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A Dissertation

Entitled

Synthesis and Biological Evaluation of Open-Chain Epothilones

By

Sara R. Fedorka

Submitted to the Graduate Faculty as partial fulfillment of the requirements for the Doctor of Philosophy Degree in Medicinal Chemistry

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August 2012

An Abstract of

Synthesis and Biological Evaluation of Open-Chain Epothilones

By

Sara R. Fedorka

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Epothilones are naturally occurring anticancer agents that inhibit the growth of cancer cells through the stabilization of microtubules, which leads to the arrest of cell division in the G2/M phase. They have captured the attention of the scientific community due to the similarity of their mechanism of action to the blockbuster drug paclitaxel. Many macrocyclic epothilone analogues have been synthesized and tested for anticancer activity against a variety of cell lines including breast, ovarian, and prostate cancers.

We have successfully synthesized several open-chain epothilones analogues where the C9-C14 sector of cyclic epothilones has been deleted and the molecule rigidified with a cyclopentene molecular scaffold. The methyl group at C20 was replaced with different 2-substituted thiazole moieties of varying degrees of size and electronic properties. Steglich esterification reaction conditions were utilized to couple the acyl and alcohol precursors that were synthesized separately.

The cytotoxicity of these open-chain epothilones was screened in the National Cancer Institute's 60 cell line assay. An acetylene substituted open-chain epothilone analogue showed selective activity predominately against lung cancer cell NCI-H522 and to a lesser extent on melanoma cancer cell line LOX IMVI, ovarian cancer cell line IGROV1, and renal cancer cell line UO-31.

We also synthesized precursors to an open-chain epothilone with hydrophobic substitutions at C10 and C14. Preliminary solution molecular dynamic simulations have shown that these hydrophobic functionalities impose further conformational constraint in aqueous media due to hydrophobic collapse; which we hypothesize may lead to a biological conformation similar to macrocyclic epothilones. The acyl moiety with a phenyl substitution at C10 is synthesized by diastereoselective Aldol reaction, while substituents at C14 are incorporated through enolate alkylation of previously synthesized 2-substituted cyclopentenones.

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Last and certainly not least, I would like to thank my family especially my parents David and Karan, my sisters Rachel and Hanna, my brother Zack, and my niece Addison for their constant love and support. I am grateful to my grandparents Charles, Helen, Wanda, and Larry for their advice, wisdom, and guidance throughout my entire life. I owe a special thank you to my Uncle Chuck and Aunt Alana for their spiritual guidance and keeping me on the right path. Finally, thanks to my roommates: Abby, Bennett, and Tobie who keep me constantly laughing.

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LIST OF ABBREVIATIONS

ADP	Adenosine diphosphate
ATP	Adenosine triphosphate
brsm	Based on recovered starting material
CBS	Corey, Bakshi, and Shibata
CNS	Central nervous system
CSA	(1S)-(+)-10-Camphorsulfonic acid
CDI	1,1'-Carbonyldiimidazole
DCC	N,N'-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DIPA	Diisopropylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
EtOH	Ethanol
EDC	N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide
FDA	Food and Drug Administration
GBF	Gesellschaft für Biologisch-chemische Forschung
GDP	Guanosine diphosphate
GTP	Guanosine triphosphate
HBEC	Human bronchial epithelial cells
HBTU	*O*-(Benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate
HCl	Hydrochloric acid
HOBt	1-Hydroxybenzotriazole hydrate
HPLC	High performance liquid chromatography
LDA	Lithium diisopropylamide
MAPs	Microtubule associated proteins
MDA	Microtubule destabilizing agents
MDR	Multiple drug resistance
MeOH	Methanol
Mg	Magnesium
MSA	Microtubule stabilizing agents
MTD	Maximum tolerated dose
MTOC	Microtubule organizing center
NaHMDS	Sodium bis(trimethylsilyl)amide

NCI	National cancer institute
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NSCLC	Non-small cell lung cancer
PCC	Pyridinium chlorochromate
Pgp	*p*-Glycoprotein
RT	Room temperature
SAR	Structure-activity relationship
TBSCl	*tert*-Butylchlorodimethylsilane
TBSOT*f*	*tert*-Butyldimethylsilyl trifluoromethanesulfonate
TFA	Trifluoroacetic acid
TMS	Trimethylsilyl
THF	Tetrahydrofuran

Chapter 1

Significance

The American Cancer Society estimated that cancer claimed the lives of 1,500 Americans per day in 2011.[1] It is the second highest killer of the U.S. population behind heart disease, with an average annual medical cost of 100 billion dollars.[1] Cancer is caused by changes in gene expression, either through genetic predisposition or environmental exposure, which leads to unregulated cellular division and abnormal cell growth.[2] Normally, the process of cellular division is well regulated and proceeds through various protein checkpoints that allow for detection and repair of damaged genetic material before the cell divides.[3] In cancerous cells the damaged cellular components are not repaired and instead become inherited by daughter cells. After several cellular divisions, genetic instability occurs leading to the development of tumors.[4] Malignant tumors will release growth signaling factors that promote the formation of new blood vessels. The blood vessels will infiltrate the tumor mass providing a source of nutrition as well as a mode of transportation for malignant tumor cells to spread throughout the body.[2] The standard method of treatment of most cancers involves an aggressive combination of surgery, radiation and chemotherapy.[4] The most effective chemotherapeutics used for cancer treatment are drugs that induce apoptosis by disrupting microtubule dynamics during cellular division.[5]

1.1 The role of microtubules in cellular division

During mitosis, sister chromatids are condensed and separated by microtubules to opposite ends of the cell for cellular fission.[3] The assembly of microtubules begins with the formation of α,β tubulin heterodimers from cellular proteins α and β tubulin (Figure 1).[5] Each tubulin subunit binds a molecule of guanosine triphosphate (GTP) before the formation of the tubulin heterodimer. The GTP on α tubulin becomes inaccessible at the heterodimer interface once a strong bond is formed between the tubulin subunits.[5] However, the GTP bound to β tubulin is exposed to the extracellular matrix and can undergo hydrolysis to guanosine diphosphate (GDP). The hydrolysis of the phosphate group, along with binding of microtubule associated proteins (MAPs) and magnesium ions, will initiate polymerization of the α,β tubulin heterodimer subunits from the microtubule organizing center (MTOC) into organized strands called protofilaments.[6] In humans, thirteen protofilaments will aggregate and elongate into hollow cylindrical structures characteristic of microtubules, which will attach themselves to the centriole of the sister chromatids. The microtubules will align the chromatids along the equatorial plane of the cell before depolymerization to α,β tubulin heterodimers.[6] The chromosomes are efficiently separated for cellular division by the push/pull force generated by polymerization and depolymerization of microtubules.[7]

The ability of microtubules to polymerize and depolymerize, depending on cellular needs is known as "dynamic instability." Microtubules consist of a plus end and minus end, and are in constant equilibrium between growth and shrinkage.[5] Polymerization and elongation occur at a faster rate than depolymerization at the plus end, whereas depolymerization occurs at a faster rate than polymerization at the minus end.[6] GTP bound tubulin heterodimers bind to the plus end during polymerization and form a GTP cap. This cap is a cellular signal for continued polymerization. If the rate of GTP

hydrolysis exceeds the rate of heterodimer binding, the GTP cap is lost and signals the microtubule to stop polymerization and initiate depolymerization.[5, 8] The minus end of microtubules is stabilized by γ tubulin in the MTOC, which is the centrosome in eukaryotic cells, but can become unstabilized for disassembly to tubulin subunits.[8] Besides dynamic instability, microtubules can be in a state described as "treadmilling." Treadmilling occurs when the polymerization at the plus end occurs at the same rate as depolymerization at the minus end effectively maintaining microtubule length.[9]

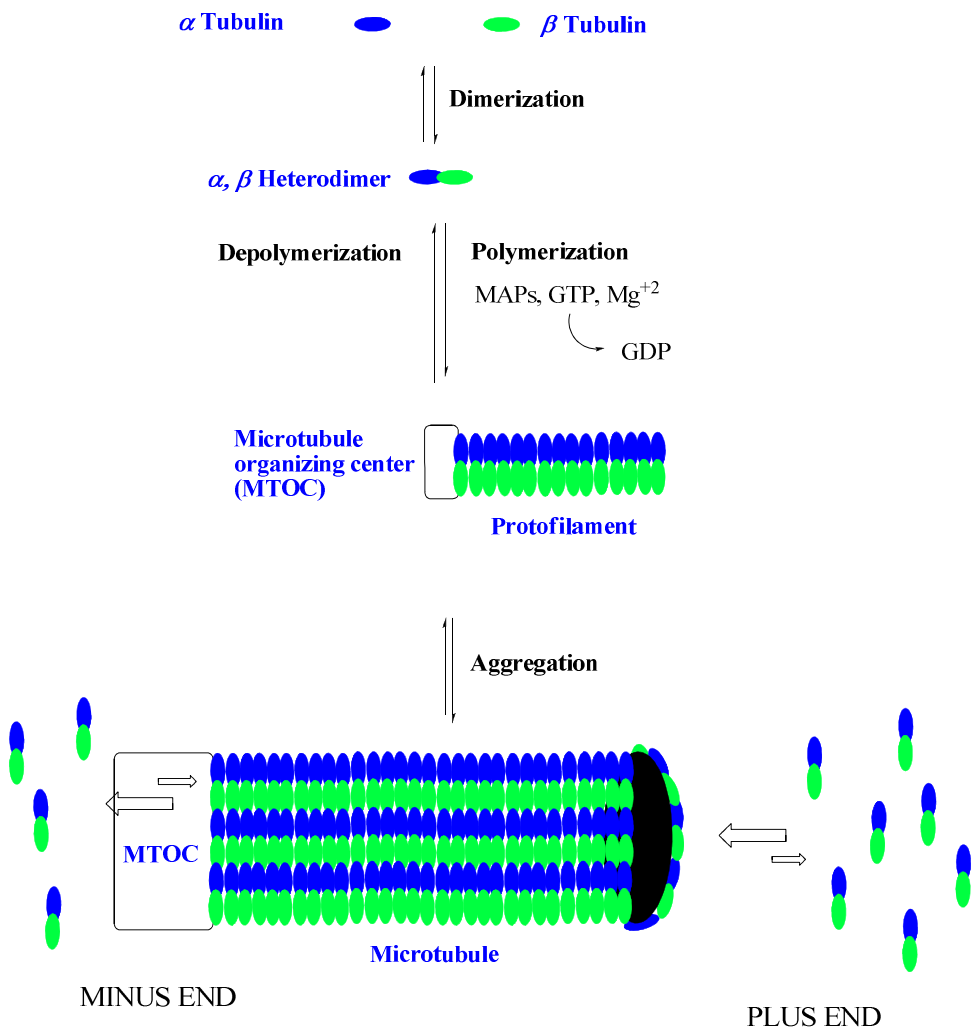
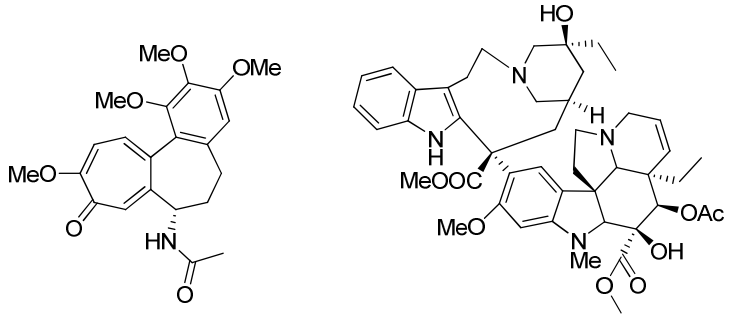


Figure 1 Association and disassociation of microtubules

Microtubule functionality is not limited to cellular division, but is the main structural feature of the cytoskeleton. The cytoskeleton maintains cellular shape and assists in the transportation of organelles and proteins within the cell.[6] Anticancer agents that disrupt microtubule dynamics to induce cell death have either a stabilizing or destabilizing effect on microtubules. Microtubule destabilizing agents (MDA) such as colchincine **1** and vinblastine **2** (Figure 2) prevent the assembly of stabilized protofilaments into microtubules by inhibiting the polymerization of tubulin heterodimers.[6]



1 Colchicine **2** Vinblastine

Figure 2 Microtubule destabilizing agents

1.2 Microtubule stabilizing agents - epothilones

Microtubule stabilizing agents (MSAs) bind to β tubulin and stimulate microtubule polymerization while inhibiting depolymerization at the minus end. Ultimately, this induces apoptotic cell death (Figure 3).[6] The first natural product reported to have microtubule stabilizing activity was paclitaxel (taxol) **3** (Figure 4), which was isolated from the bark of the pacific yew tree *Taxcus brevifolia* in 1971.[10] Taxol was approved by the U.S. Food and Drug Administration (FDA) to treat a variety of solid tumors including breast and non-small cell lung cancers.[11] It is a blockbuster anticancer drug that has

earned billions of dollars in sales worldwide.[6] Structurally, paclitaxel contains a complex diterpene ring system with eight stereocenters, an oxetane ring, and an ester side chain at C13.[12] Due to its hydrophobic nature and low water solubility, taxol is administered to patients intravenously using high concentrations of cremophor within the formulation.[13] Cremophor has been reported to cause severe hypersensitivity side effects and affect cardiac function in some patients.[11b, 13]

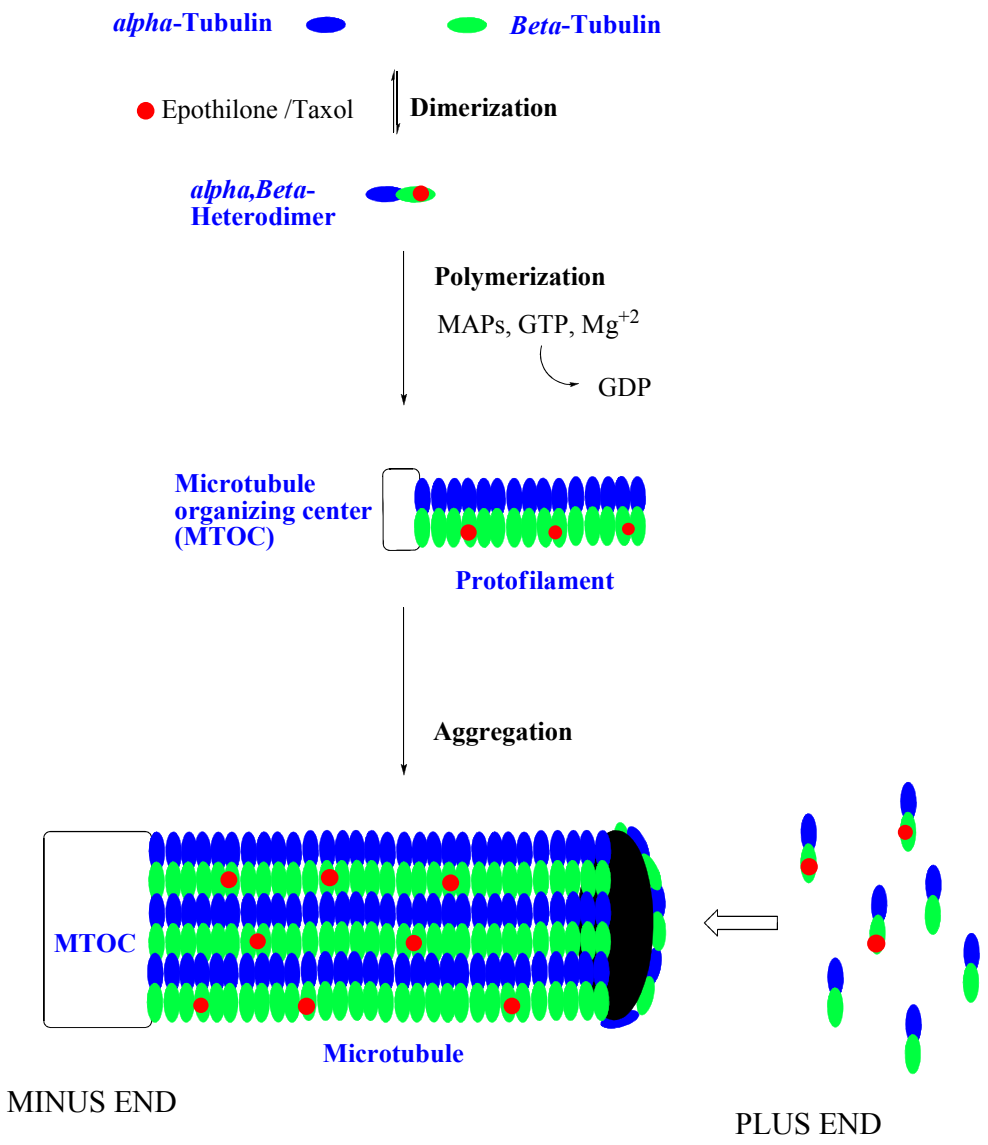
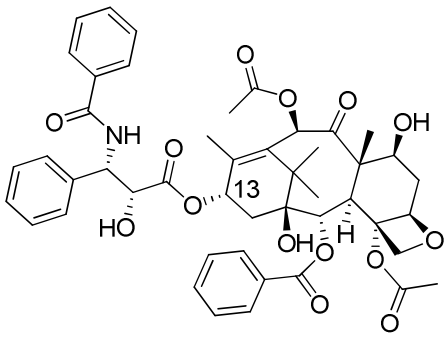
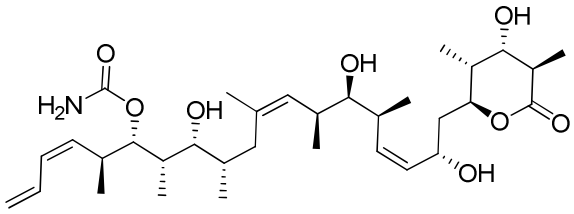


Figure 3 Microtubule stabilizing effect of epothilones and taxol

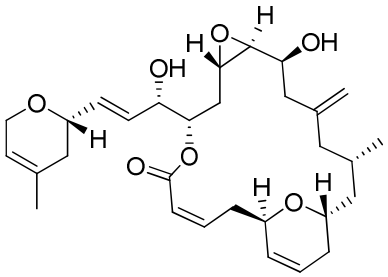
In addition to solubility issues and undesirable side effects related to cremophor, taxol has been shown to induce multiple drug resistance (MDR) in some cancer cell lines. One of the major contributors to MDR is the overexpression of *p*-glycoprotein (Pgp), which is an adenosine triphosphate (ATP) binding cassette transporter. Pgp is a protein dimer consisting of two sets of six transmembrane domains and two sets of ATP binding sites.[14] Hydrophobic drug molecules like taxol are recognized by Pgp and bind to its transmembrane domains. Pgp will use energy from the hydrolysis of ATP to ADP to effectively pump the drug molecules out of the cell.[14] The limitations of taxol in clinical use and the difficulty in developing synthetic alterations have prompted scientists to search for other lead molecules with a taxol-like mechanism of action.



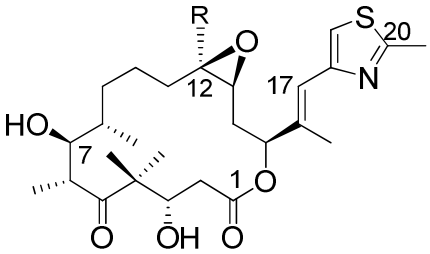
3 Paclitaxel



4 (+) - Discodermolide



5 Laulimalide



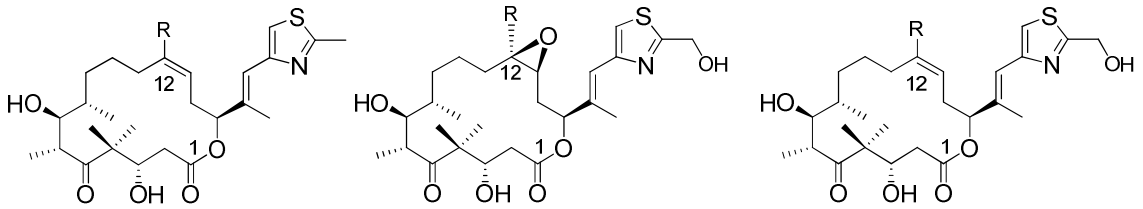
6 R= H, Epothilone A
7 R = Me, Epothilone B

Figure 4 Microtubule stabilizing agents

Two compounds isolated from marine sponges, discodermolide **4** and laulimalide **5** (Figure 4), were shown to have a similar antimitotic mechanism of action as taxol but were effective against MDR.[15] Discodermolide was isolated in 1990 from *Discodermia dissoluta*, and was initially classified as an immunosuppressive agent.[12] However, it was soon discovered that discodermolide promotes the formation of microtubules without GTP or MAPs, and competitively inhibits taxol binding to microtubules in the taxol microtubule binding site.[12] Novartis initiated a phase I clinical trial for discodermolide, but it was abandoned due to pulmonary toxicity.[16] Currently, studies are being conducted to search for active, non-toxic discodermolide analogues.[16] Laulimalide, isolated from *Cacospongia mycofijiensis*, is a potent cytotoxic agent with low nanomolar activity. It was classified as an antimitotic agent in 1999.[17] Laulimalide binds to a unique binding site on the exterior of the microtubule which is at a distance from the taxol binding pocket.[18] The biological activity and in vitro toxicity of laulimalide are currently being investigated.[18]

In the late 1980s, a new class of polyketide natural products was isolated from myxobacterium *Sorangium cellulosum* at the Gesellschaft für Biologisch-chemische Forschung (GBF) in Germany.[19] Named epothilones due to structural features (**epo**xide, **thi**azo**l**e, ket**one**), they were initially investigated as antifungal agents but were found to have considerable cytotoxicity in cell culture assays.[20] Epothilones were ignored by the pharmaceutical community until 1995 when Bollag et al.[13] discovered their microtubule stabilizing activity during the screening of natural product libraries for taxane-like activity.[20] Instantaneously epothilone A **6** and epothilone B **7** (Figure 4), the two natural products initially isolated from the *Sorangium cellulosum* strain So ce 90, stepped into the spotlight. Bollag also showed that not only did epothilones A and B induce tubulin polymerization, but epothilone B was cytotoxic to breast cancer cell line Hs578T at a lower nanomolar concentration than taxol.[13] Further examination of So ce 90 led to the

discovery of thirty-six epothilone analogues, including epothilones C through F (Figure 5 **8-11**) and deoxyepothilones E and F (Figure 5 **12, 13**).[21]



8 R= H, Epothilone C
9 R = Me, Epothilone D

10 R= H, Epothilone E
11 R = Me, Epothilone F

12 R = H, Deoxyepothilone E
13 R = Me, Deoxyepothilone F

Figure 5 Other epothilone analogues isolated from *Sorangium cellulosum*

Epothilones hold several advantages over taxol such as increased water solubility, eliminating the need for cremophor and reducing undesirable side effects.[22] They are amenable to synthetic alterations and are effective against MDR because epothilones are not recognized by Pgp.[13] Epothilones are competitive inhibitors of taxol on β tubulin, suggesting that they share a common binding site.[19]

1.3 Tubulin binding conformation and structure activity relationships of epothilones

The epothilone/taxol binding site on β tubulin is located between the M loop and H7 helix. The side chains of the amino acids surrounding the binding pocket can rearrange to optimize binding to the substrate in an induced fit.[23] Initially, epothilones and taxol were thought to share a common pharmacophore, but it has since been shown that both drugs utilize the M loop in different ways. The overlapping amino acid interactions

common to both drugs are the formation of a hydrogen bond between a hydroxyl moiety and Thr274, as well as π–stacking with His227 (Figure 6).[23-24]

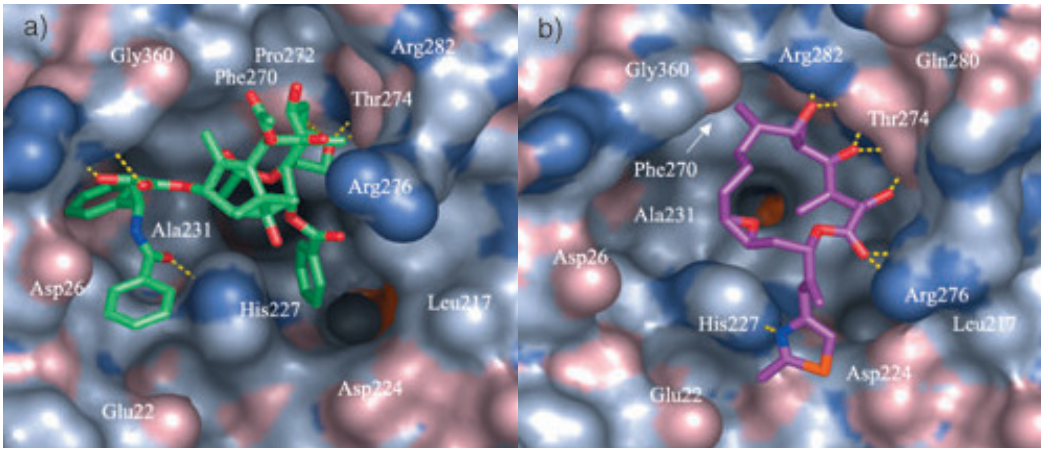


Figure 6 Interaction of (a) taxol and (b) epothilone A with amino acids in the tubulin binding site. Reprinted with permission from *Angewandte Chemie International Edition* **2005**, *44* (9), 1298-1301.

In the last ten years the bioactive conformation of epothilones has been extensively studied to determine how they interact with the amino acid residues lining the tubulin binding pocket. Such information is useful to determine what synthetic alterations can be made to optimize substrate/receptor binding. The conformational studies of epothilones began in 1999 when Taylor et al. used 2D nuclear magnetic resonance (NMR) studies to determine the lowest energy conformer of epothilone A in solution.[25] In 2004, Nettles et al.[24a] proposed a model for the binding of epothilone A to zinc-stabilized tubulin sheets using molecular modeling, electron crystallography, and NMR spectroscopy. Nettles described a parallel alignment of the C3, C5, and C7 oxygen functions which occurs due to the folding of the epoxide moiety beneath the macrocycle. The parallel orientation allows for significant hydrogen bonding interactions between these oxygen atoms and amino acids residues Thr274, Arg276, and Arg282 of the tubulin binding pocket (Figure 7). Nettles reported that Gln292 plays an essential role in the binding of epothilones and in maintaining the shape of the binding pocket. Gln292 hydrogen bonds with Arg282 which rotates the side chain of Thr274 into the optimum orientation for hydrogen bonding interaction with epothilone A.

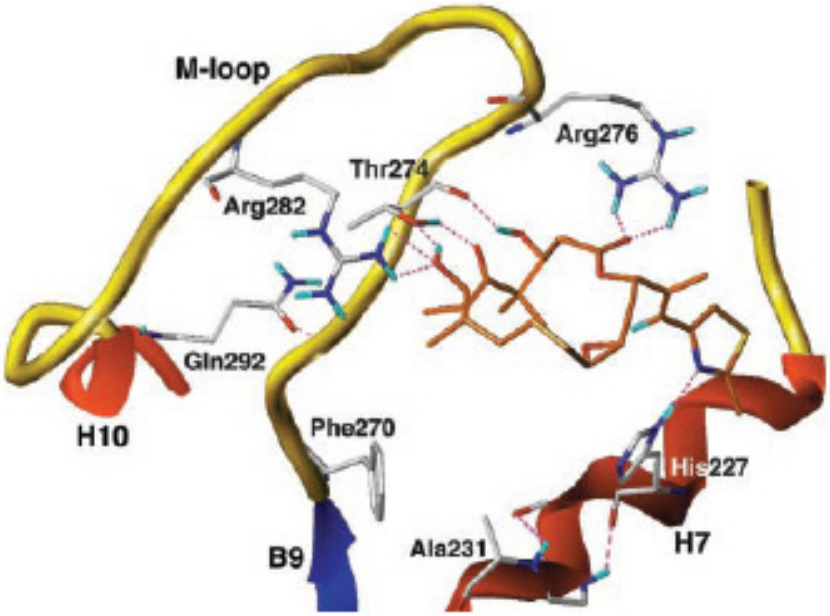


Figure 7 Nettles' model showing the hydrogen bonding between epothilone A and β tubulin. From *Science* **2004**, *305* (5685), 866-869. Reprinted with permission from AAAS.

The oxygen atom of the epoxide ring is located above a hydrophobic binding pocket with which it has minimal interaction. His227 on the H7 helix of the tubulin binding site also plays an important role by hydrogen bonding to the nitrogen atom in the thiazole ring. This hydrogen bonding interaction positions the C20 methyl moiety into a shallow hydrophobic binding pocket.

Carlomagno et al.[24b, 26] described the binding of epothilone A to monomeric tubulin using NMR Nuclear Overhauser Effect (NOE) and molecular modeling (Figure 8). This model proposed a completely different orientation of the oxygen functions at C1, C3, and C7 in the tubulin binding site as compared to Nettles' model. Carbon atoms C1-C4 exist in a *trans* conformation and are positioned away from the M loop amino acids. The oxygen functions at C1, C3, and C5 do not interact with the tubulin binding pocket; in fact, only the C7 hydroxyl forms a hydrogen bond with Arg282. This hydrogen bond interaction orients the side chain of Arg282 into a favorable position for hydrogen bonding with

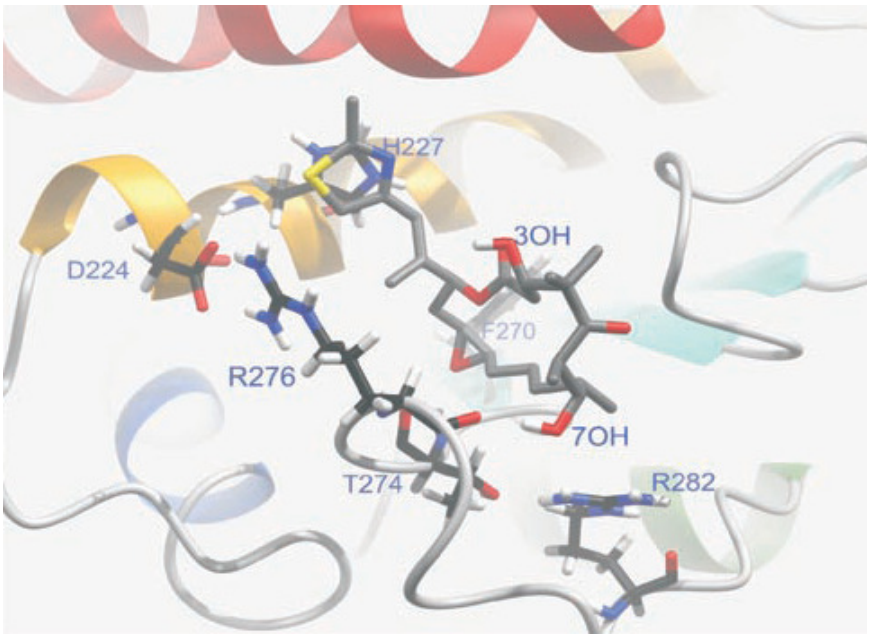


Figure 8 Carlomagno's model of epothilone A binding to tubulin using NOE studies. Reprinted with permission from *Angewandte Chemie International Edition* **2007**, *46* (11), 1864-1868.

Thr274, which in turn forms a hydrogen bond with Arg276. The side chain of Arg276 will form a stable salt bridge with negatively charged Asp224 on helix H7. Carlomagno proposed that the formation of the salt bridge maintains the shape of the binding pocket by locking the conformation of the M loop and H7 helix. The epoxide ring in Carlomagno's model is positioned underneath the macrocycle with the oxygen atom pointing toward the M loop. The hydrophobic pocket containing Phe270 is adjacent to the epoxide ring, which Carlomagno proposed could form hydrophobic interactions with the C12 methyl of epothilone B. The His227 on H7 plays an important role in the binding of epothilone A to the tubulin binding site. Instead of hydrogen bonding to the thiazole ring, Carlomagno reported that the π orbitals of the nitrogen atoms of His227 have favorable overlap with the π orbitals of the sulfur and nitrogen atoms of thiazole.

Recently ten new bioactive conformations of epothilone A in zinc-stabilized tubulin sheets were reported by Jimenez[27] using quantum chemical calculations. She reported that the most stable bioactive conformation of epothilone A from these calculations (Figure 9) forms a web of intermolecular hydrogen bonds between C7 hydroxyl and C5 ketone of epothilone A and amino acid residues Arg282 and Thr274 in the binding pocket. Also, an intramolecular hydrogen bond is formed between the C7 hydroxyl and the C5 ketone. The C4 geminal methyl groups form Van der Waals interactions with Leu273 in the tubulin binding pocket. The methyl groups at C8 and C14 assist in stabilizing the bound conformation of epothilones by forming intramolecular Van der Waals interactions. According to Jimenez,[27] the epoxide ring is more stable when positioned above the plane of the macrocycle instead of underneath as proposed by Nettles and Carlomagno. Fragment C9-C15 is located outside of the tubulin binding pocket and has no interaction with the protein. The biggest difference between the model proposed by Jimenez and other proposed models is the degree of receptor interaction of the aromatic thiazole ring. Jimenez reported that His227 and the thiazole ring were positioned away from each other and had no hydrogen bonding interaction or π-orbital overlap. Instead, the C3 hydroxyl forms an intramolecular hydrogen bond with the nitrogen of the thiazole ring.

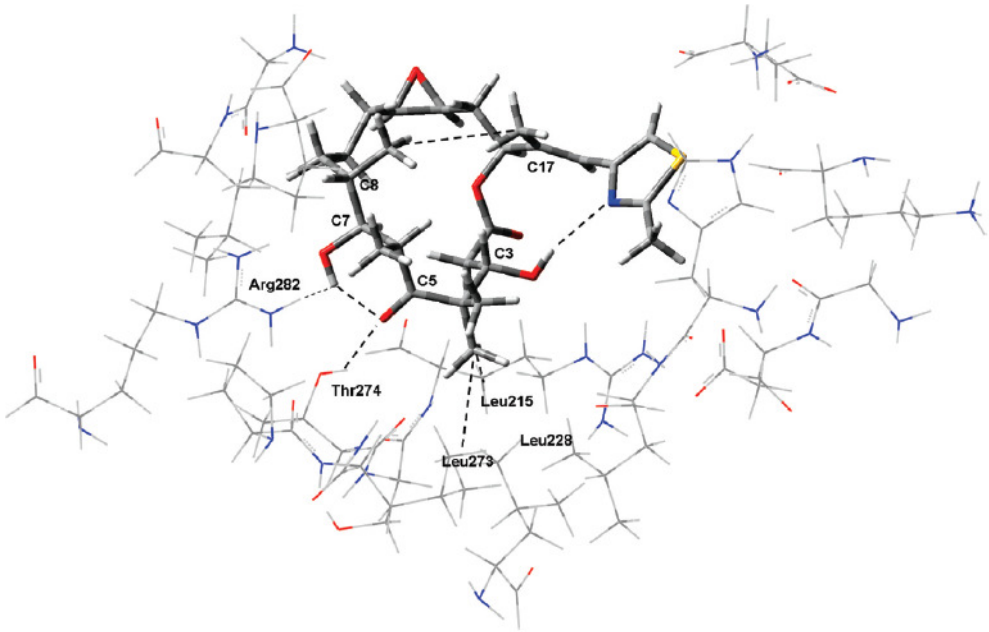


Figure 9 Structure of the most stable epothilone A - tubulin complex as proposed by Jimenez. Reprinted with permission from *Journal of Chemical Information and Modeling*, **2010,** *50* (12), 2176-2190. Copyright 2012 American Chemical Society.

All of the proposed binding models stress the importance of hydrogen bonding interaction between the tubulin binding site and the C7 hydroxyl. The thiazole ring has either important intermolecular hydrogen bonding, or π orbital overlap between the nitrogen of the thiazole ring and the nitrogen atoms of His227. The binding experiments performed by Nettles, Carlomagno, Jimenez, and others have given significant insight into the in vitro bioactive conformation of epothilone A. Interestingly, the other nine stable bioactive conformations proposed by Jimenez have similarities with conformations proposed by Nettles, Carlomango, and others.[27] It is a possibility that more than one bioactive conformation of epothilone A can produce the favorable substrate/receptor interactions within the binding site. However, all of the proposed models are based on in vitro experiments using tubulin with different degrees of stabilization and polymerization. It is also possible that the bioactive conformation of epothilones is vastly different in vivo.[23]

The efforts of Nicolaou,[6, 28] Danishefsky,[29] and others in the late 1990s led to the synthesis and biological evaluation of hundreds of epothilone analogues. A structure-activity relationship (SAR) profile was designed based on how the biological activity was affected by synthetic alterations. The experimental results of the SAR study were validated by the recent conformational studies of epothilone A in the tubulin binding pocket. The epothilone structure is divided into three sections based on SAR information.[6, 28f] Sector C1-C8 is critical for biological activity due to hydrogen bonding interaction of hydroxyl C7 with the binding pocket (Figure 10). The removal or reduction of the C5 ketone decreases biological activity. According to Nettles and Jimenez, this ketone has hydrogen bonding interaction with Thr274.[6, 24a] The C3 hydroxyl has minimal interaction with the tubulin binding site; instead it can stabilize the bioactive conformation through intramolecular hydrogen bonding with the oxygen functions at C1, C5 or the oxygen of the epoxide ring.[27] Biologically active epothilone analogues have been synthesized in which the C3 hydroxyl has been bioisosterically replaced with a cyano moiety,[30] dehydrated to E-3-deoxy-2,3-didehydroepothilone analogue,[31] or totally removed.[31-32] However, inversion of stereochemistry at C3 results in a significant loss of biological activity, possibly due to steric interaction with the C6 proton.[24b] A reduction in biological activity occurs if the C6 or C8 methyl is removed.[6]

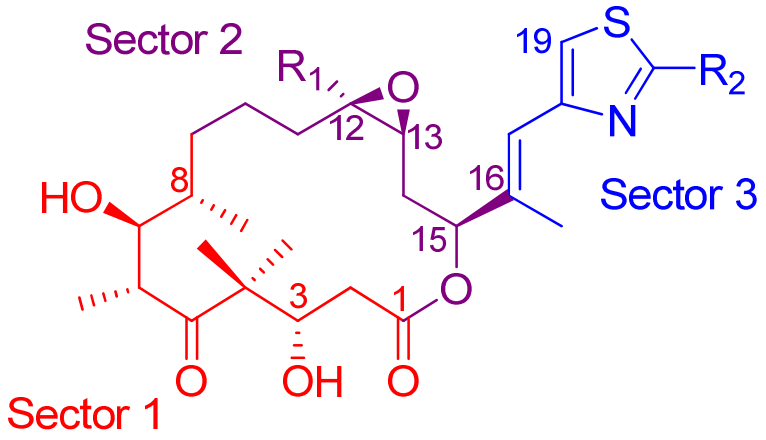


Figure 10 The three biologically relevant sectors of epothilones

The sector from C9-C15 (Sector 2) containing the epoxide ring is flexible and folded above or below the macrocylic ring.[24, 27] This sector when folded below the macrocycle is positioned adjacent to a hydrophobic pocket containing amino acid residue Phe270.[24] Synthetic alterations incorporating large functional groups at the C12-C13 epoxide ring retain biological activity, possibly due to hydrophobic interaction with Phe270 (Figure 11). Compound **14** is the *trans* epoxide of epothilone A. It has equipotent cytotoxic activity as compared to epothilone A.[33] Interestingly, the *trans* epoxide of epothilone B has been synthesized and it is less potent than epothilone B.[33] Changes to the epoxide heteroatom and ring size in compounds **15-17** are well tolerated without a significant loss in biological activity.[28c, 30, 34] Several analogues of aziridine **16** have been synthesized with alkyl and small aryl groups at the R position.[30] These analogues have favorable biological activity suggesting that the fragment C9-C15 can form favorable hydrophobic interactions with Phe270 in the binding pocket. The epoxide ring is not required for biological activity as evident from the potent biological activity of epothilone C and D. Both *cis* and *trans* **18** are biologically active and therefore, biological activity is independent of the geometry of the double bond.[33]

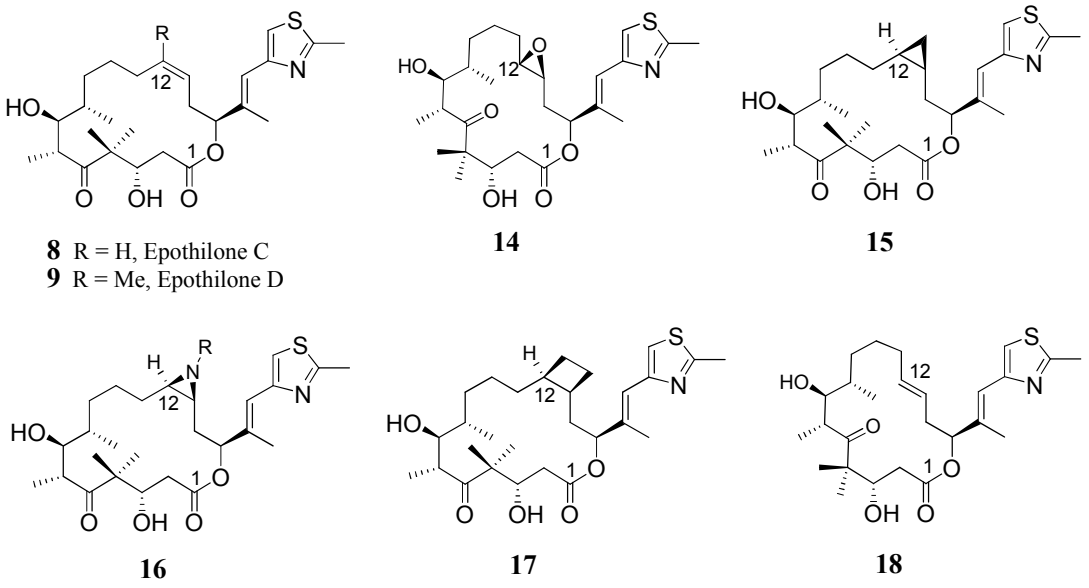


Figure 11 Active epothilone analogues with alterations at C12-C13

Sector 3 (Figure 10) containing C16-C20 is critical for biological activity and consists of an aromatic moiety connected to the macrocycle via an olefinic spacer.[6] Direct connection of the aromatic ring to the macrolactone ring results in a significant decrease in biological activity.[6] In natural epothilones the aromatic ring is a thiazole ring, but active analogues with other aromatic ring systems have been synthesized, including pyridines, imidazoles, and oxazoles.[28g, 35] The aromatic ring must contain a nitrogen atom in the *ortho* position for biological activity. Nicolaou et al.[28g] confirmed this phenomenon by synthesizing pyridine epothilone analogues with the nitrogen atom in the *ortho*, *meta*, or *para* ring positions. A 100-fold decrease in biological activity was observed for the *meta* and *para* positions of the heteroatom, due to the disruption of intramolecular and intermolecular hydrogen bonding within the tubulin binding pocket.[24a, 27] Aromatic rings with two or more heteroatoms, such as benzothiazole and benzoimidazoles, have potent biological activity even when the heteroatom is not in the *ortho* position.[28a] This may be due to favorable π-orbital overlap between the heteroatoms of the aromatic ring and the delocalized imidazole π-electrons of His227 in the binding pocket.[24b] In natural epothilones, the C20 methyl group is believed to occupy a small binding pocket which cannot accommodate bulky substituents. As the size of the C20 substituent increases, a decrease in biological activity was observed.[6, 33] However, no correlating systematic study has been carried out to correlate the size of the substituent to biological activity.[36] Recently Altmann and Carlomango[37] explored the tubulin binding affinity, microtubule binding activity, and antiproliferative activity of epothilone analogues with a C20-propyl, C20-butyl, and C20-hydroxypropyl group. Interestingly, as the size of the C20 group increased, a small decrease in tubulin-polymerizing activity and microtubule binding affinity was observed.[37] The antiproliferative activity of the analogue with a C20-propyl was similar to that of epothilone A; however, the antiproliferative activities of C20-butyl and C20-hydroxypropyl decreased 40- and >100-fold, respectively.[37] NMR studies could not explain the differences in the biochemical properties of the C20-substiuted epothilones. The C20-hydroxypropyl analogue was found to interact with soluble tubulin and the conformation of the macrolide ring of the analogue bound to tubulin closely resembled that of epothilone A, while the

conformation of the C20-hydroxypropyl group was less clear due to overlap of NMR resonances.[37]

1.4 Epothilones in clinical trials

Currently there is one epothilone analogue in clinical use and four epothilones in various stages of clinical trials (Figure 12).[38] Ixabepilone **19**, the semisynthetic amide analogue of epothilone B, was approved by the FDA for the treatment of metastatic and advanced breast cancer.[38b, 39] It has been tested in twenty-one cell lines, and showed activity at low nanomolar potency.[38a, 40] Ixabepilone is water soluble and can be given orally instead of intravenously.[38a] At the maximum tolerated dose (MTD), patients treated with ixabepilone exhibited neutropenia, neuropathy, fatigue, nausea, vomiting, and diarrhea.[38a]

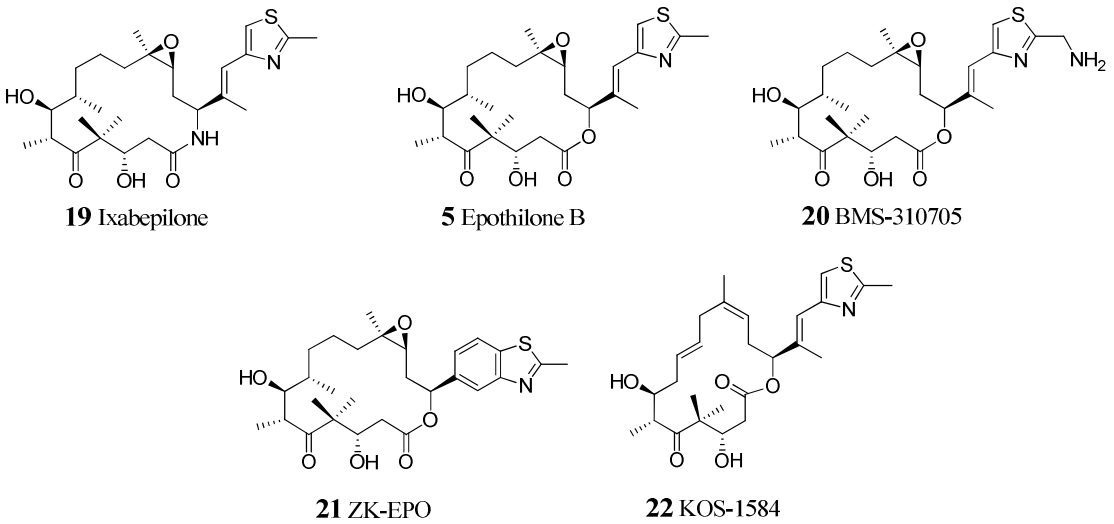


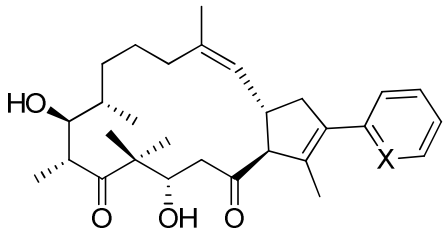
Figure 12 Epothilones in clinical use or clinical trials

Epothilone B, **5**, was the first epothilone to enter clinical trials.[38b] Also known as patupilone, it is currently undergoing phase II trials against breast, lung, ovarian, renal,

and non-small cell lung cancers.[38] Recently it was found that patupilone can cross the blood brain barrier and access the central nervous system (CNS). It is currently being studied in patients with brain tumors.[41] The most common side effect reported for patupilone at the MTD is diarrhea.[41b] BMS-310705, **20**, is more water soluble than ixabepilone and is orally bioavailable. It is currently undergoing phase I and phase II clinical trials and has shown partial responses in breast and stomach cancers.[38b] ZK-EPO, **21**, also known as sagopilone, is a benzothiazole analogue of epothilone B. It is the only completely synthetic analogue to reach clinical trials and is currently being evaluated in patients with metastatic breast cancer.[38a] KOS-1584, **22**, is structurally more rigid by incorporation of a double bond at C9-C10. It is currently undergoing phase I clinical trials.[38b]

1.5 Drug design and rationale

Previously, our lab reported the synthesis of two conformationally constrained epothilone analogues **23** and **24** (Figure 13).[42] A methylene bridge was inserted between C14 and C17 to create a five membered cyclic structure to help rigidify the epothilone side chain. In a preliminary in vitro cytotoxic assay, compound **24** showed activity against CCRF-CEM (human T-cell lymphoblasts) and SR leukemia cell lines with IC_{50} values of 2.7 nM and 2.9 nM, respectively.



23 X = CH_2
24 X = N

Figure 13 Conformationally constrained epothilones

The most important sectors for biological activity of epothilones are C1-C8 and C16-C20. We wanted to explore whether deleting C10-C13 and rigidifying the two biologically relevant sectors C1-C8 and C16-C20, with a cyclopentene molecular scaffold, could satisfy the requirements for tubulin binding. Previously our lab synthesized two such open-chain epothilone analogues **25** and **26**[43] (Figure 14) in which the thiazole ring has been replaced with a pyridine ring.

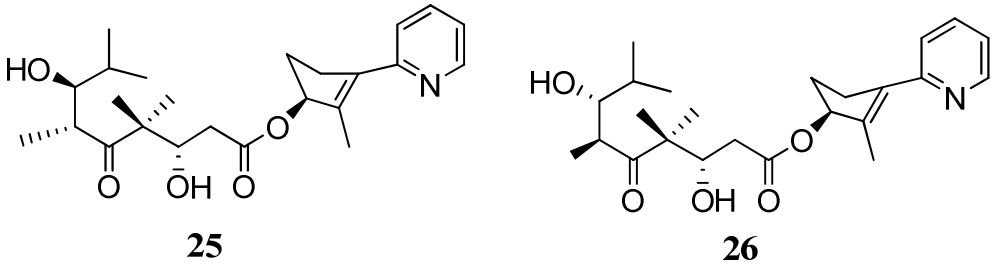


Figure 14 Open-chain epothilone analogues

Compounds **25** and **26** were tested in the National Cancer Institute (NCI) 60 cell line assay. Diastereomer **25**, with stereochemical assignments as in natural epothilones, had weak but selective activity against SNB-75 (IC_{50} = 21.9 μM) and OVCAR-4 (IC_{50} = 41.5 μM) cell lines.[43] In 2008 a computational study was performed by Rusinska-Roszak et al.[44] using quantum chemical calculations to compare the conformations of compound **25** and epothilone A. Seven stable conformers of open-chain epothilone **25** are shown in Figure 15. Different intramolecular hydrogen bonding interactions occur between the oxygen functionalities at C1, C3, C5, C7 and the oxygen of the ester. The most stable conformer is structure I with intramolecular hydrogen bonding occurring between oxygen functionalities at C1 and C3 as well as between oxygen functionalities at C5 and C7 (Figure 16).

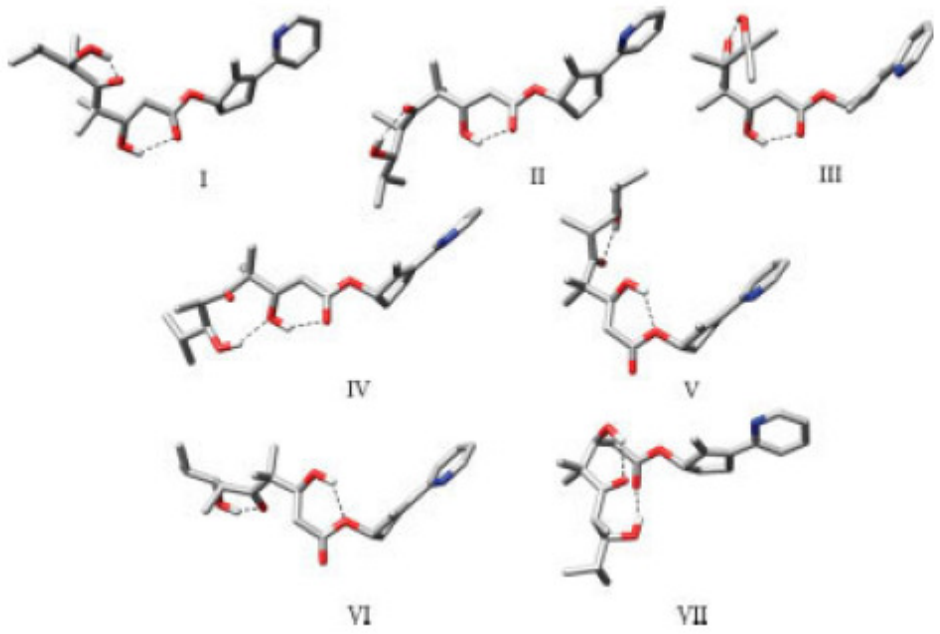


Figure 15 Stable conformations of open-chain epothilone **25**. Reprinted with permission from *International Journal of Quantum Chemistry* **2008**, *108* (5), 967-973.

Chosen conformers of open-chain epothilone **25** were superpositioned with various macrocyclic conformations of epothilone A and epothilone B. Conformers III and XX were compared with different bioactive conformations of epothilone A, while conformer XIV was compared with a conformer of epothilone B reported by Wang.[44-45] Essentially, this study showed a high degree of similarity between the conformations of macrocylic epothilones, and open-chain epothilone **25,** which therefore, meets the fundamental requirements for tubulin binding.

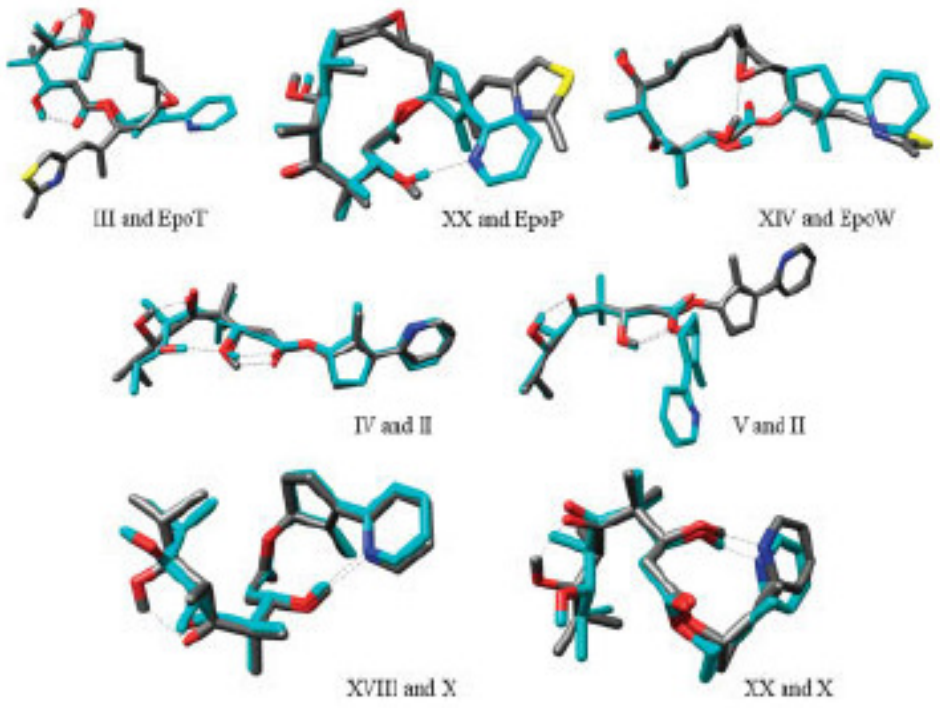


Figure 16 Superposition of open-chain epothilone **25** conformers with macrocyclic epothilones A and B and superpositioning between different conformers of open-chain epothilone **25**. Reprinted with permission from *International Journal of Quantum Chemistry* **2008**, *108* (5), 967-973.

In continuation of this work, we wanted to explore if the activity of the open-chain epothilones could be improved by chemical modification of its structure. This dissertation focuses on the synthesis of a library of open-chain epothilones with a variety of substituents at C20 of the thiazole ring (Figure 17). Thiazole was chosen as the aromatic moiety to be consistent with the aromatic moiety of natural epothilones. Substituents on the thiazole ring are of different degrees of hydrophobicity, hydrophilicity, and size. They were chosen to determine the nature and tolerance of the binding site. Open-chain epothilone analogues with stereochemical assignments similar to those in natural epothilones and their diastereomers were designed.

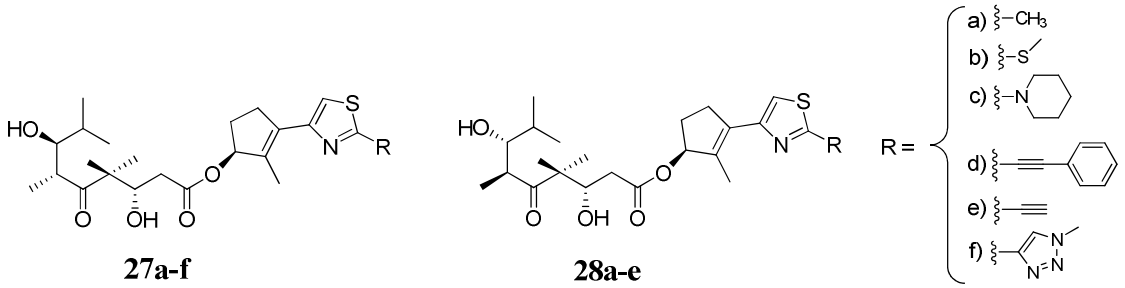


Figure 17 Structure of open-chain epothilones with 2-substituted thiazole

In addition, we designed several open-chain epothilone analogues with hydrophobic aromatic substituents at C10 and C14 (Figure 18). These molecules may undergo hydrophobic collapse in an aqueous environment due to the attraction of the phenyl rings at C10 and C14, and assume a conformation that mimics the macrocyclic epothilone conformation.

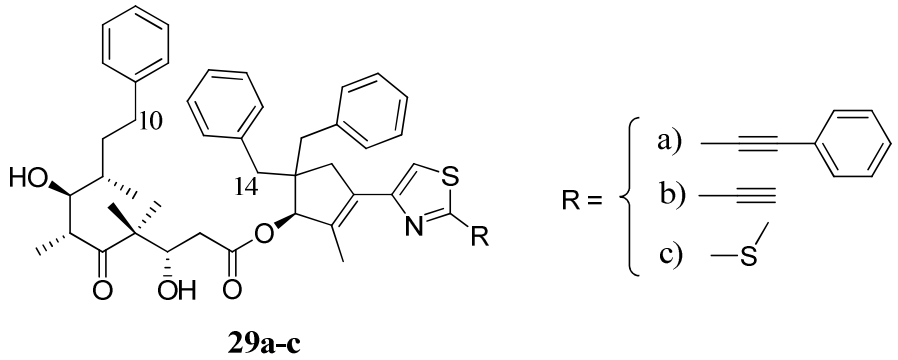


Figure 18 Structure open-chain epothilone with hydrophobic end groups

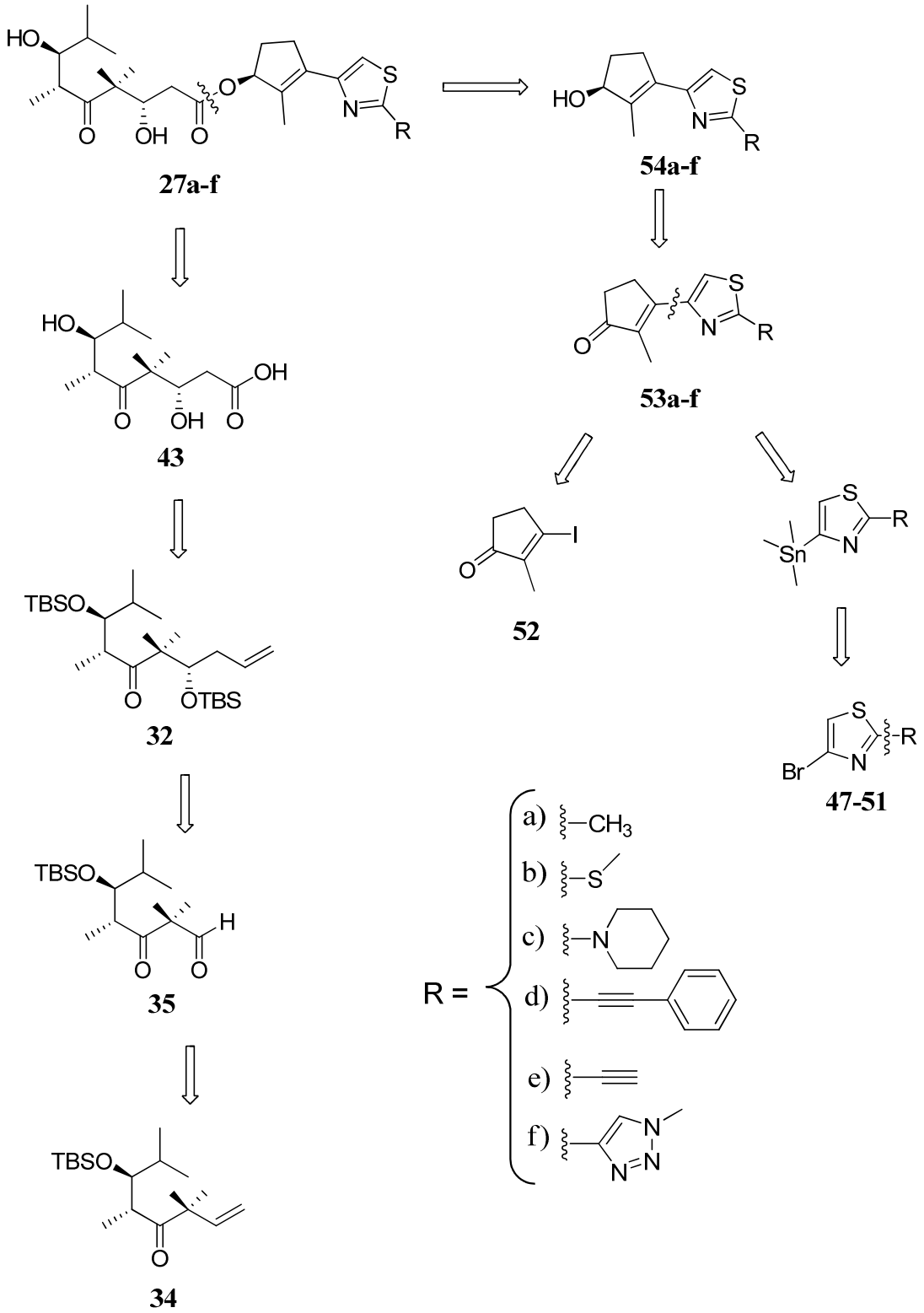
Following their chemical synthesis, the open-chain epothilones analogues **27a-f** and **28a-e** were tested in the National Cancer Institute's 60 cell line assay, while compounds **29a-c** will be tested by the NCI to determine their cytotoxicity.

Chapter Two

Results and Discussion

2.1 Synthesis of open-chain epothilones 27a-f and 28a-e

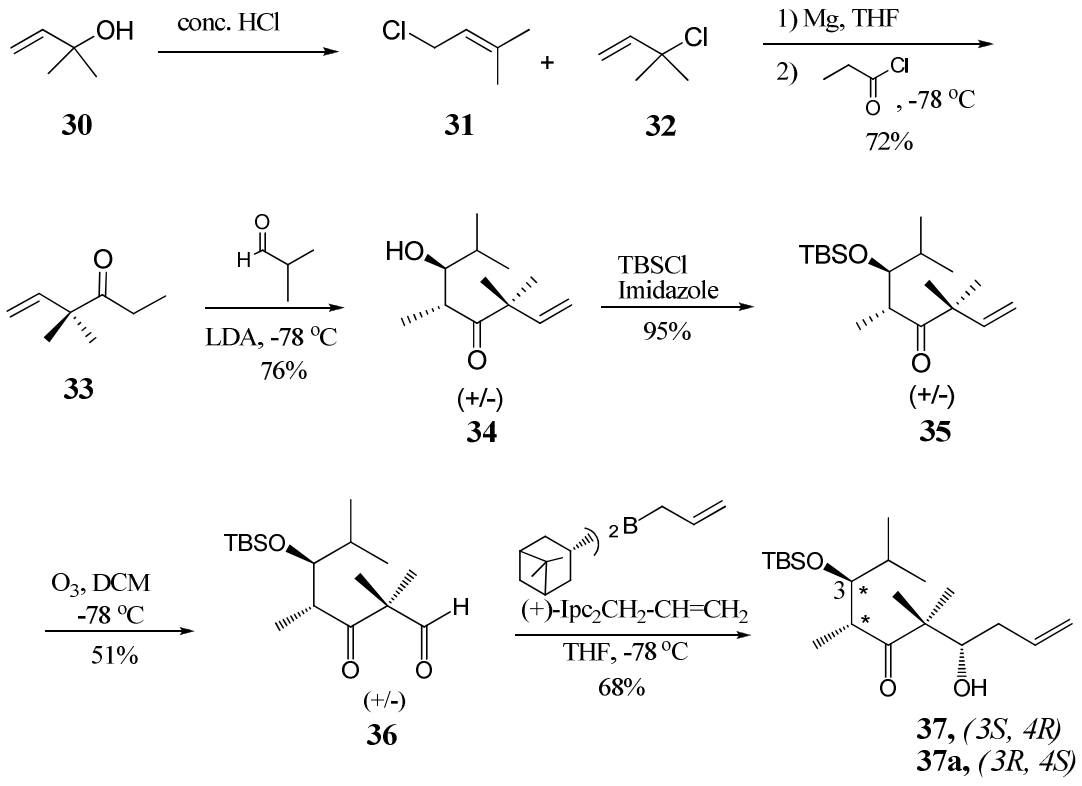
We first synthesized the open-chain epothilone analogues **27a-f** and **28a-e.** In analogues **27a-f** the acyl fragment has identical stereocenter assignments as in natural macrocylic epothilones, whereas analogues **28a-e** consist of a diastereomeric form of the acyl fragment. The key synthetic step in the synthesis of **27a-f** is the esterification between carboxylic acid **43** and (*S)*-alcohol moieties **54a-f** shown in the retrosynthetic analysis (Scheme 1). We have previously reported the synthesis of the carboxylic acid **43**.[43] However, we improved the efficiency of this synthetic strategy. The synthesis of (*S*)-alcohol moieties **54a-f** was achieved by the enantioselective reduction of ketones **53a-f** with Corey-Bakshi-Shibata (CBS) oxazaborolidine catalyst. The reduction of piperidinyl ketone **54c** with CBS reagent was unsuccessful and resulted in a racemic mixture. The aryl substituted ketones **53a-f** were synthesized by palladium catalyzed Stille coupling between 2-substituted bromothiazoles **47**-**51** and iodocyclopenteone **52**.



Scheme 1 Retrosynthetic analysis of open-chain epothilones **27a-f**

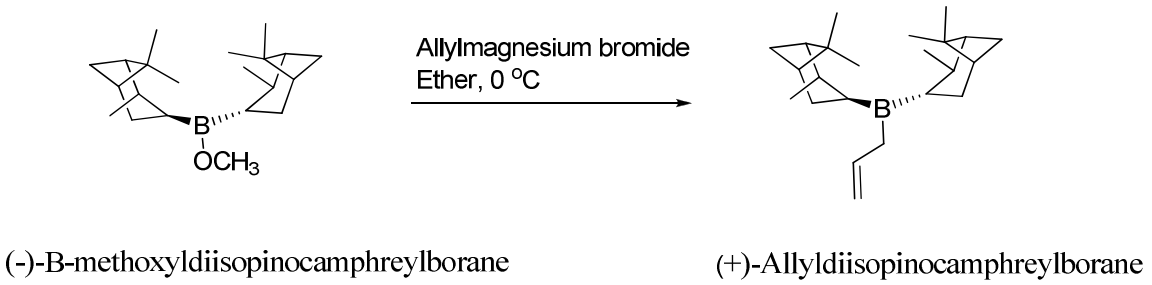
2.1.1 Synthesis of allylic alcohols 37 and 37a

The synthesis of allylic alcohols **37** and **37a** is shown in Scheme 2. Addition of concentrated hydrochloric acid (HCl) to 2-methyl-but-3-en-2-ol **30** at 0 ^{o}C gave mainly 1-chloro-3-methyl-but-ene **31** with a trace amount of 3-chloro-3-methylbut-1-ene **32**.[46] The prenyl chloride mixture was not separated but converted to the corresponding Grignard reagent in the presence of magnesium turnings. The Grignard reagent was reacted with propionyl chloride at -78 ^{o}C, and the crude product was purified by fractional distillation to obtain Mori's ketone **33**.[47] Aldol reaction of Mori's ketone with isobutylaldehyde in the presence of lithium diisopropylamide (LDA) yielded a racemic mixture of alcohol **34**[47-48] of which the hydroxyl group was protected with *tert*-butylchlorodimethylsilane (TBSCl) to obtain silyl ether **35**. Ozonolysis of **35** gave a racemic mixture of aldehyde **36**, which was stereoselectively converted to allylic alcohol diastereomers **37** and **37b** using (+)-allyldiisopinocamphreylborane as described by Brown et al.[49]



Scheme 2 Synthesis of allylation product **37**

(+)-Allyldiisopinocamphreylborane was prepared by reacting allylmagnesium bromide with commercially available (-)-β-methoxydiisopinocamphreylborane at 0 ^{o}C (Scheme 3).[49] The enantioselectivity of the Brown's allylation reaction is controlled through a six-membered transition state in which the allylic group on borane selectively attacks the *re* face of the aldehyde to minimize steric interactions with the bulky diisopinocamphreyl groups (Figure 19).



Scheme 3 Preparation of Brown's allylation reagent

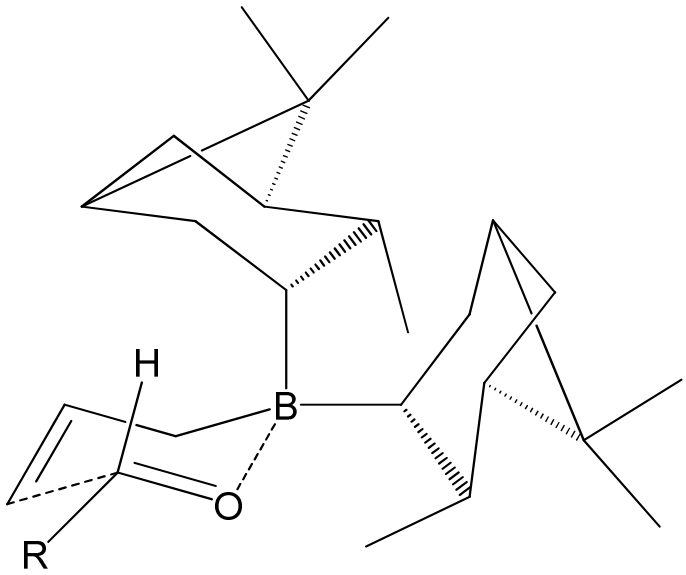
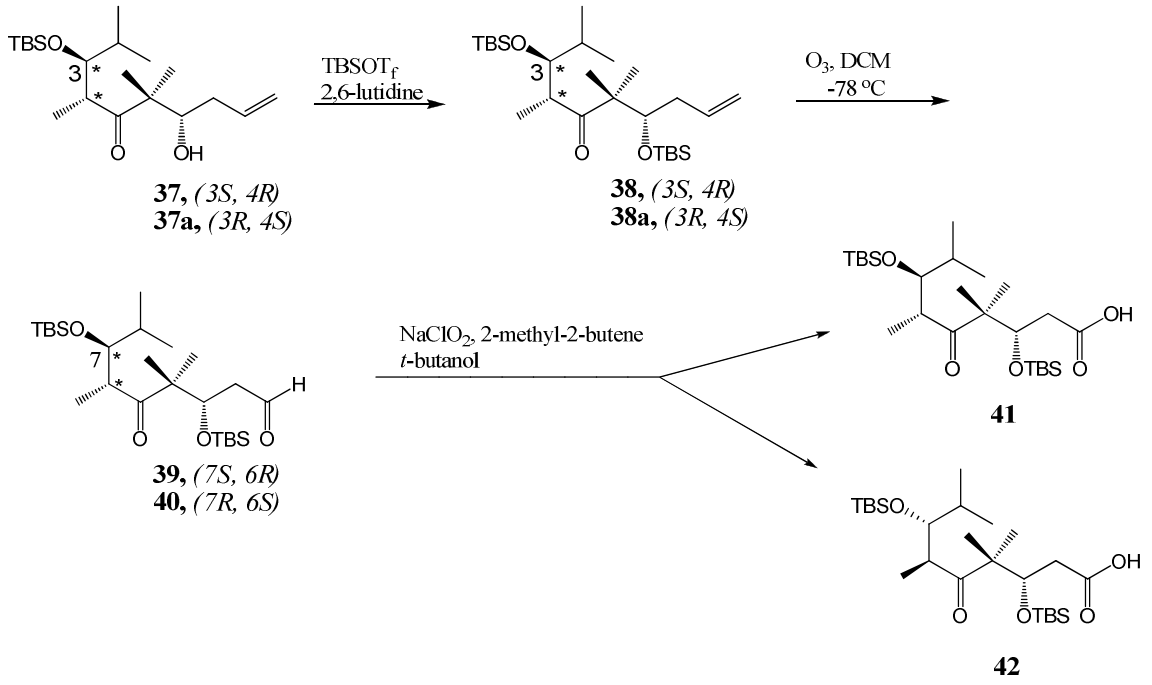


Figure 19 The six-membered transition state of Brown's allylation reaction

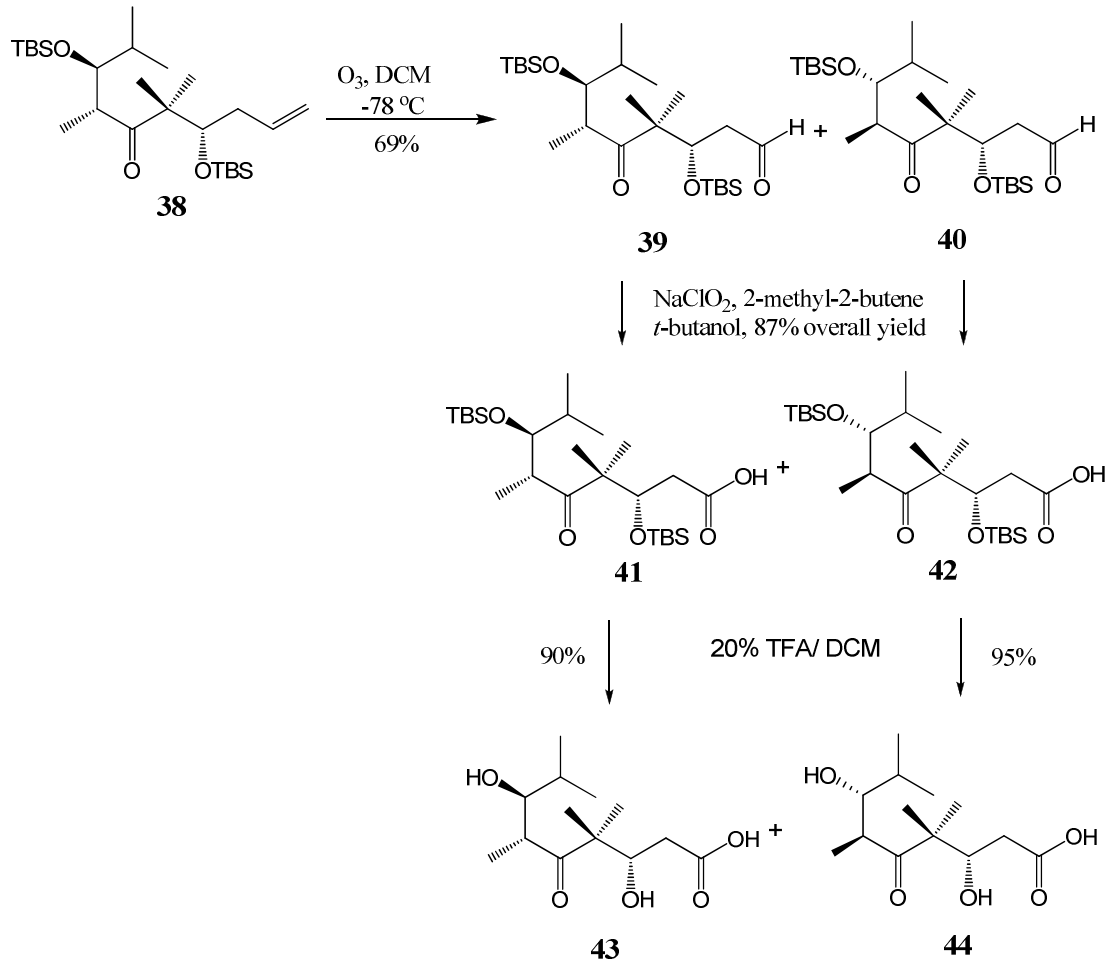
2.1.2 Synthesis of carboxylic acid diastereomers 43 and 44

In our previously reported synthesis of carboxylic acids **41** and **42**, the hydroxyl group of racemic allylation product **37/37a** was protected before ozonolysis to aldehydes **39/40** (Scheme 4). Pinnick oxidation of **39/40**[50] gave a mixture of carboxylic acids **41** and **42** which were separated by flash chromatography. The separation proved difficult and resulted in incomplete separation of diastereomers **41** and **42**.



Scheme 4 Previously reported synthesis of carboxylic acids **41** and **42**[43]

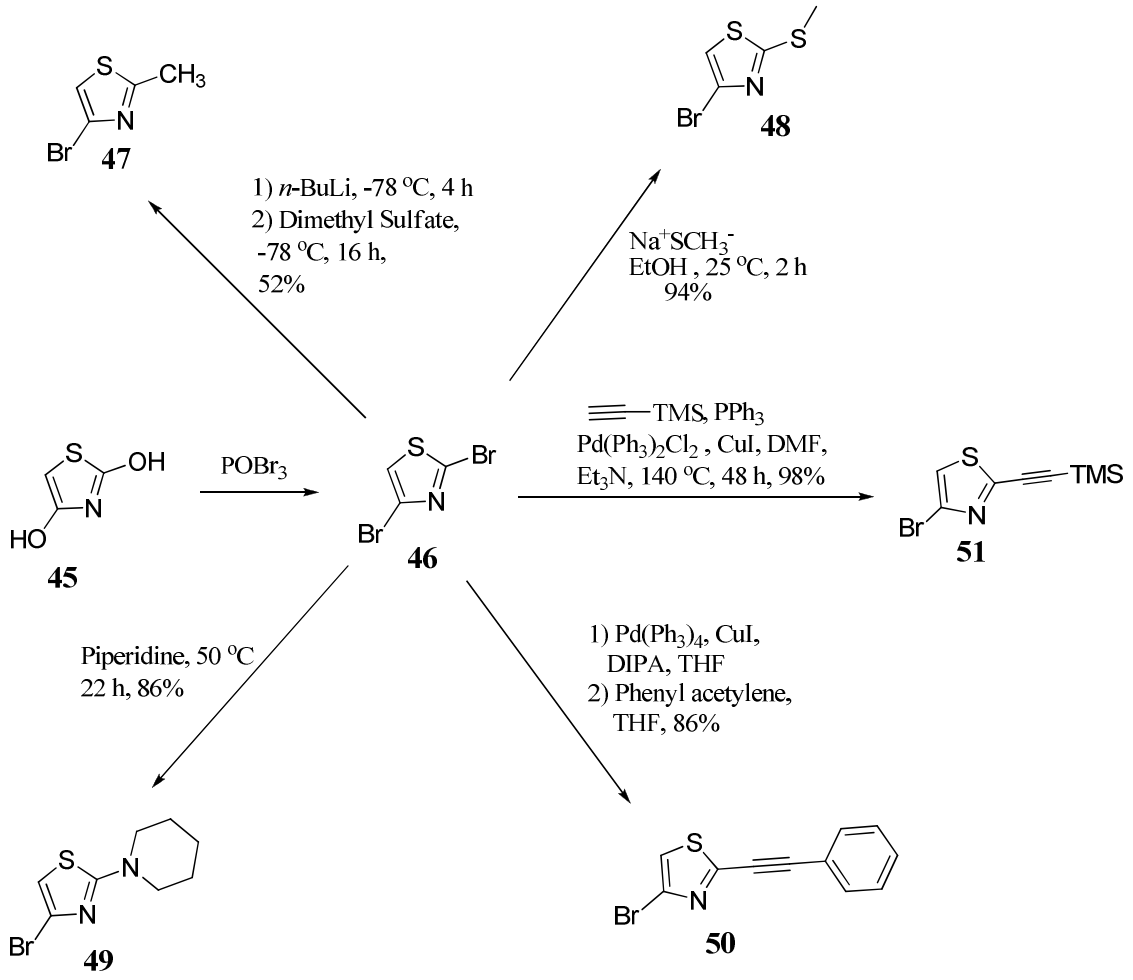
In our improved procedure, the diastereomeric aldehydes **39** and **40** were separated efficiently by flash chromatography (Scheme 5). The separated diastereomeric aldehydes **39** and **40** were individually oxidized under Pinnick oxidation conditions[50] to separately obtain carboxylic acids **41** and **42** in a 1:3 ratio respectively. The *tert*-butyldimethylsilyl (TBS) protecting groups were removed with 20% trifluoroacetic acid (TFA) in dichloromethane (DCM) to individually obtain carboxylic acid **43** and carboxylic acid **44**.



Scheme 5 Synthesis of carboxylic acids **43** and **44**

2.1.3 Synthesis of 2-substituted thiazole cyclopentenols 54a-f

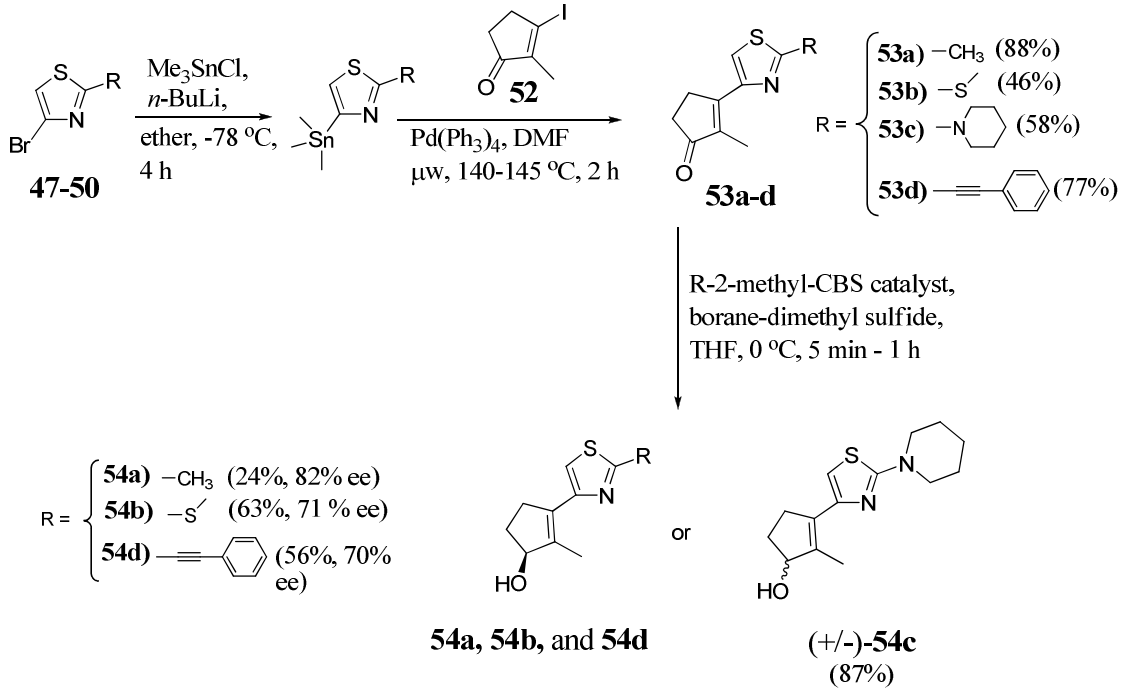
The synthesis of 2-substituted thiazole cyclopentenols **54a-f** began with commercially available 2,4-dihydroxythiazole **45**, which was heated with phosphorous oxybromide at 110 °C to give 2,4-dibromothiazole **46** (Scheme 6), which was isolated by sublimation.[51] However, it became more cost effective to purchase commercially available **46** instead of synthesizing it. Nucleophilic addition/elimination or palladium catalyzed Sonagoshira reaction of 2,4-dibromothiazole **46** produced 2-substituted bromothiazole derivatives **47**-**50** in reasonably good yields. The synthesis of compounds **47**, **48**, and **50** has previously been reported.[28b, 52]



Scheme 6 Synthesis of 2-substituted bromothiazole derivatives **47-51**

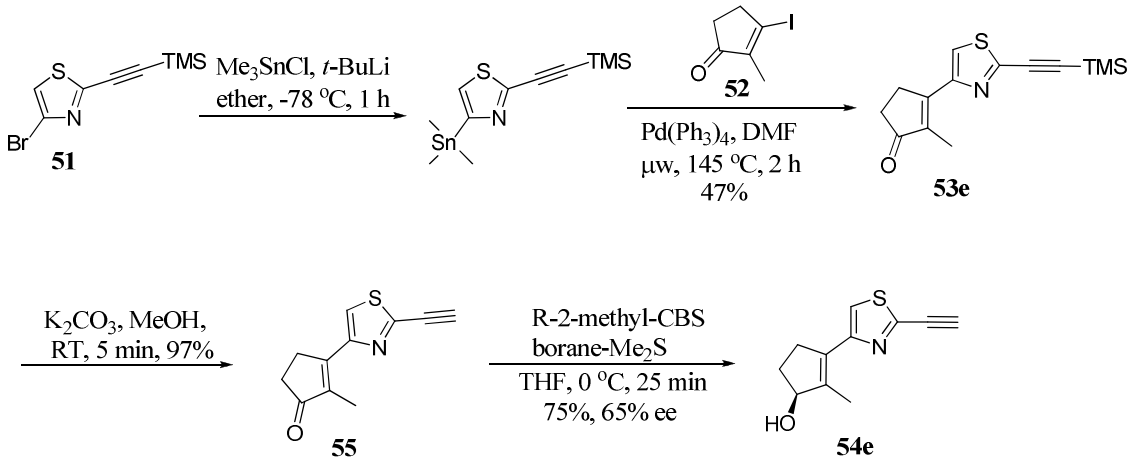
Bromothiazoles **47**-**50** were treated with *n*-BuLi followed by trimethyltin chloride at -78 °C to produce the corresponding tin derivatives, which were partially purified by passing through a silica gel plug deactivated with 5% triethylamine in hexanes (Scheme 7).[28b] Palladium catalyzed Stille coupling between the tin derivatives and iodocyclopentenone **52** gave the 2-substituted cyclopentenones **53a-d**.[28b] Enantioselective reduction of cyclopentenones **53a, 53b,** and **53d** using CBS reaction conditions afforded the cyclopentenols **54a, 54b,** and **54d**, respectively.[53] Enantioselective reduction of piperdinyl ketone **53c** to alcohol **54c** under similar conditions was not successful, and the racemic mixture of piperidinyl alcohols was used in esterification without further

separation. The stereochemistry of the newly generated stereocenter was determined by Mosher ester analysis.[54]



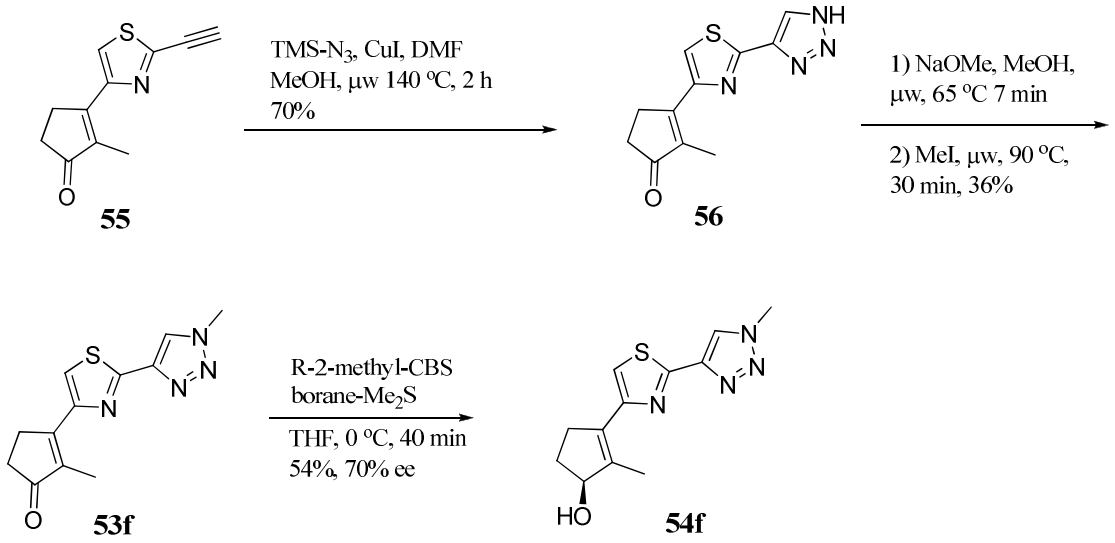
Scheme 7 Synthesis of 2-substituted cyclopentenols **54a-d**

Treatment of acetylene derivative **51** with *n*-BuLi proved inefficient for lithium halogen exchange; *t*-BuLi was more efficient for stannylation with trimethyltin chloride (Scheme 8). The tin derivative was partially purified by passing through a silica gel plug deactivated with 5% triethylamine in hexanes and was immediately subjected to Stille coupling with iodocyclopenteone **52.**[28b] Desilylation of the TMS protecting group of **53e** with potassium carbonate afforded the acetylene ketone **55** in excellent yield. It was subjected to CBS reduction to obtain cyclopentenol **54e**.[53]



Scheme 8 Synthesis of the acetylene cyclopentenol **54e**

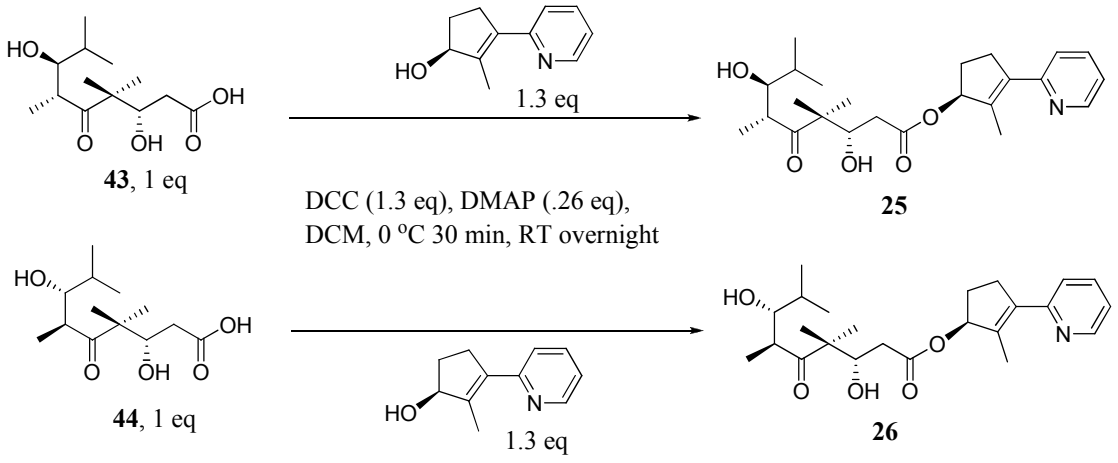
Compound **55** was also subjected to azide-alkyne Huisgen cycloaddition with trimethylsilyl azide in the presence of CuI in a mixture of dimethylformamide (DMF) and methanol (9:1) to give the triazole **56** (Scheme 9).[55] Triazole **56** was insoluble in most organic solvents except for large quantities of methanol, conditions not amenable to CBS reduction. Therefore, it was methylated[56] with methyl iodide in the presence of sodium methoxide to increase solubility in organic solvents before CBS reduction to the corresponding cyclopentenol **54f**. The stereochemistry of the secondary alcohol function was confirmed by Mosher ester analysis as before.[54]



Scheme 9 Synthesis of triazole cyclopentenol **54f**

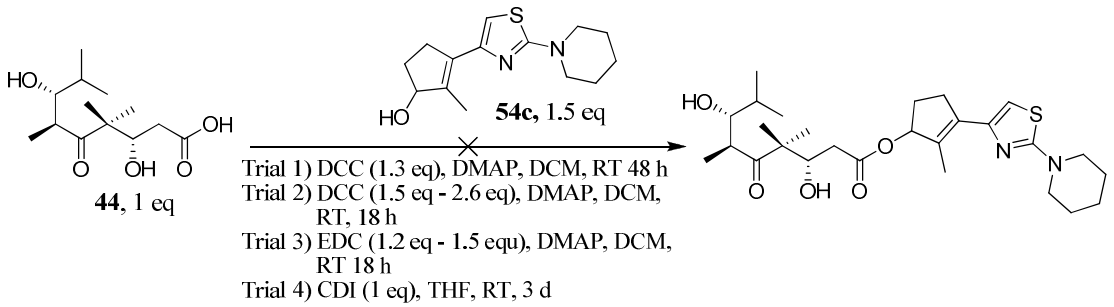
2.1.4 Exploring esterification reaction conditions for open-chain epothilones

In the previously reported synthesis of open-chain epothilones **25** and **26**, esterification of carboxylic acids **43** and **44** with the cyclopentenol was carried out using dicyclohexylcarbodiimde (DCC) and a catalytic amount of 4-dimethylaminopyridine (DMAP) under Steglich esterification conditions (Scheme 10).[57]



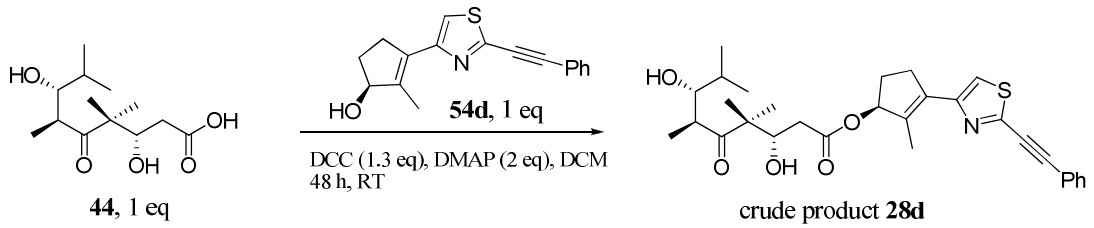
Scheme 10 Esterification of open-chain epothilones **25** and **26**

We began our investigation into the esterification of open-chain epothilones **27a-f** and **28a-e** by first attempting coupling of carboxylic acid **44** with piperidinyl alcohol **54c** using the same Steglich esterification conditions as previously reported (Scheme 11).[43] Unfortunately, this set of reaction conditions did not yield the desired open-chain epothilone product; varying the molar equivalents of reagents, temperature, and time was did not improve the outcome. Coupling agents 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and carbonyldiimidazole (CDI) also did not produce the desired open-chain epothilone.



Scheme 11 Attempted esterification reaction using DCC, EDC, and CDI

After the unsuccessful esterification trials with piperidinyl alcohol, we decided to return to the original reaction conditions with DCC (1.3 eq) using phenyl acetylene substituted alcohol **54d** instead of the piperidinyl substituted alcohol **54c** (Scheme 12). Interestingly, the NMR spectrum of the crude product showed the formation of **28d**; however purification by preparative thin-layer chromatography on silica gel plates resulted in disintegration of the product. At this point, we decided to reinvestigate the esterification reaction between **44** and piperidinyl alcohol **54c** and other (*S*)-alcohol moieties.



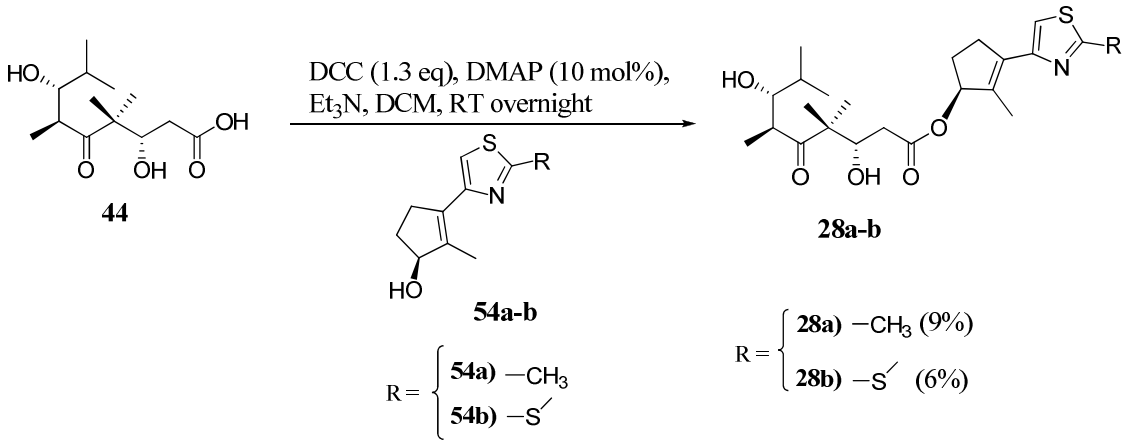
Scheme 12 Synthesis of crude product **28d**

Upon treatment of carboxylic acid **44** with piperidinyl alcohol **54c**, we observed that the ester product does form in small quantities. However during purification on silica gel preparative thin-layer chromatography plates, the product disintegrated. We suspected that the major problem was not the coupling of the carboxylic acid and alcohol moieties, but the instability of the ester functionality of open-chain epothilones on silica gel. Attempts to separate the product by reverse phase high performance liquid chromatography (HPLC) using 60-90% acetonitrile in water and pure acetonitrile; or preparative thin layer chromatography on silica gel plates deactivated with 5% triethylamine in hexanes; or by column chromatography on neutral alumina were not successful. Finally, upon further investigation, we were able to successfully isolate the open-chain epothilone analogues by preparative TLC on silica gel plates, which were first deactivated with 5% triethylamine in hexanes and allowed to dry overnight.

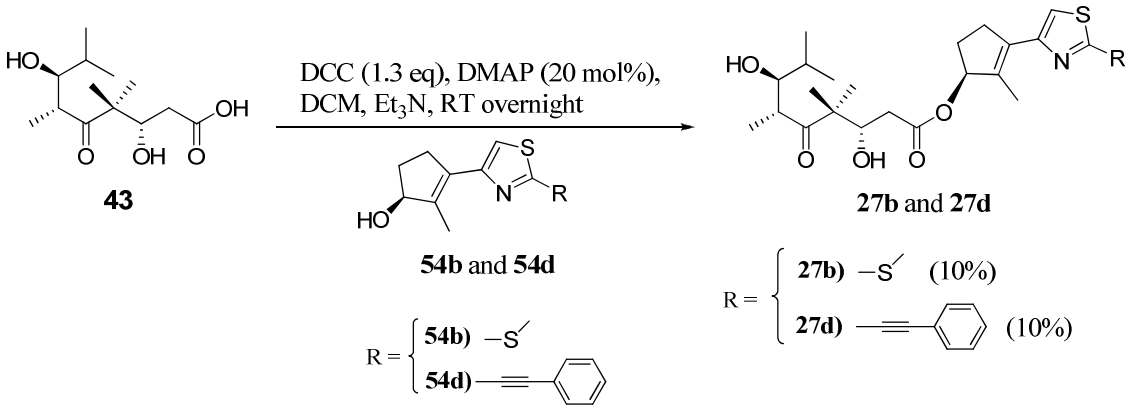
2.1.5 Esterification reaction conditions to obtain open-chain epothilones 27a-f and 28a-e

The first open-chain epothilone analogues synthesized were **28a-c** using the carboxylic acid **44** with *(S)*-alcohols **54a-c** and **27b-d** using carboxylic acid **43** with *(S)*-alcohols **54b-d** (Schemes 13-15). We suspected that residual TFA from the desilylation of carboxylic acids **43** and **44** may be responsible for low percent yields of the esterification reactions. Therefore, triethylamine (1-2 eq) was added to the reaction mixture. The

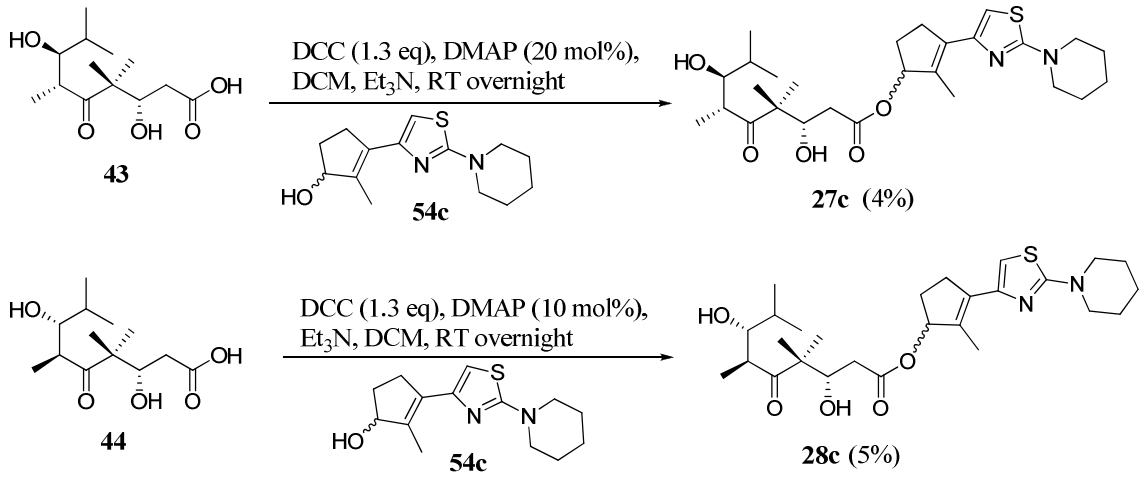
addition of triethylamine increased the percent yield of the esterification product, but also increased the formation of an uncharacterized side product.



Scheme 13 Synthesis of open-chain epothilones **28a-b**



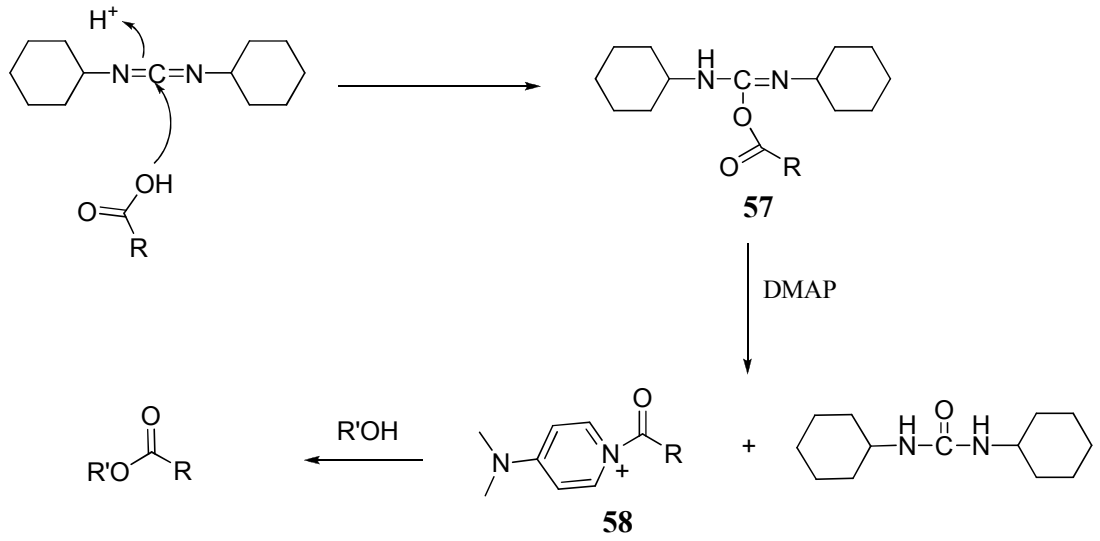
Scheme 14 Synthesis of open-chain epothilones **27b** and **27d**



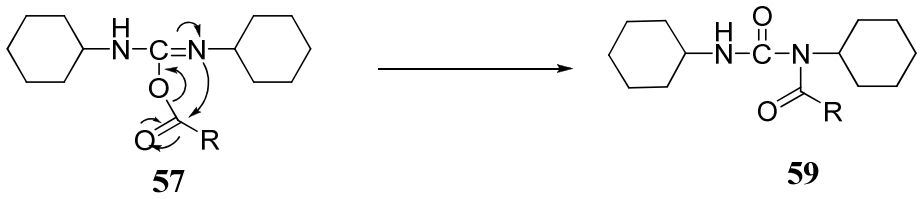
Scheme 15 Synthesis of open-chain epothilones **27c** and **28c**

The mechanism of Steglich esterification is shown in Scheme 16. Nucleophilic attack by the carboxylic acid on the electron deficient carbon of DCC leads to the formation of intermediate **57**. Acyl transfer to DMAP forming intermediate **58** released cyclohexyl urea as a byproduct. Finally DMAP is released by the transfer of the acyl group to the alcohol function, leading to the formation of the ester product. During Steglich esterification, intramolecular acyl transfer to imine nitrogen of the Schiff base can take place to form irreversible side product **59** (Scheme 17).[58] This side reaction can effectively lower the percent yield of the Steglich esterification by depleting the amount of DCC and carboxylic acid in the reaction mixture. To avoid the formation of this byproduct, DMAP hydrochloride, *p*-tolunesulfonic acid, or camphorsulfonic acid can be added in catalytic amounts. Addition of catalytic amounts (10-20 mol%) of (1S)-(+)-10-camphorsulfonic acid (CSA) to the esterification reaction mixture of carboxylic acid **43** with alcohol **54a** (Schemes 18) had a remarkable effect on the percent yield of open-chain epothilone **27a**. The highest percent yield obtained in this reaction under normal Steglich conditions was 8%; however, addition of CSA increased the percent yield to 23%. Unfortunately, the synthesis of open-chain epothilone analogue **27a** was the only esterification reaction performed in the presence and in the absence of CSA. The effect

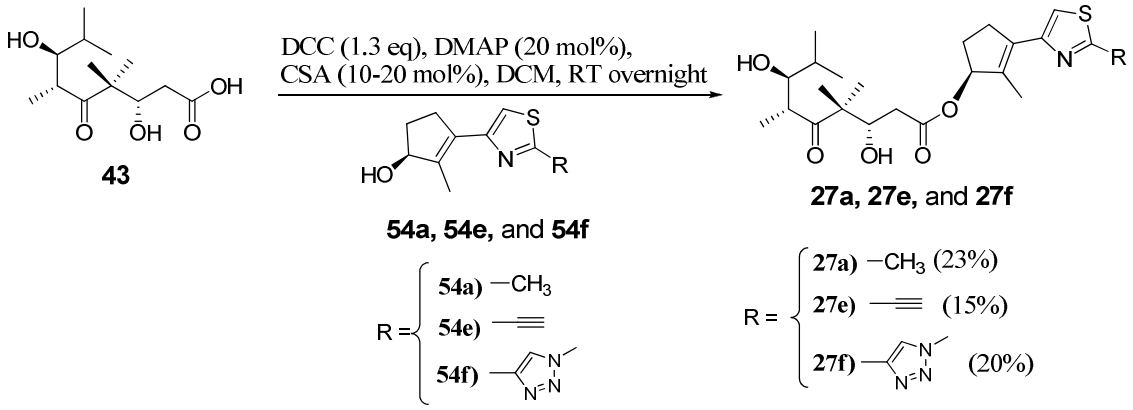
of CSA on the percent yields of **27b-f** and **28a-e** were not evaluated. The esterification of open-chain epothilones **27e**, **27f**, **28d**, and **28e** are shown in Schemes 18-20. Product **28e** was obtained as a diastereomeric mixture.



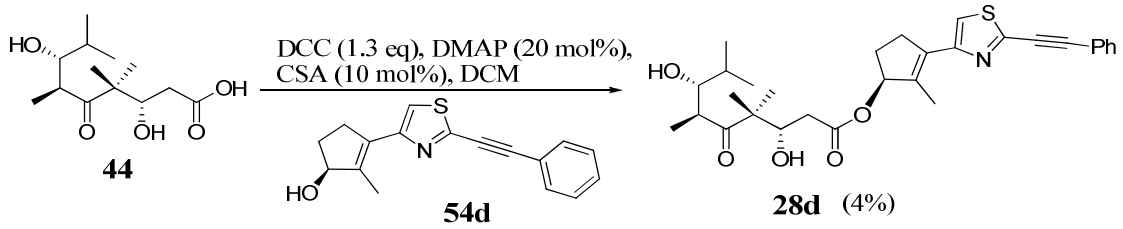
Scheme 16 Mechanism of Steglich esterification



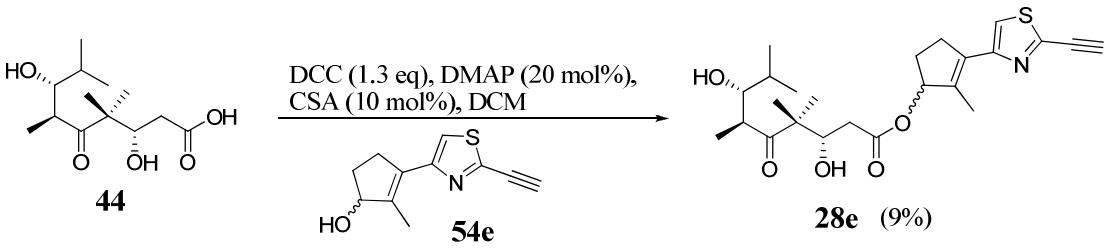
Scheme 17 Formation of irreversible side product of Steglich esterification



Scheme 18 Synthesis of open-chain epothilones **27a, 27e,** and **27f**



Scheme 19 Synthesis of open-chain epothilone **28d**



Scheme 20 Synthesis of open-chain epothilone **28e**

2.2 Synthesis of open-chain epothilones designed to undergo hydrophobic collapse

We designed a library of open-chain epothilone analogues in which hydrophobic phenyl, substituted phenyl, and naphthalene functionalities were incorporated at C10 and C14 (Scheme 21). The purpose of incorporating the hydrophobic groups at these positions is to induce hydrophobic collapse, due to the interaction of the two hydrophobic groups in aqueous media to mimic the conformation of macrocyclic epothilones. As before, these open-chain epothilones can be synthesized by the esterification of the aryl substituted carboxylic acid and the aryl substituted alcohol. The aryl substituted alcohol can be synthesized from the ketones **53b, 53d,** and **53e** by enolate alkylation; while the aryl substituted carboxylic acids can be synthesized by diastereoselective Aldol reaction between the aldehydes **72a-c** and ketone **88**. Solution molecular dynamics performed on open-chain epothilone analogue **60** showed hydrophobic collapse of the molecule in aqueous media (Figure 20).[59]

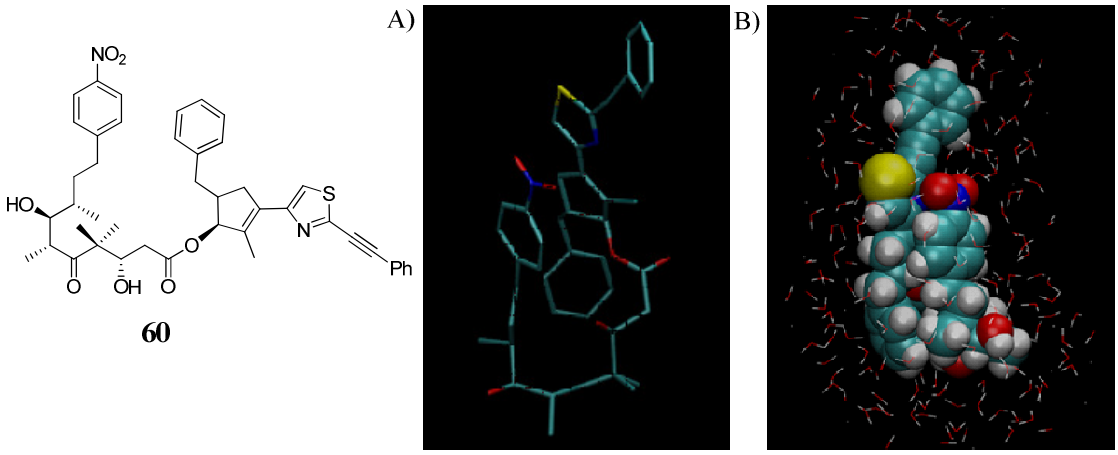
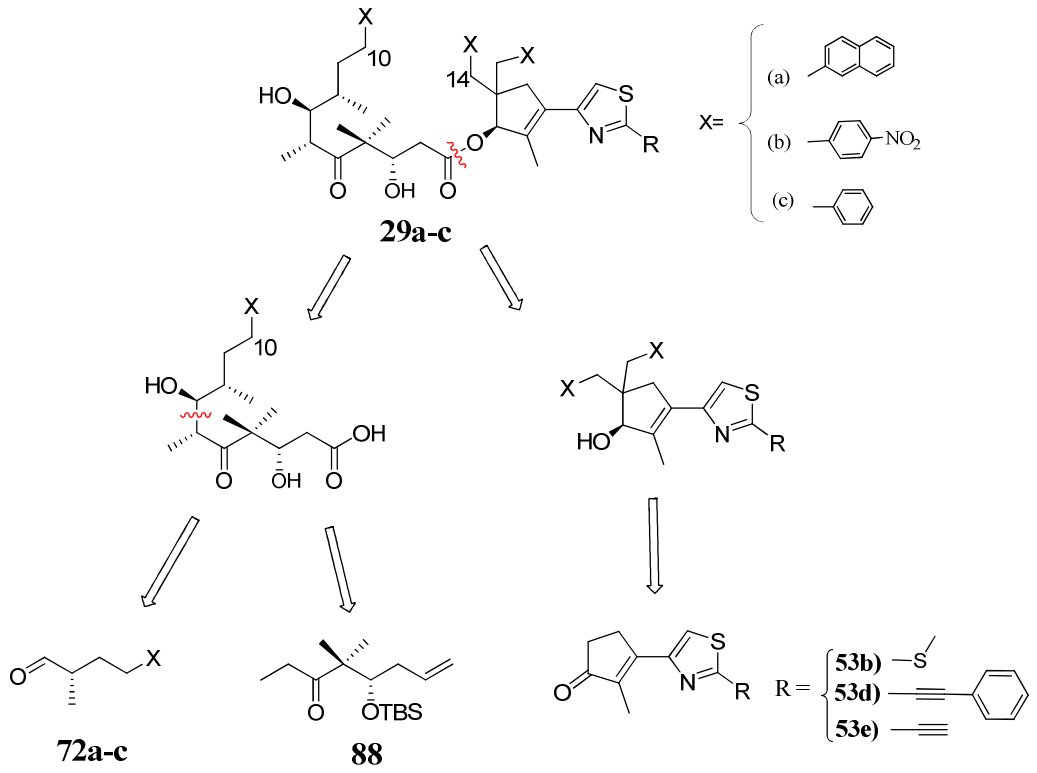


Figure 20 Solution molecular dynamic simulations of open-chain epothilone **60** showing hydrophobic collapse. Panel B shows the water molecules around the open-chain epothilone molecule.[59]

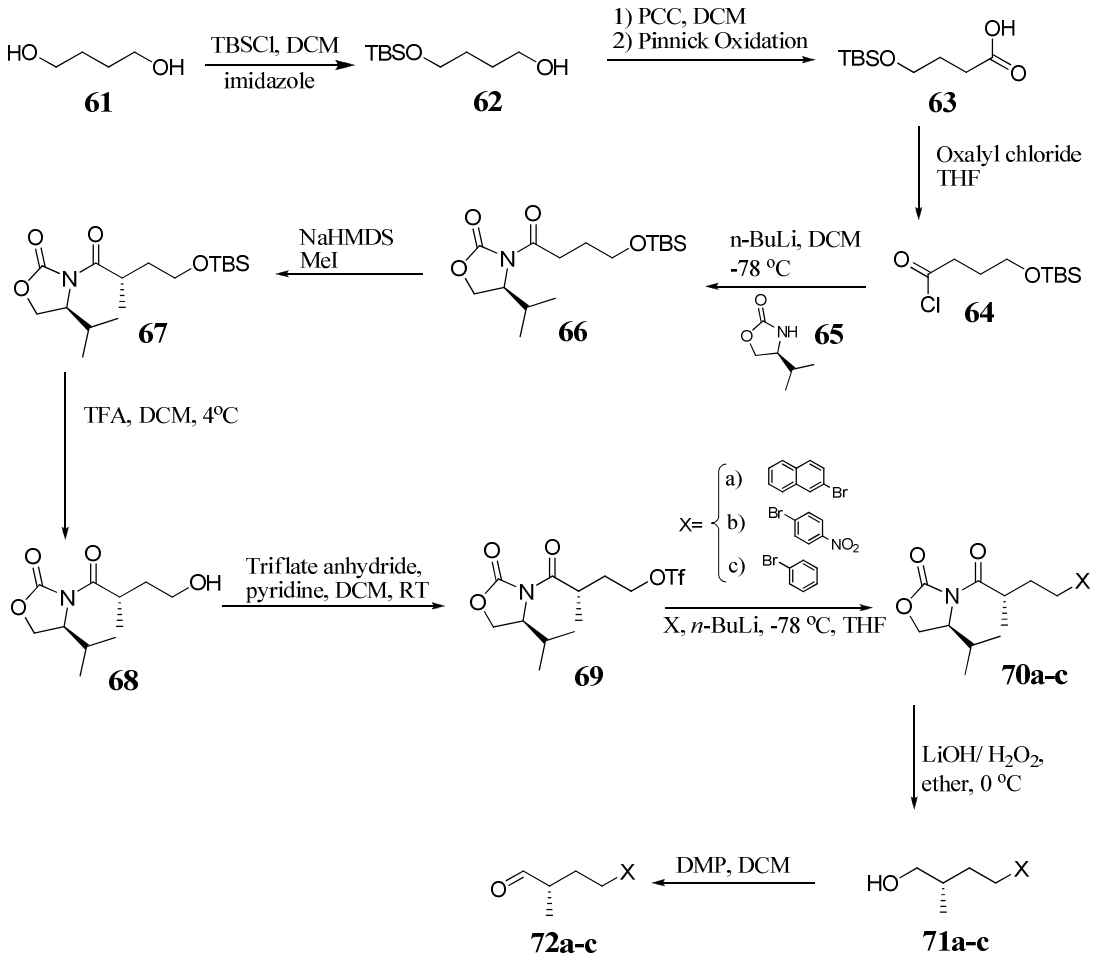


Scheme 21 Proposed disconnection strategy for open-chain epothilones with aryl substitutions at C10 and C14 (numbering system corresponds to macrocyclic epothilones)

2.2.1 Proposed syntheses of aldehydes 72a-c

We began our synthetic efforts with the synthesis of aldehydes **72a-c**. The first synthetic strategy proposed involved a parallel synthetic approach to incorporate a variety of aryl substituents at C10 of a common precursor triflate **69**. We proposed to synthesize aldehydes **72a-c** as shown in Scheme 22 by the monosilylation of commercially available 1,4-butanediol **61**, followed by oxidation to give carboxylic acid **63**. Treatment of **63** with oxalyl chloride would give the acid chloride **64**, which will be stereoselectively alkylated to compound **67** using Evan's auxillary **65**.[60] Conversion to triflate **69** with triflic anhydride followed by nucleophilic substitution of the trifluoromethanesulfonyl group by appropriate aryl lithium derivatives will give the aryl substituted intermediates

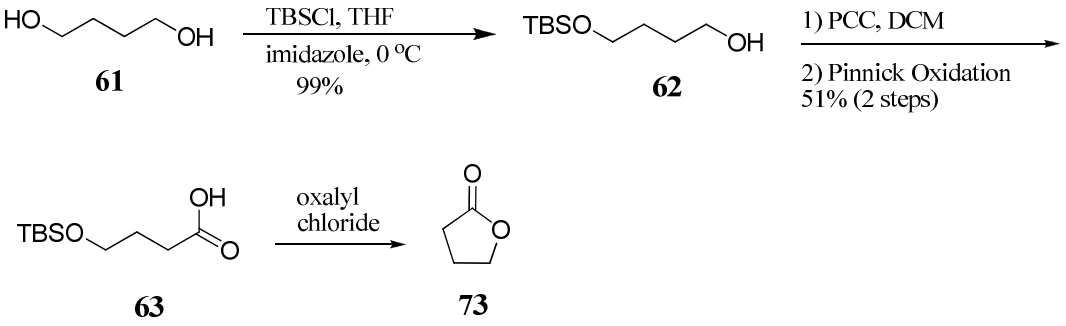
70a-c. Cleavage of the Evan's auxillary with lithium hydroperoxide using Schinzer's protocol[61] and subsequent oxidation of alcohols **71a-c** will yield aldehydes **72a-c**.



Scheme 22 First proposed strategy for the synthesis of aldehydes **72a-c**

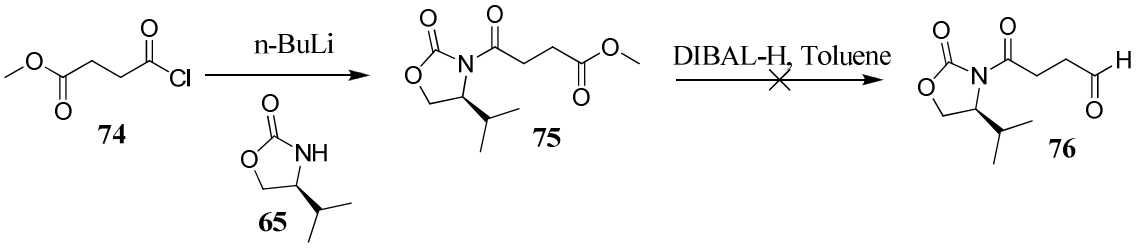
The first attempted synthesis of aldehydes **72a-c** began with the monosilylation of 1,4-butanediol with TBSCl to obtain the alcohol **62** (Scheme 23).[62] Product **62** was oxidized to the corresponding aldehyde with pyridinium chlorochromate (PCC),[63] which was oxidized to the carboxylic acid **63** using Pinnick oxidation conditions.[50] Conversion of carboxylic acid **63** to the corresponding acid chloride **64** proved problematic. When oxalyl chloride was added, γ-buytrolactone **73** was formed through desilylation of the

primary alcohol function followed by spontaneous cyclization of the acid chloride, or the intermediate leading to the acid chloride.



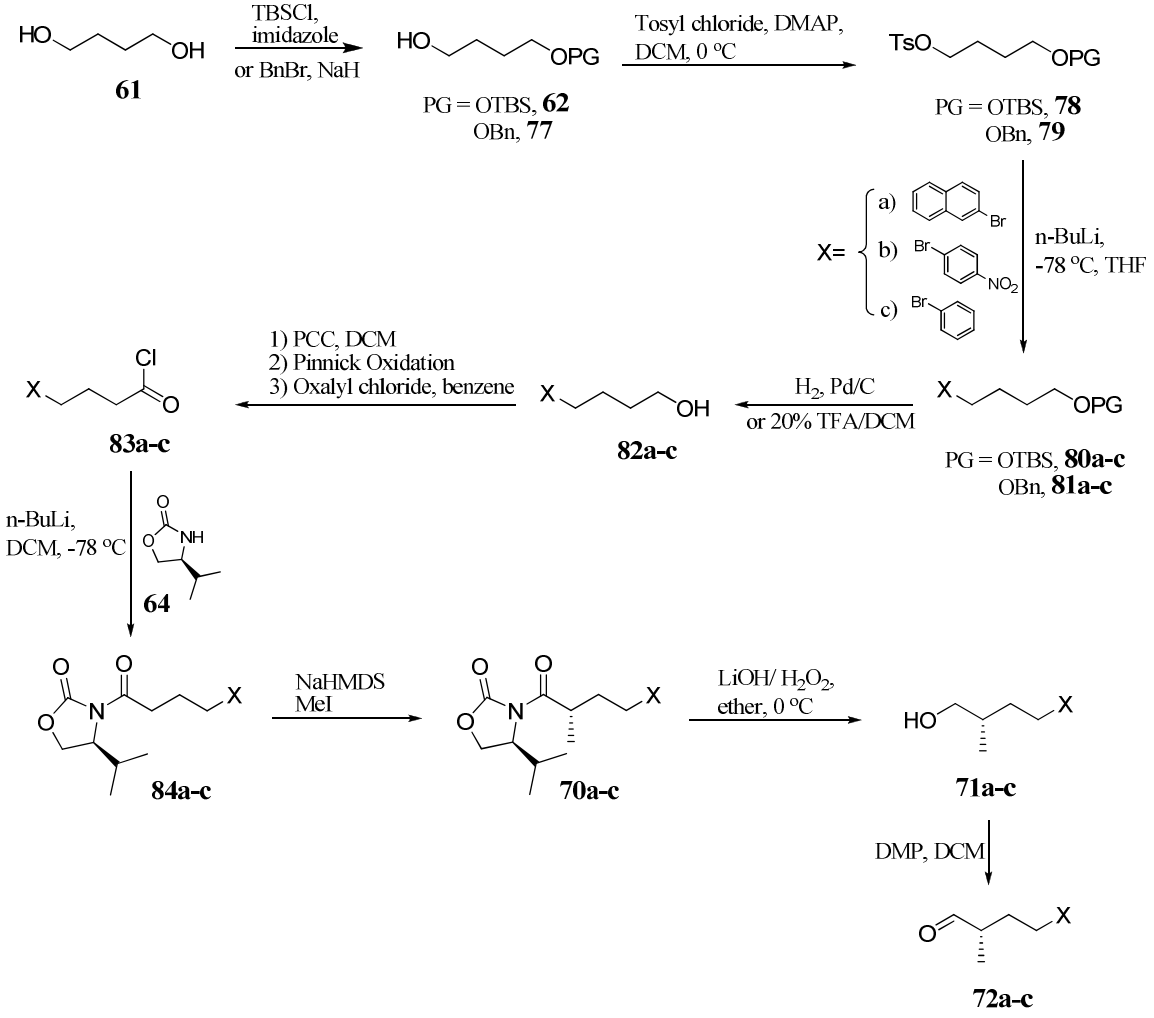
Scheme 23 First attempted synthesis of precursors to aldehydes **72a-c**

An alternative route was therefore attempted (Scheme 24). Evan's auxillary **65** was treated with *n*-BuLi and reacted with commercially available acid chloride **74** to form the acylated product **75**.[42, 60] However, attempts to reduce the methyl ester group of **75** with diisobutylaluminum hydride (DIBAL-H) to the corresponding aldehyde were not successful and led to the formation of a cyclized product of an unknown structure.



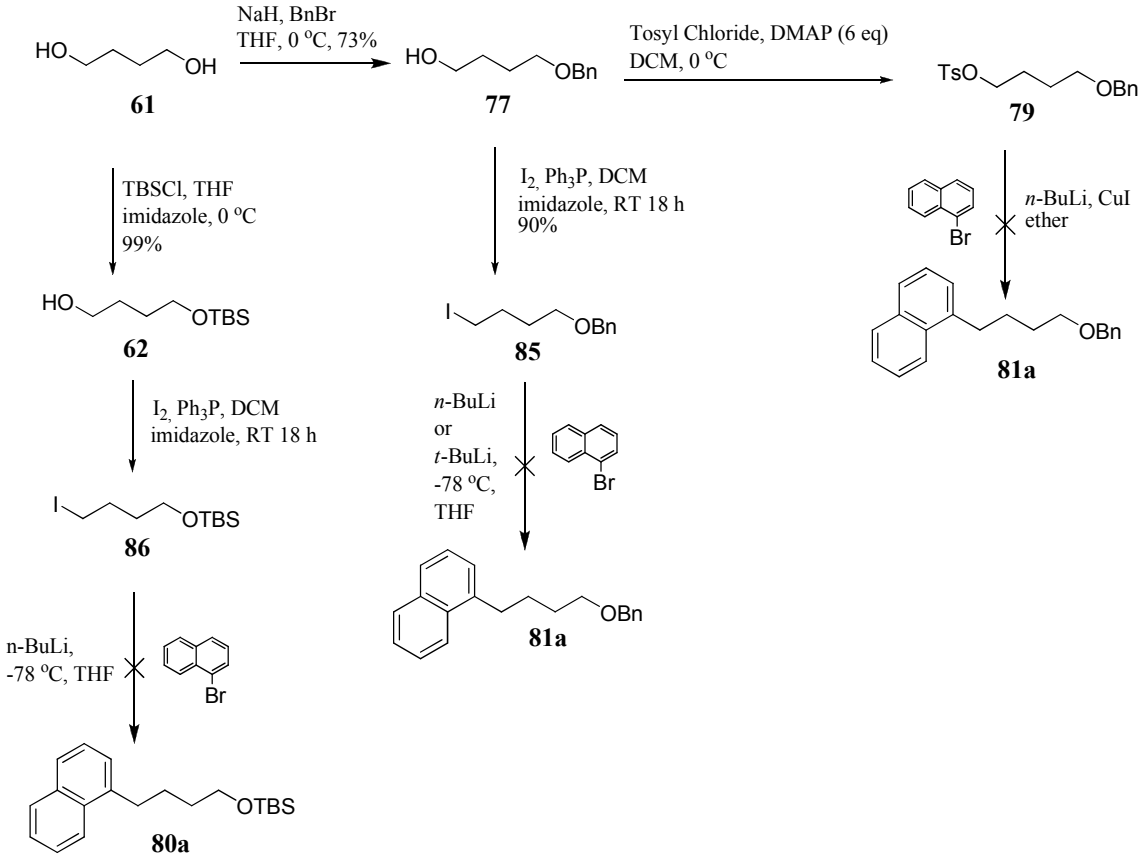
Scheme 24 An alternative approach to aldehydes **72a-c**

Therefore, we decided to incorporate the hydrophobic aromatic groups at an earlier stage in the synthesis to avoid thermodynamically favorable formation of a five or six membered cyclic product (Scheme 25).



Scheme 25 Second proposed synthesis of aldehydes **72a-c**

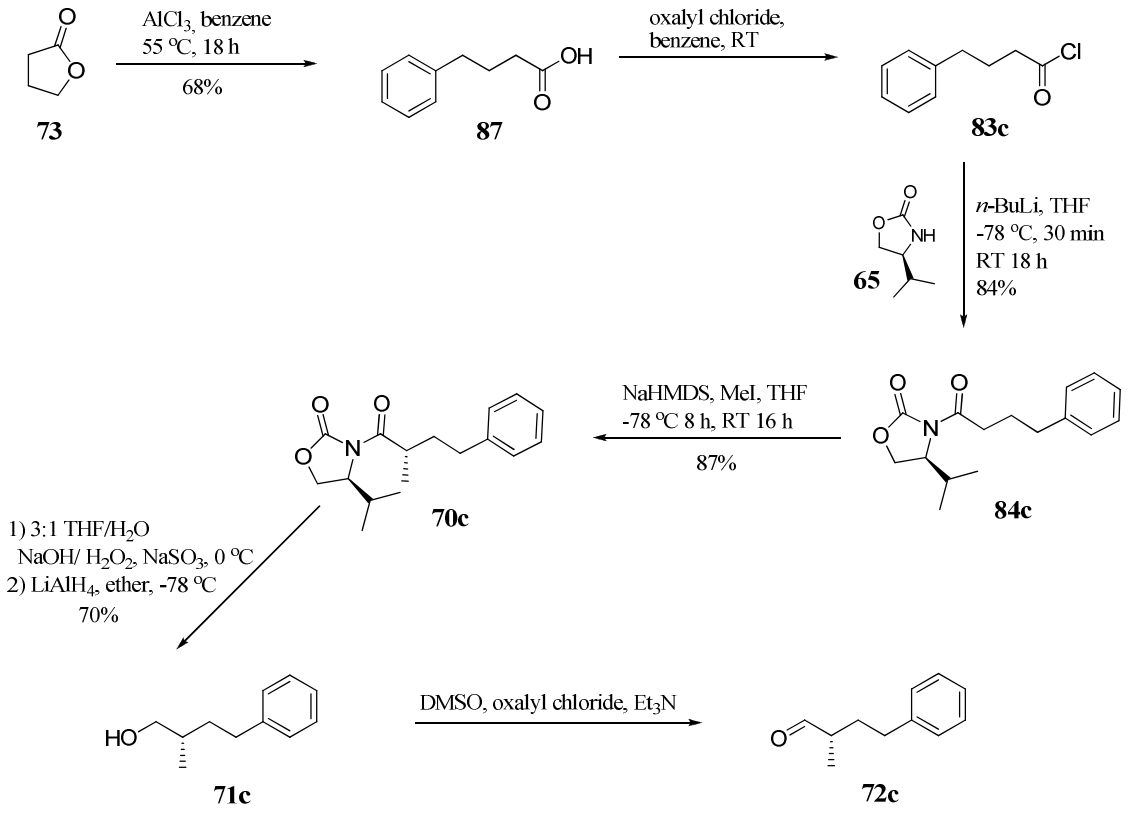
In the new synthetic strategy, 1,4-butandiol **61** was monobenzylated[64] and successfully converted to the tosyl derivative **79**, which was immediately taken to the next step without purification (Scheme 26).[65] Attempted nucleophilic substitution of the tosyl group with lithiated naphthalene was unsuccessful, and the in situ conversion of the organo lithium derivative to a softer nucleophile with copper iodide did not help.[66] Alcohols **62** and **77** were reacted with iodine and triphenylphosphine to obtain the corresponding iodo derivatives **85** and **86**. However, treatment of **85** and **86** with the lithium derivative of naphthalene did not produce the desired products **80a** and **81a**.



Scheme 26 Attempted synthesis of **80a** and **81a**

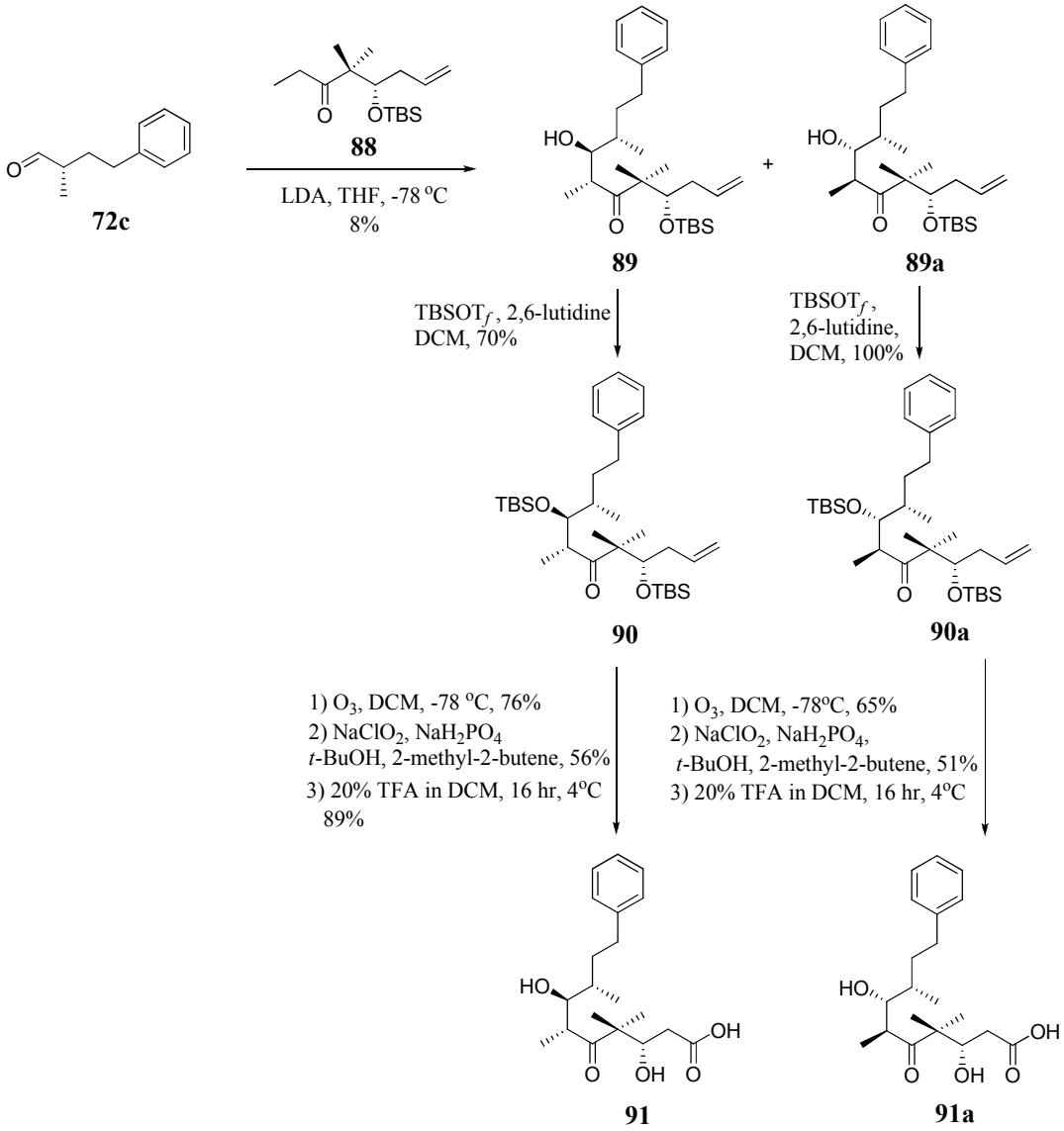
2.2.2 Synthesis of carboxylic acids 91 and 91a.

After the failed attempts to synthesize **72a-c,** we decided to synthesize **72c** via an alternative route as shown in Scheme 27. The synthesis of **72c** began with the Friedel-Craft's alkylation of benzene with commercially available γ-butyrolactone **73** to obtain carboxylic acid **87**.[67] It was treated with oxalyl chloride to give acid chloride **83c.** It was coupled to Evan's auxillary **65** and subjected to stereoselective alkylation using NaHMDS and methyl iodide to obtain **70c**.[42, 68] Hydrolytic cleavage of the chiral auxillary with lithium hydroxide and hydrogen peroxide using Schinzer's protocol,[61] followed by reduction of the carboxylic acid formed with lithium aluminum hydride gave the chiral alcohol **71c**. Swern oxidation of alcohol **71c** yielded the aldehyde **72c**, which was immediately taken to the next step without further purification.[68b]



Scheme 27 Synthesis of aldehyde **72c**

Aldehyde **72c** was reacted with an excess of ketone **88** in an Aldol reaction to furnish diastereomers **89** and **89a** in respective diastereometric ratio of (5:1) (Scheme 28).[69] Diastereomers **89** and **89a** were separated by column chromatography. The (*S*)-configuration of the newly created chiral center of **89** was established by Mosher ester analysis.[54] Products **89** and **89a** were converted to the TBS ethers and ozonolyzed to the corresponding aldehydes. The aldehydes were oxidized to the carboxylic acids using Pinnick oxidation conditions,[50] and the silyl protecting groups were removed to obtain carboxylic acids **91** and **91a**.



Scheme 28 Synthesis of carboxylic acids **91** and **91a**

In the above Aldol reaction, treatment of ketone **88** with LDA resulted in the formation of the *Z*-enolate over the *E*-enolate. This is due to unfavorable steric interactions between the terminal methyl group and the methyl groups at C4. The reaction time was kept under 10 min to minimize Aldol equilibration to obtain the desired diastereomer **89** through the lower energy transition state.

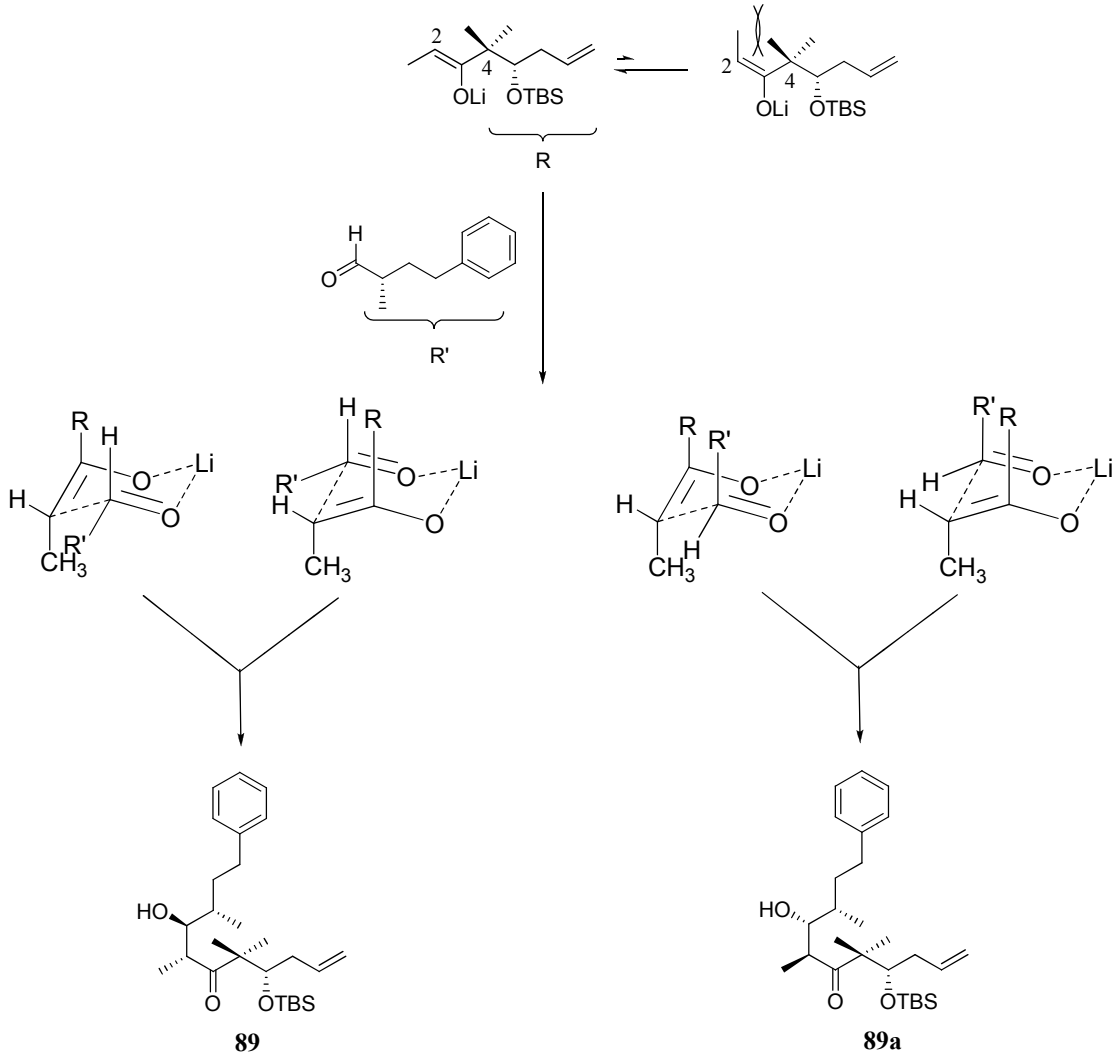
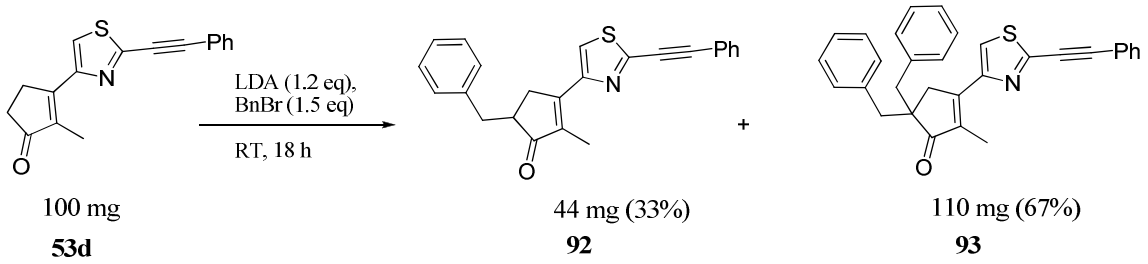


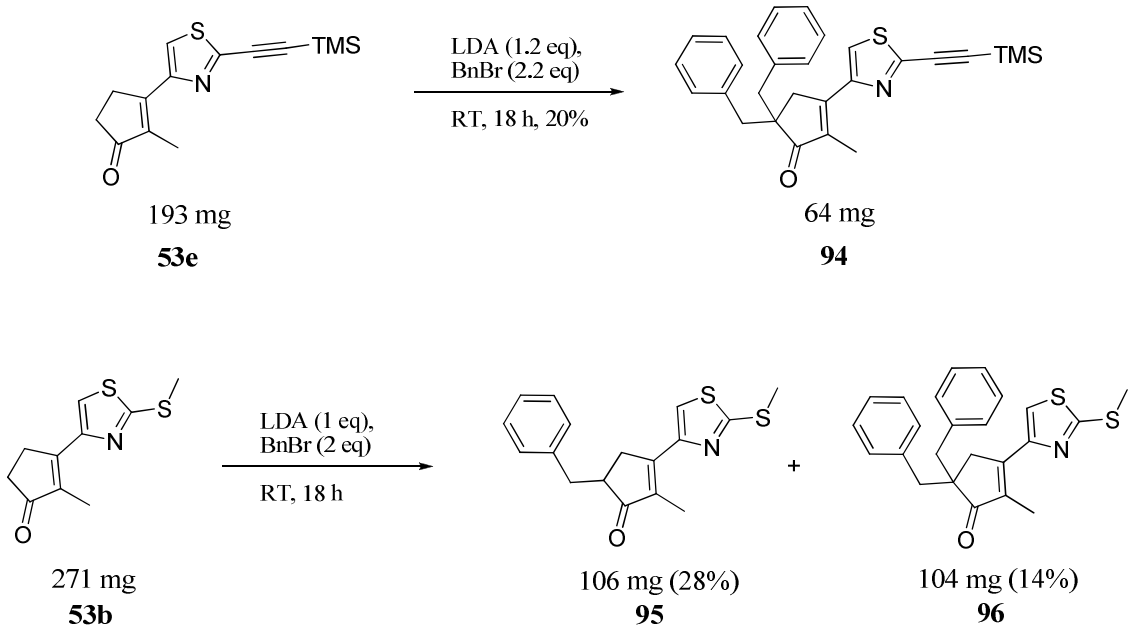
Figure 21 Transition state of Aldol reaction to furnish diastereomers **89** and **89a**

2.2.3 Synthesis of alcohols 92-96

When phenyl acetylene ketone **53d** was treated with LDA and reacted with benzyl bromide, the major product obtained was dialkylated product **93.** Monoalkylated derivative **92** was isolated as a minor product (Scheme 29). Ketones **53e** and **53b** were also alkylated using LDA and benzyl bromide (Scheme 30). The monoalkylated product of TMS acetylene ketone **53e** was not isolated.

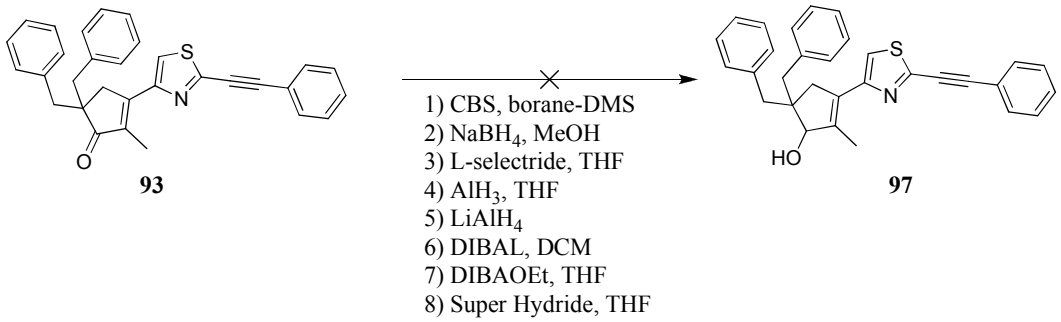


Scheme 29 α-Alkylation of ketones **92** and **93**

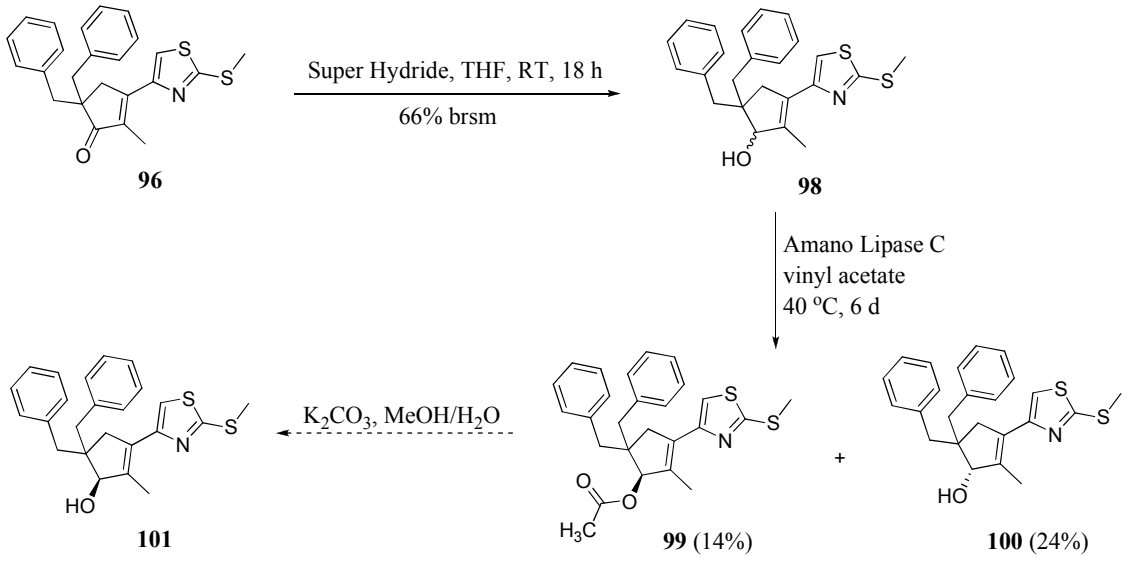


Scheme 30 α-Alkylation of ketones **94-96**

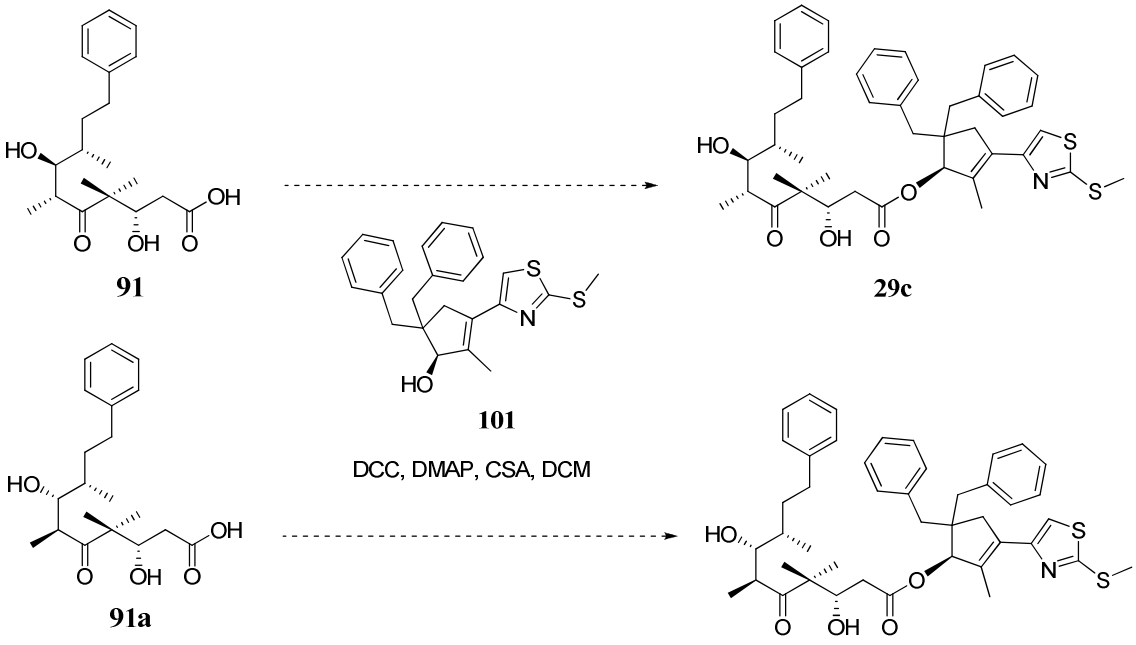
The reduction of dialkylated products **93-94** and **96** proved to be challenging, possibly due to steric bulk of the substitutents at the α position. Several reaction conditions were explored to reduce phenyl acetylene ketone **93** to alcohol **97** (Scheme 31), but to no avail. Finally, it was possible to reduce the ketone **96** with super hydride to obtain a mixture of enantiomeric alcohols **98**, which were partially purified before enzymatic resolution of the enantiomers with Amano lipase C (Scheme 32). The stereochemistry of **100** was determined as before by Mosher ester analysis.[54] The acetate protecting will be removed in the presence of potassium carbonate to obtain alcohol **101**. In the final step, carboxylic acids **91** and **91a** will undergo a Steglich esterification with alcohol **101** to obtain the open-chain epothilone **29c** and its diastereomer (Scheme 33).



Scheme 31 Attempted synthesis of alcohol **96**



Scheme 32 Synthesis and enzymatic resolution of alkylated alcohols **100** and **101**



Scheme 33 Synthesis of **29c** and its diastereomer

2.3 Biological evaluation of open-chain epothilones 27a-f

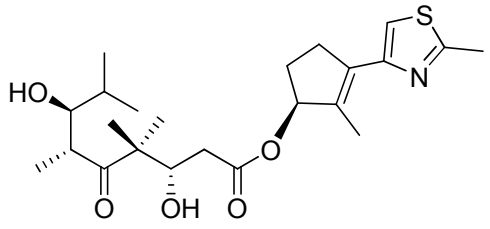
Open-chain epothilone analogues **27a-f** were tested for antiproliferative activity in the National Cancer Institute (NCI) 60 cell line, single-dose (10 μM) assay. The growth percent of the cells in the assay (Figures 22-27) is reported as a single number where a value of 100 or greater is indicative of no growth inhibition, and a negative number indicates that the compound is lethal to the cells.[70] A value between 0 and 100 is a marker of growth inhibition. A value of 30 is equal to 70% growth inhibition. Open-chain epothilones **27a-d** and **27f** demonstrated little effect on growth inhibition in the 60 cell lines; however, open-chain epothilone **27e** was selectively lethal to non-small cell lung cancer (NSCLC) cell line NCI H522 (62%); and to a lesser extent to melanoma cancer cell line LOX IMVI (22%), ovarian cancer cell line IGROV1 (31%), and renal cancer cell line UO-31 (35%).

Developmental Therapeutics Program One Dose Mean Graph	NSC: D-756048 / 1	Conc: 1.00E-5 Molar	Test Date: Feb 28, 2011
	Experiment ID: 1102OS07		Report Date: Dec 07, 2011

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	101.61
HL-60(TB)	94.26
K-562	111.05
MOLT-4	104.17
RPMI-8226	99.05
Non-Small Cell Lung Cancer	
A549/ATCC	102.73
EKVX	93.20
HOP-62	98.54
HOP-92	74.20
NCI-H226	103.14
NCI-H23	91.65
NCI-H322M	118.86
NCI-H460	104.05
NCI-H522	95.31
Colon Cancer	
COLO 205	107.43
HCC-2998	88.60
HCT-116	102.75
HCT-15	100.39
HT29	106.63
KM12	103.57
SW-620	101.03
CNS Cancer	
SF-268	107.55
SF-295	99.79
SF-539	92.15
SNB-19	100.99
SNB-75	120.99
U251	103.28
Melanoma	
LOX IMVI	90.84
MALME-3M	108.14
M14	97.41
MDA-MB-435	98.29
SK-MEL-2	114.02
SK-MEL-28	118.53
SK-MEL-5	108.49
UACC-257	103.03
UACC-62	100.91
Ovarian Cancer	
IGROV1	117.99
OVCAR-3	105.66
OVCAR-5	97.57
OVCAR-8	101.78
NCI/ADR-RES	91.19
Renal Cancer	
ACHN	96.18
CAKI-1	92.84
RXF 393	104.17
SN12C	93.81
TK-10	110.09
UO-31	94.83
Prostate Cancer	
PC-3	94.10
DU-145	104.51
Breast Cancer	
MCF7	112.35
MDA-MB-231/ATCC	98.34
HS 578T	109.40
BT-549	106.12
T-47D	97.85
MDA-MB-468	108.51
Mean	101.89
Delta	27.69
Range	46.79

Mean Growth Percent - Growth Percent

150 100 50 0 -50 -100 -150



27a

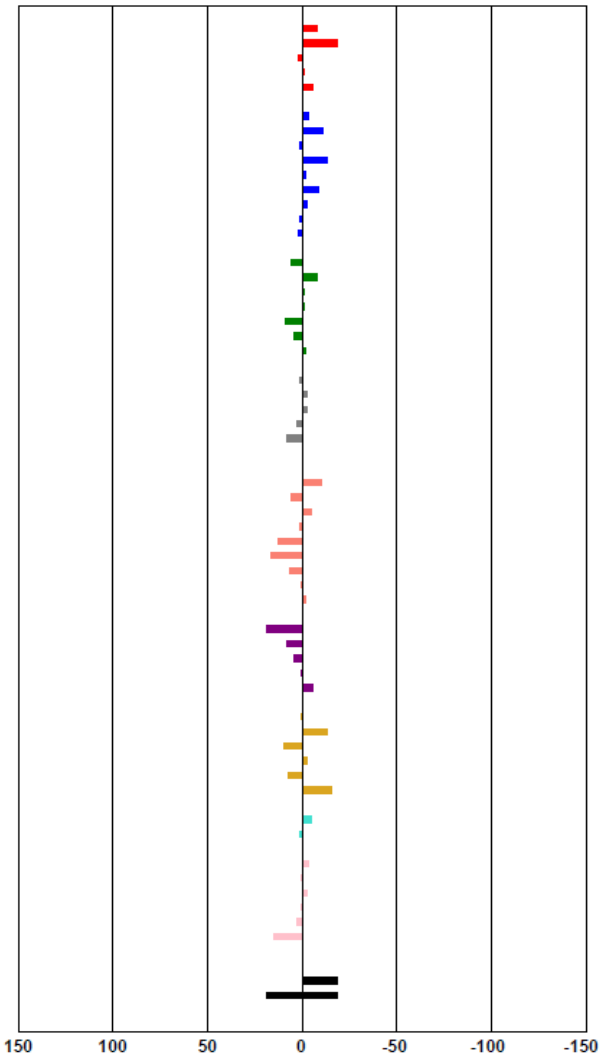
Figure 22 Antiproliferative activity of **27a** in the NCI 60 cell line assay

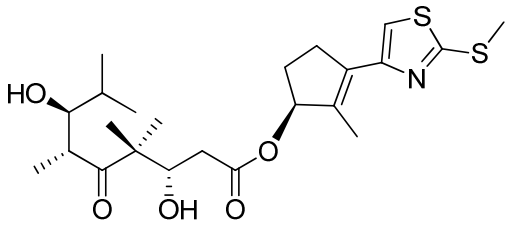
Developmental Therapeutics Program
One Dose Mean Graph

NSC: D-756049 / 1	Conc: 1.00E-5 Molar	Test Date: Feb 28, 2011
Experiment ID: 1102OS07		Report Date: Dec 07, 2011

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	93.20
HL-60(TB)	82.62
K-562	103.19
MOLT-4	99.72
RPMI-8226	95.57
Non-Small Cell Lung Cancer	
A549/ATCC	97.73
EKVX	90.52
HOP-62	102.35
HOP-92	87.70
NCI-H226	99.45
NCI-H23	92.74
NCI-H322M	98.55
NCI-H460	102.69
NCI-H522	103.31
Colon Cancer	
COLO 205	106.86
HCC-2998	93.01
HCT-116	100.27
HCT-15	99.93
HT29	110.22
KM12	105.31
SW-620	99.59
CNS Cancer	
SF-268	102.00
SF-295	98.48
SF-539	98.79
SNB-19	104.07
SNB-75	108.96
U251	101.15
Melanoma	
LOX IMVI	90.96
MALME-3M	107.18
M14	96.37
MDA-MB-435	102.63
SK-MEL-2	113.51
SK-MEL-28	117.27
SK-MEL-5	107.50
UACC-257	101.92
UACC-62	99.00
Ovarian Cancer	
IGROV1	119.61
OVCAR-3	108.94
OVCAR-5	105.71
OVCAR-8	101.25
NCI/ADR-RES	95.78
Renal Cancer	
ACHN	101.58
CAKI-1	88.23
RXF 393	110.55
SN12C	98.55
TK-10	108.77
UO-31	85.93
Prostate Cancer	
PC-3	96.17
DU-145	102.72
Breast Cancer	
MCF7	97.64
MDA-MB-231/ATCC	101.45
HS 578T	98.18
BT-549	101.92
T-47D	103.72
MDA-MB-468	116.36
Mean	101.04
Delta	18.42
Range	36.99

Mean Growth Percent - Growth Percent





27b

Figure 23 Antiproliferative activity of **27b** in the NCI 60 cell line assay

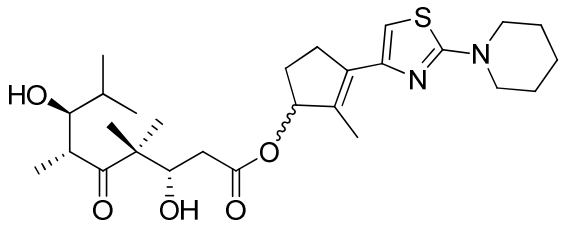
Developmental Therapeutics Program
One Dose Mean Graph

NSC: D-756052 / 1	Conc: 1.00E-5 Molar	Test Date: Feb 28, 2011
Experiment ID: 1102OS07		Report Date: Dec 07, 2011

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	106.77
HL-60(TB)	101.41
K-562	108.34
MOLT-4	89.71
RPMI-8226	99.63
Non-Small Cell Lung Cancer	
A549/ATCC	94.91
EKVX	118.59
HOP-62	101.16
HOP-92	68.72
NCI-H226	91.18
NCI-H23	97.48
NCI-H322M	105.92
NCI-H460	98.21
NCI-H522	88.55
Colon Cancer	
COLO 205	112.66
HCC-2998	103.15
HCT-116	90.78
HCT-15	95.92
HT29	100.50
KM12	104.55
SW-620	101.54
CNS Cancer	
SF-268	101.44
SF-295	129.73
SF-539	87.25
SNB-19	95.62
SNB-75	76.28
U251	100.25
Melanoma	
LOX IMVI	97.23
MALME-3M	102.39
M14	92.03
MDA-MB-435	106.21
SK-MEL-2	105.09
SK-MEL-28	101.87
SK-MEL-5	97.33
UACC-257	96.66
UACC-62	86.21
Ovarian Cancer	
IGROV1	104.18
OVCAR-3	103.68
OVCAR-5	90.77
OVCAR-8	102.77
NCI/ADR-RES	98.54
Renal Cancer	
ACHN	98.57
CAKI-1	94.79
RXF 393	92.67
SN12C	95.75
TK-10	101.11
UO-31	83.12
Prostate Cancer	
PC-3	93.03
DU-145	98.60
Breast Cancer	
MCF7	94.93
MDA-MB-231/ATCC	76.71
HS 578T	97.23
BT-549	88.70
T-47D	97.79
MDA-MB-468	85.07
Mean	97.33
Delta	28.61
Range	61.01

Mean Growth Percent - Growth Percent

150 100 50 0 -50 -100 -150



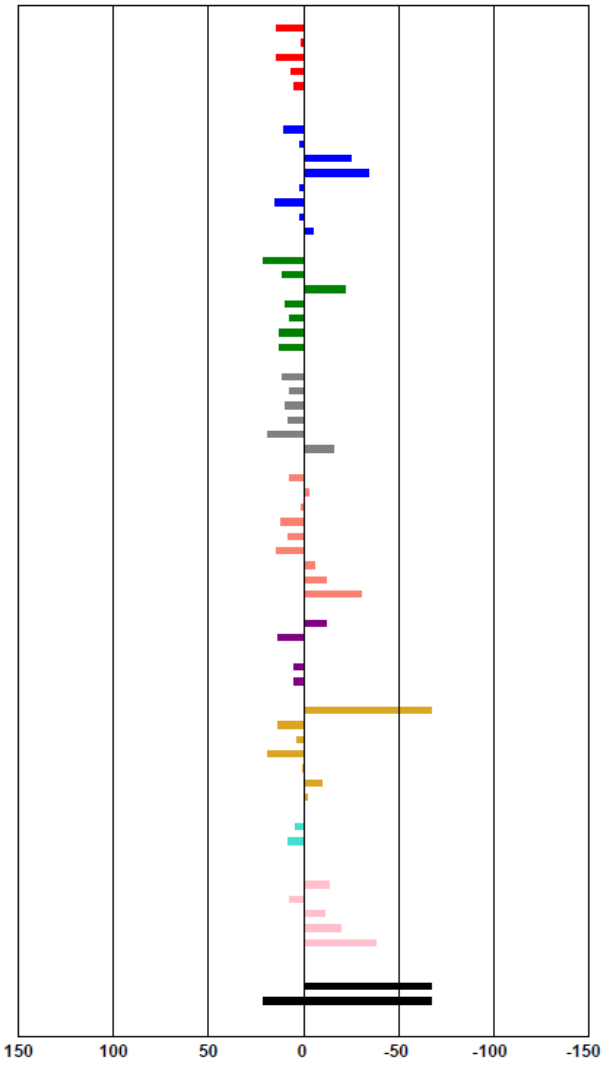
27c

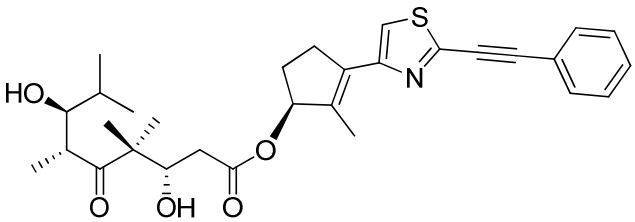
Figure 24 Antiproliferative activity of **27c** in the NCI 60 cell line assay

Developmental Therapeutics Program One Dose Mean Graph	NSC: D-756051 / 1	Conc: 1.00E-5 Molar	Test Date: Feb 28, 2011
	Experiment ID: 1102OS07		Report Date: Dec 07, 2011

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	104.19
HL-60(TB)	90.74
K-562	103.82
MOLT-4	96.37
RPMI-8226	94.50
Non-Small Cell Lung Cancer	
A549/ATCC	89.12
EKVX	100.08
HOP-62	91.91
HOP-92	64.73
NCI-H226	55.74
NCI-H23	91.43
NCI-H322M	104.89
NCI-H460	91.95
NCI-H522	85.05
Colon Cancer	
COLO 205	110.95
HCC-2998	100.99
HCT-116	68.03
HCT-15	99.46
HT29	96.71
KM12	102.49
SW-620	102.71
CNS Cancer	
SF-268	100.85
SF-295	96.86
SF-539	99.12
SNB-19	97.54
SNB-75	108.55
U251	73.84
Melanoma	
LOX IMVI	96.86
MALME-3M	87.30
M14	90.62
MDA-MB-435	101.36
SK-MEL-2	97.56
SK-MEL-28	103.67
SK-MEL-5	83.72
UACC-257	77.77
UACC-62	59.53
Ovarian Cancer	
IGROV1	77.79
OVCAR-3	102.93
OVCAR-5	89.07
OVCAR-8	94.57
NCI/ADR-RES	94.78
Renal Cancer	
A498	22.40
ACHN	103.26
CAKI-1	93.09
RXF 393	108.47
SN12C	90.17
TK-10	79.86
UO-31	87.63
Prostate Cancer	
PC-3	94.22
DU-145	97.62
Breast Cancer	
MCF7	89.47
MDA-MB-231/ATCC	76.12
HS 578T	96.59
BT-549	78.80
T-47D	70.26
MDA-MB-468	51.64
Mean	89.64
Delta	67.24
Range	88.55

Mean Growth Percent - Growth Percent





27d

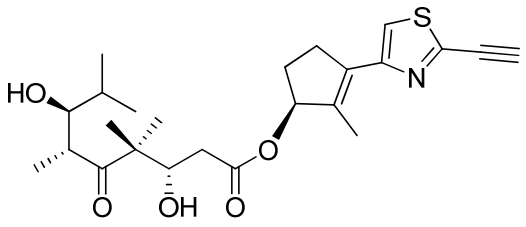
Figure 25 Antiproliferative activity of **27d** in the NCI 60 cell line assay

Developmental Therapeutics Program One Dose Mean Graph	NSC: D-756050 / 1	Conc: 1.00E-5 Molar	Test Date: Feb 28, 2011
	Experiment ID: 1102OS07		Report Date: Dec 07, 2011

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	88.16
HL-60(TB)	112.71
K-562	112.93
MOLT-4	105.14
RPMI-8226	95.42
Non-Small Cell Lung Cancer	
A549/ATCC	89.45
EKVX	114.30
HOP-62	25.16
HOP-92	102.74
NCI-H226	118.20
NCI-H23	82.40
NCI-H322M	115.11
NCI-H460	99.31
NCI-H522	-62.01
Colon Cancer	
COLO 205	109.31
HCC-2998	109.36
HCT-116	102.77
HCT-15	104.09
HT29	89.47
SW-620	119.31
CNS Cancer	
SF-295	101.80
SF-539	112.86
SNB-19	105.59
SNB-75	89.58
U251	75.78
Melanoma	
LOX IMVI	-22.55
MALME-3M	104.22
M14	98.92
MDA-MB-435	104.14
SK-MEL-2	110.93
SK-MEL-28	103.24
SK-MEL-5	103.06
UACC-257	102.40
UACC-62	93.11
Ovarian Cancer	
IGROV1	-31.92
OVCAR-5	110.70
OVCAR-8	94.89
NCI/ADR-RES	95.23
Renal Cancer	
A498	99.07
ACHN	86.08
CAKI-1	114.58
RXF 393	121.95
SN12C	95.52
TK-10	132.09
UO-31	-35.68
Prostate Cancer	
PC-3	92.57
Breast Cancer	
MCF7	95.41
MDA-MB-231/ATCC	87.94
HS 578T	100.05
BT-549	86.35
T-47D	105.17
MDA-MB-468	91.98
Mean	89.58
Delta	151.59
Range	194.10

Mean Growth Percent - Growth Percent

150 100 50 0 -50 -100 -150



27e

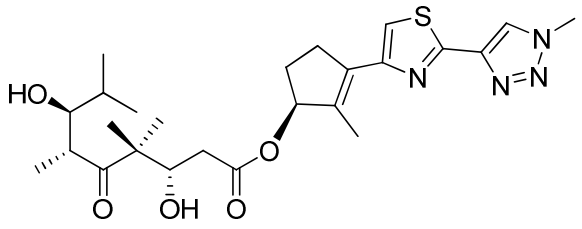
Figure 26 Antiproliferative activity of **27e** in the NCI 60 cell line assay

Developmental Therapeutics Program One Dose Mean Graph	NSC: D-759913 / 1	Conc: 1.00E-5 Molar	Test Date: Jun 20, 2011
	Experiment ID: 1106OS69		Report Date: Dec 07, 2011

Panel/Cell Line	Growth Percent
Non-Small Cell Lung Cancer	
A549/ATCC	98.29
EKVX	94.55
HOP-62	103.63
NCI-H226	105.75
NCI-H23	96.84
NCI-H322M	103.44
NCI-H460	109.43
NCI-H522	95.48
Colon Cancer	
COLO 205	108.84
HCC-2998	98.96
HCT-116	100.80
HCT-15	102.94
HT29	98.88
KM12	108.01
SW-620	109.44
CNS Cancer	
SF-268	114.11
SF-295	98.11
SF-539	103.26
SNB-19	103.17
SNB-75	97.85
U251	107.64
Melanoma	
LOX IMVI	99.66
M14	103.34
MDA-MB-435	95.74
SK-MEL-2	111.29
SK-MEL-28	113.89
SK-MEL-5	106.66
UACC-257	95.13
UACC-62	97.85
Ovarian Cancer	
IGROV1	111.79
OVCAR-3	108.14
OVCAR-4	101.76
OVCAR-5	101.66
OVCAR-8	96.16
NCI/ADR-RES	105.06
SK-OV-3	109.67
Renal Cancer	
786-0	96.62
A498	65.33
ACHN	107.61
CAKI-1	97.14
SN12C	98.50
TK-10	93.02
UO-31	97.06
Prostate Cancer	
PC-3	105.45
DU-145	102.21
Breast Cancer	
MCF7	101.65
MDA-MB-231/ATCC	96.35
HS 578T	106.26
BT-549	96.81
T-47D	94.14
MDA-MB-468	89.07
Mean	101.26
Delta	35.93
Range	48.78

Mean Growth Percent - Growth Percent

150 100 50 0 -50 -100 -150



27f

Figure 27 Antiproliferative activity of **27f** in the NCI 60 cell line assay

Further biological evaluation of open-chain epothilones **27a-f** and **28e** was performed in the laboratory of Dr. William R. Taylor, Professor, Department of Biological Sciences at the University of Toledo, Toledo, Ohio. Time lapse microscopy was performed to image cell line NCI H522 in the absence and presence of open-chain epothilone **27e** (Figure 28). The time interval between each image is 1 hr 12 min. The top twelve panels show the proliferation and division of NCI H522 cells in the absence of drug. The bottom twelve panels show the effect of adding 10 μM of **27e** to the NCI H522 cell line. Around the seventh hour, the cells began to exhibit morphological signs of mitosis by rounding up. With time however, they underwent cell death instead of mitosis. Twelve hours after the initiation of the experiment, most of the NSCLC cells were dead.

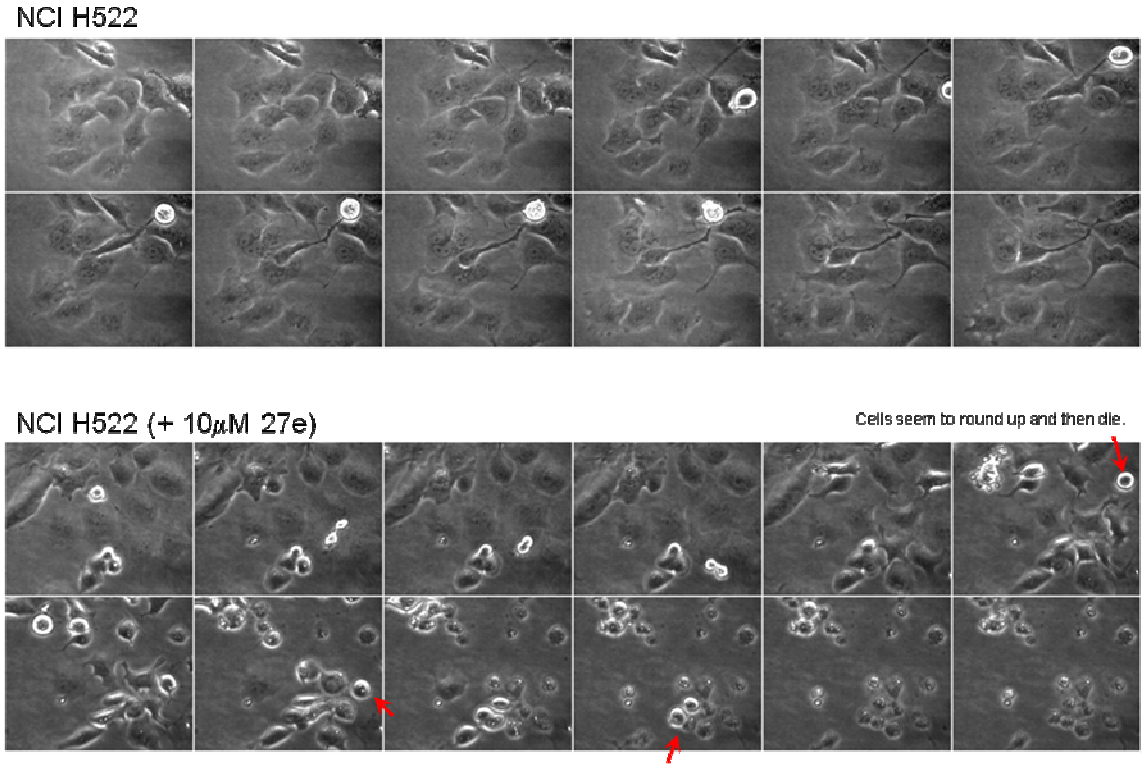


Figure 28 Time lapse microscopy with **27e**

The cytotoxicity of open-chain epothilones **27b**, **27f**, and **28e** were tested against NCI H522 cells at 10 μM (Figure 29). Compounds **27b** and **27f** had no effect on the cells, where as compound **28e**, which is a diastereomer of **27e**, exhibited cytotoxic activity. The open-chain epothilones are unstable in nucleophilic solvents, especially methanol and water. We suspected that the observed cytotoxicity of **27e** and **28e** may be caused by alcohol **54e** formed by the hydrolysis of the ester. Therefore, we tested alcohol **54e** on the NCI H522 cell line and as speculated, it exhibited cytotoxicity. Interestingly the precursor to alcohol **54e**, ketone **55** was also found to be toxic to NCI H522 cells.

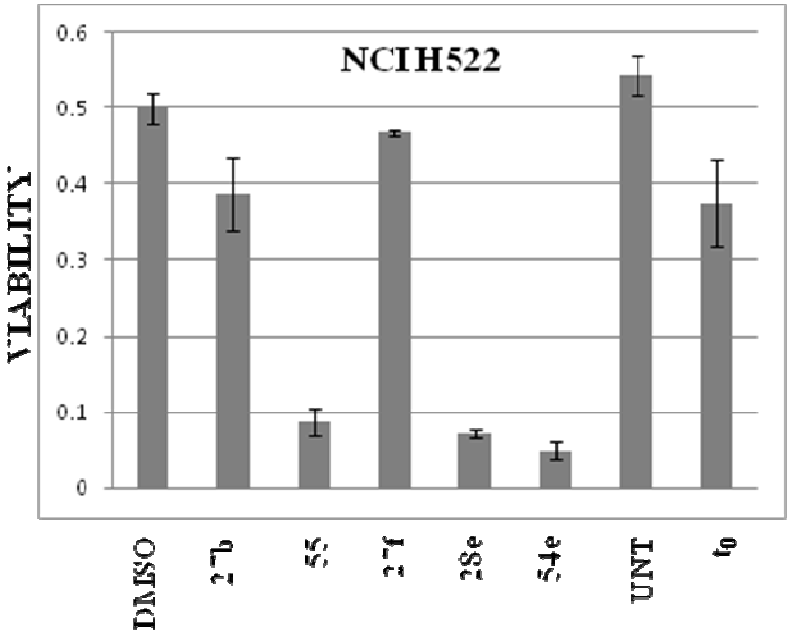


Figure 29 Cytotoxicity studies of compounds **27b**, **27f**, **28e**, **54e**, and **55** on NCI H522

To determine the selectivity of these compounds, they were also tested on normal human lung epithelial cell line HBEC and normal human fetal lung fibroblast cell line WI38 at a concentration of 10 μM (Figures 30 and 31). Compounds **27e**, **28e**, and **54e**, were not toxic against HBEC, but did exhibit cytotoxcity against WI38. Interestingly, compound **55** showed no cytotoxicity against either cell line.

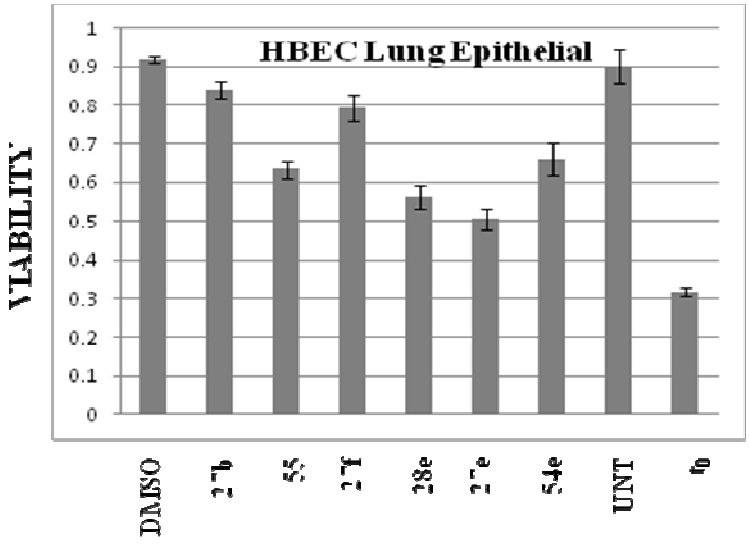


Figure 30 Cytotoxcity studies of compounds **27b**, **27e**, **27f**, **28e**, **54e**, and **55** with human bronchial epithelial cells (HBEC)

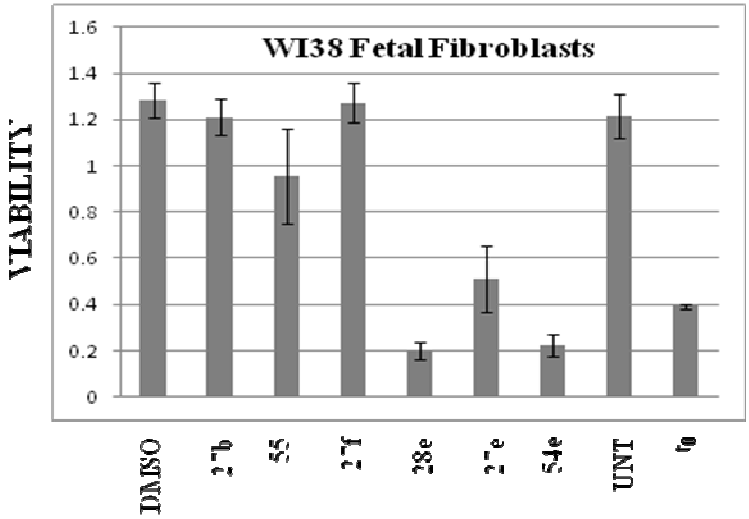


Figure 31 Cytotoxicity studies of compounds **27b**, **27e**, **27f**, **28e**, **54e**, and **55** with WI38 fetal fibroblasts

Open-chain epothilones **27e** and **28e** and their alcohol precursor **54e** showed potent cytotoxic activity against NCI H522 and showed no cytotoxicity against normal lung epithelial cell line HBEC. Ketone **55** is potent against NCI H522 and was found to be more selective as it did not show cytotoxic activity against either HBEC or WI38 cell lines. As the intended target of open-chain epothilones were microtubules, we tested the effect of compound **54e** on microtubules by immunofluorescence microscopy. Actin and tubulin were stained green by the addition of mouse monoclonal antibodies followed by Alexflour 408 (antimouse antibody). The DNA in this experiment was stained blue with 4',6-diamidino-2-phenylindole. When NCI H522 cells were treated with compound **54e** over 8 hr, no change in tubulin or actin was observed. This suggests that the mechanism of action of compounds **54e** and **55** is not by the stabilization of microtubules. Further biological evaluation of compounds **27e**, **28e, 54e**, and **55** are currently in progress.

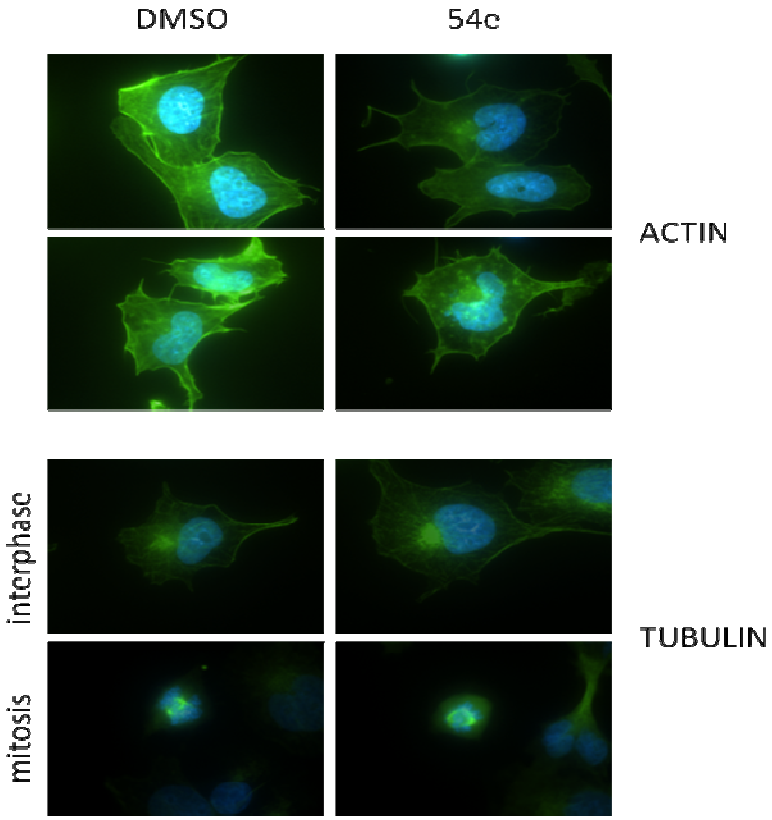
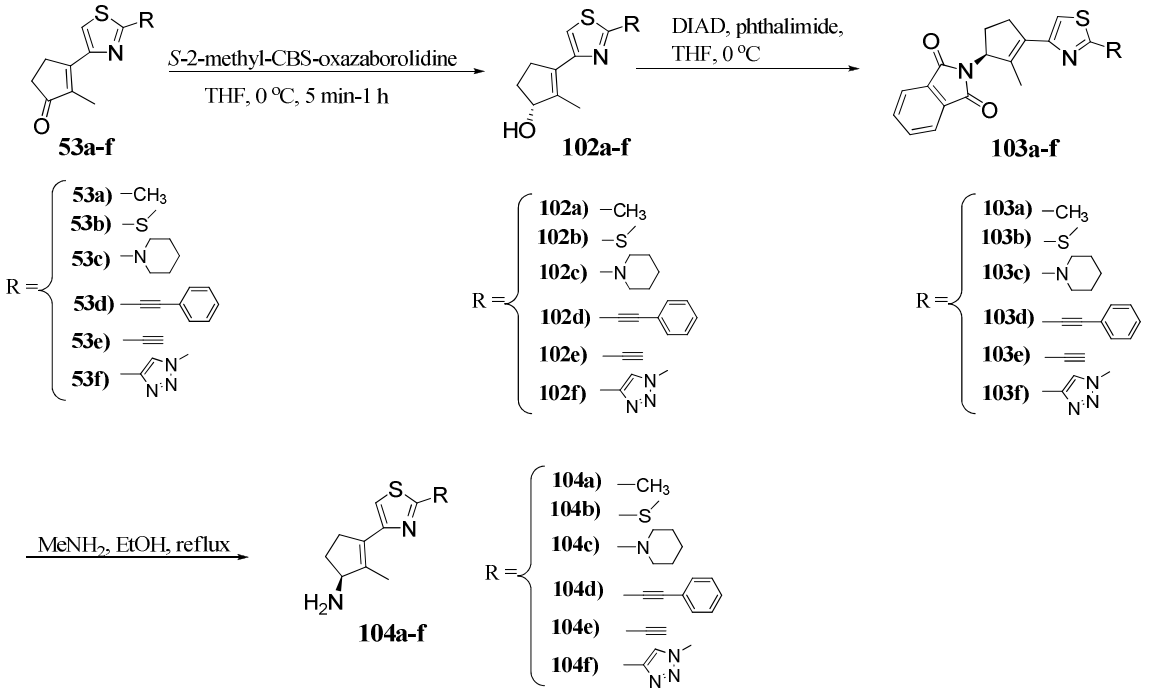


Figure 32 Immunofluorescence assay of NCI H522 with alcohol **54e**

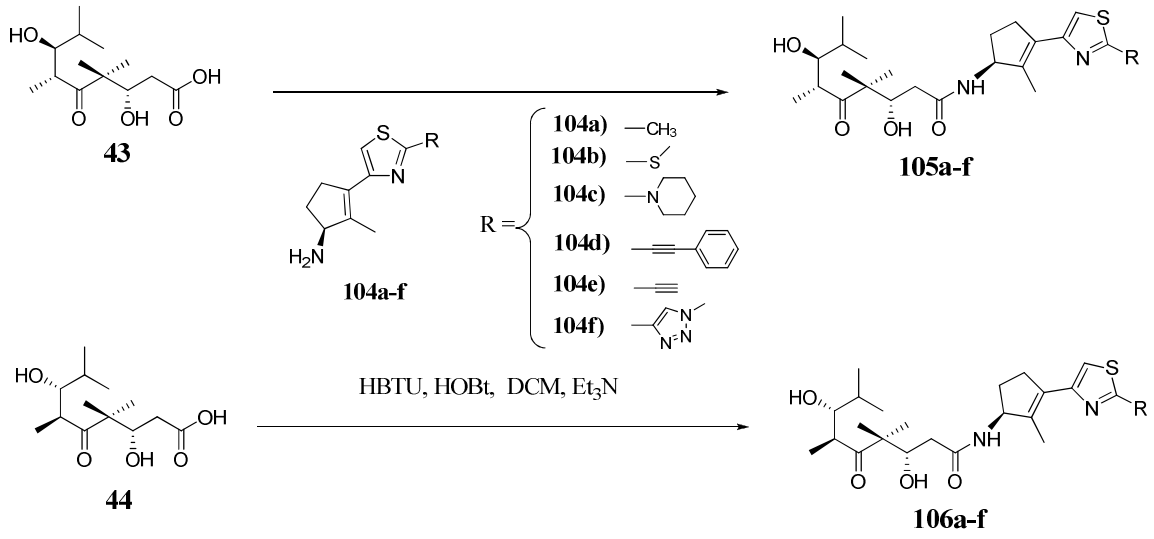
2.4 Future Directions

The only FDA approved epothilone, ixabepilone **19** has been shown to be more potent against twenty-one tumor and taxane-resistant cell lines compared to epothilone B.[39] In vivo, the amide bond of ixabepilone **19** is more resistant to hydrolytic cleavage compared to the ester bond of epothilone B. The lack of cytotoxic activity of open-chain epothilones **27a-f** and **28a-e** may be due to the ready hydrolysis of their ester bond. Therefore, it is necessary to construct the amide (aza) analogues of these open-chain epothilones. The aza analogues **105a-f** and **106a-f** can be synthesized as shown in Scheme 34. Stereoselective reduction of ketones **53a-f** with (*S*)-2-methyl-CBS oxazaborolidine will give the (*R*)-cyclopentenols **102a-f**. Mitsunobu reaction conditions with phthalimide[71] will convert **102a-f** to the (*S*)-phthalimide derivatives **103a-f**, which can be converted to the corresponding (*S*)-cyclopentenamines **104a-f** with methyl amine.[71]



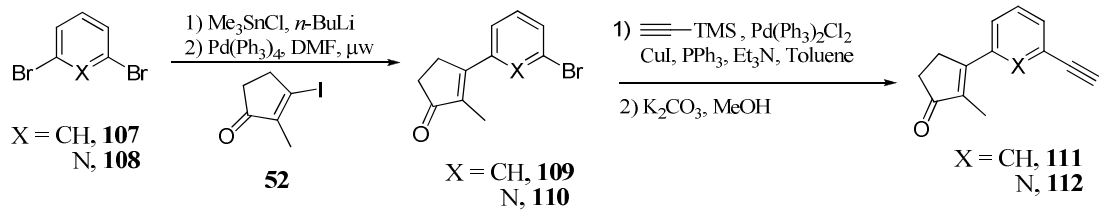
Scheme 34 Synthesis of amines **104a-f**

Amide formation between carboxylic acids **43** and **44** and cyclopentenamines **104a-f** will yield the desired aza open-chain epothilone analogues **105a-f** and **106a-f** (Scheme 35).



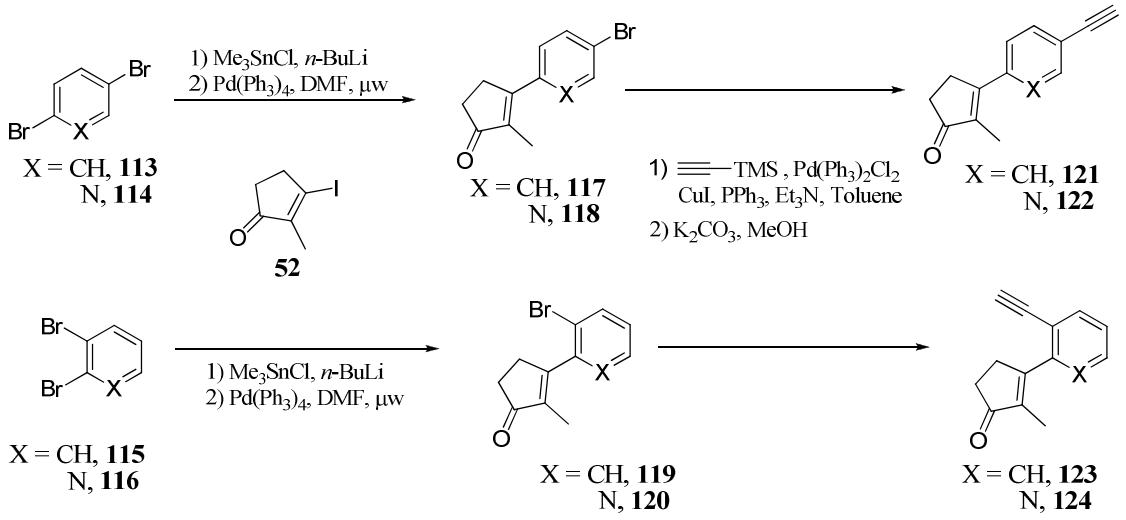
Scheme 35 Synthesis of aza analogues of open-chain epothilones

In addition to the described aza open-chain epothilone analogues, the open-chain epothilone analogues **29a-b** with hydrophobic substitutions at C10 and C14 can be completed. We also proposed to generate an SAR profile to determine what structural alterations will enhance the cytotoxicity of compounds **54e** and **55**. Additional analogues that can be synthesized are shown in Schemes 36-38. These synthetic alterations will determine whether the nature of the aromatic ring, position of the acetylene moiety, and oxygen functionality of the cyclopentenone are important. The synthesis of cyclopentenones **111** and **112** will begin with commercially available 1,3-dibromobenzene **107** or 1,6-dibromopyridine **108**, which will be subjected to Stille coupling with iodocyclopentenone **52**. The resulting cyclopentenones **109** and **110** will be subjected to Sonagoshira coupling and desilylated to obtain acetylated cyclopentenones **111** and **112**.



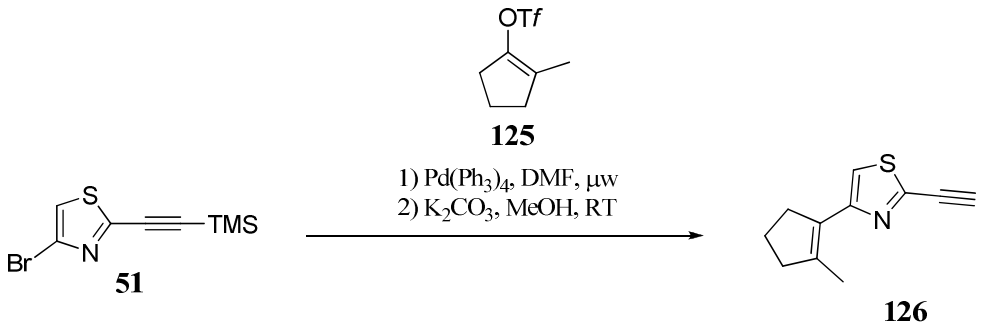
Scheme 36 Synthesis of cyclopentenones **111** and **112**

Cyclopentenones **121-124** will be synthesized from commercially available dibromobenzenes **113** and **115** and dibromopyridines **114** and **116**. These compounds will be subjected to Stille coupling with iodocyclopentenone **52** followed by Sonagoshira coupling and subsequent desilylation to obtain cyclopenteones **121-124**. These analogues will help determine whether positioning of the acetylene moiety is critical for biological activity.



Scheme 37 Synthesis of cyclopentenones **121-124**

Finally compounds **126** will be prepared from 2-substituted bromothiazole **51** by Stille coupling with triflate **125**. This analogue will determine if oxygen function is necessary for biological activity.



Scheme 38 Synthesis of compound **126**

Chapter 3

3.1 Experimental Section

General Synthesis:

All reactions were carried out under nitrogen atmosphere using anhydrous solvents, unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium and benzophenone under nitrogen prior to use. NMR spectra were recorded on Varian VXRS 400 MHz, Varian INOVA 600 MHz, and Bruker AVANCE 600 MHz instruments calibrated using undeuterated solvent as an internal reference. Optical rotations were recorded on Rudolph Autopol III and Rudolph Autopol IV 589/586 polarimeters. High-resolution mass spectra (HRMS) were recorded on a LCT Electrospray mass spectrometer at the Central Instrument Facility Mass Spectrometry Laboratory (The Wayne State University, Detroit Michigan) and on a Q-Tof II mass spectrometer at Mass Spectrometry and Proteomics Facility (The Ohio State University, Columbus Ohio). Infrared spectroscopy was performed using liquid film on salt plates with a Perkin-Elmer spectrum R-1 FTIR spectrometer. Ozone was generated by passing oxygen through a Welsbach Model T-408 commerical ozone generator. A Biotage Initiator was used in microwave synthesis. Reactions were monitored by thin-layer chromatography (TLC) using TLC plates purchased from Analtech Inc. using commercial solvents. Crude products were purified on silica gel preparative thin layer chromatography plates 1000 m purchased from Analtech Inc. Silica get (40-63 mm) purchased from Dynamic Absorbants Inc. and RediSep prepackaged cartridges from Teledyne ISCO Inc. on a Combiflash Companion were used in flash chromatography. HPLC analysis was

performed on a Waters 1525 Binary Pump system with Waters 2487 Dual Wavelength Absorbance detector on a Supelco C18 reverse phase column (5 μm, 15 cm x 4.6 mm) and on a Symmetry C18 reverse phase column (5 μm, 15 cm x 4.6 mm) using a gradient of 60-100% acetonitrile in water over 10-20 min; UV detection at 254 nm at a flow rate of 1 mL/ min. Lipase PS-C "Amano" I from Amano Enzyme Inc, Nagoya, Japan was used in enzyme resolution.

1-Chloro-3-methyl-but-ene (31) and 3-chloro-3-methylbut-1-ene (32).

2-Methyl-but-3-en-2-ol **30** (100 mL, 82.4 g, 0.957 mol) was treated with concentrated HCl (300 mL, 12 M) and stirred for 1 h at 0 ^{o}C. The reaction mixture was poured into water (500 mL) and extracted with DCM (3 x 300 mL). The combined organic extracts was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The prenyl chloride mixture was partially purified by fractional distillation at atmospheric pressure to give a mixture of products **31** and **32** (102.038 g):

Data for prenyl chloride **31**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.44-5.39 (m, 1H), 1.98 (m, 6H), 4.07 (d, J = 8.0 Hz, 2H), 1.74-1.70 (m, 6H).

Data for prenyl chloride **32**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.11 (q, J = 10.4 Hz, 1H), 5.05 (m, 2H), 1.98 (m, 6H).

4,4-Dimethylhex-5-en-3-one (33).

Magnesium turnings (12.101 g, 0.490 mol, 4.5 equiv), a few iodine crystals, and a few drops of the prenyl chloride mixture were placed in a 3-neck flask equipped with a condenser and dropping funnel under nitrogen. Anhydrous THF (55 mL) was added and the reaction mixture was stirred at room temperature for 10 min. Anhydrous THF (33 mL) was added and the reaction mixture was cooled to -10 to -15 ^{o}C. A mixture of **31** and **32** (17.095 g, 0.107 mol, 1 equiv), prepared as above, in THF (110 mL) was added

dropwise through the dropping funnel over 1.5 h. After the addition was complete, the reaction mixture was warmed to room temperature and stirred for an additional 1 h. It was transferred dropwise to a solution of propionyl chloride (28.931 g, 0.330 mol, 2 equiv) in anhydrous THF (110 mL) over 45 min at -78 ^{o}C under nitrogen. The reaction mixture was allowed to warm up to room temperature over 2 h. The crude reaction mixture was quenched with water (330 mL) and extracted with ether (3 x 55 mL). The combined organic extract was washed with 2.0 M sodium hydroxide (550 mL) and brine (275 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The product was purified by distillation at reduced pressure to obtain the ketone **33** (10.542 g, 72%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.91 (q, *J* = 8.0 Hz, 1H), 5.12 (dd, *J* = 16.0, 4.0 Hz, 2H), 2.47 (q, *J* = 8.0 Hz, 2H), 1.20 (s, 6H), 0.98 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 213.03, 142.59, 113.71, 50.42, 30.29, 23.35, 7.96.

(*5R*, *6S*) and (*5S*, *6R*)-6-Hydroxy-3,3,5,7-tetramethyl-oct-1-en-4-one ((+/-) 34).

n-BuLi (123 mL, 2.5 M solution in hexanes, 0.308 mol, 1.2 equiv) was added dropwise to a solution of DIPA (47 mL, 0.400 mol, 1.3 equiv) and anhydrous THF (323 mL) at -78 ^{o}C. The reaction mixture was stirred for 30 min at -78 ^{o}C and ketone **33** (32.384 g, 0.257 mol, 1 equiv) was added dropwise. After stirring for 45 min at -78 ^{o}C , isobutyraldehyde (27.6 mL, 0.308 mol, 1.2 equiv) was added dropwise. The reaction mixture was stirred for 45 min at -78 ^{o}C and allowed to warm to room temperature. Water (350 mL) was added and the crude reaction mixture was extracted with EtOAc (3 x 100 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The product was purified by fractional distillation at reduced pressure to obtain **34** (38.602 g, 76%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.88 (dd, *J* = 10.2, 7.2 Hz, 1H), 5.20 (dd, *J* = 10.2, 4.8 Hz, 2H), 3.31 (s, 1H), 3.21-3.17 (m, 2H), 1.65 (m, 1H), 1.24 (d, *J* = 15.0 Hz, 6H), 0.98 (dd, *J* = 13.2, 6.6 Hz, 6H), 0.84 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 219.05, 141.28, 115.33, 76.67, 51.71, 40.77, 30.63, 23.18, 22.93, 19.14, 19.01, 10.89.

(*5R,6S*) and (*5R,6R*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-3,3,5,7-tetramethyl-1-oct-1-en-4-one ((+/-) 35).

Anhydrous DMF (34 mL), imidazole (11.772 g, 0.17 mol, 3 equiv) and, *tert*-butyldimethylsilyl chloride (TBSCl) (17.341 g, 0.11 mol, 2 equiv), were placed in a three necked round-bottom flask under nitrogen. Compound **34** (11.425 g, 0.057 mol, 1 equiv) was added and the reaction mixture was stirred at 38 ^{o}C for 120 h under nitrogen. The reaction was monitored by TLC (20 % EtOAc-hexanes). Water (50 mL) was added to quench the reaction, and the organic layer was separated from the aqueous layer. The aqueous layer was extracted with ether (3 x 50 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel in 20% hexanes-ethyl acetate to obtain the pure product **35** (17.172 g, 95%): TLC R_f = 0.81 (20% EtOAc-hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.93 (dd, *J* = 10.4, 6.8 Hz, 1H), 5.19-5.13 (m, 2H), 3.73 (dd, *J* = 8.0, 2.0 Hz, 1H), 3.11-3.04 (m, 1H), 1.44-1.39 (m, 1H), 1.22 (d, *J* = 10.0 Hz, 6H), 1.02 (d, *J* = 7.2 Hz, 3H), 0.89-0.79 (m, 9H), 0.75 (d, *J* = 6.8 Hz, 3H), 0.04 (d, *J* = 4.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 216.15, 142.49, 114.39, 77.90, 51.65, 45.24, 32.97, 26.40, 23.83, 21.11, 18.67, 16.12, -3.32, -3.55.

(*4R,5S*)-5-(*tert*-Butyldimethylsilyloxy)-2,2,4,6-tetramethyl-3-oxoheptanal ((+/-) 36).

Ozone was passed through a solution of alkene **35** (13.891 g, 0.044 mol, 1 equiv) in DCM (43 mL) at -78 ^{o}C until the reaction mixture reached a dark blue color. Nitrogen was bubbled through the solution for 15 min before dimethyl sulfide (3.3 mL, 0.044 mol, 1 equiv) was added. The reaction mixture was stirred at room temperature overnight and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel in 25% DCM-hexanes to give **36** (7.140 g, 51%): TLC R_f = 0.60 (50% DCM-hexanes); ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.60 (s, 1H), 3.77 (dd, *J* = 7.8, 2.4 Hz, 1H), 2.99-2.97 (m, 1H), 1.46-1.43 (m, 2H), 1.33 (d, *J* = 5.4 Hz, 6H), 0.89-0.81 (m, 9H), 0.79 (d, *J* = 6.6 Hz, 3H), 0.04-0.02 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 212.63, 200.72, 77.12, 61.36, 46.36, 33.34, 26.32, 20.63, 19.88, 18.63, 16.40, 15.70, -3.42.

(*3S,4R,7S*)-3-(*tert*-Butyldimethylsilyloxy)-7-hydroxy-2,4,6,6-tetramethyldec-9-en-5-one and (*3R,4S,7S*)-3-(*tert*-butyldimethylsilyloxy)-7-hydroxy-2,4,6,6-tetramethyldec-9-en-5-one (37 and 37a)

Allylmagnesium bromide (9.9 mL, 9.91 mmol, 1.1 equiv) was added dropwise to a solution of (-)-B-methoxydiisopinocamphreylborane (3.253 g, 10.27 mmol, 1.14 equiv) in anhydrous ether (60 mL) at 0 ^{o}C. The reaction mixture was stirred at room temperature for 1 h and ether was removed under reduced pressure. The residue was extracted with pentane (3 x 22 mL), and the pentane extract was filtered under nitrogen and used without further purification. A solution of aldehyde **36** (2.831 g, 9.01 mmol, 1 equiv) in anhydrous ether (34 mL) was cooled to -100 ^{o}C and the solution of (+)-allyldiisopinocamphreylborane (9.91 mmol) in pentane (66 mL) prepared above was cannulated to the aldehyde solution. After the reaction mixture was stirred at -100 ^{o}C for 1 h, anhydrous MeOH (1.6 mL) was added. The reaction mixture was slowly warmed to room temperature and solutions of saturated sodium bicarbonate (17 mL) and H_2O_2 (7 mL, 50% solution in water) were added. The reaction mixture was stirred at room temperature overnight and extracted with EtOAc (3 x 30 mL). The combined organic extract was washed with saturated aqueous ammonium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel in 2% EtOAc-hexanes to obtain a mixture of **37** and **37a** (3.460 g, 68%): TLC R_f = 0.21 (10% EtOAc-hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.92-5.80 (m, 1H), 5.12-5.07 (m, 2H), 3.79-3.70 (m, 2H), 3.13-3.05 (m, 1H), 2.67 (d, *J* = 5.2 Hz, 1H), 2.49 (d, *J* = 4.0 Hz, 1H), 2.24-2.19 (m, 1H), 2.06-1.97 (m, 1H), 1.21 (s, 1H), 1.16 (d, *J* = 5.2 Hz, 3H), 1.10 (s, 1H), 1.05 (t, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.84 (d, *J* = 6.4 Hz, 3H), 0.05 (d, *J* = 2.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 220.93, 136.26, 136.16, 117.76, 117.48, 78.12, 78.00, 75.68, 75.47, 52.48, 52.39, 45.68, 45.49, 36.42, 36.38, 33.11, 32.87, 26.47, 22.60, 22.41, 21.44, 21.35, 19.72, 18.80, 16.85, 16.56, 16.10, -3.18, -3.20, -3.47, -3.49.

(*3S,4R,7S*)-3,7-Bis-(*tert*-butyldimethylsilyloxy)-2,4,6,6-tetramethyldec-9-en-5-one and (*3R,4S,7S*)- 3,7-bis-(*tert*-butyldimethylsilyloxy)-2,4,6,6-tetramethyldec-9-en-5-one (38 and 38a).

A solution of alcohols **37** and **37a** (11.815 g, 0.033 mol, 1 equiv) in anhydrous DCM (118 mL) was cooled to 0 ^{o}C and 2,6-lutidine (9.7 mL, 0.083 mol, 2.5 equiv) was added. The reaction mixture was stirred at 0 ^{o}C for 10 min and *tert*-butyldimethylsilyltrifluoromethane sulfonate (TBSOT*f*) (11.5 mL, 0.050 mol, 1.5 equiv) was added dropwise. After stirring the reaction mixture at 0 ^{o}C for 1 h, saturated aqueous ammonium chloride (118 mL) was added. The organic phase was separated from the aqueous phase, which was extracted with ether (3 x 230 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The product was purified by column chromatography on silica gel in 25% DCM-hexanes to obtain the products **38** and **38a** (13.187 g, 83%): TLC R_f = 0.30 (25% DCM-hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.87-5.73 (m, 1H), 4.96 (t, *J* = 9.2 Hz, 2H), 4.07-4.05 (m, 1H), 3.97-3.95 (m, 1H), 3.09-3.00 (m, 1H), 2.18-1.99 (m, 2H), 1.51-1.41 (m, 1H), 1.18 (d, *J* = 10.8 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 6H), 0.89-0.82 (m, 21H), 0.08-0.02 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 219.10, 218.51, 137.04, 137.01, 116.51, 116.43, 77.85, 77.73, 76.24, 75.34, 54.48, 54.27, 45.99, 45.44, 39.82, 39.32, 33.23, 32.91, 26.48, 26.32, 26.30, 26.27, 24.96, 23.17, 21.49, 21.33, 19.51, 18.81, 18.49, 18.48, 16.38, 16.06, 16.02, 15.94, -3.05, -3.13, -3.19, -3.24, -3.47, -3.53, -3.74, -3.76.

(*3S,6R,7S*)-3,7-Bis(*tert*-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxononanal and (*3S,6S,7R*)-3,7-bis(*tert*-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxononanal (39 and 40).

Ozone was passed through a solution of diastereomers **38** and **38a** (1.002 g, 2.12 mmol, 1 equiv) in DCM (12 mL) at -78 ^{o}C until the reaction mixture reached a dark blue color. Nitrogen was bubbled through the solution for 15 min and triphenylphosphine (612 mg, 2.33 mmol, 1.1 equiv) was added. The reaction mixture was stirred at room temperature overnight and concentrated in vacuo. The mixture of aldehydes was separated by flash

chromatography on silica gel in 10% DCM-hexanes, monitored by NMR, to obtain the (*3S,6R,7S*) diastereomer **39** (150 mg), the mixture of the two aldehydes (416 mg) followed by (*3S,6S,7R*) diastereomer **40** (245 mg) with an overall percent yield of 69%

Data for the (*3S,6R,7S*) diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.76 (s, 1H), 4.57 (t, *J* = 5.2 Hz, 1H), 3.70 (d, *J* = 7.6 Hz, 1H), 3.07-3.00 (m, 1H), 2.51-2.37 (m, 3H), 1.43-1.33 (m, 1H), 1.21-1.17 (m, 6H), 1.03-1.00 (m, 6H), 0.66 (m, 21H), 0.03-0.01 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 218.18, 201.55, 77.85, 70.42, 53.92, 49.24, 45.44, 33.25, 26.43, 26.20, 26.12, 22.71, 21.31, 19.44, 18.76, 18.31, 16. 16.035, -3.24, -3.51, -3.10, -4.22.

Data for the (*3S,6S,7R*) diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 4.45 (t, *J* = 4.8 Hz, 1H), 3.70 (d, *J* = 6.8 Hz, 1H), 3.05-3.01 (m, 1H), 2.48-2.32 (m, 3H), 1.44-1.38 (m, 1H), 1.14 (s, 6H), 1.04 (s, 3H), 0.98 (d, *J* = 8.0 Hz, 3H), 0.81 (m, 21H), 0.01 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 218.98, 201.47, 77.87, 71.25, 53.80, 49.79, 46.09, 46.05, 39.92, 32.89, 29.92, 26.46, 26.17, 26.10, 26.06, 24.12, 21.51, 18.791, 18.74, 18.32, 16.09, 15.86, -3.15, -3.46, -3.86, -4.28.

(*3S,6R,7S*)-3,7-Bis(*tert*-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxononanoic acid (41).

To a solution of aldehyde **39** (710 mg, 1.50 mmol, 1 equiv) and 2-methyl-2-butene (7.6 mL) in *t*-butanol (32 mL) was added a solution of $NaClO_2$ (1.244 g, 13.76 mmol, 9.1 equiv) and NaH_2PO_4 (1.248 g, 10.38 mmol, 6.9 equiv) in water (9 mL) dropwise. The reaction mixture was stirred for 1 h at room temperature, and the reaction was quenched with saturated aqueous ammonium chloride (40 mL) and water (40 mL). The reaction mixture was extracted with EtOAc (3 x 15 mL). The combined organic extract was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was taken

directly to the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.52-4.49 (m, 1H), 3.73 (dd, *J* = 8.0, 2.0 Hz, 1H), 3.09-3.01 (m, 1H), 2.47 (dd, *J* = 16.4, 3.6 Hz, 1H), 2.33 (dd, *J* = 16.4, 6.8 Hz, 1H), 1.46-1.38 (m, 1H), 1.18-1.16 (m, 1H), 1.16-1.14 (m, 3H), 1.03-1.01 (m, 6H), 0.98-0.82 (m, 21H), 0.03 (m, 10H).

(*3S,6R,7S*)-3,7-Dihydroxy-4,4,6,8-tetramethyl-5-oxononanoic acid (43).

A solution of the carboxylic acid **41** (350 mg, 0.720 mmol) in DCM (15 mL) was cooled to 0 ^{o}C. Trifluoroacetic acid (3.0 mL, 20% in DCM) was added and the reaction mixture was stirred at 4 ^{o}C for 25 h. Water (5 mL) was added and the mixture was evaporated to dryness under reduced pressure. The residue was dried azeotropically with toluene to obtain carboxylic acid **43** (168 mg, 90%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.23 (dd, *J* = 10.0, 2.4 Hz, 1H), 3.33 (dd, *J* = 8.8, 1.6 Hz, 1H), 3.26-3.21 (m, 1H), 2.51-2.37 (m, 3H), 1.69-1.63 (m, 1H), 1.15 (d, *J* = 1.6 Hz, 6H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 222.47, 177.25, 76.79, 72.47, 52.33, 41.079, 36.71, 30.66, 21.61, 19.54, 19.30, 19.17, 10.61.

(*3S,6S,7R*)-3,7-Bis(tert-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxononanoic acid (42).

To a solution of aldehyde **40** (282 mg, 0.569 mmol, 1 equiv) and 2-methyl-2-butene (3.0 mL) in *t*-butanol (12 mL) was added a solution of $NaClO_2$ (497 mg, 5.50 mmol, 9.1 equiv.) and NaH_2PO_4 (497 mg, 4.15 mmol, 6.9 equiv.) in water (4 mL) dropwise. The reaction mixture was stirred at room temperature for 1 h and the reaction was quenched with saturated aqueous ammonium chloride (15 mL) and water (15 mL). The reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was passed through a silica gel plug to obtain carboxylic acid **42** (241 mg, 87%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.39 (m, 1H), 3.72 (dd, *J* = 8.0, 1.2 Hz, 1H), 3.08 (m, 1H),

2.46 (dd, J = 16.4, 2.8 Hz, 1H), 2.29 (dd, J = 16.4, 6.8 Hz, 1H), 1.45-1.42 (m, 1H), 1.22-1.19 (m, 3H), 1.08 (s, 3H), 1.03 (d, J = 7.2 Hz, 3H), 0.88-0.73 (m, 24H), 0.03 (m, 10H); ^{13}C ($CDCl_3$, 100 MHz): δ 218.51, 178.65, 77.87, 73.40, 53.81, 46.07, 40.43, 32.94, 26.48, 26.22, 23.73, 21.53, 19.04, 18.80, 18.41, 16.18, 15.90, -3.18, -3.46, -4.05.

(*3S,6S,7R*)-3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoic acid (44).

A solution of carboxylic acid **42** (882 mg, 1.81 mmol) in DCM (58 mL) was cooled to 0 ^{o}C and trifluoroacetic acid (11.6 mL, 20% in DCM) was added. The reaction mixture was stirred at 4 ^{o}C for 25 h. Water (15 mL) was added and the reaction mixture was evaporated to dryness under reduced pressure. The residue was dried azeotropically with toluene to obtain carboxylic acid **44** (450 mg, 95%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.26 (dd, J = 10.0, 2.4 Hz, 1H), 3.30-3.22 (m, 2H), 2.53-2.40 (m, 2H), 1.70-1.63 (m, 1H), 1.20 (s, 3H), 1.15 (s, 3H), 1.06 (d, J = 7.2 Hz, 3H), 1.00 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 222.61, 176.67, 76.58, 72.44, 52.16, 41.33, 36.38, 30.82, 21.60, 19.66, 19.21, 19.05, 10.54.

2-Methyl-4-bromothiazole (47).[52]

A solution of 2,4-dibromothiazole **46** (2.000 g, 8.23 mmol, 1 equiv) in anhydrous ether (10 mL) was cooled to -78 ^{o}C and *n*-BuLi (3.6 mL, 9.05 mmol, 1.1 equiv) was added dropwise. After the reaction mixture was stirred at -78 ^{o}C for 1 h, a solution of dimethyl sulfate (1.9 mL, 20.58 mmol, 2.5 equiv) in anhydrous ether (2 mL) was added. The reaction mixture was stirred at -78 ^{o}C for 4 h after which it was allowed to warm to room temperature. After stirring for 14 h, the reaction mixture was poured into saturated aqueous ammonium chloride (10 mL) and extracted with EtOAc (3 x 4 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The product was purified by flash chromatography on silica gel in EtOAc-hexanes to obtain product **47** (0.765, 52%): TLC R_f = 0.68 (20% EtOAc-

hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (s, 1H), 2.71 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.20, 123.94, 116.30, 19.41.

2-(Methylthio)-4-bromothiazole (48).[28b]

Sodium thiomethoxide (1.580 g, 21.48 mmol, 3 equiv) was added to a solution of 2,4-dibromothiazole **46** (1.732 g, 7.18 mmol, 1 equiv) in ethanol (48 mL). The reaction mixture was stirred at room temperature for 3 h. Water (100 mL) was added and the reaction mixture was extracted with ether (3 x 100 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The product was recrystallized from EtOAc-hexanes to give **48** (1.415g, 94%): TLC R_f = 0.48 (2% EtOAc-hexanes); mp 36-40 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.05 (s, 1H), 2.68 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.09, 124.41, 115.66, 16.84.

2-(Piperidin-1-yl)-4-bromothiazole (49).[28b]

Anhydrous piperidine (16.5 mL, 0.5 M) was added to 2,4-dibromothiazole **46** (2.020 g, 8.34 mmol, 1 equiv). The reaction mixture was heated to 50 ^{o}C with stirring for 22 h. The reaction mixture was cooled to room temperature, quenched with water (54 mL), and extracted with ether (3 x 54 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel in 5% EtOAc-hexanes and recrystallized from DCM-hexanes to give product **49** (1.300 g, 86%): TLC R_f = 0.43 (5% EtOAc-hexanes); mp 68 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.35 (s, 1H), 3.42 (d, J = 5.6 Hz, 4H), 1.63 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.03, 121.70, 102.97, 49.26, 25.14, 24.08.

2-(Phenylethynyl)-4-bromothiazole (50).

A mixture of 2,4-dibromothiazole **46** (2.917 g, 12.0 mmol, 1 equiv), $Pd(Ph_3)_4$ (0.685 g, 0.60 mmol, 15 mol%), and CuI (0.228 g, 0.12 mmol, 10 mol%) was placed in a three-necked round bottom flask under nitrogen. Anhydrous THF (30 mL) was added, followed by *N,N*-diisopropylamine (2.55 mL, 18.02 mmol, 1.5 equiv). A solution of phenylacetylene (2.00 g, 17.98 mmol, 1.5 equiv) in anhydrous THF (6 mL) was slowly added to the reaction mixture via a syringe pump over 7 h. The reaction mixture was stirred for an additional 9 h. Water (50 mL) was added and the reaction mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extract was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel in 5% EtOAc in hexanes and recrystallized from EtOAc-hexanes to obtain **50** (3.174 g, 86%): TLC R_f = 0.59 (10 % EtOAc-hexanes); mp 79-80 ^oC; IR $\bar{\nu}_{max}$: 3300, 3000, 2900, 2350 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6): δ 7.79 (s, 1H), 7.66 (m, 2H), 7.51 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.93, 132.249, 130.12, 128.78, 126.11, 121.10, 118.82, 95.69, 81.60; HRMS (m/z): $[M + Na]^+$ calcd for $C_{11}H_6NSBr$, 285.9302; found, 285.9314.

2–((Trimethylsilyl)ethynyl)-4-bromothiazole (51).

A mixture of 2,4-dibromothiazole **46** (3.000 g, 12.34 mmol, 1 equiv), triphenylphosphine (486 mg, 1.851 mmol, 5 mol%), CuI (120 mg, 0.617 mmol, 5 mol%), and $Pd(Ph_3)_2Cl_2$ (120 mg, 0.173 mmol, 1.4 mol%) was placed in a three-neck roundbottom flask under nitrogen. Anhydrous toluene (42 mL) was added, followed by anhydrous Et_3N (2.2 mL, 15.04 mmol, 1.3 equiv) and trimethylsilylacetylene (2.6 mL, 18.51 mmol, 1.5 equiv). The reaction mixture was refluxed at 140 ^oC for 2 d. It was poured into water (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extract was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel in DCM-hexanes to obtain **51** (2.625 g, 81%): TLC R_f = 0.72 (10 % EtOAc-hexanes); mp 37 ^oC; IR $\bar{\nu}_{max}$: 3300, 2900, 2250 cm^{-1}; ^1H NMR

(400 MHz, $CDCl_3$): δ 7.18 (s, 1H), 0.24 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.54, 125.87, 118.85, 103.03, 95.52, -0.41; HRMS (m/z): $[M + H]^+$ calcd for $C_8H_{11}NSSiBr$, 259.9565; found, 259.9565.

2-Methyl-3-(2-methylthiazol-4-yl)cyclopent-2-enone (53a).

A solution of 2-methyl-4-bromothiazole **47** (351 mg, 1.97 mmol, 1 equiv) in anhydrous ether (3 mL) was cooled to -78 ^oC and *n*-BuLi (1.30 mL of 2.5 M solution in THF, 3.35 mmol, 1.7 equiv) was added dropwise. The reaction mixture was stirred at -78 ^oC for 2 h and a solution of trimethyltin chloride (785 mg, 3.94 mmol, 2 equiv) in anhydrous ether (2 mL) was added dropwise. The reaction mixture was stirred for an additional 1 h and allowed to warm to room temperature slowly. It was diluted with hexanes, passed through a silica gel plug deactivated with 5% Et_3N-hexanes, and eluted with EtOAc. The partially purified product was concentrated in vacuo to obtain a reddish oil, which was immediately taken to the next step. ^1H NMR (600 MHz, $CDCl_3$): δ 7.19 (s, 1H), 2.75 (s, 3H), 0.33 (t, J = 3.6 Hz, 9H). A mixture of 3-iodo-2-methylcyclopent-2-enone **52** (350 mg, 1.57 mmol, 0.8 equiv) and $Pd(Ph_3)_4$ (455 mg, 0.394 mmol, 20 mol%) was placed in a μw vial under nitrogen. A solution of the tin derivative, prepared above, in anhydrous DMF (4.5 mL) was added via a syringe, and the vial was heated for 2 h 15 min at 145 ^oC in the microwave synthesizer. The reaction mixture was poured into water (15 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extract was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel in EtOAc-hexanes and recrystallized from EtOAc-hexanes to obtain **53a** (336 mg, 88%): TLC R_f = 0.39 (40% EtOAc-hexanes); mp 89-90 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (s, 1H), 2.95-2.92 (m, 2H), 2.73 (s, 3H), 2.49-2.47 (m, 2H), 2.09 (t, J = 2.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 210.24, 165.80, 158.67, 152.28, 136.60, 120.32, 33.89, 28.24, 19.56, 10.33; HRMS (m/z): $[M + Na]^+$ calcd for $C_{10}H_{11}NOS$, 216.0459; found, 216.0461.

2-Methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enone (53b).

A solution of 2-thiomethyl-4-bromothiazole **48** (300 mg, 1.43 mmol, 1 equiv) in anhydrous ether (10 mL) was cooled to -78 ^{o}C. *n*-BuLi (1.80 mL, 1.6 M in hexanes, 2.86 mmol, 2 equiv) was added dropwise and the reaction mixture was stirred at -78 ^{o}C for 2 h. A solution of trimethyltin chloride (708 mg, 3.57 mmol, 2.5 equiv) in anhydrous ether (3 mL) was added dropwise. The reaction mixture was stirred at -78 ^{o}C for an additional 1 h and was allowed to warm slowly to room temperature. The reaction mixture was diluted with hexanes, passed through a silica gel plug deactivated with 5% Et_3N-hexanes, and eluted with EtOAc. The partially purified product was concentrated in vacuo to obtain a reddish oil, which was taken immediately to the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (s, 1H), 2.69 (s, 3H), 0.32 (t, *J* = 28.0 Hz, 9H). 3-Iodo-2-methylcyclopent-2-enone **52** (318 mg, 1.43 mmol, 1 equiv) and $Pd(Ph_3)_4$ (330 mg, 0.286 mmol, 20 mol%) were placed in a μw vial under nitrogen. A solution of the tin derivative, prepared above, in anhydrous DMF (15 mL) was added via syringe, and the vial was heated for 2 h in the microwave synthesizer at 145 ^{o}C. The reaction mixture was poured into water (30 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extract was dried over anhydrous sodium sulfate and concentrated in vacuo. The product was purified by flash column chromatography on silica gel in EtOAc-hexanes and recrystallized from EtOAc-hexanes to obtain **53b** (148 mg, 46%): TLC R_f = 0.60 (40% EtOAc-hexanes); mp 102 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46 (s, 1H), 2.92-2.90 (m, 2H), 2.73 (s, 3H), 2.52-2.50 (m, 2H), 2.14 (t, *J* = 2.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 210.27, 166.73, 157.83, 152.64, 137.03, 119.64, 33.93, 27.92, 16.71, 10.40; HRMS (m/z): $[M + Na]^+$ calcd for $C_{10}H_{11}NOS$, 248.0180; found, 248.0189.

2-Methyl-3-(2-(piperidin-1-yl)thiazol-4-yl)cyclopent-2-enone (53c).

A solution of 2-piperdin-1-yl-4-bromothiazole **49** (550 mg, 2.22 mmol, 1 equiv) in anhydrous ether (19 mL) under nitrogen was cooled to -78 ^{o}C. *n*-BuLi (1.60 mL, 1.6 M in hexanes, 2.66 mmol, 1.2 equiv) was added dropwise and the reaction mixture was stirred at -78 ^{o}C for 2 h. A solution of trimethyltin chloride (590 mg, 3.33 mmol, 1.5

equiv) in anhydrous ether (7 mL) was added dropwise. The reaction mixture was stirred at -78 ^{o}C for an additional 1 h and was allowed to warm slowly to room temperature. The reaction mixture was diluted with hexanes, passed through a silica gel plug deactivated with 5% Et_3N-hexanes, and eluted with EtOAc. The partially purified product was concentrated in vacuo to obtain a yellowish oil, which was taken immediately to the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.56 (s, 1H), 3.47 (m, 4H), 1.65 (m, 6H), 0.27 (t, *J* = 20 Hz, 9H). 3-Iodo-2-methylcyclopent-2-enone **52** (338 mg, 1.52 mmol, 1 equiv) and $Pd(Ph_3)_4$ (352 mg, 0.304 mmol, 20 mol%) were placed in a μw vial under nitrogen. A solution of the tin derivative, prepared above, in anhydrous DMF (10 mL) was added via syringe. The vial was heated for 2 h in the microwave synthesizer at 140 ^{o}C. The reaction mixture was poured into water (20 mL) and extracted with EtOAc (3 x 8 mL). The combined organic extract was dried over anhydrous sodium sulfate and concentrated in vacuo. The product was purified by flash column chromatography on silica gel in EtOAc-hexanes and recrystallized from EtOAc-hexanes to obtain **53c** (341 mg, 58%): TLC R_f = 0.57 (40% EtOAc-hexanes); mp 108 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.88 (s, 1H), 3.49 (m, 4H), 2.85 (m, 2H), 2.46 (m, 2H), 2.13 (t, *J* = 2.0 Hz, 3H), 1.66 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 221.25, 210.71, 170.84, 159.11, 149.68, 136.08, 109.85, 49.76, 33.93, 27.60, 25.33, 24.37, 10.39. HRMS (m/z): $[M + Na]^+$ calcd for $C_{14}H_{18}N_2O$, 285.1038; found, 285.1046.

2-Methyl-3-(2-(phenylethynyl)thiazol-4-yl)cyclopent-2-enone (53d).

A solution of 2-(phenylethynyl)-4-bromothiazole **50** (1.000 g, 3.78 mmol, 1 equiv) in anhydrous ether (15 mL) was cooled to -78 ^{o}C and *n*-BuLi (2.3 mL, 2.5 M in hexanes, 5.67 mmol, 1.5 equiv) was added dropwise. The reaction mixture was stirred at -78 ^{o}C for 2 h and a solution of trimethyltin chloride (1.503 g, 7.56 mmol, 2 equiv) in anhydrous ether (5 mL) was added dropwise. The reaction mixture was stirred for an additional 1 h at -78 ^{o}C before it was allowed to warm to room temperature slowly. The reaction mixture was diluted with hexanes, passed through a silica gel plug deactivated with 5% Et_3N-hexanes, and eluted with EtOAc. The partially purified product was concentrated in

vacuo to obtain a reddish oil, which was used immediately in the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (m, 2H), 7.38 (m, 3H), 0.37 (t, *J* = 27.6 Hz, 9H). 3-Iodo-2-methylcyclopent-2-enone **52** (678 mg, 3.02 mmol, 0.8 equiv) and $Pd(Ph_3)_4$ (873 mg, 0.756 mmol, 20 mol%) were placed in a μw vial under nitrogen. A solution of the tin derivative, prepared above, in anhydrous DMF (15 mL) was added via syringe. The vial was heated for 2 h 15 min in the microwave synthesizer at 145 ^oC. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extract was dried over anhydrous sodium sulfate and concentrated in vacuo. The product was purified by flash column chromatography on silica gel in EtOAc-hexanes and recrystallized from EtOAc-hexanes to obtain the product **53d** (816 mg, 77%): TLC R_f = 0.45 (40% EtOAc-hexanes); mp 117 ^oC; IR $\bar{\nu}_{max}$: 3320, 3200, 2900, 2250, 1800, 1750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (s, 1H), 7.61 (m, 2H), 7.38 (m, 3H), 3.03 (m, 2H), 2.54 (m, 2H), 2.13 (t, *J* = 2.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 210.09, 157.99, 153.08, 148.76, 137.61, 132.27, 130.03, 128.76, 121.87, 121.24, 95.08, 82.16, 33.96, 28.40, 10.44; HRMS (m/z): $[M + Na]^+$ calcd for $C_{17}H_{13}NOS$, 302.0616; found, 302.0620.

2-Methyl-3-(2-((trimethylsilyl)ethynyl)thiazol-4-yl)cyclopent-2-enone (53e).

A solution of 2–((trimethylsilyl)ethynyl)-4-bromothiazole **51** (100 mg, 0.384 mmol, 1 equiv) in anhydrous ether (3 mL) under nitrogen was cooled to -78 ^oC and *t*-BuLi (240 μL, 1.6 M in hexanes, 0.384 mmol, 1 equiv) was added dropwise. The reaction mixture was stirred at -78 ^oC for 1 h and a solution of trimethyltin chloride (150 mg, 0.768 mmol, 2 equiv) in anhydrous ether (2 mL) was added via syringe. The reaction mixture was stirred at -78 ^oC for an additional 1 h and was allowed to warm to room temperature slowly. The reaction mixture was diluted with hexanes, passed through a silica gel plug deactivated with 5% Et_3N-hexanes, and eluted with EtOAc. It was concentrated in vacuo to obtain a yellow oil, which was immediately taken to the next step. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33 (s, 1H), 0.34 (t, *J* = 14.8 Hz, 9H), 0.25 (m, 3H). 3-Iodo-2-methylcyclopent-2-enone **52** (83 mg, 0.384 mmol, 1 equiv) and $Pd(Ph_3)_4$ (88 mg, 0.078

mmol, 20 mol%) were placed in a μw vial under nitrogen. A solution of the tin derivative, prepared above, in anhydrous DMF (2 mL) was added via syringe. The μw vial was heated for 2 h 15 min in the microwave synthesizer at 145 ^{o}C. The reaction mixture was poured into water (30 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extract was dried over anhydrous sodium sulfate and concentrated in vacuo. The product was purified by flash column chromatography on silica gel in EtOAc-hexanes and recrystallized from DCM-hexanes to obtain **53e** (50 mg, 47%): TLC R_f = 0.63 (40% EtOAc-hexanes); mp 108-110 ^{o}C; IR $\bar{\nu}_{max}$: 3300, 2900, 2200, 1750 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.58 (s, 1H), 2.99 (t, *J* = 2.0 Hz, 2H), 2.52 (m, 2H), 2.10 (d, *J* = 2.0 Hz, 3H), 0.28 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 209.71, 157.66, 152.65, 148.22, 137.37, 121.79, 102.05, 96.15, 33.74, 28.18, 10.23, -0.46; HRMS (m/z): $[M + Na]^+$ calcd for $C_{14}H_{17}NOSSi$, 298.0698; found, 298.0680.

3-(2-Ethynylthiazol-4-yl)-2-methylcyclopent-2-enone (55).

A solution of 2-methyl-3-(2-((trimethylsilyl)ethynyl)thiazol-4-yl)cyclopent-2-enone **53e** (50 mg, 0.182 mmol, 1 equiv) and K_2CO_3 (3 mg, 0.022 mmol, 12 mol%) in methanol (1 mL) was stirred for 5 min. The crude product was poured into water (8 mL) and extracted with EtOAc (3 x 3 mL). The combined organic extract was dried over anhydrous sodium sulfate and concentrated in vacuo. The product was recrystallized from DCM-hexanes to obtain **55** (36 mg, 98%): TLC R_f = 0.33 (40% EtOAc-hexanes); mp 138-139 ^{o}C; IR $\bar{\nu}_{max}$: 3000, 2900, 2250, 1750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (s, 1H), 3.52 (s, 3H), 2.99-2.96 (m, 2H), 2.53-2.51 (m, 2H), 2.11 (t, *J* = 2.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 209.98, 157.56, 153.08, 147.50, 137.84, 121.90, 83.24, 76.31, 33.92, 28.31, 10.38; HRMS (m/z): $[M + Na]^+$ calcd for $C_{11}H_9NOS$, 226.0303; found, 226.0298.

3-(2-(1H-1,2,3-Triazol-4-yl)thiazol-4-yl)-2-methylcyclopent-2-enone (56).

3-(2-Ethynylthiazol-4-yl)-2-methylcyclopent-2-enone **55** (60 mg, 0.295 mmol, 1 equiv) and CuI (3 mg, 0.015 mmol, 5 mol%) were placed in a μw vial under nitrogen. Anhydrous DMF (3.6 mL) and anhydrous MeOH (440 μL, 9:1 ratio DMF/MeOH) were added, followed by azidotrimethylsilane (58 μL, 0.443 mmol, 1.5 equiv). The vial was heated for 2 h in the microwave synthesizer at 140 ^{o}C. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (3 x 4 mL). The combined organic extract was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel in EtOAc-hexanes and recrystallized from methanol to obtain product **56** (51 mg, 70%): TLC R_f = 0.34 (50% EtOAc-hexanes); mp 241-243 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (S, 1H), 7.67 (s, 1H), 3.04-2.98 (m, 2H), 2.57-2.55 (m, 2H), 2.20 (d, *J* = 4.0 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 208.87, 158.46, 157.43, 152.32, 141.26, 135.32, 141.26, 135.47, 122.25, 33.25, 27.46, 9.99; HRMS (m/z): $[M + Na]^+$ calcd for $C_{11}H_{10}N_4OS$, 269.0473; found, 269.0489.

2-Methyl-3-(2-(1-methyl-1H-1,2,3-triazol-4-yl)thiazol-4-yl)cyclopent-2-enone (53f).

3-(2-(1H-1,2,3-triazol-4-yl)thiazol-4-yl)-2-methylcyclopent-2-enone **56** (25 mg, 0.102 mmol, 1 equiv) and NaOMe (5 mg, 0.100 mmol, 0.99 equiv) were placed in a μw vial under nitrogen and anhydrous MeOH (2 mL) was added. The reaction mixture was heated for 7 min in the microwave synthesizer at 65 ^{o}C and methyl iodide (7 μL, 0.112 mmol, 1.1 equiv) was added. The reaction mixture was reheated in the microwave synthesizer for 30 min at 90 ^{o}C. The insoluble starting material was filtered off using DCM. Purification by preparative thin-layer chromatography on silica gel in 60% EtOAc-hexanes gave the product **53f** (9.6 mg, 36%): TLC R_f = 0.44 (50% EtOAc-hexanes); mp 154-156 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.62 (s, 1H), 4.25 (s, 3H), 3.02-2.99 (m, 2H), 2.55-2.53 (m, 2H), 2.17 (t, *J* = 2.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 210.21, 158.19, 158.03, 153.40, 143.07, 137.36, 132.36, 120.48,

42.30, 33.93, 28.18, 10.41; HRMS (m/z): $[M + Na]^+$ calcd for $C_{12}H_{12}N_4OS$, found 283.0630; found, 283.0620.

(*S*)-2-Methyl-3-(2-methylthiazol-4-yl)cyclopent-2-enol (54a).

A solution of 2-methyl-3-(2-methylthiazol-4-yl)cyclopent-2-enone **53a** (100 mg, 0.517 mmol, 1 equiv) and *(R)*-2-methyl-CBS-oxazaborolidine (29 mg, 0.103 mmol, 20 mol%) in anhydrous THF (2 mL) was cooled to 0 ^oC. A solution of borane-Me_2S (260 μL of 2.0 M solution in THF, 0.517 mmol, 1 equiv) was added dropwise. The reaction mixture was stirred at 0 ^oC for 1 h and the reaction was quenched by slow addition of water (5 mL) at 0 ^oC. The reaction mixture was extracted with EtOAc (3 x 2 mL), and the combined organic extract was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by preparative thin-layer chromatography on silica gel in 50% EtOAc-hexanes to obtain the product **54a** (25 mg, 24%): TLC R_f = 0.34 (40% EtOAc-hexanes); mp 70-71 ^oC; $[\alpha]^{25}_D$ = -18.0^o (*c* 0.75, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 6.94 (s, 1H), 4.72 (d, *J* = 5.6 Hz, 1H), 2.86-2.77 (m, 1H), 2.70 (s, 3H), 2.65-2.57 (m, 1H), 2.41-2.32 (m, 1H), 2.13 (d, *J* = 0.4 Hz, 3H), 1.76-1.66 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.98, 153.10, 138.67, 131.66, 115.26, 82.38, 32.91, 32.72, 19.55, 13.36; HRMS (m/z): $[M + Na]^+$ calcd for $C_{10}H_{11}NOS$, 218.0616; found, 218.0620.

(*S*)-2-Methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enol (54b).

A solution of 2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enone **53b** (100 mg, 0.444 mmol, 1 equiv) and (*R*)-2-methyl-CBS-oxazaborolidine (25 mg, 0.089 mmol, 20 mol%) in anhydrous THF (2 mL) was cooled to 0 ^oC. A solution of borane-Me_2S (220 μL of 2.0 M solution in THF, 0.444 mmol, 1 equiv) was added dropwise. The reaction mixture was stirred at 0 ^oC for 1 h and the reaction was quenched by slow addition of water (5 mL) at 0 ^oC. The reaction mixture was extracted with EtOAc (3 x 2 mL). The combined organic extract was dried over anhydrous sodium sulfate and concentrated in

vacuo. The crude product was purified by preparative thin-layer chromatography on silica gel in 60% EtOAc-hexanes to obtain product **54b** (64 mg, 63%): TLC R_f = 0.48 (40% EtOAc-hexanes); mp 46-49 ^oC; $[\alpha]^{25}_D$ = -5.8^o (*c* 1.40, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 6.95 (s, 1H), 4.71 (m, 1H), 2.83-2.76 (m, 1H), 2.70 (s, 3H), 2.61-2.55 (m, 1H), 2.42-2.34 (m, 1H), 2.18 (s, 3H), 1.77-1.69 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.25, 153.35, 139.23, 130.69, 114.73, 82.15, 32.52, 32.45, 16.69, 13.41; HRMS (m/z): $[M + H]^+$ calcd for $C_{10}H_{13}NOS_2$, 228.0517; found, 228.0525.

2-Methyl-3-(2-(piperidin-1-yl)thiazol-4-yl)cyclopent-2-enol (54c).

A solution of 2-methyl-3-(2-(piperidin-1-yl)thiazol-4-yl)cyclopent-2-enone **53c** (100 mg, 0.380 mmol, 1 equiv) and (*R*)-2-methyl-CBS-oxazaborolidine (21 mg, 0.076 mmol, 20 mol%) in anhydrous THF (4 mL) was cooled to 0 ^oC. A solution of borane-Me_2S (190 μL of 2.0 M solution in THF, 0.380 mmol, 1 equiv) was slowly added. The reaction mixture was stirred at 0 ^oC for 1 h and the reaction was quenched by slow addition of water (8 mL). The reaction mixture was extracted with EtOAc (3 x 3 mL). The combined organic extract was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by preparative thin-layer chromatography on silica gel in 50% EtOAc-hexanes to obtain **54c** (88 mg, 87%): TLC R_f = 0.53 (40% EtOAc-hexanes); mp 93-95 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 6.35 (s, 1H), 4.67 (t, *J* = 5.2 Hz, 1H), 3.44 (m, 4H), 2.76-2.72 (m, 1H), 2.52-2.49 (m, 1H), 2.36-2.30 (m, 1H), 2.20 (s, 3H), 1.71-1.62 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.88, 150. 137.98, 131.63, 104.57, 82.52, 49.65, 32.63, 32.13, 25.31, 24.38, 13.35; HRMS (m/z): $[M + H]^+$ calcd for $C_{14}H_{20}N_2OS$, 265.1375; found, 265.1375.

(*S*)-2-Methyl-3-(2-(phenylethynyl)thiazol-4-yl)cyclopent-2-enol (54d).

A solution of 2-methyl-3-(2-(phenylethynyl)thiazol-4-yl)cyclopent-2-enone **53d** (100 mg, 0.358 mmol, 1 equiv) and (*R*)-2-methyl-CBS-oxazaborolidine (20 mg, 0.072 mmol, 20

mol%) in anhydrous THF (2 mL) was cooled to 0 ^{o}C. A solution of borane-Me_2S (179 μL of 2.0 M solution in THF, 0.358 mmol, 1 equiv) was added dropwise. After the reaction mixture was stirred at 0 ^{o}C for 5 min, it was quenched by slow addition of water (4 mL) at 0 ^{o}C. The reaction mixture was extracted with EtOAc (3 x 1 mL). The combined organic extract was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by preparative thin-layer chromatography on silica gel in 20% EtOAc-DCM to obtain product **54d** (56 mg, 56%): TLC R_f = 0.55 (20% EtOAc-DCM); $[\alpha]^{25}_{D}$ = + 3.5^{o} (*c* 0.650, $CHCl_3$); IR $\bar{\nu}_{max}$: 3350, 2900, 2300 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.59 (m, 2H), 7.38 (m, 3H), 7.15 (s, 1H), 4.74 (d, *J* = 3.6 Hz, 1H), 2.89 (m, 1H), 2.69 (m, 1H), 2.41 (m, 1H), 2.15 (s, 3H), 1.76 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.17, 147.79, 139.98, 132.19, 131.14, 129.70, 128.68, 121.658, 117.38, 93.95, 82.78, 82.31, 32.99, 32.69, 13.51; HRMS (m/z): $[M + H]^+$ calcd for $C_{17}H_{15}NOS$, 282.0953; found, 282.0953.

(*S*)-3-(2-Ethynylthiazol-4-yl)-2-methylcyclopent-2-enol (54e).

A solution of 3-(2-ethynylthiazol-4-yl)-2-methylcyclopent-2-enone **53e** (95 mg, 0.340, 1 equiv) and (*R*)-2-methyl-CBS-oxazaborolidine (19 mg, 0.072 mmol, 20 mol %) in anhydrous THF (2 mL) was cooled to 0 ^{o}C. A solution of borane-Me_2S (170 μL, 0.340 mmol, 1 equiv) in THF was added dropwise. The reaction mixture was stirred at 0 ^{o}C for 25 min and the reaction was quenched by slow addition of water (5 mL) at 0 ^{o}C. The reaction mixture was extracted with EtOAc (3 x 2 mL). The combined organic extract was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by preparative thin-layer chromatography on silica gel in 25% EtOAc-DCM to obtain the partially purified product **54e** (72 mg, 75%): TLC R_f = 0.58 (40% EtOAc-DCM); mp 69-71 ^{o}C; $[\alpha]^{25}_{D}$ = -12.8^{o} (*c* 1.50, $CHCl_3$); IR $\bar{\nu}_{max}$: 3300, 2900, 2300 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (s, 1H), 4.73 (d, *J* = 4.4 Hz, 1H), 3.44 (s, 1H), 2.88-2.81 (m, 1H), 2.67-2.60 (m, 1H), 2.43-2.34 (m, 1H), 2.14 (d, *J* = 8.8 Hz, 3H), 1.78-1.70 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.15, 146.52, 140.24, 130.83, 117.48, 82.30,

82.14, 32.91, 32.67, 13.49; HRMS (m/z): [M + Na]$^+$ calcd for $C_{11}H_{11}NOS$, 228.0458; found, 228.0459.

(*S*)-2-Methyl-3-(2-(1-methyl-1H-1,2,3-triazol-4-yl)thiazol-4-yl)cyclopent-2-enol (54f).

A solution of 2-methyl-3-(2-(1-methyl-1H-1,2,3-triazol-4-yl)thiazol-4-yl)cyclopent-2-enone **53f** (20 mg, 0.071 mmol, 1 equiv) and (*R*)-2-methyl-CBS-oxazaborolidine (5 mg, 0.015 mmol, 20 mol%) in anhydrous THF (1.5 mL) was cooled to 0 ^{o}C. A solution of borane-Me_2S (40 μL of 2.0 M solution in THF, 0.077 mmol, 1 equiv) was added dropwise. The reaction mixture was stirred at 0 ^{o}C for 40 min and quenched by the slow addition of water (5 mL). The reaction mixture was extracted with EtOAc (3 x 2 mL), and the combined organic extract was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by preparative thin-layer chromatography on silica gel in 5% MeOH- DCM to obtain **54f** (11 mg, 54%): TLC R_f = 0.51 (60% EtOAc-hexanes); mp 140-141 ^{o}C; $[\alpha]^{25}_D$ = -5.9^o (*c* 0.540, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.12 (s, 1H), 4.75 (d, *J* = 5.4 Hz, 1H), 4.24 (s, 3H), 2.87-2.85 (m, 1H), 2.67-2.65 (m, 1H), 2.43-2.40 (m, 1H), 2.22 (s, 3H), 1.78-1.74 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.26, 154.27, 143.57, 139.66, 132.20, 131.09, 115.85, 82.37, 42.21, 32.82, 32.71, 13.46; HRMS (m/z): [M + Na]$^+$ calcd for $C_{12}H_{14}N_4OS$, 285.0786; found, 285.0776.

(*3S,6R,7S*)-((*S*)-2-Methyl-3-(2-methylthiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (27a).

A mixture of (*3S,6R,7S*)-3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoic acid **43** (20 mg, 0.077 mmol, 1equiv), (*S*)-2-methyl-3-(2-methylthiazol-4-yl)cyclopent-2-enol **54a** (15 mg, 0.077 mmol, 1 equiv), DCC (20 mg, 0.100 mmol, 1.3 equiv), DMAP (1 mg, 0.008 mmol, 10 mol%), and CSA (4 mg, 0.015 mmol, 20 mol%) in anhydrous DCM (300 μL) was stirred under nitrogen overnight. The reaction mixture was filtered through a cotton

wool plug and purified by preparative thin-layer chromatography on silica gel plates (deactivated with 5% Et_3N in hexanes) in 25% EtOAc-hexanes to obtain **27a** (5 mg, 23%): TLC R_f = 0.44 (40% EtOAc-hexanes); $[\alpha]^{25}_D$= +5.3° (*c* 0.300, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (s, 1H), 5.79 (s, 1H), 4.25-4.22 (m, 1H), 3.36-3.23 (m, 4H), 2.89-2.84 (m, 1H), 2.70 (s, 3H), 2.66 (m, 1H), 2.51-2.34 (m, 3H), 2.08 (s, 3H), 1.86-1.78 (m, 1H), 1.71-1.60 (m, 1H), 1.16 (s, 6H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 222.37, 173.29, 165.15, 152.50, 134.67, 134.12, 116.09, 85.53, 76.64, 72.78, 72.71, 52.40, 41.04, 37.10, 33.55, 30.79, 29.53, 21.69, 19.75, 19.61, 19.33, 19.28, 19.23, 13.69, 10.64; HRMS (m/z): $[M + Na]^+$ calcd for $C_{23}H_{35}NO_5S$, 460.2134; found 460.2144.

(*3S,6S,7R*)-((*S*)-2-Methyl-3-(2-methylthiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (28a).

A mixture of (*3S,6S,7R*)-3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoic acid **44** (34 mg, 0.128 mmol, 1 equiv), (*S*)-2-methyl-3-(2-methylthiazol-4-yl)cyclopent-2-enol **54a** (25 mg, 0.128 mmol, 1 equiv), DCC (36 mg, 0.166 mmol, 1.3 equiv), and DMAP (15 mg, 0.128 mmol, 1 equiv) was placed in a round bottomed flask under nitrogen. Anhydrous DCM (300 μL) and anhydrous Et_3N (18 μL, 0.128 mmol, 1 equiv) were added and the reaction mixture was stirred at room temperature overnight. The crude product was passed through a cotton wool plug with DCM before being purified by successive preparative thin-layer chromatography on silica gel plates (deactivated with 5% Et_3N-hexanes) in 40% EtOAc-hexanes, 30% EtOAc-hexanes, and 85% EtOAc-hexanes to obtain the product **28a** (7 mg, 9%): $[\alpha]^{25}_D$ = -13.1° (*c* 0.350, $CHCl_3$); TLC R_f = 0.54 (40 % EtOAc-hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (s, 1H), 5.79 (s, 1H), 4.26 (m, 1H), 3.28 (m, 4H), 2.88 (m, 1H), 2.70 (s, 3H), 2.66 (m, 1H), 2.45 (m, 3H), 2.08 (d, *J* = 6.0 Hz, 3H), 1.83 (m, 1H), 1.65 (m, 1H), 1.18 (s, 3H), 1.13 (s, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 222.34, 173.39, 173.32, 165.15, 152.47, 134.67, 134.14, 134.10, 116.06, 85.52, 76.60, 72.64, 72.55, 52.21, 41.22, 36.88, 36.84, 33.51, 30.79, 29.49, 21.49, 19.75, 19.56, 19.18,

19.12, 19.08, 13.66, 13.61, 10.39; HRMS (m/z): $[M + H]^+$ calcd for $C_{23}H_{35}NO_5S$, 438.2314; found, 438.2306.

(*3S,6R,7S*)-((*S*)-2-Methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (27b).

A mixture of (*3S,6R,7S*)-3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoic acid **43** (66 mg, 0.253 mmol, 1 equiv), (*S*)-2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enol **54b** (78 mg, 0.343 mmol, 1.4 equiv), DCC (75 mg, 0.328 mmol, 1.3 equiv), DMAP (32 mg, 0.253 mmol, 1 equiv) was placed under nitrogen. Anhydrous Et_3N (64 μL, 0.506 mmol, 2 equiv) and anhydrous DCM (300 μL) were added and the reaction mixture was stirred overnight. The reaction mixture was filtered through a cotton wool plug and purified by successive preparative thin-layer chromatography on silica gel (deactivated with 5% Et_3N-hexanes) in 40% EtOAc-hexanes, 90% EtOAc-hexanes, 85% EtOAc-hexanes to obtain **27b** (12 mg, 10%): TLC R_f = 0.56 (40% EtOAc-hexanes); $[\alpha]^{25}_D$= -4.6° (*c* 0.600, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (s, 1H), 5.80 (t, *J* = 3.2 Hz, 1H), 4.26-4.22 (m, 1H), 3.35-3.22 (m, 4H), 2.87-2.80 (m, 1H), 2.69 (s, 3H), 2.67-2.62 (m, 1H), 2.51-2.35 (m, 3H), 2.12 (s, 3H), 1.86-1.78 (m, 1H), 1.69-1.64 (m, 1H), 1.16 (s, 6H), 1.04 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 222.38, 173.24, 165.59, 152.76, 134.73, 133.90, 85.46, 76.62, 72.75, 72.62, 52.36, 41.02, 37.08, 37.05, 33.14, 30.74, 29.47, 21.67, 21.65, 19.68, 19.29, 19.24, 19.19, 16.73, 13.72, 13.70, 10.60; HRMS (m/z): $[M + Na]^+$ calcd for $C_{23}H_{35}NO_5S_2$, 492.1854; found, 492.1858.

(3S,6S,7R)-((*S*)-2-Methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (28b).

A mixture of (*3S,6S,7R*)-3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoic acid **44** (71 mg, 0.273 mmol, 1.2 equiv), (*S*)-2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enol

54b (52 mg, 0.229 mmol, 1 equiv), DCC (61 mg, 0.300 mmol, 1.3 equiv), and DMAP (28 mg, 0.229 mmol, 1 equiv) was placed in a round bottom flask under nitrogen. Anhydrous DCM (400 μL) and anhydrous Et_3N (43 μL, 0.318 mmol, 1.4 equiv) were added, and the reaction mixture was stirred overnight. The product was passed through a cotton plug with DCM before being purified by successive preparative thin-layer chromatography on silica gel plates (deactivated with 5% Et_3N-hexanes) in 20% EtOAc-hexanes, 30% EtOAc-hexanes, 85% EtOAc-hexanes to obtain the product **28b** (8 mg, 6%): TLC R_f = 0.56 (40% EtOAc-hexanes); $[\alpha]^{25}_D$ = -13.8° (*c* 0.400, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (s, 1H), 5.79 (s, 1H), 4.25 (m, 1H), 3.26 (m, 4H), 2.86 (m, 1H), 2.70 (s, 3H), 2.68 (m, 1H), 2.42 (m, 3H), 2.12 (s, 3H), 1.84 (m, 1H), 1.66 (m, 1H), 1.18 (s, 3H), 1.13 (s, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 222.35, 173.29, 152.76, 134.66, 133.92, 115.66, 85.50, 76.60, 72.64, 72.55, 52.24, 36.90, 36.90, 36.85, 33.15, 30.79, 29.48, 21.48, 19.74, 19.18, 19.14, 19.10, 16.74, 13.75, 13.70, 10.40; HRMS (m/z): $[M + Na]^+$ calcd for $C_{23}H_{35}NO_5S_2$, 492.1854; found, 492.1862.

(*3S,6R,7S*)-((*R*)-2-Methyl-3-(2-(piperidin-1-yl)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate and (*3S,6R,7S*)-((*S*)-2-methyl-3-(2-(piperidin-1-yl)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (27c).

A mixture of (*3S,6R,7S*)-3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoic acid **43** (44 mg, 0.170 mmol, 1 equiv), 2-methyl-3-(2-(piperidin-1-yl)thiazol-4-yl)cyclopent-2-enol **54c** (45 mg, 0.170 mmol, 1 equiv), DCC (46 mg, 0.221 mmol, 1.3 equiv), DMAP (21 mg, 0.170, 1 equiv), was placed under nitrogen. Anhydrous Et_3N (47 μL, 0.340 mmol, 2 equiv) followed by anhydrous DCM (400 μL) were added and the reaction mixture was stirred overnight. The reaction mixture was filtered through a cotton wool plug and purified by successive preparative thin-layer chromatography on silica gel (deactivated with 5% Et_3N-hexanes) in 30% EtOAc-hexanes, 50% EtOAc-hexanes to obtain a diasteromeric mixture **27c** (3 mg, 4%): TLC (20% EtOAc-hexanes); ^{1}H NMR (400 MHz,

$CDCl_3$): δ 6.39 (s, 1H), 5.77 (s, 1H), 4.21 (d, *J* = 10.2 Hz, 1H), 3.44 (m, 4H), 3.34-3.28 (m, 4H), 2.78 (m, 1H), 2.59 (m,1H), 2.50-2.36 (m, 3H), 2.13 (s, 3H), 1.82-1.79 (m, 1H), 1.63 (m, 6H), 1.15 (s, 6H), 1.04 (d, *J* = 8.0 Hz, 3H), 1.00 (d, *J* = 8.0 Hz, 3H), 0.85 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 222.31, 173.35, 173.32, 170.90, 149.47, 134.77, 134.72, 133.34, 133.28, 105.46, 105.42, 85.82, 76.60, 72.73, 72.66, 52.38, 52.34, 49.71, 40.10, 37.10, 37.02, 32.82, 30.74, 29.44, 25.388, 25.35, 24.42, 21.68, 21.64, 19.72, 19.22, 19.18, 13.66, 13.64, 10.61; HRMS (m/z): $[M + Na]^+$ calcd for $C_{27}H_{42}N_2O_5S$, 529.2712; found, 529.2729.

(*3S,6S,7R*)-((*R*)-2-Methyl-3-(2-(piperidin-1-yl)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate and (*3S,6S,7R*)-((*S*)-2-methyl-3-(2-(piperidin-1-yl)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (28c).

A mixture of (*3S,6S,7R*)-3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoic acid **44** (44 mg, 0.170 mmol, 1 equiv), 2-methyl-3-(2-(piperidin-1-yl)thiazol-4-yl)cyclopent-2-enol **54c** (45 mg, 0.170 mmol, 1 equiv.), DCC (48 mg, 0.221 mmol, 1.3 equiv), and DMAP (21 mg, 0.170, 1 equiv) was placed in a round bottomed flask under nitrogen. Anhydrous DCM (400 μL) and anhydrous Et_3N (47 μL, 0.340 mmol, 2 equiv) were added and the reaction mixture was stirred overnight. The product was passed through a cotton plug with DCM before being purified by successive preparative thin-layer chromatography on silica gel plates (deactivated with 5% Et_3N-hexanes) in 50% EtOAc-hexanes, 40% EtOAc-hexanes to obtain a mixture of diasteromeric products **28c** (4 mg, 5%): TLC (20% EtOAc-hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.39 (s, 1H), 5.77 (d, *J* = 10.4 Hz, 1H), 4.26 (d, *J* = 10.4, 1H), 3.43 (m, 4H), 3.28 (m, 4H), 2.78 (m, 1H), 2.56 (m, 1H), 2.41 (m, 3H), 2.13 (s, 3H), 1.80 (m, 1H), 1.70 (m, 6H), 1.15 (s, 3H), 1.09 (s, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 222.30, 173.44, 173.37, 170.91, 149.48, 134.81, 134.75, 133.32, 133.29, 105.46, 85.86, 79.61, 72.64, 72.55, 52.24, 49.72, 41.21, 36.88, 36.83, 32.83, 30.79, 29.46, 25.40, 25.36,

24.43, 21.51, 19.77, 19.18, 19.06, 19.03, 13.68, 13.63, 10.38; HRMS (m/z): $[M + Na]^+$ calcd for $C_{27}H_{42}N_2O_5S$, 529.2712; found, 529.2731.

(*3S,6R,7S*)-((*S*)-2-Methyl-3-(2-(phenylethynyl)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (27d).

A mixture of (*3S,6R,7S*)-3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoic acid **43** (52 mg, 0.199 mmol, 1equiv), (*S*)-2-methyl-3-(2-(phenylethynyl)thiazol-4-yl)cyclopent-2-enol **54d** (55 mg, 0.199 mmol, 1 equiv), DCC (53 mg, 0.259 mmol, 1.3 equiv), DMAP (25 mg, 0.199 mmol, 1 equiv), was placed under nitrogen. Anhydrous Et_3N (55 μL, 0.398 mmol, 2 equiv) and anhydrous DCM (400 μL) were added and the reaction mixture was stirred overnight. The reaction mixture was filtered through a cotton wool plug and purified by successive preparative thin-layer chromatography on silica gel (deactivated with 5% Et_3N-hexanes) in 40% EtOAc-hexanes, 5% EtOAc-hexanes, 25% EtOAc-hexanes to obtain **27d** (10 mg, 10%): TLC R_f = 0.45 (40% EtOAc-hexanes); $[\alpha]^{25}_D$ = -13.5° (*c* 0.275, $CHCl_3$); IR $\bar{\nu}_{max}$: 3500, 3200, 2900 , 2100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (dd, *J* = 7.6, 5.6 Hz, 2H), 7.39-7.33 (m, 3H), 7.19 (s, 3H), 5.82 (s, 1H), 4.27-4.22 (m, 2H), 3.35-3.22 (m, 4H), 2.93-2.89 (m, 1H), 2.79-2.71 (m, 1H), 2.52-2.36 (m, 3H), 2.10 (s, 3H), 1.89-1.82 (m, 1H), 1.70-1.64 (m, 1H), 1.16 (s, 6H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 222.34, 173.20, 153.50, 147.97, 135.49, 134.06, 132.20, 129.76, 128.70, 121.59, 118.06, 94.12, 85.30, 82.68, 76.62, 72.76, 72.69, 52.37, 41.03, 37.07, 33.61, 30.76, 29.49, 21.68, 19.70, 19.32, 19.27, 19.21, 13.79, 10.62; HRMS (m/z): $[M + Na]^+$ calcd for $C_{30}H_{37}NO_5S$, 546.2290; found 546.2285.

(*3S,6S,7R*)-((*S*)-2-Methyl-3-(2-(phenylethynyl)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (28d).

A mixture of (*3S,6S,7R*)-3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoic acid **44** (62 mg, 0.223 mmol, 1equiv), (*S*)-2-methyl-3-(2-(phenylethynyl)thiazol-4-yl)cyclopent-2-enol **54d** (63 mg, 0.223 mmol, 1 equiv), DCC (59 mg, 0.289 mmol, 1.3 equiv), DMAP (3 mg, 0.022 mmol, 10 mol%), and CSA (10 mg, 0.045 mmol, 20 mol%) was placed in a round bottomed flask under nitrogen. Anhydrous DCM (400 μL) was added and the reaction mixture was stirred overnight. The product was passed through a cotton wool plug with DCM before being purified by successive preparative thin-layer chromatography on silica gel plates (deactivated with Et_3N-hexanes) in 25% EtOAc-hexanes, 5% EtOAc-benzene, 50% EtOAc-hexanes to obtain **28d** (6 mg, 4%): TLC R_f = 0.52 (40 % EtOAc-hexanes); $[\alpha]^{25}_D$ = -13.5° (*c* 0.275, $CHCl_3$); IR $\bar{\nu}_{max}$ 3500, 3000, 2000, 1600; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (dd, *J* = 12.4, 4.4 Hz, 2H), 7.39 (m, 3H), 7.20 (s, 1H), 5.82 (s, 1H), 4.25 (m, 1H), 3.35 (m, 3H), 2.95 (m, 1H), 2.75 (m, 1H), 2.47 (m, 3H), 2.11 (d, *J* = 5.6 Hz, 3H), 1.84 (m, 1H), 1.69 (m, 1H), 1.19 (s, 3H), 1.14 (s, 3H), 1.05 (d, *J* = 6.4 Hz, 3H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.86 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 222.35, 173.27, 153.51, 147.99, 135.50, 134.11, 132.22, 129.78, 128.71, 121.60, 118.07, 94.14, 85.34, 82.68, 76.61, 72.65, 72.56, 52.23, 41.23, 36.89, 36.84, 33.60, 30.79, 29.49, 21.50, 19.75, 19.19, 19.14, 19.09, 13.79, 13.75, 10.40; HRMS (m/z): $[M + Na]^+$ calcd for $C_{30}H_{37}NO_5S$, 546.2290; found, 546.2302.

(*3S,6R,7S*)-((*S*)-3-(2-Ethynylthiazol-4-yl)-2-methylcyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (27e).

A mixture of (*3S,6R,7S*)-3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoic acid **43** (38 mg, 0.146 mmol, 1 equiv), (*S*)-3-(2-ethynylthiazol-4-yl)-2-methylcyclopent-2-enol **54e** (30 mg, 0.146 mmol, 1 equiv), DCC (39 mg, 0.190 mmol, 1.3 equiv), DMAP (4 mg, 0.029 mmol, 20 mol%), and CSA (2 mg, 0.007 mmol, 5 mol%) was placed under nitrogen. Anhydrous DCM (300 μL) was added and the reaction mixture was stirred

overnight. The reaction mixture was filtered through a cotton wool plug and purified by successive preparative thin-layer chromatography on silica gel (deactivated with 5% Et_3N-hexanes) in 10% Acetronitrile-DCM, 50% DCM-hexanes, 10% acetone-hexanes to obtain **27e** (10 mg, 15%): TLC R_f = 0.69 (50% acetone-hexanes); $[\alpha]^{25}_D$ = -6.3° (*c* 0.600, $CHCl_3$); IR $\bar{\nu}_{max}$: 3300, 3050, 2900, 2100, 1750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.17 (s, 1H), 5.81 (s, 1H), 4.25-4.22 (m, 1H), 3.45 (s, 1H), 3.35-3.20 (m, 4H), 2.92-2.89 (m, 1H), 2.78-2.70 (m, 1H), 2.51-2.35 (m, 3H), 2.15 (s, 3H), 1.85-1.82 (m, 1H), 1.70-1.57 (m, 1H), 1.16 (s, 6H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 222.37, 173.18, 153.48, 146.71, 135.78, 133.71, 118.20, 85.24, 82.31, 76.80, 76.62, 72.75, 72.68, 52.36, 41.03, 37.06, 33.51, 30.75, 29.46, 21.67, 19.70, 19.27, 19.20, 13.75, 10.61; HRMS (m/z): $[M + Na]^+$ calcd for $C_{24}H_{33}NO_5S$, 470.1977; found 470.1957.

(*3S,6S,7R*)-((*R*)-3-(2-ethynylthiazol-4-yl)-2-methylcyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate and (*3S,6S,7R*)-((*S*)-3-(2-ethynylthiazol-4-yl)-2-methylcyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (28e).

A mixture of (*3S,6S,7R*)-3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoic acid **44** (70 mg, 0.269 mmol, 1 equiv), (*S*)-3-(2-ethynylthiazol-4-yl)-2-methylcyclopent-2-enol **54e** (55 mg, 0.269 mmol, 1 equiv), DCC (73 mg, 0.349 mmol, 1.3 equiv), DMAP (3 mg, 0.027 mmol, 10 mol%), and CSA (13 mg, 0.054 mmol, 20 mol%) was placed in a roundbottomed flask under nitrogen. Anhydrous DCM (400 μL) was added and the reaction mixture was stirred overnight. The reaction mixture was passed through a cotton wool plug with DCM before being purified by successive preparative thin-layer chromatography on silica gel plates (deactivated with Et_3N-hexanes) in 10% acetone-hexanes, 5% acetone-benzene, 25% EtOAc-hexanes to obtain **28e** (10 mg, 9%) as a mixture of diastereomers: TLC R_f = 0.58 (40% EtOAc-hexanes); $CHCl_3$); IR $\bar{\nu}_{max}$ 3300, 3100, 3000, 2000, 1750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.17 (s, 1H), 5.81 (s, 1H), 4.24 (m, 1H), 3.45 (s, 3H), 3.26 (m, 3H), 2.92 (m, 1H), 2.72 (m, 1H), 2.35 (m, 3H), 2.14 (d, *J* = 21.2 Hz, 3H), 1.98 (m, 1H), 1.66 (m, 1H), 1.18 (s, 3H), 1.13 (s, 3H), 1.06 (d, *J* =

6.8 Hz, 3H), 1.00 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 222.36, 173.32, 173.25, 153.52, 153.49, 146.74, 135.84, 135.81, 133.77, 133.74, 118.22, 85.29, 85.27, 82.33, 76.82, 76.62, 72.66, 72.57, 52.25, 52.22, 41.25, 36.90, 36.86, 34.19, 33.53, 30.81, 29.47, 21.51, 19.76, 19.20, 19.18, 19.12, 13.78, 13.73, 10.43.

(*3S,6R,7S*)-((*S*)-2-Methyl-3-(2-(1-methyl-1H-1,2,3-triazol-4-yl)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (27f).

A mixture of (*3S,6R,7S*)-3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoic acid **43** (55 mg, 0.201 mmol, 1 equiv), (*S*)-2-methyl-3-(2-(1-methyl-1H-1,2,3-triazol-4-yl)thiazol-4-yl)cyclopent-2-enol **54f** (52 mg, 0.201 mmol, 1 equiv), DCC (54 mg, 0.261 mmol, 1.3 equiv), DMAP (5 mg, 0.040 mmol, 20 mol%), and CSA (2 mg, 0.010 mmol, 5 mol%) in anhydrous DCM (400 μL) was stirred under nitrogen overnight. The reaction mixture was filtered through a cotton wool plug and purified by successive preparative thin-layer chromatography on silica gel (deactivated with 5% Et_3N-hexanes) in 40% EtOAc-hexanes, 35% acetone-hexanes to obtain **27f** (21 mg, 20%): TLC R_f = 0.44 (40 % EtOAc-hexanes); $[\alpha]^{25}_D$ = -4.5^o (*c* 1.17, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.16 (s, 1H), 5.82 (d, J = 2.4Hz, 1H), 4.26 (d, J = 2.4 Hz, 1H), 4.18 (s, 3H), 3.35-3.23 (m, 4H), 2.94-2.88 (m, 1H), 2.75-2.71 (m, 1H), 2.52-2.34 (m, 3H), 2.15 (s, 3H), 1.89-1.81 (m, 1H), 1.71-1.60 (m, 1H), 1.16 (s, 1H), 1.04 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 222.35, 173.22, 157.40, 153.59, 143.46, 135.08, 134.04, 132.19, 116.60, 85.40, 76.60, 72.74, 72.66, 52.36, 42.23, 41.01, 37.07, 33.43, 30.74, 29.50, 21.66, 19.69, 19.30, 19.25, 19.17, 13.74, 13.71, 10.61; HRMS (m/z): $[M + Na]^+$ calcd for $C_{25}H_{36}N_4O_5S$, 527.2304; found, 527.2308.

4-(*tert*-Butyldimethylsilyloxy)butan-1-ol (62).[62]

A solution of imidazole (5.132 g, 70.9 mmol, 88 mol%) and 1,4-butanediol **61** (22.130 g, 245.4 mmol, 3 equiv) in anhydrous THF (100 mL) was cooled to 0 ^{o}C before TBSCl

(12.126 g, 80.5 mmol, 1 equiv) in anhydrous THF (25 mL) was added dropwise. The reaction mixture was stirred at 0 ^{o}C for 1 h before being allowed to warm to room temperature. Ether (300 ml) was added followed by water (300 mL) and the crude reaction mixture was extracted with EtOAc (3 x 100 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Product **61** (16.347 g, 99%) was obtained as a colorless oil and used without further purification: TLC R_f = 0.47 (20% EtOAc-hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65-3.59 (m, 4H), 1.65-1.59 (m, 4H), 0.88 (m, 9H), 0.06-0.01 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 63.57, 62.98, 30.48, 30.12, 26.18, 26.11, -5.18.

4-(*tert*-Butyldimethylsilyloxy)butanoic acid (63).[62]

PCC (25.782 g, 0.118 mol, 2 equiv) was added to a solution of 4-(tert-butyldimethylsilyloxy)butan-1-ol **62** (12.224 g, 0.059 mol, 1 equiv) in DCM (350 mL). The reaction mixture was stirred at room temperature for 3 h and the solvent was removed in vacuo. The reaction mixture was partially purified on a silica gel plug in 30% EtOAc-hexanes to obtain the product (15.664 g) which was used immediately in the next step: ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.76 (s, 1H), 3.62 (t, J = 6.0 Hz, 2H), 2.49-2.46 (m, 2H), 1.85-1.81 (m, 2H), 0.88-0.85 (m, 9H), 0.07-0.01 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.95, 62.29, 41.01, 26.11, 25.87, 25.69, -3.35, -5.19.

The aldehyde (15.664 g, 0.077 mol, 1 equiv), prepared above, was dissolved in *t*-butanol (400 mL) and 2-methyl-2-butene (40 mL). A solution of $NaClO_2$ (64.178 g, 0.708 mol, 9.2 equiv) and $Na_2H_2PO_4$ (64.718 g, 0.531 mol, 6.9 equiv) in water (187 mL) was added slowly. The reaction mixture was stirred for 1 h at room temperature and poured into saturated aqueous ammonium chloride (250 mL). The reaction mixture was extracted with EtOAc (3 x 100 mL) and washed with 2 M NaOH. The aqueous layer was washed with 2 M HCl and extracted with EtOAc. The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to obtain carboxylic acid

63 (6.662 g, 51%): TLC R_f = 0.46 (33% EtOAc-hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.66 (t, *J* = 6.0 Hz, 2H), 2.43 (t, *J* = 7.2 Hz, 2H), 1.84-1.80 (m, 2H), 0.87 (d, *J* = 3.2 Hz, 9H), 0.03 (d, *J* = 3.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.64, 62.31, 31.07, 27.74, 26.10, 18.51, -5.21.

(*S*)-Methyl 4-(4-isopropyl-2-oxooxazolidin-3-yl)-4-oxobutanoate (75).

A solution of Evan's auxillary **65** (82 mg, 0.664 mmol, 1 equiv) in anhydrous THF (2 mL) under nitrogen was cooled to -78 ^{o}C. *n*-BuLi (320 μL, 2.5 M in hexanes, 0.796 mmol, 1.2 equiv) was added dropwise. After the reaction mixture was stirred at -78 ^{o}C for 30 min, methyl 4-chloro-4-oxobutanoate **74** (82 mL, 0.664 mmol, 1 equiv) was added in anhydrous THF (2 mL). The reaction mixture was stirred for an additional 1 h at -78 ^{o}C, and slowly allowed to warm to room temperature. It was poured into saturated aqueous ammonium chloride (5 mL) and extracted with EtOAc (3 x 2 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The product was purified by flash column chromatography on silica gel in 2% MeOH-DCM to obtain the partially purified product **75** (198 mg): ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.41-4.37 (m, 1H), 4.35-4.19 (m, 1H), 3.62 (s, 2H), 3.22-3.20 (m, 1H), 2.62-2.59 (m, 2H), 2.37-2.30 (m, 1H), 0.86-0.81 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.07, 172.00, 154.33, 63.81, 58.66, 52.04, 31.00, 29.05, 28.57, 28.34, 18.11, 18.85.

4-(Benzyloxy)butan-1-ol (77).

A solution of 1,4-butandiol **61** (5.044 g, 0.055 mol, 1 equiv) in anhydrous THF (10 mL) was added dropwise to a cooled solution of NaH (2.214 g, 60% dispersion in oil, 0.055 mol, 1 equiv) in anhydrous THF (10 mL) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1h and benzyl bromide (6.5 mL, 0.054 mol, 0.99 equiv) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 48 h. The reaction mixture was poured into saturated aqueous ammonium chloride (50 mL) and

extracted with EtOAc (3 x 20 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The reaction mixture was purified by flash chromatography on silica gel in EtOAc-hexanes to obtain **77** (7.335 g, 73%): TLC R_f = 0.48 (50% EtOAc-hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.16 (m, 5H), 4.42 (s, 2H), 3.56 (t, *J* = 6.0 Hz, 2H), 3.44 (t, *J* = 5.6 Hz, 2H), 1.64-1.57 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.97, 128.30, 127.61, 127.56, 72.96, 70.22, 62.62, 30.07, 26.62.

4-(Benzyloxy)-1-iodobutane (85).

A solution of triphenylphosphine (175 mg, 0.667 mmol, 1.2 equiv) and iodine (172 mg, 0.667 mmol 1.2 equiv) in DCM (3 mL) was stirred for 1 h at room temperature. Imidazole (45 mg, 0.667 mmol, 1.2 equiv) was added followed by a solution of 4-(benzyloxy)-1-butan-1-ol **77** (101 mg, 0.555 mmol, 1 equiv) in DCM (1 mL). The reaction mixture was stirred overnight at room temperature. The product was purified on a silica gel plug in 100% DCM to obtain product **86** (144 mg, 90%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.25 (m, 5H), 4.48 (s, 2H), 3.49 (t, *J* = 6.8 Hz, 2H), 3.21 (t, *J* = 6.8 Hz, 2H), 1.94-1.89 (m, 2H), 1.73-1.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.57, 128.60, 127.82, 73.15, 69.22, 30.83, 30.60, 7.16.

4-(*tert*-Butyldimethylsilyloxy)-1-iodobutane (86).

A solution of triphenylphosphine (156 mg, 0.587 mmol, 1.2 equiv) and iodine (150 mg, 0.587 mmol, 1.2 equiv) in DCM (3 mL) was stirred for 1 h at room temperature. Imidazole (40 mg, 0.587 mmol, 1.2 equiv) was added followed by a solution of 4-(*tert*-butyldimethylsilyloxy)butan-1-ol **62** (100 mg, 0.489 mmol, 1 equiv) in DCM (1 mL). The reaction mixture was stirred overnight at room temperature. The reaction mixture was purified on a silica plug in 100% DCM to obtain **85** (116 mg, 75%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.63 (t, *J* = 6.4 Hz, 2H), 3.20 (t, *J* =7.2 Hz, 2H), 1.90 (m, 2H), 1.59 (m,

2H), 0.88 (m, 9H), 0.02 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 62.16, 33.74, 30.40, 26.16, 7.42, -5.09.

4-Phenylbutanoic acid (87).[68b]

γ–Butyrolactone **73** (1.78 mL, 2.29 mmol, 1 equiv) was added dropwise to a solution of $AlCl_3$ (4.583 g, 34.3 mmol, 1.5 equiv) in benzene (20 mL). The reaction mixture was heated to 55 ^{o}C and stirred overnight. The HCl gas was vented through a funnel immersed in water. The reaction mixture was cooled to room temperature and quenched with water (20 mL). The crude reaction mixture was extracted with EtOAc (3 x 10 mL) and the combined organic extract was washed with 2 M NaOH (2 x 30 mL). The aqueous extract was washed with 2 M HCl (2 x 30 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to obtain **87** (2.597 g, 68%): TLC R_f = 0.45 (33% EtOAc-hexanes); mp 42-43 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.25 (m, 2H), 7.19-7.15 (m, 3H), 2.66 (t, *J* = 7.6 Hz, 2H), 2.36 (t, *J* = 7.6 Hz, 2H), 1.99-1.91 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.38, 128.69, 126.26, 35.20, 33.40, 26.42.

4–Phenylbutanoyl chloride (83c).[68b]

Oxalyl chloride (17 mL, 34.0 mmol, 1.1 equiv) was added dropwise to a stirred solution of 4-phenylbutanoic acid **87** (5.016 g, 31.0 mmol, 1 equiv) in benzene (32 mL). The reaction mixture was stirred at room temperature for 48 h. The reaction mixture was concentrated in vacuo to obtain **83c** (4.934 g), which was immediately taken to the next step: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.27 (m, 2H), 7.22-7.14 (m, 3H), 2.87 (t, *J* = 7.2 Hz, 2H), 2.66 (t, *J* = 7.2 Hz, 2H), 2.05-1.98 (m, 2H).

(*S*)-4-Isopropyl-3-(4-phenylbutanoyl)oxazolidin-2-one (84c).[68b]

A solution of Evan's auxillary **65** (2.394 g, 0.018 mol, 1 equiv) in anhydrous THF (20 mL) was cooled to -78 ^{o}C and *n*-BuLi (7.2 mL, 2.5 M solution in hexanes, 0.018 mol, 1 equiv) was added dropwise. The reaction mixture was stirred at -78 ^{o}C for 30 min and acid chloride **83c** (3.7187 g, 0.020 mol, 1.1 equiv) in anhydrous THF (10 mL) was added slowly. After the reaction mixture was stirred at -78 ^{o}C for 30 min, it was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with aqueous sodium bicarbonate (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The product was purified by flash chromatography on silica gel in 15% EtOAc-hexanes to obtain **84c** (4.330 g, 84%): TLC R_f = 0.40 (20% EtOAc-hexanes); $[\alpha]^{25}_{D}$ = 59.4^{o} (*c* 5.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.24 (m, 2H), 7.23-7.14 (m, 3H), 4.40-4.36 (m, 1H), 4.23-4.14 (m, 2H), 3.01-2.87 (m, 2H), 2.69 (t, *J* = 8.0 Hz, 2H), 2.36-2.31 (m, 1H), 2.02-1.95 (m, 2H), 0.89 (d, *J* = 7.2 Hz, 3H), 0.85 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.05, 154.15, 141.66, 128.61, 128.48, 126.06, 63.44, 58.47, 35.28, 35.11, 28.48, 26.18, 18.10, 14.78.

(*S*)-4-Isopropyl-3-((*S*)-2-methyl-4-phenylbutanoyl)oxazolidin-2-one (70c).[68b]

Sodium bis(trimethylsilyl)amide (6 mL, 5.91 mmol, 1.2 equiv) was added dropwise to a solution of (*S*)-4-isopropyl-3-(4-phenylbutanoyl)oxazolidin-2-one **84c** (1.356 g, 4.93 mmol, 1 equiv) in anhydrous THF (16 mL) at -78 ^{o}C. After the reaction mixture was stirred at -78 ^{o}C for 30 min, methyl iodide (1.20 mL, 19.7 mmol, 4 equiv) in anhydrous THF (3 mL) was added dropwise. The reaction mixture was stirred for 8 h at -78 ^{o}C. It was allowed to warm to room temperature and stirred overnight. The reaction mixture was poured in saturated aqueous ammonium chloride (20 mL) and extracted with EtOAc (3 x 8 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The product was purified by flash chromatography on silica gel in 20% EtOAc-hexanes to obtain **70c** (1.235 g, 87%): TLC R_f = 0.45 (20% EtOAc-hexanes); $[\alpha]^{25}_{D}$ =71.1^{o} (*c* 5.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-

7.24 (m, 2H), 7.17-7.14 (m, 3H), 4.35-4.31 (m, 1H), 4.21-4.13 (m, 2H), 3.80-3.75 (m, 1H), 2.62-2.57 (m, 2H), 2.33-2.28 (m, 1H), 2.13-2.04 (m, 1H), 1.72-1.63 (m, 1H), 1.23 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 7.2 Hz, 3H), 0.85 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.85, 153.68, 141.87, 128.56, 128.40, 125.97, 63.28, 58.46, 37.68, 34.91, 33.92, 28.51, 18.31, 18.04, 14.79.

(*S*)-2-Methyl-4-phenylbutan-1-ol (71c).

A solution of **70c** (111 mg, 0.384 mmol, 1 equiv) in a 3:1 mixture of THF and distilled H_2O (2 mL) was cooled to 0 ^{o}C. Aqueous 30% hydrogen peroxide (50 μL, 1.61 mmol, 4.2 equiv) and lithium hydroxide (32 mg, 0.767 mmol, 2 equiv) in water (400 μL) was added slowly. After the reaction mixture was stirred at 0 ^{o}C for 1 h, a solution of sodium sulfite (1.2 mL, 1.5 M solution in water, 1.73 mmol, 4.5 equiv) was added. The reaction mixture was concentrated in vacuo, and the aqueous layer was washed with DCM (3 x 1 mL) to recover **65**. The aqueous layer was acidified to pH 1~2 using 1 M HCl and extracted with ether (3 x 3 mL). The combined organic extract was combined, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to obtain the carboxylic acid product (60 mg), which was immediately used in the next step: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.24 (m, 2H), 7.18-7.15 (m, 3H), 2.66 (t, J = 7.2 Hz, 2H), 2.52-2.47 (m, 1H), 2.07-1.98 (m, 1H), 1.77-1.68 (m, 1H), 1.22 (d, J = 6.8 Hz, 3H).

A solution of carboxylic acid (60 mg, 0.337 mmol, 1 equiv) in anhydrous ether (1 mL) was cooled to -78 ^{o}C and $LiAlH_4$ (200 μL, 0.404 mmol, 1.2 equiv) was added slowly. After the reaction mixture was stirred at -78 ^{o}C for 30 min, it was warmed to 0 ^{o}C and stirred for 1.5 h. Water (30 μL) was added dropwise followed by 15% NaOH (30 μL) and water (86 μL). After the reaction mixture was allowed to warm to room temperature, anhydrous sodium sulfate was added and the reaction mixture was allowed to stir overnight. The reaction mixture was filtered through a plug of celite and concentrated in vacuo. The product was purified by flash chromatography on silica gel in 20% EtOAc-

hexanes to obtain **71c** (44 mg, 70%): TLC R_f = 0.39 (20% EtOAc-hexanes); $[\alpha]^{25}_D$ = -18.4° (*c* 2.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.24 (m, 2H), 7.18-7.14 (m, 3H), 3.54-3.50 (m, 1H), 3.47-3.43 (m, 1H), 2.73-2.65 (m, 1H), 2.62-2.54 (m, 1H), 1.79-1.61 (m, 2H), 1.47-1.38 (m, 1H), 1.36 (s, 1H), 0.98 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.77, 128.52, 125.90, 68.37, 35.55, 35.17, 33.48, 16.70.

(*S*)-2-Methyl-4-phenylbutanal (72c).[68b]

A solution of oxalyl chloride (3.6 mL, 7.24 mmol, 1.7 equiv) in anhydrous DCM (12 mL) was cooled to -78 °C and DMSO (1.1 mL, 14.91 mmol, 3.5 equiv) was added slowly. The reaction mixture was stirred for 30 min before alcohol **71c** (699 mg, 4.26 mmol, 1 equiv) was added at -78 °C. After stirring for 30 min, triethylamine (2.7 mL, 19.17 mmol, 4.5 equiv) was added dropwise, and the reaction mixture was allowed to warm to room temperature. Water (40 mL) was added and the reaction mixture was extracted with DCM (3 x 10 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to obtain **72c** (530 mg) which was immediately used in the next step: ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.61 (d, *J* = 1.8 Hz, 1H), 7.28-7.25 (m, 2H), 7.19-7.15 (m, 3H), 2.66-2.62 (m, 2H), 2.36-2.33 (m, 1H), 2.04-2.02 (m, 1H), 1.66-1.62 (m, 2H), 1.13 (d, *J* = 7.2 Hz, 3H).

(*4S,7R,8S,9S*)-4-(*tert*-Butyldimethylsilyloxy)-8-hydroxy-5,5,7,9-tetramethyl-11-phenylundec-1-en-6-one and (*4S,7S,8R,9S*)-4-(*tert*-butyldimethylsilyloxy)-8-hydroxy-5,5,7,9-tetramethyl-11-phenylundec-1-en-6-one (89 and 89a).

n-BuLi (5.1 mL of 2.5M solution in hexanes, 12.84 mmol, 3.9 equiv) was added to a solution of DIPA (1.8 mL, 12.84 mmol, 3.9 equiv) in anhydrous THF (15 mL) at -78 °C. After the addition was complete, the reaction mixture was warmed to room temperature for 30 min. The LDA solution was cooled to -78 °C before a solution of ketone **88** (2.518 g, 8.95 mmol, 2.7 equiv) in anhydrous THF (10 mL) was added dropwise. The reaction

mixture was stirred for 1h at -78 ^{o}C and allowed to warm to -40 ^{o}C. After stirring at -40 ^{o}C for 30 min, the reaction mixture was cooled to -78 ^{o}C and aldehyde **71c** was added in a solution of THF (2 mL). The reaction mixture was stirred for 10 min and quenched with a solution of acetic acid (295 μL) in water (1 mL). The reaction mixture was allowed to warm to room temperature and saturated aqueous ammonium chloride (20 mL) was added. The reaction mixture was extracted with EtOAc (3 x 5 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The diastereomeric products were separated by flash column chromatography on silica gel in 10% ether-hexanes to obtain **89** (100 mg) and **89a** (21 mg) in an overall percent yield of 8%:

Data for (*4S,7R,8S,9S*) diastereomer **89**: TLC R_f = 0.44 (20% ether-hexanes); $[\alpha]^{25}_{D}$ = -10.2^{o} (*c* 7.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.26 (m, 2H), 7.18-7.14 (m, 3H), 5.81-5.71 (m, 1H), 5.00-4.96 (dd, *J* = 16.8, 6.4 Hz, 2H), 3.91-3.89 (m, 1H), 3.43 (d, *J* = 8.0 Hz, 1H), 3.23-3.19 (m, 2H), 2.74-2.66 (m, 1H), 2.55-2.48 (m, 1H), 2.18-2.03 (m, 2H), 1.71-1.60 (m, 1H), 1.41-1.30 (m, 2H), 1.23 (s, 3H), 1.15 (s, 3H), 1.06 (dd, *J* = 11.2, 4.8 Hz, 6H), 0.98 (d, *J* = 6.4 Hz, 3H), 0.85 (s, 9H), 0.03 (d, *J* = 10.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 222.15, 142.54, 136.53, 128.59, 128.53, 126.03, 116.91, 76.50, 75.13, 54.50, 41.81, 39.81, 35.44, 35.12, 33.26, 26.26, 23.91, 19.32, 15.72, 10.94, -3.20, -3.80.

Data for (*4S,7S,8R,9S*) diastereomer **89a**: TLC R_f = 0.47 (20% ether-hexanes); $[\alpha]^{25}_{D}$ = 11.6^{o} (*c* 5.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.24 (m, 2H), 7.18-7.15 (m, 3H), 5.78-5.71 (m, 1H), 5.00 (t, *J* = 6.4 Hz, 2H), 3.98 (t, *J* = 6.4 Hz, 1H), 3.47-3.43 (m, 2H), 3.17-3.15 (m, 1H), 2.71-2.67 (m, 1H), 2.55-2.50 (m, 1H), 2.12-2.09 (m, 2H), 1.67-1.62 (m, 1H), 1.35-1.31 (m, 1H), 1.12 (d, *J* = 8.0 Hz, 6H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.97 (d, *J* = 7.2 Hz, 3H), 0.84 (s, 9H), 0.04 (d, *J* = 14.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 222.21, 142.53, 136.43, 128.58, 128.53, 126.02, 116.90, 75.81, 75.04, 54.41, 41.61, 39.74, 35.32, 35.01, 33.26, 26.26, 23.59, 19.40, 18.45, 15.80, 10.98, -3.27, -3.89.

(*4S,7R,8S,9S*)-4,8-Bis-(*tert*-butyldimethylsiloxy)-5,5,7,9-tetramethyl-11-phenylundec-1-en-6-one (90).

A solution of (*4S,7R,8S,9S*)-4-(*tert*-butyldimethylsilyloxy)-8-hydroxy-5,5,7,9-tetramethyl-11-phenylundec-1-en-6-one **89** (132 mg, 0.295 mmol, 1 equiv) in DCM (3 mL) was cooled to 0 ^{o}C and 2,6-lutidine (86 μL, 0.739 mmol, 2.5 equiv) was added followed by TBSOT*f* (100 μL, 0.443 mmol, 1.5 equiv). After stirring for 2 h at 0 ^{o}C, the reaction mixture was quenched with saturated aqueous ammonium chloride (5 mL) and extracted with EtOAc (3 x 2 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The product was purified by flash column chromatography on silica gel in 15% DCM-hexanes to obtain **90** (248 mg, 70%): TLC R_f =0.48 (20% DCM-hexanes); $[\alpha]^{25}_{D}$ = -1.2^{o} (*c* 2.26, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.25 (m, 2H), 7.16 (d, *J* = 7.2 Hz, 3H), 5.86-5.76 (m, 1H), 4.99 (dd, *J* = 16.8, 7.2 Hz, 2H), 3.96-3.93 (m, 1H), 3.91 (d, *J* = 8.4 Hz, 1H), 3.12-3.05 (m, 1H), 2.66-2.51 (m, 2H), 2.14-2.01 (m, 2H), 1.76-1.67 (m, 1H), 1.57-1.46 (m, 1H), 1.32-1.24 (m, 1H), 1.18 (s, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.93-0.90 (m, 21H), 0.08-0.06 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 218.97, 142.60, 137.06, 128.57, 128.45, 125.79, 116.52, 76.67, 76.14, 54.20, 46.08, 39.85, 37.64, 36.74, 33.92, 26.49, 26.31, 25.09, 18.83, 18.49, 18.20, 16.35, 13.65, -2.97, -3.15, -3.30, -3.72.

(*3S,6R,7S,8S*)-3,7-Dihydroxy-4,4,6,8-tetramethyl-5-oxo-10-phenyldecanoic acid (91).

Ozone was passed through a solution of **89** (109 mg, 0.195 mmol, 1 equiv) in DCM (3 mL) at -78 ^{o}C until the reaction mixture reached a dark blue color. Nitrogen was bubbled through the solution for 15 min and triphenylphosphine (81 mg, 0.308 mmol, 1.5 equiv) was added. The reaction mixture was stirred overnight and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel in 30% DCM-hexanes to obtain the corresponding aldehyde product (189 mg, 76%): TLC R_f = 0.55 (50% DCM-hexanes); $[\alpha]^{25}_{D}$ = 4.7^{o} (*c* 0.68, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 7.27-7.25 (m, 2H), 7.16-7.13 (m, 3H), 4.43 (t, *J* = 4.8 Hz, 1H), 3.88 (d, *J* = 8.4

Hz, 1H), 3.09-3.03 (m, 1H), 2.64-2.35 (m, 4H), 1.73-1.66 (m, 1H), 1.55-1.48 (m, 1H), 1.23-1.19 (m, 4H), 1.04 (d, J = 6.8 Hz, 3H), 0.93-0.87 (m, 21H), 0.09-0.04 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 218.76, 201.44, 142.43, 128.59, 128.45, 125.83, 76.69, 71.11, 53.76, 49.82, 46.12, 37.43, 36.64, 33.76, 26.47, 26.12, 24.19, 18.82, 18.38, 18.33, 16.42, 13.58, -3.16, -3.29, -3.80, -4.24.

To a solution of the aldehyde product (189 mg, 0.335 mmol, 1 equiv) prepared above and 2-methyl-2-butene (1.6 mL) in *t*-butanol (6.9 mL) was added a solution of $NaClO_2$ (282 mg, 3.12 mmol, 9.1 equiv) and NaH_2PO_4 (292 mg, 2.42 mmol, 6.9 equiv) in water (2 mL) dropwise. The reaction mixture was stirred for 1 h at room temperature and the reaction was quenched with saturated aqueous ammonium chloride (10 mL) and water (10 mL). The reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The product was purified by flash column chromatography on silica gel in 100% DCM to obtain the corresponding carboxylic acid (108 mg, 56%): TLC R_f = 0.39 (10% EtOAc-hexanes); $[\alpha]^{25}_{D}$ = -5.5^o (c 5.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.22 (m, 2H), 7.14-7.11 (t, J = 4.4 Hz, 3H), 4.33-4.31 (m, 1H), 3.88 (d, J = 8.4 Hz, 1H), 3.09-3.03 (m, 1H), 2.63-2.47 (m, 2H), 2.44-2.40 (dd, J = 16.4, 2.4 Hz, 1H), 2.30-2.25 (dd, J = 16.4, 6.8 Hz, 1H), 1.71-1.64 (m, 1H), 1.54-1.46 (m, 1H), 1.23-1.21 (m, 1H), 1.19 (s, 3H), 1.04 (d, J = 6.8 Hz, 3H), 0.93 (s, 3H), 0.89-0.84 (m, 21H), 0.07-0.03 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 218.67, 177.62, 142.47, 128.60, 128.46, 125.83, 76.73, 73.33, 53.82, 46.16, 40.39, 37.49, 36.70, 33.77, 26.47, 26.21, 23.88, 18.80, 18.40, 16.60, 16.54, 13.57, -3.18, -3.30, -4.00.

To a cooled solution of the carboxylic acid (108 mg, 0.186 mmol, 1 equiv) in DCM (5 mL) was added TFA (1 mL) at 0 ^{o}C. The reaction mixture was stirred at 4 ^{o}C for 18 h. Water (4 mL) was added and the reaction mixture was evaporated to dryness under reduced pressure. The residue was dried azeotropically with toluene and purified by flash column chromatography on silica gel in 50% EtOAc-hexanes to obtain **91** (58 mg, 89%):

TLC R_f = 0.46 (50% EtOAc-hexanes); $[\alpha]^{25}_D$ = -33.6° (*c* 2.91, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.25 (m, 2H), 7.23-7.15 (m, 3H), 4.20 (dd, *J* = 7.6, 2.4 Hz, 1H), 3.52-3.49 (m, 1H), 3.21-3.19 (m, 1H), 2.72-2.66 (m, 1H), 2.56-2.37 (m, 4H), 1.67-1.62 (m, 2H), 1.52-1.51 (m, 2H), 1.43-1.34 (m, 2H), 1.16 (d, *J* = 14.8 Hz, 6H), 1.02 (t, *J* = 7.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (222.12, 177.30, 142.48, 128.60, 128.55, 128.47, 126.06, 74.92, 72.47, 52.07, 41.83, 36.45, 35.36, 35.16, 33.17, 26.45, 21.75, 19.05, 15.49, 11.56.

(*4S,7S,8R,9S*)-4,8-Bis-(*tert*-butyldimethylsiloxy)-5,5,7,9-tetramethyl-11-phenylundec-1-en-6-one (90a).

As reported earlier. (151 mg, 100%): TLC R_f = 0.60 (30% DCM-hexanes); $[\alpha]^{25}_D$ = 3.9° (*c* 7.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.19 (m, 2H), 7.14-7.11 (m, 3H), 5.85-5.75 (m, 1H), 4.97 (d. *J* = 12.8 Hz, 2H), 4.01 (m, 1H), 3.88 (d, *J* = 7.6 Hz, 1H), 3.09-3.02 (m, 1H), 2.63-2.47 (m, 2H), 2.12-1.98 (m, 2H), 1.74-1.66 (m, 1H), 1.52-1.42 (m, 1H), 1.29-1.23 (m, 2H), 1.12 (s, 3H), 1.03 (d, *J* = 7.6 Hz, 3H), 0.96 (s, 3H), 0.84 (m, 19H), 0.06 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 218.31, 142.59, 136.97, 128. 52, 128.47, 125.81, 116.46, 76.70, 75.23, 54.48, 45.54, 39.34, 38.17, 36.69, 34.04, 26.50, 26.33, 23.15, 19.36, 18.83, 18.50, 16.78, 13.77, -3.20, -3.21, -3.37, -3.70.

***(3S,6S,7R,8S*)-3,7-Dihydroxy-4,4,6,8-tetramethyl-5-oxo-10-phenyldecanoic acid (91a).**

Ozone was passed through a solution of **89a** (143 mg, 0.255 mmol, 1 equiv) in DCM (6 mL) at -78 °C until the reaction mixture reached a dark blue color. Nitrogen was bubbled through the solution for 15 min and triphenylphosphine (116 mg, 0.441 mmol, 1.7 equiv) was added. The reaction mixture was stirred overnight and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel in 35% DCM-hexanes to obtain the corresponding aldehyde product (94 mg, 65%): TLC R_f = 0.52

(50% DCM-hexanes); $[\alpha]^{25}_{D}$ = 11.1° (*c* 4.11 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (t, *J* = 2.4 Hz, 1H), 7.52-7.21 (m, 2H), 7.14-7.11 (m, 3H), 4.52-4.49 (m, 1H), 3.83 (d, *J* = 8.4 Hz, 1H), 3.07-3.02 (m, 1H), 2.63-2.47 (m, 2H), 2.31-2.29 (m, 2H), 1.69-1.66 (m, 1H), 1.51-1.47 (m, 1H), 1.14 (s, 3H), 0.99 (d, *J* = 9.6 Hz, 3H), 0.94 (s, 3H), 0.88-0.73 (m, 21H), 0.04 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 218.08, 201.47, 142.36, 128.54, 128.48, 125.87, 76.91, 70.20, 53.92, 49.34, 45.57, 37.74, 36.60, 33.73, 36.60, 33.73, 26.46, 26.16, 22.83, 19.09, 18.79, 18.33, 17.15, 13.61, -3.21, -3.31, -3.96, -4.20.

To a solution of the aldehyde product (94 mg, 0.167 mmol, 1 equiv), prepared above, and 2-methyl-2-butene (859 μL) in *t*-butanol (3.5 mL) was added a solution of $NaClO_2$ (140 mg, 1.53 mmol, 9.1 equiv) and NaH_2PO_4 (139 mg, 1.16 mmol, 6.9 equiv) in water (1 mL) dropwise. The reaction mixture was stirred for 1 h at room temperature and it was quenched with saturated aqueous ammonium chloride (5 mL) and water (5 mL). The reaction mixture was extracted with EtOAc (3 x 4 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The product was purified by flash column chromatography on silica gel in 100% DCM to obtain the corresponding carboxylic acid (50 mg, 51%): TLC R_f = 0.54 (20% EtOAc-hexanes); $[\alpha]^{25}_{D}$ = 1.8° (*c* 2.48, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (t, *J* = 7.2 Hz, 2H), 7.15 (t, *J* = 7.2 Hz, 3H), 4.48-4.46 (m, 1H), 3.88 (d, *J* = 8.4 Hz, 1H), 3.10-3.07 (m, 1H), 2.62-2.51 (m, 2H), 2.38-2.23 (m, 2H), 1.73-1.69 (m, 1H), 1.54-1.49 (m, 1H), 1.16 (s, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.94 (s, 3H), 0.89- 0.81 (s, 21H), 0.08-0.05 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 217.81, 178.25, 142.38, 128.54, 128.50, 125.91, 76.91, 72.20, 54.06, 45.61, 40.08, 37.76, 36.66, 33.79, 26.48, 26.23, 22.39, 18.95, 18.81, 17.04, 13.67, -3.20, -3.31, -4.17, -4.31.

To a cooled solution of the carboxylic acid (50 mg, 0.086 mmol, 1 equiv) in DCM (2.1 mL) was added TFA (420 μL) at 0 °C. The reaction mixture was stirred at 4 °C for 16 h. Water (1 mL) was added and the reaction mixture was evaporated to dryness under

reduced pressure. The residue was dried azeotropically with toluene to obtain **91a**: TLC R_f = 0.31 (50% EtOAc-hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.24 (m, 2H), 7.22-7.11 (m, 3H), 4.20 (d, *J* = 8.8 Hz, 1H), 3.56-3.53 (m, 1H), 3.21-3.17 (m, 1H), 2.73-2.65 (m, 1H), 2.56-3.37 (m, 4H), 1.70-1.62 (m, 1H), 1.57-1.50 (m, 1H), 1.44-1.35 (m, 1H), 1.15 (d, *J* = 10.4 Hz, 6H), 1.05 (d, *J* = 4.8 Hz, 3H), 1.02 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 222.13, 177.33, 142.50, 128.55, 126.05, 75.01, 72.59, 52.19, 41.73, 36.63, 35.34, 35.20, 33.15, 26.44, 21.81, 19.39, 15.42, 11.67.

5-Benzyl-2-methyl-3-(2-(phenylethynyl)thiazol-4-yl)cyclopent-2-enone and 5,5-dibenzyl-2-methyl-3-(2-(phenylethynyl)thiazol-4-yl)cyclopent-2-enone (92 and 93).

A solution of DIPA (60 μL, 0.42 mmol, 1.2 equiv) in anhydrous THF (400 μL) was cooled to -78 ^{o}C and *n*-BuLi (140 μL, 2.5 M in hexanes, 0.356 mmol, 1 equiv) was added dropwise. After the reaction mixture was stirred at -78 ^{o}C for 30 min, it was allowed to warm to room temperature and a solution of 2-methyl-3-(2-(phenylethynyl)thiazol-4-yl)cyclopent-2-enone **53d** in anhydrous THF (1.2 mL) was added, followed by benzyl bromide (23 μL, 0.133 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 2 h. Water (6 mL) was added and the reaction mixture was extracted with EtOAc (3 x 4 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The product was purified by flash column chromatography on silica gel in 7% EtOAc-hexanes to obtain monoalkylated product **92** (44 mg, 33%) and dialkylated product **93** (110 mg, 67%):

Data for monoalkylated product **92**: TLC R_f =0.48 (20% EtOAc-hexanes); IR $\bar{\nu}_{max}$: 3750, 3100, 2250, 1750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (dd, *J* = 5.6 Hz, 1.6 Hz, 2H), 7.41-7.24 (m, 3H), 7.22-7.18 (m, 6H), 3.36 (dd, *J* =14.0, 4.0 Hz, 1H), 3.10-3.03 (m, 1H), 2.87-2.83 (m, 1H), 2.75-2.70 (m, 1H), 2.61-2.55 (m, 1H), 2.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 210.91, 156.77, 152.97, 148.71, 139.82, 136.68, 132.26, 130.02, 129.08, 128.74, 128.69, 126.51, 122.11, 121.21, 95.09, 82.12, 46.33, 37.59, 34.84, 10.58; HRMS (m/z): $[M + Na]^+$ calcd for $C_{24}H_{19}NOS$, 392.1085; found, 392.1074.

Data for dialkylated product **93**: TLC R_f = 0.55 (20% EtOAc-hexanes); IR $\bar{\nu}_{max}$: 3500, 3100, 2100, 1750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.58 (dd, *J* = 6.4, 1.6 Hz, 2H), 7.40-7.36 (m, 3H), 7.32 (s, 1H), 7.17-7.08 (m, 10H), 3.14 (d, *J* = 13.2 Hz, 2H), 2.92 (d, *J* = 1.6 Hz, 2H), 2.79 (d, *J* = 13.2 Hz, 2H), 1.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 213.07, 156.40, 152.56, 148.39, 137.48, 137.08, 132.25, 130.32, 130.00, 128.74, 128.22, 126.66, 121.77, 121.25, 94.97, 82.13, 52.79, 43.87, 37.44, 29.92, 10.23; HRMS (m/z): $[M + Na]^+$ calcd for $C_{31}H_{25}NOS$, 482.1555; found, 482.1561.

5,5-Dibenzyl-2-methyl-3-(2-((trimethylsilyl)ethynyl)thiazol-4-yl)cyclopent-2-enone (94).

A solution of DIPA (120 μL, 0.841 mmol, 1.2 equiv) in anhydrous THF (3 mL) was cooled to -78 °C and *n*-BuLi (336 μL, 2.5 M in hexanes, 0.841 mmol, 1 equiv) was added dropwise. After the reaction mixture was stirred at -78 °C for 30 min, it was allowed to warm to room temperature and a solution of 2-methyl-3-(2-((trimethylsilyl)ethynyl)thiazol-4-yl)cyclopent-2-enone **53e** (193 mg, 0.700 mmol, 1 equiv) in anhydrous THF (1.2 mL) was added dropwise, followed by benzyl bromide (180 μL, 1.54 mmol, 2.2 equiv). The reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The product was purified by preparative thin-layer chromatography on silica gel plates in 20% EtOAc-hexanes to obtain dialkylated product **94** (64 mg, 20%): TLC R_f =0.41 (10% EtOAc-hexanes); IR $\bar{\nu}_{max}$: 3100, 2800, 2350, 2100, 1750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (s, 1H), 7.16-7.06 (m, 10 H), 3.12 (d, *J* = 13.2 Hz, 2H), 2.88 (d, *J* = 1.6 Hz, 2H), 2.78 (d, *J* = 13.2 Hz, 2H), 1.84 (s, 3H), 0.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 213.08, 156.37, 152.31, 148.06, 137.46, 137.08, 130.30, 128.21, 126.65, 121.73, 102.15, 96.21, 52.77, 43.86, 37.44, 10.25, -0.31; HRMS (m/z): $[M + Na]^+$ calcd for $C_{28}H_{29}NOSSi$, 478.1637; found, 478.1639.

5-Benzyl-2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enone and 5,5-dibenzyl-2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enone (95 and 96).

A solution of DIPA (94 μL, 0.668 mmol, 1 equiv) in anhydrous THF (2 mL) was cooled to -78 ^{o}C and *n*-BuLi (270 μL, 2.5 M in hexanes, 0.668 mmol, 1 equiv) was added dropwise. After the reaction mixture was stirred at -78 ^{o}C for 30 min, a solution of 2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enone **53b** (271 mg, 0.668 mmol, 1 equiv) in anhydrous THF (2 mL) was added at -78 ^{o}C followed by benzyl bromide (80 μL, 0.668 mmol, 1 equiv). The reaction mixture was stirred at -78 ^{o}C for 3 h and allowed to warm to room temperature overnight. The reaction mixture was poured into saturated aqueous ammonium chloride (10 mL) and extracted with EtOAc (3 x 3 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The product was purified by flash column chromatography on silica gel in 10% EtOAc-hexanes to obtain monoalkylated product **95** (107 mg, 28%) and dialkylated product **96** (104 mg, 14%):

Data for monoalkylated product **95**: TLC R_f = 0.59 (25% EtOAc-hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (s, 1H), 7.30-7.24 (m, 2H), 7.22-7.07 (m, 3H), 3.33 (dd, *J* = 14.4, 4.4 Hz, 1H), 2.98-2.89 (m, 1H), 2.84-2.78 (m, 1H), 2.67 (d, *J* = 2.4 Hz, 3H), 2.63-2.51 (m, 2H), 2.51 (d, *J* = 1.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 211.05, 156.49, 152.51, 139.95, 136.09, 130.37, 129.07, 128.70, 128.18, 126.50, 119.88, 46.28, 37.70, 34.24, 16.72, 10.56.

Data for dialkylated product **96**: TLC R_f = 0.67 (25% EtOAc-hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19-7.07 (m, 11H), 3.12 (d, *J* = 13.2 Hz, 2H), 2.80-2.74 (m 4H), 2.65 (s, 3H), 1.91 (t, *J* = 2.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 213.17, 166.28, 156.04, 152.14, 137.52, 136.41, 130.34, 130.23, 126.72, 126.64, 119.52, 52.53, 43.78, 43.63, 36.17, 16.67, 16.53, 10.26.

5,5-Dibenzyl-2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enol (98).

To a solution of 5,5-dibenzyl-2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enone **96** (32 mg, 0.079 mmol, 1 equiv) in anhydrous THF (500 μL) under nitrogen was added lithium triethylborohydride (742 μL, 6.96 mmol, 88 equiv). The reaction mixture was stirred overnight. It was poured into saturated aqueous ammonium chloride (10 mL) and extracted with EtOAc (3 x 3 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel in 15% EtOAc-hexanes to obtain the partially purified product **98** (19 mg, 66% brsm): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.25 (m, 5H), 7.22-7.08 (m, 5H), 6.73 (s, 1H), 4.54 (s, 1H), 2.87-2.89 (m, 4H), 2.68 (s, 3H), 2.67-2.64 (m, 2H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.14, 139.60, 139.03, 138.39, 131.11, 130.61, 128.32, 128.16, 126.32, 126.17, 84.92, 50.02, 42.57, 40.60, 39.56, 16.74, 13.38.

(*S*)-5,5-Dibenzyl-2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enyl acetate and (*R*)-5,5-Dibenzyl-2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enol (99 and 100).

To a solution of 5,5-dibenzyl-2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enol **98** (8 mg, 0.020 mmol) in vinyl acetate (200 μL) was added Lipase PS-C "Amano" I (6 mg). The reaction mixture was stirred for 6 d at 40 ^{o}C. The reaction mixture was passed through a cotton wool plug in 100% DCM and concentrated in vacuo. The product was purified by flash column chromatography in 10% EtOAc-hexanes to separately obtain acetate **99** (1.2 mg, 14%) and enol **100** (1.9 mg, 24%):

Data for acetate **99**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23–7.13 (m, 10H), 6.73 (s, 1H), 5.94 (s, 1H), 3.64 (m, 1H), 3.35 (s, 2H), 2.94-2.72 (m, 4H), 2.68 (s, 3H), 2.14 (s, 3H), 1.84 (s, 3H).

Data for enol **100**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.08 (m, 10H), 6.73 (s, 1H), 4.11 (t, J = 7.2 Hz, 1H), 3.33 (s, 1H), 2.86-2.81 (m, 3H), 2.71-2.63 (m, 4H), 2.02-2.01 (m, 3H).

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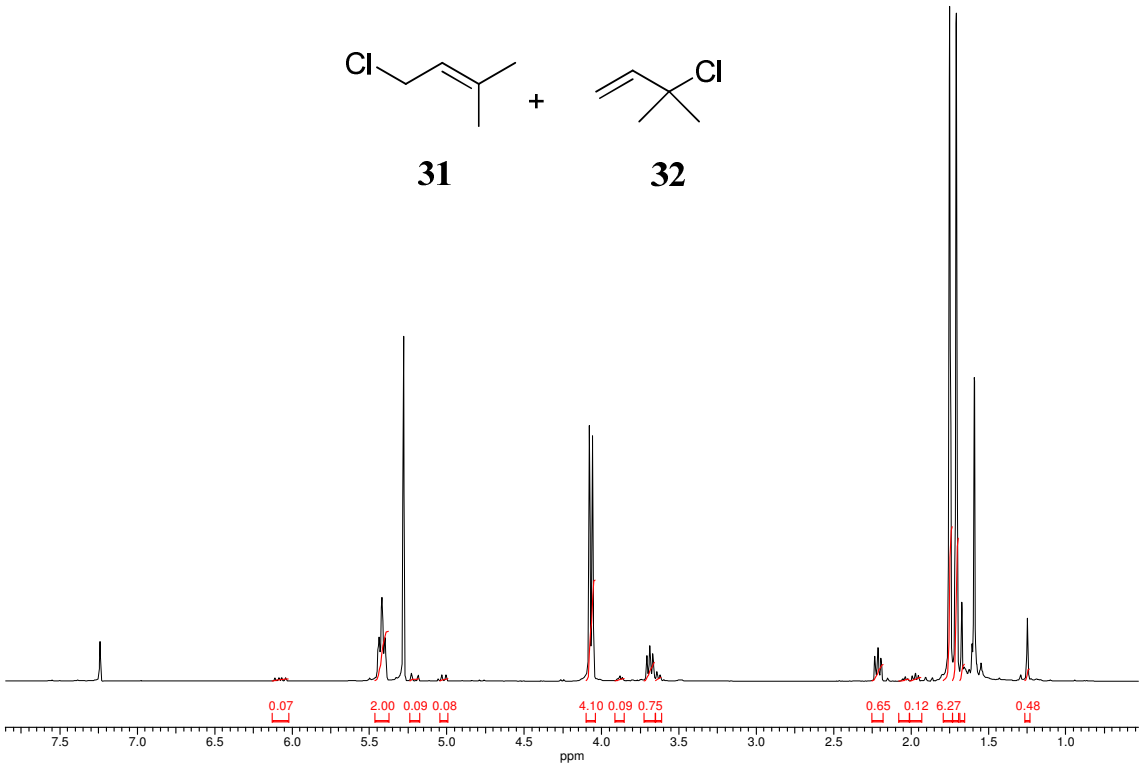
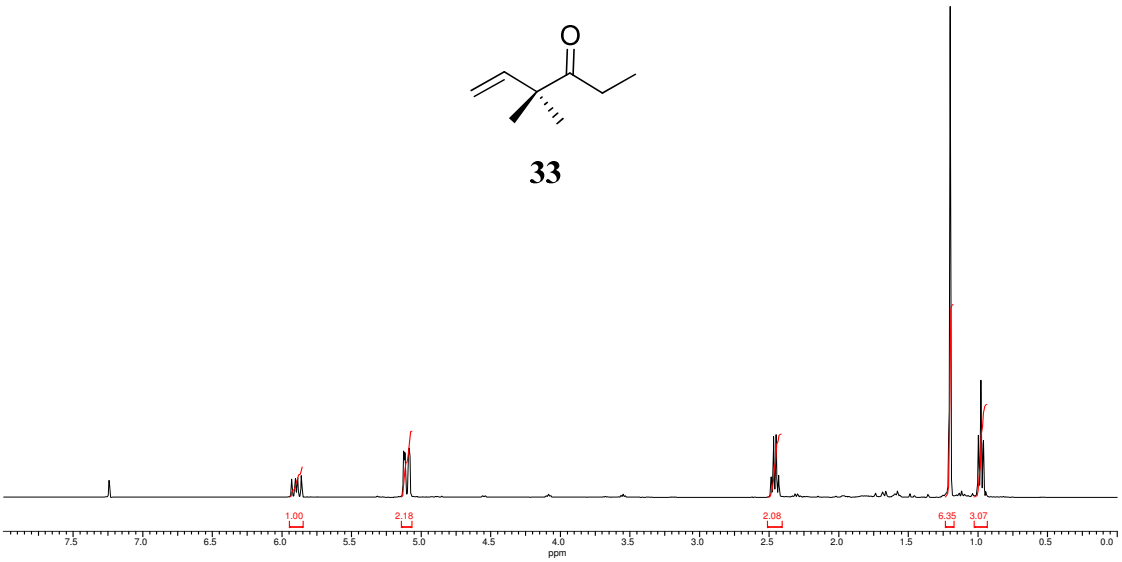
Appendix

^{1}H and ^{13}C NMR Spectra

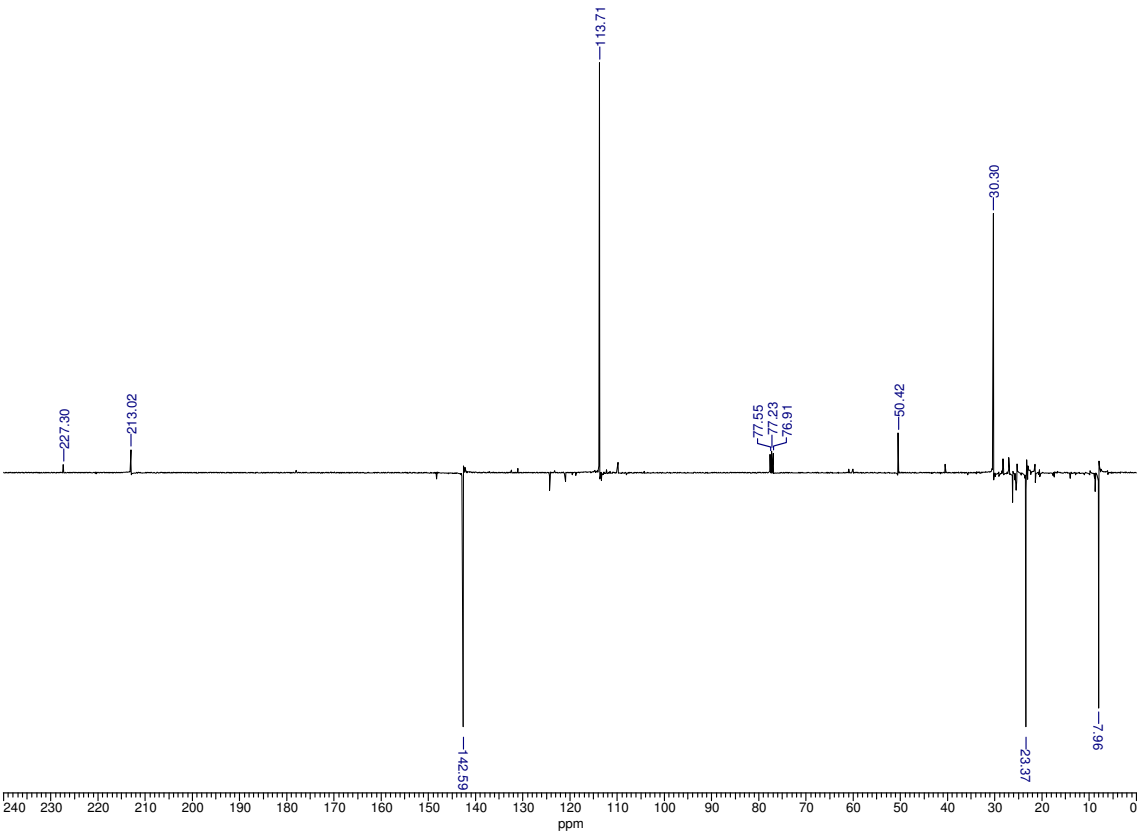
^{1}H NMR of 1-chloro-3-methyl-but-ene (31) and 3-chloro-3-methylbut-1-ene (32)



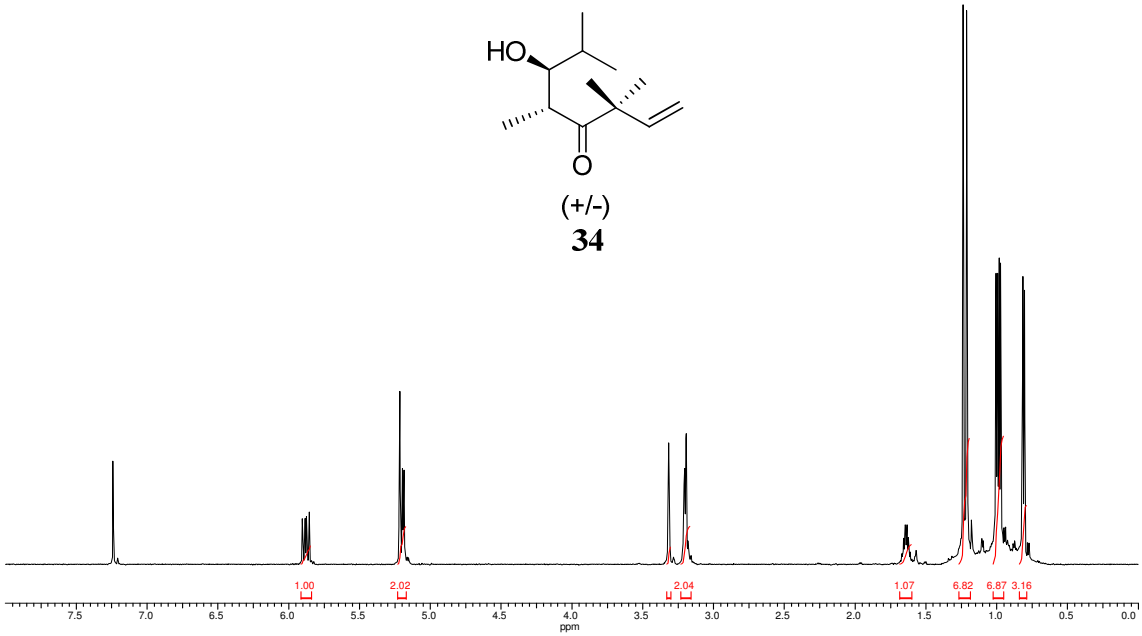
^{1}H NMR of 4,4-dimethylhex-5-en-3-one (33)



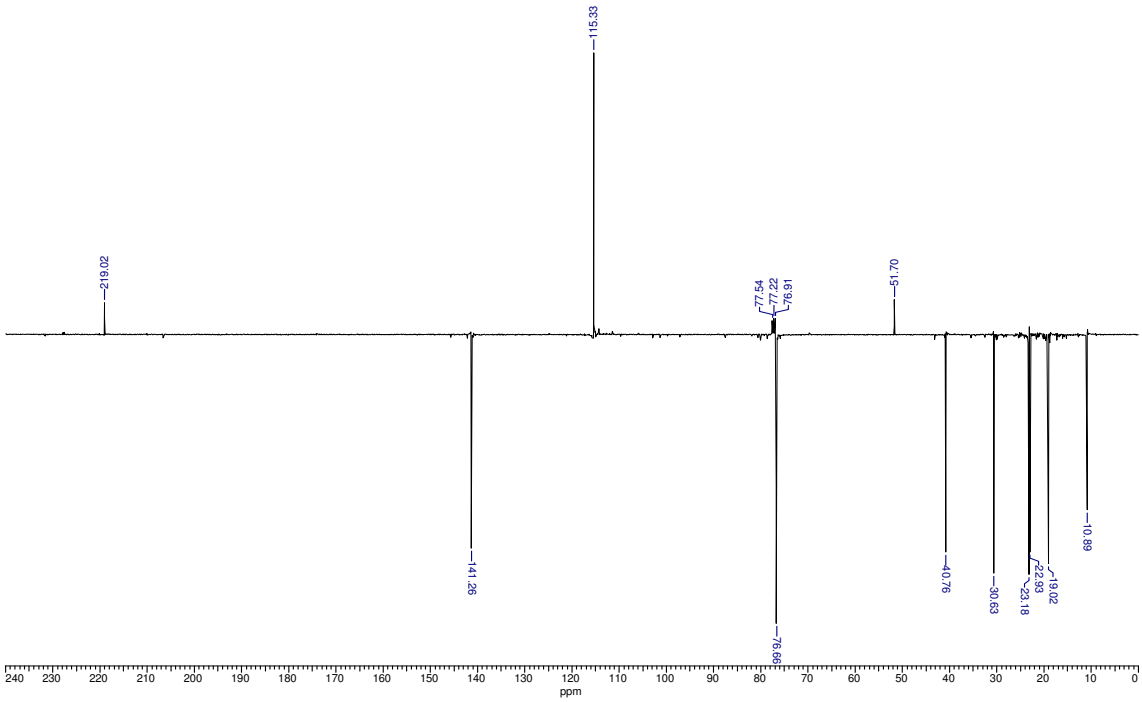
^{13}C NMR of 4,4-dimethylhex-5-en-3-one (33)



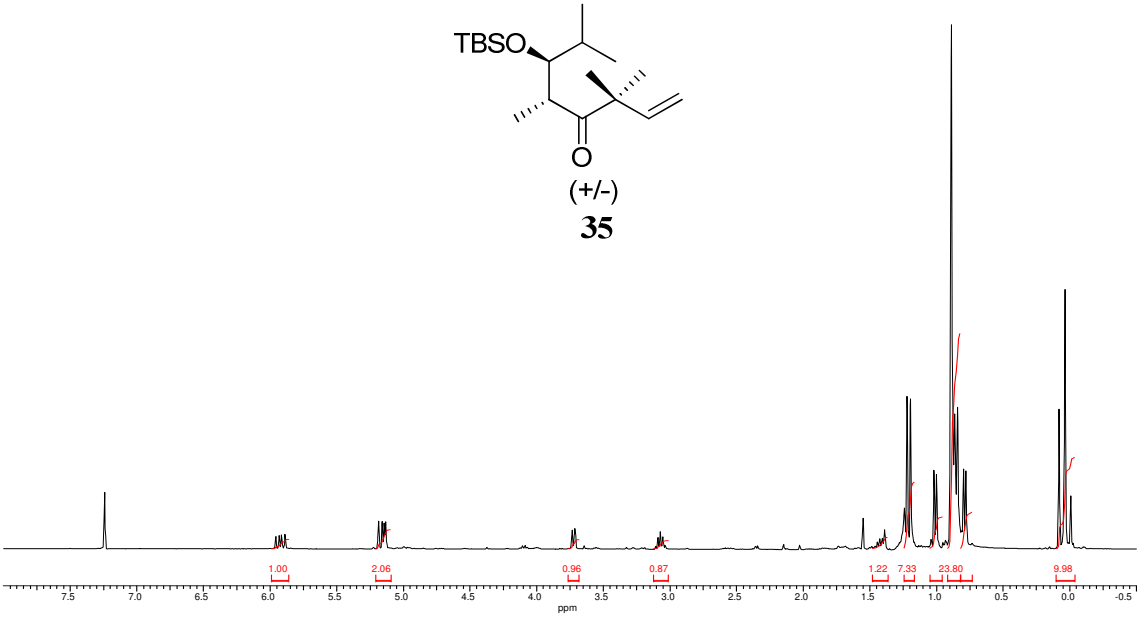
^{1}H NMR of (*5R*, *6S*) and (*5S*, *6R*)-6-hydroxy-3,3,5,7-tetramethyl-oct-1-en-4-one ((+/-) 34)



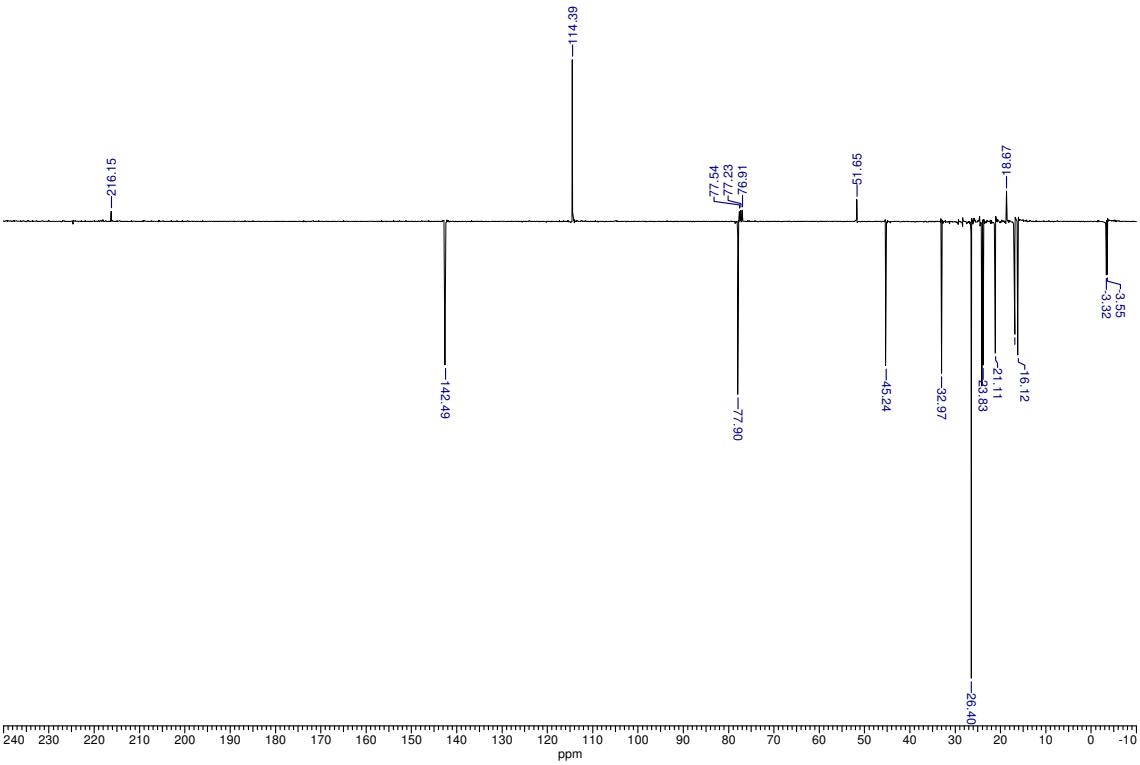
^{13}C NMR of (*5R*, *6S*) and (*5S*, *6R*)-6-hydroxy-3,3,5,7-tetramethyl-oct-1-en-4-one ((+/-) 34)



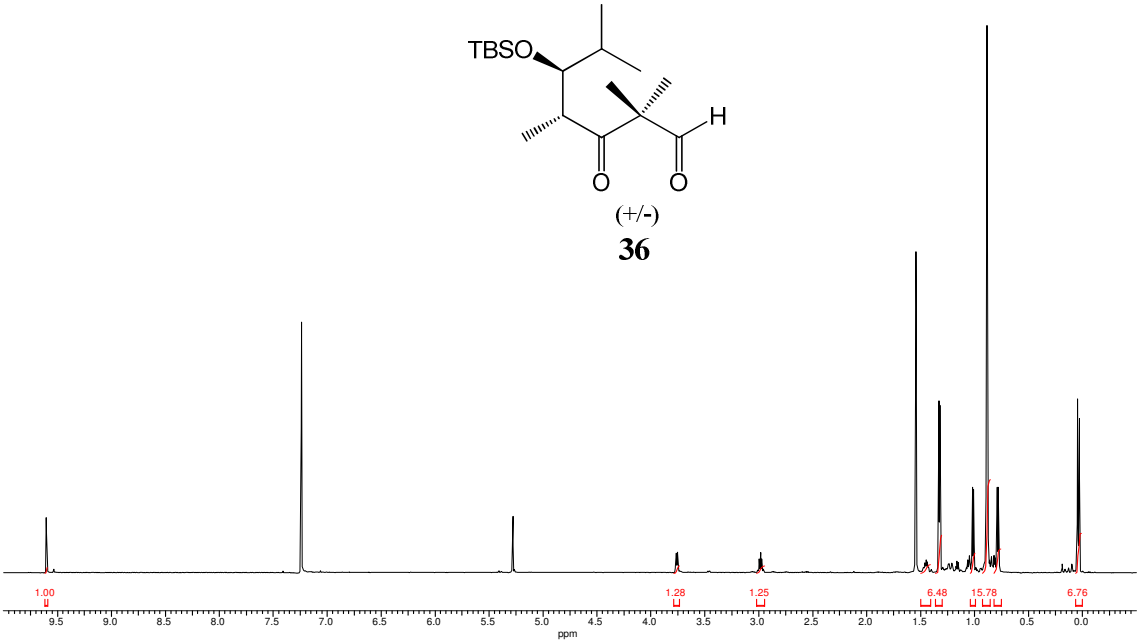
^{1}H NMR of (*5R,6S*) and (*5R,6R*)-6-(*tert*-butyl-dimethyl-silanyloxy)-3,3,5,7-tetramethyl-1-oct-1-en-4-one ((+/-) 35)



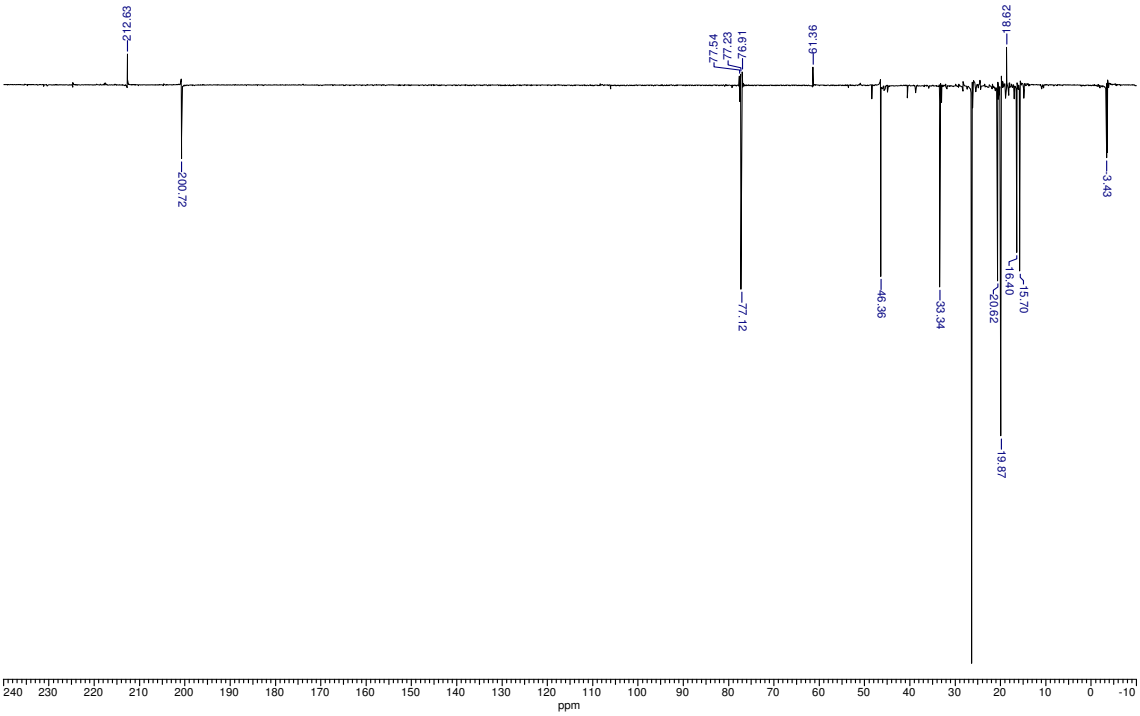
^{13}C NMR of (*5R,6S*) and (*5R,6R*)-6-(*tert*-butyl-dimethyl-silanyloxy)-3,3,5,7-tetramethyl-1-oct-1-en-4-one ((+/-) 35)



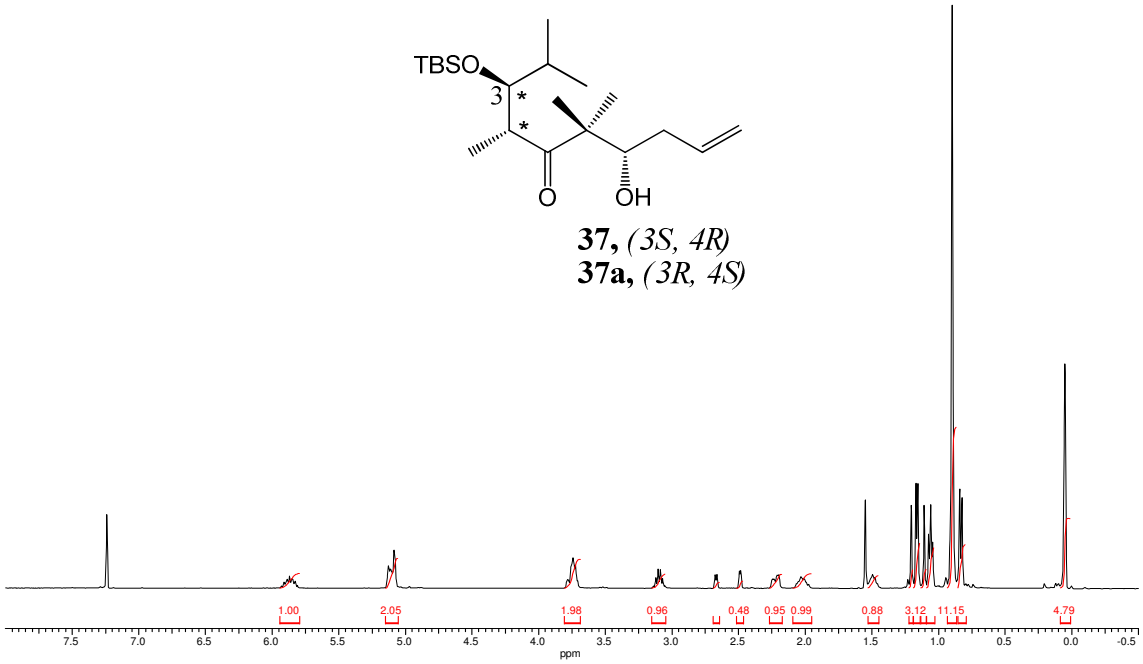
^{1}H NMR of (*4R,5S*)-5-(*tert*-butyldimethylsilyloxy)-2,2,4,6-tetramethyl-3-oxoheptanal ((+/-)36)



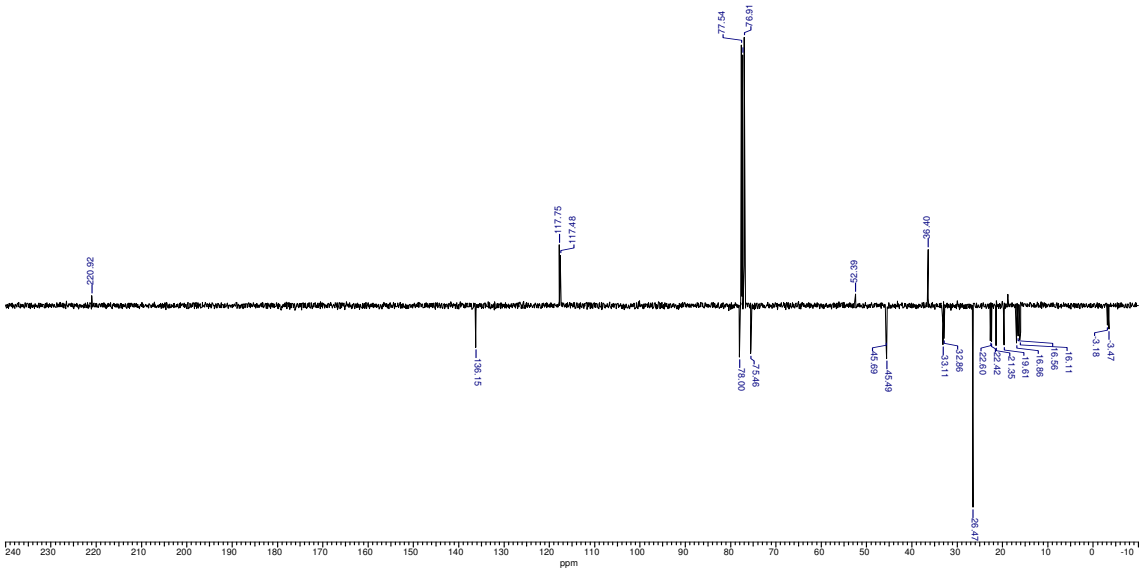
^{13}C NMR of (*4R,5S*)-5-(*tert*-butyldimethylsilyloxy)-2,2,4,6-tetramethyl-3-oxoheptanal ((+/-)36)



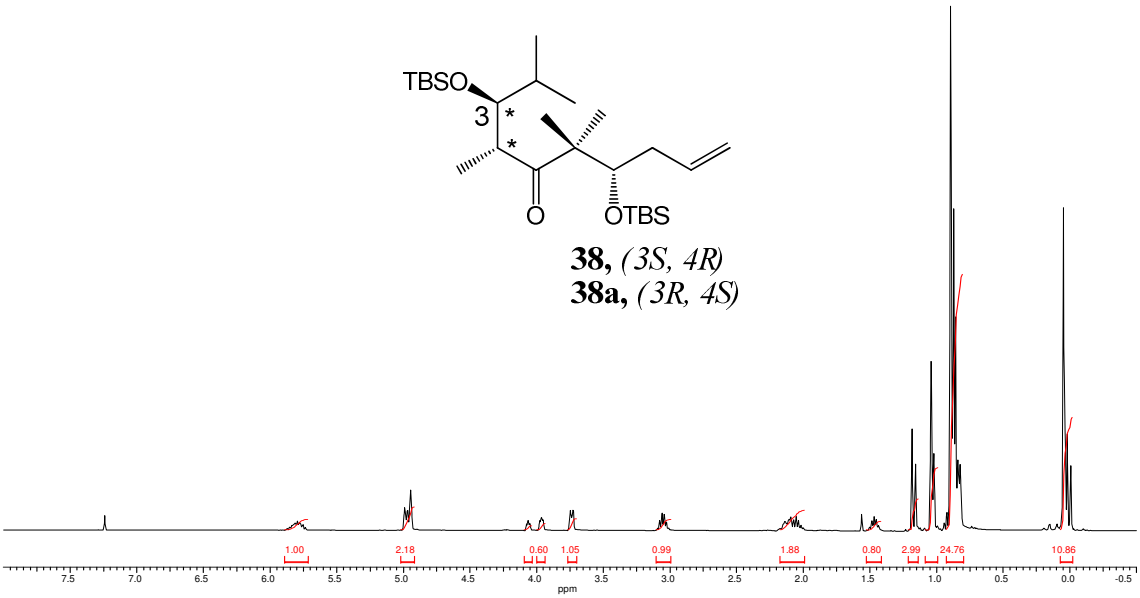
^{1}H NMR of (*3S,4R,7S*)-3-(*tert*-butyldimethylsilyloxy)-7-hydroxy-2,4,6,6-tetramethyldec-9-en-5-one and (*3R,4S,7S*)-3-(*tert*-butyldimethylsilyloxy)-7-hydroxy-2,4,6,6-tetramethyldec-9-en-5-one (37 and 37a)



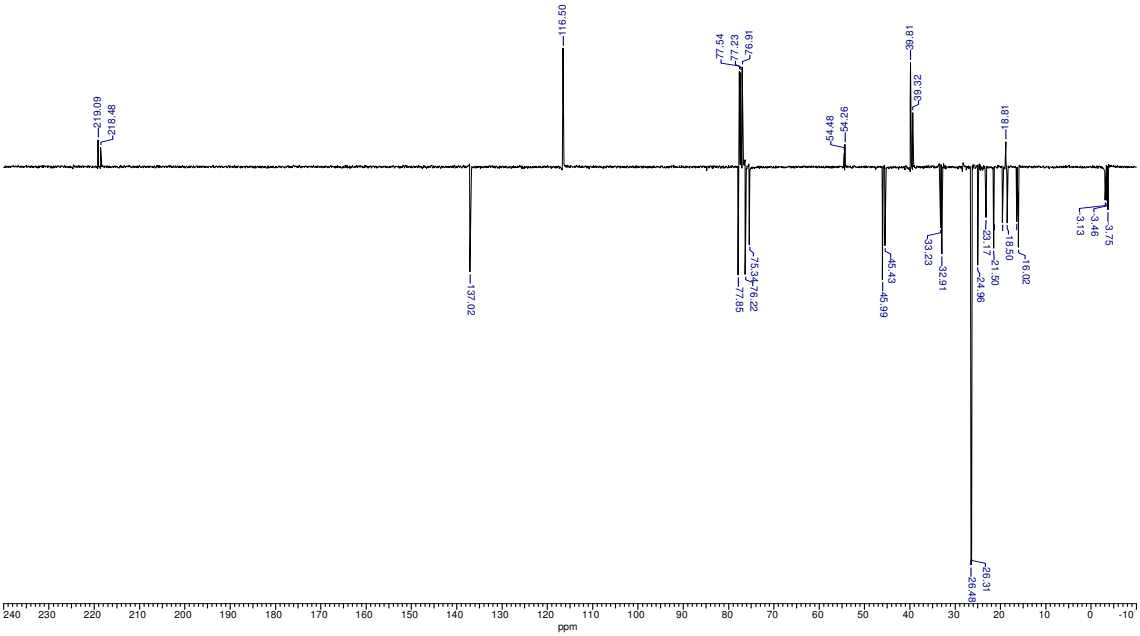
^{13}C NMR of (*3S,4R,7S*)-3-(*tert*-butyldimethylsilyloxy)-7-hydroxy-2,4,6,6-tetramethyldec-9-en-5-one and (*3R,4S,7S*)-3-(*tert*-butyldimethylsilyloxy)-7-hydroxy-2,4,6,6-tetramethyldec-9-en-5-one (37 and 37a)



^{1}H NMR of (*3S,4R,7S*)-3,7-bis-(*tert*-butyldimethylsilyloxy)-2,4,6,6-tetramethyldec-9-en-5-one and (*3R,4S,7S*)- 3,7-bis-(*tert*-butyldimethylsilyloxy)-2,4,6,6-tetramethyldec-9-en-5-one (38 and 38a)

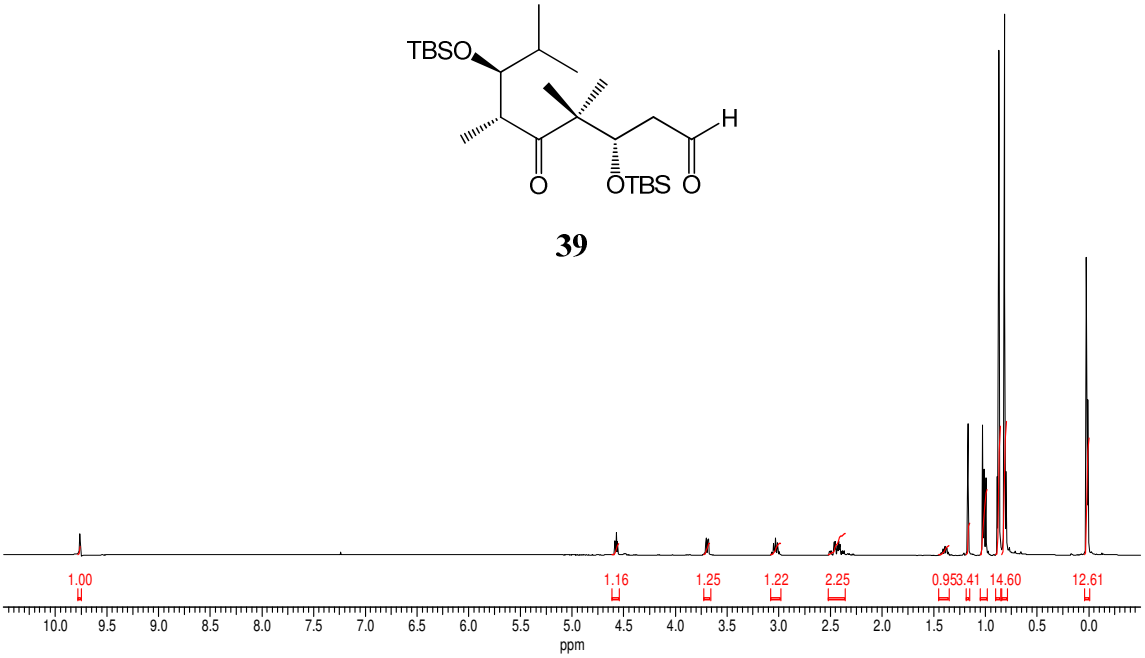


^{13}C NMR of (*3S,4R,7S*)-3,7-bis-(*tert*-butyldimethylsilyloxy)-2,4,6,6-tetramethyldec-9-en-5-one and (*3R,4S,7S*)- 3,7-bis-(*tert*-butyldimethylsilyloxy)-2,4,6,6-tetramethyldec-9-en-5-one (38 and 38a)

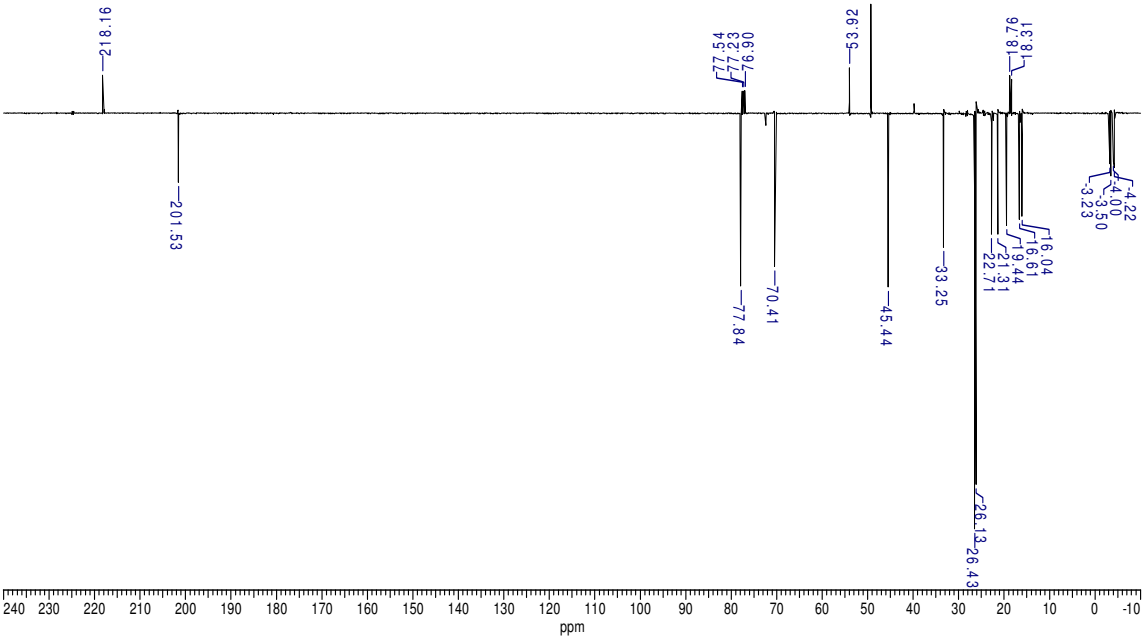


^{1}H NMR of (*3S,6R,7S*)-3,7-bis(tert-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxononanal (39)

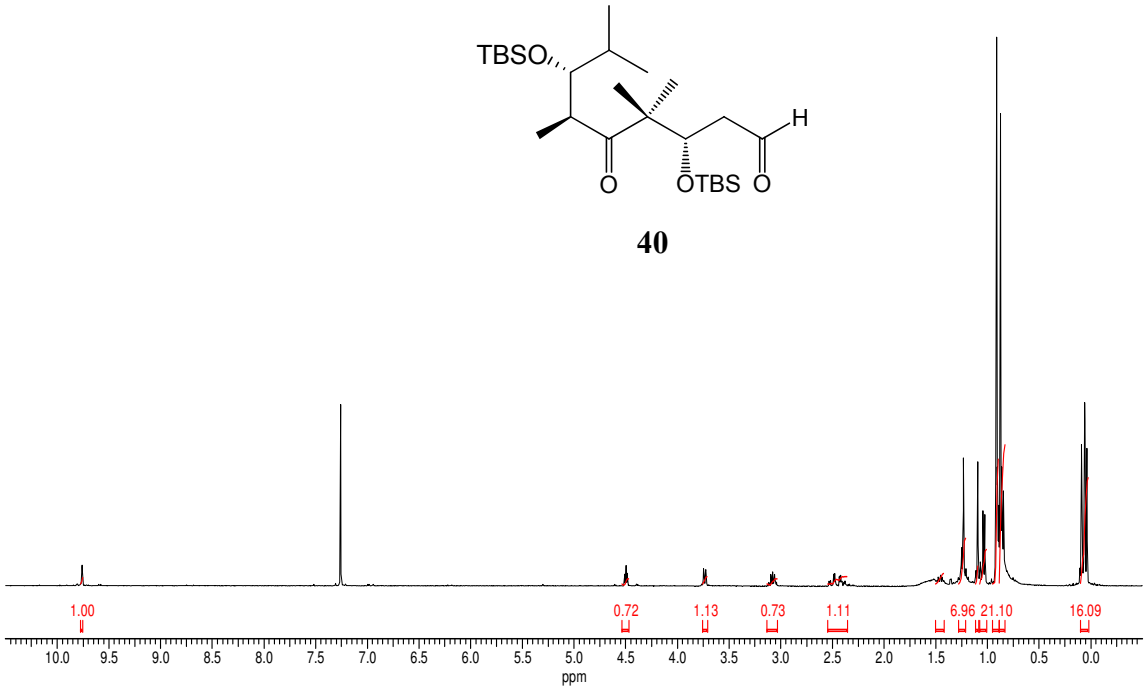
39



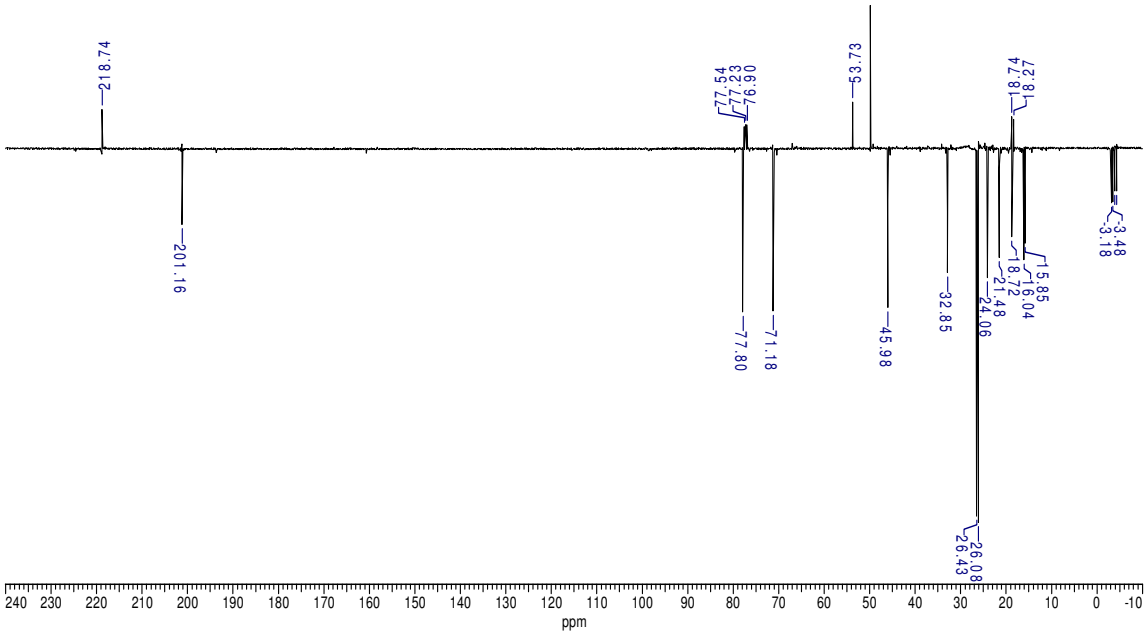
^{13}C NMR of (*3S,6R,7S*)-3,7-bis(tert-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxononanal (39)



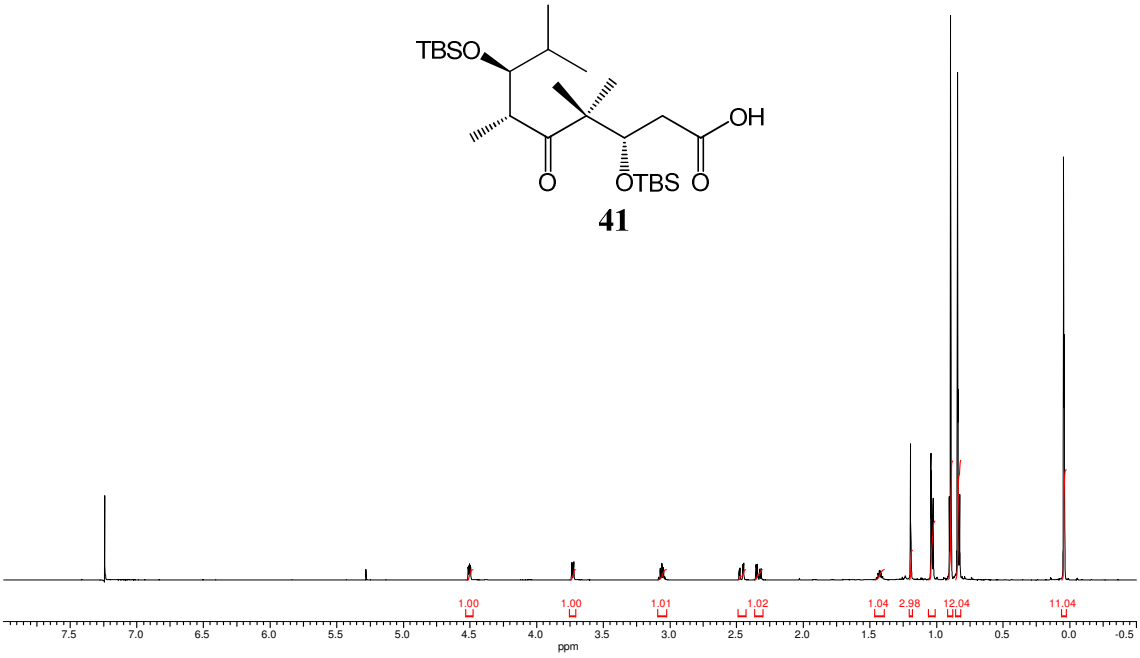
^{1}H NMR of (*3S,6S,7R*)-3,7-bis(tert-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxononanal (40)



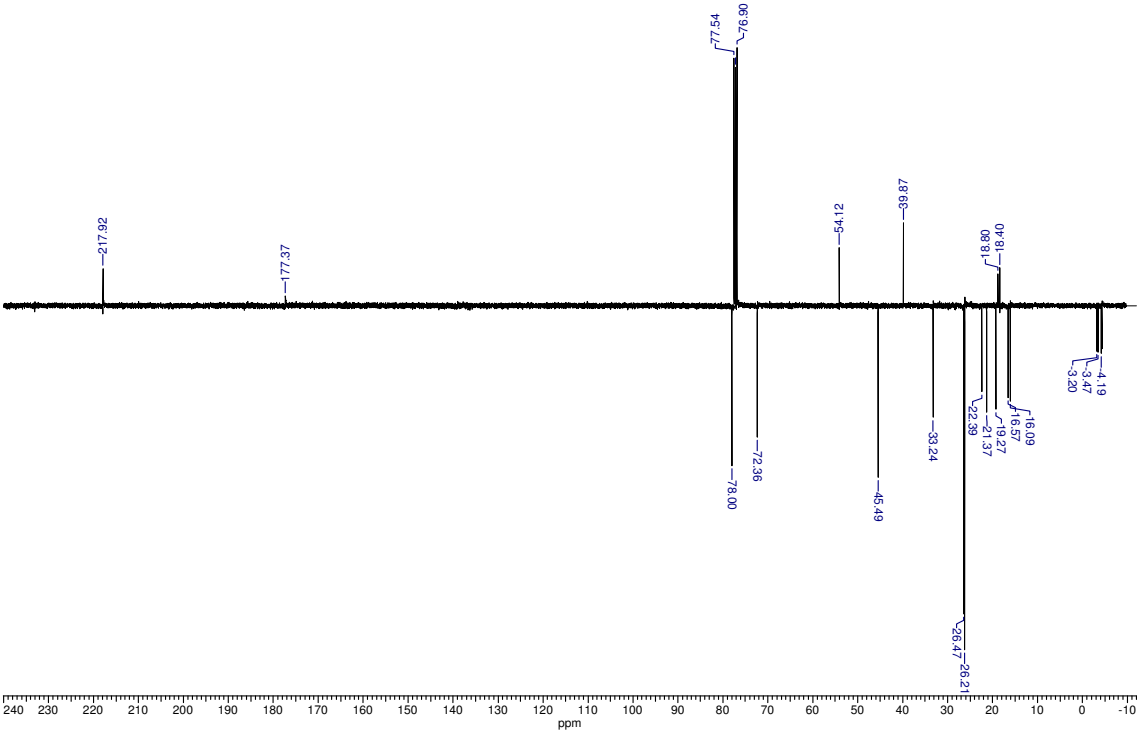
^{13}C NMR of (*3S,6S,7R*)-3,7-bis(tert-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxononanal (40)



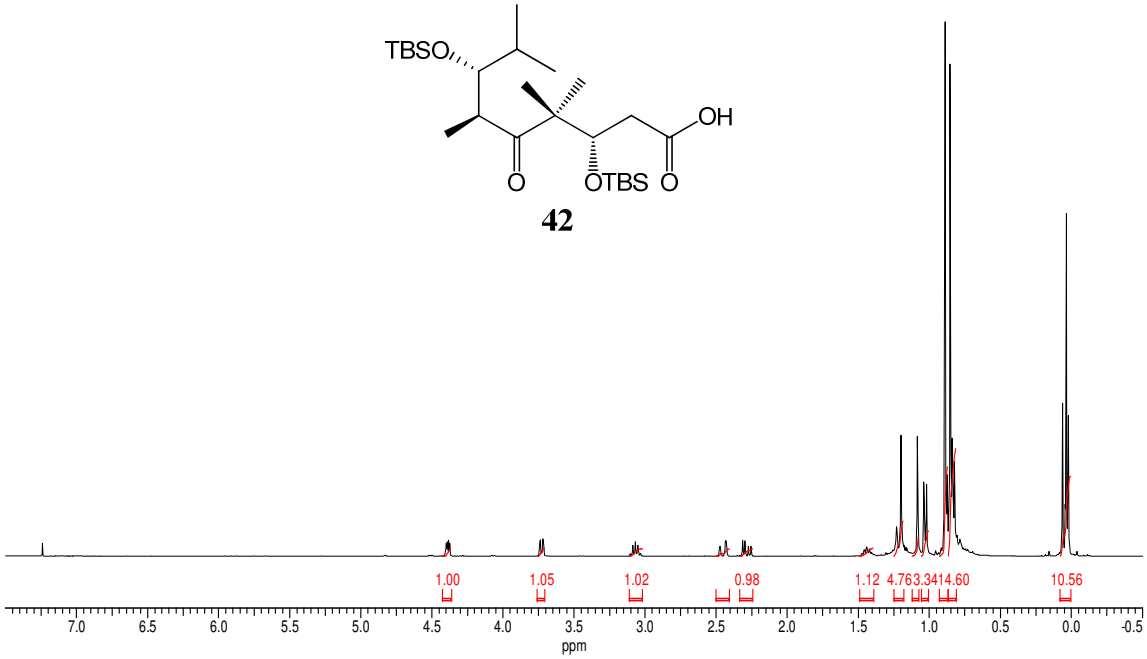
^{1}H NMR of (*3S,6R,7S*)-3,7-bis(*tert*-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxononanoic acid (41)



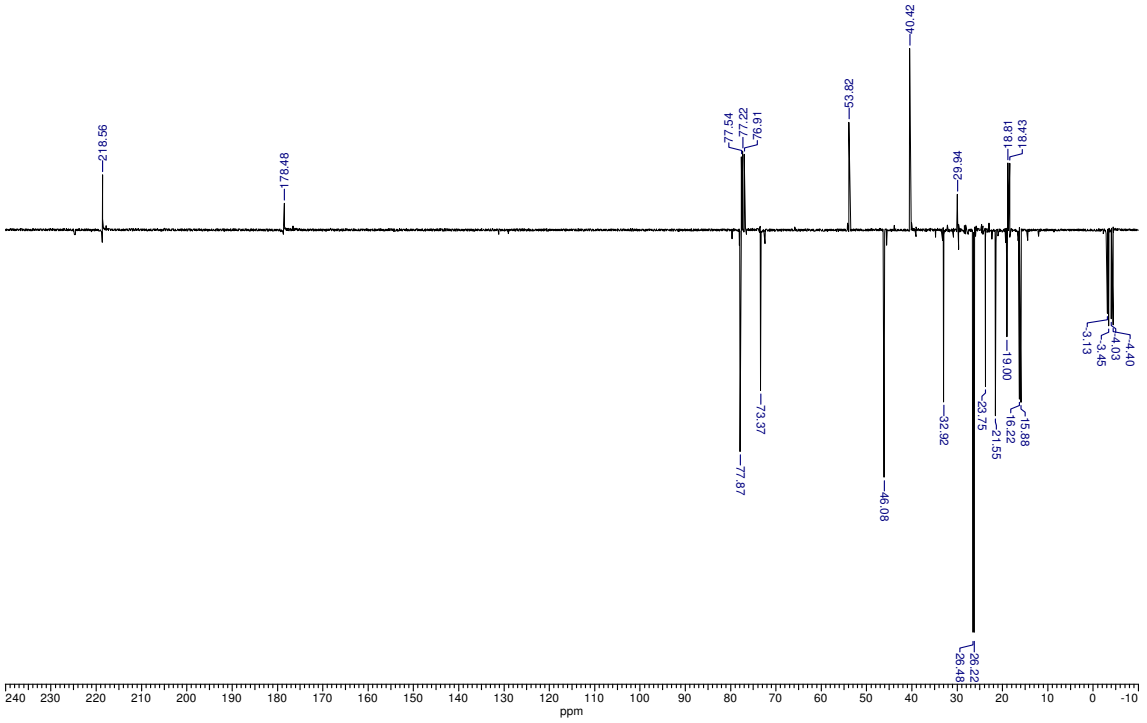
^{13}C NMR of (*3S,6R,7S*)-3,7-bis(*tert*-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxononanoic acid (41)



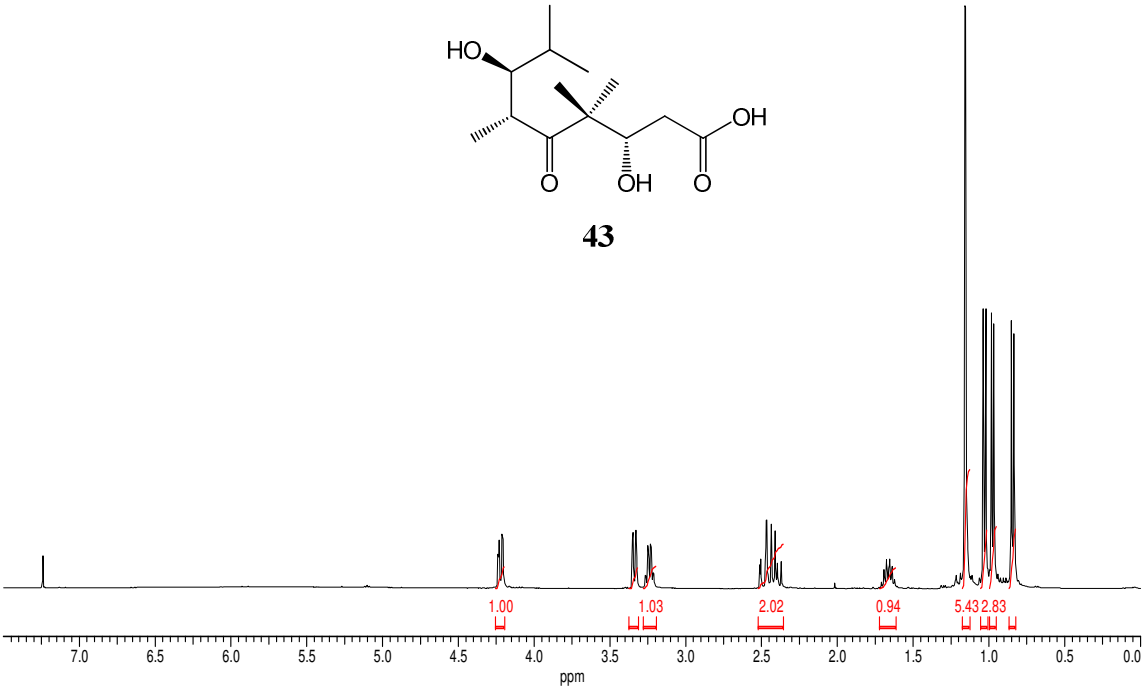
^{1}H NMR of (*3S,6S,7R*)-3,7-bis(tert-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxononanoic acid (42)



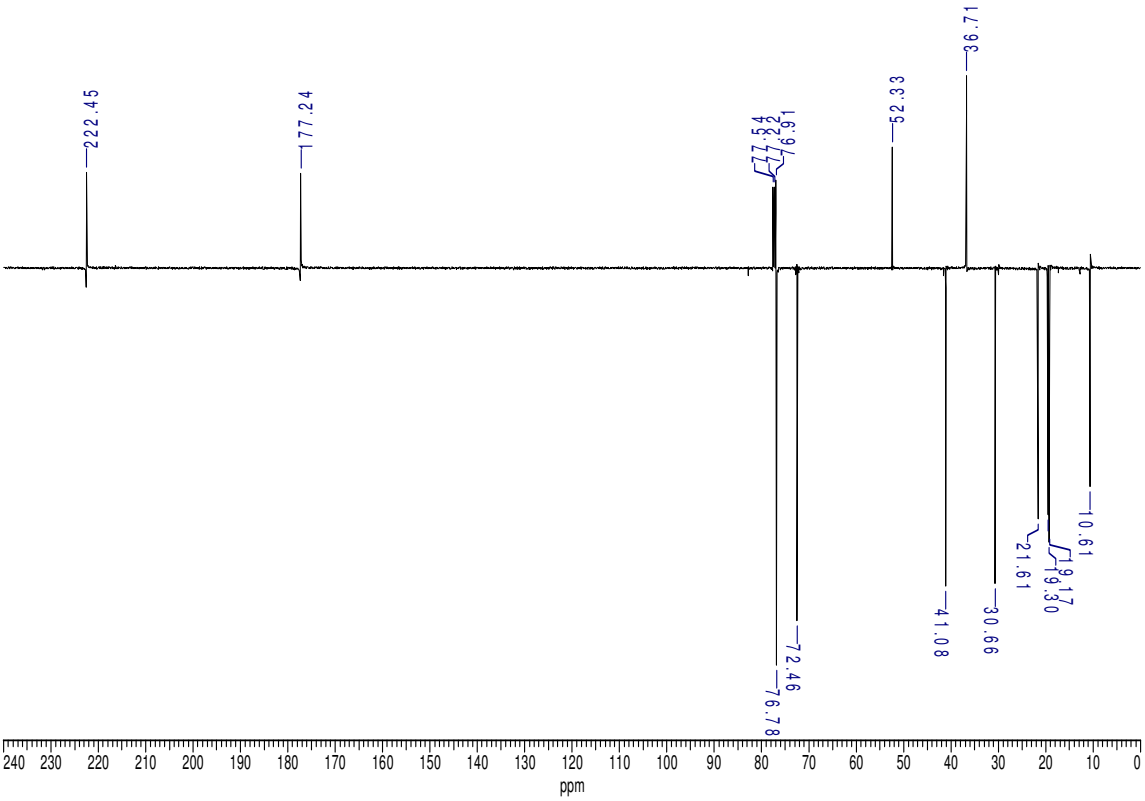
^{13}C NMR of (*3S,6S,7R*)-3,7-bis(tert-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxononanoic acid (42)



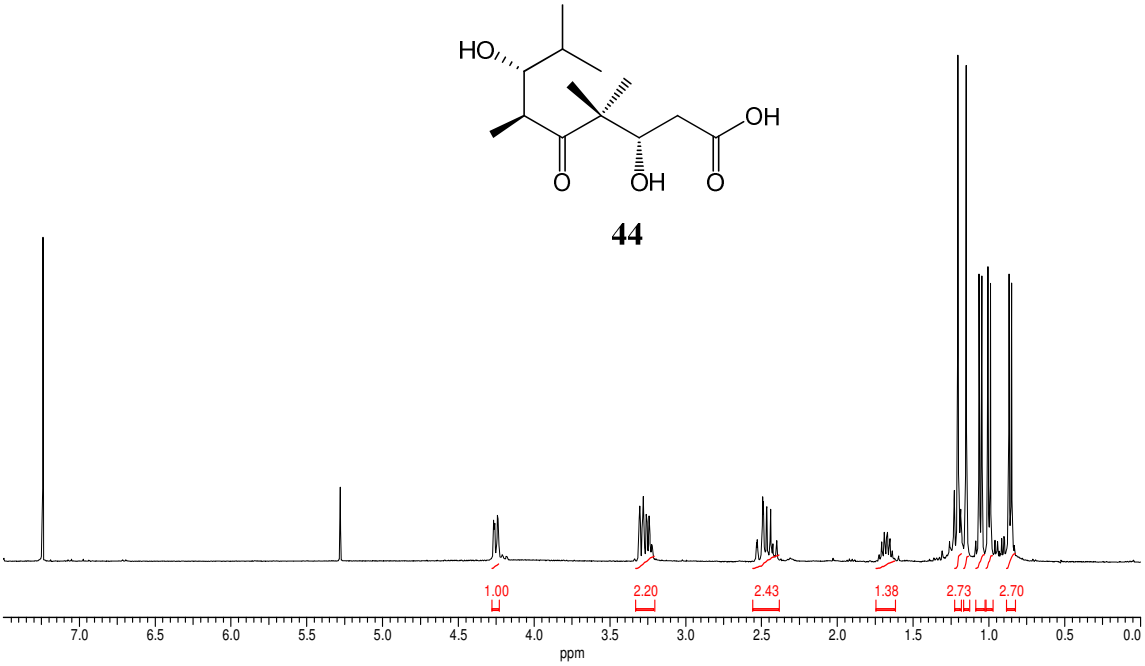
^{1}H NMR of (*3S,6R,7S*)-3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoic acid (43)



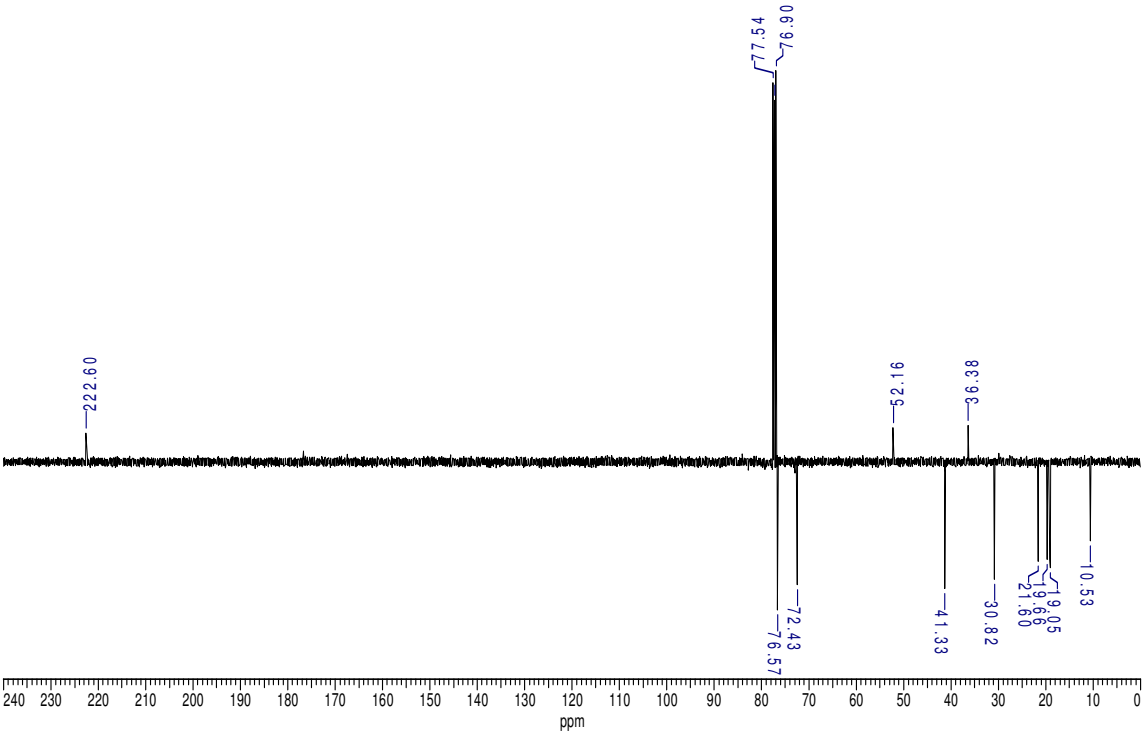
^{13}C NMR of (*3S,6R,7S*)-3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoic acid (43)



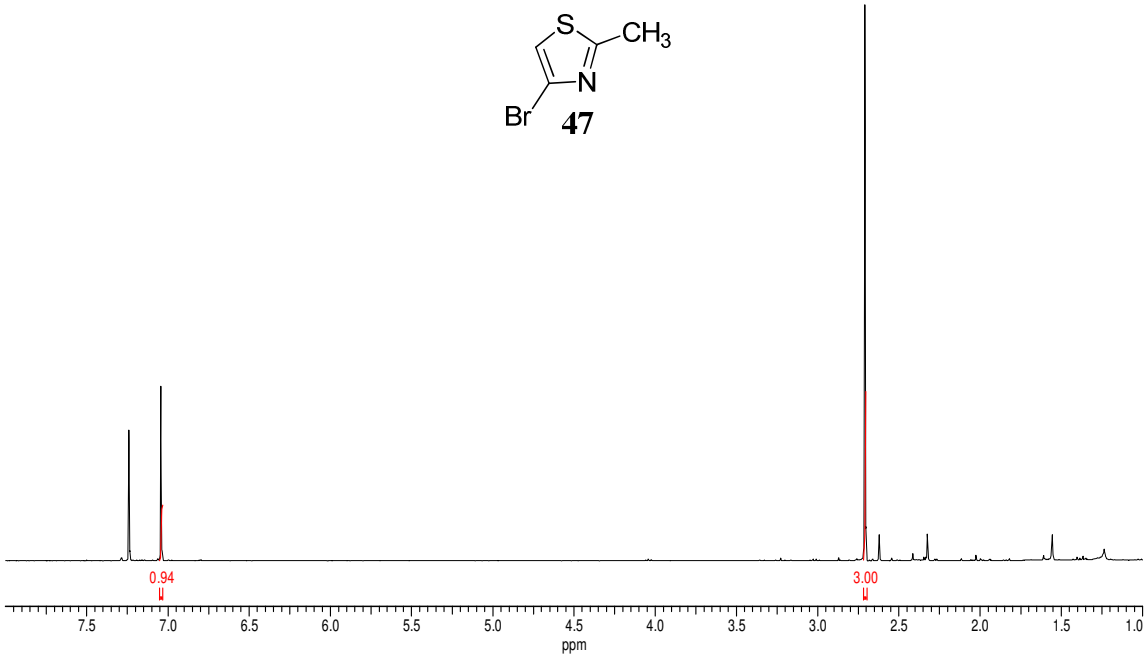
1H NMR of (*3S,6S,7R*)-3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoic acid (44)



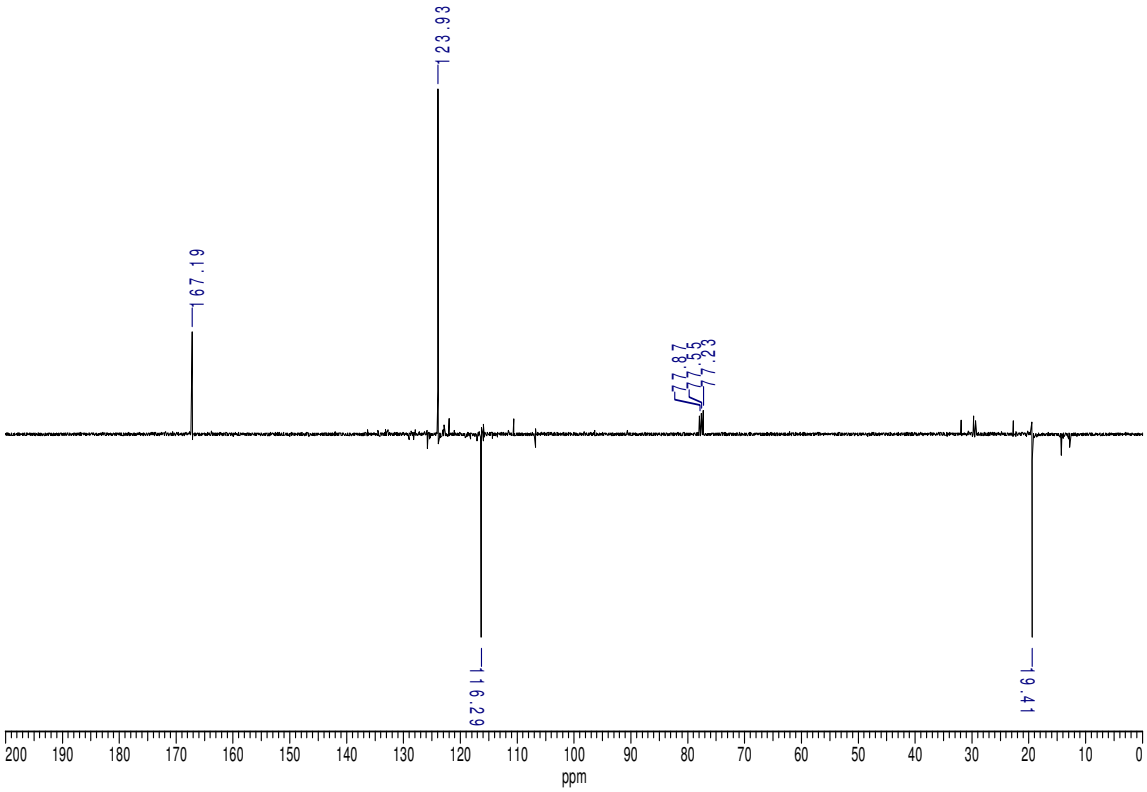
13C NMR of (*3S,6S,7R*)-3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoic acid (44)



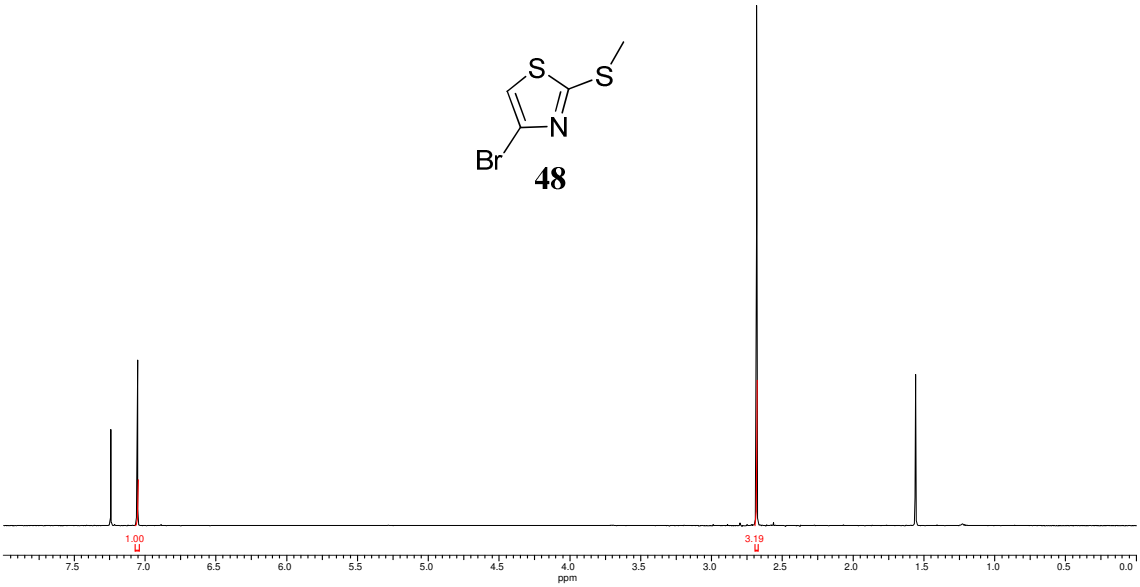
^{1}H NMR of 2-methyl-4-bromothiazole (47)



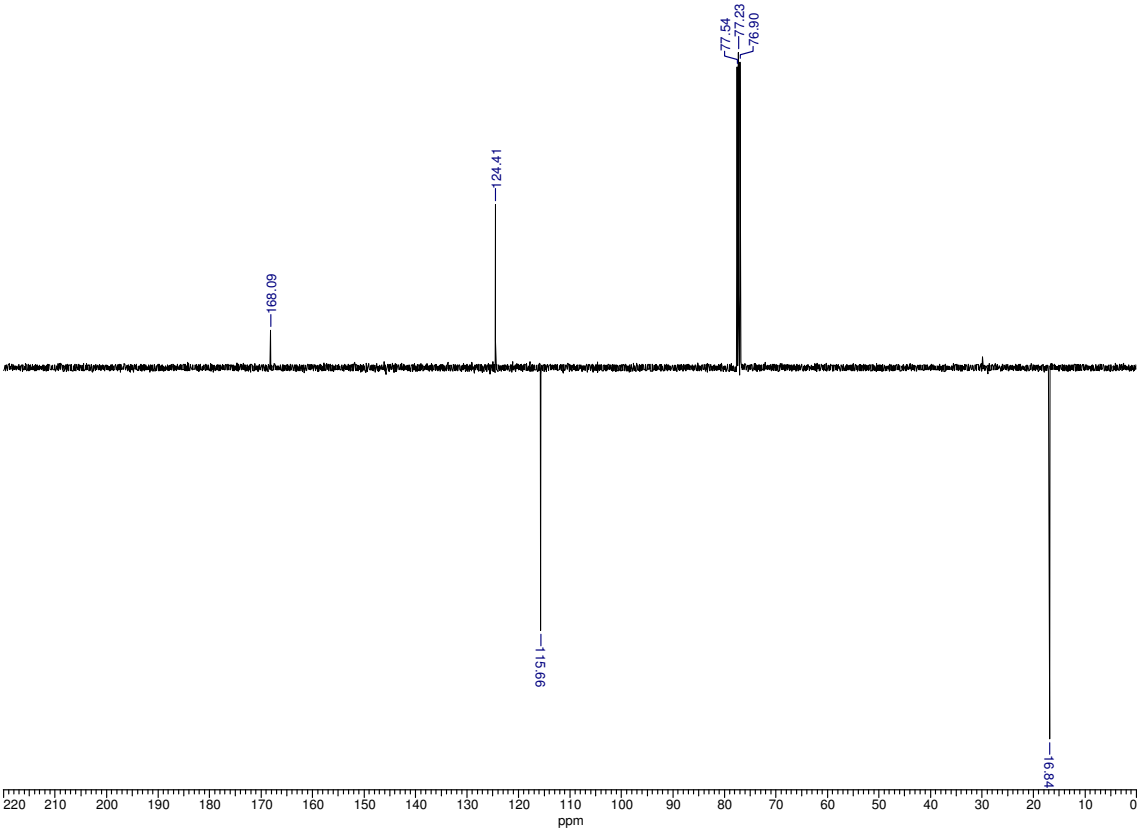
^{13}C NMR of 2-methyl-4-bromothiazole (47)



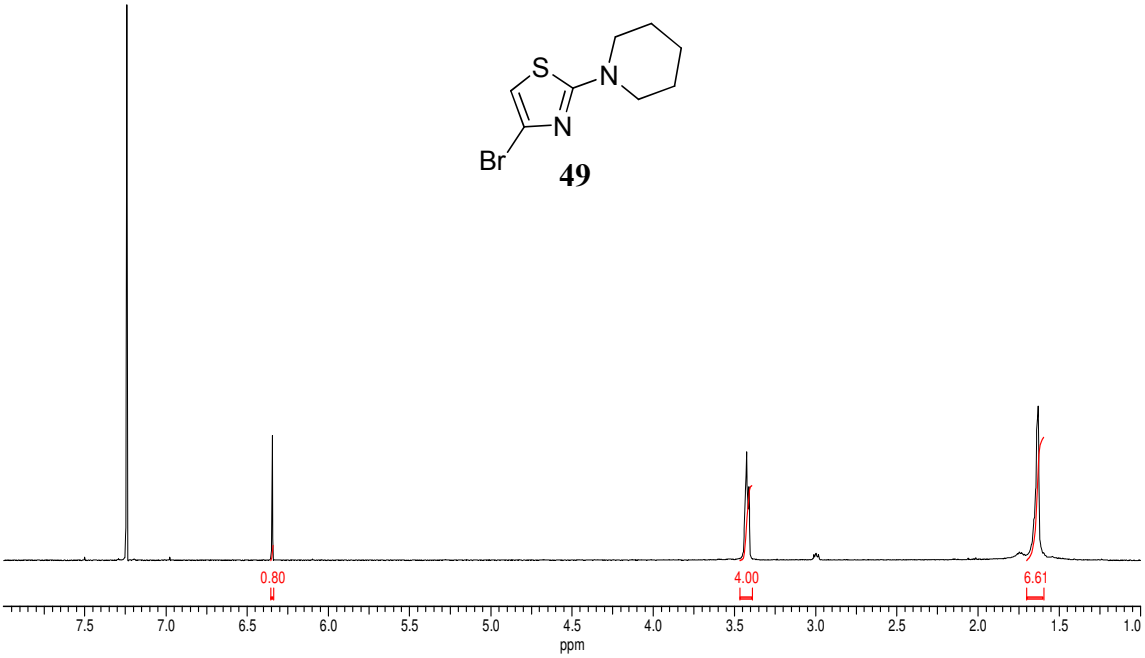
^{1}H NMR of 2-(methylthio)-4-bromothiazole (48)



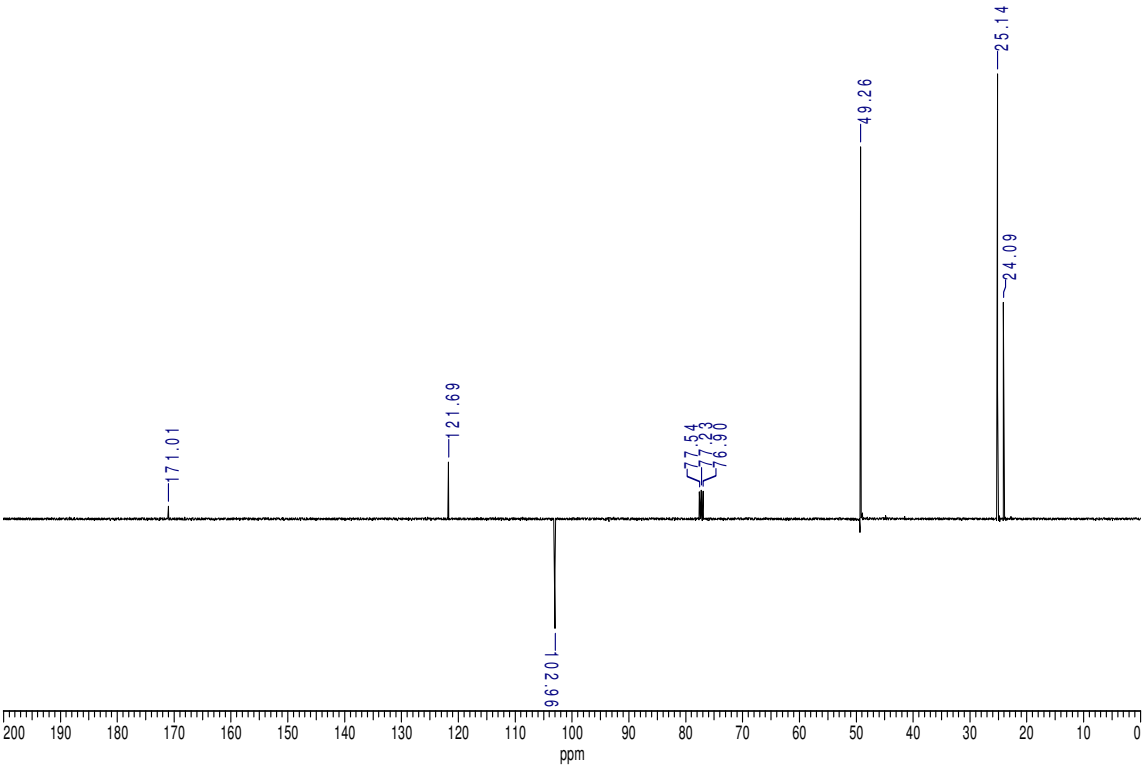
^{13}C NMR of 2-(methylthio)-4-bromothiazole (48)



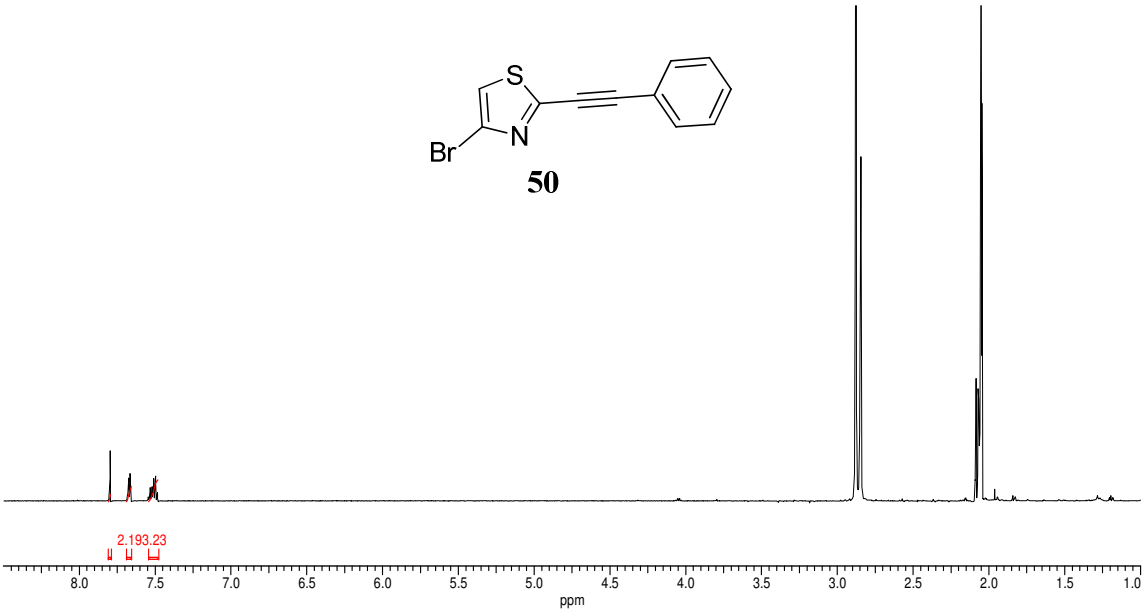
^{1}H NMR of 2-(piperidin-1-yl)-4-bromothiazole (49)



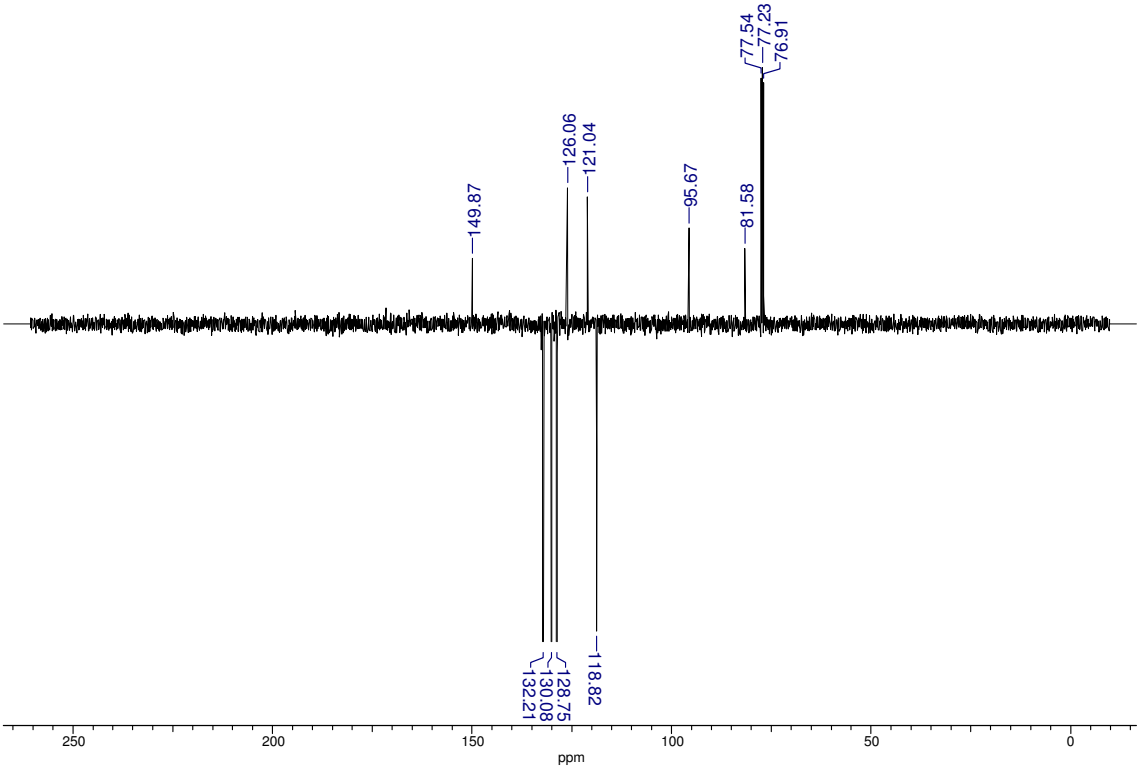
^{13}C NMR of 2-(piperidin-1-yl)-4-bromothiazole (49)



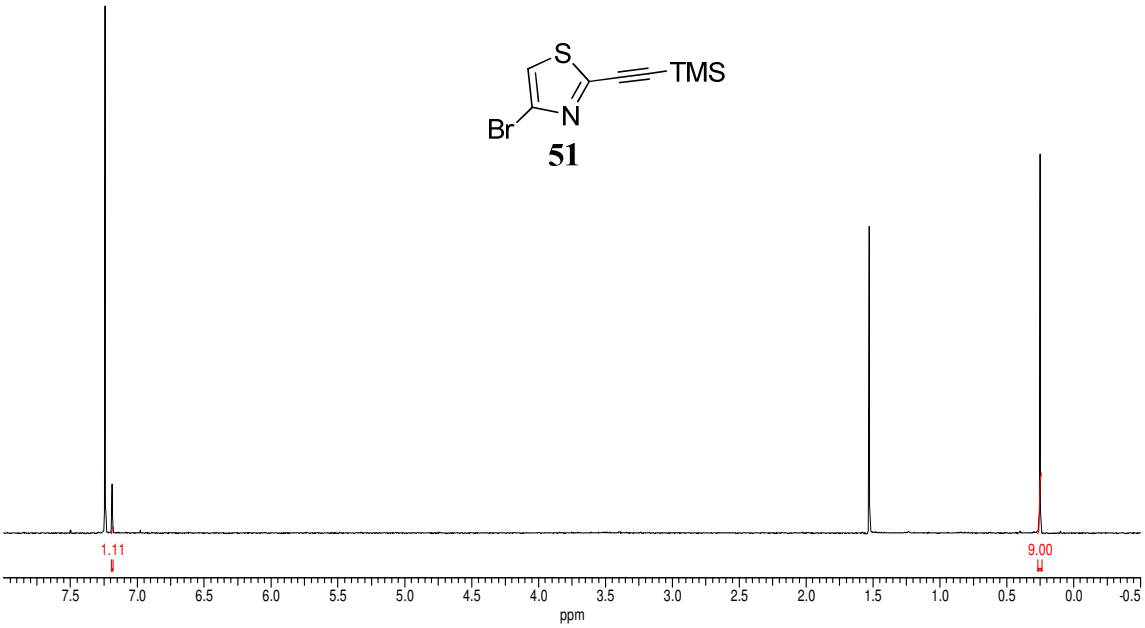
^{1}H NMR of 2-(phenylethynyl)-4-bromothiazole (50)



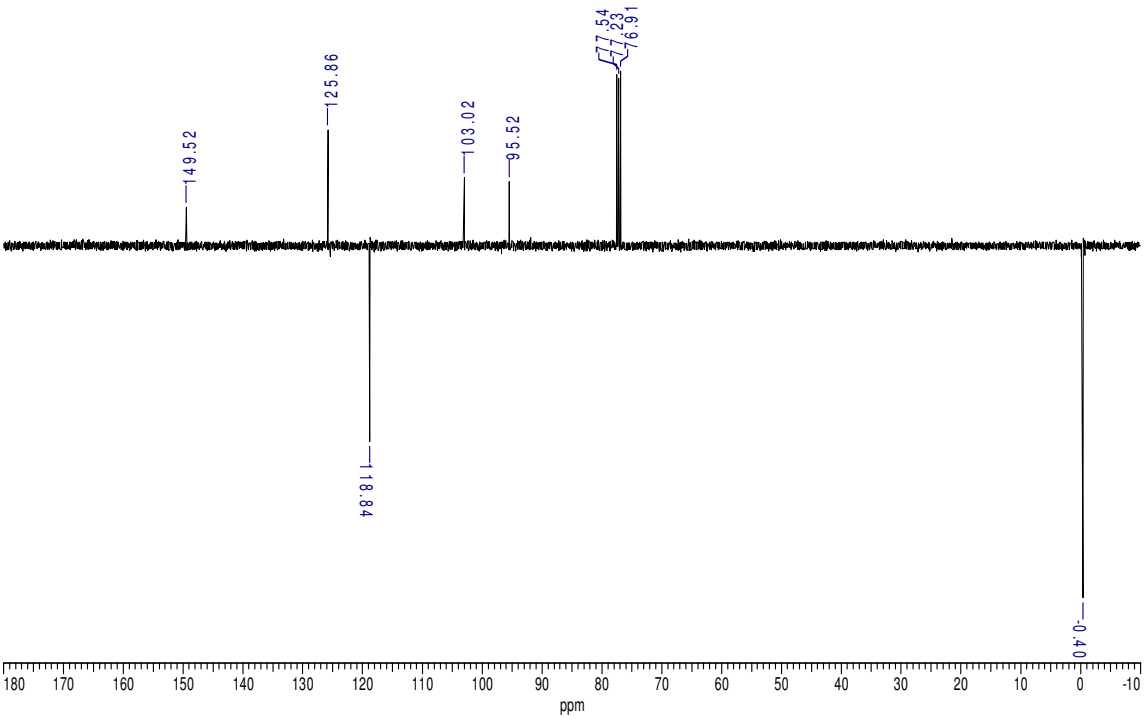
^{13}C NMR of 2-(phenylethynyl)-4-bromothiazole (50)



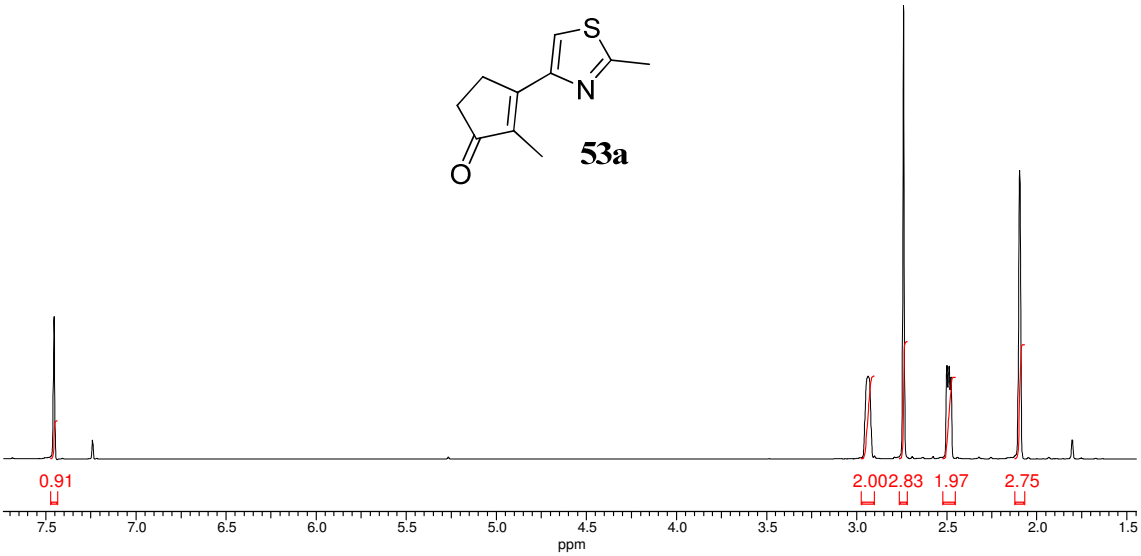
^{1}H NMR of 2–((trimethylsilyl)ethynyl)-4-bromothiazole (51)



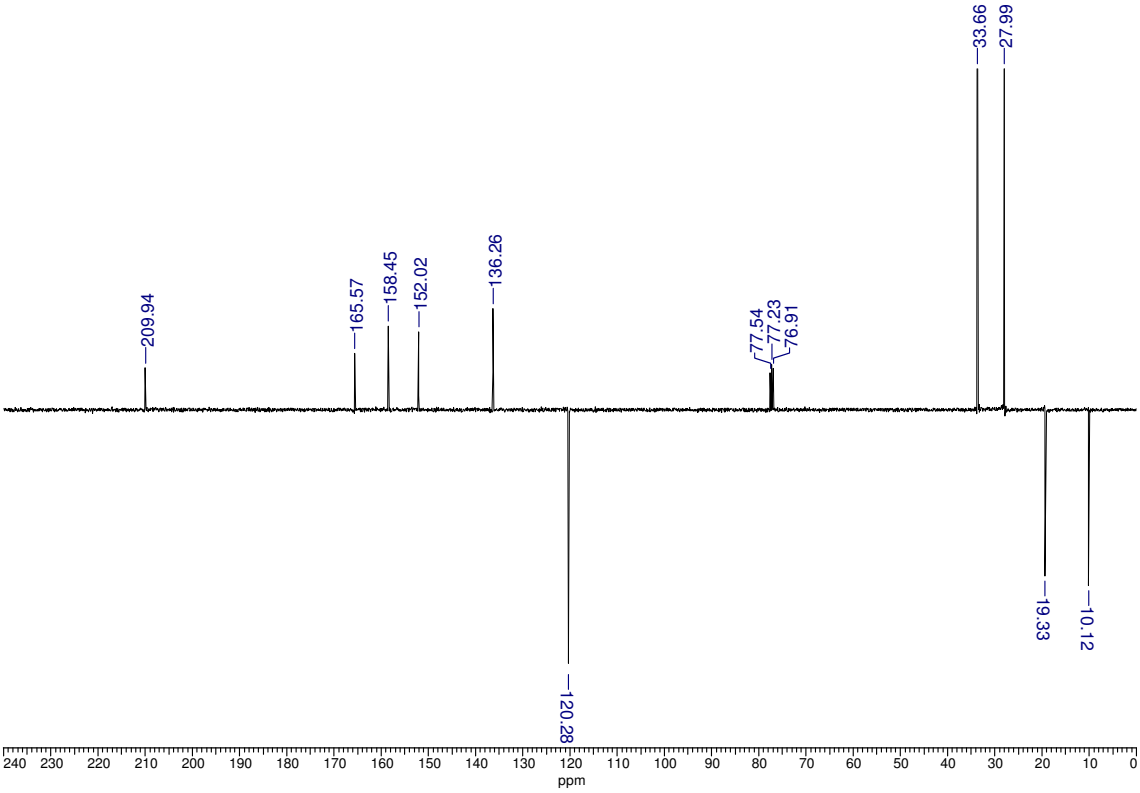
^{13}C NMR of 2–((trimethylsilyl)ethynyl)-4-bromothiazole (51)



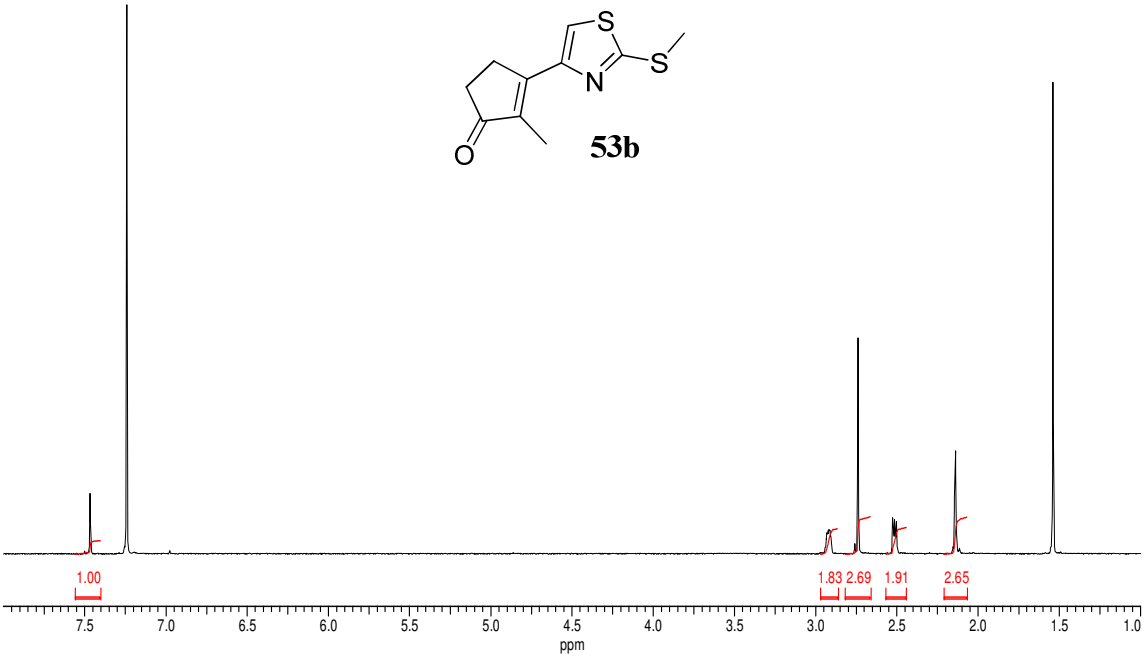
^{1}H NMR of 2-methyl-3-(2-methylthiazol-4-yl)cyclopent-2-enone (53a)



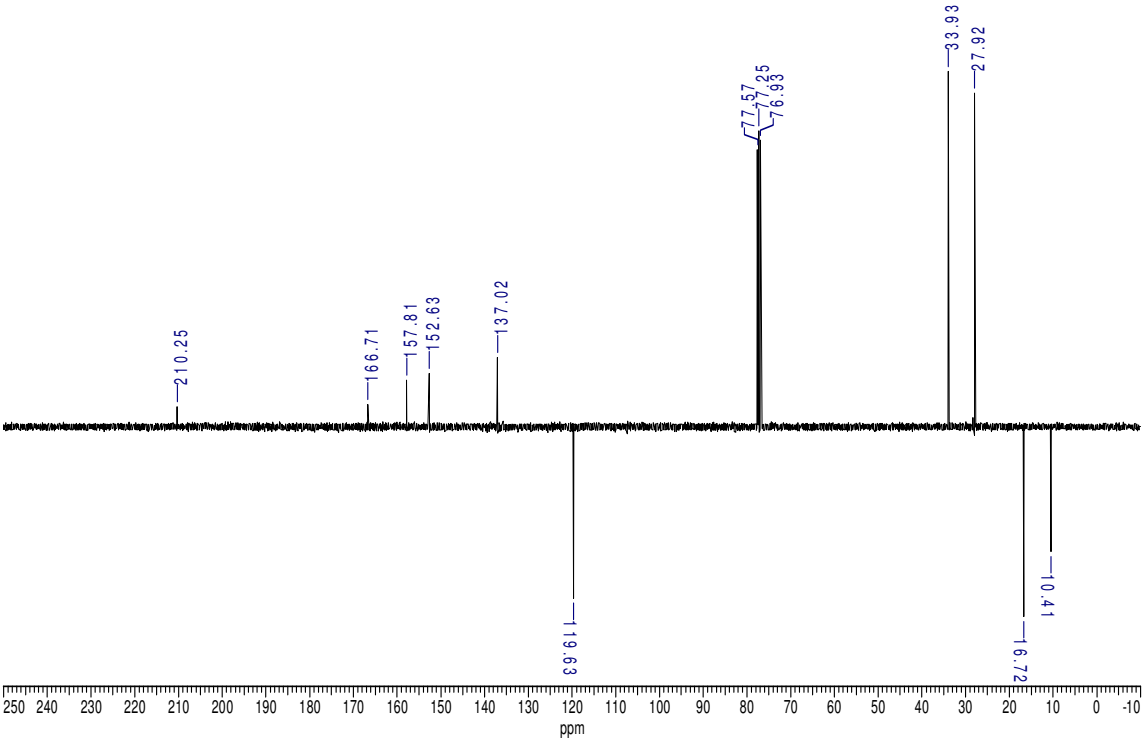
13C NMR of 2-methyl-3-(2-methylthiazol-4-yl)cyclopent-2-enone (53a)



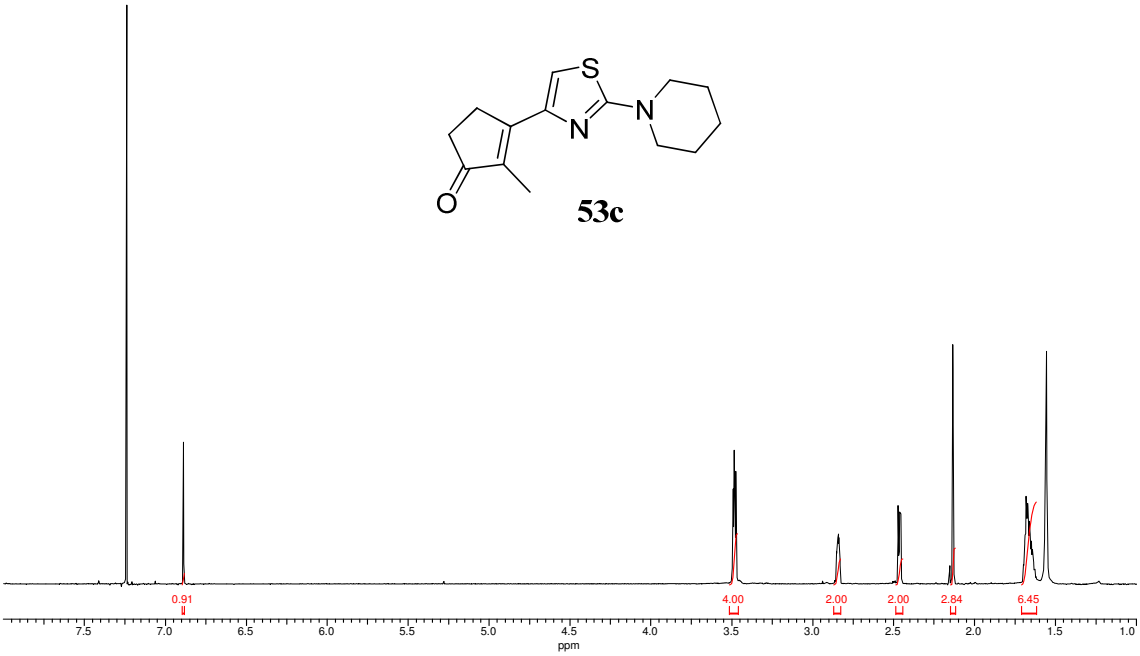
^{1}H NMR of 2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enone (53b)



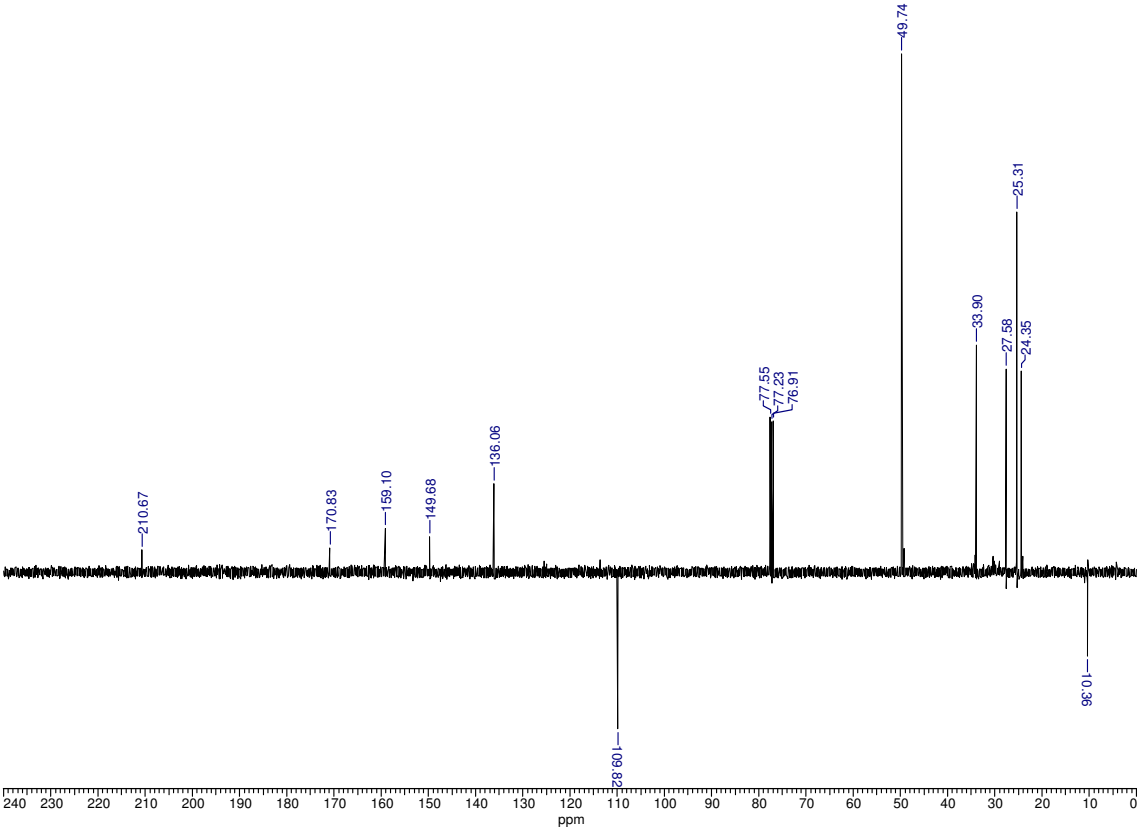
^{13}C NMR of 2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enone (53b)



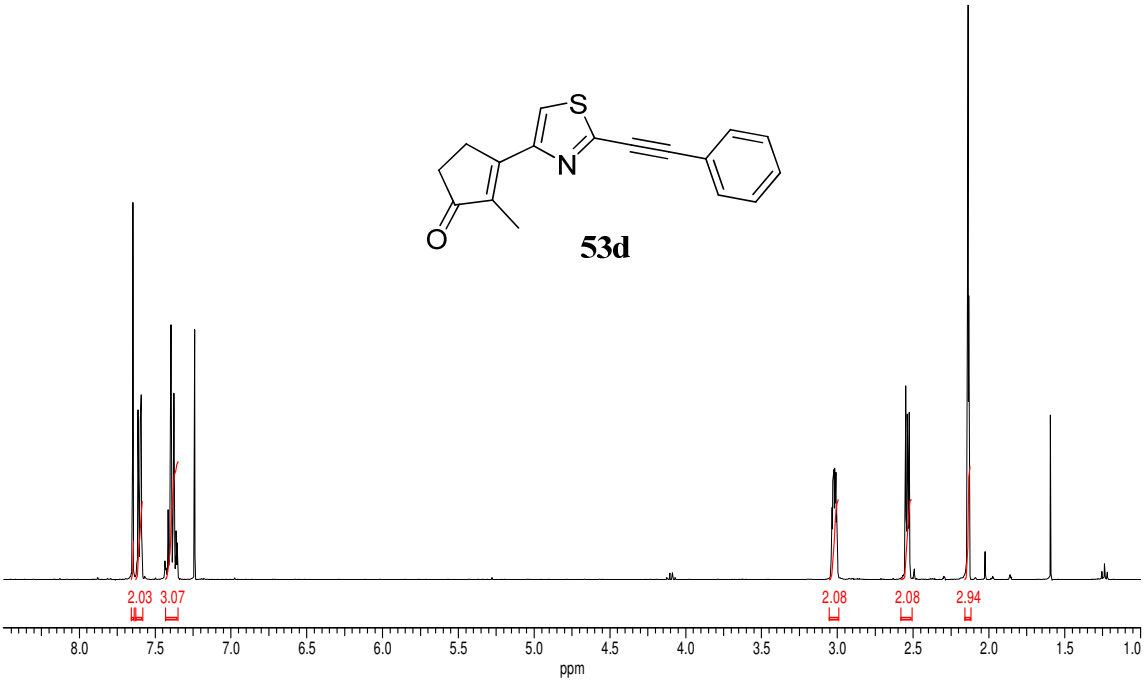
^{1}H NMR of 2-methyl-3-(2-(piperidin-1-yl)thiazol-4-yl)cyclopent-2-enone (53c)



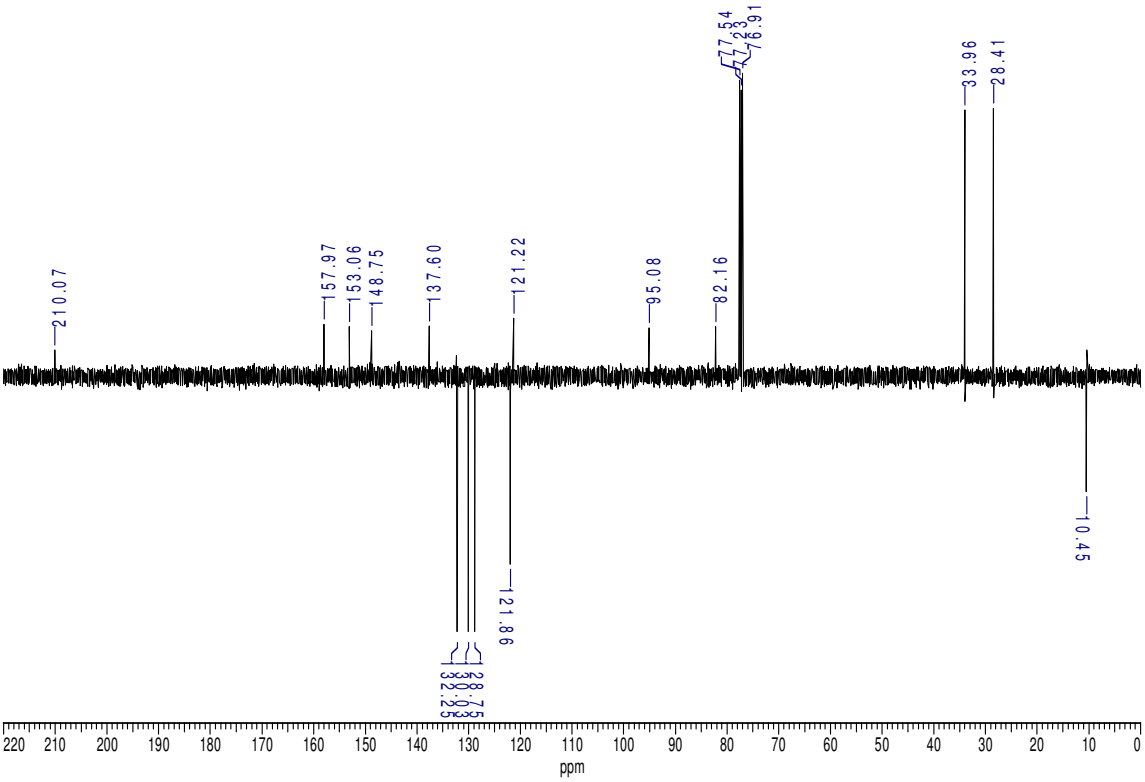
^{13}C NMR of 2-methyl-3-(2-(piperidin-1-yl)thiazol-4-yl)cyclopent-2-enone (53c)



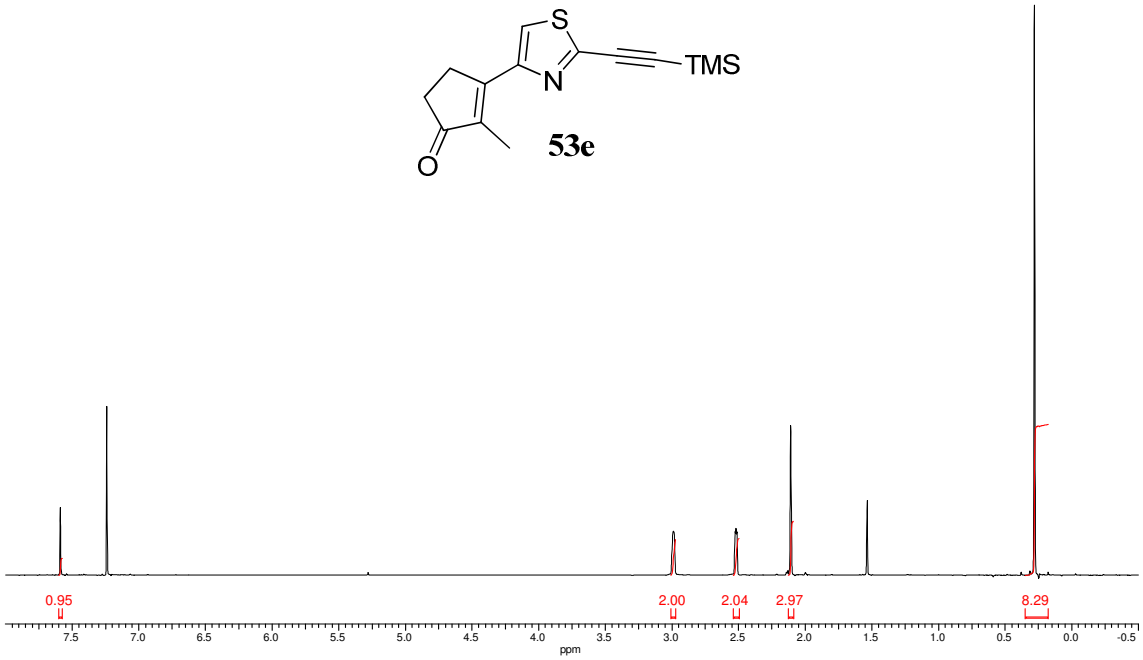
^{1}H NMR of 2-methyl-3-(2-(phenylethynyl)thiazol-4-yl)cyclopent-2-enone (53d)



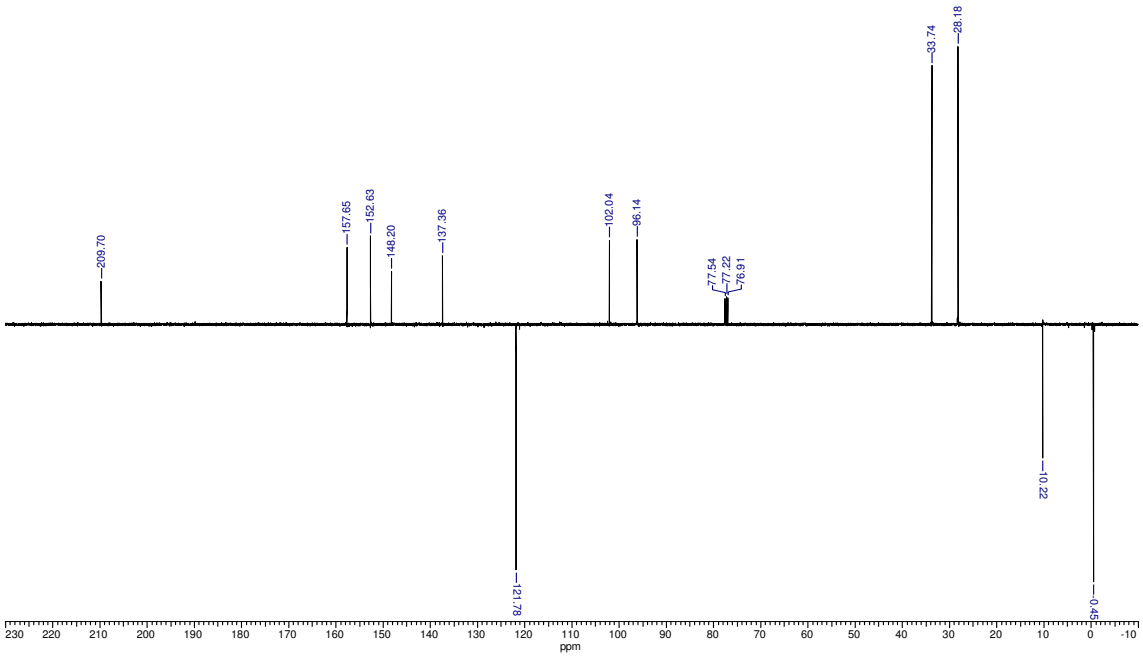
^{13}C NMR of 2-methyl-3-(2-(phenylethynyl)thiazol-4-yl)cyclopent-2-enone (53d)



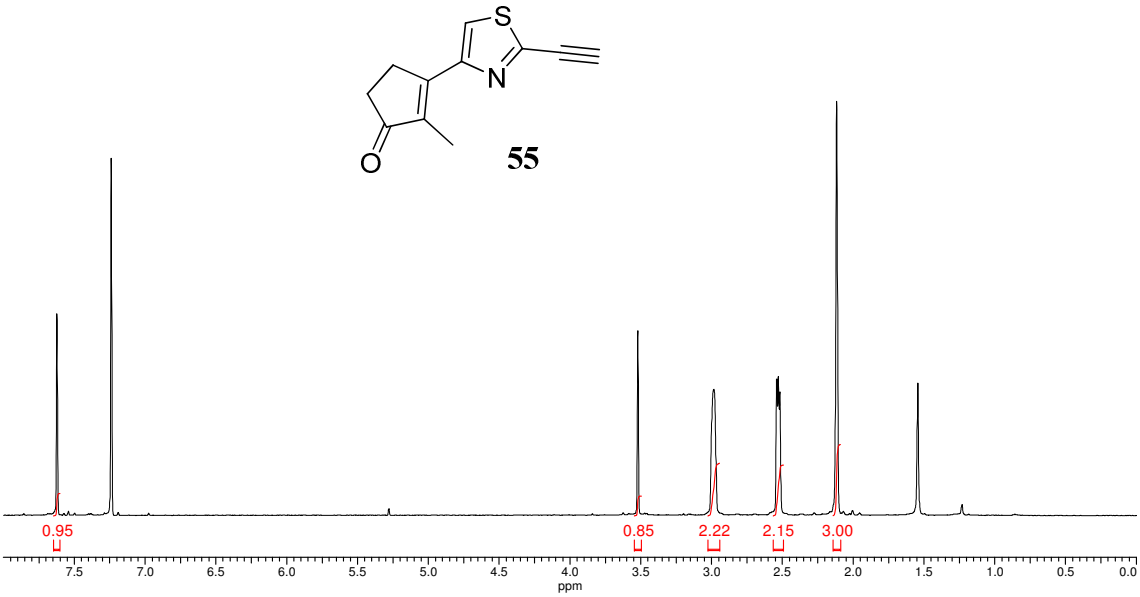
^{1}H NMR of 2-methyl-3-(2-((trimethylsilyl)ethynyl)thiazol-4-yl)cyclopent-2-enone (53e)



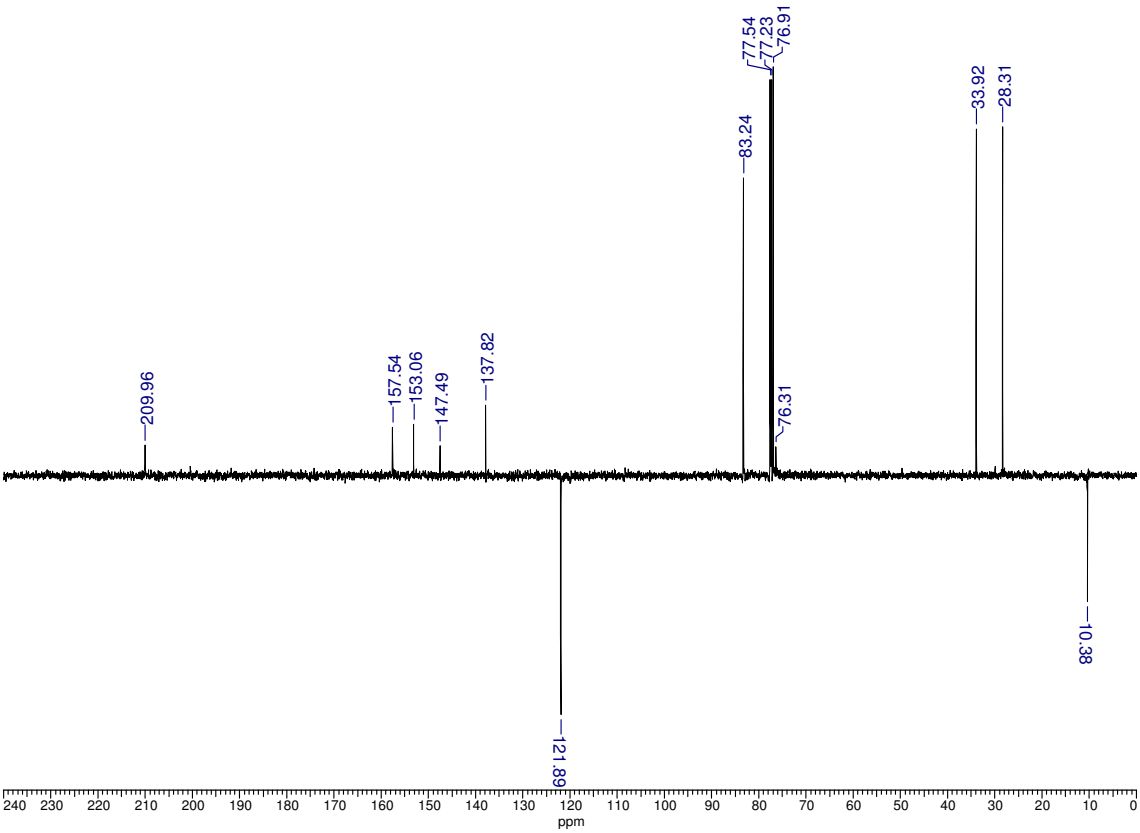
^{13}C NMR of 2-methyl-3-(2-((trimethylsilyl)ethynyl)thiazol-4-yl)cyclopent-2-enone (53e)



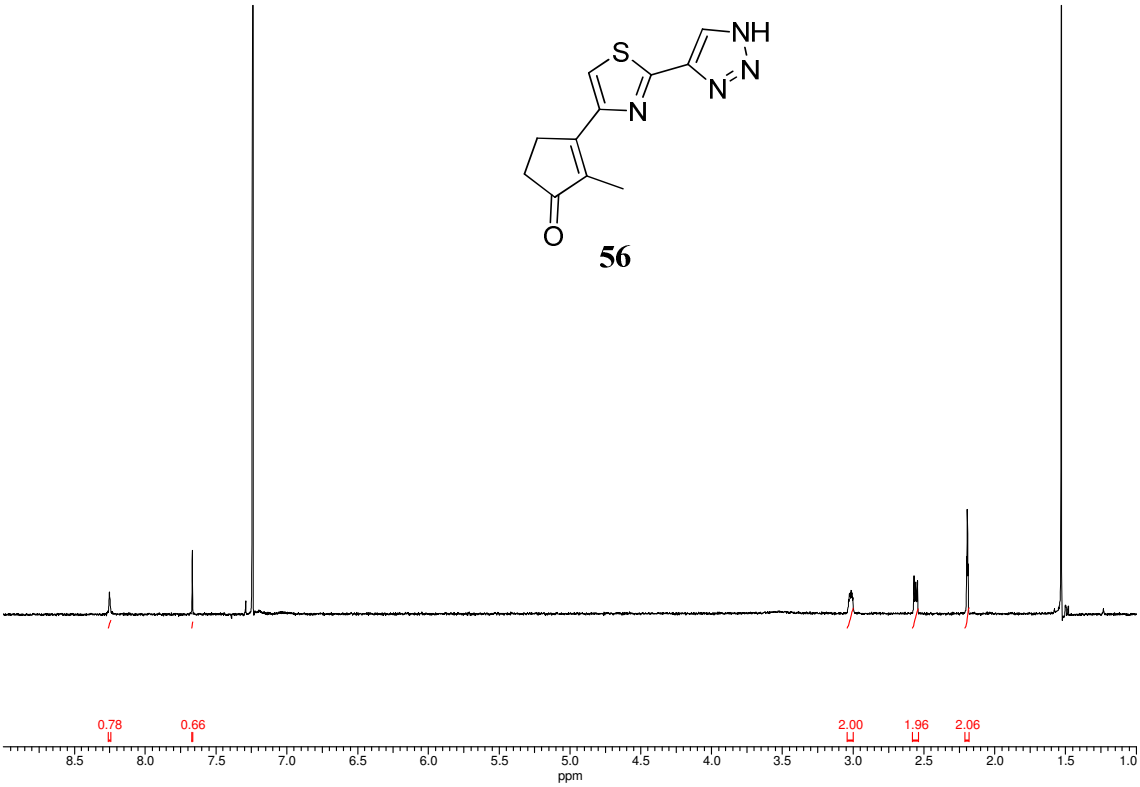
^{1}H NMR of 3-(2-ethynylthiazol-4-yl)-2-methylcyclopent-2-enone (55)



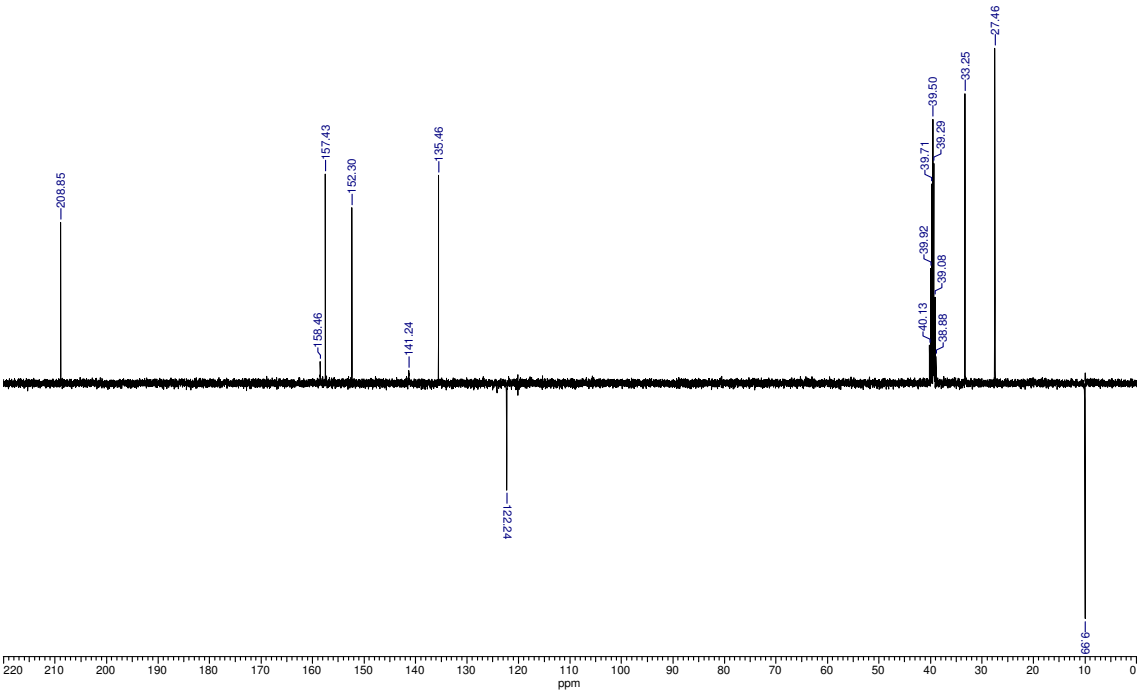
13C NMR of 3-(2-ethynylthiazol-4-yl)-2-methylcyclopent-2-enone (55)



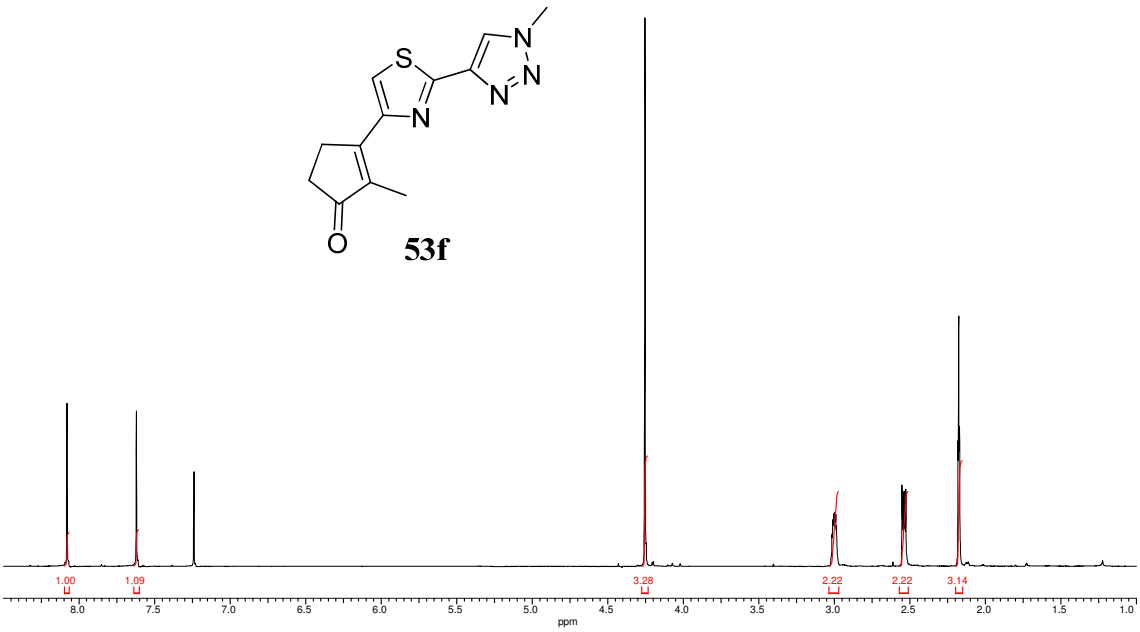
^{1}H NMR of 3-(2-(1H-1,2,3-triazol-4-yl)thiazol-4-yl)-2-methylcyclopent-2-enone (56)



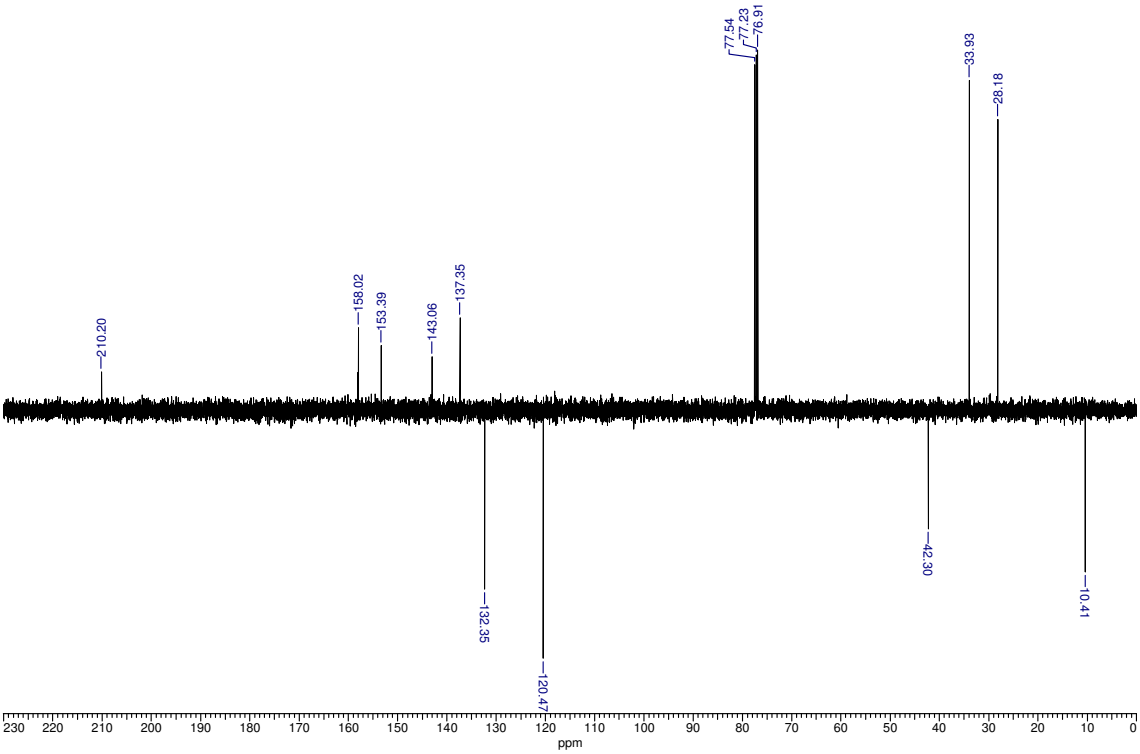
^{13}C NMR of 3-(2-(1H-1,2,3-triazol-4-yl)thiazol-4-yl)-2-methylcyclopent-2-enone (56)



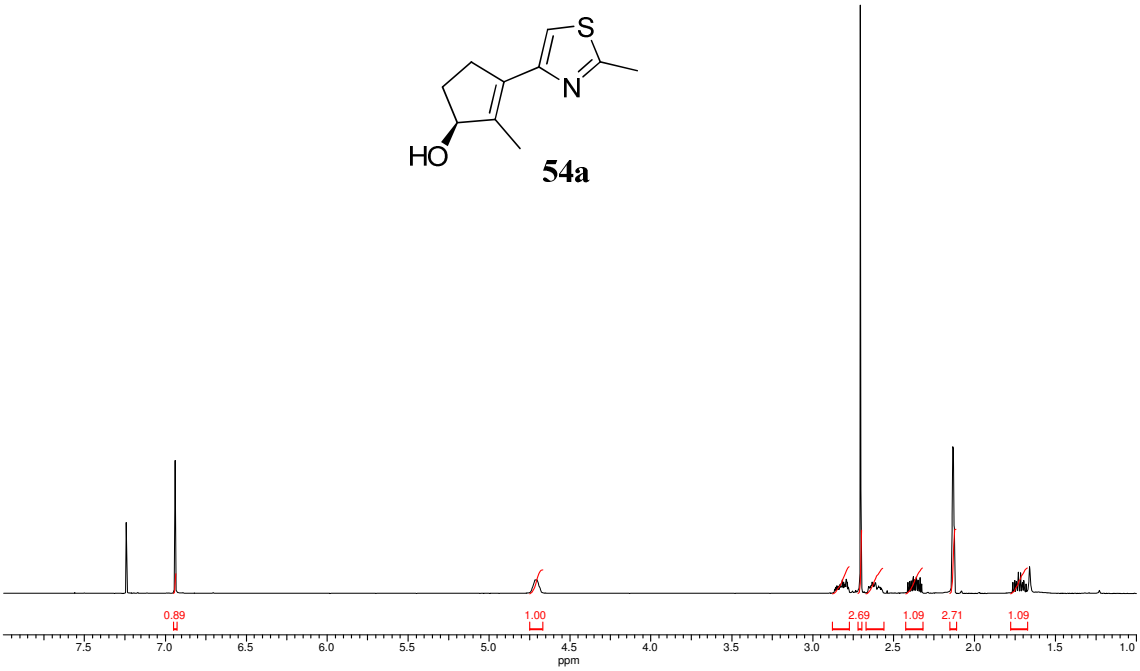
^{1}H NMR of 2-methyl-3-(2-(1-methyl-1H-1,2,3-triazol-4-yl)thiazol-4-yl)cyclopent-2-enone (53f)



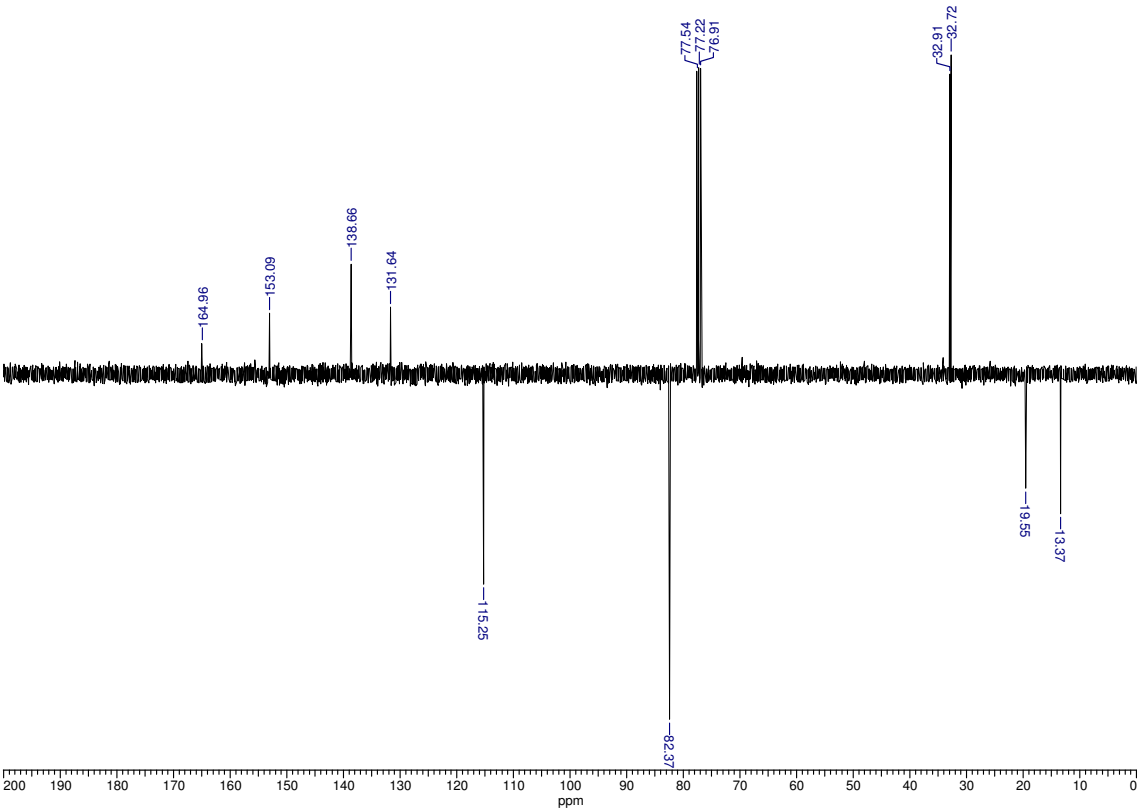
^{13}C NMR of 2-methyl-3-(2-(1-methyl-1H-1,2,3-triazol-4-yl)thiazol-4-yl)cyclopent-2-enone (53f)



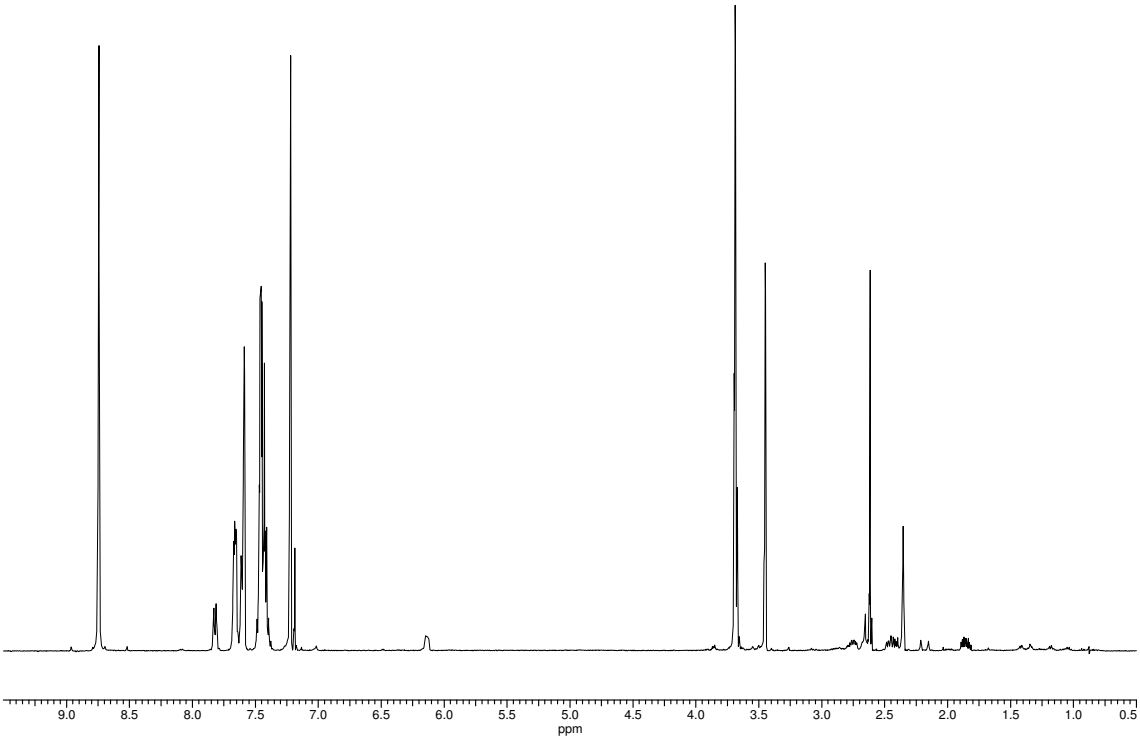
^{1}H NMR of (*S*)-2-methyl-3-(2-methylthiazol-4-yl)cyclopent-2-enol (54a)



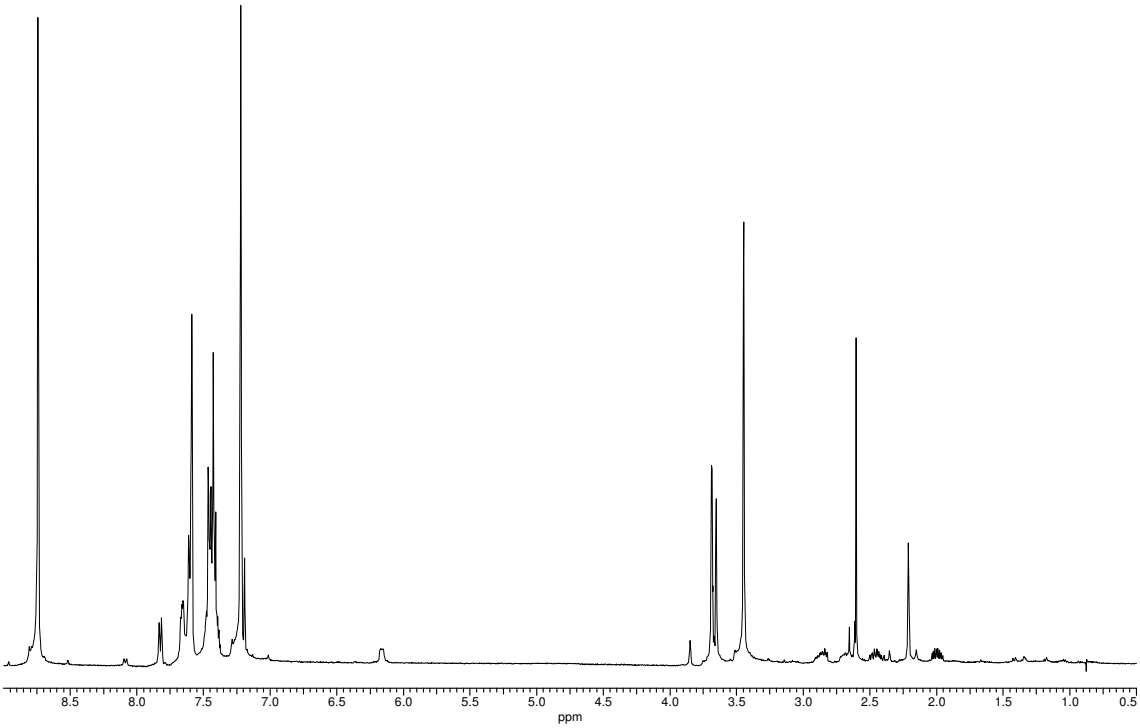
^{13}C NMR of (*S*)-2-methyl-3-(2-methylthiazol-4-yl)cyclopent-2-enol (54a)



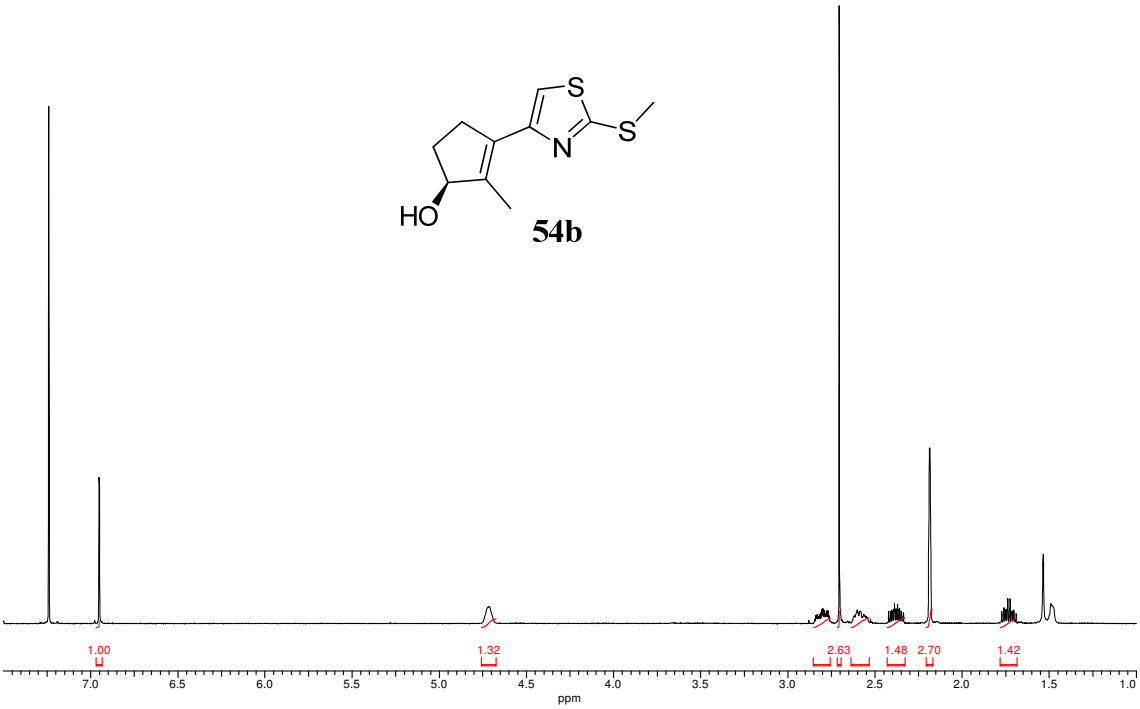
^{1}H NMR of S-Mosher ester of (54a)



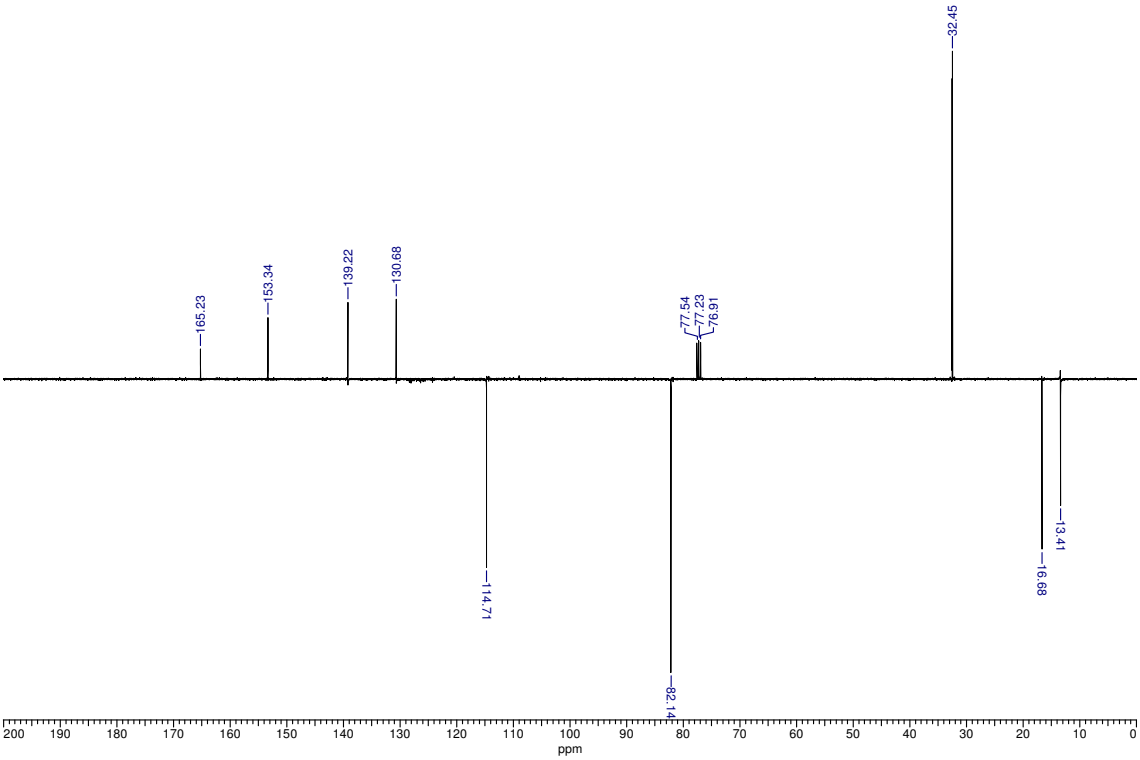
^{1}H NMR of R-Mosher ester of (54a)



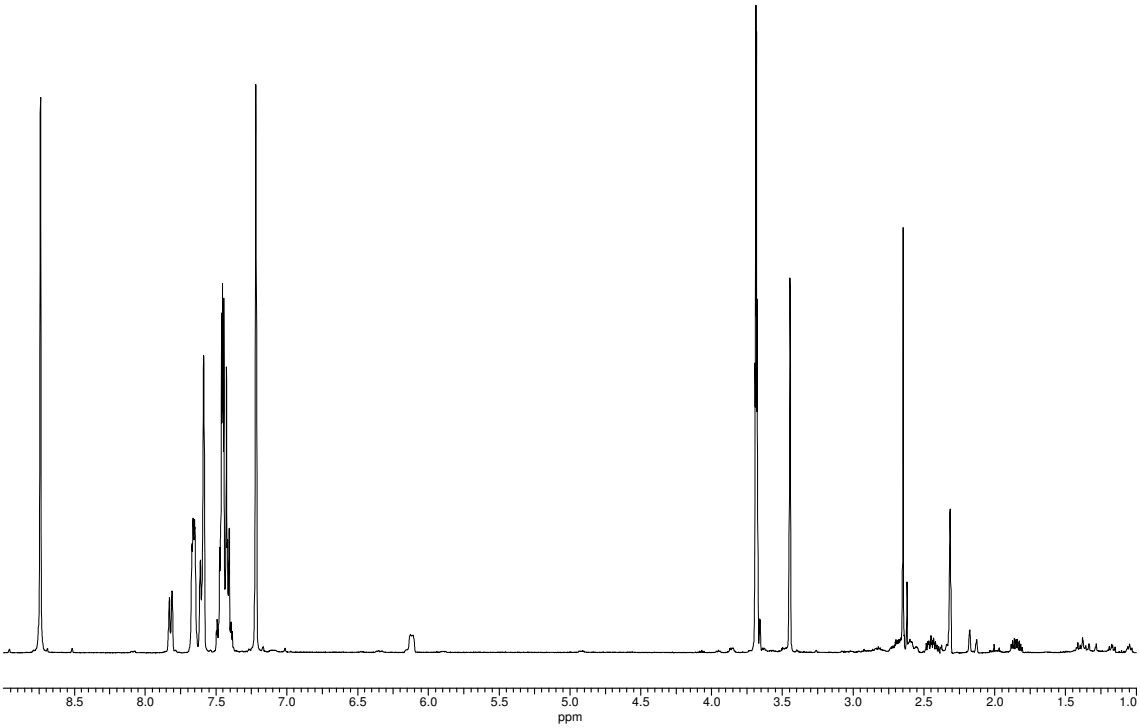
^{1}H NMR of (*S*)-2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enol (54b)



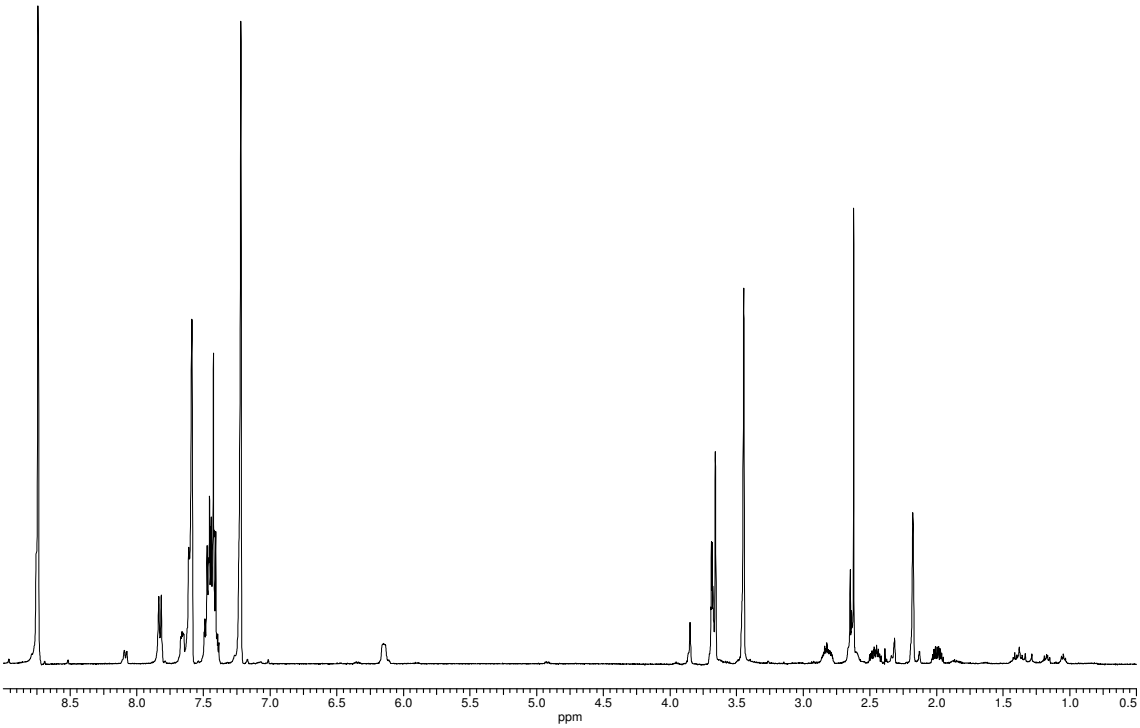
^{13}C NMR of (*S*)-2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enol (54b)



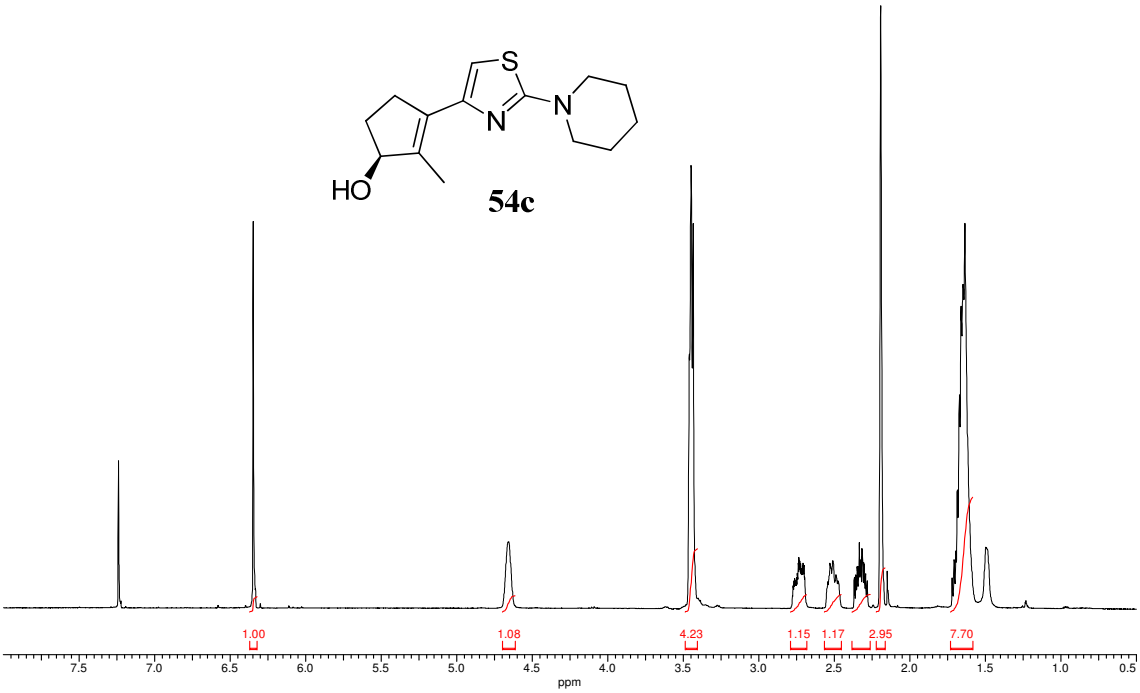
^{1}H NMR of S-Mosher ester of (54b)



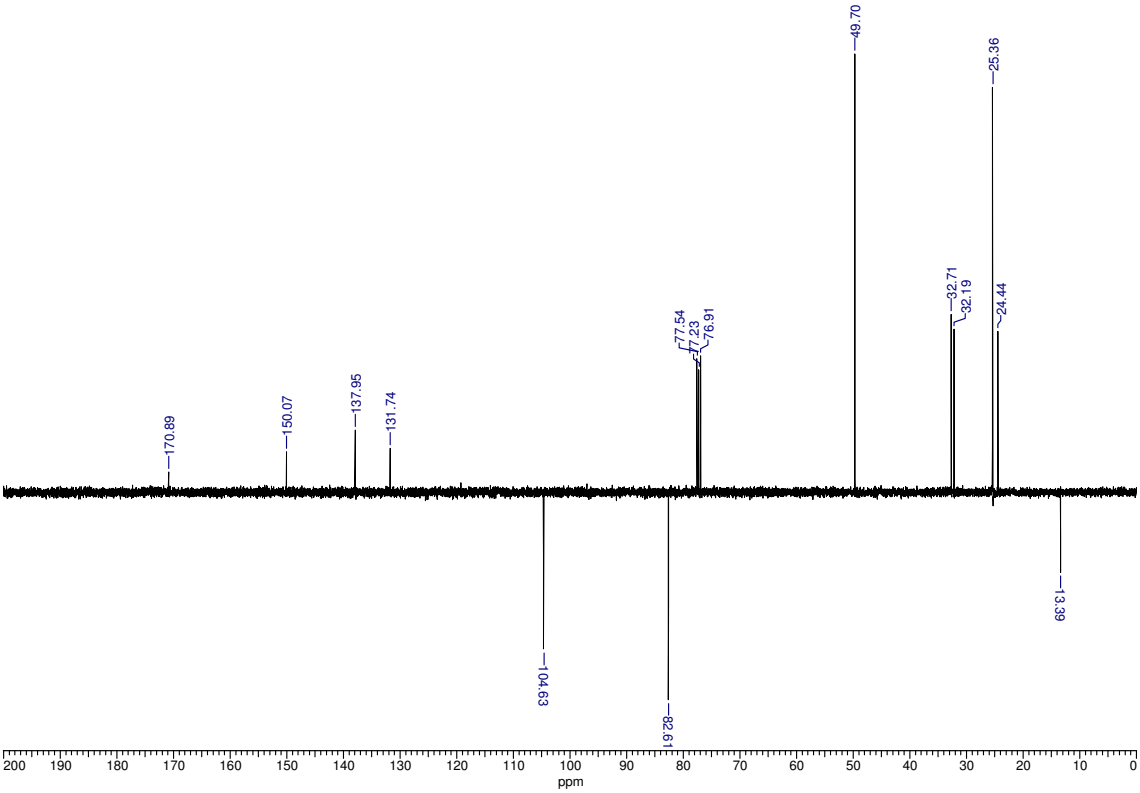
^{1}H NMR of R-Mosher ester of (54b)



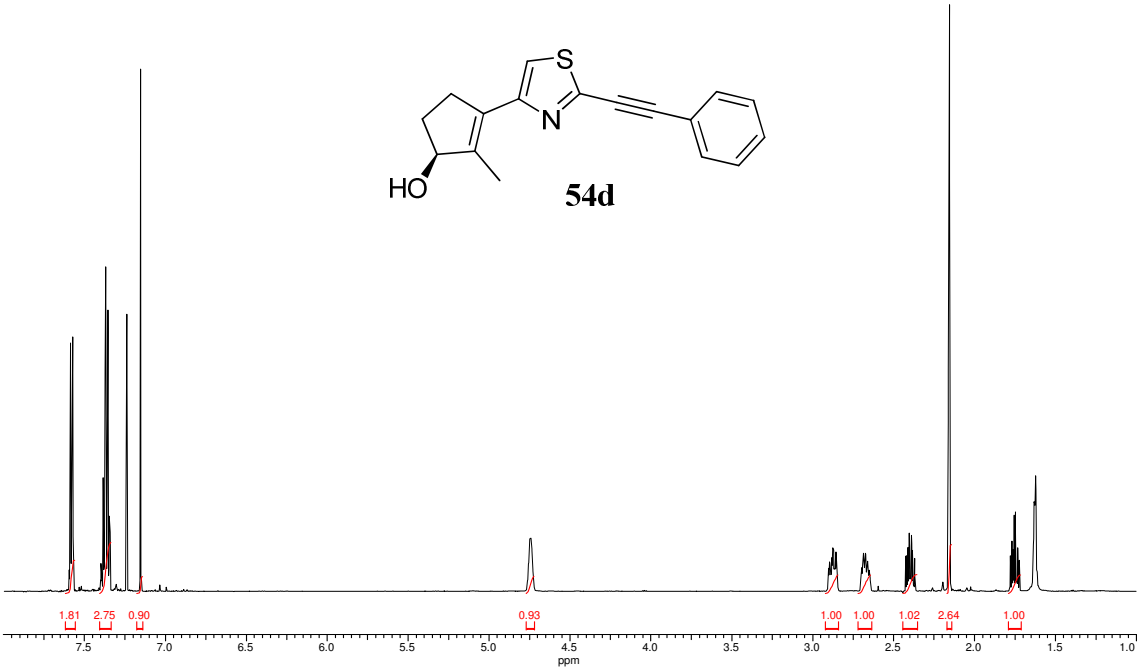
^{1}H NMR of 2-methyl-3-(2-(piperidin-1-yl)thiazol-4-yl)cyclopent-2-enol (54c)



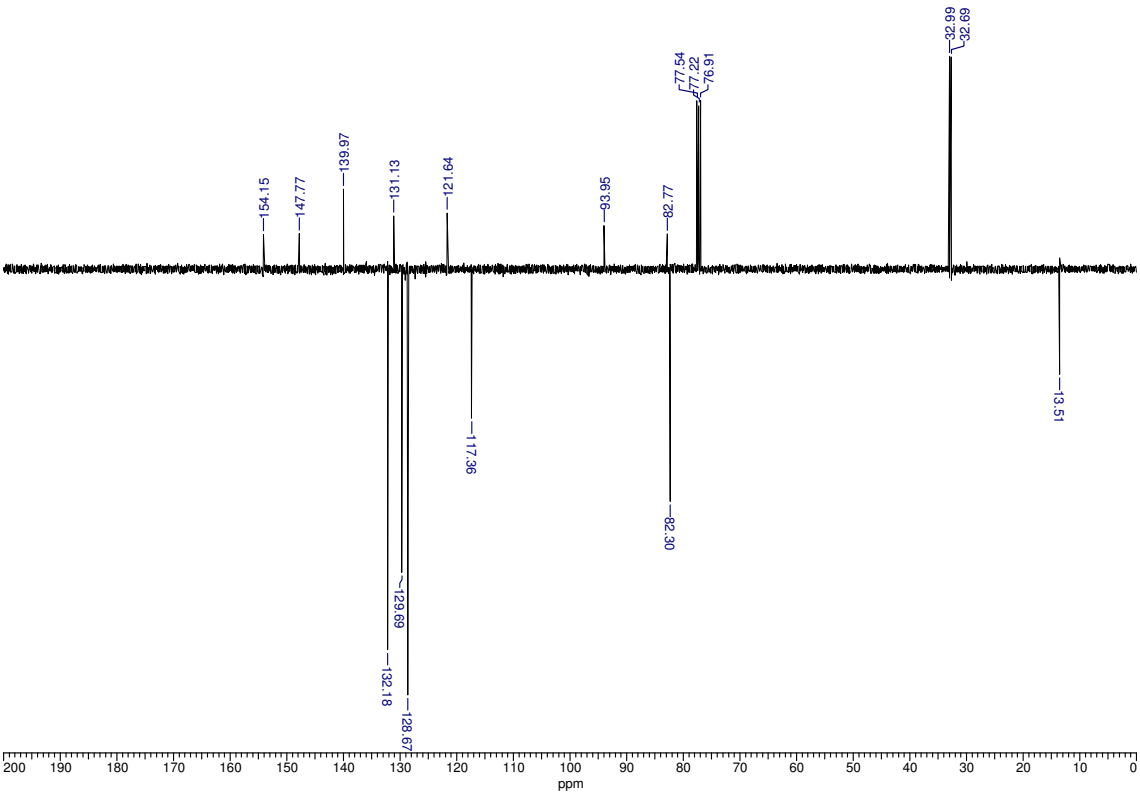
^{13}C NMR of 2-methyl-3-(2-(piperidin-1-yl)thiazol-4-yl)cyclopent-2-enol (54c)



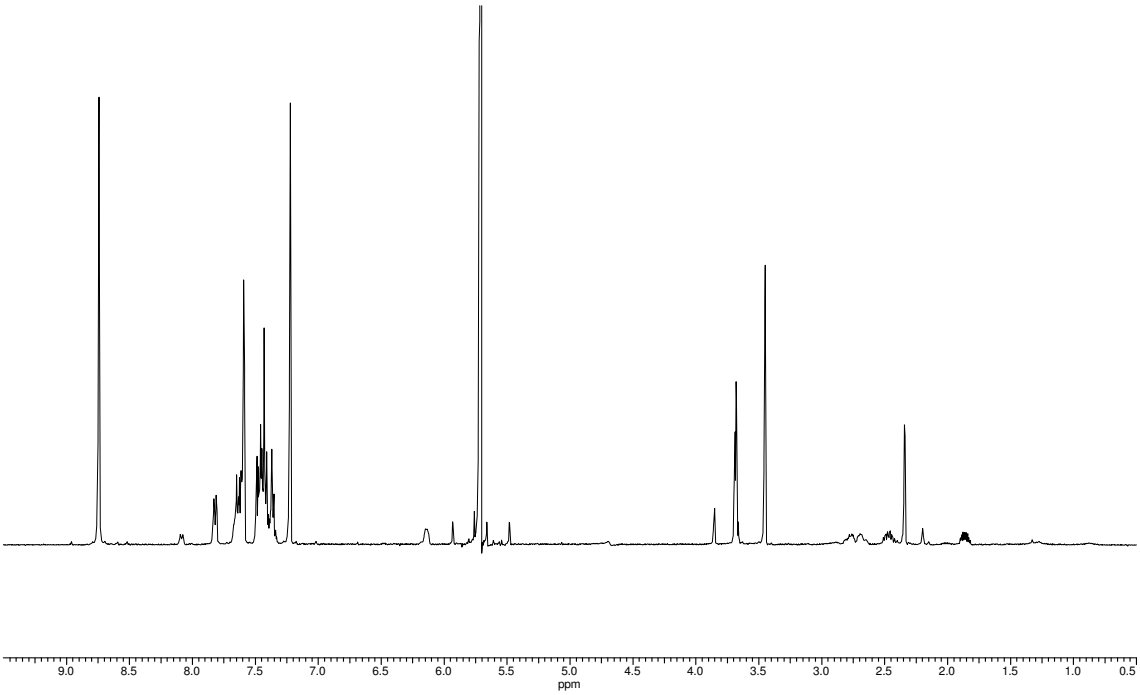
^{1}H NMR of (*S*)-2-methyl-3-(2-(phenylethynyl)thiazol-4-yl)cyclopent-2-enol (54d)



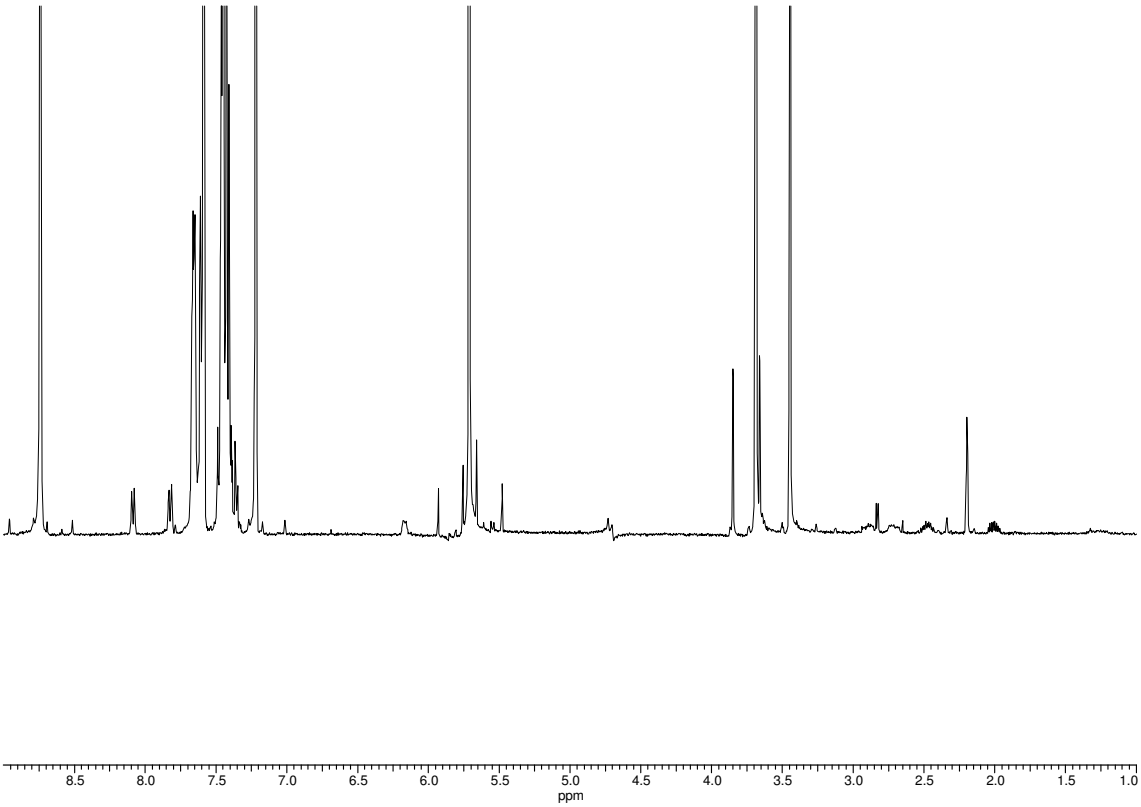
^{13}C NMR of (*S*)-2-methyl-3-(2-(phenylethynyl)thiazol-4-yl)cyclopent-2-enol (54d)



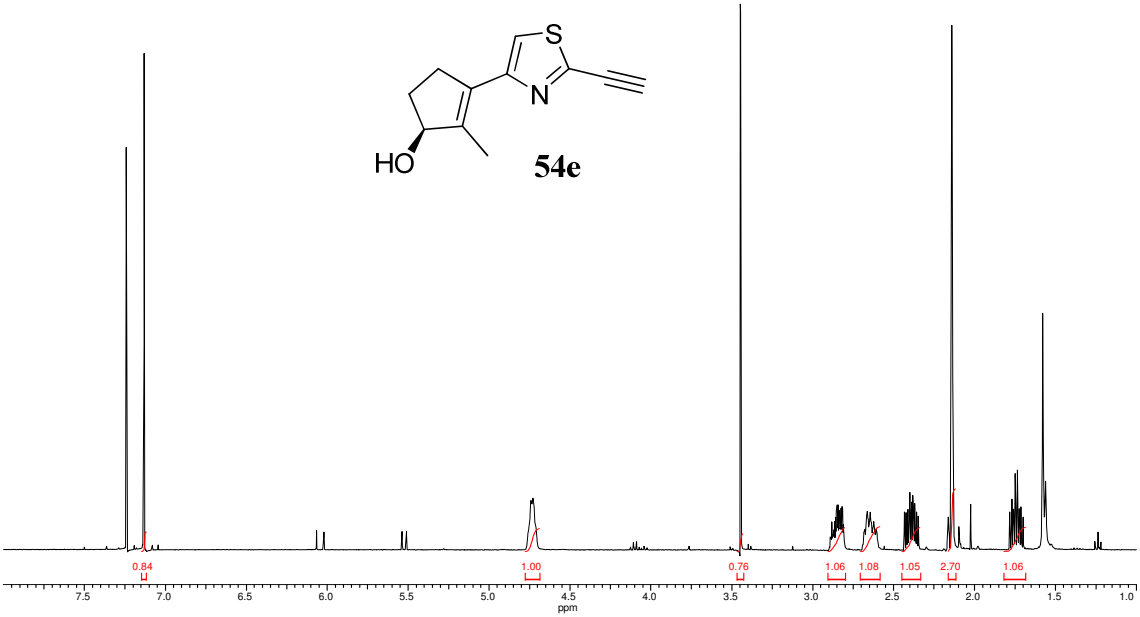
^{1}H NMR of S-Mosher ester of (54d)



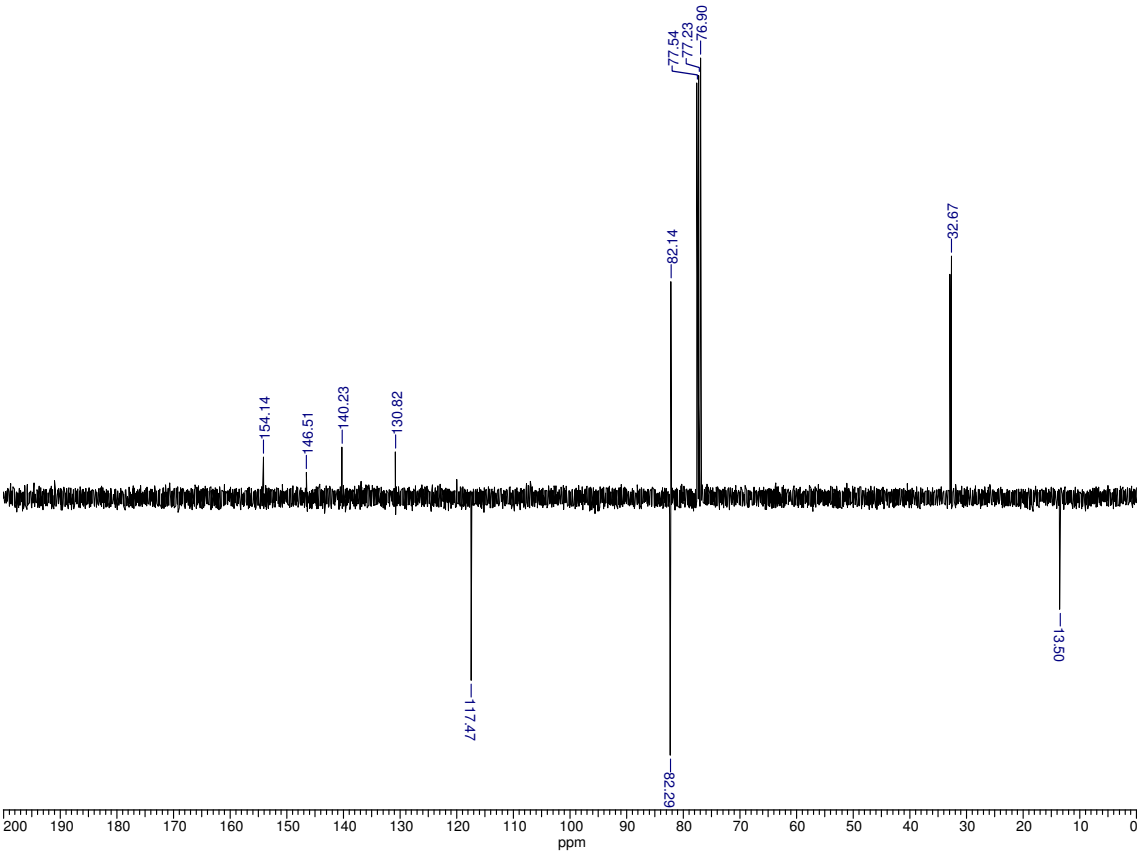
^{1}H NMR of R-Mosher ester of (54d)



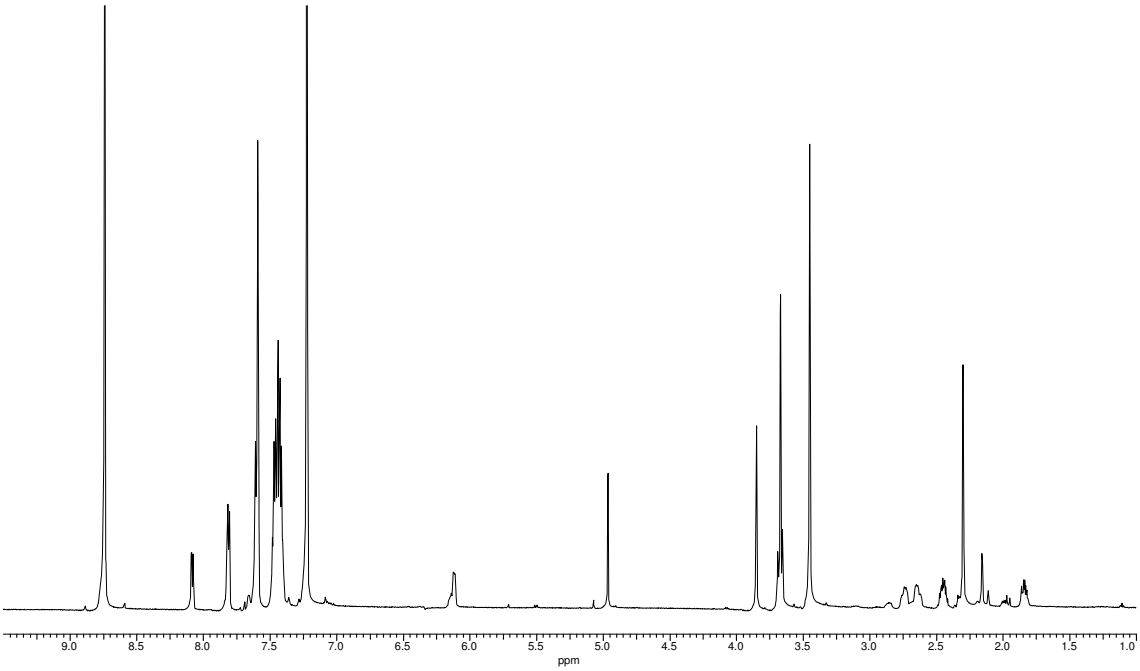
^{1}H NMR of (*S*)-3-(2-ethynylthiazol-4-yl)-2-methylcyclopent-2-enol (54e)



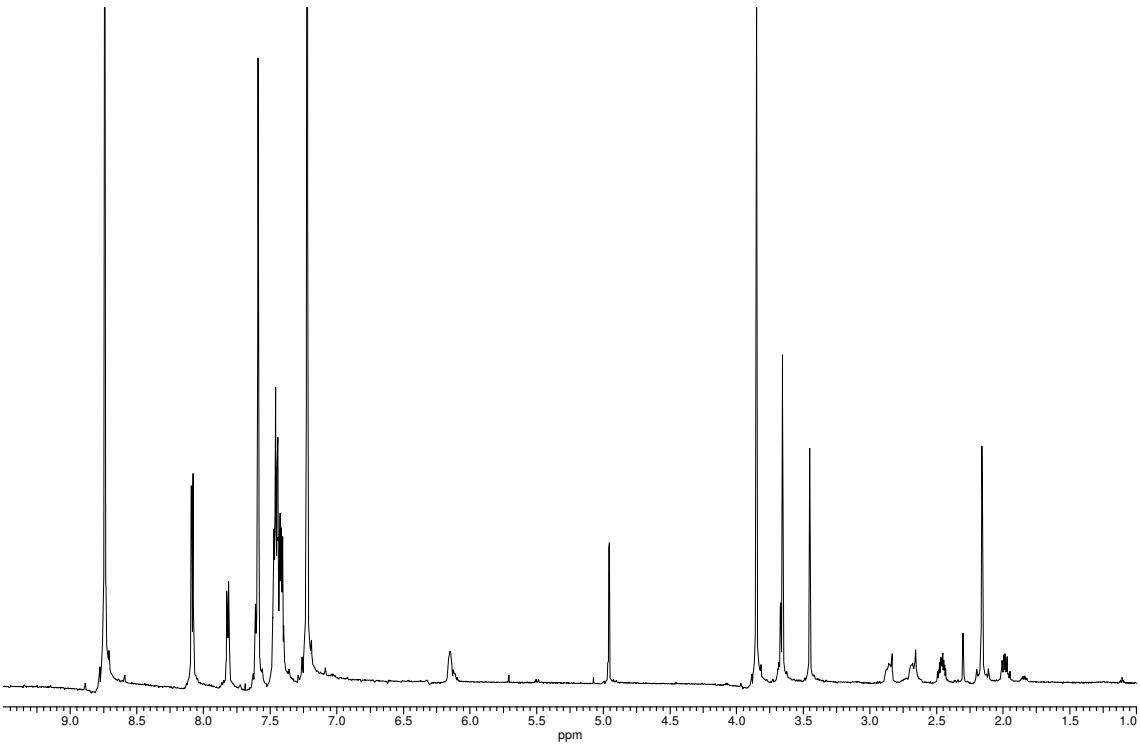
^{13}C NMR of (*S*)-3-(2-ethynylthiazol-4-yl)-2-methylcyclopent-2-enol (54e)



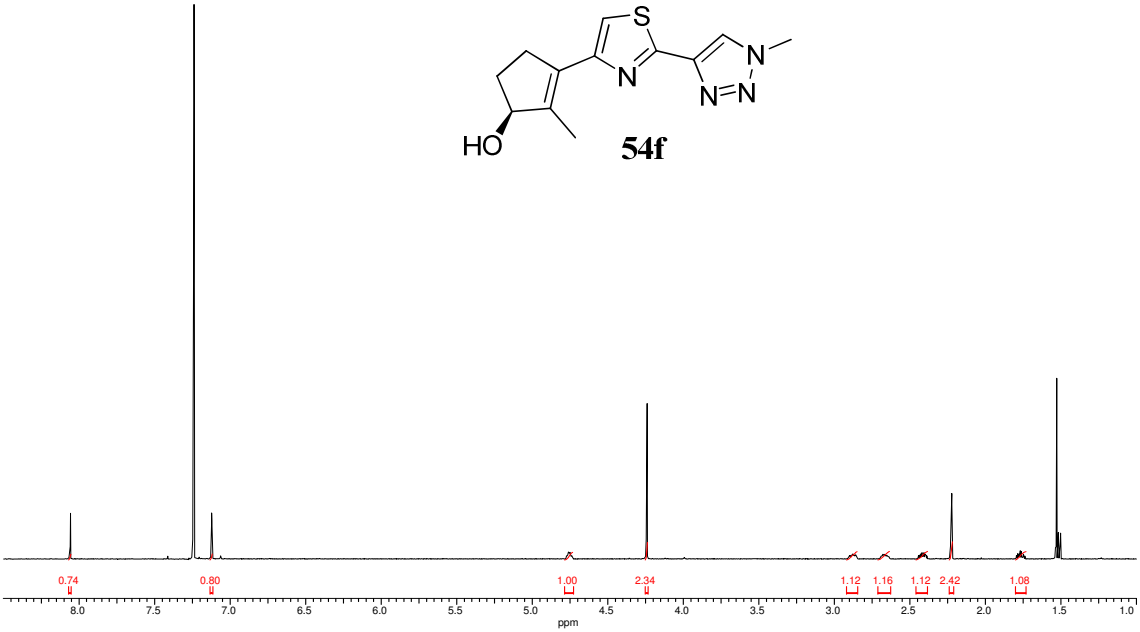
^{1}H NMR of S-Mosher ester of (54e)



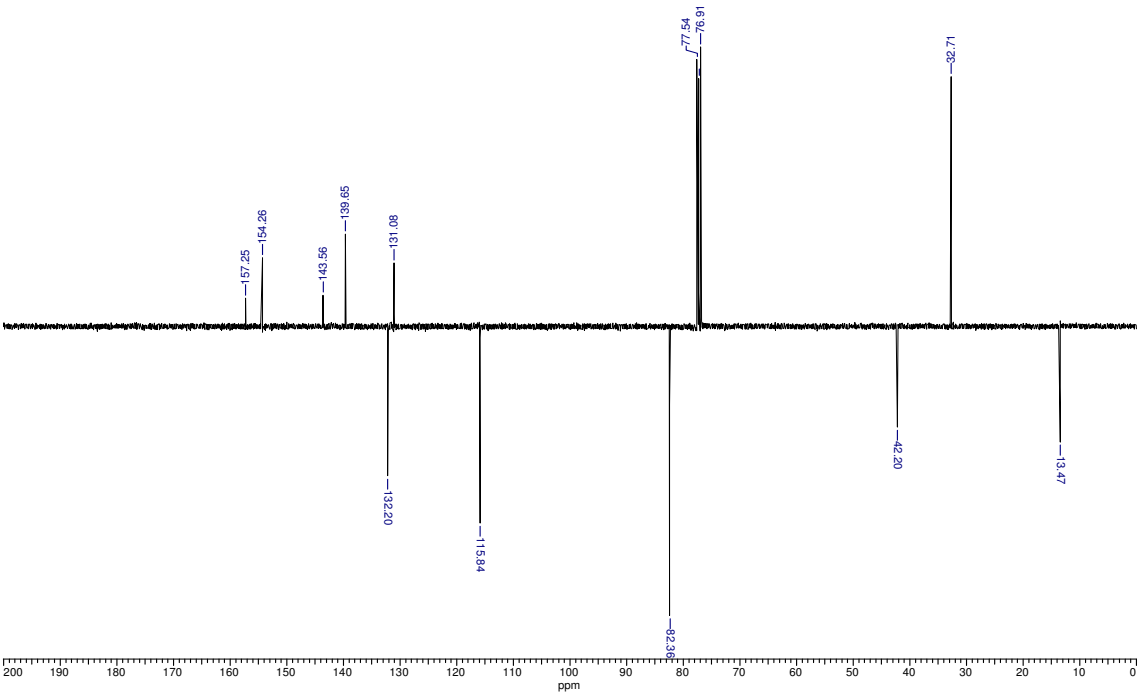
^{1}H NMR of R-Mosher ester of (54e)



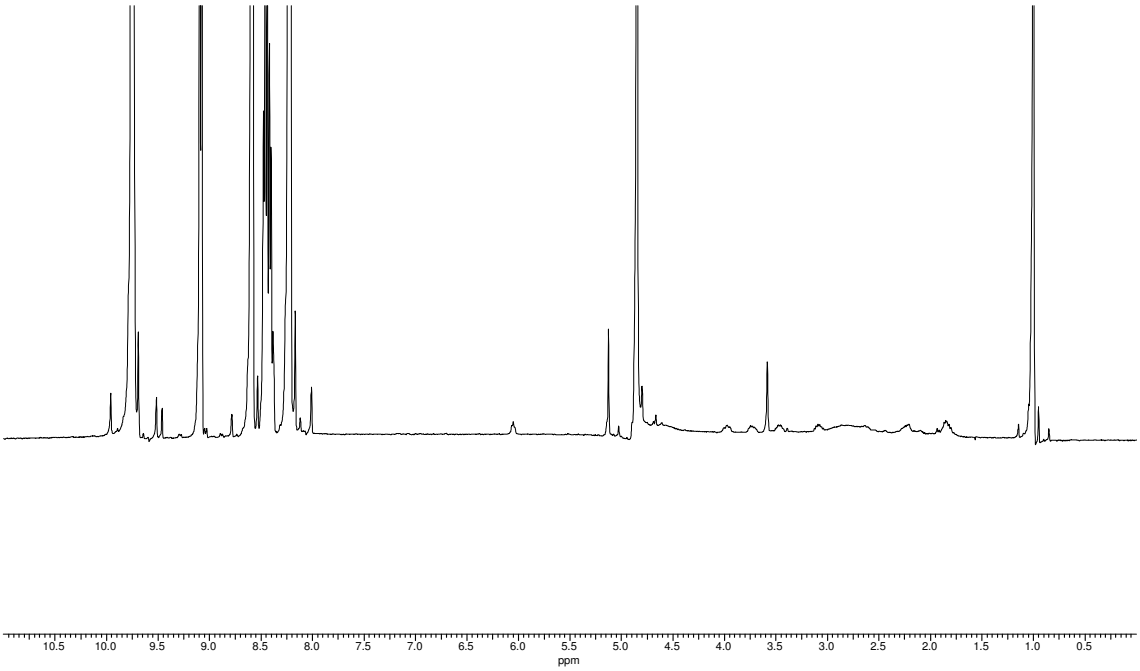
^{1}H NMR of (*S*)-2-methyl-3-(2-(1-methyl-1H-1,2,3-triazol-4-yl)thiazol-4-yl)cyclopent-2-enol (54f)



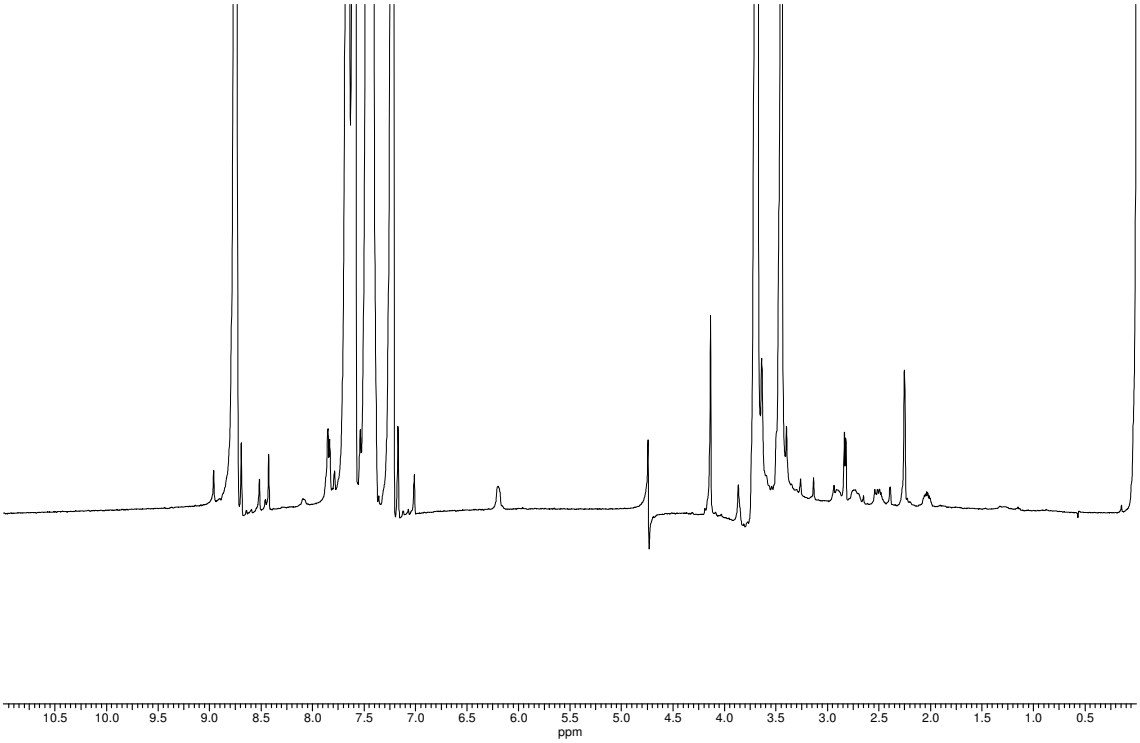
^{13}C NMR of (*S*)-2-methyl-3-(2-(1-methyl-1H-1,2,3-triazol-4-yl)thiazol-4-yl)cyclopent-2-enol (54f)



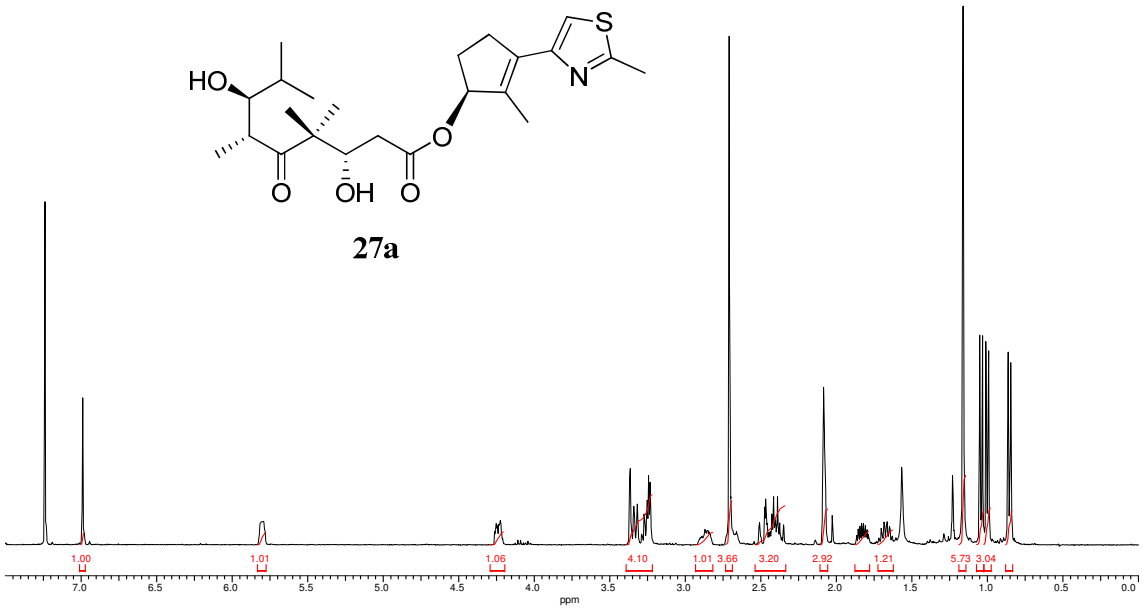
^{1}H NMR of S-Mosher ester of (54f)



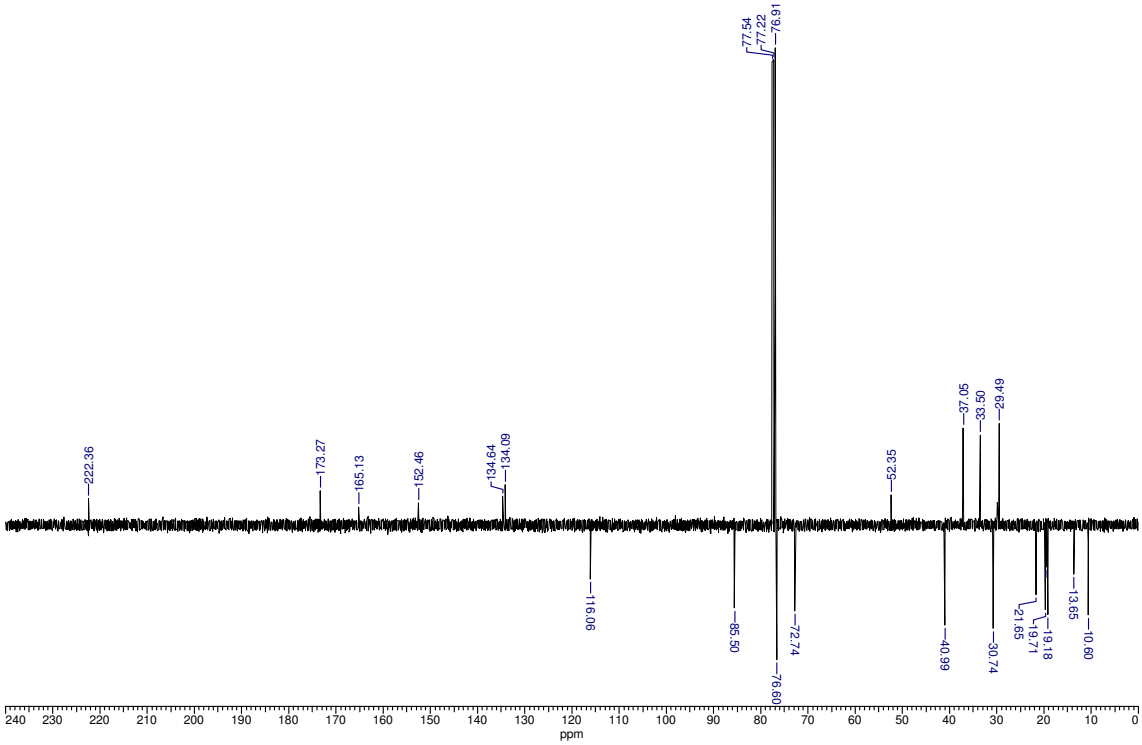
^{1}H NMR of R-Mosher ester of (54f)



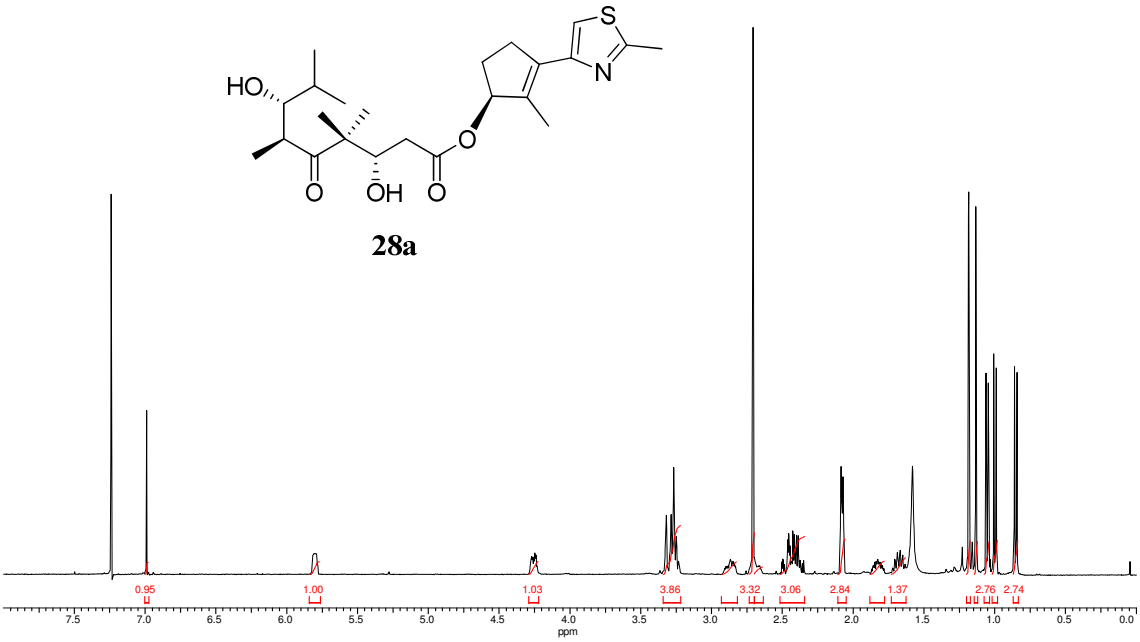
^{1}H NMR of (*3S,6R,7S*)-((*S*)-2-methyl-3-(2-methylthiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (27a)



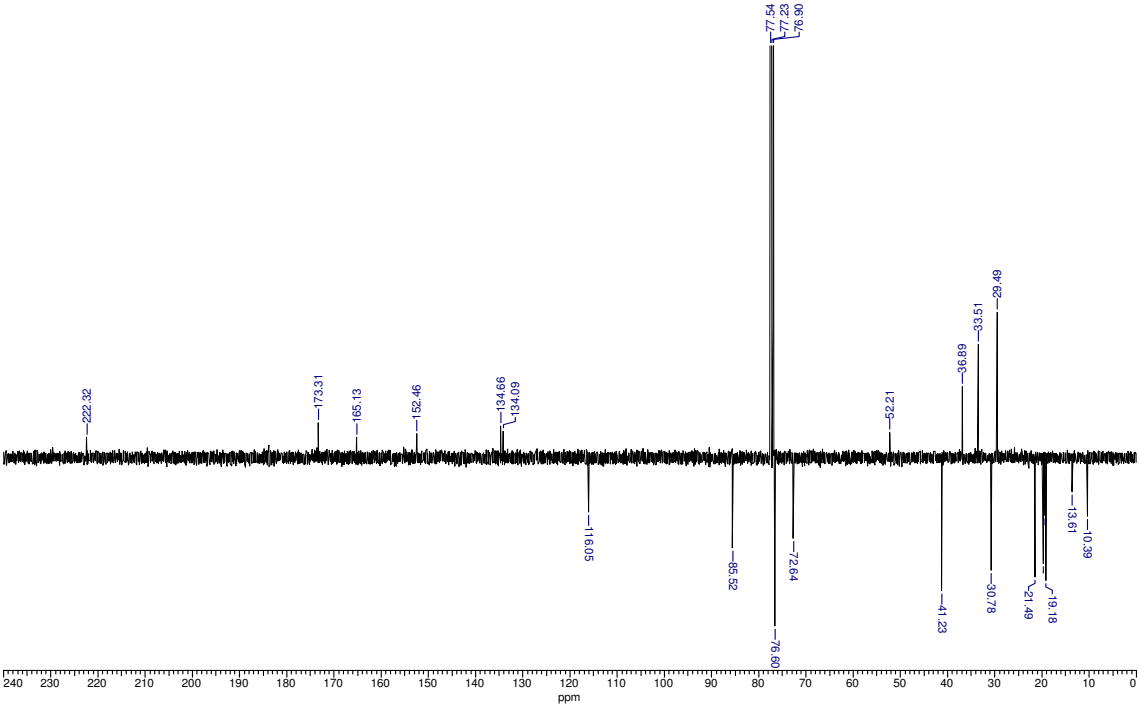
^{13}C NMR of (*3S,6R,7S*)-((*S*)-2-methyl-3-(2-methylthiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (27a)



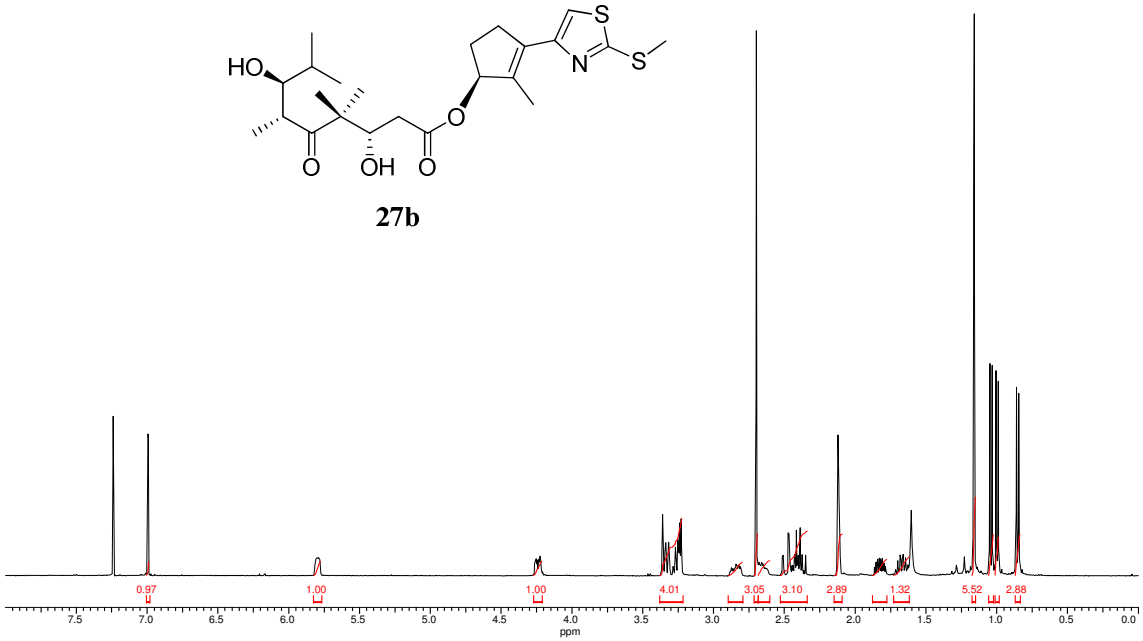
^{1}H NMR of (*3S,6S,7R*)-((*S*)-2-methyl-3-(2-methylthiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (28a)



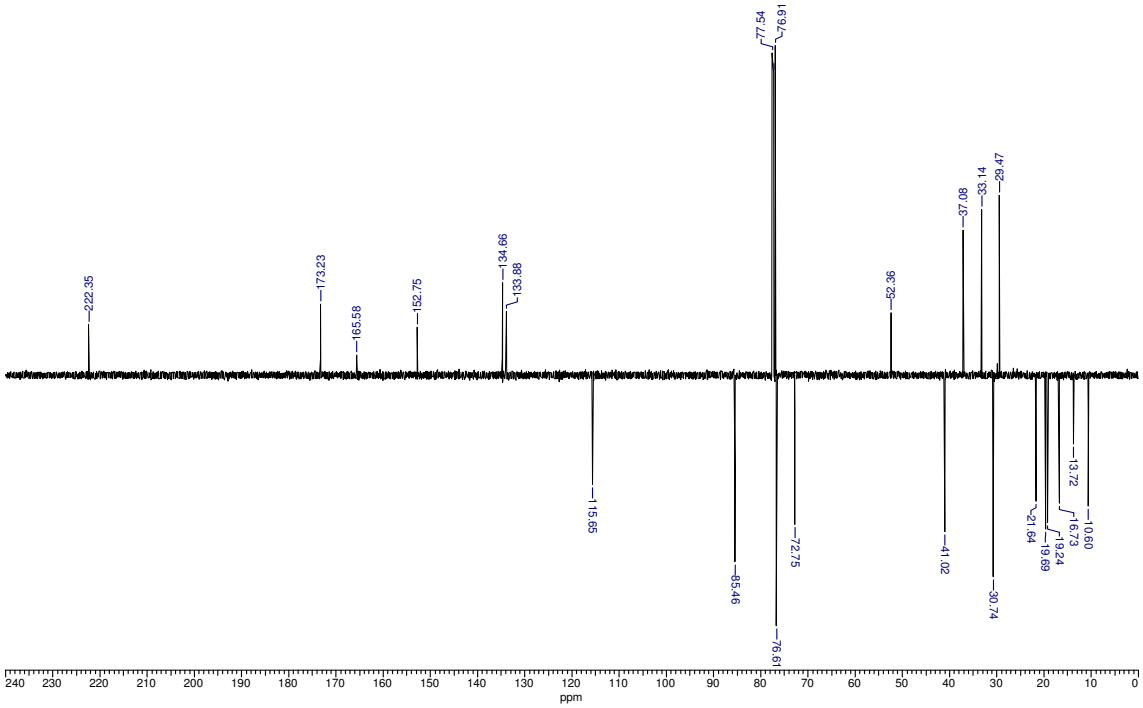
^{13}C NMR of (*3S,6S,7R*)-((*S*)-2-methyl-3-(2-methylthiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (28a)



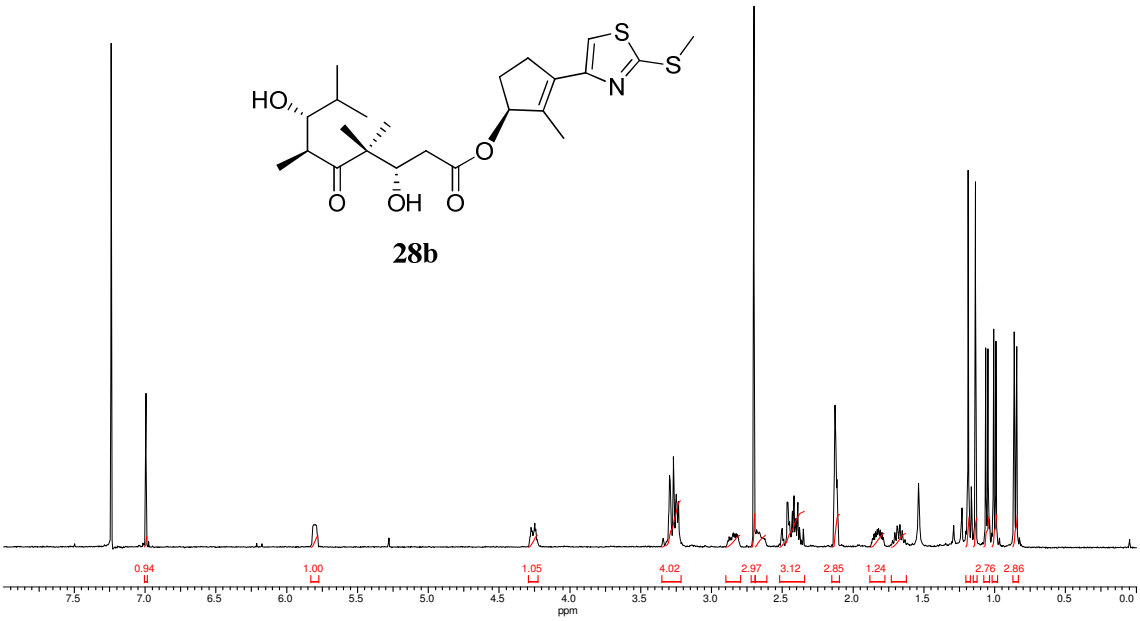
^{1}H NMR of (*3S,6R,7S*)-((*S*)-2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (27b)



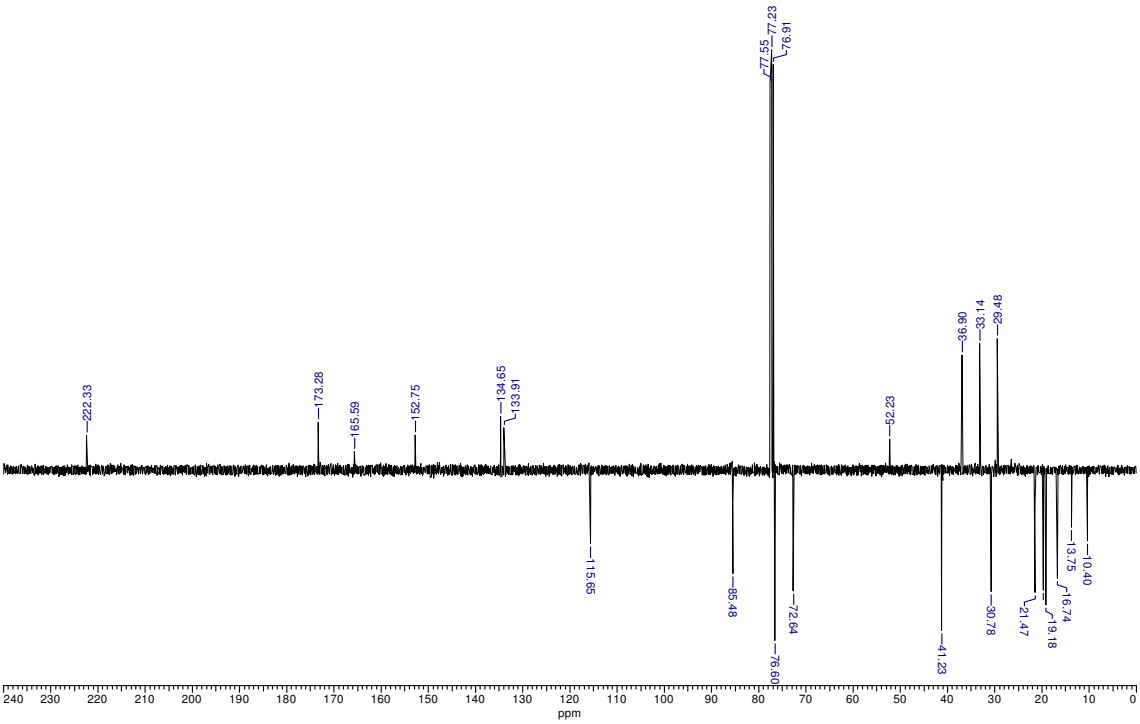
^{13}C NMR of (*3S,6R,7S*)-((*S*)-2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (27b)



^{1}H NMR of (*3S,6S,7R*)-((*S*)-2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (28b)

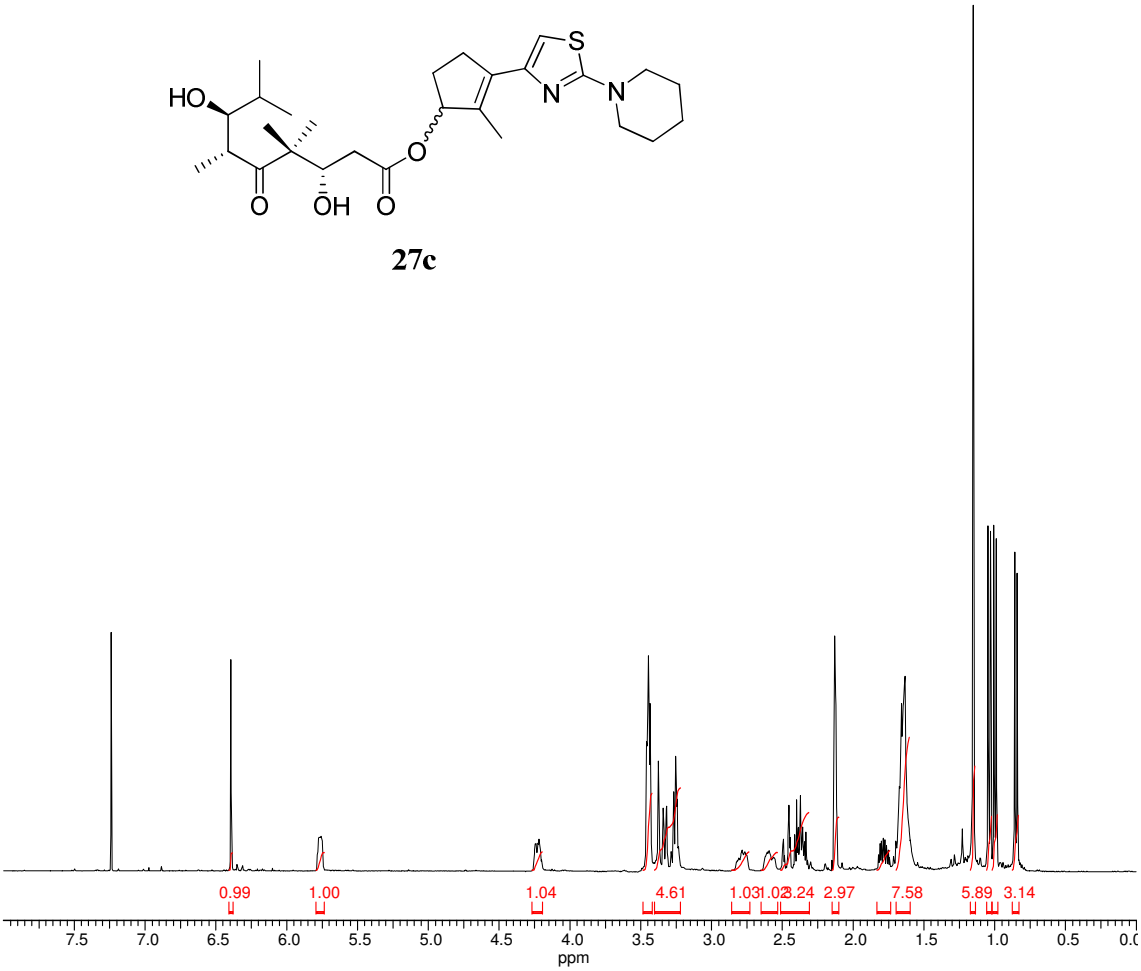


^{13}C NMR of (*3S,6S,7R*)-((*S*)-2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (28b)

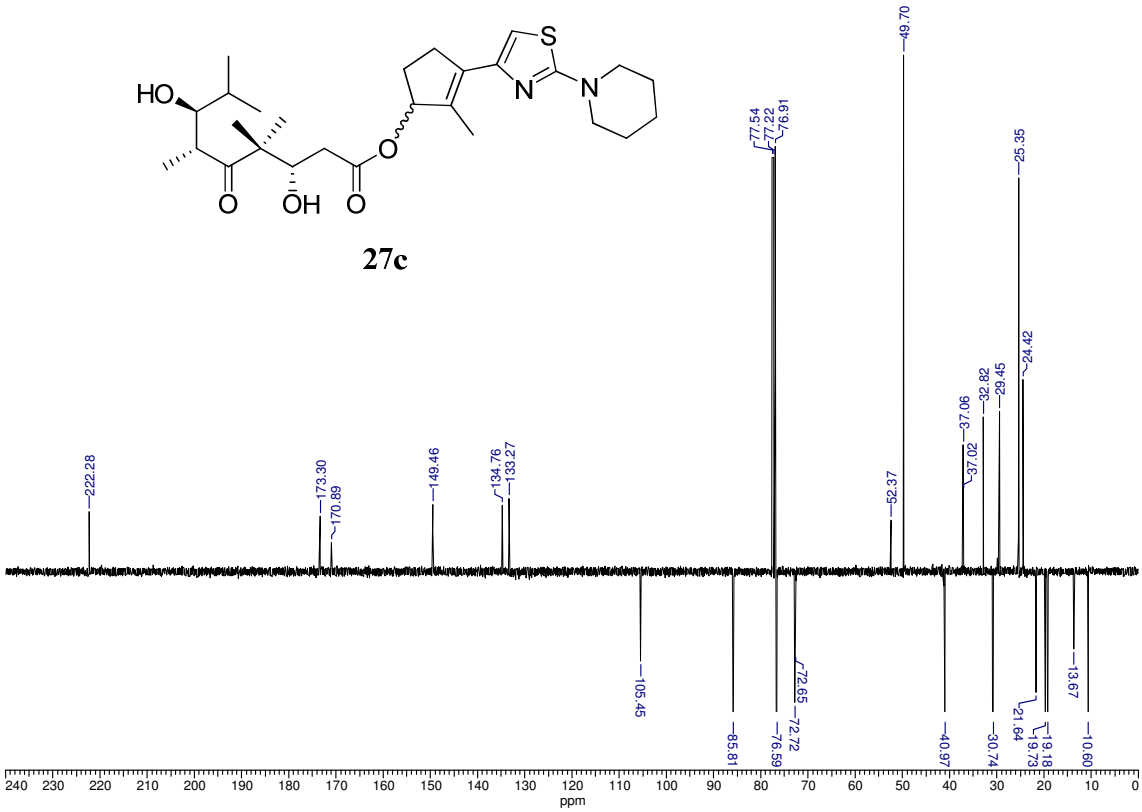


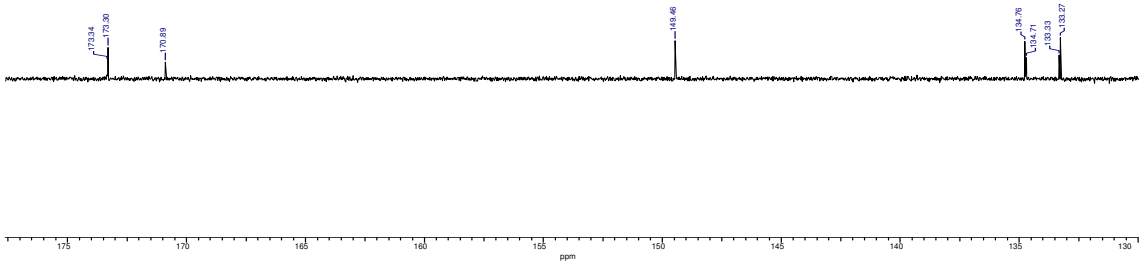
^{1}H NMR of (*3S,6R,7S*)-((*R*)-2-methyl-3-(2-(piperidin-1-yl)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate and (*3S,6R,7S*)-((*S*)-2-methyl-3-(2-(piperidin-1-yl)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (27c)

27c

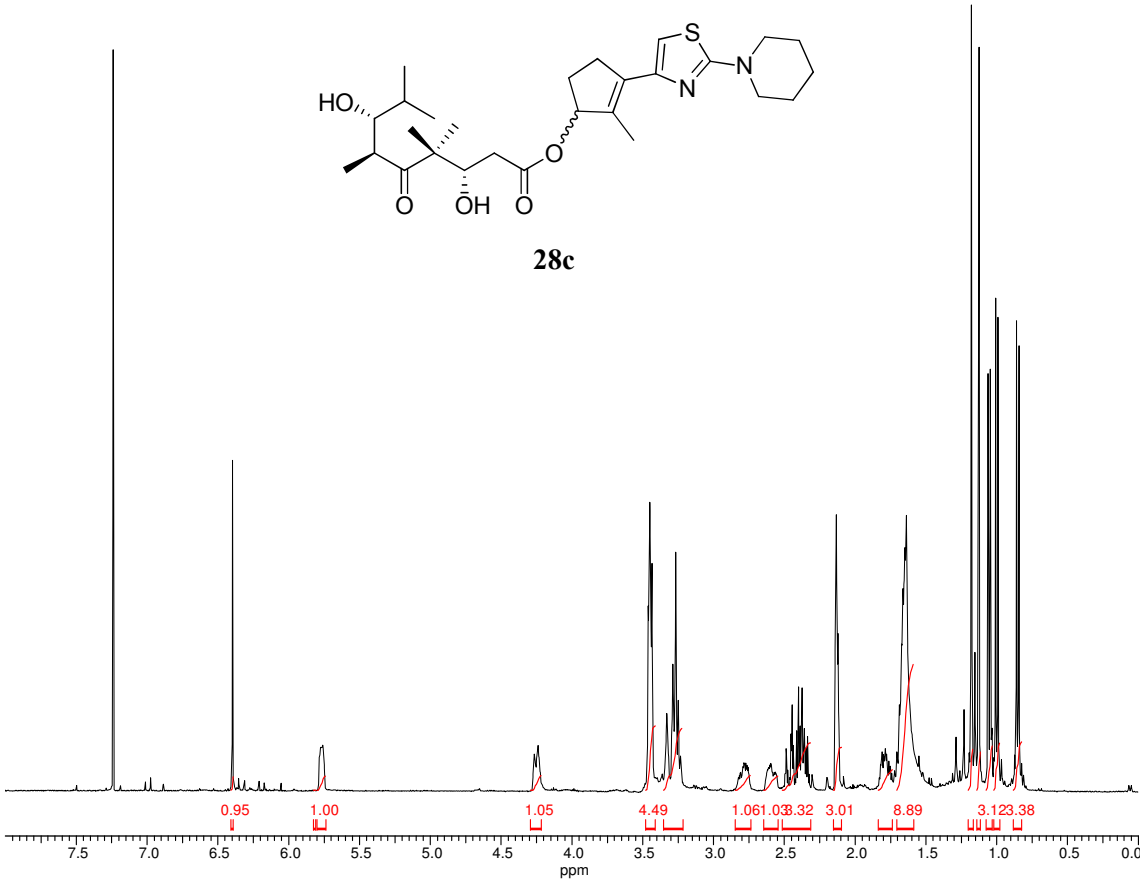


^{13}C NMR of (*3S,6R,7S*)-((*R*)-2-methyl-3-(2-(piperidin-1-yl)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate and (*3S,6R,7S*)-((*S*)-2-methyl-3-(2-(piperidin-1-yl)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (27c)

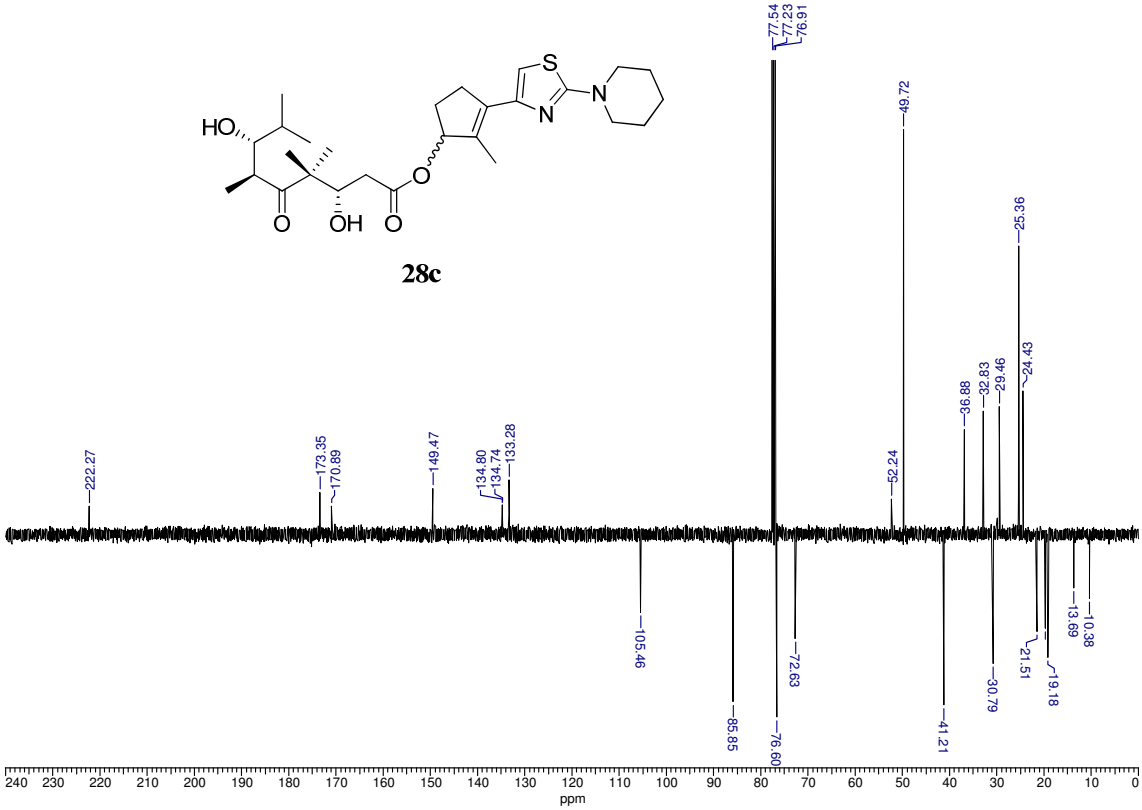


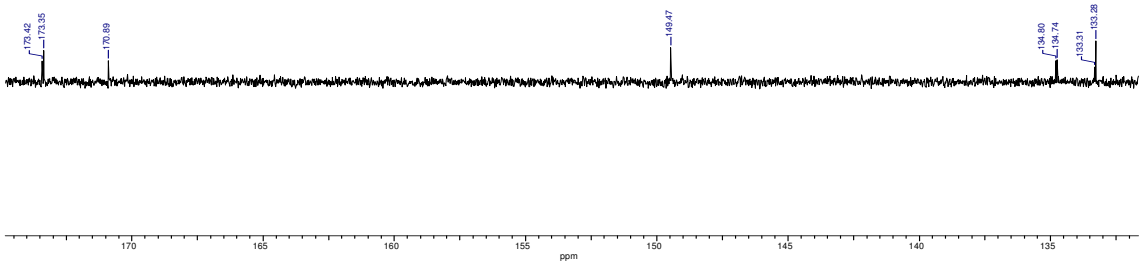


^{1}H NMR of (*3S,6S,7R*)-((*R*)-2-methyl-3-(2-(piperidin-1-yl)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate and (*3S,6S,7R*)-((*S*)-2-methyl-3-(2-(piperidin-1-yl)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (28c)



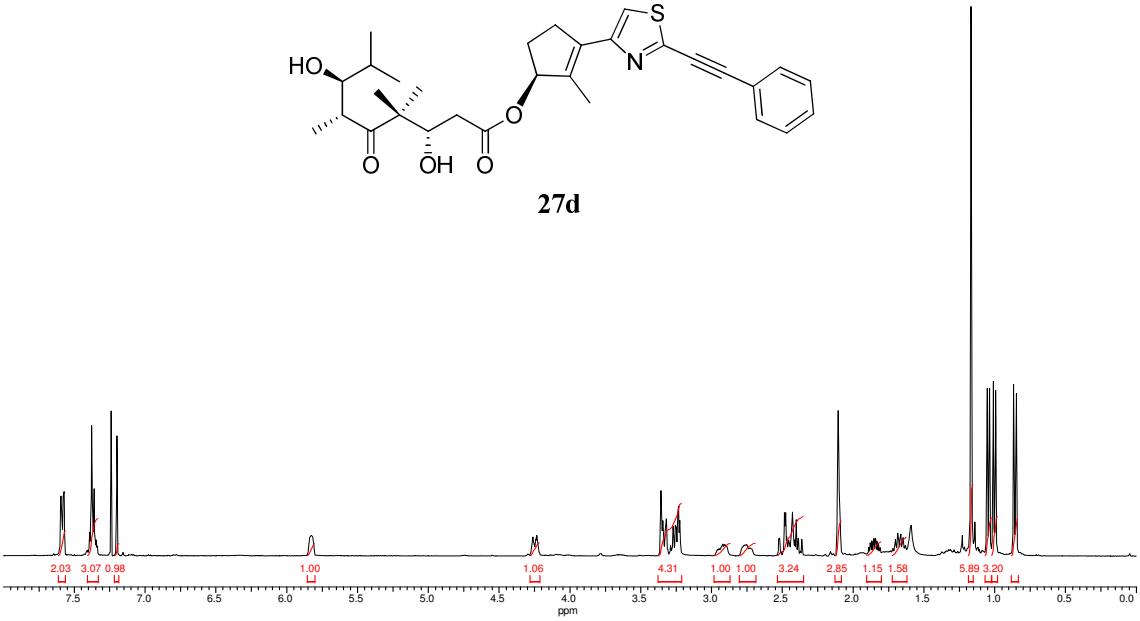
^{13}C NMR of (*3S,6S,7R*)-((*R*)-2-methyl-3-(2-(piperidin-1-yl)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate and (*3S,6S,7R*)-((*S*)-2-methyl-3-(2-(piperidin-1-yl)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (28c)



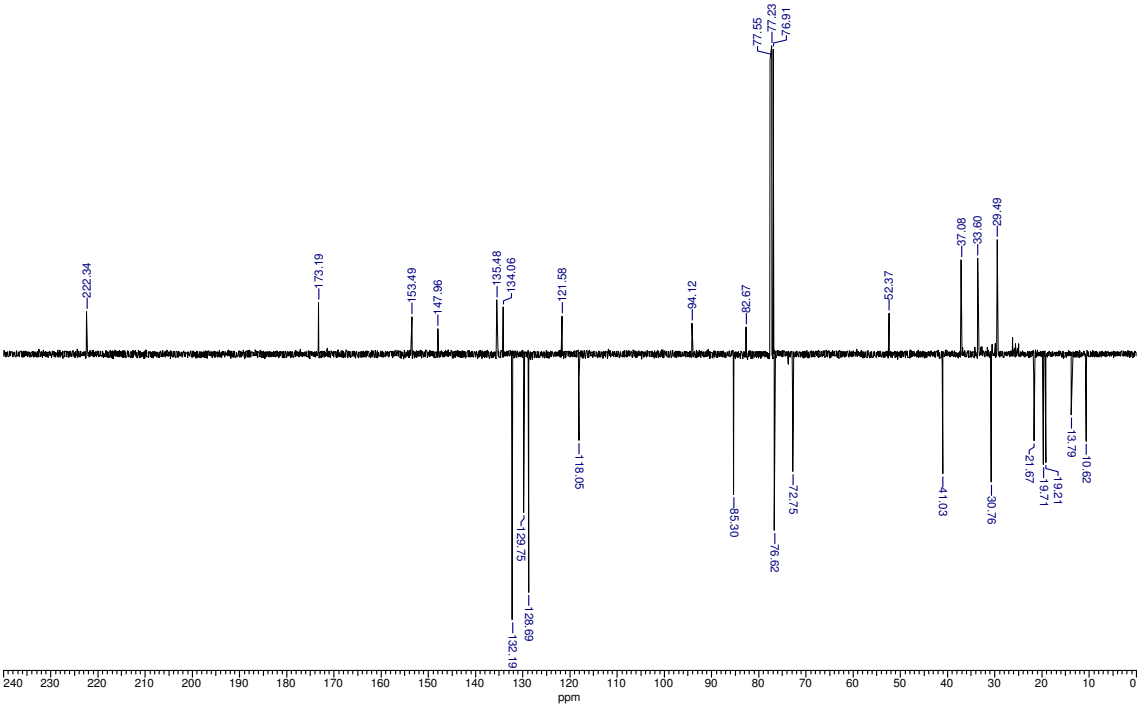


^{1}H NMR of (*3S,6R,7S*)-((*S*)-2-methyl-3-(2-(phenylethynyl)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (27d)

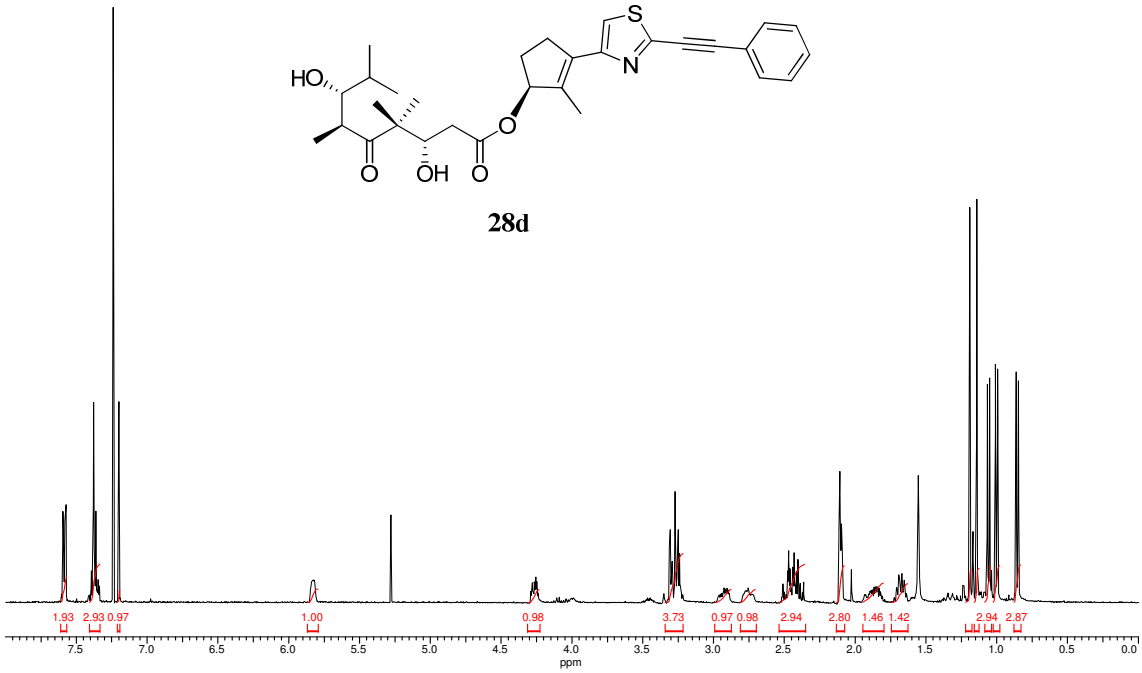
27d



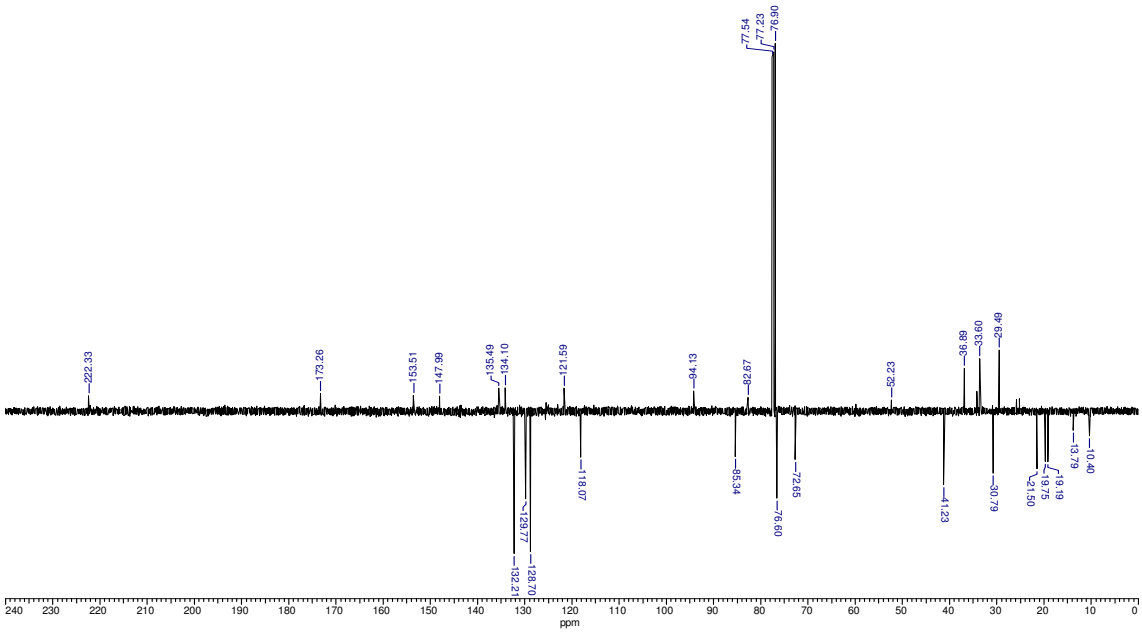
^{13}C NMR of (*3S,6R,7S*)-((*S*)-2-methyl-3-(2-(phenylethynyl)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (27d)



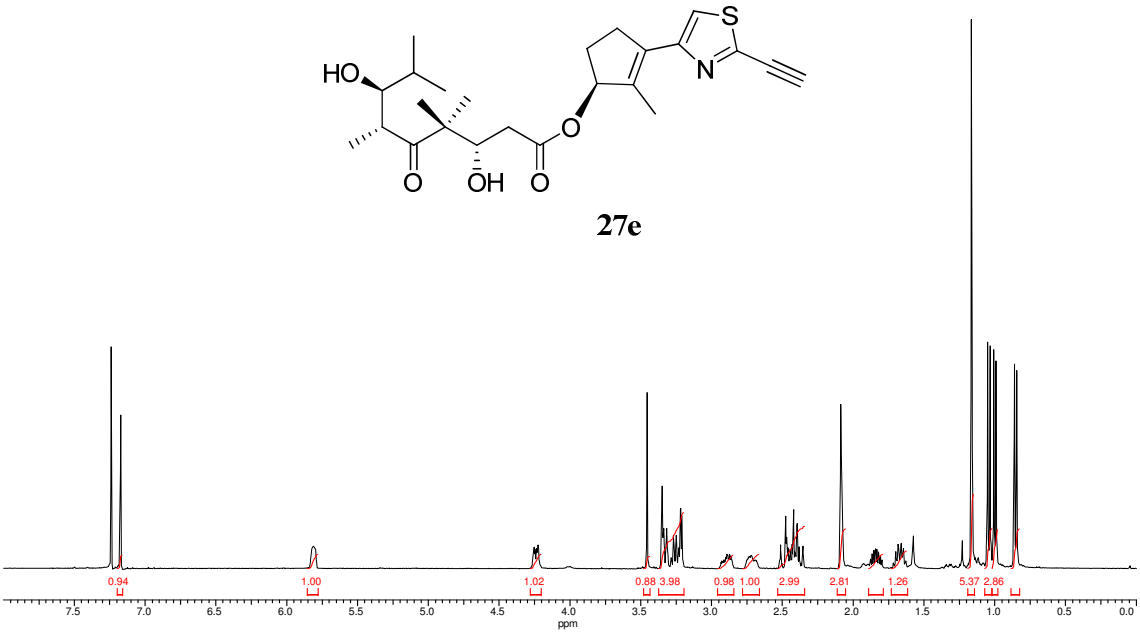
^{1}H NMR of (*3S,6S,7R*)-((*S*)-2-methyl-3-(2-(phenylethynyl)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (28d)



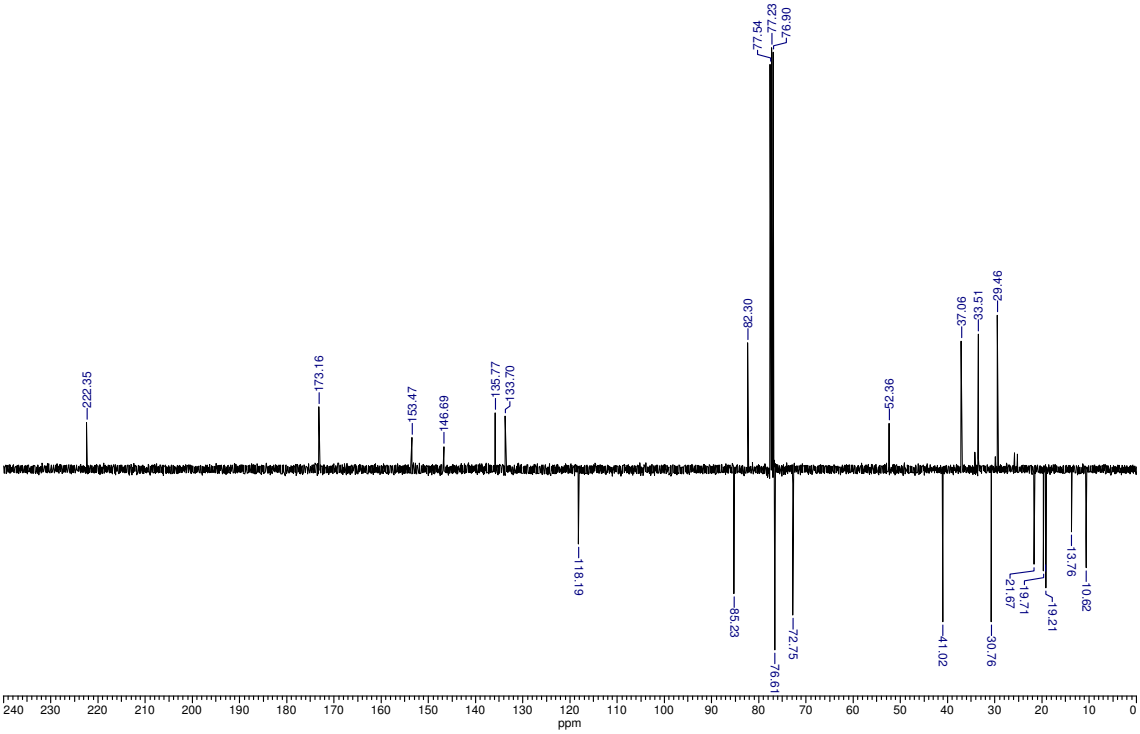
^{13}C NMR of (*3S,6S,7R*)-((*S*)-2-methyl-3-(2-(phenylethynyl)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (28d)



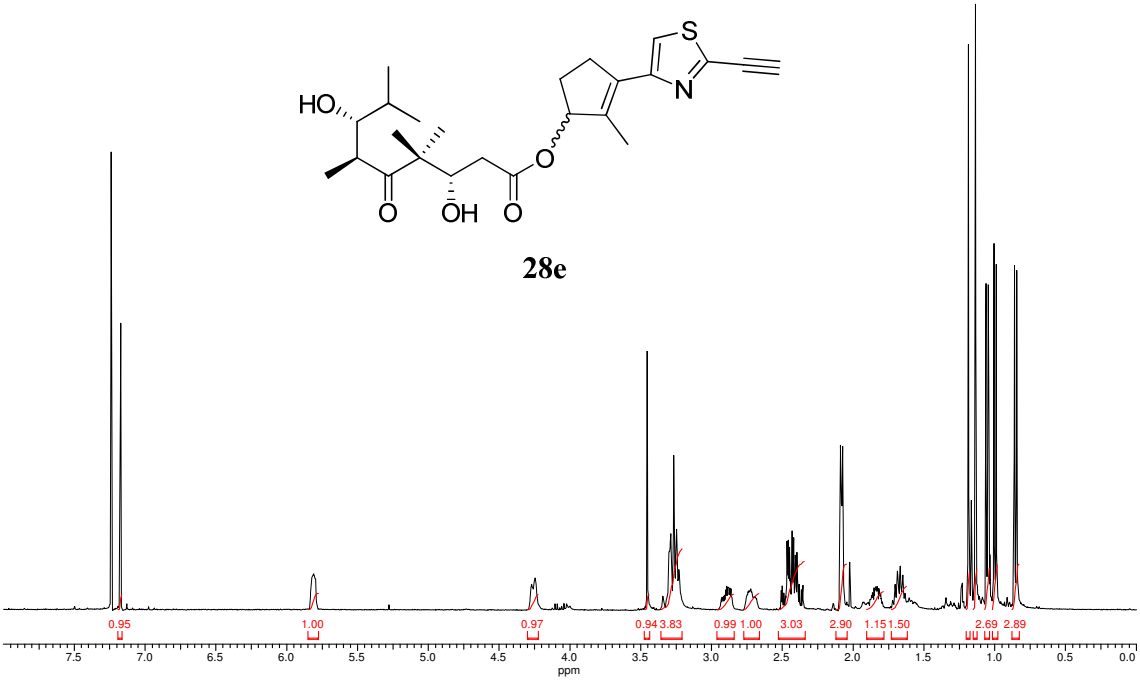
^{1}H NMR of (*3S,6R,7S*)-((*S*)-3-(2-ethynylthiazol-4-yl)-2-methylcyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (27e)



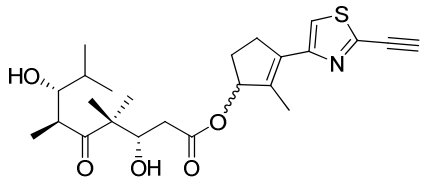
^{13}C NMR of (*3S,6R,7S*)-((*S*)-3-(2-ethynylthiazol-4-yl)-2-methylcyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (27e)



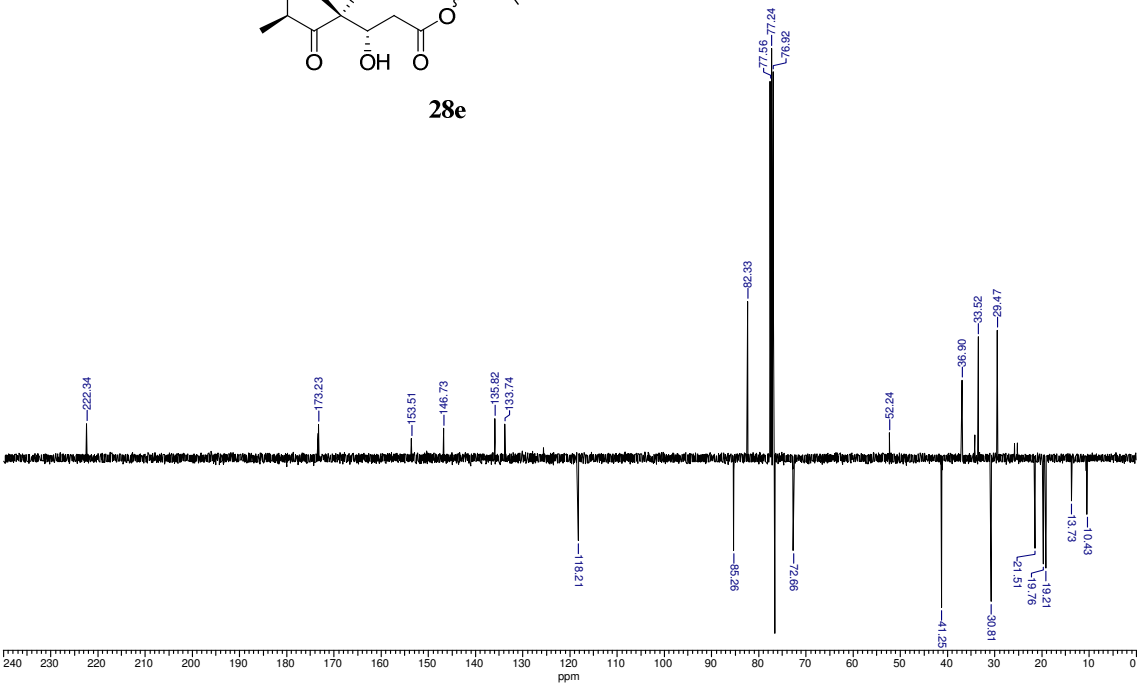
^{1}H NMR of (*3S,6S,7R*)-((*R*)-3-(2-ethynylthiazol-4-yl)-2-methylcyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate and (*3S,6S,7R*)-((*S*)-3-(2-ethynylthiazol-4-yl)-2-methylcyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (28e)



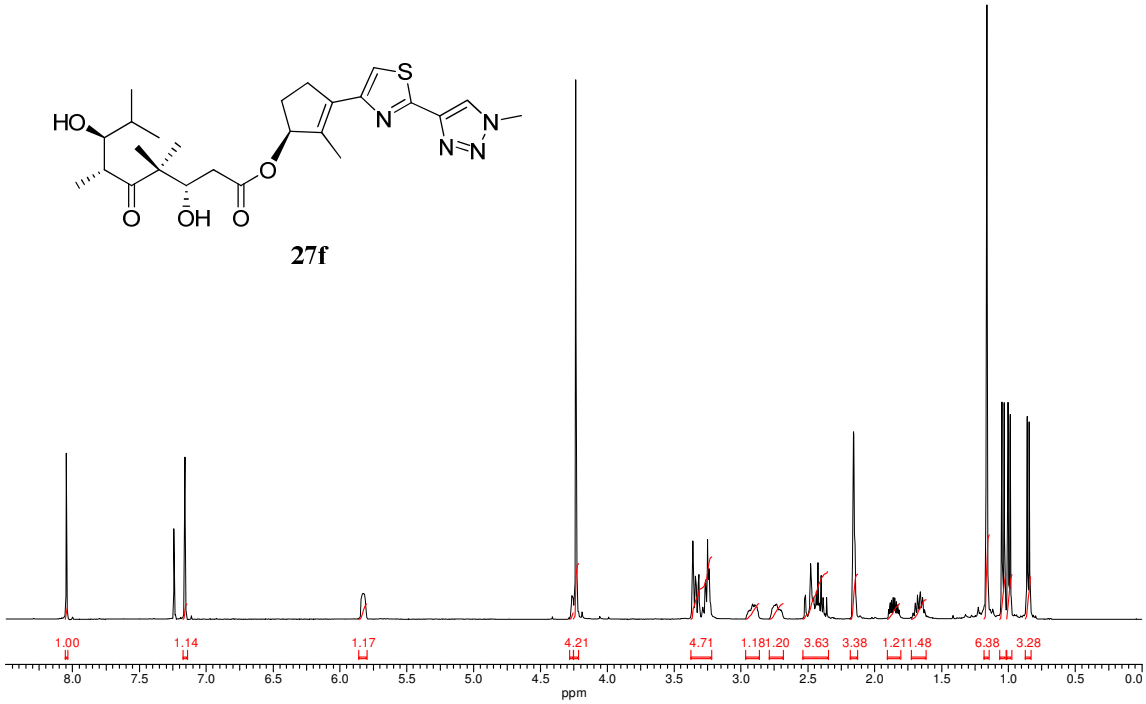
^{13}C NMR of ((*3S,6S,7R*)-((*R*)-3-(2-ethynylthiazol-4-yl)-2-methylcyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate and (*3S,6S,7R*)-((*S*)-3-(2-ethynylthiazol-4-yl)-2-methylcyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (28e)



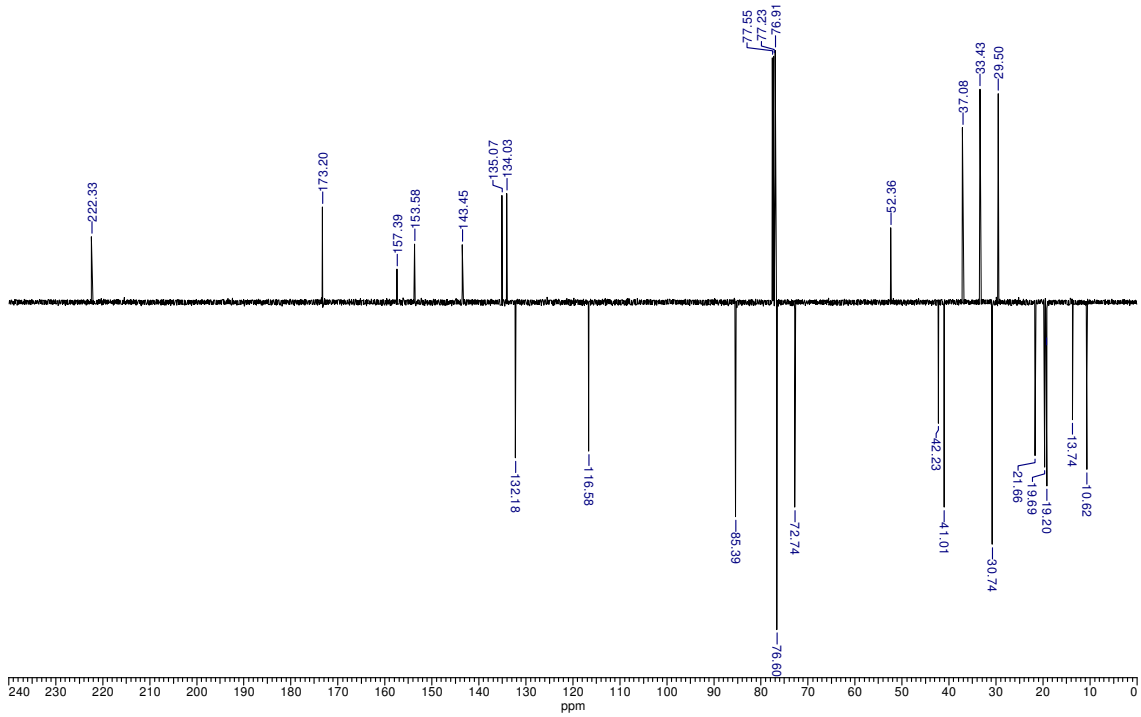
28e



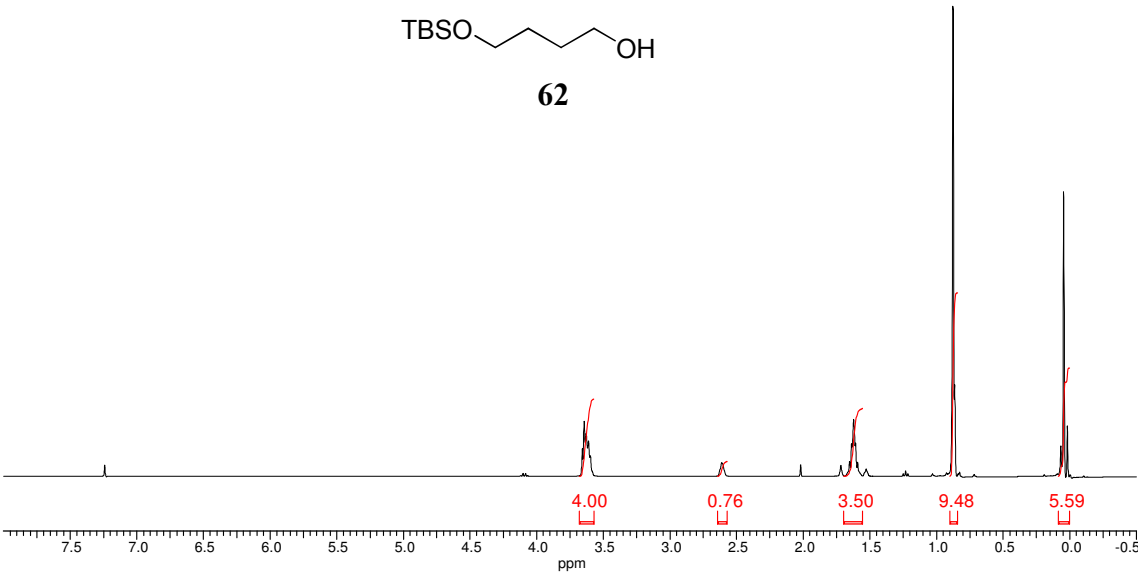
^{1}H NMR of (*3S,6R,7S*)-((*S*)-2-methyl-3-(2-(1-methyl-1H-1,2,3-triazol-4-yl)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (27f)



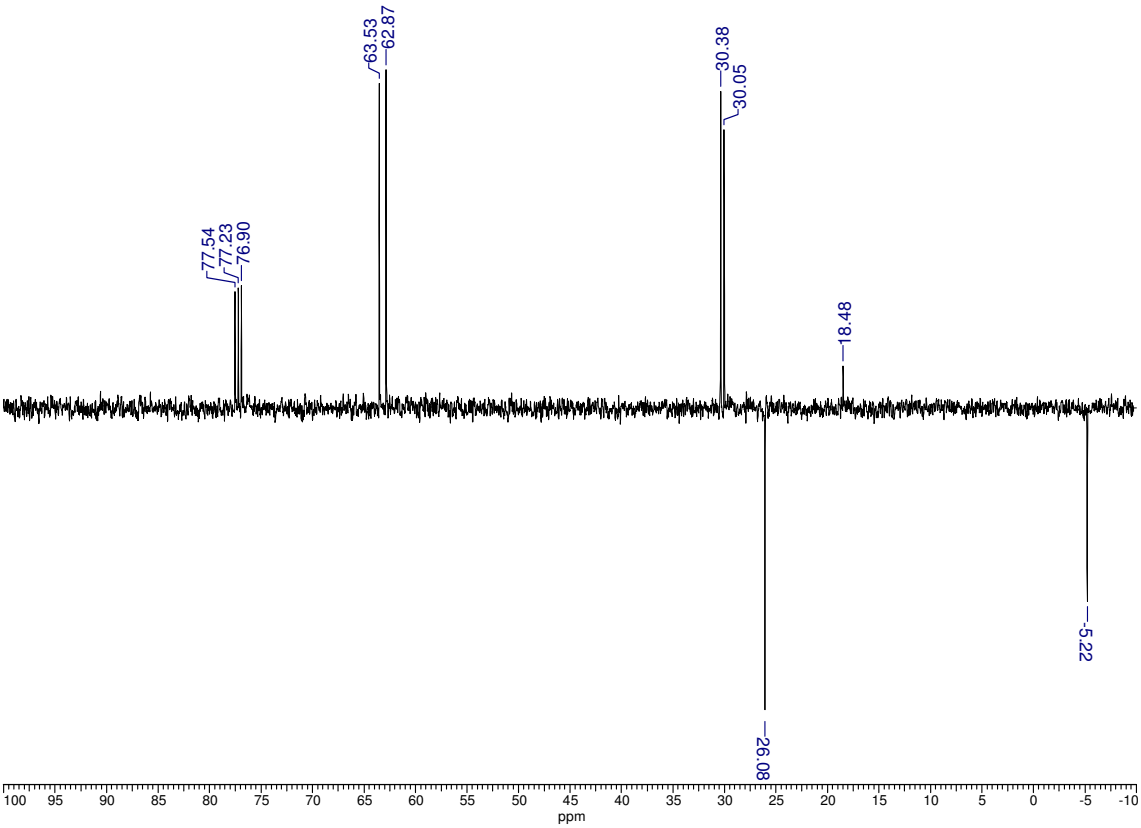
^{13}C NMR of (*3S,6R,7S*)-((*S*)-2-methyl-3-(2-(1-methyl-1H-1,2,3-triazol-4-yl)thiazol-4-yl)cyclopent-2-enyl) 3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxononanoate (27f)



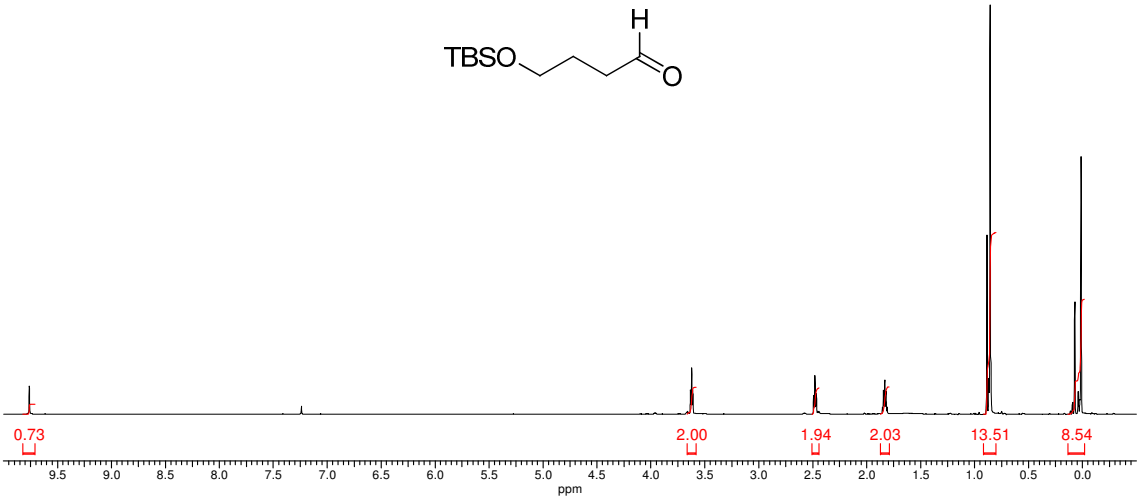
^{1}H NMR of 4-(*tert*-butyldimethylsilyloxy)butan-1-ol (62)



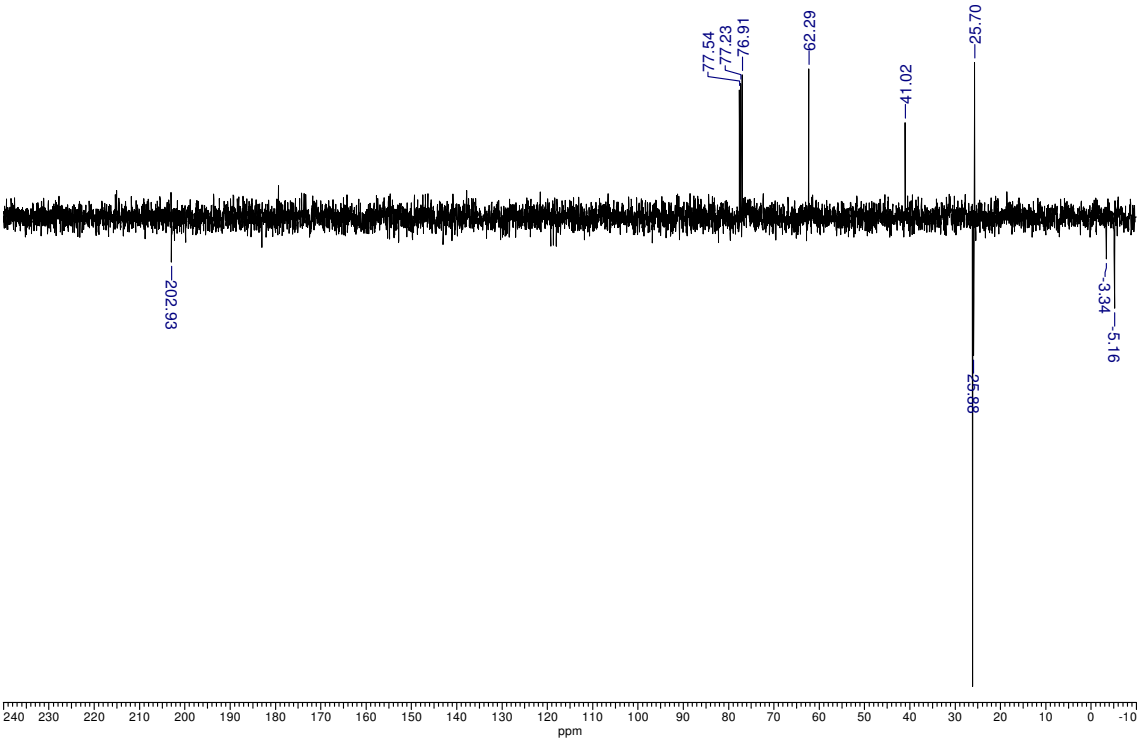
^{13}C NMR of 4-(*tert*-butyldimethylsilyloxy)butan-1-ol (62)



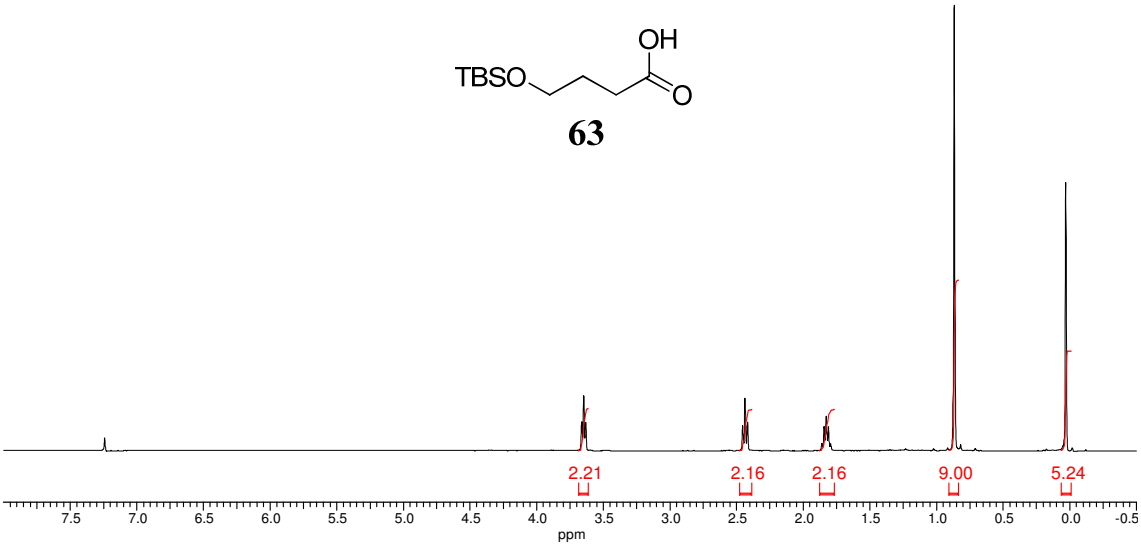
^{1}H NMR of 4-(tert-butyldimethylsilyloxy)butanal



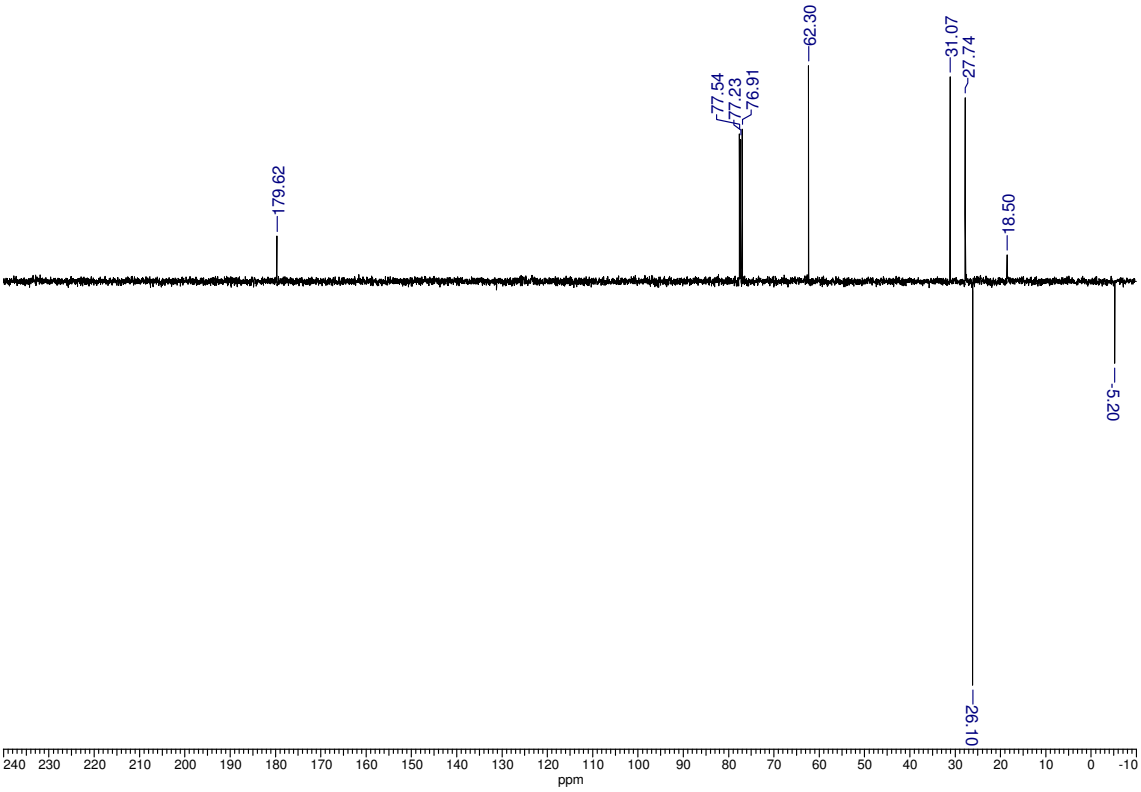
^{13}C NMR of 4-(tert-butyldimethylsilyloxy)butanal



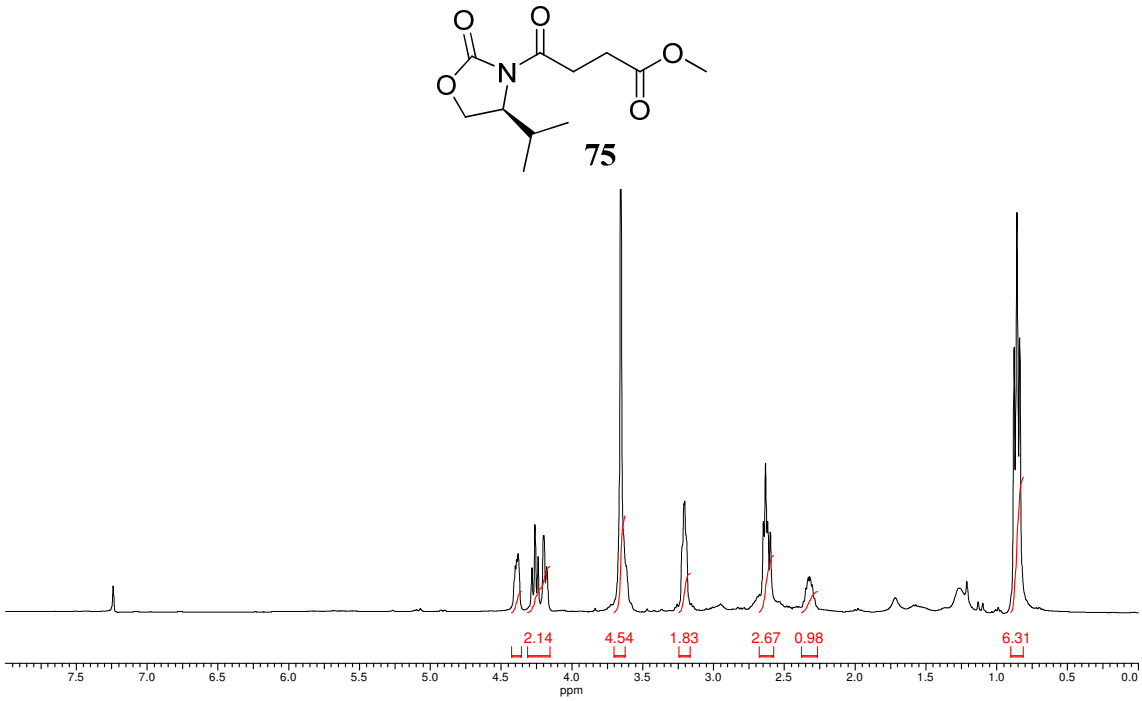
^{1}H NMR of 4-(*tert*-butyldimethylsilyloxy)butanoic acid (63)



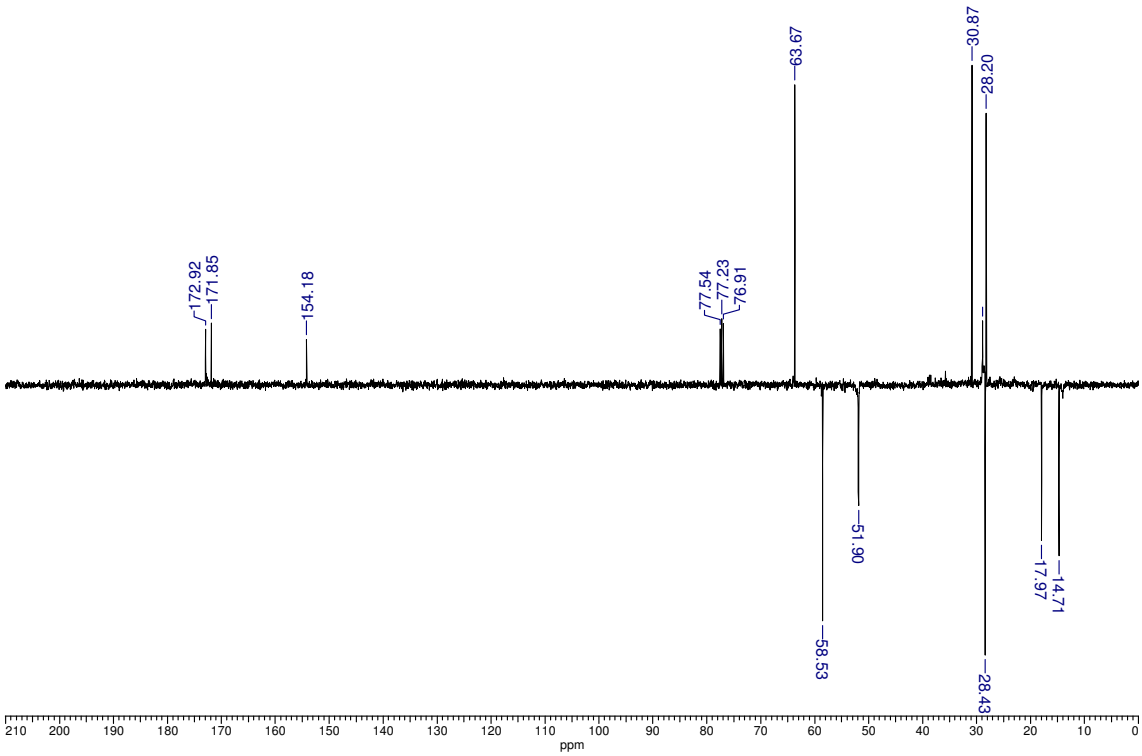
^{13}C NMR of 4-(*tert*-butyldimethylsilyloxy)butanoic acid (63)



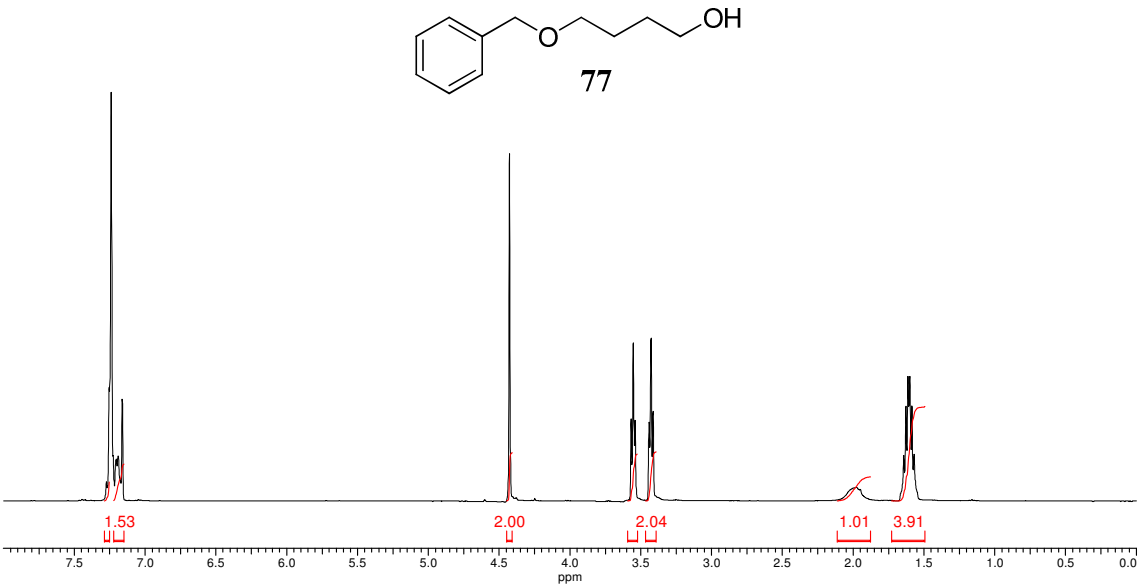
^{1}H NMR of (*S*)-methyl 4-(4-isopropyl-2-oxooxazolidin-3-yl)-4-oxobutanoate (75)



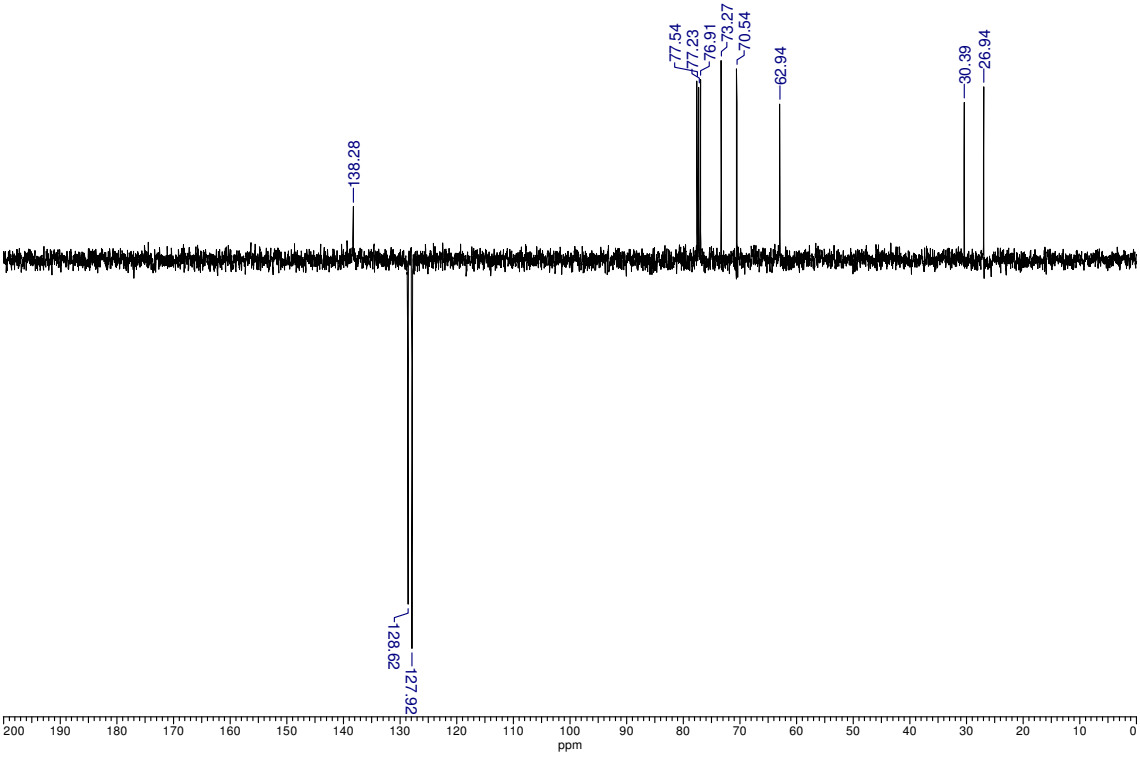
^{13}C NMR of (*S*)-methyl 4-(4-isopropyl-2-oxooxazolidin-3-yl)-4-oxobutanoate (75)



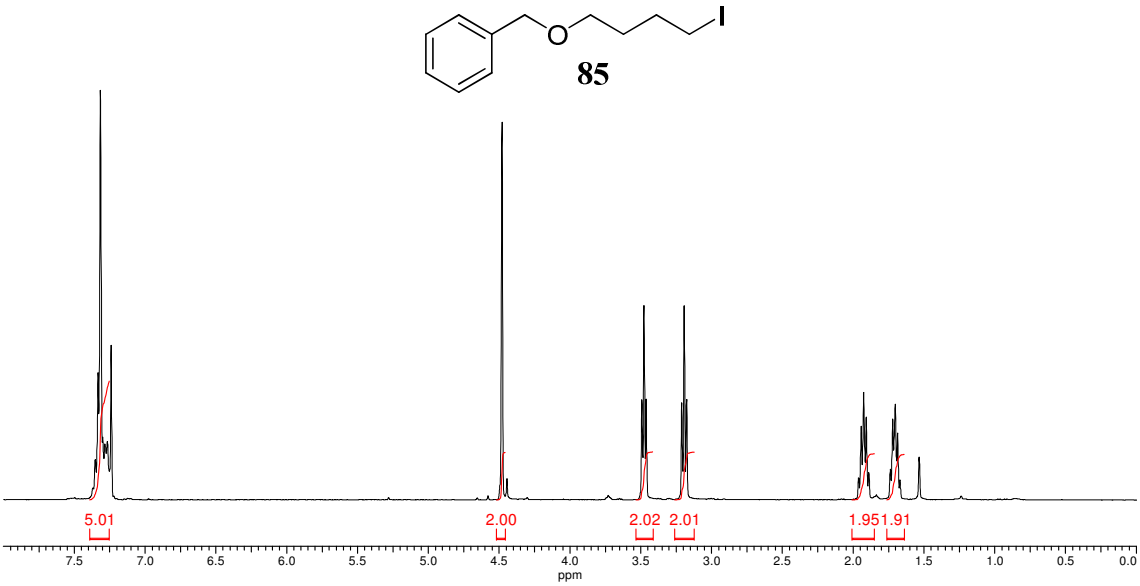
^{1}H NMR of 4-(benzyloxy)butan-1-ol (77)



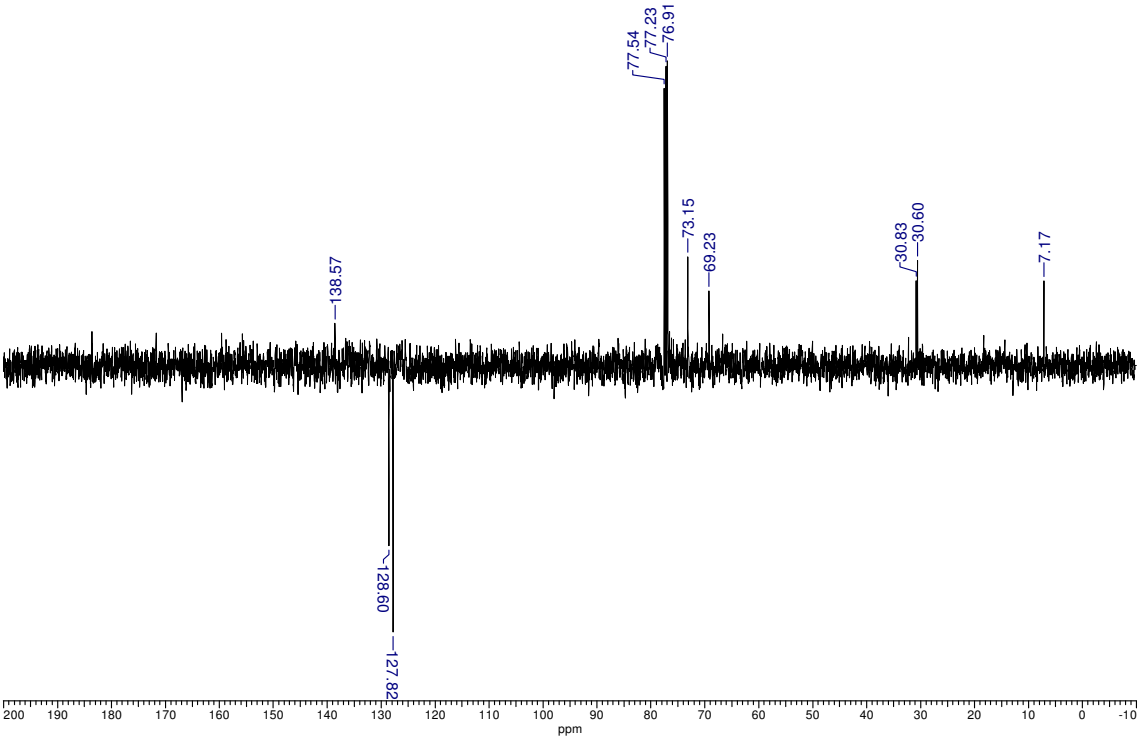
^{13}C NMR of 4-(benzyloxy)butan-1-ol (77)



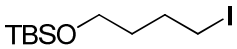
^{1}H NMR of 4-(benzyloxy)-1-iodobutane (85)



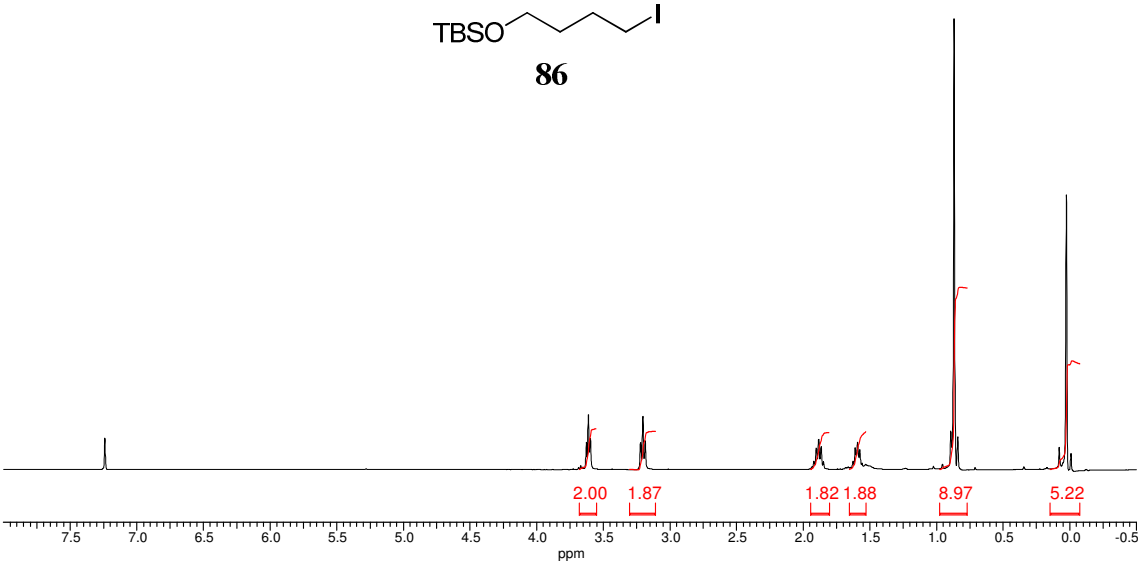
^{13}C NMR of 4-(benzyloxy)-1-iodobutane (85)



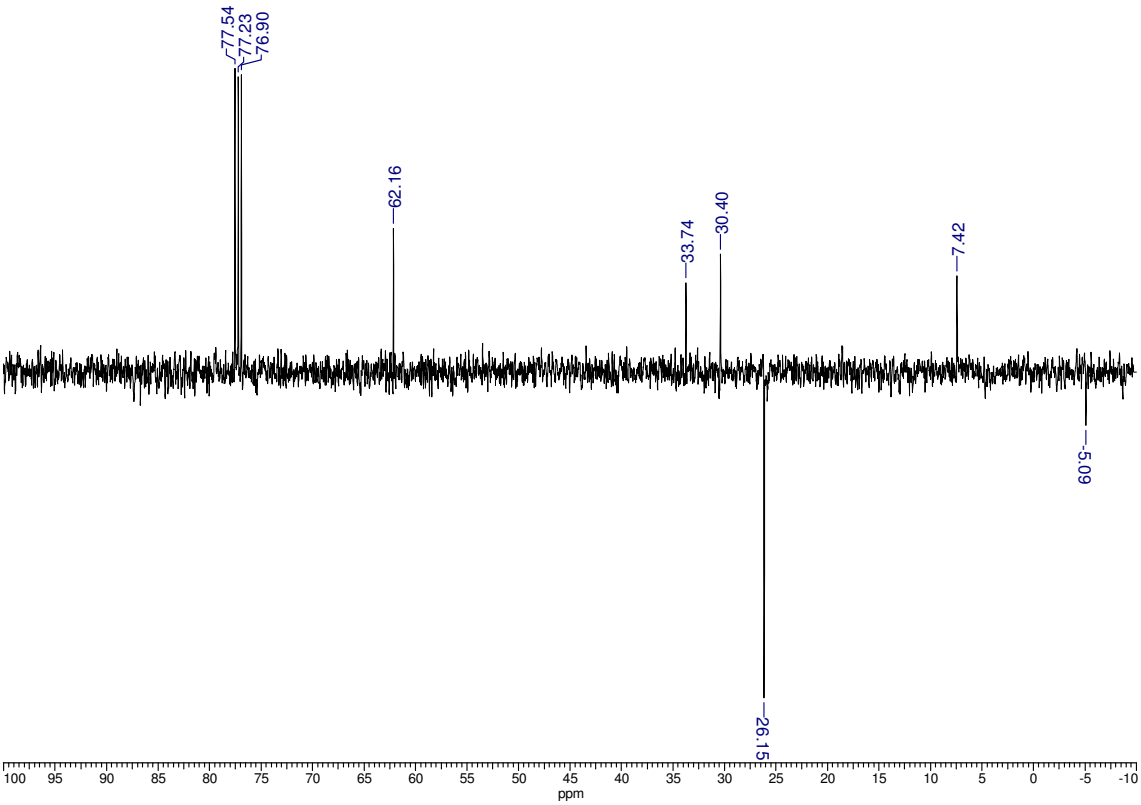
^{1}H NMR of 4-(*tert*-butyldimethylsilyloxy)-1-iodobutane (86)



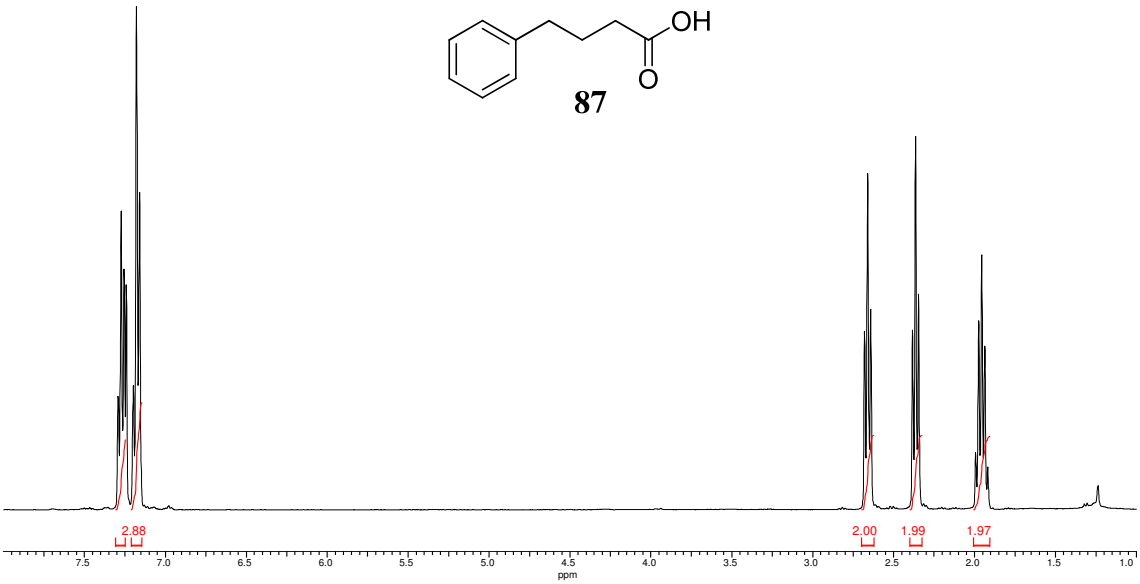
86



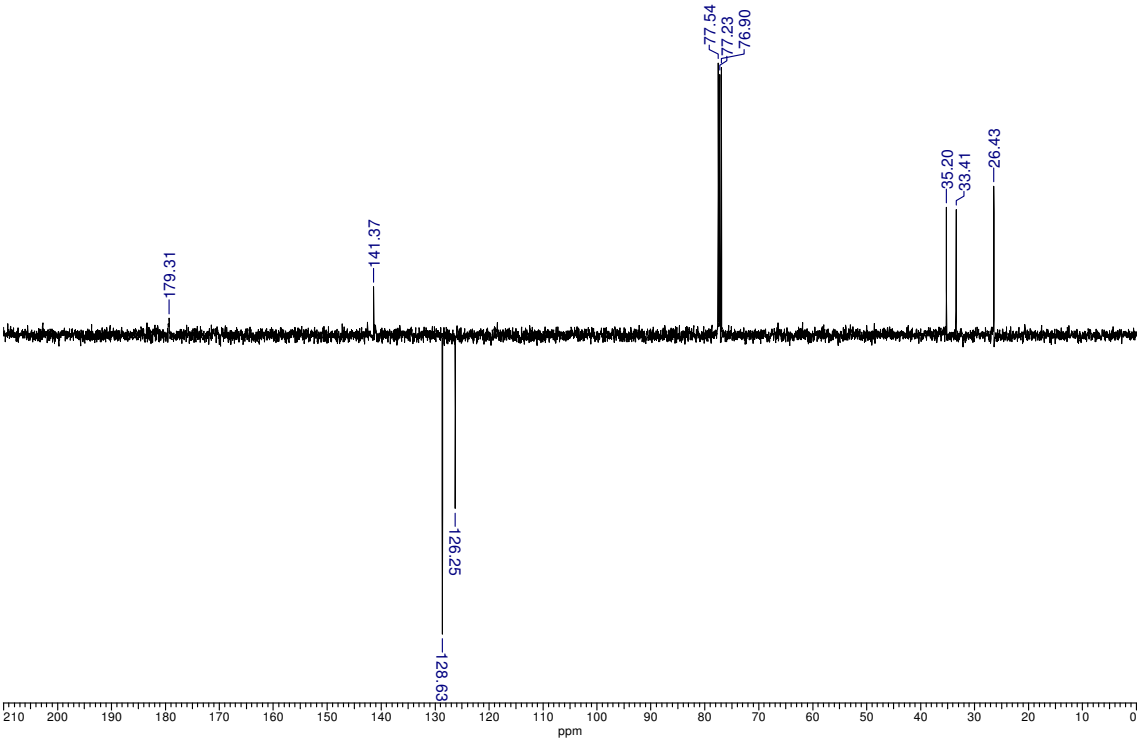
^{13}C NMR of 4-(*tert*-butyldimethylsilyloxy)-1-iodobutane (86)



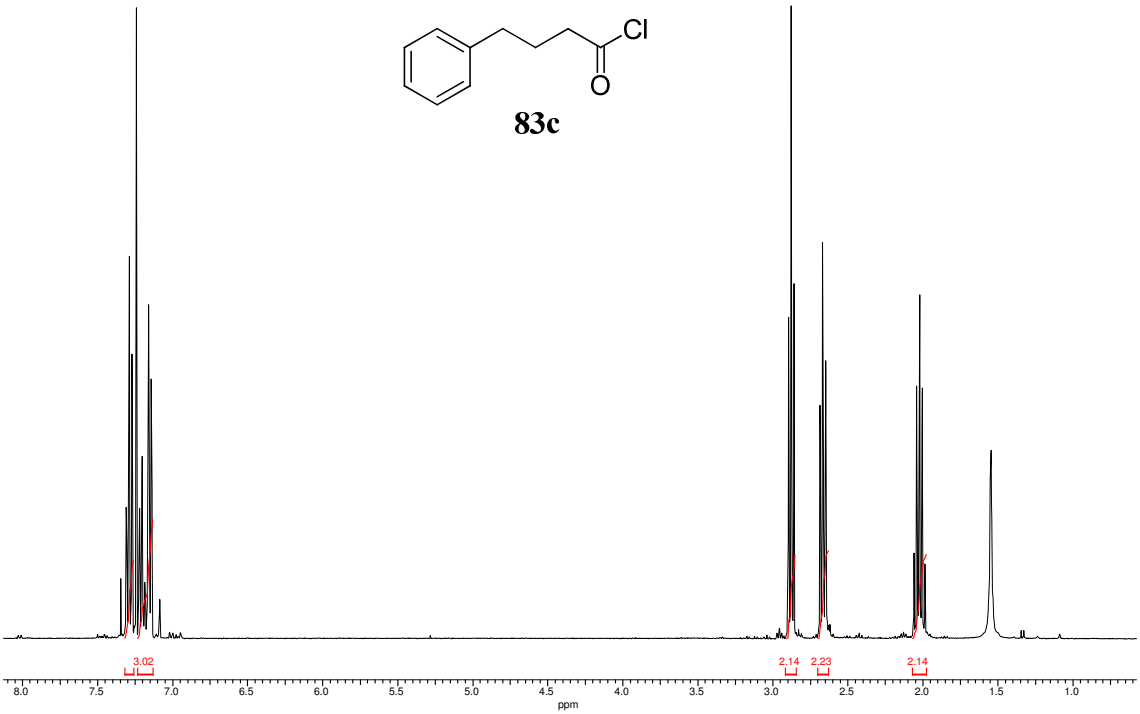
^{1}H NMR of 4-phenylbutanoic acid (87)



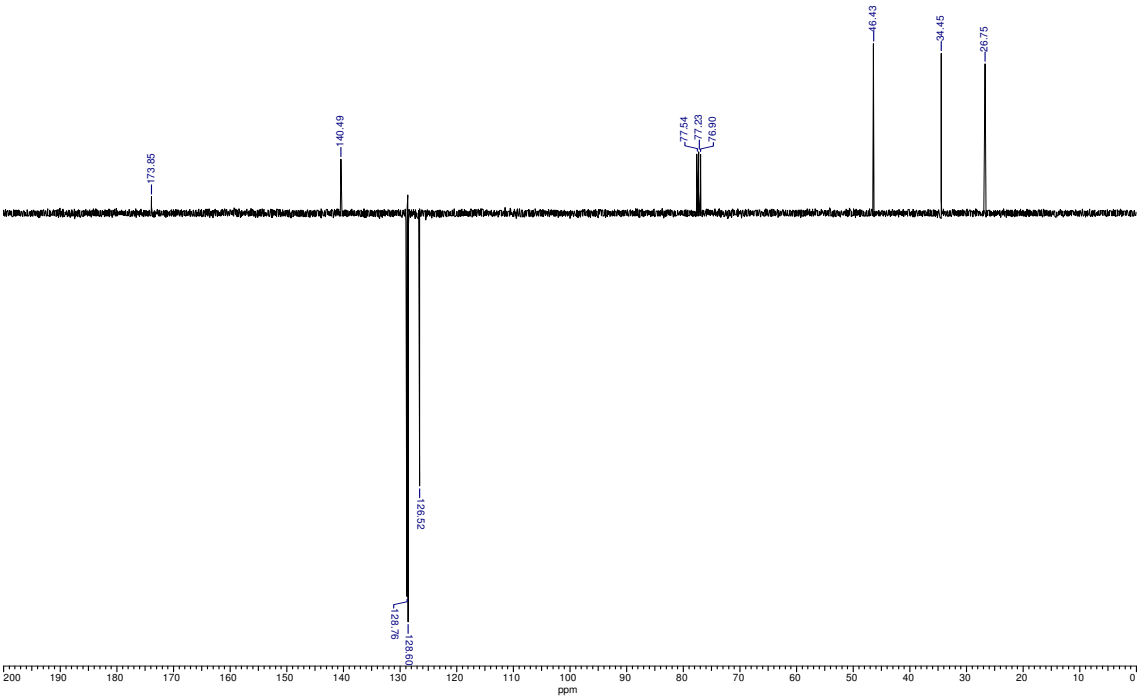
^{13}C NMR of 4-phenylbutanoic acid (87)



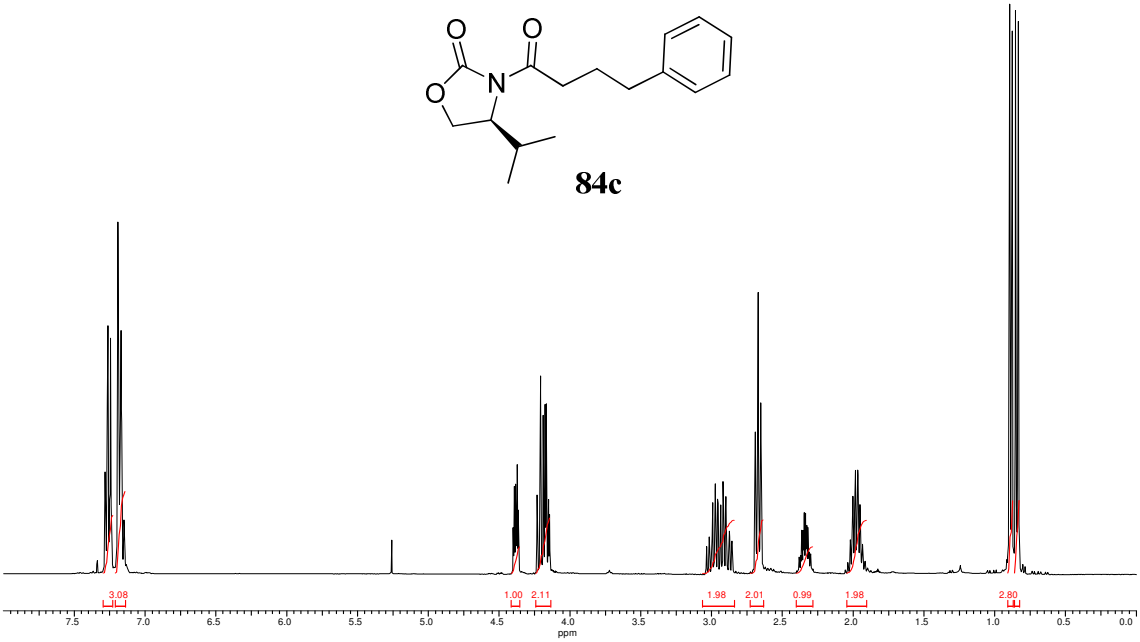
^{1}H NMR of 4–phenylbutanoyl chloride (83c)



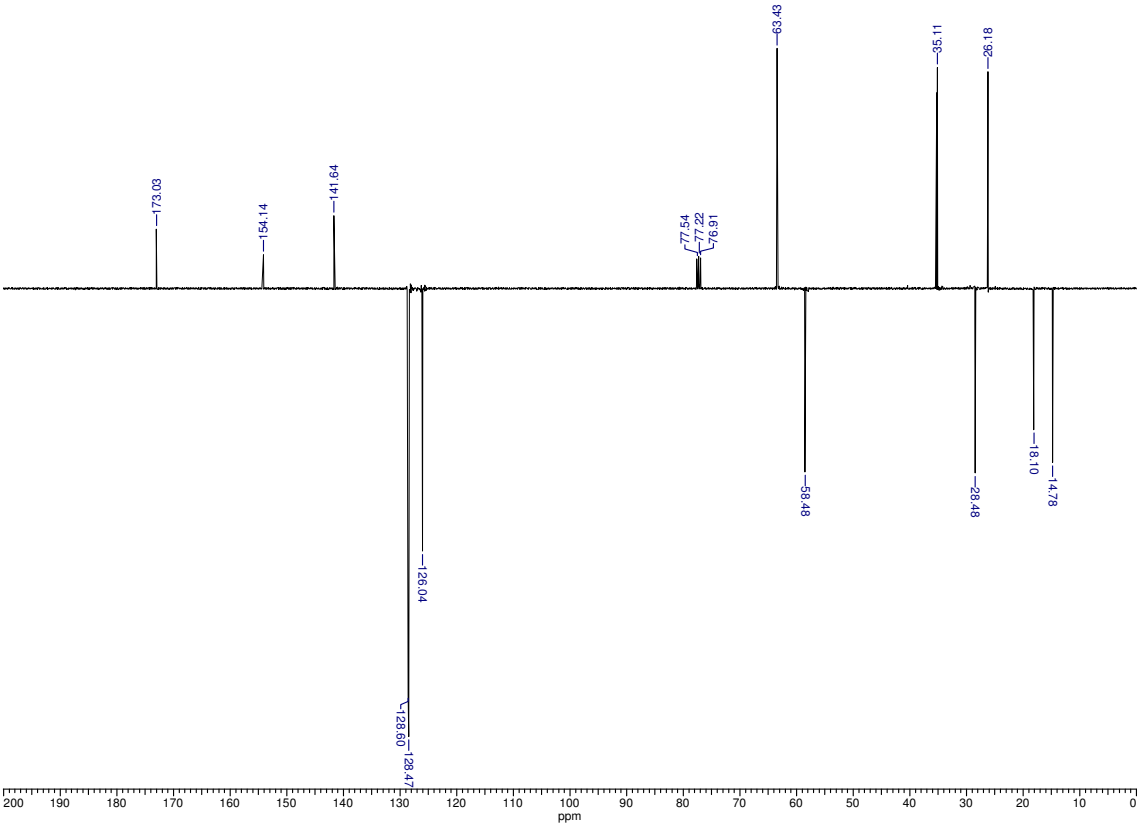
^{13}C NMR of 4–phenylbutanoyl chloride (83c)



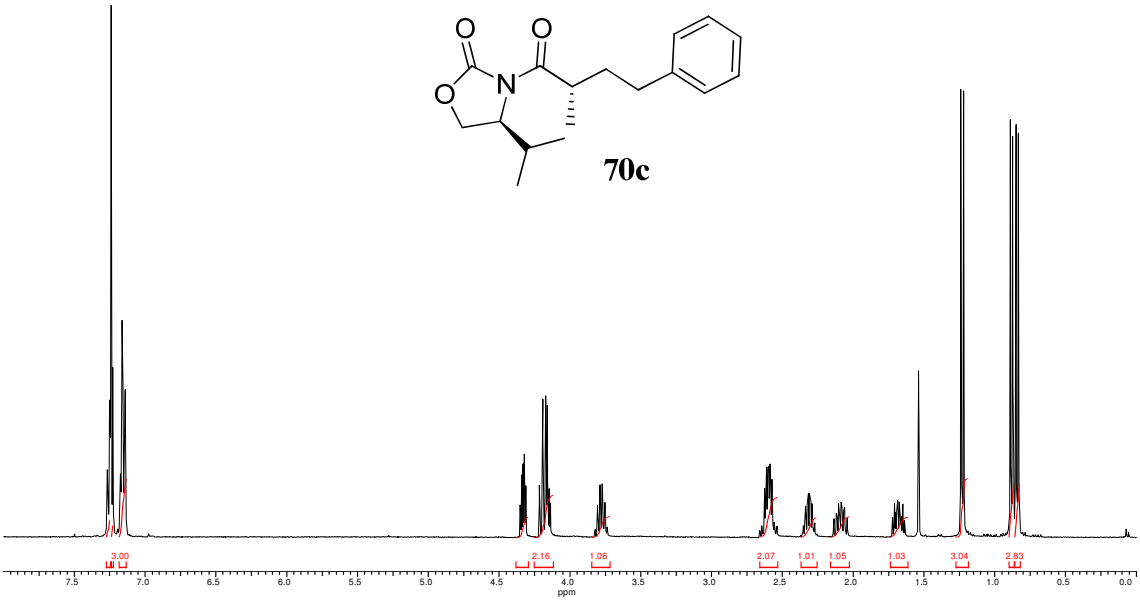
^{1}H NMR of (*S*)-4-isopropyl-3-(4-phenylbutanoyl)oxazolidin-2-one (84c)



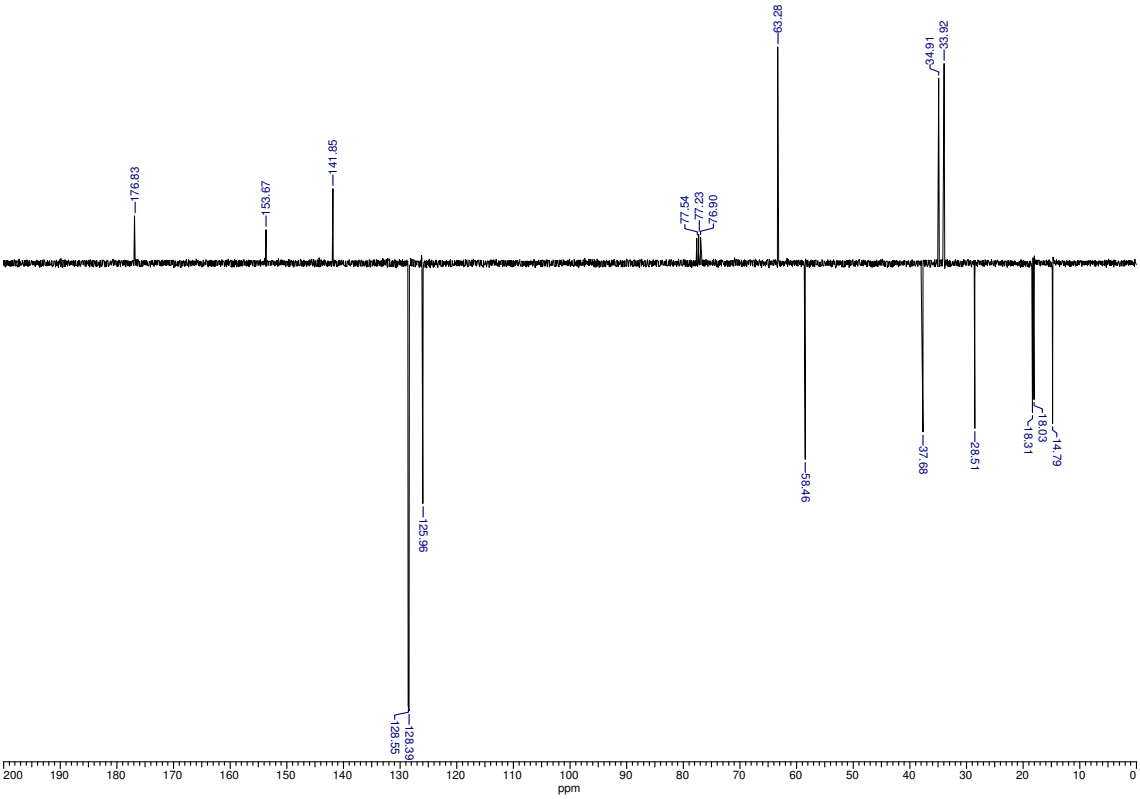
^{13}C NMR of (*S*)-4-isopropyl-3-(4-phenylbutanoyl)oxazolidin-2-one (84c)



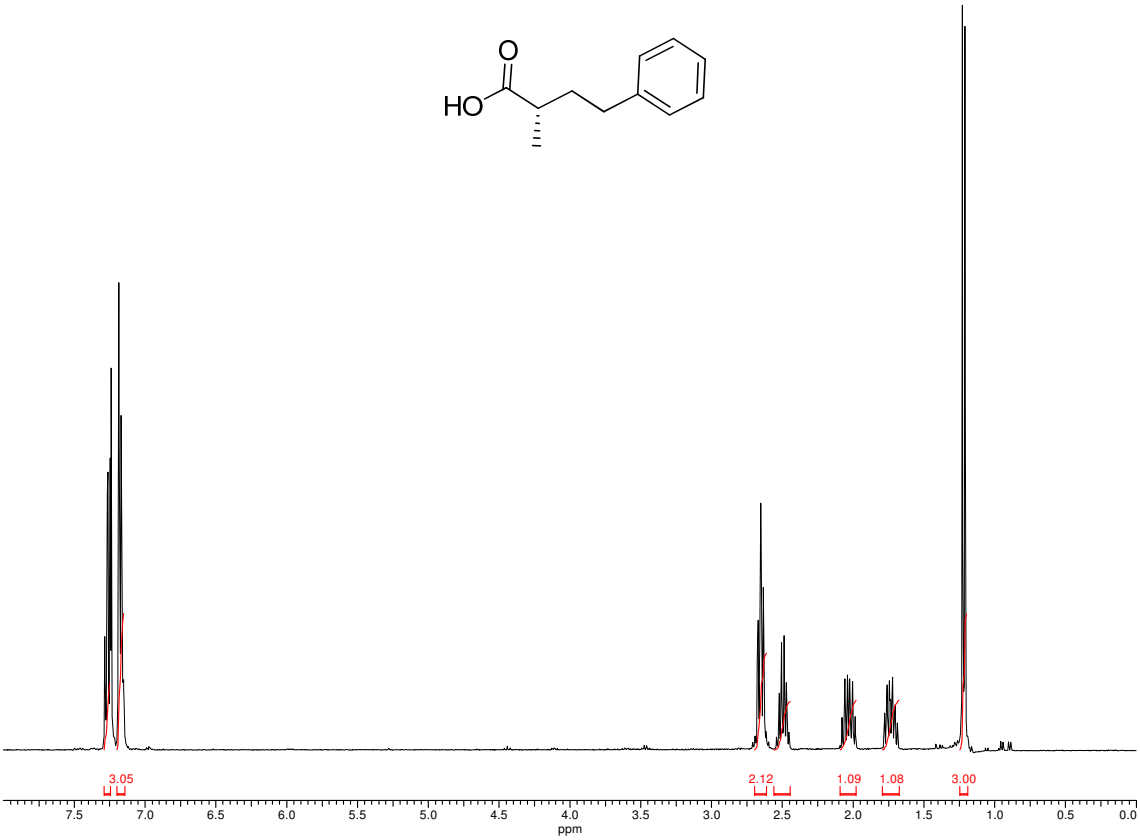
^{1}H NMR of (*S*)-4-isopropyl-3-((*S*)-2-methyl-4-phenylbutanoyl)oxazolidin-2-one (70c)



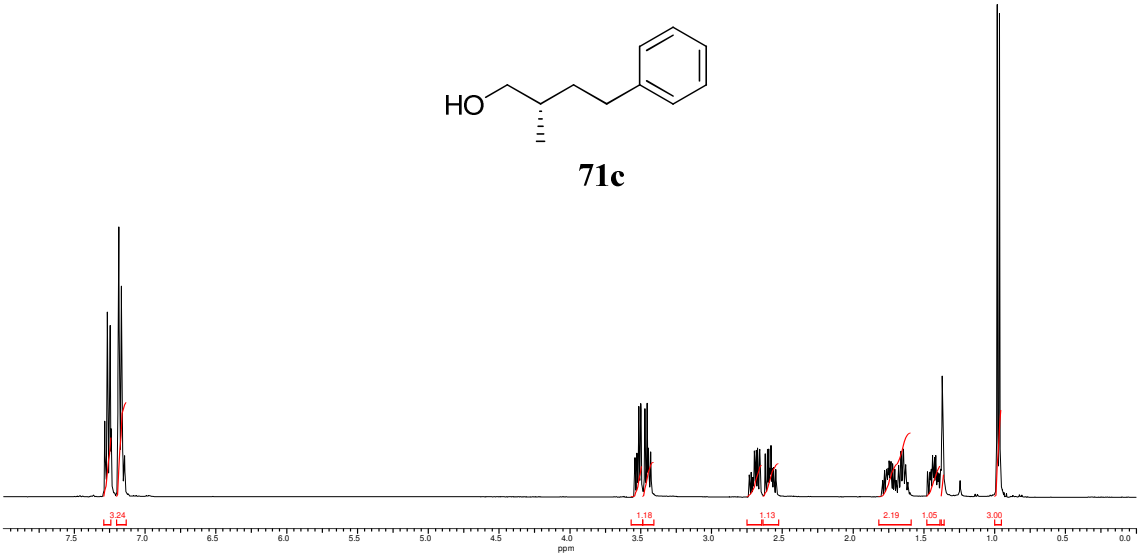
^{13}C NMR of (*S*)-4-isopropyl-3-((*S*)-2-methyl-4-phenylbutanoyl)oxazolidin-2-one (70c)



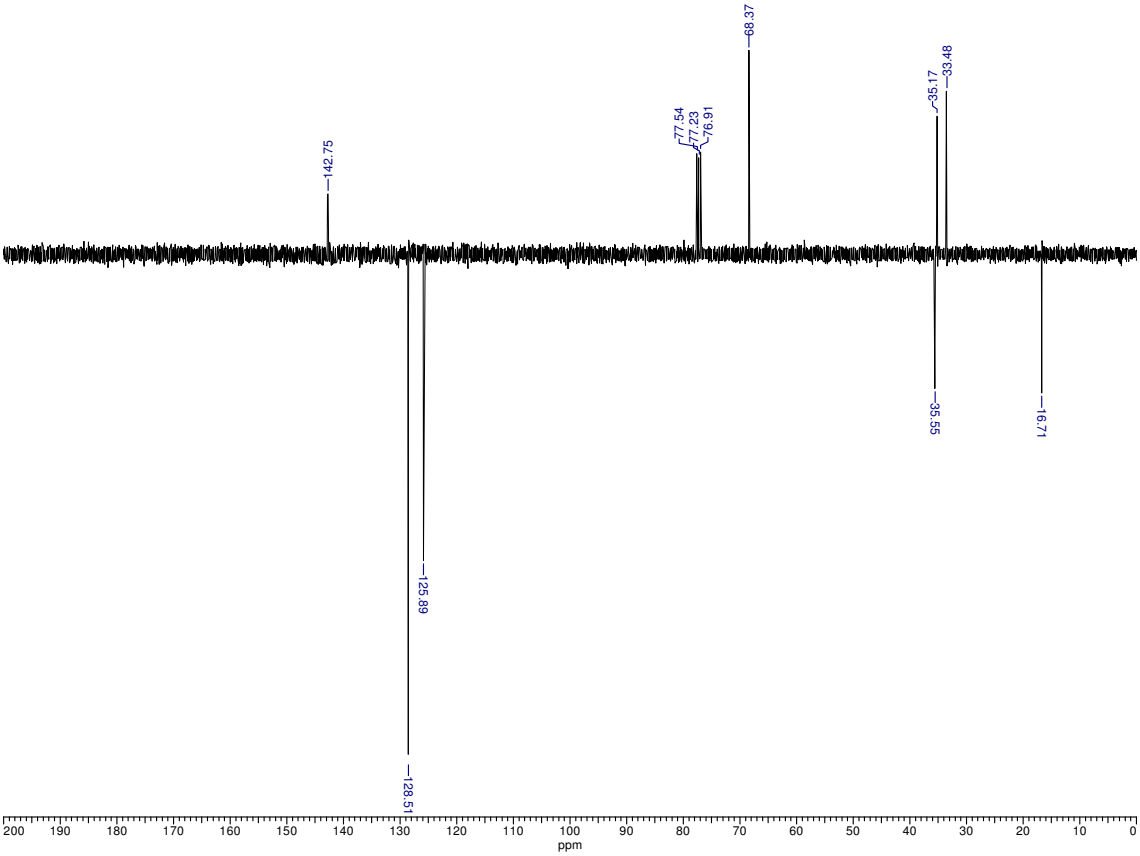
^{1}H NMR of (*S*)-2-methyl-4-phenylbutanoic acid



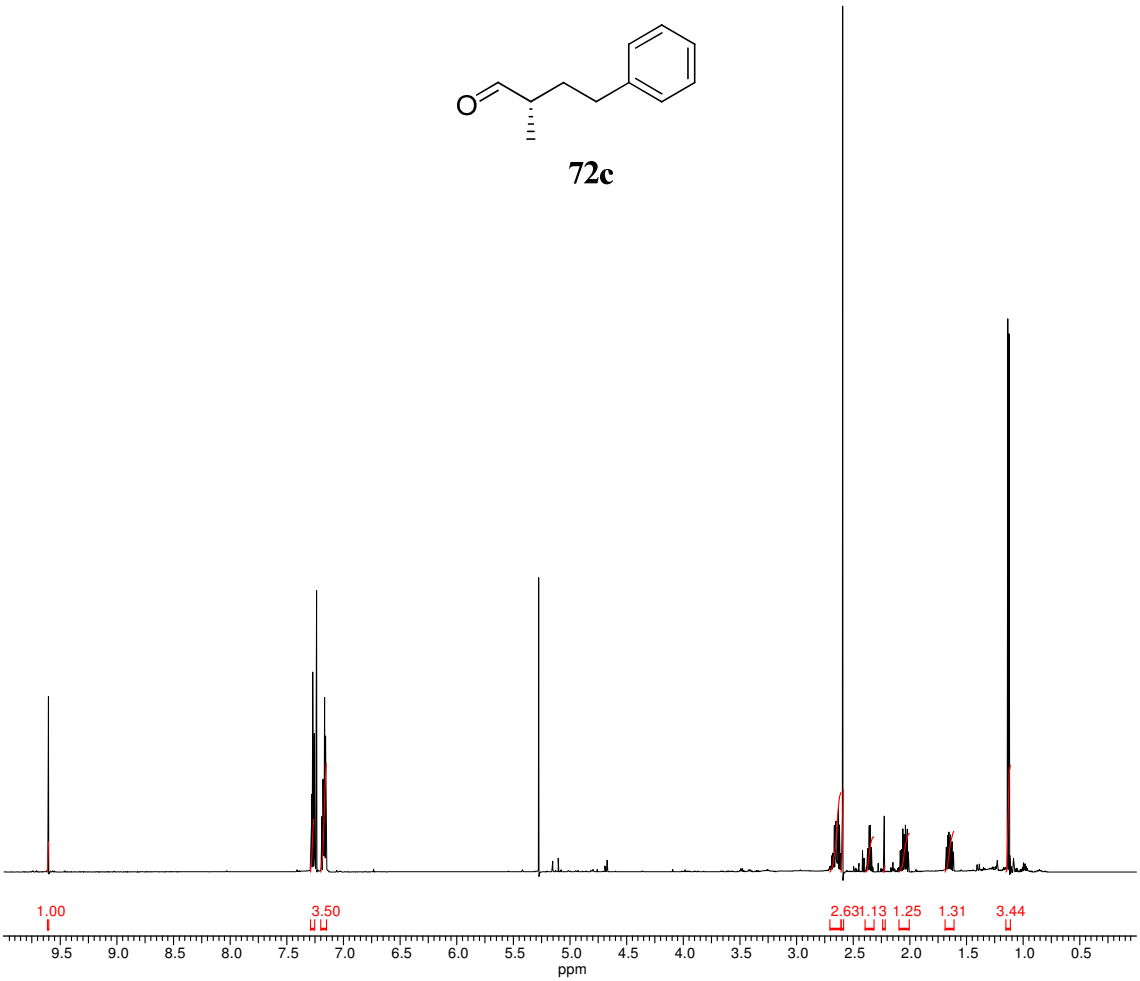
^{1}H NMR of (*S*)-2-methyl-4-phenylbutan-1-ol (71c)



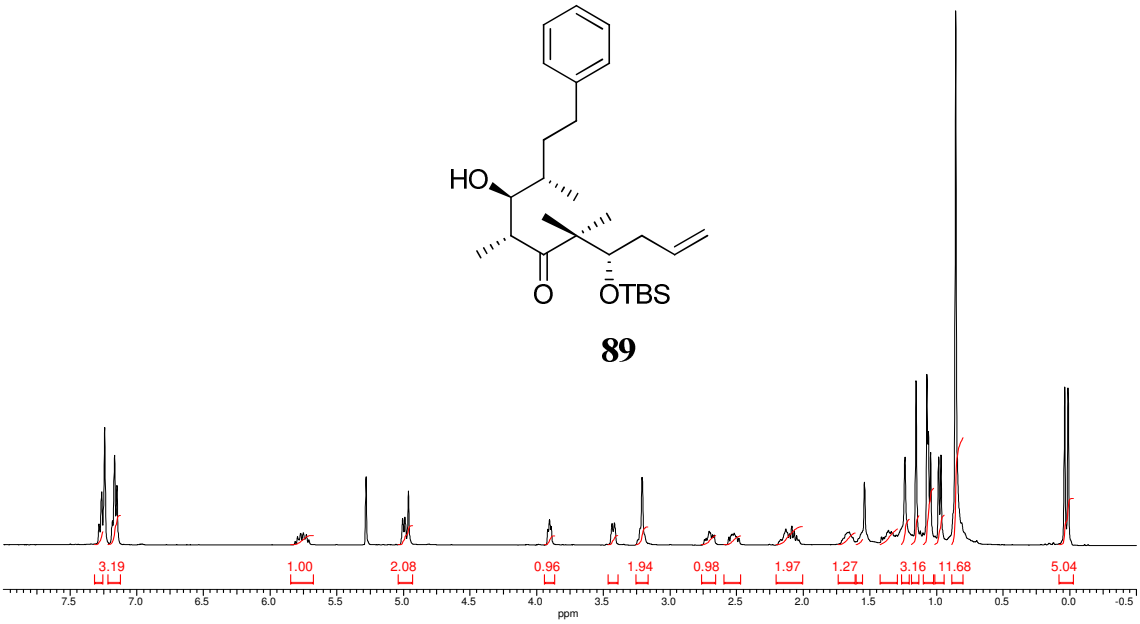
^{13}C NMR of (*S*)-2-methyl-4-phenylbutan-1-ol (71c)



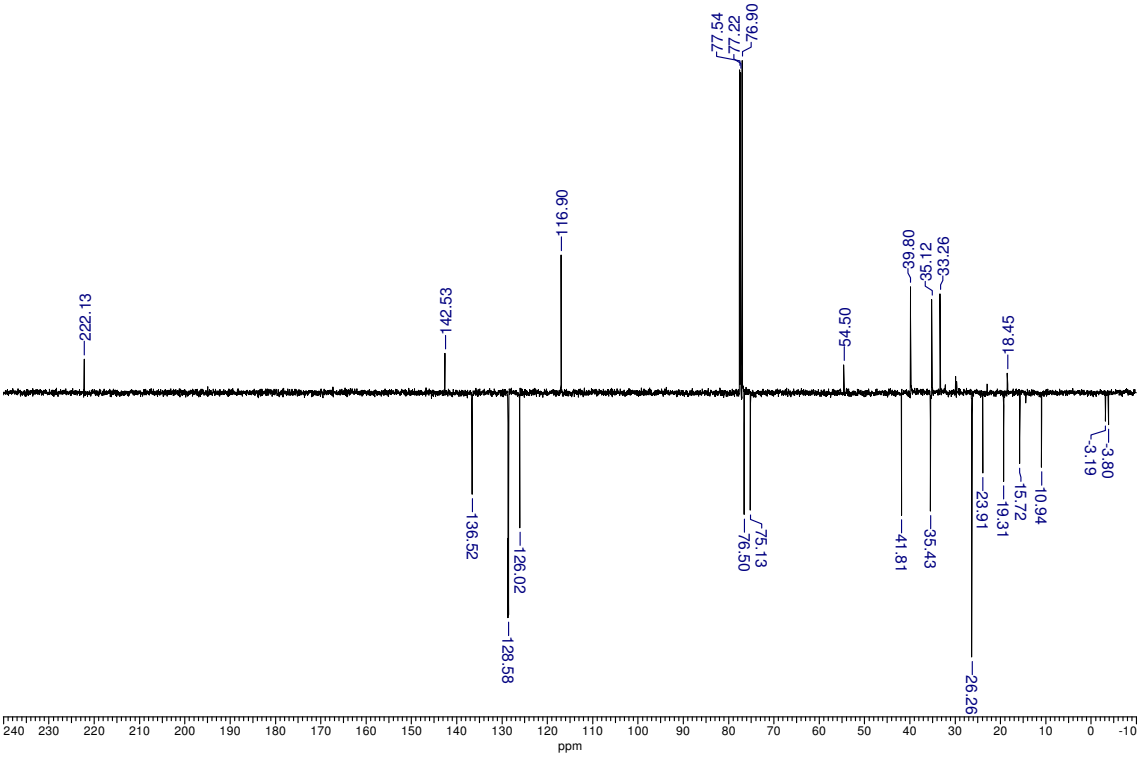
^{1}H NMR of (*S*)-2-methyl-4-phenylbutanal (72c)



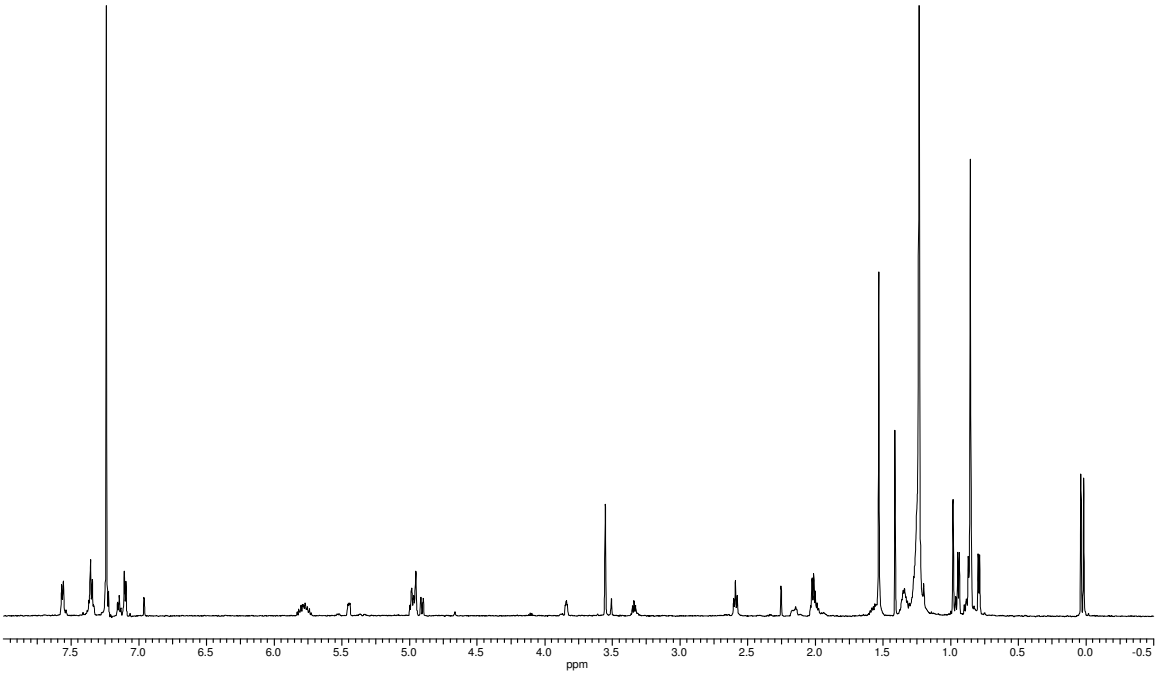
^{1}H NMR of (*4S,7R,8S,9S*)-4-(*tert*-butyldimethylsilyloxy)-8-hydroxy-5,5,7,9-tetramethyl-11-phenylundec-1-en-6-one (89)



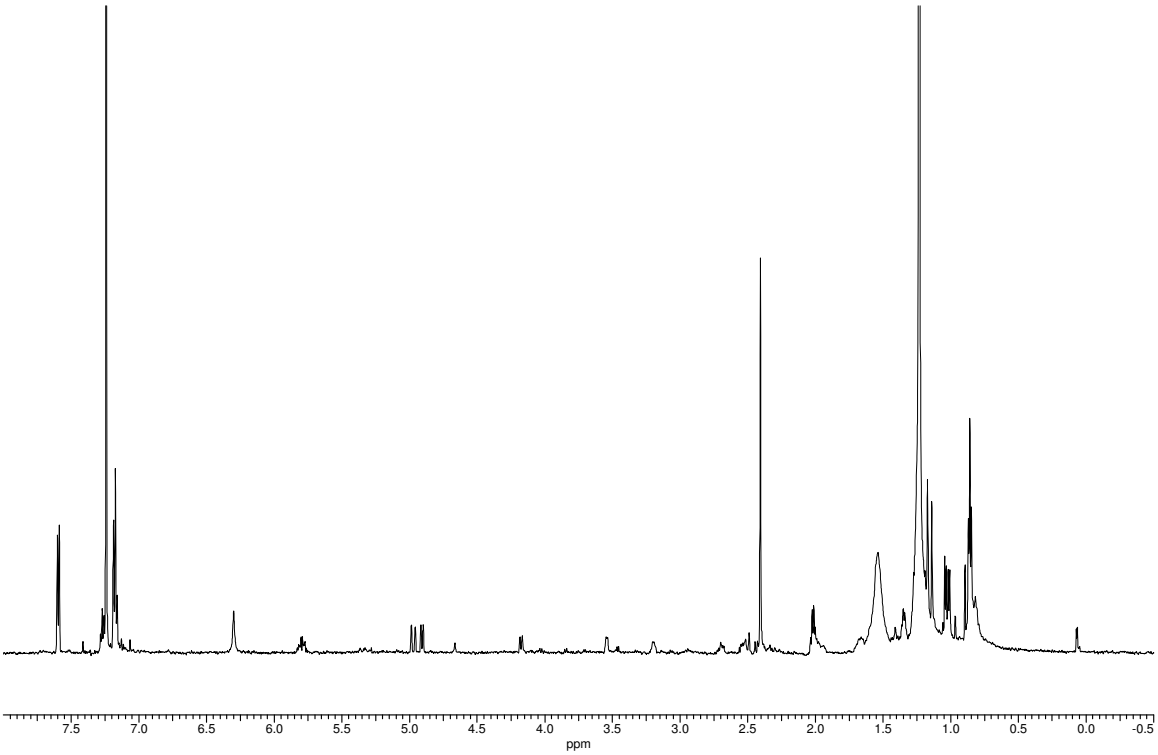
^{13}C NMR of (*4S,7R,8S,9S*)-4-(*tert*-butyldimethylsilyloxy)-8-hydroxy-5,5,7,9-tetramethyl-11-phenylundec-1-en-6-one (89)



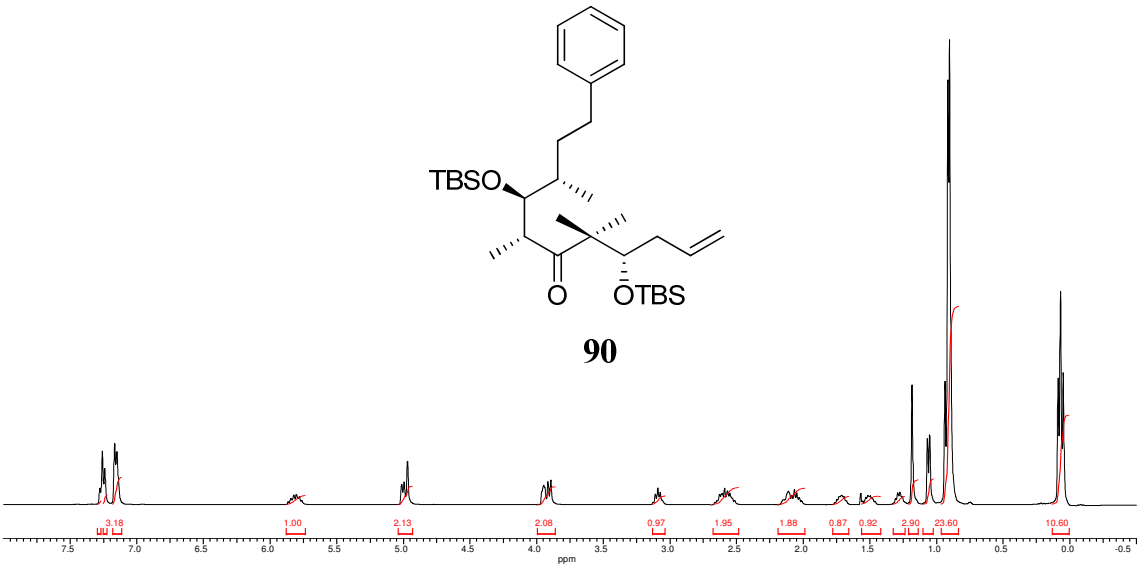
^{1}H NMR of S-Mosher ester of (89)



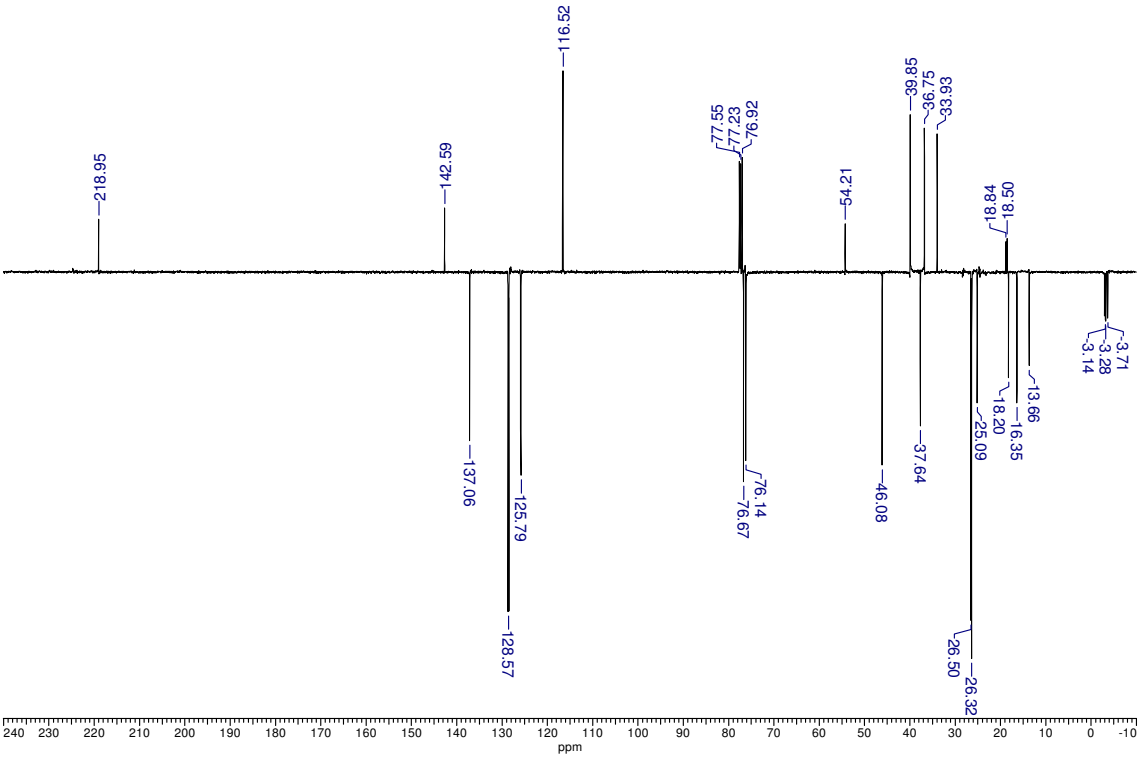
^{1}H NMR of R-Mosher ester of (89)



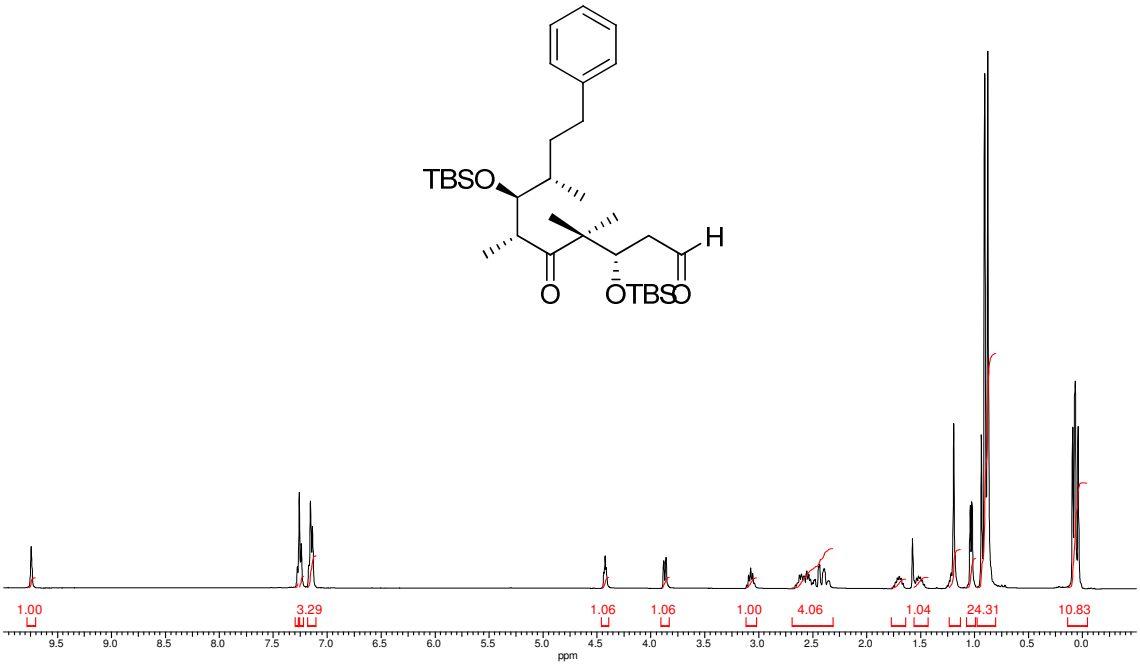
^{1}H NMR of (*4S,7R,8S,9S*)-4,8-bis-(*tert*-butyldimethylsiloxy)-5,5,7,9-tetramethyl-11-phenylundec-1-en-6-one (90)



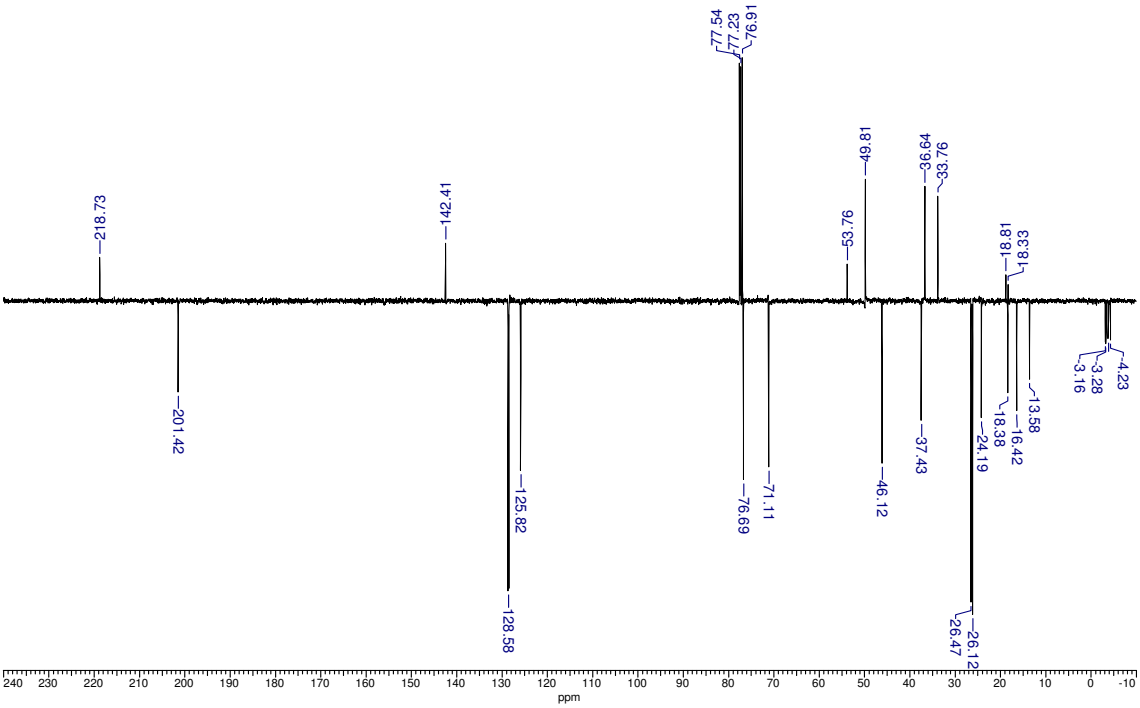
^{13}C NMR of (*4S,7R,8S,9S*)-4,8-bis-(*tert*-butyldimethylsiloxy)-5,5,7,9-tetramethyl-11-phenylundec-1-en-6-one (90)



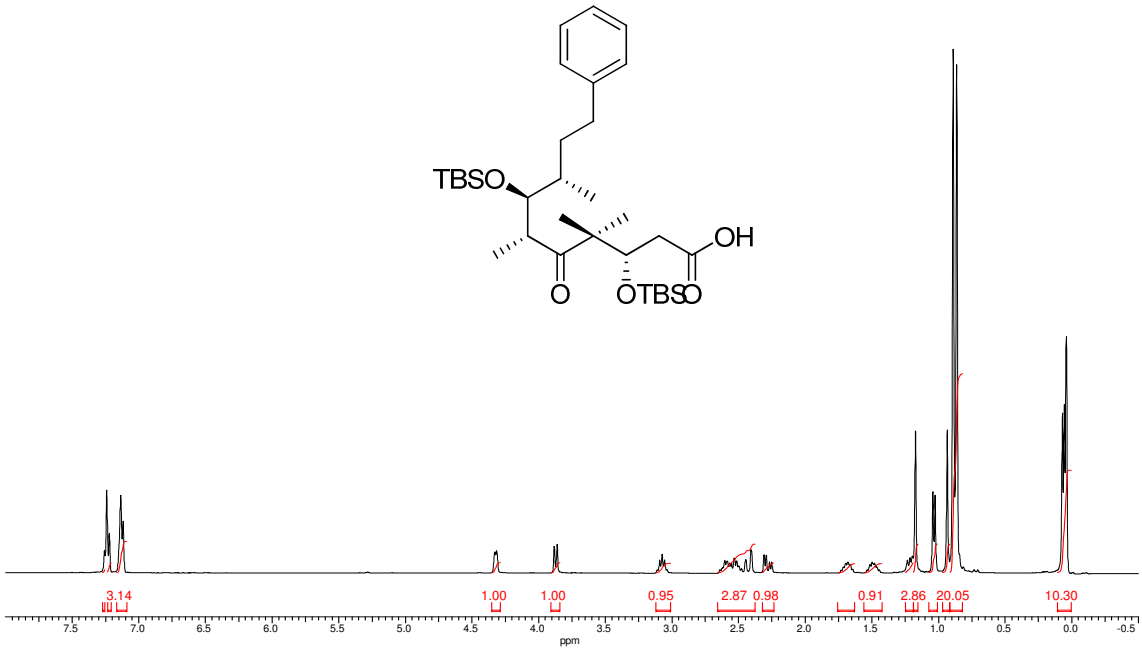
^{1}H NMR of (*3S,6R,7S,8S*)-3,7-bis(tert-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxo-10-phenyldecanal



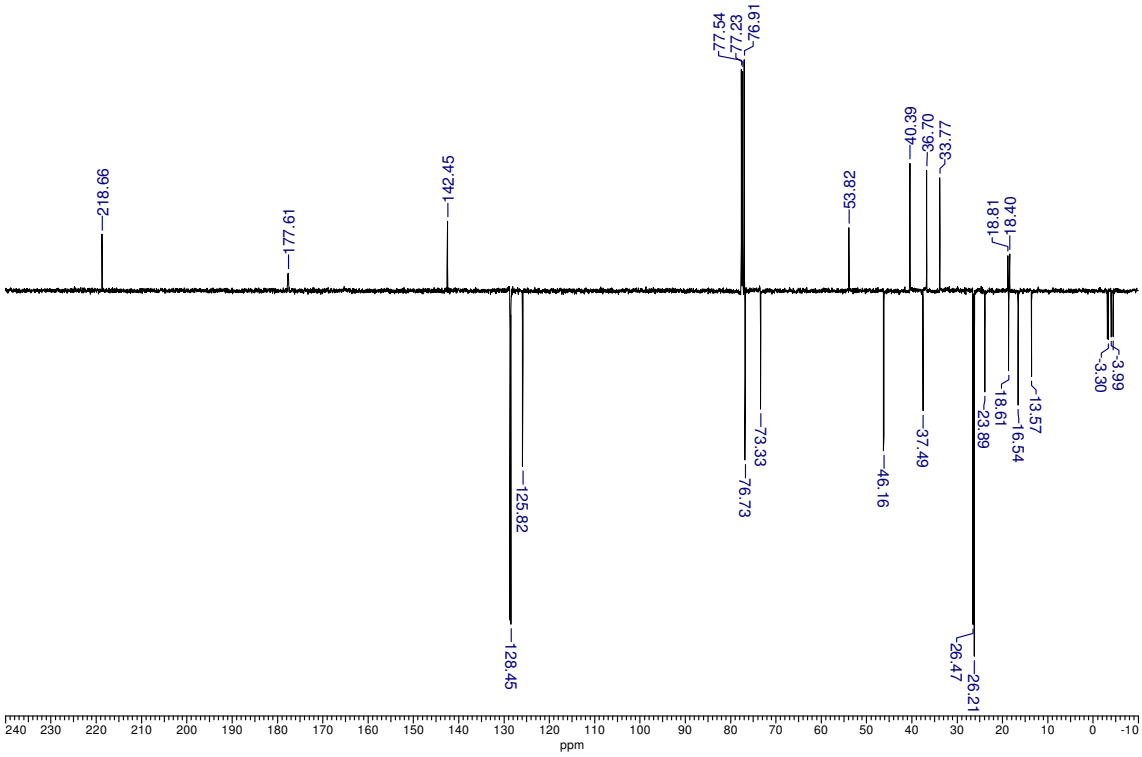
^{13}C NMR of (*3S,6R,7S,8S*)-3,7-bis(tert-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxo-10-phenyldecanal



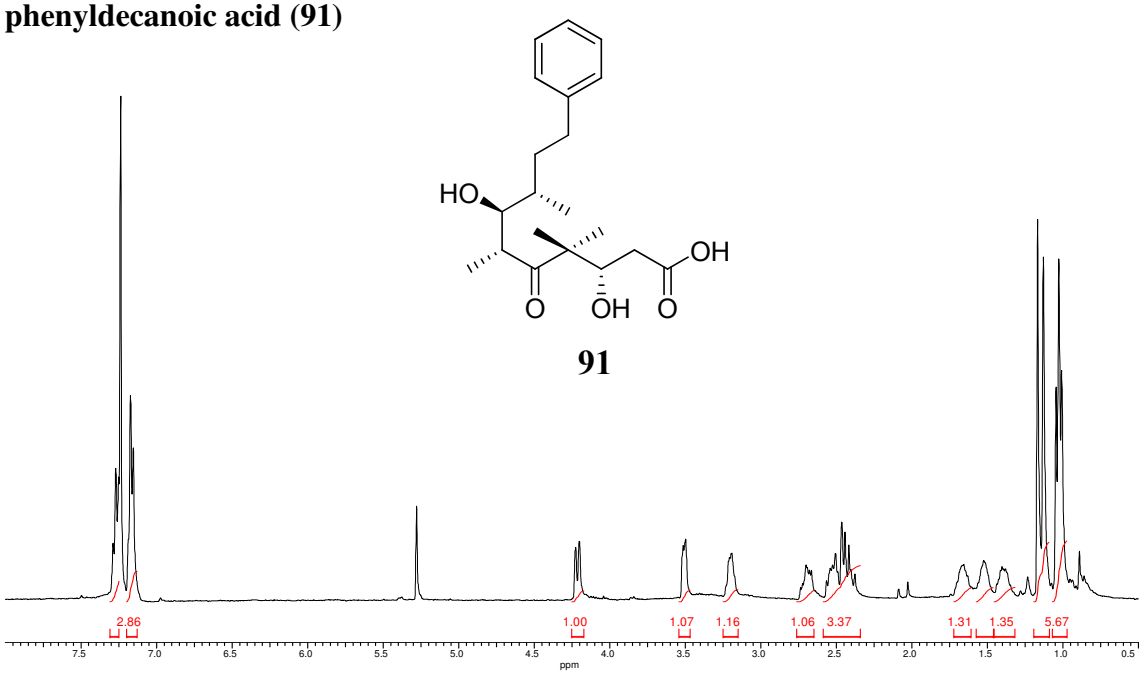
^{1}H NMR of (*3S,6R,7S,8S*)-3,7-bis(tert-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxo-10-phenyldecanoic acid



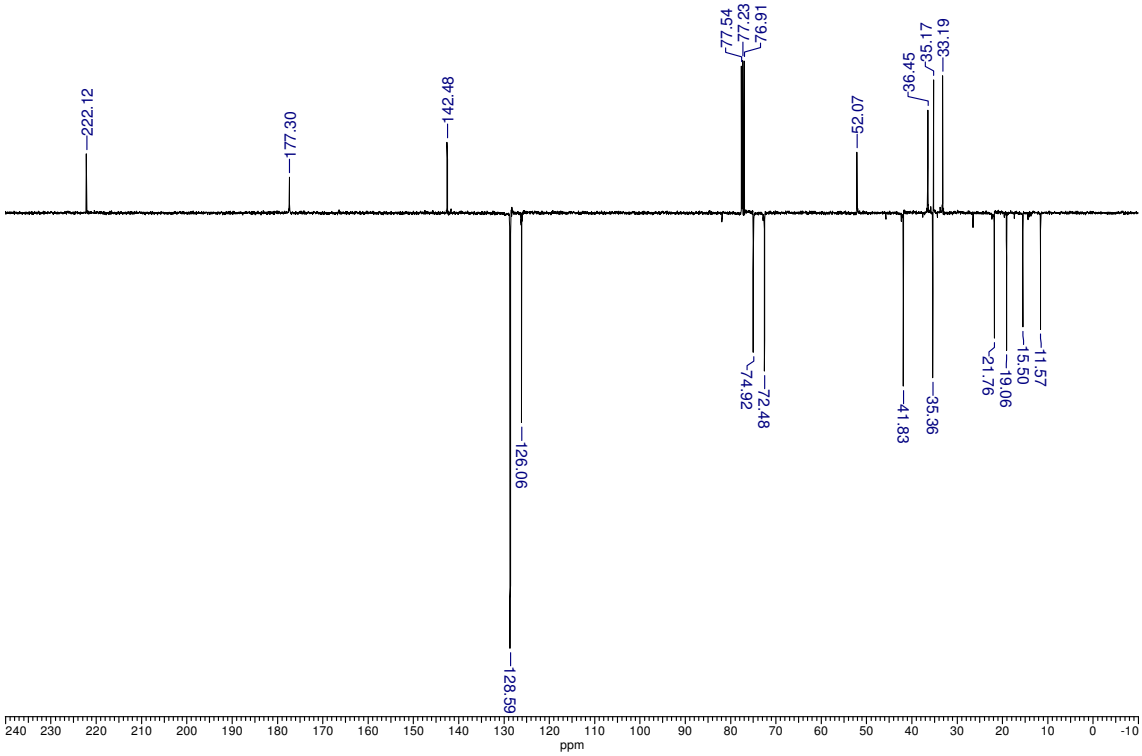
^{13}C NMR of (*3S,6R,7S,8S*)-3,7-bis(tert-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxo-10-phenyldecanoic acid



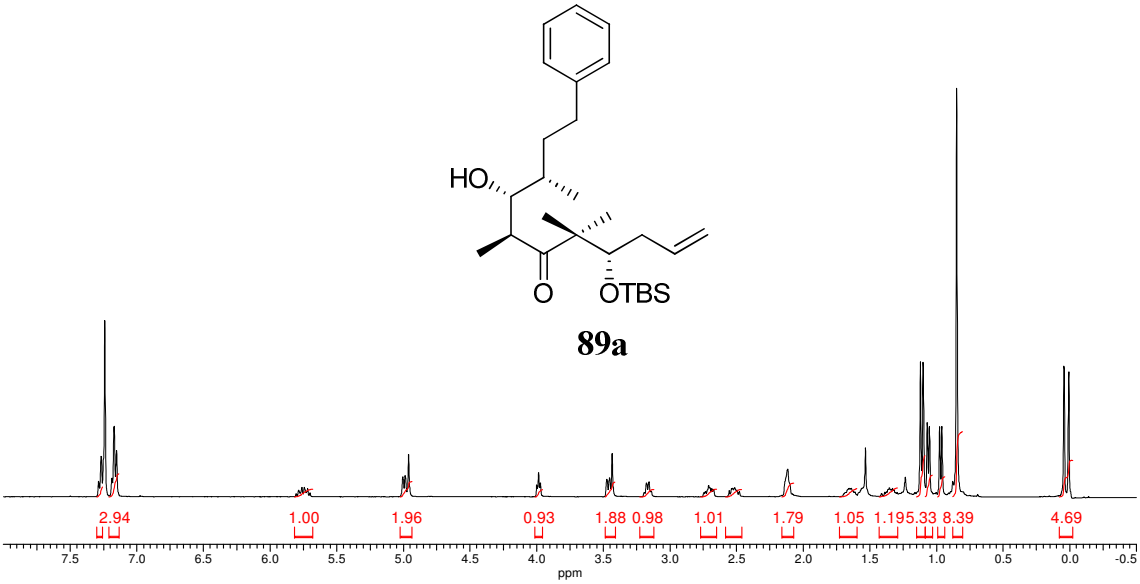
^{1}H NMR of (*3S,6R,7S,8S*)-3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxo-10-phenyldecanoic acid (91)



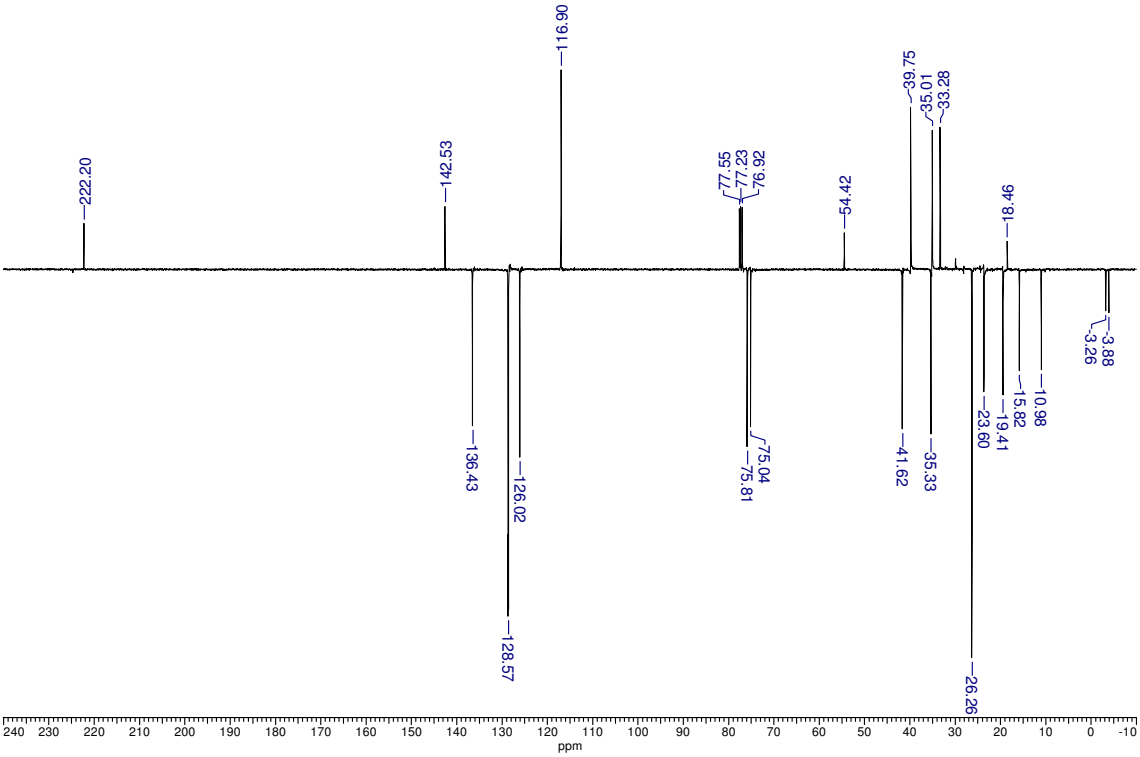
^{13}C NMR of (*3S,6R,7S,8S*)-3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxo-10-phenyldecanoic acid (91)



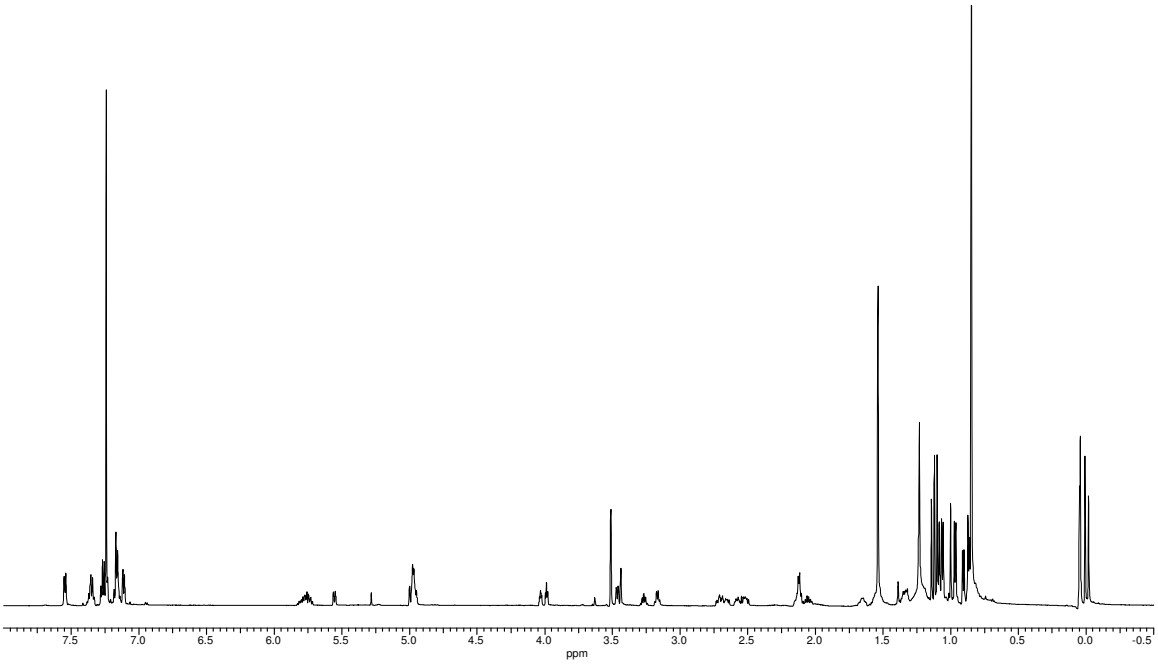
^{1}H NMR of (*4S,7S,8R,9S*)-4-(*tert*-butyldimethylsilyloxy)-8-hydroxy-5,5,7,9-tetramethyl-11-phenylundec-1-en-6-one (89a)



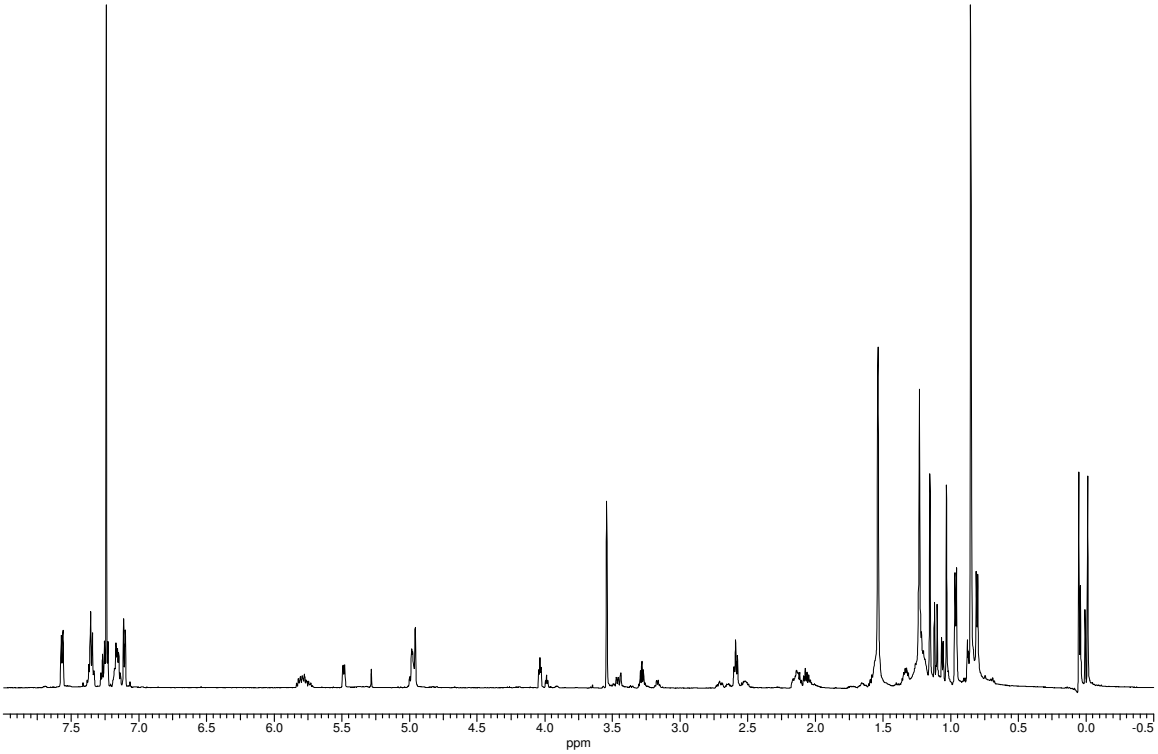
^{13}C NMR of (*4S,7S,8R,9S*)-4-(*tert*-butyldimethylsilyloxy)-8-hydroxy-5,5,7,9-tetramethyl-11-phenylundec-1-en-6-one (89a)



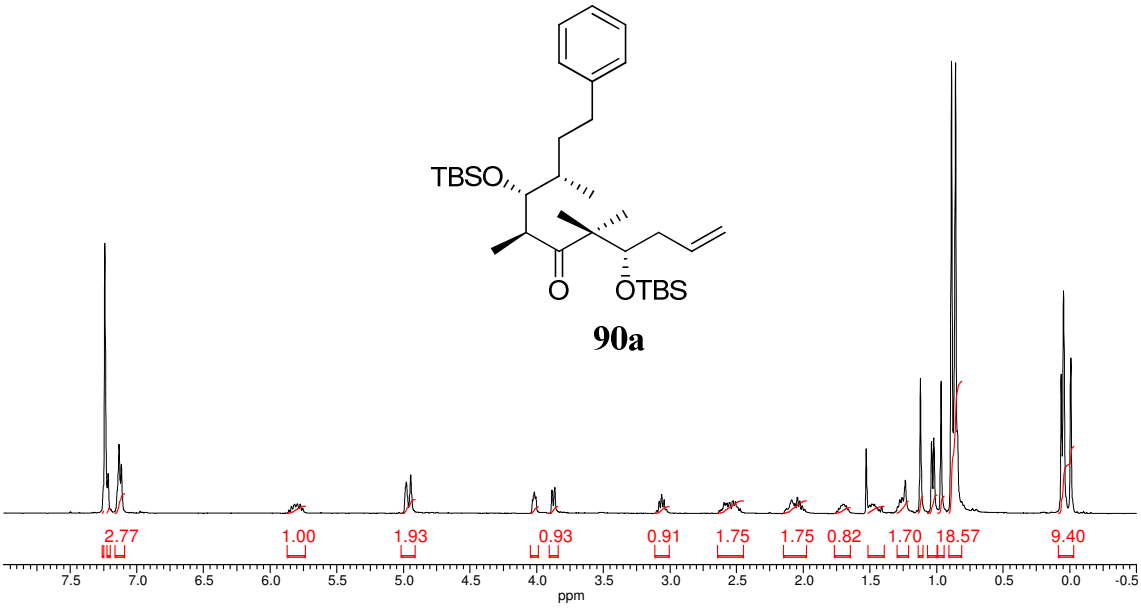
^{1}H NMR of S-Mosher ester of (89a)



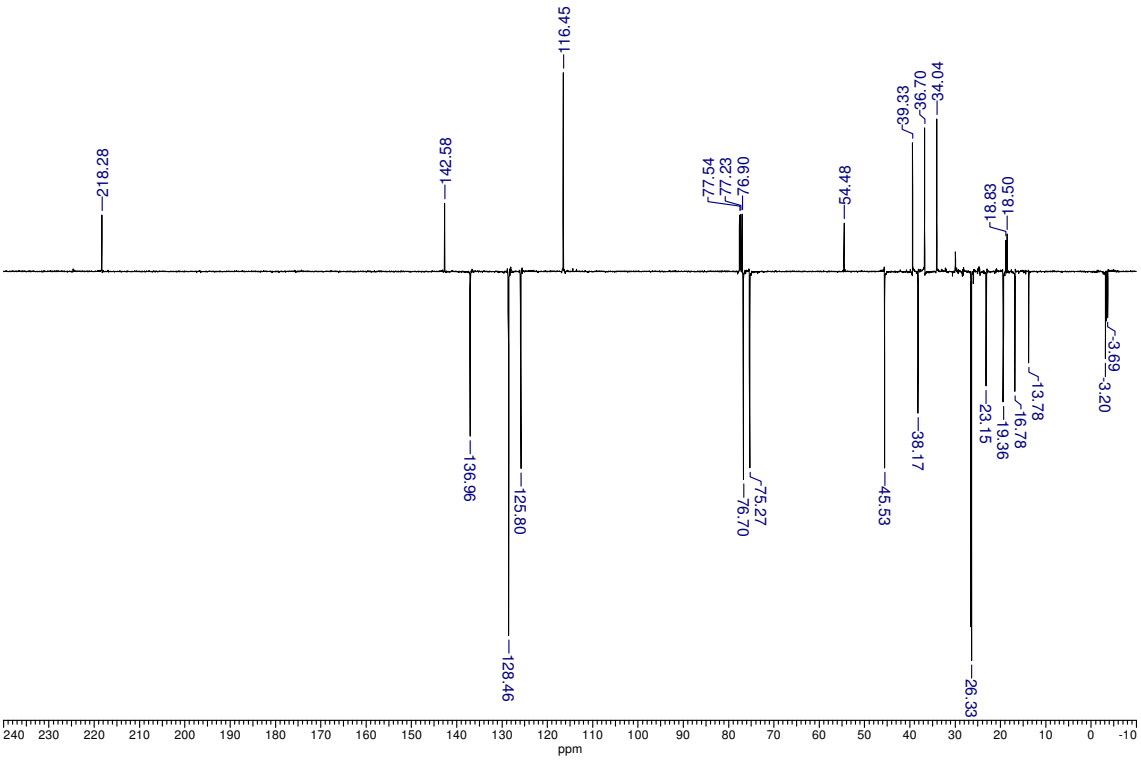
^{1}H NMR of R-Mosher ester of (89a)



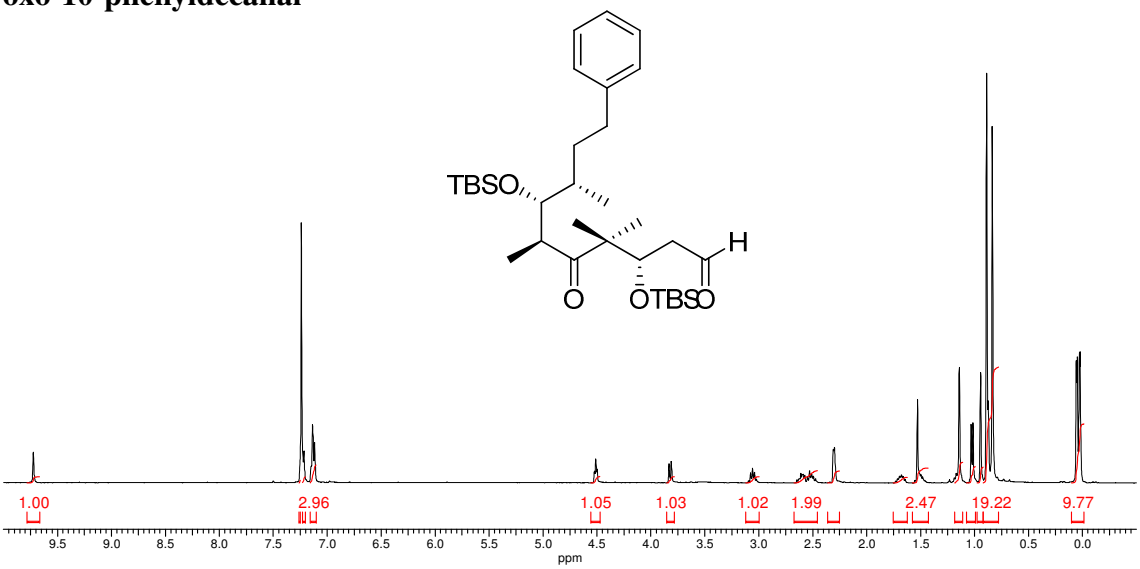
^{1}H NMR of (*4S,7S,8R,9S*)-4,8-bis-(*tert*-butyldimethylsiloxy)-5,5,7,9-tetramethyl-11-phenylundec-1-en-6-one (90a)



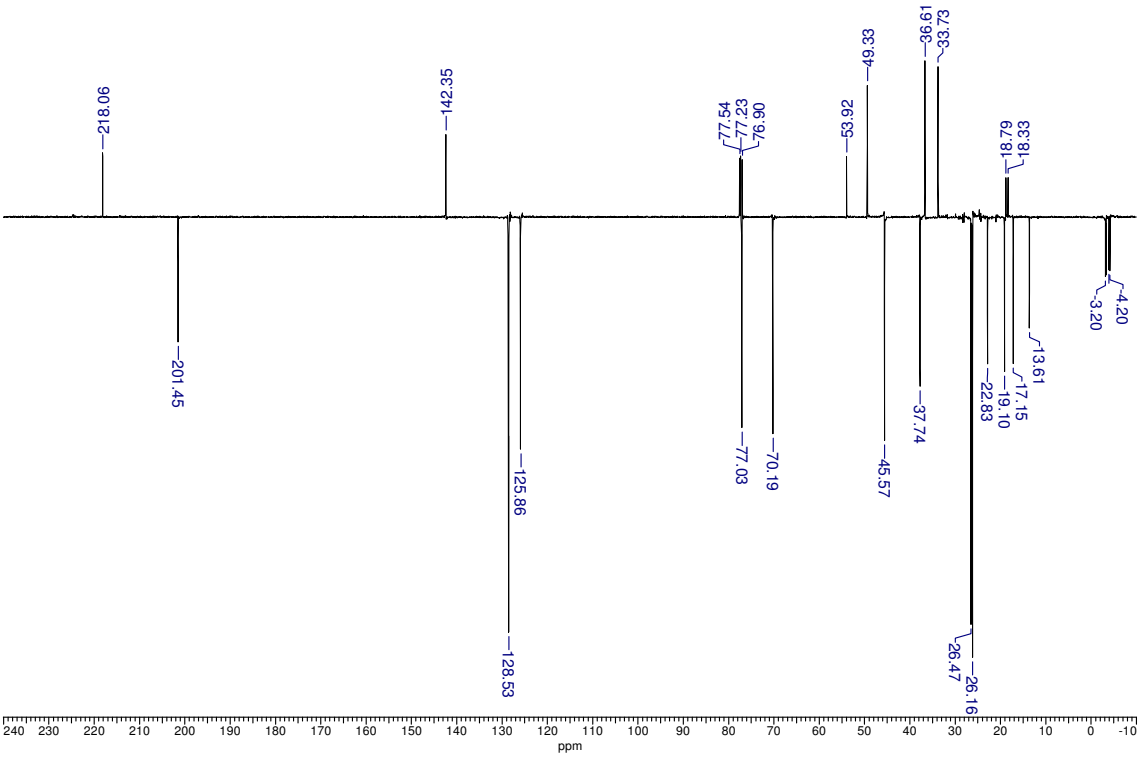
^{13}C NMR of (*4S,7S,8R,9S*)-4,8-bis-(*tert*-butyldimethylsiloxy)-5,5,7,9-tetramethyl-11-phenylundec-1-en-6-one (90a)



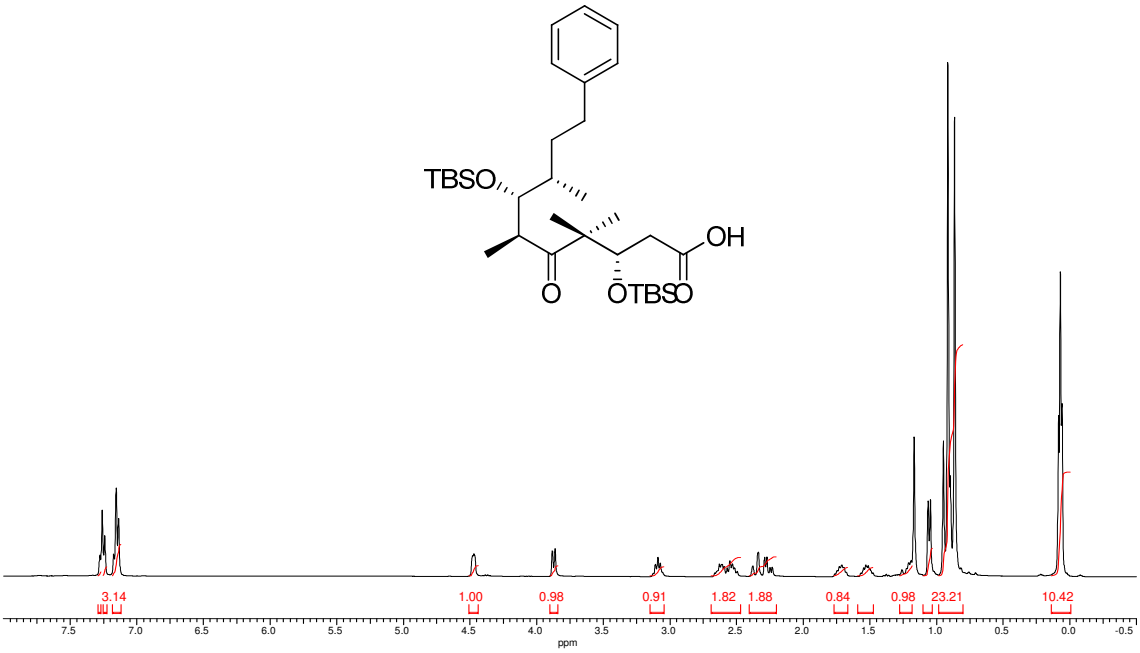
^{1}H NMR of (*3S,6S,7R,8S*)-3,7-bis(tert-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxo-10-phenyldecanal



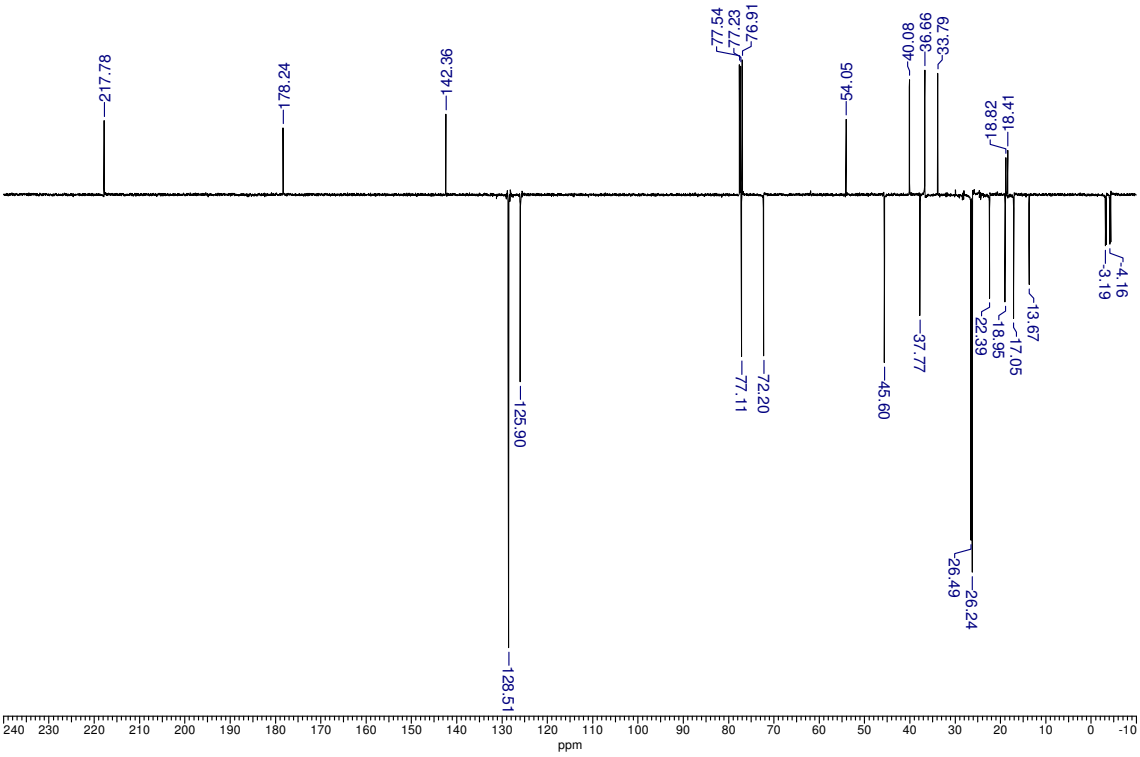
^{13}C NMR of (*3S,6S,7R,8S*)-3,7-bis(tert-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxo-10-phenyldecanal



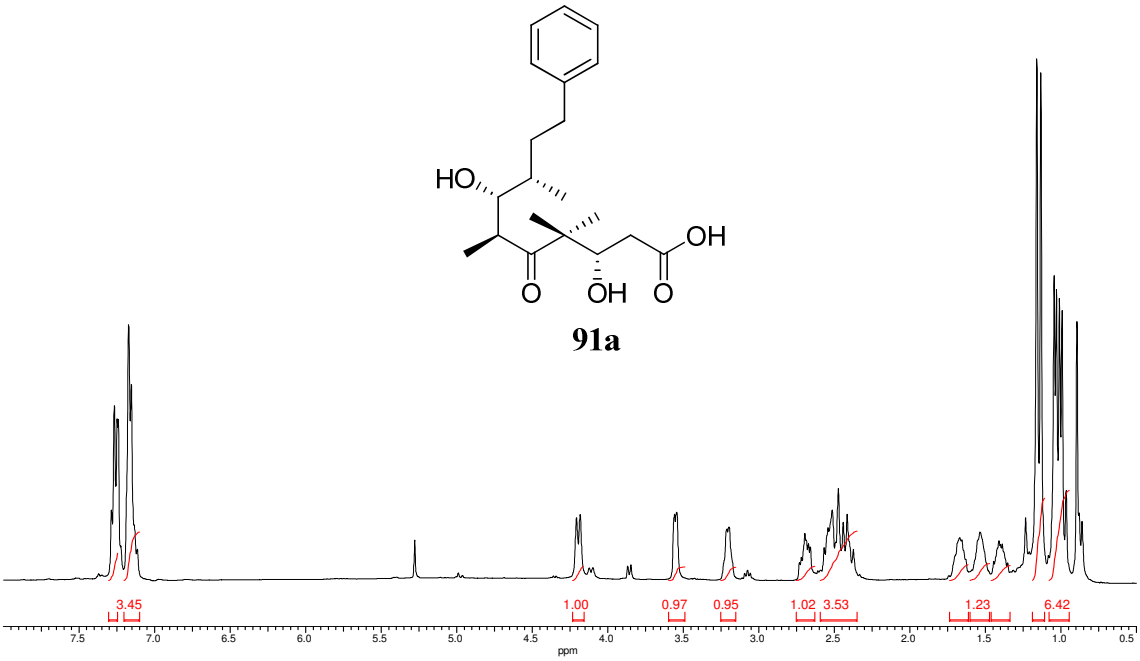
^{1}H NMR of (*3S,6S,7R,8S*)-3,7-bis(tert-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxo-10-phenyldecanoic acid



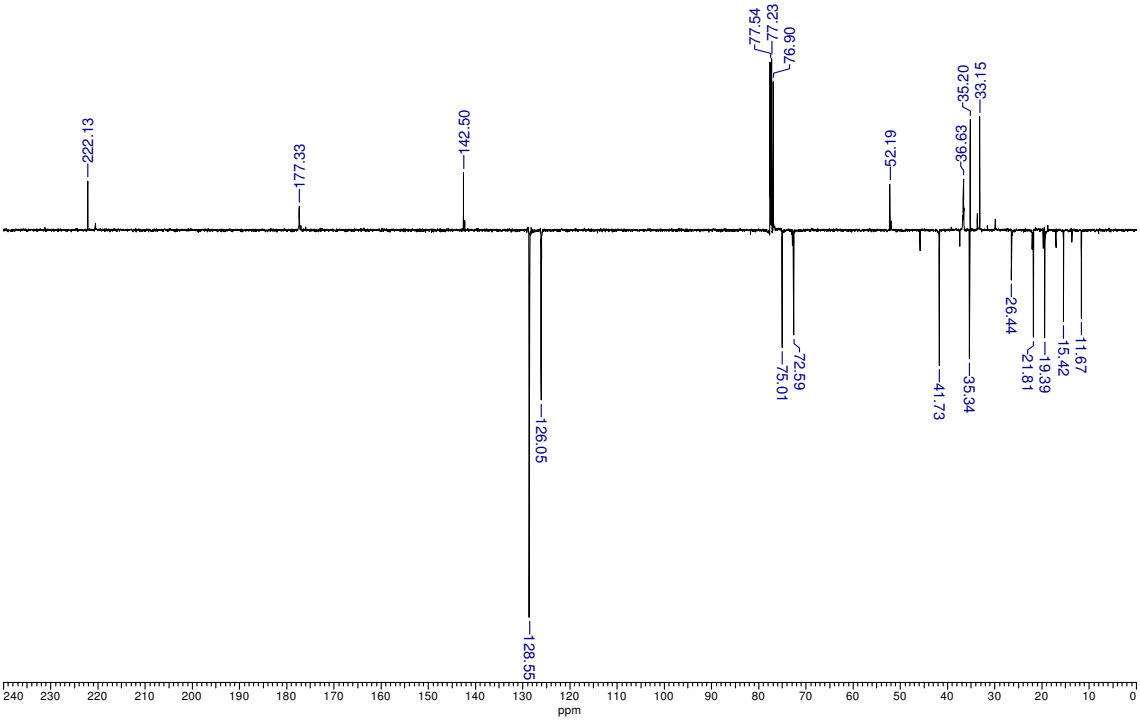
^{13}C NMR of (*3S,6S,7R,8S*)-3,7-bis(tert-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxo-10-phenyldecanoic acid



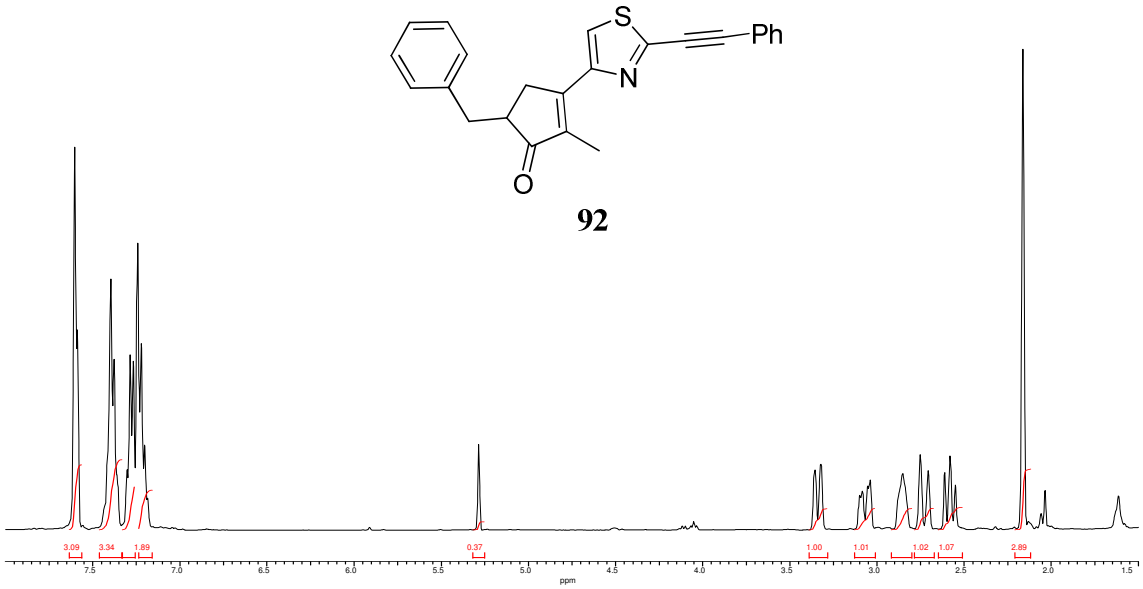
^{1}H NMR of *(3S,6S,7R,8S)*-3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxo-10-phenyldecanoic acid (91a)



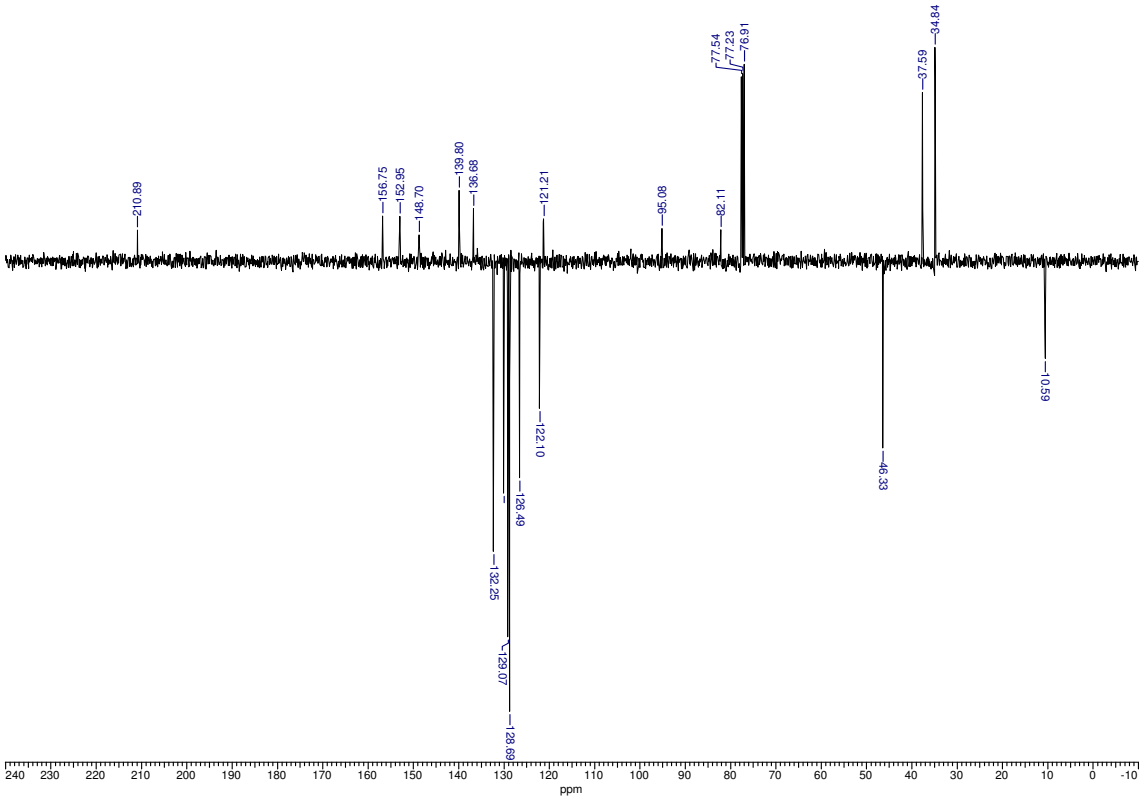
^{13}C NMR of *(3S,6S,7R,8S)*-3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxo-10-phenyldecanoic acid (91a)



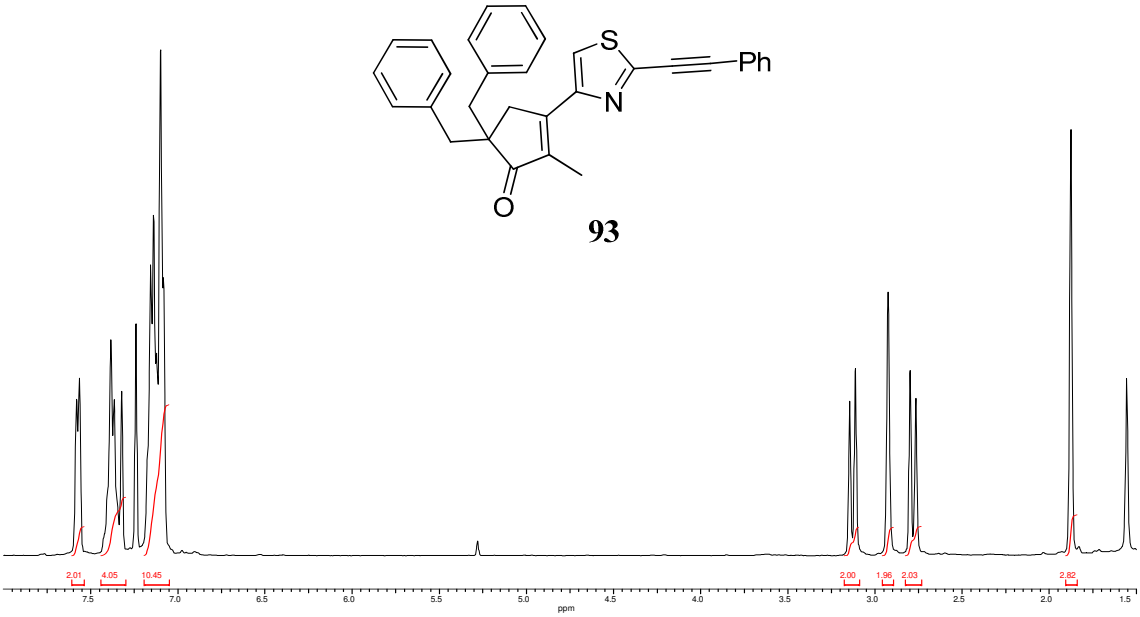
^{1}H NMR of 5-benzyl-2-methyl-3-(2-(phenylethynyl)thiazol-4-yl)cyclopent-2-enone (92)



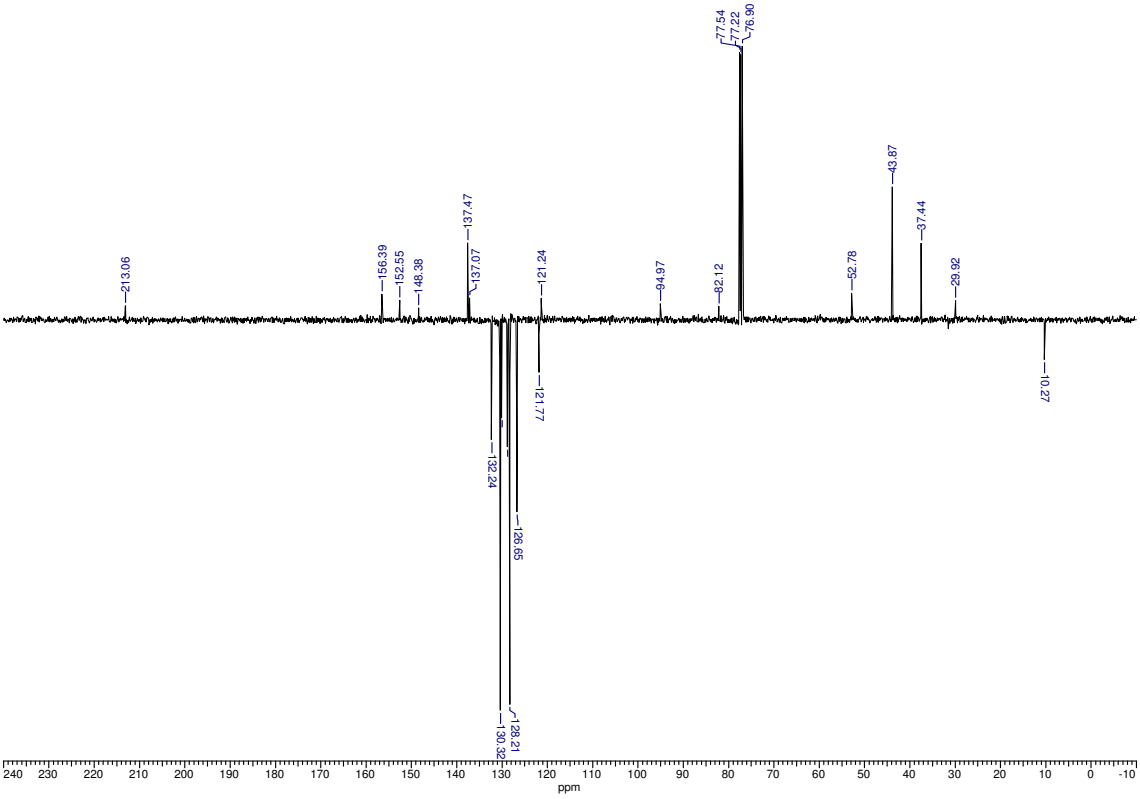
^{13}C NMR of 5-benzyl-2-methyl-3-(2-(phenylethynyl)thiazol-4-yl)cyclopent-2-enone (92)



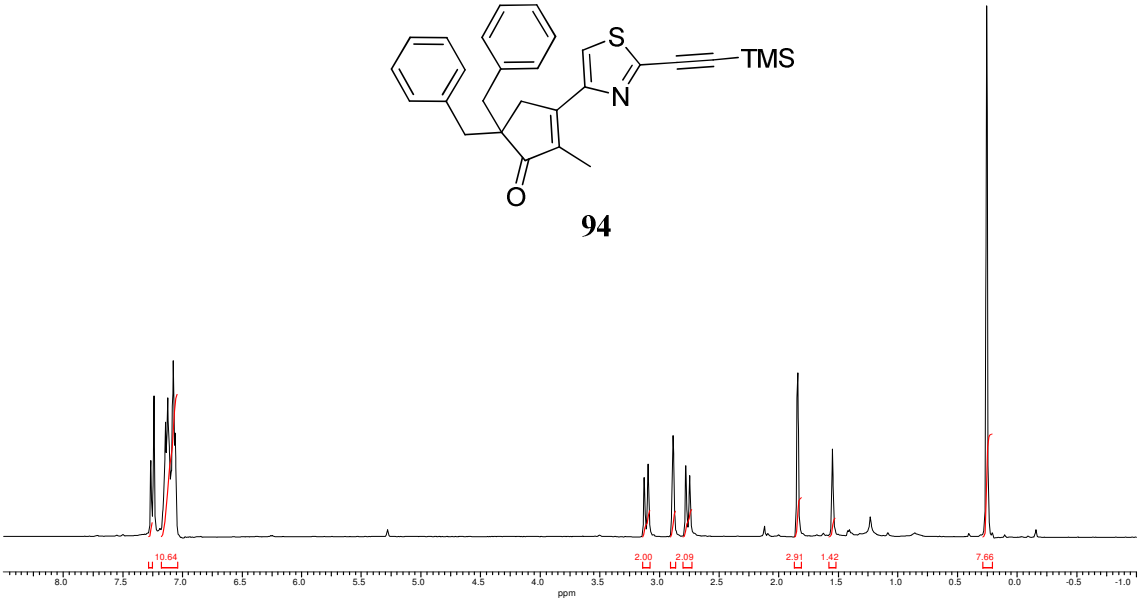
^{1}H NMR of 5,5-dibenzyl-2-methyl-3-(2-(phenylethynyl)thiazol-4-yl)cyclopent-2-enone (93)



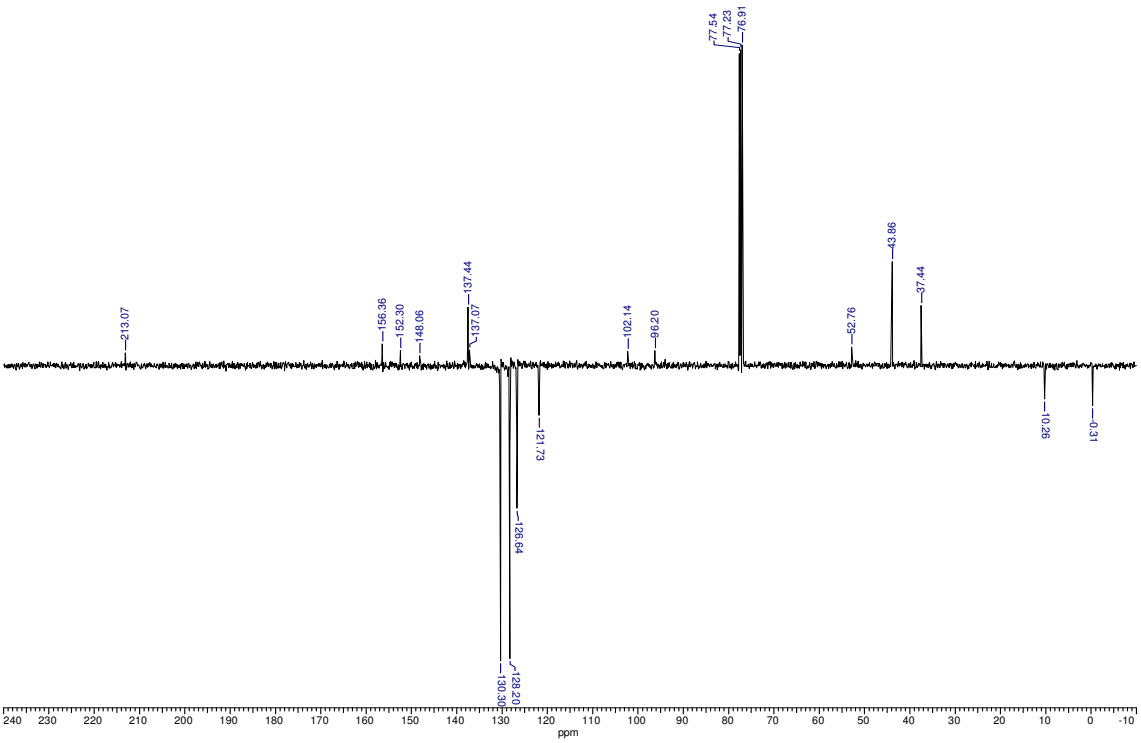
^{13}C NMR of 5,5-dibenzyl-2-methyl-3-(2-(phenylethynyl)thiazol-4-yl)cyclopent-2-enone (93)



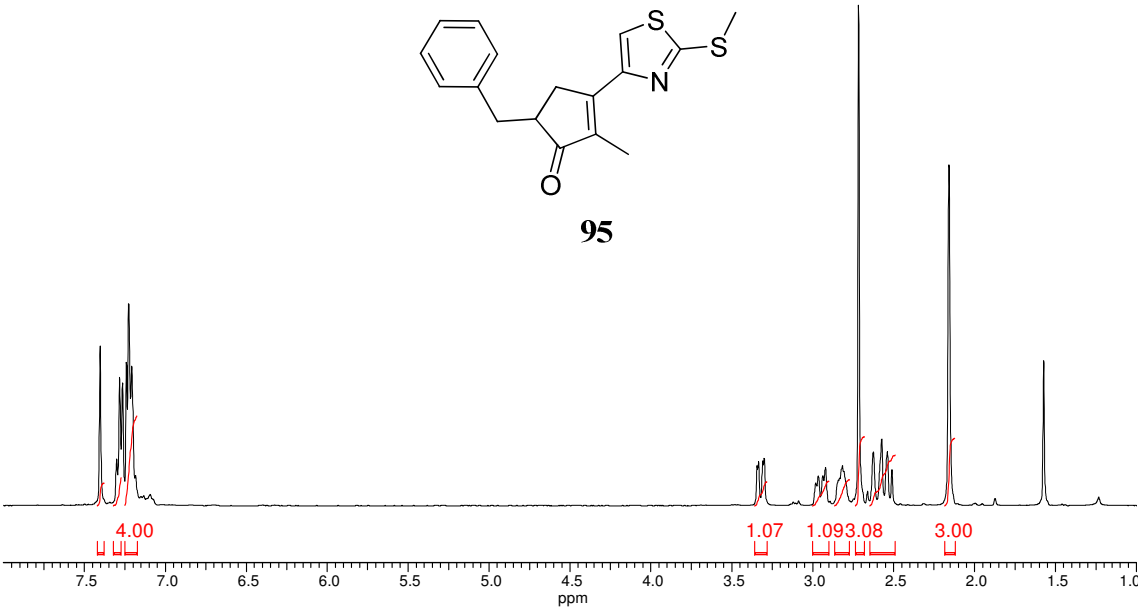
^{1}H NMR of 5,5-dibenzyl-2-methyl-3-(2-((trimethylsilyl)ethynyl)thiazol-4-yl)cyclopent-2-enone (94)



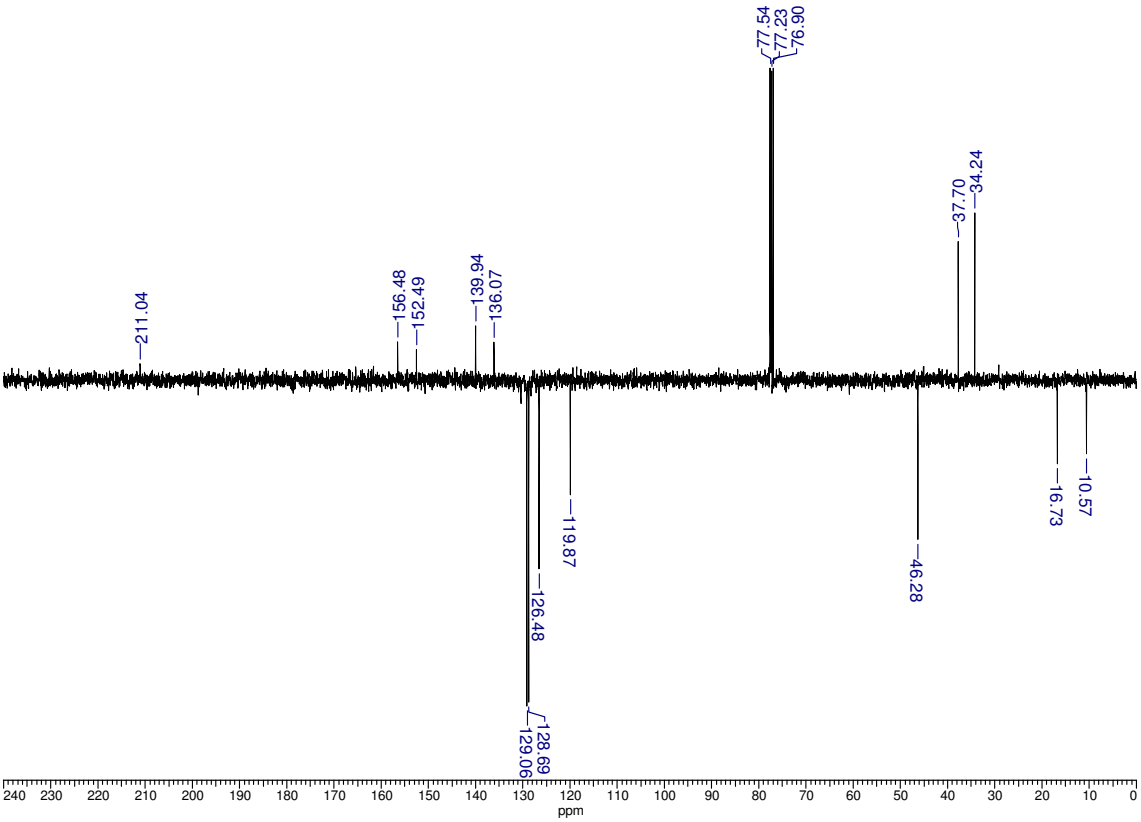
^{13}C NMR of 5,5-dibenzyl-2-methyl-3-(2-((trimethylsilyl)ethynyl)thiazol-4-yl)cyclopent-2-enone (94)



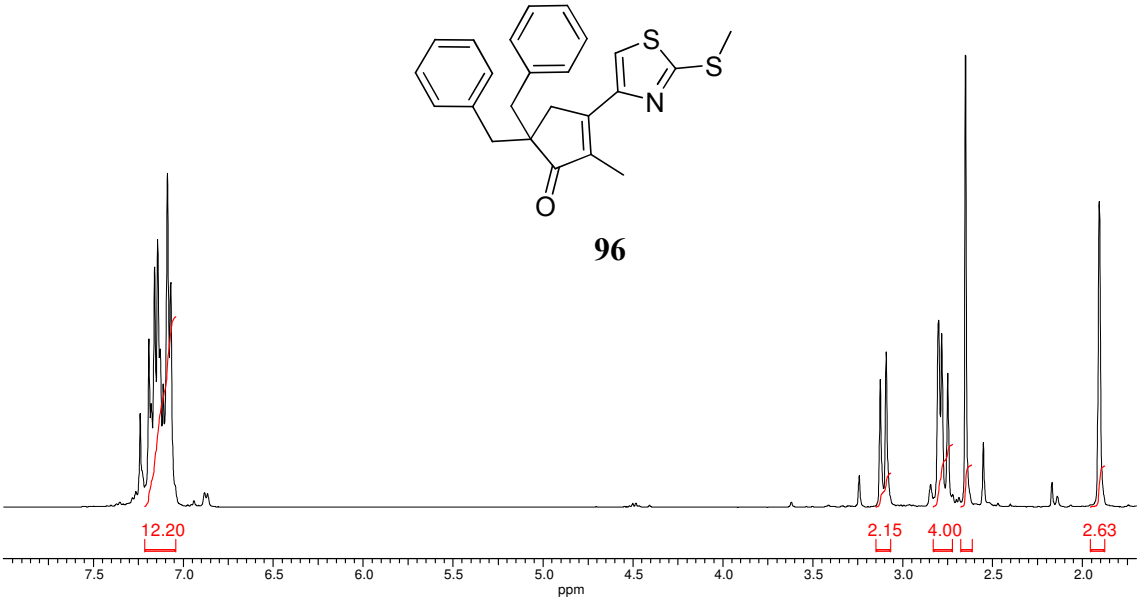
^{1}H NMR of 5-benzyl-2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enone (95)



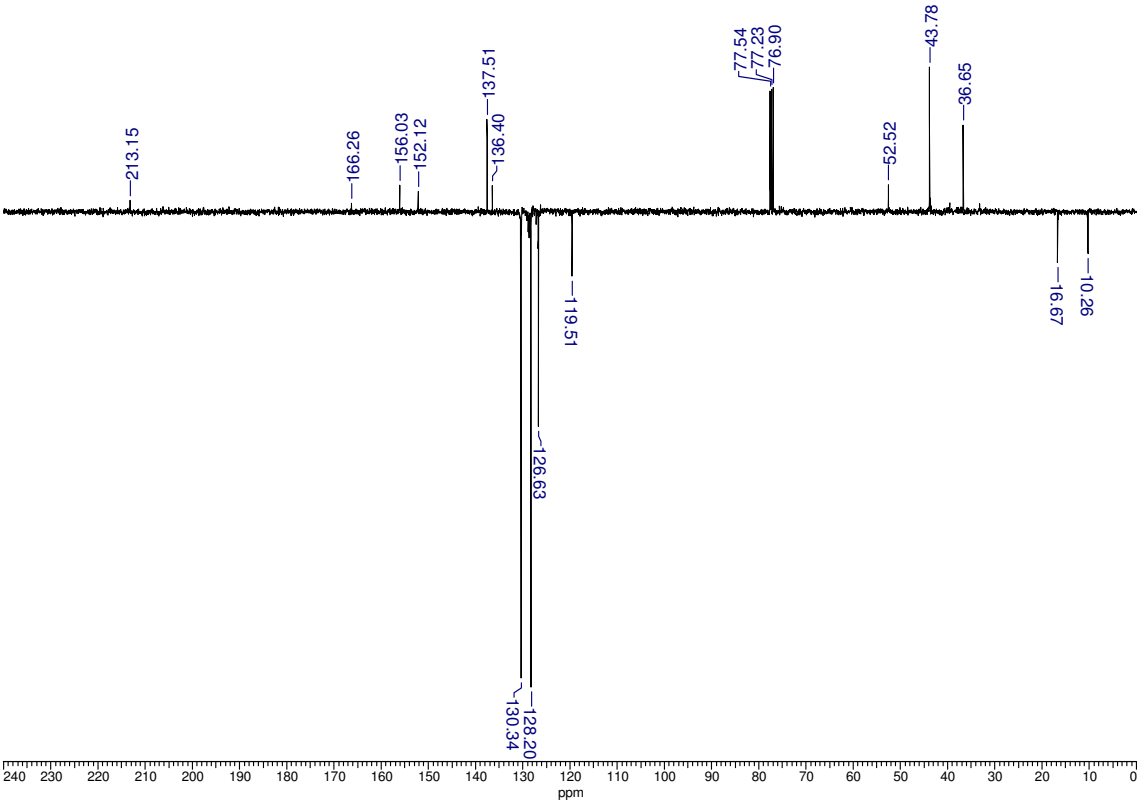
^{13}C NMR of 5-benzyl-2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enone (95)



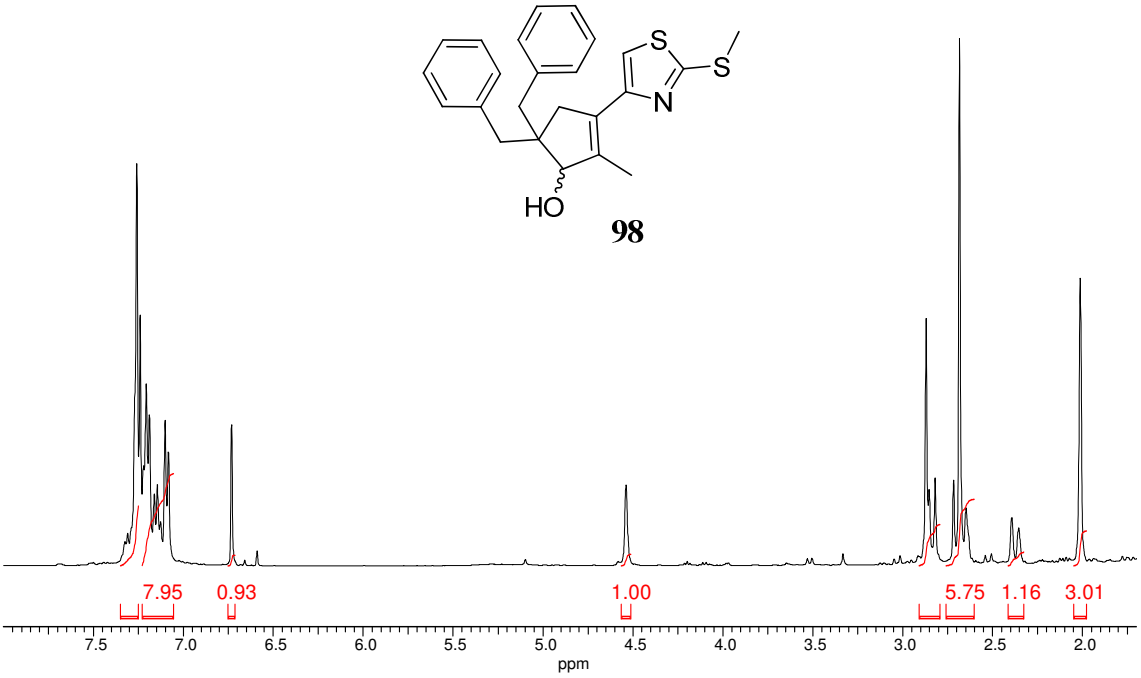
^{1}H NMR of 5,5-dibenzyl-2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enone (96)



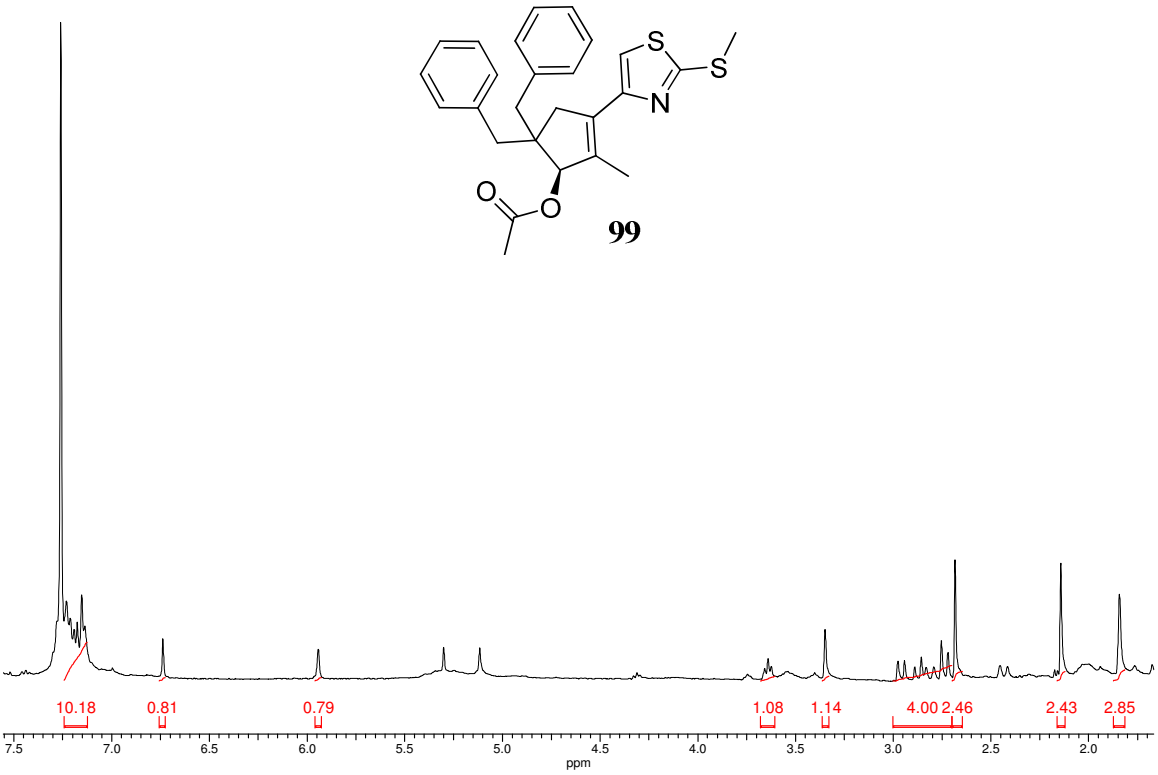
^{13}C NMR of 5,5-dibenzyl-2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enone (96)



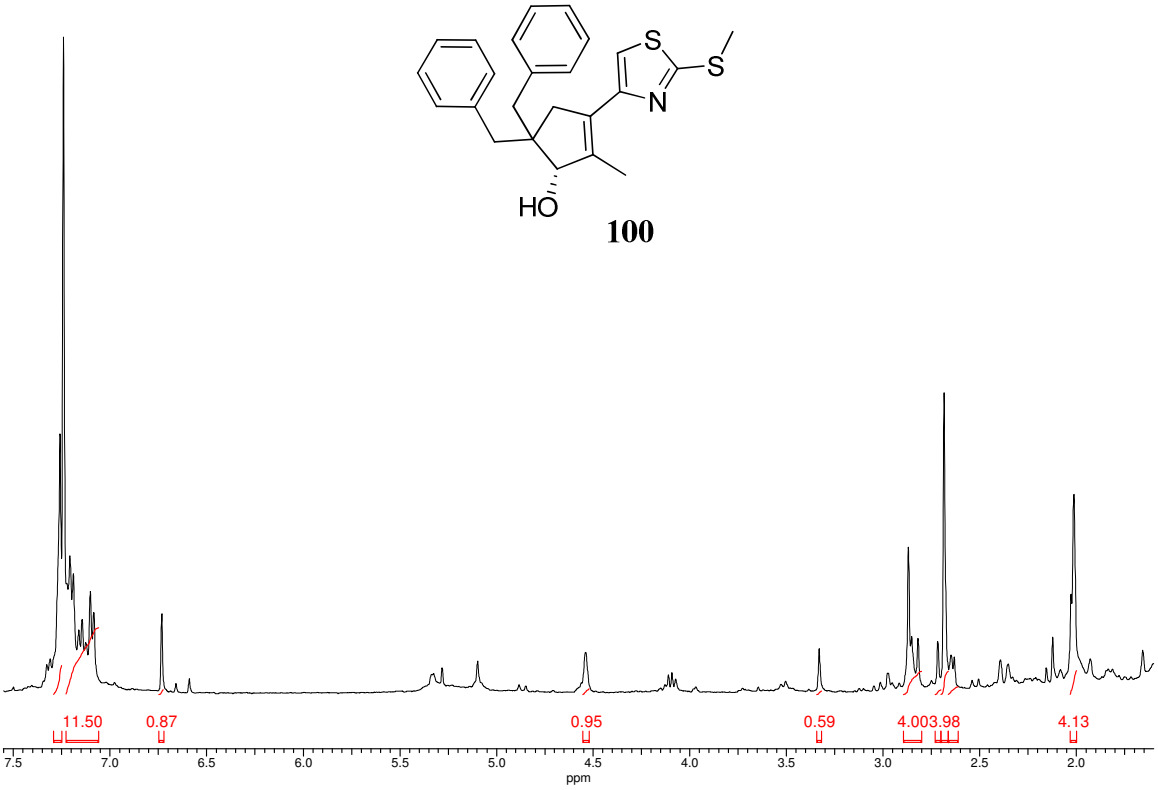
^{1}H NMR of 5,5-dibenzyl-2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enol (98)



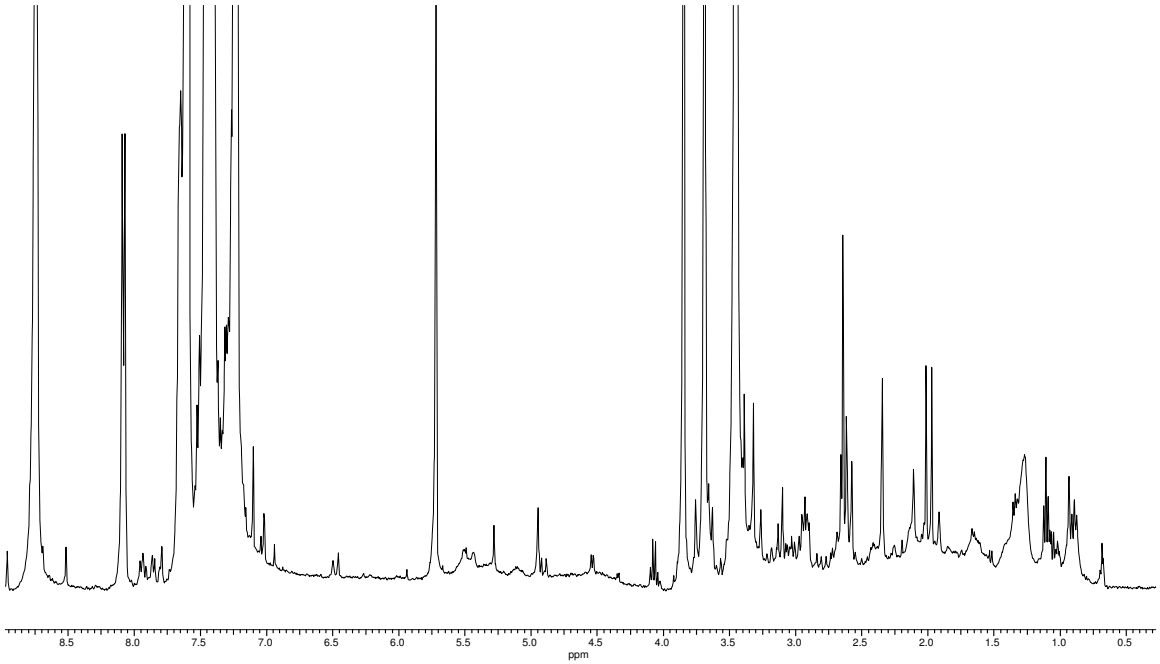
^{1}H NMR of (*S*)-5,5-dibenzyl-2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enyl acetate (99)



^{1}H NMR of (*R*)-5,5-dibenzyl-2-methyl-3-(2-(methylthio)thiazol-4-yl)cyclopent-2-enol (100)



^{1}H NMR of S-Mosher ester of (100)



^{1}H NMR of R-Mosher ester of (100)