UNIVERSITY OF CALIFORNIA, SAN DIEGO

SAN DIEGO STATE UNIVERSITY

Total Synthesis of Lagunamide A via Remote Vinylogous Mukaiyama Aldol Reactions, Chemical Studies Toward the Total Synthesis of Micromide and Preliminary Studies Toward the Total Synthesis of Azaspirene

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

Doctor of Philosophy

in

Chemistry

by

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2016

The Dissertation of Brent Andrew Banasik 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

2016

DEDICATION

Dedicated to my patient & loving wife, Adele & our new handful, Broden

along with our family and friends.

EPIGRAPH

"Cars weren't made with brake pedals to slow us down,

brakes exist so that we can go faster."

-Unknown

"...Unfortunately, all of the good chemistry jokes Argon"

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LIST OF ABBREVIATIONS

Ac	Acetyl
Bn	Benzyl
Brine	Saturated aqueous sodium chloride solution
BOC	t-Butoxycarbonyl
BOM	Benzyloxymethyl
Bu	Butyl
Bz	Benzoyl
Cbz	Carboxybenzyl
CSA	Camphorsulfonic acid
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DIPEA	*N,N*-Diisopropylethylamine, Hünig's base
DMAP	4-*N,N*-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMP	Dess-Martin Periodinane
DMS	Dimethyl Sulfide
DMSO	Dimethyl sulfoxide
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et	Ethyl
Et_2O	Diethyl Ether

equiv	Equivalents
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HOAt	1-Hydroxy-7-azabenzotriazole
HOBt	Hydroxybenzotriazole
HMPA	Hexamethylphosphoramide
HWE	Horner-Wadsworth-Emmons reaction
Imid.	Imidazole
KHMDS	Potassium hexamethyldisilazide
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
Me	Methyl
MOM	Methoxymethyl
NaHMDS	Sodium hexamethyldisilazide
NMO	*N*-Methylmorpholine *N*-oxide
Ns	4-Nitrobenzenesulfonyl or Nosyl
PCC	Pyridinium chlorochromate
PDC	Pyridinium Dichromate
Ph	Phenyl
PMB	*p*-Methoxybenzyl
PPTS	Pyridinium *p*-toluenesulfonate
i-Pr	Isopropyl
Pyr	Pyridine
RCM	Ring closing metathesis
rt	Room temperature
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide

TBDPS	*t*-Butyldiphenylsilyl
TBS	*t*-Butyldimethylsilyl
TBS-OTf	Trifluoromethanesulfonic acid tert-butyldimethylsilyl ester
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
Tol	Toluene
Troc	2,2,2- Trichloroethoxycarbonyl
Ts	Toluenesulfonyl or Tosyl

ACKNOWLEDGEMENTS

I would like to thank Dr. Bergdahl for his insight, mentorship and camaraderie inside and outside of the lab. Dr. Tadeusz Molinski and committee members Dr. Doug Grotjahn, Dr. Patricia Jennings, Dr. Scott Kelley and Dean Stanley Maloy I thank you for your encouraging yet firm counsel. Special acknowledgement goes to the Bergdahl graduate students Lee Wang, Michael Kelly, Tim Montgomery, Arielle Kanner, David Schmit, Scott Burley, Urszula Milewicz, Lucas Fallot, Paul Smith and Brent Thomas whom I have had the pleasure of working alongside. Dr. LeRoy Lafferty, Josh Swider and the UCSD MS Facility were fundamental in spectroscopic scrutiny.

Co-authors Lee Wang, Arielle Kanner and Dr. B. Mikael Bergdahl express their consent for approval of published (and manuscript in preparation) materials included in **Chapter 3**, **4**, **5** and **6** of this dissertation.

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Publications and Manuscripts In Preparation:

1) Banasik, B.; Wang, L.; Kanner, A.; Bergdahl, B. M. "Further insight into the asymmetric vinylogous Mukaiyama aldol reaction (VMAR); Application to the synthesis of the C27–C45 segment of lagunamide A." *Tetrahedron*, **2016**, 72, 19, 2481-2490.

2) Banasik, B.; Wang, L.; Bergdahl, B. M. "Expedient total synthesis of lagunamide A via remote asymmetric vinylogous Mukaiyama aldol reactions." *Journal of Organic Chemistry*, **2016** (Manuscript in preparation).

3) Banasik, B.; Kanner, A.; Bergdahl, B. M. "Enantiomeric resolution of α-substituted aldehydes via Kobayashi's protocol for vinylogous Mukaiyama aldol reaction." *Tetrahedron: Asymmetry*, **2016** (Manuscript in preparation).

4) Wang, L.; Banasik, B.; Nevchas, I.; Bergdahl, B. M. "Asymmetric total synthesis for the proposed structure of micromide and revision of absolute stereochemistry." *Tetrahedron*, **2016** (Manuscript in preparation).

5) Zhou, Q.; Li, Y.; Nie, R.; Friel, P.; Mitchell, D.; Evanoff, R.; Pouchnik, D.; Banasik, B.; McCarrey, J.; Small, C.; Griswold, M. D. "Expression of stimulated by retinoic acid gene 8 (Stra8) and maturation of murine gonocytes and spermatogonia induced by retinoic acid in vitro." *Biology of Reproduction*. **2008**; 78, 3, 537-545.

ABSTRACT OF THE DISSERTATION

Total Synthesis of Lagunamide A via Remote Vinylogous Mukaiyama Aldol Reactions,
Chemical Studies Toward the Total Synthesis of Micromide and
Preliminary Studies Toward the Total Synthesis of Azaspirene

Brent Andrew Banasik
Doctor of Philosophy in Chemistry
University of California, San Diego, 2016
San Diego State University, 2016
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Lagunamide A represents a class of novel cyclic depsipeptide obtained from the marine cyanobacterium *Lyngbya majuscula*. With an array of biological activity and impressive IC_{50} values including anti-malarial properties (IC_{50} 0.19-0.91 μM), significant cytotoxic properties against P388 murine leukemia cell lines (IC_{50} 6.4-20.5 nM) and ileocecal colon cancer (1.6 nM), lagunamide A shows promise as an extremely powerful therapeutic agent. Unexpectedly, in a recent total synthesis of lagunamide A an incorrectly assigned configuration of stereochemistry was reported. Moreover, natural lagunamide A was isolated in 0.00012% yield from 15 L (~169 g isolated dry, powdered weight) of the cyanobacterium laden sea grass via arduous processes, reaffirming the need for an economically robust total synthesis to further encourage biological study. In light of this information an efficient alternative total synthesis was proposed. Through this optimized approach the target molecule was synthesized in significantly higher overall yield and greater selectivity. Specifically, remote stereocontrol via two iterative

vinylogous Mukaiyama aldol reactions (VMAR) lead to a formal total synthesis of the C27-C45 fragment in record yield. Solution and solid phase peptide coupling methodology to construct the C5-C26 fragment of lagunamide A was explored. An optimized convergent strategy lead to the synthesis of lagunamide A and unveiled interesting chemical studies on Kobayashi's protocol for VMAR, specifically a detailed account of relative rate of reaction for (*R*) vs. (*S*)-α-substituted aldehyde additions, including an enantiomeric resolution of a small panel of α-substituted aldehydes and proposed transition states.

Micromide is a cytotoxic alkaloid anti-tumor agent (IC_{50}: 260 nM against KB cells) isolated from *Symploca* cyanobateria. The focus of this research was to develop an efficient and convergent strategy for the total synthesis of micromide. Key synthetic manipulation involved *N*-methylation protocol, solution phase peptide coupling and asymmetric acetate aldol reactions. The reported configuration of micromide was not equivalent to that of synthetic micromide, even though LC-MS data demonstrated the correct molecular weight. *Epi*-micromide was synthesized in ~1% overall yield (103 mg) via solution phase methodology and 7.5% overall yield (50 mg) via solid support methodology. Computational analysis of the ^{13}C NMR data hypothesized that inversion of C35 would reveal the corrected structure for micromide. Preliminary chemical studies towards an expedient synthesis of azaspirene, an effective angiogenesis inhibitor isolated from the soil fungus *Neosartorya sp*., are proposed from (+)-tartaric acid. An efficient synthetic pathway for theses bioactive molecules could ultimately lead to structural analogs for structure-activity relationship (SAR) studies against various cancer cell lines.

1 Introduction

The total synthesis of complex natural products is an essential effort to produce rare bioactive compounds and a hallmark of modern organic chemistry. The focus of this dissertation is the total synthesis of lagunamide A, presented in **Chapters 2-7**, including notes on synthesis, method developments and biochemical progress. **Chapter 2** stresses the importance of marine natural products, specifically lagunamide A obtained from the marine cyanobacterium Lyngbya *majuscula*, that featured impressive IC_{50} values including anti-malarial properties (IC_{50} 0.19-0.91 μM), significant cytotoxic properties against P388 murine leukemia cell lines (IC_{50} 6.4-20.5 nM) and Ileocecal colon cancer (1.6 nM). **Chapter 3** focuses on the efforts towards an optimized synthesis of the C27-C45 fragment of lagunamide A; including *syn*-aldol, *anti*-Ghosh, and Kobayashi's VMAR methodology in pursuit of a method that eventually provided the fragment with record yield and ease when compared to previous reports. Both solution and solid phase syntheses of the tetra-peptide (C5-C32 fragment) of lagunamide A are discussed in **Chapter 4**. A succinct, optimized, convergent and asymmetric total synthesis of lagunamide A is presented in **Chapter 5**. **Chapter 6** focuses on several chemical studies for Kobayashi's VMAR. Herein, the effect of α-substitution in aldehyde addition, compatibility of β-etherial aldehyde protecting groups, resolution of enantiomers via stereochemical bias and proposal of transition states for these observations. Creation of biosensors for lagunamide A is discussed in **Chapter 7**, the outcome of which would aid in isolation of the corresponding binding protein and elucidation of the mechanism of action.

Chapter 8 focuses on the correction of the absolute stereochemistry for micromide. Micromide is a cytotoxic alkaloid anti-tumor agent (IC_{50}: 260nM against KB cells) isolated from *Symploca* cyanobateria. The reported configuration of micromide was not equivalent to that of synthetic micromide, even though LCMS data demonstrated the correct molecular weight. *Epi*-micromide was synthesized in 1% overall yield (103 mg) via solution phase methodology and 7.5% overall yield (50 mg) via solid support methodology. Computational analysis of ^{13}C NMR for natural vs. synthetic micromide revealed key differences, the chemical studies of which are underway.

The inhibition of tumor-angiogenesis has proven to be an effective method in the treatment of cancer. Small molecule drugs that inhibit angiogenesis have been used in chemotherapy since bevacizumab was FDA approved in 2004. **Chapter 9** focuses on Azaspirene, a known inhibitor of tumor-angiogenesis that is part of the pseurotin family of compounds whose members have shown a wide variety of biological properties. There are two total syntheses currently published for azaspirene. However, both routes are quite lengthy and suffer from poor overall yields and thus research into this type of cancer therapy using azaspirene has been impeded.

Future work and additional suggestions are discussed in **Chapter 10**. The main focus is completion of biosensors for lagunamide A and their utilization to determine the corresponding binding protein and help elucidate a mechanism of action. Our chemical studies on Kobayashi's protocol for the VMAR discovered interesting means of catalysis, enantiomeric resolution and favored transition states that need further development for practical applications in synthesis. Stereochemical reconfiguration of synthetic

micromide to reproduce the bioactivity found in nature are underway, guided by computational analysis of key ^{13}C NMR spectroscopic differences between natural and synthetic micromide. A simple and robust total synthesis of azaspirene remained elusive via our originally proposed pathway; however, the chemical studies towards the spiro-cyclic core developed alternative routes that are currently underway in our laboratory.

Experimental details and ^{1}H NMR characterization for all compounds are presented in **Chapter 11**. The majority of compounds were further characterized by optical rotation, FTIR, ^{13}C NMR spectroscopy and APCI/LC/HR MS.

2 Bioactive Marine Macro-Cyclic Depsipeptides and Lagunamide A

2.1 Introduction

My research within the Bergdahl group has focused primarily on the total synthesis of the marine macro-cyclic depsipeptide lagunamide A. The route pursued a novel, efficient chemical strategy that was highly convergent and allowed for simple modification of subunits for development of structure-activity relationships (SAR). Various new methodologies in chemical synthesis, such as an *anti*-addition "Gosh" aldol reaction as well as novel methodology for remote stereocontrol of vinylogous Mukaiyama aldol reactions (VMAR) and catalytic bismuth (III) triflate mediated vinylogous aldol condensations were revealed throughout the total synthesis of lagunamide A.

2.2 Significance of research

Natural products are purified organic compounds produced from a living organisms' metabolism that often have therapeutic impact in humans, for example penicillin, morphine or the prevalent cancer therapeutic taxol, which is a molecule originally isolated from the yew tree.[1] Entire research programs are dedicated to the collection, stereochemical elucidation and biochemical characterization of bioactive natural product molecules. Marine cyanobacterial strains in particular produce many structurally intriguing biologically active macro-cyclic hybrid polyketide-polypeptide secondary metabolites.[2] Lagunamides and some structurally related compounds such as

kulokekahilides, aurilides and pulau'amides (**Figure 2.1**) may have important potential applications such as antibacterial, cytotoxic, antimicrobial, antimalarial and neurotoxic properties.[3] Natural products collected from nature are often hard to come by and necessitate chemical synthesis to aquire sufficient quantities of purified material for therapeutic use. For example, to extract approximately 5 mg of Aurilide compound from *Dolabella auricularia* one would need to gather 31 Kg of the sea hare by hand at a depth of one meter off the Shima Peninsula, Japan and commence a multi-month, multi-process extraction and purification to afford an ineffectual 0.00000019% isolated yield.[4] Similarly, the interesting molecule named lagunamide A[5] was recently isolated in 0.00012% yield from 15 L (~169 g isolated dry, powdered weight) of the cyanobacterium *Lyngbya majuscule* on sea grass via similar arduous processes. The total synthesis of bioactive molecules such as lagunamide A would allow for an economical, scalable production and streamlined research into the mode of action for potential therapeutic development.

2.3 Potential therapeutic applications

Hybrid polyketide-polypeptide macro-cyclic natural products displayed an expansive array of structure and activity.[3] This relationship made them prime targets for total synthesis and biochemical study to determine mode of action as well as modification to construct a small library and screen for new or improved function. The sheer number of these compounds found in nature and their impressive variety of biological activities suggests that if we understand the structure-activity relationship, slightly changing the chemical makeup of these molecules at certain positions may have increased activity for

a given biological activity, or changed its usefulness into something else entirely. Structurally related lagunamide, kulokekahilide, aurilide and pulau'amide molecular classes, shown in **Figure 2.1**, have cytotoxic, antimalarial, antibacterial, antiswarming, antimicrobial and neurotoxic biological activities.[3]

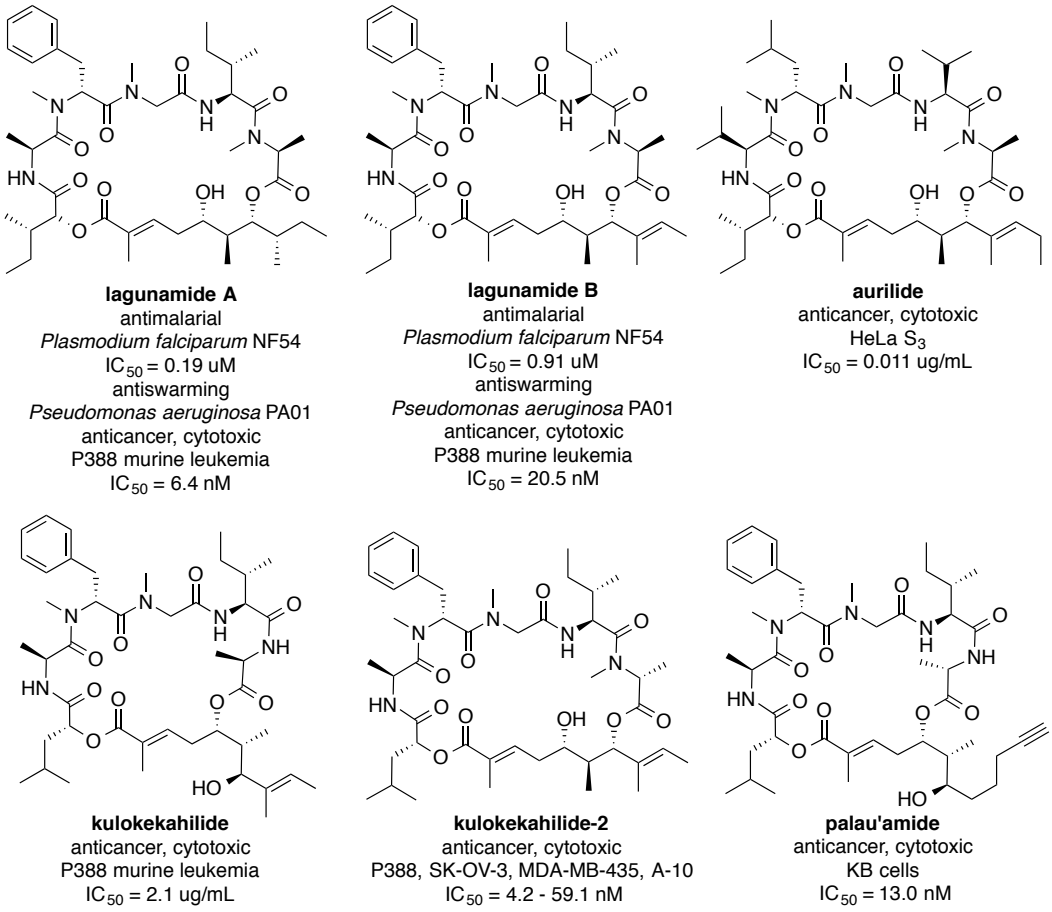


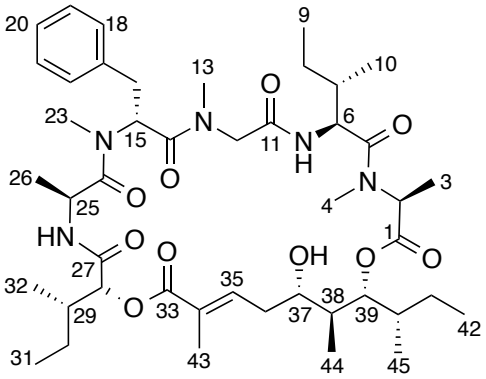
Figure 2.1 Bioactive Depsipeptides.

Lagunamides were the first ever aurilide-like macro-cyclic depsipeptide class of molecule that showed anti-malarial activity, which cements that small changes to similar molecules had drastic effects on bioactive outcome. Once an efficient total synthesis is established and there is a stockpile of the molecule, and in conjunction with

computational analysis and determination of the mode of action, it becomes increasingly plausible to design optimized molecules that, for example, would have higher affinity to a binding sight due to the improved substrate steric, electronic or conformational interactions.

2.4 Discovery, bioactivity and structure of lagunamide A

Lagunamide A was of particular interest due to its significant antimalarial properties when tested against *Plasmodium falciparum* and potent cytotoxic activity against P388 murine leukemia cell lines, with IC_{50} values of 0.19 uM and 6.4 nM, respectively.[5] This bioactive molecule was discovered by the Tan research group as part of their drug discovery program and took nearly four years to elucidate, identify and publish. They discovered a persistent strain of the marine cyanobacterium *Lyngbya majuscula* during low tide in the western lagoon of Pulau Hantu Besar, Singapore and repeatedly extracted the biomass. The 100% ethyl acetate-eluted fraction showed a high occurrence of toxicity in brine shrimp lethality assay (BSLA) and was thus purified via SIP PAK C_{18} solid-phase fractionation and reversed-phase HPLC to afford lagunamide A as a colorless, amorphous solid. Spectroscopic analysis included 2D NMR, Marfey's method, Mosher's ester, J_{H-H} coupling constant values and LCMS to determine the absolute confirmation.



lagunamide A

Figure 2.2 Absolute stereochemical configuration of lagunamide A.

The HRMS (ESI) of lagunamide A revealed a [M+Na^+] peak at *m/z* 864.5093 consistent with a molecular formula of $C_{45}H_{71}N_5O_{10}$. The ^1H and ^{13}C data for lagunamide A indicate presence of rotational conformers with overlapping signals in $CDCl_3$, however a single conformer dominated in CD_3OD and allowed the Tan group to determine the presence of seven carbonyl groups, three *N*-methyl amide groups and a mono-substituted phenyl ring. Advanced 1D and 2D-NMR experiments determined the skeleton of lagunamide A, most importantly short and long-range HMBC to elucidate the peptidic fragment as a *N*-Me-Ala-Ile-*N*-Me-Gly-*N*-Me-Phe-Ala-Hila sequence and COSY correlations to map out the terpenoid fragment. HMBC cross peaks between the H28 α–proton of the peptide/Hila moiety and the C33 carbonyl carbon of the terpenoid substructure revealed the macro-cyclic depsipeptides scaffolding of lagunamide A. The four contiguous stereocenters from C37 to C40 were determined by assigning C37 unambiguously as *S*-confirmation via MTPA-ester derivatives (Mosher's Protocol), then comparing relative $J_{H\text{-}H}$ values of C38, C39, C40 to determine if neighboring moieties were *syn* or *anti* to each other. Unfortunately, C37 to C40 stereochemistry was

incorrectly assigned by false positives from the J_{H-H} NMR analysis and assignment of protons (See **Chapter 2.5** *Revision of stereochemistry* for further discussion).

2.5 Revision of stereochemistry

Due to miss-assignment of H38 with H40 and *vice-versa* the absolute confirmation of lagunamide A was initially consigned incorrectly. J_{H-H} values were used to determine *anti* or *syn* neighboring relationships from feasible Newman projections (**Figure 2.3**, image from Tripathi *et al*.[5]) that unfortunately ended in supporting false positives with stereocenters 38*S*, 39*S* and 40*S*, presented in **Figure 2.4** below.

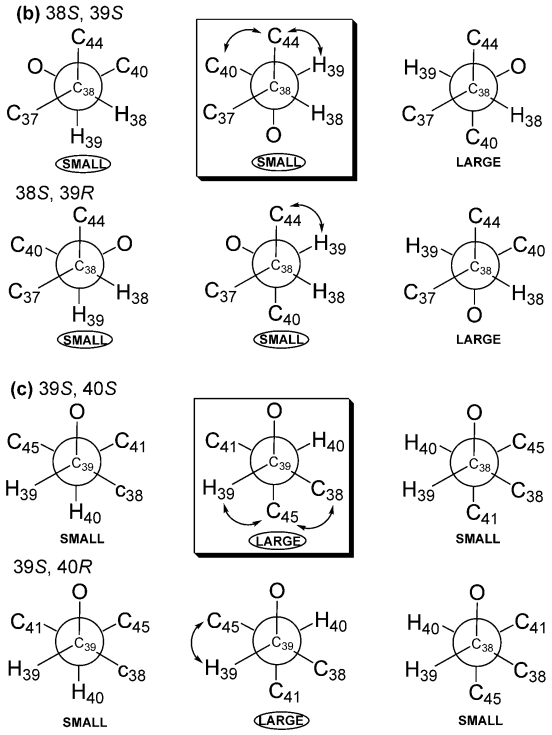


Figure 2.3 Newman projections for predicted J_{H-H} coupling constants

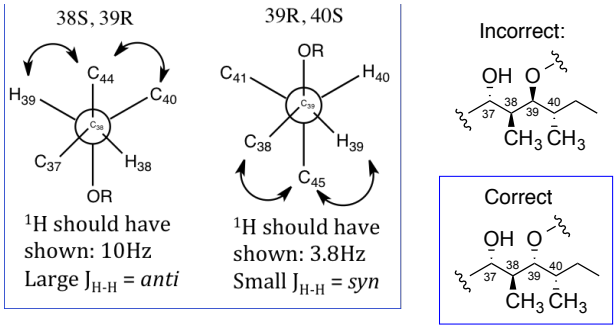


Figure 2.4 False-positive Newman projections and revision of stereochemistry

By completion of a diverse total synthesis with many analogues of lagunamide A, the Ye group revised and confirmed the absolute stereochemistry of lagunamide A correctly to 38*S*, 39*R* and 40*S*.[6] Also, during the established trivial amino acid elucidation protocol, L-isoleucine (with miss-assignment at C7) was originally reported as an L-*allo*-isoleucine. Shown side-by-side in **Figure 2.5** are the originally reported and revised stereochemical models of lagunamide A.

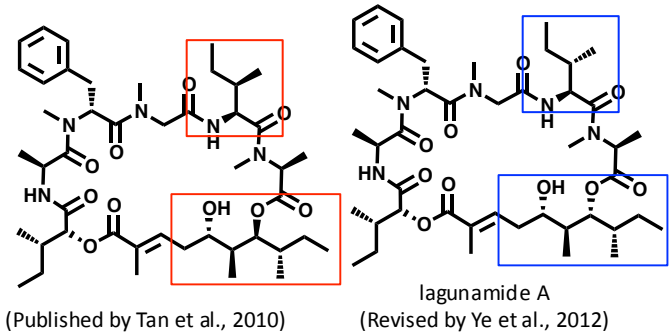


Figure 2.5 Revision of absolute stereochemistry of lagunamide A

2.6 Implied mode of action for lagunamide A

Cyanobacterial compounds similar to lagunamide A such as apratoxin A, largazole and dolastatin 10 are valuable targets for therapeutic development due to their specific interference with discrete cellular targets such as actin filaments, microtubules and histone deacetylase.[3] No specific mechanism of action is entirely known for lagunamide A, but preliminary studies by the Tan[7] Group were conducted through studying effects on programmed cell death and apoptosis. The morphological observation in **Figure 2.6** (normal HCT8 cells and those treated with lagunamide A, image from Tripathi *et al.*[7]) showed loss of cell proliferation and blebbing morphology which indicated apoptosis in cancer cells.[7]

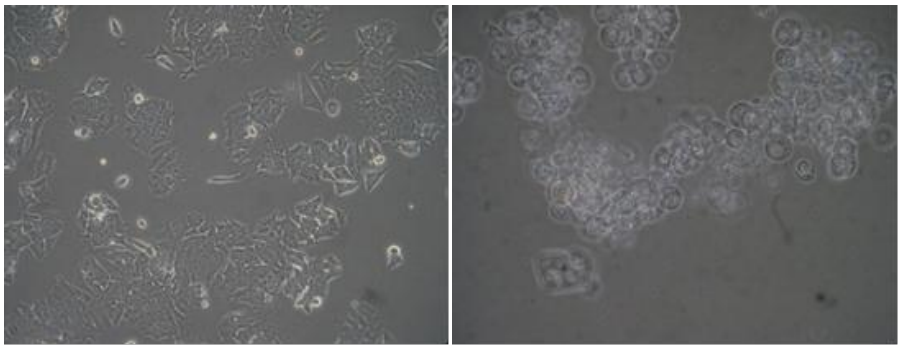


Figure 2.6 200x images of untreated HCT 8 cells (left) and HCT 8 cells treated with lagunamide A (right).

Table 2.1 (image from Tripathi *et al.*[7]) displayed the broad biological activity of various macrocyclic depsipeptides against diverse cell lines. Furthermore, p53 tumor suppressor oncogene knockdown studies on foreskin fibroblast cells (BJ) indicated a more specific mode of action.[7] Decisively, lagunamide A was three times more effective

against normal BJ cells when compaired to BJ shp53 cells, with mutations for uncontrolled cellular division. As such, lagunamide A may utilize p53 to induce apoptosis in the cell. A series of western blot experiments of human colon tumor (HCT8) and human breast cancer (MCF7) cell lysates showed that the cytotoxicity of lagunamide A may be due to either passive diffusion or active transport that triggers mitochondrial mediated apoptosis, summarized in **Figure 2.7** (image from Tripathi *et al*.[7]).

Table 2.1 IC_{50} values (nM) of lagunamide A (1), lagunamide B (2), aurilide (3), aurilide B (4), aurilide C (5), and kulokekahilide-2 (6) against various cell lines.

Cell Lines	Cell Types	1	2	3 [a]	4 [b]	5 [b]	6 [c]
BJ	Foreskin fibroblast	20.2					
BJ shp53	p53 knocked down fibroblast	58.8					
P388	Murine leukemia	6.4	20.5				4.2
A549	Lung adenocarcinoma epithelial	2.9					
NCI-H460	Lung large-cell carcinoma				10	50	
PC3	Prostate carcinoma	2.5					
HCT8	Ileocecal colorectal adenocarcinoma	1.6	5.2				
SK-OV3	Ovarian carcinoma	3.8					7.5
HeLaS3	Human epithelial carcinoma			11			
MDA-MB-435	Human breast carcinoma						14.6
A10	Vascular smooth muscle						59.1
Neuro-2a	Mouse neuroblastoma				40	130	

Specifically, the level of pro-capsase 3 was significantly lower in HCT8 cells exposed to lagunamide A, which suggested downstream processing of apoptotic cascade.[7] Similarly, MCF7 cells had the lowest levels of capsase 9 when compared to the vehicle, taxol and lagunamide B. Coincidentally, a recent report by Sato[8] and co-workers revealed aurilide, which is a structurally similar molecule to lagunamide A, induced apoptosis via a mitochondrial-mediated pathway.

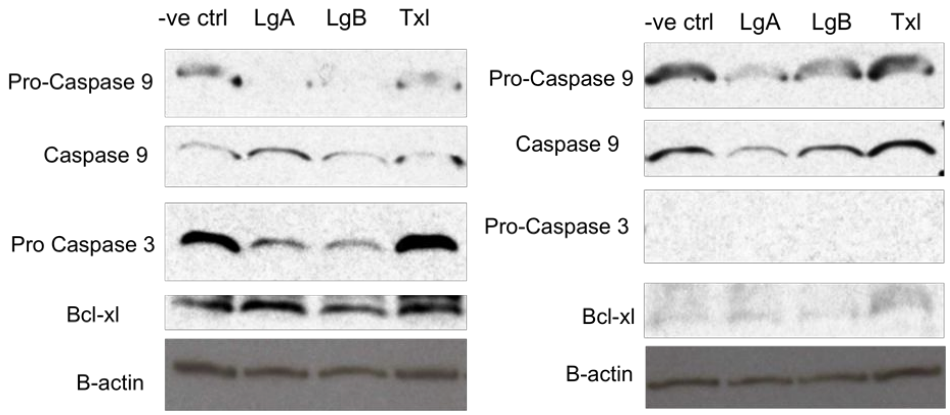


Figure 2.7 Western blot analysis of (left) lagunamide A (LgA), lagunamide B (LgB), and taxol (Txl)-treated HCT8 cells and (right) lagunamide A (LgA), lagunamide B (LgB), and taxol (Txl)-treated MCF7 with representative antibodies; lysates from DMSO.

3 Synthesis of the C27-C45 "Southern Hemisphere" of Lagunamide A

3.1 Introduction

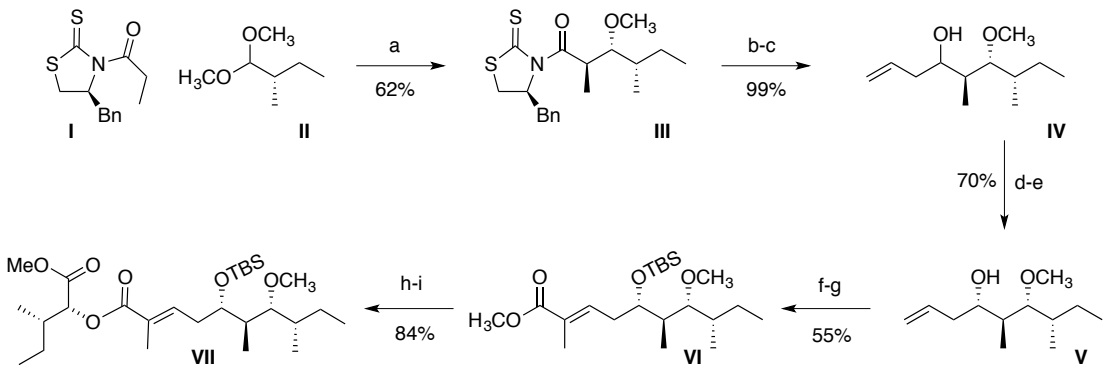
The depsipeptide lagunamide A is comprised of a "northern hemisphere" C1-C26 pentapeptide fragment and a "southern hemisphere" C27-C45 terpenoid fragment (refer to **Figure 2.2**). The Southern fragment of lagunamide A is correlated to a diverse structure activity relationship for this class of bioactive molecule. By designing a convergent synthesis that is customizable at different connections along the way, chemists have access to enormous libraries of compounds with potential therapeutic use. A convergent retrosynthesis of lagunamide A is presented in **Chapter 3.3**. Significant synthetic insight was gained in making the C27-C45 fragment of lagunamide, especially asymmetric installation of the hydroxyl group at C37 and protecting group chemistry, the efforts of which are highlighted in **Chapter 3.4.2**. Specifically, asymmetric installation of the C37 hydroxyl group was investigated after Evans *syn*-aldol addition, Ghosh *anti*-aldol addition and numerous allylation and vinylogous transformations that eventually afforded an optimized, direct and asymmetric C27-C45 "southern hemisphere" formal synthesis via remote induction of stereochemistry by Kobayashi's protocol[9] for the vinylogous Mukaiyama aldol reaction (VMAR).

3.2 Previous synthesis

Lui *et al.*[10] described an efficient synthesis of the C27-C45 fragment of lagunamide A in 2014. The C27-C45 "Southern hemisphere" of lagunamide A is a

complex polyketide moiety with four contiguous stereocenters, extended by vinylogy to an α,β-unsaturated ester fragment that is flanked by a (2*R,3S*)-2-hydroxy-3-methyl-pentanoic acid derivative of *D*-allo-isoleucine. Access to this fragment is crucial for high overall yield and embodies the synthetic complexity for this class of cyclic-depsipeptide. This synthesis described a general, but direct method to afford fragment **VII** in 22% overall yield. The Chang[10] synthesis (**Scheme 3.1**) was initiated with Crimmins[11] *anti*-acetate aldol reaction of thiazolidinethione **I** with acetal **II** to construct *anti*-product **III** in 62% yield with moderate 82:18 diastereomeric ratio. Reductive cleavage of the chiral auxiliary with DIBAL-H and immediate reaction with allylmagnesium chloride to the aldehyde resulted in the nearly racemic (40:60) mixture of alcohol **IV** in 99% yield over two steps. This stereoselectivity can be explained via transition state proposed by Felkin *et al*.[12] This mixture of diastereomeric alcohols was next homogenized via Dess-Martin Periodinane oxidation then reduced in an asymmetric manner to afford alcohol **V** (8:1 dr) in 70% yield over two steps.

Silyl-protection as the TBS-ether and subsequent olefin cross-metathesis of intermediate **V** with methyl methacrylate by Grubbs 1st or 2nd generation catalysis produced the desired alkene **VI** (*E*-geometry confirmed by NOESY analysis) in 55% yield over two steps.[13] Methyl ester **VI** was patiently saponified over 3 days to the corresponding carboxylic acid then coupled with methyl (2R,3S)-2-hydroxy-3-methylpentanoate[10] using DCC and DMAP in DCM to provide the desired target fragment **VII** in 84% yield over two steps.



Reagents and conditions: (a) $TiCl_4$, DIPEA, CH_2Cl_2, 0 °C, 1 h, then $SnCl_4$, **II**, -84 °C to 0 °C; (b)DIBAL-H, CH_2Cl_2, -84 °C, 10 min; (c) allylmagnesium chloride, THF, 0 °C, 1 h; (d) Dess-Martin periodinane, CH_2Cl_2, 0°C, 30 min; (e) $NaBH_4$, CH_3OH, 0 °C, 15 min; (f) TBSOTf, Et_3N, CH_2Cl_2, 0 °C, 1 h; (g) methyl methacrylate, Grubbs catalyst 2nd generation, CH_2Cl_2, reflux, 16 h; (h) KOH(aq), THF, rt, 3 d; (i) methyl (2*R*,3*S*)-2-hydroxy-3-methylpentanoate, DCC, DMAP, CH_2Cl_2, rt, 22 h.

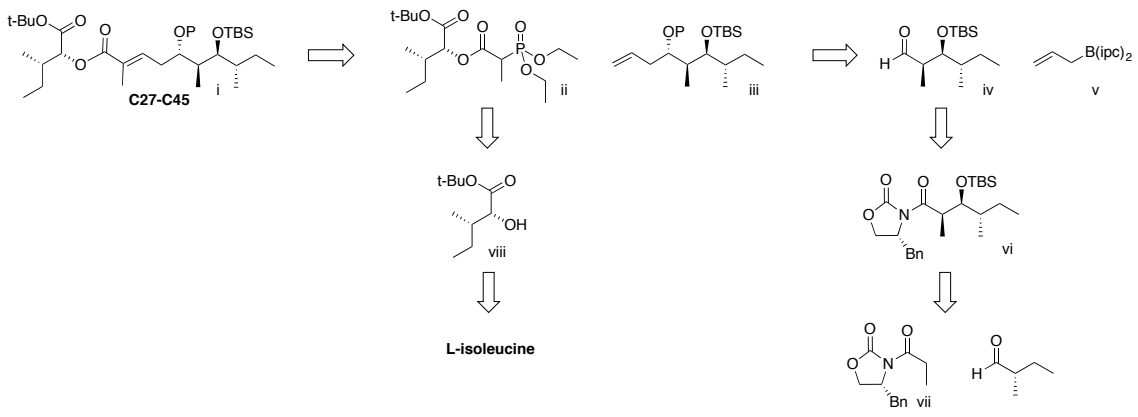
Scheme 3.1 Chang synthesis of C27-C45 fragment of lagunamide A

The synthesis published by Chang[10] and coworkers (**Scheme 3.1**) helped to confirm absolute stereochemistry of the C27-C45 fragment obtained via acetonide derivatization and validated the efficacy of our allylation procedure (See **Chapter 3.4.4** for further discussion). Nevertheless, the Chang synthesis was not direct and lacked sensible protecting groups that left significant room for improvement when designing a formal synthesis of lagunamide A. Prior to this publication, we had hypothesized a synthesis that would access the C27-C45 fragment of lagunamide A in a directly asymmetric fashion, in higher overall yield and with better protecting group strategy to ultimately aid in the total synthesis of lagunamide A.

3.3 Retrosynthetic strategy for C27-C45 fragment of lagunamide A

Retrosynthesis for the C27-C45 fragment (i) of lagunamide A (designed prior to revision of stereochemistry by Lu *et al*.[6] and discussed in **Chapter 2.5**) was proposed

below (**Scheme 3.2**). Convergent HWE olefination of an *L*-Ile phosphonate moiety (ii) and terminal alkene (iii) with orthogonal protection groups deconstructed the C27-C45 fragment of lagunamide A. Evans[14] chiral oxazolidinone auxiliary (vii) proved useful in asymmetric synthesis to provide a key intermediate aldehyde (iv) with three contiguous stereocenters from syn-aldol adduct (vi). Asymmetric (+)-Ipc_2B(allyl)borane (v) allylation of aldehyde (iv) would provide the homoallylic moiety (iii). Chemical studies towards synthesis of the C27-C45 fragment of lagunamide A via development of Evans *syn*-aldol methodology is presented in subsequent **Chapter 3.4.1**.

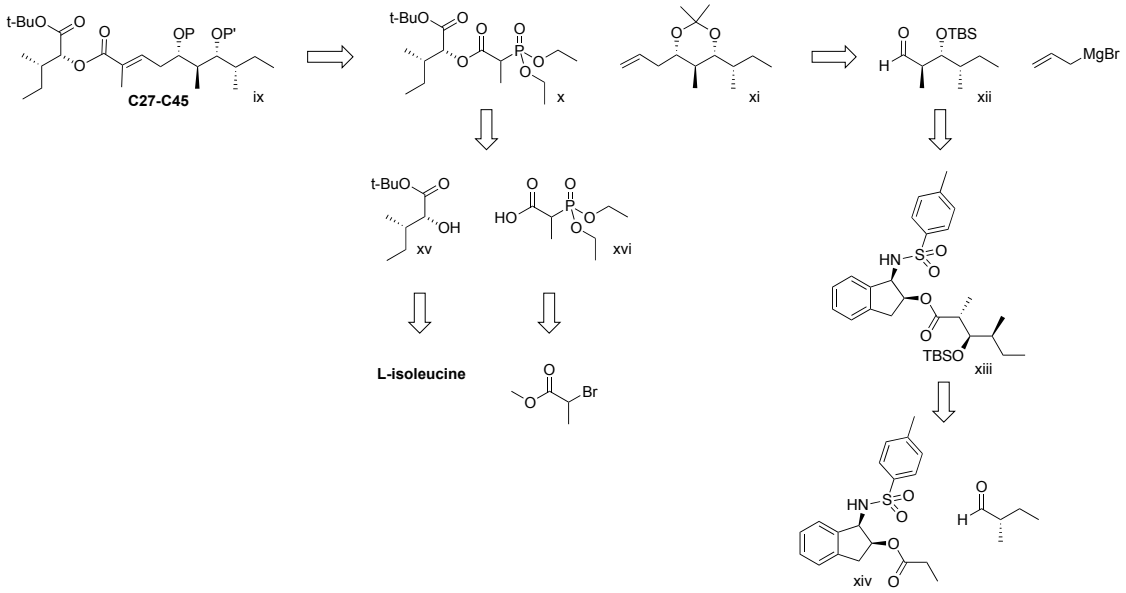


Scheme 3.2 S*yn*-aldol retrosynthesis for the C27-C45 fragment of lagunamide A.

3.3.1 Revised retrosynthetic strategies for C27-C45 fragment of lagunamide A

Retrosynthesis for the C27-C45 fragment of lagunamide A (designed after revision of stereochemistry by Lu *et al*.[6]) is illustrated below (**Scheme 3.3**). Thus, HWE olefination of an *L*-Ile phosphonate moiety (x) and acetonide alkene (xi) deconstructed the C27-C45 fragment of lagunamide A. Simple allylation via allylmagnesium bromide of aldehyde (xii), followed by selective oxidation, asymmetric reduction and protection

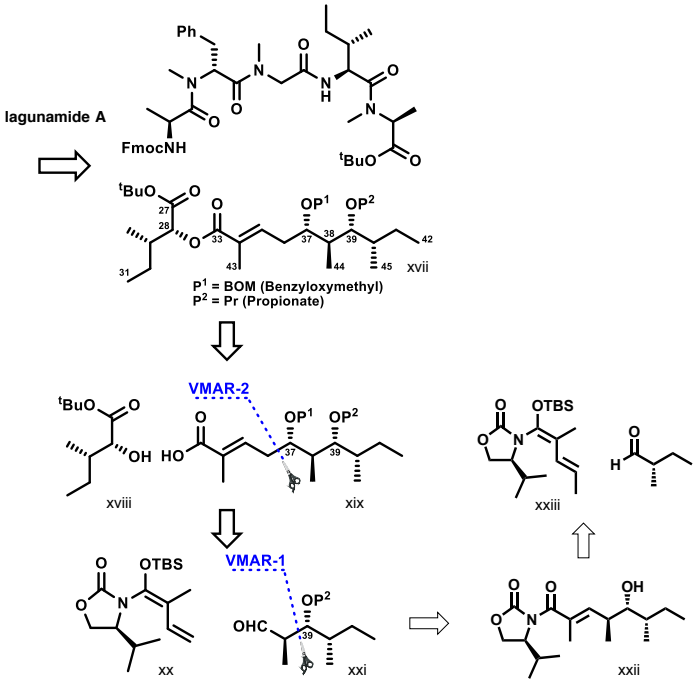
would afford homoallylic moiety (xi). Ghosh[15] *anti*-aldol auxiliary (xiv) would prove useful in asymmetric synthesis to supply a key intermediate aldehyde (xii) with three contiguous stereocenters from *anti*-aldol adduct (xiii). A chemical study towards synthesis of the C27-C45 fragment (ix) of lagunamide A via development of Ghosh *anti*-aldol methodology is presented in the subsequent **Chapter 3.4.3**.



Scheme 3.3 A*nti*-aldol retrosynthesis for the C27-C45 fragment of lagunamide A.

A second simple retrosynthesis of the C27-C45 fragment of lagunamide A was proposed in **Scheme 3.4** using remote stereocontrol by vinylogous Mukaiyama aldol reactions to create the vinylogous alcohol moiety in less steps. The C27-C45 fragment (xvii) was separated via esterification of α-hydroxy moiety (xviii) and α,β-unsaturated acid (xix). Kobayashi protocol for VMAR[9] produced this key α,β-unsaturated moiety with four contiguously defined stereocenters by two iterations of VMAR. *Anti*-alcohol (xxii) was produced from VMAR reagent (xxiii) and readily available (2*S*)-methyl-1-

butanal, which is commercially available or obtained via oxidation of (2*S*)-methyl-1-butanol.



Scheme 3.4 Retrosynthetic strategy towards lagunamide A employing VMAR's.

The VMAR strategy to lagunamide A was hypothesized to produce a formal synthesis in a directly asymmetric fashion and in higher overall economic yield then previous reports. Likewise, this strategy would provide a suitable intermediate with thoughtful protecting group strategy and defined points of bond formation to complete the total synthesis of lagunamide A by coupling with the "Northern hemisphere" peptide fragment of the molecule (Please refer to **Chapter 5** for discussion on the convergent total synthesis of lagunamide A).

3.4 C27-C45 "Southern" polypropionate fragment, results and discussion

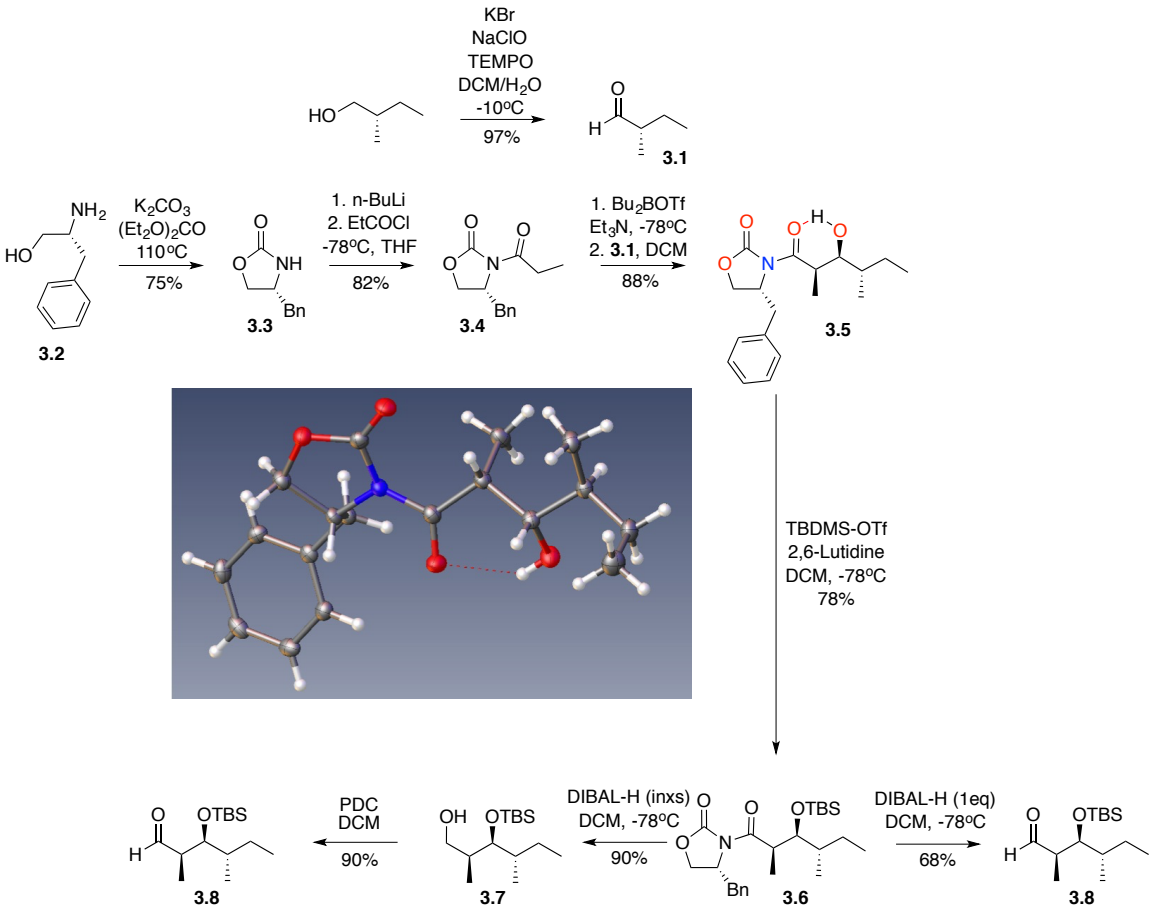
The following segments described our efforts from conception to optimized formal synthesis of the C27-C45 fragment of lagunamide A, both pre and post-revision of absolute stereochemistry. We primarily utilized Evans *syn*-aldol, Ghosh *anti*-aldol and Kobayashi VMAR protocol to construct stereocenters C37 through C40. Elongation of the C37-C40 artifact was achieved thru coupling with the α-hydroxy-*D*-allo-Ile-OH moiety, of which chemical synthesis is disclosed in detail. These subdivisions were concluded with optimized binary formal syntheses of lagunamide A. Confirmation of absolute stereochemistry was accomplished through NMR experimentation of acetonide derivatives.

3.4.1 Evans aldol addition

Evans developed the use of chiral amino acids as a platform to make oxazolidinone auxiliaries that proved extremely powerful and useful in asymmetric synthesis.[14] Specifically, oxazolidinones are robust directing group auxiliaries for the creation of *syn*-aldol products.[16] The absolute stereochemistry of natural lagunamide A was first reported by Ye and coworkers[5] as C37*(S)*, C38*(S)*, C39*(S)* and C40*(S)* (See **Chapter 2.5** Revision of stereochemistry). As such, our retrosynthetic approach took advantage of the C38*(S)*-C39*(S) syn*-aldol moiety in the directed synthesis of three crucial consecutive stereocenters. Thus oxazolidinone **3.3** was prepared by the reduction of *D*-phenylalanine to *D*-phenylalanol (**3.2**), then cyclized with diethylcarbonate and then acylated to afford **3.4** in 53% yield over 3 steps (**Scheme 3.5**). (*S*)-2-Methyl-1-butanal

(**3.1)** was prepared by NaClO/TEMPO oxidation[17] from commercially available (*S*)-2-methyl-1-butanol and queued for subsequent *syn*-aldol addition. (*S*)-Methyl-butanal (**3.1**) proved to be a difficult compound to purify. Distillation and bisulfite adducts[18] were unsatisfactory. The reaction was optimized to near quantitative yield, lightly concentrated, dried and analyzed by NMR (~0.2M-0.3M aldehyde **3.1** in CH_2Cl_2). The *syn*-aldol product (**3.5)** was obtained via freshly prepared 0.25M aldehyde **3.1** in CH_2Cl_2, Bu_2BOTf and oxazolidinone **3.4** with triethylamine. Intermediate alcohol **3.5** was prepared in high yield (88%) and excellent d.r. (>99:1). After recrystallization from hot hexanes in ethyl acetate the absolute stereochemistry was confirmed unambiguously by x-ray diffraction (**Scheme 3.5**).

Silyl-protection of *syn*-alcohol **3.5** proceeded smoothly via TBS-OTf/2,6-lutidine, but not conventional TBS-Cl/imidazole protocol, presumably because of stabilizing intra-molecular hydrogen bonding represented in the crystal structure analysis shown in **Scheme 3.5**. Subsequent selective DIBAL-H (1 equiv) reduction of **3.6** to aldehyde **3.8** in 68% yield or complete reduction with DIBAL-H (>2 equiv) to primary alcohol **3.7** followed by selective oxidation with PDC in 81% yield over 2 steps afforded the targeted intermediate aldehyde **3.8**. Aldehyde **3.8** was efficiently achieved in 4 linear steps from known compound (*R*)-4-benzyl-3-propionyloxazolidin-2-one (**3.4**) in 56% overall yield. Aldehyde **3.8** provided three crucial stereocenters of lagunamide A and geared our synthesis for further exploration of asymmetric C37(*S*) bond formations (See **Chapter 3.4.2**).



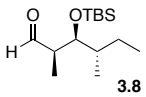
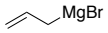
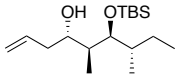
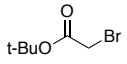
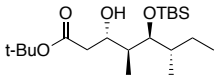
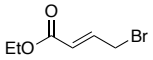
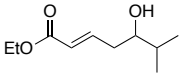
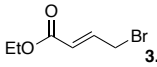
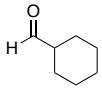
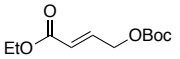
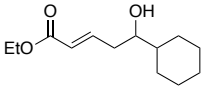
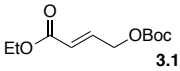
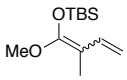
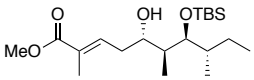
Scheme 3.5 Chirality via *syn*-aldol.

3.4.2 Method development for additions at C37

Installation of chirality at the C37 stereocenter of lagunamide A proved challenging. Several methods for asymmetric addition to aldehyde **3.8** (prior to revision of absolute stereochemistry of lagunamide A) were explored for installing (*S*)-stereochemistry at this position. All reactions in **Table 3.1** were insightful, and ultimately led towards developing a vinylogous addition and optimized route for the total synthesis. Generally, the Felkin-Ahn[12] model for aldehyde **3.8,** with α-(*R*)-methyl stereochemistry,

predicted steric clash for nucleophilic approach that disfavored (*S*)-stereochemical additions. Furthermore, Newman projections correlated that the least hindered trajectory of approach, taking into account the Bürgi-Dunitz[19] angle, would favor the undesired major product. The observed major products in **Table 3.1** correlated well with these predictive models. As such, a direct and asymmetric synthesis would have to overcome these clashes in nucleophile-electrophile approach.

Table 3.1 Method development for additions at C37 of lagunamide A.

Entry	Aldehyde[a]	Substrate[b]	Product[c]
1	 **3.8**	 **3.9**	 **3.10**, 95% (40:60 dr)
2	**3.8**		 **3.11**, 71% (43:57 dr)
3		 **3.12**	 **3.13**, 61% (racemic)
4	**3.8**	 **3.12**	No Reaction
5		 **3.14**	 **3.15**, 30% (racemic)
6	**3.8**	 **3.14**	No Reaction
7	**3.8**	 **3.16**	 **3.17**, 40% (~30:70 dr)

a) See Experimental Section for synthesis, otherwise commercially available. b) See Experimental Section for substrate synthesis. c) See Experimental Section for reaction conditions, purificaiton and characterization data.

The results from **Table 3.1** aided in the development of a facile approach towards asymmetric elongation at C37 towards lagunamide A. Allylation of aldehyde **3.8** with

freshly prepared allylmagnesium bromide (**3.9**) resulted in a (40:60 d.r.) mixture of alcohols **3.10** in high 95% yield (entry 1). Elaboration of the allylation method was eventually optimized and explained in **Chapter 3.4.4**, specifically **Scheme 3.7**. Aldehyde **3.8** and *tert*-butyl bromoacetate (entry 2) were combined in a low valent copper-mediated Reformatsky[20] reaction to make β-hydroxy moiety **3.11** in 70% yield (43:57 d.r.). Coupling of isopropanal (in excess equiv) by Reformatsky-type addition with ethyl (*E*)-4-bromobut-2-enoate (**3.12**) via a $CuCl_2 \cdot 2H_2O$ protocol[20] was investigated due to the fact that γ-vinylogous type addition instead of traditional α-addition had not been previously disclosed in the literature and showed a promising 61% yield of homoallylic alcohol **3.13**, although when applied to key aldehyde **3.8,** no product was formed (entries 3 and 4). An enantioselective iridium catalyzed vinylogous Reformatsky aldol reacton[21] showed promise in catalytically coupling ethyl (*E*)-4-((*tert*-butoxycarbonyl)oxy)but-2-enoate (**3.14**) with cyclohexanal to form homoallylic alcohol **3.15**. However, when applying this methodology to aldehyde **3.8** no desired product was formed, possibly due to steric bulk and silyl migration of the substrate and improbability to tolerate the necessary olefinic methyl substitution in substrate **3.14** (entries 5 and 6).[22] Perhaps the most promising method for addition at C37 was the vinylogous Mukaiyama aldol reaction in entry 7. Silyl ketene acetal[23] (**3.16**) was added to aldehyde **3.8** with $BF_3 \cdot Et_2O$ in DCM:Et_2O (10:1) as described in the aurilide synthesis by Suenaga[24] to produce vinylogous alcohol **3.17** in 40% yield albeit unfavorable towards the desired stereochemistry (~30:70 dr). The vinylogous Mukaiyama aldol reaction favorably supplied a methyl-substituted α,β-unsaturated vinylogous moiety in one step and with further development of stereocontrol

we would improve upon economical synthesis of this crucial fragment (See **Chapter 3.4.5**).

3.4.3 Ghosh *anti*-aldol addition

After stereochemistry of lagunamide A was revised to C37(*S*)-C38(*S*)-C39(*R*), originally from C37*(S)*-C38*(S)*-C39*(S)*, by Ye and co-workers[6] the project was steered to synthesize representative *anti*-α-alkyl-β-hydroxycarbonyl units (**Scheme 3.6**). In a method similar to that as provided by Ghosh,[15] a simplified indanyl ring decorated with the *p*-toluenesulfonamido group was an efficient auxiliary to impart *anti*-aldol diastereoselectivity.[25] As such, (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol was derivatized as the *p*-tosylate at the amino position to produce **3.18** and then the acylated alcohol produced auxiliary **3.19** in 80% overall yield. The titanium enolate of **3.19** was reacted with titanium (IV) chloride-activated aldehyde **3.1** to afford *anti*-alcohol **3.20** in 98% yield with excellent selectivity (95:5 dr). The absolute stereochemistry obtained was rationalized and proposed based upon the Zimmerman-Taxler transition state model where π-stacking of the *p*-tosyl and indanyl aromatic rings are connected via a bicyclic seven-membered titanium-enolate and a six-membered titanium-activated aldehyde complex (**Figure 3.1**).[15,26]

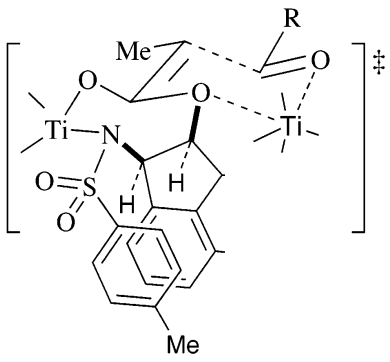
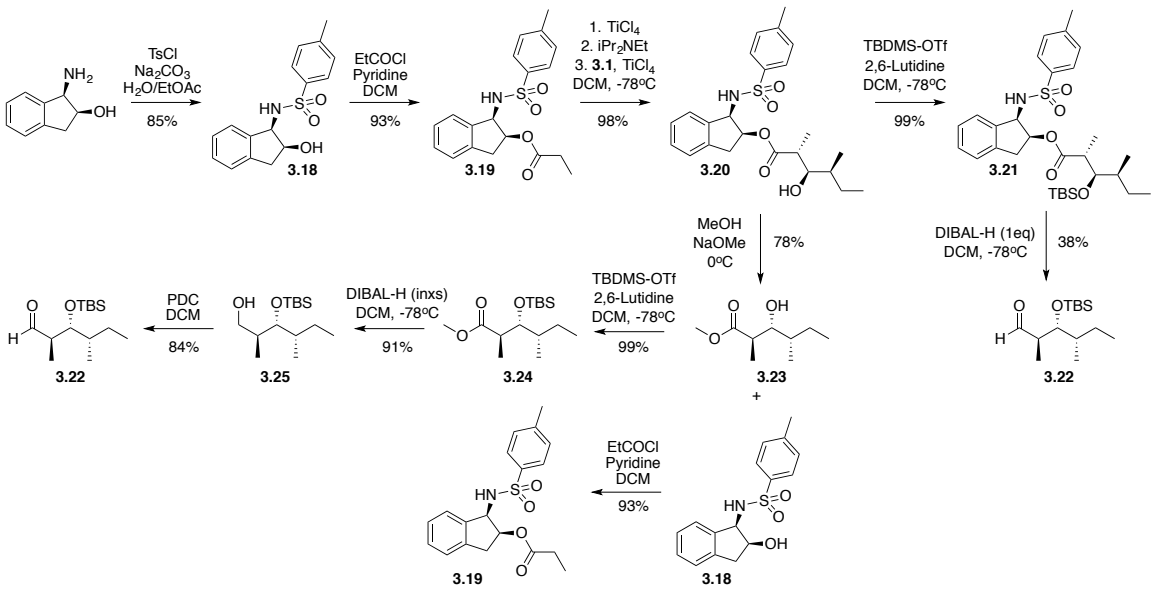


Figure 3.1 Proposed bicyclic transition state of **3.19.**

Anti-alcohol fragment **3.20** contained the intended three contiguous C37(*S*)-C38(*S*)-C39(*R*) stereocenters that would eventually be functionalized into protected aldehyde **3.22.** Silylation using TBSOTf/2,6-lutidine protection conditions provided compound **3.21** and selective reductive cleavage via DIBAL-H concluded aldehyde **3.22** in 38% overall yield from *anti*-alcohol **3.20** in two steps. Conversely, in four steps, *anti*-alcohol **3.20** was cleaved via alkaline methanolic sodium methoxide to ester-alcohol **3.23**, silyl-protected by employing TBSOTf/2,6-lutidine, then completely reduced to the primary alcohol **3.25** via excess DIBAL-H where selective PDC oxidation finally afforded aldehyde **3.22** in roughly twice the yield (60% overall), but at the expense of double the number of steps. Aldehyde **3.22** was subjected to similar reactions as displayed in **Table 3.1**; however, the outcome was similar due to steric clashes of the α-methyl stereochemistry. The best procedure for obtaining aldehyde **3.22** was an allylation sequence, visited in **Scheme 3.7** below, and ultimately optimized via remote stereocontrol in a vinylogous Mukaiyama aldol reaction.



Scheme 3.6 Ghosh *anti*-aldol addition.

3.4.4 C27-C45 fragment via allylation and HWE protocol

Binary approaches toward the synthesis of the C27-C45 fragment of lagunamide A are presented in **Scheme 3.7**. These fragments were thoughtfully functionalized so that convergent peptide coupling reactions with the "northern hemisphere" peptide fragment was straightforward (See **Chapter 5**: *Convergent asymmetric total synthesis of lagunamide A*).

Aldehyde **3.22** (with crucial contiguous C37(*S*)-C38(*S*)-C39(*R*) stereocenters, synthesized via Ghosh auxiliary in **Scheme 3.6**) was subjected to indiscriminate allylation via freshly prepared allylmagnesium bromide to afford a mixture of alcohols **3.26** (~40:60 dr of desired product) in 98% yield.[27] Briefly, allylmagnesium bromide was synthesized *in situ* from allyl bromide and activated magnesium metal turnings in 0^{o}C

ether as to avoid the 1,5-hexadiene Wurtz coupled products formed with THF as solvent.[28] The mixture of alcohols **3.26** was homogenized to one diastereomer by Dess-Martin periodinane (DMP) oxidation to ketone **3.27** in 95% yield. Asymmetric reduction of ketone **3.27** to homoallylic alcohol **3.28** was accomplished in 75% yield using $NaBH_4$ in MeOH to afford almost entirely one diastereomer (>98:2 dr). Selectivity was anticipated due to distal bulk of the TBS-ether conformation to limit one side of approach for $NaBH_4$. Removal of said TBS protecting group with 40% aqueous HF liberated 1,3-diol **3.29** in 90% yield. The 1,3-diol intermediate (**3.29**) would be useful in more then one route towards C27-C45 fragment synthesis (**Scheme 3.7**).

In the first of two similar routes, 1,3-diol **3.29** was protected with 2,2-dimethoxypropane using catalytic *p*-TsOH (5mol%) to form acetonide derivative **3.30** in 83% purified yield. Ozonolysis of terminal olefin **3.30** followed by reductive workup of the consequent Criegee[29] molozonide in dimethyl sulfide resulted in aldehyde **3.31** in 60% yield. Stabilized Horner-Wadsworth-Emmons olefination[30] joined aldehyde **3.31** with phosphonate **3.35** alongside activation with lithium chloride and DIPEA produced C27-C45 fragment **3.36** in 99% yield as exclusively the *E*-geometry isomer (>99:1). Phosphonate **3.35** was derived from combining methyl bromopropionate and triethyl phosphite to form intermediary phosphonate **3.32**. Subsequent alkaline hydrolysis of crude **3.32** in aqueous NaOH (10 M) produced acid **3.33** that was subsequently coupled with alcohol **3.34** (See **Chapter 3.4.6** for synthesis of alcohol **3.34**) via DIPC/collidine and provided the desired phosphonate **3.35** in 68% yield over a total of three steps. Compound **3.36** contained all of the six stereocenters that made up the C27-C45 fragment

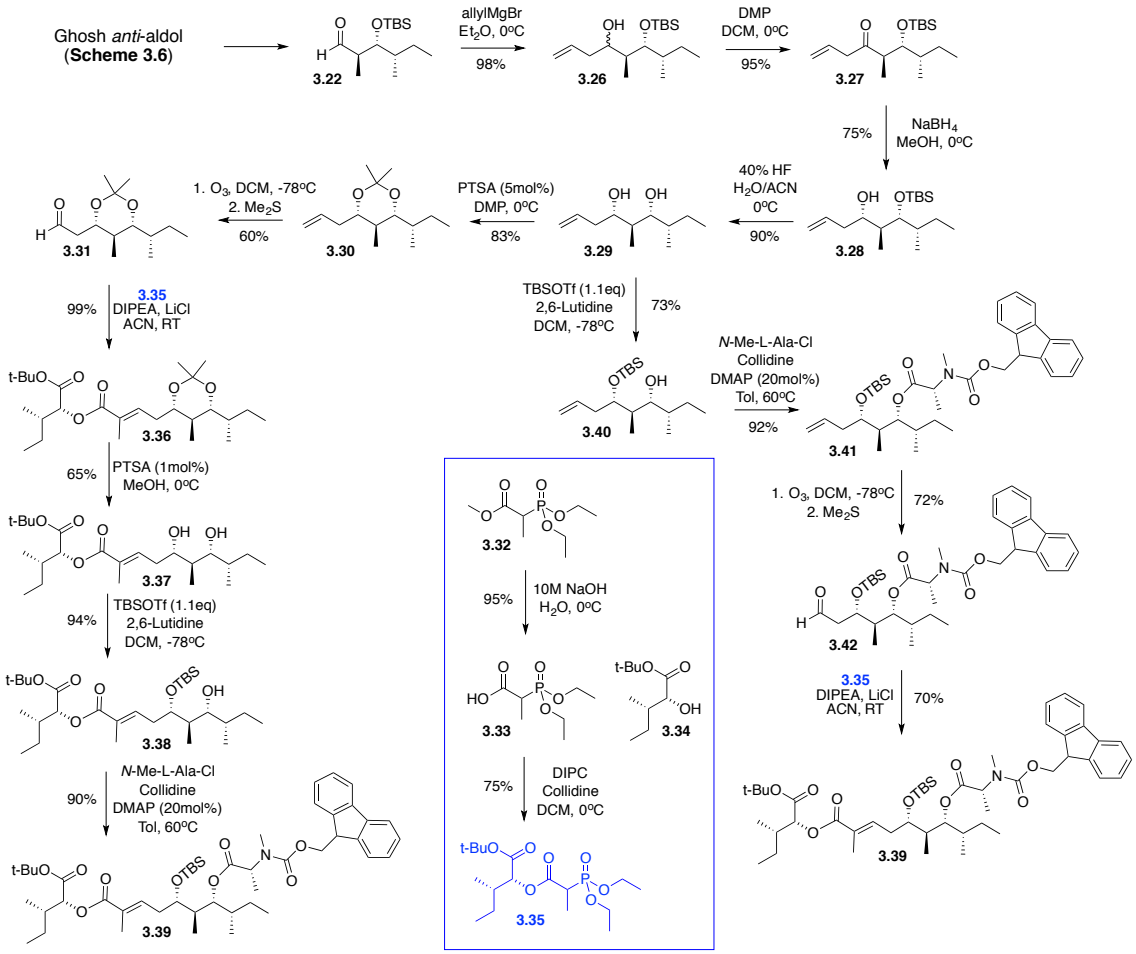
of lagunamide A, and thereby completed a formal synthesis (demonstrated by Lu *et al.*[6]) where intermediate **3.36** was carried onward to produce synthetic lagunamide A. In addition, compound **3.36** (and for the same reason **3.30**) was instrumental in confirmation of stereochemistry as the acetonide had NMR characteristics defined for rigidified *syn*-1,3-diols as described by Evans[31] and Rychnovsky.[32] Generally, *syn*-acetonides have methyl group ppm shifts of 19.4 ± 0.21 and 30.0 ± 0.15 with an acetal carbon shift of 98.1 ± 0.83 ppm whereas *anti*-acetonides have ppm shifts of 24.6 ± 0.76 and 24.6 ± 0.76 with an acetal carbon shift of 100.6 ± 0.25 ppm.

Our synthesis was strengthened by continued chemical studies toward a usable fragment for the total synthesis of lagunamide A. Previous reports[6,33] disclosed that coupling was improbable at the *N*-Me-Glycine/*L*-Isoleucine juncture, that macro-cyclization towards lagunamide A was not possible via RCM and that esterification at the C37 hydroxyl was difficult albeit sorted out. As such, the 1,3-diol motif was protected orthogonally as the TBS-ether (C37) and *N*-Me-Alanine-ester (C39), respectively. Our strategy involved de-protection of acetonide **3.36** with 1 mol% *p*-TSOH in methanol to produce 1,3-diol **3.37** in modest 65% yield. Mono-silylation of the less sterically demanding hydroxyl (C37) was accomplished with TBSOTf (1.1eq)/2,6-lutidine and produced silyl-ether **3.38** in 94% yield. In this system it appeared that >1.1eq of TBSOTf was tolerable, undoubtedly because the mono-TBS product was bulky enough to fend off a secondary silylation whereas TESOTf were susceptible to di-silylation. Finally, the quite sterically congested hydroxyl **3.38** was esterified with *N*-Me-*L*-Ala-Cl alongside collidine/DMAP to afford the targeted intermediate **3.39** in 90% yield (*L*:*D*-Ala ~8:2 dr).

Likewise, the same transformation was completed by *N*-Me-*L*-Ala-Cl with DIPEA as a single diastereomer in 48% yield. Compound **3.39** is a protected formal product for the total synthesis of lagunamide A (See **Chapter 5.4**). The target compound was difficult to characterize with NMR due to rotational amide-bond conformers.

In an alternative approach to the target fragment **3.39** it was demonstrated that 1,3-diol **3.29** may also be selectively mono-silylated by TBSOTf/2,6-lutidine at the less sterically congested hydroxyl to generate silyl-ether **3.40** in 73% yield. When similar reactions to produce compounds **3.40** and **3.38** were compared, diol **3.40** was relatively more prone to di-silylation and as a result suffered a 73% to 90% yield, respectively (**Scheme 3.7**). Similarly, the sterically congested hydroxyl **3.40** was esterified with *N*-Me-*L*-Ala-Cl alongside collidine/DMAP to afford the targeted intermediate **3.41** in 92% yield (*L*-Ala:*D*-Ala ~8:2 dr). The same transformation was accomplished by *N*-Me-*L*-Ala-Cl with DIPEA as a single diastereomer in 45% yield.

Ozonolysis of the terminal olefin **3.41** followed by reductive workup of the corresponding Criegee[29] molozonide in dimethyl sulfide resulted in aldehyde **3.42** in 72% yield. Horner-Wadsworth-Emmons (HWE) olefination[30] was applied to join aldehyde **3.42** with phosphonate **3.35** alongside activation with lithium chloride and DIPEA produced the protected C27-C45 fragment **3.39** in 70% yield as one exclusive *E*-geometrical isomer (>99:1). Compound **3.39,** from the first and second synthesis (**Scheme 3.7**), were spectroscopically identical and consistent with previously reported chemical scaffolds.[6,33]



Scheme 3.7 Routes to C27-C45 fragment via allylation and HWE methodology

3.4.5 Remote stereocontrol of vinylogous Mukaiyama aldol reactions

Until recently, there have been limited reports of acyclic stereocontrol beyond close proximity (i.e. 1,2 and 1,3-relationships), most of which were also dependent on intra-molecular metal chelation.[34] Conversely, the Kobayashi protocol for vinylogous Mukaiyama aldol reactions (VMAR) used vinylketene silyl *N,O*-acetals that showed efficient and non-chelation remote 1,7-type (**Figure 3.2**) and 1,6,7-type (**Figure 3.3**) asymmetric inductions.[9]

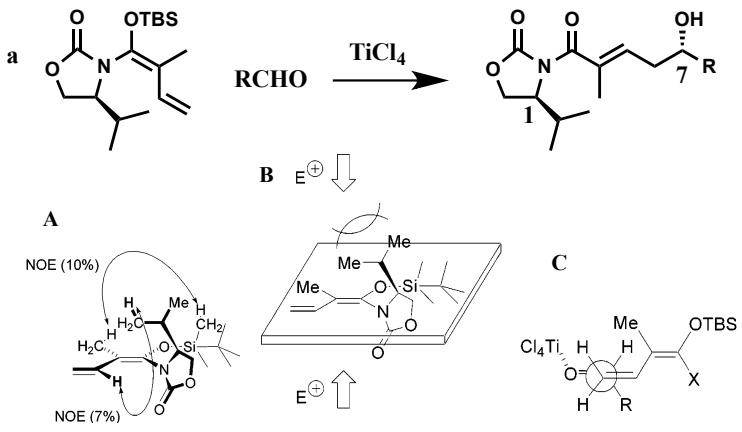


Figure 3.2 VMAR1 and proposed transition state.

The stereochemical outcome (**Figure 3.2a**) for various aliphatic, unsaturated and aromatic aldehydes with titanium (IV) chloride were determined by comparison to known compounds as well as modified Mosher's method.[35] The geometry of the vinylketene silyl *N,O*-acetal for VMAR1 was determined to be the *E,O*-enolate by nuclear Overhauser[36] correlation (**Figure 3.2A**). The proposed transition state (**Figure 3.2B**) exhibited a planarity caused by nearly perpendicular relationship of dienol ether with chiral auxiliary (determined by energy-minimized Spartan calculations) that rationalized approach of an electrophile from the face unhindered by the auxiliary chiral valine moiety. The proposed transition state for nucleophilic attack with pre-coordinated aldehyde-titanium (IV) chloride complex (**Figure 3.2C**) was proposed using the Newman projection.

Interestingly, a similar vinylketene silyl *N,O*-acetal extended by a methyl substitution for VMAR2 (**Figure 3.3b**) had similar *E,E*-geometry, but produced the *anti*-aldol product under the same reaction conditions as previously indicated.[37] The most

reasonable transition state (**Figure 3.3D**) minimized steric interactions and lead to the major *anti*-isomer. A second transition state represents formation of the unfavorable *syn*-isomer (**Figure 3.3E**) displayed significant steric interactions between the nucleophile and electrophile interface and was expectedly the minor isomer.

A contemporary development in the VMAR reaction mechanism explored rate enhancement by addition of catalytic amounts of water. Kobayashi and co-workers[38] proposed that either $TiCl_4$ aggregates were broken up by dissociation upon coordination with water or double activation with a proton and hydrated $TiCl_4$ with the carbonyl oxygen accelerated the reaction, although the specific role of water in VMAR remains obscure.

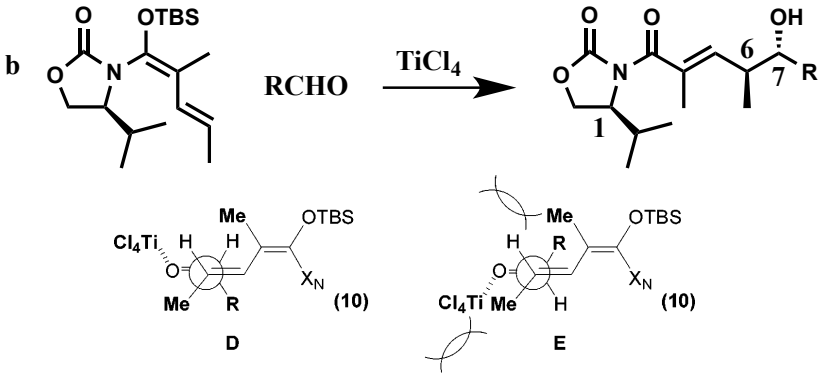


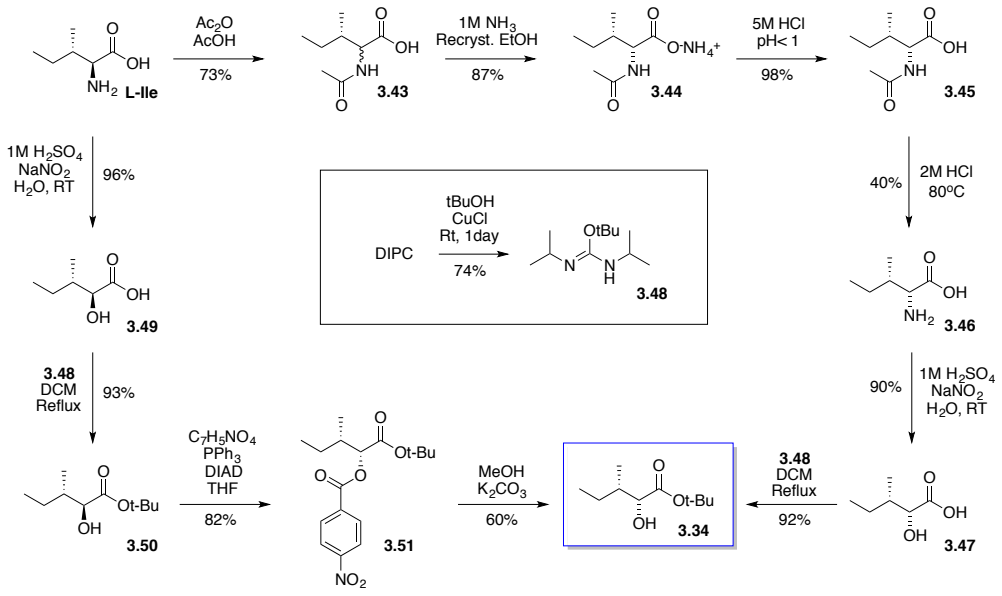
Figure 3.3 VMAR2 and proposed transition state.

3.4.6 Synthesis of the D-allo-α-Hydroxy-Isoleucine fragment

The *D*-allo-α-hydroxy-Isoleucine moiety (**3.34**) of lagunamide A presented an interesting synthetic challenge. The obvious precursor with the correct two adjacent

stereocenters seen in the natural product is *D*-allo-Ile, which is available for roughly $1,000/g whereas the precursor *L*-Ile with the correct β-stereocenter (and one incorrect α-stereocenter) is commercially available for approximately $1/g (Sigma-Aldrich, 2013). Two scalable, practical syntheses of the *D*-allo-α-hydroxy-Isoleucine moiety were devised from inexpensive *L*-Ile as a starting material (**Scheme 3.8**).

The first route pursued a modified protocol designed by Yajima *et al*.[39] (**Scheme 3.8**, top left to right). Specifically, we scrambled the α-carbon stereocenter of *L*-Ile with acetic anhydride in acetic acid while simultaneously acetylating the free amine to produce the racemate of **3.43** as white crystals. This mixture was recrystallized from hot water in 73% yield.[40] At this point the mixture remained inseparable, however when acid **3.43** was treated with 1M ammonium hydroxide solution then recrystallized from absolute ethanol the resolution of ammonium salt **3.44** was achieved as very nearly one diastereomer (~9:1 d.r.). The difference in solubility between Ac-*D*-aIle-NH_4 and Ac-*L*-Ile-NH_4 (0.25 g and 2.29 g in 100 mL) suggests there is an approximately ten fold difference in solubility in favor of the desired diastereomer.[39] The difference in solubility is due largely in part to variations in hydrogen-bonding length determined thru x-ray crystal structure analysis. The ammonium salt **3.44** was acidified with 5M HCl (pH < 1) and collected as the white precipitate **3.45** in a near quantitative yield. Incubation in 2M HCl at 80 $^{\circ}$C followed by dissolution in ethanol and neutralization with Et_3N afforded *D*-allo-Ile (**3.46**) in a modest 40% yield. Diazotization of *D*-allo-Ile in H_2SO_4 with aqueous $NaNO_2$ produced the α-hydroxy acid **3.47** in 90% yield.[41]



Scheme 3.8 D-allo-α-Hydroxy-isoleucine fragment (**3.34**) synthesis.

In order to incorporate the fragment the carboxylic acid fragment needed to be protected leaving the free α-hydroxy functionality. An interesting method presented by Calo *et al*.[42] utilized *N*,*N*-diisopropyl-*O*-*t*-butylisourea (**3.48**) prepared from equal parts tBuOH and DIPC with 1 mol% cuprous chloride to produce *tert*-butyl esters with α-hydroxy functionality present.[43] This method smoothly converted acid **3.47** with isourea **3.48** in methylene chloride to the targeted *D*-allo-α-hydroxy-isoleucine fragment (**3.34**) in 92% yield. Overall, the first proposed route (**Scheme 3.8**, top left to right) constructed target molecule **3.34** in 21% yield in six steps from *L*-isoleucine.

In the second and improved route (**Scheme 3.8**, top left to bottom) we carried out a modified protocol designed by Dai *et al*.[6] Similarly, *L*-Ile was used as an affordable starting material. By the $NaNO_2/H_2SO_4$ diazotization method previously discussed, our synthesis began with conversion of *L*-Ile to α-hydroxy acid **3.49** in 96% yield as a single

diastereomer.[41] Then by the *tert*-butyl protection strategy via isourea **3.48** previously discussed, acid **3.49** was converted into *tert*-butyl ester **3.50** in 93% yield. Characteristic Mitsunobu[44] inversion of stereochemistry by employing *para*-nitrobenzoic acid,[45] PPh_3, and DIAD in THF produced the activated di-ester **3.51** with good selectivity (98:2 dr) in 82%yield. Finally, anhydrous alkaline K_2CO_3 hydrolysis of **3.51** in methanol produced the desired *D*-allo-α-hydroxy-isoleucine fragment (**3.34**) in 60% yield. Overall, the second route (**Scheme 3.8**, top left to bottom) constructed the target molecule **3.34** in 44% yield in four steps from *L*-Ile, resulting in more then double the yield compared to our previous efforts and reduced the number of total steps from six to four.

3.5 Optimized synthesis of the C27-C45 fragment of lagunamide A

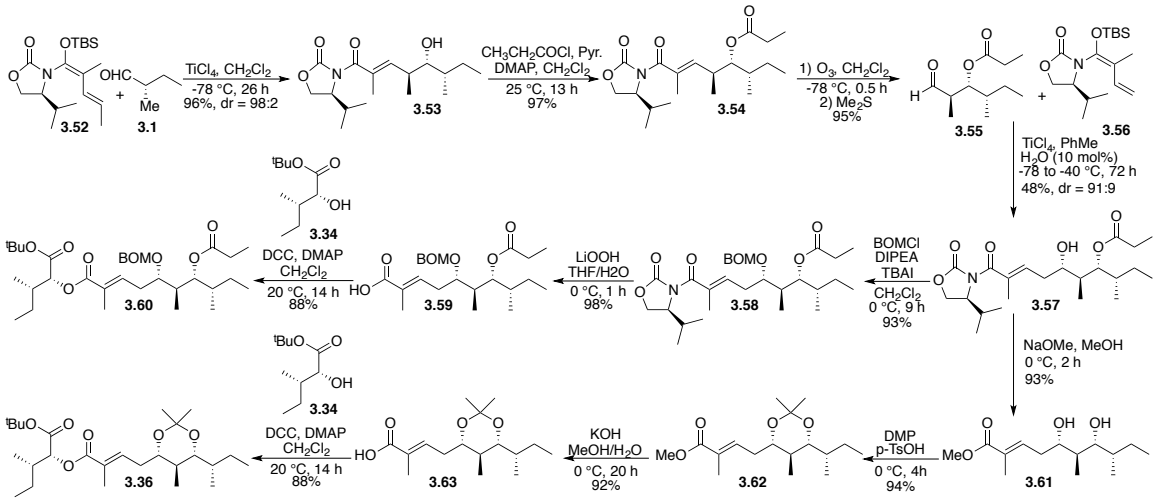
Two similar economical and asymmetric formal syntheses of the C27-C45 southern hemisphere fragment of lagunamide A have been completed in six and seven linear steps from a known compound **3.53** in 35% and 30% overall yield, respectively. This synthesis is highlighted by iterations of Kabayashi's protocol for the Vinylogous Mukaiyama Aldol Reaction (VMAR) to selectively install the three contiguous stereocenters at C37, C38 and C39 respectively.[9]

Our formal synthesis reported short, direct and a highly asymmetric routes with excellent overall yield of the C27-C45 fragment compared to previous efforts towards lagunamide A[6,33] (**Scheme 3.9**). These crucial intermediates were achieved mainly via two asymmetric vinylogous additions, a powerful instrument that has attracted widespread attention in the synthetic organic community.[21] Specifically, this

manipulation has shown tremendous usefulness in modern natural product synthesis.[4,46] The version of a vinylogous Mukaiyama aldol reaction (VMAR) utilizing chiral oxazolidinones was first introduced by Kobayashi[9] in 2004. In this paper we report two such remote "1,6,7- and 1,7-remote" asymmetric induction reactions (**Scheme 3.2** and **3.3**, respectively) as a general means to establish the required stereochemistry at C37, C38 and C39 positions within the C27-C45 fragment (**3.36, 3.60**) of lagunamide A. The reported route herein takes advantage of two VMAR's utilizing the Kobayashi protocol[9] to greatly increase the efficiency to access this portion of lagunamide A achieving high 35% overall yield from commercially available (*S*)-2-methyl-butanal (**3.1**).

Synthesis was initiated with Kobayashi's protocol for the VMAR to construct *anti*-alcohol **3.53** from (*S*)-methyl-butanal (**3.1**) pre-coordinated with titanium (IV) chloride and chiral vinylketene silyl *N,O*-acetal **3.52** in CH_2Cl_2 at -78 $^{\circ}$C for 26 hours as a clear oil in 96% yield with excellent 98:2 diastereomeric ratio (d.r.) (**Scheme 3.9**).[47] Protection of *anti*-alcohol **3.53** with propionyl chloride mediated esterification followed by subsequent ozonolysis of **3.54** afforded protected aldehyde **3.55** in 95% yield over two steps. For an in depth discussion on optimization of Lewis acid as well as protecting group compatibility, please refer to **Chapter 6.3** for chemical studies on Kobayashi's protocol for the vinylogous Mukaiyama aldol reaction. Thus, intermediate **3.55** was equipped for a second iteration of Kobayashi's VMAR protocol with *N,O*-silyl ketene acetal **3.56** to asymmetrically achieve complex vinylogous homoallylic alcohol **3.57** in modest 48% yield, but with good selectivity (91:9 dr). Tedious purification of vinylketene silyl *N,O*-acetal **3.56** was necessary via Varian C-8 30 x 250 mm prep-scale

HPLC or severely hampered reaction yield. The reaction conditions were further optimized by addition of 10 mol% deionized water in dry toluene (opposed to DCM) with 12 hour oscillations of temperature between -78 °C and -40 °C for 72 hours. Addition of catalytic water proved to reduce reaction time and perhaps dissociated titanium chelates or further activated the titanium-aldehyde complex.[38]



Scheme 3.9 Two formal synthesis of lagunamide A via iterations of VMAR.

To differentiate functionality at C37 and C39 vinylogous alcohol **3.57** was protected as the BOM ether employing BOM-Cl, $iPrNEt_2$ alongside TBAI to afford **3.58** with orthogonal 1,3-diol protecting groups was achieved in a 93% yield. *In situ* generation of LiOOH in THF/H_2O (3:1) facilitated selective auxiliary cleavage to construct the doubly protected acid **3.59** resulting in 98% yield. Steglich esterification[48] of acid **3.59** with α-hydroxy ester **3.34**, using dicyclohexylcarbodiimide (DCC) in the presence of catalytic amount of DMAP at ambient temperature prepared orthogonally

protected intermediate **3.60** in 88% purified yield, with 35% overall yield in 6 linear steps.

With the intention of creating protecting group flexibility at C37 and C39 as well as to establish the absolute stereochemistry of fragment **3.57** NMR experiments were performed on the rigidified acetonide derivative **3.62**. Thus, compound **3.62** was synthesized by di-hydrolytic cleavage in methanolic sodium methoxide[49] to 1,3-diol ester **3.61** followed by the 1,3-diol acetonide formation in DMP in the presence of catalytic amount of p-TsOH in 87% yield over two steps (**Scheme 3.9**). Decisively, the ^{13}C NMR chemical shifts of the acetonide **3.62** methyl groups and the ketal carbon seen in **Figure 3.4** were 19.50, 30.01, and 97.87 ppm, respectively, which is characteristic of *syn*-1,3-diol acetonides (19.4 ± 0.21, 30.0 ± 0.15, and 98.1 ± 0.83 ppm) opposed to *anti*-1,3-diol acetonides (24.6 ± 0.76 and 100.6 ± 0.25 ppm).[31] Also, NOESY analysis observed NOE from CH_2-36 to H-35 and CH_3-43 to CH_2-36, confirming that only the desired *E*-geometry was present. 2D gCOSY, gHMBCAD, HSQCAD NMR experiments further correlated absolute configuration of **3.62**.

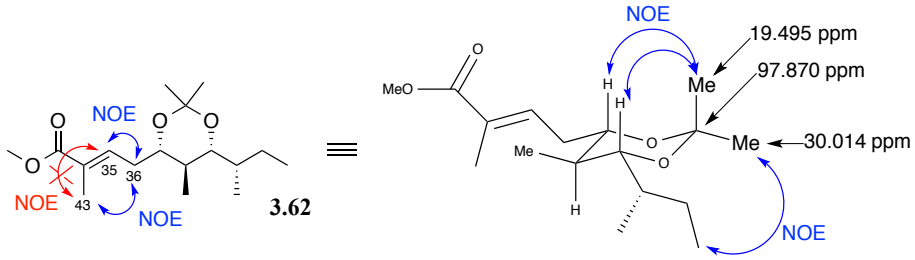


Figure 3.4 Major NOE observations and ^{13}C NMR shifts of *syn*-acetonide **3.62**.

As proof of concept we set out to construct an intermediate compound (**3.36**) for lagunamide A that was directly from the literature using our VMAR methodology (**Scheme 3.9**). Methyl ester **3.62** was hydrolyzed with potassium hydroxide in MeOH/H_2O (4:1) at 0 $^{\circ}$C, which furnished carboxylic acid **3.63** in 92% yield. Thus, Steglich esterification of acid **3.63** with α-hydroxy ester **3.34**, using DCC and DMAP at ambient temperature prepared formal intermediate **3.36** in 88% isolated yield (30% overall yield). The C27-C45 fragment (**3.36**) was identical with previous literature reportes, as well as our previous synthesis of the same compound. This synthesis fulfilled our objective as the continuation of the Ye protocol[6] would afford lagunamide A.

3.6 Conclusions

We presented two similar formal synthesis of lagunamide, both in superior yield (previously 22% yield by Liu *et al*.[10] in 2014) and in fewer overall steps (previously 11 steps by Lu *et al*.[6] in 2012) then previously reported.[6,10,50] These syntheses described a direct vinylogous asymmetric approach to the C27–C45 southern fragment (**3.60, 3.36**) of lagunamide A with thoughtful consideration of protecting group strategy, mainly through iterations of Kobayashi's VMAR protocol. The first C27-C45 fragment **3.60** was synthesized in 6 linear steps with an overall yield of 35%. Alternative C27-C45 fragment **3.36** was a formal intermediate to lagunamide A from the literature and synthesized in 30% overall yield in 8 linear steps by analogous VMAR methodology.

Co-authors Lee Wang and Arielle Kanner provided their written permission to include published materials disclosed in this chapter.[51]

4 Synthesis of the "Northern hemisphere" peptide fragment of lagunamide A

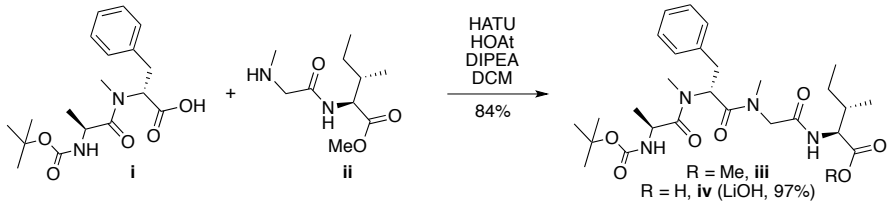
4.1 Introduction

Peptide coupling reactions have been diversely explored throughout the literature.[52,53] Two previous efforts towards the peptide fragment of lagunamide A are presented in this chapter (**Chapter 4.2**).[6,33] In order to synthesize the peptide fragment of lagunamide A both solution (C11-C26 fragment, **Scheme 4.3**) and solid (C5-C26 fragment, **Scheme 4.5**) phase peptide coupling strategies were explored. Due to our recent efforts towards the synthesis and proposed stereochemical revision of Micromide[54,55] (Manuscript in preparation), a marine anti-cancer natural product with multiple conjoined peptides, we developed *N*-methylation and coupling protocols using *p*-nosyl amino acid derivatives.[56] Solid phase peptide coupling reactions using 2-chlorotrityl chloride solid support resins alongside interesting cyclic Fmoc-*N*-methylation transformations *en route* to well-established, scalable and prompt construction of multi-peptide fragments were disclosed.[57]

4.2 Previous syntheses

Unlike our efforts from inexpensive bulk amino acids, both of the previously reported syntheses of the C5-C26 and C11-C32 peptide section of lagunamide A, presented below, were purchased with the desired protecting groups and *N*-methylation.[6,33] Dai *et al*.[6] disclosed the first synthesis of tetrapeptide **iii** with the coupling of dipeptides **i** and **ii** using HATU[58] as a coupling reagent to produce **iii** in 84%

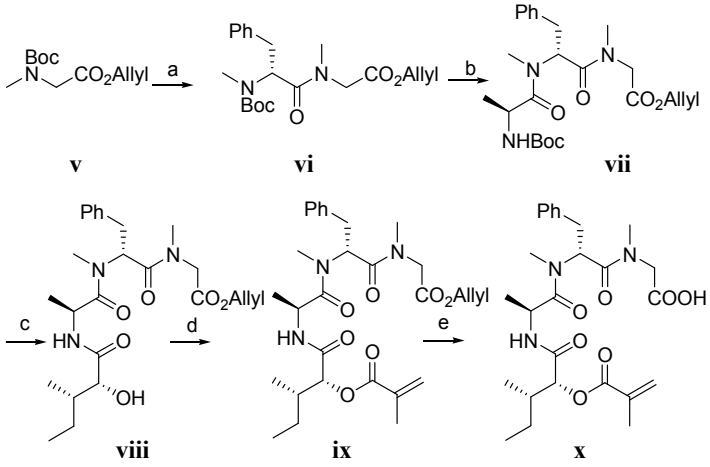
yield (**Scheme 4.1**). Dipeptides **i** and **ii** were synthesized by analogous HATU solution phase couplings. Tetrapeptide **iii** was hydrolyzed with LiOH in THF-H_2O-MeOH to afford free carboxylic acid **iv** in 97% yield, that provided an intermediate with good functional group linkers for later coupling with the "southern hemisphere" of lagunamide A. Please refer to **Scheme 5.1** for the specific use of peptide fragment **iv** in the convergent strategy for synthesis of lagunamide A.



Scheme 4.1 Dai *et al*. tetrapeptide synthesis.

Huang *et al*.[33] disclosed the synthesis of functionalized free acid tetrapeptide **x** by coupling of chemically modified peptides in a linear sequence via solution phase (**Scheme 4.2**). The Boc group of protected *N*-methyl glycine **v** was liberated with TFA then coupled using conventional HATU/DIPEA methods to produce dipeptide **vi** in 89% yield. Tripeptide **vii** (HATU/DIPEA coupling method) and then tetrapeptide **viii** (EDC/HOBt coupling method[59]) were obtained by similar sequence in 38% yield over two steps. Tetrapeptide **viii** was coupled to methacrylic acid under Yamaguchi esterification[60] conditions to generate the functionalized α-hydroxy peptide fragment **ix** in 87% yield. The free carboxylic acid **x** was then liberated by activation of the allylic double bond (**ix**) with palladium and then reduction by PhNHMe in excellent 95% yield that provided the corresponding intermediate for peptide coupling.[61] For the specific use

of peptide fragment **x** in the convergent strategy towards synthesis of lagunamide A, please see **Scheme 5.2**.



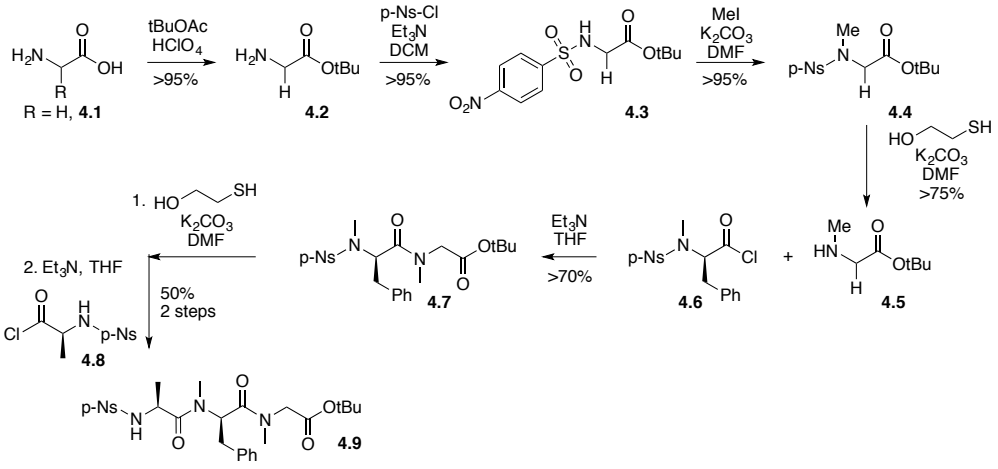
Preparation of peptide fragment. Reagents and conditions: a. (1) TFA/CH_2Cl_2, 0 $^oC\sim$ rt; (2) D-Boc-*N*-Me-Phe-OH, HATU, DIPEA, CH_2Cl_2, 0 $^oC\sim$ rt, 89% (2 steps); b. (1) TFA/CH_2Cl_2, 0 $^oC\sim$ rt; (2) L-Boc-Ala-OH, HATU, DIPEA, CH_2Cl_2, 0 $^oC\sim$ rt, 68% (2 steps); c. (1) TFA/CH_2Cl_2, 0 $^oC\sim$ rt; (2) (*2R,3S*)-2-hydroxy-3-methylpentanoic acid, HOBt, EDC, DMF, -15 $^oC\sim$ rt, 56% (2 steps); d. methacrylic acid, $Cl_3C_6H_2COCl$, TEA, toluene, 87%; e. $Pd(PPh_3)_4$, PhNHMe, THF, 95%.

Scheme 4.2 Huang *et al*. tetrapeptide synthesis.

The previous syntheses for the C5-C26 (**Scheme 4.1**) and C11-C32 (**Scheme 4.2**) peptide fragments of lagunamide A were constructed by utilization of solution phase peptide coupling reagents. These syntheses were fairly high yielding and allowed for interesting functionalization. The major drawbacks to solution phase peptide coupling reactions are merely waste of solvent and time during purification. Alternatively, we envisioned a simple, scalable, linear peptide fragment synthesis via solid support that was completed from non-functionalized amino acids.

4.3 Solution phase peptide coupling

As mentioned, our recent efforts towards the synthesis and proposed stereochemical revision of micromide[54,55] (manuscript in preparation), a marine anti-cancer natural product with multiple conjoined peptides, aided in the development for *N*-methylation and coupling protocols using *p*-nosylated amino acid derivatives.[62] Thus, tert-butyl esterification using *tert*-butyl acetate in the presence of $HClO_4$ produced ester **4.2** that was subsequently nosylated by *p*-nitrobenzenesulfonyl chloride and triethylamine in DCM to afford compound **4.3** in 90% yield over two steps. Compound **4.3** was sufficiently *N*-methylated by iodomethane and K_2CO_3 in DMF to furnish our functionalized derivative **4.4** in 95% yield.



Scheme 4.3 Solution phase functionalization and peptide coupling strategy.

This general "OtBu-*p*-nosyl-*N*-methylation" sequence was applicable to a multitude of amino acids and henceforth bulk amino acid starting materials were derivatized by this representative approach. Intermediate **4.4** was coupled by generation

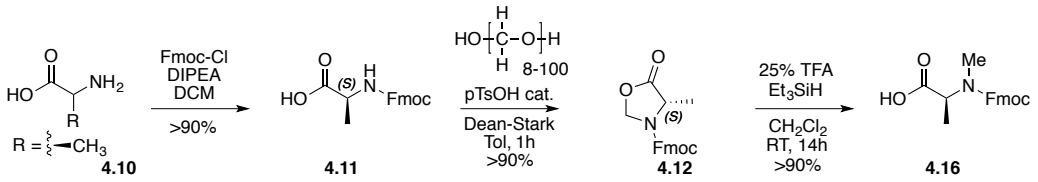
of the free amine **4.5** with 2-mercaptoethanol and K_2CO_3 in DMF followed by *p*-Ns-*N*-Me-*D*-Phe-Cl (**4.6**, acid chloride prepared by $(COCl)_2$ and catalytic DMF from the corresponding carboxylic acid)[63] mediated coupling with triethylamine in THF to produce dipeptide **4.7** in 53% yield over two steps. In a similar sequence dipeptide **4.7** was coupled with *p*-Ns-*N*-*L*-Ala-Cl (**4.8**) in 50% yield over two steps to furnish the C11-C26 (**4.9)** tripeptide portion of lagunamide A. Tripeptide **4.9** was completed in 23% overall yield from simple and affordable starting materials; glycine, *D*-phenylalanine and *L*-alanine.

4.4 Solid phase peptide coupling

In order to couple peptides via solid phase it was similarly desired to functionalize, namely by Fmoc-protection and *N*-methylation, an array of economical non-derivatized amino acids. By the strategy depicted in **Scheme 4.4** the necessary amino acids were Fmoc-protected and *N*-methylated for our synthesis, exemplified by the transformation of *L*-isoleucine (**4.10**) to functionalized Fmoc-*N*-Me-*L*-Ile-OH (**4.13**) as our primary archetype. These transformations were generally completed in greater then 75% overall yield in three linear steps.

First, a raw amino acid (e.g. *L*-Ala, **4.10**) was protected by Fmoc-Cl with DIPEA in methylene chloride to produce Fmoc-*N*-L-Ala-OH (**4.11**) in 93% yield (**Scheme 4.4**). Subsequent intra-molecular cyclization of **4.11** was prompted via a Dean-Stark[64] set-up with paraformaldehyde in the presence of catalytic amount of *p*-toluenesulfonic acid in refluxing toluene afforded the 5-oxazolidinone moiety **4.12** in a very high yield (95%).

Finally, ring decomposition of 5-oxazolidinone **4.12** was initiated in 25% TFA with triethylsilane and methylene chloride to afford functionalized Fmoc-*N*-Me-*L*-Ala-OH **4.13** in 92% yield. The protocol in **Scheme 4.4** was exploited to produce all of the building blocks necessary for our solid phase peptide approach (**Scheme 4.5**).

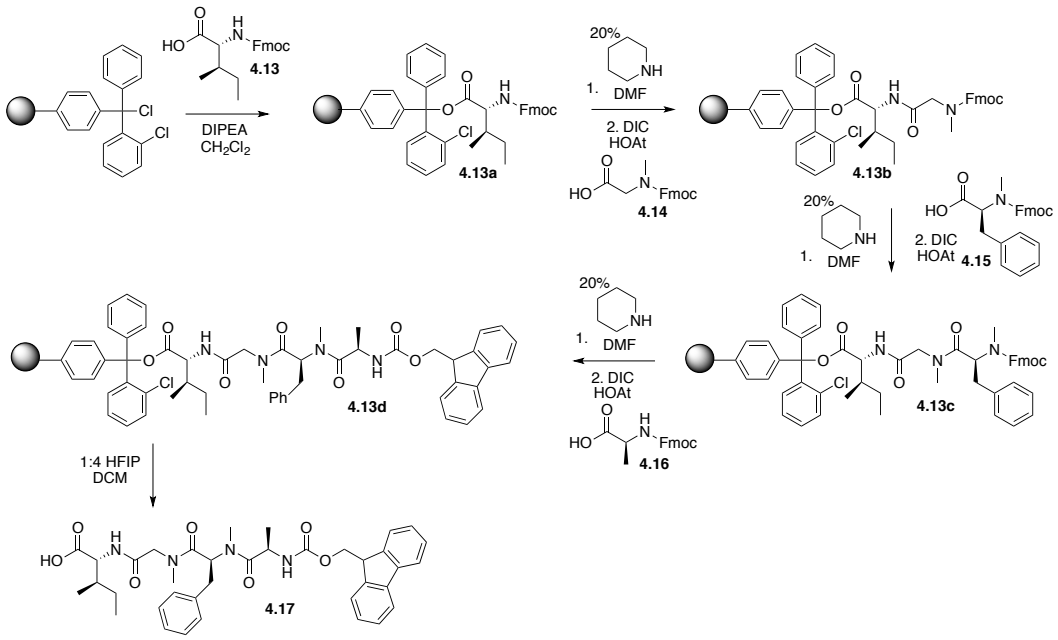


Scheme 4.4 *N*-methylation strategy.

With our cache of amino acid building blocks in hand (**Scheme 4.4**), we commenced solid phase peptide production (**Scheme 4.5**). Esterification of the 2-chlorotrityl chloride resin with Fmoc-protected amino acids in the presence of DIPEA had been studied under various conditions and displayed little byproduct formation, straightforward coupling conditions and characteristically quantitative cleavage of peptide chains from the regenerative resin.[65] 2-chlorotrityl chloride resin was employed for our peptide coupling strategy in hopes of obtaining reported esterification, peptide bond formation and peptide cleavage reactions in nearly quantitative yield.[66]

Fmoc-*N*-Me-*L*-Ile-OH **4.13** was esterified with 2-chlorotrityl chloride resin at 0.6 equivalents Fmoc-amino acid per mmol of resin by DIPEA in DCM at ambient temperatures to tether intermediate **4.13a** (**Scheme 4.5**). Henceforth, the entire peptide fragment was synthesized sequentially in a fritted plastic syringe then cleaved from the resin before characterization was finalized. This simple system was developed so that the

resin could be easily retained, agitated, incubated, and so solvents/reagents/byproducts could be easily flushed away leaving only peptide-affixed resin sans purification.



Scheme 4.5 Solid phase peptide coupling strategy.

Accordingly, resin-tethered peptide **4.13a** was agitated in a solution of 20% piperidine in DMF to cleave the Fmoc group, washed several times and subsequently coupled with Fmoc-*N*-Me-Gly-OH (**4.14**) to produce Fmoc-protected resin-tethered dipeptide **4.13b**. In an equivalent sequence as described above, Fmoc-*N*-Me-*D*-Phe-OH (**4.15**) was coupled sequentially followed by another iteration with Fmoc-*N*-*L*-Ala-OH (**4.16**) to produce the Fmoc-protected resin-tethered tetrapeptide **4.13d**. A mixture of hexafluoro-2-propanol in methylene chloride (1:4) was sufficient to mildly cleave our desired tetrapeptide **4.17** as the free carboxylic acid and to regenerate the 2-chlorotrityl chloride resin for reiterative usage. Tetrapeptide **4.17** was purified on prep-scale HPLC

and accomplished in 55% overall yield in eight major steps (with an average of 93% yield per step).

4.5 Conclusions

In order to synthesize the peptide fragment of lagunamide A both solution (C11-C26 fragment, **Scheme 4.3**) and solid (C5-C26 fragment, **Scheme 4.5**) phase peptide coupling strategies were explored. N-methylation and coupling protocols using *p*-nosyl amino acid derivatives for solution phase were developed to produce the C11-C26 fragment **4.9** in 23% overall yield. Interesting 2-oxazolidinone Fmoc-*N*-methylation transformations alongside solid phase peptide coupling reactions were likewise developed using 2-chlorotrityl chloride resins to produce C5-C26 fragment **4.17** in 55% overall yield. Both of these peptide fragment formation protocols were scalable and supported synthesis from economical (un-derivatized) amino acid starting materials. Our work disclosed the first ever linear synthesis of the peptide portion of lagunamide A via solid support. Synthesis on solid support provided greater overall efficiency in time, reagent use and yield.

Special acknowledgemnt goes to graduate student Lee Wang[56] who was instrumental in peptide design of many fragments disclosed in this chapter.

5 Convergent Asymmetric Total Synthesis of Lagunamide A

5.1 Introduction

Due to scarceness in nature, a scalable and efficient total synthesis of lagunamide A is crucial to continue experiments and define thresholds for therapeutic development. Two previously completed total syntheses of lagunamide A were crucial towards optimizing our route to lagunamide A. This is discussed in detail below. Our convergent total synthesis of lagunamide A provided the natural product in the fewest amount of steps and with the highest overall yield to date.

5.2 Previous syntheses

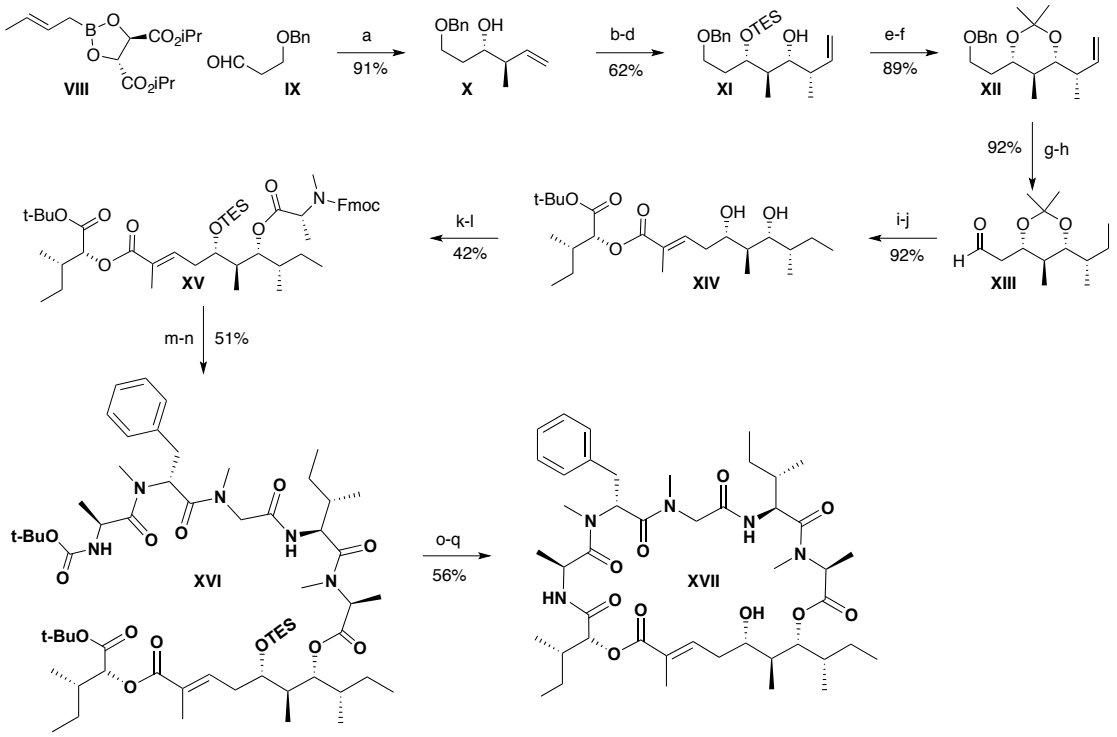
Lu *et al.*[6] (Ye group) disclosed the first total synthesis of lagunamide A that ultimately resulted in the stereochemical reassignment of the natural product configuration (**Scheme 5.1**). The Ye group correlated an obvious distinction between several key features of lagunamides[5] and the known 26-member cyclodepsipeptides kulokekahilide[67] and aurilide[24], that were also isolated from *Lyngbya majuscula* and had similar molecular scaffolds. They hence noticed that assignment of stereochemistry at the C39 position appeared unusual when compared to these known natural products and ultimately, by epimerizing this position, were successful in the first completed synthesis of lagunamide A with revision of absolute stereochemistry.

Preparation of known homoallylic alcohol **X** by Roush crotylboration[68] of boronate **VII** and 3-(benzyloxy)proponal **IX** was completed in 91% yield as a single

diastereomer.[69] Triethylsilyl protection of the alcohol followed by oxidative cleavage of the olefin afforded the corresponding aldehyde that was converted to homoallylic alcohol **XI** by reagent controlled *anti*-crotylation via addition of (*E*)-2-butene.[70] Next, desilylation (HCl in MeOH) afforded the corresponding 1,3-diol that was then re-protected as acetonide derivative **XII** in 89% yield over two steps. Intermediate **XII** was reduced via hydrogenation that simultaneously reduced the olefin and removed the benzyl ether so that the corresponding primary alcohol was exposed for oxidation to aldehyde **XIII** in 92% yield in two steps. Horner-Wadsworth-Emmons olefination of **XIII** with a phosphonate fragment (derived from D-*allo*-Ile[6] and methyl 2-(diethoxyphosphoryl) propanoic acid[71]) followed by deprotection of the acetonide protecting group via acid catalyzed PTSA in methanol furnished 1,3-diol **XIV** in 92% yield over two steps.

Fragment **XIV** completed the carbon scaffold and absolute stereochemistry for the "Southern hemisphere" terpenoid portion of lagunamide A. Fortunately, mono-protection of the less sterically demanding hydroxy (**XIV**) was moderately possible. Esterification of the more sterically demanding hydroxyl was accomplished with Fmoc-*N*-Me-*L*-Ala-Cl with DMAP in toluene to afford **XV** in 42% yield over the previous two steps. Treatment of **XV** with diethyl amine was a general and efficient method for removal of the Fmoc protecting group to release the free amine needed for the HATU promoted couplings to the carboxyl terminus of the quadrapeptide (*N*-Boc-protected) fragment of lagunamide A to synthesize **XVI** in 51% yield over two steps. Macro-lactamization was affected by simultaneous cleavage of the *tert*-butyl ester, the *N*-Boc-protecting group and the TES-

hydroxyl protecting group by TFA, and followed by the immediate coupling via HATU activation and ring closure to afford lagunamide A (**XVII**) in 56% yield.



Reagents and conditions: (a) MS 4A , toluene, -78 ºC; (b) TESOTf, 2,6-lutidine, DCM, -78ºC; (c) OsO_4, $NaIO_4$, 2,6- lutidine, dioxane-H_2O; (d) E-2-butene, KOtBu, n-BuLi, -78ºC, (-)-Ipc_2- BOMe, BF_3-OEt_2; thenEt_3N, H_2O_2; (e) HCl, MeOH; (f) DMP, PPTS, 60 ºC; (g) H_2,Pd/C,MeOH; (h) Dess-Martin periodinane, $NaHCO_3$, DCM; (i) HWE Phosphonate, DIPEA, LiCl, MeCN; (j) PTSA, MeOH; (k) TESOTf (1.0 eq.), 2,6-lutidine, DCM; (l) Fmoc-N-Me-Ala-Cl, DMAP, toluene, 60 ºC; (m) Et2NH, MeCN; (n) Peptide fragment, HATU, HOAT, collidine, DMF; (o) TFA, DCM; (p) HATU, HOAT, collidine, DMF; (q) 40% aq HF, ACN.

Scheme 5.1 Ye synthesis of lagunamide A.

Absolute stereochemistry was confirmed by comparing the ^{13}C NMR spectra for natural, synthetic and derivatives of lagunamide A (**Figure 5.1**). The Ye synthesis corrected the absolute stereochemistry of lagunamide A, an extraordinary undertaking, and thus redirected our synthetic efforts mid-way through our synthesis project. The Ye synthesis also elucidated key fragments and strategy towards a convergent synthesis and successful points of ring closure by peptide bond formation. The aforementioned

synthesis suffered through protecting group strategy, a relatively burdensome linear synthesis and consequently low overall yield.

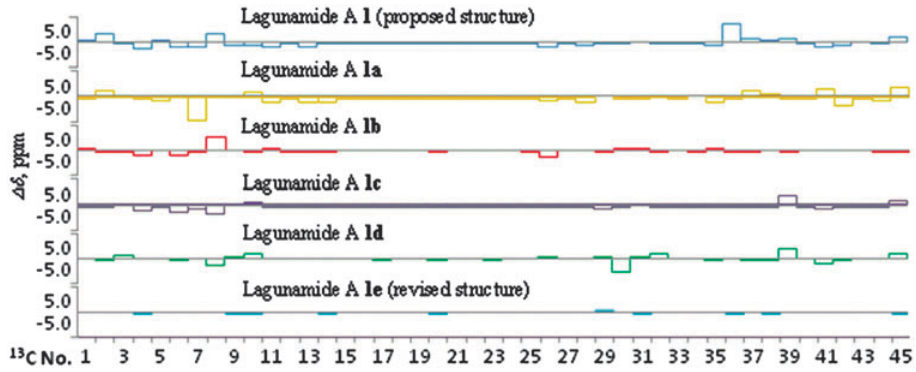
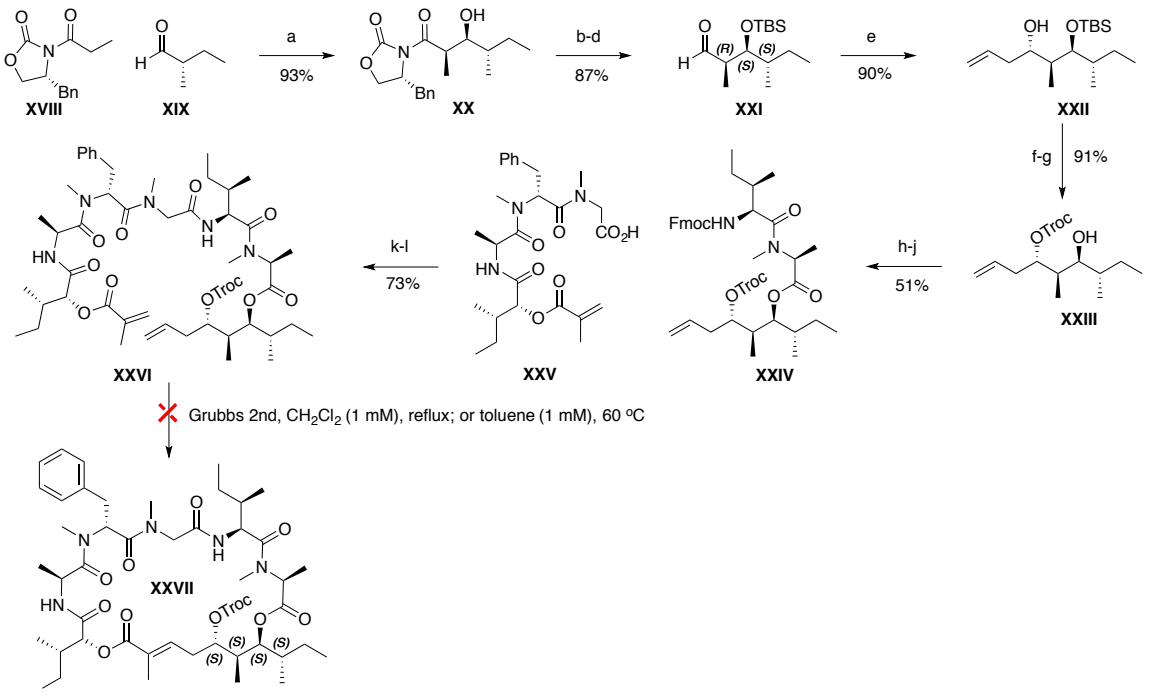


Figure 5.1 Differences in ^{13}C NMR shifts between natural lagunamide a, derivatives of synthetic lagunamide A and the revised structure for lagunamide A.

The second total synthesis of lagunamide A was disclosed by Wei *et al.*[33] and displayed interesting methods prior to stereochemical reassignment of the natural product configuration, as well as a diverse synthesis of analogs and interesting new attempts at macro-cyclization. Specifically, ring-closing metathesis (RCM) was explored in **Scheme 5.2** and the optimized total synthesis is presented in **Scheme 5.3**. Of particular interest to our synthetic approach were allylation optimizations for (*R*-*S*-*S*) aldehyde **XXI** (objective prior to revision of stereochemical target, **Table 5.1**) and esterification of alcohol **XXXIII** in **Table 5.2**.

Aldol condensation of aldehyde **XIX** with Evan's chiral oxazolidinone auxiliary[72] **XVIII** established *syn*-alcohol **XX** in 93% yield (99:1 dr). Silyl-protection (TBSOTf) of the hydroxyl group and subsequent reductive cleavage of the auxiliary produced a

primary alcohol that was exposed for Swern oxidation to produce (*R*-*S*-*S*) aldehyde **XXI** in 87% yield over this sequence of three steps. Optimization for allylation of aldehyde **XXI** with allylmagnesium chloride was summarized in **Table 5.1**. Next, the congested hydroxy functionality of **XXII** was protected by TrocCl and the TBS ether was cleaved by 40% aqueous HF to afford secondary alcohol **XXIII** in 91% yield overall. L-*N*-Fmoc-*L*-Ala-Cl was a difficult moiety to introduce, took extensive optimizations (seen in **Table 5.2**) and was eventually installed in 61% yield with minimal epimerization at the α-carbon position (>99:1 dr).

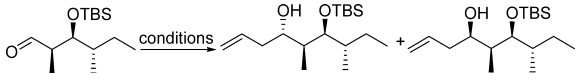


Reagents and Conditions: (a) Bu_2BOTf, TEA, CH_2Cl_2, -78 oC; (b)TBSOTf, 2, 6-lutidine, 0 ºC (c) $LiBH_4$, MeOH/THF, 0 ºC; (d) $(COCl)_2$, DMSO, TEA, -78 ºC; (e) $ZnCl_2$ (2.5 eq), AllylMgCl (1.5 eq), THF, -78 ºC; (f) TrocCl, DMAP (cat.), pyridine, CH_2Cl_2; (g) 40% aqueous HF, CH_3CN; (h) L-N-Me-Ala-Fmoc-Cl, DIPEA, CH_2Cl_2, reflux; (i) Et_2NH/ CH_3CN, rt; (j) L-Fmoc-alle-OH, HATU, DIPEA, CH_2Cl_2, 0 ºC ~ rt; (k) Et_2NH/ CH_3CN, rt; (l) HATU, DIPEA, CH_2Cl_2, 0 ºC ~ rt

Scheme 5.2 Failed Huang synthesis of *epi*-lagunamide A.

Finally, straightforward HATU, DIPEA and *N*-Fmoc-*D*-*allo*-Ile-OH peptide coupling supplied intermediate **XXIV** in 51% yield over three steps. At this point the Huang group synthesized peptide **XXV** with methacrylate functionality via solution phase in anticipation of their desired RCM strategy for macro-cyclization.[50] Functionalized peptide **XXV** and intermediate **XXVI** were converged by HATU-mediated peptide coupling to produce di-alkene **XXVI** in 73% overall yield. Although various attempts with different solvents and temperatures were surveyed, unfortunately, the RCM reaction of **XXVI** under Grubb's 2nd generation catalyst was unsuccessful and no product **XXVII** was obtained. Regardless, the unsuccessful Huang group route revealed a great deal of insight towards the chemical studies of lagunamide A, and specifically fundamental difficulties at various ring closure sites.

Table 5.1 Allylation of (*R*-*S*-*S*) aldehyde **XXI** at the C37 position of lagunamide A.



XXI **XXIIa** **XXIIb**

entry	reagent	Lewis acid	yield (%)[c]	**XXIIa:XXIIb**[d]
1[a]	AllylMgCl	–	92	11:89
2[b]	AllylMgCl	Et_2BOMe	87	16:84
3[b]	AllylMgCl	$CeCl_3$	85	17:83
4[b]	AllylMgCl	$Cu(OTf)_2$	89	14:86
5[b]	AllylMgCl	$AlMe_2Cl$	90	25:75
6[b]	AllylMgCl	$InCl_3$	82	33:67
7[b]	AllylMgCl	$SnCl_2$	85	14:86
8[b]	AllylMgCl	$NiCl_2(PPh_3)_2$	78	20:80
9[b]	AllylMgCl	LiBr	88	17:83
10[b]	AllylMgCl	$Pd(OAc)_2$	89	14:86
11[b]	AllylMgCl	$BF_3{\cdot}Et_2O$	90	15:85
12[b]	AllylMgCl	$ZnCl_2$	90	90:10

[a]AllylMgCl (1.5 equiv), THF, −78 °C. [b]Lewis acid (2.5 equiv), AllylMgCl (1.5 equiv), THF, −78 °C. [c]Combined yields. [d]Determined by isolated products.

The Huang group performed exhaustive studies to improve allylation conditions at the C37 position of lagunamide A (see **Table 5.1**). Ultimately, 2.5 equivalents of $ZnCl_2$ with allylmagnesium chloride and aldehyde **XXI** were able to reverse the stereochemical outcome commiserate on aldehyde α-methyl stereochemistry via chelation control to afford the desired *anti*-Felkin product in 90:10 ratio. The Huang group was certainly distressed to then reveal that due to the correction of stereochemistry from (*R*-*S*-*S*) to (*R*-*R*-*S*) aldehyde fragment of lagunamide A that chelation control with $ZnCl_2$ was rendered obsolete because there was no further steric demand for selectivity and produced a roughly 2:3 mixture of diastereomers (see **Figure 5.2**).

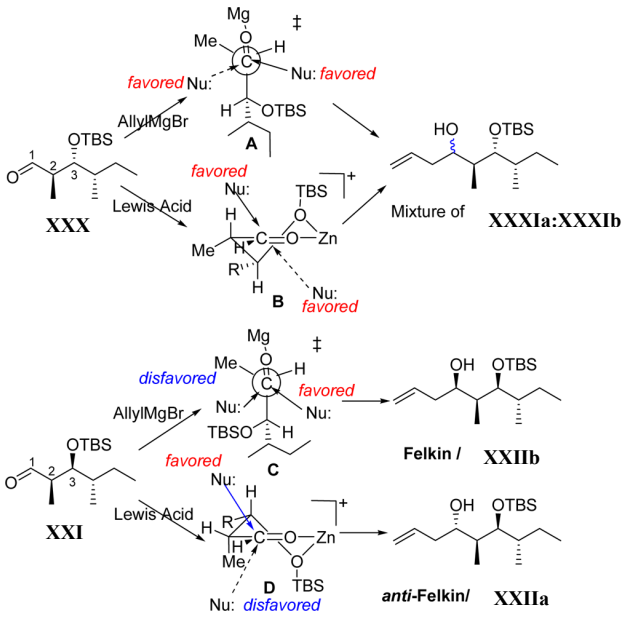


Figure 5.2 Allylation of (*R*-*R*-*S*) aldehyde **XXX** and (*R*-*S*-*S*) aldehyde **XXI**.

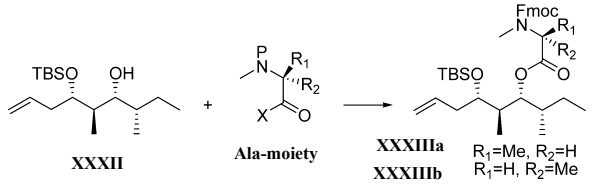
Again the Huang group performed exhaustive studies, this time to improve the esterification conditions of congested alcohol **XXXII** with an alanine amino acid moiety

(See **Table 5.2**). This coupling was made difficult by epimerization of the amino acid at the α-stereocenter to the carbonyl. When traditionally robust Yamaguchi conditions[73] were employed (entry 1) the esterification product was produced (24:76 d.r.) in favor of the incorrect stereoisomer. Interestingly, when *D*-Ala-OH moiety was coupled (entry 2) the esterification product was produced (2:98 d.r.) in favor of the starting material stereochemistry without scrambling of the stereocenter, which suggests that the epimerization likely occurred after the formation of the ester bond. Finally, entries 7 and 8 correlated that the amount of DMAP used affected the amount of racemization observed with acid *L*-Ala-Cl moiety and ultimately the optically pure ester **XXXIII** was obtained through the exclusion of DMAP (entry 9) in 55% yield and >99:1 d.r.

In order to complete the total synthesis of lagunamide A, the Huang group began their efforts with Paterson *anti*-aldol[74] methodology (**Scheme 5.3**). Thus, the *E-boron*-enolate of ketone **XXVIII** was introduced using $(c\text{-hex})_2BCl$ and Me_2NEt such that the correct *anti*-aldol product **XXIX** was produced in 74% yield with excellent diastereoselectivity (>99:1) when reacted with aldehyde **XIX**. Sequential hydroxyl TBS protection, $NaBH_4$ mediated reduction of the ketone and hydrolysis of the benzoate moiety produced a mixture of 1,2-diols that were equipped for oxidative cleavage via $NaIO_4$ to afford aldehyde **XXX** in 46% over these multiple steps. The diastereoselectivities in the homoallylic alcohol **XXXI** formation via allylation were very poor (~39:61 ratio in favor of the incorrect isomer for most cases) and could not be remedied through Lewis acid interaction (See **Figure 5.1**). Thus, the mixture of diastereomeric alcohols **XXXI** were homogenized via DMP oxidation followed by

$NaBH_4$ mediated reduction in an asymmetric manner, TBS removal in 40% aqueous HF and then protection of the less sterically hindered homoallylic alcohol (TBSOTf) to afford alcohol **XXXII** (~9:1 d.r.) in 60% yield over four steps. Fmoc-*N*-*L*-Ala-Cl was then coupled as presented in **Table 5.2** to afford ester **XXXIII** in 55% yield.

Table 5.2 Esterification of alcohol **XXXII** with alanine moiety.

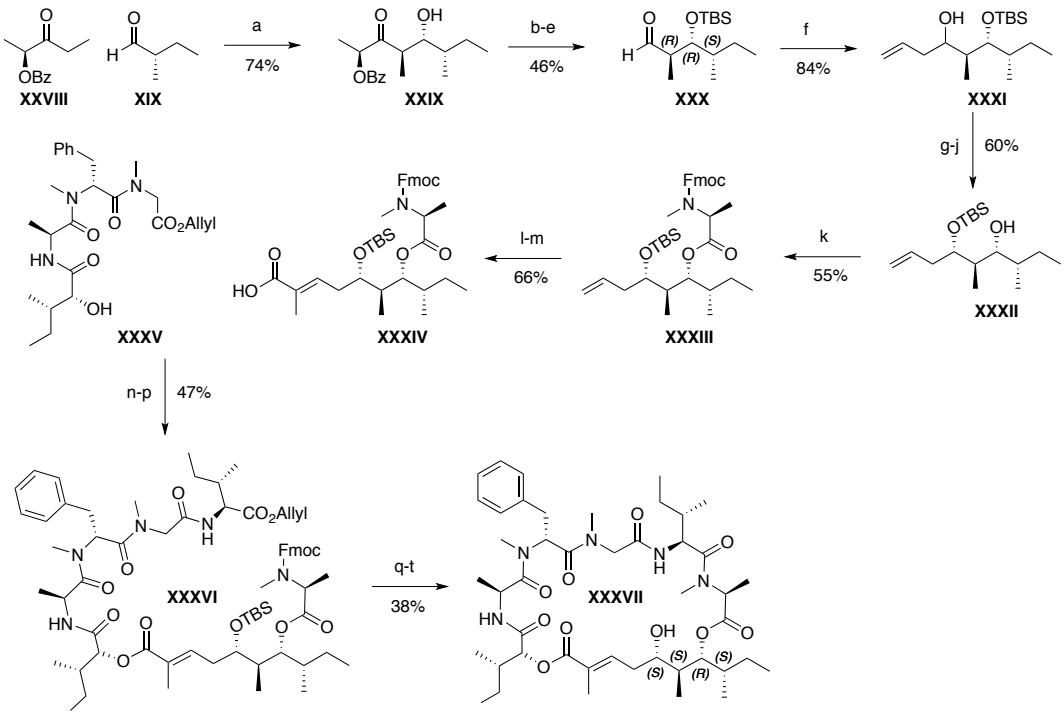


	Ala-moiety					
entry	R_1	R_2	X	P	**XXXIIIa:b**	yield (%)[j]
1[a]	Me	H	OH	Fmoc	24:76	92
2[a]	H	Me	OH	Fmoc	2:98	89
3[b]	Me	H	OH	Boc	24:76	73
4[c]	Me	H	OH	Fmoc	23:77	69
5[d]	Me	H	OH	Fmoc	–	NR
6[e]	Me	H	OH	Fmoc	33:67	48
7[f]	Me	H	Cl	Fmoc	58:42	57
8[g]	Me	H	Cl	Fmoc	70:30	56
9[h]	Me	H	Cl	Fmoc	>99:1	55

[a]$Cl_3C_6H_2COCl$ (1.2 equiv), acid (1.2 equiv), TEA (1.5 equiv), DMAP (2.0 equiv), rt, 30 min. [b](1) Conditions in footnote *a*; (2) TMSOTf, 2,6-lutidine, DCM; (3) FmocOsu, DIPEA, DCM. [c]MNBA (1.2 equiv), acid (2 equiv), TEA (3 equiv), DMAP (0.2 equiv), rt, 30 min. [d]2-Chloro-1-methylpyridinium iodide (2.2 equiv), acid (2 equiv), DIPEA (5 equiv), DCM reflux. [e]EDCI (2 equiv), acid (2 equiv), TEA (2 equiv), DMAP (1 equiv) DCM, rt, 12 h. [f]Acid chloride (5.0 equiv), DIPEA (5.5 equiv), DMAP (0.5 equiv), DCM, −15 °C, 5 h. [g]Acid chloride (5.0 equiv), colidine (10 equiv), DMAP (0.2 equiv), toluene, 60 °C, 8 h. [h]Acid chloride (2.5 equiv), DIPEA (5 equiv), DCM, reflux, 8 h. [i]Determined by HPLC of the crude products. [j]Combined yields of **XXXIIIa and XXXIIIb**

Cross-metathesis of terminal alkene intermediate **XXXIII** with methacrylaldehyde was achieved by Grubbs 2nd generation catalyst in 80% yield (E/Z>99:1). Pinnick oxidation[75] of the α,β-unsaturated aldehyde with sodium chlorite alongside hydrogen peroxide generated carboxylic acid **XXXIV** in 66% over two steps. Shiina coupling[76] employed MNBA/DMAP to join carboxylic acid **XXXIV** with α-

alcohol derivatized peptide fragment **XXXV** followed by peptide coupling of Boc-*N*-*L*-Ile-OH to produce ester **XXXVI** in 47% yield over the previous three steps. Macro-cyclization was achieved by intramolecular peptide coupling. Chronological de-protection of the allyl ester via $Pd(PPh_3)_4$ with *N*-methylalanine followed by simultaneous Boc/TBS de-protection with TFA exposed an intermediate subject to HATU/DIPEA-mediated cyclization to successfully yield the desired product 7,39-*epi*-lagunamide A (**XXXVII**) in 38% yield over the previous four steps.



Reagents and Conditions: (a) $(c\text{-hex})_2BCl$, Me_2NEt, -78 ºC ~ -26 ºC; (b) TBSOTf, 2,6-lutidine, 0 ºC; (c) $NaBH_4$, MeOH/THF, 0 oC; (d) K_2CO_3, MeOH, rt; (e) $NaIO_4$, MeOH/H_2O (2/1), rt; (f) AllylMgCl, THF, -78 ºC; (g) Dess-Martin periodinane, CH_2Cl_2, 0ºC, 30 min; (h) $NaBH_4$, CH_3OH, 0 ºC, 15 min; (i) 40% HF aq, ACN; (j) TBSOTf, 2,6-Lutidine, CH_2Cl_2, 0 ºC, 1 h; (k) acid chloride (2.5 eq.), DIPEA (5 eq.), DCM reflux, 8h; (l) methacrylaldehyde, Grubbs 2nd, CH_2Cl_2, reflux, E:Z > 99:1; (m) $NaClO_2$, NaH_2PO_4, t-BuOH, 2-methylbut-2-ene, rt; (n) MNBA, DMAP, CH_2Cl_2, rt; (o) $Pd(PPh_3)_4$, PhNHMe, THF, rt; (p) L-Boc-alle-OH, HATU, DIPEA, CH_2Cl_2, 0 ºC ~ rt; (q) $Pd(PPh_3)_4$, PhNHMe, THF, rt; (r) Et_2NH/ CH_3CN, rt; (s) HATU, DIPEA, CH_2Cl_2, rt; (t) 40% aquous HF, CH_3CN

Scheme 5.3 Completed Huang synthesis of lagunamide A.

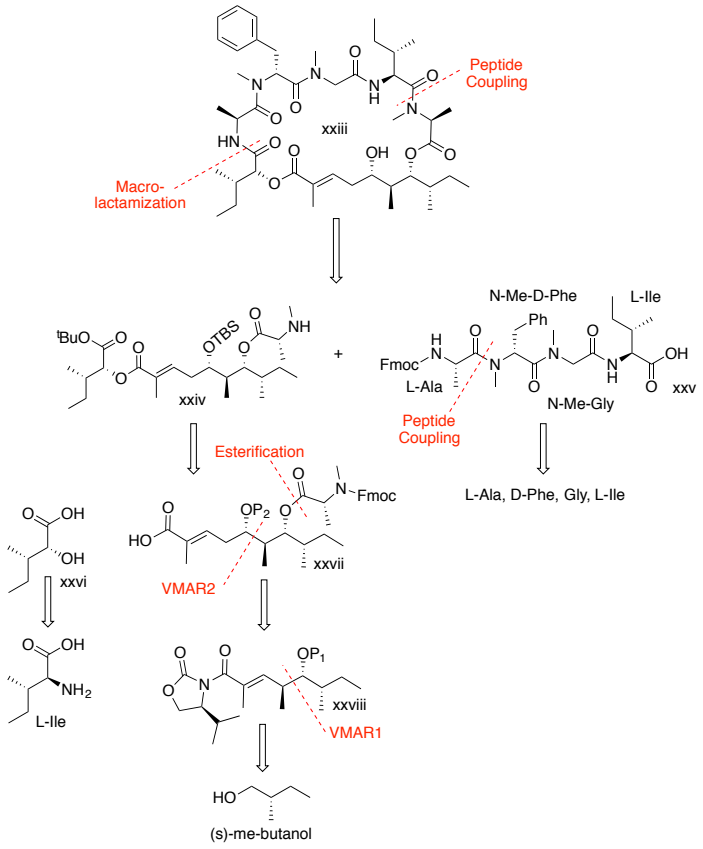
The Huang group provided an asymmetric total synthesis of lagunamide A (3.0% overall yield in 20 linear steps) and several diverse analogs that were detailed in this report. The most impactful transformations were expounded in **Table 5.1** (allylation survey) and **Table 5.2** (esterification survey). This synthesis also revealed some key points for peptide bond mediated ring closure and that RCM was not a suitable macro-cyclization strategy for lagunamide A. The Huang synthesis was not directly asymmetric, whereby the transformation of aldehyde **XXX** to homoallylic alcohol **XXXI** could not be controlled via chelation and resulted in a 39:61 mixture of diastereomers.

5.3 Retrosynthetic strategy for lagunamide A

We anticipated macro-cyclization to afford the natural product lagunamide A (xxiii) via peptide bond formation at a non-*N*-methylated juncture followed by a second peptide bond disconnection, again at a non-*N*-methylated position, to reveal the terpenoid (xxiv) and tetrapeptide (xxv) fragments (**Scheme 5.4**). We hypothesized that peptide bond formation would be more efficient when coupled at less sterically crowded positions.

We have previously discussed the synthesis of the "southern hemisphere" and its precursors by way of iterative VMAR's (xxvii, xxviii, **Chapter 3**) and *D*-*allo*-Hila-moiety (xxvi, specifically **Chapter 3.4.6**) synthesis. In this retrosynthetic strategy we proposed a disconnection between fragment xxvii as the carboxylic acid and the α-hydroxy moiety of the xxvi fragment. Likewise, we have previously discussed synthesis of the "northern hemisphere" tetrapeptide (xxv, **Chapter 4**) fragment from "naked"

amino acid precursors. The overall convergent synthetic scheme utilizing these two major fragments, alongside the entirety of our linear synthesis previously discussed, is depicted in **Scheme 5.5**.



Scheme 5.4 Retrosynthetic strategy for lagunamide A.

5.4 Results and discussion

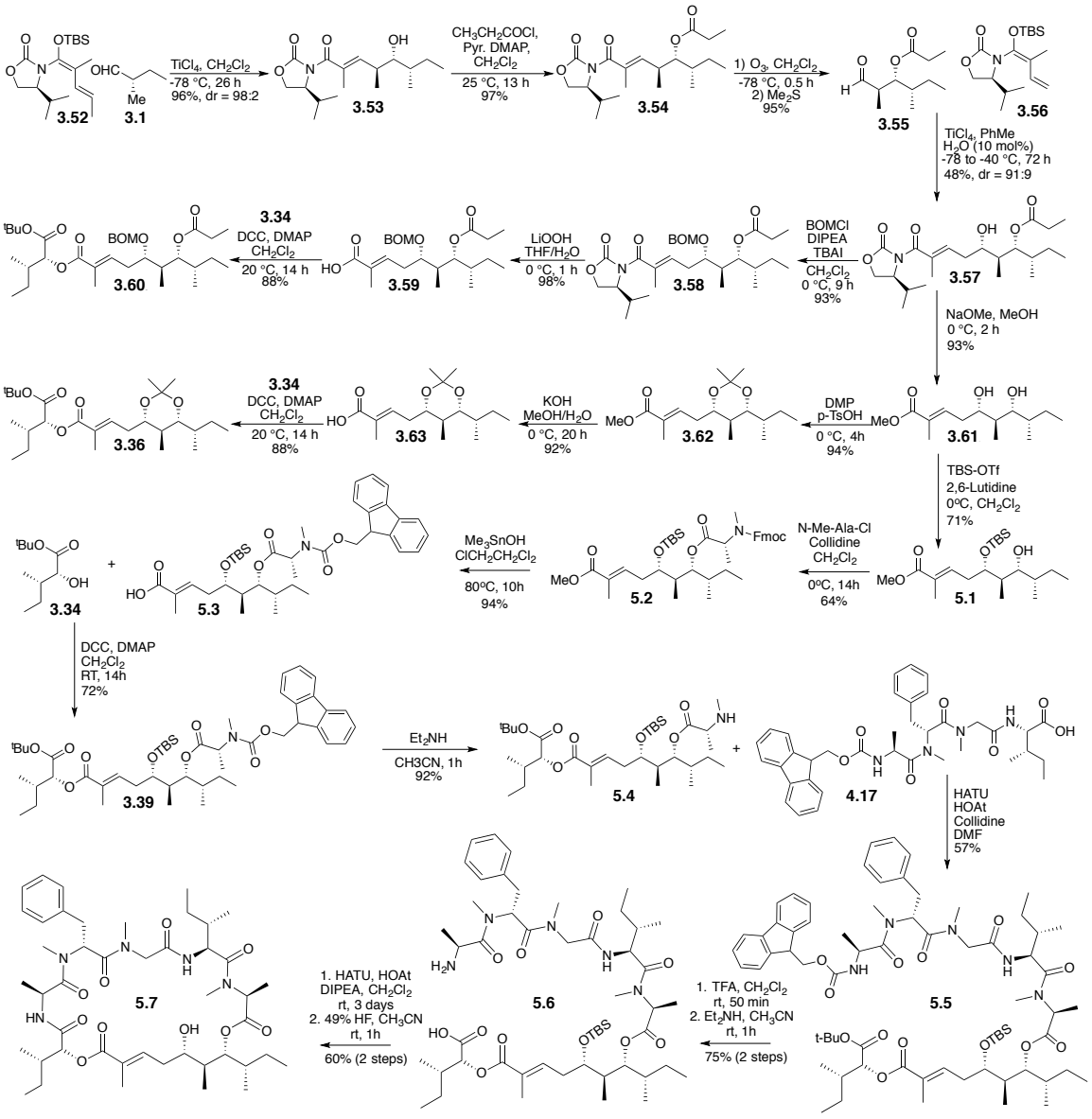
The synthesis in **Scheme 5.5** was highlighted by formal products that contained the necessary stereochemistry and protecting group strategy for the C27-C45 fragment of lagunamide A (**3.60**, **3.36** and **3.39**) presented in **Chapter 3**, where the syntheses were discussed in detail. **Scheme 5.5** presented yet another route to the C27-C45 fragment

followed by a completed total synthesis of lagunamide A via convergent strategy; refer to **Chapter 3**: Synthesis of the C27-C45 "Southern Hemisphere" of Lagunamide A and **Chapter 4**: Synthesis of the "Northern hemisphere" peptide fragment of lagunamide A for more detail.

The previously established intermediate 1,3-diol (**3.61)** was selectively mono-protected at the less sterically demanding hydroxyl with TBS-OTf (1 equiv) alongside 2,6-lutidine in DCM to produce silyl-ether **5.1** in 71% yield, similar to previous reports.[77] Acid chloride mediated (Fmoc-*N*-Me-*L*-Ala-Cl) coupling of congested hydroxyl **5.1** with collidine furnished the di-protected ester **5.2** in 64% yield (See **Table 5.2** for optimization of esterification conditions).[33] Compounds derivatized with the Fmoc-*N*-Me-*L*-Alanine moiety existed as rotational conformers and were difficult to characterize via ^{1}H NMR.[78] An impressively mild and selective method that hydrolyzes methyl esters was developed by Nicolaou *et al*.[79] Thus, **5.2** was exposed to trimethyltin hydroxide at 80 $^{\circ}$C in 1,2-DCE for 9 hours to afford the corresponding carboxylic acid in 94% yield (**5.3**). Due to the relative hazards of trimethyltin chloride,[80] used as a precursor to synthesize trimethyltin hydroxide, scalability, and the relative toxicity of tin for natural product development in general, we essentially preferred our route towards **3.36** followed by deprotection, mono-silylation and Fmoc-N-Me-Ala-Cl mediated esterification to produce the spectroscopically identical fragment **3.39**.

Thus, Fmoc-protected **3.39** was subjected to diethylamine (Et_2NH) in acetonitrile and evaporated to produce the correspondent amine **5.4** (isolated as the TFA salt) in quantitative yield by TLC. Crude **5.4** was subsequently converged with tetrapeptide **4.17**

via HATU, HOAt and collidine in DMF to establish the globally protected hybrid terpenoid-peptide (**5.5**) intermediate in 57% yield.



Scheme 5.5 Convergent asymmetric total synthesis of lagunamide A.

The intermediates that lead to lagunamide A were monitored via TLC, characterized solely by LCMS and were reacted sequentially from their crude products.

First, *tert*-butyl ester **5.5** was deprotected by (1:4) TFA in CH_2Cl_2 and concentrated such that the Fmoc group was removed by (1:4) diethylamine in CH_3CN to afford the corresponding fragment **5.6** in quantitative yield (by TLC) over the two-step deprotection sequence. Intermediate **5.6** was prepared for intra-molecular macro-lactamization via HATU, HOAt and DIPEA in CH_2Cl_2, concentrated and followed by a TBS-ether deprotection in 49% aq. HF in CH_3CN to furnish the desired natural product, lagunamide A (**5.7**) in roughly 40% yield over the previous four steps. Crude residue was purified by either 33% acetone in hexanes gradient on silica gel column or by Varian C-8 30 x 250 mm prep-HPLC from 10-100% methanol in water spiked with 0.1% formic acid (retention time ~10 min). For detailed spectroscopic analysis both methods of purification were necessary in succession. Synthetic lagunamide A was spectrascopically identical to literature reports[5,6,50] and produced in 5% overall yield, previsously <3% overall yield by Dai *et al*.[6]

5.5 Conclusions

Lagunamide A (**5.7**) was successfully synthesized by the convergent strategy of coupling the "southern" terpenoid fragment (**5.4**) with the "northern" peptide fragment (**4.17**) followed by macro-lactamization in 20% overall yield. The crucial secondary amine fragment **5.4** was achieved via multiple formal syntheses, but the route was predominantly optimized by iterations of Kobayashi's protocol for the VMAR. We reached fragment **4.17** via peptide coupling on solid support, a method previously unemployed for this class of molecule. Our total synthesis of lagunamide A featured the highest yield in fewest amount of synthetic steps to date, specifically achieved in 5%

overall yield (previously <3% overall) and in 14 linear steps (previously 17 steps) from known compound **3.53**.

Co-author Lee Wang provided written permission to include published and manuscript in preparation materials disclosed in this chapter.[51]

6 Chemical Studies on Kobayashi's VMAR methodology

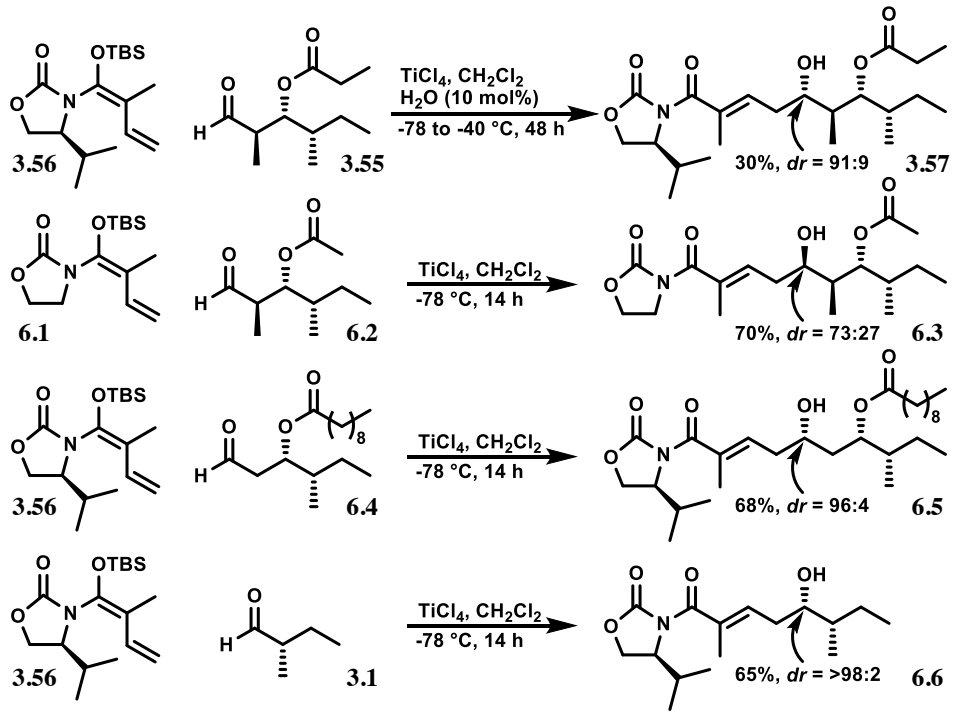
6.1 Introduction

The VMAR demonstrated impressive versatility and stereocontrol through remote induction of an electrophilic addition as shown by the high diastereomeric ratio of the product. Even though the asymmetric VMAR was a very powerful tool, it had limitations as illustrated for the conversion of aldehyde **3.55** to vinylogous aldol product **3.57** in 48% yield when toluene with 10 mol% H_2O was used as a medium (previously disclosed in **Scheme 5.5**). We paneled suitable substrates with site-specific chirality knockouts (**Scheme 6.1**) and explored the mechanism of "1,7-remote" induction of stereochemistry by VMAR methodology and ultimately proposed a feasible transition state model for *(S)*- and *(R)*-2-methyl substituted aldehydes (**Figure 6.1**).

6.2 Proposed transition state, results and discussion

When the VMAR was conducted in the conventional CH_2Cl_2 solvent, the yield dropped significantly to 30% of product **3.57**, but the lack of change in d.r. suggested a slow reaction with the aldehyde at low temperature. The amount of hydrolyzed vinylketene silyl *N,O*-acetal **3.56** formed over an extended amount of time also implied that the VMAR with aldehyde **3.55,** with absolute 2(*R*)-methyl stereochemistry, was rate determining. Thus, it appeared as if the actual (*S*)-valine based chiral auxiliary (**3.56**) was detrimental to the overall yield of the VMAR using α-(*R*)-methyl substituted aldehydes. To confirm this suspicion of stereochemical crowding during the reaction, the VMAR

was first conducted without the influence of the (*S*)-valine based auxiliary and the bulk of the *iso*-propyl group in the VMAR (**Scheme 6.1**). Thus, achiral vinylketene silyl *N,O*-acetal **6.1**, lacking the chiral recognition within the 2-oxazolidone moiety, reacted readily with the stereochemically congested aldehyde **6.2** at -78 °C to give **6.3** in 70% yield, but with the opposite major diastereomer of product compared to the aldol products **3.57, 6.5** and **6.6**.



Scheme 6.1 Influence of substituted aldehydes on asymmetric VMAR.

We next explored the absence of the 2(*R*)-methyl stereocenter using aldehyde **6.4**. Vinylogous aldol product **6.5** was formed more rapidly at -78 °C, than in comparison to aldol product **3.57**, as the expected main diastereomer (96:4 d.r.) in 68% yield. 2-(*S*)-Methylbutanal (**3.1**) had chirality that reinforced stereochemistry of product **6.6** when

condensed with vinylketene silyl *N,O*-acetal **3.56**. Consequently, formation of the major diastereomer **3.57** was facilitated by the influence of specific α-methyl chirality of the aldehyde, but the rate of the VMAR was impeded particularly with α-(*R*)-methyl substituted aldehydes and the (*S*)-valine based auxiliary.

Based on our results from the aforementioned VMAR "knockout" experiments, the following transition state models for vinylketene silyl *N,O*-acetal **3.56**, and its nucleophilic approach to 2(*S*)- and 2(*R*)-methyl-substituted aldehydes were proposed, respectively (**Figure 6.1**). Based on Spartan calculations and NOE experiments the auxiliary can adopt a nearly perpendicular configuration against the π-system of the diene segment.[9] As seen in both proposed transition state models, the larger substituent faced away from the chiral auxiliary while the methyl group of larger 2(*R*)-methyl-substituted aldehyde pointed towards the auxiliary creating an unfavorable interaction.

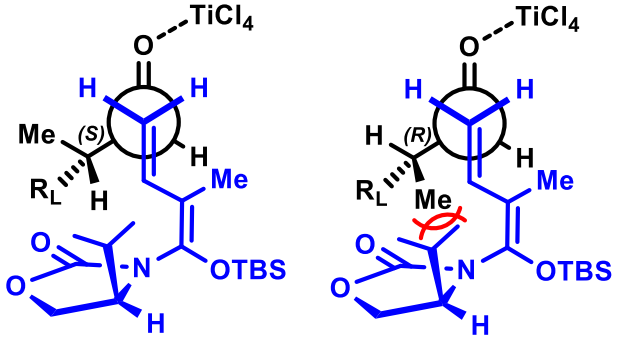


Figure 6.1 Proposed transition states for the nucleophilic attack of vinylketene *N,O*-acetal (**3.56**) to (*S*)- and (*R*)-2-methyl substituted aldehydes, respectively.

6.3 Chemical studies toward compatible β-ethereal protecting groups

Small panels of β-ethereal protected aldehydes were surveyed for compatibility with Kobayashi's protocol for "1,7-remote" VMAR (**Table 6.1**). Protecting groups for our survey needed to meet requirements for both VMAR compatibility and complex synthesis of the aldehyde intermediate. A silyl-ether protecting group was the most obvious and advantageous choice; however, the smaller silyl-protecting groups (**3.22**-TBS and **6.8**-TIPS) were hydrolyzed under acidic VMAR conditions or were too bulky (**6.7**-TBDPS) and unreactive under these conditions. ChemBio3D energy minimalized models of aldehydes **3.22** (TBS) vs. **6.7** (TBDPS) demonstrated congestion from the β-ethereal silyl group around the electrophilic center (**Figure 6.2**).

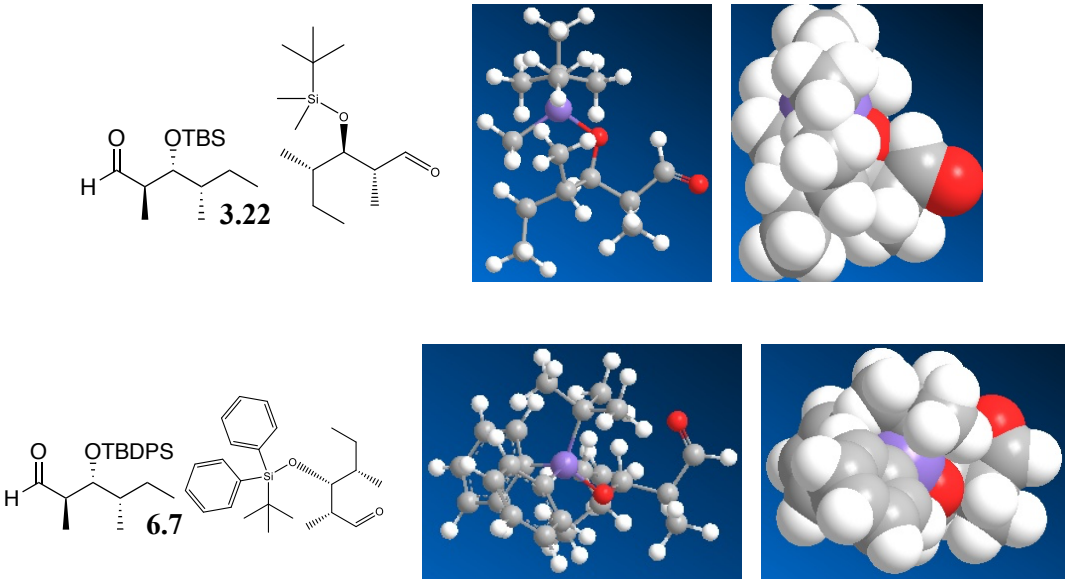
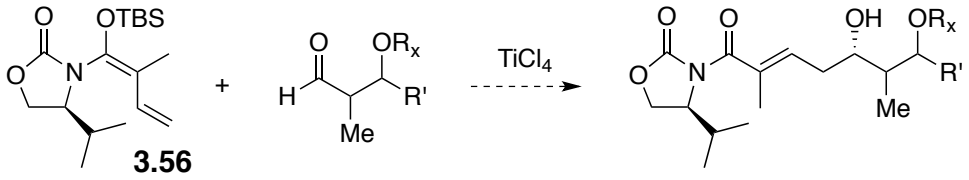


Figure 6.2 Energy minimized ChemBio3D models.

The β-THP-ether (**6.9**) and β-BOM protected ether of the aldehydes were similarly hydrolyzed under VMAR conditions employing $TiCl_4$. Ultimately, protection

via propionate ester **3.55** produced the desired aldol fragment **3.57** in 48% yield. Carbon-bound hydroxyl protecting groups were difficult for various reasons, particularly compatibility for our synthesis. Henceforth, our synthesis focused on VMAR compatible ester protecting groups that were sterically insignificant, compatible to the reaction conditions and determined thru these succinct protecting group chemical studies.

Table 6.1 Chemical studies towards compatible VMAR protecting groups.



R_1 = TBS, R' = $C(CH_3)CH_2CH_3$ (**3.22**)	R_1 = No Product[a]
R_2 = TBDPS, R' = $C(CH_3)CH_2CH_3$ (**6.7**)	R_2 = No Product[b]
R_3 = TIPS, R' = H (**6.8**)	R_3 = No Product[a]
R_4 = THP, R' = H (**6.9**)	R_4 = No Product[a]
R_5 = BOM, R' = $C(CH_3)CH_2CH_3$ (**6.10**)	R_5 = No Product[a]
R_6 = Me, PMB, R' = H	R_6 = No Product[c]
R_7 = Propionate, R' = $C(CH_3)CH_2CH_3$ (**3.55**)	R_7 = 48% yield (**3.57**)[d]

[a] Only hydrolyzed products were recovered. [b] Unreacted aldehyde and hydrolyzed product of (**3.56a**) were recovered. [c] Aldehyde substrate was too difficult to synthesize. [d] In general reactions were ran in ~1M DCM, 1 eq. aldehyde, 1 eq. TiCl4 and 2 eq. **3.56**; Reported 48% yield based on optimized reaction conditions, see experimental.

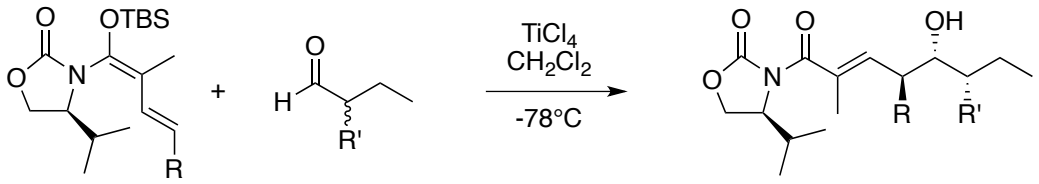
6.4 Enantiomeric resolution of α-substituted aldehydes.

Crystallization, chiral column chromatography and chiral agent derivatives are popular methods for resolution of enantiomeric mixtures.[81] When chiral compounds interact with chiral entities, either chemical (e.g. Mosher's acid)[82] or biological, we can expect stereospecific manifestation of end products or activity.[3] Specifically, kinetic

resolutions are when one enantiomer reacts much faster then the other. Thus, chiral separations and resolution are meaningful for an expansive collection of research interests.

The proposed transition states for Kobayashi's VMAR protocol (See **Figure 6.1**) demonstrated a stereochemical bias for reactivity of (*S*)- vs. (*R*)-α-substituted aldehyde substrates. Based on our recent publication[51] (See **Scheme 6.1**) and our proposed transition (See **Figure 6.1**) state, an application for enantiomeric resolution of α-substituted aldehydes through Kobayashi's protocol for VMAR was envisioned. Hence, an enantiomeric resolution of racemic 2-methylbutanal was demonstrated in **Table 6.2**. Initially, 3 equivalents of racemic 2-methylbutanal reacted with 1 equivalent of **3.56** to produce the aldol fragment **6.6** in 95% yield with a 75:25 ratio (50% diastereomeric excess) of the predicted major diastereomer. Diastereomeric ratio was determined via crude ^{1}H-NMR; furthermore, simple silica gel chromatography was employed to afford the corresponding optically pure compounds. Delighted by this result, it was predicted that VMAR **3.52** with an extended methyl substitution along the conjugated π-system would result in higher selectivity mainly due to steric demand. Predictably, when 3.0 equiv of racemic 2-methylbutanal was reacted with 1.0 equiv of **3.52** the aldol fragment **3.53** was constructed in 96% yield with an 85:15 ratio (75% diastereomeric excess) of the desired major diastereomer.

Table 6.2 Enantiomeric resolution of α-substituted aldehydes via VMAR.



Entry	Reagents	Aldehyde equiv.	Product d.r.[a]
1	R = H **3.56**, R' = Me	3.0	95% yield, **6.6** (75:25)
2	R = Me **3.52**, R' = Me	3.0	96% yield, **3.53** (85:15)
3	R = Me **3.52**, R' = Ph **6.11**	3.0	86% yield, **6.12** (70:30)

Note: Generally, reaction condition included 1 equiv VMAR reagent and 66% $TiCl_4$ pre-coordinated aldehyde.
[a] d.r. determined via crude ^{1}H-NMR analysis.

Interestingly, the analogous construction of aldol fragment **6.12** from *rac*-2-phenylbutyraldehyde[84] (**6.11**) was assembled in 86% yield with a slightly depressed diastereomeric ratio (70:30). Increased resolution was anticipated due to increased steric bulk about the α-carbon; however, the assignment of large and small groups in our proposed transition state (**Figure 6.1**) would be inverted with such small aldehyde substrates. Overall, This "remote-1,6,7-VMAR" induction of stereochemistry manipulated an α-racemic aldehyde mixture into a stereo-controlled aldol product with three contiguous stereocenters.. Future application and scope of this observation are being considered and will be reported in due course.

6.5 Conclusions

Vinylogous Mukaiyama aldol reactions is an interestingly powerful instrument that showed versatile precedent, specifically in natural product synthesis.[43,73] The "1,6,7-

and 1,7-remote" type version of VMAR (Kobayashi's protocol) gave excellent yield and stereo-selectivity for multiple substrates; However, our probe (**Scheme 6.1** & **Table 6.1**) into the limitations of Kobayashi's VMAR suggested detrimental interaction with crowded (*R*)-2-methyl substituted aldehydes (see **Figure 6.1** for proposed transition state models) and problematic compatibility with β-ethereal protected aldehyde moieties, yet presented an interesting means of enantiomeric resolution (**Table 6.2**) that had yet to be explored in current literature.

Co-authors Lee Wang[56] and Arielle Kanner[86] provided their written permission to include published materials disclosed in this chapter.

7 Creating Biosensors for Lagunamide A

7.1 Introduction

Naturally occurring bioactive molecules, such as lagunamide A, are important tools for development of drug-like lead compounds. Natural products have the distinct advantage of coevolution with protein targets, usually correlated to extremely high selectivity. Determination of the molecular target(s) of lagunamide A would help determine the mechanism of action and provide a looking glass in to the convoluted cellular machinery of inhibition.

Biotinylation is a modern technique for determination of protein targets.[87] Biotin has high specific affinity for streptavidin and/or avidin. This tight binding affinity is exploited for purification (usually affinity chromatography) or detection (usually enzyme reporters such as horseradish peroxidase or fluorescent probes).[88] Convenient methods such as ELISA, electron microscopy and western blots help localize these derivatives.[89] Covalent bonding with biotin tags are unlikely to perturb the function of a molecule and lengthy linkers can probe deep into a number of enzymatic pockets in a proven method for the isolation of natural product receptors.[90]

7.2 Related work

Sato *et al*.[8] completed an important study to determine that Prohibitin 1 (PHB1) was the binding target protein of aurilide, a potent cytotoxic marine natural product that resulted in mitochondrial-induced apoptosis in cultured human cells.[8,91] Aurilide is

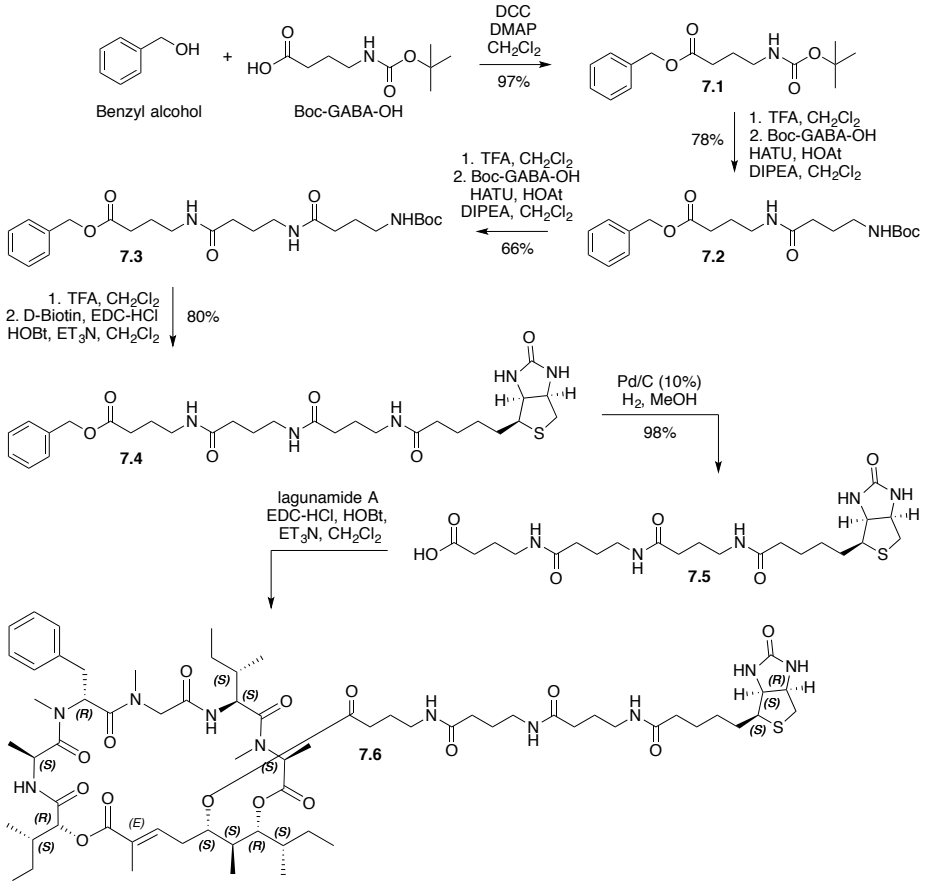
structurally similar and in the same macro-cyclic depsipeptide class of molecule as the more recently discovered lagunamide A. Furthermore, recent biochemical studies by Tripathi *et al*.[7] determined that the cytotoxic effect of lagunamide A might act via induction of mitochondrial-mediated induction of apoptosis. Since structure-activity relationships (SAR) for aurilide showed that modification of the C35-hydroxy group (comparable to the C37-hydroxyl group of lagunamide A) had little to no impact on biological activity, it was decided that an analogous approach to biotinylation of this moiety would be similarly adventageous.[92]

7.3 Results and discussion

The goal to synthesize an elongated biotin linker that could be efficiently coupled directly to lagunamide A. Due to our laborious efforts to acquire synthetic lagunamide A, we wanted the biotin and linker moiety to be a single construct that was subsequently converged with synthetic lagunamide A in one simple step. Our research supported a linker of roughly 10-20 covalent bond lengths that positioned the biotin handle well outside of the protein binding pocket.[93,94]

In order to synthesize the entirety of the biotin linker prior to conjugation with lagunamide A, we needed an orthogonal protecting group strategy for the *C*- and *N*-terminus of the linker. Thus, Steglich esterification of commercially available 4-(*tert*-Butoxycarbonylamino)butyric acid (Boc-GABA-OH) with benzyl alcohol mediated by DCC and DMAP in CH_2Cl_2 produced a completely protected monomer unit (**7.1**) in 97% yield. Repeating units of Boc-GABA-OH made for a stepwise and uniform elongation of

the linker via peptide bond fragments with advantageous protecting group strategy (**Scheme 7.1**).



Scheme 7.1 Synthetic biosensor for lagunamide A.

When **7.1** was exposed to TFA in CH_2Cl_2 the *N*-Boc protecting group was cleaved while the C-terminus benzyl ester remained protected. Evaporation of this mixture resulted in the crude TFA salt that was successively coupled with a second Boc-GABA-OH unit via HATU/HOAt and excess of DIPEA to produce dimer unit **7.2** in 78% yield over 2 steps. The identical TFA-mediated *N*-Boc removal and HATU-mediated Boc-GABA-OH coupling protocol was repeated to finalize the trimer fragment (**7.3**)

comprised of the desired chain length in 66% yield over the previous two steps. Trimer **7.3** was *N*-Boc deprotected with TFA and evaporated to produce the crude TFA salt that was subsequently extended by D-biotin through EDC·HCl-mediated[95] coupling to form the biotinylated trimer linker **7.4** scaffold in 80% yield. Inard *et al*.[96] demonstrated that sulfur containing biotin derivatives were inert towards palladium, and thus palladium-mediated hydrogenation of benzyl ester **7.4** liberated the free carboxylic acid of the biotinylated linker **7.5** in 84% yield. Biotinylated linker **7.5** was equipped for direct esterification with lagunamide A.

7.4 Conclusion

Since our entire biotin-linker moiety was synthesized prior to combination with lagunamide A, we spared valuable steps in constructing our biosensor. Conceptually, this combinatory biosensor strategy would be expedient for a number of hydroxylor amine-comprised small molecule or natural product compounds.

8 Chemical Studies Toward the Total Synthesis of Micromide

8.1 Introduction

Micromide, a cytotoxic alkaloid (IC_{50} = 260nM against KB cells) isolated from a *Symploca* genus of cyanobacterium, was discovered in 2004 by Williams *et al*.[54] This bioactive natural product had an interesting pentapeptide sequence flanked by a Thz-*N*-Me-Gly fragment on the C-terminus and (*R*)-3-methoxy-hexanoic acid on the *N*-terminus and represented an interesting synthetic target. Exhaustive separations allocated micromide in 0.12% overall yield, based on the crude extract, alongside scarceness in nature solidified necessity for scalable synthetic synthesis.

8.2 Previous works

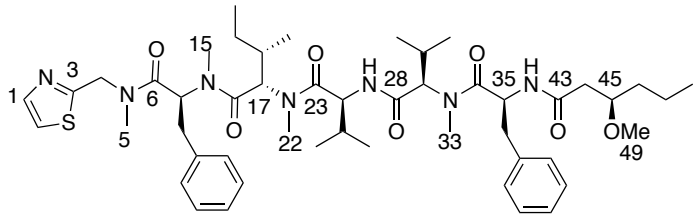


Figure 8.1 Proposed structure of micromide.

Recently, Han *et al*.[55] reported a completed total synthesis of micromide. Improbably, they employed the exact peptide and convergent fragment coupling strategy previously completed by the Bergdahl group.[97,98] The general *N*-methylation and solution phase peptide coupling sequence was previously reviewed in **Scheme 4.3**. Predictably, the NMR spectra for synthetic micromide from the Han *et al*.[55] effort and the Bergdahl

effort matched; however, we had delayed our submission for publication because the synthetic spectra did not match the spectra or biological activity for natural micromide. This led us to the conclution that Han *et al*. published a synthesis of an epimer of micromide and either misinterpreted or failed to acknowledge that the absolute stereochemistry for synthetic *vs.* natural micromide were substantially different.

8.3 Retrosynthetic strategy for micromide

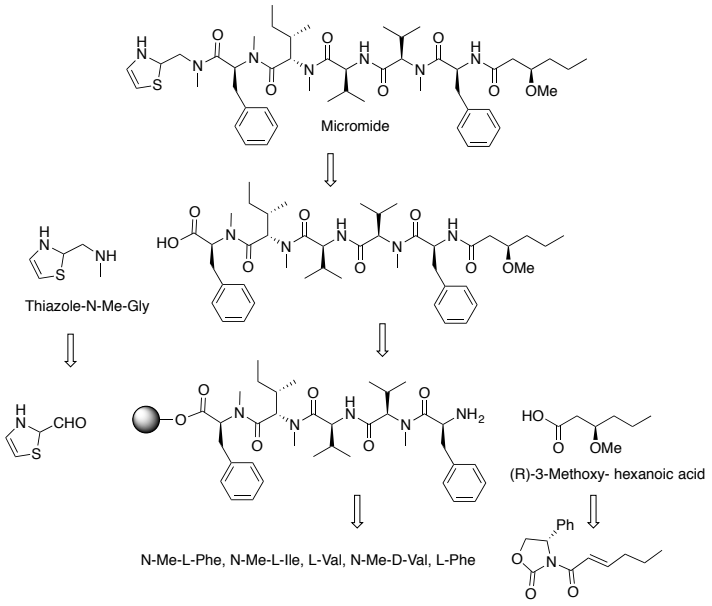


Figure 8.2 Retrosynthetic strategy for micromide.

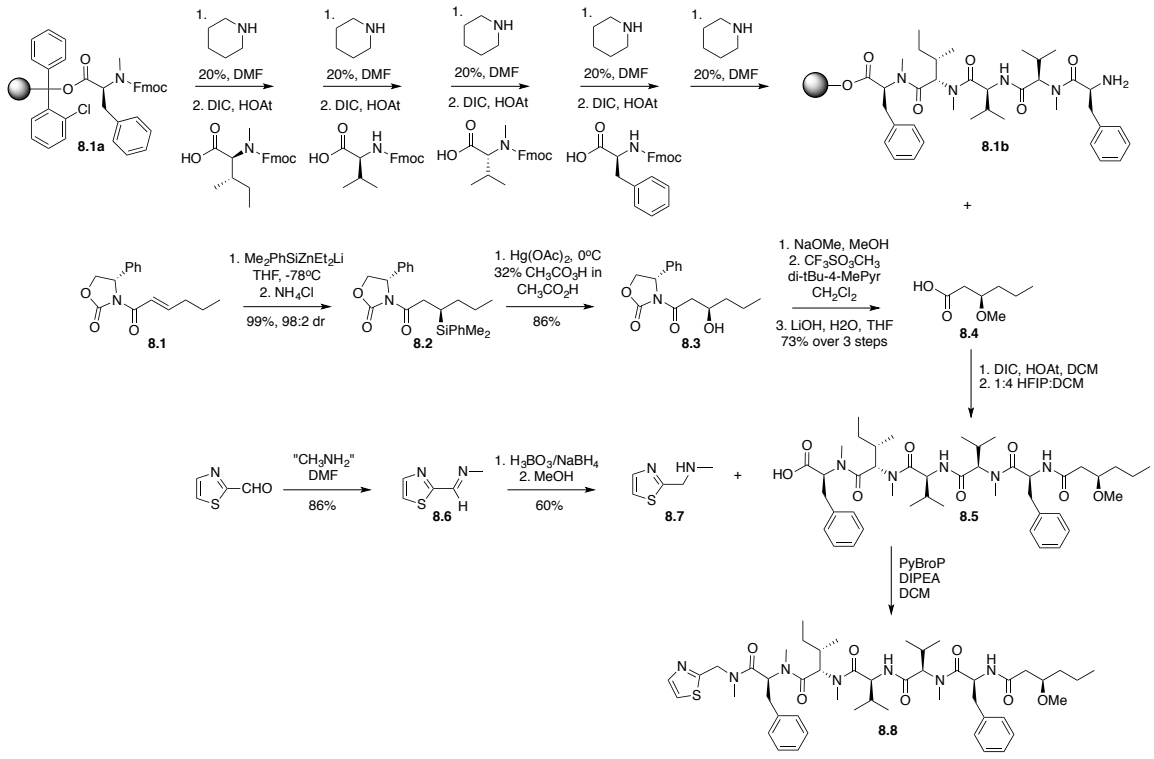
Micromide has many structural similarities to polyketide derived compounds from common cyanobacterial metabolites.[2] Indicative features included a *D*-amino acid, modified cysteine unit, *N*-methylated peptide bonds and β-methoxy acid moiety, probably derived from acetate units.[54] The proposed synthetic strategy for micromide was to separate the molecule into three main fragments, converged via peptide bonds (**Figure**

8.2). The first of these connections was with Thiazole-*N*-Me-Gly fragment and the entirety of the right side of the molecule. The peptide fragment was left still attached to solid phase and connected with (R)-3-methoxy-hexanoic acid, a fragment that was synthesized thru asymmetric conjugate addition directed by chiral auxiliary.

8.4 Results and discussion

We noticed a different ^{1}H and ^{13}C NMR spectra alongside different optical degrees of rotation (lit.[54] $[\alpha]_D^{20}$ = -32.2° (c 5.0, $CHCl_3$, 589 nm) *vs*. $[\alpha]_D^{20}$ = -28° (c 5.0, $CHCl_3$, 589 nm). In addition, ^{1}H NMR temperature experiments established a rapid equilibrium at +80 °C based on the broadening of rotational conformer signals. In order to support our claim that natural and synthetic micromide were epimers, an alternative synthesis of the proposed structure for micromide was hypothesized via solid phase that would confirm the absolute stereochemistry of synthetic micromide and reinforce the dissimilarity between the natural vs. synthetic epimers. The *N*-methylation and solid phase peptide coupling sequence was previously reviewed in **Scheme 4.4** and **Scheme 4.5**, respectively. *Epi*-micromide by completed by sequentially converging three key intermediates (**Scheme 8.1**); First, resin-tethered **8.1a** was elongated to pentapeptide fragment **8.1b** then while still on solid phase was joined by DCC-mediated coupling with (*R*)-3-methoxy-hexanoic acid (**8.4**) followed by cleavage from solid support (**8.5**, 66 mg, 11.5% overall yield) and consequent PyBroP-mediated coupling with Thz-*N*-Me-Gly **8.7** to produce *epi*-micromide (**8.8**) in 65% yield over the final convergent coupling. *Epi*-micromide (**8.8**) constructed on solid support was spectroscopically identical to our previous solution phase synthesis and literature reports (See *Appendix* for spectra).[55]

Generally, (*R*)-3-methoxy-hexanoic acid (**8.4**) was prepared (98:2 dr) via conjugate monosilylzincate or monosilylcuprate addition to a chiral α,β-unsaturated carbonyl compound **8.1** in a method to use the phenyldimethylsilyl group as a masked hydroxyl group (**8.2** to **8.3**) that was methylated and unveiled thru auxiliary cleavage.[99,100] Thz-*N*-Me-Gly[101] **8.7** was produced via modified Kempf *et al*.[102] reductive amination of thiazole-2-carbaldehyde with CH_3NH_3Cl in aqueous NaOH and formed imine **8.6**, then subsequently reduced (solvent-free with mortar and pestle) by boric acid/sodium borohydride and refluxed in MeOH to produce thizole-methylamine fragment **8.7** in 52% yield over the previous three steps.[103]



Scheme 8.1 Total synthesis of *epi*-micromide via sold support.

In order to revise the absolute stereochemistry of micromide the corrected structure could be synthesized through systematic variations of the seven proposed stereocenters; however, this approach would require making over 5,000 diastereomeric combinations. Conceptually, the "split-pot" synthesis of the peptide portion of micromide would be fairly practical on solid support, although arduous and needless to say non-scientific. Our investigation was prioritized by mapping the ^{13}C NMR shifts of synthetic *vs*. natural micromide on a simple Excel spreadsheet algorithm (**Figure 8.3**). Interestingly, carbon C35 and C36 (both related to *L*-Phe moiety) deviated most from natural micromide by 50.10 ppm vs. 52.78 ppm and 36.90 ppm vs. 35.69 ppm, synthetic *vs*. natural, respectively. It was hypothesized that inverting the C35 stereocenter would solve the true structure of micromide. These chemical studies are currently underway in our laboratory.[56]

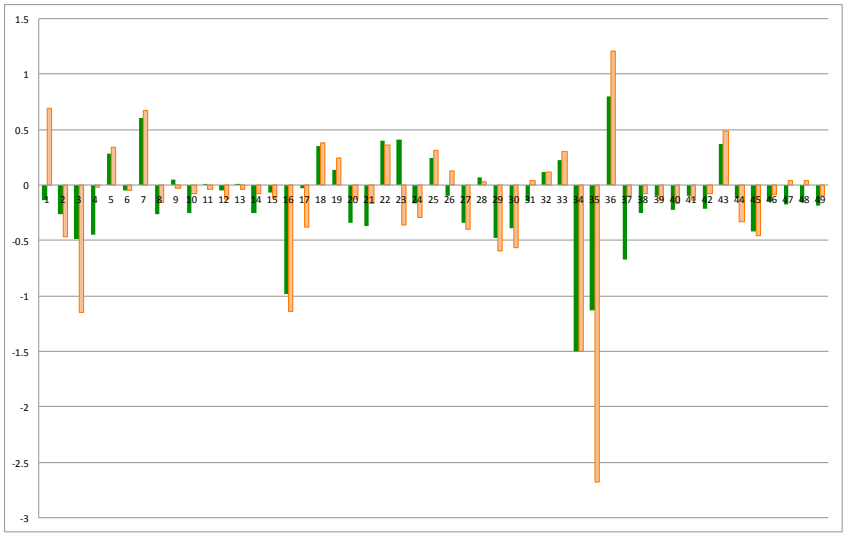


Figure 8.3 Standard deviation of natural (green) vs. synthetic (orange) ^{13}C-NMR shifts.

8.5 Conclusion

The reported spectrum of micromide was not equivalent to that of synthetic micromide, even though LCMS data demonstrated the correct molecular weight. *Epi*-micromide was synthesized in >1% overall yield (103 mg) via solution phase methodology and 7.5% overall yield (50 mg) via solid support methodology. The most questionable stereocenter was computationally determined and hypothesized that inversion of C35 would reveal the corrected structure for micromide. The chemical studies disclosed in this chapter are currently underway.

Special acknowledgement goes to graduate students Lee Wang[56] and Isabelle Nevchas[104] who have focused their thesis research on the total synthesis and stereochemical revision of micromide.

9 Preliminary Studies Toward the Total Synthesis of Azaspirene

9.1 Introduction

Azaspirene was first isolated from the soil fungus *Neosartorya sp*. by Osada *et al*.[105] Azaspirene was reported to inhibit endothelial migration (VEGF) with an ED_{100} of 27.1 uM and inhibited angiogenesis without any signs of hemorrhage or thrombosis in chicken chorioallantoic membrane (CAM) assay.[106] In general, tumor growth, progression and metastasis are dependent on angiogenesis vindicating azaspirene as an important potential therapeutic.[107]

9.2 Previous works

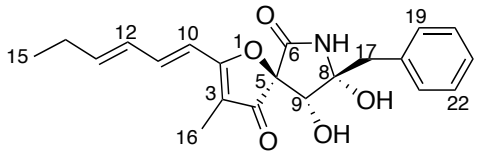
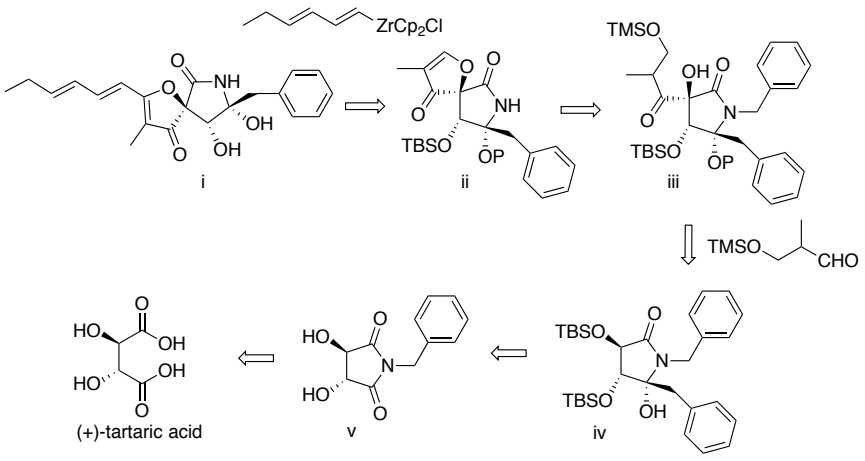


Figure 9.1 Structure of azaspirene.

Previous syntheses of azaspirene were excellent achievements; however, complicated undertakings that generally required lengthy amounts of cumbersome linear steps. Hayashi *et al*.[108] completed azaspirene from methyl-2-pentenoate in 2.2% overall yield. Aoki *et al*.[109] completed azaspirene from *D*-glucose in 33 linear steps.

9.3 Retrosynthetic strategy for azaspirene

Our retrosynthetic strategy for azaspirene (i) was routed through the γ-lactam spirocyclic core (ii), created via intra-molecular cyclization of (iii), that would be directly conjugated by methods developed in our laboratory to afford azaspirene (i) in one scalable step (**Scheme 9.1**).[110,111] Two of the three total stereocenters in azaspirene were represented in the natural chirality of *L*-(+)-tartaric acid, thus a series of amine condensation, hydroxyl protections and Grignard reaction presented a key intermediate (iv) en route to a total synthesis of azaspirene from advantageous, economical starting material.

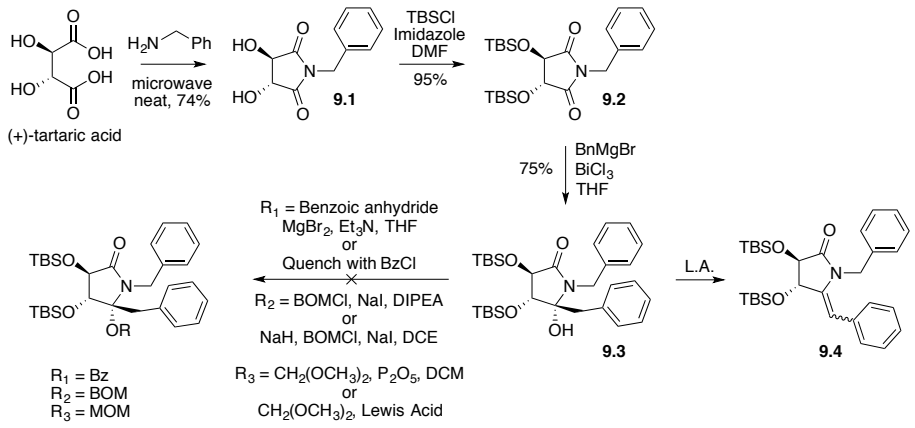


Scheme 9.1 Retrosynthetic strategy for azaspirene from (+)-tartaric acid.

9.4 Results and discussion

L-(+)-Tartaric acid was cyclized in neat benzyl amine via microwave irradiation and produced succinimide **9.1** in 74% yield (**Scheme 9.2**). Succinimide **9.1** was completely protected with TBS-Cl and imidazole to form *L*-*O*-TBS-*N*-benzyl-tartarimide

9.2 in 95% yield.[112] TBS protected tartaimide **9.2** was reacted with benzyl magnesium bromide in THF to produce a roughly 1:1 (*syn:anti*) mixture of **9.3** in 74% combined yield. Due to the C^2-symmetry of **9.2** only two diastereomers of **9.3** were possible.[113] Diasteromers were easily resolved by silica gel chromatography and the undesired *anti*-**9.3** product was unambiguously resolved via X-ray crystallography. Several Lewis acids were surveyed for increased reactivity of the moderately electron rich imide and impart chelation-controlled stereoselectivity.[114,115] Bismuth (III) chloride optimized this addition to a 4.3:1 ratio of *syn:anti* diastereomers in nearly quantitative yield (75% isolated yield of pure *syn*-**9.3**). Several tertiary alcohol (**9.3**) protections were attempted.[116–118] Unfortunately, our exhaustive methods were met with non-reactivity or dehydrated enamine compound **9.4**, a molecular sink that could not be effectually applied towards the synthesis of azaspirene. Furthermore, the α-hydrogen in **9.3**/**9.4** was electronically unfavorable to remove and hampered any hope of aldol addition following our retrosynthetic strategy.



Scheme 9.2 Preliminary studies towards the synthesis of azaspirene.

9.5 Conclusion

Preliminary studies were conducted towards the asymmetric synthesis of azaspirene. The natural chirality of *L*-(+)-tartaric acid was successfully utilized in the substituted lactam scaffold of azaspirene; however, the labile alcohol (**9.3**) was unreactive towards mild conditions or dehydrated by standard protection protocol. Overall, the single diastereomer of lactam **9.3** was constructed in 53% yield over three steps. Alternative advances towards the spirocyclic core of azaspirene are currently underway in our laboratory.

Special acknowledgement goes to graduate students David Schmit,[119] Tim Montgomery[120] and Michael Kelly[121] who have focused their thesis work on the total synthesis of azaspirene and are slated to report their findings in due course.

10 Future Work

10.1 The future of lagunamide A

The total synthesis of lagunamide A was completed in as little as 14 steps and in 5% overall yield, a drastic improvement from previous reports (**Chapter 3 & 5**). With proficient access to synthetic lagunamide A, our group intended to discover the corresponding binding protein in various cell lines and aid in determination of the mechanism for inhibition. Construction of biosensors (**Chapter 7**) is an integral strategy for elucidating the mechanism of action for bioactive compounds. The Bergdahl lab is also interested in structure activity relationships, made accessible via our synthetic route, that would be accelerated and eventually computationally driven, once the binding pocket and mode of action for lagunamide A had been further explored.

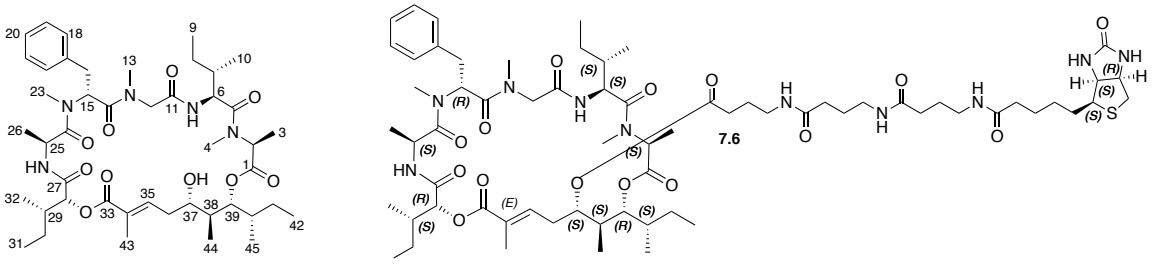
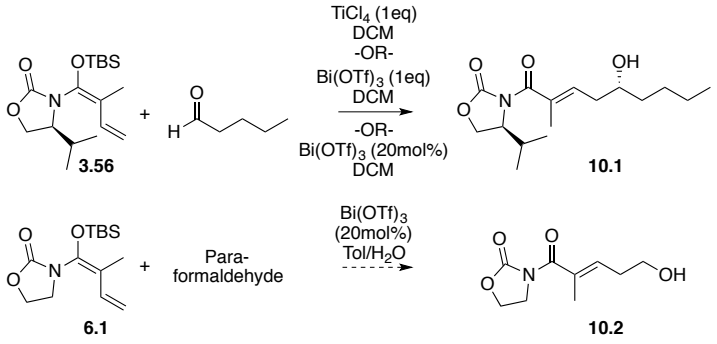


Figure 10.1 Structure of lagunamide A and derivatized biosensor.

10.1.1 Chemical studies toward catalytic Lewis acids in VMAR methodology

Along our completed total synthesis of lagunamide A, various Lewis acids were surveyed for substrate tolerance and reactivity similar to orthodox titanium (IV) chloride.

One major detriment in Kobayashi's protocol for VMAR was stoichiometric coordination of $TiCl_4$. Unfortunately, our research[86] did not discover any reagents superior to $TiCl_4$ for our specific, complex aldehyde compounds; however, it was ascertained that bismuth (III) trifluoromethanesulfonate produced the corresponding aldol product **10.1** (42% isolated yield) via "remote-1,7" addition of VMAR **3.56** with valeraldeyde (**Scheme 10.1**). $Bi(OTf)_3$ has shown tremendous utility in organic chemistry, and was developed specifically for classical Mukaiyama aldol reactions in water.[122–124] We attempted the VMAR addition of **3.56** with valeraldehyde and catalytic loading of $Bi(OTf)_3$ to discover that roughly the same amount of aldol product **10.1** was produced (37% isolated yield). Conceptually, we envisioned "green" chemistry that would produce vinylogous Divergolide C, D and Hygrocin A moieties (**10.2**), a class of anti-bacterial ansa-macrolides isolated from *Streptomyces sp*.,[125] from catalytic amounts of $Bi(OTf)_3$, achiral VMAR **6.1** and paraformaldehyde in water, where the heterogeneous catalyst[126] could be filtered from the reaction and reused akin to previous "green" adaptation of aqueous wittig chemistry developed in our lab.[127]



Scheme 10.1 Chemical studies towards catalytic VMAR methodology.

To our knowledge, stoichiometric $TiCl_4$ has been the only Lewis acid reported for Kobayashi's VMAR protocol in the literature. $Bi(OTf)_3$ represented a novel development with unprecedented application and catalytic loading. Development of this method would prove more economical and potentially tolerant to more functional groups with milder reaction conditions, showcased by the proposed synthesis of Divergolides C, D and Hygrocin A vinylogous aldol fragments.

Special acknowledgement goes to graduate students Lee Wang[56] and Arielle Kanner[86] who have focused their thesis work on chemical synthesis regarding the lagunamide A project and vinylogous Mukaiyama aldol reactions.

10.2 The future of micromide

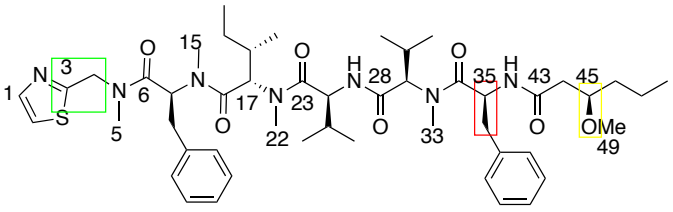


Figure 10.2 Proposed structure of micromide and proposed sites for revision.

We determined that the proposed structure of micromide was incorrect, reinforced by several chemical syntheses of *epi*-micromide. We also determined the most improbable stereocenter(s) through computational analysis of the ^{13}C NMR chemical shift standard deviations in synthetic *vs.* natural micromide. Future work has resolved to produce the proposed C35-epimer of micromide and finally revise the absolute stereochemistry. This research is underway in our laboratory and will be reported in due

course. If C35 is not the incorrect stereocenter, or there are further revisions necessary, a "split-pot" solid phase methodology (**Figure 10.3**) towards micromide becomes more viable approach. Also, the growing library of micromide epimers produced in the Bergdahl lab will be tested for bioactivity.

Special acknowledgement goes to graduate student Lee Wang[56] has focused his thesis research on the total synthesis and stereochemical revision of micromide.

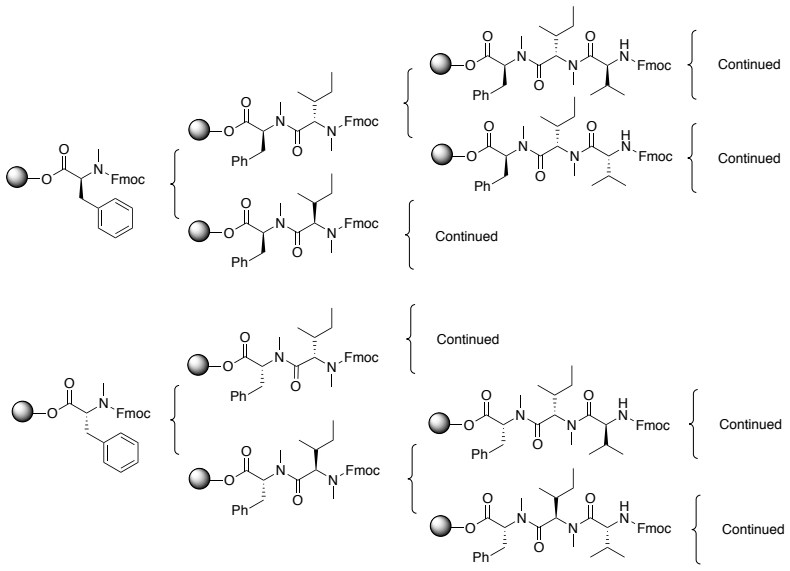


Figure 10.3 "Split-pot" approach towards micromide via solid support.

10.3 The future of azaspirene

Our preliminary studies towards the total synthesis of azaspirene revealed that access toward the lactam core via (+)-tartaric acid was fruitful; however, derivatization of the cyclic core towards the desired 1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione skeleton was impeded by undesired reactivity of corresponding tertiary C8-hydroxyl (**Figure**

10.4). Specifically, we proposed later stage introduction of the C8-benzyl group and synthesis of a lactone core that would allow for electronically favorable enolate formation. Alternative routes towards the total synthesis of azaspirene are currently underway in our laboratory.

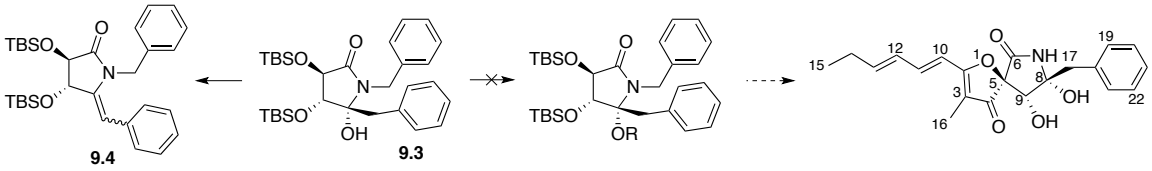


Figure 10.4 Chemical studies towards azaspirene.

Special acknowledgement goes to graduate students David Schmit,[119] Tim Montgomery[120] and Michael Kelly[121] who have focused their thesis work on the total synthesis of azaspirene and will report their findings in due course.

11 Experimental section

11.1 Chemicals and instruments

General. Melting points were recorded on Thomas Hoover Uni-Melt capillary melting point apparatus. Optical rotations were recorded on Perkin Elmer Model 343 polarimeter. IR spectra were recorded on Perkin Elmer FT-IR spectrum RXI. ^{1}H NMR spectra were recorded on a Varian 400, 500, and 600-MHz instrument using $CDCl_3$ or DMSO-d^6 with TMS as internal standard (δ = 0 ppm). $CDCl_3$ (δ = 77.00 ppm) or DMSO-d^6 (δ = 39.52 ppm) was used as internal references for ^{13}C (100, 126 and 151 MHz) NMR. Preparative HPLC was carried out using Shimadzu SCL-10A/SPD-10A instrument with preparative Varian pursuit 10 C8 50-G 50mm column. Mass spectra were recorded using a Thermo Finnigan LCQ Deca, Agilent 6330 ion trap or an APCI Expressions instrument. High-resolution mass spectra were recorded using the Agilent 6230 ESI-TOFMS. Analytical thin-layer chromatography was performed on Silicycle glass backed 60Å ultra pure silica gel. Flash chromatography was conducted using a Biotage Isolera one instrument with pre-packed silica gel columns (AnaLogix, Sepra Si 50) or self-packed Luknova and Biotage snap columns filled with silica gel (Sorbent Technologies, 60Å, 230-400 mesh). All reactions were conducted under an argon atmosphere and in septum-capped oven-dried glassware unless otherwise specified. All solvents and reagents were purchased from Aldrich, Fisher Scientific, Combi-blocks, TCI America, Chem Impex or Oakwood Scientific.

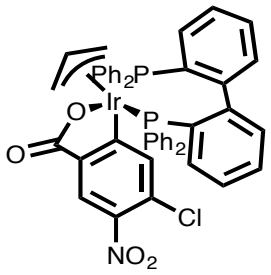
Chemicals. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium-benzophenone ketyl and were collected when the indicator became deep blue or purple under inert argon atmosphere. Methylene chloride was distilled from calcium hydride under water free atmosphere. All reagents and solvents were purchased from Aldrich or Fisher Scientific unless otherwise specified.

11.2 Complex reagent preparation

We met several circumstances where complex reagents were available for purchase; however, as synthetic chemists we were inclined to prepare these compounds from more affordable starting material. The following includes protocols for complex reagent synthesis that were alternatively available for purchase.

Preparation of (S)-2-methyl-butanal (3.1):[41] 125 mL of household bleach (2.2 equiv, 101.7 mmol, NaClO) was adjusted to pH 9 with $NaHCO_3$(s). A 250 mL flask was charged with (S)-2-methyl-butanol (5 mL, 46.23 mmol), KBr (0.550 g, 4.623 mmol), TEMPO (0.072 g, 0.4623 mmol) in 17.5 mL DCM: 5 mL DI H2O and stirred at -10 °C. The NaClO solution was added in three equal portions over 10 min, the reaction turned yellow and ultimately dark red. Reaction mixture was quenched within 15 min as a pale yellow solution by separating phases and extracting 3 x 20 ml DCM, then the combined phases were washed with 40 ml 10% HCl/KI (0.154 g, 0.9246 mmol), then 50 ml 10% NaS_2O_4, washed 50 ml H_2O then finally dried over Na_2SO_4. The mixture was filtered and evaporated lightly to ~18 ml and determined aldehyde molarity in DCM via ^1H NMR. Mixture was stored over Na_2SO_4 in the freezer or used immediately.

Preparation of dibutylboryl trifluoromethanesulfonate:[128] Trifluromethane-sulfonic acid (1.0 mL, 1.01 equiv) added to tributylborane (1 equiv) and the reaction mixture was raised to 50 °C in a distillation apparatus under argon. The balance of triflic acid was added dropwise and stirred 30 min. The boryl triflate was isolated in 80-90% yield via short path distillation (bp 60 °C @ ~2.0mmHg).



Preparation of achiral iridium-catalyst complex (3.15a):[21] To a mixture of $[Ir(cod)Cl]_2$ (30 mg, 1 equiv), achiral diphenylphosphino-biphenyl (47 mg, 2 equiv), cesium carbonate (58 mg, 4 equiv), 4-chloro-3-nitrobenzoic acid (36 mg, 4 equiv) and allyl acetate (24 uL, 5 equiv) in a sealed tube under argon was added 0.9 mL anhydrous THF. Reaction mixture was stirred 30min at ambient temperature, then heated to 80^{o}C for 1.5 hr then equilibrated to ambient temp. Reaction was filtered and washed with 2 mL THF then diluted with 50 mL hexanes and sonicated for 5min, collected by filtration and dried under reduced pressure to afford 83 mg of yellow powder in 73% yield.

Preperation of allylmagnesium bromide solution:[129] Oven dried flask was charged with activated magnesium turnings (0.555 g, 2 equiv) then suspended in 15.0 mL dry ether and cooled to 0 °C. Allyl bromide was added dropwise while equilibrated to

ambient temperatures and stirred 1 hour at room temperature. Resulting solution was fluid grey with excess magnesium metal (expect ~0.5M from ~50% conversion).

Preparation of Dess-Martin Periodinane:[130] 2-iodobenzoic acid (40 mmol, 1 equiv) was mixed with 400 mL DI H_2O and slowly heated to 70 ^oC and stirred 1 hr. A mixture of oxone (120 mmol, 3 equiv) in 100 mL water was added slowly and stirred another 1 hr at 70 °C, then equilibrated to ambient temperatures overnight. Reaction mixture was cooled to 0 °C then IBX was filtered and washed with 6 x 25 mL DI water then acetone 2 x 25 mL. The filtrate was quenched with 14 g Na_2SO_3(s) and neutralized with aq. NaOH. IBX crystals were dried in vacuum dessicator overnight (Caution, explosive!). Crude crystals were then slowly suspended in acetic anhydride (27 mL) and acetic acid (23 mL) under argon atmosphere. Fitted condenser and slowly heated to 85 °C and stirred 1.5 hr. Cooled ambient temperatures and recrystallized at ambient temperatures overnight so that crystals were filtered and washed with dry ether 4 x 25 mL and lightly HI-VAC or vacuum desiccator concentrated to dryness, roughly 80% yield white crystalline solid.

Preparation of trimethyltin hydroxide:[131] Trimethyltin hydroxide was obtained by reacting $SnMe_3Cl$ (1 equiv, caution toxic!) with KOH (1 equiv) ($SnMe_3Cl$:KOH 10:3 w/w%) in 1.0 mM methanol then filtered off KCl precipitate. $SnMe_3OH$ was evaporated to dryness in 87% yield as white powder.

Preparation of MNBA:[132] 2-methyl-6-nitrobenzoic anhydride (MNBA) was obtained by first dissolving 2-methyl-6-nitrobenzoic acid (2.50 g, 1.0 equiv) in 40.0 mL dry DCM under argon at room temperature followed by dropwise addition of oxalyl

chloride (1.30 mL, 1.1 equiv) and DMF catalyst (100 uL, 0.1 equiv) and stirred 1 hr to produce the corresponding acid chloride that was used crude in the subsequent reaction.[133] Crude acid chloride (1.0 equiv) and 2-methyl-6-nitrobenzoic acid (2.50 g, 1.0 equiv) were suspended in 20 mL DCM at 0 °C under argon. Added pyridine (1.25 mL, 1.1 equiv) dropwise, equilibrated to ambient temperatures and stirred 24 hours. Quenched with 50 mL cold water, extracted with DCM, washed combined organics with saturated aqueous copper (II) sulfate, saturated aqueous $NaHCO_3$, brine and dried with Na_2SO_4. The mixture was filtered, evaporated and recrystallized from 45 mL DCM in 58% yield as yellowish brown crystals.

11.3 General experimental procedures

General procedure for acetylation of oxazolidinones: *n*-Butyllithium (2.5 M in hexane, 1.01 equiv) was added dropwise to a solution of oxazolidinone (1.0 equiv) in anhydrous THF (~ 0.5M) at –78 ºC under argon. The resulting mixture was stirred for 15 min and then freshly distilled acid chloride (1.0 equiv) in dry THF was added via cannula at –78 ºC, dropwise. The reaction was stirred for an additional 45 min at –78 ºC and then warmed to ambient temperature. Saturated aqueous ammonium chloride was added and the resulting mixture stirred for 30 min. The solvent was removed under reduced pressure and the remaining aqueous phase transferred to a separation funnel. The aqueous phase was extracted with DCM, the combined organics were washed with 3.0 M NaOH, water, brine, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crude product was purified with silica gel flash chromatography in ethyl acetate and hexanes in high yield, generally as a white solid.

General procedure for ozonolysis of alkenes: A solution of alkene (1.0 equiv) in anhydrous CH_2Cl_2 (~ 0.1M) 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. Consuption of starting material was confirmed via TLC. 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 completely faded. Excess dimethyl sulfide (5.0-20.0 equiv) were then added dropwise over 5 min at –78 ºC. The temperature was then equilibrated to ambient temperature and the mixture stirred an additional 12 hours. (Non-aqueous workup) The solvent was removed under reduced pressure and the remaining crude product was purified on a silica gel plug (ethyl acetate in hexanes, generally 0–15% as a gradient) to afford aldehydes, largely as clear oil and in near quantitative conversion and isolated yield. Alternatively, when alpha-stereochemistry was inconsequential, another method was employed by the same setup previously described and spiked with the organocatalyst pyridine (3 equiv) to orchestrate an *in situ* reductive workup. Crude products can be easily concentrated and purified on silica gel.[134]

General procedure for VMAR:[9] To a stirred solution of aldehyde (1.0 equiv) in toluene or DCM (~ 1.0-2.0M) at –78 ºC under argon was slowly added $TiCl_4$ (neat or 1.0M solution, 1.01 equiv). The reaction mixture was stirred for 20 min at –78 ºC and a solution of vinylketene silyl *N,O*-acetal (1.25-5.25 equiv) in toluene or DCM at –78 ºC was added dropwise over 10 min via cannula and stirred. Optionally, the reaction was sped with addition of 10 mol% deionized water at –78 ºC. The resulting reaction mixture was then stirred at -78^{o}C providing a dark violet to heterogeneous, dark orange reaction

mixture (toluene) or orange solution in (DCM). After the 24-72 hour reaction time and confirmation by TLC (or optionally, oscillating temperatures of –78 ºC and –40 ºC, switching every 12 hours for a total of 72 hours) a mixture of saturated aqueous Rochelle salt and saturated aqueous $NaHCO_3$ was added (1:1) at -40 ºC. The mixture was then stirred vigorously at ambient temperature until the resulting slurry became homogeneous and then transferred to a separation funnel. The aqueous phase was extracted with ethyl acetate (4x) and the combined organic phases were washed with water followed by brine. The organic phase was then dried over anhydrous sodium sulfate. After filtration the solvent was removed under reduced pressure and the remaining crude product was purified with flash chromatography using ethyl acetate in hexanes (0–35%) gradient to give aldol product with great selectivity in good (48-99%) yield as clear oil.

General procedure for silyl ether protection of hydroxyl:[135] Congested hydroxyl substrate was dissolved in DCM (~1.0M) under argon at 0^oC and added freshly distilled 2,6-lutidine (4 equiv) then TBSOTf (2 equiv) dropwise and stirred equilibrating to ambient temperatures overnight hours. Quenched with 25 mL water, extracted DCM (4x) then washed with 1N HCl, brine and dried with $MgSO_4$. Filtered, concentrated under reduced pressure and crude residue was chromatographed on silica gel with 0-20% ethyl acetate in hexanes to afford silyl-ether in generally high (75-99%) yields.

General procedure for *tert*-butyl and *para*-nosyl protection of amino acids: Amino acid was combined with *tert*-butyl acetate (17.3 equiv) and cooled to 0 °C. $HClO_4$ (1.5 equiv) was cautiously added dropwise with dry-ice condenser fitted on top of the reaction apparatus and stirred for 5-8 hours. Mixture was neutralized with saturated

aqueous sodium carbonate and aqueous phase was extracted with DCM. Organics were extracted with 2% HCl (5x) then basified with solid Na_2CO_3. Resultant aqueous phase was extracted with DCM to afford the free amine, dried with Na_2SO_4 and then used without further purification (generally near quantitative yields). Crude substrate was dissolved in DCM (~1.0M) with drying tube fitted fask cooled to 0°C. Et_3N (2 equiv) was added dropwise then 4-nitrobenzenesulfonyl chloride (1.01 equiv) portion-wise. Equilibrated to ambient temperatures and stirred overnight hours. Diluted with minimal DCM then washed organics with 1% HCl, 5% Na_2CO_3, brine and dried over $MgSO_4$. Filtered, evaporated and chromatographed with 50% ether/pentane over silica gel column to produce, generally yellowish-white crystals in high yield (>75% yield).

General procedure for *N*-methylation of *t*-butyl and *p*-Ns protected amino acids: Nosylated amine **207** (1.0 equiv, 5.0 mmol) and K_2CO_3 (2.1 equiv, 10.5 mmol, 1.45 g) was dissolved in DMF at 0 °C under argon. After 10 minutes of stirring, iodomethane (3.2 equiv, 16 mmol, 2.27 g) was added dropwise to the solution via syringe and the reaction was stirred at ambient temperature overnight. The next day, the reaction was washed with water and CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated. 50% Et_2O/pentane on a silica gel column gave 86 – 99% product.

General procedure for *para*-nosyl amine deprotection: Mercaptoethanol (1.5 equiv, 7.5 mmol, 0.53 mL) was added to amine **208** (1.0 equiv, 5.0 mmol) and K_2CO_3 (2.0 equiv, 10 mmol, 1.38 g) in 20 mL DMF and 1 mL water at 0 ºC. The reaction mixture was subsequently stirred at ambient temperature overnight (15 hours). The crude reaction mixture was then washed with two times water and EtOAc, dried over $MgSO_4$,

filtered and concentrated. Silica gel column with 10-50% Et_2O/CH_2Cl_2 (0.1% triethylamine was added if the product streaked off of the column) provided 78-95% product with out further purification.

***tert*-Butyl ester Deprotection reactions**: To the *N*-nosylated-*t*-butyl-ester (1.0 equiv, 5.0 mmol) in CH_2Cl_2 was added TFA (13 equiv, 65 mmol, 4.83 mL) dropwise at 0 ºC. The reaction was stirred at ambient temperature overnight. The next day, the reaction was washed with water then the organic layer was extracted with 1.0 M NaOH. The combined aqueous layers were acidified with HCl to pH 0 and subsequently extracted two times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The product was pure enough to use in the next step (>95% purity).

General procedure for solution phase peptide coupling:[136,137] To acid (1.2 equiv, 6.0 mmol) dissolved in 5 mL CH_2Cl_2 was added oxalyl chloride (2.0 equiv, 10 mmol, 0.86 mL) and DMF (0.1 equiv, 0.5 mmol, 0.1 mL) at 0 ºC. The mixture was warmed to ambient temperature and stirred or 2 hours. The reaction was concentrated *in vacuo* and freshly distilled CH_2Cl_2 was added to the flask and evaporated again. The flask was pumped on vacuum for 1 hour then used in one of the two following procedures. *Preferred Method: Coupling via Triethylamine and Acid Chloride:* The acid chloride was dissolved in 5 mL THF. To the solution was added amine (1 equiv, 5 mmol) and triethylamine (2 equiv, 10 mmol, 1.39 mL) and the reaction was stirred overnight. The next day, the reaction was washed with CH_2Cl_2 and water, followed by 1N NaOH. The organic layer was dried over $MgSO_4$, filtered and concentrated.

Purification via silica gel column using 30% Et_2O/pentane gave 75 – 95% product. *Alternate Route: Shotten-Baumann Approach*: The acid was dissolved in CH_2Cl_2 and water before the addition of amine (1 equiv, 5 mmol) and K_2CO_3 (2 equiv, 10 mmol, 1.38 g). The reaction was stirred vigorously at ambient temperature overnight. The next day, the reaction was washed with CH_2Cl_2 and water, followed by 1N NaOH. The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification via silica gel column using 30% Et_2O/pentane gave 65 - 68% product.

General procedure for preparation of ylides:[138] A mixture of PPh_3 (1.0 equiv) and methyl-2-bromopropionate (1.0 equiv) in 40.0 mL water was stirred 24 hrs at 70 °C. Mixture was cooled to ambient temperature then solution of NaOH (6 M) was added, stirred 10 min then added DCM until solid dissolved. Organic layer was separated and aqueous layer was extracted 2 x DCM, concentrated, triturated with hexanes and filtered. The resulting solid was dried *in vacuo* to provide pale yellow or white solid ylide in generally high 75-85% yields.

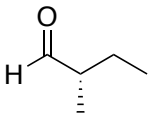
General procedure for Fmoc-protection of amino acids: Dissolved Na_2CO3 (2 equiv) in DI H_2O (6.5% w/w) and cooled to 0 °C then suspended/dissolved the free amino acid in solution, stirred and added Fmoc-OSu (0.83 equiv in 10% w/w H_2O) dropwise over 15 min. Mixture was removed from ice bath and stirred 1 hr, then acidified to pH 2 with 6M HCl and extracted with EtOAc and dried over Na_2SO_4. Evaporated to 1/10 of the original volume and recrystallized in petroleum ether and EtOAc to afford white solids in generally high yield >90% yields.

General procedure for *N*-methylation of Fmoc-protected amino acids: Fmoc-protected amino acid was refluxed in touene (Dean-Stark) with catalytic *p*TsOH (0.12 equiv) and an excess of paraformaldehyde (>10 equiv) for 1 hour. Mixture was washed with $NaHCO_3$ 3 x 100 mL and dried over $MgSO_4$. The mixture was filtered, concentrated *in vacuo* and chromatographed via silica gel column (EtOAc in hexanes). The corresponding cyclic oxazol-compound was dissolved in DCM with TFA (4:1) and added Et_3SiH (1.4 equiv) and stirred 14 hrs prior to evaporation, extraction with EtOAc, washed with water, dried over Na_2SO_4. The mixture was filtered, concentrated then chromatographed over silica gel (EtOAc in hexanes) column or reversed phase prep-HPLC (5-95% ACN in 0.1% formic acid H_2O).

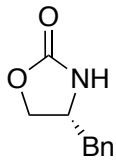
General procedure for solid phase peptide coupling: *Coupling to resin*: CTC resin (1 equiv) was loaded into syringe with DCM and Fmoc-protected amino acid (1.2 equiv) and charged with DIPEA (2.5 equiv) and incubated with gentle shaking overnight. The reaction was capped with MeOH wash then dried win vacuum desiccator. ***Solid phase coupling reactions***: A few beads may be removed to perform chloranil test. After storage *in vacuo*, the resin was stirred in 20% piperidine/DMF for 1 hr then wash 3 x DMF and 3 x DCM. Dissolved Fmoc-protected amino acid (3.0 equiv) to be coupled in minimal DMF and added to syringe alongside HOAt (3.0 equiv) followed by DIC (3.0 equiv) and tirred 6 hours. Flushed with resin rinse in DMF, then 10% Ac_2O/pyridine for 10 min, washed 3 x DMF then 3 x DCM. Iterations of this protocol were used to elongate the peptide chain length. ***Cleavage from solid support***: Beads were swelled with DCM then trated with 95% TFA/DCM for 30 min then filtered off and washed with near TFA.

The filtrate was slowly added to cold MTBE (8-10 ml MTBE per 1 mL filtrate) and either recrystallized or chromatographed via silica gel column or prep-HPLC as white or pale yellow solids.

11.4 Methods & compounds characterized

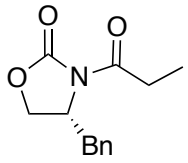


(*S*)-2-methyl-butanal (3.1):[41] Title compound was prepared from (*S*)-2-methyl-butanol via the complex reagent synthesis protocol to afford aldehyde **3.1** (3.48 g in 14.83 mL DCM, 93% yield); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.61 (dd, *J* = 1.9, 0.5 Hz, RCHO, 1H), 2.26 (hd, *J* = 6.9, 2.0 Hz, R_3CH, 1H), 1.79 – 1.69 (m, RCH_2R, 1H), 1.49 – 1.37 (m, RCH_2R, 1H), 1.08 (dd, *J* = 7.0, 0.5 Hz, RCH_3, 3H), 0.94 (td, *J* = 7.5, 0.5 Hz, RCH_3, 3H).

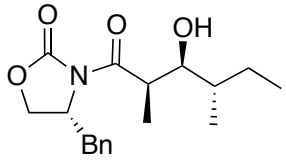


(*R*)-4-benzyloxazolidin-2-one (3.3):[139] D-phenylalanol **3.2** (0.149 mol, 1.0 equiv) charged flask was added 47 mL diethyl carbonate (0.388 mol, 2.6 equiv). To resultant slurry was added potassium carbonate (0.015 mol, 0.1 equiv) and reaction was fitted with a condenser and mixed at 110 °C overnight. Contents transferred to separation funnel and extracted with DCM (3 x 75 mL) then washed combined organics with brine (50 mL) and dried over sodium sulfate. Crude residue was concentrated *in vacuo* and chromatographed on a silica gel column (30-50% ethyl acetate in hexanes gradient) to afford white crystalline solid **3.3** (21.98 g, 75% yield); ^{1}H NMR (400 MHz, Chloroform-

d) δ 7.37 – 7.24 (m, Ar-H, 4H), 7.18 – 7.16 (m, Ar-H, 1H), 5.58 (s, NH, 1H), 4.45 (ddd, *J* = 8.6, 7.9, 0.7 Hz, NR_2CH, 1H), 4.18 – 4.03 (m, OCH_2R, 2H), 2.88 (d, *J* = 6.8 Hz, RCH_2Ph, 2H).

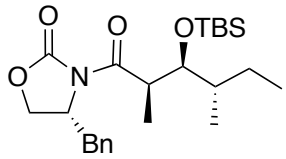


(*R*)-4-benzyl-3-propionyloxazolidin-2-one (3.4):[140] Title compound was prepared by general procedure for acetylation of oxazolidinones. Crude products were pulverized and triturated with excess cold hexanes to afford colorless white **3.4** crystals (3.209 g, 82% yield); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.31 (m2H), 7.30 – 7.27 (m, , Ar-H, 1H), 7.23 – 7.19 (m, , Ar-H, 2H), 4.72 – 4.62 (m, NR_2CH, 1H), 4.24 – 4.12 (m, OCH_2R, 2H), 3.31 (dd, *J* = 13.4, 3.3 Hz, RCH_2Ph, 1H), 3.06 – 2.87 (m, RCH_2R, 2H), 2.78 (dd, *J* = 13.4, 9.6 Hz, RCH_2Ph, 1H), 1.21 (td, *J* = 7.3, 0.5 Hz, RCH_3, 3H).

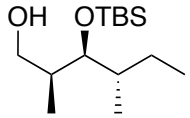


(*R*)-4-benzyl-3-((2*R*,3*S*,4*S*)-3-hydroxy-2,4-dimethylhexanoyl) oxazolidin-2-one (3.5):[16] Dissolved **3.4** (250 mg, 1.07 mmol) in 3 ml DCM and cooled to 0 °C followed by dropwise addition of dibutylboron triflate (353 mg, 1.29 mmol), then dropwise addition of Et_3N (0.210 mL , 1.50 mmol) and stirred for 10 min. Cooled -78 °C. Added (S)-2-methyl-butanal (**3.1**) (0.126 mL, 1.18 mmol) dropwise, stirred 30 min, then warmed to 0 °C and stirred 2 hrs. Quenched reaction in 1.5 mL pH 7 phosphate buffer and 4.5 mL MeOH, then added 4.5 mL of a 2:1 methanol: 30% H_2O_2 mixture and stirred and additional 3 hrs. Crude products were concentrated *in vacuo* then extracted 3 x 8 mL

ether, washed with 8 mL 5% sodium bicarbonate then 8 mL brine and dried over $MgSO_4$. Residue was purified over 15 g silica gel column (20-80% ethyl acetate in hexanes gradient) to afford clear, viscous oil **3.5** that crystallized over the next 3 days (302 mg, 88% yield); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.31 (m, Ar-H, 2H), 7.31 – 7.27 (m, Ar-H, 1H), 7.23 – 7.18 (m, Ar-H, 2H), 4.70 (ddt, *J* = 9.4, 7.5, 3.2 Hz, R_2CHR, 1H), 4.27 – 4.16 (m, R_2CHAr, 2H), 3.96 (qd, *J* = 7.0, 2.3 Hz, $ROCH_2R$, 1H), 3.63 (ddd, *J* = 9.0, 3.3, 2.3 Hz, $ROCH_2R$, 1H), 3.26 (dd, *J* = 13.4, 3.5 Hz, RC*H*(OH)R, 1H), 2.92 (d, *J* = 3.3 Hz, ROH, 1H), 2.79 (dd, *J* = 13.4, 9.4 Hz, $COCHR_2$, 1H), 1.86 – 1.74 (m, R_2CH2R, 1H), 1.58 – 1.47 (m, R_2CH2R, 1H), 1.23 (d, *J* = 7.0 Hz, RCH_3, 3H), 1.20 – 1.14 (m, R_2CHR_2, 1H), 0.91 (t, *J* = 7.5 Hz, RCH_3, 3H), 0.87 (d, *J* = 6.8 Hz, RCH_3, 3H).

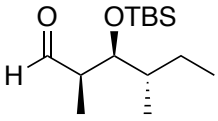


(*R*)-4-benzyl-3-((2*R*,3*S*,4*S*)-3-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethylhexanoyl)oxazolidin-2-one (3.6): Title compound was prepared by general procedure for silyl ether protection of hydroxyl, 300 mg of clear oil; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 (t, *J* = 7.2 Hz, Ar-H, 2H), 7.29 (dd, *J* = 7.6, 3.2 Hz, Ar-H, 1H), 7.22 (d, *J* = 7.4 Hz, Ar-H, 2H), 4.68 – 4.57 (m, R_2CHR, 1H), 4.17 (d, *J* = 4.9 Hz, R_2CHAr, 2H), 4.01 – 3.94 (m, $ROCH_2R$, 1H), 3.28 (dd, *J* = 13.4, 3.2 Hz, RC*H*(OSi)R, 1H), 2.76 (dd, *J* = 13.4, 9.7 Hz, R_2CH2R, 1H), 1.50 – 1.42 (m, RCH_3, 3H), 1.23 (d, *J* = 6.4 Hz, RCH_3, 3H), 0.95 – 0.90 (m, $Si(CH_3)_3$, 12H), 0.87 (t, *J* = 7.2 Hz, RCH_3, 3H), 0.07 (s, $SiCH_3$, 3H), 0.05 (s, $SiCH_3$, 3H).



(2*S*,3*S*,4*S*)-3-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethylhexan-1-ol

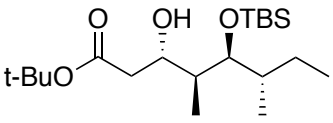
(3.7):[135] DIBAL-H (3.46 mL, 1M in DCM, 3.46 mmol) was added drowise to 3.6 (0.500 g, 1.15 mmol) in 20 ml dry DCM at -78 °C and stirred until equilibrated to ambient temperatures overnight. Mixture was quenched with 15 mL saturated sodium potassium tartrate and stirred for 6 hours. Mixture was extracted 3 x 20 mL DCM and the combined organics were dreid over $MgSO_4$. Purified silica gel column (10% ethyl acetate in hexanes) to afford **3.7** as a clear oil (0.125 g, 79% yield); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.64 (dd, *J* = 5.2, 2.5 Hz, ROH, 1H), 3.58 (ddd, *J* = 10.3, 7.9, 4.9 Hz, RC*H*$_2$OH, 1H), 3.47 (dt, *J* = 10.3, 5.6 Hz, RC*H*$_2$OH, 1H), 1.95 – 1.82 (m, R_2CHOTBS, 1H), 1.71 (t, *J* = 5.3 Hz, $RCHR_2$, 1H), 1.60 – 1.48 (m, RCH_2R, 1H), 1.15 – 1.00 (m, $RCHR_2$, 1H), 0.92 (d, *J* = 2.2 Hz, RCH_2R, 1H), 0.91 (s, $SiC(CH_3)_3$, 9H), 0.92 – 0.86 (m, RCH_3, 9H), 0.08 – 0.05 (m, 2x $SiCH_3$, 6H).



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

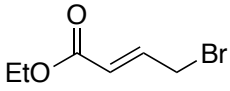
(3.8):[141] Title compound was produced either from **3.6** or **3.7**: In the first method, alcohol **3.7** (0.083 g, 0.336 mmol) was dissolved in 5 mL DCM under argon at room temperature then charged with PDC (0321 g, 0.840 mmol) and stirred overnight. Reaction mixture was diluted with 5 mL ether then filtered solid chromium with silica gel plug and concentrated **3.8** (0.084 g, 90%) as a clear oil without further purification. In the second method, amide **3.6** was treated with DIBAL-H (1 equiv) and stirred for 1 hr under argon. Mixture was quenched with 6 mL sat. ammonium chloride then extracted 3 x 10 mL

DCM, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purified silica gel column (0-10% ethyl acetate in hexanes gradient) to afford 3.8 as clear oil (0.040 g, 68% yield); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.74 (t, *J* = 1.3 Hz, RCHO, 1H), 5.32 – 5.28 (m, $R_2CH(OSi)$, 1H), 4.05 – 3.98 (m, CHOC*H*R_2, 1H), 2.52 – 2.43 (m, RCHR, 1H), 1.50 – 1.39 (m, RCH_2R, 2H), 1.32 – 1.22 (m, RCH_3, 3H), 1.11 (dt, *J* = 7.0, 1.2 Hz, RCH_3, 3H), 0.92 – 0.88 (m, RCH_3, 3H), 0.88 – 0.87 (m, $SiC(CH_3)_3$, 9H), 0.09 – 0.00 (m, 2x $SiCH_3$, 6H).

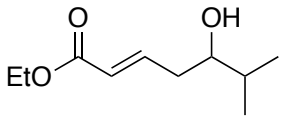


***tert*-butyl (3*S*,4*S*,5*S*,6*S*)-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-4,6-dimethyloctanoate (3.11a):** Aldehyde **3.8** (0.231 g, 0.8509 mmol) was charged with tert-butyl-bromoacetate (0.251 mL, 1.7017 mmol), then $CuCl_2{\cdot}2H_2O$ (0.435 g, 2.5527 mmol) and dissolved in 8 ml dry THF at ambient temperature and stirred under argon atmosphere. Magnesium turnings (0.067 g, 2.7229 mmol) were added in one lot and stirred 14 hrs. Rxn progressed from green to dark brown within the first half hour. Reaction mixture was treated with 8 mL H_2O: 15 mL EtOAc mixture then filtered. Added 20 mL 1N HCl to filtrate and extracted 3 x 15 mL EtOAc. Combined organics were washed with 25 mL brine and dried over Na_2SO_4 then concentrated *in vacuo*. Purified silica gel column (0-25% EtOAc in hexanes gradient) to afford **3.11a** (0.227 g, 72%, 43:57 dr); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.92 (ddd, *J* = 6.2, 3.6, 1.8 Hz, R_2CH(OH), 1H), 3.83 – 3.73 (m, R_2CH(OTBS), 1H), 3.31 – 3.26 (m, RO_2CH_2R, 1H), 2.59 – 2.50 (m, RO_2CH_2R, 1H), 2.32 – 2.22 (m, RCH_2R, 1H), 1.71 – 1.36 (m, tBu, 9H), 1.27 (d, *J* = 3.2 Hz, RCH_3, 3H), 0.95 – 0.84 (m, $SiC(CH_3)_3$ & RCH_3, 12H), 0.84 – 0.79

(m, RCH_3, 3H), 0.11 – 0.05 (m, 2x $SiCH_3$, 6H). ***tert*-butyl (3*R*,4*S*,5*S*,6*S*)-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-4,6-dimethyloctanoate (3.11b):** Purified as described previously on silica gel column (0-25% EtOAc in hexanes gradient) to afford **3.11b** (0.227 g, 72%, 57:43 dr); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.99 – 3.92 (m, R_2CH(OH), 1H), 3.67 (ddt, *J* = 4.9, 3.1, 1.6 Hz, R_2CH(OTBS), 1H), 2.89 (dt, *J* = 3.2, 1.5 Hz, RO_2CH_2R, 1H), 2.43 – 2.38 (m, RO_2CH_2R, 2H), 1.70 – 1.51 (m, RCH_2R, 1H), 1.51 – 1.38 (m, RCH_2R & tBu, 10H), 1.30 – 1.24 (m, RCH_3, 3H), 1.14 – 1.02 (m, $RCHR_2$, 1H), 0.91 – 0.89 (m, $SiC(CH_3)_3$ & RCH_3 & & RCH_3, 15H), 0.08 – 0.06 (m, 2x $SiCH_3$, 6H).

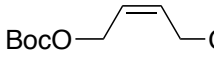


ethyl (*E*)-4-bromobut-2-enoate (3.12):[142] 100 mL RBF cooled under argon and added ethyl transcrotonate (1.00 ml, 8.043 mmol), N-bromosuccinimide (1.446 g, 8.124 mmol), 25 mL CCl_4 and then AIBN (0.013 g, 0.081 mmol) initiator and refluxed for 2 hrs. Filtered through glass frit, washed with DCM and dried over Na_2SO_4. Concentrated and purified via silica gel chromatography (0-10% Et_2O in hexanes gradient) to afford **3.12** (2.117 g, 68.2% yield) as clear, colorless oil; R_f = 0.3, 10% EtOAc/Hex; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.07 – 6.93 (m, C=CHR, 1H), 6.10 – 5.96 (m, C=CHR, 1H), 4.21 (qd, *J* = 7.2, 0.9 Hz, RCH_2R, 2H), 4.02 – 3.99 (m, RCH_2R, 2H), 1.32 – 1.27 (m, RCH_3, 3H).

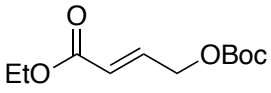


ethyl (E)-5-hydroxy-6-methylhept-2-enoate (3.13): Charged oven-dried flask with Ethyl-4-bromocrotonate **3.12** (0.605 g, 3.134 mmol) then added isobutyraldehyde (0.143 mL, 1.567 mmol) and finally cupric chloride dehydrate (0.801 g,

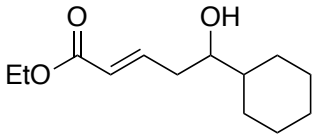
4.701 mmol) and stirred in 10 ml THF under argon atmosphere 10 min. Added magnesium turnings (0.117 g, 5.014 mmol) and stirred 16 hrs. Reaction mixture was treated with 8 mL water: 15 mL EtOAc solution, filtered, washed with EtOAc. Added 15 mL 1N HCl to filtrate and extracted 3 x 10 mL EtOAc, combined organics and washed with brine and dried over sodium sulfate. Concentrated residue was chromatographed via silica gel column (0-30% Et2O in hexanes gradient) to provide the racemic title compound **3.12** (0.178 g, 68.0% yield) as oil; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.86 (d, *J* = 4.7 Hz, C=CHR, 1H), 4.68 (d, *J* = 2.9 Hz, C=CHR, 1H), 4.46 (d, *J* = 7.3 Hz, ROH, 1H), 4.35 (d, *J* = 4.7 Hz, RCH_2OR, 1H), 3.53 (d, *J* = 4.9 Hz, RCH_2OR, 1H), 2.92 (d, *J* = 3.9 Hz, $R_2CH(OH)$, 1H), 2.51 (d, *J* = 7.3 Hz, 1H), 2.20 (d, *J* = 2.9 Hz, R_3CH, 1H), 1.95 – 1.74 (m, RCH_2R, 2H), 1.07 (s, CH_2CH_3, 3H), 0.90 (d, *J* = 2.3 Hz, $CHCH_3$ x 2, 6H).



(*Z*)-but-2-ene-1,4-diyl di-*tert*-butyl bis(carbonate) (3.14a): To 250 mL oven-dried RBF was added Bu_4NHSO_4 (1.726 g, 5.084 mmol) and then charged with *cis*-2-butenediol (2.46 ml, 29.909 mmol) and the mixture was dissolved with 35 mL 23.9 w/v% NaOH solution (6N) and 75 mL DCM. Boc_2O (17.362 g, 79.550 mmol) was added as solid and reaction mixture stirred at ambient temperature 40 hrs. Reaction transferred to sep funnel, diluted with 30 mL DCM and washed with 3 x 300 mL water, organic layer was next dried over Na2SO4, filtered and concentrated to afford title compound **3.14a** (8.635 g, 99.8 % yield) as colorless oil to be used without further purification; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.78 (ddd, *J* = 5.2, 4.0, 1.2 Hz, C=CH x 2, 2H), 4.71 – 4.61 (m, $ROCH_2CR$ x 2, 4H), 1.48 (s, tBu x 2, 18H).

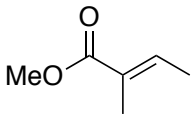


ethyl (*E*)-4-((*tert*-butoxycarbonyl)oxy)but-2-enoate (3.14): First, olefin **3.14a** (2.00 g, 6.917 mmol) was ozonated following the general proceure for ozonolysis of alkenes to produce an intermediate aldehyde in quantitative yield that was used directly without further purification and dissolved in 50 mL THF alongside ethyl triphenylphosphoranylidene acetate (5.316 g, 15.528 mmol). Reaction vessel was equipped with a condenser and heated to reflux at 77 °C for 2 h. Cooled to ambient temperature and diluted with 36 mL hexanes. The resultant suspension was filtered through a celite pad. The filtrate was concentrated and chromatographed via silica gel column (0-10% EtOAc in hexanes gradient) to afford the title compound **3.14** (2.642 g, 83% yield) as a colorless oil over two steps; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.93 (dt, *J* = 15.8, 4.7 Hz, C=CH, 1H), 6.06 (dt, *J* = 15.7, 1.9 Hz, C=CH, 1H), 4.72 (dd, *J* = 4.7, 2.0 Hz, RCCH$_2$OR, 2H), 4.21 (q, *J* = 7.1 Hz, CH$_3$C*H*$_2$OR, 2H), 1.50 (s, tBu, 9H), 1.29 (t, *J* = 7.1 Hz, RCH$_3$, 3H).

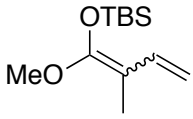


ethyl (*E*)-5-cyclohexyl-5-hydroxypent-2-enoate (3.15): To a sealable microwave pressure tube was added achiral Ir-catalyst **3.15a** (0.0162 g, 0.015 mmol) and stir magnet with 0.2 mL 1,4-dioxane then sealed and flushed with argon. Aceloxy-crotonate **3.14** (0.1328 g, 0.600 mmol) and cyclohexyl methanol (0.0369 mL, 0.300 mL) with 0.4 mL 1,4-dioxane were premixed under argon and added to catalyst solution dropwise. Reaction vessel was sealed and placed in 90 °C oil bath and stirred 48 hrs. Mixture was extracted with dioxane and concentrated *in vacuo*. Purified via silica gel

column (2-25% EtOAc in hexanes gradient) to afford the title compound **3.15** (0.020 g, 30.0% yield) as a colorless oil; R_f = 0.4, 20% EtOAc/Hex; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.00 (ddd, *J* = 15.6, 7.8, 6.9 Hz, C=CH, 1H), 5.91 (dt, *J* = 15.7, 1.5 Hz, C=CH, 1H), 4.19 (q, *J* = 7.1 Hz, RCH_2OR, 2H), 3.51 (ddd, *J* = 8.3, 5.8, 3.8 Hz, R_2CHOR, 1H), 2.43 (dddd, *J* = 14.6, 6.9, 3.8, 1.6 Hz, RCH_2R, 1H), 2.38 – 2.26 (m, RCH_2R, 1H), 2.13 (s, ROH, 1H), 2.04 (s, ROH, 1H), 1.87 – 1.72 (m, cyclohexyl, 2H), 1.71 – 1.61 (m, cyclohexyl, 2H), 1.53 (d, *J* = 25.0 Hz, cyclohexyl, 3H), 1.29 (t, *J* = 7.1 Hz, cyclohexyl, 3H), 1.19 – 0.98 (m, RCH_3, 3H).

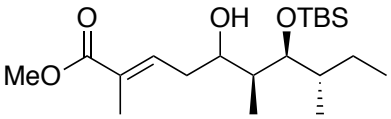


methyl (*E*)-2-methylbut-2-enoate (3.16a):[143] Tiglic acid (4.00 g, 39.952 mmol) was dissolved in 38.0 mL MeOH and slowly charged with 2 mL conc. H_2SO_4 then stirred at 80 °C with fitted condenser and under argon atmosphere for 48 hrs. Cooled reaction to ambient temperature and added 25 mL DI H_2O slowly then extracted 3 x 30 mL Et_2O, washed with 30 mL sodium bicarbonate and dried over $MgSO_4$. Concentration *in vacuo* afforded the title compound **3.16a** (4.12 g, 90.3% yield) as an oil that was used without further purification; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.85 (qq, *J* = 7.0, 1.4 Hz, C=CH, 1H), 3.73 (s, $ROCH_3$, 3H), 1.83 (q, *J* = 1.2 Hz, RCH_3, 3H), 1.79 (dq, *J* = 7.1, 1.2 Hz, RCH_3, 3H).



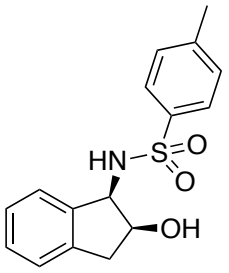
***tert*-butyl((1-methoxy-2-methylbuta-1,3-dien-1-yl)oxy)dimethylsilane (3.16):**[23] Oven dried 100 mL RBF with stir bar under arong charged with 35 mL dry THF and diisopropyl amine (2.915 ml, 19.275 mmol) was cooled to 0 °C under argon. Added

n-BuLi (7.71 mL, 2.5 M in hexanes, 19.275 mmol) dropwise and stirred 90 min. Reaction mixture cooled to -78 °C and added DMPU (2.533 mL, 21.026 mmol) and stirred 30 min, reaction turned turbid. Added methyl tiglate (2.105 mL, 17.522 mmol) dropwise, stirred 30 min. Addition of TMS-Cl (2.446 mL, 19.275 mmol) dropwise cleared turbidity. Stirred 2 h and equilibrated to RT. Added pentanes to precipitate insoluble salts. Washed 3 x cold water and dried organics over $MgSO_4$ followed by filtration thru celite pad and concentration *in vacuo*. Crude residue was distilled under HI-VAC (bp 45 ^oC @ 2mmHg) to produce **3.16** (2.90 g, 89% yield) as clear oil; ^1H NMR (400 MHz, Chloroform-*d*) δ 6.91 – 6.51 (m, RCH=C, 1H), 4.96 – 4.69 (m, R=CH_2, 2H), 3.57 (s, $ROCH_3$, 3H), 1.70 – 1.57 (m, RCH_3, 3H), 0.95 (s, Si-tBu, 9H), 0.25 (m, Si-CH_3 x 2, 6H).

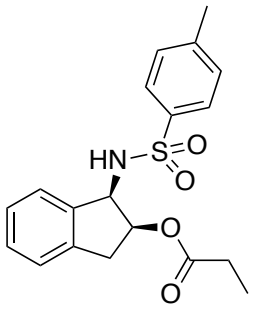


methyl (6*S*,7*S*,8*S*,*E*)-7-((*tert*-butyldimethylsilyl)oxy)-5-hydroxy-2,6,8-trimethyldec-2-enoate (3.17):[24] To a stirred solution of aldehyde in DCM:Et_2O (10:1, 2.5 mL) cooled to -78 °C under argon was added silane **3.16** (0.112 g, 0.5949 mmol) and $BF_3{\cdot}Et_2O$ (37.5 µl, 0.2947 mmol) and stirred 2 hrs and then equilibrated to ambient temperatures. Added 4 mL of mixture: 3.125 mL THF – 625 µl H_2O – 12 ul 0.75M HCl (5:1:0.4) then stirred 15 min. Added 5 mL ice cold sat. $NaHCO_3$ and stirred 15 min. Extracted 3 x 15 mL hexanes, washed combined extracts with 8 mL brine and dried over Na_2SO_4. Filtered and concentrated *in vacuo*. 125 mg crude residue was chromatographed via silica gel chromatography (0-10% ether in hexanes gradient) to afford homoallylic alcohols **3.17** (26 mg, 40.0% yield) as pale yellow oil; ^1H NMR (400 MHz, Chloroform-*d*) δ 6.04 (dd, *J* = 17.1, 10.5 Hz, C=CH, 1H), 5.36 (dd, *J* = 17.1, 1.2

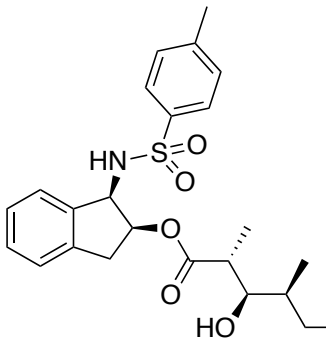
Hz, R_2CH(OH), 1H), 5.13 (dd, *J* = 10.5, 1.2 Hz, ROH, 1H), 3.72 (s, $ROCH_3$, 3H), 3.47 (q, *J* = 7.0 Hz, R_2CH(OSi), 1H), 1.89 – 1.73 (m, RCH_2R, 2H), 1.52 (s, RCH_3, 3H), 1.30 – 1.17 (m, R_3CH x 2, 1H + 1H), 0.99 – 0.76 (m, Si-tBu + RCH_3 x 2, 9H + 3H + 3H), 0.09 – 0.01 (m, Si-CH_3 x 2, 6H).



***N*-((1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)-4-methyl-benzenesulfonamide (3.18):**[25] 200 mL 3-neck RBF with stir bar charged with Na_2CO_3 (2.842 g, 26.8115 mmol) and 12 mL DI H_2O, stirred 20 min. This solution was added to a solution of (+)-*cis*-aminoindanol (2.000 g, 13.4057 mmol) in 30 mL EtOAc, stired 20 min. Tosyl chloride (2.556 g, 13.4057 mmol) in 4.8 mL EtOAc:THF (1:1) was added dropwise over 40 min and stirred 12 hrs. Phases were separated, organics washed with 10 mL H_2O, 10 mL 1M HCl, 20 mL H_2O and dried over Na_2SO_4. Evaporated until crystallized then added 30 mL Et_2O, pulverized and washed 5 x 30 mL Et_2O. Solids were dried under HI-VAC to afford **3.18** (1.886 g, 85% yield) as white crystals; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 8.0 Hz, Ar-H x 2, 2H), 7.36 (d, *J* = 8.0 Hz, Ar-H x 2, 2H), 7.24 – 7.15 (m, Ar-H x 2, 2H), 7.11 (d, *J* = 7.3 Hz, Ar-H x 2, 2H), 5.20 (d, *J* = 9.2 Hz, R_2NH, 1H), 4.71 (dd, *J* = 9.2, 4.8 Hz, R_2CH(OH), 1H), 4.35 (dd, *J* = 5.9, 4.4 Hz, R2C*H*(NHR), 1H), 3.07 (dd, *J* = 16.7, 5.2 Hz, RCH_2R, 1H), 2.89 (d, *J* = 16.7 Hz, RCH_2R, 1H), 2.46 (s, Ar-CH_3, 3H), 1.91 (d, *J* = 5.2 Hz, ROH, 1H).

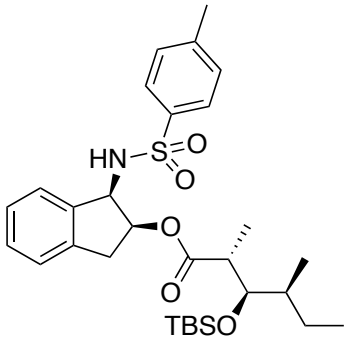


(1*R*,2*S*)-1-((4-methylphenyl)sulfonamido)-2,3-dihydro-1*H*-inden-2-yl propionate (3.19): Ts-*N*-aminoindanol **3.18** (0.982 g, 3.236 mmol) was dissolved in 20 mL dry DCM under argon and cooled to 0 °C. Propionyl chloride (0.339 mL, 3.884 mmol) was added dropwise followed by pyridine (0.443 mL, 5.502 mmol) and stirred 15 hrs. Mixture was quenched with 25 mL 2N HCl. Separated phases and washed with 30 mL $NaHCO_3$, 30 mL brine and dried over Na_2SO_4. Filtered, concentrated and triturated with cold hexanes to afford the title compound **3.19** (1.084 g, 93.2% yield) as white crystals; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 – 7.77 (m, Ar-H x 2, 2H), 7.32 (dq, *J* = 7.9, 0.6 Hz, Ar-H x 2, 2H), 7.27 (d, *J* = 2.8 Hz, Ar-H x 2, 2H), 7.24 (d, *J* = 3.1 Hz, Ar-H x 2, 2H), 7.19 – 7.15 (m, R_2NH, 1H), 5.16 (td, *J* = 5.1, 1.6 Hz, $R_2CH(OR)$, 1H), 5.00 (d, *J* = 3.5 Hz, $R_2CH(NHR)$, 1H), 3.14 – 3.06 (m, RCH_2R, 1H), 2.94 – 2.85 (m, RCH_2R, 1H), 2.45 (s, Ar-CH_3, 3H), 2.25 (m, $RO_2CH_2CH_3$, 2H), 1.05 (t, *J* = 7.5 Hz, $RO_2CH_2CH_3$, 3H).

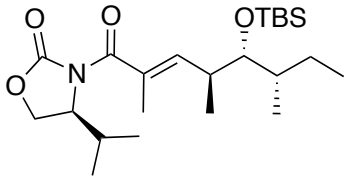


(1*R*,2*S*)-1-((4-methylphenyl)sulfonamido)-2,3-dihydro-1*H*-inden-2-yl (2*R*,3*R*,4*S*)-3-hydroxy-2,4-dimethylhexanoate (3.20): *Solution 1* was prepared by dissolving 3.19 (1.750 g, 4.8687 mmol) in 50 mL dry DCM then cooled to 0 °C, then dropwise addition of 1M TiC_4 (5.36 mL, 5.355 mmol), stirred 5 min, slowly added iPrNEt (2.54 mL, 14.606 mmol) and stirred. *Solution 2* was prepared by dissolving aldehyde **3.1** (2.76 mL, 5.3M, 14.6061 mmol) with DCM to 80 mL total volume then added TiCl4 (16.07 mL, 1M, 16.0667 mmol) dropwise, stirred 5 min, then added ACN (839 µl, 16.0667 mmol) all at -78 °C and stirred under argon. *Solution 1* was added slowly via cannula to *Solution 2* over about 30 min. Stirred 3 hrs then quenched with 100 mL sat. NH_4Cl and equilibrated to ambient temperatures. Diluted with minimal water to homogeneity and extracted 4 x 20 mL DCM, washed combined organics with 100 mL brine and dried over Na_2SO_4 then filtered and concentrated *in vacuo*. Crude residue was chromatographed via silica gel column (0-10% EtOAc in DCM gradient) to afford the title compound **3.20** (2.119 g, 97.7% yield) as a clear, pale yellow oil; R_f = 0.3, 5% EtOAc/DCM; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 (d, *J* = 8.3 Hz, Ar-H x 2, 2H), 7.81 (d, *J* = 8.2 Hz, Ar-H x 2, 2H), 7.38 – 7.29 (m, Ar-H x 2, 2H), 7.25 – 7.15 (m, Ar-H x 2, 2H), 7.11 (d, *J* = 7.3 Hz, R_2NH, 1H), 5.56 – 5.32 (m, R_2CHOR, 1H), 5.20 (d, *J* = 9.1 Hz, R_2CHNR, 1H), 4.71 (dd, *J* = 9.2, 4.9 Hz, R2C*H*(OH), 1H), 4.12 (q, *J* = 7.1 Hz, RCH_2R, 1H), 3.45 (s, ROH, 1H), 3.07 (dd, *J* = 16.8, 5.3 Hz, RCH_2R, 1H), 2.46 (s, Ar-

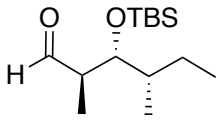
CH_3, 3H), 2.04 (m, R_3CH, 1H), 1.54 – 1.48 (m, R_3CH, 1H), 1.33 – 1.17 (m, R_2CH_2R, 2H), 1.13 – 0.89 (m, RCH_3, 3H), 0.89 – 0.73 (m, RCH_3 x 2, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 181.85, 129.92, 128.64, 127.56, 127.34, 124.99, 124.65, 75.01, 73.89, 59.88, 46.27, 37.52, 34.57, 27.54, 22.74, 21.72, 14.47, 14.11, 0.15.



(1*R*,2*S*)-1-((4-methylphenyl)sulfonamido)-2,3-dihydro-1*H*-inden-2-yl (2*R*,3*R*,4*S*)-3-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethylhexanoate (3.21): Title compound was prepared by the general procedure for silyl ether protection of hydroxyl **3.20** with TBS-OTf/2,6-lutidine to afford **3.21** (0.790 g, 99% yield) as a sticky oil; R_f = 0.9, 100% DCM; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 8.2 Hz, Ar-H x 2, 2H), 7.32 (d, *J* = 8.0 Hz, Ar-H x 2, 2H), 7.23 (d, *J* = 5.4 Hz, Ar-H x 2, 2H), 7.14 (d, *J* = 6.6 Hz, Ar-H x 2, 2H), 5.22 (s, R_2NH, 1H), 4.98 (d, *J* = 2.4 Hz, R_2CHOR + R_2CHNR, 2H), 3.74 – 3.69 (m, R_2CHOSi, 1H), 3.07 (dd, *J* = 17.1, 4.8 Hz, RCH_2R, 1H), 2.91 (d, *J* = 17.1 Hz, RCH_2R, 1H), 2.45 (s, Ar-CH_3, 3H), 1.34 (s, R_2CHR, 1H), 1.12 (m, *J* = 6.0 Hz, RCH_3 + RCH_2R + R_3CH, 3H +2H + 1H), 1.02 (d, *J* = 7.1 Hz, RCH_3, 3H), 0.84 – 0.80 (m, Si-tBu + RCH_3, 9H + 3H), -0.02 (m, Si-CH_3 x 2, 6H).

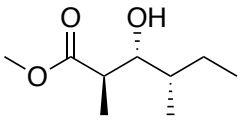


(*S*)-3-((4*S*, 5*R*, 6*S*, *E*)-5-((*tert*-butyldimethylsilyl)oxy)-2, 4, 6-trimethyloct-2-enoyl)-4-isopropyloxazolidin-2-one (3.22a): The title compound was prepared by general procedure for silyl ether protection of hydroxyl **3.53** via TBSOTF/2,6-lutidine to produce **3.22a** (1.468 g, 88% yield); $[\alpha]_D^{20}$ = +21.9° (c 1.14, CH_2Cl_2); FTIR (neat, cm^{-1}) 2965.9, 2876.5, 1789.8, 1682.6, 1464.0, 1362.2, 1300.6, 1205.6, 1054.9, 772.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.15 (dd, *J* = 9.8, 1.6 Hz, C=CH, 1H), 4.47 (dt, *J* = 9.0, 4.7 Hz, $ROCH_2R$, 1H), 4.29 (t, *J* = 8.8 Hz, $ROCH_2R$, 1H), 4.16 (dd, *J* = 8.9, 5.2 Hz, $RNCHR_2$, 1H), 3.49 (t, *J* = 3.9 Hz, $R_2CH(OSi)$, 1H), 2.70 (ddt, *J* = 10.1, 6.8, 3.5 Hz, R_3CH, 1H), 2.44 – 2.32 (m, R_3CH, 1H), 1.94 – 1.88 (m, RCH_3, 3H), 1.53 – 1.43 (m, RCH_2R, 1H), 1.30 – 1.23 (m, R_3CH, 1H), 1.11 – 1.04 (m, RCH_2R, 1H), 1.01 (d, *J* = 7.0 Hz, RCH_3, 3H), 0.94 – 0.82 (m, RCH_3 x 4 + Si-tBu, 21H), 0.06 – 0.05, Si-CH_3 x 2, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.25, 153.60, 141.67, 129.66, 79.67, 63.51, 58.58, 40.02, 36.58, 28.37, 26.26, 26.09, 18.53, 18.09, 18.04, 15.27, 15.06, 13.95, 12.30, -3.58, -3.85.



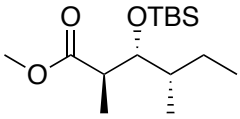
(2*R*,3*R*,4*S*)-3-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethylhexanal (3.22): Title compound was prepared in multiple ways. First, **3.21** (0.370 g, 1.282 mmol) was dissolved in 30 mL dry DCM and subject to DIBAL-H (1.28 mL, 1M, 1.282 mmol) at 0 °C under argon and stirred 14 hours. TLC'd reaction to completion then quenched with 30 mL sat. sodium potassium tartrate, stirred 1 hr then diluted with 20 mL DI H_2O

and extract 4 x DCM and dried combined organics over $MgSO_4$. Filtered, concentrated and chromatographed over silica gel column (5-10% EtOAc in hexanes) to afford the title compound **3.22** (0.227 g, 68% yield) pale yellow oil. Second, aldehyde was prepared from **3.22a** by the general procedure for ozonolysis of alkenes to produce the title compound **3.22** (0.776 g, 79% yield) as clear oil. Alternatively, alcohol **3.25** (1 equiv) was oxidized via PDC (3 equiv) to afford **3.22** (90% yield); R_f = 0.6, 10% EtOAc/hex; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.73 (dd, *J* = 2.8, 0.7 Hz, RCHO, 1H), 3.78 – 3.69 (m, $R_2OCH(OSi)$, 1H), 2.54 – 2.45 (m, R_3CH, 1H), 1.56 – 1.38 (m, RCH_2R, 2H), 1.15 – 1.06 (m, R_3CH, 1H), 1.04 (dd, *J* = 7.1, 0.7 Hz, RCH_3, 3H), 0.89 – 0.82 (m, RCH_3 x 2 + Si-tBu, 15H), 0.03 (d, *J* = 1.7 Hz, Si-CH_3 x 2, 6H).

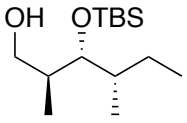


methyl (2*R*,3*R*,4*S*)-3-hydroxy-2,4-dimethylhexanoate (3.23): Dissolved **3.20** (2.00 g, 4.488 mmol) in 40 mL MeOH at 0 °C and added solution of sodium methoxide in methanol (0.500 g, 22.442 mmol in 20 mL MeOH) dropwise and stirred for 16 hours. Reaction mixture was quenched with 50 mL sat. NH_4Cl and stirred 1 hr then diluted with 50 mL DI H_2O. Extracted aqueous 5 x 15 mL CH_2Cl_2 and dried over Na_2SO4, filtered, concentrated *in vacuo* then chromatographed the residue via silica gel column (30% then 100% Et_2O in pentanes stepwise gradient) to afford the title compound **3.23** (0.506 g, 66%) as a yellow oil; Rf = 0.8, 45% Et_2O/pent; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.71 (s, OCH_3, 3H), 3.69 – 3.61 (m, $R_2OCH(OH)$, 1H), 2.58 – 2.50 (m, R_3CH, 1H), 2.48 (d, *J* = 6.8 Hz, R_3CH, 1H), 1.54 – 1.41 (m, RCH_2R, 2H), 1.37 – 1.29 (m, 1H), 1.21 (d, *J* = 7.2 Hz, RCH_3, 3H), 1.18 (d, *J* = 7.2 Hz, 1H), 0.91 (t, *J* = 7.1 Hz, RCH_3,

3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.55, 73.48, 51.77, 45.36, 34.55, 27.81, 22.74, 14.39, 14.10.

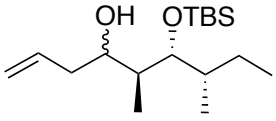


methyl (2*R*,3*R*,4*S*)-3-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethyl hexanoate (3.24): The title compound was prepared by the general procedure for silyl ether protection of hydroxyl **3.20** (0.450 g, 2.612 mmol) with TBSCl/imidazole to afford **3.24** (0.425 g, 70%) as clear oil; R_f = 0.7, 5% EtOAc/hex; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.98 – 3.93 (m, $R_2OCH(OSi)$, 1H), 3.66 (t, *J* = 1.2 Hz, OCH_3, 3H), 2.69 – 2.60 (m, R_3CH, 1H), 1.52 – 1.38 (m, R_3CH, 1H), 1.32 – 1.27 (m, RCH_2R, 2H), 1.08 (dd, *J* = 7.1, 0.9 Hz, RCH_3, 3H), 0.93 – 0.88 (m, RCH_3, 3H), 0.87 (m, Si-tBu + RCH_3, 12H), 0.04 (m, Si-CH_3 x 2, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.55, 73.55, 51.53, 45.53, 32.97, 25.93, 23.00, 18.16, 14.17, 12.10, -4.28, -4.74.

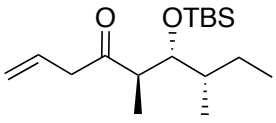


(2*S*,3*R*,4*S*)-3-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethylhexan-1-ol (3.25): Ester **3.24** (0.370 g, 1.282 mmol) was dissolved in 30 mL dry DCM and subject to DIBAL-H (2.56 mL, 1M, 2.56 mmol) at 0 °C under argon and stirred 14 hours. TLC'd reaction to completion then quenched with 30 mL sat. sodium potassium tartrate, stirred 1 hr then diluted with 20 mL DI H_2O and extract 4 x DCM and dried combined organics over $MgSO_4$. Filtered, concentrated and chromatographed over silica gel column (5-10% EtOAc in hexanes) to afford the title compound **3.25** (0.227 g, 90% yield) pale yellow oil; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.15 – 4.05 (m, $R_2CH(OSi)$, 1H), 2.04 (d, *J* =

2.6 Hz, RCH_2R, 2H), 1.55 (s, ROH, 1H), 1.40 (m, R_3CH + RCH_2R, 3H), 1.25 (m, R_3CH , 1H), 0.91 (m, Si-tBu + RCH_3 x 3, 18H), 0.08 – 0.01 (m, Si-CH_3 x 2, 6H).

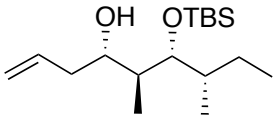


(5*S*,6*R*,7*S*)-6-((*tert*-butyldimethylsilyl)oxy)-5,7-dimethylnon-1-en-4-ol (3.26): Aldehyde **3.22** (0.700 g, 2.706 mmol) was dissolved in 25.0 mL dry ether and cooled to 0 °C. Allylmagnesium bromide (~1.0M, 8.125 mmol) prepared by the general procedure for allylmagnesium bromide synthesis, was added dropwise under argon atmosphere then stirred 14 hrs overnight while equilibrating to ambient temperatures. Mixture was quenched with 25 mL sat. NH_4Cl, extracted 4 x 15 mL EtOAc and combined organics were dried over $MgSO_4$. Filtered, concentrated *in vacuo* and chromatographed residue on silica gel column (0-5% EtOAc in hexanes gradient) to afford the title compound **3.26** (0.797 g, 98% yield, 40:60 dr) as a yellow liquid; R_f = 0.5, EtOAc/hex; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.09 – 5.68 (m, C=CH, 1H), 5.26 – 4.94 (m, $C=CH_2$, 2H), 4.11 (ddt, *J* = 7.9, 6.4, 1.6 Hz, R_2CH(OH), 1H), 3.73 – 3.49 (m, R_2CH(OSi), 1H), 3.47 – 3.08 (m, ROH, 1H), 2.47 – 2.24 (m, RCH_2R, 1H), 2.19 – 2.00 (m, RCH_2R, 1H), 1.79 – 1.39 (m, RCH_2R, 2H), 1.22 – 1.05 (m, R_3CH, 1H), 0.99 (m, R_3CH x 2, 2H), 0.95 – 0.82 (m, Si-tBu + RCH_3 x 3, 18H), 0.10 (m, Si-CH_3 x 2, 6H).



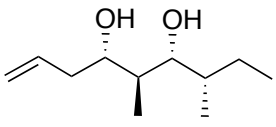
(5*R*,6*R*,7*S*)-6-((*tert*-butyldimethylsilyl)oxy)-5,7-dimethylnon-1-en-4-one (3.27): Dess-Martin Periodinane (2.25 g, 5.303 mmol) was prepared by the general procedure for DMP and added to a solution of alcohol **3.26** (0.797 g, 2.662 mmol) in 50 mL CH_2Cl_2 at 0 °C under argon atmosphere. Reaction stirred while

equilibrating to ambient temperatures for 18 hrs. Quenched with sat. sodium sulfite, extracted 3 x 20 mL DCM and dried the combined organics over $MgSO_4$, filtered and concentrated *in vacuo*. Crude residue was chromatographed on silica gel column (0-5% EtOAc in hexanes gradient) to afford the title compound **3.27** (0.754 g, 95% yield) as a pale yellow liquid; R_f = 0.6, 7% EtOAc/hex; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.95 (ddt, *J* = 17.1, 10.2, 6.8 Hz, C=CH, 1H), 5.17 (dq, *J* = 10.3, 1.5 Hz, C=CH_2, 1H), 5.11 (dq, *J* = 17.2, 1.6 Hz, C=CH_2, 1H), 3.88 (dd, *J* = 8.1, 2.0 Hz, R_2CH(OSi), 1H), 3.31 (ddt, *J* = 17.8, 7.1, 1.4 Hz, RCH_2R, 1H), 3.22 (ddt, *J* = 17.7, 6.7, 1.5 Hz, RCH_2R, 1H), 2.87 – 2.78 (m, R_3CH, 1H), 1.47 – 1.38 (m, RCH_2R, 2H), 1.18 (dtd, *J* = 14.5, 7.2, 2.7 Hz, R_3CH, 1H), 0.97 (d, *J* = 7.0 Hz, RCH_3, 3H), 0.88 (d, *J* = 16.1 Hz, Si-tBu + RCH_3 x 2, 15H), 0.04 (s, Si-CH_3, 3H), -0.06 (s, Si-CH_3, 3H).

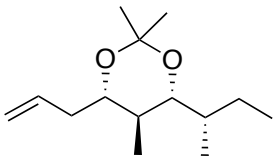


(4*S*,5*S*,6*R*,7*S*)-6-((*tert*-butyldimethylsilyl)oxy)-5,7-dimethylnon-1-en-4-ol (3.28): Solution of ketone **3.27** (0.750 g, 2,512 mol) in 35 mL dry MeOH was cooled to 0 °C and added $NaBH_4$ (0.525 g, 13.817 mmol) portion-wise. After 1 hr the reaction was quenched with 10 mL 2M NaOH, concentrated, extracted 3 x 20 mL EtOAc and dried over $MgSO_4$. Organics were filtered, concentrated *in vacuo* and purified via silica gel column (0-5% EtOAc in hexanes gradient) to afford the desired diastereomer **3.28** (0.563 g, 75% yield, >98:2 dr) as a clear liquid; R_f = 0.6, 10% EtOAc/hex; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.93 (dddd, *J* = 16.4, 10.3, 8.0, 6.0 Hz, C=CH, 1H), 5.16 – 5.08 (m, C=CH_2, 2H), 3.62 (tt, *J* = 8.3, 2.7 Hz, R_2CH(OH), 1H), 3.56 (dd, *J* = 5.8, 3.2 Hz, R_2CH(OSi), 1H), 3.18 (d, *J* = 2.1 Hz, ROH, 1H), 2.39 (d, *J* = 15.2 Hz, RCH_2R, 1H), 2.10

(dt, *J* = 15.0, 7.9 Hz, RCH_2R, 1H), 1.80 – 1.68 (m, R_3CH, 1H), 1.53 – 1.40 (m, RCH_2R, 1H), 1.18 (ddd, *J* = 12.9, 8.3, 6.3 Hz, R_3CH, 1H), 0.93 – 0.86 (m, Si-tBu + RCH_3 x 3, 18H), 0.11 (s, Si-CH_3, 3H), 0.08 (s, Si-CH_3, 3H).

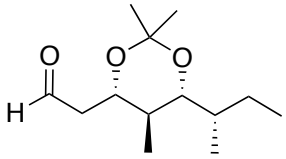


(4*S*,5*S*,6*R*,7*S*)-5,7-dimethylnon-1-ene-4,6-diol (3.29): Dissolved silyl ether **3.28** (0.300 g, 0.998 mmol) in 5 mL CH_3CN in Teflon reactor followed by a dropwise addition of 1.0 mL 49% HF that stirred for 5 hours while yellow mixture turned clear. Mixture was diluted with 10 mL EtOAc, washed 2 x 20 mL brine, concentrated and purified via silica gel column (10-50% EtOAc in hexanes gradient) to afford the title compound **3.29** (0.170 g, 90% yield) as clear oil; R_f = 0.7, 50% EtOAc/hex; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.88 (q, *J* = 8.5, 7.9 Hz, C=CH, 1H), 5.19 (d, *J* = 2.4 Hz, $C=CH_2$, 1H), 5.16 (d, *J* = 7.3 Hz, $C=CH_2$, 1H), 3.70 (t, *J* = 8.6 Hz, R_2CH(OH), 1H), 3.56 (d, *J* = 9.1 Hz, R_2CH(OH), 1H), 3.07 (d, *J* = 36.7 Hz, ROH, 2H), 2.47 (d, *J* = 15.0 Hz, RCH_2R, 1H), 2.17 (dt, *J* = 15.6, 8.8 Hz, RCH_2R, 1H), 1.68 (d, *J* = 9.5 Hz, RCH_2R, 1H), 1.44 – 1.31 (m, RCH_2R + R_3CH x 2, 3H), 0.93 (tt, *J* = 5.7, 3.0 Hz, RCH_3, 3H), 0.85 (dd, *J* = 6.8, 2.4 Hz, RCH_3, 3H), 0.78 (ddd, *J* = 14.1, 6.9, 2.5 Hz, RCH_3, 3H).

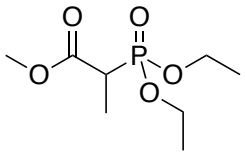


(4*S*,5*S*,6*R*)-4-allyl-6-((*S*)-*sec*-butyl)-2,2,5-trimethyl-1,3-dioxane (3.30): Dissolved 1,3-diol **3.29** (0.300 g, 1.610 mmol) in 9.0 mL 2,2-dimethoxy propane then added catalytic pTsOH (0.014 g, 0.081 mmol) under argon at room temperature and stirred 15 hours overnight. Reaction mixture was diluted with 10 mL EtOAc and

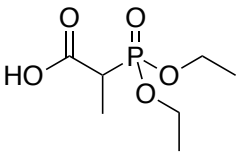
evaporated to dryness. Crude residue was purified via silica gel column (0-8% EtOAc in hexanes linear gradient) to afford the title compound **3.30** (0.303 g, 83% yield) as a clear liquid; R_f = 0.8, 5% EtOAc/hex; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.92 (ddt, *J* = 17.1, 10.2, 6.8 Hz, C=CH, 1H), 5.10 – 5.00 (m, C=CH_2, 2H), 3.51 (ddd, *J* = 10.2, 7.2, 3.2 Hz, R_2C*H*(OR), 1H), 3.44 (dd, *J* = 10.3, 2.2 Hz, R_2C*H*(OR), 1H), 2.39 (dddt, *J* = 14.8, 6.3, 3.1, 1.5 Hz, RCH_2R, 1H), 2.18 (dtt, *J* = 14.6, 7.2, 1.3 Hz, RCH_2R, 1H), 1.51 (ddtd, *J* = 26.9, 10.1, 6.8, 2.8 Hz, RCH_2R, 2H), 1.39 (s, CCH_3, 3H), 1.34 (s, CCH_3, 3H), 1.32 – 1.26 (m, R_3CH x 2, 2H), 0.87 (t, *J* = 7.4 Hz, RCH_3, 3H), 0.83 (d, *J* = 6.8 Hz, RCH_3, 3H), 0.73 (d, *J* = 6.6 Hz, RCH_3, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.52, 116.16, 97.79, 75.46, 74.49, 37.79, 35.19, 34.99, 30.23, 26.89, 19.63, 12.50, 12.16, 12.15, 11.75.



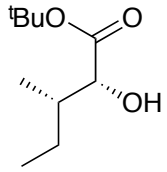
2-((4*S*,5*S*,6*R*)-6-((*S*)-*sec*-butyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)acetaldehyde (3.31): The title compound was prepared by the general procedure for ozonolysis of alkenes (**3.30**) to afford **3.31** (0.040 g, 60% yield) as yellow oil; R_f = 0.5, 5% EtOAc/hex; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.79 (dt, *J* = 2.8, 1.3 Hz, RCHO, 1H), 4.07 – 3.99 (m, R_2C*H*(OR), 1H), 3.51 (ddd, *J* = 10.2, 2.2, 1.0 Hz, R_2C*H*(OR), 1H), 2.60 (ddt, *J* = 15.9, 3.0, 1.3 Hz, RCH_2R, 1H), 2.49 (dddd, *J* = 15.9, 8.3, 3.1, 1.0 Hz, RCH_2R, 1H), 1.59 – 1.48 (m, RCH_2R, 2H), 1.42 (s, CCH_3, 3H), 1.40 – 1.34 (m, R_3CH, 1H), 1.32 (s, CCH_3, 3H), 1.31 – 1.24 (m, R_3CH, 1H), 0.88 (td, *J* = 7.4, 1.0 Hz, RCH_3, 3H), 0.84 (dd, *J* = 6.8, 1.1 Hz, RCH_3, 3H), 0.75 (dd, *J* = 6.7, 1.0 Hz, RCH_3, 3H).



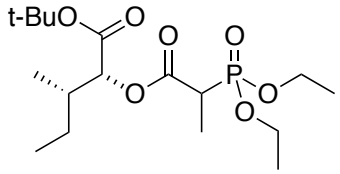
methyl 2-(diethoxyphosphoryl)propanoate (3.32):[71] To oven-dried 10 mL RBF under argon was charged methyl bromopropionate (676 µl, 5.988 mmol) then triethyl phosphite (1.03 mL, 5.988 mmol) and heated to 130 °C with distillation head attached for 16 hrs. Equilibrated to ambient temperatures then fomoved volatiles *in vacuo* to afford the title compound **3.32** (1.11 g, 78% yield); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.14 (tt, *J* = 8.3, 5.6 Hz, OC*H*$_2$CH$_3$ x 2, 4H), 3.74 (s, OCH$_3$, 3H), 3.03 (dq, *J* = 23.4, 7.2 Hz, R$_3$CH, 1H), 1.43 (dd, *J* = 17.9, 7.3 Hz, RCH$_3$, 3H), 1.34 – 1.29 (m, RCH$_3$ x 2, 6H).



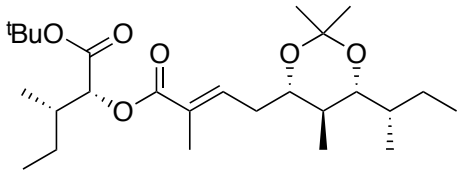
2-(diethoxyphosphoryl)propanoic acid (3.33):[144] Stirred crude 2-phosphonopropionate **3.32** (0.560 g, 2.353 mmol) in 1.0 mL DI H_2O at 0 °C then added solid NaOH (0.100 g, 2.471 mmol) to 10M NaOH concentration and stirred for 16 hrs. The reaction mixture was cooled to 0 °C and acidified to pH 1 with concentrated HCl, extracted with 3 x 20 mL DCM, dried over $MgSO_4$ and then filtered and concentrated under reduced pressure to afford **3.33** (0.420 g, 80% yield) without further purification; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.47 (s, RCOOH, 1H), 4.07 – 3.96 (m, OC*H*$_2$CH$_3$ x 2, 4H), 2.89 (dq, *J* = 23.9, 7.3 Hz, R$_3$CH, 1H), 1.25 (dd, *J* = 18.3, 7.3 Hz, RCH$_3$, 3H), 1.17 – 1.11 (m, RCH$_3$ x 2, 6H).



2*R*-Hydroxy-3*S*-methylpentanoic acid *tert*-butyl ester (3.34).[41] Ester **3.51** (3.05 g, 9.04 mmol) was dissolved in anhydrous methanol (25 mL) and cooled to ~0 °C 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 and the residue was transferred to a separation funnel and extracted with EtOAc (4 × 15 mL). The combined organic phases were washed with brine (50 mL), then dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified on a silica gel column (0–10% gradient of CH_2Cl_2 in toluene) to give the product **3.34** in 60% (1.03 g) as colorless oil, $[\alpha]^{20}_D$ -6.36º (c=1.14, CH_2Cl_2). lit.[6] oil, $[\alpha]^{20}_D$ -3.1º (c=0.7, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.04 (dd, CHC*H*OH, *J* = 5.6, 2.8 Hz, 1H), 2.74 (d, CHCHO*H*, *J* = 5.6 Hz, 1H), 1.77 (dtq, CH_2CH(Me)CH, *J* = 6.9, 6.9, 2.8 Hz, 1H), 1.58–1.46 (m, CH_2CH_3, "*partly hidden*", 1H), 1.49 (s, ^{t}Bu, 9H), 1.37–1.25 (m, CH_2CH_3, 1H), 0.95 (t, CH_3CH_2, *J* = 7.4 Hz, 3H), 0.81 (d, CH_3CH, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.79, 82.42, 73.20, 38.68, 28.21, 26.19, 13.10, 12.02; FTIR (neat, cm^{-1}) 3502, 2968, 1724, 1459, 1369, 1256, 1130, 849; MS (ESI) m/z calcd for $C_{10}H_{21}O_3$ $[M+H]^+$ 189.14, found 188.85.



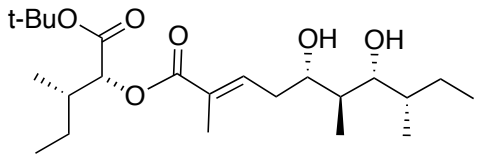
***tert*-butyl (2*R*,3*S*)-2-((2-(diethoxyphosphoryl)propanoyl) oxy)-3-methylpentanoate (3.35):** Phosphoryl propanoic acid **3.33** (0.803 g, 3.585 mmol), DIPC (0.561 mL, 3.585 mmol) and collidine (0.347 mL, 2.629 mmol) were successively added to a solution of alpha-alcohol **3.34** (0.450 g, 2.390 mmol) in 22.5 mL dry DCM at 0 °C under argon atmosphere and stirred while equilibrating to room temperature overnight hours. The reaction mixture was quenched with brine, extracted 3 x 20 mL EtOAc, then combined organics were washed with brine and dried over Na_2SO4. Organics were concentrated to 1.80 g with urea of which was extracted with 15% EtOAc in hexanes and purified on silica gel column (10-50% EtOAc in hexanes linear gradient) to afford the title compound **3.35** (0.679 g, 75% yield) as a clear, pale yellow oil; R_f = 0.3, 50% EtOAc/hex; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.92 (ddd, *J* = 14.8, 5.4, 3.2 Hz, $R_2CH(OR)$, 1H), 4.20 – 4.11 (m, OCH_2CH_3 x 2, 4H), 3.27 – 3.02 (m, R_3CH, 1H), 1.96 (ddq, *J* = 12.2, 8.8, 5.3, 4.4 Hz, R_3CH, 1H), 1.55 – 1.49 (m, RCH_2R, 1H), 1.45 (d, *J* = 4.8 Hz, Si-tBu, 9H), 1.35 – 1.27 (m, RCH_2R + RCH_3 x 2, 7H), 1.23 (tt, *J* = 11.4, 5.1 Hz, RCH_3, 3H), 0.98 – 0.88 (m, RCH_3 x 2, 6H).



***tert*-Butyl {6'*R* (1'''*S*-methylpropyl)-2', 2', 5'*S*-trimethyl-1', 3'-dioxane-4'*S*-yl}- (2''-methylbute-2'' *E*-enoyl)- 2*R*-oxo- 3*S*-methyl pentanoate (3.36)**. Compound **3.36** was prepared in multiple ways. *First method*: A

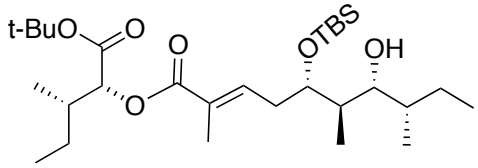
solution of phosphonate **3.35** (0.350 g, 0.920 mmol) in 3.0 mL dry CH_3CN was added to a pre-activated solution of LiCl (0.078 g, 1.840 mmol) in 3.0 mL CH_3CN, then added DIPEA (0.130 mL, 0.736 mmol) dropwise and stirred for 30 min at room temperature under argon atmosphere. Next, a solution of aldehyde **3.31** (0.084 g, 0.368 mmol) in 3.0 mL CH_3CN was added dropwise and the reaction mixture stirred for 15 hours overnight. Reaction was quenched with 15.0 mL sat. NH_4Cl and extracted with 3 x 15 mL Et_2O such that the combined organics were washed with brine and dried over Na_2SO_4. Filtered, concentrated in vacuo and chromatographed crude residue via silica gel column (0-15% EtOAc in hexanes gradient) to afford the title compound **3.36** (0.160 g, 99% yield) as a pale yellow oil. *Second method*: An oven dried round bottomed flask (5 mL) was charged with acid **3.63** (40.0 mg, 0.141 mmol) and alcohol **3.34** (34.0 mg, 181 mmol) and dissolved in freshly distilled CH_2Cl_2 (1.5 mL). The reaction mixture was placed under an argon atmosphere and cooled to 0 ºC using an ice-water bath. DCC (46.0 mg, 0.225 mmol) and DMAP (27.0 mg, o.225 mmol) were then added, the flask was sealed and the reaction mixture was stirred for 14 h at ambient temperature. The reaction was quenched with sat. NH_4Cl (6.0 mL) and the resulting mixture was transferred to a separation funnel and the aqueous phase was extracted with CH_2Cl_2 (4 × 10 ml). The combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure and the crude product was purified by silica gel chromatography using ethyl acetate in hexanes as a gradient (0–10%) to afford product **3.36** (56.0 mg, 88%) as a pale yellow clear oil; R_f = 0.6, 20% Et_2O/hex; $[\alpha]^{20}_D$ +14.0º (c=0.45, CH_2Cl_2, dr = 91:1). lit.[25] oil, $[\alpha]^{20}_D$ +5.2º (c=0.7, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (ddq, MeC=C*H*CH_2, *J* = 7.7, 6.4, 1.4 Hz, 1H), 4.93 (d, (CO)C*H*(OR)CH, *J* = 3.3 Hz, 1H), 3.59 (ddd, CH_2C*H*(OR)CH, *J* =

10.3, 7.3, 3.3 Hz, 1H), 3.44 (dd, CHC*H*(OR)CH, *J* = 10.2, 2.2 Hz, 1H), 2.52–2.44 (m, C=CHCH_2CH, 1H), 2.37–2.27 (m, C=CHCH_2CH, 1H), 2.03–1.97 (m, CHC*H*(Me)CH, 1H), 1.86 (d, H_3CC=CH, *J* = 1.4 Hz, 3H), 1.62–1.49 (m, CHCH_2CH$_3$, 2H), 1.46 (s, OC(CH_3)$_3$, 9H), 1.46–1.40 (m, CH(OR)C*H*CH(OR), "*partly hidden*", 1H), 1.38 (s, CCH_3, 3H), 1.37–1.33 (m, CH(OR)C*H*CH$_2$, "*partly hidden*", 1H), 1.32 (s, CCH_3, 3H), 1.30–1.25 (m, CHCH_2CH$_3$, "*partly hidden*", 2H), 0.98 (d, *J* = 6.9 Hz, CHCH_3, 3H), 0.93 (t, *J* = 7.5 Hz, CH$_2$CH_3, 3H), 0.87 (t, *J* = 7.4 Hz, CH$_2$CH_3, 3H), 0.82 (d, *J* = 6.8 Hz, CHCH_3, 3H), 0.74 (d, *J* = 6.6 Hz, CHCH_3, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.40, 167.60, 140.20, 128.36, 97.91, 81.80, 75.37, 75.13, 73.98, 36.94, 35.33, 35.13, 32.86, 30.15, 28.18, 26.83, 26.41, 19.61, 14.38, 12.72, 12.44, 12.17, 11.90, 11.84; FTIR (neat, cm^{-1}) 3386, 2965, 2930, 2878, 1749, 1716, 1461, 1380, 1229, 1130, 740; LC-MS (ESI) *m/z* calcd for $C_{26}H_{46}O_6Na$ $[M+Na]^+$ 477.32, found 477.29.



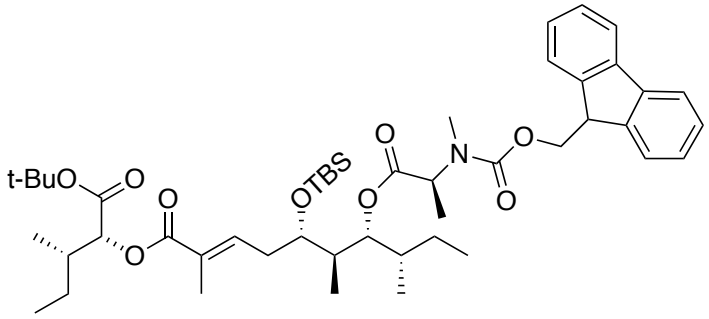
(2*R*,3*S*)-1-(*tert*-butoxy)-3-methyl-1-oxopentan-2-yl (5*S*,6*S*,7*R*,8*S*,*E*)-5,7-dihydroxy-2,6,8-trimethyldec-2-enoate (3.37): Acetonide **3.36** (0.075 g, 0.1650 mmol) was dissolved in 3.0 mL dry MeOH then charged with catalytic pTsOH (<1 mg, 1 mol%) and stirred 16 hours. The reaction was quenched with 8 mL satd. $NaHCO_3$ and evaporated, residue was extracted with 4 x 10 mL EtOAc and combined organics were washed with 30 mL brine, dried over Na_2SO_4, then filtered and concentrated under reduced pressure. 100 mg of crude pale yellow oil was purified via silica gel column chromatography (0-35% EtOAc in hexanes gradient) to afford the title compound **3.37** (0.063 g, 94% yield) as clear oil; R_f = 0.9, 20% EtOAc/hexanes; $[\alpha]^{20}_D$ -

1.0° (c 1.50, CH_2Cl_2); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.03 (t, *J* = 6.6 Hz, C=CH, 1H), 4.94 (d, *J* = 3.3 Hz, $R_2CH(OR)$, 1H), 3.88-3.85 (m, RCH_2R, 1H), 3.62-3.51 (m, RCH_2R, 1H), 2.54-2.48 (m, R_3CH, 1H), 2.46-2.35 (m, RCH_2R, 1H), 2.08-1.95 (m, RCH_2R, 1H), 1.90 (d, *J* = 1.4 Hz, RCH_3, 3H), 1.79-1.68 (m, RCH_2R, 1H), 1.58-1.49 (m, RCH_2R + R_3CH, "*overlapping signals*" 2H), 1.46 (s, OtBu, 9H), 1.38-1.25 (m, R_3CH + RCH_2R, "*overlapping signals*" 3H), 0.99 (t, J = 5.8 Hz, RCH_3, 3H), 0.96-0.90 (m, RCH_3 x 2, "*partially hidden*" 6H), 0.85 (t, J = 5.7 Hz, RCH_3, 3H), 0.79 (d, J = 6.9 Hz, RCH_3, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 167.5, 139.6, 129.6, 81.9, 79.1, 75.9, 75.3, 41.1, 37.0, 36.9, 34.6, 28.2, 27.1, 26.4, 14.5, 13.1, 12.9, 12.2, 11.9, 11.7; FTIR (neat, cm^{-1}) 3396, 2969, 1714, 1648, 1560, 1458, 1368, 1236, 1227, 1036, 849; APCI-MS *m/z* calcd for $C_{23}H_{43}O_6$ $[M+H]^+$ 415.3, found 415.0.



(2*R*,3*S*)-1-(*tert*-butoxy)-3-methyl-1-oxopentan-2-yl (5*S*,6*R*,7*R*,8*S*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-7-hydroxy-2,6,8-trimethyldec-2-enoate (3.38): 1, 3-diol **3.37** (0.030 g, 0.072 mmol) dissolved in 1.0 mL dry CH_2Cl_2 under inert argon atmosphere was charged with 2,6-lutidine (0.017 mL, 0.144 mmol) then TBSOTf (0.016 mL, 0.080 mmol) at -78 °C and stirred 1h. Reaction mixture was quenched with 5 mL cold DI water and extracted with CH_2Cl_2 (3 x 10 mL). Combined organics were washed with 1M HCl (15 mL), then Brine (15 mL) and dried over Na_2SO4. Organics were filtered, concentrated and chromatographed via silica gel column (0-15% EtOAc/Hex gradient) to afford the title compound **3.38** (0.036 g, 94% yield) as a

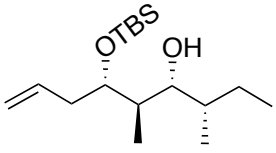
clear glass; R_f = 0.7, 20% EtOAc/Hex; $[\alpha]^{20}_D$ +0.02° (c 2.50, CH_2Cl_2) {similar (TES-ether) lit.[6] $[\alpha]^{20}_D$ +0.03° (c 1.3, CH_2Cl_2)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (t, *J* = 6.6 Hz, C=CH, 1H), 4.89 (d, *J* = 3.4 Hz, $R_2CH(OR)$, 1H), 4.12 - 4.06 (m, $R_2CH(OSi)$, 1H), 3.41 – 3.37 (m, $R_2CH(OH)$, 1H), 2.42 – 2.35 (m, RCH_2R, 2H), 2.15 (d, *J* = 4.1 Hz, R_3CH, 1H), 1.98 (pd, *J* = 7.0, 3.4 Hz, R_3CH, 1H), 1.87 (s, RCH_3, 3H), 1.82 – 1.73 (m, R_3CH, 1H), 1.45 (s, OtBu, 9H), 1.42 – 1.24 (m, RCH_2R + RCH_3, "*overlapping signals"* 3H), 0.98 (d, *J* = 6.9 Hz, RCH_3, 3H), 0.94 – 0.86 (m, RCH_3 x 2 + Si-tBu, "*overlapping signals"* 15H), 0.81 (d, *J* = 6.9, RCH_3 x 2, "*partially hidden*" 6H), 0.08 (s, Si-CH_3, 3H), 0.06 (s, Si-CH_3, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 167.6, 140.7, 128.4, 81.8, 75.8, 75.1, 74.3, 41.9, 36.9, 36.8, 33.3, 28.2, 27.3, 26.3, 26.0, 18.1, 14.5, 12.8, 12.2, 11.9, 11.8, 11.7, -4.3, -4.5; FTIR (neat, cm^{-1}) 2961, 1750, 1715, 1462, 1369, 1252, 1162, 1108, 1074, 954, 837, 775, 739; APCI-MS *m/z* calcd for $C_{29}H_{57}O_6Si$ $[M+H]^+$ 529.4, found 529.5.



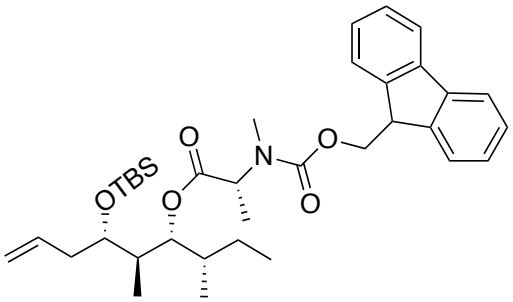
(2*R*,3*S*)-1-(*tert*-butoxy)-3-methyl 1-oxopentan-2-yl (5*S*, 6*R*, 7*R*, 8*S*, *E*)-7-((*N*-(((9*H*-fluoren-9-yl) methoxy) carbonyl)-*N*-methyl-*D*-alanyl)oxy)-5-((*tert*-butyldimethylsilyl) oxy)-2,6,8-trimethyl-dec-2-enoate (3.39): This compound was prepared in multiple ways. *First method*: DIPEA (50 μL, 0.283 mmol) was added to a solution of sterically congested alcohol **3.38**

(30 mg, 0.057 mmol) in 10.0 mL dry CH_2Cl_2 at 0 °C under argon atmosphere. Next, Fmoc-N-Me-L-Ala-Cl (0.142 mmol in 3.0 mL CH_2Cl_2) was added dropwise slowly over 2 min, then the reaction was brought to reflux for 19 hours (0.25 equiv DMAP may be added to increase yield at expense of ~70:30 dr). The reaction mixture was cooled to room temperature then quenched with 10 mL saturated NH_4Cl and extracted 4 x 10 mL EtOAc. The combined organics were washed successively with 10 mL saturated solutions of $NaHCO_3$, NH_4Cl then brine and dried over Na_2SO_4. Solids were filtered and filtrate was concentratued under reduced pressure to afford 70 mg crude yellow oil that was purified via silica gel column chromatography (0-10% EtOAc in hexanes gradient) to afford **3.39** (35 mg, 90% yield). *Second method*: A solution of 2-(diethoxyphosphoryl) propanoic acid **3.35** (16 mg, 0.0499 mmol) in 150 µL ACN was added to pre-activated LiCl (4 mg, 0.0999 mmol) in 150 µL ACN, followed by drop-wise addition of DIPEA (6 µL, 0.0328 mmol). Reaction stirred for 30 min at ambient temperature. Aldehyde **3.42** (10 mg, 0.0164 mmol) in 150 µL ACN was added drop-wise and mixture was stirred 14 hr until completion by TLC. Reaction was quenched with 10 mL saturated NH_4Cl (aq) and extraxted 3 x 15 mL diethyl ether. Combined organics were washed with 30 mL brine then dried over Na_2SO_4, concerntrated under reduced pressure and crude residue was purified on silica gel column (0-10% ethyl acetate in hexanes gradient) to afford **3.39** (7 mg, 70% yield) as a clear oil; R_f = 0.7, 10% EtOAc/Hex; $[\alpha]^{20}_D$ -23.7° (c 2.00, $CHCl_3$) {similar (TES-ether) lit.[6] $[\alpha]^{20}_D$ -29.3° (c 1.4, CH_2Cl_2)}; ^{1}H NMR (400 MHz, $CDCl_3$) *existed as rotational conformers*: δ 7.77 (d, *J* = 7.5 Hz, ArH x 2, 2H), 7.60 (m, ArH x 2, 2H), 7.40 (t, *J* = 7.5 Hz, Ar-H x 2, 2H), 7.31 (t, *J* = 7.5 Hz, Ar-H x 2, 2H), 6.88 – 6.79 (m, C=CH, 1H), 4.94 – 4.88 (m, $ROCH_2Ar$ + $R_2CH(OR)$, "*overlapping signals*" 3H),

4.48 – 4.34 (m, R_3CH x 2, "*overlapping signals*" 2H), 4.30 – 4.20 (m, $R_2CH(OR)$, 1H), 3.74 (m, $R_2CH(OSi)$, 1H), 2.95 (s, RCH_3, 1H), 2.43 – 2.22 (m, RCH_2R, 2H), 2.09 – 1.92 (m, RCH_2R, 2H), 1.86 (s, RCH_3, 3H), 1.66 – 1.59 (m, RCH_2R, 2H), 1.47 – 1.42 (m, OtBu + RCH_3, "*overlapping signals"* 12H), 1.35 – 1.23 (m, RCH_2R + R_3CH, "*overlapping signals"* 3H), 1.00 – 0.79 (m, Si-tBu + RCH_3 x 5, "*overlapping signals"* 24H), 0.04 - 0.01 (m, $SiCH_3$ x 2, "*overlapping signals"* 6H); ^{13}C NMR (101 MHz, $CDCl_3$) *existed as rotational conformers*: δ 172.0, 169.3, 167.6, 156.6, 144.2, 141.4, 141.1, 128.2, 127.8, 127.3, 125.1, 120.1, 81.7, 81.6, 78.3, 77.2, 75.2, 71.1, 67.9, 54.4, 49.5, 47.4, 47.1, 41.3, 36.9, 36.4, 30.9, 30.3, 28.2, 26.9, 26.2, 25.9, 25.9, 18.1, 15.3, 14.5, 12.8, 12.6, 12.1, 11.8, 10.0, -4.4, -4.5; FTIR (neat, cm^{-1}) 3414, 2966, 2933, 2881, 1739, 1710, 1452, 1384, 1368, 1309, 1264, 1214, 1159, 1130, 1079, 910, 837, 738; APCI-MS *m/z* calcd for $C_{48}H_{74}NO_9Si$ $[M+H]^+$ 836.5, found 836.2.

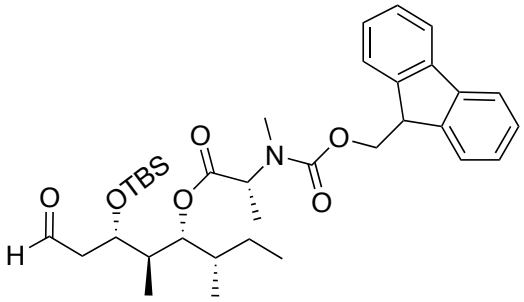


(3*S*,4*R*,5*R*,6*S*)-6-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethylnon-8-en-4-ol (3.40): 1, 3-diol (**3.29**) was mono-silated via the general procedure for silyl-ether protection of hydroxyl with TBS-OTf (1.1 equiv)/2,6-lutidine in DCM at -78 ^oC to afford the title compound **3.40** (0.016 g, 67% yield) as a clear oil; R_f = 0.7, 10% EtOAc/hex; *NMR scale shows incorrect ppm, see chromatogram*.

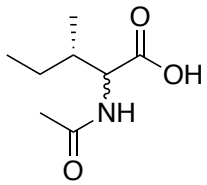


(3*S*,4*R*,5*R*,6*S*)-6-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethylnon-8-en-4-yl *N*-(((9*H*-fluoren-9-yl) methoxy) carbonyl)-*N*-methyl-*D*-alaninate (3.41): Collidine (53 μL, 0.399 mmol) and DMAP (1 mg, 0.001 mmol) were added to a solution of alcohol **3.40** (12 mg, 0.0399 mmol) in 2.5 mL dry toluene and stirred at 0 °C. Next, freshly prepared Fmoc-N-Me-L-Ala-Cl (0.1196 mmol in 2.0 mL toluene) was slowly added dropwise via cannula. The reaction was sealed and stirred at 60 °C for 14 hours overnight. The reaction mixture initiated as a yellow, cloudy mixture and was quenched heterogeneous. The reaction was quenched with 10 mL sat. NH_4Cl and extracted with 4 x 10 mL EtOAc. The combined organics were washed with 10 mL sat. $NaHCO_3$, 10 mL sat. NH_4Cl, 10 mL brine then dried over Na_2SO_4. Mixture was filtered and concentrated under reduced pressure. The crude residue was purified via silica gel column chromatography (0-10% EtOAc in hexanes linear gradient) to afford the title compound **3.41** (22 mg, 92% yield) as a clear glass; R_f = 0.5, 10% EAH; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.77 (dd, *J* = 7.9, 3.6 Hz, Ar-H, 2H), 7.63 – 7.56 (m, Ar-H, 2H), 7.42 – 7.37 (m, Ar-H, 2H), 7.34 – 7.28 (m, Ar-H, 2H), 5.77 (dt, *J* = 18.6, 9.3 Hz, C=CH, 1H), 5.09 – 4.82 (m, C=CH_2 + RCH_2R, 4H), 4.39 (td, *J* = 7.3, 4.0 Hz, R_3CH x 2, 2H), 4.26 (dt, *J* = 14.9, 7.7 Hz, $R_2CH(OR)$, 1H), 3.62 (dd, *J* = 24.6, 12.4 Hz, $R_2CH(OR)$, 1H), 2.94 (dd, *J* = 10.6, 3.8 Hz, NCH_3, 3H), 2.20 (t, *J* = 10.2 Hz, RCH_2R, 1H), 2.05 – 1.98 (m, RCH_2R + R_3CH, 2H), 1.61 (t, *J* = 6.9 Hz, RCH_2R, 2H), 1.45 (dd, *J* = 7.7, 3.5 Hz, RCH_3,

3H), 1.27 (qt, *J* = 14.0, 10.1, 8.4 Hz, RCH_2R, 2H), 1.13 (dd, *J* = 13.6, 7.1 Hz, R_3CH, 1H), 0.93 – 0.78 (m, RCH_3 + Si-tBu, 18H), 0.02 (s, Si-CH_3 x 2, 6H).

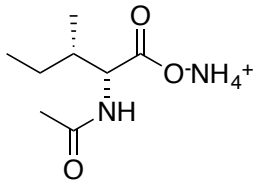


(3*S*,4*R*,5*R*,6*S*)-6-((*tert*-butyldimethylsilyl) oxy) -3, 5-dimethyl-8-oxooctan-4-yl *N*-(((9*H*-fluoren-9-yl) methoxy) carbonyl)-*N*-methyl-*D*-alaninate (3.42): The title compound was prepared by the general procedure for ozonolysis of alkenes (**3.41**) to afford **3.42** (0.013 g, 72% yield) as clear oil; R_f = 0.4, 10% EtOAc/hex; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.76 – 9.64 (m, RCHO, 1H), 7.77 (d, *J* = 7.6 Hz, Ar-H, 2H), 7.61 (d, *J* = 7.8 Hz, Ar-H, 2H), 7.40 (t, *J* = 7.5 Hz, Ar-H, 2H), 7.31 (t, *J* = 7.4 Hz, Ar-H, 2H), 5.30 (d, *J* = 0.7 Hz, R_3CH, 1H), 4.84 (p, *J* = 7.6 Hz, R_3CH, 1H), 4.77 (dd, *J* = 10.5, 2.4 Hz, R_3CH, 1H), 4.42 – 4.36 (m, RCH_2R, 2H), 4.26 (t, *J* = 6.9 Hz, RCH_2R, 2H), 2.96 (d, *J* = 11.1 Hz, RCH_3, 3H), 2.49 (dd, *J* = 7.7, 5.0 Hz, R_3CH, 1H), 2.07 (ddd, *J* = 10.5, 7.1, 3.5 Hz, R_3CH, 1H), 1.65 – 1.57 (m, R_3CH, 1H), 1.48 (dd, *J* = 11.0, 7.4 Hz, RCH_3, 3H), 1.31 – 1.09 (m, RCH_2R, 2H), 0.93 – 0.87 (m, RCH_3 x 3, 9H), 0.85 (s, Si-tBu, 9H), 0.10 – 0.01 (m, Si-CH_3 x 2, 6H).

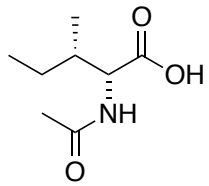


(3*S*)-2-acetamido-3-methylpentanoic acid (3.43):[40] To solution of L-isoleucine (6.500 g, 49.50 mmol) in 40 mL AcOH was added dropwise 6.5 mL acetic

anhydride. The resulting solution was stirred at 80 °C for 3 hrs the evaporated to dryness. Recrystallization from hot H_2O afforded the title compound **3.43** (6.236 g, 73% yield) as white crystals; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.57 (s, RCOOH, 1H), 7.93 (dd, J = 33.9, 8.6 Hz, NH, 1H), 4.26 (ddd, J = 68.7, 8.6, 5.4 Hz, R_3CH, 1H), 2.52 (p, J = 1.9 Hz, R_3CH, 2H), 1.88 (d, J = 5.9 Hz, RCH_3, 3H), 1.47 – 1.07 (m, RCH_2R, 2H), 0.90 – 0.83 (m, RCH_3 x 2, 6H).

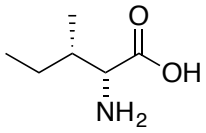


ammonium acetyl-*D*-alloisoleucinate (3.44): Treated **3.43** (5.00 g, 28.867 mmol) with 115 mL ammonium hydroxide (1M, 115.467 mmol) solution then added 35 µL of concentrated NH_4OH and stirred overnight hours. Diluted with 20 mL EtOH then concentrated. Crude ammonium salt residue was resolved by recrystallization of the desired diastereomer from EtOH to afford the title compound **3.44** (2.394 g, 87% yield) as white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41 (d, J = 8.7 Hz, NH, 1H), 4.10 (dd, J = 8.8, 4.2 Hz, R_3CH, 1H), 1.84 (s, RCH_3, 3H), 1.80 (td, J = 6.9, 4.2 Hz, R_3CH, 1H), 1.36 – 1.21 (m, RCH_2R, 1H), 1.12 – 0.99 (m, RCH_2R + R_3CH, 2H), 0.84 (t, J = 7.4 Hz, RCH_3, 3H), 0.78 (d, J = 6.9 Hz, RCH_3, 3H).

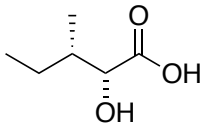


acetyl-*D*-alloisoleucine (3.45): Ammonium salt **3.44** (1.00 g, 5.257 mmol) was dissolved in 12.5 mL DI H_2O then added 5M HCl until pH<1. The reaction mixture was cooled in the freezer the filtered off white solid Ac-D-allo-Ile **3.45** (0.892,

98% yield) as an off white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.75 (d, J = 8.8 Hz, NH, 1H), 3.21 (dd, J = 8.8, 4.8 Hz, R_3CH, 1H), 0.75 (s, RCH_3, 3H), 0.74 – 0.63 (m, R_3CH, 1H), 0.24 – 0.11 (m, RCH_2R, 1H), 0.08 – -0.07 (m, RCH_2R, 1H), -0.25 – -0.32 (m, RCH_3 x 2, 6H).

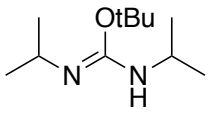


***D*-alloisoleucine (3.46):** Dissolved **3.45** (0.838 g, 4.838 mmol) in 12 mL 2M HCl and heated to 80 °C for 2 hrs. Mixture was evaporated and the crude residue was dissolved in 10 mL EtOH and neutralized with NEt_3 so that the title compound **3.46** (0.253 g, 40% yield) was collected by filtration; ^{1}H NMR (400 MHz, Deuterium Oxide) δ 3.80 (dd, J = 3.5, 1.8 Hz, R_3CH, 1H), 2.13 (dt, J = 10.6, 6.8 Hz, RCH_2R, 1H), 1.50 (dt, J = 14.3, 7.1 Hz, R_3CH, 1H), 1.40 (dt, J = 13.2, 7.4 Hz, RCH_2R, 1H), 1.07 – 0.96 (m, RCH_3 x 2, 6H).

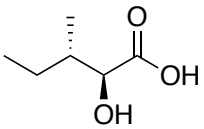


(2*R*,3*S*)-2-hydroxy-3-methylpentanoic acid (3.47): *D*-allo-isoleucine (0.420 g, 3.202 mmol) was dissolved in 1 M H_2SO_4 (8.50 mL) and the solution cooled to ~0 ºC using an ice-water bath. Sodium nitrite (1.679 g, 24.335 mmol) was dissolved in water (8.50 mL) and then slowly added to the cold stirred amino acid solution over 4 hours. The reaction was allowed to warm to ambient temperature and the mixture continued to stir for 38 h. The aqueous solution was then saturated with sodium chloride, transferred to a separation funnel and extracted with EtOAc (3 × 75 mL). The combined organic layers were washed with water 2 x 20 mL and brine 2 x 20 mL, dried over

anhydrous sodium sulfate. Removal of solvent under reduced pressure gave **3.49** (0.304 g, 72% yield); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.29 (dd, *J* = 2.9, 1.0 Hz, R_3CH, 1H), 1.88 (ddd, *J* = 7.8, 5.1, 1.8 Hz, R_3CH, 1H), 1.61 – 1.49 (m, RCH_2R, 1H), 1.39 – 1.31 (m, RCH_2R, 1H), 1.00 – 0.84 (m, RCH_3 x 2, 6H).

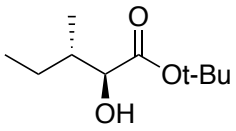


***tert*-butyl (*Z*)-*N*,*N*'-diisopropylcarbamimidate (3.48):**[43] CuCl (64 mg, 0.64 mmol, 1 mol%) was added to a solution of *N,N*-diisopropylcarbodiimide (10.0 mL, 63.9 mmol, 1 equiv) in *t*BuOH (6.97 mL, 73.5 mmol) and stirred for 16 hours at ambient temperature. Solution was distilled to afford *N,N*-diisopropyl-OtBu-isourea **3.48** (5.75 g, 50%, bp 85 °C @ 2 mmHg) as a clear liquid; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.66 (dp, *J* = 7.9, 6.4 Hz, R_3CH, 1H), 3.13 (pd, *J* = 6.1, 1.4 Hz, R_3CH, 1H), 1.47 (s, OtBu, 9H), 1.09 (d, *J* = 6.4 Hz, RCH_3 x 2, 6H), 1.05 (d, *J* = 6.2 Hz, RCH_3 x 2, 6H).

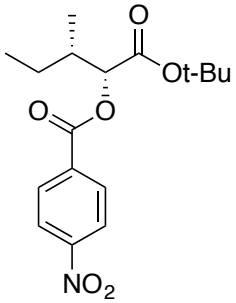


2*S*-Hydroxy-3*S*-methylpentanoic acid (3.49).[145] *L*-isoleucine (10.0 g, 76.2 mmol) was dissolved in 1 M H_2SO_4 (200 mL) and the solution cooled to ~0 ºC using an ice-water bath. Sodium nitrite (42.1 g, 610 mmol) was dissolved in water (200 mL) and then slowly added to the cold stirred amino acid solution over 4 hours. 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 separation funnel and extracted with EtOAc (3 × 75 mL). The combined organic layers were washed with water 2 x 100ml and brine 2 x 100 ml and dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure gave **3.49** (9.97 g, 99%); mp 39.5-44.3 ºC,

$[\alpha]^{20}_{D}$ +17.7º (c=2.0, $CHCl_3$) {lit.[145], mp 50–52 ºC), $[\alpha]^{20}_{D}$ +21.9º (c=1, $CHCl_3$)}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.19 (d, C*H*OH, *J* = 3.6 Hz, 1H), 1.95–1.84 (m, CH_3CH, 1H), 1.50–1.38 (m, CH_3CH_2, 1H), 1.37–1.24 (m, CH_3CH_2, 1H), 1.03 (d, CH_3CH, *J* = 6.9 Hz, 3H), 0.93 (t, CH_3CH_2, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.77, 74.47, 38.62, 24.19, 15.87, 11.96.

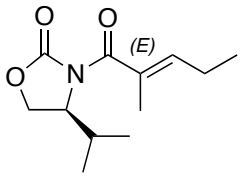


***tert*-butyl (2*S*,3*S*)-2-hydroxy-3-methylpentanoate (3.50):**[42] *N,N*-diisopropyl-OtBu-isourea **3.48** (1.0 mL) was added to a solution of α-hydroxy acid **3.49** (50 mg, 0.379 mmol) in 8.0 mL CH_2Cl_2 and heated to reflux for 12 hr. Mixture was evaporated under reduced pressure then chromatographed via silica gel column (0-10% EtOAc in hexanes gradient) to afford α-hydroxy ester **3.50** (65 mg, 92% yield) as a clear liquid; R_f = 0.4, 10% EAH; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.94 (ddd, *J* = 5.6, 3.5, 2.0 Hz, R_3CH, 1H), 2.83 – 2.76 (m, ROH, 1H), 1.76 (ddddd, *J* = 9.1, 6.9, 4.6, 3.6, 2.2 Hz, R_3CH, 1H), 1.48 (dd, *J* = 2.3, 1.2 Hz, OtBu, 9H), 1.43 – 1.31 (m, RCH_2R, 1H), 1.30 – 1.17 (m, RCH_2R, 1H), 0.96 (dd, *J* = 6.9, 2.2 Hz, RCH_3, 3H), 0.93 – 0.86 (m, RCH_3, 3H).



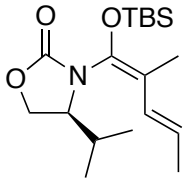
1-(*tert*-Butoxy)-3*S*-methyl-1-oxopentan-2*R*-yl-4-nitrobenzoate (3.51): An oven-dried two-necked round-bottom flask (250 mL) was charged under an argon atmosphere with alcohol **3.50** (1.50 g, 7.97 mmol), 4-nitrobenzoic acid (2.24 g,

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, "DIAD", (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 separation funnel and the aqueous phase was extracted with EtOAc (3 × 150 mL). The combined organic phases were washed with water (3 × 50 mL), brine (50 mL), and dried over anhydrous sodium sulfate. After filtration of the organic solvent, the solution was concentrated under reduced pressure and the crude product purified by flash chromatography. The crude was diluted with 5 mL diethyl ether, injected into a 100g silica column and ran with diethyl ether-hexanes as a gradient (0% 2 CV, 0–20% 10 CV, 20% 2 CV) to afford product **3.51** in 82% yield (2.20 g) as a bright yellow oil, $[\alpha]^{20}_{D}$ -29.1º (c=2.3, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, Ar*H*, *J* = 8.8 Hz, 2H), 8.24 (d, Ar*H*, *J* = 8.8 Hz, 2H), 5.19 (d, C*H*CO, *J* = 3.2 Hz, 1H), 2.16–2.12 (m, CH_3CH, 1H), 1.57–1.49 (m, CH_3CH_2, "*partly hidden*", 1H), 1.48 (s, *t*Bu, 9H), 1.46–1.33 (m, CH_3CH_2, 1H), 1.09 (d, CH_3CH, *J* = 6.9 Hz, 3H), 0.99 (t, CH_3CH_2, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.35, 164.31, 150.65, 135.36, 130.84, 123.56, 82.44, 76.33, 36.72, 28.01, 26.22, 14.32, 11.70.



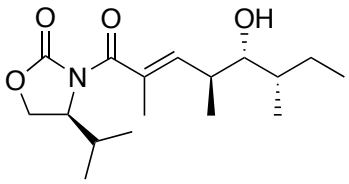
N-(2'-Methyl-2'E-pentenoyl)-4S-isopropyl-1,3-oxazolid- in-2-one (3.52a).[146] Butyllithium (2.5 M in hexane, 15.6 mL, 39.1 mmol, 1.01 equiv) was added dropwise to a solution of (S)-(+)-4-isopropyl-1,3-oxazolidin-2-one[147] (5.00 g, 38.7 mmol) in anhydrous THF (70.0 mL) at –78 ºC under argon. The resulting mixture was stirred for 15 min and a freshly distilled 2-methyl-2E-pentenoyl chloride (5.13 g, 38.7 mmol) in dry THF (30 mL) was added via syringe at –78 ºC. The reaction was stirred for an additional 45 min at –78 ºC and then warmed to ambient temperature. Saturated aqueous ammonium chloride (50 mL) was added and the resulting mixture stirred for 30 min. The solvent was removed under reduced pressure and the remaining aqueous phase transferred to a separation funnel. The aqueous phase was extracted with DCM (2 × 100 mL), the combined organics were washed with 3.0 M NaOH (25 mL), water (25 mL), brine (25 mL), dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crude product was purified with flash chromatography using hexanes/ethyl acetate 0–20% as a gradient to give 96% (8.37 g) of **A** as a white solid; mp 39–40 ºC (lit.[146], oil), $[\alpha]^{20}_{D}$ +80.4º (c=0.95, $CHCl_3$) {lit.[146] $[\alpha]^{20}_{D}$ +84.2º (c=1.0, $CHCl_3$)}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.07 (tq, $CH_2CHC(CO)$, J = 7.2, 1.5 Hz, 1H), 4.51 (m, NCH, 1H), 4.31 (dd, OCH_2, J = 8.9, 8.9 Hz, 1H), 4.17 (dd, OCH_2, J = 8.9, 5.4 Hz, 1H), 2.40–2.32 (m, $CH(CH_3)_2$, 1H), 2.24–2.17 (m, CH_3CH_2CH, 2H), 1.90 (t, $CH_3C(CO)$, J = 1.2 Hz, 3H), 1.05 (t, CH_3CH_2, J = 7.6 Hz, 3H), 0.94–0.89 (2d, CH_3CH, J = 7.2 Hz each, 3H each); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.90, 153.60, 141.02, 130.25,

63.37, 58.27, 28.28, 21.64, 17.82, 15.02, 13.41, 12.76; FTIR (cm^{-1}) 2964, 1788, 1682, 1466, 1396, 1368, 1279, 1220, 1048, 734.



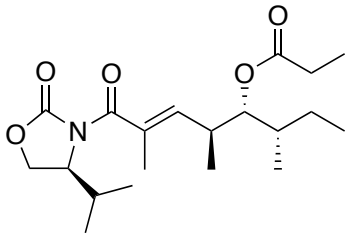
***N*-(1'-*tert*-Butyldimethylsilyloxy-2'-methyl-penta-1'*E*,3' *E*-dienyl)-4*S*-isopropyl-1,3-oxazolidin-2-one (3.52).**[9] A premade solution of potassium hexamethyldisilylamide (KHMDS) (4.00 g, 20.1 mmol) in anhydrous THF (50 mL) was added dropwise to a solution of imide **3.52a** (3.00 g, 13.3 mmol) 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% (4.34 g) of **3.52** as a white solid, mp 39–43 ºC, $[\alpha]^{20}_{D}$ -53.8º (c=0.84, $CHCl_3$) {lit.[20] oil, $[\alpha]^{25}_{D}$ -50.4º (c=0.84, $CHCl_3$)}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.21 (d, C*H*CHCH$_3$, *J* = 15.5 Hz, 1H), 5.63 (dq, CH=C*H*CH$_3$, *J* = 15.5, 6.5 Hz, 1H), 4.34–4.29 (m, OC*H*$_2$, 1H), 4.15–4.09 (m, OC*H*$_2$, 1H), 4.03–3.97 (m, NC*H*, 1H), 1.98–1.90 (m, C*H*(CH$_3$)$_2$, 1H), 1.80–1.77 (dd, CHCHC*H*$_3$, *"partly hidden"*, *J* = 6.5, 1.6 Hz, 3H), 1.78 (s, C=CC*H*$_3$, 3H), 0.98 (s, ^{t}Bu, 9H), 0.94–0.91 (d, CH(C*H*$_3$)$_2$, *J* = 6.9

Hz, 6H), 0.19, 0.14 (2s, Si(CH_3)$_2$, 3H each); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.04, 134.81, 128.27, 124.50, 115.13, 64.54, 59.52, 29.52, 25.81, 18.92, 18.49, 18.20, 16.45, 12.45, -4.16, -4.72.



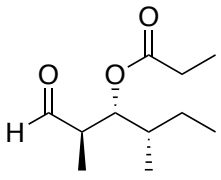
***N*-(5'*R*-Hydroxy-2',4'*S*,6'*S*-trimethyl-2'*E*-octenoyl)-4*S*-isopropyl-1,3-oxazolidin-2-one (3.53).**[148] A solution of $TiCl_4$ (6.63 mmol, 1.50 equiv) in CH_2Cl_2 (20 mL) was added dropwise to a solution of (*S*)-2-methylbutanal[17] (**3.1**) (13.25 mmol, 3.00 equiv) in CH_2Cl_2 (30 mL) at –78 ºC. The resulting reaction mixture was stirred for 30 min at –78 ºC and a solution of vinylketene silyl *N,O*-acetal (**3.52**) (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 hr 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 separation 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 the aldol product (**3.53**) in a 96% (1.38 g) as colorless oil, $[\alpha]^{20}_D$ +21.6º (c=0.97, MeOH). {lit.[148] oil, $[\alpha]^{20}_D$ +24.2º (c=0.91, MeOH)} ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (dq, CHC*H*=CCH$_3$, *J* = 10.4, 1.5 Hz, 1H), 4.57 (ddd, NC*H*, *J* = 8.9, 5.8, 4.5 Hz, 1H), 4.34 (dd, OCH_2, *J* = 9.0, 8.9 Hz, 1H), 4.18 (dd, OCH_2, *J* = 9.0, 5.8 Hz, 1H), 3.30 (dd, C*H*OH, *J* =

8.9, 2.4 Hz, 1H), 3.00 (bs, CHO*H*, 1H), 2.78–2.69 (ddq, CHC*H*(Me)CHOH, *J* = 10.4, 9.1, 6.7 Hz, 1H), 2.38–2.31 (m, C*H*(CH_3)$_2$, 1H), 1.95 (d, CH_3C=CH, *J* = 1.5 Hz, 3H), 1.60–1.53 (m, C*H*(Me)CH_2, "*partly hidden*", 1H), 1.53–1.47 (m, CH(Me)CH_2, "*partly hidden*", 1H), 1.43–1.37 (m, CH(Me)CH_2, "*partly hidden*", 1H), 0.95–0.90 (m, 4×CH_3, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.63, 154.48, 142.58, 131.13, 76.82, 63.45, 58.09, 37.32, 35.84, 28.45, 27.34, 17.83, 15.66, 15.21, 13.90, 12.11, 11.97; FTIR (neat, cm^{-1}) 3526, 2964, 1772, 1686, 1464, 1369, 1301, 1209, 996, 776, 688.



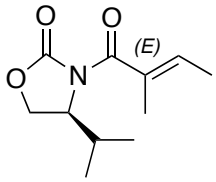
***N*-(2',4'*S*,6'*S*-Trimethyl-5'*R*-propionyloxy-2'*E*-octenoyl) - 4*S*-isopropyl-1,3-oxazolidin-2-one (3.54)**. Alcohol **3.53** (1.93 g, 6.20 mmol, 1.00 equiv) was charged in a dry 100 mL round bottom flask under argon. The substrate was dissolved in freshly distilled CH_2Cl_2 (18 mL) and then the solution was cooled to 0 ºC using an ice/water bath. Anhydrous pyridine (2.00 mL, 24.79 mmol, 4.00 equiv) was added followed by drop-wise addition of freshly distilled propionyl chloride (2.17 mL, 24.79 mmol, 4.00 equiv) 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 hours. Saturated ammonium chloride (20 mL) was then added to the resulting homogeneous solution at room temperature. The reaction mixture was then transferred to a separation funnel and phases separated. The aqueous phase was then extracted with CH_2Cl_2 (3 × 20 mL), the combined organics were washed with 1M NaOH (20 mL), Brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

The crude material was the purified using a silica gel column (0–25% ethyl acetate in hexanes gradient) to give the aldol product (**3.54**) in 97% (2.21 g) as colorless oil; $[\alpha]^{20}_{D}$ +62.5º (c=1.55, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (dq, CHC*H*=CCH_3, *J* = 9.8, 1.5 Hz, 1H), 4.87 (dd, CHC*H*(OR)CH, *J* = 6.8, 5.3 Hz, 1H), 4.45 (ddd, NC*H*, *J* = 8.7, 4.7, 4.4 Hz, 1H), 4.29 (dd, OCH_2, *J* = 8.8, 8.7 Hz, 1H), 4.18 (dd, OCH_2, *J* = 8.8, 4.7 Hz, 1H), 2.91–2.83 (ddq, C*H*(Me)CH(OR), *J* = 9.8, 6.8, 6.8 Hz, 1H), 2.42–2.36 (m, C*H*$(CH_3)_2$, "*partly hidden*", 1H), 2.36–2.30 (dq, C(O)CH_2CH_3, *J* = 7.6, 3.4 Hz, 2H), 1.91 (d, CH_3C=CH, *J* = 1.5 Hz, 3H), 1.72–1.63 (m, C*H*(Me)CH_2, 1H), 1.41–1.32 (m, CH(Me)CH_2CH_3, 1H),1.20–1.09 (m, CH(Me)CH_2CH_3, "*partly hidden*", 1H), 1.13 (t, CH_2CH_3, *J* = 7.6 Hz, 3H), 0.98 (d, CHCH_3, *J* = 6.8 Hz, 3H), 0.92 (d, CHCH_3, *J* = 6.8 Hz, 3H), 0.92–0.89 (t, CH_2CH_3, "*partly hidden*", *J* = 6.8 Hz, 3H), 0.90 (d, CH(CH_3)$_2$, "*partly hidden*", *J* = 6.8 Hz, 3H), 0.89 (d, CH(CH_3)$_2$, "*partly hidden*", *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.30, 171.65, 153.34, 138.61, 131.36, 78.76, 63.38, 58.38, 36.12, 34.74, 28.31, 27.69, 26.28, 17.88, 16.41, 14.88, 13.67, 13.63, 11.38, 9.27; FTIR (neat, cm^{-1}) 2965, 1787, 1736, 1684; HRMS (ESI) m/z calcd for $C_{20}H_{33}NO_5Na$ $[M+Na]^+$ 390.2251, found 390.2248.



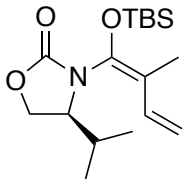
2*R*,4*S*-Dimethyl-3*R*-propionyloxy-1-hexanal (3.55). A solution of compound **3.54** (1.01 g, 2.73 mmol) in anhydrous CH_2Cl_2 (50 mL) was cooled to –78 ºC. A slow stream of ozone gas was then bubbled through the solution for roughly 30 min until the solution turned light blue. The blue solution was 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 then added drop-wise over 5 min at –78 ºC. The temperature was then raised to ambient temperature and the mixture stirred an additional 12 hours. The solvent was removed under reduced pressure and the remaining crude product was purified on a silica gel plug (hexanes in ethyl acetate, 0–15% as a gradient) to afford **3.55** as a clear oil in 95% (0.519 g); $[\alpha]^{20}_{D}$ –0.85º (c=3.75, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (d, C*H*O, *J* = 3.2 Hz, 1H), 5.13 (dd, CHC*H*(OR)CH, *J* = 7.5, 4.6 Hz, 1H), 2.69–2.60 (ddq, *H*CCHO, *J* = 7.5, 7.0, 3.2 Hz, 1H), 2.36–2.29 (q, C(O)CH_2CH$_3$, *J* = 4.8 Hz, 2H), 1.75–1.66 (m, C*H*(Me)CH$_2$,1H), 1.45–1.32 (m, CH(Me)CH_2, 1H), 1.25–1.12 (m, CH(Me)CH_2, "*partly hidden*", 1H), 1.14 (t, CH$_2$CH_3, *J* = 7.6 Hz, 3H), 1.09 (d, CHCH_3, *J* = 7.1 Hz, 3H), 0.93 (t, "*partly hidden*", CH$_2$CH_3, *J* = 7.5 Hz, 3H), 0.92 (d, CHCH_3, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.83, 174.13, 75.82, 48.55, 36.17, 27.74, 26.29, 13.51, 11.64, 11.19, 9.34; FTIR (neat, cm^{-1}) 2974, 1736, 1706; HRMS (ESI) m/z calcd for $C_{11}H_{20}O_3$ $[M+H]^+$ 201.1485, found 201.1488.



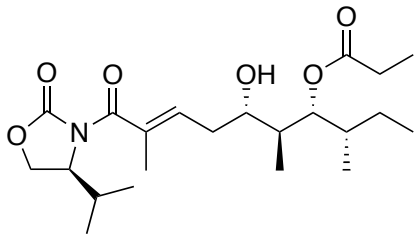
***N*-(2'-Methyl-2'*E*-butanoyl)-4*S*-isopropyl-1,3-oxazolidin-2-one (3.56a).**[149] Compound **3.56a** was synthesized following the identical procedure as for the preparation of compound **3.52a**. Starting with (*S*)-(+)-4-isopropyl-1,3-oxazolidin-2-one[147] (5.00 g, 38.7 mmol) gave 96% (8.30 g) of compound **3.56a** as a white solid; mp 54–55 ºC, $[\alpha]^{20}_{D}$ +98.0º (c=1.07, $CHCl_3$). (lit.[149] mp 63–64 ºC, $[\alpha]^{20}_{D}$ +91.8º (c=0.7, $CHCl_3$). ^{1}H

NMR (500 MHz, $CDCl_3$) δ 6.20 (qq, $CH_3HC{=}CCH_3(CO)$, J = 7.0, 1.3 Hz, 1H), 4.52 (ddd, NCH, J = 8.9, 5.5, 4.4 Hz, 1H), 4.31 (dd, OCH_2, J = 8.9, 8.9 Hz, 1H), 4.17 (dd, OCH_2, J = 8.9, 5.5 Hz, 1H), 2.41–2.31 (m, $CH(CH_3)_2$, 1H), 1.90 (q, $CH_3HC{=}CCH_3(CO)$, J = 1.3 Hz, 3H), 1.80 (dq, $CH_3HC{=}CCH_3(CO)$, J = 7.0, 1.3 Hz, 3H), 0.95–0.88 (2d, $(CH_3)_2CH$, J = 7.0 Hz each, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.81, 153.66, 134.51, 131.82, 63.40, 58.29, 28.29, 17.85, 15.04, 14.05, 13.34.



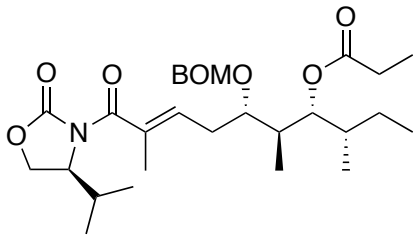
***N*-(1'-*tert*-Butyldimethylsilyloxy-2'-methyl-buta-1'*E*,3'dienyl)-4*S*-isopropyl-1,3-oxazolidin-2-one (3.56).**[9] A solution of solid KHMDS (3.20 g, 16.02 mmol) in anhydrous THF (230 mL) was added dropwise to a solution of imide **3.56a** (1.81 g, 10.68 mmol) in THF (110 mL) at –78 ºC. After the 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 separation funnel, the phases separated and the aqueous phase extracted with ethyl acetate (4 × 20 mL). The combined organic phases were 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 crude product was then purified with flash chromatography using hexanes/ethyl acetate 0–40%

as a gradient to give 86% (2.99 g) of vinylketene silyl *N,O*-acetal **3.56** as a white solid; mp 44–49 ºC, $[\alpha]^{20}_{D}$ -71.0º (c=0.87, $CHCl_3$). {lit.[9] mp 48.7 ºC, $[\alpha]^{25}_{D}$ -65.7º (c=0.87, $CHCl_3$)}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (dd, *H*C=CH_2, *J* = 17.1, 10.0 Hz, 1H), 5.05 (d, HC=C*H*$_2$, *J* = 17.1 Hz, 1H), 4.94 (d, HC=C*H*$_2$, *J* = 10.9, 1H), 4.27–4.20 (m, OC*H*$_2$, 1H), 4.07–4.00 (m, OC*H*$_2$, 1H), 3.97–3.89 (m, NC*H*, 1H), 1.91–1.82 (m, C*H*$(CH_3)_2$, 1H), 1.71 (s, C=C(C*H*$_3$), 3H), 0.90 (s, ^{t}Bu, 9H), 0.84, 0.83 (2d, CH(C*H*$_3$)$_2$, "partly overlap", *J* = 7.0 Hz, 3H each), 0.12, 0.10 (2s, Si(C*H*$_3$)$_2$, 3H each); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.90, 136.83, 133.92, 115.23, 112.42, 64.52, 59.46, 29.49, 25.76, 18.34, 18.08, 16.39, 11.64, -4.23, -4.71.



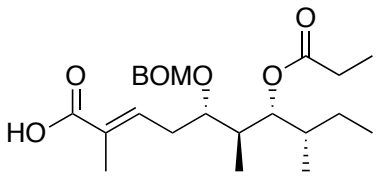
***N*-(5'*S*-Hydroxy-2',6'*S*,8'*S*-trimethyl-7'*R*-propionyloxy-2'*E*-decenoyl)-4*S*-isopropyl-1,3-oxazolidin-2-one (3.57)**. To a stirred solution of aldehyde **3.55** (0.350 g, 1.75 mmol) in toluene (2.0 mL) at –78 ºC under argon was slowly added $TiCl_4$ (2.65 mL, 1.0 M solution in toluene, 2.65 mmol). The reaction mixture was stirred for 20 min at –78 ºC and a solution of vinylketene silyl *N,O*-acetal **3.56** (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 the 72 hour reaction time a mixture of saturated aqueous Rochelle salt and saturated aqueous

$NaHCO_3$ was added (1:1, 25 mL) at -40 ºC. The mixture was then stirred vigorously at ambient temperature until the resulting slurry became homogeneous and then transferred to a separation funnel. The aqueous phase was extracted with ethyl acetate (4 × 20 mL) and the combined organic phases were 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 remaining crude product was purified with flash chromatography using hexanes/ethyl acetate 0–35% as a gradient to give 48% (344 mg) of aldol product **3.57** (*dr* = 91:9) as a clear oil, $[\alpha]^{20}_{D}$ +47.2º (c=1.06, MeOH, *dr* = 91:9); ^{1}H NMR (500 MHz, $CDCl_3$) "*Major diasteromer*" δ 6.09 (dd, C=C*H*CH_2, *J* = 7.3 Hz, 1H), 4.90 (dd, CHC*H*(OR)CH, *J* = 10.0, 2.8 Hz, 1H), 4.50 (ddd, NC*H*, *J* = 9.0, 5.0, 4.8 Hz, 1H), 4.30 (dd, OC*H*$_2$CH, *J* = 9.0, 9.0 Hz, 1H), 4.17 (dd, OC*H*$_2$CH, *J* = 9.0, 5.0 Hz, 1H), 3.64–3.58 (m, CH_2C*H*(OH)CH, 1H), 2.87 (s, CHO*H*, 1H), 2.50–2.41 (m, CHC*H*$_2$CH(OH), "*partly hidden*", 1H), 2.39 (q, C(OR)C*H*$_2$$CH_3$, "*partly hidden*", *J* = 7.6 Hz, 2H), 2.37–2.31 (m, CHC*H*$(CH_3)_2$, "*partly hidden*", 1H), 2.28 (m, CHC*H*$_2$CH(OH), 1H), 1.92 (s, HC=CC*H*$_3$, 3H), 1.80–1.71 (m, CH(OH)C*H*CH_3, 1H), 1.71–1.63 (m, CH(OR)C*H*CH_3, 1H), 1.35–1.24 (m, CHC*H*$_2$$CH_3$, 1H), 1.22–1.12 (m, CHC*H*$_2$$CH_3$, "*partly hidden*" 1H), 1.17 (t, CH_2C*H*$_3$, *J* = 7.6 Hz, 3H), 0.94–0.88 (m, 4 × CHC*H*$_3$ + CH_2C*H*$_3$, 15H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.12, 171.84, 153.73, 135.96, 132.28, 77.58, 69.04, 63.54, 58.44, 39.15, 35.78, 33.38, 28.49, 27.90, 27.23, 18.02, 15.19, 13.99, 12.68, 11.96, 9.51, 9.03; FTIR (neat, cm^{-1}) 3527, 2966, 1782, 1733, 1683, 1203; HRMS (ESI) m/z calcd for $C_{22}H_{37}NO_6Na$ $[M+Na]^+$ 434.2513, found 434.2515.



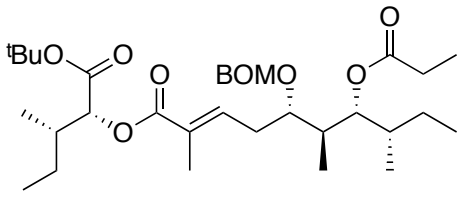
***N*-(5'*S*-Benzyloxymethoxy-2',6'*S*,8'*S*-trimethyl-7'*R*-propionyloxy-2'*E*-decenoyl)-4*S*-isopropyl-1,3-oxazolidin-2-one (3.58)**. To a stirred solution of **3.57** (*dr* = 91:9) (300 mg, 0.729 mmol) in anhydrous CH_2Cl_2 (6.0 mL), diisopropylethylamine (0.240 mL, 1.312 mmol) and tetrabutyl-ammonium iodide (0.068 g, 0.182 mmol) under argon was added benzyloxymethylchloride (0.220 mL, 1.093 mmol, 1.50 equiv). The resulting reaction mixture was stirred for 9 h at room temperature. The mixture was then quenched with MeOH (5 mL), stirred for 10 min and the solvents evaporated under reduced pressure. The residue was dissolved in ethyl acetate (10.0 mL), water (8 mL) was added and the mixture transferred to a separation funnel. The aqueous phase was extracted with ethyl acetate (3 × 8 mL) and combined organics were dried over anhydrous Na_2SO_4. The solvent was filtered, concentrated under reduced pressure and the residual yellow oil was purified with flash chromatography using hexanes/ethyl acetate 0–20% as a gradient to give 93% (360 mg) of **3.58** (*dr* = 91:9) as a colorless oil; $[\alpha]^{20}_D$ +56.7º (c=3.50, $CDCl_3$, *dr* = 91:9). ^{1}H NMR (400 MHz, $CDCl_3$) "*Major diasteromer*" δ 7.33–7.31 (m, Ar*H*, 5H), 6.03 (ddq, MeC=C*H*CH_2, *J* = 8.1, 6.6, 1.5 Hz, 1H), 5.03 (dd, CHC*H*(OR)CH, *J* = 9.7, 2.5 Hz, 1H), 4.80 (d, OCH_2O, *J* = 7.1 Hz, 1H), 4.72 (d, OCH_2O, *J* = 7.1 Hz, 1H), 4.69 (d, OCH_2Ar, *J* = 12.0 Hz, 1H), 4.54 (d, OCH_2Ar, *J* = 12.0 Hz, 1H), 4.46 (ddd, NC*H*, *J* = 8.9, 5.3, 4.3 Hz, 1H), 4.27 (dd, OCH_2CH, *J* = 8.9, 8.9 Hz, 1H), 4.13 (dd, OCH_2CH, *J* = 8.9, 5.3 Hz, 1H), 3.60 (ddd, CH_2C*H*(OR)CH, *J* = 7.8, 5.9, 1.7 Hz, 1H), 2.71–2.62 (m, CHCH_2CH, 1H), 2.51–2.40

(m, CHCH_2CH, 1H), 2.32 (q, C(CO)CH_2CH$_3$, J = 7.6 Hz, 2H), 2.35–2.27 (m, CHCH(CH$_3$)$_2$, "*partly hidden*", 1H),1.90 (d, (CH_3)C=CH, J = 1.5 Hz, 3H), 1.91–1.86 (m, CHCHCH, "*partly hidden*", 1H),1.66–1.57 (m, CHCHCH$_2$, 1H), 1.35–1,27 (m, CHCH_2CH$_3$, 1H), 1.13 (t, C(CO)CH$_2$CH_3, J = 7.6 Hz, 3H), 1.12–1.02 (m, CHCH_2CH$_3$, 1H), 0.90 (t, CH$_2$CH_3, J = 7.0 Hz, 3H), 0.90 (d, CHCH_3, "*partly hidden*", J = 6.9 Hz, 3H), 0.89 (d, CHCH_3, "*partly hidden*", J = 6.9 Hz, 3H), 0.87 (d, CHCH_3, J = 6.9 Hz, 3H), 0.85 (d, CHCH_3, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.31, 171.76, 153.55, 138.29, 135.30, 132.60, 128.48, 127.88, 127.64, 96.04, 78.19, 76.45, 69.89, 63.52, 58.32, 38.21, 36.48, 32.46, 28.46, 28.00, 27.26, 17.97, 15.14, 13.98, 12.48, 12.13, 10.22, 9.56; FTIR (neat, cm^{-1}) 2966, 1786, 1733, 1683, 1456, 1212, 1038, 739; HRMS (ESI) m/z calcd for $C_{30}H_{45}NO_7Na$ $[M+Na]^+$ 554.3088, found 554.3086.



5*S*-Benzyloxymethoxy-2,6*S*,8*S*-trimethyl-7*R*-propionyl-oxy-2*E*-decenoic acid (3.59). To a 0.05 M ice-cold solution of substrate **3.58** (160 mg, 0.301 mmol) in THF:H_2O (8.0 mL, 3:1) was added 30% H_2O_2 (0.267 mL, 1.48 mmol) followed by the addition of LiOH (17 mg, 0.62 mmol). The reaction mixture was stirred for 30 min at 0 ºC. Excess of peroxide was then quenched with 10% excess aqueous Na_2SO_3 (1.5 M, 1.82 mL) at 0 ºC and resulting reaction mixture was stirred an additional 15 min. Resultant mixture was buffered to pH ~9 with saturated aqueous $NaHCO_3$ and the organic solvent removed under reduced pressure. The residue was transferred to a separation funnel the aqueous phase was extracted with CH_2Cl_2 (5 × 10 mL) and the

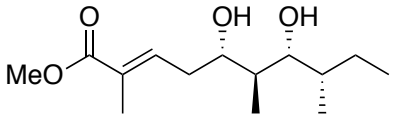
combined organic phases were dried over anhydrous Na_2SO_4. The solvent was filtered, concentrated under reduced pressure and the crude product purified with flash chromatography using ethyl acetate/hexanes 25–75% as a gradient to give 98% (124 mg) of **3.59** as a clear oil; $[\alpha]^{20}_D$ +49.8º (c=1.33, $CDCl_3$, *dr* = 91:9). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.35 (m, Ar*H*, 1H), 7.35–7.30 (m, Ar*H*, 4H), 6.87 (ddq, MeC=C*H*CH_2, *J* = 8.3, 6.8, 1.4 Hz, 1H), 5.04 (dd, CHC*H*(OR)CH, *J* = 9.6, 2.5 Hz, 1H), 4.79 (d, OC*H*$_2$O, *J* = 7.1 Hz, 1H), 4.73 (d, OC*H*$_2$O, *J* = 7.1 Hz, 1H), 4.69 (d, ArC*H*$_2$O, *J* = 11.9 Hz, 1H), 4.54 (d, ArC*H*$_2$O, *J* = 11.9 Hz, 1H), 3.62 (ddd, CH_2C*H*(OR)CH, *J* = 7.8, 6.0, 1.7 Hz, 1H), 2.75–2.64 (m, C=CHC*H*$_2$CH, 1H), 2.50–2.40 (m, C=CHC*H*$_2$CH, 1H), 2.32 (q, C(CO)C*H*$_2$CH$_3$, *J* = 7.5 Hz, 2H), 1.85 (d, (C*H*$_3$)C=CH, *J* = 1.4 Hz, 3H), 1.87–1.76 (m, CHC*H*(Me)CH, "*partly hidden*", 1H), 1.66–1.54 (m, CHC*H*(Me)CH_2, 1H), 1.37–1.23 (m, CHC*H*$_2$CH$_3$, 1H), 1.13 (t, C(CO)CH_2C*H*$_3$, *J* = 7.6 Hz, 3H), 1.15–1.03 (m, CHC*H*$_2$CH$_3$, "*partly hidden*", 1H), 0.91 (t, CH_2C*H*$_3$, *J* = 7.2 Hz, 3H), 0.90 (d, CHC*H*$_3$, *J* = 6.8 Hz, "*partly hidden*", 3H), 0.84 (d, CHC*H*$_3$, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.13, 172.43, 140.91, 137.94, 128.44, 128.32, 127.54, 126.95, 95.67, 77.91, 76.12, 69.76, 38.06, 36.28, 32.79, 27.82, 27.04, 12.36, 12.27, 11.92, 10.15, 9.38; FTIR (neat, cm-1) 2969, 1730, 1686, 1648, 1456, 1276, 1193, 911, 735; HRMS (ESI) m/z calcd for $C_{24}H_{35}O_6$ $[M-H]^-$ 419.2439, found 419.2438.



1-*tert*-Butoxy-1-oxo-3*S*-methyl-2*R*-pentanyl 5'*S*-(benzyloxymethoxy)-2',6'*S*,8'*S*-trimethyl-7'*R*-(propionyloxy)dec-2'- *E*-enoate (3.60).

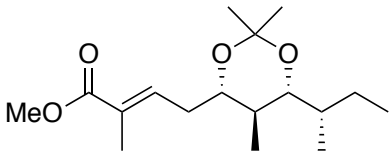
Carboxylic acid **3.59** (50.0 mg, 0.119 mmol) and alcohol **3.34** (30.0 mg, 0.159 mmol) were dissolved in distilled CH_2Cl_2 (2.0 mL) under argon atmosphere and the mixture cooled in an ice-water bath. DCC (40.0 mg, 0.190 mmol) and DMAP (24.0 mg, 0.190 mmol) were added at ~0 ºC, the mixture stirred for 1 h and an additional 14 h at ambient temperature. Saturated aqueous NH_4Cl (10 mL) was added to the grey turbid reaction and the mixture transferred to a separation funnel. The aqueous phase was extracted with CH_2Cl_2 (4 × 12 mL), the combined organics dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was then purified by silica gel chromatography using ethyl acetate in hexanes as a gradient (0–15%) to afford product **3.60** (62.0 mg, 88%) as a clear oil; $[\alpha]^{20}_D$ +24.8º (c=1.50, $CDCl_3$, *dr* = 91:9). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.31 (m, Ar*H*, 5H), 6.76 (ddq, MeC=C*H*CH_2, *J* = 8.2, 6.4, 1.6 Hz, 1H), 5.04 (dd, CHC*H*(OR)CH, *J* = 9.7, 2.4 Hz, 1H), 4.93 (d, *J* = 3.3 Hz, (CO)C*H*(OR)CH, 1H), 4.80 (d, OCH_2O, *J* = 7.0 Hz, 1H), 4.72 (d, OCH_2O, *J* = 7.0 Hz, 1H), 4.69 (d, ArCH_2O, *J* = 12.0 Hz, 1H), 4.55 (d, ArCH_2O, *J* = 12.0 Hz, 1H), 3.61 (ddd, CH_2C*H*(OR)CH, *J* = 8.8, 5.5, 1.6 Hz, 1H), 2.72–2.64 (m, C=CHCH_2CH, 1H), 2.52–2.44 (m, C=CHCH_2CH, 1H), 2.34–2.26 (m, HC(OR)C*H*(Me)CH_2, "*partly hidden*", 1H), 2.31 (q, C(CO)C$H_2$$CH_3$, *J* = 7.6 Hz, 2H), 2.02–1.94 (m, CHC*H*(Me)CH, 1H), 1.87 (bs, CH_3C=C, 3H), 1.84–1.76 (m, CHC*H*(Me)CH_2, 1H), 1.65–1.55 (m, CH(Me)C$H_2$$CH_3$, "*partly hidden*", 1H), 1.45 (s, ^{t}Bu, 9H), 1.46–1.44 (m, CH(Me)C$H_2$$CH_3$, "*partly hidden*", 1H), 1.34–1.27 (m, CH(Me)C$H_2$$CH_3$, 1H), 1.13 (t, *J* = 7.6 Hz, CH_2CH_3, 3H), 1.10–1.04 (m, CH(Me)C$H_2$$CH_3$, 1H), 0.97 (d, *J* = 6.9 Hz, CHCH_3, 3H), 0.93 (d, *J* = 6.8 Hz, "*partly hidden*", CHCH_3, 3H), 0.90 (t, *J* = 6.8 Hz, "*partly hidden*", CH_2CH_3, 3H), 0.89 (t, *J* = 6.8 Hz, "*partly hidden*", CH_2CH_3, 3H), 0.83 (d, *J* = 6.7 Hz, CHCH_3, 3H); ^{13}C NMR (126

MHz, $CDCl_3$) δ 174.26, 169.21, 167.41, 138.93, 138.18, 129.07, 128.50, 127.92, 127.70, 95.85, 81.86, 77.93, 76.31, 75.27, 69.89, 37.94, 36.90, 36.43, 32.65, 28.18, 27.99, 27.24, 26.39, 14.40, 12.78, 12.43, 12.12, 11.81, 10.02, 9.60; FTIR (neat, cm^{-1}) 3450, 2967, 2935, 2879, 1725, 1719, 1649, 1461, 1368, 1247, 1108, 1041, 912, 733; MS (ESI) m/z calcd for $C_{34}H_{54}O_8Na$ $[M+Na]^+$ 613.37, found 613.40.



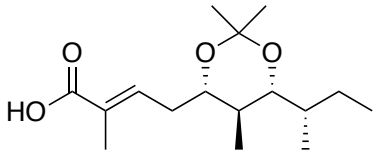
Methyl 5*S*,7*R*-Dihydroxy-2,6*S*,8*S*-trimethyldec-2*E*-enoate (3.61). Vinylogous alcohol **3.57** (250 mg, 0.608 mmol) was dissolved in anhydrous MeOH (10 mL) and stirred at 0 ºC under argon. A methanolic sodium methoxide solution, prepared at 0 ºC by adding sodium metal (0.055g, 1.822 mmol) to anhydrous MeOH (5.0 mL) under argon, was added dropwise to the substrate over 10 min. The reaction mixture was stirred for 2 h at 0 ºC and the reaction was quenched with saturated ammonium chloride (20 mL). The volatiles were removed *in vacuo* and the resulting heterogeneous slurry was diluted with minimal water (1–2 mL) and then transferred to a separation funnel. The aqueous phase was extracted with CH_2Cl_2 (5 × 10 mL), the combined organics dried over anhydrous sodium sulfate and filtered. The organic solvent was added silica gel (~2.5 g), the solvent removed under reduced pressure and the residual material dry loaded onto a silica gel column. The crude product was then purified by silica gel chromatography using ethyl acetate in hexanes as a gradient (0–50%) to afford product **3.61** (145 mg, 93%) as a clear oil; $[\alpha]^{20}_D$ +24.8º (c=0.52, $CDCl_3$, *dr* = 91:9). ^1H NMR (500 MHz, $CDCl_3$) (*Major diastereomer, **5S***) δ 6.86 (ddq, MeC=C*H*CH_2, *J* = 7.3, 7.3, 1.5 Hz, 1H), 4.07–4.01 (m, CH_2CH(OH), 1H),

3.74 (s, ROCH_3, 3H), 3.57–3.52 (m, CHC*H*(OH)CH, 1H), 2.86 (bs, RO*H*, 1H), 2.52–2.43 (m, C=CHCH_2CH, 1H), 2.34–2.25 (m, C=CHCH_2CH, 1H), 2.20 (bs, RO*H*, 1H), 1.88 (d, H_3CC=CH, *J* = 1.5 Hz, 3H), 1.87–1.81 (m, CHC*H*CH, "*partly hidden*", 1H), 1.61–1.51 (m, CHC*H*CH_2, 1H), 1.44–1.36 (m, C$H_2$$CH_3$, 1H), 1.28–1.20 (m, C$H_2$$CH_3$, 1H), 0.93 (t, CH_2CH_3, "*partly hidden*", *J* = 7.5 Hz, 3H), 0.91 (d, CHCH_3, "*partly hidden*", *J* = 6.3 Hz, 3H), 0.90 (d, CHCH_3, "*partly hidden*", *J* = 6.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.58, 139.30, 129.52, 77.98, 72.82, 51.88, 39.10, 37.21, 33.24, 26.70, 12.90, 12.85, 11.92, 11.79; FTIR (neat, cm^{-1}) 3437, 2961, 1698, 1458; MS (ESI) m/z calcd for $C_{14}H_{26}O_4$ $[M+H]^+$ 259.18, found 259.05. ^{1}H NMR (500 MHz, $CDCl_3$) (<u>*Minor diastereomer,* ***5R***</u>) δ 6.93 (ddq, MeC=C*H*CH_2, *J* = 8.0, 6.4, 1.5 Hz, 1H), 3.83 (ddd, CH_2C*H*(OH)CH, *J* = 7.8, 7.8, 3.6 Hz, 1H), 3.74 (s, ROCH_3, 3H), 3.57 (dd, CHC*H*(OH)CH, *J* = 9.3, 2.2 Hz, 1H), 2.53–2.44 (m, C=CHCH_2CH, 1H), 2.43–2.33 (m, C=CHCH_2CH, 1H), 1.87 (d, H_3CC=CH, *J* = 1.5 Hz, 3H), 1.77–1.66 (m, CHC*H*CH, 1H), 1.60–1.52 (m, CHC*H*CH_2, "*partly hidden*", 1H), 1.45–1.25 (m, C$H_2$$CH_3$, "*partly hidden*", 2H), 0.94 (t, CH_2CH_3, *J* = 7.4 Hz, 3H), 0.86 (d, CHCH_3, *J* = 6.8 Hz, 3H), 0.79 (d, CHCH_3, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.56, 138.85, 129.65, 79.47, 76.06, 51.86, 41.00, 37.02, 34.45, 27.13, 13.18, 12.87, 12.15, 11.69.



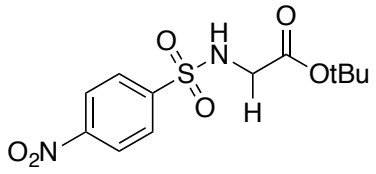
Methyl (6*R*-[1'*S*-methylpropyl]-2,2,5*S*-trimethyl-1,3-dioxane-4*S*-yl)-2''-methylbut-2''*E*-enoate (3.62). Diol **3.61** (60.0 mg, 0.232 mmol) was dissolved in 2,2-dimethoxypropane (3.0 mL) at room temperature. The reaction mixture was charged with catalytic amount of *p*-TsOH (12 mg, 70 mmol), sealed under an argon

atmosphere and the reaction mixture stirred for 4 h. Saturated $NaHCO_3$ (1.0 mL) was carefully added and excess of organic solvent was removed under reduced pressure. Water (5.0 mL) and ethyl acetate (5.0 mL) was added and the mixture was transferred to a separation funnel. The aqueous phase was extracted with ethyl acetate (4 × 15 ml) the combined organic phases were dried over anhydrous sodium sulfate and then filtered. After removal of the solvent under reduced pressure the crude product was purified by silica gel chromatography using ethyl acetate in hexanes as a gradient (0–5%) to afford product **3.62** (64.0 mg, 94%) as a clear oil; $[\alpha]^{20}_{D}$ +4.89º (c=0.47, CH_2Cl_2, dr = 91:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (ddq, MeC=C*H*CH_2, *J* = 6.9, 6.9, 1.5 Hz, 1H), 3.74 (s, OC*H*$_3$, 3H), 3.57 (ddd, CH_2C*H*(OR)CH, *J* = 10.4, 7.5, 3.2 Hz, 1H), 3.45 (dd, CHC*H*(OR)CH, *J* = 10.2, 2.2 Hz, 1H), 2.52–2.43 (m, C=CHC*H*$_2$CH, 1H), 2.33–2.24 (m, C=CHC*H*$_2$CH, 1H), 1.84 (d, *H*$_3$CC=CH, *J* = 1.5 Hz, 3H), 1.57–1.51 (m, CHC*H*CH, "*partly hidden*", 1H), 1.52–1.44 (m, CHC*H*CH_2, "*partly hidden*", 1H), 1.42–1.22 (m, CHC*H*$_2$CH$_3$, 2H), 1.39 (s, CC*H*$_3$, 3H), 1.33 (s, CC*H*$_3$, 3H), 0.88 (t, CH_2C*H*$_3$, *J* = 7.4 Hz, 3H), 0.84 (d, CHC*H*$_3$, *J* = 6.8 Hz, 3H), 0.75 (d, CHC*H*$_3$, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (*Major diastereomer*, **5*S***, "*syn*") δ 168.74, 139.35, 128.75, 98.00, 77.41, 74.25, 51.81, 35.55, 35.17, 33.11, 30.18, 26.86, 19.64, 12.82, 12.52, 12.15, 12.14; ^{13}C NMR (126 MHz, $CDCl_3$) (*Minor diastereomer*, **5*R*** "*anti*") δ 168.61, 138.96, 129.03, 100.50, 77.25, 68.83, 51.85, 38.16, 36.60, 30.57, 26.36, 25.43, 23.68, 13.96, 12.88, 12.49, 12.14; FTIR (neat, cm^{-1}) 2970, 2336, 1716, 1380, 1259; HRMS (ESI) m/z calcd for $C_{17}H_{30}O_4Na$ $[M+Na]^+$ 321.2036, found 321.2034.

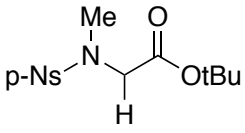


(6*R*-[1'*S*-methylpropyl]-2,2,5*S*-trimethyl-1,3-dioxane-4*S*-yl)-2"-methylbut-2"*E*-enoic acid (3.63). To a stirred solution of methyl ester **3.62** (50.0 mg, 168 mmol) in methanol (4.0 mL) at 0 ºC was added a solution of KOH (94.0 mg, 1.68 mmol) in water (1.0 mL). The resulting mixture was then stirred for 20 h at room temperature and the reaction was quenched with saturated ammonium chloride (5 mL) and acidified with 10% HCl (2 mL). The volatiles were removed under reduced pressure, the mixture was transferred to a separation funnel and the aqueous phase was extracted with ethyl acetate (4 × 10 mL). The combined organic phases were dried over anhydrous sodium sulfate and filtered. After removal of the solvent under reduced pressure the crude product was purified by silica gel chromatography using ethyl acetate in hexanes as a gradient (0–60%) to afford carboxylic acid **3.63** (45.0 mg, 94%) as a clear oil, $[\alpha]^{20}_{D}$ +5.33º (c=0.45, DMSO, dr = 91:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (bs, COO*H*, 1H), 6.70 (ddd, MeC=C*H*CH$_2$, *J* = 7.8, 6.4, 1.5 Hz, 1H), 3.61 (ddd, CH$_2$C*H*(OR)CH, *J* = 10.3, 7.6, 3.1 Hz, 1H), 3.48 (dd, CHC*H*(OR)CH, *J* = 10.2, 2.2 Hz, 1H), 2.49–2.40 (m, C=CHC*H*$_2$CH, "*partly hidden*", 1H), 2.26–2.17 (m, C=CHC*H*$_2$CH, 1H), 1.72 (d, *H*$_3$CC=CH, *J* = 1.5 Hz, 3H), 1.57–1.50 (m, CHC*H*(Me)CH, 1H), 1.44–1.36 (m, CHC*H*(Me)CH$_2$, "*partly hidden*", 1H), 1.36 (s, CC*H*$_3$, 3H), 1.34–1.17 (m, RCHC*H*$_2$CH$_3$, "*partly hidden*", 2H), 1.22 (s, CC*H*$_3$, 3H), 0.83 (t, CH$_2$C*H*$_3$, *J* = 7.5 Hz, 3H), 0.75 (d, CHC*H*$_3$, *J* = 6.8 Hz, 3H), 0.71 (d, CHC*H*$_3$, *J* = 6.6 Hz, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.68, 138.21, 128.69, 97.30, 74.37, 73.31, 34.88, 34.21, 32.17, 29.98, 26.29, 19.52, 12.43, 12.37, 11.74, 11.28; FTIR (neat, cm^{-1}) 3101, 2644, 1686,

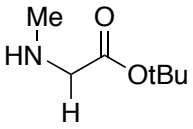
1642, 1422, 1380, 1266, 952, 908, 886, 740; MS (ESI) m/z calcd for $C_{16}H_{27}O_4$ $[M-H]^-$ 283.20, found 283.13.



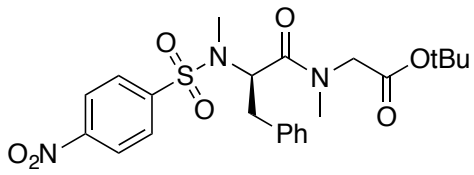
***tert*-butyl ((4-nitrophenyl)sulfonyl)glycinate (4.3):** Title compound was produced by the general method for *tert*-butyl and *para*-nosyl protection of amino acids to afford **4.3** (4.80 g, 96% yield) as yellow solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.40 – 8.31 (m, Ar-H x 2, 2H), 8.09 – 8.01 (m, Ar-H x 2, 2H), 5.13 (s, NH, 1H), 3.75 (s, NCH_2R, 2H), 1.36 (s, OtBu, 9H).



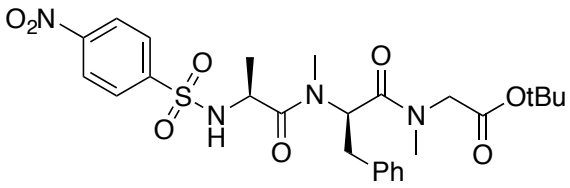
***tert*-butyl *N*-methyl-*N*-((4-nitrophenyl)sulfonyl)glycinate (4.4):** The title compound was produced by the general procedure for *N*-methylation of *t*-butyl and *p*-Ns protected amino acids (**4.3**) to afford **4.4** (3.79 g, 98% yield) as yellow solids; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.38 – 8.30 (m, Ar-H x 2, 2H), 8.06 – 7.93 (m, Ar-H x 2, 2H), 3.99 (s, NCH_2R, 2H), 2.97 (s, J = 0.6 Hz, NCH_3, 3H), 1.39 (d, J = 0.7 Hz, OtBu, 9H).



***tert*-butyl methylglycinate (4.5):** The title compound was produced by the general procedure for *para*-nosyl amine (**4.4**) deprotection to afford **4.5** (0.357 g, 75% yield) as a yellow oil; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.31 (s, NH, 1H), 3.25 (s, NCH_2R, 2H), 2.44 (s, NCH_3, 3H), 1.48 (s, OtBu, 9H).

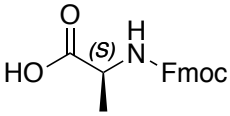


***tert*-butyl *N*-methyl-*N*- (*N*-methyl-*N*- ((4-nitro phenyl) sulfonyl)-*D*-phenylalanyl) glycinate (4.7):** The title compound was produced by the general procedure for solution phase peptide coupling to afford **4.7** (0.248 g, 70% yield) as yellow oil; ^{1}H NMR (600 MHz, DMSO-*d*6) δ 8.31 (dd, *J* = 9.0, 2.6 Hz, Ar-H x 2, 2H), 7.91 – 7.87 (m, Ar-H x 2, 2H), 7.27 – 7.18 (m, Ar-H x 5, 5H), 5.17 (dd, *J* = 8.4, 6.7 Hz, R_3CH, 1H), 3.89 (dd, *J* = 91.3, 17.1 Hz, NCH_2R, 2H), 3.11 (s, NCH_3, 3H), 3.05 (m, CH_2Ph, 2H), 2.97 (s, NCH_3, 3H), 1.41 (s, OtBu, 9H); ^{13}C NMR (151 MHz, DMSO) δ 169.32, 167.80, 149.61, 143.78, 136.41, 128.95, 128.36, 128.30, 126.62, 124.44, 80.97, 56.10, 50.05, 36.15, 33.95, 30.41, 27.65.

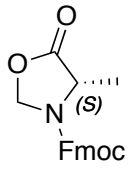


***tert*-butyl *N*-methyl-*N*-(*N*-methyl-*N*-(((4-nitrophenyl)sulfonyl)-*L*-alanyl)-*D*-phenylalanyl)glycinate (4.9):** The title compound was produced by the general procedure for solution phase peptide coupling to afford **4.9** (0.167 g, 50% yield) as yellow oil; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.27 (d, *J* = 8.9 Hz, Ar-H x 2, 2H), 7.99 – 7.95 (m, Ar-H x 2, 2H), 7.24 – 7.15 (m, Ar-H x 5, 5H), 5.74 – 5.67 (m, NCH_2R, 2H), 5.31 (dd, *J* = 4.5, 1.8 Hz, R_3CH, 1H), 4.26 – 4.15 (m, R_3CH, 1H), 3.92 (dd, *J* = 17.1 Hz, CH_2Ph, 2H), 2.90 (s, NCH_3, 3H), 2.75 (s, NCH_3, 3H), 1.48 (s, OtBu, 9H), 0.80 (d, *J* = 6.9 Hz, RCH_3, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.36,

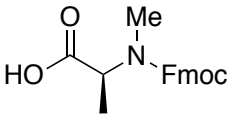
169.61, 167.76, 146.23, 136.11, 129.09, 128.73, 128.41, 128.34, 128.08, 126.85, 124.29, 82.05, 67.28, 53.46, 50.54, 49.39, 35.98, 34.91, 32.42, 30.36, 28.05, 19.25.



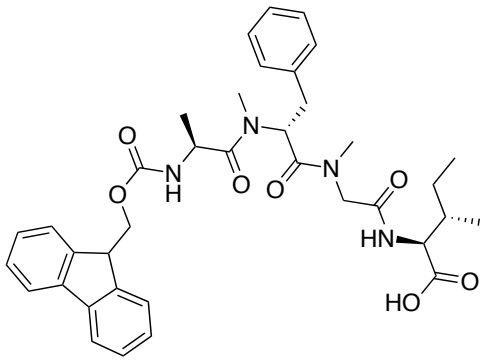
(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L*-alanine (4.11): The title compound was produced by the general procedure for Fmoc-protection of amino acids to afford **4.11** (5.67 g, 93% yield); ^{1}H NMR *existed as rotational conformers* (500 MHz, Chloroform-*d*) δ 7.77 (dd, *J* = 7.7, 3.4 Hz, Ar-H x 2, 2H), 7.60 (d, *J* = 6.7 Hz, Ar-H x 2, 2H), 7.40 (td, *J* = 7.5, 3.2 Hz, Ar-H x 2, 2H), 7.32 (td, *J* = 7.5, 3.3 Hz, Ar-H x 2, 2H), 5.29 (s, NH, 1H), 4.52 – 4.35 (m, OCH_2R + R_3CH, 2H + 1H), 4.23 (td, *J* = 6.8, 3.0 Hz, R_3CH, 1H), 1.77 – 0.89 (m, RCH_3, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.91, 143.83, 141.46, 127.90, 127.24, 120.16, 105.14, 77.16, 67.30, 49.58, 47.28, 18.49.



(9*H*-fluoren-9-yl) methyl (*S*)-4-methyl-5-oxooxazolidine-3-carboxylate (4.12): The title compound was produced during the general procedure for *N*-methylation of Fmoc-protected amino acids to afford **4.12** (5.57 g, 91% yield) as white crystals; ^{1}H NMR *existed as rotational conformers* (400 MHz, Chloroform-*d*) δ 7.78 (m, Ar-H, 2H), 7.62 – 7.49 (m, Ar-H, 2H), 7.44 – 7.39 (m, Ar-H, 2H), 7.36 – 7.31 (m, Ar-H, 2H), 5.36 - 5.14 (m, NCH_2O, 2H), 4.61 (s, Fmoc-CH_2O, 2H), 4.24 - 3.89 (m, Fmoc-CHR + $NCHR_2$, 1H + 1H), 1.48 - 1.16 (m, RCH_3, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.73, 143.35, 141.43, 127.97, 127.21, 124.57, 120.12, 120.11, 67.36, 50.53, 47.14, 27.05.

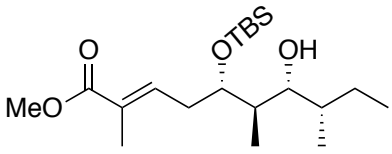


N-(((9H-fluoren-9-yl)methoxy)carbonyl)-N-methyl-L-alanine (4.16): The title compound was produced by the general procedure for *N*-methylation of Fmoc-protected amino acids to afford **4.16** (2.15 g, 94% yield) as white powder; ^{1}H NMR *existed as rotational conformers* (500 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 6.8 Hz, Ar-H x 2, 2H), 7.58 (d, *J* = 23.5 Hz, Ar-H x 2, 2H), 7.40 (d, *J* = 7.1 Hz, Ar-H x 2, 2H), 7.34 – 7.29 (m, Ar-H x 2, 2H), 4.88 (s, R_3CH, 1H), 4.66 – 4.35 (m, OCH_2R, 2H), 4.28 (d, *J* = 8.1 Hz, R_3CH, 1H), 2.92 (d, *J* = 5.5 Hz, N-CH_3, 3H), 1.59 – 1.23 (m, RCH_3, 3H).



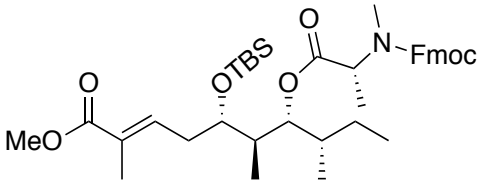
***N*-(*N*-((((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L*-alanyl)-*N*-methyl-*D*-phenylalanyl)-*N*-methylglycyl-*L*-isoleucine (4.17):** Intermediates for peptide coupling were synthesized by the general procedure for Fmoc-protection of amino acids (**4.13** and **4.16**) and the general procedure for *N*-methylation of Fmoc-protected amino acids (**4.14** and **4.15**). Peptide **4.17** was ultimately produced via the general procedure for solid phase peptide coupling in 55% overall yield (0.735g purified wt.) as white powder; ^{1}H NMR (500 MHz, Chloroform-*d*) *Existed as rotational conformers* δ 7.76 – 7.72 (m, 2H), 7.55 (dd, *J* = 7.5, 4.7 Hz, 2H), 7.38 (td, *J* = 7.5, 1.4 Hz, 2H), 7.29 (td, *J* = 7.5, 1.1 Hz, 2H), 7.25 – 7.01 (m, 5H), 6.78 – 6.67 (m, 1H), 5.88 – 5.70 (m, 1H), 4.66 – 4.43 (m, 2H), 4.32 (dddd, *J* = 23.6, 15.3, 10.5, 7.3 Hz, 2H), 4.23 –

4.05 (m, 2H), 3.95 – 3.68 (m, 1H), 3.11 (dt, *J* = 17.4, 9.0 Hz, 1H), 3.06 (s, 1H), 3.04 – 2.98 (m, 4H), 2.96 (d, *J* = 5.6 Hz, 1H), 2.90 – 2.78 (m, 2H), 1.92 (s, 1H), 1.54 – 1.35 (m, 1H), 1.26 – 1.07 (m, 0H), 0.96 – 0.64 (m, 10H), 0.48 (d, *J* = 6.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) *Existed as rotational conformers* δ 173.2, 171.1, 169.3, 168.3, 155.8, 144.0, 141.4, 136.3, 129.4, 129.1, 127.8, 125.3, 120.1, 77.2, 67.1, 56.8, 55.7, 54.0, 53.6, 47.2, 37.7, 36.9, 35.3, 25.2, 18.1, 15.6, 11.7; MS (ESI) *m/z* calcd for $C_{37}H_{45}N_4O_7$ $[M+H]^+$ 657.32, found 657.00.



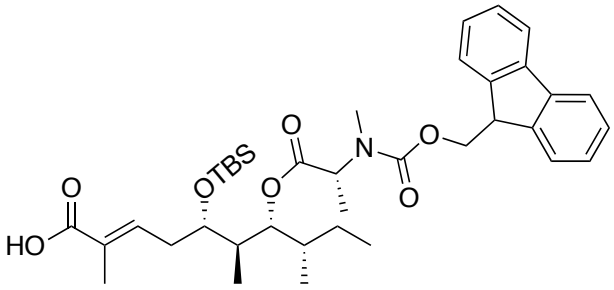
methyl (5*S*, 6*R*, 7*R*, 8*S*, *E*)-5-((*tert*-butyldimethylsilyl) oxy)-7-hydroxy-2,6,8-trimethyldec-2-enoate (5.1): 1,3-diol (**3.61**) was mono-silated via the general procedure for silyl-ether protection of hydroxyl with TBS-OTf (1.4 equiv)/2,6-lutidine in DCM at -78 °C to afford the title compound **5.1** (0.010 g, 70% yield) as a clear oil; $[\alpha]_D^{20}$ = +18.9° (c 0.90, $CDCl_3$); FTIR (neat, cm^{-1}) 3524.2, 2956.2, 2858.3, 1715.7, 1648.2, 1458.2, 1254.5, 1073.7, 951.9, 836.6, 775.8, 740.9; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (ddt, *J* = 7.2, 5.7, 1.5 Hz, C=CH, 1H), 4.01 (dt, *J* = 6.9, 4.7 Hz, ROH, 1H), 3.73 (s, OCH_3, 3H), 3.42 (ddd, *J* = 9.6, 4.0, 2.1 Hz, $R_2CH(OSi)$, 1H), 2.42 – 2.34 (m, RCH_2R, 2H), 2.18 (d, *J* = 4.0 Hz, R_3CH, 1H), 1.85 (q, *J* = 1.0 Hz, RCH_3, 3H), 1.76 (dqd, *J* = 9.5, 6.9, 4.6 Hz, RCH_2R, 1H), 1.52 – 1.28 (m, RCH_2R + R_3CH x 2, 3H), 0.90 (d, *J* = 11.4 Hz, Si-tBu + RCH_3, 12H), 0.83 (d, *J* = 6.7 Hz, RCH_3, 3H), 0.81 (d, *J* = 6.9 Hz, RCH_3, 3H), 0.07 (m, Si-CH_3 x 2, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.67, 140.02, 128.73, 76.05, 74.80, 51.83, 41.72, 36.70, 33.32, 27.37, 25.96, 18.14, 12.82,

12.36, 12.23, 11.83, -4.41, -4.44; MS (ESI) *m/z* calcd for $C_{20}H_{40}O_4Si$ $[M+H]^+$ 372.2696, found 372.2693.



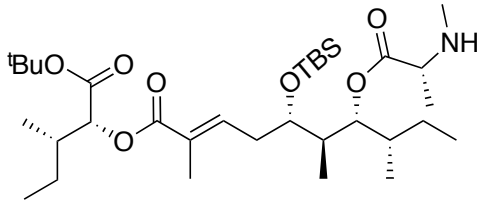
methyl (5*S*, 6*R*, 7*R*, 8*S*, *E*)-7-((*N*-(((9*H*-fluoren-9-yl) methoxy) carbonyl)-*N*-methyl-*D*-alanyl) oxy)-5-((*tert*-butyldimethylsilyl) oxy)-2, 6, 8-trimethyldec-2-enoate (5.2): Collidine (53 μL, 0.399 mmol) and DMAP (1 mg, 0.001 mmol) were added to a solution of alcohol **5.1** (12 mg, 0.0399 mmol) in 2.5 mL dry toluene and stirred at 0 °C. Next, freshly prepared Fmoc-N-Me-L-Ala-Cl (0.1196 mmol in 2.0 mL toluene) was slowly added dropwise via cannula. The reaction was sealed and stirred at 60 °C for 14 hours overnight. The reaction mixture initiated as a yellow, cloudy mixture and was quenched heterogeneous. The reaction was quenched with 10 mL sat. NH_4Cl and extracted with 4 x 10 mL EtOAc. The combined organics were washed with 10 mL sat. $NaHCO_3$, 10 mL sat. NH_4Cl, 10 mL brine then dried over Na_2SO_4. Mixture was filtered and concentrated under reduced pressure. The crude residue was purified via silica gel column chromatography (0-10% EtOAc in hexanes linear gradient) to afford the title compound **5.2** (18 mg, 60% yield) as a clear oil; R_f = 0.8, 20% EAH; $[\alpha]_D^{20}$ = -160° (c 0.80, $CDCl_3$); FTIR (neat, cm^{-1}) 3051.9, 1737.2, 1708.5, 1452.1, 1399.7, 1318.2, 1266.3, 1165.3, 1095.2, 740.4; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.76 (d, *J* = 7.5 Hz, Ar-H x 2, 2H), 7.61 (d, *J* = 7.9 Hz, Ar-H x 2, 2H), 7.40 (t, *J* = 7.5 Hz, Ar-H x 2, 2H), 7.31 (t, *J* = 7.4 Hz, Ar-H x 2, 2H), 6.77 (t, *J* = 7.6 Hz, C=CH, 1H), 4.90 (d, *J* = 8.3 Hz, RCH_2R, 2H), 4.40 (p, *J* = 10.5 Hz, R_3CH x 2, 2H), 4.25 (dd, *J* = 15.7, 8.5 Hz, R_3CH,

1H), 3.75 (d, *J* = 10.0 Hz, R_3CH, 1H), 3.58 (s, OCH_3, 3H), 2.95 (s, NCH_3, 3H), 2.32 – 2.16 (m, RCH_2R, 2H), 2.04 (q, *J* = 5.4, 3.4 Hz, R_3CH, 1H), 1.79 (s, RCH_3, 3H), 1.67 – 1.57 (m, R_3CH, 1H), 1.45 (dd, *J* = 7.4, 1.2 Hz, RCH_3, 3H), 1.30 – 1.06 (m, RCH_2R, 2H), 0.91 (d, *J* = 7.0 Hz, RCH_3 x 2, 6H), 0.86 (d, *J* = 3.1 Hz, Si-tBu + RCH_3, 12H), 0.02 (m, Si-CH_3 x 2, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.25, 168.71, 156.65, 144.23, 144.17, 141.45, 141.00, 128.38, 127.81, 127.19, 125.25, 120.11, 120.09, 71.10, 67.92, 54.29, 51.59, 47.40, 41.34, 36.40, 30.55, 27.02, 25.90, 18.09, 15.38, 12.67, 12.51, 12.11, 9.81, 0.15, -4.67.

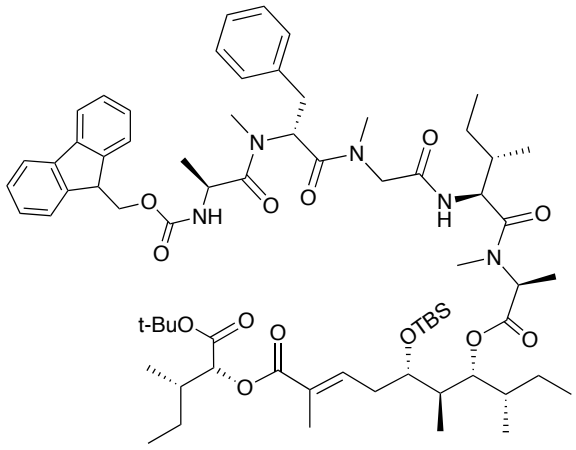


(5*S*,6*R*,7*R*,8*S*,*E*)-7-((*N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*N*-methyl-*D*-alanyl)oxy)-5-((*tert*-butyldimethylsilyl)oxy)-2,6,8-trimethyldec-2-enoic acid (5.3):[79] Ester **5.2** (10 mg, 0.0147 mmol) was dissolved in 1.5 mL 1,2-dichloroethane then charged with trimethyltin hydroxide (15 mg, 0.0735 mmol), prepared from trimethyltin chloride,[80,131] and stirred sealed at 85 °C until TLC analysis indicated a completed reaction. The reaction mixture was concentrated and extracted with 3 x 10 mL EtOAc. The combined organics were washed with 0.01N $KHSO_4$ (or 5% HCl) 3 x 10 mL, then brined 1 x 10 mL and dried over Na_2SO_4. The mixture was filtered and concentrated to afford acid **5.3** (10 mg, 94% yield) as an amorphous solid that was used without further purification; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 (dt, *J* = 7.4, 1.0 Hz, Ar-H x 2, 2H), 7.70 (dt, *J* = 7.5, 1.0 Hz, Ar-H x 2, 2H), 7.38 (td, *J* = 7.5, 1.2 Hz, Ar-

H x 2, 2H), 7.30 (td, *J* = 7.4, 1.2 Hz, Ar-H x 2, 2H), 6.73 (t, *J* = 7.3 Hz, C=CH, 1H), 5.00 (d, *J* = 9.9 Hz, RCH_2R, 1H), 4.12 (q, *J* = 7.1 Hz, R_3CH, 1H), 3.86 (d, *J* = 32.0 Hz, R_3CH, 1H), 3.72 (s, RCH_3, 3H), 3.62 (d, *J* = 8.8 Hz, R_3CH, 1H), 2.73 (s, RCH_3, 3H), 2.40 – 2.18 (m, RCH_2R, 3H), 2.04 (m, R_3CH, 1H), 1.83 (s, RCH_3, 3H), 1.66 (d, *J* = 11.0 Hz, R_3CH, 1H), 0.92 (m, RCH_3 x 3, 9H), 0.87 (s, Si-tBu, 9H), 0.07 – 0.00 (m, Si-CH_3 x 2, 6H).

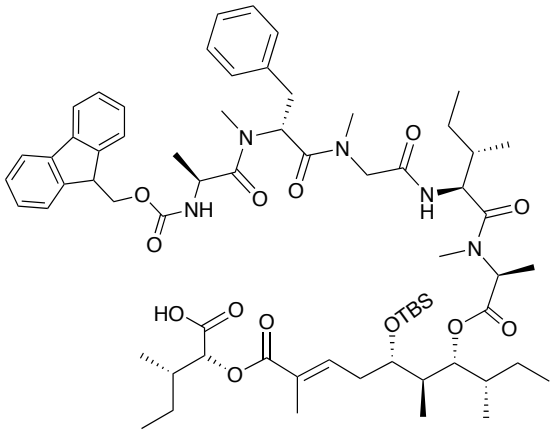


(2*R*,3*S*)-1-(*tert*-butoxy)-3-methyl-1-oxopentan-2-yl (5*S*, 6*R*, 7*R*, 8*S*, *E*)-5-((*tert*-butyldimethylsilyl)oxy)-2, 6, 8-trimethyl-7-((methyl-*D*-alanyl)oxy)dec-2-enoate (5.4): Et_2NH (100 μL, 0.9567 mmol) (freshly distilled from KOH) was added to a solution of **3.39** (40 mg, 0.0478 mmol) in 2.5 mL anhydrous CH_3CN and stirred at ambient temperatures for 50 min. Reaction progress TLC to completion. Volatiles were removed *in vacuo* to afford the free amine as a TFA salt. Residue was dried for an additional 2 hours under HI-VAC to afford **5.4** (quant. %yield, 0.0478 mmol) used without further purification; R_f = 0.05, 10% EAH; MS (ESI) *m/z* calcd for $C_{33}H_{63}NO_7Si$ $[M+H]^+$ 614.43, found 614.33.



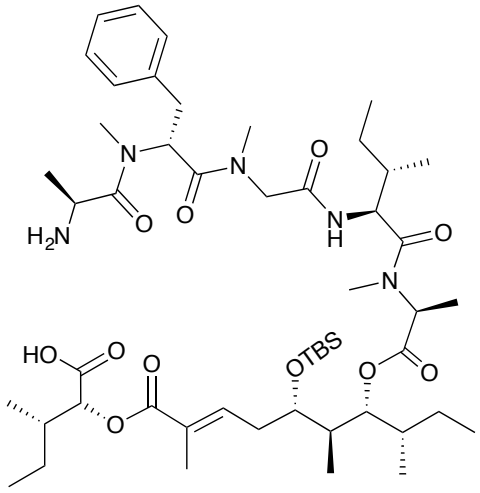
(3*S*, 4*R*, 5*R*, 6*S*, *E*) -10-(((2*R*, 3*S*)-1-(*tert*-butoxy)-3-methyl-1-oxopentan-2-yl) oxy)-6-((*tert*-butyldimethylsilyl)oxy)-3, 5, 9- tri methyl-10-oxodec-8-en-4-yl (5*S*, 8*R*, 14*S*, 17*S*)-8-benzyl-14-((*S*)-*sec*-butyl)-1-(9*H*-fluoren-9-yl)-5, 7, 10, 16, 17-pentamethyl-3, 6, 9, 12, 15- pentaoxo-2-oxa-4, 7, 10, 13, 16- pentaazaocta decan-18-oate (5.5): Crude amine **5.4** (25 mg, 0.0407 mmol) and acid **4.17** (54 mg, 0.0814 mmol) were set to converge in DMF (3.5 mL) that was cooled to 0°C and stirred under inert argon atmosphere. HATU (46 mg, 0.1221 mmol) followed by HOAt (11 mg, 0.0814 mmol) were added portion-wise then collidine (27 μL, 0.2035 mmol) was added dropwise. The reaction mixture equilibrated to ambient temperature and stirred 16 h. The mixture was quenched with ice water (8 mL) and extracted EtOAc (3 x 15 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (20 mL), then saturated aqueous NH_4Cl (20 mL), then Brine (40 mL) and dried over Na_2SO_4. Organics were filtered, concentrated *in vacuo* and chromatographed via silica gel column (0-100% EtOAc/Hexanes gradient) to afford the title compound **5.5** (34 mg, 64% yield) as an amorphous solid; R_f = 0.1, 60% EtOAc/Hex; $[\alpha]^{20}_D$ +18.1° (c 1.0, CH_2Cl_2) {similar (TES-ether, *N*-Boc) lit.[6] $[\alpha]^{20}_D$ +13.8° (c 1.4, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) *existed as rotational conformers* δ 7.74 (d, *J* = 7.5 Hz, Ar-H x 2, 2H), 7.60 – 7.54 (m, Ar-

H x 2, 2H), 7.41 – 7.35 (t, *J* = 7.5 Hz, Ar-H x 2, 1H), 7.32 – 7.27 (m, Ar-H x 2, 2H), 7.25 – 7.18 (m, Ar-H x 5, 5H), 6.92 – 6.78 (m, NH, 2H), 5.98 - 5.88 (m, 1H), 5.84 – 5.70 (m, 2H), 4.90 (m, OCH_2Ar, 4H), 4.60 – 4.50 (m, 2H), 4.38 – 4.26 (m, 2H), 4.25 – 4.14 (m, 2H), 4.10 - 3.74 (m, 3H), 3.25 – 3.10 (m, 2H), 3.09 – 2.91 (m, NMe, 6H), 2.90 - 2.80 (m, 3H), 2.36 – 2.28 (m, 1H), 2.28- 2.18 (m, 2H), 2.08 – 1.94 (m, 3H), 1.90 – 1.80 (m, RCH_3, 4H), 1.78 – 1.68 (m, 1H), 1.65 – 1.56 (m, 2H), 1.48 – 1.40 (m, ROtBu, 12H), 1.38 – 1.32 (m, 2H), 1.32 – 1.24 (m, 4H), 1.16 – 1.04 (m, 3H), 1.02 – 0.94 (m, 6H), 0.94 – 0.82 (m, 30H), 0.03 - 0.00 (m, SiMe x 2, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) *existed as rotational conformers* δ 172.7, 172.3, 171.9, 170.3, 169.2, 168.0, 167.8, 155.6, 144.1, 144.0, 142.3, 141.4, 136.7, 129.5, 128.5, 128.5, 127.8, 127.2, 125.3, 120.1, 81.7, 81.6, 78.4, 77.4, 77.2, 75.3, 70.9, 67.1, 54.2, 53.6, 52.7, 51.8, 47.3, 41.4, 37.6, 36.9, 36.4, 35.4, 34.8, 31.7, 30.9, 29.8, 28.2, 27.1, 26.2, 26.0, 25.4, 24.0, 22.8, 20.9, 18.1, 15.8, 14.9, 14.6, 14.3, 12.8, 12.5, 12.1, 11.8, 10.0, -4.3, -4.5; FTIR (neat, cm^{-1}) 3348, 2968, 2253, 1721, 1705, 1642, 1452, 1410, 1248, 1203, 1103, 1082, 910, 838, 735, 647; LC-MS (ESI) m/z calcd for $C_{70}H_{105}N_5O_{13}Si$ $[M+Na]^+$ 1274.73, found 1274.67.

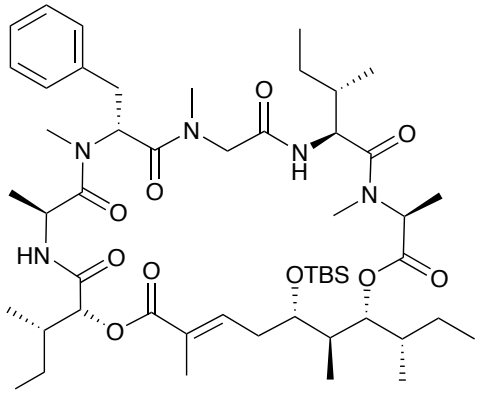


(5*S*, 8*R*, 14*S*, 17*S*, 20*R*, 21*R*, 22*S*, 28*R*, *E*)-8-benzyl-14, 20, 28-tri((*S*)-*sec*-butyl)-22-((*tert*-butyldimethylsilyl)oxy)-1-(9*H*-fluoren-9-

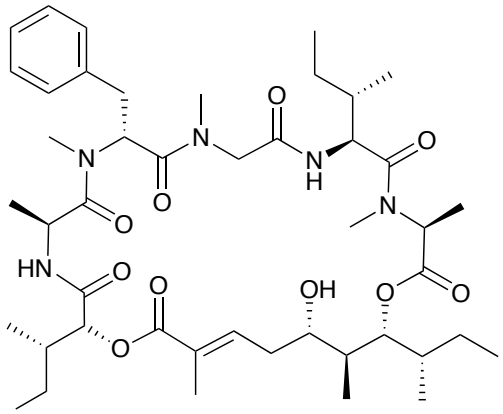
yl)-5, 7, 10, 16, 17, 21, 25-heptamethyl-3, 6, 9, 12, 15, 18, 26-heptaoxo-2, 19, 27-trioxa-4, 7, 10, 13, 16-pentaazanonacos-24-en-29-oic acid (5.5a): Trifluoroacetic acid (610 μL, 7.983 mmol) was added to a solution of ester **5.5** (20 mg, 0.0159 mmol) in 4.0 mL dry DCM at 0 °C and stirred for 2 h. Next, all volatiles were removed *in vacuo* then dried on HI-VAC and additional 2 h to liberate **5.5a** (quantitative consumption via TLC, 0.0159 mmol) that was used without further purification; LC-MS (ESI) m/z calcd for $C_{66}H_{96}N_5O_{13}Si$ $[M-H]^-$ 1194.67, found 1194.53.



(2*R*,8*S*,9*R*,10*R*,13*S*,16*S*,22*R*,25*S*,*E*)-25-amino-22-benzyl-2, 10, 16-tri((*S*)-*sec*-butyl)-8-((*tert*-butyldimethylsilyl)oxy)-5, 9, 13, 14, 20, 23-hexamethyl-4, 12, 15, 18, 21, 24-hexaoxo-3, 11-dioxa-14, 17, 20, 23-tetraazahexacos-5-enoic acid (5.6): Crude residue **5.5a** (0.0159 mmol) was treated with diethyl amine (1.0 mL, 9.606 mmol) in 5.0 mL dry CH_3CN at ambient temperature and stirred under argon atmosphere for 50 min. Volatiles were evaporated *in vacuo* and the crude residue was dried for an additional 2 hrs on HI-VAC to afford the crude title compound **5.6** (quantitative consumption via TLC, 0.0159 mmol) as a brown oily residue that was used without further purification; LC-MS (ESI) m/z calcd for $C_{51}H_{86}N_5O_{11}Si$ $[M-H]^-$ 972.60, found 972.47.

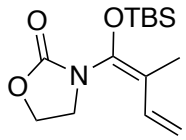


(3*S*,6*S*,12*R*,15*S*,18*R*,24*S*,25*R*,26*R*,*E*)-12-benzyl-6, 18, 26-tri((*S*)-*sec*-butyl)-24-((*tert*-butyldimethylsilyl)oxy)-3, 4, 10, 13, 15, 21, 25-heptamethyl-1,19-dioxa-4,7,10,13,16-pentaazacyclohexacos-21-ene-2,5,8,11,14,17,20-heptaone (5.6a): Charged HATU (60 mg, 0.1588 mmol) and DIPEA (55 μL, 3.175 mmol) into a solution of crude **5.6** (0.0159 mmol) in 10.0 mL dry DCM under argon atmosphere at ambient temperature and stirred 3 h. Added HOAt (11 mg, 0.0794 mmol) and capped reaction flask to stir 3 days. The mixture was concentrated *in vacuo* and dried an additional 2 h on HI-VAC to afford crude **5.6a** (quantitative consumption via TLC, 0.0159 mmol) as a brown residue that was used without further purification; LC-MS (ESI) m/z calcd for $C_{51}H_{85}N_5O_{10}SiNa$ $[M+Na]^+$ 978.60, found 978.67.



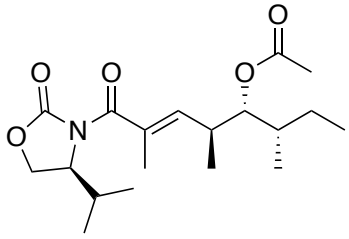
lagunamide A, (3*S*, 6*S*, 12*R*, 15*S*, 18*R*, 24*S*, 25*S*, 26*R*, *E*)-12-benzyl-6, 18, 26-tri((*S*)-*sec*-butyl)-24-hydroxy-3, 4, 10, 13, 15, 21, 25-heptamethyl-1, 19-dioxa-4, 7, 10, 13, 16-pentaazacyclohexacos-21-ene-2, 5, 8, 11, 14,

17, 20-heptaone (5.7):[6,33] Crude silyl-ether **5.6a** (0.0159 mmol) was dissolved in CH_3CN (8.0 mL) and stirred at 0 °C then added 49% aq. HF (2.0 mL). Equilibrated to ambient temperatures and stirred for 1 hr. Reaction mixture was diluted with EtOAc (100 mL) and the combined organics were washed with sat. aq. $NaHCO_3$ (2 x 20 mL, Caution- evolves gas!), Brine (2 x 20 mL) and then dried over Na_2SO_4. The mixture was filtered and concentrated *in vacuo*. 34 mg of crude brown oil was chromatographed via C-18 reverse phase column (10-100% MeOH/H_2O with 0.1% formic acid) followed by silica plug (30% Acetone/Hex) to afford the title compound, lagunamide A, **5.7** (5 mg, 39% yield over the 4 steps) as an amorphous solid that was spectroscopically identical to literature reports[6,50,5]; R_f = 0.25, 30% Acetone/Hex; $[\alpha]^{20}_D$ -33.3° (c 0.1, MeOH) {lit.[6] $[\alpha]^{20}_D$ -33.8° (c 0.1, MeOH), lit.[50] $[\alpha]^{20}_D$ -34.9° (c 0.04, MeOH), lit.[5] $[\alpha]^{20}_D$ -36° (c 0.5, CH_2Cl_2)}; ^{1}H NMR (500 MHz, MeOD): δ 7.32 (m, 1H), 7.26-7.14 (m, 5H), 5.46 (dd, J = 10.3, 5.2 Hz, 1H), 5.05 (d, J = 6.2 Hz, 1H), 4.92 (m, 1H), 4.84 (m, 1H), 4.52 (q, J = 6.9 Hz, 1H), 4.20 (d, J = 18.4 Hz, 1H), 3.95 (q, J = 6.8 Hz, 1H), 3.76 (m, 1H), 3.57 (d, J = 18.3 Hz, 1H), 3.30 (m, "*hidden signal*" 3H), 3.09-3.02 (m, 1H), 3.04 (m, 3H), 2.96 (dd, J = 12.1, 5.8 Hz, 1H), 2.89 (m, 3H), 2.28-2.20 (m, 1H), 2.20-2.11 (m, 1H), 2.09-2.05 (m, 1H), 1.94 (m, 3H), 1.90-1.80 (m, 2H), 1.77-1.60 (m, 2H), 1.60-1.45 (m, 1H), 1.43 (d, J = 7.5 Hz, 3H), 1.38-1.26 (m, 3H), 1.19-1.10 (m, 2H), 1.05 (d, J = 6.8 Hz, 3H), 1.01-0.89 (m, 21H), 0.86 (d, J = 7.1 Hz, 3H) ppm; FTIR (neat, cm^{-1}) 3436, 2929, 2600, 2341, 2055, 1740, 1634, 1521, 1246, 1120, 750; LC-MS (ESI) *m/z* calcd for $C_{45}H_{70}N_5O_{10}$ $[M-H]^-$ 840.51, found 840.67.

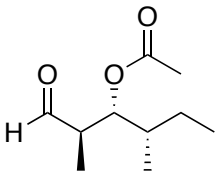


***N*-(1'-*tert*-Butyldimethylsilyloxy-2'-methyl-buta-1'*E*,3'-dienyl)-4*S*-1,3-oxazolidin-2-one (6.1)**. A solution of solid KHMDS (3.20 g, 16.02 mmol) in anhydrous THF (230 mL) was added drop wise over 30 min to a solution of oxazolidin-2-one **6.1a**[150] (1.81 g, 10.7 mmol) in anhydrous THF (110 mL) under an argon atmosphere at -78 ºC. The mixture was stirred for an additional 90 min at -78 ºC, followed by the drop wise addition of a solution of TBSCl (4.83 g, 18.16 mmol) in THF (25 mL) over 30 min at -78 ºC. The reaction was stirred and maintained at -78 ºC for 45 min. The reaction was then quenched with a saturated aq. NH_4Cl (75 mL) and the temperature of the reaction mixture was equilibrated to ambient temperature and the mixture stirred for an additional 30 min. The two phase mixture was then transferred to a separation funnel, the phases separated and the aqueous phase extracted with ethyl acetate (4 × 30 mL). The combined organic phases were washed with water (100 mL), brine (100 mL) and dried over anhydrous sodium sulfate. The solvent was filtered, concentrated under reduced pressure and the crude product purified by silica gel chromatography using ethyl acetate in hexanes as a gradient (0–40%) to afford the achiral vinylketene silyl *N,O*-acetal **6.1** as a white solid in 86% yield (2.61 g), mp 44–48 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (dd, C*H*=CH_2, *J* = 17.2, 10.9 Hz, 1H), 5.16 (dd, CH=CH_2, *J* = 17.2, 1.2 Hz, 1H), 5.03 (dd, CH=CH_2, *J* = 10.9, 1.2 Hz, 1H), 4.41 (dd, OCH_2CH$_2$, *J* = 8.1, 8.1 Hz, 2H), 3.76 (dd, CH_2CH_2N, *J* = 8.1, 8.1 Hz, 2H), 1.80 (s, CCH_3, 3H), 0.98 (s, OSiC(CH_3)$_3$, 9H), 0.20 (s, OSi(CH_3)$_2$, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.71, 137.55, 133.30, 114.83, 113.07, 62.34, 44.99, 25.78,

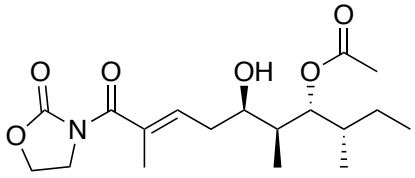
18.22, 11.54, -4.40; FTIR (neat, cm^{-1}) 2931, 2860, 1760, 1650, 1472, 1260; MS (ESI) *m/z* calcd for $C_{14}H_{26}NO_3Si$ $[M+H]^+$ 284.16, found 284.12.



***N*-(2',4'*S*,6'*S*-Trimethyl-5'*R*-acetyloxy-2'*E*-octenoyl)-4*S*-isopropyl-1,3-oxazolidin-2-one (6.2a)**. Synthesis of acetate **6.2a** follows the same protocol as the preparation of ester **3.54**. Thus, alcohol **3.53** (770 mg, 2.47 mmol) was treated with acetyl chloride, pyridine, DMAP in CH_2Cl_2. After work-up and purification with silica gel flash chromatography using (0-20% EtOAc in hexanes as a gradient) provided compound **6.2a** in 99% yield (876 mg) as a clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (dq, MeC=C*H*CH, *J* = 9.8, 1.4 Hz, 1H), 4.85 (dd, CHC*H*(OR)CH, *J* = 6.9, 5.2 Hz, 1H), 4.44 (ddd, NC*H*CH_2, *J* = 8.8, 4.8, 4.5 Hz, 1H), 4.29 (dd, OC*H*$_2$CH, *J* = 8.8, 8.8 Hz, 1H), 4.17 (dd, OC*H*$_2$CH, *J* = 8.8, 4.8 Hz, 1H), 2.91–2.81 (m, C=CHC*H*Me, 1H), 2.46–2.33 (m, CHC*H*$(CH_3)_2$, 1H), 2.02 (s, COC*H*$_3$, 3H), 1.91 (d, *H*$_3$CC=CH, *J* = 1.4 Hz, 3H), 1.72–1.60 (m, C*H*(Me)CH_2, 1H), 1.42–1.30 (m, C*H*$_2$$CH_3$, 1H), 1.20–1.08 (m, C*H*$_2$$CH_3$, 1H), 0.97 (d, C*H*$_3$$CH_2$, *J* = 6.9 Hz, 3H), 0.92 (d, C*H*$_3$CH, *J* = 6.9 Hz, "*partly hidden*", 3H), 0.89 (t, C*H*$_3$$CH_2$, *J* = 7.5 Hz, "*partly hidden*", 3H), 0.89 (d, C*H*$_3$CH, *J* = 6.9 Hz, "*partly hidden*", 3H), 0.88 (d, C*H*$_3$CH, *J* = 6.9 Hz, "*partly hidden*", 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.81, 171.25, 153.50, 138.73, 131.60, 79.14, 63.51, 58.52, 36.12, 34.82, 28.39, 26.39, 21.04, 18.03, 16.50, 15.00, 13.81, 13.66, 11.54.



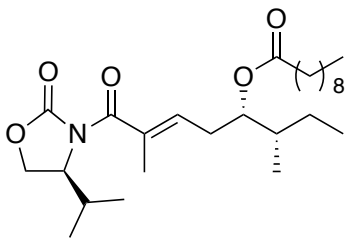
2*R*,4*S*-Dimethyl-3*R*-acetyloxy-1-hexanal (6.2). Synthesis of aldehyde **6.2** follows the same protocol as the preparation of aldehyde **3.55** via general procedure for ozonolysis of alkenes. Thus, substrate **6.2a** (450 mg, 1.27 mmol) was treated ozone at -78 ºC and subsequently reductive workup via Me_2S. After work-up and purification with flash chromatography using EtOAc and hexanes as a gradient (0–10%) provided aldehyde **6.2** in 90% yield (213 mg) as a clear oil. Aldehyde **6.2** was used immediately in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (d, CHO, *J* = 3.2 Hz, 1H), 5.12 (dd, CHC*H*(OR)CH, *J* = 7.6, 4.6 Hz, 1H), 2.70–2.60 (m, CHOC*H*(Me), 1H), 2.05 (s, COCH_3, 3H), 1.76–1.65 (m, C*H*CH_2, 1H), 1.45–1.34 (m, CH_2CH_3, 1H), 1.25–1.13 (m, CH_2CH_3, 1H), 1.09 (d, CH_3CH, *J* = 7.1 Hz, 3H), 0.93 (t, CH_3CH_2, *J* = 7.1 Hz, "*partly hidden*", 3H), 0.92 (d, CH_3CH, *J* = 7.1 Hz, "*partly hidden*", 3H).



***N*-(5'*S*-Hydroxy-2',6'*S*,8'*S*-trimethyl-7'*R*-acetyloxy-2'*E*-decenoyl)-1,3-oxazolidin-2-one (6.3)**, *major diastereomer*. To a stirred solution of aldehyde **6.2** (50.0 mg, 0.269 mmol) in distilled CH_2Cl_2 (3.0 mL) under argon at -78 °C was added neat $TiCl_4$ (0.050 ml, 0.402 mmol). After the reaction mixture was stirred for an additional 20 min a solution of vinylketene silyl *N,O*-acetal **6.1** (228 mg, 0.804 mmol) in CH_2Cl_2 (6.0 mL) was slowly added over 20 min at -78 °C under an argon atmosphere. After allowing the reaction mixture to stir for 14 h at -78 °C the resulting orange solution

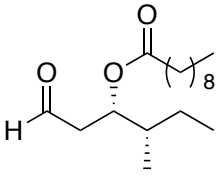
was quenched with saturated aqueous mixture of Rochelle Salt and saturated $NaHCO_3$ (50:50, 20 mL). The temperature was then increased to ambient temperature and the mixture stirred an additional 30 min. The mixture was transferred to a separation funnel and the aqueous phase was extracted with ethyl acetate (4 × 15 mL). The combined organic phases were washed with water (30 mL), brine (40 mL) and dried over anhydrous sodium sulfate. The solvent was filtered, concentrated under reduced pressure and the crude product purified by silica gel chromatography using ethyl acetate in hexanes as a gradient (0–40%) spiked with 2.5% methylene chloride to give a 73:27 distereomeric mixture of aldol products **6.3** in 70% yield (67.5 mg) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ *(Major diastereomer)* 6.03 (ddq, MeC=C*H*CH, *J* = 7.9, 6.5, 1.5 Hz, 1H), 4.89 (dd, CHC*H*(OR)CH, *J* = 10.0, 2.6 Hz, 1H), 4.42 (dd, OCH_2CH$_2$, *J* = 8.2, 8.2 Hz, 2H), 4.01 (dd, NCH_2CH$_2$, *J* = 8.2, 8.2 Hz, 2H), 3.67–3.59 (m, C*H*OH, 1H), 2.91–2.77 (bs, CHO*H*, 1H), 2.51–2.40 (m, C=CHCH_2CH, 1H), 2.40–2.31 (m, C=CHCH_2CH, 1H), 2.27–2.18 (m, CH$_3$C*H*, 1H), 2.11 (s, COCH_3, 3H), 1.96–1.89 (m, CH$_3$C*H*, "*partly hidden*", 1H), 1.92 (d, H_3CC=CH, *J* = 1.5 Hz, 3H), 1.79–1.64 (m, CH_2CH$_3$, 2H), 0.90 (t, CH_3CH$_2$, *J* = 7.2 Hz, "*partly hidden*", 3H), 0.89 (d, CH_3CH, *J* = 6.8 Hz, "*partly hidden*", 3H), 0.89 (d, CH_3CH, *J* = 6.8 Hz, "*partly hidden*", 3H); δ (*Minor diastereomer*) 5.97 (ddq, MeC=C*H*CH, *J* = 7.9, 6.5, 1.5 Hz, 1H), 4.87 (dd, CHC*H*(OR)CH, *J* = 10.0, 3.2 Hz, 1H), 4.41 (dd, OCH_2CH$_2$, *J* = 8.2, 8.2 Hz, 2H), 4.02 (dd, NCH_2CH$_2$, *J* = 8.2, 8.2 Hz, "*partly hidden*", 2H), 3.78–3.69 (m, C*H*OH, 1H), 2.91–2.77 (bs, CHO*H*, 1H), 2.52–2.42 (m, C=CHCH_2CH, "*partly hidden*", 1H), 2.36–2.29 (m, C=CHCH_2CH, "*partly hidden*", 1H), 2.22–2.14 (m, CH$_3$C*H*, "*partly hidden*", 1H), 2.11 (s, COCH_3, 3H), 1.96–1.89 (m, CH$_3$C*H*, "*partly hidden*", 1H), 1.93 (d, H_3CC=CH, *J* = 1.5 Hz, 3H), 1.82–1.66 (m,

C*H*$_2$CH$_3$, "*partly hidden*", 2H), 0.94 (d, C*H*$_3$CH, *J* = 6.8 Hz, 3H), 0.93–0.87 (m, C*H*$_3$CH$_2$ and C*H*$_3$CH, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (*Major diastereomer*) 172.84, 171.82, 153.20, 136.04, 131.59, 77.86, 69.09, 62.29, 43.43, 39.21, 35.72, 33.41, 27.25, 21.06, 14.00, 12.63, 11.98, 9.04; FTIR (neat, cm^{-1}) 3524, 2929, 1784, 1727, 1680, 1384, 1243, 1038, 762; HRMS (ESI) m/z calcd for $C_{18}H_{29}NO_6Na$ $[M+Na]^+$ 378.1887, found 378.1886.

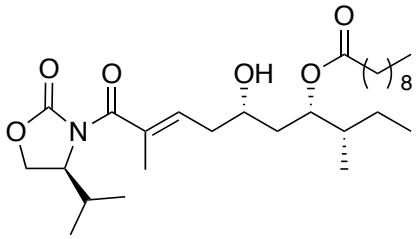


***N*-(2',6'*S*-Dimethyl-5'*S*-decanoyloxy-2'*E*-octenoyl)-4*S*-isopropyl-1,3-oxazolidin-2-one (6.4a)**. Synthesis of *n*-decanoate **6.4a** follows the same protocol as the preparation of ester **3.54**. Thus, alcohol **6.6** (150 mg, 0.505 mmol) was treated with decanoyl chloride, pyridine, DMAP in CH_2Cl_2. After work-up and purification with flash chromatography using EtOAc and hexanes as a gradient (0–20%) provided compound **6.4a** in 99% yield (225 mg) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01–5.94 (m, C=C*H*CH$_2$, 1H), 4.99–4.92 (m, CH$_2$C*H*(OR)CH, 1H), 4.49 (ddd, NC*H*, *J* = 8.8, 5.2, 4.3 Hz, 1H), 4.30 (dd, OC*H*$_2$, *J* = 8.8, 8.8 Hz, 1H), 4.17 (dd, OC*H*$_2$, *J* = 8.8, 5.2 Hz, 1H), 2.54–2.40 (m, C*H*Me$_2$, "*partly hidden*", 1H), 2.38–2.32 (m, C=CC*H*$_2$, "*partly hidden*", 1H), 2.35 (t, (CO)C*H*$_2$CH$_2$, *J* = 7.6 Hz, 2H), 2.30–2.27 (m, C=CC*H*$_2$, "*partly hidden*", 1H), 1.91 (s, C=CC*H*$_3$, 3H), 1.68–1.59 (m, (CO)CH$_2$C*H*$_2$ + C*H*CH$_3$, "*partly hidden*", 3H), 1.46–1.08 (m, (C*H*$_2$)$_7$, "*partly hidden*", 14H), 0.93–0.85 (m, (CH$_3$)$_5$, "*partly hidden*", 15H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.18, 173.73,171.67,

134.00, 133.13, 75.36, 63.58, 58.44, 37.80, 34.73, 34.04, 32.02, 30.74, 29.54, 29.39, 29.22, 28.48, 25.97, 24.86, 22.81, 18.01, 15.16, 14.22, 14.18, 14.01, 11.74.



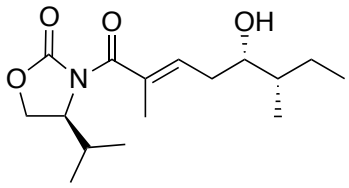
3*S*-Decanoyloxy-4*S*-methyl-1-hexanal (6.4). Synthesis of aldehyde **6.4** follows the same protocol as the preparation of aldehyde **3.55** via general procedure for ozonolysis of alkenes. Thus, substrate **6.4a** (200 mg, 0.443 mmol) was treated with ozone at -78 ºC and subsequently Me_2S. After reductive work-up and purification with flash chromatography using EtOAc and hexanes as a gradient (0–15%) provided aldehyde **6.4** in 90% yield (113 mg) as a clear oil. Aldehyde **6.4** was used immediately in the next step; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73–9.71 (m, CHO, 1H), 5.32 (ddd, CH_2CH(OR)CH, J = 8.5, 5.6, 3.2 Hz, 1H), 2.68–2.60 (m, CH_2CHO, 1H), 2.60–2.54 (m, CH_2CHO, 1H), 2.34 (dd, $COCH_2CH_2$, J = 7.5, 7.5 Hz, 2H), 2.28 (m, $COCH_2CH_2$, 2H), 1.67–1.55 (m, $CHCH_3$ and CH_2, 3H), 1.50–1.40 (m, $CHCH_2CH_3$, 1H),1.35–1.20 (m, 5 × CH_2, 10H), 1.20–1.10 (m, $CHCH_2CH_3$, 1H), 0.95 – 0.85 (m, 3 × CH_3, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.04, 173.56, 71.61, 46.16, 38.63, 34.60, 33.99, 32.01, 29.54, 29.28, 25.53, 25.16, 24.86, 22.81, 14.35, 14.23, 11.77.



***N*-(5'*S*-Hydroxy-2',8'*S*-dimethyl-7'*S*-decanoyloxy-2'*E*-decenoyl)-4*S*-isopropyl-1,3-oxazolidin-2-one (6.5)**. To a solution of aldehyde **6.4**

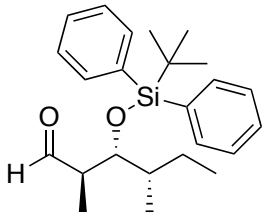
(60.0 mg, 0.211 mmol) in CH_2Cl_2 (3.0 mL) at -78 ºC was added neat $TiCl_4$ (25 mL, 0.232 mmol) under argon and reaction mixture stirred for 20 min. Then a solution of **3.56** (69 mg, 0.212 mmol) in distilled CH_2Cl_2 (3.0 mL) was added dropwise over 20 min at -78 ºC under an argon atmosphere. The 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 $NaHCO_3$ (50:50, 10 mL) at -78 ºC. The reaction mixture was warmed to room temperature, stirred for an additional 30 min, then transferred to a separation funnel and the aqueous phase extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with water (20 mL), brine (30 mL) and dried over anhydrous Na_2SO_4, filtered and the organic solvent removed under reduced pressure. The crude product was purified by silica gel chromatography using ethyl acetate in hexanes as a gradient (0–40%) spiked with 2.5% methylene chloride to give aldol product **6.5** (96:4 dr) as a colorless oil in 68% yield (72 mg), $[\alpha]^{20}_D$ +56.8º (c=0.82, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 (ddq, C=C*H*CH_2, *J* = 9.4, 6.3, 1.5 Hz, 1H), 5.02 (ddd, CH_2C*H*(OR)CH, *J* = 8.8, 4.0, 4.0 Hz, 1H), 4.54 (ddd, NC*H*, *J* = 8.9, 5.4, 4.4 Hz, 1H), 4.32 (dd, OC*H*$_2$CHN, *J* = 8.9, 8.9 Hz, 1H), 4.17 (dd, OC*H*$_2$CHN, *J* = 8.9, 5.4 Hz, 1H), 3.79–3.71 (m, C*H*OH, 1H), 3.00 (bs, O*H*, 1H), 2.43–2.30 (m, C=CHC*H*$_2$, "*partly hidden*", 2H), 2.29 (dd, COC*H*$_2$CH$_2$, *J* = 8.1, 7.0 Hz, 2H), 1.95–1.86 (m, C*H*CH_3, "*partly hidden*", 1H), 1.92 (bs, C=CC*H*$_3$, 3H), 1.79–1.65 (m, C*H*(Me)CH_2, "*partly hidden*", 1H), 1.65–1.55 (m, CHC*H*$_2$CH, 2H), 1.50–1.37 (m, CH(Me)C*H*$_2$CH$_3$, 1H), 1.34 – 1.23 (m, 7 × C*H*$_2$, 14H), 1.20 – 1.09 (m, CH(Me)C*H*$_2$CH$_3$, 1H), 0.96 – 0.84 (m, 5 × C*H*$_3$, 15H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.82, 171.39, 154.15, 134.58, 133.26, 74.23, 68.36, 63.47, 58.17, 38.80, 38.60, 36.33, 34.66, 31.80, 29.38, 29.23, 29.21, 29.15, 28.43, 25.66, 25.04,

22.61, 17.81, 15.13, 14.03, 13.92, 13.72, 11.70; FTIR (neat, cm^{-1}) 2961, 2928, 2858, 1783, 1730, 1684, 1464, 1366, 1298, 1206, 773; HRMS (ESI) m/z calcd for $C_{28}H_{49}NO_6Na$ $[M+Na]^+$ 518.3452, found 518.3448.

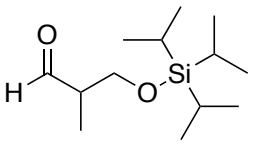


***N*-(5'*S*-Hydroxy-2',6'*S*,-dimethyl-2'*E*-octenoyl)-4*S*-iso propyl-1,3-oxazolidin-2-one (6.6)**. To a solution of (*S*)-methylbutanal (**3.1**) (87.0 mg, 1.01 mmol) in CH_2Cl_2 (15 mL) at -78 ºC was added neat $TiCl_4$ (101 mL, 0.922 mmol) under argon and reaction mixture stirred for 20 min. Then a solution of **3.52** (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 $NaHCO_3$ (50:50, 20 mL) at -78 ºC. The reaction mixture was warmed to room temperature, stirred for an additional 30 min, then transferred to a separation funnel and the aqueous phase extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with water (30 mL), brine (40 mL) and dried over anhydrous Na_2SO_4, filtered and the organic solvent removed under reduced pressure. The crude product was purified by silica gel chromatography using ethyl acetate in hexanes as a gradient (0–30%) spiked with 2.5% methylene chloride to give aldol product **6.6** (>98:2 dr) as a colorless oil in 65% yield (178 mg), $[\alpha]^{20}_D$ +21.8º (c=1.5, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ 6.04 (ddq, MeC=C*H*CH_2, *J* = 9.8, 5.9, 1.6 Hz, 1H), 4.55 (ddd, NC*H*, *J* = 9.0, 5.4, 4.5 Hz, 1H), 4.32 (dd, OCH_2CH, *J* = 9.0, 9.0 Hz, 1H), 4.18 (dd, OCH_2CH, *J* =

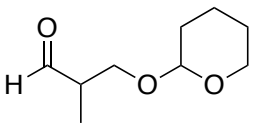
9.0, 5.4 Hz, 1H), 3.64–3.57 (m, C*H*OH, 1H), 2.69 (bs, RO*H*, 1H), 2.43 (ddd, C=CCH_2, *J* = 13.7, 9.8 Hz, 1H), 2.39–2.31 (m, C*H*$(CH_3)_2$, *J* = 7.0, 4.5 Hz, 1H), 2.28–2.20 (m, C=CCH_2, 1H), 1.94 (bt, C=CCH_3, *J* = 1.6 Hz, 3H), 1.60–1.50 (m, C*H*CH_2CH_3, 1H), 1.52–1.44 (m, CHCH_2CH_3, 1H), 1.25–1.15 (m, CHCH_2CH_3, 1H), 0.95 (d, CHCH_3, *J* = 7.0 Hz, 3H), 0.93 (d, CHCH_3, *J* = 7.0 Hz, "*partly hidden*", 3H), 0.92 (t, CH_2CH_3, *J* = 7.5 Hz, "*partly hidden*", 3H), 0.91 (d, CHCH_3, *J* = 7.0 Hz, "*partly hidden*", 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.55, 154.24, 135.94, 132.85, 73.59, 63.46, 58.16, 40.04, 33.86, 28.43, 25.75, 17.83, 15.14, 14.14, 13.67, 11.72; FTIR (neat, cm^{-1}) 3529, 2968, 2928, 1772, 1686, 1389, 1366, 1297, 1211, 1054, 1015, 913, 737; LC-MS (ESI) m/z calcd for $C_{16}H_{27}NO_4$ $[M+H]^+$ 298.19, found 298.00.



(2*R*,3*R*,4*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-2,4-dimethylhexanal (6.7): The title compound was prepared from alcohol **3.53** by the general procedure for silyl-ether protection of a hydroxyl with TBDPS-OTf/2,6-lutidine followed by the general procedure for ozonolysis of alkenes to afford **6.7** (0.349 g, 60% yield over 2 steps) as a clear oil; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.74 (d, *J* = 2.4 Hz, RCHO, 1H), 7.71 – 7.64 (m, Ar-H x 4, 4H), 7.39 (m, Ar-H x 6, 6H), 3.84 (t, *J* = 3.7 Hz, R_2CH(OSi), 1H), 2.51 (qdd, *J* = 7.1, 3.6, 2.4 Hz, R_3CH, 1H), 1.64 – 1.46 (m, RCH_2R, 2H), 1.08 (s, Si-tBu, 9H), 1.00 (d, *J* = 7.1 Hz, RCH_3, 3H), 0.81 (d, *J* = 6.9 Hz, RCH_3, 3H), 0.75 (t, *J* = 7.3 Hz, RCH_3, 3H).

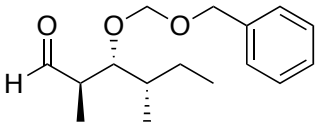


2-methyl-3-((triisopropylsilyl)oxy)propanal (6.8):[151] 2-methylprop-ane-1,3-diol (2.00 mL, 22.53 mmol) was mono-silated by the general procedure silyl-ether proection of a hydroxy with TIPS-OTf/2,6-lutidine to afford primary alcohol **6.8a** (0.545 g, 98% yield) as a pale yellow oil that was subsequently oxidized via DMP (1.5 equiv) in 15 mL dry DCM under argon atmosphere and stirred 4 hours. The reaction mixture was quenched with 10 mL sat. $NaHCO_3$, stirred and filtered with minimal volume 3 x 3 mL DCM. The filtrate was dried with Na_2SO4, filtered and concentrated *in vacuo*. The crude residue was chromatographed via silica gel column (0-10% EtOAc in hexanes gradient) to afford the title compound, aldehyde **6.8** (0.118 g, 78% yield) as a clear oil; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.78 (d, *J* = 1.6 Hz, RCHO, 1H), 3.97 (dd, *J* = 10.0, 5.2 Hz, RCH_2O, 1H), 3.91 (dd, *J* = 10.0, 6.3 Hz, RCH_2O, 1H), 2.60 – 2.50 (m, R_3CH, 1H), 1.30 – 1.12 (m, Si-CHR_2 x 3, 3H), 1.11 (d, *J* = 7.0 Hz, RCH_3, 3H), 1.06 (d, *J* = 1.0 Hz, TIPSi, 18H).



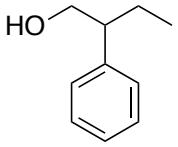
2-methyl-3- ((tetrahydro- 2*H*- pyran- 2-yl) oxy) propanal (6.9):[152] Dissolved 2-methylprop-ane-1,3-diol (2.00 mL, 22.53 mmol) in 30 mL dry DCM then added catalytic (+)-camphorsulfonic acid (0.005 g, 0.0225 mmol) then 3,4-dihydro-2H-pyran (0.202 mL, 2.25 mmol) at ambient temperature under argon and stirred 15 h. Reaction mixture was quenched with sat. $NaHCO_3$ until basic then washed with brine and organics were dried Na_2SO_4. Mixture was filtered, concentrated *in vacuo* and the residue

was chromatographed via silica gel column (0-50% EtOAc in hexanes gradient) to afford the corresponding primary alcohol **6.9a** (0.233 g, 60% yield) as yellow oil that was subsequently oxidized via DMP (1.5 equiv) in 15 mL dry DCM under argon atmosphere and stirred 4 hours. The reaction mixture was quenched with 10 mL sat. $NaHCO_3$, stirred and filtered with minimal volume 3 x 3 mL DCM. The filtrate was dried with Na_2SO4, filtered and concentrated *in vacuo*. The crude residue was chromatographed via silica gel column (0-10% EtOAc in hexanes gradient) to afford the title compound, aldehyde **6.9** (0.102 g, 65% yield) as a clear oil; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.76 – 9.73 (m, RCHO, O_2CHR, 1H), 4.61 (td, *J* = 4.7, 4.2, 2.7 Hz, OCH_2R, 1H), 4.01 – 3.91 (m, OCH_2R, 1H), 3.87 – 3.77 (m, OCH_2R, 1H), 3.64 – 3.55 (m, OCH_2R, 1H), 3.55 – 3.46 (m, R_3CH, 1H), 2.65 (dtt, *J* = 14.0, 7.1, 1.8 Hz, RCH_2R, 1H), 2.12 – 2.01 (m, RCH_2R, 2H), 1.87 – 1.74 (m, RCH_2R, 1H), 1.73 – 1.63 (m, RCH_2R, 1H), 1.61 – 1.43 (m, RCH_2R + RCH_3, 1H + 3H), 1.19 – 1.07 (m, RCH_3, 3H).

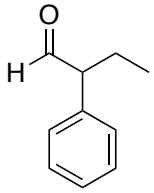


(2*R*,3*R*,4*S*)-3-((benzyloxy)methoxy)-2,4-dimethylhexanal (6.10): Dissolved *anti*-alcohol **3.53** (0.100 g, 0.3211 mmol) in 1.5 mL dry DCM under argon at 0 ^oC. Added iPr_2NEt (0.100 mL, 0.5779 mmol) dropwise and stirred 10 min. Added BOM-Cl (0.100 mL, 80%, 0.4816 mmol) and TBAI (0.180 g) and stirred sealed for 17 hr overnight at ambient temperatures. The resultant orange solution was quenched with 1.0 mL MeOH, stirred and evaporated under reduced pressure. The residue was worked up in 3 mL EtOAc and 2 mL H_2O and extracted 3 x 5 mL EtOAc. The combined organics were dried over Na_2SO_4, filtered and concentrated to afford the corresponding

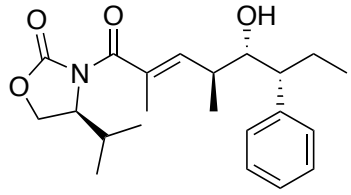
BOM-protected *anti*-alcohol **6.10a** (0.118 g, 85% yield) that was selectively oxidized by the general procedure for ozonolysis of alkenes without further purification to afford aldehyde **6.10** (0.042 g, 70% yield) as a clear oil; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.76 (d, *J* = 2.9 Hz, RCHO, 1H), 7.36 – 7.28 (m, Ar-H x 5, 5H), 4.77 (s, OCH_2O, 2H), 4.62 (d, *J* = 11.9 Hz, OCH_2O, 1H), 4.55 (d, *J* = 11.9 Hz, OCH_2O, 1H), 3.73 (dd, *J* = 6.3, 4.1 Hz, $R_2CH(OR)$, 1H), 2.67 (qdd, *J* = 7.1, 6.3, 2.9 Hz, R_3CH, 1H), 1.69 – 1.44 (m, RCH_2R, 2H), 1.26 – 1.18 (m, R_3CH, 1H), 1.10 (d, *J* = 7.1 Hz, RCH_3, 3H), 0.96 – 0.92 (m, RCH_3 x 2, 6H).



2-phenylbutan-1-ol (6.11a): A solution of *rac*-2-phenyl-butyric acid (14.5 g, 88.5 mmol) in ether (200 mL) was added dropwise via addition funnel over 4 hours to a vigerously stirred suspension of LAH (3.35 g, 88.5 mmol) in dry ether (100 mL), a rate that maintained a gentle, rolling boil. The reaction stirred overnight (16 hrs) at ambient temperatures and was then cooled to 0 °C. The cooled mixture was charged with 5% H_2SO_4 dropwise to resolve the aluminum salts. The organics were separated, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Distillation under vacuum afforded *rac*-2-phenylbutanol (11.85 g, 85%, bp 120 °C @ 23 mbar). Proton and carbon data were consistent with the literature.[84] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 (m, Ar-H x 2, 2H), 7.24 – 7.15 (m, Ar-H x 3, 3H), 3.74 – 3.63 (m, RCH_2R, 2H), 2.65 (ddt, *J* = 9.3, 7.7, 5.7 Hz, R_3CH, 1H), 1.81 – 1.68 (m, RCH_2R, 2H), 1.62 – 1.48 (m, ROH, 1H), 0.82 (t, *J* = 7.4 Hz, RCH_3, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.45, 128.62, 128.18, 126.70, 77.16, 67.32, 50.54, 25.06, 12.03.

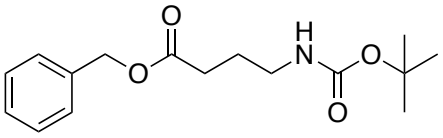


2-phenylbutanal (6.11): A solution of **6.11a** (11.85 g, 100 mmol) in dichloromethane (200 mL) was added to an ice-cooled, stirred suspension of PCC (11.25 g, 100 mmol) in dichloromethane (50 mL). Reaction was monitored via TLC until completed, then filtered over silica gel plug. The solvent was removed and crude residue was purified via silica gel column (0-10% EtOAc in hexanes gradient) to afford the title racemic compound **6.11** (8.65 g, 78% yield) as clear oil. Proton and carbon data were consistent with the literature.[84] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.67 (d, *J* = 2.1 Hz, 1H), 7.40 – 7.33 (m, 2H), 7.32 – 7.24 (m, 1H), 7.21 – 7.15 (m, 2H), 3.40 (ddd, *J* = 8.4, 6.7, 2.1 Hz, 1H), 2.11 (dqd, *J* = 14.0, 7.4, 6.7 Hz, 1H), 1.82 – 1.69 (m, 1H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 201.09, 129.11, 128.93, 127.62, 77.16, 60.97, 23.06, 11.82.

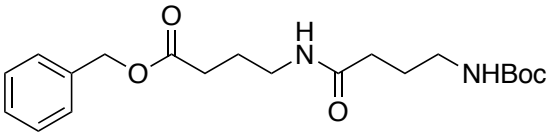


(*S*)-3-((4*S*,5*S*,6*R*,*E*)-5-hydroxy-2,4-dimethyl-6-phenyloct-2-enoyl)-4-isopropyloxazolidin-2-one (6.12): The title compound was enantiomerically resolved (0.075 g, 85% yield, 70:30 dr) via general procedure for vinylogous Mukaiyama aldol reaction using *rac*-aldehyde **6.11** (3.0 equiv), $TiCl_4$ (1.5 equiv) and VMAR **3.52** (1.0 equiv); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.35 (m, ArH, 2H), 7.32 – 7.27 (m, ArH, 2H), 7.25 – 7.19 (m, ArH, 1H), 5.83 (dq, *J* = 10.4, 1.5 Hz, C=CH, 1H), 4.55 (ddd, *J* = 8.8, 5.7, 4.6 Hz, OCH_2R, 1H), 4.34 (td, *J* = 9.0, 0.6 Hz, OCH_2R, 1H), 4.18 (dd,

J = 9.0, 5.7 Hz, R_3CH, 1H), 3.60 (dd, *J* = 8.4, 4.0 Hz, R_2CH(OH), 1H), 3.00 (s, ROH, 1H), 2.64 (td, *J* = 7.5, 4.0 Hz, R_3CH, 1H), 2.44 – 2.28 (m, R_3CH, 2H), 1.84 (p, *J* = 7.4 Hz, RCH_2R, 2H), 1.70 (dd, *J* = 1.5, 0.5 Hz, RCH_3, 3H), 0.96 (d, *J* = 6.5 Hz, RCH_3, 3H), 0.94 – 0.89 (m, RCH_3, 6H), 0.82 (t, *J* = 7.4 Hz, RCH_3, 3H).

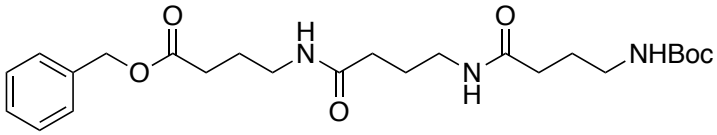


benzyl 4-((*tert*-butoxycarbonyl) amino) butanoate (7.1): Ice bath cooled solution of benzyl alcohol (100 µL, 0.9617 mmol) and Boc-GABA-OH (0.391 g, 1.923 mmol) in 10.0 mL freshly distilled DCM was charged with DCC (0.496 g, 2.404 mmol) and DMAP (0.294 g, 2.404 mmol) in one lot under argon atmosphere and stirred 14 hours overnight. Reaction was TLC'd to completion then quenched with 15 ml sat. NH_4Cl, extracted 4 x 15 mL DCM and the combined organics were dried over $MgSO_4$. The mixture was filtered and concentrated to produce crude solids that were extracted with 10% EtOAc/hex (Boc-GABA-OH and other impurities were generally insoluble) and purified via silica gel column chromatography (0-25% EtOAc in hexanes gradient) to afford the title compound, monomer **7.1** (0.273 g, 97% yield) as white crystals; R_f = 0.5, 25% EAH; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.23 (m, Ar-H x 5, 5H), 5.09 (s, CH_2Ph, 2H), 4.79 (s, NH, 1H), 3.13 (q, *J* = 6.6 Hz, NCH_2, 2H), 2.37 (t, *J* = 7.4 Hz, RCH_2R, 2H), 1.80 (p, *J* = 7.1 Hz, RCH_2R, 2H), 1.41 (s, OtBu, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.93, 155.92, 135.83, 128.42, 128.09, 128.05, 78.88, 66.13, 39.73, 31.39, 28.30, 25.17; FTIR (neat, cm^{-1}) 3320, 2933, 1731, 1708, 1683, 1540, 1365, 1163, 995, 851, 754, 699, 675.



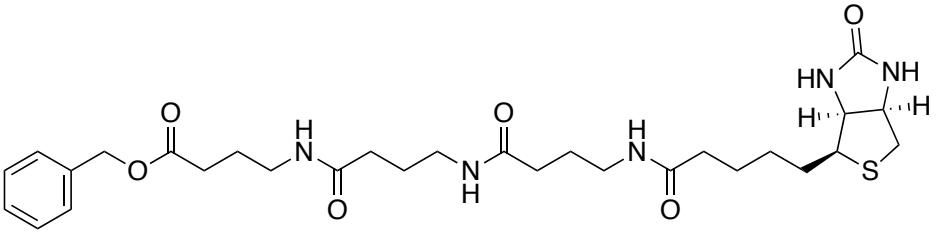
benzyl 4- (4- ((*tert*- butoxycarbonyl) amino) butanamido) butanoate (7.2): Dissolved carbamate **7.1** (0.500 g, 1.704 mmol) in 6.0 mL freshly distilled DCM was charged with 3 mL TFA (34.04 mmol) and stirred for 80 minutes at ambient temperature under argon flow. Consumption of starting material was confirmed via TLC. The reaction mixture was concentrated *in vacuo* and dried an additional 2 hrs on HI-VAC to afford a crude (corresponding TFA salt) residue that was re-dissolved in 8 mL CH_2Cl_2 and charged with Boc-GABA-OH (0.693 g, 3.408 mmol), HATU (1.620 g, 4.260 mmol) and DIPEA (1.48 mL, 8.520 mmol) successively under argon at ambient temperature and stirred sealed for 18 h. The reaction mixture was optionally stirred 3 hours then charged with HOAt (1.5 equiv), resulting in similar yields. The reaction was ultimately quenched with 20 mL cold DI H_2O and extracted with 4 x 15 mL DCM. The combined organics were then washed with 20 mL sat. $NaHCO_3$, 20 mL sat. NH_4Cl, 20 mL brine and dried over Na_2SO_4. The resultant combination was filtered and concentrated *in vacuo* then purified via silica gel column chromatography (50-100% EtOAc in hexanes gradient) to afford the title compound, dimer **7.2** (0.503 g, 78% yield) as a pale yellow solid; R_f = 0.4, 100% EtOAc; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.28 (m, Ar-H x 5, 5H), 6.37 (s, NH, 1H), 5.12 (s, CH_2Ph, 2H), 4.79 (s, NH, 1H), 3.29 (td, *J* = 6.9, 5.7 Hz, RCH_2R, 2H), 3.14 (q, *J* = 6.1 Hz, RCH_2R, 2H), 2.43 (t, *J* = 7.3 Hz, RCH_2R, 2H), 2.18 (t, *J* = 7.0 Hz, RCH_2R, 2H), 1.86 (p, *J* = 7.1 Hz, RCH_2R, 2H), 1.81 – 1.71 (m, RCH_2R, 2H), 1.43 (s, OtBu, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.24, 172.82, 156.61, 135.84, 128.59, 128.29, 128.22, 79.47, 66.41, 39.66, 38.97, 33.49, 31.76,

28.39, 26.41, 24.60; FTIR (neat, cm^{-1}) 3422, 2984, 2942, 1709, 1653, 1540, 1366, 1253, 1229, 1167, 847.



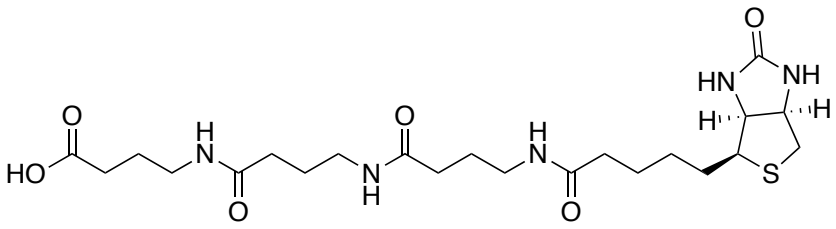
benzyl 2, 2- dimethyl- 4, 9, 14-trioxo-3-oxa- 5, 10, 15-triazanonadecan-19-oate (7.3): Dissolved carbamate **7.2** (0.350 g, 0.925 mmol) in 8.0 mL freshly distilled DCM was charged with 3 mL TFA (34.04 mmol) and stirred for 80 minutes at ambient temperature under argon flow. Consumption of starting material was confirmed via TLC. The reaction mixture was concentrated *in vacuo* and dried an additional 2 hrs on HI-VAC to afford a crude (corresponding TFA salt) residue that was re-dissolved in 10.0 mL CH_2Cl_2 and charged with Boc-GABA-OH (0.235 g, 1.156 mmol), HATU (0.528 g, 1.388 mmol) and DIPEA (0.645 mL, 3.700 mmol) successively under argon at ambient temperature and stirred for 1 h. The reaction mixture was then charged with HOAt (0.130 g, 0.462 mmol), sealed and stirred 18 h. The reaction was quenched with 20 mL cold DI H_2O and extracted with 4 x 15 mL DCM. The combined organics were then washed with 20 mL sat. $NaHCO_3$, 20 mL sat. NH_4Cl, 20 mL brine and dried over Na_2SO_4. The resultant combination was filtered and concentrated *in vacuo* then purified via silica gel column chromatography (solvent mixture was 60:15:15:10 of EtOAc:ACN:MeOH:H_2O isocratic gradient) to afford the title compound, trimer **7.3** (0.255 g, 66% yield) as pale yellow solid; R_f = 0.6, 100% EtOAc; ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.98 (dt, J = 10.3, 5.7 Hz, NH, 1H), 7.33 (dd, J = 21.2, 4.4 Hz, Ar-H x 5, 5H), 5.11 (s, NH x 2, 2H), 4.83 (s, CH_2Ph, 2H), 3.25 – 3.15 (m, RCH_2R x 2, 4H), 3.07 (t, J = 6.9 Hz, RCH_2R, 2H), 2.41 (t, J = 7.4 Hz, RCH_2R,

2H), 2.21 (t, J = 7.5 Hz, RCH_2R x 2, 4H), 1.86 – 1.69 (m, RCH_2R x 3, 6H), 1.43 (s, OtBu, 9H); ^{13}C NMR (101 MHz, CD_3OD) δ 175.37, 175.35, 175.27, 174.36, 158.32, 137.50, 129.45, 129.10, 129.09, 79.79, 67.15, 40.72, 39.74, 39.55, 34.28, 34.26, 32.26, 28.77, 27.21, 26.66, 25.67; FTIR (neat, cm^{-1}) 3327, 2944, 2486, 1740, 1708, 1690, 1652, 1633, 1542, 1526, 1452, 1418, 1365, 1279, 1254, 1224, 1162, 1027, 1003, 852, 736, 693.



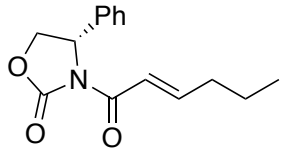
benzyl 4-(4-(4-(5- ((3a*S*, 4*S*, 6a*R*)-2- oxohexahydro- 1*H*- thieno [3,4-*d*]imidazol-4-yl) pentanamido) butanamido) butanamido) butanoate (7.4): Dissolved carbamate trimer **7.3** (0.050 g, 0.1079 mmol) in 5.0 mL freshly distilled DCM was charged with 0.650 mL TFA and stirred for 90 minutes at ambient temperature under argon flow. Consumption of starting material was confirmed via TLC. The reaction mixture was concentrated *in vacuo* and dried an additional 2 hrs on HI-VAC to afford a crude (corresponding TFA salt) residue that was re-dissolved in 1.75 mL DMF and charged with *D*-Biotin (0.027 g, 0.1079 mmol), HOBt (0.020 g, 0.1295 mmol) and EDC·HCl (0.025 g, 0.1295 mmol) under argon atmosphere at ambient temperature. 0.500 mL Et_3N was added dropwise via cannula, the reaction mixture was sealed and stirred for 18 hrs. To the resultant mixture was added 0.500 mL DCM:DMSO (1:1) that was then acidified to ~pH 1 with concentrated HCl, added dropwise. The mixture was homogenized with the addition of 350 μL DI H_2O. Without further workup, the reaction mixture was injected directly onto prep-HPLC (Varian C-8 30 x 250 mm, 5-95% ACN in H_2O spiked with 0.1% formic acid, 8.5 min

retention time) and subsequently lyophilized to afford the title compound **7.4** (0.060 g, 80% yield) as a white powder; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.81 (t, J = 5.7 Hz, NH, 1H), 7.77 (t, J = 5.4 Hz, NH x 2, 2H), 7.41 – 7.29 (m, Ar-H x 5, 5H), 6.41 (s, NH, 1H), 6.35 (s, NH, 1H), 5.09 (s, CH_2Ph, 2H), 3.09 (m, RCH_2R, 6H), 2.37 (t, J = 7.5 Hz, RCH_2R, 2H), 2.08 – 2.01 (m, RCH_2R, 6H), 1.66 (p, J = 7.1 Hz, RCH_2R, 2H), 1.59 (p, J = 7.2 Hz, RCH_2R, 4H), 1.55 – 1.40 (m, RCH_2R, 2H), 1.31 (dq, J = 15.8, 7.1 Hz, RCH_2R, 2H); ^{13}C NMR (101 MHz, DMSO) δ 172.50, 171.92, 171.72, 171.61, 162.68, 136.22, 128.40, 127.95, 127.88, 65.37, 61.02, 59.18, 55.38, 38.11, 37.73, 35.21, 32.91, 32.87, 30.93, 28.21, 28.01, 25.49, 25.28, 24.56.



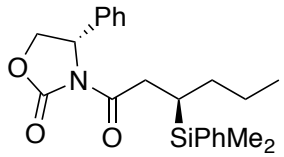
4- (4- (4- (5- ((3a*S*, 4*S*, 6a*R*)-2-oxohexahydro-1*H*-thieno [3,4-*d*]imidazol-4-yl) pentanamido) butanamido) butanamido) butanoic acid (7.5): Benzyl ester 7.4 (0.060 g, 0.102 mmol) was dissolved in dry methanol (1 mL, 0.1M) and 10% Pd/C was added under inert argon atmosphere. The resulting mixture was evacuated with H_2 (g) and then stirred under an atmosphere of H_2 (g) (1 bar) for 12 hrs. The mixture was filtered thru a celite pad and concentrated to produce the title compound **7.5** (95% yield, 85:15 conversion from starting material) ^{1}H NMR (500 MHz, Methanol-d_4) δ 4.49 (ddd, J = 7.9, 5.0, 0.9 Hz, 1H), 4.30 (dd, J = 7.9, 4.5 Hz, 1H), 3.19 (td, J = 7.0, 2.1 Hz, 8H), 2.92 (dd, J = 12.7, 4.9 Hz, 1H), 2.70 (d, J = 12.8 Hz, 1H), 2.20 (dtd, J = 11.2, 9.1, 8.2, 2.3 Hz, 9H), 1.78 (dddd, J = 15.2, 8.8, 5.3, 1.7

Hz, 6H), 1.69 – 1.54 (m, 4H), 1.48 – 1.40 (m, 2H); APCI-MS *m/z* calcd for $C_{22}H_{36}N_5O_6S$ $[M-H]^-$ 498.4, found 498.6.



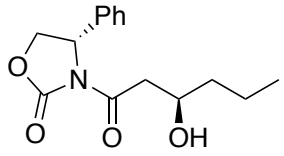
(*S*,*E*)-3-(hex-2-enoyl)-4-phenyloxazolidin-2-one-(8.1):

Oxazolidinone (1 equiv, 28.81 mmol, 4.70 g) in 80 mL THF was cooled to -78 ºC under argon and the mixture stirred for 10 minutes. n-Butyllithium (2.5 M in hexane, 30.25 mmol, 12.1 mL, 1.05 equiv) was added dropwise and the reaction was stirred at -78 ºC for 15 minutes. 2-Hexenoyl chloride (1.05 equiv, 30.25 mmol, 4.01 g) in 20 mL THF was then added and stirred or 30 minutes before being warmed to ambient temperature and stirred for an additional 2 hours. The reaction was quenched with saturated NH_4Cl and subsequently extracted three times with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification on a silica gel column using 10% Et_2O/pentane gave 5.93 g of **8.1** as a white solid (88%, 25% Et_2O/Pentane, R_f = 0.7); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.39 – 7.24 (m, Ar*H*, 5H), 7.25 (dt, J = 15.3 Hz, 1.5 Hz, COC*H*=CH, 1H) 7.08 (dt, J = 15.3 Hz, 7.0 Hz, COCH=C*H*, 1H), 5.48 (dd, J = 8.8 Hz, 3.8 Hz, OC*H*$_2$CHAr, 1H), 4.69 (t, J = 8.8 Hz, OCH$_2$C*H*Ar, 1H), 4.27 (dd, J = 8.8 Hz, 3.8 Hz, OC*H*$_2$CHAr, 1H), 2.36 (m, CH=CHC*H*$_2$, 2H), 1.50 (m, C*H*$_2$CH$_3$, 2H), 0.93 (t, J = 7.6 Hz, CH$_2$C*H*$_3$, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): 164.7, 153.7, 152.0, 139.1, 129.1, 128.6, 125.9, 120.3, 69.9, 57.7, 34.6, 21.3, 13.6.

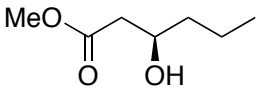


(*S*)-3-((*R*)-3-(dimethyl(phenyl)silyl)hexanoyl)-4-phenyloxazolidin-2-one (8.2): Dimethylphenylsilylchloride (1.5 equiv, 4.85 mmol, 0.82 mL) was stirred with freshly cut lithium granules (15 equiv, 48.5 mmol, 0.40 g) in 8 mL freshly distilled THF at 0 ºC under argon for 5 hours and then placing the reaction mixture in the refrigerator at 0 ºC overnight (additional 17 hours). The dark red solution (0.61M, 2.0 equiv, 1.69 mmol, 2.8 mL) was transferred via double-ended cannula to a strawberry flask and at -78 ºC under argon, cold 1.0 M $ZnEt_2$ in hexanes (2 equiv, 1.69 mmol, 0.17 ml) was added dropwise along the wall of the flask and the temperature was raised to 0 ºC. After 30 minutes, the resulting yellowish-brown solution was then cooled to -78 ºC before the addition, by cannula, of the enone **8.1** (1 equiv, 0.85 mmol, 0.22 g) dissolved in 10 mL THF. After 7 hours at -78 ºC, the reaction was complete and quenched with aqueous NH_4Cl and the reaction mixture turned yellow within seconds. The product was extracted two times with Et_2O, followed by washing the combined organic layer with water. The organic layer was then dried over $MgSO_4$, filtered and finally concentrated. The product was purified on a silica gel column using 20% Et_2O/pentane as an eluent to obtain 0.34 g of desired product **8.2** as a clear oil (99.7%, 30% Et_2O/Pentane, R_f = 0.6); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.47 – 7.23 (m, Ar*H*, 10H), 5.25 (dd, J = 8.8 Hz, 3.5 Hz, OCH_2CHAr, 1H), 4.56 (t, J = 9.1 Hz, OCH_2CHAr, 1H), 4.19 (dd, J = 8.8 Hz, 3.8 Hz, OCH_2CHAr, 1H), 2.91 (m, COCH_2CH, 2H), 1.54 (m, $COCH_2CH$, 1H), 1.36 – 1.11 (m, $CH_2CH_2CH_3$, 4H), 0.72 (t, J = 6.8 Hz, CH_2CH_3, 3H), 0.22 (2s, $Si(CH_3)_2$, 6H); ^{13}C-NMR

(125 MHz, $CDCl_3$): 173.0, 153.5, 139.1, 138.2, 133.9, 129.0, 128.8, 128.5, 127.6, 126.0, 69.8, 5.5, 36.4, 32.5, 22.1, 20.5, 14.1, -4.0, -4.2.

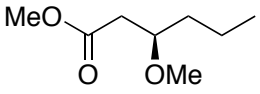


(*S*)-3-((*R*)-3-hydroxyhexanoyl)-4-phenyloxazolidin-2-one (8.3): Silane **8.2** (1 equiv, 5.74 mmol, 2.27 g) and $Hg(OAc)_2$ (1.3 equiv, 7.47 mmol, 2.38 g) in 32% peracetic acid in acetic acid (1 mL) was stirred at ambient temperature with an argon balloon for 6 hours. Et_2O (500 mL) was added and the mixture was washed with sodium thiosulfate (1.0 M, 300 mL), water (300 mL), $NaHCO_3$ (2.0 M, 300 mL), and brine (200 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated. Purification via flash chromatography (10% Et_2O/pentane) gave 1.37 g of desired product **8.3** as a colorless oil (86%, 40% Et_2O/Pentane, $R_f = 0.1$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.39 – 7.26 (m, Ar*H*, 4H), 5.43 (dd, J = 8.5 Hz, 3.5 Hz, OCH_2CHAr, 1H), 4.67 (t, J = 8.8Hz, OCH_2CHAr, 1H), 4.24 (dd, J = 9.1 Hz, 3.8 Hz, OCH_2CHAr, 1H), 4.03 (m, C*H*OH, 1H), 3.13 (dd, J = 17.0 Hz, 2.9 Hz, COCH_2CH, 1H), 3.03 (dd, J = 17.0 Hz, 9.0 Hz, $COCH_2CH$, 1H), 2.80 (d, J = 4.7 Hz, O*H*, 1H), 1.53 – 1.34 (m, $CH_2CH_2CH_3$, 4H), 0.91 (t, J = 7.3 Hz, CH_2CH_3, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): 172.3, 153.7, 138.7, 129.1, 128.6, 125.6, 70.0, 67.5, 57.4, 42.6, 38.6, 18.5, 13.8.

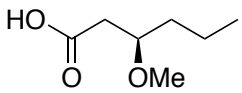


methyl (*R*)-3-hydroxyhexanoate (8.4a): Hydroxy **8.3** (1 equiv, 8.19 mmol, 1.86 g) was dissolved in 30 mL MeOH at 0 ºC. Sodium methoxide (1.1 equiv, 9.02 mmol, 0.48 g) was added and the reaction was stirred for 1.5 hours. The reaction was quenched with saturated aqueous NH_4Cl, and extracted two times with CH_2Cl_2, dried

over $MgSO_4$, and concentrated. The crude product was then purified on a silica gel column using 10% Et_2O/Pentane to obtain 85% of **8.4a** as a clear volatile liquid; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.02 (m, C*H*OH, 1H), 3.71 (s, OC*H*$_3$, 3H), 2.94 (broad s, O*H*, 1H), 2.51 (dd, J = 16.1 Hz, 3.2 Hz, COCH$_2$C*H*, 1H), 2.41 (dd, J = 16.4 Hz, 9.0 Hz, COC*H*$_2$CH, 1H), 1.56 – 1.35 (m, C*H*$_2$C*H*$_2$CH$_3$, 4H), 0.94 (t, J = 6.8 Hz, CH$_2$C*H*$_3$, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): 173.1, 67.5, 51.4, 41.2, 38.6, 18.5, 13.7.

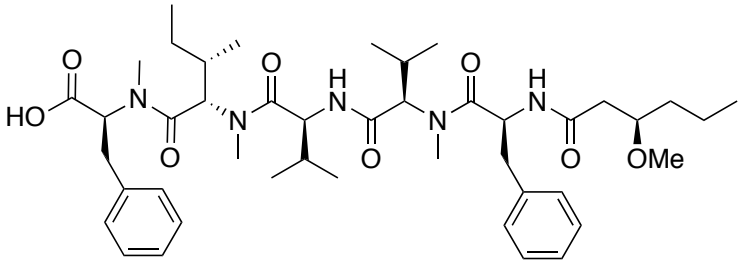


methyl (*R*)-3-methoxyhexanoate (8.4b): 2,6-Di-*tert*-butylpyridine (2.8 equiv, 0.81 g, 3.93 mmol) and methyl triluoromethane-sulfonate (2.8 equiv, 0.45 mL, 3.93 mmol) were added to a solution of alcohol **8.4a** (1 equiv, 0.21 g, 1.4 mmol) in 5 mL CH_2Cl_2 at 0 ºC under argon. The mixture was allowed to warm to ambient temperature and stirred for an additional 23 hours. A saturated solution of $NaHCO_3$ was then added and the organic layer washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography on silica using 25% Et_2O/pentane as eluent gave the methyl ether **8.4b** (0.20 g, 87 %) as a colorless and volatile liquid; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.68 (s, CO_2C*H*$_3$, 3H), 3.64 (m, CH$_2$C*H*OCH$_3$, 1H), 3.34 (s, CH$_2$CHOC*H*$_3$, 3H), 2.55 – 2.37 (m, COC*H*$_2$CH, 2H), 1.58 – 1.33 (m, CHC*H*$_2$C*H*$_2$CH$_3$, 4H), 0.93 (t, J = 7.0 Hz, CH$_2$C*H*$_3$, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): 172.0, 56.7, 51.2, 41.2, 39.1, 38.6, 35.9, 18.1, 13.8

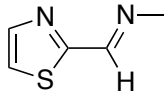


(*R*)-3-methoxyhexanoic acid (8.4): 1.0M LiOH in water (2.0 equiv, 0.39 mmol, 0.4 mL) was added to ester **8.4b** (1 equiv, 0.03 g, 0.19 mmol) in THF (2 mL) at ambient temperature. After 2 hours, the reaction was quenched with 10 mL of 10%

H_2SO_4 and extracted three times with CH_2Cl_2, dried over $MgSO_4$ and concentrated. Purification on a silica gel plug using 100% CH_2Cl_2 gave 99% of **8.4** as a light yellow oil (28 mg); $[\alpha]_D^{20}$ = -23.19 (c = 1.04, 589 nm); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 10.59 (broad s, CO_2H, 1H), 3.65 (m, CH_2CHOCH_3, 1H), 3.42 (s, CH_2CHOCH_3, 3H), 2.54 (d, J = 16.2 Hz, $COCH_2CH$, 1H), 1.68 – 1.31 (m, $COCH_2CH$, 2H), 1.58 – 1.33 (m, $CHCH_2CH_2CH_3$, 4H), 0.92 (t, J = 7.1 Hz, CH_2CH_3, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): 174.9, 57.4, 38.9, 35.9, 18.8, 14.2, 0.01.

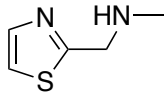


***N*-(*N*-*N*-(((*R*)-3-methoxy-hexanoyl)-*L*-phenylalanyl)-*N*-methyl-*D*-valyl-*L*-valyl-*N*-methyl-*L*-isoleucyl)-*N*-methyl-*L*-phenylalanine (8.5)**: The title compound was synthesized by the general method for Fmoc-protection, N-methylation protocol and general procedure for solid phase peptide synthesis; (50% Et_2O/CH_2Cl_2, R_f = 0.1); *NMR existed as complex mixture of rotational conformers*; LC-MS (ESI) m/z calcd for $C_{44}H_{67}N_5O_8$ $[M-H]^-$ 793.49, found 793.56.

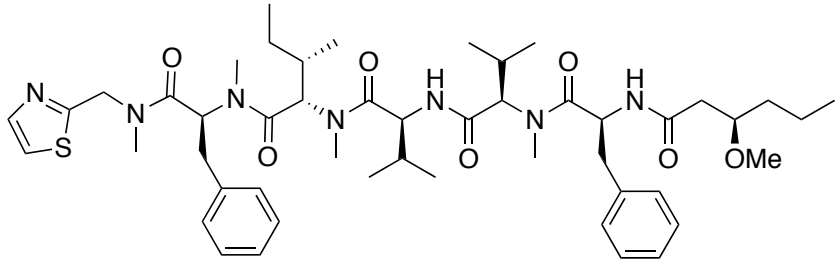


(*E*)-*N*-methyl-1-(thiazol-2-yl)methanimine (8.6): Thiazole-2-carbaldehyde (1 equiv, 27.44 mmol, 3.46 g) was dissolved in 7.5 mL of DMF and 22.5 mL of water at ambient temperature. CH_3NH_3Cl (6 equiv, 164.64 mmol, 11.12 g) was added followed by NaOH (5.7 equiv, 0.16 mmol, 6.21 g) in 31 mL of water. The reaction was stirred at ambient temperature for 2 days. Once complete, the product was taken up in Et_2O and

the aqueous layer was washed two more times with Et_2O. The combined organic layers were then washed with water, dried over $MgSO_4$, and concentrated in vacuo **8.6** (86%, 50% Et_2O/pentane, R_f = 0.4) was obtained via a short silica gel column; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.46 (m, N=CH, 1H), 7.91 (d, *J* = 3.18 Hz, C=CHN, 1H), 7.38-7.41 (m, C=CHS, 1H), 3.57 (d, *J* = 1.71 Hz, NCH_3, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): 167.2, 156.6, 143.9, 121.3, 47.9.

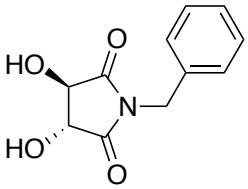


***N*-methyl-1-(thiazol-2-yl)methanamine (8.7)**: Imine **8.6** (1 equiv, 7.2 mmol, 0.92 g), $B(OH)_3$ (1 equiv, 7.2 mmol, 0.45 g), and $NaBH_4$ (1 equiv, 7.2 mmol, 0.27 g) were ground in a mortar and pestle for 10 minutes. The powder was taken up in a saturated solution of $NaHCO_3$ and CH_2Cl_2 and stirred overnight. The aqueous layer was washed two additional times with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated. Purification via short silica gel column using 100% Et_2O gave 200 mg of the presumed borate complex product of **8.7** (100% Et_2O, R_f = 0.3). The borate complex was taken up in 50 mL anhydrous MeOH and refluxed for 10 hours. The MeOH was subsequently removed *in vacuo* to provide 125 mg of a product as a yellow oil; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 3.3 Hz, C=CHN, 1H), 7.27 (d, *J* = 3.6 Hz, , C=CHS, 1H), 4.10 (s, RCH_2R, 2H), 2.53 (s, RCH_3, 3H), 1.89 (s, NH, 1H).



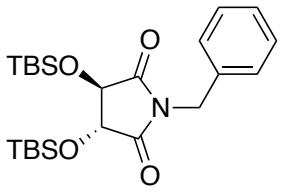
(*R*)-*N*-((4*S*, 7*S*, 10*S*, 13*R*, 16*S*)-4-benzyl-7-((*S*)-*sec*-butyl)-10, 13-diisopropyl-2, 5, 8, 14-tetramethyl-3, 6, 9,

12, 15-pentaoxo-17-phenyl-1-(thiazol-2-yl)-2, 5, 8, 11, 14-pentaazaheptadecan-16-yl)-3-methoxyhexanamide (synthetic *epi*-micromide) (8.8): Acid **8.5** (1 equiv, 49 mg, 61.7 μmol) was stirred with HATU (0.7 equiv, 16 mg, 43.1 μmol) and TBTU (0.7 equiv, 14 mg, 43.1 μmol) in DMF (0.5M) at 0 ^{o}C before the addition of thiazole amine **8.7** (1 equiv, 8 mg, 61.7 μmol) and DIEA (3 equiv, 0.18 mmol, 32 μL). The reaction was warmed to ambient temperature and was stirred overnight. The next day, 1% aq. HCl was introduced to the reaction and extracted two times with Et_2O. The combined organic layers were washed with a saturated solution of $NaHCO_3$ dried over $MgSO_4$, filtered and concentrated *in vacuo*. Silica gel chromatography gave *epi*-micromide (**8.8**) as light yellow oil (64%, 30% Et_2O/CH_2Cl_2, R_f = 0.4); ^{1}H NMR *existed as rotational conformers* (500 MHz, $CDCl_3$): δ = 0.564 (t, J = 6.5 Hz, 3 H), 0.73 (m, 6 H), 0.84 (m, 3 H), 0.91 (m, 9 H), 1.15 (m, 1 H), 1.33 (m, 2 H), 1.45–1.60 (m, 1 H), 1.75 (m, 2 H), 1.87–2.03 (m, 2 H), 2.15 (m, 1 H), 2.32 (m, 2 H), 2.54 (s, 3 H), 2.75 (s, 3 H), 2.94 (s, 3 H), 2.95 (m, 1 H), 2.97 (m, 1 H), 3.04 (s, 3 H), 3.10 (m, 1 H), 3.22 (m, 1 H), 3.34 (s, 3 H), 3.55 (m, 1 H), 4.43– 4.50 (m, 2 H), 4.65 (m, 1 H), 4.97–5.05 (m, 2 H), 5.07–5.10 (m, 1 H), 5.93 (t, J = 8.0 Hz, 1 H), 6.89 (m, 1 H), 7.05 (m, 1 H), 7.17– 7.25 (m, 10 H), 7.29 (d, J = 3.5 Hz, 1 H), 7.68 (d, J = 3.5 Hz, 1 H); LC-MS (ESI): calcd. for $C_{49}H_{74}N_7O_7S$: $[M + H]^+$ 904.54; found 904.53



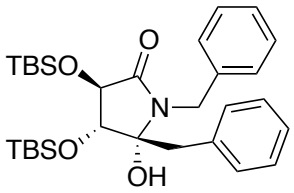
(3*R*,4*R*)-1-benzyl-3,4-dihydroxypyrrolidine-2,5-dione (9.1)[112]: *L*-Tartaric acid (2.00 g, 13.3 mmol, 1.5 equiv) and benzyl amine (971 μl, 8.89 mmol, 1.0 equiv) were added to a microwave vial and capped. The reaction was heated to 200 °C

for 5 minutes in the microwave. The crude reaction was dissolved in 30 mL of THF and extracted using 20 mL of saturated ammonium chloride. The organic layer was concentrated *in vacuo* to give a white solid that was consecutively washed with dichlormethane, twice with water, and again dichloromethane in a filter funnel. *N*-benzyl tartarimide **9.1** was collect as a white solid (1.46 g, 74% yield); ^{1}H NMR (400 MHz, DMSO) δ ppm 7.18 - 7.41 (m, Ar*H*, 5H), 6.20 - 6.34 (m, O*H*, 2H), 4.56 (dd, $C_6H_5CH_2N$, *J*=21.9, 15.3 Hz, 2H), 4.30 - 4.45 (m, HOC*H*, 2H); LCMS: calc. for $C_{11}H_{11}NO_4$, 221.1, found *m/z* = 222.1 $[M + H]^+$



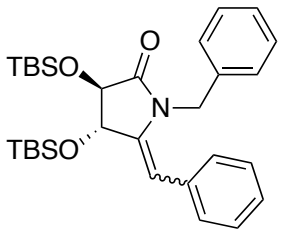
(3*R*, 4*R*)-1-benzyl-3, 4-bis((*tert*-butyl dimethyl silyl) oxy) pyrrol-idine-2, 5-dione (9.2): *L*-Benzyl tartarimide **9.1** (5.00 g, 22.6 mmol, 1.0 equiv) was chased 3 times with 3 mL of toluene and was immediately dissolved in 35 mL of dry *N,N*-dimethylformamide and was added *t*-butyldimethylsilyl chloride (17.0 g, 113 mmol, 5.0 equiv) and imidazole (9.26 g, 136 mmol, 6.0 equiv). The reaction was stirred overnight at room temperature. The next day the reaction was poured into 400 mL of diethyl ether and 150 mL of water and stirred until the layers were clear. The organic phase was separated and extracted 4 times with 100 mL of water, then was dried over magnesium sulfate, and concentrated *in vacuo*. The crude product was purified via flash chromatography (silica gel, 10% ethyl acetate/hexane) to give *O*-TBS protected *N*-benzyl tartarimide **9.2** as a clear oil (9.66 g, 95% yield); ^{1}H NMR (400 MHz, DMSO) δ ppm 7.22 - 7.38 (m, Ar*H,* 5 H), 4.78 (s, SiOC*H*C, 2 H), 4.59 (d, C_6H_5CHN, *J*=15.1 Hz, 1 H),

4.49 (d, C_6H_5CHN, *J*=14.9 Hz, 1 H), 0.89 - 0.95 (m, *tert*-butyl, 18 H), 0.18 (s, $SiCH_3$, 6 H), 0.13 (s, $SiCH_3$, 6 H).

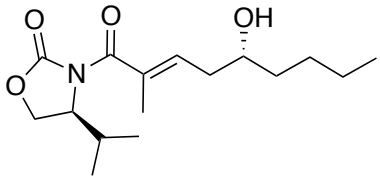


(3*R*,4*R*,5*R*)-1,5-dibenzyl-3,4-bis((*tert*-butyldimethylsilyl)oxy)-5-hydroxypyrrolidin-2-one (9.3)[153]: To a 2-neck flask attached a reflux condenser under argon was added magnesium turnings (0.267 g, 11.0 mmol, 5.0 equiv) and 15 mL of freshly distilled THF. The flask was cooled to 0 °C and benzyl bromide (1.22 mL, 10.2 mmol, 4.7 equiv) was added dropwise. The reaction stirred for 1 hour and began to gently reflux. The reaction was again cooled to 0 °C and *O*-TBS protected *N*-benzyl tartarimide **9.2** (1.00 g, 2.20 mmol, 1.0 equiv) along with bismuth (III) chloride (0.001 g, 0.044 mmol, .02 equiv) were added dissolved in 5 mL of THF. The reaction stirred at room temperature for 6 hours and was quenched with ammonium chloride. The reaction was filtered through celite using diethyl ether and concentrated *in vacuo*. The crude material was redissolved in 30 mL of diethyl ether and extracted 2 times with 20 mL of water. The organics were combined, dried over sodium sulfate, and concentrated *in vacuo*. The crude material was purified via flash chromatography (silica gel, 10% ethyl acetate/hexane) to give Grignard addition product **9.3** in correct stereochemistry *R*-*R*-*R* as a clear oil (0.775 g, 65% isolated yield); ^{1}H NMR (400 MHz, DMSO) δ ppm 7.12 - 7.34 (m, Ar*H*, 10 H), 5.08 (d, RO*H*, *J* = 1.6 Hz, 1 H), 4.54 (d, C_6H_5CHN, *J*=15.8 Hz, 1 H), 4.34 (d, C_6H_5CHN, *J*=15.8 Hz, 1 H), 3.96 (dd, OC*H*C, *J*=19.0, 1.4 Hz, 2 H), 2.99 (d, C_6H_5CHC, *J*=13.9 Hz, 1 H), 2.71 (d, C_6H_5CHC, *J* = 13.8 Hz, 1 H), 0.91 - 0.97 (m, *tert*-butyl, 9 H), 0.71 - 0.78 (m, *tert*-butyl, 9 H), 0.15 - 0.22 (m, $SiCH_3$, 6 H), -0.18 - -0.13 (m,

SiC*H*$_3$, 3 H), -0.26 - -0.21 (m, SiC*H*$_3$, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 170.65, 138.64, 135.87, 131.14, 128.39, 127.97, 127.43, 126.96, 126.71, 90.93, 77.06, 74.69, 43.73, 42.18, 25.80, 25.50, 18.17, 17.88, -4.36, -4.96, -5.07, -5.75; LCMS: calc. for $C_{30}H_{47}NO_4Si_2$, 541.3, found *m/z* = 542.3 $[M + H]^+$.



(3*R*,4*S*)-1-benzyl-5-benzylidene-3,4-bis((*tert*-butyldimethylsilyl) oxy) pyrrolidin-2-one (9.4): Preparation of the title compound discussed in the manuscript via Lewis acid dehydration of compound **9.3**; ^{1}H NMR (600 MHz, DMSO) δ ppm 7.17 - 7.34 (m, Ar*H*, 10H), 6.06 (s, C_6C_5CHC, 1H), 4.85 (dd, $C_6H_5CH_2N$, *J* = 23.2, 16.4 Hz, 2H), 4.79 (s, SiOC*H*, 1H), 4.06 (s, SiOC*H*, 1H), 0.86 - 0.89 (m, *tert*-butyl, 9H), 0.74 - 0.78 (m, *tert*-butyl, 9H), 0.17 - 0.20 (m, SiC*H*$_3$, 3H), 0.12 - 0.15 (m, SiC*H*$_3$, 3H), -0.04 - -0.01 (m, SiC*H*$_3$, 3H), -0.15 - -0.12 (m, SiC*H*$_3$, 3H).



(*S*)-3-((*R*,*E*)-5-hydroxy-2-methylnon-2-enoyl)-4-isopropyloxazolidin-2-one (10.1): Stirred VMAR **3.56** (0.100 g, 0,3072 mmol) and valeraldehyde (65 µL, 0.6144 mmol) in 4.0 mL dry DCM under argon -10 °C then added $Bi(OTf)_3$ (0.009 g, 0.131 mmol) stirred a clear solution with heterogeneous white solids until it yellowed around 6 hours later. Reaction mixture was quenched with (1:1) saturated solutions of Rochelle's salt and $NaHCO_3$ (10 mL). Mixture was extracted with EtOAc and DCM, organic phases were combined and dried over Na_2SO_4, filtered and

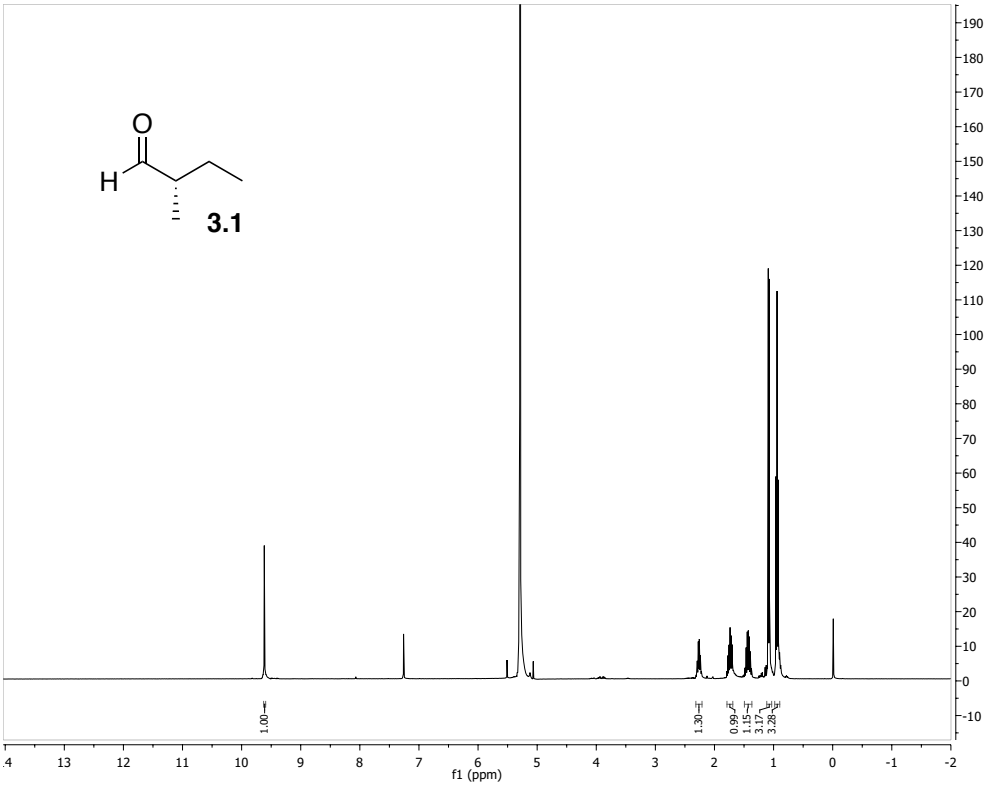
concentrated *in vacuo*. The residue was chromatographed via silica gel column (0-25% EtOAc in hexanes gradient) to afford the title compound **10.1** (0.057 g, 42% yield) as pale yellow oil; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.09 – 5.98 (m, C=CH, 1H), 4.55 (ddd, *J* = 8.8, 5.4, 4.4 Hz, OCH_2R, 1H), 4.33 (t, *J* = 8.9 Hz, , OCH_2R, 1H), 4.19 (dd, *J* = 9.0, 5.4 Hz, R_3CH, 1H), 3.72 (s, $R_2CH(OH)$, 1H), 2.75 (s, ROH, 1H), 2.43 – 2.24 (m, RCH_2R, 2H), 1.95 (d, *J* = 1.2 Hz, RCH_3, 3H), 1.63 – 1.23 (m, RCH_2R x 3, 6H), 0.96 – 0.88 (m,RCH_3 x 3, 9H).

Appendix

^{1}H-NMR

^{13}C-NMR

HR/LC-MS (ESI)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3.17
3.28
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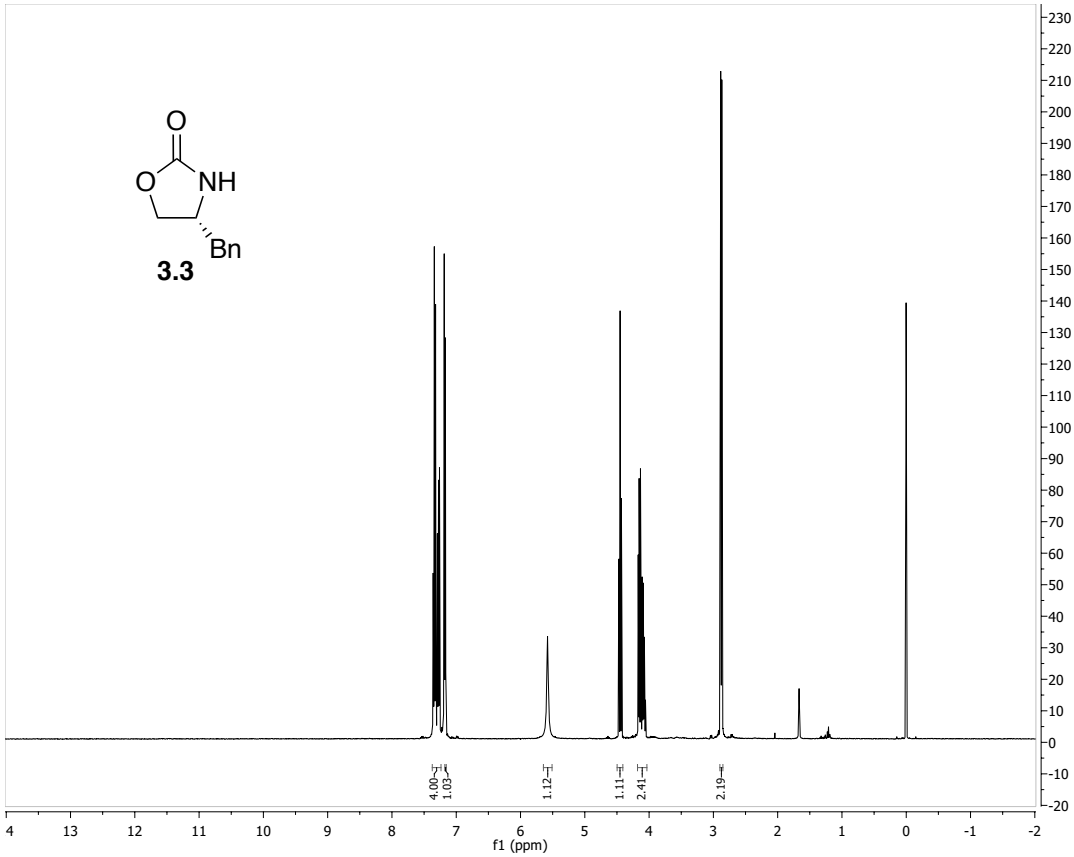
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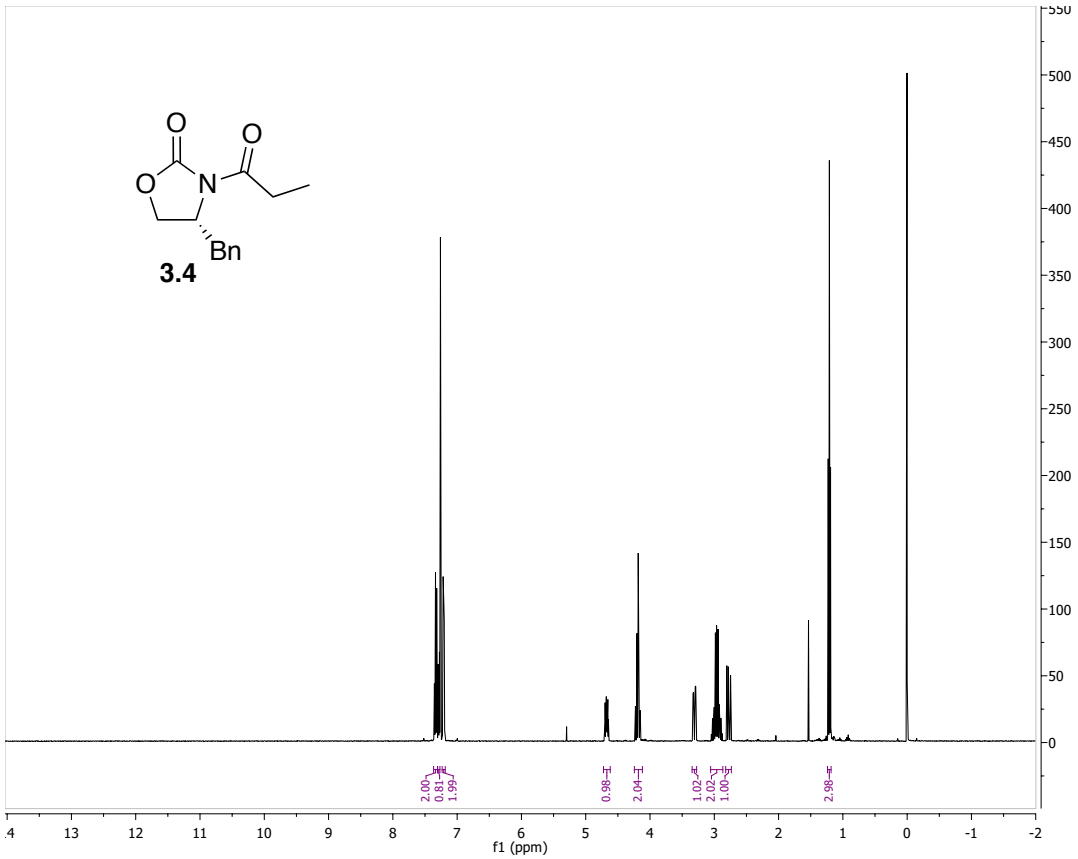
2.19
f1 (ppm)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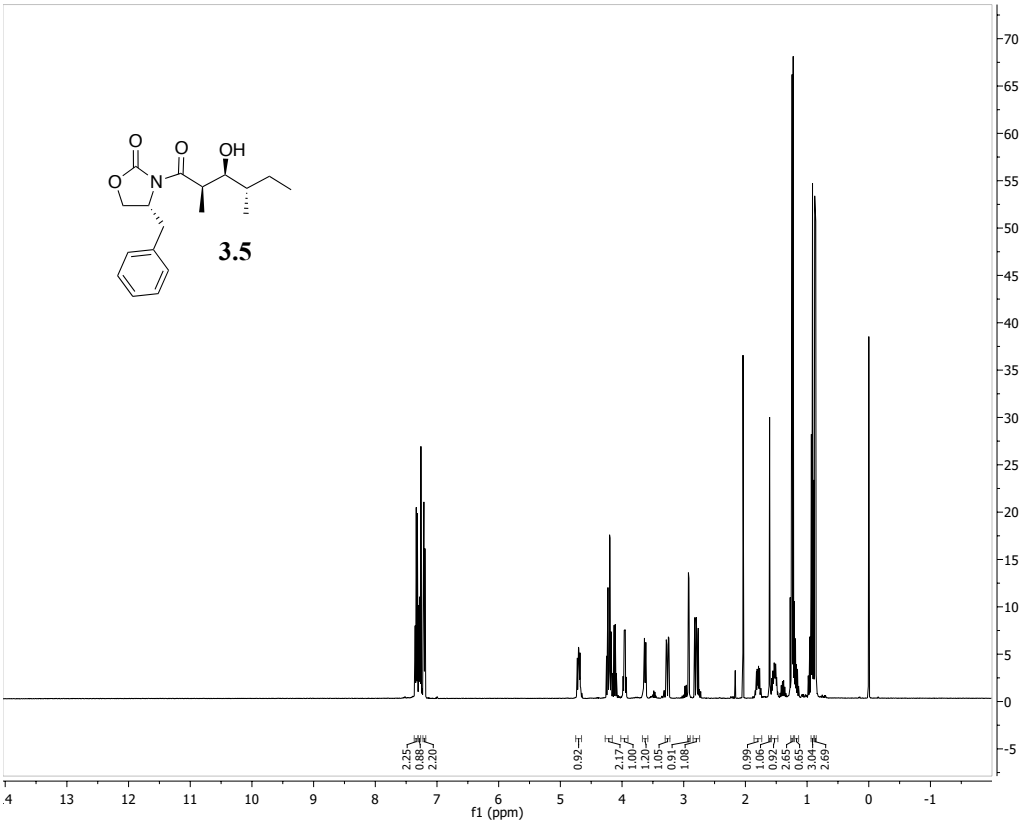
O
O
N
Bn
3.4
f1 (ppm)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1.08
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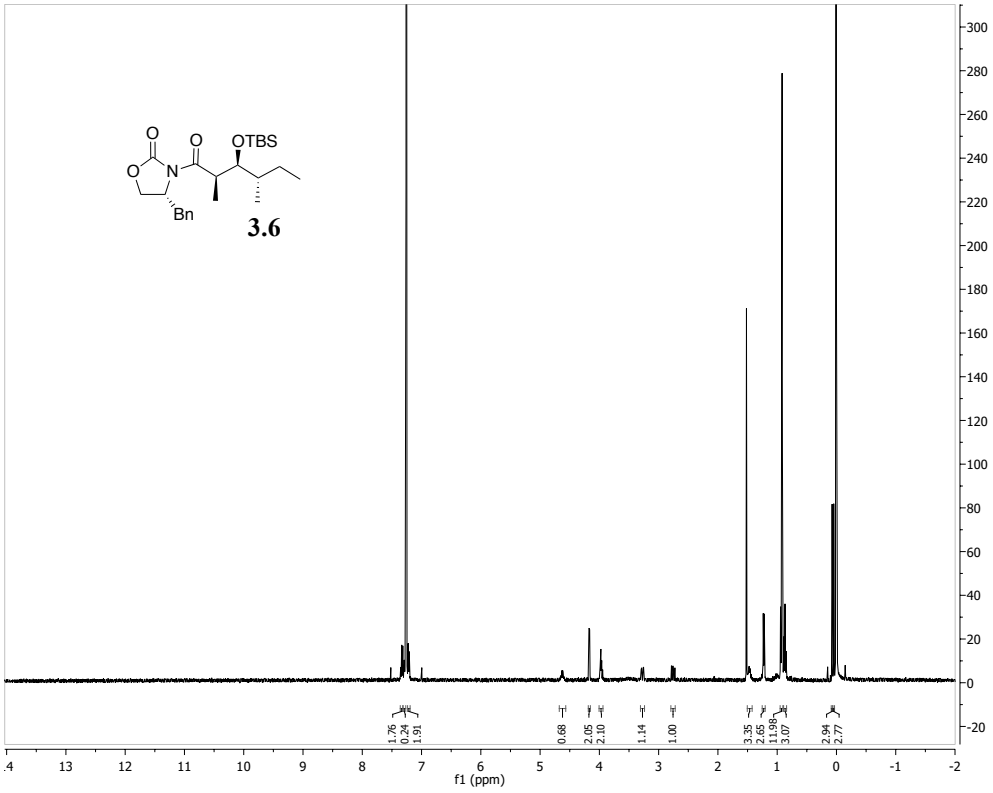
1.06
0.92
2.65
0.65
3.04
2.69
f1 (ppm)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O
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Bn
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0.24
1.91
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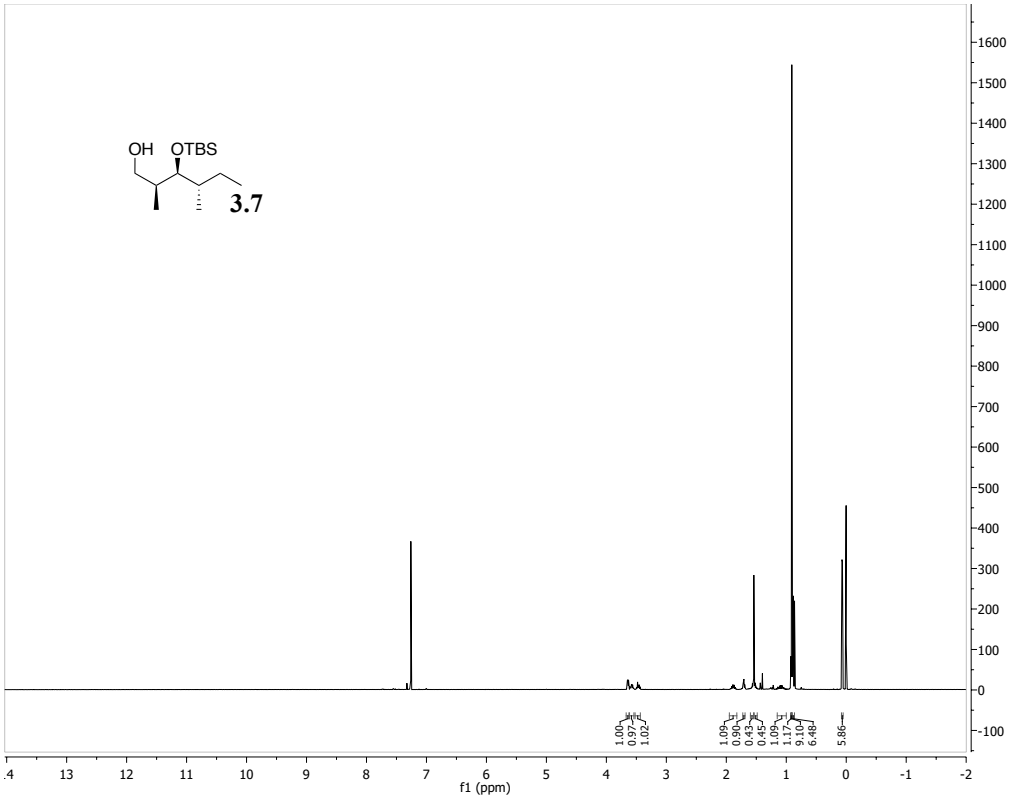
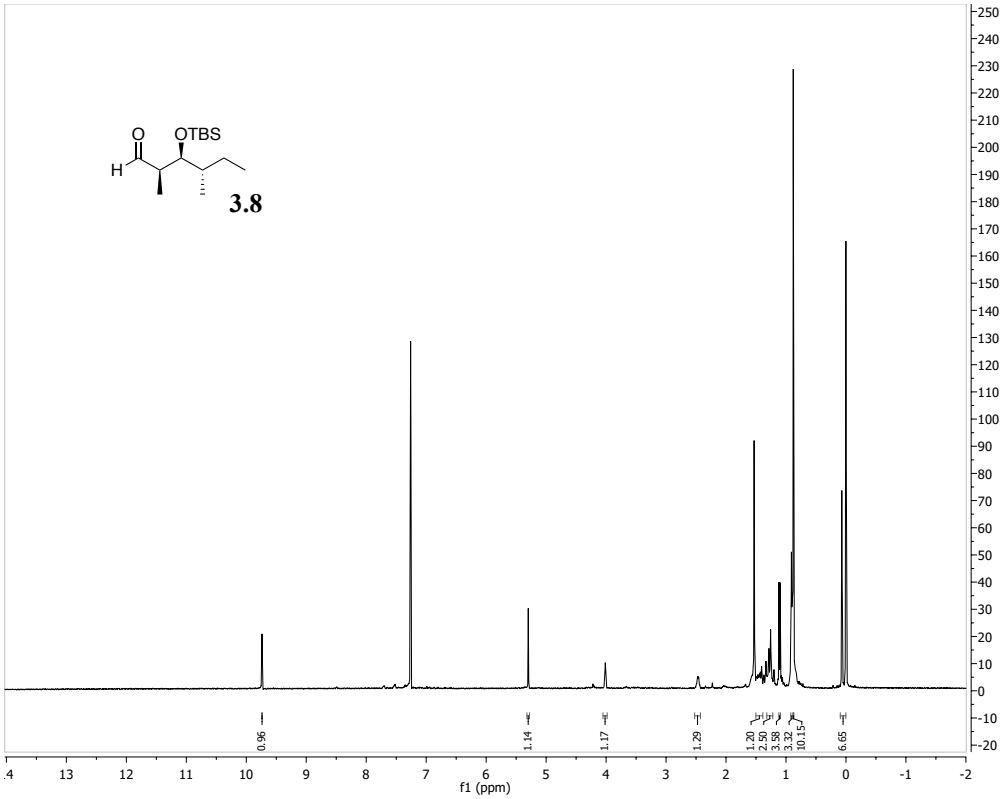
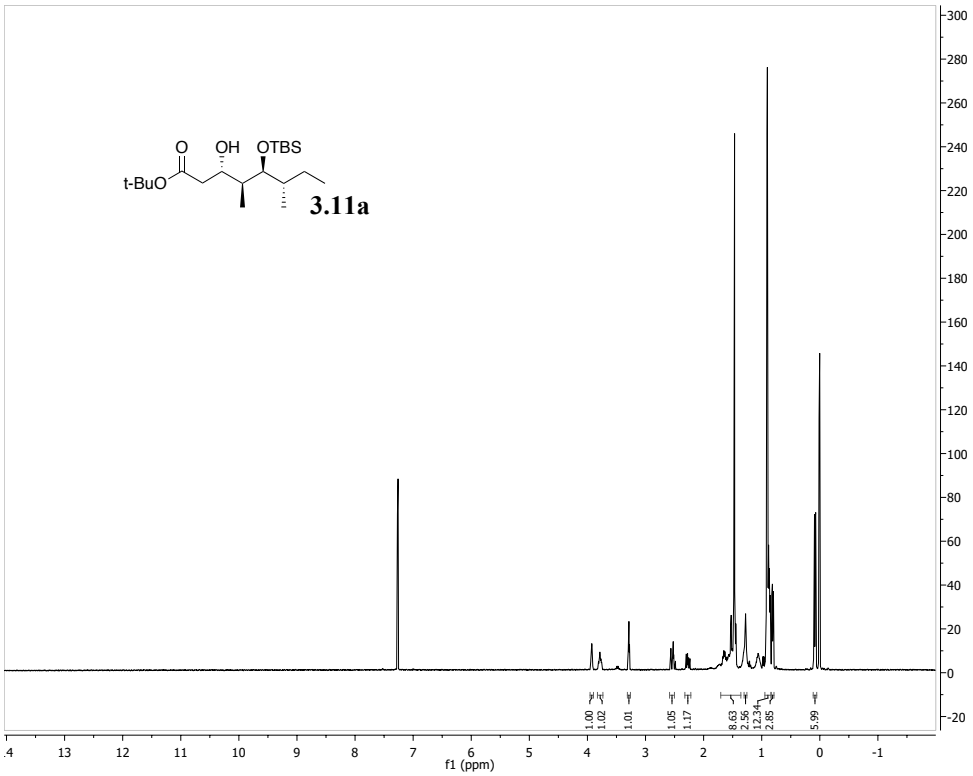
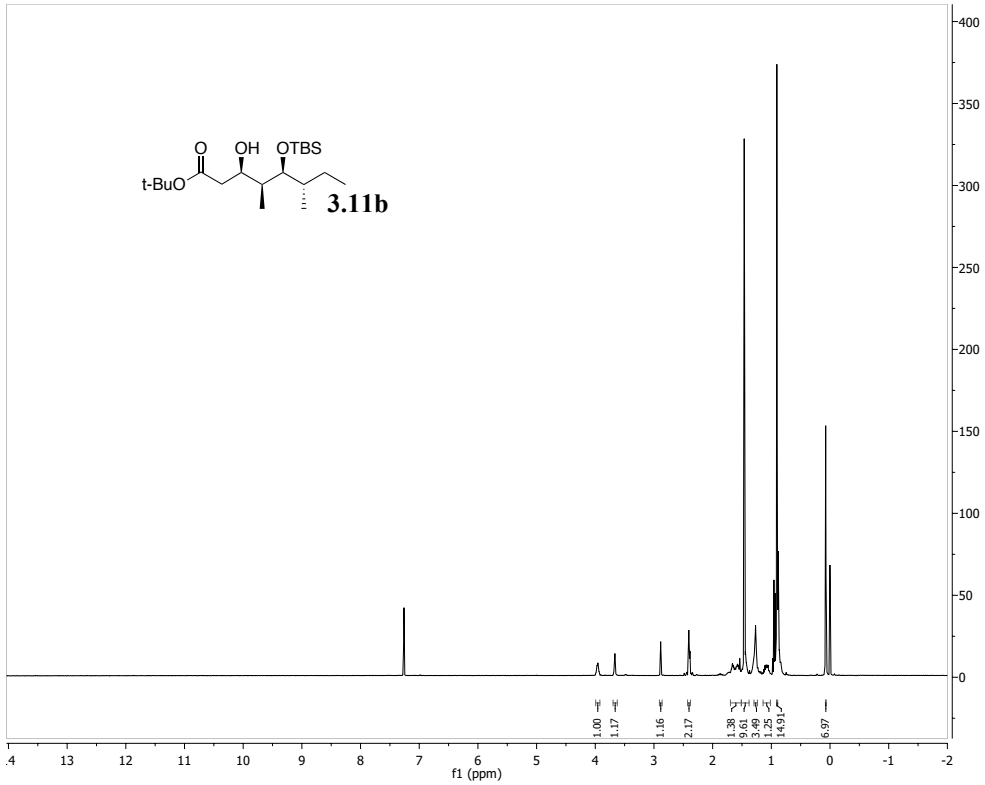
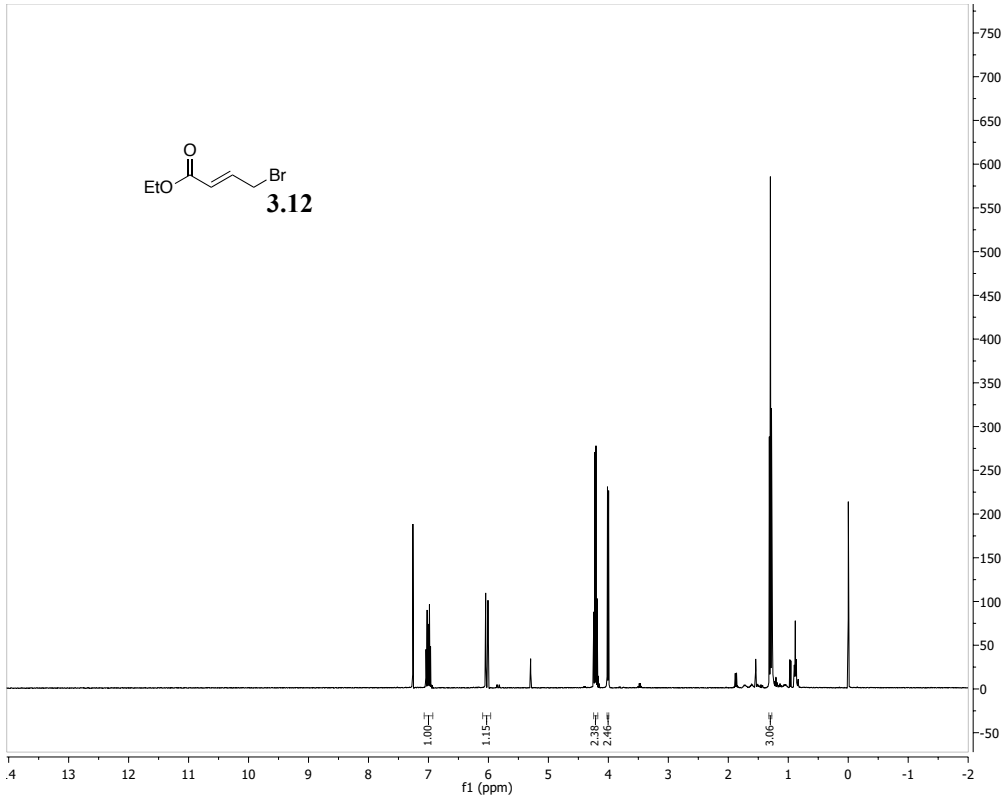
2.65
1.98
3.07
2.94
2.77
f1 (ppm)

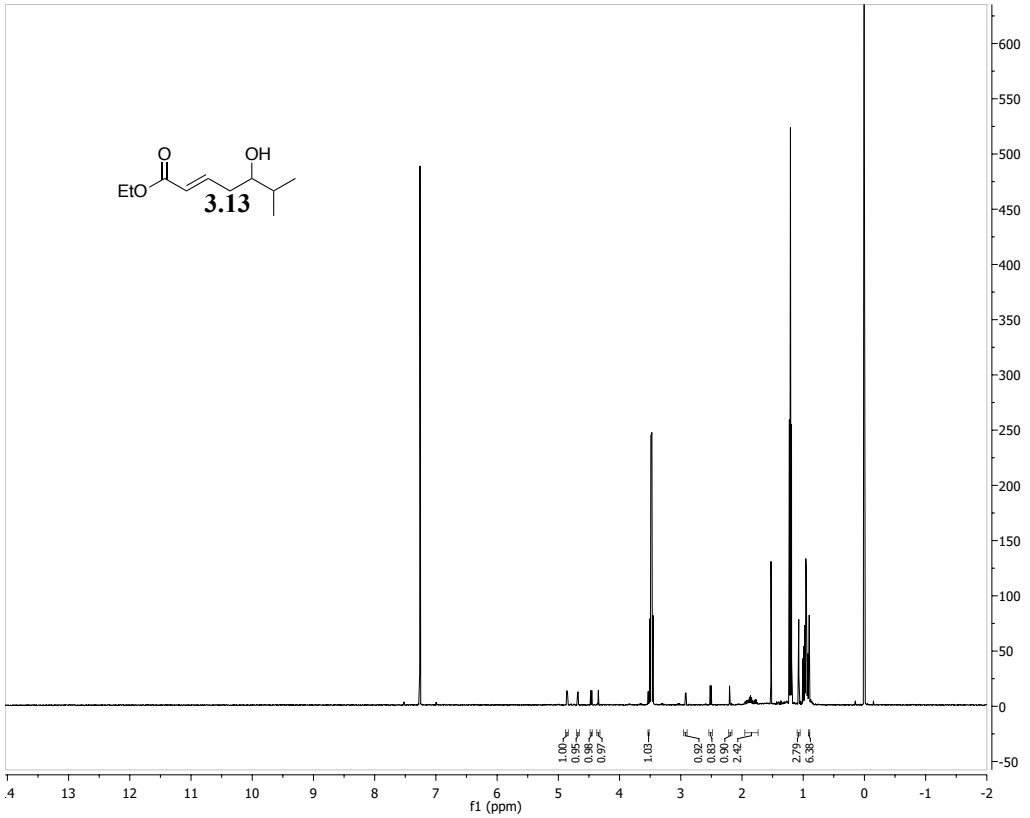

OH
OTBS
3.7
f1 (ppm)

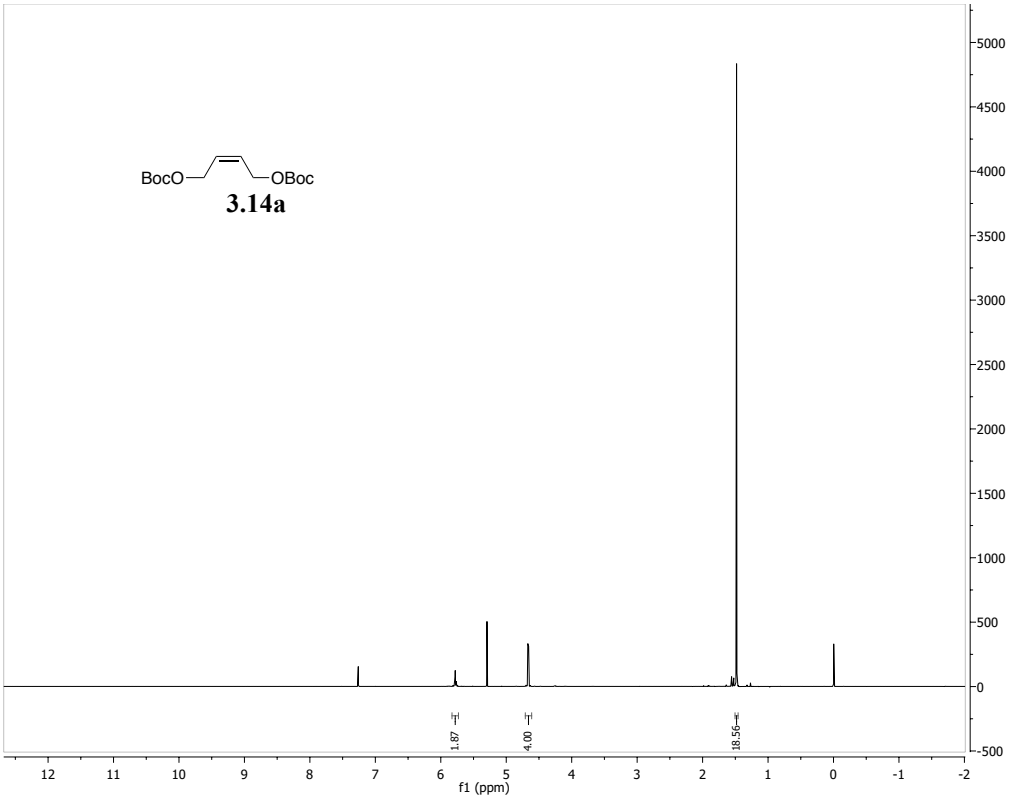

O
OTBS
H
3.8
0.96
1.14
1.17
1.29
1.20
2.50
3.58
3.32
10.15
6.65
f1 (ppm)

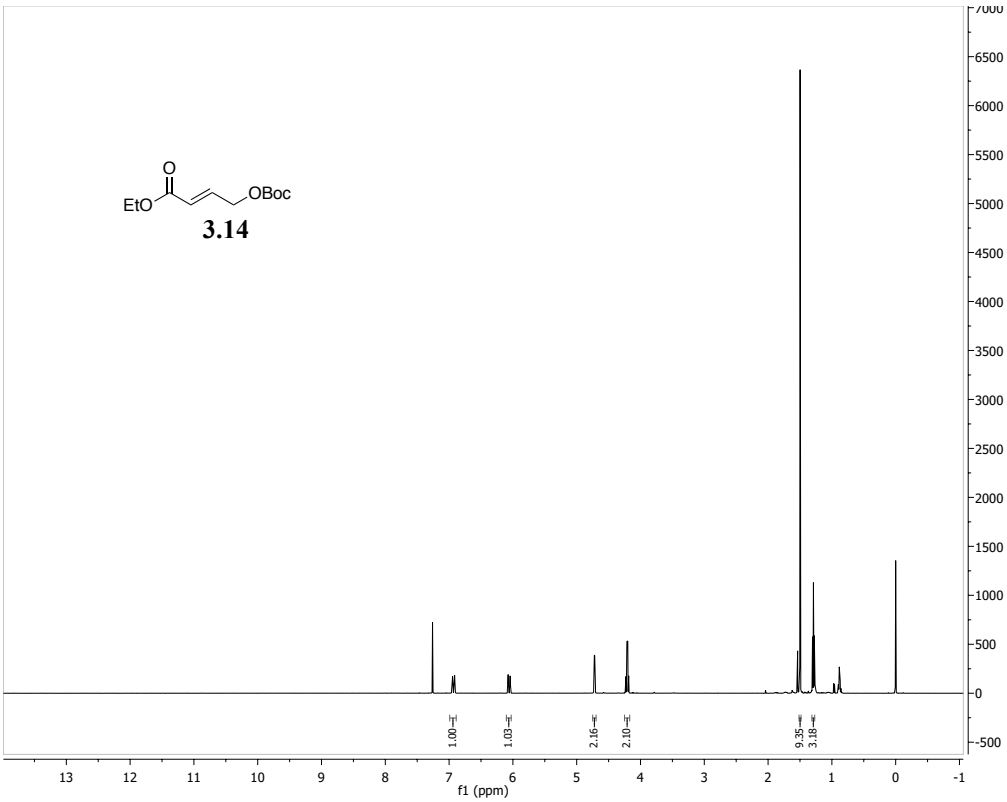

O
OH
OTBS
t-BuO
3.11a
f1 (ppm)

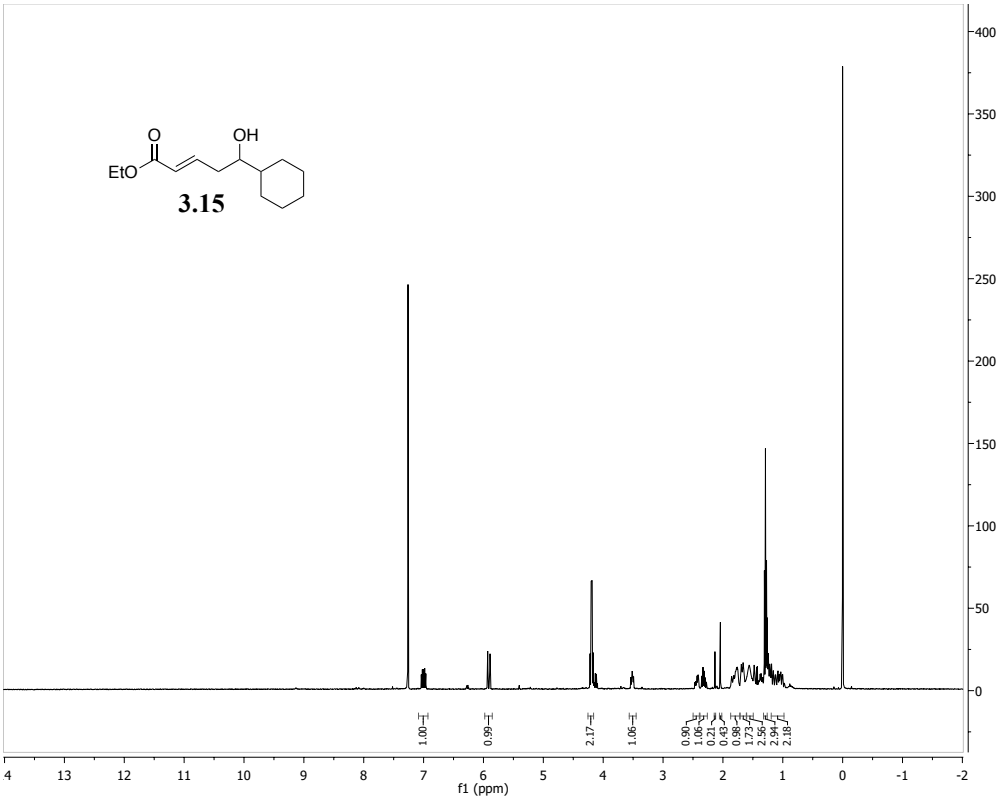

O
OH
OTBS
t-BuO
3.11b
f1 (ppm)

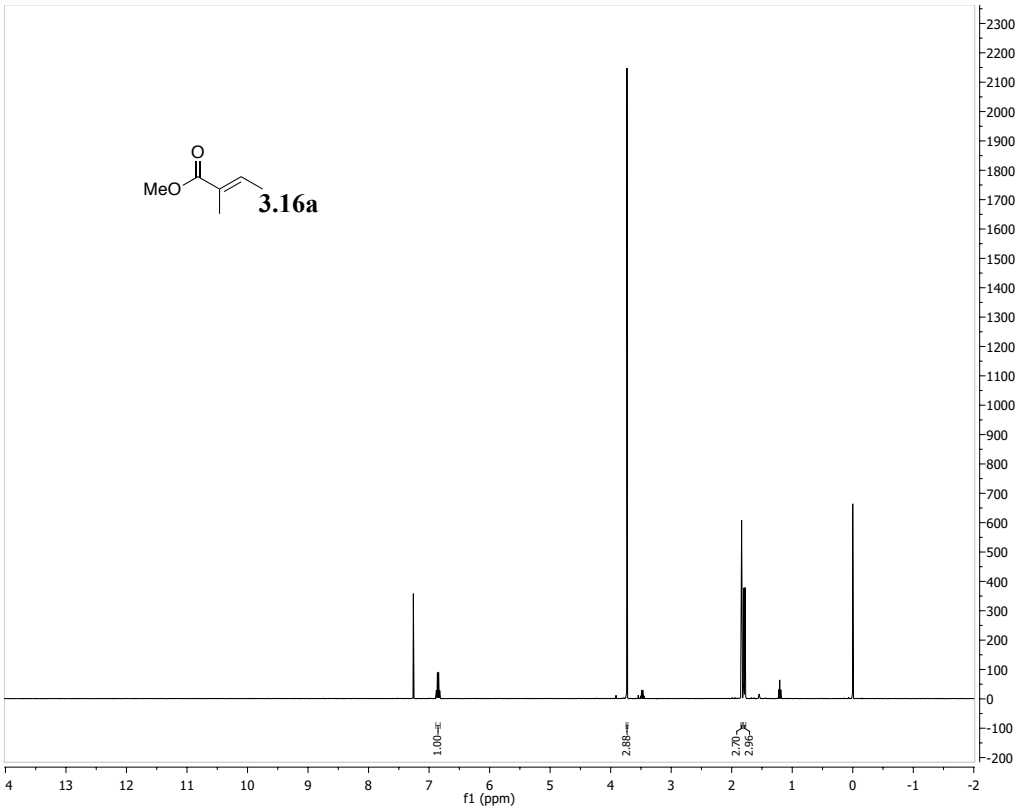

O
EtO
Br
3.12
1.00
1.15
2.38
2.46
3.06
f1 (ppm)

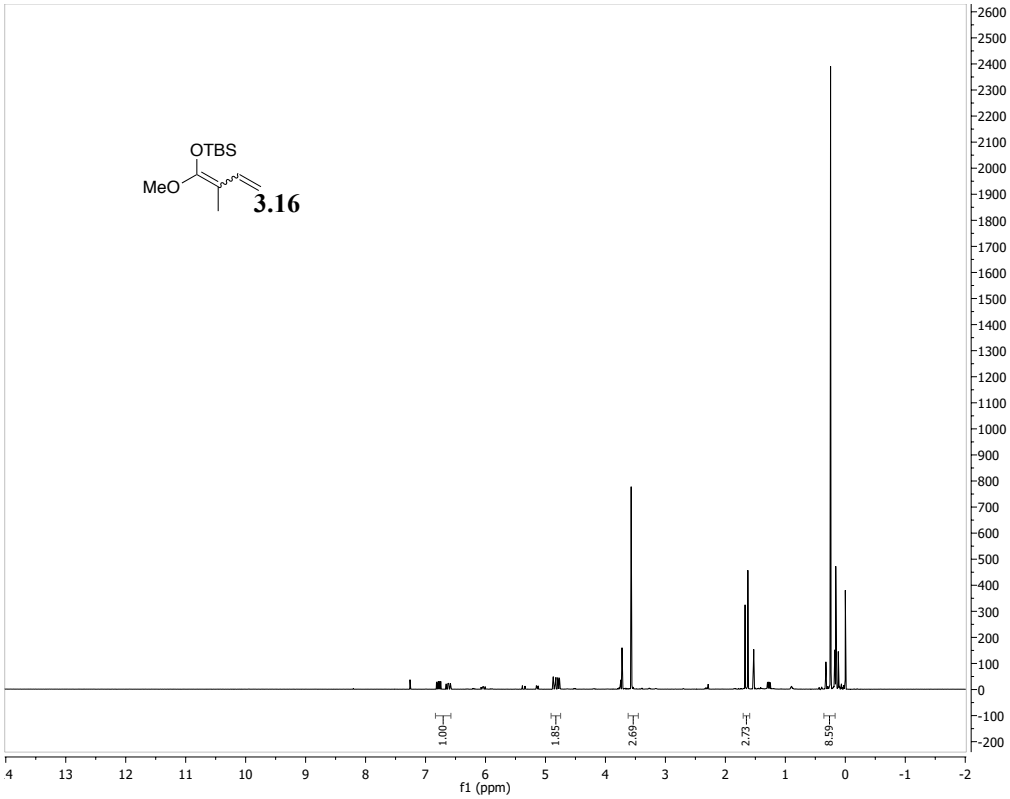

O
OH
EtO
3.13
f1 (ppm)

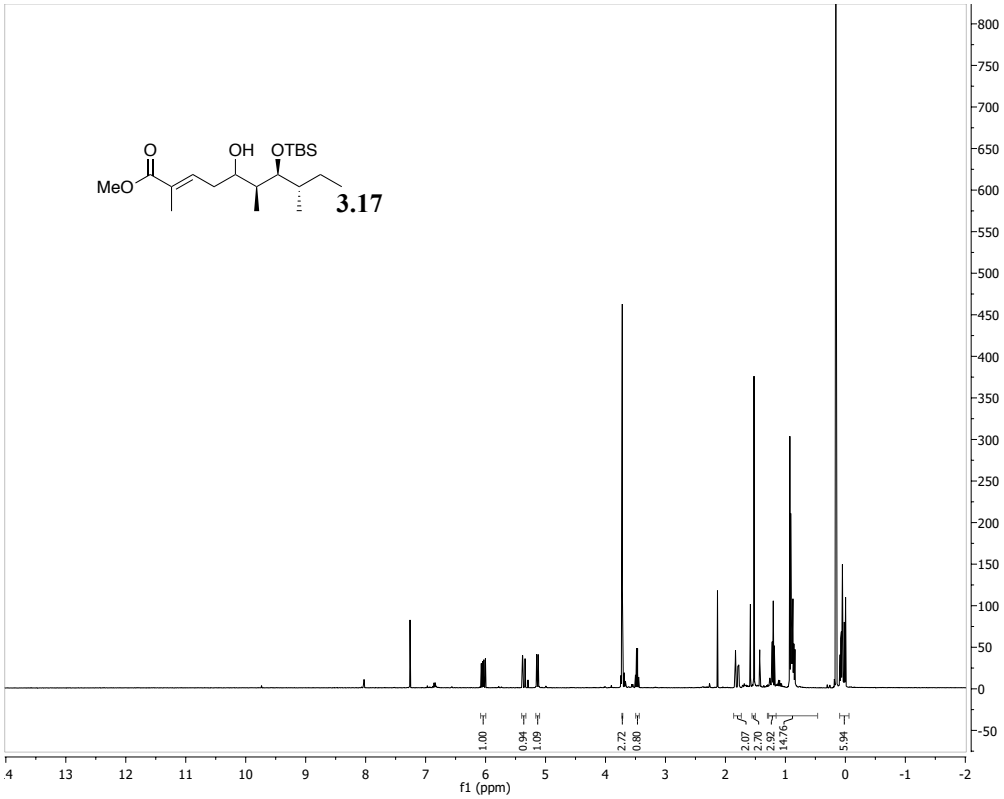

BocO
OBoc
3.14a
1.87
4.00
18.56
f1 (ppm)

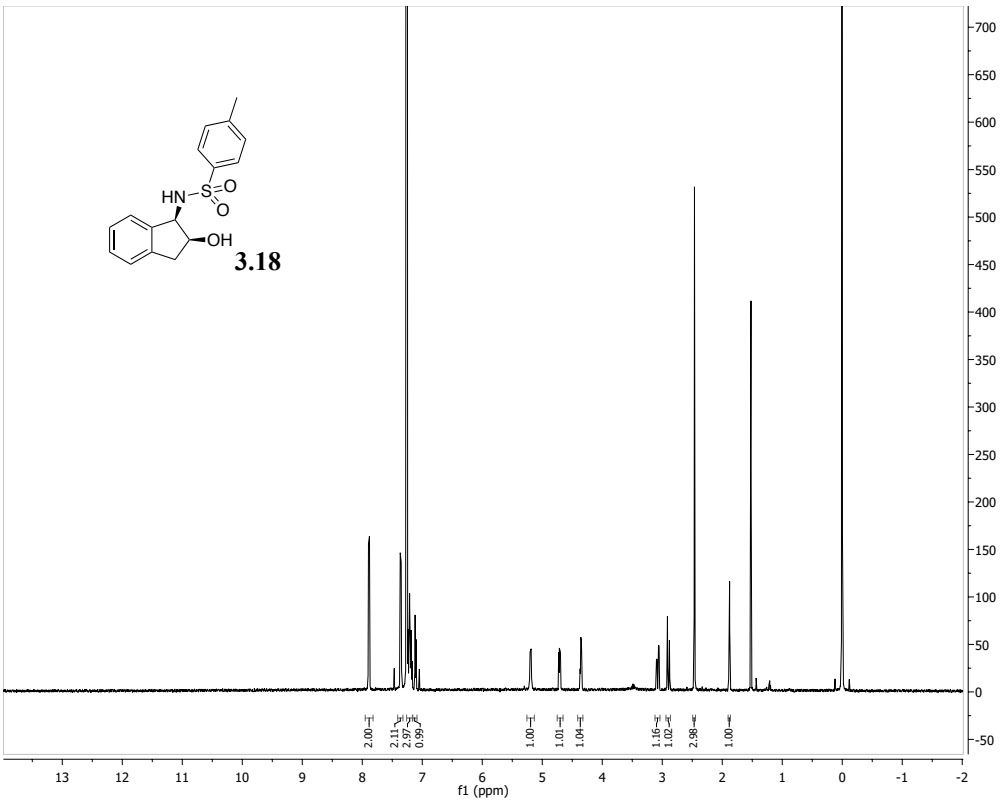

O
EtO
OBoc
3.14
1.00
1.03
2.16
2.10
9.35
3.18
f1 (ppm)

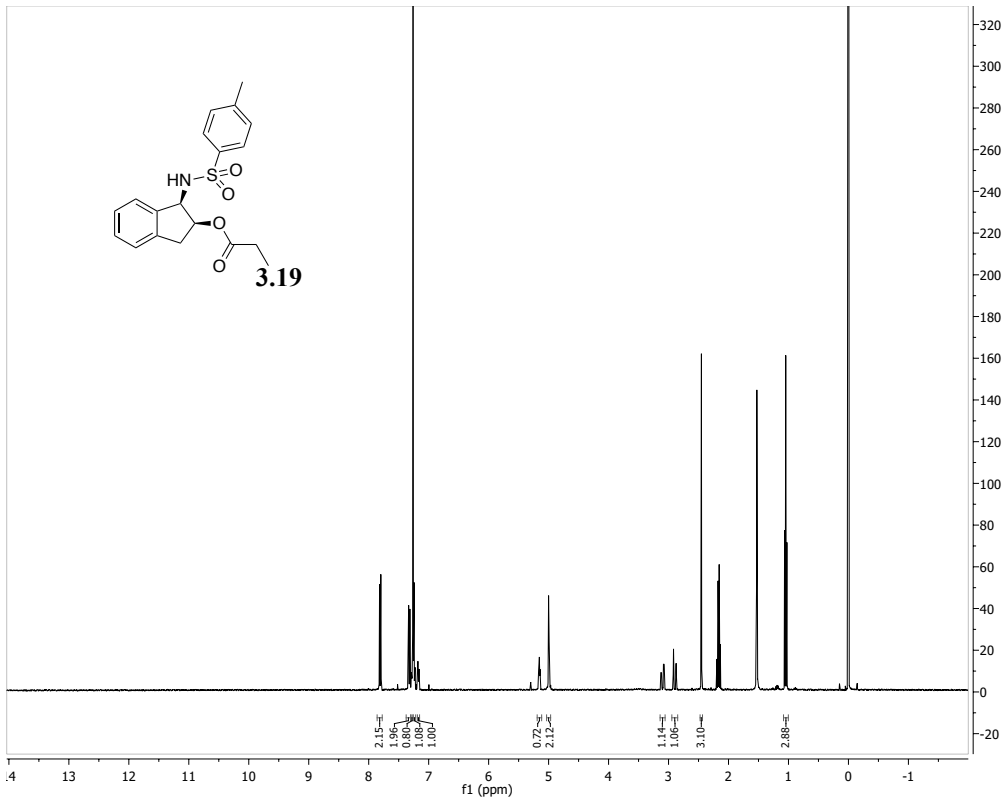

O
OH
EtO
3.15
400
350
300
250
200
150
100
50
0
1.00
0.99
2.17
1.06
0.90
1.06
0.21
0.43
0.98
1.73
1.94
2.94
2.18
4
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

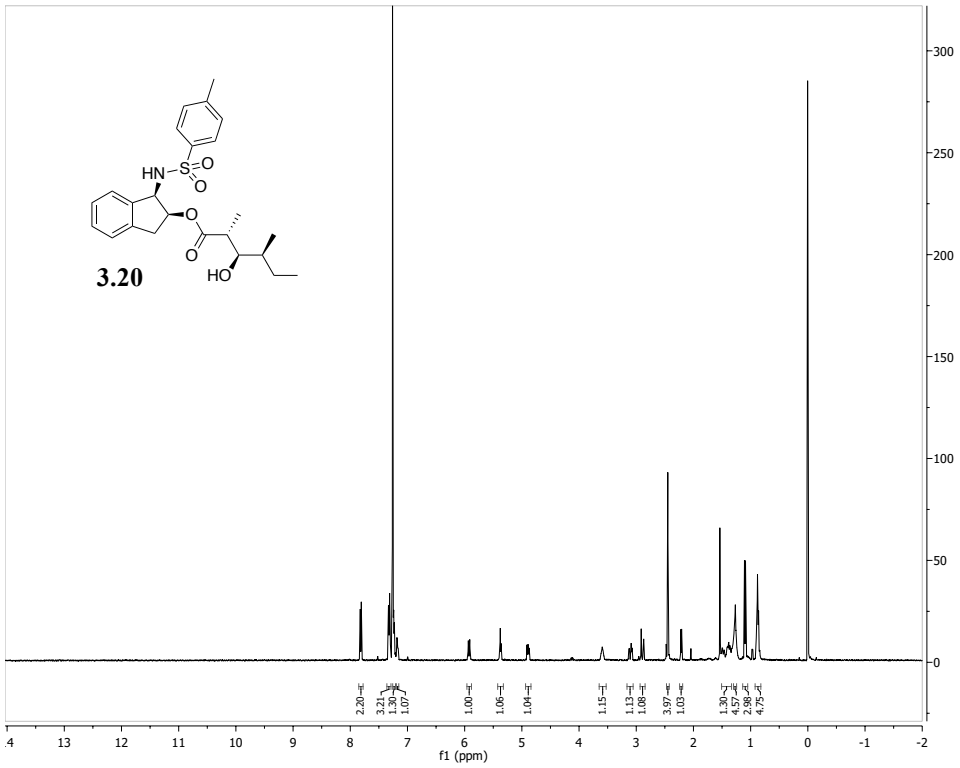

MeO
O
3.16a
1.00
2.88
2.70
2.96
f1 (ppm)

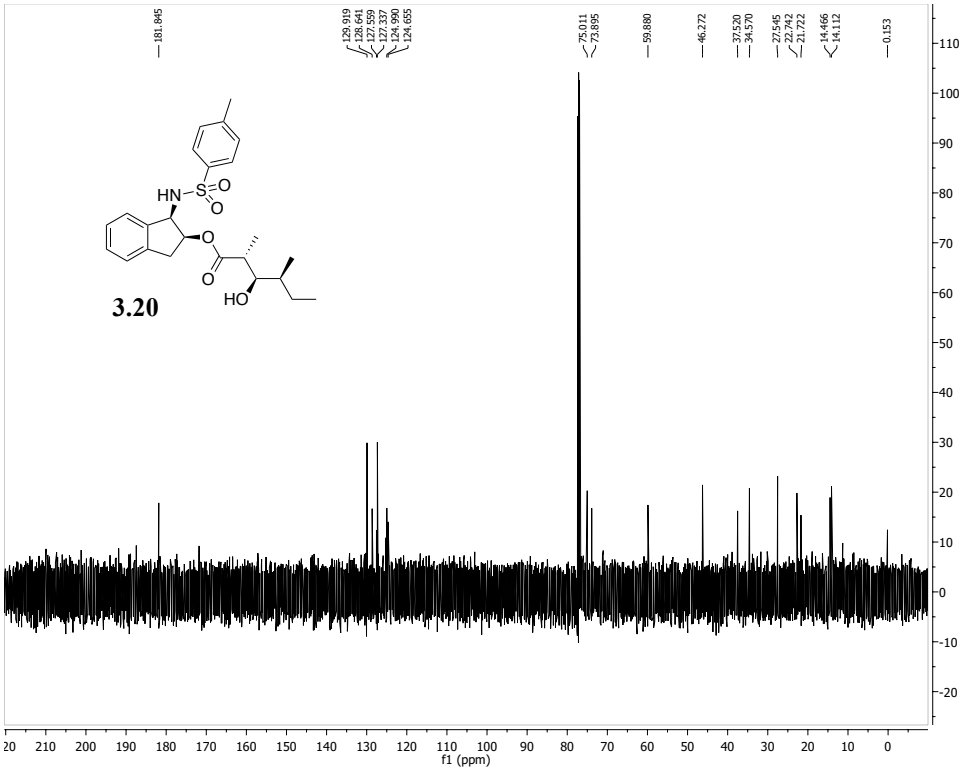

OTBS
MeO
3.16
1.00
1.85
2.69
2.73
8.59
f1 (ppm)

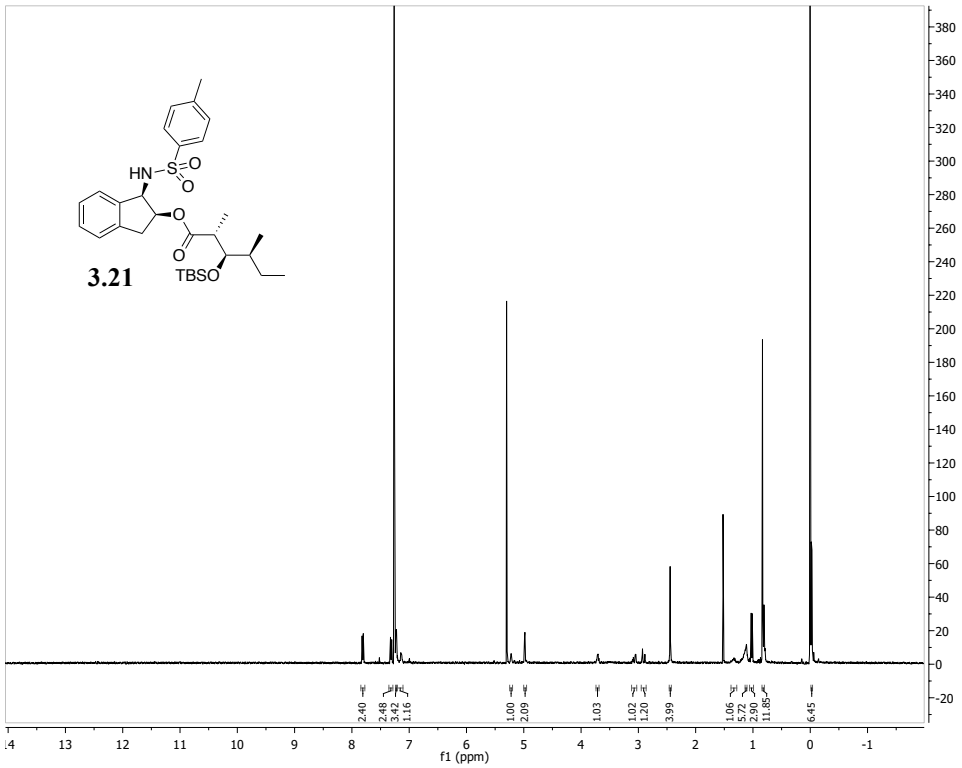

O
OH
OTBS
MeO
3.17
f1 (ppm)

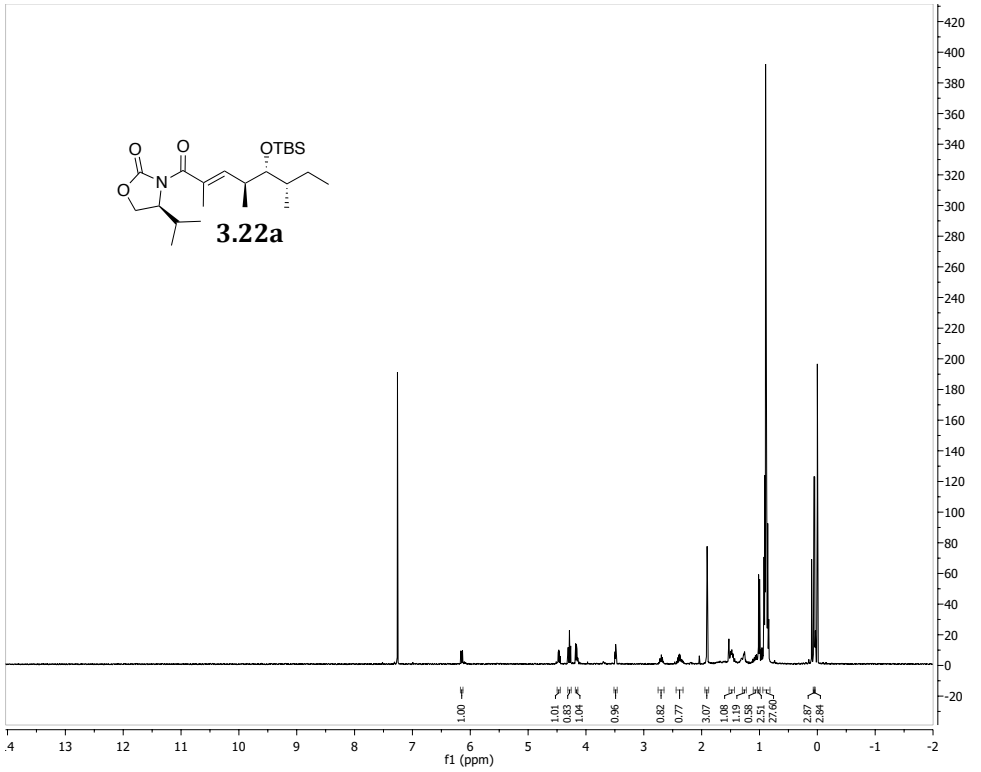

HN
S
O
O
OH
3.18
2.00
2.11
2.97
0.99
1.00
1.01
1.04
1.16
1.02
2.98
1.00
f1 (ppm)

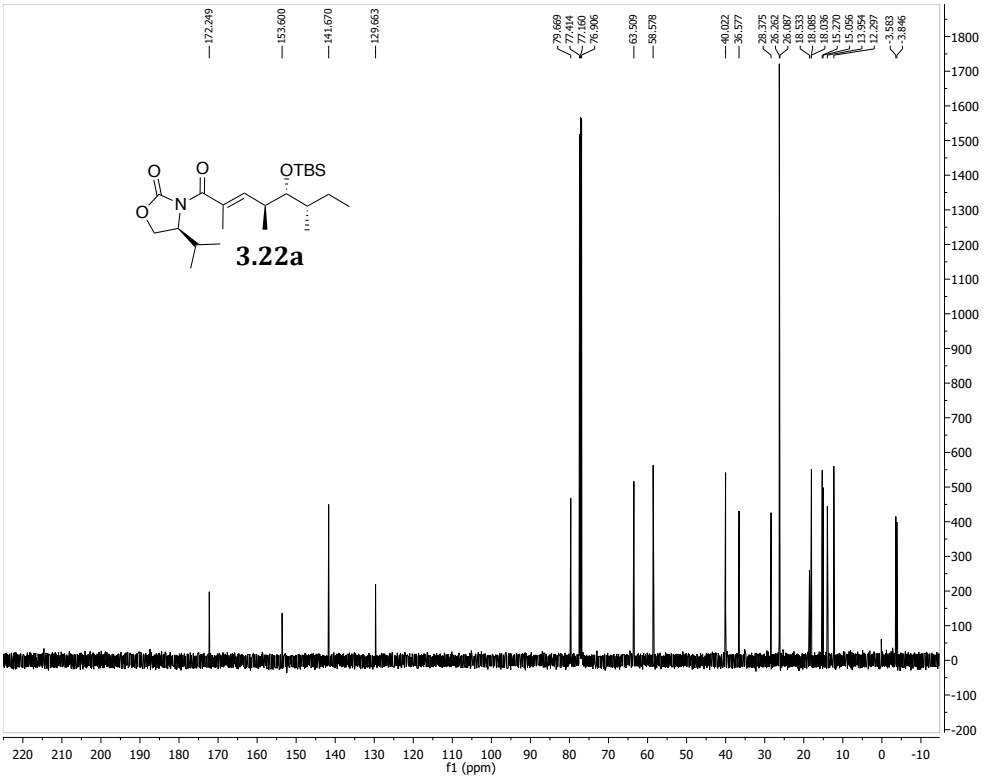

HN
S
O
O
O
O
3.19
2.15
1.96
0.80
1.08
1.00
0.72
2.12
1.14
1.06
3.10
2.88
f1 (ppm)

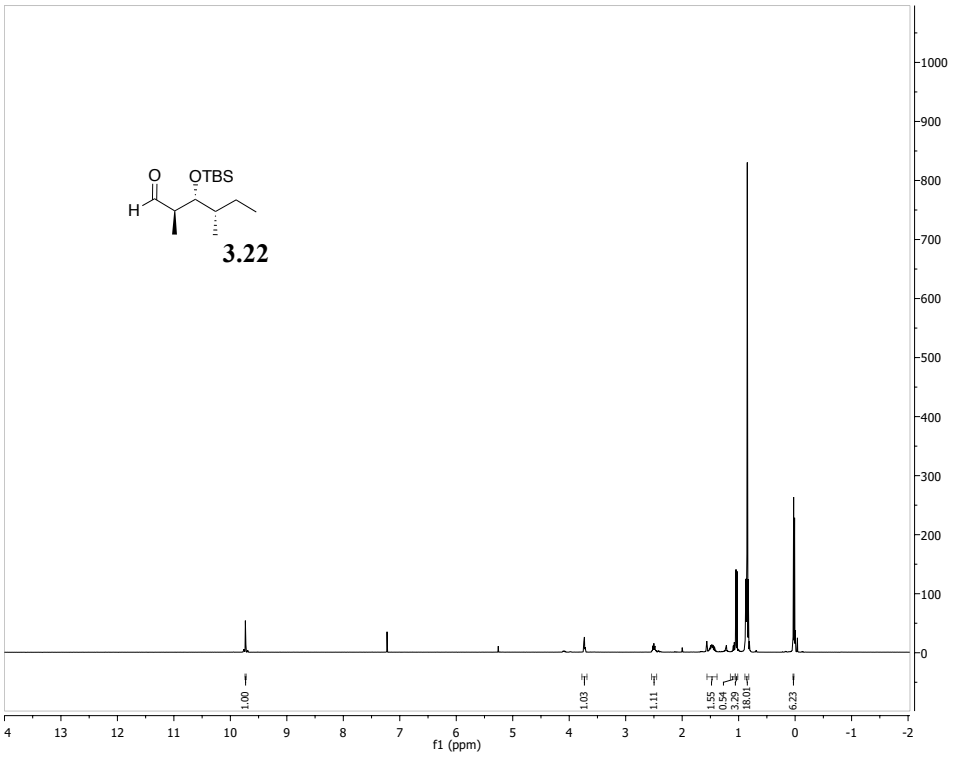

3.20
f1 (ppm)

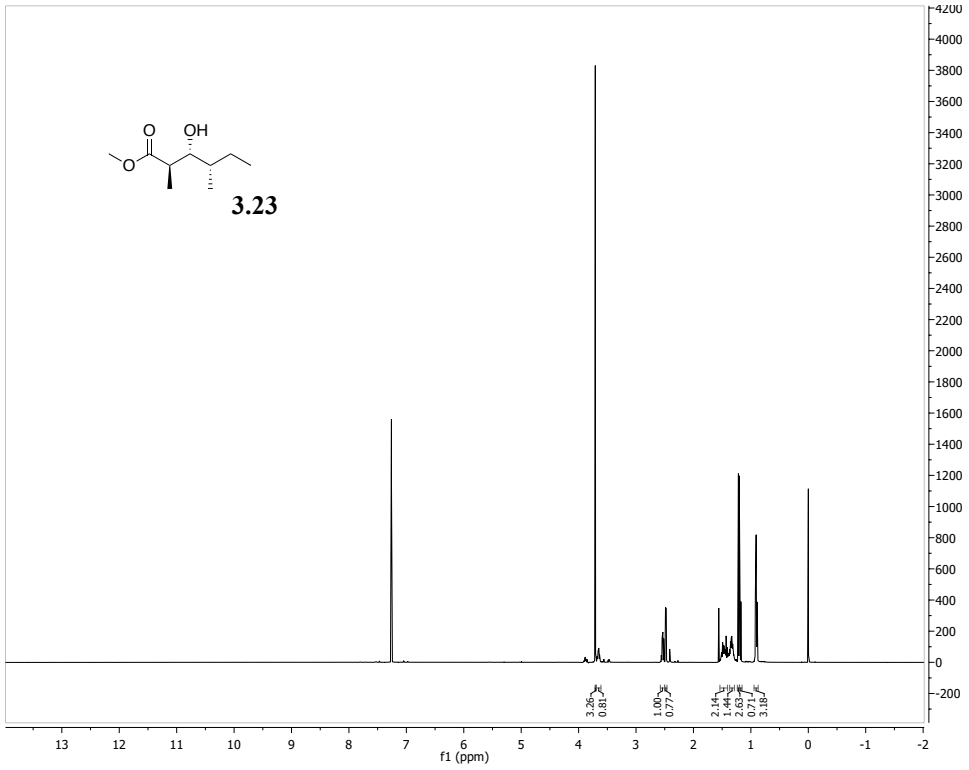

3.20
f1 (ppm)

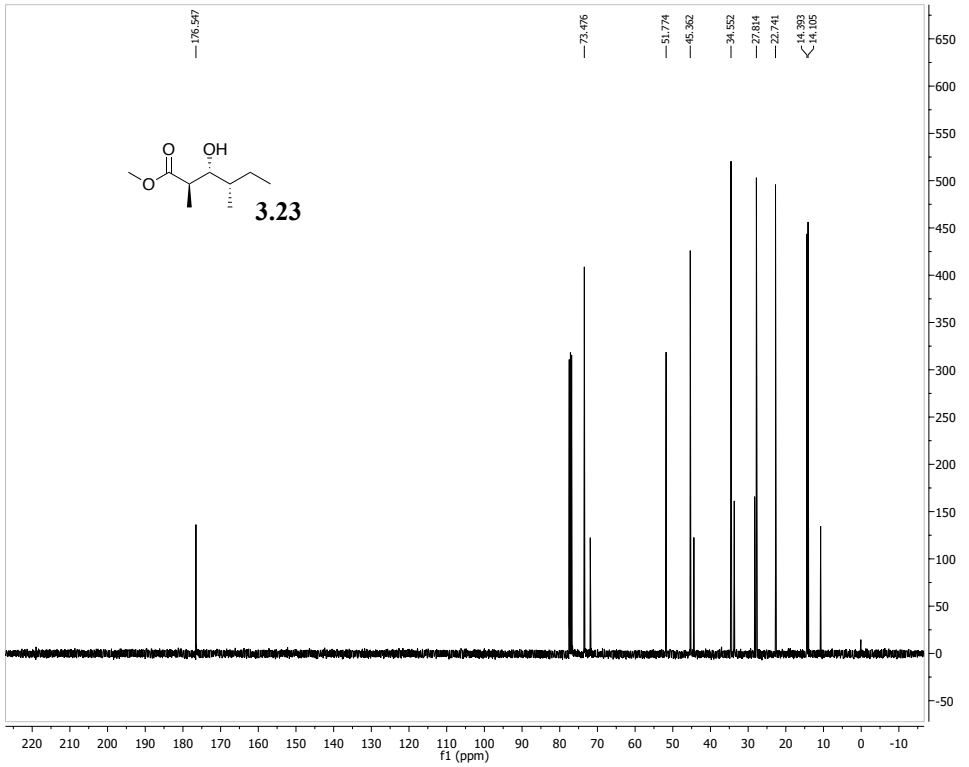

HN
S
O
O
O
O
TBSO
3.21
f1 (ppm)

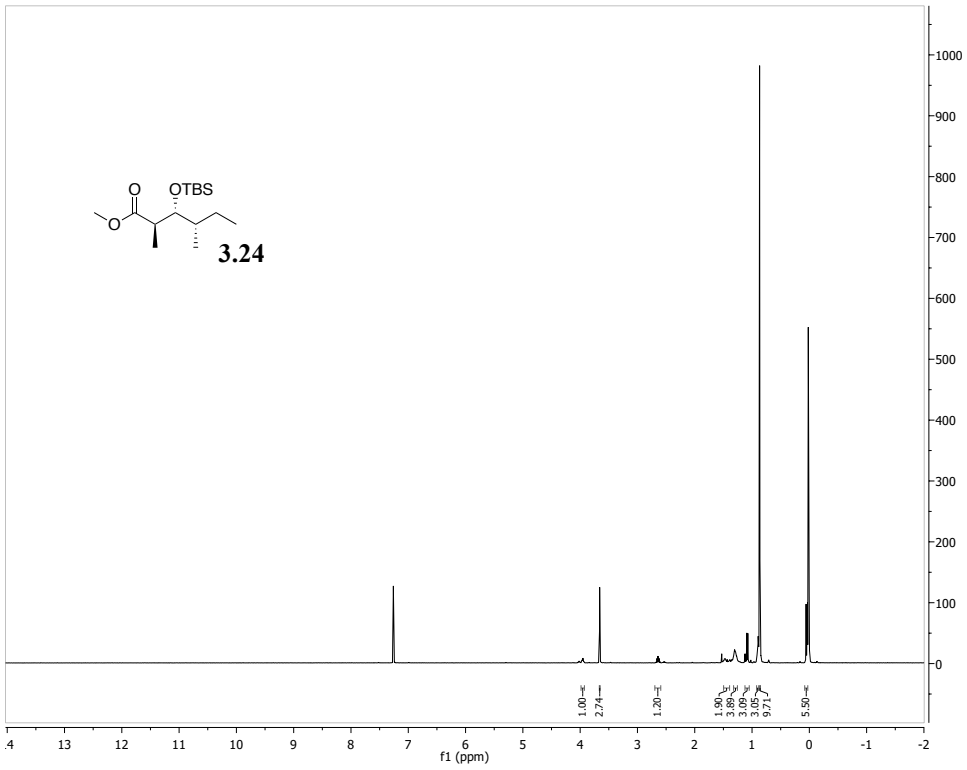

OTBS
3.22a
f1 (ppm)

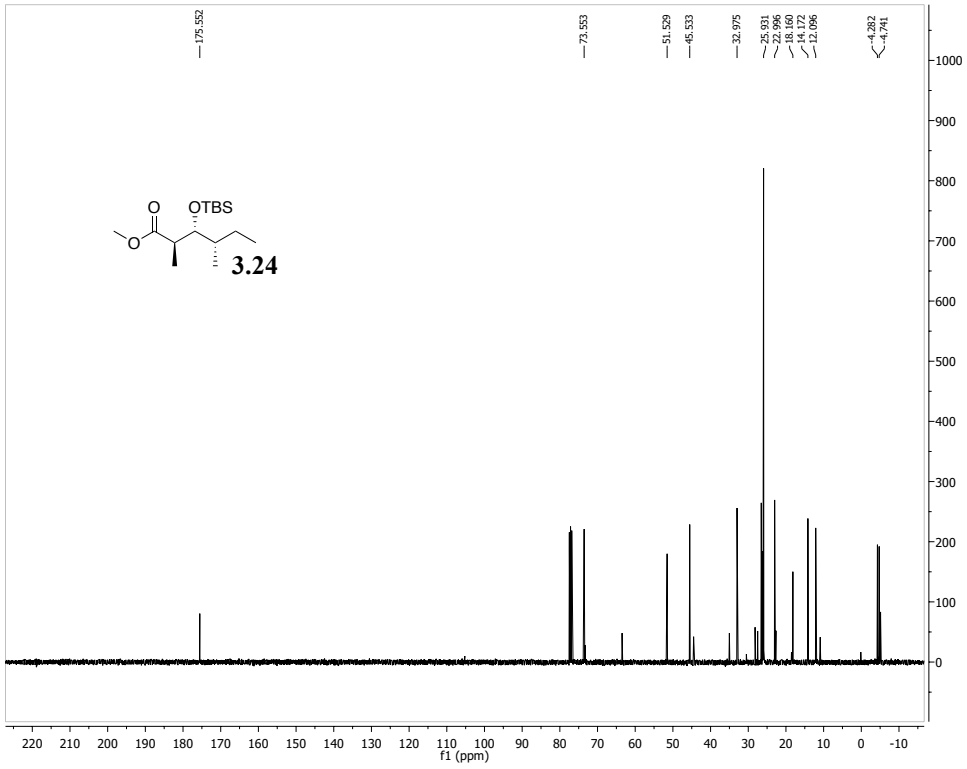

OTBS
3.22a
f1 (ppm)

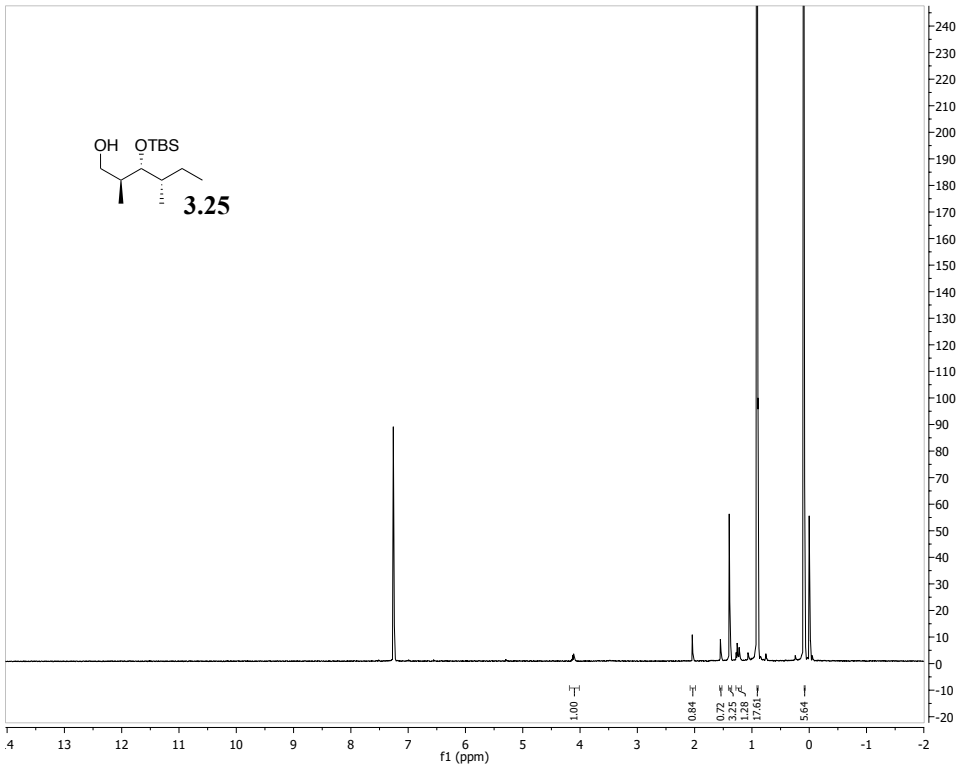

O
OTBS
H
3.22
1000
900
800
700
600
500
400
300
200
100
0
1.00
1.03
1.11
1.55
0.54
3.29
18.01
6.23
4
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

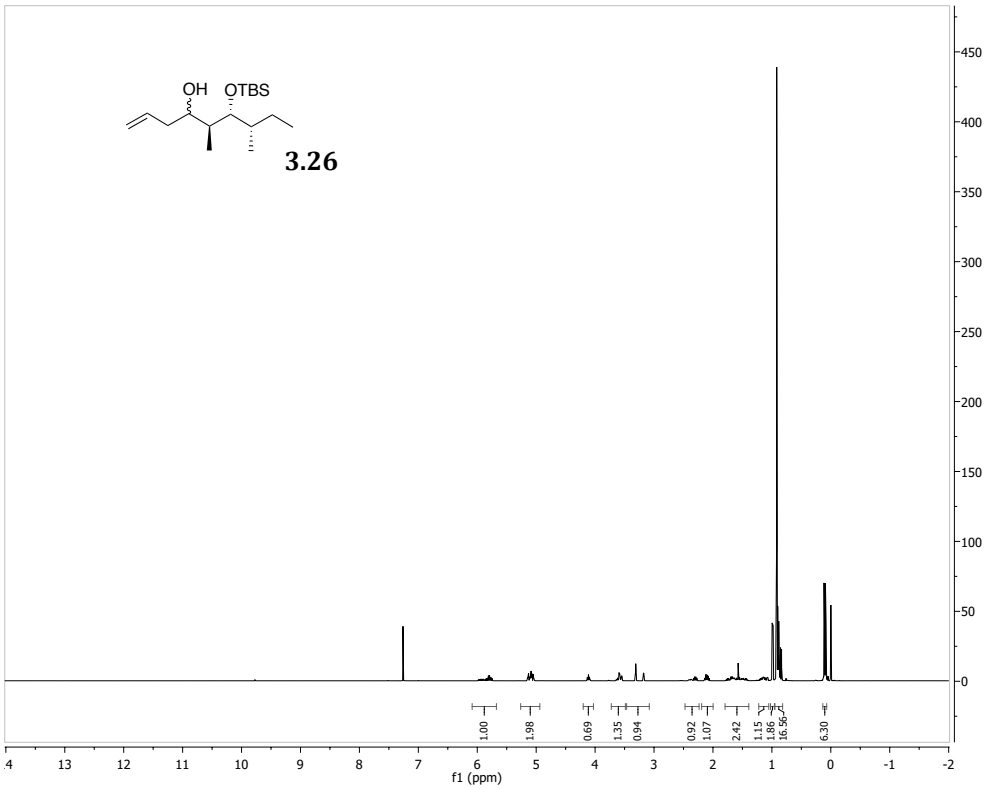

O
OH
O
3.23
3.26
0.81
1.00
0.77
2.14
1.44
2.63
0.71
3.18
f1 (ppm)

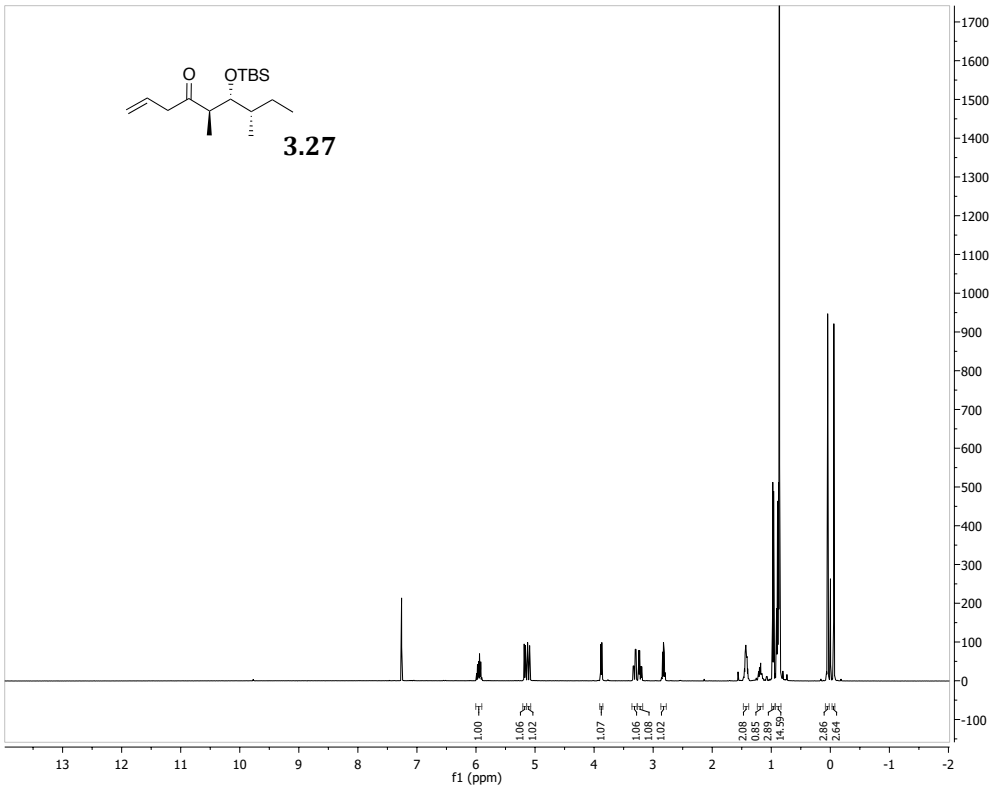

176.547
73.476
51.774
45.362
34.552
27.814
22.741
14.393
14.105
O
OH
O
3.23
f1 (ppm)

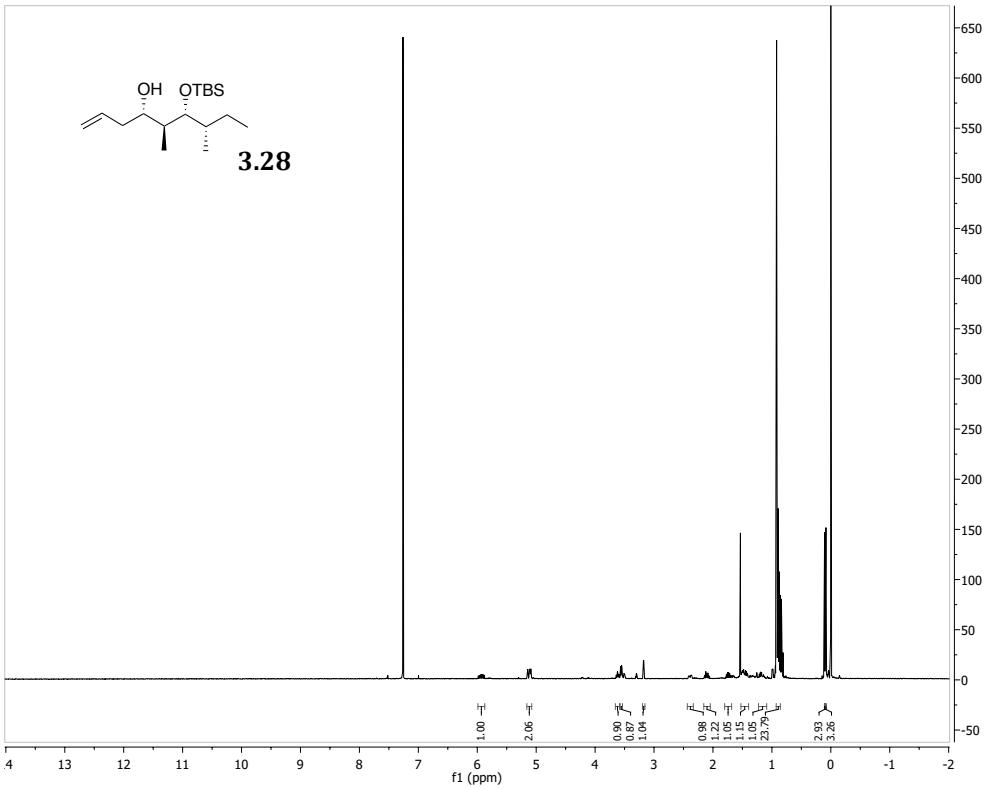

O
OTBS
O
3.24
1.00
2.74
1.20
1.90
3.89
3.08
3.05
9.71
5.50
f1 (ppm)

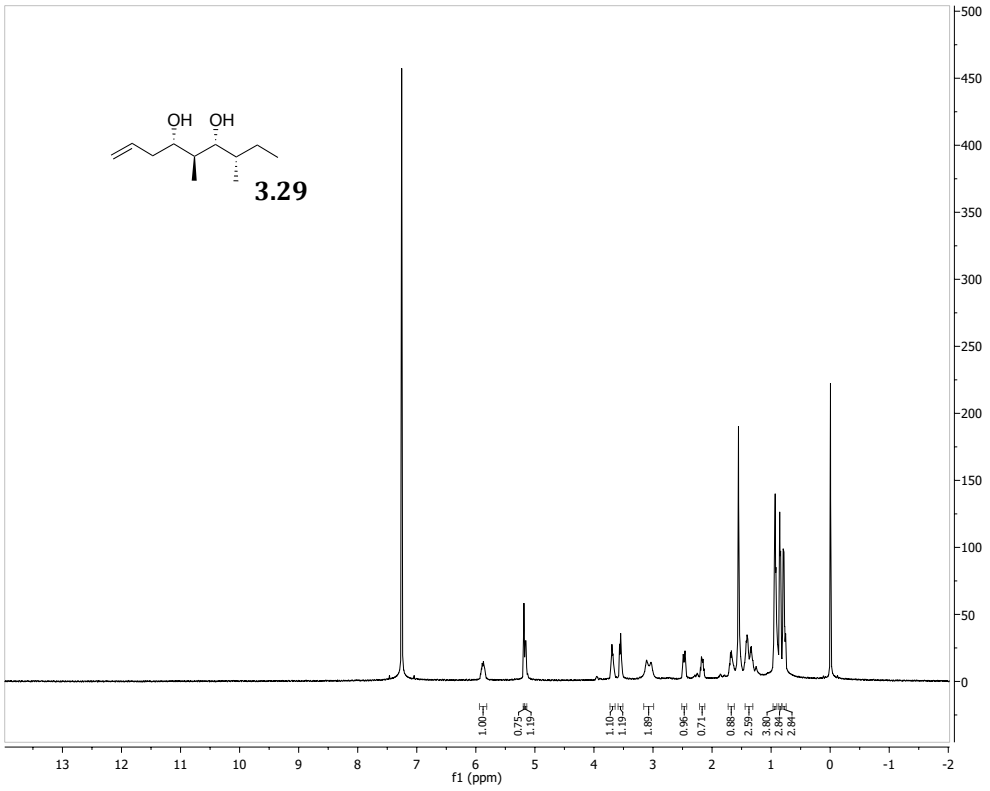

175.552
73.553
51.529
45.533
32.975
25.931
22.996
18.160
14.172
12.096
-4.282
-4.741
O
OTBS
O
3.24
f1 (ppm)

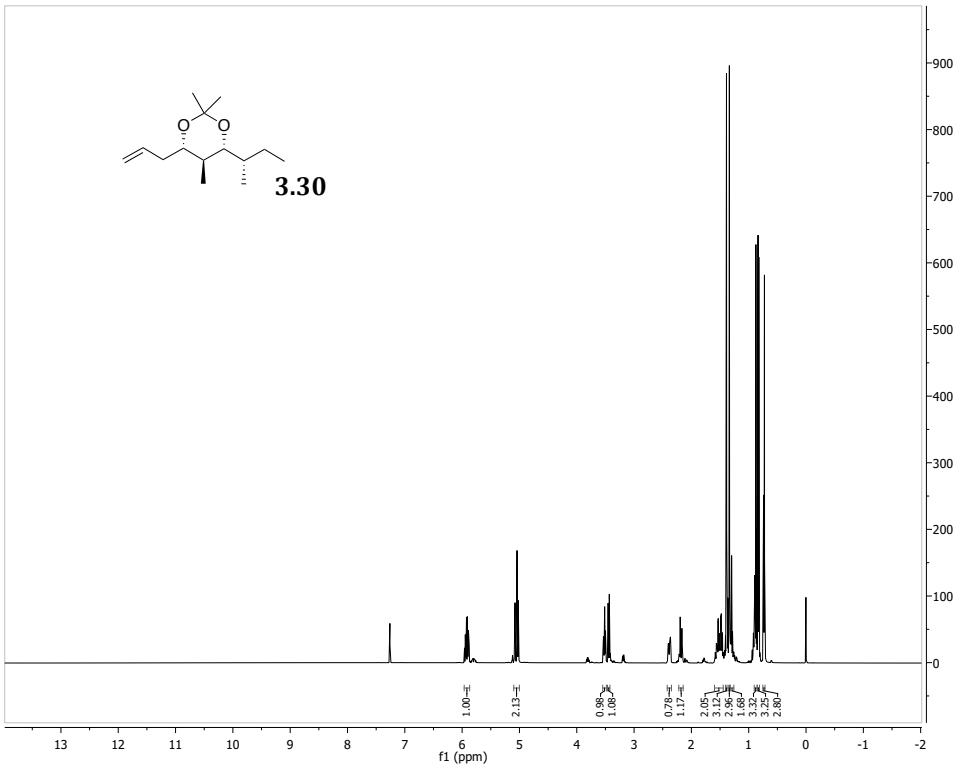

OH
OTBS
3.25
1.00
0.84
0.72
3.25
1.28
17.61
5.64
f1 (ppm)

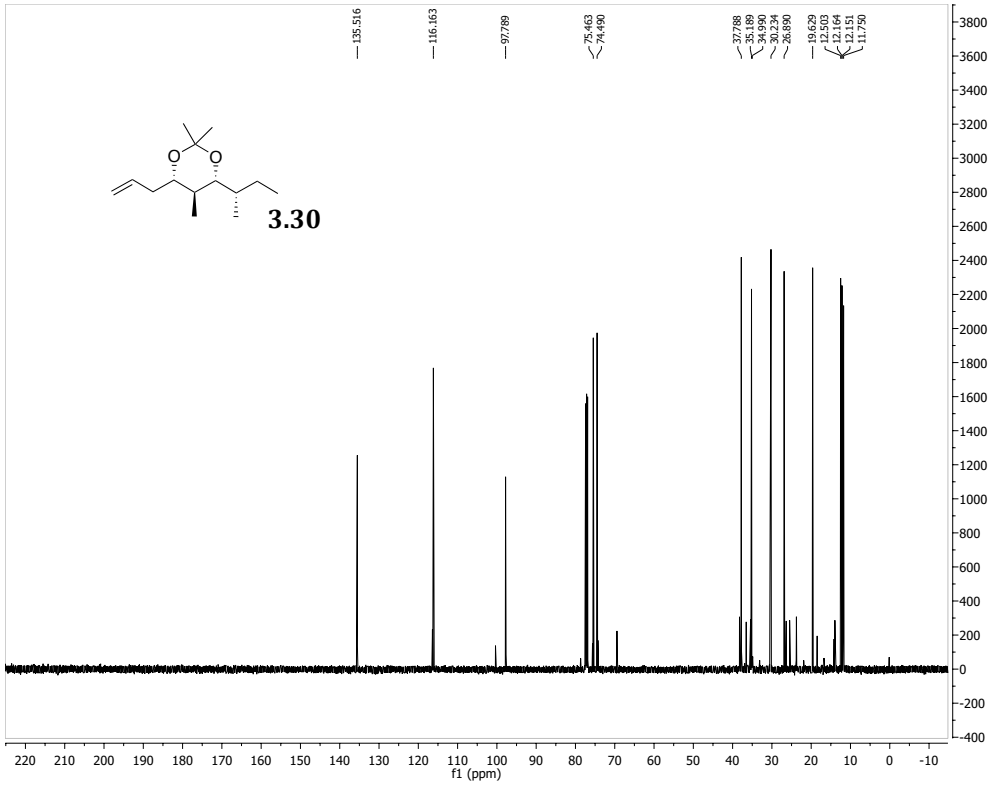

OH
OTBS
3.26
f1 (ppm)

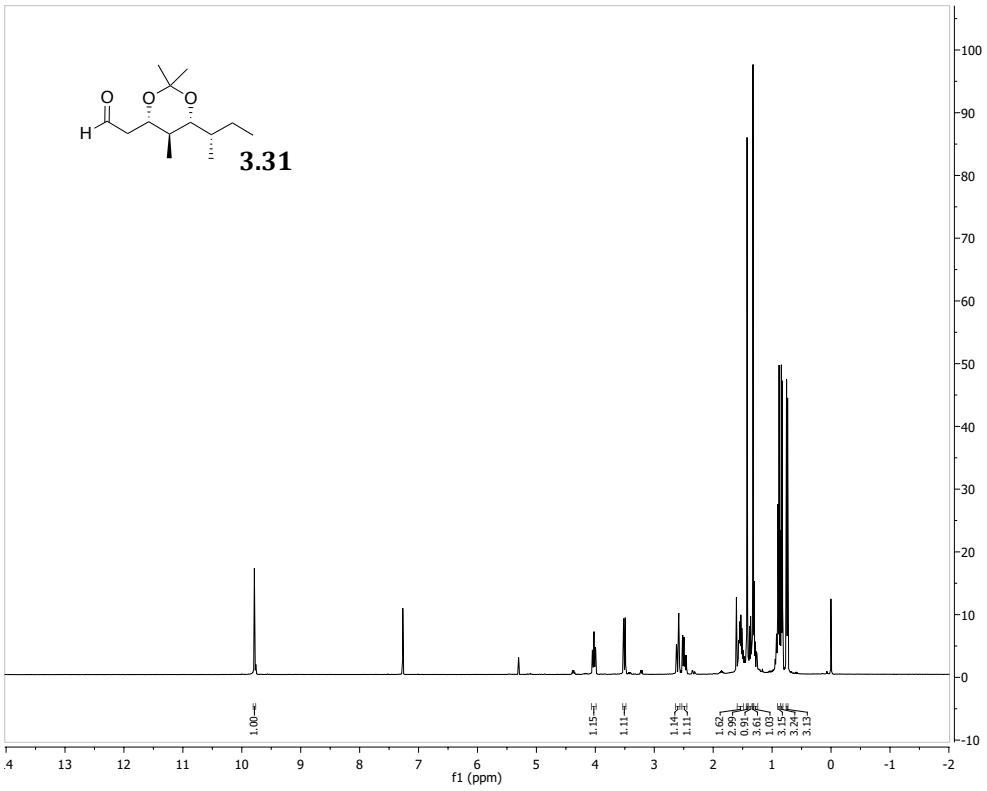

O
OTBS
3.27
1.00
1.06
1.02
1.07
1.06
1.08
1.02
2.08
0.85
2.89
14.59
2.86
2.64
f1 (ppm)

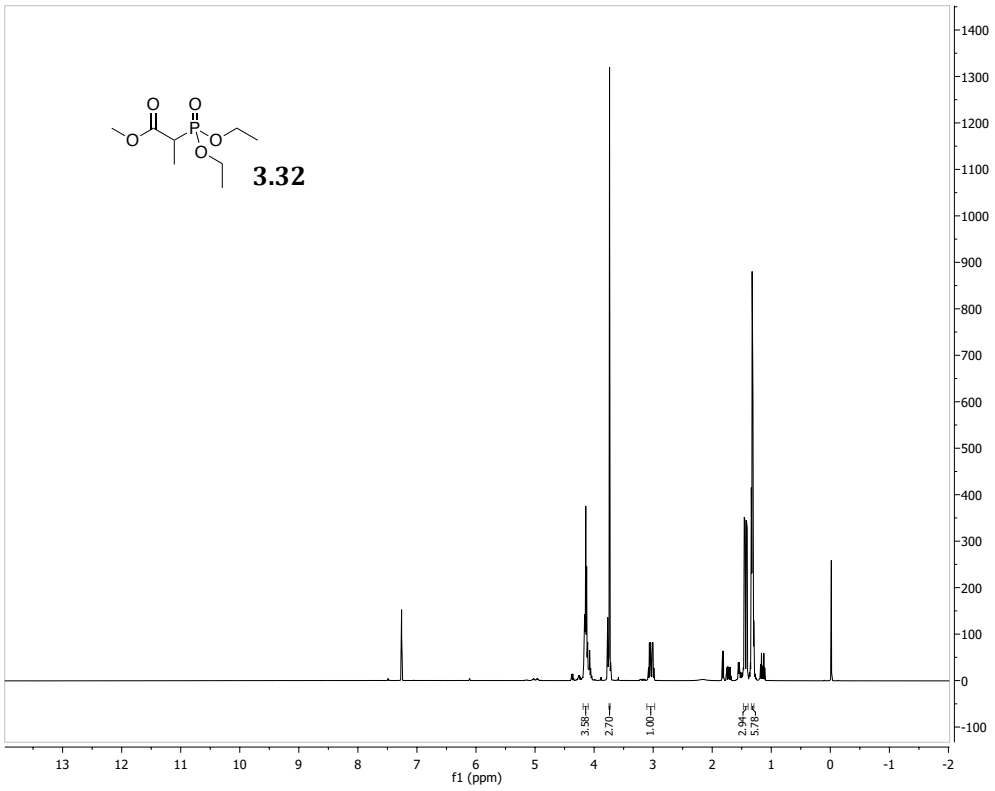

OH
OTBS
3.28
1.00
2.06
0.90
0.97
1.04
0.98
1.22
1.15
1.15
1.05
23.79
2.93
3.26
f1 (ppm)

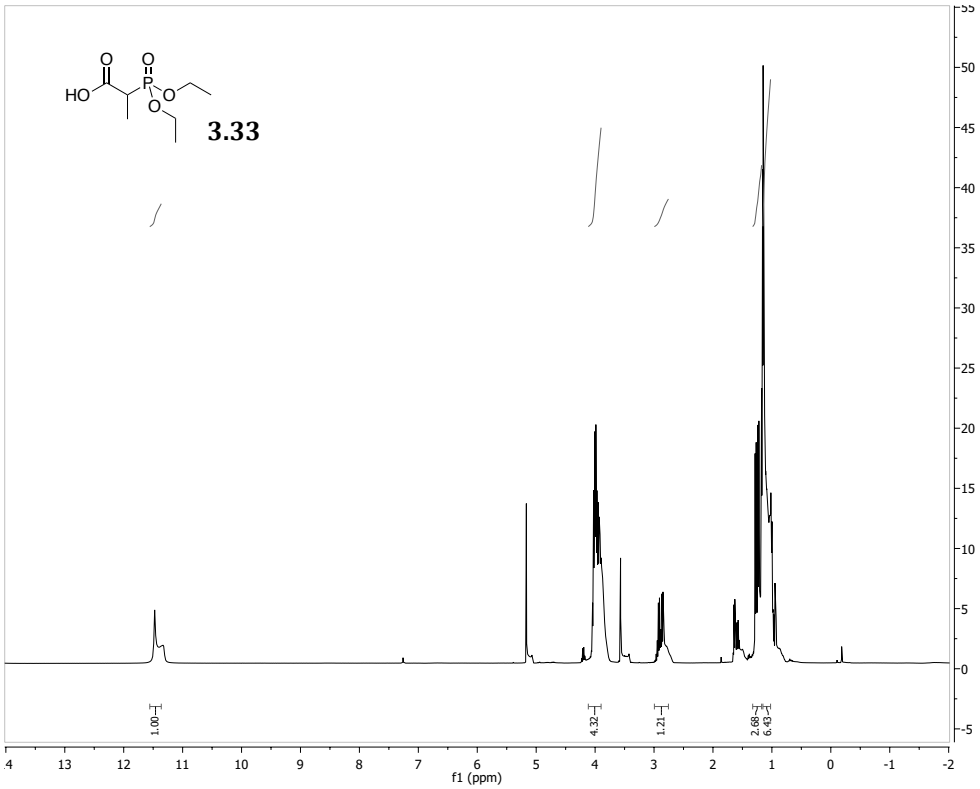

OH
OH
3.29
f1 (ppm)

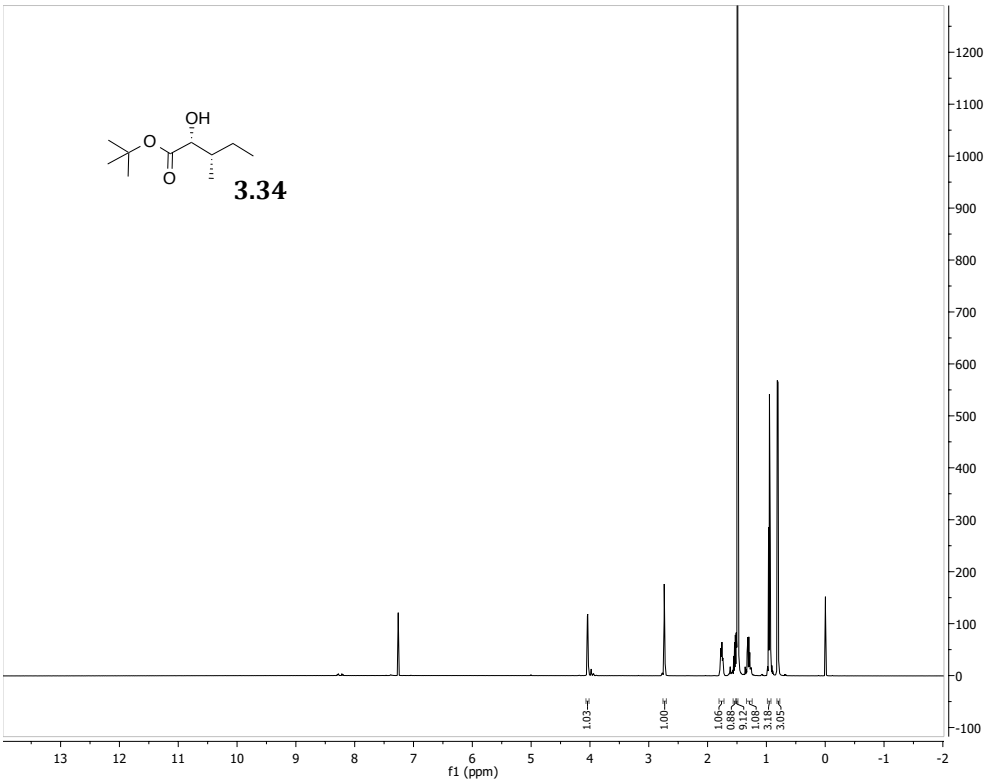

3.30
f1 (ppm)

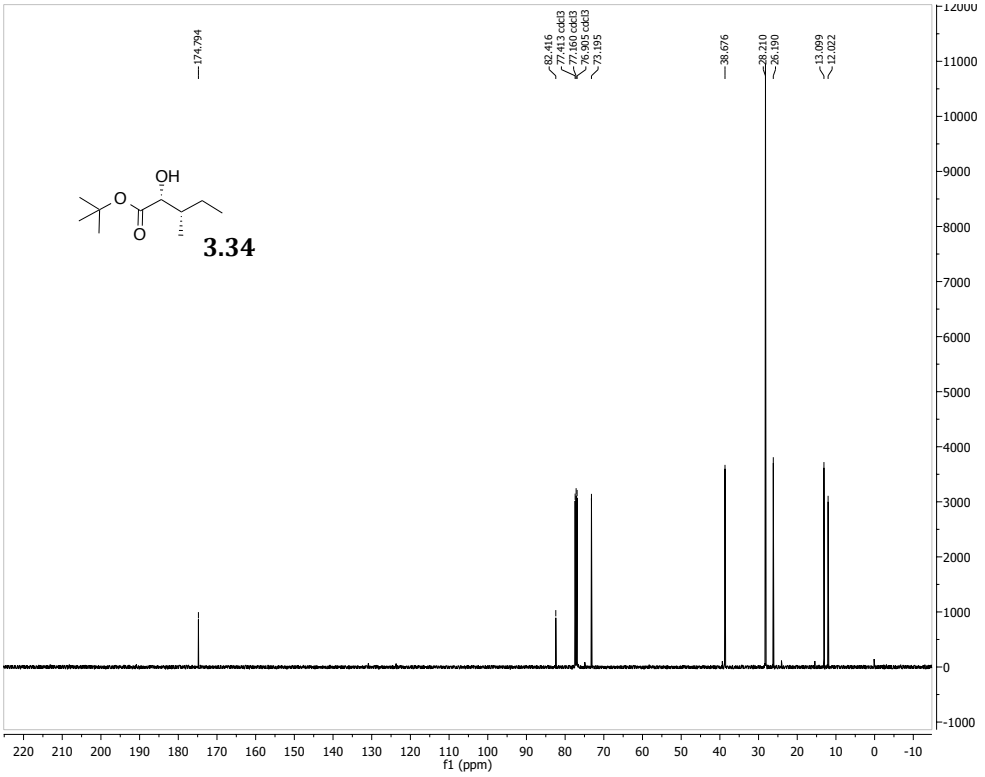

135.516
116.163
97.789
75.463
74.490
37.788
35.189
34.990
30.234
26.890
19.629
12.503
12.164
12.151
11.750
3.30
f1 (ppm)

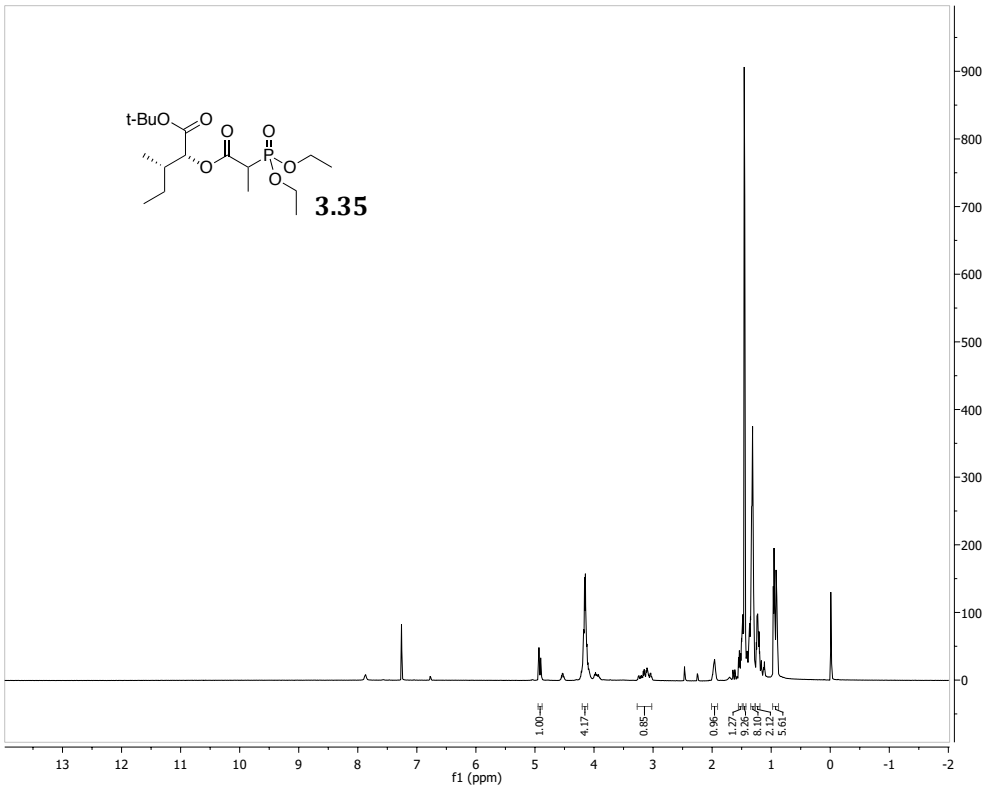

3.31
f1 (ppm)

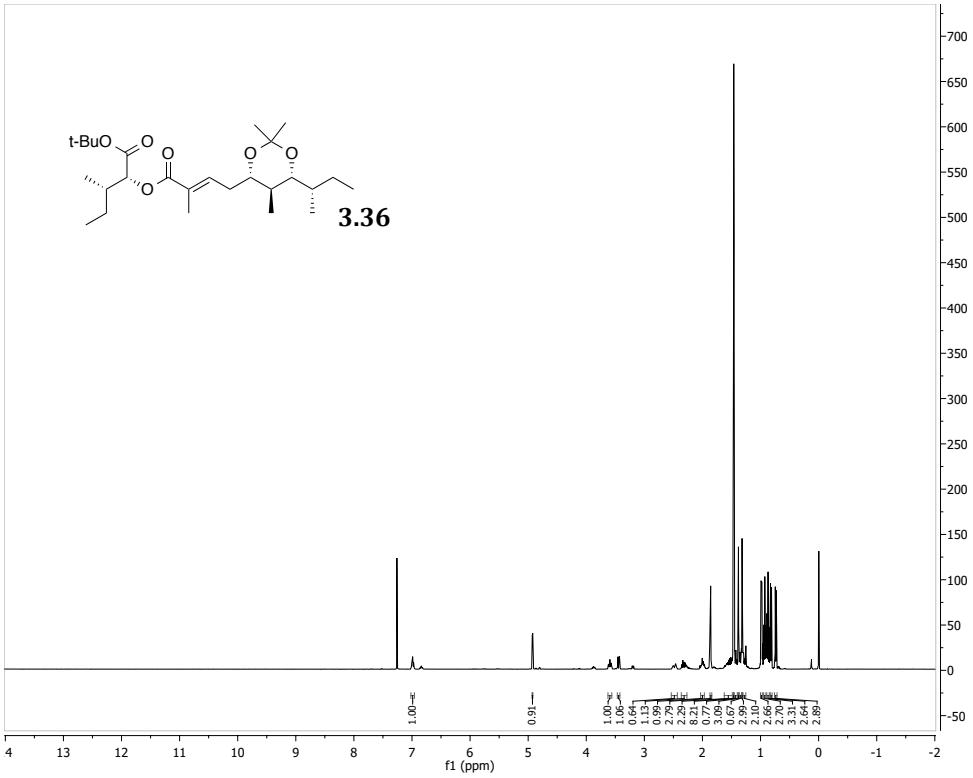

3.32
f1 (ppm)

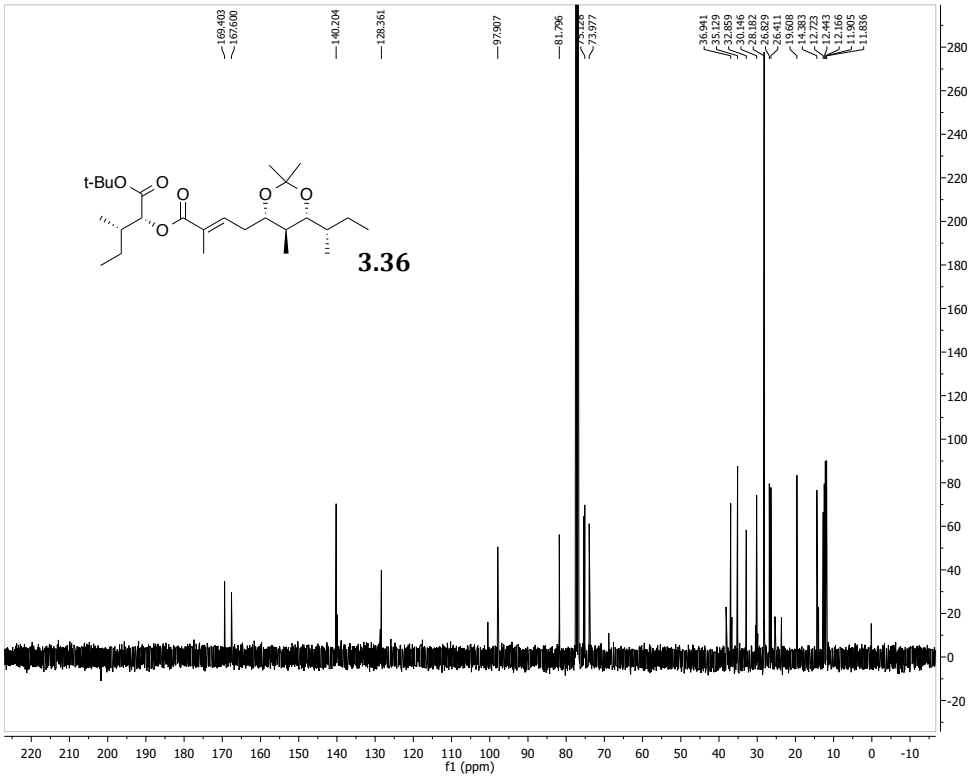

HO
O
O
P
O
O
3.33
1.00
4.32
1.21
2.68
6.43
f1 (ppm)

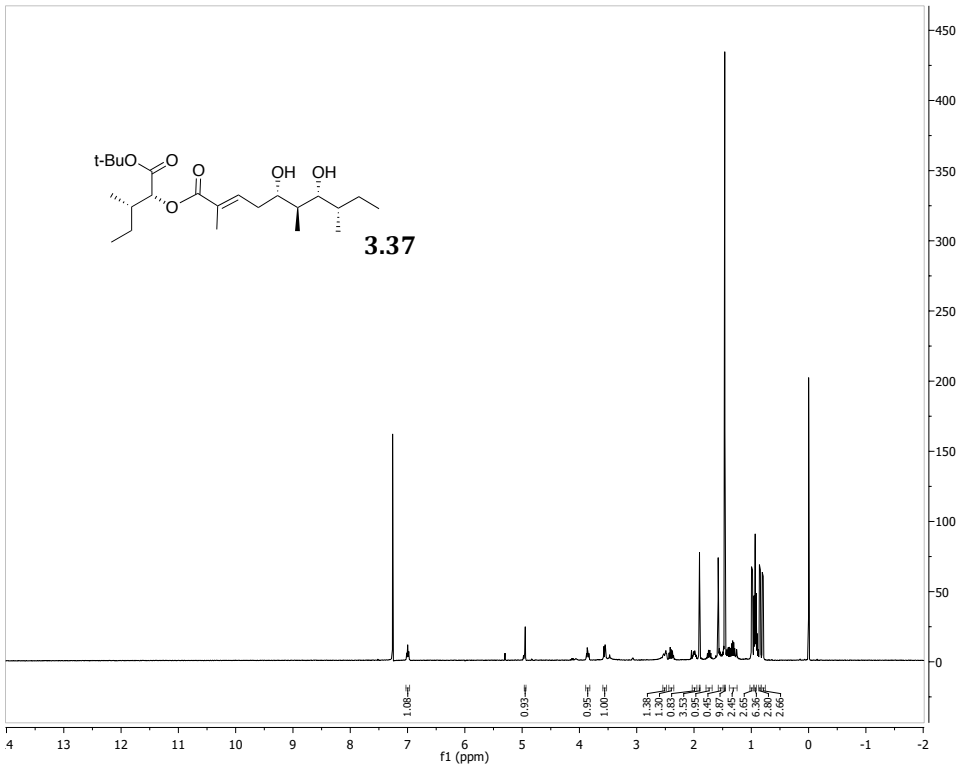

OH
O
O
3.34
1.03
1.00
1.06
0.88
9.12
1.08
3.18
3.05
f1 (ppm)

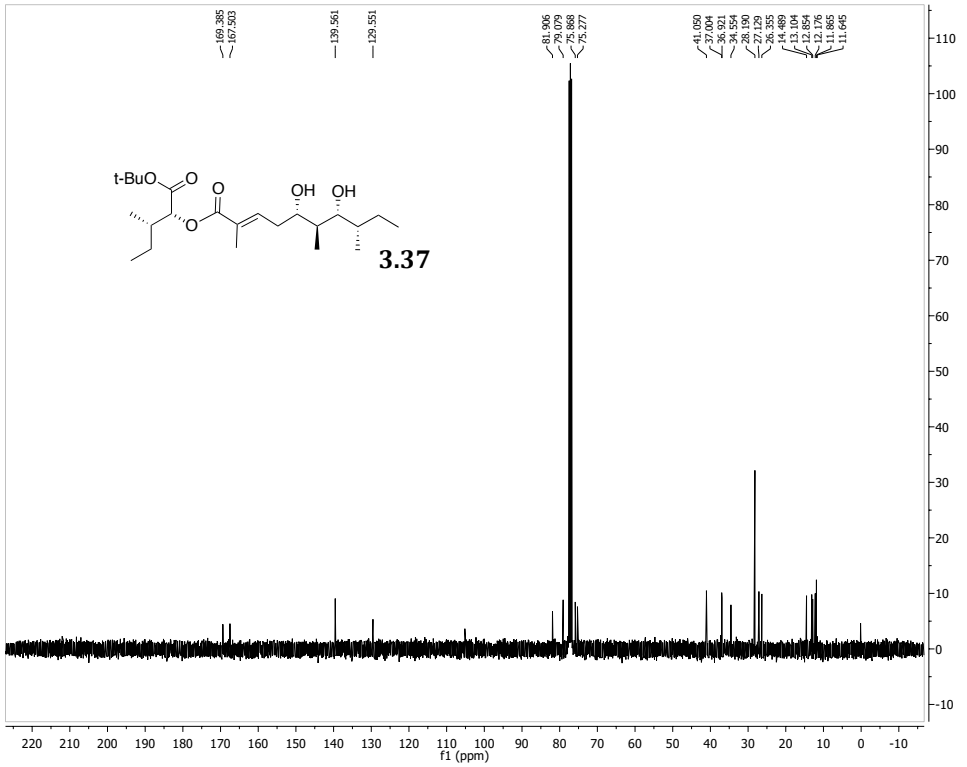

174.794
82.416
77.413 cdcl3
77.160 cdcl3
76.905 cdcl3
73.195
38.676
28.210
26.190
13.099
12.022
OH
O
O
3.34
f1 (ppm)


t-BuO
O
O
O
O
P
O
O
O
3.35
900
800
700
600
500
400
300
200
100
0
1.00
4.17
0.85
0.96
1.27
9.26
8.10
2.12
5.61
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)


t-BuO
O
O
O
O
O
3.36
f1 (ppm)


169.403
167.600
140.204
128.361
97.907
81.796
75.125
73.977
36.941
35.129
32.859
30.146
28.182
26.829
25.641
19.608
14.383
12.723
12.443
12.166
11.905
11.836
t-BuO
O
O
O
O
O
3.36
f1 (ppm)


t-BuO
O
O
O
OH
OH
3.37
f1 (ppm)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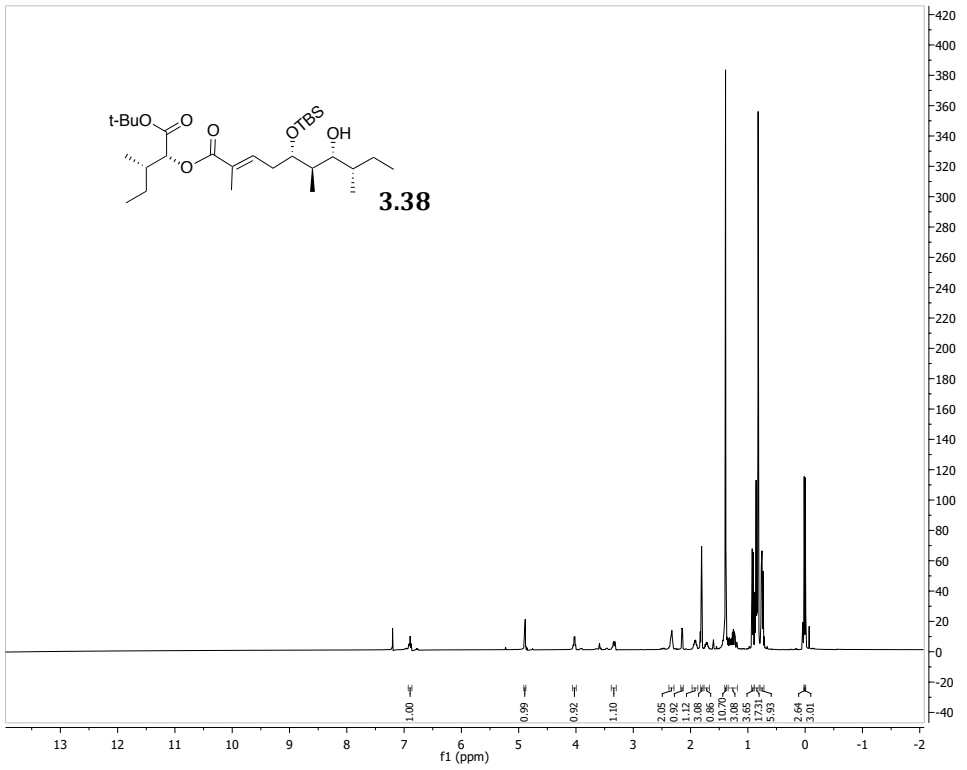
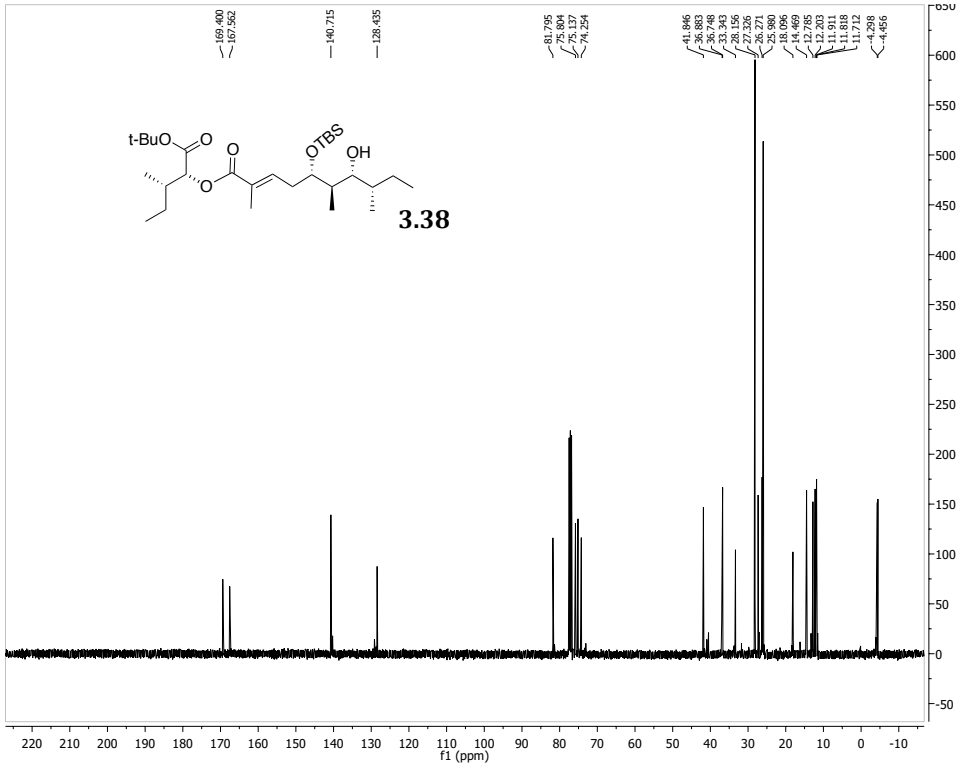
167.503
139.561
129.551
81.906
79.079
75.868
75.277
41.050
37.004
36.921
34.554
28.190
27.129
26.355
14.489
13.104
12.854
12.176
11.865
11.645
t-BuO
O
O
O
OH
OH
3.37
f1 (ppm)


t-BuO
O
O
O
OTBS
OH
3.38
f1 (ppm)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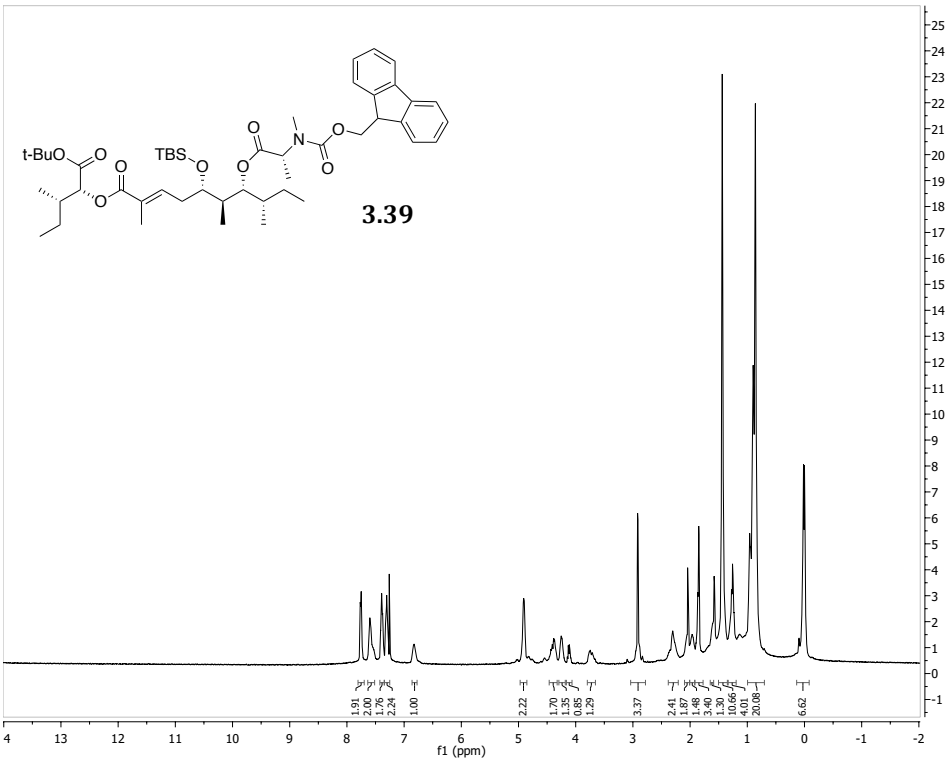
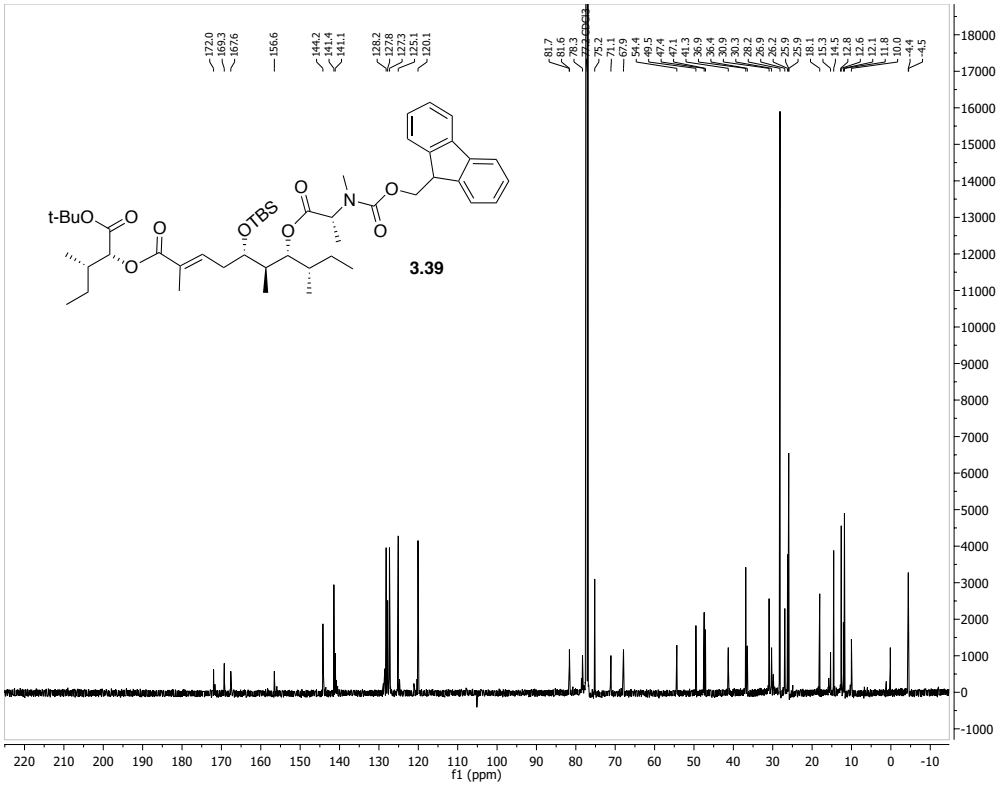
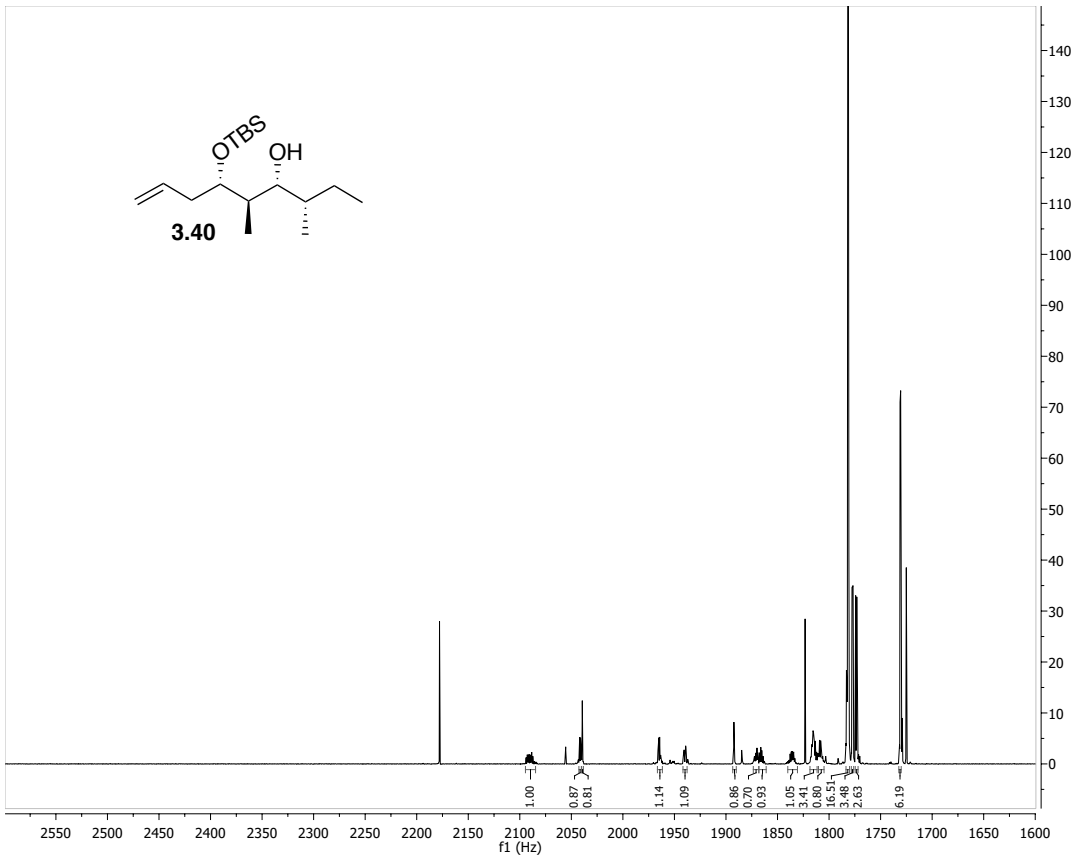
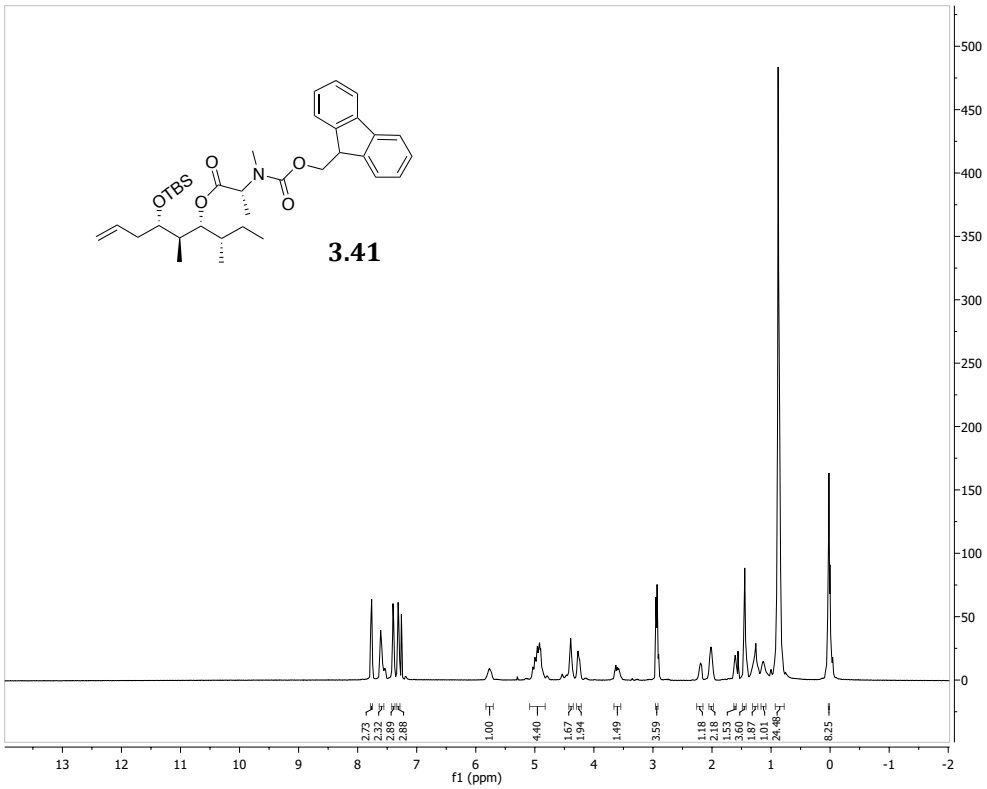
167.562
140.715
128.435
81.795
75.964
75.137
74.254
41.846
36.883
36.748
33.343
28.156
27.326
26.271
25.980
25.896
14.469
12.785
12.203
11.911
11.818
11.712
-4.298
-4.456
t-BuO
O
O
O
OTBS
OH
3.38
f1 (ppm)

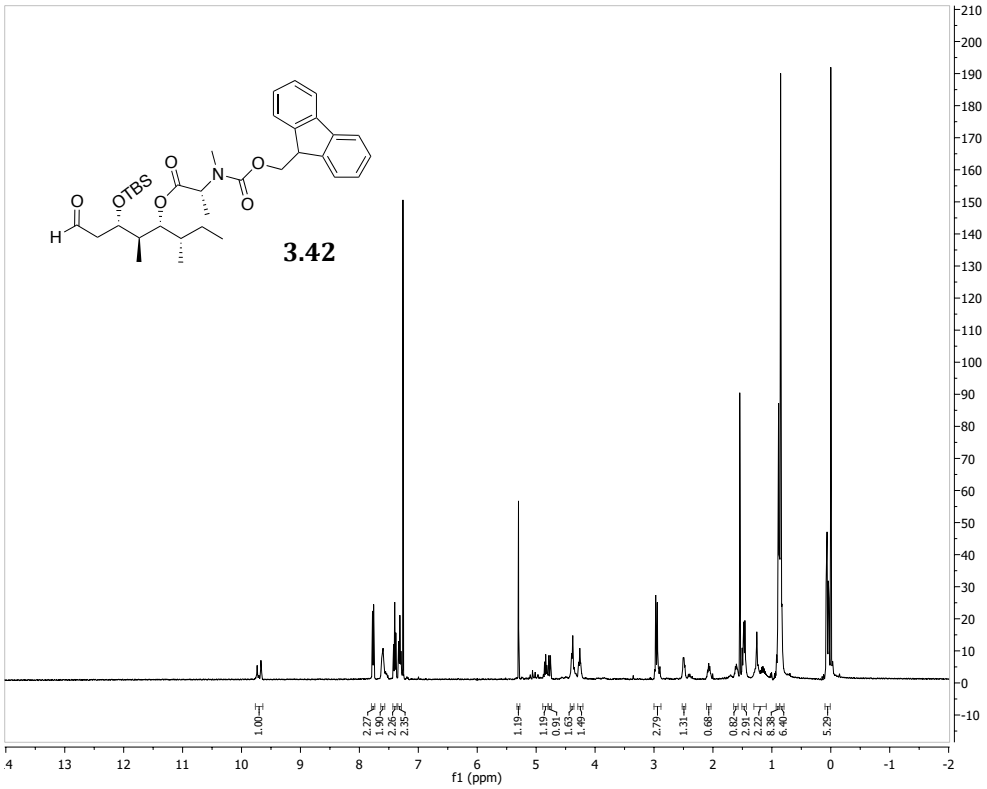

t-BuO
TBS
3.39
f1 (ppm)

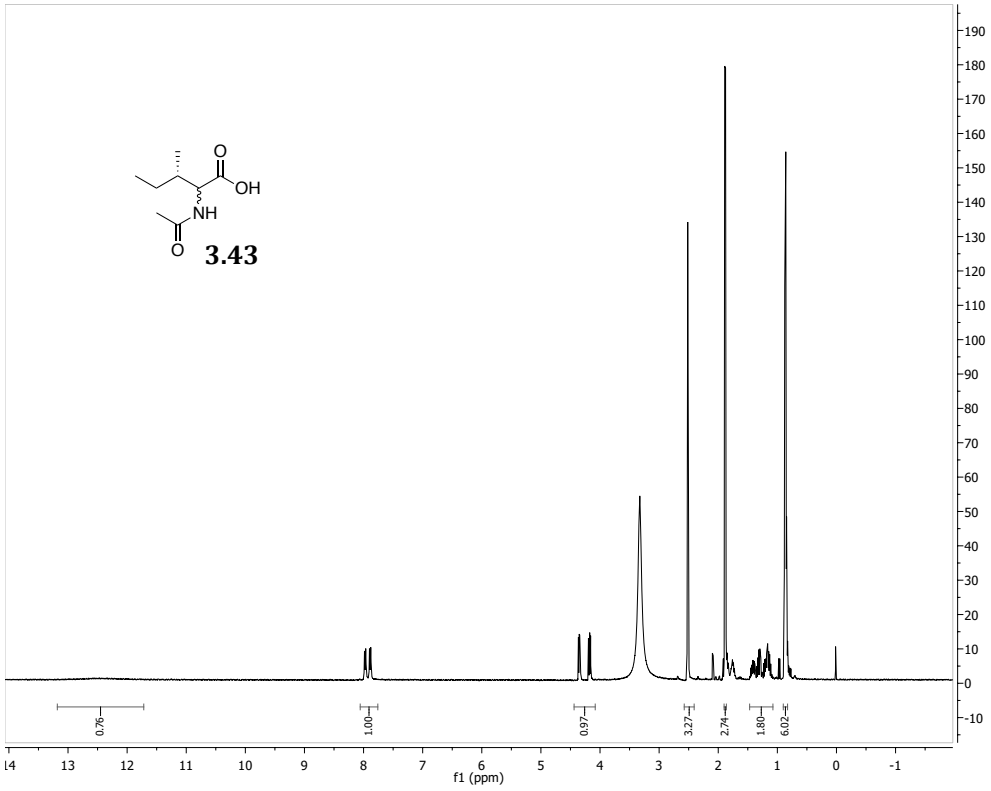

172.0
169.3
167.6
156.6
144.2
141.4
141.1
128.2
127.8
127.3
125.1
120.1
81.7
81.6
79.3
77.2
75.2
71.1
67.9
54.4
49.5
47.4
47.1
44.3
36.9
36.4
30.9
30.3
28.2
26.9
26.2
25.9
25.9
18.1
15.3
14.5
12.8
12.6
12.1
11.8
10.0
4.4
-4.5
t-BuO
OTBS
3.39
f1 (ppm)

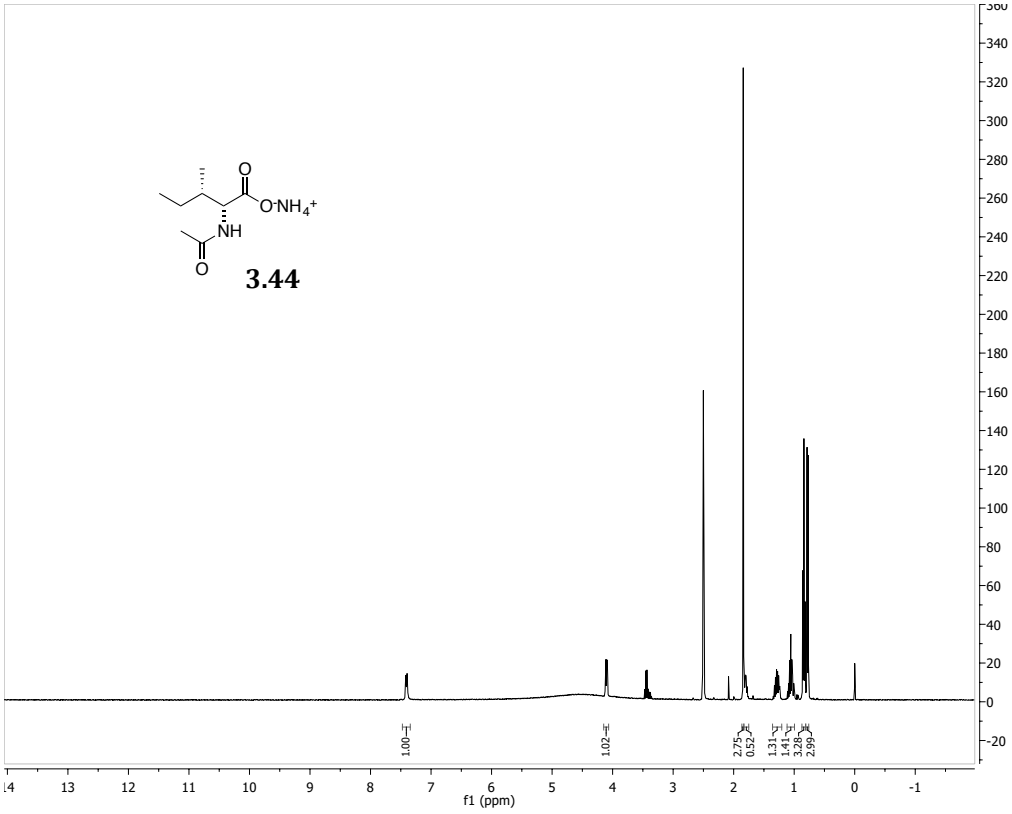

OTBS
OH
3.40
1.00
0.87
0.81
1.14
1.09
0.86
0.70
0.93
1.05
3.41
0.80
1.51
3.48
2.63
6.19
f1 (Hz)



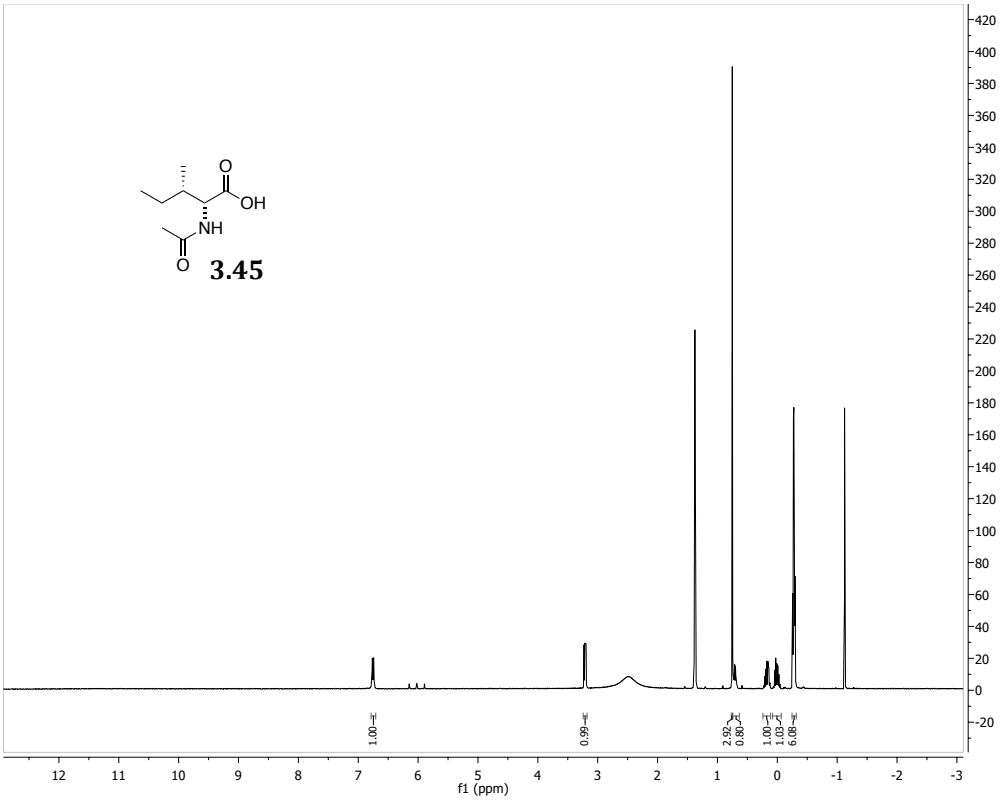
3.41

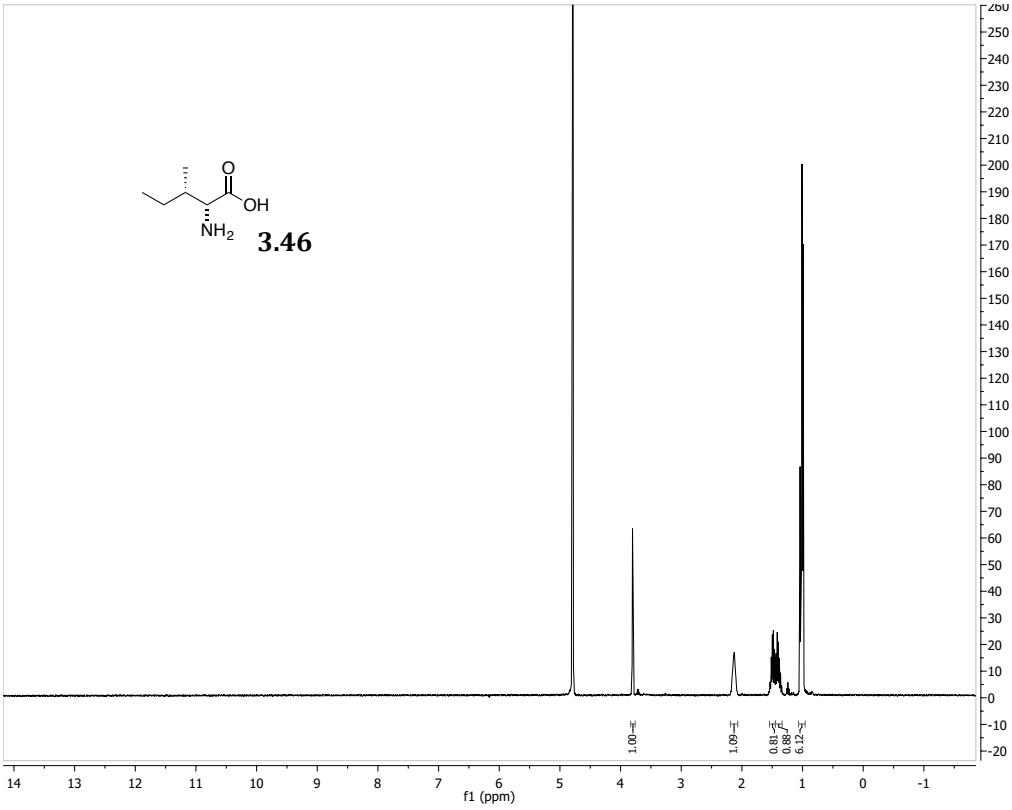

OTBS
O
H
O
O
N
O
O
3.42
f1 (ppm)

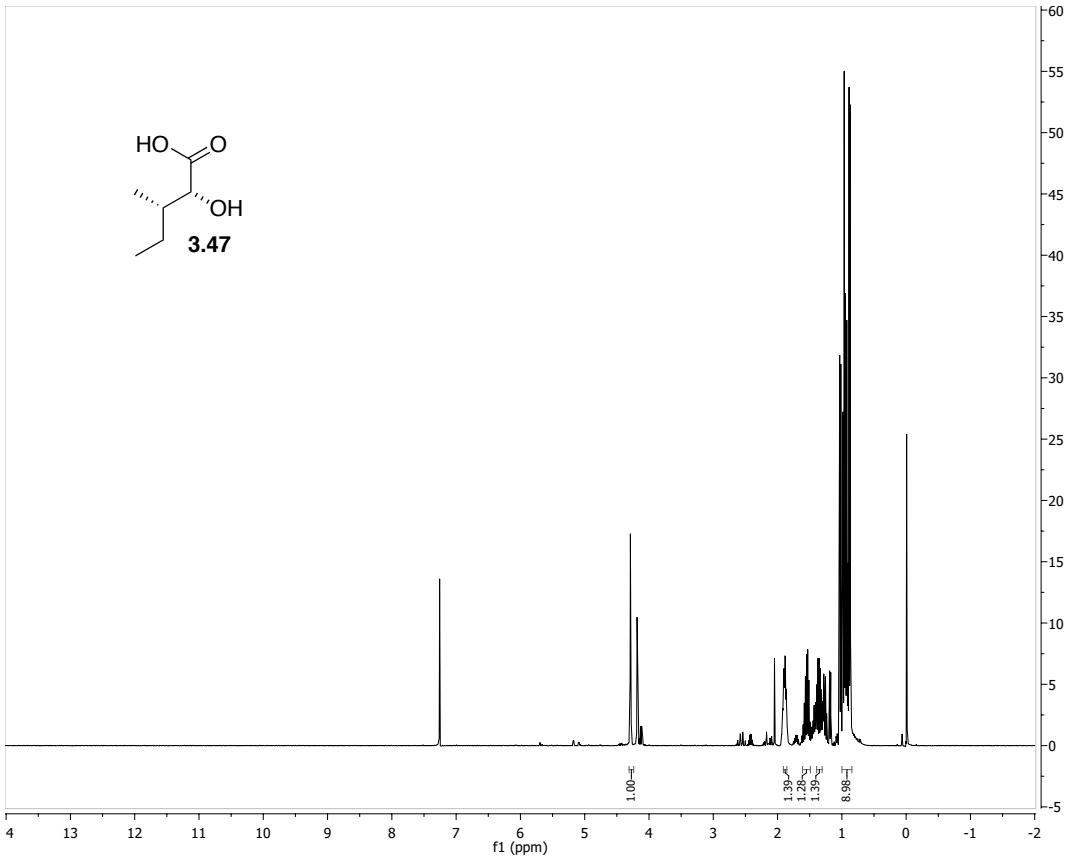

O
OH
NH
O
3.43
0.76
1.00
0.97
3.27
2.74
1.80
6.02
f1 (ppm)

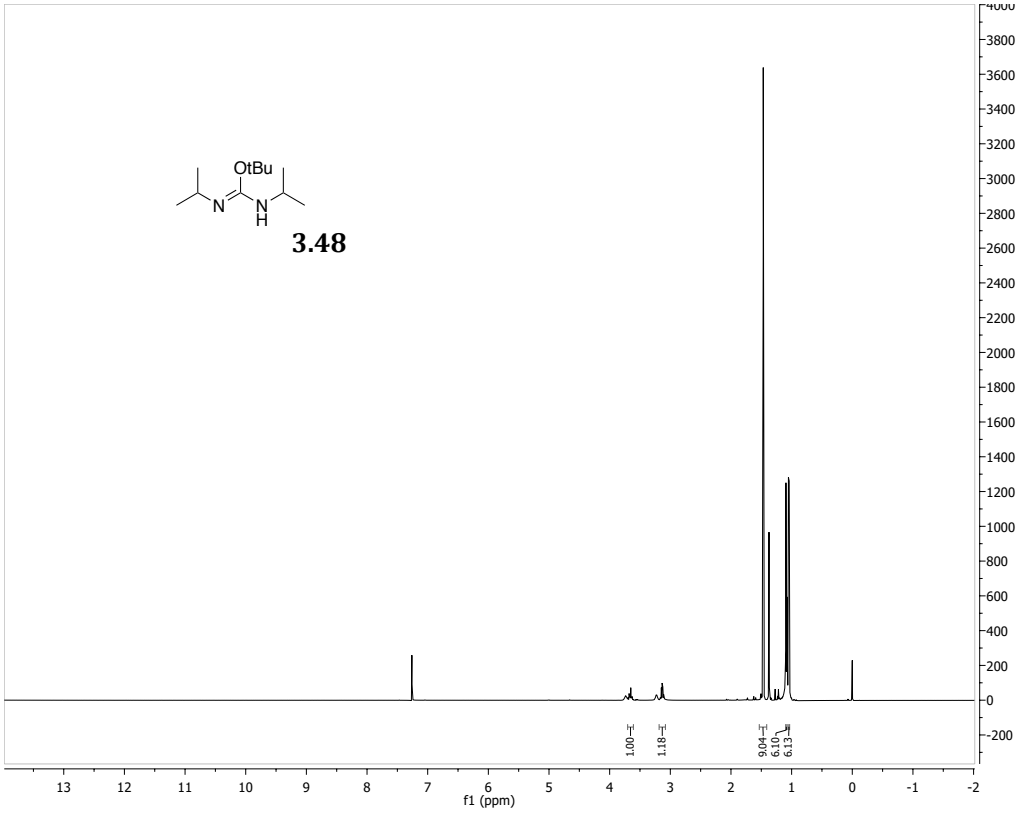


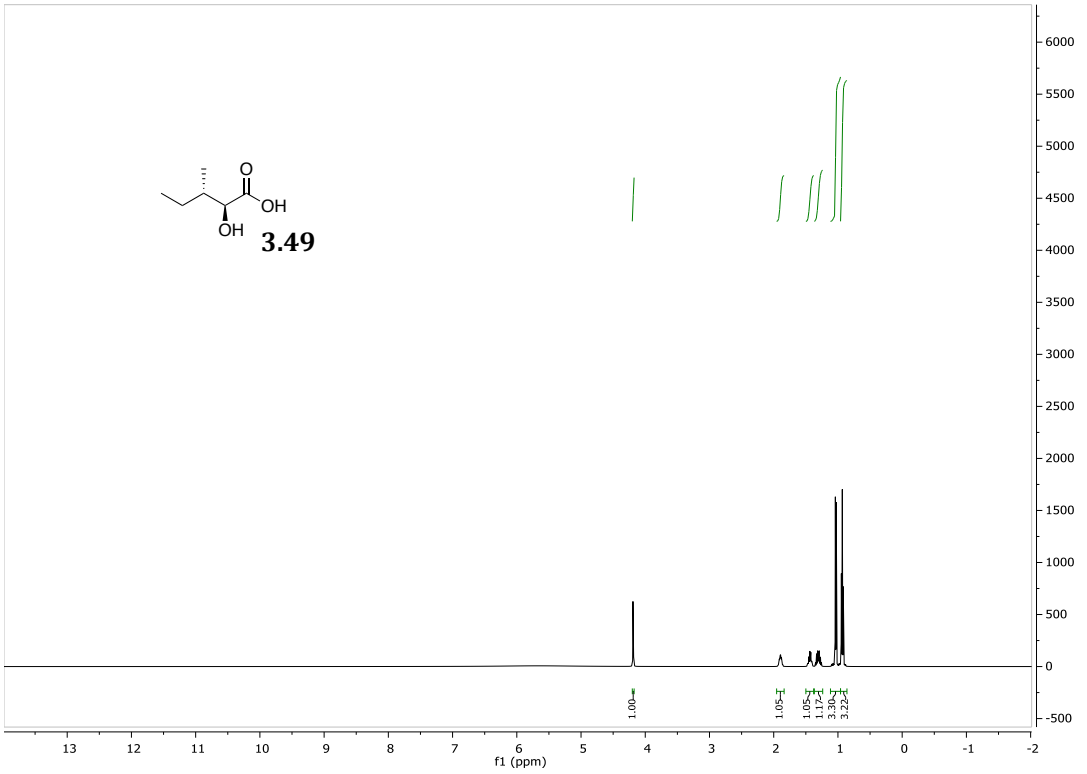
3.44

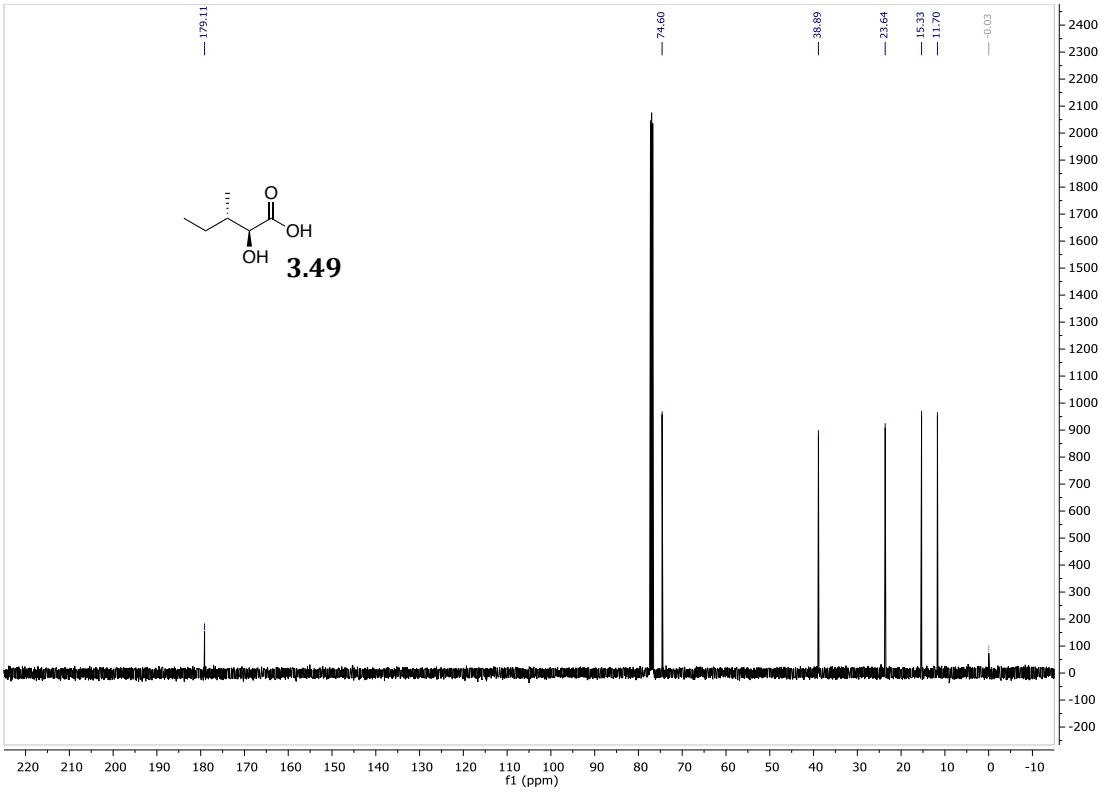

O
OH
NH
O
3.45
1.00
0.99
2.92
0.80
1.00
1.03
6.08
f1 (ppm)

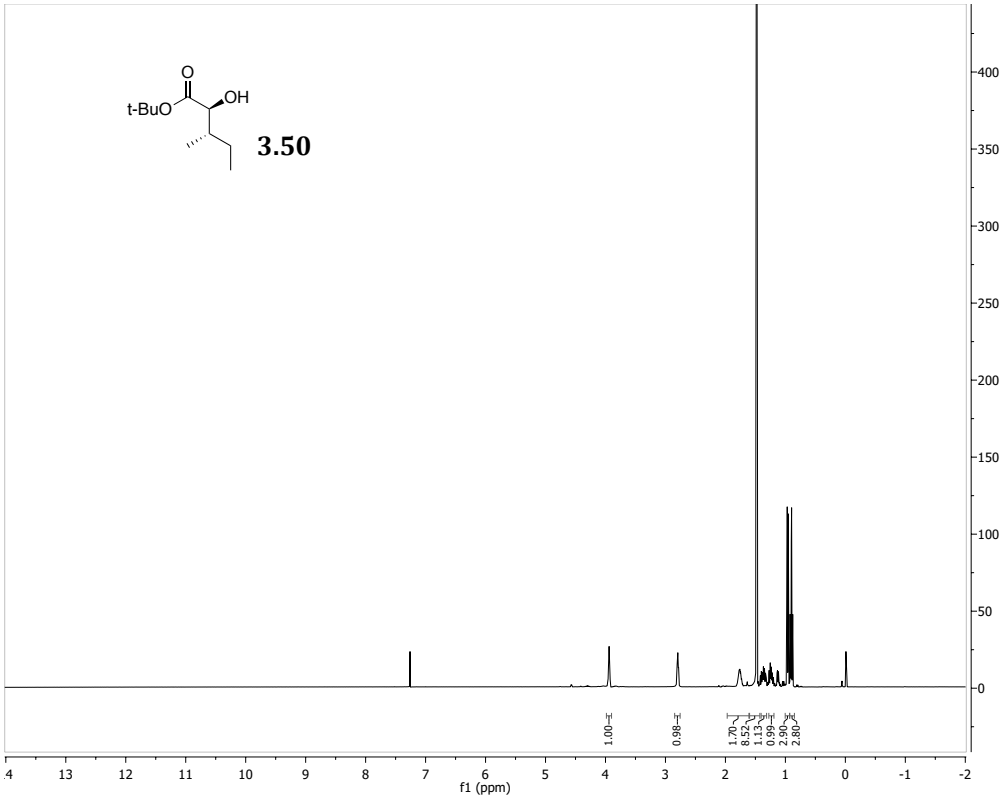

O
OH
NH2
3.46
1.00
1.09
0.81
0.88
6.12
f1 (ppm)

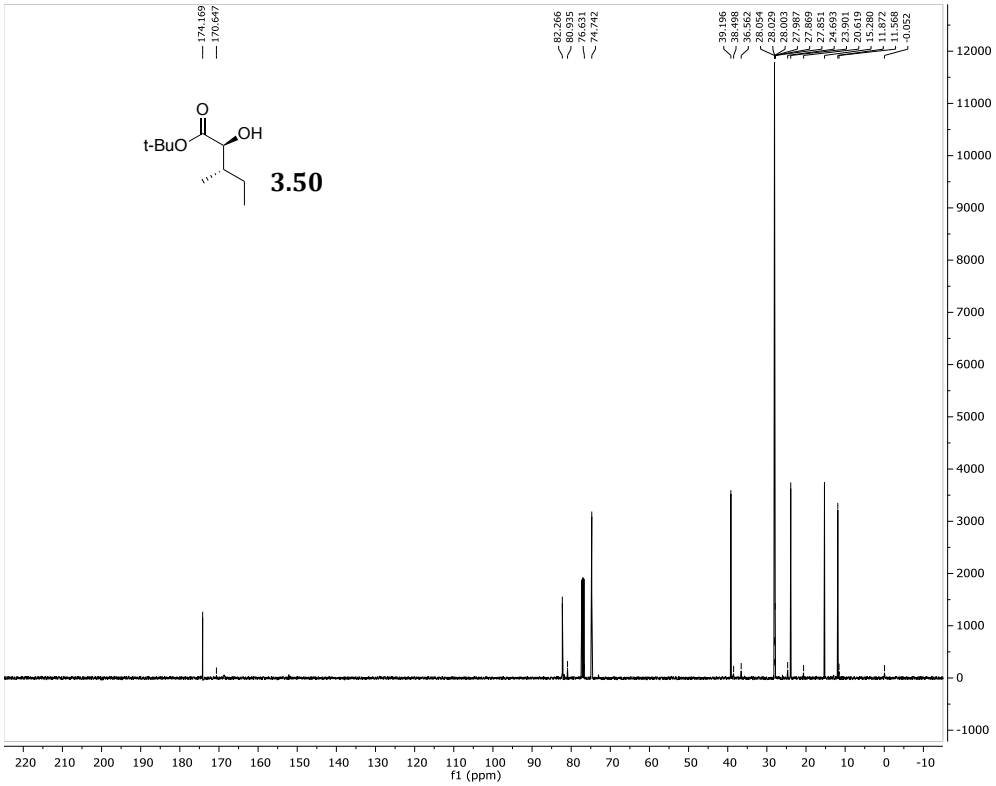

HO
O
OH
3.47
1.00
1.39
1.28
1.39
8.98
f1 (ppm)

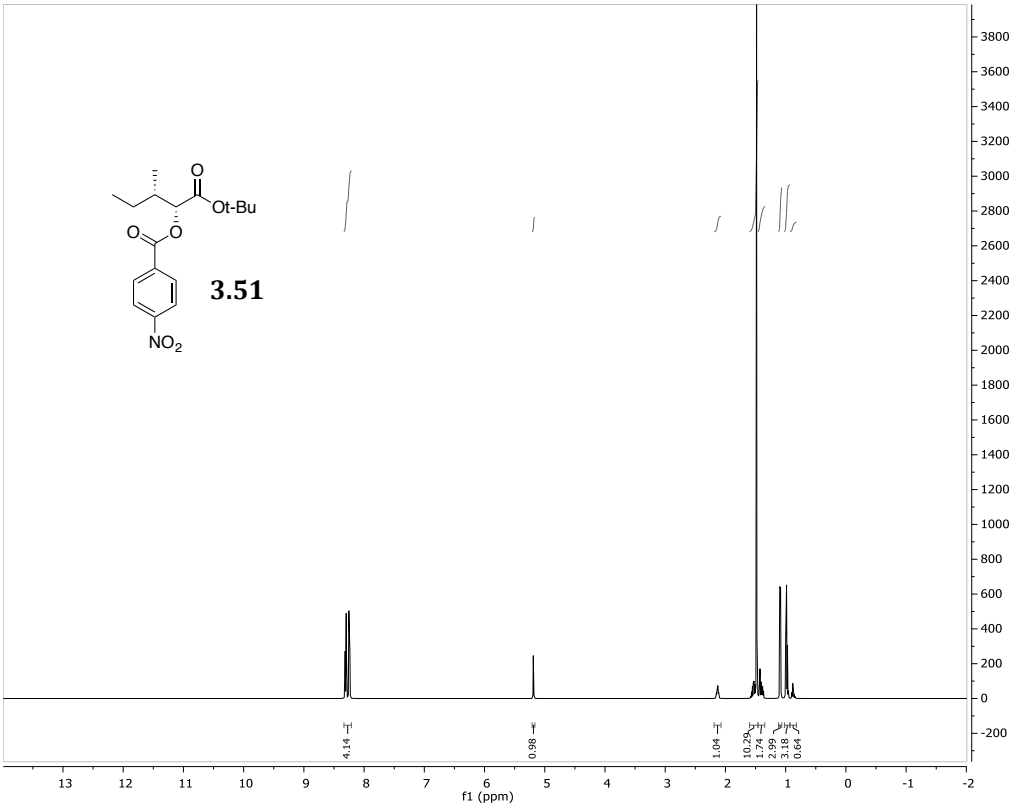

OtBu
N
N
H
3.48
1.00
1.18
9.04
6.10
6.13
f1 (ppm)

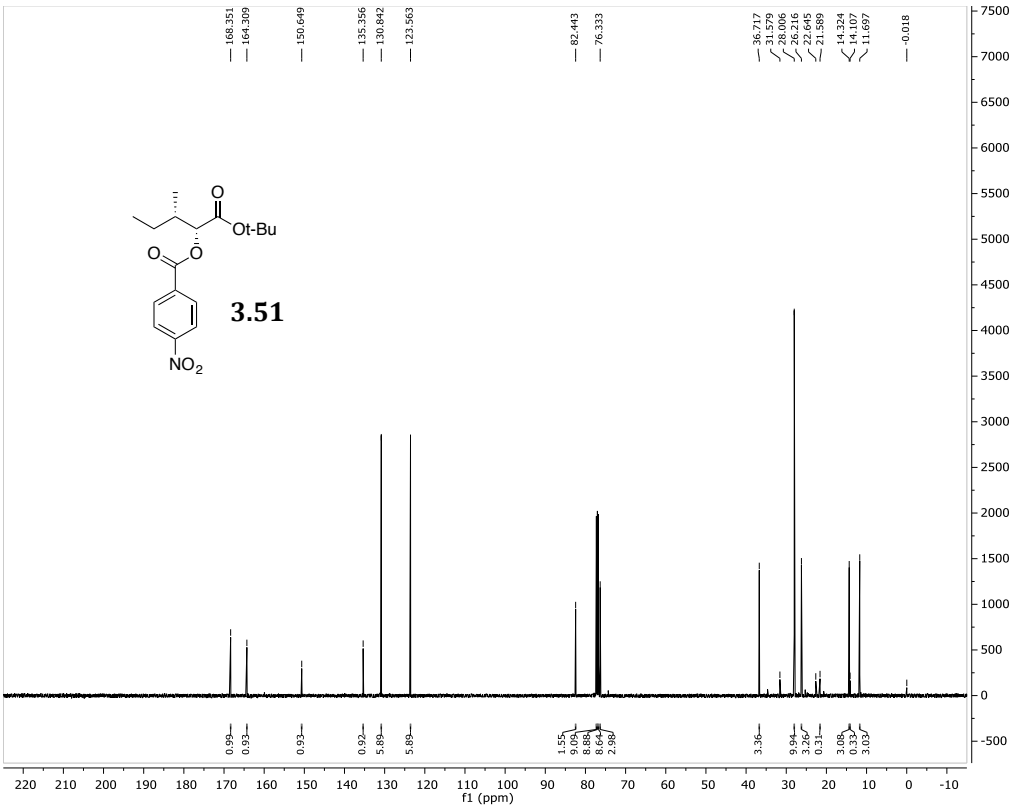

O
OH
OH
3.49
1.00
1.05
1.05
1.17
3.30
3.22
f1 (ppm)

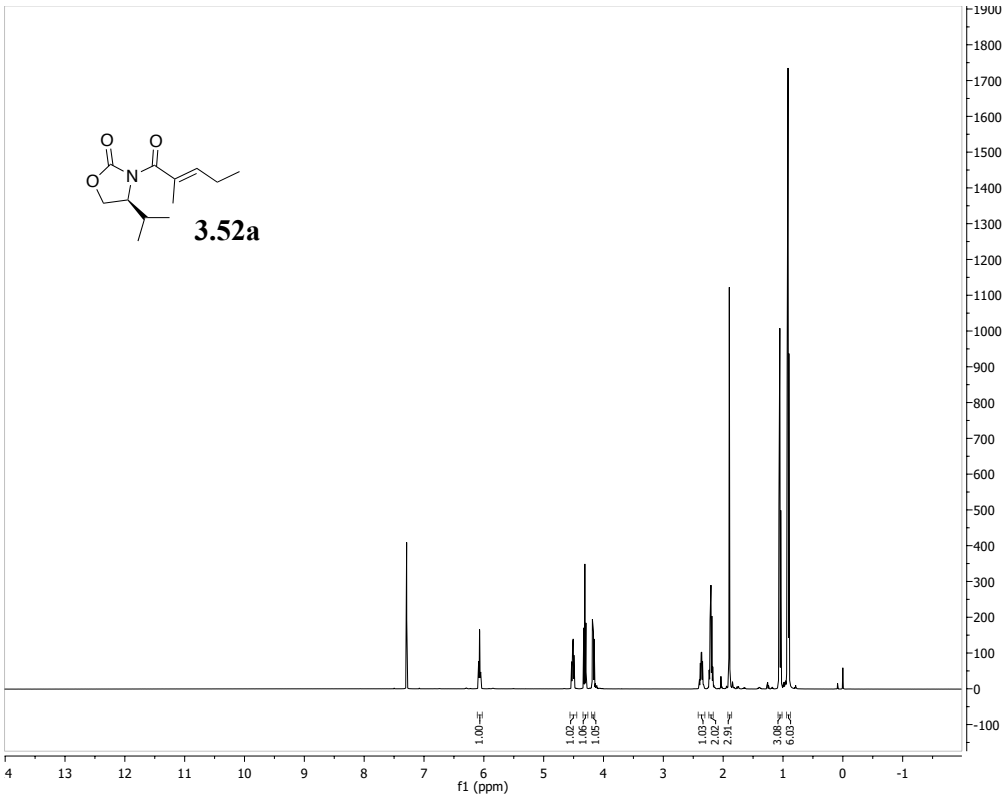

179.11
74.60
38.89
23.64
15.33
11.70
-0.03
O
OH
OH
3.49
f1 (ppm)

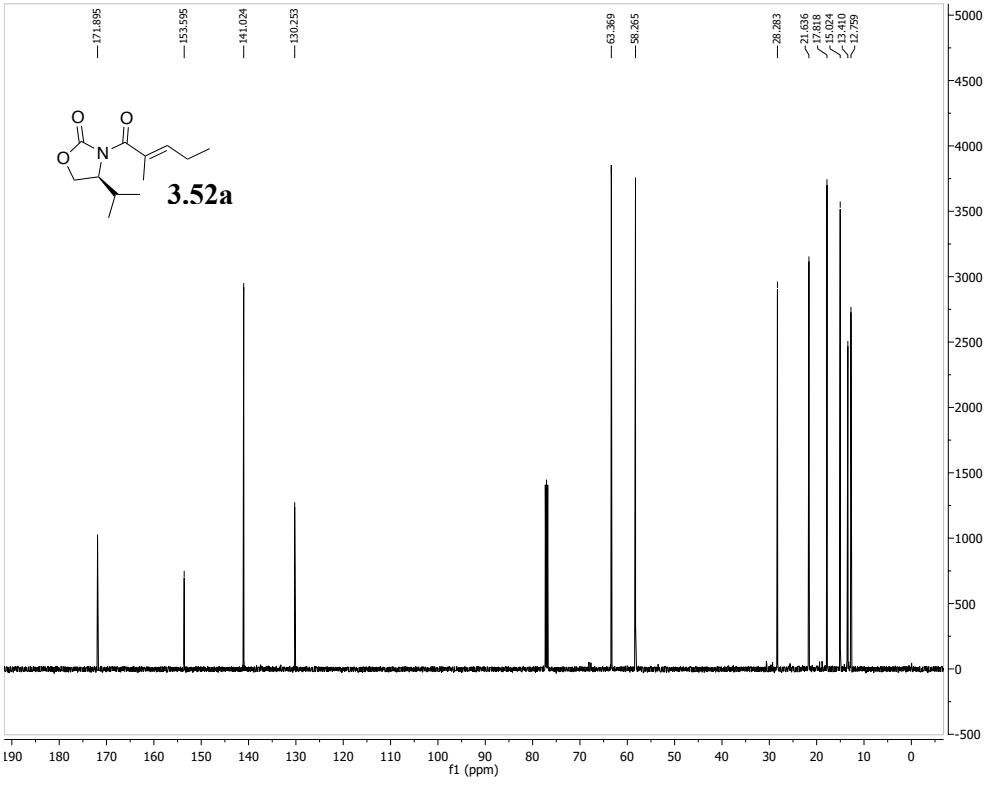

t-BuO
OH
3.50
f1 (ppm)


t-BuO
OH
3.50
f1 (ppm)


Ot-Bu
O
O
O
NO2
3.51
4.14
0.98
1.04
10.29
1.74
2.99
3.18
0.64
f1 (ppm)


168.351
164.309
150.649
135.356
130.842
123.563
82.443
76.333
36.717
31.579
28.006
26.216
22.645
21.589
14.324
14.107
11.697
-0.018
Ot-Bu
O
O
O
NO2
3.51
f1 (ppm)


3.52a
1.00
1.02
1.06
1.05
1.03
2.02
2.91
3.08
6.03
f1 (ppm)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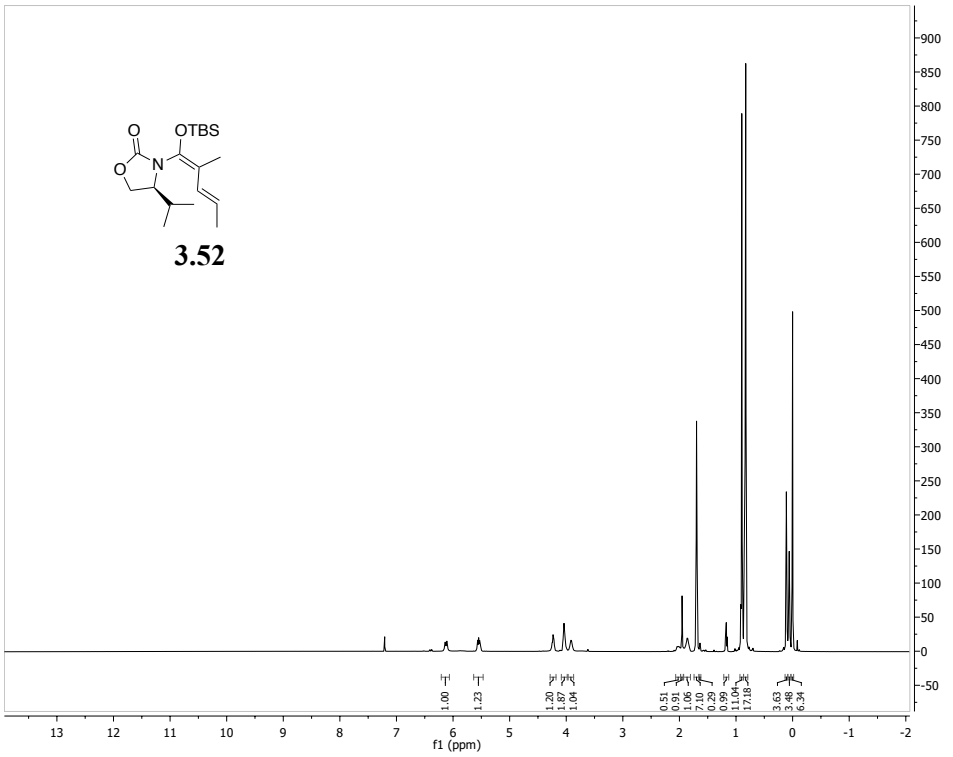
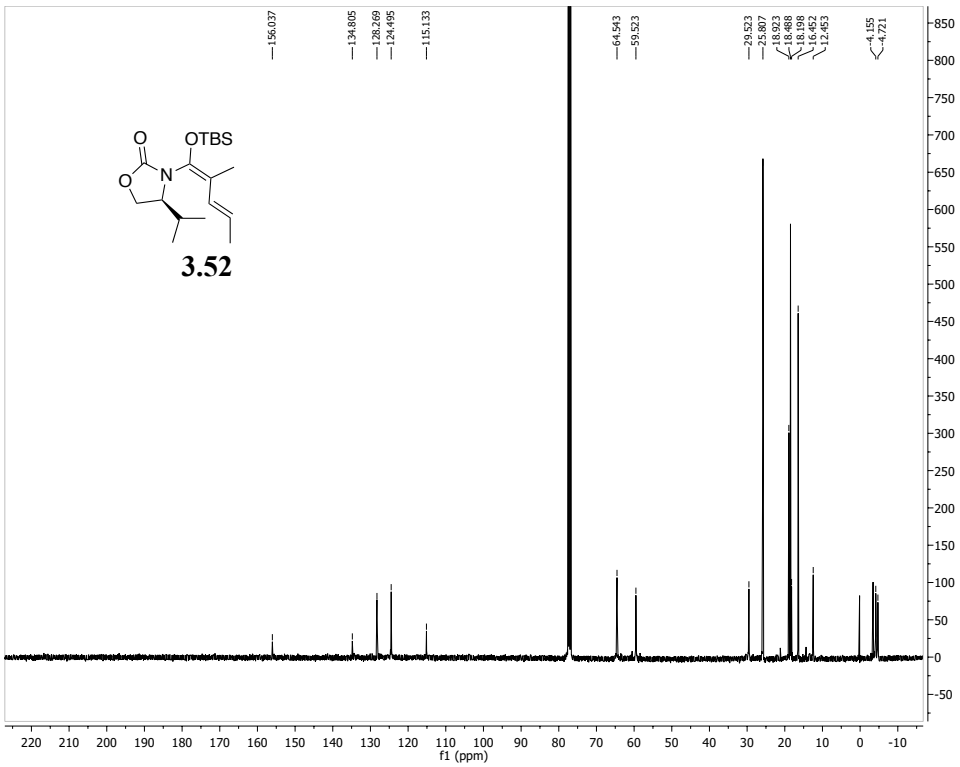
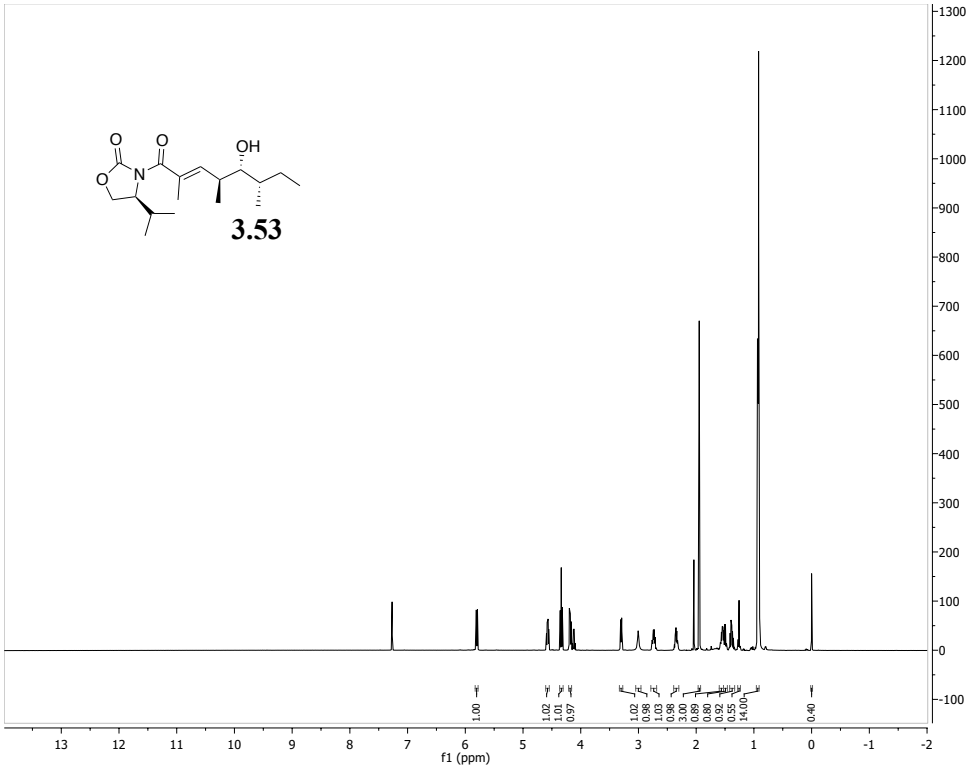
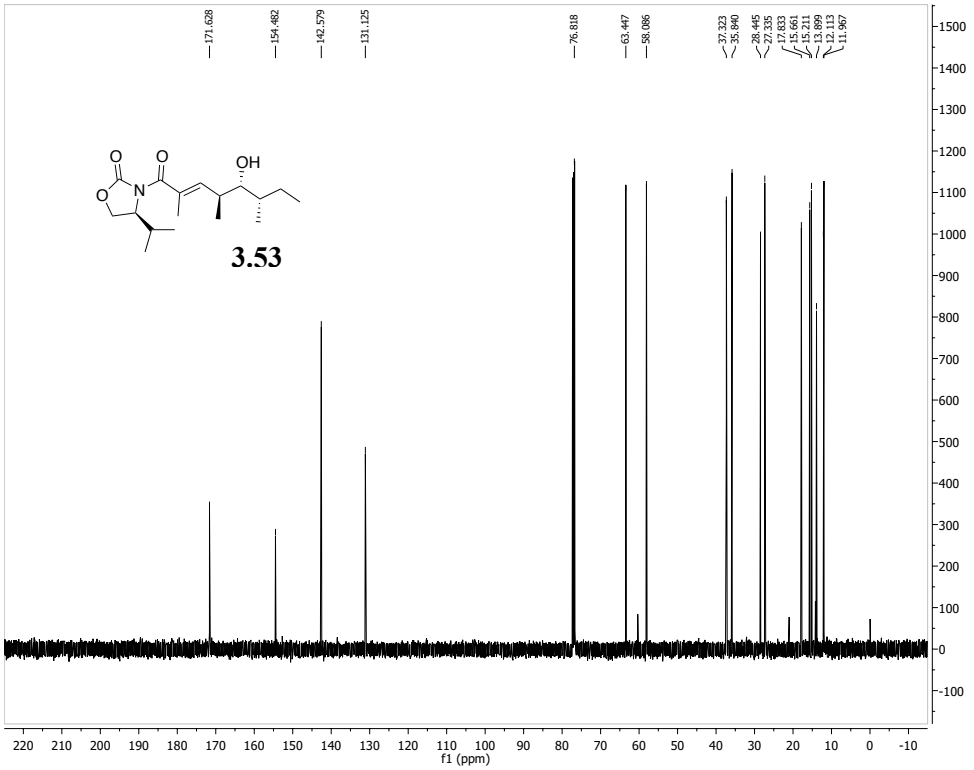
153.595
141.024
130.253
63.369
58.265
28.283
21.636
17.818
15.024
13.410
12.759
3.52a
f1 (ppm)


O
OTBS
O
N
3.52
1.00
1.23
1.20
1.87
1.04
0.51
0.91
1.06
7.10
0.29
0.99
1.04
17.18
3.63
3.48
6.34
f1 (ppm)


156.037
134.805
128.269
124.495
115.133
64.543
59.523
29.523
25.807
18.923
18.488
18.198
16.452
12.453
4.155
-4.721
O
OTBS
O
N
3.52
f1 (ppm)


3.53
f1 (ppm)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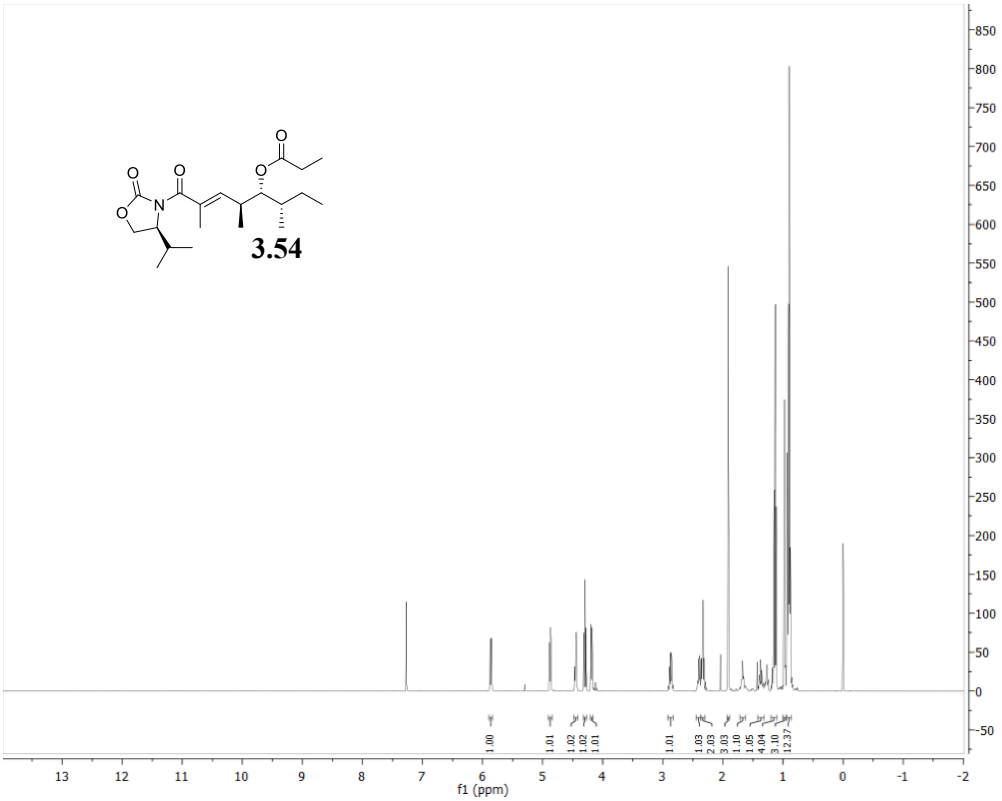
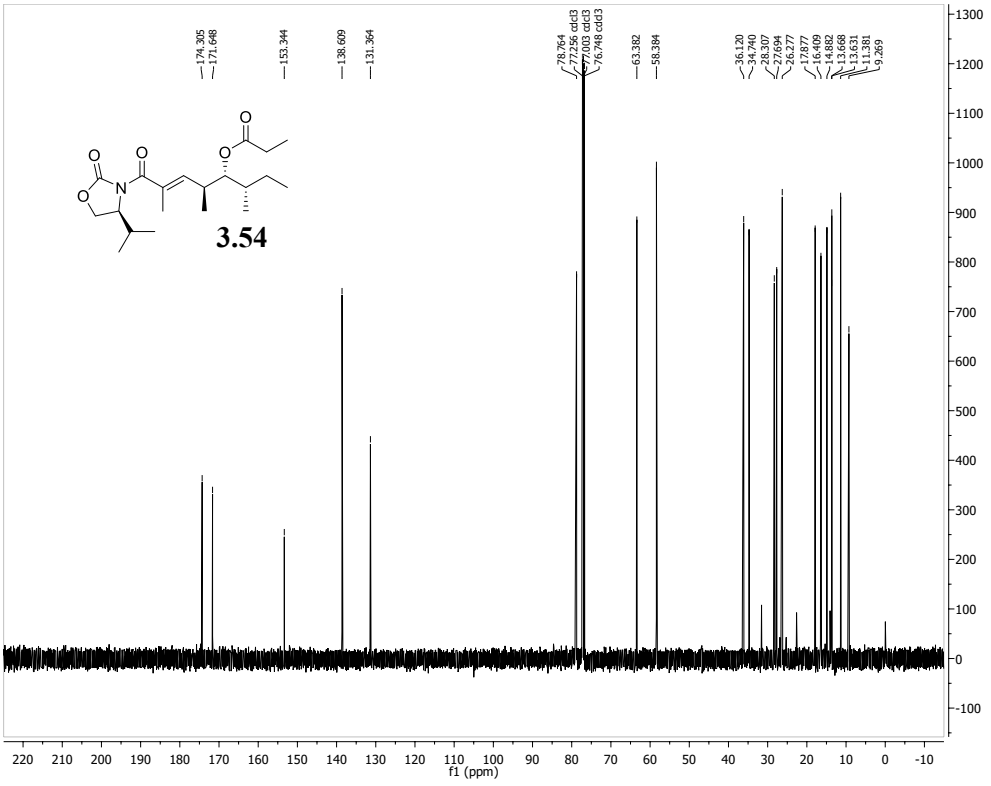
154.482
142.579
131.125
76.818
63.447
58.086
37.323
35.840
28.445
27.335
17.833
15.661
15.211
13.899
12.113
11.967
3.53
f1 (ppm)


3.54
f1 (ppm)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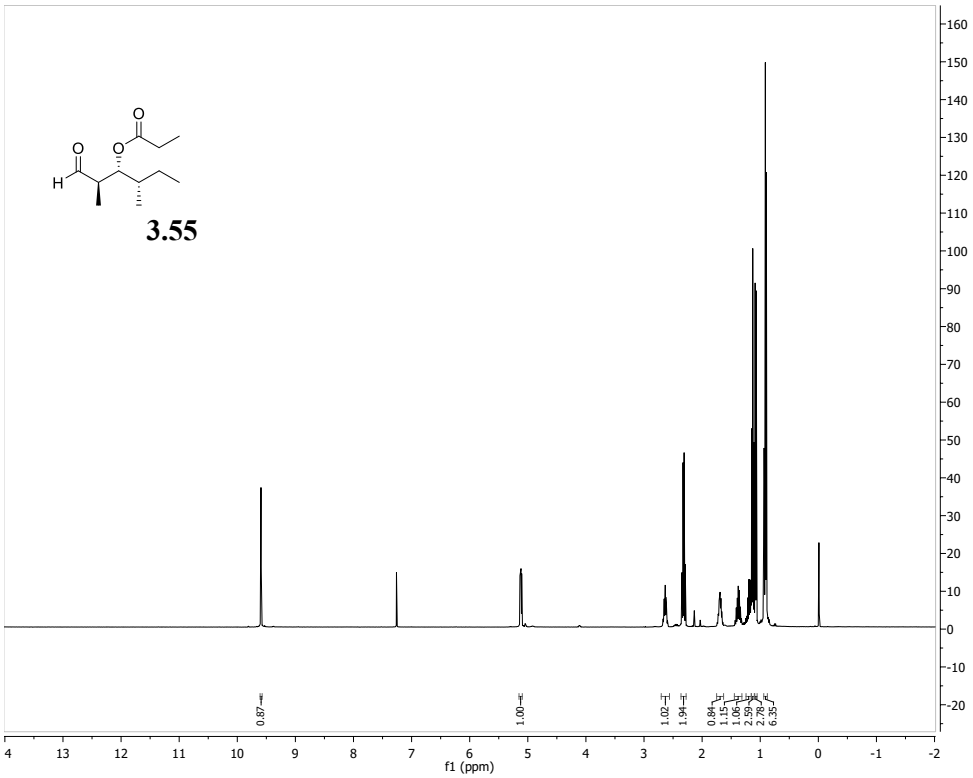
171.648
153.344
138.609
131.364
78.764
77.256 cdcl3
77.003 cdcl3
76.748 cdcl3
63.382
58.384
36.120
34.240
28.307
27.694
26.277
17.877
16.409
14.882
13.668
13.631
11.381
9.269
3.54
f1 (ppm)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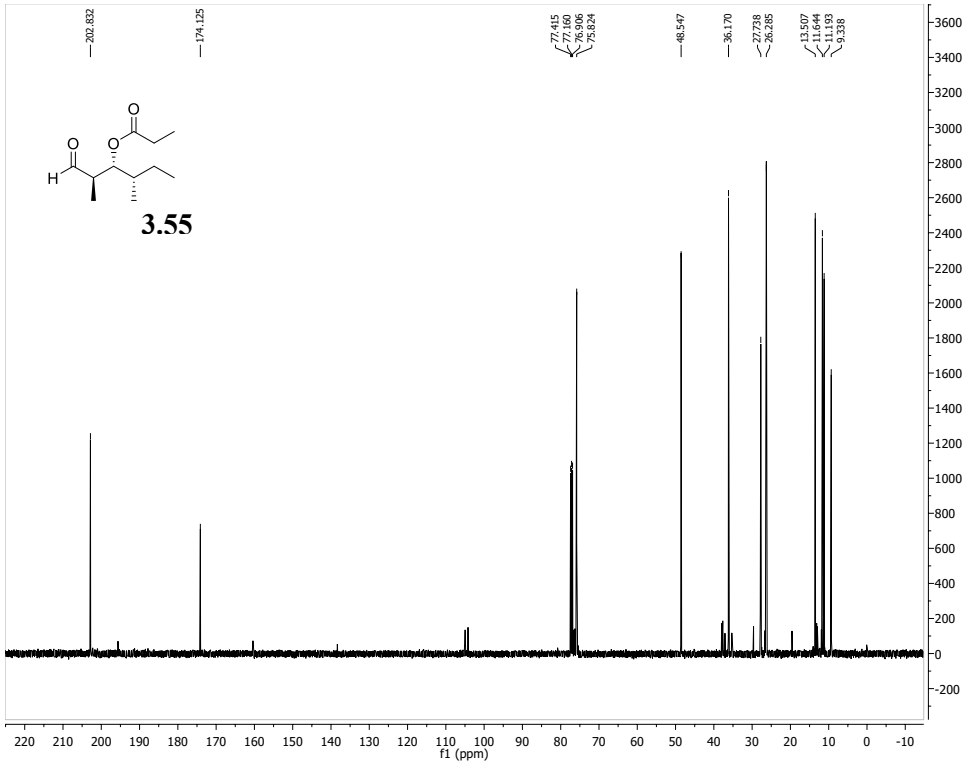
1.94
0.84
1.15
1.06
2.59
2.78
6.35
f1 (ppm)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77.415
77.160
76.906
75.824
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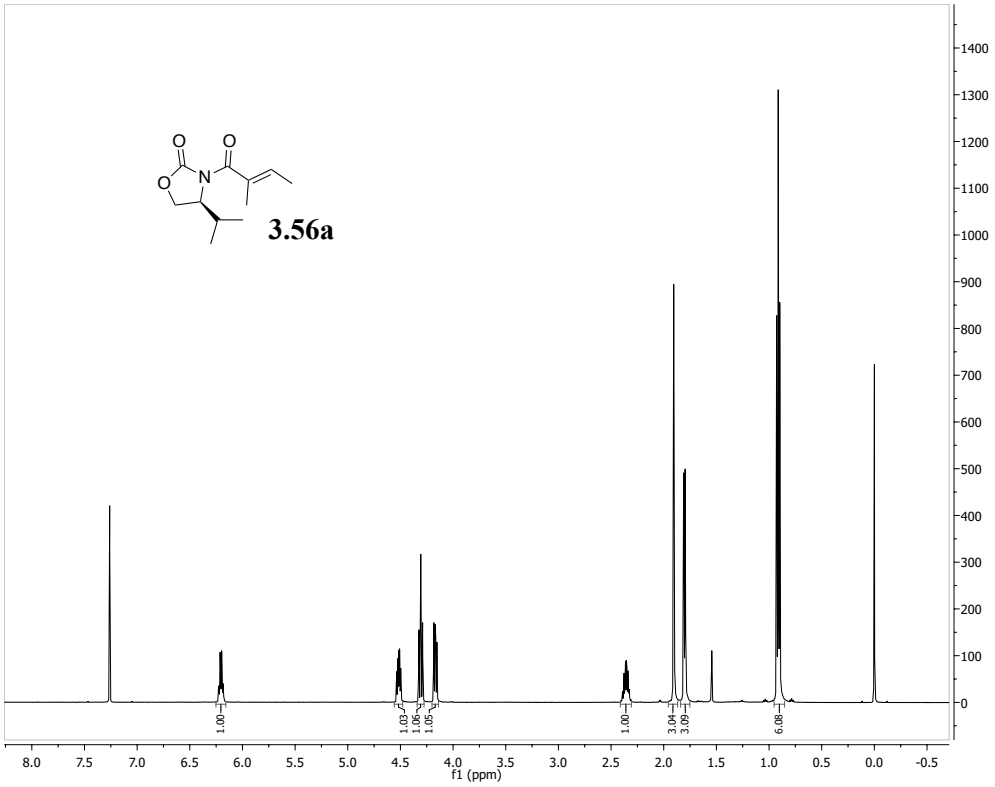
36.170
27.738
26.285
13.507
11.644
11.193
9.338
3.55
f1 (ppm)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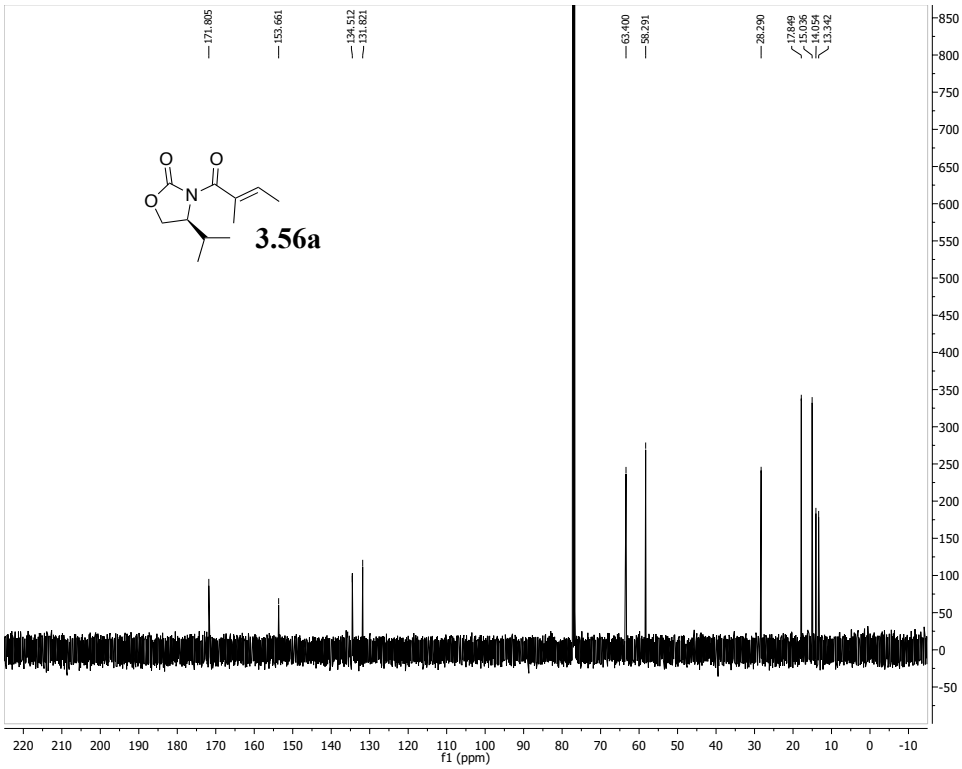
1.03
1.06
1.05
1.00
3.04
3.05
6.08
f1 (ppm)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153.661
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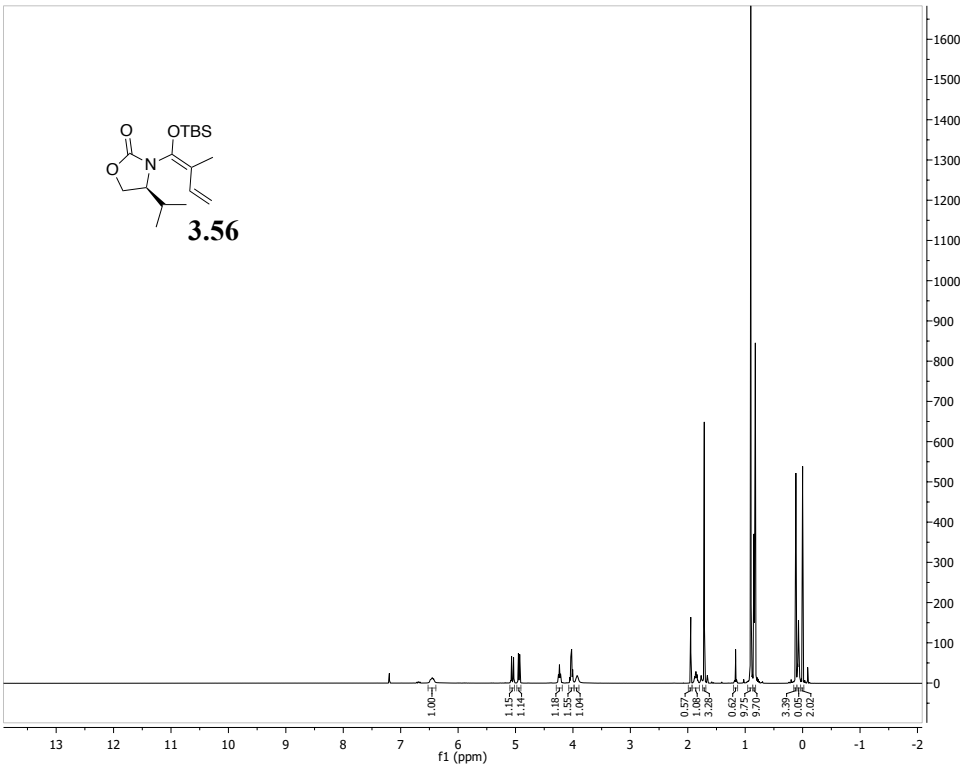
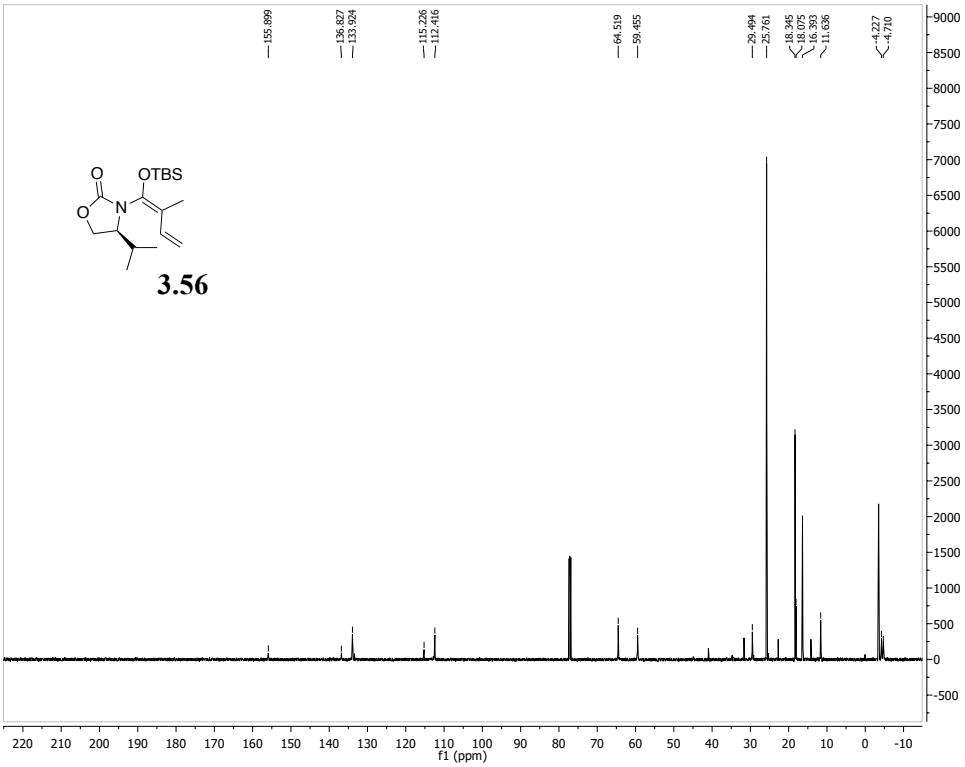
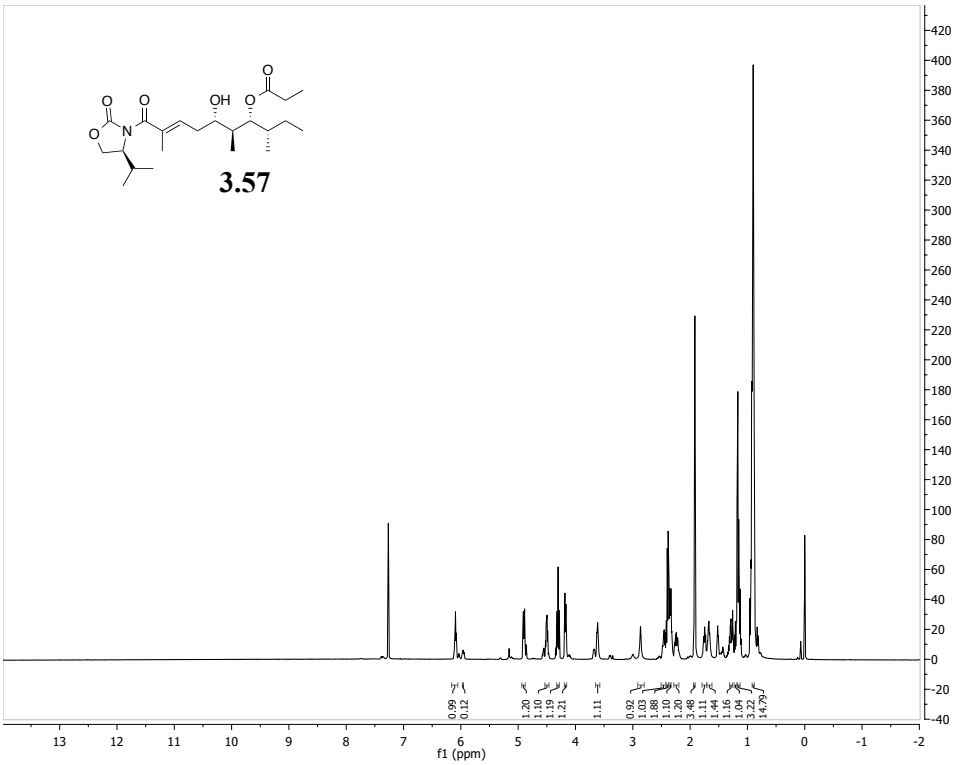
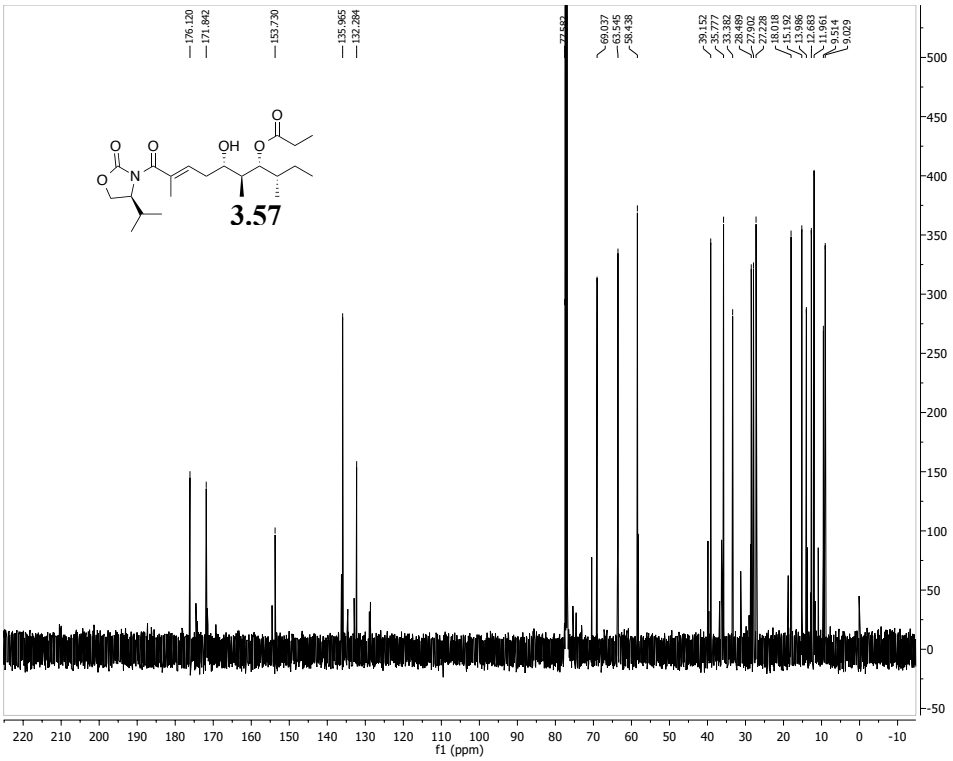
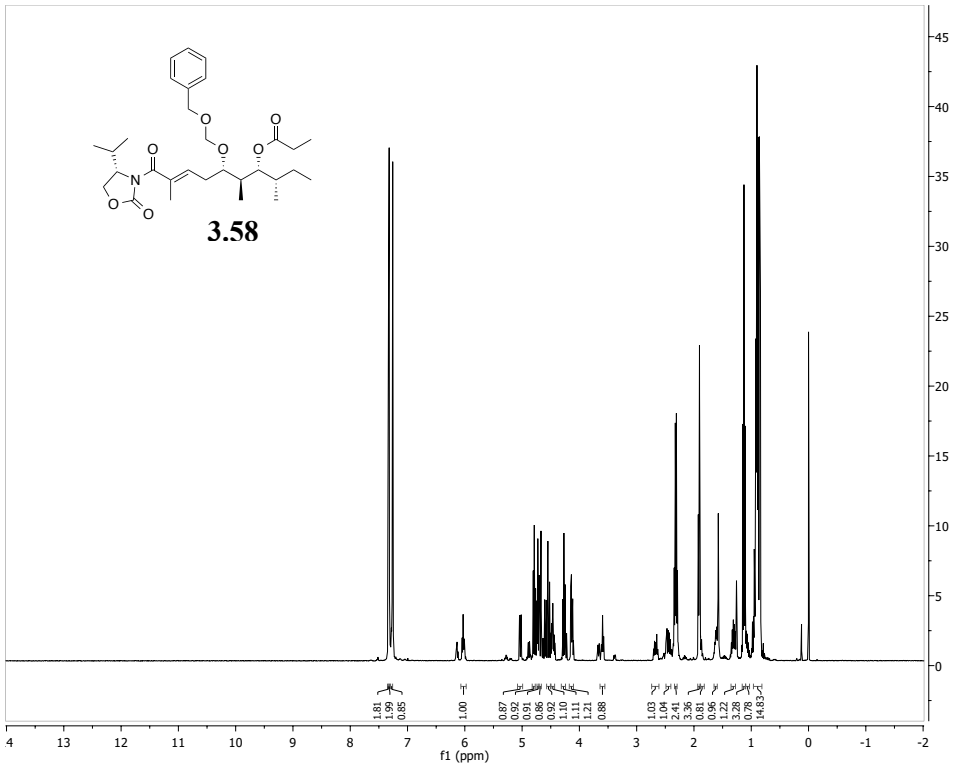
58.291
28.290
17.849
15.036
14.054
13.342
3.56a
f1 (ppm)

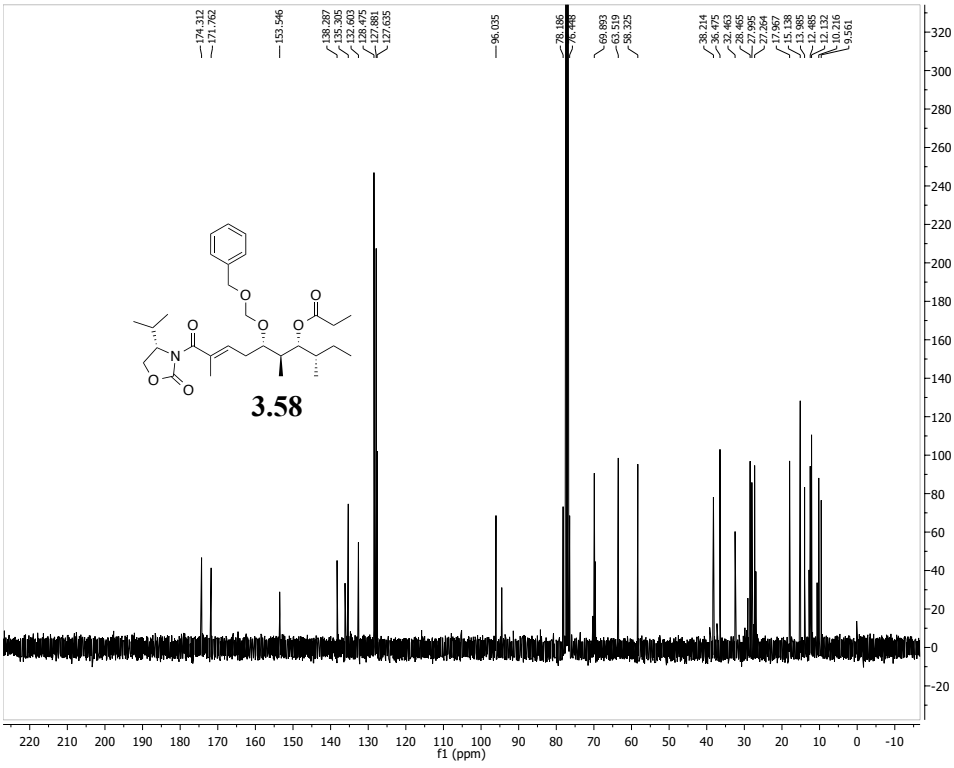

O
OTBS
O
N
3.56
1.00
1.15
1.14
1.18
1.55
1.04
0.57
1.08
3.28
0.62
9.75
9.70
3.39
0.05
2.02
f1 (ppm)

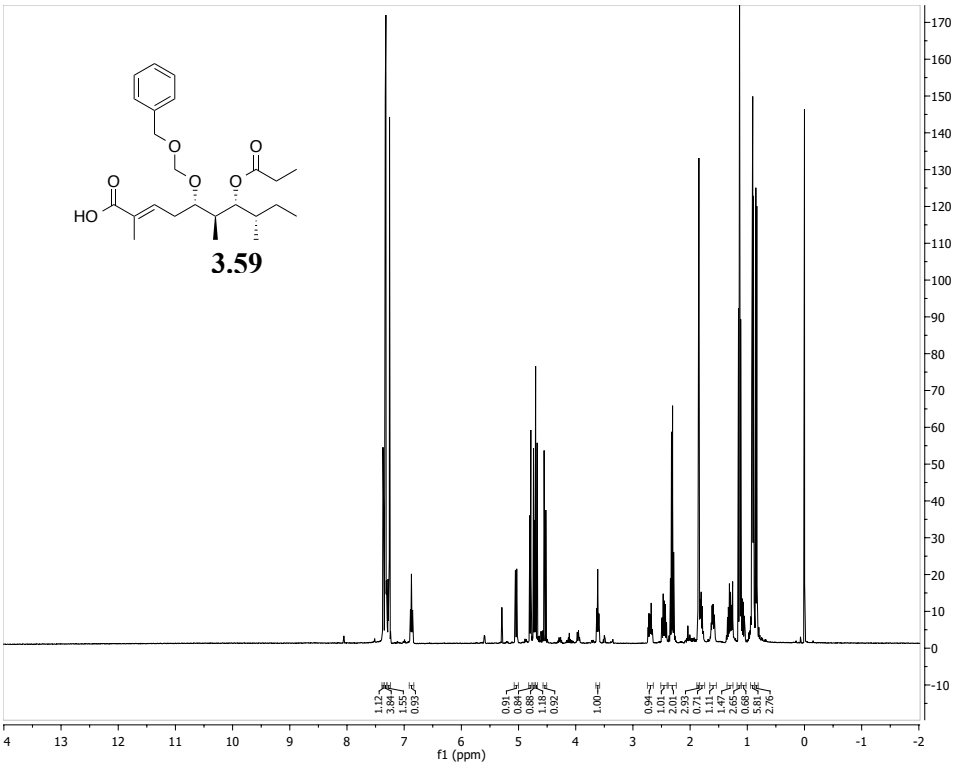

155.899
136.827
133.924
115.226
112.416
64.519
59.455
29.494
25.761
18.345
18.075
16.393
11.656
-4.227
-4.710
O
OTBS
O
N
3.56
f1 (ppm)


3.57
f1 (ppm)

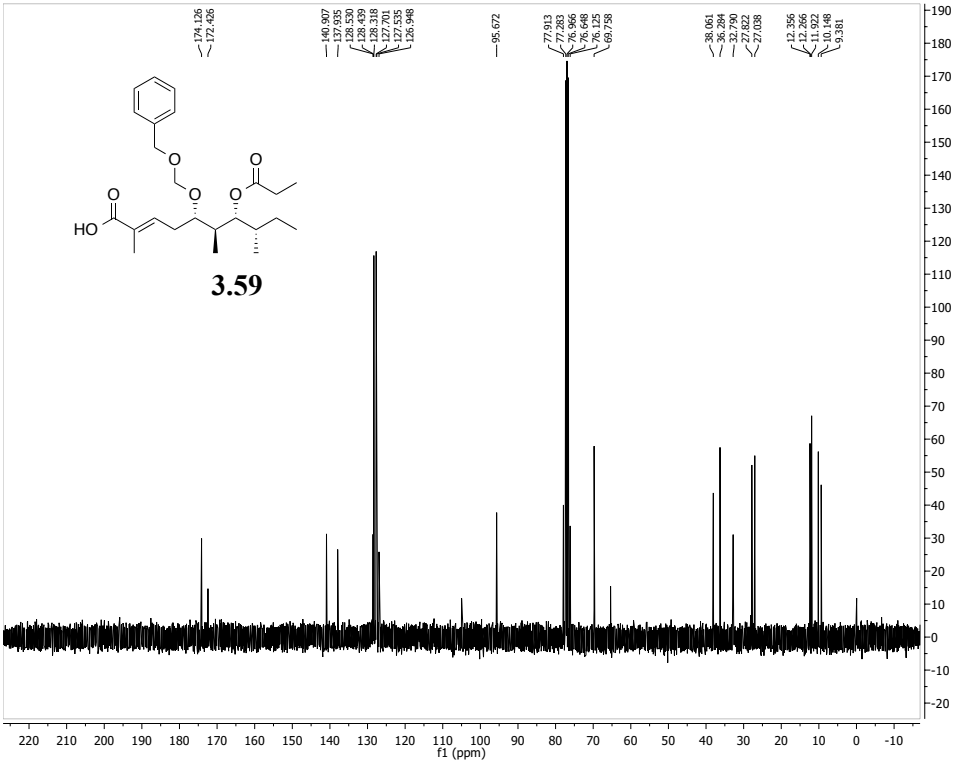

3.57
f1 (ppm)


3.58
f1 (ppm)

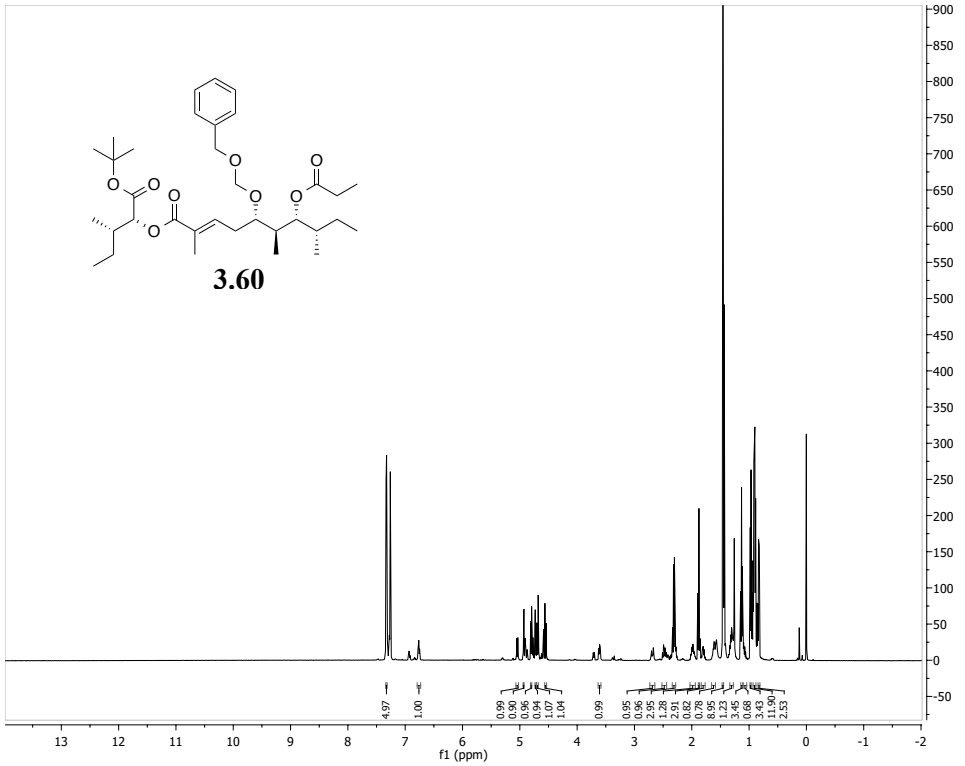

174.312
171.762
153.546
138.287
135.305
132.603
128.475
127.981
127.635
96.035
78.186
76.948
69.893
63.519
38.325
38.214
36.475
32.463
29.665
27.995
27.264
17.967
15.138
13.985
12.485
12.152
10.216
9.561
3.58
f1 (ppm)

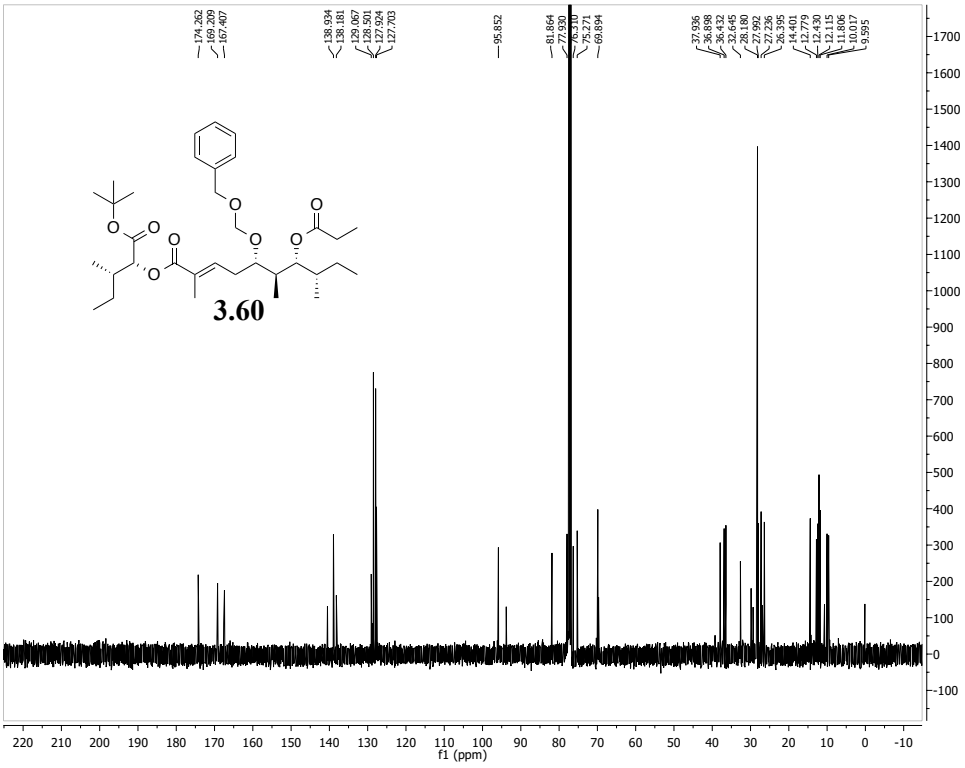

HO
O
O
O
O
O
f1 (ppm)

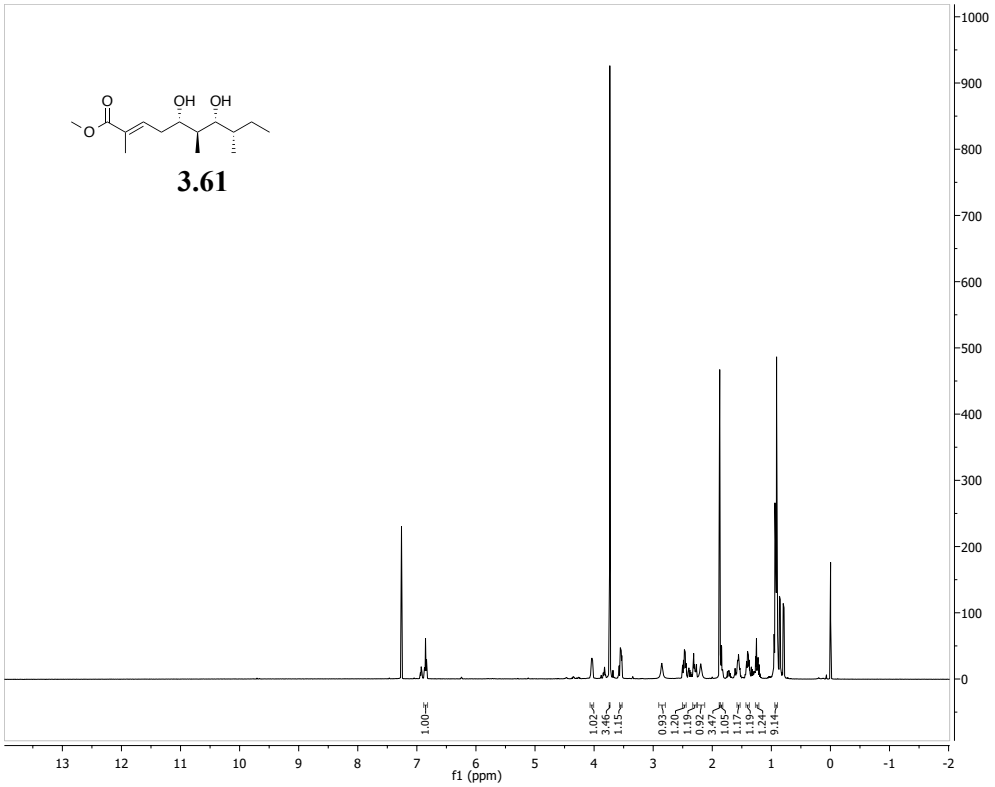
3.59

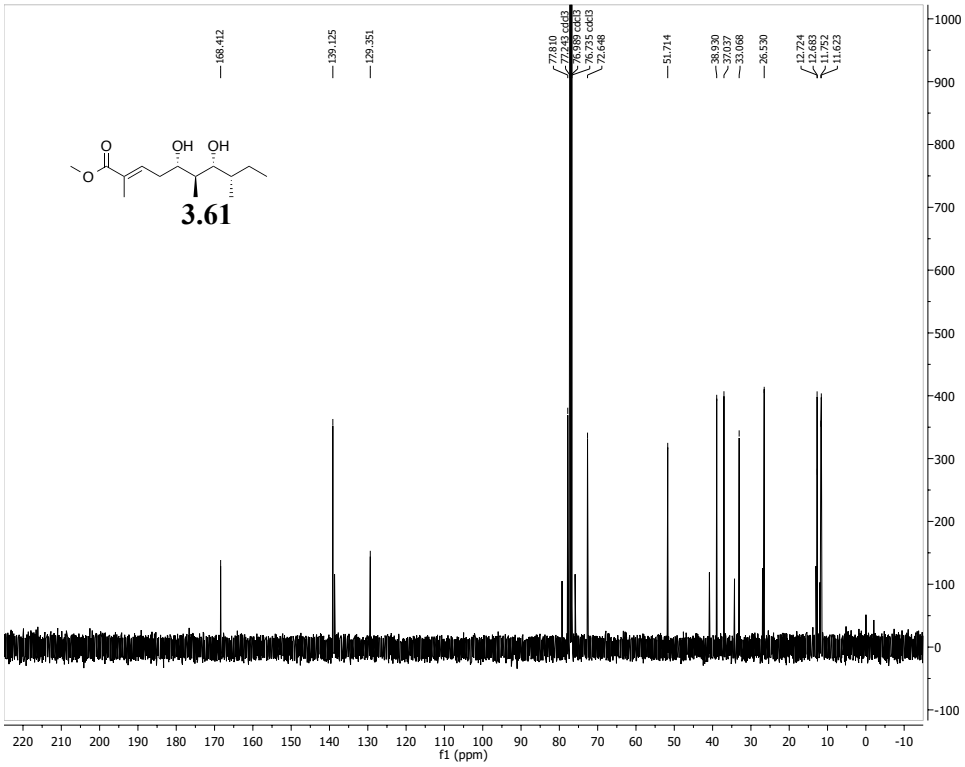

174.126
172.426
140.907
137.935
128.530
128.499
128.315
127.701
127.535
126.948
95.672
77.913
77.283
76.966
76.648
76.125
69.758
38.061
36.284
32.790
27.822
27.038
12.356
12.266
11.922
10.148
9.381
HO
O
O
O
O
O
f1 (ppm)

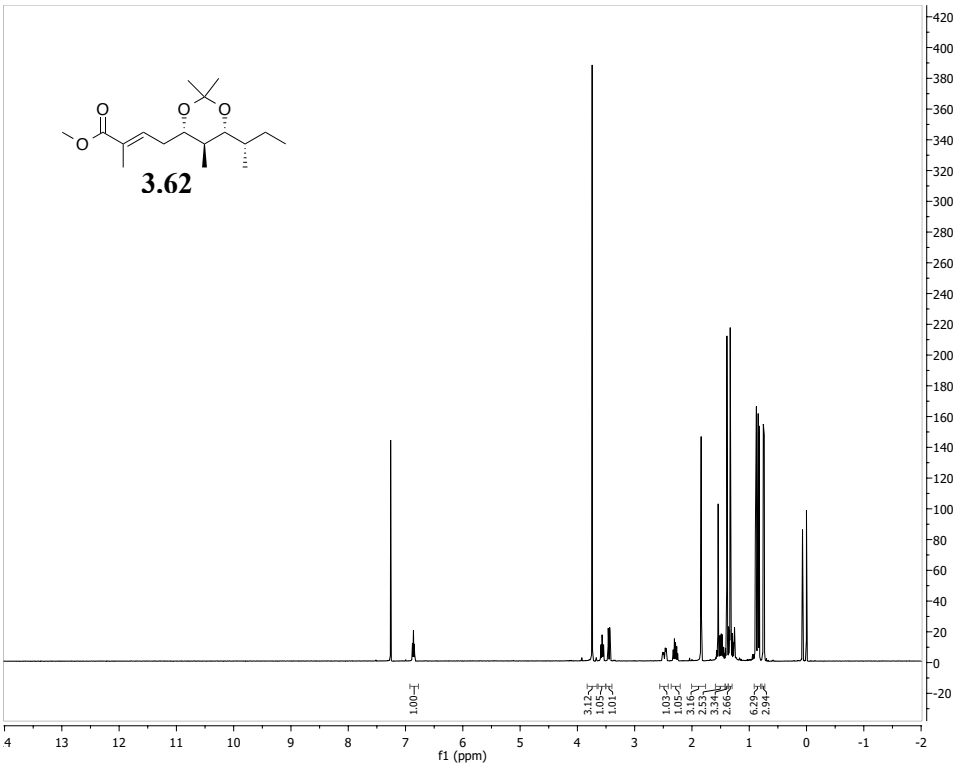
3.59

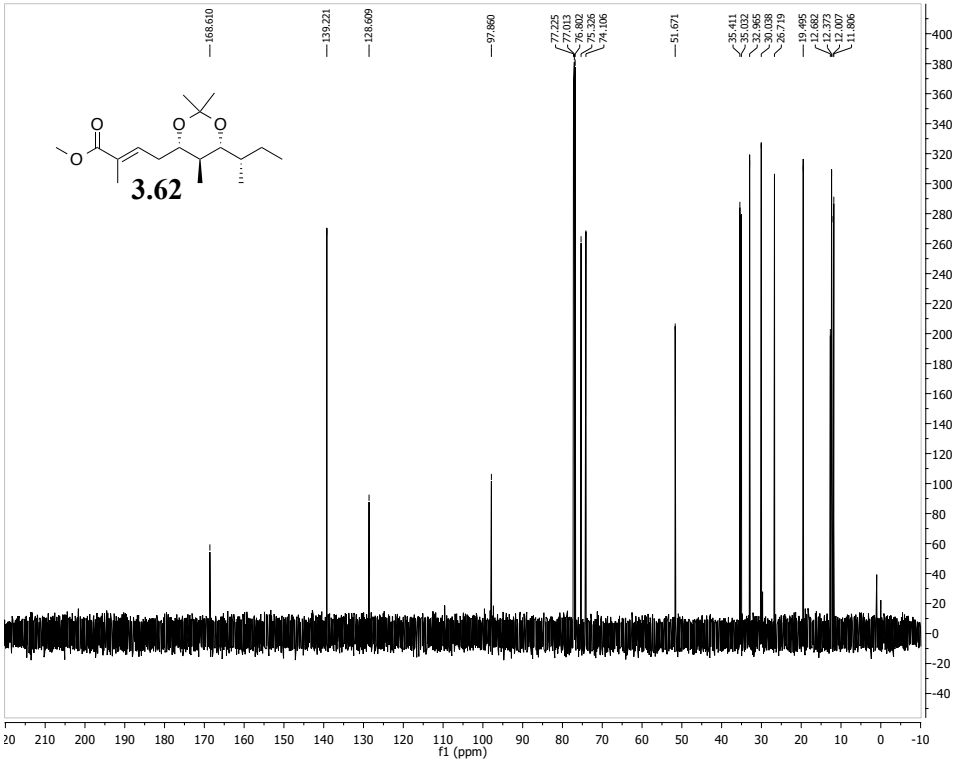

3.60
4.97
1.00
0.99
0.90
0.96
0.94
1.07
1.04
0.99
0.95
0.96
2.95
1.28
2.91
0.82
0.78
8.95
1.23
3.45
0.68
3.43
11.90
2.53
f1 (ppm)

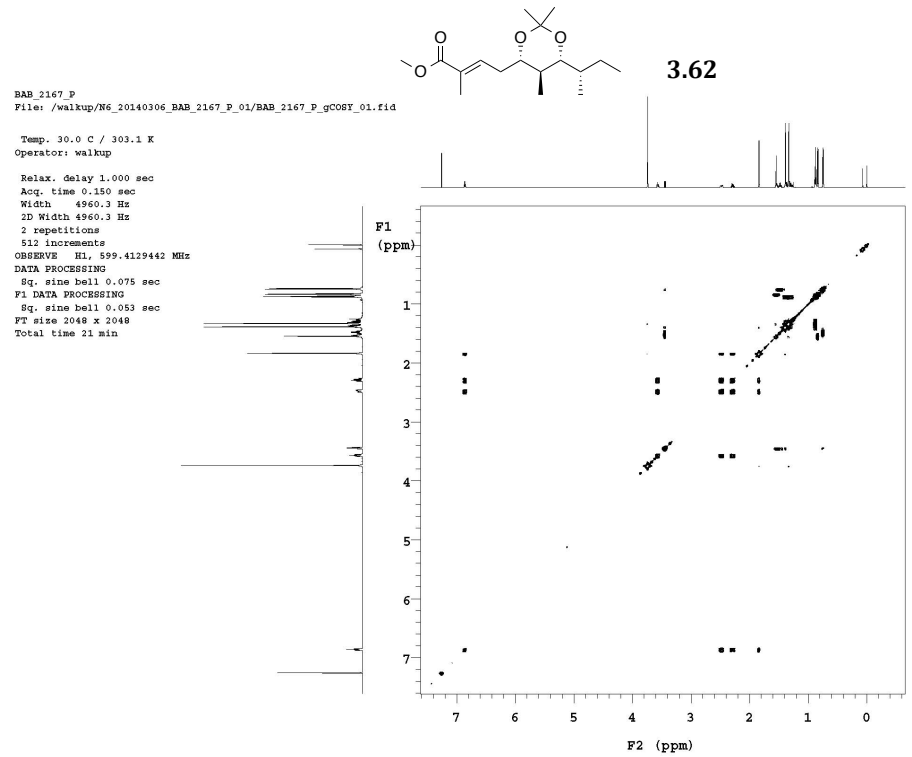

174.262
169.209
167.407
138.934
138.181
129.067
128.501
127.924
127.703
95.852
81.864
77.930
76.310
75.777
69.894
37.936
36.898
36.432
32.645
28.180
27.992
27.296
26.395
14.401
12.779
12.430
12.115
11.806
10.107
9.595
3.60
f1 (ppm)

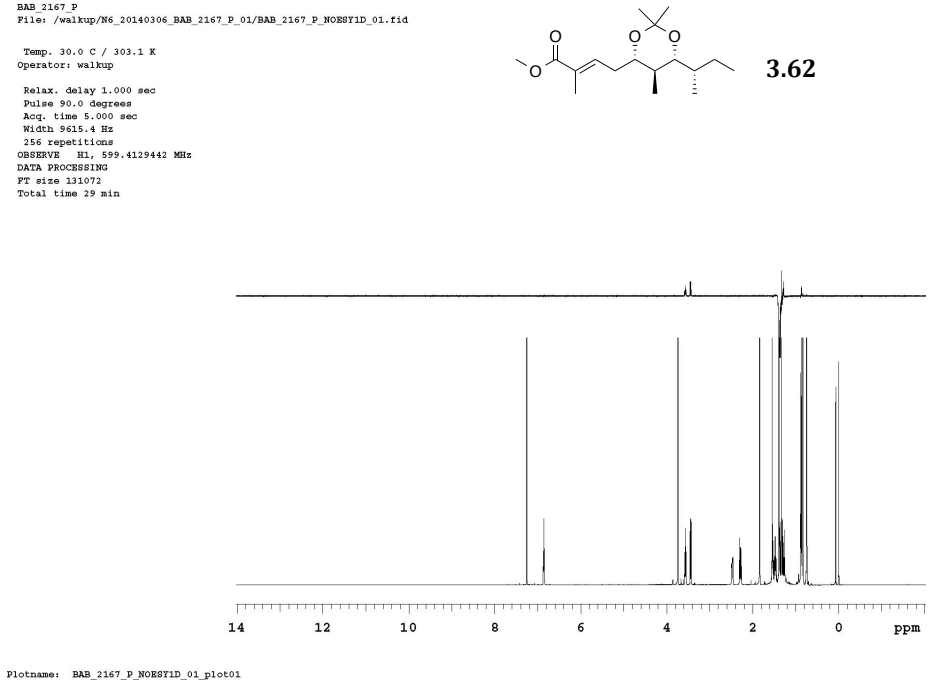

3.61
f1 (ppm)


168.412
139.125
129.351
77.810
77.343 cdcl3
76.899 cdcl3
76.735 cdcl3
72.048
51.714
38.930
33.707
33.068
26.530
12.724
12.683
11.752
11.623
3.61
f1 (ppm)


3.62
1.00
3.12
1.05
1.01
1.03
1.05
3.16
2.53
3.34
2.66
6.29
2.94
f1 (ppm)


168.610
139.221
128.609
97.860
77.225
77.013
76.802
75.326
74.106
51.671
35.411
35.032
32.965
30.038
26.719
19.495
12.682
12.373
12.007
11.866
3.62
f1 (ppm)

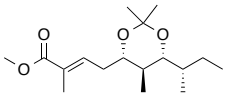

3.62
BAB_2167_P
File: /walkup/N6_20140306_BAB_2167_P_01/BAB_2167_P_gCOSY_01.fid
Temp. 30.0 C / 303.1 K
Operator: walkup
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 4960.3 Hz
2D Width 4960.3 Hz
2 repetitions
512 increments
OBSERVE H1, 599.4129442 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.053 sec
FT size 2048 x 2048
Total time 21 min
F1 (ppm)
F2 (ppm)
Plotname: BAB_2167_P_gCOSY_01_plot01


3.62
BAB_2167_P
File: /walkup/N6_20140306_BAB_2167_P_01/BAB_2167_P_NOESY1D_01.fid
Temp. 30.0 C / 303.1 K
Operator: walkup
Relax. delay 1.000 sec
Pulse 90.0 degrees
Acq. time 5.000 sec
Width 9615.4 Hz
256 repetitions
OBSERVE H1, 599.4129442 MHz
DATA PROCESSING
FT size 131072
Total time 29 min
ppm
Plotname: BAB_2167_P_NOESY1D_01_plot01

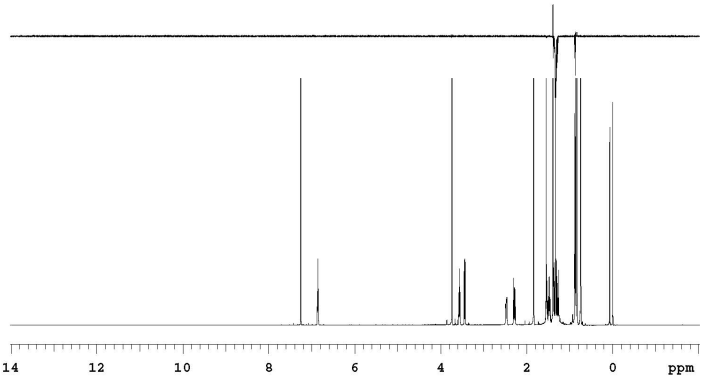
BAB_2167_P
File: /walkup/N6_20140306_BAB_2167_P_01/BAB_2167_P_NOESY1D_02.fid

Temp. 30.0 C / 303.1 K
Operator: walkup

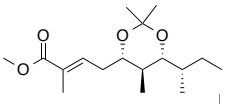
Relax. delay 1.000 sec
Pulse 90.0 degrees
Acq. time 5.000 sec
Width 9615.4 Hz
256 repetitions
OBSERVE H1, 599.4129442 MHz
DATA PROCESSING
FT size 131072
Total time 29 min



3.62



Plotname: BAB_2167_P_NOESY1D_02_plot01

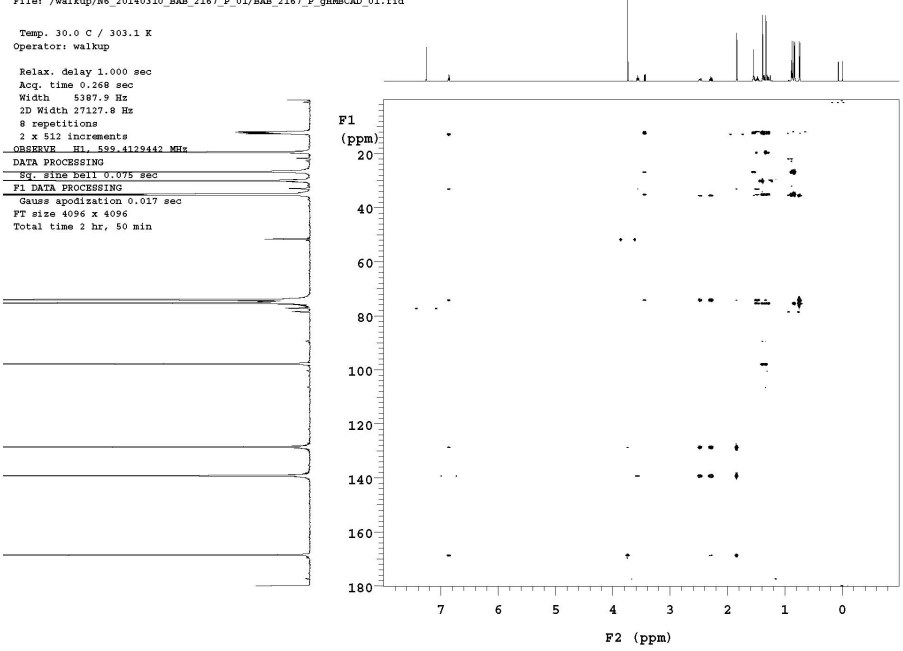


3.62

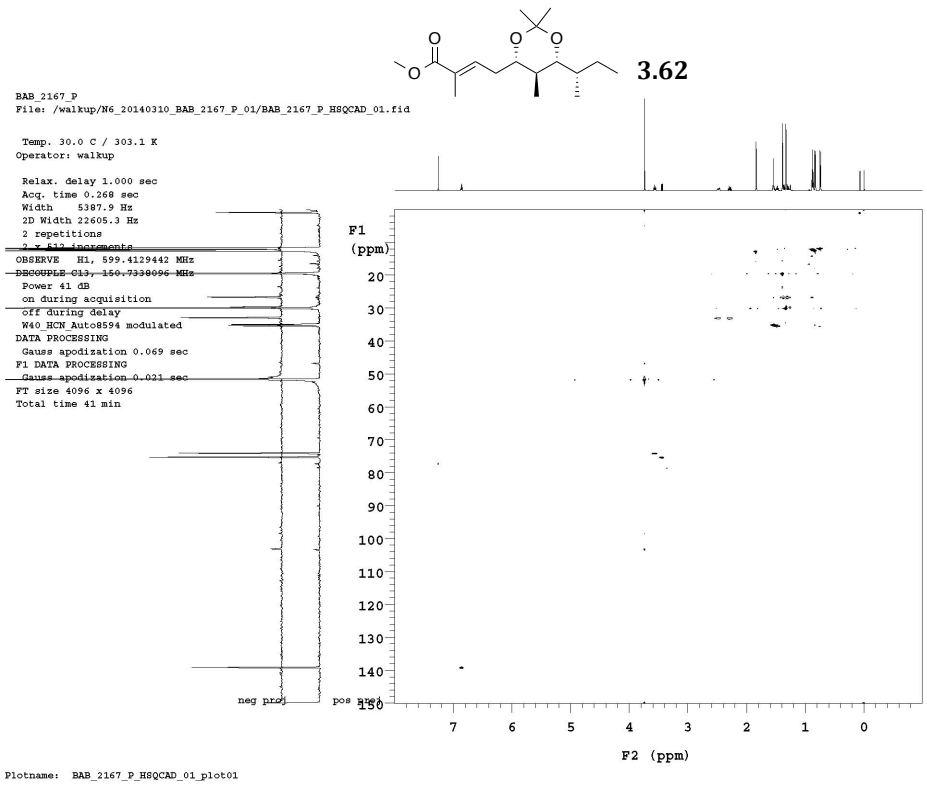
BAB_2167_P
File: /walkup/N6_20140310_BAB_2167_P_01/BAB_2167_P_gHMBCAD_01.fid

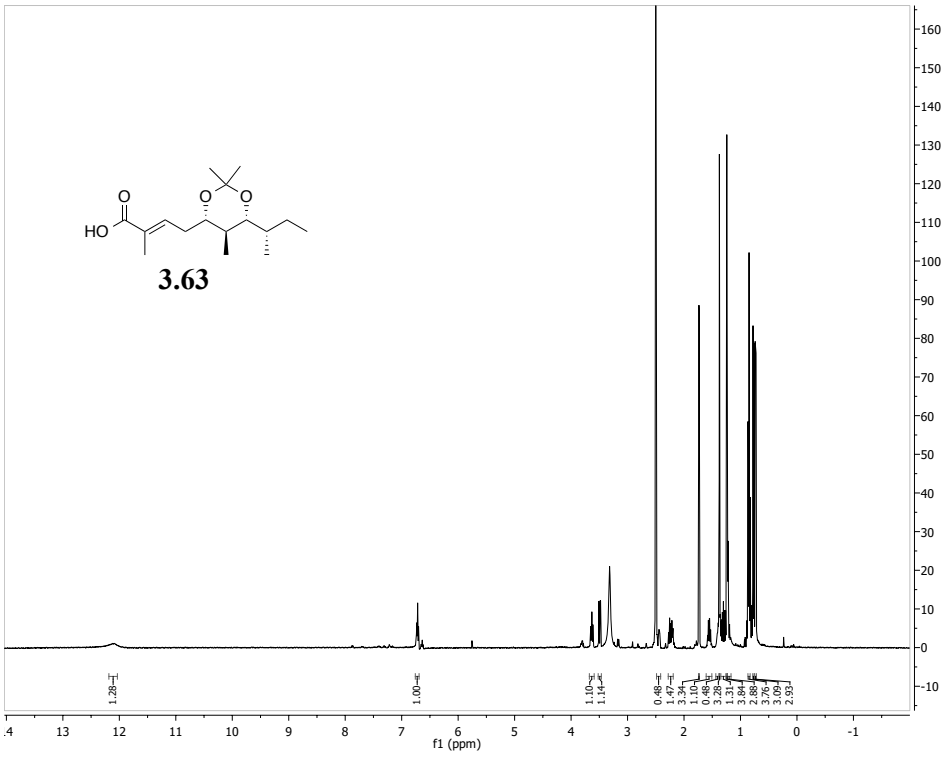
Temp. 30.0 C / 303.1 K
Operator: walkup

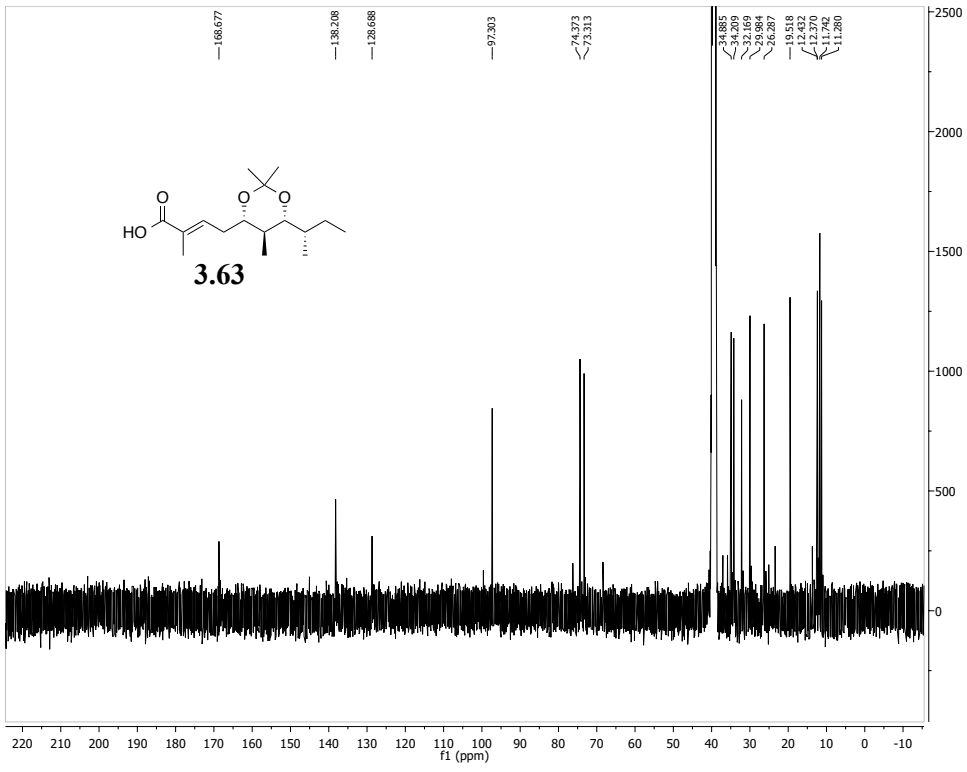
Relax. delay 1.000 sec
Acq. time 0.268 sec
Width 5387.9 Hz
2D Width 27127.8 Hz
8 repetitions
2 x 512 increments
OBSERVE H1, 599.4129442 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Gauss apodization 0.017 sec
FT size 4096 x 4096
Total time 2 hr, 50 min

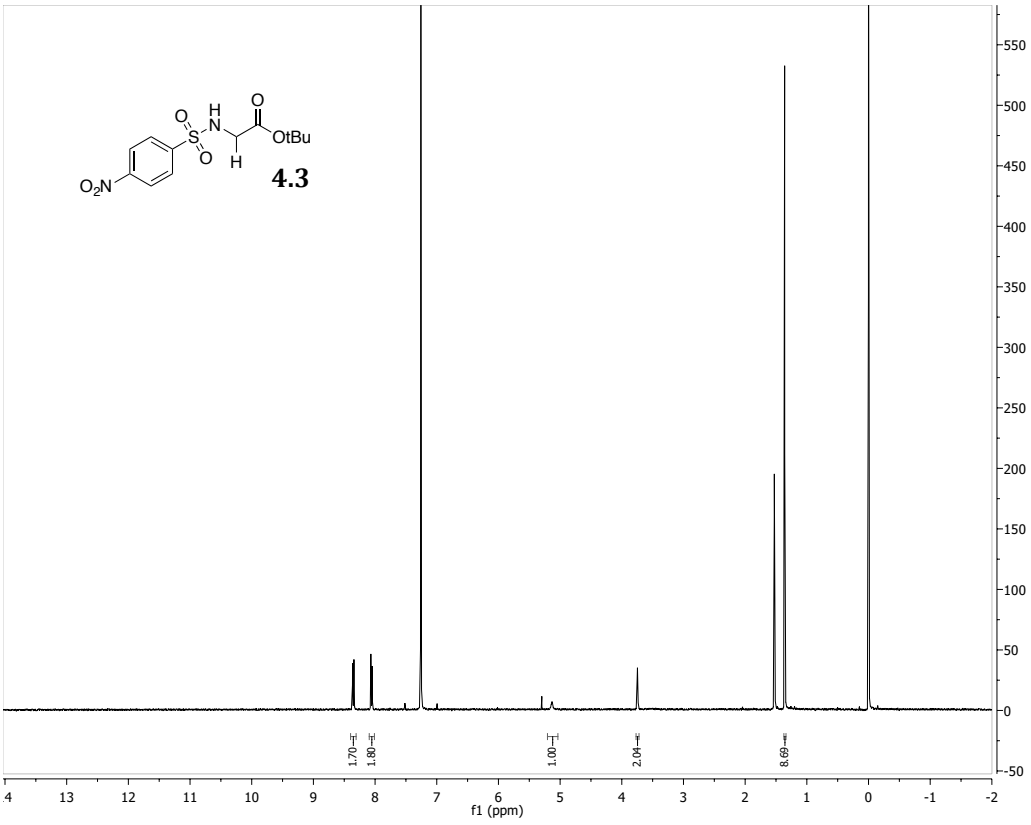


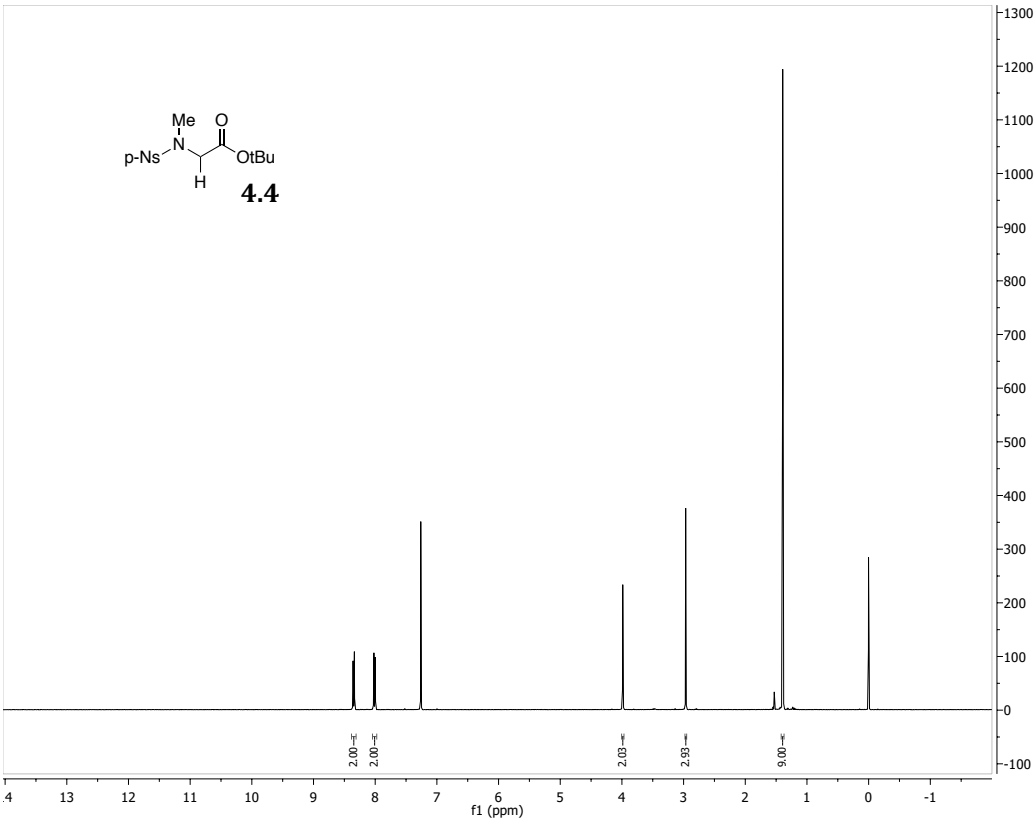
Plotname: BAB_2167_P_gHMBCAD_01_plot01

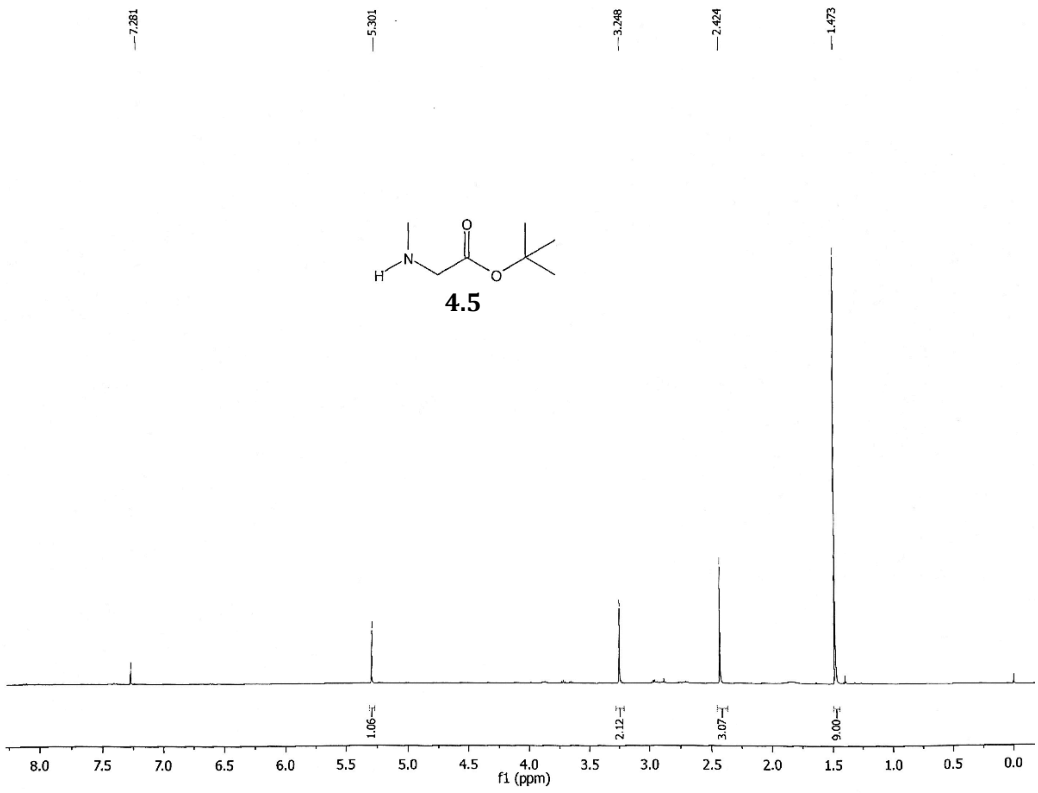

3.62
BAB_2167_P
File: /walkup/N6_20140310_BAB_2167_P_01/BAB_2167_P_HSQCAD_01.fid
Temp. 30.0 C / 303.1 K
Operator: walkup
Relax. delay 1.000 sec
Acq. time 0.268 sec
Width 5387.9 Hz
2D Width 22605.3 Hz
2 repetitions
OBSERVE H1, 599.4129442 MHz
DECOUPLE C13, 150.7338096 MHz
Power 41 dB
on during acquisition
off during delay
W40_HCN_Auto8594 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.021 sec
FT size 4096 x 4096
Total time 41 min
F1 (ppm)
F2 (ppm)
neg proj
pos proj
Plotname: BAB_2167_P_HSQCAD_01_plot01


HO
O
O
O
3.63
f1 (ppm)

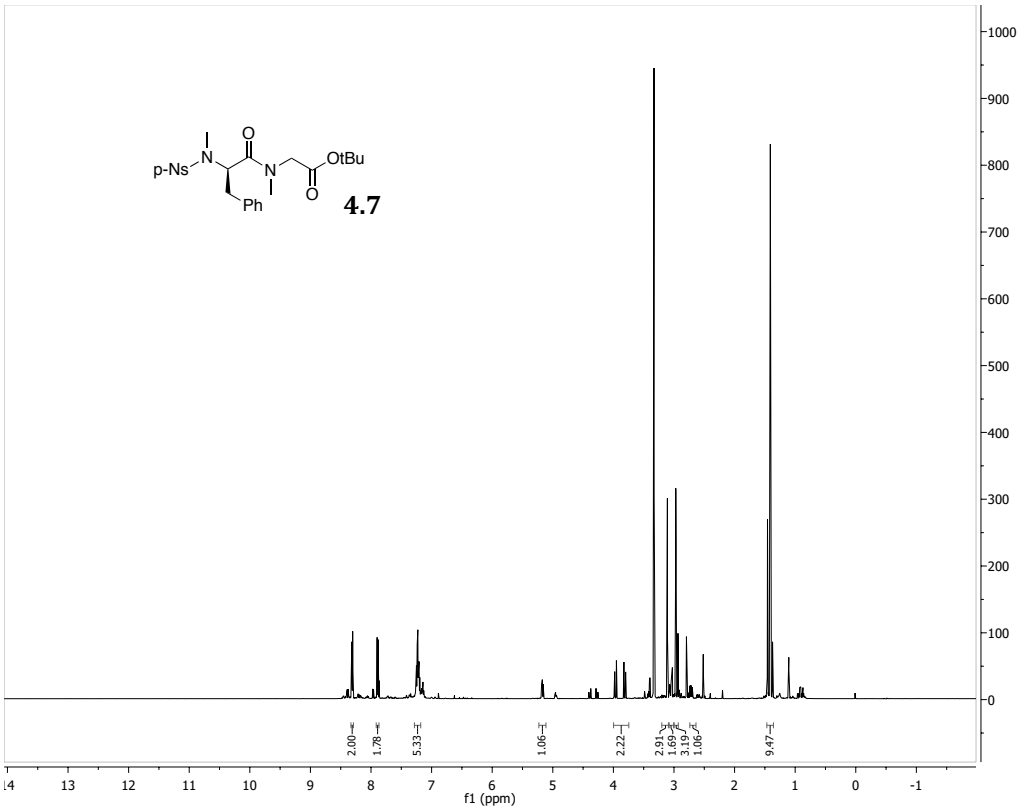

168.677
138.208
128.688
97.303
74.373
73.313
34.885
34.209
32.169
29.984
26.287
19.518
12.432
12.270
11.742
11.280
HO
O
O
O
3.63
f1 (ppm)

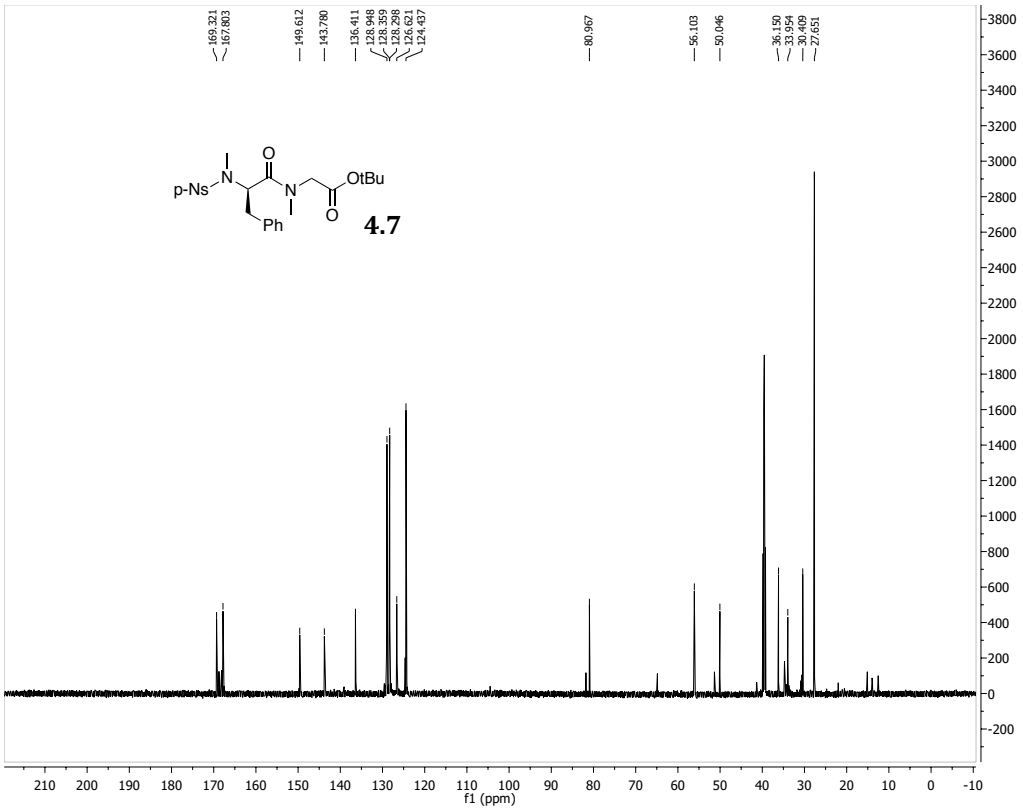

O
H
N
O
S
O
O
OtBu
H
O2N
4.3
1.70
1.80
1.00
2.04
8.69
f1 (ppm)

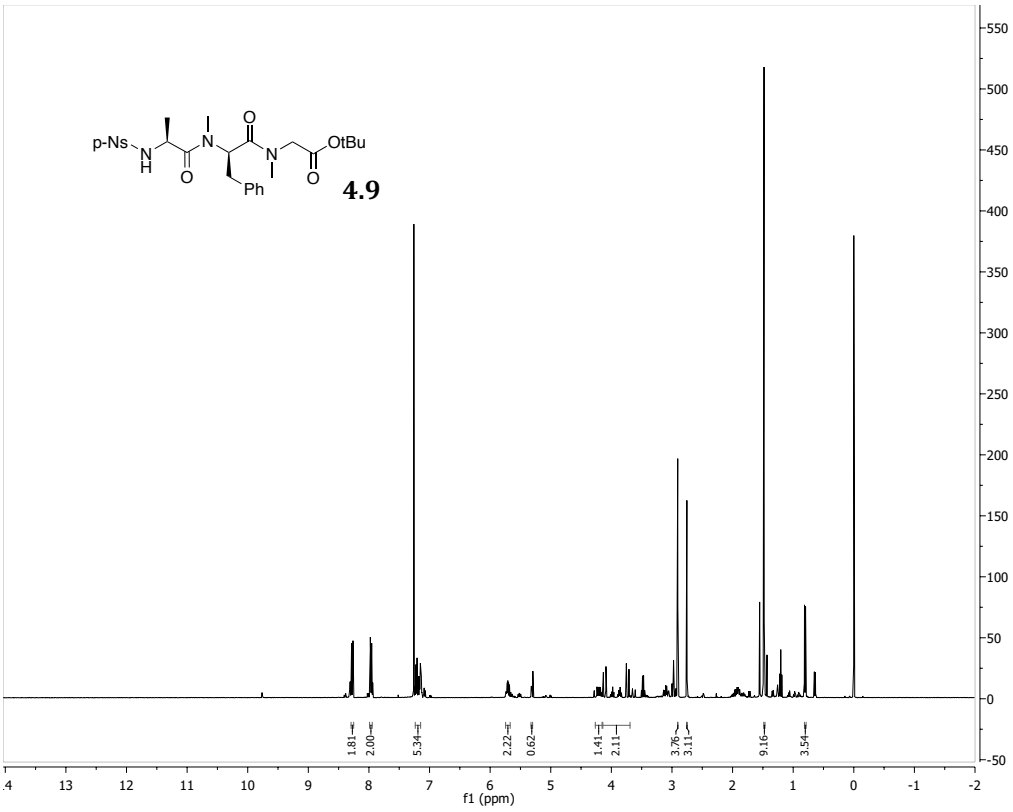

Me
O
N
p-Ns
OtBu
H
4.4
2.00
2.00
2.03
2.93
9.00
f1 (ppm)

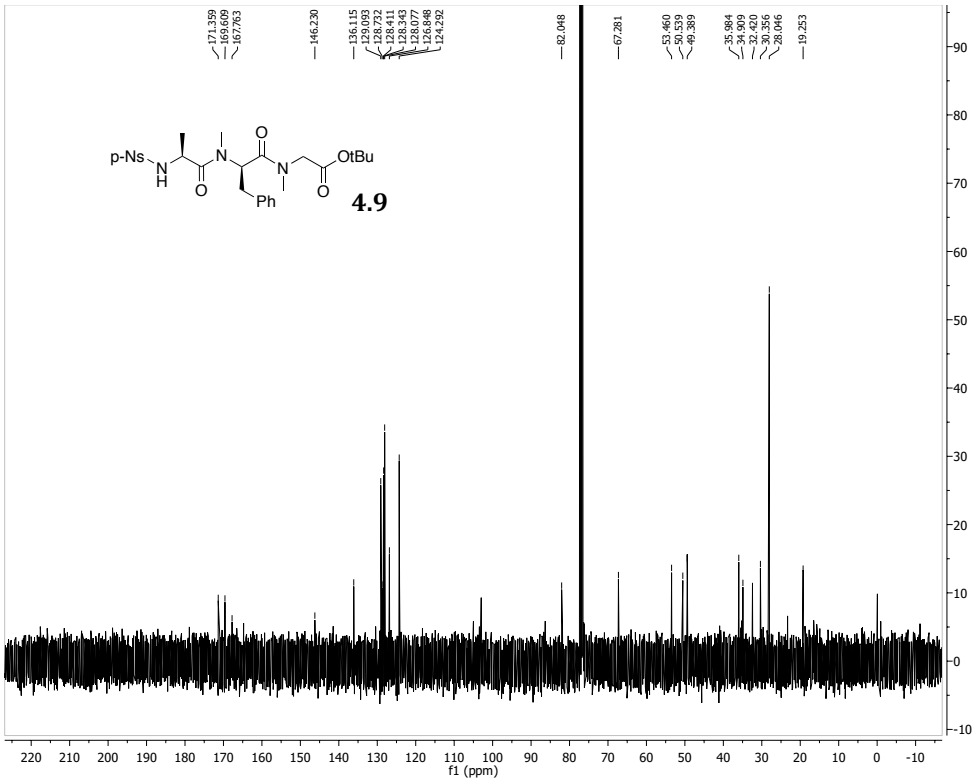

7.261
5.301
3.248
2.424
1.473
O
N
H
O
1.06
2.12
3.07
9.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

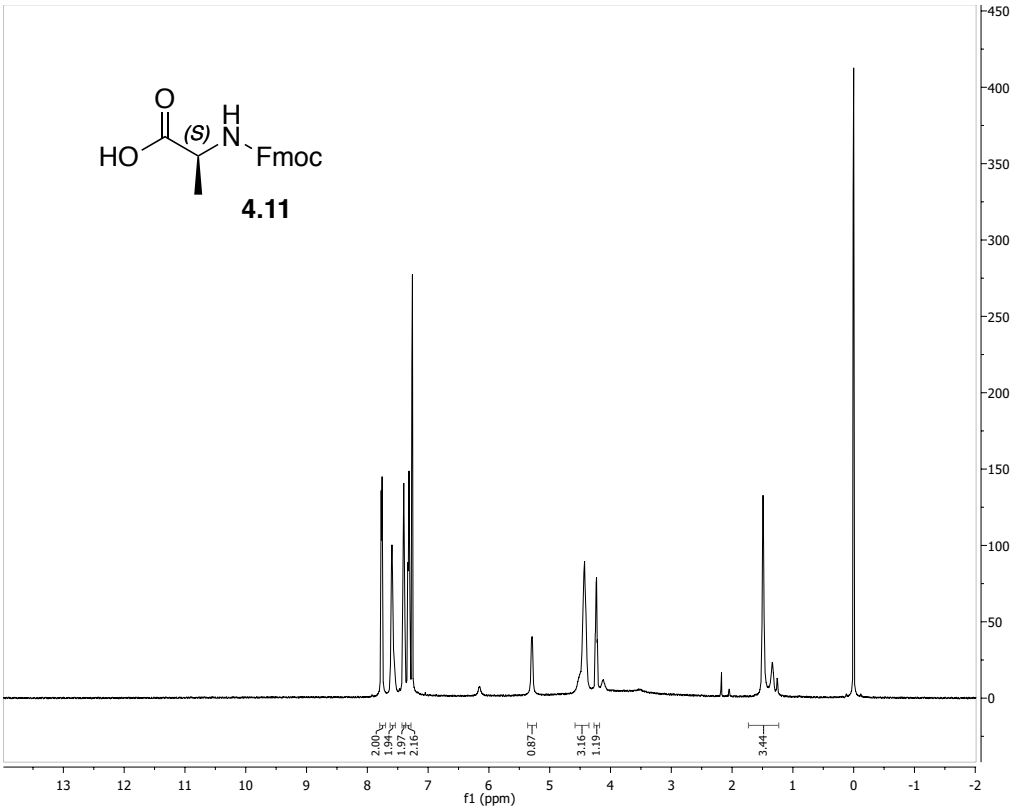
4.5

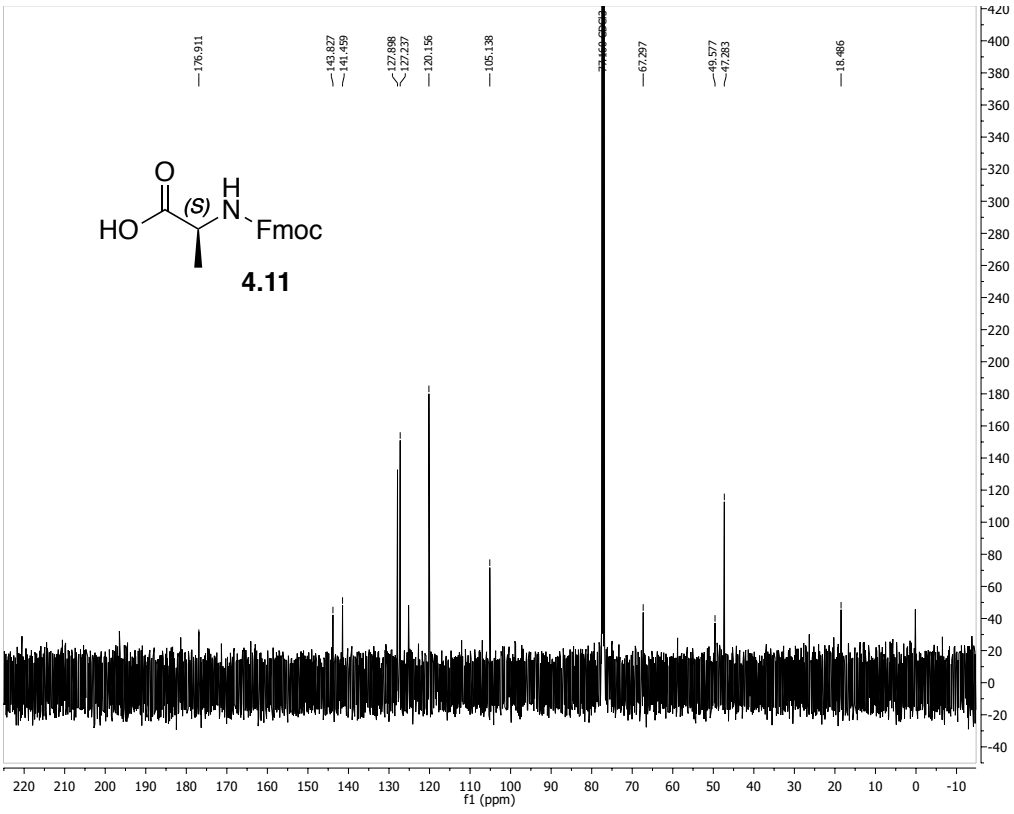

p-Ns
N
O
N
OtBu
O
Ph
4.7
1000
900
800
700
600
500
400
300
200
100
0
2.00
1.78
5.33
1.06
2.22
2.91
1.69
3.19
1.06
9.47
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

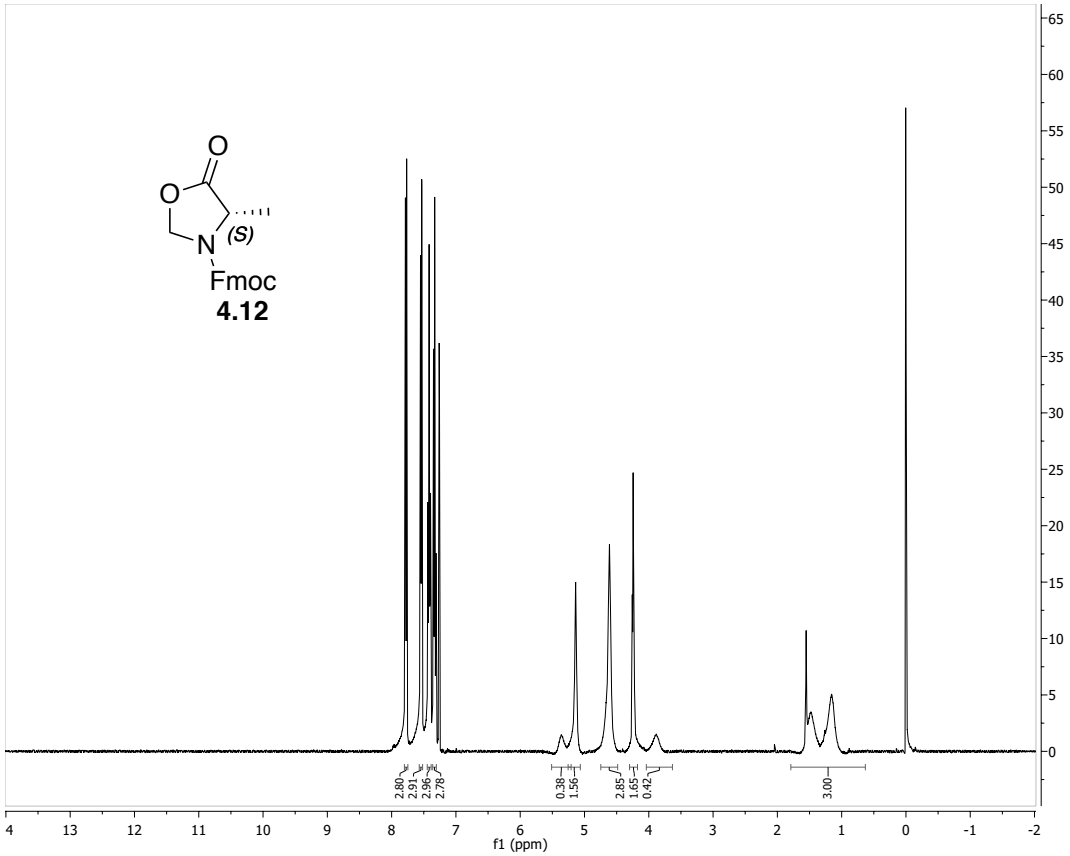

169.321
167.803
149.612
143.780
136.411
128.948
128.359
128.298
126.621
124.457
80.967
56.103
50.046
36.150
33.954
30.409
27.651
p-Ns
N
O
N
OtBu
O
Ph
4.7
f1 (ppm)

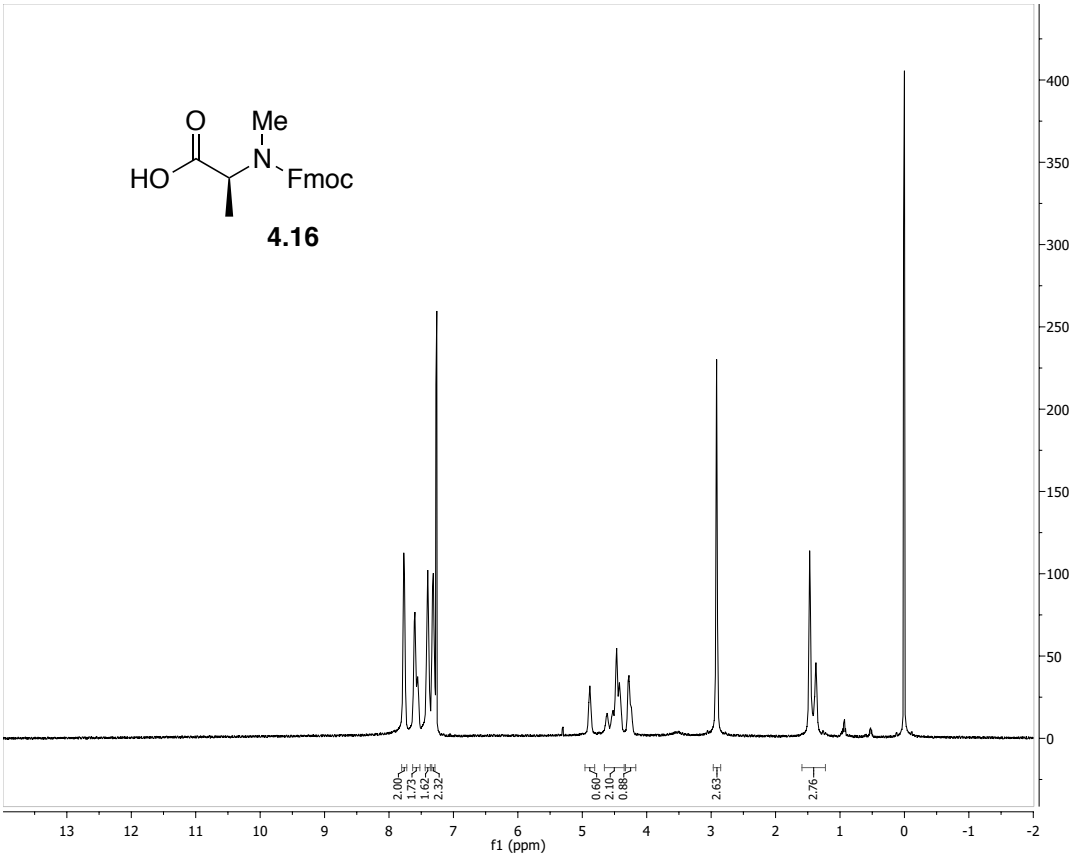

p-Ns
N
H
O
N
O
N
O
OtBu
Ph
4.9
1.81
2.00
5.34
2.22
0.62
1.41
2.11
3.76
3.11
9.16
3.54
f1 (ppm)

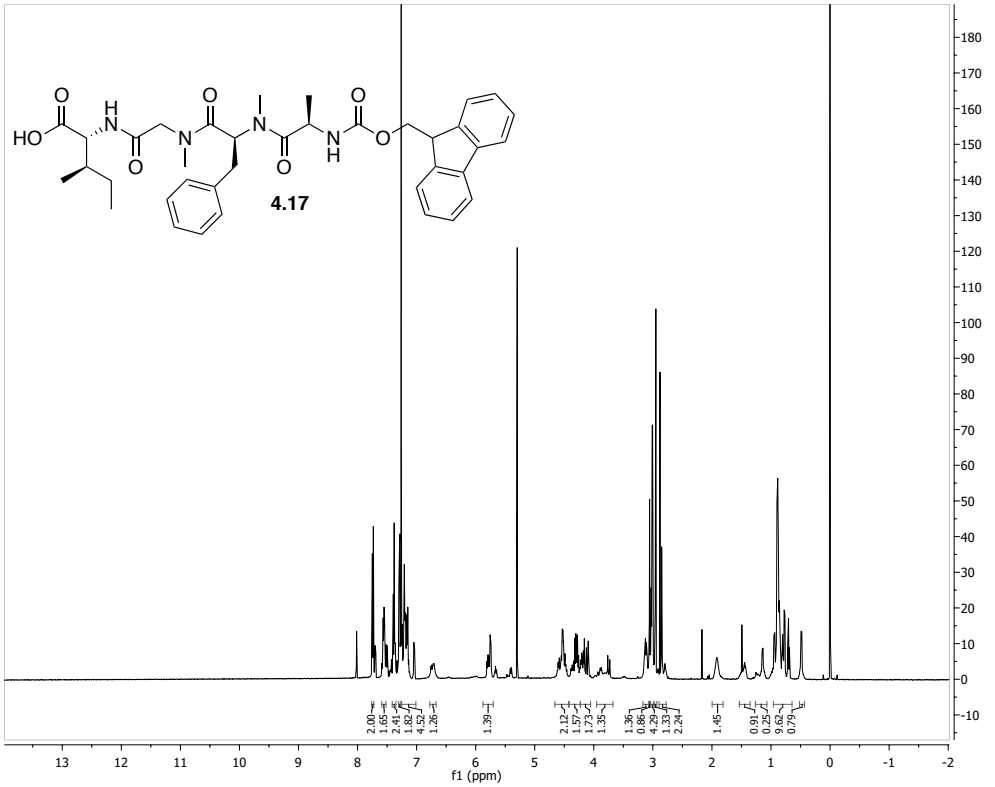

171.359
169.609
167.763
146.230
136.115
129.093
128.732
128.411
128.343
128.077
126.848
124.292
82.048
67.281
53.460
50.539
49.389
35.984
34.909
32.420
30.356
28.046
19.253
p-Ns
N
H
O
N
O
N
O
OtBu
Ph
4.9
f1 (ppm)

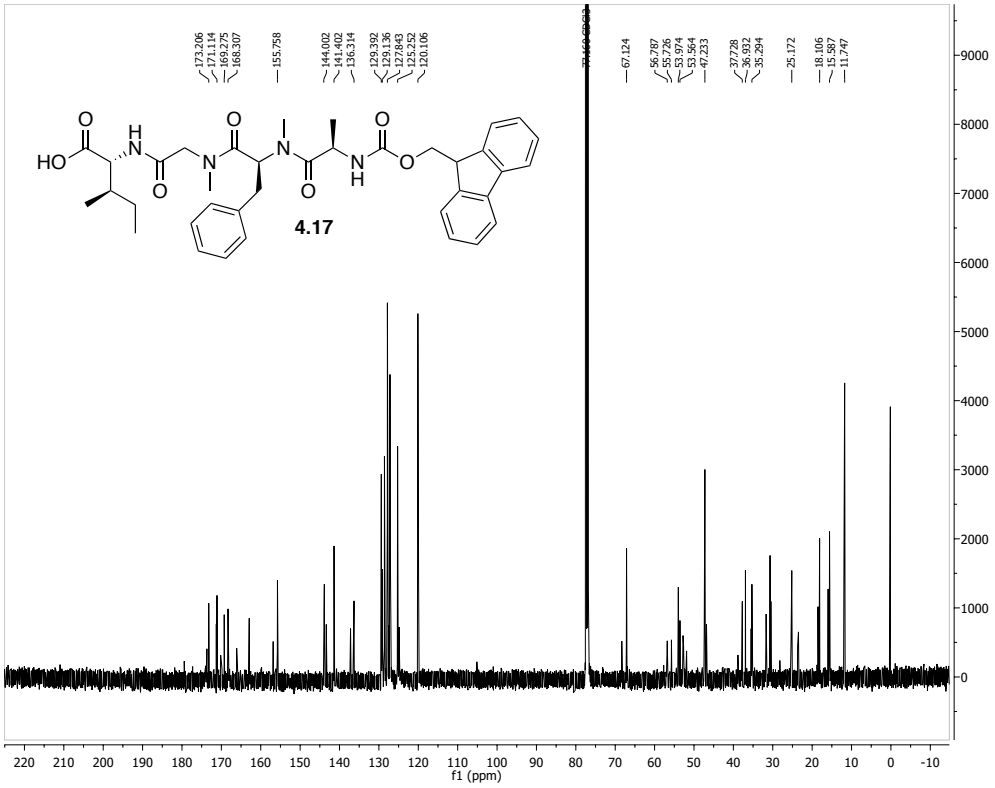

HO
(S)
H
N
Fmoc
4.11
f1 (ppm)

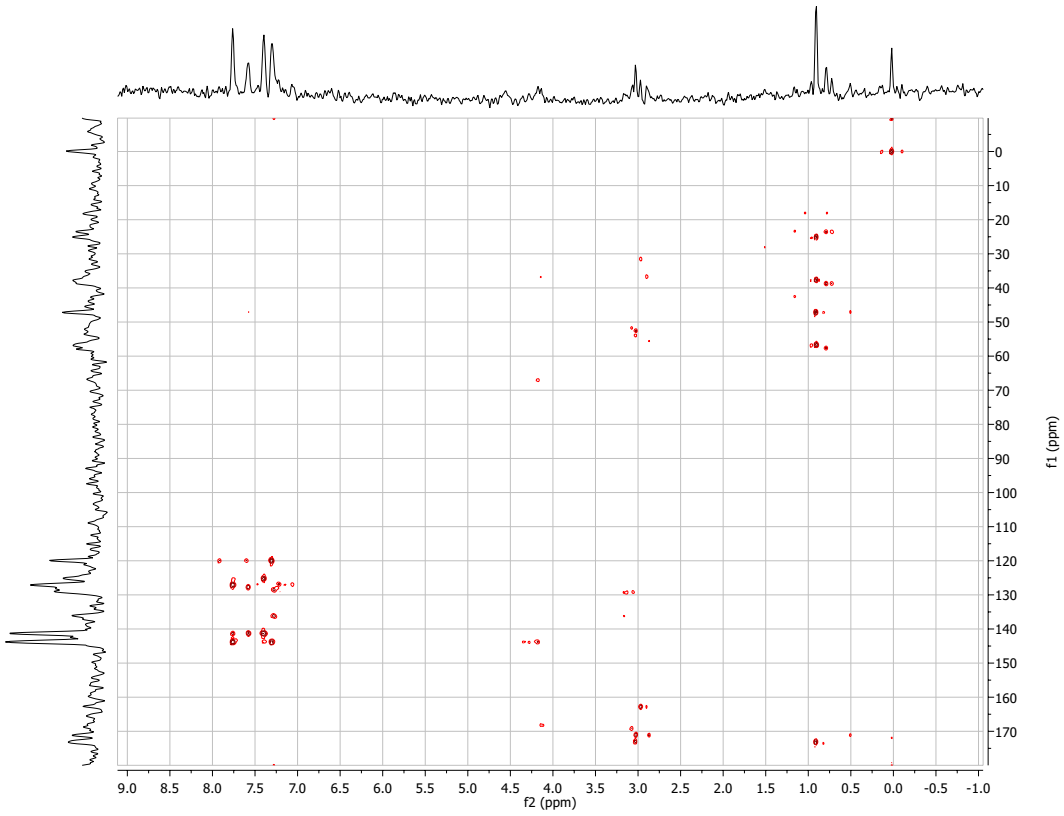

176.911
143.827
141.459
127.898
127.237
120.156
105.138
67.297
49.577
47.283
18.486
HO
(S)
H
N
Fmoc
4.11
f1 (ppm)

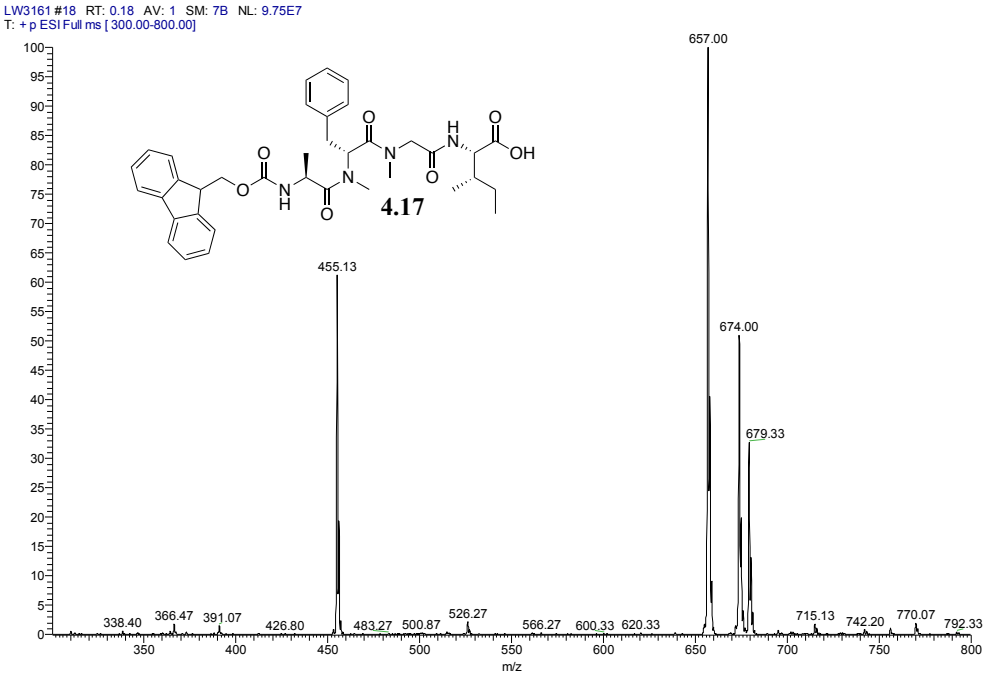

O
O
N
(S)
Fmoc
4.12
2.80
2.91
2.96
2.78
0.38
1.56
2.85
1.65
0.42
3.00
f1 (ppm)

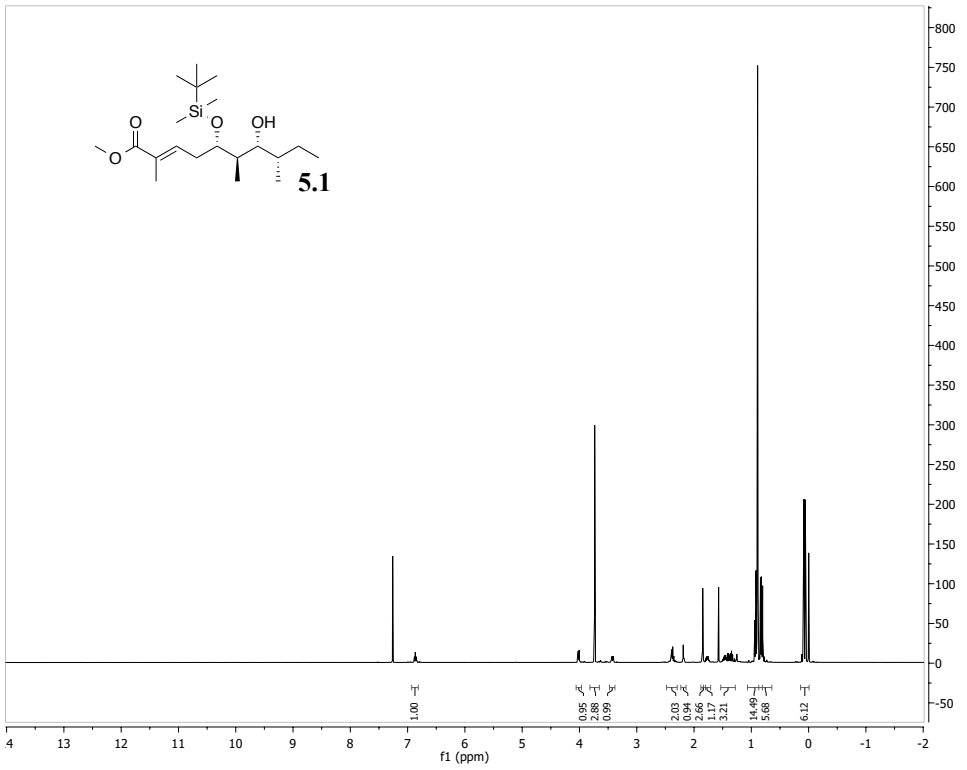

O
Me
HO
N
Fmoc
4.16
400
350
300
250
200
150
100
50
0
2.00
1.73
1.62
2.32
0.60
2.10
0.88
2.63
2.76
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

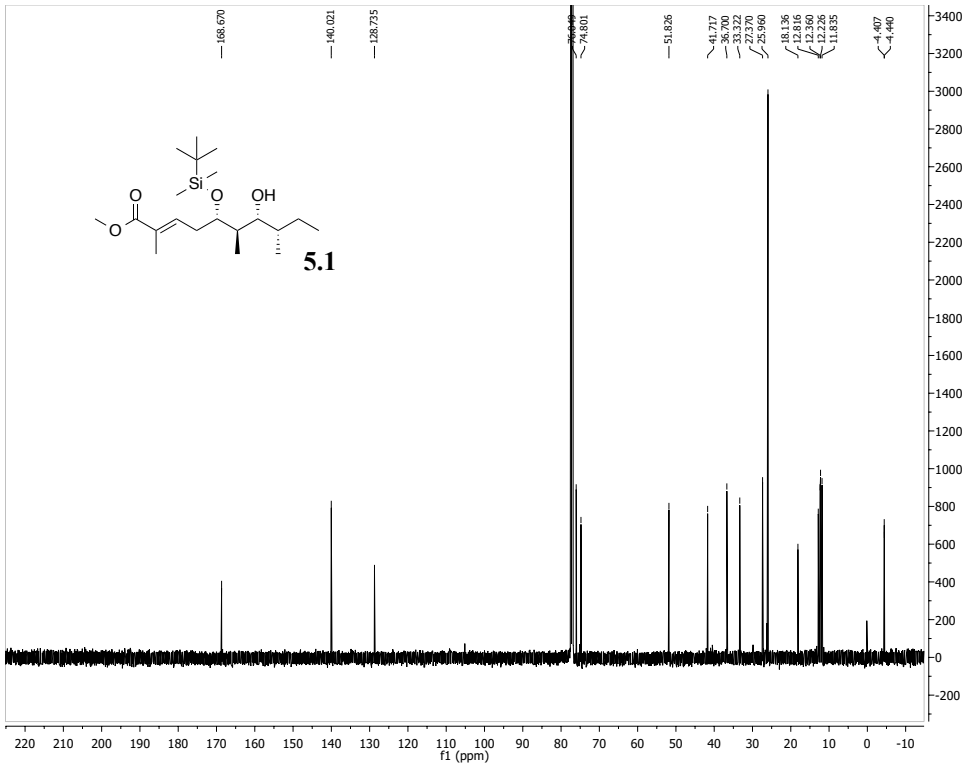

4.17
f1 (ppm)

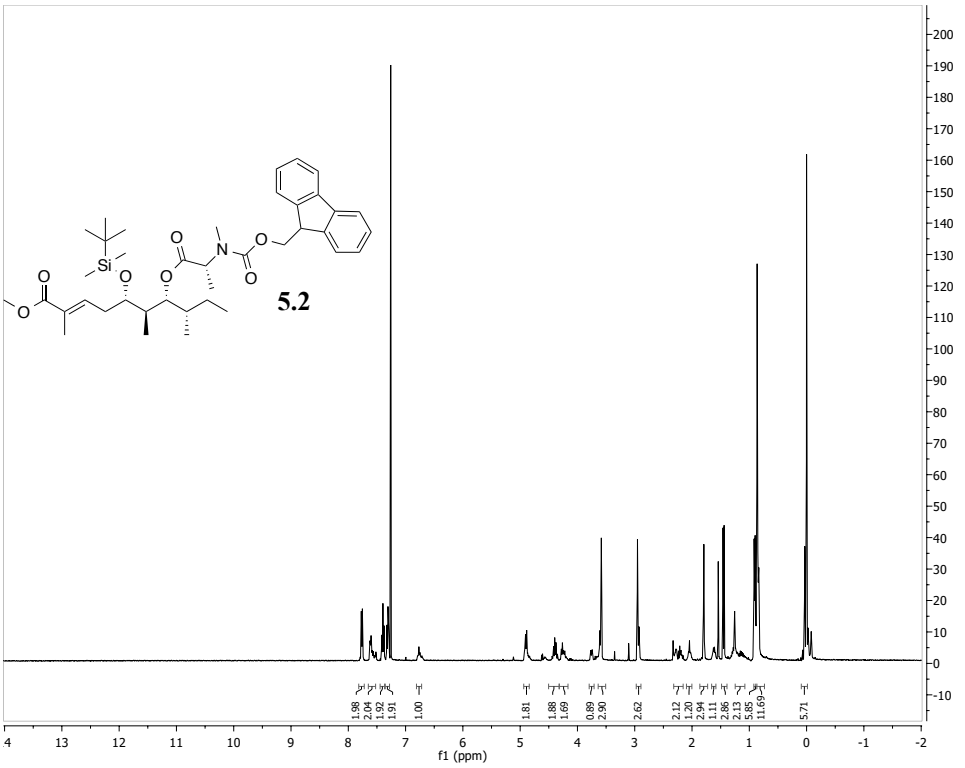

4.17
f1 (ppm)

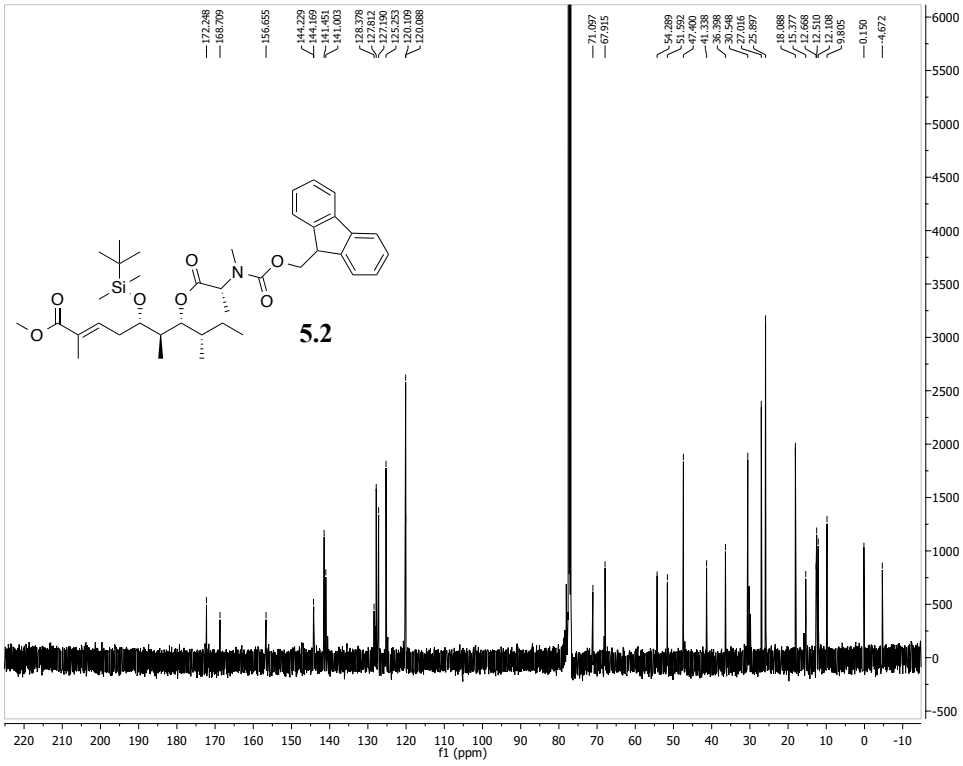

f2 (ppm)
f1 (ppm)

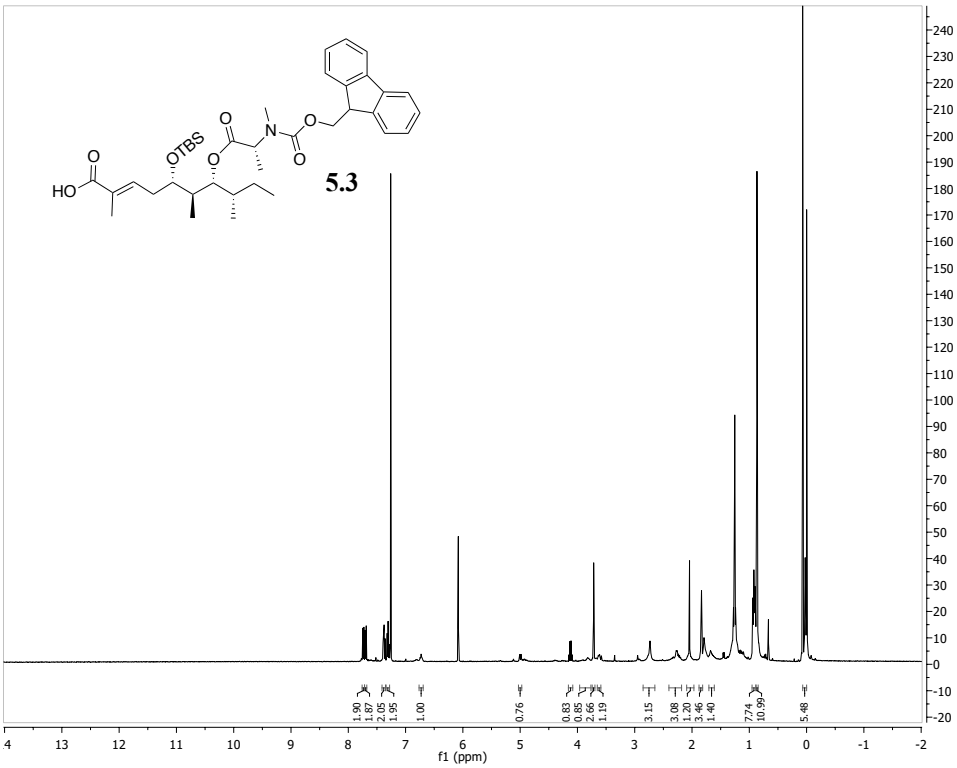

LW3161 #18 RT: 0.18 AV: 1 SM: 7B NL: 9.75E7
T: + p ESI Full ms [300.00-800.00]
4.17
657.00
455.13
674.00
679.33
m/z

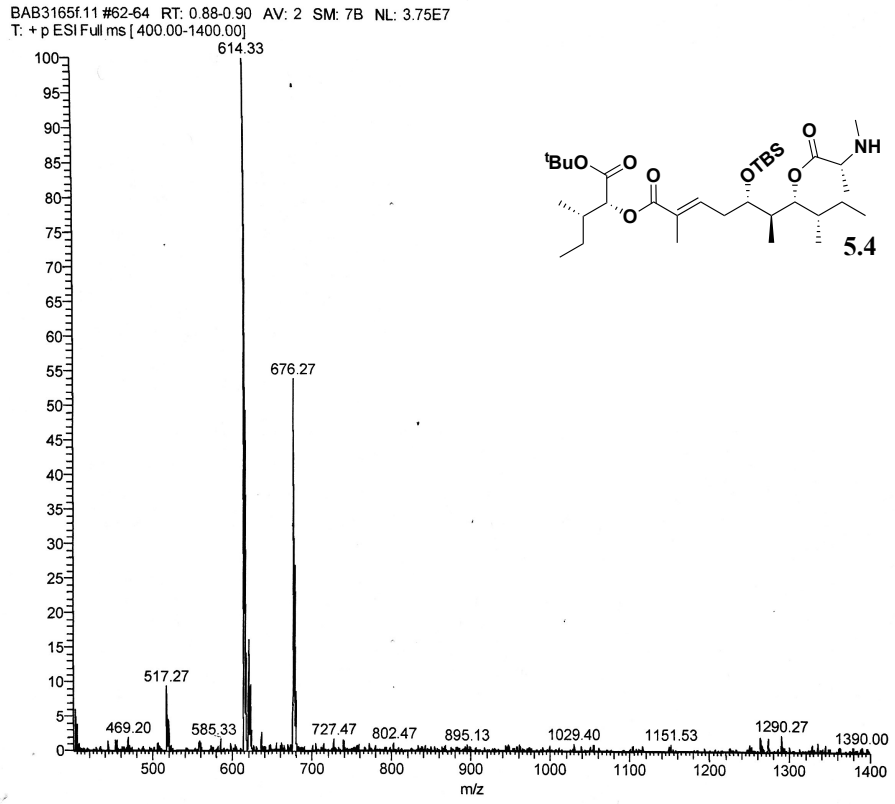

5.1
1.00
0.95
2.88
0.99
2.03
0.94
2.66
1.17
3.21
14.49
5.68
6.12
f1 (ppm)

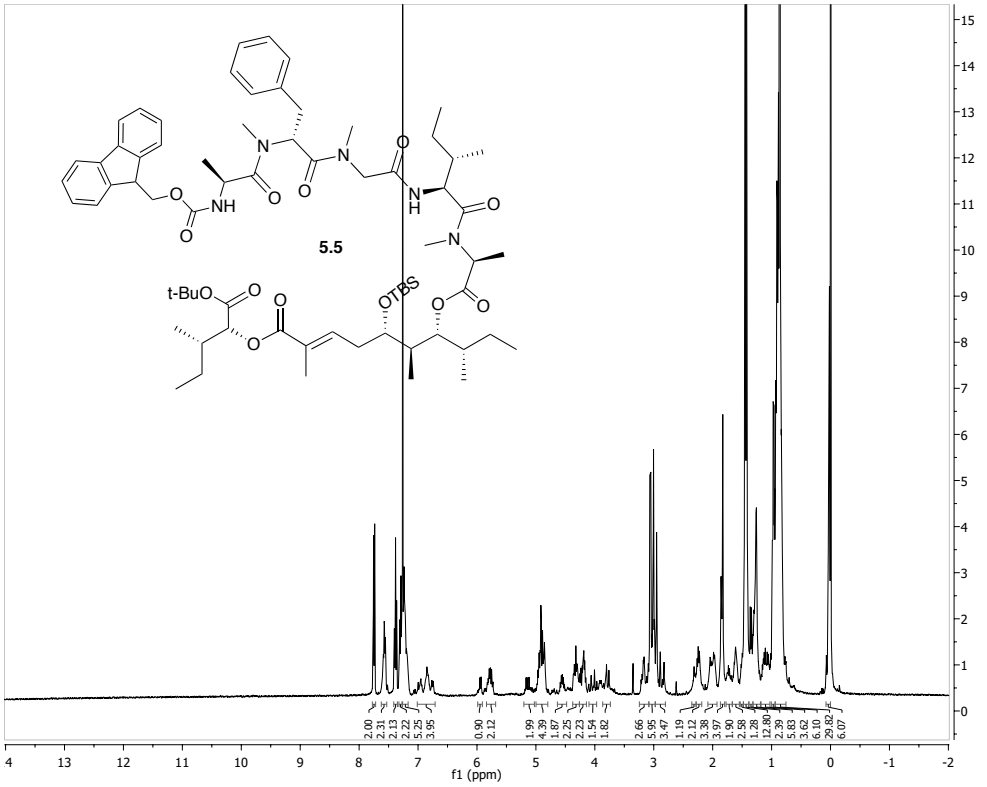

168.670
140.021
128.735
74.801
51.826
41.717
36.700
33.322
27.370
25.960
18.136
12.816
12.360
12.226
11.835
-4.407
-4.440
5.1
f1 (ppm)

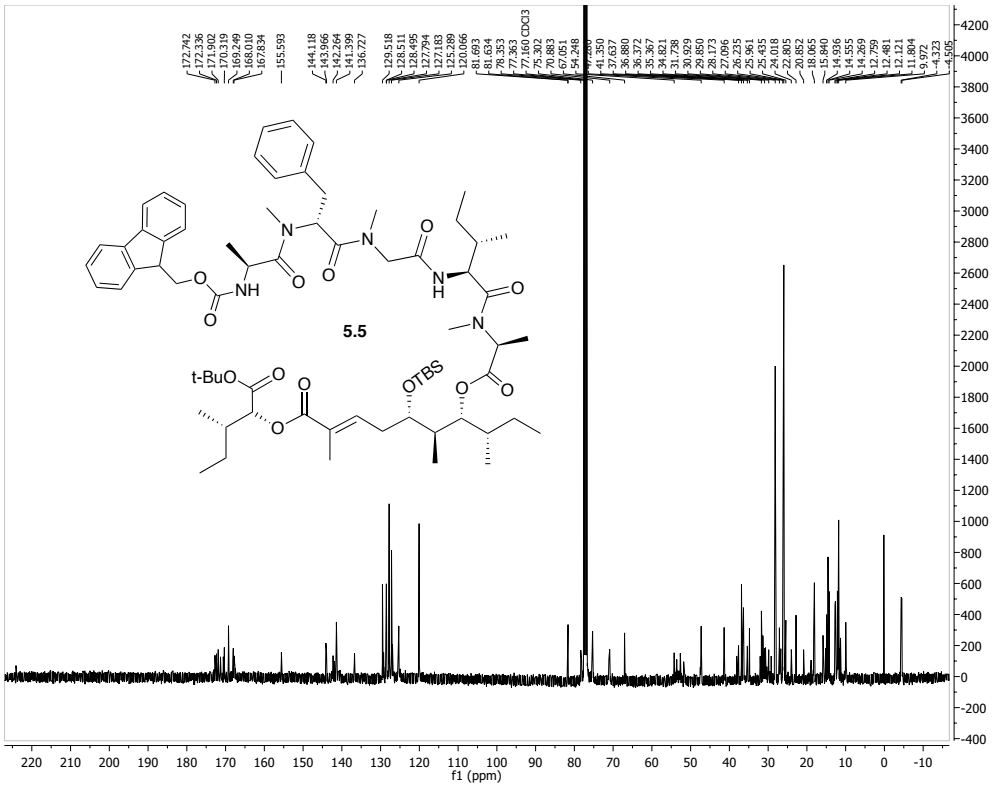

5.2
1.98
2.04
1.92
1.91
1.00
1.81
1.88
1.69
0.89
2.90
2.62
2.12
1.20
2.94
1.11
2.86
2.13
5.85
11.69
5.71
f1 (ppm)

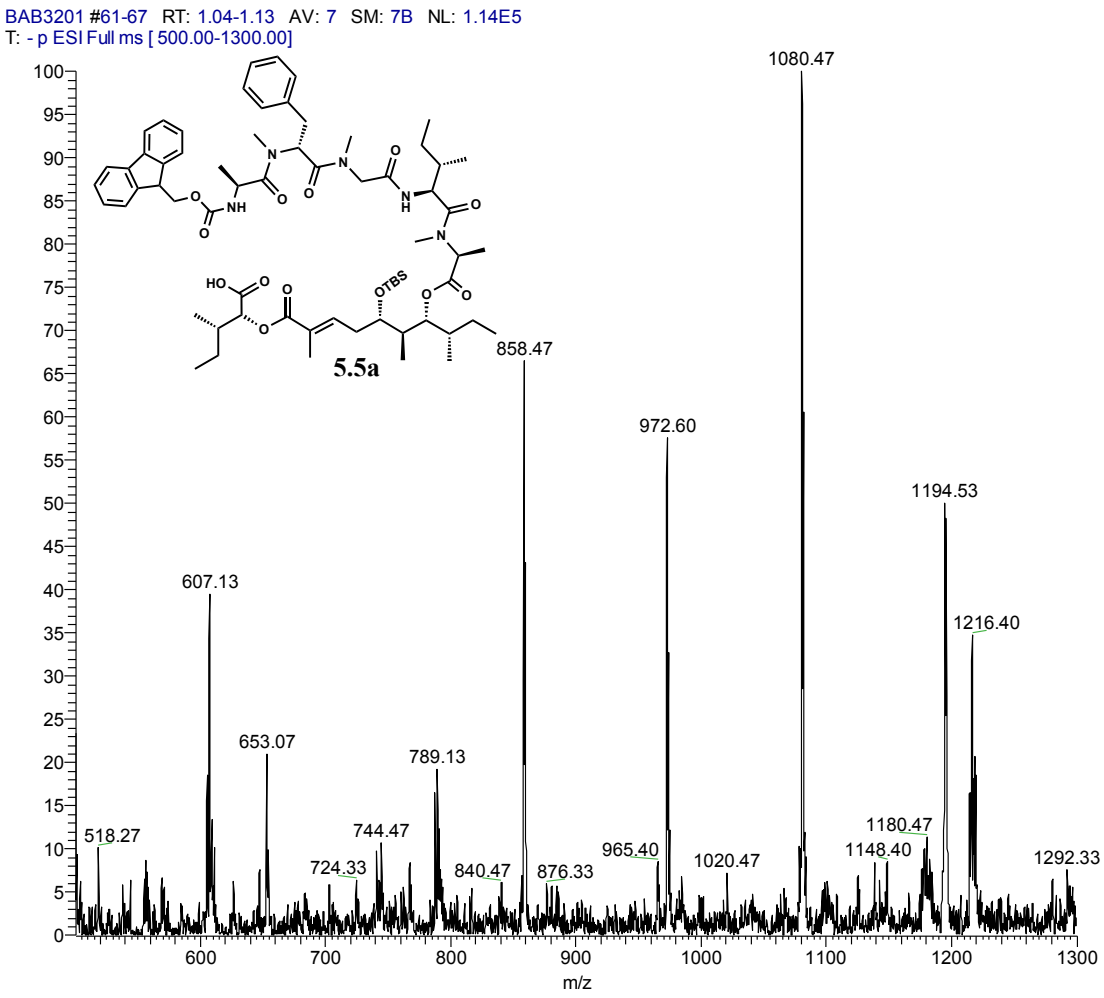

172.248
168.709
156.655
144.229
144.169
141.451
141.003
128.378
127.812
127.190
125.253
120.109
120.088
71.097
67.915
54.289
51.592
47.400
41.338
36.398
30.548
27.016
25.897
18.088
15.377
12.668
12.510
12.108
9.805
0.150
-4.672
5.2
f1 (ppm)

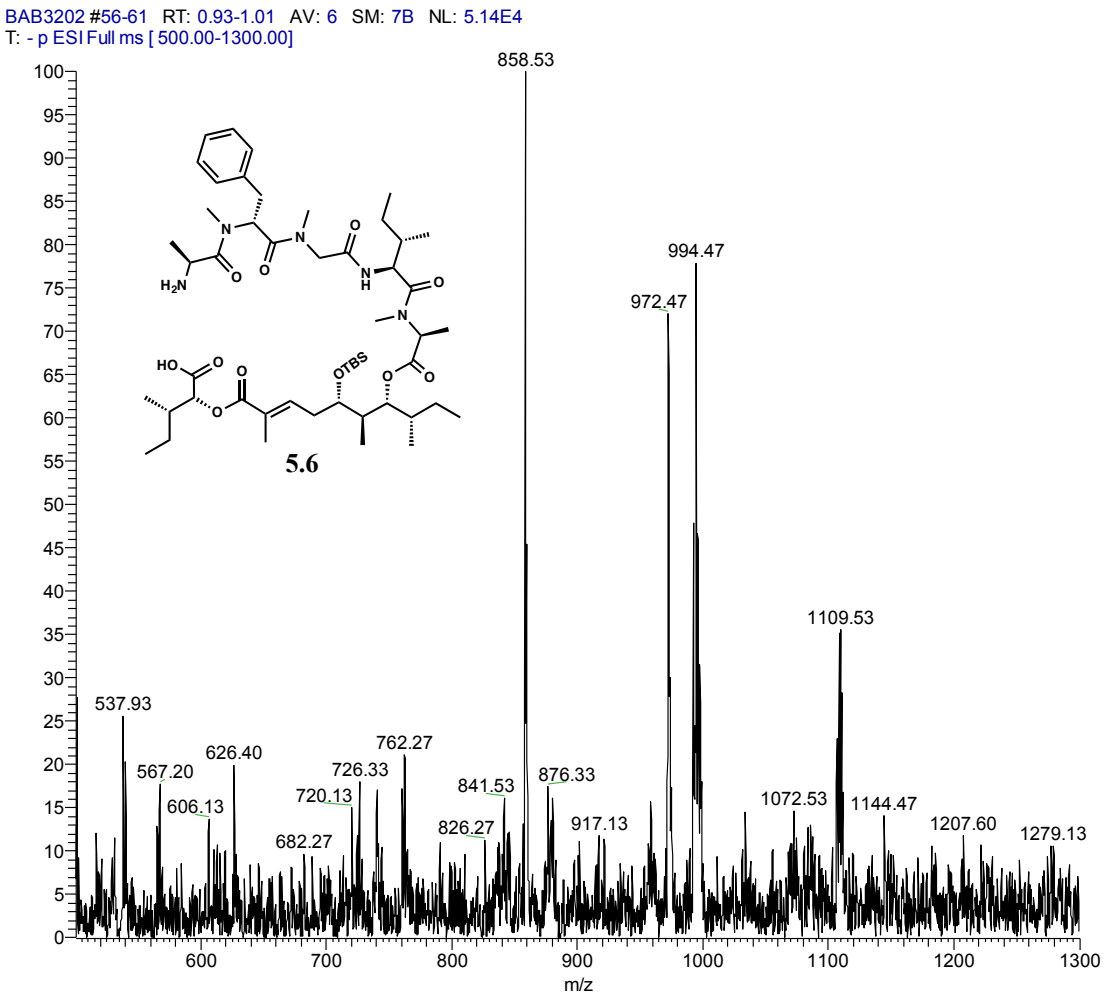

HO
O
OTBS
O
O
N
O
O
O
5.3
1.90
1.87
2.05
1.95
1.00
0.76
0.83
0.85
2.66
1.19
3.15
3.08
1.20
1.46
1.40
7.74
10.99
5.48
f1 (ppm)


BAB3165f.11 #62-64 RT: 0.88-0.90 AV: 2 SM: 7B NL: 3.75E7
T: + p ESI Full ms [400.00-1400.00]
614.33
676.27
517.27
469.20
585.33
727.47
802.47
895.13
1029.40
1151.53
1290.27
1390.00
m/z
tBuO
O
OTBS
NH
5.4

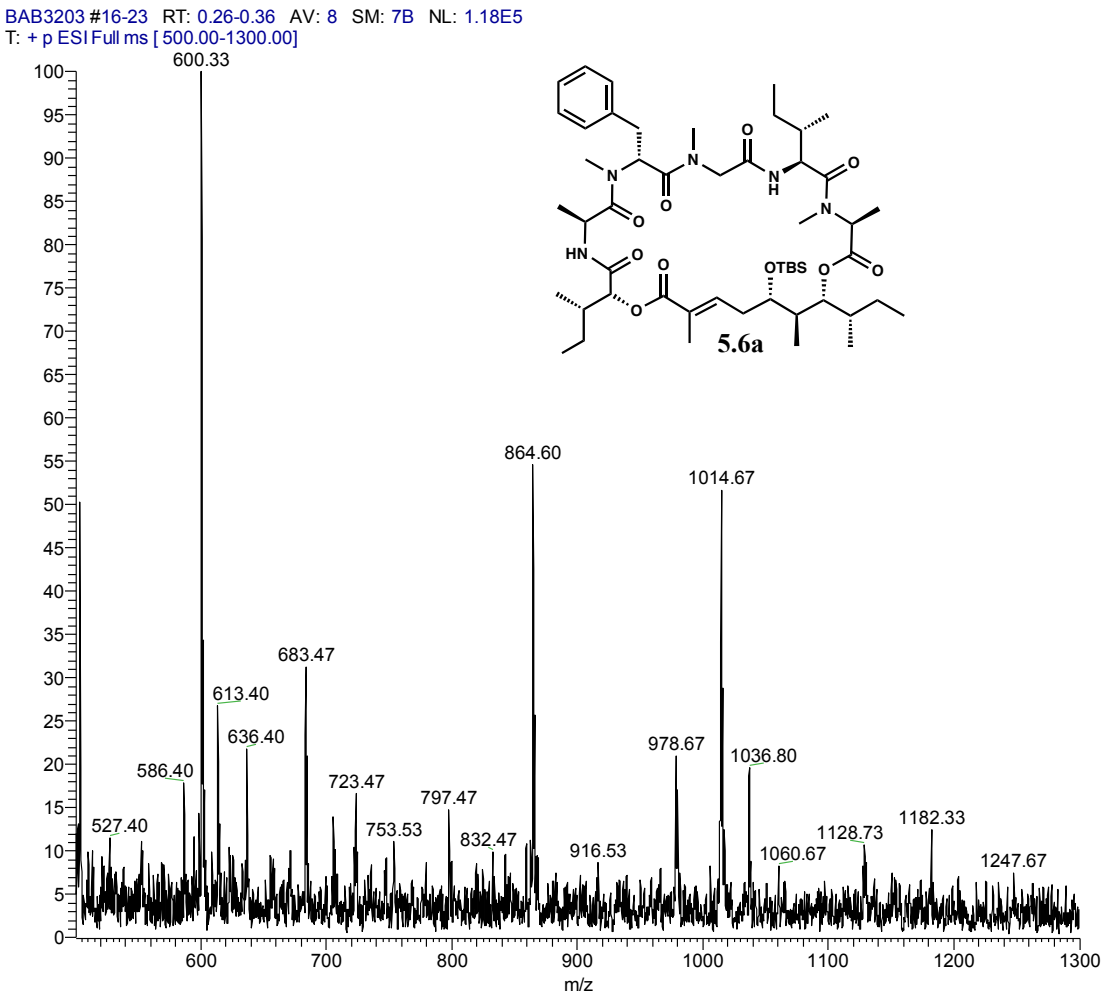

5.5
t-BuO
OTBS
f1 (ppm)

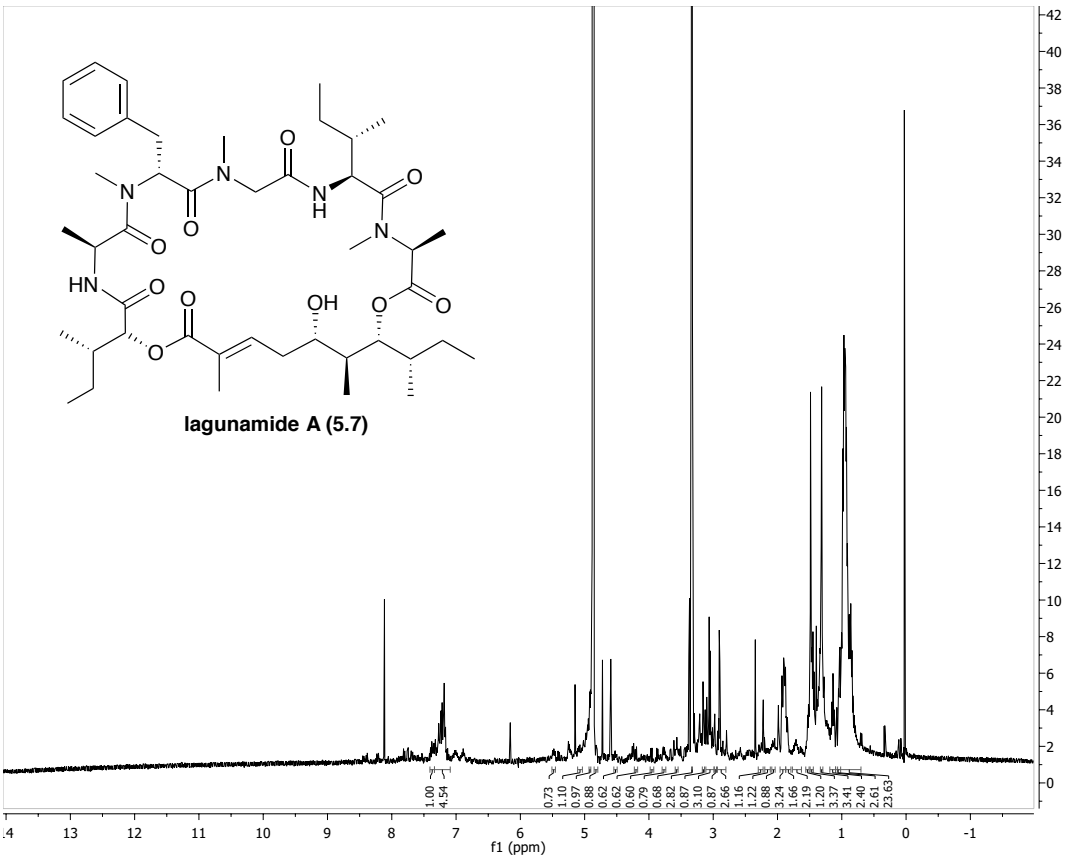

5.5
t-BuO
OTBS
f1 (ppm)

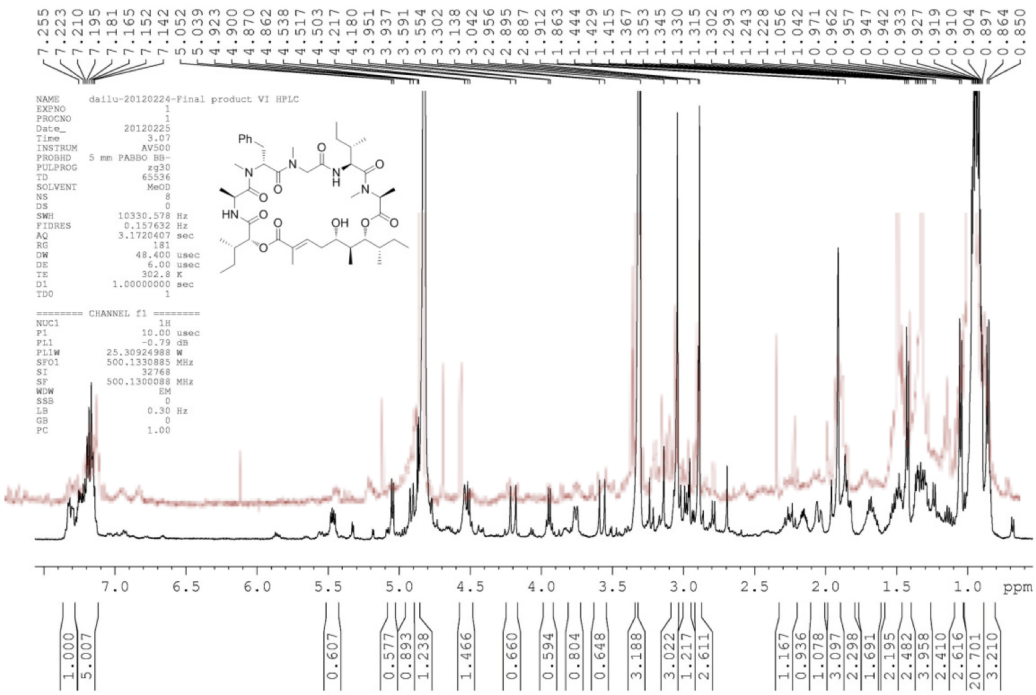

BAB3201 #61-67 RT: 1.04-1.13 AV: 7 SM: 7B NL: 1.14E5
T: - p ESI Full ms [500.00-1300.00]
5.5a
1080.47
858.47
972.60
1194.53
607.13
1216.40
653.07
789.13
518.27
744.47
724.33
840.47
876.33
965.40
1020.47
1180.47
1148.40
1292.33
m/z

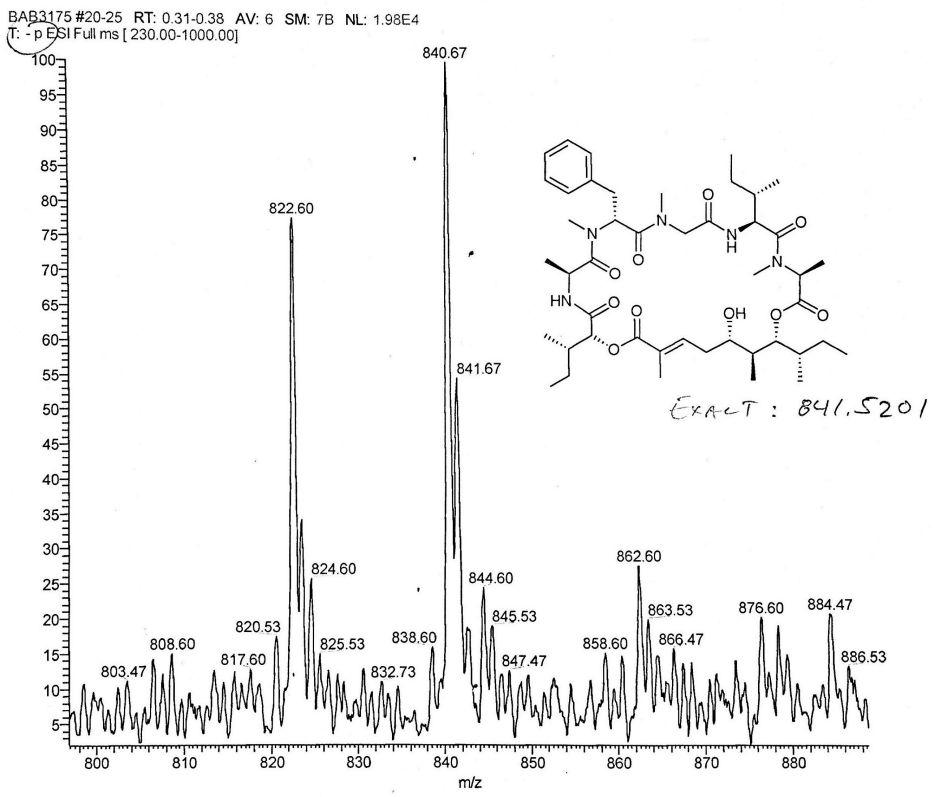

BAB3202 #56-61 RT: 0.93-1.01 AV: 6 SM: 7B NL: 5.14E4
T: - p ESI Full ms [500.00-1300.00]
858.53
994.47
972.47
1109.53
537.93
626.40
567.20
762.27
726.33
606.13
720.13
841.53
876.33
682.27
826.27
917.13
1072.53
1144.47
1207.60
1279.13
m/z

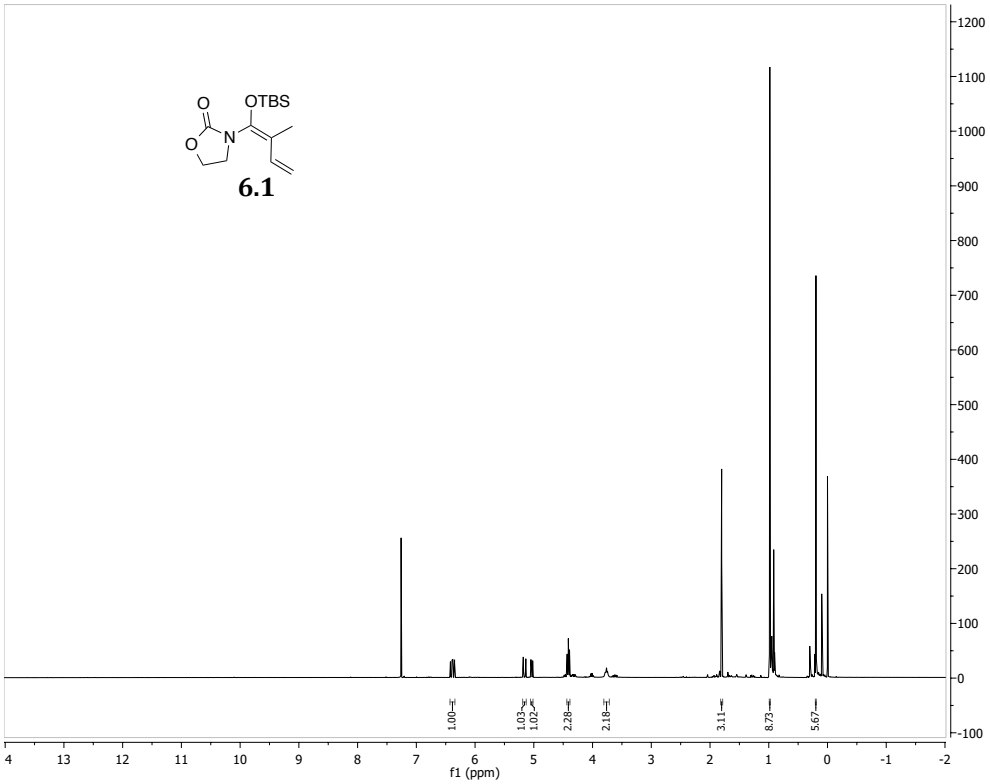
5.6

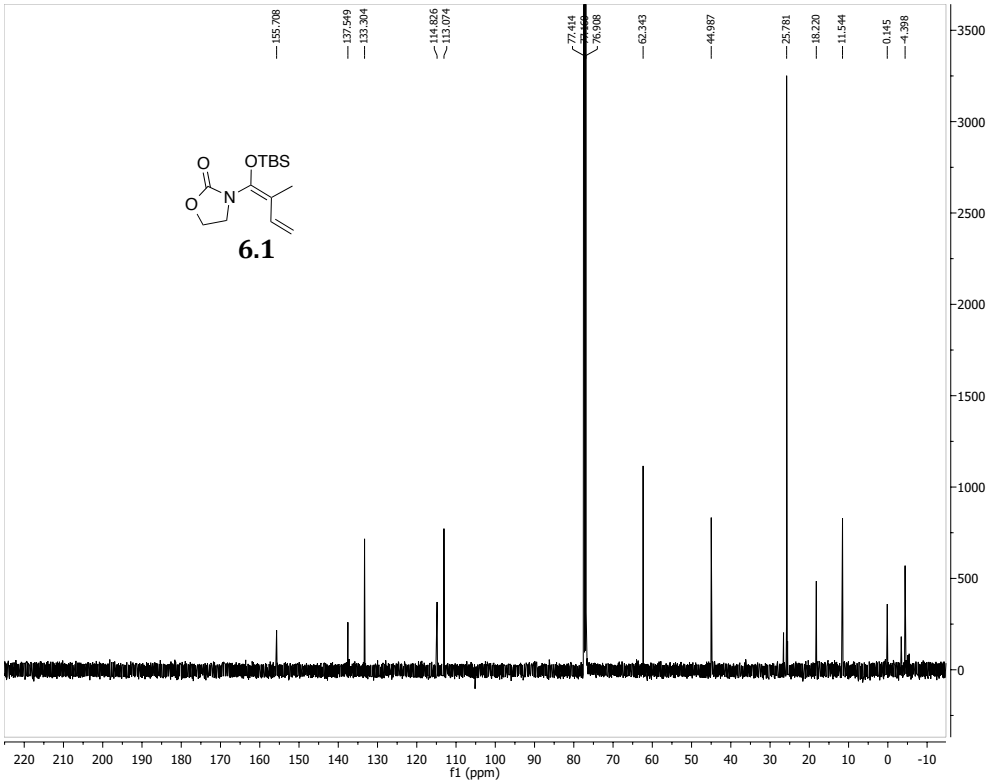

BAB3203 #16-23 RT: 0.26-0.36 AV: 8 SM: 7B NL: 1.18E5
T: + p ESI Full ms [500.00-1300.00]
600.33
864.60
1014.67
683.47
613.40
636.40
586.40
723.47
797.47
978.67
1036.80
527.40
753.53
832.47
916.53
1060.67
1128.73
1182.33
1247.67
m/z
5.6a

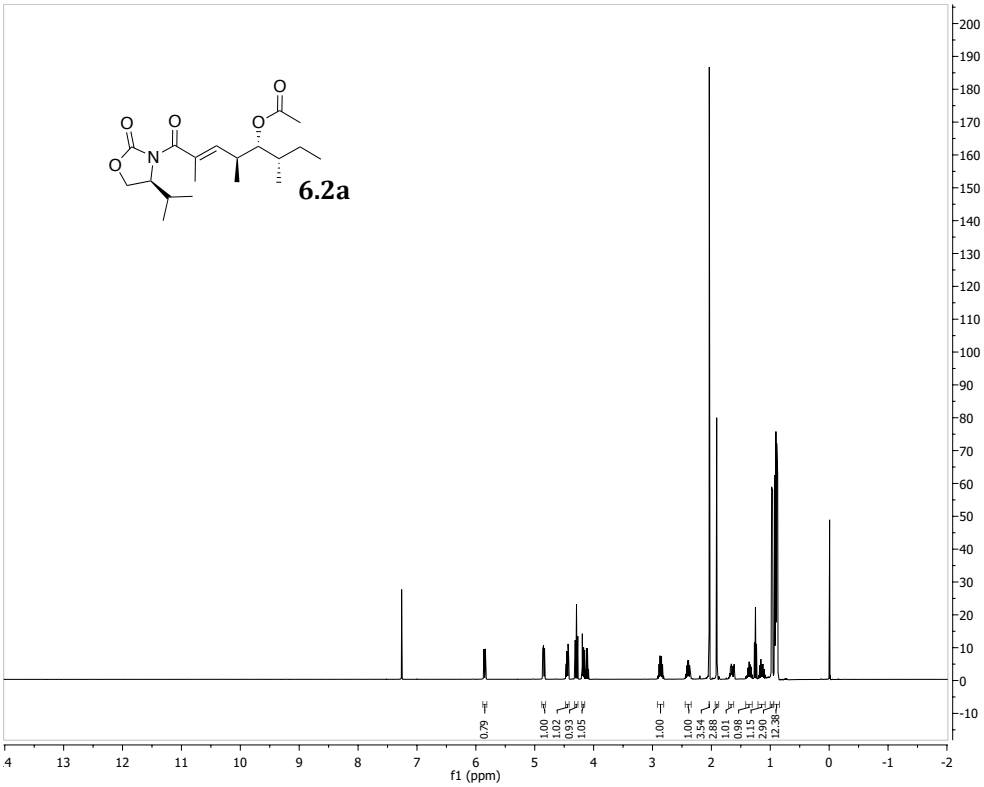

lagunamide A (5.7)
f1 (ppm)

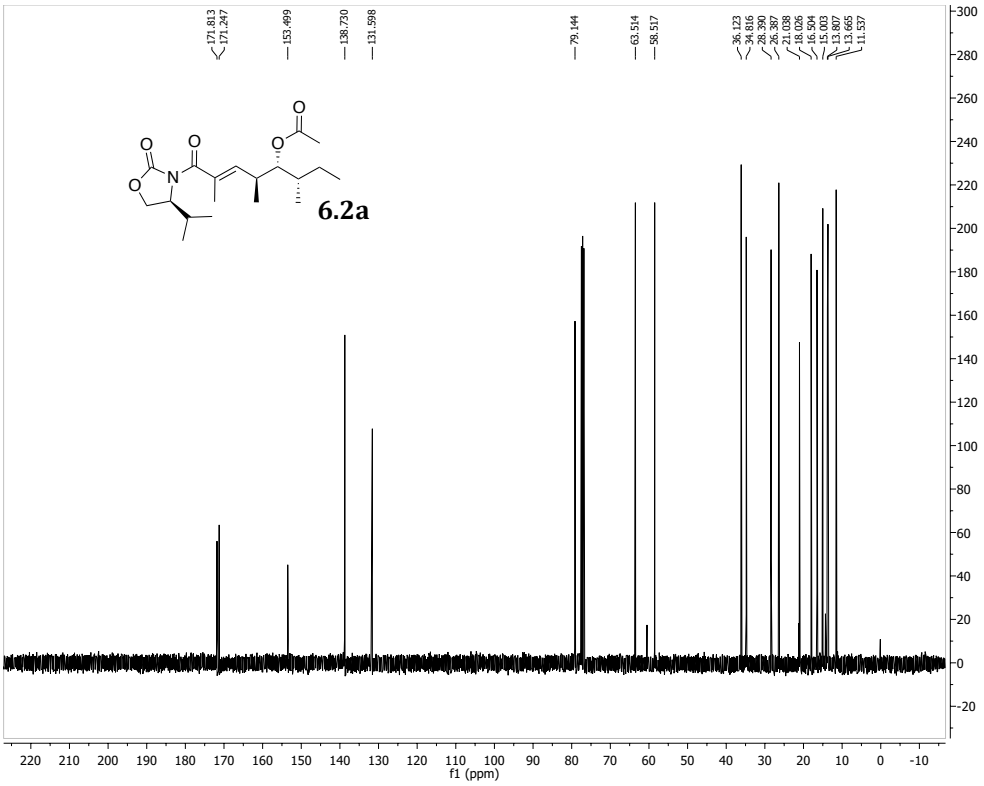

ppm

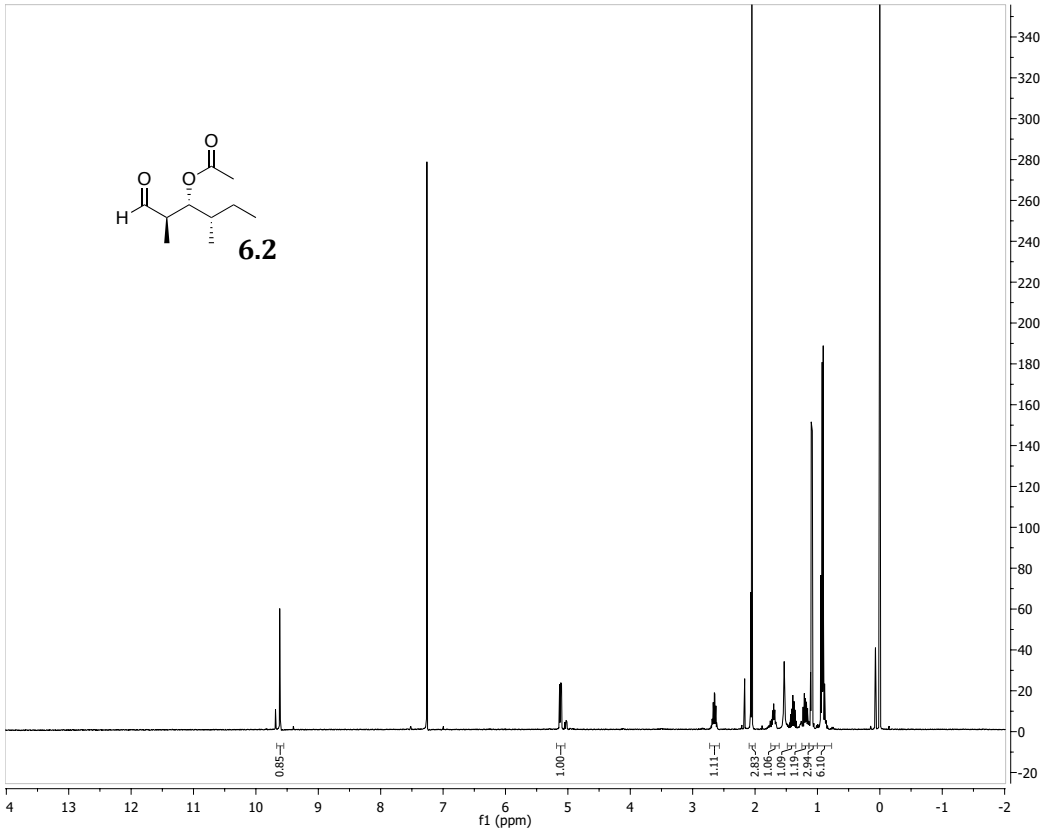

BAB3175 #20-25 RT: 0.31-0.38 AV: 6 SM: 7B NL: 1.98E4
T: - p ESI Full ms [230.00-1000.00]
840.67
822.60
841.67
824.60
844.60
862.60
845.53
863.53
876.60
884.47
820.53
808.60
825.53
838.60
858.60
866.47
803.47
817.60
832.73
847.47
886.53
m/z
EXACT : 841.5201

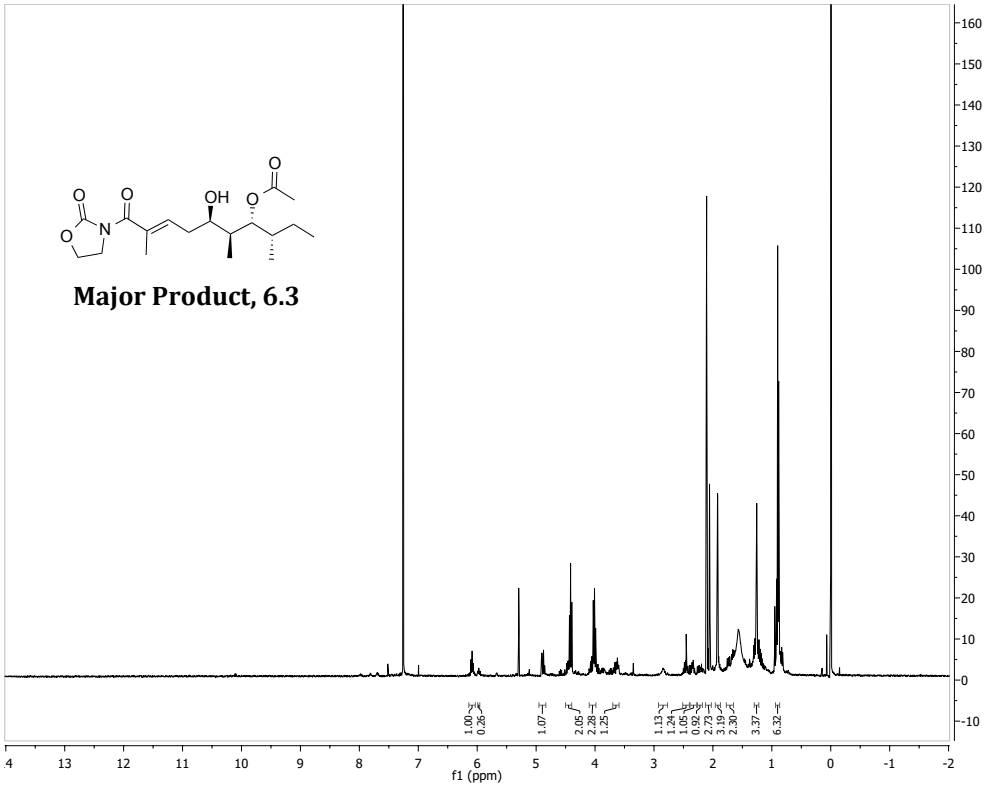

OTBS
6.1
1.00
1.03
1.02
2.28
2.18
3.11
8.73
5.67
f1 (ppm)

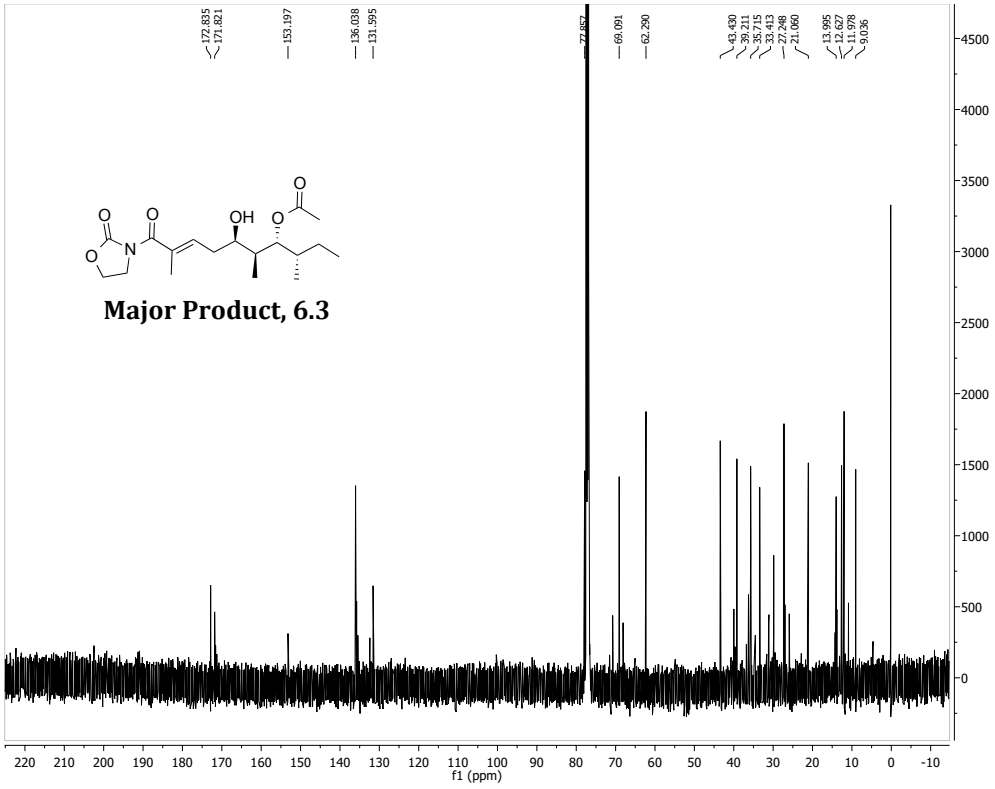

155.708
137.549
133.304
114.826
113.074
77.414
77.160
76.908
62.343
44.987
25.781
18.220
11.544
0.145
-4.398
OTBS
6.1
f1 (ppm)

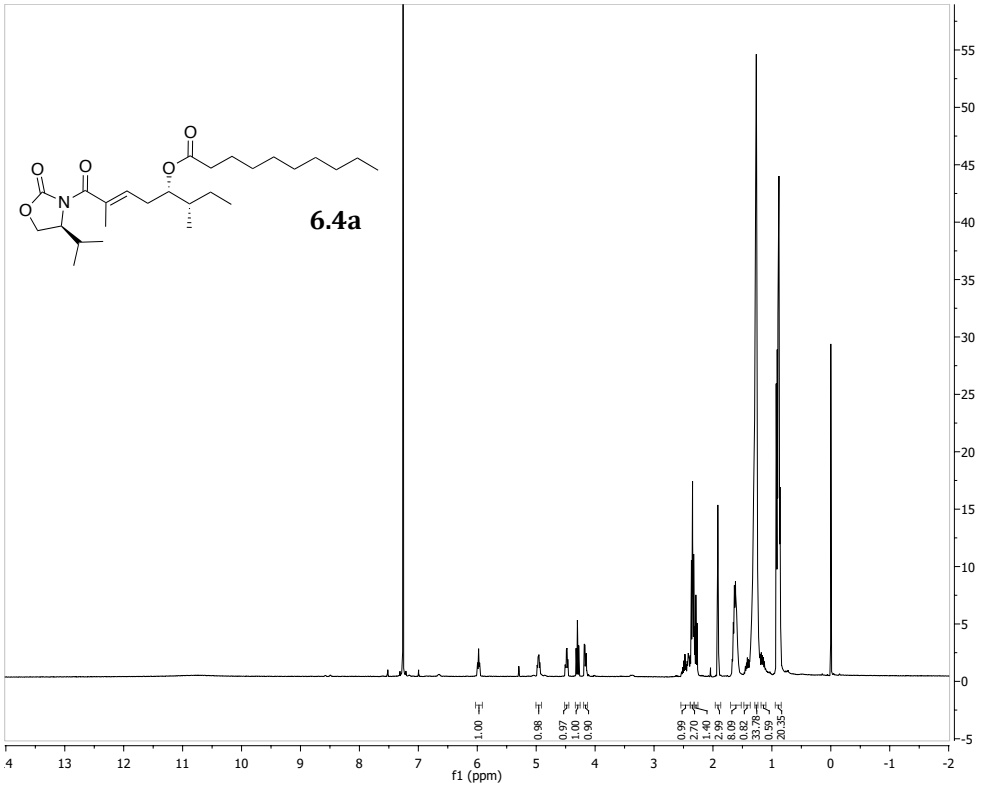

6.2a
0.79
1.00
1.02
0.93
1.05
1.00
1.00
3.54
2.88
1.11
0.98
1.15
2.90
12.38
f1 (ppm)

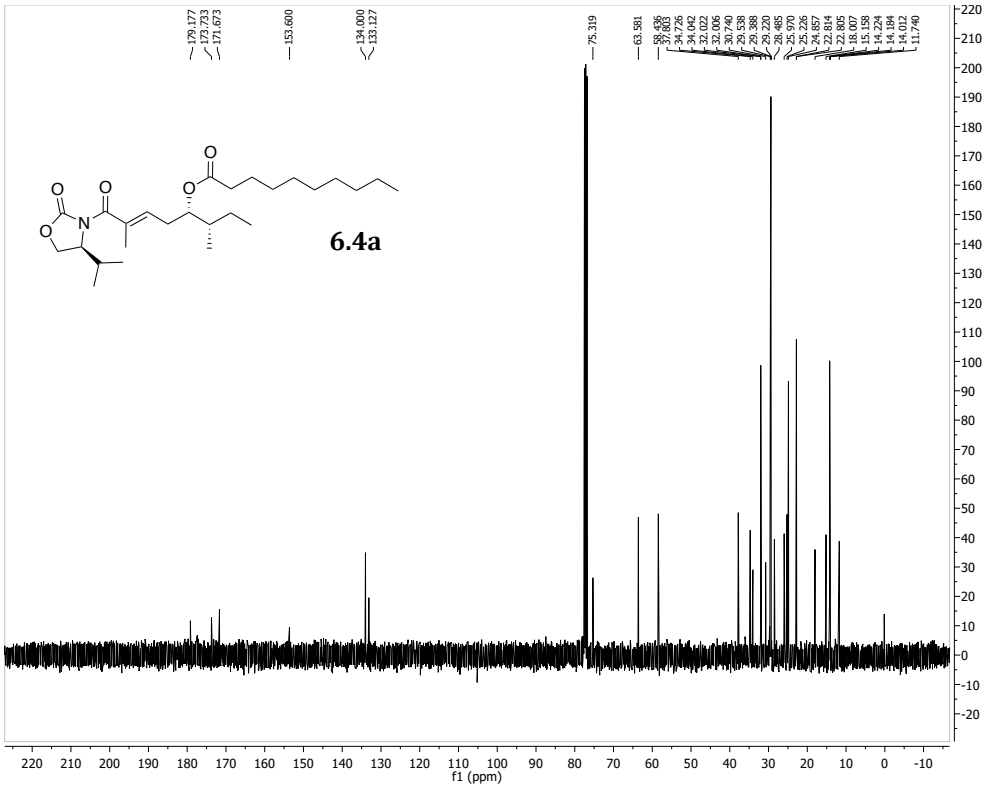

171.813
171.247
153.499
138.730
131.598
79.144
63.514
58.517
36.123
34.816
28.390
26.387
21.038
18.026
16.594
15.503
13.807
13.665
11.537
6.2a
f1 (ppm)

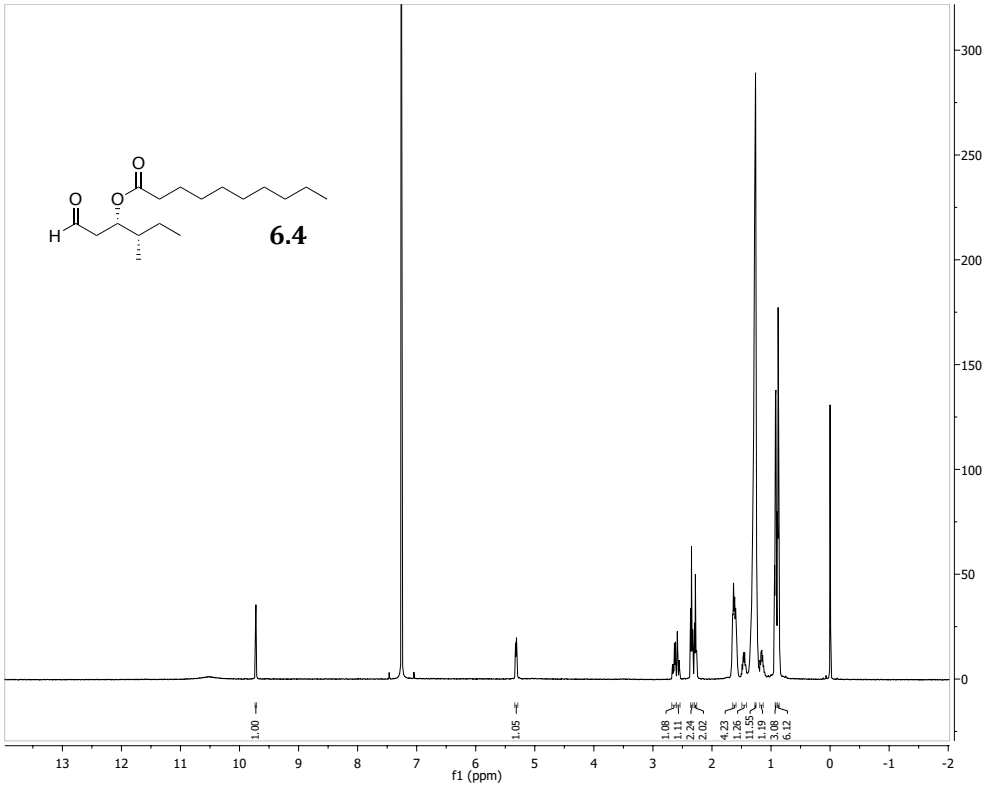

O
O
H
O
6.2
0.85
1.00
1.11
2.83
1.06
1.09
1.19
2.94
6.10
f1 (ppm)

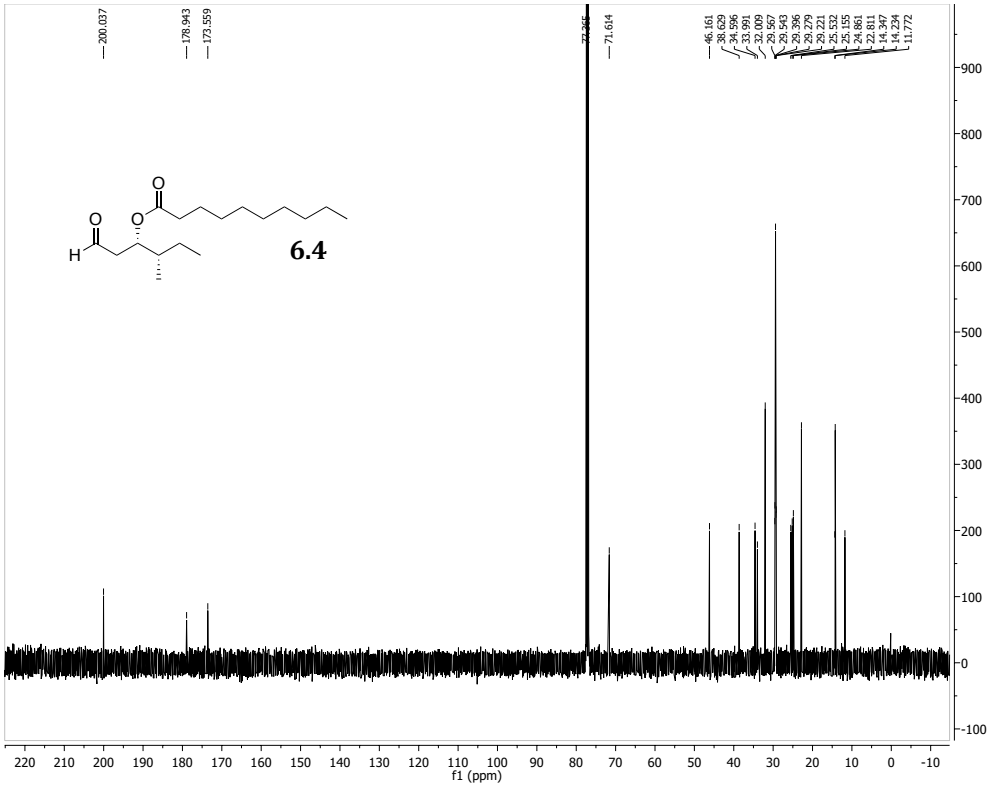

Major Product, 6.3
f1 (ppm)

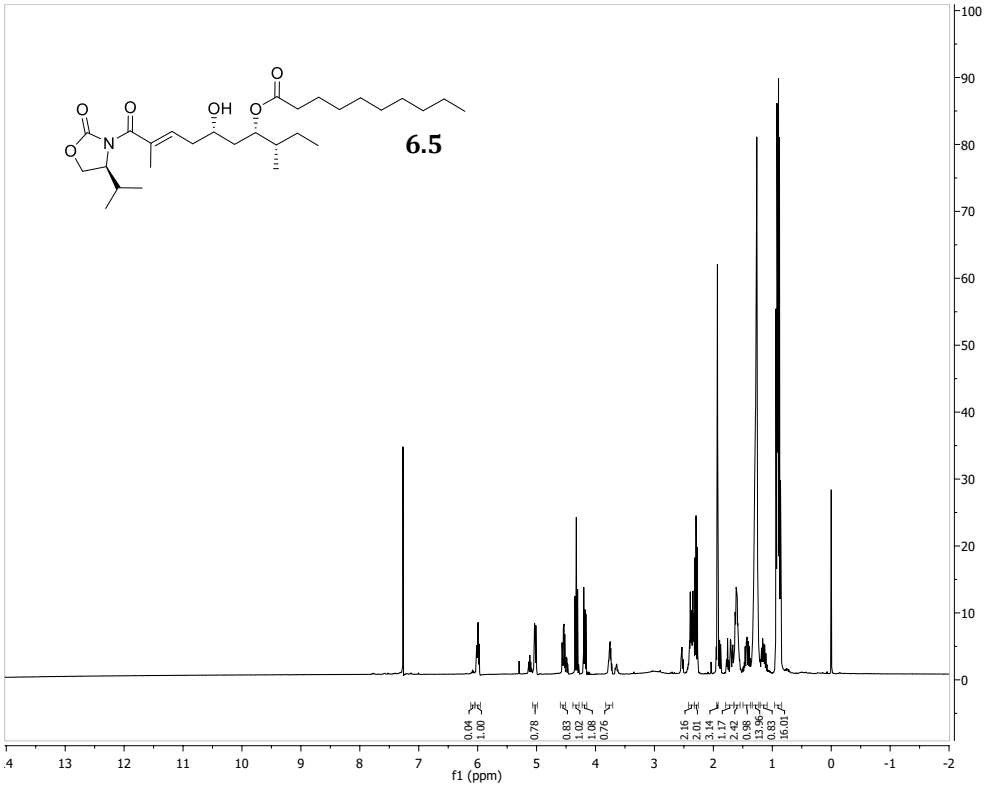

172.835
171.821
153.197
136.038
131.595
77.257
69.091
62.290
43.430
39.211
35.715
34.413
27.748
21.060
13.995
13.677
11.978
9.036
Major Product, 6.3
f1 (ppm)

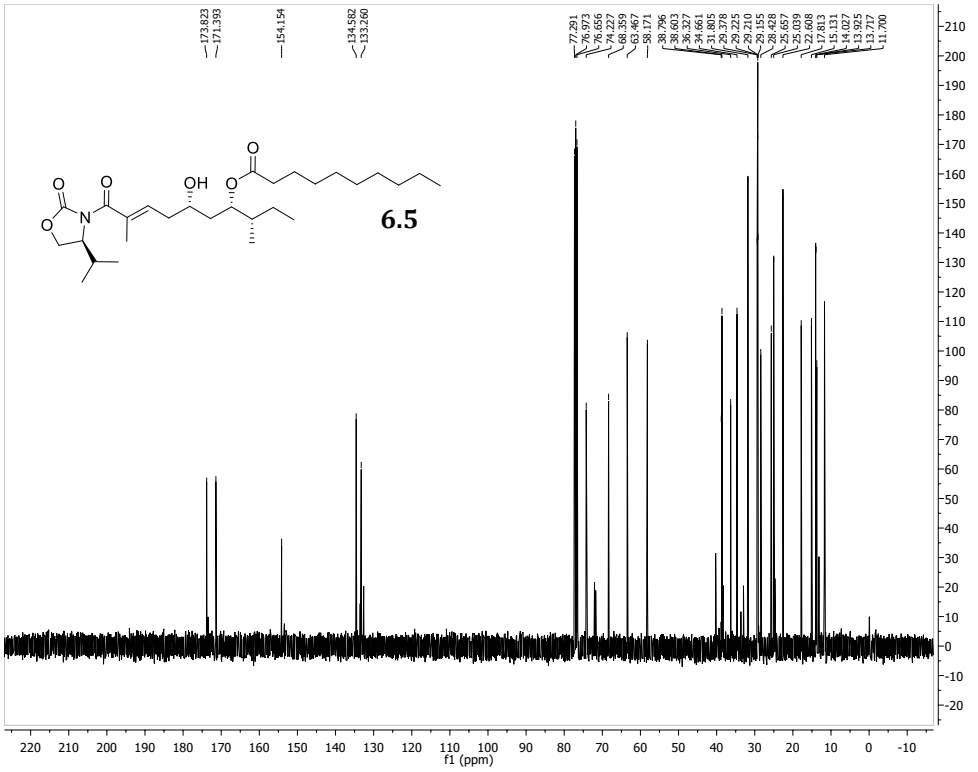

6.4a
1.00
0.98
0.97
1.00
0.90
0.99
2.70
1.40
2.99
8.09
0.82
3.79
3.09
20.35
f1 (ppm)

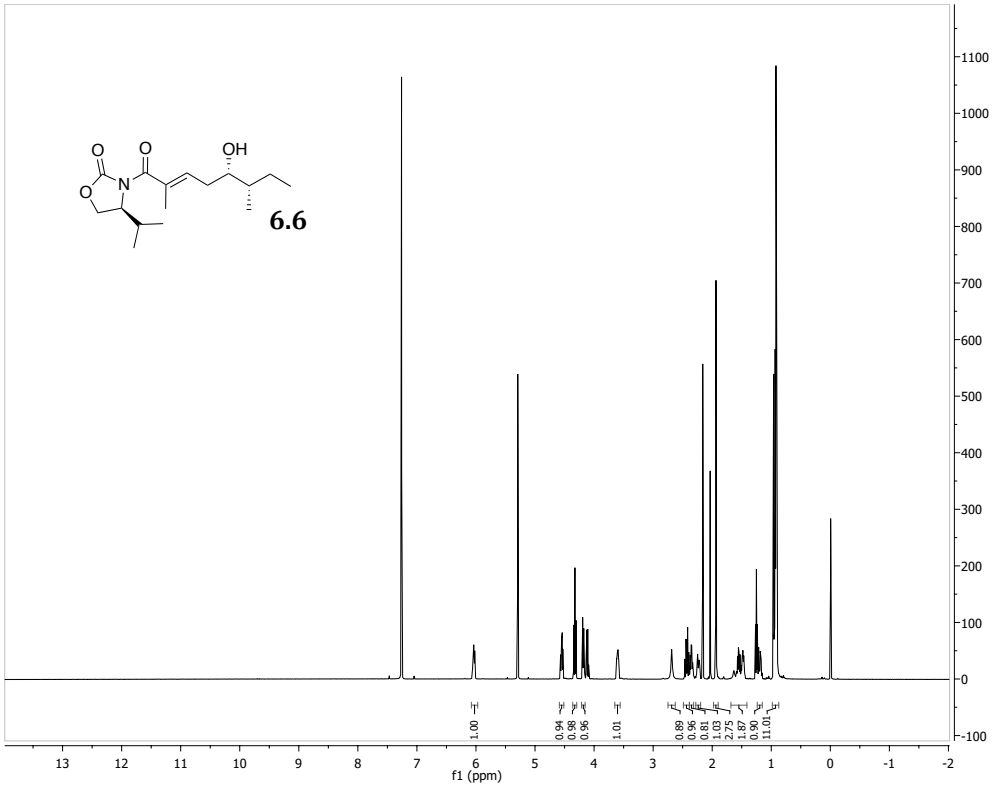

179.177
173.733
171.673
153.600
134.000
133.127
75.319
63.581
58.436
57.803
34.726
34.042
32.022
32.006
30.740
29.558
29.388
29.220
28.485
25.970
25.226
24.657
22.814
22.805
18.707
15.158
14.224
14.184
14.012
11.740
6.4a
f1 (ppm)

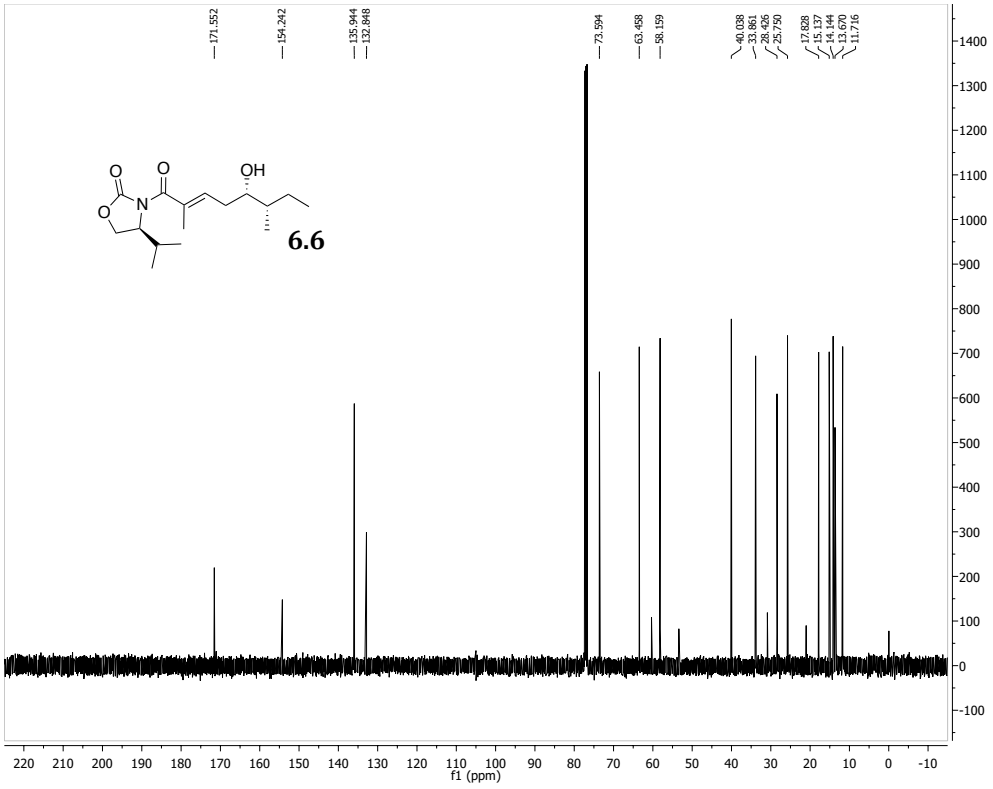

6.4
1.00
1.05
1.08
1.11
2.24
2.02
4.23
1.26
11.55
1.19
3.08
6.12
f1 (ppm)

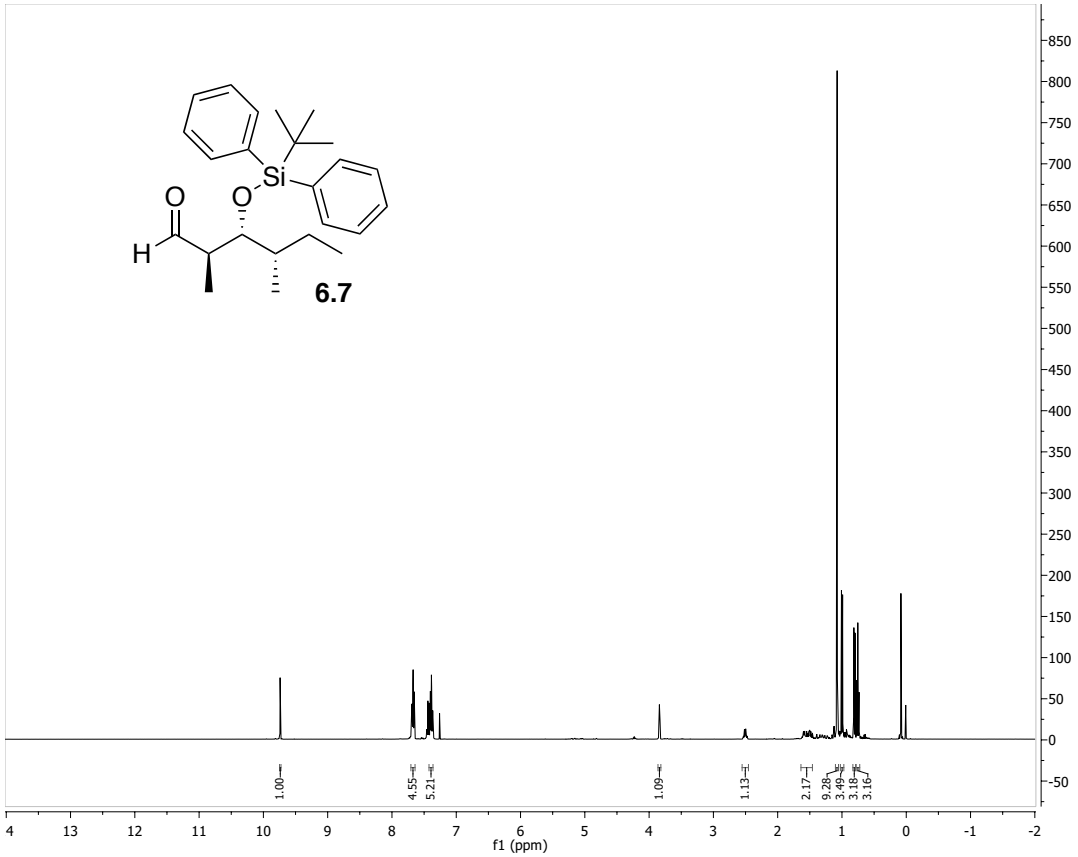

200.037
178.943
173.559
77.365
71.614
46.161
38.629
34.596
33.991
32.009
29.567
29.345
29.396
29.279
29.221
25.532
25.155
24.861
22.811
14.397
14.294
11.772
6.4
f1 (ppm)

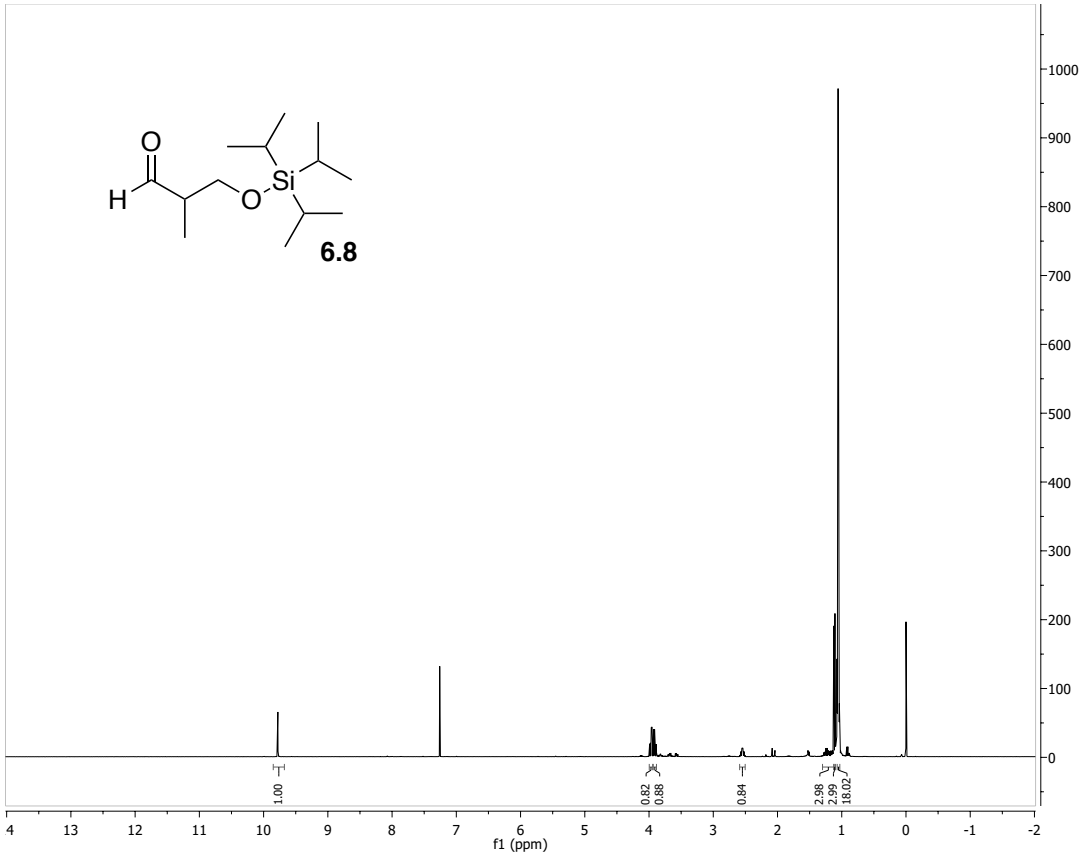

6.5
f1 (ppm)

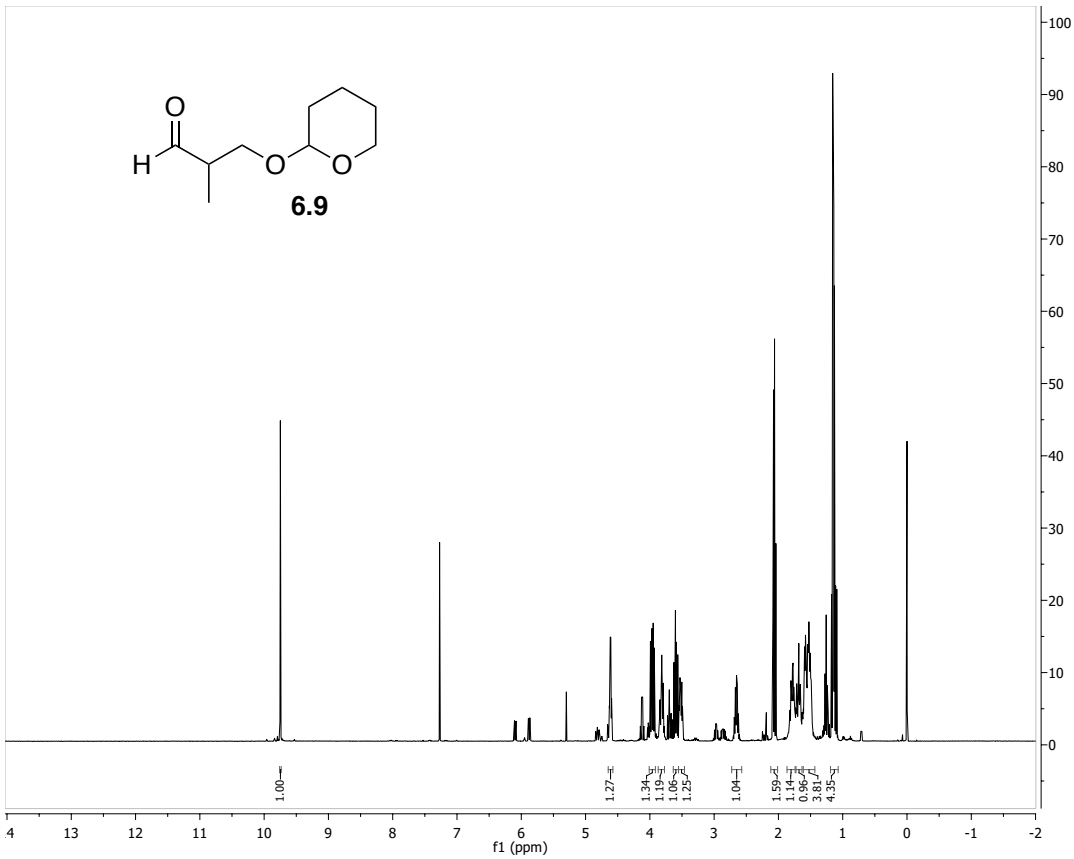

173.823
171.393
154.154
134.582
133.260
77.291
76.973
76.656
74.227
68.359
63.497
58.171
38.796
38.603
36.327
34.661
31.805
29.378
29.225
29.210
29.155
28.428
25.657
25.039
22.608
17.813
15.131
14.027
13.925
13.717
11.700
6.5
f1 (ppm)

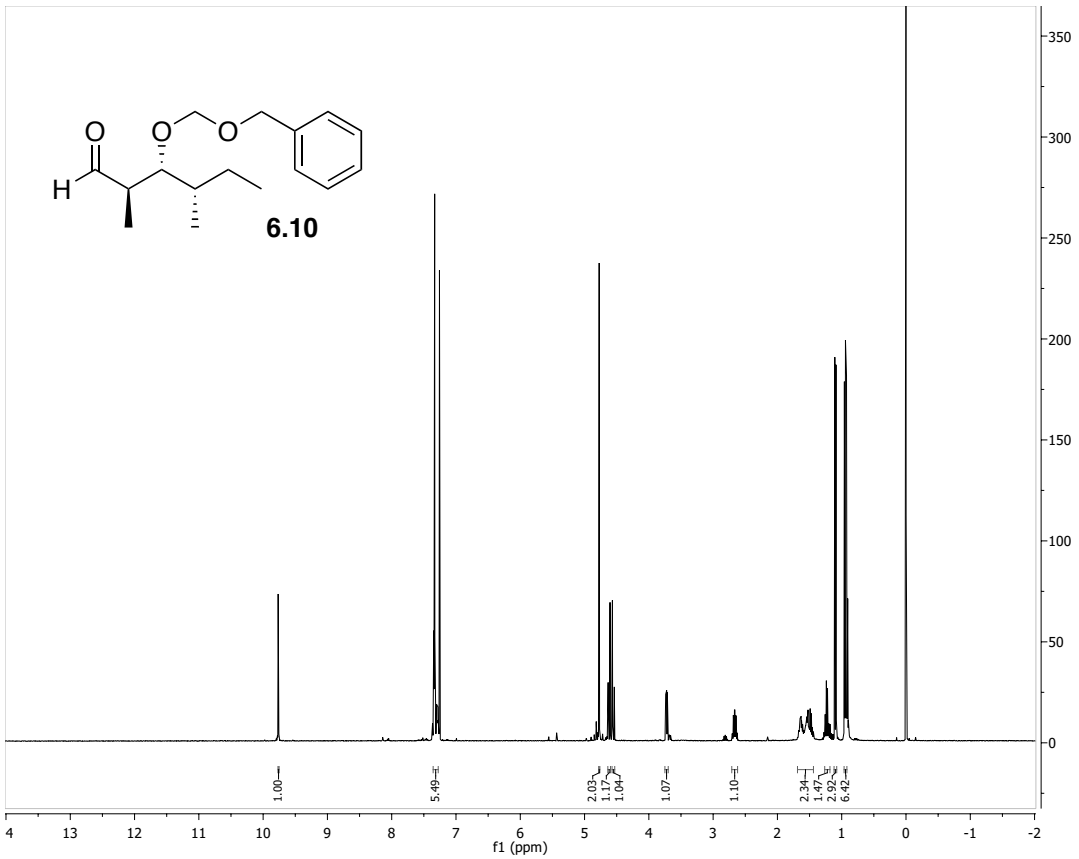

6.6
1.00
0.94
0.98
0.96
1.01
0.89
0.96
0.81
1.03
2.75
1.57
0.90
11.01
f1 (ppm)

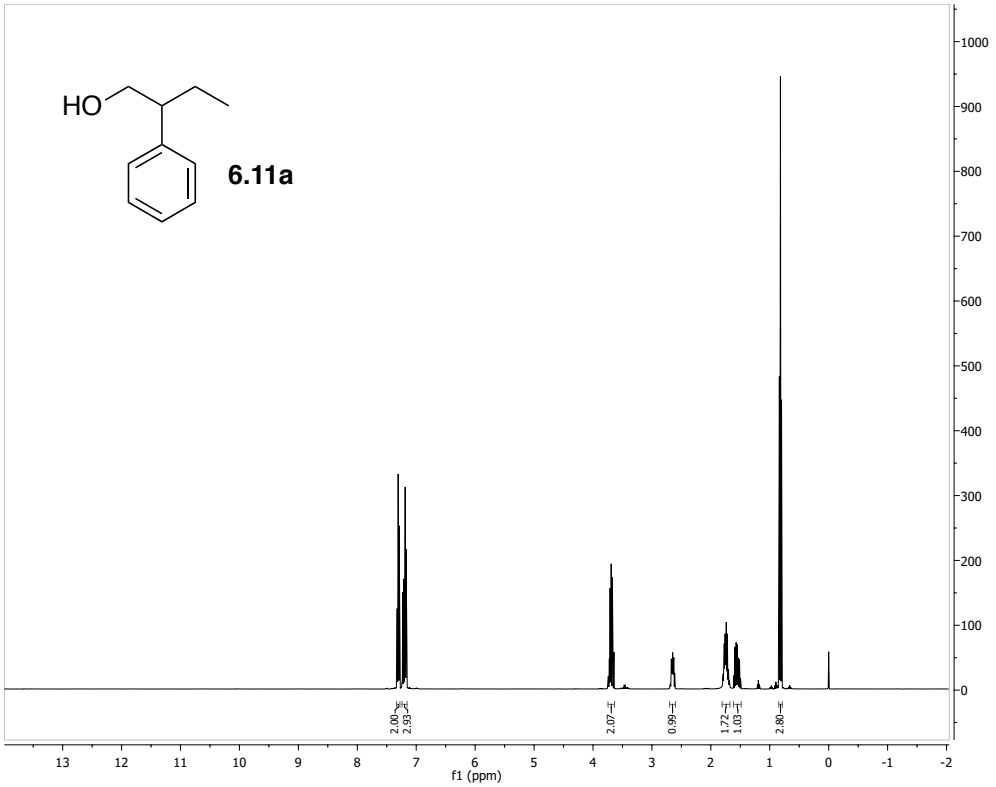

171.552
154.242
135.944
132.848
73.594
63.458
58.159
40.038
33.861
28.425
25.750
17.828
15.137
14.144
13.670
11.716
6.6
f1 (ppm)

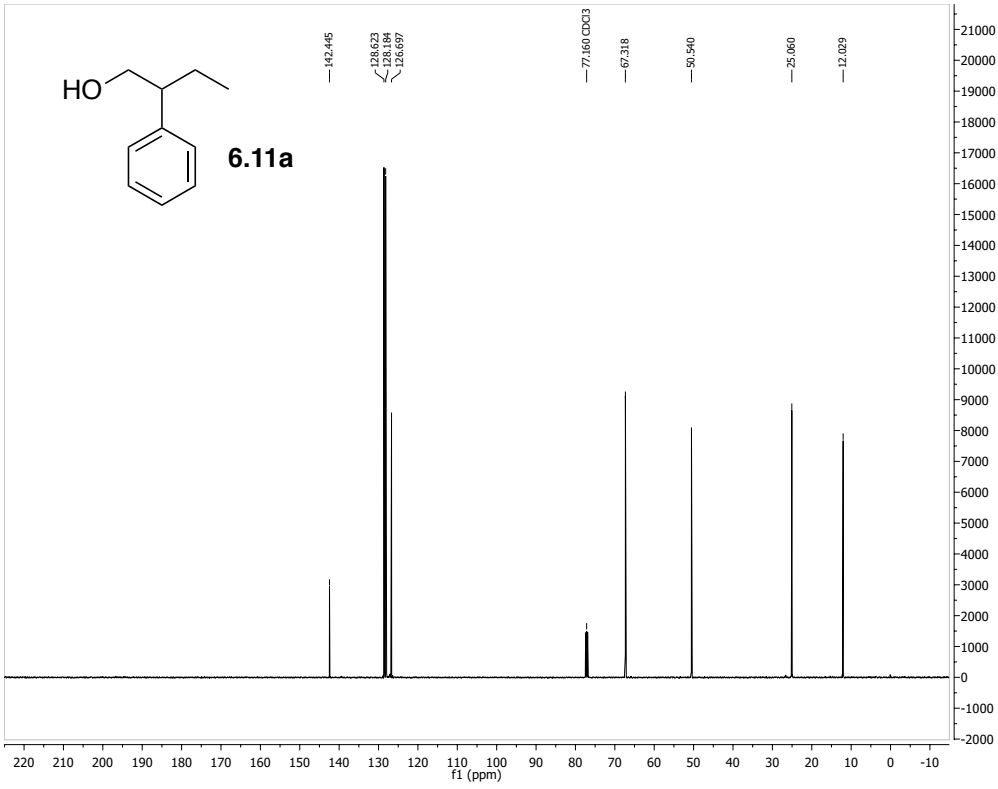

Si
O
O
H
6.7
1.00
4.55
5.21
1.09
1.13
2.17
9.28
3.49
3.18
3.16
f1 (ppm)

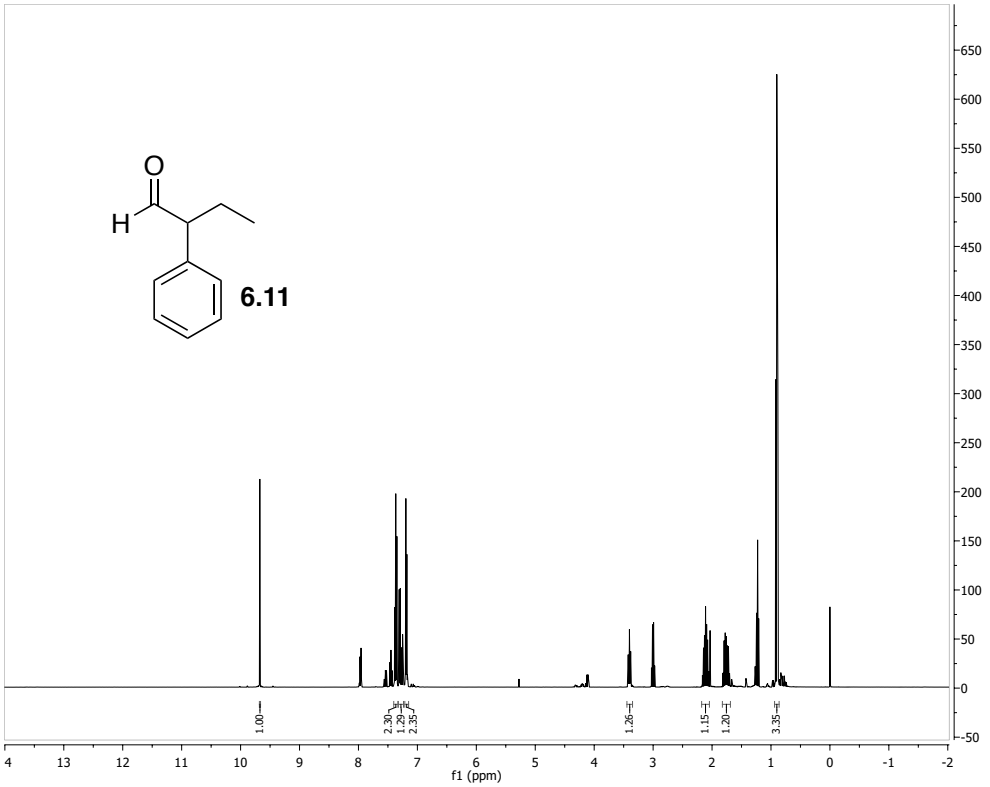

O
H
O
Si
6.8
1000
900
800
700
600
500
400
300
200
100
0
1.00
0.82
0.88
0.84
2.98
2.99
18.02
4
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

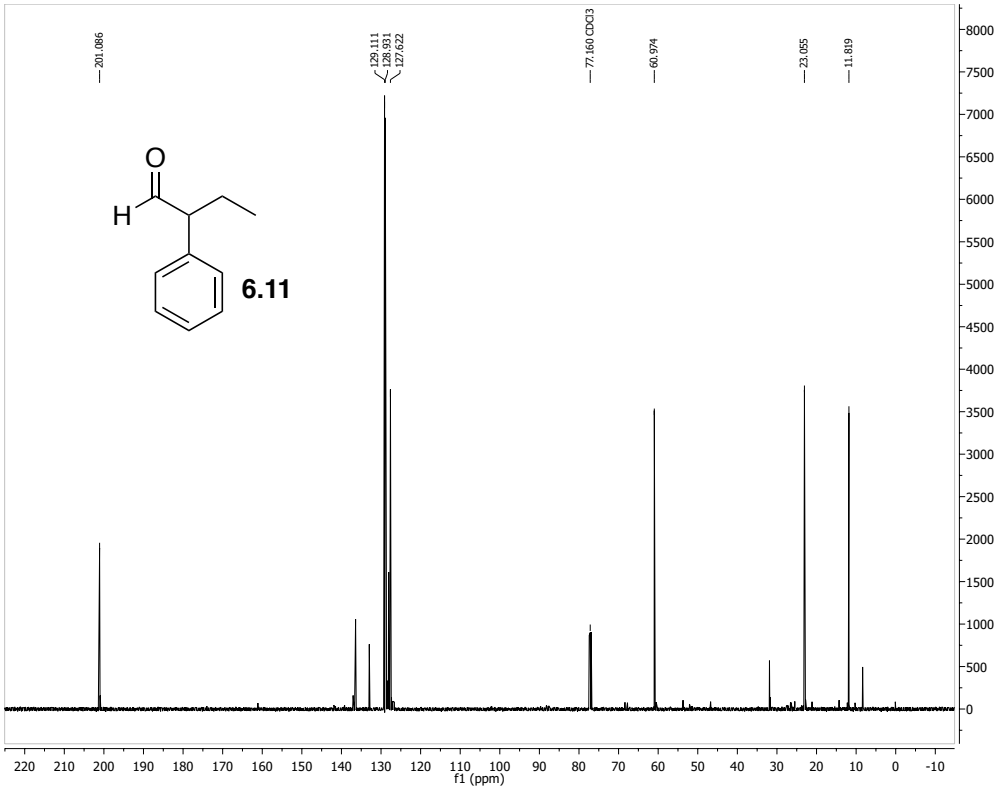

O
H
O
O
6.9
100
90
80
70
60
50
40
30
20
10
0
1.00
1.27
1.34
1.19
1.06
1.25
1.04
1.59
1.14
0.96
3.81
4.35
4
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

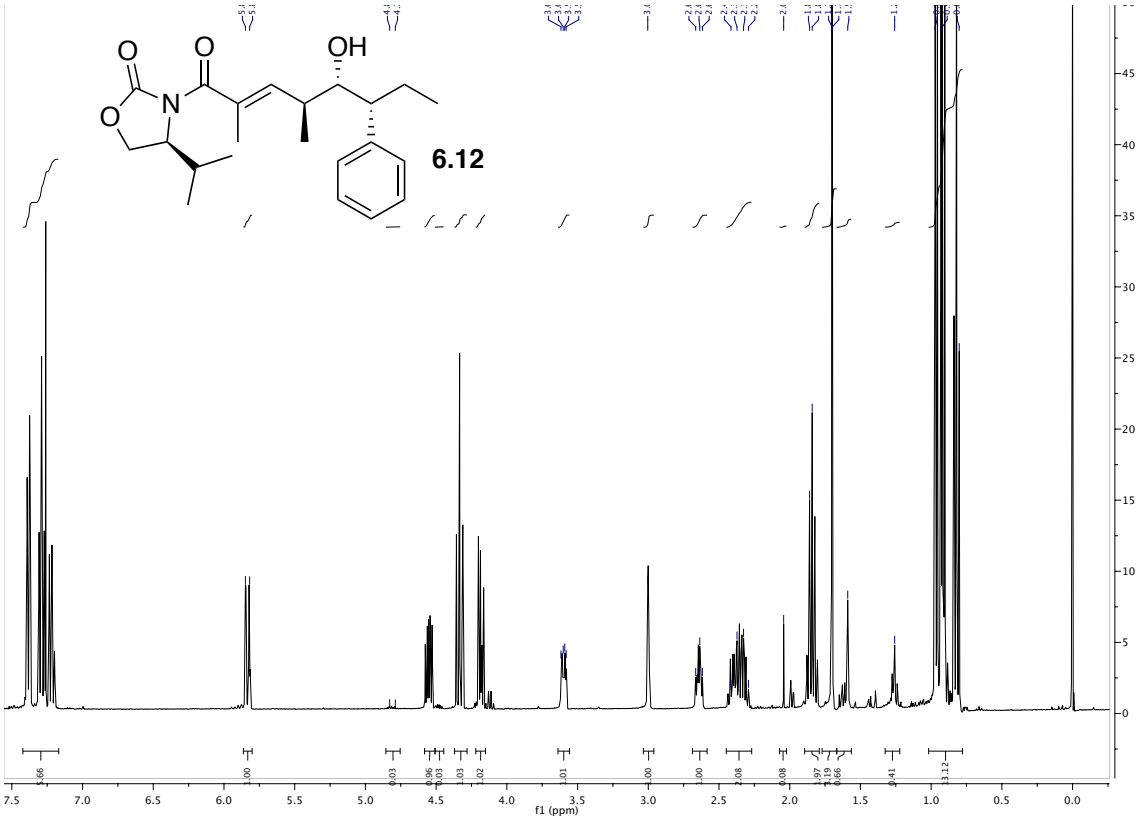

O
O
O
H
6.10
350
300
250
200
150
100
50
0
1.00
5.49
2.03
1.17
1.04
1.07
1.10
2.34
1.47
2.92
6.42
4
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

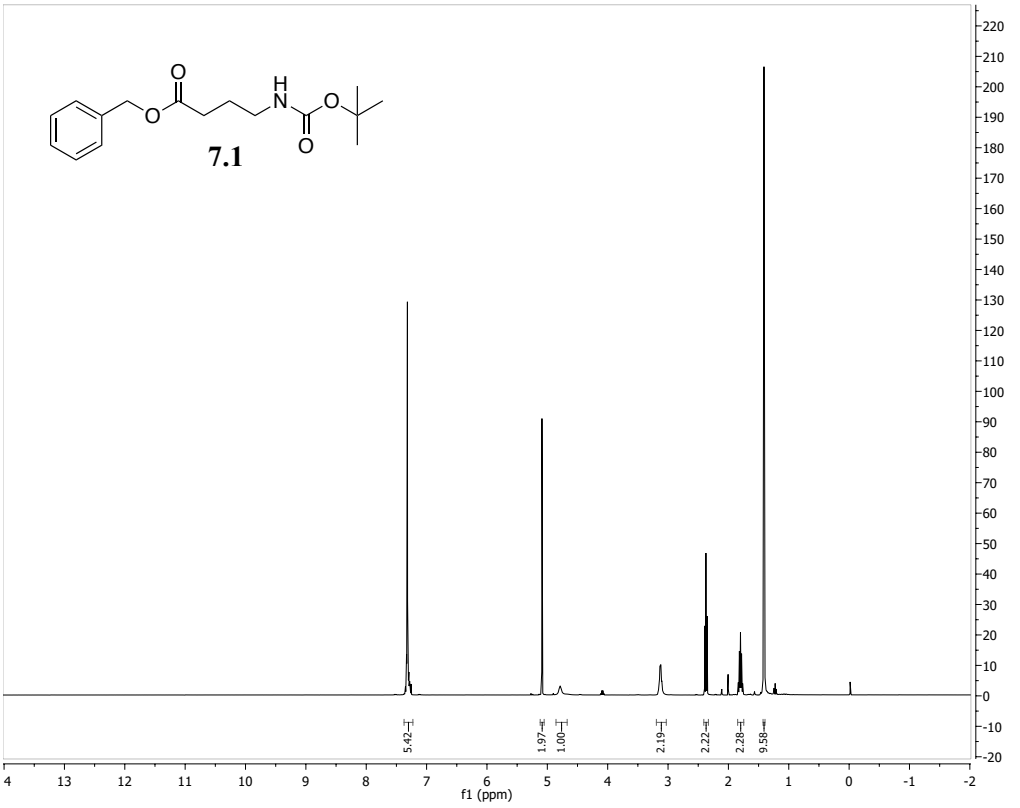

HO
6.11a
2.00
2.93
2.07
0.99
1.72
1.03
2.80
f1 (ppm)

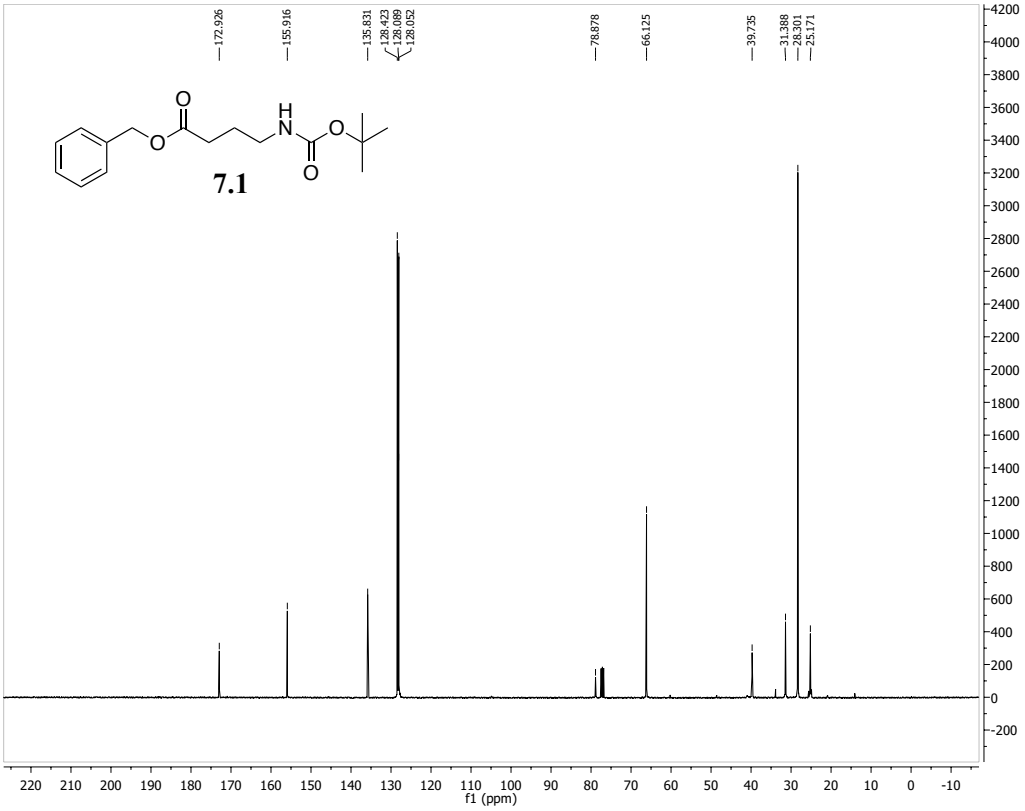

HO
6.11a
142.445
128.623
128.184
126.697
77.160 CDCl3
67.318
50.540
25.060
12.029
f1 (ppm)

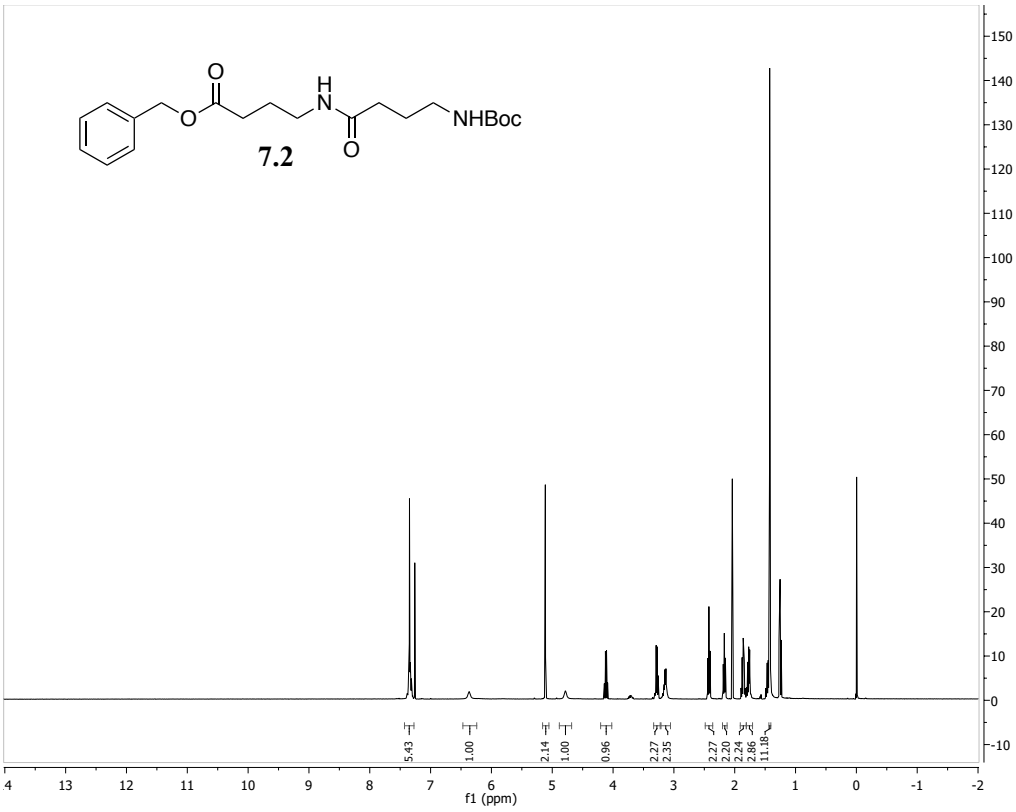

O
H
6.11
1.00
2.30
1.29
2.35
1.26
1.15
1.20
3.35
f1 (ppm)

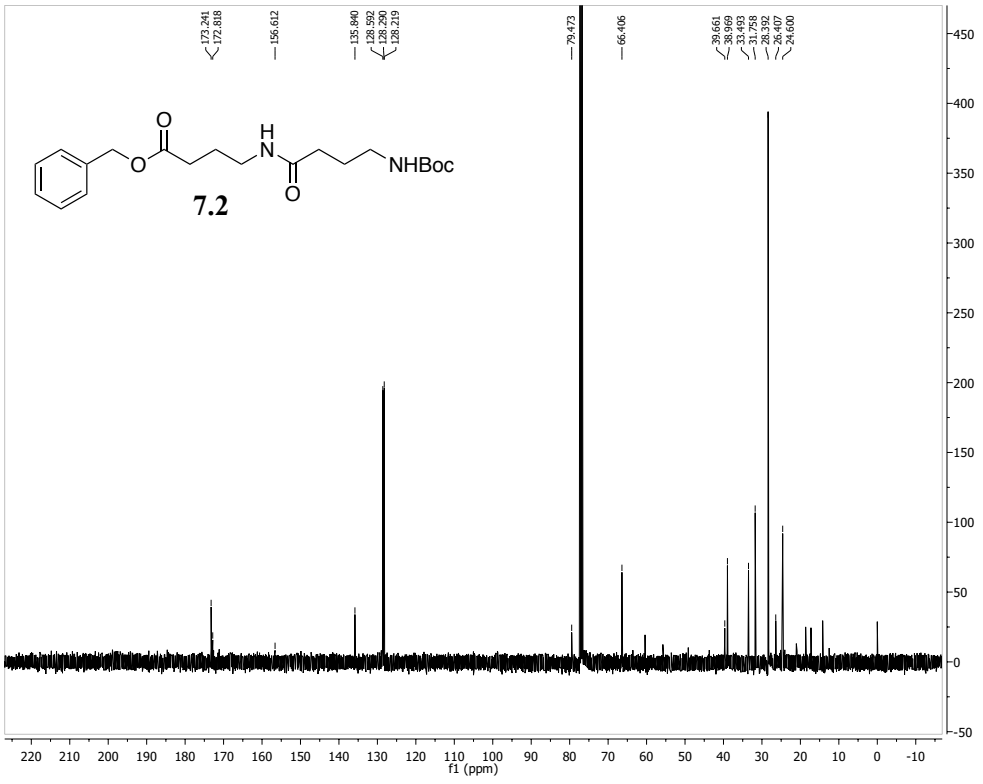

201.086
129.111
128.931
127.622
77.160 CDCl3
60.974
23.055
11.819
O
H
6.11
f1 (ppm)

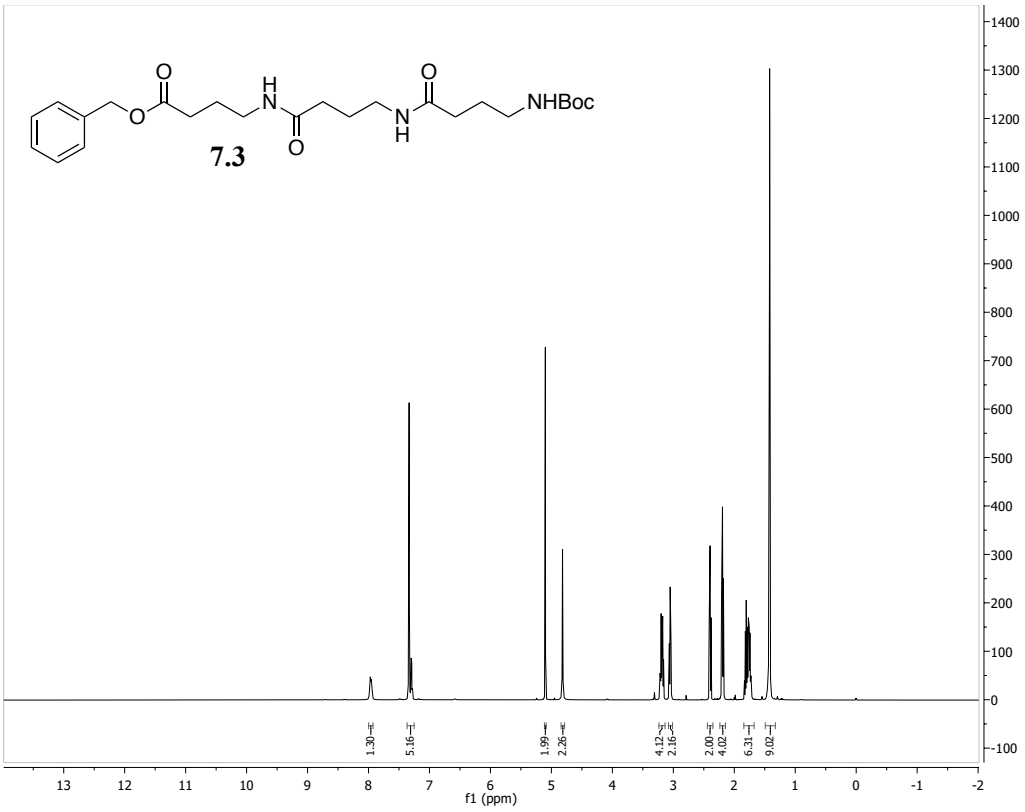

O
O
N
O
OH
6.12
f1 (ppm)

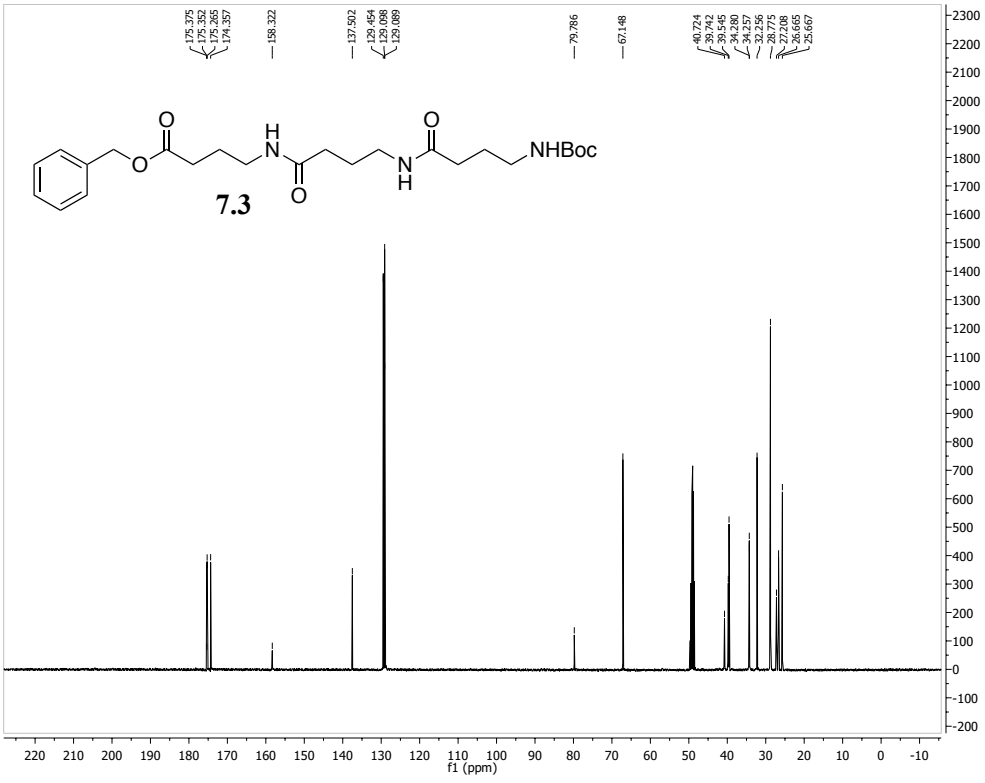

7.1
5.42
1.97
1.00
2.19
2.22
2.28
9.58
f1 (ppm)

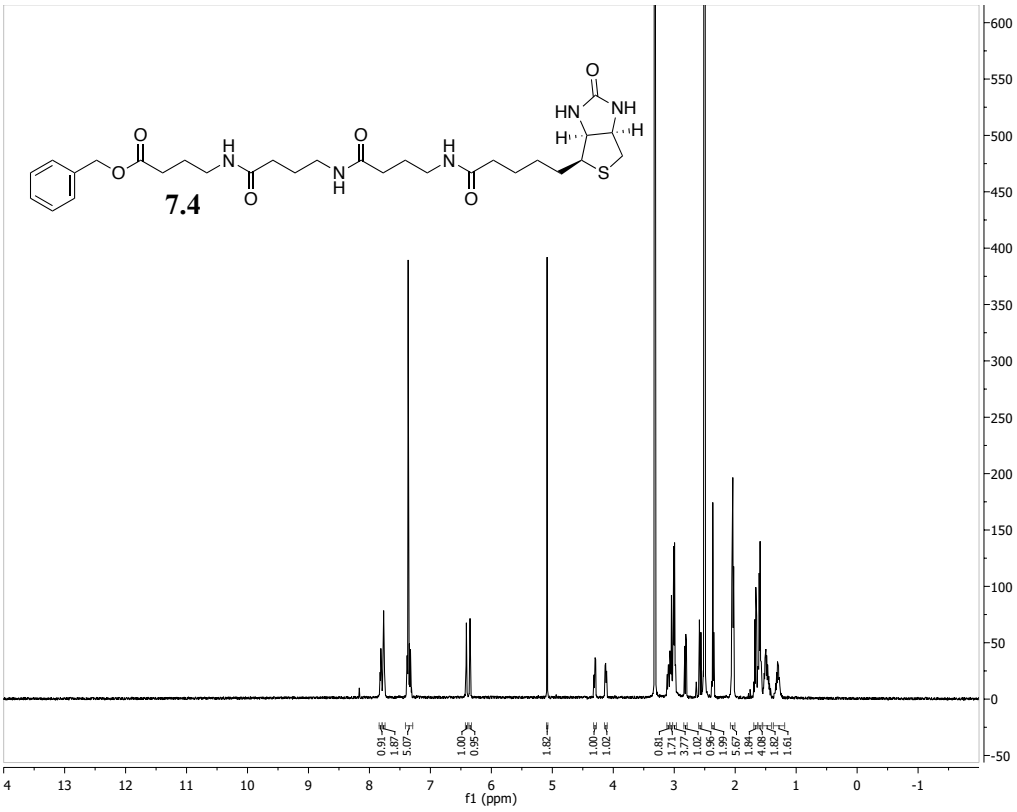

172.926
155.916
135.831
128.423
128.089
128.052
78.878
66.125
39.735
31.388
28.301
25.171
7.1
f1 (ppm)

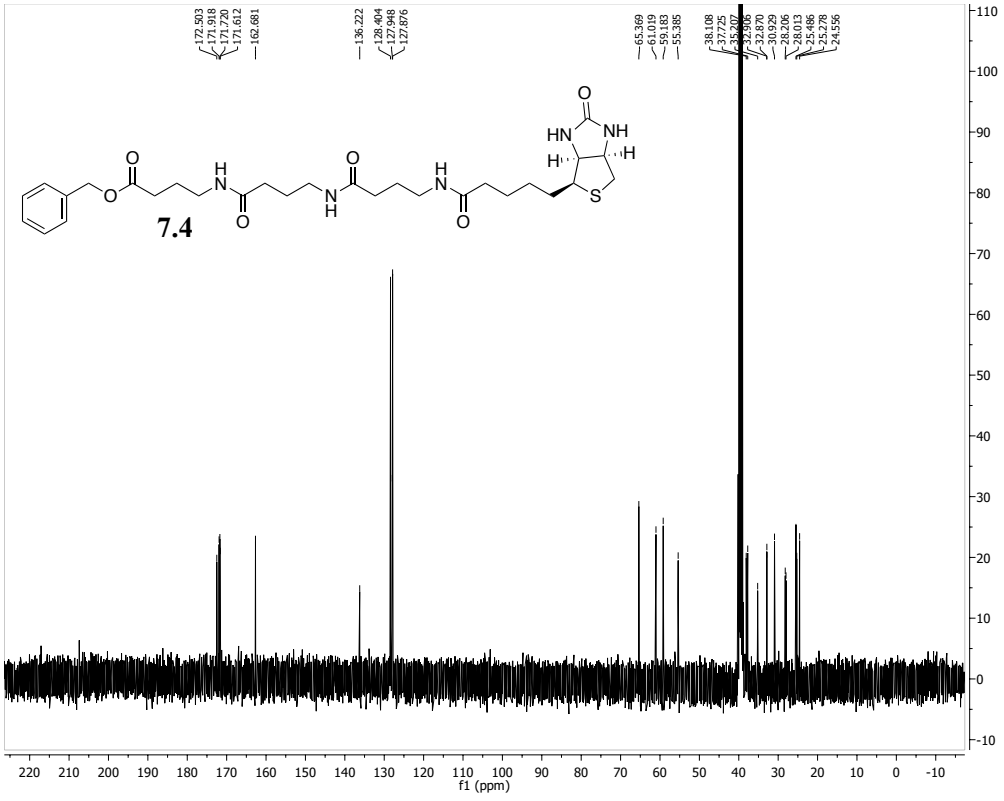

O
O
H
N
O
NHBoc
7.2
5.43
1.00
2.14
1.00
0.96
2.27
2.35
2.27
2.20
2.24
2.86
11.18
f1 (ppm)

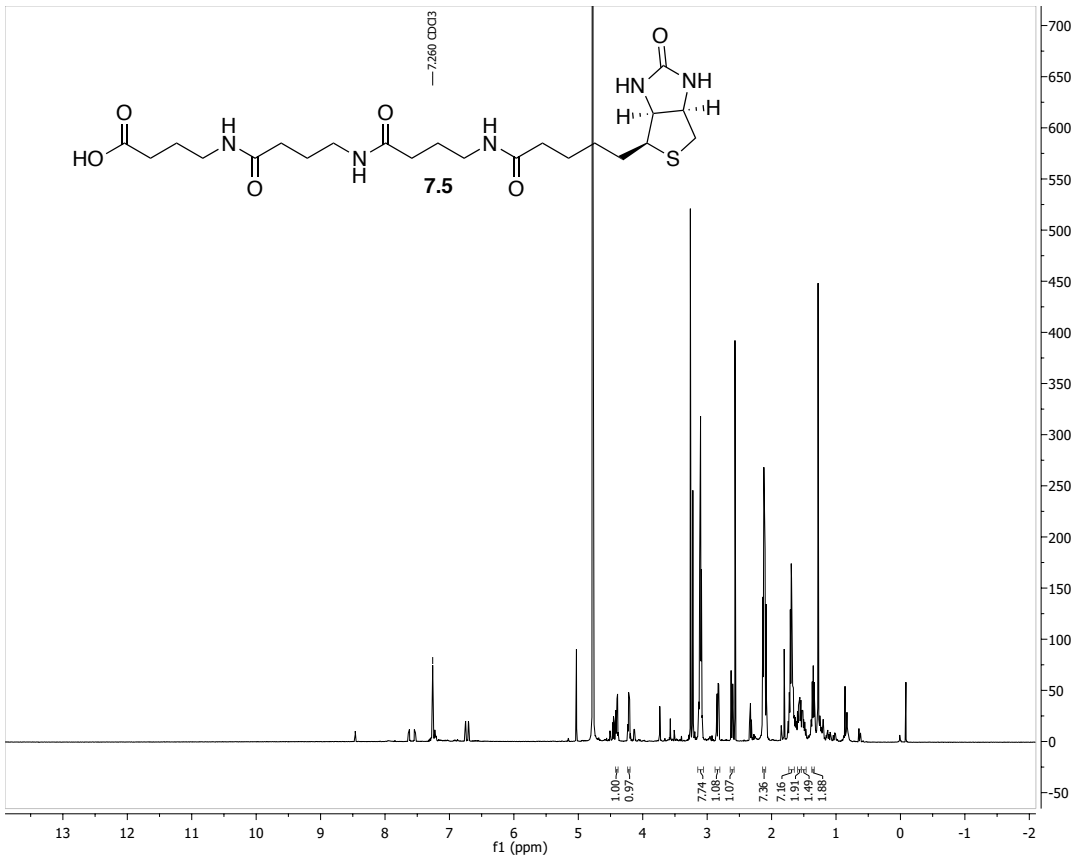

173.241
172.818
156.612
135.840
128.592
128.290
128.219
79.473
66.406
39.661
38.969
33.493
31.758
28.592
26.407
24.600
O
O
H
N
O
NHBoc
7.2
f1 (ppm)

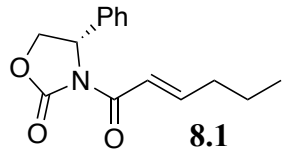

7.3
NHBoc
1.30
5.16
1.99
2.26
4.12
2.16
2.00
4.02
6.31
9.02
f1 (ppm)


175.375
175.352
175.265
174.357
158.322
137.502
129.454
129.098
129.089
79.786
67.148
40.724
39.742
39.545
34.257
34.208
32.256
28.775
27.208
26.665
25.667
7.3
NHBoc
f1 (ppm)

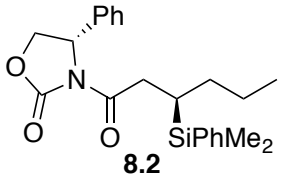

7.4
f1 (ppm)


7.4
f1 (ppm)


7.260 CDCl3
7.5
f1 (ppm)

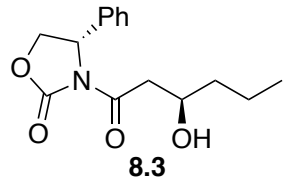


8.1

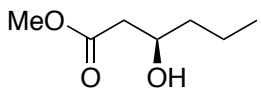

Ph
O
N
O
O
SiPhMe2

8.2

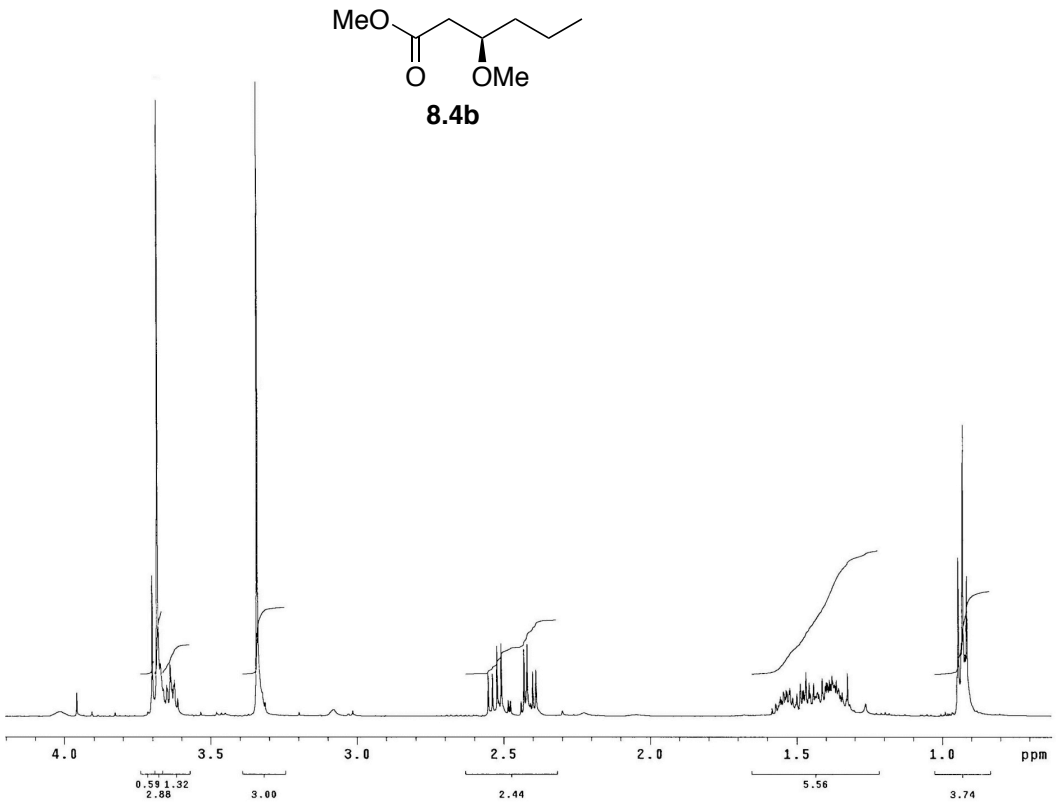
9
8
7
6
5
4
3
2
1
ppm
2.10 2.09
6.27
0.98
1.00
1.01
2.02
1.01
1.03
3.10
3.03
3.23
2.99

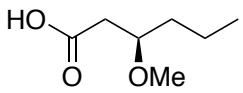


8.3

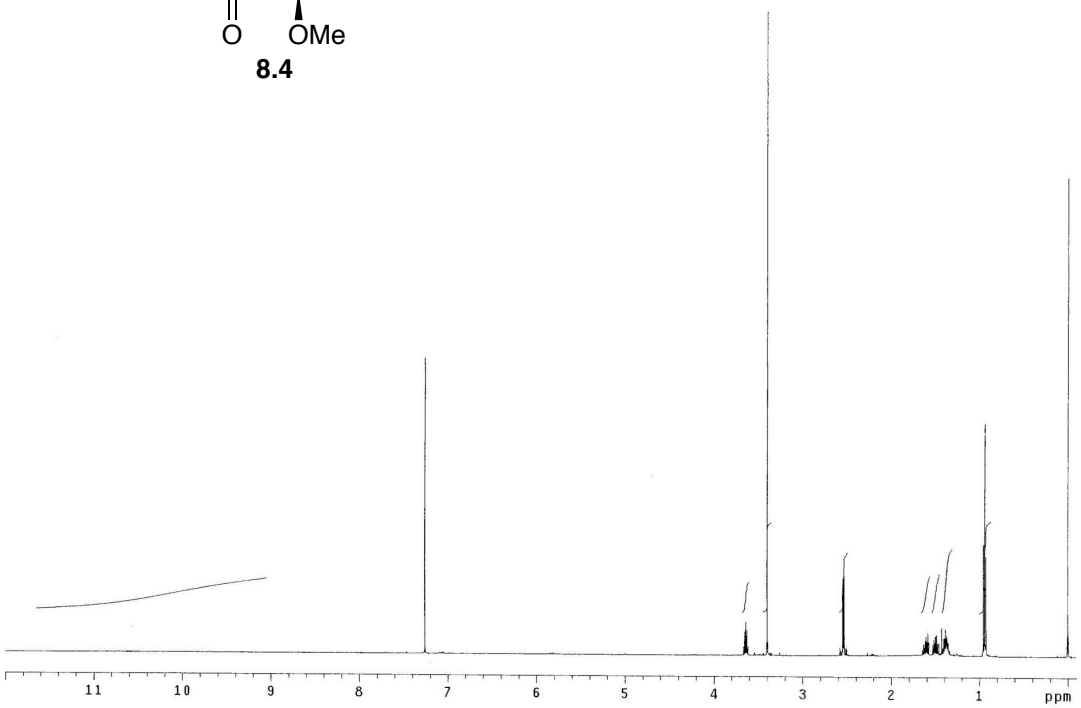


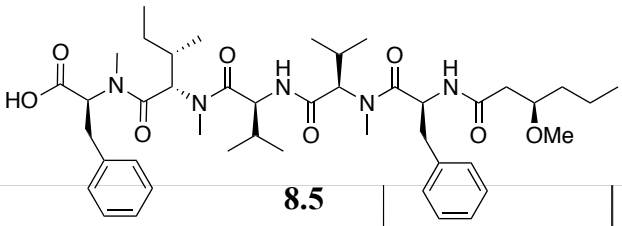
8.4a


MeO
O
OMe
8.4b
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.59 1.32
2.88
3.00
2.44
5.56
3.74

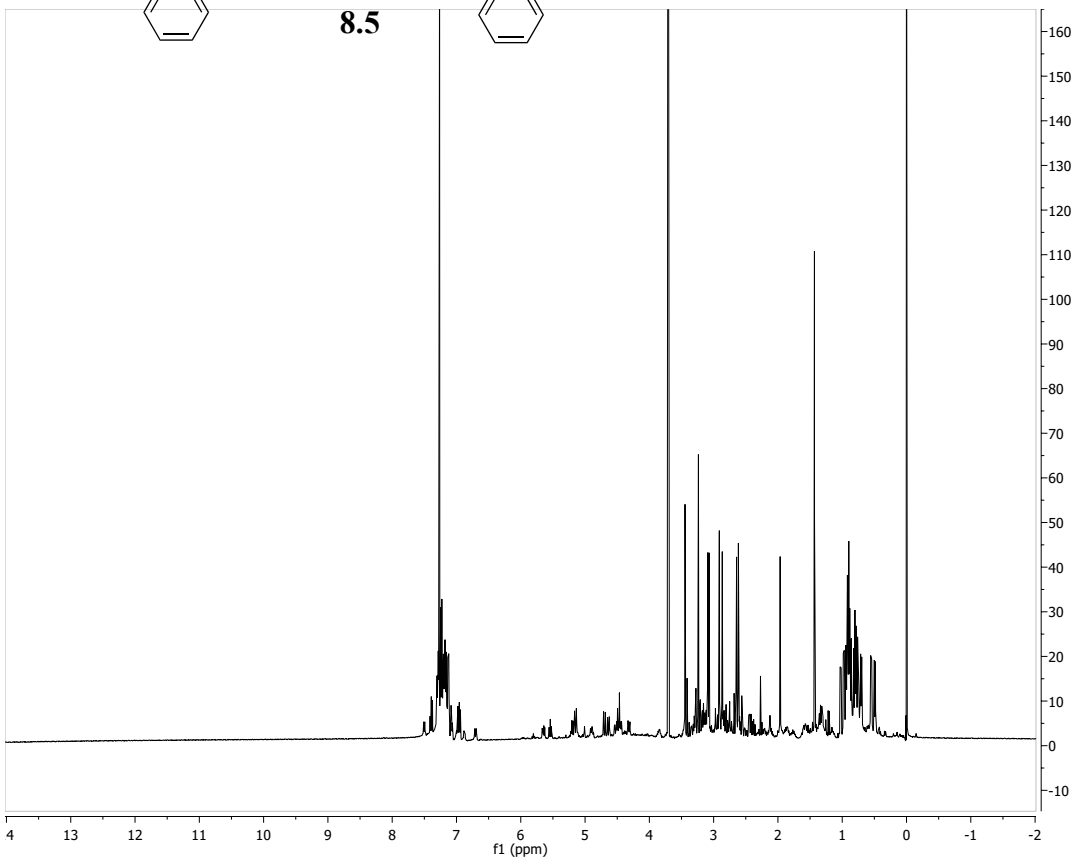


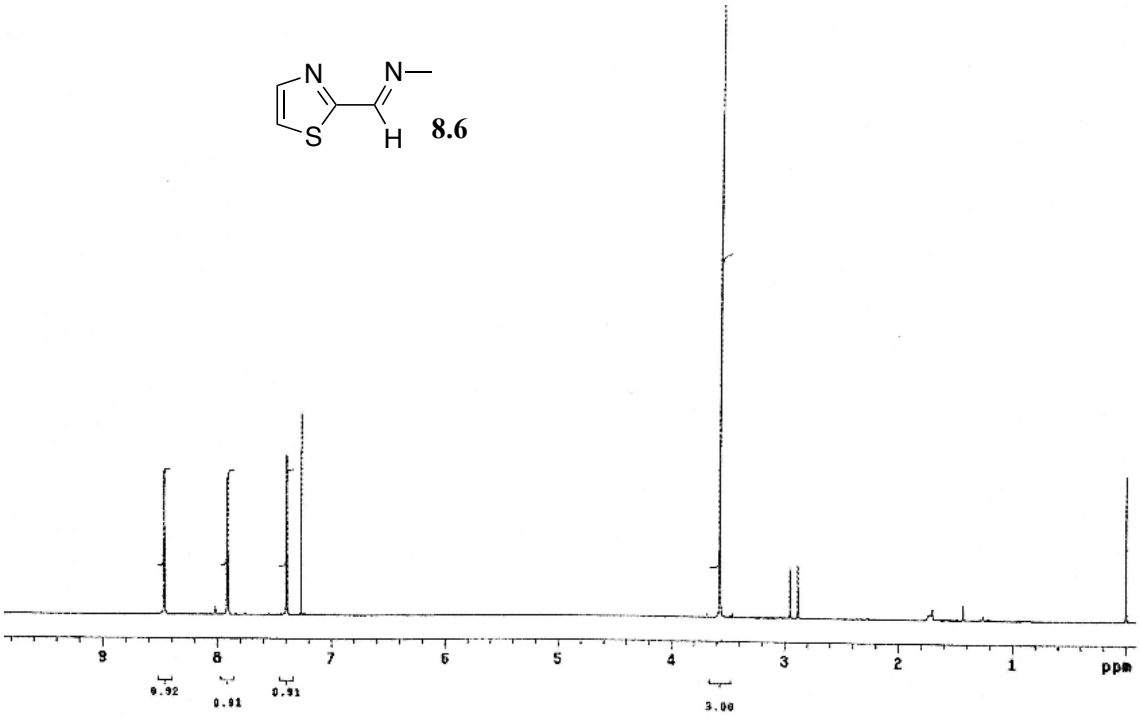
8.4

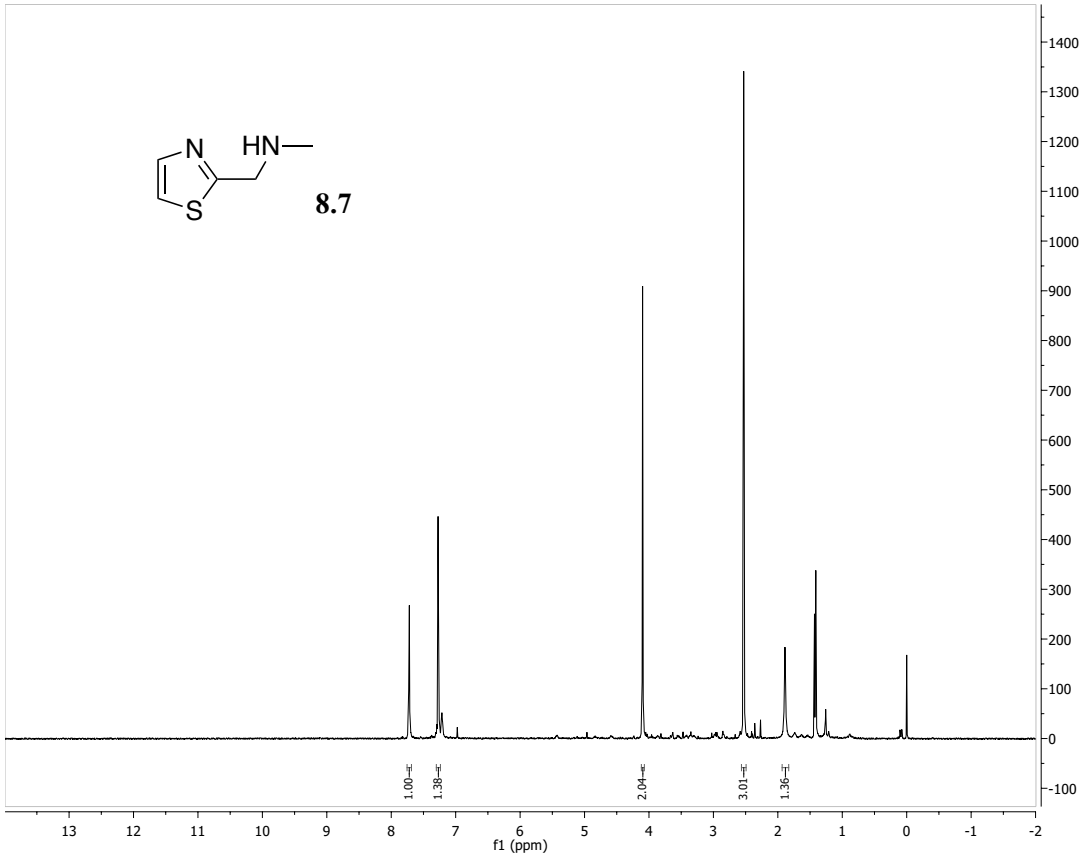



HO
O
N
O
N
O
H
N
O
N
O
H
N
O
OMe

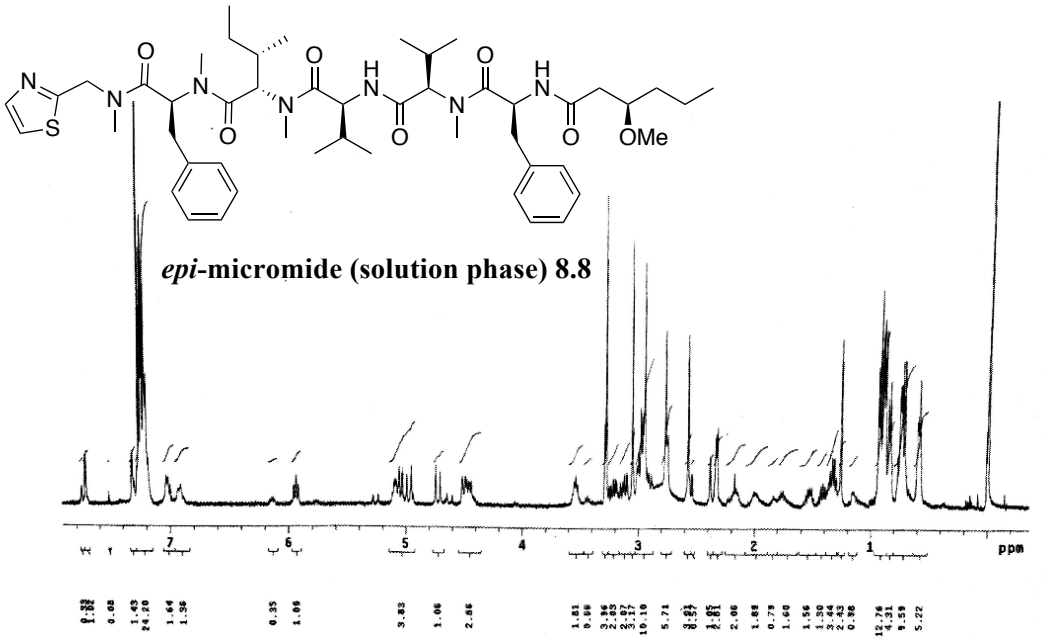
8.5


160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
4
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

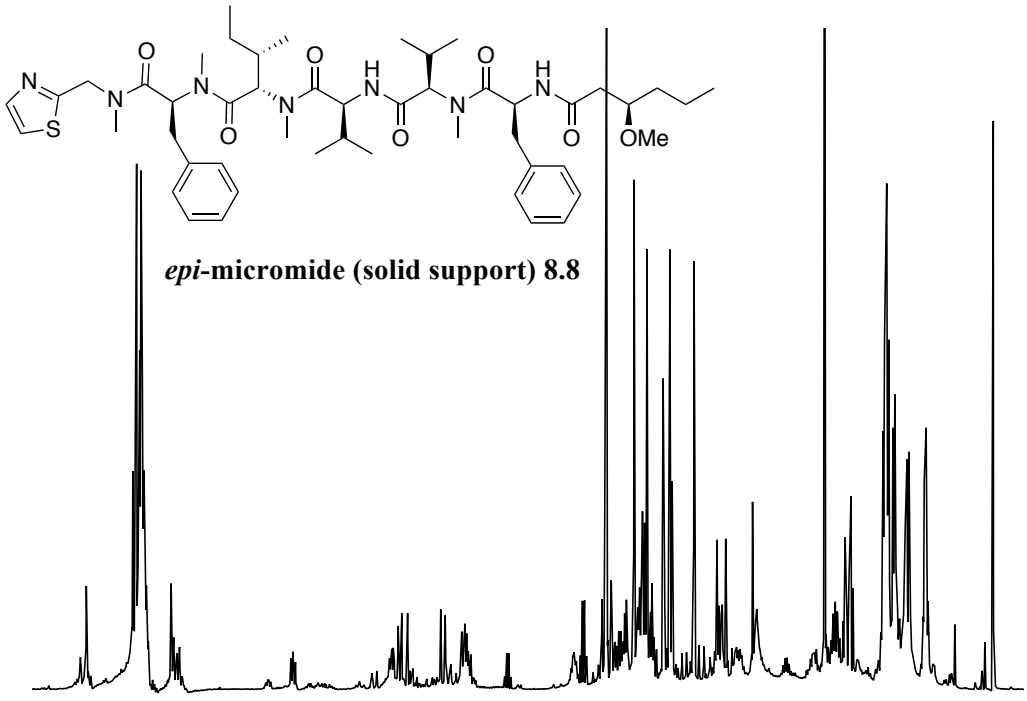

N
N—
S
H
8.6
9
8
7
6
5
4
3
2
1
ppm
0.92
0.91
0.91
3.00



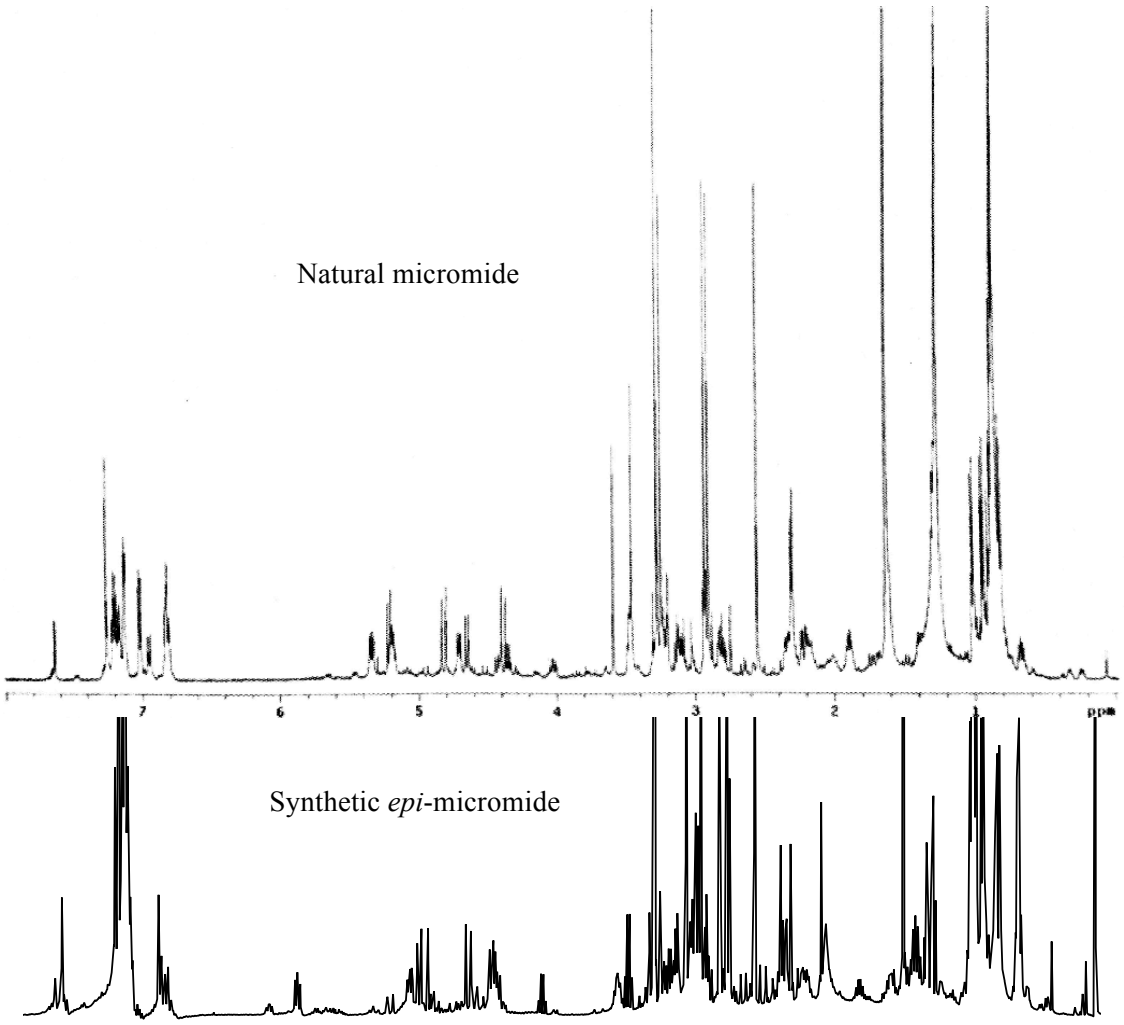
8.7

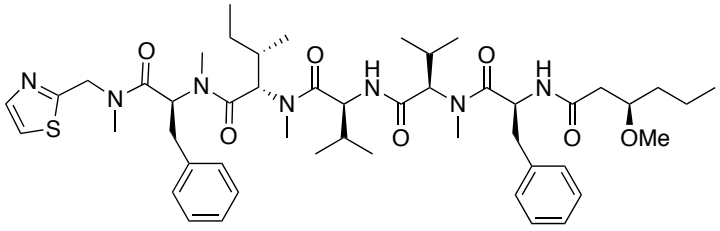


***epi*-micromide (solution phase) 8.8**

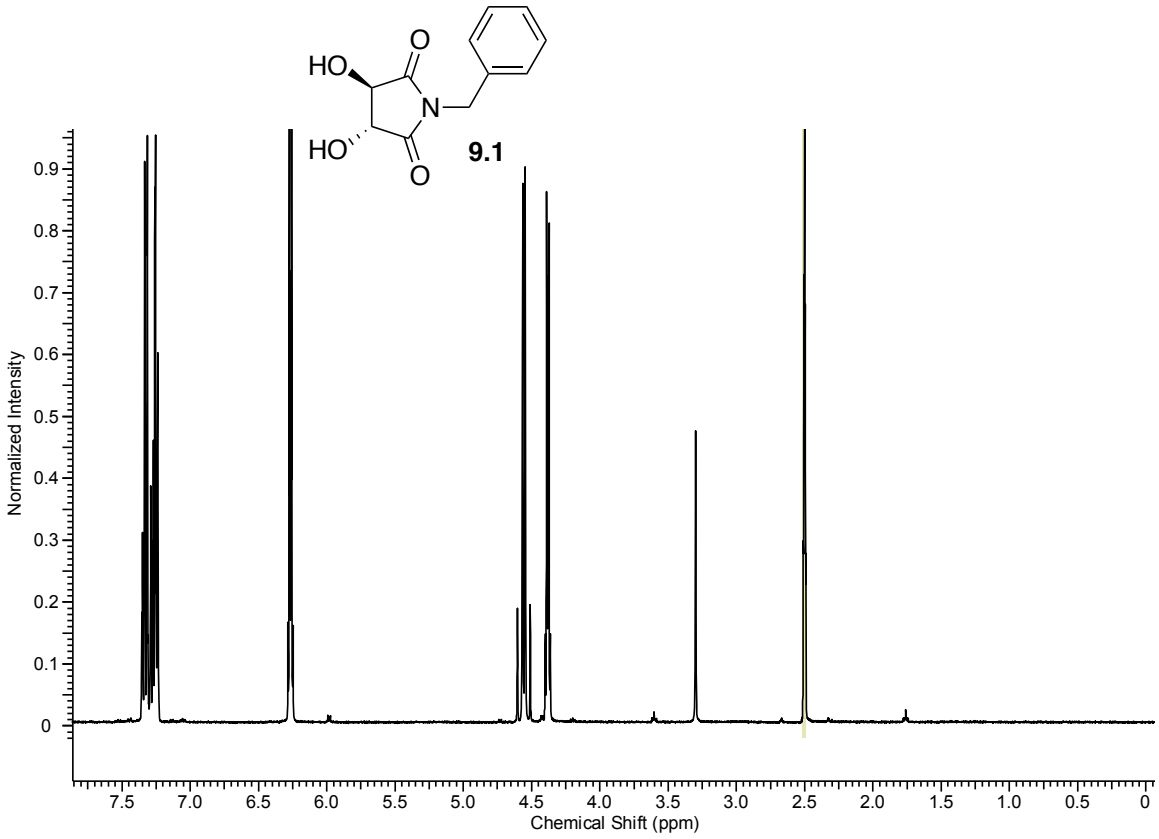


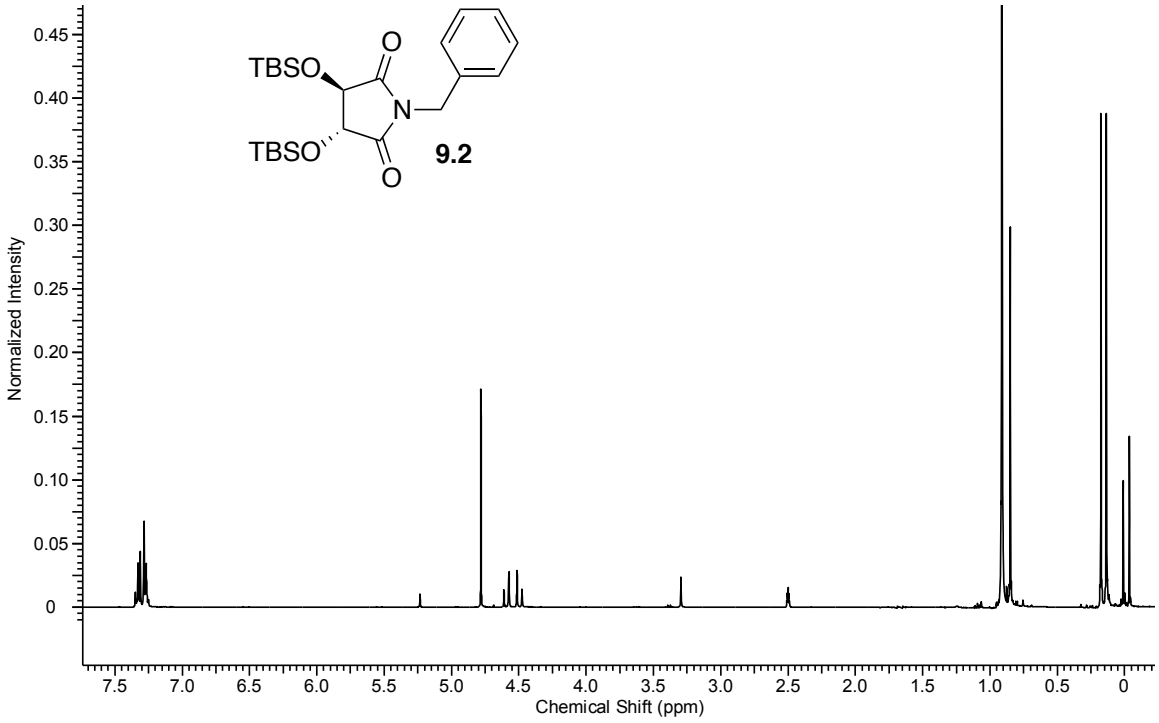
***epi*-micromide (solid support) 8.8**

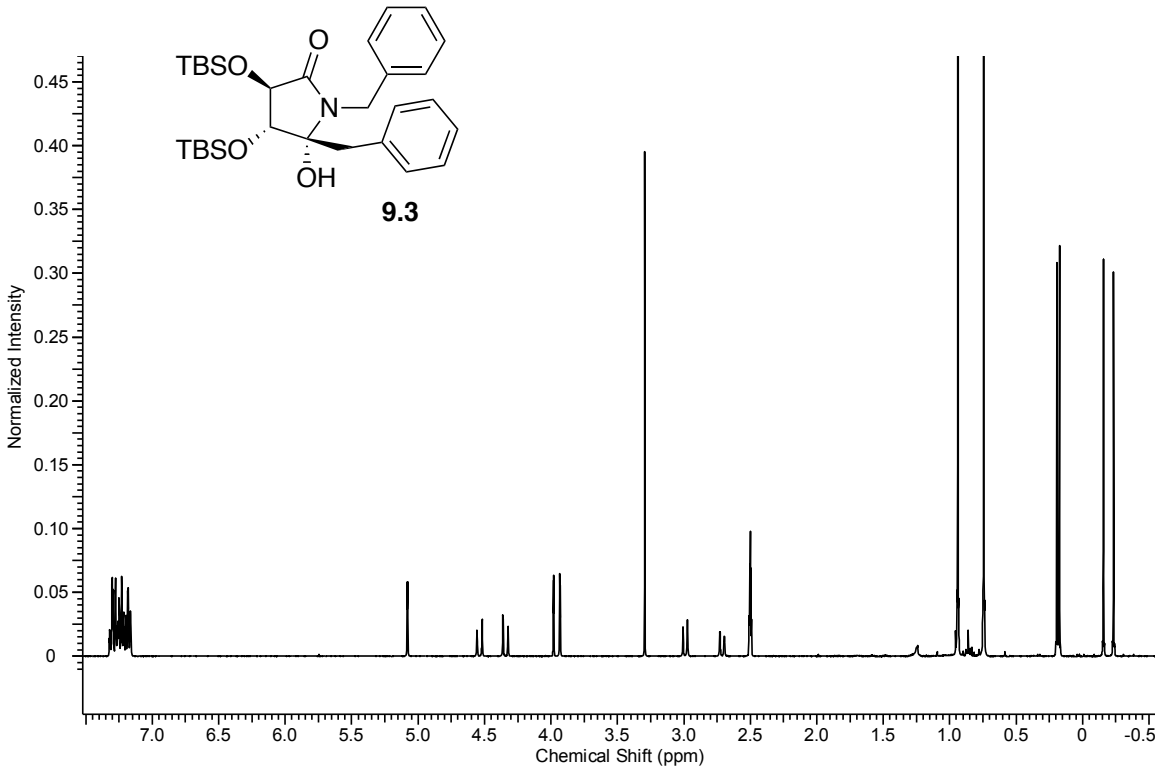


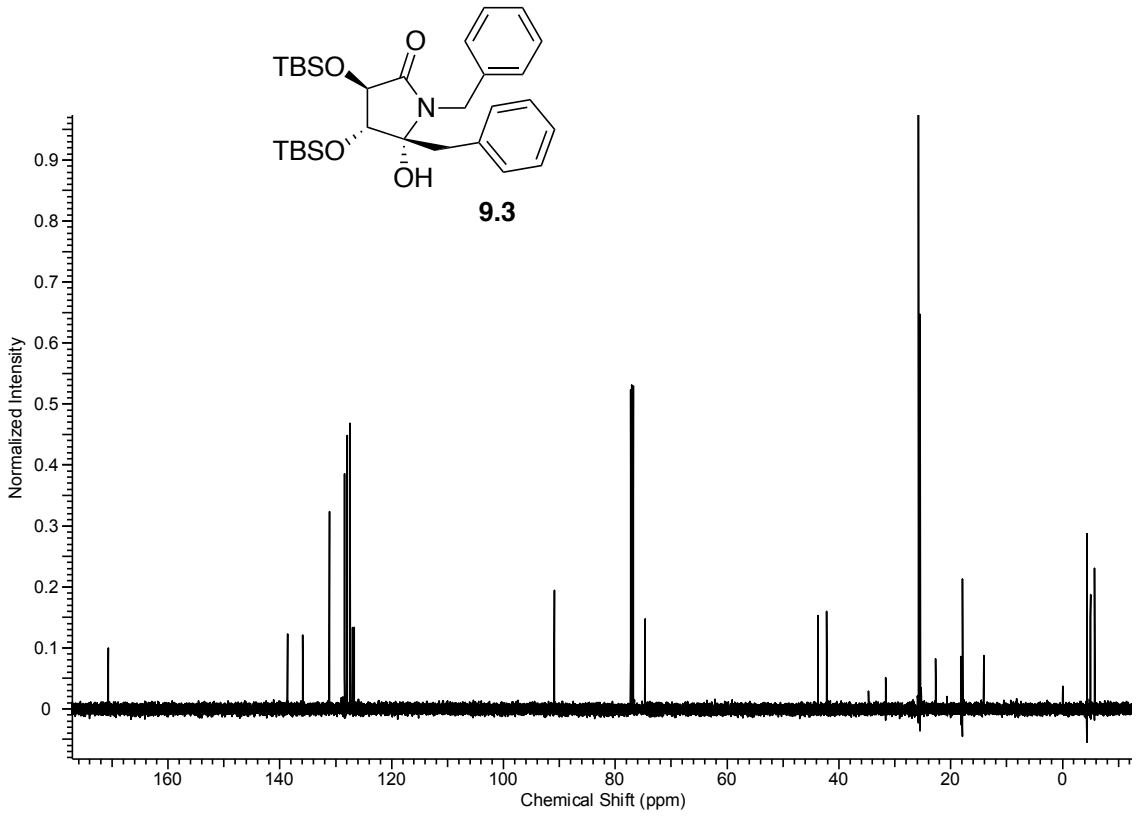


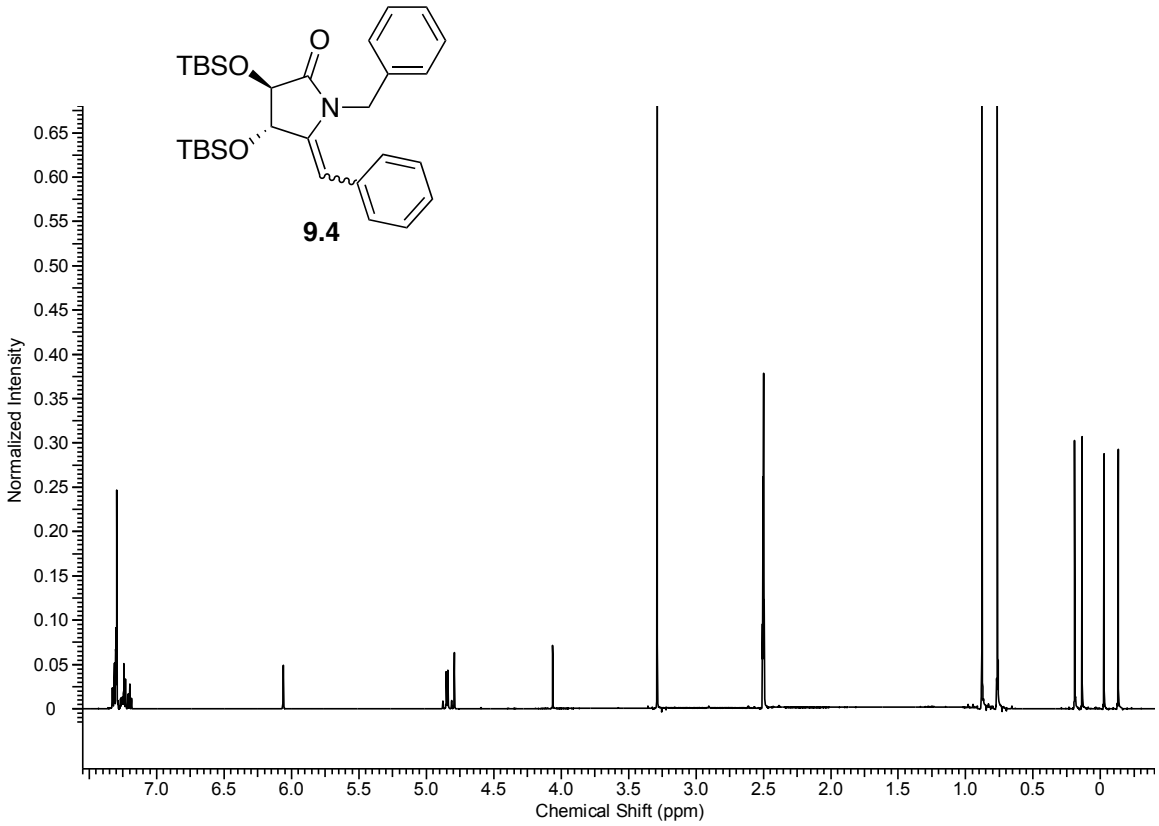
Synthetic *epi*-micromide (**8.8**)

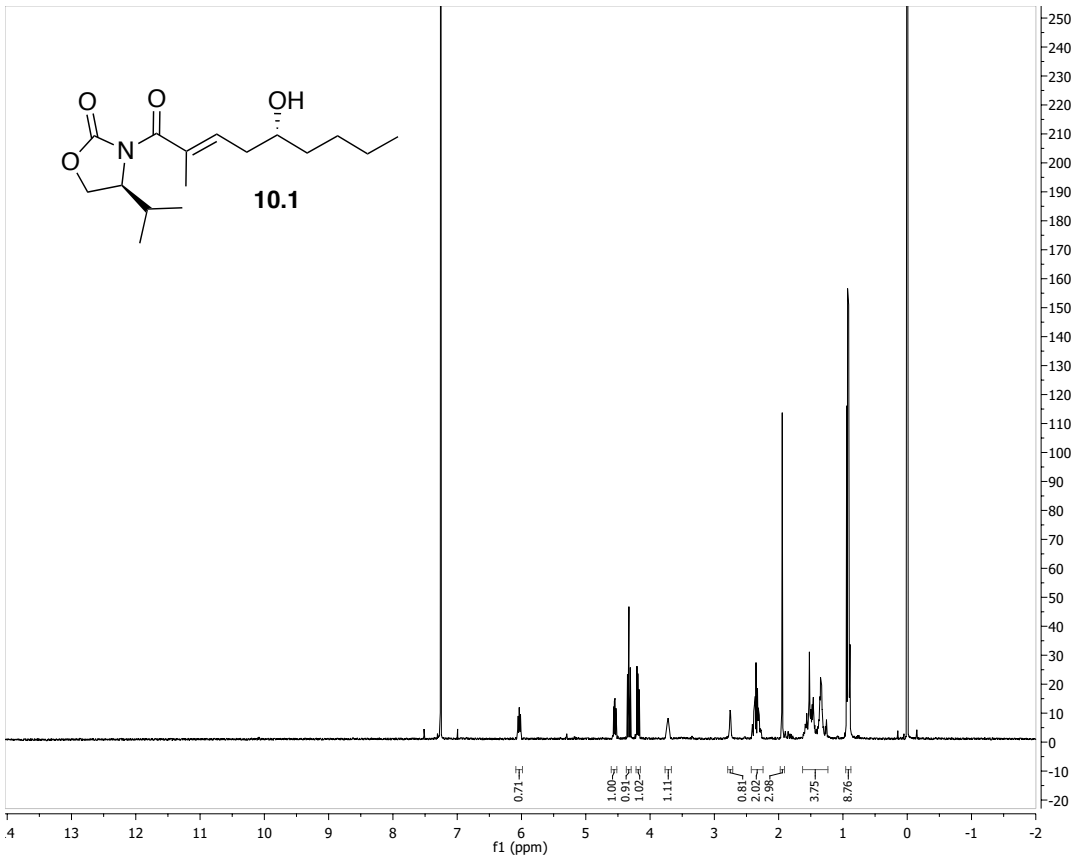

HO
O
N
HO
O
9.1
Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


TBSO
TBSO
O
N
O
O
9.2
Normalized Intensity
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


TBSO
O
N
TBSO
OH
9.3
Normalized Intensity
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
Chemical Shift (ppm)


TBSO
O
N
TBSO
OH
9.3
Normalized Intensity
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


TBSO
O
N
TBSO
9.4
Normalized Intensity
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


O
O
OH
N
O
10.1
f1 (ppm)

References

(1) Holton, R. a; Kim, H.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116* (10), 1599–1600.

(2) Tan, L. T. *Phytochemistry* **2007**, *68* (7), 954–979.

(3) Tan, L. T. *J. Appl. Phycol.* **2010**, *22* (5), 659–676.

(4) Suenaga, K.; Mutou, T.; Shibata, T.; Itoh, T.; Fujita, T.; Takada, N.; Hayamizu, K.; Takagi, M.; Irifune, T.; Kigoshi, H.; Yamada, K. *Tetrahedron* **2004**, *60* (38), 8509–8527.

(5) Tripathi, A.; Puddick, J.; Prinsep, M. R.; Rottmann, M.; Tan, L. T. *J. Nat. Prod.* **2010**, *73* (11), 1810–1814.

(6) Dai, L.; Chen, B.; Lei, H.; Wang, Z.; Liu, Y.; Xu, Z.; Ye, T. *Chem. Commun. (Camb)*. **2012**, *48* (69), 8697–8699.

(7) Tripathi, A.; Fang, W.; Leong, D. T.; Tan, L. T. *Mar. Drugs* **2012**, *10* (5), 1126–1137.

(8) Sato, S. I.; Murata, A.; Orihara, T.; Shirakawa, T.; Suenaga, K.; Kigoshi, H.; Uesugi, M. *Chem. Biol.* **2011**, *18* (1), 131–139.

(9) Shirokawa, S. I.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, a; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126* (42), 13604.

(10) Liu, H.-M.; Chang, C.-Y.; Lai, Y.-C.; Yang, M.-D.; Chang, C.-Y. *Tetrahedron: Asymmetry* **2014**, *25* (2), 187–192.

(11) Crimmins, M. T., Dechert, A. R. **2009**, *11* (7), 1199–1635 – 1638.

(12) Chérest, Marc, Felkin, Hugh, Prudent, N. *Tetrahedron Lett.* **1968**, *9* (18), 2219–2204.

(13) Chang, C.-Y. *J. Chinese Chem. Soc. (Taipei, Taiwan)* **2011**, *58* (1), 31–34.

(14) Evans, D. A.; Leester, D. W.; W, J. J. M.; J, S. *J. Org. Chem* **1999**, *64*, 6411–6417.

(15) Ghosh, A. K.; Kim, J. H. *Org. Lett.* **2003**, *5* (7), 1063–1066.

(16) Gage, J. R.; Evans, D. A.; Derussy, D. T.; Paquette, L. A. *Org. Synth.* **1990**, *68*, 83.

(17) Lucio, P.; Montanari, F.; Quici, S. *Org. Synth.* **1990**, *69*, 212.

(18) Kjell, D. P.; Slattery, B. J.; Semo, M. J. *J. Org. Chem.* **1999**, *64* (15), 5722–5724.

(19) Burgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30* (12), 1563–1572.

(20) Chattopadhyay, A.; Dubey, A. K. *J. Org. Chem.* **2007**, *72* (24), 9357–9359.

(21) Hassan, A.; Zbieg, J. R.; Krische, M. J. *Angew. Chemie - Int. Ed.* **2011**, *50* (15), 3493–3496.

(22) Zbieg, J. *Personal communication with co-author*; 2013.

(23) Ratjen, L.; García-García, P.; Lay, F.; Beck, M. E.; List, B. *Angew. Chemie - Int. Ed.* **2011**, *50* (3), 754–758.

(24) Suenaga, K.; Mutou, T.; Shibata, T.; Itoh, T.; Fujita, T.; Takada, N.; Hayamizu, K.; Takagi, M.; Irifune, T.; Kigoshi, H.; Yamada, K. *Tetrahedron* **2004**, *60* (38), 8509–8527.

(25) Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Senanayake, C. H. *J. Am. Chem. Soc.* **2002**, *124*, 7880–7881.

(26) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79* (8), 1920–1923.

(27) Mejuch, T.; Gilboa, N.; Gayon, E.; Wang, H.; Houk, K. N.; Marek, I. *Acc. Chem. Res.* **2013**, *46* (7), 1659–1669.

(28) Wurtz, A. *Ann. der Chemie und Pharm.* **1855**, *96* (3), 364–375.

(29) Criegee, R. *Angew. Chemie-International Ed. English* **1975**, *14* (11), 745–752.

(30) Wadsworth, W.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83* (7), 1733 – &.

(31) Evans, D. a.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31* (49), 7099–7100.

(32) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31* (7), 945–948.

(33) Huang, W.; Ren, R.-G.; Dong, H.-Q.; Wei, B.-G.; Lin, G.-Q. *J. Org. Chem.* **2013**, *78* (21), 10747–10762.

(34) Hoyveda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev* **1993**, *93*, 1307–1370.

(35) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113* (May), 4092–4096.

(36) Anderson, W. A.; Freeman, R. *J. Chem. Phys.* **1962**, *37* (1), 85.

(37) Symkenberg, G.; Kalesse, M. *Org. Lett.* **2012**, *14* (6), 1608–1611.

(38) Yamaoka, M.; Nakazaki, A.; Kobayashi, S. *Tetrahedron Lett.* **2010**, *51* (2), 287–

289.

(39) Yajima, T.; Horikawa, T.; Takeda, N.; Takemura, E.; Hattori, H.; Shimazaki, Y.; Shiraiwa, T. *Tetrahedron Asymmetry* **2008**, *19* (11), 1285–1287.

(40) Yajima, T.; Kimura, M.; Nakakoji, M.; Horikawa, T.; Tokuyama, Y.; Shiraiwa, T. *Biosci. Biotechnol. Biochem.* **2009**, *73* (10), 2293–2298.

(41) Pettit, G. R.; Hu, S.; Knight, J. C.; Chapuis, J. C. *J. Nat. Prod.* **2009**, *72* (3), 372–379.

(42) Calo, F.; Richardson, J.; Barrett, A. G. M. *J. Org. Chem.* **2008**, *73* (24), 9692–9697.

(43) Ikubo, M.; Inoue, A.; Nakamura, S.; Jung, S.; Sayama, M.; Otani, Y.; Uwamizu, A.; Suzuki, K.; Kishi, T.; Shuto, A.; Ishiguro, J.; Okudaira, M.; Kano, K.; Makide, K.; Aoki, J.; Ohwada, T. *J. Med. Chem.* **2015**, *58* (10), 4204–4219.

(44) Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev.* **2009**, *109* (6), 2551–2651.

(45) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32* (26), 3017–3020.

(46) Kalesse, M.; Cordes, M.; Symkenberg, G.; Lu, H.-H. *Nat. Prod. Rep.* **2014**, *31* (4), 563–594.

(47) Shirokawa, S. I.; Shinoyama, M.; Ooi, I.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2007**, *9* (5), 849–852.

(48) Neises, B.; Steglich, W. *Angew. Chemie Int. Ed. English* **1978**, *17* (7), 522–524.

(49) Zampella, A.; Bassarello, C.; Bifulco, G.; Gomez-Paloma, L.; D'Auria, M. V. *European J. Org. Chem.* **2002**, No. 5, 785–790.

(50) Huang, W.; Ren, R. G.; Dong, H. Q.; Wei, B. G.; Lin, G. Q. *J. Org. Chem.* **2013**, *78* (21), 10747–10762.

(51) Banasik, B. A.; Wang, L.; Kanner, A.; Bergdahl, B. M. *Tetrahedron* **2016**, *72* (19), 2481–2490.

(52) El-Faham, A.; Albericio, F. *Chem. Rev.* **2011**, *111* (11), 6557–6602.

(53) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61* (46), 10827–10852.

(54) Williams, P. G.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J. *J. Nat. Prod.* **2004**, *67* (1), 49–53.

(55) Han, J.; Lian, J.; Tian, X.; Zhou, S.; Zhen, X.; Liu, S.; Scott, J. D.; Williams, R. M.; Nicolaou, K. C.; Estrada, A. a.; Zak, M.; Lee, S. H.; Safina, B. S. *European J. Org. Chem.* **2014**, *2014* (32), 7232–7238.

(56) Wang, L. Total Synthesis of Micromide, Doctoral Dissertation, UCSD/SDSU, 2016- 2017.

(57) Bonkowski, B. *Mod. Chem. Appl.* **2013**, *01* (04), 2–5.

(58) Carpino, L. *J. Am. Chem. Soc.* **1993**, *115* (13), 4397–4398.

(59) Sheehan, J.; Cruickshank, P.; Boshart, G. *J. Org. Chem.* **1961**, *26* (7), 2525–2528.

(60) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *A Rapid Esterification by Means of Mixed Anhydride and Its Application to Large-ring Lactonization*; 1979; Vol. 52.

(61) Lemaire-Audoire, S.; Savignac, M.; Genêt, J. P.; Bernard, J. *Tetrahedron Lett.* **1995**, *36* (8), 1267–1270.

(62) Aurelio, L.; Brownlee, R. T. C.; Hughes, A. B. **2004**.

(63) Vilsmeier, A.; Haack, A. *Berichte der Dtsch. Chem. Gesellschaft (A B Ser.* **1927**, *60* (1), 119–122.

(64) Dean, E. W.; Stark, D. D. *J. Ind. Eng. Chem.* **1920**, *12* (5), 486–490.

(65) Barlos, K.; Chatzi, O.; Gatos, D.; Stavropoulos, G. *Int. J. Pept. Protein Res.* **2009**, *37* (6), 513–520.

(66) Athanassopoulos, P.; Barlos, K.; Gatos, D.; Hatzi, O.; Tzavara, C. *Tetrahedron Lett.* **1995**, *36* (31), 5645–5648.

(67) Nakao, Y.; Yoshida, W. Y.; Takada, Y.; Kimura, J.; Yang, L.; Mooberry, S. L.; Scheuer, P. J. *J. Nat. Prod.* **2004**, *67* (8), 1332–1340.

(68) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112* (2), 6339–6348.

(69) Suenaga, K.; Kimura, T.; Kuroda, T.; Matsui, K.; Miya, S.; Kuribayashi, S.; Sakakura, A.; Kigoshi, H. *Tetrahedron* **2006**, *62* (35), 8278–8290.

(70) Brown, Herbert C and Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293–294.

(71) Sharma, V.; Kelly, G. T.; Watanabe, C. M. H. *Org. Lett.* **2008**, *10* (3), 4815–4818.

(72) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.

(73) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31* (44), 6367–6370.

(74) Paterson, I.; Wallace, D.; Cowden, C. *Synthesis (Stuttg).* **1998**, 639–652.

(75) Raach, A.; Reiser, O. *J. fur Prakt. Chemie* **2000**, *342* (6), 605–608.

(76) Shiina, I.; Ibuka, R.; Kubota, M. *Chem. Lett.* **2002**, No. 3, 286–286.

(77) Liu, J.; Ma, X.; Liu, Y.; Wang, Z.; Kwong, S.; Ren, Q.; Tang, S.; Meng, Y.; Xu, Z.; Ye, T. *Synlett* **2012**, *23* (5), 783–787.

(78) Liu, S. *J. Phys. Chem. A* **2013**, *117* (5), 962–965.

(79) Nicolaou, K. C.; Estrada, A. a.; Zak, M.; Lee, S. H.; Safina, B. S. *Angew. Chemie - Int. Ed.* **2005**, *44* (9), 1378–1382.

(80) Chen, J.; Huang, C.; Zheng, L.; Simonich, M.; Bai, C.; Tanguay, R.; Dong, Q. *Neurotoxicol. Teratol.* **2011**, *33* (6), 721–726.

(81) Stalcup, A. M. *Annu. Rev. Anal. Chem.* **2010**, *3* (1), 341–363.

(82) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34* (9), 2543–2549.

(83) Sekhon, B. S. *J. Mod. Med. Chem.* **2013**, *1*, 10–36.

(84) Bühler, H.; Miehlich, B.; Effenberger, F. *ChemBioChem* **2005**, *6* (4), 711–717.

(85) Matsui, R.; Seto, K.; Sato, Y.; Suzuki, T.; Nakazaki, A.; Kobayashi, S. *Angew. Chem. Int. Ed. Engl.* **2011**, *50* (3), 680–683.

(86) Kanner, A. Studies into the vinylogous mukaiyama reaction and the application towards the total synthesis of lagunamide A, Masters Thesis, SDSU, Spring 2016.

(87) Elia, G. *Proteomics* **2008**, *8* (19), 4012–4024.

(88) Sadaghiani, A. M.; Verhelst, S. H.; Bogyo, M. *Curr. Opin. Chem. Biol.* **2007**, *11* (1), 20–28.

(89) Thermo Scientific. *Thermo Sci. Pierce Assay Dev. Tech. Handb. https//tools.thermofisher.com/content/sfs/brochures/1602127-Assay-Development-Handbook.pdf,* **2016**, 1–73.

(90) Lewis, M.; Hung-Wen, L. *Compr. Nat. Prod. II Chem. Biol. 10 Vol. Set, Elsevier* **2010**, *Amsterdam*, 7388.

(91) Suenaga, K.; Mutou, T.; Shibata, T.; Itoh, T.; Kigoshi, H.; Yamada, K. *Tetrahedron Lett.* **1996**, *37* (37), 6771–6774.

(92) Suenaga, K.; Kajiwara, S.; Kuribayashi, S.; Handa, T.; Kigoshi, H. *Bioorg. Med. Chem. Lett.* **2008**, *18* (14), 3902–3905.

(93) Konoki, K.; Sugiyama, N.; Murata, M.; Tachibana, K.; Hatanaka, Y. *Tetrahedron* **2000**, *56* (46), 9003–9014.

(94) Xu, H.; Sabit, H.; Amidon, G. L.; Showalter, H. D. H. *Beilstein J. Org. Chem.* **2013**, *9*, 89–96.

(95) Nakajima, N.; Ikada, Y. *Bioconjug. Chem.* **1995**, *6* (1), 123–130.

(96) Inard, C.; Fourcade, E.; Baron, R.; Tovar, D.; Chaisemartin, L.; Blonski, C.; Faye, J. C. *Bioconjugate Chem.* **2006**, *17*, 1030–1035.

(97) McDermott, J. R.; Benoiton, N. L. *Can. J. Chem.* **1973**, *51* (15), 2562–2570.

(98) Miller, S. C.; Scanlan, T. S. *J. Am. Chem. Soc.* **1997**, *119* (9), 2301–2302.

(99) Dambacher, J.; Bergdahl, M. *J. Org. Chem.* **2005**, *70* (2), 580–589.

(100) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc. Perkin Trans. 1* **1995**, *3* (4), 317.

(101) Dondoni, A.; Perrone, D. *J. Org. Chem.* **1995**, *60* (15), 4749–4754.

(102) Kempf, D. J.; Codacovi, L.; Wang, X. C.; Kohlbrenner, W. E.; Wideburg, N. E.; Saldivar, A.; Vasavanonda, S.; Marsh, K. C.; Bryant, P. *J. Med. Chem.* **1993**, *36* (3), 320–330.

(103) Byung, T. C.; Sang, K. K. *Tetrahedron* **2005**, *61* (24), 5725–5734.

(104) Nevchas, I. Chemical Methodologies Toward the Total Synthesis of Virginiamycin M1 and Micromide Natural Products, Masters Thesis, SDSU, 2009.

(105) Asami, Y.; Kakeya, H.; Onose, R.; Yoshida, A.; Matsuzaki, H.; Osada, H. *Org. Lett.* **2002**, *4* (17), 2845–2848.

(106) Asami, Y.; Kakeya, H.; Komi, Y.; Kojima, S.; Beebe, K.; Neckers, L.; Osada, H. *Cancer Sci.* **2009**, *99* (9), 1853–1858.

(107) Limaverde-Sousa, G.; Sternberg, C.; Ferreira, C. G. *Cancer Treat. Rev.* **2014**, *40* (4), 548–557.

(108) Hayashi, Y.; Shoji, M.; Yamaguchi, J.; Sato, K.; Yamaguchi, S.; Mukaiyama, T.; Sakai, K.; Asami, Y.; Kakeya, H.; Osada, H. *J. Am. Chem. Soc.* **2002**, *124* (41), 12078–12079.

(109) Aoki, S.; Oi, T.; Shimizu, K.; Shiraki, R.; Takao, K.; Tadano, K. *Bull. Chem. Soc. Jpn.* **2004**, *77* (9), 1703–1716.

(110) Bergdahl, M.; El-Batta, A. *Org. Synth.* **2007**, *84* (2007), 192.

(111) El-Batta, A.; Bergdahl, M. *Tetrahedron Lett.* **2007**, *48* (10), 1761–1765.

(112) Jeong, H. J.; Lee, J. M.; Kim, M. K.; Lee, S.-G. *J. Heterocycl. Chem.* **2002**, *39* (5), 1019–1024.

(113) Yoda, H.; Shimojo, T.; Takabe, K. *Tetrahedron Lett.* **1999**, *40* (7), 1335–1336.

(114) Bartoli, G.; Bellucci, M. C.; Bosco, M.; Marcantoni, E.; Sambri, L. *Chem. - A Eur. J.* **1998**, *4* (11), 2154–2161.

(115) Bertus, P.; Szymoniak, J. *Org. Lett.* **2007**, *9* (4), 659–662.

(116) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118* (7), 1809–1810.

(117) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97* (21), 6260–6261.

(118) Arnone, A.; Bravo, P.; Frigerio, M.; Salani, G.; Viani, F.; Zappalà, C.; Cavicchio, G.; Crucianelli, M. *Tetrahedron* **1995**, *51* (30), 8289–8310.

(119) Schmit, D. Progress toward a scalable synthesis of azaspirene, an angiogenesis inhibitor and Synthesis of compounds targeting subdomain IIa of the IRES of the hepatitis C virus, Doctoral Dissertation, UCSD/SDSU, Fall 2014.

(120) Montgomery, T. Total synthesis of azaspirene. Alkenylzincate and disilylzincate conjugate addition by CuIDMS, Doctoral Dissertation, UCSD/SDSU, Summer 2016.

(121) Kelly, M. Total synthesis of azaspirene and aqueous wittig reactions, Doctoral Dissertation, UCSD/SDSU, Fall 2016.

(122) Leonard, N.; Wieland, L.; Mohan, R. *Tetrahedron* **2002**, *58* (618), 8373–8397.

(123) Sanderson, J.; Bayse, C. a. *Tetrahedron* **2008**, *64* (33), 7685–7689.

(124) Kwie, F. H. a; Baudoin-Dehoux, C.; Blonski, C.; Lherbet, C. *Synth. Commun.* **2010**, *40* (7), 1082–1087.

(125) Hager, A.; Kuttruff, C. a.; Hager, D.; Terwilliger, D. W.; Trauner, D. *Synlett* **2013**, *24* (15), 1915–1920.

(126) Le Roux, C.; Gaspard-Iloughmane, H.; Dubac, J.; Jaud, J.; Vignaux, P. *J. Org. Chem.* **1993**, *58* (7), 1835–1839.

(127) El-Batta, A.; Jiang, C.; Zhao, W.; Anness, R.; Cooksy, A. L.; Bergdahl, M. *J. Org. Chem.* **2007**, *72* (14), 5244–5259.

(128) Evans, D. a; Nelson, J. V; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111.

(129) Mazerolles, P.; Boussaguet, P.; Huc, V. *Org. Synth.* **1999**, *76*, 221.

(130) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59* (24), 7549–7552.

(131) Renamy, S. V.; Bassene, S.; Diop, C. A. K.; Sidibe, M.; Diop, L.; Mahon, M. F.; Molloy, K. C. *Appl. Organomet. Chem.* **2004**, *18* (9), 455–459.

(132) Shiina, I.; Ibuka, R.; Kubota, M. *Chem. Lett.* **2002**, No. 3, 286–286.

(133) Ahmad, S.; Ngu, K.; Miller, K. J.; Wu, G.; Hung, C. pin; Malmstrom, S.; Zhang, G.; O'Tanyi, E.; Keim, W. J.; Cullen, M. J.; Rohrbach, K. W.; Thomas, M.; Ung, T.; Qu, Q.; Gan, J.; Narayanan, R.; Pelleymounter, M. A.; Robl, J. A. *Bioorganic Med. Chem. Lett.* **2010**, *20* (3), 1128–1133.

(134) Willand-Charnley, R.; Fisher, T. J.; Johnson, B. M.; Dussault, P. H. *Org. Lett.* **2012**, *14* (9), 2242–2245.

(135) Kazmierczak, F.; Helquist, P. *J. Org. Chem.* **1989**, *54* (16), 3988–3992.

(136) Clarke, H. *J. Org. Chem.* **1959**, *24* (10), 1610–1611.

(137) Smiley, J. D.; Ashwell, G. *J. Biol. Chem.* **1961**, *236* (2), 357–364.

(138) Handa, M.; Scheidt, K. a; Bossart, M.; Zheng, N.; Roush, W. R. *J. Org. Chem.* **2008**, *73* (3), 1031–1035.

(139) Nicolas, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, *58* (3), 766–770.

(140) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68* (September), 83.

(141) Freeman, F.; Kim, D. S. H. L.; Rodriguez, E. *J. Org. Chem.* **1992**, *57* (6), 1722–1727.

(142) Abeywickrema, A. N.; Beckwith, A. L. J.; Gerba, S. *J. Org. Chem.* **1987**, *52* (18), 4072–4078.

(143) Guldbrandt, M.; Johansen, T. N.; Frydenvang, K.; Bräuner-Osborne, H.; Stensbøl, T. B.; Nielsen, B.; Karla, R.; Santi, F.; Krogsgaard-Larsen, P.; Madsen, U. *Chirality* **2002**, *14* (4), 351–363.

(144) Luke, G. P.; Seekamp, C. K.; Wang, Z.; Chenard, B. L. *J. Org. Chem.* **2008**, *73* (16), 6397–6400.

(145) Bauer, T.; Gajewiak, J. *Tetrahedron* **2004**, *60* (41), 9163–9170.

(146) Jahns, C.; Hoffmann, T.; Müller, S.; Gerth, K.; Washausen, P.; Höfle, G.; Reichenbach, H.; Kalesse, M.; Müller, R. *Angew. Chem. Int. Ed.* **2012**, *51* (21), 5239–5243.

(147) Fukuzawa, Shin-ichi , Matsuzawa, Hiroshi and Yoshimitsu, S. *J. Org. Chem* **2000**, *65* (6), 1702–1706.

(148) Hosokawa, S.; Matsushita, K.; Tokimatsu, S.; Toriumi, T.; Suzuki, Y.; Tatsuta, K. *Tetrahedron Lett.* **2010**, *51* (42), 5532–5536.

(149) Haesler, J.; Schindelholz, I.; Riguet, E.; Bochet, C. G.; Hug, W. *Nature* **2007**, *446* (7135), 526–529.

(150) Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T.; Date, T.; Okamura, K.; Inagaki,

S. *J. Org. Chem.* **1991**, *56* (23), 6556–6564.

(151) Reggelin, M.; Junker, B.; Heinrich, T.; Slavik, S.; Bühle, P. *J. Am. Chem. Soc.* **2006**, *128* (12), 4023–4034.

(152) Myers, A.; Zheng, B. *Org. Synth.* **2004**, *10*, 165.

(153) Yoda, H.; Shimojo, T.; Takabe, K. *Tetrahedron Lett.* **1999**, *40* (7), 1335–1336.