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Chemical Studies Toward the Total Synthesis of Lagunamide A

Incorporating the Application of Diastereoselective Vinylogous Mukaiyama Aldol Reaction via Kinetic Resolution Methodology

A dissertation submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy

in

Chemistry

by

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2021

The Dissertation of Simranjeet Monny Singh is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Chair

University of California, San Diego

San Diego State University

2021

DEDICATION

To my family, friends, and the many mentors in my life.

EPIGRAPH

Only the disciplined ones are free in life. If you aren't disciplined, you are a slave to your moods. You are a slave to your passions. That's a fact.

-Eliud Kipchoge, 1st human to run full marathon under 2 hours.

There's no way around hard work. Embrace it. You have to put in the hours because there's always something which you can improve.

-Roger Federer, The best tennis player in history.

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LIST OF ABBREVIATIONS

ACN	Acetonitrile
BOC	*N*-*tert*-butoxycarbonyl
CDP	Cyclic depsipeptide
COSY	Correlation spectroscopy
CTC	Chlorotrityl Chloride
DCM	Dichloromethane
DIBAL	Diisobutylaluminium hydride
DIC	*N*,*N*-Diisopropylcarbodiimide
DIPEA	*N*,*N*-Diisopropylethylamine
DMF	Dimethylformamide
DMAP	4-Dimethylaminopyridine
DMP	Dess–Martin periodinane
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EtOAc	Ethyl acetate
FDA	Food and Drug Administration
Fmoc	Fluorenylmethyloxycarbonyl chloride
HATU	hexafluorophosphate azabenzotriazole tetramethyl uranium
HDAC	Histone deacetylase
HMBC	Heteronuclear Multiple Bond Correlation
HMDS	Bis(trimethylsilyl)amide
HOAt	1-Hydroxy-7-azabenzotriazole
HOBt	1-Hydroxybenzotriazole
HPLC	High-performance liquid chromatography
HRESIMS	High resolution electro-spray-ionization mass spectrometry
HSQC	Heteronuclear single quantum correlation

HWE	Horner-Wadsworth-Emmons
LAH	Lithium aluminium hydride
LCMS	Liquid chromatography–mass spectrometry
LDA	Lithium diisopropylamide
MNBA	2-Methyl-6-nitrobenzoic anhydride
MTM	Methylthiomethyl
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
PHB1	prohibitin 1
PMB	p-Methoxybenzyl
SAR	Structural-activity-relationships
TBS	*tert*-butyldimethylsilyl
TBDP	*tert*-butyldiphenyl
TEA	triethylamine
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TES	triethylsilyl
THF	tetrahydrofuran
TLC	thin-layer-chromatography
TMS	trimethylsilyl
TFA	trifluoroacetic acid
TsOH	Toluenesulfonic acid
VMAR	Vinylogous Mukaiyama Aldol Reaction

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ABSTRACT OF THE DISSERTATION

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Lagunamide A is a cyclic depsipeptide isolated from marine cyanobacterium *Langbya majuscula* from deep oceans of Pulau Hantu Besar, Singapore. Upon isolation it was revealed to be a potent antimalarial, cytotoxic against leukemia and colon cancer. Latest Structure Activity Relationship research shows Lagunamide A to be active against various cancer cells including A549, HeLa, U2OS, HepG2, BEL-7404, BGC-823, HCT116, MCF-7, HL-60, and A375; with

IC50 values ranging from 4.7 nM to 19.8 nM. The diversity exemplifies the natural products potential for future therapeutics as other cyclic depsipeptides have in the past. The investigation of various Vinylogous Mukaiyama Aldol Reactions (VMAR) of β-oxyaldehydes led to the efficient construction of the polyketide carbon framework of Lagunamide A. Solution state synthesis of multiple peptides fragments of Lagunamide A were achieved to avoid epimerization of crucial stereocenters. The peptide portion and the polyketide framework were converged leading to precious intermediates. HR-MS data shows the detection of Lagunamide A although a modified synthetic route would be needed for larger quantities of the natural product.

An investigation of Vinylogous Mukaiyama Aldol Reaction was done to test if kinetic resolution could be achieved using Kobayashi's protocol. An unexplored territory of VMAR is reacting vinylketene *N,O*-acetal with a racemic mixture of aldehydes to produce stereotriades. Differences in selectivity were observed depending on the size of α-substitutions. Single diastereomers of stereotriades can be produced using this platform of VMAR.

Introduction: History of Cyclic depsipeptides and application towards therapeutics

The term cyclic depsipeptide (CDP's) was first introduced in the mid-1960's and was often referred to as cyclodepsipeptides or peptolides.[1,2] The terms were used to describe a peptide related compound, cyclic in nature, and composed of amino- and hydroxyacid residues conjoined as a part of amide and ester bonds. They were first reported in the 1940's with the isolation of enniatin A from fungas *Fusarium Orthoceras* var. *enniatinum*.[3] A few decades later scientists were starting to elucidate their biosynthesis and has remained an active area of research to date.[4-6] Investigation into the diversity of CDP family members illustrated they are synthesized by non-ribosomal peptide synthases and polyketide synthase/fatty acid synthase enzyme systems. Simply put they are constructed by both polyketide synthase pathway and fatty acid synthase. The biosynthetic pathways of CDPs have yet to be thoroughly understood since few enzymes are currently available to the prospective biosynthetic products and programing of corresponding enzymes.[7] Not only are the CDP molecules structurally diverse but they also exhibit a wide range of activities: histone deacetylase (HDAC) and protease inhibition activities (romidepsin and cyanopeptolin S),[8-10] antibacterial,[11] antifungal (dentigerumycin),[12] immunosuppressive (tacrolimus),[13] antimalarial (lagunamides),[14] HIV-inhibitory (mirabamides),[15] and cytotoxic activities, such as kahalalide F, which is currently in clinical trials as an anti-cancer drug.[16,17] Taking the notable bioactivities into consideration, the applications of CDPs are increasingly studied from a synthetic and chemical biological aspects, and for their potential in application towards medicinal chemistry in both academic and industrial laboratories. From the total synthesis point of view, scientists have aimed their efforts in providing access of these exotic molecules for biological studies. By synthesizing CDPs or other natural products, it allows for the synthesis of analogues for determining modes of action as well as structural-activity-

relationships (SARs). Considering the time and effort required for isolating small molecules from their corresponding source, fungus, plant, marine, and bacterial etc., and how limited the amount can be, a viable synthetic pathway is a necessity in order to prepare an ample amount needed for a study. Many natural products can be extremely fragile and therefore a direct modification of them can be cumbersome. The synthetic approach may bypass this issue by introducing early changes in the synthetic strategy. Then changes are carried forward ultimately producing analogues of natural product. Since a properly devised synthesis of natural products should provide sufficient material, it has attracted pharmaceutical investigation for exploitation of these molecules for their potential therapeutics of antitumor, antimicrobial, etc.

One focus of CDPs is their potency against tumor cells. These invaluable properties have led the research to investigate them further in clinical trials to evaluate as potential chemotherapeutic agents.[18] Since the 1950s, many CDPs with cytotoxic activity against tumor cells have been discovered. A recent study of cyclic depsipeptides, as potential cancer therapeutics are summarized below (Table 1). These CDPs are undergoing clinical trials for their antitumor activities. The study discussed possible mode of action as well as what fragments of the molecule might be responsible for activity.

Table 1. List of CDPs that have gone through Phase II or further clinical trials.

Compound	**Source**	**Molecular Target**	**Current status**	**Oncological Use**
Romidepsin	Bacteria	HDAC	Available for clinical use	CTCL/PTCL
Aplidine	Marine animal	Oxidative stress	Phase III	Multiple myeloma
PM02734	Synthesis	ErbB pathway	Phase II	Non-small-cell-lung
Didemnin B	Marine animal	eEF1A	Phase II (discontinued)	Solid Tumors
Kahalalide F	Marine animal	ErbB pathway	Phase II (discontinued)	Psoriasis
Cryptophysin	Bacteria	Tublin	Phase II (discontinued)	Solid Tumors
LY355703	Bacteria	Tublin	Phase II (discontinued)	Solid Tumors

Each molecule undergoes its unique mode of action with their corresponding targets. Romidepsin is a bicyclic CDP that was demonstrated to prolong the life of mice with ascetic tumors: P388, L1210 leukemia, and B16 melanoma. It was noted that romidepsin was active against P388 cells where other drugs had failed. Romidepsin induces apoptosis by depleting the proto-oncogene epidermal growth receptor and inhibits the histone deacetylase. It was also demonstrated to have clinical efficacy in patients with refractory cutaneous T-cell lymphoma. For this reason, the FDA (Food and Drug Administration) gave approval for romisepsin's use as treatment against CTCL/PTCL.

Other natural products, such as didemnin B did not show as much promising results. In preclinical trials the molecule demonstrated efficient inhibition of the growth of L1210 leukemia cells in mice and increased the survival rate. This led to the study of entering phase I and II clinical trials against various human tumors (epithelial ovarian cancer, renal cell carcinoma, breast cancer, melanoma, small cell lung cancer, myeloma, prostate cancer, and lymphoma. The

trials were eventually stopped due to severe secondary effect. Eventually an analogue of didemnin B, aplidine, showed new promise as a therapeutic. Aplidine had antitumor activity against human melanoma, lymphoma, breast, ovarian, lung, colorectal, and gastric carcinomas *in vitro* in soft agar cloning assay. Aplidine entered phase I clinical trials and eventually entered Phase II. Several trials were done and in some cases showed limited antitumor activity. After several phase II trials with positive response rates the compound was demonstrated to have limited and reproducible antitumor activity against multiple myeloma. Aplidine was eventually advanced to phase III clinical trial for relapsed/refractory multiple myeloma with dexamethasone, and anti-inflammatory steroid.[18]

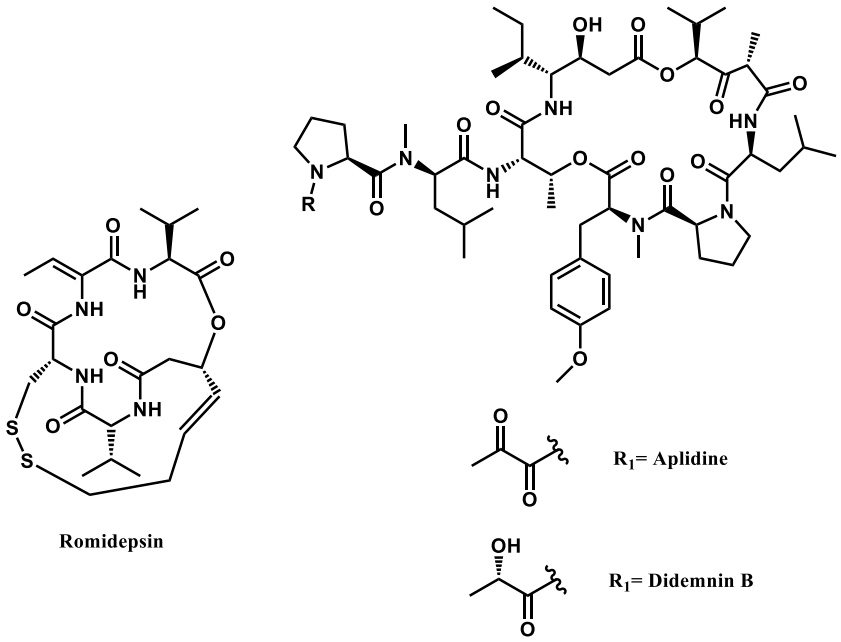


Figure 1. Structures of CDPs: Romidepsin, Aplidine, and Didemnin B.

The motivation natural product synthesis including CDPs is exemplified from the journey of Didemnin B. It went through failing as a potential therapeutic only to be attempted again by its analogue, aplidine. CDPs and their analogues need to be produced in sufficient quantities for

multiple clinical trials. If the lead compounds fail an analogue can potentially take its place and achieve the final goal of become a therapeutic for disease.

Chapter 1 Background of Lagunamide A

1.1 26-Membered Macrocyclic Depsipeptides, Lagunamides, and Lagunamide A

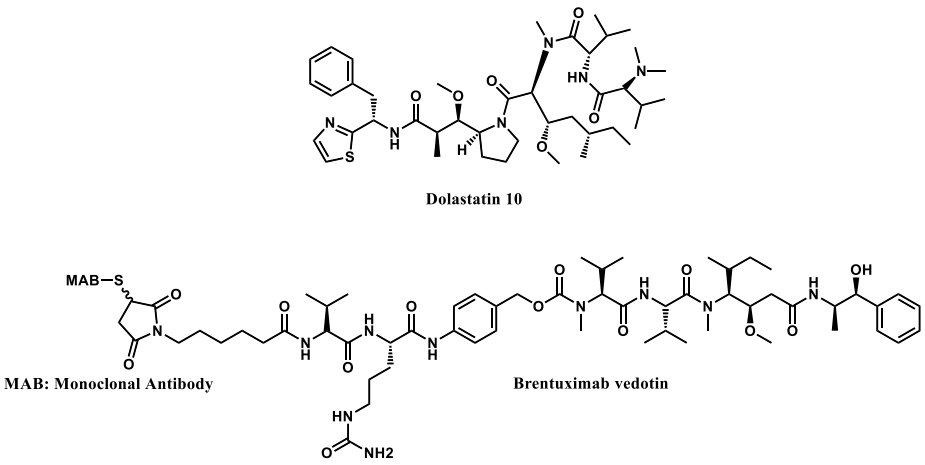


Figure 2. Structures of Dolastatin 10 and Brentuximab vedotin

Through countless examples, natural products isolated from marine cyanobacterium provided scientists with some of the most structurally intriguing bioactive molecules to use as tools for unmet medical needs, various diseases, and cancer.[19] One example is brentuximab vedotin, an FDA approved drug for treatment of Hodgkin Lymphoma and systemic anaplastic large cell lymphoma.[20] This anti-body drug conjugate was developed from the pharmacophore of dolastatin 10, a secondary metabolite of cyanobacterium determined to have activity in the nanomolar and picomolar range.[21,22] The insights gained from studying this cancer therapeutic is used as a model for general drug design today. Not all natural products are applied for medicinal needs and in fact most do not meet the criteria for various reasons. But in the pursuit, some natural products become tools for elucidating new mode of action, which open the door for other molecules to be used as drugs in the future.

One of the latest additions to CDP's belongs to the class of lagunamides. Lagunamide D (Figure 3)[19] was isolated from a mixture of marine cyanobacterium *Dichothrix sp*., *Langbya sp*., and *Rivularia sp*. from Loggerhead Key in the Dry Tortugas in Florida. The significance of its isolation is that it was the first time a 26-membered macrocyclic depsipeptide of this type was isolated from the Atlantic ocean.[19] Others structures of the same series are the: auralides, lagunamides, kulokekahalide-2, odoamide, and palau'amide, all were isolated from the Pacific ocean.[19] The isolation of lagunamide D in the Atlantic ocean signifies the potential that this class of CDPs might be more abundant around the world than what scientists may of originally believed. Although the structural differences between these 26-membered macrocyclic depsipeptides may be insignificant, the trivial differences between leads to distinct alterations of how they engage with specific targets in a cellular environment. Aurilide was the first small molecule that could interact directly by targeting prohibitin 1 (PHB1), a mitochondrial inner membrane protein found in in mammalian cells.[23] Thus, it became an invaluable chemical tool for studying the fundamental nature of PHB1 in a way that could not be accomplished previously. With the discovery of lagunamide D, the studies conducted on lagunamides and other 26-membered macrocyclic depsipeptides will provide crucial information to yield future drug candidates.

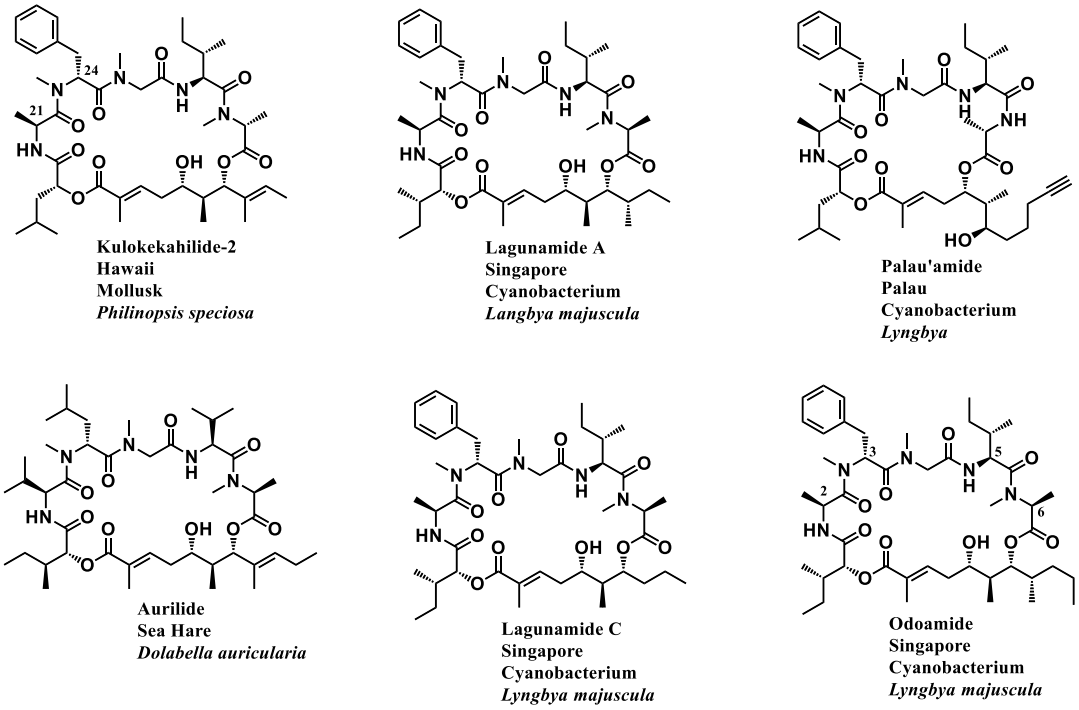


Figure 3. Series of 26-membered macrocyclic depsipeptide discovered around the world.

To date, several total synthesis of CDP's that belong to the 26-membered macrocyclic depsipeptides have been achieved. A brief history of some of these follows below. Aurilide, a marine cytotoxic was isolated in 1996 from the Japanese Sea Hare *Dolabella auricularia*[24] and its first total synthesis was reported in 2004 which subsequently led to a biological study to find its crucial protein target.[25] Aurilide represents the first small molecule that inhibits prohibitin function in regulation of OPA1 and mitochondria-inducted apoptosis thus serving as a chemical tool for studying prohibitin-mediated regulation of apoptosis.[23] Kulokekahilide-2, another cytotoxic despipeptide, was isolated from a Cephalaspidean Mollusk *Philinopsis speciose* in 2004.[26] It took an additional eight years later to investigate the SAR against various cancer cell lines.[26a] The study concluded the preserving cyclic Kulokekalilide (versus linear Kulokekalilide), chirality of 21-L-Ala, and modification of 24-D-MePhe would be crucial for the exploration of

new analogues. Odoamide's isolation from marine cyanobacterium *Okeania speciose* showed potent cytotoxic activity against HeLa S3 cervical cancer cells with IC50 of 26.3 nM was reported in 2016.[27] The synthesis of odoamide was completed at the same time by the same group that isolated the molecule.[28] The SAR study was done where the analogues were synthesized using solid-phase technique, which will be discussed in chapter 3. This study revealed that the stereochemistry of L-Ala2, D-MePhe3, and L-Ile5 were essential for maintaining potent activity. At the same time the synthetic analogue including D-MeAla6 moiety exhibited additional potent activity. Both the 26- and 24- cyclic membered isomers also showed potent activity. An assessment of the physiochemical activity revealed that odoamide itself and its analogues showed good membrane permeability with different serum protein binding behaviors to affect their cytoxicities.[29]

In 2010, the Tan group reported the isolation of Lagunamide A and B (Figure 4),[30] a cytotoxic antimalarial cyclodepsipeptide from the marine cyanobacterium *Langbya majuscula* from Pulau Hantu Besar, Singapore.[30] Both natural products exhibited activity against malaria with IC50 values of 019 µM and 0.91µM when tested against *Plasmodium falciparum*. Lagunamide A and B also demonstrated potent cytotoxic activity against P388 murine leukemia cells lines with IC50 values of 6.4 and 20.5 nM respectively. The molecules also exhibited antiswarming activities when tested against the *Pseudomonas aeruginosa* PA01.

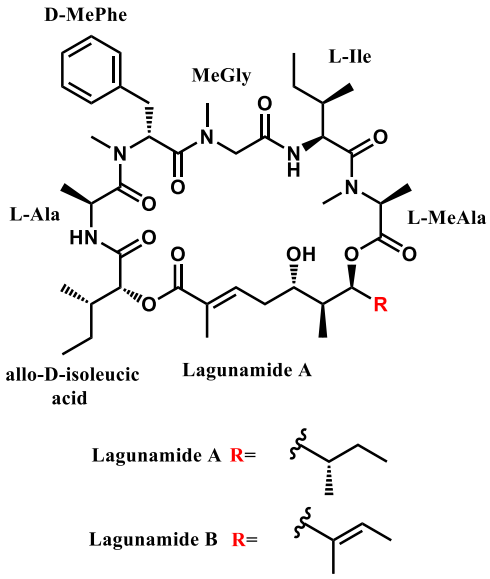


Figure 4. Structures of Lagunamide A and B proposed in initial isolation.

1.2 Lagunamide A: Isolation and Structural Elucidation by Tan group

The bacterial strains that originate from *Langbya* genis produce some of the most intriging secondary matabolites with high biological activity. As discussed in the introduction of CDPs, these small molecues have antimicrobial, antimalarial, cytotoxic, and neurotoxic activities. The 26-membered macrocyclic depsipeptides discussed in the previous section contain both polyketide and polypeptide fragments. This is different from other CDP's. The organic extracts from a drug discovery voyage of the western lagoon of Pulau Hantu Besar in Singapore revealed several cytotoxic compounds. The strain of L. *majuscula* collected was from shallow water during low tide in 2007.[30] The cyanobacterial material was extracted with a 50/50 mixture of $CHCl_3$ and MeOH. The individual fractions were tested on brine shrimp lethality bioassay. The compounds in this mixture were purified by using SEP PAK C18 followed HPLC chromatography to yield Lagunamide A and B, the former being the main focus of this article.

The molecular formula of Lagunamde A ($C_{45}H_{71}N_5O_{10}$) and the HRMS-ESI data revealed a $[M+Na]^+$ ion peak at 864.5093 m/z. The NMR data initially collected in $CDCl_3$ (^1H and ^{13}C) was complex in nature as hypothesized due to multiple conformers existing at once. Analysis determined several peptide moieties and one rotamer was observed when the natural product was analyzed using CD_3OD to obtain ^1H and ^{13}C NMR spectrum. The proton spectrum showed 3 *N*-methylated amide signals and the ^{13}C spectrum revealed 7 carbonyl signals.[30]

Analysis of the 1D and 2D NMR data revealed two sections of the natural product consistent with a peptide portion and polyketide portion (Figure 5).[30]

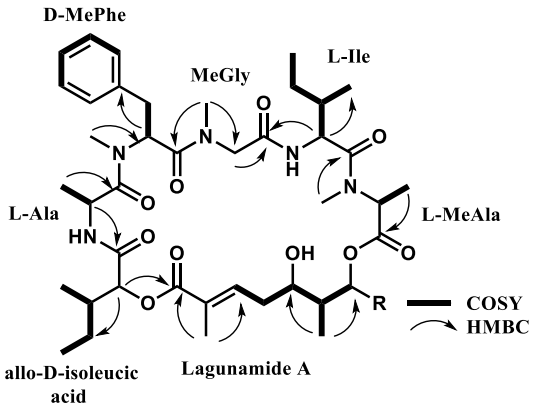


Figure 5. 2D NMR correlations of Lagunamide A in CD_3OD.

The data revealed five standard amino acids and one hydroxy acid fragment in Lagunamide A. The amino acids were determined to be N-Me-Ala, Ile, N-Me-Gly, N-Me-Phe, and Ala respectively. HMBC data was used to make connection between substructures of polyketide and polypeptide as well as the sequence of the amino acids. For determination of absolute stereochemistry of the amino acids fragments, lagunamide A was hydrolyzed in 6M HCl and was analyzed using advanced Marfey's method. This revealed the absolute configuration of the amino acids (Ala, N-Me-Phe, N-Me-Ala, and Ile), assigned as L, D, L, and

L-allo, respectively. The configuration at C37 is consistent with the other CDP's described earlier but still had to be verified by converting the free alcohol at C37 to R and S-MTPA esters. The differences in chemical shifts in the ^{1}H spectrum revealed the S-configuration. The relative configuration of C-38, C-39, and C-40 were determined by the Karplus relationships of the $^{3}J_{H\text{-}H}$ values (Figure 6).[30] By analyzing the coupling constants and the NOESY correlations confirmed the absolute configurations reported to be: 37S, 38S, 39S and 40S, respectively.

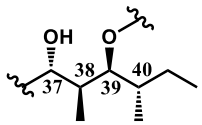


Figure 6. Configuration of C38-C40 of Lagunamide A assigned upon isolation

1.3 Biological activity of Lagunamide A

Upon isolation of lagunamide A and B by the Tan group both lagunamides were tested for antimalarial activity against the NF54 strain. The effectiveness was measured with IC50 values of 0.19 and 0.91 µM against *Plasmodium falciparum*. The lagunamides are the first 26 membered cyclic depsipeptides that are related to aurilide to show antimalarial properties. It was noted that the small difference between lagunamde A and B, being a degree of unsaturation at C40-C41, resulted in a 4.7x higher activity for lagunamide A. Both lagunamides also exhibited activity against P388 cancer cells line and the IC50 values were reported to be 6.4nM and 20.5 nM for Lagunamde A and B, respectively. The anti-swarming activity was determined by testing against gram negative bacterial strain *Pseudomonas aeruginosa* PA01. Both compounds were tested at 100 ppm, exerting 62% for lagunamide A and 56% for lagunamde B. The biological

activities reported by the Tan group demonstrated the importance of seeking new natural products from cyanobacterium as a potential source for new therapeutics.[30]

1.4 Total Synthesis of Lagunamde A by Ye Group

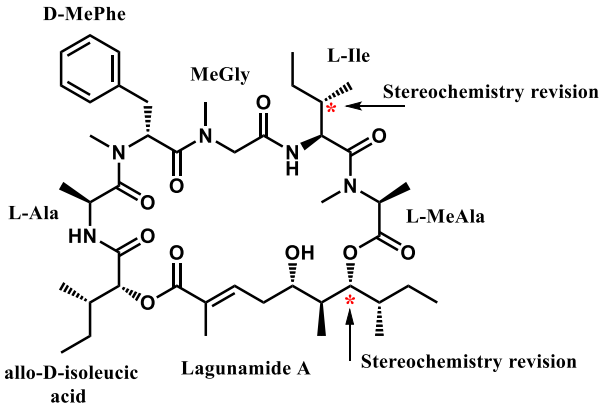
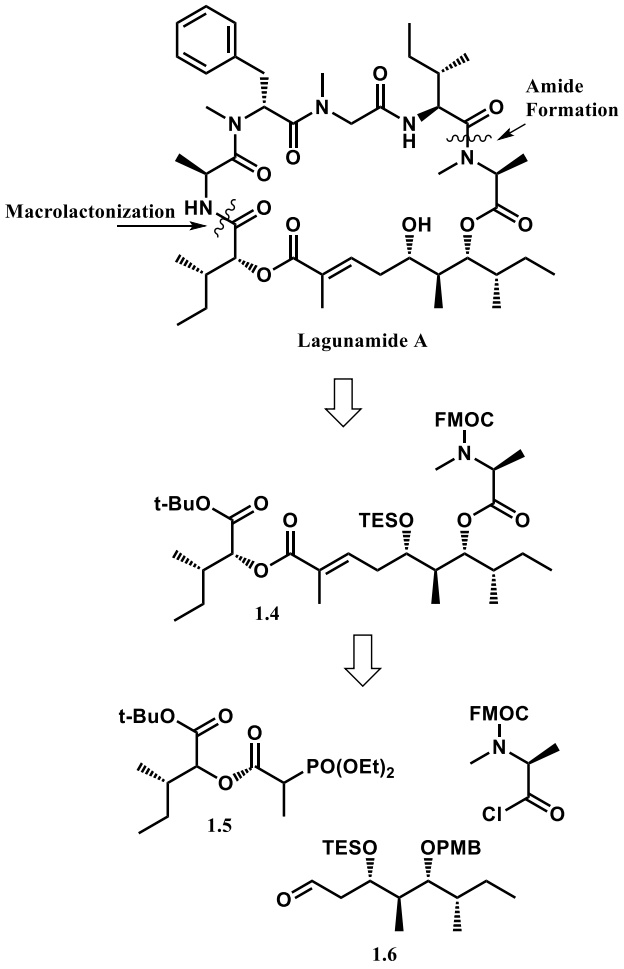


Figure 7. Structure of lagunamide A. Revision of stereochemistry in first total synthesis.

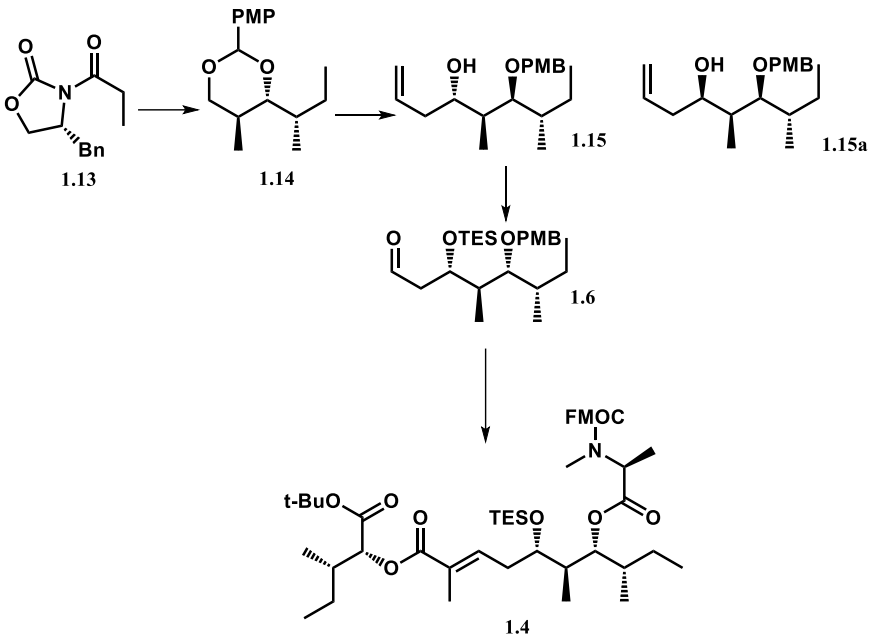
The first total synthesis of lagunamide A was reported in 2012 by the Ye group.[31] This report also included a stereochemically revised structure of lagunamide A, as shown in Figure 7, and the two revised stereocenters are shown in red asterisks (Figure 7). They first attempted to synthesize the proposed structure by the Tan group. The retrosynthesis is shown in Scheme 1. They proposed the coupling of tetrapeptide **1.10** directly with polyketide fragment **1.4**. Aldehyde **1.6** was prepared by (*S*)-2-methylbutanal treatment with boron enolate derived from Evans (*R*)-oxazolidinone **1.13** for aldol product which was converted to the corresponding anisylidine acetal **1.14** (Scheme 2). DIBAL reduction of acetal gave an alcohol which was oxidized to aldehyde using DMP. The aldehyde was further allylated which gave homoallylic alcohol **1.15**. The relative stereochemistry of 1,3 diol system was confirmed by analyzing the ^{13}C chemical shifts of the acetonide protecting group upon conversion to the corresponding acetonide. The ^{13}C chemical shifts NMR data was in agreement with 1,3 anti-configuration reported and accepted in

literature.[38,39] The allylic alcohol was then protected as TES silyl ether and alkene is oxidatively cleaved to give aldehyde **1.6**.



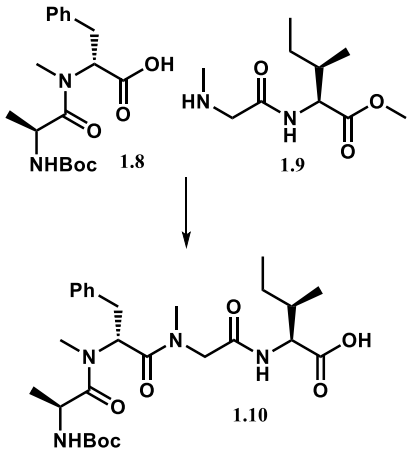
Scheme 1. Retrosynthesis proposed by Ye's group of initially proposed structure of Lagunamide A

The enoate **1.4** was then formed from aldehyde **1.6** in a HWE reaction with phosphonate **1.5**. After a series of probing protecting groups, Fmoc-N-MeAla-Cl was ultimately incorporated to give fragment enoate **1.4**.



Scheme 2. Ye's synthesis of polyketide fragment **1.4**.

The tetrapeptide was constructed from dipeptides **1.8** and **1.9** and connecting them in the presence of HATU to give methyl ester of peptide **1.10**. The free acid of **1.10** was obtained by reaction of the methyl ester with LiOH.

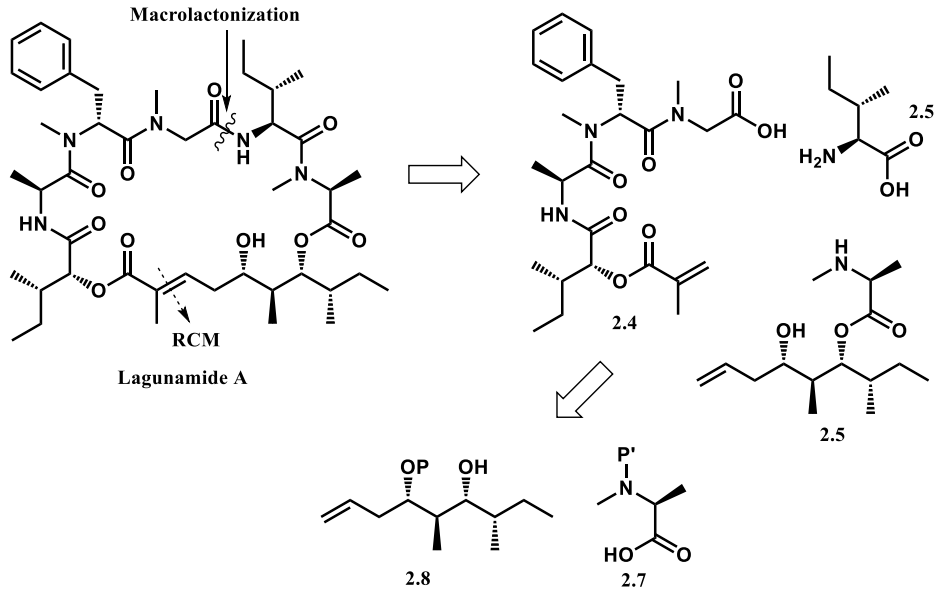


Scheme 3. Ye's synthesis of tetrapeptide **1.10** of lagunamide A.

The crucial tetrapeptide was then incorporated to fragment **1.4** via Fmoc deprotection followed by using HATU for amide formation shown in Scheme 1. A global deprotection of BOC, TES, and t-butyl was then accomplished with TFA, Macrolactamisation for ring closure using HATU gave what was believed to lagunamide A. The ^{1}H and ^{13}C of expected Lagunamide A did not match that of the natural product. To obtain the correct structure of lagunamide A, two additional diastereomers of aldehyde **1.6** was made and probing of these changes in the stereochemistry ultimately yielded the correct stereochemical configuration of the natural product. Observing the similarities of aurilide A-C and kulokekuhilide-2 led to the C39 epimer synthesis of lagunamide A. Upon switching L-allo-isoleucine to L-isoleucine ultimately led to the matching spectral ^{1}H and ^{13}C data to that of the natural product, which ultimately led to the first total synthesis of lagunamide A. It should be noted that the epimerization of L-Isoleucine was not discussed in Ye's synthesis but it is mentioned in Lin's and Kazmaier's total synthesis of lagunamide A. This topic is mentioned in the next two sections and possible strategies for avoiding the problem of epimerization will continued to be discussed throughout this thesis.

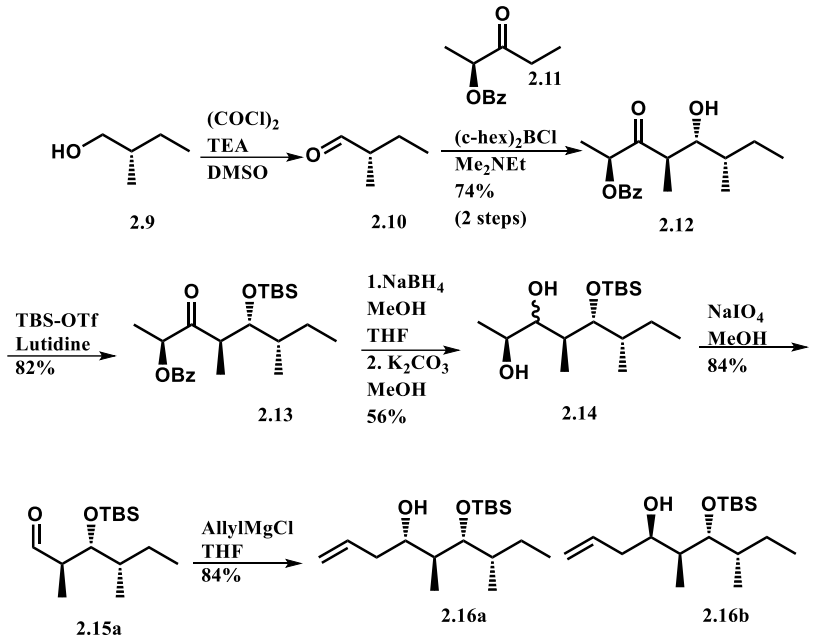
1.5 Lin's total synthesis of Lagunamde A

In 2013 Lin's group reported the second total synthesis of Lagunamde A.[32] The retrosynthetic strategy reported by Lin is shown in Scheme 4. For the first time the synthesis of a 26-membered macrocyclic depsipeptides attempted a ring cross-metathesis (RCM) to form the double bond along C34 and C35 using Grubbs second generation catalyst. This approach would ultimately lead to lagunamide A, which is different than the macrolactamisation reported by Ye for the ring closure.



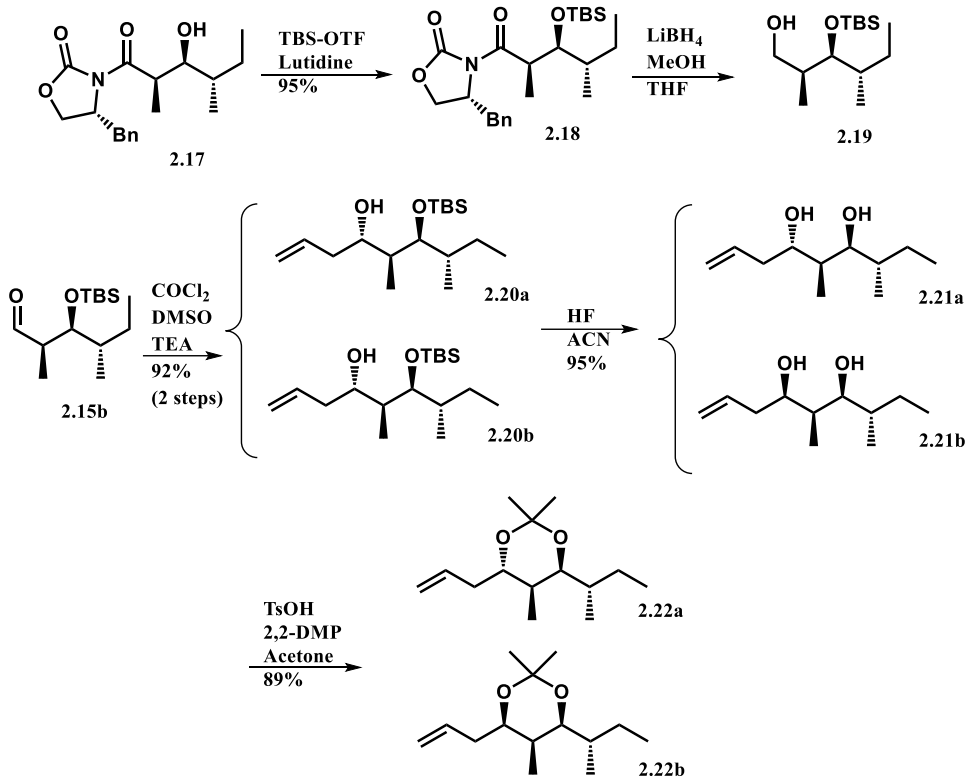
Scheme 4. Retrosynthesis of lagunamide A as reported by Lin's Group.

The key stereocenters at C37-C40 of polyketide fragment were installed using an asymmetric Paterson anti-aldol (Scheme 5) reaction. Ketone **2.11** complexed with $(c\text{-hex})_2BCl$ and dimethylethylamine was reacted with aldehyde **2.10** to give alcohol **2.12**. This established the stereochemistry of C38 localized in lagunamide A. After TBS protection, stereoselective reduction of ketone **2.12** and hydrolysis of the benzoyl protecting group gave 1,2 diol **2.14**. Oxidative cleavage of the carbon-carbon bond using $NaIO_4$ gave aldehyde **2.15a**. This stereotriade was allylated using allylmagnesium chloride to give a mixture of **2.16a** and **2.16b**. This established the stereochemistry of C37 and C38 as seen in lagunamide A The diastereomeric ratio of **2.16a/2.16b** was unfortunately poor and could not be used for constructing the polyketide. Thus, the synthetic route was changed to a different strategy illustrated in Scheme 6.[32]



Scheme 5. Lin's method of installing stereocenters C37-C40 of polyketide fragment of Lagunamide A.

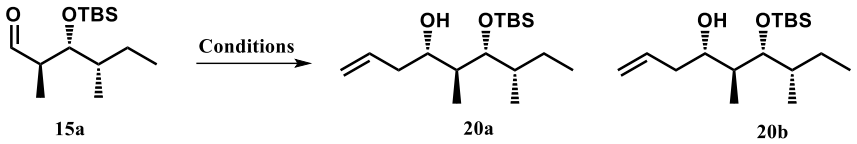
An aldol reaction was performed on aldehyde **2.10** to give syn product **2.17** for establishing the stereochemistry of C38-C40 of lagunamide A. After TBS protection of **2.17**, cleavage of chiral oxazolidinone with $LiBH_4$ gave free alcohol **2.19**. Swern oxidation gave aldehyde **2.15b**. This intermediate was allylated to give a mixture of **2.20a** and **2.20b**. Various conditions were investigated to obtain a diastereomeric ratio of **2.20a** over **2.20b** (Table 2).[32]



Scheme 6. Lin's route using Evans aldol for obtaining aldehyde **2.15b** for allylation.

After a thorough investigation in Lin's report, they determined that $ZnCl_2$ was the best candidate to be used to produce a high diastereomeric ratio of **2.20a** over **2.20b** (90/10). After separation of **2.20a** from **2.20b**, they were reacted with 2,2-dimethyoxypropane and catalytic amounts of TsOH for conversion to corresponding acetonides **2.22a** and **2.22b**, which was conducted in order to determine the stereochemical relationship of the 1,3-diols products. The ^{13}C chemical shifts of the acetonide protecting groups corresponded to literature values of the anti-1,3 acetonide **2.22a** and syn-1,3 acetonide **2.22b**, respectively.[38,39]

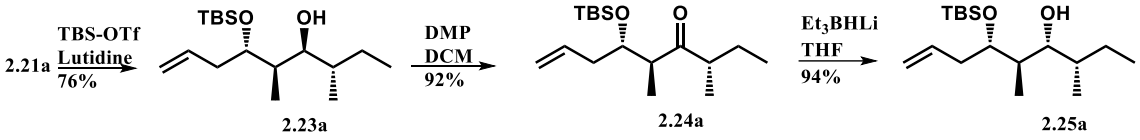
Table 2. Allylation of aldehyde **2.15b** to achieve a high ratio of **2.20a/2.20b**.



15a 20a 20b

Entry	reagent	Lewis Acid	Yield	2.20a:2.20b
1	AllylMgCl	-	92	11:89
2	AllylMgCl	Et_2BOMe	87	16:84
3	AllylMgCl	$CeCl_3$	85	17:83
4	AllylMgCl	$Cu(OTf)_2$	89	14:86
5	AllylMgCl	$AlMe_2Cl$	90	25:75
6	AllylMgCl	$InCl_3$	82	33:67
7	AllylMgCl	$SnCl_2$	85	14:86
8	AllylMgCl	$NiCl_2(PPh_3)_2$	78	20:80
9	AllylMgCl	LiBr	88	17:83
10	AllylMgCl	$Pd(OAc)_2$	89	14:86
11	AllylMgCl	BF_3Et_2O	90	15:85
12	AllylMgCl	$ZnCl_2$	90	90:10

After the stereochemistry of diol **2.21a** was determined, the less stereochemically crowded alcohol was TBS protected to intermediate **2.23a** (Scheme 7).[32] Alcohol **2.23a** was then oxidized using DMP to give **2.24a**. Stereoselective reduction of **2.24a** using Et_3BHLi gave **2.25a**, a product which displays the correct stereochemistry observed at C37-C40 of lagunamide A.



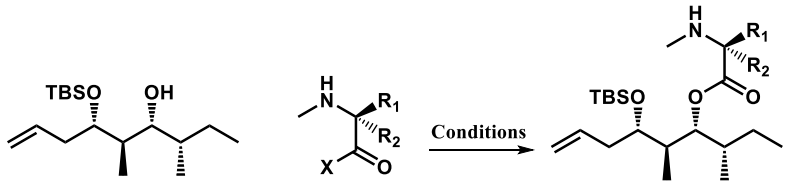
2.23a 2.24a 2.25a

Scheme 7. Lin's route of converting 1,3 diol system for polyketide fragmant.[32]

The Yamaguchi conditions in Lin's report reveal an important fact not presented in Ye's total synthesis of lagunamide A. Table 3 shows epimerization of L-N-Me-Fmoc-Ala-OH under Yamaguchi conditions for esterification of alcohol **2.25a**. Two diastereomers were isolated,

2.27aa and **2.27ab**. The diastereomeric ratio of **2.27aa/2.27ab** was determined by analysis of crude mixture using HPLC. Various conditions were tested, and the epimerization was caused by the use DMAP, and it was suspected that the epimerization occurred after ester bond formation. Without the presence of DMAP, optically pure diastereomer **2.27aa** was isolated and used for the continuation of the synthesis of lagunamide A. In Ye's total synthesis of lagunamide A, DMAP was used and epimerization was not reported.

Table 3. Epimerization of alcohol **2.25a** under esterification conditions.



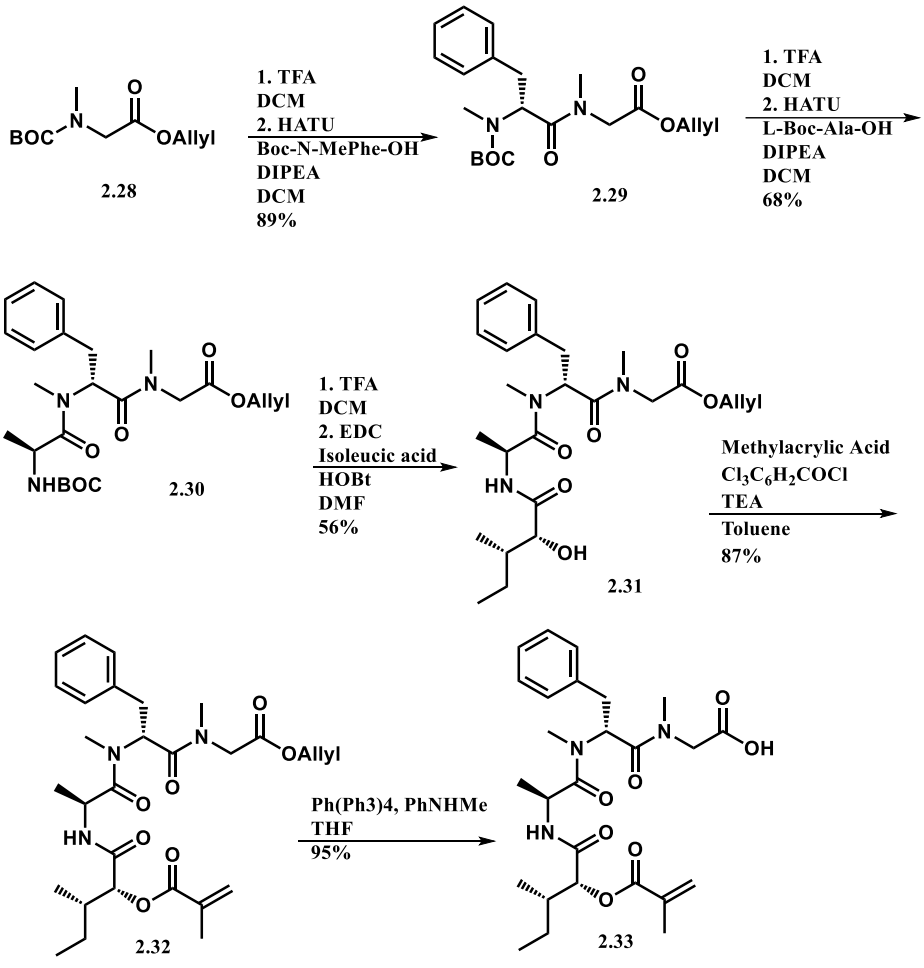
2.25a **2.26**

2.27aa: R_1=Me, R_2=H
2.27ab: R_1=H, R_2=Me

Entry	R_1	R_2	X	P	2.27aa/2.27ab	yield (%)
1	Me	H	OH	Fmoc	24:76	92
2	H	Me	OH	Fmoc	2:98	89
3	Me	H	OH	Boc	24:76	73
4	Me	H	OH	Fmoc	23:77	69
5	Me	H	OH	Fmoc	-	NR
6	Me	H	OH	Fmoc	33:67	48
7	Me	H	Cl	Fmoc	58:42	57
8	Me	H	Cl	Fmoc	70:30	56
9	Me	H	Cl	Fmoc	>99:1	55

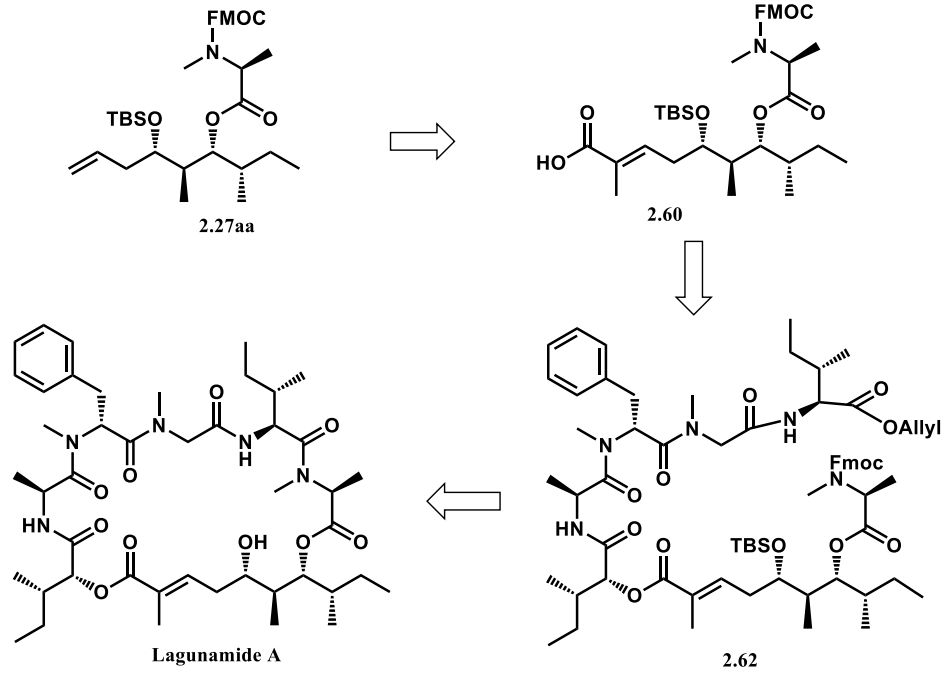
Construction of peptide fragment was accomplished using common strategy of taking advantage of Boc-protected amino acids and HATU, one of the most common methods of constructing amide bonds. Sarcosine (**2.28**) was coupled to D-Me-Phe giving dipeptide **2.29** and

the same strategy was used to couple L-Ala. A widely used peptide coupling agent, EDC, was used to incorporate the (2R,3S)-2-hydroxy-3-methylpentanoic acid fragment to give **2.31**. Methacrylic acid was converted to an anhydride in situ using 2,4,6-trichloro-benzoyl chloride. The anhydride was next reacted with **2.31** which produced tetramer **2.32**. Then the allyl protecting group was removed using PhNHMe with $Pd(PPh_3)_4$ to give **2.33** (Scheme 7). The free acid of sarcosine of **2.33** can be used for peptide coupling and the alkene of acrylic acid can be used for the cross metathesis proposed by Lin.



Scheme 8. Lin's peptide synthesis of lagunamide A.

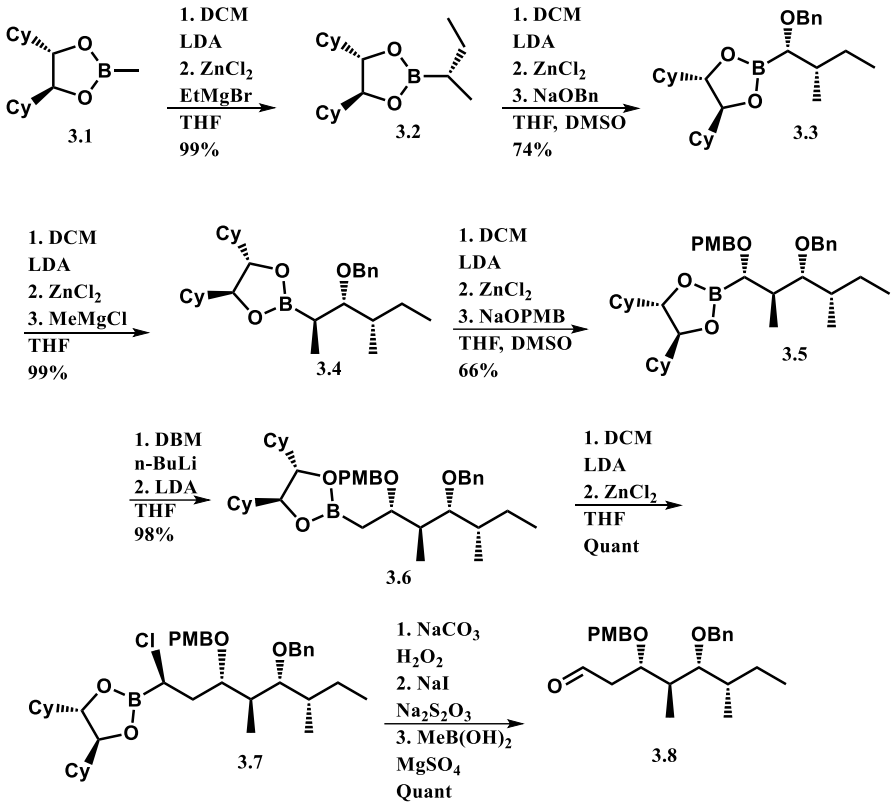
The group resorted to an alternative route to complete the synthesis of lagunamide A (Scheme 9).[32] The Grubbs second generation catalyst was attempted under various conditions of changing solvent and temperature, but the new strategy unfortunately failed. Lin reported no specific data other than stating no cyclization product was observed. The simpler fragment **2.27aa** was reacted with methacrylaldehyde under cross metathesis conditions using Grubbs second generation catalyst to give an aldehyde. This aldehyde was oxidized to give free acid **2.60**. The free acid acts as a linker for attaching peptide **2.31** using MNBA. In order to avoid epimerization of L-Boc-allo-Ile-OH, it was attached as a monomer with HATU to give **2.62**. The Fmoc and allyl deprotections were achieved using Et_2NH and $Pd(PPh_3)_4$/ PhNHMe. The cyclization was completed with HATU. The final deprotection of TBS using $HF_{(aq)}$ 40% ultimately gave lagunamide A. Lin's total synthesis thoroughly reported epimerization. Lin also completed the synthesis of five analogues which will be discussed in the section 1.7.



Scheme 9. Lin's alternative synthetic route to complete total synthesis of lagunamide A.

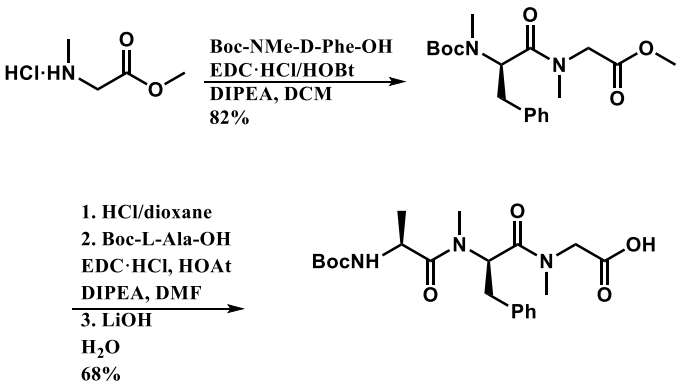
1.6 Kazmaier's Total synthesis of lagunamide A

The total synthesis reported by Kazmaier took advantage of the Matteson homologation, which utilizes a chiral boronic ester, to construct the stereocenters of the polyketide fragment of lagunamide A.[33] This linear approach is displayed in Scheme 9. The synthesis starts with the simple methylboronic ester **3.1**, under Matteson homologation conditions, ethyl Grignard is employed to install the first stereocenter to give boronic ester **3.2**. In the next step a benzyl alcoholate is used as a nucleophile to give ester **3.3**. The next stereocenter was installed using a methyl Grignard which gave **3.4**. Another homologation was followed with p-methoxybenzylate giving ester **3.5**. The introduction of the CH_2 group was difficult but was achieved by reacting dibromomethane with n-BuLi at -60°C to give **3.6**. After one more homologation (**3.7**) the species was oxidized to give aldehyde **3.8**.



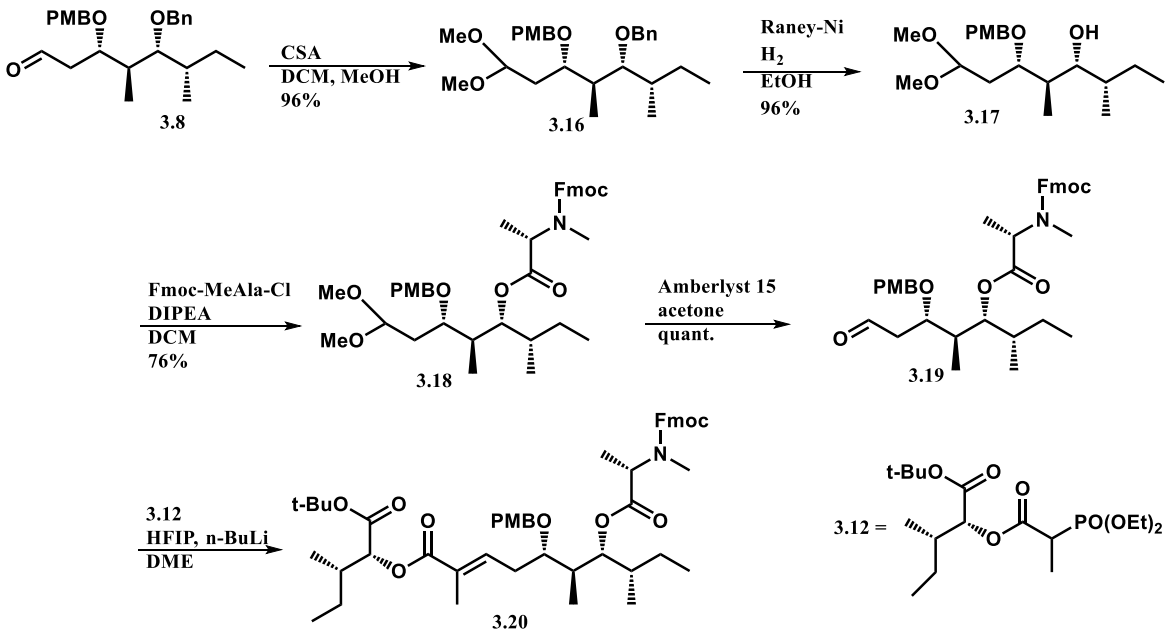
Scheme 10. Matteson Homologation approach for constructing polyketide of lagunamide A by Kazmaier.

A tripeptide was synthesized using Boc-protected amino acids (Scheme 11).[33] Using the tripeptide and adding Ile as a monomer bypasses the epimerization of Ile which is shown in Scheme 13. The HCl salt of sarcosine was reacted with Boc-protected D-N-Me-Phe-OH and coupled with EDC. HCl/Dioxane was used for Boc-deprotection and Boc-protected L-Ala-OH is coupled again with EDC. The methyl ester was next converted to free acid of the tripeptide.

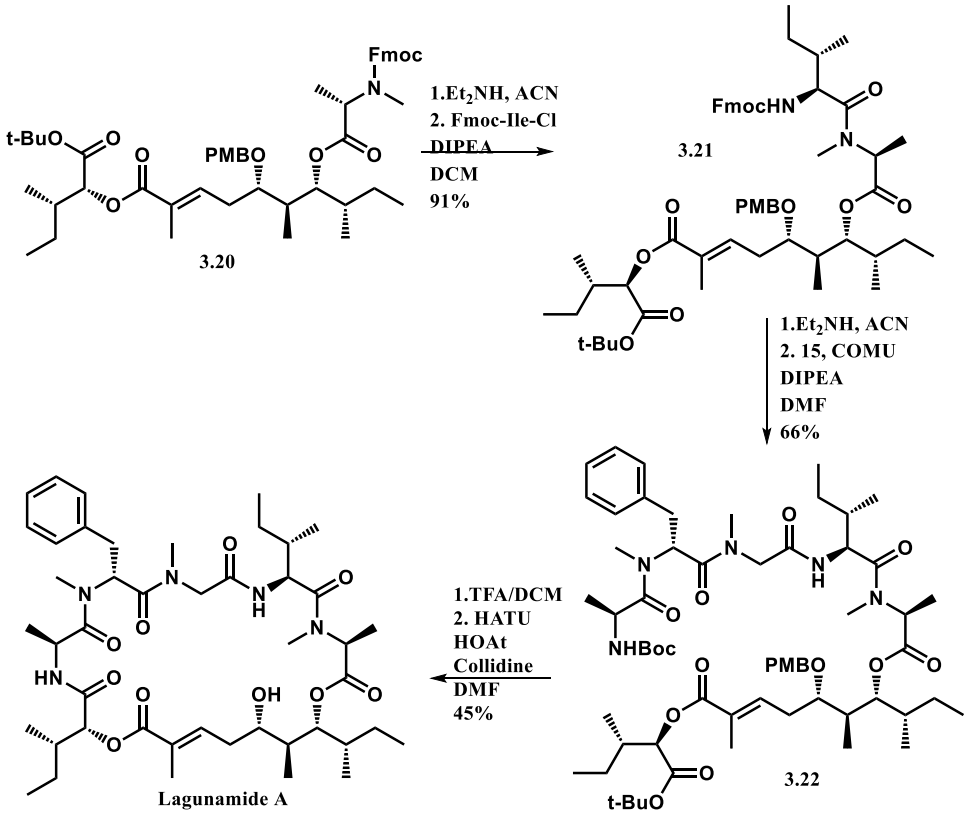


Scheme 11. Tripeptide synthesis by Kazmaier.

The bottom half of lagunamide A was completed by converting aldehyde **3.8** to acetal **3.16**. The benzylic ether was hydrogenated giving **3.17** (Scheme 12). Under the same conditions as described by Lin's total synthesis, L-N-Me-Fmoc-Ala-OH was added the same way to avoid epimerization. Acid chloride of L-N-Me-Fmoc-Ala-OH was made in situ to react with **3.17** to form ester **3.18**. Amberlyst-15 was used to convert acetal back to aldehyde giving **3.19**. An HWE reaction was next used to establish the α,β-unsaturated ester **3.20**. The base used in the HWE reaction, hexafluoroisoproponal lithium salt, surprisingly epimerized the alpha position of L-alanine in a ratio of 8/2. Out of the three total synthesis of lagunamide A to date, this was a second time the epimerization of L-N-Me-Fmoc-Ala-OH was reported. After Fmoc-deprotection with Et_3NH, tripeptide was introduced with COMU. The BOC and PMB deprotection were achieved using TFA. The final cyclization was done using HATU to obtain Lagunamide A. The Matteson homologation approach is high yielding but linear in its nature and is not an optimum in a long synthetic sequence. Important strategies were introduced for avoiding epimerization of stereocenters along the peptide sequence.



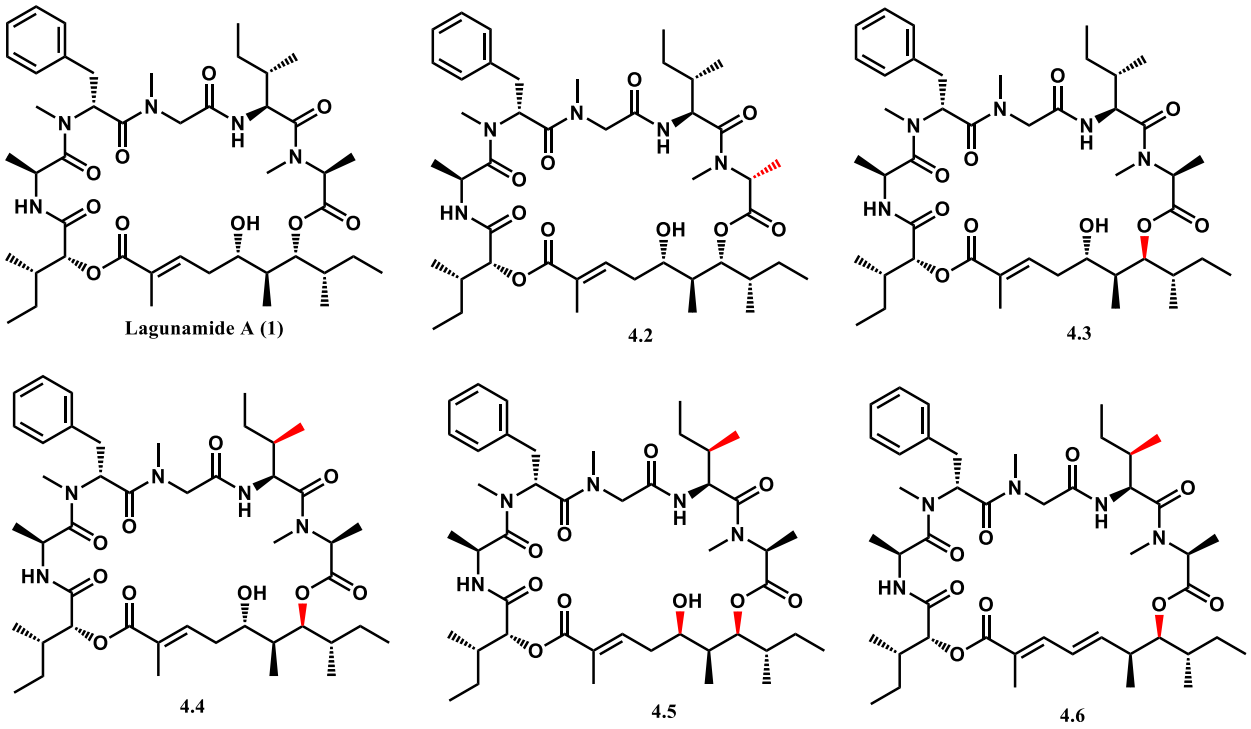
Scheme 12. Completion of polyketide of lagunamide A by Kazmaier.



Scheme 13. Completion of lagunamide A by Kazmaier.

1.7 Wei's Structure Activity Relationship of lagunamide A and its analogues

The Wei group presented a SAR study of various analogues to elucidate which regions of the molecule were responsible for its activity in anti-cancer activity.[34] The antiproliferative activities of the analogues were tested against lung cancer cells A549, cervical cancer cells HeLa, osteosarcoma cells U2OS, liver cancer cells HepG2 and BEL-7404, stomach cancer cells BGC-823, colon cancer cells HCT116, breast cancer cells MCF-7, leukemia cells HL-60, melanoma cells A375. Lagunamide A exhibited less than 20 nM activity against all cells lines (Figure 8). Analogue **4.2** has a modification where the stereochemistry at C-2 position was switched and the activity of the analogue had a 3-fold drop compared to Lagunamide A.



IC50 (nM)	Lagunamide A (1)	4.2	4.3	4.4	4.5	4.6
A549	8.7	62.3	273.9	3400.3	>10000	>10000
HeLa	17	67.3	191.6	1377.7	>10000	>10000
U2OS	8.6	59.3	437.9	4036.7	>10000	>10000
HepG2	11.4	67.4	246.6	2537.3	>10000	>10000
BEL-7404	11	59.9	725	5859.3	>10000	>10000
BGC-823	4.7	42.5	231	3430.3	>10000	>10000
HCT116	8.2	52.4	200	3799.7	>10000	>10000
MCF-7	18.7	145.8	946.4	839.8	>10000	>10000
HL-60	19.8	92.6	713.9	8630.3	>10000	>10000
A375	8.3	56.3	212.6	970.2	>10000	>10000

Figure 8. Analogues of lagunamide A and corresponding IC50 values against diverse human cancer cells.

When the stereochemistry of the ester position at C39 was switched there was a reported 20-fold decrease in activity compared to lagunamide A. Analogue structures **4.4** and **4.5** are

reported epimers of lagunamide A and the activities of these continued to drop compared to the natural product. When the alcohol moiety localized in the C37 position of lagunamide A was dehydrated there was no activity observed above 10 μM for analogue **4.6**. The alcohol as well as the R-configuration of the oxygen atom at C39 were identified to be the key contributors responsible for the activity of lagunamide A. The Wei group sought out to determine the molecular mechanism of action of lagunamide A causing cancer cell death. Huang[34] depicted the following in A549 cells: (Figure 9A(a)) pseudopodia retraction, chromatin (Figure 9A(b)), and karyopyknosis Figure 9A(c) at 10 nM for 24 h also nuclear cracking, DNA release into cytoplasm Figure 9B(b), and lysosome packing damaged organelle (Figure 9B(c)) observed by TEM. Their finding indicated that A549 cells underwent apoptosis pathway when lagunamide A was introduced. This was further confirmed by a Annexin V-positive, up to 80% of cells, suggested extremely high apoptosis rate in A549 cells (Figure 9C). Apoptosis also occurred in HeLa, HepG2, and HCT116 cells increased to 81%, 50%, and 40%.

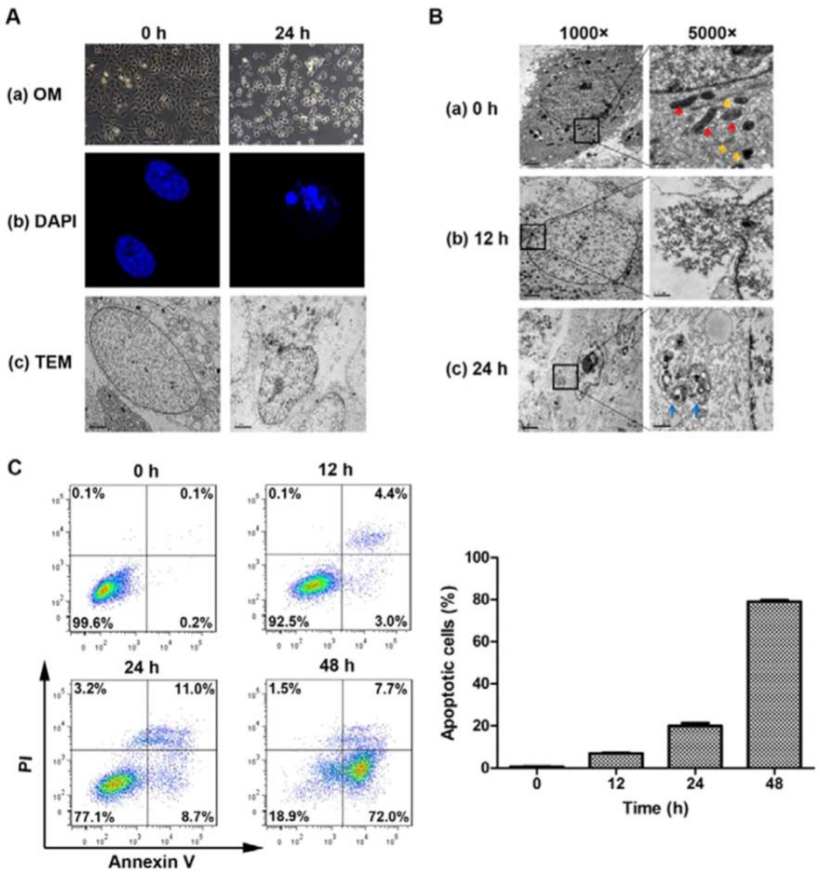


Figure 9. Induced apoptosis in A549 cells by lagunamide A. (A) morphological variation under optical microscope. Chromatin conditionally treated cells stained by DAPI detected with confocal laser scanning microscopy. Karyomorphism conditionally treated cells visualized on TEM. (B) Karyomorphism and organelle visualized on TEM. (C) Conditionally treated A549 cells stained with PI/Annexin V analyzed by FACScan flow cytometry.

During early stages of apoptosis the caspases are activated which lead to cleavage of critical cellular substrates including PARP. Apoptosis-related proteins were analyzed by Wei as well as quantified by immunoblot after treating A549 cells with DMSO or lagunamide A.[34] Of the cells treated exposed to lagunamide A, Capsase-7 and PARP were rendered, and cleavage form of Capsase-7 and PARP increases over time. Lagunamide A also increased the capsase-3 activity over time. Wei's work also concluded that A549 cells exposed to lagunamide A

underwent mitochondrial instinct apoptosis mediated by MMP, ROS overproduction, and regulation of both anti and pro-apoptotic Bcl-2 family proteins. This study shows promising results of lagunamide A as a substance targeting the modulation of BcL-2 family of proteins, which have been identified to be involved in mitochondrial apoptosis through regulation of MMP.

Chapter 2 Lagunamide A: Synthesis of Polyketide fragment

2.1 Former work by Bergdahl group of Lagunamide A

Our group has been interested in developing an efficient total synthesis of lagunamide A for some time. The SAR studies by Wei demonstrated the potential of this natural product as a therapeutic towards cancer (section 1.7). The small structural differences between lagunamide A and its analogues lead to large differences in activity across a board range of cancer cell lines. This demonstrates the importance of developing a synthetic route that focuses not only on installing the stereocenters with precision, but also preventing the stereocenters from epimerization while conducting chemical reactions leading up to the target compound. This section will discuss a synthetic route in the constructing the crucial polyketide fragment applying Vinylogous Mukaiyama Aldol reaction (VMAR). It will also discuss the limitations of the work done previously, the specific strategy used as an alternative, and where the project was concluded previously. An alternative route, analogous to Ye's and Lin's synthesis, were used to construct the natural product and the ^{1}H NMR spectra of the species isolated by former coworker (Brent Banasik) is shown (Figure 10).

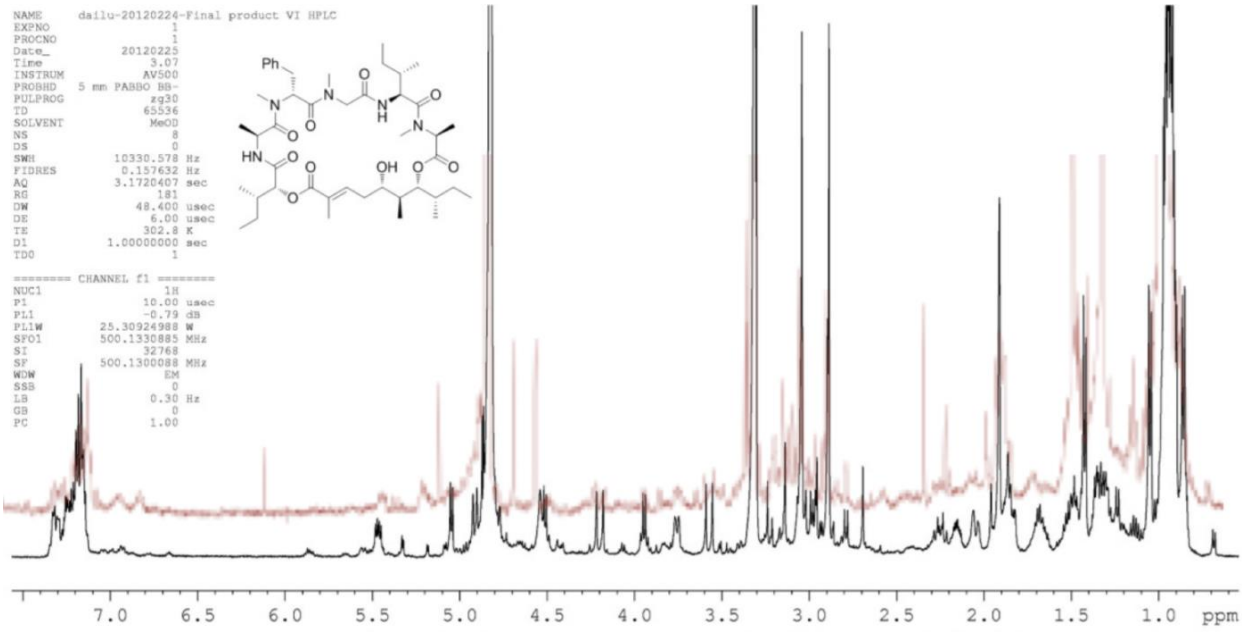
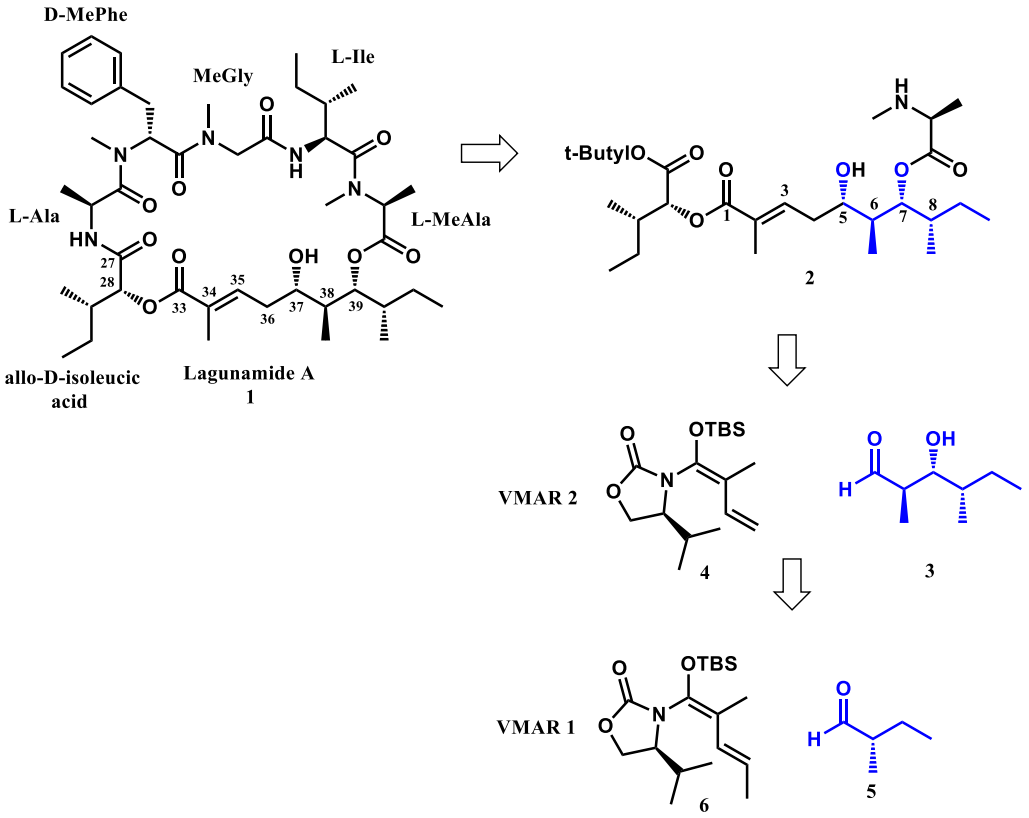


Figure 10. ^{1}H NMR in CD_3OD of synthetic material isolated by former coworkers (red) and laguamide A isolated by Tan (black).

Low resolution mass spectrometry of lagunamide A was presented in Brent Banasik thesis. A side by side comparison of the ^{1}H NMR of lagunamide A isolated by Tan and was previously isolated in our lab is shown in Figure 10. Since a clean NMR couldn't be obtained, the work presented in this thesis represents a second attempt at synthesizing the natural product. Material was unfortunately too scarce to collect good ^{1}H and ^{13}C NMR spectra. Furthermore when attempts were made to purify the impure material, multiple fractions complex fractions were collected via HPLC, which most likely contained various diastereomers.

The retrosynthetic strategy for the construction of lagunamide A using VMAR for a short efficient route for the construction of the polyketide fragment of lagunamide A as reported is illustrated below (Scheme 14).[35] The stereocenters of C39-C40 correspond to stereocenters from C5 to C8 within fragment **2** which can be installed using two iterative VMAR's. In these two VMAR reactions different silylketene acetals were coupled to chiral auxiliaries derived from

inexpensive amino acid derivatives. Enoate **2** was a product obtained from a second VMAR employing aldehyde **3** with vinylketene silyl *N,O*-acetal **4**. Aldehyde **3** is derived from the first VMAR done with aldehyde **5** with vinylketene silyl *N,O*-acetal **6**. The next section will go into details of the VMAR reaction developed by Kobayashi.[37a]



Scheme 14. Efficient retrosynthesis of polyketide fragment of lagunamide A using two VMAR's.

2.2 First VMAR and Kobayashi's method

The first reported Vinylogous Mukaiyama Aldol Reaction was published in 1973 (Figure 11).[36] This VMAR utilized a silyl enol ether obtained from crotonaldehyde, which was subsequently reacted with cinnamaldehyde dimethyl acetal in the presence of $TiCl_4$ as a Lewis acid. Since the birth of VMAR, not only has there been many developments in the field, it has

become an invaluable and instrumental tool for the construction of complex natural products and polyketides for the last 47 years.[37] Key methodologies and pertinent work will be discussed through this thesis accordingly.

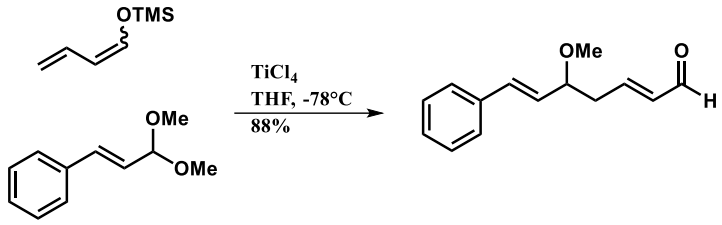
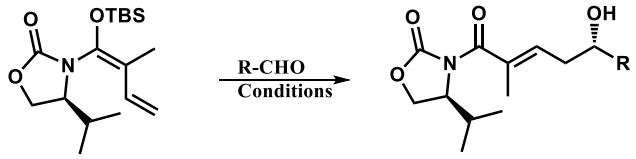


Figure 11. First VMAR reaction reported in 1973 by Mukaiyama.

In this section the Kobayashi VMAR protocol will first be discussed.[37a] Thus this method takes advantage of vinylketene silyl *N,O*-acetals connected to chiral oxazolidinones. Table 4[37a] shows the use of vinyl ketene silyl *N,O*-acetal **4** under standard VMAR conditions with various aldehydes to give the corresponding aldol products. It should be noted that the aldehydes used in these entries are aliphatic even though a few complex aldehydes have been reported in the VMAR's. A brief overview of VMAR's using complex aldehydes will be discussed in section 2.7. Kobayashi[37a] depicted and proposed the chiral directing group is perpendicular to the conjugated diene. This was also confirmed by NOE experiments done of the molecule (Figure 12[37a]).

Table 4. VMAR of vinyl ketene silyl *N*,*O*-acetal derived from tiglate moiety reported by Kobayashi.



Entry	R	Product	Yield (%)	d.s
1	$CH_3(CH_2)4$	5a	97	42:1
2	$CH_3(CH_2)10$	5b	92	94:1
3	$(CH_3)_2CH$	5c	95	40:1
4	*E*-CH_3CH=CH	5d	54	20:1
5	*E*-CH_3CH_2CH=C(CH_3)	5e	55	86:1
6	Ph	5f	94	30:1

From the reported NOE experiments it was proposed in the transition state, the isopropyl group essentially blocks the approach of the electrophilic aldehyde. The vinyl ketene silyl *N*,*O*-acetal **6** (Scheme 14) was also investigated. Kobayashi reported the methyl group positioned at the end of the diene was always in an anti- relationship in the VMAR product.

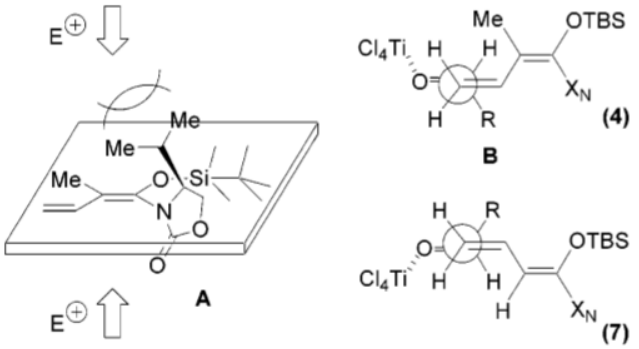


Figure 12. Proposed transition state of reaction in VMAR.

By using different variations of the silylketene acetals in the VMAR a differentiation of the basic carbon framework shown in Figure 13 can be achieved.[37] Motifs II, III, and IV are methyl substitution variations derived from motif I. Motif III and IV can be achieved using Kobayashi's reported protocol as shown earlier. These will be further discussed in section 2.3 during the first investigation of using VMAR's for the construction of the polyketide segment of lagunamide A. Motif II can be achieved using a VMAR under Felkin-Anh controlled VMAR which will be discussed later in the thesis when encountering the VMAR's of different functionalized aldehydes. Motif I will not be discussed here. It should be noted the motif I carbon framework was formed in the first VMAR reported in 1973 by Mukaiyama.[36]

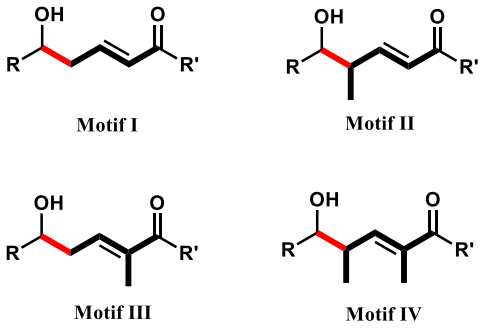
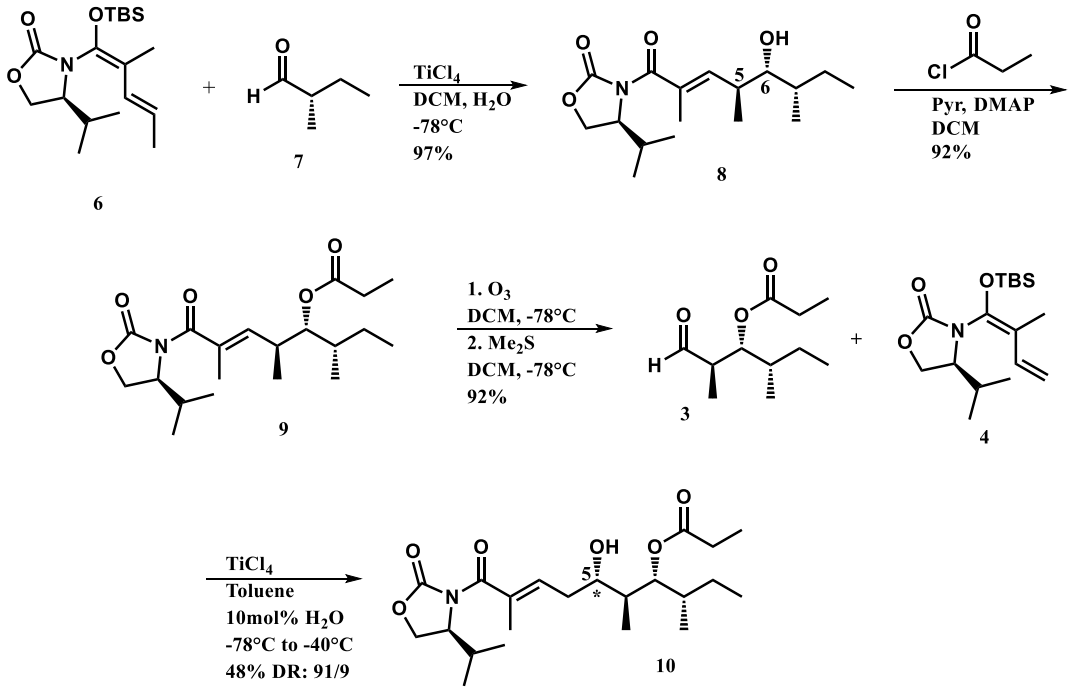


Figure 13. Substitutions patterns observed in polyketides.

2.3 Reinvestigation of Kobayashi's method for polyketide of lagunamide A



Scheme 15. Applying Kobayashi's VMAR protocol for construction of polyketide of lagunamide A.

As reported previously in our group, Kobayashi's method is an attractive approach to use for installing the C37-C40 stereocenters with precision. The second iterative VMAR (Scheme 14) contains the crucial α,β-unsaturated imide moiety. My work on the project and this thesis started with the VMAR strategy and the results shown in Scheme 15.[35] The first VMAR with vinylketene silyl *N,O*-acetal **6** and chiral butanal **7** in the presence of $TiCl_4$ gave aldol product **8** in 97% yield. As depicted in Scheme 15, the C38 and C39 stereocenters of the natural product correspond to the 5,6 anti-relationship of the 1st VMAR product. The direct route to aldehyde **3** was to protect alcohol as ester **9** in 92% yield, which provides the alkene and then via ozonolysis the aldehyde **3** in 92% yield. When reacted with vinylketene silyl *N,O*-acetal **4,** under modified VMAR conditions aldol product **10** was achieved. The stereocenter localized on C37 of

lagunamide A corresponds to C5 of imide **10**. The α,β-unsaturated moiety of the polyketide is also embedded in the product making this an efficient approach for the construction of the desired polyketide. Banasik[35] *et al*. reported the 1,3 relative stereochemistry by installing the acetonide shown in Figure 14, and measuring the ^{13}C NMR chemical shifts.[35]According to report by Evans, the quaternary carbon of syn-acetonides have a ^{13}C chemical shift of roughly 98 ppm.[38,39] For the anti-relationship the ^{13}C chemical shifts of the quaternary carbons are reported to be roughly 100.5 ppm. [38,39] The dimethyl groups of the syn-acetonides have ^{13}C chemical shifts corresponding to 19 and 30 ppm.[38,39] For the anti-relationship the ^{13}C chemical shifts of the dimethyl groups are roughly 24-25 ppm. [38,39] Using this information, the relative stereochemistry of acetonide in Figure 14 and VMAR product **10** is syn.

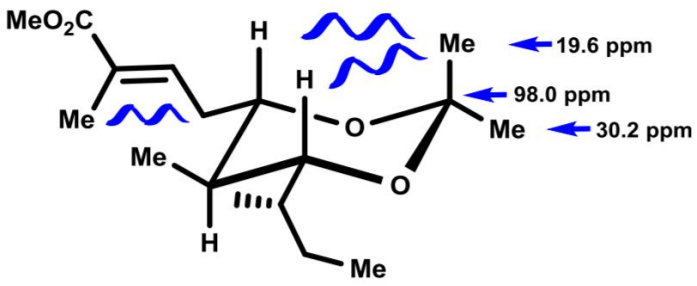


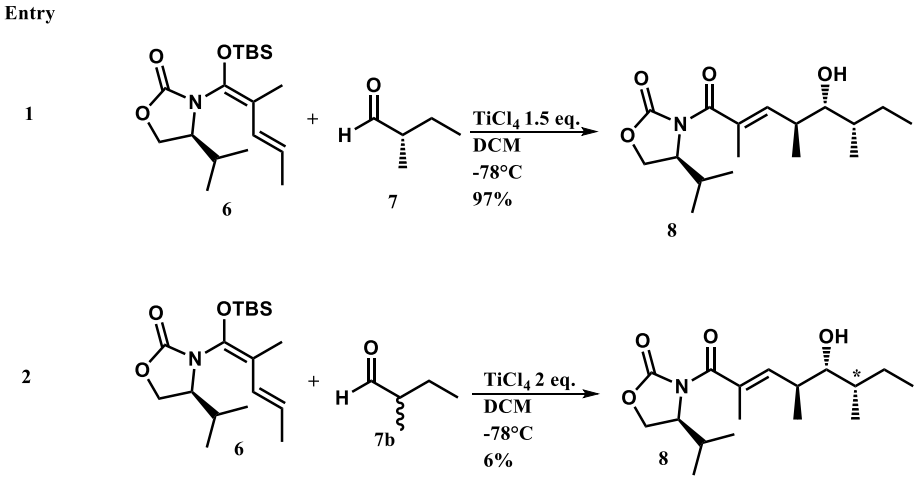
Figure 14. NOE correlations and ^{13}C NMR chemical shifts of syn-acetonide protecting group.

This VMAR method is efficient but not reliable to produce enough material to continue the synthesis towards lagunamide A. The two VMAR reactions were difficult to practice and slightly irreproducible. As a consequence, the strategy presented in Scheme 10 by Lin's total synthesis was used to construct the polyketide fragment **2** in order to continue the synthesis. Particularly, the second VMAR was investigated in detail and presented in section 2.5. Before the second VMAR could be studied in detail, the first VMAR yielding alcohol **8** had to be

optimized and reliable in order to be practical in supplying large quantities of material for the synthesis of lagunamide A.

2.4 Kobayashi's method for the first VMAR

The VMAR's are valuable for constructing the polyketide carbon framework for natural product synthesis. VMAR's are difficult reactions to perform and must be mastered to produce the high material demand needed for total synthesis for natural products. The first VMAR of the two iterative VMAR for the construction of polyketide of Lagunamide A is shown in Scheme 16. Alcohol **8** is produced in 97% as a pure diastereomer of the desired stereotriade for lagunamide A when the enantiomerically pure aldehyde **7** is used. We noticed when a racemic mixture of aldehyde **7b** was used only 6% yield of a diastereomeric mixture of products is produced (entry 2). The reasons for investigating the use of racemic mixture of aldehydes will be discussed in chapter 6. The low yield was used as an opportunity to learn why the reaction sometimes gave high and low yields. The investigation was necessary for continuous reproducibility in the first VMAR (entry 1) for long term use for the construction of the polyketide of Lagunamide A.



Scheme 16. First VMAR with chiral butanal **7** and racemic aldehyde **7b**.

Table 5 summarizes the yield of the diastereomeric mixture of products of VMAR (entry 2) when changing the amount of Lewis acid. The highest yield of 99% was obtained when the lowest amount of lewis acid (1.5 equiv) was used. When the amount of lewis acid was increased (2 - 4 equiv) the yield significantly dropped to 6% - 9%.

Table 5. Varying amount of $TiCl_4$ used in VMAR with racemic butanal

Entry	$TiCl_4$	Isolated yield	Crude DR
1	1.5 eq.	99%	77/23
2	2 eq.	6%	UD
3	4 eq.	9%	76/24

UD = Undetermined

Another variable that is surprisingly important to the VMAR's is the addition of water to the reaction. Kobayashi reported a rate enhancement when 10 mol% of water is added to a VMAR utilizing vinylketene silyl *N*,*O*-acetals.[40] When the addition of was investigated (table 6) the yield increased significantly from 6% to 84% (entry 1 and 2). The best conditions were the addition of water (1 equiv) and the reduction of Lewis acid (1.5 equiv) to give 97% yield.

Table 6. Varying amount of H_2O used in VMAR with racemic butanal

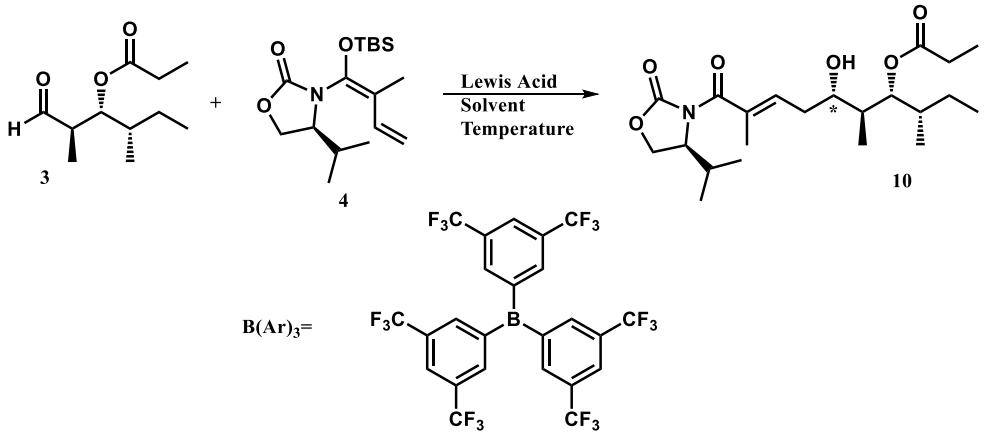
Entry	Water	$TiCl_4$	Isolated yield	Crude DR
1	0 eq.	2 eq.	6%	UD
2	1 eq.	2 eq.	84%	77/23
3	2 eq.	2 eq.	59%	77/23
4	1 eq.	1.5 eq.	97%	73/27

UD = Undetermined

Reducing the amount of Lewis acid and the addition of water lead to 90+ yield of the first VMAR (entry 1) on multi-gram scale reactions. Using these optimized conditions, the start of the synthesis proceeded smoothly with consistent production of alcohol **8** in large quantities.

2.5 Optimization attempts of 2nd VMAR

The second iterative VMAR (Scheme 17) also needed investigated due to the fact alcohol **10** contained the core carbon framework of the polyketide for Lagunamide A and the yield was low. Various conditions were investigated and are summarized in table 7. Unfortunately, alcohol **10** could not be obtained any higher than 30% yield. Various conditions explored were changes in temperature, reaction time, solvent, changing Lewis acids, addiction of water, and amount of Lewis acid used. Standard conditions (entry 1 – 4) always gave 30% yield of **10**. The use of boron, tin, and titanium Lewis acids commonly used in VMAR's were employed but unfortunately led to no product formation (entry 7 – 11). It was obvious another solution would be needed for the construction of the polyketide fragment of lagunamide A. Unfortunately, in all cases no starting material was isolated and acetal **4** had converted to imide shown in the experimental section.

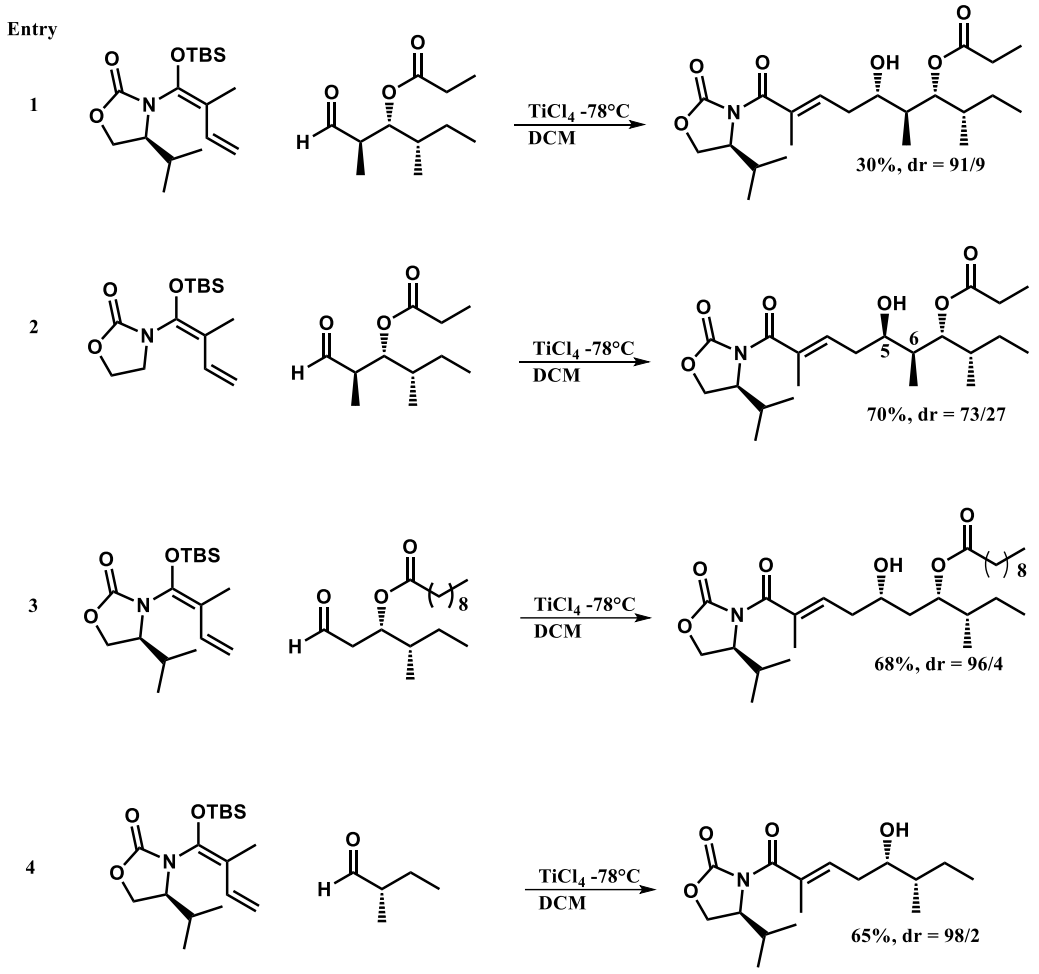


Scheme 17. General scheme of second VMAR

Table 7. Attempted optimization conditions of second VMAR.

Entry	3 (eq)	4 (eq)	10 (%)	H_2O (eq)	Lewis Acid (eq)	Solvent	Temp. (°C)	Time (h)
1	2.25	1	30	0	$TiCl_4$ (1.5)	DCM	-78	18
2	2.25	1	30	1	$TiCl_4$ (1.5)	DCM	-78	18
3	1.5	1	30	1	$TiCl_4$ (1.1)	DCM	-78	48
4	1.5	1	30	0	$TiCl_4$ (1.1)	DCM	-78	48
5	1.5	1	0	1	$TiCl_4$ (1.5)	DCM	-40 to -78	18
6	1	3	15	0	$TiCl_4$ (3.0)	DCM	-78	216
7	1.5	1	0	0	$SnCl_4$ (1.1)	DCM	-78	18
8	1.1	1	0	0	$BF_3{\cdot}OEt_2$ (1.5)	DCM	-78	18
9	1	2	0	0	$B(Ar)_3$	DCM/Ether	-78	18
10	1	2	0	0	$B(Ar)_3$	DCM/Ether	0 to RT	18
11	2	1	0	0	$TiCl_4/AgSbF_6$ (1.5)	DCM/Tol.	-78 to RT	18

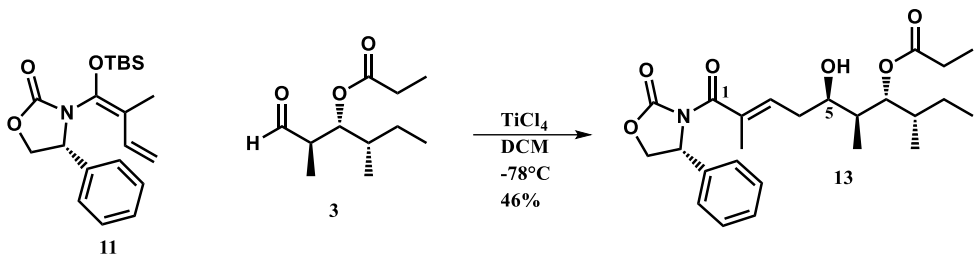
Something we noticed in former work in our group (entry 2, Scheme 18),[35] was when the directing group is removed from the vinylketene silyl *N,O*-acetal the stereochemistry in the C5 position changes and a higher yield is observed. One possible route was to perform a Mitsunobu reaction to invert the stereochemistry and give the correct polyketide product for the construction of Lagunamide A, which is discussed in the next section.



Scheme 18. Former work reported in our group probing 2nd VMAR.[35]

2.6 Attempts of alcohol inversion for second VMAR

In published work by Banasik the major diastereomer (ratio: 73/27) shown (entry 2, Scheme 18)[35] adopts the a 5,6-syn product. If an opposite chiral directing group were to be employed to improve the diastereomeric ratio then a possible alcohol inversion could be useful strategy to install the correct stereochemistry in the end. First a slightly different vinylketene silyl *N,O*-acetal **11** was synthesized and reacted with aldehyde **3**. Under a set of conditions alcohol **13** was produced in modest 46% yield (Scheme 19) with anticipated stereochemistry.



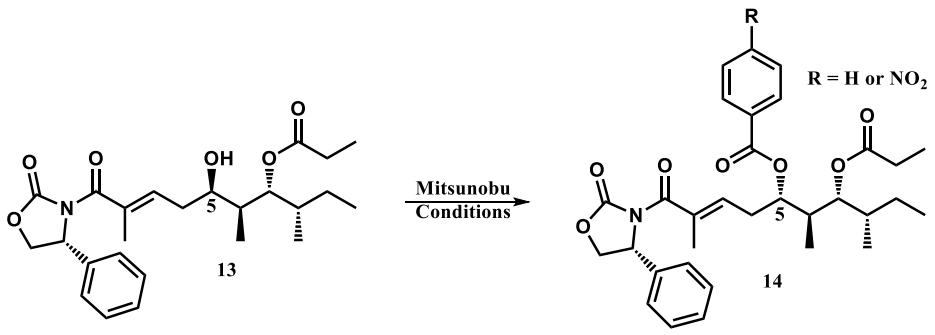
Scheme 19. Synthesis of alcohol **13**.

A few variations were investigated to improve the yield (table 8). First, original VMAR conditions gave 46%. A second attempt was made using toluene to promote potentially increased chelation of $TiCl_4$ to aldehyde **3**, but the result remained unchanged (entry 2). In the last entry the reaction time was extended to 4 days but still with the same outcome. Regardless the Mitsunobu reaction was attempted to invert the stereochemistry of alcohol **13** positioned at C5.

Table 8. Investigating different conditions for optimizing alcohol **13**.

Entry	H_2O (eq)	Solvent	Time (h)	Yield (%)
1	1	DCM	18	46
2	0	Tol.	18	46
3	1	DCM	96	46

The Mitsunobu reaction is one of the most reliable methods available for inversion of stereochemistry of alcohol functional groups. This method converts an alcohol to a phosphrous-oxygen as a leaving group created from the use of PPh_3 which is further displaced by a suitable nucleophile using a carboxylate species. It is this displacement step which causes the stereochemistry to invert in an S_N2 fashion.[42]



Scheme 20. Mitsunobu attempt of VMAR 2 product **13**.

The goal was to try and switch the stereochemistry at C5 position of **13**, a product of a second VMAR (Scheme 20). When standard Mitsunobu conditions were employed (table 9, entry 1) no product was observed but starting material reclaimed. The conditions were pushed with a slight increase in reagents (entry 2), neither starting material nor Mitsunobu product was observed. The E/Z isomers of elimination along the C4-C5 product were observed. The Mitsunobu reaction has been reported to be specific in terms of the substrate employed and the reaction condition required for a successful reaction can vary. The solvent and the acidity of the nucleophilic carboxylate are two important variables to consider and alter.[42] The nucleophile, para-nitro benzoic acid (p-NO_2-BA) was switched to benzoic acid (BA), slightly more nucleophilic, and the solvent was switched to toluene which is commonly used in the reaction. In entry 3, elimination was observed again and when reagent equivalence was reduced only starting material was observed. With this investigation it was apparent inversion of C5 stereocenter of 13 would not be an easy task.

Table 9. Mitsunobu attempts of alcohol **13**.

Entry	DEAD/DIAD (eq)	PPh_3 (eq)	Carbox. Acid (eq.)	Solvent	Product 14 %
1	3.5	3	p-NO_2-BA (3.0)	THF	0
2	4.4	3	p-NO_2-BA (4.4)	THF	0
3	4	4.4	BA (6.0)	Tol.	0
4	2	2	BA (2.0)	Tol.	0

Alcohol **13** was precious in the sense it could not be made readily. For this reason, a simpler substrate **15** (Scheme 21) was used to practice alcohol inversions. When the first attempt was made (entry 1) all starting material was eliminated and no product was observed (table 10). Elimination is induced by temperature and when the same conditions were employed but when the reaction was started at 0°C product was observed was not isolated due to impurities of the Mitsunobu reagents (entry 2). Other conditions were also attempted to increase conversion of starting material to product but not product was observed (entry 3, 4).

Scheme 21. Mitsunobu attempt of VMAR alcohol **15**.

Table 10. Mitsunobu attempts of alcohol **15**

Entry	DEAD/DIAD (eq)	PPh_3 (eq)	Carbox. Acid	Solvent	Product 16 %
1	3	3.5	p-NO_2-BA	THF	0
2	3	3.5	p-NO_2-BA	THF	0
3	3	3	p-NO_2-BA	Tol.	0
4	3	3	AcOH	Tol.	0

2.7 Background of 2nd Iterative VMAR's

Up until this point only the investigation of obtaining the polyketide fragment using Kobayashi's VMAR had been investigated. The second iterative VMAR had been a challenge to obtain in modest quantity and scaleup led to no isolation of product. A thorough investigation of the second iterative VMAR in the literature revealed two important observations. The first, Kobayashis protocol of VMAR had been extensively employed on aliphatic aldehydes. The method produces high yielding aldol products in the absence of any heteroatoms present within the aldehyde. Second, there are few methods of second iterative VMAR's using β-oxyaldehydes (Figure 15). The reactions reported here are representative samples of VMAR's utilizing β-oxyaldehydes. Entry 1 is from our groups previously reported method. Kobayashi recognized the problem earlier when employing vinylketene silyl *N,O*-acetal in VMAR and published unique condition for obtaining high yielding VMAR products obtaining from β-oxyaldehydes (entry 2).[43]

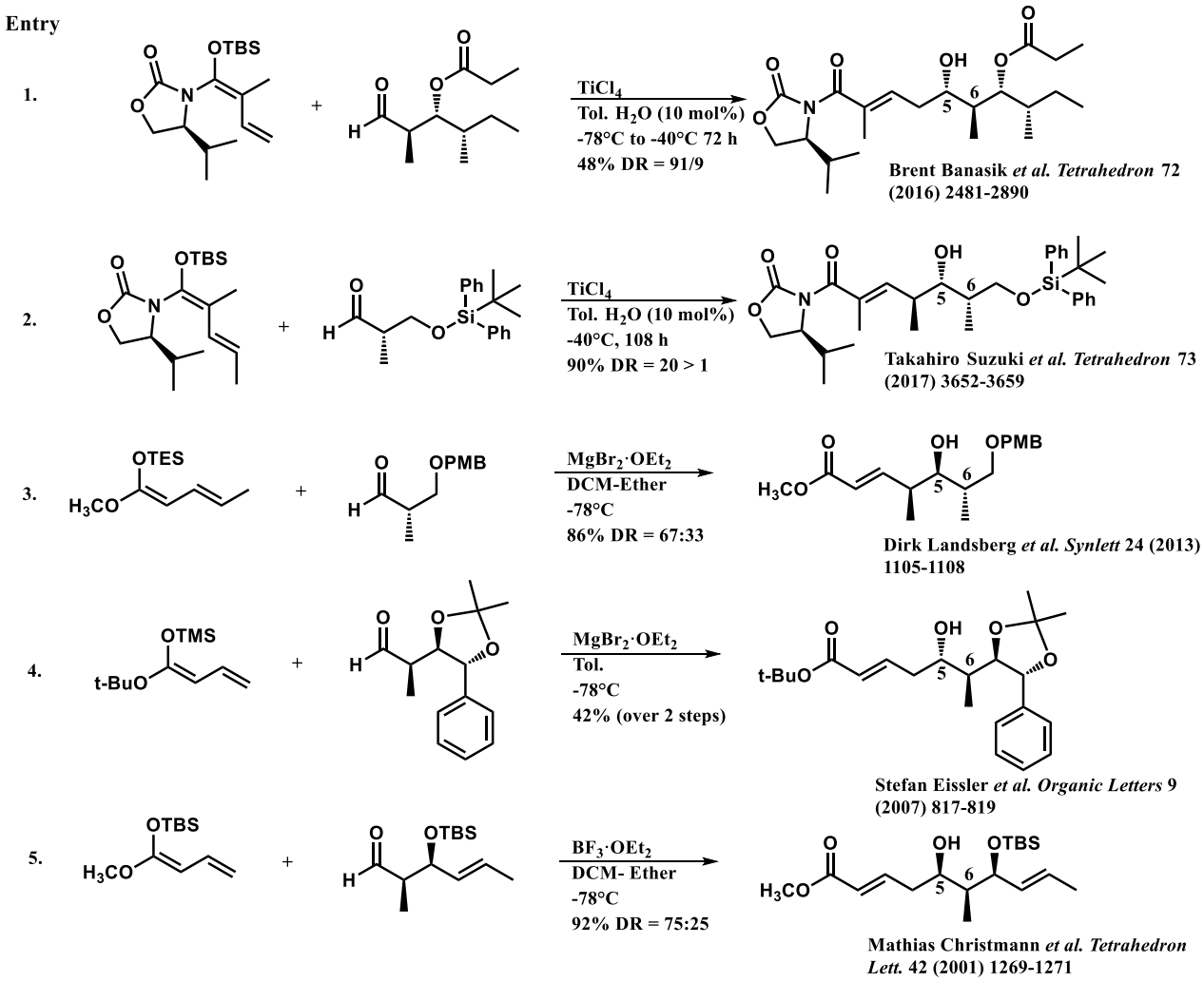
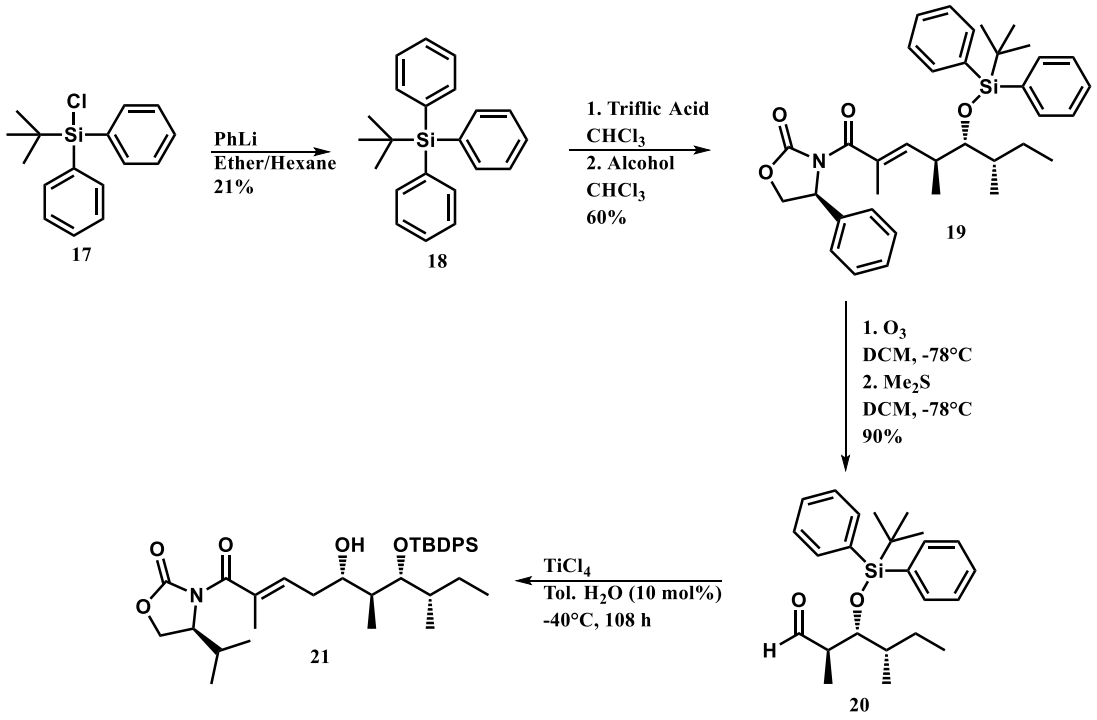


Figure 15. Representative sample of second iterative VMAR's.

Kobayashi thoroughly investigated variables issue and published a method where unique set of conditions and employed a protecting group highly resistant to chelation of Lewis acids (Scheme 22). Silane **18** was made by reacting TBDPCl with phenyl lithium to give the silane product in 21%. Method of converting silane **18** to t-butyl-diphenyl silyl-triflate in situ for alcohol protection was done to give silyl ether **19** in 60%. Oxidative cleavage of the alkene using ozone gave aldehyde **20** in 90%. When this chelation- resistant protecting group was exposed to Lewis acids was employed under the conditions employed by Kobayashi was used, unfortunately

no product (**21**) was observed. The vinylketene silyl *N,O*-acetal fully converted to de-silylated starting material and unreacted aldehyde **20**.



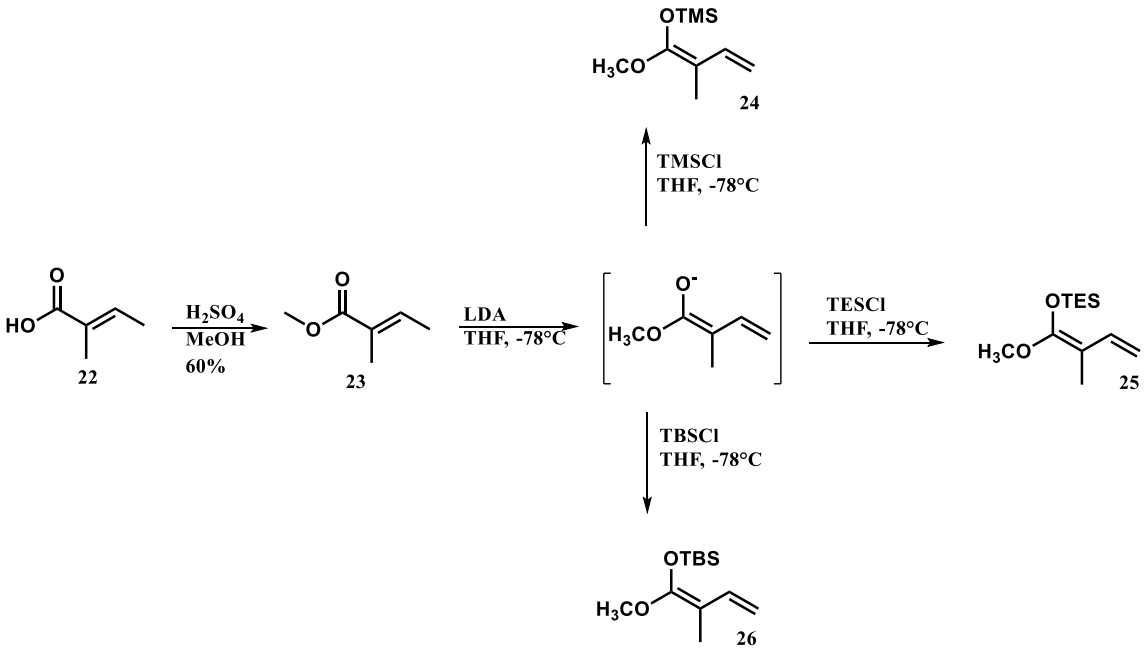
Scheme 22. Attempt at applying of Kobayashi's method for VMAR of a β-oxyaldehyde.

The aldehyde demonstrated by Kobayashi (Figure 15, entry 2) is in a sense simpler than our aldehyde **20** used in our study for the polyketide synthesis towards lagunamide A. The aldehyde used in our study is larger and exhibit two additional chiral centers. This might represent a major contributor of steric hindrance preventing chelation of $TiCl_4$. A second important observation is alpha-stereocenter, which adopts the opposite configuration than what is being used for our substrate. After this method was investigated, other iterative VMAR's were investigated for the possible adaptation to our substrate to construct the polyketide.

2.8 First viable route of the polyketide via VMAR utilizing Bidentate Lewis Acid

One of the most noteworthy VMAR's was reported by Landsberg and coworkers (Figure 15, entry 3).[44] Their work focuses on investigating various Lewis acids and determining the outcome of diastereomeric ratio of products. They utilized a bidentate Lewis acid in the presence of a β-oxyaldehyde for establishing a 5,6 anti-relationship of the VMAR product. This reaction utilizes the asymmetric induction provided by a chiral PMB-protected aldehyde. The vinylketene silyl acetal itself is lacking the chiral directing group used previously in VMAR reactions and this VMAR undergoes a chelation-controlled transition state when $MgBr_2 \cdot OEt_2$ is employed. Scheme 23 shows how vinylketene silyl acetals are synthesized.

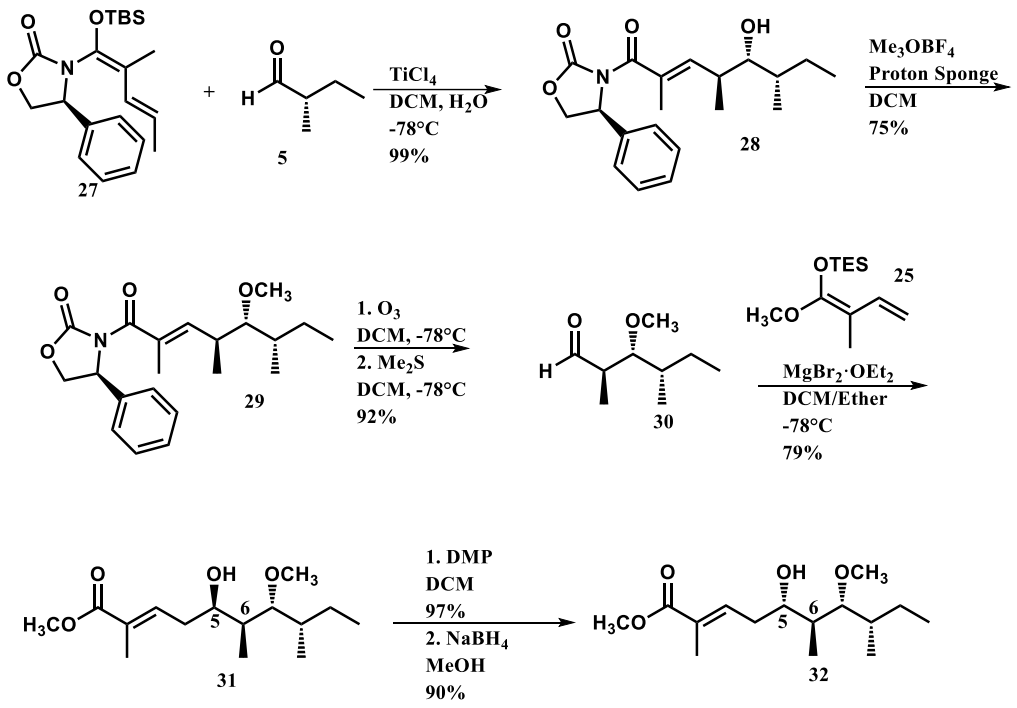
The vinylketene silyl acetals (Scheme 23) are more reactive than the corresponding *N*,*O*-vinylketene silyl acetals **4** and **6**, they are readily available from tiglic methyl ester **23**.



Scheme 23. Synthesis of achiral vinylketene silyl acetals.

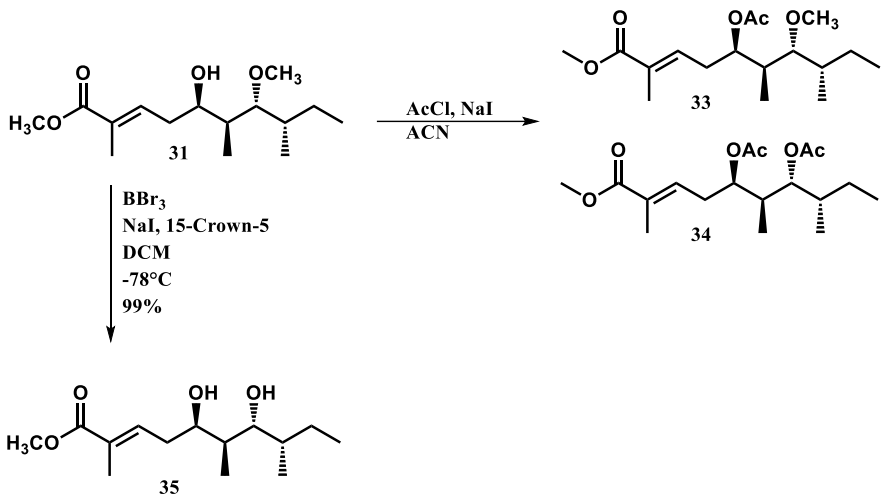
LDA is used with **23** to create the lithium dienolate, in situ, and due to silicon's higher affinity for oxygen, they can be trapped as silyl acetals. The most reactive vinylketene silyl acetal out of the three above is **24** and the least reactive is **26**.

Eissler and coworkers (Figure 15, entry 4) used a method for establishing the 5,6 anti-relationship for their VMAR intermediate for the total synthesis of Cryptophycin-52.[45] One important aspect in these reactions (Figure 15, entry 3 and 4) is the protecting group localized on the β-oxygen of the aldehyde, PMB and 1,2-acetonide, the first carbon of both protecting groups is sp^3 hybridized and neither donates or withdraw electrons from the β-oxygen. The β-oxygen and the oxygen atom of the aldehyde essentially act as a neutral donor ligand for the bidendate $MgBr_2 \cdot OEt_2$. It is important to mimic the same electronics for this oxygen and appropriate Lewis acids must be employed. Silyl ethers and esters cannot be used. For this reason, a simple methyl ether was chosen as a protecting group. The strategy was employed and demonstrated in the modified route in Scheme 24. First, alcohol **28** was converted to the methyl ether **29** using trimethyloxonium tetrafluoroborate salt in 75%. Oxidative cleavage of alkene using ozone then gave aldehyde **30** in 92%, which was immediately used in the second iterative VMAR. It is worth emphasizing here that the methyl ether does not influence the electronics of the beta-oxygen and is small enough to allow $MgBr_2 \cdot OEt_2$ to interact in a bidentate manner. When the second iterative VMAR was performed, **31** was isolated possessing the unexpected 5,6-syn VMAR stereochemistry. The correct stereochemistry needed is the 5,6 anti-relationship for constructing lagunamide A observed in alcohol **32**. Compound, **31** was isolated in 79%, a 5,6-syn VMAR product, as a single diastereomer. The stereochemistry of C5 for alcohols **31** and **32** were verified using 1,3- acetonides (Scheme 26). A brief discussion will explain the unexpected 5,6-syn VMAR stereochemistry of alcohol **31** using Figure 16.



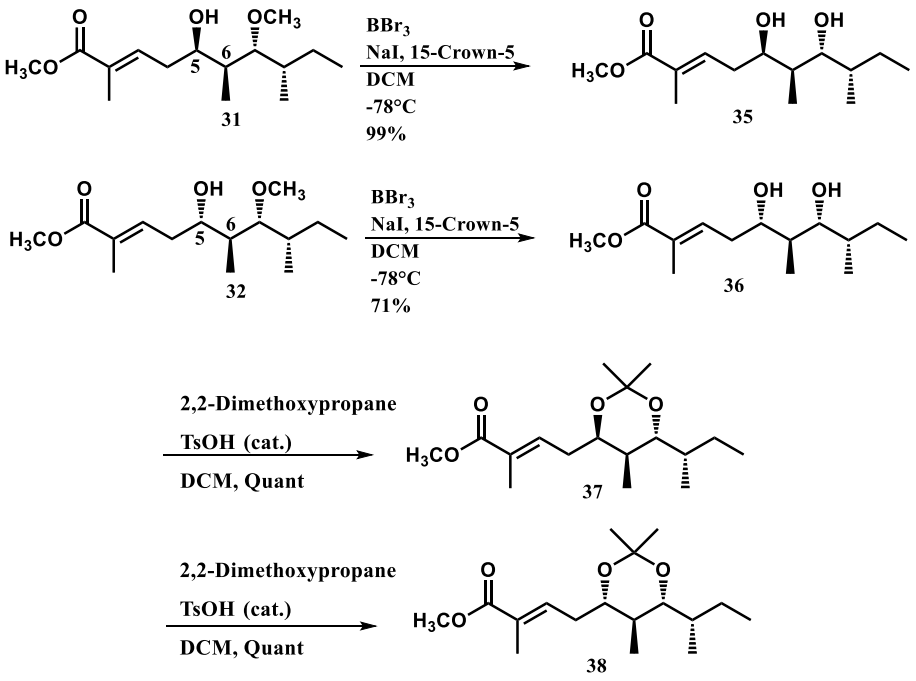
Scheme 24. Synthesis of polyketide using VMAR of β-oxyaldehyde employing bidendate lewis acid.

To convert alcohols **31** and **32** to 1,3 acetonides for determining stereochemistry at the C5 position, they first needed to be deprotected. Methyl ethers are relatively stable and first attempts for removal of methyl ether were conversion to acetate (Scheme 25) which could be saponified readily. Alcohol **31** was submitted to the harsh conditions of acetyl iodide and what was isolated was a mixture of monoacetate **33** and diacetate **34** in trace amounts.



Scheme 25. Conversion and deprotection of methyl ether **31**.

Deprotection proceeded smoothly with BBr_3 and NaI to directly give diol **35**. Both diols **35** (99%) and **36** (71%) were isolated under the same conditions. They were converted to their corresponding 1,3-acetonides using 2,2 dimethoxypropane to give **37** and **38** (Scheme 26), respectively. Using method of analysis of ^{13}C chemical shifts described by Evans (Figure 14), the relative stereochemistry was verified. The 1,3-syn acetonide **38** matched the spectroscopic data produced by former coworkers where the quaternary carbon chemical shift is 98 ± 1 ppm and the dimethyl carbons are 19 ± 1 and 30 ± 1 ppm. For the 1,3-anti acetonide **37** the corresponding ^{13}C chemical shifts also to the expected 100 ± 1 ppm, and two 24 ± 1 ppm, respectively.



Scheme 26. Determination of 5,6 relationship of alcohols via 1,3-acetonides.

We are also speculating about potential chelation-controlled reaction providing the unexpected 5,6-syn VMAR product can be explained by the 2,3 reinforcing vs 2,3 opposing structures illustrated (Figure 16). The stereochemistry of the aldehyde in the beta position used by Stephan and coworkers influences the bulky 1,2 acetonide substituent that allows the nucleophile to approach in a way that leads to give the 5,6-anti product (Figure 16, bottom).[46] In our model the beta position has the opposite stereochemistry and the bidendate Lewis acid chelation only allows the approach of the nucleophile to give the 5,6-syn product. The VMAR is considerably more complex and obtaining the desired 5,6-anti product is still challenging. As displayed in Scheme 24, alcohol **31** was converted to a simple ketone in 97%. The unstable product was the reduced with $NaBH_4$ to give alcohol **32** in 90% with DR of 89/11, with the major product as shown in Scheme 24. This strategy of conducting a stereoselective reduction was previously demonstrated by Liu and coworkers.[47] Since the α,β-unsaturated ester does not

need to be added via additional steps, the strategy employed on the VMAR product makes for a more efficient approach.

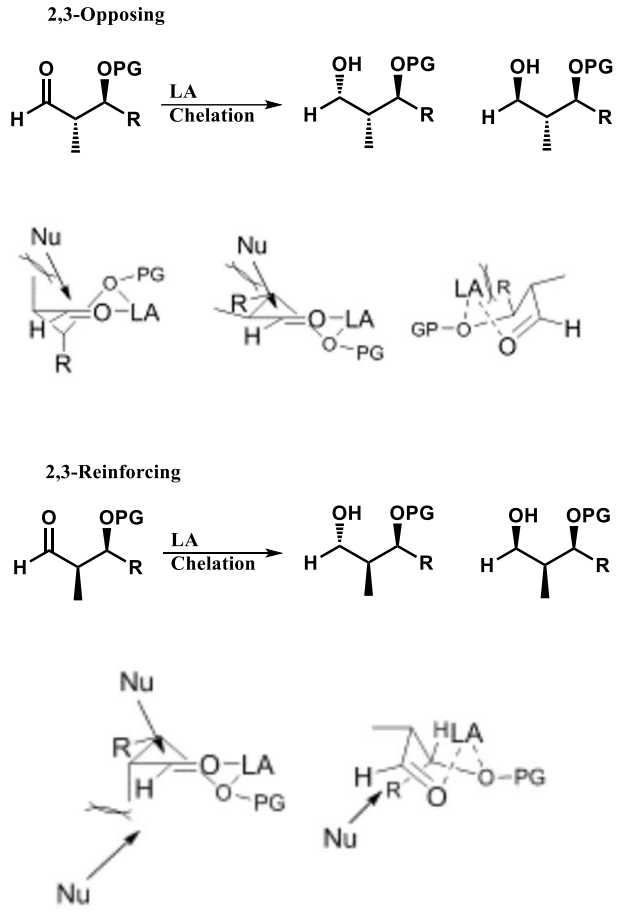
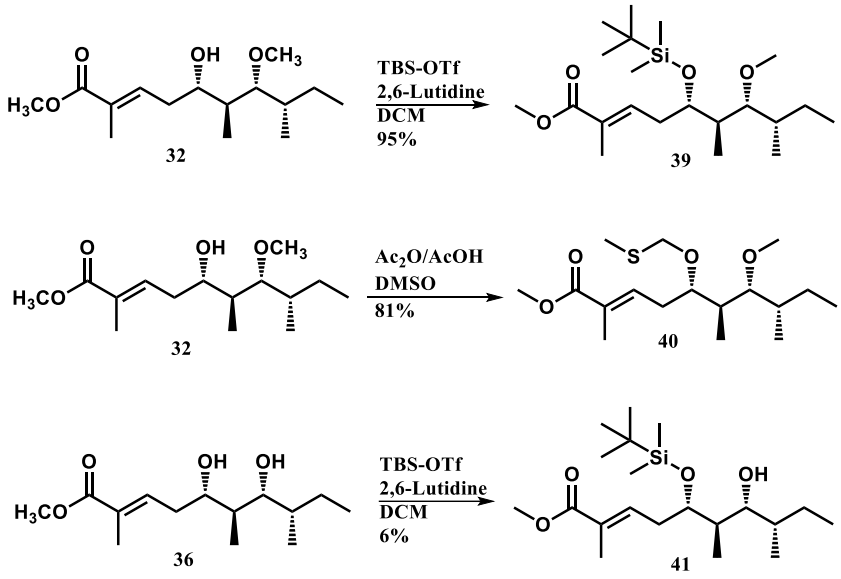


Figure 16. Chelation control VMAR: 2,3-reinforcing vs 2,3-opposing.

In order to continue the synthesis of lagunamide A, alcohol **32** had to be protected. Thus, simple protection of **32** as a silyl ether leads to intermediate **39** (95%) which was originally published by Liu.[47] The NMR data of intermediate **39** matches Liu NMR data verifying its structure. An intermediate challenging however, is the selective deprotection of a methyl ether without interfering with a silyl ether. MTM protection gives **40** but unfortunately was not stable enough under conditions for removal of methyl ether. Unfortunately, the product obtained could not be identified as starting materials nor diol **36**. One possible way to circumvent this problem

is to mono-TBS protect diol **36** as was demonstrated by former coworkers to give intermediate **41** in 71% (Scheme 27).



Scheme 27. TBS protections of C5 alcohol.

When selective TBS protection was attempted, unfortunately only trace amounts of product and di-TBS protected material were isolated as a mixture (Table 11, entry 1). Starting material was recovered. Another attempt was made using excess TBS-OTf and the outcome remained unchanged (entry 2). When TEA was used as a base, only 6% of the desired product was isolated (entry 3). Lower temperatures were used at the start of the reaction to prevent the formation of di-TBS protected (entry 4 and 5) but no product was isolated. Since most of the material recovered was starting material. The reaction time was increased to 3 days and unfortunately no product was isolated. The desired product **41** could not be isolated in good yields, the result could not be reproduced.

Table 11. Attempts of TBS protection of Diol 36.

Entry	TBS-OTf (eq)	Base (eq)	Temp. (°C)	Time (h)	Product 41 %
1	1.1	2,6 Lutidine (1.1)	0 to RT	18	0
2	1.5	2,6 Lutidine (1.5)	0 to RT	18	0
3	2	TEA (3.0)	0 to RT	18	6
4	1.2	2,6 Lutidine (1.2)	-78 to RT	18	0
5	1.2	TEA (1.2)	-78 to RT	18	0
6	1.5	2,6 Lutidine (1.5)	0 to RT	72	0

The polyketide fragment was synthesized using two iterative VMAR's but this pathway could not be pursued because the alcohol is the C5 position could not be selectively protected. A protecting group in the C5 position of intermediate **32** or **36** would be needed since two ester bonds are formed as lagunamide A is constructed and must be protected from Lewis bases. Because the 5,6 syn product **31** was isolated in the second iterative VMAR and a simple oxidation followed by reduction gives the correct diastereomer to be used for lagunamide A, this opens the possibility of using the most common VMAR reaction of β-oxylaldehyde to be used as a substitute. This method is demonstrated in the next section.

2.9 Second viable route of polyketide via VMAR of Felkin-Anh model

Christmann and coworkers investigated various boron Lewis acids in VMAR for their pursuit in constructing Ratjadone.[48] Their investigation led to their use of a unique Lewis acid which can be used in catalytic amounts which undergoes a Felkin-Anh type transition state (Figure 17),[48], to give an expected 5,6 syn product (Figure 15, entry 5). In all VMAR's employing β-oxyaldehydes, this type of reaction has been used extensively in literature.[22] The

most common Lewis acid is $BF_3 \cdot OEt_2$ and a dienolate commonly trapped as the corrosponding TMS analogue. Christmann and coworkers employed a slightly less reactive TBS trapped dienolate with $BF_3 \cdot OEt_2$ to give a high yielding VMAR product. This method was employed in hopes that a high yielding VMAR reaction could be done and the expected 5,6 syn product could be altered to give the precise diastereomer needed for lagunamide A as demonstrated in the previous section.

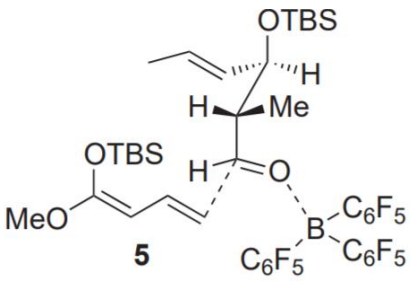
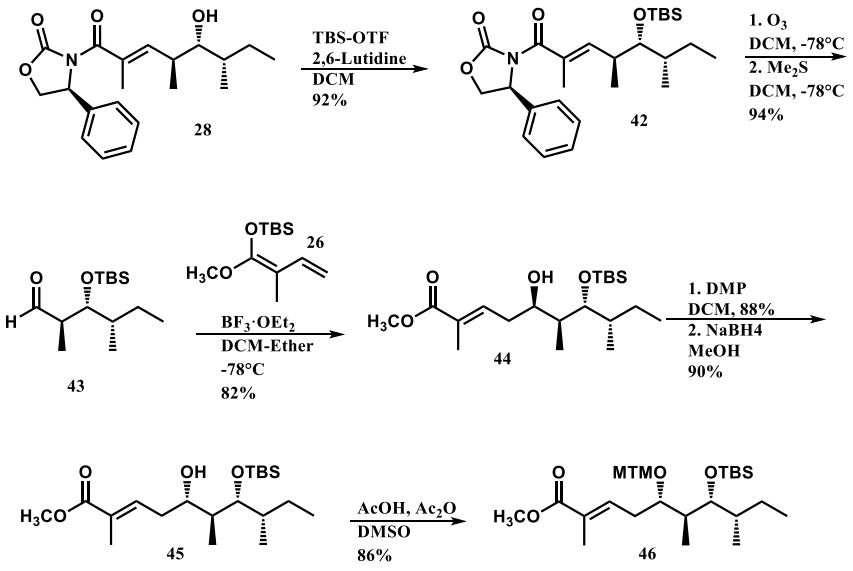


Figure 17: VMAR following Felkin-Anh transition state model

In order for this method to be successful in the VMAR alcohol **28** was first TBS protected to give intermediate **42** in 92% (Scheme 28). The alkene was oxidatively cleaved using ozone to give aldehyde **43** in 94%. The beta oxygen atom of aldehyde **43** is electronically deficient due to the fact the valence electrons are delocalized into the silicon atom of the protecting group. This is important when employing a mono-dentate Lewis acid such as $BF_3 \cdot OEt_2$ to prevent chelation of the beta oxygen. The carbonyl must be activated appropriately so that the nucleophile establishes the bond for product formation. When the reaction was conducted it produced a high yielding VMAR product **44** in 82% using a stable vinylketene acetal **26**. As previous demonstrated (Scheme 23), the alcohol was oxidized using DMP to give ketone in 88%. It can be further reduced in a stereoselective manner to give alcohol **45** in 90% using $NaBH_4$. Intermediate **45** was next converted to MTM protected product **46** using

AcOH/Ac_2O in DMSO in 86%. This intermediate is important because of the presence to 3 different protecting groups. Depending on drastically different reaction conditions, the methyl ester, MTM and TBS protecting groups can be removed in a very selective fashion. Thus, two different pathways are shown in Figure 16 leading to fragment 2.



Scheme 28. Route for employing Felkin-Anh controlled VMAR for polyketide.

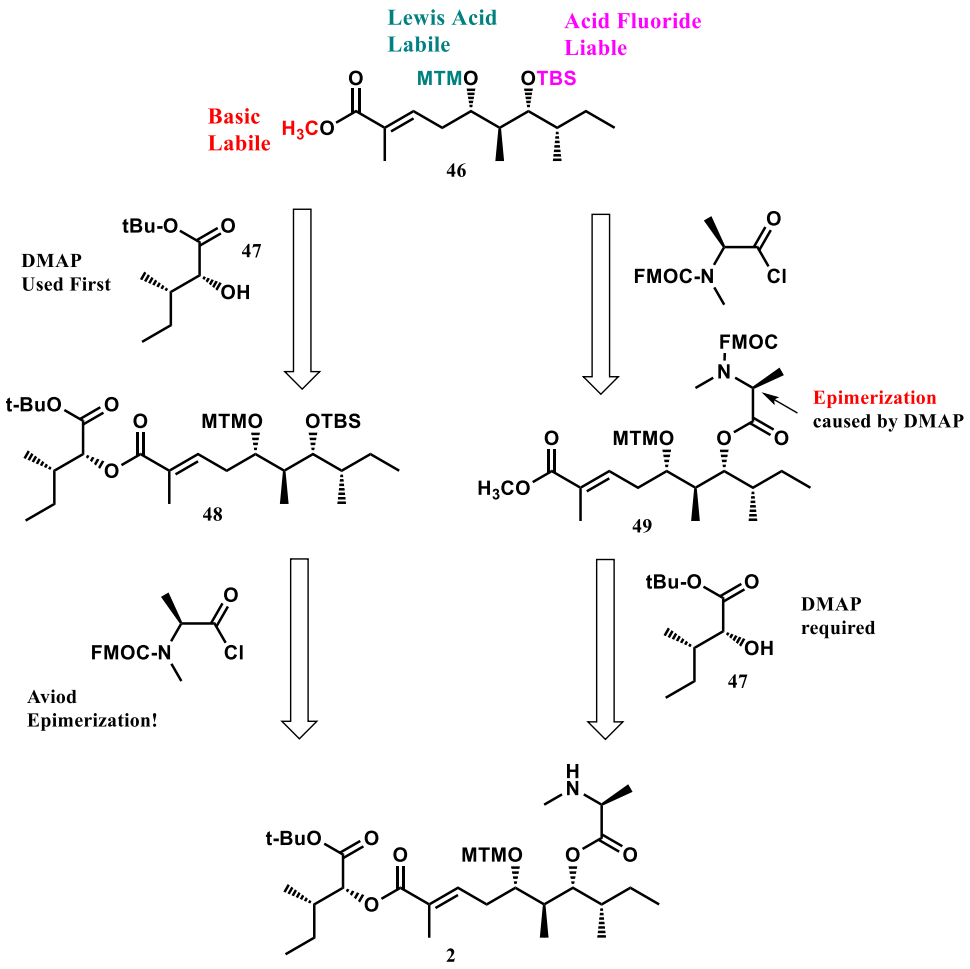


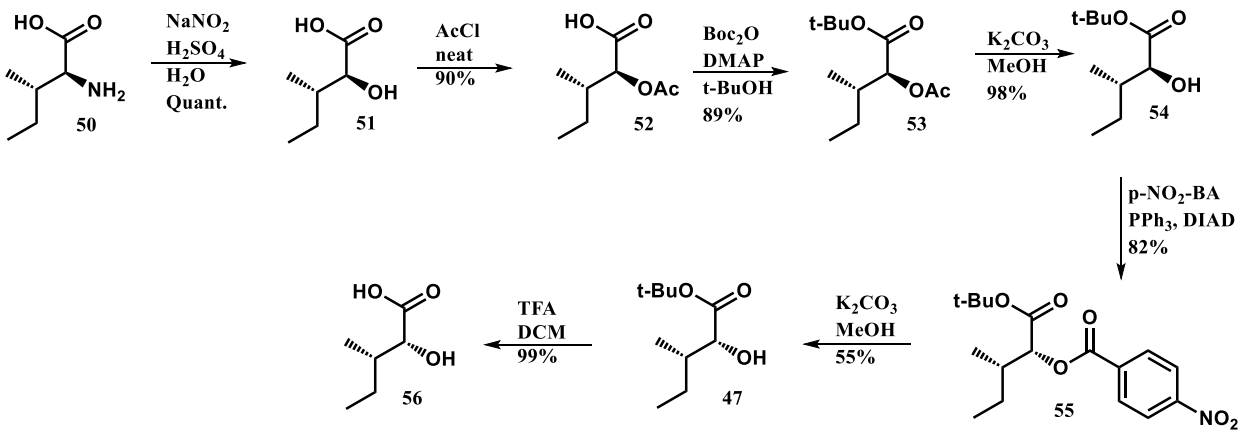
Figure 18. Two different pathways towards fragment 2.

The methyl ester of intermediate **46** can be hydrolyzed using a hydroxide source, the MTM-group can be removed using Lewis acids, and the TBS group can be cleaved using fluoride sources. There are two different pathways to intermediate **2** depending on which protecting group is removed first. For pathway illustrated on the right side (Figure 18), the TBS could be removed first, and the free alcohol could be reacted with L-N-Me-Fmoc-Ala-Cl to produce intermediate **49**. The methyl ester could be hydrolyzed using a base and the free acid could be reacted with alcohol **47** to give intermediate **2**. A second pathway on the left side (Figure 18) could also be utilized by hydrolyzing the methyl ester **46** to give a free acid which

could be reacted with **47** to give new ester **48**. Then the TBS protecting group could be removed using fluoride sources. The alcohol obtained could next be coupled with the acid chloride of L-N-Me-Fmoc-Ala-Cl to give fragment **2**. Because of epimerization reported by Lin and Kazmaier the pathway on the right should be avoided.[32,33] The pathway on the right side of Figure 18 was pursued formally in our lab. DMAP was reported by Lin to epimerize the alpha-stereocenter of alanine after the ester bond has been made. Previous efforts by Banasik used reagent quantities not only in this sensitive esterification but in steps moving forwards in the synthesis. Most likely this is one reason a clean ^{1}H NMR of lagunamide A could not be produced previously (Figure 10).

2.10 Synthesis of D-Isoleucic Acid

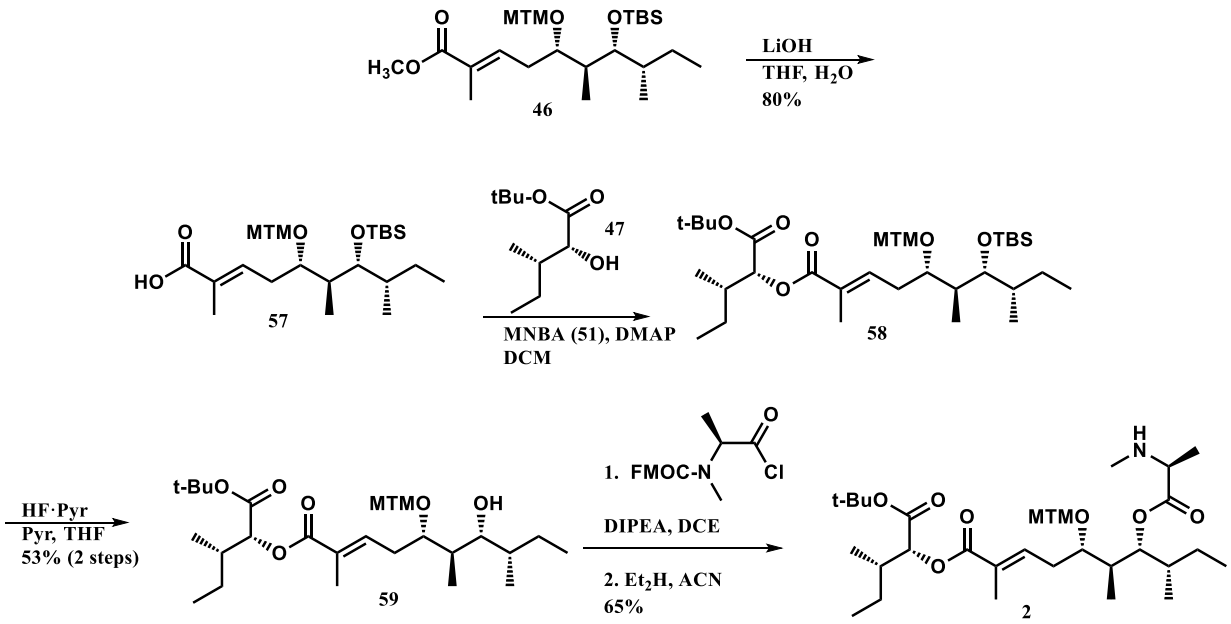
The synthetic strategy of making of D-Isoleucic Acid is shown in Scheme 29. The conversion was initiated by first converting L-Ile **50** to hydroxyisoleucic acid **51** using a diazotization reaction in quantitative yield. Free alcohol was converted to acetate **52** in 90% under neat conditions using acetyl chloride as the solvent. The free acid is converted to t-butyl ester **53** in 89% using the Boc-anhydride. The acetate was then cleaved using K_2CO_3 to give free alcohol **54** in 98%. The alcohol stereochemistry was inverted using Mitsunobu conditions to give ester **55** in 82%. Ester **55** was reacted again using K_2CO_3 to give t-butyl ester **47** in 55%. The t-butyl ester is easily removed using TFA/DCM to give D-Isoleucic Acid **56**. The use of this free acid will be demonstrated in Chapter 3. The strategy above was demonstrated by former coworker Lee Wang.



Scheme 29. Mitsunobu method for conversion of L-Isoleucic acid to D-Isoleucic Acid.

2.11 Conclusion: Synthesis of Southern Hemisphere of lagunamide A

Fragment **2** represents an important intermediate for the synthesis of lagunamide A. The polyketide fragment has been a challenge to construct, as demonstrated thus far. With both L-MeAla and D-Isoleucic acid localized on either side of the polyketide, they act as linkers for the peptide fragment of lagunamide A. The next chapter will discuss the construction of various peptides. As shown in Figure 18, methyl ester of **46** is removed using aqueous LiOH to give free acid **57** in 80% (Scheme 30). Ester of D-Isoleucic acid **47** and polyketide acid **57** is conjoined using MNBA to give ester **58**. The TBS group is selectively removed using HF·Pyr to give free alcohol **59** in 53% yield over two steps. Epimerization reported by Lin and Kazmaier was avoided by omitting DMAP in esterification reaction of alcohol **59** with N-Me-Fmoc-L-Ala-Cl. Fragment **2** was isolated after Fmoc deprotection in 65% yield. The overall yield of fragment **2** is 13% over 11 steps completing the construction of the southern hemisphere of Lagunamide A.

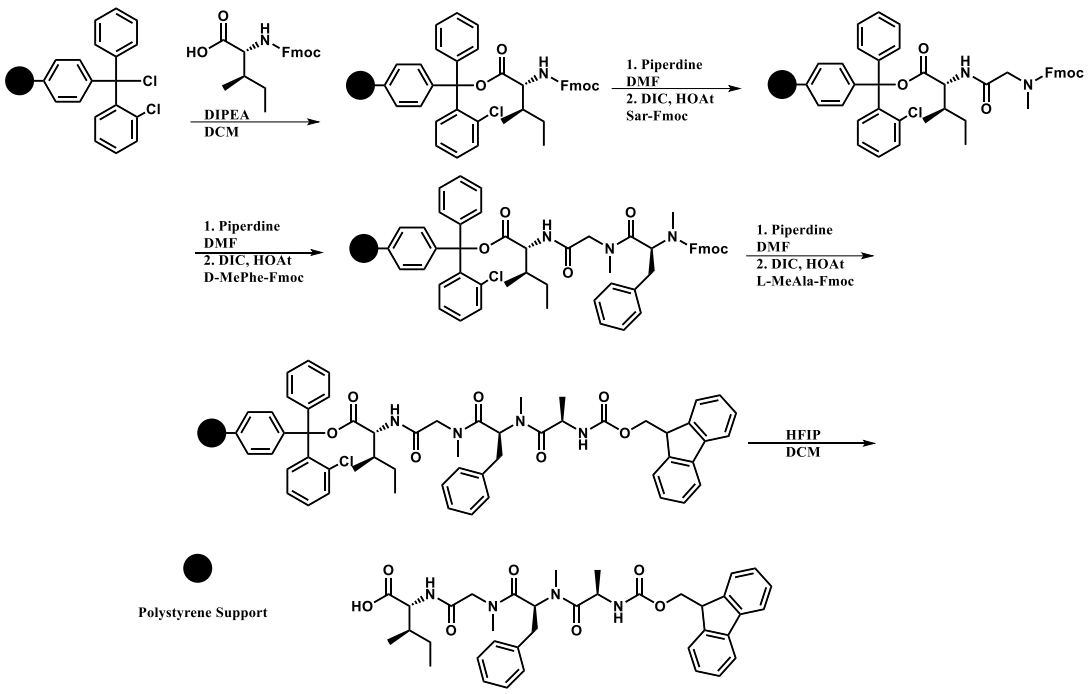


Scheme 30. Synthesis of fragment 2.

Chapter 3 Synthesis of peptides of Lagunamide A

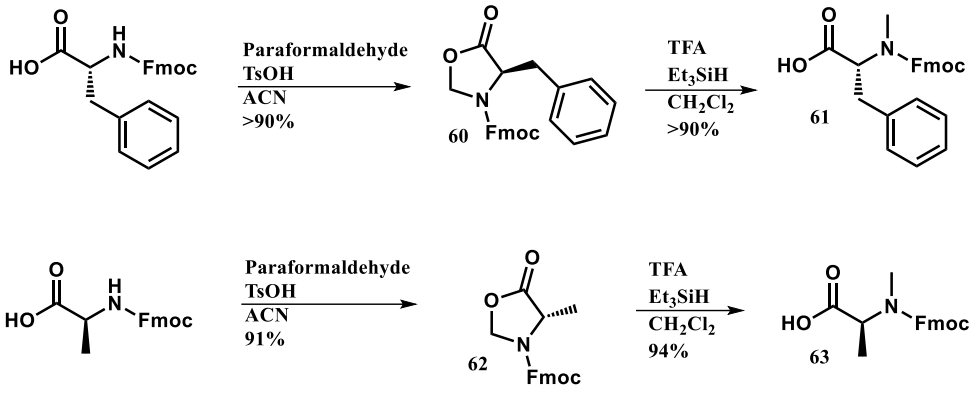
3.1 Former synthesis of tetrapeptide via solid state chemistry

One method of using 2-chlorotrityl chloride resin has been demonstrated to be a straightforward coupling strategy for synthesizing linear peptides without the labors associated with isolation, purification, and repetitive coupling of individual amino acids. As the peptide is built the reagents used are easily washed away keeping the intermediates intact to the CTC resin until the peptide completion where it is cleaved off the resin. The synthesis starts by anchoring Fmoc-Ile to CTC polystyrene support. Fmoc was removed using by 20% piperidine in DMF. The particles are washed with DMF, followed by addition of Fmoc-sarcosine coupled by DIC and K-Oxyma and the synthesis continued. The process was repeated for successive Fmoc deprotection, washings with DMF, followed by reacting the next amino acid in the sequence with DIC/K-Oxyma to give tetrapeptide. The cleavage was done using hexafluoro-2-proponal in DCM to give free acid of tetrapeptide in overall 55% yield. Former coworker Lee Wang synthesized a tetrapeptide of lagunamide A using solid state support synthesis (Scheme 31).



Scheme 31. Solid support synthesis of tetrapeptide using CTC resin.

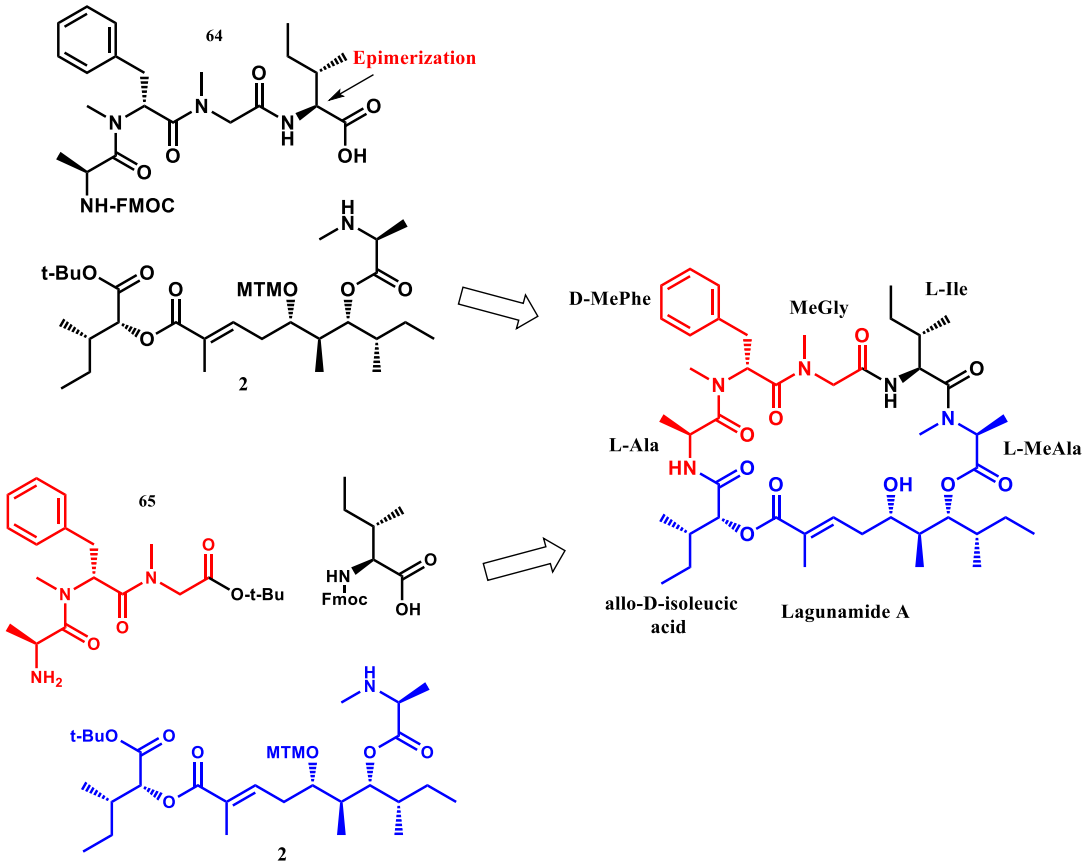
Two amino acids of Lagunamide A are N-methylated, D-Phe and L-Ala. Fmoc protected amino acids are convenient to use since the deprotection reactions can be done rapidly using dialkylamines. Fmoc protected amino acids are converted to 5-oxazolidinone (**60** and **62**. Scheme 32). The methylene group between the nitrogen and oxygen originate from the paraformaldehyde carbon and upon uncyclized using TFA/Et_3SiH, the methylene group is converted to the methyl group on the nitrogen of free acid (**61** and **63**). Both L-Fmoc-N-Me-Ala-OH and D-N-Me-Fmoc-Phe-OH amino acids were obtained in high yields. They can be used to construct the peptide of lagunamide A.



Scheme 32. N-methylations of Fmoc protected amino acids.

3.2 Tripeptide and tetrapeptide synthesis via solution state

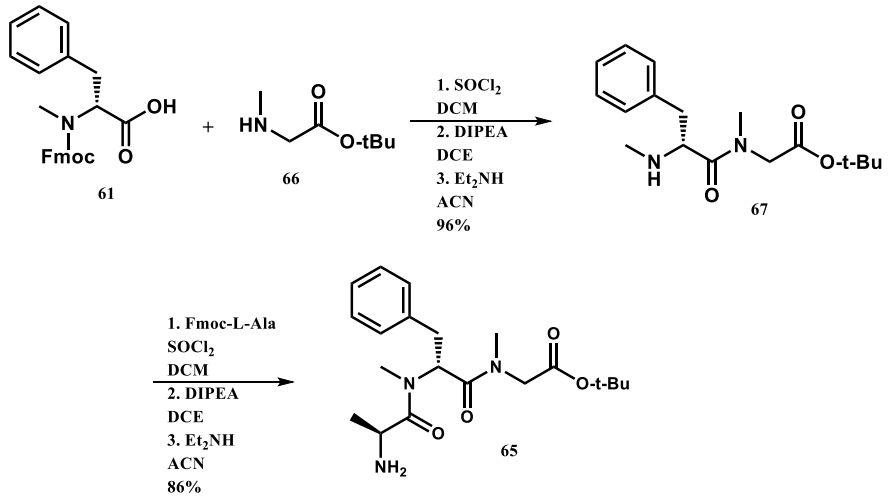
As demonstrated in the SAR of work done by the Wei group, changes to stereochemistry of lagunamide A shows a significant decrease in activity against various cancer cells. Tetrapeptide **64** (Scheme 31) is the same as tetrapeptide used in the total synthesis of odoamide.[49] The total synthesis of odoamide initially reported the epimerization of alpha stereocenter of L-Ile of **64** when activated for amide formation. Lin's synthesis of Lagunamide A also mentioned the same issue and Kazmaier avoided the epimerization by attaching L-Ile as a monomer. Previous attempt at synthesis of Lagunamide A in our group employed the strategy of using the tetramer and coupling it to fragment **2** (Scheme 33). Rather, one proposal was to attach L-Ile as a monomer and the tripeptide **65** could be coupled thereafter. This potential route should avoid epimerization of L-Ile and L-Ala (Figure 18).



Scheme 33. Two alternative pathways towards lagunamide A utilizing either a tetrapeptide or the tripeptide.

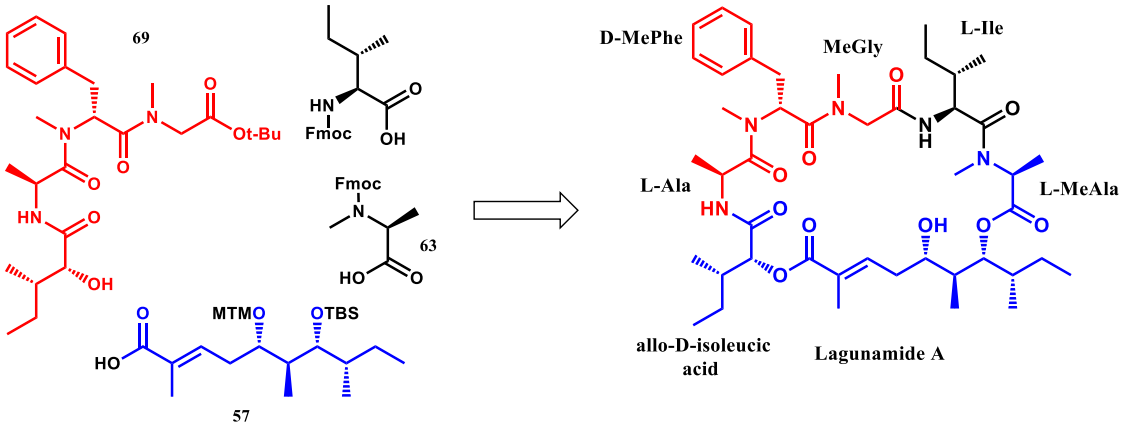
The synthesis of tripeptide was done is a manner that would be dependable in producing quantities of **65**. The solid-state support strategy employed for tetramer **64** using CTC was avoided since large quantities of the desired peptide could not be obtained at once. But the same strategy of Fmoc-protected amino acids were used (Scheme 32). Herein, D-N-Me-Fmoc-Phe-OH (**61**) was converted to the acid chloride in situ using $SOCl_2$ and reacted with t-butyl ester of sarcosine (**66**) (Scheme 34). After Fmoc deprotection using Et_2NH, dipeptide **67** was obtained in 96%. The same strategy was employed for adding the next amino acid in the sequence where the acid chloride of L-Fmoc-Ala-OH was formed in situ and reacted with dipeptide **67**. After Fmoc deprotection tripeptide **65** was obtained in 86%. Thus far the synthesis of fragment **2** and

tripeptide **65** have been demonstrated. Coupling these two groups with commercially available L-Ile potentially leads to Lagunamide A (Scheme 35).



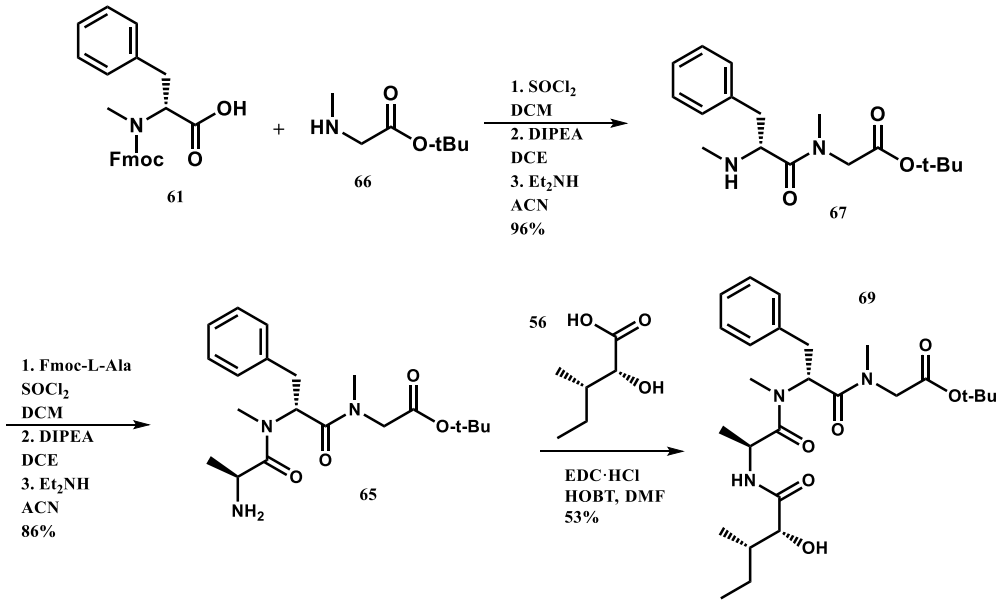
Scheme 34. Synthesis of tripeptide **65**.

Since the epimerization L-Ile is avoided by adding it as a monomer to L-MeAla of fragment this increases the total number of steps in the synthesis by two. Taking into consideration synthetic strategies employed for the construction other cyclodepsipeptides, the total synthesis of aurilide potentially reveals a more efficient route for attaching peptide sequences to polyketide.[50] Although the amino acid sequence of aurilide is different, it was demonstrated larger tetrapeptide much like the one shown in Scheme 36 could be coupled to polyketide directly to the polyketide fragment. This eliminated the use of a linker where D-Isoleucic acid **47** is attached to polyketide **57** to form **58** (Scheme 30).



Scheme 35. An efficient route of conjoining polyketide with a tetrapeptide.

To utilize this strategy the free D-Isoleucic Acid was reacted with tripeptide **65** and gave new tetrapeptide **69** in 53% using EDC coupling agent. The next chapter demonstrates the convergence of **69** with polyketide **50** as proposed.

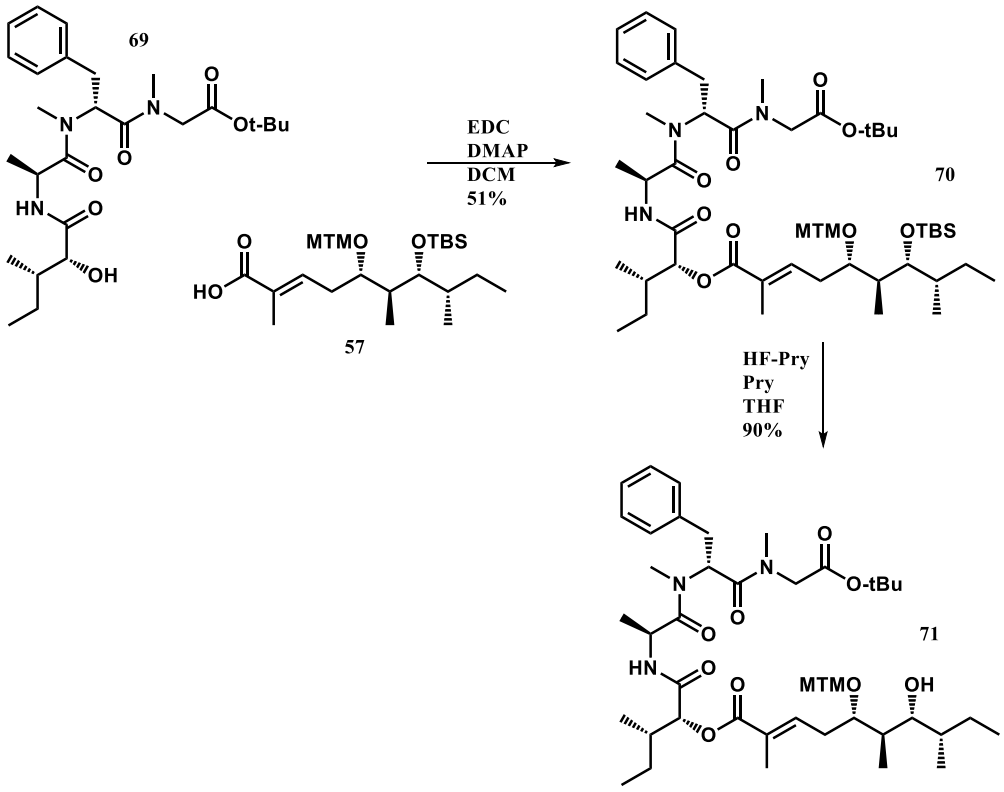


Scheme 36. Synthesis of tetrapeptide **69**.

Chapter 4 Chemical studies towards Completion of Lagunamide A

4.1 Convergence of polyketide and tetrapeptide

Since an efficient route of synthesizing polyketide **57** and tetrapeptide **69** have been established it allows for the synthetic route to take advantage converging two large pieces of lagunamide A for its construction. Polyketide **57** and tetrapeptide **69** are conjoined using EDC in the presence of DMAP to give fragment **70** in modest 51% yield (Scheme 37). It is important to state that L-MeAla has not been introduced and DMAP can be used as a catalyst for esterification. The significance of forming ester **70** is that it utilizes the precious polyketide in a more efficient manner than previously proposed. Fragment **2** is obtained in 13% over 11 steps and polyketide **57** is an intermediate to fragment **2**, which is synthesized in 38% over 8 steps. A second note to consider, since L-Ile is added as a monomer, this added two potential steps in the synthesis. By adding D-Isoleucic acid as a part of tetramer **69** it reduced two steps in the synthesis. Another important aspect of being able to form ester **70** will be discussed in the future work section. Ester **70** was reacted with HF·Pry for TBS deprotection to give free alcohol **71** in 90% yield. In the next section will discuss the continuation of the synthesis.

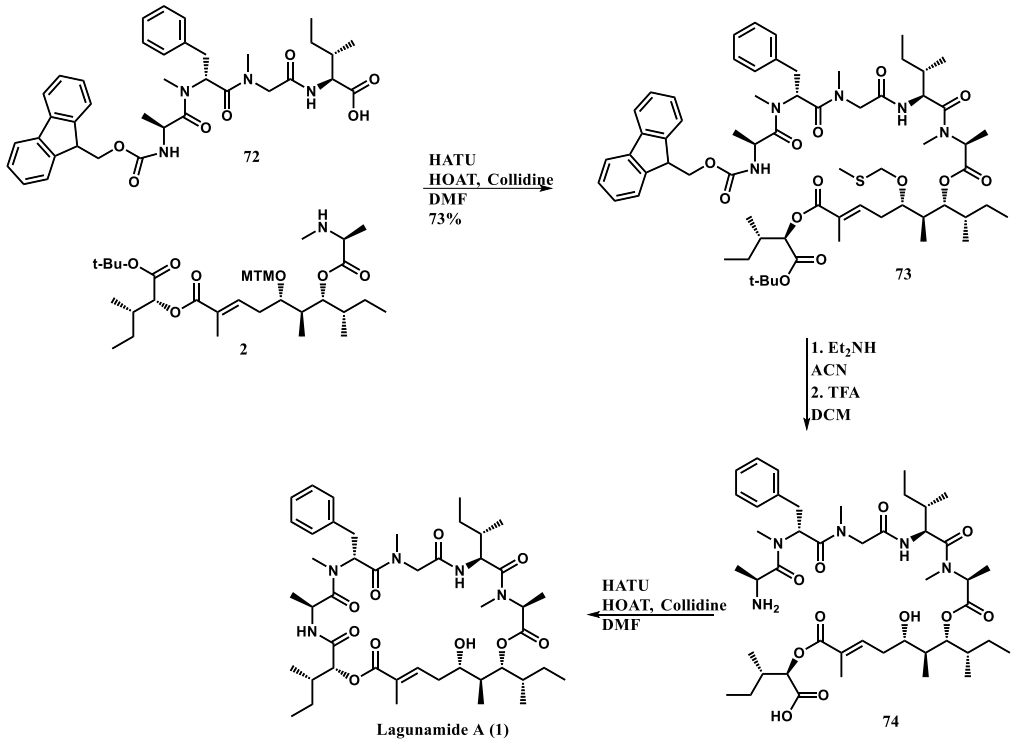


Scheme 37. Coupling of tetrapeptide **69** and polyketide **57**.

4.2 Completion of Total Synthesis of lagunamide A

From free alcohol **71** the synthesis can be continued starting with addition of L-MeAla. Unfortunately, when the reaction to couple L-MeAla-OH using acid chloride conditions was attempted no product was observed and starting material was recovered. When additional amounts of reagent were used neither starting material nor product were isolated. An equally efficient pathway would be to use tetrapeptide **72** made using solid state peptide synthesis, coupling to polyketide fragment **2** (Scheme 38). Lin's total synthesis followed this pathway of attaching the peptide portion and no epimerization was reported. This contradicts the epimerization reported by Ye and Kazmaier as well for the total synthesis of odoamide (Chapter 1). Regardless, the work published on odoamide reported the separation of epimers via HPLC.

Ye and Kazmaier were also able to separate the epimerized mixture using HPLC. Epimerization of L-MeAla was avoided by omitting DMAP. Epimers of L-Ile could be separated using HPLC. This pathway is again chosen to keep the number of steps of the total synthesis as short as possible. Tetrapeptide **72** is coupled to polyketide **2** using HATU to give acyclic-protected-Lagunamide A **73**. Simple diethylamine deprotects Fmoc of L-Ala followed by t-butyl ester and MTM removal using TFA gave **74** in one pot. The crude mixture of **74** was carried forward for the cyclization to give Lagunamide A using HATU.



Scheme 38. Chemical studies towards Completion of Lagunamide A

4.3 Future Work: Application of convergence of Polyketide to tetrapeptide to Total synthesis of Lagunamide C

As mentioned at the start of this thesis the 26-membered CPDs in the series (Figure 3) are structurally similar among one another. As mentioned previously, it is the small changes that give such diversity in bioactivity. In some cases, the change can be the addition or removal of one methyl group of the polyketide chain. This is the case for lagunamide A, lagunamide D, and odoamide (Figure 19). In terms of lagunamide B, it is the difference in degree of unsaturation. To date there is no total synthesis of Lagunamide C. The peptide sequence of the natural product is the same. The polyketide chain is similar to work presented in this dissertation, but the one difference in the insertion of CH_2 in the C39 position of the natural product. For this reason, the strategies demonstrated previously can be used to for the potential synthesis of lagunamide C.

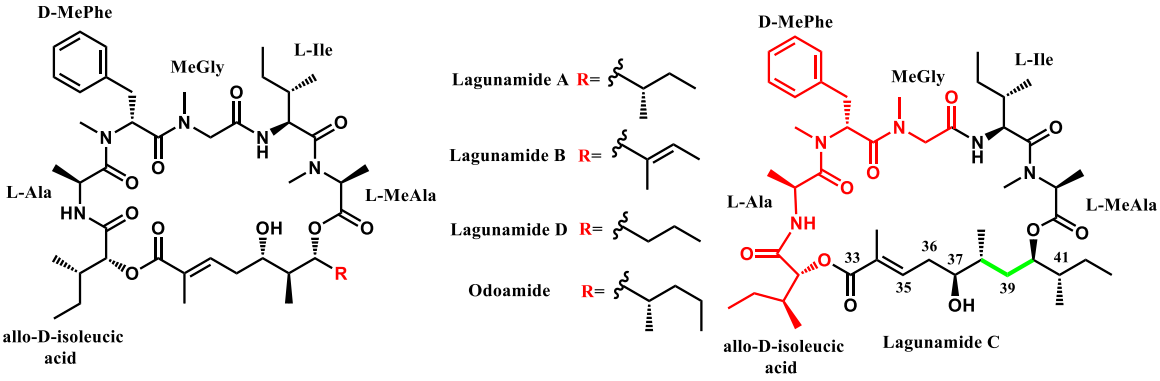


Figure 19. Structural differences between 26-membered CDPs.

Retrosynthesis of lagunamide C (Figure 20) shows most of the individual pieces used for its potential construction are the same as lagunamide A. The one difference is the aldehyde used in the VMAR reaction to potentially produce the polyketide fragment. As show previously VMAR's employing β-oxyaldehydes are rare and challenging (Figure 15). Because of the one difference in position of the protected aldehyde there is the potential of applying Kobayashi's

protocol viable for this polyketide than for lagunamide A. Since tetrapeptide **60** can be synthesized with ease using the same Scheme as previously discussed and polyketide can be used for the linkage for lagunamide C. A new method for attaching L-MeAla to fragment **71** without epimerization would need to be developed. If successful, the method could be applied to the total synthesis of lagunamide C. The synthesis can employ the same protecting group strategy and epimerizations could also be avoided as previously stated. The construction of lagunamide C could be an interesting analogue of lagunamide A, a potential therapeutic of cancer (Figure 8).

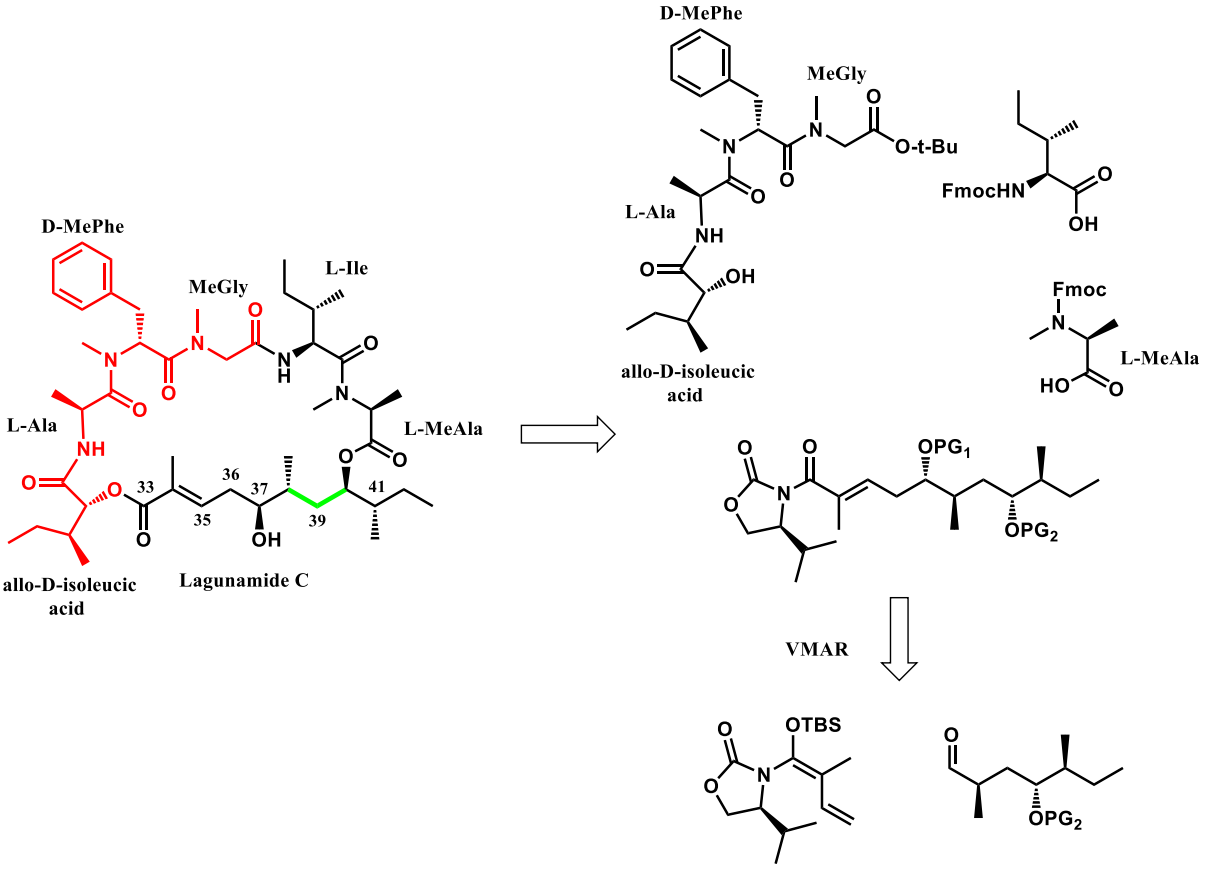


Figure 20. Retrosynthesis of lagunamide C.

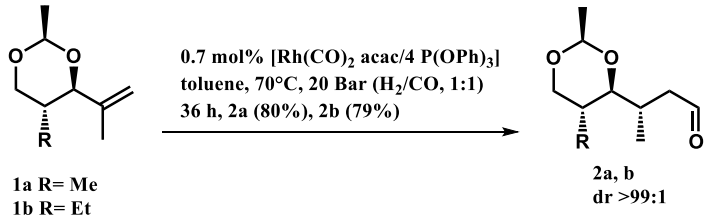
Since the discovery of aurilide and its application of being the first small molecule being able to bind to prohibitin 1, it allowed scientists to study new biology revolving around it. Small

changes in the structures of the 26-membered cyclic depsipeptides lead to diversity of activity. Studying the applications of CDP's are important for their use in chemical tools for investigating mechanisms in a biochemical setting as well as potential therapeutics for disease.

Chapter 5 Kinetic Resolution using VMAR

5.1 Introduction: Stereotriades

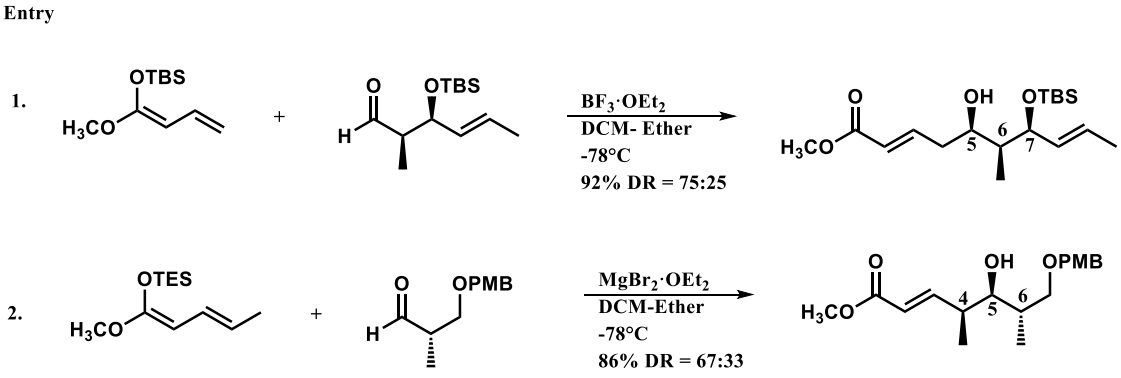
As outlined in Chapter 1 of this thesis, establishing stereocenters along a carbon-carbon framework is not only difficult but valuable in the construction of polyketides for natural product synthesis. As seen in the analogues of lagunamide A by Wei, establishing stereocenters correctly can influence the activity of the natural product. One platform for establishing theses stereocenters is the use of transition metal catalyzed reactions.[51] The potential of transition metals playing a role in establishing adjacent stereocenters has been demonstrated well and can continue to do so in an economically and ecologically manner. One example of the use of rare earth metals for used for establishing stereocenters is shown below (Scheme 39). Here a diastereoselective rhodium catalyzed hydroformylation is used to form a stereotriade.[51] The reaction itself was the first to demonstrate a stereoselective hydroformylation of an acyclic olefin that could be achieved to give an all-anti stereotriade and obtain high ratio of the desired diastereomer. Although this method could be used establishing the C37-C39 stereocenters of lagunamide A, it is more expensive than the methods reported in Chapter 1.



Scheme 39. Stereoselective hydroformylation of acyclic olefin.

5.2 Diastereoselective VMAR's

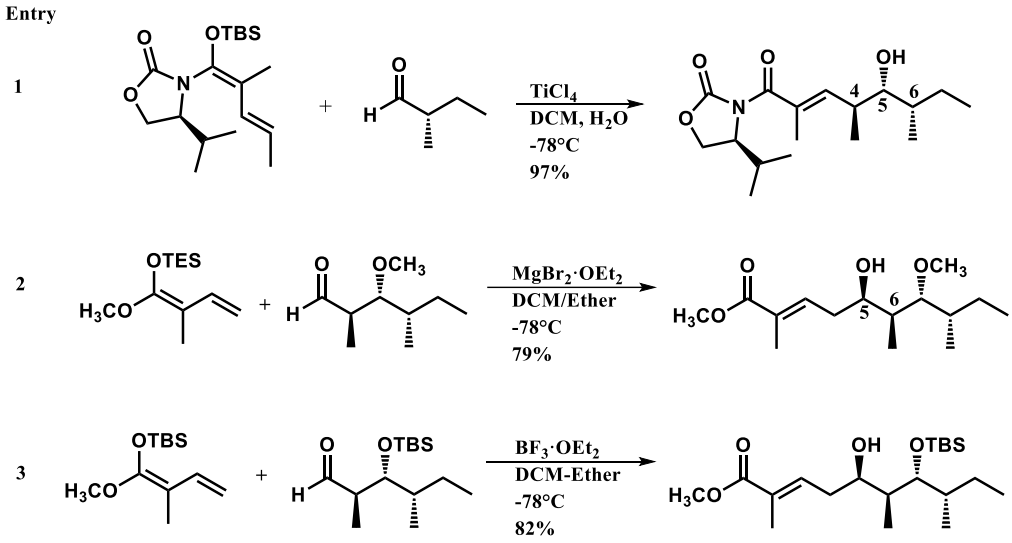
The stereoselective rhodium hydroformylation is yet another platform for establishing valuable stereotriades. As shown in the previous chapter simple diastereoselective VMAR can be used for obtaining the same desired carbon framework. In one example a silyl ketene acetal in the presence of α-chiral aldehyde was used for establishing the all-5,6,7-syn stereotriade intermediate for the synthesis of Rajadone (Scheme 40, entry 1). As discussed previously the reaction undergoes Felkin addition of trapped diene. The diasteromeric ratio (DR) of products is moderate 75:25. Another method of obtaining stereotriades of the same platform is Kalesse's investigation of various Lewis acids for obtaining the 4,5-syn, 5,6-anti (entry 2). In the example shown the reaction undergoes chelation-controlled conditions to give the 5,6 anti-relationship. The DR is a moderate 67:33. In both examples the asymmetry needed for selectivity is provided by the one α-methyl and depending on if the β-oxygen can chelate to Lewis acid also influences DR. It should also be noted that two different motifs (Figure 13) are exploited here.



Scheme 40. VMAR of α-chiral aldehydes for stereotriades.

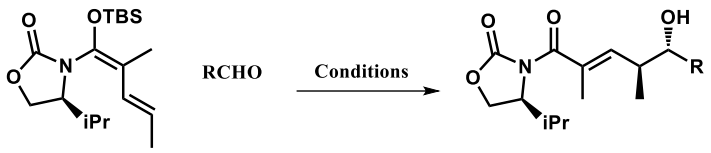
Stereotriade's can also be synthesized using Kobayashi's protocol of VMAR. The product of the first VMAR is a good example where chiral butanal is reacted with chiral vinylketene silyl *N,O*-acetal to give sterotriade (Scheme 40, entry 1). As exemplified, they can be

further reacted to give fragments with additional stereocenters and functionalization to be used for further transformations (entry 2 and entry 3). In using Kobayashi's protocol, the principal asymmetry is provided by the directing group of the oxazolidone to give the 4,5-anti relationship.



Scheme 41. Other platforms of VMAR's of α-chiral aldehydes for stereotriades.

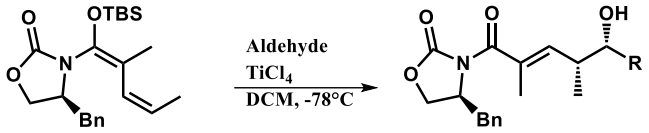
This anti-4,5 relationship was first achieved in Kobayashis VMAR article from 2004 (Figure 21).[25] In his paper the 4,5-anti was demonstrated using various aldehydes representative sample. In these cases, the DR were reported to be extremely high (>50:1). Since this report, numerous examples have demonstrated the utility using chiral vinylketene silyl *N,O*-acetal as a platform for achieving stereotriades and other carbon frameworks rich with stereochemical information.



Entry	R	Temp (°C)	Yield (%)	d.s
1	$CH_3(CH_2)_4$	-78	87	>50:1
2	$(CH_3)_2CH$	-78	99	>50:1
3	(*E*)-CH_3CH_2CH=$C(CH_3)$	-78 to -40	67	>50:1
4	Ph	-78 to -55	90	20:1

Figure 21. Kobayashis VMAR demonstrating 4,5 anti-relationship

In 2012 Kalesse and coworkers demonstrated using the same platform of VMAR, utilizing vinylketene silyl *N,O*-acetal, the 4,5 syn-relationship can easily be achieved (Figure 22).[53] This was demonstrated due the fact, the *E,E* configuration of the trapped diene is normally used and exploited heavily. Kalasse and coworkers demonstrated the *E,Z* configuration of the diene can be utilized to give the 4,5 syn product.



Entry	Aldehyde	yield (%)	dr
1	acetaldehyde	75	>20:1
2	isovaleraldehyde	84	>20:1
3	cyclohexanecarbaldehyde	74	>20:1
4	hexanal	73	>20:1
5	E-Crotonaldehyde	71	>20:1
6	benzaldehyde	64	>20:1

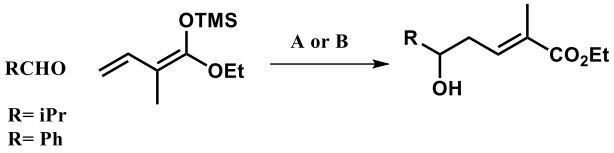
Figure 22. Kobayashi's VMAR demonstrating 4,5 syn-relationship

Various aldehydes were probed and high diasteroselectivity was achieved (Figure 22) Being able to dictate the configuration of the 4,5 relationship relative to the E/Z geometry expands upon the capabilities of this platform of VMAR. Being able to choose the configuration of the directing group of the oxazolidone only gives the freedom of obtaining various diastereomers. These utilities and variations of VMAR with chiral aldehydes lead various desired stereotriades for polyketides, natural products, and carbon frameworks rich with stereochemical information.

5.3 Enantioselective VMAR's

An important contribution to the field of research are enantioselective VMAR's. In the examples shown below, no asymmetric information is provided by the aldehyde nor the vinylketene silyl acetal. Here a chiral ligand is employed with a Lewis acid to achieve

enantioselectivity or diastereoselectivity. Various methods have been developed. Here are a few representative samples. One of the simplest takes advantage of $Ti(OiPr)_4$ undergoing ligand exchange with chiral (R)- Binol species to generate in situ the active Lewis acid species which selectively differentiates the formation of one enantiomer over another (Figure 23).[54] Moderate selectivity was achieved, % 70 ee. Similar selectivities were achieved using CuF_2 complexed with chiral (S)-Tol-BINAP, again forming an active species in situ.[4] Moderate % ee may not be usable for total synthesis of natural products and chiral chromatography may still be necessary.



		R	method	yield (%)	% ee
method A:	$Ti(OiPr)_4$, (*R*)-Binol	iPr	A	18	70
	(20 mol%), DCM, RT	iPr	B	68	77
method B:	(*S*)- Tol-BINAP-CuF_2	Ph	A	45	75
	(10 mol%, THF, RT	Ph	B	80	70

Figure 23. Enantioselective VMAR using Ti-BINOL and Cu-Tol-BINAP

In order to achieve higher % ee the chiral ligands had to become more elaborate. In one example, $Cu(OTf)_2$ is complexed with sulfoximine ligand (Figure 24).[55] The ligand itself is bidentate in nature. The complex is employed in VMAR with reactive ketones to give chiral tertiary alcohols. Under the unique conditions shown, high yields and extremely high % ee was achieved. In this case chiral chromatography would not be needed and material isolated could be used for continued total synthesis of natural products.

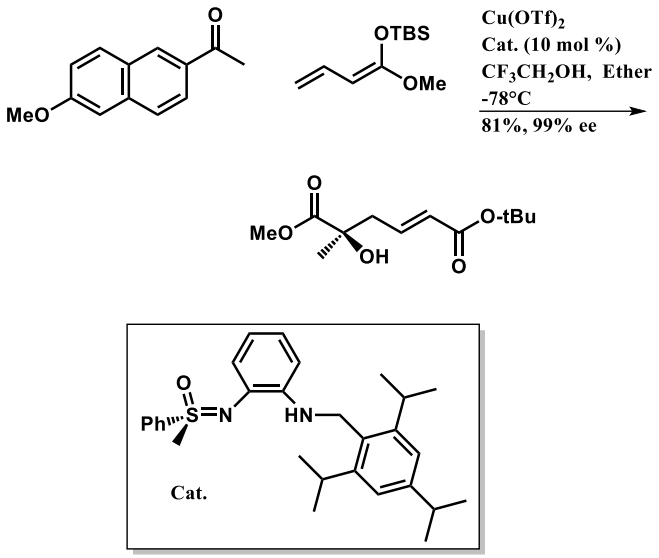


Figure 24. Enantioselective VMAR using $Cu(OTf)_2$ with Sulfoximine ligand.

The ligands become more and more complex to achieve VMAR of electronically deficient aldehydes demonstrated by List (Figure 25).[6] Here enantioselective VMAR using disulfonimide was demonstrated where the product was not only enantiomerically pure (98:2) but a TBS transfer from trapped dienolate gives protected VMAR product. The same catalyst was used to perform a rare bis-VMAR using a trapped triene to also give silyl protected product in high enantiomeric ratio (95:5). Such a large chiral Lewis acid was necessary for remote induction to terminal carbon of triene where bond formation occurs.

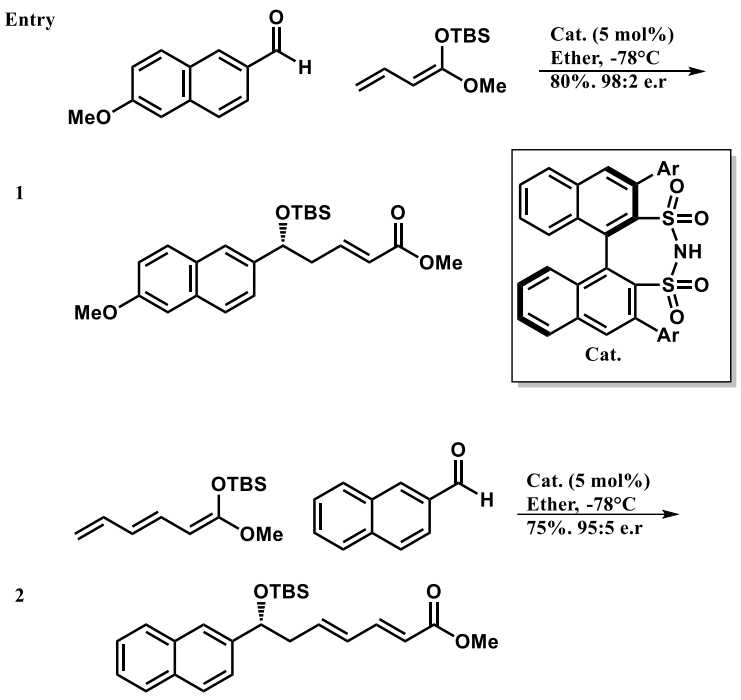


Figure 25. Enantioselective VMAR using disulfonimide

The work presented above is a representative sample of enantioselective VMAR. If high enantioselectivity is to be achieved, ligands and Lewis acids become more and more exotic. Chiral BINOL ligands are commercially available but for optically pure VMAR products, ligand synthesis and design must be conducted.

5.4 Proposed transition state of Kobayashi's VMAR

Whether the platform for synthesis of stereotriades is using rare earth metals such as rhodium for stereoselective hydroformylation of acyclic olefin (Scheme 39) or diasteroselective VMAR's (Figure 21), stereotriades have been recognized as valuable carbon frameworks for the creation of biologically active molecules. One possible pathway is to take advantage of the diastereoselectivity of Kobayashi's platform of VMAR. Figure 26 is a depiction of the proposed transition state proposed by our group using vinylketene *N,O*-acetal with α-substituted

aldehydes.[35] This could be used to explain the stereoselectivity of VMAR previously discussed (Figure 21 and 22). The model hints to the possibility of certain conformations of large and small substituents in the alpha position of the aldehyde being preferred over one another as it approaches for bond formation.

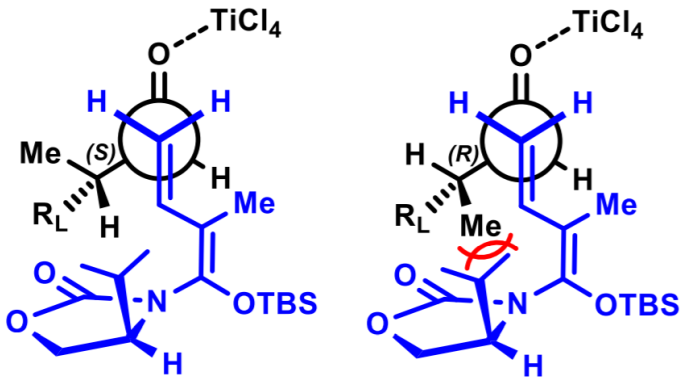


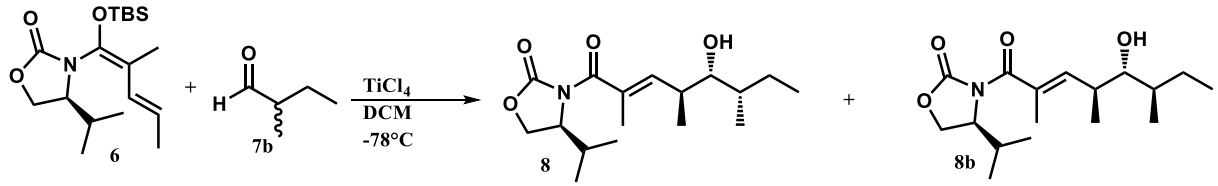
Figure 26. Proposed transition state of VMAR

More specifically, there is a stereochemical clash between the directing group of the chiral auxiliary and the larger methyl group (right). This interaction is thermodynamically unfavorable over the preferred route (left) where only the smallest group, or the hydrogen atom is allowed to interact. The directing group has the ability to differentiate unfavorable interactions.

Chapter 6 Kinetic Resolution using VMAR

6.1 Diastereoselective VMAR employing Kinetic Resolution

Rather than using rare earth metals for the synthesis of stereotriades, an unexplored territory in VMAR is reacting vinylketene *N,O*-acetal with a racemic mixture of aldehydes. Where diasteroselective VMAR and a different element of enantioselective VMAR is utilized. Instead of forming a mixture of enantiomers with a certain degree of optical purity, an enantiomeric mixture of aldehydes is reacted and transformed as a VMAR diastereomeric mixture (Scheme 42). In this scenario vinylketene *N,O*-acetal **6** is reacted with racemic butanal **7b** giving a diastereomeric mixture of stereotriades **8** and **8b**. Preliminary results by Arielle Kanner are summarized in table 12.



Scheme 42. Synthesis of stereotriade mixture with racemic 2-methyl-butanal in VMAR.

When 3 equiv of racemic butanal was used with 1.5 equiv of $TiCl_4$, 61% of mixture **8/8b** was isolated (entry 1). When 6 equiv of racemic butanal was used with 3 equiv of $TiCl_4$, almost no change in yield was observed (entry 2). When 9 equiv of racemic 2-methylbutanal was used with 4.5 equiv of $TiCl_4$, almost no product was isolated (entry 3).

Table 12. Preliminary data of VMAR with racemic butanal.

Entry	Butanal 7b (eq.)	$TiCl_4$ (eq)	Yield (%)	Dr (8:8b)
1	3	1.5	61	78:22
2	6	3	70	80:20
3	9	4.5	trace	86:14

As discussed previously in Chapter 1, first VMAR to product alcohol **8** was not reliable and an extensive study was conducted to understand the fundamental nature of the reaction in hopes that it could be used for the synthesis of lagunamide A. The study is summarized in table 13**.**

The first attempt of VMAR shown in Scheme 42 yielded only 6% of **8** and **8b**. An investigation led to results were summarized in table 13. First the reaction time was extended under same conditions from 24 to 72 hours and little increase in yield was observed (entry 2). Based on the work presented by Kobayashi about rate enhancement by water a new variable was introduced.[40] When 1 equiv of water was introduced under the same conditions the isolated yield increases substantially to 84% (entry 3). An additional amount of water was introduced to the system and yield dropped to 59% (entry 4) but still higher than the reference (entry 1). Under dry conditions and increased amount of Lewis acid led to low yield of 9% (entry 5) and when water was introduced the yield remained low, 17% (entry 6). The previous 2 entries suggest these is a level of Lewis acid is not tolerable. When $TiCl_4$ was reduced to 1.5 equiv and the amount of aldehyde reduced to 2.25 equiv close to quantitative yield was obtained, 97% (entry 7). When the amount of Lewis acid was kept the same and 6 equiv of aldehyde was used the yield remained near quantitative, 99% (entry 8). A final test where the amount of aldehyde was kept constant from the previous entry and 5 equiv of Lewis acid was used, only 21% isolated yield was

observed (entry 9). These experiments verified the excess amount of Lewis acid is the culprit in low yields in the VMAR reaction and should be limited. Water addition can in fact rate enhance and consistently give high yields in VMAR. But only if a minimum amount of Lewis acid is used.

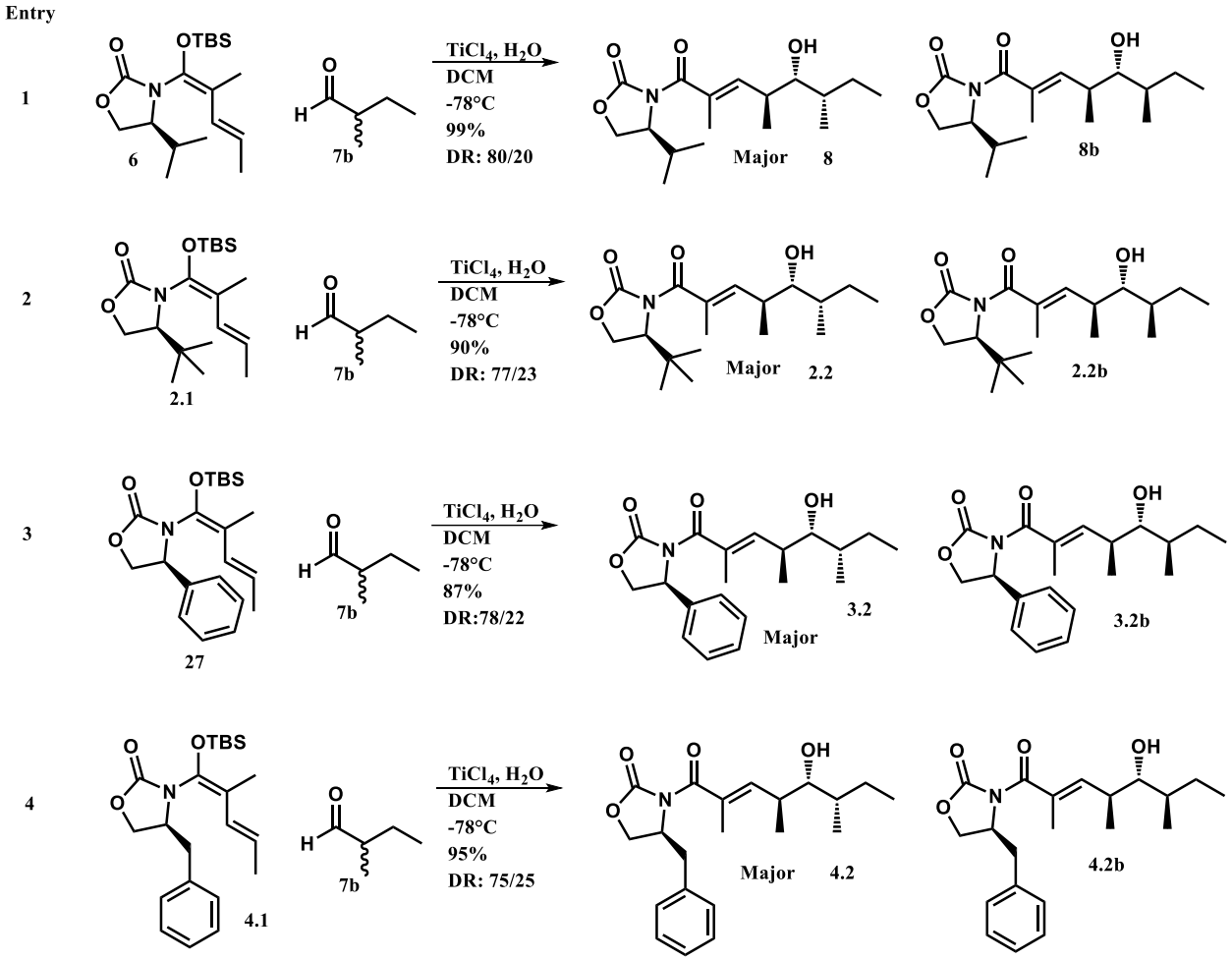
Table 13. Extensive investigation into variables responsible for high yields in VMAR.

Entry	Time (h)	H_2O (eq)	Butanal (eq)	$TiCl_4$ (eq)	Isolated Yield (%)	Crude Dr	Isolated Dr
1	24	0	3	2	6	X	77/22
2	72	0	3	2	13	90/10	85/15
3	72	1	3	2	84	77/23	77/23
4	72	2	3	2	59	77/23	77/23
5	72	0	6	4	9	76/24	89/11
6	72	1	6	4	17	80/20	77/23
7	72	1	2.25	1.5	97	73/27	73/27
8	72	0	6	1.5	99	80/20	78/24
9	72	0	6	5	21	X	91/9

After a thorough investigation, the VMAR with racemic butanal can be dissected. The goal of the project is to test if vinylketene *N,O*-acetals can selectively differentiate one enantiomer over the other of the aldehyde to selectively produce a DR of products. The 2-methyl-butanal is the smallest chiral aldehyde and vinylketene *N,O*-acetal is able to differentiate between the α-methyl and α-ethyl group. The DR range for high yielding VMAR aldol ranges from 73/27 to 80/20. According to the proposed transition state (Figure 26) there is an interaction with the directing group on the oxazolidinone and the alpha substituents of the aldehyde. Since there are countless methods of creating alpha stereocenters utilizing various platforms the kinetic resolution of the stereotriades will be the focus of the study moving forward.

6.2 Diastereoselective VMAR with various directing groups

Four different directing groups were employed on the vinylketene *N*,*O*-acetals (Scheme 43). Aside from Evans auxiliary **6** (iso-propyl), the t-butyl (**2.1**), phenyl (**27**), and benzyl (**4.1**) directing groups were employed. An important question to ask is if differences in selectivity would be observed between **6**, **2.1**, **27**, and **4.1** in trying to obtain stereotriades.



Scheme 43. Synthesis of stereotriade mixtures with racemic 2-methyl-butanal in VMAR.

Optimized conditions elucidated from investigation (Table 13) was used to give high yielding VMAR stereotriades (Scheme 43). When t-butyl directing group **2.1** was employed the combined yield of **2.2**/**2.2b** is 90% with DR of 77/23 (entry 2). When the phenyl group **27** was

employed the data was consistently observed where with the combined yield of **3.2/3.2b** in 87% with DR of 78/22 (entry 3). Lastly when the benzyl directing group **4.1** was employed the combined yield of **4.2/4.2b** is 95% with DR of 75/25. The data shows there is no difference in the capacity of directing group to differentiate one enantiomer over another. Across all vinylketene *N,O*-acetals used the combined yields are high for the synthesis of stereotriades. This platform of Kobayashi's VMAR is able to differentiate this small difference.

6.3 Diastereoselective VMAR aldehyde scope 1

In order to take the next step and determine if higher selectivities could be achieved the investigation into changing the alpha substituents of the aldehyde is pursued. One potential substitute to the butanal is aldehyde **5.1** (Figure 27). The alpha substituents are the large planar phenyl ring and the smaller ethyl group. There is free rotation of the ethyl substituent of the butanal but still relatively small much like the methyl group. The aromatic ring extends further from the alpha position and may be able to interact better with the directing group of the vinylketene *N,O*-acetals. If the interaction is successful, then a higher DR of VMAR stereotiade product could possibly be achieved.

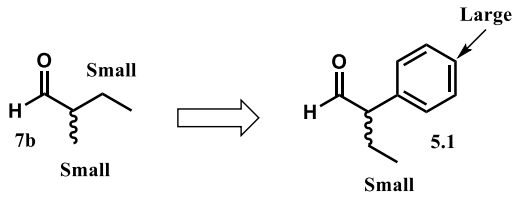
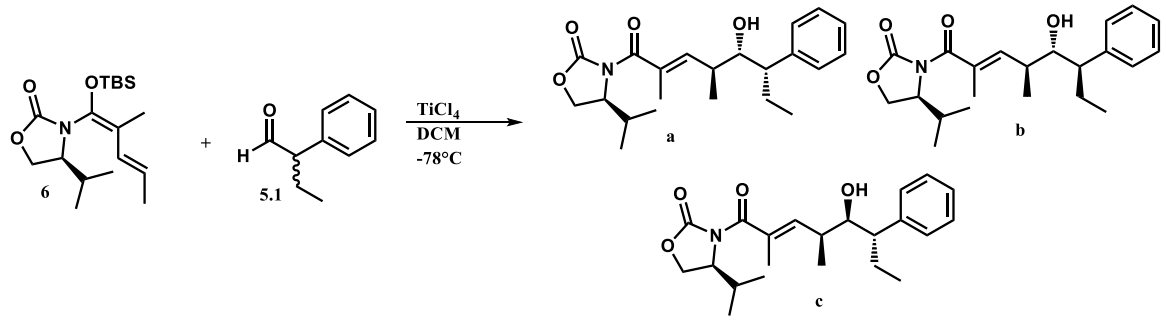


Figure 27. Comparison of alpha substituents of racemic aldehydes in VMAR.

Preliminary studies by Arielle Kanner were done employing aldehyde **5.1**, reacting with vinylketene *N,O*-acetal **6** and results are summarized in Figure 28. The expectation was that selectivity would be enhanced but instead multiple diastereomers were isolated. The stereotriades

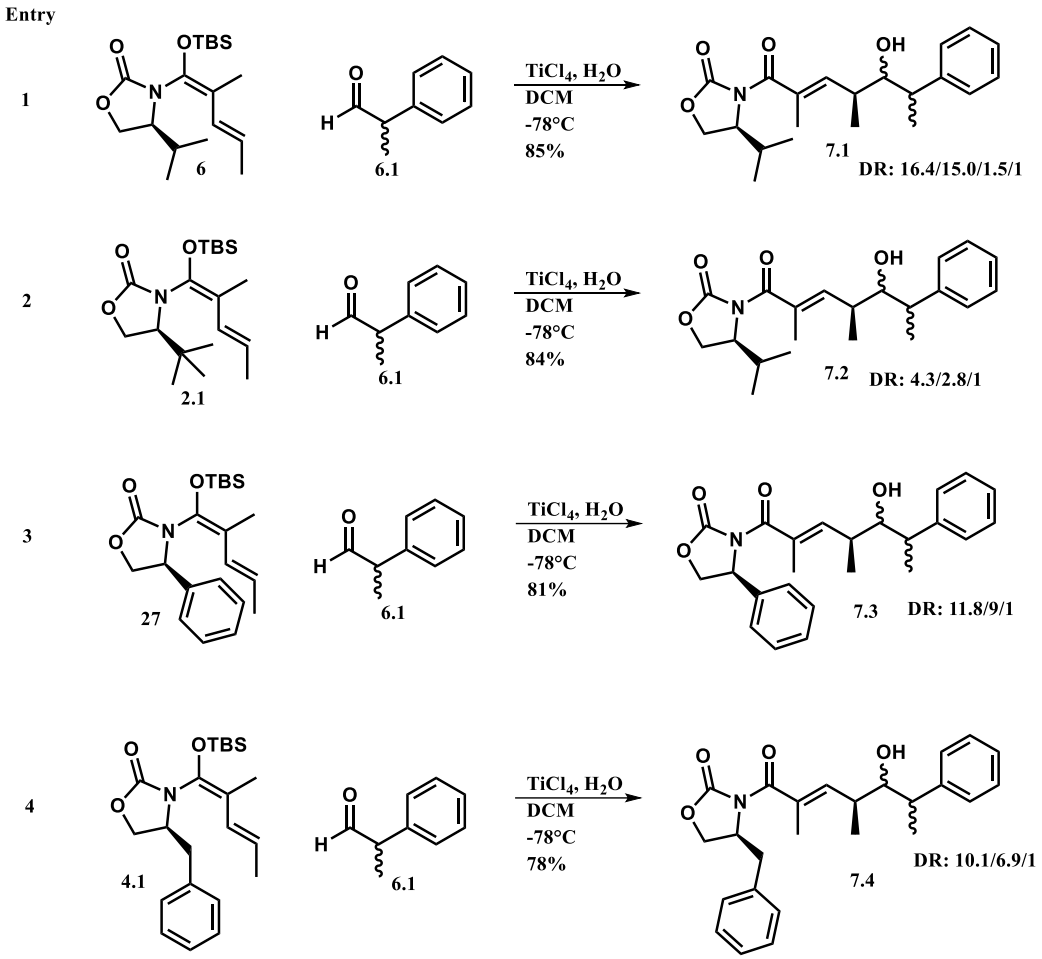
shown are proposed structures are shown. Varying the amount of aldehyde and Lewis acid did not change the yield and DR of the isolated products. The two major diastereomers **a** and **b** were almost a 1 to 1 ratio. Selectivity using **5.1** was surprisingly reduced compared to the butanal aldehyde. One proposal is to use an aldehyde with a methyl group and a phenyl group to create a larger difference between the alpha substitutions.



Entry	Aldehyde (eq.)	$TiCl_4$ (eq.)	Yield (%)	Dr (a:b:c)
1	3	1.5	83	6:3:01
2	6	3	83	10:6:01
3	9	4.5	80	11:5:01

Figure 28. Preliminary data of aldehyde **5.1**.

The alpha ethyl of **5.1** switched with an even smaller methyl would be aldehyde **6.1** (Scheme 44). In the case the constant between this aldehyde and butanal is the small methyl group. The optimized conditions described in table 13 were not employed in the preliminary investigation (Figure 28). In the next experiments with aldehyde **6.1**, all vinylketene *N*,*O*-acetals were investigated.



Scheme 44. Synthesis of stereotriade mixtures with racemic aldehyde 6.1 in VMAR.

Analysis of crude ^{1}H NMR revealed there were multiple diastereomers present when vinylketene *N,O*-acetals **6**, **2.1**, **27**, and **4.1**. The distal attribute of the aromatic ring had no increase in the selectivity of stereotriades: **7.1**, **7.2**, **7.3**, and **7.4**. In fact, of the top two diastereomers were almost in a 1:1 ratio to 1.5:1 ratio. The unexpected result led to ask why there is a drop is selectivity and what could be done to improve upon it. One hypothesis was that the planar conformation of the aromatic ring led the reduction in selectivity. The 3 position of butanal **7b** is of sp^3 hybridized but the same position of aldehyde **5.1** is sp^2 (Figure 29). This planar geometry in this position could be a factor in the drop of selectivity being observed. On

proposal was to employ aldehyde **8.1** where the phenyl group is switched with a cyclohexyl group. The fully saturated ring not only has a sp^3 hybridization in the beta position of the aldehyde but the ring itself provided dihedral interactions that could potentially aid in providing the steric hindrance needed for higher selectivity.

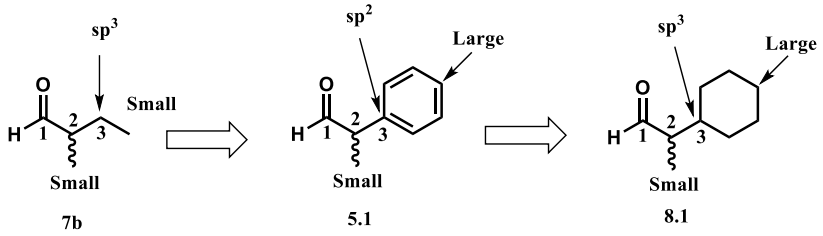
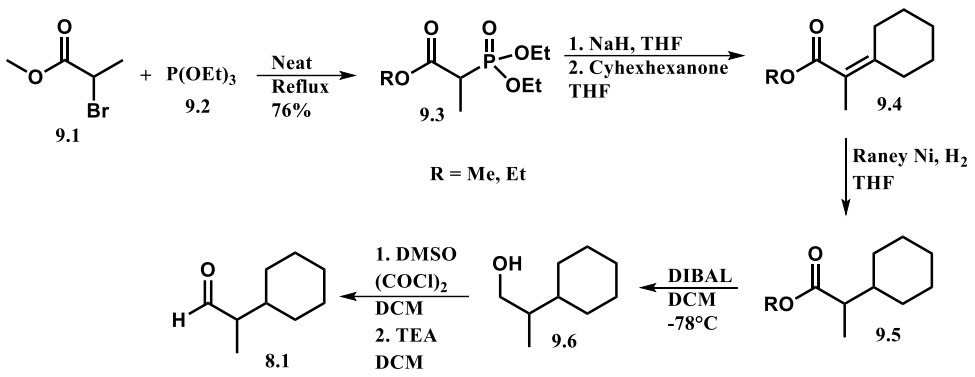


Figure 29. Comparison of aldehydes under VMAR.

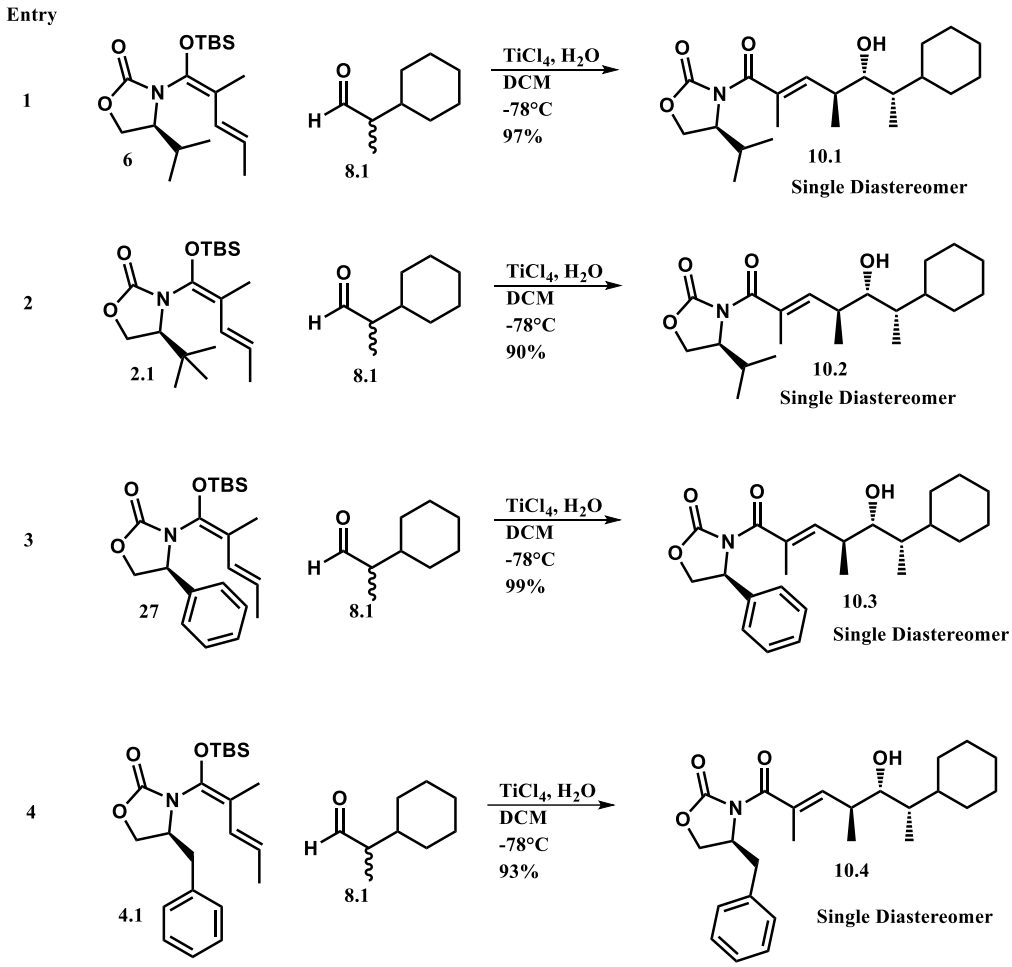
A simple symmetric synthesis of aldehyde **8.1** was done (Scheme 45). The synthesis starts with methyl ester of α-bromo propionate **9.1**, reacted with triethyl phosphite **9.2** to give phosphonate ester **9.3**. Both the mixed methyl and ethyl esters of **9.3** are formed but can and will be used for the duration of the synthesis. The esters are submitted to Horner-Wadsworth-Emmons reaction using cyclohexanone to give α,β unsaturated ester **9.4.** The ester is hydrogenated using Raney-Ni under an atmosphere of H_2 gas to give saturated ester **9.5**. Selective DIBAL reduction was attempted to give desired aldehyde but instead alcohol **9.6** was obtained. The alcohol was oxidized under traditional Swern oxidation conditions to give aldehyde **8.1**.



Scheme 45. Synthesis of aldehyde **8.1**.

6.4 Diastereoselective VMAR demonstrating Kinetic resolution

Under optimized conditions (Table 2.2) which have been employed thus far, the same method of VMAR was employed for cyclohexyl aldehyde **8.1** against vinylketene *N*,*O*-acetals **6**, **2.1**, **27**, and **4.1** (Scheme 46). When applying the optimized VMAR conditions (entry 1) it became apparent upon analysis of crude ^{1}H NMR there was only one diastereomer observed. Sterotriade **10.1** was isolated in 97% as a single diastereomer. This result verified Kobayashi's protocol of VMAR could perform kinetic resolution in an enantioselective fashion in racemic aldehyde setting. The investigation continued as the suspected differences in capability of each of the four directing groups may be observed (isopropyl, t-butyl, phenyl, and benzyl). When vinylketene *N*,*O*-acetal **2.1** was employed a difference in reaction time was observed.



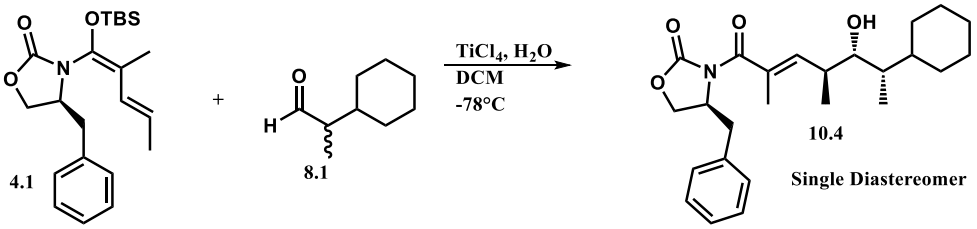
Scheme 46. Aldehyde 8.1 employed with vinylketene *N*,*O*-acetals **6**, **2.1**, **3.1**, and **4.1** in VMAR.

Instead of a 24 hour reaction time, the completion needed seven days. Upon analysis of crude ^{1}H NMR sterotriade **10.2** was observed to be a single diastereomer isolated in 90% yield. Since a single diastereomer was observed the selectivity between the isopropyl and t-butyl directing group was observed to be the same. The phenyl and benzyl have the advantage being able to interact further in space compared to the other directing groups. Since kinetic resolution was already demonstrated with **6** and **2.1**, it should be no surprise vinylketene *N*,*O*-acetals **27**, and **4.1** were able to produce single diastereomers in VMAR. Aldol product **10.3** was isolated in

99% yield and **10.4** was isolated in 93% yield. No differences in selectivity were observed but more importantly all four directing groups demonstrated extremely high selectivity against racemic cyclohexyl aldehyde **8.1** achieving kinetic resolution.

6.5 Diastereoselective VMAR demonstrating Kinetic resolution on Aldehyde

Up until this point the main focus of kinetic resolution has focused on the formation of the precious stereotriades. Attempts at isolation of less desired aldehyde were made. Excess aldehyde is used to obtain high yields of more valuable sterotriades. Vinylketene *N*,*O*-acetal **4.1** was chosen and aldehyde **8.1** was limited in an effort to resolve one enantiomer (Scheme 47).



Scheme 47. VMAR attempts at isolation of aldehyde **8.1**.

When aldehyde **8.1** was limited to 1.8 equivalence from normal amounts of 3 equiv, the yield of sterotriade **10.4** dropped to 53% and vinylketene *N*,*O*-acetal **4.1** co-eluted with aldehyde **8.1** and optical rotation of aldehyde **8.1** cannot be made (Table 14, entry 1). An effort to increase yield and convert vinylketene *N*,*O*-acetal to product was made by using one equiv of Lewis acid but vinylketene *N*,*O*-acetal could not be consumed (entry 2). A third attempt was made where just under 2 equiv of aldehyde is used so that one equivalent of unreactive aldehyde could potentially be made. Unfortunately only 71% of stereotriade was isolated and a mixture of aldehyde, Vinylketene *N*,*O*-acetal, silyl ether, and other impurities coeluted.

Table 14. Attempts of isolation of aldehyde 8.1 in VMAR.

Entry	Aldehyde (eq.)	$TiCl_4$ (eq)	Yield (%)
1	1.8	1.5	53
2	1.8	1	65
3	1.95	1.2	71

Even though pure aldehyde **8.1** could not be isolated, kinetic resolution has been demonstrated as the transformation of aldehyde to stereotriade on the VMAR platform.

Chapter 7 Experimental

General procedure for N-methylation of Fmoc-protected amino acids

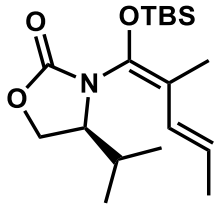
Fmoc-protected amino acid was refluxed in toluene (Dean-Stark) with catalytic pTsOH (0.12 equiv) and an excess of paraformaldehyde (>10 equiv) for 1 hour. The mixture was washed with $NaHCO_3$ (3 x 100 mL) and dried over $MgSO_4$. The mixture was filtered, the filtrate was concentrated in vacuo and the residue was purified via flash chromatography on silica gel column (EtOAc in hexanes). The corresponding cyclic oxazole-compound was dissolved in DCM with TFA (4:1) and Et_3SiH was added (1.4 equiv) and the mixture was stirred 14 h prior to evaporation, extraction with EtOAc, washing with water, and drying over Na_2SO_4. The mixture was filtered, the filtrate was concentrated then purified via chromatography over silica gel column (EtOAc in hexanes).

General procedure for synthesis of vinylketene silyl *N,O*-acetal

A solution of sodium hexamethyldisilylamide (NaHMDS) (1.5 equiv) in anhydrous THF (1 M) was added dropwise to a solution of the corresponding imide (1.0 equiv) in THF at –78 ºC. The resulting reaction mixture was stirred for 90 min at –78 ºC followed by the dropwise addition of a premade solution of TBSCl (1.25 equiv) in anhydrous THF. The reaction mixture was stirred for an additional 45 min at –78 ºC and then quenched with saturated ammonium chloride. After transferring the reaction mixture to a separatory funnel the mixture was extracted with ethyl acetate. The combined organic extract was washed with water, brine, drying over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure. The residual crude product was purified with flash chromatography using EtOAc/Hexanes 0–10% as a gradient giving vinylketene silyl *N,O*-acetal.

General procedure for VMAR

To a stirring solution of aldehyde (3.0 equiv) in DCM at –78 ºC under argon atmosphere was slowly added neat $TiCl_4$ (1.5 equiv). The reaction mixture is stirred for 30 min at –78 ºC and a solution of vinylketene silyl *N*,*O*-acetal (1.0 equiv) in DCM was added dropwise followed by the addition of H_2O (1 equiv.) The resulting reaction mixture is then stirred at –78 ºC until completion upon which a mixture of saturated aqueous Rochelle salt and saturated aqueous $NaHCO_3$ was added (1:1) at –78 ºC. The reaction mixture was transferred to a separation funnel. The aqueous phase was extracted with ethyl acetate (4x) and the combined organic extract was washed with brine, drying over anhydrous sodium sulfate, filtered, the solvent was removed under reduced pressure. The remaining crude residue was purified with flash chromatography using ethyl acetate in hexanes to yield VMAR product.

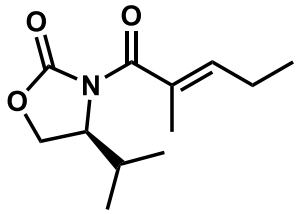


(*S*)-3-((1*E*,3*E*)-1-((tert-butyldimethylsilyl)oxy)-2-methylpenta-1,3-dien-1-yl)-4-isopropyloxazolidin-2-one (6)[35]

A premade solution of potassium hexamethyldisilylamide (KHMDS) (4.00 g, 20.1 mmol) in anhydrous THF (50 mL) was added dropwise to a solution of imide **6a** (3.00 g, 13.3 mmol) in THF (130 mL) at –78 ºC. The resulting reaction mixture was stirred for 90 min at –78 ºC followed by the dropwise addition of a premade solution of TBSCl (3.41 g, 22.6 mmol) in anhydrous THF (25 mL). The reaction mixture was stirred an additional 45 min at –78 ºC and

then quenched with saturated ammonium chloride (50 mL). After transferring the reaction mixture to a separation funnel the mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic extract was washed with water (25 mL), brine (25 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure. The residual crude product was then purified with flash chromatography using hexanes/ethyl acetate 0–20% as a gradient to give 96% yield (4.34 g) of **6** as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.21 (d, *J* = 15.5 Hz, 1H), 5.63 (dq, *J* = 15.5, 6.6 Hz, 1H), 4.31 (t, *J* = 8.9 Hz, 1H), 4.12 (t, *J* = 8.5 Hz, 1H), 4.00 (s, 1H), 1.98 – 1.90 (m, 1H), 1.80 – 1.75 (m, 6H), 0.97 (s, 9H), 0.95 (s, 6H), 0.19 (s, 3H), 0.14 (s, 3H).

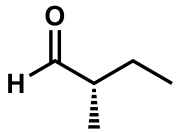


(*S*,*E*)-4-isopropyl-3-(2-methylpent-2-enoyl)oxazolidin-2-one (6a)[57]

To a solution of (*S*)-oxazolidone (1 g, 7.75 mmol), (*E*)-2-methylpent-2-enoic acid (0.93 g, 8.135 mmol) and 4-(dimethylamino)pyridine (DMAP) (0.12 g, 0.93mmol) in DCM (8 mL) cooled to 0 ºC was added N,N'-Diisopropylcarbodiimide (DIC) (1.32 mL, 8.52 mmol). The reaction mixture was stirred at ambient temperature for 3 days, followed by the reaction being quenched with water (10 mL) and diluted with DCM (50 mL). The reaction mixture was transferred to a separatory funnel and the mixture was washed with an aqueous solution of 1 M HCl (50 mL), and the aqueous phase was extracted with DCM (3 × 100 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and the solvent

was removed under reduced pressure. The residual oil was purified by flash chromatography using ethyl acetate/hexanes (20%) to give 70% yield (1.22 g) of **6a** as a white solid.

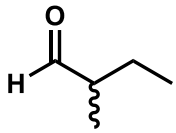
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.08 (tq, *J* = 7.3, 1.4 Hz, 1H), 4.52 (ddd, *J* = 8.8, 5.5, 4.4 Hz, 1H), 4.31 (t, *J* = 8.9 Hz, 1H), 4.17 (dd, *J* = 9.0, 5.5 Hz, 1H), 2.37 (pd, *J* = 7.0, 4.4 Hz, 1H), 2.25 – 2.16 (m, 2H), 1.90 (q, *J* = 1.1 Hz, 3H), 1.05 (t, *J* = 7.5 Hz, 3H), 0.91 (dd, *J* = 7.8, 7.0 Hz, 6H).



(*S*)-2-methylbutanal (7) [66]

A 1L, three-necked, round bottomed flask was fitted with mechanical stirrer, pressure-equalizing dropping funnel, and a thermometer. The flask was charged with (*S*)-(-)-2-methyl-1-butanol (5.0 g, 0.056 mol), potassium bromide (0.672 g, 5.65 mmol) in water (2.82 mL). The reaction mixture was vigorously stirred and cooled to -10 °C with a salt-ice bath, then aqueous sodium hypochlorite (62.2 mL of 1 M, 0.0622 mol) at pH 9.5 was added over 15-20 min. The reaction temperature was carefully maintained between 10 and 15 °C. The mixture was stirred for a further 3 min. The orange organic phase was separated, and the aqueous phase extracted with DCM (10 mL). The combined organic extracts were washed with 10% aqueous hydrochloric acid (100 mL) containing potassium iodide (0.180 g, 1.13 mmol), followed by 10% aqueous sodium thiosulfate (10 mL), and water (10 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered, and used directly without further purification.

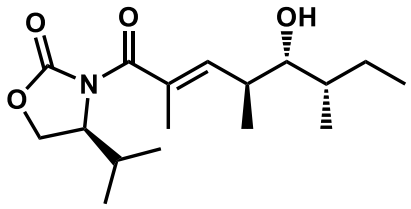
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (d, *J* = 1.9 Hz, 1H), 2.26 (hd, *J* = 6.9, 2.0 Hz, 1H), 1.73 (tt, *J* = 14.3, 6.8 Hz, 1H), 1.43 (dp, *J* = 14.4, 7.3 Hz, 1H), 1.08 (dd, *J* = 7.1, 0.8 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 3H).



(*S*)-2-methylbutanal (7b)[66]

A 1L, three-necked, round bottomed flask was fitted with mechanical stirrer, pressure-equalizing dropping funnel, and a thermometer. The flask was charged with (*S*)-(-)-2-methyl-1-butanol (5.0 g, 0.056 mol), potassium bromide (0.672 g, 5.65 mmol) in water (2.82 mL). The reaction mixture was vigorously stirred and cooled to -10 °C with a salt-ice bath, then aqueous sodium hypochlorite (62.2 mL of 1 M, 0.0622 mol) at pH 9.5 was added over 15-20 min. The reaction temperature was carefully maintained between 10 and 15 °C. The mixture was stirred for a further 3 min. The orange organic phase was separated, and the aqueous phase extracted with DCM (10 mL). The combined organic extracts were washed with 10% aqueous hydrochloric acid (100 mL) containing potassium iodide (0.180 g, 1.13 mmol), followed by 10% aqueous sodium thiosulfate (10 mL), and water (10 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered, and used directly without further purification.

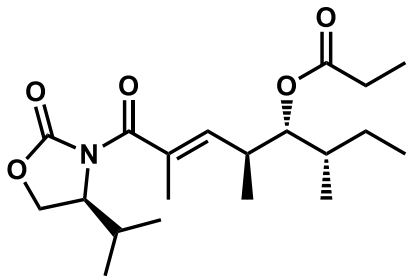
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (d, *J* = 1.9 Hz, 1H), 2.26 (hd, *J* = 6.9, 2.0 Hz, 1H), 1.73 (tt, *J* = 14.3, 6.8 Hz, 1H), 1.43 (dp, *J* = 14.4, 7.3 Hz, 1H), 1.08 (dd, *J* = 7.1, 0.8 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 3H).



(*S*)-3-((4*S*,5*R*,6*S*,*E*)-5-hydroxy-2,4,6-trimethyloct-2-enoyl)-4-isopropyloxazolidin-2-one (8)[35]

A solution of $TiCl_4$ (6.63 mmol, 1.50 equiv) in CH_2Cl_2 (20 mL) was added dropwise to a solution of (*S*)-2-methylbutanal **7** (13.25 mmol, 3.00 equiv) in CH_2Cl_2 (30 mL) at –78 ºC. The resulting reaction mixture was stirred for 30 min at –78 ºC and a solution of vinylketene silyl *N*,*O*-acetal **6** (1.50 g, 4.42 mmol, 1.00 equiv) dissolved in CH_2Cl_2 (100 mL) was added dropwise over 30 min. The reaction mixture was stirred for 22 h at –78 ºC and then quenched with a mixture of saturated aqueous Rochelle salt and saturated aqueous $NaHCO_3$ (50 mL, 1:1) at –78 ºC. The reaction mixture was warmed to room temperature while stirring, transferred to a separatory funnel and extracted with ethyl acetate (4 × 20 mL). The combined organic extracts were washed with water (50 mL) and brine (60 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified using a silica gel column (hexanes/ethyl acetate 0–25% as a gradient) to give 96% yield (1.32 g) alcohol **8** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (dq, *J* = 10.3, 1.5 Hz, 1H), 4.57 (ddd, *J* = 8.9, 5.8, 4.5 Hz, 1H), 4.34 (t, *J* = 9.0 Hz, 1H), 4.18 (dd, *J* = 9.0, 5.8 Hz, 1H), 3.30 (dt, *J* = 8.9, 2.6 Hz, 1H), 3.03 (dd, *J* = 2.8, 1.3 Hz, 1H), 2.73 (ddq, *J* = 10.3, 8.9, 6.6 Hz, 1H), 2.35 (pd, *J* = 7.0, 4.5 Hz, 1H), 1.95 (d, *J* = 1.5 Hz, 3H), 1.58 – 1.46 (m, 3H), 1.38 (dp, *J* = 13.3, 7.3 Hz, 1H), 0.96 – 0.88 (m, 15H).

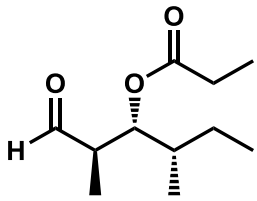


(3*S*,4*R*,5*S*,*E*)-8-((*S*)-4-isopropyl-2-oxooxazolidin-3-yl)-3,5,7-trimethyl-8-oxooct-6-en-4-yl propionate (9)[35]

Alcohol **8** (1.93 g, 6.20 mmol, 1.00 equiv) was charged in a dry 100 mL round bottom flask under argon. The substrate was dissolved in distilled CH_2Cl_2 (18 mL) and then the solution was cooled to 0 ºC using an ice/water bath. Anhydrous pyridine (2.00 mL, 24.79 mmol) was added followed by drop-wise addition of freshly distilled propionyl chloride (2.17 mL, 24.79 mmol) over 5 min. After the addition of DMAP (350 mg, 3.10 mmol) the pale-yellow heterogeneous reaction mixture was stirred towards ambient temperature over 13 h. Saturated ammonium chloride (20 mL) was added to the resulting homogeneous solution at room temperature. The reaction mixture was transferred to a separation funnel and phases separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic extract was washed with 1M NaOH (20 mL), brine (40 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. The residual crude product was then purified using a silica gel column (0–25% ethyl acetate in hexanes gradient) to give 97% yield (2.21 g) of ester **9** as colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (dq, *J* = 9.8, 1.5 Hz, 1H), 4.87 (dd, *J* = 6.8, 5.3 Hz, 1H), 4.45 (ddd, *J* = 8.7, 4.7, 4.4 Hz, 1H), 4.29 (dd, *J* = 8.8, 8.7 Hz, 1H), 4.18 (dd, *J* = 8.8, 4.7 Hz, 1H), 2.91–2.83 (ddq, *J* = 9.8, 6.8, 6.8 Hz, 1H), 2.42–2.36 (m,1H), 2.36–2.30 (dq, *J* = 7.6, 3.4 Hz, 2H),

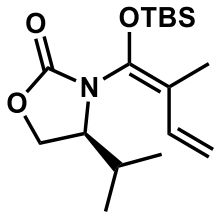
1.91 (d, *J* = 1.5 Hz, 3H), 1.72–1.63 (m, 1H), 1.41–1.32 (m, 1H),1.20–1.09 (m, 1H), 1.13 (t, *J* = 7.6 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.92–0.89 (t, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H)



(2*R*,3*R*,4*S*)-2,4-dimethyl-1-oxohexan-3-yl propionate (3)[35]

A solution of compound **9** (1.01 g, 2.73 mmol) in anhydrous CH_2Cl_2 (50 mL) was cooled to -78 ºC. A slow stream of ozone gas was then bubbled through the solution for 30 min until the solution turned light blue. The blue solution was flushed by bubbling oxygen for 15 min at -78 ºC followed by bubbling argon for 15 min until the blue color faded. Excess dimethyl sulfide (1.25 ml, 17.02 mmol) was then added dropwise over 5 min at -78 ºC. The temperature was then raised to ambient temperature and the mixture stirred an additional 12 h. The solvent was removed under reduced pressure. The residual crude product was then purified on a silica gel plug hexanes/ethyl acetate, 0–15% as a gradient) to give 92% yield (0.519 g) of **3** as a colorless oil.

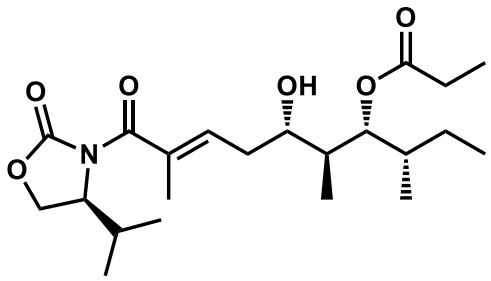
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (d, *J* = 3.2 Hz, 1H), 5.13 (dd, *J* = 7.5, 4.6 Hz, 1H), 2.69–2.60 (ddq, *J* = 7.5, 7.0, 3.2 Hz, 1H), 2.36–2.29 (q, *J* = 4.8 Hz, 2H), 1.75–1.66 (m,1H), 1.45–1.32 (m, 1H), 1.25–1.12 (m, 1H), 1.14 (t, *J* = 7.6 Hz, 3H), 1.09 (d, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 7.5 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H



(*S*,*E*)-3-(1-((tert-butyldimethylsilyl)oxy)-2-methylbuta-1,3-dien-1-yl)-4-isopropyloxazolidin-2-one (4)[35]

A solution of solid KHMDS (3.20 g, 16.02 mmol) in anhydrous THF (230 mL) was added dropwise to a solution of imide (1.81 g, 10.68 mmol) in THF (110 mL) at –78 ºC. After the reaction mixture was stirred for 90 min at –78 ºC a solution of TBSCl (4.83 g, 18.16 mmol) in THF (25 mL) was added dropwise over 20 min at –78 ºC. The reaction mixture was stirred at –78 ºC until completion was verified via TLC analysis (~45 min). The reaction was then quenched with saturated aqueous NH_4Cl (50 mL) at –78 ºC. The temperature of the resulting mixture was allowed to reach ambient temperature and stirred for an additional 30 min. The two phase mixture was then transferred to a separatory funnel. The two phases were separated, and the aqueous phase was extracted with ethyl acetate (4 × 20 mL). The combined organic extract was washed with water (50 mL), brine (50 mL) and dried over anhydrous sodium sulfate. After filtration the solvent was removed under reduced pressure and the residual crude product was then purified with flash chromatography using hexanes/ethyl acetate 0–40% as a gradient to give 86% yield (2.99 g) of vinylketene silyl *N*,*O*-acetal **4** as a white solid.

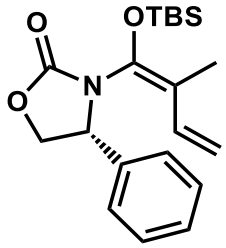
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.54 (dd, *J* = 17.2, 11.0 Hz, 1H), 5.14 (dd, *J* = 17.4, 1.3 Hz, 1H), 5.03 (dd, *J* = 10.8, 1.3 Hz, 1H), 4.32 (t, *J* = 8.8 Hz, 1H), 4.11 (t, *J* = 8.4 Hz, 1H), 4.02 (s, 1H), 1.95 (dq, *J* = 13.4, 6.9 Hz, 1H), 1.80 (s, 3H), 0.98 (s, 9H), 0.20 (s, 3H), 0.15 (d, *J* = 2.0 Hz, 3H).



(3*S*,4*R*,5*S*,6*S*,*E*)-6-hydroxy-10-((S)-4-isopropyl-2-oxooxazolidin-3-yl)-3,5,9-trimethyl-10-oxodec-8-en-4-yl propionate (10)[35]

To a stirred solution of aldehyde **3** (0.350 g, 1.75 mmol) in toluene (2.0 mL) at –78 ºC under argon was slowly added $TiCl_4$ (2.65 mL, 1.0 M solution in toluene, 2.65 mmol). The reaction mixture was stirred for 20 min at –78 ºC and a solution of vinylketene silyl *N*,*O*-acetal 4 (1.30 g, 4.00 mmol) in toluene (2.5 mL) at –78 ºC was added dropwise over 10 min and stirred. The reaction mixture was stirred for one hour at –78 ºC and 10 mol% deionized water was added. The resulting reaction mixture was then stirred at oscillating temperatures of –78 ºC and –40 ºC, switching every 12 hours for a total of 72 hours providing a dark violet to heterogeneous, dark orange reaction mixture. After 72 h of reaction time a mixture of saturated aqueous Rochelle salt and saturated aqueous $NaHCO_3$ (1:1, 25 mL) was added at -40 ºC. The mixture was stirred vigorously at ambient temperature until the resulting slurry became homogeneous and was transferred to a separatory funnel. The aqueous phase was extracted with ethyl acetate (4 × 20 mL) and the combined organic extract was washed with water (30 mL), followed by brine (40 mL). The organic phase was then dried over anhydrous sodium sulfate. After filtration the solvent was removed under reduced pressure and the residual crude product was purified with flash chromatography using hexanes/ethyl acetate 0–35% as a gradient to give 48% yield (344 mg) of aldol product **10** (dr = 91:9) as a clear oil.

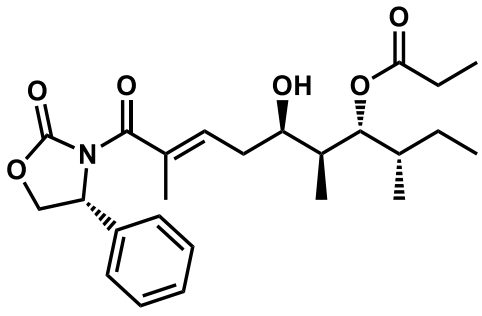
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.09 (dd, *J* = 7.3 Hz, 1H), 4.90 (dd, *J* = 10.0, 2.8 Hz, 1H), 4.50 (ddd, *J* = 9.0, 5.0, 4.8 Hz, 1H), 4.30 (dd, *J* = 9.0, 9.0 Hz, 1H), 4.17 (dd, *J* = 9.0, 5.0 Hz, 1H), 3.64–3.58 (m, 1H), 2.87 (s, 1H), 2.50–2.41 (m, 1H), 2.39 (q, *J* = 7.6 Hz, 2H), 2.37–2.31 (m, 1H), 2.28 (m, 1H), 1.92 (s, 3H), 1.80–1.71 (m, 1H), 1.71–1.63 (m, 1H), 1.35–1.24 (m, 1H), 1.22–1.12 (m, 1H), 1.17 (t, *J* = 7.6 Hz, 3H), 0.94–0.88 (m, 15H)



(*R*,*E*)-3-(1-((tert-butyldimethylsilyl)oxy)-2-methylbuta-1,3-dien-1-yl)-4-phenyloxazolidin-2-one (11)

The title compound was prepared using general procedure for the synthesis of vinylketene silyl *N*,*O*-acetal to give 70% yield (1.5 g) of **11** as a white solid.

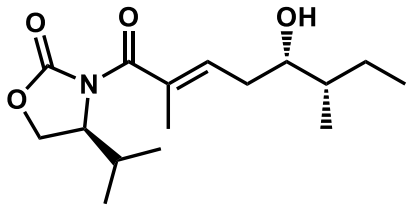
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 6.47 (dd, *J* = 17.3, 10.9 Hz, 1H), 5.23 – 4.87 (m, 3H), 4.67 (t, *J* = 8.9 Hz, 1H), 4.28 (t, *J* = 8.9 Hz, 1H), 1.66 (s, 3H), 1.00 – 0.97 (m, 9H), 0.23 (s, 3H), 0.20 (s, 3H).



(3*S*,4*R*,5*S*,6*R*,*E*)-6-hydroxy-3,5,9-trimethyl-10-oxo-10-((*R*)-2-oxo-4-phenyloxazolidin-3-yl)dec-8-en-4-yl propionate (13)

To a stirred solution of aldehyde **3** (0.050 g, 0.25 mmol) in DCM (2.0 mL) at –78 ºC under argon atmosphere was slowly added neat $TiCl_4$ (30 µL, 0.275 mmol). The reaction mixture was stirred for 30 min at –78 ºC and a solution of vinylketene silyl *N*,*O*-acetal **11** (180 mg, 0.5 mmol) in DCM (10 mL) at –78 ºC was added dropwise over 10 min. The resulting reaction mixture was then stirred overnight at –78 ºC. A mixture of saturated aqueous Rochelle salt and saturated aqueous $NaHCO_3$ (1:1, 5 mL) was added at -78 ºC. The mixture was stirred vigorously at ambient temperature until the resulting slurry became homogeneous and was transferred to a separatory funnel. The aqueous phase was extracted with ethyl acetate (4 × 20 mL) and the combined organic extracts were washed with water (30 mL) followed by brine (40 mL). The organic phase was dried over anhydrous sodium sulfate. After filtration the solvent was removed under reduced pressure and the residual crude product was purified with flash chromatography using hexanes/ethyl acetate 0–45% as a gradient to give 46% yield (51 mg, 0.114 mmol) of aldol product **13** as a clear oil.

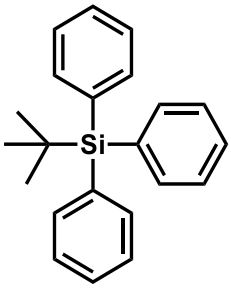
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 5H), 6.18 (ddq, *J* = 8.1, 6.6, 1.5 Hz, 1H), 5.46 (dd, *J* = 8.9, 7.1 Hz, 1H), 4.89 (dd, *J* = 10.0, 2.6 Hz, 1H), 4.70 (t, *J* = 8.9 Hz, 1H), 4.23 (dd, *J* = 8.9, 7.1 Hz, 1H), 3.59 (t, *J* = 7.1 Hz, 1H), 2.94 (s, 1H), 2.47 (dddd, *J* = 15.2, 8.8, 6.6, 1.2 Hz, 1H), 2.39 (q, *J* = 7.6 Hz, 2H), 2.22 (ddd, *J* = 14.2, 8.4, 5.3 Hz, 1H), 1.88 (d, *J* = 1.4 Hz, 3H), 1.77 – 1.62 (m, 2H), 1.34 – 1.19 (m, 2H), 1.16 (t, *J* = 7.6 Hz, 3H), 0.93 – 0.86 (m, 9H).



(*S*)-3-((5*S*,6*S*,*E*)-5-hydroxy-2,6-dimethyloct-2-enoyl)-4-isopropyloxazolidin-2-one (15)[35]

To a solution of (*S*)-methylbutanal **7** (87.0 mg, 1.01 mmol) in CH_2Cl_2 (15 mL) at -78 ºC was added neat $TiCl_4$ (101 mL, 0.922 mmol) under argon and reaction mixture was stirred for 20 min. Then a solution of **4** (300 mg, 0.922 mmol) in distilled CH_2Cl_2 (3.0 mL) was added dropwise over 20 min at -78 ºC under an argon atmosphere. The reaction mixture was stirred for 14 h at -78 ºC the resulting orange solution was quenched with a mixture of saturated aqueous Rochelle salt and saturated $NaHCO_3$ (1:1, 10 mL) at -78 ºC. The reaction mixture was warmed to room temperature, stirred for an additional 30 min, then transferred to a separatory funnel and the aqueous phase was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with water (30 mL), brine (40 mL) and dried over anhydrous sodium sulfate, filtered and the organic solvent removed under reduced pressure. The residual crude product was purified by silica gel chromatography using ethyl acetate/hexanes as a gradient (0–30%) spiked with 2.5% methylene chloride to give 79% yield (216 mg) of **15** as a colorless oil.

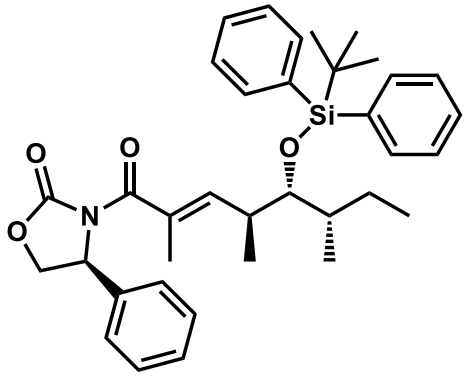
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (dd, *J* = 9.2, 6.4 Hz, 1H), 4.56 (dt, *J* = 9.4, 5.0 Hz, 1H), 4.33 (t, *J* = 8.9 Hz, 1H), 4.19 (dd, *J* = 9.0, 5.5 Hz, 1H), 3.61 (d, *J* = 9.5 Hz, 1H), 2.73 (d, *J* = 3.4 Hz, 1H), 2.48 – 2.31 (m, 1H), 2.24 (d, *J* = 14.0 Hz, 1H), 1.94 (t, *J* = 1.3 Hz, 3H), 1.66 – 1.43 (m, 1H), 1.34 – 1.16 (m, 2H), 0.99 – 0.88 (m, 12H).



tert-butyltriphenylsilane (18)[58]

TBSCl (5.0 g, 18.2 mmol) was dissolved in diethyl ether (20 mL) and cooled to 0 ºC. A solution of phenyl lithium (1.8 M, 32.7 mL, 58.9 mmol) in ether/hexane was added dropwise and stirred overnight. The reaction mixture was cooled to 0 ºC, then diluted with diethyl ether, and quenched slowly with addition of small portions of water (10 mL). The reaction mixture was poured in a separatory funnel and organic phase is washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried over sodium sulfate sodium sulfate, filtered, and the solvent removed under reduced pressure to give 21% yield (2.21 g) of **18** as colorless crystals.

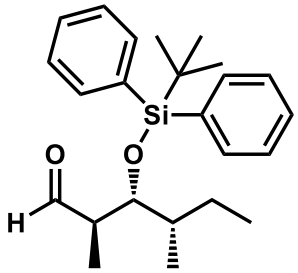
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.50 (m, 6H), 7.51 – 7.30 (m, 9H), 1.18 (s, 9H).



(*S*)-3-((4*S*,5*R*,6*S*,*E*)-5-((tert-butyldiphenylsilyl)oxy)-2,4,6-trimethyloct-2-enoyl)-4-phenyloxazolidin-2-one (19)

Silane **18** (1.1 g, 3.48 mmol) is dissolved in $CHCl_3$ (2 mL) and cooled to 0ºC. Neat triflic acid (0.52 g, 0.31 mL, 3.46 mmol) was added dropwise and the solution was stirred for 30 min. A solution of alcohol **23** (642 mg, 1.86 mmol) in DCM (6 mL) was added to the solution followed by the addition of neat 2,6 lutidine (0.478 mL, 3.72 mmol) and stirred overnight. The reaction mixture was cooled to 0°C and quenched with water (1 mL). After transferring the reaction mixture to a separatory funnel, the mixture was extracted with DCM (3 × 75 mL). The combined organic extracts were washed with HCl (1 M, 100 mL), brine (50 mL), dried with anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure. The residual crude product was then purified with flash chromatography using ethyl acetate/hexanes (20%) to give 65% yield (709 mg) of **19** as a white solid.

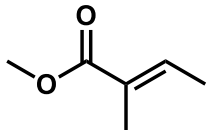
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (td, *J* = 5.0, 4.4, 2.3 Hz, 3H), 7.47 – 7.35 (m, 12H), 6.48 (d, *J* = 9.6 Hz, 1H), 5.46 (dd, *J* = 8.7, 6.8 Hz, 1H), 4.69 (t, *J* = 8.8 Hz, 1H), 4.22 (dd, *J* = 8.8, 6.9 Hz, 1H), 3.64 (t, *J* = 3.0 Hz, 1H), 2.66 (ddt, *J* = 12.7, 8.2, 4.1 Hz, 1H), 1.77 (d, *J* = 1.4 Hz, 3H), 1.64 (dd, *J* = 6.0, 3.5 Hz, 1H), 1.52 (ddt, *J* = 10.3, 7.0, 3.7 Hz, 1H), 1.14 (s, 9H), 1.07 – 0.99 (m, 2H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.74 (t, *J* = 7.4 Hz, 3H).



(2*R*,3*R*,4*S*)-3-((tert-butyldiphenylsilyl)oxy)-2,4-dimethylhexanal (20)

A solution of compound **19** (150 mg, 0.257 mmol) in anhydrous CH_2Cl_2 (10 mL) was cooled to –78 ºC. A slow stream of ozone gas was then bubbled through the solution for roughly 30 min until the solution turned light blue. The blue solution was flushed by bubbling oxygen for 15 min at –78 ºC followed by bubbling argon for 15 min until the blue color faded. Excess dimethyl sulfide (1.25 ml, 17.02 mmol) was added dropwise over 5 min at –78 ºC. The temperature was raised to ambient temperature and the mixture was stirred for an additional 12 h. The solvent was removed under reduced pressure and the remaining crude product was purified on a silica gel plug (hexanes in ethyl acetate, 0–10% as a gradient) to give 90% yield (88 mg) of **20** as a colorless oil.

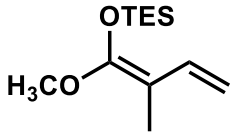
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (d, *J* = 2.4 Hz, 1H), 7.71 – 7.64 (m, 4H), 7.39 (m, 6H), 3.84 (t, *J* = 3.7 Hz, 1H), 2.51 (qdd, *J* = 7.1, 3.6, 2.4 Hz, 1H), 1.64 – 1.46 (m, 2H), 1.08 (s, 9H), 1.00 (d, *J* = 7.1 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H), 0.75 (t, *J* = 7.3 Hz, 3H).



methyl (*E*)-2-methylbut-2-enoate (23)[59]

Tiglic acid (20.0 g, 0.199 mol) was dissolved in 100 mL of MeOH. Concentrated H_2SO_4 (5 mL) was added dropwise at room temperature. The reaction was monitored by TLC. Upon completion the reaction mixture was poured into a separatory funnel with water (100 mL). The mixture was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The crude product was distilled to give 60% (13.6 g) of **23** as a colorless oil.

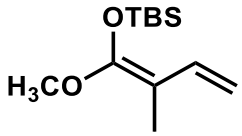
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (qq, *J* = 7.1, 1.5 Hz, 1H), 3.73 (s, 3H), 1.87 – 1.80 (m, 4H).



(*Z*)- ((1-methoxy-2-methylbuta-1,3-dien-1-yl)oxy)triethylsilane (25)[60]

To a solution of lithium diisopropyl amide (LDA) (105 mmol) in dry THF (100mL), cooled to -78 ℃, was added methyl tiglate (11.4 g, 100 mmol) over a period of 30 min. After 60 min, triethylchlorosilane (18.1 g, 120 mmol) in THF (25 mL) was added at -78 ℃, and the mixture was allowed to reach room temperature slowly over 1.5 h. The solvent was removed under reduced pressure, replaced by pentane, filtered, and the resulting mixture concentrated under reduced pressure. Distillation of the crude residue gave the corresponding diene in 74% yield (17 g) of **25** as a colorless oil.

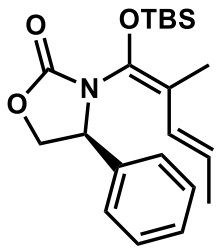
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (dd, *J* = 17.5, 10.8 Hz, 1H), 4.85 (ddd, *J* = 17.5, 7.4, 1.7 Hz, 2H), 3.59 (d, *J* = 1.0 Hz, 3H), 1.64 (s, 3H), 0.99 (dt, *J* = 14.1, 8.0 Hz, 9H), 0.82 – 0.68 (m, 6H).



(*Z*)-tert-butyl((1-methoxy-2-methylbuta-1,3-dien-1-yl)oxy)dimethylsilane (26)[60]

To a solution of lithium diisopropyl amide (LDA) (105 mmol) in dry THF (100mL), cooled to -78 °C, was added methyl tiglate (11.4 g, 100 mmol) over a period of 30 min. After 60 min, TBSCl (18.0 g, 120 mmol) in THF (25 mL) was added at -78 °C, and the mixture was allowed reach room temperature slowly for 1.5 h. The solvent was removed under reduced pressure, replaced by pentane, filtered, and concentrated. Distillation of the crude residue gave the corresponding diene in 87% yield (19.8 g) of **26** as a colorless oil.

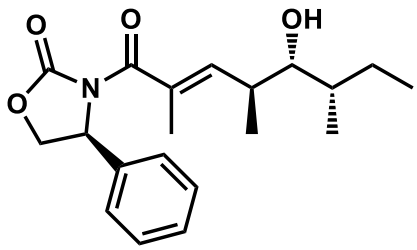
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77 (dd, *J* = 17.5, 10.9 Hz, 1H), 4.87 (ddd, *J* = 17.5, 6.6, 1.7 Hz, 1H), 4.80 (ddd, *J* = 10.8, 9.1, 1.7 Hz, 1H), 3.58 (s, 3H), 1.64 (s, 3H), 0.98 (s, 9H), 0.18 (s, 6H).



(*S*)-3-((1*E*,3*E*)-1-((tert-butyldimethylsilyl)oxy)-2-methylpenta-1,3-dien-1-yl)-4-phenyloxazolidin-2-one (27)

The title compound was prepared using general procedure for the synthesis of vinylketene silyl *N*,*O*-acetal to give 89% (3.15 g) of **27** as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 6.11 (d, *J* = 15.5 Hz, 1H), 5.52 (s, 1H), 5.06 (s, 1H), 4.67 (t, *J* = 8.9 Hz, 1H), 4.30 (t, *J* = 8.8 Hz, 1H), 1.78 – 1.74 (m, 3H), 1.63 (s, 3H), 0.98 (s, 9H), 0.22 (s, 3H), 0.19 (s, 3H).



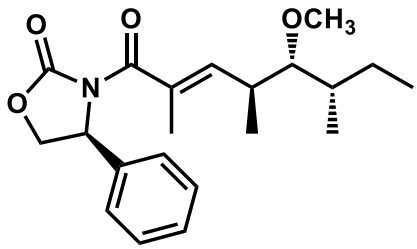
(*S*)-3-((4*S*,5*R*,6*S*,*E*)-5-hydroxy-2,4,6-trimethyloct-2-enoyl)-4-phenyloxazolidin-2-one (28)

Neat $TiCl_4$ (0.534 mL, 4.86 mmol, 1.1 equiv) was added dropwise to a solution of aldehyde **5** (13.25 mmol, 3.00 equiv) in DCM (30 mL) at -78 °C. The resulting reaction mixture was stirred for 30 min at -78 °C and a solution of vinylketene silyl *N*,*O*-acetal **27** (1.65 g, 4.42 mmol, 1.00 equiv) dissolved in DCM (100 mL) was added dropwise over 30 min. The reaction mixture was stirred for 22 h at -78 °C and then quenched with a mixture of saturated aqueous Rochelle Salt and saturated $NaCO_3$ (50 mL, 1:1). The mixture was warmed to room temperature while stirring, transferred to a separatory funnel, and extracted with DCM (3 × 75 mL). The combined organic extracts were washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified using silica gel column (ethyl acetate/hexanes 0 to 30% as a gradient) to give 99% yield (1.5 g) of **28** as a white solid.

$[\alpha]_D^{25}$ -26.5° (c= 4.1 ,MeOH) δ_H(500 MHz, $CDCl_3$): 7.44 – 7.32 (5H, m), 5.90 (1H, dq, *J* = 10.3, 1.5 Hz), 5.53 (1H, dd, *J* = 9.1, 7.9 Hz), 4.73 (1H, t, *J* = 9.1 Hz), 4.26 (1H, dd, *J* = 9.0, 7.9 Hz), 3.34 (1H, dt, *J* = 9.0, 2.6 Hz), 2.96 (1H, dd, *J* = 2.9, 1.3 Hz), 2.73 (1H, ddq, *J* = 10.3, 8.8, 6.6 Hz), 1.91 (3H, d, *J* = 1.4 Hz), 1.56 – 1.46 (2H, m), 1.45 – 1.33 (1H, m), 0.97 – 0.86 (9H, m)

^{13}C NMR (126 MHz, $CDCl_3$): (171.1, 154.5, 144.0, 137.7, 131.2, 129.4, 129.1, 126.5, 77.0, 69.8, 58.5, 37.6, 36.0, 27.5, 15.8, 13.9, 12.3, 12.1).

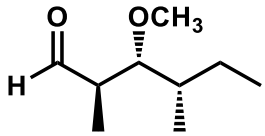
HRMS: $C_{20}H_{27}NO_4$ Found: [M+Na] 368.1827 , Calc: [M+Na] 368.1837



(*S*)-3-((4*S*,5*R*,6*S*,*E*)-5-methoxy-2,4,6-trimethyloct-2-enoyl)-4-phenyloxazolidin-2-one (29)

To a solution of alcohol **23** (0.100 g, 0.289 mmol) in DCM (2.1 mL) cooled to 0 °C was added proton sponge (0.090 g, 0.405 mmol) and Me_3BF_4 (0.090 g, 0.607 mmol). After stirring at room temperature for 48 h the mixture was quenched with of saturated aqueous $NaHCO_3$ (10 mL). The reaction mixture was transferred to a separatory funnel and extracted with DCM (3 × 20 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography using ethyl acetate/hexanes (25%) to give 70% yield (0.073 g) of **29** as a white solid.
$[\alpha]_D^{25}$ -120° (c= 3.7 ,$CHCl_3$) δ_H(500 MHz, $CDCl_3$): 7.41 – 7.36 (5H, m), 6.15 (1H, dq, *J* = 9.8, 1.5 Hz), 5.44 (1H, dd, *J* = 8.7, 6.9 Hz), 4.68 (1H, t, *J* = 8.8 Hz), 4.21 (1H, dd, *J* = 8.8, 6.9 Hz), 3.42 (3H, s), 2.87 (1H, t, *J* = 5.5 Hz), 2.83 – 2.72 (1H, m), 1.89 (3H, d, *J* = 1.4 Hz), 1.56 (1H,

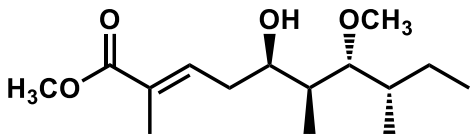
ddd, *J* = 12.9, 6.8, 5.1 Hz), 1.49 – 1.37 (1H, m), 1.23 – 1.11 (1H, m), 1.01 (3H, d, *J* = 6.8 Hz), 0.93 – 0.85 (6H, m) ^{13}C NMR (126 MHz, $CDCl_3$): (171.4, 153.4, 142.6, 138.2, 130.3, 129.3, 128.9, 126.3, 89.1, 70.0, 61.4, 58.6, 37.8, 36.2, 26.5, 17.2, 14.3, 13.6, 11.6) HRMS: $C_{21}H_{29}NO_4$ Found: [M+Na] 382.1987 , Calc: [M+Na] 382.1994, IR: 3680, 2972, 2873, 1784, 1243, 1057, 760



(2*R*,3*R*,4*S*)-3-methoxy-2,4-dimethylhexanal (30)

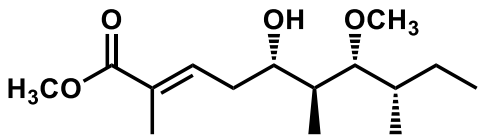
Methyl ether **29** (0.100 g, 0.278 mmol) was dissolved in DCM (12.5 mL) and the solution was cooled to -78°C. A gentle stream of ozone was bubbled through the solution for 30 min followed by oxygen for an additionally 30 min. Excess dimethyl sulfide (Me_2S) (1 mL) was added dropwise at -78 °C and warmed to room temperature. After stirring overnight and the solution was concentrated in vacuo. The product was purified with a short silica gel plug with ethyl acetate/hexanes (12%) to give 92% (0.0446 g) of aldehyde **30** as a clear oil and was immediately used in the next step.

δ_H(500 MHz, $CDCl_3$): 9.79 (1H, d, *J* = 2.5 Hz), 3.41 (3H, s), 3.24 (1H, dd, *J* = 6.8, 4.2 Hz), 2.63 (1H, pd, *J* = 7.0, 2.5 Hz), 1.59 (1H, dtd, *J* = 9.0, 4.3, 2.1 Hz), 1.54 – 1.42 (1H, m), 1.37 – 1.22 (1H, m), 1.06 (3H, d, *J* = 7.0 Hz), 0.98 – 0.88 (6H, m)



methyl (5*R*,6*S*,7*R*,8*S*,*E*)-5-hydroxy-7-methoxy-2,6,8-trimethyldec-2-enoate (31)

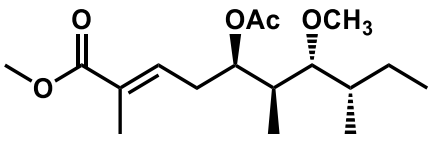
Magnesium dibromide etherate ($MgBr_2OEt_2$) (0.329 g, 1.275 mmol) was cooled to -78 °C and aldehyde **30** (0.044 g, 0.255 mmol) as a DCM-ether solution (9:1, 0.1 M, 2.5 mL) was added dropwise followed by the addition of neat TES-ketene acetal **25** (0.087 g, 0.383 mmol). After the mixture was stirred overnight at -78 °C, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ (1 mL). After transferring the reaction mixture to a separatory funnel, the mixture was extracted with DCM (3 × 20mL). The combined organic extract was dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and purified by flash chromatography using ethyl acetate/hexanes (20%) to give 79% yield (0.062 g) as a colorless oil. $[\alpha]_D^{25}$ -8.9° (c= 7.6 ,$CHCl_3$) δ_H(500 MHz, $CDCl_3$): 6.80 (1H, dddd, *J* = 8.4, 7.1, 3.0, 1.5 Hz), 4.05 (1H, ddd, *J* = 7.9, 5.9, 1.7 Hz), 3.72 (3H, s), 3.48 (3H, s), 3.03 – 2.96 (1H, m), 2.42 (1H, dddd, *J* = 14.1, 8.2, 7.0, 1.2 Hz), 2.24 (1H, dddd, *J* = 15.1, 7.9, 5.8, 1.0 Hz), 1.86 (3H, s), 1.78 – 1.71 (1H, m), 1.67 (1H, dtd, *J* = 8.8, 6.6, 4.2 Hz), 1.43 (1H, dddd, *J* = 14.9, 13.2, 6.7, 4.2 Hz), 1.21 – 1.08 (1H, m), 0.99 (3H, d, *J* = 7.1 Hz), 0.94 (3H, d, *J* = 6.8 Hz), 0.89 (3H, t, *J* = 7.4 Hz) ^{13}C NMR (126 MHz, $CDCl_3$): (168.5, 139.2, 129.1, 90.8, 70.7, 61.7, 51.8, 38.2, 37.6, 34.1, 26.6, 14.5, 12.7, 11.7, 11.54) IR: 3705, 2966, 2865, 1711, 1257, 1055, 1032, 732



methyl (5*S*,6*S*,7*R*,8*S*,*E*)-5-hydroxy-7-methoxy-2,6,8-trimethyldec-2-enoate (32)

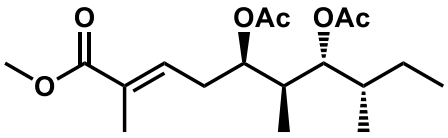
To a solution of alcohol **31** (0.036 g, 0.133 mmol) in DCM (1.5 mL) was cooled to 0 °C, and Dess martin periodinane (DMP) (0.169 g, 0.399 mmol) was added portion wise. After the

addition, the solution was stirred at 0 °C for 30 min, and srirred at room temperature overnight. After which the reaction mixture was cooled to 0 °C and quenched with saturated sodium sulfite solution (1 mL). The reaction mixture was extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography using ethyl acetate/hexanes (20%) to give 97% (0.035 g) of ketone as a colorless oil used immediately in the next step. A solution of ketone (0.035 g, 0.129 mmol) in MeOH (1.5 mL) was cooled to 0 °C, and $NaBH_4$ (0.015 g, 0.387 mmol) was added portionwise. After 25 min, the reaction was quenched by addition of 2M NaOH (1 mL). The reaction mixture was transferred into a separatory funnel and extracted with EtOAc (3 × 20mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography using ethyl acetate/hexanes (20%) to give 90% yield (0.032 g) of alcohol **32** as a colorless oil. $[\alpha]_D^{25}$ -55.5° (c= 4.2, $CHCl_3$) δ_H(500 MHz, $CDCl_3$): 6.96 (1H, ddq, *J* = 7.9, 6.4, 1.5 Hz), 4.10 – 3.89 (1H, broad, s), 3.79 (1H, td, *J* = 7.9, 3.4 Hz), 3.73 (3H, s), 3.48 (3H, s), 3.02 (1H, dd, *J* = 8.5, 2.4 Hz), 2.47 – 2.39 (1H, m), 2.31 (1H, dtd, *J* = 15.7, 7.9, 1.0 Hz), 1.86 (3H, q, *J* = 1.1 Hz), 1.82 – 1.71 (1H, m), 1.60 – 1.51 (1H, m), 1.46 (1H, dtd, *J* = 14.8, 7.4, 5.6 Hz), 1.39 – 1.28 (1H, m), 0.93 (3H, t, *J* = 7.4 Hz), 0.89 (3H, d, *J* = 6.8 Hz), 0.81 (3H, d, *J* = 6.9 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): (168.7, 139.5, 128.9, 91.2, 74.0, 61.4, 51.8, 41.5, 38.4, 33.7, 27.8, 14.7, 13.2, 12.8, 12.45). IR: 3705, 2966, 2864, 2075, 1789, 1686, 1345, 1200, 1057.



methyl (5*S*,6*S*,7*R*,8*S*,*E*)-5-acetoxy-7-methoxy-2,6,8-trimethyldec-2-enoate (33)

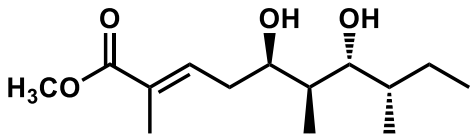
To a solution of alcohol **31** (25mg, 0.0919 mmol) and NaI (55 mg, 0.367 mmol) in ACN (1 mL) at 0 °C was added neat acetylchloride (26 µL, 0.367 mmol). The reaction mixture was stirred vigorously overnight. After cooling to 0 °C the reaction mixture was diluted with DCM (10 mL) and quenched with MeOH (1 mL). The reaction mixture was poured into a separatory funnel with water (5 mL) and extracted with DCM (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography using ethyl acetate/hexanes (10%) to give 3mg of title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.71 (ddt, *J* = 7.5, 6.0, 1.5 Hz, 1H), 5.33 – 5.26 (m, 1H), 3.73 (s, 3H), 3.40 (s, 3H), 2.88 (dd, *J* = 9.4, 2.0 Hz, 1H), 2.60 (dtd, *J* = 14.1, 7.0, 1.1 Hz, 1H), 2.44 – 2.34 (m, 1H), 2.06 (s, 3H), 1.91 – 1.81 (m, 3H), 1.76 – 1.64 (m, 1H), 1.57 – 1.41 (m, 1H), 1.37 – 1.26 (m, 1H), 1.18 – 1.03 (m, 1H), 0.93 – 0.83 (m, 12H).



(3*S*,4*R*,5*S*,6*S*,*E*)-10-methoxy-3,5,9-trimethyl-10-oxodec-8-ene-4,6-diyl diacetate (34)

To a solution of alcohol **31** (25mg, 0.0919 mmol) and NaI (55 mg, 0.367 mmol) in ACN (1 mL) at 0 °C was added neat acetylchloride (26 µL, 0.367 mmol). The reaction mixture was stirred vigorously overnight. After cooling to 0 °C the reaction mixture was diluted with DCM

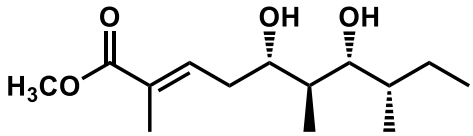
(10 mL) and quenched with MeOH (1 mL). The reaction mixture was poured into a separatory funnel with water (5 mL) and extracted with DCM (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography using ethyl acetate/hexanes (10%) to give 3 mg of title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (ddt, *J* = 9.8, 7.2, 1.5 Hz, 1H), 5.01 (ddd, *J* = 7.9, 6.7, 2.2 Hz, 1H), 4.89 (dd, *J* = 9.9, 2.6 Hz, 1H), 3.75 (s, 3H), 2.58 (dtd, *J* = 14.9, 6.9, 1.2 Hz, 1H), 2.44 – 2.31 (m, 1H), 2.03 (s, 3H), 2.02 (s, 3H), 1.88 (q, *J* = 1.1 Hz, 3H), 1.79 – 1.68 (m, 1H), 1.66 – 1.58 (m, 1H), 1.57 – 1.48 (m, 1H), 1.19 – 1.00 (m, 1H), 0.95 – 0.80 (m, 12H).



methyl (5*R*,6*S*,7*R*,8*S*,*E*)-5,7-dihydroxy-2,6,8-trimethyldec-2-enoate (35)

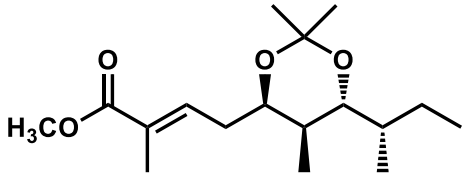
To a solution of alcohol **31** (0.292 g, 1.07 mmol) in DCM (56 mL) at -78°C was added a 15-crown-5 solution (0.3 M in DCM, 1.0 mL, 5.37 mmol,) saturated with NaI. A solution of BBr_3 (210 μL, 2.19 mmol) in DCM (41 mL) was then added dropwise at -78 °C. The reaction mixture was slowly warmed to 0°C over 3 h and stirred overnight at room temperature. The reaction mixture was diluted with ether (100 mL) and quenched with saturated aqueous NH_4Cl (10 mL) and 15% sodium thiosulfate (10 mL). The aqueous layer was extracted with ether (4 × 100 mL). The combined organic extracts were washed with saturated brine solution (50 mL), dried with anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography with EtOAc/hexanes (60%) to give diol 99% yield (0.273 g) of **35** as colorless oil. $[\alpha]_D^{25}$ +14.5° (c= 2.0, $CHCl_3$) δ_H(400 MHz,

$CDCl_3$): 6.85 (1H, tq, *J* = 7.3, 1.5 Hz), 4.13 – 3.99 (1H, m), 3.73 (3H, s), 3.55 (1H, dd, *J* = 7.4, 4.5 Hz), 2.47 (1H, dddd, *J* = 15.1, 8.5, 7.3, 1.1 Hz), 2.39 – 2.24 (1H, m), 1.86 (3H, dt, *J* = 9.1, 1.5 Hz), 1.62 – 1.16 (4H, m), 0.99 – 0.76 (12H, m). ^{13}C NMR (126 MHz, $CDCl_3$): (168.6, 139.3, 129.5, 77.9, 72.8, 51.9, 39.0, 37.1 33.1, 26.7, 12.9, 12.9, 11.9, 11.8).



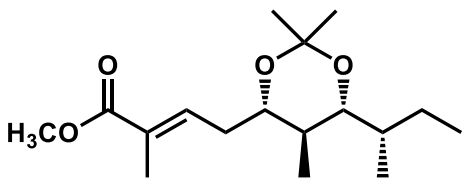
methyl (5*S*,6*S*,7*R*,8*S*,*E*)-5,7-dihydroxy-2,6,8-trimethyldec-2-enoate (36)

To a solution of alcohol **32** (0.026, g, 0.095 mmol) in DCM (4.6 mL) at -78 °C was added a 15-crown-5 solution (0.3 M in DCM, 100 μL, 0.537 mmol) saturated with NaI. A solution of BBr_3 (20 μL, 0.194 mmol) in DCM (2.8 mL) was then added dropwise to the reaction at -78 °C. The reaction was slowly warmed to 0°C over 3 h and stirred overnight at room temperature. The reaction mixture was diluted with ether (5 mL) and quenched with of saturated aqueous NH_4Cl (1 mL) and 15% sodium thiosulfate (1 mL). The aqueous layer was extracted with ether (4 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried with anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography using ethyl acetate/hexanes (60%) to give 71% (0.017 g) of diol **36** as a colorless oil. $[\alpha]_D^{25}$ +24.8° (c= 0.5, $CHCl_3$) δ_H(500 MHz, $CDCl_3$): 6.90 (^1H, ddd, *J* = 7.8, 6.5, 1.5 Hz), 3.85 – 3.76 (1H, m), 3.75 (3H, s), 3.72 – 3.63 (1H, m), 2.64 – 2.54 (1H, m), 2.36 (1H, ddt, *J* = 22.9, 15.2, 7.7 Hz), 1.93 – 1.81 (3H, m), 1.57 (2H, m), 1.52 – 1.31 (2H, m), 0.91 (3H, t, *J* = 7.4 Hz), 0.86 (3H, d, *J* = 7.3 Hz), 0.81 (3H, d, *J* = 6.7 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): (168.5, 137.8, 129.4, 79.1, 77.0, 51.9, 37.4, 35.9, 33.8, 26.8, 12.8, 12.5, 12.1, 11.6). IR: 3437, 2961, 1698, 1458.



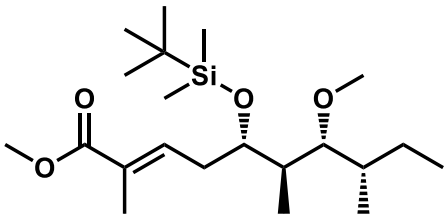
methyl (*E*)-4-((4*R*,5*S*,6*R*)-6-((*S*)-sec-butyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-2-methylbut-2-enoate (37)

Diol **35** (0.020 g, 0.0077 mmol) was dissolved is 2,2-dimethoxypropane (1 mL) at room temperature. The reaction mixture was charged with catalytic amounts of p-TsOH (4 mg, 0.023 mmol), sealed under argon atmosphere and the reaction mixture stirred for 4 h. Saturated $NaHCO_3$ (1.0 mL) was carefully added and the diluted with EtOAc (5.0 mL) and H_2O (5.0 mL). The layers were separated, and aqueous phase was extracted with EtOAc (3 × 5.0 mL). The combined organic extracts were washed with saturated brine solution (5 mL), dried with anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography using ethyl acetate/hexanes (1:20) to give 100% yield (0.0226 g) of **37** as a colorless oil. $[\alpha]_D^{25}$ +4.3° (c= 1.3, $CHCl_3$) δ_H(500 MHz, $CDCl_3$): 6.74 (^{1}H, ddd, *J* = 7.7, 6.2, 1.5 Hz), 3.88 (1H, ddd, *J* = 8.5, 6.0, 4.6 Hz), 3.73 (3H, s), 3.19 (1H, dd, *J* = 7.6, 3.3 Hz), 2.37 – 2.26 (1H, m), 2.22 (1H, dt, *J* = 15.3, 6.8 Hz), 1.86 – 1.84 (3H, s), 1.80 (1H, td, *J* = 7.1, 4.8 Hz), 1.50 – 1.37 (2H, m), 1.31 (6H, s), 1.27 – 1.19 (1H, m), 0.93 – 0.88 (6H, m), 0.86 (3H, d, *J* = 2.7 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): (168.6, 139.0, 129.0, 100.5, 77.2, 68.8, 51.9, 38.1, 36.5, 30.5, 26.3, 25.4, 23.6, 14.0, 12.9, 12.5, 12.2).



methyl (*E*)-4-((4*S*,5*S*,6*R*)-6-((*S*)-sec-butyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-2-methylbut-2-enoate (38)

The same procedure of synthesize **37** was used to produce 100 % yield (15.9 mg) of **38**. $[\alpha]_D^{25}$ +4.9° (c= 0.5, $CHCl_3$). δ_H(500 MHz, $CDCl_3$): 6.86 (^{1}H, td, *J* = 7.0, 1.6 Hz), 3.74 (3H, s), 3.57 (1H, ddd, *J* = 10.4, 7.7, 3.1 Hz), 3.45 (1H, dd, *J* = 10.2, 2.2 Hz), 2.48 (1H, dq, *J* = 16.2, 2.9 Hz), 2.29 (1H, dt, *J* = 15.8, 7.4 Hz), 1.84 (3H, d, *J* = 1.4 Hz), 1.55 – 1.41 (2H, m), 1.39 (3H, s), 1.33 (3H, s), 1.32 – 1.20 (2H, m), 0.87 (3H, t, *J* = 7.4 Hz), 0.83 (3H, d, *J* = 6.8 Hz), 0.74 (3H, d, *J* = 6.6 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): (168.8, 139.4, 128.7, 98.0, 75.4, 74.2, 51.9, 35.5, 35.1, 33.1, 30.1, 26.8, 19.6, 12.8, 12.5, 12.1, 11.9) IR: 3101, 2644, 1686, 1642, 1422, 1422, 1380, 1266, 952, 908, 866, 740.

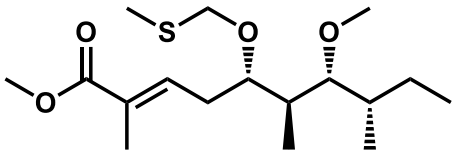


methyl (5*S*,6*R*,7*R*,8*S*,*E*)-5-((tert-butyldimethylsilyl)oxy)-7-methoxy-2,6,8-trimethyldec-2-enoate (39)[61]

To a solution of alcohol **32** (50 mg, 0.183 mmol) in of DCM (5 mL) was cooled to 0 °C. Neat TBSOTf (84 µL, 0.36 mmol) and 2,6 lutidine (42 µL, 0.369 mmol) was added dropwise at 0 °C and the solution was stirred overnight. The reaction mixture is cooled to 0 °C and quenched

with water (5 mL). The reaction mixture was transferred to a separatory funnel and the mixture was extracted with DCM (3 × 20 mL). The combined organic extract was washed with HCl (1M, 10 mL), brine (10 mL), dried over anhydrous sodium sulfate, filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography using EtOAc/hexanes (10%) to give 95% (67.4 mg) of **39** as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (td, *J* = 7.5, 1.6 Hz, 1H), 4.02 (dt, *J* = 7.9, 3.7 Hz, 1H), 3.73 (s, 3H), 3.39 (s, 3H), 2.91 (dd, *J* = 9.5, 2.3 Hz, 1H), 2.29 (t, *J* = 7.7 Hz, 2H), 1.87 – 1.83 (m, 3H), 1.52 – 1.43 (m, 2H), 1.35 (s, 2H), 0.94 (t, *J* = 7.3 Hz, 3H), 0.87 (s, 9H), 0.84 (t, *J* = 6.6 Hz, 6H), 0.03 (s, 3H), 0.02 (s, 3H)

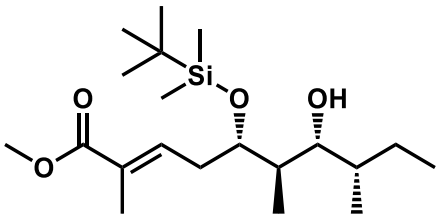


methyl (5*S*,6*S*,7*R*,8*S*,*E*)-7-methoxy-2,6,8-trimethyl-5-((methylthio)methoxy)dec-2-enoate (40)

To a solution of **32** (0.100 g, 0.36 mmol) in DMSO (2.5 mL) was added the mixture of Ac_2O (1.75 mL) and AcOH (0.312 mL) at room temperature. The solution was stirred for 2 days at room temperature. The reaction mixture was diluted with water (5 mL) and the solution was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with 5% aqueous phosphate (5 mL) buffer, brine (5 mL), dried over sodium sulfate, filtered, and the

solvent was removed under reduced pres sure. The crude residue was purified by flash chromatography using ethyl acetate/hexanes (10%) to give 81% yield (0.96 mg) of **40** as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 – 6.91 (m, 1H), 4.71 – 4.61 (m, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 4.05 – 3.98 (m, 1H), 3.73 (s, 3H), 3.40 (s, 3H), 2.89 (dd, *J* = 8.9, 2.9 Hz, 1H), 2.39 – 2.30 (m, 2H), 2.15 (s, 3H), 2.13 – 2.00 (m, 1H), 1.87 (q, *J* = 1.1 Hz, 3H), 1.56 – 1.41 (m, 3H), 1.40 – 1.27 (m, 1H), 0.94 (t, *J* = 7.3 Hz, 3H), 0.87 (dd, *J* = 6.9, 6.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.59, 140.57, 128.55, 86.56, 76.49, 73.33, 61.08, 51.75, 37.97, 37.61, 29.38, 27.68, 14.08, 12.97, 12.78, 12.34, 11.28.

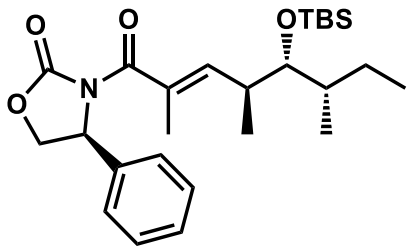


methyl (5*S*,6*R*,7*R*,8*S*,*E*)-5-((tert-butyldimethylsilyl)oxy)-7-hydroxy-2,6,8-trimethyldec-2-enoate (41)

To a solution of diol **36** (50 mg, 0.194 mmol) in DCM (5 mL) was cooled to 0 ℃. Neat TBSOTf (84 µL, 0.36 mmol) and 2,6 lutidine (42 µL, 0.369 mmol) was added dropwise at 0 ℃ and the solution was stirred overnight. The reaction is cooled to 0 ℃ and quenched with water (5 mL). The reaction mixture was transferred to a separatory funnel and the aqueous phase was

washed with DCM (3 × 20 mL). The combined organic extract was washed with HCl (1M, 10 mL), brine, dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography using ethyl acetate/hexanes (10%) to give 8.4 % yield (4 mg) of **41** as a clear oil.

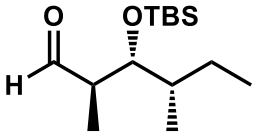
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (td, *J* = 7.4, 1.6 Hz, 1H), 4.01 (dt, *J* = 6.9, 4.7 Hz, 1H), 3.74 (s, 3H), 3.43 (dd, *J* = 9.7, 2.1 Hz, 1H), 2.44 – 2.34 (m, 2H), 1.87 – 1.83 (m, 3H), 1.80 – 1.72 (m, 2H), 1.61 (s, 1H), 1.54 – 1.21 (m, 2H), 0.95 – 0.90 (m, 3H), 0.89 (s, 9H), 0.83 (d, *J* = 6.7 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H), 0.08 (s, 3H), 0.06 (s, 3H).



(*S*)-3-((4*S*,5*R*,6*S*,*E*)-5-((tert-butyldimethylsilyl)oxy)-2,4,6-trimethyloct-2-enoyl)-4-phenyloxazolidin-2-one (42)

To a solution of alcohol **28** (0.400 g, 1.15 mmol) DCM (40 mL) was cooled to 0 ℃ and freshly distilled 2,6-Lutidine (0.33 mL , 2.30 mmol, 2.0 equiv) was added followed by neat TBS-OTf (0.55 mL, 2.30 mmol) at 0 ℃. The reaction mixture was stirred overnight at room temperature. The reaction mixture was cooled to 0 ℃ and quenched with water (20 mL). The reaction was transferred to a separatory funnel and extracted with DCM (3 × 100 mL). The combined organic extracts were washed with HCl (1M, 100 mL), brine (100 mL), dried over

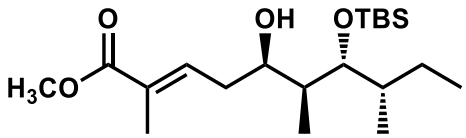
anhydrous sodium sulfate, filtered, and the solvent removed under reduced pressure. The crude residue was purified by flash chromatography using ethyl acetate/hexanes (20%) to give 92% yield (0.490 g) of **42** as a white solid. $[\alpha]_D^{25}$ +10.0° (c= 5.5, $CHCl_3$) δ_H(500 MHz, $CDCl_3$): 7.41 – 7.30 (5H , m), 6.29 (1H, dq, *J* = 9.7, 1.4 Hz), 5.44 (1H, dd, *J* = 8.7, 6.9 Hz), 4.68 (1H, t, *J* = 8.8 Hz), 4.20 (1H, dd, *J* = 8.8, 6.9 Hz), 3.47 (1H, dd, *J* = 4.7, 3.0 Hz), 2.70 (1H, dqd, *J* = 10.0, 7.0, 3.1 Hz), 1.88 (3H, d, *J* = 1.4 Hz), 1.54 – 1.42 (2H, m), 1.09 – 1.02 (1H, m), 1.00 (3H, d, *J* = 6.9 Hz), 0.91 (9H, s), 0.87 (3H, d, *J* = 6.8 Hz), 0.85 (3H, t, *J* = 7.2 Hz), 0.05 (3H, s), 0.04 (3H, s). ^{13}C NMR (126 MHz, $CDCl_3$): (171.5, 153.4, 142.9, 138.2, 129.4, 129.3, 128.8, 126.3, 79.7, 70.0, 58.5, 40.1, 36.5, 26.2, 25.9, 18.5, 18.2, 15.4, 13.5, 12.2, -3.6, -3.9). HRMS: $C_{26}H_{41}NO_4Si$ Found: [M+Na] 482.2695, Calc: [M+Na] 482.2702.



(2*R*,3*R*,4*S*)-3-((tert-butyldimethylsilyl)oxy)-2,4-dimethylhexanal (43)

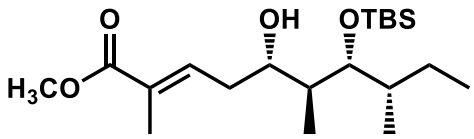
Silyl ether **42** (0.100 g, 0.217 mmol) was dissolved in DCM (12.5 mL) and the solution was cooled to -78 °C. A gentle stream of ozone was bubbled through the solution for 30 minutes followed by oxygen for an additionally 30 min. Excess dimethyl excess (Me_2S) (1 mL) was added dropwise at -78 °C and warmed to room temperature. After stirring overnight and solution was concentrated under reduced pressure. The product was purified with a short silica gel plug using ethyl acetate/hexanes (10%) to give 94% yield (0.204 mg) of aldehyde **43** as a clear oil. $[\alpha]_D^{25}$ -31.5° (c= 6.4, $CHCl_3$) δ_H(500 MHz, $CDCl_3$): 9.77 (1H, d, *J* = 2.9 Hz), 3.76 (1H, dd, *J* = 4.6, 3.8 Hz), 2.54 (1H, ddd, *J* = 7.3, 4.6, 2.8 Hz), 1.50 (2H, dp, *J* = 11.9, 4.6 Hz), 1.13 – 1.09 (1H, m), 1.08 (3H, d, *J* = 7.1 Hz), 0.90 (3H, d, *J* = 6.9 Hz), 0.90 (3H, t, *J* = 6.9 Hz), 0.88 (9H, s),

0.06 (3H, s), 0.05 (3H, s). ^{13}C NMR (126 MHz, $CDCl_3$): (205.5, 78.3, 50.0, 40.1, 26.1, 25.8, 18.4, 14.6, 12.5, 12.3, -3.9, -4.2).



methyl (5*R*,6*S*,7*R*,8*S*,*E*)-7-((tert-butyldimethylsilyl)oxy)-5-hydroxy-2,6,8-trimethyldec-2-enoate (44)

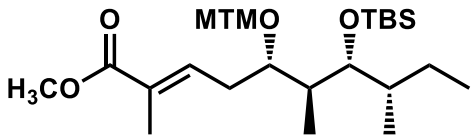
To a stirring solution of aldehyde **43** (0.742 g, 2.87 mmol) at -78 °C and ketene acetal **26** (1.64 g, 7.19 mmol, 2.5 mmol) in DCM/Ether (9:1, 27 mL)) was added neat BF_3 (0.89 mL, 7.19 mmol) dropwise. The solution was stirred overnight at -78 °C. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The reaction mixture was transferred to a separatory funnel and extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography using ethyl acetate/hexanes (20%) to give 82% yield (0.875 mg) of **44** as a colorless oil. $[\alpha]_D^{25}$ +9.7° (c= 3.5, $CHCl_3$). δ_H(500 MHz, $CDCl_3$): 6.79 (1H, td, *J* = 7.7, 6.7, 0.9 Hz), 4.22 (1H, t, *J* = 7.3 Hz), 3.73 (3H, s), 3.58 (1H, dd, *J* = 5.9, 2.7 Hz), 3.51 (1H, s), 2.42 (1H, dt, *J* = 14.8, 7.1 Hz), 2.22 (1H, dt, *J* = 14.8, 7.0 Hz), 1.89 – 1.84 (3H, m), 1.66 (2H, td, *J* = 7.3, 6.2, 2.5 Hz), 1.62 – 1.50 (1H, m), 1.12 (1H, ddd, *J* = 11.1, 8.6, 6.1 Hz), 1.02 (3H, d, *J* = 7.2 Hz), 0.92 (9H, s), 0.91 – 0.86 (6H, m), 0.12 (3H, s), 0.10 (3H, s). ^{13}C NMR (126 MHz, $CDCl_3$): (168.6, 139.1, 129.2, 82.9, 70.6, 51.9, 40.0, 38.0, 34.5, 26.3, 25.8, 18.4, 16.0, 12.8, 12.4, 12.2, -3.7, -3.8). HRMS: $C_{20}H_{40}O_4Si$ Found: [M+H] 373.2728, Calc: [M+H] 373.2774. IR: 3705, 2965, 2075, 1788, 1688, 1313, 1053.



methyl (5*S*,6*S*,7*R*,8*S*,*E*)-7-((tert-butyldimethylsilyl)oxy)-5-hydroxy-2,6,8-trimethyldec-2-enoate (45)

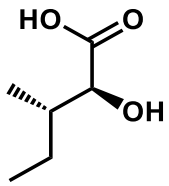
To a solution of alcohol **44** (1.52 g, 4.09 mmol) in DCM (100 mL) was cooled to 0 ℃, and (dess martin periodinane) DMP (5.2 g, 12.3 mmol) was added portionwise. After the addition, the solution was stirred at 0 ℃ for 30 min, and at room temperature overnight. After which the reaction mixture was cooled to 0 ℃ and quenched with saturated sodium sulfite solution (50 mL). The reaction mixture was transferred to a separatory funnel and extracted with DCM (3 ×50 mL). The combined organic extracts were washed with of brine (100 mL), dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography using ethyl acetate/hexanes (20%) to give 88% yield (1.34 g) of ketone as a colorless oil and used immediately without further purification. A solution of ketone (1.34 g, 3.59 mmol) in of MeOH (48 mL) was cooled to 0 ℃, and $NaBH_4$ (573 mg, 19.85 mmol) was added portion wise. After 25 min, the reaction was quenched by the addition of NaOH (2 M, 100 mL). The reaction mixture was transferred to a separatory funnel and extracted with EtOAc (3 × 100 mL). The combined organic extract was washed with brine (100 mL), dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography using ethyl acetate/hexanes (20%) to give 90% yield (1.20 g) of alcohol **45** as a colorless oil. $[\alpha]_D^{25}$ +9.2° (c= 2.4, $CHCl_3$) δ_H(400 MHz, $CDCl_3$): 6.93 (1H, t, *J* = 7.0 Hz), 3.71 (3H, s), 3.69 – 3.56 (1H, m), 3.50 (1H, dd, *J* = 5.8, 3.3 Hz), 2.41 (1H, dt, *J* = 15.9, 4.8 Hz), 2.27 (1H, dt, *J* = 15.7, 7.7 Hz), 1.84 (3H, s), 1.73 (1H, h, *J* = 7.2 Hz), 1.50 – 1.36 (1H, m), 1.29 – 0.97 (2H, m), 0.90 (9H, s),

0.89 – 0.85 (6H, m), 0.83 (3H, d, *J* = 7.0 Hz), 0.10 (3H, s), 0.07 (3H, s). ^{13}C NMR (126 MHz, $CDCl_3$): (168.6, 139.4, 129.1, 81.3, 73.1, 51.8, 42.1, 40.8, 33.7, 26.2, 26.1, 18.4, 16.1, 14.5, 12.8, 12.3, -3.8, -4.1). IR: 3705, 2972, 2075, 1712, 1510, 1359, 1057, 833.



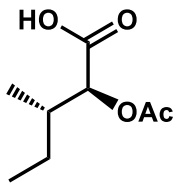
methyl (5*S*,6*S*,7*R*,8*S*,*E*)-7-((tert-butyldimethylsilyl)oxy)-2,6,8-trimethyl-5-((methylthio)methoxy)dec-2-enoate (46)

To a solution of **45** (0.593 g, 1.6 mmol) in 5.0 mL of DMSO was added the mixture of Ac_2O (3.5 mL) and AcOH (0.625 mL) at room temperature. The solution was stirred for 2 days at room temperature. The reaction mixture was diluted with water (10 mL) and transferred to a separatory funnel. The reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic extract was washed with 5% aqueous phosphate (10 mL) buffer, brine (10 mL), dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography using ethyl acetate/hexanes (10%) to give 86% yield (0.576 g) of **46** as a colorless oil. $[\alpha]_D^{25}$ -38.4° (c= 3.7, $CHCl_3$). δ_H(500 MHz, $CDCl_3$): 6.93 (^{1}H, t, *J* = 6.9 Hz), 4.63 (1H, d, *J* = 11.6 Hz), 4.54 (1H, d, *J* = 11.6 Hz), 3.99 (1H, dd, *J* = 8.4, 4.6 Hz), 3.73 (3H, s), 3.52 (1H, dd, *J* = 6.8, 2.9 Hz), 2.37 (1H, s), 2.35 – 2.26 (1H, m), 2.16 (3H, s), 2.06 – 1.98 (1H, m), 1.85 (3H, q, *J* = 1.2 Hz), 1.50 – 1.41 (1H, m), 1.25 – 1.15 (1H, m), 1.10 – 1.01 (1H, m), 0.91 (9H, s), 0.91 – 0.86 (9H, m), 0.06 (3H, s), 0.05 (3H, s). ^{13}C NMR (126 MHz, $CDCl_3$): (168.6, 140.3, 128.6, 77.3, 76.2, 73.2, 51.8, 39.3, 38.8, 29.4, 27.3, 26.3, 26.0, 18.6, 14.2, 13.9, 12.6, 11.5, -3.5, -3.6).



2*S*-Hydroxy-3*S*-methylpentanoic acid (51)

L-isoleucine (10.0 g, 76.2 mmol) was dissolved in H_2SO4 (1 M, 200 mL) and the solution was cooled to ~0 ºC using an ice-water bath. Sodium nitrite (42.1 g, 610 mmol) was dissolved in water (200 mL) and then slowly added to the cold stirred amino acid solution over 4 h. The reaction was allowed to warm to ambient temperature and the mixture continued to stir for 18 h. The aqueous solution was then saturated with sodium chloride, transferred to a separatory funnel and extracted with EtOAc (3 × 75 mL). The combined organic extracts were washed with water (2 × 100 ml), brine (2 x 100 mL), dried over anhydrous sodium sulfate, filtered, and the solvent removed under reduced pressure to give 99% yield (9.97 g) of **51** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.19 (d, *J* = 3.6 Hz, 1H), 1.95–1.84 (m, 1H), 1.50–1.38 (m, 1H), 1.37–1.24 (m, 1H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.93 (t, *J* = 7.5 Hz, 3H).

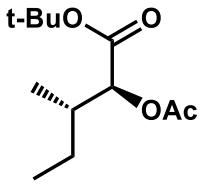


(2*S*,3*S*)-2-acetoxy-3-methylpentanoic acid (52)

Neat acetyl chloride (23 mL) was slowly added to hydroxyisoleucic acid **51** (10.7 g, 81 mmol) under argon with bubbler charged with saturated aqueous sodium carbonate. The solution was refluxed until HCl gas no longer evolved and stirred at ambient temperature for 18 h. The reaction was diluted in CH_2Cl_2 (200 mL). With vigorous stirring, water was slowly added (50

mL), and the mixture was stirred for 2 h. The reaction mixture was transferred to a separatory funnel, the organic layer was then separated and washed with water (100 mL), brine (100 mL), dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure to give 90% yield (12.7 g) of **45** as colorless oil.

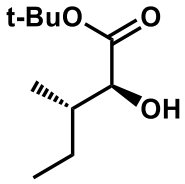
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (d, *J* = 4.5 Hz, 1H), 2.16 (s, 3H), 2.07 – 1.96 (m, 1H), 1.54 (dtd, *J* = 14.9, 7.4, 4.8 Hz, 1H), 1.41 – 1.25 (m, 1H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.95 (t, *J* = 7.5 Hz, 3H).



tert-butyl (2*S*,3*S*)-2-acetoxy-3-methylpentanoate (53)

Ester **52** (5.0 g, 28.7 mmol) was dissolved in anhydrous t-BuOH (75 mL) under argon atmosphere. BOC anhydride (9.4 g 43 mmol) and DMAP (0.88 g, 7.2 mmol) was added and the reaction was stirred for 14 h. Volatiles was removed under reduced pressure and the crude residue was dissolved in diethyl ether (100 mL) and transferred to a separatory funnel. The organic layer was washed with water (2 × 100 mL), brine (100 mL), dried over anhydrous sodium sulfate, filtered, and the organic layer removed under reduced pressure and the residue was purified by flash chromatography to give 89% yield (4.44 g) of **53** as a colorless oil.

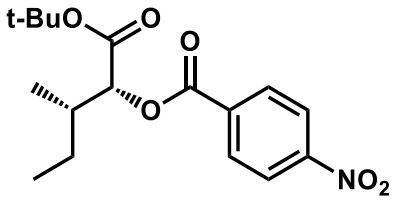
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (d, *J* = 4.6 Hz, 1H), 2.12 (s, 3H), 1.93 (dqt, *J* = 9.2, 6.9, 4.6 Hz, 1H), 1.59 – 1.41 (m, 1H), 1.47 (s, 9H), 1.37 – 1.23 (m, 1H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.93 (t, *J* = 7.5 Hz, 3H).



tert-butyl (2*S*,3*S*)-2-hydroxy-3-methylpentanoate (54)

A mixture of MeOH (50 mL), water (72 mL), and K_2CO_3 (18 g, 130 mmol), **53** (10.0 g, 43.4 mmol) were dissolved and stirred vigorously. The reaction was monitored by TLC and after 2 days, the mixture was extracted CH_2Cl_2 (3 × 100 mL) The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and solvent was removed under reduced pressure. The residue was distilled in vacuo to give 8.0 g (dr 93:7, 98%) of **54** as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (ddd, J = 5.6, 3.5, 2.0 Hz, 1H), 2.83 – 2.76 (m, 1H), 1.76 (ddddd, J = 9.1, 6.9, 4.6, 3.6, 2.2 Hz, 1H), 1.48 (dd, J = 2.3, 1.2 Hz, 9H), 1.43 – 1.31 (m, 1H), 1.30 – 1.17 (m 1H), 0.96 (dd, J = 6.9, 2.2 Hz, 3H), 0.93 – 0.86 (m, 3H).

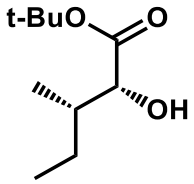


1-(tert-Butoxy)-3*S*-methyl-1-oxopentan-2*R*-yl-4-nitrobenzoate (55)

An oven-dried two-necked round-bottom flask (250 mL) was charged under an argon atmosphere with alcohol **54** (1.50 g, 7.97 mmol), 4-nitrobenzoic acid (2.24 g, 13.5 mmol), and

triphenylphosphine (3.55 g, 13.5 mmol) in freshly distilled THF (50 mL). The homogenous reaction mixture was stirred and cooled to 0 ºC using an ice-water bath. Diisopropyl azodicarboxylate, (13.5 mmol) was added dropwise by syringe, maintaining the reaction temperature below 10 ºC. The reaction was allowed to warm to ambient temperature and stirred for an additional 18 h. The reaction was quenched with saturated sodium bicarbonate (20 mL). The THF was removed under reduced pressure and the residue was transferred to a separatory funnel and the aqueous phase was extracted with EtOAc (3 × 150 mL). The combined organic extracts were washed with water (3 × 50 mL), brine (50 mL), dried over anhydrous sodium sulfate, filtered, and the organic solvent was removed under reduced pressure and the crude product purified by flash chromatography using ethyl acetate/hexane (0–20%) to afford 82% (2.20 g) of **55** as a bright yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.8 Hz, 2H), 8.24 (d, *J* = 8.8 Hz, 2H), 5.19 (d, *J* = 3.2 Hz, 1H), 2.16–2.12 (m, 1H), 1.57–1.49 (m, 1H), 1.48 (s, 9H), 1.46–1.33 (m, 1H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.99 (t, *J* = 7.4 Hz, 3H)

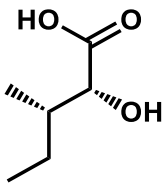


tert-butyl (2*R*,3*S*)-2-hydroxy-3-methylpentanoate (47)

Ester **55** (3.05 g, 9.04 mmol) was dissolved in anhydrous methanol (25 mL) and cooled to 0 ºC with an ice-water bath. Solid anhydrous K_2CO_3 (1.88 g, 13.6 mmol) was added in one portion and the resulting mixture stirred vigorously for 1 h. Water (25 mL) was added and the reaction mixture was rapidly stirred until the solids dissolved. Methanol was then removed under

reduced pressure. The residue was transferred to a separatory funnel and extracted with EtOAc (4 x 15 mL). The combined organic extracts were washed with brine (50 mL), then dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified on a silica gel column using DCM/toluene (0-10%) to give 61% yield (1.03 g) of **47** as colorless oil.

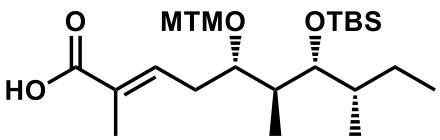
^{1}H NMR (500 MHz, $CDCl_3$) d 4.04 (dd, *J* = 5.6, 2.8 Hz, 1H), 2.74 (d , *J* = 5.6 Hz, 1H), 1.77 (dtq, *J* = 6.9, 6.9, 2.8 Hz, 1H), 1.58-1.46 (m, 1H), 1.49 (s, t Bu, 9H), 1.37-1.25 (m, 1H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H)



(2*R*,3*S*)-2-hydroxy-3-methylpentanoic acid (56)

To **47** (30 mg, 0.105 mmol) dissolved in DCM (1 mL) was cooled to 0 °C. TFA (0.1 mL) was added dropwise and the solution was stirred overnight. The volatiles were removed under reduced pressure to give free acid **56** which was used without further purification.

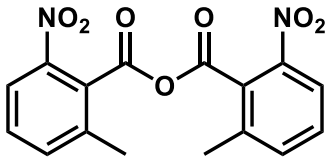
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.29 (d, *J* = 2.8 Hz, 1H), 1.90 (qd, *J* = 6.9, 2.7 Hz, 1H), 1.55 (dp, *J* = 14.6, 7.3 Hz, 1H), 1.36 (dt, *J* = 13.7, 7.4 Hz, 1H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H).



(5*S*,6*S*,7*R*,8*S*,*E*)-7-((tert-butyldimethylsilyl)oxy)-2,6,8-trimethyl-5-((methylthio)methoxy)dec-2-enoic acid (57)

To a solution of **46** (0.156 g, 0.361 mmol) in MeOH (2.35 mL) and THF (2.35 mL) was added LiOH (1 M, 2.35 mL) at 0 °C dropwise. The reaction mixture was stirred for 2 days. The mixture was cooled to 0 °C, diluted with EtOAc (10 mL), and HCl (1 M, 10 mL) was slowly added. The mixture was transferred to a separatory funnel was extracted EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography using ethyl acetate/hexanes (10%) to give 80% yield (0.120 g) of **57** as a colorless oil.

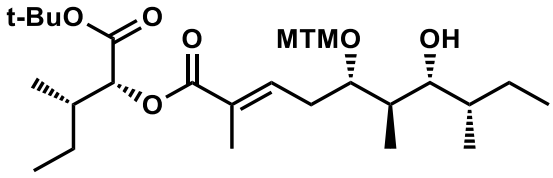
$[\alpha]_D^{25}$ -67.3° (c= 2.2, $CHCl_3$). δ_H(500 MHz, $CDCl_3$): 7.08 (1H, t, *J* = 6.8 Hz), 4.63 (1H, d, *J* = 11.6 Hz), 4.53 (1H, d, *J* = 11.6 Hz), 4.03 (1H, dt, *J* = 9.7, 3.4 Hz), 3.55 – 3.45 (1H, m), 2.38 (1H, s), 2.33 (1H, dt, *J* = 16.7, 8.5 Hz), 2.16 (3H, s), 2.06 – 1.99 (1H, m), 1.85 (3H, d, *J* = 1.5 Hz), 1.52 (1H, m), 1.45 (1H, dt, *J* = 12.3, 6.0 Hz), 1.30 – 1.12 (1H, m), 0.91 (9H, s), 0.91 – 0.86 (9H, m), 0.06 (3H, s), 0.05 (3H, s). ^{13}C NMR (126 MHz, $CDCl_3$): (173.5, 143.2, 128.1, 77.3, 76.0, 73.18, 39.1, 38.9, 29.6, 27.2, 26.3, 26.1, 18.6, 14.2, 13.9, 12.6, 11.5, -3.4, -3.5). IR: 3705, 2965, 2863, 2072, 1682, 1250, 1054, 1031.



2-methyl-6-nitrobenzoic anhydride (51a)[62]

A solution of 2-methyl-6-nitrobenzoic acid (5.00 g, 27.6 mmol) and thionyl chloride (20.1 mL, 276 mmol) in DCM (50 mL) was stirred for 15 h at room temperature. The solvent and thionyl chloride were distilled under reduced pressure at 50 °C and then DCM (40 mL), 2-methyl-6- nitrobenzoicacid (5.00 g, 27.6 mmol), and pyridine (2.40 mL, 30.4 mmol) were successively added at 0 °C. After the reaction mixture had been stirred for 24 h at room temperature, cooled water (100 mL) was added at 0 °C. The mixture was transferred to a separatory funnel and was extracted with DCM (100 mL), and the organic extracts were washed with saturated aqueous copper(II) sulfate, saturated aqueous sodium hydrogen carbonate, cold water, and brine, and dried over sodium sulfate. Filtration of the mixture and evaporation of the solvent under reduced pressure produced 8.80 g of the crude 2-methyl-6-nitrobenzoic anhydride (MNBA). The first recrystallization of the crude product from dichloromethane (ca. 90 mL) at 0 °C gave 81% yield (7.70 g) of pure MNBA as a white solid.

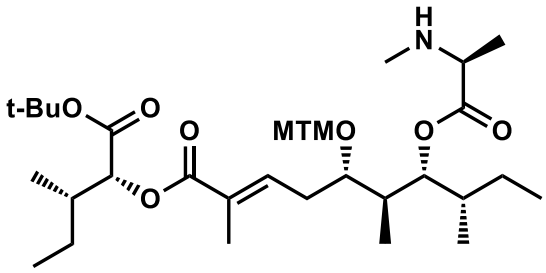
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 – 8.04 (m, 2H), 7.62 (dt, *J* = 7.6, 0.9 Hz, 2H), 7.54 (t, *J* = 8.0 Hz, 2H), 2.57 (s, 6H).



(2*R*,3*S*)-1-(tert-butoxy)-3-methyl-1-oxopentan-2-yl (5*S*,6*R*,7*R*,8*S*,*E*)-7-hydroxy-2,6,8-trimethyl-5-((methylthio)methoxy)dec-2-enoate (59)

Acid **57** (0.220 g, 0.523 mmol) and MNBA (0.317 g, 0.916 mmol) were dissolved in DCM (1.7 mL) and cooled to 0 °C. DMAP (0.192 g, 1.57 mmol), and t-butyl ester of allo-D-isoleucic acid (0.197 g, 1.05 mmol) in DCM (1.7 mL) was added dropwise at 0 °C. After stirring

overnight, the reaction mixture was cooled to 0 °C and quenched with of HCl (1M, 5 mL). The reaction mixture was diluted with H_2O (10 mL), transferred to a separatory funnel, and extracted using DCM (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), the organic extracts were dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography using ethyl acetate/hexanes (10%) to give ester **23** which was used in the next step without further purification. To a solution of **23** (0.523 mmol) in THF (3.5 mL) and Pyridine (0.87 mL), the solution is cooled to 0 °C. HF-Pyridine (2.18 mL) was added dropwise and stirred overnight. The solution was cooled to 0 °C and diluted with EtOAc (50 mL), poured into saturated aqueous solution $NaHCO_3$ (100 mL) at 0 °C, and stirred till gas evolution has ceased. The mixture is extracted using EtOAc (3 × 75mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography using ethyl acetate/hexanes (30%) to give 53% yield (0.131 g) of alcohol **59** as a colorless oil. $[\alpha]_D^{25}$ +13.1° (c= 3.6, $CHCl_3$). δ_H(500 MHz, $CDCl_3$): 7.01 (1H, td, J=7.2, 1.5 Hz), 4.96 (1H, d, J=3.3 Hz), 4.64 (2H, d, J=2.8 Hz), 4.10 (1H, dt, J=7.2, 4.7 Hz), 3.41 (1H, d, J=9.7 Hz), 2.53 – 2.45 (1H, m), 2.40 (1H, dt, J=15.5, 7.4 Hz), 2.24 (1H, s), 2.16 (3H, s), 1.98 (1H, m), 1.89 (3H, d, J=1.3 Hz), 1.52 - 1.37 (2H, m), 1.46 (9H, s), 1.37 – 1.17 (3H, m), 0.98 (3H, d, *J*=6.9 Hz), 0.93 (3H, t, *J*=7.7 Hz), 0.91 (3H, t, *J*=7.7 Hz), 0.84 (6H, d, *J*=6.8 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): (169.4, 167.5, 140.3, 128.7, 81.9, 78.6, 75.9, 75.1, 73.7, 38.8, 36.9, 36.8, 29.8, 28.2, 27.3, 26.3, 14.5, 14.4, 12.8, 12.2, 11.8, 11.7, 11.6). IR: 3705, 2966, 2075, 1711, 1412, 1370, 1061, 1012. HRMS: $C_{25}H_{46}O_6S$ Found: [M+H] 475.3091, Calc: [M+H] 475.3093.

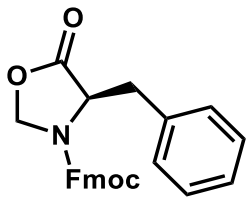


(2*R*,3*S*)-1-(tert-butoxy)-3-methyl-1-oxopentan-2-yl (5*S*,6*S*,7*R*,8*S*,*E*)-2,6,8-trimethyl-7-((methyl-L-alanyl)oxy)-5-((methylthio)methoxy)dec-2-enoate (2)

To a solution of Fmoc-L-MeAla-OH (115 mg, 0.354 mmol) in DCM (2 mL) was added DMF (1 drop) and $SOCl_2$ (0.27 mL) at room temperature. After stirring for 1 hr the volatiles were removed under reduced pressure. A solution of alcohol **59** (56 mg, 0.118 mmol) in 1,2-dichloromethane (1.1 mL) was added to the acid chloride prepared. The solution is cooled to 0 °C and freshly distilled N,N-Diisopropylethylamine (0.112 mL, 0.638 mmol) was added. The solution was warmed to 40 °C and stirred overnight. The reaction mixture was cooled to 0 °C and quenched with saturated aqueous $NaHCO_3$ (1 mL). The mixture is extracted with DCM (3 × 10 mL). The combined organic extract was washed brine (10 mL), dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The residual material was dissolved in ACN (7 mL) and cooled to 0 °C and diethylamine (2.3 mL) is added dropwise. The reaction is stirred for 30 minutes, the volatiles are removed under reduced pressure. The crude residue was purified by flash chromatography using EtOAc (100%) to give 65% yield (43mg) of amine **2** as a light-yellow oil.

$[\alpha]_D^{25}$ -55.3° (c= 21.7, $CHCl_3$). δ_H(500 MHz, $CDCl_3$): 6.87 (^{1}H, t, *J*=7.1 Hz), 4.93 (1H, d, *J*=2.6 Hz), 4.91 (1H, d, *J*=3.5 Hz), 4.62 (1H, d, *J*=11.7 Hz), 4.52 (1H, d, *J*=11.7 Hz), 3.75 (1H, d, *J*=9.8 Hz), 3.29 (1H, q, *J*=7.0 Hz), 2.40 (3H, s), 2.36 – 2.24 (1H, m), 2.19 (1H, q, *J*=6.9, 6.0 Hz), 2.09

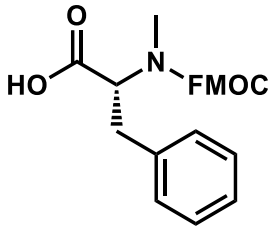
(3H, s), 2.01 – 1.92 (2H, m), 1.89 (3H, s), 1.72 – 1.59 (1H, m), 1.44 (9H, s), 1.44 – 1.38 (1H, m), 1.33 (3H, d, *J*=7.1 Hz), 1.31 – 1.22 (3H, m), 1.15 (1H, dt, *J*=14.3, 7.4 Hz), 0.95 (3H, d, *J*=6.9 Hz), 0.94 – 0.87 (12H, m). ^{13}C NMR (126 MHz, $CDCl_3$): (175.5, 169.2, 167.5, 140.5, 128.8, 81.7, 77.0, 75.2, 75.0, 73.11, 58.7, 36.8, 36.3, 36.1, 34.9, 28.8, 28.1, 27.0, 26.2, 19.6, 14.4, 14.1, 12.8, 12.6, 12.1, 11.8, 10.4). HRMS: $C_{29}H_{53}NO_7S$ Found: [M+H] 560.3670, Calc: [M+H] 560.3621.



(2*S*)-N-Fluorenylmethyloxycarbonyl-2-aminomethyl-3-phenylpropanoic acid (Fmoc-N-methylphenylalanine) (60)[63]

The title compound was produced during the general procedure for N-methylation of Fmoc-protected amino acids to afford **60**.

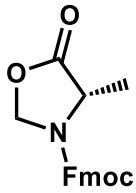
^{1}H NMR (400 MHz, $CDCl_3$) 7.76 (2H, d, *J* = 6.6 Hz), 7.62-7.48 (2H, m), 7.41 (2H, t, *J* = 7.2 Hz), 7.35 (2H, t, *J* = 6.6 Hz), 7.25-7.13 (4H, m), 6.71 (1H, s), 5.07 (2H, s), 4.69 (1H, dd, *J* = 5.1, 10.5 Hz,), 4.51 (1H, s), 4.25 (1H, t, *J* = 5.1 Hz), 4.12-3.98 (1H, m), 3.39-2.42 (2H, m).



N-(((9H-fluoren-9-yl)methoxy)carbonyl)-N-methyl-D-phenylalanine (61)[64]

Following the procedure described in the preparation of Fmoc-N-Me-Ala-OH (**63**), this compound was prepared from Fmoc-D-Phe-OH.

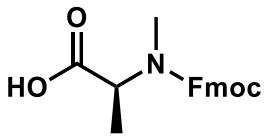
^{1}H NMR (400 MHz, $CDCl_3$): 7.75–6.95 (13H,m), 4.95 (1H, dd, *J* = 10.8, 4.7 Hz), 4.39–4.31 (2H, m), 4.20 (1H, t, *J* = 7.0 Hz), 3.40 (1H, dd, *J* = 14.5, 4.6 Hz), 3.15–3.09 (1H, m), 2.80 (3H, s).



(9H-fluoren-9-yl) methyl (*S*)-4-methyl-5-oxooxazolidine-3-carboxylate (62)[63]

The title compound was produced during the general procedure for N-methylation of Fmoc-protected amino acids to afford **62**.

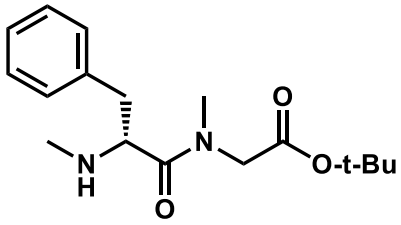
^{1}H NMR existed as rotational conformers (400 MHz, $CDCl_3$) δ 7.78 (m, 2H), 7.62 – 7.49 (m, 2H), 7.44 – 7.39 (m, 2H), 7.36 – 7.31 (m, 2H), 5.36 - 5.14 (m, 2H), 4.61 (s, 2H), 4.24 - 3.89 (m, 2H), 1.48 - 1.16 (m, 3H).



N-(((9H-fluoren-9-yl)methoxy)carbonyl)-N-methyl-L-alanine (63)[65]

The oxazolidinone from Fmoc-L-Ala **62** (0.97 g, 3.0 mmol) was dissolved in $CHCl_3$ (15 mL), trifluoroacetic acid (15 mL), and triethylsilane (1.43 mL, 9.0 mmol) were added. The mixture was stirred at room temperature for 22 h followed by concentration under reduced pressure to an oil. The oil was dissolved in CH_2Cl_2 and reconcentrated three times under reduced pressure. The resultant oil crystallized on standing. The crystals were dissolved in ether and concentrated to a crystalline solid which was washed with 5% ether in hexane and dried to give 98% yield (0.96 g) of **63** as white crystals.

^{1}H NMR existed as rotational conformers (400 MHz, $CDCl_3$) δ 9.78 (br s), 7.2-7.8 (m, 8H), 4.2-5.0 (m, 4H), 2.92 (s, 3H), 1.43 (d, 3H, *J* = 7.5 Hz).

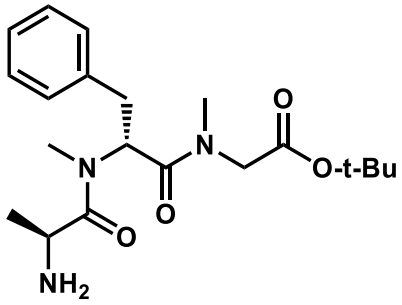


tert-butyl N-methyl-N-(methyl-D-phenylalanyl)glycinate (67)

To a solution of Fmoc-N-methyl-D-Phe-OH (2.5 g, 6.23 mmol) in DCM (35 mL) was added DMF (1 drop) and $SOCl_2$ (4.6 mL) at room temperature and stirred overnight. The volatiles were removed under reduced pressure. A solution of HCl salt of Sar-O-tBu (1.15 g, 6.23 mmol) was added in 1,2-dichloromethane (35 mL) to the acid chloride prepared. The solution was cooled to 0 °C and freshly distilled N,N-Diisopropylethylamine (2.7 mL, 15.57mmol) is added. The solution is stirred overnight. The reaction mixture is cooled to 0 °C and quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture is extracted DCM (3 × 25

mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The material was dissolved in ACN (75 mL) and cooled to 0 °C and diethylamine (25 mL) was added dropwise. The reaction mixture was stirred for 90 minutes, the volatiles were removed under reduced pressure. The crude residue was purified by flash chromatography using MeOH/DCM (5%) to give amine 96% yield (1.82 g) of **67** as a light-yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.13 (m, 5H), 4.26 (d, *J* = 17.0 Hz, 1H), 3.82 (dd, *J* = 7.8, 6.1 Hz, 1H), 3.69 – 3.62 (m, 1H), 2.99 (ddd, *J* = 13.4, 6.2, 3.1 Hz, 1H), 2.89 (ddd, *J* = 15.9, 13.5, 8.1 Hz, 1H), 2.74 (s, 3H), 2.38 (s, 3H), 1.46 (s, 9H).

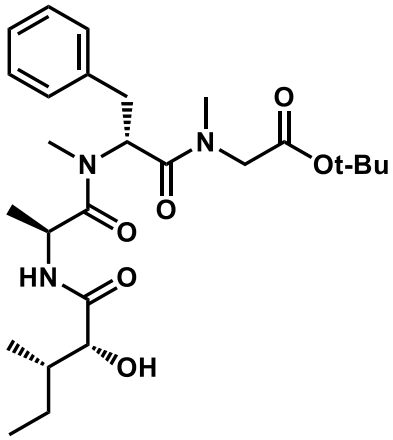


tert-butyl N-(N-(L-alanyl)-N-methyl-D-phenylalanyl)-N-methylglycinate (65)

To a solution of Fmoc-L-Ala-OH (1.27 g, 4.06 mmol) in DCM (15.0 mL) was added DMF (1 drop) and $SOCl_2$ (3.0 mL) at room temperature. After stirring overnight, the volatiles were removed under reduced pressure. A solution of amine **67** (0.5 g, 1.62 mmol) was in 1,2-dichloromethane (6.0 mL) was added to the acid chloride prepared. The solution is cooled to 0 °C and freshly distilled N,N-Diisopropylethylamine (0.7 mL) was added. The solution is stirred overnight. The reaction is cooled to 0 °C and quenched with saturated aqueous saturated $NaHCO_3$ (5 mL). The reaction mixture was transferred to a separatory funnel and extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried over

anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The residual material was dissolved in ACN (25 mL), cooled to 0 °C, and diethylamine (8.3 mL) was added dropwise. The reaction was stirred for 30 min, the volatiles are removed under reduced pressure. The crude residue was purified by flash chromatography MeOH/DCM (10%) to give amine 84% yield (0.51 g) of **65** as a light yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.12 (m, 5H), 5.84 (dd, *J* = 9.5, 6.3 Hz, 1H), 4.14 (d, *J* = 17.0 Hz, 1H), 3.82 – 3.75 (m, 1H), 3.23 – 3.09 (m, 2H), 3.00 (s, 3H), 2.96 (s, 3H), 1.45 (s, 9H), 0.88 (d, *J* = 6.8 Hz, 3H).

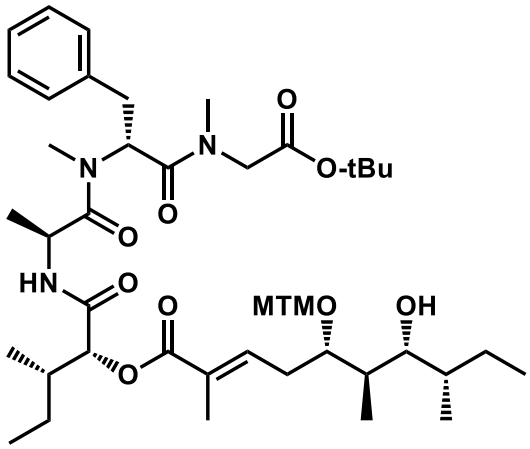


tert-butyl N-(N-(((2*R*,3*S*)-2-hydroxy-3-methylpentanoyl)-L-alanyl)-N-methyl-D-phenylalanyl)-N-methylglycinate (69)

Tripeptide **65** (100.0 mg, 0.266 mmol), 2-hydroxy-3-methylpentanoic acid **56** (39 mg, 0.295 mmol), HOBt (71.9 mg, 0.532mmol) and EDCI (87 mg, 0.472 mmol) are dissolved in DMF (0.5 mL) and stirred overnight. The reaction mixture was diluted with EtOAc (10 mL) and water (10 mL). The reaction mixture was transferred to a separatory funnel. The organic extract was washed with saturated aqueous saturated $NaHCO_3$ (5 mL), brine solution, dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The

crude product was purified by flash chromatography using ethyl acetate/hexanes (80%) to give 53% yield (69.3 mg) of tetrapeptide **69** as a white solid.

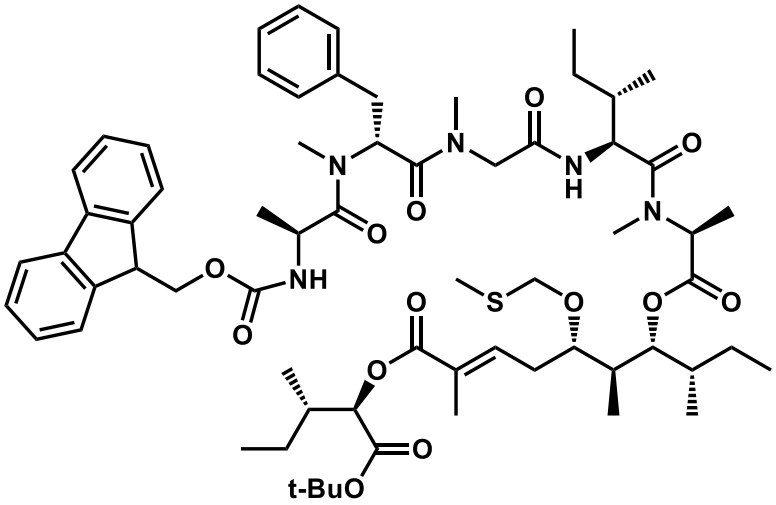
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.17 (m, 5H), 7.01 – 6.93 (m, 1H), 5.85 (dd, *J* = 9.7, 6.1 Hz, 1H), 4.79 (p, *J* = 7.0 Hz, 1H), 4.17 (d, *J* = 17.0 Hz, 1H), 4.07 (d, *J* = 2.7 Hz, 1H), 3.80 (d, *J* = 17.0 Hz, 1H), 3.17 (ddd, *J* = 20.3, 14.2, 5.6 Hz, 2H), 3.03 (s, 3H), 2.98 (s, 3H), 1.46 (d, *J* = 3.2 Hz, 9H), 1.40 – 1.15 (m, 3H), 1.00 – 0.90 (m, 3H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.75 (d, *J* = 6.6 Hz, 3H).



(8*R*,11*S*,14*R*,15*S*)-8-benzyl-2,2,6,9,11,15-hexamethyl-4,7,10,13-tetraoxo-3-oxa-6,9,12-triazaheptadecan-14-yl (5*S*,6*R*,7*R*,8*S*,*E*)-7-hydroxy-2,6,8-trimethyl-5-((methylthio)methoxy)dec-2-enoate (71)

To a stirred solution of acid **57** (120 mg, 0.287 mmol) and tetrapeptide **69** (118 g, 0.240 mmol) in DCM (1.0 mL) was added 4-(dimethyl-amino)pyridine (21 mg, 0.172 mmol) and 1-ethyl-3-3'-(dimethylaminopropyl)carbodiimide hydrochloride (55.0 mg, 0.287 mmol), and the reaction mixture was stirred at ambient temperature for 13 h. The mixture was diluted with EtOAc (10 mL), washed with aqueous solution of HCl (1 M, 5.0 mL), water (5.0 mL), saturated aqueous $NaHCO_3$ (5.0 mL), brine (5.0 mL), dried over anhydrous sodium sulfate, filtered, and

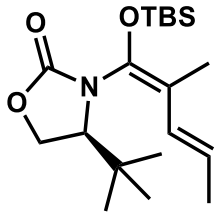
solvent was removed under reduced pressure. The residual oil was purified by flash chromatography using ethyl acetate/hexanes (50%) to give ester **70**. The material is dissolved in a 5:3:12 mixture of HF-Pyridine, Pyridine, and THF (2.0 mL) and stirred overnight. The reaction mixture is diluted with EtOAc (10 mL), poured into saturated aqueous $NaHCO_3$ (75 mL) cooled to 0 °C. The reaction mixture was poured into a separatory funnel and aqueous phase is extracted with EtOAc (3 × 50 mL). The combined organic extract was washed with brine (25 mL) and the solvent was removed under reduced pressure. The residual oil was purified by flash chromatography using ethyl acetate/hexanes (70%) to give 53% yield (0.188 mg) of **71** as a colorless oil. The molecule was observed via NMR to be a complex rotomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 6.64 (m, 6H), 5.95 – 5.58 (m, 1H), 5.39 – 5.13 (m, 2H), 4.92 – 4.50 (m, 1H), 4.28 – 3.92 (m, 2H), 3.93 – 3.58 (m, 1H), 3.38 – 3.08 (m, 2H), 3.12 – 2.81 (m, 6H), 2.78 – 2.29 (m, 2H), 2.29 – 1.73 (m, 11H), 1.40 – 1.16 (m, 11H), 1.14 – 1.00 (m, 5H), 1.00 – 0.69 (m, 36H).



(3*S*,4*R*,5*S*,6*S*,*E*)-10-(((2*R*,3*S*)-1-(tert-butoxy)-3-methyl-1-oxopentan-2-yl)oxy)-3,5,9-trimethyl-6-((methylthio)methoxy)-10-oxodec-8-en-4-yl (5*S*,8*R*,14*S*,17*S*)-8-benzyl-14-((*S*)-

sec-butyl)-1-(9H-fluoren-9-yl)-5,7,10,16,17-pentamethyl-3,6,9,12,15-pentaoxo-2-oxa-4,7,10,13,16-pentaazaoctadecan-18-oate (73)

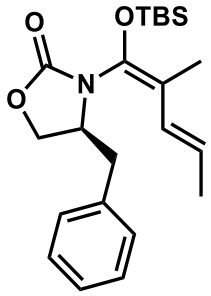
To amine **2** (15.9 mg, 0.0284 mmol) and tetrapeptide **64** (19.0 mg, 0.0284 mmol) were dissolved in DMF (6.0 mL). HATU (11.0 mg, 0.0284 mmol), HOAt (7.81 mg, 0.0568 mmol), and collidine (37 uL, 0.284 mmol) were added. The reaction mixture was stirred at room temperature overnight and quenched with ice water (5.0 mL). The reaction mixture was transferred into a separatory funnel and aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (5.0 mL), NH_4Cl (5.0 mL), brine (5.0 mL) successfully dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography using ethyl acetate/hexanes (50%) to give 73% yield (25.1 mg) of **73** as a white solid. The molecule was observed via NMR to be a complex rotomeric mixture. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.94 – 7.02 (m, 13H), 5.85 (d, J = 26.7 Hz, 1H), 4.69 – 4.13 (m, 3H), 3.40 – 3.24 (m, 2H), 3.23 – 2.79 (m, 6H), 2.58 (d, J = 11.1 Hz, 1H), 2.26 – 1.75 (m, 2H), 1.65 – 1.06 (m, 8H), 1.06 – 0.50 (m, 13H).



(*S*)-4-(tert-butyl)-3-((1*E*,3*E*)-1-((tert-butyldimethylsilyl)oxy)-2-methylpenta-1,3-dien-1-yl)oxazolidin-2-one (2.1)

The title compound was prepared using general procedure for the synthesis of vinylketene silyl *N*,*O*-acetal to give 65% yield (0.504 g) of **2.1** as colorless crystals.

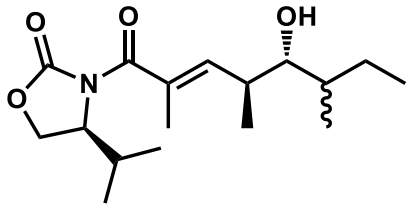
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 (dq, *J* = 15.5, 1.7 Hz, 1H), 5.63 (dq, *J* = 15.5, 6.6 Hz, 1H), 4.27 (t, *J* = 9.2 Hz, 1H), 4.16 (dd, *J* = 9.0, 7.8 Hz, 1H), 3.91 (dd, *J* = 9.3, 7.8 Hz, 1H), 1.79 (dd, *J* = 6.6, 1.7 Hz, 3H), 1.76 (s, 3H), 0.99 (s, 9H), 0.93 (s, 9H), 0.18 (s, 3H), 0.13 (s, 3H).



(*S*)-4-benzyl-3-((1*E*,3*E*)-1-((tert-butyldimethylsilyl)oxy)-2-methylpenta-1,3-dien-1-yl)oxazolidin-2-one (4.1)

The title compound was prepared using general procedure for the synthesis of vinylketene silyl *N*,*O*-acetal to give 83% yield (1.76 g) of **4.1** as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 6.93 (m, 5H), 6.16 (d, *J* = 15.5 Hz, 1H), 5.68 (dq, *J* = 15.5, 6.7 Hz, 1H), 4.33 – 4.20 (m, 2H), 4.13 (s, 1H), 3.13 (d, *J* = 13.5 Hz, 1H), 2.62 (t, *J* = 11.5 Hz, 1H), 1.83 – 1.80 (m, 3H), 0.99 (s, 9H), 0.21 (s, 3H), 0.14 (s, 3H).

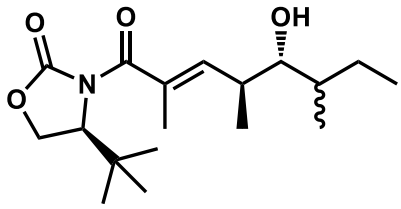


(*S*)-3-((4*S*,5*R*,6*S*,*E*)-5-hydroxy-2,4,6-trimethyloct-2-enoyl)-4-isopropyloxazolidin-2-one (8/8b)

Neat $TiCl_4$ (0.663 mmol) was added dropwise to a solution of racemic-2-methylbutanal **7b** (0.884 mmol) in CH_2Cl_2 (1 mL) at –78 ºC. The resulting reaction mixture was stirred for 30

min at –78 ºC and a solution of vinylketene silyl *N*,*O*-acetal **6** (0.100 g, 0.294 mmol, 1.00 equiv) dissolved in CH_2Cl_2 (6 mL) was added dropwise over 30 min. The reaction mixture was stirred for 22 hr at –78 ºC and then quenched with a mixture of saturated aqueous Rochelle Salt and saturated aqueous $NaHCO_3$ (1:1) at –78 ºC. The reaction mixture was warmed to room temperature while stirring, transferred to a separatory funnel and extracted with ethyl acetate (3 × 10 mL). The combined organic extract was washed with water (5 mL), brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified using a silica gel column (hexanes/ethyl acetate 0–25% as a gradient) to give 96% yield (88 mg) of alcohol mixture **8/8b** as a colorless oil.

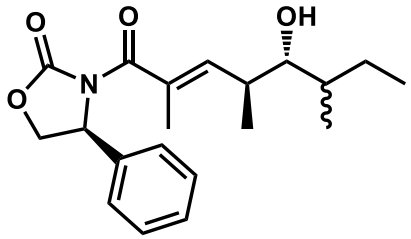
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (dq, *J* = 10.3, 1.5 Hz, 1H), 4.57 (ddd, *J* = 8.9, 5.8, 4.5 Hz, 1H), 4.34 (t, *J* = 9.0 Hz, 1H), 4.18 (dd, *J* = 9.0, 5.8 Hz, 1H), 3.30 (dt, *J* = 8.9, 2.6 Hz, 1H), 3.03 (dd, *J* = 2.8, 1.3 Hz, 1H), 2.73 (ddq, *J* = 10.3, 8.9, 6.6 Hz, 1H), 2.35 (pd, *J* = 7.0, 4.5 Hz, 1H), 1.95 (d, *J* = 1.5 Hz, 3H), 1.58 – 1.46 (m, 3H), 1.38 (dp, *J* = 13.3, 7.3 Hz, 1H), 0.96 – 0.88 (m, 15H).



(*S*)-4-(tert-butyl)-3-((4*S*,5*R*,6*S*,*E*)-5-hydroxy-2,4,6-trimethyloct-2-enoyl)oxazolidin-2-one (2.2/2.2b)

The title compound was prepared using **2.1** and aldehyde **7b** in general procedure of VMAR to give 90% (87 mg, DR: 77/23) of **2.2/2.2b** as a colorless oil.

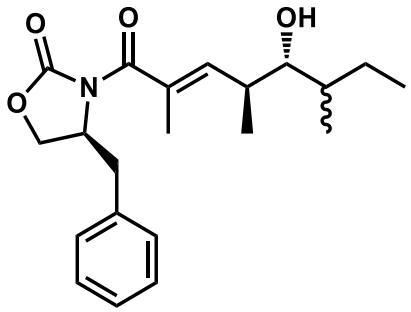
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 – 5.94 (m, 1H), 4.62 (ddd, *J* = 6.8, 4.1, 2.7 Hz, 1H), 4.35 – 4.26 (m, 2H), 3.33 (dd, *J* = 9.1, 2.4 Hz, 1H), 3.14 (s, 1H), 2.78 (dddd, *J* = 15.5, 13.2, 9.9, 7.1 Hz, 1H), 1.95 (t, *J* = 1.3 Hz, 3H), 1.64 – 1.39 (m, 3H), 1.00 – 0.92 (m, 18H).



(*S*)-3-((4*S*,5*R*,6*S*,*E*)-5-hydroxy-2,4,6-trimethyloct-2-enoyl)-4-phenyloxazolidin-2-one (3.2/3.2b)

The title compound was prepared using **27** and aldehyde **7b** in general procedure of VMAR to give 96% (97.6 mg, DR: 77/23) of **3.2/3.2b** as white crystals.

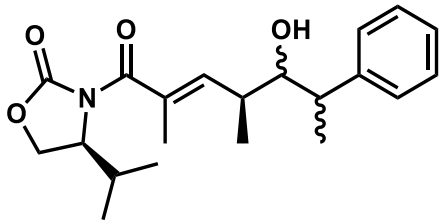
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.32 (m, 5H), 5.93 (ddq, *J* = 26.8, 10.3, 1.5 Hz, 1H), 5.52 (ddd, *J* = 9.0, 7.8, 3.7 Hz, 1H), 4.72 (td, *J* = 9.0, 3.3 Hz, 1H), 4.25 (ddd, *J* = 9.0, 7.8, 4.1 Hz, 1H), 3.34 (dt, *J* = 8.9, 2.7 Hz, 1H), 2.96 (dd, *J* = 2.9, 1.3 Hz, 1H), 2.82 – 2.68 (m, 1H), 1.91 (dd, *J* = 2.9, 1.4 Hz, 3H), 1.62 – 1.46 (m, 1H), 1.39 (dp, *J* = 13.3, 7.3 Hz, 1H), 0.98 – 0.89 (m, 9H).



(*S*)-4-benzyl-3-((4*S*,5*R*,6*S*,*E*)-5-hydroxy-2,4,6-trimethyloct-2-enoyl)oxazolidin-2-one (4.2/4.2b)

The title compound was prepared using **4.1** and aldehyde **7b** in general procedure of VMAR to give 95% (99.5 mg, DR: 75:25) of **4.2/4.2b** as a colorless oil.

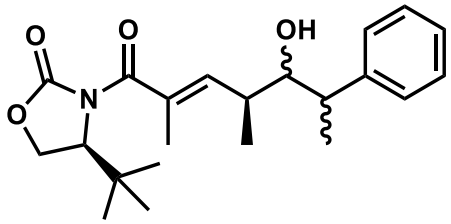
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.13 (m, 5H), 5.79 (dd, *J* = 10.3, 1.5 Hz, 1H), 4.82 (tddd, *J* = 8.5, 6.3, 5.1, 3.4 Hz, 1H), 4.31 (td, *J* = 8.7, 3.6 Hz, 1H), 4.19 (ddd, *J* = 9.1, 6.5, 2.7 Hz, 1H), 3.36 – 3.26 (m, 1H), 2.97 – 2.85 (m, 1H), 2.84 – 2.70 (m, 1H), 1.99 (dd, *J* = 2.6, 1.4 Hz, 3H), 1.60 – 1.55 (m, 1H), 1.46 – 1.34 (m, 3H), 1.05 – 0.90 (m, 9H).



(*S*)-3-((4*S*,5*S*,6*S*,*E*)-5-hydroxy-2,4-dimethyl-6-phenylhept-2-enoyl)-4-isopropyloxazolidin-2-one (7.1)

The title compound was prepared using **6** and aldehyde **5.1** in general procedure of VMAR to give 85% (54 mg, DR: 16.6: 15: 1.45: 1) of **7.1** as a colorless oil.

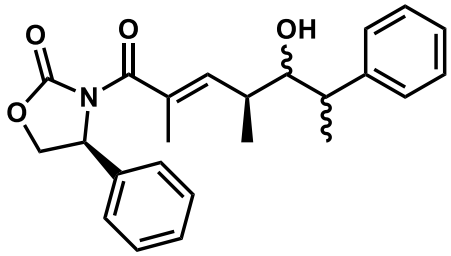
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.08 (m, 5H), 5.90 (dq, *J* = 10.3, 1.5 Hz, 1H), 4.52 (ddd, *J* = 8.9, 5.7, 4.5 Hz, 1H), 4.29 (t, *J* = 9.0 Hz, 1H), 4.13 (dd, *J* = 9.0, 5.7 Hz, 1H), 3.52 (dd, *J* = 6.4, 5.4 Hz, 1H), 2.92 (qd, *J* = 7.0, 5.3 Hz, 1H), 2.60 (dp, *J* = 10.3, 6.7 Hz, 1H), 2.30 (pd, *J* = 7.0, 4.5 Hz, 1H), 1.30 (d, *J* = 7.1 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.87 (dd, *J* = 8.8, 7.0 Hz, 6H).



(*S*)-4-(tert-butyl)-3-((4*S*,5*S*,6*S*,*E*)-5-hydroxy-2,4-dimethyl-6-phenylhept-2-enoyl)oxazolidin-2-one (7.2)

The title compound was prepared using **2.1** and aldehyde **5.1** in general procedure of VMAR to give 84% (90.5 mg, DR: 4.3:2.8:1) of **7.2** as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.14 (m, 5H), 6.07 (dq, *J* = 10.5, 1.5 Hz, 1H), 4.60 (dd, *J* = 7.2, 4.2 Hz, 1H), 4.34 – 4.26 (m, 2H), 3.56 (ddd, *J* = 7.3, 4.8, 2.4 Hz, 1H), 2.99 (qd, *J* = 7.1, 4.6 Hz, 1H), 2.95 – 2.92 (m, 1H), 2.55 – 2.47 (m, 1H), 1.75 (d, *J* = 1.5 Hz, 3H), 1.39 (d, *J* = 7.1 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.94 (s, 9H).

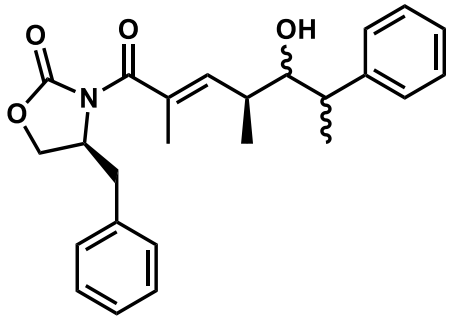


(*S*)-3-((4*S*,5*S*,6*S*,*E*)-5-hydroxy-2,4-dimethyl-6-phenylhept-2-enoyl)-4-phenyloxazolidin-2-one (7.3)

The title compound was prepared using **27** and aldehyde **5.1** in general procedure of VMAR to give 81% (93.8 mg, DR: 11.8:9:1) of **7.3** as white crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.13 (m, 5H), 6.06 (dq, *J* = 10.4, 1.4 Hz, 1H), 5.51 (dd, *J* = 9.0, 7.9 Hz, 1H), 4.72 (t, *J* = 9.0 Hz, 1H), 4.25 (dd, *J* = 9.0, 7.9 Hz, 1H), 3.58 (t, *J* = 6.3 Hz, 1H),

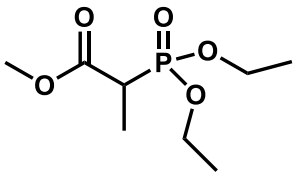
2.98 (qd, *J* = 7.0, 5.3 Hz, 1H), 2.68 (s, 1H), 2.53 (dp, *J* = 10.4, 6.7 Hz, 1H), 1.74 (d, *J* = 1.5 Hz, 3H), 1.38 (d, *J* = 7.1 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H).



(*S*)-4-benzyl-3-((4*S*,5*S*,6*S*,*E*)-5-hydroxy-2,4-dimethyl-6-phenylhept-2-enoyl)oxazolidin-2-one (7.4)

The title compound was prepared using **4.1** and aldehyde **5.1** in general procedure of VMAR to give 78% (91.8 mg, DR: 10.1:6.9:1) of **7.4** as a colorless oil.

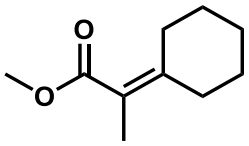
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.16 (m, 1H), 5.92 (dq, *J* = 10.4, 1.5 Hz, 1H), 4.78 (tdd, *J* = 8.7, 6.4, 3.5 Hz, 1H), 4.28 (t, *J* = 8.7 Hz, 1H), 4.17 (dd, *J* = 9.0, 6.4 Hz, 1H), 3.53 (t, *J* = 6.2 Hz, 1H), 3.31 (dd, *J* = 13.5, 3.4 Hz, 1H), 2.95 (qd, *J* = 7.0, 5.1 Hz, 1H), 2.86 (dd, *J* = 13.5, 9.0 Hz, 1H), 2.66 (s, 1H), 2.53 (dp, *J* = 10.4, 6.7 Hz, 1H), 1.80 (d, *J* = 1.5 Hz, 3H), 1.37 (d, *J* = 7.1 Hz, 3H), 1.04 (d, *J* = 6.7 Hz, 3H).



methyl 2-(diethoxyphosphoryl)propanoate (9.3)

Methyl 1-bromopropionate **9.1** (5 mL, 0.0447 mol) is refluxed with triethylphosphite **9.2** (7.68 mL, 0.0447 mol) under neat conditions and distilled to give phosphate **9.3** in 76 % (7.6 g, 0.0339 mol) and is used without further purification.

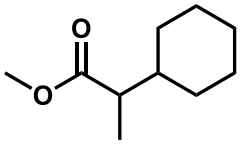
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.27 – 4.03 (m, 4H), 3.79 – 3.73 (m, 3H), 3.03 (ddq, *J* = 23.4, 11.7, 7.3 Hz, 1H), 1.44 (ddd, *J* = 18.0, 7.3, 2.1 Hz, 3H), 1.37 – 1.28 (m, 6H).



methyl 2-cyclohexylidenepropanoate (9.4)

Phosphate **9.3** (7.0 g, 0.0312 mol) was added to a solution of NaH (1.1 g, 0.0312 mol) in THF (15 mL) and allowed to react till H_2 gas evolution ceased. The mixture is cooled to 0ºC and a solution of cyclohexanone (4.49 g, 0.0312 mol) in of THF (9 mL) was added slowly. The mixture was stirred for 3 h and quenched slowly with cold water (5 mL). The reaction mixture was poured into a separatory funnel and extracted with EtOAc (50 mL). The organic extract was washed with brine (10 mL), dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The crude residue **9.4** was used in the next step without further purification.

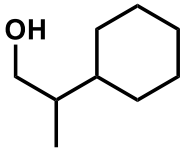
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (s, 3H), 2.42 (d, *J* = 5.7 Hz, 2H), 2.36 – 2.30 (m, 2H), 2.22 (t, *J* = 5.6 Hz, 1H), 1.90 – 1.82 (m, 3H), 1.79 – 1.67 (m, 2H), 1.59 – 1.55 (m, 2H).



methyl 2-cyclohexylpropanoate (9.5)

Crude Methyl ester **9.4** (2.5 g, 14.88 mmol) was dissolved in of THF (150 mL). A slurry Raney-Ni (11.9 g) was added, and the reaction mixture was stirred under an atmosphere of H_2 gas. The reaction was monitored by TLC. Upon completion the Raney-Ni was filtered, and the organic solvent was concentrated under reduced pressure to give crude residue **9.5** and was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (s, 3H), 2.26 (p, *J* = 7.1 Hz, 1H), 1.78 – 1.49 (m, 7H), 1.32 – 1.18 (m, 2H), 1.11 (d, *J* = 7.0 Hz, 3H), 1.08 – 0.84 (m, 2H).

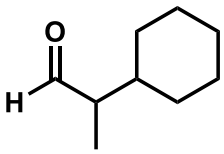


2-cyclohexylpropan-1-ol (9.6)

Crude Methyl ester **9.4** (1.86 g, 11.33 mmol) was dissolved in DCM (20 mL) and cooled to -78ºC. A THF solution of DIBAL (11.33 mmol, 21.2 mL) was added dropwise. After stirring for 2 h, the reaction was quenched with cold water (50 mL) and the reaction mixture was transferred to a separatory funnel. The aqueous phase was extracted with EtOAc (100 mL). The organic layer is washed with brine (20 mL), dried over anhydrous sodium sulfate, and

concentrated under reduced pressure. The crude residue **9.6** was used without further purification.

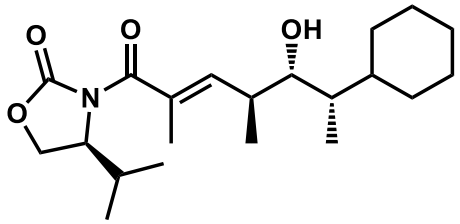
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.60 (dd, *J* = 10.5, 5.7 Hz, 1H), 3.45 (dd, *J* = 10.5, 9 Hz, 1H), 1.79 – 1.69 (m, 2H), 1.63 (dddd, *J* = 14.4, 7.8, 3.9, 1.7 Hz, 4H), 1.54 – 1.46 (m, 1H), 1.42 – 1.29 (m, 2H), 1.20 – 0.93 (m, 3H), 0.88 (d, *J* = 6.9 Hz, 3H).



2-cyclohexylpropanal (8.1)

Dry DMSO (2.23 mL, 31.5 mmol) was added to DCM (150 mL) and cooled to -78ºC. $(COCl)_2$ (1.34mL. 15.96 mmol) is added dropwise and stirred for 30 min at -78ºC. Alcohol **9.6** (1.5g, 11.2 mmol) was added and stirred for an additional 1 h maintaining temperature. Triethylamine (TEA) (7.36 mL, 56 mmol) was added and maintaining temperature for 15 min at -78 ºC followed by warming to room temperature and stirring for 30 min. The reaction mixture was quenched with water (100 mL) and the reaction mixture was transferred to a separatory funnel. The organic phase was washed with 1M HCl (50mL), saturated aqueous $NaHCO_3$ (50 mL), brine, and dried over anhydrous sodium sulfate. The solvent was removed under and reduced pressure. A short silica plug was performed using diethyl ether to give aldehyde **8.1** which was used as a DCM stock solution without further purification.

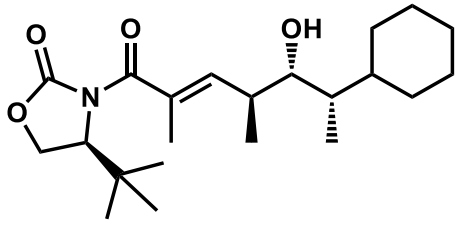
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.65 (d, *J* = 2.3 Hz, 1H), 2.27 – 2.16 (m, 1H), 1.79 – 1.58 (m, 7H), 1.34 – 1.20 (m, 2H), 1.19 – 1.05 (m, 2H), 1.04 (d, *J* = 7.0 Hz, 3H).



(*S*)-3-((4*S*,5*R*,6*S*,*E*)-6-cyclohexyl-5-hydroxy-2,4-dimethylhept-2-enoyl)-4-isopropyloxazolidin-2-one (10.1)

The title compound was prepared using **6** and aldehyde **8.1** in general procedure of VMAR to give 99% (68.4 mg) of **10.1** as a colorless oil.

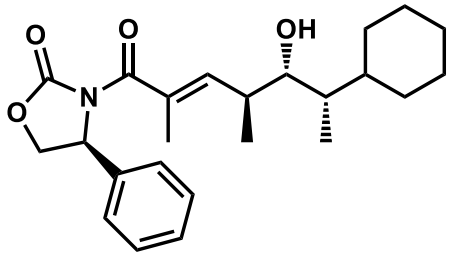
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (dq, *J* = 10.3, 1.5 Hz, 1H), 4.58 (ddd, *J* = 8.9, 5.8, 4.5 Hz, 1H), 4.34 (t, *J* = 9.0 Hz, 1H), 4.19 (dd, *J* = 9.0, 5.9 Hz, 1H), 3.46 (dd, *J* = 9.0, 1.8 Hz, 1H), 3.02 (s, 1H), 2.75 (ddq, *J* = 10.1, 8.8, 6.6 Hz, 1H), 2.40 – 2.28 (m, 1H), 1.95 (d, *J* = 1.5 Hz, 3H), 1.87 (d, *J* = 12.7 Hz, 2H), 1.78 – 1.53 (m, 4H), 1.37 (ddq, *J* = 10.8, 7.6, 4.2, 3.6 Hz, 2H), 1.29 – 1.02 (m, 3H), 0.99 – 0.86 (m, 12H).



(*S*)-4-(tert-butyl)-3-((4*S*,5*R*,6*S*,*E*)-6-cyclohexyl-5-hydroxy-2,4-dimethylhept-2-enoyl)oxazolidin-2-one (10.2)

The title compound was prepared using **2.1** and aldehyde **8.1** in general procedure of VMAR to give 99% (44.0 mg) of **10.2** as a colorless oil.

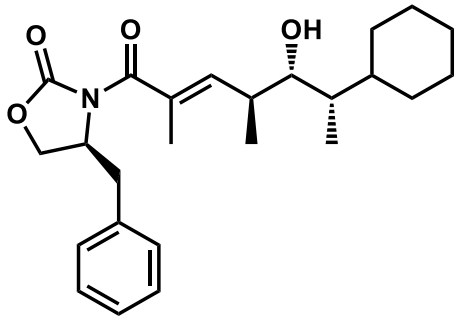
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 – 5.94 (m, 1H), 4.64 (dd, *J* = 7.1, 4.2 Hz, 1H), 4.37 – 4.27 (m, 2H), 3.50 (d, *J* = 9.1 Hz, 1H), 3.13 (d, *J* = 2.7 Hz, 1H), 2.85 – 2.74 (m, 1H), 1.96 (d, *J* = 1.4 Hz, 3H), 1.88 (d, *J* = 12.7 Hz, 2H), 1.68 (dd, *J* = 29.8, 11.8 Hz, 4H), 1.46 – 1.06 (m, 7H), 0.96 (s, 9H), 0.93 (t, *J* = 6.9 Hz, 6H)



(*S*)-3-((4*S*,5*R*,6*S*,*E*)-6-cyclohexyl-5-hydroxy-2,4-dimethylhept-2-enoyl)-4-phenyloxazolidin-2-one (10.3)

The title compound was prepared using **27** and aldehyde **8.1** in general procedure of VMAR to give 99% (76.5 mg) of **10.3** as white crystals.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.32 (m, 5H), 5.93 – 5.87 (m, 1H), 5.53 (dd, *J* = 9.1, 7.9 Hz, 1H), 4.73 (t, *J* = 9.1 Hz, 1H), 4.26 (dd, *J* = 9.0, 7.9 Hz, 1H), 3.53 – 3.48 (m, 1H), 2.94 (s, 1H), 2.80 – 2.69 (m, 1H), 1.91 (d, *J* = 1.4 Hz, 3H), 1.87 (d, *J* = 11.7 Hz, 3H), 1.81 – 1.68 (m, 1H), 1.65 (d, *J* = 12.1 Hz, 2H), 1.55 (s, 1H), 1.38 (dt, *J* = 10.7, 7.2 Hz, 3H), 1.32 – 1.10 (m, 4H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H).



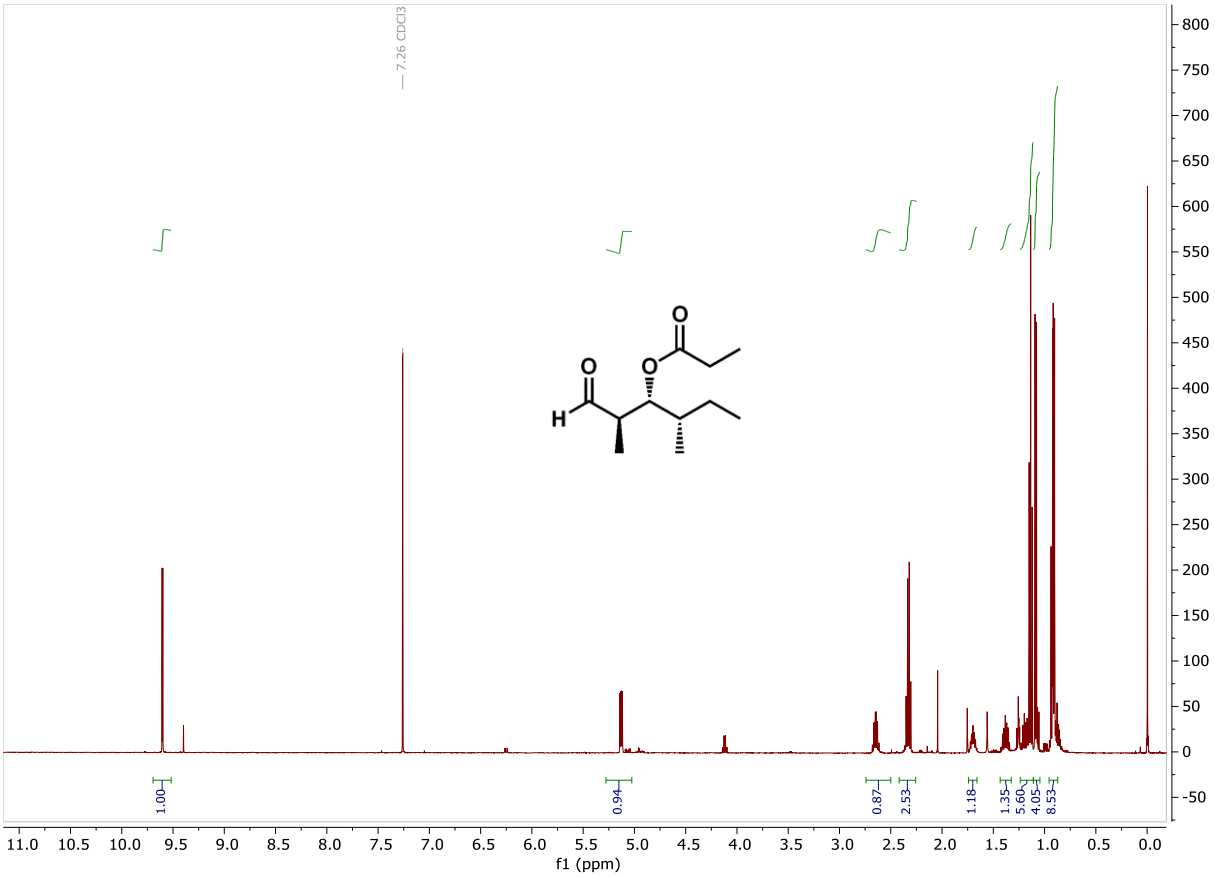
(*S*)-4-benzyl-3-((4*S*,5*R*,6*S*,*E*)-6-cyclohexyl-5-hydroxy-2,4-dimethylhept-2-enoyl)oxazolidin-2-one (10.4)

The title compound was prepared using **4.1** and aldehyde **8.1** in general procedure of VMAR to give 93% (74.4 mg) of **10.4** as a colorless oil.

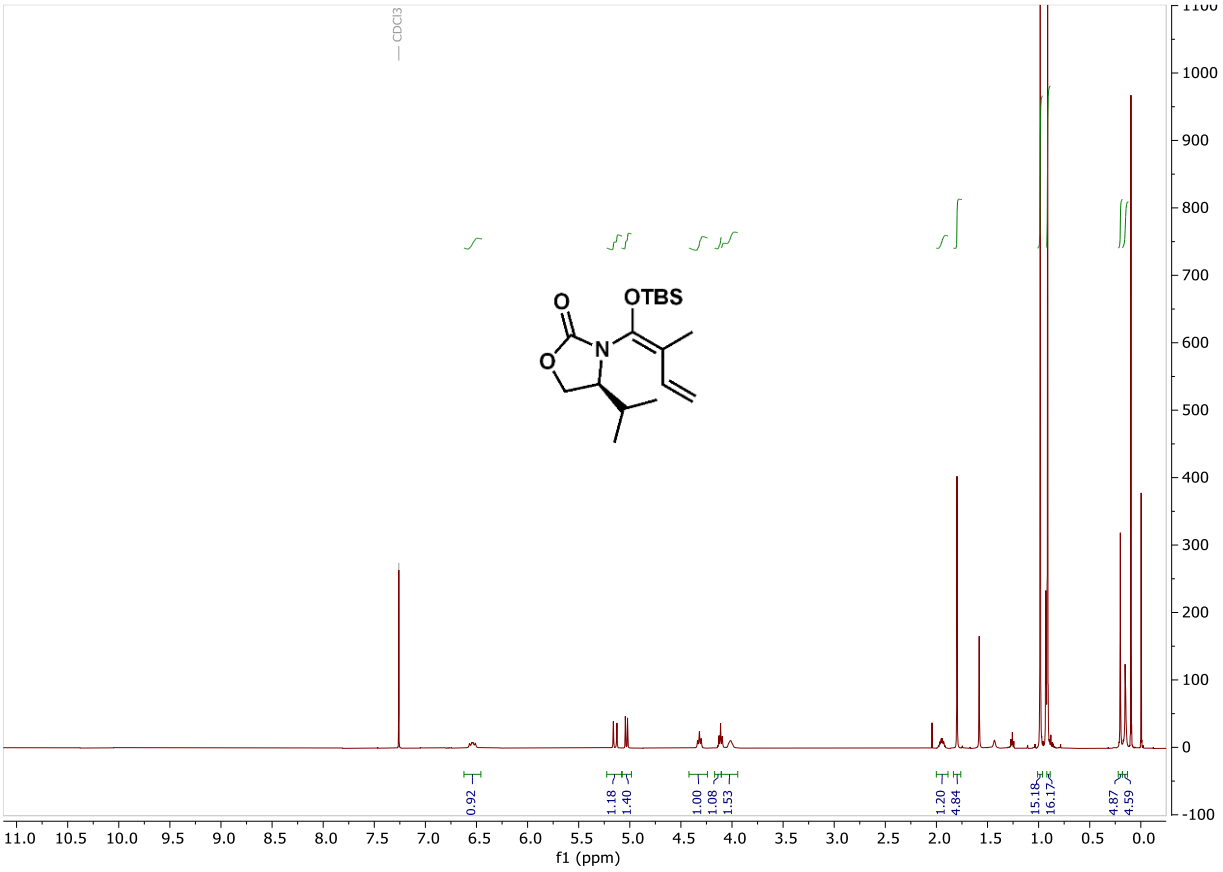
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.13 (m, 5H), 5.77 (dq, *J* = 10.3, 1.5 Hz, 1H), 4.80 (tdd, *J* = 8.7, 6.6, 3.4 Hz, 1H), 4.29 (t, *J* = 8.7 Hz, 1H), 4.16 (dd, *J* = 9.0, 6.6 Hz, 1H), 3.43 (dd, *J* = 8.8, 2.0 Hz, 1H), 3.29 (dd, *J* = 13.5, 3.4 Hz, 1H), 2.88 (dq, *J* = 14.7, 8.1, 5.7 Hz, 1H), 2.75 (ddq, *J* = 10.2, 8.7, 6.6 Hz, 1H), 1.96 (d, *J* = 1.5 Hz, 3H), 1.85 (dd, *J* = 9.6, 6.0 Hz, 2H), 1.74 – 1.67 (m, 2H), 1.66 – 1.60 (m, 1H), 1.40 – 1.31 (m, 2H), 1.31 – 1.08 (m, 4H), 0.92 (d, *J* = 6.4 Hz, 9H).

Spectra

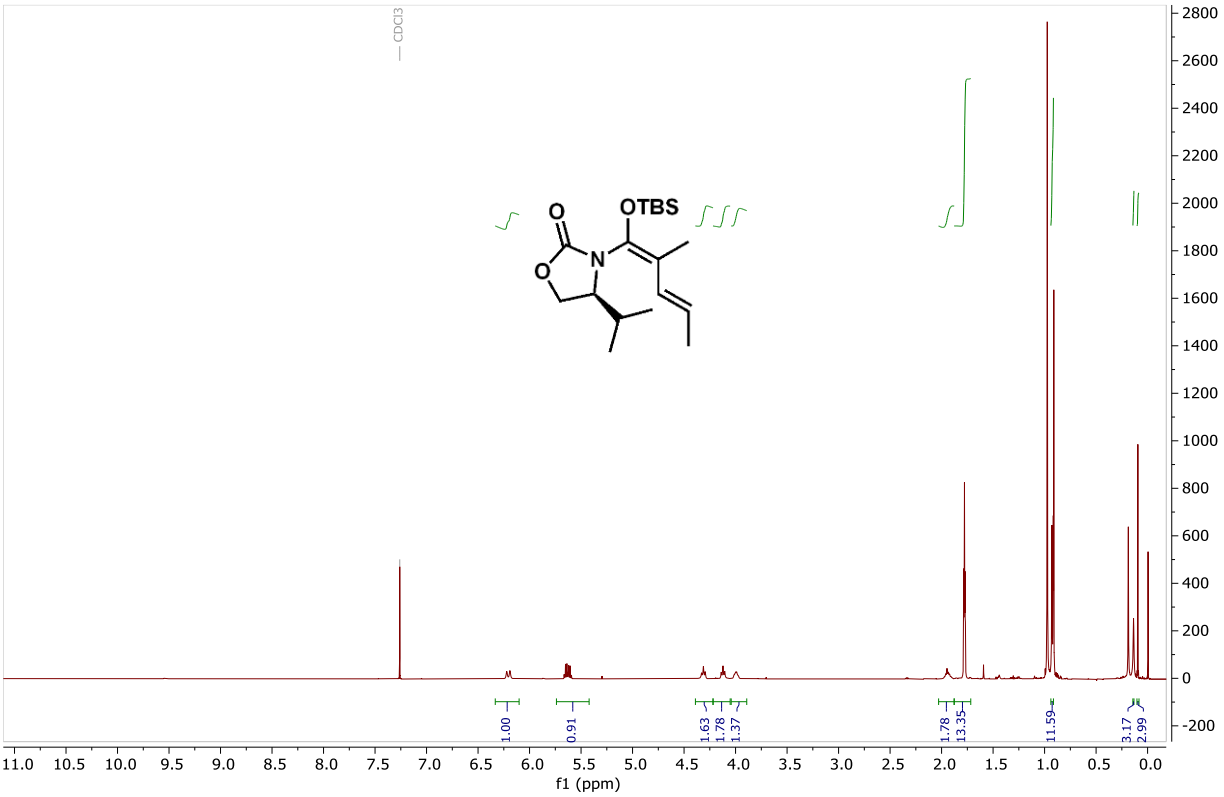
(2*R*,3*R*,4*S*)-2,4-dimethyl-1-oxohexan-3-yl propionate (3)



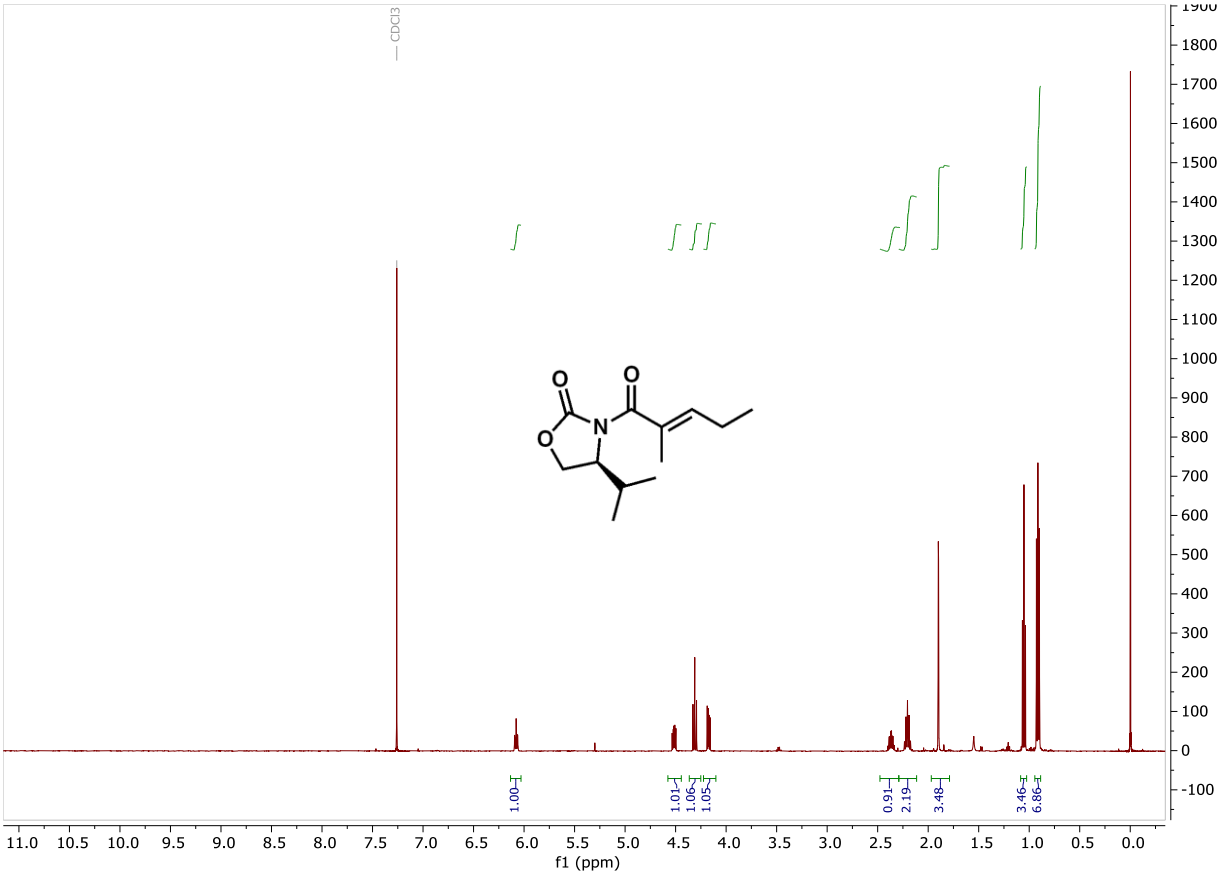
(*S*,*E*)-3-(1-((tert-butyldimethylsilyl)oxy)-2-methylbuta-1,3-dien-1-yl)-4-isopropyloxazolidin-2-one (4)



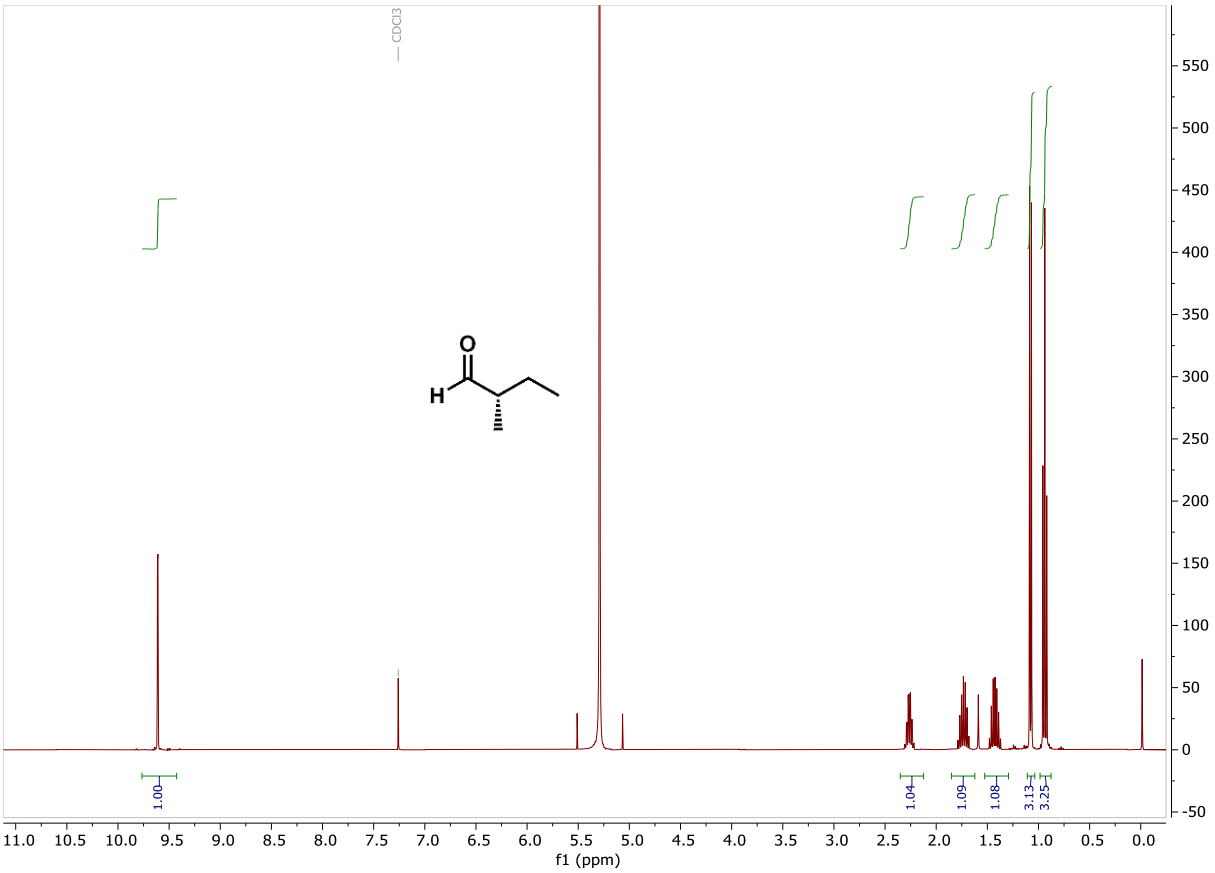
(*S*)-3-((1*E*,3*E*)-1-((tert-butyldimethylsilyl)oxy)-2-methylpenta-1,3-dien-1-yl)-4-isopropyloxazolidin-2-one (6)



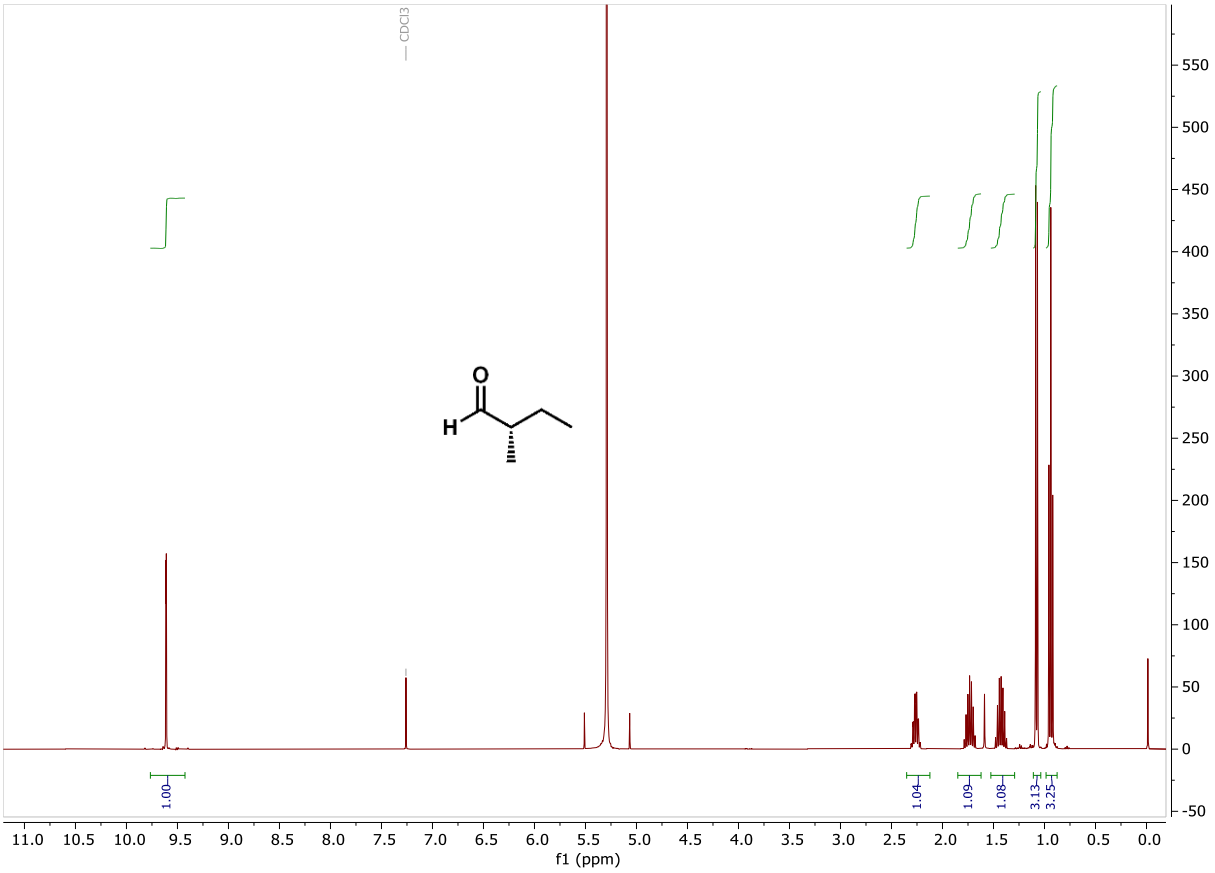
(*S*,*E*)-4-isopropyl-3-(2-methylpent-2-enoyl)oxazolidin-2-one (6a)



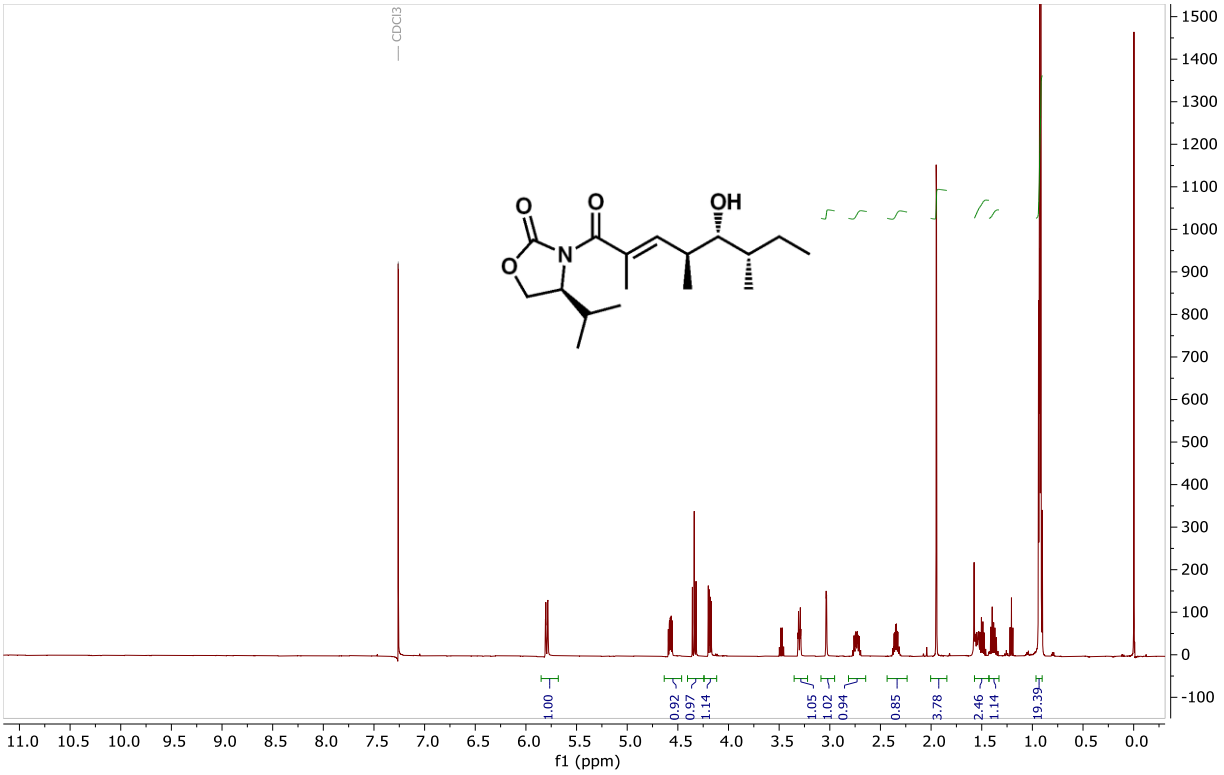
(*S*)-2-methylbutanal (7)



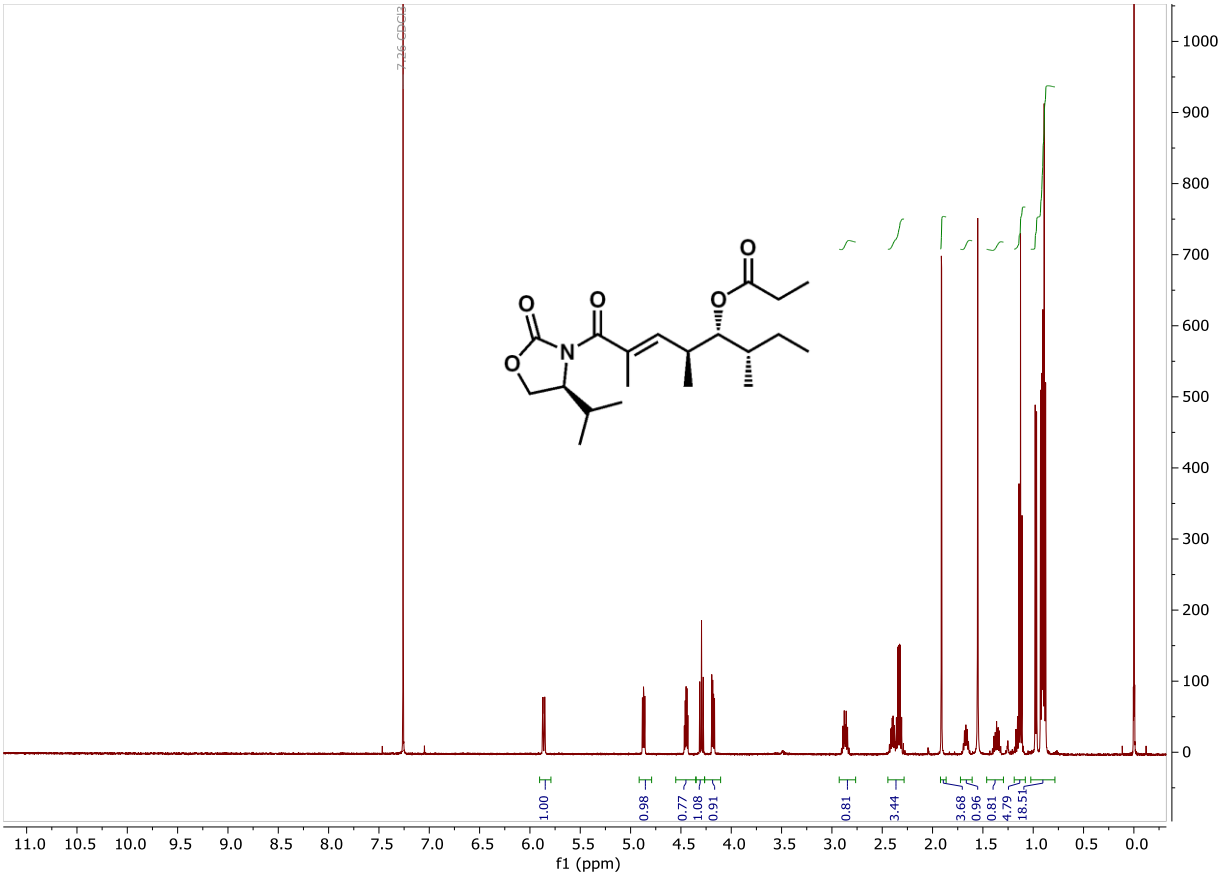
(*S*)-2-methylbutanal (7b)



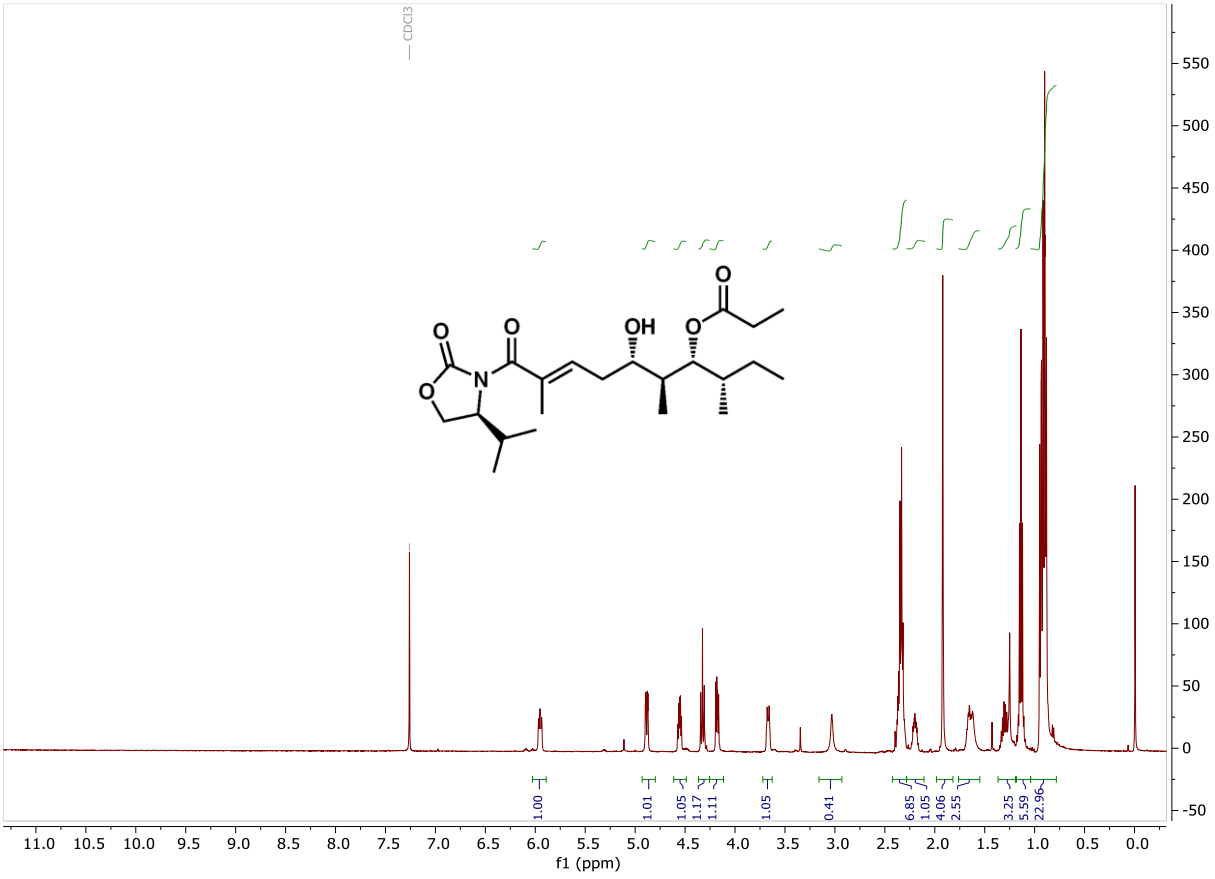
(*S*)-3-((4*S*,5*R*,6*S*,*E*)-5-hydroxy-2,4,6-trimethyloct-2-enoyl)-4-isopropyloxazolidin-2-one (8)



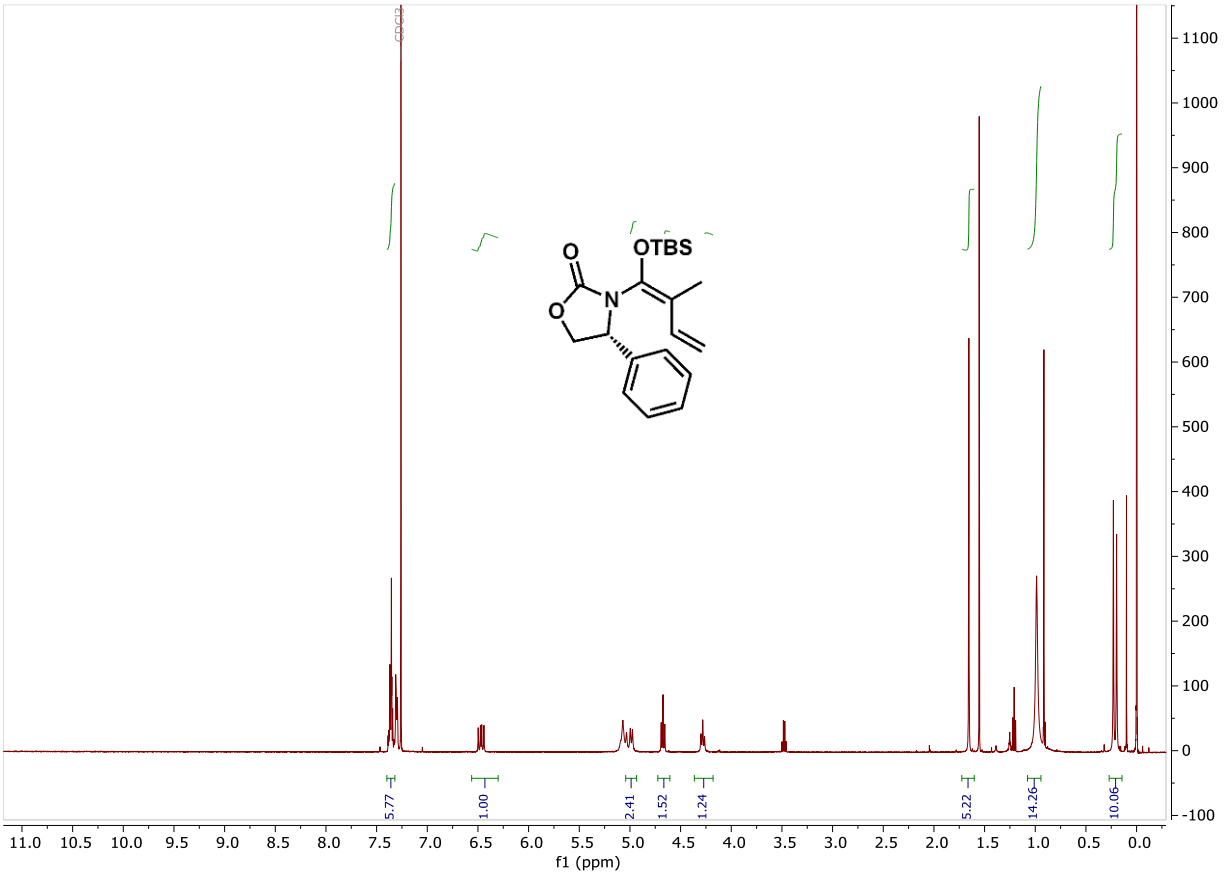
(3*S*,4*R*,5*S*,*E*)-8-((*S*)-4-isopropyl-2-oxooxazolidin-3-yl)-3,5,7-trimethyl-8-oxooct-6-en-4-yl propionate (9)



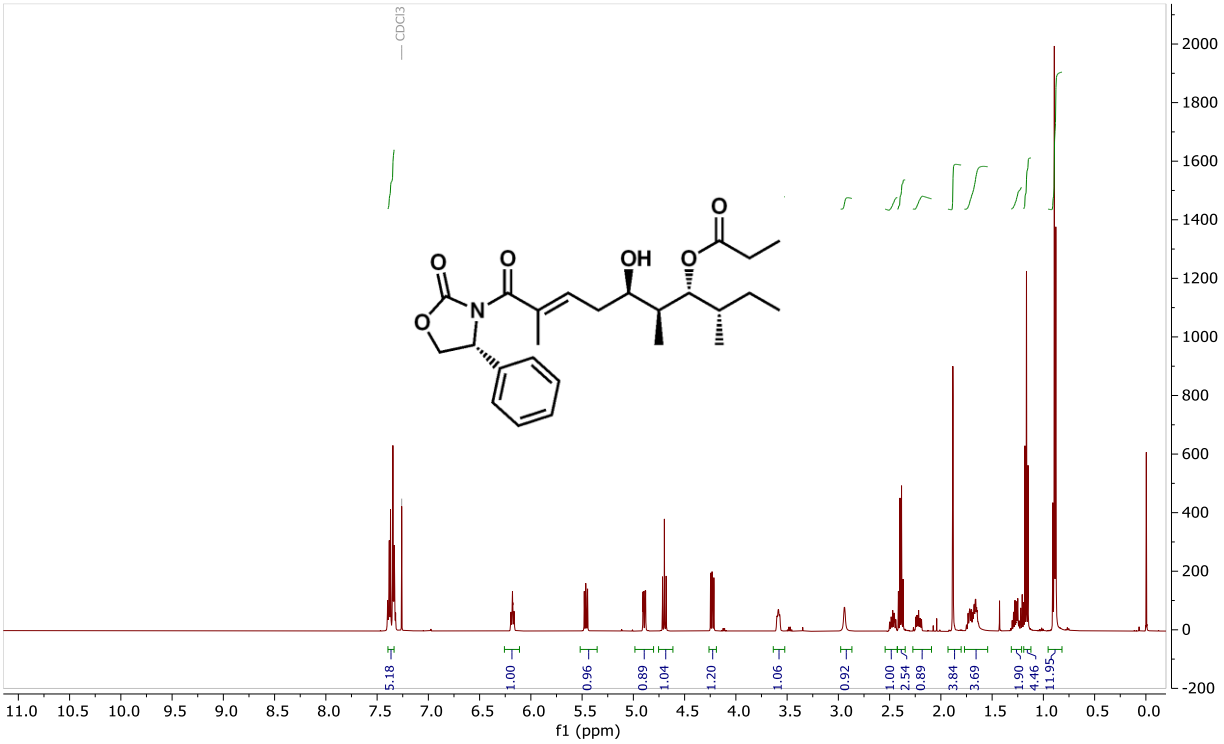
(3*S*,4*R*,5*S*,6*S*,*E*)-6-hydroxy-10-((S)-4-isopropyl-2-oxooxazolidin-3-yl)-3,5,9-trimethyl-10-oxodec-8-en-4-yl propionate (10)



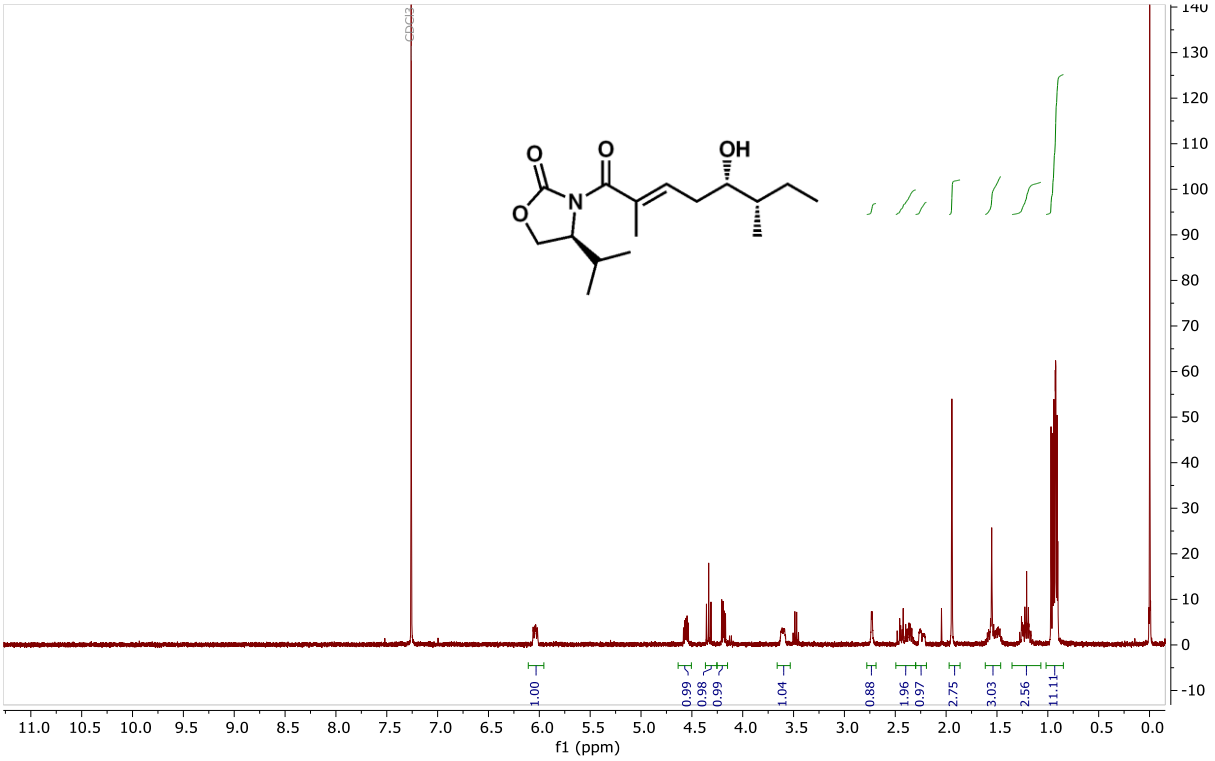
(*R*,*E*)-3-(1-((tert-butyldimethylsilyl)oxy)-2-methylbuta-1,3-dien-1-yl)-4-phenyloxazolidin-2-one (11)



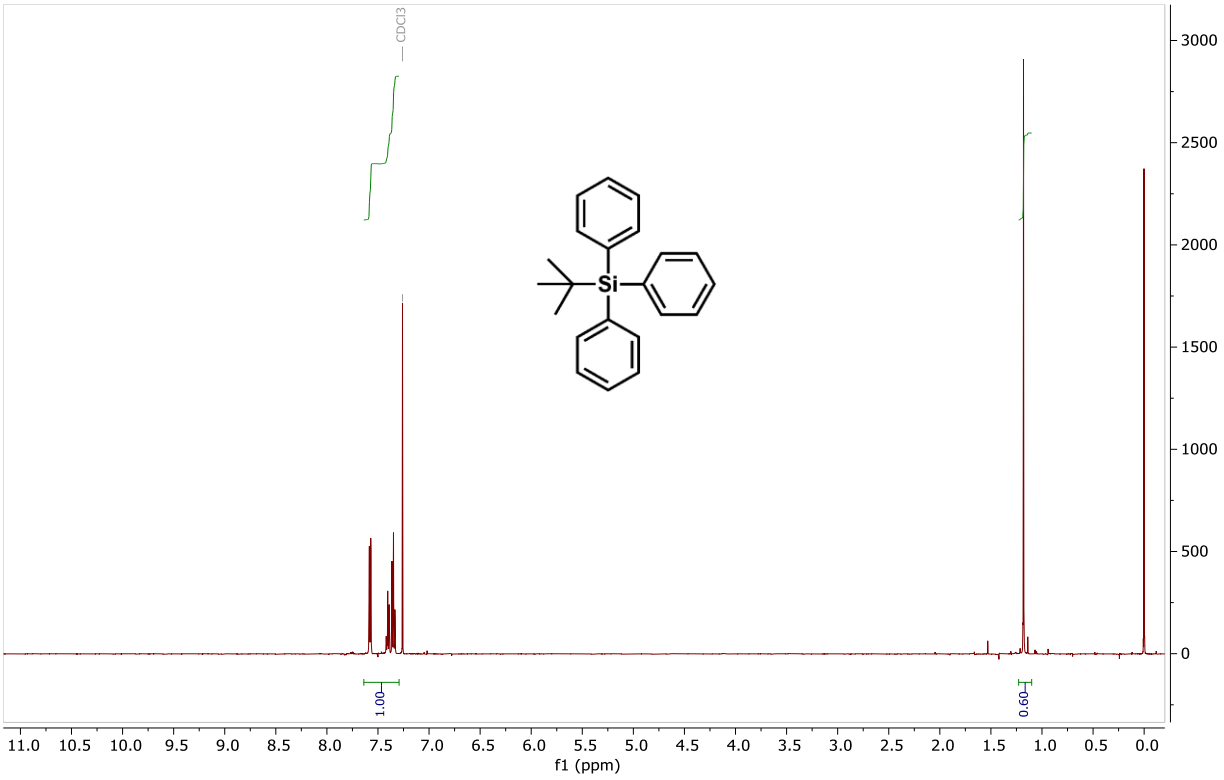
(3*S*,4*R*,5*S*,6*R*,*E*)-6-hydroxy-3,5,9-trimethyl-10-oxo-10-((*R*)-2-oxo-4-phenyloxazolidin-3-yl)dec-8-en-4-yl propionate (13)



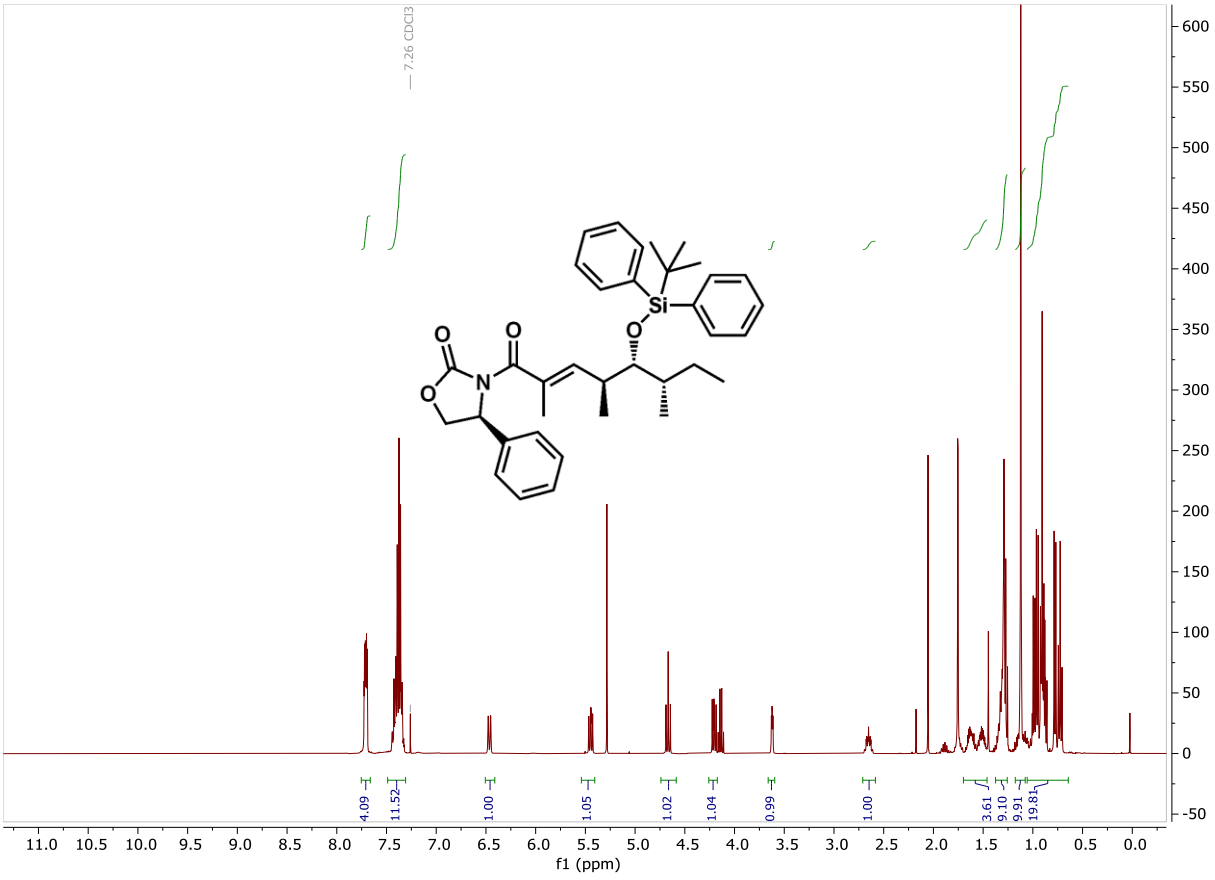
(*S*)-3-((5*S*,6*S*,*E*)-5-hydroxy-2,6-dimethyloct-2-enoyl)-4-isopropyloxazolidin-2-one (15)



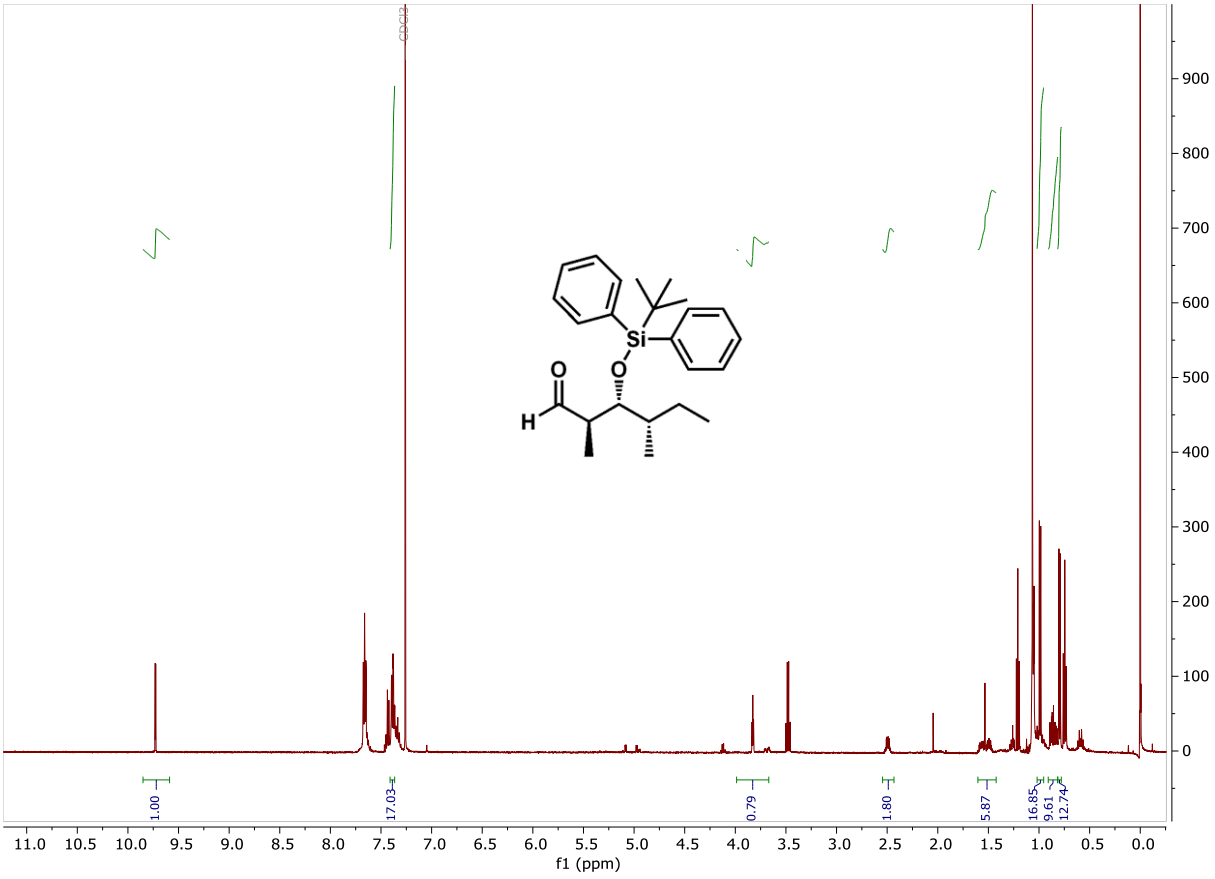
tert-butyltriphenylsilane (18)



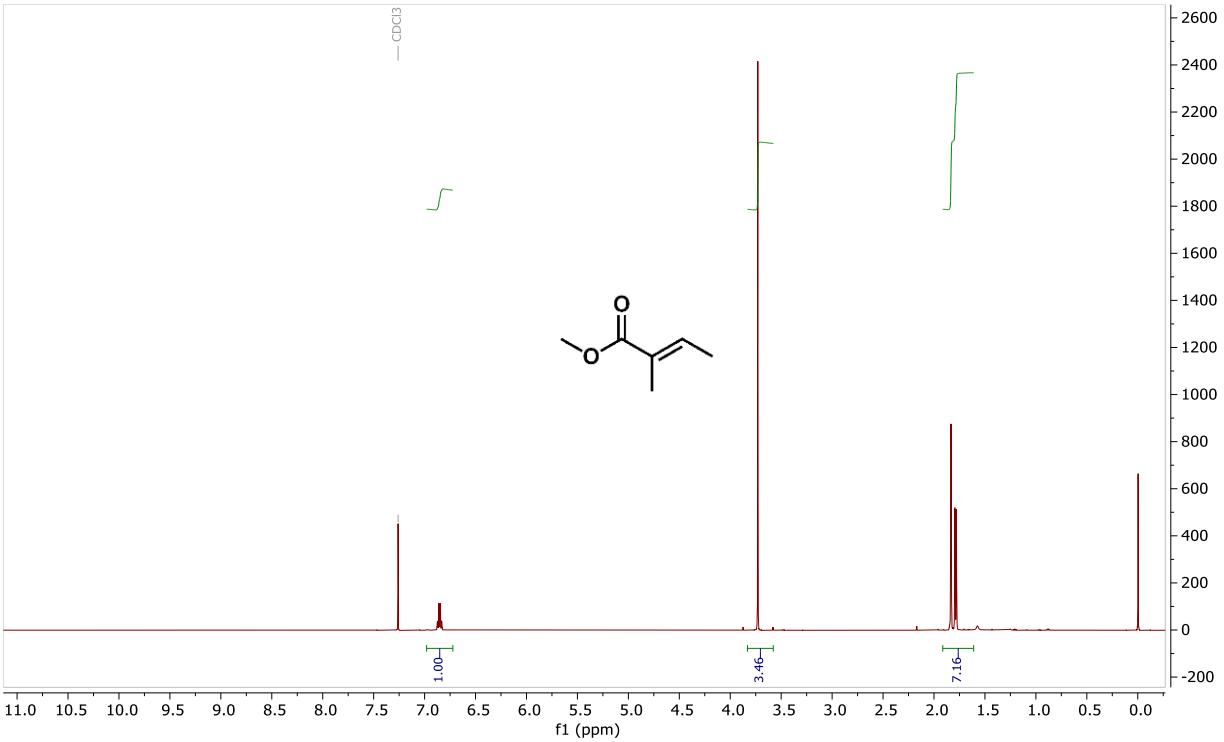
(*S*)-3-((4*S*,5*R*,6*S*,*E*)-5-((tert-butyldiphenylsilyl)oxy)-2,4,6-trimethyloct-2-enoyl)-4-phenyloxazolidin-2-one (19)



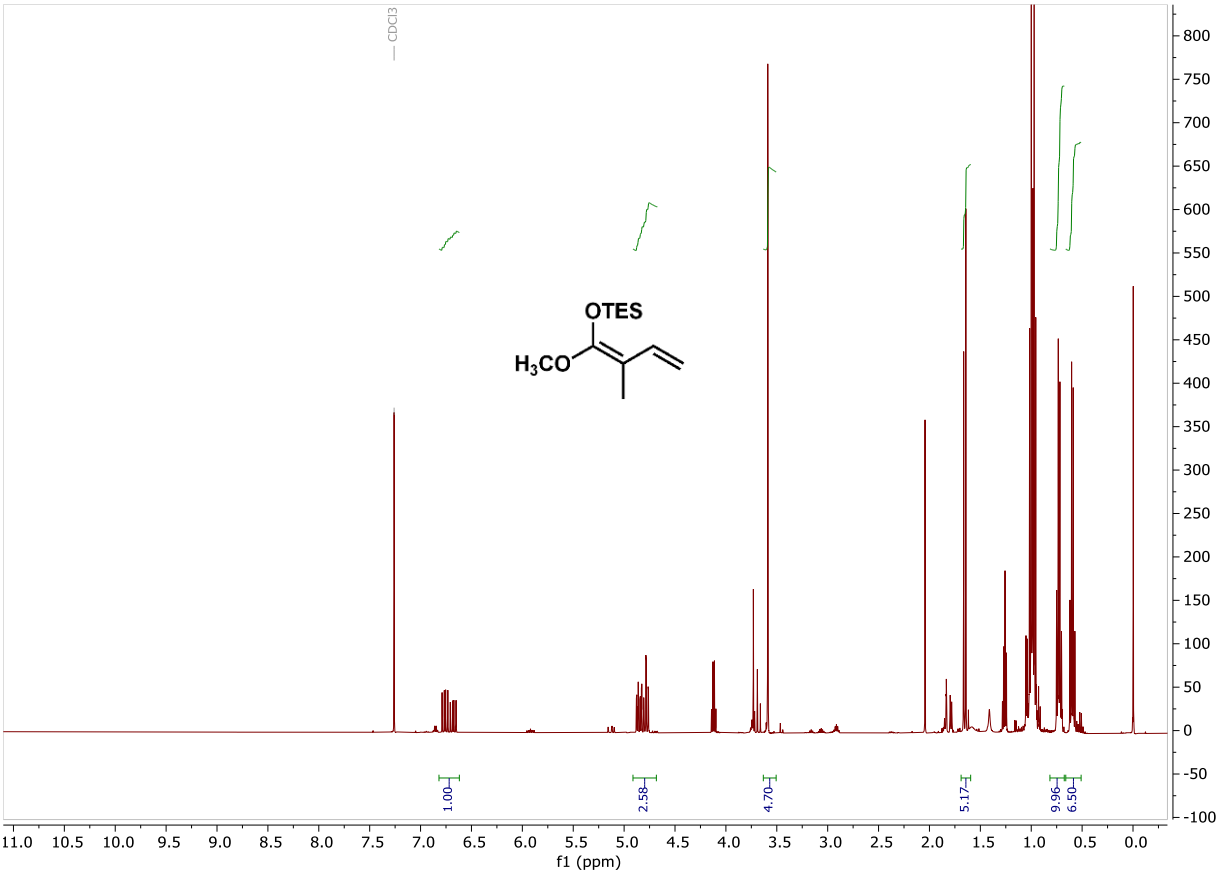
(2*R*,3*R*,4*S*)-3-((tert-butyldiphenylsilyl)oxy)-2,4-dimethylhexanal (20)



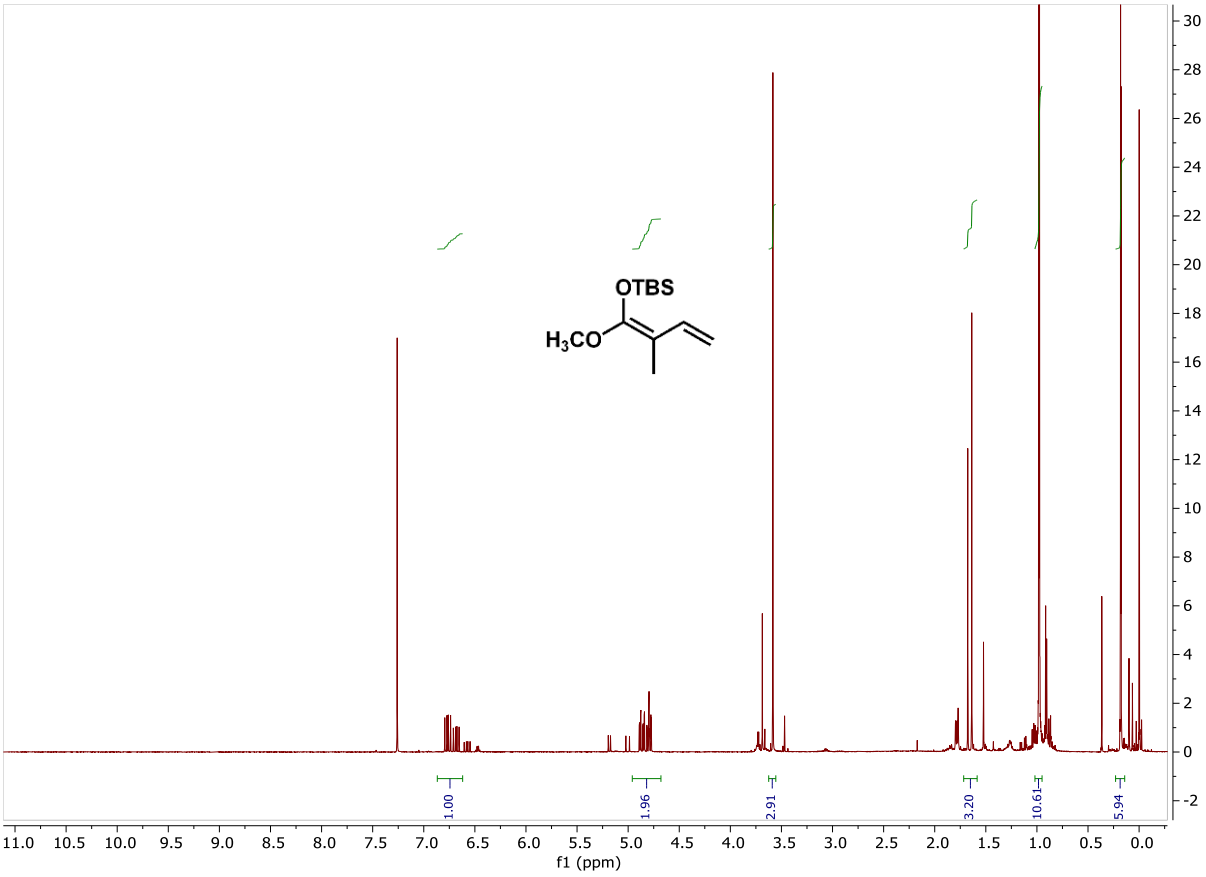
methyl (*E*)-2-methylbut-2-enoate (23)



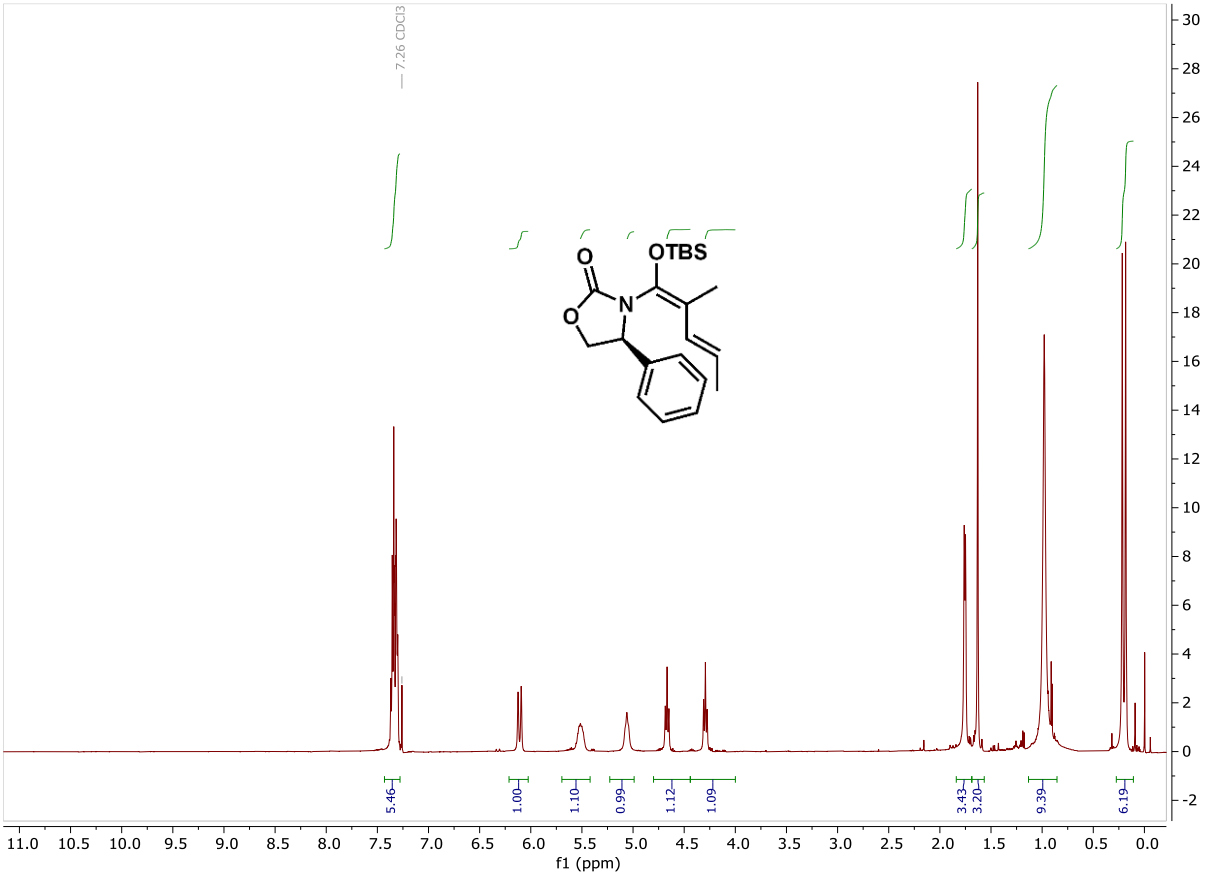
(*Z*)- ((1-methoxy-2-methylbuta-1,3-dien-1-yl)oxy)triethylsilane (25)



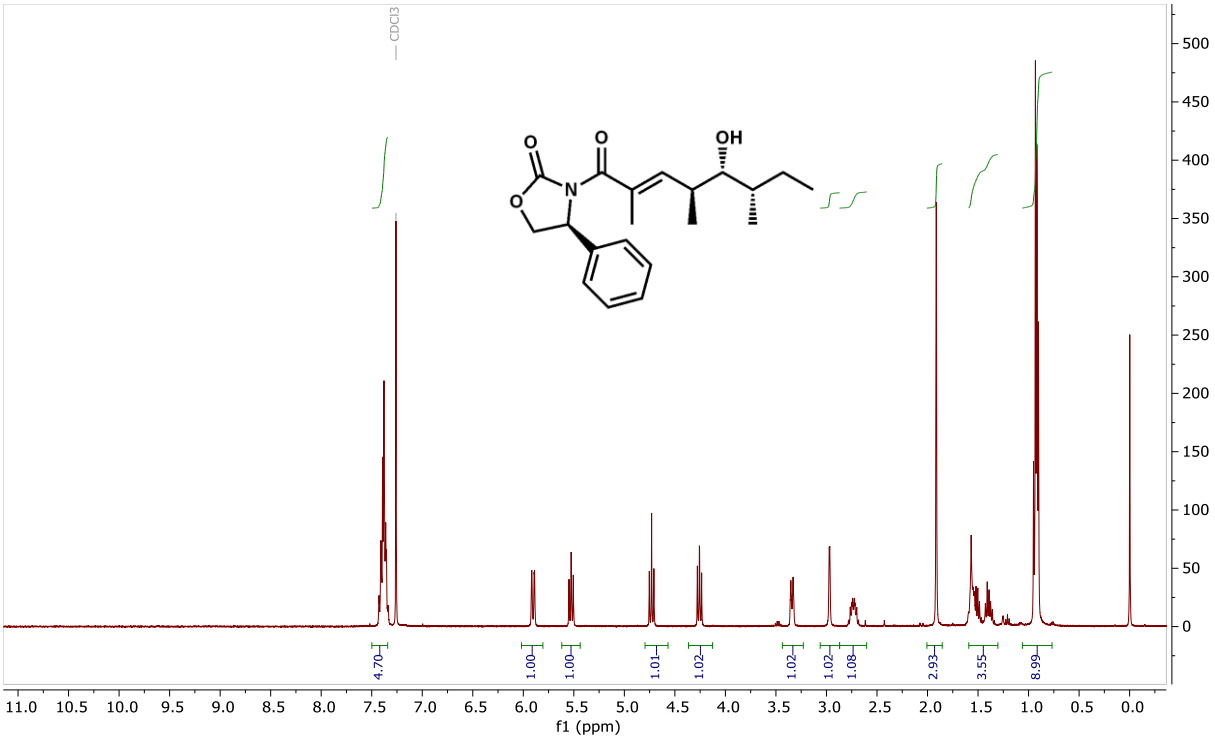
(*Z*)-tert-butyl((1-methoxy-2-methylbuta-1,3-dien-1-yl)oxy)dimethylsilane (26)



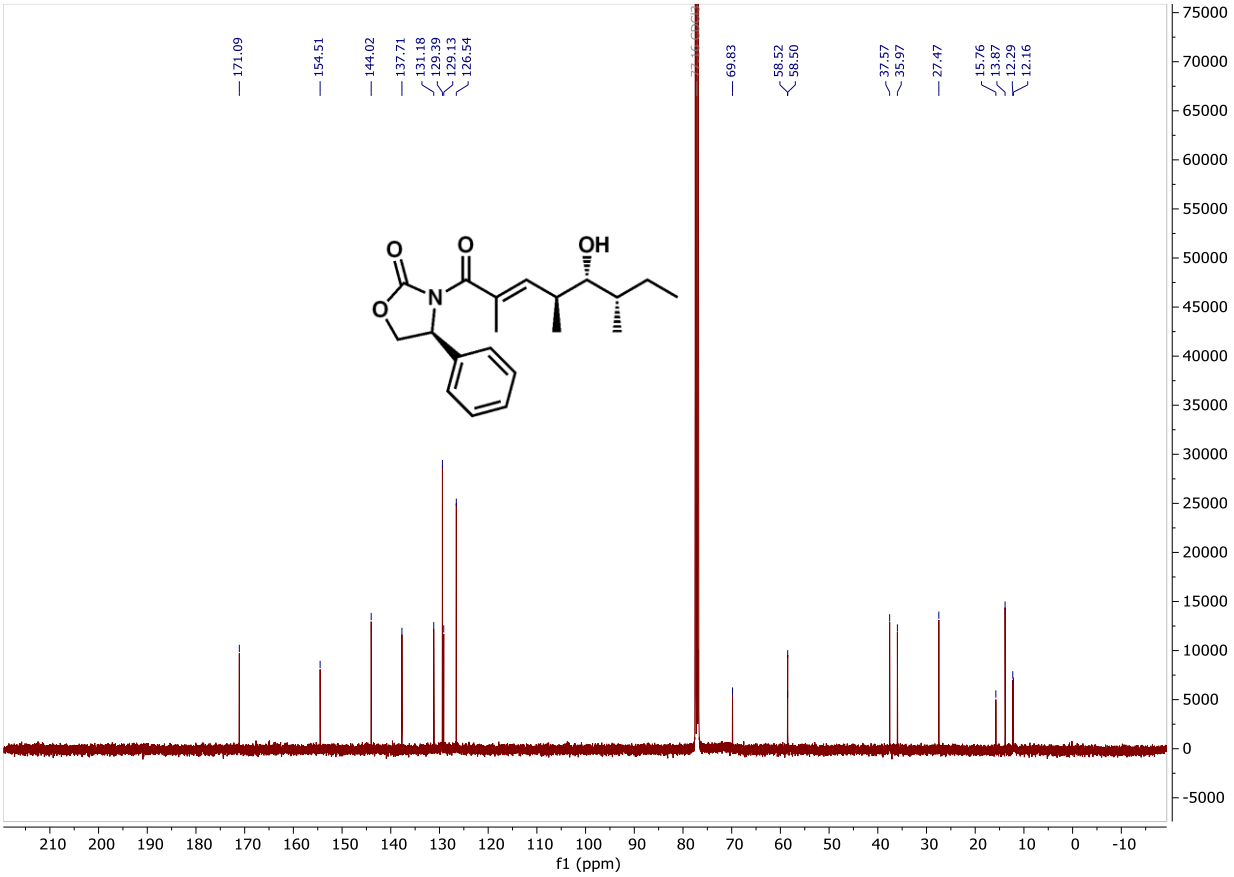
(*S*)-3-((1*E*,3*E*)-1-((tert-butyldimethylsilyl)oxy)-2-methylpenta-1,3-dien-1-yl)-4-phenyloxazolidin-2-one (27)



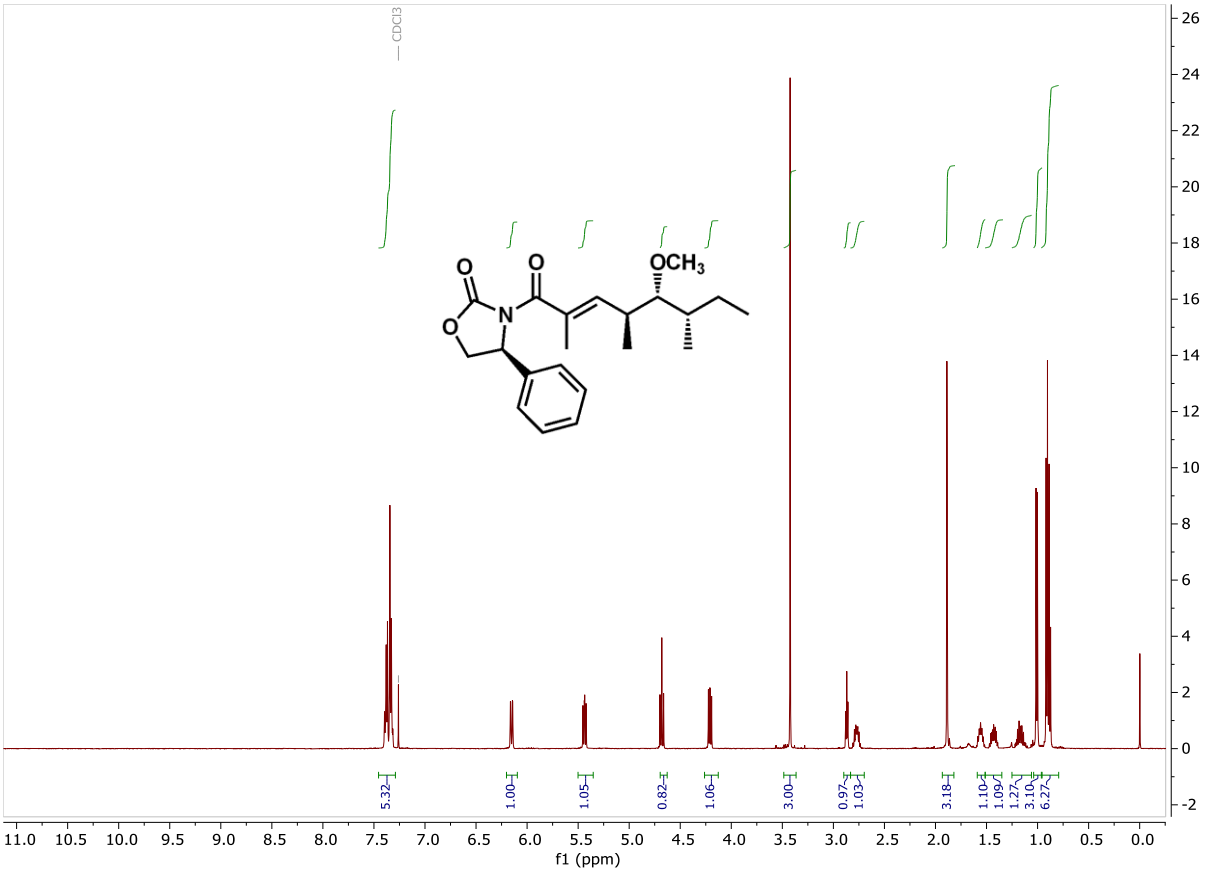
(*S*)-3-((4*S*,5*R*,6*S*,*E*)-5-hydroxy-2,4,6-trimethyloct-2-enoyl)-4-phenyloxazolidin-2-one (28)



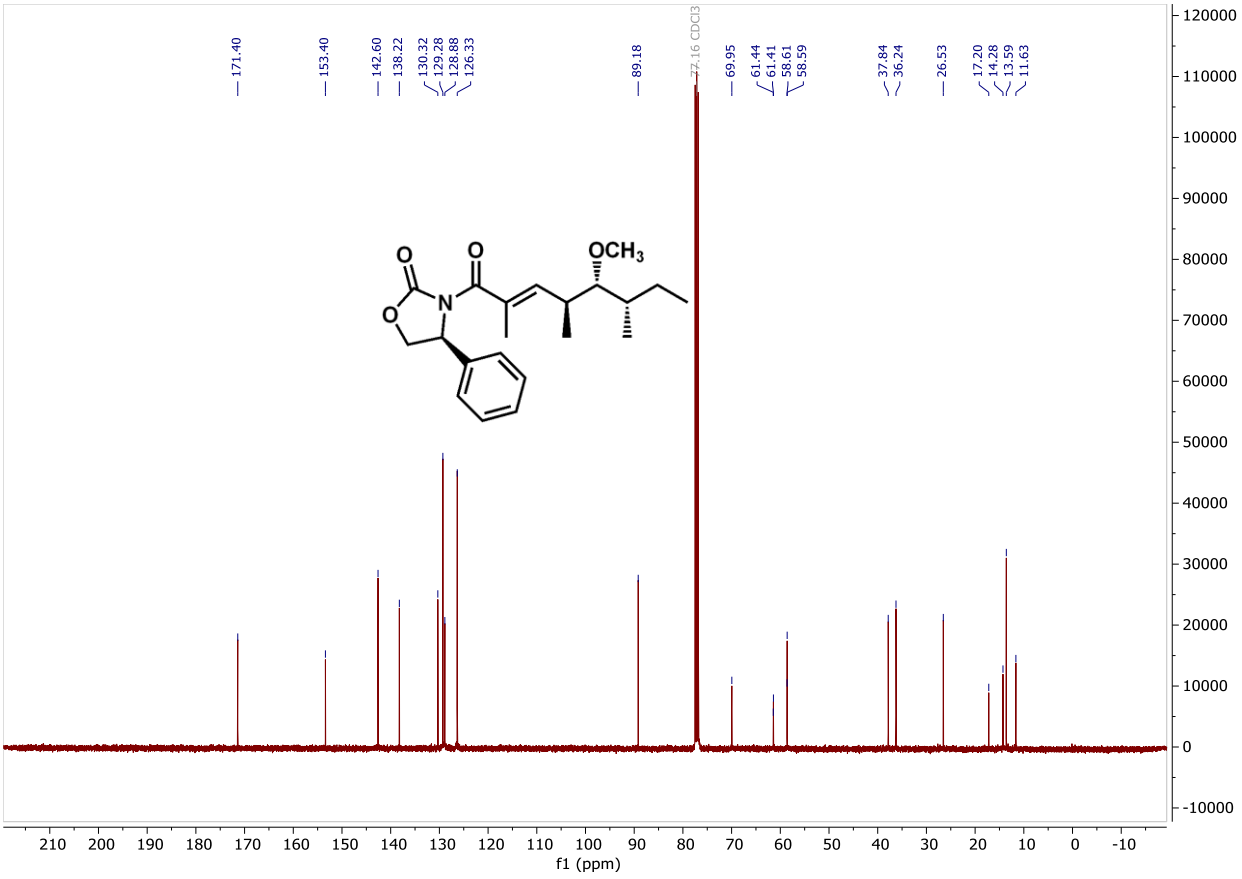
(*S*)-3-((4*S*,5*R*,6*S*,*E*)-5-hydroxy-2,4,6-trimethyloct-2-enoyl)-4-phenyloxazolidin-2-one (28)



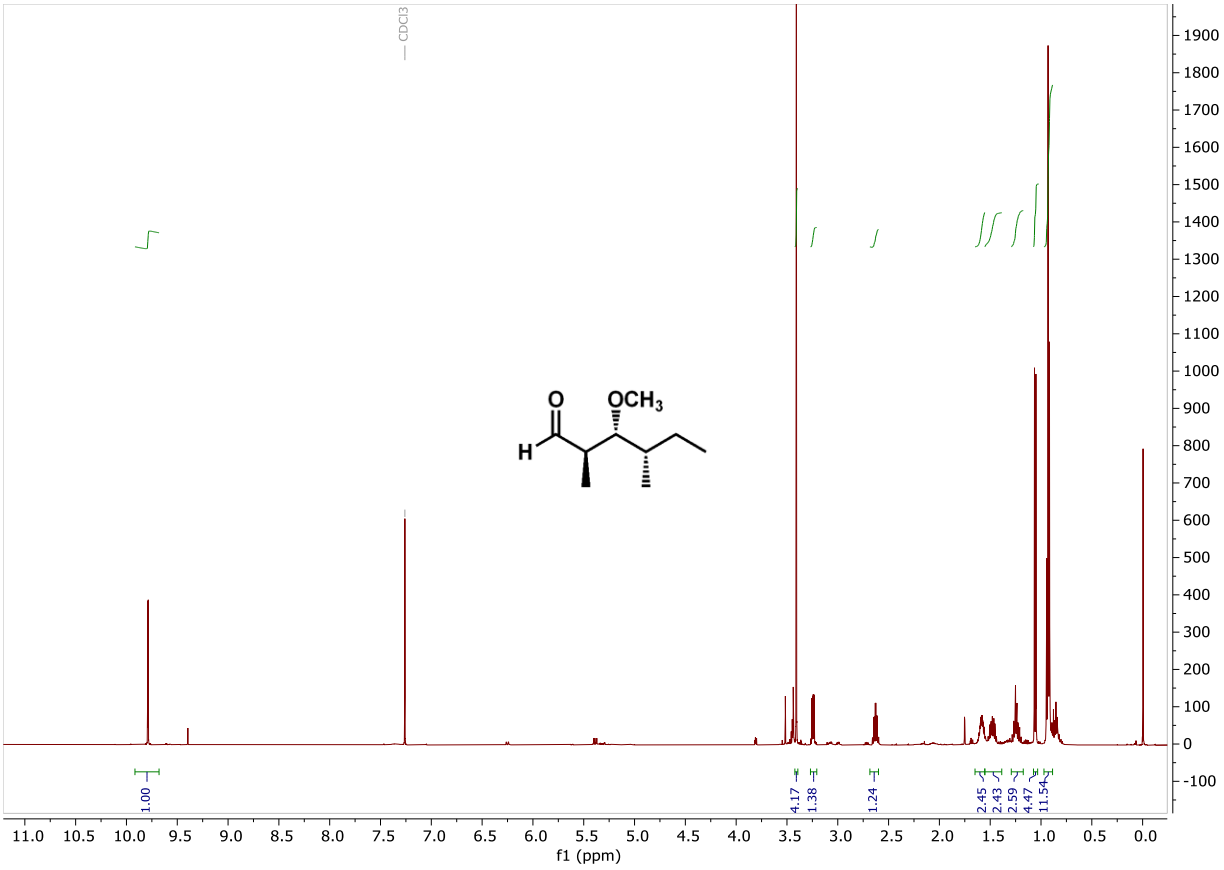
(*S*)-3-((4*S*,5*R*,6*S*,*E*)-5-methoxy-2,4,6-trimethyloct-2-enoyl)-4-phenyloxazolidin-2-one (29)



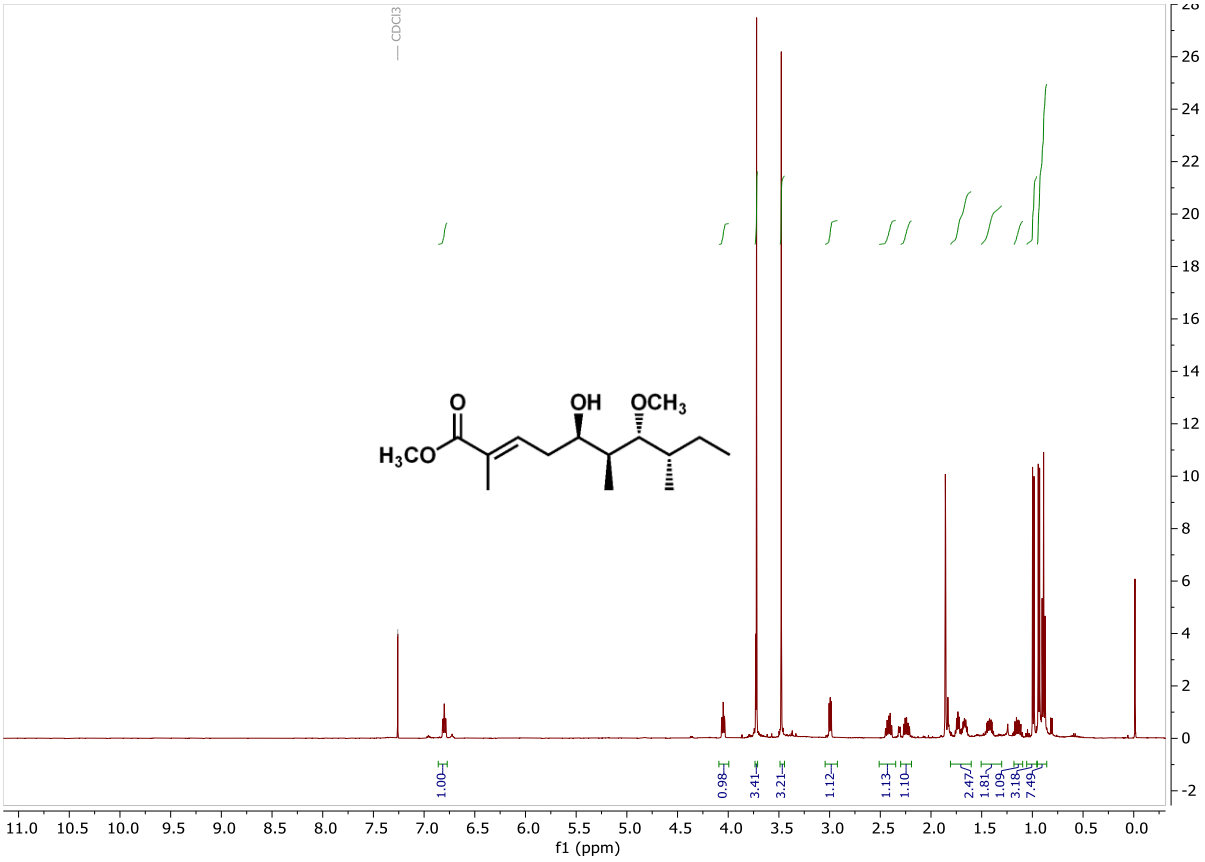
(*S*)-3-((4*S*,5*R*,6*S*,*E*)-5-methoxy-2,4,6-trimethyloct-2-enoyl)-4-phenyloxazolidin-2-one (29)



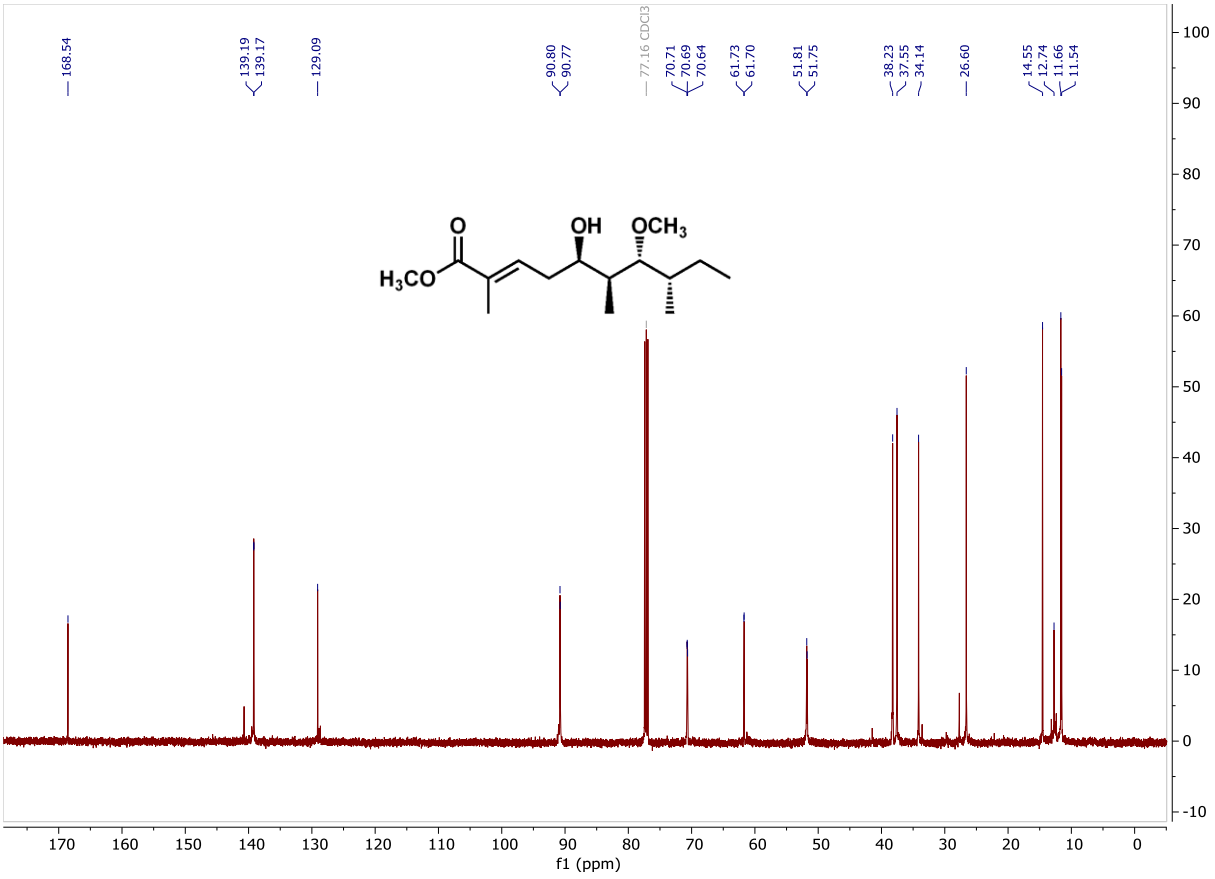
(2*R*,3*R*,4*S*)-3-methoxy-2,4-dimethylhexanal (30)



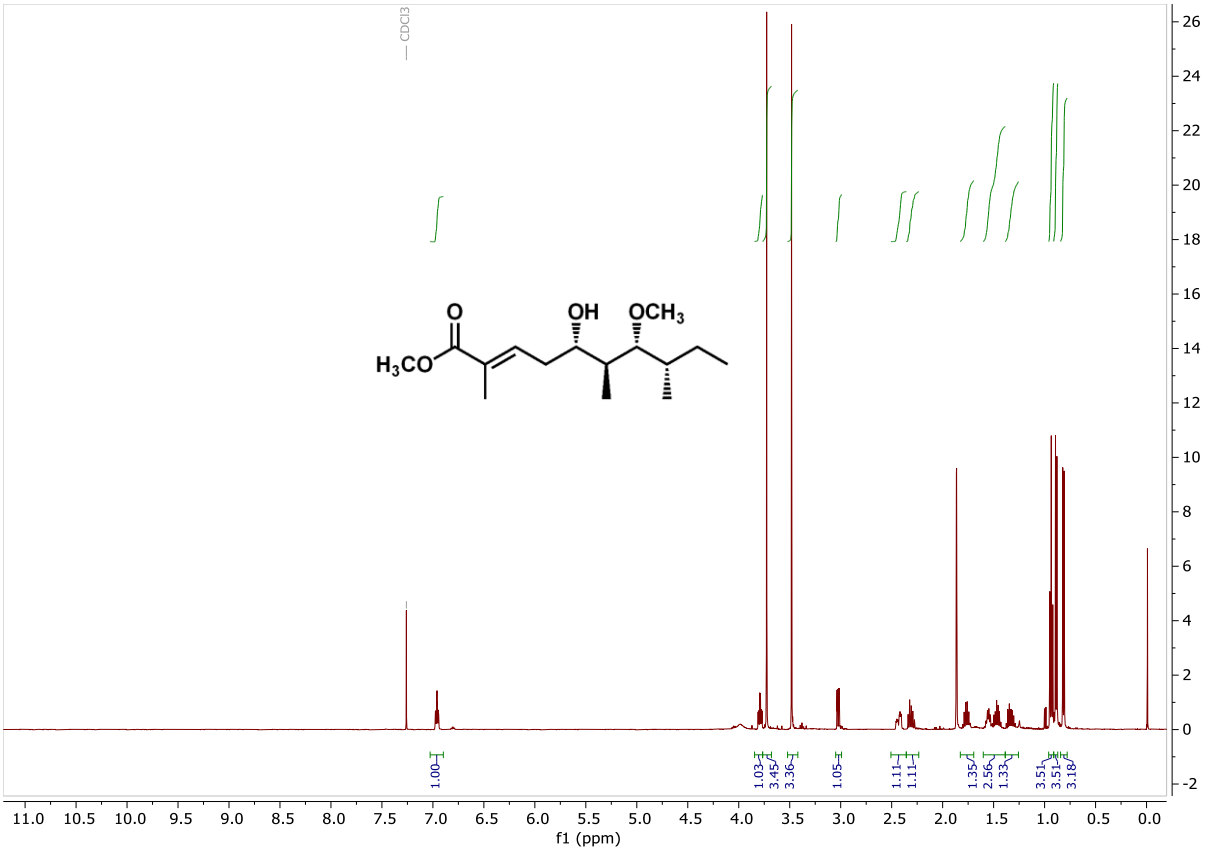
methyl (5*R*,6*S*,7*R*,8*S*,*E*)-5-hydroxy-7-methoxy-2,6,8-trimethyldec-2-enoate (31)



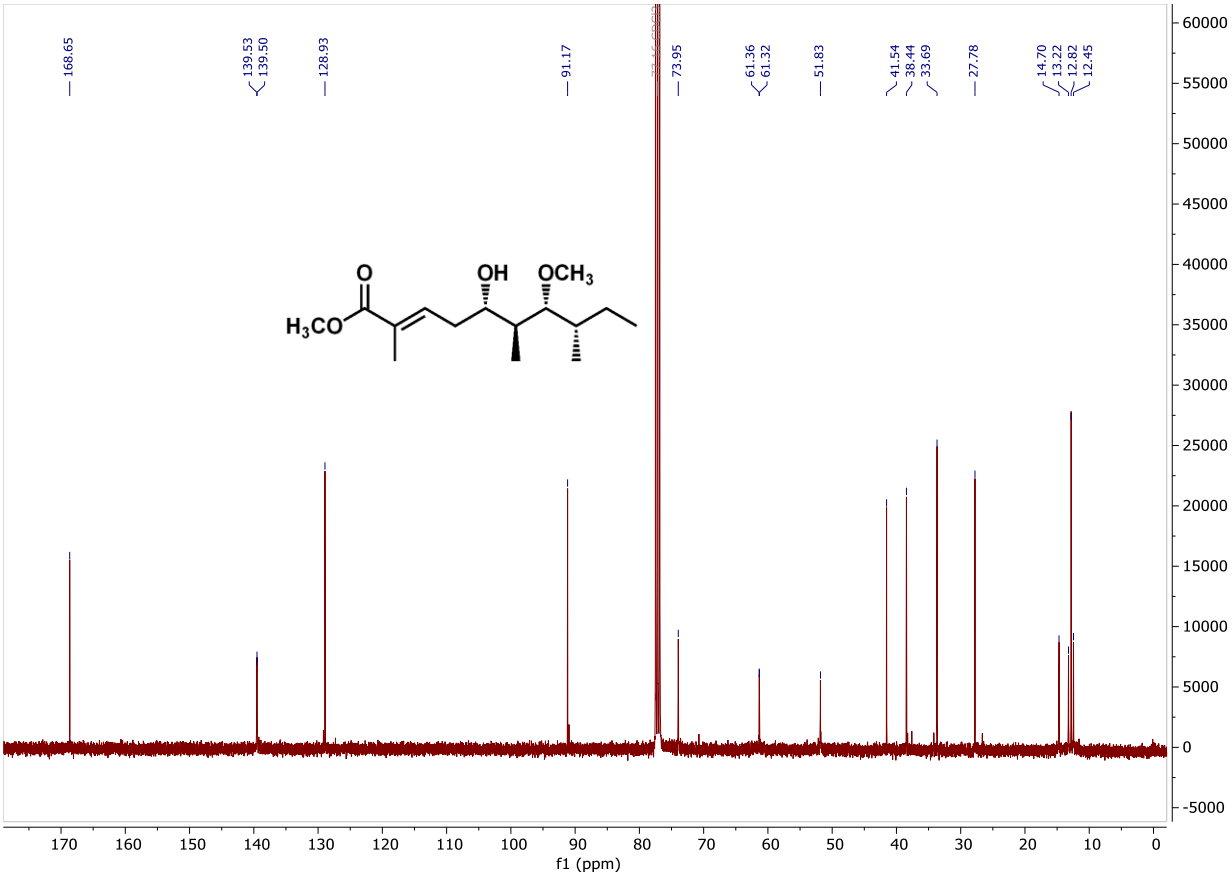
methyl (5*R*,6*S*,7*R*,8*S*,*E*)-5-hydroxy-7-methoxy-2,6,8-trimethyldec-2-enoate (31)



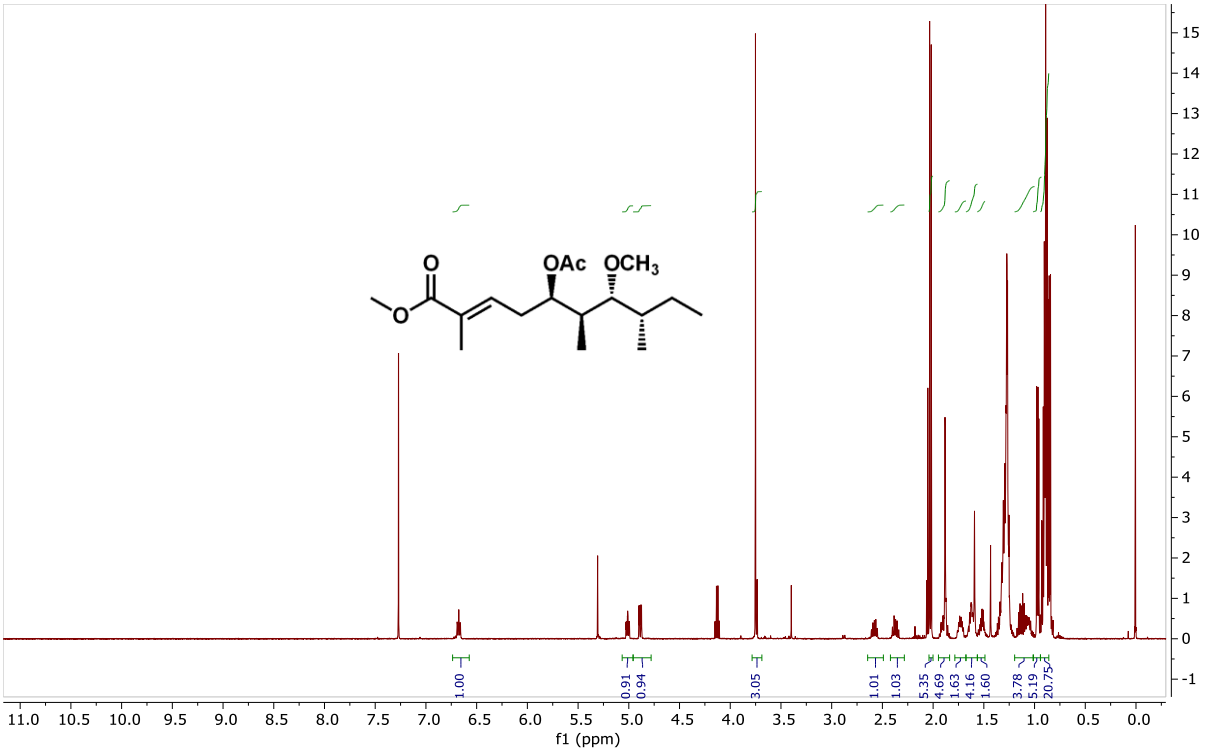
methyl (5*S*,6*S*,7*R*,8*S*,*E*)-5-hydroxy-7-methoxy-2,6,8-trimethyldec-2-enoate (32)



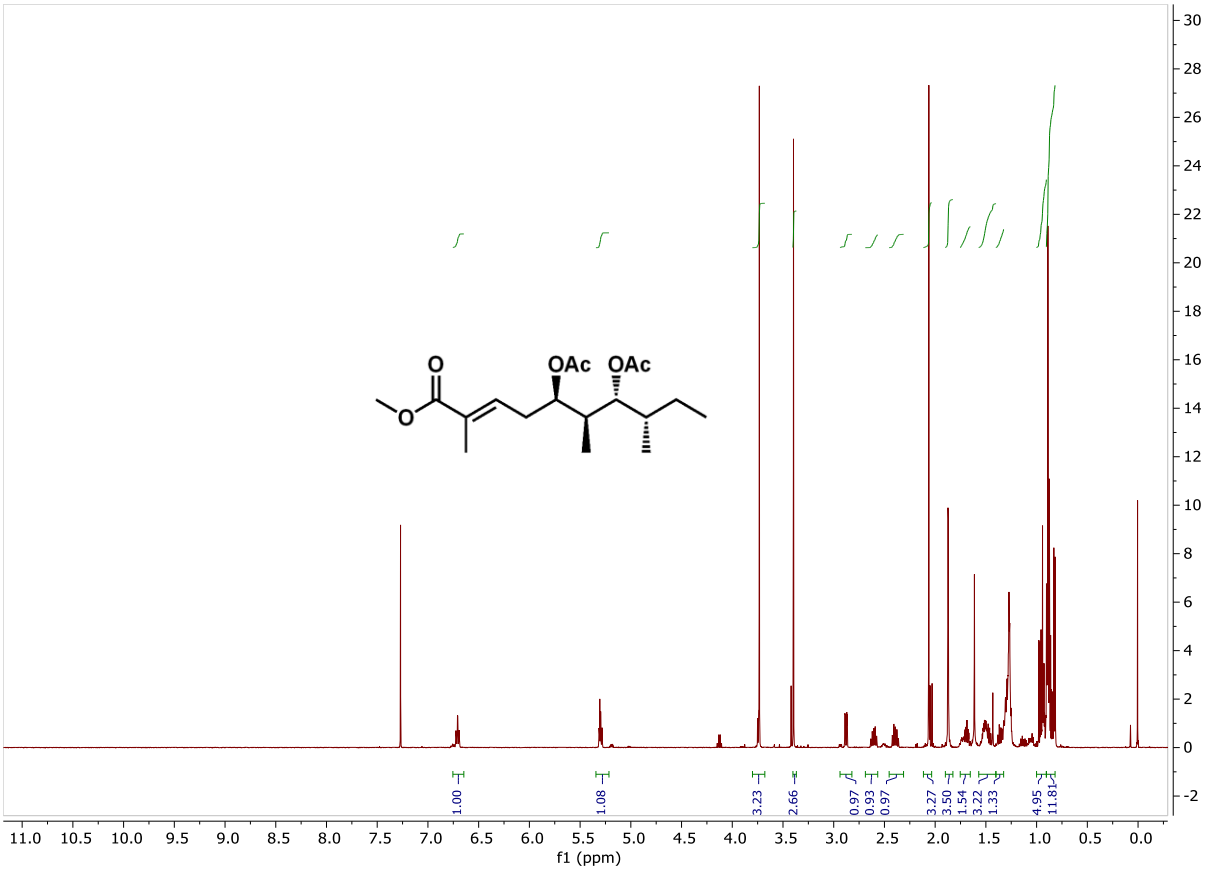
methyl (5*S*,6*S*,7*R*,8*S*,*E*)-5-hydroxy-7-methoxy-2,6,8-trimethyldec-2-enoate (32)



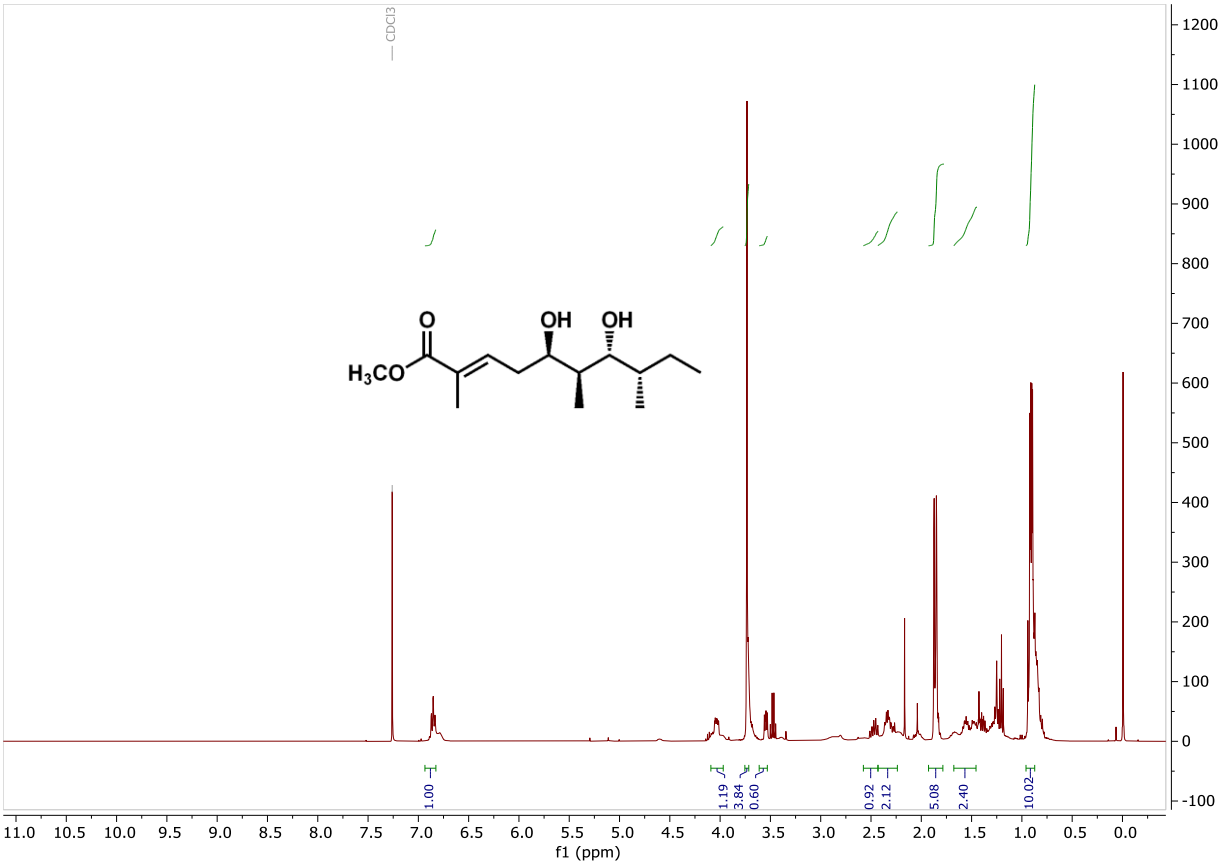
methyl (5*S*,6*S*,7*R*,8*S*,*E*)-5-acetoxy-7-methoxy-2,6,8-trimethyldec-2-enoate (33)



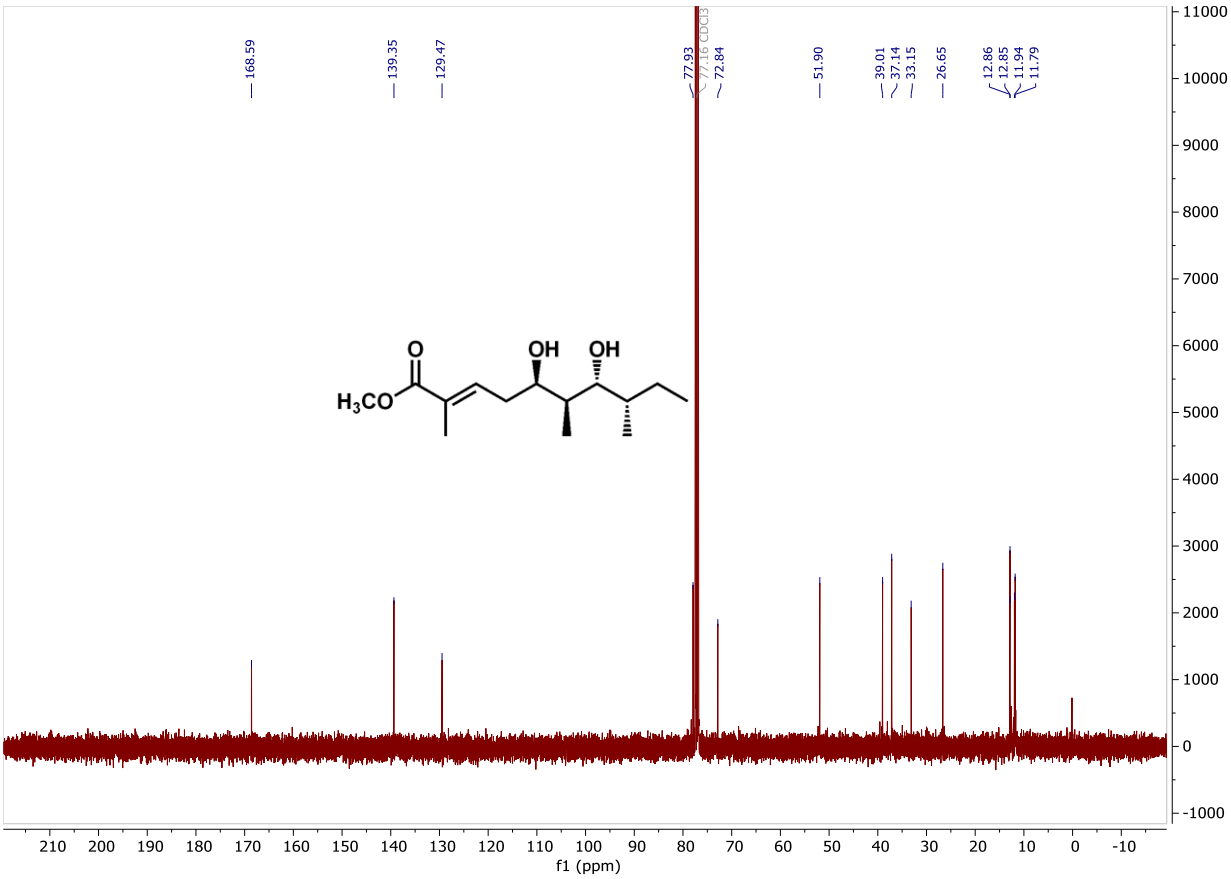
(3*S*,4*R*,5*S*,6*S*,*E*)-10-methoxy-3,5,9-trimethyl-10-oxodec-8-ene-4,6-diyl diacetate (34)



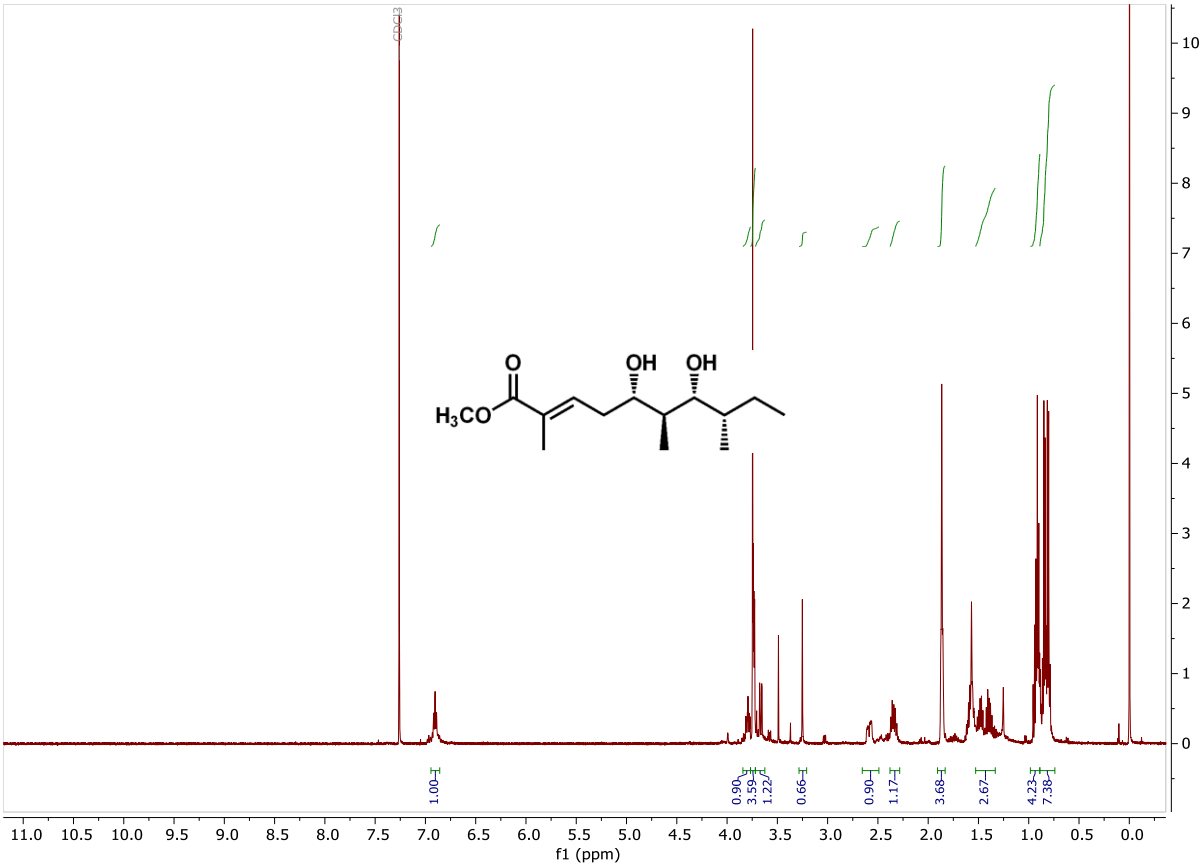
methyl (5*R*,6*S*,7*R*,8*S*,*E*)-5,7-dihydroxy-2,6,8-trimethyldec-2-enoate (35)



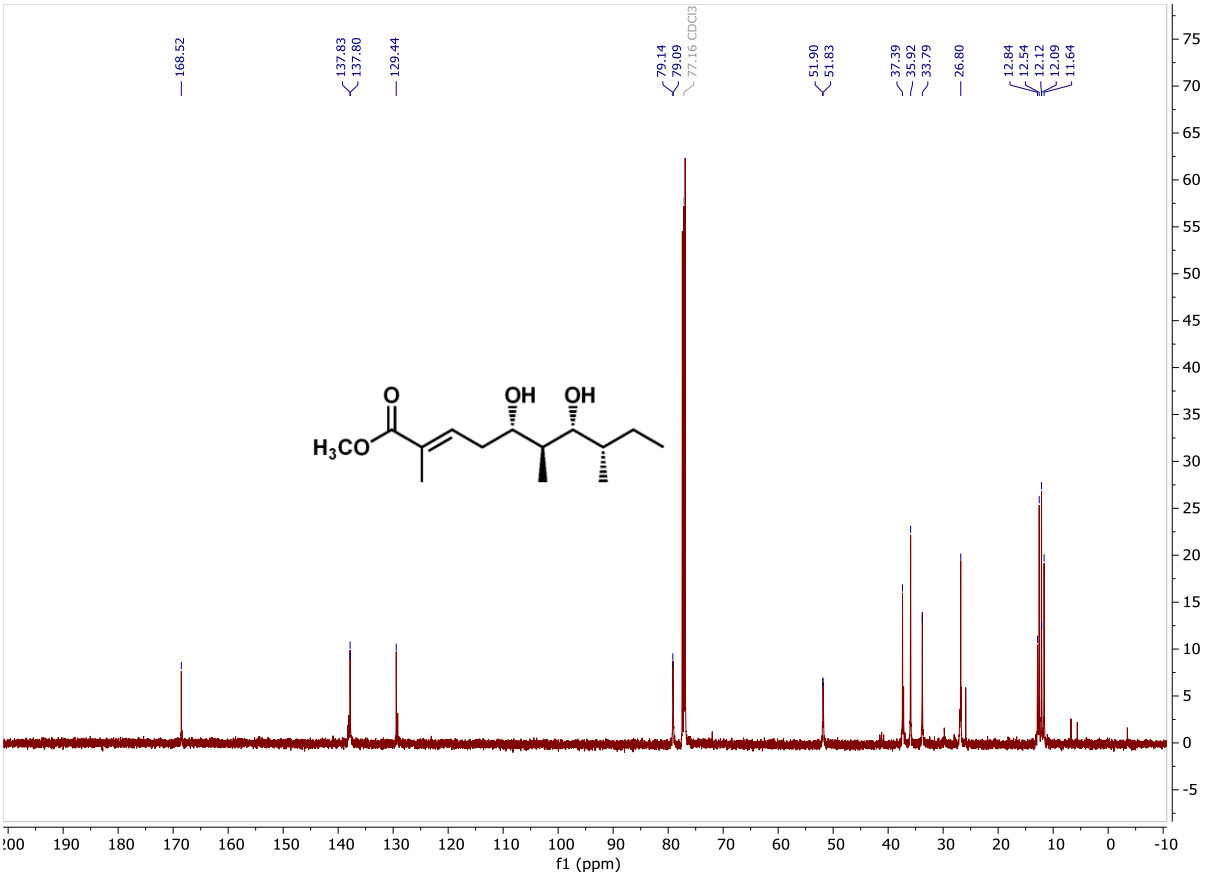
methyl (5*R*,6*S*,7*R*,8*S*,*E*)-5,7-dihydroxy-2,6,8-trimethyldec-2-enoate (35)



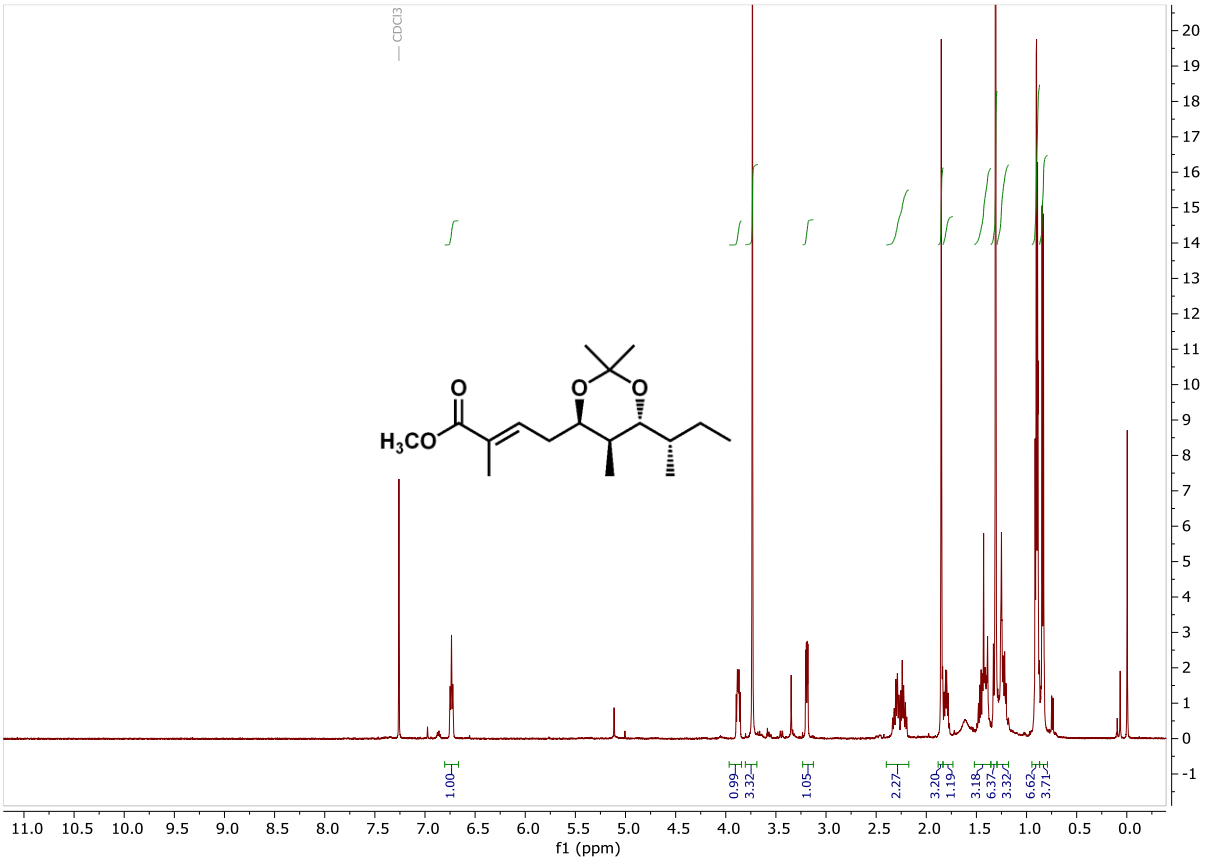
methyl (5*S*,6*S*,7*R*,8*S*,*E*)-5,7-dihydroxy-2,6,8-trimethyldec-2-enoate (36)



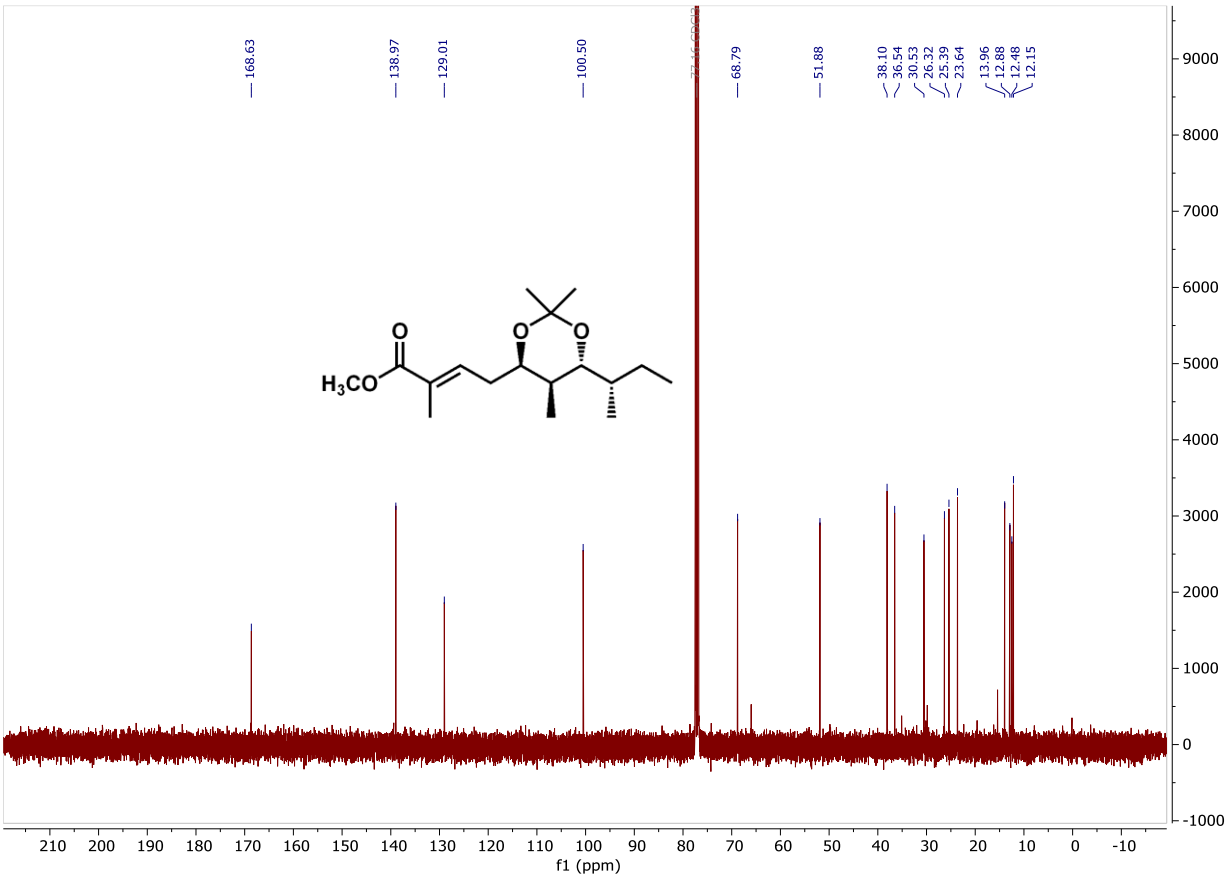
methyl (5*S*,6*S*,7*R*,8*S*,*E*)-5,7-dihydroxy-2,6,8-trimethyldec-2-enoate (36)



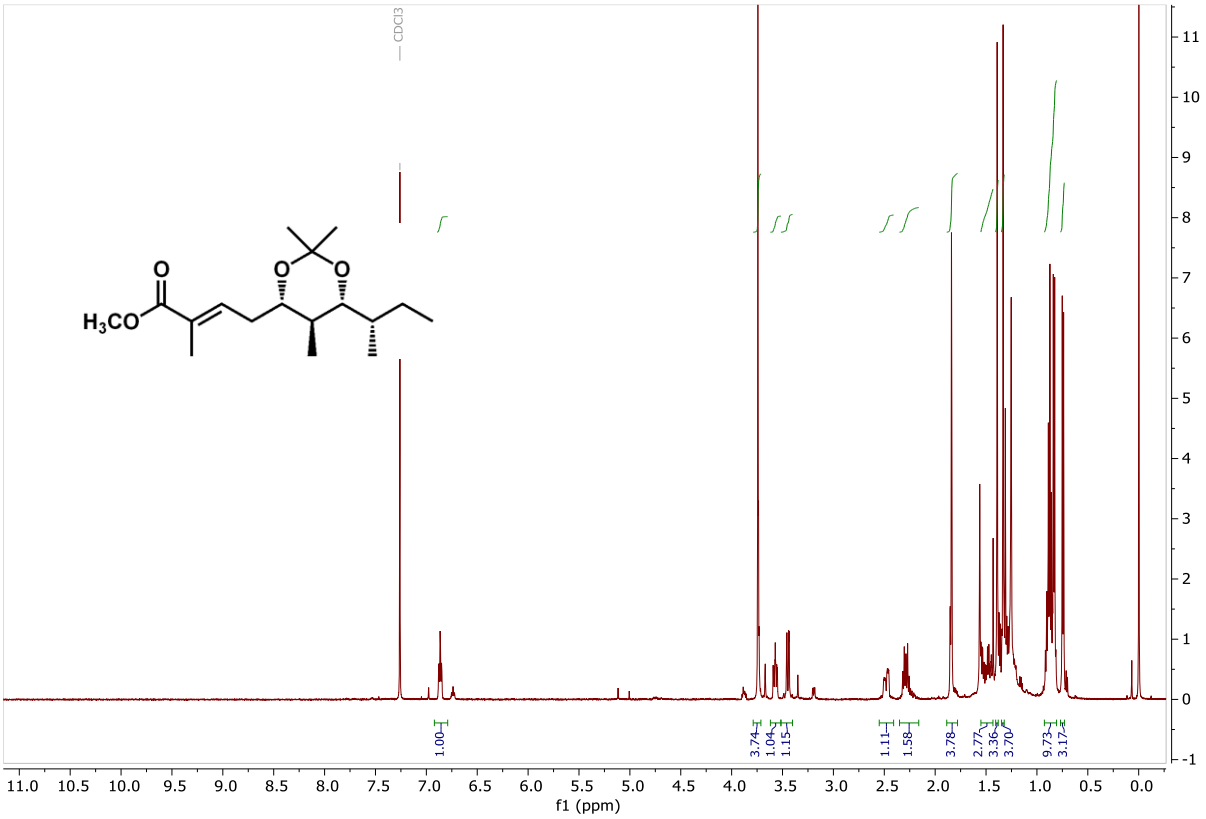
methyl (*E*)-4-((4*R*,5*S*,6*R*)-6-((*S*)-sec-butyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-2-methylbut-2-enoate (37)



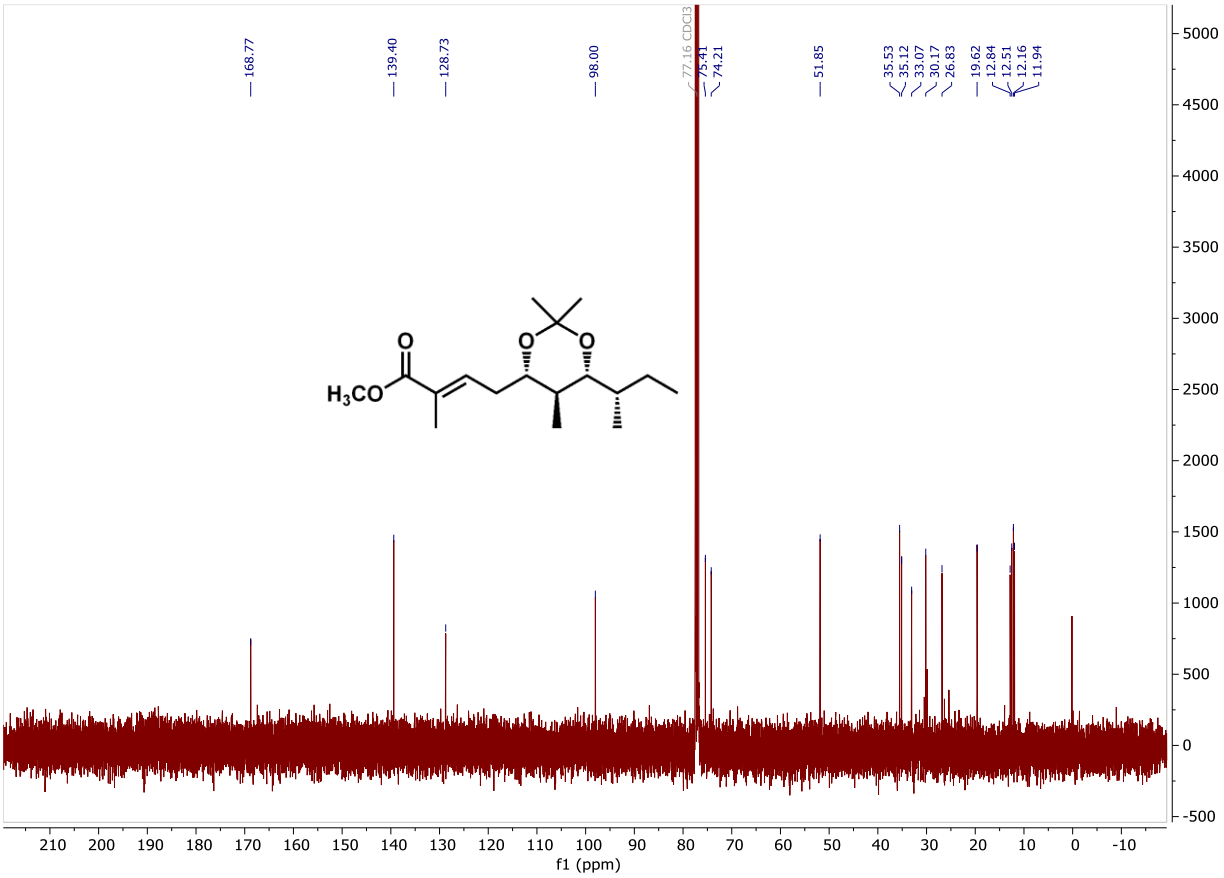
methyl (*E*)-4-((4*R*,5*S*,6*R*)-6-((*S*)-sec-butyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-2-methylbut-2-enoate (37)



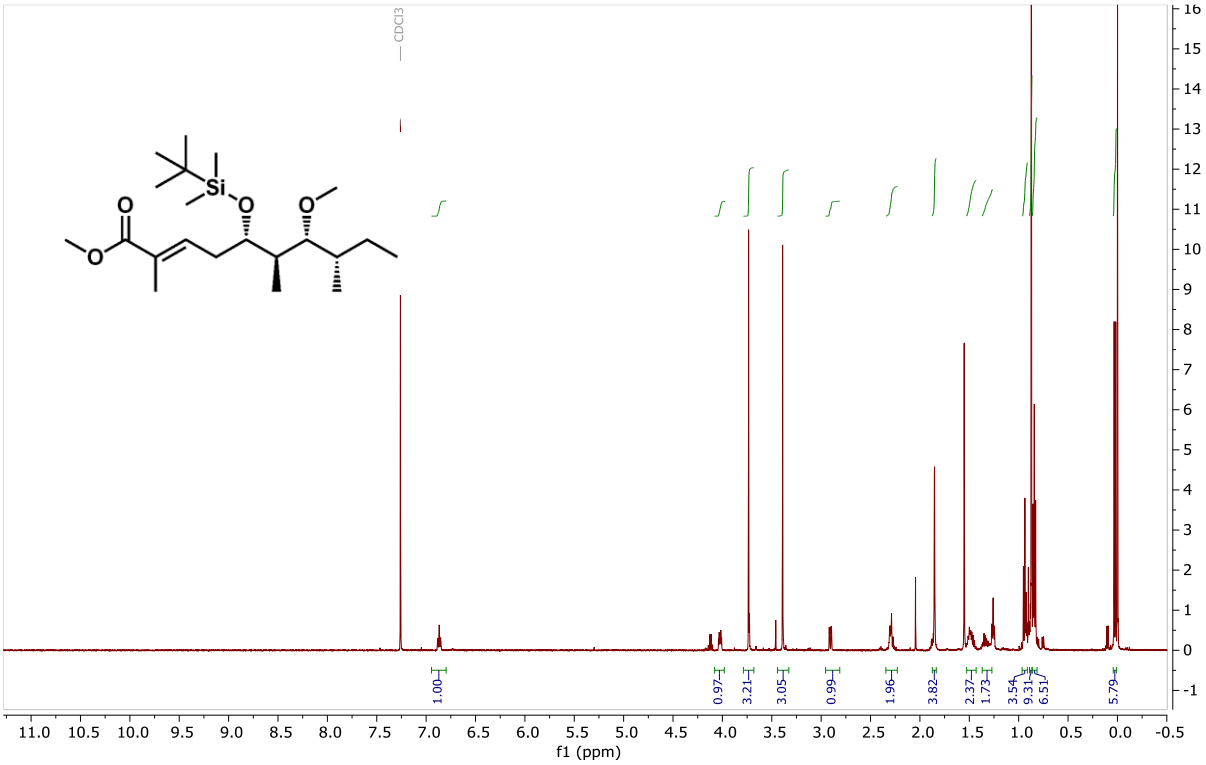
methyl (*E*)-4-((4*S*,5*S*,6*R*)-6-((*S*)-sec-butyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-2-methylbut-2-enoate (38)



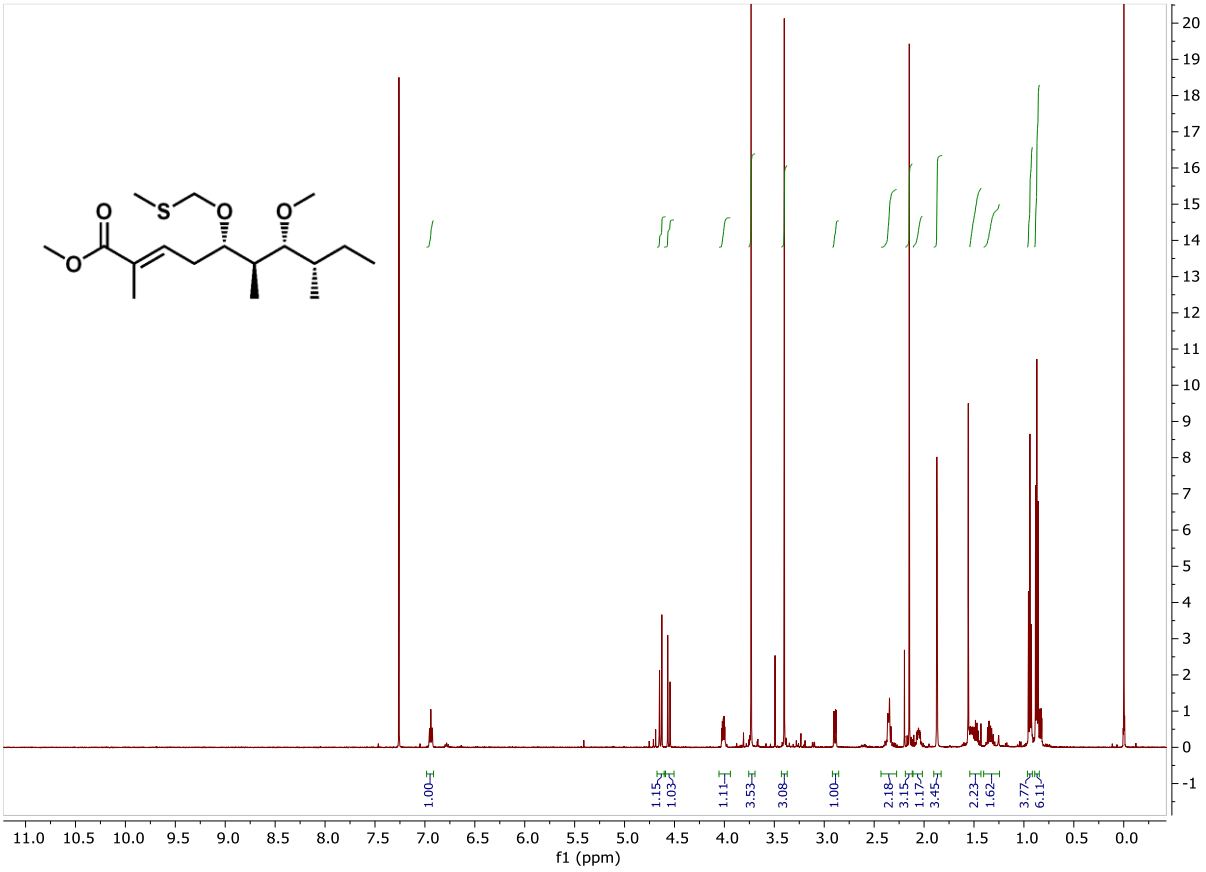
methyl (*E*)-4-((4*S*,5*S*,6*R*)-6-((*S*)-sec-butyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-2-methylbut-2-enoate (38)



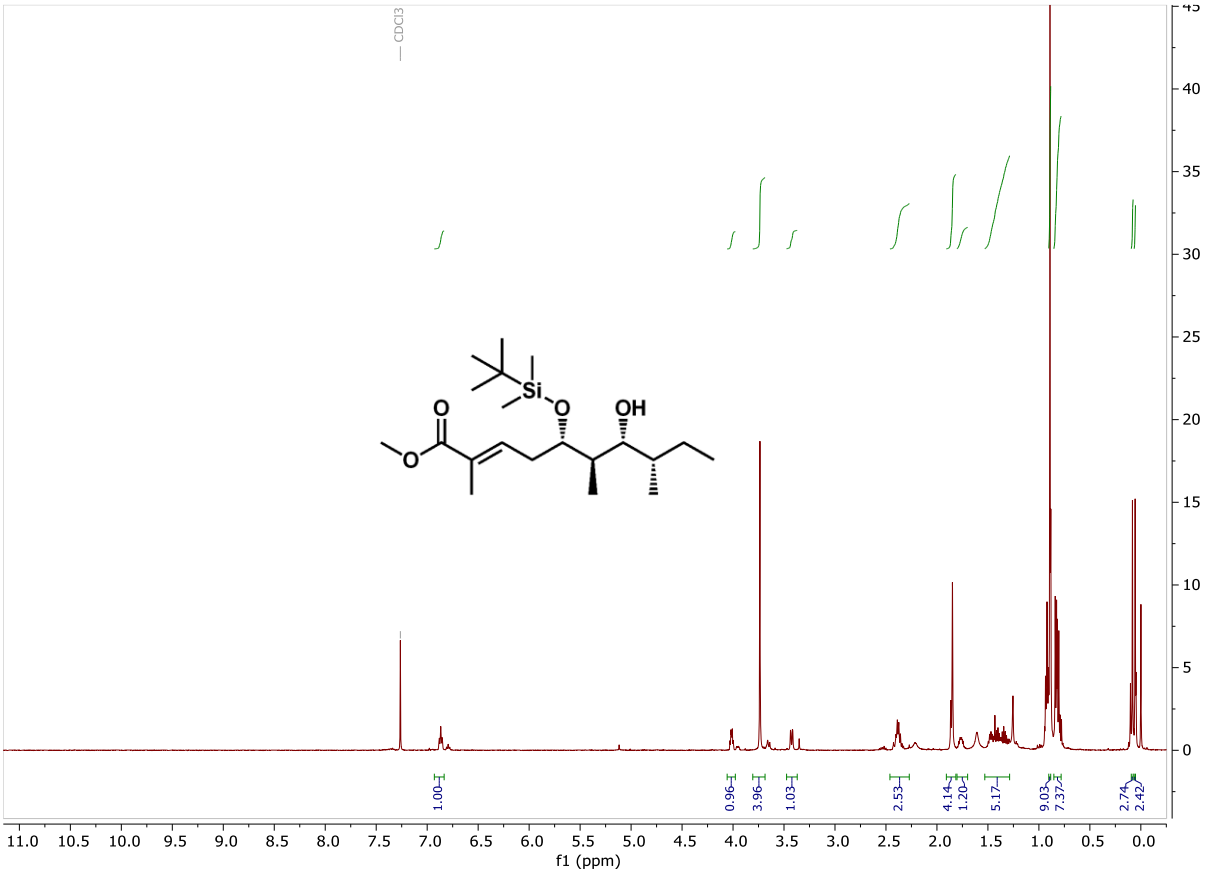
methyl (5*S*,6*R*,7*R*,8*S*,*E*)-5-((tert-butyldimethylsilyl)oxy)-7-methoxy-2,6,8-trimethyldec-2-enoate (39)



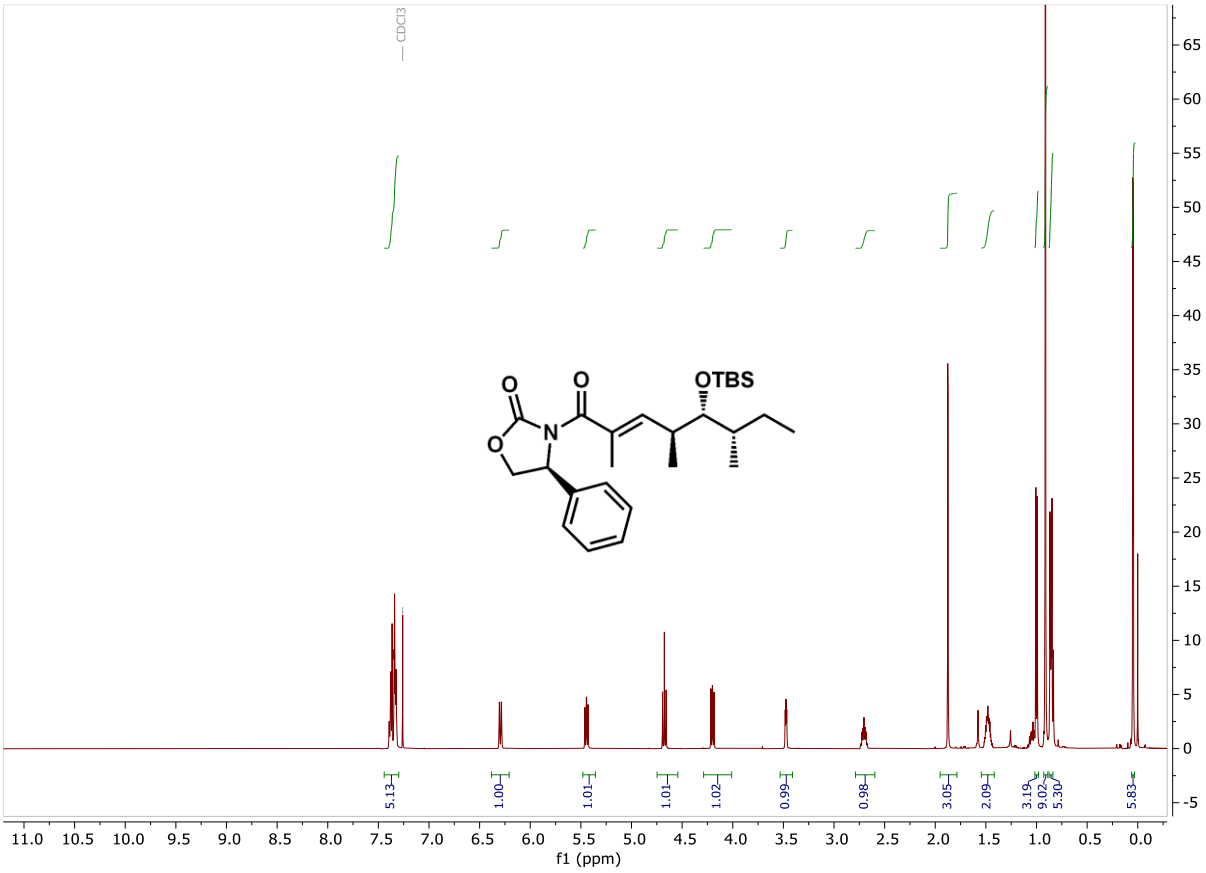
methyl (5*S*,6*S*,7*R*,8*S*,*E*)-7-methoxy-2,6,8-trimethyl-5-((methylthio)methoxy)dec-2-enoate (40)



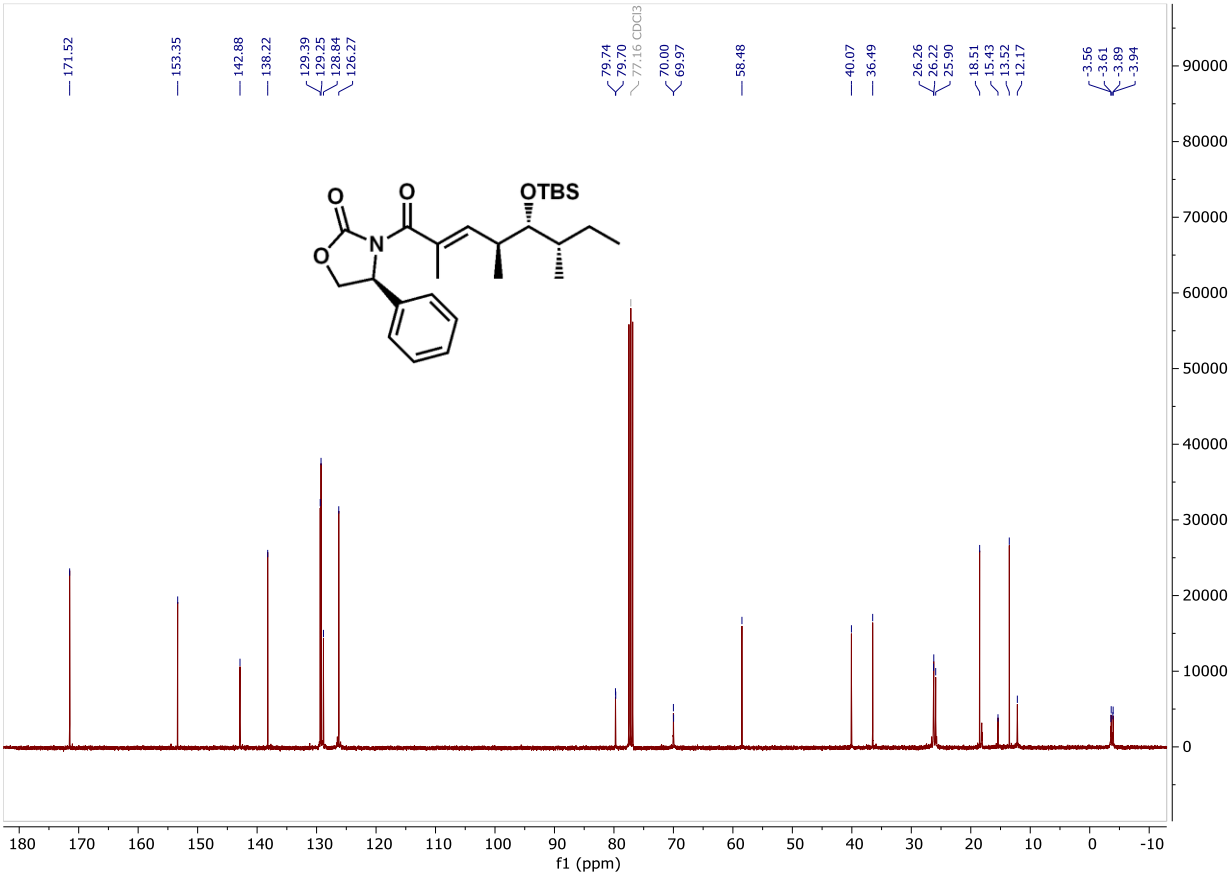
methyl (5*S*,6*R*,7*R*,8*S*,*E*)-5-((tert-butyldimethylsilyl)oxy)-7-hydroxy-2,6,8-trimethyldec-2-enoate (41)



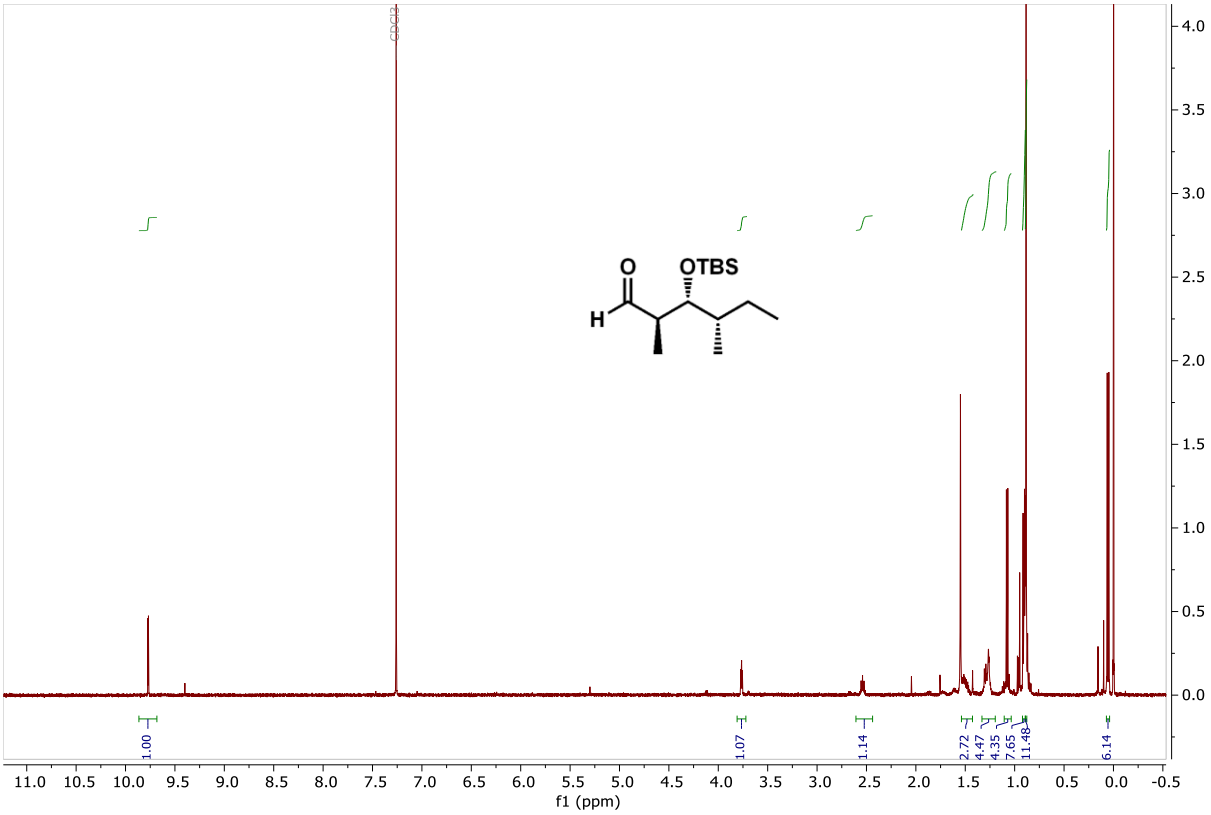
(*S*)-3-((4*S*,5*R*,6*S*,*E*)-5-((tert-butyldimethylsilyl)oxy)-2,4,6-trimethyloct-2-enoyl)-4-phenyloxazolidin-2-one (42)



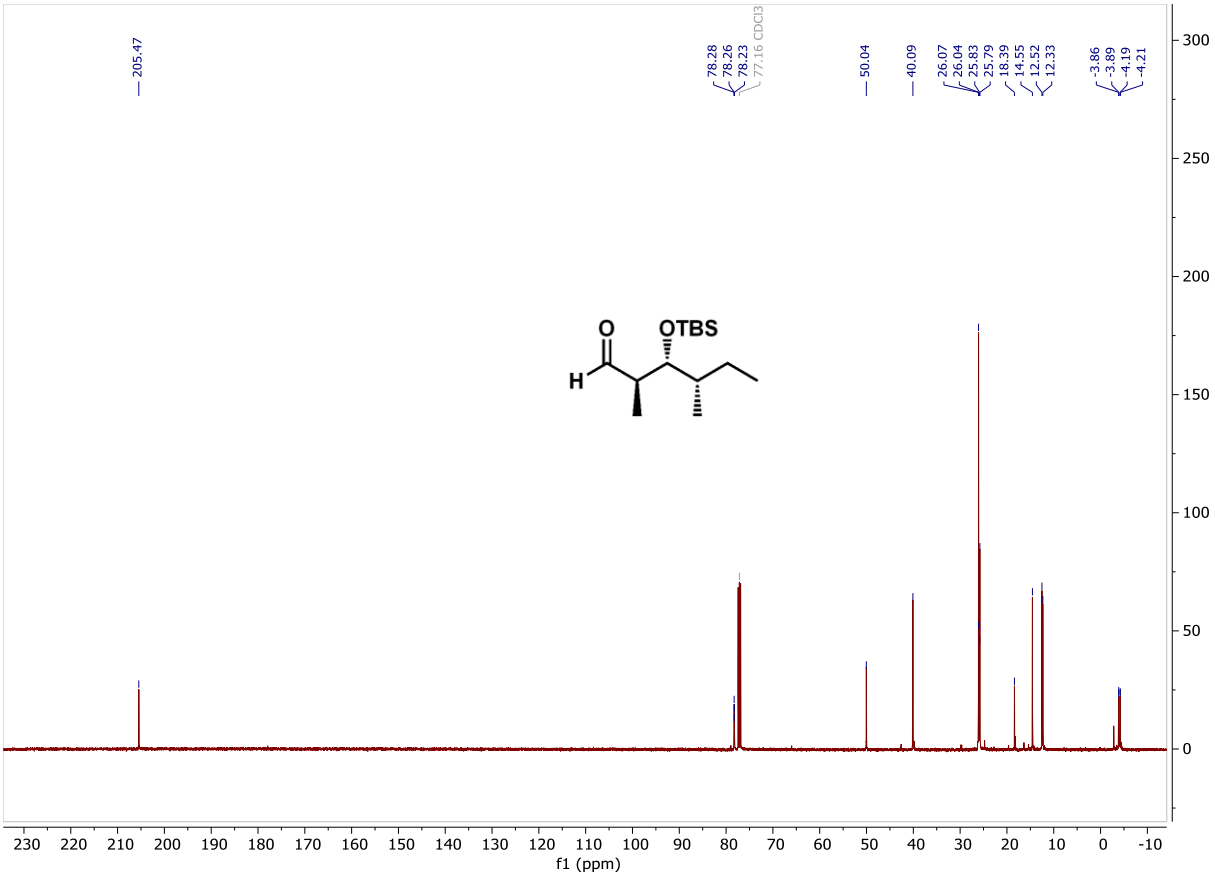
(*S*)-3-((4*S*,5*R*,6*S*,*E*)-5-((tert-butyldimethylsilyl)oxy)-2,4,6-trimethyloct-2-enoyl)-4-phenyloxazolidin-2-one (42)



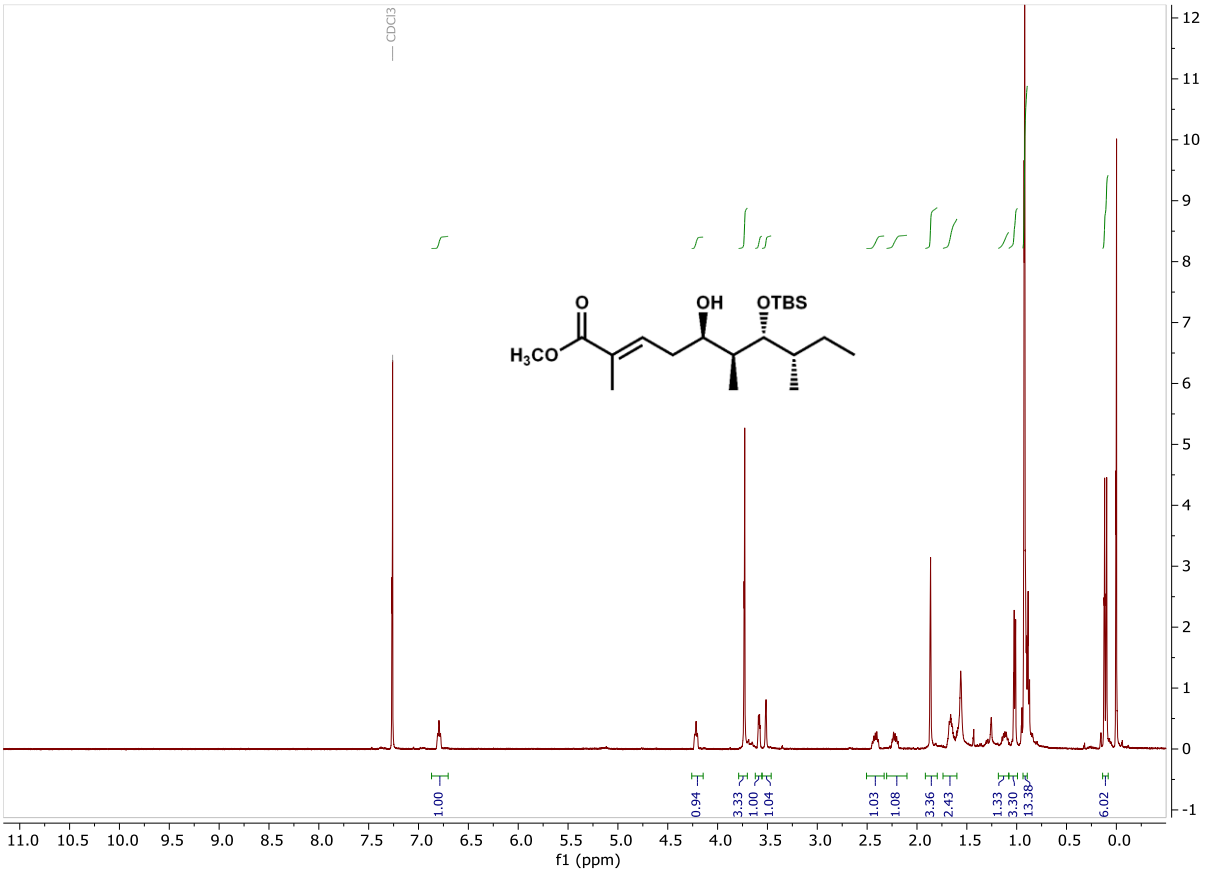
(2*R*,3*R*,4*S*)-3-((tert-butyldimethylsilyl)oxy)-2,4-dimethylhexanal (43)



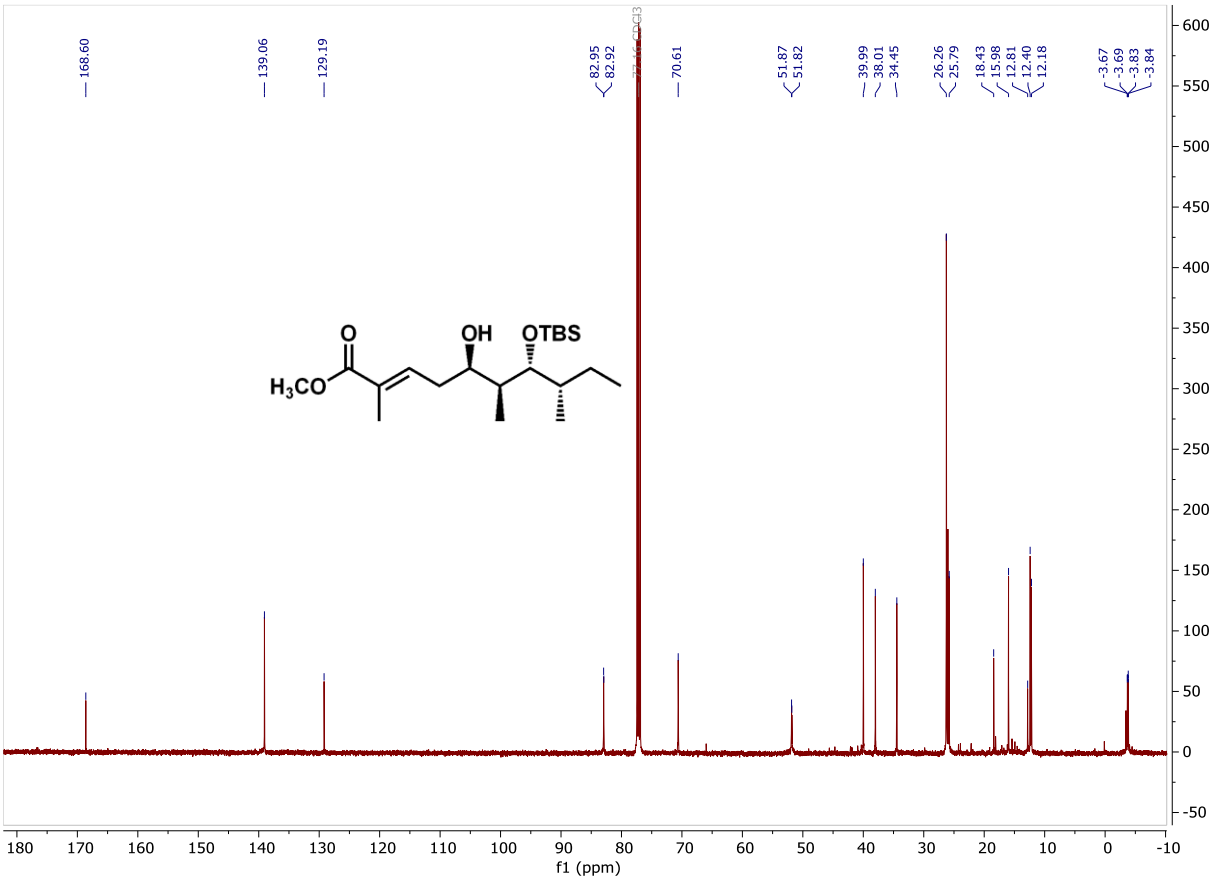
(2*R*,3*R*,4*S*)-3-((tert-butyldimethylsilyl)oxy)-2,4-dimethylhexanal (43)



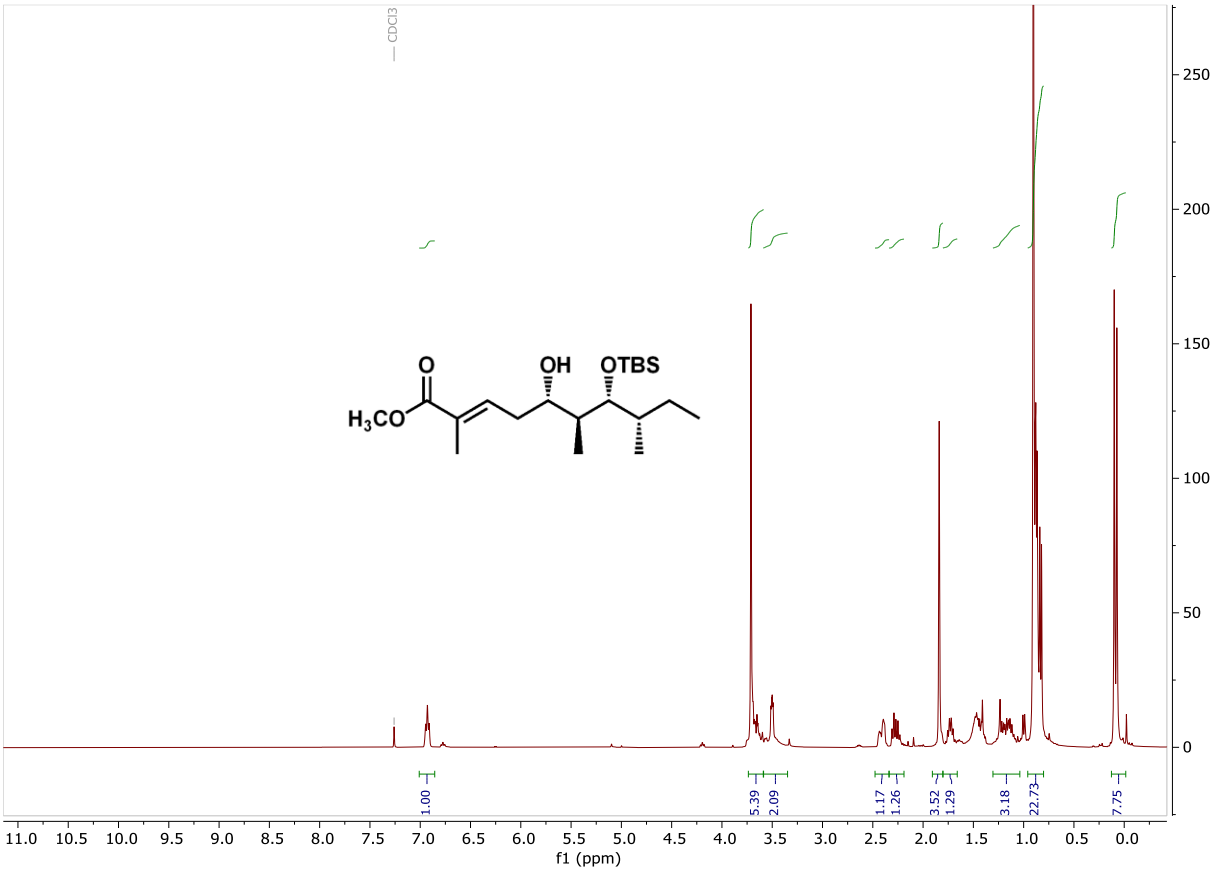
methyl (5*R*,6*S*,7*R*,8*S*,*E*)-7-((tert-butyldimethylsilyl)oxy)-5-hydroxy-2,6,8-trimethyldec-2-enoate (44)



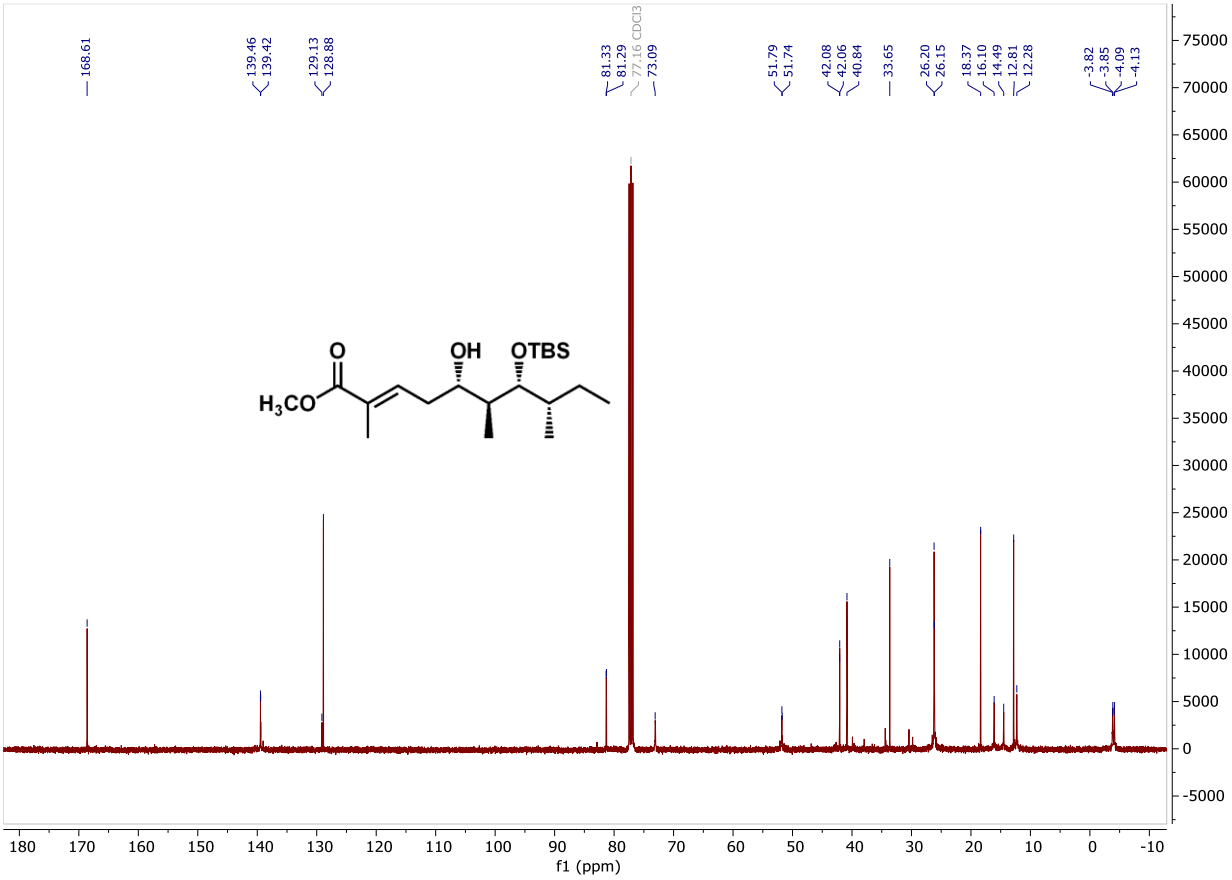
methyl (5*R*,6*S*,7*R*,8*S*,*E*)-7-((tert-butyldimethylsilyl)oxy)-5-hydroxy-2,6,8-trimethyldec-2-enoate (44)



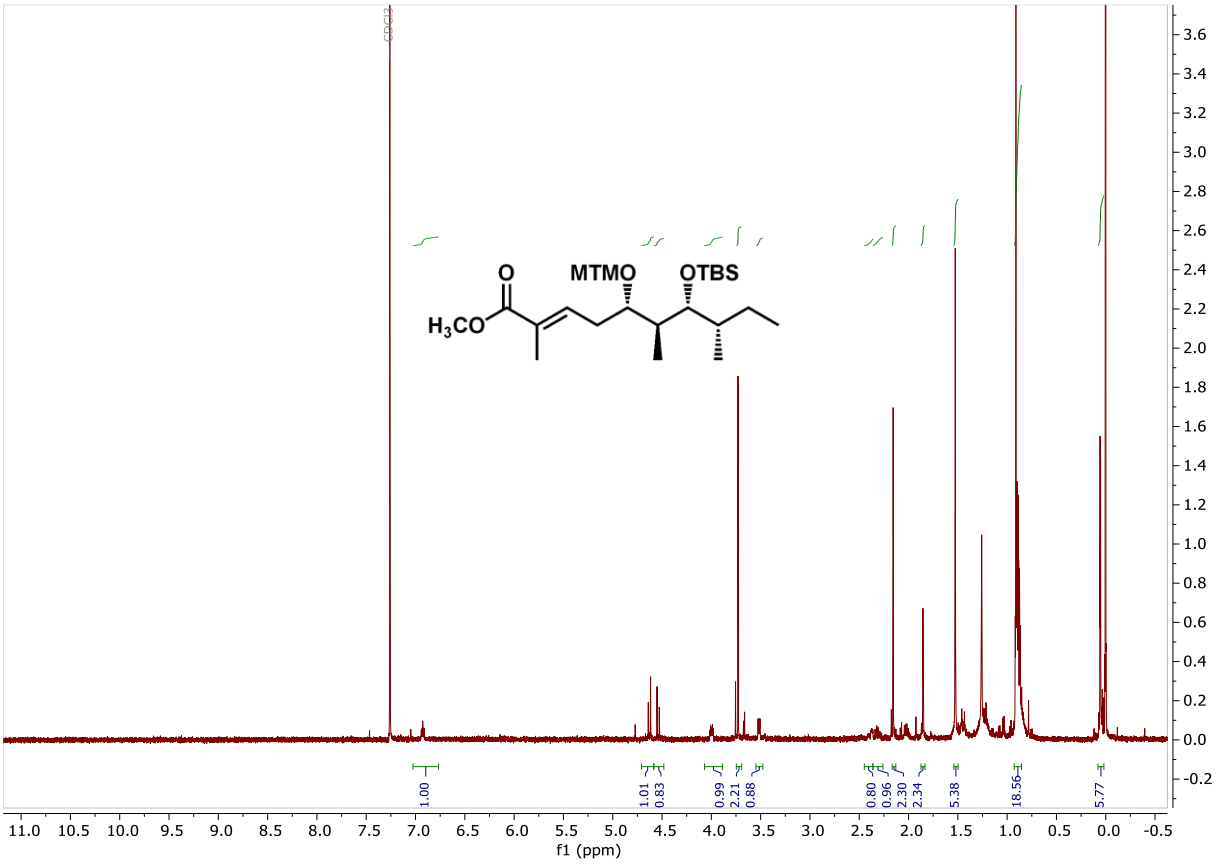
methyl (5*S*,6*S*,7*R*,8*S*,*E*)-7-((tert-butyldimethylsilyl)oxy)-5-hydroxy-2,6,8-trimethyldec-2-enoate (45)



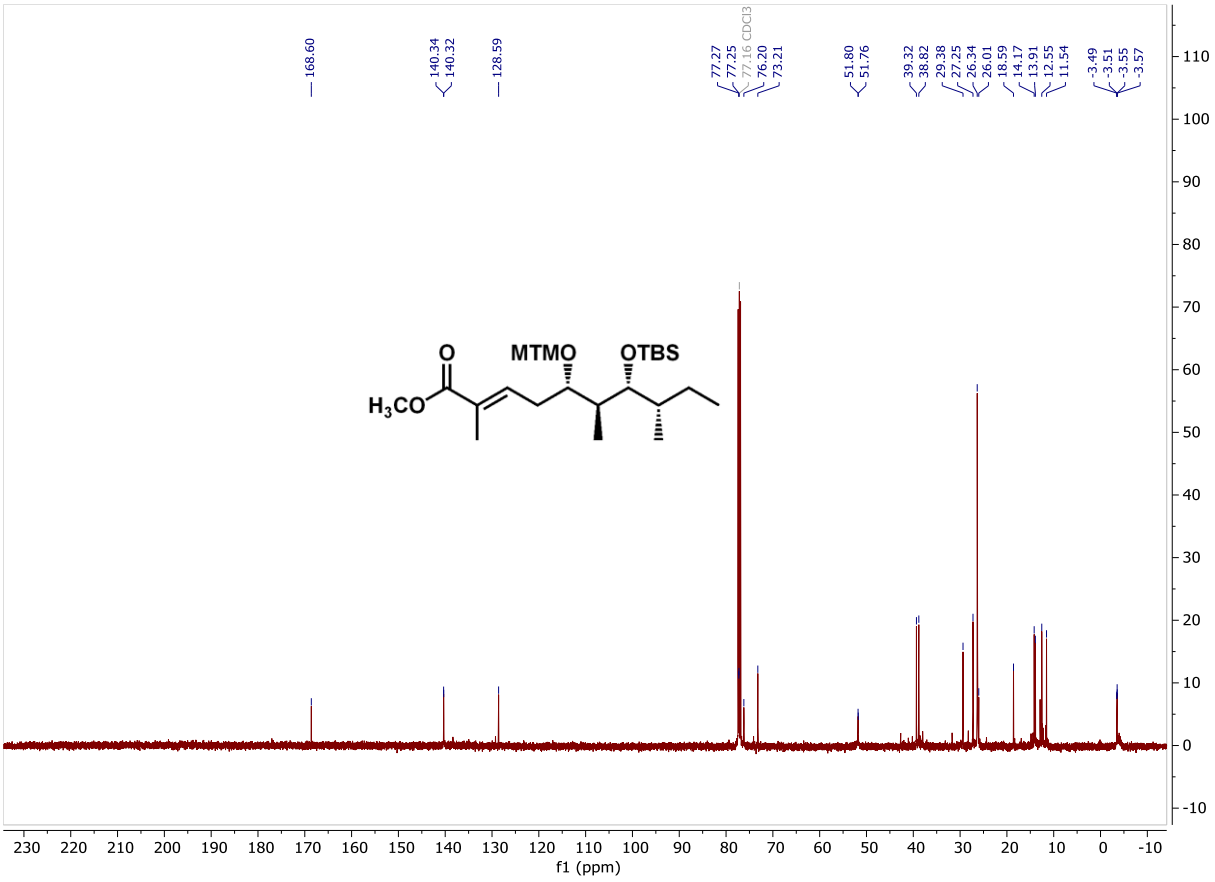
methyl (5*S*,6*S*,7*R*,8*S*,*E*)-7-((tert-butyldimethylsilyl)oxy)-5-hydroxy-2,6,8-trimethyldec-2-enoate (45)



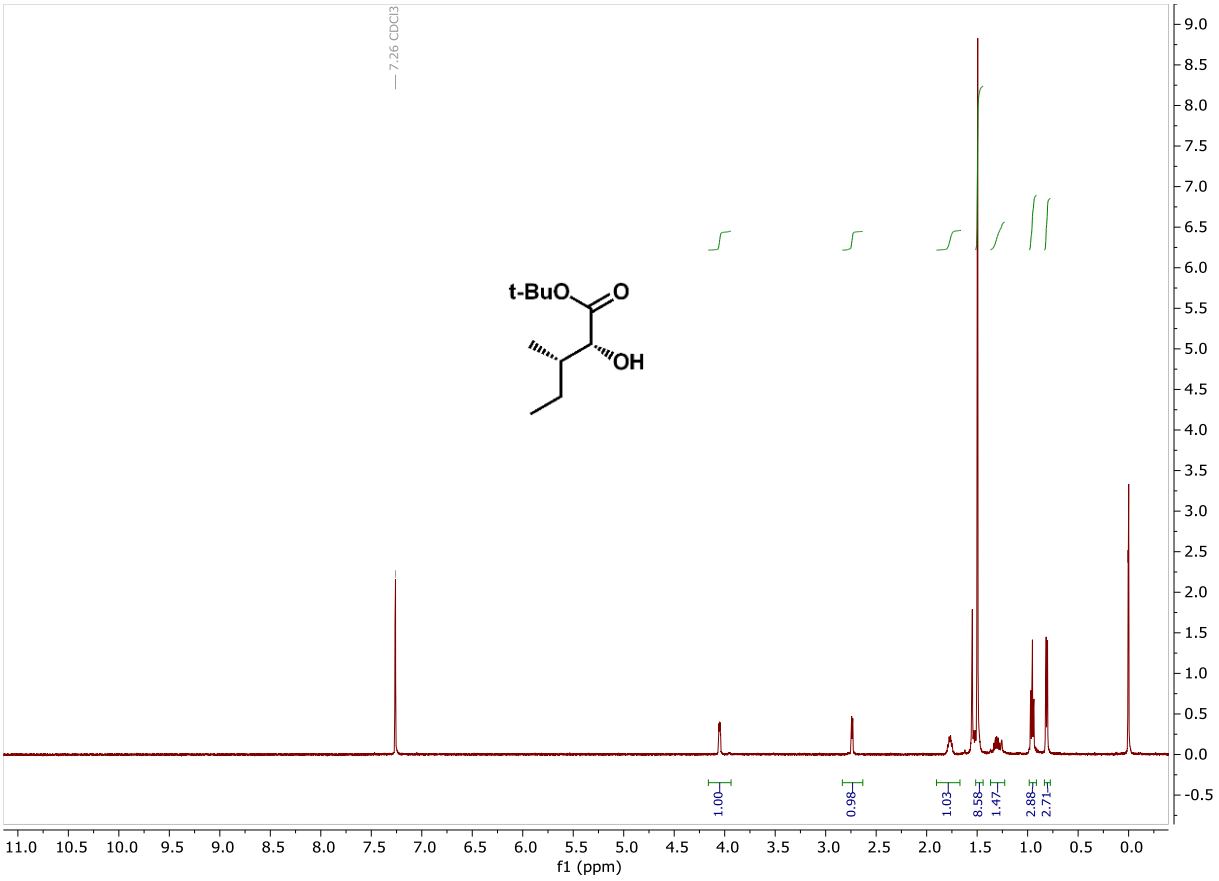
methyl (5*S*,6*S*,7*R*,8*S*,*E*)-7-((tert-butyldimethylsilyl)oxy)-2,6,8-trimethyl-5-((methylthio)methoxy)dec-2-enoate (46)



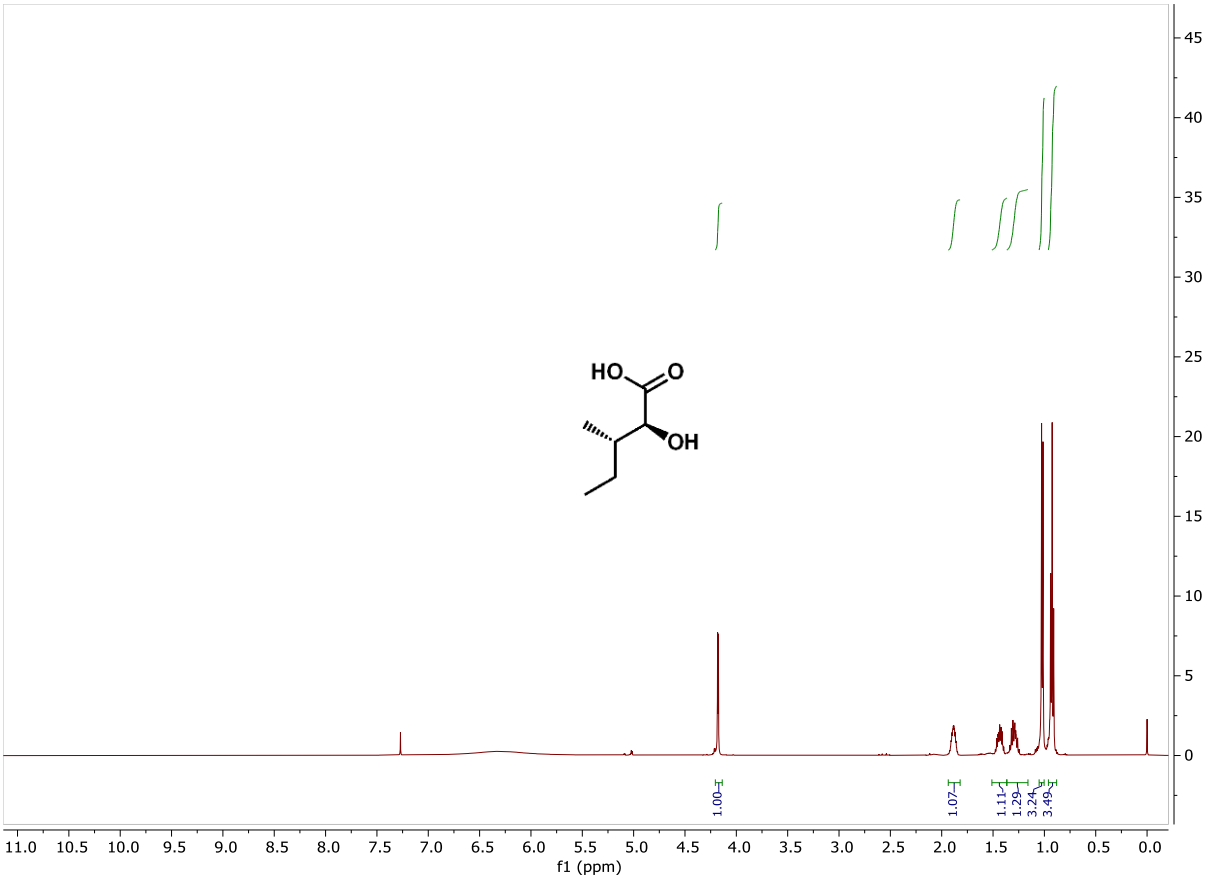
methyl (5*S*,6*S*,7*R*,8*S*,*E*)-7-((tert-butyldimethylsilyl)oxy)-2,6,8-trimethyl-5-((methylthio)methoxy)dec-2-enoate (46)



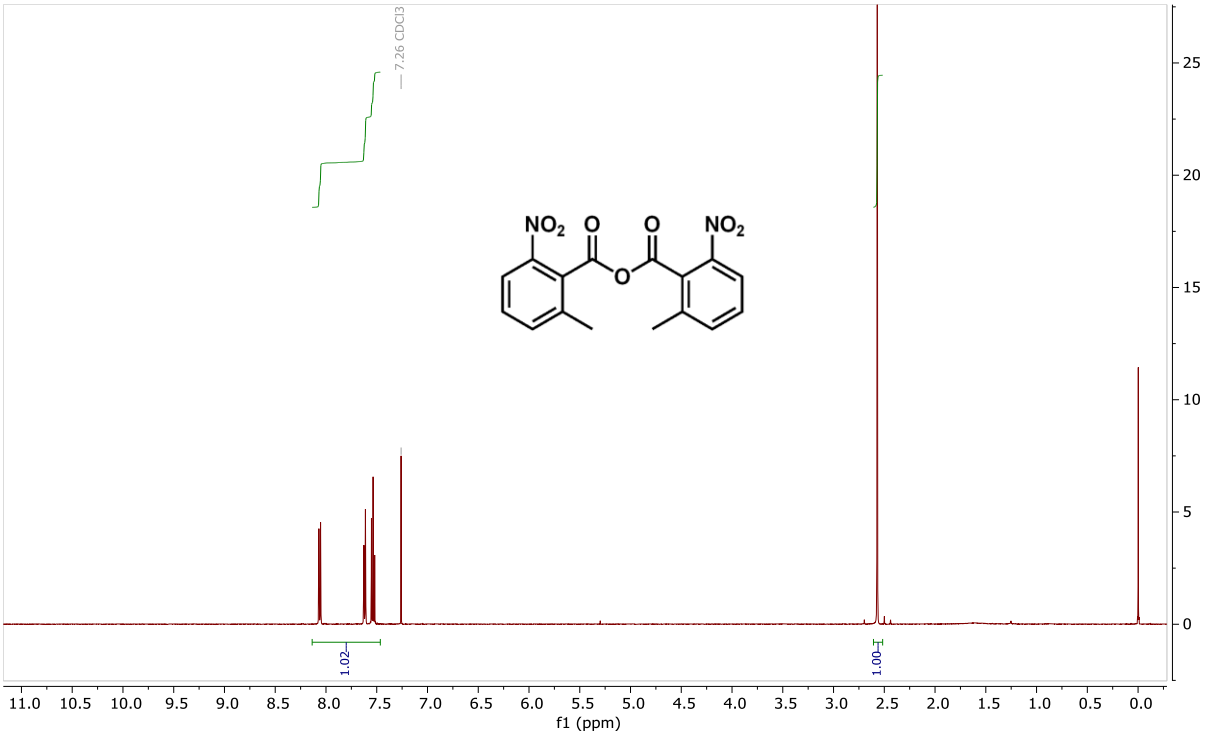
tert-butyl (2*R*,3*S*)-2-hydroxy-3-methylpentanoate (47)



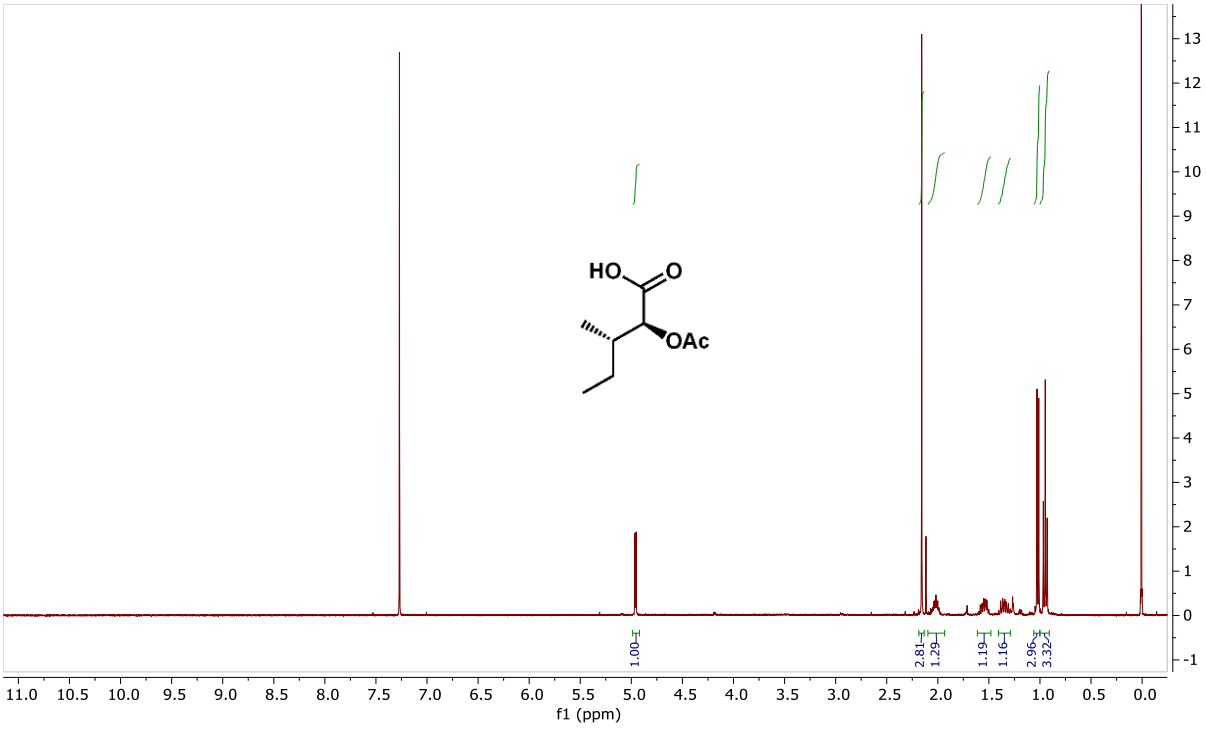
2*S*-Hydroxy-3*S*-methylpentanoic acid (51)



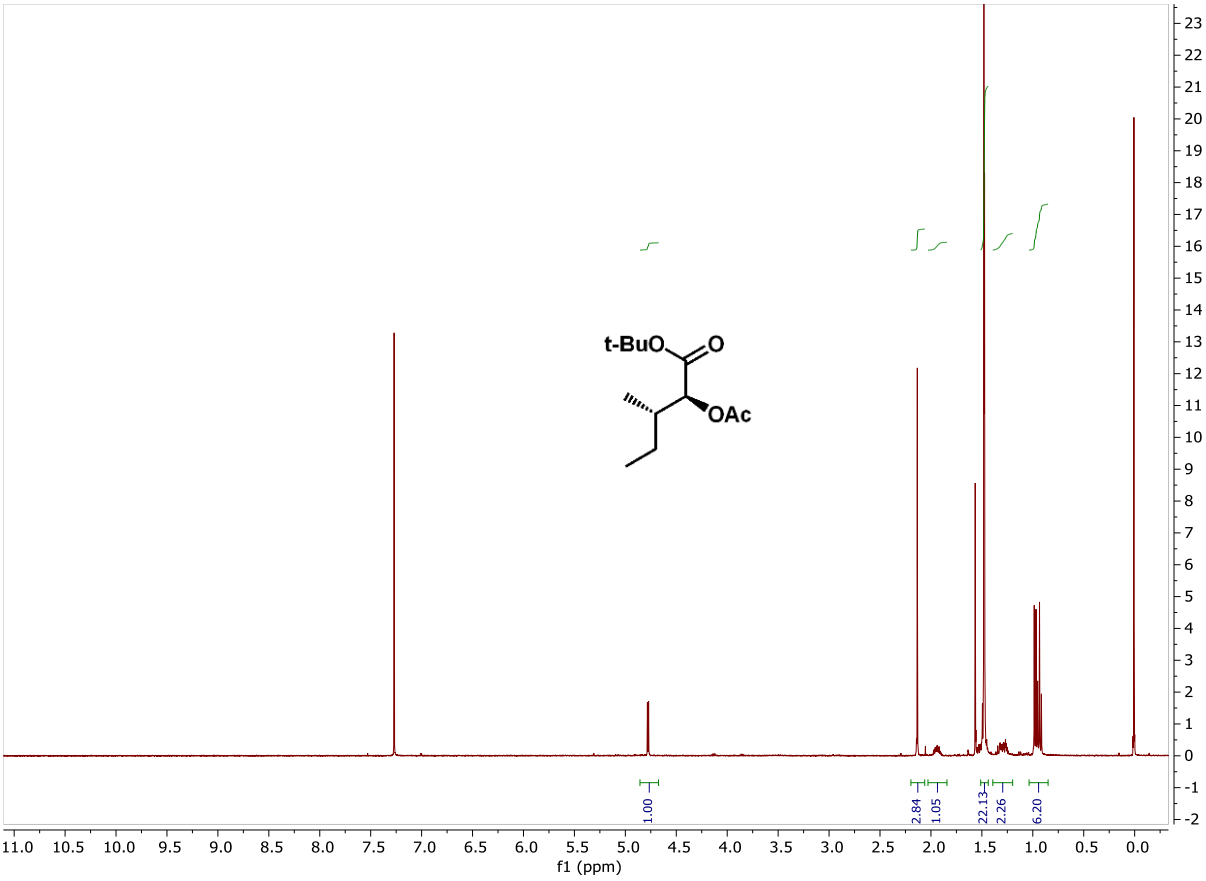
2-methyl-6-nitrobenzoic anhydride (51a)



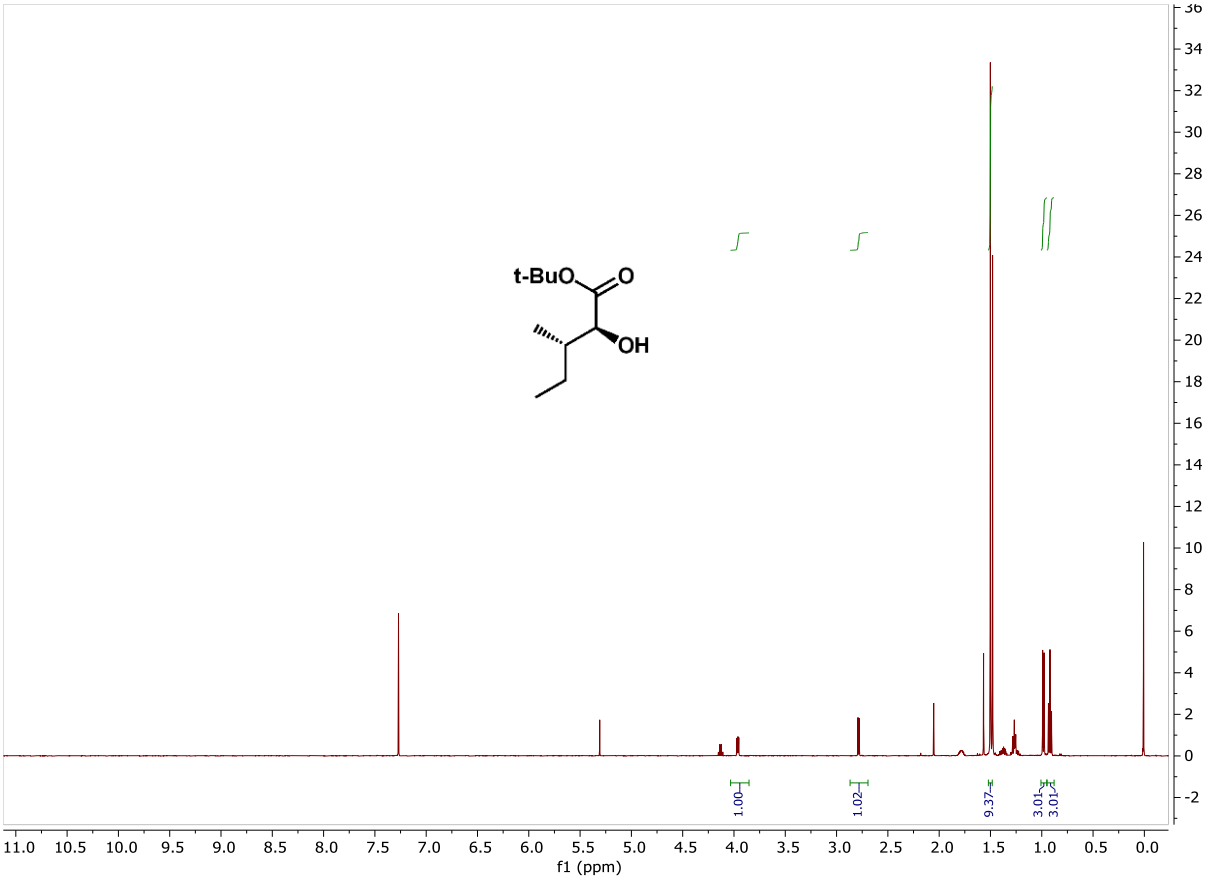
(2*S*,3*S*)-2-acetoxy-3-methylpentanoic acid (52)



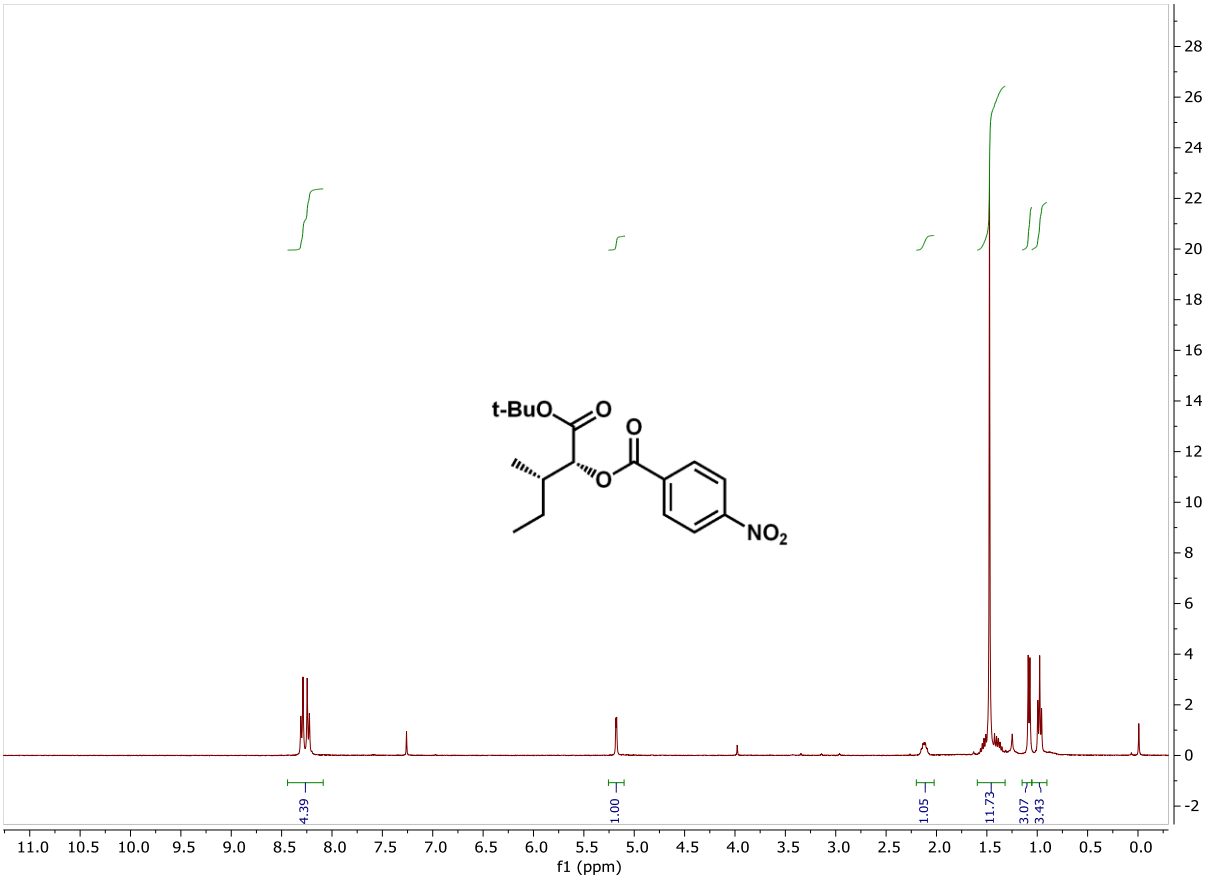
tert-butyl (2*S*,3*S*)-2-acetoxy-3-methylpentanoate (53)



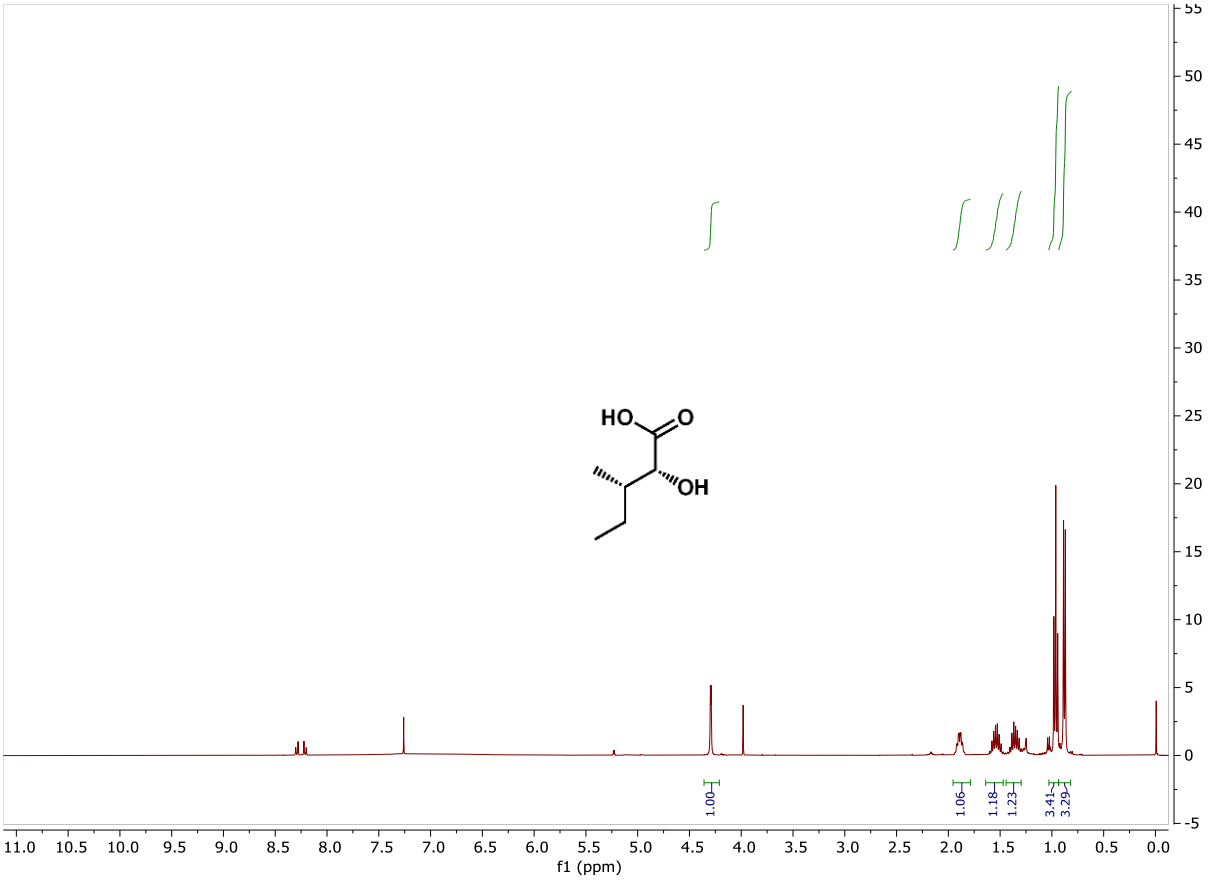
tert-butyl (2*S*,3*S*)-2-hydroxy-3-methylpentanoate (54)



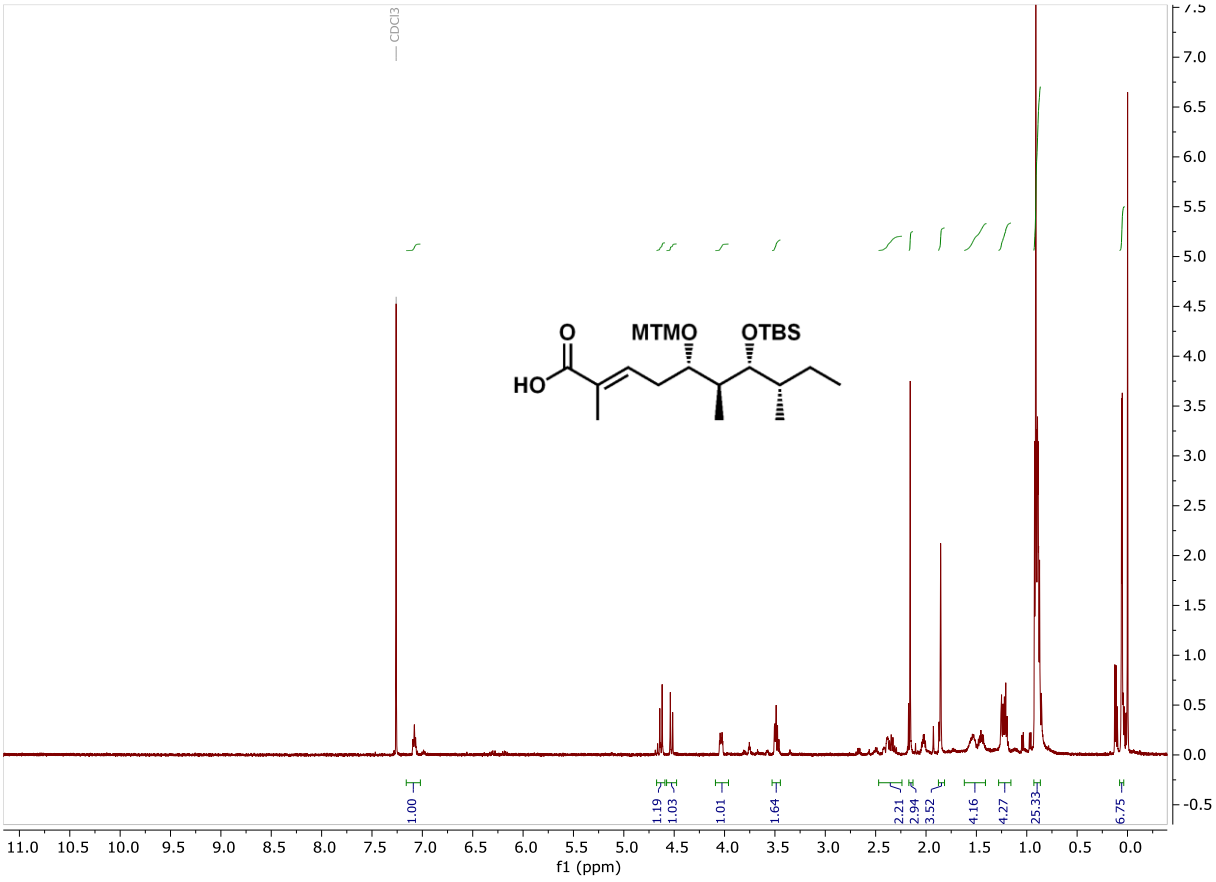
1-(tert-Butoxy)-3*S*-methyl-1-oxopentan-2*R*-yl-4-nitrobenzoate (55)



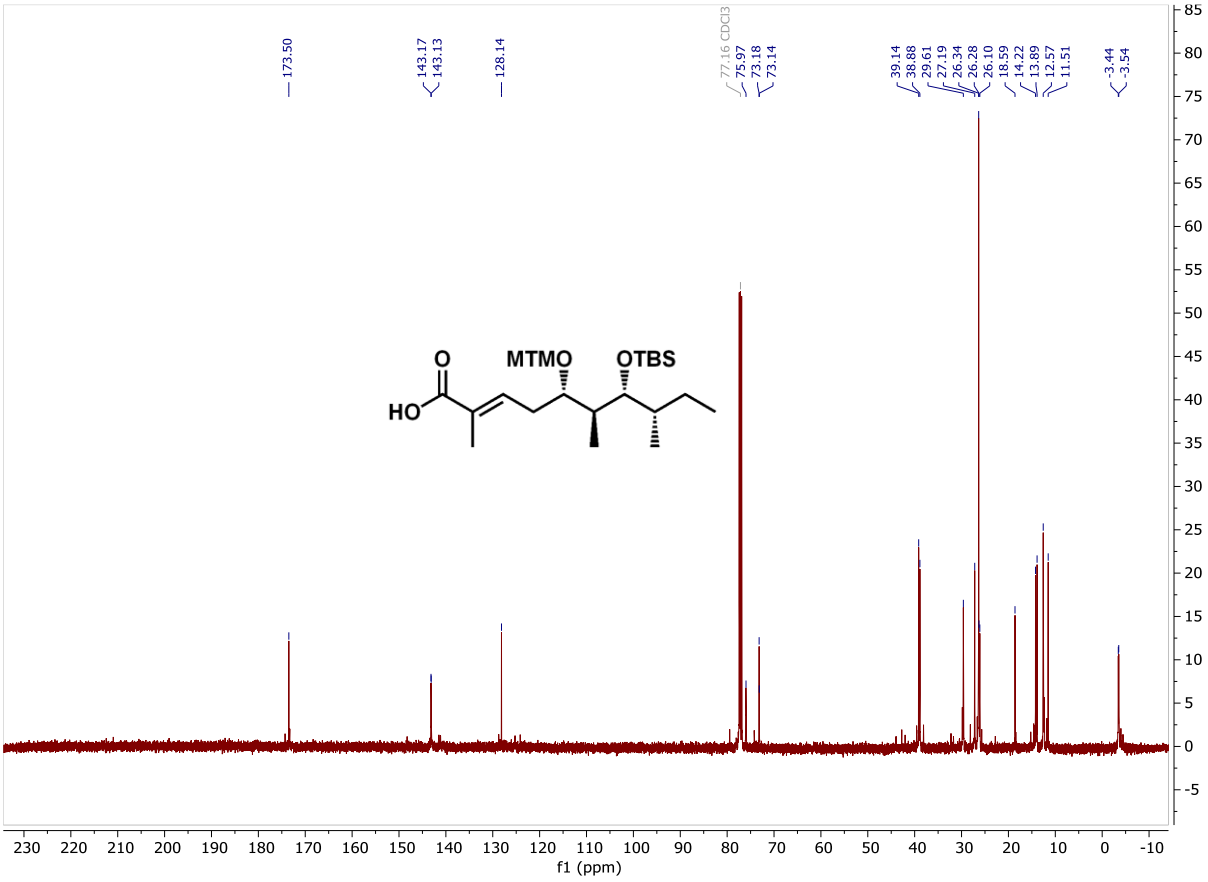
(2*R*,3*S*)-2-hydroxy-3-methylpentanoic acid (56)



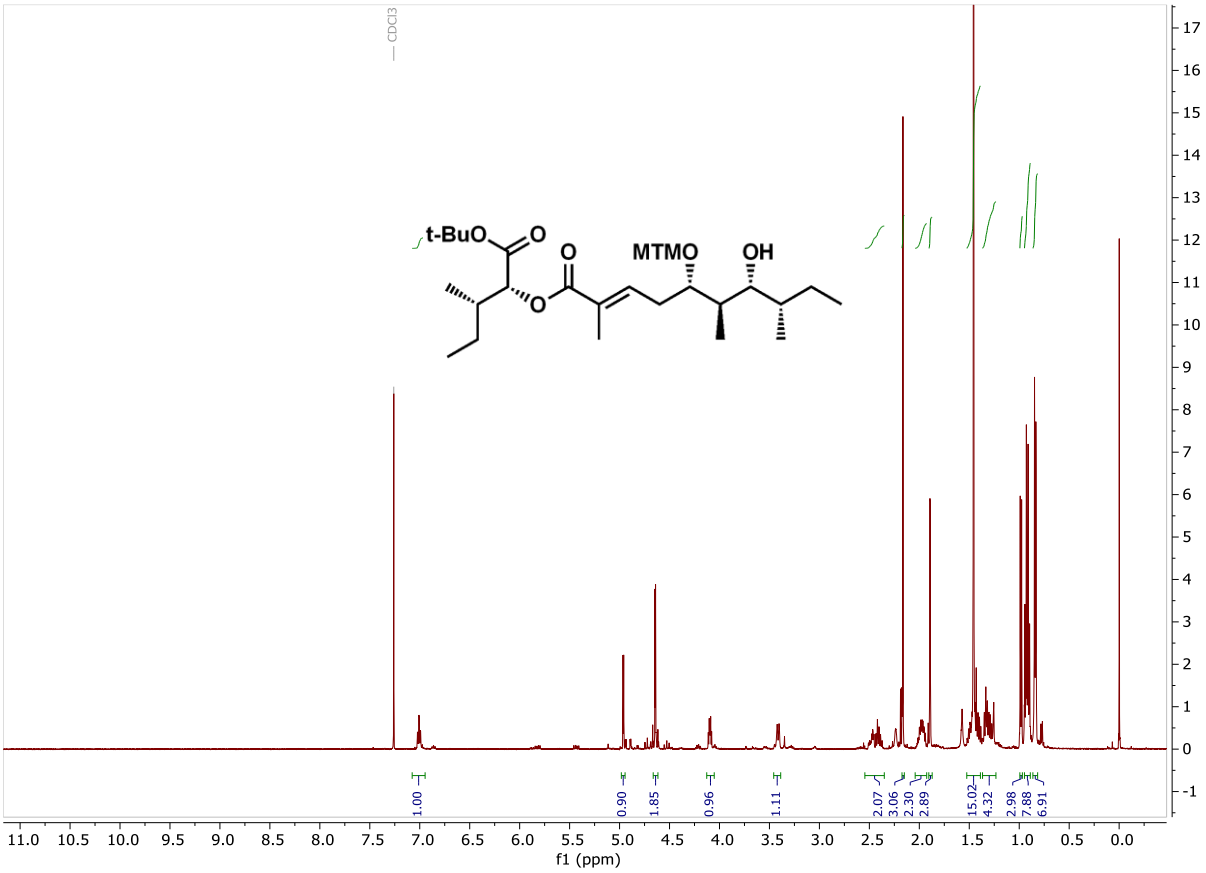
(5*S*,6*S*,7*R*,8*S*,*E*)-7-((tert-butyldimethylsilyl)oxy)-2,6,8-trimethyl-5-((methylthio)methoxy)dec-2-enoic acid (57)



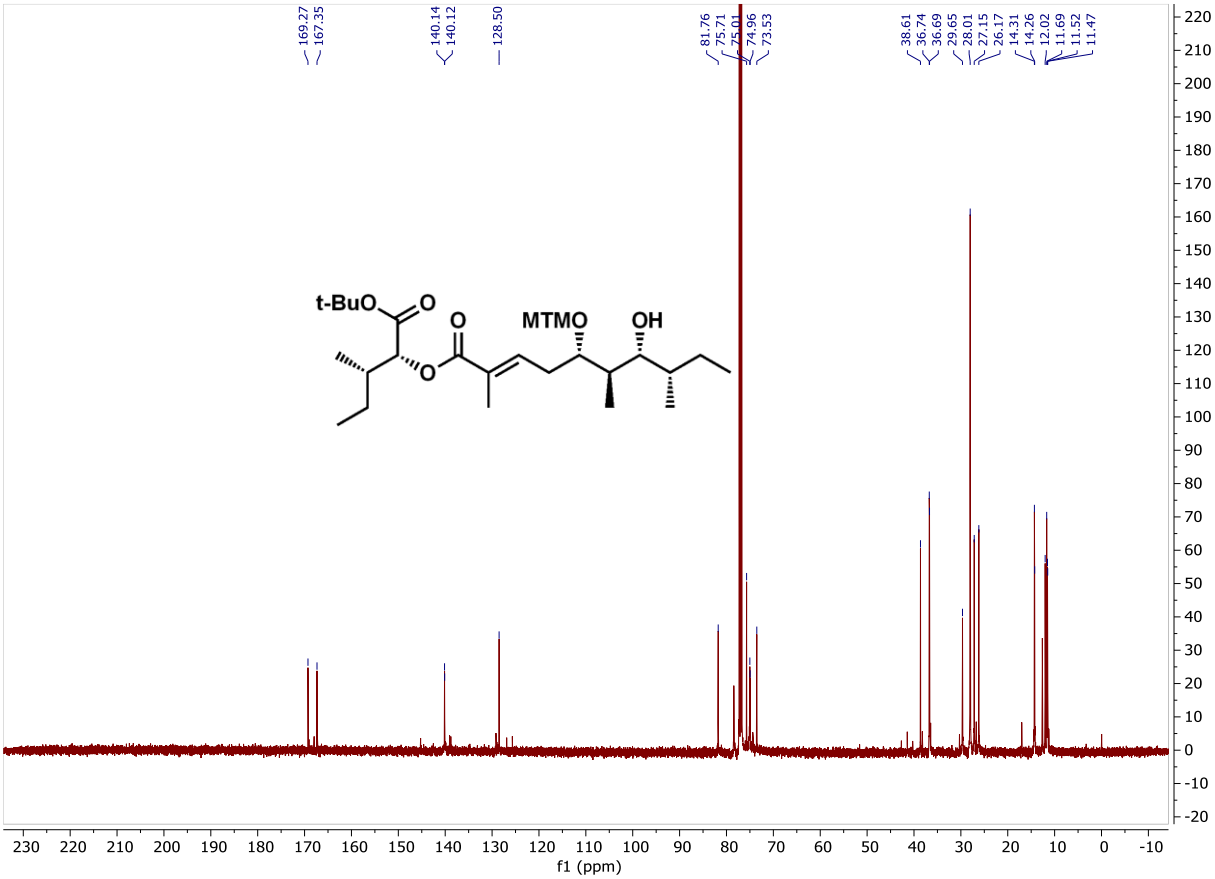
(5*S*,6*S*,7*R*,8*S*,*E*)-7-((tert-butyldimethylsilyl)oxy)-2,6,8-trimethyl-5-((methylthio)methoxy)dec-2-enoic acid (57)



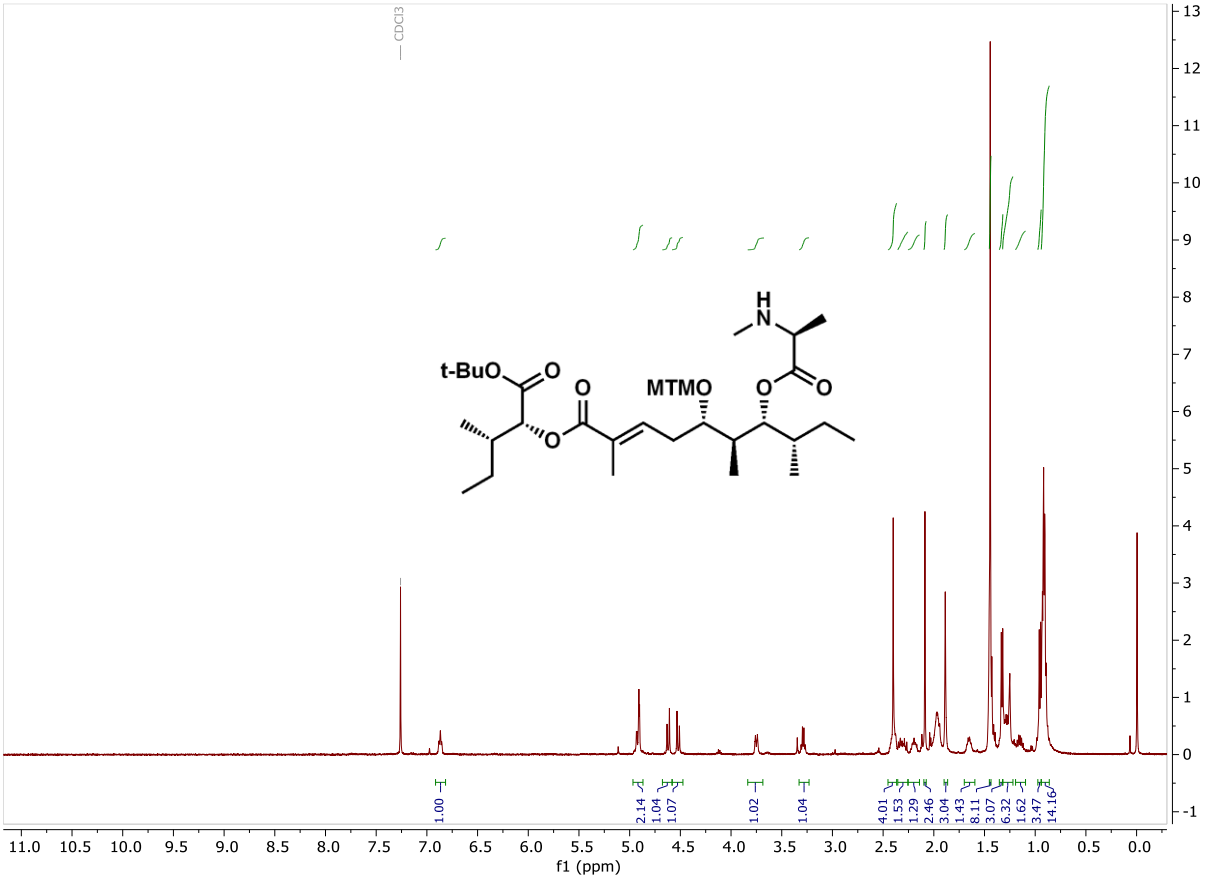
(2*R*,3*S*)-1-(tert-butoxy)-3-methyl-1-oxopentan-2-yl (5*S*,6*R*,7*R*,8*S*,*E*)-7-hydroxy-2,6,8-trimethyl-5-((methylthio)methoxy)dec-2-enoate (59)



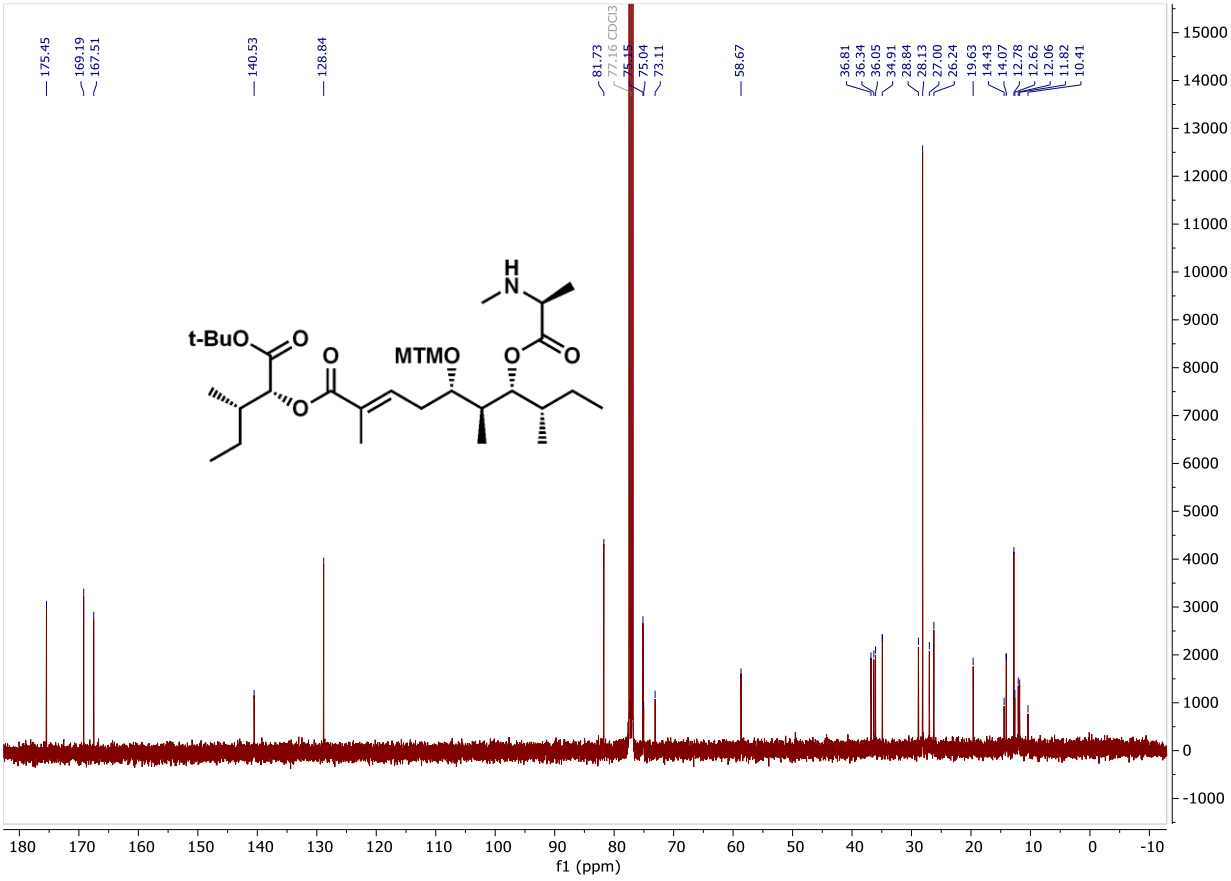
(2*R*,3*S*)-1-(tert-butoxy)-3-methyl-1-oxopentan-2-yl (5*S*,6*R*,7*R*,8*S*,*E*)-7-hydroxy-2,6,8-trimethyl-5-((methylthio)methoxy)dec-2-enoate (59)



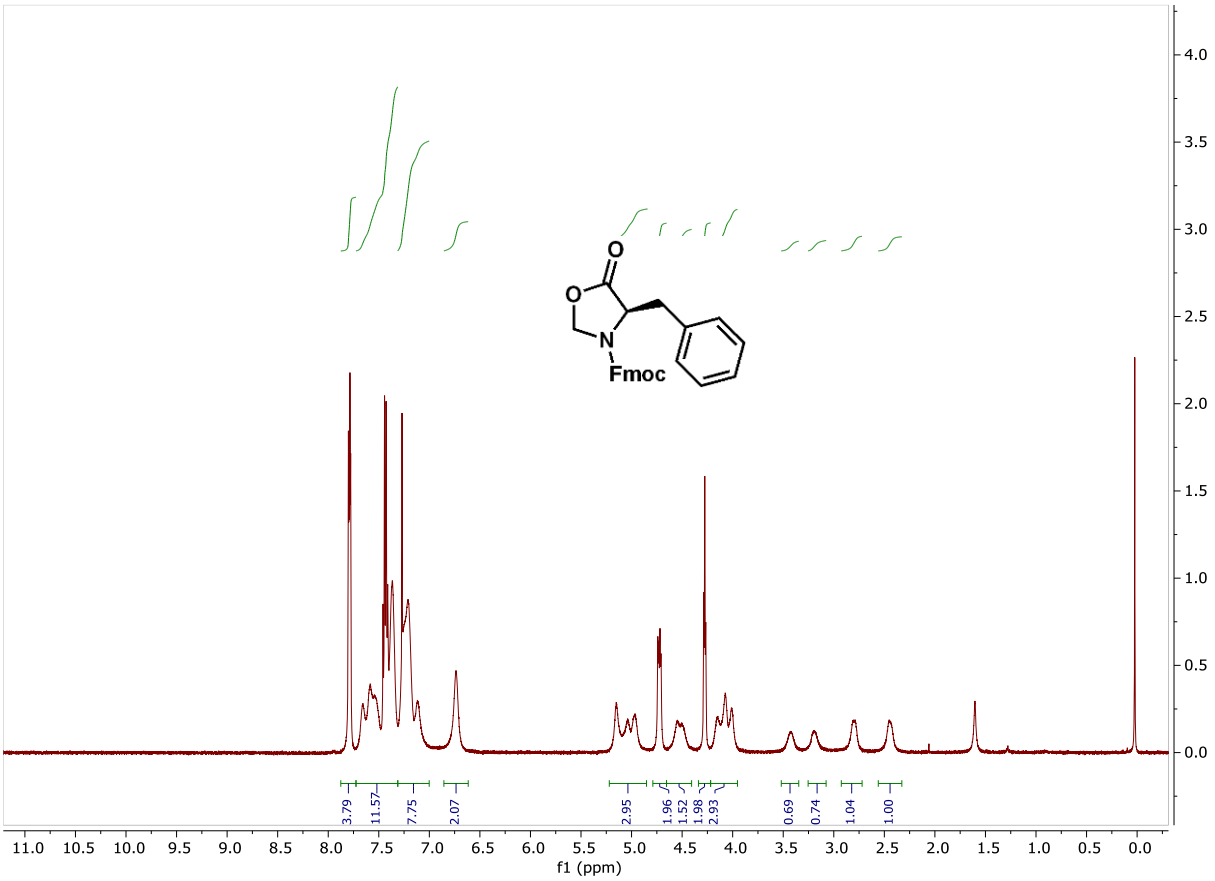
(2*R*,3*S*)-1-(tert-butoxy)-3-methyl-1-oxopentan-2-yl (5*S*,6*S*,7*R*,8*S*,*E*)-2,6,8-trimethyl-7-((methyl-L-alanyl)oxy)-5-((methylthio)methoxy)dec-2-enoate (2)



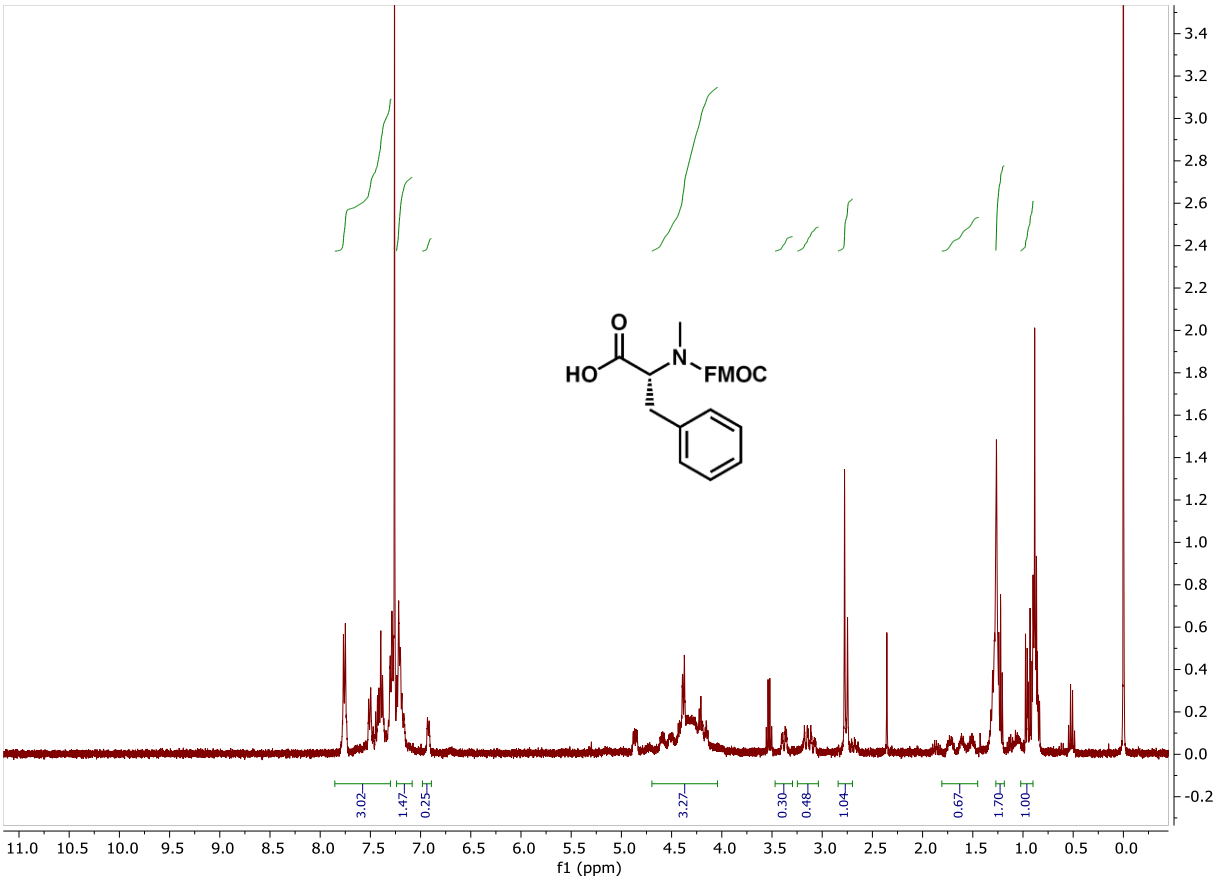
(2*R*,3*S*)-1-(tert-butoxy)-3-methyl-1-oxopentan-2-yl (5*S*,6*S*,7*R*,8*S*,*E*)-2,6,8-trimethyl-7-((methyl-L-alanyl)oxy)-5-((methylthio)methoxy)dec-2-enoate (2)



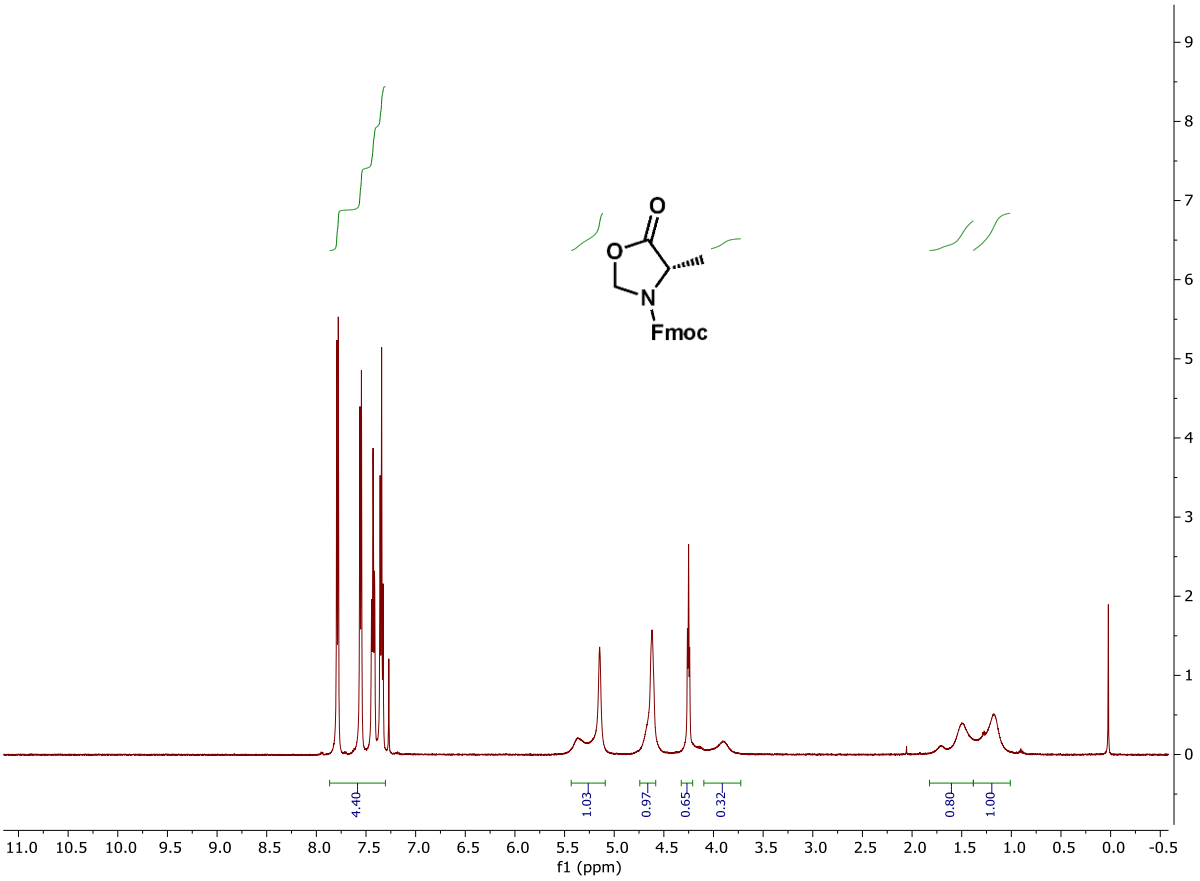
(2*S*)-N-Fluorenylmethyloxycarbonyl-2-aminomethyl-3-phenylpropanoic acid (Fmoc-N-methylphenylalanine) (60)



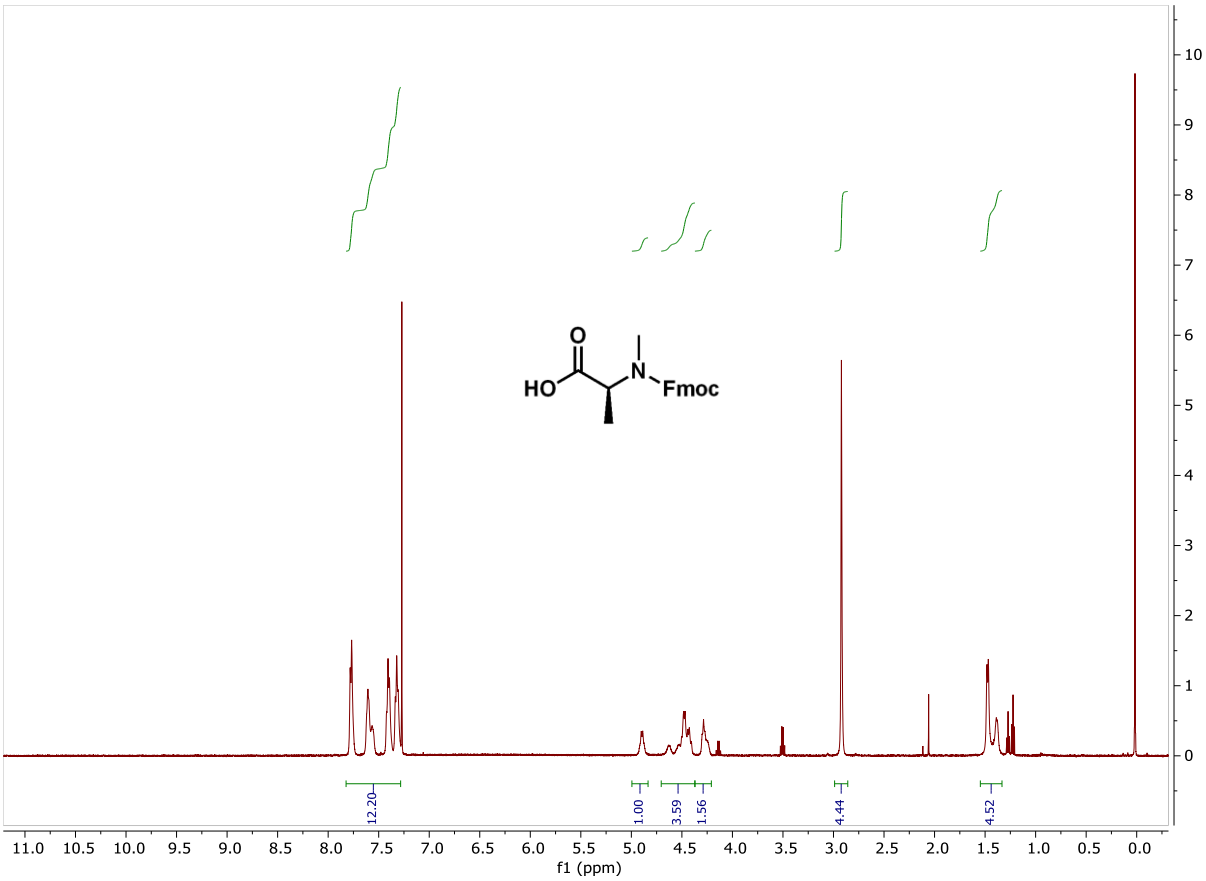
N-(((9H-fluoren-9-yl)methoxy)carbonyl)-N-methyl-D-phenylalanine (61)



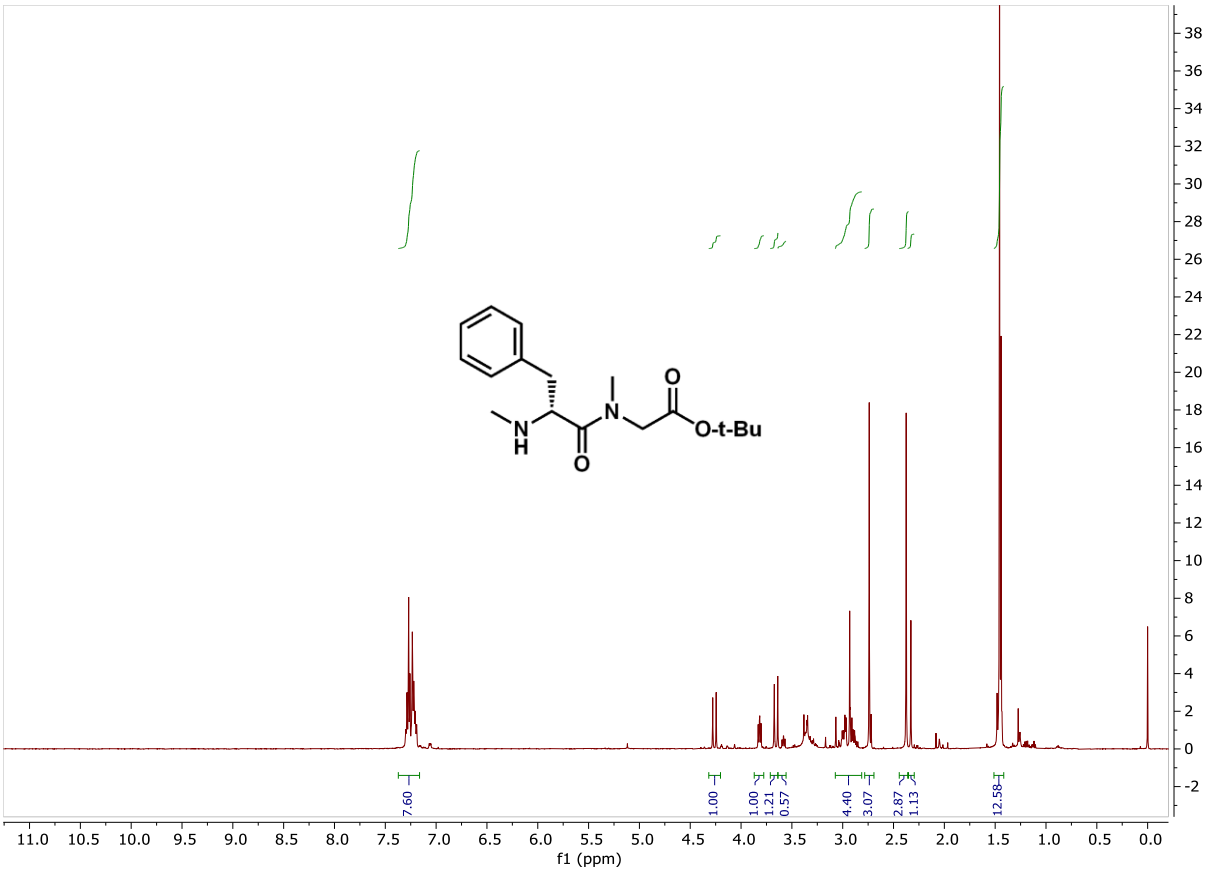
(9H-fluoren-9-yl) methyl (*S*)-4-methyl-5-oxooxazolidine-3-carboxylate (62)



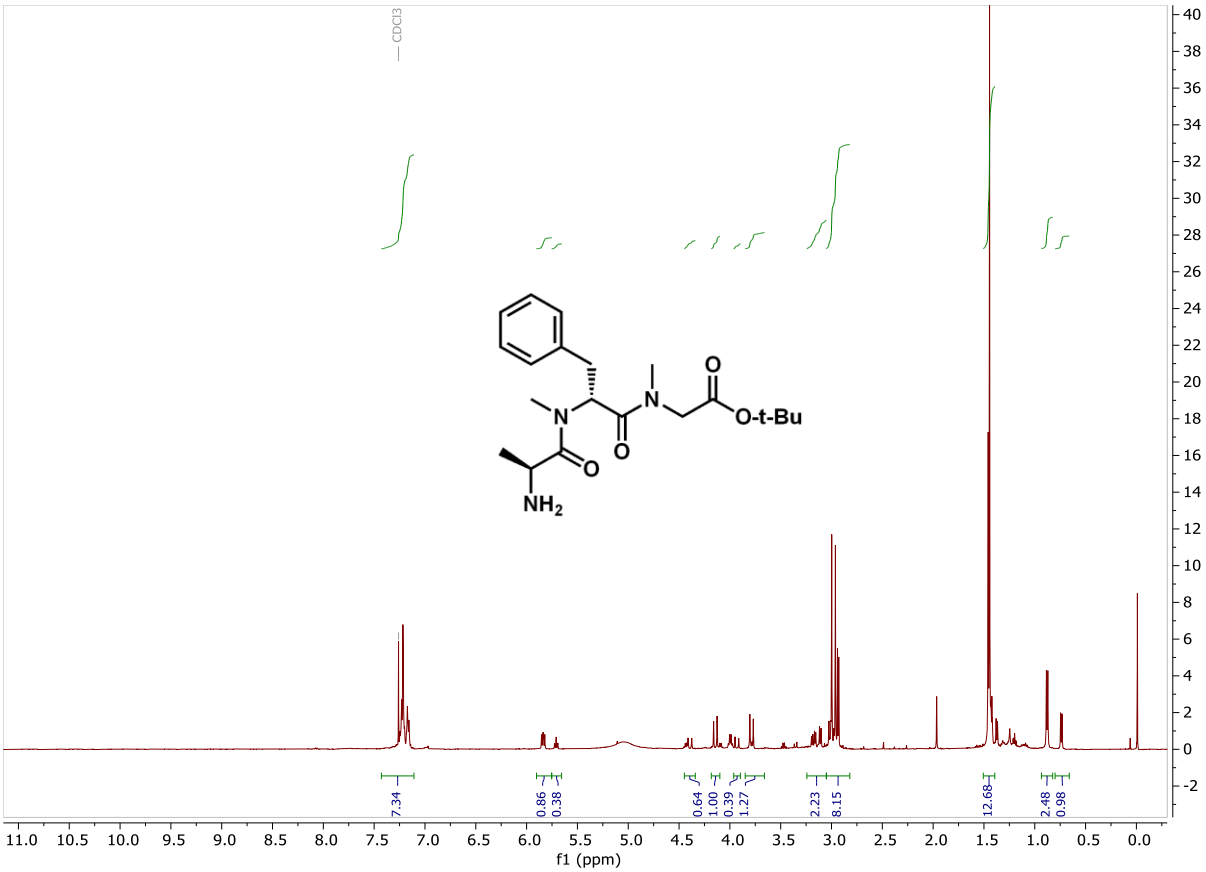
N-(((9H-fluoren-9-yl)methoxy)carbonyl)-N-methyl-L-alanine (63)



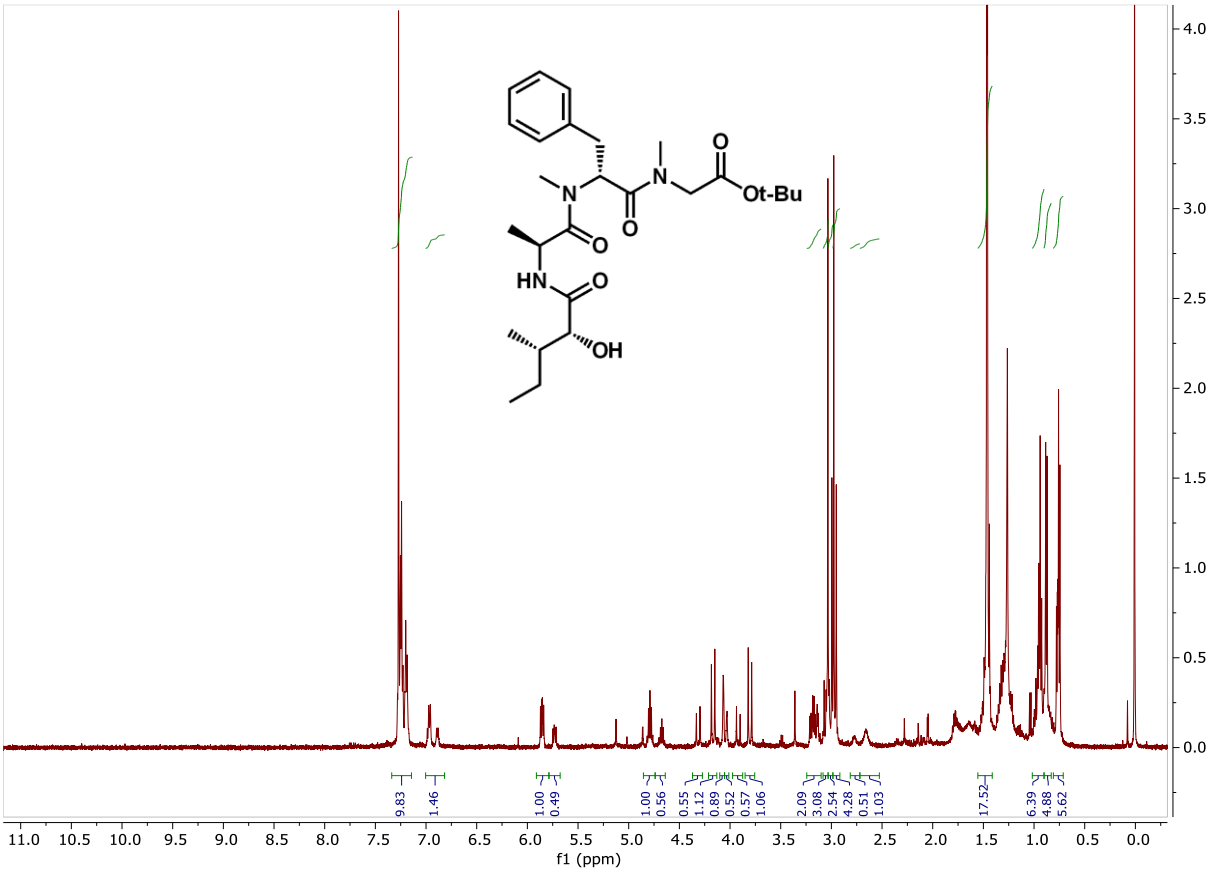
tert-butyl N-methyl-N-(methyl-D-phenylalanyl)glycinate (67)



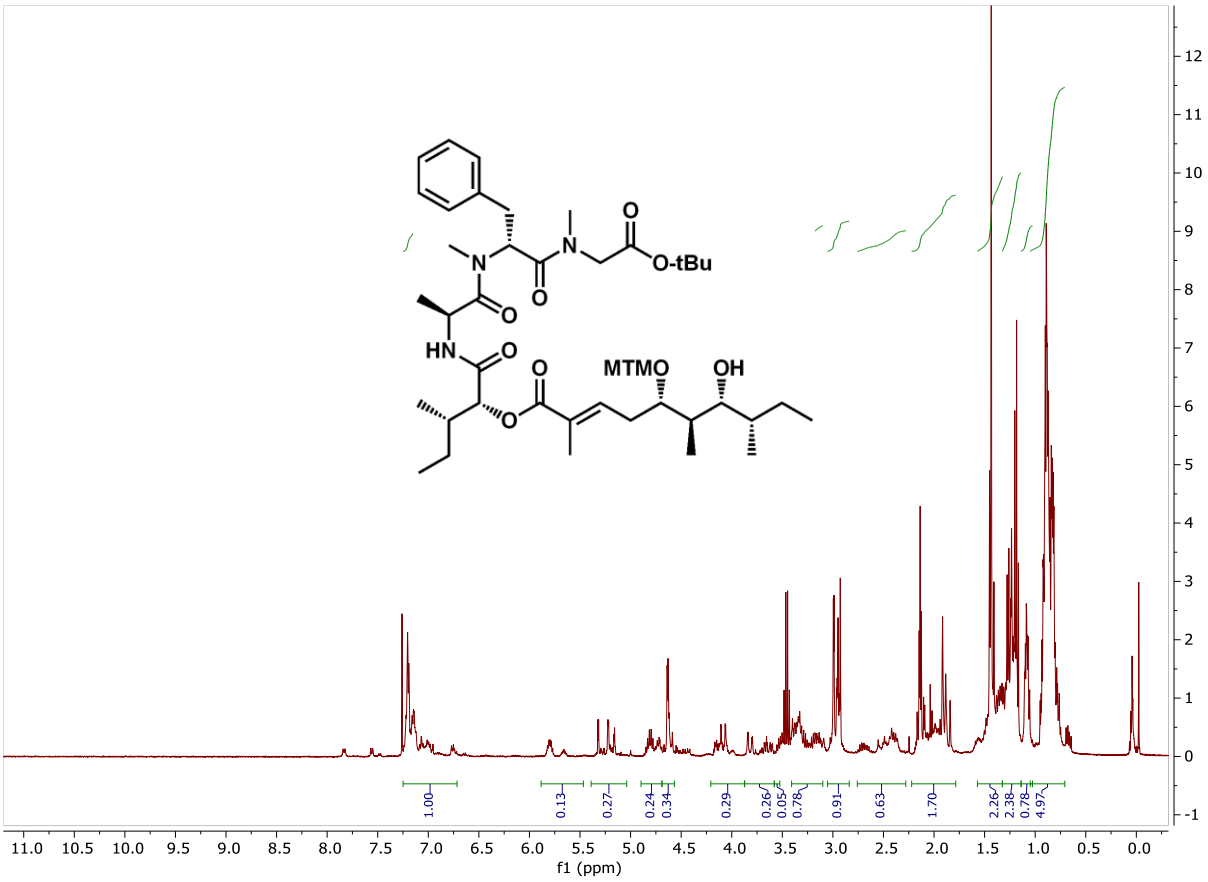
tert-butyl N-(N-(L-alanyl)-N-methyl-D-phenylalanyl)-N-methylglycinate (68)



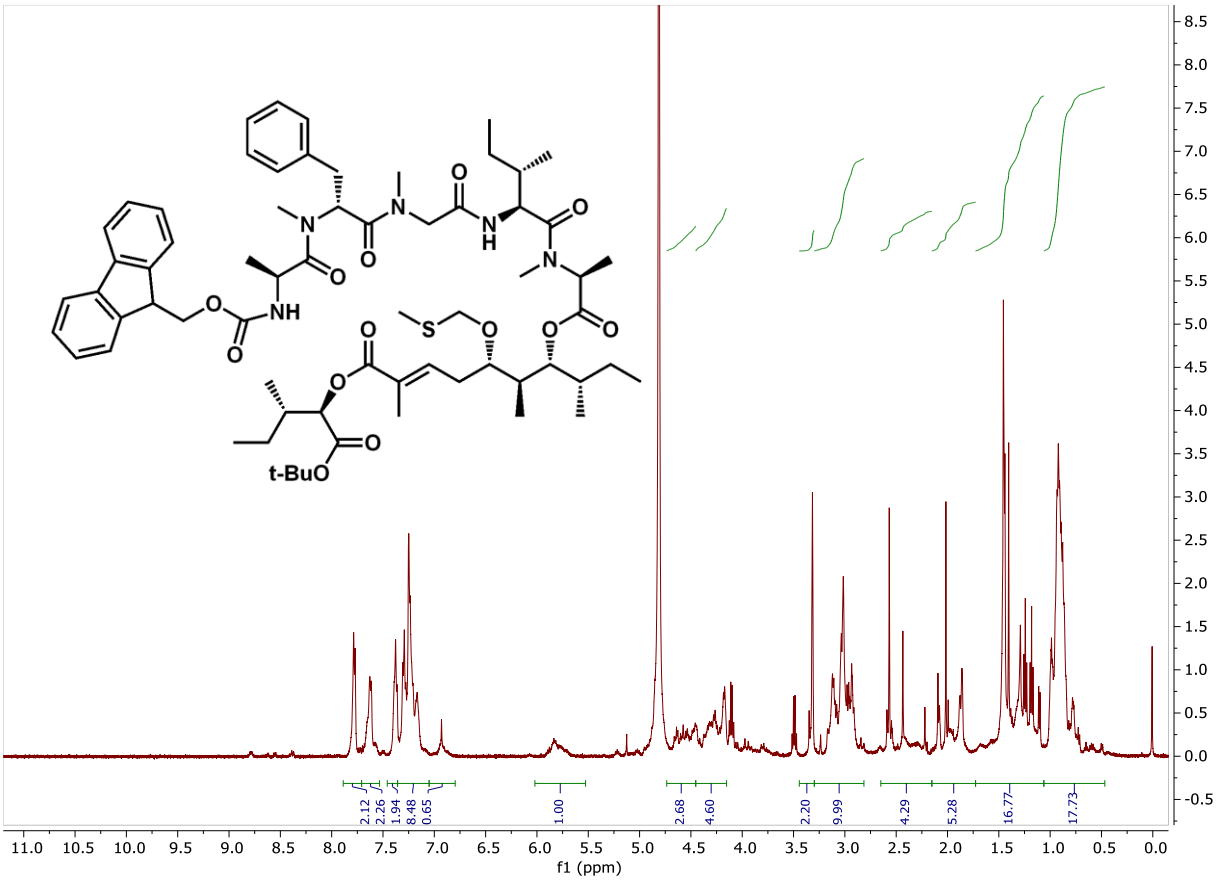
tert-butyl N-(N-(((2*R*,3*S*)-2-hydroxy-3-methylpentanoyl)-L-alanyl)-N-methyl-D-phenylalanyl)-N-methylglycinate (69)



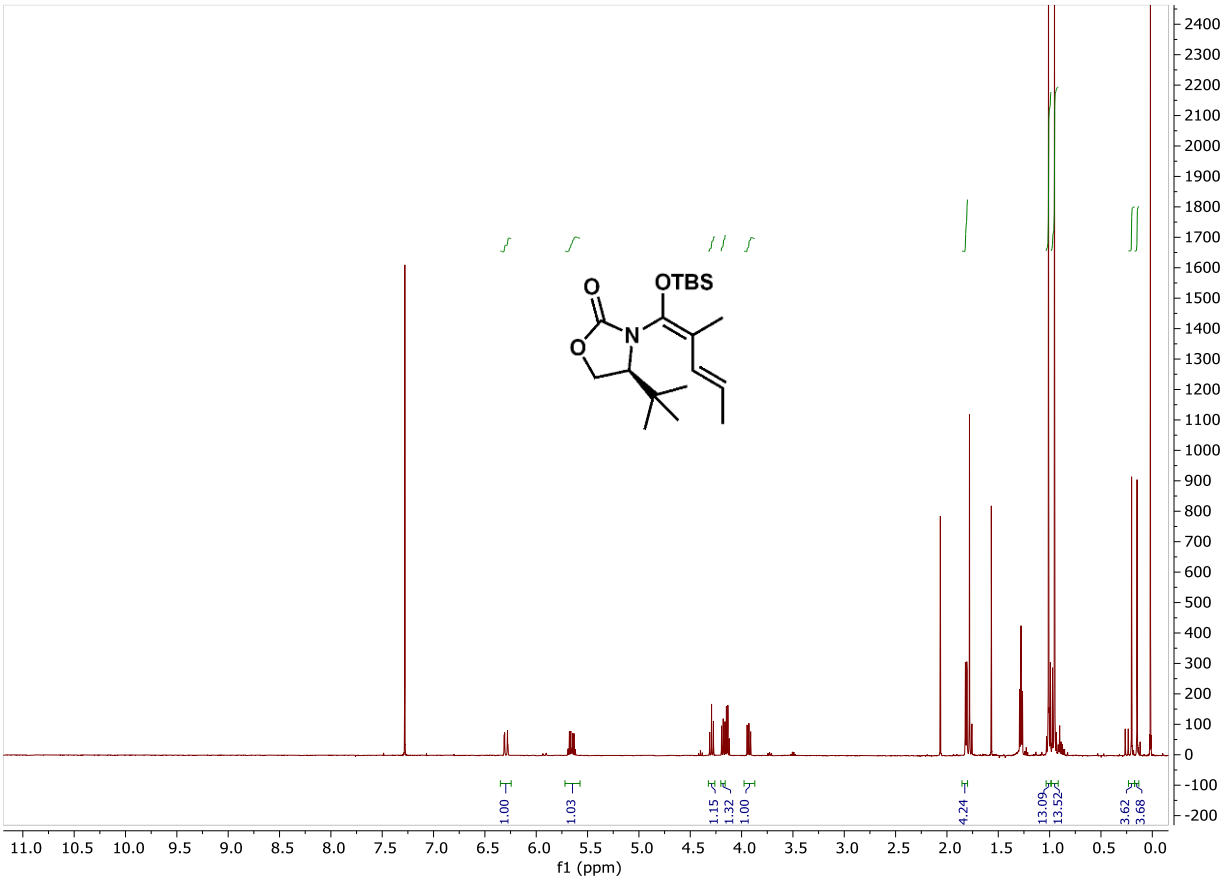
(8*R*,11*S*,14*R*,15*S*)-8-benzyl-2,2,6,9,11,15-hexamethyl-4,7,10,13-tetraoxo-3-oxa-6,9,12-triazaheptadecan-14-yl (5*S*,6*R*,7*R*,8*S*,*E*)-7-hydroxy-2,6,8-trimethyl-5-((methylthio)methoxy)dec-2-enoate (71)



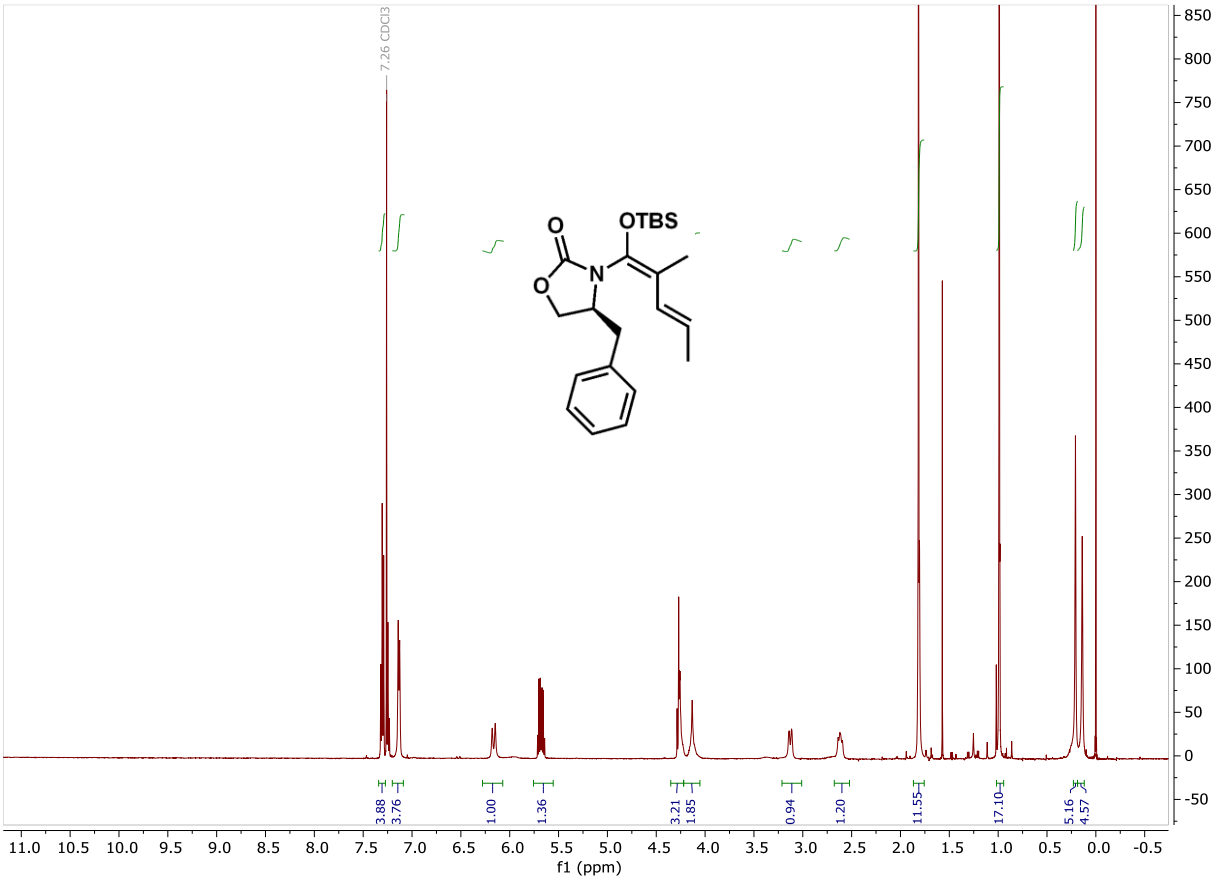
(3*S*,4*R*,5*S*,6*S*,*E*)-10-(((2*R*,3*S*)-1-(tert-butoxy)-3-methyl-1-oxopentan-2-yl)oxy)-3,5,9-trimethyl-6-((methylthio)methoxy)-10-oxodec-8-en-4-yl (5*S*,8*R*,14*S*,17*S*)-8-benzyl-14-((*S*)-sec-butyl)-1-(9H-fluoren-9-yl)-5,7,10,16,17-pentamethyl-3,6,9,12,15-pentaoxo-2-oxa-4,7,10,13,16-pentaazaoctadecan-18-oate (73)



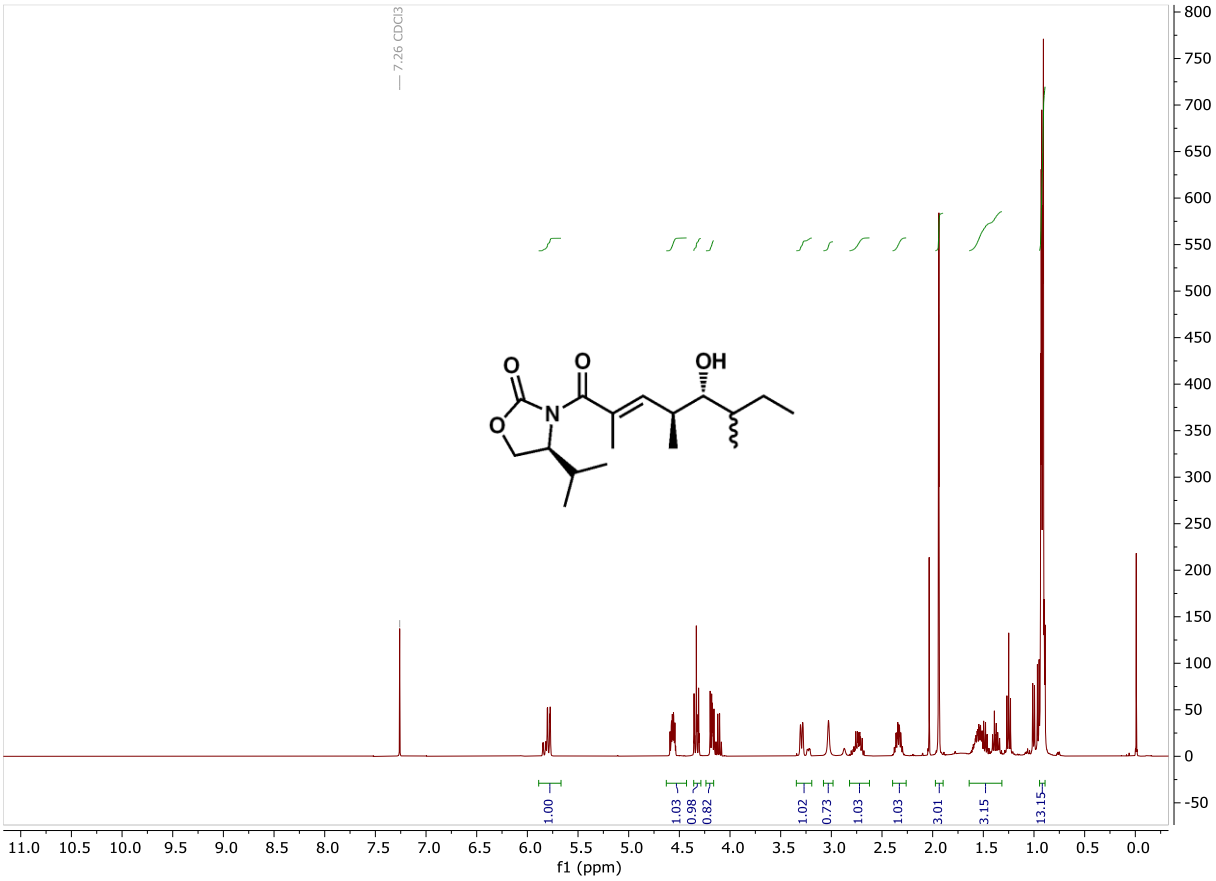
(*S*)-4-(tert-butyl)-3-((1*E*,3*E*)-1-((tert-butyldimethylsilyl)oxy)-2-methylpenta-1,3-dien-1-yl)oxazolidin-2-one (2.1)



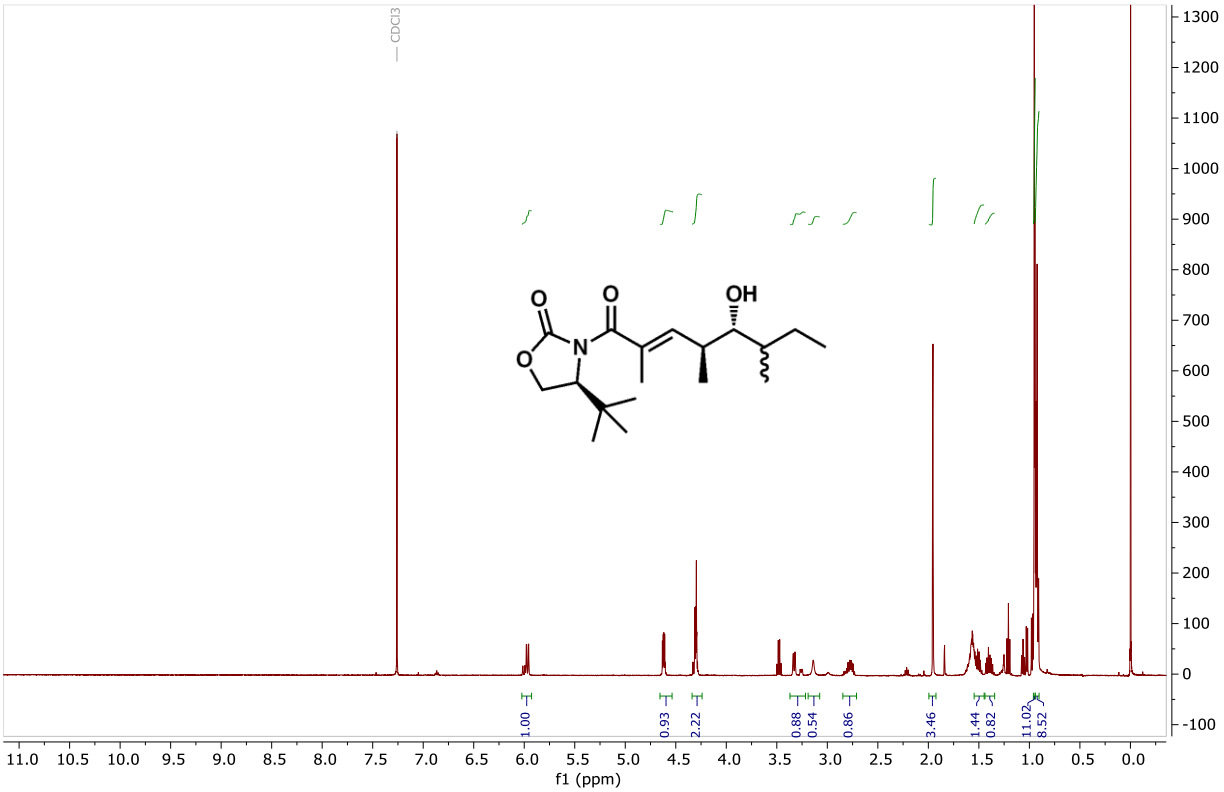
(*S*)-4-benzyl-3-((1*E*,3*E*)-1-((tert-butyldimethylsilyl)oxy)-2-methylpenta-1,3-dien-1-yl)oxazolidin-2-one (4.1)



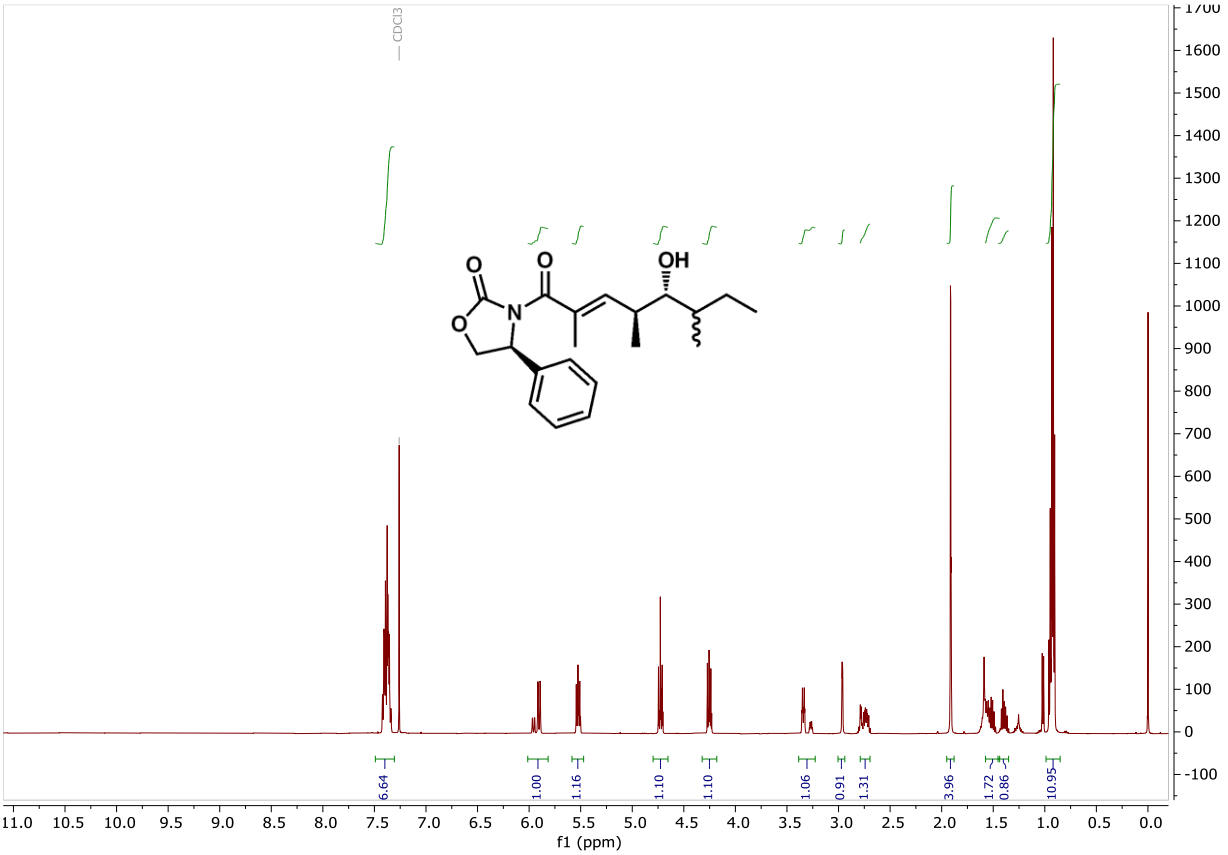
(*S*)-3-((4*S*,5*R*,6*S*,*E*)-5-hydroxy-2,4,6-trimethyloct-2-enoyl)-4-isopropyloxazolidin-2-one (8/8b)



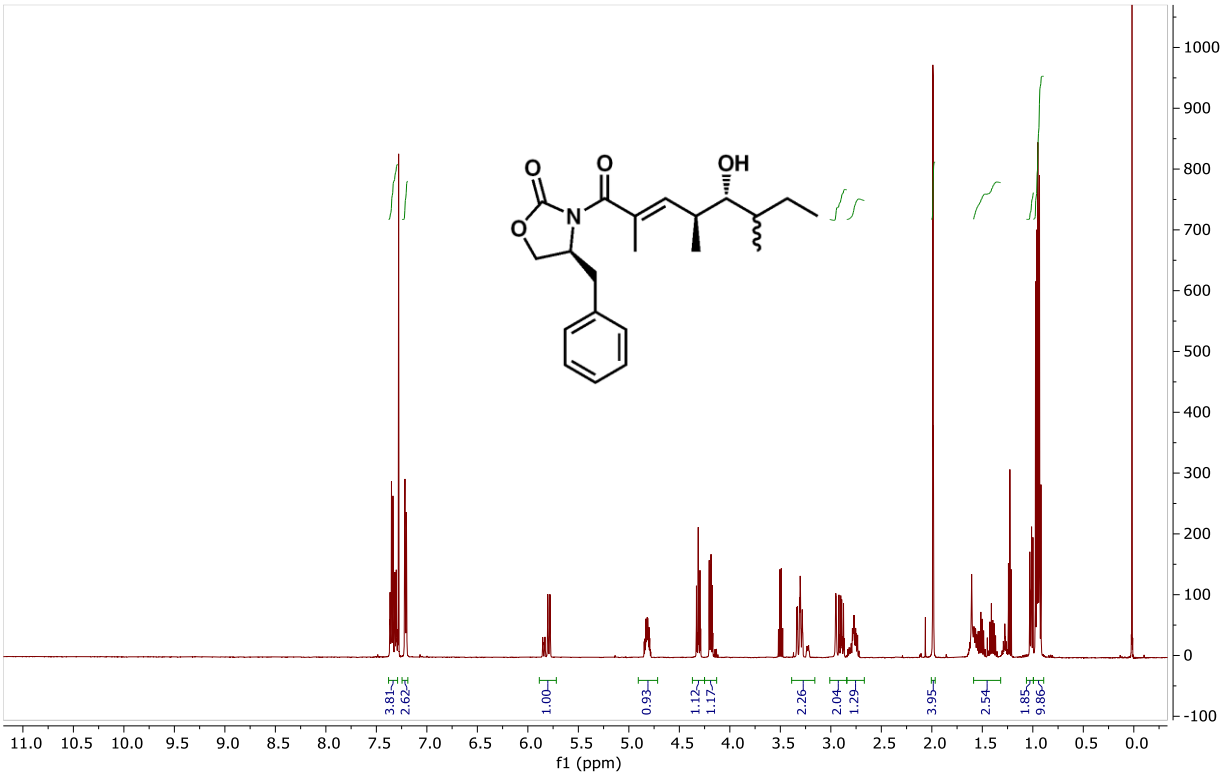
(*S*)-4-(tert-butyl)-3-((4*S*,5*R*,6*S*,*E*)-5-hydroxy-2,4,6-trimethyloct-2-enoyl)oxazolidin-2-one (2.2/2.2b)



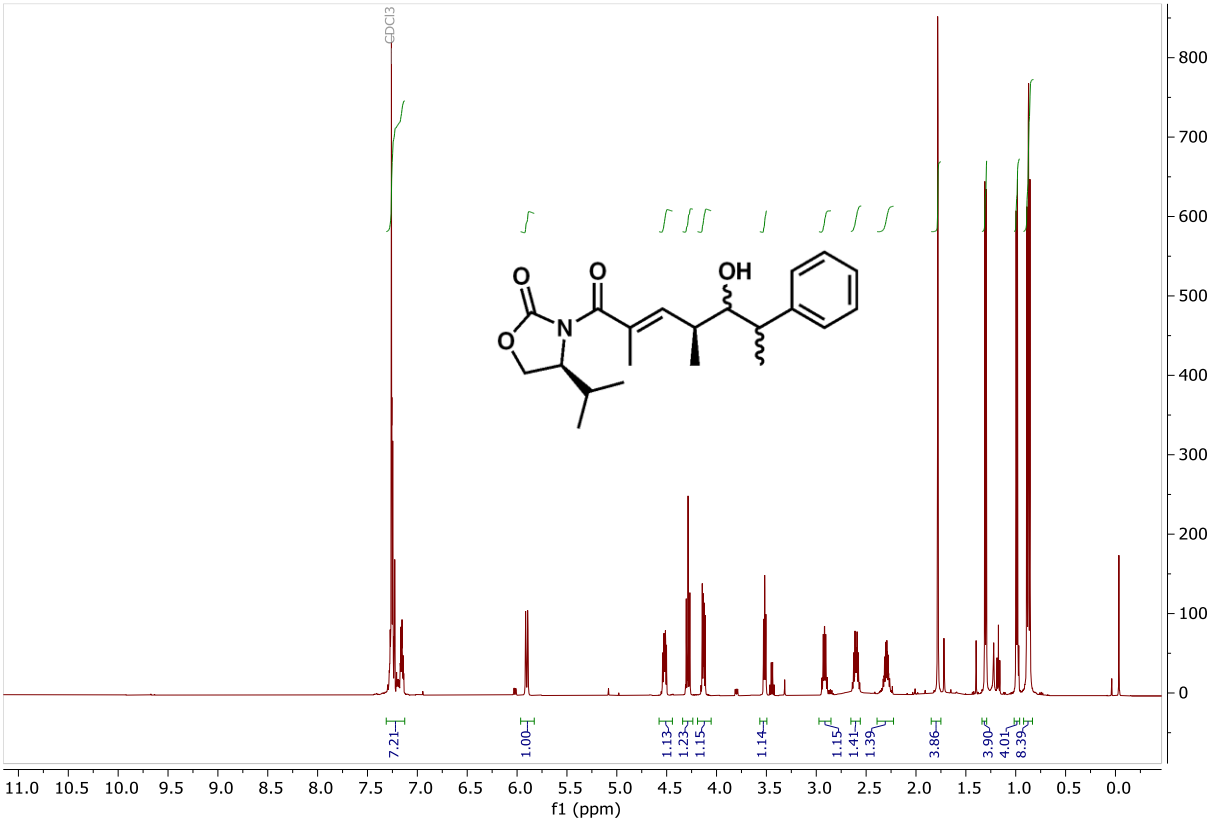
(*S*)-3-((4*S*,5*R*,6*S*,*E*)-5-hydroxy-2,4,6-trimethyloct-2-enoyl)-4-phenyloxazolidin-2-one (3.2/3.2b)



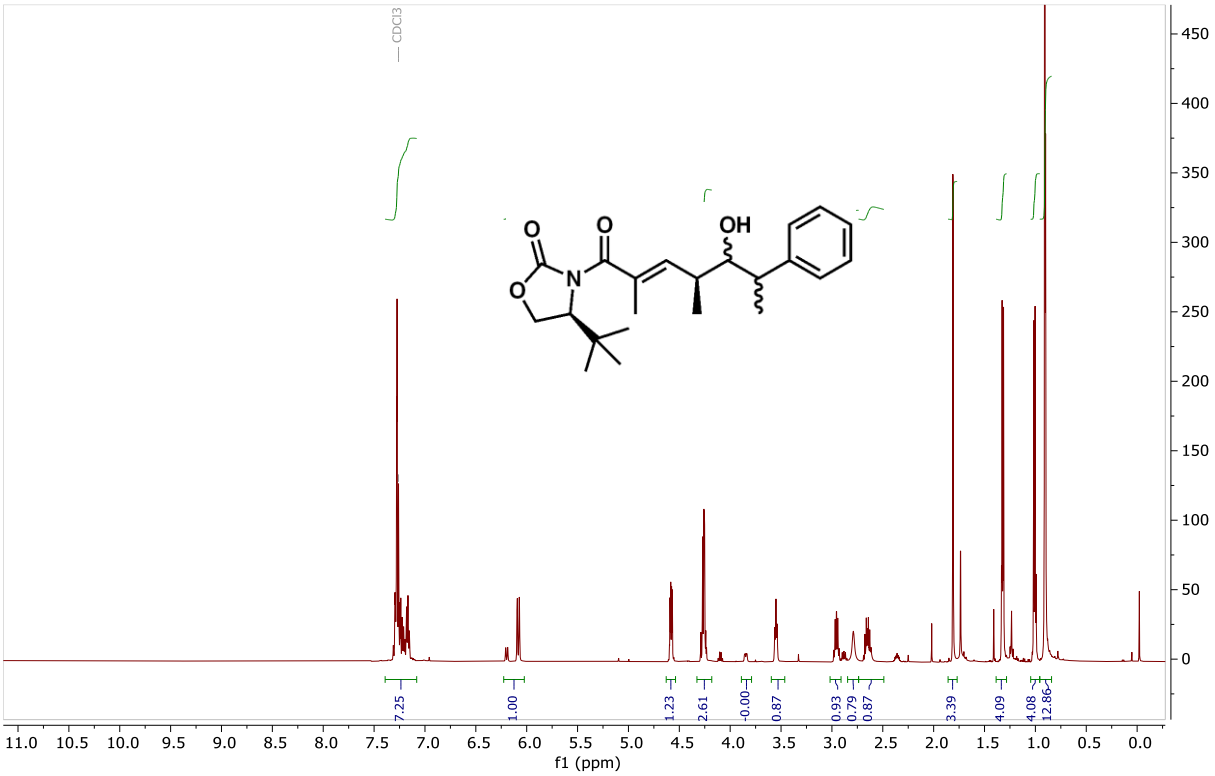
(*S*)-4-benzyl-3-((4*S*,5*R*,6*S*,*E*)-5-hydroxy-2,4,6-trimethyloct-2-enoyl)oxazolidin-2-one (4.2/4.2b)



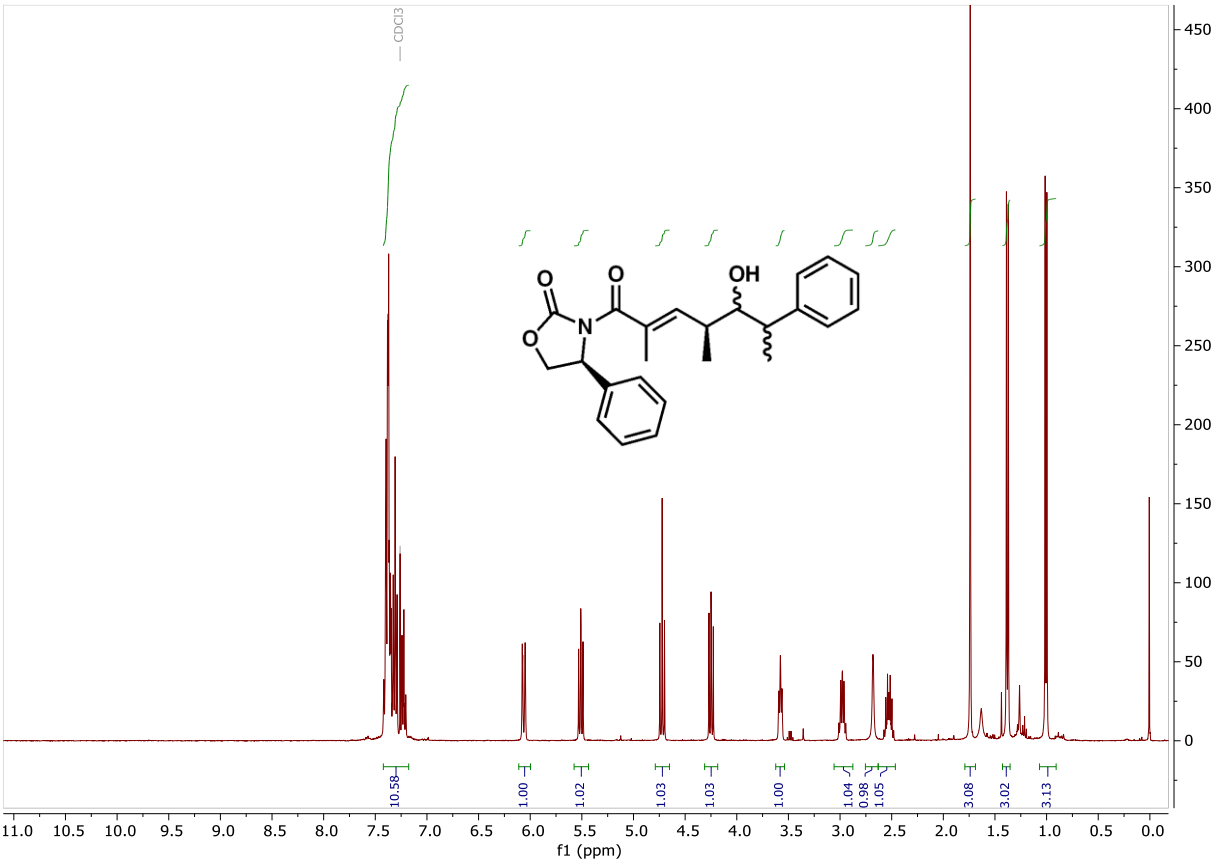
(*S*)-3-((4*S*,5*S*,6*S*,*E*)-5-hydroxy-2,4-dimethyl-6-phenylhept-2-enoyl)-4-isopropyloxazolidin-2-one (7.1)



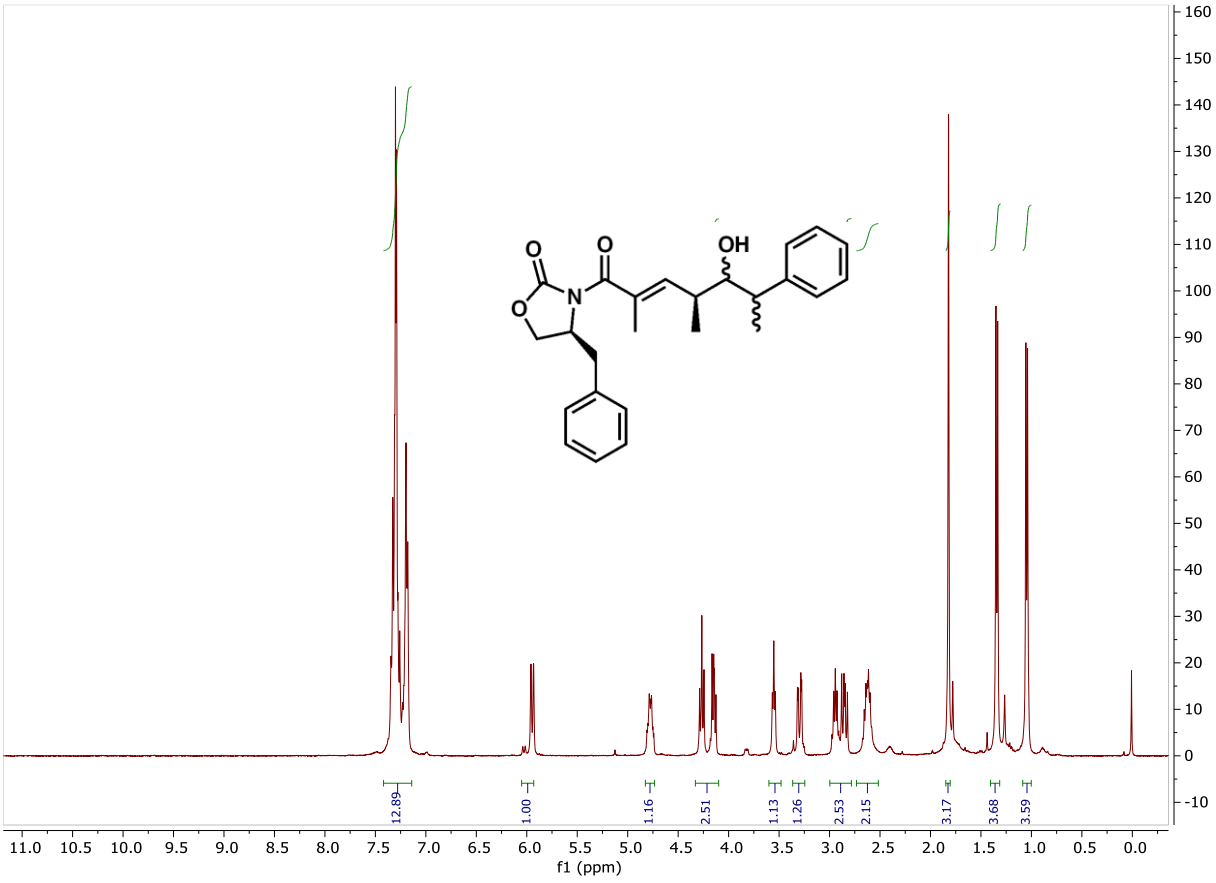
(*S*)-4-(tert-butyl)-3-((4*S*,5*S*,6*S*,*E*)-5-hydroxy-2,4-dimethyl-6-phenylhept-2-enoyl)oxazolidin-2-one (7.2)



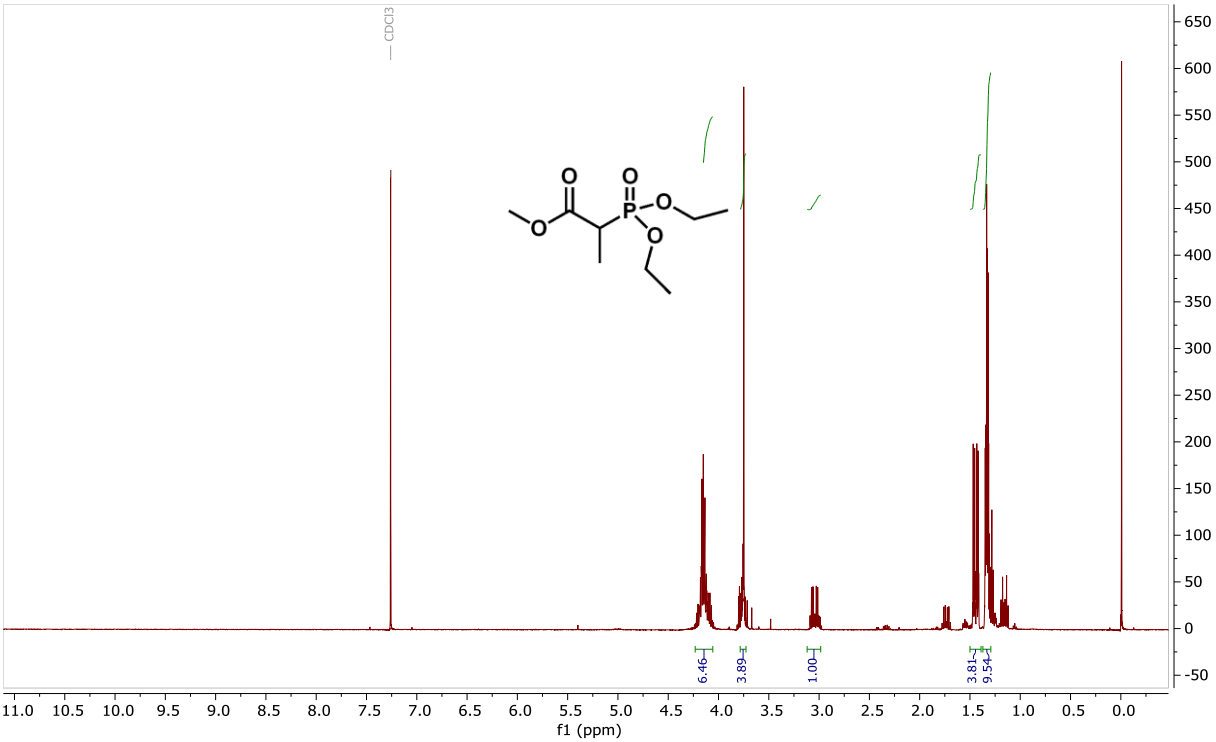
(*S*)-3-((4*S*,5*S*,6*S*,*E*)-5-hydroxy-2,4-dimethyl-6-phenylhept-2-enoyl)-4-phenyloxazolidin-2-one (7.3)



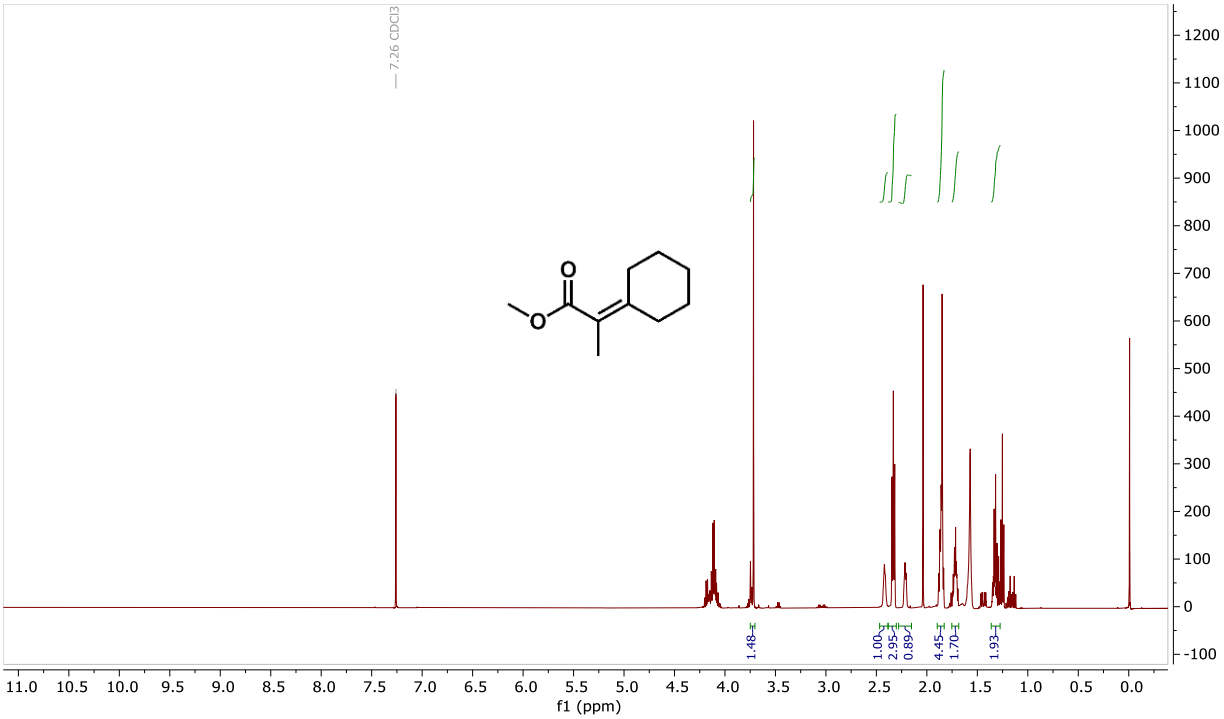
(*S*)-4-benzyl-3-((4*S*,5*S*,6*S*,*E*)-5-hydroxy-2,4-dimethyl-6-phenylhept-2-enoyl)oxazolidin-2-one (7.4)



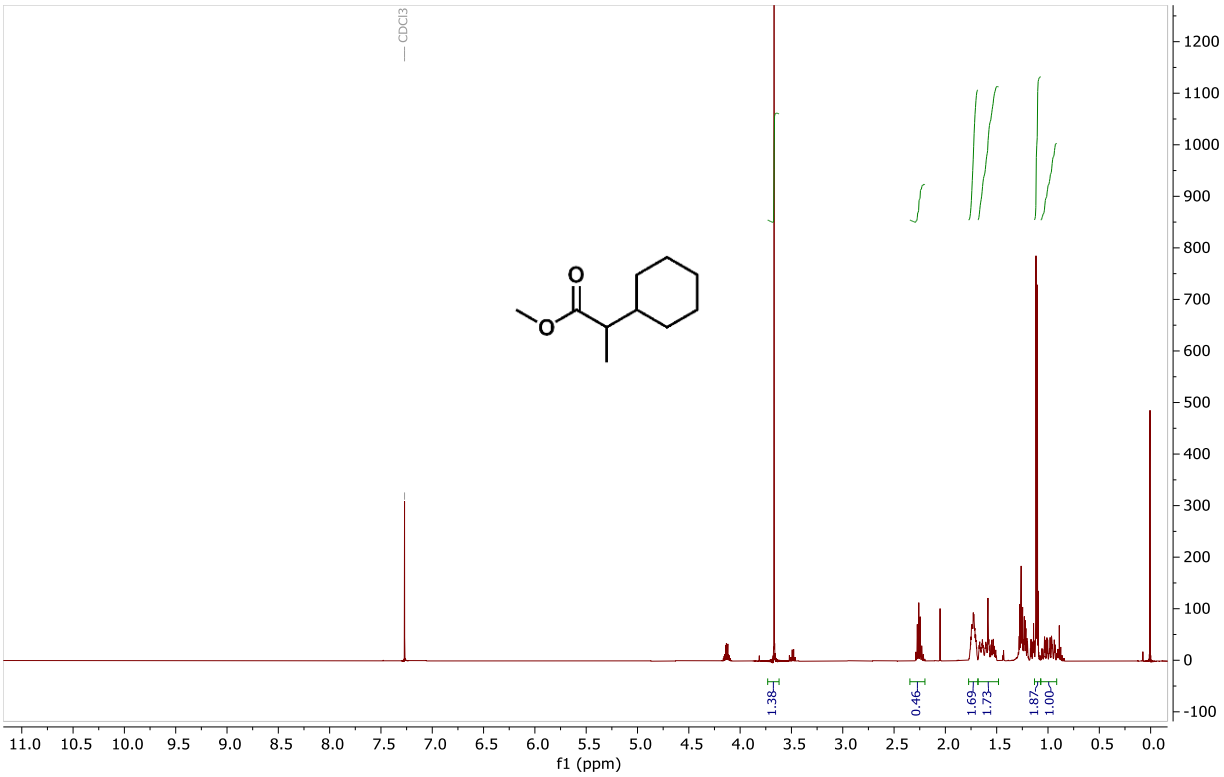
methyl 2-(diethoxyphosphoryl)propanoate (9.3)



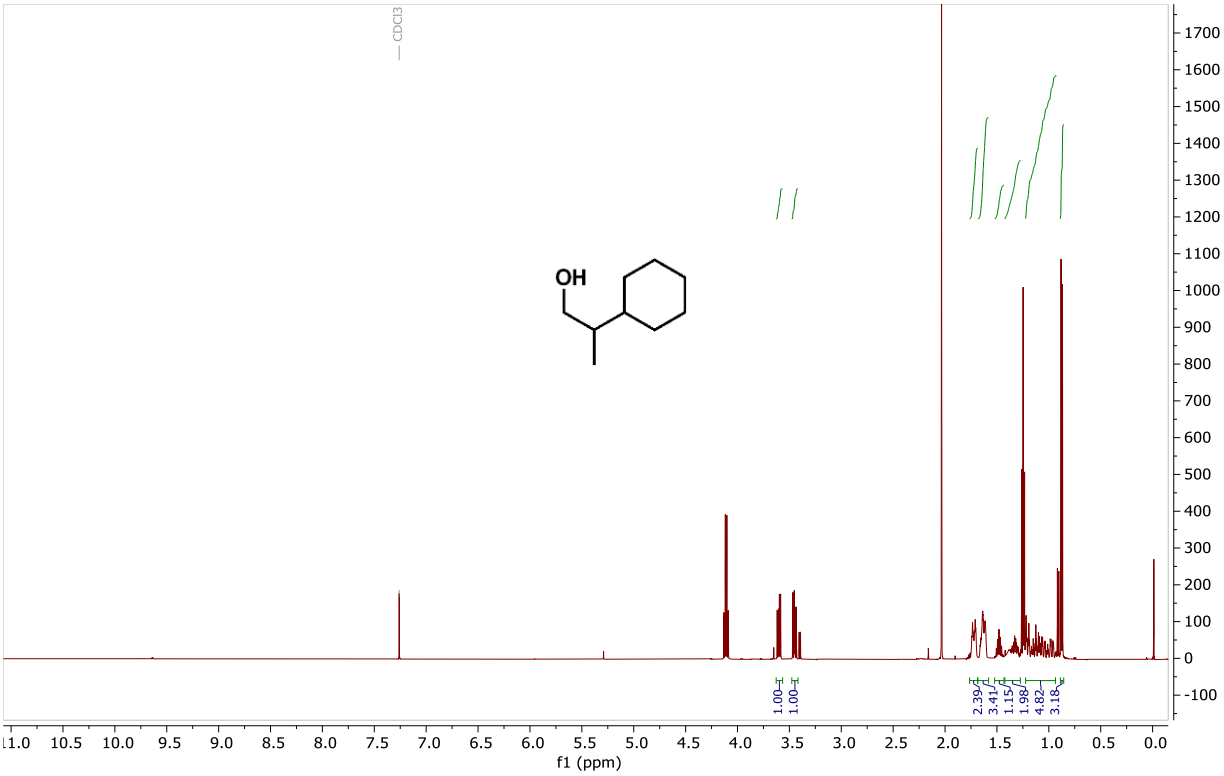
methyl 2-cyclohexylidenepropanoate (9.4)



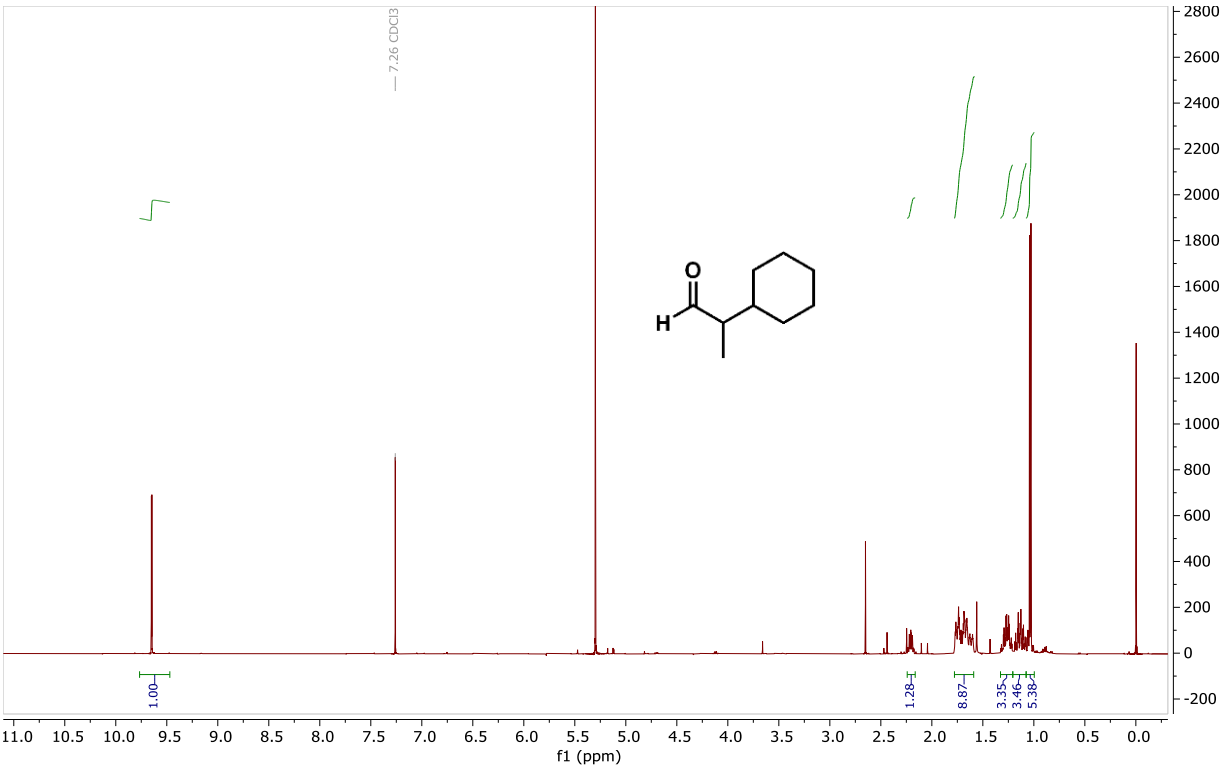
methyl 2-cyclohexylpropanoate (9.5)



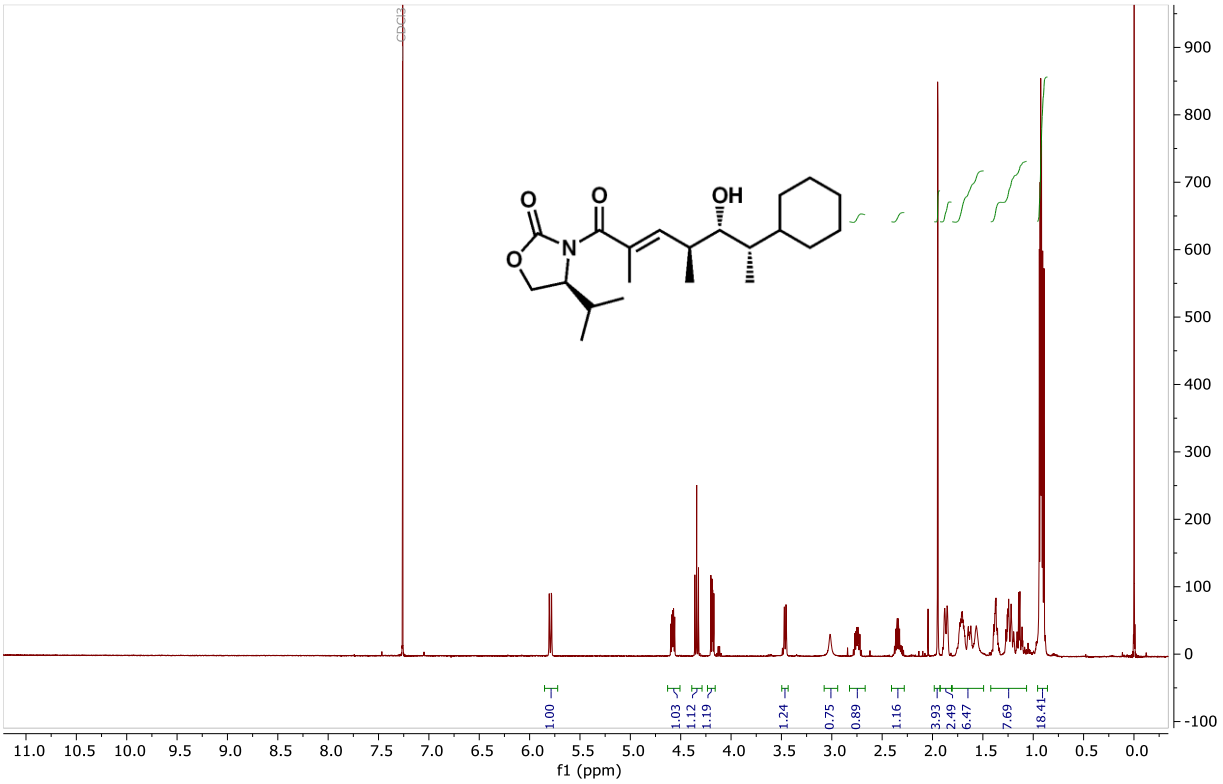
2-cyclohexylpropan-1-ol (9.6)



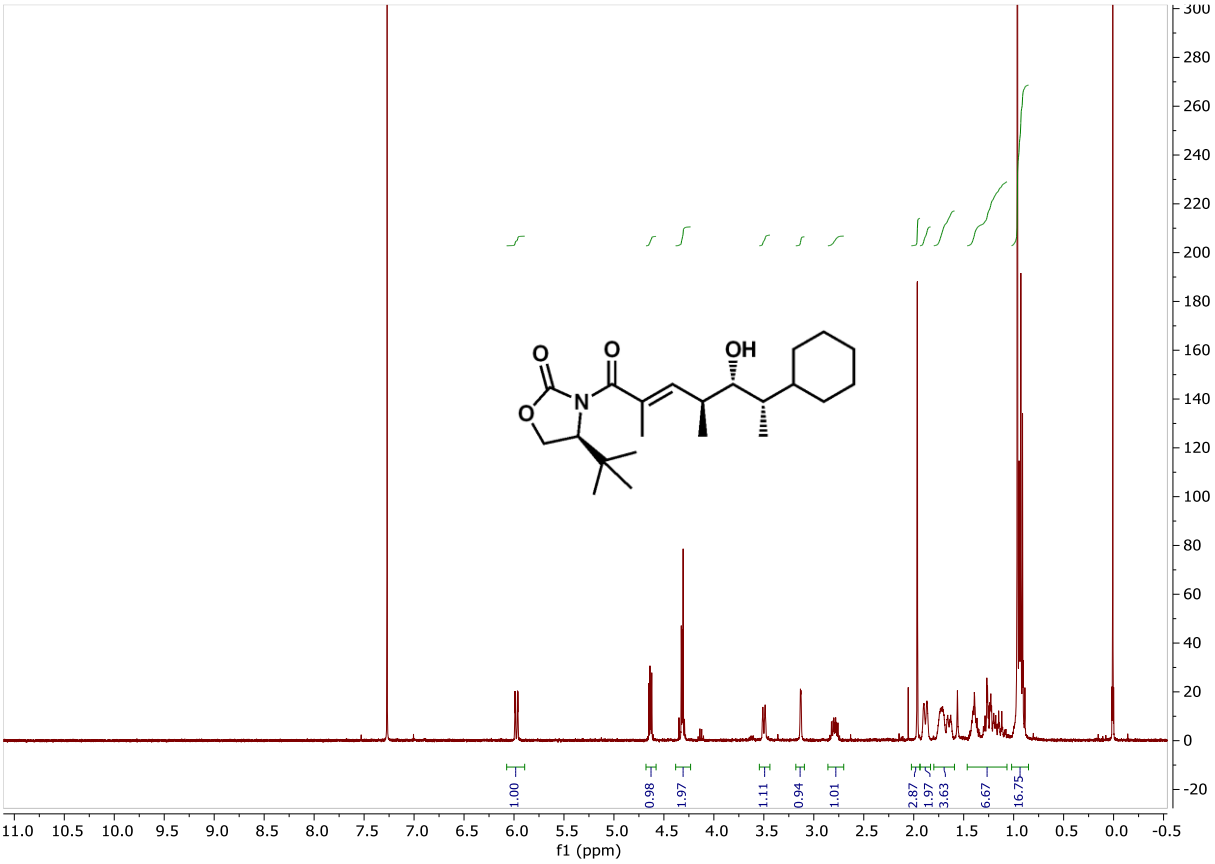
2-cyclohexylpropanal (8.1)



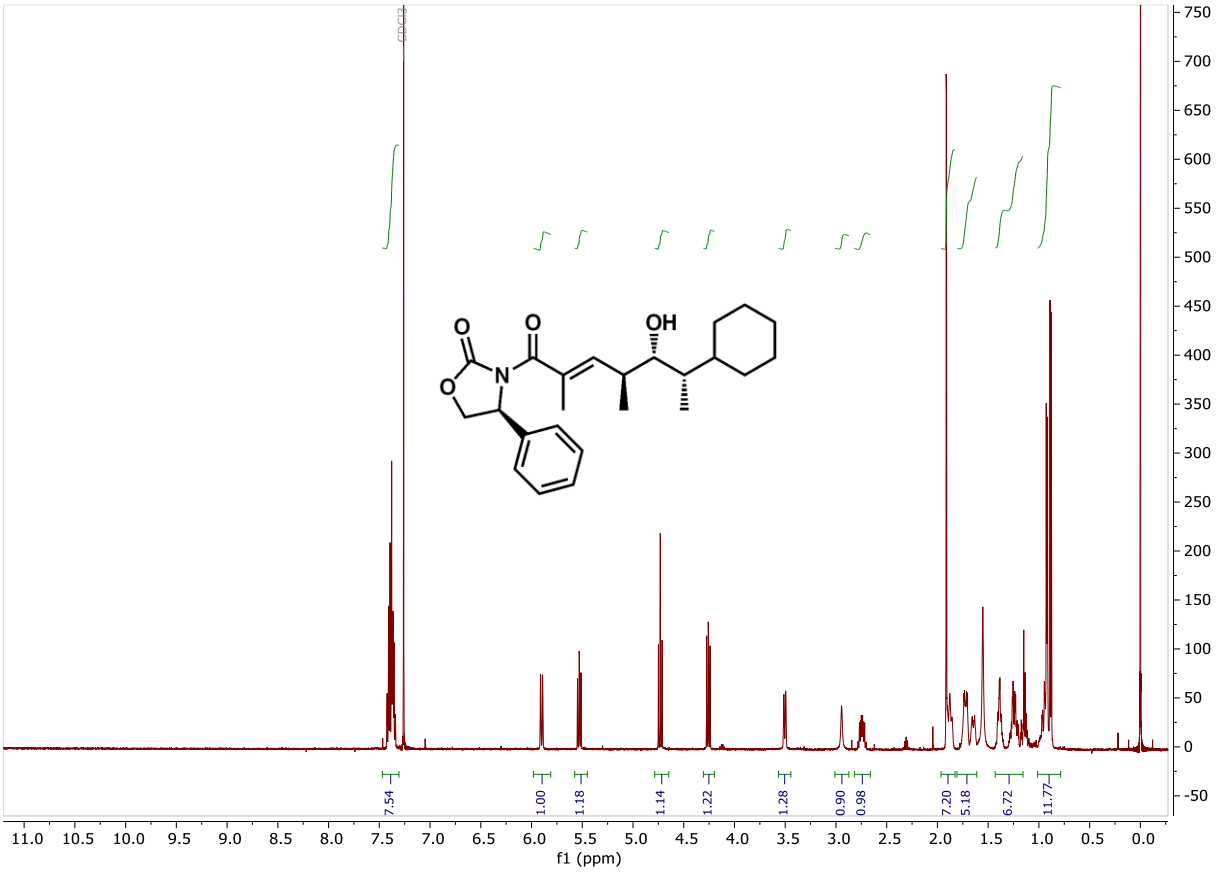
(*S*)-3-((4*S*,5*R*,6*S*,*E*)-6-cyclohexyl-5-hydroxy-2,4-dimethylhept-2-enoyl)-4-isopropyloxazolidin-2-one (10.1)



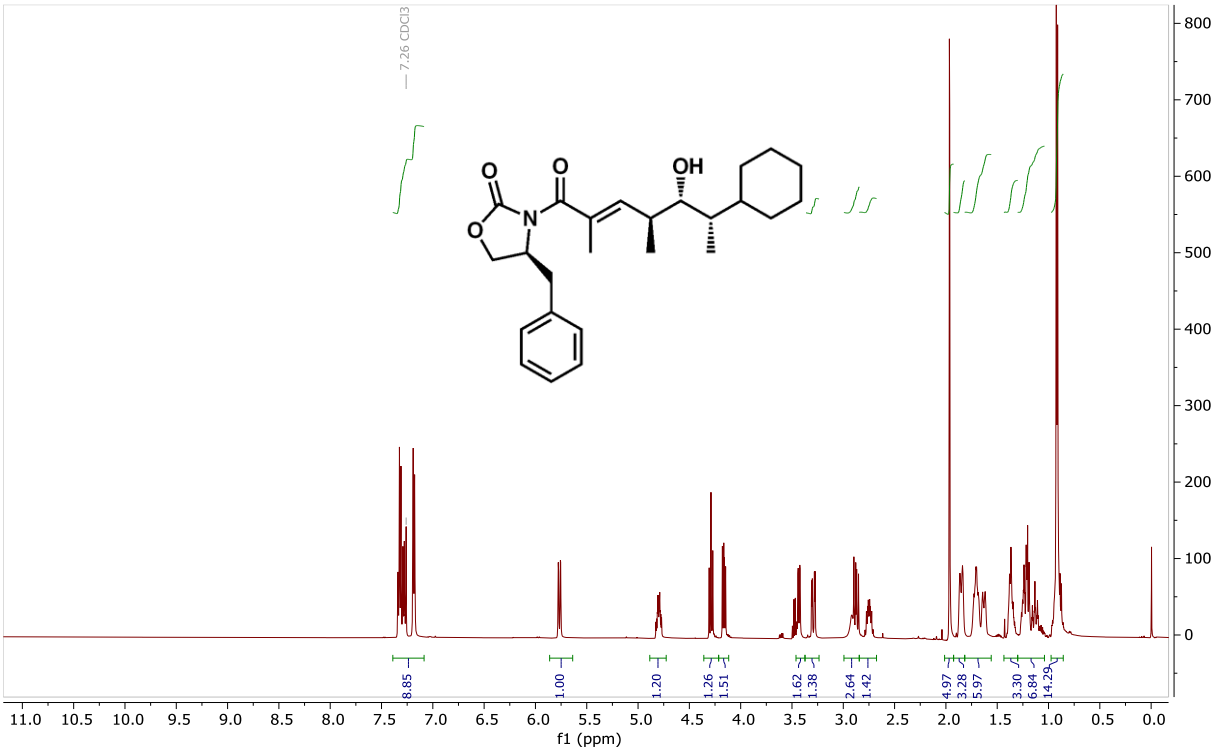
(*S*)-4-(tert-butyl)-3-((4*S*,5*R*,6*S*,*E*)-6-cyclohexyl-5-hydroxy-2,4-dimethylhept-2-enoyl)oxazolidin-2-one (10.2)



(*S*)-3-((4*S*,5*R*,6*S*,*E*)-6-cyclohexyl-5-hydroxy-2,4-dimethylhept-2-enoyl)-4-phenyloxazolidin-2-one (10.3)



(*S*)-4-benzyl-3-((4*S*,5*R*,6*S*,*E*)-6-cyclohexyl-5-hydroxy-2,4-dimethylhept-2-enoyl)oxazolidin-2-one (10.4)



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