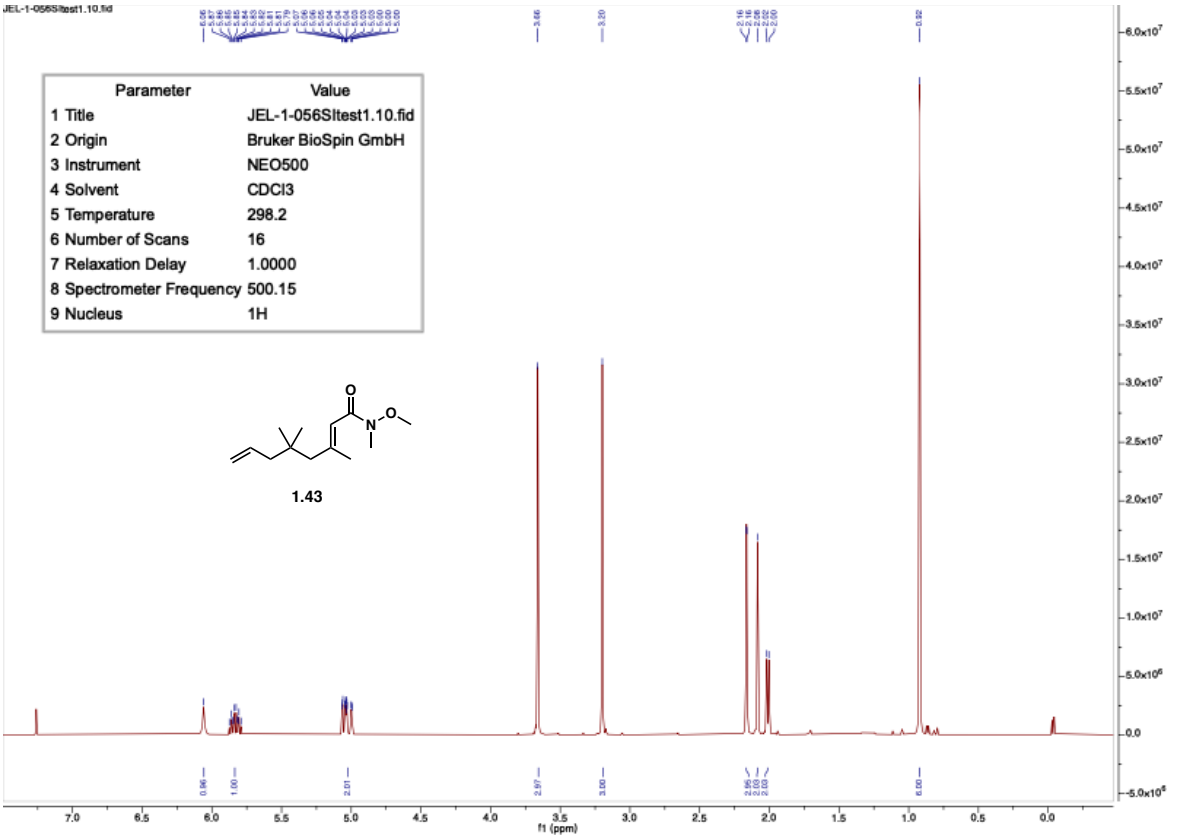
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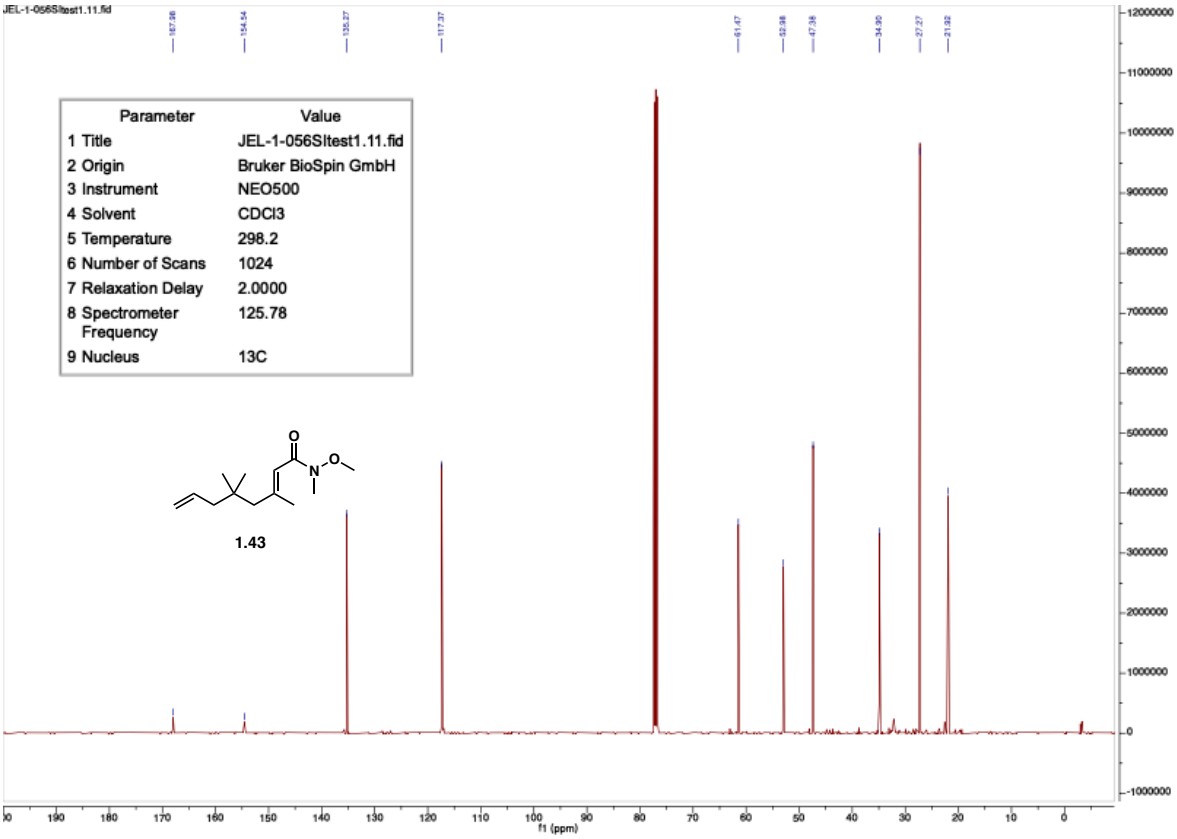
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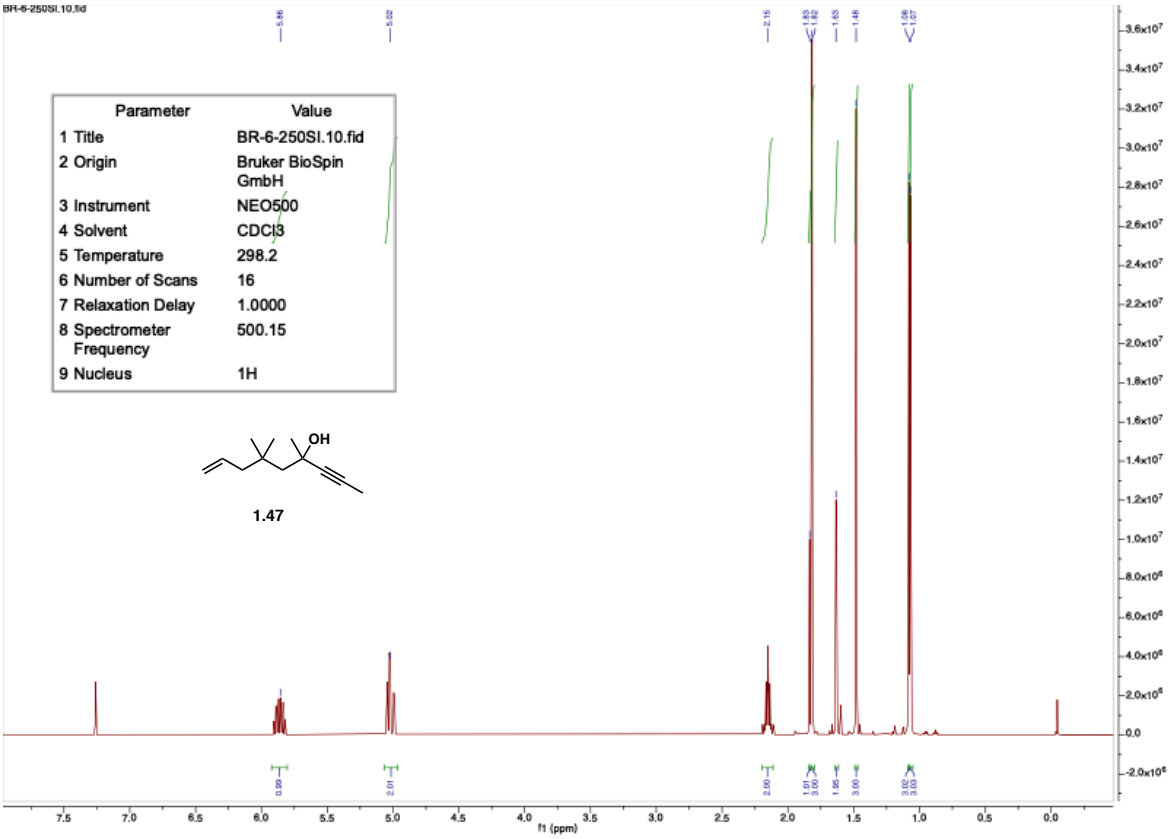
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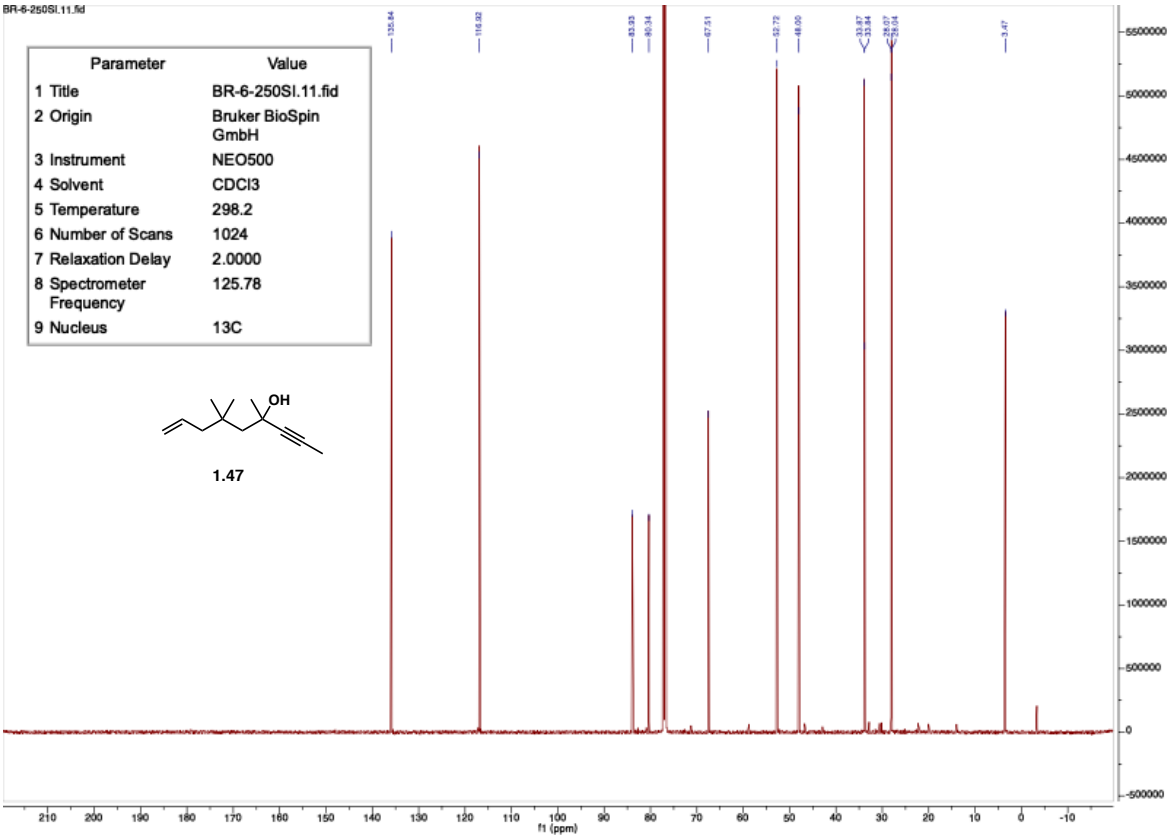
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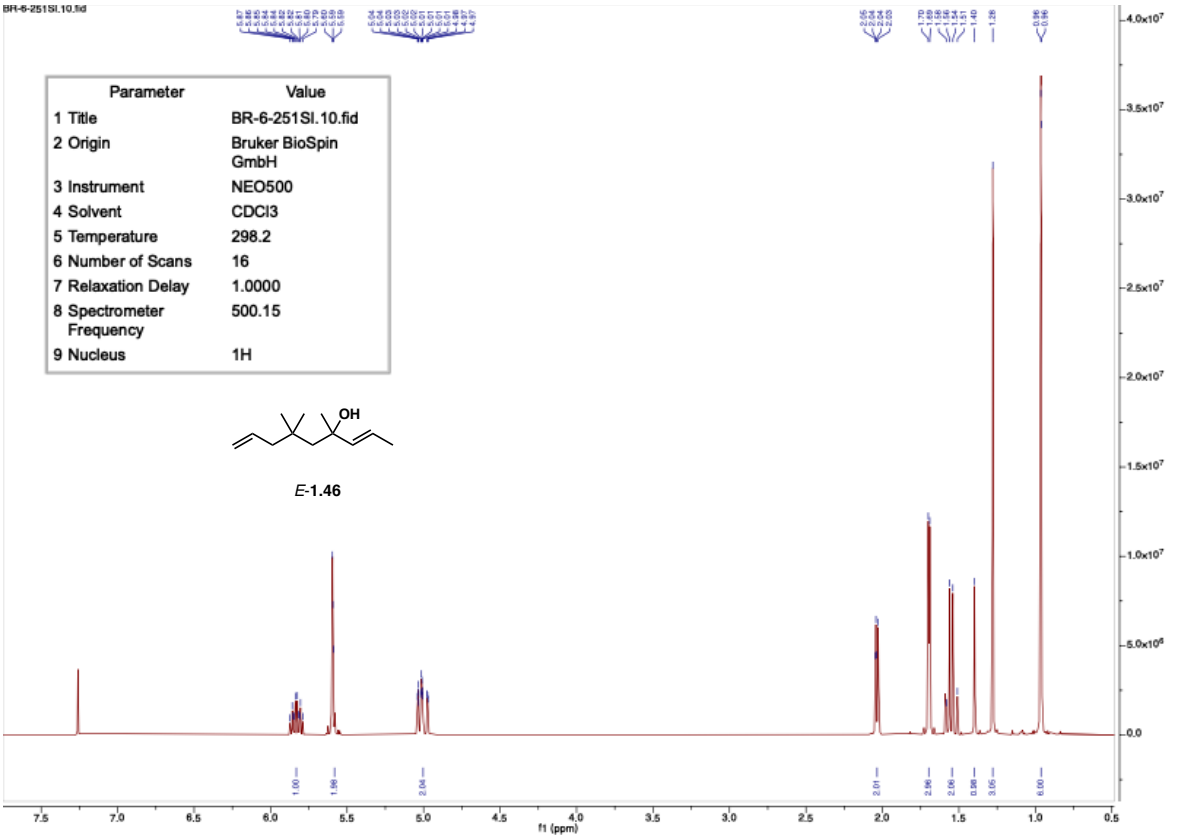
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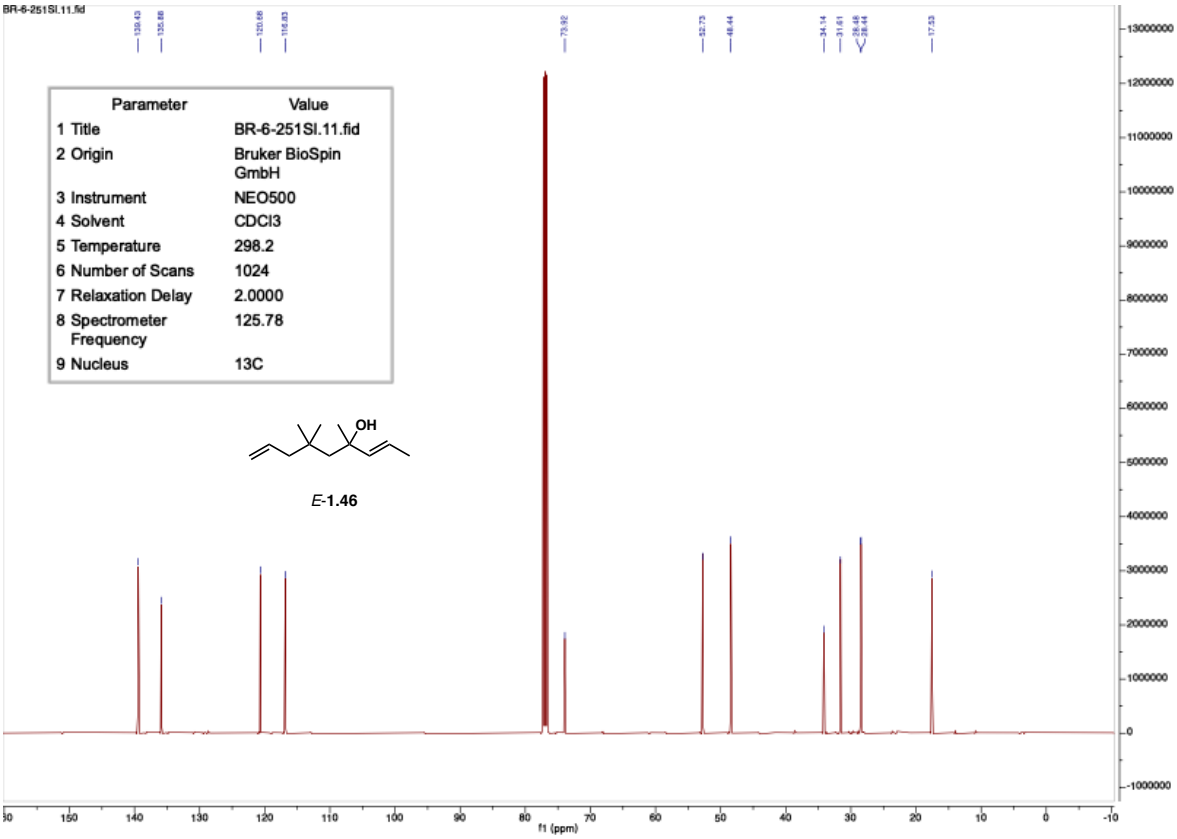
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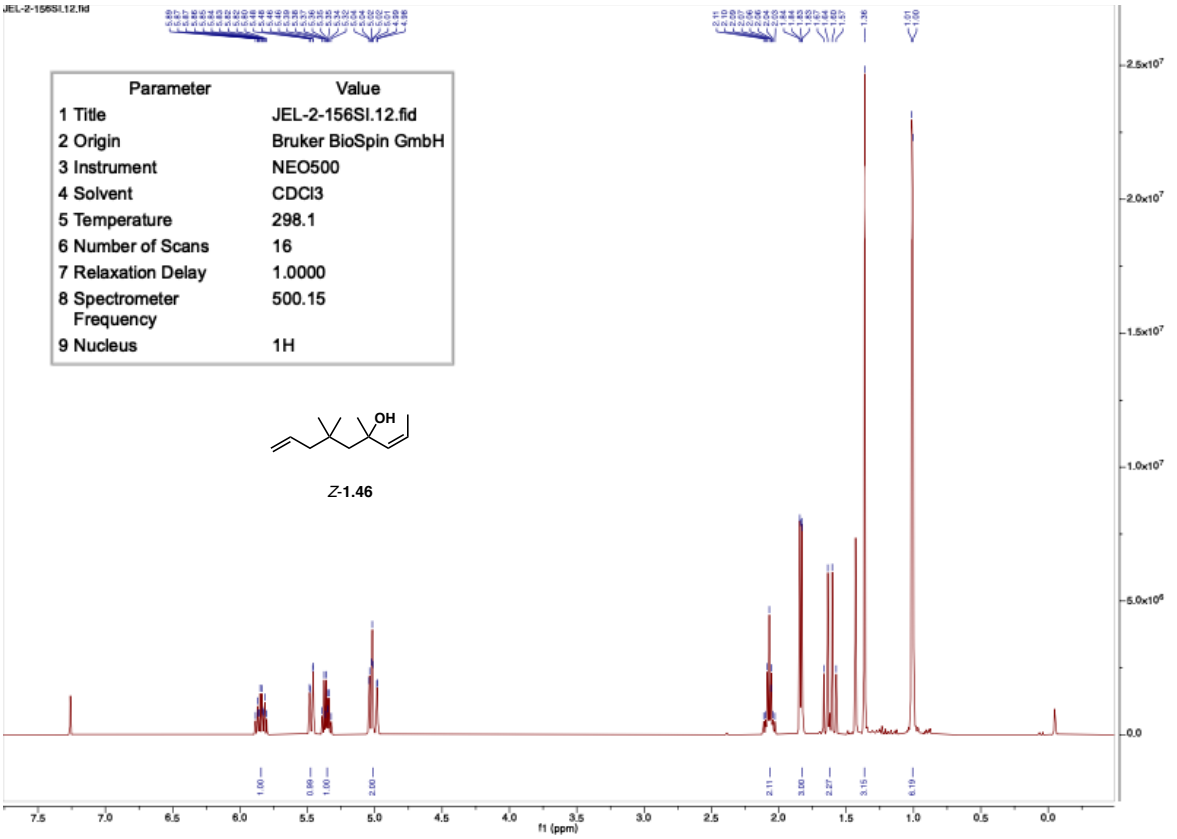
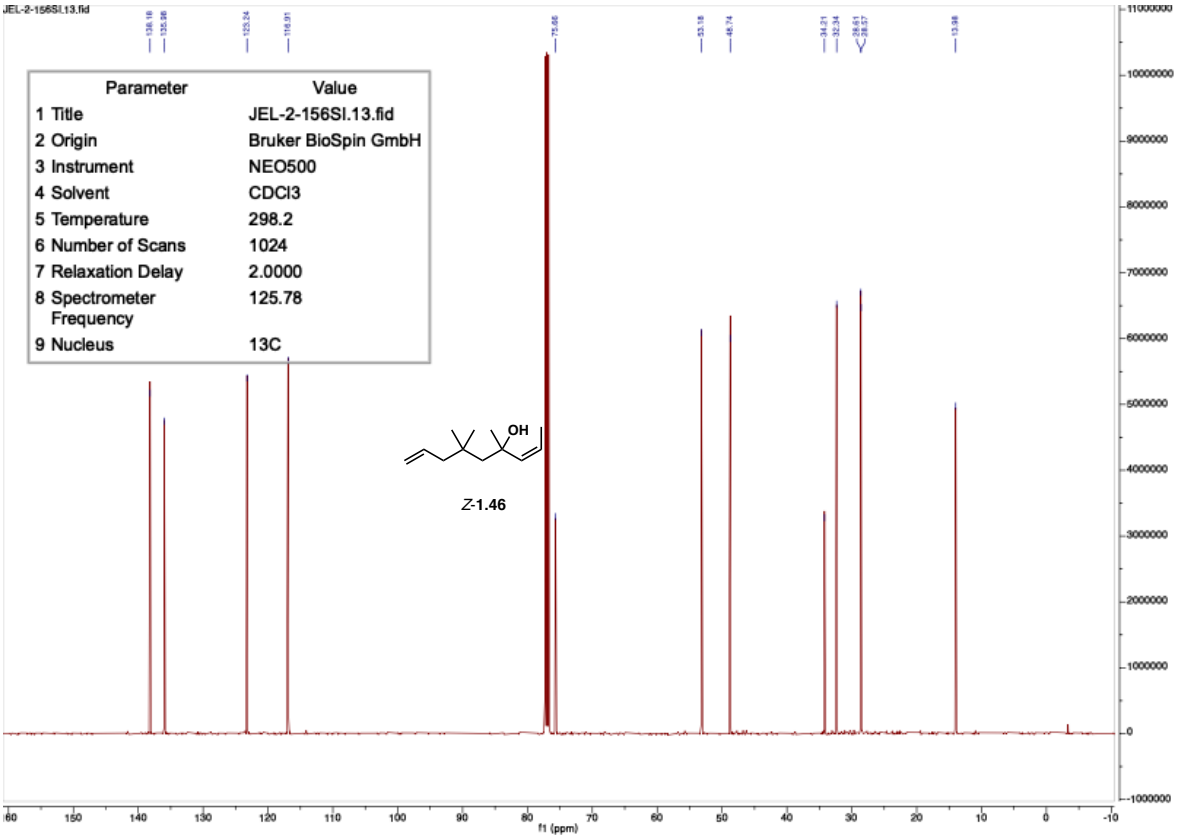
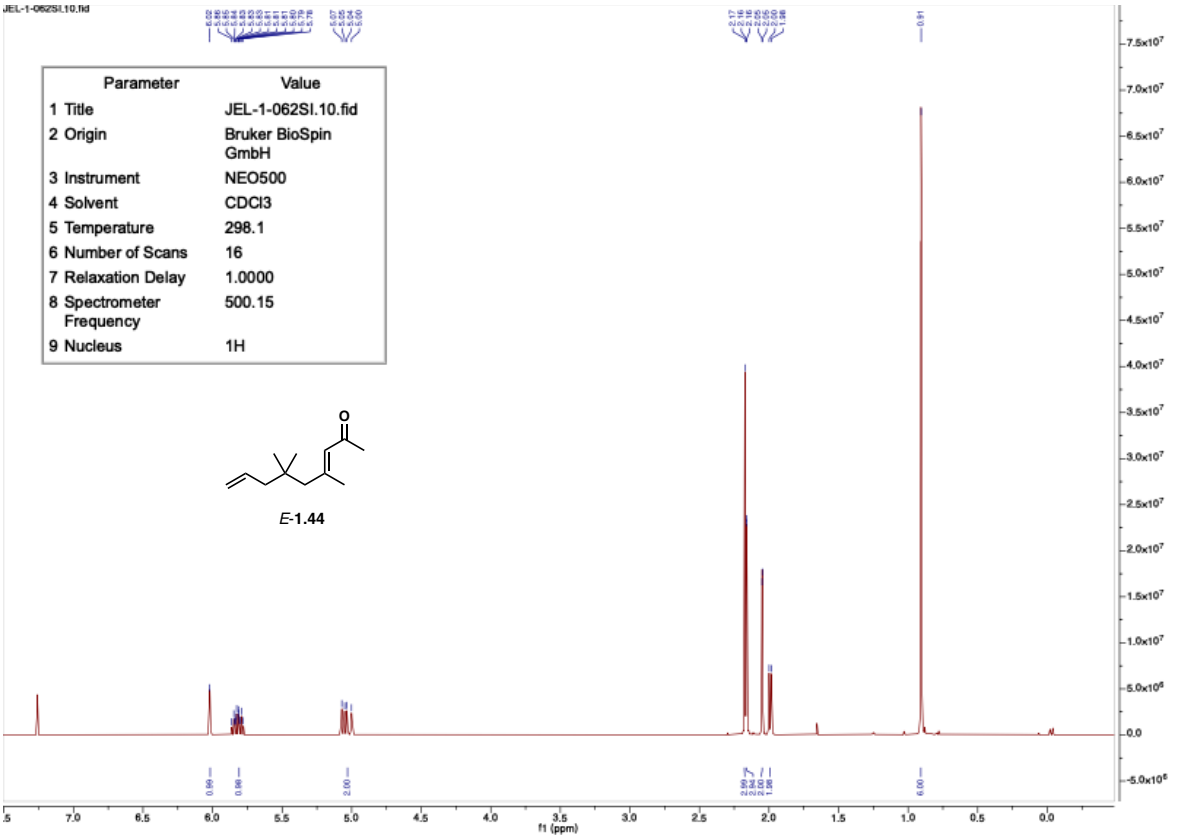
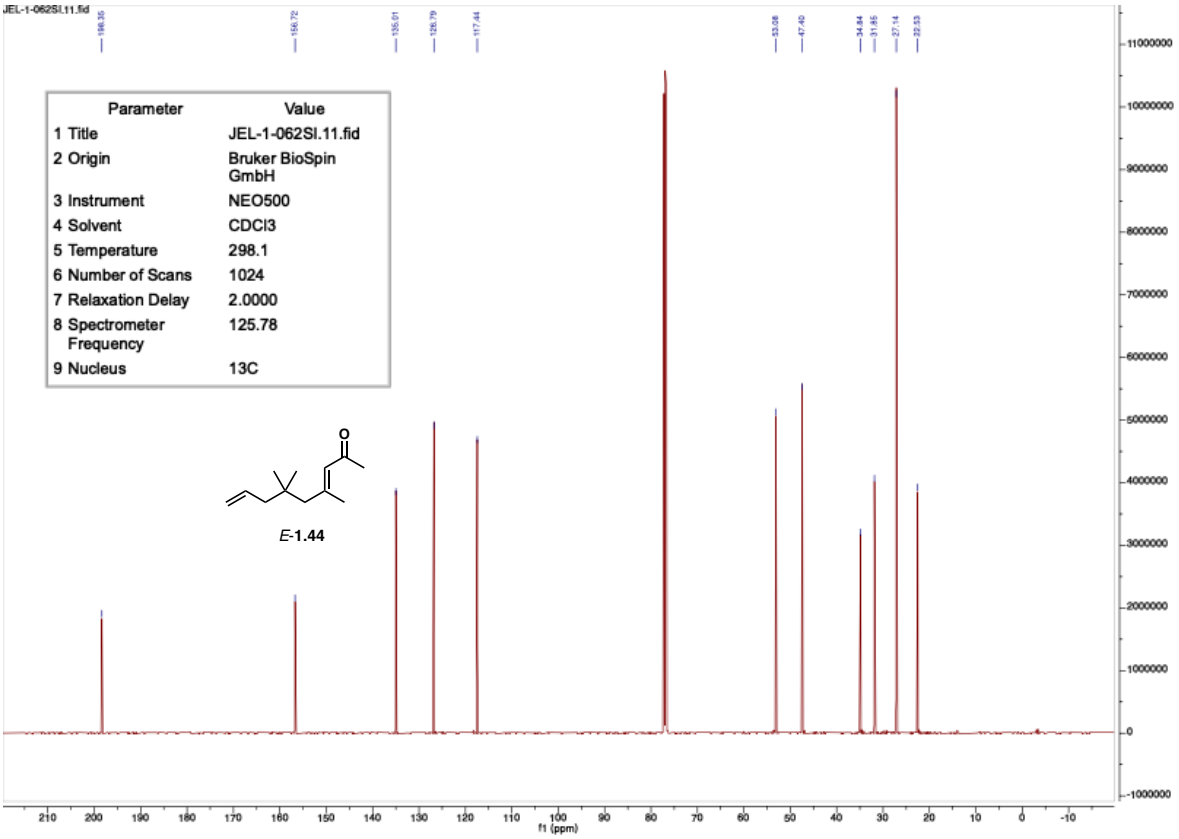
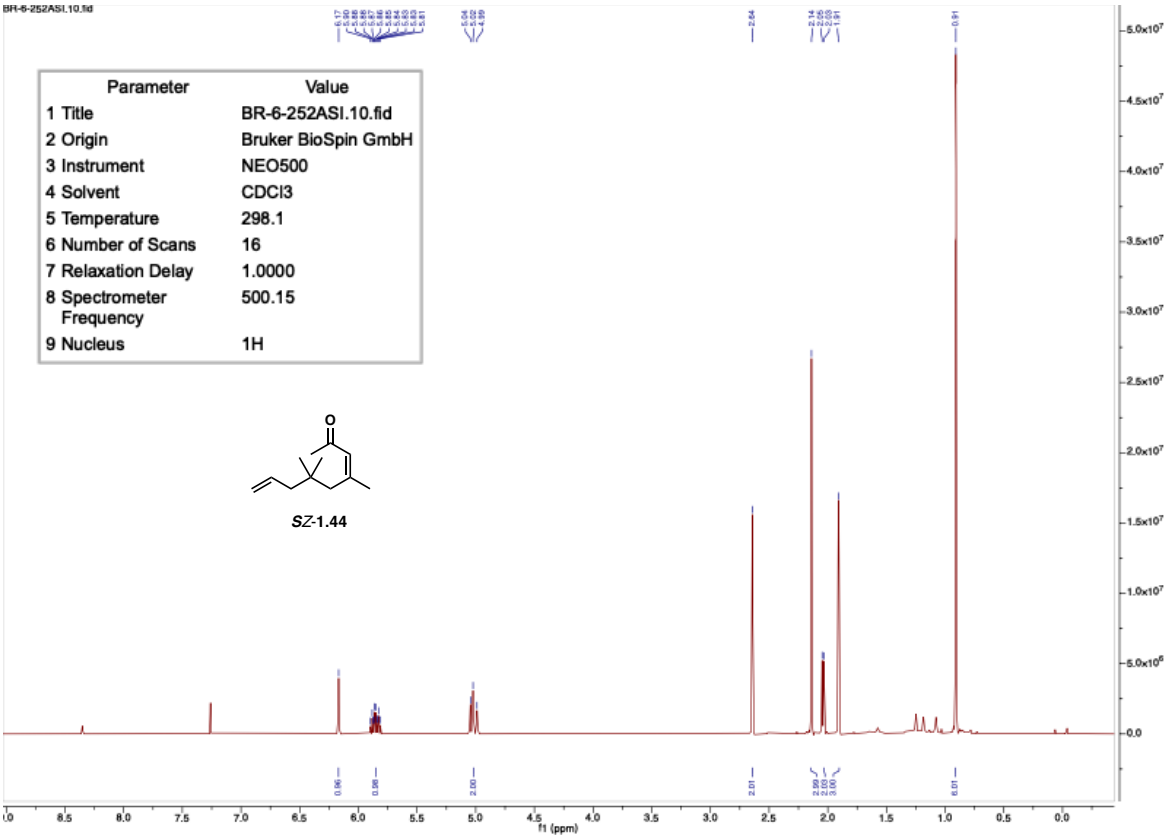
1 Title BR-6-251SI.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
OH
E-1.46
f1 (ppm)

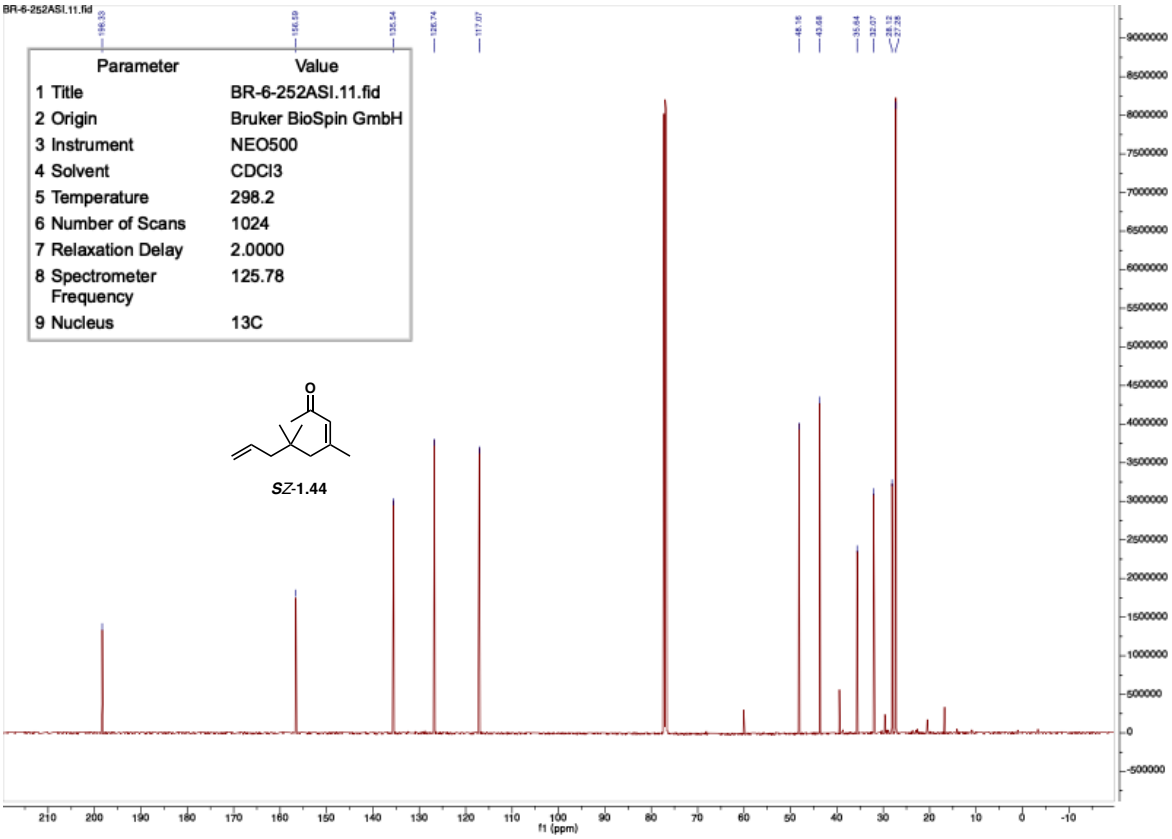

JEL-2-156SI.12.fid
Parameter Value
1 Title JEL-2-156SI.12.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
OH
Z-1.46
f1 (ppm)

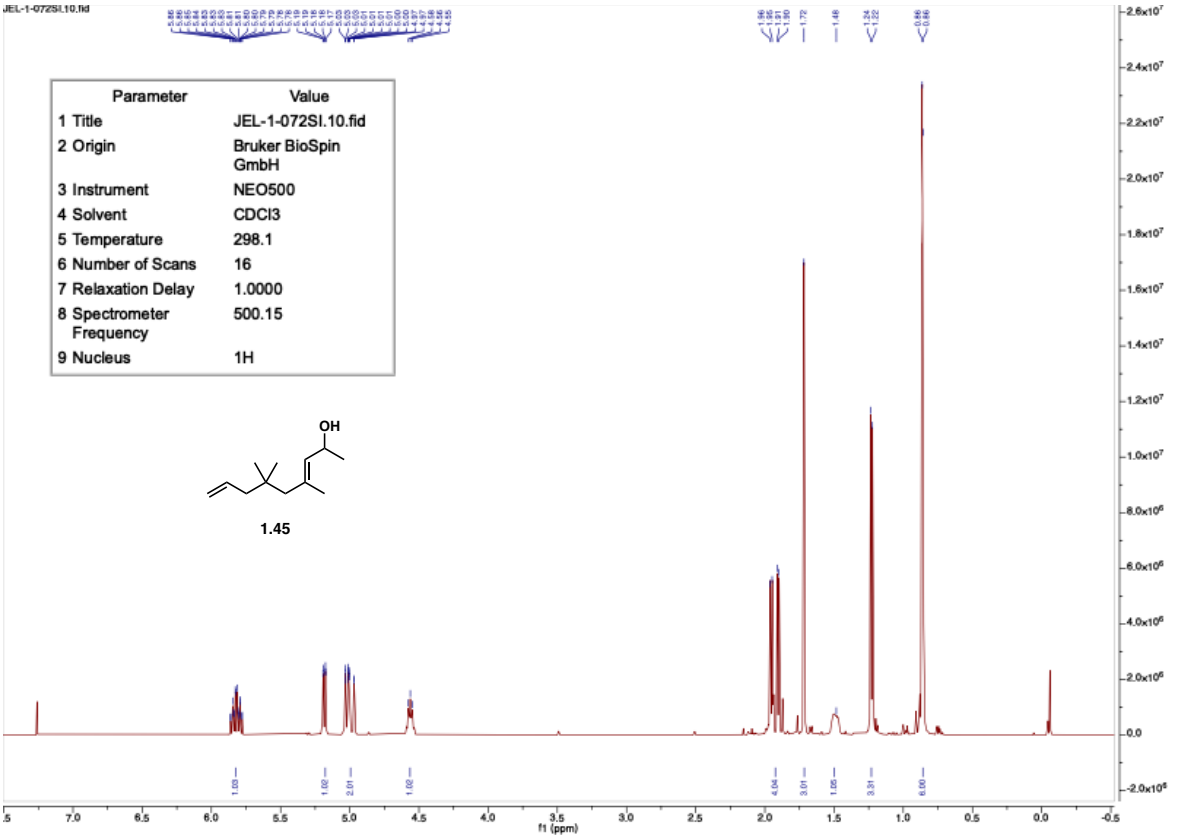

JEL-2-156SI.13.fid
Parameter Value
1 Title JEL-2-156SI.13.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
OH
Z-1.46
f1 (ppm)

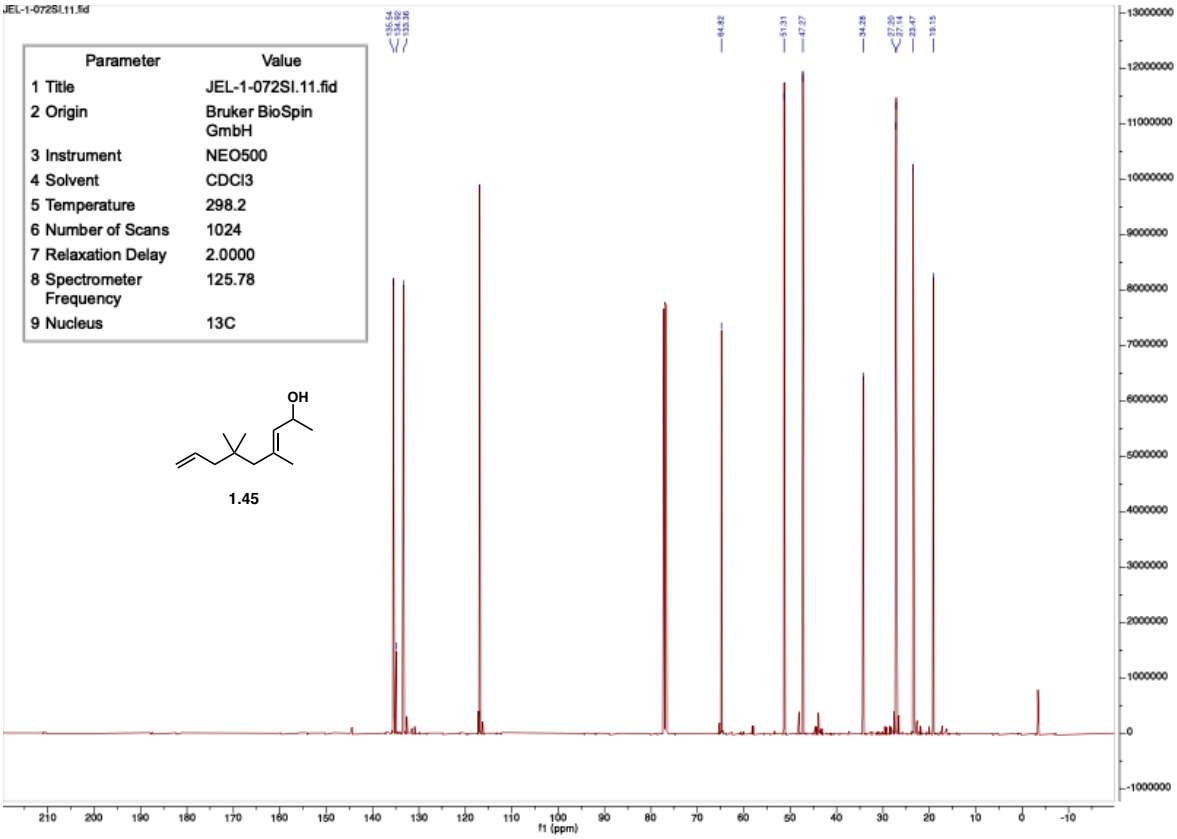

JEL-1-062SI.10.fid
Parameter Value
1 Title JEL-1-062SI.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
O
E-1.44
f1 (ppm)

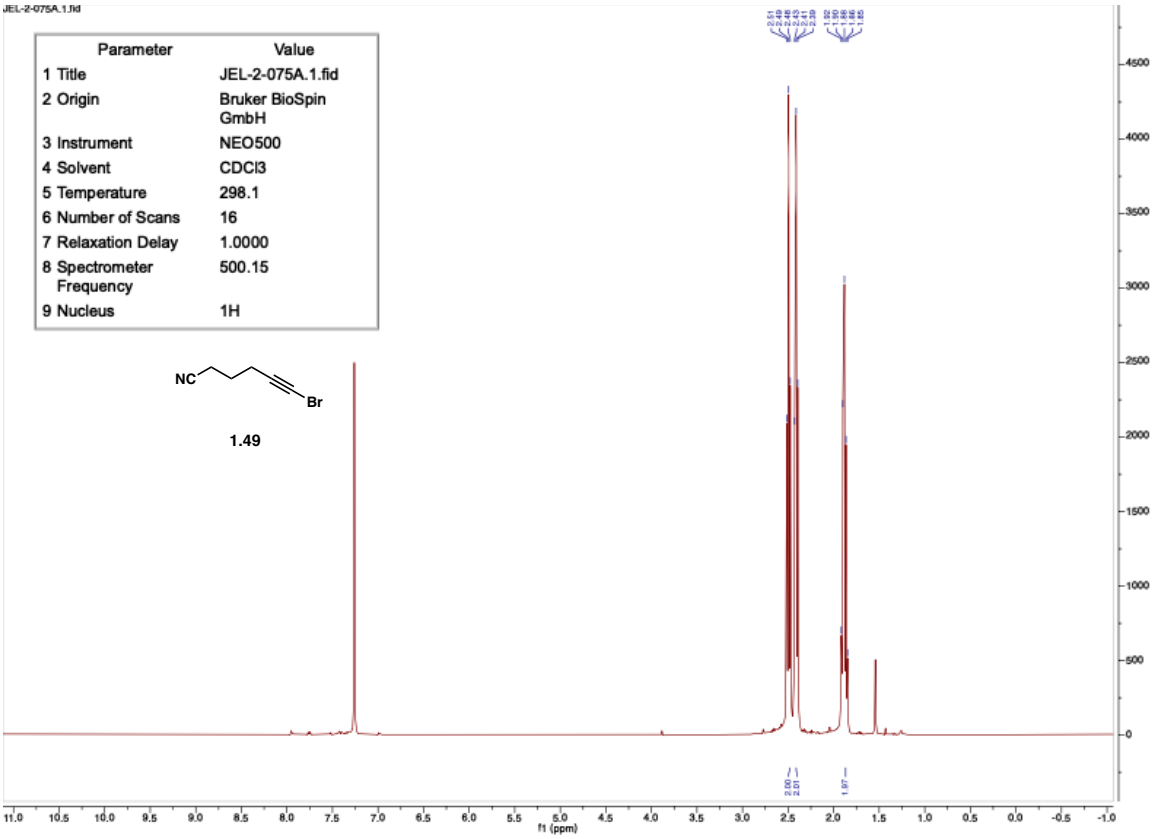

JEL-1-062SI.11.fid
Parameter Value
1 Title JEL-1-062SI.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
O
E-1.44
f1 (ppm)

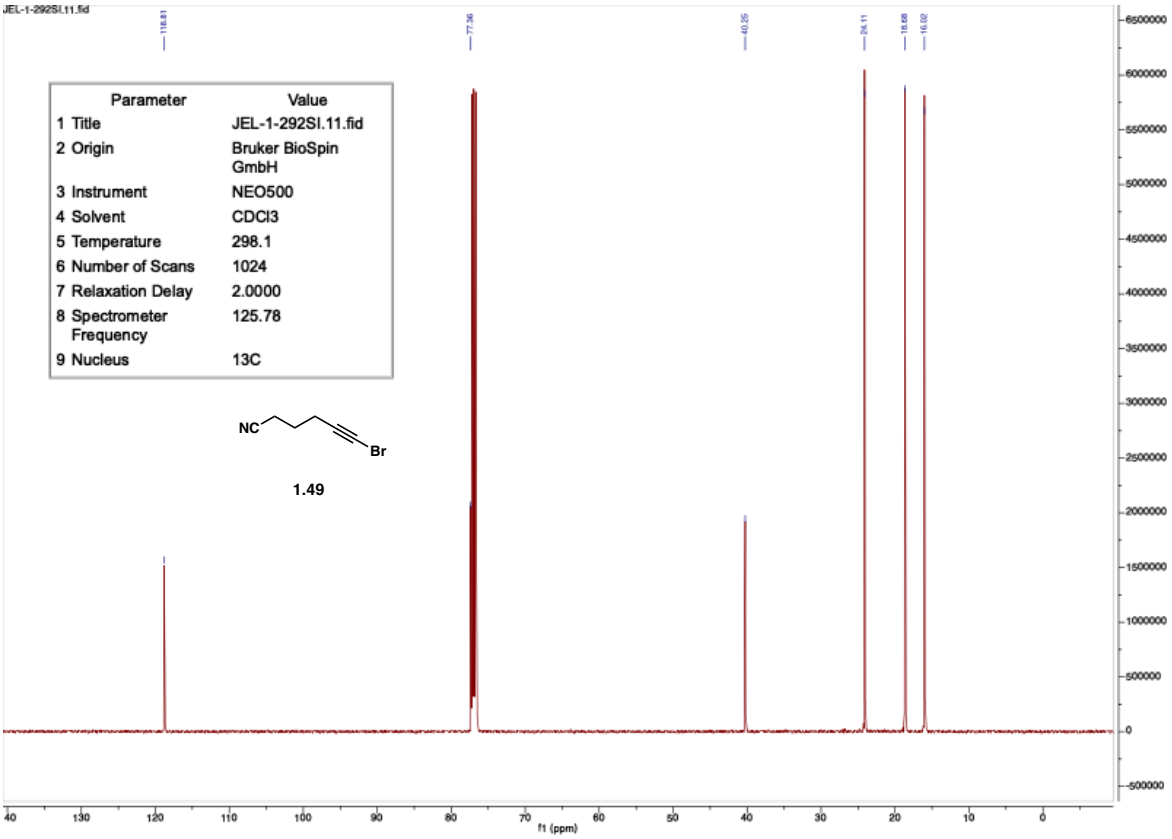

BR-6-252ASI.10.fid
Parameter Value
1 Title BR-6-252ASI.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
SZ-1.44
f1 (ppm)

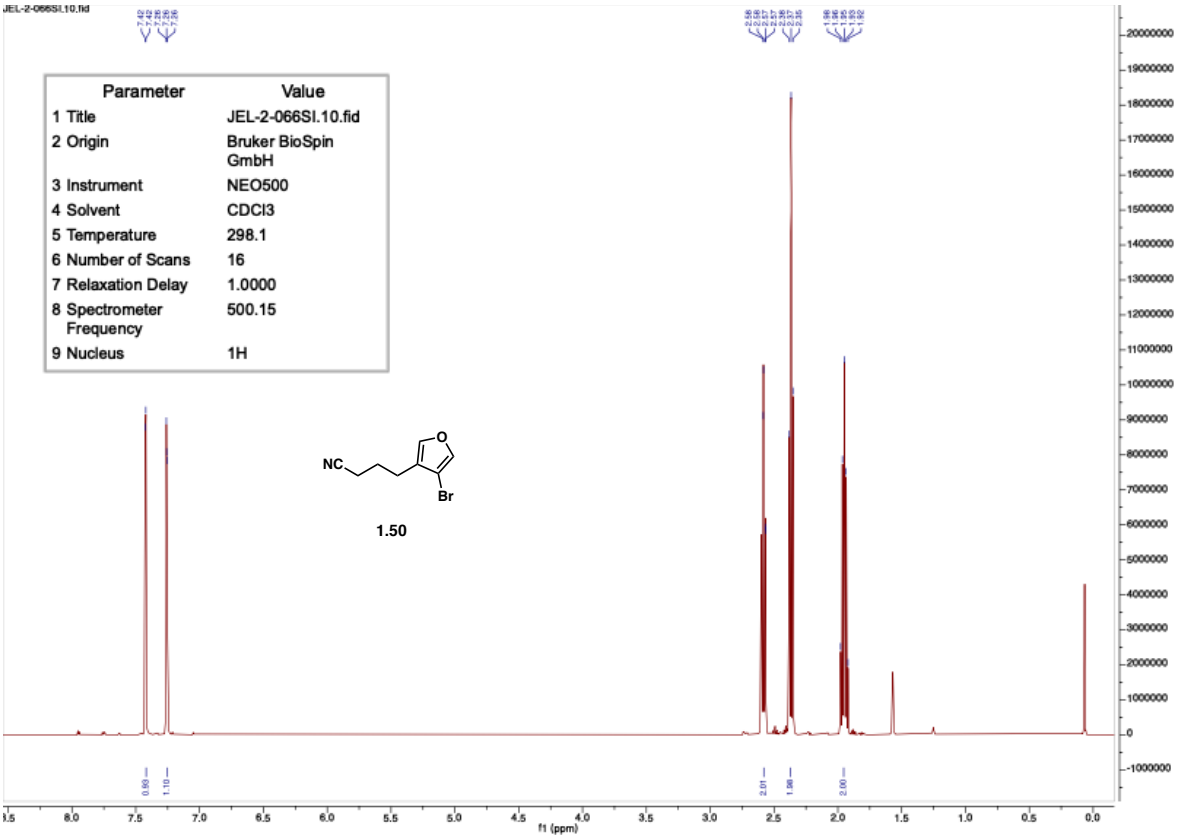

BR-6-252ASI.11.fid
Parameter Value
1 Title BR-6-252ASI.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
SZ-1.44
f1 (ppm)

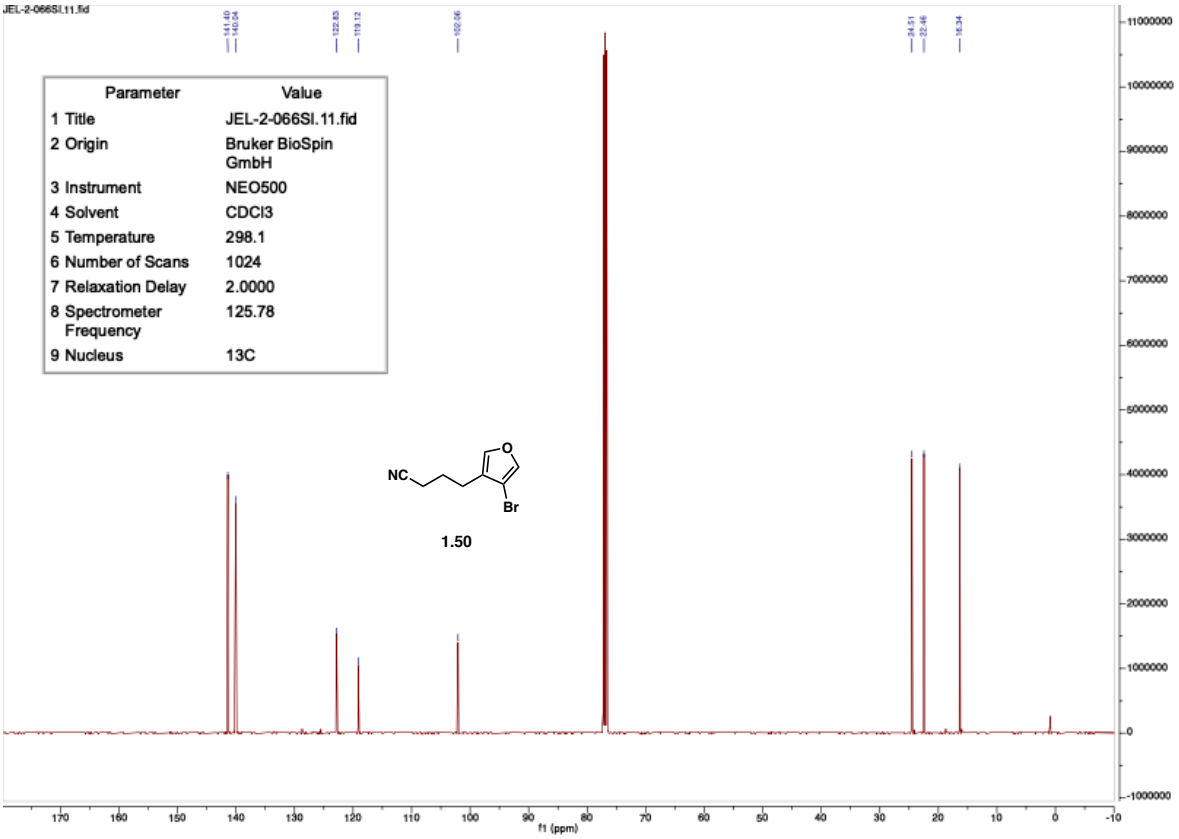

JEL-1-072SI.10.fid
Parameter Value
1 Title JEL-1-072SI.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
OH
1.45
f1 (ppm)

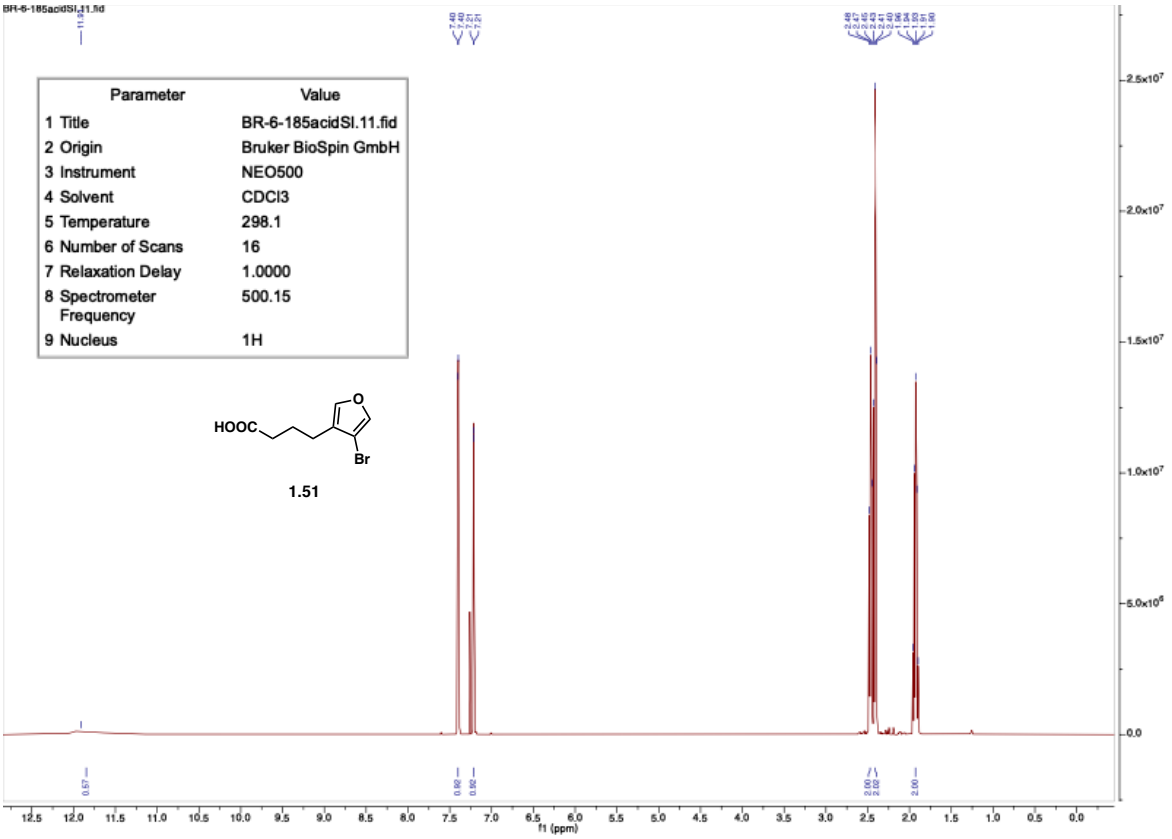

JEL-1-072SI.11.fid
Parameter Value
1 Title JEL-1-072SI.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
OH
1.45
f1 (ppm)

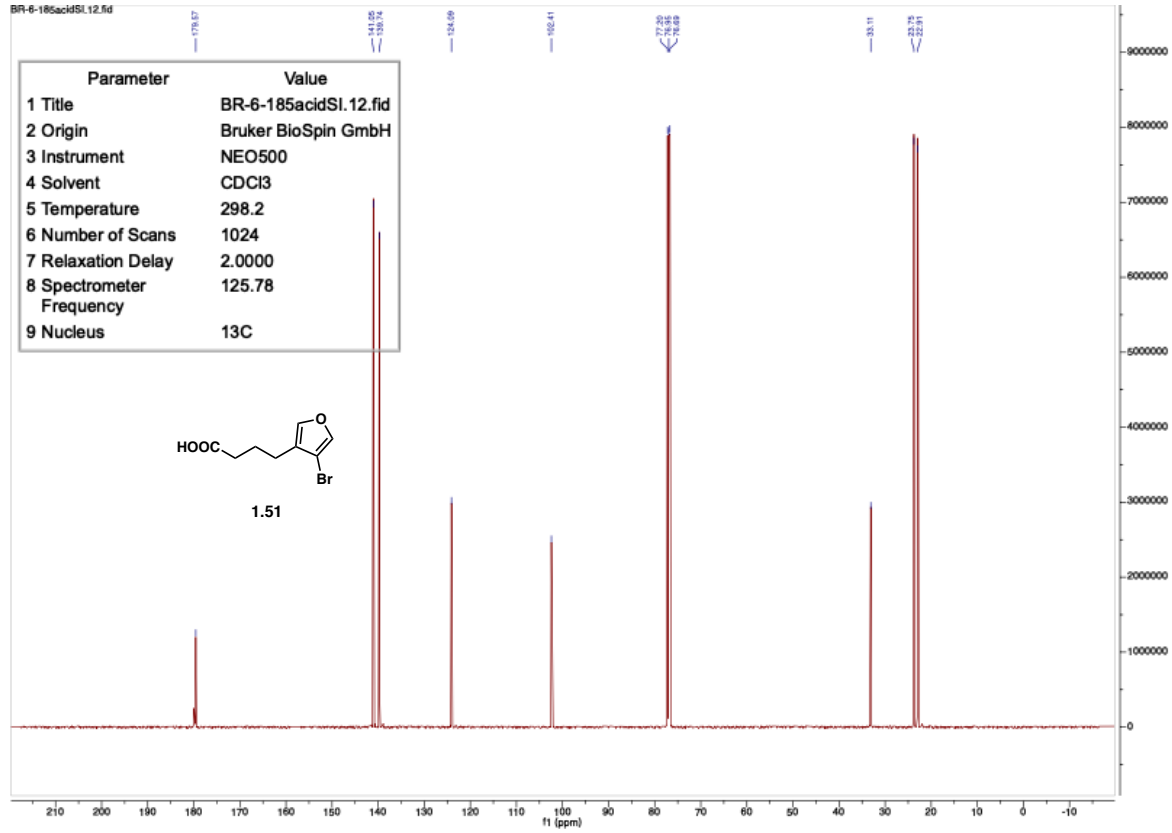

JEL-2-075A.1.fid
Parameter Value
1 Title JEL-2-075A.1.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
NC
Br
1.49
f1 (ppm)

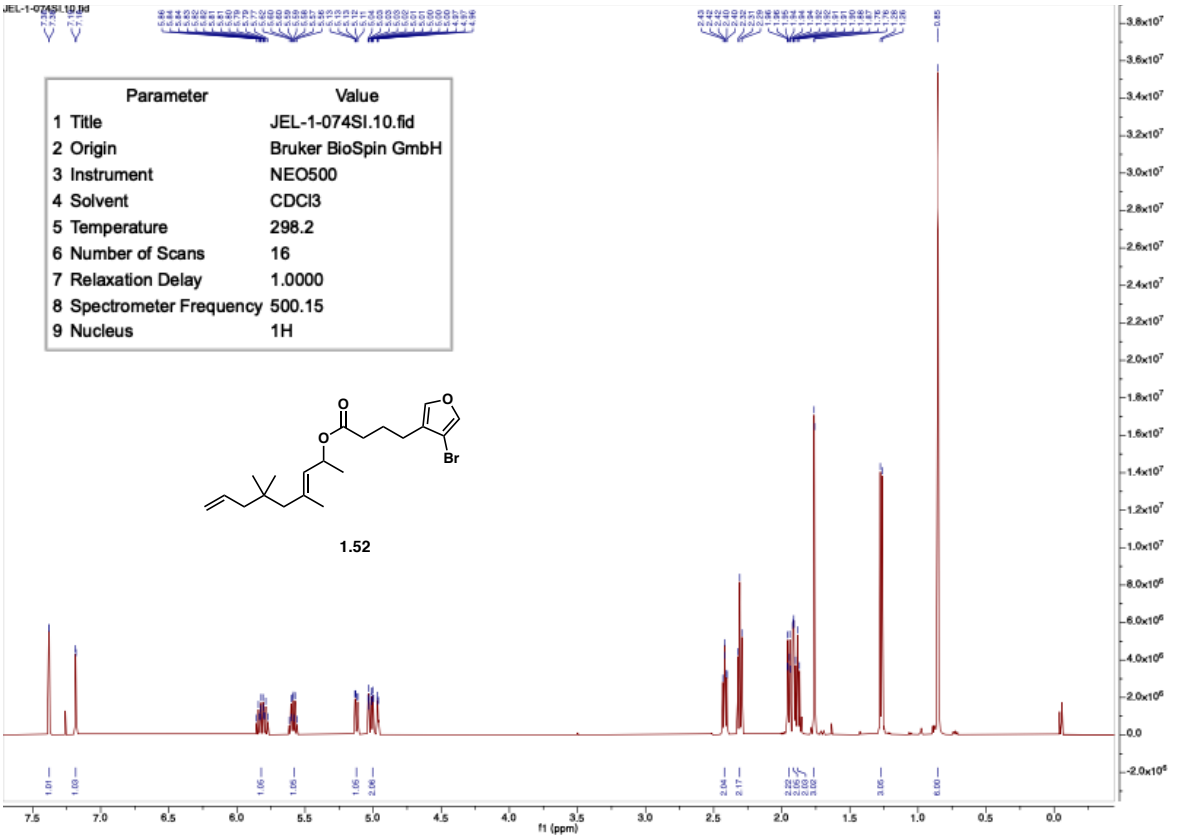

JEL-1-292SI.11.fid
Parameter Value
1 Title JEL-1-292SI.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
NC
Br
1.49
f1 (ppm)

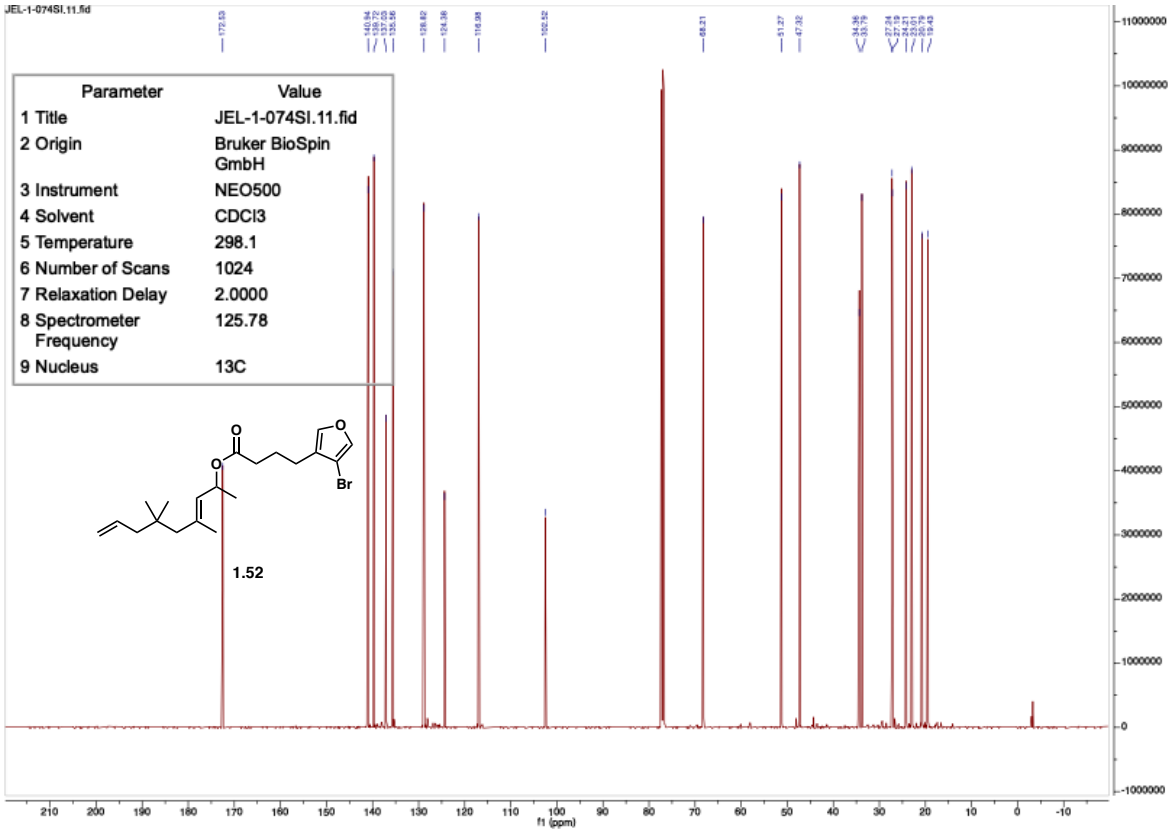

JEL-2-066SI.10.fid
Parameter Value
1 Title JEL-2-066SI.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
NC
O
Br
1.50
f1 (ppm)

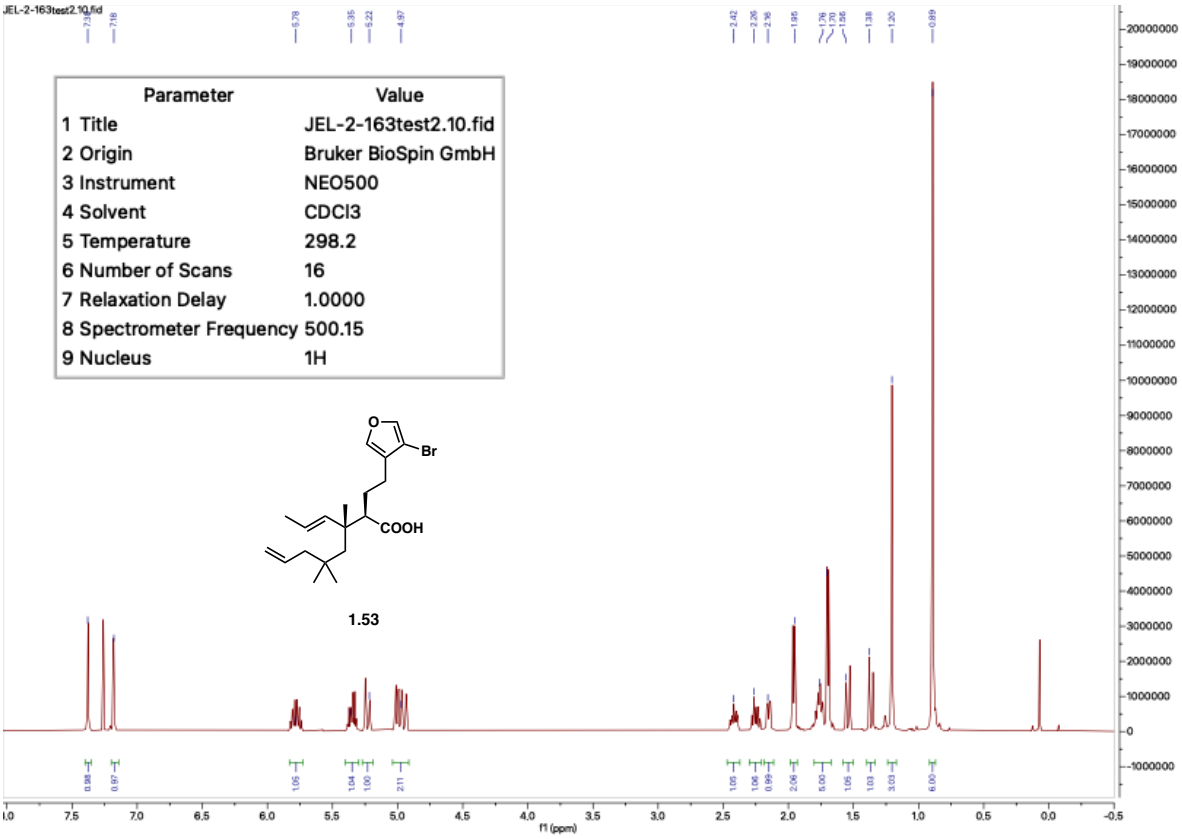

JEL-2-066SI.11.fid
Parameter Value
1 Title JEL-2-066SI.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
NC
O
Br
1.50
f1 (ppm)

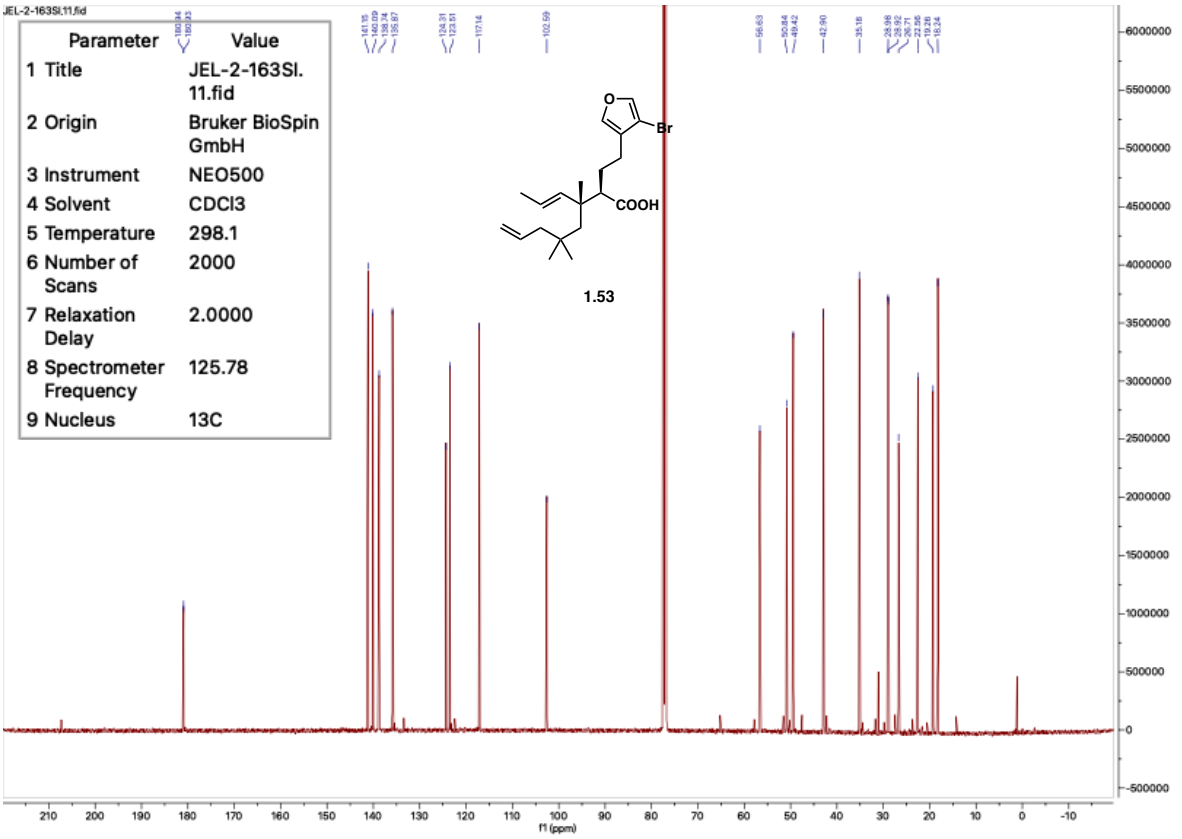

BR-6-185acidSI.11.fid
Parameter Value
1 Title BR-6-185acidSI.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
HOOC
O
Br
1.51
f1 (ppm)

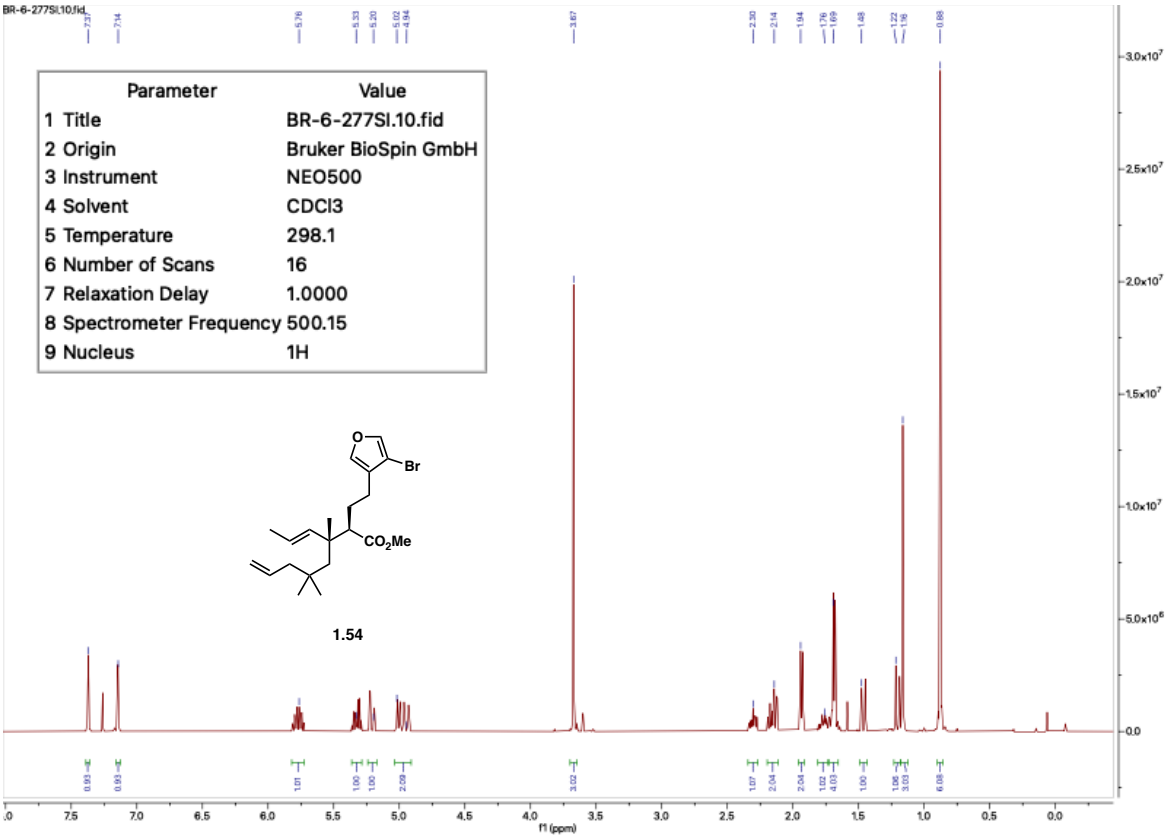

BR-6-185acidSI.12.fid
Parameter Value
1 Title BR-6-185acidSI.12.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
HOOC
O
Br
1.51
f1 (ppm)

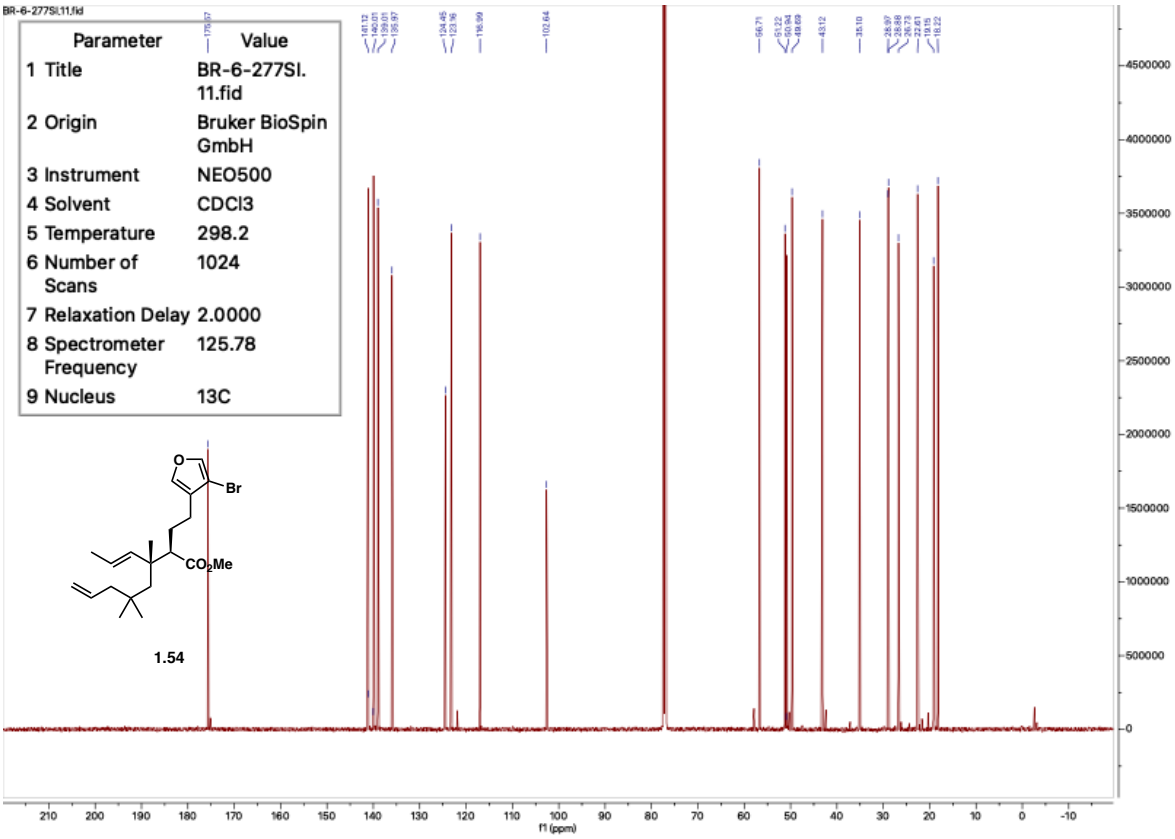

Parameter Value
1 Title JEL-1-074SI.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
Br
1.52
f1 (ppm)

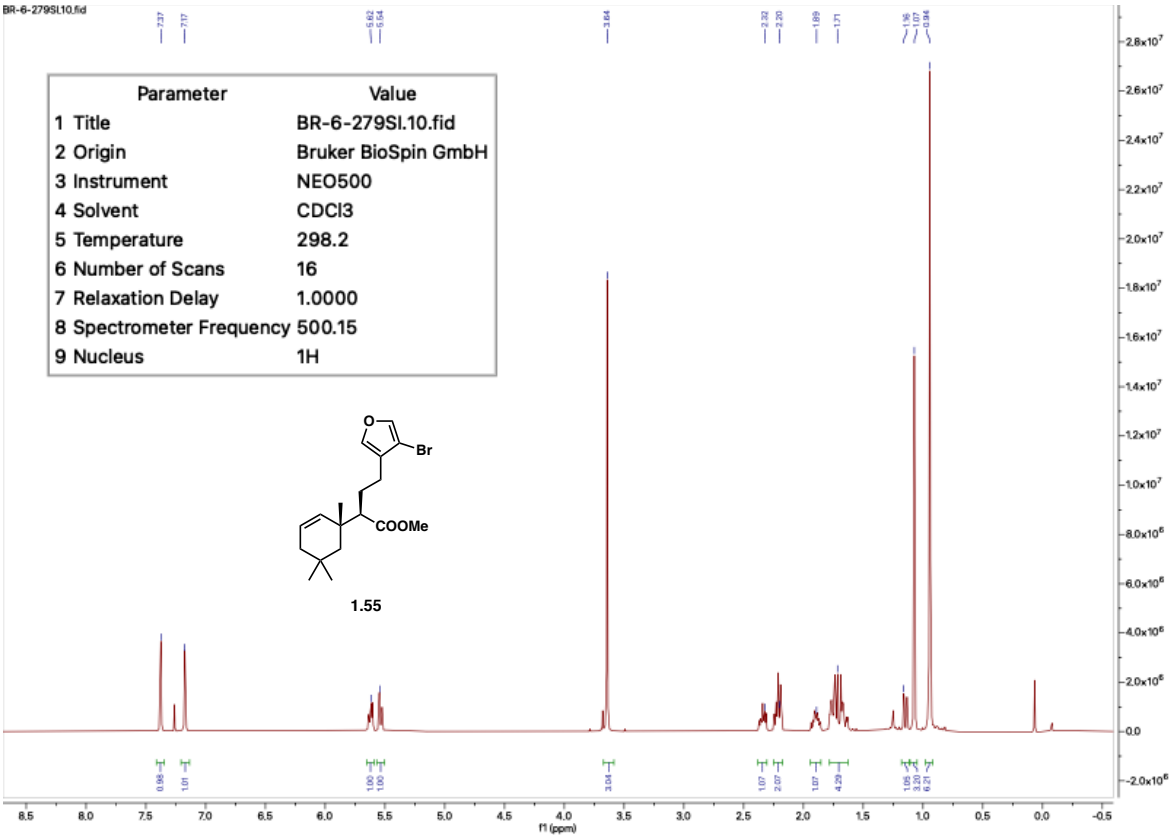

Parameter Value
1 Title JEL-1-074SI.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
Br
1.52
f1 (ppm)

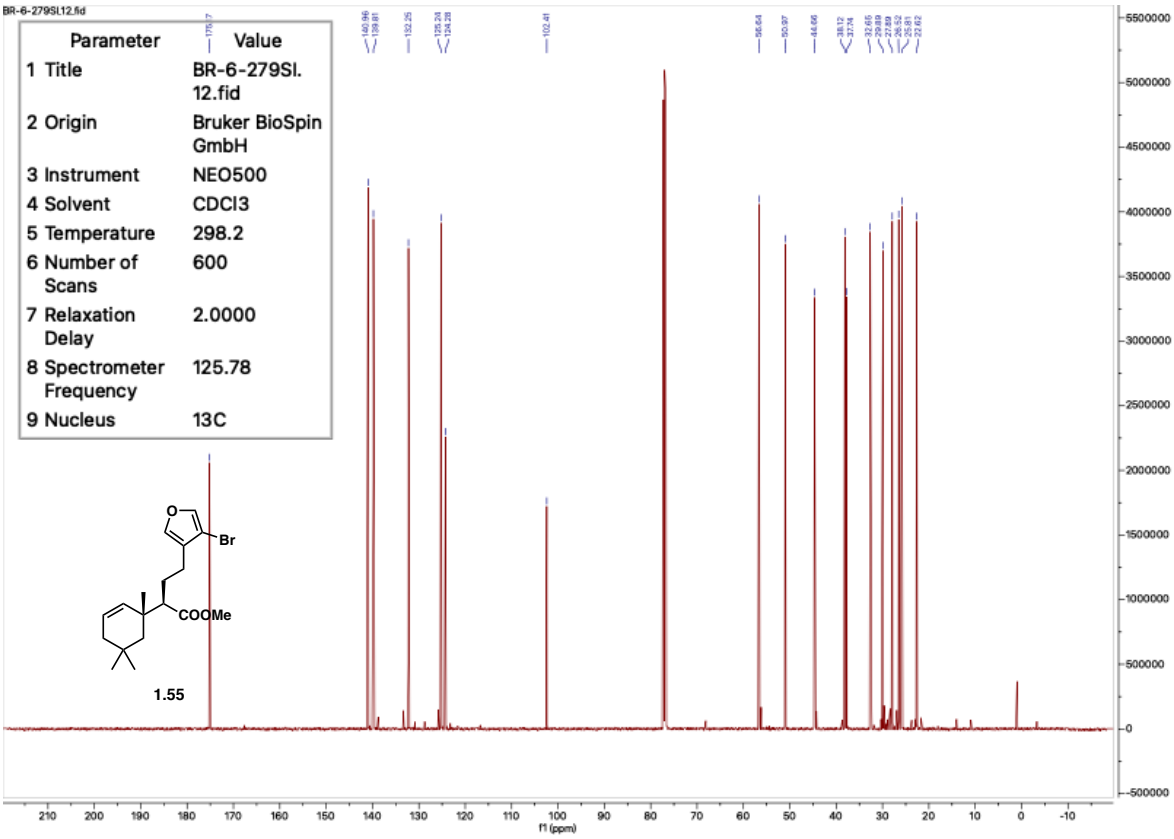

JEL-2-163test2.10.fid
Parameter Value
1 Title JEL-2-163test2.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
Br
COOH
1.53
f1 (ppm)

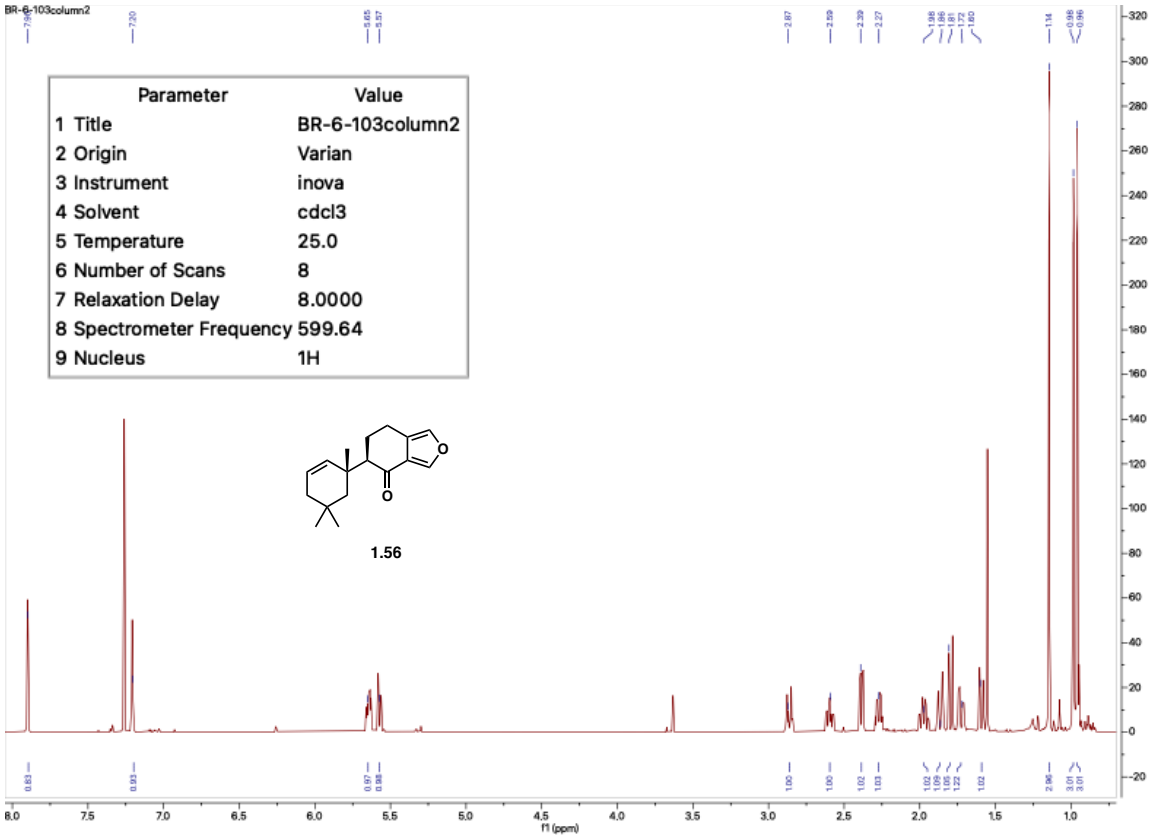

JEL-2-163Sl.11.fid
Parameter Value
1 Title JEL-2-163Sl.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 2000
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
Br
COOH
1.53
f1 (ppm)


BR-6-277SI.10.fid
Parameter Value
1 Title BR-6-277SI.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
Br
CO2Me
1.54
f1 (ppm)

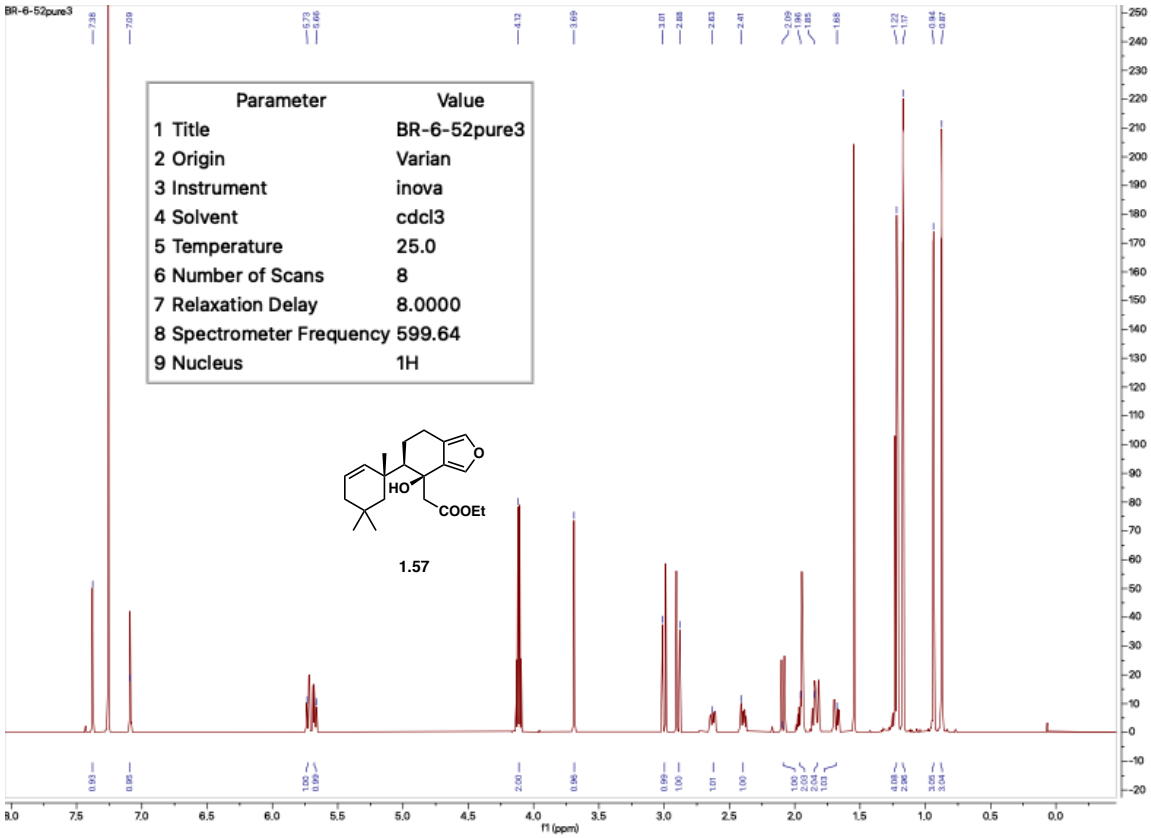

BR-6-277SI.11.fid
Parameter Value
1 Title BR-6-277SI.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
Br
CO2Me
1.54
f1 (ppm)


BR-6-279SL10.fid
Parameter Value
1 Title BR-6-279Sl.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
Br
COOMe
1.55
f1 (ppm)

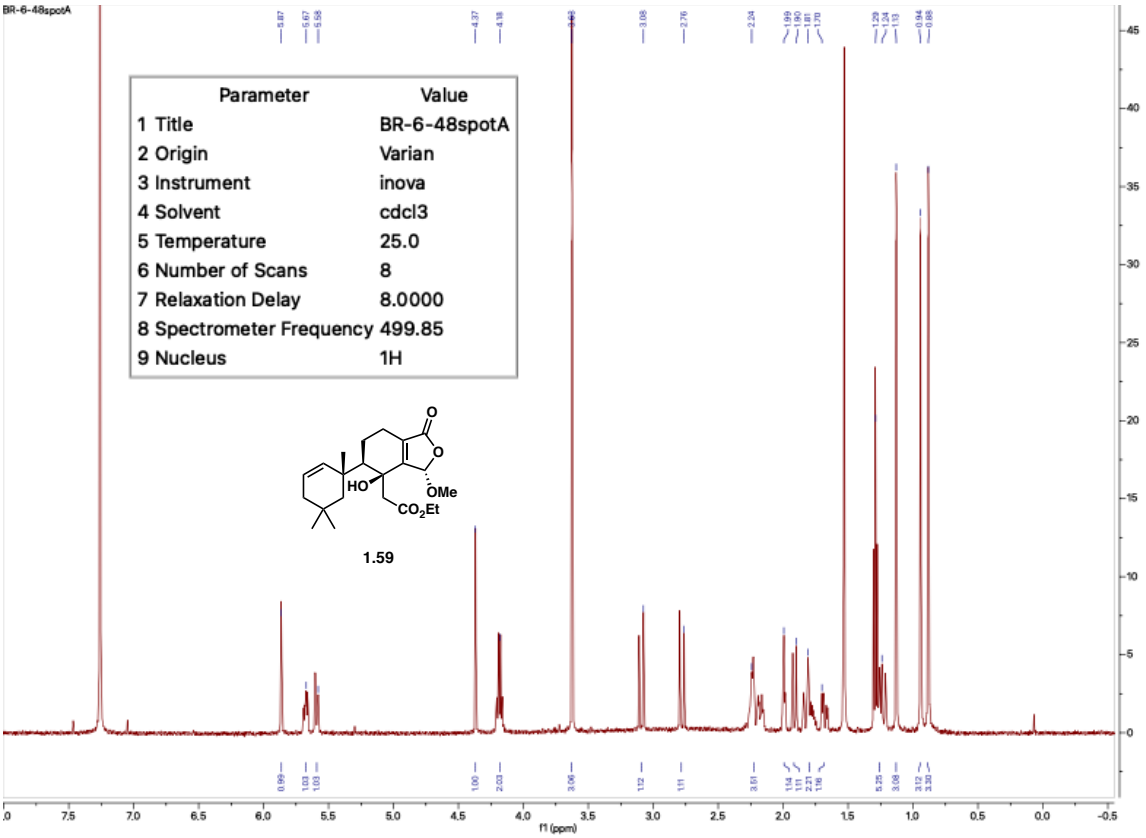

BR-6-279SL12.fid
Parameter Value
1 Title BR-6-279Sl. 12.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 600
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
Br
COOMe
1.55
f1 (ppm)


BR-6-103column2
Parameter Value
1 Title BR-6-103column2
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 8
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 599.64
9 Nucleus 1H
O
O
f1 (ppm)

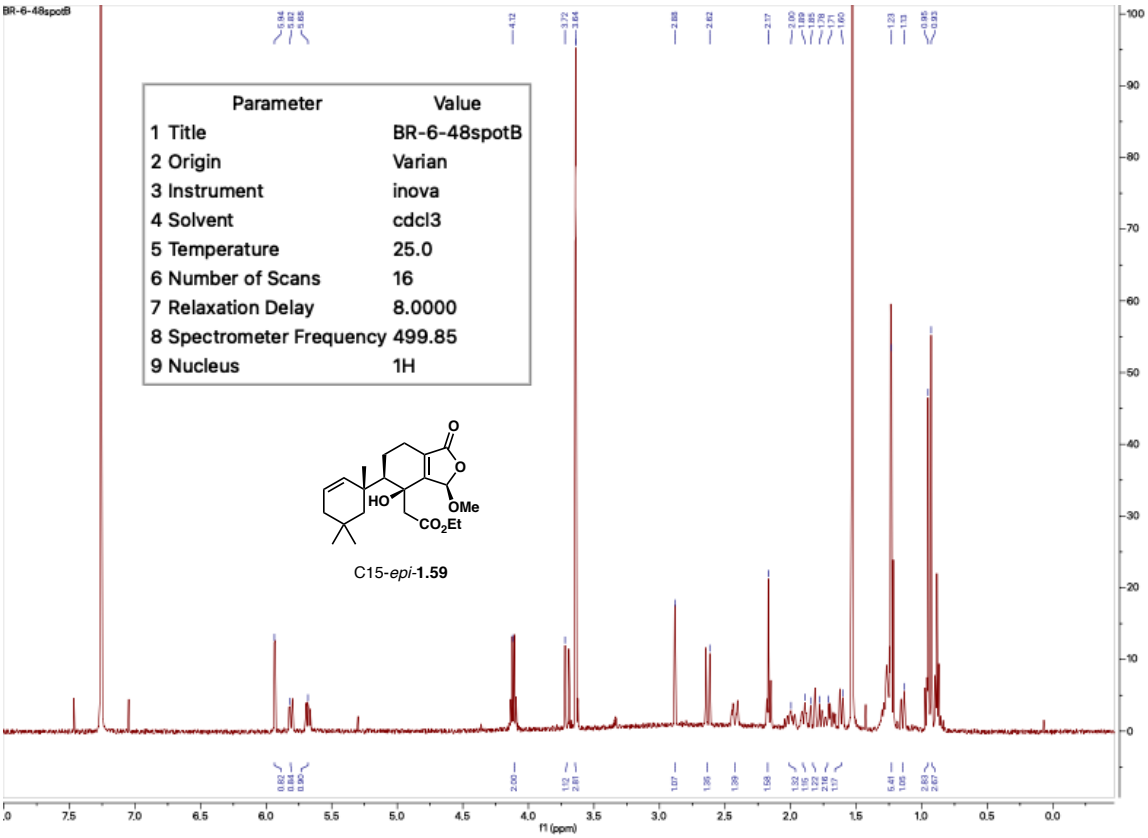
1.56


BR-6-52pure3
Parameter Value
1 Title BR-6-52pure3
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 8
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 599.64
9 Nucleus 1H
HO
COOEt
O
f1 (ppm)

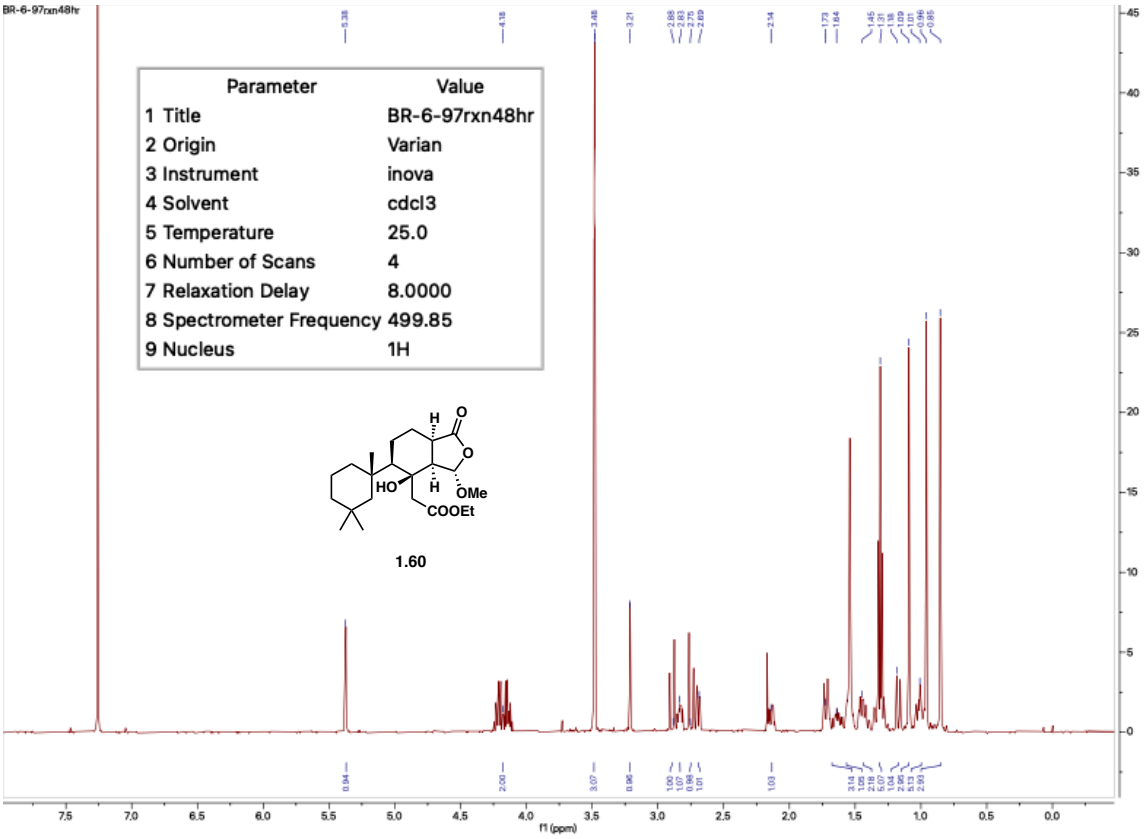
1.57



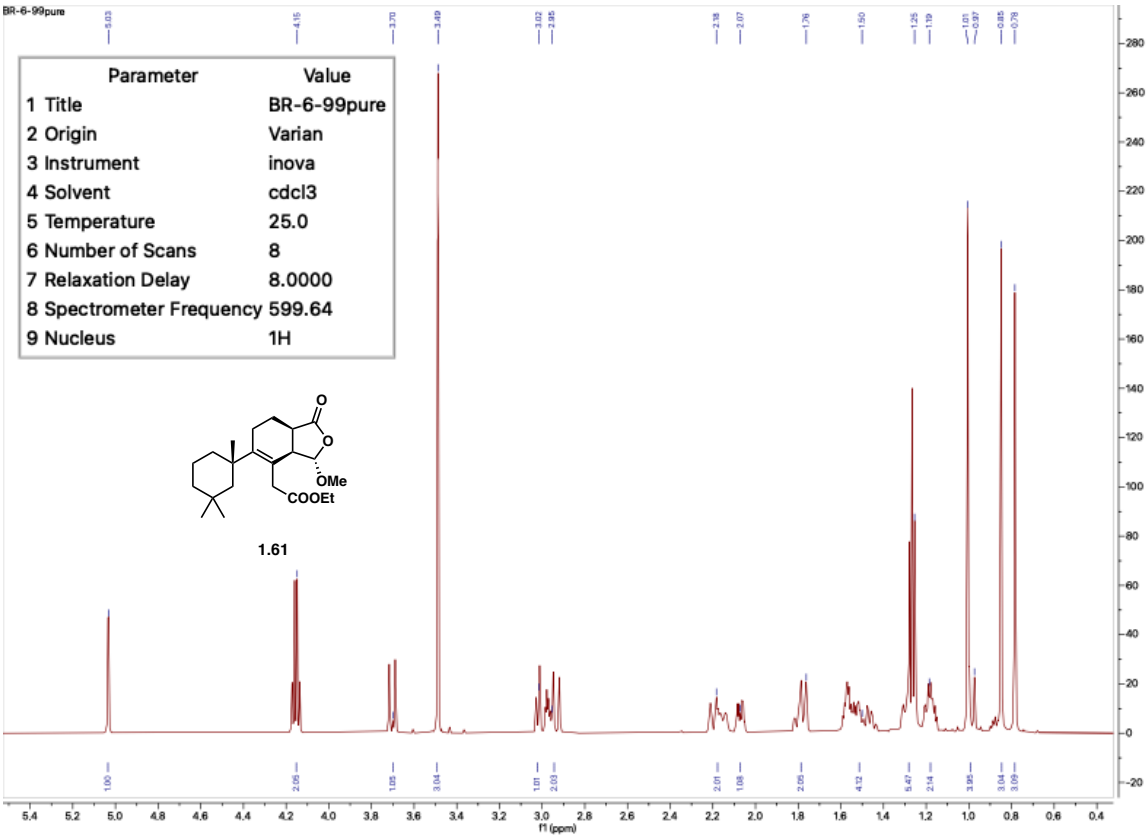
1.59



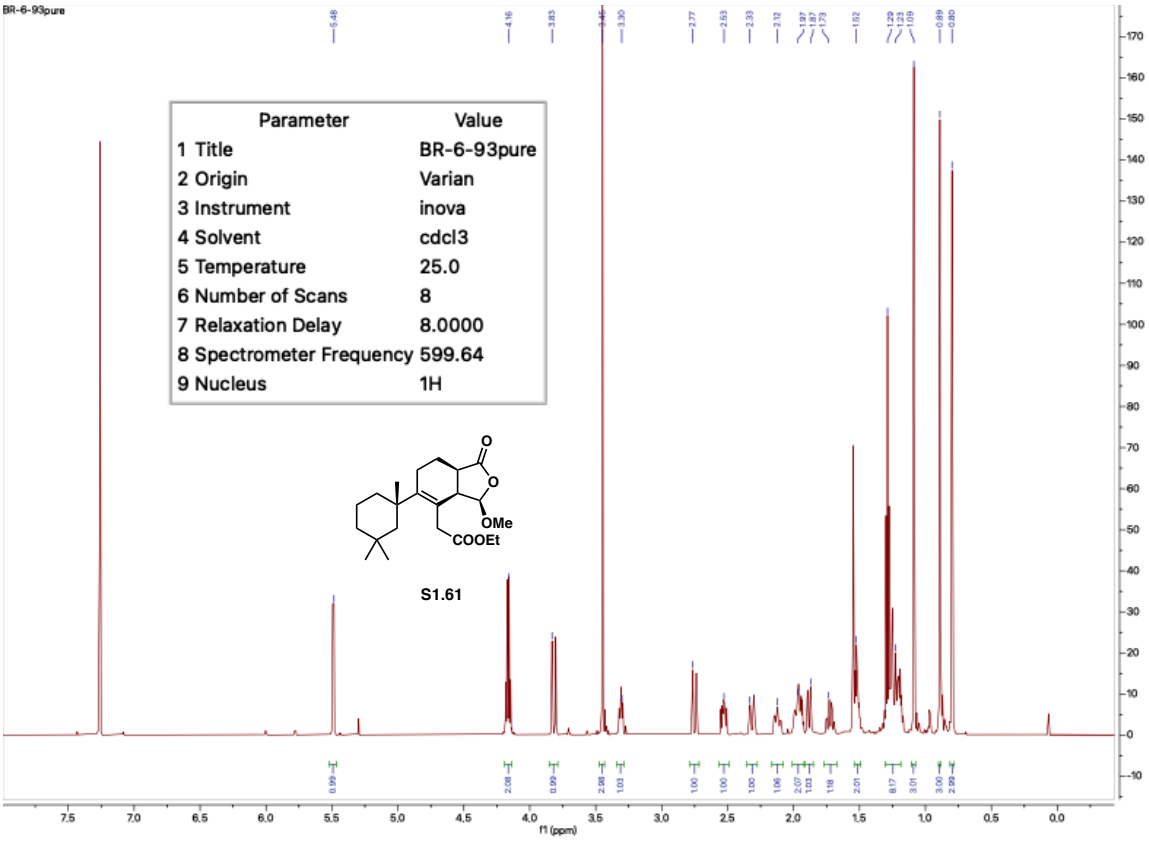
C15-*epi*-**1.59**


BR-6-97rxn48hr
Parameter Value
1 Title BR-6-97rxn48hr
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 4
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 499.85
9 Nucleus 1H
H
O
O
HO
H
OMe
COOEt
f1 (ppm)

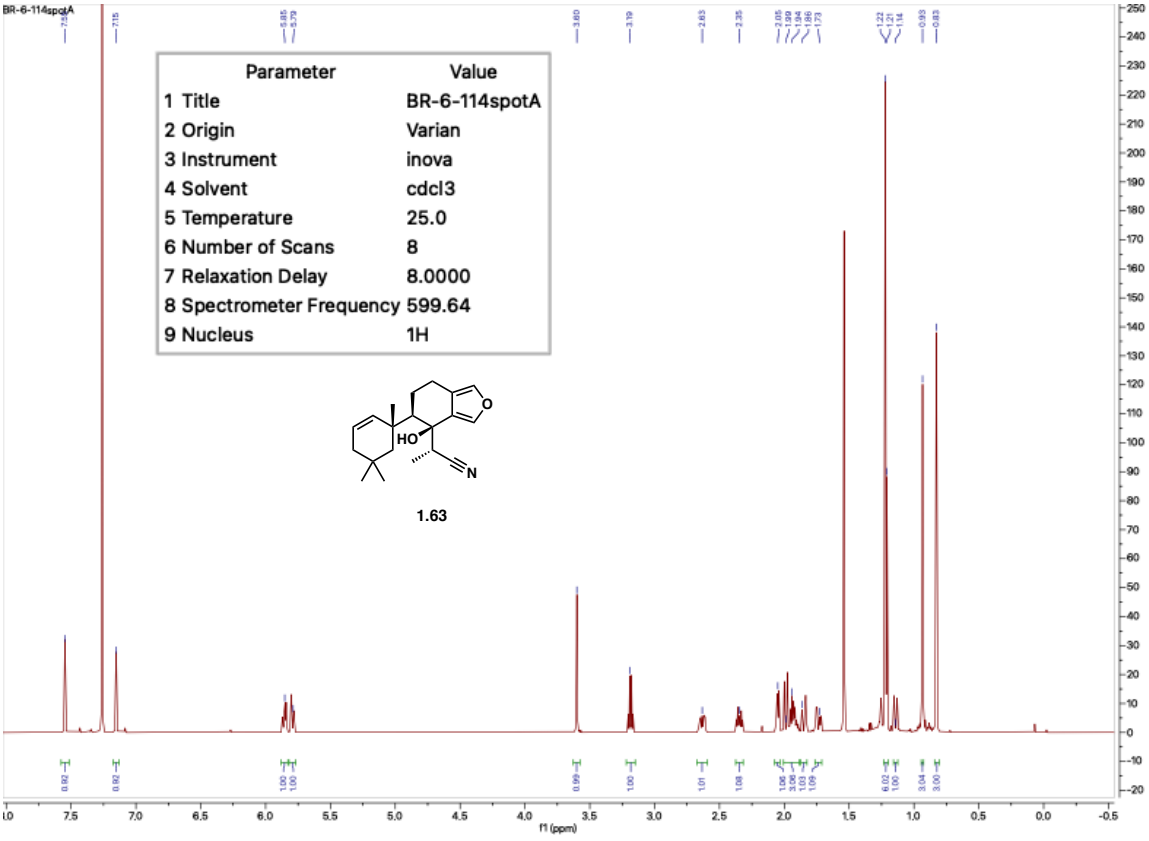
1.60


BR-6-99pure
Parameter Value
1 Title BR-6-99pure
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 8
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 599.64
9 Nucleus 1H
O
O
OMe
COOEt
f1 (ppm)

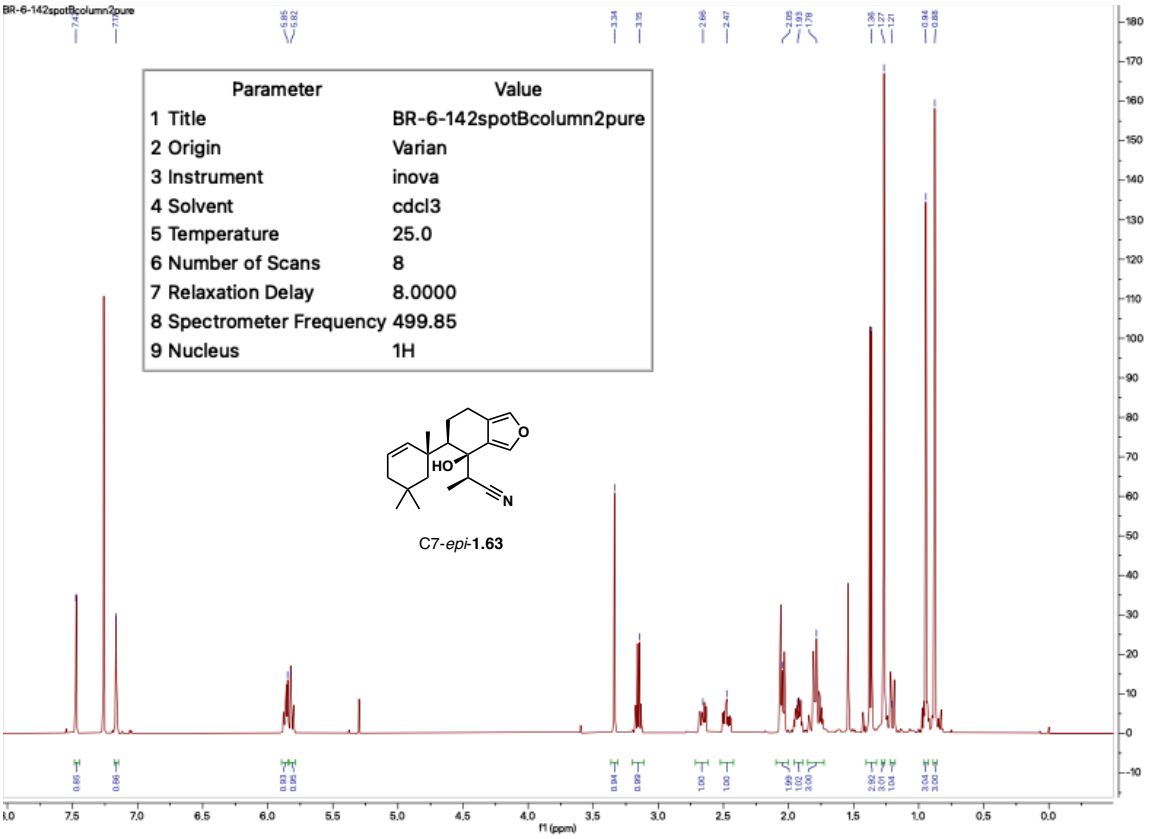
1.61


BR-6-93pure
Parameter Value
1 Title BR-6-93pure
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 8
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 599.64
9 Nucleus 1H
O
O
OMe
COOEt
f1 (ppm)

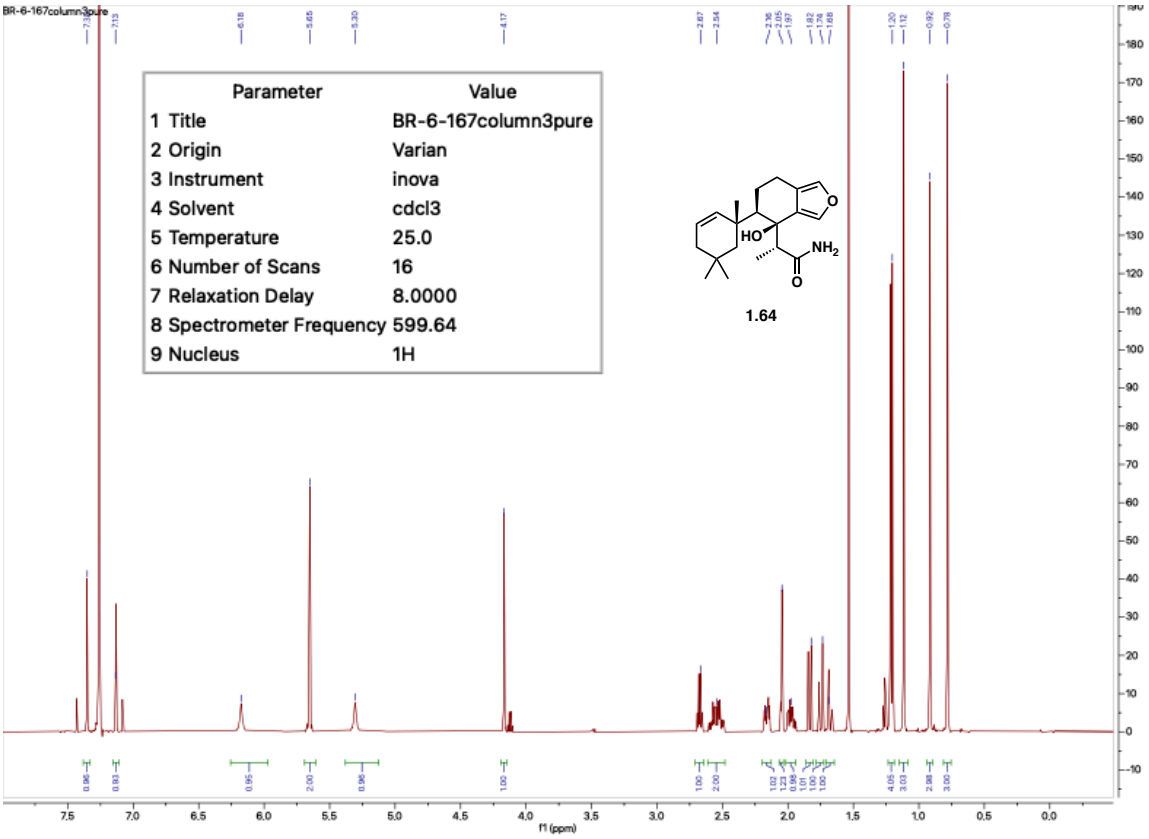
S1.61


BR-6-114spotA
Parameter Value
1 Title BR-6-114spotA
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 8
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 599.64
9 Nucleus 1H
HO
O
N
f1 (ppm)

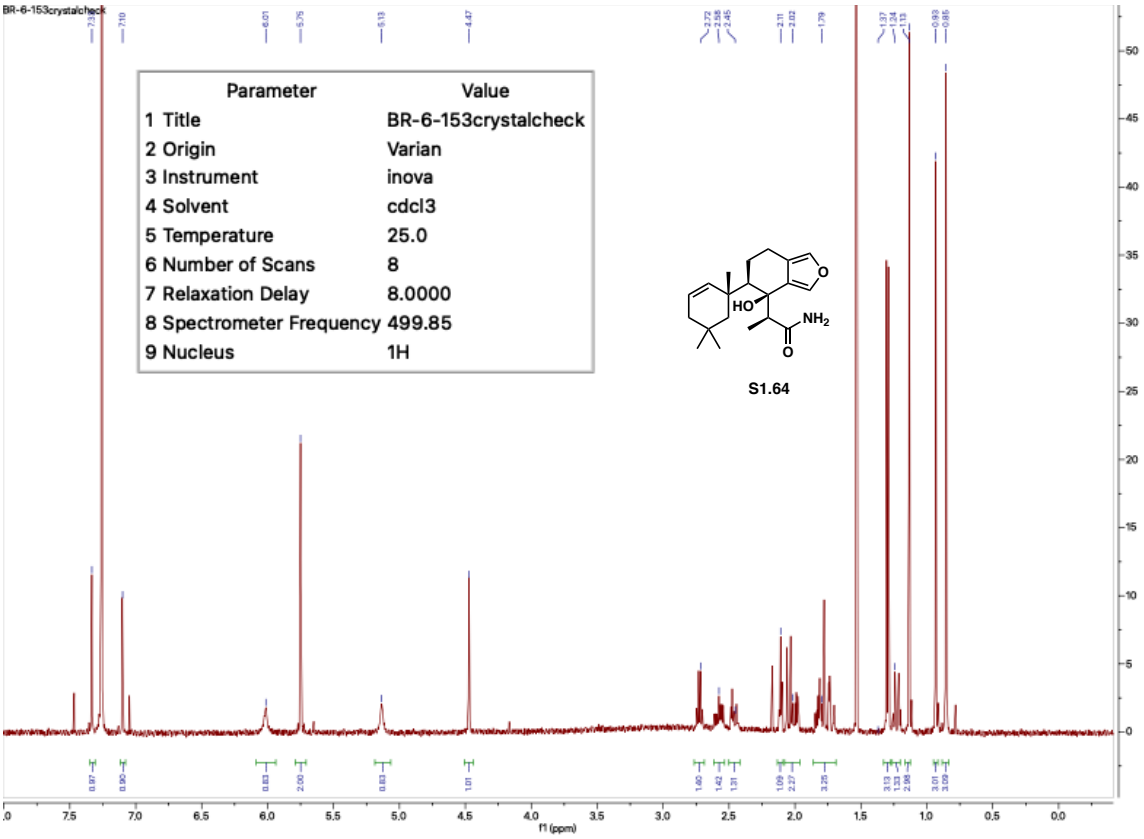
1.63



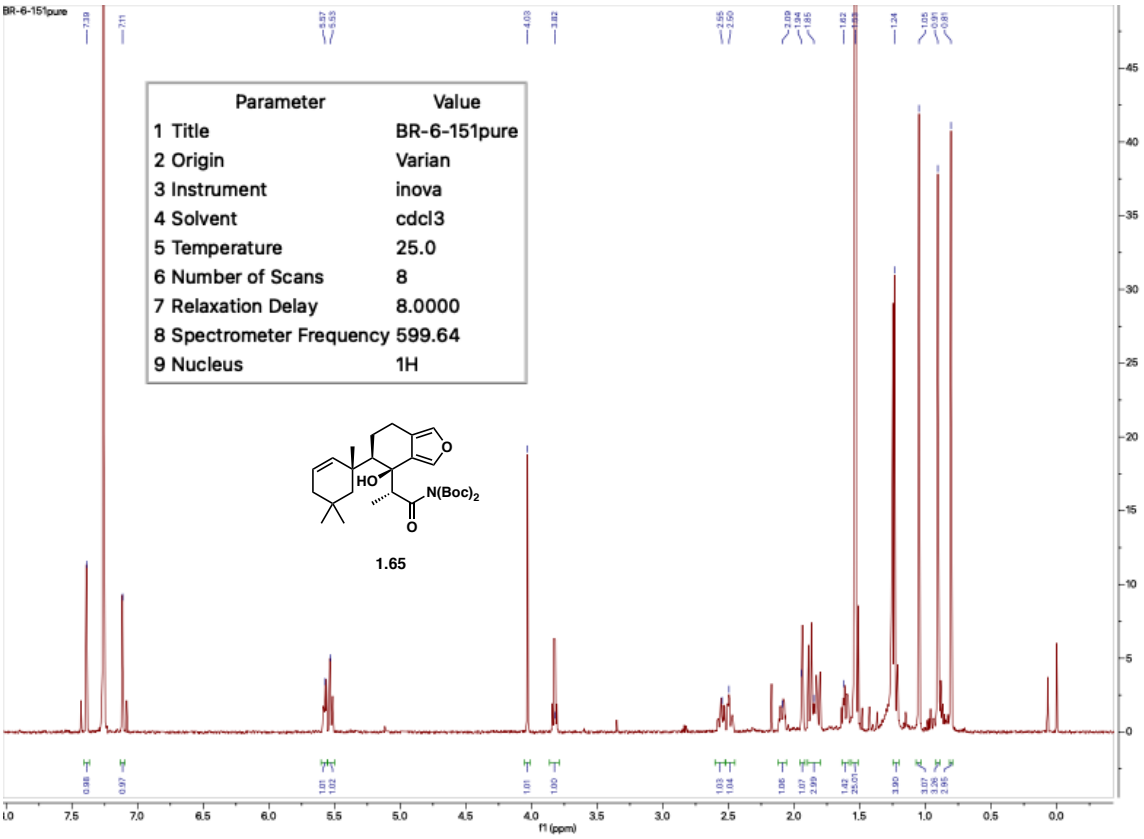
C7-epi-**1.63**



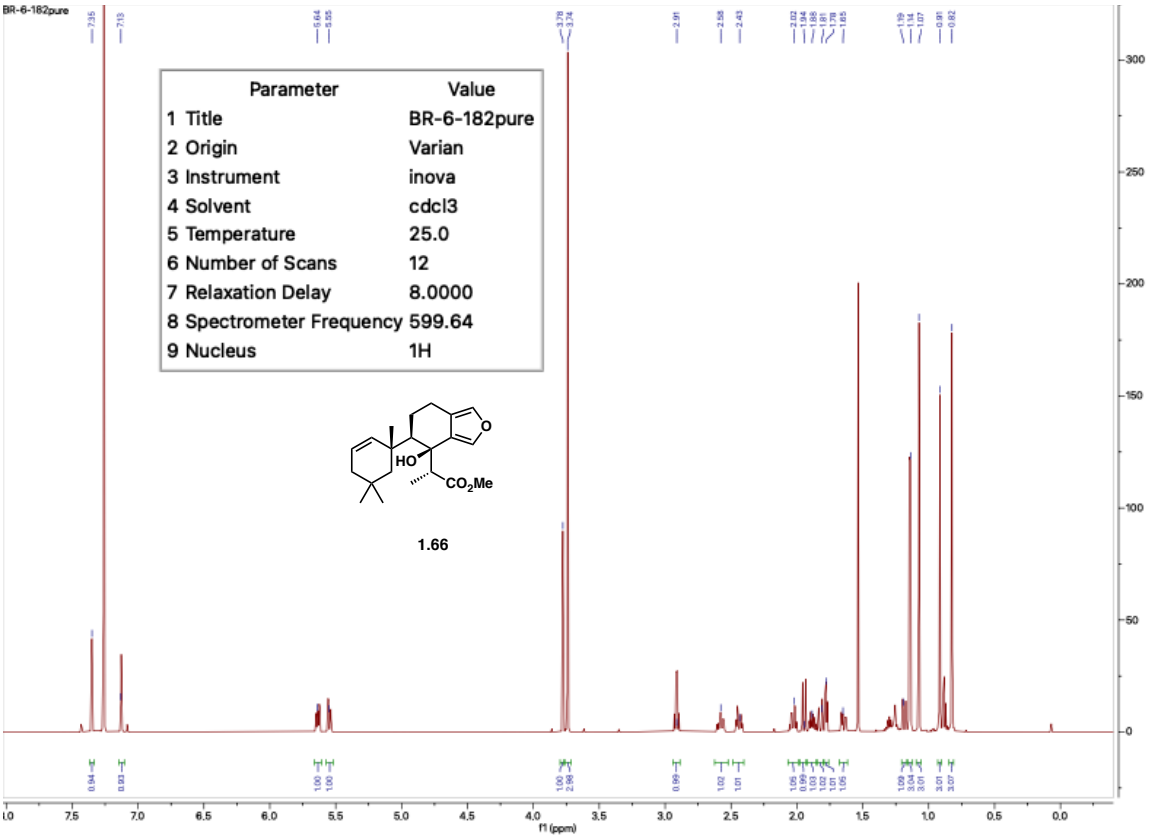
1.64


BR-6-153crystalcheck
Parameter Value
1 Title BR-6-153crystalcheck
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 8
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 499.85
9 Nucleus 1H
HO
O
NH2
O
f1 (ppm)

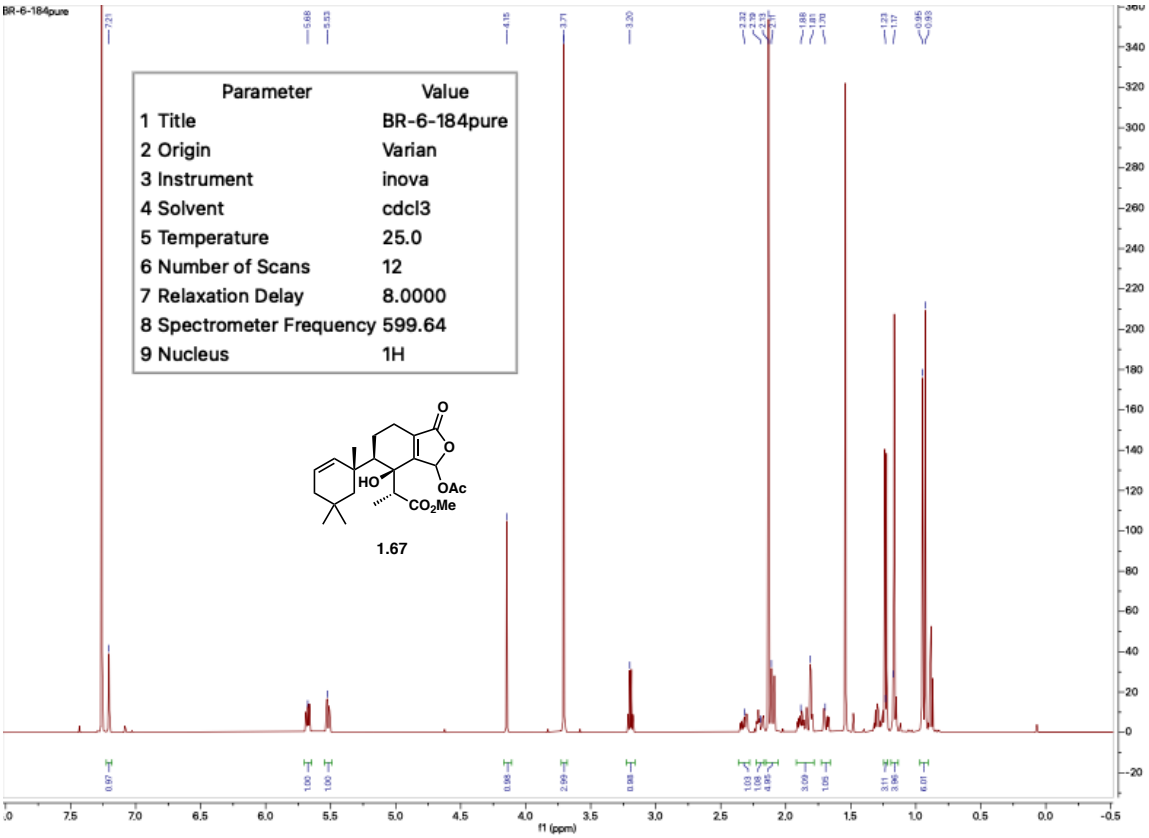
S1.64


BR-6-151pure
Parameter Value
1 Title BR-6-151pure
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 8
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 599.64
9 Nucleus 1H
HO
O
N(Boc)2
O
f1 (ppm)

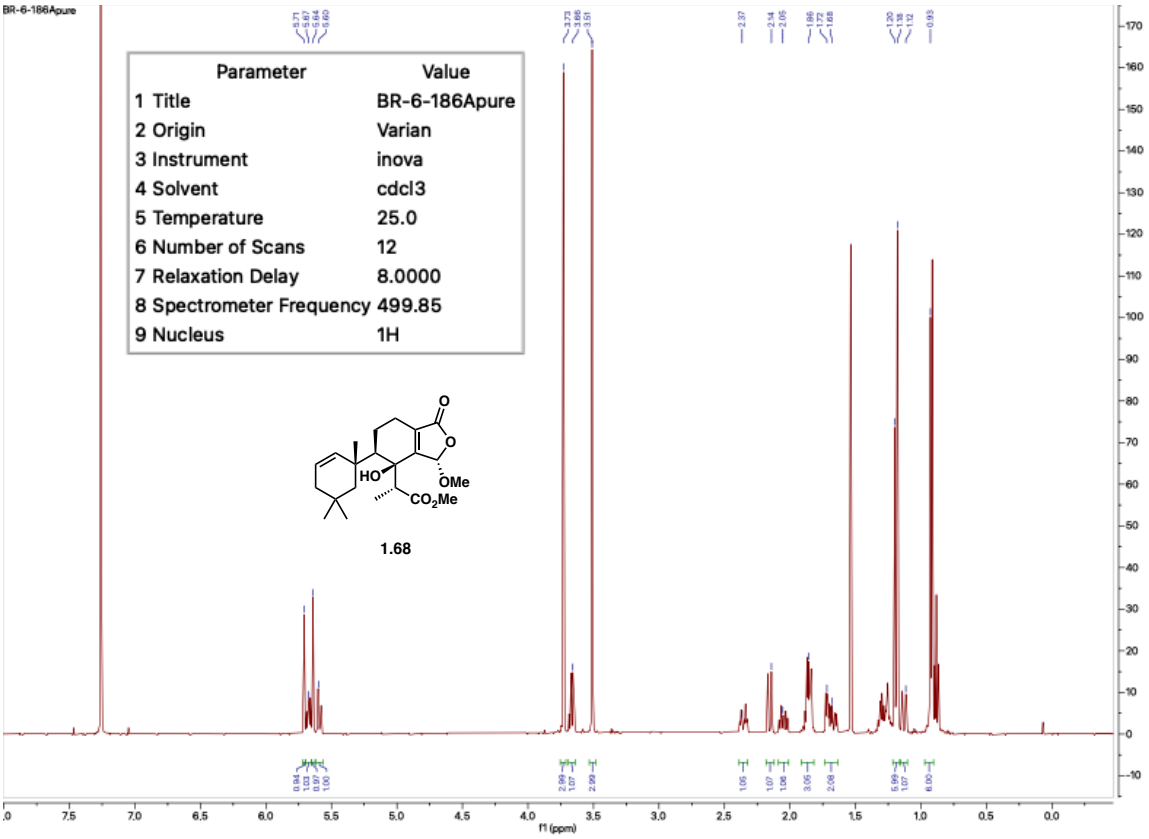
1.65


BR-6-182pure
Parameter Value
1 Title BR-6-182pure
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 12
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 599.64
9 Nucleus 1H
HO
CO2Me
O
f1 (ppm)

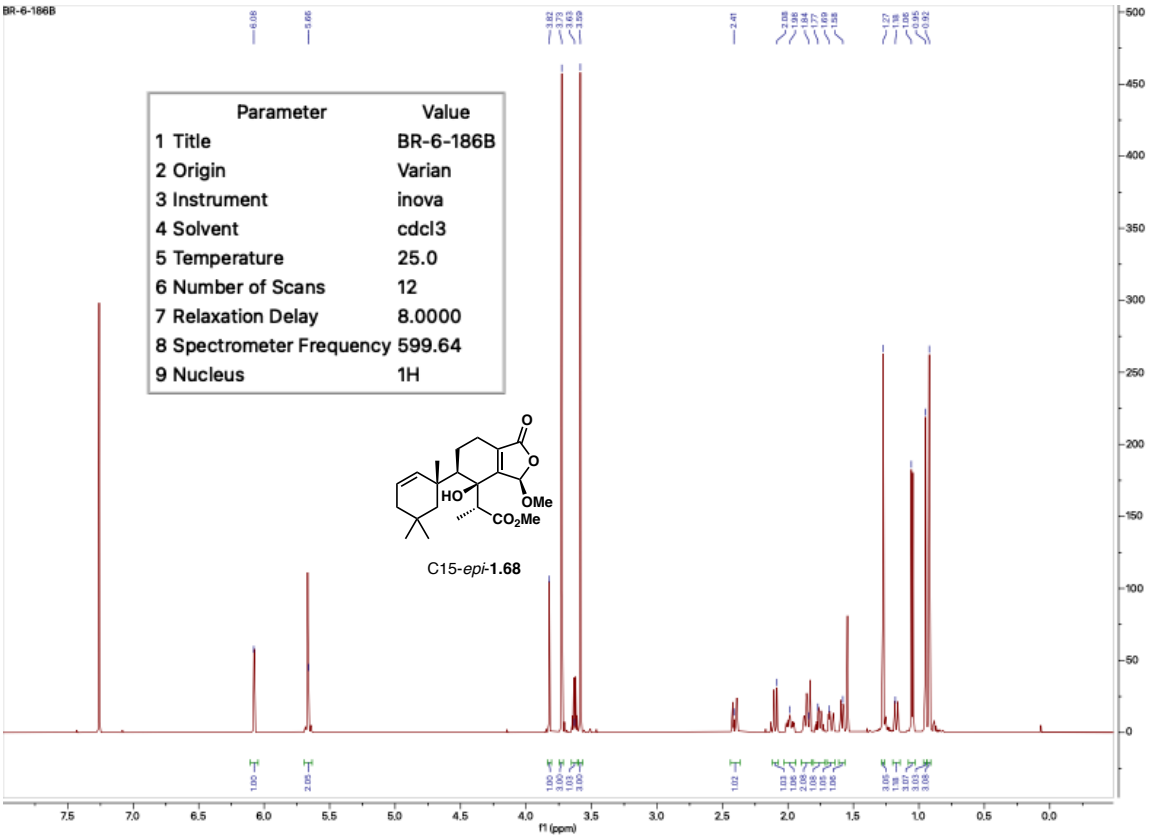
1.66


BR-6-184pure
Parameter Value
1 Title BR-6-184pure
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 12
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 599.64
9 Nucleus 1H
HO
CO2Me
OAc
O
f1 (ppm)

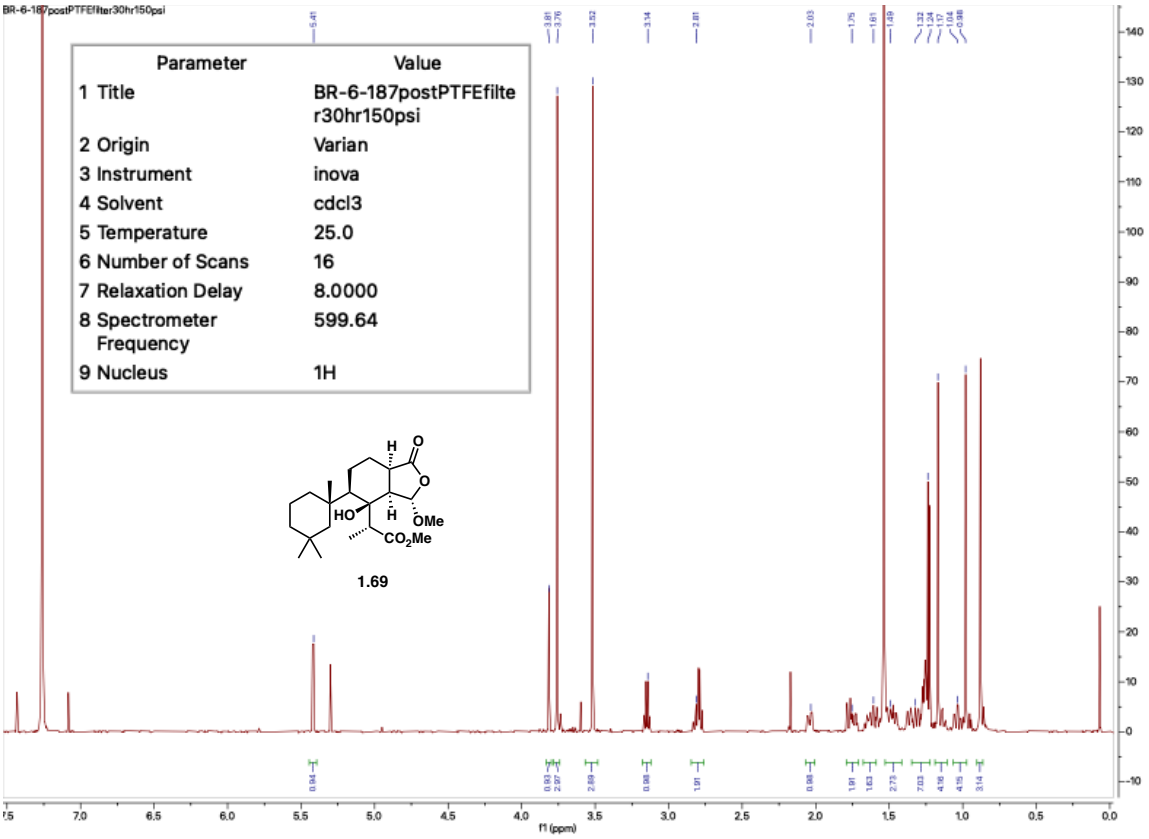
1.67



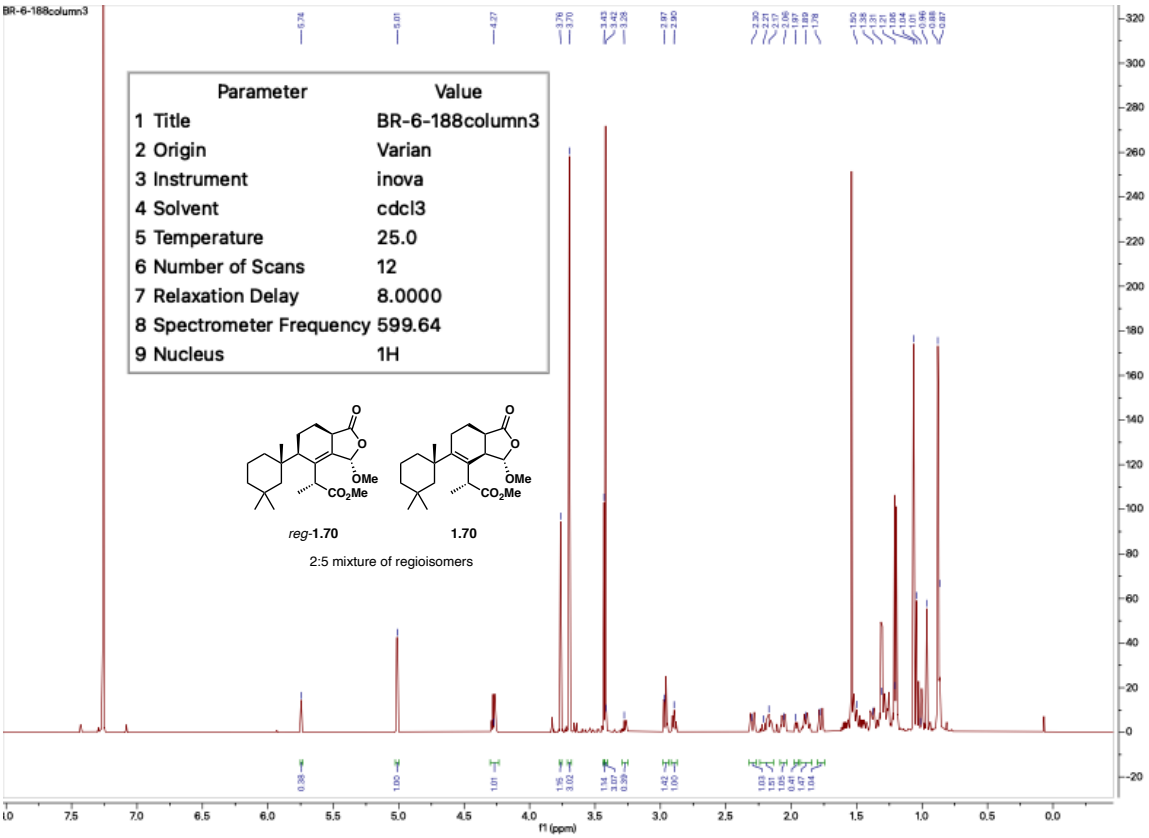
1.68



C15-*epi*-**1.68**

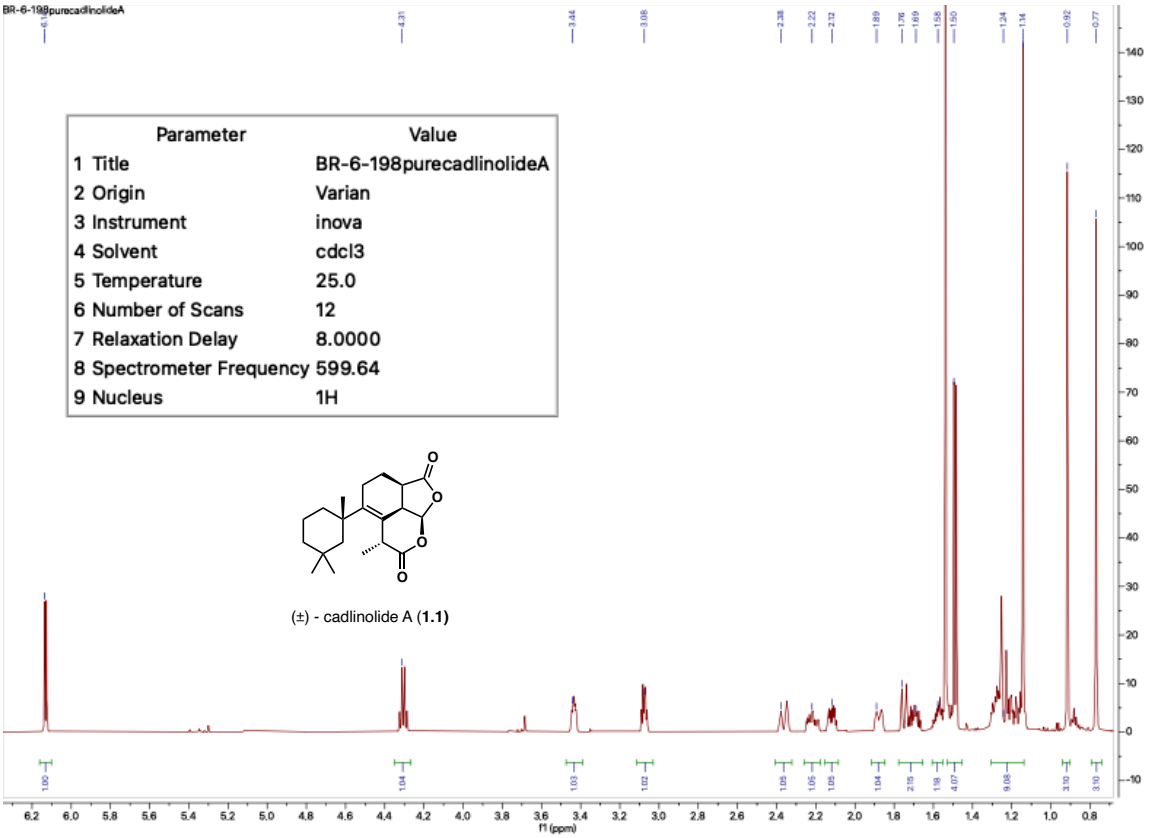


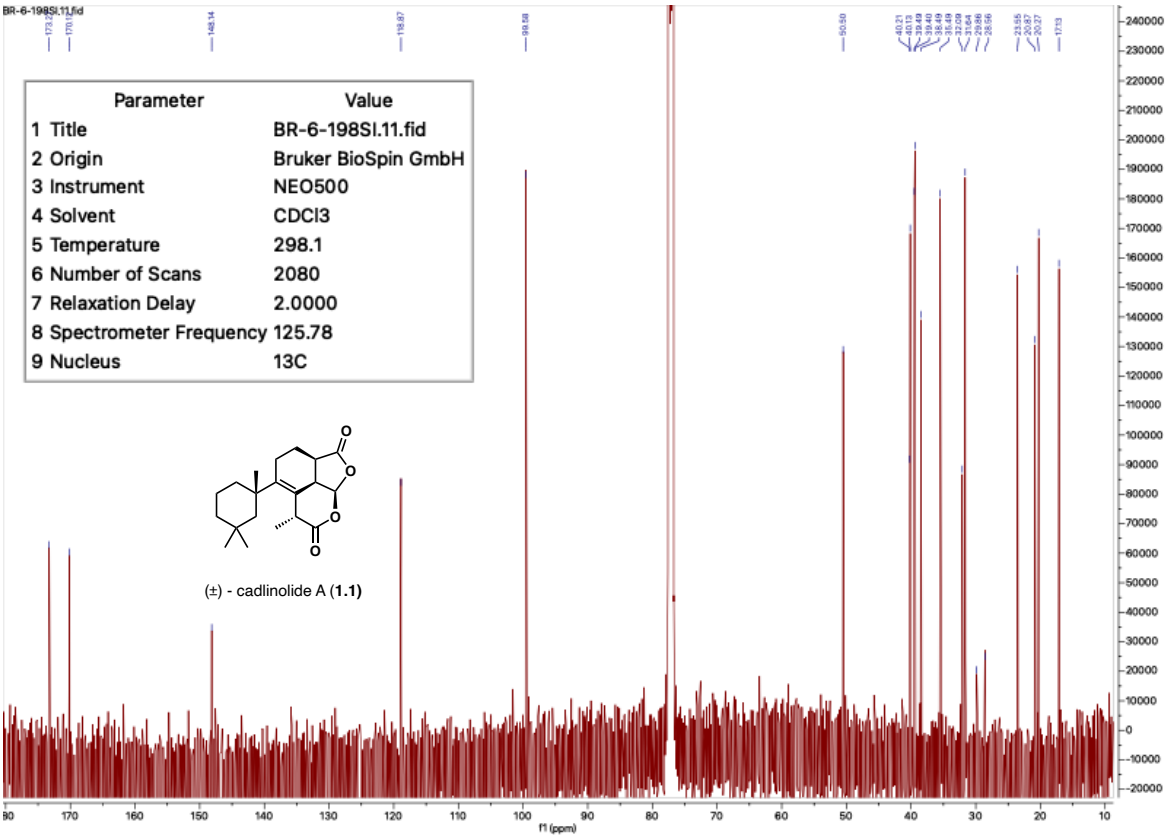
1.69

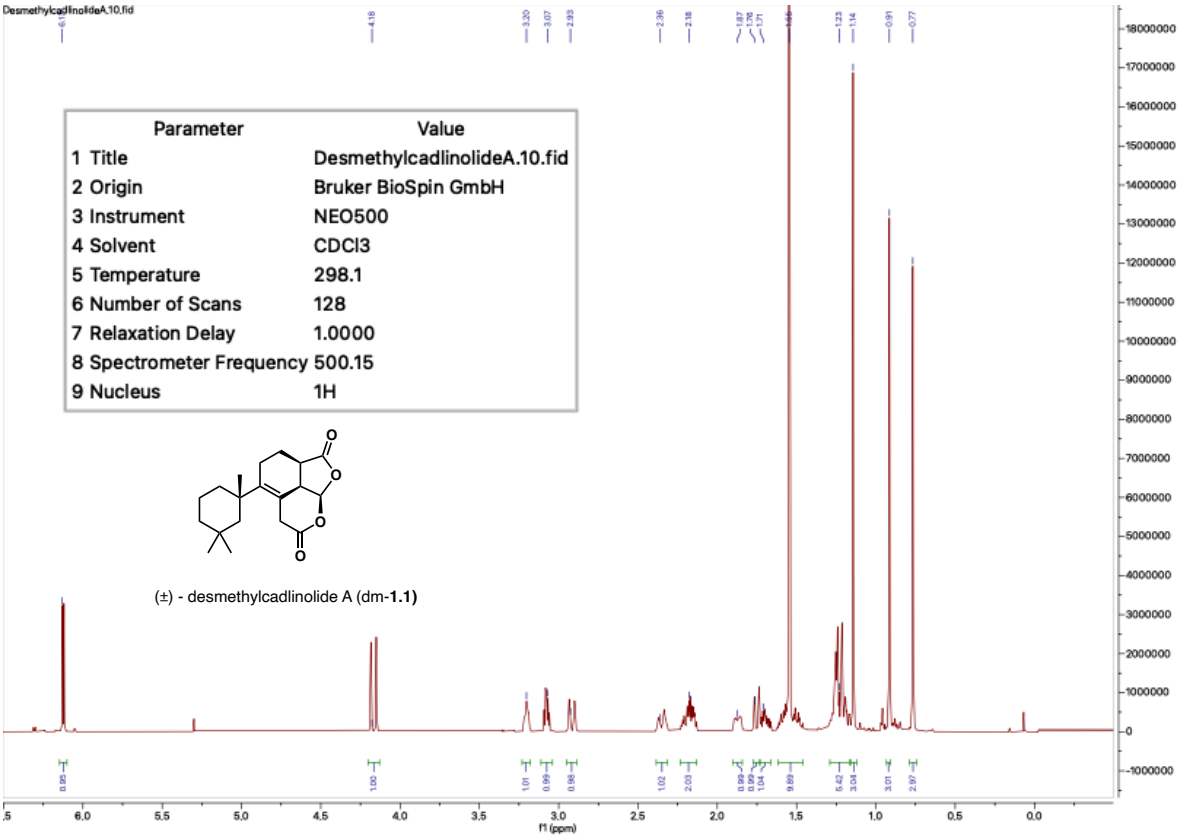


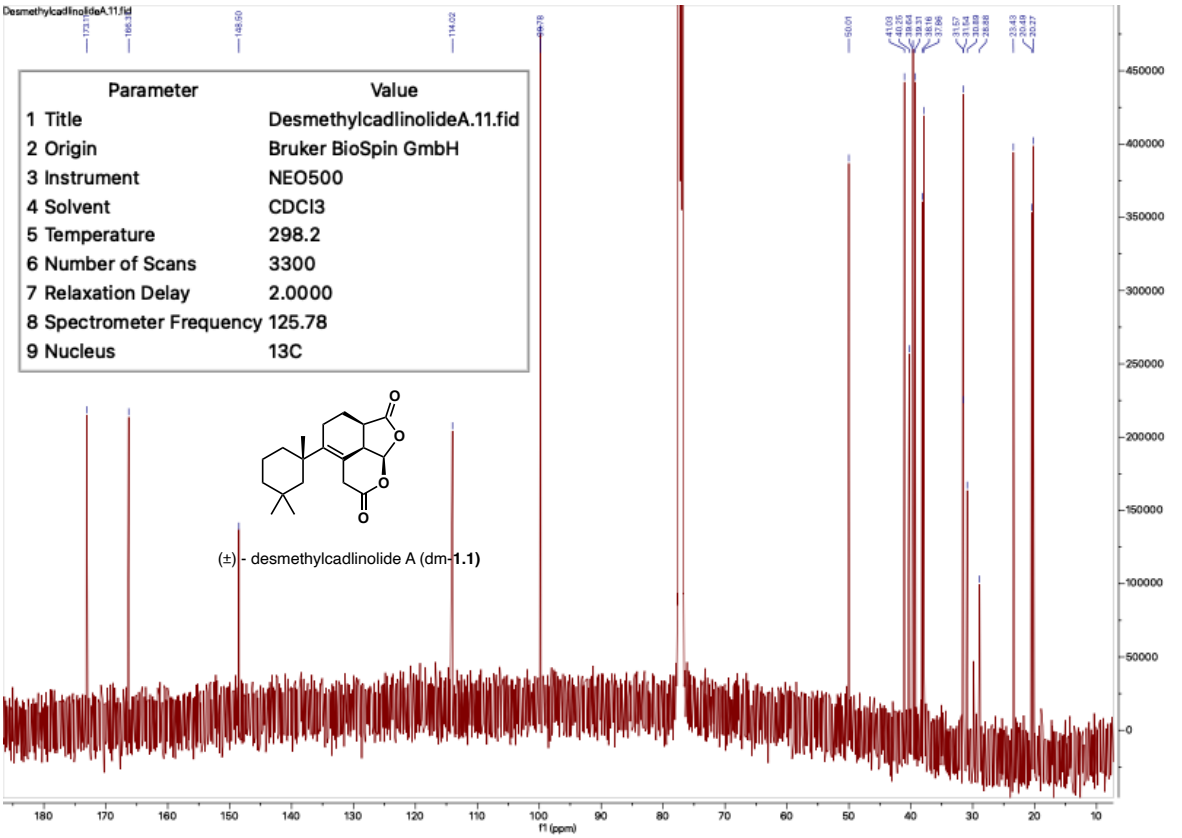
reg-**1.70** **1.70**

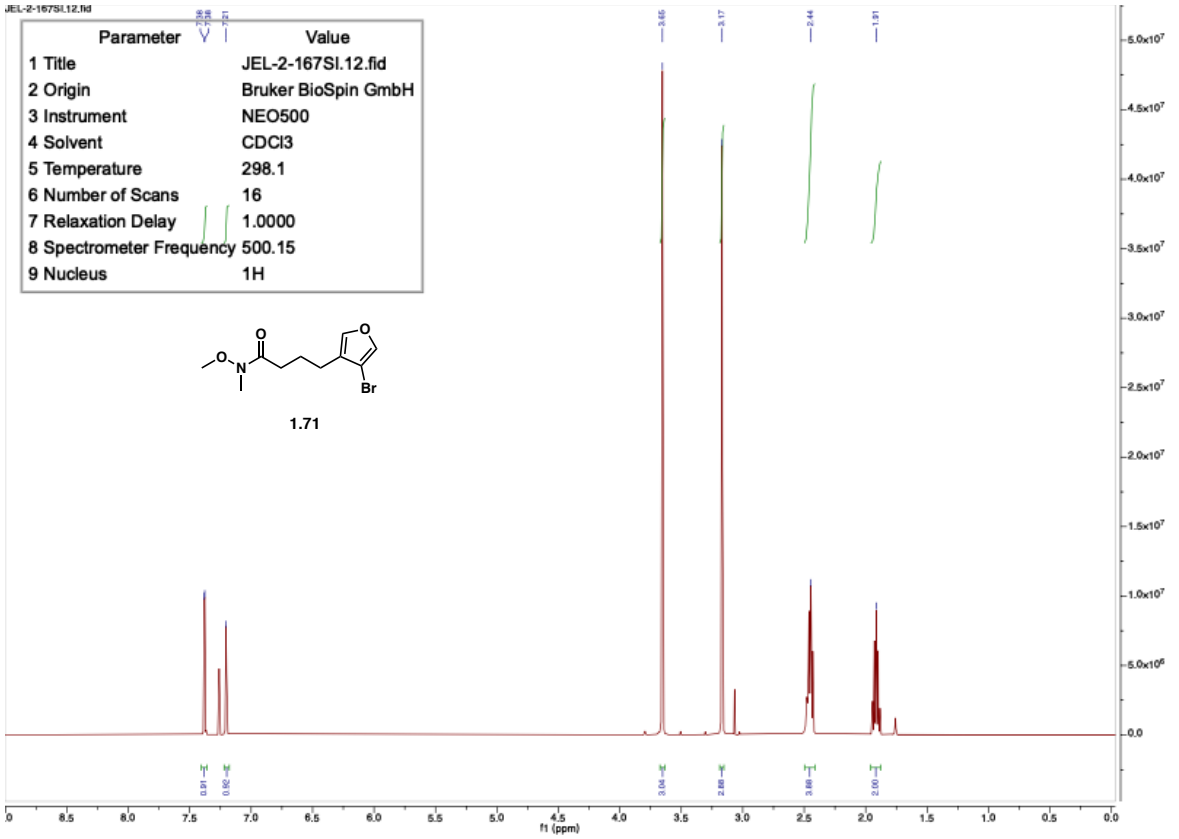
2:5 mixture of regioisomers

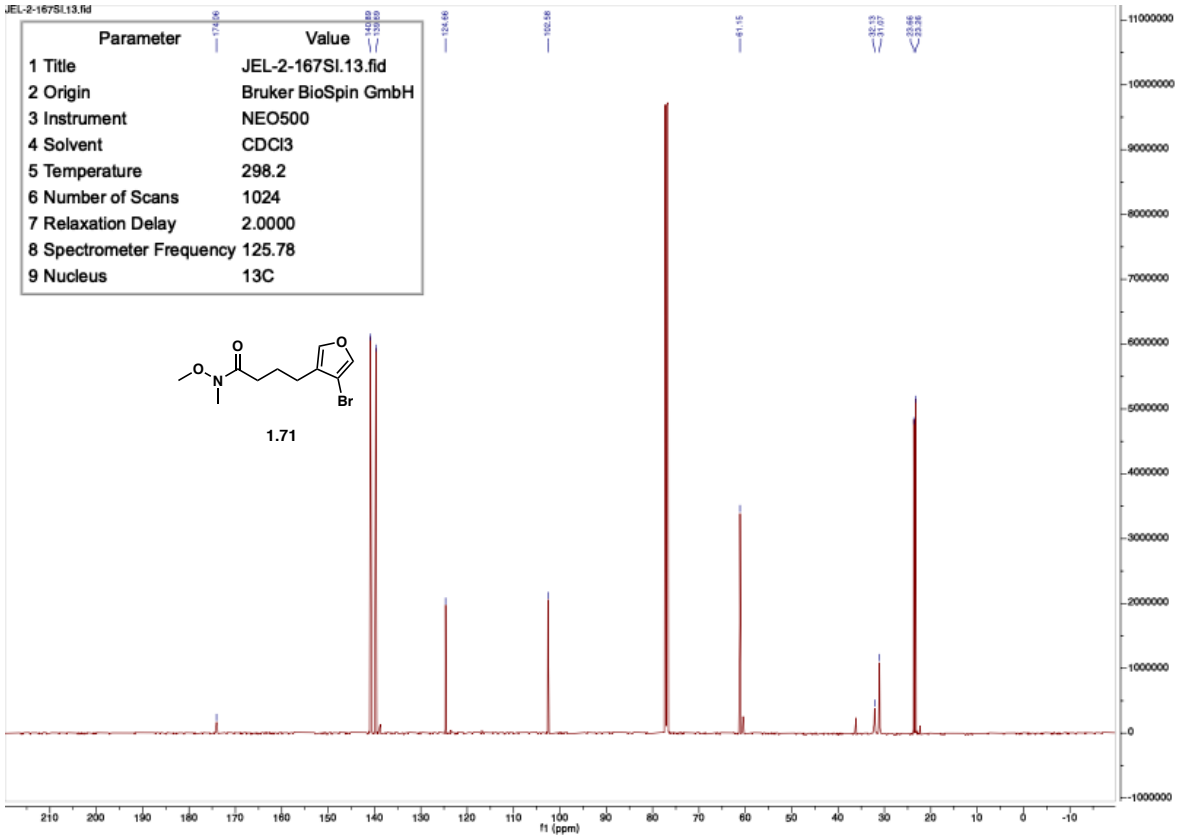

BR-6-198purecadlinolideA
Parameter Value
1 Title BR-6-198purecadlinolideA
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 12
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 599.64
9 Nucleus 1H
(±) - cadlinolide A (1.1)
f1 (ppm)

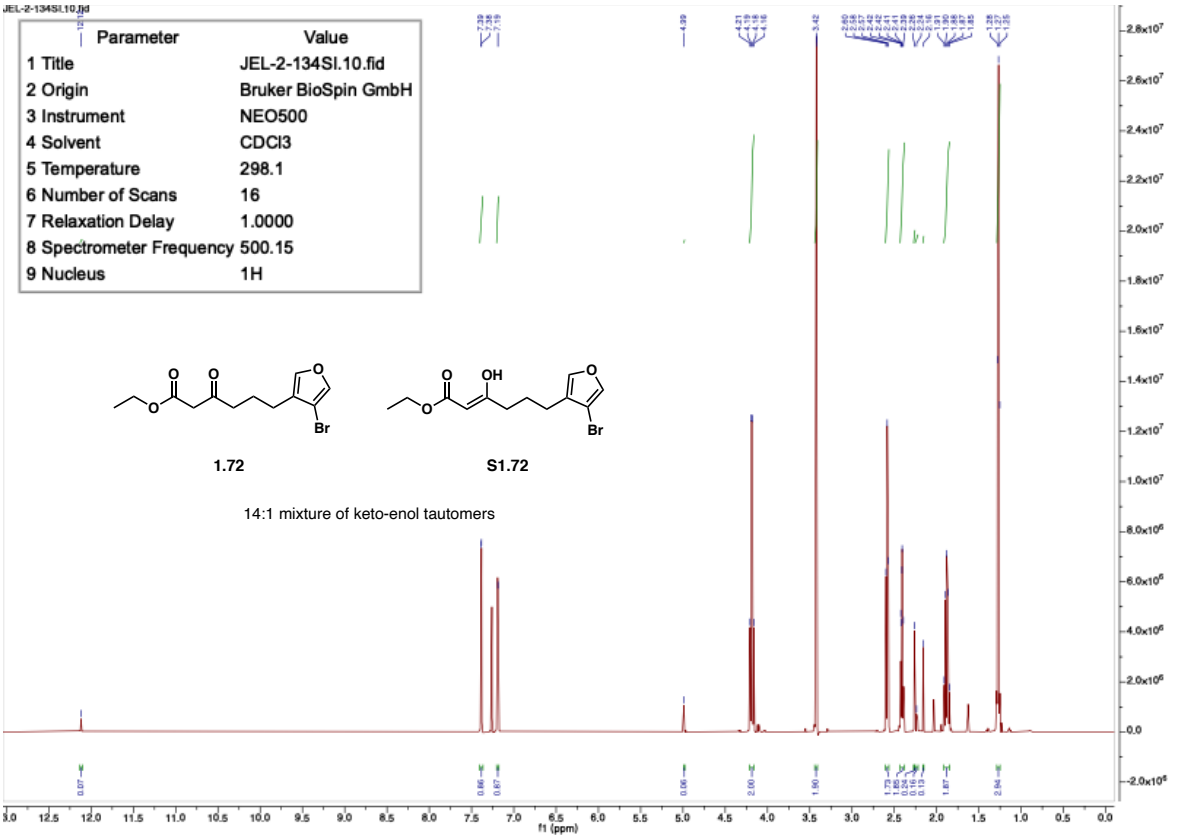

BR-6-198Sl.11.fid
Parameter Value
1 Title BR-6-198Sl.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 2080
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
(±) - cadlinolide A (1.1)
f1 (ppm)

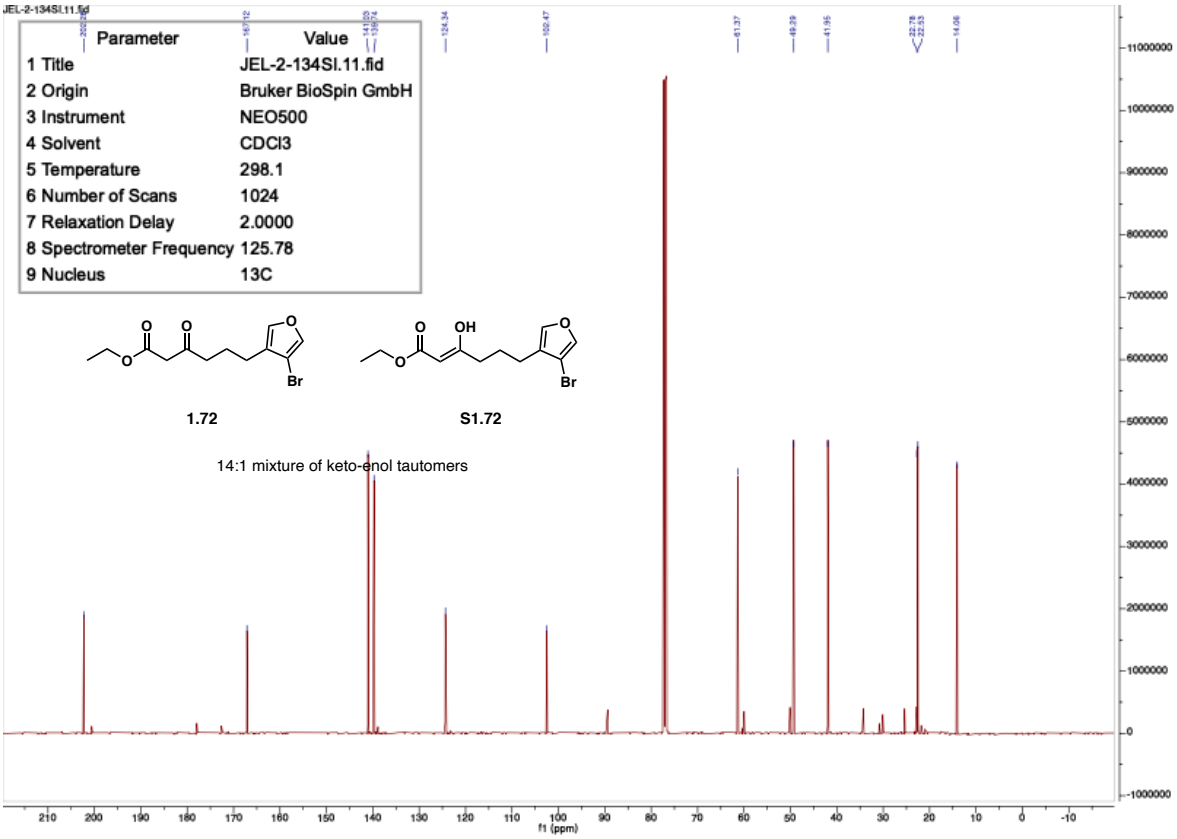

DesmethylcadlinolideA.10.fid
Parameter Value
1 Title DesmethylcadlinolideA.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 128
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
(±) - desmethylcadlinolide A (dm-1.1)
f1 (ppm)

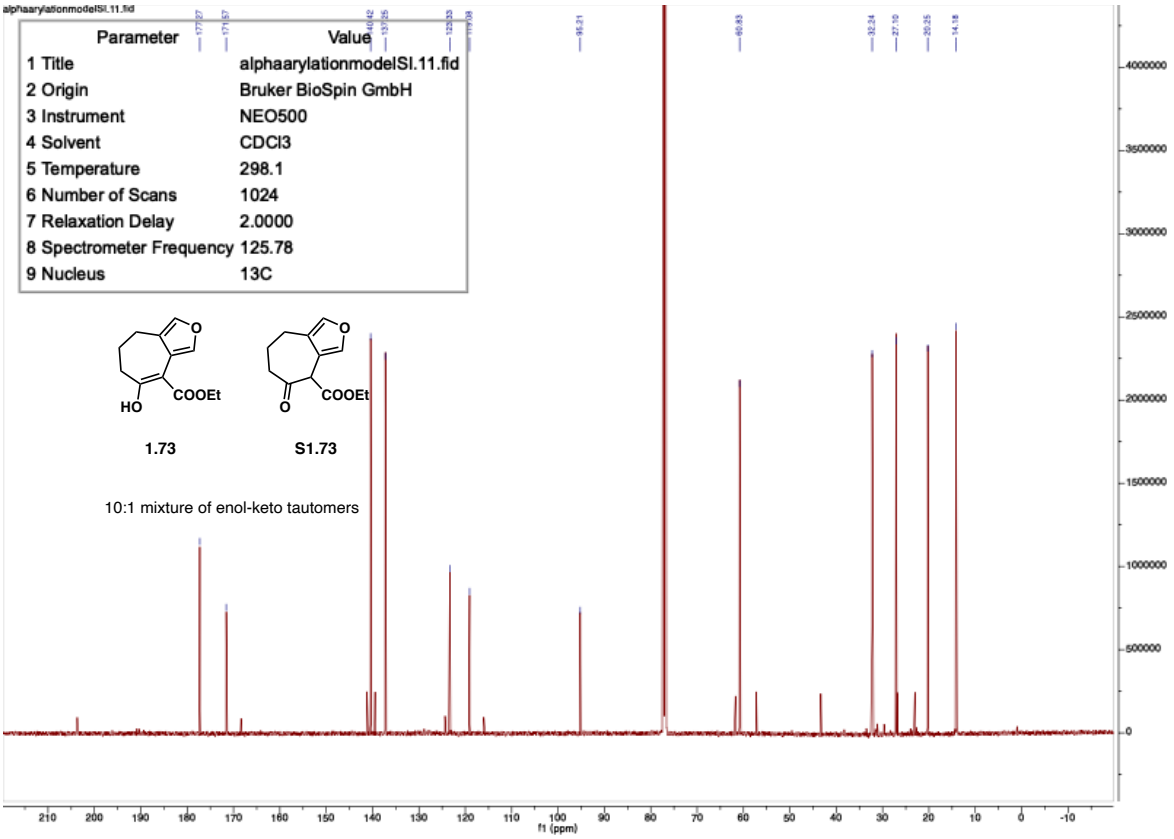

DesmethylcadlinolideA.11.fid
Parameter Value
1 Title DesmethylcadlinolideA.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 3300
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
(±) - desmethylcadlinolide A (dm-1.1)
f1 (ppm)

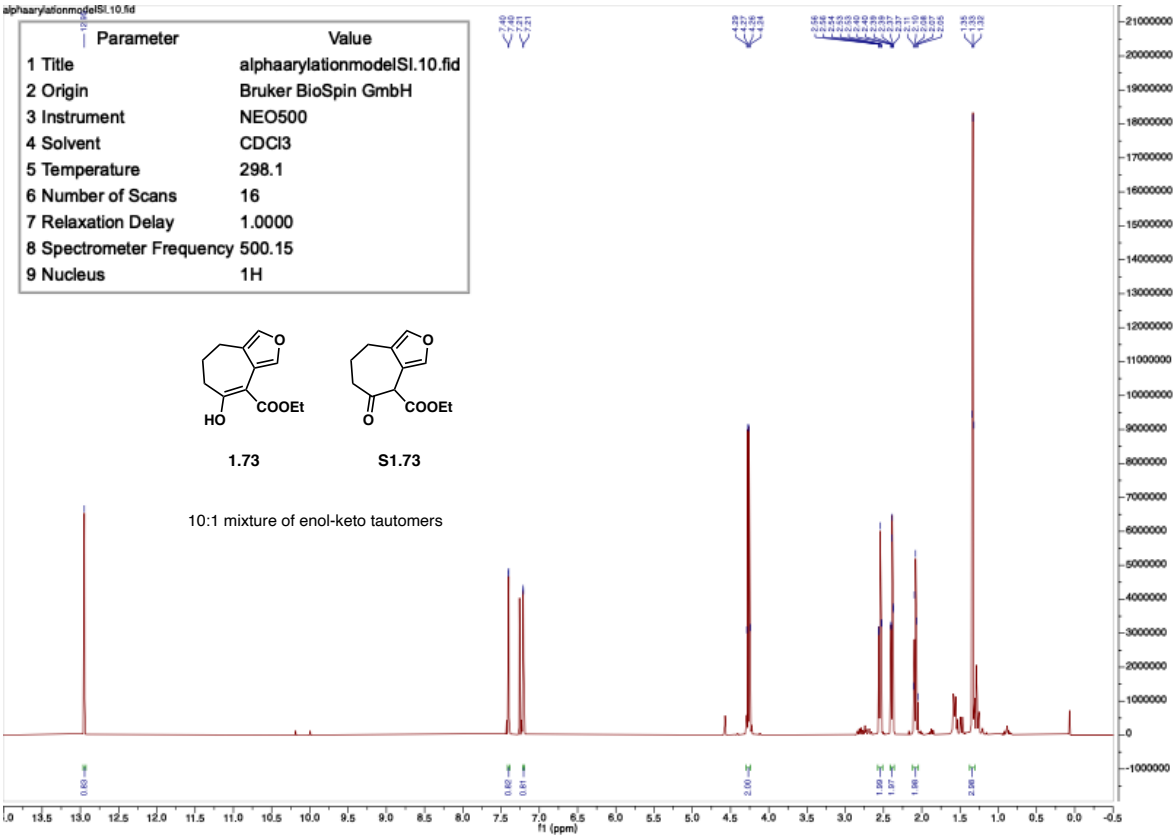

JEL-2-167SI.12.fid
Parameter Value
1 Title JEL-2-167SI.12.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
O
N
O
Br
1.71
f1 (ppm)

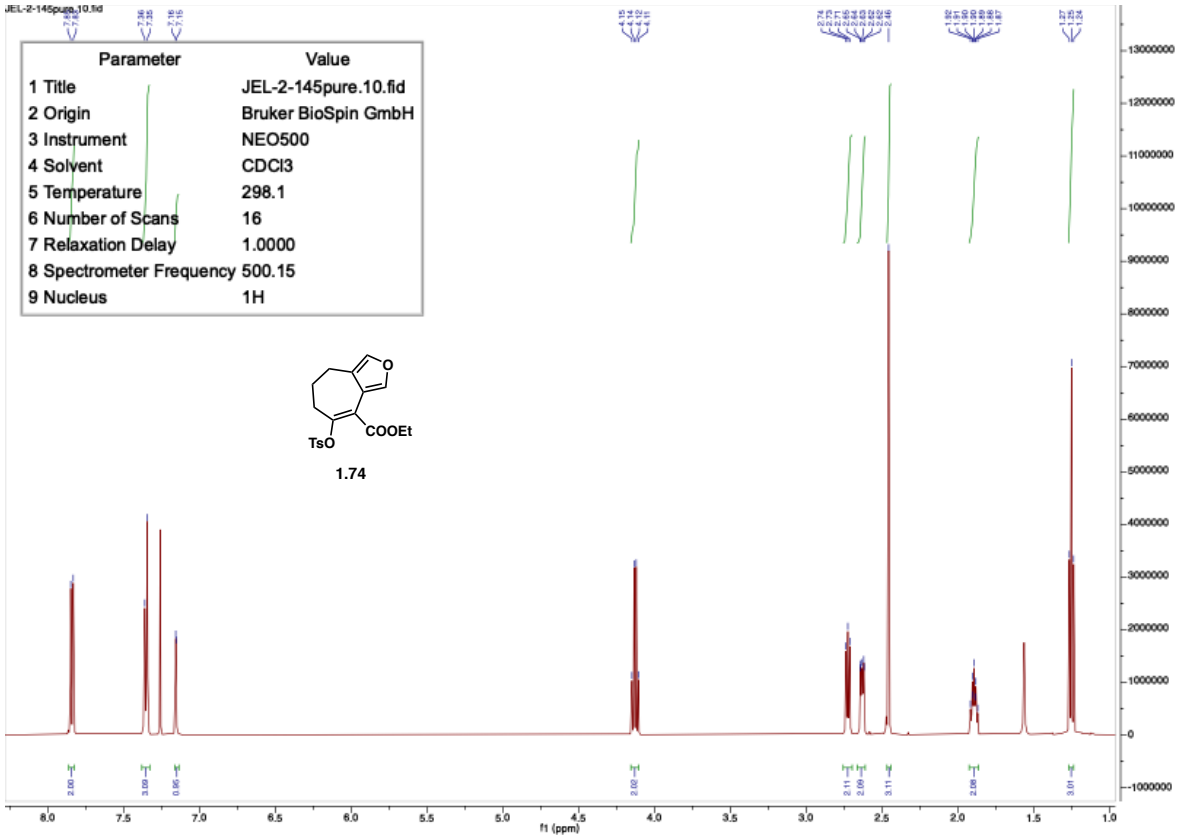

JEL-2-167SI.13.fid
Parameter Value
1 Title JEL-2-167SI.13.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
O
N
O
Br
1.71
f1 (ppm)

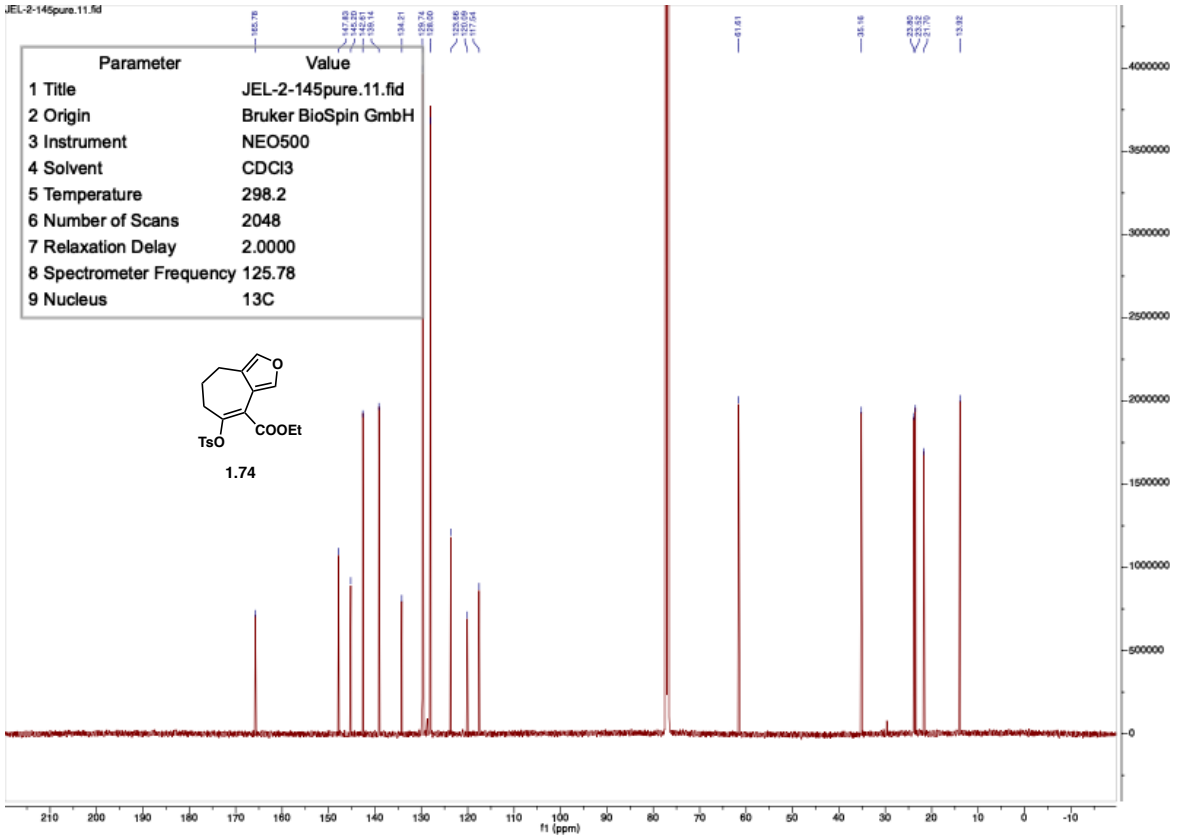

Parameter Value
1 Title JEL-2-134SI.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
1.72
S1.72
14:1 mixture of keto-enol tautomers
f1 (ppm)

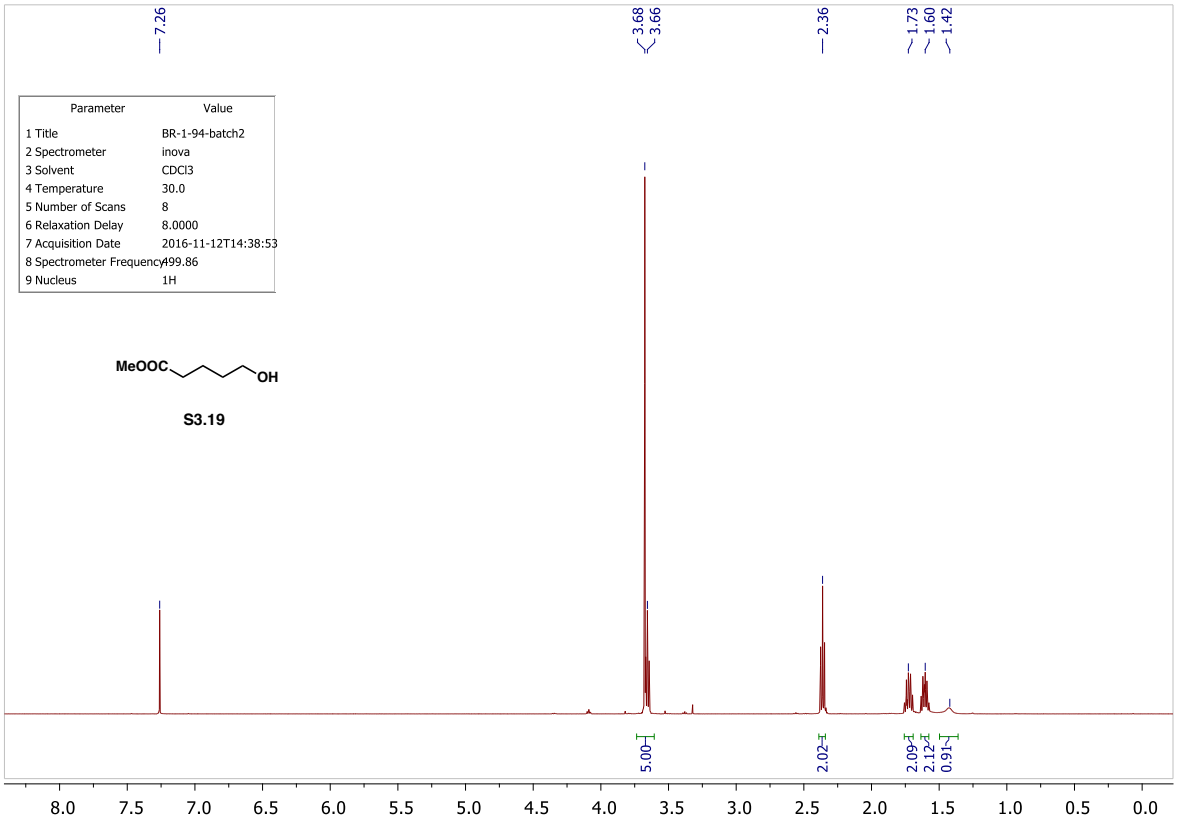

Parameter Value
1 Title JEL-2-134SI.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
1.72
S1.72
14:1 mixture of keto-enol tautomers
f1 (ppm)

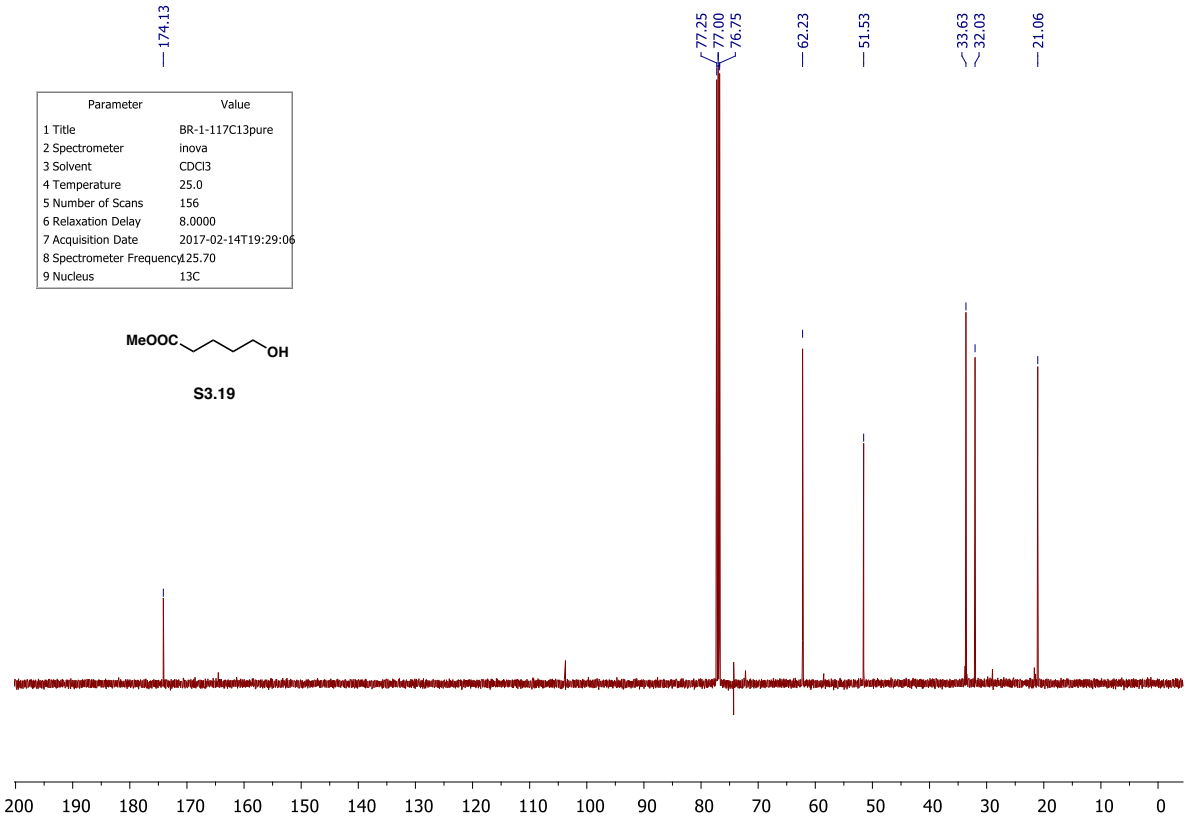

alphaarylationmodelSI.11.fid
Parameter Value
1 Title alphaarylationmodelSI.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
HO
COOEt
O
1.73
S1.73
10:1 mixture of enol-keto tautomers
f1 (ppm)

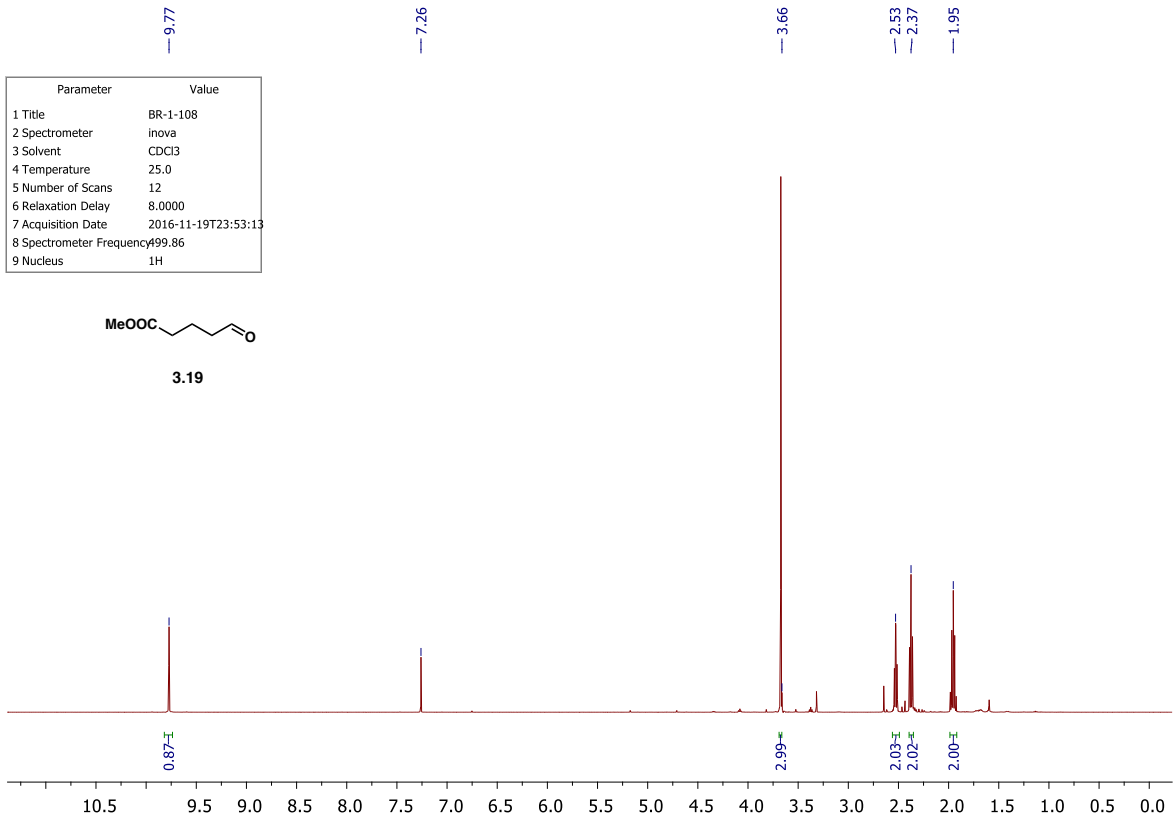

alphaarylationmodelSI.10.fid
Parameter Value
1 Title alphaarylationmodelSI.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
HO
COOEt
O
1.73
S1.73
10:1 mixture of enol-keto tautomers
f1 (ppm)

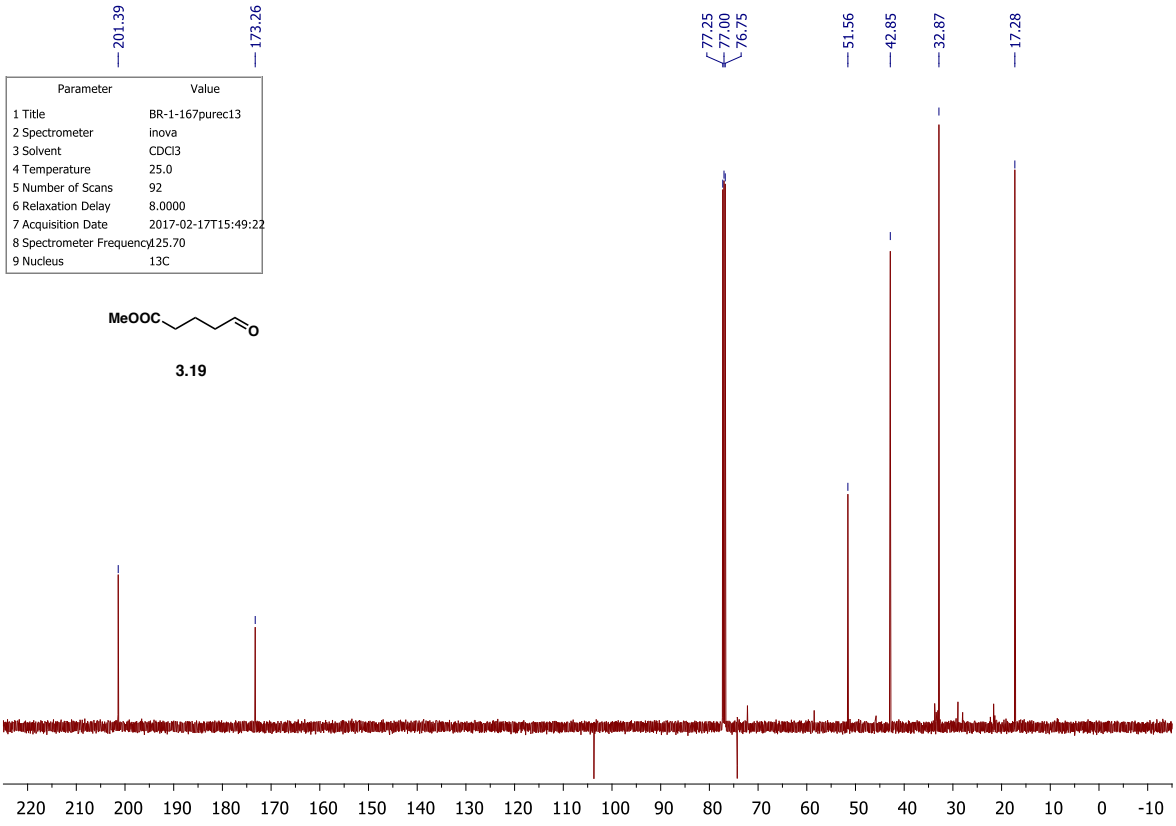

JEL-2-145pure.10.fid
Parameter Value
1 Title JEL-2-145pure.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
TsO
COOEt
1.74
f1 (ppm)

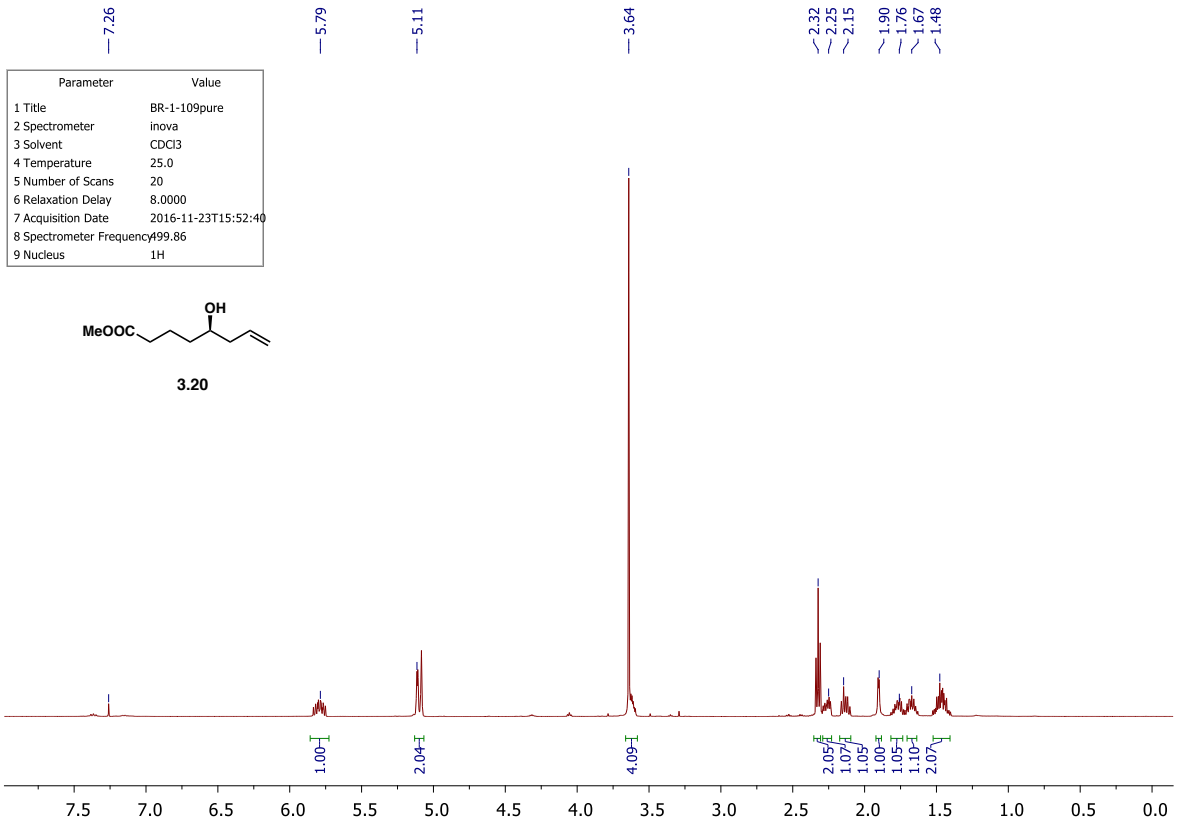

JEL-2-145pure.11.fid
Parameter Value
1 Title JEL-2-145pure.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 2048
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
TsO
COOEt
1.74
f1 (ppm)

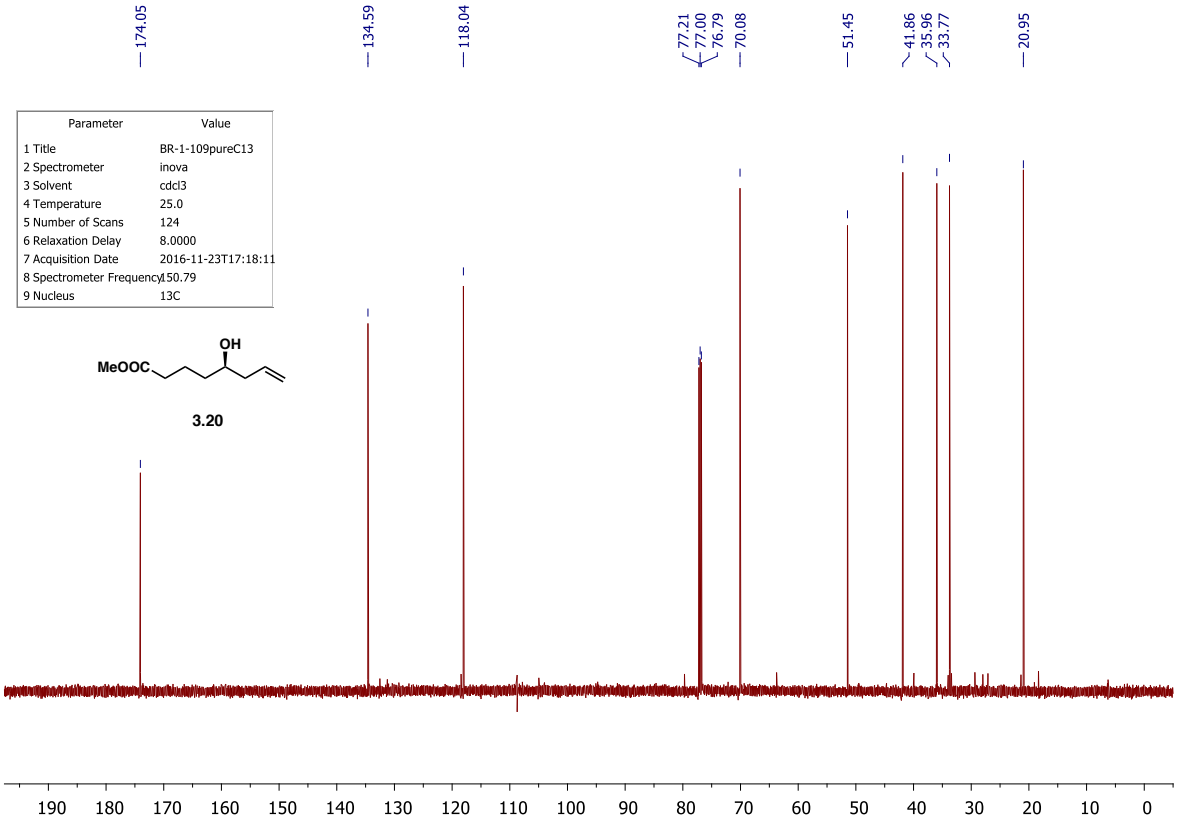

7.26
3.68
3.66
2.36
1.73
1.60
1.42
Parameter Value
1 Title BR-1-94-batch2
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 30.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Acquisition Date 2016-11-12T14:38:53
8 Spectrometer Frequency 499.86
9 Nucleus 1H
MeOOC
OH
S3.19
5.00
2.02
2.09
2.12
0.91
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

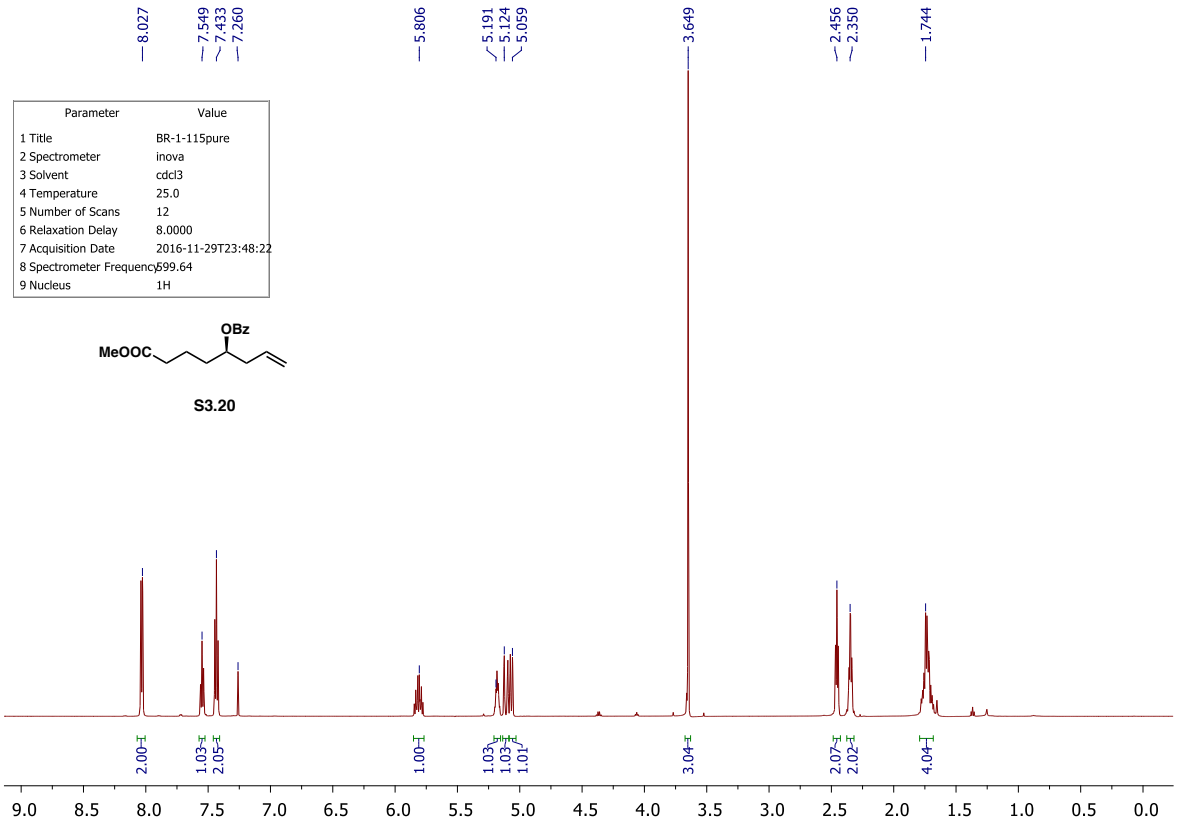

174.13
77.25
77.00
76.75
62.23
51.53
33.63
32.03
21.06
Parameter Value
1 Title BR-1-117C13pure
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 25.0
5 Number of Scans 156
6 Relaxation Delay 8.0000
7 Acquisition Date 2017-02-14T19:29:06
8 Spectrometer Frequency 125.70
9 Nucleus 13C
MeOOC
OH
S3.19
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

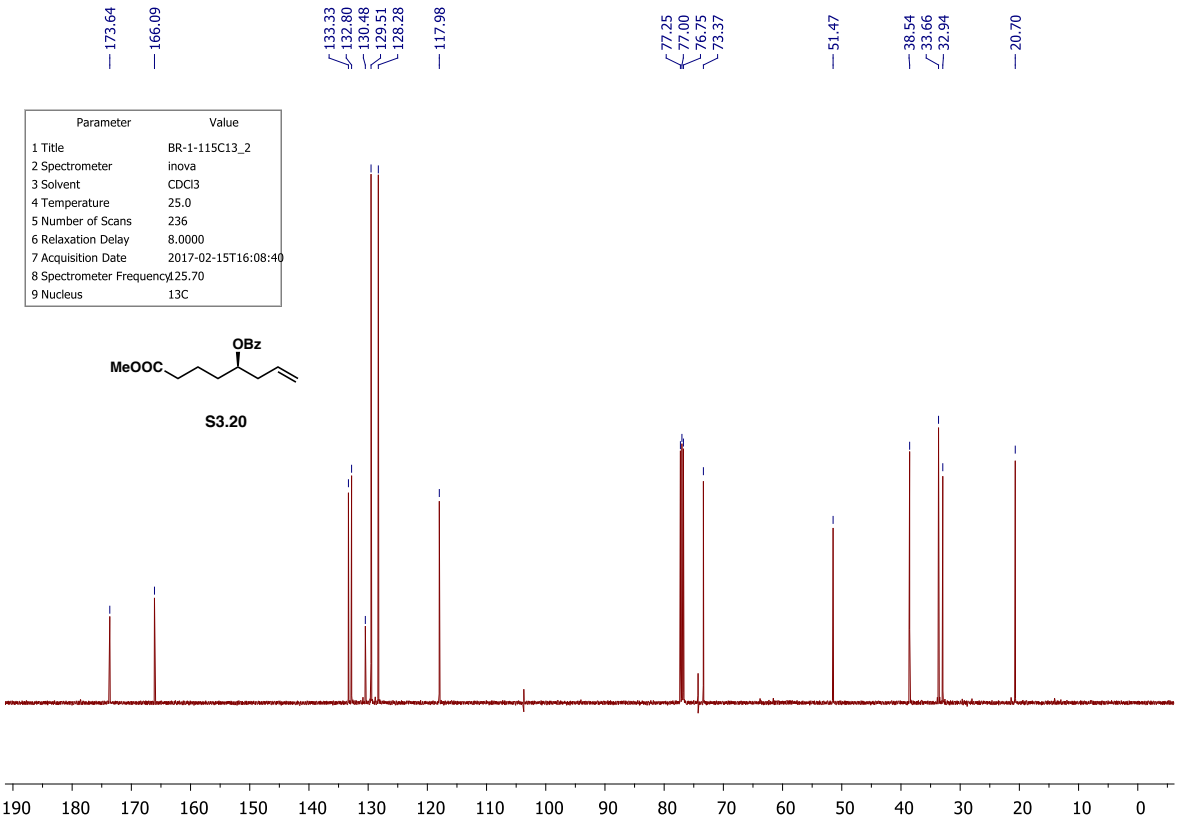

9.77
7.26
3.66
2.53
2.37
1.95
Parameter Value
1 Title BR-1-108
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 25.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Acquisition Date 2016-11-19T23:53:13
8 Spectrometer Frequency 499.86
9 Nucleus 1H
MeOOC
O
3.19
0.87
2.99
2.03
2.02
2.00
10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

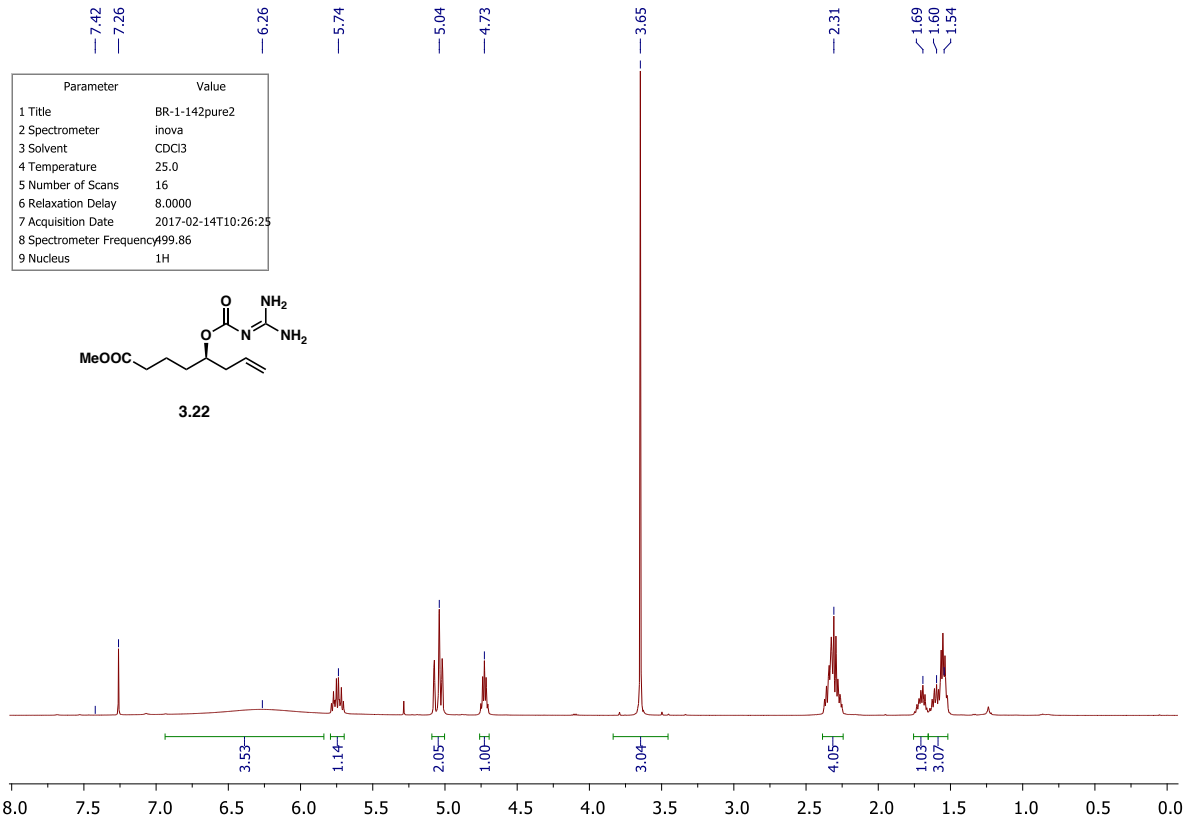

201.39
173.26
77.25
77.00
76.75
51.56
42.85
32.87
17.28
Parameter Value
1 Title BR-1-167purec13
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 25.0
5 Number of Scans 92
6 Relaxation Delay 8.0000
7 Acquisition Date 2017-02-17T15:49:22
8 Spectrometer Frequency 125.70
9 Nucleus 13C
MeOOC
O
3.19
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

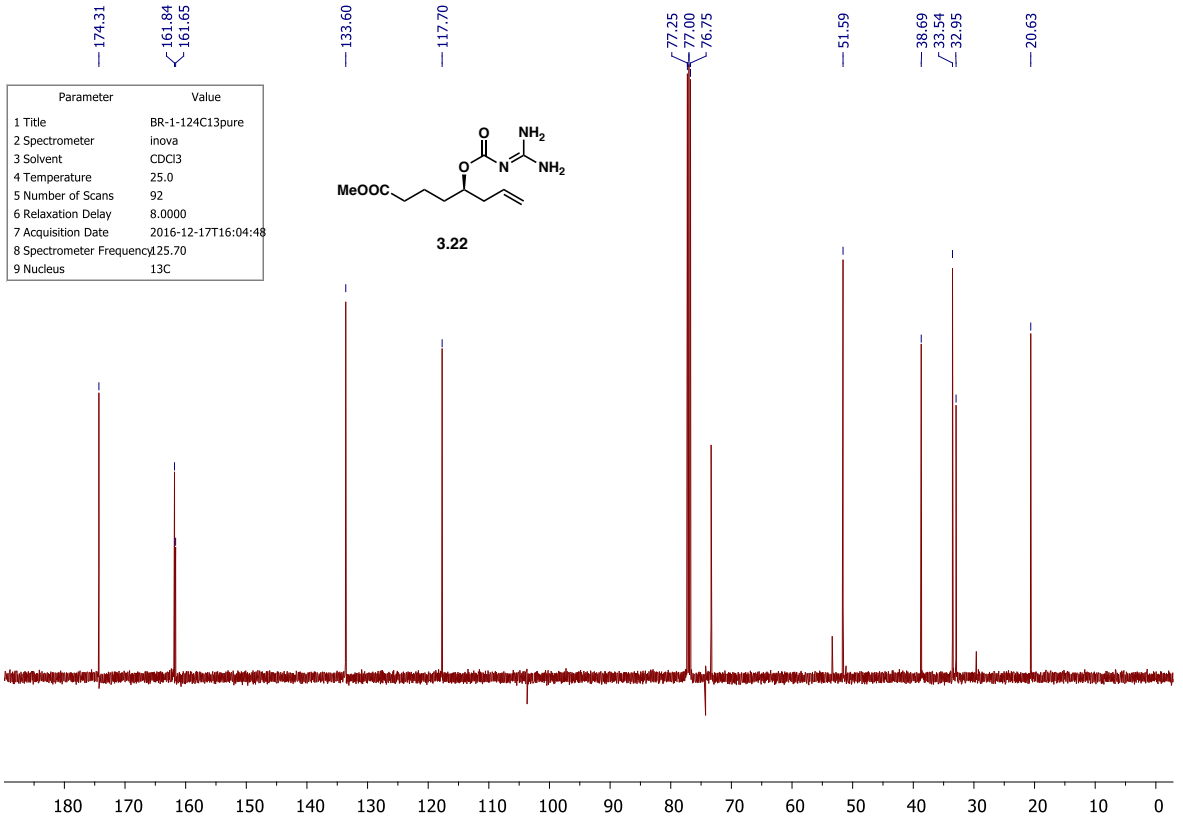

7.26
5.79
5.11
3.64
2.32
2.25
2.15
1.90
1.76
1.67
1.48
Parameter Value
1 Title BR-1-109pure
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 25.0
5 Number of Scans 20
6 Relaxation Delay 8.0000
7 Acquisition Date 2016-11-23T15:52:40
8 Spectrometer Frequency 499.86
9 Nucleus 1H
OH
MeOOC
3.20
1.00
2.04
4.09
2.05
1.07
1.05
1.00
1.05
1.10
2.07
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

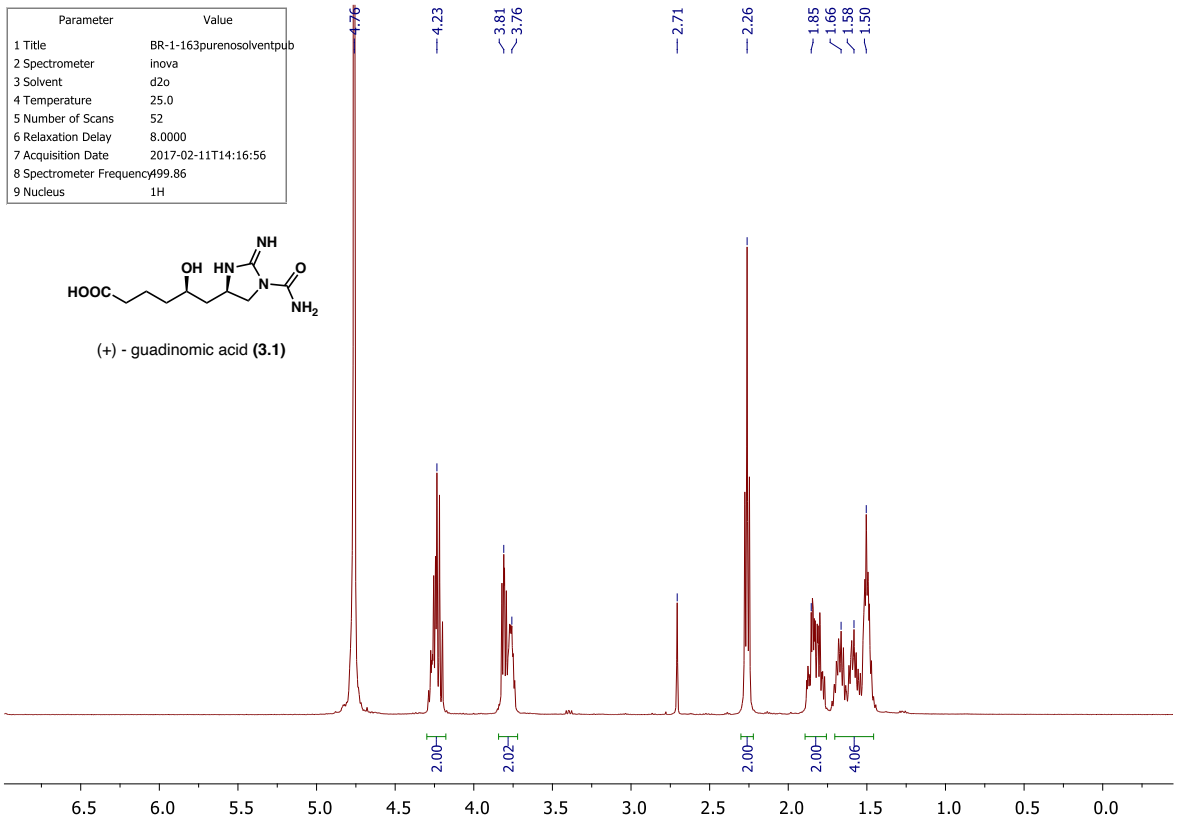

174.05
134.59
118.04
77.21
77.00
76.79
70.08
51.45
41.86
35.96
33.77
20.95
Parameter Value
1 Title BR-1-109pureC13
2 Spectrometer inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 124
6 Relaxation Delay 8.0000
7 Acquisition Date 2016-11-23T17:18:11
8 Spectrometer Frequency 150.79
9 Nucleus 13C
OH
MeOOC
3.20
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


8.027
7.549
7.433
7.260
5.806
5.191
5.124
5.059
3.649
2.456
2.350
1.744
Parameter Value
1 Title BR-1-115pure
2 Spectrometer inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Acquisition Date 2016-11-29T23:48:22
8 Spectrometer Frequency 599.64
9 Nucleus 1H
OBz
MeOOC
S3.20
2.00
1.03
2.05
1.00
1.03
1.03
1.01
3.04
2.07
2.02
4.04
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

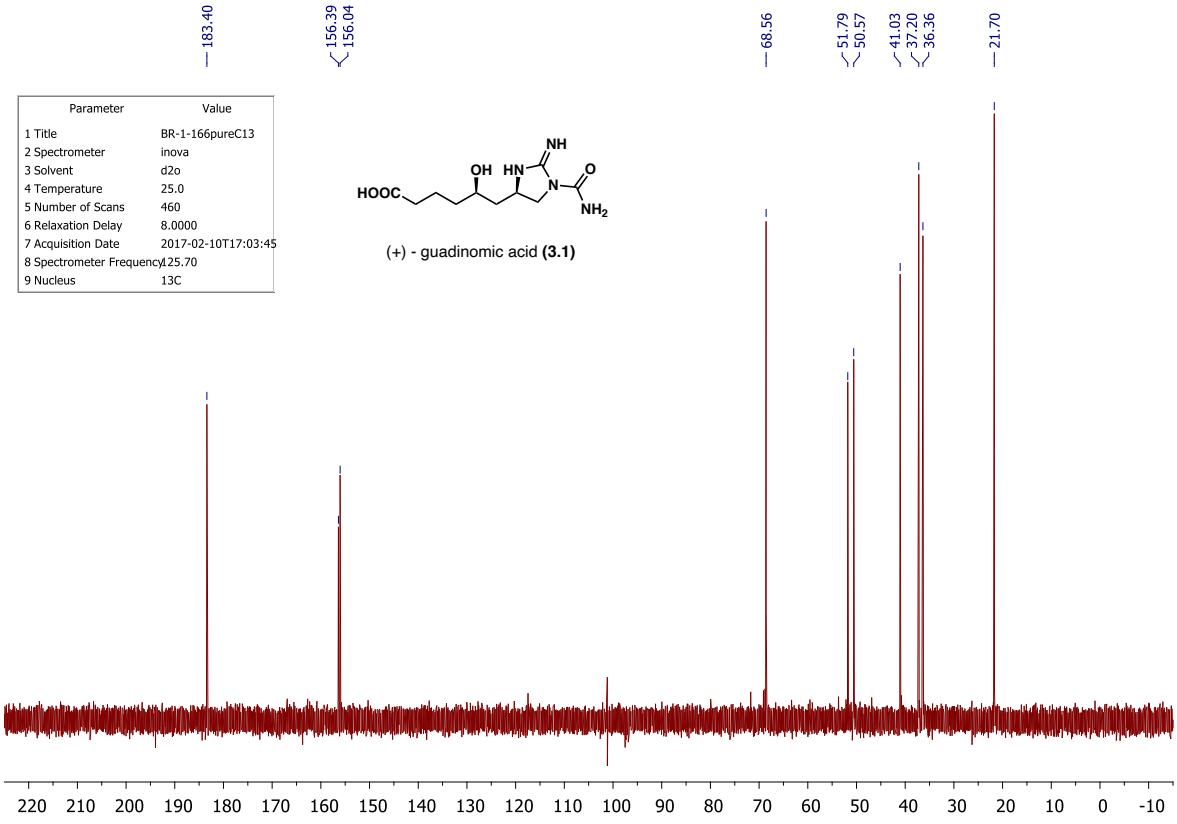

173.64
166.09
133.33
132.80
130.48
129.51
128.28
117.98
77.25
77.00
76.75
73.37
51.47
38.54
33.66
32.94
20.70
Parameter Value
1 Title BR-1-115C13_2
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 25.0
5 Number of Scans 236
6 Relaxation Delay 8.0000
7 Acquisition Date 2017-02-15T16:08:40
8 Spectrometer Frequency 125.70
9 Nucleus 13C
OBz
MeOOC
S3.20
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


7.42
7.26
6.26
5.74
5.04
4.73
3.65
2.31
1.69
1.60
1.54
Parameter Value
1 Title BR-1-142pure2
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 25.0
5 Number of Scans 16
6 Relaxation Delay 8.0000
7 Acquisition Date 2017-02-14T10:26:25
8 Spectrometer Frequency 499.86
9 Nucleus 1H
MeOOC
3.22
3.53
1.14
2.05
1.00
3.04
4.05
1.03
3.07
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


174.31
161.84
161.65
133.60
117.70
77.25
77.00
76.75
51.59
38.69
33.54
32.95
20.63
Parameter Value
1 Title BR-1-124C13pure
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 25.0
5 Number of Scans 92
6 Relaxation Delay 8.0000
7 Acquisition Date 2016-12-17T16:04:48
8 Spectrometer Frequency 125.70
9 Nucleus 13C
MeOOC
3.22
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0



(+) - guadinomic acid **(3.1)**



Parameter Value
1 Title BR-1-166pureC13
2 Spectrometer inova
3 Solvent d2o
4 Temperature 25.0
5 Number of Scans 460
6 Relaxation Delay 8.0000
7 Acquisition Date 2017-02-10T17:03:45
8 Spectrometer Frequency 125.70
9 Nucleus 13C

(+) - guadinomic acid **(3.1)**