SYNTHETIC, CHEMICAL, AND BIOLOGICAL STUDIES OF FR901464 AND STUDIES OF THE SILVER AND ZIRCONIUM PROMOTED ALKYNYL ADDITION REACTION

by

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The total synthesis of FR901464 was accomplished in at total of 29 steps, which is the shortest synthesis to date. Degradation studies were performed on the fully functionalized right fragment of FR901464 and this insight was used to rationally design a more stable analog, which led to the rational development of meayamycin, an FR901464 analog with enhanced biological properties. Additional analogs were synthesized examining the A-ring, C4' position, and the C3 position of the B-ring. These analogs demonstrated that the A-ring of FR901464 is optimal, the C4' acetate should remain intact for higher potency, and the spiroepoxide is required for antiproliferative properties. The low potency of the desepoxy analogs indicate that FR901464 covalently modifies is target(s) via its epoxide, which led to the synthesis of cold iodide-containing analog, which could be used for target identification experiments.

Due to the concern of non-specific reactions of epoxides with endogenous thiols, a method was developed to study the consumption of epoxides with thiols. Experiments of common epoxide motifs showed that these reactions were negligible under biologically relevant conditions. Moreover, a model system for the amide chain of FR901464 demonstrated that its Z-enamide will not react non-specifically with endogenous thiols.

There was a need for a general method for the alkynyl addition to epoxides to give propargylic alcohols as products. Towards this end, the Ag/Zr-promoted alkynyl addition methodology discovered in the Koide laboratories was successfully applied. These studies began

with the preparation of 11 silver acetylides and examining their safety as reagents for organic synthesis. Subsequently, these silver acetylides were shown to add to epoxides via 1,2-shifts to give propargylic alcohols in the presence of Cp_2ZrCl_2 and AgOTf. The scope and limitations of both the epoxide and alkyne were realized and was demonstrated in over 20 successful reactions. Moreover, the 11 new silver acetylides used in the epoxide alkynyl addition methodology should be readily applicable to the aldehyde alkynyl addition methodology. Finally, mechanistic studies were undertaken and were crucial in understanding the roles of all additives necessary for this alkynyl addition reaction to be successful, culminating in the generation of a proposed mechanism.

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ABBREVIATIONS

18-c-6	18-crown-6 ether
[α]	specific rotation
Ac	acetyl
acac	aceylacetonate
app	apparent
aq	aqueous
atm	atmosphere
br	broad
Bu	butyl
cat	catalytic
CBS	Corey-Bakshi-Shibata (oxazaborilidine)
Cp	cyclopentadienyl
CPBA	chloroperoxybenzoic acid
d	day(s); doublet (spectral)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DIPT	diisopropyl tartrate
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
dr	diastereomeric ratio
EI	electron ionization
equiv	equivalent
er	enantiomeric ratio

ESI	electrospray ionization
Et	ethyl
FBS	fetal bovine serum
GI_{50}	concentration required to inhibit growth by 50%
h	hour(s)
Hex	hexyl
HRMS	high resolution mass spectrometry
Hz	Hertz
i	iso
IC_{50}	mean inhibitory concentration
imid	imidazole
J	coupling constant
L	liter
LRMS	low resolution mass spectrometry
m	milli; multiplet (spectral)
m-	*meta*
M	molar
Me	methyl
Mes	2,4,6-trimethylphenyl (mesityl)
MHz	megahertz
mol	mole(s)
NBS	*N*-bromosuccinimide
MW	molecular weight
NF-κB	nuclear factor kappa B
NHK	Nozaki-Hiyama-Kishi
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
p-	*para*
PMB	*p*-methoxybenzyl

PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PMP	*p*-methoxyphenyl
PPTS	pyrinium *p*-toluenesulfonate
Pr	propyl
py	pyridine
q	quartet
Red-Al®	sodium bis(2-methoxyethoxy)aluminum dihydride
R_f	retention factor
s	second(s); singlet (spectral)
SiO_2	silica gel
S_N2	bimolecular nucleophillic substitution
temp	temperature
t	*tert*
TBAF	tetra-*n*butylammonium fluoride
TBDPS	*t*buytldiphenylsilyl
TBHP	*t*butylhydroperoxide
TBS	*t*butyldimethylsilyl
TES	triethylsilyl
TLC	thin-layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
THF	tetrahydrofuran
Ts	*p*-toluenesulfonyl

PREFACE

I would like to express my sincerest appreciation to Professor Kazunori Koide for the opportunity to study in his laboratory. His guidance and influence were paramount to my growth as a scientist and a person. His dedication towards excellence is something I think we should all aspire to. I also thank my committee members, Professors Billy Day, Paul Floreancig, and Peter Wipf for their thoughtful and critical insight towards my research, as well as Professor Scott Nelson for his mentorship of my proposal.

I would also like to thank our collaborators that have provided helpful discussions and exciting new results. These collaborators include Professor Billy Day, Dr. Andreas Vogt, Professor Chet Mathis, Dr. N. Scott Mason, Professor Paula Grabowski, Dr. Paul Robbins, and Dr. R. Balachandran. Next, I would like to thank the facilities managers, Drs. Fu-Tyan Lin and Damodaran Krishanan for NMR spectroscopy assistance, Drs. Kasi Somayajula and John Williams for mass spectrometry, and Dr. Steve Geib for X-ray crystallography.

My greatest thanks is owed to my family, immediate and extended, for supporting and believing in me throughout my education. My parents, James and Julia, provided the love, foundation, and map that I needed to succeed in school and more importantly, life. My sisters, Jill and Laura, have also been an inspiration of work ethic and competitive spirit that have helped me grow up to who I am now.

I would like to thank my friends from James B. Conant H.S., the University of Illinois, and the University of Pittsburgh. Finally, I would like to thank some influential people in my life. In particular, to Mrs. Vallejo, who got me excited about chemistry at an early age, and Coaches Raymond and Kernats who taught me about being a man and a competetitor.

I have learned a tremendous amount about life and chemistry during my stay at Pittsburgh, but mostly about life. I learned that e-mail can be a great form of communication, but how it can be over used. I learned who my real frinds were, and who were really important to me, during this process I met many wonderful people that I hold very dearly. Finally, I have had the pleasure of working with some very talented chemists, who also were fine individuals, in the Koide laboratories, although this was not the case for all. Overall, I can not complain about my graduate school experience, it provided me with more educational opportunities than science alone.

1.0 CHEMICAL AND BIOLOGICAL STUDIES OF FR901464

1.1 CANCER BACKGROUND AND CURRENT THERAPEUTIC REGIMENS

Cancer historically has been and remains the leading disease-related cause of death in the human population, responsible for 7 million deaths in 2005.[1,2] In 2005, the National Cancer Institute (NCI) made public their Cancer Trends Progress Report available online, which shows that the rate of cancer incidence has remained nearly constant from 1978 to 1998 at 500 incidences per 100,000 people (1/200 people) per year. Moreover, the death rate for individuals with cancer in 2002 was 200 out of 100,000 per year, which showed no improvement from 1978, but was a slight improvement over the 215 out of 100,000 per year death rate in 1991. In China, which accounts for approximately 1/5 of the world population, deaths due to cancer in 2000 were estimated to be 1.4 million people, and projected to increase to 1.8 and 2.4 million deaths in 2010 and 2020, respectively.[3] Moreover, the incidence of cancer in China was estimated to increase by 14.6% from 2000–2005.[4] These trends also extend to Europe where cancer incidence increased by 300,000, a 10% increase, from 2004–2006, and the mortality from cancer was rising.[5] These expected increases in cancer incidence and mortalities are alarming, and reflect cancer being a pandemic disease.

Tumors may develop when controlled cellular processes such as signal transduction and gene expression become irregular.[1] There are more than 200 molecular mechanisms postulated

for tumorigenesis, each with many variants.[6] Few chemotherapeutic regimens have yielded remission of cancer for extended periods of time, partly because of the numerous cancer types. Currently available drugs are limited to targeting DNA, nuclear hormone receptors, a tyrosine kinase, the proteasome, and microtubules. More recently, inhibitors of histone deacetylase (HDAC) have also demonstrated promising results in clinical trials.[7]

Modern-day chemotherapy has its origins in World War I, when mustard gas was used in battlefields. Military doctors noticed that deceased soldiers that were exposed to mustard gas died due to bone marrow aplasia. This observation led to the discovery that nitrogen mustard operates by inducing DNA damage, and in 1942 a hospital in the United States used these compounds to treat patients with lymphoma, albeit with little success.

Platinum-based DNA damaging agents, cisplatin and carboplatin (Figure 1), remain the backbone of cancer chemotherapy.[8] Their modes of action involve the cross-linking of DNA strands inhibiting DNA replication to cause tumor cell death. These heavy-metal agents have dose-dependent toxicities and require careful dosing in patients. Additional DNA-damaging agents are mitomycin C, tirapazamine, and bleomycin (Figure 1).[9,10] Mitomycin C causes DNA alkylation and subsequent crosslinking by two discrete mechanisms; the first mechanism involves aziridine opening in an acidic environment to form a carbocation, and in the second mitomycin C acts as a prodrug in a reducing enviroments, where its quinone is reduced and subsequently opens its aziridine ring via a quinone methide.[11] Tirapazamine is reduced to a radical under hypoxic conditions, and subsequently abstracts a hydrogen atom from DNA causing strand breaks, wheras bleomycin may be activated by O_2 and Fe^{II} complexes to produce a bleomycin radical and $O_2^{\bullet -}$, which cause DNA and RNA damage. An alternative to these DNA damaging agents is the supplementation of nucleoside analogs such as 5-fluorouracil and

gemcitabine (Gemzar®), which act by being incorporated into DNA during DNA synthesis and subsequently terminating chain elongation.[10]

Toposisomerases have critical function in DNA replication and chromosome condensation and segregation, and thus the inhibition of topoisomerases I and II is commonly used strategy in treating many cancers. Topoisomerase I is responsible for creating single strand DNA breaks, and topoisomerase II is responsible for creating double strand DNA breaks. Camptothecin™ (Figure 1) is an inhibitor of topoisomerase I and generates a cytotoxic poison by stabilizing this enzyme in its catalytic form.[18,19] Etoposide (Figure 1), a semisynthetic derivative of podophyllotoxin, is a clinically prescribed inhibitor of topoisomerase II that does not intercalate DNA or have the cardiotoxicity seen with anthracyclines such as adriamycin (Figure 1).[12]

Estradiol (structure not shown), the most potent endogenous estrogen, has been implicated in both the initiation and promoters of carcinogenesis.[13] Many human breast cancer cell lines require estrogen for proliferation in vitro and in vivo; thus, targeting the estrogen receptor (ER) has been a common method to treat breast cancer. This proliferation can be blocked by administration of ligands that compete with estrogen for the ER binding site. tamoxifen (Figure 1) is a partial antagonist of the ER in humans and is an effective drug for treating breast cancer, but a tamoxifen regimen loses efficacy over time, and >80% of tumors will develop resistance.[1,13]

Chronic myelogenous leukemia (CML) is a clonal hematopoietic stem cell disorder, accounting for 15–20% of all cases of leukemia. Juxtaposition of the breakpoint cluster region on chromosome 22 and the c-abl oncogene on chromosome 9 is present in 95% of patients with CML; the resulting protein functions as a constitutively activated tyrosine kinase. Gleevec™

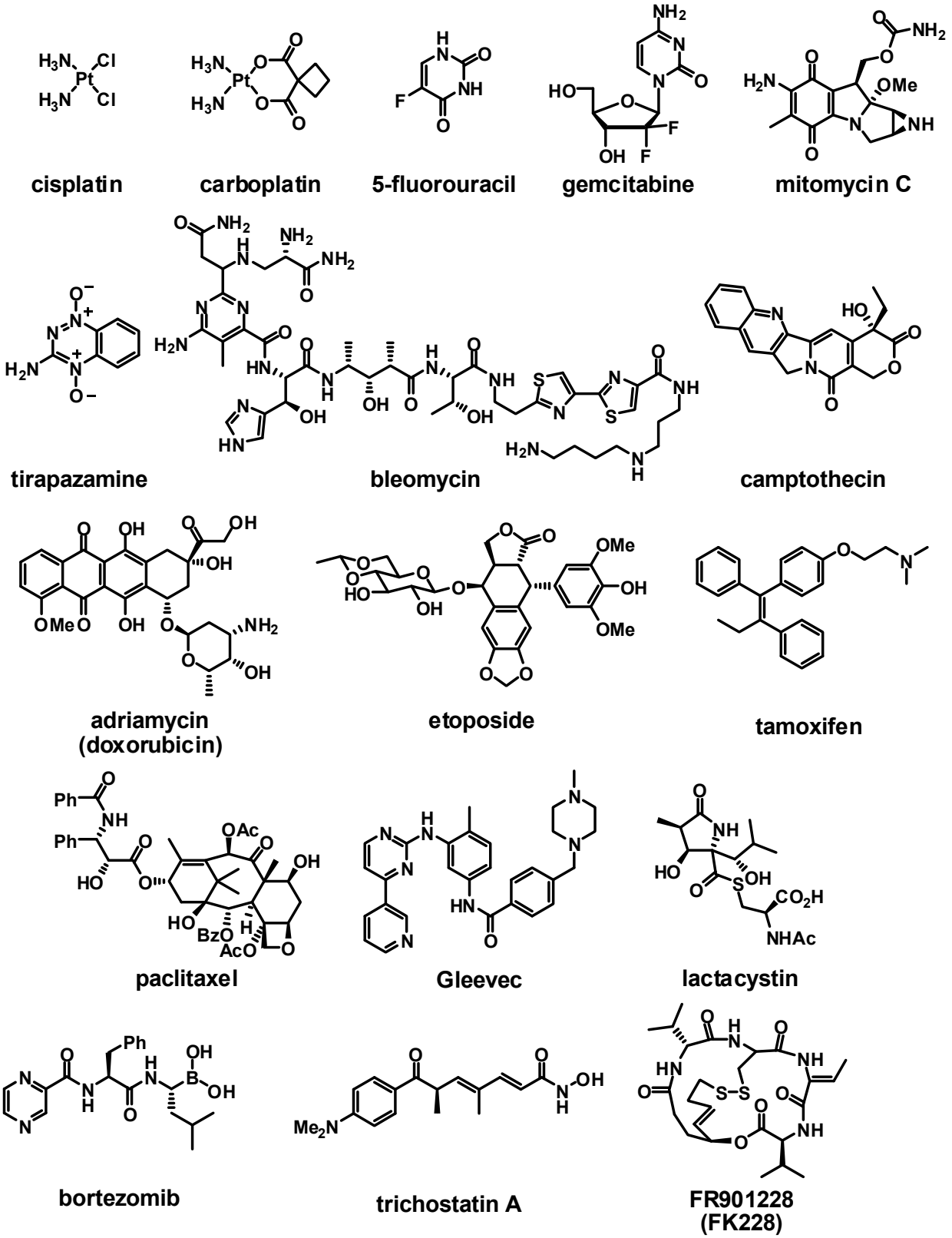


Figure 1. Structures of anticancer drugs/agents

(Figure 1) specifically inhibits the proliferation of cell lines containing the protein from this juxtaposition, demonstrating the potential of very specific targeting of molecular pathogenic events in cancer.[14]

Lactacystin (Figure 1) is a natural product that was shown to induce neuritogenesis,[15,16] and later to inhibit cancer cell proliferation by proteasome inhibition.[17] Due to the importance of the latter pathway, bortezomib (Velcade®) was subsequently developed as a reversible inhibitor (K_i 0.6 nM) of the 20S catalytic core of the 26S proteosome.[18,19] As a result, apoptosis occurs, which is presumably a direct result of the stabilization of pro- and antiapoptotic proteins and the inhibition of NF-κB.[18,19]

Compounds such as the vinca alkaloids and paclitaxel (Figure 1) have utility in the treatment of cancer by their perturbing activities against microtubules.[20,21] During eukaryotic cell division, microtubules form the mitotic spindle, the key machinery for mediating segregation of chromosomes to the two new daughter cells. Perturbing the mitotic spindle may cause arrest of the cell cycle in the mitotic phase, eventually leading to apoptosis.

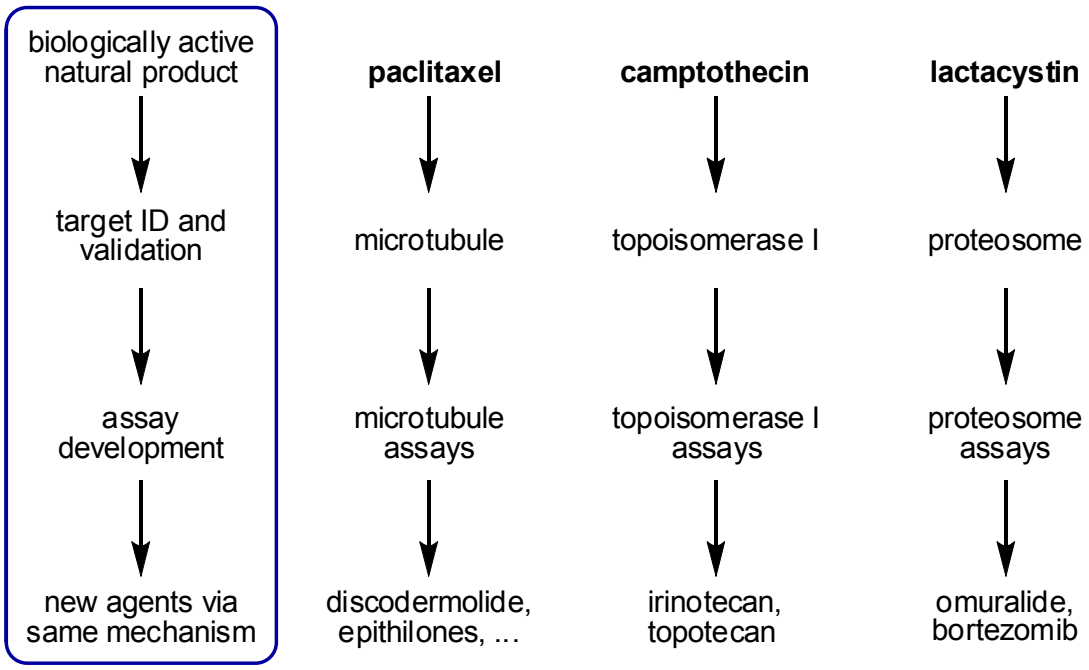
Histone deacetylases (HDAC) remove the acetyl groups from lysine residues of proteins, and their substrates are involved in transcription, cell proliferation, and cell death.[22,23] HDAC inhibitors selectively activate gene transcription by remodeling of the DNA-histone complex. Inhibition of these enzymes causes hyper-acetylation of the histone lysine residues, thereby neutralizing the positive charges that attract the negatively charged DNA and making the DNA more accessible. Other targets of HDACs are E2F, p53, and the cyclin dependent kinase (cdk) inhibitors $p21^{WAF1/Cip1}$ and $p27^{Kip1}$; this could account for the antiproliferative activity associated with HDAC inhibitors. Trichostatin A (Figure 1), the first reversible inhibitor of HDAC

identified, functions by inducing apoptosis and inhibiting angiogenesis in a plethora of carcinoma cell lines in vitro. FR901228 (aka FK228, shown in Figure 1), a natural product, also functions by inhibition of HDAC and has progressed to phase II clinical trials.[24-28]

Few of these chemotherapeutic regimens have yielded remission of cancer for extended periods of time, and their lack of differentiation between cancer and normal cells leads to high toxicity.[1,29] Moreover, there is concern amongst oncologists that a plateau has been reached with existing cancer therapies.[10]

Discoveries of anticancer agents with novel modes of action continue to be of paramount importance for cancer chemotherapy.[1,29-32] Wall and Wani developed a new paradigm to guide the isolation of natural products, such as camptothecin and paclitaxel, by using the bioactivity of crude extracts.[33-35] This bioactivity-directed fractionation method is now commonly used for discovering compounds with novel modes of action. This approach can be extended to target identification and validation, development of new screening methods, and the development of new agents based on their novel mode of action (Scheme 1). The use of natural products for this method specifically directed towards cancer therapy was brought to great fruition from the research on Taxus brevifolia research, which allowed for the validation of the microtubule as a druggable target.[35-37] This discovery led to the development of microtubule screening methods, and the discoveries of discodermolide and the epothilones as perturbers of microtubules.[38,39] Moreover, research into the unique mode of action of camptothecin led to the discovery of topoisomerase I as a drug target, the development of drugs such as irinotecan and topotecan, and the isolation of the natural products lamellarin D, kalihinol F and wakayin.[12] More recently, the elucidation of the novel biological mechanism induced by lactacystin has demonstrated the

proteosome as a target for cancer therapy.[17] Since this discovery, omuralide and bortezomib have been discovered using this novel target.[16-18]



Scheme 1. Paradigm for development of novel biological modes of action

1.2 ISOLATION AND CHARACTERIZATION OF FR901464 AND BIOLOGICALLY RELATED COMPOUNDS

1.2.1 Discovery of FR901464

As part of a drug discovery program, the Nakajima group at Fujisawa Pharmaceutical Co., Ltd. (now Astellas Pharma, Inc.) employed a reporter assay in human breast adenocarcinoma cells using the stably transfected simian virus 40 (SV40) promoter and chloroamphenicol acetyltransferase (CAT) reporter gene (pSV2-CAT) in their search for natural products with

novel modes of action. They isolated the structurally unique compounds FR901463, FR901464, and FR901465 from the culture broth of a bacterium *Pseudomonas* sp. No. 2663 based on their ability to activate transcription in cancer cells (structures shown in Figure 2).[40] These compounds were also reported as WB2663A, B, and C, respectively, in a European patent by the same group.[41] The culture broth (400 L) of this bacterium yielded FR901463 (512 mg), FR901464 (819 mg), and FR901465 (70 mg), after purification by silica gel and reverse phase chromatographies. Of these compounds, FR901464 was shown to be the most potent in vitro and in vivo. The IC_{50} of FR901464 was shown to be 1.0–3.4 nM in MCF-7 (human breast), A549 (human lung), HCT116 (human colon), SW480 (human leukemia), and P388 (murine leukemia) tumor cell lines.[40] FR901464 displayed a dose-dependent, prominent effect at 0.1–0.56 mg/kg against A549, colon 38, and Meth A fibrosarcoma xenografts implanted in mice, thereby showing its clinical potential.[42] The structures of FR901463, FR901464, and FR901465 were shown to be quite similar, differing only in their B-rings. Specifically, these compounds differed at C2 and C18. The relative stereochemistry of FR901464 was assigned by the Fujisawa group, and the absolute stereochemistry was subsequently shown by the Jacobsen group after their total synthesis.[41,43]

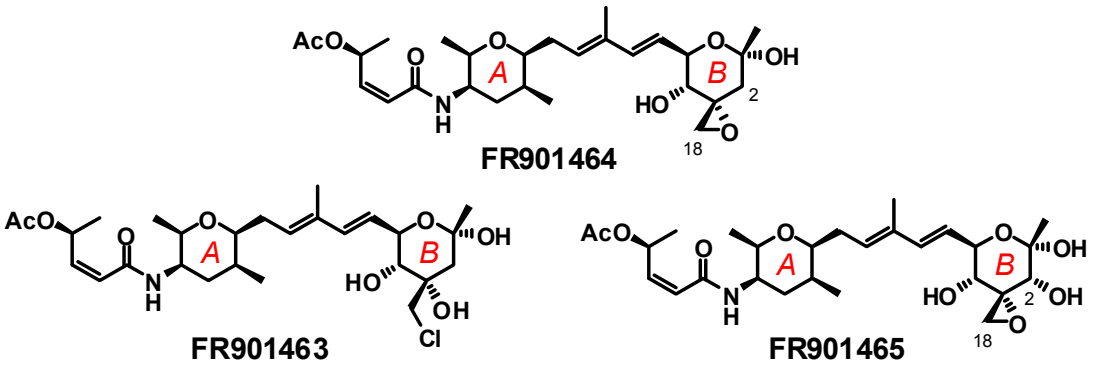


Figure 2. Structures of FR901463, FR901464, and FR901465

The biological activity of FR901464 was shown to be distinct from agents with other known modes of action. Transcriptional activation of tumor cells was observed in FR901464-treated (20 nM) MCF-7 cells transfected with a plasmid containing the SV40 promoter via increased activity of the downstream CAT reporter gene.[40] CAT induction became significant at 6 h after treatment with FR901464 and increased linearly to 24 h when the observations were halted. In the absence of FR901464, no activity was observed although no positive control was used for these experiments. The RNA transcript levels of inducible genes were measured by extraction from the cells, RT-PCR amplification (25 cycles), and subsequent resolution by electrophoresis with comparison to the endogenous levels. Human c-myc (oncogene), E2F-1 (transcription factor), p53 (tumor suppressor gene), and $p21^{WAF1/Cip1}$ (cyclin dependent kinase inhibitor) were compared to non-inducible genes, G3PDH (glyceraldehyde-3-phosphate dehydrogenase) and β-actin. The authors claimed that the amounts of c-myc, E2F-1, p53, and $p21^{WAF1/Cip1}$ were all lowered, while the amount of G3PDH and β-actin remained the same.[42] However, after inspection of the published gels, c-myc is much lower in FR901464-treated cells, p53 appears to be slightly lower, and E2F-1 and $p21^{WAF1/Cip1}$ transcript levels may be lower, but the small quantities do not give definitive data. Examination of the cell cycle distribution of FR901464-treated MCF-7 cells indicated G_1 and G_2/M phase arrest. Internucleosomal degradation of genomic DNA was observed with the same kinetics as the transcriptional activation. Comparison of FR901464 to other anticancer agents with known modes of action revealed the unique mode of action of this natural product, since FR901464 produced phenotypes distinctly different from paclitaxel, adriamycin, camptothecin, trichostatin A, and, later, FR901228.[24,42]

1.2.2 Isolation of herboxidiene (GEX1), TMC-205, and the pladienolides

Microorganisms may produce potent phytotoxic natural products that could be used as herbicides towards weeds or other unwanted vegetation. In 1992, Monsanto Agricultural Co. was screening for potent herbicides from natural sources and reported the isolation of herboxidiene (Figure 3) from *Streptomyces* sp. A7847.[44,45] The absolute stereochemistry of this natural product was later determined by Edmunds and Oppolzer.[46] Later, herboxidiene was isolated by Yoshida and coworkers at Kyowa Hakko Kogyo Co. while screening natural products based on their ability to affect transcription using an SV40 promoter.[47,48] Yoshida found this compound, renamed GEX1A, to act as an antiproliferative agent against human tumor cell lines in vitro with IC_{50} values of 3.7–7.6 nM and its efficacy in xenograft models, causing G_1 and G_2/M phase arrest in the cell cycle.[48] Moreover, GEX1A did not enhance the expression of endogenous genes involved in the cell cycle, proliferation, or apoptosis, but shorter sized transcripts of cdc25A and cdc2 genes were observed as well as their normal sized ones.[47] GEX1A is toxic in vivo as low as 0.13 mg/kg, causing a decrease in white blood cells, platelets, and body weight.[48] Yoshida concluded that GEX1A appears to function by a novel biological mode of action.

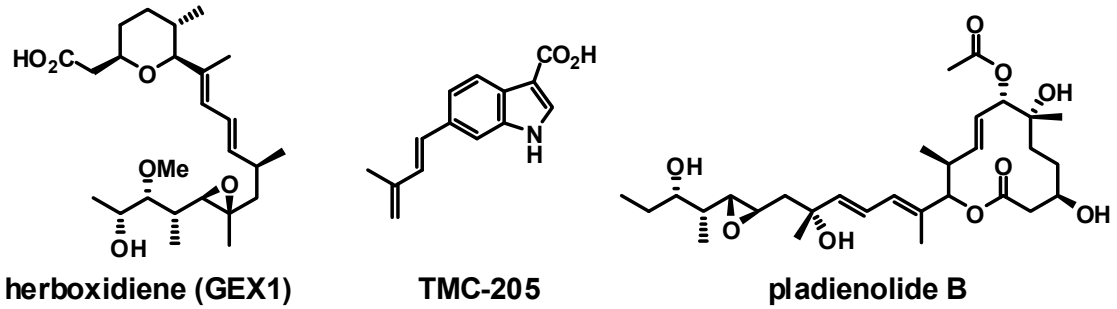


Figure 3. Structures of herboxidiene, TMC-205, and pladienolide B

In 2001, the Sakuarai group at Tanabe Seiyaku Co., Ltd. reported on the transcriptional activation in HeLa cells using an SV40 promoter with TMC-205 (Figure 3).[49] The culture broth of a fungus (7 L) yielded only 3.3 mg of this compound.[49] The transcriptional activation was shown to be concentration-dependent and increased linearly from 6–24 h.[49] Removal of the SV40 enhancer element disabled the transcriptional perturbing activity of TMC-205, suggesting that its mechanism of action involves the binding of transcriptional factors to the SV40 enhancer element. This light-sensitive agent also was cytotoxic against various human and murine tumor cell lines in vitro, with effective concentrations against 13 cell lines ranging from 64–203 μM.[49]

Many types of tumors are severely hypoxic and have a series of signaling pathways to adapt to this environment. Accordingly, these signaling pathways could be a potent target for antitumor agents. The Sakai group at Eisai Co., Ltd. used a reporter gene under the control of the VEGF promoter to screen for natural products that increase transcription in cancer cells. From this screen, they isolated seven structurally-related compounds named the pladienolides from the culture broth of the bacterium *Streptomyces platensis* Mer-11107.[50,51] The most potent of these was pladienolide B, which had IC_{50} values of 0.4–8.9 nM in 45 cancer cell lines including six drug-resistant cell lines (Figure 3).[52] This compound was also effective in a xenograft model at 2.5 mg/kg/day. In 2007, a research group at Eisai Co., Ltd. demonstrated that the target of pladienolide B is the SF3b splicing factor using ^{3}H-labeled, fluorescent reporter-tagged, and photoaffinity/biotin tagged pladienolide probes. This target was subsequently validated by small interfering RNA (siRNA), and unequivocally implicated the splicing machinery as the target of pladienolide; however, FR901464 was the first compound discovered that alters this novel antitumor drug target.[53]

FR901464, herboxidiene (GEX1A), TMC-205, and the pladienolides were all isolated using screening methods that monitor transcriptional activity in cancer cells. Although no rationale is given for this screening method, it was subsequently validated with the development of E7107, an analog of pladienolide B currently in phase I clinical trials.[54,55]

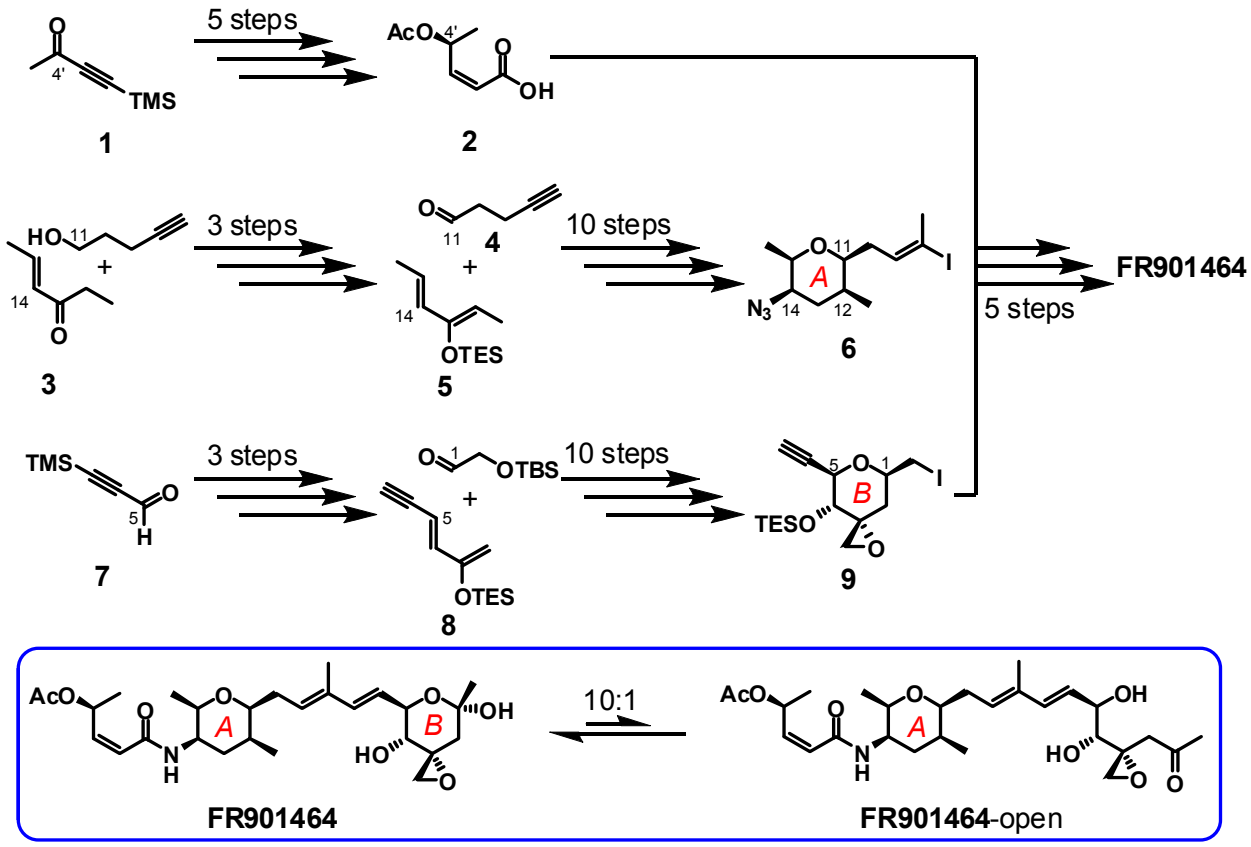
1.3 PREVIOUS TOTAL SYNTHESES OF FR901464

The impressive biological activity and novel structure of FR901464 caught the attention of many synthetic organic chemists. Since its reported activity, this compound has been synthesized by the Jacobsen, Kitahara, and finally the Koide group.[43,56-58] The Funk group also undertook studies on FR901464 but have yet to report a successful synthetic route.

1.3.1 Synthesis by the Jacobsen group

The first total synthesis of FR901464 was accomplished by the Jacobsen group in 2000 as depicted in Scheme 2.[43,56] Acid fragment **2** was efficiently prepared in five steps from ynone **1** utilizing Noyori's asymmetric reduction to install the C4' stereocenter.[59] Their A-ring preparation commenced with 4-penyn-1-ol and its conversion to aldehyde **4** according to the literature.[60] Although not described, TES-enol ether **5** was presumably prepared from commercially available ketone **3** in one step. The key step for the A-ring preparation involved the enantioselective hetero-Diels-Alder reaction of these two fragments using a chromium catalyst developed in the Jacobsen group.[61] This powerful reaction correctly installed the C11, C12, and C15 stereocenters. To arrive at vinyl iodide **6**, nine additional steps were required,

including a Rubottom oxidation, alkynye inward isomerization, and hydrozirconation. The preparation of the B-ring fragment began with the three step conversion of aldehyde **7** to TES-enol ether **8**. The subsequent step involved another hetero-Diels-Alder reaction with (*t*butyldimethylsiloxy)acetaldehyde using their chromium catalyst that correctly installed the C1 and C5 stereocenters. To arrive at alkyne **9**, nine additional steps were required, including a Rubottom oxidation and directed epoxidation. The endgame of the Jacobsen synthesis involved the Negishi coupling of vinyl iodide **6** and alkyne **9**, and four additional steps to complete the total synthesis. It should be mentioned that installation of the spiroepoxide with $VO(acac)_2$ after the union of advanced intermediates was not regioselective and therefore the epoxide was installed prior to the Negishi coupling. This synthesis was accomplished in 37 total steps, with 19 steps in the longest linear sequence.[56,62] Considering the complexity and instability of the target compound, this is an efficient and concise synthesis of FR901464. Moreover, this work unambiguously established the stereochemistry of the natural product from extensive analog synthesis as well as established the equilibrium of FR901464 and its B-ring opened form, FR901464-open.[56]

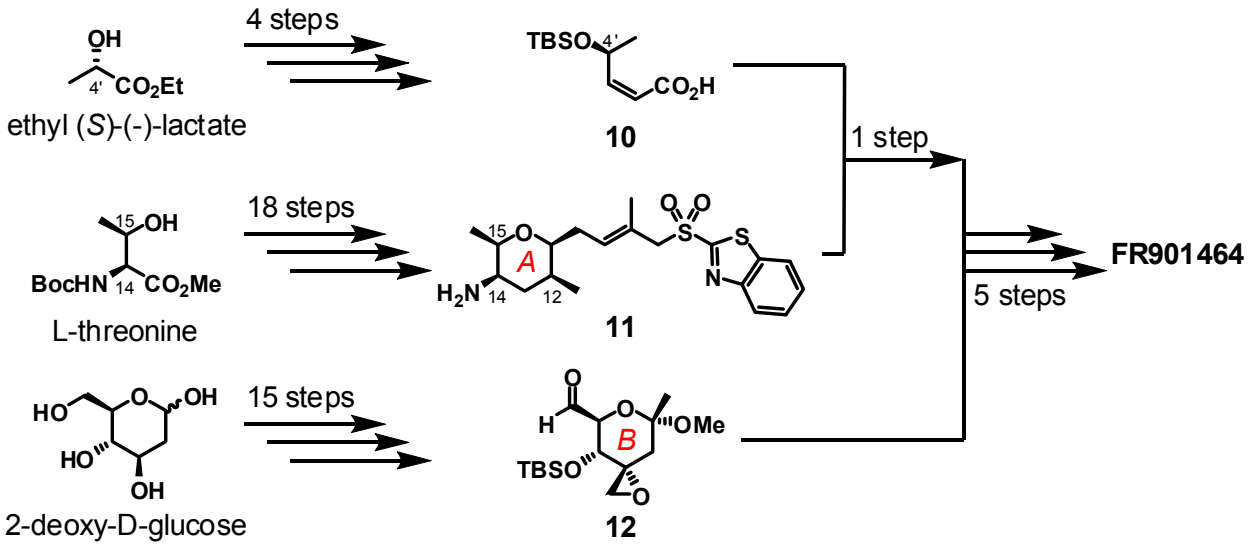


Scheme 2. Jacobsen's total synthesis of FR901464

1.3.2 Synthesis by the Kitahara group

The Kitahara group unveiled their first generation total synthesis of FR901464 in 2001 using the chiral pool as the source of their starting materials.[57] Due to several problems in the late stages of their synthesis, they devised a second generation total synthesis in 2006 which will be discussed.[58] Acid **10** was prepared by the four step conversion of ethyl (*S*)-(−)-lactate that already contained the C4' stereocenter (Scheme 3). Preparation of the A-ring fragment began from L-threonine, which contains the C14 and C15 stereocenters of FR901464. Sulfone **11** was prepared from L-threonine in 18 linear steps including a substrate controlled stereoselective

hydrogenation, which established the C11 and C12 stereocenters in high selectivity, and three Wittig reactions. The preparation of the A-ring began from commercially available 2-deoxy-D-glucose. The synthesis of aldehyde **12** was accomplished in 15 linear steps involving standard carbohydrate chemistry. Completion of the Kitahara synthesis involved the coupling of acid **10** and amine of sulfone **11**, a remarkable modified Julia coupling of a sulfone to aldehyde **12**, and four additional steps were required to accomplish the total synthesis of FR901464. The Kitahara group also found epoxide installation to be low yielding (22%) after union of advanced interemediates.[57] This total synthesis was accomplished in 41 total steps, with 22 steps in the longest linear sequence.[58,62]



Scheme 3. Kitahara's total synthesis of FR901464

1.4 STUDIES ON STRUCTURE ACTIVITY RELATIONSHIP AND ON THE MODE OF ACTION OF FR901464

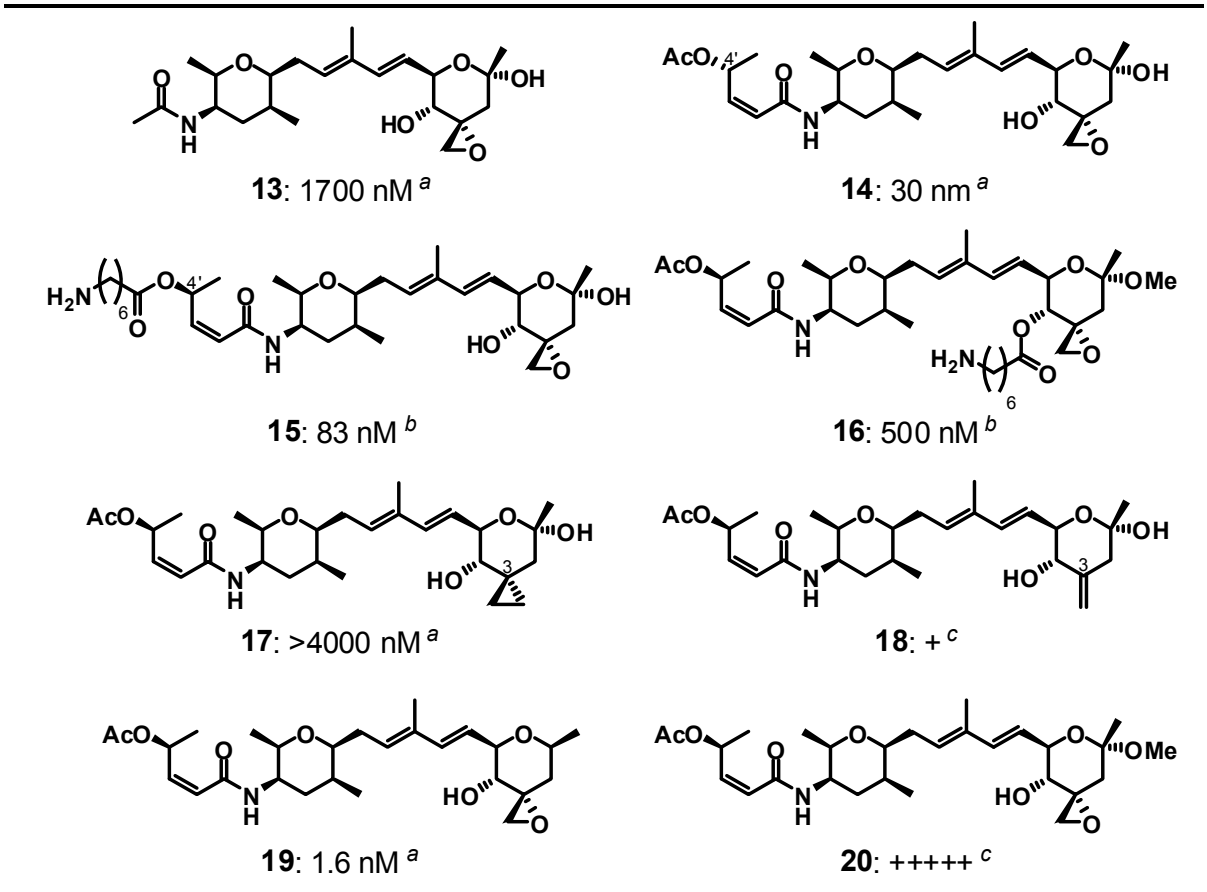
1.4.1 Synthesis of analogs of FR901464

The unprecedented biological profile of FR901464 has resulted in the preparation of various analogs. The Jacobsen group was the first group to undertake analog studies upon completion of their total synthesis.[56] The amide sidechain of FR901464 was the first fragment examined. Acetamide **13** gave an IC_{50} of 1700 nM as compared to 2.0 nM for FR901464 in Tag Jurkat cells, thereby showing the importance of the α,β-unsaturated amide moiety in the side chain.[56] The C4' stereocenter was shown to exert a small effect on the antiproliferative activity with **14**, having a 15-fold lower activity than the natural product.[56] Takahashi demonstrated the C4' ester is amenable to modification since **15** only gave a 40-fold decrease as compared to FR901464 in activity in EL4 murine lymphoma cells.[63] Next, the B-ring fragment was probed. Takahashi established that ester **16** had an IC_{50} of 500 nM, a 250-fold decrease in activity as compared to the natural product, demonstrating the sensitivity of the C4-OH moiety.[63] The importance of the oxygen atom of the spiroepoxide was demonstrated by the Jacobsen and Kitahara groups. Cyclopropane **17** was inactive at 4000 nM, and alkene **18** was less effective than FR901464 at stimulating the cytomegalovirus (CMV) promoter-driven transcription by a factor, as the authors termed it, of "+++."[56,64] It was not explained why CMV was employed to drive the transcriptional activity induced by FR901464 or the magnitude of their ± scale. Finally, the C1 position was modified by the Jacobsen and Kitahara groups to give enhanced biological results. Tetrahydropyran **19** had an IC_{50} of 1.6 nM and methyl glycoside **20** (later named spliceostatin A) promoted transcription slightly better than FR901464 by a factor of "+."[56,64,65] Therefore, further

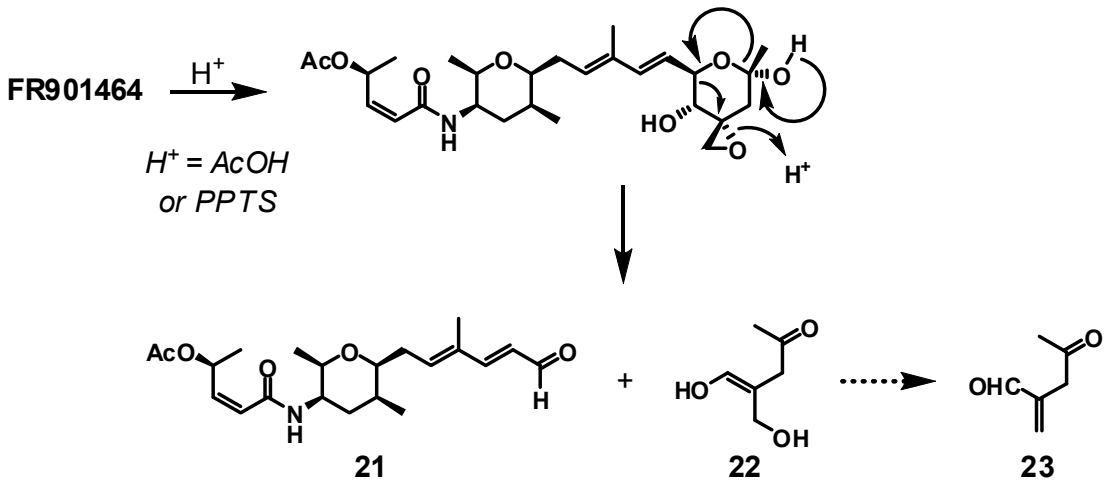
analog studies could be directed at the amide chain, the unstudied A-ring, and the B-ring at positions C1 but not C4-OH.

While derivatizing FR901464 position C1 under acidic conditions, in unknown solvents, the Kitahara group noticed significant decomposition. The decomposition products claimed by Kitahara were aldehyde **21** and presumably **22**, although it may give **23**, but no experimental data to support either product were reported (Scheme 4).[64]

Table 1. FR901464 analogs and their biological activities



[a] IC_{50} determined in Tag Jurkat cells; [b] IC_{50} determined in EL4 cells;
[c] Determined by CMV promoter activation



Scheme 4. Kitahara's proposed decomposition of FR901464 under acidic conditions

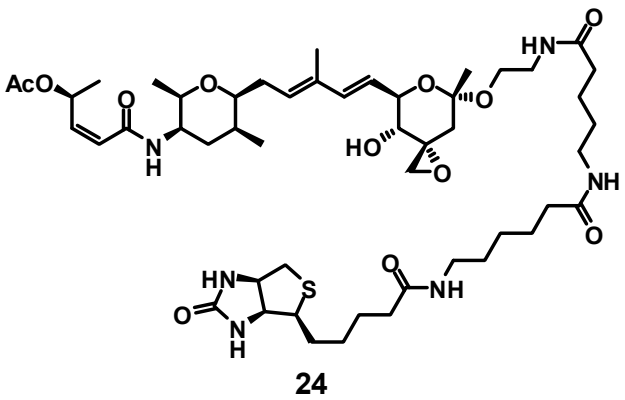
1.4.2 Studies on the novel mode of action of FR901464

Eukaryotic tumor cells evolve adaptive responses to environmental stresses for survival, many of these responses are redox dependent.[66] The human form of the enzyme thioredoxin (Trx) is involved in the reversible redox reactions in many thiol-dependent cellular functions, including gene expression, signal transduction, and proliferation.[67] Trx typically has a CGPC active site sequence, but there is some variability within the thioredoxin suprafamily.[67] Transmembrane thioredoxin-related protein (TMX) is a member of the thioredoxin family that has a unique CPAC sequence in its active site. TMX is primarily localized in the endoplasmic reticulum (ER), and also inhibits the ER stress-induced apoptosis by caused by brefeldin A.[68,69] In December of 2005, a patent was disclosed implicating TMX as a target of FR901464, which was validated by siRNA experiments.[70] Moreover, this patent describes a method for screening anticancer agents using this protein. TMX remains an exciting target for chemotherapy, but has not garnered attention in oncology since its discovery in 2001. However, thioredoxin has been targeted for

chemotherapy, and PX-12 (1-methylhydroxypropyl 2-imidazoloyl disulfide), an inhibitor of Trx, is currently in clinical development.[71,72]

It has been approximated that 15% of all human genetic diseases are due to deviations in pre-mRNA splicing.[73] Yet, how and why these deviations occur is unknown, and studying the mechanisms of the spliceosome had been limited to using small polypeptide inhibitors for known splicing proteins.[74] In 2007, **20** (spliceostatin A) was also shown to target the SF3b RNA splicing factor.[65] To gain insight into the mechanism in which FR901464 arrests the cell cycle, the expression of cdks were monitored for their implication in cell cycle progression. There was no change in the level of cdk expression, whereas the cdk inhibitors, p16 and p27, were upregulated. Moreover, a truncated form of p27 was produced in FR901464-treated cells. This truncated protein was named p27*, and was shown not to be a product of the proteosome. The production of p27* was also observed by treatment of cells with spliceostatin A in concentrations as low as 5.8 nM. Biotinylated probe **24** (Figure 4) was chemically synthesized and shown to cause the production of p27* at 500 nM. HeLa cell extracts were mixed with **24** and purified on a streptavidin column. The binding proteins were removed from the column by washing with buffer and purified by electrophoresis to identify SAP155, SAP145, and SAP130 as targets of **24**. A competition experiment showed spliceostatin was able to inhibit these proteins from binding to **24**. The ease of removal of these proteins from the streptavidin column demonstrated non-covalent binding between these proteins and **24**. Treatment of HeLa cells with siRNA for SAP155, SAP145, and SAP130 all caused the formation of p27*. However, the siRNA for SAP155 or SAP130 knocked down the levels of both p27 and p27*. Finally, endogenous cdk2 was inhibited in cells expressing p27*, implicating this as the antiproliferative mode of action for

FR901464. Therefore, it appears that the spliceosome, which had not been thought of as a chemotherapeutic target previously, is a target of FR901464.



24

Figure 4. Structure of biotinylated analog **24**

1.5 PREVIOUS TOTAL SYNTHETIC EFFORTS TOWARD FR901464 IN THE KOIDE GROUP

The long term goals for this project were the elucidation of the unique mode of action of this natural product and to impact medicine by developing agents that could be used for cancer treatment. Toward these ends, a concise, flexible total synthesis was required for access of this natural product and the rapid development of analogs.

1.5.1 Experiments on the stability of FR901464

Lessons learned from the two previous syntheses are that the epoxide should be installed prior to union of advanced intermediates and a minimum of transformations should take place after the union of these intermediates for maximum yield and convergency.[62] The following stability studies conducted in the Koide laboratories gave valuable information to influence the endgame of the synthesis including the choice of protecting groups. The Jacobsen and Kitahara syntheses demonstrated the acid lability of FR901464 via both the instability on silica gel and the low-yielding hydrolysis of the C1 methyl glycosidic bond of **20**.[43,56-58] However, the stability of FR901464 towards a range of acids and bases was unknown. To address these concerns, the stability of small (~0.1 mg) samples of the natural product (a gift from Fujisawa Pharmaceutical Co., Ltd) was examined under the conditions shown in Table 2. Exposure of FR901464 to EtOH in toluene, even in the presence of SiO_2, gave no reaction (entries 1 and 2). However, subjection of FR901464 to EtOH in the presence of AcOH or PPTS led to decomposition of the natural product (entries 3 and 4). The isolation of FR901464 precluded the use of MeOH due to the observation of a methanol-containing artifact of the natural product, presumably **20**.[41] Treatment of FR901464 with MeOH in toluene gave no reaction (entry 5), but upon addition of SiO_2 a less polar compound (as judged by TLC, entry 6) was generated, presumably **20**. Exposure of FR901464 to excess pyridine in THF/CH_2Cl_2 gave no reaction at 0 °C, but slow decomposition upon warming to 23 °C (entry 7). Finally, treatment of FR901464 with HF•py in THF/CH_2Cl_2 gave no reaction at 0 °C, but upon addition of pH 7 buffer some decomposition occurred (entry 8). From these studies, the lability of FR901464 towards weak acid (entries 3 and 4), weak base

(entry 7), and even buffers (entry 8) was realized. These studies proved valuable in the total synthesis of FR901464, especially in the late stages of the synthesis.

Table 2. Acid and base lability studies of FR901464

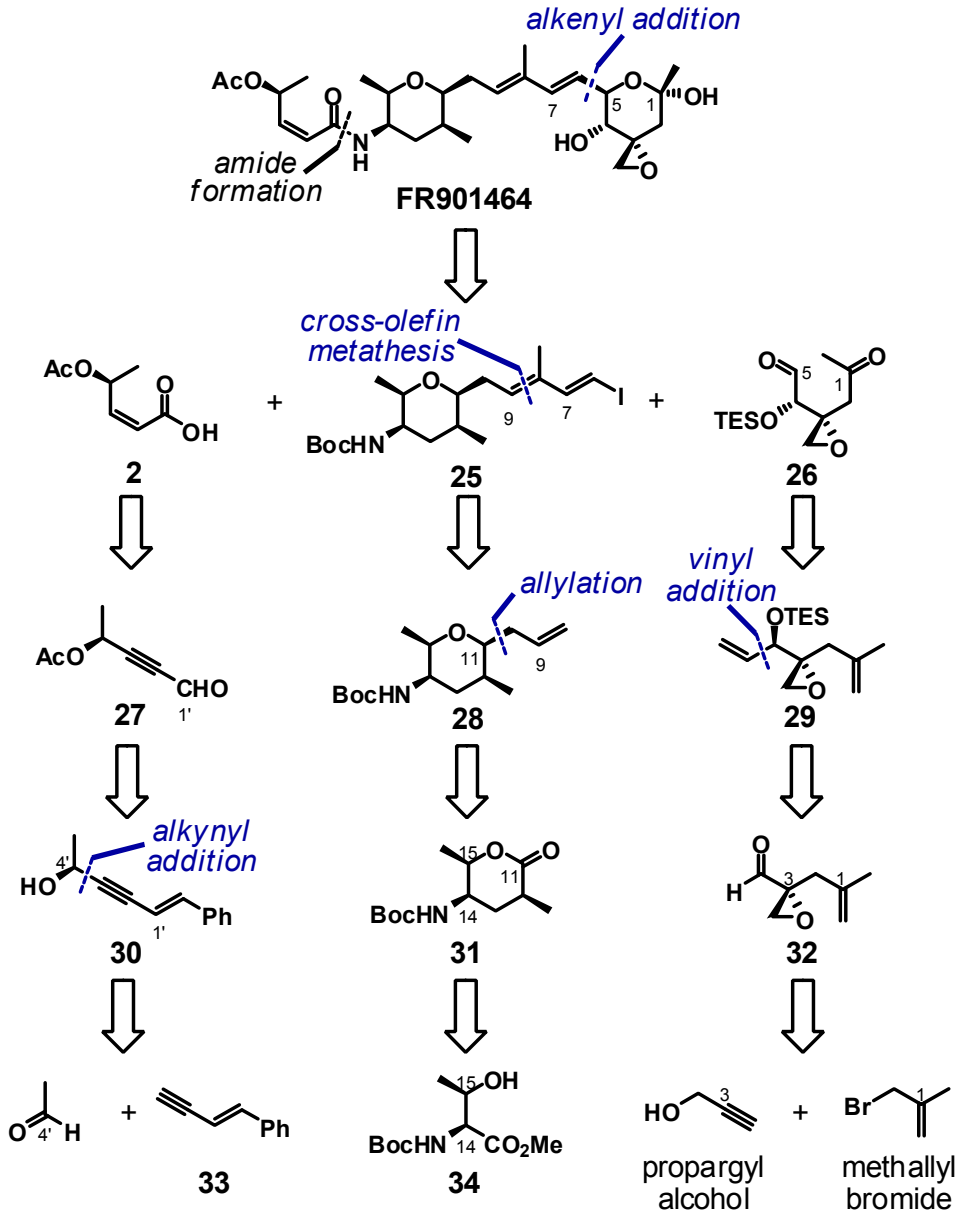
entry	additive(s)	solvent	temp (°C)	result[a]
1	EtOH	toluene	23	no reaction
2	EtOH, SiO_2	toluene	23	no reaction
3	EtOH, AcOH	toluene	23	decomposition
4	EtOH, PPTS	toluene	23	decomposition
5	MeOH	toluene	23	no reaction
6	MeOH, SiO_2	toluene	23	non-polar byproduct formation
7	py (10 equiv)	THF/CH_2Cl_2	0 to 23	decomposition
8	HF•py	THF/CH_2Cl_2	0	no reaction[b]

[a] Determined by TLC analysis; [b] Decomposition upon addition of pH 7 buffer

1.5.2 First generation retrosynthetic analysis

Due to the instability of FR901464 towards weak acids and bases, a coupling strategy utilizing advanced intermediates with a minimum number of labile protecting groups was desirable. Therefore, a mild coupling reaction was necessary to unite functionalized fragments, and a Nozaki-Hiyama-Kishi (NHK) reaction of **25** and **26** was envisioned as the final coupling to form the C5–C6 bond (Scheme 5). [75,76] NHK reaction conditions are mild and generally proceed in accordance with Felkin selectivity for additions into α-chiral aldehydes.[77] Another obvious disconnection of FR901464 would be at the amide bond to give acid **2**, vinyl iodide **35**, and ketoaldehyde **27** as the three fragments. Acid **2** could be derived from ynal **27** by oxidation of the aldehyde and partial hydrogenation of the alkyne. This ynal could be prepared from alcohol **30** by an ozonolysis and acetylation of the hydroxyl group. This alcohol could be prepared by an asymmetric alkynylation reaction of acetaldehyde and enyne **33**. Vinyl iodide **25** could be

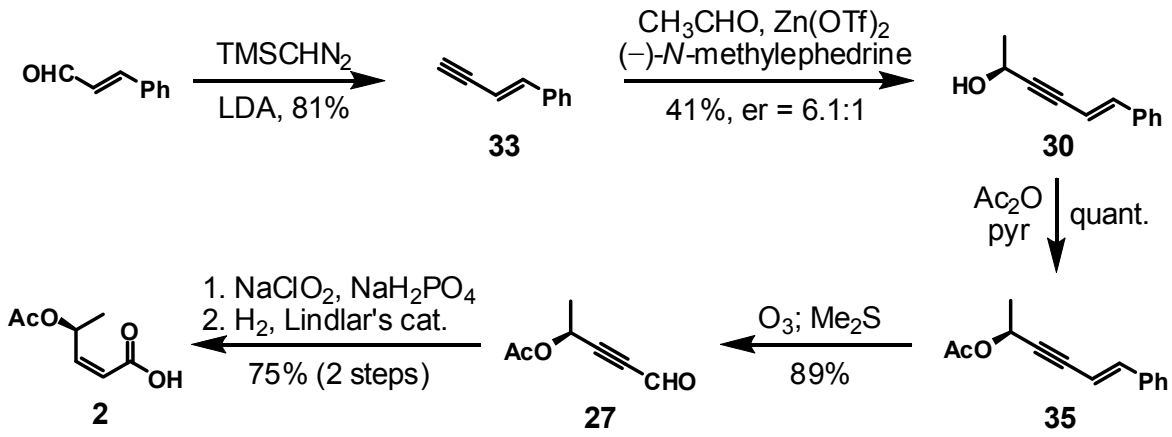
formed from tetrahydropyran **28** by a cross-olefin metathesis reaction to generate the C8–C9 alkene. This tetrahyropyran could be formed through an allylation–reduction sequence of **31**. Lactone **31** could be derived from the commercially available L-threonine-derivative **34** that contains the C14 and C15 stereocenters. The ketoaldehyde fragment could arise from diene **29**



Scheme 5. First generation retrosynthetic approach toward FR901464

by oxidative cleavage reactions of both alkenes. This diene could be generated from epoxyaldehyde **32** by a vinyl addition reaction and subsequent protection of the hydroxy group. Finally, this epoxyaldehyde could be prepared by the condensation of commercially available propargyl alcohol and methallyl bromide and successive oxidation reactions.

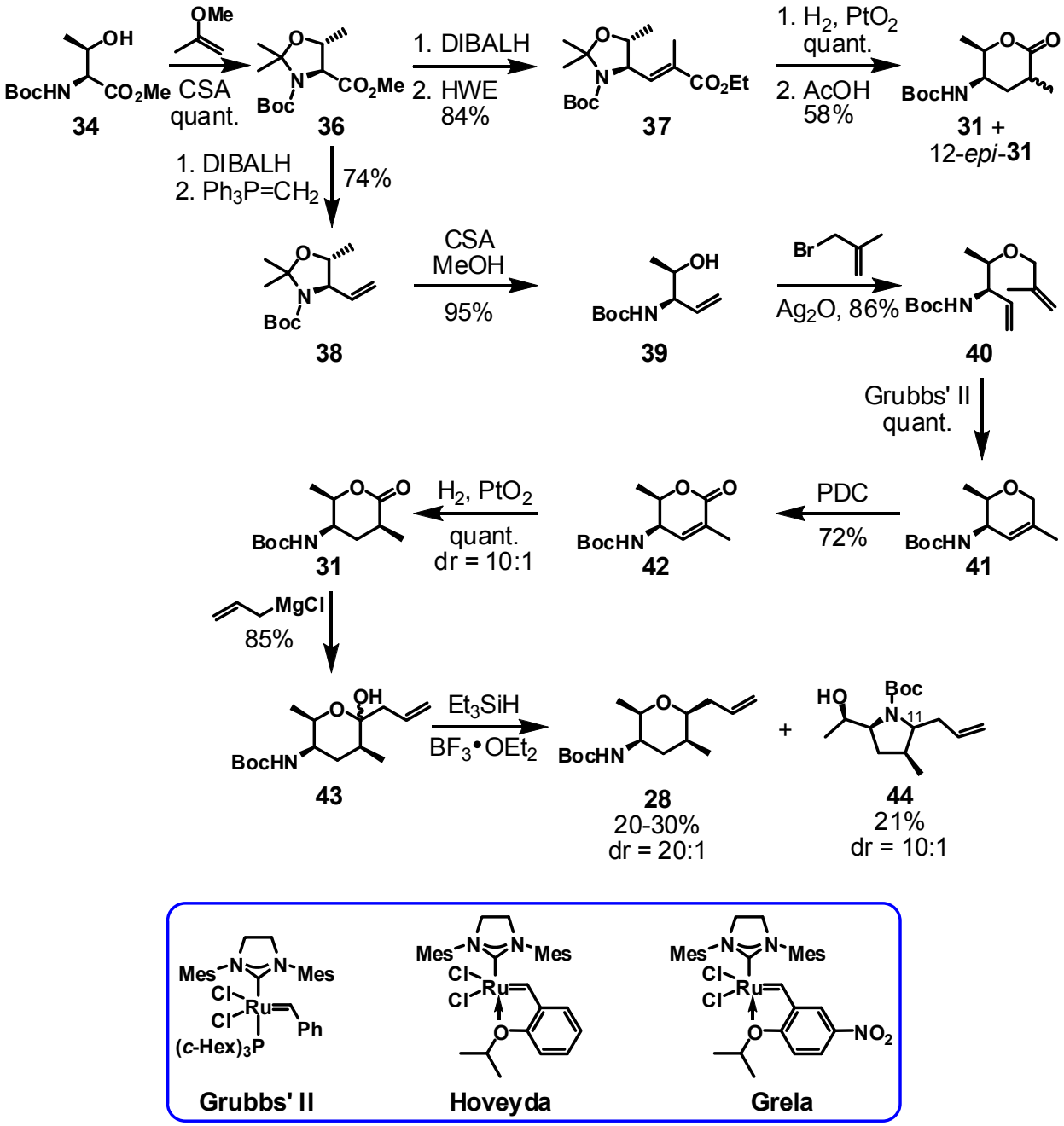
This synthetic endeavor commenced with the concise preparation of acid **2** by Dr. Naka (Scheme 6). A styryl unit was chosen to mask an aldehyde that would effectively suppress the volatility and water solubility of otherwise low molecular weight intermediates. Homologation of commercially available cinnamaldehyde with $TMSCHN_2$ and LDA gave enyne **33** in 84% yield.[78] The Corey-Fuchs method was less efficient in forming **33**,[79] and the Seyforth-Ohira-Bestman method gave 1-(1-methoxybut-3-ynyl)benzene as the major product.[80,81] Subsequent Carreira asymmetric alkynyl addition to acetaldehyde gave alcohol **30** in 41% yield with a 6.1:1 er.[82] This transformation was explored in more detail (Table 3). The catalytic version of this reaction was unsuccessful.[83] Subsequent acetylation of alcohol **30** was accomplished in quantitative yield to afford **35**. This ester was then subjected to ozonolysis conditions and after reductive workup aldehyde **27** was obtained in 89% yield. Finally, oxidation of this aldehyde and subsequent partial hydrogenation of the ynoic acid gave **2** in 75% two step yield. Therefore, acid **2** could be prepared in six linear steps from cinnamaldehyde.[7]



Scheme 6. Preparation of acid **2**

The synthesis of the A-ring, performed by Dr. Naka and Dr. Sivaramakrishan, began from commericailly available L-thereonine derivative **34** which was derivatized into its acetonide in quantitative yield (Scheme 7). This acetonide was partially reduced with DIBALH to give Garner's aldehyde,[84] and subsequently transformed to **36** by a Horner-Emmons-Wadsworth reaction in 84% yield over two steps. The subsequent hydrogenation of this unsaturated ester gave a 2:1 mixture of diastereomers that was realized after acetonide removal and lactonization to give **31** and 12-*epi*-**31** as an inseparable mixture. Since poor substrate control was obtained in a linear system, a more rigid, cyclic substrate was desired. Towards this end, acetonide **36** was reduced with DIBALH and subsequently homologated by a Wittig reaction to give **38** in 74% over two steps. This material was deprotected with CSA/MeOH to give **39** in 95% yield. This alcohol was transformed into ether **40** in 86% yield by the action of Ag_2O and methallyl bromide. This ether was transformed to dihydropyran **41** by a ring-closing metathesis using Grubbs' II catalyst[85] in quantitative yield. It was later shown that the ruthenium catalyst developed by Hoveyda was similarly effective in this transformation, but could not be recovered.[86] This substrate was then regioselectively oxidized with PDC to give lactone **42** in

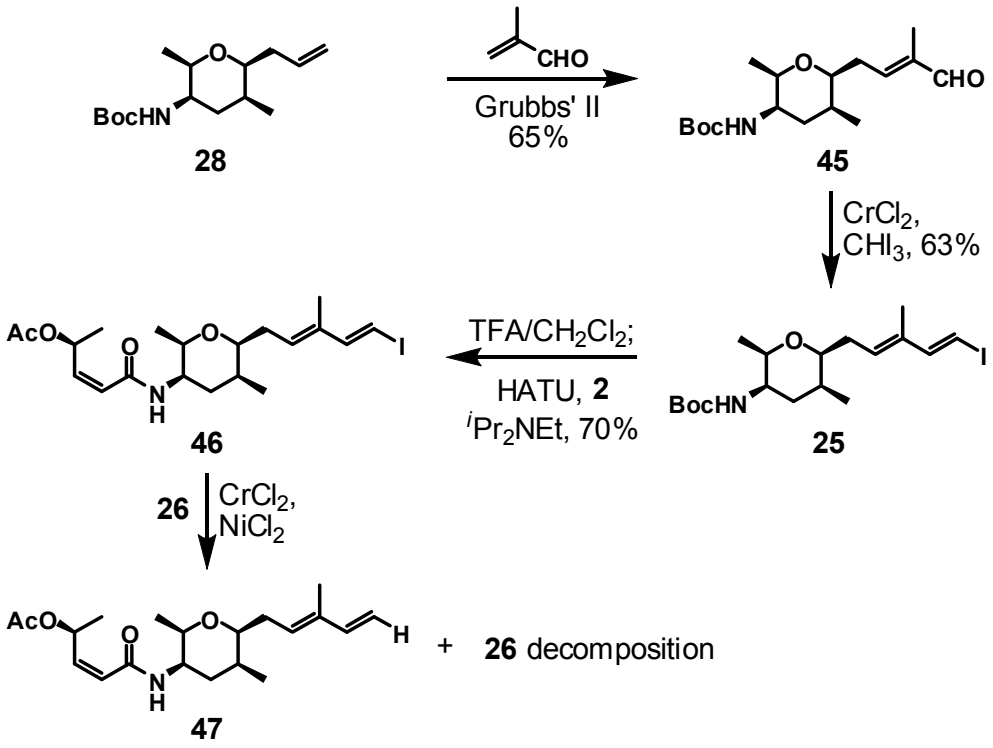
72% yield. Alternatively, this regioselective oxidation could be accomplished with PCC to give unsaturated lactone **42** in 67% yield. This unsaturated lactone was hydrogenated by the action of PtO_2 in EtOH to give **31** in quantitative yield and a 10:1 dr. This lactone was allylated with allyl



Scheme 7. Preparation of tetrahydropyran **28**

magnesium chloride to give **43** in 85% yield. Subsequent reduction of this hemiketal with BF_3•OEt_2 and Et_3SiH gave **28** in 20–34% yields and a 10:1 dr along with the stereoselective production of pyrrolidine **44** in 21% yield (this strategy is further discussed in section 1.6.2).

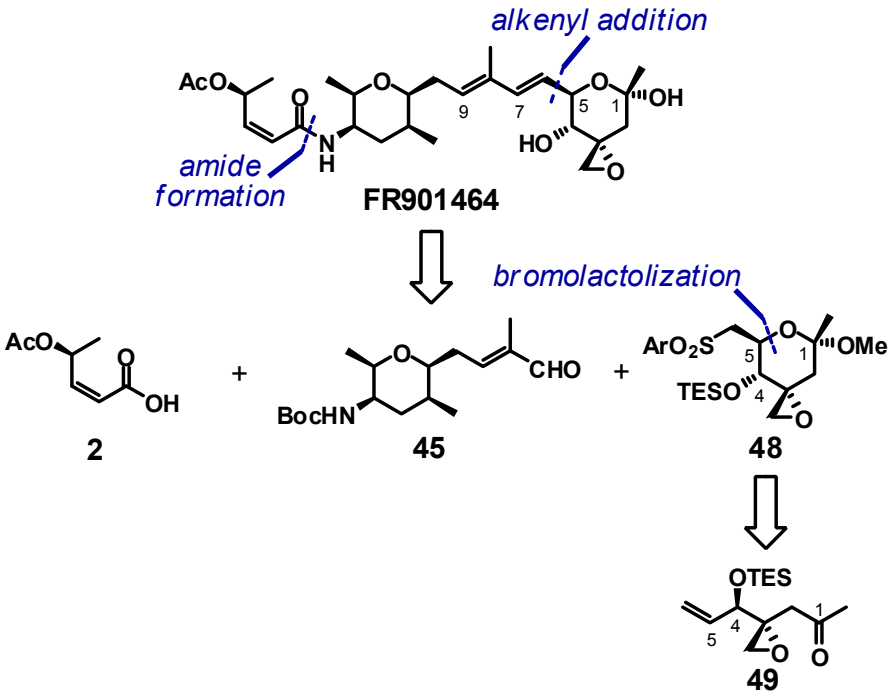
The examination of the Nozaki-Hiyama-Kishi (NHK) coupling is shown in Scheme 8. Cross-olefin metathesis of tetrahydropyran **28** and methacrolein gave **45** stereoselectively in 65% yield. Treatment of aldehyde **45** to Takai olefination conditions gave vinyl iodide **25** in 63% yield.[87] Deprotection of the Boc-carbamate of **25** with TFA and subsequent coupling with acid **2** by the action of HATU gave **46** in 70% yield. Subjection of vinyl iodide **46** and ketoaldehyde **26** (synthesis shown in Scheme 19) to NHK coupling conditions gave protodeiodination of **46** to give **47** and decomposition of **26**. This strategy is further discussed below.



Scheme 8. Examination of the NHK coupling strategy

1.5.3 Second generation retrosynthetic analysis

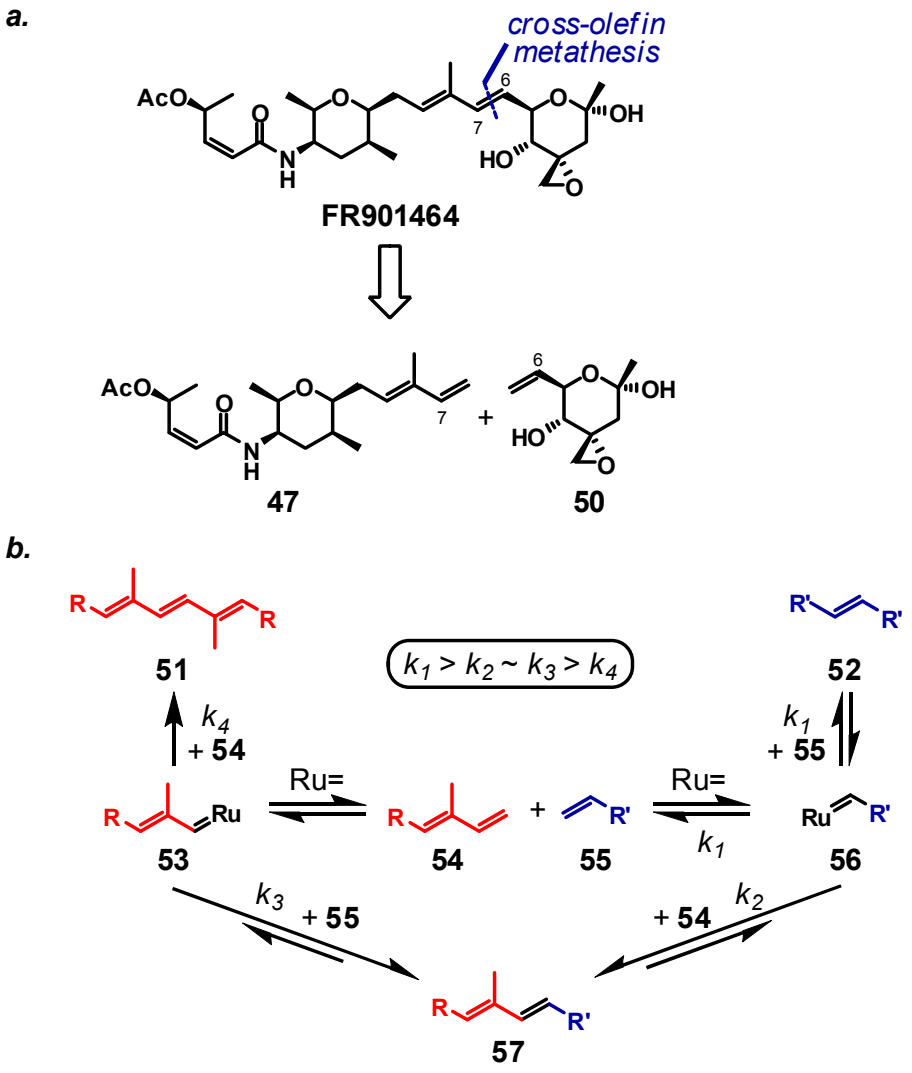
The second generation retrosynthesic analysis featured a modified Julia-Kocienski coupling to form the C6–C7 alkene and amide bond formation from acid **2**, aldehyde **45**, and sulfone **48** (Scheme 9). Julia olefinations are typically highly E-selective and functional group compatible and therefore could serve as an ideal strategy.[88-90] Acid **2** and aldehyde **45** were already prepared. However, B-ring fragment **48** would require new methodology to prepare this type of intermediate from enone **49**. Unfortunately, sulfone **48** could not be prepared (see section 1.6.4), and this strategy was abandoned.



Scheme 9. Second generation retrosynthetic approach toward FR901464

1.5.4 Third generation retrosynthetic analysis

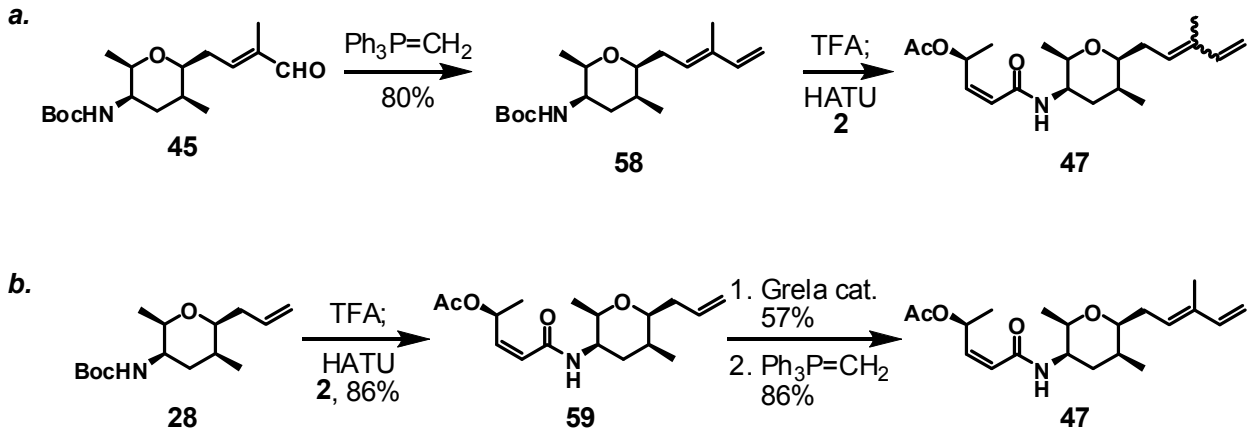
With the troubles encountered in the late stages of the synthesis, a new, bolder approach to unite two fully functionalized fragments was envisioned (Scheme 10*a*). This retrosynthetic analysis involved formation of the C6–C7 alkene again for the final coupling of diene **47** and monoene **50** by a cross-olefin metathesis reaction. Metatheses using ruthenium-based catalysts are tolerant of functional groups and have enjoyed application in complex molecule synthesis.[91,92] At the onset of this endeavor 1,3-diene–ene cross-metatheses were relatively unexplored transformations and had not been utilized in natural product synthesis (Scheme 10*b*).[93] This was thought to be a viable approach because: (1) a ruthenium catalyst (Ru=) would preferentially react with **55** to form ruthenium alkylidene **56** rather than the conjugated olefins of diene **54**; (2) the resulting alkylidene **56** would preferentially reversibly react with **55** to form **52**, but could be minimized by slow addition of **55** to the reaction mixture; (3) eventually, alkylidene **56** would reversibly react with the sterically more accessible olefin of diene **54** to form the thermodynamically favored **57**; and (4) if ruthenium alkylidene **53** is generated from the ruthenium catalyst and diene **54**, this species will react faster with **55** than with diene **54** to form **57** faster than the thermodynamically favored **51**. This strategy was later substantiated in 2005 by the Crimmins group during their total synthesis of apoptolidinone.[94] A potential disadvantage of this strategy would be the contamination of **57** (or FR901464) by highly toxic ruthenium byproducts. However, there are many convenient methods for ruthenium removal of metatheses reactions including the addition of $P(CH_2OH)_3$,[95] activated charcoal,[96] DMSO,[97] $Ph_3P{=}O$,[97] mesopourous silicates,[98] or $Pb(OAc)_4$.[99]



Scheme 10. Third generation retrosynthetic approach toward FR901464

With this coupling strategy in mind, a method to form diene **47** was pursued (Scheme 11). Initially, previously prepared aldehyde **45** was transformed to diene **58** by a Wittig homologation in 80% yield (Scheme 10*a*). The Boc group of this diene was removed by the action of TFA, and subsequently coupled to acid **2** to give adduct **47** as a mixture of stereo- and geometrical isomers. To avoid the acid-sensitivity of the diene, Boc removal was performed prior to installation of the diene. Treatment of **28** with TFA and subsequent amide formation with **2** gave **59** in 86% yield. This allowed for the selective cross-olefin metathesis of **59** and

methacrolein in the presence of the Grela catalyst (structure, Scheme 7)[100,101] to give an unsaturated aldehyde in 57% yield. Wittig homologation of this aldehyde gave diene **47** in 86% yield, thereby completing the synthesis of the left fragment coupling partner.[7,102] The preparation of the right fragment and successful conclusion of this strategy is discussed below.



Scheme 11. Preparation of diene **47**

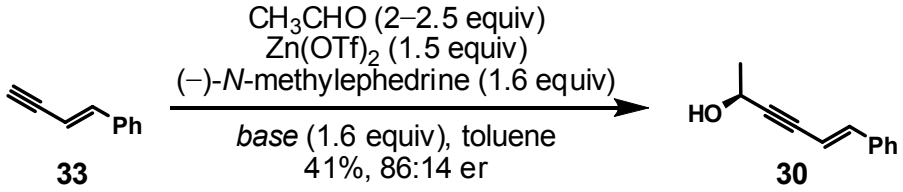
1.6 CONTRIBUTION TO THE TOTAL SYNTHESIS OF FR901464 BY BRIAN J. ALBERT

1.6.1 Acid chain studies

With a successful strategy for the preparation of acid **2** in hand, efforts were directed towards improving the enantioselectivity of forming Carreira asymmetric alkynylation adduct **30** (Table 3). Using only 2.0–2.5 equiv of CH_3CHO and Et_3N as the base led to formation of **30** in an improved 45% yield, but surprisingly decreased the er to 3.3:1 (entry 1). In 2003 Carreira, based on Noyori's diethyl zinc model,[103] proposed transition state **60** where the X–group could be the

base chosen for the reaction (Figure 5).[104] Therefore, different bases were examined in this alkynyl addition reaction. When DBU was employed as the base, a higher yield of **30** was obtained but in a lower (2.3:1) er (entry 2). A smaller base, Me_2NEt gave **30** in 45% yield and a modest 2.5:1 er (entry 3). Using a larger base, $^{i}Pr_2NEt$, gave adduct **30** in 59% yield and 3.5:1 er (entry 4). Lowering of the temperature for these reaction conditions gave **30** in 36% yield and 4.7:1 er (entry 5). Finally, executing this reaction from 0 to 23 °C gave **30** in 33% and 3.8:1 er (entry 6). Therefore, there appears to be an effect of the base on the observed enantioselectivity of this reaction. It should be mentioned that slow addition of acetaldehyde, which is unstable, was crucial in suppressing aldol condensation. Without an excess of acetaldehyde in the reaction mixture, the enantioselectivity was significantly lower. Later, it was discovered that the er of **30** could be improved to 98:2 by one recrystallization in Et_2O/hexanes at –20 °C.

Table 3. Base effects in the preparation of **30**



entry	base	yield (%)	temp (°C)	er
1	Et_3N	45	23	3.3:1[b]
2	DBU	51	23	2.3:1[a]
3	Me_2NEt	45	23	2.5:1[b]
4	$^{i}Pr_2NEt$	59	23	3.5:1[a]
5	$^{i}Pr_2NEt$	36	0	4.7:1[a]
6	$^{i}Pr_2NEt$	33	0 to 23	3.8:1[a]

[a] Determined by chiral HPLC, (S,S) Whelk column, 25 cm, 5% ^{i}PrOH/hexanes, 1 mL/min. [b] Detemined by optical rotation of **35**

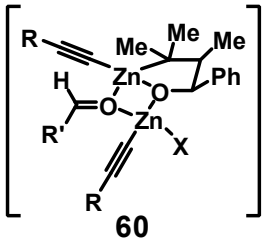
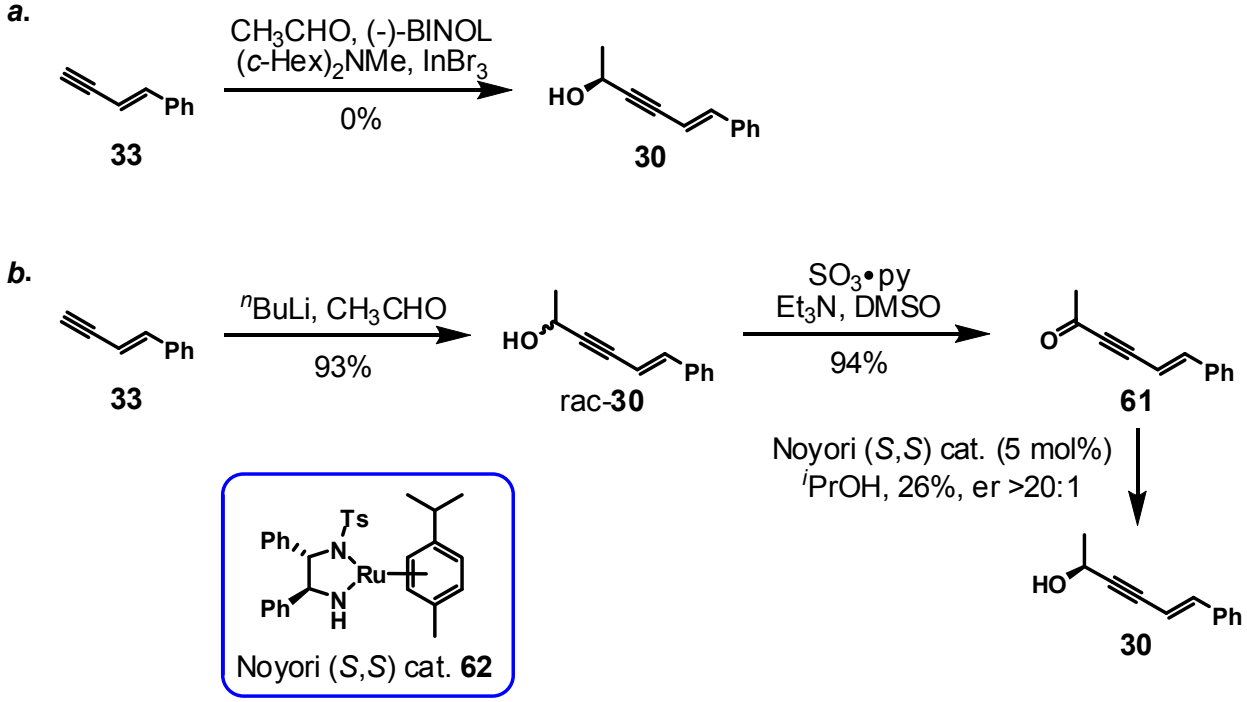


Figure 5. Carreira's proposed asymmetric alkynylation transition state

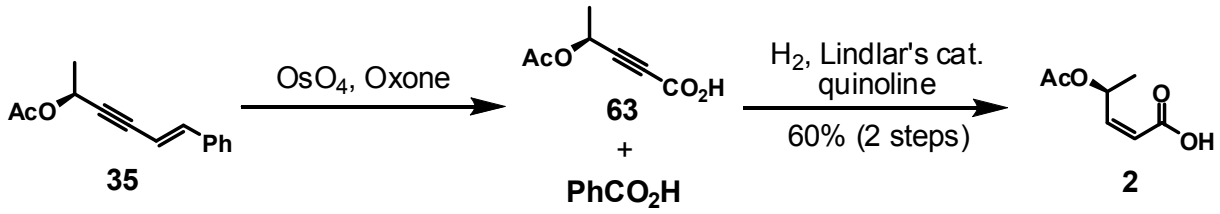
Although **30** could be produced in high er, the overall yield was quite low (10–20%). Therefore, alternative methods were envisioned to prepare **30** similarly. In 2005, the Shibasaki group developed an alkynyl addition reaction utilizing $InBr_3$ and BINOL.[105] However, when applied to enyne **33** and acetaldehyde, no desired product was generated (Scheme 12*a*). Therefore, this strategy was slightly modified, and enyne **33** was added to acetaldehyde



Scheme 12. Alternative method for the preparation of **30**

by the action of ^{n}BuLi to give rac-**30** in 93% (Scheme 12*b*). This alcohol was then oxidized using Parikh-Doering conditions to give unsaturated ketone **61** in 94% yield. The transfer hydrogenation reaction of this ketone with Noyori's (*S*,*S*) catalyst **62** gave the desired propargylic alcohol **30** in 26% yield and >20:1 er.[59] Unfortunately, the turnover number for this catalyst was 5.2 and therefore this method was abandoned. Alternatively, reduction of this material with catalyst **67** (structure, Scheme 12) and catechol borane gave **30** in quantitative yield but only in 2.5:1 er.

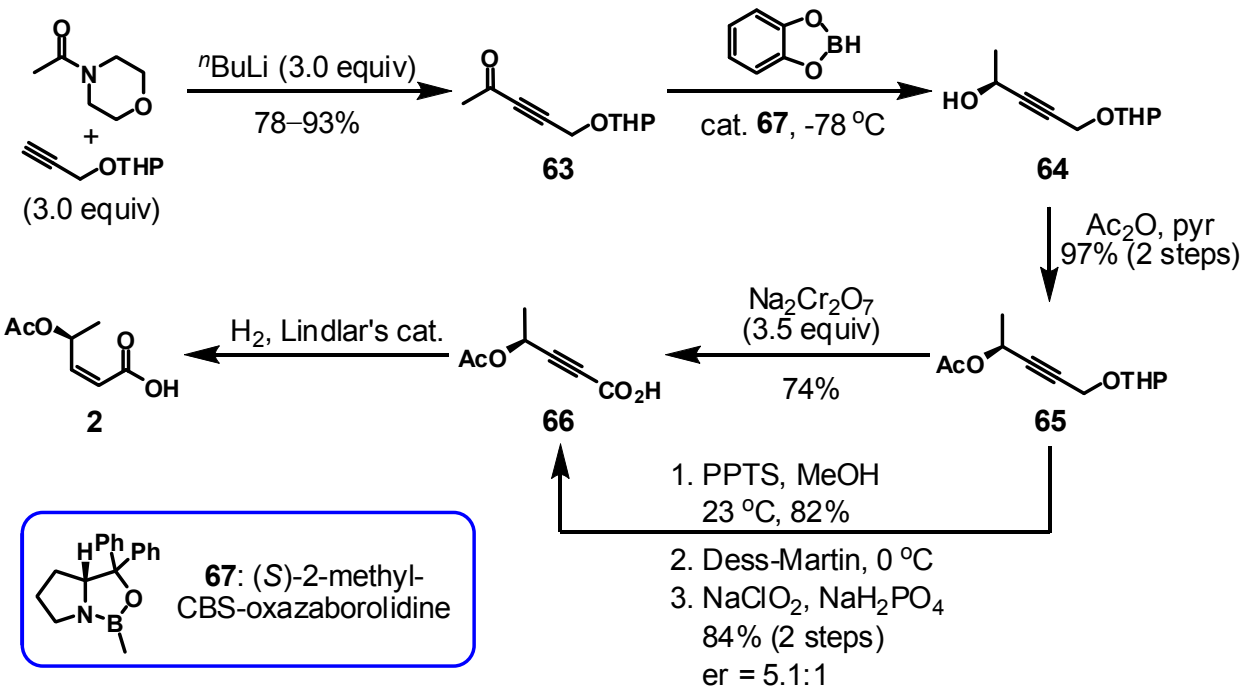
With the preparation of acid **2** requiring a respectable 6 linear steps, shortening the sequence was desired if it did not jeopardize the scalability of the sequence. Toward this end, the two-step oxidation of **35** to ynoic acid **63** was targeted for improvement. Treatment of **35** with less than 1 mol % of OsO_4 and Oxone® gave ynoic acid **63** and benzoic acid in nearly quantitative yields as an inseparable mixture (Scheme 13).[106] After partial hydrogenation of this mixture, acid **2** was generated in a 60% two step yield free of impurities from benzoic acid.



Scheme 13. Alternative method enveiled for the preparation of acid **2**

Developing a more scalable route to acid **2** was desired due to the cost and safety issues of using $TMSCHN_2$ in large scale, and the low yielding approach for the preparation of propargylic alcohol **30**. Coupling of *N*-acetylmorpholine and tetrahydro-2-(2-propynoxy)-*2H*-pyran by the action of ^{n}BuLi gave ynone **63** in 78–93% yields (Scheme 14).[107] Reduction of this

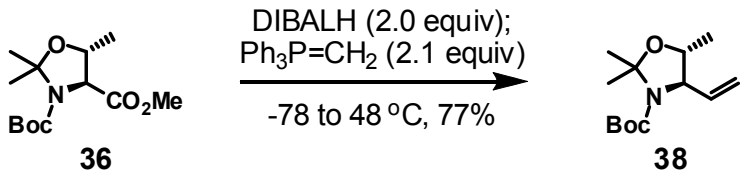
ynone with a substoichiometric amount of commercially available **67** and catechol borane in $EtNO_2$ gave **64** in near quantitative yield, and acetylation of this material gave **65** in 97% yield over two steps.[108,109] Subsequent THP-removal and concomitant oxidation of the putative alcohol to ynoic acid **66** was accomplished in 74% yield and revealed that the er was 5.1:1. Finally, partial hydrogenation gave acid **2** in a total of five steps. Alternatively, the THP-group of **65** could be removed via methanolysis under acidic conditions in 82% yield. Subsequent successive oxidations with Dess-Martin periodinane and $NaClO_2$ gave **66** in 84% also in a 5.1:1 er, indicating that no epimerization occurs in the formation of **66** from **65**.[110]



Scheme 14. Alternate preparation of acid **2**

1.6.2 A-Ring studies

With established schemes to fully functionalized A-ring fragments, methods were desired to make the routes shorter and/or more efficient. The first synthetic step that was improved was the preparation of **38** (Scheme 15). Partial reduction of ester **36** with DIBALH, addition of $Ph_3P{=}CH_2$ at −78 °C, and subsequent mild heating gave **38** in 77% yield in one pot without epimerization.[111] This procedure was executed on 30 g scale several times without mishap, thereby demonstrating the utility of this procedure. Moreover, this one-pot procedure avoided tedious aqueous workups of the Garner aldehyde. The DIBALH purchased from Aldrich gave superior results to that purchased from other vendors.

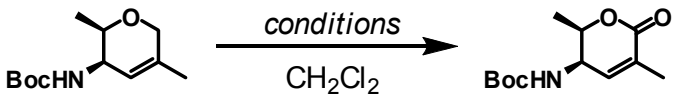


Scheme 15. One-pot procedure for the preparation of **38**

Although two procedures were established to prepare the preparation of unsaturated lactone **42**, the efficiencies were of concern for large-scale preparation of A-ring fragments. In scale-up efforts, the use of 2.0 equiv of PCC and 4.1 equiv of aq. ^{t}BuOOH gave **42** in 49% yield (entry 1, Table 4). Increasing the amount of PCC to 2.5 or 3.0 equiv gave **42** in lower yield, demonstrating the adverse effect of using more PCC (entries 2 and 3). The use 10 equiv of CrO_3/3,5-dimethylpyrazole generated **42** in 67% yield (entry 4).[112,113] However, concerned with the amount of chromium waste generated, the amount was reduced to 8.0 equiv of CrO_3, which gave **42** in 70% yield (entry 5). Further reduction of reagents to 6.0 equiv gave **42** in only 53%

yield (entry 6), indicating that 8 equivalents was optimal. With an improved method to prepare unsaturated lactone **42** from dihydropyran **41**, the amount of toxic waste generated was still of concern. Therefore, a rhodium catalyst developed by Doyle was used to oxidize dihydropyran **41** to **42**, but in only 42% yield (entry 7).[114]

Table 4. Preparations of dihydropyran **42**



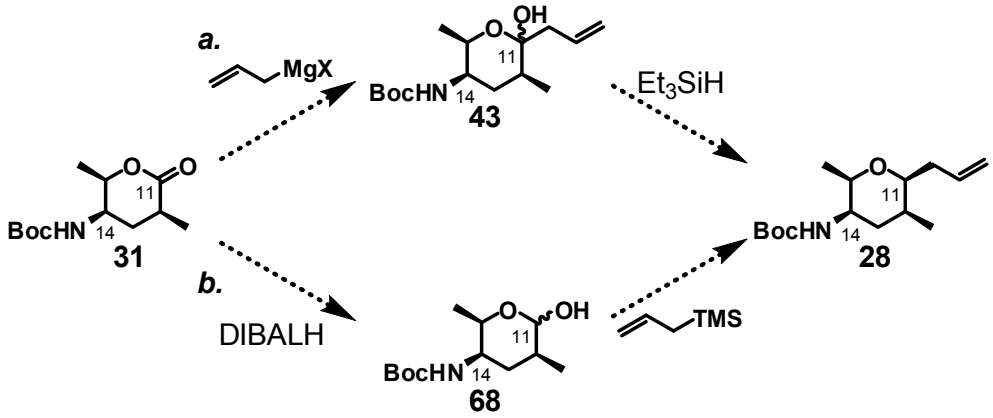
41 **42**

entry	reagents (equiv)	temp (°C)	yield (%)
1	PCC (2.0) ^{t}BuOOH^a (4.1)	23	49
2	PCC (2.5) ^{t}BuOOH^a (4.0)	23	47
3	PCC (3.0) ^{t}BuOOH^a (3.0)	23	32
4	CrO_3 (10.0) ^{t}BuOOH^a (10.0)	-30 to 0	67
5	CrO_3 (8.0) ^{t}BuOOH^a (8.0)	-30 to 0	70
6	CrO_3 (6.0) ^{t}BuOOH^a (6.0)	-30 to 23	53
7	$Rh_2(cap)_4$ (0.007) ^{t}BuOOH^a (2.0), K_2CO_3 (0.5)	0 to 23	42

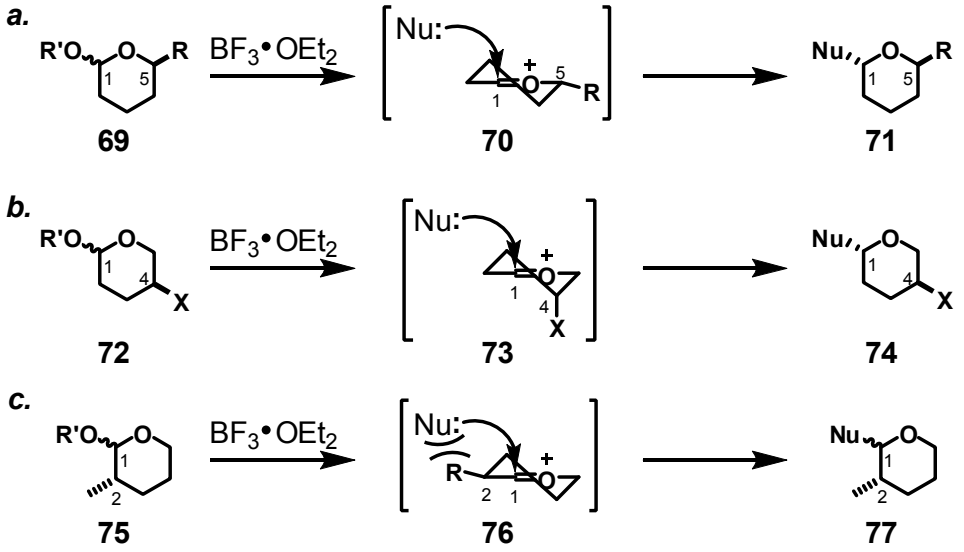
^{a} 70% wt/wt in H_2O

Tetrahydropyran **28** could be prepared from lactone **31** by an allylation/reduction sequence (Scheme 16*a*), but a reduction/allylation sequence could give the same product, and possibly in higher yield (Scheme 16*b*). To help decide between these pathways, the reactions of

similar substrates were consulted. Bartlett and Holmes treated **69** with BF_3•OEt_2 and allyltrimethylsilane to generate putative oxocarbenium ion **70**, which subsequently gave 1,5-*trans*-**71** in >10:1 dr (Scheme 17*a*).[115] Therefore, nucleophiles prefer to add in *trans*-fashion to 5-substituted oxocarbenium ions. Woerpel and coworkers performed other nucleophilic additions to putative oxocarbenium ions probing the C2 and C4 positions, which would be relevant to the preparation of **28**.[116,117] Electronegative substituents at position C4 of **72** prefer pseudoaxial positioning in **73**, and therefore give rise to 1,4-*trans*-**74** in a 7−100:1 dr (Scheme 17*b*). However, no nitrogen-based C4-substituents, found in **31** and **28**, were examined by Woerpel in this study. Exposure of **75** to these reaction conditions generated oxocarbenium ion **76**, which Woerpel postulates has a steric interaction with the incoming nucleophile, and therefore produced **77** non-selectively (Scheme 17*c*). From these results, pathway *a* (Scheme 16) should be chosen for the synthesis of **28**. The C15-methyl group and C14-carbamate moiety should reinforce nucleophilic addition from the α-face, but the C12-methyl group may prove detrimental to the addition.



Scheme 16. Two pathways to synthesize tetrahydropyran **28** from **31**

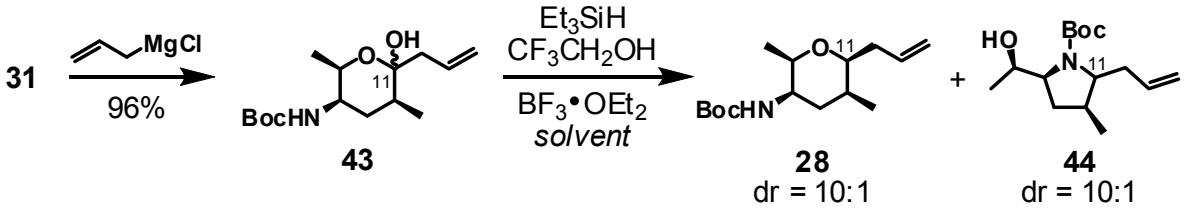


Scheme 17. Models for nucleophilic additions to substituted THP-oxocarbenium ions

The allylation/reduction sequence of lactone **31** to form tetrahydropyran **28** was examined due to its low yield (typically 20–25%). Treatment of lactone **31** with allylmagnesium chloride at −78 °C gave hemiketal **43** in 96% yield (Table 5). The key to this 11% improvement was to add the Grignard reagent down the flask sides in order to avoid bis-addition to lactone **31**. Reduction of this hemiketal with a 10:4:8 ratio of $Et_3SiH/BF_3•OEt_2/CF_3CH_2OH$ in CH_2Cl_2 at −78 °C reproducibly gave tetrahydropyran **28** in 39% yield and pyrrolidine **44** in 20% yield (entry 1). Using this reagent combination in CH_2Cl_2 at –42 °C produced tetrahydropyran **28** in only 29% yield (entry 2). Therefore, low temperature was beneficial in forming tetrahydropyran **28**. To examine if such a large excess of reagents were necessary, a 5:2:4 ratio of $Et_3SiH/BF_3•OEt_2/CF_3CH_2OH$ in CH_2Cl_2 at −78 °C, was found to give tetrahydropyran **28** and pyrrolidine **44** in 30% and 33% yields, respectively (entry 3). Finally, using MeCN as the solvent led to almost exclusive formation of pyrrolidine **44** and tetrahydropyran **28** in only 5% yield.

Thus, this sequence was improved, affording tetrahydropyran **28** in greater yields during large-scale A-ring fragment preparations.

Table 5. Optimization of the allylation/reduction sequence of lactone **31**

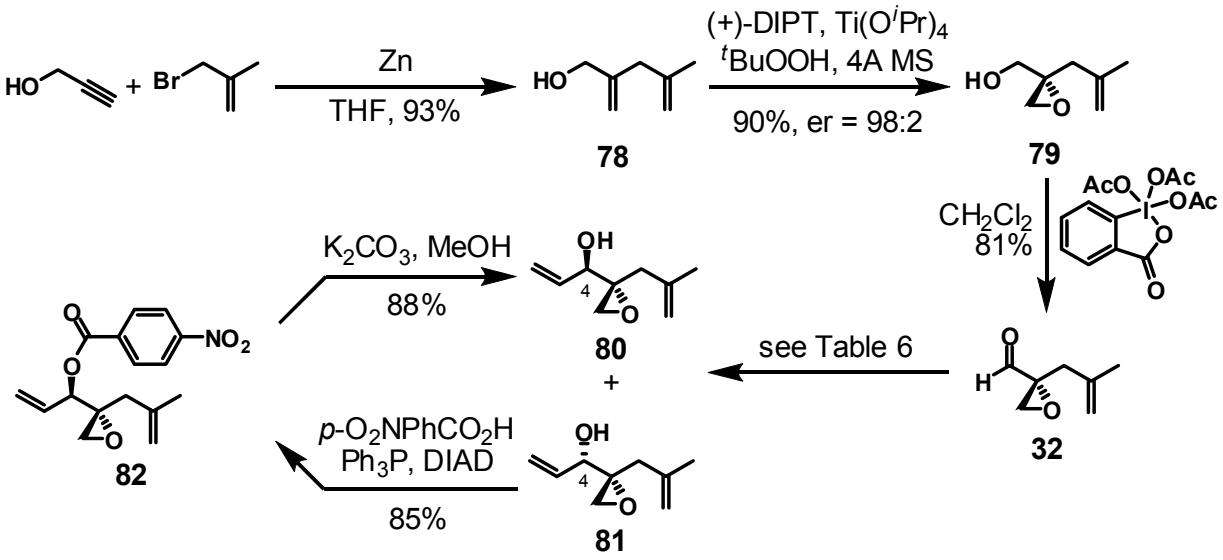


entry	$Et_3SiH/BF_3•OEt_2/CF_3CH_2OH$ (equiv)	solvent	temp (^oC)	yield (%) of **28** (yield (%) of **44**)
1	10:4:8	CH_2Cl_2	-78	38 (39)
2	10:4:8	CH_2Cl_2	-42	29 (20)
3	5:2:4	CH_2Cl_2	-78	30 (33)
4	10:4:8	MeCN	-42	5 (35)

1.6.3 Forward synthesis of the first retrosynthetic analysis

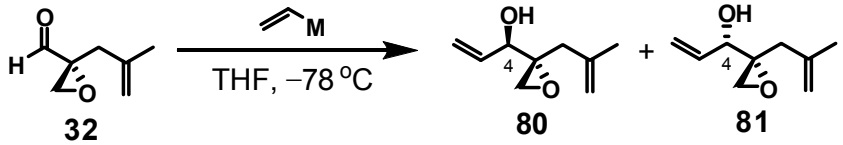
Preparation of the B-ring fragment was envisioned with installation of the epoxide early on in the synthetic sequence. Although this could have proven detrimental to the completion of the total synthesis, in the end, the payoff was immense. Utilizing a known protocol,[118] propargyl alcohol and methallyl bromide were coupled by the action of zinc dust to give skipped diene **78** in 93% yield (Scheme 18). This reaction proved to be quite reproducible and scalable, routinely performed on 80 g scale. The subsequent regioselective Sharpless asymmetric epoxidation of **78** gave epoxyalcohol **79** in 90% yield and excellent enantioselectivity (er = 98:2).[119] This reaction reproducibly gave **79** in >80% yield on 30 g scale, allowing for facile scale-up of this

intermediate. Oxidation of this epoxyalcohol with the Dess-Martin periodinane gave **32** in 81% yield.[110] Alternatively, a Parikh-Doering oxidation could be used to prepare **32** in 65–70% yields in larger scale preparations. Obtaining high levels of substrate control for the vinyl addition to this epoxyaldehyde proved quite difficult (Table 6). Simple addition of vinylmagnesium bromide to **32** gave allylic alcohols **80** and **81** in 53% combined yield in a 1.0:1 ratio, respectively. The elucidation of the stereochemistry of the C4 position of these allylic alcohols is described Scheme 23. The addition of 1.0 equiv of $ZnCl_2$ gave a 0.3:1 ratio of **80**:**81**, but the addition of 2.0 or 4.0 equiv of $ZnCl_2$ afforded these alcohols without selectivity (entries 2–4). Therefore, the generation of the desired diastereomer, **80**, as the major product remained elusive. Addition of hexanes, to precipitate some of the inorganic salts, and 2.0 equiv of $ZnCl_2$ to the reaction mixture produced allylic alcohols **80** and **81** in 54% combined yield in a 2.0:1 ratio, respectively (entry 5). Treatment of vinylbromide with ^{t}BuLi, to generate vinyllithium in situ,[120] and subsequent addition of epoxyaldehyde **32** afforded allylic alcohols in 46% yield non-selectively (entry 6). Finally, to overcome the poor selectivities using substrate control, reagent control was attempted. Addition of vinylmagnesium bromide, $ZnCl_2$, and (–)-*N*-methylephedrine to **32** gave allylic alcohols **80** and **81** in 42% yield and a 1.0:1 ratio, respectively (entry 7). Although low selectivity was obtained in this transformation, the focus remained on moving the synthetic sequence forward. Towards this end, undesired C4 diastereomer **81** was subjected to Mitsunobu reaction conditions using *p*-nitrobenzoic acid as the latent nucleophile to invert the C4 stereocenter, thereby generating **82**. This ester was subsequently cleaved with basic methanol to produce **80** in 75% yield over two steps.



Scheme 18. Initial right fragment preparation studies

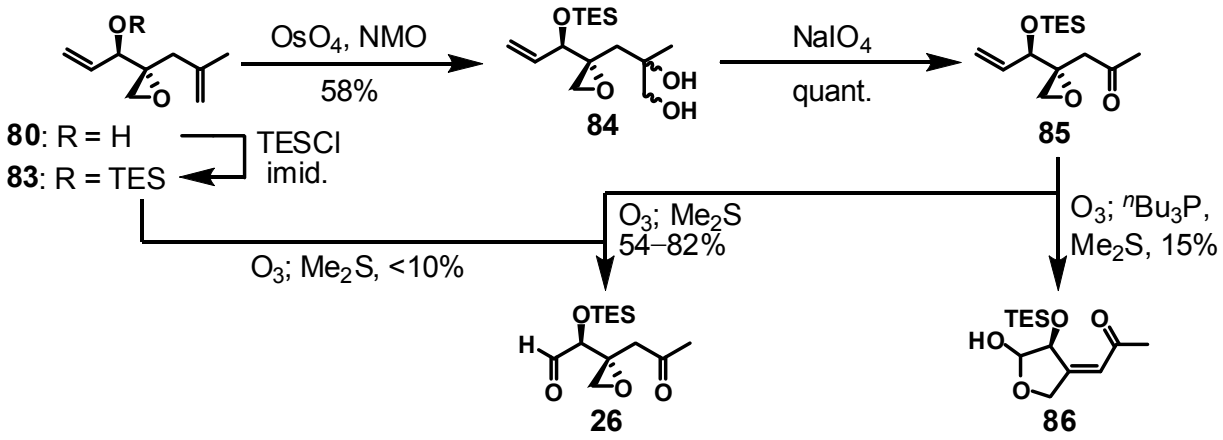
Table 6. Preparation of allylic alcohols **80** and **81**



entry	M (2 equiv)	additive(s) (equiv)	yield (%)[a]	**80**:**81**
1	-MgBr	---	51	1.0:1[b]
2	-MgBr	$ZnCl_2$ (1.0)	71	0.3:1[b]
3	-MgBr	$ZnCl_2$ (2.0)	42	1.0:1[b]
4	-MgBr	$ZnCl_2$ (4.0)	42	1.0:1[b]
5	-MgBr	$ZnCl_2$ (2.0) ^{n}hexane	54	2.0:1[c]
6	-Br	^{t}BuLi (2.0)	46	1.0:1[c]
7	-MgBr	$ZnCl_2$ (2.0), toluene (−)-NME[d] (2.0)	42	1.0:1[c]

[a] Combined yield. [b] Ratios determined from isolated products. [c] Ratios determined by crude ^{1}H NMR analysis. [d] (−)-NME = (−)-*N*-methylephedrine.

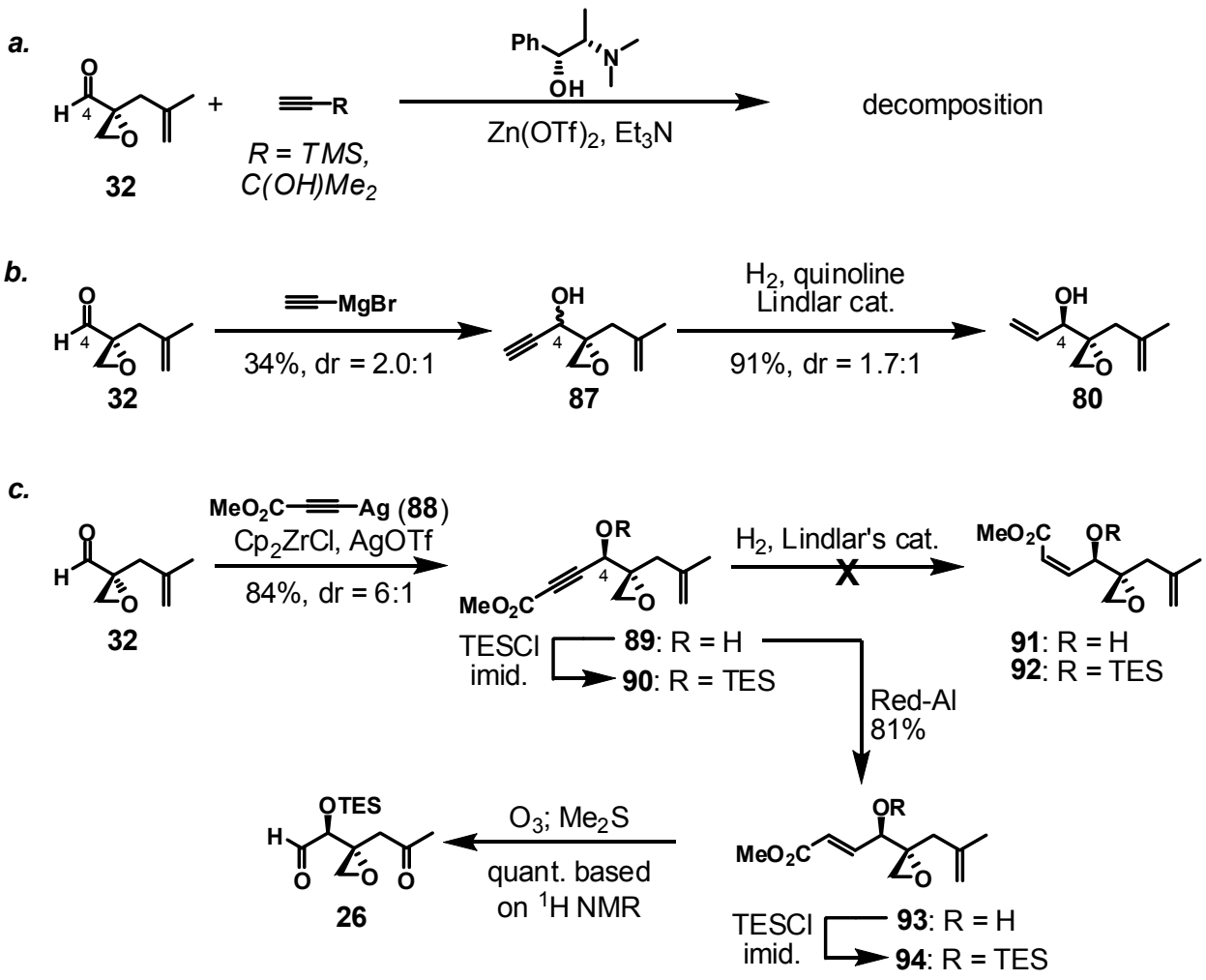
With a moderate quantity of allylic alcohol **80** produced, the preparation of ketoaldehyde **26** was explored (Scheme 19). Protection of **80** as its TES-ether was accomplished in quantitative yield by the action of TESCl/imidazole to provide diene **83**. Subsequent ozonolysis of this diene reproducibly afforded ketoaldehyde **26** in <10% yield. Sequential regioselective dihydroxylation of the 1,1-disubstituted olefin and subsequent oxidative cleavage gave enone **85** in 58% yield over two steps. Ozonolysis of this enone followed by reductive workup using Me_2S/$^nBu_3P$ of this enone afforded unsaturated ketone **86** in 15% yield. However, employing only Me_2S in the reductive workup step successfully produced *unstable* ketoaldehyde in 54–82% yields. With a successful method to prepare ketoaldehyde **26** in hand, it became evident that the large-scale separation of allylic alcohols **80** and **81** was a major obstacle, and a better method to form the C4 stereocenter was desired.



Scheme 19. The first method to prepare ketoaldehyde **26**

Despite an established route towards ketoaldehyde **26**, a better method to install the C4-stereocenter was sought. Treatment of epoxyaldehyde **32** with either trimethylsilylacetylene or 2-methyl-3-propyn-2-ol gave no desired product under Carreira's conditions, and caused

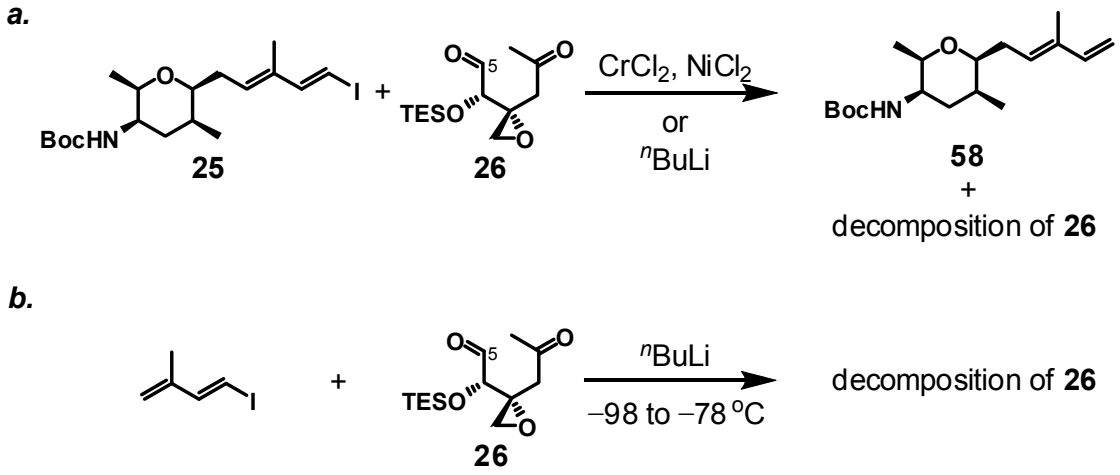
decomposition of aldehyde **32** under mild heating (Scheme 20*a*).[82] Alternatively, the alkynylation of **32** with ethynylmagnesium bromide gave **87** in 34% yield as a 2:1 mixture of diastereomers (Scheme 20*b*). Warming of this reaction gave **87** in higher yield but the desired compound was contaminated with Payne rearrangement products. To elucidate the stereoselectivity of this alkynyl addition reaction, propargylic alcohols **87** were subjected to partial hydrogenation conditions to afford allylic alcohols **80** and **81** in a 1.7:1 ratio, respectively. Finally, the Ag/Zr-promoted alkynyl addition of silver acetylide **88** to **32** produced ynoate **89** in 84% yield and a 6:1 dr (Scheme 20 *c*).[121] This exquisite transformation is further discussed in Chapter 2. Satisfied with the diastereoselectivity and yield from this alkynyl addition reaction, efforts were focused on preparing ketoaldehyde **32** from **89**. The partial hydrogenations of this propargylic alcohol and its TES-ether, **90**, failed to afford Z-enoates **91** or **92**, respectively. Therefore, utilizing another methodology developed in the Koide laboratories,[122] intramolecular hydride delivery was accomplished by treating **89** with Red-Al® to selectively give E-enoate **93** in 81% yield. Protection of the hydroxy group of **93** was accomplished with TESCl/imidazole affording **94** in quantitative yield. Ozonolysis of this material and subsequent reductive workup with Me_2S gave ketoaldehyde in quantitative yield as determined by ^1H NMR. Thus, access to ketoaldehyde **26** was now attainable in only seven steps and without the need for successive oxidative cleavage reactions. Therefore, all that remained was the coupling to form the C5–C6 bond of FR901464.



Scheme 20. Alternative methods to install the C4-stereocenter

The first generation coupling strategy was examined using ketoaldehyde **26**. It was previously discovered that subjection of vinyl iodide **46** and ketoaldehyde **26** under NHK reaction conditions gave proto-deiodination of **46** and decomposition of **26** (Scheme 8). Similarly, treatment of vinyl iodide **25** and ketoaldehyde **26** to NHK reaction conditions gave **58** and decomposition of the ketoaldehyde (Scheme 21*b*). Therefore, a bolder strategy was envisioned involving lithium-halogen exchange where bond formation would be expected to occur rapidly, which could prevent the decomposition of **26**. However, this reaction would be expected to be difficult in the presence of the N-H bond found in the carbamate moiety.

Nonetheless, treatment of vinyl iodide **25** with ^{n}BuLi in the presence of ketoaldehyde **26** afforded **58** and decomposition of the ketoaldehyde (Scheme 21*b*). To examine if the carbamate was the cause of the failed couplings, treatment of (*E*)-1-iodo-3-methylbuta-1,3-diene with ^{n}BuLi in the presence of ketoaldehyde **26** again produced only decomposition products (Scheme 21*c*). With the realization of the ketoaldehyde instability and the difficulty in forming the C5–C6 bond in the late stages of the synthesis, alternative coupling strategies were explored.

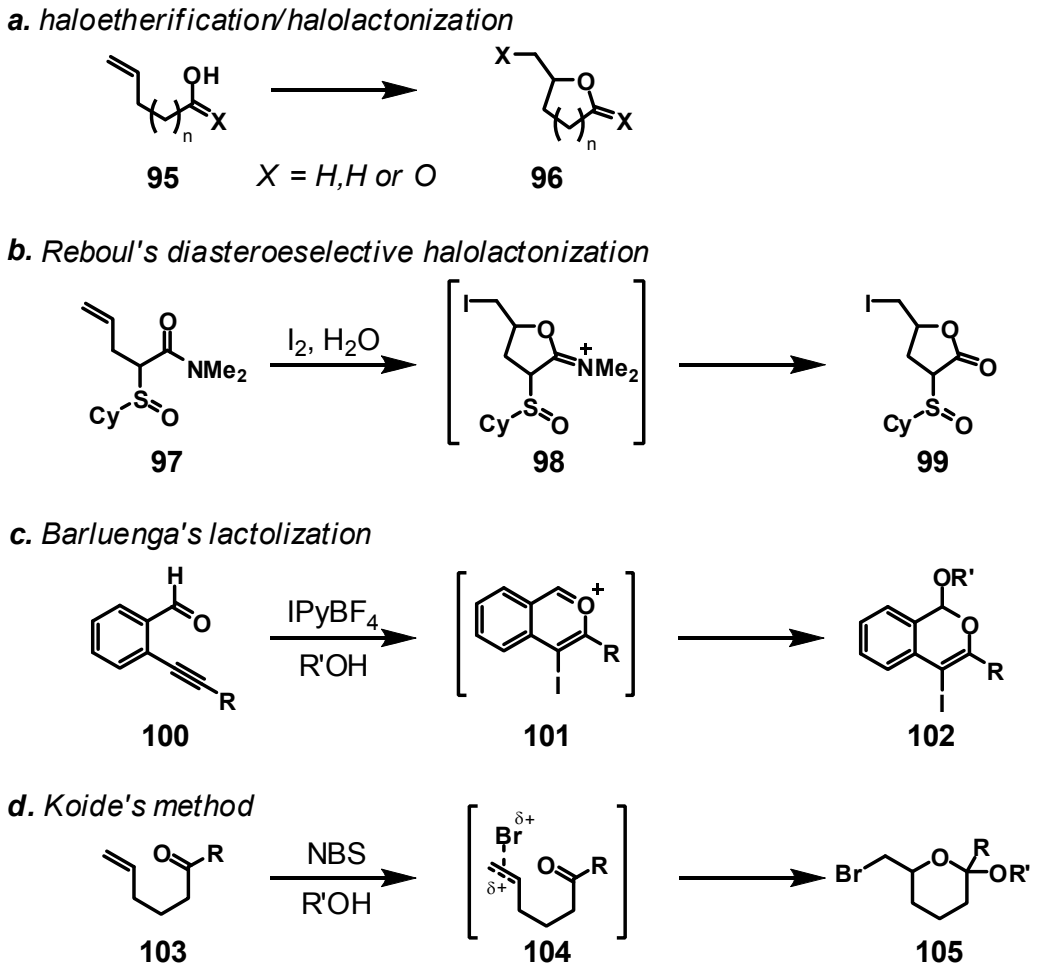


Scheme 21. Further coupling attempts using the first retroynthetic strategy

1.6.4 Forward synthesis of the second retrosynthetic analysis

Since the highly-functionalized sulfone intermediate **48** was desired for use in the Julia coupling, it was recognized that previously prepared intermediates could allow for rapid preparation of such a sulfone. A bromolactolization was envisioned to provide such an intermediate (Scheme 22*d*). This method would differ from other tactics often employed, involving the intramolecular attack of a hydroxy group onto a pendant aldehyde/ketone to give hemiacetal/hemiketal

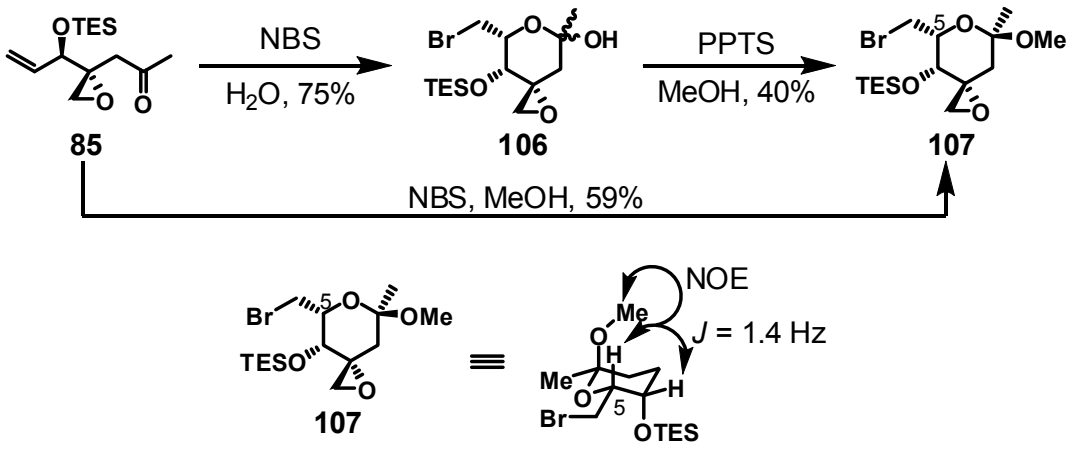
products.[123-129] One of the most common methods for electrophilic cyclizations involves the haloetherification or halolactonization of alcohols or carboxylic acids, **95**, to electrophile-activated alkenes to give **96** as products (Scheme 21*a*). Similarly, amides **97** may be utilized under comparable reaction conditions to form iminium ions **98** that are ultimately hydrolyzed to provide lactones **99** where the pendant sulfoxide induces stereoselectivity in the bond forming stereocenter (Scheme 22*b*).[125] Treatment of *o*-alkynyl benzaldehyde derivatives **100** with bispyridine iodonium tetrafluoroborate is thought to generate oxocarbenium **101**, which can be trapped intermolecularly by alcohols to form acetals **102** (Scheme 22*c*).[124] Similarly, it was postulated that the activation of the alkene in an enolizable aliphatic enal/enone **103** with NBS or another electrophilic reagent could generate the π-complex **104**, which would allow for cyclization using the carbonyl oxygen and subsequent trapping with an alcohol or water (R'OH) to give hemiacetal/hemiketal **105** (Scheme 22*d*). However, enolization and subsequent C–C bond formation could occur to give carbocyclic products. This intramolecular cyclization would be expected to proceed via the π-complex **104** rather than a bromonium or β-halocarbenium ions, since π-complexes are known species[123,130,131] and they match kinetic models where onium or β-halocarbenium ions species would not.[132] While the approach shown in Scheme 22*d* was an unknown tactic, the exciting possibility of exploring this reaction inspired the examination of the postulate.



Scheme 22. Electrophilic cyclization tactics

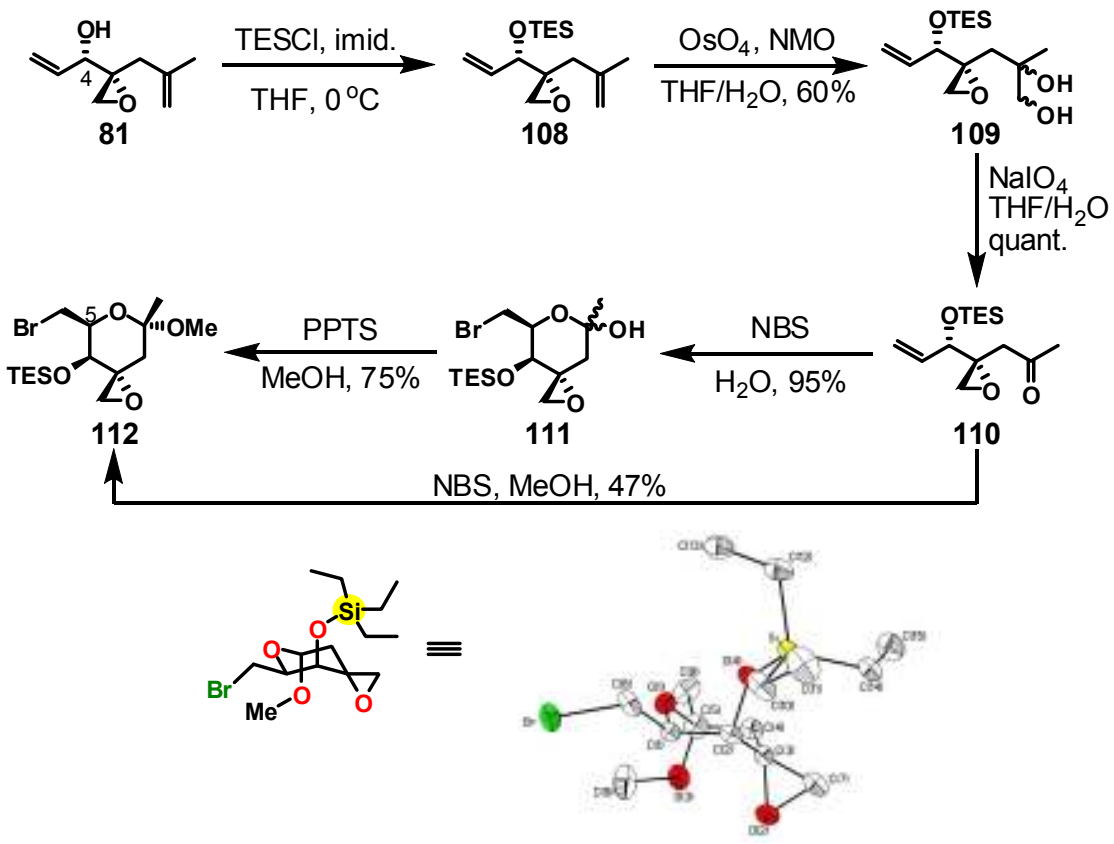
Treatment of enone **85** with NBS in THF/H_2O (8:1) gave **106** as a single diastereomer in 75% yield (Scheme 23). This hemiketal was in equilibrium with its open keto-alcohol conformer and thus, for unambiguous structural determination, methyl glycoside **107** was prepared in 40% yield by treating **106** with PPTS and MeOH. NMR analysis of methyl glycoside **107** revealed the NOE between the -OMe and C5-H, indicating the diaxial relationship. Moreover, the C4–C5 *J*-value was 1.4 Hz, indicating the equatorial placement of the C4-OTES group. Disappointingly, **107** had the incorrect C5-stereochemistry and could not be used in the preparation of **48**.

Treatment of **85** with NBS in the presence of MeOH gave **107** again in 59% yield, thereby supporting the postulate that external nucleophiles could trap putative oxocarbenium ions.[133]



Scheme 23. Preparation of methyl glycoside **107**

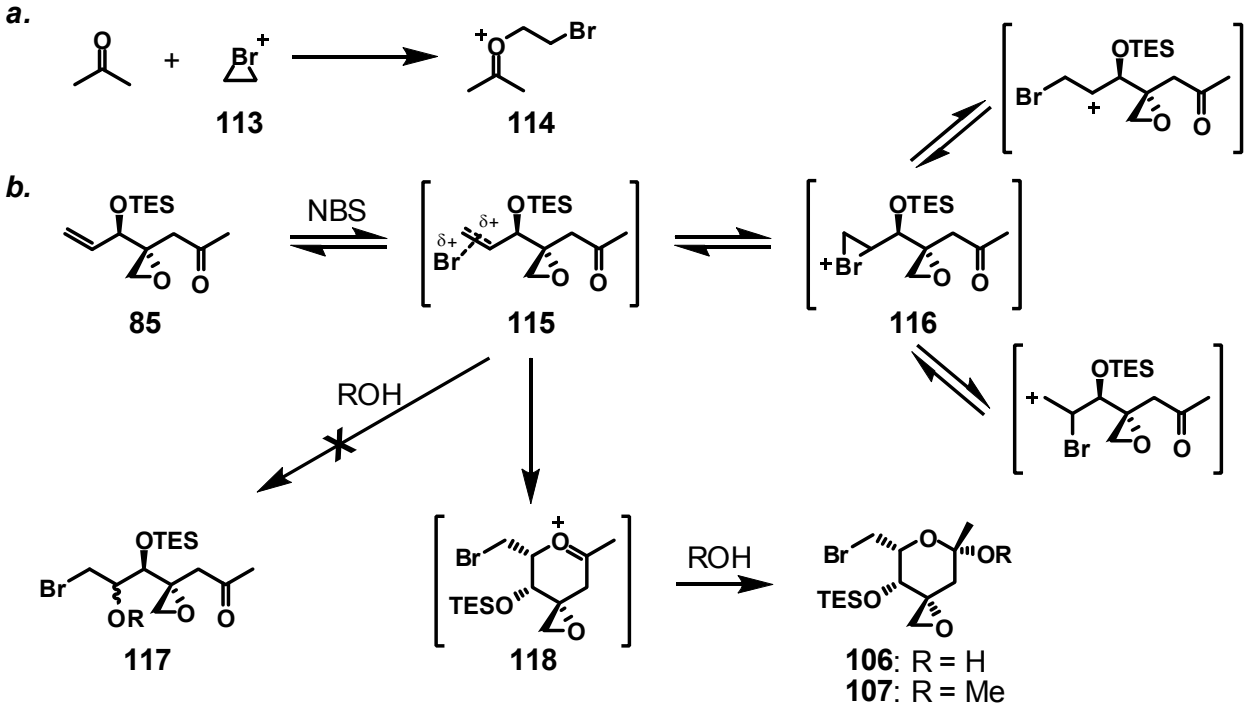
Although the NBS-promoted cyclization of enone **85** gave the incorrect stereochemistry at C5, the efficiency of this reaction was encouraging. It seemed reasonable that switching to its C4-epimer could reverse the observed stereoselectivity in the cyclization. Therefore, enone **110** was prepared as shown in Scheme 24. Exposure of this enone to NBS in acetone/H_2O (8:1) gave **111** as a single diastereomer in 95% yield. Treatment of **111** with PPTS and methanol afforded methyl glycoside **112** in 75% yield. Alternatively, methyl glycoside **112** could be prepared from enone **110** in 47% yield by exposure to NBS in MeOH. The absolute stereochemistry of this material was confirmed by X-ray crystallographic analysis, also revealing the diastereoselectivities for the vinyl and alkynyl additions into epoxyaldehyde **32**.



Scheme 24. Preparation of methyl glycoside **112**

With the successful stereoselective preparations of **106** and **111**, it was not clear whether H_2O attacked a bromide ion-activated alkene **115** to generate bromohydrin **117** (R = H), which could spontaneously cyclize to lactol **106**, or the carbonyl oxygen atom (or its hemiketal) intramolecularly reacted (Scheme 25*b*). In collaboration with Professor Kendall Houk, it was predicted that the reaction of acetone with bromonium ion **113** to **114** is exothermic by 40–50 kcal/mol (quantum mechanical calculations using Gaussian 98 and Gaussian 03 using Hartree-Fock at 3-21G level of theory with B3LYP functional & 6-31G basis sets; Scheme 25*a*). Although these numbers should be taken with caution, as they are unrefined and neglect the bromine counterion, they illustrate the distinct driving force for the intramolecular reaction. It was also observed that the reactions of **85** and **110** in the presence of methanol did not show any

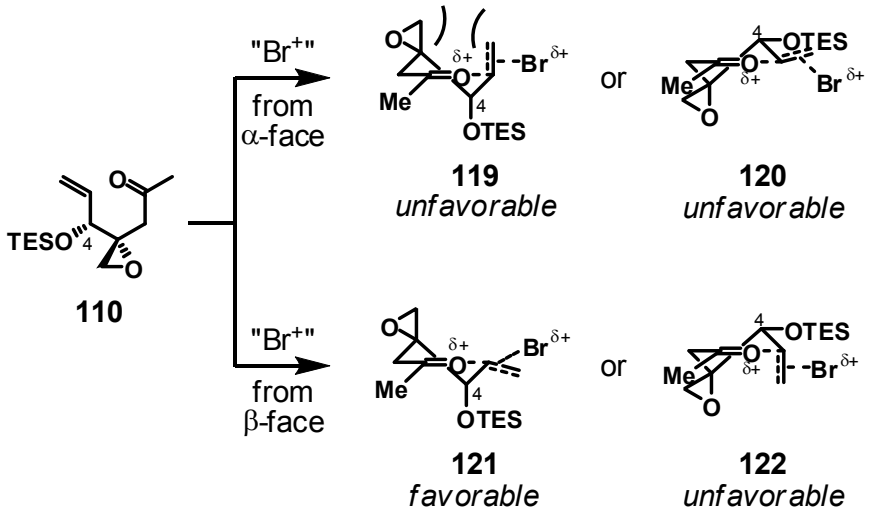
generation of methyl ethers **117** by analysis of the crude reaction mixture. Therefore, treatment of enone **85** with NBS should rapidly generate oxocarbenium ion **118** that can react with MeOH to give glycoside **107**.[133]



Scheme 25. Explanation for the observed reactions of **85**

To explain the high stereoselectivity for these cyclization reactions, all four possible half-chair transition states were analyzed (Scheme 26). Approach of the electrophilic bromide from the α-face of the C5–C6 alkene of **110** would give rise to the π-complexes **119** and **120**.[123,134] Half-chair **119** is destabilized by the pseudo-1,3-diaxial interaction of the spiroepoxide and the forming C6-methylene bromide. Transition state **120** places σ^*_{C4-O} nearly parallel to π_{C5-C6}, suffering from the inside alkoxy effect,[135] and additionally may suffer steric repulsion from the bulky -OTES and forming C6-methylene bromide. Approach of the electrophilic bromide from

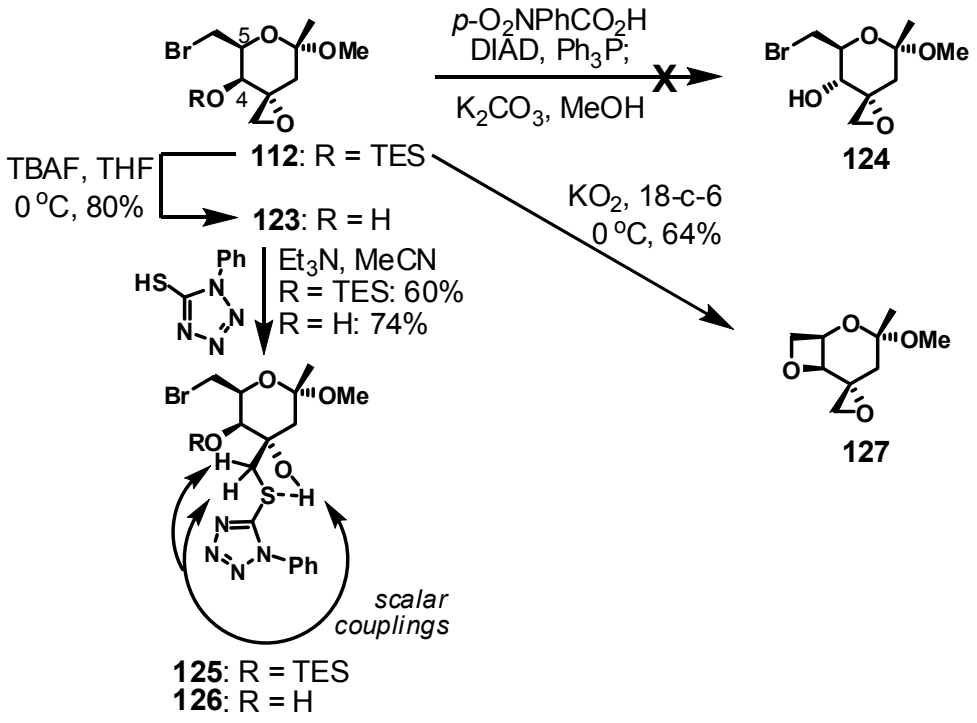
the β-face of the C5–C6 alkene would give rise to the π-complexes **121** and **122**. Transition state **121** is electronically preferred stereoelectronically and sterically. Half-chair **122** places its σ^*_{C4-O} nearly parallel to π_{C5-C6}, destabilized by the inside alkoxy effect. Thus, transition state **121** is the most favorable, and is thought to lead to the experimentally observed products **111** and **112**.[133]



Scheme 26. Model to explain the observed stereoselectivity for the cyclizations of **110**

With a method to prepare **112** containing the entire carbon skeleton of sulfone **48** in hand, further functionalizations towards **48** were examined. The first task was the installation of the C6-thioether (Scheme 27). Treatment of methyl glycoside **112** with 1-phenyl-1*H*-tetrazole-5-thiol gave epoxide-opened product **125** in 60% yield. Moreover, addition of NaI or use of Cs_2CO_3 as the base gave similar results. To examine whether the bulky, axial C4-OTES group was blocking the C6 position from S_N2 attack, **112** was deprotected by the action of TBAF to give **123** in 80% yield. Treatment of this material to 1-phenyl-1*H*-tetrazole-5-thiol and Et_3N gave epoxide-opened product **126** in 74% yield. Since thiolate anions preferentially react with the spiroepoxide rather than the methylene bromide, conversion of the methylene bromide to a

hydroxy group could allow for a mild Mitsunobu reaction to introduce the thioether. Towards this end, treatment of **112** with KO_2 and 18-crown-6 gave oxetane **127** in 64% yield with no evidence of desired product formation. With no success in the preparation of a C6-thioether, a Mitsunobu reaction of **123** was attempted to invert the C4-hydroxy group using *p*-nitrobenzoic acid as the nucleophile. After methanolysis, alcohol **123** was observed, not **124**, presumably due to the crowded steric environment.[136] Due to the difficulty in inverting the C4-hydroxy group and the sensitivity of the spiroepoxide towards thiols, the Julia-olefination synthetic strategy was abandoned.

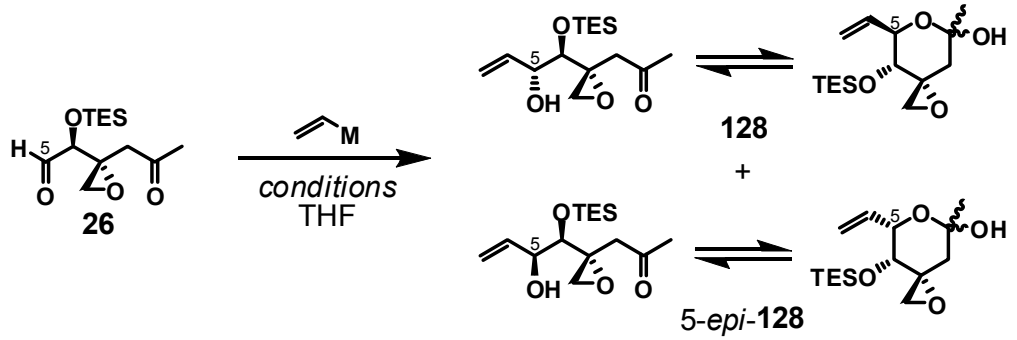


Scheme 27. Unsuccessful preparations of a B-ring sulfone coupling partner

1.6.5 Forward synthesis of the third retrosynthetic analysis

To pursue the cross-olefin metathesis strategy, the remaining task was to prepare a right fragment. With ketoaldehyde **26** in hand, a direct approach would be a chemoselective vinyl addition to this ketoaldehyde to afford a coupling partner (Table 7). Treatment of fragile **26** with vinylmagnesium bromide gave an inseparable mixture of **128** and 5-*epi*-**128** in 40% yield with no diastereoselectivity (entry 1). Addition of HMPA or TMEDA slightly improved the desired Felkin selectivity and overall yield of **128** (entries 2 and 3). In situ generation of vinyllithium from vinyltributyltin and ^{n}BuLi, and subsequent addition of **26** gave **128** and 5-*epi*-**128** in 33% yield with no diastereoselectivity (entry 4). Addition of HMPA gave these alcohols in better diastereoselectivity (dr = 2:1) but in only 16% yield (entry 5). Neither switching the solvent to CH_2Cl_2 or toluene, nor preparing the organocerium reagent from $CeCl_3$ improved this difficult transformation (not shown).[137,138] Moreover, alkynyl additions to ketoaldehyde **26** required higher temperatures (≥ −20 °C). However, enough materials were synthesized to examine the viability of the coupling strategy.[102]

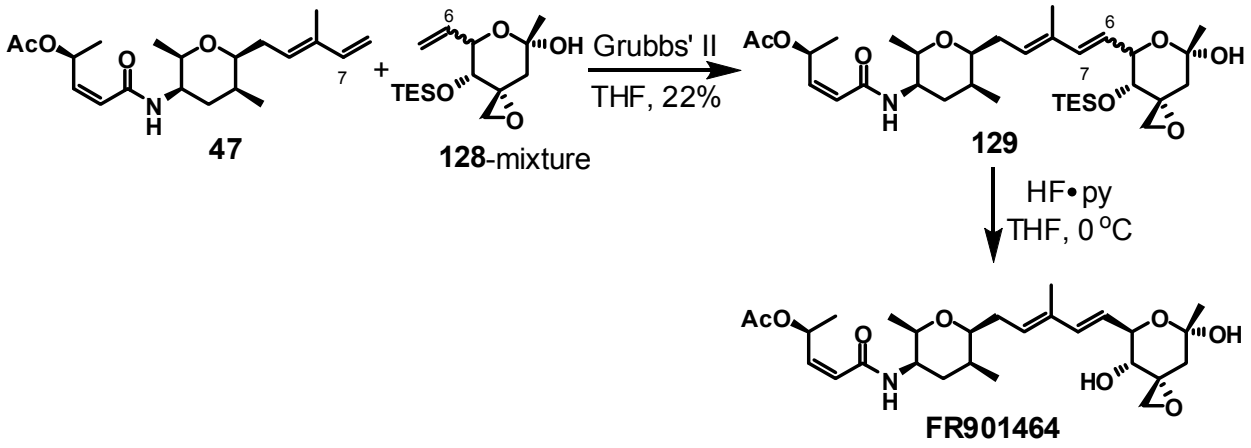
Table 7. Preparation of right fragment coupling partners **128** and 5-*epi*-**128**



entry	M (2 equiv)	additive(s) (equiv)	yield (%)[a]	**128**:5-*epi*-**128**[b]
1	-MgBr	---	40	1.0:1
2	-MgBr	HMPA (2.5)	46	1.3:1
3	-MgBr	TMEDA (2.5)	31	2.0:1
4	-Li[c]	---	33	1.0:1
5	-Li[c]	HMPA (2.5)	16	2.0:1

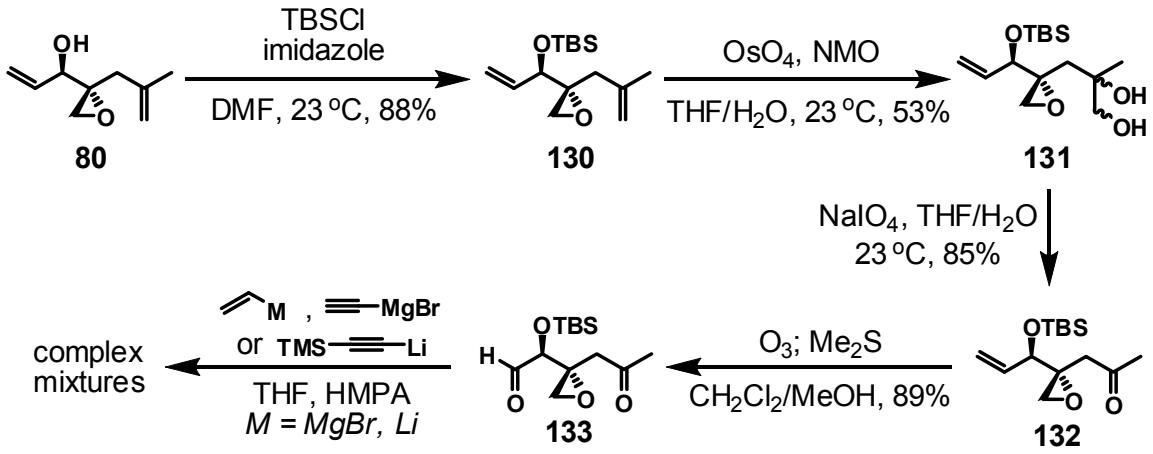
[a] Combined yield; [b] Determined by ^{1}H NMR analysis;
[c] Prepared from CH_2=$CHSnBu_3$ and ^{n}BuLi

With fully functionalized coupling fragments **47** and **128** in hand, the stage was set to test the cross-olefin metathesis coupling strategy. Treatment of **47** and the C6-epimeric mixture **128**-mixture gave inseparable metathesis adducts **129** in 22% yield (Scheme 28). Subsequent removal of the TES ethers of **129** was accomplished by the action of HF•py to furnish FR901464 and presumably its C5 epimer. The successful preparation of FR901464 was confirmed by HPLC analysis using an authentic sample of FR901464 showing the viability of this coupling strategy! However, it was clear that a method to prepare a diastereomerically pure right fragment was of paramount importance to avoid wasting precious materials and tedious purification.



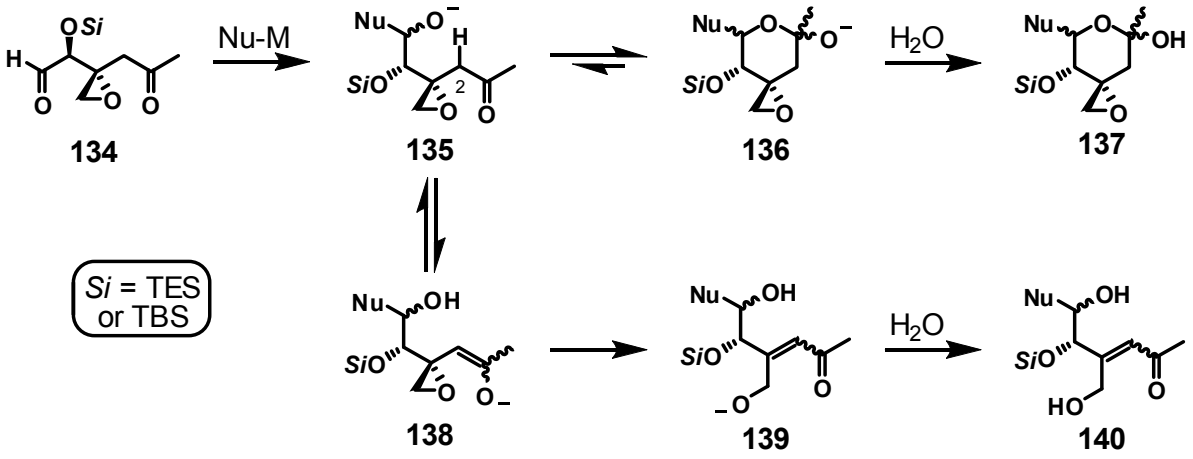
Scheme 28. First synthesis of FR901464 in the Koide group

In order to prepare a right fragment more efficiently, formation of the C5 stereocenter required much to be improvement. The use of a TBS ether rather than the TES ether could favor Felkin addition to ketoaldehyde **133** by suppressing α-alkoxy group chelation. Towards this end, **130** was prepared in 88% yield from allylic alcohol **80** by the action of TBSCl/imidazole (Scheme 29). Regioselective oxidative cleavage of the 1,1-disubstituted alkene of **130** was accomplished in 45% yield over the two steps to give enone **132** via diol **131**. This enone was subjected to ozonolysis conditions and subsequent reductive workup afforded **133** in 89% yield. Disappointingly, subjection of this ketoaldehyde to vinyl or alkynyl additions only gave complex mixtures, apparently due to poor chemoselectivity of the aldehyde and ketone.



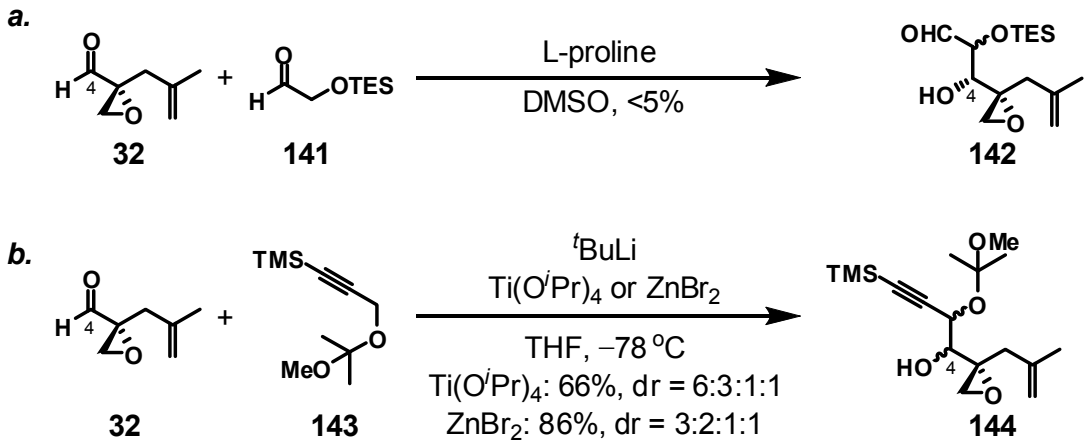
Scheme 29. Preparation and use of ketoaldehyde **133**

To explain the poor yields for the additions to ketoaldehydes **26** and **133** and their temperature sensitivity during these reactions, the following mechanism is proposed (Scheme 30). After chemoselective addition to the aldehyde of **134**, alkoxide **135** will be formed. This alkoxide will presumably be in equilibrium with hemiketal alkoxide **136** which could protect it from further reactions to give **137** upon aqueous workup. However, alkoxide **135** could also reversibly deprotonate the C2 position thereby giving enolate **138**. This enolate would be expected to undergo facile β-elimination affording enones **139** irreversibly and **140** upon aqueous workup. From the experimental results, C2-deprotonation presumably occurs rapidly at ≥ –20 °C explaining why alkynyl addition reactions afforded no desired products and the low yields for the alkenyl addition reactions.



Scheme 30. Proposed explanation for the low yielding additions to **26** and **133**

Because of the poor selectivity and yields for additions to ketoaldehydes, other methods were explored to develop a functionalized right fragment to use for the cross metathesis strategy. Several methods to simultaneously install the C4 and C5 stereoecenters were explored. The first method employed, developed by MacMillan, involved the use L-proline to mediate an aldol reaction of epoxyaldehyde **32** and **141** (Scheme 31*a*).[139] However, aldol adduct **142** was obtained in only <5% yield as a C5-epimeric mixture, implying that the equilibrium lies strongly towards the starting materials. Since reagent control was unsuccessful in installing the C4 and C5 stereocenters silmultaneously, substrate control was revisited. Propargyl addition reactions have been shown to be highly *anti*-selective and would contain all of the requisite carbons for **128**.[140,141] The in situ formation of the allenyl-titatinium or zinc reagents and subsequent addition of epoxyaldehyde **32** afforded **144** in 66% and 86% yields and in 6:3:1:1 and 3:2:1:1 dr, respectively (Scheme 31*b*). Because of the low observed diastereoselectivities and the difficult task of proving the configuration of the diastereomers, this transformation was deemed not worthy of further investigation.



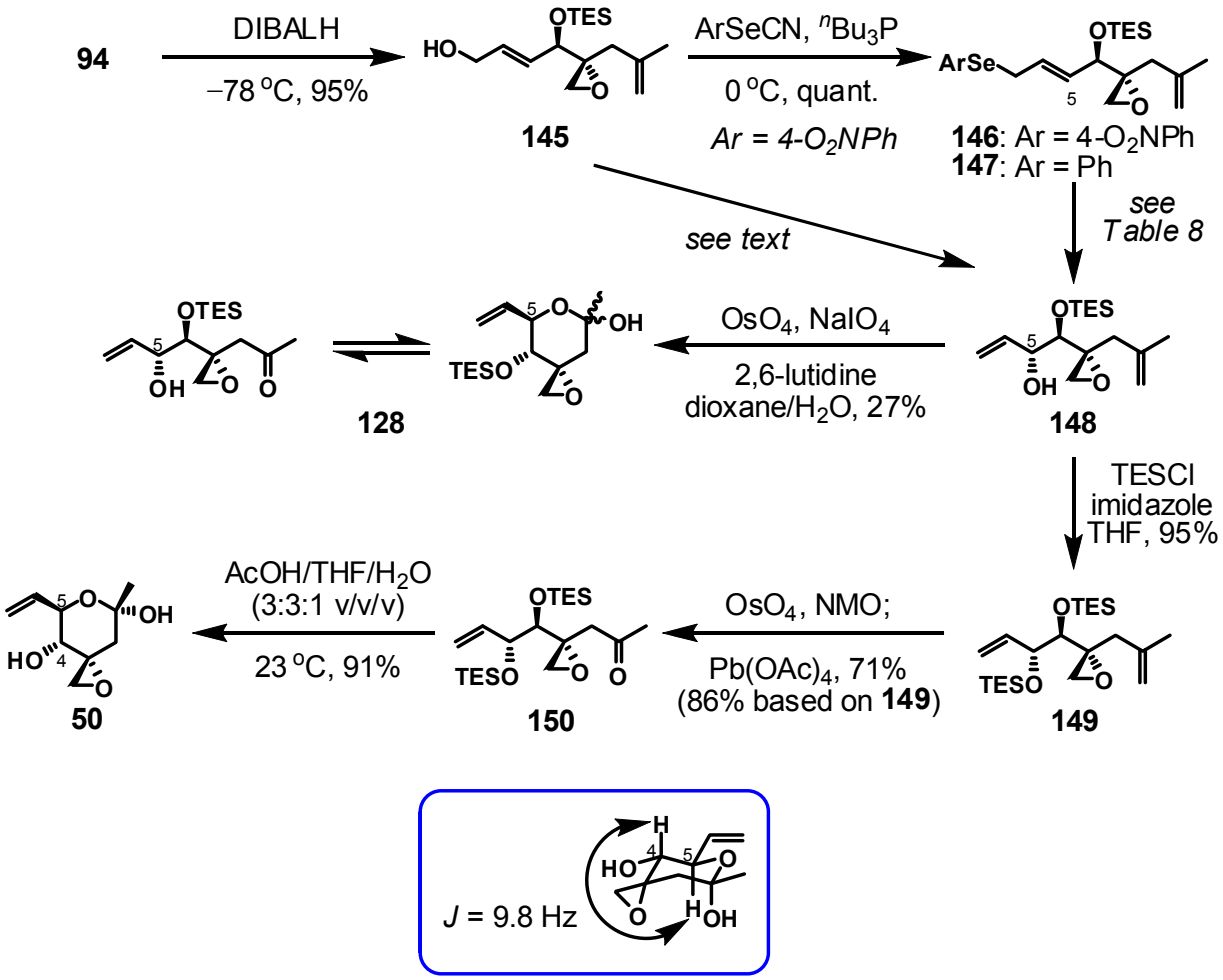
Scheme 31. Methods to introduce the C4 and C5 stereocenters simultaneously

Since the introduction of the C4 and C5 stereocenters could not be accomplished in high selectivity, previously prepared enoate **94** was revisited. Treatment of this enoate with 3.0 equiv of DIBALH in THF gave alcohol **145** in 95% yield (Scheme 32). The use of CH_2Cl_2 also gave **145** but generated many products. At this point, both an asymmetric Sharpless epoxidation and a [2,3]-Mislow-Evans-like rearrangement strategy were envisaged to introduce the C5-stereocenter. Despite no reported diastereoselective [2,3]-sigmatropic rearrangements using primary allylic alcohols, this strategy made for a bold approach but with potentially high payoff. With this in mind, selenide **146** was prepared in quantitative yield from alcohol **145**. With little optimization of this [2,3]-sigmatropic rearrangement strategy for linear systems, this reaction was investigated thoroughly. Utilizing typical conditions, H_2O_2 and py, alcohols **148** and 5-*epi*-**148** were produced in a combined 94% yield and a 4.0:1 dr repectively (entry 1, Table 8). Since sulfoxides and their sulfenates in the Mislow-Evans reaction have been modeled to have hydrogen bonding capabilities in their transitions states,[142] it is possible that a protic solvent could enhance the substrate control. Performing this reaction in EtOH gave **148** and its C5-epimer in 87% combined yield in an unimproved 4.0:1 dr (entry 2). Similarly, the reaction in

acetone gave **148** and its C5-epimer in 96% combined yield but now in a 3.5:1 dr (entry 3), and in CH_2Cl_2 **148** and 5-*epi*-**148** were obtained in a 67% combined yield and a 3.5:1 dr (entry 4). Therefore, the only solvent effect observed was for the rate of the reaction and not the stereoselectivity; thus, the base employed in the reaction was examined.

A bulkier base, 2,6-lutidine, was employed in this reaction and gave **148** and its C5-epimer in a combined 73% yield and a 4.0:1 dr (entry 5). More nucleophilic bases such as DMAP and 4-pyrrolidinopyridine generated alcohol **148** and 5-*epi*-**148** in a combined yield of 95 and 84% yields and a 7.5:1 and 8.1:1 dr, respectively (entries 6 and 7). To test if these results were due to the strength of the bases employed, Et_3N was utilized in the reaction and gave **148** and 5-*epi*-**148** in 80% combined yield and a 3.7:1 dr (entry 8). Thus, the nucleophilicity of the base employed appears to be the cause of the increased observed diastereoselectivity, with the slightly more nucleophilic base, 4-pyrrolodinopyridine, giving the highest diastereoselectivity. The amount of the more economical base, DMAP, was then optimized. Decreasing the amount of DMAP below 3.0 equiv proved to be detrimental to the stereoselectivity with 3.0, 1.5, and 0.5 equiv of DMAP giving diastereomeric ratios of 7.8:1, 5.3:1, and 3.3:1, respectively (entries 9, 10, and 11). Therefore, the amount of DMAP necessary for this reaction should be at least 3 equivalents. Finally, to examine if the nitro-group on the phenyl ring had any role in the stereoselectivity of this reaction, phenyl selenide **147** was prepared, and subsequently used in this reaction to produce **148** and 5-*epi*-**148** in 91% combined yield and a 7.0:1 dr (entry 12). Therefore, the nitro group has no major role in this reaction, other than suppressing the volatility of toxic selenium byproducts. It was later shown that alcohol **145** could be converted to **148** in one pot using the same strategy and 4.0 equiv of DMAP in the oxidation step to give **148** and 5-*epi*-**148** in a combined 91% yield and a 7.0:1 dr.

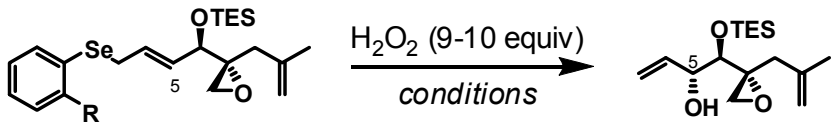
Alcohol **148** was then subjected to oxidative cleavage conditions that gave desired enone **128** in 27% yield, but lacked regioselectivity. Therefore, **148** was protected as its bis-TES ether **149** in 95% yield to crowd the steric environment around the monosubstituted alkene. Subjection of this material to dihydroxylation conditions and subsequent oxidative cleavage conditions gave enone **150** in 71% yield (86% based on recovered **149**). It should be mentioned that the oxidative cleavage of the putative diol was accomplished with $NaIO_4$ as well, but in only 39% yield (86% based on recovered **149**), presumably due to the poor water solubility of the bis-TES protected diol. Alkene **150** was found to be unreactive under the cross metathesis conditions with **47**, and



Scheme 32. Preparation of **50**

therefore global deprotection was accomplished using 3:3:1 AcOH/THF/H_2O to give **50** in 91% yield. More commonly employed reagents such as HF•py and TBAF/AcOH gave **50** in 43 and 31% yields, respectively. These low yields were partly due to the water solubility of **50** as well as its acid and base lability (see below). Therefore, the synthesis of fully-functionalized B-ring fragment **50** was accomplished in 11 linear steps, but the viability of this material towards the cross metathesis coupling strategy was unknown.

Table 8. Optimization of the [2,3]-sigmatropic rearrangement strategy



146: R = NO_2
145: R = H

148

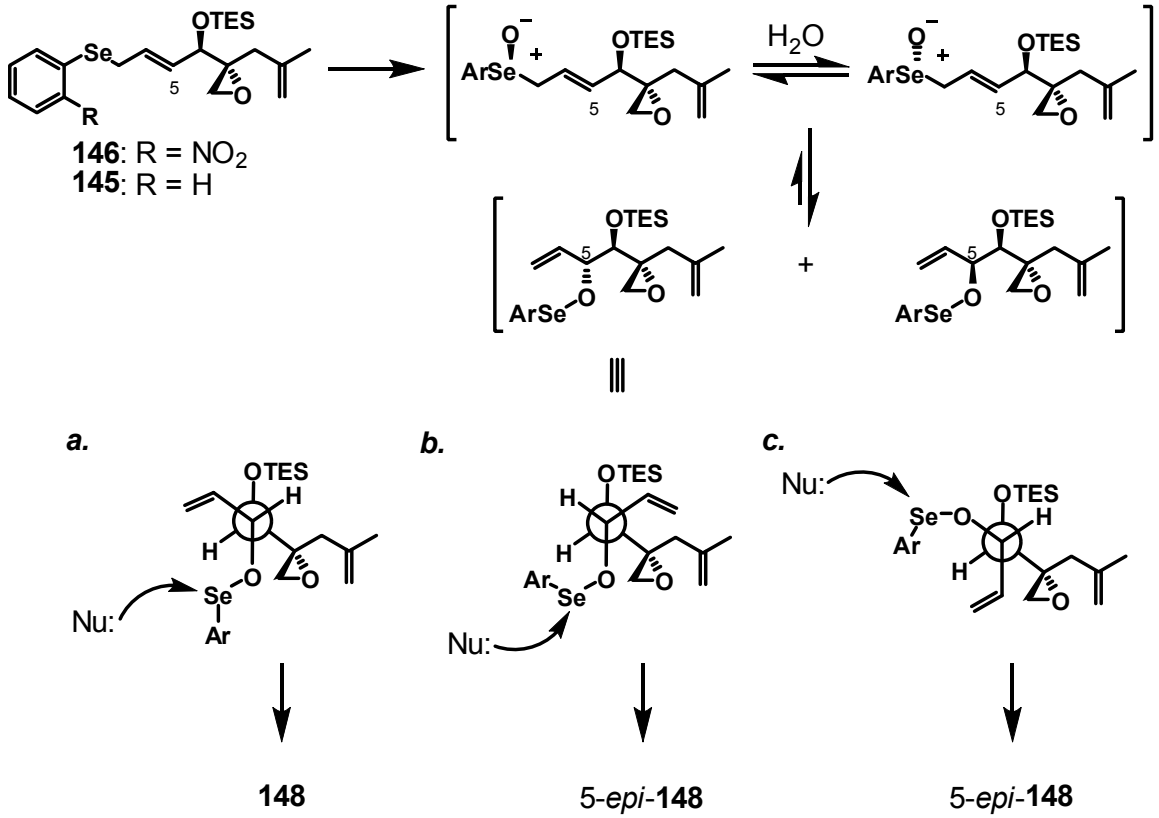
entry	R	base (equiv)	solvent	temp (^oC)	yield (%)[a]	dr
1	NO_2	py (5)	THF	–20	94	4.0:1
2	NO_2	py (5)	EtOH	–44 to –20	87	4.0:1
3	NO_2	py (5)	acetone	–20	96	3.5:1
4	NO_2	py (5)	CH_2Cl_2	0 to 20	67	3.5:1
5	NO_2	2,6-lutidine (5)	THF	–44 to 23	73	4.0:1
6	NO_2	DMAP (5)	THF	–44 to 23	95	7.5:1
7	NO_2	4-pyrrolidino-py (5)	THF	–44 to 23	84	8.1:1
8	NO_2	Et_3N (5)	THF	–44 to 23	80	3.7:1
9	NO_2	DMAP (3)	THF	–44 to 23	80	7.8:1
10	NO_2	DMAP (1.5)	THF	–44 to 23	87	5.3:1
11	NO_2	DMAP (0.5)	THF	–44 to 23	34	3.3:1
12	H	DMAP (5)	THF	–44 to 23	91	7.0:1

[a] Combined yield. [b] Determined by ^1H NMR analysis.

To explain the high diastereoselectivity for the formation of **148** over its C5-epimer six Newman projections of the putative selenates were analyzed. Oxidation of selenide **146** or **145** would give a mixture of water sensitive epimeric selenoxides.[143] These selenoxides are in equilibrium with their epimeric selenates intermediates.[143] The cleavage of the Se–O bond is rate determining in this reaction, and thus, the preceding reversible sigmatropic rearrangements and the epimerizable selenoxide stereochemistry will not be discussed.[143] Of the six possible rotamers, three were easily omitted and thus not shown. Of the remaining three, the selenate shown in Scheme 33*a* sterically is accessible for the attack of a nucleophile on the selenium atom, explaining the formation of **148**. The selenates shown in Scheme 33*b* and *c* give rise to 5-*epi*-**148** upon cleavage of the Se–O bond. The one shown in 33*b* should be destabilized by gauche interactions, but it places its oxygen atoms *anti* to each other that could stabilize the forming negative charge after Se–O bond cleavage. Finally, there are less severe gauche interactions in the selenate shown in 33*c* than in 33*b*, and the selenate sterically more accessible towards nucleophiles. A more nucleophilic base, such as DMAP, would lower the transition state energy to break the Se–O bond. The selenate shown in *a* would electronically be favored over *c* which could explain the higher observed diastereoselectivity observed under the reaction conditions that utilize more nucleophilic bases.

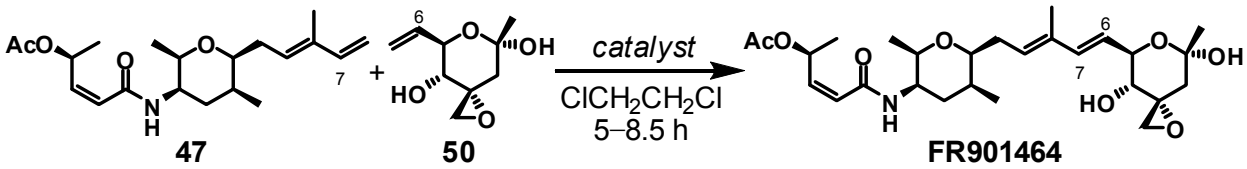
With two fully functionalized fragments, the metathesis was again examined. Treatment of diene **47** with a slight excess of more reactive **50** with Grubbs' II gave FR901464 in 12% yield (Table 9). The use of the Hoveyda catalyst gave FR901464 in 13% yield. However, the use of the Grela catalyst was much more efficient, affording FR901464 in 28% yield and after one recycling of starting materials gave this natural product in a combined 40% yield with only the E-C5–C6 isomer formed. This was a remarkable result since **50** was shown to form an unreactive

homodimer by its preparation and subjection to the metathesis conditions. Moreover, B-ring fragment **50** was shown to decompose in 1,2-dichloroethane at ≥47 °C, thereby limiting the temperature for the metathesis reaction. This completed the total synthesis of FR901464 in a total of 28 steps and 13 steps in the longest linear sequence. Thus, this represents the most concise synthesis to date by a total of nine steps, thereby accomplishing a goal of this work.[62]



Scheme 33. Selenate rotamers leading to **148** and 5-*epi*-**148**

Table 9. Optimization of the preparation of FR901464



catalyst	temperature	yield (%)
Grubbs' II	42	12
Hoveyda	42	13
Grela	23	28 (40)[a]

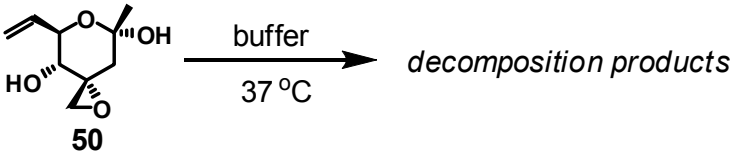
[a] Yield after one recycling of recovered starting materials

1.7 CHEMICAL REACTIVITY OF FR901464 AND THE DEVELOPMENT OF MEAYAMYCIN

1.7.1 Discovery of the source of the instability of FR901464

The instability of FR901464 towards weak acids and bases in organic solvents was previously studied, which prompted the study of FR901464 under aqueous conditions. The total synthesis of FR901464 gave insight into the reactive moieties of this natural product, with the right fragment being the most chemically reactive fragment. Therefore, the decomposition of fully functionalized B-ring fragment **50** was studied in aqueous phosphate buffers at 37 °C to mimic more biologically relevant conditions (Table 10). The half-life of **50** in pH 6 buffer was estimated to be 12 h. In pH 7 buffer, the half-life of **50** was 8 h, and in pH 7.4 buffer, the half-life was estimated to be only 4 h.

Table 10. Instability of **50** at different pH values in aqueous buffers

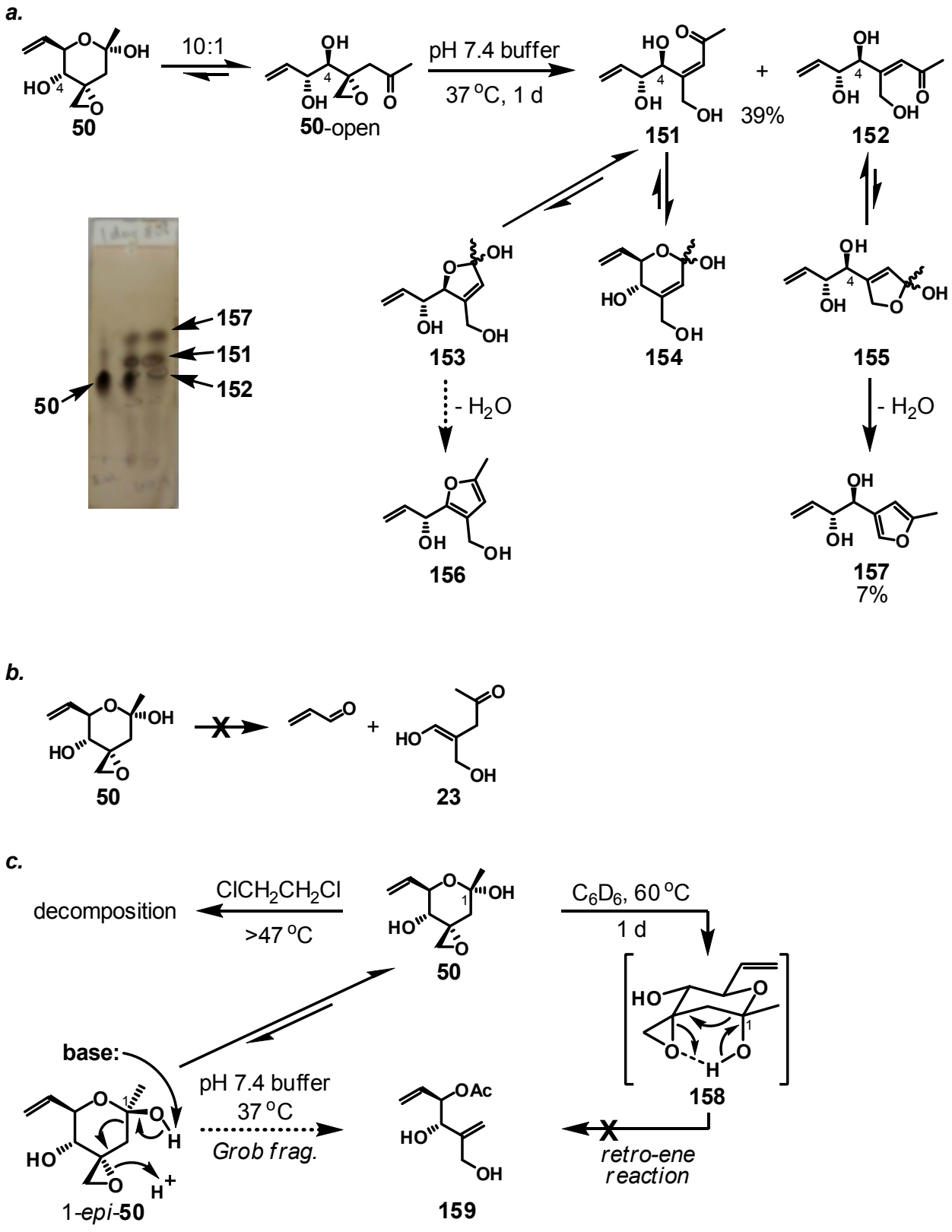


50

pH	$t_{1/2}$ (h)[a]
6	12
7	8
7.4	4

[a] Estimated by TLC analysis

As a consequence of the instability of **50** in buffers, this decomposition was further investigated mechanistically. Subjection of **50** to pH 7.4 buffer at 37 °C for 1 d produced ≥3 products, as judged by TLC analysis. Purification and analysis of the major products formed in the decomposition of **50** in pH 7.4 buffer revealed the formation of **151**, **152**, and furan **157** (Scheme 34*a*). Hemiketal **50** was observed to exist as its linear ketoalcohol form, **50**-open, in CD_2Cl_2 or D_2O in a 10:1 ratio in accordance with Jacobsen's observation.[56] Therefore, **50**-open could enolize and rapidly undergo β-elimination opening of the epoxide to form enones **151** and **152** that were obtained in 39% combined yield. The E-enone could exist in equilibrium with its 5-membered ring hemiketal **155**, which could undergo dehydration to give furan **157** in 7% yield. Alternatively, Z-enone **151** could exist as its five and six-membered ring hemiketals **153** and **154**, respectively, but of the three compounds, **153** should be thermodynamically disfavored due to its ring strain. Therefore, furan **156** is not observed over the time course studied. In postulating the other pathways, Kitahara's mechanism that would produce **23** and acrolein (Scheme 34*b*),[64] and a Grob or retro-ene reaction would form acetate **159** (Scheme 34*c*).[144,145] Acrolein was carefully searched for by NMR and HPLC, but not even trace amounts were



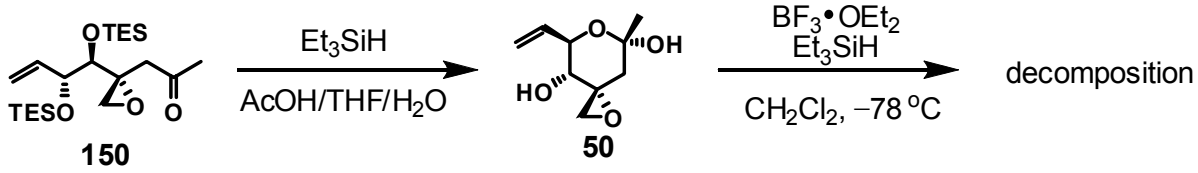
Scheme 34. Decomposition pathways of **50**

observed, and therefore, Kitahara's decomposition pathway appears not to be relevant in aqueous conditions. However, a remote possibility it that acrolein could possibly evaporate before detection. A retro-ene pathway was considered plausible due to the instability of **50** in $ClCH_2CH_2Cl$ ≥47 °C, but heating of this compound at 60 °C in C_6D_6 for 1 d gave only minor decomposition products (Scheme 34*c*). With no significant quantity of **159** generated via **158** in C_6D_6, a retro-ene pathway is unlikely, and the decomposition observed in $ClCH_2CH_2Cl$ could be attributed to trace amounts of HCl. Acetate **159** was possibly observed by crude ^{1}H NMR, specifically looking for the methyl group of the acetate moiety around 2 ppm. However, with the complex equilibria of enones **151** and **159** and the amount of products observed in the crude ^{1}H NMR, this was clearly insuffient evidence. Since no chromophore exists in **159**, HPLC analysis was of little help in proving the formation of this acetate. However, an IR spectra of the crude mixture showed a stretch around 1735 cm^{-1}, indicative of an ester, presumably **159**. Although, this acetate was not obtained in pure form, and thus its formation is only speculated upon. This study revealed that the opening of the hemiketal moiety in **50** leads to the major decomposition products, and preventing this opening could vastly improve the stability of the right fragment of FR901464.[102] With is poor stability in buffers, FR901464 could be of little use as a biological probe or of therapeutic potential.

1.7.2 Preparation of a more stable B-ring fragment

As previsouly demonstrated by the Jacobsen and Kitahara groups, locking the right fragment of FR901464 in its closed form should prevent the major decomposition pathway, namely the enolization-β-elimination predicament. Initial efforts were focused on reducing the C1-position under acidic conditions. Addition of excess Et_3SiH to **150** in 2.5:2.5:1 AcOH/THF/H_2O was

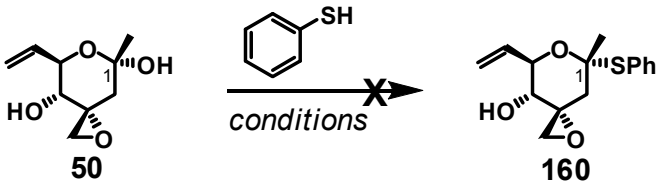
attempted in the hopes of silyl ether removal and concomitant reduction of the C1 hemiketal, but only silyl ether hydrolysis was realized, affording **50** in 53% yield (Scheme 35). More acidic conditions were employed and **50** was treated with excess Et_3SiH and BF_3•OEt_2 at −78 °C which resulted in decomposition. Therefore, reduction of the C1 position was deemed too difficult due to the lack of success of these experiments.



Scheme 35. Attempted reductions of **50** and **150**

With no success towards the reduction of C1, the preparation of a C1-thioglycoside could prove of utility without further functionalizations or allow for reduction of C1. Towards this end, the subjection of **50** to thiophenol under various acidic conditions was examined (Table 11). Treatment of **50** with 2.0 equiv of thiophenol in 3:3:1 AcOH/THF/H_2O gave loss of the epoxide (entry 1). Therefore, stronger acids were utilized in the absence of competing nucleophiles. Treatment of **50** with thiophenol and a catalytic amount of PPTS in CH_2Cl_2 gave similar results (entry 2). The use of chloroacetic acid or CSA gave decomposition products with loss of the epoxide and no formation of **160** (entries 3 and 4). Therefore, functionalization at C1 from a hemiketal appears to be limited to oxygen nucleophiles, with thiols and hydride sources not producing the desired adducts.

Table 11. Failed thioglycoside formations



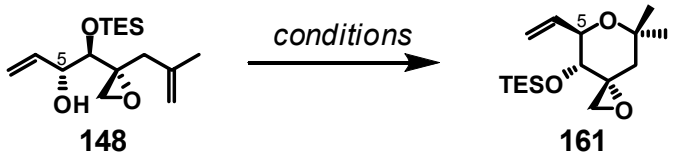
50 **160**

entry	equiv thiophenol	acid (equiv)	solvent	temp (°C)	result
1	2.0	AcOH[a]	THF/H_2O[a]	23	epoxide loss
2	1.4	PPTS (0.10)	CH_2Cl_2	23	epoxide loss
3	1.7	$ClCH_2CO_2H$ (0.10)	CH_2Cl_2	0	epoxide loss
4	2.0	CSA (0.10)	CH_2Cl_2	0	epoxide loss

[a] AcOH/THF/H_2O 3:3:1 v/v/v solvent system employed

With no success in adding a hydride or thiol to the C1 position of **50**, incorporation of a methyl group at C1 was also envisioned to avoid the sensitive hemiketal moiety. A methyl analog should also be more stable than Kitahara's methyl glycoside and would be similar in size to the hydroxy group of FR901464, whereas Jacobsen's analog **19** is not.[56,64] Therefore, 1,1-dimethyl right fragment analog **161** was seemingly readily accessible from previously prepared diene **148** via its putative tertiary carbocation under acidic conditions (Table 12). However, treatment of **148** with a catalytic amount of PPTS gave no reaction (entry 1). CSA caused decomposition (entry 2). Treatment of **148** with Amberlyst® 15 acidic resin gave no reaction (entry 3). Therefore, protic catalysts were abandoned and Lewis acidic catalysts were examined. Using a catalytic amount of AgOTf gave decomposition when heated to 80 °C (entry 4).[146] Moreover, Widenhoefer's conditions utilizing a platinum catalyst gave no formation of **161**.[147] While tetrachloroethane was not employed as the solvent, Cl_3CCH_3, dioxane (also used successfully by Widenhoefer), benzene and chlorobenzene were all ineffective solvents.

Table 12. Failed etherification reactions of **148**

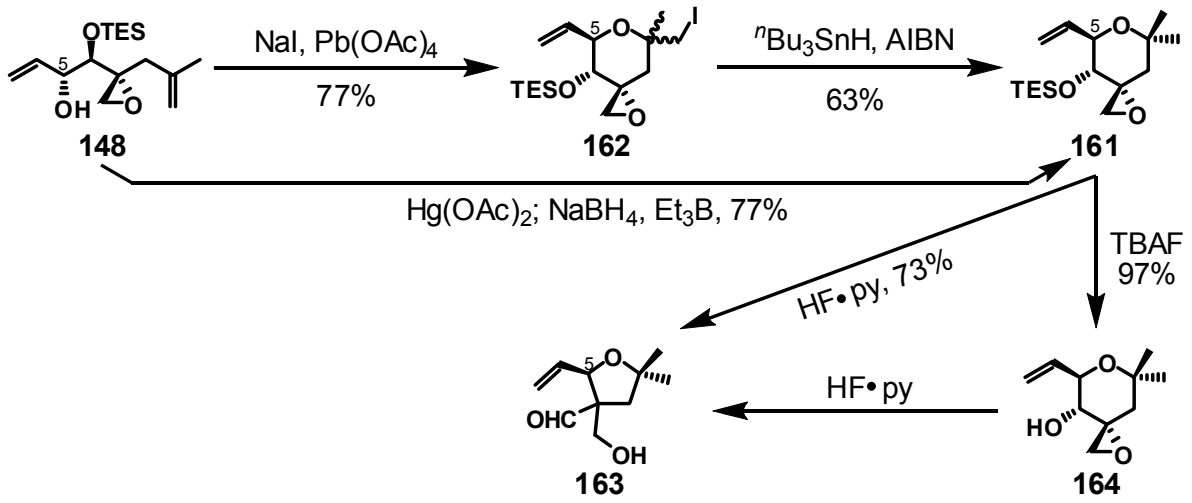


148 **161**

entry	conditions (equiv)	solvent	temp (°C)	result[a]
1	PPTS (0.10)	Et_2O	23	no reaction
2	CSA (0.10)	CH_2Cl_2	23	decomposition
3	Amberlyst 15	$CHCl_3$	−28 to 23	no reaction
4	AgOTf (0.10)	$ClCH_2CH_2Cl$	23 to 80	decomposition
5	$Pt_2Cl_2(CH_2{=}CH_2)_2$ (0.02) (p-$CF_3Ph)_3P$ (0.04)	benzene[b]	75	<5%

[a] Determined by ^1H NMR and or TLC. [b] Cl_3CCH_3, dioxane, and PhCl were ineffective solvents in promoting this reaction.

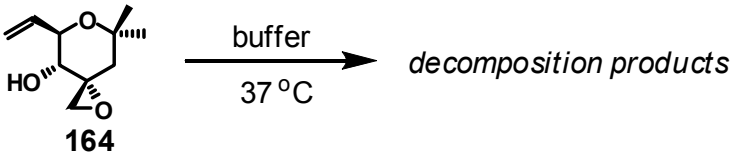
Typical iodoetherification conditions with NIS provided **162** in 27% yield with the major product being a tetrahydrofuran derivative with loss of the C4-OTES group, but the use of NaI and $Pb(OAc)_4$ gave **162** in a much improved yield of 77% (Scheme 36).[148] Radical-promoted deiodination of **162** afforded tetrahydropyran **161** in 63% yield. Alternatively, treatment of **148** with $Hg(OAc)_2$ and subsequent reduction with $NaBH_4$ and Et_3B gave desired **161** in 77% yield.[149] Deprotection of **161** was accomplished with HF•py, but unexpectedly gave pinacol-like rearranged product **163**. Fortunately, treatment of **161** with TBAF cleanly produced desired **164** in 97% yield. Subjection of this material to HF•py again generated ring-contracted aldehyde **163**, implicating the possible acid lability of **164**.



Scheme 36. Preparation of **164**

With a right fragment in hand that should prevent the major decomposition pathway, the stability was tested in aqueous conditions (Table 13). The potential acid-lability was realized during the preparation of **164**, and therefore this material was exposed to 0.1 N H_2SO_4 at 37 °C it had a half-life of 3.5 h, but yielded no ring-contracted aldehyde **163**. The half-lives of **164** at pH 3 and 4 were determined to be 24 and 40 h, repectively. Moreover, the pH 5 and 6 half-lives were determined to be 48 and 40 h, respectively. Finally, at pH 7 and 7.4 the half-lives of **164** were found to be approximately 48 h. Therefore, the stability of **164** was much better than that of **50**, approximately 10-fold higher at pH 7 and 7.4 in aqueous buffers. With this improved stability, the next conquest undertaken was the preparation of an FR901464 analog with this right fragment.

Table 13. Instability of **164** at different pH values in aqueous buffers



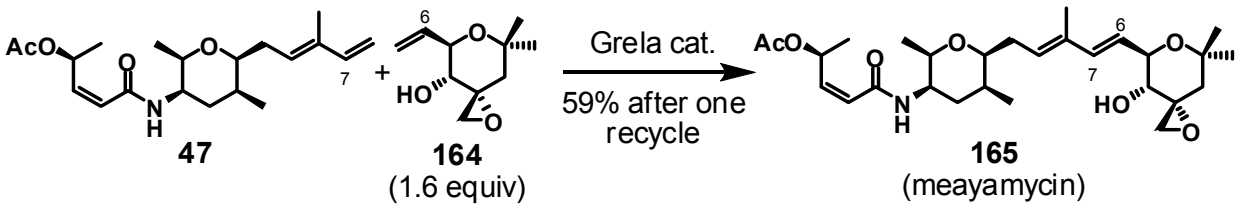
164

pH	$t_{1/2}$ (h)[a]
0.1 N H_2SO_4	3.5
3	24
4	40
5	48
6	40
7	48
7.4	48

[a] Estimated by TLC analysis

1.7.3 Synthesis and initial biological testing of meayamycin

The next step was to examine the cross metathesis of **164** with left fragment **47**, and to test the biological properties of this FR901464 analog. Analog **165**, later named meayamycin, was prepared by the cross metathesis strategy, which was accomplished by treating **47** with a slight excess of **164** and Grela's catalyst to afford meayamycin in 59% yield after one recycling of recovered starting materials (Scheme 37). With the more stable right fragment, higher reaction temperatures could be used, and consequently the yield of this metathesis reaction was improved as compared to the synthesis of FR901464.



Scheme 37. Preparation of meayamycin

The stability of meayamycin in biological experimental conditions was of chief concern. The reported half-life of FR901464 was later reported to be 45 min in 10% FBS-containing culture media.[65] HPLC was used to determine the half-lives of meayamycin in aqueous buffers at 37 °C using benzoic acid as the internal standard (Figure 6), and then in human and mouse sera at 37 °C using rhodamine B as the internal standard (Figure 7). The half-lives of meayamycin were determined to be 125, 301, 139, and 82.6 h in pH 5, 6, 7, and 7.4 buffers, respectively. Therefore, meayamycin was shown to be mildly acid- and base-sensitive from the lower half-lives at pH 5 and 7.4. In more biologically relevant experiments, the half-life of meayamycin was determined to be 2.2 h in mouse serum and 9.3 h in human serum. With many esterases, C4'-desacetyl meayamycin, **170** (structure, Scheme 39), was also rapidly generated. From these experiments, meayamycin was shown to have significantly improved stability over FR901464, but the lability of its acetate may be of concern in a biological setting.

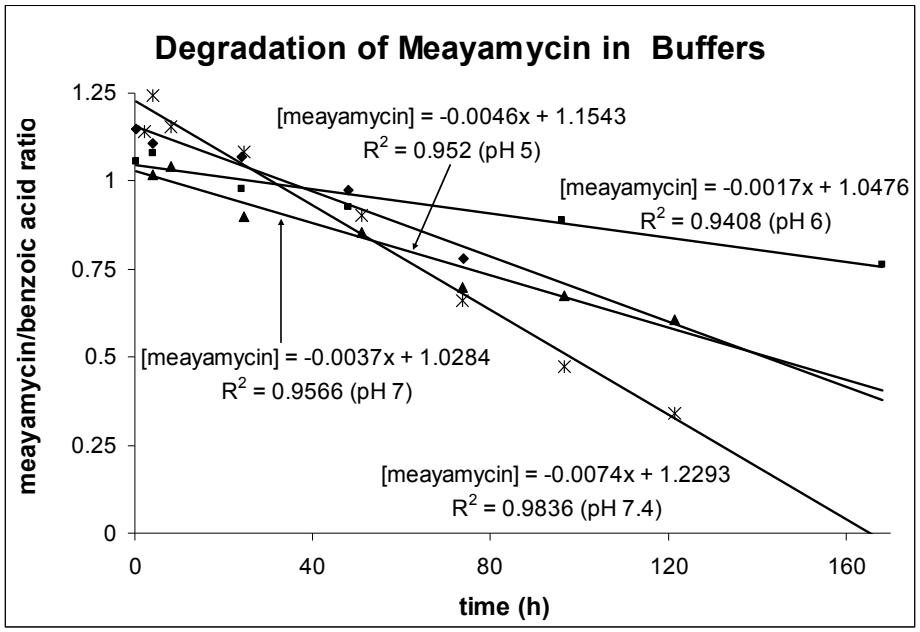


Figure 6. Half-life determination of 10 μM meayamycin in buffers

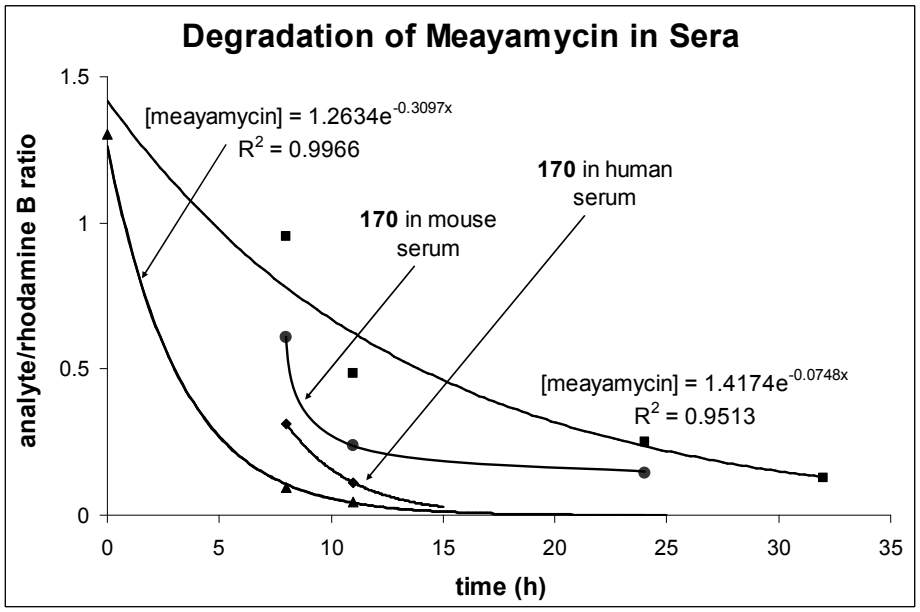
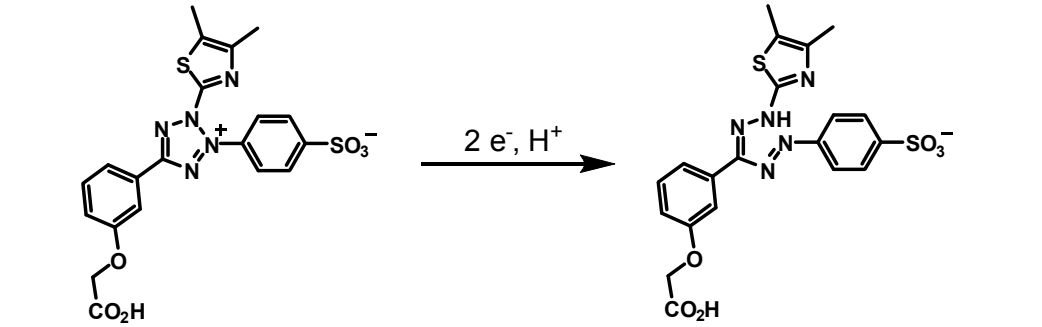


Figure 7. Half-life determination of 10 μM meayamycin in human (■) and mouse sera (▲)

With the preparation of meayamycin, the stage was set to test the hypothesis that the replacement of the C1-OH group with a methyl group will impact the biological profile. The

model cell line chosen to examine the antiproliferative effect of FR901464 and meayamycin was the MCF-7 breast cancer line. This cell line was chosen partially because it was used by Fujisawa to test the potency of FR901464.[40] The MTS assay was chosen as the method to examine the cell viability and proliferation[150] because of its simplicity, commercial availability, and reproducibility. The MTS tetrazolium salt and formazan product are water soluble, and therefore no detergents or ethanol are required (Scheme 38). The intracellular reduction of MTS to its formazan requires two electrons to reductively cleave the tetrazolium core of MTS, which can be monitored easily using a standard plate reader. This reaction progress and thus the amount of viable cells is measure by the change in absorbance because the formazan product at absorbs at 490 nm, where the MTS reagent does not. To judge the effectiveness of meayamycin, MCF-7 cells were treated with this analog and FR901464 for 7 or 10 days, then analyzed after adding the MTS reagent. Antiproliferative assays were also performed for 5 days, but generally gave higher variability with the MTS assay. Growth inhibition was concentration-dependent for MCF-7 cells treated with FR901464 and meayamycin (Figure 8). FR901464 was shown to have an impressive GI_{50} of 1.1 nM in accordance with the literature value,[40] but surprisingly meayamycin displayed a 10 pM GI_{50} value![102] Moreover, these results were reproducible, and confirmed by manual cell counting using visible microscopy and Trypan blue dye. As a positive control paclitaxel was employed and displayed a GI_{50} of 0.50 nM (Figure 9), similar to the reported value of 2.0 nM in the same cell line.[151] Therefore, the more stable FR901464 analog, meayamycin, indeed gave enhanced biological properties in accordance with the hypothesis.



Scheme 38. Intracellular reduction of MTS to its formazan

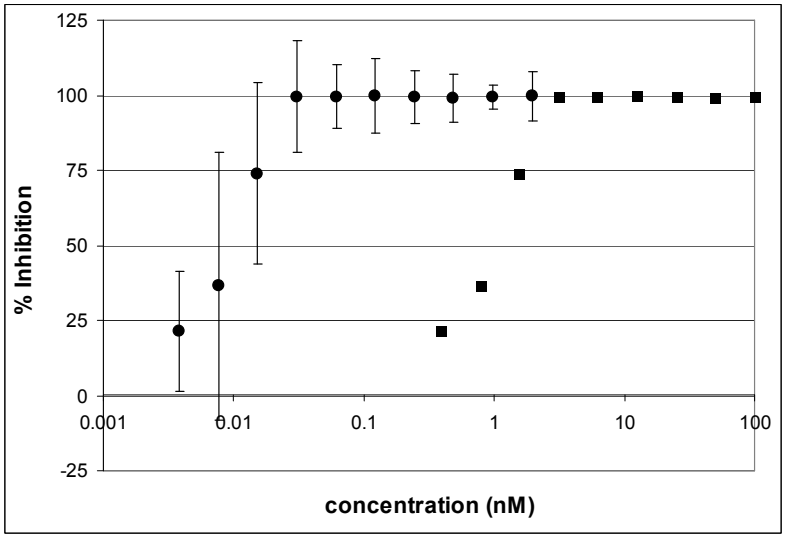


Figure 8. Growth inhibition of MCF-7 cells by FR901464 (■) and meayamycin (●)

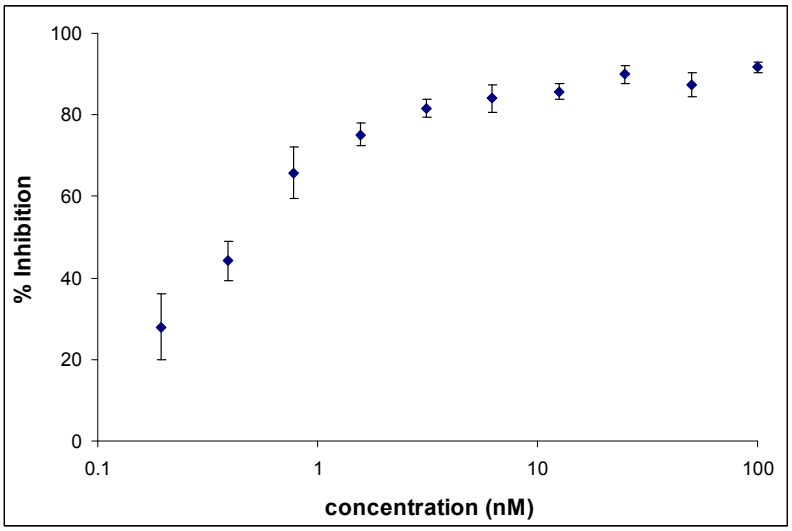


Figure 9. Growth inhibition of MCF-7 cells by paclitaxel

1.8 OTHER ANALOG SYNTHESES AND ANTIPROLIFERATIVE ACTIVITIES

1.8.1 Desired analogs

While the potent antiproliferative activity of meayamycin was a major success, other moieties of FR901464 warranted exploration. The first moiety to be probed was the C12 methyl group, found in the A-ring of FR901464. The A-ring of FR901464 and meayamycin likely exists in a chair conformation placing the C12 methyl and C14 amide groups axial (Figure 9*a*). This placement creates an unfavorable steric interaction between these groups, but could be offset by H-bonding of the amide N-H and the pyran oxygen atom. The destabilization of the A-ring conformation FR901464 could populate conformer FR901464', where the C11 aliphatic and C15 methyl groups are placed axially (Figure 9*b*). FR901464' is expected to be minor due to the larger diaxial interaction between the aliphatic and methyl groups with the smaller C11–O and

C15–O bonds. Therefore, removal of the C12 methyl group could stabilize conformer **166** by eliminating the destabilizing diaxial interaction, and the equilibrium of **166** and **166'** should lie well to the left.

The epoxide moiety may be unnecessary for biological activity (Figure 9*c*). Jacobsen's cyclopropyl analog **17** was not antiproliferative in TAG-Jurgat cells. However, analogs without the epoxide moiety but retaining the oxygen atom have not been prepared to date. Therefore, analogs **167**, **168**, and **169** should give a more definitive answer to the reversible/covalent modifier quandary for FR901464 and meayamycin.

The acetate group was shown to be labile in the half-life studies of meayamycin in sera (Figure 9*d*). Therefore, meayamycin's C4'-desacetyl analog, **170**, should be prepared to understand the potency of this relevant metabolite. Finally, with previous problems preparing acid chain **2** in high yield and enantioselectivity, prepation of an achiral acid chain was desired (Figure 9*e*). Therefore, a C4'-primary acetate **171** or -tertiary acetate **172** could prove synthetically more accessible, but their effects on the biological properties could be similar to meayamycin, since Jacobsen's C4'-epimer analog **14** gave only a 15-fold decrease in potency.

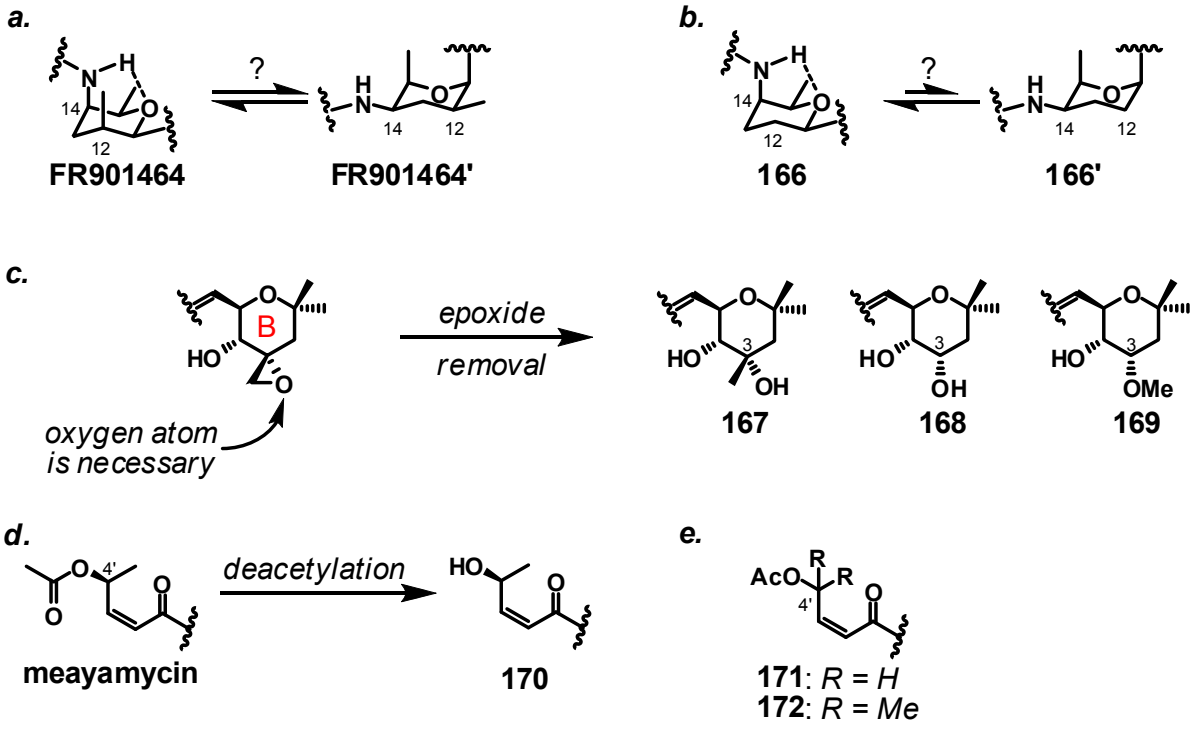
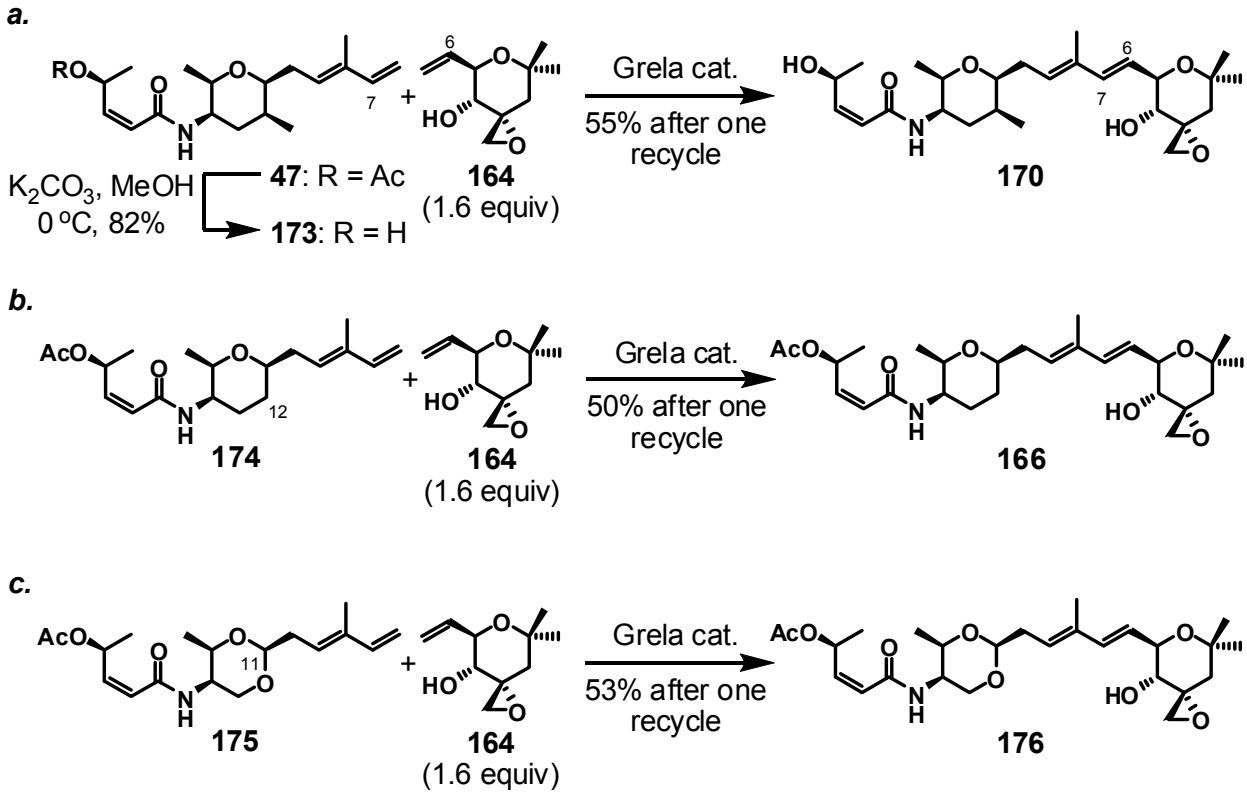


Figure 10. Rationale for the preparation of more analogs

1.8.2 Preparation of desired analogs

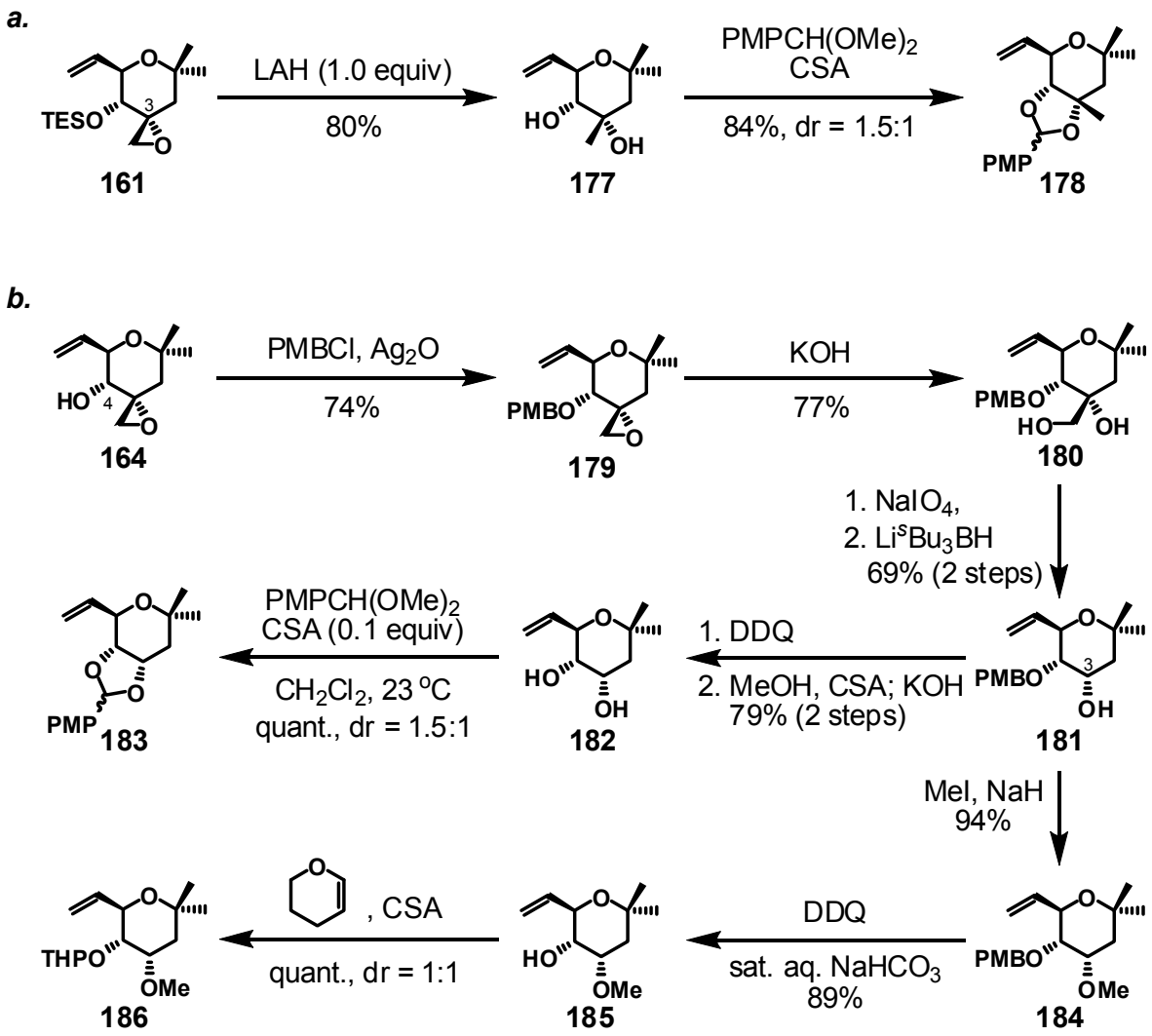
With these many analogs in mind, efforts were focused on preparing the C4-desacetyl, C12-desmethyl, and a C11 acetal analogs, also without the C12-methyl group similar to Wender's SAR studies of bryostatin.[152] Left fragment **47** was deacetylated by the action of K_2CO_3 and MeOH to give **173** in 82% yield (Scheme 39*a*). This material was treated with an excess of **164** and a catalytic amount of the Grela catalyst to generate desired adduct **170** in 55% yield after one recycling of recovered starting materials. Left fragments **174** and **175**, prepared by Dr. Miaosheng Li, were coupled to **164** with the Grela catalyst to give **166** and **176** in 50% and 53% yields, respectively, after one recycling of recovered starting materials (Scheme 39*b* and *c*)



Scheme 39. Preparation of analogs **170**, **166**, and **176**

To prepare **167**, **168**, and **169**, previsouly synthesized materials were utilized for rapid preparation of the necessary right fragment coupling partners. Spiroepoxide **161** was reduced with LAH to give **177** in 80% yield with concomitant removal of the silyl ether (Figure 39*a*). This diol was protected as its *p*-methoxyphenyl acetal, **178**, in 84% yield and a 1.5:1 dr. Right fragment **164** was treated with PMBCl and Ag_2O to afford **179** in 74% yield (Scheme 40*b*). This material was exposed to KOH in warm DMSO to generate diol **180** in 77% yield. This diol was cleaved using $NaIO_4$ to give an unstable ketone that was immediately reduced with Li^sBu_3BH to afford **181** as a single diastereomer in 69% yield over two steps. This material was then oxidized with DDQ to give a mixture of esters and acetals, which was then methanolized using a catalytic

amount of CSA, and subsequent addition of KOH cleaved the esters to form diol **182** in 79% two-step yield. This diol was protected as its *p*-methoxyphenyl acetal, **183**, in quantitative yield

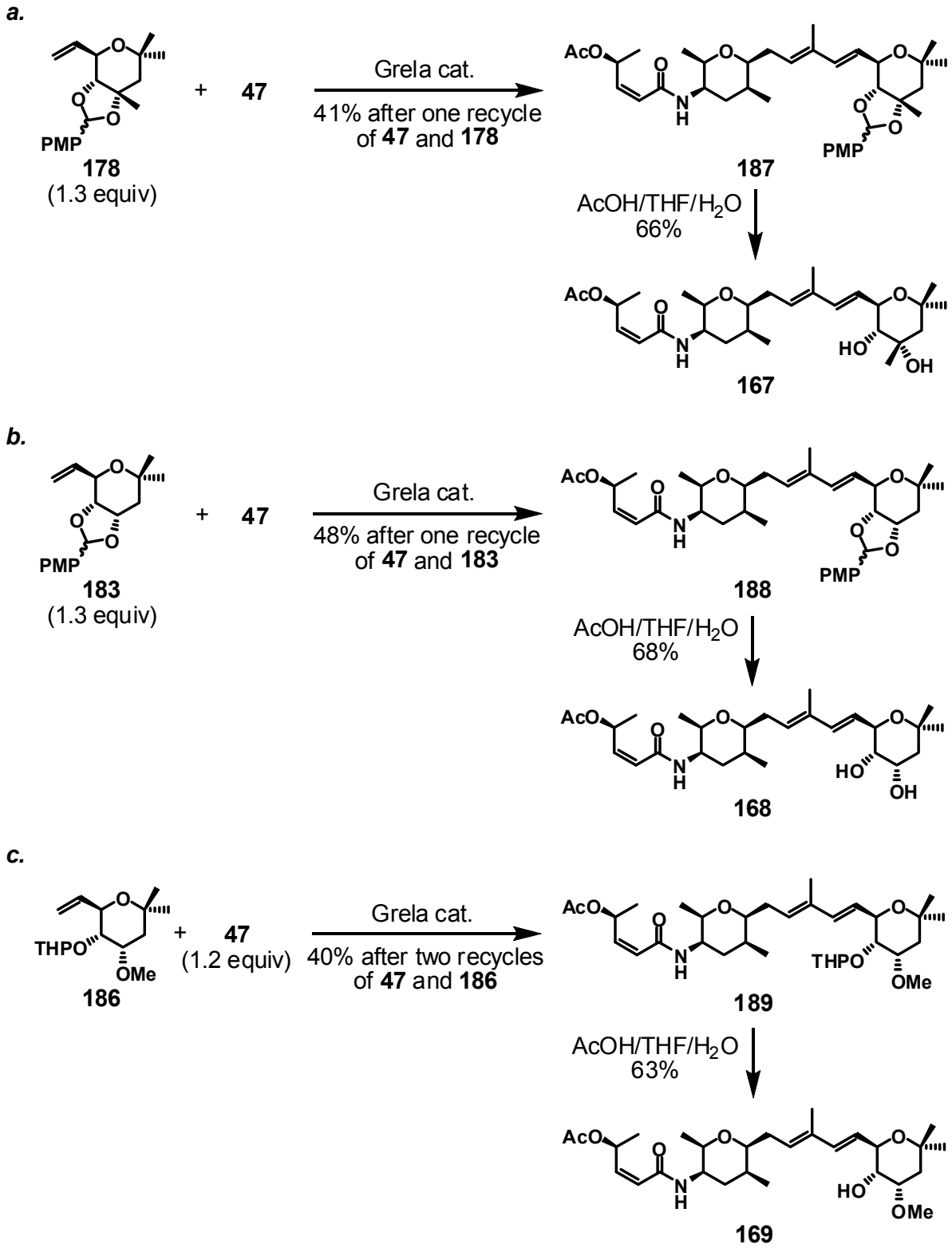


Scheme 40. Preparation of right fragment analogs

and a 1.5:1 dr. Alternatively, alcohol **181** was methylated by the action of NaH and MeI to give **184** in 94% yield. PMB group removal was accomplished with DDQ to give alcohol **186** in 89% yield, which was protected as its THP ether, **186**, in quantitative yield with CSA and 3,4-

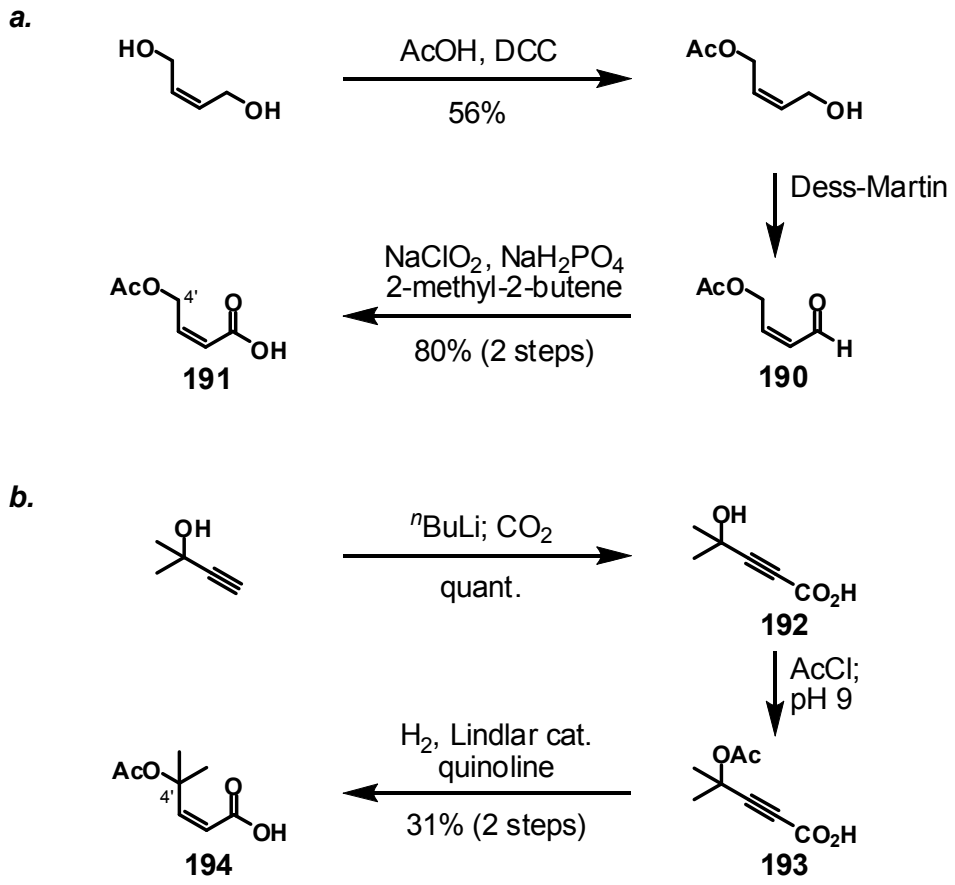
dihydro-2*H*-pyran. This completed the preparations of the three desired right fragments to examine whether the epoxide moiety is necessary for the activity of FR901464 and meayamycin.

The completion of the desired right fragment analogs is shown in Scheme 41. Treatment of **177** and left fragment **47** gave no reaction. Fortunately, treatment of **47** and **178** with the Grela catalyst gave desired adduct **187** in 41% yield after one recycling of starting materials (Scheme 41*a*). Deprotection of this material was accomplished with 3:1:1 AcOH/THF/H_2O to give desired analog **167** in 66% yield. Similarly, the cross-olefin metathesis reaction of diol **182** and **47** gave only decomposition of **182**. However, metathesis of acetal **183** and left fragment **47** in the presence of the Grela catalyst furnished **188** in 48% yield after one recycling of recovered starting materials (Scheme 41*b*). This material was then subjected to 3:1:1 AcOH/THF/H_2O to give **168** in 68% yield. Moreover, coupling of **185** and **47** was found to afford **169** in <5% yield, but **186** and **47** were successfully coupled in the presence of the Grela catalyst to give adduct **189** in 40% yield after two recycling of recovered starting materials (Scheme 41*c*). Interestingly, the reactivity of **186** was lower than left fragment, and therefore **47** was used in excess to increase the coupling efficiency. Adduct **189** was deprotected with 3:1:1 AcOH/THF/H_2O to afford **169** in 63% yield. The non-reactivity and/or decomposition of these free alcohols could be explained by bidentate-chelation to the ruthenium catalyst and subsequent chloride displacement thereby blocking the coordination site trans to the *N*-heterocyclic carbene.[153,154] Suppression of these phenomena was readily accomplished by protection of the C4-hydroxy group. For unknown reasons, **50** and **164** were devoid of such complications.



Scheme 41. Preparation of analogs **167**, **168**, and **169**

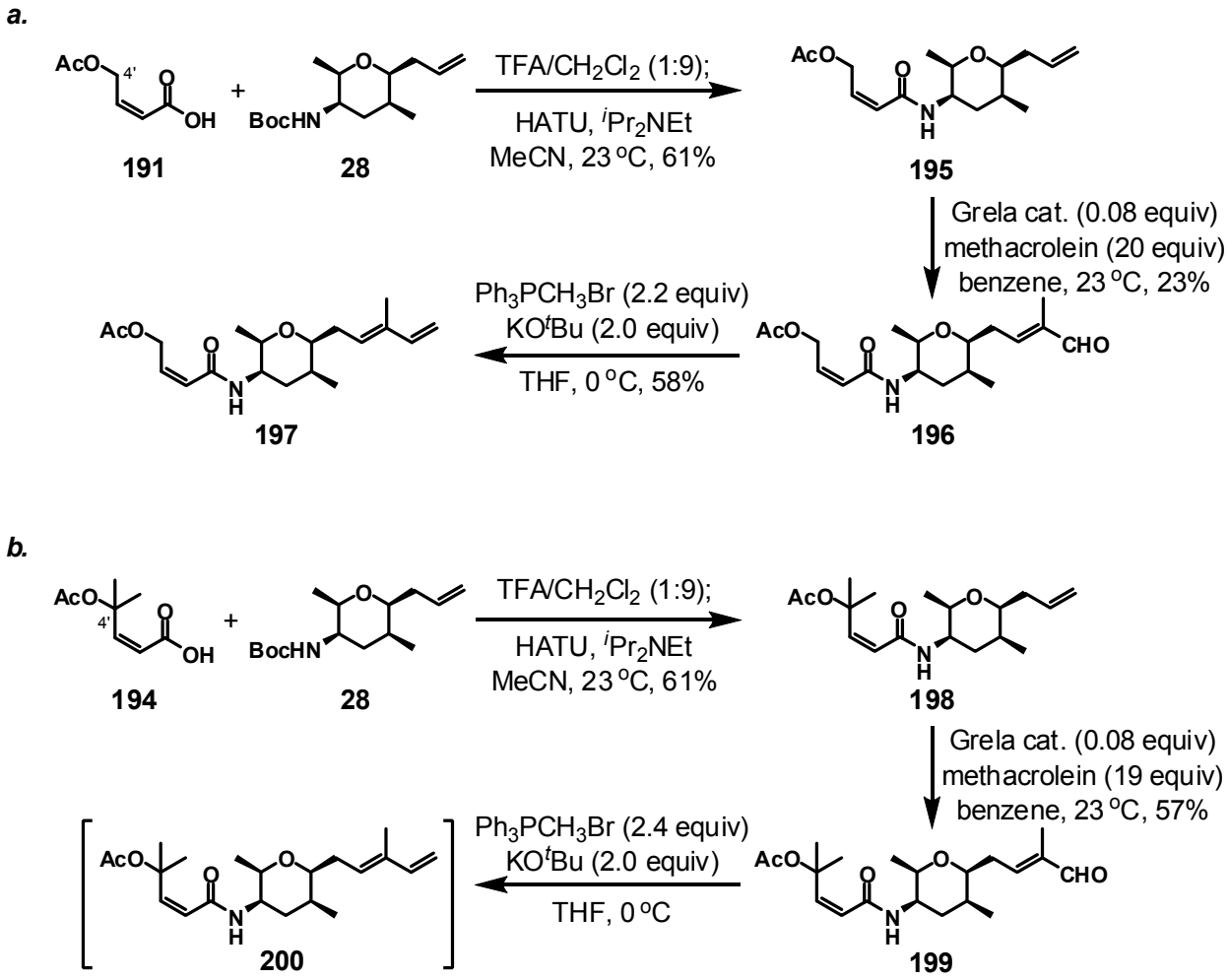
Removal of the C4' stereocenter was investigated due to the preparations of acid **2** being hampered by low enantioselectivity and chemical yields. Removal of this stereocenter would increase the scalability of the preparation of an acid chain, but its impact on the biological activity was unknown. One acid chain analog would be devoid of the C4' methyl group and its preparation began with the mono-acetylation of *cis*-butenediol in 56% yield (Scheme 42*a*). Oxidation of this mono-acetate with the Dess-Martin reagent[110] afforded aldehyde **190**. This aldehyde was further oxidized with $NaClO_2$ to give desired acid **191** in 80% for the two-step oxidation sequence, and completed the synthesis in a total of three steps and in 45% total yield. Alternatively, removal of the C4' stereocenter could be accomplished by the addition of another



Scheme 42. Preparation of C4' acid chain analogs

methyl group at this position. Towards this end, the bisanion of 2-methyl-3-butyn-2-ol was generated by treatment with excess ^{n}BuLi, and through this solution was added CO_2 which gave acid **192** in quantitative yield upon acidic workup (Scheme 42 *b*). This ynoic acid was acetylated by the action of AcCl to give **193**, and the resulting acetate was subjected to partial hydrogenation conditions to afford enoic acid **194** in 31% yield for the two steps. Therefore, the preparation of this acid chain analog was accomplished in three total steps and 31% overall yield.

With acid chain analogs **191** and **194** in hand, the preparation of fully functionalized left fragments was undertaken. Deprotection of tetrahydropyran **28** was accomplished with TFA, and subsequent coupling with acid **191** generated amide **195** in 61% yield (Scheme 43*a*). Cross metathesis of **195** and methacrolein gave enal **196** in 23% yield. Wittig homologation of this enal gave desired diene **197** in 58% yield. Similarly, the preparation of amide **198** was accomplished by the deprotection of **28** with TFA and subsequent coupling to acid **194** in 61% yield (Scheme 43*b*). Cross-olefin metathesis of this material with methacrolein gave **199** in 57% yield, and Wittig homologation of this aldehyde gave diene **200**, but this diene appears to be a mixture as indicated by the ^{1}H NMR. With Dr. Miaosheng Li's improved method to form acid **2** by a Noyori reduction of **63**,[59] these left fragments were temporarily abandoned. Interestingly, the steric environments of the enamides appears to effect the yields of the cross metatheses with methacrolein. More substitution at C4' give metathesis adducts in higher yields, and less substitution, as seen in **195**, gives lower yields.



Scheme 43. Preparation of C4' analogs

1.8.3 Biological testing of these analogs

With these analogs in hand, their antiproliferative activities were tested in MCF-7 cells. Antiproliferative experiments were again performed over 7 days. Concentration-dependent growth inhibition by A-ring analogs **166** and **177** was observed (Figure 10). The GI_{50} for **166** was determined to be 0.16 nM, and the GI_{50} for **177** was determined to be 5.4 nM. The positive controls for this experiment were meayamycin that gave a GI_{50} of 65 pM in this experiment.

Therefore, the removal of the C12-methyl group has a somewhat deleterious effect on the antiproliferative activity, but these analogs remained remarkably potent. NMR studies of these A-rings were performed in CD_3OD to understand whether a conformational change or the loss of a hydrophobic interaction was responsible for the losses in activity. D_2O would have been an ideal solvent for these NMR studies, but **47**, **147**, and **175** were found to be poorly soluble. Inspection of the *J*-values of these fully functionalized left fragements revealed only subtle differences (Figure 11). Therefore, the decrease in activity of **166** and **167** is presumably due to a loss in a hydrophobic interaction. Although **166** and **167** were synthetically easier to prepare, the removal of the C12-methyl group decreased the potency, yet **166** was still quite potent.

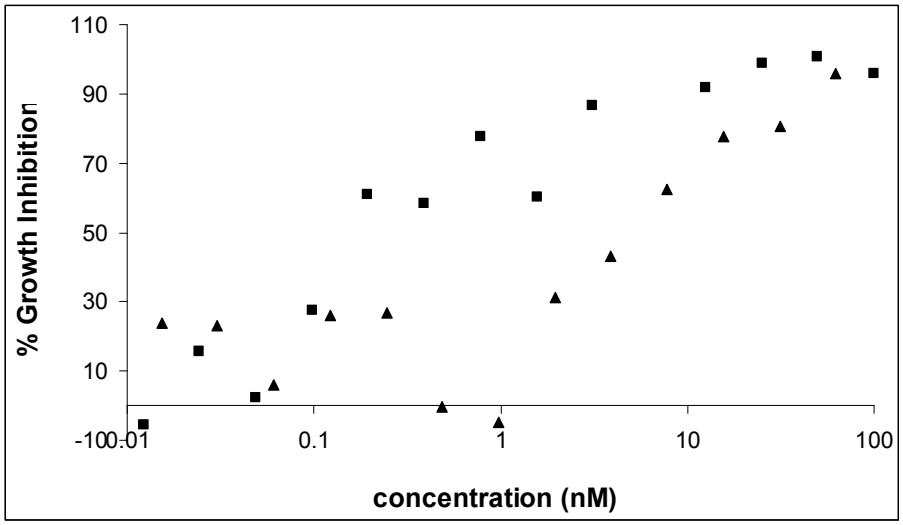


Figure 11. Relative growth inhibition of MCF-7 cells by **166** (■) and **167** (▲)

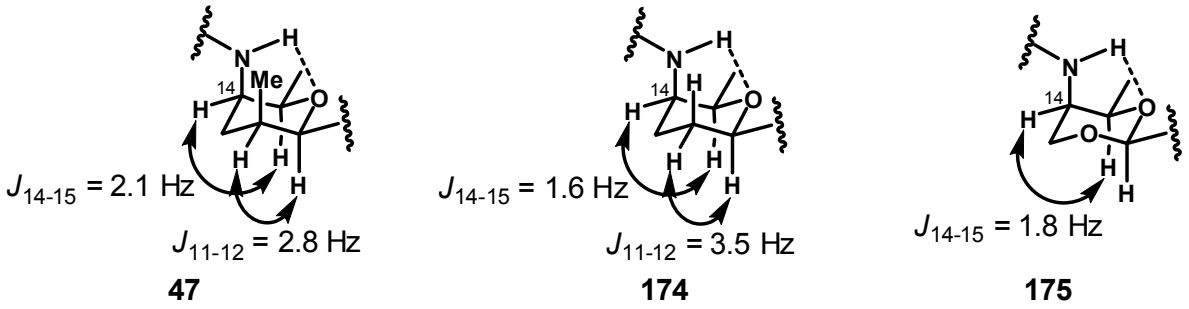


Figure 12. *J*-Values for left fragment analogs

No growth inhibitory effects were observed for desepoxy analogs **167**, **168**, and **169** in MCF-7 cells (data not shown). As positive controls, meayamycin and 5-fluorouracil displayed antiproliferative potential (data not shown). These results clearly demonstrate that the epoxide moiety is needed for growth inhibition of MCF-7 cells, suggesting covalent modification of its target(s).

The concentration-dependent growth inhibition of MCF-7 cells by C4'-desacetyl analog **174** is shown in Figure 12. The GI_{50} for **174** was determined to be a respectable 0.60 nM, but this was a 60-fold decrease in activity, and therefore the acetate group should be retained for potency.

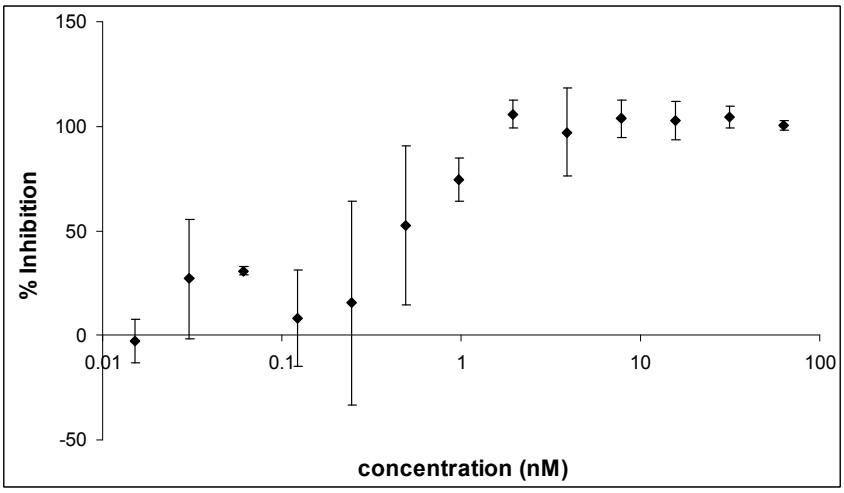


Figure 13. Relative growth inhibition of MCF-7 cells by **174**

1.8.4 Biological probe development for target identification

It was assumed that FR901464 and meayamycin act by covalent modification of intracellular protein(s), and this hypothesis was later supported by the finding that the removal of the spiroepoxide is detrimental to the growth inhibition of MCF-7 cells. However, examination of meayamycin-treated cells based on their abilities to recover from short exposures to meayamycin would give further support to this hypothesis. For noncovalent modification of an intracellular target of meayamycin, the majority of the meayamycin would be removed upon removal of the media. Upon addition of fresh, meayamycin-free media, diffusion could occur, thereby removing most of this compound from within the cell and allowing for cell proliferation. However, for the scenario of covalent modification, a nucleophilic residue would open the epoxide to generate an alcohol. Upon removing the meayamycin-containing media and adding fresh media, most of the unbound molecules would be removed, but the covalently bound meayamycin would silence the cell proliferation.

To investigate this hypothesis cultures of MCF-7 cells were treated with meayamycin for 4, 8, 24, 48, and 72 h, and after 72 total h cell numbers were determined by the MTS method. In parallel, MCF-7 cells were treated with 0.1 and 1.0 nM meayamycin for the indicated period of time, the media was removed, replaced with fresh media, and allowed to incubate for 72 total hours (Figure 13). This experiment was repeated for 7 days, and gave nearly identical results (not shown). After 4 h of exposure to meayamycin (0.1 or 1.0 nM), there wass 65–70% growth inhibition, but after exposure from 8–72 h there was almost 100% growth inhibition. From these results, it appears that the binding of meayamycin is covalent. Moreover, 8 h of exposure to

meayamycin is required to exhibit its full antiproliferative potential. However, without spectrometric experiments the covalent binding of meayamycin to its target(s) can only be speculated upon.

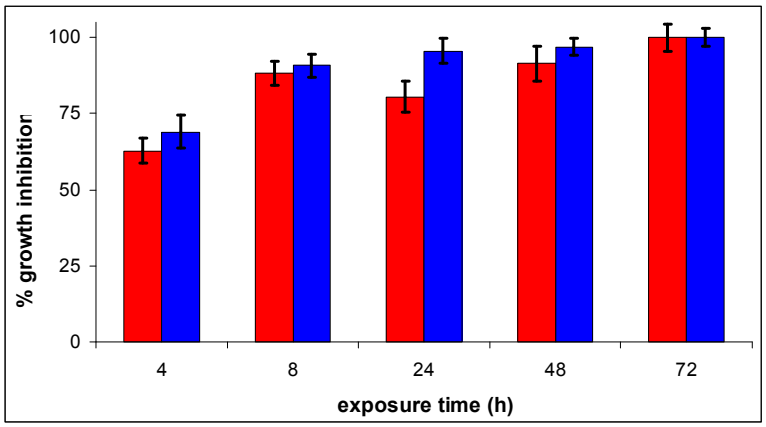
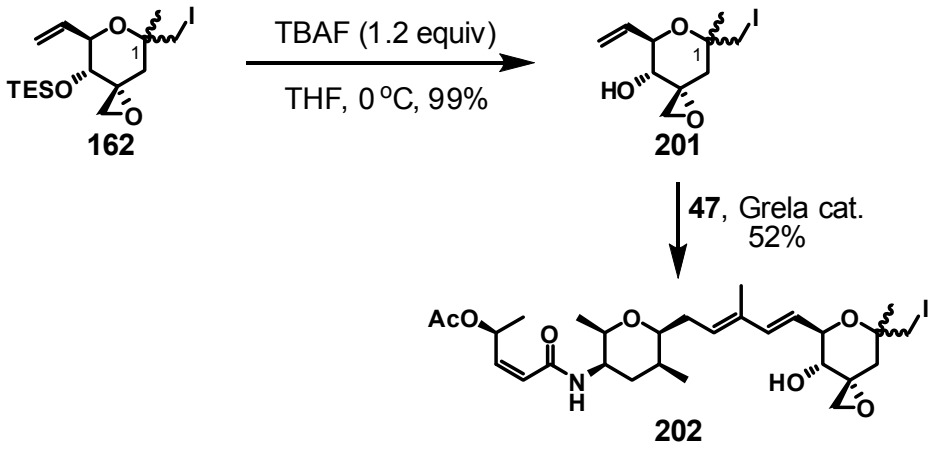


Figure 14. Time dependent growth inhibition of MCF-7 cells by meayamcin; 0.1 nM (red) and 1.0 nM (blue)

The discovery of SF3b as a target of FR901464 was predicated on reversible binding, which is in direct opposition to the data presented here. Moreover, their identification experiment involved the mixing of **24** and cell extracts at 4 °C for 6 h.[65] Therefore, the RIKEN group could have missed covalently bound proteins responsible for the antiproliferative activity, including TMX, which they previously reported as an FR901464 target. Based on meayamycin covalently modifying its intracellular target(s), the preparation of a radiolabeled meayamycin analog was desired for target identification experiments. It was previously found that incorporation of an iodine atom, in the preparation of **162**, was possible, and thus incorporation of a ^{125}I atom into an FR901464 analog would seemingly be facile. The high sensitivity of detection of ^{125}I makes it an ideal isotope for the discovery of potentially small quantities of protein adducts. One concern was the susceptibility of an alkyl iodide towards substitution reactions, but the epoxide was

found to be more reactive towards a variety of nucleophiles in **162** and **201**, consistent with the non-reactivity of related neopentyl iodides. Moreover, **162** and **201** are stable towards homolytic cleavage of the C–I bond under ambient light at 23 °C for several days in benzene. Towards this end, **162** was deprotected with TBAF to give **201** in nearly quantitative yield (Scheme 44). Cross-olefin metathesis of this alkene with diene **47** gave **202** in 52% yield (dr = 1.5:1) after one recycling of recovered of starting materials.



Scheme 44. Preparation of iodides **202**

The antiproliferative activity of **202** was examined, and the GI_{50} was determined to be 1.4 nM (Figure 14). However, MCF-7 cells are not typically used for target identification, presumably due to the difficulty and time required to grow a sufficient number of such cells, but HeLa cells are easy to grow and are often used. Thus, the antiproliferative activity of **202** was tested in this cell line, and the GI_{50}s for meayamycin and **202** were shown to be 0.10 nM and 0.75 nM, respectively. Therefore, less than a 10-fold decrease in activity was observed (Figure 15), indicating that **202** is a suitable probe for target identification experiments.

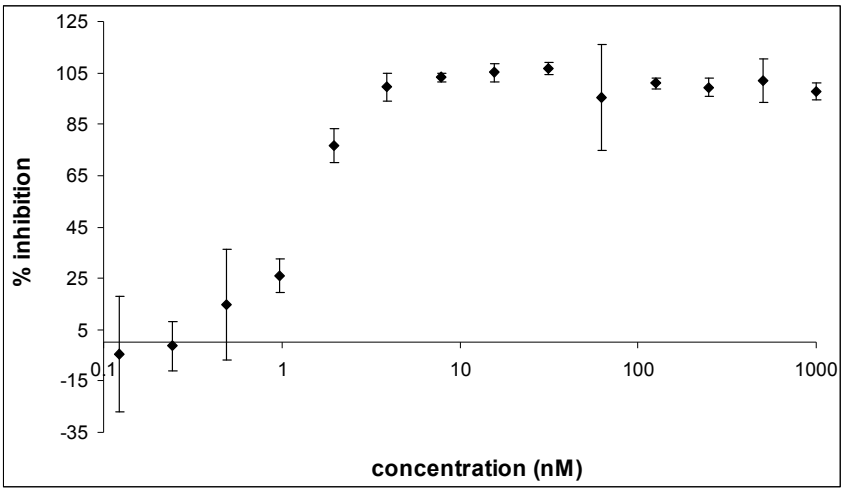


Figure 15. Relative growth inhibition of MCF-7 cells by **202**

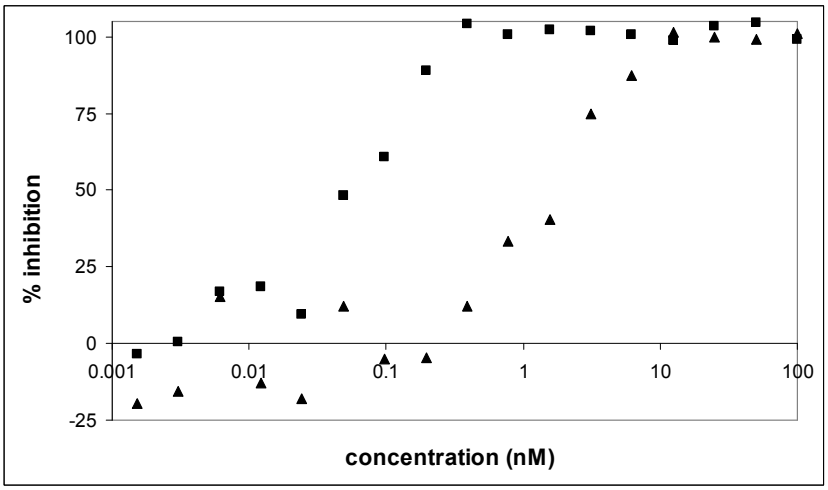
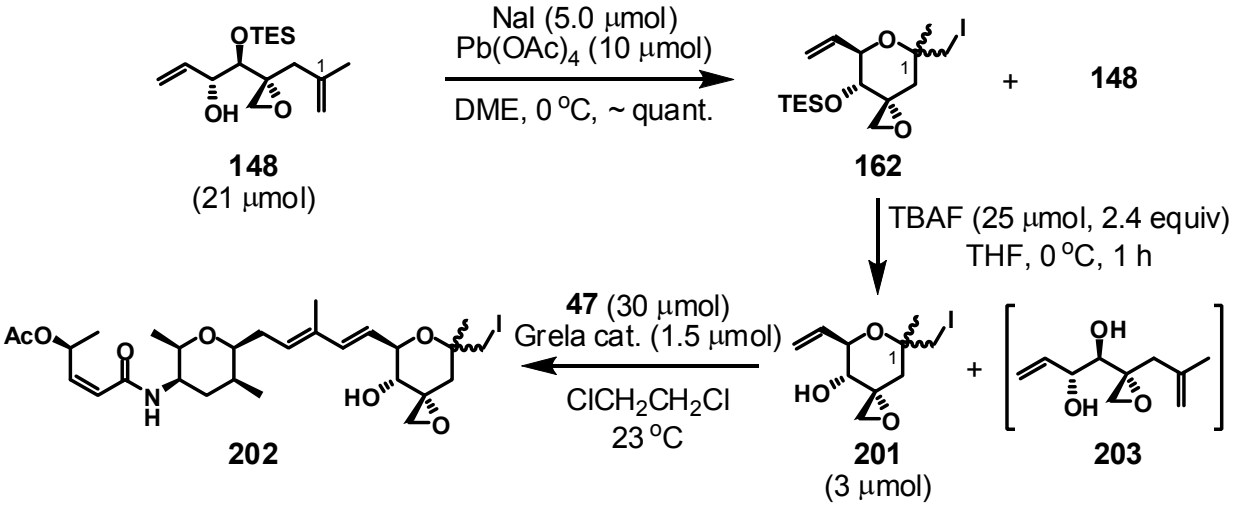


Figure 16. Relative growth inhibition of HeLa cells by meayamycin (■) and **202** (▲)

Although iodides **202** were easily prepared on a semi-preparative scale, their preparation on a much smaller scale would be required for target identification experiments, and thus the viability of a microscale preparation of **202** was investigated. Typically, $Na^{125}I$ is purchased in an aqueous solution, but H_2O was expected to have a deleterious effect on the iodoetherification reaction. This assumption was later confirmed by Professor Chet Mathis and Dr. Scott Mason at

the PET facility in the University of Pittsburgh Medical School. However, the removal of H_2O was accomplished by azeotroping with dry MeCN to afford a dry sample of NaI, which was employed in the iodoetherification reaction conditions with diene **148** to generate **162** in quantitative yield, based on NaI as determined by crude ^{1}H NMR (Scheme 45). A larger sample (10 μmol of **162** and **148** combined) of this mixture was then deprotected with excess TBAF to give **201** and presumably **203**. Finally, 3 μmol of **201** was subjected to the cross-olefin metathesis conditions to generate **202**. This result was confirmed by TLC and HPLC using authentic materials as references. The first two reactions of this three step sequence were validated by Dr. Mason using carrier added Na^{125}I, showing the desired incorporation of ^{125}I in the products. Moreover, the purification of these radioactive mixtures only require filtrations through Celite 545® and Florisil for the iodoetherification and deprotection reactions, respectively, making this a simple task. Therefore, the microscale preparation of **202** was shown to be viable and could be used for target identification experiments for FR901464.



Scheme 45. Microscale procedure to prepare iodide **202**

1.9 REACTIVITY OF ELECTROPHILIC MOIETIES OF FR901464 WITH THIOLS

FR901464 contains two electrophiles, namely a spiroepoxide and an α,β-unsaturated enamide, which could react with its target protein(s) or non-specifically with small molecules or proteins. An understanding of the reactivity of these moieties towards thiols or other nucleophiles would be crucial in understanding the reactivity of FR901464 for biological experiments. Despite the importance of reactions of epoxides and α,β-unsaturated enamides towards biologically relevant thiols, presumably the most abundant and powerful nucleophile in a biological setting, kinetic data for these transformations are quite limited.

1.9.1 Reactions of epoxides with thiols

Epoxides are common features of many biologically active natural products and drugs (Figure 17). For example, FR901464 and meayamycin display encouraging results in cancer cells by unknown mechanisms. The following small molecules form a covalent bond with their target proteins via epoxide opening reactions. Trapoxin B binds to histone deacetylases,[155] and its analogs are currently in clinical trials for cancer therapy. Epoxomicin is a specific electrophile for the 20S proteosome.[156] Fumagillin binds to methionine aminopeptidase 2,[157] and its analog TNP-470 is now in phase III trials for cancer therapy.[158] However, epoxides do not necessarily form covalent bonds with their biological targets. The epothilones are a class of natural products that non-covalently modify their biological target, microtubules. Triptolide is an ingredient in traditional Chinese herbal therapy *lei gong teng*, used to treat inflammatory disorders, and also does not form covalent bonds with its target proteins, in spite of its three epoxides.[159,160] Finally, scopolamine is a clinically prescribed for motion sickness. Despite the importance of these

molecules, and their proven efficacy in cell and organism based experiments, there remains concern about toxicity, presumably arising from non-specific reactions in a biological setting, which has been seen in environmental legislation.[161] Non-specific reactions of epoxides with extra- and intracellular components would be expected to come from powerful nucleophiles, such as thiols found in abundant thiol-containing proteins, and small molecules such as glutathione, which could greatly decrease the concentration of epoxide-containing probe.

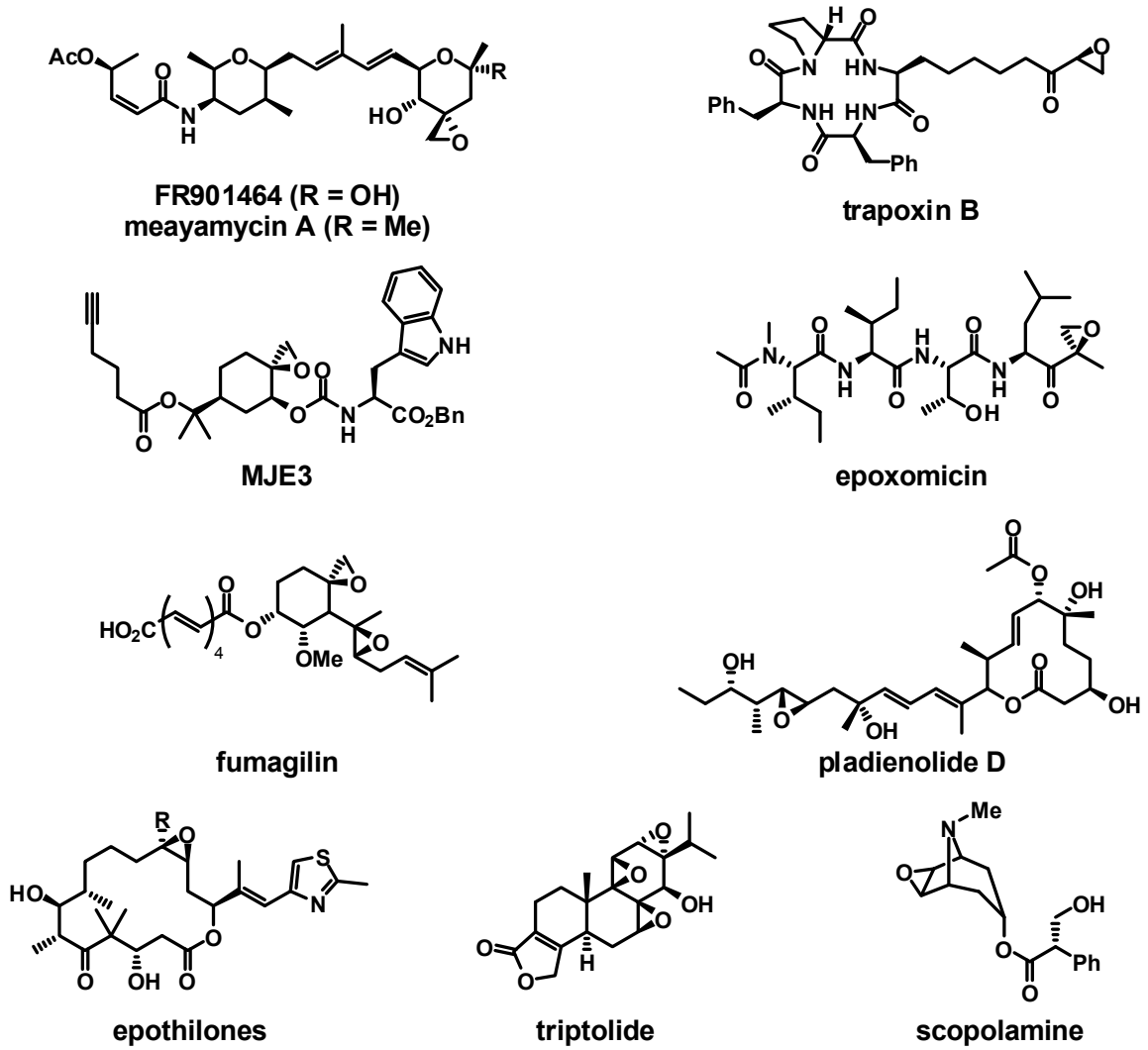
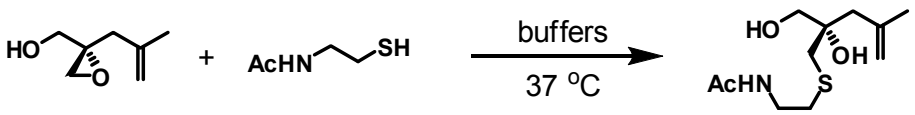


Figure 17. Structures of epoxide containing natural products and biological probes

While interested in the biology of spiroepoxide containing compounds FR901464 and meayamycin, it was not clear if their epoxides would react non-specifically with thiols before reaching their intended targets.[162] Quantitative analyses of epoxide opening by thiols has been limited to arene oxides and ethylene oxide at 30 and 20 °C, respectively, and α,α'-bisepoxy cyclohexanones at 22 °C in 4:1 THF/H_2O.[163,164] Many common epoxide motifs found in Figure 17 were not examined, and therefore presented an opportunity to study this significant reaction. Moreover, these studies could help to understand the biological results obtained using FR901464 and its analogs. However, in designing experiments to address this question, one must consider that the local concentrations of thiols and epoxides may vary in vivo, thiols may be activated enzymatically under certain biological conditions (e.g., glutathione transferases),[165] and that epoxide hydrolases can cause enzymatic depletion of epoxides.

To address the unanswered concern if nonenzymatic covalent bonding of epoxides was of major biological consequence, a model system was required. The model system initially chosen was condensation of epoxyalcohol **79** and *N*-acetylcysteamine to give **204**, due to the water solubility and accessibility of these substrates (Scheme 46).[133] Moreover, the pK_a of the mercapto group of *N*-acetylcysteamine (9.92) is close to that of glutathione (9.42 ± 0.17) and other biologically relevant thiols like cysteine (pK_a = 10.2). Glutathione was avoided because undesirable kinetic resolutions could complicate data obtained from condensation reactions with chiral epoxides, and the characterization of complex products would not be trivial. To obtain kinetic data, the reaction of **79** and *N*-acetylcysteamine in buffered D_2O was monitored in an NMR tube at 37 °C (method A). This method gave **204** as the major, expected S_N2 product, verified by its preparation in organic solvent. However, this method was not general due to overlap of signals in the NMR spectra when using other epoxides. Consequently, epoxides were

extracted from an aqueous reaction mixture using $CDCl_3$, and their consumption was quantified by comparison to an internal standard by ^1H NMR spectroscopy (method B). The internal standard chosen was benzyl alcohol due to its favorable solubility properties and non-reactivity in the assay conditions. The accuracy of this method was validated by comparing the results for the consumption of **79** by methods A and B (not shown). Figure 18 displays the experimental data for the consumption of **79** in pH 6, 7, and 8 buffers. Consumption of **79** (20 mM) by *N*-acetylcysteamine (100 mM) in pH 6 phosphate buffer gave a half-life of 70 h.[166] In pH 7 and 8 buffer, **79** had half-lives of 7.0 and 1.7 h, respectively. To verify this was an S_N2 process, the concentration of *N*-acetylcysteamine was lowered to 40 mM in pH 7 buffer, and as expected for a bimolecular reaction, the half-life of **79** was 17.9 h under these conditions (Figure 17).



79 **204**

Scheme 46. Reaction of epoxyalcohol **79** and *N*-acetylcysteamine

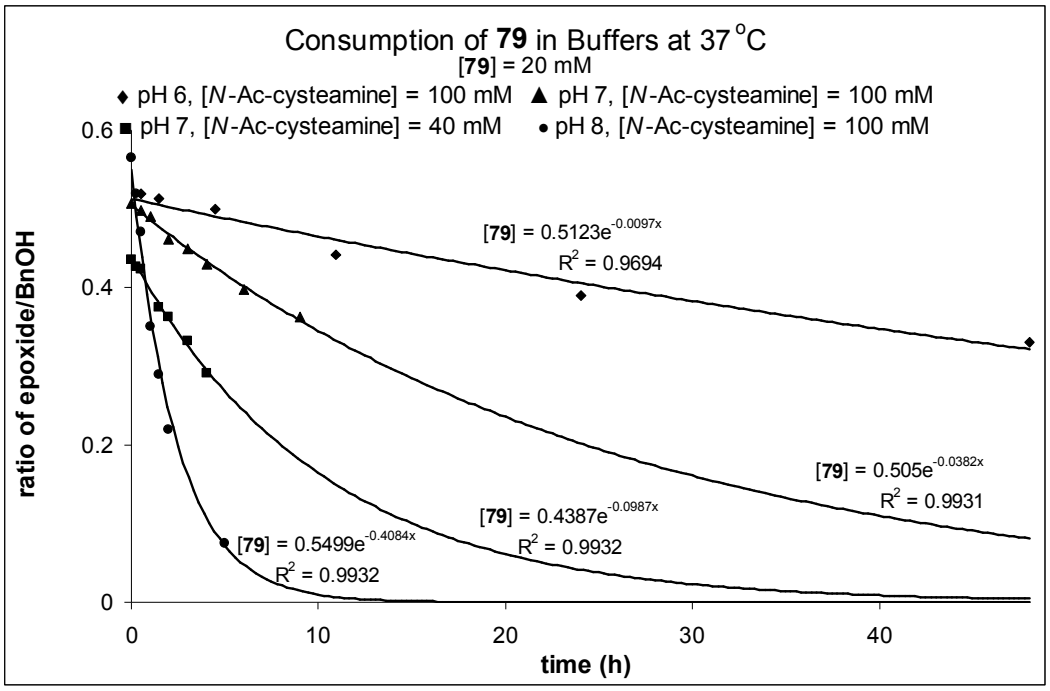


Figure 18. Consumption of **79** by *N*-acetylcysteamine in aqueous buffers at 37 °C

With an established method to determine the half-lives of epoxides in the presence of *N*-acetylcysteamine, other common epoxide motifs were explored. The half-lives for spiroepoxide **205** (20 mM) in the presence of *N*-acetylcysteamine (100 mM) in pH 7 and 8 phosphate buffers were determined to be 3.7 and 0.85 h, respectively (Figure 18). A monosubstituted epoxide, 1,2-epoxy-5-hexene, displayed half-lives of 2.1 and 0.59 h at pH 7 and pH 8, repectively (Figure 19). Cyclohexene oxide gave half-lives of 9.3 and 2.1 h under the same conditions, respectively (Figure 20). Finally, α,β-unsaturated ketone, 2-cyclohexen-1-one oxide, was too reactive under the typical reaction conditions, and therefore the conditions were modified. To successfully measure the half-lives of 2-cyclohexen-1-one oxide with *N*-acetylcysteamine, the concentrations were lowered to 1 and 2 mM, respectively, giving half-lives of 1.8 and 0.22 h at pH 7 and 8, respectively (Figure 21).[166] This result was not a complete surprise, since the Wipf group has documented the high reactivity of these substrates, presumably through attack of the more

electrophilic carbonyl by the thiol and subsequent opening of the epoxide with the putative thioether, rather than simple S_N2 reactions.[164]

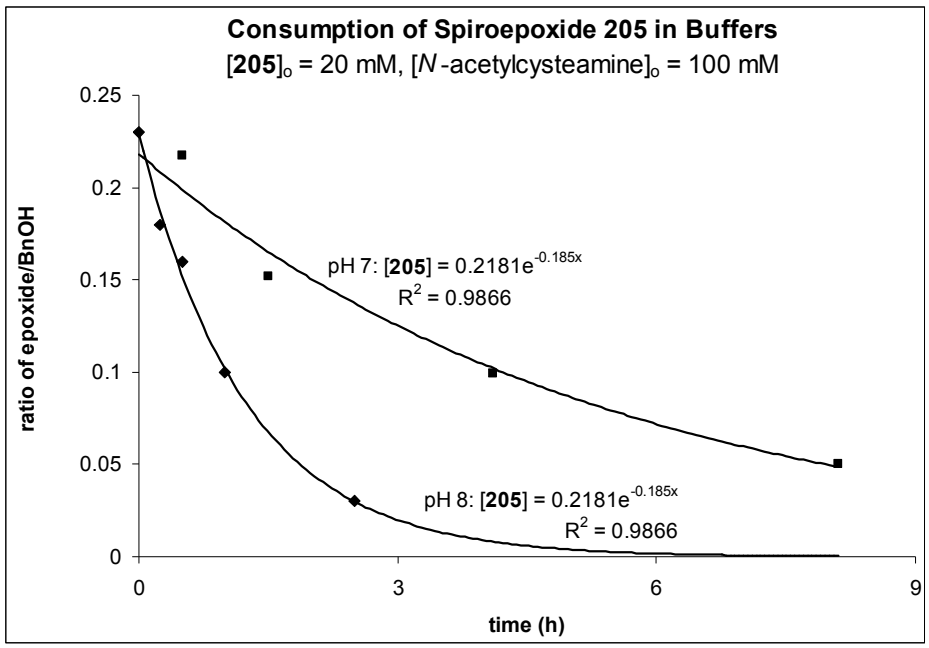


Figure 19. Consumption of epoxide **205** at 37 °C in phosphate buffers

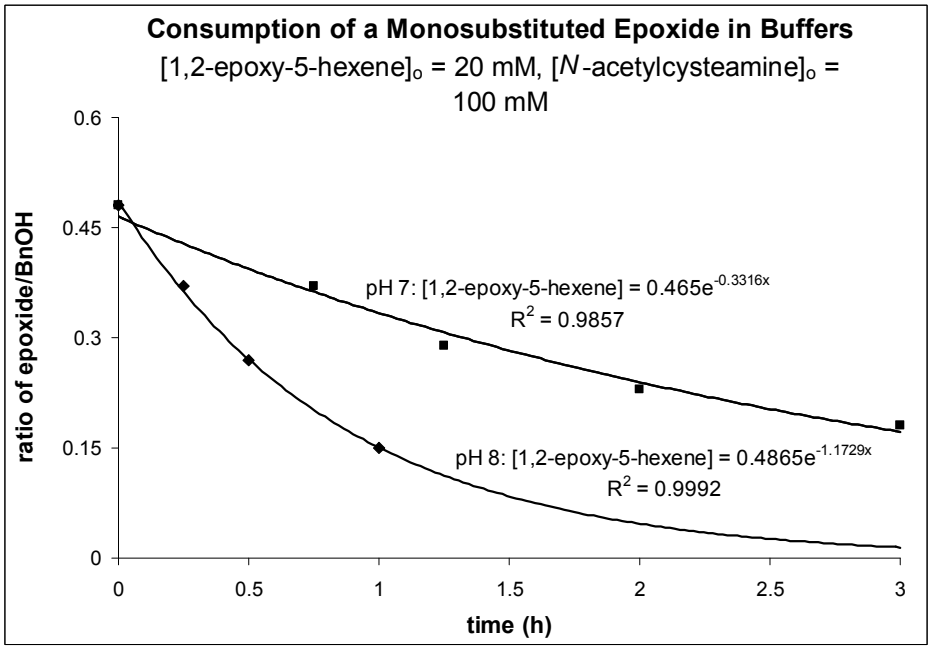


Figure 20. Consumption of 1,2-epoxy-5-hexene by *N*-acetylcysteamine in buffers at 37 °C

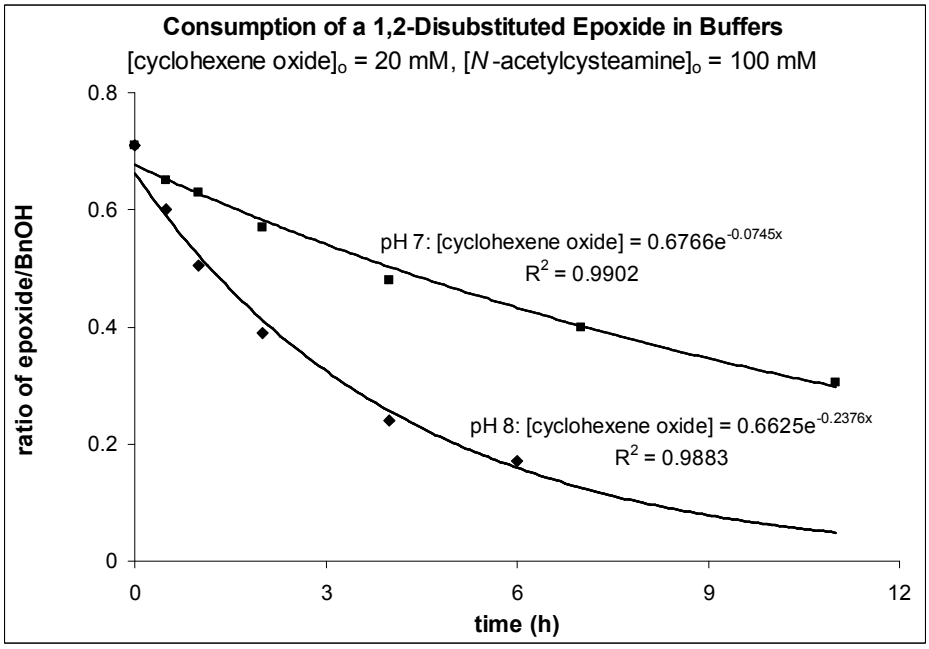


Figure 21. Consumption of cyclohexene oxide by *N*-acetylcysteamine in buffers at 37 °C

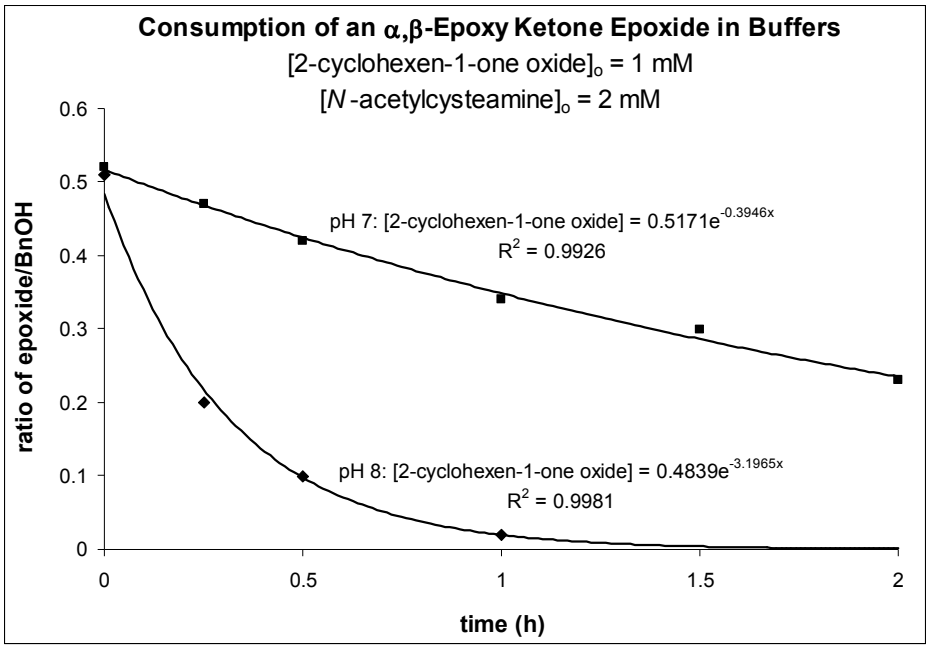
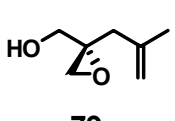
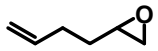
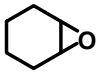
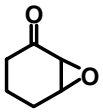


Figure 22. Consumption of 2-cyclohexen-1-one by *N*-acetylcysteamine in buffers at 37 °C

Unlike these cell-free experiments, the concentrations of biological thiols should be nearly constant due to the homeostatic environment, and in a large excess relative to epoxides. Thus, to gauge the reaction rates of these epoxides under biological conditions, the experimentally determined half-lives (summarized in Table 14) were converted to pseudo-first order by determining the initial rate (these half-lives not shown). Next, the psuedo-first order half-lives were adjusted to biologically relevant conditions using lower concentrations of thiols and epoxides. Intra- and extracellular concentrations of total thiols are approximately 12 mM and 0.3 mM, respectively,[167,168] indicating the intracellular environment as the major concern for the epoxide opening. Small molecule agents are typically used below 10 μM, and typically around 1 μM. Thus, the following biological half-lives ($t_{1/2}^{biol}$) were calculated for the epoxide motifs using 1 μM as the concentration of epoxide and 12 μM for the concentration of thiols at pH 7 and 8 (Table 14). As seen for epoxyalcohol **79**, spiroepoxide **205**, 1,2-epoxy-5-hexene, and cyclohexene oxide, the half-

lives were 8.2–130 y! Considering the high concentration of epoxide, these reactions are clearly inconsequential in biological experiments. One exception is the reactive 2-cyclohexen-1-one oxide, which has biological half-lives of 220 and 27 h at pH 7 and 8, respectively (Table 14).[166] This could explain the non-specific covalent binding of trapoxin B.[155]

Table 14. Half-lives of epoxides at 37 °C in pH 7/pH 8 phosphate buffers

	 **79**	 **205**			
$t_{1/2}^{exp}$	7.0 h/1.7 h	3.7 h/0.85 h	2.1 h/0.59 h	9.3 h/2.9 h	7.0 h/1.7 h
$t_{1/2}^{biol\ a}$	97 y/23 y	51 y/12 y	29 y/8.2 y	130 y/40 y	220 h/27 h

[a] half-lives under biologically relevant conditions: [epoxide] = 1 μM, [thiols] = 12 mM.

While the opening of epoxides with small molecule thiols appears to be biologically irrelevant, the non-specific opening with proteins remained unknown. To address this unanswered question, epoxyalcohol **79** was reacted with bovine serum albumin in pH 7 buffer (Figure 23). This protein was chosen due to its solubility at high concentrations and its reactive cysteine residue.[169] The consumption of epoxyalcohol **79** gave a half-life of 46 h under the experimental conditions, which extrapolates to a biological half-life of 10.5 y. Therefore, non-specific interactions with proteins fit the previous model, showing no reactivity towards epoxides under biological conditions.

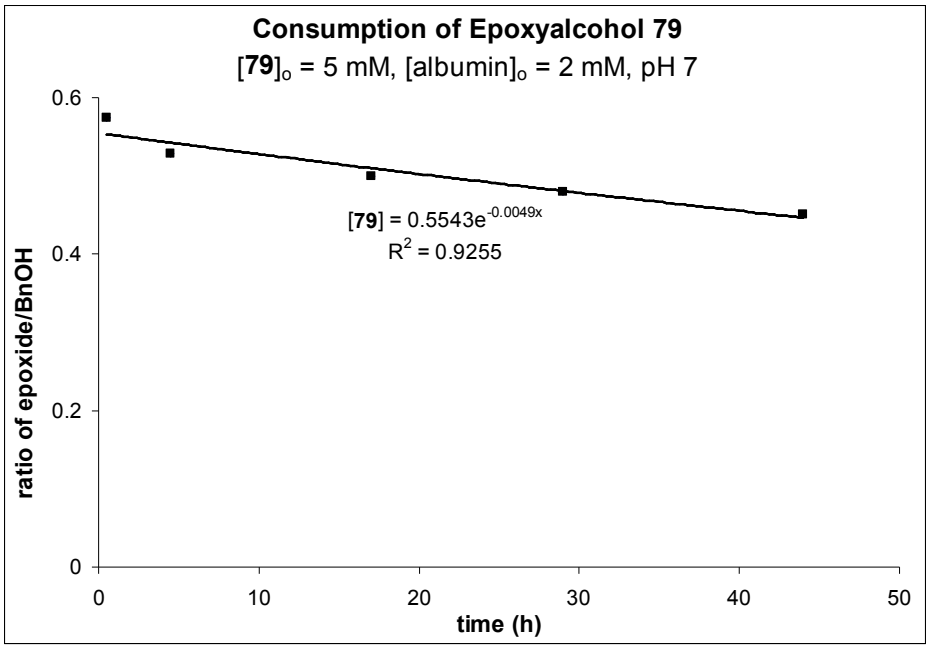


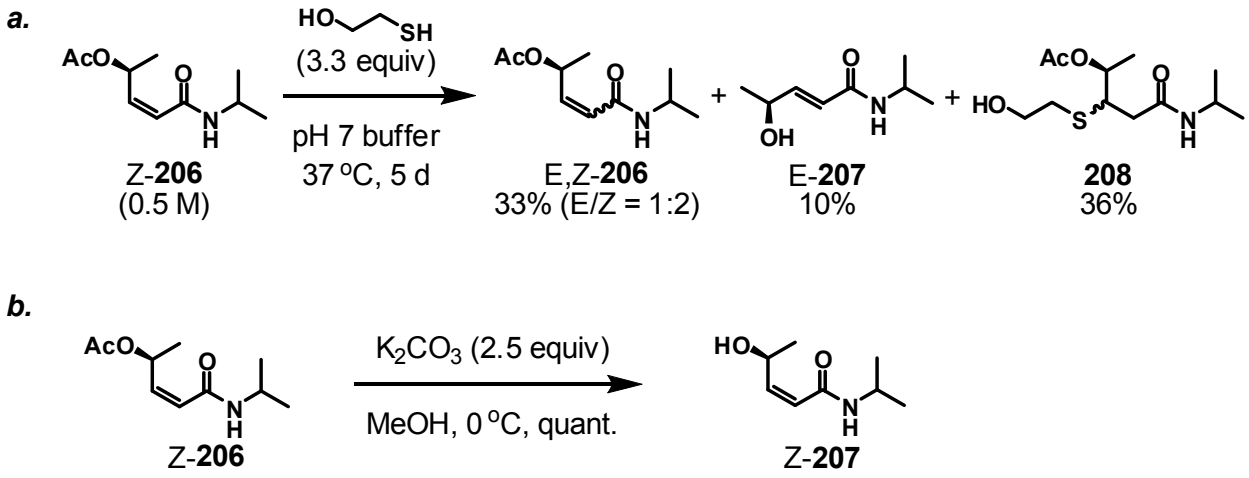
Figure 23. Consumption of epoxyalcohol **79** by albumin at 37 °C in pH 7 phosphate buffer

1.9.2 Reactions of α,β-unsaturated enamides with thiols

The reaction of thiols with acrylamide has generated much interest due to the associated neurotoxicity of this small molecule.[170-173] At comparable steric environments, amines are 280 times less nucleophilic towards α,β-unsaturated compounds in buffers.[170] Since this discovery, acrylamide has been shown to have deleterious effects on enzymes, and undergo reactions with endogenous small molecule thiols to generate the carcinogen, glycidamide.[171,173] The half-life of acrylamide in plasma, assuming 0.6 mM concentration of serum albumin, is approximated to be 60 h at 37 °C,[173] and the half-life intracellularly, assuming 3 mM glutathione concentration, was approximated to be 60 h under the same conditions.[173]

While well-defined kinetics for the additions of thiols to acrylamide exist, kinetics of additions to Z-enamides remained unknown. As a model system, unsaturated amide Z-**206**,

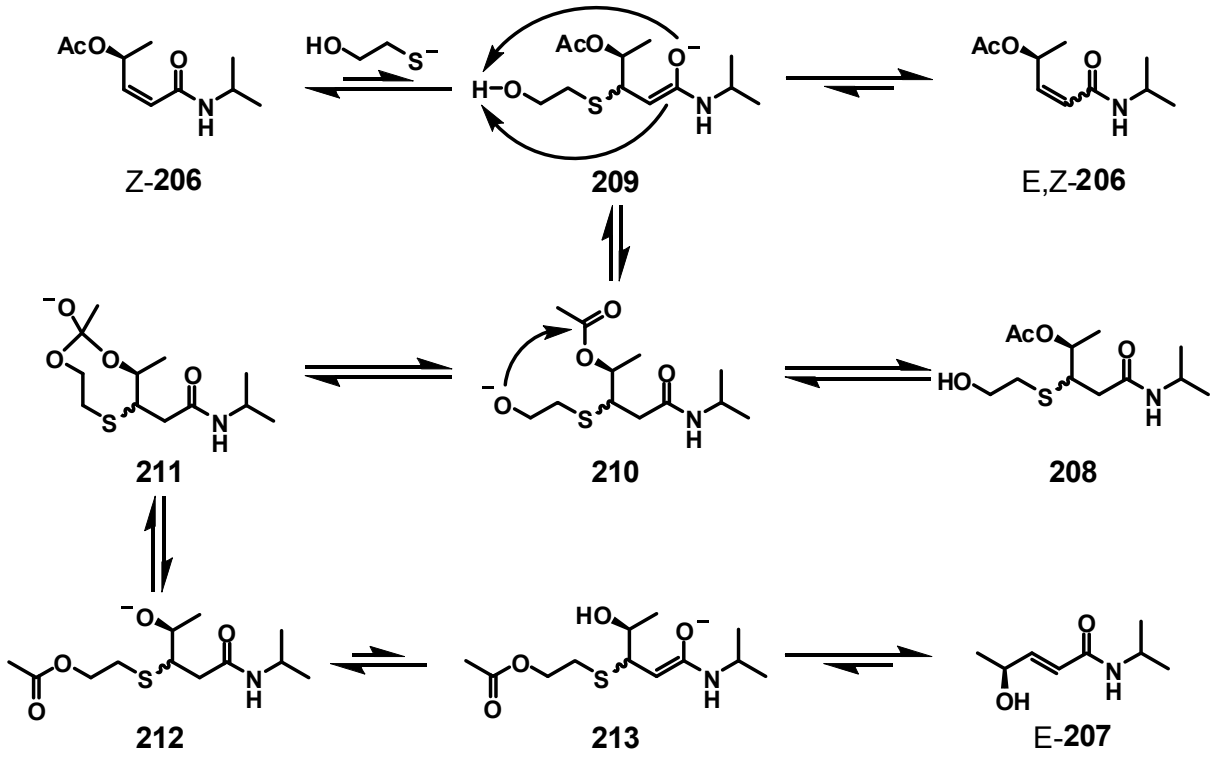
prepared by the condensation of **2** and isopropylamine, was treated with mercaptoethanol in pH 7 buffer at 37 °C. After 5 d at this temperature, the mixture consisted of **206** as a 1:2 E/Z mixture, E-**207**, and **208**, as a 3:1 unassigned diastereomeric ratio in 36, 10, and 36% yields respectively (Scheme 47*a*). To verify the scrambled geometry in observed in **207**, Z-**206** was deacetylated with basic methanol to give Z-**206** in quantitative yield (Scheme 47*b*). Therefore, it appears that non-specific thiol additions should be of no concern to the amide chain of FR901464 considering the high concentrations employed in *a*.



Scheme 47. Reactions of Z-**206**

The following mechanism could explain the observed products from the reaction of mercaptoethanol and Z-**206** (Scheme 48). Addition of a mercaptoethanol anion to Z-**206** would produce enolate **209**, presumably as a diastereomeric mixture. This enolate could lose mercaptoethanol by β-elimination to give E/Z-**206**, or could undergo proton exchanges intra- or intermolecularly to form alkoxide **210**. This alkoxide could be protonated by an equivalent of mercaptoethanol or water to give **208**, or reversibly attack the pendant acetyl group to form tetrahedral intermediate **211**. This tetrahedral intermediate could form acetate **212**, which then

could undergo proton exchange to give enolate **213**. This enolate could eject 2-mercaptoethyl acetate by β-elimination to give E-**207**, presumably the thermodynamic geometrical isomer. This reaction presumably had not reached equilibrium due to the 1:2 E/Z ratio, the Z-isomer presumably being thermodynamically disfavored, in amide E/Z-**206**. Based on this assumption, thiol additions should be negligible to the side chain of FR901464 in biological experiments.



Scheme 48. Plausible mechanisms for the formation of E/Z-**206**, E-**207**, and **207**

1.10 SUMMARY AND FUTURE DIRECTIONS

The total synthesis of FR901464 was accomplished in a total of 29 steps, which is the shortest synthesis to date. The instability of FR901464 was studied, which led to the rational development of meayamycin, an FR901464 analog with enhanced biological properties. Additional analogs were synthesized to examine the A-ring, C4' position, and the C3 position of the B-ring. These analogs demonstrated that the A-ring of FR901464 may be optimal, the C4' acetate should remain intact, and the spiroepoxide is required for antiproliferative properties. The desepoxy analogs lack of potency strongly suggest that FR901464 covalently modifies its target(s) via its epoxide, which led to the synthesis of a non-radioactive iodide-containing analog **202**, which in its ^{125}I form could be used for target identification experiments. Due to the concern of non-specific reactions of epoxides with endogenous thiols, a method was developed to study the consumption of epoxides with thiols. Experiments of common epoxide motifs showed that these reactions were negligible under biologically relevant conditions. Moreover, a model system for the amide chain of FR901464 demonstrated that its Z-enamide should not readily react non-specifically with endogenous thiols.

To address the instability of the C4'-acetate group, Dr. Li prepared a C4' carbamate, named meayamycin B (Figure 24). This compound has better stability in serum and is a more potent antiproliferative agent in a variety of cell lines. Dr. Li is also preparing fluorescent probes to visualize the localization of FR901464 in the cell.

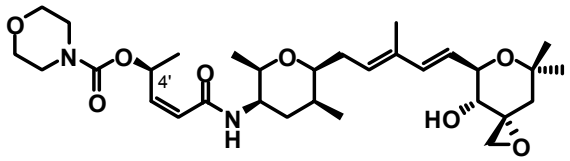


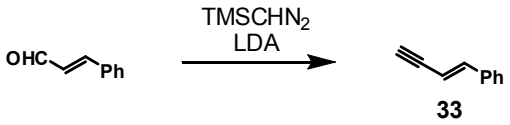
Figure 24. Structure of meayamycin B

In the future, target identification experiments will be performed to determine the FR901464-binding proteins. Iodides **202** should be suitable probes for these experiments, and the synthesis of these compounds have been outlined here. If meayamycin or meayamycin B proceed to clinical trials, their syntheses may need to be revised in terms of the number of steps as well as the final cross coupling reaction. Electrophilic right fragment analogs, that could containe an aldehyde, ketone, or boronic acid at position C3, could serve as the electrophilic moieties that will not covalently modify their targets should be synthesized. Finally, a simplified left fragment could produce a potent compound when conjugated to the right fragment of meayamycin. Towards this end, Sami Osman is nearing completion of TMC-205 (Figure 3), which could serve as a left-fragment replacement when conjugated to the right fragment of meayamycin.

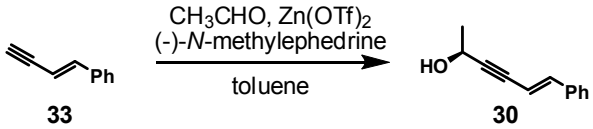
1.11 EXPERIMENTAL SECTION

General techniques. All reactions were carried out with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone, and methylene chloride (CH_2Cl_2) was distilled from calcium hydride. Acetonitrile was distilled from CaH_2 and stored over 3Å molecular sieves. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogenous materials, unless otherwise

stated. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25-mm Merck silica gel plates (60F-254) using UV light (254 nm), 2.4% phosphomolybdic acid/1.4% phosphoric acid/5% sulfuric acid in H_2O, anisaldehyde in ethanol, or 0.2% ninhydrin in ethanol and heat as developing agents. TSI silica gel (230-400 mesh) was used for flash column chromatography. NMR spectra were recorded on AM300 or AM500 (Bruker) instruments and calibrated using a solvent peak or tetramethylsilane as an internal reference. The following abbreviations are used to indicate the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. High resolution mass spectra were obtained by using EBE geometry.



Preparation of and data for 33. See K. Miwa, T. Aoyama, T. Shiori *Synlett* **1994**, 107.

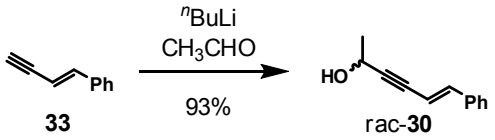


General procedure for the preparation of (*E*)-(2*S*)-6-phenylhex-5-en-3-yn-2-ol (30). To a flask containing $Zn(OTf)_2$ (13.6–16.4 g, 37.5–45.0 mmol) and (–)-*N*-methylephedrine (7.18–8.61 g, 40.0–48.0 mmol) was added the base (see Table 3, 40–48 mmol) followed by **33** (3.20–3.85 g, 25.0–30.0 mmol) in toluene (15 mL) at 23 °C under a nitrogen atmosphere. After 1.5 h at the same temperature, the reaction mixture was placed at the desired reaction temperature, and acetaldehyde (2.8–3.3 mL, 50–60 mmol) in toluene (70–85 mL) was passed through activated 4Å molecular sieves and added dropwise to the reaction mixture. After 17 h at

the same temperature, the reaction mixture was diluted with saturated aqueous NH_4Cl (70–75 mL), filtered through a pad of Celite 545®, rinsed with H_2O (1 × 15 mL) then EtOAc (3 × 30 mL), and the layers were separated. The aqueous residue extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with aqueous HCl (1 N, 60 mL) then brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (5 → 15% EtOAc in hexanes) on silica gel (125–150 mL) to afford **30** as a pale yellow oil.

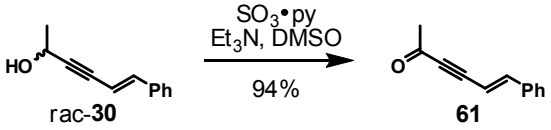
Data for **30**: R_f = 0.40 (30% EtOAc in hexanes); $[\alpha]_D^{23}$ –2.4 (*c* 4.1, $CHCl_3$);* IR (neat): 3334 (br, O-H), 3059, 3028, 2980, 2917, 2849, 2207, 1447, 1165, 1074, 1010, 953, 896 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 7.33–7.20 (m, 5H), 6.89 (d, 1H, *J* = 16.3 Hz), 6.11 (dd, 1H, *J* = 16.3, 1.7 Hz), 4.65 (br q, 1H, *J* = 6.4 Hz), 1.91 (br s, 1H), 1.46 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 141.7, 136.0, 128.7, 128.4, 126.2, 107.4, 93.1, 83.2, 58.9, 24.3; HRMS (EI+) calcd. for $C_{12}H_{12}O$ $[M]^+$ 172.0888, found 172.0889.

* $[\alpha]_D$ reported is for material in a 86:14 er



Procedure for the preparation of rac-30. To a stirred solution of **33** (1.28 g, 9.98 mmol) in THF (4.5 mL) was added ^{n}BuLi (1.6 M in hexanes, 6.25 mL, 10.0 mmol) at –78 °C under a nitrogen atmosphere. After 15 min at the same temperature, acetaldehyde (850 μL, 15.1 mmol) was added. After 10 min at the same temperature, the reaction mixture was warmed to 0 °C. After 1 h at the same temperature, the reaction mixture was quenched with saturated aqueous

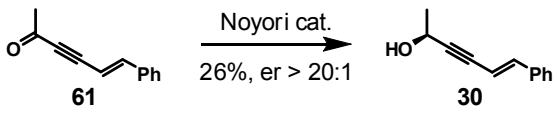
NH_4Cl (30 mL). The reaction mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (5 → 15% EtOAc in hexanes) on silica gel (50 mL) to afford a mixture of **rac-30** (1.59 g, 93%) as a pale yellow oil.



rac-**30** **61**

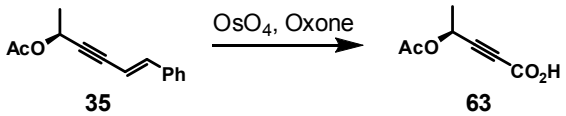
Procedure for the preparation of 61. To a stirred solution of **61** (1.13 g, 6.54 mmol) and Et_3N (3.70 mL, 26.5 mmol) in DMSO (7.0 mL) and CH_2Cl_2 (14 mL) was added SO_3•py (2.08 g, 13.0 mmol) at –44 °C under a nitrogen atmosphere. After 20 min at the same temperature, the reaction mixture was warmed to 0 °C. After 1 h at the same temperature, the reaction mixture was quenched with aqueous HCl (0.1 N, 200 mL). The reaction mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with aqueous HCl (0.1 N, 200 mL) then brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (2.5 → 7.5% EtOAc in hexanes) on silica gel (40 mL) to afford a mixture of **61** (1.04 g, 94%) as a pale yellow oil.

Data for **61**: See A. R. Katritzky, J. Yao, M. Qi *J. Org. Chem.* **1997**, *62*, 8201–8204



61 30

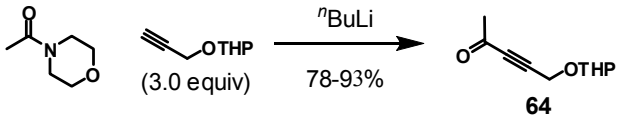
Procedure for the preparation of 30 by a Noyori reduction. See K. Mataumura, S. Hashiguchi, T. Ikariya, R. Noyori *J. Am. Chem. Soc.* **1997**, *119*, 8738-8739. Yield: 26%



35 63

Preparation of (*S*)-4-acetoxypent-2-ynoic acid (63) by OsO_4-Oxone® procedure. To a stirred solution of **35** (196 mg, 0.915 mmol) and Oxone® (2.25 g, 3.66 mmol) in DMF (4.5 mL) was added OsO_4 (1.7 mg, 6.7 μmol) at 23 °C under an open atmosphere. After 9 h at the same temperature, the reaction mixture was quenched with Na_2SO_3 (692 mg, 5.49 mmol) and stirred for 15 min. The reaction mixture was then diluted with H_2O (5 mL) and aqueous HCl (1.0 N, 5 mL). The resulting mixture was extracted with EtOAc (5 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (20 → 100% EtOAc in hexanes) on silica gel (15 mL) to afford a mixture of **63**, benzoic acid, and DMF (529 mg).

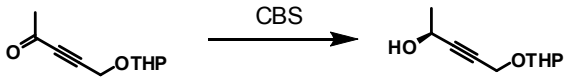
Data for **63**: R_f = 0.22 (1.0% AcOH in EtOAc); $[\alpha]_D^{23}$ −128 (*c* 1.60, $CHCl_3$); IR (neat): 3188 (broad, O-H), 2984, 2941, 2248, 1749 (C=O), 1719 (C=O), 1374, 1227, 1049 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 5.54 (q, 1H, *J* = 6.8 Hz), 2.11 (s, 3H), 1.57 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 169.9, 156.8, 87.3, 75.6, 59.4, 20.8, 20.1; HRMS (EI+) calcd. for $C_7H_6O_3$ $[M - H_2O]^+$ 138.0317, found 138.0322.



64

Preparation of 64. To a stirred solution of tetrahydro-2-(prop-2-ynyloxy)-2*H*-pyran (21.01 g, 150 mmol) in THF (90 mL) was added ^{n}BuLi (1.6 M in hexanes, 92 mL) dropwise over 20 min at 0 °C under a nitrogen atmosphere. After an additional 15 min at the same temperature, *N*-acetylmorpholine (5.8 mL, 50 mmol) in THF (8 mL) was added dropwise to the reaction mixture, and then the container that initially contained *N*-acetylmorpholine was rinsed with THF (2 × 1 mL) and added to the reaction mixture at the same temperature. After an additional 1.4 h at 0 °C, the reaction mixture was cannulated into a flask containing AcOH (120 mL) and H_2O (60 mL) at 0 °C, the reaction container was rinsed with Et_2O (50 mL), and then the resulting layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (300 mL). The combined aqueous layers were extracted with Et_2O (50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (2.5 → 10% EtOAc in hexanes) on silica gel (600 mL) to afford **64** (7.141 g, 78%) as a colorless oil.

Data for **64**: See R. C. Larock, C. L. Liu *J. Org. Chem.* **1983**, *48*, 2151–2158.

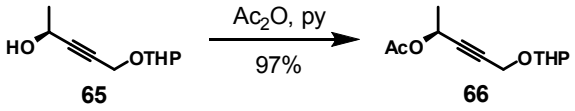


64 65

Preparation of 65. To a stirred solution of (*S*)-2-methyl-CBS-oxazaborolidine (554 mg, 2.00 mmol) and catechol borane (1.7 mL, 16 mmol) in $EtNO_2$ (25 mL) was added **64** (1.83 g, 10.0 mmol) in $EtNO_2$ (7 mL) via syringe pump over 20 min which was followed by a rinse of the container that originally contained **64** with $EtNO_2$ (1 mL) at −78 °C under a nitrogen atmosphere.

After an additional 2.7 h at the same temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (35 mL), and the mixture was then diluted with Et_2O (100 mL). The layers were separated and the organic layer was washed with aqueous NaOH (1 N, 2 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 → 30% EtOAc in hexanes) on silica gel (100 mL) to afford **65** and a small amount of catechol (1.979 g) as a pale yellow oil.

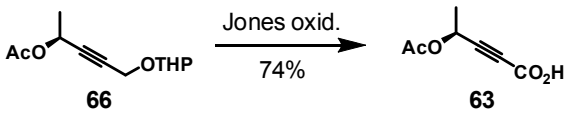
Data for **65**: See R. W. Bates, D. Díez-Martín, W. J. Kerr, J. G. Knight, S. V. Ley, A. Sakellaridis *Tetrahedron* **1990**, *46*, 4063–4082.



Preparation of 66. To a stirred solution of **65** and catechol (1.59 g, ~8.0 mmol) in pyridine (15 mL) was added Ac_2O (3.5 mL, 37 mmol) at 23 °C under an open atmosphere. After 41.5 h at the same temperature, the reaction mixture was diluted with H_2O (330 mL) and saturated aqueous $NaHCO_3$ (20 mL). The resulting mixture was then extracted with Et_2O (3 × 75 mL). The combined organic layers were washed with saturated aqueous $CuSO_4$ (1 × 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (5 → 10% EtOAc in hexanes) on silica gel (75 mL) to afford **66** (1.79 g, 97% for the two steps) as a colorless oil.

Data for **66**: R_f = 0.54 (30% EtOAc in hexanes); IR (neat): 2941, 1743 (C=O), 1442, 1372, 1235, 1120, 1053, 1025 cm–1; $[\alpha]_D^{25}$ –68.0 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 5.51 (br q, 1H, *J* = 6.7 Hz), 4.82–4.78 (m, 1H), 4.34 (dd, 1H, *J* = 15.7, 1.7 Hz), 4.26 (dd, 1H, *J* = 15.7, 1.6 Hz), 3.84 (br ddd, 1H, *J* = 11.9, 9.0, 3.2 Hz), 3.58–3.50 (m, 1H), 2.08 (s,

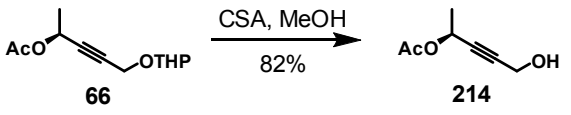
3H), 1.89−1.53 (m, 6H), 1.50 (d, 1H, J = 6 Hz); ^{13}C NMR (75 MHz, 293K, CD_2Cl_2) δ 169.8, 96.7, 84.22, 84.19, 80.7, 61.9, 60.3, 54.11, 54.08, 30.1, 25.3, 21.3, 21.0.



66 **63**

Preparation of 63 from 66. To a stirred solution of **66** (113 mg, 0.501 mmol) in acetone (2 mL) was added cold $Na_2Cr_2O_7$ (0.5 N in 2 N H_2SO_4, 3.5 mL) dropwise at 0 °C under an open atmosphere. After 2 h at the same temperature, the reaction was warmed to 23 °C. After 30 min at the same temperature, the reaction was cooled to 0 °C, and to the reaction mixture was added Na_2SO_3 (63.3 mg, 0.502 mmol). After an additional 15 min at the same temperature, the reaction mixture was poured onto aqueous HCl (1 N, 30 mL), and the mixture was extracted with EtOAc (5 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (20 → 100% EtOAc in hexanes containing 1% AcOH) on silica gel (5 mL) to afford **63** (68.4 mg, 74%) as a colorless oil.

Data for **63**: See B. J. Albert, A. Sivaramakrishnan, T. Naka, K. Koide *J. Am. Chem. Soc.* **2006**, *128*, 2792–2793.

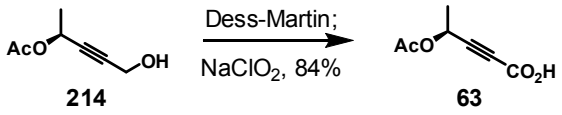


66 **214**

Preparation of 214. To a stirred solution of **66** (450 mg, 2.00 mmol) in MeOH (20 mL) was added PPTS (101 mg, 0.402 mmol) at 0 °C under an open atmosphere. After 30 min at the same temperature, the reaction mixture was warmed to 23 °C. After an additional 17 h at the

same temperature, the reaction mixture was quenched with Et_3N (70 μL, 0.50 mmol), and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 → 40% EtOAc in hexanes) on silica gel (25 mL) to afford **214** (234 mg, 82%) as a colorless oil.

Data for **214**: R_f = 0.33 (40% EtOAc in hexanes); IR (neat): 3422 (br), 2939, 1736 (C=O), 1373, 1239, 1025, 849 cm^{-1}; $[\alpha]^{22}_D$ –94.6 (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 5.48 (qdd, 1H, *J* = 6.7, 1.7, 1.7 Hz), 4.33 (dd, 1H, *J* = 16.1, 1.7 Hz), 4.26 (dd, 1H, 16.1, 1.7 Hz), 2.08 (s, 3H), 1.78–1.72 (br s, 1H), 1.50 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 170.1, 83.6, 83.2, 60.4, 50.5, 21.0, 20.9; HRMS (EI+) calcd. for $C_7H_8O_2$ $[M - H_2O]^+$ = 124.0524, found 124.0520.



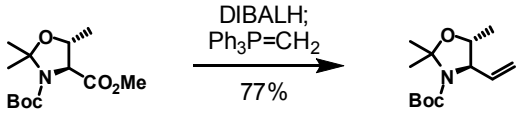
214 **63**

To a stirred solution of **214** (142 mg, 1.00 mmol) in CH_2Cl_2 (20 mL) was added Dess-Martin periodinane (638 mg, 1.50 mmol) at 0 °C under an open atmosphere. After 1.5 h at the same temperature, the reaction mixture was diluted with hexanes (4 mL), filtered through a pad of Florisil (2 mL), rinsed with 40% Et_2O in hexanes (2 × 5 mL), and concentrated under reduced pressure. Crude ^1H NMR showed the clean formation of an aldehyde that was immediately subjected to the next reaction without further purification.

To a stirred solution of this crude aldehyde (~1.00 mmol) and 2-methyl-2-butene (1.0 mL, 9.3 mmol) in ^{t}BuOH (2.5 mL) was added a solution of NaH_2PO_4 (414 mg, 3.00 mmol) and $NaClO_2$ (227 mg, 2.01 mmol) in H_2O (2.5 mL) at 23 °C under an open atmosphere. After 30 min at the same temperature, aqueous HCl (1 N, 6 mL) was added followed by sodium chloride until

the aqueous layer was saturated. The aqueous residue was extracted with EtOAc (4 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (20 → 100% EtOAc in hexanes containing 1% AcOH) on silica gel (15 mL) to afford **66** (133 mg, 84%) as a colorless oil.

Data for **63**: See B. J. Albert, A. Sivaramakrishnan, T. Naka, K. Koide *J. Am. Chem. Soc.* **2006**, *128*, 2792–2793.



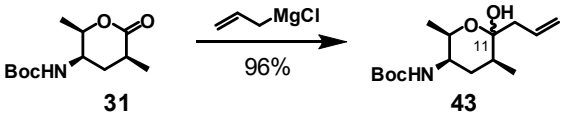
36 **38**

Preparation of 38 by a one-pot procedure. To a stirred solution of Ph_3PCH_3Br (53.58 g, 150.0 mmol) in THF (150 mL) at 0 °C was added KO^{t}Bu (16.40 g, 146.2 g) in one portion. The resulting mixture was stirred for an additional one hour at the same temperature prior to use.

To a stirred solution of aminoester **36** (20.53 g, 75.11 mmol) in CH_2Cl_2 (250 mL) was added DIBALH (1 M in hexanes, 150 mL) dropwise over 2.5 h at −78 °C under a nitrogen atmosphere. After an additional 1.5 h at the same temperature, the ylide THF solution was added dropwise over 1.8 h. After an additional 15 min, the reaction mixture was warmed to 23 °C, and after an additional 2.8 h at the same temperature, the reaction mixture was warmed to 48 °C. After an additional 14 h at the same temperature, the reaction mixture was cooled to 23 °C, diluted with H_2O (100 mL) then aqueous HCl (1 N, 300 mL), and the layers were separated. The aqueous residue was extracted with EtOAc (4 × 200 mL). The combined organic layers were washed with brine (1 × 500 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under

reduced pressure. The resulting residue was purified by flash chromatography (1 → 5% EtOAc in hexanes) on silica gel (800 mL) to afford **38** (13.91 g, 77%) as a colorless oil.

Data for **38**: R_f = 0.48 (10% EtOAc in hexanes); IR (neat): 2979, 2935, 2880, 1702 (C=O), 1478, 1456, 1378, 1307, 1135, 1084 cm^{-1}; $[\alpha]_D^{22}$ +16.6 (*c* 3.93, $CHCl_3$); ^1H NMR (300 MHz, 333K, C_6D_6) δ 5.58 (ddd, 1H, *J* = 17.2, 10.1, 7.2 Hz), 5.02 (d, 1H, *J* = 17.2 Hz), 4.95 (dd, 1H, *J* = 10.4, 1.3 Hz), 3.75–3.64 (m, 2H), 1.73 (s, 3H), 1.57 (s, 3H), 1.41 (s, 9H), 1.10 (d, 3H, *J* = 6.0); ^{13}C NMR (75 MHz, 333K, C_6D_6) δ 152.2, 138.6, 115., 94.4, 79.3, 75.7, 67.6, 28.5, 27.3, 26.1, 17.7; HRMS (EI+) calcd. For $C_{12}H_{20}NO_3$ $[M - CH_3]^+$ 226.1443, found 226.1446.

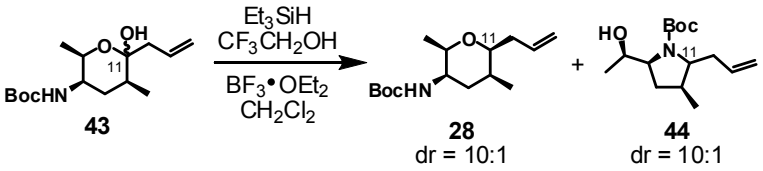


31 **43**

Preparation of 43. To a stirred solution of lactone **31** (1.520 g, 6.25 mmol) in THF (30 mL) at −78 °C was added allylmagnesium chloride (2.0 M solution in THF, 7.0 mL, 12 mmol) down the flask side under a nitrogen atmosphere. After 1.5 h at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl (25 mL) and most of the organic solvent was removed under reduced pressure. The aqueous residue was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (10 → 50% EtOAc in hexanes) on silica (100 mL) to afford hemiketal **43** (1.712 g, 96%) as a colorless oil.

Data for **43**: R_f = 0.26 (40% EtOAc in hexanes); IR (neat): 3437 (N-H), 3391 (br O-H), 2976, 2933, 1709 (C=O), 1692 (C=O), 1641, 1510, 1366, 1170, 1050 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 6.02–5.81 (m, 1H), 5.20–5.08 (m, 2H), 4.71 (br d, 1H, *J* = 9.0 Hz), 3.73–3.67

(m, 1H), 3.40–3.33 (m, 1H), 3.30–3.27 (m, 2H), 2.78–2.70 (m, 1H), 2.27 (br d, 1H, J = 7.4 Hz), 2.02–1.93 (m, 2H), 1.45 (s, 9H), 1.16 (d, 3H, J = 6.3 Hz), 1.13 (d, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 212.6, 156.3, 130.8, 118.5, 79.2, 69.1, 53.7, 46.5, 42.5, 35.7, 28.3, 20.2, 18.0; HRMS (EI+) calcd. for $C_{12}H_{22}NO_4$ $[M - C_3H_5]^+$ 244.1549, found 244.1550.

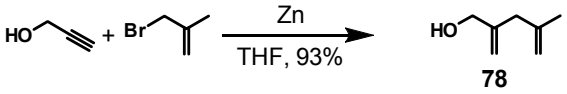


Preparation of 19. To a stirred solution of **43** (3.342 g, 11.71 mmol) in CH_2Cl_2 (50 mL) was added CF_3CH_2OH (6.8 mL, 93 mmol) and triethylsilane (18.5 mL, 116 mmol) at 23 °C under a nitrogen atmosphere. The reaction was cooled to −78 °C, then BF_3•OEt_2 (5.9 mL, 47 mmol) complex was added slowly down the flask side. After an additional 3 h at the same temperature, saturated aqueous $NaHCO_3$ (50 mL) was added at −78 °C, and the layers were separated. The aqueous residue was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (75 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (2 → 12.5% EtOAc in hexanes) on silica gel (150 mL) to afford **28** (1.242 g, 39%) and **44** (707 mg, 22%) as colorless oils.

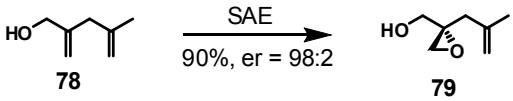
Data for **28**: R_f = 0.30 (10% EtOAc in hexanes); IR (neat): 3460 (N-H), 2977, 2934, 1718 (C=O), 1642, 1496, 1366, 1171, 1058 cm^{-1}; $[\alpha]_D^{22}$ −10.1 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 5.80 (dddd, 1H, J = 17.1, 10.2, 7.6, 6.3 Hz), 5.14–5.08 (m, 1H), 5.05 (br d, 1H, J = 10.2 Hz), 4.77 (br d, 1H, J = 9.1 Hz), 3.64–3.56 (m, 2H), 3.51 (ddd, J = 7.4, 7.4, 2.9 Hz), 2.38–2.28 (m, 1H), 2.17–2.06 (m, 1H), 1.93–1.90 (m, 2H), 1.78–1.70 (m, 1H), 1.44 (s, 9H), 1.15

(d, 3H, J = 6.3 Hz), 1.04 (d, 3H, J = 7.4 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 155.9, 134.8, 116.6, 80.6, 78.9, 76.3, 48.3, 37.4, 36.0, 28.8, 28.4, 17.7, 14.9; HRMS (EI+) calcd. for $C_{12}H_{22}NO_3$ $[M - C_3H_5]^+$ 228.1600, found 228.1593.

Data for **44**: R_f = 0.32 (30% EtOAc in hexanes); IR (neat) 3386 (br O-H), 2974, 2931, 2868, 1692 (C=O), 1663, 1450, 1397, 1367, 1172, 1233, 1113 cm^{-1}; $[\alpha]_D^{22}$ +19.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 5.82–5.68 (m, 1H), 5.05 (br s, 1H), 5.02–5.00 (m, 1H), 3.73 (ddd, J = 7.9, 7.9, 5.9 Hz), 3.62–3.54 (m, 1H), 3.48–3.43 (ddd, J = 7.4, 7.4, 2.9 Hz), 2.28 (br t, 2H), 2.05–1.97 (m, 1H), 1.75–1.64 (m, 2H), 1.62–1.51 (m, 1H), 1.48 (s, 9H), 1.09 (d, 3H, J = 6.1 Hz), 0.95 (d, 3H, J = 6.8 Hz); ^{13}C NMR (75 MHz, 293K, C_6D_6) δ 158.1, 135.2, 117.2, 80.1, 72.7, 65.7, 64.8, 39.0, 35.7, 34.9, 28.4, 21.3, 18.9; HRMS (EI+) calcd. for $C_{12}H_{22}NO_3$ $[M - C_3H_5]^+$ 228.1600, found 228.1598.



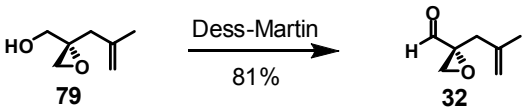
Preparation of allyl alcohol 78. See Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 107–108. Yield: 93%



Preparation of epoxyalcohol 79. To a stirred suspension of activated 4Å molecular sieves (51.39 g) in CH_2Cl_2 (900 mL) was added (+)–diisopropyl tartrate (4.5 mL, 21 mmol) at 23 °C under a nitrogen atmosphere. The reaction mixture was cooled to –25 °C then titanium isopropoxide (5.2 mL, 18 mmol) was added, followed by ^{t}BuOOH (5–6 M in isooctane, 84 mL,

420–504 mmol). The mixture was stirred for 45 min at –25 °C to allow for the catalyst to generate, then allyl alcohol **78** (25.4 g, 126 mmol) in CH_2Cl_2 (50 mL) was added over 25 min. The reaction was stirred for an additional 3.5 h at –20 to –25 °C, then was quenched with 3 M NaOH (25 mL) and vigorously stirred for 1 h at 23 °C. To the resulting reaction mixture was added solid NaCl, anhydrous Na_2SO_4, and Celite 545®. The mixture was filtered through a pad of Celite 545®, eluting with 60% EtOAc in hexanes (1 L), and concentrated under reduced pressure. The residue was purified by flash chromatography (10 → 30% EtOAc in hexanes) on silica gel (1.0 L) to afford epoxyalcohol **79** (26.21 g, 90% yield) as a colorless liquid.

Data for **79**: R_f = 0.33 (40% EtOAc in hexanes); IR (neat): 3431 (br), 2922, 1650, 1449, 1045, 896 cm^{-1}; $[\alpha]^{22}_D$ –47.8 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 4.88–4.86 (m, 1H), 4.82–4.81 (m, 1H), 3.77 (dd, 1H, *J* = 12.4, 4.3 Hz), 3.66 (dd, 1H, *J* = 12.4, 8.6 Hz), 2.95 (br d, 1H, *J* = 4.8 Hz), 2.71 (br d, 1H, *J* = 4.8 Hz), 2.53 (br d, 1H, *J* = 14.4 Hz), 2.22 (br d, 1H, *J* = 14.4 Hz), 1.78 (s, 3H), 1.65 (dd, 1H, *J* = 8.6, 4.5 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 140.8, 113.8, 62.4, 58.6, 49.7, 40.6, 23.0; HRMS (EI+) calcd. for $C_7H_{11}O_2$ $[M - H]^+$ = 127.0759, found 127.0760.

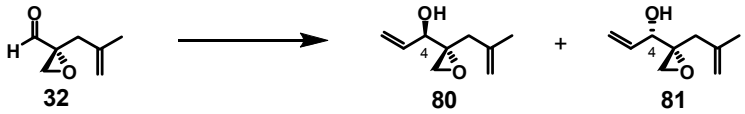


Preparation of epoxyaldehyde 32 by Dess-Martin oxidation. To a stirred solution of Dess–Martin periodinane (77.5 g, 183 mmol) in CH_2Cl_2 (350 mL) was added epoxyalcohol **79** (15.4 g, 122 mmol) in CH_2Cl_2 (50 mL) dropwise at 0 °C under a nitrogen atmosphere. The reaction was slowly warmed to 23 °C. After 3.5 h, the reaction was diluted with Et_2O (200 mL), and poured onto a saturated aqueous solution of $NaHCO_3$ (700 mL) containing $NaHSO_3$ (100 g,

961 mmol) and vigorously stirred for 45 min at 23 °C. After the two layers were separated, the aqueous layer was extracted with Et_2O (2 × 250 mL). The combined organic layers were washed with a saturated aqueous $NaHCO_3$ (250 mL), then brine (250 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford **32** (13.9 g, ~81 %) as a pale yellow crude residue. The crude residue was not further purified due to the volatility of **32**.

Preparation of epoxyaldehyde 32 by Parikh-Doering oxidation. To a stirred solution of **79** (9.62 g, 72.3 mmol) and Et_3N (42.0 mL, 300 mmol) in DMSO (65 mL) and CH_2Cl_2 (185 mL) was added SO_3•py (23.9 g, 153 mmol) at –44 °C under a nitrogen atmosphere. After 15 min at the same temperature, the reaction mixture was warmed to 0 °C. After 4 h at the same temperature, the reaction mixture was quenched with aqueous HCl (0.3 N, 1.5 L). The reaction mixture was extracted with CH_2Cl_2 (8 × 150 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (5 → 20% Et_2O in hexanes) on silica gel (250 mL) to afford a mixture of **32** (6.50 g, 69%) as a pale yellow oil.

Data for **32**: R_f = 0.48 (30% EtOAc in hexanes); IR (neat): 2975, 2918, 2826, 1727 (C=O), 1652, 1449, 898, 871 cm^{-1}; $[\alpha]_D^{22}$ +24.5 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.96 (s, 1H), 4.88–4.87 (m, 1H), 4.77–4.76 (m, 1H), 3.07 (d, 1H, J = 4.8 Hz), 3.04 (d, 1H, J = 4.8 Hz), 2.66 (d, 1H, J = 15.3 Hz), 2.54 (d, 1H, J = 15.3 Hz), 1.76 (br s, 3H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 198.5, 139.7, 114.1, 60.3, 49.3, 35.0, 23.5; HRMS (EI+) calcd. for $C_7H_9O_2$ $[M - H]^+$ 125.0603, found 125.0602.



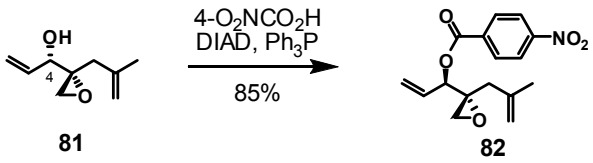
Preparation of alcohols 6 and 7 with divinyl zinc (Table 6, entry 2). Preparation of divinyl zinc: Zinc chloride (8.10 g, 59.5 mmmol) was heated to 130 °C under reduced pressure for 2 h, then placed under a nitrogen atmosphere, and dissolved in THF (32 mL). Vinyl magnesium bromide (1.0 M in THF, 118 mL) was added dropwise at 23 °C, and then the insoluble salts were allowed to settle after addition was complete.

To a stirred solution of divinyl zinc (130 mL, 51.6 mmol) was added epoxyaldehyde **32** (3.60 g, 28.5 mmol) in THF (10 mL) over 20 min at –72 °C under a nitrogen atmosphere. The resulting reaction mixture was stirred for an additional 45 min at –78 °C, then warmed to 0 °C. After 15 min at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl (50 mL). The resulting mixture was then filtered through a pad of Celite 545®, the layers were separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O (25 mL), then brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (10% EtOAc in hexanes) on silica gel (400 mL) to afford **80** (0.831 g, 16% yield) and **81** (2.22 g, 55%) as colorless oils.

Data for alcohol **80**: R_f = 0.29 (25% EtOAc in hexanes); IR (neat): 3425 (br), 2929, 1650, 1437, 1376, 1056, 927, 895 cm^{-1}; $[\alpha]_D^{22}$ –38.9 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, 293K, C_6D_6) δ 5.75 (ddd, 1H, *J* = 17.2, 10.5, 5.7 Hz), 5.21 (ddd, 1H, *J* = 17.2, 1.7, 1.7 Hz), 5.01 (ddd, 1H, *J* = 10.5, 1.6, 1.6 Hz), 4.76–4.75 (m, 1H), 4.71–4.70 (m, 1H), 3.95 (dddd, 1H, *J* = 6.9, 5.7, 1.4, 1.3 Hz), 2.57 (d, 1H, *J* = 5.1 Hz), 2.35 (d, 1H, *J* = 14.5 Hz), 2.31 (d, 1H, *J* = 5.2 Hz), 2.25 (d, 1H, *J* = 14.5 Hz), 1.62 (br s, 3H), 1.46 (d, 1H, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 140.9,

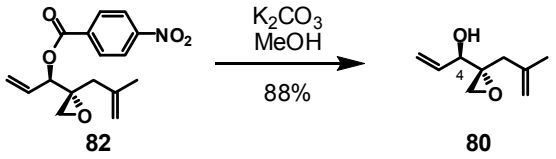
136.1, 117.6, 114.3, 73.2, 60.0, 49.5, 39.3, 23.3; HRMS (EI+) calcd. for $C_9H_{13}O_2$ $[M - H]^+$ 153.0916, found 153.0917.

Data for alcohol **81**: R_f = 0.32 (25% EtOAc in hexanes); IR (neat): 3451 (br), 2920, 1650, 1435, 1377, 1065, 1029, 928; $[\alpha]_D^{22}$ +49.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 5.81 (ddd, 1H, *J* = 17.2, 10.3, 6.7 Hz), 5.41 (ddd, 1H, *J* = 17.2, 1.5, 1.2 Hz), 5.28 (ddd, 1H, *J* = 10.3, 1.5, 1.0 Hz), 4.90–4.88 (m, 1H), 4.80–4.79 (m, 1H), 4.27 (br d, 1H, *J* = 7.7 Hz), 2.89 (d, 1H, *J* = 4.8 Hz), 2.63 (d, 1H, *J* = 4.8 Hz), 2.48 (br d, 1H, *J* = 14.6 Hz), 2.35 (br d, 1H, *J* = 14.7 Hz), 2.19 (br s, 1H), 1.79 (br s, 3H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 140.7, 135.8, 118.2, 114.6, 71.2, 60.0, 48.2, 39.7, 23.2; LRMS (EI+) calcd. for $C_9H_{12}O$ $[M - H_2O]^+$ 136.0888, found 136.0892.



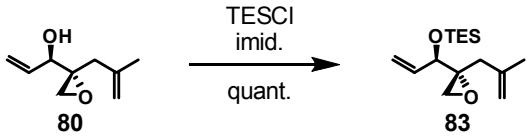
Preparation of ester 82. To a stirred solution of Ph_3P (1.58 g, 6.01 mmol) and 4-O_2N-$PhCO_2H$ (1.00 g, 6.01 g) in THF (8 mL) was added DIAD (1.15 mL, 5.84 mmol) dropwise followed by the dropwise addition of **81** (311 mg, 2.02 mmol) in THF (1 mL) and then the container that initially contained **81** was rinsed with THF (2 × 0.5 mL) and added to the reaction mixture at 0 °C under a nitrogen atmosphere. After 5 min at the same temperature, the reaction mixture was warmed to 23 °C. After 55 min at the same temperature, most of the solvent was removed under reduced pressure. The residue was purified by flash chromatography (2.5 → 10% EtOAc in hexanes) on silica gel (150 mL) to afford **82** (522 mg, 85% yield) as colorless oil.

Data for alcohol **82**: R_f = 0.44 (20% EtOAc in hexanes); IR (neat): 3078, 2920, 1731 (C=O), 1529, 1348, 1270, 1102, 720 cm^{-1}; $[\alpha]_D^{22}$ +14.6 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 8.34–8.28 (m, 2H), 8.27–8.21 (m, 2H), 5.95 (ddd, 1H, *J* = 17.2, 10.5, 6.6 Hz), 5.60 (br d, 1H, *J* = 6.6 Hz), 5.43 (br d, 1H, *J* = 17.2 Hz), 5.40 (br d, 1H, *J* = 10.5 Hz), 4.91 (br s, 1H), 4.82 (br s, 1H), 2.89 (br d, 1H, *J* = 4.6 Hz), 2.77 (br d, 1H, *J* = 4.6 Hz), 2.60 (br d, 1H, 14.6 Hz), 2.40 (br d, 1H, *J* = 14.6 Hz), 1.81 (br s, 3H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 163.3, 150.6, 140.3, 135.2, 131.5, 130.7, 123.6, 119.9, 114.7, 76.7, 58.5, 49.5, 39.9, 23.1; HRMS (ESI+) calcd. for $C_{16}H_{17}NO_2Na$ $[M + Na]^+$ 326.1004, found 326.1019.



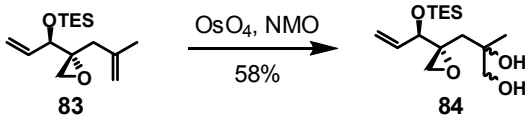
82 **80**

Preparation of 81 from ester 82. To a stirred solution of K_2CO_3 (1.73 g, 12.5 mmol) in MeOH (10 mL) was added nitrobenzoate **82** (1.52 g, 5.03 mmol) in MeOH (10 mL) dropwise 0 °C under an open atmosphere. After 30 min at the same temperature, saturated aqueous NH_4Cl (10 mL) and concentrated under reduced pressure. The aqueous residue was diluted with H_2O (10 mL), and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (2.5 → 15% EtOAc in hexanes) on silica gel (65 mL) to afford **80** (683 mg, 88%) as colorless oil.

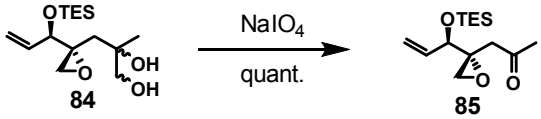


Preparation of TES ether 83. To a stirred solution of imidazole (1.18 g, 17.3 mmol) in THF (15 mL) was added chlorotriethylsilane (2.4 mL, 14 mmol), followed by the dropwise addition of alcohol **80** (1.91 g, 12.4 mmol) in THF (10 mL) at 0 °C under a nitrogen atmosphere. After an additional 30 min at the same temperature, saturated aqueous NH_4Cl (10 mL) was added, the layers were separated, and then the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with H_2O (30 mL) then brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and reduced under pressure. The resulting residue was purified by flash chromatography (1 → 5% EtOAc in hexanes) on silica gel (100 mL) to afford **83** (3.32 g, quant. yield) as a colorless oil.

Data for **83**: R_f = 0.67 (20% EtOAc in hexanes); IR (neat): 2955, 2913, 2877, 1650, 1459, 1416, 1089, 1007, 831, 743 cm^{-1}; $[\alpha]_D^{22}$ –7.2 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 5.86 (ddd, 1 H, *J* = 17.2, 10.4, 6.2 Hz), 5.30 (ddd, 1 H, *J* = 17.2, 1.6, 1.6 Hz), 5.19 (ddd, 1H, *J* = 10.5, 1.5, 1.5 Hz), 4.84–4.83 (m, 1H), 4.74–4.73 (m, 1H), 4.02 (ddd, 1H, *J* = 6.2, 1.3, 1.3 Hz), 2.80 (d, 1H, *J* = 5.0 Hz), 2.66 (d, 1H, *J* = 5.0 Hz), 2.55 (d, 1H, *J* = 14.6 Hz), 2.28 (br d, 1H, *J* = 14.6 Hz), 1.74 (br s, 3H), 1.00–0.93 (m, 9H), 0.66–0.58 (m, 6H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 141.2, 137.3, 116.3, 114.1, 75.9, 60.7, 49.2, 37.7, 23.5, 6.7, 6.5, 5.8, 4.8; HRMS (EI+) calcd. for $C_{15}H_{28}O_2Si$ $[M]^+$ 268.1859, found 268.1851.



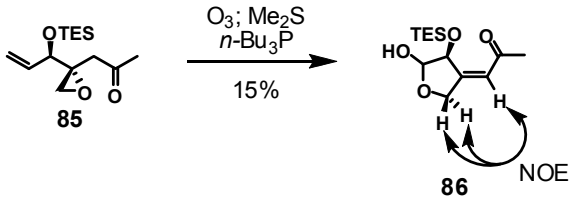
Preparation of diol 84. To a stirred solution of TES ether **83** (225 mg, 0.839 mmol) in THF (4 mL) and H_2O (0.5 mL) was added OsO_4 (10 mg, 0.038 mmol), and then NMO•H_2O (114 mg, 0.842 mmol) at 23 °C under an open atmosphere. The resulting brown solution was stirred for 1.5 h at the same temperature, then diluted with Et_2O (10 mL). To the reaction mixture was added solid $NaHCO_3$ and Na_2SO_3, then anhydrous Na_2SO_4. The mixture was filtered through cotton, and concentrated under reduced pressure. The residue was purified by flash chromatography (30% EtOAc in hexanes) on silica gel (8 mL) to afford **84** (146 mg, 58% yield) as a mixture of diastereomers (dr ~1.5:1 at C1).



Preparation of 85. To a stirred solution of diol **84** (22.1 mg, 0.073 mmol) in THF (0.20 mL), and H_2O (0.2 mL), was added $NaIO_4$ (15.8 mg, 0.074 mmol) at 23 °C under an open atmosphere. After 1 h at the same temperature, the resulting reaction mixture was diluted with Et_2O (5 mL) and H_2O (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O (5 mL) then brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (5 → 15% EtOAc in hexanes) on silica gel (4 mL) to afford **85** (19.6 mg, quant.) as a colorless oil.

Data for **85**: R_f = 0.45 (30% Et_2O in hexanes); IR (neat): 2956, 1717 (C=O), 1415, 1239, 1086, 1007, 930, 743 cm^{-1}; $[\alpha]^{22}_D$ –3.9 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 5.80

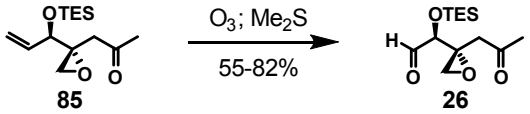
(ddd, 1H, *J* = 17.1, 10.4, 5.4 Hz), 5.32 (ddd, 1H, *J* = 17.1, 1.7, 1.7 Hz), 5.18 (ddd, 1H, *J* = 10.4, 1.6, 1.6 Hz), 3.90 (ddd, 1H, *J* = 5.4, 1.5, 1.5 Hz), 2.82 (d, 1H, *J* = 4.4 Hz), 2.78 (d, 1H, *J* = 15.4 Hz), 2.76 (d, 1H, *J* = 4.4 Hz), 2.71 (d, 1H, *J* = 15.4 Hz), 2.17 (s, 3H), 0.97 (t, 3H, *J* = 7.9 Hz), 1.00–0.94 (m, 9H), 0.67–0.58 (m, 6H); ^{13}C NMR (75 MHz, 293K, C_6D_6) δ 203.9, 137.4, 115.7, 77.8, 58.8, 49.6, 42.9, 30.8, 7.0, 5.1; HRMS (EI+) calcd. for $C_{14}H_{24}O_2Si$ $[M - H_2O]^+$ 252.1547, found 252.1546.



Preparation of enone 86. To a solution of **85** (70 mg, 0.26 mmol) in methanol (0.65 mL) and CH_2Cl_2 (0.65 mL) was bubbled O_3 until a blue color persisted at −78 °C, then O_2 was bubbled through the reaction mixture to remove the excess O_3 as indicated by the disappearance of the blue color. At the same temperature was added Me_2S (350 μL, 4.77 mmol), then allowed to slowly warm to 23 °C over 3.25 h, then most of the solvent was removed under reduced pressure. The reaction mixture was diluted with Et_2O (15 mL), then washed with H_2O (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography (5 → 30% EtOAc in hexanes) on silica gel (2 mL) to afford **86** (15 mg, 15%) as a colorless oil.

Data for **86**: R_f = 0.43 (30% EtOAc in hexanes); IR (neat): 3431 (br, O-H), 2956, 1697 (C=O), 1639, 1363, 1041, 972, 746 cm^{-1}; ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 6.47 (app q, 1H, *J* = 2.5 Hz), 5.35 (d, 1H, *J* = 4.5 Hz), 4.88 (app dt, 1H, *J* = 18.0, 2.5 Hz), 4.80–4.72 (m, 1H), 4.56–4.51 (m, 1H), 2.28 (s, 3H), 0.96 (t, 9H, *J* = 7.9 Hz), 0.67 (q, 6H, *J* = 7.9 Hz); ^{13}C NMR (75

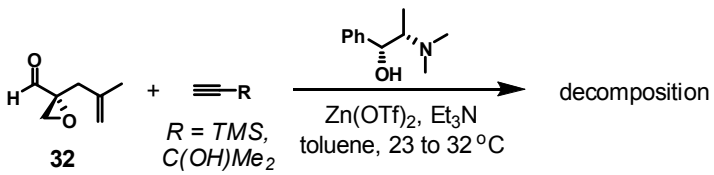
MHz, 293K, C_6D_6) δ 197.6, 160.2, 120.1, 94.8, 75.0, 69.3, 31.0, 6.5, 4.7; HRMS (ESI+) calcd. for $C_{13}H_{24}O_4NaSi$ $[M + Na]^+$ 295.1342, found 295.1368.



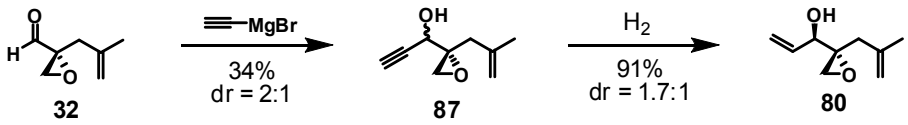
Preparation of ketoaldehyde 26 from enone 85. To a solution of **85** (80 mg, 0.30 mmol) in methanol (0.8 mL) and CH_2Cl_2 (0.8 mL) was bubbled O_3 until a blue color persisted at −78 °C, then O_2 was bubbled through the reaction mixture to remove the excess O_3 as indicated by the disappearance of the blue color. At the same temperature was added Me_2S (350 μL, 4.77 mmol), then allowed to slowly warm to 23 °C over 2.5 h, then most of the solvent was removed under reduced pressure. The reaction mixture was diluted with Et_2O (20 mL), then washed with H_2O (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography (5 → 30% EtOAc in hexanes) on silica gel (5 mL) to afford **26** (60 mg, 75%) as a colorless oil.

Data for **26**:† R_f = 0.24–0.34 (30% EtOAc in hexanes); ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 9.53 (d, 1H, *J* = 1.1 Hz), 3.80 (d, 1H, *J* = 1.1 Hz), 3.28 (br d, 1H, *J* = 17.3 Hz), 3.13 (dd, 1H, *J* = 4.1, 1.4 Hz), 2.75 (d, 1H, *J* = 4.1 Hz), 2.42 (d, 1H, *J* = 17.3 Hz), 2.18 (s, 3H), 0.98 (t, 9H, *J* = 7.7 Hz), 0.66 (q, 6H, *J* = 7.7 Hz).

† No further characterization was performed due to the instability of this compound.



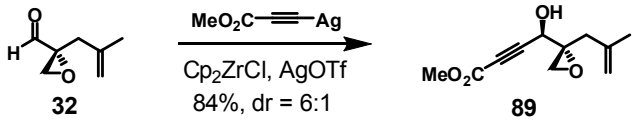
Procedure for the unsuccessful asymmetric alkynyl addition reactions to aldehyde 32. See D. E. Frantz, R. Fassler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807.



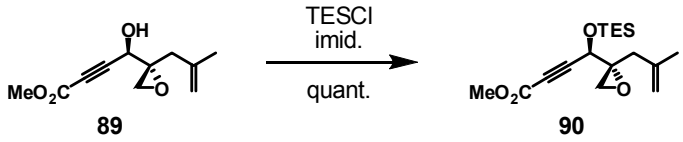
Preparation of alcohols 80 and 81 with ethynylmagnesium bromide, then partial hydrogenation. To a stirred solution of ethynylmagnesium bromide (0.5 M in THF, 2.0 mL) was added **32** (125 mg, 1.0 mmol) in THF (0.6 mL), and then the container that initially contained **32** was rinsed with THF (2 × 0.2 mL) and added to the reaction mixture at −78 °C under a nitrogen atmosphere. After 50 min at the same temperature, additional ethynylmagnesium bromide (0.5 M in THF, 1.5 mL) was added to the reaction mixture. After an additional 90 min at −78 °C, the reaction was quenched with saturated aqueous NH_4Cl (3 mL) and most of the solvent was removed under reduced pressure. The aqueous residue was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (5 → 15% EtOAc in hexanes) on silica gel (6 mL) to afford approximately a 2:1 mixture of diastereomers of **87** (52 mg, 34%) as colorless oils.

To a stirred solution of **87** (33 mg, 0.22 mmol) in EtOH (2 mL) was added quinoline (25 μL) and Lindlar's catalyst (5% wt/wt, 4.7 mg, 2.2 μmol) in one portion at 23 °C under an open atmosphere. After 25 min at the same temperature, the reaction mixture was placed under an

atmosphere of H_2, and vigorously stirred. After an additional 12 h, thre reaction mixture was filtered through filter paper, rinsed with 15% EtOAc in hexanes, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (5 → 15% EtOAc in hexanes) on silica gel (2 mL) to afford approximately a 1.7:1 mixture of diastereomers of **80:81** (31 mg, 91% yield) as colorless oil.

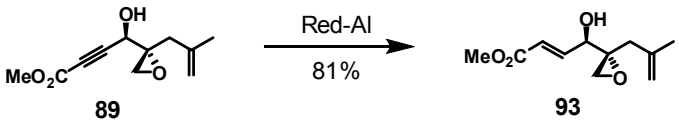


Preparation of and data for 89. See S. P. Shahi, K. Koide *Angew. Chem., Int. Ed.* **2004**, *43*, 2525.

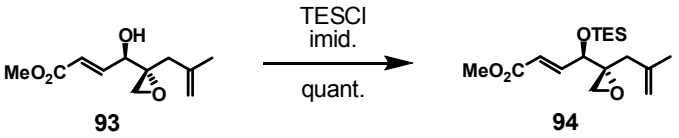


Preparation of and data for 90. To a stirred solution of imidazole (14 mg, 0.20 mmol) in THF (200 μL) was added chlorotriethylsilane (40 μL, 0.24 mmol) followed by the dropwise addition of alcohol **89** (28 mg, 0.13 mmol) in THF (200 μL) at 0 °C under a nitrogen atmosphere. After an additional 30 min at the same temperature, saturated aqueous NH_4Cl (3 mL) was added, and the mixture extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (2 → 5% EtOAc in hexanes) on silica gel (4 mL) to afford **90** (32 mg, 74%) as a colorless oil.

Data for **90**: R_f = 0.60 (30% EtOAc in hexanes); IR (neat): 2956, 2239, 1720 (C=O), 1265, 1108, 741 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 4.89–4.88 (m, 1H), 4.82 (br s, 1H), 4.46 (s, 1H), 3.79 (s, 3H), 2.89 (d, 1H, *J* = 4.8 Hz), 2.71 (d, 1H, *J* = 4.8 Hz), 2.65 (d, 1H, *J* = 14.5 Hz), 2.46 (d, 1H, *J* = 14.5 Hz), 1.77 (br s, 3H), 0.99 (t, 9H, *J* = 7.9 Hz), 0.68 (q, 6H, *J* = 7.9 Hz); ^{13}C NMR (75 MHz, 293K, C_6D_6) δ 153.4, 140.8, 114.9, 85.2, 77.6, 66.8, 66.0, 52.1, 48.7, 37.7, 23.5, 6.8, 5.0; HRMS (ESI+) calcd. for $C_{17}H_{28}O_4SiNa$ $[M + Na]^+$ 347.1655, found 347.1664.

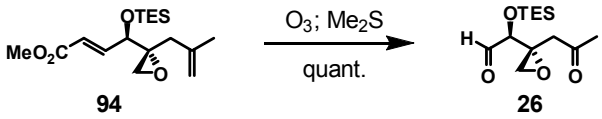


Preparation and data for 93. See C. T. Meta, K. Koide *Org. Lett*. **2004**, *6*, 1785.



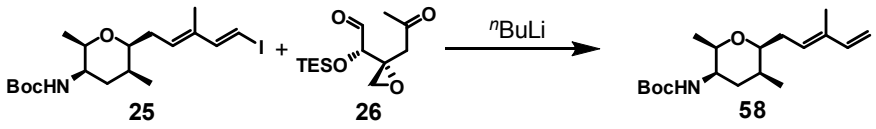
Preparation of 94. To a stirred solution of imidazole (1.02 g, 15.0 mmol) in THF (20 mL) was added chlorotriethylsilane (2.35 mL, 14.0 mmol), followed by the dropwise addition of alcohol **93** (2.11 g, 9.96 mmol) in THF (3 mL), and then the container that initially contained **93** was rinsed with THF (2 × 1 mL) and added to the reaction mixture at 0 °C under a nitrogen atmosphere. After an additional 45 min at the same temperature, H_2O (50 mL) was added, and most of the THF was removed under reduced pressure. The aqueous residue was extracted with Et_2O (2 × 40 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1.5 → 3% EtOAc in hexanes) on silica gel (150 mL) to afford **94** (3.27 g, quantitative yield) as a colorless oil.

Data for **94**: R_f = 0.30 (10% EtOAc in hexanes); IR (neat): 2954, 1728 (C=O), 1281, 1167, 978, 744 cm^{-1}; $[\alpha]_D^{22}$ +9.9 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 6.94 (dd, 1H, *J* = 15.5, 4.6 Hz), 6.10 (dd, 1H, *J* = 15.5, 1.8 Hz), 4.85–4.84 (m, 1H), 4.73–4.71 (m, 1H), 4.13 (dd, 1H, *J* = 4.6, 1.8 Hz), 3.77 (s, 3H), 2.75 (br d, 1H, *J* = 4.8 Hz), 2.71 (d, 1H, *J* = 4.8 Hz), 2.46 (br d, 1H, *J* = 14.5 Hz), 2.35 (br d, 1H, *J* = 14.5 Hz), 1.72 (br s, 3H), 0.97 (q, 9H, *J* = 7.9 Hz), 0.64 (q, 6H, *J* = 7.9 Hz); ^{13}C NMR (75 MHz, 293K, C_6D_6) 166.3, 147.2, 141.0, 121.8, 114.7, 76.8, 60.1, 51.2, 48.4, 36.2, 23.7, 7.0, 5.0; HRMS (ESI+) calcd. for $C_{17}H_{30}O_4SiNa$ [M + Na]$^+$ 349.1811, found 349.1794.



94 **26**

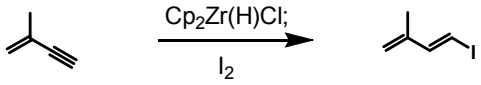
Preparation of ketoaldehyde 26 from enoate 94. A solution of enoate **94** (2.6 mg, 8.0 μmol) in methanol (30 μL) and CH_2Cl_2 (30 μL) was bubbled O_3 until a blue color persisted at –78 °C, then O_2 was bubbled through the reaction mixture to remove the blue color. At the same temperature was added Me_2S (10 μL, 0.014 mmol), then allowed to slowly warm to 23 °C over 3 h, then most of the solvent was removed under reduced pressure. The reaction mixture was diluted with Et_2O (10 mL), then washed with H_2O (1 mL) and brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The ^1H NMR of the resultant crude residue revealed clean formation of ketoaldehyde **26**.



25 26 58

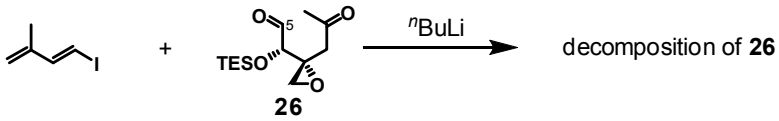
Preparation of 58 from 25. To a stirred solution of **25** (14 mg, 0.033 mmol) and ketoaldehyde **26** (9.1 mg, 0.033 mmol) in THF (200 μL) was added ^{n}BuLi (1.6 M in hexanes, 25 μL, 0.040 mmol) down the flask side at -98 °C under a nitrogen atmosphere. The reaction mixture was slowly warmed to −72 °C over 10 min, and then quenched by the addition of saturated aqueous NH_4Cl (2 mL) at the same temperature. The aqueous residue was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (5 → 25% EtOAc in hexanes) on silica gel (2 mL) to afford **58** (7.1 mg, 70%) as a colorless oil.

Data for **58**: R_f = 0.59 (30% EtOAc in hexanes); IR (neat): 3454 (N-H), 2877, 1717 (C=O), 1496, 1365, 1170, 1077, 902 cm^{-1}; $[\alpha]_D^{22}$ -34.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 6.42 (dd, 1H, *J* = 17.4, 10.7 Hz), 5.65 (br app t, 1H, *J* = 6.9 Hz), 5.11 (d, 1H, *J* = 17.4 Hz), 4.98–4.90 (m, 2H), 3.65–3.61 (m, 1H), 3.55 (qd, 1H, *J* = 6.4, 1.6 Hz), 3.05 (ddd, 1H, *J* = 9.7, 7.9, 3.2 Hz), 2.51 (ddd, 1H, *J* = 15.7, 6.8, 2.6 Hz), 2.30–2.18 (m, 1H), 1.89 (app dt, 1H, *J* = 13.1, 3.1 Hz), 1.75 (br s, 3H), 1.54–1.50 (m, 1H), 1.46 (s, 9H), 1.13 (d, 3H, *J* = 6.4 Hz), 0.85 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (75 MHz, 293K, C_6D_6) 166.3, 147.2, 141.0, 121.8, 114.7, 76.8, 60.1, 51.2, 48.4, 36.2, 23.7, 7.0, 5.0; HRMS (EI+) calcd. for $C_{18}H_{31}NO_3$ $[M]^+$ 309.2304, found 309.2305.



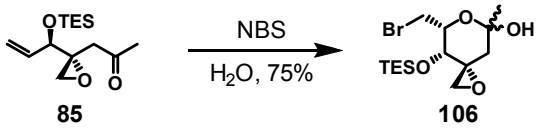
Preparation of (*E*)-1-iodo-3-methylbuta-1,3-diene. To a light-protected stirred solution of $Cp_2Zr(H)Cl$ (856 mg, 3.32 mmol) in benzene (7 mL) and THF (7 mL) was added 2-methyl-1-buten-3-yne (300 μL, 3.15 mmol) at 23 °C under a nitrogen atmosphere. After 30 min at the same temperature, iodine (862 mg, 3.40 mmol) was added in one portion. After 15 min at the same temperature, the reaction was quenched by the addition of aqueous $Na_2S_2O_3$ (10% wt/wt, 7 mL), and the mixture was concentrated under reduced pressure. The aqueous residue was extracted with pentane (20 mL). The organic layer was washed with H_2O (15 mL) then brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by filtration through a plug of silica gel (5 mL), rinsing with 1:1 pentane/CH_2Cl_2 (25 mL), and concentrated under reduced pressure to afford (*E*)-1-iodo-3-methylbuta-1,3-diene (358 mg, 57%) as a pale yellow oil.

Data for (*E*)-1-iodo-3-methylbuta-1,3-diene: ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 7.15 (br d, 1H, J = 14.7 Hz), 6.33 (ddd, 1H, J = 14.7, 0.5, 0.5 Hz), 5.00–4.97 (m, 2H), 1.83 (dd, 3H, J = 1.3, 0.9 Hz).



Decompostion of 26. To a stirred solution of **26** (33.2 mg, 0.122 mmol) and (*E*)-1-iodo-3-methylbuta-1,3-diene (24.3 mg, 0.126 mmol) in THF (600 μL) was added ^{n}BuLi (1.6 M in hexanes, 90 μL, 0.14 mmol) down the flask side at -98 °C under a nitrogen atmosphere. The reaction mixture was slowly warmed to –72 °C over 10 min, and then quenched by the addition

of saturated aqueous NH_4Cl (2 mL) at the same temperature. The aqueous residue was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (5 → 30% EtOAc in hexanes) on silica gel (2 mL) to afford only decomposition products.



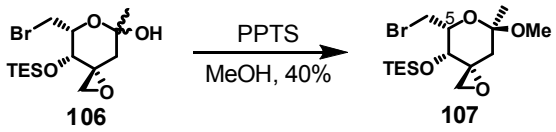
85 **106**

Preparation of lactol 106. To a light–protected stirred solution of **85** (162 mg, 0.598 mmol) in THF (2.4 mL) and H_2O (0.30 mL) was added recrystallized NBS (113 mg, 0.633 mmol) in one portion under an open atmosphere at 0 °C. The reaction mixture was slowly warmed to 23 °C over 2 h. After 2.5 h, 2–methyl–2–butene (0.1 mL) was added to the resulting reaction mixture, then H_2O (5 mL) at 23 °C. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (1 × 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 → 20% EtOAc in hexanes) on silica gel (7.5 mL) to afford **106** (164 mg, 75%) as a colorless oil.

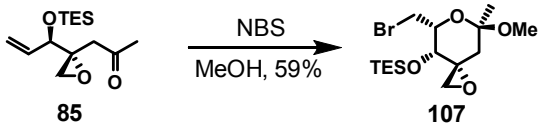
Data for **106**: R_f = 0.21 (20% EtOAc in hexanes); IR (neat): 3453 (br), 2956, 2877, 1716 (w), 1413, 1235, 1149, 1074, 1053, 976, 879, 744 cm^{-1}; $[\alpha]^{22}_D$ –32.1 (*c* 1.0, $CHCl_3$); ^1H NMR* (300 MHz, 293K, $CDCl_3$) δ 4.18 (ddd, 1H, *J* = 8.1, 5.7, 1.3 Hz), 3.51 (dd, 1H, *J* = 9.7, 8.1 Hz), 3.45 (br s, 1H), 3.37 (dd, 1H, *J* = 9.7, 5.7 Hz), 2.83 (d, 1H, *J* = 4.6 Hz), 2.78 (dd, 1H, *J* = 4.6, 1.6 Hz), 2.45 (br d, 1H, *J* = 12.6 Hz), 1.53 (s, 3H), 1.27 (dd, 1H, *J* = 12.7, 1.0 Hz), 0.98 (t, 9H, *J* = 7.8 Hz), 0.76–0.64 (m, 6H); ^{13}C NMR* (75 MHz, 293K, $CDCl_3$) δ 97.9, 73.4, 70.9, 57.9, 53.3,

36.7, 30.4, 30.0, 6.9, 4.9; HRMS (EI+) calcd. for $C_{12}H_{22}BrO_4Si$ [M – Et]$^+$ 337.0471, found 337.0478.

**The presence of anomers precluded a comprehensive assignment of all resonances*.*



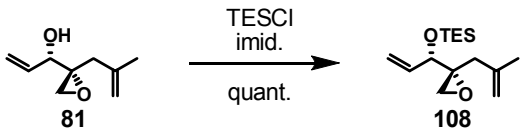
Preparation of methyl glycoside 107 by PPTS catalyzed ketalization. To a stirred solution of lactol **106** (98.8 mg, 0.270 mmol) in CH_2Cl_2 (0.70 mL) and MeOH (0.30 mL) was added PPTS (6.6 mg, 0.026 mmol) at 23 °C under a nitrogen atmosphere. After 15 h at the same temperature, saturated aqueous $NaHCO_3$ (5 mL) was added to the resulting reaction mixture at 23 °C. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (2.5 → 30% EtOAc in hexanes) on silica gel (6 mL) to afford methyl glycoside **107** (40.5 mg, 40% yield) as a colorless oil.



Preparation of methyl glycoside 15 by NBS cyclization. To a light–protected, stirred mixture of powdered 3Å MS (132 mg), recrystallized NBS (125.1 mg, 0.703 mmol), MeCN (1.0 mL), and MeOH (0.20 mL) was added ketone **85** (128 mg, 0.474 mmol) in MeCN (0.80 mL) dropwise at 0 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm to 23 °C over 75 min. After 2 h at the same temperature, 2–methyl–2–butene (10 drops), then Et_3N (5

drops) was added to the reaction mixture. The resulting reaction mixture was then filtered through a plug of silica gel (5 mL), and rinsed with 20% EtOAc in hexanes (20 mL), then Et_2O (20 mL). The eluent was then concentrated under reduced pressure, and the residue was purified by flash chromatography (1 $\rightarrow$ 7.5% EtOAc in hexanes) to afford methyl glycoside **107** (105.8 mg, 59%) as a colorless oil.

Data for **107**: R_f = 0.36 (20% EtOAc in hexanes); IR (neat): 2956, 1231, 1147, 1086, 1071, 1040, 744 cm^{-1}; $[\alpha]^{22}_D$ –70.6 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, 293K, C_6D_6) δ 3.80 (ddd, 1H, *J* = 6.7, 6.7, 1.4 Hz), 3.51 (dd, 1H, *J* = 9.9, 6.7 Hz), 3.44 (dd, 1H, *J* = 9.9, 6.7 Hz), 3.23 (br s, 1H), 3.00 (s, 3H), 2.56 (d, 1H, *J* = 4.8 Hz), 2.50 (dd, 1H, *J* = 12.7, 1.6 Hz), 2.30 (dd, 1H, *J* = 4.8, 1.7 Hz), 1.17 (d, 1H, *J* = 12.8 Hz), 1.14 (s, 3H), 1.03 (t, 9H, *J* = 7.9 Hz), 0.85–0.63 (m, 6H); ^{13}C NMR (126 MHz, 293K, C_6D_6) δ 100.4, 73.9, 72.1, 57.7, 53.3, 48.0, 38.3, 31.5, 23.1, 7.1, 5.3; HRMS (EI+) calcd. for $C_{14}H_{27}BrO_3Si$ $[M - CH_4O]^+$ 350.0913, found 350.0903.

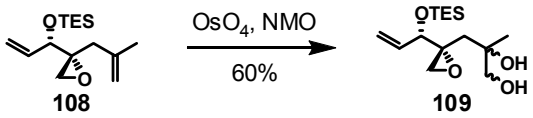


81 **108**

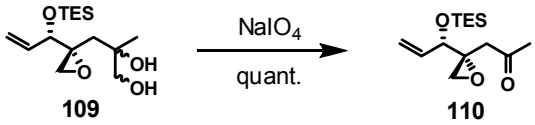
Preparation of TES ether 108. To a stirred solution of imidazole (2.18 g, 32.1 mmol) in THF (30 mL) was added chlorotriethylsilane (4.3 mL, 26 mmol), followed by the dropwise addition of alcohol **81** (3.49 g, 22.6 mmol) in THF (20 mL) at 0 °C under a nitrogen atmosphere. After an additional 30 min at the same temperature, saturated aqueous NH_4Cl (15 mL) was added, the layers were separated, and then the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with H_2O (30 mL) then brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and reduced under pressure. The resulting residue was purified

by flash chromatography (1 → 5% EtOAc in hexanes) on silica gel (225 mL) to afford **108** (6.08 g, quant. yield) as a colorless oil.

Data for **108**: R_f = 0.68 (20% EtOAc in hexanes); IR (neat): 2955, 2913, 2877, 1650, 1459, 1417, 1144, 1093, 1006, 893, 743 cm^{-1}; $[\alpha]_D^{22}$ –13.0 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 5.89 (ddd, 1H, *J* = 17.2, 10.4, 6.0 Hz), 5.31 (ddd, 1H, *J* = 17.2, 1.9, 1.4 Hz), 5.19 (ddd, 1H, *J* = 10.4, 1.9, 1.2 Hz), 4.85–4.82 (m, 1H), 4.74–4.72 (m, 1H), 4.04 (app dt, 1H, *J* = 6.0, 1.3, 1.3 Hz), 2.71 (d, 1H, *J* = 5.2 Hz), 2.59 (d, 1H, *J* = 5.3 Hz), 2.49 (br d, 1H, *J* = 14.5 Hz), 2.34 (br d, 1H, *J* = 14.5 Hz), 1.75 (dd, 3H, *J* = 1.4, 0.9 Hz), 0.96 (t, 9H, *J* = 7.9 Hz), 0.60 (q, 6H, *J* = 7.9 Hz): ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 141.3, 137.5, 116.4, 113.9, 74.8, 59.8, 49.7, 37.9, 23.5, 6.7, 6.5, 5.8, 4.9; HRMS (EI+) calcd. for $C_{15}H_{27}O_2Si$ $[M - H]^+$ 267.1780, found 267.1776.

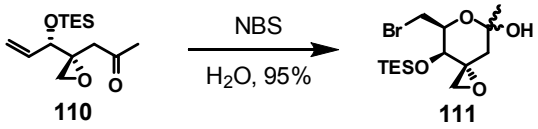


Preparation of diol 109. To a stirred solution of TES-ether 108 (728 mg, 2.71 mmol) in THF (14 mL) and H_2O (1.4 mL) was added OsO_4 (31.2 mg, 0.123 mmol), then NMO•H_2O (367 mg, 2.71 mmol) at 23 °C under an open atmosphere. The resulting brown solution was stirred for 11 h at the same temperature, then saturated aqueous Na_2SO_3 was added (15 mL) and vigourously stirred for 30 min. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 → 40% EtOAc in hexanes) on silica gel (25 mL) to afford 109 (498 mg, 60% yield, 69% BORSM) as a mixture of diastereomers (dr ~ 1.5:1 at C1).



Preparation of 110. To a stirred solution of diol **109** (187 mg, 0.619 mmol) in THF (2 mL) and H_2O (2 mL) was added $NaIO_4$ (135 mg, 0.630 mmol) at 23 °C under an open atmosphere. After 1.5 h at the same temperature, the resulting reaction mixture was diluted with Et_2O (5 mL) and H_2O (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (5 → 15% EtOAc in hexanes) on silica gel (12 mL) to afford **110** (171 mg, quant. yield) as a colorless oil.

Data for **110**: R_f = 0.50 (30% Et_2O in hexanes); IR (neat): 2956, 1717 (C=O), 1416, 1139, 1007, 849, 742 cm^{-1}; $[\alpha]_D^{22}$ –48.0 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 5.85 (ddd, 1H, *J* = 17.2, 10.4, 6.0 Hz), 5.32 (ddd, 1H, *J* = 17.2, 1.7, 1.4 Hz), 5.24 (ddd, 1H, *J* = 10.4, 1.7, 1.3 Hz), 4.06 (br d, 1H, *J* = 6.0 Hz), 3.01 (br d, 1H, *J* = 15.4 Hz), 2.80 (d, 1H, *J* = 4.8 Hz), 2.77 (d, 1H, *J* = 4.8 Hz), 2.42 (d, 1H, *J* = 15.4 Hz), 2.18 (s, 3H), 0.97 (t, 3H, *J* = 7.9 Hz), 0.94 (t, 6 H, *J* = 7.9 Hz, 7.9 Hz), 0.60 (q, 2H, *J* = 7.8 Hz) 0.58 (q, 4H, *J* = 7.9 Hz*)*; ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 205.7, 136.7, 117.2, 75.4, 58.4, 51.0, 44.6, 31.3, 6.7, 6.6, 5.8, 4.6; HRMS (EI+) calcd. for $C_{14}H_{25}O_3Si$ $[M - H]^+$ 269.1573, found 269.1575.

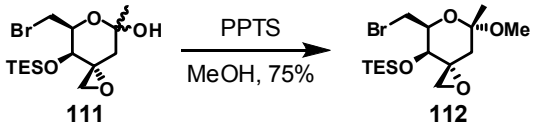


110 **111**

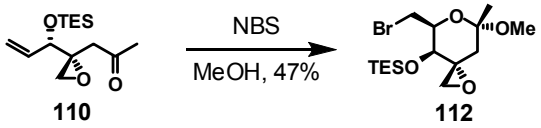
Preparation of lactol 14. To a light–protected stirred solution of **110** (19.2 mg, 0.710 mmol) in acetone (0.40 mL) and H_2O (0.050 mL) was added of recrystallized NBS (16.0 mg, 0.144 mmol) in one portion at 23 °C under an open atmosphere. The reaction mixture was stirred for 40 min at the same temperature, then 2–methyl–2–butene (10 drops) was added, then H_2O (5 mL) at 23 °C. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (5 → 20% EtOAc in hexanes) on silica gel (3 mL), to afford **111** (24.8 mg, 95% yield) as a colorless oil.

Data for **111**: R_f = 0.37 (30% EtOAc in hexanes); IR (neat): 3451 (br), 2957, 2877, 1716, 1413, 1316, 1235, 1149, 1053, 1011, 842, 744; $[\alpha]_D^{22}$ +21.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR* (300 MHz, 293K, $CDCl_3$) δ 4.27 (ddd, 1H, *J* = 8.7, 5.4, 1.3 Hz), 3.47 (dd, 1H, *J* = 9.6, 8.8 Hz), 3.38 (dd, 1H, *J* = 9.7, 5.4 Hz), 3.35 (br s, 1H), 2.82 (d, 1H, *J* = 4.2 Hz), 2.75 (d, 1H, *J* = 4.2 Hz), 2.54 (d, 1H, *J* = 13.9 Hz), 1.48 (s, 3H), 1.25 (dd, 1H, *J* = 13.9, 0.8 Hz), 1.00–0.95 (m, 9H), 0.70–0.57 (m, 6H); ^{13}C NMR* (75 MHz, 293K, $CDCl_3$) δ 97.3, 71.5, 69.2, 57.7, 52.1, 36.4, 29.7, 28.9, 6.9, 5.2; HRMS (EI+) calcd. for $C_{14}H_{26}BrO_3Si$ $[M - H_2O]^+$ 349.0835, found 349.0823.

**The presence of anomers precluded a comprehensive assignment of all resonances*.



Preparation of methyl glycoside 112 by PPTS catalyzed ketalization. To a stirred mixture of lactol **111** (1.14 g, 3.11 mmol) in anhydrous methanol (3 mL) and methylene chloride (9 mL), was added PPTS (75.9 mg, 0.302 mmol) in one portion under a nitrogen atmosphere at 23 °C. After 12 h, the resulting reaction mixture was diluted with Et_2O (5 mL) then H_2O (5 mL) at 23 °C. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 25 mL). The combined organics were washed with brine (2 × 25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (2.5 → 10% EtOAc in hexanes) on silica gel (60 mL) to afford methyl glycoside **112** (894 mg, 75% yield) as a white crystalline solid.

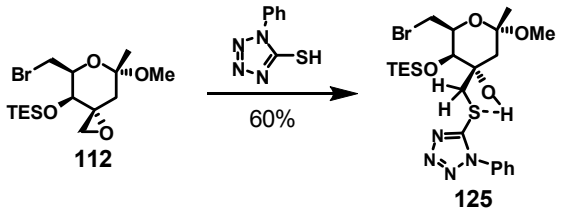


Preparation of methyl glycoside 112 by NBS cyclization. To a light–protected stirred mixture of powdered 3Å MS (138 mg), recrystallized NBS (90.8 mg, 0.510 mmol), MeOH (0.15 mL), and MeCN (1.0 mL) was added ketone **110** in MeCN (0.5 mL) dropwise at 0 °C under a nitrogen atmosphere. The resulting reaction mixture was slowly warmed to 23 °C over 1 h. After 3.3 h at the same temperature, 2–methyl–2–butene was added (0.25 mL), saturated aqueous $NaHCO_3$ (3 mL), and then Et_2O (4 mL). The reaction mixture was filtered through a pad of Celite 545®, and rinsed with H_2O (5 mL) and Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced

pressure. The resulting residue was purified by flash chromatography (1 → 10% EtOAc in hexanes) on silica gel (9 mL) to afford methyl glycoside **112** (65.3 mg, 47%) as a white crystalline solid.

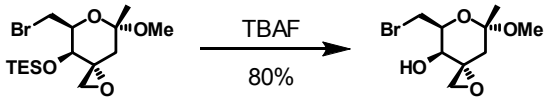
Data for **112**: R_f = 0.35 (20% EtOAc in hexanes); m.p. = 44–46 °C; IR (neat): 2955, 1186, 1152, 1086, 1069, 1042, 848, 743 cm^{-1}; $[\alpha]_D^{22}$ +75.0 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, 293K, C_6D_6) δ 4.29 (app t d, 1H, *J* = 6.8, 1.3 Hz), 3.47 (dd, 1H, *J* = 9.9, 7.0 Hz), 3.36 (dd, 1H, *J* = 9.9, 6.6 Hz), 3.16 (br s, 1H), 3.13 (s, 3H), 2.33 (d, 1H, *J* = 4.7 Hz), 2.26 (d, 1H, *J* = 13.9 Hz), 2.19 (d, 1H, *J* = 4.7 Hz), 1.21 (dd, 1H, *J* = 13.9, 0.9 Hz), 1.20 (s, 3H), 0.86 (t, 9H, *J* = 7.9 Hz), 0.46–0.38 (m, 6H); ^{13}C NMR (125 MHz, 293K, $CDCl_3$) δ 99.2, 71.6, 70.7, 56.6, 51.0, 48.5, 37.0, 30.9, 23.3, 6.8, 5.2; HRMS (EI+) calcd. for $C_{12}H_{22}BrO_4Si$ $[M - C_4H_{10}]^+$ 337.0471, found 337.0480.

See Appendix A for X-ray crystal.



Preparation of 125. To a stirred solution of methyl glycoside **112** (51 mg, 0.13 mmol) in MeCN (250 μL) was added 4-phenyl-tetrazolethiol (27 mg, 0.15 mmol) in one portion followed by Et_3N (35 μL, 0.25 mmol) at 23 °C under a nitrogen atmosphere. After 30 min at the same temperature, the reaction mixture was warmed to reflux. After 3 h at reflux, the reaction mixture was cooled, filtered through a pad of Florisil (1 mL), rinsed with 20% EtOAc in hexanes, and concentrated. The resulting residue was purified by flash chromatography (2.5 → 15% EtOAc in hexanes) on silica gel (4 mL) to afford **125** (45 mg, 60%) as a colorless oil.

Data for **125**: R_f = 0.13 (10% EtOAc in hexanes); IR (neat): 3446 (br, O-H), 2954, 1500, 1412, 1383, 1237, 1100, 1016, 741 cm^{-1}; $[\alpha]_D^{22}$ +57.4 (*c* 0.7, $CHCl_3$); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 7.61–7.53 (m, 5H), 4.96 (br d, 1H, *J* = 1.2 Hz); 4.09 (ddd, 1H, *J* = 7.6, 5.6, 1.1 Hz), 3.84 (dd, 1H, *J* = 12.5, 1.6 Hz), 3.67 (br s, 1H), 3.50 (br d, 1H, *J* = 12.5 Hz), 3.45 (dd, 1H, *J* = 10.1, 7.6 Hz), 3.38 (dd, 1H, *J* = 10.1, 5.6 Hz), 3.29 (s, 3H), 1.98 (d, 1H, *J* = 14.0 Hz), 1.91 (d, 1H, *J* = 14.0 Hz), 1.36 (s, 3H), 1.00 (t, 9H, *J* = 7.9 Hz), 0.76–0.67 (m, 6H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 154.8, 133.9, 130.1, 129.8, 123.9, 100.6, 72.6, 72.3, 70.1, 48.3, 43.4, 37.7, 32.0, 23.3, 7.0, 5.5; HRMS (ESI+) calcd. for $C_{22}H_{35}BrO_4SiSNa$ $[M + Na]^+$ 581.1229, found 581.1234.

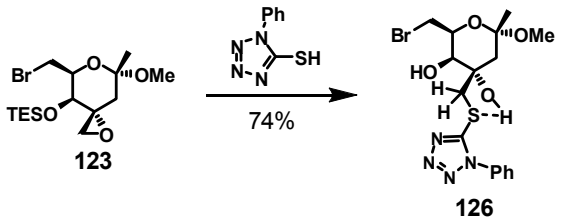


112 **123**

Preparation of 123. To a stirred solution of methyl glycoside **112** (101 mg, 0.265 mmol) in THF (1 mL) was added TBAF (1M in THF, 300 μL) dropwise at 0 °C under a nitrogen atmosphere. After 20 min at the same temperature, the reaction mixture was diluted with Et_2O (5 mL), filtered through a plug of silica gel (3 mL), rinsed with Et_2O, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (40 → 50% EtOAc in hexanes) on silica gel (5 mL) to afford **123** (53.6 mg, 76%) as a colorless oil.

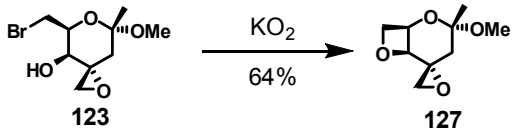
Data for **123**: R_f = 0.27 (60% EtOAc in hexanes); IR (neat): 3432 (br, O-H), 2926, 1265, 1026, 739 cm^{-1}; $[\alpha]_D^{22}$ +97.0 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 4.24 (app td, 1H, *J* = 7.2, 1.4 Hz), 3.50 (app d, 2H, 7.2 Hz), 3.34 (s, 3H), 3.22 (d, 1H, *J* = 7.9 Hz), 2.74 (br d, 1H, *J* = 4.4 Hz), 2.63 (d, 1H, *J* = 4.4 Hz), 2.41 (d, 1H, *J* = 14.7 Hz), 1.93 (br d, 1H, 7.9 Hz), 1.44 (s, 3H), 1.43 (dd, 1H, *J* = 14.7, 1.0 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 99.4, 70.7, 70.3,

56.3, 50.2, 48.6, 37.1, 30.2, 23.1; HRMS (ESI+) calcd. for $C_9H_{15}BrO_4Na$ [M + Na]$^+$ 289.0051, found 289.0087.



Preparation of 126. To a stirred solution of methyl glycoside **123** (4.0 mg, 0.02 mmol) in MeCN (50 μL) was added 4-phenyl-tetrazolethiol (2.9 mg, 0.02 mmol) in one portion followed by Et_3N (5 μL, 0.04 mmol) at 0 °C under a nitrogen atmosphere. After 15 min at the same temperature, the reaction mixture was warmed to 23 °C. After an additional 2 h at the same temperature, the reaction mixture was warmed to 50 °C. After 3 h at reflux, the reaction mixture was cooled, filtered through a pad of silica gel (0.5 mL), rinsed with EtOAc (5 mL), and concentrated. The resulting residue was purified by flash chromatography (20 → 60% EtOAc in hexanes) on silica gel (0.5 mL) to afford **126** (4.8 mg, 72%) as a colorless oil.

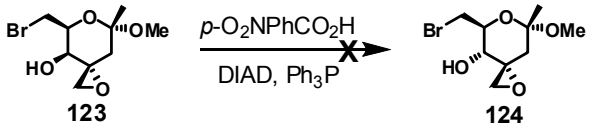
Data for **126**: R_f = 0.27 (60% EtOAc in hexanes); IR (neat): 3442 (br, O-H), 2931, 1500, 1385, 1236, 1016, 762 cm^{-1}; $[\alpha]_D^{22}$ +12.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, 293K, C_6D_6) δ 7.16–7.12 (m, 2H), 6.93–6.88 (m, 3H), 5.56 (br d, 1H, *J* = 5.6 Hz), 4.93 (br d, 1H, *J* = 1.5 Hz), 4.17 (br dd, 1H, *J* = 8.0, 4.8 Hz), 3.81 (br d, 1H, *J* = 5.6 Hz), 3.71 (dd, 1H, *J* = 10.4, 8.0 Hz), 3.65 (dd, 1H, *J* = 14.2, 1.5 Hz), 3.44 (dd, 1H, *J* = 10.4, 4.8 Hz), 2.93 (d, 1H, *J* = 14.2 Hz), 2.89 (s, 3H), 1.95 (br d, 1H, *J* = 13.9 Hz), 1.34 (dd, 1H, *J* = 13.9, 1.3 Hz), 1.14 (s, 3H); ^{13}C NMR (75 MHz, 293K, C_6D_6) δ 156.5, 133.8, 129.9, 129.6, 124.0, 100.6, 72.2, 70.7, 68.0, 47.8, 43.2, 39.9, 33.0, 23.3; HRMS (ESI+) calcd. for $C_{16}H_{21}BrO_4SNa$ [M + Na]$^+$ 467.0365, found 467.0345.



123 127

Preparation of 127. To a stirred solution of **123** (13 mg, 0.035 mmol) and 18-crown-6 (9.3 mg, 0.13 mmol) in DMSO (225 μL) was added KO_2 (19 mg, 0.070 mmol) in one portion at 23 °C under a nitrogen atmosphere. After 30 min at the same temperature, the reaction mixture was diluted with brine (3 mL) and Et_2O (5 mL), the layers were separated, and the aqueous residue was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (20 → 30% EtOAc in hexanes) on silica gel (1 mL) to afford **127** (4.1 mg, 64%) as a colorless oil.

Data for **127**: R_f = 0.24 (30% EtOAc in hexanes); IR (neat): 2947, 1379, 1232, 1190, 1168, 1093, 1058, 965 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 4.83 (dd, 1H, *J* = 7.1, 4.3 Hz), 4.60 (ddd, 1H, *J* = 4.5, 4.3, 2.1 Hz), 4.44 (br d, 1H, *J* = 4.5 Hz), 4.32 (ddd, 1H, *J* = 7.1, 2.1, 1.0 Hz), 3.32 (s, 3H), 2.81 (d, 1H, *J* = 4.5 Hz), 2.63 (d, 1H, *J* = 4.5 Hz), 2.55 (d, 1H, *J* = 14.6 Hz), 1.61, dd, 1H, *J* = 14.6 Hz), 1.48 (s, 3H); ^{13}C NMR (75 MHz, 293K, C_6D_6) δ 156.5, 133.8, 129.9, 129.6, 124.0, 100.6, 72.2, 70.7, 68.0, 47.8, 43.2, 39.9, 33.0, 23.3; LRMS (ESI+) calcd. for $C_9H_{14}O_4Na$ $[M + Na]^+$ 209, 4%; $C_9H_{14}O_4Na$ $[M + H]^+$ 181, 5%.

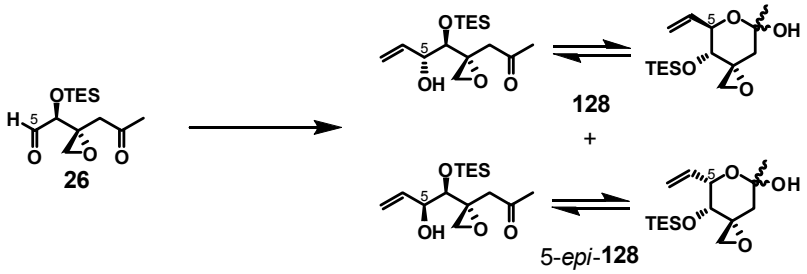


123 124

Procedure for the Mitsunobu reaction of 123. To a stirred solution of **123** (9.8 mg, 0.037 mmol) in THF (200 μL) was added *p*-O_2NPhCO_2H (13 mg, 0.078 mmol), DIAD (20 μL, 0.10 mmol), and Ph_3P (22 mg, 0.083 mmol) at 0 °C under a nitrogen atmosphere. After two h at

the same temperature, the reaction mixture was warmed to 23 °C. After 14 additional h at the same temperature, the reaction mixture was diluted with EtOAc (15 mL), washed with brine (5 mL), dried over over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 → 30% EtOAc in hexanes) on silica gel (2 mL) to afford a mixture (53 mg) as a yellow solid.

To a stirred solution of the yellow solid (44 mg) in MeOH (0.50 mL) was added K_2CO_3 (46 mg, 0.33 mmol) at 23 °C under an open atmosphere. After 45 min at the same temperature, the reaction mixture was diluted with saturated aqueous NH_4Cl (0.5 mL), and most of the solvent was removed under reduced pressure. The aqueous layer was extracted with EtOAc (10 mL), dried over over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 → 50% EtOAc in hexanes) on silica gel (3 mL) to afford **123** (1.4 mg, 17% for the two steps) as a colorless oil.

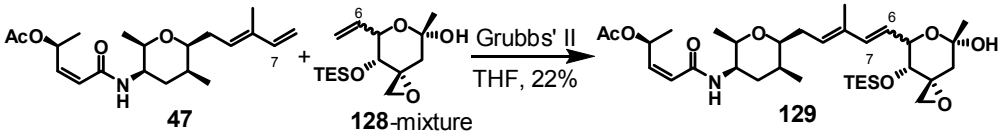


General procedure for the preparation of 128 and 5-*epi*-128. To a stirred solution of **26** (42–88 mg, 0.15–0.32) in THF (0.50–0.80 mL) was added additives (1.9–2.5 equiv) followed by the addition of vinyl metal solution (2 equiv) down the flask side at −78 °C under a nitrogen atmosphere. After 15–60 min at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl (3–5 mL). The resulting mixture was then extracted with Et_2O (3 × 5–10 mL). The combined organic layers were washed with pH 4 phosphate buffer (5 mL) then brine (10

mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (5 → 30% EtOAc in hexanes) on silica gel (2–5 mL) to afford **128** and 5-*epi*-**128** as colorless oils.

Data for **128** and 5-*epi*-**128:** R_f = 0.28 (30% EtOAc in hexanes); ^{1}H NMR* (300 MHz, 293K, $CDCl_3$) δ 5.98–5.84 (m), 5.44 (ddd, *J* = 12.2, 1.6, 1.6 Hz), 5.40–5.18 (m), 4.49 (br d, *J* = 7.1 Hz), 4.37 (br dd, *J* = 9.2, 6.7 Hz), 4.14 (s), 3.84 (br d, *J* = 3.4 Hz), 3.82–3.75 (m), 3.71 (d, *J* = 9.2 Hz), 3.47 (d, 18.0 Hz), 3.28 (s), 3.22 (br d, *J* = 17.1 Hz), 3.13 (dd, *J* = 4.1, 1.4 Hz), 3.05 (d, *J* = 4.8 Hz), 3.01 (d, *J* = 8.4 Hz), 2.98 (dd, *J* = 4.2, 1.2 Hz), 2.97–2.95 (m), 2.82 (d, *J* = 4.2 Hz), 2.78 (dd, *J* = 4.6, 1.6 Hz), 2.75 (d, *J* = 4.6 Hz), 2.59 (d, *J* = 4.7 Hz), 2.54 (d, *J* = 18.0 Hz), 2.42 (d, *J* = 17.3 Hz), 2.31 (d, *J* = 14.0 Hz), 2.23 (s), 2.18 (s), 1.64 (d, *J* = 14.0 Hz), 1.55 (s), 1.47 (s), 0.99–0.92 (m), 0.72–0.58 (m).

**The presence of anomers precluded a comprehensive assignment of all resonances*.*

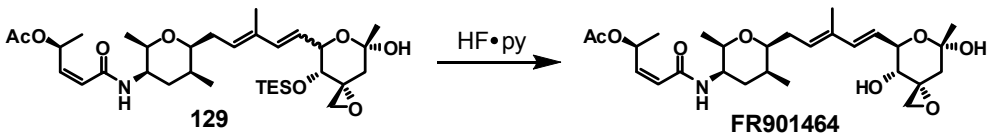


Preparation of 129. To a stirred solution of diene **47** (7.0 mg, 0.020 mmol) and **128**-mixture (6.1 mg, 0.020 mmol) in THF (200 μL) was added Grubbs' 2nd generation catalyst (1.7 mg, 0.002 mmol) in one portion at 23 °C under a nitrogen atmosphere. After 5 min at the same temperature, the reaction vessel was then placed in a pre-heated oil bath (40 °C). After 2.5 h at the same temperature, additional Grubbs' 2nd generation catalyst (1.7 mg, 0.002 mmol) in THF (100 μL) was added. After an additional 1.5 at the same temperature, the reaction mixture was cooled, filtered through silica gel (1 mL), and eluted with 60% EtOAc in hexanes (20 mL). To the eluent was added activated charcoal (200 mg), and the mixture was stirred. After 14 h of

stirring, the mixture was filtered though a pad of Celite 545® (5 mL), rinsed with Et_2O (25 mL), and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (5 → 50% EtOAc in hexanes) on silica gel (1.8 mL) to afford **129** (2.8 mg, 22%) as a colorless oil.

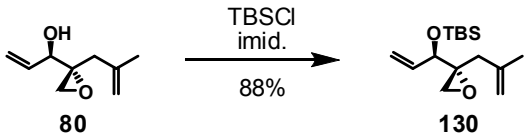
Data for **129**: R_f = 0.28 (50% EtOAc in hexanes); ^{1}H NMR – **129 anti-hemiketal**† (300 MHz, 293K, $CDCl_3$) δ 6.35 (br d, *J* = 15.1 Hz), 6.30–6.24 (m), 6.00 (br d, *J* = 9.8 Hz), 5.90 (dd, *J* = 11.5, 7.8 Hz), 5.71 (br d, *J* = 10.7 Hz), 5.61 (br dd, *J* = 15.3, 6.3 Hz), 5.50–5.45 (m), 4.42 (br app t, *J* = 8.6 Hz), 3.99–3.92 (m), 3.74 (d, *J* = 9.3 Hz), 3.70–3.65 (m), 3.54–3.48 (m), 3.04 (d, *J* = 4.7 Hz), 2.59 (d, *J* = 4.7 Hz), 2.44–2.40 (m), 2.39–2.35 (m), 2.32 (d, *J* = 13.9 Hz), 2.05 (s), 1.98–1.93 (m), 1.77 (br s), 1.76–1.74 (m), 1.63 (d, *J* = 14.0 Hz), 1.47 (s), 1.40 (d, *J* = 6.5 Hz), 1.16 (d, *J* = 6.0 Hz), 1.01 (d, *J* = 7.3 Hz), 0.98–0.90 (m), 0.72–0.56 (m).

†The complex spectra of the small quantity inseparable mixture of compounds prohibited further characterization.



Preparation of FR901464 from 129. To a stirred solution of **129** (0.3 mg, 0.5 μmol) in THF (50 μL) was added HF•pyridine (neat, 2 drops) at 0 °C under an open atmosphere. After 45 min at the same temperature, the reaction mixture was diluted with Et_2O (20 mL). The mixture was washed with H_2O (10 × 1 mL) and saturated aqueous $CuSO_4$ (1 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. TLC and HPLC* analysis of the resulting crude residue and an authentic sample of FR901464, including a coinjection of the authentic and synthetic materials, strongly suggested that FR901464 was produced.

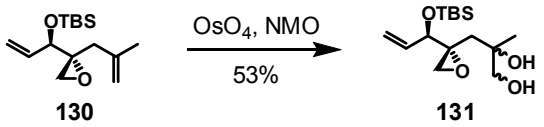
* HPLC analysis was performed on a Varian Microsorb 100 C18 column, 250 × 4.6 mm, 1.0 mL/min, 5% MeCN/H_2O→100% MeCN linear gradient elution from 0 to 31.67 min, retention time = 17.4 min.



80 **130**

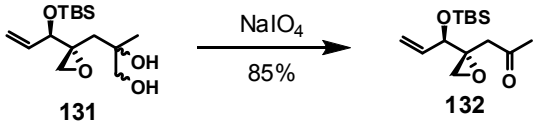
Preparation of 130. To a stirred solution of imidazole (421 mg, 6.19 mmol) in DMF (3 mL) was added *t*butyldimethylsilyl chloride (809 mg, 5.37 mmol) then **80** (636 mg, 4.12 mmol) in DMF (1 mL), and then the container that initially contained **80** was rinsed with DMF (2 × 0.5 mL) and added to the reaction mixture at 23 °C under a nitrogen atmosphere. After 4 h at the same temperature, the reaction mixture was diluted with H_2O (100 mL), and extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (5 → 20% EtOAc in hexanes) on silica gel (8 mL) to afford the **130** (968 mg, 88%) as a colorless oil.

Data for **130**: R_f = 0.63 (20% EtOAc in hexanes); IR (neat): 2930, 1254, 837, 778 cm^{-1}; $[\alpha]_D^{22}$ –2.0 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 5.85 (ddd, 1H, *J* = 17.2, 10.4, 5.7 Hz), 5.29 (ddd, 1H, *J* = 17.2, 1.6, 1.6 Hz), 5.18 (ddd, 1H, *J* = 10.4, 1.3, 1.3 Hz), 4.83 (br s, 1H), 4.72 (br s, 1H), 3.99 (br d, 1H, *J* = 5.7 Hz), 2.76 (d, 1H, *J* = 5.0 Hz), 2.55 (d, 1H, *J* = 14.5 Hz), 2.29 (d, 1H, *J* = 14.5 Hz), 1.73 (br s, 3H), 0.93 (s, 9H), 0.10 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, 293K, C_6D_6) δ 141.6, 137.9, 115.6, 114.3, 78.1, 60.5, 48.6, 36.6, 26.0, 23.8, –4.5, –4.7; HRMS (EI+) calcd. for $C_{15}H_{28}O_2SiNa$ $[M + Na]^+$ 291.1756, found 291.1754.



130 131

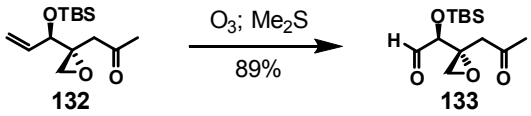
Preparation of 131. To a stirred solution of **130** (800 mg, 3.0 mmol) in THF (14 mL) and H_2O (1.4 mL) was added OsO_4 (7.5 mg, 0.03 mmol) then NMO•H_2O (410 mg, 3.0 mmol) at 23 °C under an open atmosphere. The resulting solution was stirred at 16 h at the same temperature, then saturated aqueous Na_2SO_3 (15 mL) was added, and the mixture was vigorously stirred for 30 min. The layers were then separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers washed with saturated aqueous Na_2SO_3 (20 mL) and brine (30 mL), were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (10 → 40% EtOAc in hexanes) on silica (35 mL) to afford the **131** (480 mg, 53%, 62% based on recovered **130**) as a colorless oil. The diastereomeric mixture was used directly without further purification.



131 132

Preparation of 132. To a stirred solution of **131** (377 mg, 1.25 mmol) in THF (3 mL) and H_2O (3 mL) was added $NaIO_4$ (279 mg, 1.30 mmol) at 23 °C under an open atmosphere. After 1.5 h at the same temperature, the resulting mixture was diluted with Et_2O (7 mL) and H_2O (2 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (5 → 15% EtOAc in hexanes) on silica (15 mL) to afford the **132** (286 mg, 85%) as a colorless oil.

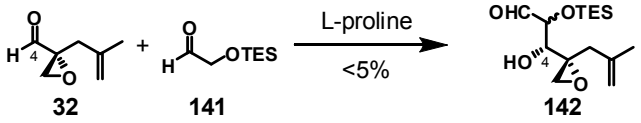
Data for **132**: R_f = 0.50 (30% Et_2O in hexanes); IR (neat): 2956, 1717 (C=O), 1254, 1033, 838, 778 cm^{-1}; $[\alpha]_D^{22}$ –2.3 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 5.72 (ddd, 1H, *J* = 17.1, 10.4, 4.8 Hz), 5.30 (ddd, 1H, 17.1, 1.6, 1.6 Hz), 5.04 (ddd, 1H, *J* = 10.4, 1.6, 1.6 Hz), 3.79 (br d, 1H, *J* = 4.8 Hz), 2.66 (br d, 1H, *J* =15.0 Hz), 2.63 (d, 1H, *J* = 4.6 Hz), 2.54 (br d, 1H, *J* = 15.0 Hz), 2.48 (br d, 1H, *J* = 4.6 Hz), 1.88 (br s, 3H), 1.05 (s, 9H), 0.21 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (75 MHz, 293K, C_6D_6) δ 203.7, 137.4, 115.8, 78.0, 58.7, 49.6, 42.6, 30.9, 26.0, 18.5, –4.6, –4.9; HRMS (EI+) calcd. for $C_{14}H_{26}O_3SiNa$ $[M + Na]^+$ 293.1549, found 293.1532.



Preparation of ketoaldehyde 133. To a solution of enone **132** (131 mg, 0.484 mmol) in MeOH (1.25 mL) and CH_2Cl_2 (1.25 mL) was bubbled O_3 until a blue color persisted at –78 °C, then O_2 was bubbled through the reaction mixture to remove the blue color. At the same temperature was added Me_2S (350 μL, 4.77 mmol), then allowed to slowly warm to 23 °C over 2.5 h, then most of the solvent was removed under reduced pressure. The reaction mixture was diluted with Et_2O (20 mL), then washed with H_2O (5 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (5 → 30% EtOAc in hexanes) on silica gel (5 mL) to afford the **133** (118 mg, 89%) as a colorless oil.

Data for **133**:[†] R_f = 0.24–0.34 (30% EtOAc in hexanes); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 9.53 (br s, 1H), 3.80 (br s, 1H), 3.37 (dd, 1H, *J* = 14.9, 0.9 Hz), 3.12 (br d, 1H, *J* = 4.1 Hz), 2.75 (d, 1H, *J* = 4.1 Hz), 2.42 (d, 1H, *J* = 14.9 Hz), 2.18 (s, 3H), 0.95 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H).

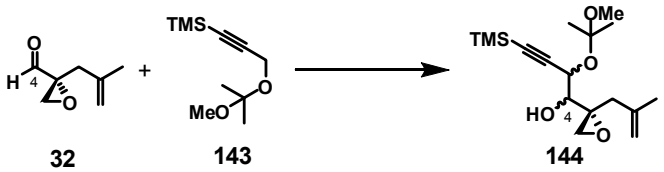
† No further characterization was performed due to the instability of this compound.



Preparation of 142. To a stirred solution of **32** (34 mg, 0.27 mmol) and L-proline (6.5 mg, 0.056 mmol) in DMSO (0.40 mL) was added **141** (77 mg, 0.44 mmol) in DMSO (0.20 mL) at 23 °C under a nitrogen atmosphere. After 30 h at the same temperature, the reaction mixture was diluted with H_2O (25 mL), and the aqueous residue was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (5 → 30% EtOAc in hexanes) on silica gel (6 mL) to afford the **142** (4.3 mg, 5%) as a colorless oil.

Data for **133**: R_f = 0.18 (30% EtOAc in hexanes); ^{1}H NMR‡ (300 MHz, 293K, $CDCl_3$) δ 9.64 (d, 1H, *J* = 1.1 Hz), 4.02 (d, 1H, *J* = 4.3 Hz), 2.95 (br d, 1H, *J* = 4.9 Hz), 2.72 (d, 1H, *J* = 4.9 Hz), 2.53 (d, 1H, *J* = 14.5 Hz), 2.22 (d, 1H, *J* = 14.5 Hz), 1.79 (br s, 3H), 1.04–0.91 (m, 9H), 0.75–0.57 (m, 6H).

‡ Data given for the major diastereomer.

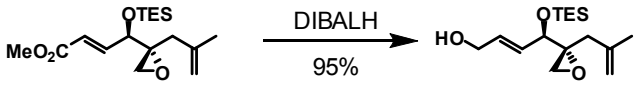


Preparation of 144 using Ti(O^{i}Pr)$_4$. To a stirred solution of **143** (680 mg, 3.4 mmol) in THF (8 mL) was added ^{t}BuLi (1.7 M in pentane, 2.0 mL, 3.4 mmol) then Ti(O^{i}Pr)$_4$ (1.0 mL, 3.4

mmol) at −78 °C under a nitrogen atmosphere. After 35 min at the same temperature, **32** (290 mg, 2.3 mmol) was added in THF (1.0 mL) dropwise, and then the vessel that originally contained **32** was rinsed with THF (2 × 0.5 mL) and added to the reaction mixture at −78 °C. After 1 h at the same temperature, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (5 mL), most of the solvent was removed under reduced pressure, and the aqueous residue was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (5 → 30% EtOAc in hexanes) on silica gel (35 mL) to afford the **144** (463 mg, 66%) as a colorless oil.

Data for **133**: R_f = 0.46 (40% EtOAc in hexanes); ^{1}H NMR* (300 MHz, 293K, $CDCl_3$) δ 4.90 (br s, 1H), 4.87 (br s, 1H), 4.62, (d, 1H, *J* = 3.7 Hz), 3.78 (dd, 1H, *J* = 8.5, 3.7 Hz), 3.25 (s, 3H), 2.98 (br d, 1H, *J* = 4.9 Hz), 2.68 (br d, 1H, *J* = 14.7 Hz), 2.60 (d, 1H, 4.9 Hz), 2.40 (br d, 1H, *J* = 14.7 Hz), 1.80 (br s, 3H), 1.47 (s, 3H), 1.40 (s, 3H), 0.18 (s, 9H).

* Data given for the major, unassigned diastereomer. Diastereomeric ratios were determined by comparison of the –OMe and –TMS groups.

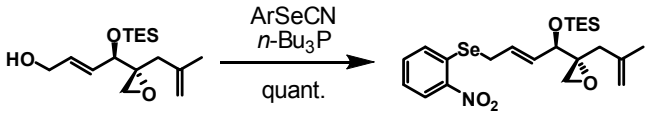


94 **145**

Preparation of 145. To a stirred solution of enoate **94** (968 mg, 2.96 mmol) in THF (10 mL) was added DIBALH (1 M in hexanes, 8.9 mL) slowly down the flask side at −78 °C under a nitrogen atmosphere. After an additional 1 h at the same temperature, saturated aqueous NH_4Cl (5 mL) was added at −78 °C, and the reaction mixture was allowed to warm to 23 °C. After an additional 1.5 h at the same temperature, the reaction mixture was diluted with Et_2O (15 mL),

dried over anhydrous Na_2SO_4, filtered through a pad of Celite 545®, rinsed with Et_2O (3 × 25 mL), and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (5 → 20% EtOAc in hexanes) on silica gel (40 mL) to afford **145** (838 mg, 95%) as a colorless oil.

Data for **145**: R_f = 0.23 (20% EtOAc in hexanes); IR (neat): 3421 (br, O-H), 2955, 1458, 1124, 1096, 1005, 972, 743; $[\alpha]_D^{22}$ -13.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 5.89 (dddd, 1H, *J* = 15.5, 5.2, 5.2, 1.1 Hz), 5.74 (dddd, 1H *J* = 15.5, 5.9, 1.3, 1.3 Hz), 4.84–4.83 (m, 1H), 4.74–4.73 (m, 1H), 4.19 (br app t, 2H, *J* = 5.0 Hz), 4.07 (dd, 1H, *J* = 5.9, 1.1 Hz), 2.80 (br d, 1H, *J* = 5.0 Hz), 2.67 (br d, 1H, *J* = 5.0 Hz), 2.55 (br d, 1H, *J* = 14.5 Hz), 2.27 (br d, 1H, *J* = 14.5 Hz), 1.75 (br s, 3H), 0.96 (t, 9H, *J* = 7.9Hz), 0.62 (q, 6H, *J* = 7.9 Hz); ^{13}C NMR (75 MHz, 293K, C_6D_6) δ 141.7, 131.6, 129.8, 114.3, 76.5, 62.6, 60.9, 48.8, 37.3, 23.8, 7.1, 5.3; HRMS (ESI+) calcd. for $C_{16}H_{30}O_3SiNa$ $[M + Na]^+$ 321.1862, found 321.1850.

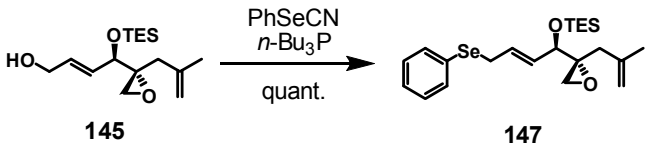


145 **146**

Preparation of 146. To a stirred solution of 2-nitrophenyl selenocyanate (1.10 g, 4.82 mmol) in THF (7 mL) was added **145** (1.20 g, 4.02 mmol) in THF (4 mL), and then the container that initially contained **27** was rinsed with THF (2 × 1 mL) and added to the reaction mixture followed by the dropwise addition of freshly distilled ^{n}Bu$_3$P (1.4 mL, 5.6 mmol) at 0 °C under a nitrogen atmosphere. After 30 min at the same temperature, the reaction mixture was poured onto saturated aqueous $NaHCO_3$ (125 mL). The layers were separated, and the aqueous residue was extracted with Et_2O (3 × 65 mL). The combined organic layers were washed with brine (75

mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1 → 5% EtOAc in hexanes) on silica gel (100 mL) to afford **146** (2.06 g, quantitative yield) as a pale yellow oil.

Data for **146**: R_f = 0.20 (10% EtOAc in hexanes); IR (neat): 2954, 1516, 1332, 1304, 1100, 970, 730; $[\alpha]_D^{22}$ -24.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 8.29 (dd, 1H, *J* = 7.9, 1.2 Hz), 7.56–7.50 (m, 2H), 7.33 (ddd, 1H, *J* = 8.4, 5.3, 3.2 Hz), 5.92–5.74 (m, 2H), 4.82 (br s, 1H), 4.67 (br s, 1H), 4.05 (br d, 1H, *J* = 5.8 Hz), 3.69–3.59 (m, 2H), 2.79 (br d, 1H, *J* = 5.1 Hz), 2.63 (d, 1H, *J* = 5.1 Hz), 2.43 (d, 1H, *J* = 14.5 Hz), 2.16 (d, 1H, *J* = 14.5 Hz), 1.70 (br s, 3H), 0.92 (t, 9H, *J* = 7.9 Hz), 0.57 (q, 6H, *J* = 7.9 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 146.9, 141.0, 133.9, 133.5, 133.2, 129.3, 126.3, 126.1, 125.5, 114.1, 74.3, 60.6, 49.1, 38.1, 27.7, 23.4, 6.7, 4.8; HRMS (ESI+) calcd. for $C_{22}H_{33}NO_4SeSiNa$ $[M + Na]^+$ 506.1242, found 506.1229.

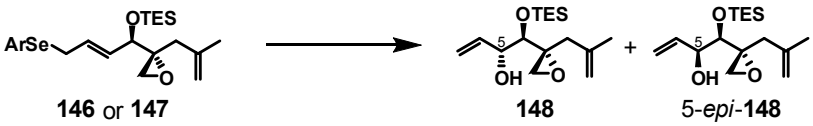


145 **147**

Preparation of 147. To a stirred solution of phenyl selenocyanate (175 μL, 1.43 mmol) and **145** (2.99 mg, 1.00 mmol) in THF (3.5 mL) was added freshly distilled ^{n}Bu$_3$P (1.4 mL, 5.6 mmol) dropwise at 0 °C under a nitrogen atmosphere. After 20 min at the same temperature, the reaction mixture was poured onto saturated aqueous $NaHCO_3$ (35 mL). The layers were separated, and the aqueous residue was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1 → 4% EtOAc in hexanes) on silica gel (25 mL) to afford **147** (493 mg, quantitative yield) as a pale yellow oil.

Data for **147**.* R_f = 0.20 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 7.51−7.46 (m, 2H), 7.32−7.23 (m, 3H), 5.82 (dddd, 1H, *J* = 15.2, 7.4, 7.3, 1.1 Hz), 5.49 (dddd, 1H, *J* = 15.2, 6.6, 1.1, 1.1 Hz), 4.80 (br s, 1H), 4.66 (br s, 1H), 3.96 (br d, 1H, *J* = 6.6Hz), 2.70 (d, 1H, *J* = 5.1 Hz), 2.57 (d, 1H, *J* = 5.1 Hz), 2.34 (d, 1H, *J* = 14.5 Hz), 2.13 (d, 1H, *J* = 14.5 Hz), 1.69 (br s, 3H), 0.93 (t, 9H, *J* = 7.9 Hz), 0.57 (q, 6H, *J* = 7.9 Hz).

* This compound was not further characterized due to its rapid oxidation.



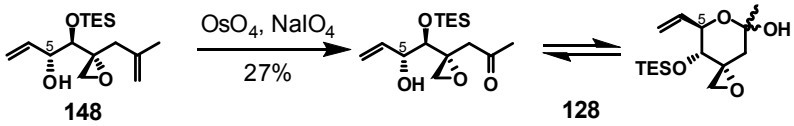
146 or **147** **148** 5-*epi*-**148**

General procedure for the preparation of 148 and 5-*epi*-148. To a stirred solution of **146** or **147** (0.05−4.0 mmol) in solvent (0.25−20 mL) was added base (5−20 mmol) followed by the dropwise addition of aqueous H_2O_2 (30% v/v, 2.5−40 mmol) at –44 °C under an open atmosphere. After 15 min at the same temperature, the reaction was warmed to the temperature indicated in Table 3. After an additional 12 h at the same temperature, the reaction mixture was diluted with Et_2O (10−40 mL) and hexanes (0−10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (2 → 8% EtOAc in hexanes) on silica gel to afford **148** and 5-*epi*-**148** as colorless oils.

Data for **148**: R_f = 0.24 (10% EtOAc in hexanes); IR (neat): 3471 (br, O-H), 2955, 1648, 1459, 1239, 1112, 1007, 917, 895, 743; $[\alpha]_D^{25}$ +6.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, 293K, C_6D_6) δ 5.89 (ddd, 1H, *J* = 17.2, 10.5, 5.6 Hz), 5.27 (ddd, 1H, *J* = 17.2, 1.6, 1.6 Hz), 5.04 (ddd, 1H, *J* = 10.5, 1.6, 1.6 Hz), 4.86–4.83 (m, 1H), 4.81–4.78 (m, 1H), 4.04 (ddddd, 1H, *J* = 7.1, 5.6, 3.6, 1.6, 1.6 Hz), 3.22 (d, 1H, *J* = 7.1 Hz), 2.70 (d, 1H, *J* = 14.2 Hz), 2.64 (d, 1H, *J* = 4.9 Hz),

2.62 (d, 1H, J = 14.2 Hz), 2.47 (d, 1H, J = 4.9 Hz), 1.79 (br s, 3H), 1.58 (d, 1H, J = 3.6 Hz), 1.02 (t, 9H, J = 7.9 Hz), 0.75–0.65 (m, 6H); ^{13}C NMR (75 MHz, 293K, C_6D_6) δ 141.8, 138.6, 115.7, 114.6, 80.8, 74.5, 59.3, 50.2, 36.7, 24.2, 7.1, 5.3; HRMS (EI+) calcd. for $C_{13}H_{25}O_2Si$ [M – C_3H_5O]$^+$ 241.1624, found 241.1624.

Data for ***epi*-148**: R_f = 0.31 (10% EtOAc in hexanes); IR (neat): 3502 (br, O-H), 2955, 1649, 1458, 1240, 1092, 1053, 1006, 927, 744; $[\alpha]_D^{25}$ –7.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, 293K, C_6D_6) δ 5.69 (ddd, 1H, J = 17.1, 10.5, 5.6 Hz), 5.37 (ddd, 1H, J = 17.1, 1.6, 1.6 Hz), 5.02 (ddd, 1H, J = 10.5, 1.9, 1.5 Hz), 4.83–4.80 (m, 1H), 4.69–4.67 (m, 1H), 4.12–4.06 (m, 1H), 3.18 (d, 1H, J = 6.4 Hz), 2.62 (d, 1H, J = 14.4 Hz), 2.51 (d, 1H, J = 14.4 Hz), 2.50 (d, 1H. J = 4.7 Hz), 2.44 (d, 1H. J = 4.2 Hz). 2.24 (d, 1H, J = 4.7 Hz), 1.73 (br s, 3H), 1.01 (t, 9H, J = 7.9 Hz), 0.75–0.65 (m, 6H); ^{13}C NMR (75 MHz, 293K, C_6D_6) δ 141.2, 137.9, 116.1, 115.0, 81.8, 73.9, 59.3, 49.5, 36.2, 24.2, 7.1, 5.3; HRMS (ESI+) calcd. for $C_{13}H_{25}O_2SiNa$ [M + Na]$^+$ 321.1862, found 321.1838.

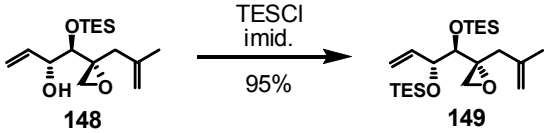


Preparation of enone 128 from 148. To a stirred solution of **148** (5.6 mg, 0.019 mmol) and 2,6-lutidine (3.5 μL, 0.030 mmol) in dioxane (150 μL) and H_2O (50 μL) was added OsO_4 (2.5 wt% in ^{t}BuOH, 5.0 μL, 4.0 μmol) and $NaIO_4$ (10.1 mg, 0.047 mmol) in one portion at 0 °C under an open atmosphere. After an additional 0.7 h at the same temperature, the reaction was warmed to 23 °C. After an additional 8.3 h at the same temperature, the reaction mixture was diluted with Et_2O (5 mL) and H_2O (5 mL). The layers were separated, and the aqueous residue was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL)

and brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (5 → 30% EtOAc in hexanes) on silica gel (0.8 mL) to afford **128** (1.5 mg, 27%, 36% based on recovered **148**) as a pale yellow oil.

Data for **128**: R_f = 0.28 (30% EtOAc in hexanes); ^{1}H NMR* (300 MHz, 293K, CDCl3) δ 5.98−5.84 (m), 5.44 (ddd, *J* = 12.2, 1.6, 1.6 Hz), 5.37 (ddd, *J* = 17.3, 1.8, 1.8 Hz), 5.28 (br d, *J* = 11.1 Hz), 5.21 (ddd, *J* = 10.5, 1.6, 1.6 Hz), 4.37 (br dd, *J* = 9.2, 6.7 Hz), 4.14 (s), 3.84 (br d, *J* = 3.4 Hz), 3.82−3.75 (m), 3.71 (d, *J* = 9.2 Hz), 3.47 (d, 18.0 Hz), 3.05 (d, *J* = 4.8 Hz), 3.01 (d, *J* = 8.4 Hz), 2.98 (dd, *J* = 4.2, 1.2 Hz), 2.82 (d, *J* = 4.2 Hz), 2.59 (d, *J* = 4.7 Hz), 2.54 (d, *J* = 18.0 Hz), 2.31 (d, *J* = 14.0 Hz), 2.23 (s), 1.64 (d, *J* = 14.0 Hz), 1.47 (s), 0.99−0.92 (m), 0.72−0.58 (m); HRMS (ESI+) calcd. for $C_{15}H_{28}O_4Si$ $[M + Na]^+$ 323.1655, found 323.1664.

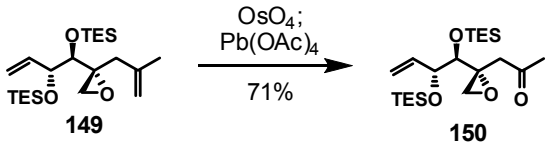
* The presence of anomers precluded a comprehensive assignment of all magnetic resonances.



Preparation of 149. To a stirred solution of imidazole (218 mg, 3.20 mmol) in THF (3 mL) was added chlorotriethylsilane (470 μL, 2.80 mmol), followed by the dropwise addition of alcohol **148** (596 mg, 2.00 mmol) in THF (1 mL), and then the container that initially contained **148** was rinsed with THF (2 × 0.5 mL) and added to the reaction mixture, at 0 °C under a nitrogen atmosphere. After an additional 1.5 h at the same temperature, H_2O (14 mL) was added, and most of the THF was removed under reduced pressure. The aqueous residue was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (20 mL),

dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1.5 → 3% EtOAc in hexanes) on silica gel (40 mL) to afford **149** (786 mg, 95%) as a colorless oil.

Data for **149**: R_f = 0.65 (5% EtOAc in hexanes); IR (neat): 2955, 1648, 1458, 1239, 1100, 1006, 788, 744; $[\alpha]_D^{22}$ -10.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 5.80 (ddd, 1H, *J* = 17.3, 10.2, 7.2 Hz), 5.23 (br ddd, 1H, *J* = 17.3, 1.0, 1.0 Hz), 5.16 (br dd, *J* = 10.2, 1.0 Hz), 4.85–4.83 (m, 1H), 4.69 (br s, 1H), 4.09 (br dd, 1H, *J* = 7.2, 7.2 Hz), 3.21 (d, 1H, *J* = 7.2 Hz), 2.72 (d, 1H, *J* = 5.0 Hz), 2.69 (d, 1H, *J* = 5.0 Hz), 2.58 (app s, 2H), 1.75 (br s, 3H), 0.96 (t, 9H, *J* = 7.8 Hz), 0.95 (t, 9H, *J* = 7.9 Hz), 0.67–0.55 (m, 12H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 141.3, 139.4, 116.9, 114.3, 80.6, 76.2, 59.4, 49.9, 35.6, 24.1, 6.9, 6.8, 5.2, 5.0; HRMS (EI+) calcd. for $C_{22}H_{44}O_3Si_2$ $[M]^+$ 412.2829, found 412.2841.

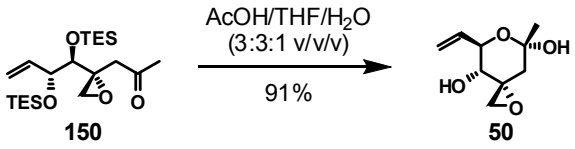


Preparation of 150. To a stirred solution of **149** (412 mg, 0.998 mmol) in THF/H_2O (10:1, 4.4 mL) was added NMO•H_2O (129 mg, 0.954 mmol) in one portion, followed by the addition of OsO_4 (2.5 mg, 9.8 μmol) at 0 °C under an open atmosphere. After 5 min at the same temperature, the reaction was warmed to 23 °C. After an additional 18 h at the same temperature, the reaction mixture was diluted with Et_2O (2 mL), saturated aqueous Na_2SO_3 (10 mL), and saturated aqueous $NaHCO_3$ (1 mL). After 30 min of vigorous stirring, the mixture was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with saturated aqueous Na_2SO_3 (10 mL), then aqueous HCl (0.1 N, 12 mL), dried over anhydrous Na_2SO_4,

filtered, and concentrated under reduced pressure. The resulting crude material (477 mg) was taken to the next step without further purification: R_f = 0.24 (20% EtOAc in hexanes).

To a solution of the crude tan oil (471 mg) in benzene (5 mL) was added $Pb(OAc)_4$ (534 mg, 1.20 mmol) in one portion at 0 °C under an open atmosphere. After 3 min at the same temperature, the reaction was warmed to 23 °C. After an additional 17 min at the same temperature, the reaction mixture was diluted with Et_2O (5 mL), filtered through a pad of Celite 545®, rinsed with Et_2O (4 × 10 mL), and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1.25 → 5% EtOAc in hexanes) on silica gel (25 mL) to return diene **149** (74 mg) and afford **150** (293 mg, 71%; 86% BORSM) as a colorless oil.

Data for **150**: R_f = 0.23 (5% EtOAc in hexanes); IR (neat): 2913, 1717 (C=O), 1415, 1239, 1100, 1006, 742; $[\alpha]_D^{22}$ -19.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, 293K, C_6D_6) δ 5.81 (ddd, 1H, *J* = 17.4, 10.3, 7.3 Hz), 5.14 (ddd, 1H, *J* = 17.2, 1.7, 1.0 Hz), 4.98 (ddd, 1H, *J* = 10.3, 1.8, 0.8 Hz), 4.06 (br dd, 1H, *J* = 7.2, 6.5 Hz), 3.20 (d, 1H, *J* = 6.5 Hz), 2.93 (d, 1H, *J* = 14.2 Hz), 2.83 (d, 1H, *J* = 4.5 Hz), 2.77 (d, 1H, *J* = 14.2 Hz), 2.66 (d, 1H, *J* = 4.5 Hz), 1.93 (s, 3H), 1.06 (t, 9H, *J* = 7.9 Hz), 0.99 (t, 9H, *J* = 8.0 Hz), 0.78–0.70 (m, 6H), 0.66–0.58 (m, 6H); ^{13}C NMR (75 MHz, 293K, C_6D_6) δ 204.1, 139.5, 117.0, 81.5, 76.9, 57.6, 51.0, 42.5, 31.5, 7.2, 7.1, 5.4, 5.4; HRMS (ESI+) calcd. for $C_{21}H_{42}O_4Si_2Na$ $[M + Na]^+$ 437.2519, found 437.2533.

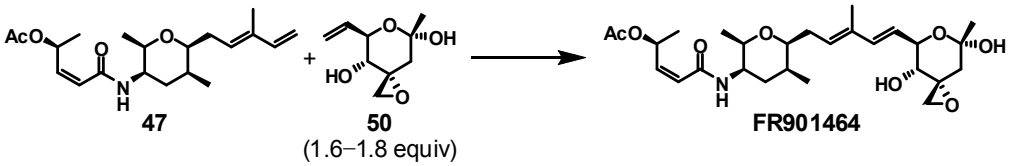


150 **50**

Preparation of 50. To a flask containing **150** (104 mg, 0.251 mmol) was added AcOH/THF/H_2O (3:3:1 v/v/v, 2.8 mL) at 0 °C under an open atmosphere. After 10 min at the same temperature, the reaction was warmed to 23 °C. After an additional 30 h at the same

temperature the reaction was diluted with toluene (5 mL), and then concentrated under reduced pressure. The resulting residue was purified by flash chromatography (20 → 50% EtOAc in hexanes) on silica gel (6 mL) to afford **50** (42.5 mg, 91%) as a colorless oil.

Data for **50**: R_f = 0.15 (60% EtOAc in hexanes); IR (neat): 3384, 2923, 1701 (C=O, weak), 1647, 1412, 1212, 1182, 1085, 1021, 907, 819, 730; $[\alpha]_D^{22}$ +54.4 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (300 MHz, 293K, CD_2Cl_2) δ 5.97 (ddd, 1H, *J* = 17.3, 10.5, 6.1 Hz), 5.38 (ddd, 1H, *J* = 17.3, 1.8, 1.4 Hz), 5.25 (ddd, 1H, *J* = 10.5, 1.8, 1.4 Hz), 4.19 (dddd, 1H, *J* = 9.8, 6.1, 1.4, 1.2 Hz), 3.54 (app t, 1H, *J* = 10.1 Hz), 3.31 (br s, 1H), 3.06 (d, 1H, *J* = 4.4 Hz), 2.55 (d, 1H, *J* = 4.4 Hz), 2.33 (d, 1H, *J* = 14.4 Hz), 1.64 (d, 1H, *J* = 14.4 Hz), 1.43 (s, 3H); ^{13}C NMR (75 MHz, 293K, CD_2Cl_2) δ 136.4, 117.6, 96.7, 73.7, 67.9, 58.1, 48.0, 41.9, 29.1; HRMS (EI+) calcd. for $C_9H_{12}O_3$ $[M - H_2O]^+$ 168.0786, found 168.0790.

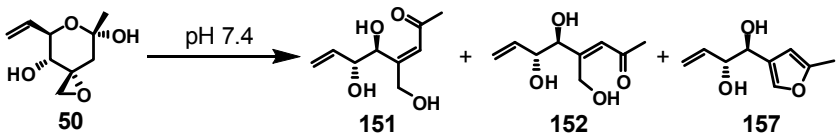


Preparation of FR901464 using the Grela catalyst. A solution of **50** (33.6 mg, 0.180 mmol) was prepared in $ClCH_2CH_2Cl$ (200 μL) at 23 °C under an open atmosphere. To a stirred solution of **47** (35.1 mg, 0.100 mmol) in $ClCH_2CH_2Cl$ (100 μL) was added the solution of **50** (50 μL), followed by Grela catalyst (1.7 mg, 2.5 μmol) at 23 °C under an open atmosphere. After 1.5 h at the same temperature, additional Grela catalyst (1.7 mg, 2.5 μmol) and **50** (50 μL) were added. This addition process was repeated after 3.5 and 6.0 h after the reaction was initiated. After 10 total hours, the reaction was concentrated under reduced pressure. The resulting residue

was purified by flash chromatography (10 → 90% EtOAc in hexanes) on silica gel (8 mL) to give **47** (24.2 mg, 69%), **50** (11.7 mg, 35%), and FR901464 (14.4 mg, 28%) as pale tan oils.

To a stirred solution of recovered **47** (24.2 mg, 0.0690 mmol) and recovered **50** (11.7 mg, 0.0628 mmol) in $ClCH_2CH_2Cl$ (200 μL) was added Grela catalyst (4.3 mg, 6.3 μmol) at 23 °C under an open atmosphere. After an additional 11 h at the same temperature, the reaction was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 → 90% EtOAc in hexanes) on silica gel (5 mL) to give **47** (7.8 mg, 32%) and FR901464 (5.7 mg, 18%) as pale tan oils. The combined yield of FR901464 after one cycle is 20.1 mg (40%).

Data for FR901464 were consistent with the literature (Nakajima, H.; Takase, S.; Terano, H.; Tanaka, H. *J. Antibiot.* **1997**, *50*, 96 and Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 9974). See Appendix 2 for comparison of spectral data.



General procedure for the half-life determination for the decomposition of 50. To a vial was added **50** (0.8−0.9 mg, 4−5 μmol) under an open atmosphere at 23 °C. The reaction mixture was then sealed and warmed to 37 °C. The decomposition was then estimated by TLC analysis (80% EtOAc/hexanes) after 2, 5, 9, and 25 h.

^{1}H NMR and HPLC studies of the decomposition of 50. Deuterated pH 7.4 buffer was prepared by evaporating 4 mL of 50 mM pH 7.4 phosphate buffer, dissolving the remaining salts in 0.5 mL of D_2O and subsequent evaporation of most of the solvent, and finally diluting the resulting mixture to 4 mL with D_2O. To an NMR tube was added **50** (8.1 mg, 0.044 mmol) in the

pH 7.4 D_2O/phospate buffer (0.8 mL) at 23 °C under an open atmosphere. The NMR tube was then submerged in a 37 °C incubator. The NMR tube was removed after 30 min, 2.5 h, 18 h, and 24 h for ^1H NMR experiments to be run. Additionally, aliquots were taken out after 3.5 h, 18.5 and 24.5 h, and subsequently analyzed by HPLC. Neither the ^1H NMR experiments nor the HPLC traces showed the formation of acrolein.

Preparation of 151, 152, and 157 by the decomposition of 50. To a flask was added **50** (17.5 mg, 0.0940 mmol) and then pH 7.4 phosphate buffer (50 mM, 1.0 mL) under an open atmosphere at 23 °C. The reaction mixture was then sealed and warmed to 37 °C. After 25 h at the same temperature the reaction was cooled to ambient temperature, diluted with MeCN (3 mL), and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (20 → 70% EtOAc in hexanes) on silica gel (7 mL) to afford **A (90)** (1.1 mg, 7%), **B**‡ (3.6 mg, 21%), and **C**‡ (3.3 mg, 19%) as a colorless oils.

‡ We interpret **B** and **C** to be compounds **151** and **152**, but are unable to assign them.

Data for **157 (A)**: R_f = 0.47 (80% EtOAc in hexanes); ^1H NMR (300 MHz, 293K, CD_2Cl_2) δ 7.27 (br s, 1H), 6.02 (br s, 1H), 5.86 (ddd, 1H, *J* = 17.3, 10.6, 6.0 Hz), 5.32 (ddd, 1H, *J* = 17.3, 1.6, 1.5 Hz), 5.22 (ddd, 1H, *J* = 10.5, 1.6, 1.5 Hz), 4.58 (br app t, 1H, *J* = 4.1 Hz), 4.28−4.21 (m, 1H), 2.26 (d, 3H, *J* = 0.8 Hz), 2.18 (br d, 1H, *J* = 4.3 Hz), 2.05 (br d, 1H, *J* = 4.4 Hz); ^{13}C NMR (75 MHz, 293K, CD_2Cl_2 + CD_3OD) δ 137.7, 137.1, 125.2, 117.2, 105.6, 76.1, 70.5, 13.6; HRMS (EI+) calcd. for $C_9H_{12}O_3$ $(M)^+$ 168.0786, found 168.0789.

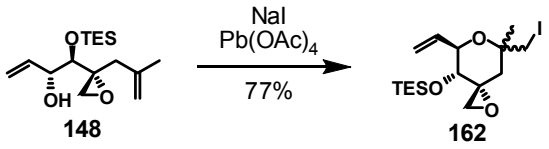
Data for **Compound B**:* R_f = 0.38, 0.27;† (80% EtOAc in hexanes); HRMS (EI+) calcd. for $C_8H_{11}O_3$ $[M - CH_3O]^+$ 155.0708, found 155.0704; LRMS (EI+) $C_8H_{11}O_3$ $[M - CH_3O]^+$ 155 (22%), $C_6H_{10}O_3$ $[M - C_3H_4O]^+$ 130 (48%), $C_6H_8O_2$ $[M - C_3H_8O_2]^+$ 112 (84%).

*** Compound B** exists as hemiketal and linear ketoalcohol conformers. As a result the NMR spectral data for **B** can not easily be reported.

† This compound gave two spots on TLC, however only one peak by HPLC analysis (HPLC analysis was performed on a Varian Microsorb 100 C18 column, 250 × 4.6 mm, 1.0 mL/min, 5% MeCN/H_2O→95% MeCN linear gradient elution from 0 to 30 min, retention time = 8.0 min, monitored at 220 nM).

Data for **Compound C**:§ R_f = 0.30 (80% EtOAc in hexanes); HRMS (EI+) calcd. for $C_9H_{12}O_3$ $[M - H_2O]^+$ 168.0786, found 168.0795; LRMS (EI+) $C_9H_{12}O_3$ $[M - H_2O]^+$ 168 (15%), $C_6H_{10}O_3$ $[M - CH_5O]^+$ 153 (60%), $[M - H_4O_2]^+$ 150 (32%), $C_6H_{10}O_3$ $[M - C_3H_4O]^+$ 130 (48%), $C_6H_8O_2$ $[M - C_3H_8O_2]^+$ 112 $[M - C_3H_6O_2].^+$

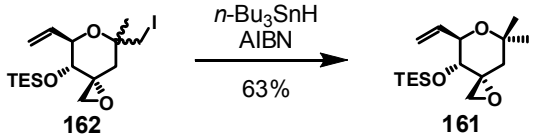
§ **Compound C** exists as hemiketal and linear ketoalcohol conformers. As a result the NMR spectral data for **C** can not easily be reported.



Preparation of 162 on a preparative scale. To a stirred solution of **148** (299 mg, 1.00 mmol) in 1,2-dimethoxyethane (10 mL) was added NaI (301 mg, 2.01 mmol) in one portion followed by $Pb(OAc)_4$ (799 mg, 1.80 mmol) in one portion at –44 °C under a nitrogen atmosphere. After an additional 15 min at the same temperature, the reaction mixture was warmed to 0 °C. After an additional 2.3 h at the same temperature, the reaction mixture was poured onto aqueous 0.9 N HCl (100 mL) and Et_2O (40 mL), and the layers were separated. The aqueous residue was extracted with Et_2O (2 × 40 mL). The combined organic layers were washed with saturated aqueous Na_2SO_3 (50 mL) then brine (50 mL), dried over anhydrous

Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (2 → 8% EtOAc in hexanes) on silica gel (30 mL) to recover diene **148** (50.8 mg) and afford **162** (325 mg, 77%; 92% BORSM; dr = 1.2:1) as a pale yellow oil.

Preparation of 162 on microscale. To a flask was added NaI (0.10 M in H_2O, 50 μL, 5 μmol) then MeCN (1 mL) and the mixture was concentrated under reduced pressure, and subsequently then placed under an atmosphere of nitrogen. To this flask was added diene **148** (6.3 mg, 21 μmol) in 1,2-dimethoxyethane (200 μL) followed by $Pb(OAc)_4$ (4.4 mg, 10 μmol) in one portion at 0 °C. After 4 h at the same temperature, the reaction mixture was filtered through a pad of Celite 545®, rinsed with Et_2O (10 mL) and concentrated under reduced pressure. Crude ^{1}H NMR shows ~quantitative yield of **162** (based on NaI).

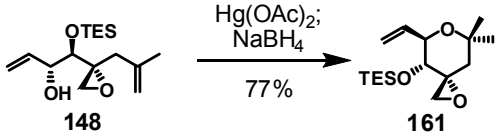


162 **161**

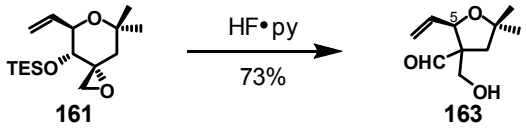
Preparation of 161 from 162. To a stirred solution of **162** (106 mg, 0.250 mmol) and tributyltin hydride (330 μL, 1.23 mmol) in toluene (5 mL) was added AIBN (20.6 mg, 0.125 mmol) in one portion at 23 °C under an open atmosphere. The reaction mixture was then warmed to 90 °C. After 5 h at the same temperature, the reaction was cooled to 23 °C and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (2 → 8% EtOAc in hexanes) on silica gel (20 mL) to afford **161** (47.2 mg, 63%) as a colorless oil.

Data for **161**: R_f = 0.48 (15% EtOAc in hexanes); IR (neat): 2956, 1460, 1227, 1133, 1008, 841, 742; $[\alpha]_D^{26}$ +71.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 5.89 (ddd 1H, *J* = 17.2, 10.3, 6.8 Hz), 5.41 (ddd, 1H, *J* = 17.2, 1.8, 1.1 Hz), 5.25 (ddd, 1H, *J* = 10.3, 1.8, 0.8

Hz), 4.16 (br dd, 1H, J = 9.3, 6.8 Hz), 3.65 (d, 1H, J = 9.3 Hz), 2.92 (d, 1H, J = 5.1 Hz), 2.45 (d, 1H, J = 5.1 Hz), 2.12 (d, 1H, J = 13.9 Hz), 1.43 (s, 3H), 1.39 (d, 1H, 13.9 Hz), 1.27 (s, 3 H), 0.95 (t, 9H, J = 7.9 Hz), 0.61 (q, 6H, J = 7.9 Hz); ^{13}C NMR (75 MHz, 293K, C_6D_6) δ 137.6, 116.8, 74.5, 73.1, 71.4, 57.9, 47.3, 43.7, 31.3, 24.1, 7.2, 7.1, 5.6, 5.4; HRMS (EI+) calcd. for $C_{16}H_{30}O_3Si$ $[M]^+$ 298.1964, found 298.1972.

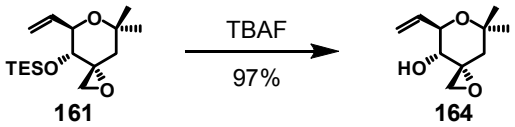


Preparation of 161 from 148. To a stirred solution of **148** (448 mg, 1.50 mmol) in THF (7.5 mL) was added $Hg(OAc)_2$ (526 mg, 1.65 mmol) in one portion at 0 °C under a nitrogen atmosphere. After an additional 0.5 h at the same temperature, the reaction was warmed to 23 °C. After an additional 1 h at the same temperature, the reaction mixture was cooled to –78 °C, and $NaBH_4$ (113 mg, 2.99 mmol) was added in one portion followed by the addition of Et_3B (1.0 M in hexanes, 1.5 mL) down the flask side. After an additional 2.8 h at –78 °C, the reaction mixture was warmed to –44 °C. After an additional 0.5 h at the same temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl (25 mL). The reaction mixture was then extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with H_2O (25 mL) then brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (2 → 10% EtOAc in hexanes) on silica gel (40 mL) to afford **161** (325 mg, 76%) as a pale yellow oil.



Preparation of and data for aldehyde 163. To a stirred solution of **161** (9.2 mg, 0.050 mmol) in THF (400 μL) was added HF•pyridine (~70% HF, 15 drops) at 0 °C under an open atmosphere. After 3 h at the same temperature, the reaction mixture was purified by flash chromatography (10 → 40% EtOAc in hexanes) on silica gel (6 mL) to afford **96** (6.7 mg, 73%) as a colorless oil.

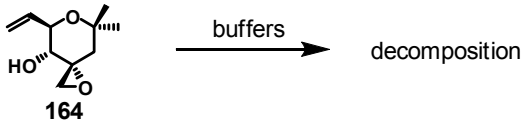
Data for **96**: R_f = 0.22 (30% EtOAc in hexanes); IR (neat): 3430 (br, O-H), 2972, 1721 (C=O), 1370, 1170, 1077, 999, 930; $[\alpha]_D^{23}$ +60.5 (*c* 0.60, $CHCl_3$); ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 9.62 (s, 1H), 5.91 (ddd, 1H, *J* = 17.1, 10.5, 6.2 Hz), 5.45 (ddd, 1H, *J* = 17.1, 1.5, 1.5 Hz), 5.28 (ddd, 1H, *J* = 10.5, 1.5, 1.5 Hz), 4.48 (br ddd, 1H, *J* = 6.2, 1.5, 1.5 Hz), 3.88 (br d, 1H, *J* = 11.1 Hz), 3.81 (br d, 1H, *J* = 11.1 Hz), 2.17 (d, 1H, *J* = 13.7 Hz), 2.13 (br s, 1H), 1.94 (d, 1H, *J* = 13.7 Hz), 1.45 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 204.2, 133.4, 118.1, 82.8, 80.9, 64.4, 63.1, 43.6, 29.6, 28.1; HRMS (EI+) calcd. for $C_{10}H_{16}O_3$ (M)+ 184.1099, found 184.1094.



Preparation of 164. To a stirred solution of **161** (299 mg, 1.00 mmol) in THF (4 mL) was added TBAF (1 M in THF, 1.2 mL) at 0 °C under an open atmosphere. After 20 min at the same temperature, the reaction mixture was diluted with Et_2O (15 mL), filtered through a pad of Florisil, rinsed with Et_2O (4 × 10 mL), and concentrated under reduced pressure. The resulting

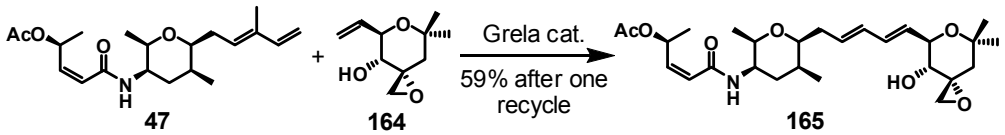
residue was purified by flash chromatography (10 → 40% EtOAc in hexanes) on silica gel (10 mL) to afford **164** (179 mg, 97%) as a white solid.

Data for **164**: m.p. = 60−62 °C; R_f = 0.39 (30% EtOAc in hexanes); IR (neat): 3403 (br, O-H), 2973, 1371, 1223, 1062, 895; $[\alpha]_D^{23}$ +72.3 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, 293K, CD_2Cl_2) δ 5.95 (ddd, 1H, *J* = 17.2, 10.5, 5.9 Hz), 5.34 (ddd, 1H, *J* = 17.2, 1.6, 1.6 Hz), 5.22 (ddd, 1H, *J* = 10.5, 1.5, 1.1 Hz), 3.91 (br dd, 1H, *J* = 9.7, 5.9 Hz), 3.44 (br app t, 1H, *J* = 10.1 Hz), 2.96 (d, 1H, *J* = 4.7 Hz), 2.46 (d, 1H, *J* = 4.7 Hz), 2.16 (d, 1H, *J* = 14.3 Hz), 1.65 (br d, 1H, *J* = 10.6 Hz), 1.39 (d, 1H, *J* = 14.3 Hz), 1.35 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (75 MHz, 293K, CD_2Cl_2) δ 137.5, 117.0, 74.8, 73.0, 68.4, 57.8, 47.8, 43.1, 31.1, 23.7; HRMS (EI+) calcd. for $C_9H_{13}O_3$ $(M - CH_3)^+$ 169.0865, found 169.0869.



164

General Procedure for the half-life determination for the decomposition of 164. To a vial was added **164** (0.2 mg, 1 μmol) and buffer (20 μL) under an open atmosphere at 23 °C. The reaction mixture was then sealed and warmed to 37 °C. The decomposition was then estimated by TLC analysis (50% EtOAc/hexanes) after 3, 5.5, 20, 25 31, 45, 50, and 56 h.



47 + **164** (1.6 equiv) → **165** (meayamycin)

Preparation of 165. A solution of **164** (27.7 mg, 0.150 mmol) was prepared in $ClCH_2CH_2Cl$ (300 μL) at 23 °C under an open atmosphere. To a stirred solution of **47** (34.8 mg, 0.100 mmol) in $ClCH_2CH_2Cl$ (200 μL) was added the solution of **164** (100 μL), benzoquinone

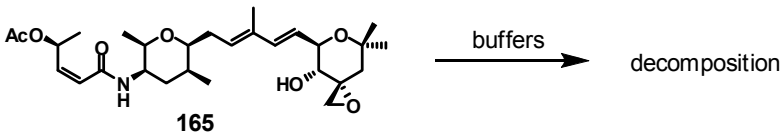
(2.1 mg, 0.019 mmol), followed by Grela catalyst (3.4 mg, 5.0 μmol) at 23 °C under an open atmosphere. The reaction mixture was then heated to 40 °C. After 2 h at the same temperature, additional Grela catalyst (3.4 mg, 5.0 μmol) and **164** (100 μL) were added. After an additional 2 h at the same temperature, **164** (100 μL) was added. After 9 total hours, the reaction was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 → 80% EtOAc in hexanes) on silica gel (7 mL) to give **165** (22.8 mg, 45%), and an inseparable mixture of **47** and **164** (35.3 mg).

To a stirred solution of recovered **47** and **164** (35.3 mg) in $ClCH_2CH_2Cl$ (300 μL) was added benzoquinone (1.0 mg, 0.010 mmol) Grela catalyst (3.4 mg, 5.0 μmol) at 23 °C under an open atmosphere. The reaction mixture was then heated to 40 °C. After an additional 14 h at the same temperature, the reaction was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 → 80% EtOAc in hexanes) on silica gel (5 mL) to give **165** (6.9 mg, 14%) as a pale tan solid. The combined yield of **165** after one cycle is 29.7 mg (59%). Some of the tan **165** was purified by semi-preparative HPLC[†] to afford meayamycin as a white solid that was subsequently used for biological experiments.

Data for **165**: R_f = 0.23 (60% EtOAc in hexanes); IR (neat): 3441 (br, N-H), 3372 (br, O-H), 2923, 1736 (C=O), 1668 (C=O), 1637, 1521, 1370, 1243, 1057, 734; $[\alpha]_D^{25}$ −8.1 (*c* 0.30, CH_2Cl_2); ^{1}H NMR (300 MHz, 293K, CD_2Cl_2) δ 6.36 (d, 1H, *J* = 15.9 Hz), 6.32−6.24 (m, 1H), 5.98 (br d, 1H, *J* = 9.0 Hz), 5.91 (dd, 1H, *J* = 11.4, 7.5 Hz), 5.72 (dd, 1H, *J* = 11.7, 1.2 Hz), 5.65 (dd, 1H, *J* = 15.9, 6.6 Hz), 5.53 (br app t, 1H, *J* = 7.1 Hz), 3.97 (br dd, 1H, *J* = 9.5, 6.6 Hz), 3.95−3.98 (m, 1H), 3.67 (qd, 1H, *J* = 6.3, 2.1 Hz), 3.58−3.50 (m, 1H), 3.49 (app t, 1H, *J* = 10.2 Hz), 2.97 (d, 1H, *J* = 4.8 Hz), 2.47 (d, 1H, *J* = 4.8 Hz), 2.42−2.30 (m, 1H), 2.28−2.16 (m, 1H), 2.18 (d, 1H, *J* = 14.4 Hz), 2.01 (s, 3H), 1.96−1.91 (m, 2H), 1.81−1.79 (m, 1H), 1.79 (br s, 3H),

1.63 (d, 1H, J = 10.5 Hz), 1.41 (d, 1H, J = 14.4 Hz), 1.36 (s, 3H), 1.35 (d, 3H, J = 6.3 Hz), 1.23 (s, 3H), 1.12 (d, 3H, J = 6.3 Hz), 1.02 (d, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, 293K, CD_2Cl_2) δ 170.6, 165.0, 143.9, 137.7, 135.0, 129.5, 125.9, 122.9, 81.2, 76.3, 74.9, 73.0, 68.9, 68.6, 57.8, 47.8, 47.4, 43.1, 36.3, 32.4, 31.1, 29.6, 23.7, 21.4, 20.2, 18.0, 15.3, 12.8; HRMS (EI+) calcd. for $C_{28}H_{43}NO_7$ $(M)^+$ 505.3040, found 505.3057.

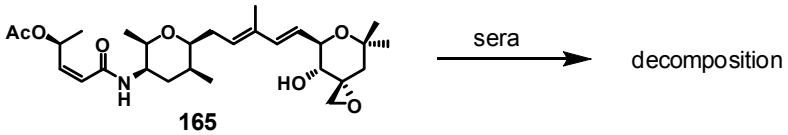
† HPLC purification was performed on a Varian Pursuit XRs 5 C18 column, 250 × 10.0 cm, 4.3 mL/min, 50% MeCN/H_2O → 100% MeCN linear gradient elution from 0.5 to 22 min, retention time = 19.6 min.



165
(meayamycin)

General Procedure for the half-life determination for the decomposition of 165 in buffers. To a corning tube (15 mL) was added phosphate buffer (10 mL), benzoic acid (10 mM in DMSO, 20 μL), and DMSO (70 μL) under an open atmosphere and warmed to 37 °C. To the reaction mixture was added meayamycin A (10 mM in DMSO, 10 μL) and the resulting mixture was sealed with a cap, vortexed for 15 s, and then placed in a 37 °C incubator. The decomposition was monitored by HPLC* at the indicated times. The resulting data were normalized by dividing the ratios of meayamycin A/benzoic acid by the ratio of the first data point.

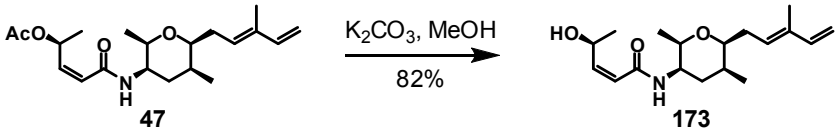
* HPLC purification was performed on a Varian Pursuit XDR C18 column, 75 × 4.6 cm, 1.0 mL/min, 10% MeCN/H_2O (containing 1% HCO_2H) → 100% MeCN linear gradient elution from 0.5 to 9.5 min, retention time = 6.7 min (retention time for benzoic acid = 4.3 min), monitored at 230 nm.



165
(meayamycin)

Procedure for the half-life determination for the decomposition of 165 in sera. To a 1 dram glass vial was added mouse serum (1.0 mL), rhodamine B (10 mM in DMSO, 2.0 μL), and DMSO (7.0 μL) under an open atmosphere and warmed to 37 °C. To the mixture was added meayamycin A or B (10 mM in DMSO, 1.0 μL) and the resulting solution was sealed with a cap, vortexed for 15 s, and then placed in a 37 °C incubator. The decomposition was monitored by HPLC* at the indicated times. The resulting data were normalized by dividing the ratios of meayamycin A or B/rhodamine B by the ratio of the first data point.

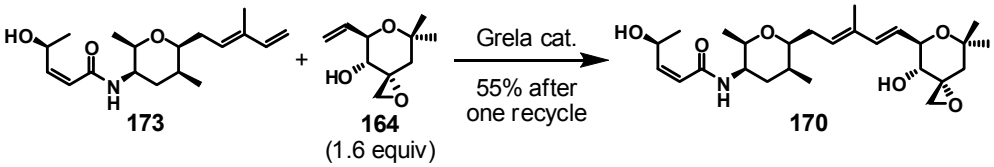
* HPLC purification was performed on a Varian Pursuit XRs 5 C18 column, 250 × 10.0 cm, 2.5 mL/min, 30% MeOH/H_2O (containing 1% HCO_2H) → 100% MeOH linear gradient elution from 0.5 to 22 min, monitored at 230 (for **165**) and 550 nM (for rhodamine B).



47 **173**

Preparation of 173. To a stirred solution of **47** (26.5 mg, 0.0758 mmol) in MeOH (380 μL) was added K_2CO_3 (26.3 mg, 0.190 mmol) at 0 ° C under an open atmosphere. After 2 h at the same temperature the reaction was diluted with saturated aqueous NH_4Cl (60 μL), and the resulting mixture was stirred for 5 min. The resulting reaction mixture was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (20 → 50% EtOAc in hexanes) on silica gel (3 mL) to give **173** (19.2 mg, 82%) as a colorless oil.

Data for **173**: R_f = 0.21 (50% EtOAc in hexanes); IR (neat): 3325, 2975, 1655 (C=O), 1621, 1522, 1456, 1116, 1062, 894 cm^{-1}; $[\alpha]_D^{26}$ +10.0 (*c* 0.95, $CHCl_3$); ^1H NMR (300 MHz, 293K, 1% CD_3OD in $CDCl_3$) δ 6.36 (dd, 1H, *J* = 17.4, 10.8 Hz), 6.16 (dd, 1H, *J* = 11.9, 5.6 Hz), 5.74 (dd, 1H, *J* = 11.9, 1.3 Hz), 5.44 (br app t, 1H, *J* = 8.1 Hz), 5.11 (d, 1H, *J* = 17.4 Hz), 4.96 (d, 1H, *J* = 10.8 Hz), 4.83–4.73 (m, 1H), 3.97–3.93 (m, 1H), 3.68 (qd, 1H, *J* = 6.6, 2.1 Hz), 3.55 (qd, 1H, *J* = 7.1, 2.5 Hz), 2.48–2.31 (m, 1H), 2.31–2.13 (m, 1H), 1.95–1.92 (m, 2H), 1.76 (br s, 3H), 1.34 (d, 3H, *J* = 6.6 Hz), 1.14 (d, 3H, *J* = 6.6 Hz), 1.01 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (125 MHz, 293K, $CDCl_3$) δ 166.1, 150.8, 141.2, 135.7, 127.9, 122.5, 111.2, 80.8, 75.8, 64.6, 47.5, 35.7, 31.8, 28.8, 22.7, 17.9, 15.2, 11.9; HRMS (EI+) calcd. for $C_{18}H_{29}NO_3$ $[M]^+$ 307.2147, found 307.2148.

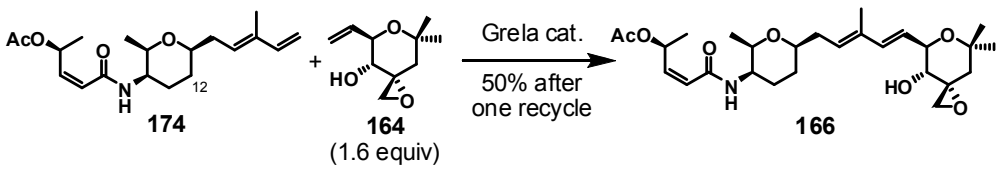


Preparation of 170. A solution of **164** (16.8 mg, 0.0912 mmol) was prepared in $ClCH_2CH_2Cl$ (100 μL) at 23 °C under an open atmosphere. To a stirred solution of **173** (17.2 mg, 0.0559 mmol) in $ClCH_2CH_2Cl$ (200 μL) was added the solution of **164** (50 μL), benzoquinone (1.0 mg, 9.3 μmol), followed by Grela catalyst (2.0 mg, 3.0 μmol) at 23 °C under an open atmosphere. The reaction mixture was then heated to 32 °C. After 3 h at the same temperature, additional Grela catalyst (1.8 mg, 2.7 μmol) and **164** (50 μL) were added. After 8 total hours, the reaction was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 → 100% EtOAc in hexanes) on silica gel (5 mL) to give **170** (16.1 mg, 62%), and an inseparable mixture of **173** and **164** (34.1 mg).

To a stirred solution of recovered **173** and **164** (12.4 mg) in $ClCH_2CH_2Cl$ (300 μL) was added Grela catalyst (1.4 mg, 2.1 μmol) at 23 °C under an open atmosphere. The reaction mixture was then heated to 32 °C. After an additional 14 h at the same temperature, the reaction was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 → 80% EtOAc in hexanes) on silica gel (3 mL) to give **170** (5.0 mg, 19%) as a pale tan solid. The combined yield of **170** after one cycle is 21.1 mg (81%). Some of the tan **170** was purified by semi-preparative HPLC[†] to afford **170** as a white solid that was subsequently used for biological experiments.

Data for **170**: R_f = 0.21 (80% EtOAc in hexanes); ^{1}H NMR (300 MHz, 293K, CD_2Cl_2) δ 6.34 (br d, 1H, *J* = 15.8 Hz), 6.16 (dd, 1H, *J* = 11.7, 5.4 Hz), 5.96 (br d, 1H, *J* = 9.3 Hz), 5.74 (dd, 1H, *J* = 11.7, 1.8 Hz), 5.65 (dd, 1H, *J* = 15.8, 6.5 Hz), 5.55–5.48 (m, 2H), 4.72–4.64 (m, 1H), 3.96 (dd, 1H, *J* = 10.2, 7.0 Hz), 3.94–3.87 (m, 1H), 3.66 (qd, 1H, *J* = 6.6, 2.1 Hz), 3.58–3.51 (m, 1H), 3.48 (app t, 1H, *J* = 10.1 Hz), 2.96 (d, 1H, *J* = 4.7 Hz), 2.46 (d, 1H, *J* = 4.7 Hz), 2.43–2.31 (m, 1H), 2.29–2.21 (m, 1H), 2.17 (d, 1H, *J* = 14.4 Hz), 1.98–1.91 (m, 2H), 1.78 (br s, 3H), 1.61 (d, 1H, *J* = 10.2 Hz), 1.40 (d, 1H, *J* = 14.4 Hz), 1.36 (s, 3H), 1.28 (d, 3H, *J* = 6.6 Hz), 1.23 (s, 3H), 1.11 (d, 3H, *J* = 6.6 Hz), 1.02 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, 293K, CD_2Cl_2) δ 166.5, 150.9, 143.0, 137.7, 135.1, 129.3, 126.0, 123.0, 102.3, 81.3, 76.1, 74.9, 68.6, 64.9, 57.8, 47.9, 47.8, 36.1, 32.4, 31.2, 29.6, 23.8, 23.0, 18.0, 15.4, 12.8; HRMS (EI+) calcd. for $C_{26}H_{41}NO_6$ $[M]^+$ 463.2934, found 463.2937.

[†] HPLC purification was performed on a Varian Pursuit XRs 5 C18 column, 250 × 10.0 cm, 4.3 mL/min, 50% MeCN/H_2O → 100% MeCN linear gradient elution from 0.5 to 22 min, retention time = 14.1 min.



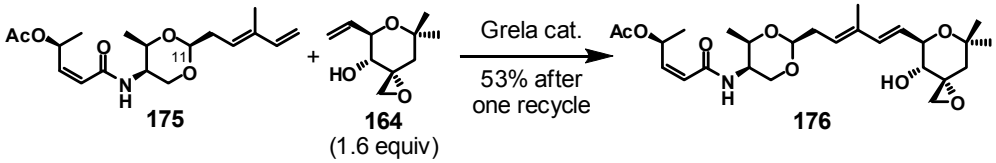
Preparation of 166. A solution of **164** (24.2 mg, 0.131 mmol) was prepared in $ClCH_2CH_2Cl$ (200 μL) at 23 °C under an open atmosphere. To a stirred solution of **174** (26.8 mg, 0.0799 mmol) in $ClCH_2CH_2Cl$ (200 μL) was added the solution of **164** (100 μL), benzoquinone (1.8 mg, 0.017 mmol), followed by Grela catalyst (2.7 mg, 4.0 μmol) at 23 °C under an open atmosphere. The reaction mixture was then heated to 35 °C. After 3 h at the same temperature, additional Grela catalyst (2.7 mg, 4.0 μmol) and **164** (100 μL) were added. After 9 total hours, the reaction was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 → 80% EtOAc in hexanes) on silica gel (5 mL) to give **166** (12.9 mg, 33%), and an inseparable mixture of **174** and **164** (34.1 mg).

To a stirred solution of recovered **174** and **164** (34.1 mg) in $ClCH_2CH_2Cl$ (300 μL) was added benzoquinone (1.0 mg, 0.010 mmol) and Grela catalyst (3.8 mg, 5.7 μmol) at 23 °C under an open atmosphere. The reaction mixture was then heated to 37 °C. After an additional 14 h at the same temperature, the reaction was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 → 80% EtOAc in hexanes) on silica gel (3 mL) to give **166** (6.8 mg, 17%) as a pale tan solid. The combined yield of **166** after one cycle is 29.7 mg (50%). Some of the tan **166** was purified by semi-preparative HPLC* to afford **166** as a white solid that was subsequently used for biological experiments.

Data for **166**: R_f = 0.35 (70% EtOAc in hexanes); IR (neat): 3350 (br), 2925, 1738 (C=O), 1699 (C=O) 1522, 1370, 1243, 1051, 972 cm^{-1}; $[\alpha]_D^{25}$ –2.6 (*c* 0.65, CH_2Cl_2); ^1H NMR (300 MHz, 293K, CD_2Cl_2) δ 6.50 (br d, 1H, *J* = 9.0 Hz), 6.35 (br d, 1H, *J* = 15.6 Hz), 6.10 (app quintet, 1H, *J* = 6.6 Hz), 5.88–5.77 (m, 2H), 5.64 (dd, 1H, *J* = 15.6, 6.6 Hz), 5.56 (br app t, 1H, *J*

= 7.4 Hz), 4.00–3.91 (m, 2H), 3.63 (qd, 1H, *J* = 6.5, 1.6 Hz), 3.48 (app t, 1H, *J* = 10.1 Hz), 3.47–3.38 (m, 1H), 2.96 (d, 1H, *J* = 4.8 Hz), 2.46 (d, 1H, *J* = 4.7 Hz), 2.40–2.31 (m, 2H), 2.17 (d, 1H, *J* = 14.2 Hz), 2.03 (s, 3H), 1.96–1.89 (m, 1H), 1.76 (br s, 3H), 1.76–1.67 (m, 1H), 1.61 (d, 1H, *J* = 10.2 Hz), 1.52–1.48 (m, 1H), 1.40 (d, 1H, *J* = 14.3 Hz), 1.36 (s, 3H), 1.34 (d, 3H, *J* = 6.6 Hz), 1.23 (s, 3H), 1.09 (d, 3H, *J* = 6.3 Hz); ^{13}C NMR (75 MHz, 293K, CD_2Cl_2) δ 170.9, 165.2, 142.0, 137.8, 135.1, 129.3, 125.9, 123.8, 78.5, 75.4, 74.9, 73.0, 69.1, 68.6, 57.8, 47.8, 47.2, 43.1, 35.6, 31.2, 29.4, 26.4, 23.7, 21.4, 20.3, 18.3, 12.7; HRMS (EI+) calcd. for $C_{27}H_{41}NO_7Na$ $[M]^+$ 514.2781, found 514.2782.

* HPLC purification was performed on a Varian Pursuit XRs 5 C18 column, 250 × 10.0 cm, 4.3 mL/min, 50% MeCN/H_2O → 100% MeCN linear gradient elution from 0.5 to 22 min, retention time = 17.9 min.



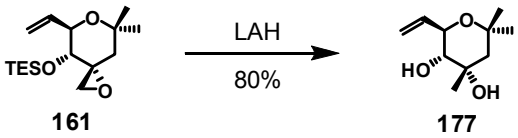
Preparation of 176. A solution of **164** (24.3 mg, 0.132 mmol) was prepared in $ClCH_2CH_2Cl$ (200 μL) at 23 °C under an open atmosphere. To a stirred solution of **175** (27.2 mg, 0.0806 mmol) in $ClCH_2CH_2Cl$ (200 μL) was added the solution of **164** (100 μL), benzoquinone (1.9 mg, 0.018 mmol), followed by Grela catalyst (2.8 mg, 4.2 μmol) at 23 °C under an open atmosphere. The reaction mixture was then heated to 35 °C. After 3 h at the same temperature, additional Grela catalyst (2.7 mg, 4.0 μmol) and **164** (100 μL) were added. After 9 total hours, the reaction was concentrated under reduced pressure. The resulting residue was purified by flash

chromatography (10 → 80% EtOAc in hexanes) on silica gel (5 mL) to give **176** (14.1 mg, 35%), and an inseparable mixture of **175** and **164** (29.9 mg).

To a stirred solution of recovered **175** and **164** (29.9 mg) in $ClCH_2CH_2Cl$ (300 μL) was added benzoquinone (1.0 mg, 0.010 mmol) and Grela catalyst (3.6 mg, 5.4 μmol) at 23 °C under an open atmosphere. The reaction mixture was then heated to 36 °C. After an additional 22 h at the same temperature, the reaction was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 → 80% EtOAc in hexanes) on silica gel (3 mL) to give **176** (6.9 mg, 14%) as a pale tan solid. The combined yield of **176** after one cycle is 21.0 mg (53%, 89% based on recovered **175**). Some of the tan **176** was purified by semi-preparative HPLC[‡] to afford **176** as a white solid that was subsequently used for biological experiments.

Data for **176**: R_f = 0.26 (70% EtOAc in hexanes); IR (neat): 3347 (br), 2977, 1735 (C=O), 1700 (C=O) 1520, 1370, 1245, 1126, 1050 cm^{-1}; $[\alpha]_D^{24}$ +3.5 (*c* 0.45, CH_2Cl_2); ^1H NMR (500 MHz, 293K, CD_2Cl_2) δ 6.75 (br d, 1H, *J* = 9.0 Hz), 6.35 (br d, 1H, *J* = 15.5 Hz), 6.20–6.13 (m, 1H), 5.89 (dd, 1H, *J* = 11.5, 8.0 Hz), 5.82 (dd, 1H, *J* = 11.5, 1.0 Hz), 5.66 (dd, 1H, *J* = 15.5, 6.5 Hz), 5.53 (br app t, 1H, *J* = 7.0 Hz), 4.64 (app t, 1H, *J* = 5.3 Hz), 3.98–3.92 (m, 3H), 3.90–3.86 (m, 2H), 3.48 (app t, 1H, *J* = 10.0 Hz), 2.96 (d, 1H, *J* = 4.7 Hz), 2.53–2.42 (m, 2H), 2.46 (d, 1H, *J* = 4.7 Hz), 2.17 (d, 1H, *J* = 14.3 Hz), 2.02 (s, 3H), 1.77 (br s, 3H), 1.61 (d, 1H, *J* = 10.5 Hz), 1.40 (d, 1H, *J* = 14.3 Hz), 1.36 (s, 3H), 1.34 (d, 3H, *J* = 6.5 Hz), 1.23 (s, 3H), 1.13 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, 293K, CD_2Cl_2) δ 170.8, 165.3, 143.0, 137.5, 135.8, 126.6, 126.3, 123.2, 102.3, 74.92, 74.89, 73.0, 71.4, 68.9, 68.6, 57.7, 47.8, 47.0, 43.0, 34.5, 31.1, 23.7, 21.4, 20.2, 17.7, 12.7; HRMS (ESI+) calcd. for $C_{26}H_{39}NO_8Na$ $[M + Na]^+$ 516.2573, found 516.2565.

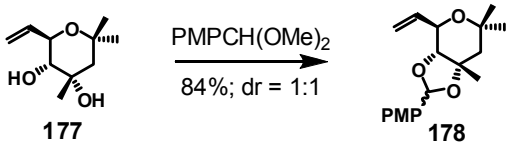
‡ HPLC purification was performed on a Varian Pursuit XRs 5 C18 column, 250 × 10.0 cm, 4.3 mL/min, 50% MeCN/H_2O → 100% MeCN linear gradient elution from 0.5 to 22 min, retention time = 16.3 min.



161 **177**

Preparation of 177. To a stirred solution of **161** (299 mg, 1.00 mmol) in Et_2O (5 mL) was added lithium aluminum hydride (1.0 M in Et_2O, 5 mL) at 0 °C under a nitrogen atmosphere. After 15 min at the same temperature, the reaction was warmed to reflux. After 1.0 h at the same temperature, the reaction was diluted with wet Et_2O (5 mL), followed by the dropwise addition of saturated aqueous NH_4Cl (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (10 → 30% EtOAc in hexanes) on silica gel (40 mL) afforded **177** (149 mg, 80%) as a viscous pale yellow oil.

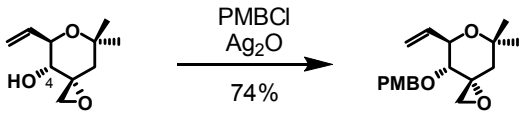
Data for **177**: R_f = 0.26 (30% EtOAc in hexanes); IR (neat): 3421 (br, O-H), 2973, 1644, 1369, 1204, 1058, 923 cm^{-1}; $[\alpha]_D^{25}$ +52.8 (*c* 1.4, CH_2Cl_2); ^1H NMR (300 MHz, 293K, CD_2Cl_2) δ 5.85 (ddd, 1H, *J* = 17.3, 10.2, 6.9 Hz), 5.35 (ddd, 1H, *J* = 17.3, 1.8, 0.9 Hz), 5.26 (ddd, 1H, *J* = 10.2, 1.8, 0.6 Hz), 4.03 (br dd, 1H, *J* = 9.5, 6.9 Hz), 3.06 (dd, 1H, *J* = 9.5, 4.6 Hz), 2.10 (br d, 1H, *J* = 1.5 Hz), 1.92 (br d, 1H, *J* = 4.6 Hz), 1.79 (d, 1H, *J* = 14.4 Hz), 1.54 (br d, 1H, *J* = 14.4 Hz), 1.40 (s, 3H), 1.23 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (75 MHz, 293K, CD_2Cl_2) δ 137.8, 118.3, 74.8, 72.7, 72.2, 70.5, 47.4, 32.4, 28.8, 24.4; HRMS (EI+) calcd. for $C_{10}H_{18}O_3$ $[M]^+$ 186.1256, found 186.1257.



177 178

Preparation of 178. To a stirred solution of **177** (28.2 mg, 0.151 mmol) and anisaldehyde dimethyl acetal (75 μL, 0.44 mmol) was added CSA (3.5 mg, 0.015 mmol) in CH_2Cl_2 (0.75 mL) at 23 °C. After 15 min at the same temperature, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL), and vigorously stirred for 30 min. The mixture was diluted with Et_2O (5 mL), washed with H_2O (5 mL) then brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by preparatory thin-layer chromatography (25% EtOAc in hexanes containing 1% Et_3N) afforded **178** (38.8 mg, 84%) as a pale yellow oil.

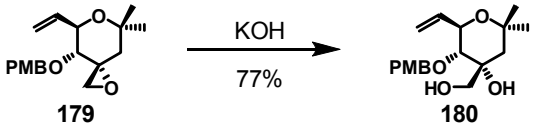
Data for **178**: R_f = 0.60 (30% EtOAc in hexanes); IR (neat): 2925, 1613, 1367, 1248, 1170, 1077, 1032, 826; ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 7.44 (br d, *J* = 8.9 Hz), 6.94–6.88 (m), 6.10 (s), 6.05–5.90 (m), 5.96 (s), 5.47–5.21 (m), 4.17 (dddd, *J* = 9.3, 5.8, 1.5, 1.5 Hz), 3.96 (dddd, *J* = 8.9, 5.4, 1.5, 1.5 Hz), 3.824 (s), 3.817 (s), 3.78 (d, *J* = 9.3 Hz), 3.65 (d, *J* = 8.9 Hz), 2.17 (d, *J* = 14.7 Hz), 2.13 (d, *J* = 14.7 Hz), 1.83 (d, *J* = 14.7 Hz), 1.76 (d, *J* = 14.7 Hz), 1.46 (s), 1.43 (s), 1.42 (s), 1.32 (s), 1.31 (s), 1.29 (s); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 160.2 (two overlapping carbons), 137.1, 136.8, 130.8, 130.3, 127.74, 127.70, 116.6, 113.7, 102.1, 101.5, 81.6, 80.7, 79.7, 72.5, 71.5, 69.7, 52.3 (two overlapping carbons), 44.8, 43.6, 31.0, 30.9, 29.1, 26.1, 25.84, 25.76; HRMS (EI+) calcd. for $C_{18}H_{24}O_4$ $[M]^+$ 304.1675, found 304.1668.



164 179

Preparation of 179. To a light-protected, stirred solution of **164** (92.6 mg, 0.503 mmol) and PMBCl (200 μL, 1.47 mmol) in DMF (1.0 mL) was added Ag_2O (174 mg, 0.751 mmol) at 23 °C under a nitrogen atmosphere. The resulting mixture was heated to 60 °C. After 43 h at the same temperature, the reaction mixture was poured onto H_2O (25 mL), and the resulting mixture was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (10 → 30% EtOAc in hexanes) on silica gel (8 mL) afforded **179** (113 mg, 74%) as a colorless oil.

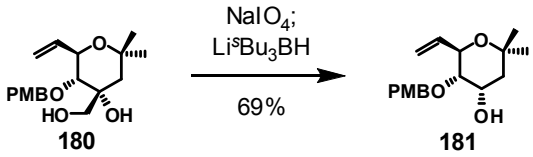
Data for **179**: R_f = 0.26 (30% EtOAc in hexanes); IR (neat): 2973, 1612, 1514, 1466, 1249, 1115, 1033, 822 cm^{-1}; $[\alpha]_D^{25}$ +40.2 (*c* 0.75, $CHCl_3$); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 7.21 (br d, 2H, *J* = 8.4 Hz), 6.86 (br d, 2H, *J* = 8.4 Hz), 5.95 (ddd, 1H, *J* = 17.3, 10.4, 6.8 Hz), 5.47 (br d, 1H, *J* = 17.3 Hz), 5.29 (br d, 1H, *J* = 10.4 Hz), 4.57 (d, 1H, *J* = 11.1 Hz), 4.36 (d, 1H, *J* = 11.1 Hz), 4.26 (dd, 1H, *J* = 9.6, 6.8 Hz), 3.81 (s, 3H), 3.40 (d, 1H, *J* = 9.6 Hz), 2.85 (d, 1H, *J* = 4.9 Hz), 2.41 (d, 1H, *J* = 4.9 Hz), 2.10 (d, 1H, *J* = 14.1 Hz), 1.43 (s, 3H), 1.36 (d, 1H, *J* = 14.1 Hz), 1.27 (s, 3H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 159.4, 136.5, 130.0, 129.6, 118.1, 113.8, 75.8, 74.3, 73.5, 73.2, 57.0, 55.2, 47.5, 43.4, 31.0, 23.7; HRMS (EI+) calcd. for $C_{18}H_{24}O_4Na$ [M + Na]$^+$ 327.1572, found 327.1556.



179 **180**

Preparation of 180. To a stirred solution of **179** (239 mg, 0.785 mmol) in DMSO (1.8 mL) and H_2O (1.2 mL) was added potassium hydroxide (221 mg, 3.94 mmol) at 23 °C under an open atmosphere. After 2 min at the same temperature, the reaction was submerged in a 55 °C oil bath. After 14 h at the same temperature, the reaction was cooled to 23 °C, diluted with H_2O (30 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (10 → 30% EtOAc in hexanes) on silica gel (10 mL) afforded **180** (195 mg, 77%) as a colorless oil.

Data for **180**: R_f = 0.22 (40% EtOAc in hexanes); IR (neat): 3446 (br O-H), 2914, 1613, 1514, 1302, 1249, 1178, 1076, 1034, 830 cm^{-1}; $[\alpha]_D^{24}$ +11.6 (*c* 0.98, $CHCl_3$); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 7.25 (br d, 2H, *J* = 8.5 Hz), 6.89 (br d, 2H, *J* = 8.5 Hz), 5.99 (ddd, 1H, *J* = 17.1, 10.2, 7.2 Hz), 5.49 (ddd, 1H, *J* = 17.1, 1.5, 0.6 Hz), 5.33 (br d, 1H, *J* = 10.2 Hz), 4.66 (d, 1H, *J* = 10.5 Hz), 4.42 (d, 1H, *J* = 10.5 Hz), 4.26 (dd, 1H, *J* = 9.5, 7.2 Hz), 3.82 (s, 3H), 3.40 (d, 1H, *J* = 10.8 Hz), 3.29 (br d, 1H, *J* = 10.8 Hz), 3.22 (d, 1H, *J* = 9.5 Hz), 2.85 (d, 1H, *J* = 4.9 Hz), 2.58–2.44 (br s, 1H), 1.76 (d, 1H, *J* = 14.4 Hz), 1.60 (d, 1H, *J* = 14.4 Hz), 1.45 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (75 MHz, 293K, CD_2Cl_2) δ 159.6, 137.1, 130.0, 129.6, 128.6, 118.3, 114.0, 78.6, 74.3, 72.9, 71.8, 70.9, 68.7, 55.3, 42.1, 32.2, 24.5; HRMS (EI+) calcd. for $C_{18}H_{26}O_5Na$ $[M]^+$ 322.1780, found 322.1782.

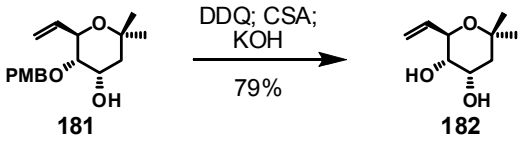


Preparation of 181. To a stirred solution of diol **180** (193 mg, 0.599 mmol) in THF (1.5 mL) and H_2O (3.0 mL) was $NaIO_4$ (155 mg, 0.725 mmol) at 23 °C under an open atmosphere. After 1.75 h at the same temperature, the reaction was diluted with H_2O (20 mL), and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford a ketone (161 mg) as a colorless oil. This material was used in the next reaction without further purification.

To a stirred solution of this crude ketone (156 mg, ~0.58 mmol) in THF (2.5 mL) was added Li^sBu_3BH (1.0 M in THF, 1.8 mL) at −78 °C under a nitrogen atmosphere. After 1 h at the same temperature, the reaction was diluted by the dropwise addition of aqueous potassium hydroxide (5% wt/wt, 1 mL), was then warmed to 0 °C, and then was added aqueous hydrogen peroxide (30%, 1 mL). After 1 h at the same temperature, the mixture was further diluted with H_2O (10 mL), and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (5 → 15% EtOAc in hexanes) on silica gel (8 mL) afforded **181** (118 mg, 69% from **180**) as a colorless oil.

Data for **181**: R_f = 0.25 (20% EtOAc in hexanes); IR (neat): 3482 (br, O-H), 2913, 1613, 1514, 1365, 1249, 1082, 1033, 927, 822 cm^{-1}; $[\alpha]_D^{24}$ +59.7 (*c* 0.99, $CHCl_3$); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 7.26 (br d, 1H, *J* = 8.6 Hz), 6.89 (br d, 1H, *J* = 8.6 Hz), 5.95 (ddd, 1H, *J* = 17.0, 10.5, 6.2 Hz), 5.41 (br d, 1H, *J* = 17.0 Hz), 5.29 (br d, 1H, *J* = 10.5 Hz), 4.53 (app s, 2H), 4.25 (dd, 1H, *J* = 9.6, 6.2 Hz), 4.25 (ddd, 1H, *J* = 3.4, 3.3, 3.2 Hz), 3.82 (s, 3H), 3.17 (dd, 1H, *J* = 9.6,

3.2 Hz), 2.48 (br s, 1H), 1.96 (dd, 1H, J = 14.6, 3.3 Hz), 1.61 (dd, 1H, J = 14.6, 3.4 Hz), 1.46 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 159.5, 137.1, 129.9, 129.5, 117.3, 113.9, 78.7, 71.5, 71.4, 68.9, 65.3, 55.3, 40.6, 32.0, 25.1; HRMS (EI+) calcd. for $C_{17}H_{24}O_4$ $[M]^+$ 292.1675, found 292.1673.

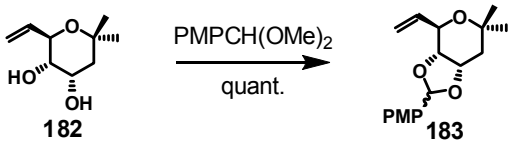


181 **182**

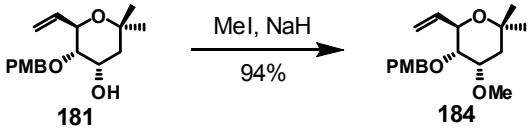
Preparation of 182. To a stirred solution of **181** (58.4 mg, 0.200 mmol) in CH_2Cl_2 (1.8 mL) and saturated aqueous $NaHCO_3$ (0.20 mL) was added DDQ (137 mg, 0.604 mmol) at 0 °C under an air atmosphere. After 10 min the reaction mixture was warmed to 23 °C. After 1 h at the same temperature, the reaction mixture was poured onto H_2O (15 mL), and the resulting mixture was extracted with Et_2O (4 × 10 mL). The combined organic layers were dried over over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 69.7 mg of a mixture of compounds.

To a stirred solution of this mixture (69 mg) in MeOH (1.0 mL) was added CSA (2.3 mg, 9.9 μmol) at 23 °C under an air atmosphere. After 12.5 h at the same temperature, the reaction was diluted with aqueous KOH (5% wt/wt, 1.0 mL). After an additional 2 h at 23 °C, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (15 mL), and the resulting mixture was extracted with CH_2Cl_2 (8 × 5 mL). The combined organic layers were dried over over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (10 → 50% EtOAc in hexanes) on silica gel (5 mL) afforded **182** (27 mg, 79%) as a colorless oil.

Data for **182**: R_f = 0.26 (40% EtOAc in hexanes); IR (neat): 3417 (br O-H), 2918, 1366, 1229, 1164, 1060, 996, 930 cm^{-1}; $[\alpha]_D^{25}$ +74.2 (*c* 0.89, $CHCl_3$); ^1H NMR (300 MHz, 293K, CD_2Cl_2) δ 5.88 (ddd, 1H, *J* = 17.4, 10.5, 7.2 Hz), 5.38 (ddd, 1H, *J* = 17.4, 1.8, 1.2 Hz), 5.29 (ddd, 1H, *J* = 10.5, 1.8, 0.6 Hz), 4.18–4.10 (m, 2H), 3.29 (dd, 1H, *J* = 9.5, 3.2 Hz), 2.48 (br s, 1H), 2.18 (br s, 1H), 1.93 (dd, 1H, *J* = 14.7, 3.2 Hz), 1.69 (dd, 1H, *J* = 14.7, 3.3 Hz), 1.44 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (75 MHz, 293K, CD_2Cl_2) δ 137.7, 118.3, 71.7, 71.6, 71.2, 67.8, 41.5, 32.1, 25.3; HRMS (EI+) calcd. for $C_9H_{16}O_3$ $[M]^+$ 172.1099, found 172.1101.

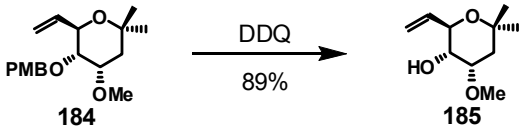


Preparation of 183. To a stirred solution of **182** (24.3 mg, 0.141 mmol) and anisaldehyde dimethyl acetal (70 μL, 0.41 mmol) was added CSA (3.2 mg, 0.014 mmol) in CH_2Cl_2 (0.7 mL) at 23 °C. After 15 min at the same temperature, the reaction mixture was quenched by the addition of Et_3N (0.10 mL) then saturated aqueous $NaHCO_3$ (1 mL), and vigorously stirred for 10 min. The mixture was diluted with Et_2O (5 mL), washed with H_2O (5 mL) then brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by preparatory thin-layer chromatography (25% EtOAc in hexanes containing 1% Et_3N) afforded **183** and anisaldehyde dimethyl acetal (69.1 mg, quant.) as a mixture.



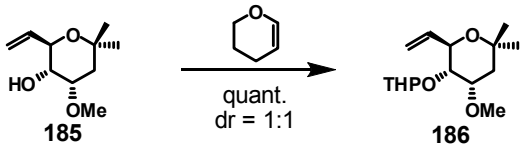
Preparation of 184. To a stirred solution of NaH (60% wt/wt in mineral oil, 40.0 mg, 1.00 mmol) in THF (0.1 mL) was added iodomethane (62 μL, 1.00 mmol) followed by **181** (58.7 mg, 0.201 mmol) in THF (0.1 mL), and the container that originally contained **181** was rinsed with additional THF (2 × 0.1 mL) and added to the reaction mixture at 23 °C under a nitrogen atmosphere. After 9.5 h at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl (5 mL), and extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (2.5 → 10% EtOAc in hexanes) on silica gel (4 mL) afforded **184** (57.6 mg, 94%) as a colorless oil.

Data for **184**: R_f = 0.37 (20% EtOAc in hexanes); IR (neat): 2972, 1613, 1513, 1364, 1248, 1032, 821 cm^{-1}; $[\alpha]_D^{25}$ +61.6 (*c* 0.90, $CHCl_3$); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 7.27 (br d, 1H, *J* = 8.4 Hz), 6.87 (br d, 1H, *J* = 8.4 Hz), 5.95 (ddd, 1H, *J* = 17.4, 10.5, 6.3 Hz), 5.41 (ddd, 1H, *J* = 17.4, 1.8, 1.2 Hz), 5.24 (br ddd, 1H, *J* = 10.5, 1.8, 0.9 Hz), 4.55 (d, 1H, *J* = 11.9 Hz), 4.50 (d, 1H, *J* = 11.9 Hz), 4.34 (dd, 1H, *J* = 9.5, 6.3 Hz), 3.81 (s, 3H), 3.65 (ddd, 1H, *J* = 3.6, 3.3, 2.9 Hz), 3.42 (s, 3H), 3.13 (dd, 1H, *J* = 9.5, 3.3 Hz), 2.02 (dd, 1H, *J* = 14.5, 3.6 Hz), 1.41 (s, 3H), 1.40 (dd, 1H, *J* = 14.5, 2.9 Hz), 1.20 (s, 3H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 159.1, 137.3, 130.4, 129.4, 117.0, 113.6, 78.6, 74.7, 71.6, 70.9, 69.9, 57.0, 55.2, 37.4, 32.0, 24.4; HRMS (EI+) calcd. for $C_{18}H_{26}O_4$ $[M]^+$ 306.1831, found 306.1829.



184 185

Preparation of 185. To a stirred solution of **184** (62 mg, 0.19 mmol) in CH_2Cl_2 (1.8 mL) and saturated aqueous $NaHCO_3$ (0.20 mL) was added DDQ (84 mg, 0.37 mmol) at 23 °C under an air atmosphere. After 1.5 h at the same temperature, the reaction mixture was poured onto H_2O (15 mL), and the resulting mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL) then brine (10 mL), dried over over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (5 → 25% Et_2O in hexanes) on silica gel (5 mL) afforded **185** (31 mg, 89%) as a pale yellow oil.

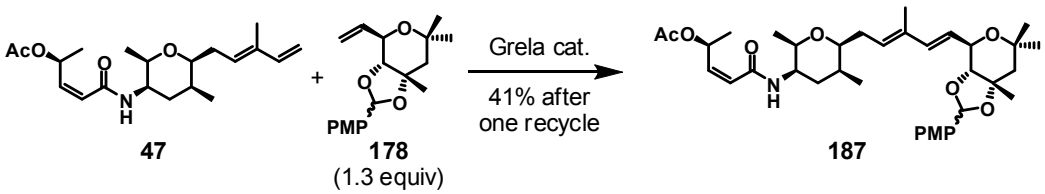


185 186

Preparation of 186. To a stirred solution of **185** (26.8 mg, 0.144 mmol) and 3,4-dihydro-2*H*-pyran (20 μL, 0.22 mmol) in CH_2Cl_2 (0.5 mL) was added CSA (1.7 mg, 7.3 μmol) at 23 °C under a nitrogen atmosphere. After 1 h at the same temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (1 mL). The resulting mixture was diluted with Et_2O (5 mL), washed with brine (5 mL), dried over over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (2.5 → 10% EtOAc in hexanes) on silica gel (5 mL) afforded **186** (41.2 mg, quant. yield) as a colorless oil.

Data for **186**: R_f = 0.24 (60% EtOAc in hexanes); IR (neat): 2940, 1442, 1365, 1126, 1101, 1073, 1035, 974 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 6.36 (d, 1H, *J* = 16.0 Hz), 6.30–6.23 (m, 1H), 5.98 (br d, 1H, *J* = 11.5, 7.5 Hz), 5.90 (ddd, 1H, *J* = 11.5, 1.5, 1.0 Hz), 5.71

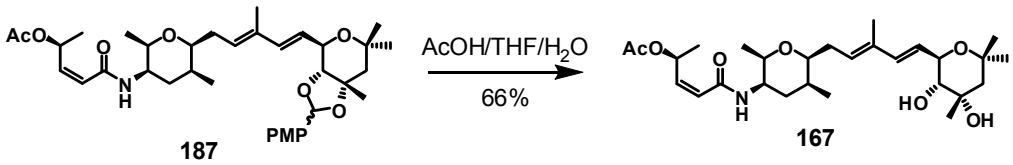
(dd, 1H, J = 11.5, 1.0 Hz), 5.57–5.51 (m, 2H), 4.07 (br app t, 1H, J = 8.5 Hz), 3.92–3.89 (m, 1H), 3.66 (qd, 1H, 9.5, 8.5, 2.3 Hz), 3.09 (d, 1H, J = 9.5 Hz), 2.40–2.33 (m, 1H), 2.25–2.19 (m, 1H), 2.14 (br s, 1H), 2.01 (s, 3H), 1.98–1.92 (m, 2H), 1.91–1.88 (m, 1H), 1.79 (d, 1H, J = 14.5 Hz), 1.78 (br s, 3H), 1.54 (d, 1H, J = 14.5 Hz), 1.41 (s, 3H), 1.34 (d, 1H, J = 6.3 Hz), 1.23 (s, 3H), 1.16 (s, 3H), 1.11 (d, 3H, J = 7.0 Hz), 1.01 (d, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 137.6, 137.0, 117.4, 117.0, 100.8, 94.7, 92.6, 78.9, 77.7, 73.3, 72.9, 71.7, 71.6, 70.3, 69.7, 63.0, 62.4, 57.0, 56.6, 37.7. 36.8, 32.2, 32.1, 30.7, 30.3, 25.5, 25.4, 24.5, 24.4, 19.8, 19.5, 18.4; HRMS (ESI+) calcd. for $C_{15}H_{26}O_4Na$ $[M + Na]^+$ 293.1729, found 293.1722.



Preparation of 187. To a stirred solution of **47** (27.4 mg, 0.0784 mmol) and **178** (31.5 mg, 0.103 mmol) in $ClCH_2CH_2Cl$ (300 μL) was added benzoquinone (1.8 mg, 0.017 mmol), followed by Grela catalyst (5.5 mg, 8.2 μmol) at 23 °C under an open atmosphere. The reaction mixture was then heated to 42 °C. After 9 h, the reaction was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 → 40% EtOAc in hexanes) on silica gel (5 mL) to give **187** (13.1 mg, 27%), and an inseparable mixture of **47** and **178** (45.6 mg).

To a stirred solution of recovered **47** and **178** (45.3 mg) in $ClCH_2CH_2Cl$ (300 μL) was added benzoquinone (1.4 mg, 0.013 mmol) and Grela catalyst (4.2 mg, 6.3 μmol) at 23 °C under an open atmosphere. The reaction mixture was then heated to 40 °C. After 16.5 h at the same temperature, the reaction was concentrated under reduced pressure. The resulting residue was

purified by flash chromatography (10 → 40% EtOAc in hexanes) on silica gel (4 mL) to give **187** (7.1 mg, 14%) as a pale tan solid. The combined yield of **187** after two cycles is 20.2 mg (41%).

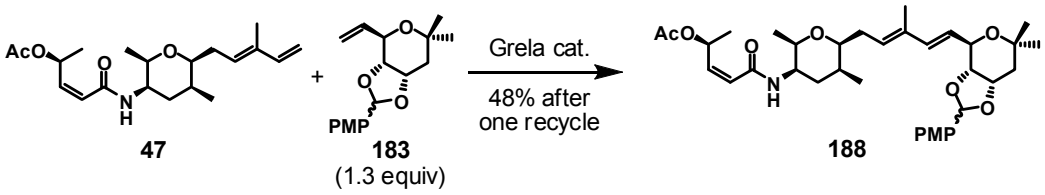


Preparation of 167 from 187. Acetal **187** (20.0 mg, 0.0320 mmol) was dissolved in AcOH/THF/H_2O (3:1:1 v/v/v, 400 μL) at 23 °C under an open atmosphere. After 20 h at the same temperature, the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography (20 → 80% EtOAc in hexanes) on silica gel (2 mL) afforded **167** (10.7 mg, 66%) as a white solid. Some of this material was purified by HPLC and used for biological experiments.*

Data for **167**: R_f = 0.24 (60% EtOAc in hexanes); IR (neat): 3423 (br), 2973, 1734 (C=O), 1665 (C=O), 1636, 1523, 1369, 1244, 1053, 970 cm^{-1}; $[\alpha]_D^{25}$ –19.5 (*c* 0.65, CH_2Cl_2); ^1H NMR (500 MHz, 293K, CD_2Cl_2) δ 6.36 (d, 1H, *J* = 16.0 Hz), 6.30–6.23 (m, 1H), 5.98 (br d, 1H, *J* = 11.5, 7.5 Hz), 5.90 (ddd, 1H, *J* = 11.5, 1.5, 1.0 Hz), 5.71 (dd, 1H, *J* = 11.5, 1.0 Hz), 5.57–5.51 (m, 2H), 4.07 (br app t, 1H, *J* = 8.5 Hz), 3.92–3.89 (m, 1H), 3.66 (qd, 1H, 9.5, 8.5, 2.3 Hz), 3.53 (ddd, 1H, *J* = 7.0, 7.0, 2.3 Hz), 3.09 (d, 1H, *J* = 9.5 Hz), 2.40–2.33 (m, 1H), 2.25–2.19 (m, 1H), 2.14 (br s, 1H), 2.01 (s, 3H), 1.98–1.92 (m, 2H), 1.91–1.88 (m, 1H), 1.79 (d, 1H, *J* = 14.5 Hz), 1.78 (br s, 3H), 1.54 (d, 1H, *J* = 14.5 Hz), 1.41 (s, 3H), 1.34 (d, 1H, *J* = 6.3 Hz), 1.23 (s, 3H), 1.16 (s, 3H), 1.11 (d, 3H, *J* = 7.0 Hz), 1.01 (d, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, 293K, CD_2Cl_2) δ 170.6, 165.0, 143.9, 139.1, 134.8, 129.9, 125.7, 122.8, 81.2, 76.3, 75.3, 72.7,

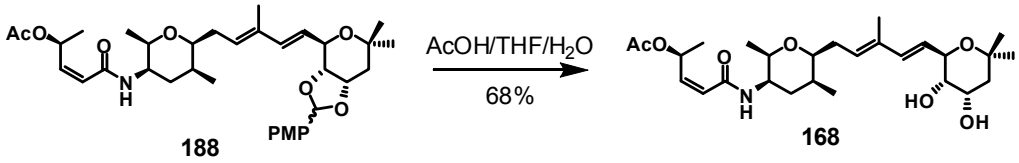
72.3, 70.5, 68.9, 47.4, 47.2, 36.2, 32.5, 32.4, 32.0, 29.6, 28.8, 24.4, 20.2, 18.0, 15.2, 12.8; HRMS (ESI+) calcd. for $C_{28}H_{45}NO_7Na$ $[M + Na]^+$ 530.3094, found 530.3091.

* HPLC purification was performed on a Varian Pursuit XRs 5 C18 column, 250 × 10.0 cm, 3.6 mL/min, 50% MeCN/H_2O → 100% MeCN linear gradient elution from 0.5 to 22 min, retention time = 14.0 min.



Preparation of 188. To a stirred solution of **47** (27.4 mg, 0.0784 mmol) and **183** (31.5 mg, 0.103 mmol) in $ClCH_2CH_2Cl$ (300 μL) was added benzoquinone (1.8 mg, 0.017 mmol), followed by Grela catalyst (5.5 mg, 8.2 μmol) at 23 °C under an open atmosphere. The reaction mixture was then heated to 40 °C. After 11 h, the reaction was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 → 40% EtOAc in hexanes) on silica gel (5 mL) to give **188** (13.9 mg, 30%), and an inseparable mixture of **47** and **183** (39.0 mg).

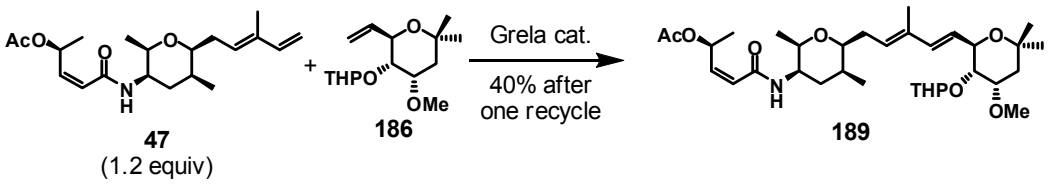
To a stirred solution of recovered **47** and **183** (38.7 mg) in $ClCH_2CH_2Cl$ (300 μL) was added benzoquinone (1.4 mg, 0.013 mmol) and Grela catalyst (4.2 mg, 6.3 μmol) at 23 °C under an open atmosphere. The reaction mixture was then heated to 40 °C. After 13 h at the same temperature, the reaction was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 → 40% EtOAc in hexanes) on silica gel (4 mL) to give **188** (7.1 mg, 14%) as a pale tan solid. The combined yield of **188** after two cycles is 22.0 mg (48%).



Preparation of 169 from 188. THP-ether **188** (21.6 mg, 0.0353 mmol) was dissolved in AcOH/THF/H_2O (3:1:1 v/v/v, 500 μL) at 23 °C under an open atmosphere. After 3 h at the same temperature, the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography (20 → 80% EtOAc in hexanes) on silica gel (2 mL) afforded **168** (11.8 mg, 68%) as a white solid. Some of this material was purified by HPLC and used for biological experiments.[†]

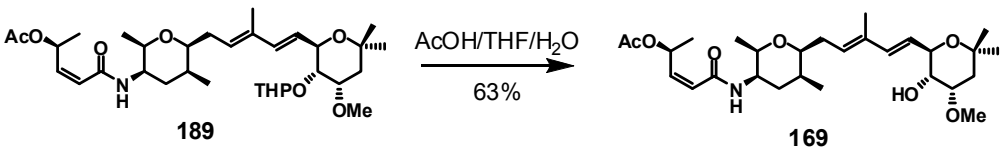
Data for **168**: R_f = 0.22 (60% EtOAc in hexanes); IR (neat): 3439 (br), 2973, 1725 (C=O), 1664 (C=O), 1635, 1523, 1367, 1244, 1050 cm^{-1}; $[\alpha]_D^{25}$ –8.6 (*c* 0.28, CH_2Cl_2); ^1H NMR (500 MHz, 293K, CD_2Cl_2) δ 6.37 (d, 1H, *J* = 15.5 Hz), 6.29–6.23 (m, 1H), 5.96 (br d, 1H, *J* = 9.0 Hz), 5.90 (dd, 1H, *J* = 11.5, 7.5 Hz), 5.71 (dd, 1H, *J* = 11.5, 1.5 Hz), 5.55–5.52 (m, 1H), 5.53 (dd, 1H, *J* = 15.5, 7.5 Hz), 4.15 (dd, 1H, *J* = 9.5, 7.5 Hz), 4.13–4.09 (m, 1H), 3.93–3.88 (m, 1H), 3.66 (qd, 1H, *J* = 6.3, 2.3 Hz), 3.55–3.51 (m, 1H), 3.29 (ddd, 1H, *J* = 9.5, 3.5, 2.8 Hz), 2.40–2.33 (m, 2H), 2.26–2.18 (m, 1H), 2.02–2.00 (m, 1H), 2.01 (s, 3H), 1.96–1.92 (m, 3H), 1.89 (d, 1H, *J* = 3.5 Hz), 1.78 (br s, 3H), 1.80–1.74 (m, 1H), 1.66 (dd, 1H, *J* = 14.5, 2.5 Hz), 1.42 (s, 3H), 1.34 (d, 3H, *J* = 6.5 Hz), 1.17 (s, 3H), 1.11 (d, 3H, *J* = 6.3 Hz), 1.01 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, 293K, CD_2Cl_2) δ 170.6, 164.9, 143.9, 139.1, 134.8, 130.0, 125.5, 122.8, 81.1, 76.3, 71.73, 71.68, 71.4, 68.9, 67.8, 47.4, 41.4, 36.2, 32.4, 32.2, 29.6, 25.4, 21.4, 20.2, 17.9, 15.3, 12.8; HRMS (ESI+) calcd. for $C_{27}H_{43}NO_7Na$ $[M + Na]^+$ 516.2937, found 516.2937.

† HPLC purification was performed on a Varian Pursuit XRs 5 C18 column, 250 × 10.0 cm, 3.2 mL/min, 40% MeCN/H_2O → 100% MeCN linear gradient elution from 0.5 to 22 min, retention time = 12.2 min.



Preparation of 189. A solution of **47** (42.4 mg, 0.121 mmol) was prepared in $ClCH_2CH_2Cl$ (200 μL) at 23 °C under an open atmosphere. To a stirred solution of **186** (27.2 mg, 0.101 mmol) in $ClCH_2CH_2Cl$ (300 μL) was added the solution of **47** (100 μL), benzoquinone (2.2 mg, 0.020 mmol), followed by Grela catalyst (3.4 mg, 5.0 μmol) at 23 °C under an open atmosphere. The reaction mixture was then heated to 45 °C. After 1.5 h at the same temperature, additional Grela catalyst (3.4 mg, 5.0 μmol) and **47** (100 μL) were added. After 8.5 total hours, the reaction was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 → 40% EtOAc in hexanes) on silica gel (5 mL) to give **189** (16.5 mg, 28%), and an inseparable mixture of **47** and **186** (45.9 mg).

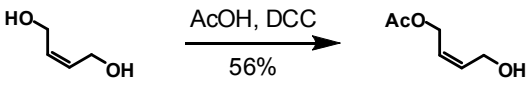
To a stirred solution of recovered **47** and **186** (45.5 mg) in $ClCH_2CH_2Cl$ (400 μL) was added benzoquinone (2.0 mg, 0.019 mmol) and Grela catalyst (6.1 mg, 9.0 μmol) at 23 °C under an open atmosphere. The reaction mixture was then heated to 40 °C. After 13 h at the same temperature, the reaction was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 → 40% EtOAc in hexanes) on silica gel (4 mL) to give **189** (5.4 mg, 9%) as a pale tan solid. This recycling procedure was repeated one more time to give **189** (1.8 mg, 3%). The combined yield of **189** after two cycles is 23.7 mg (40%).



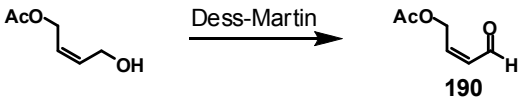
Preparation of 169 from 189. THP-ether **189** (23.5 mg, 0.0397 mmol) was dissolved in AcOH/THF/H_2O (3:1:1 v/v/v, 500 μL) at 23 °C under an open atmosphere. After 15 h at the same temperature, the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography (20 → 80% EtOAc in hexanes) on silica gel (2 mL) afforded **169** (12.7 mg, 63%) as a white solid. Some of this material was purified by HPLC and used for biological experiments.[‡]

Data for **169**: R_f = 0.31 (60% EtOAc in hexanes); IR (neat): 3444 (br), 3364 (br), 2933, 1737 (C=O), 1668 (C=O), 1637, 1521, 1368, 1244, 1051 cm^{-1}; $[\alpha]_D^{25}$ +4.5 (*c* 0.53, CH_2Cl_2); ^1H NMR (500 MHz, 293K, CD_2Cl_2) δ 6.21 (br d, 1H, *J* = 16.0 Hz), 6.30–6.23 (m 1H), 5.96 (br d, 1H, *J* = 9.0 Hz), 5.90 (dd, 1H, *J* = 11.5, 8.0 Hz), 5.71 (dd, 1H, *J* = 11.5, 1.3 Hz), 5.61 (dd, 1H, *J* = 16.0, 6.7 Hz), 5.50 (br app t, *J* = 7.0 Hz), 4.06 (br dd, 1H, *J* = 9.5, 6.7 Hz), 3.92–3.88 (m, 1H), 3.65 (qd, 1H, *J* = 6.3, 3.0 Hz), 3.61 (ddd, 1H, *J* = 3.5, 3.3, 3.0 Hz), 3.39 (s, 3H), 3.23 (ddd, 1H, *J* = 9.8, 9.5, 3.5 Hz), 2.39–2.32 (m, 1H), 2.38 (d, 1H, *J* = 9.8 Hz), 2.24–2.18 (m, 1H), 2.08 (dd, 1H, *J* = 14.8, 3.3 Hz), 2.01 (s, 3H), 1.98–1.91 (m, 2H), 1.80–1.74 (m, 1H), 1.77 (br s, 3H), 1.47 (dd, 1H, 14.8, 3.0 Hz), 1.35 (s, 3H), 1.34 (d, 3H, *J* = 6.5 Hz), 1.17 (s, 3H), 1.11 (d, 3H, *J* = 6.3 Hz), 1.01 (d, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, 293K, CD_2Cl_2) δ 170.6, 164.9, 143.9, 137.3, 135.1, 128.9, 126.6, 122.8, 81.2, 77.6, 76.2, 72.0, 71.6, 71.5, 68.9, 56.8, 47.4, 37.2, 36.2, 32.3, 32.1, 29.5, 24.4, 21.4, 20.2, 18.0, 15.3, 12.7; HRMS (ESI+) calcd. for $C_{28}H_{45}NO_7Na$ $[M + Na]^+$ 530.3094, found 530.3094.

‡ HPLC purification was performed on a Varian Pursuit XRs 5 C18 column, 250 × 10.0 cm, 3.2 mL/min, 50% MeCN/H_2O → 100% MeCN linear gradient elution from 0.5 to 22 min, retention time = 14.0 min.

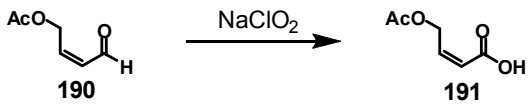


Preparation and data for (*Z*)-4-acetoxy-2-buten-1-ol. See Bauman, H.; Duthaler, R. O. *Helv. Chim. Acta* **1988**, *71*, 1025−1034.



Preparation of 190. To a stirred solution of (*Z*)-4-acetoxy-2-buten-1-ol (521 mg, 4.00 mmol) in CH_2Cl_2 (20 mL) was added Dess-Martin periodinane (3.39 g, 7.99 mmol) at 23 °C under a nitrogen atmosphere. After an additional 1.5 h at the same temperature, the reaction was quenched by the addition of EtOH (250 μL). After an additional 3 min, the reaction mixture was concentrated under reduced pressure, filtered through a pad of Florisil (15 mL), and rinsed with 40% Et_2O in pentane (75 mL). The filtrate was concentrated under reduced pressure and afforded a mixture of aldehyde **190** and AcOH (718 mg) as a colorless oil. This material was used in the next reaction without further purification.

Data for **190**: R_f = 0.44 (40% EtOAc in hexanes); ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 10.04 (d, 1H, *J* = 6.3 Hz), 6.55 (td, 1H, *J* = 11.5, 6.1 Hz), 6.13 (ddt, 1H, *J* = 11.5, 6.3, 1.9 Hz), 5.11 (dd, 1H, *J* = 6.1, 1.9 Hz), 2.13 (s, 3H).

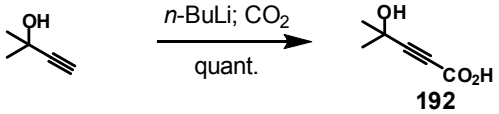


190 191

Preparation of 191. To a stirred solution of **190** (714 mg, ~4.0 mmol) and 2-methyl-2-butene (6.5 mL, 60 mmol) in ^{t}BuOH (10 mL) was added the mixture of $NaClO_2$ (257 mg, 2.84 mmol) and NaH_2PO_4 (393 mg, 2.84 mmol) in H_2O (10 mL) at 23 °C under an open atmosphere. After an additional 0.5 h at the same temperature, the reaction was quenched by the addition of EtOH (250 μL). After an additional 3 min, the reaction mixture was poured onto aqueous HCl (1N, 18 mL), and the resulting mixture was extracted with EtOAc (4 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (5 → 30% EtOAc in hexanes

containing 1% AcOH) on silica gel (75 mL) afforded acid **191** (485 mg, 80% from **XX**) as a colorless oil.

Data for **191**: R_f = 0.26 (40% EtOAc in hexanes containing 1% AcOH); IR (neat): 3057 (br, O-H), 1744 (C=O), 1700 (C=O), 1437, 1374, 1233, 1042 cm^{-1}; ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 6.41 (dt, 1H, J = 11.7, 5.0 Hz), 5.91 (dt, 1H, J = 2.4 Hz), 5.18 (dd, 1H, J = 5.0, 2.4 Hz), 2.12 (s, 3H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 171.0, 170.8, 147.5, 120.0, 62.7, 20.7; HRMS (EI+) calcd. for $C_6H_9O_4$ $[M + H]^+$ 145.0501, found 145.0497.

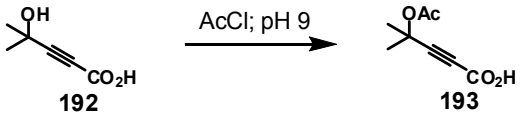


192

Preparation of 192. To a stirred solution of 2-methyl-3-butyn-2-ol (390 μL, 4.02 mmol) in THF (28 mL) at −78 °C was added ^{n}BuLi (5.3 mL, 8.5 mmol) under a nitrogen atmosphere. After 1 h at the same temperature, the reaction mixture was warmed to 0 °C, and dry CO_2 was

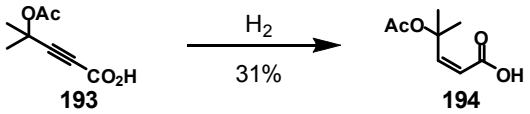
bubbled through the reaction mixture. After 2 h at 23 °C, the reaction was diluted with aqueous NaOH (1N, 75 mL), and washed with CH_2Cl_2 (30 mL). The resulting aqueous layer was acidified with aqueous HCl (12 N, 9 mL) until the pH was approximately 1, and then extracted with EtOAc (8 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford acid **192** (524 mg, quant. yield) as a white solid. This material was used in the next reaction without further purification.

Data for **192**: R_f = 0.13 (1% AcOH in EtOAc); ^{1}H NMR (300 MHz, 293K, CD_3OD) δ 1.50 (s, 6H).



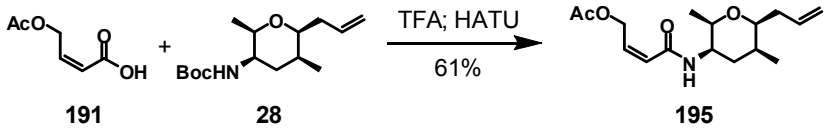
192 **193**

Preparation of 193. To crude **192** (509 mg, 3.97 mmol) in CH_2Cl_2 (1 mL) was added added acetyl chloride (4.0 mL, 56 mmol) slowly over 5 min at 0 °C under a nitrogen atmosphere. After 10 min at the same temperature, the reaction mixture was warmed to 23 °C. After 30 min at the same temperature, the solvents were evaporated under a stream of dry nitrogen. The resulting residue was dissolved in pH 9.5 H_2O (Na_2CO_3) at 23 °C. After 5 min at the same temperature, the mixture was diluted with aqueous HCl (3N, 0.5 mL) until the pH was approximately 2. The aqueous mixture was then extracted with EtOAc (5 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (20 → 100% EtOAc in hexanes containing 1% AcOH) on silica (25 mL) to afford acid **193** (671 mg, 99%).



Preparation of 194. To a mixture of Lindlar catalyst (85.1 mg, 0.040 mmol) in EtOH (45 mL) was added quinoline (55 μL, 0.47 mmol), and was stirred for 30 min at 23 °C. To the mixture was added a solution of **193** (665 mg, 3.95 mmol) in EtOH (5 mL) and the container that originally contained **193** was rinsed with additional EtOH (2 × 5 mL), and the resulting mixture was stirred vigorously under a hydrogen atmosphere (1 atm) for 16 h at 23 °C. The mixture was filtered through paper filter and washed with EtOAc. The filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography (10 → 40% EtOAc in hexanes containing 1% AcOH) afforded acid **194** (212 mg, 31%) as a colorless oil.

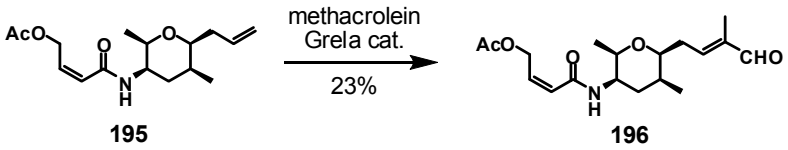
Data for **194**: R_f = 0.46 (30% EtOAc in hexanes containing 1% AcOH); IR (neat): 3197 (br, O-H), 2984, 1734 (C=O), 1705 (C=O), 1368, 1252, 1127 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 6.36 (d, 1H, *J* = 13.1 Hz), 5.74 (d, 1H, *J* = 13.1 Hz), 2.01 (s, 3H), 1.68 (s, 6H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 170.9, 170.2, 152.0, 117.3, 80.5, 26.0, 21.7; HRMS (EI+) calcd. for $C_8H_{12}O_4$ $[M]^+$ 172.0736, found 172.0734.



Preparation of 195. To a stirred solution of **28** (135 mg, 0.501 mmol) was added TFA/CH_2Cl_2 (1:9, 5 mL) at 0 °C under an open atmosphere. After 1.5 h at the same temperature, the reaction was concentrated under reduced pressure to give a lavender oil. This material was used in the next reaction without further purification.

To a stirred solution of acid **191** (86.4 mg, 0.599 mmol) in CH_3CN (3 mL) at 23 °C was added *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethylronium hexafluorophoshate (246 mg, 0.647 mmol), followed by *N,N*-diisopropylethylamine (350 μL, 2.00 mmol) under a nitrogen atmosphere. The resulting mixture was then transferred by cannula to a stirred solution of the ammonium trifluororacetate in CH_3CN (2 mL) at the same temperature and rinsed with additional CH_3CN (1 mL). After 5 h at 23 °C, the reaction was quenched with saturated aqueous NH_4Cl (5 mL) and most of the organic solvent was removed under reduced pressure. The aqueous residue was extracted with EtOAc (4 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (10 → 40% EtOAc in hexanes) on silica (10 mL) to afford amide **195** (90.6 mg, 61%) as a colorless oil.

Data for **195**: R_f = 0.45 (40% EtOAc in hexanes); IR (neat): 3367 (br, N-H), 2937, 1742 (C=O), 1670 (C=O), 1635, 1521, 1372, 1063, 1036 cm^{-1}; $[\alpha]_D^{26}$ –41.5 (*c* 0.94, $CHCl_3$); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 6.04 (ddd, 1H, 11.5, 5.3, 5.3 Hz), 5.87–5.72 (m, 3H), 5.28–5.23 (m, 2H), 5.12 (dddd, 1H, *J* = 17.2, 1.6, 1.6, 1.6 Hz), 5.09–5.04 (m, 1H), 3.96 (qd, 1H, *J* = 6.5, 3.0 Hz), 3.67 (qd, 1H, *J* = 6.5 2.2 Hz), 3.56 (ddd, 1H, *J* = 7.3, 7.3, 2.8 Hz), 2.41–2.29 (m, 1H), 2.20–2.09 (m, 1H), 2.09 (s, 3H), 1.97–1.92 (m, 2H), 1.84–1.76 (m, 1H), 1.15 (d, 3H, *J* = 6.5 Hz), 1.03 (d, 3H, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, 293K, C_6D_6) δ 169.9, 164.7, 140.5, 135.3, 123.5, 116.6, 80.6, 75.9, 63.0, 47.1, 37.9, 35.9, 29.1, 20.4, 17.9, 15.0; HRMS (EI+) calcd. for $C_{16}H_{25}NO_4$ $[M]^+$ 295.1784, found 295.1779.

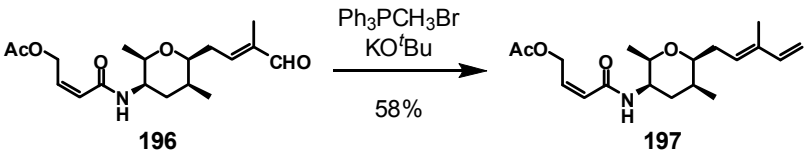


195 196

Preparation of 196. To a stirred solution of alkene **195** (73.8 mg, 0.250 mmol) and methacrolein (400 μL, 4.85 mmol) in benzene (1.25 mL) was added and benzoquinone (5.9 mg, 0.055 mmol), followed by Grela's catalyst (13.5 mg, 0.0201 mmol) at 23 °C under a nitrogen atmosphere. After 17 h at the same temperature, the solvent was removed under reduced pressure and the crude residue was purified by flash chromatography (10 → 50% EtOAc in hexanes) on silica (8 mL) to afford aldehyde **196** (19.6 mg, 23%, 46% based on recovered **195**) as a pale yellow oil.

Data for **196**: R_f = 0.45 (40% EtOAc in hexanes); IR (neat): 3367 (br, N-H), 2934, 1740 (C=O), 1671 (C=O), 1521, 1372, 1233, 1068, 1035 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 9.43 (br s, 1H), 6.54 (dd, 1H, *J* = 6.4, 6.4 Hz, 6.05 (ddd, 1H, 11.5, 5.2, 5.2 Hz), 5.88–5.80 (m, 1H), 5.79 (ddd, 1H, *J* = 11.5, 2.0, 2.0 Hz), 5.25 (app dd,* 2H, *J* = 5.2, 2.0 Hz), 4.01–3.95 (m, 1H), 3.75–3.63 (m, 2H), 2.64–2.52 (m, 1H), 2.47–2.36 (m, 1H), 2.09 (s, 3H), 2.01–1.95 (m, 2H), 1.88–1.80 (m, 1H), 1.77 (br s, 3H), 1.16 (d, 1H, *J* = 6.4 Hz), 1.07 (d, 3H, *J* = 7.4 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 190.0, 170.8, 164.9, 150.3, 140.7, 140.6, 123.0, 79.7, 76.1, 62.7, 46.8, 35.7, 32.7, 29.5, 20.9, 17.8, 15.2, 9.5; HRMS (EI+) calcd. for $C_{18}H_{27}NO_5$ $[M]^+$ 337.1889, found 337.1903.

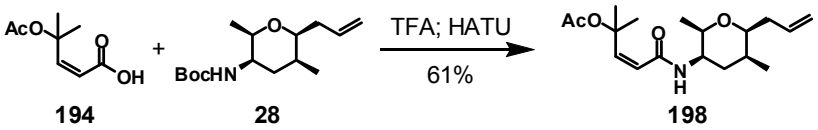
* *unable to see geminal coupling*



Preparation of 197. To a stirred suspension of methyltriphenylphosphonium bromide (33.3 mg, 0.0932 mmol) in THF (0.2 mL) at 0 °C was added KO^{t}Bu (9.4 mg, 0.0838 mmol) under a nitrogen atmosphere. After 30 min, aldehyde **196** (14.3 mg, 0.0424 mmol) was added in THF (0.1 mL) at the same temperature and the container that originally contained **196** was rinsed with additional THF (2 × 0.1 mL) and added to the ylide solution. After 2 h at 23 °C, the reaction was quenched with saturated aqueous NH_4Cl (3 mL), then most of the solvent was removed under reduced pressure, and the aqueous residue was extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (10 → 40% EtOAc in hexanes) on silica (2 mL) to afford diene **197** (8.2 mg, 58%) as a colorless oil.

Data for **197**: R_f = 0.47 (50% EtOAc in hexanes); IR (neat): 3366 (br, N-H), 2926, 1739 (C=O), 1667 (C=O), 1634, 1522, 1373, 1234, 1064 cm^{-1}; ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 6.38 (dd, 1H, *J* = 17.4, 10.7 Hz), 6.05 (ddd, 1H, 11.5, 5.3, 5.3 Hz) 5.77 (ddd, 1H, *J* = 11.5, 2.1, 2.1 Hz), 5.46 (br app t, *J* = 7.1 Hz), 5.25 (app dd,[§] 2H, *J* = 5.3, 2.1 Hz), 5.12 (d, 1H, *J* = 17.4 Hz), 4.97 (d, 1H, *J* = 10.7 Hz), 4.00–3.92 (m, 1H), 3.68 (qd, 1H, *J* = 6.5, 2.8, 2.2 Hz), 3.55 (ddd, 1H, 7.3, 7.3, 2.8 Hz), 2.45–2.35 (m, 1H), 2.32–2.22 (m, 1H), 2.09 (s, 3H), 1.96–1.92 (m, 1H), 1.85–1.77 (m, 1H), 1.77 (br s, 3H), 1.15 (d, 3H, *J* = 6.5 Hz), 1.03 (d, 3H, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 170.7, 164.9, 141.3, 140.5, 135.7, 128.0, 123.3, 111.1, 80.9, 76.0, 62.7, 47.2, 35.9, 31.9, 29.0, 20.9, 17.9, 15.2, 11.9; HRMS (EI+) calcd. for $C_{19}H_{29}NO_4$ $[M]^+$ 335.2100, found 335.2105.

§ *unable to see geminal coupling*



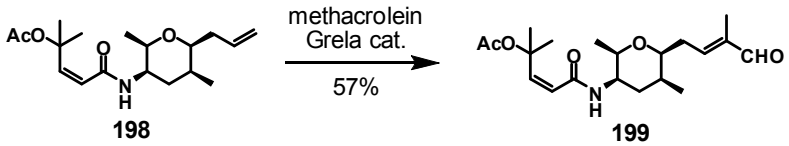
194 28 198

Preparation of 198. To a stirred solution of **28** (135 mg, 0.501 mmol) was added TFA/CH_2Cl_2 (1:9, 5 mL) at 0 °C under an open atmosphere. After 1.5 h at the same temperature, the reaction was concentrated under reduced pressure to give a lavender oil. This material was used in the next reaction without further purification.

To a stirred solution of acid **194** (104 mg, 0.604 mmol) in CH_3CN (3 mL) at 23 °C was added *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethylronium hexafluorophoshate (246 mg, 0.647 mmol), followed by *N,N*-diisopropylethylamine (350 μL, 2.00 mmol) under a nitrogen atmosphere. The resulting mixture was then transferred by cannula to a stirred solution of the ammonium trifluororacetate in CH_3CN (1.5 mL) at the same temperature and rinsed with additional CH_3CN (2 × 0.5 mL). After 4 h at 23 °C, the reaction was quenched with saturated aqueous NH_4Cl (6 mL) and most of the organic solvent was removed under reduced pressure. The aqueous residue was extracted with EtOAc (3 × 7 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (10 → 40% EtOAc in hexanes) on silica (10 mL) to afford amide **198** (110 mg, 68%) as a colorless oil.

Data for **198**: R_f = 0.44 (40% EtOAc in hexanes); IR (neat): 3359 (br, N-H), 2936, 1733 (C=O), 1669 (C=O), 1508, 1368, 1254, 1127, 1063 cm^{-1}; $[\alpha]_D^{26}$ –23.8 (*c* 0.97, $CHCl_3$); ^1H NMR (300 MHz, 293K, C_6D_6) δ 6.00 (d, 1H, *J* = 13.0 Hz), 5.74 (dddd, 1H, *J* = 17.4, 10.6, 7.8, 6.2 Hz), 5.56 (br d, 1H, *J* = 8.3 Hz), 5.26 (d, 1H, *J* = 13.0 Hz), 5.09–4.97 (m, 2H), 3.94–3.87 (m, 1H),

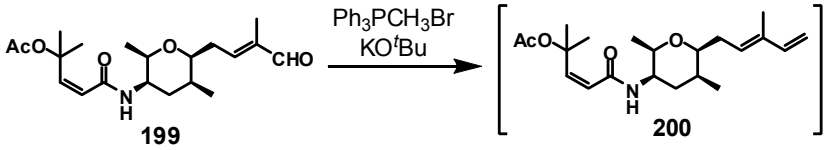
3.22–3.12 (m, 2H), 2.34–2.21 (m, 1H), 2.00–1.86 (m, 1H), 1.89 (s, 3H), 1.88 (s, 3H), 1.84–1.76 (m, 2H), 1.73 (s, 3H), 1.52–1.42 (m, 1H), 1.04 (d, 3H, J = 6.4 Hz), 0.81 (d, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, 293K, C_6D_6) δ 169.5, 165.0, 146.2, 135.4, 121.5, 116.5, 81.5, 80.6, 76.0, 47.1, 37.9, 35.9, 29.2, 26.6, 26.3, 21.8, 18.0, 15.0; HRMS (EI+) calcd. for $C_{18}H_{29}NO_4$ $[M]^+$ 323.2097, found 323.2082.



Preparation of 199. To a stirred solution of alkene **198** (81.1 mg, 0.251 mmol) and methacrolein (400 μL, 4.85 mmol) in benzene (1.25 mL) was added benzoquinone (5.9 mg, 0.055 mmol), followed by Grela's catalyst (13.4 mg, 0.0200 mmol), at 23 °C under a nitrogen atmosphere. After 17 h at 23 °C, the solvent was removed under reduced pressure and the crude residue was purified by flash chromatography (10 → 50% EtOAc in hexanes) on silica (8 mL) to afford aldehyde **199** (52.3 mg, 57%, 79% based on recovered **198**) as a pale yellow oil.

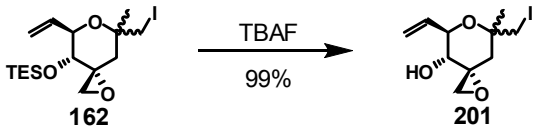
Data for **199**: R_f = 0.30 (50% EtOAc in hexanes); IR (neat): 3360 (br, N-H), 2936, 1732 (C=O), 1685 (C=O), 1671 (C=O), 1513, 1367, 1255, 1127, 1068 cm^{-1}; $[\alpha]_D^{26}$ –23.8 (*c* 0.97, $CHCl_3$); ^{1}H NMR (300 MHz, 293K, C_6D_6) δ 9.31 (s, 1H), 6.07 (ddd, 1H, J = 6.3, 6.3, 0.9 Hz), 6.00 (d, 1H, J = 13.0 Hz), 5.54 (br d, 1H, J = 8.5 Hz), 5.39 (d, 1H, J = 13.0 Hz), 3.91 (dddd, 1H, J = 8.5, 4.4, 2.2, 2.2 Hz), 3.14 qd, 1H, J = 6.4, 2.2 Hz), 3.02 (ddd, 1H, J = 8.4, 5.5, 2.9 Hz), 2.26–2.15 (m, 1H), 1.89 (s, 3H), 1.88 (s, 3H), 1.84–1.81 (m, 1H), 1.80–1.77 (m, 1H), 1.72 (s, 3H), 1.66 (br s, 3H), 1.50–1.40 (m, 1H), 1.18–1.10 (m, 1H), 1.01 (d, 3H, J = 6.4 Hz), 0.73 (d, 3H, J = 7.4 Hz); ^{13}C NMR (75 MHz, 293K, C_6D_6) δ 193.9, 169.6, 165.2, 149.5, 146.1, 140.6,

121.4, 81.4, 79.6, 76.2, 46.9, 35.7, 32.8, 29.6, 26.6, 26.3, 21.8, 17.9, 15.0, 9.4; HRMS (EI+) calcd. for $C_{18}H_{29}NO_4$ $[M - OAc]^+$ 306.2069, found 306.2069.



Preparation of 200. To a stirred suspension of methyltriphenylphosphonium bromide (85.8 mg, 0.240 mmol) in THF (0.5 mL) at 0 °C was added KO^{t}Bu (22.3 mg, 0.199 mmol) under a nitrogen atmosphere. After 30 min, aldehyde **199** (36.8 mg, 0.101 mmol) was added in THF (0.3 mL) at the same temperature and the container that originally contained **199** was rinsed with additional THF (2 × 0.1 mL) and added to the reaction mixture. After 2 h at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl (4 mL), then most of the solvent was removed under reduced pressure, and the aqueous residue was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (10 → 30% EtOAc in hexanes) on silica (4 mL) to afford diene **200** (25.5 mg, 69%) as a colorless oil.

Data for **200**: ^{1}H NMR (300 MHz, 293K, C_6D_6) δ 6.44 (dd, J = 17.4, 10.7 Hz), 6.00 (d, J = 13.0 Hz), 5.62 (br d, J = 8.7 Hz), 5.46 (br app t, J = 7.2 Hz), 5.29 (d, J = 13.0 Hz), 5.11 (d, J = 17.4 Hz), 4.98 (d, J = 12.5 Hz), 4.96 (d, J = 11.0 Hz), 4.49 (br d, 1H, J = 7.7 Hz), 3.95–3.89 (m), 3.42 (br d, J = 7.8 Hz), 3.24–3.14 (m), 2.43–2.31 (m), 2.14–2.02 (m), 1.89 (s), 1.88 (s), 1.87–1.77 (m), 1.73 (s), 1.68 (br s), 1.52–1.44 (m), 1.36–1.26 (m), 1.05 (d, J = 6.5 Hz), 0.99 (d, J = 6.3 Hz), 0.92 (d, J = 6.3 Hz), 0.82 (d, J = 7.3 Hz).

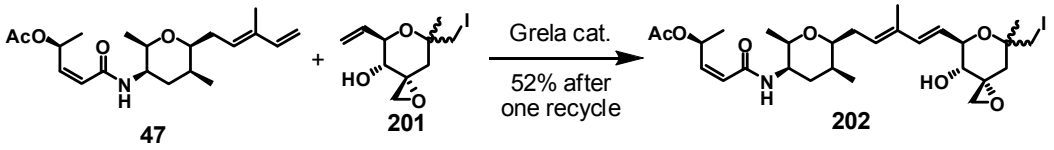


162 **201**

Preparation of 201 on a preparative scale. To a stirred solution of **162** (42.8 mg, 0.101 mmol) in THF (0.40 mL) was added TBAF (1.0 M in THF, 120 μL, 0.120 mmol) at 0 °C under an open atmosphere. After 30 min at the same temperature, the reaction mixture was diluted with Et_2O (5 mL), filtered through a pad of Florisil, rinsed with Et_2O (3 × 5 mL), and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 → 30% EtOAc in hexanes) on silica gel (2 mL) to afford **201** (31.1 mg, 99%) as a colorless oil.

Preparation of 201 on microscale. To a solution containing iodoether **162** and alcohol **148** (500 μL, ~10.5 μmol combined) in THF (75 μL) was added TBAF (1.0 M, 25 μL) at 0 °C under an open atmosphere. After 1.0 h at the same temperature, the reaction mixture was filtered through a pad of Florisil (0.5 mL), rinsed with Et_2O (3 × 2 mL), and concentrated under reduced pressure.

Data for **201**: R_f = 0.25 (30% EtOAc in hexanes); IR (neat): 3434 (br, O-H), 2923, 1458, 1377, 1267, 1065, 929, 730 cm^{-1}; ^1H NMR (300 MHz, 293K, CD_2Cl_2) δ 6.01 (ddd, 0.5H, *J* = 17.1, 10.8, 5.4 Hz), 5.98 (ddd, 0.5H, *J* = 16.8, 10.8, 5.9 Hz), 5.48 (dddd, 1H, *J* = 17.2, 7.4, 1.7, 1.7 Hz), 5.36–5.25 (m, 1H), 4.00–3.93 (m, 0.5H), 3.94 (d, 0.5H, *J* = 11.4 Hz), 3.80 (br dd, 0.5H, *J* = 9.8, 5.9 Hz), 3.60–3.44 (m, 1H), 3.37 (d, 0.5H, *J* = 11.4 Hz), 3.35 (d, 0.5H, *J* = 10.2 Hz), 3.30 (d, 0.5H, *J* = 10.2 Hz), 3.04 (d, 0.5H, *J* = 4.7 Hz), 3.03 (d, 0.5H, *J* = 4.8 Hz), 2.56 (d, 0.5H, *J* = 4.8 Hz), 2.54 (d, 0.5H, *J* = 4.7 Hz), 2.46 (d, 0.5H, *J* = 15.0 Hz), 2.38 (dd, 0.5H, *J* = 14.1, 0.6 Hz), 1.75 (d, 0.5H, *J* = 15.0 Hz), 1.53 (d, 0.5H, *J* = 14.1 Hz), 1.53 (s, 1.5H), 1.34 (s, 1.5H); ^{13}C NMR (75 MHz, 293K, CD_2Cl_2) δ 136.2, 135.9, 117.8, 116.9, 74.7, 74.4, 72.5, 72.2, 67.8, 67.3, 57.2, 57.1, 47.7, 47.4, 40.5, 39.1, 29.0, 21.3, 19.3, 14.2.



Preparation of 202 on a preparative scale. A solution of **201** (14.8 mg, 0.0477 mmol) was prepared in $ClCH_2CH_2Cl$ (100 μL) at 23 °C under an open atmosphere. To a stirred solution of **47** (14.0 mg, 0.0401 mmol) in $ClCH_2CH_2Cl$ (100 μL) was added the solution of **201** (50 μL), benzoquinone (0.9 mg, 8 μmol), followed by Grela catalyst (1.3 mg, 1.9 μmol) at 23 °C under an open atmosphere. The reaction mixture was then heated to 38 °C. After 2.5 h at the same temperature, additional Grela catalyst (1.4 mg, 2.1 μmol) and **201** (50 μL) were added. After 9 total hours, the reaction was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (20 → 60% EtOAc in hexanes) on silica gel (2 mL) to give **202** (9.4 mg, 37%), and an inseparable mixture of **47** and **201** (34.1 mg).

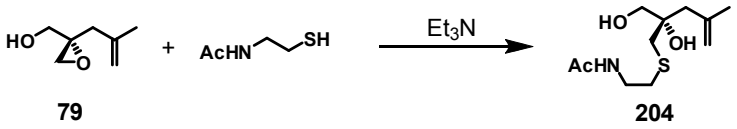
To a stirred solution of recovered **47** and **201** (12.4 mg) in $ClCH_2CH_2Cl$ (150 μL) was added Grela catalyst (1.4 mg, 2.1 μmol) and benzoquinone (0.7 mg, 6 μmol) at 23 °C under an open atmosphere. The reaction mixture was then heated to 38 °C. After an additional 8 h at the same temperature, the reaction was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (20 → 60% EtOAc in hexanes) on silica gel (2 mL) to give **202** (3.7 mg, 15%) as a pale tan solid. The combined yield of **202** after one cycle is 13.1 mg (52%). Some of the tan **202** was purified by semi-preparative HPLC[†] to afford this compound as a white solid that was subsequently used for biological experiments.

Preparation of 202 on microscale. To a stirred solution of **47** (10.4 mg, 30 μmol) was added purified **201** (0.93 mg, 3.0 μmol) in $ClCH_2CH_2Cl$ (65 μL) at 23 °C under an open atmosphere. To the mixture was added Grela catalyst (1.0 mg, 1.5 μmol) and the mixture was

allowed to stir for an additional 20 h. After 20 h, the reaction mixture was filtered through a pad of Florisil (0.5 mL), rinsed with 80% EtOAc/hexanes (3 × 2 mL), and concentrated under reduced pressure to afford **202** and **47** as a mixture.

Data for **202**: R_f = 0.29 (60% EtOAc in hexanes); ^{1}H NMR (500 MHz, 293K, CD_2Cl_2) δ 6.46 (dd, *J* = 15.5 Hz), 6.43 (d, *J* = 16.0 Hz), 6.35–6.27 (m), 6.01 (br d, *J* = 9.0 Hz), 5.94 (dd, *J* = 11.5, 7.5 Hz), 5.75 (dd, *J* = 11.5, 1.5 Hz), 5.70 (dd, *J* = 16.0, 6.5 Hz), 5.68 (dd, *J* = 16.0, 6.8 Hz), 5.62–5.56 (m), 4.03 (br dd, *J* = 9.5, 6.8 Hz), 3.98 (d, *J* = 11.5 Hz), 3.98–3.92 (m), 3.86 (br dd, *J* = 9.0, 6.5 Hz), 3.72–3.68 (m), 3.59 (app t, *J* = 10.0 Hz) 3.62–3.56 (m), 3.53 (app t, *J* = 10.5 Hz), 3.38 (d, *J* = 11.5 Hz), 3.35 (d, *J* = 10.5 Hz), 3.31 (d, *J* = 10.5 Hz), 3.05 (d, *J* = 4.8 Hz), 3.04 (d, *J* = 5.0 Hz), 2.58 (d, *J* = 4.8 Hz), 2.56 (d, *J* = 5.0 Hz), 2.48 (d, *J* = 14.8 Hz), 2.44–2.39 (m), 2.39 (d, *J* = 15.2 Hz), 2.30–2.23 (m), 2.05 (s), 1.99–1.95 (m), 1.83 (br s), 1.83–1.80 (m), 1.75 (d, *J* = 15.2 Hz), 1.66 (d, *J* = 10.5 Hz), 1.63 (d, *J* = 10.5 Hz), 1.54 (s), 1.54 (d, *J* = 14.8 Hz), 1.38 (d, *J* = 6.5 Hz), 1.35 (s), 1.15 (d, *J* = 6.5 Hz), 1.05 (d, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, 293K, CD_2Cl_2) δ 170.8, 164.9, 143.9, 138.0, 129.8, 125.0, 122.8, 81.1, 76.2, 75.4, 74.9, 73.0, 72.7, 68.9, 68.4, 68.0, 57.6, 48.1, 47.8, 47.4, 41.0, 36.2, 32.4, 32.3, 30.1, 29.5, 29.3, 21.7, 21.4, 20.2, 19.7, 17.9, 15.3, 12.7; HRMS (ESI+) calcd. for $C_{28}H_{42}INO_7Na$ $[M + Na]^+$ 654.1904, found 654.1919.

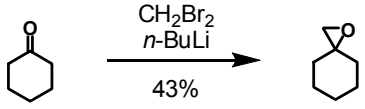
† HPLC purification was performed on a Varian Pursuit XRs 5 C18 column, 250 × 10.0 cm, 4.0 mL/min, 40% MeCN/H_2O → 100% MeCN linear gradient elution from 0.5 to 22 min, retention time = 24.7 and 25.1 min.



79 **204**

Preparation of 204 in organic solvent. To a stirred solution of Et_3N (140 μL, 1.0 mmol) and *N*-acetylcysteamine (65 μL, 0.61 mmol) was added epoxide **79** (65 mg, 0.51 mmol) in MeCN (1.0 mL) at 23 °C under an open atmosphere. The reaction mixture was then warmed to 61 °C and capped to prevent solvent evaporation. After 2 d at the same temperature, the reaction mixture was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1 → 5% MeOH in CH_2Cl_2) on silica gel (5 mL) to afford **204** (42 mg, 34%) as a pale yellow oil.

Data for **204**: TLC (5% MeOH in CH_2Cl_2): R_f = 0.24; $[\alpha]_D^{25}$ –4.2 (*c* 0.45 in $CHCl_3$); ^{1}H-NMR (300 MHz, 293K, D_2O): δ 4.97 (br s, 1H), 4.82 (br s, 1H), 3.54 (br app s, 2H), 3.38 (br app t, 2H, *J* = 6.5 Hz); 2.78 (br app s, 2H), 2.72 (br app t, 2H, *J* = 6.5 Hz), 2.33 (d, 1H, *J* = 14.1 Hz), 2.28 (d, 1H, *J* = 14.1 Hz), 1.98 (s, 3H), 1.80 (br s, 3H); ^{13}C-NMR (75 MHz, 293K, D_2O): δ 176.1, 143.8, 117.3, 77.0, 67.4, 44.8, 40.8, 40.2, 34.2, 25.9, 23.8; IR (neat): 3308 (br), 3076, 2924, 1653 (C=O), 1555, 1437, 1294, 1044, 894 cm^{-1}; HRMS (ESI+) calcd. for $C_{11}H_{21}NO_3NaS$ $[M + Na]^+$ 270.1140, found 270.1124.



205

Procedure and data for the preparation of 1-oxaspiro[2.5]octane (205): T. J. Michnik, D. S. Matteson *Synlett* **1991**, 631–632.

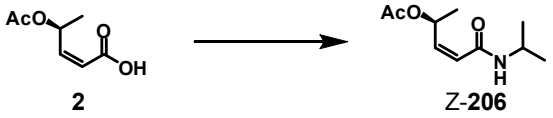
A representative procedure for the epoxide opening experiments with *N*-acetylcysteamine. To phosphate buffer (4.9 mL, 50 mM phosphate) was added benzyl alcohol (2.0 M in DMSO-d_6, 50 μL) followed by epoxide **79** (1.0 M in DMSO-d_6, 100 μL) under an open atmosphere. An aliquot (0.4 mL) of the mixture was removed and extracted with $CDCl_3$ (0.5 mL). The extract was then dried over Na_2SO_4, filtered into an NMR tube, rinsed with $CDCl_3$ (0.2 mL), and an NMR spectrum was obtained. The remaining reaction mixture was transferred to a vessel containing the thiol, vortexed, and maintained at 37 °C by immersion in a water-filled incubator. Aliquots (0.4 mL) of the reaction mixture was removed and extracted with $CDCl_3$ (0.5 mL). The extract was then dried over Na_2SO_4, filtered into an NMR tube, rinsed with $CDCl_3$ (0.2 mL), and an NMR spectra were obtained. The consumption of epoxide was determined by comparison of the integrations of epoxide signals to the benzylic signal of benzyl alcohol. Data analyses were performed on Microsoft Excel. The volumes of epoxide solutions, benzyl alcohol, and buffer were varied depending on the reaction rate. No more than 5% DMSO-d_6 total volume was employed during these reactions.

The consumption of **79**, when monitored in an NMR tube (method A), was only shown to give **204** as a product. This result also confirms that the thioetherification proceeds by a S_N2 mechanism.

Procedure for the conversion of the half-lives for 2-cyclohexen-1-one oxide in Table 14. To convert the experimentally obtained data for 2-cyclohexen-1-one oxide in Figure 21 to the data shown in Table 14, the half-lives from Figure 21 were divided by 20 (1 μM used in experiment vs. 20 μM used in other experiments shown in Table 2) and then divided by 50 (2

μM used in experiment vs. 100 μM used in other experiments in Table 14). The resulting number (in hours) was converted to seconds.

General Procedure for the Determination of $t_{1/2}^{biol}$ in Table 14. The derivative of the rate equation generated by Microsoft Excel was taken at time = 0.0 h to obtain the initial rate. The resulting linear equation, [epoxide] = (derivative at t = 0) × time, was used to determine the epoxide's pseudo-first order half-life. The resulting half-life was adjusted to biologically relevant conditions (1 μM = [epoxide] and 12 mM = [$thiol_{intracellular}$] as discussed above.

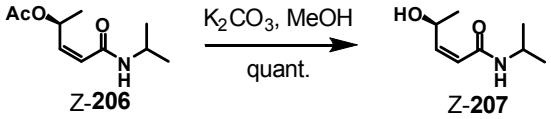


2 Z-**206**

Preparation of Z-206. To a stirred solution of acid **2** (63.4 mg, 0.401 mmol) and $^{i}Pr_2NEt$ (275 μL, 1.58 mmol) in MeCN (2 mL) was added HATU (183 mg, 0.481 mmol) and isopropyl amine (70 μL, 0.82 mmol) at 0 °C under a nitrogen atmosphere. After 5 min at the same temperature, the reaction mixture was warmed to 23°C. After 1 h at the same temperature, the reaction mixture was diluted with saturated aqueous NH_4Cl (12 mL). The aqueous residue was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with aqueous HCl (0.3 N, 10 mL) then saturated aqueous $NaHCO_3$ (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 → 50% EtOAc in hexanes) on silica gel (5 mL) to afford Z-**206** (80.7 mg, quant.) as a pale yellow oil.

Data for Z-**206**: R_f = 0.31 (80% EtOAc in hexanes); IR (neat): 3410 (br, N-H), 2977, 1725 (C=O), 1669 (C=O), 1637, 1536, 1372, 1260, 1048, 851 cm^{-1}; $[\alpha]_D^{25}$ –16.7 (*c* 0.85,

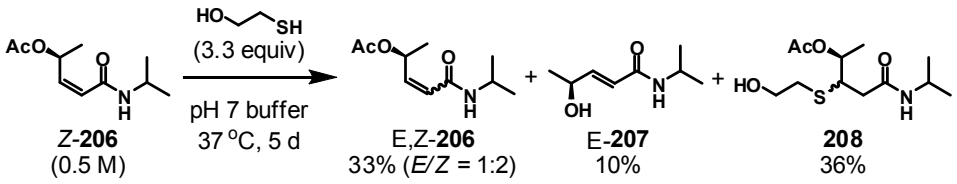
CH_3CN); ^1H NMR (300 MHz, 293K, CD_3OD) δ 6.32 (app quint d, 1H, *J* = 6.5, 1.1 Hz), 5.91 (dd, 1H, *J* = 11.6, 7.6 Hz), 5.79 (dd, 1H, *J* = 11.6, 1.1 Hz), 3.96 (hept, 1H, *J* = 6.6 Hz), 2.01 (s, 3H), 1.34 (d, 3H, *J* = 6.5 Hz), 1.14 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, 293K, CD_3OD) δ 171.4, 165.3, 143.5, 123.7, 68.9, 41.7, 22.5, 21.3, 20.3; HRMS (EI+) calcd. for $C_8H_{14}NO$ [M – OAc]$^+$ 140.1085, found 140.1074.



Z-**206** Z-**207**

Preparation of Z-207. To a stirred solution of Z-**206** (19.8 mg, 0.0994 mmol) in MeOH (0.4 mL) was added K_2CO_3 (34.3 mg, 0.248 mmol) at 0 °C under an open atmosphere. After 1 h at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl (60 μL), warmed to 23°C, diluted with EtOAc (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford, Z-**207** (16.8 mg, quant.) as a colorless oil. This material was not further purified.

Data for Z-**207**: R_f = 0.31 (80% EtOAc in hexanes); IR (neat): 3408 (br, N-H), 3284 (br, O-H), 2973, 1654 (C=O), 1621, 1539, 1458, 1255, 1115, 1057, 843 cm^{-1}; $[\alpha]_D^{25}$ –16.7 (*c* 0.85, CH_3CN); ^1H NMR (300 MHz, 293K, CD_3OD) δ 5.99 (dd, 1H, *J* = 11.8, 7.1 Hz), 5.75 (dd, 1H, *J* = 11.8, 1.2 Hz), 5.15 (app quint d, 1H, *J* = 6.6, 1.2 Hz), 3.97 (hept, 1H, *J* = 6.6 Hz), 2.01 (s, 3H), 1.25 (d, 3H, *J* = 6.5 Hz), 1.14 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, 293K, CD_3OD) δ 167.5, 149.5, 122.7, 65.4, 42.3, 23.1, 22.6, 22.5; HRMS (EI+) calcd. for $C_8H_{15}NO_2$ [M]$^+$ 157.1103, found 157.1105.



Reactions of Z-206 in the presence of mercaptoethanol. To a stirred solution of Z-**206** (6.0 mg, 0.030 mmol) in MeCN (5 μL) pH 7 phosphate buffer (55 μL) was added 2-mercaptoethanol (7 μL, 0.1 mmol) at 37 °C under an open atmosphere. After 5 d at the same temperature, the reaction was concentrated under reduced pressure. Purification of the residue by flash chromatography (3 → 80% EtOAc in hexanes) on silica gel (1 mL) returned **206** (2.0 mg, 33%, E/Z = 1:2), afforded a mixture of mercaptoethanol and **207** (3.7 mg, 10% for **207,** E only), and gave **208** (3.0 mg, 33%, dr = 3:1) as a pale yellow oil.

Data for **208**: R_f = 0.14 (60% EtOAc in hexanes); ^{1}H NMR (300 MHz, 293K, CD_3OD) δ 5.08–5.02 (m), 4.02–3.90 (m), 3.78 (t, *J* = 6.5 Hz), 3.72–3.64 (m), 2.82 (t, *J* = 6.5 Hz), 2.78–2.63 (m), 2.55–2.45 (m), 2.34–2.22 (m), 2.03 (s), 2.02 (s), 1.30 (d, *J* = 6.3 Hz), 1.28 (d, *J* = 6.4 Hz), 1.14 (d, *J* = 6.6 Hz), 1.13 (d, *J* = 6.6 Hz); HRMS (EI+) calcd. for $C_{12}H_{23}NO_4S$ $[M]^+$ 277.1348, found 277.1360.

Materials and Methods for the Growth Inhibition Assays

Materials: FR901464 and its dimethyl analog were produced by total chemical synthesis in our laboratory. The compounds were dissolved in dimethyl sulfoxide (DMSO) as 10 mM stocks and stored at –20 °C. For the experiments, aliquots were thawed at room temperature and dilutions were prepared in RPMI 1640 medium containing 2 % DMSO at 2× the desired concentration prior to addition to the cells.

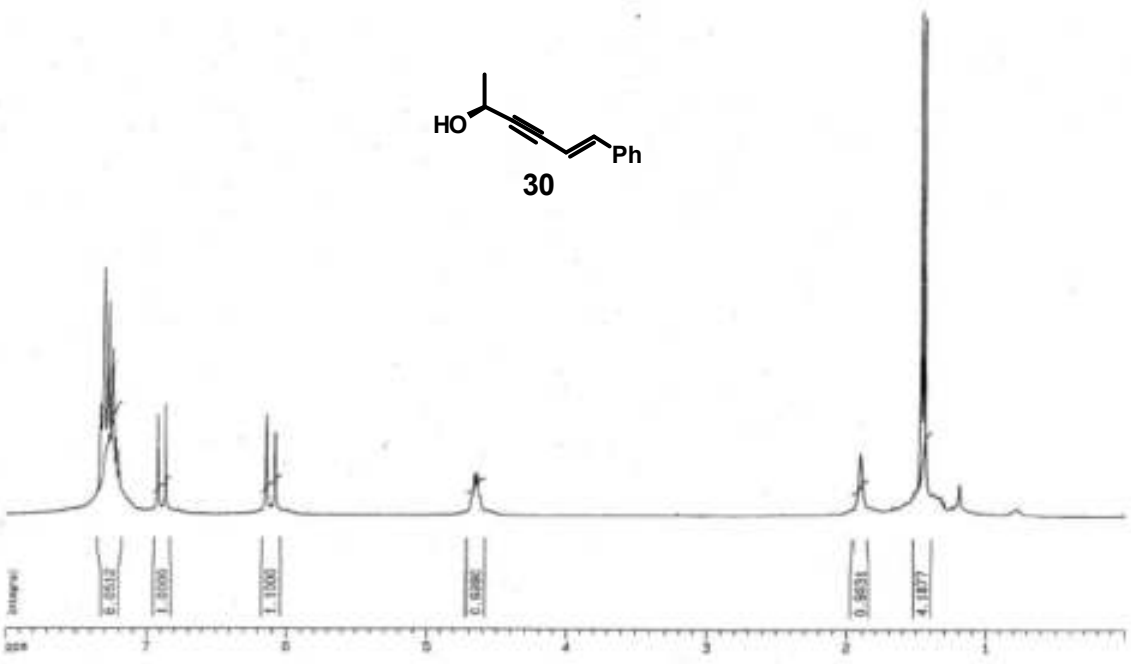
Cell Culture: MCF-7 and HeLa cells were grown at 37 °C in an atmosphere containing 5% carbon dioxide in corning cell culture dishes (150 mm) in RPMI 1640 cell culture medium containing 10% fetal bovine serum, glutamine (5 mL), and pen-strep solution (Invitrogen, 5 mL) per 500 mL of medium.

Growth Inhibition Assay: Cells were plated in 96 well plates at an initial density of 2,000 cells per well in 100 μL of medium and were incubated for 48 hours prior to compound addition. Serial two-fold dilutions were used in this experiment for the indicated ranges. The compounds were added to the cells at 2× the desired concentration in 100 μL cell culture medium (containting 2% DMSO). The cells were then incubated for an additional 5 to 10 days. Cell proliferation was measured using a commercial MTS solution (20 μL per well). The absorbance (at 490 nm and 630 nm) was measured by a Spectromax M5 plate reader (Molecular Devices). Each concentration was done in quadruplicate and the final numbers were averaged.

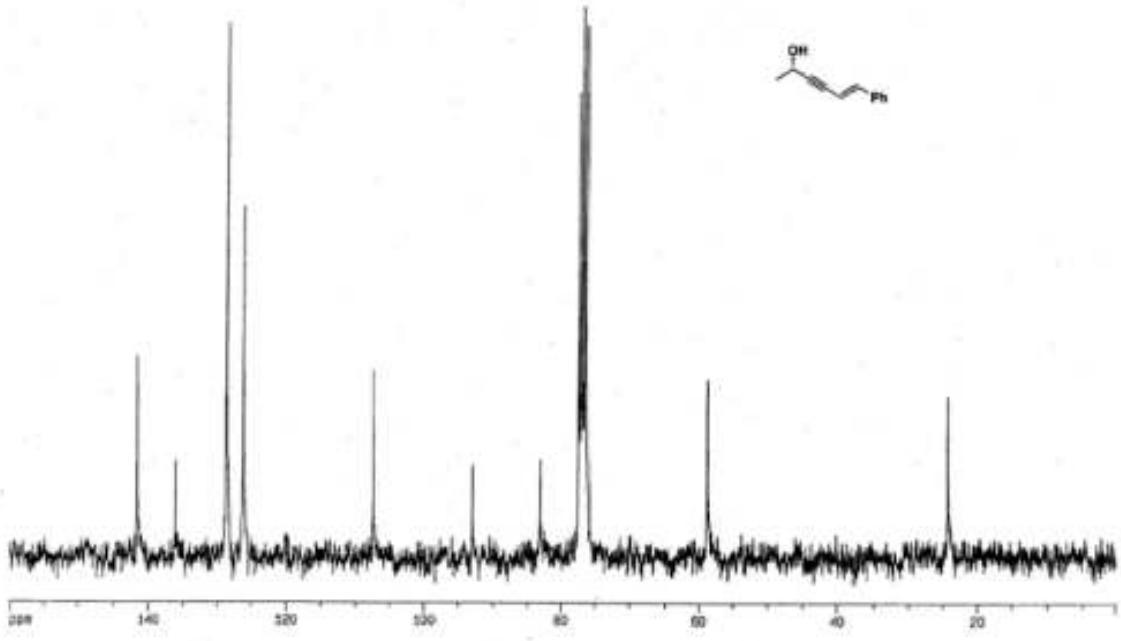
Meayamycin Reversibility Assay: Cells were plated in 96 well plates at an initial density of 5,000 cells per well in 100 μL of medium and were incubated for 48 hours prior to addition of meayamycin. Meayamycin was added to the cells at 2× the desired concentration in 100 μL cell culture medium (containting 2% DMSO). The cells were then incubated for a total additional 3 to 7 days. Meayamycin-containing cell culture media was removed after the 4, 8, 12, 24, 48, and 72 h by suction, the wells were washed with fresh cell culture media (3 × 100 μL), and finally fresh, meayamycin-free cell culture media was added to the wells (200 μL). Cell proliferation was measured using a commercial MTS solution (20 μL per well). The absorbance (at 490 nm and 630 nm) was measured by a Spectromax M5 plate reader (Molecular Devices). Each concentration was done in quadruplicate and the final numbers were averaged.

1.12 ^{1}H AND ^{13}C SPECTRA

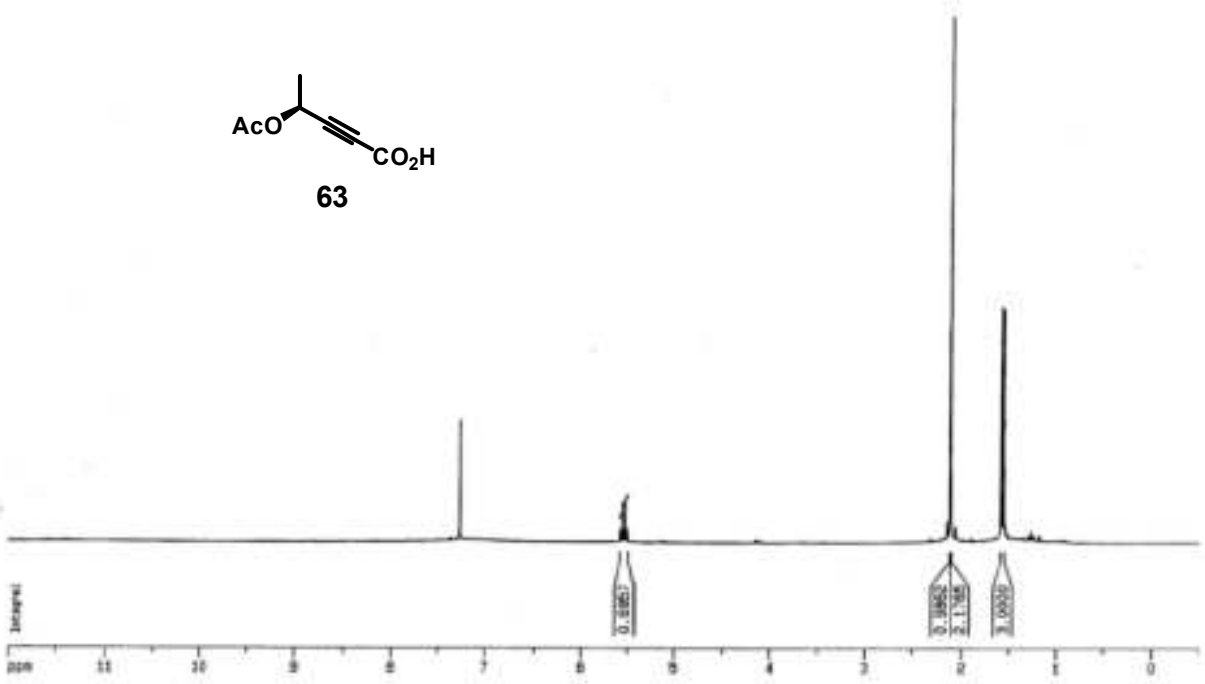
^{1}H NMR of 30: $CDCl_3$, 293 K, 300 MHz



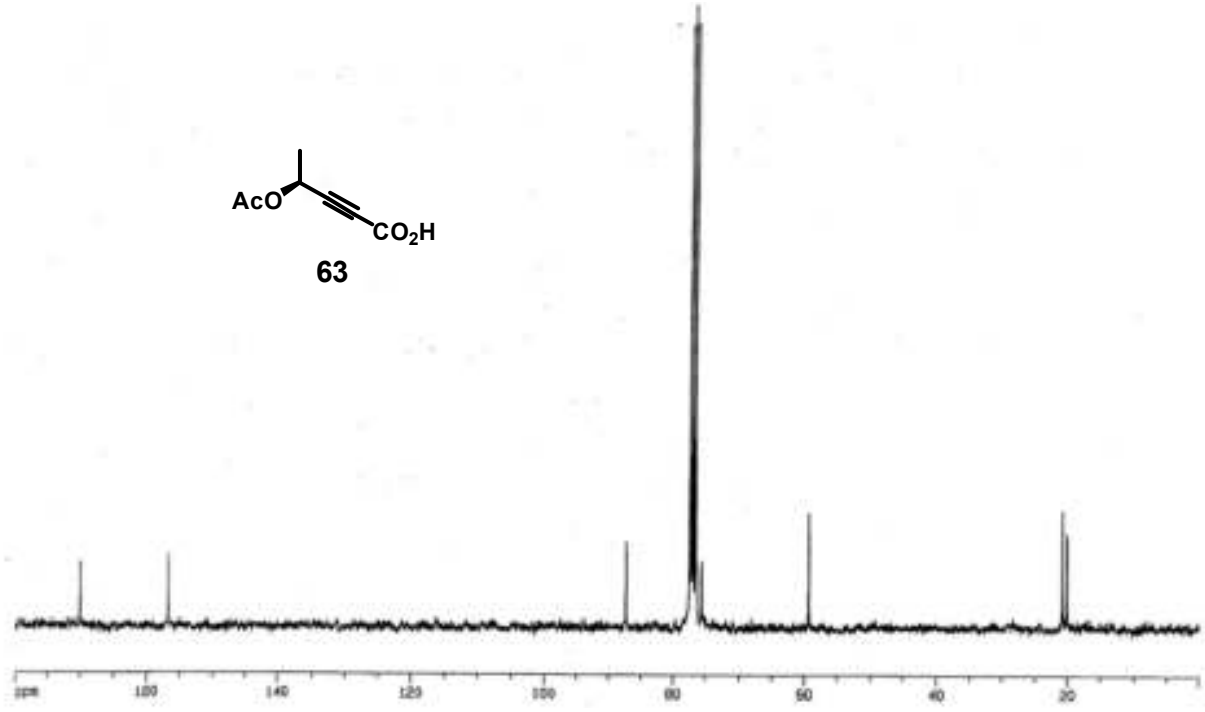
^{13}C NMR of 30: $CDCl_3$, 293 K, 75 MHz



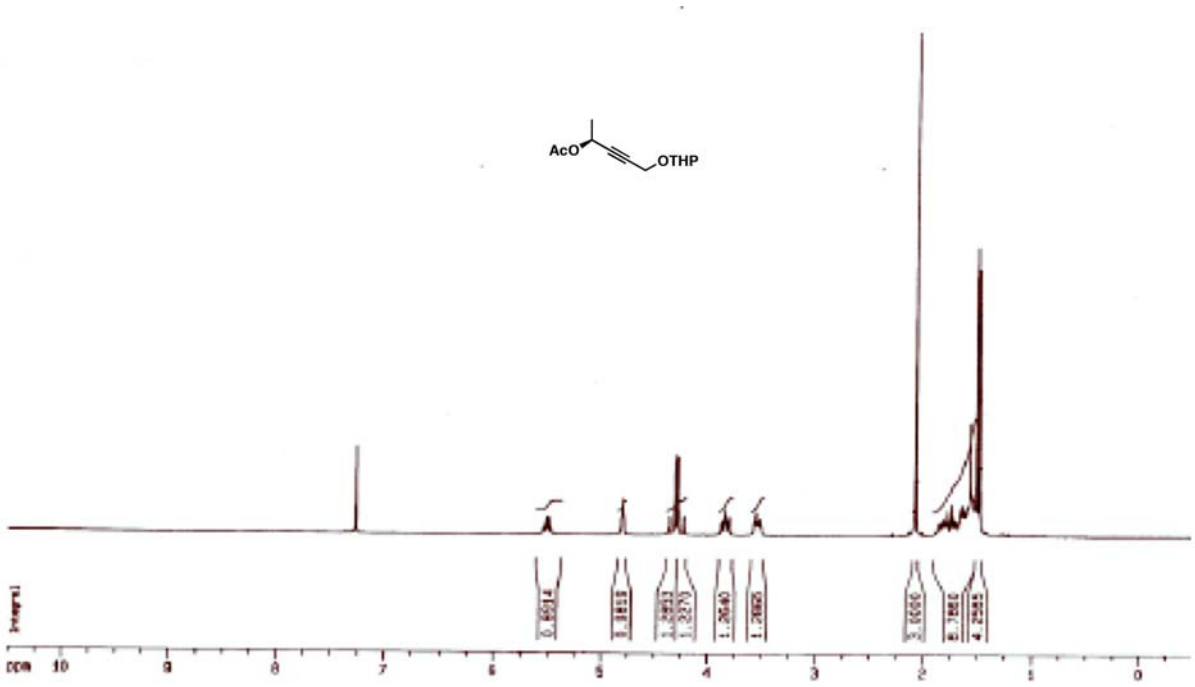
[1]**H NMR of 63**: $CDCl_3$, 293 K, 300 MHz



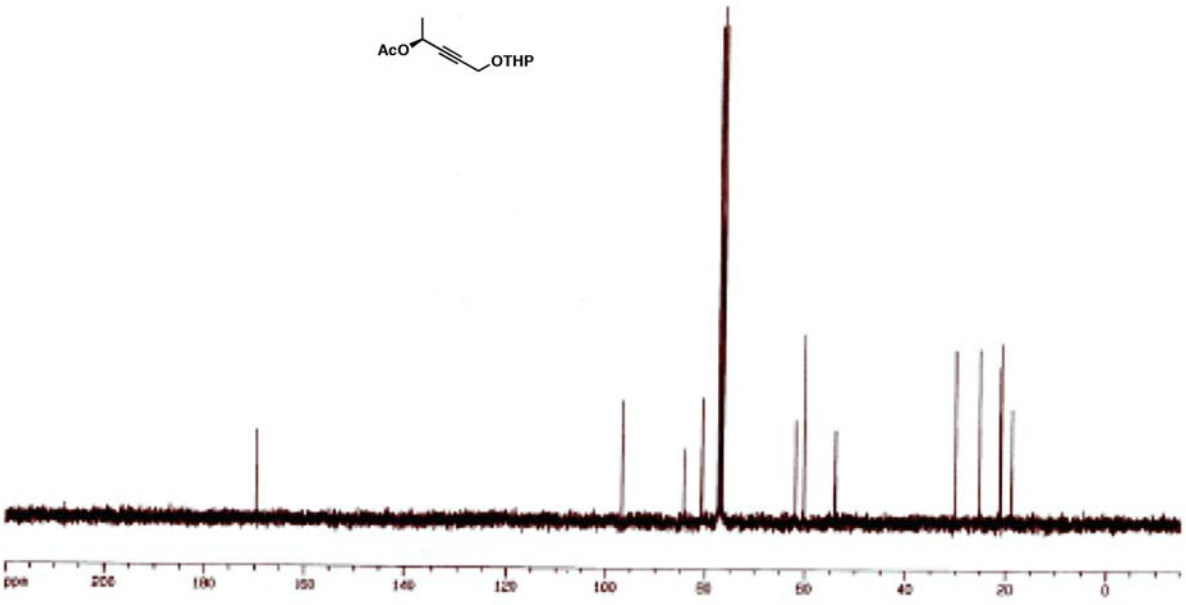
[13]**C NMR of 63**: $CDCl_3$, 293 K, 75 MHz



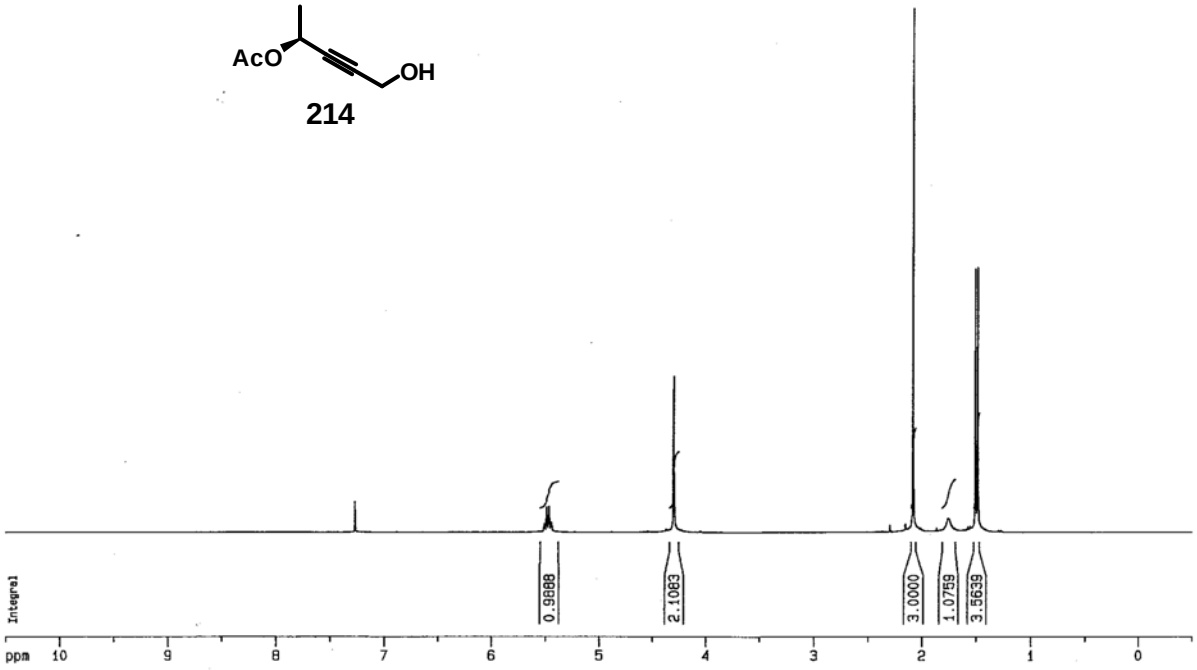
[1]**H NMR of 66**: $CDCl_3$, 293 K, 300 MHz



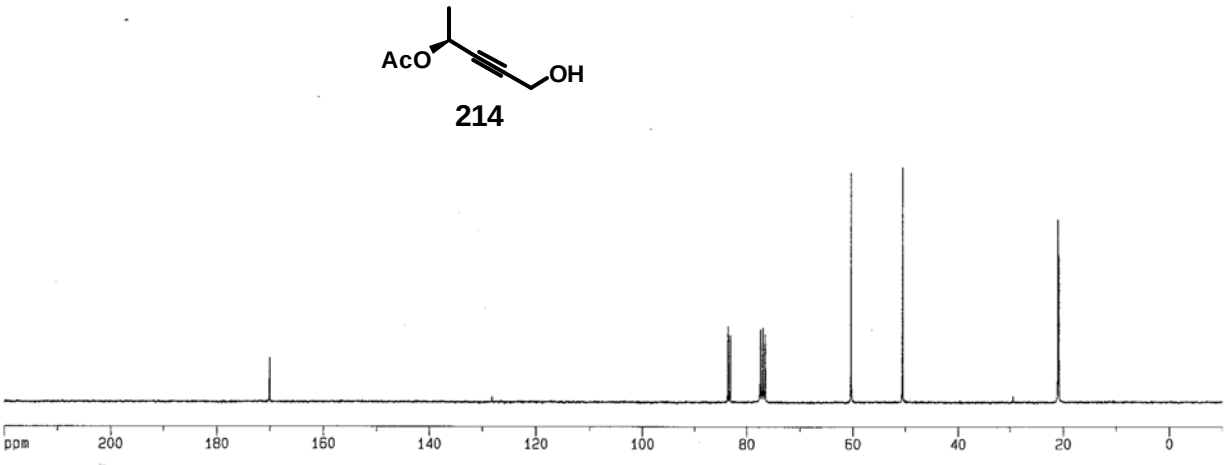
[13]**C NMR of 66**: $CDCl_3$, 293 K, 75 MHz



[1]**H NMR of 214**: 1% CD_3OD in $CDCl_3$, 293 K, 300 MHz

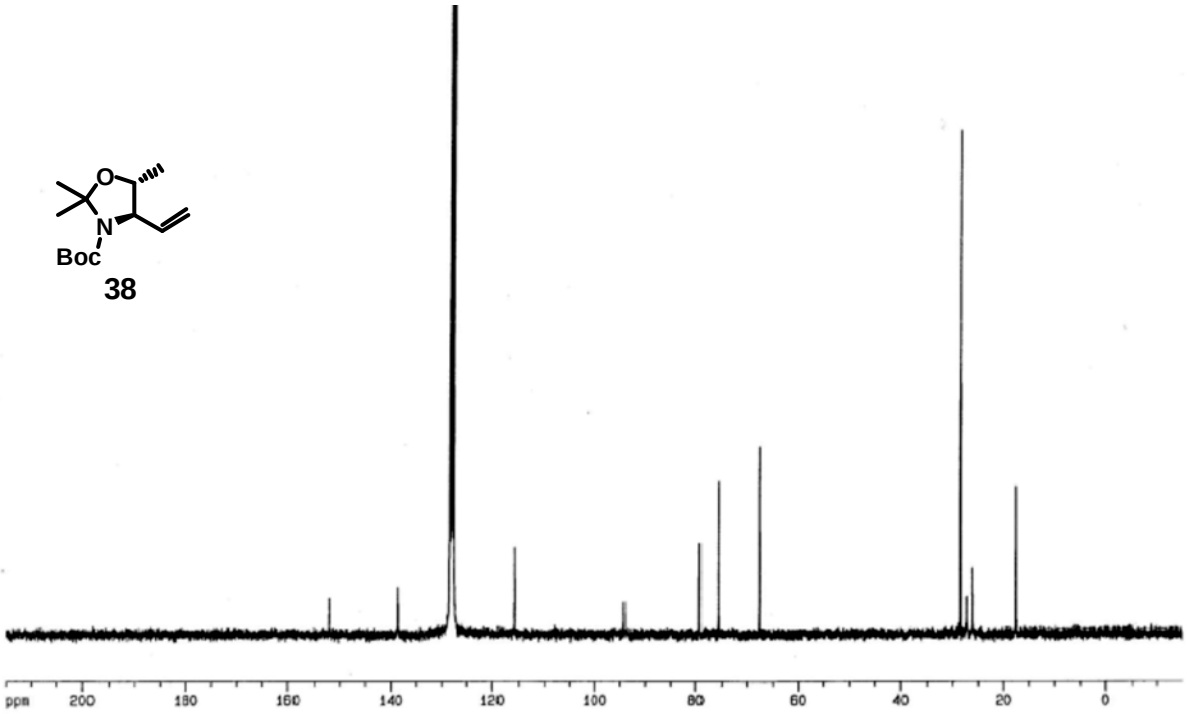


[13]**C NMR of 214**: $CDCl_3$, 293 K, 75 MHz

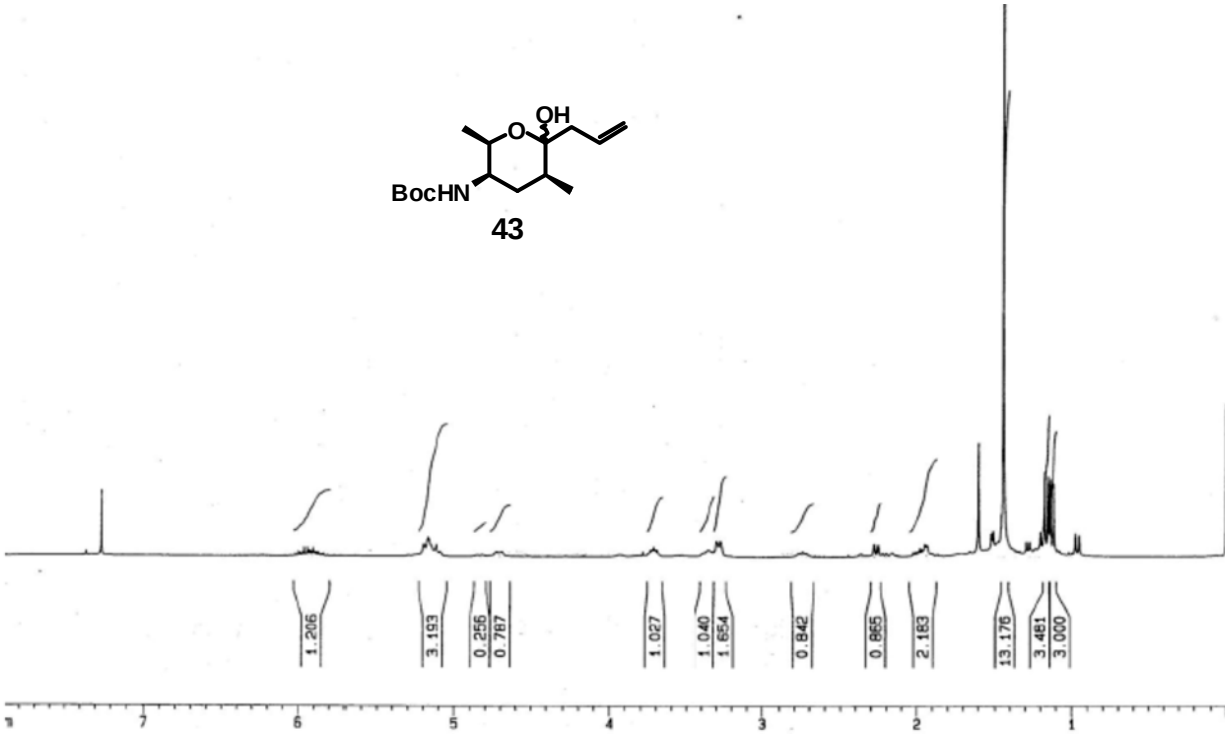


[1]**H NMR of 38**: C_6D_6, 333 K, 300 MHz

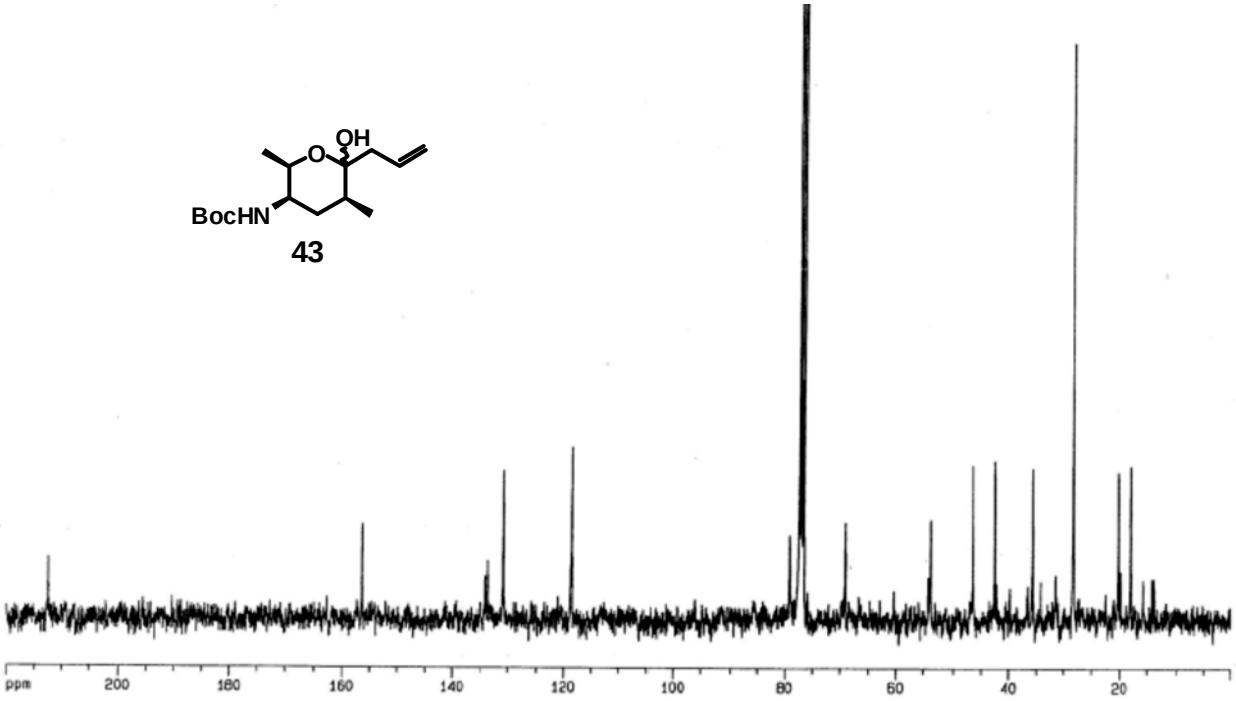
[13]**C NMR of 38**: C_6D_6, 333 K, 75 MHz



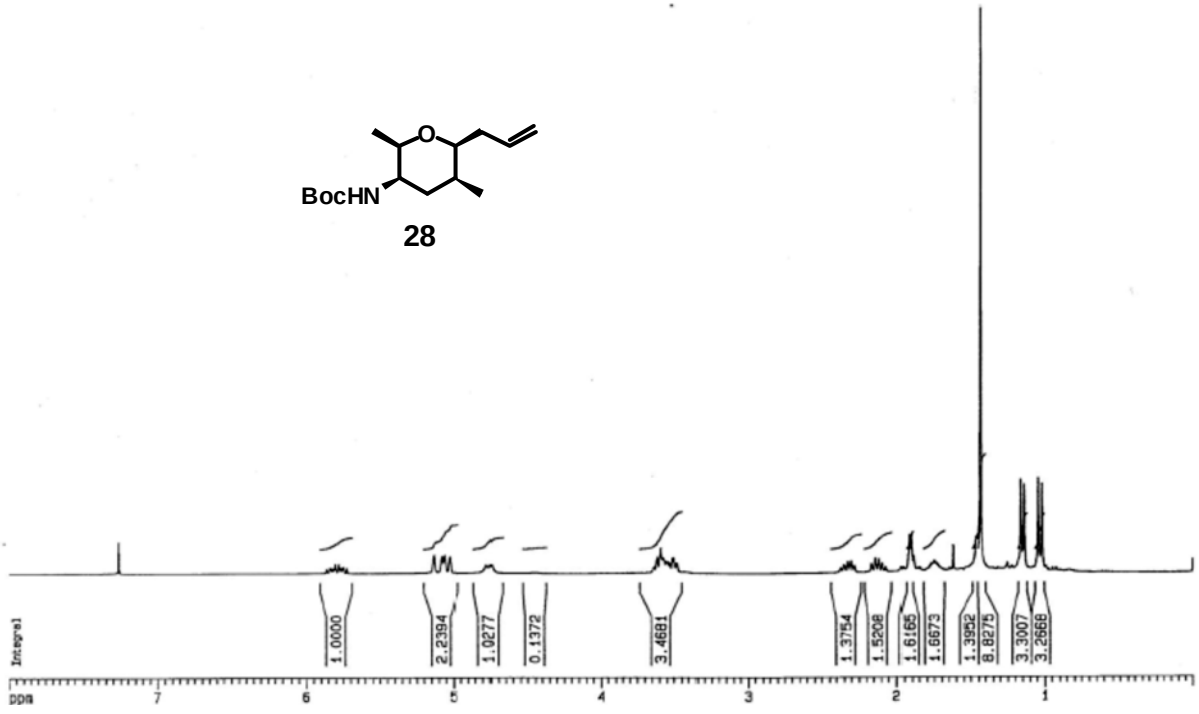
[1]**H NMR of 43**: $CDCl_3$, 293 K, 300 MHz



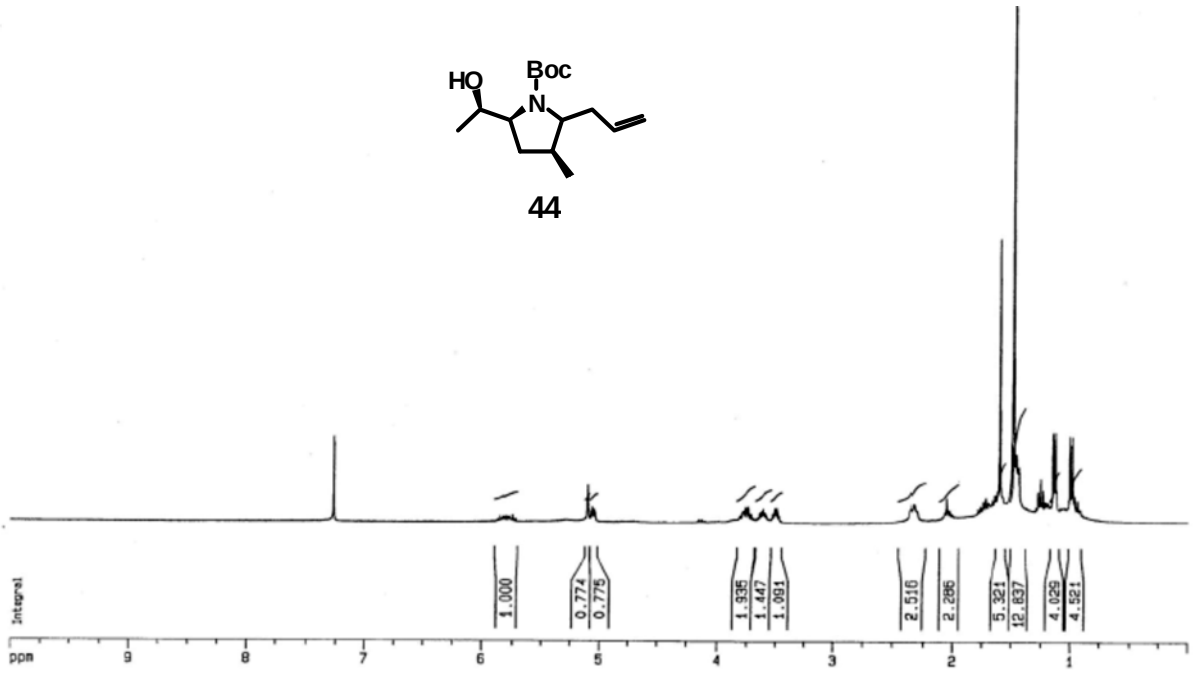
[13]**C NMR of 43**: $CDCl_3$, 293 K, 75 MHz



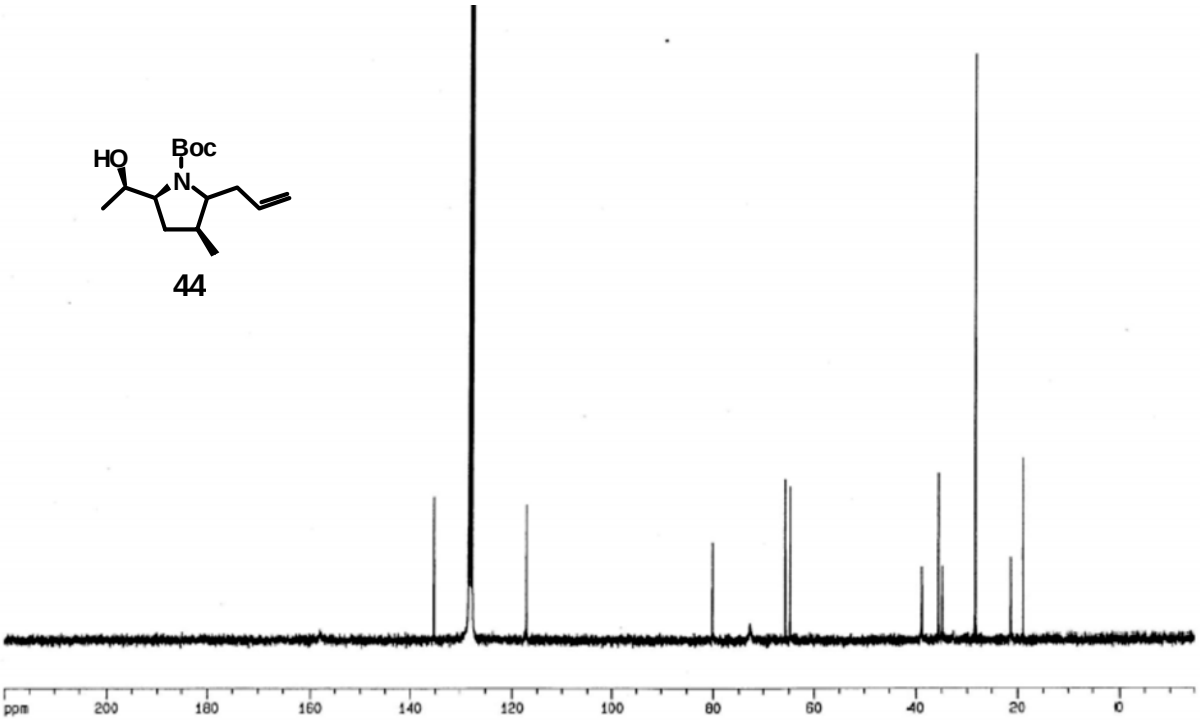
^{1}H NMR of 28: $CDCl_3$, 293 K, 300 MHz



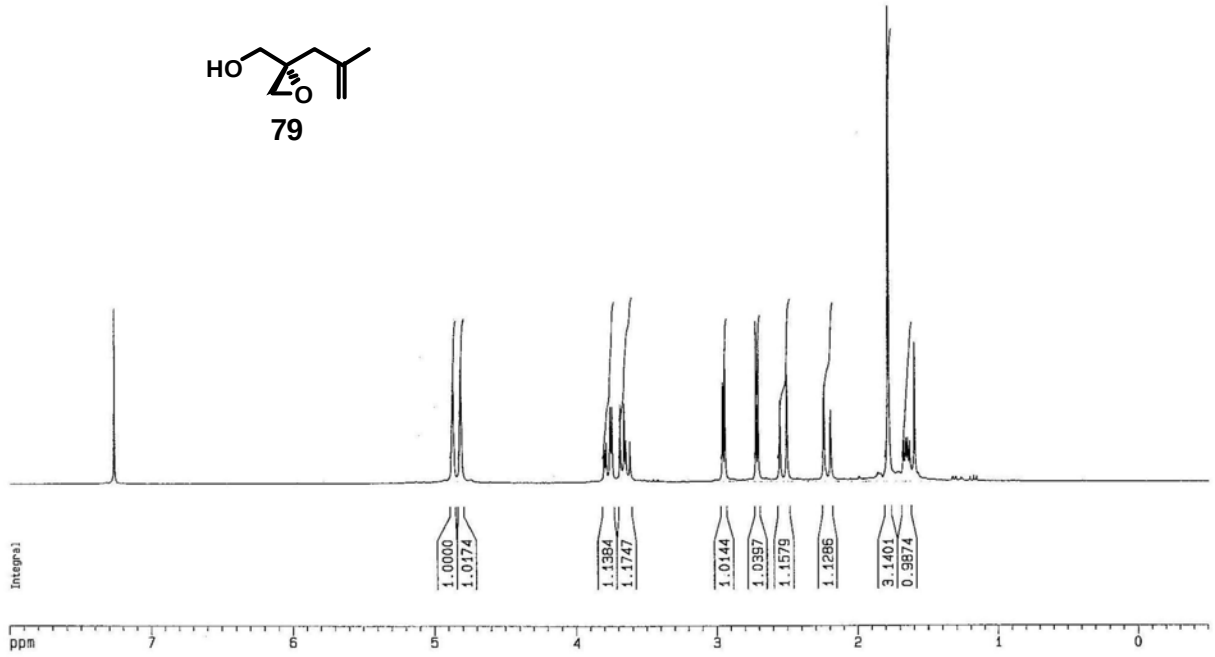
[1]**H NMR of 44**: $CDCl_3$, 293 K, 300 MHz



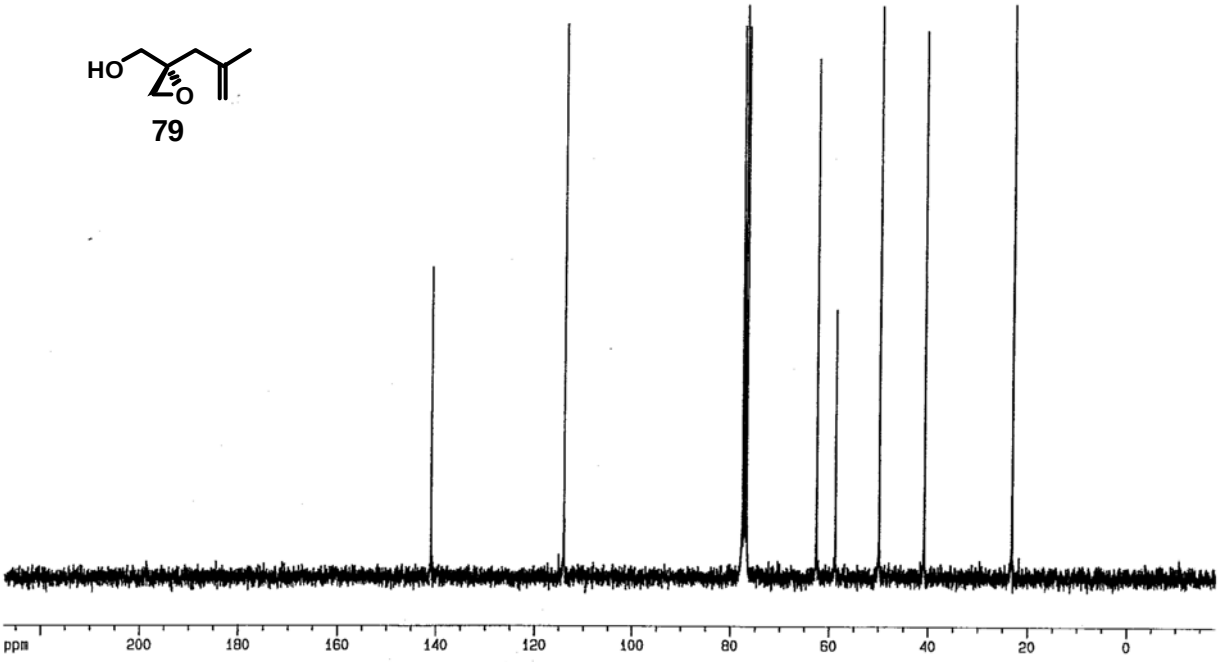
[13]**C NMR of 44**: $CDCl_3$, 293 K, 75 MHz



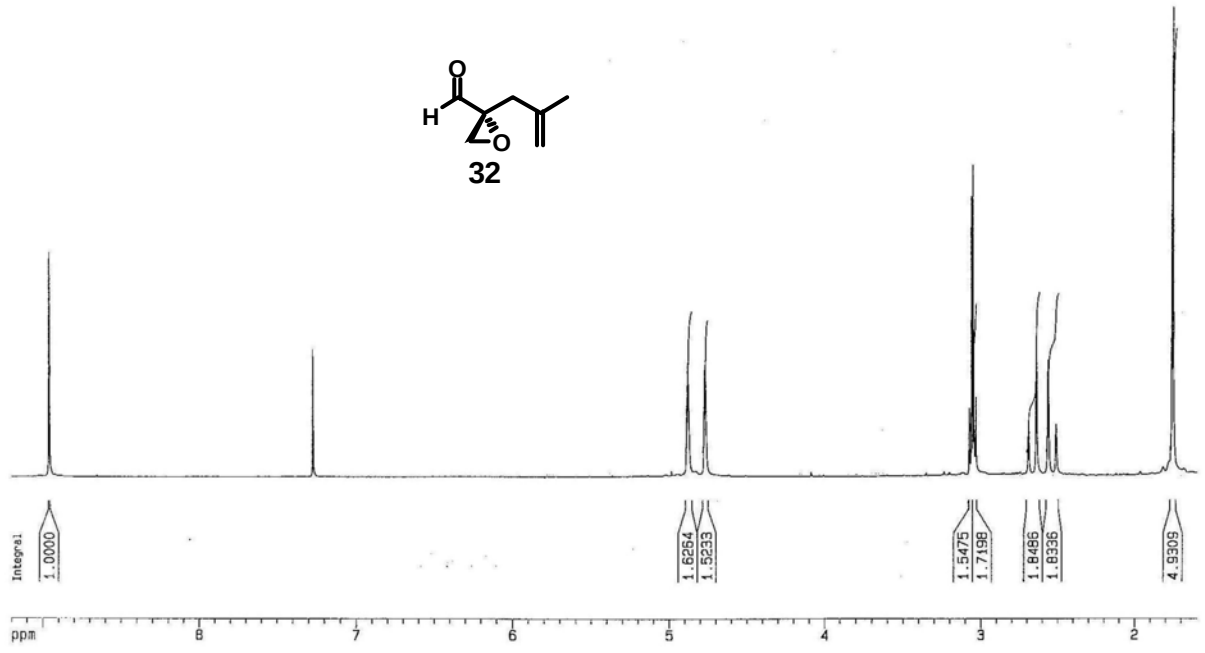
[1]**H NMR of 79**: $CDCl_3$, 293 K, 300 MHz



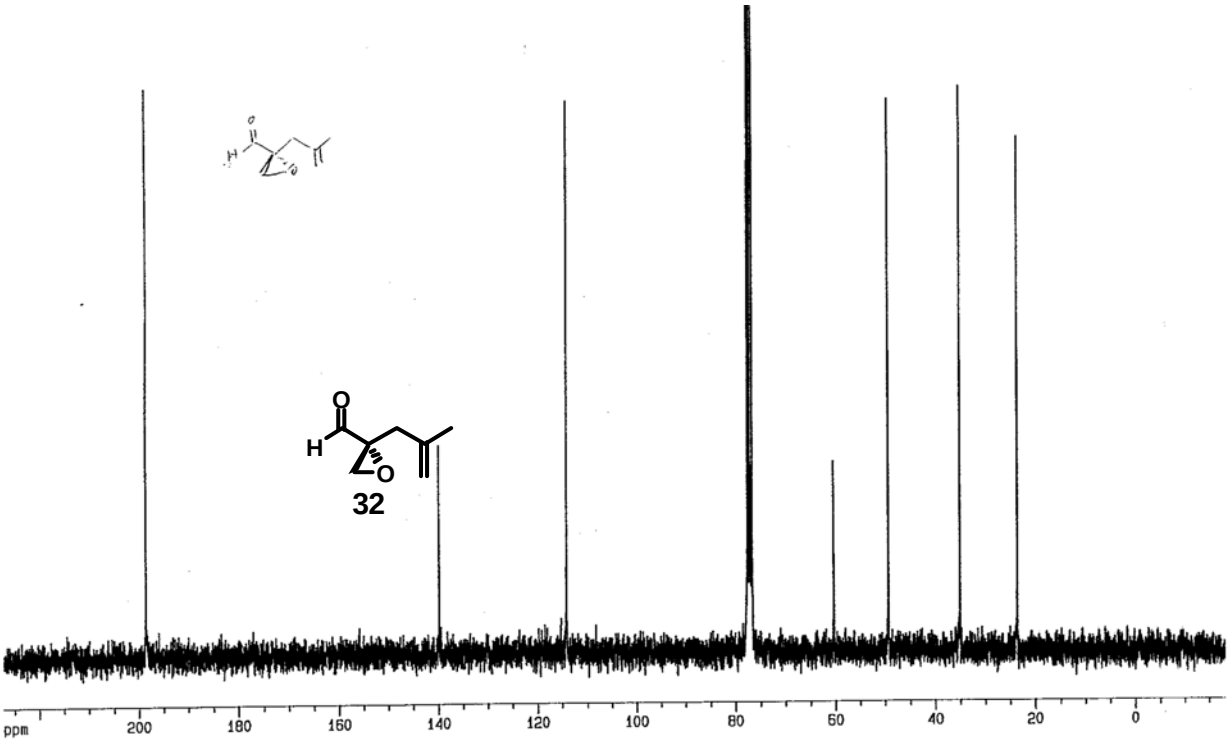
[13]**C NMR of 79**: $CDCl_3$, 293 K, 75 MHz



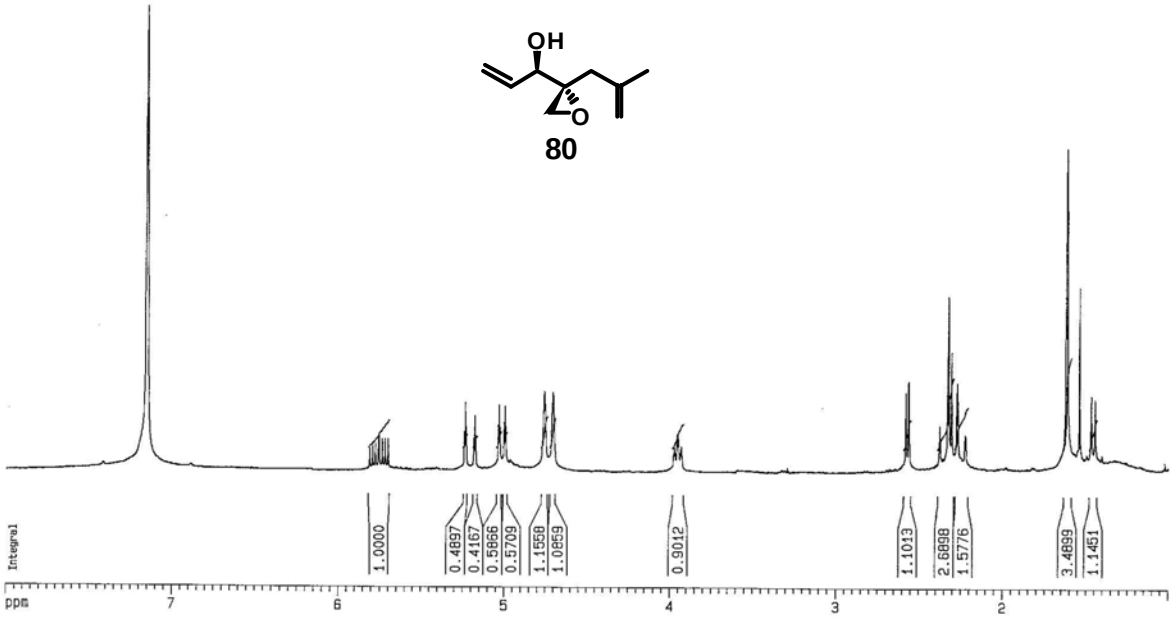
[1]**H NMR of 32**: $CDCl_3$, 293 K, 300 MHz



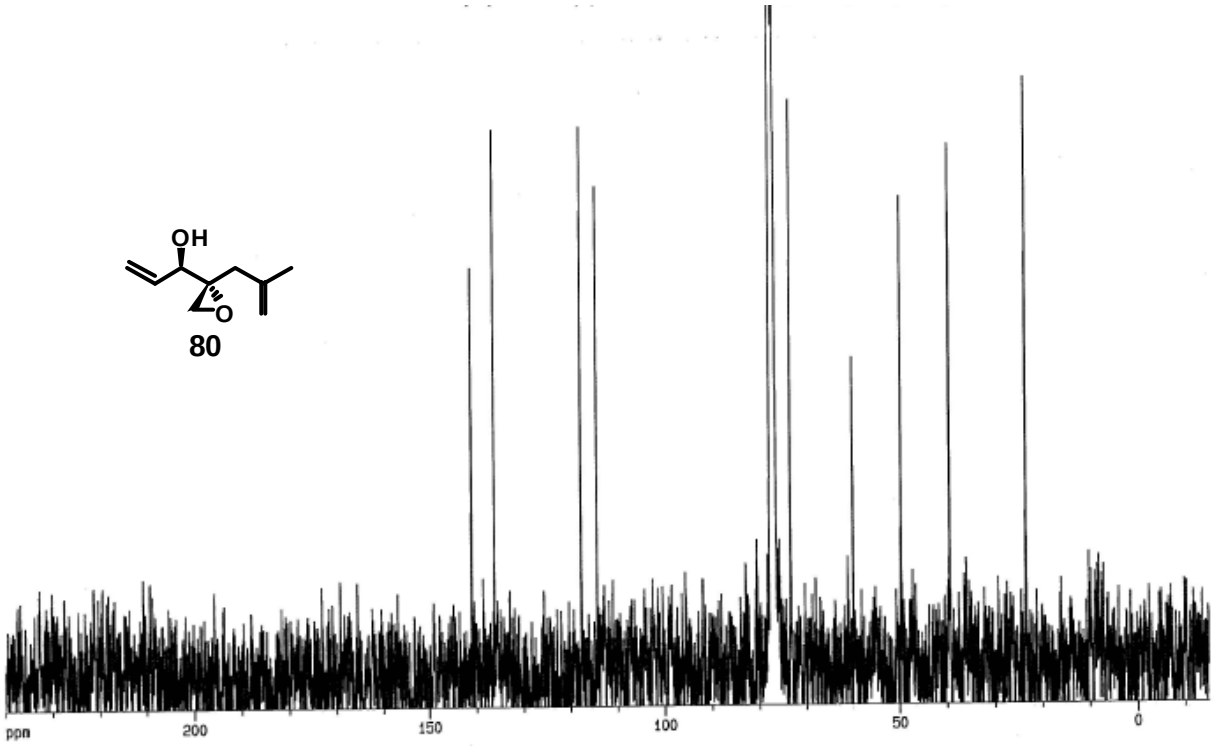
[13]**C NMR of 32**: $CDCl_3$, 293 K, 75 MHz



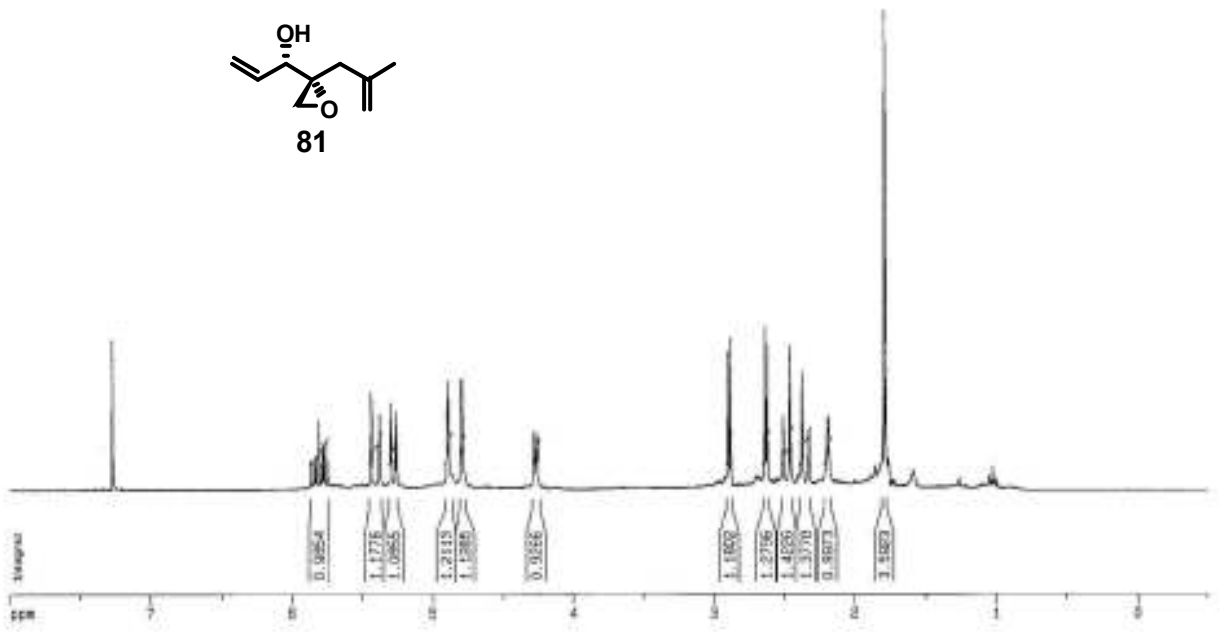
[1]**H NMR of 80**: C_6D_6, 293 K, 300 MHz



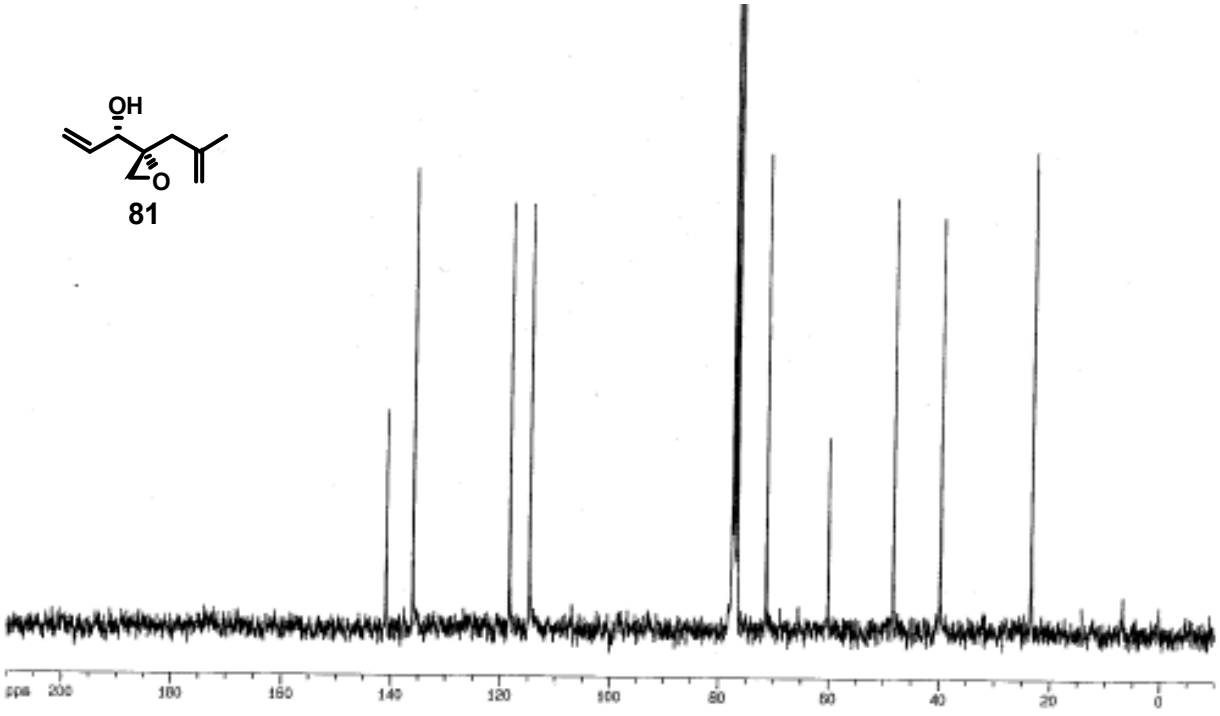
[13]**C NMR of 80**: $CDCl_3$, 293 K, 75 MHz



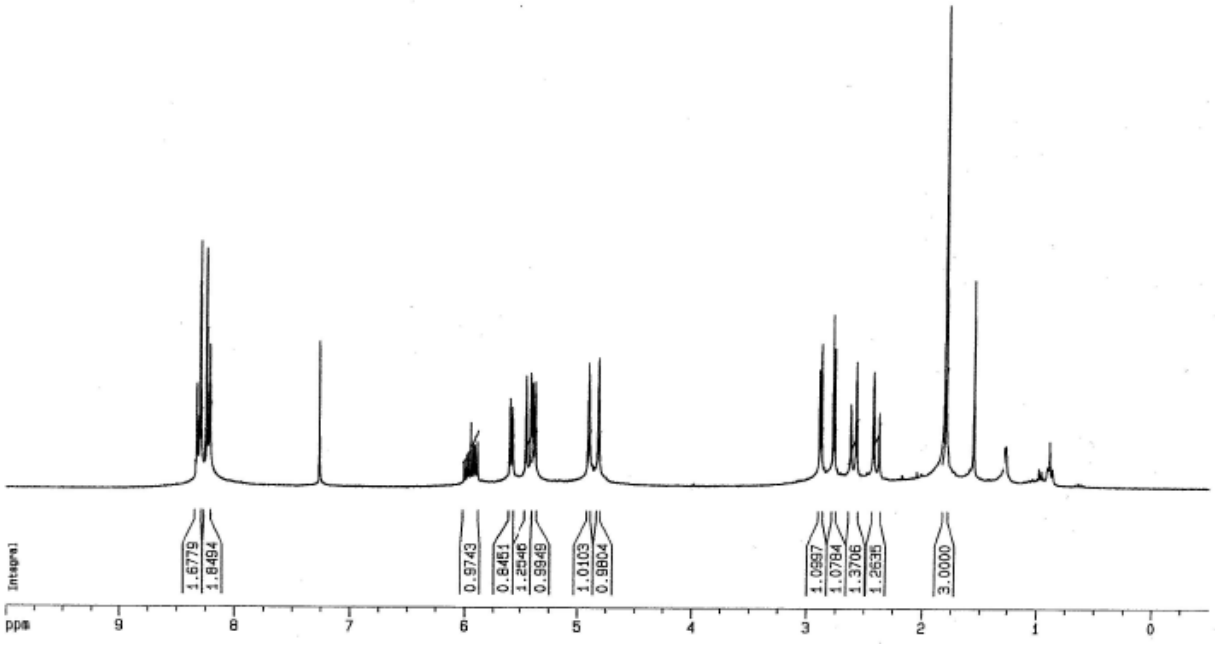
[1]**H NMR of 81**: $CDCl_3$, 293 K, 300 MHz



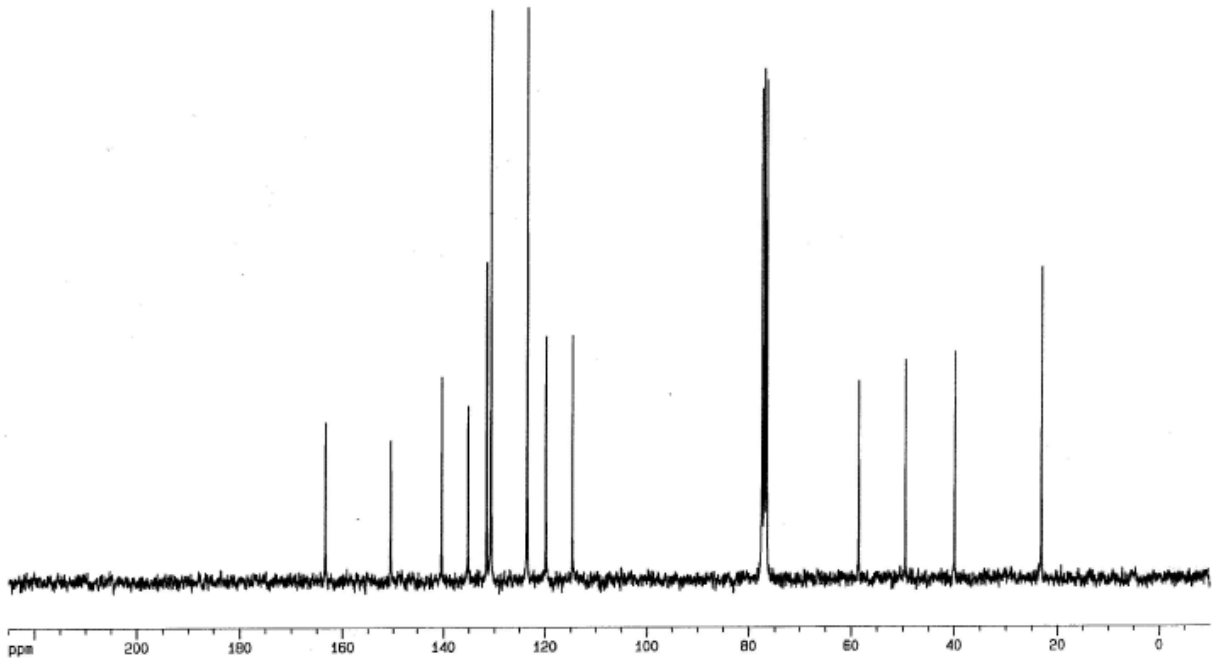
[13]**C NMR of 81**: $CDCl_3$, 293 K, 75 MHz



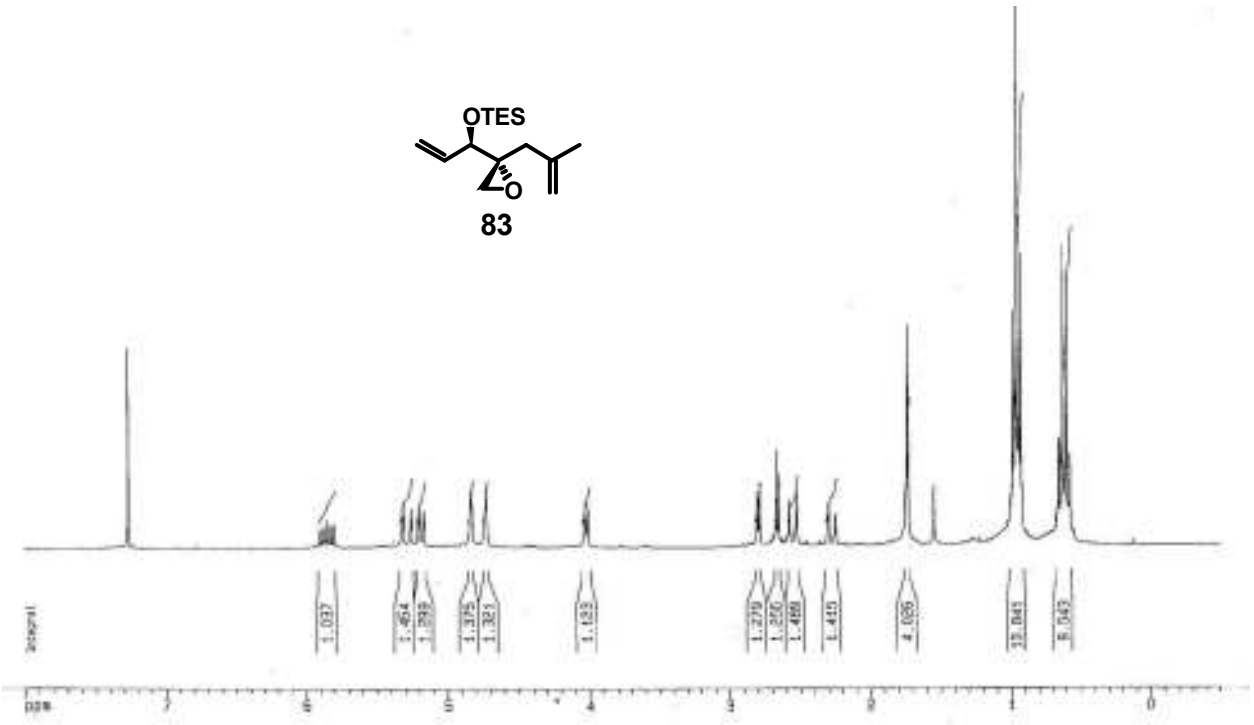
[1]**H NMR of 82**: $CDCl_3$, 293 K, 300 MHz



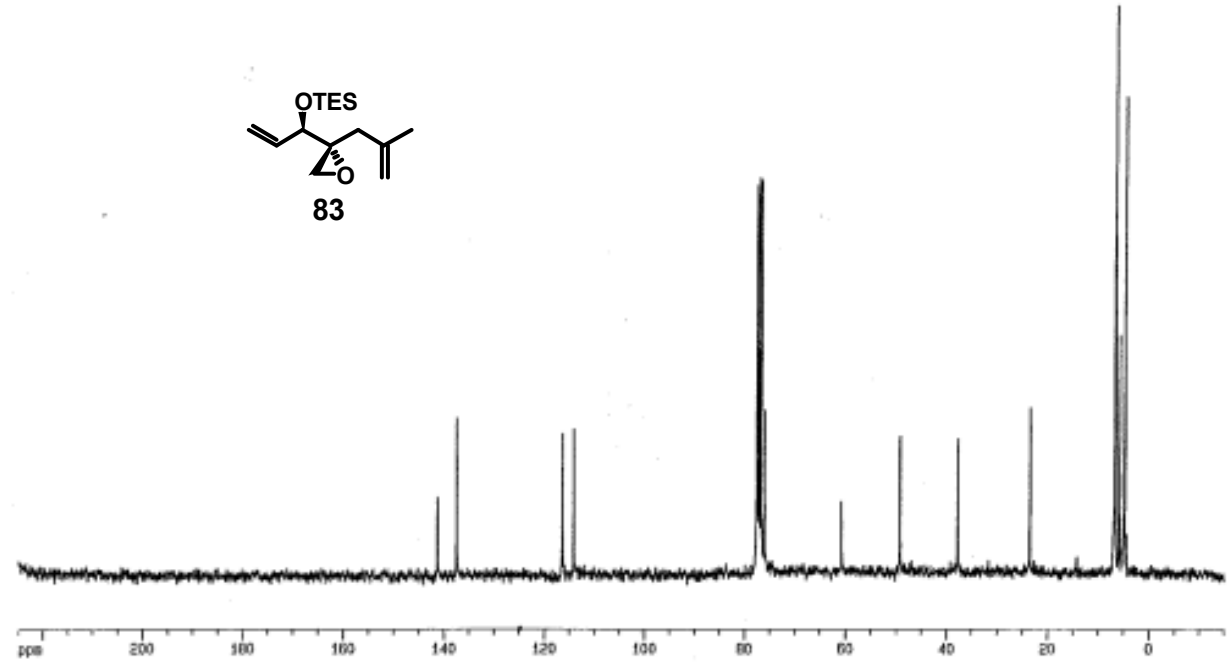
[13]**C NMR of 82**: $CDCl_3$, 293 K, 75 MHz



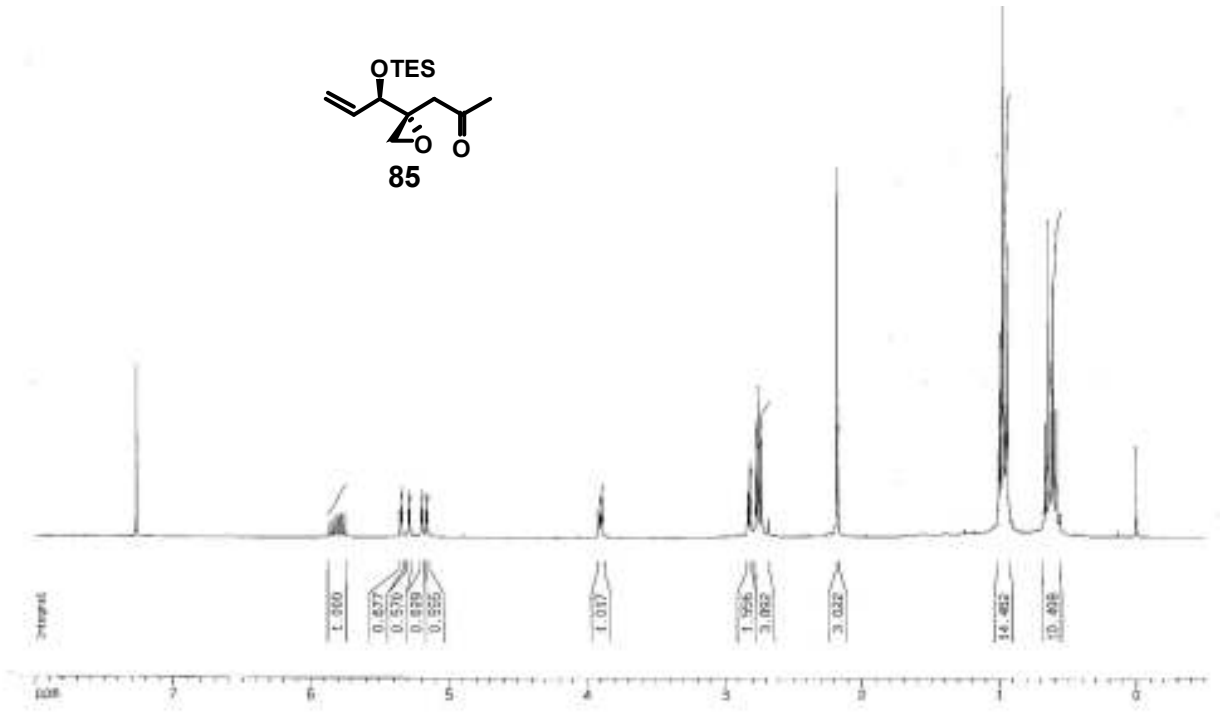
[1]**H NMR of 83**: $CDCl_3$, 293 K, 300 MHz



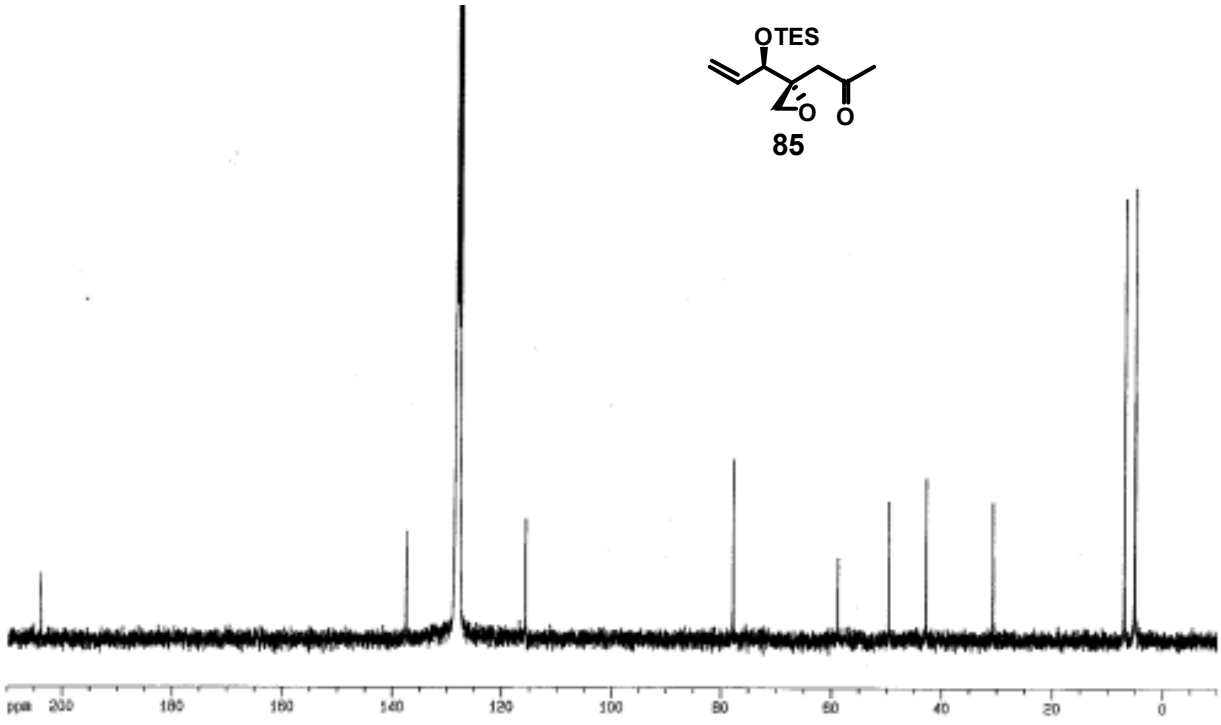
[13]**C NMR of 83**: $CDCl_3$, 293 K, 75 MHz



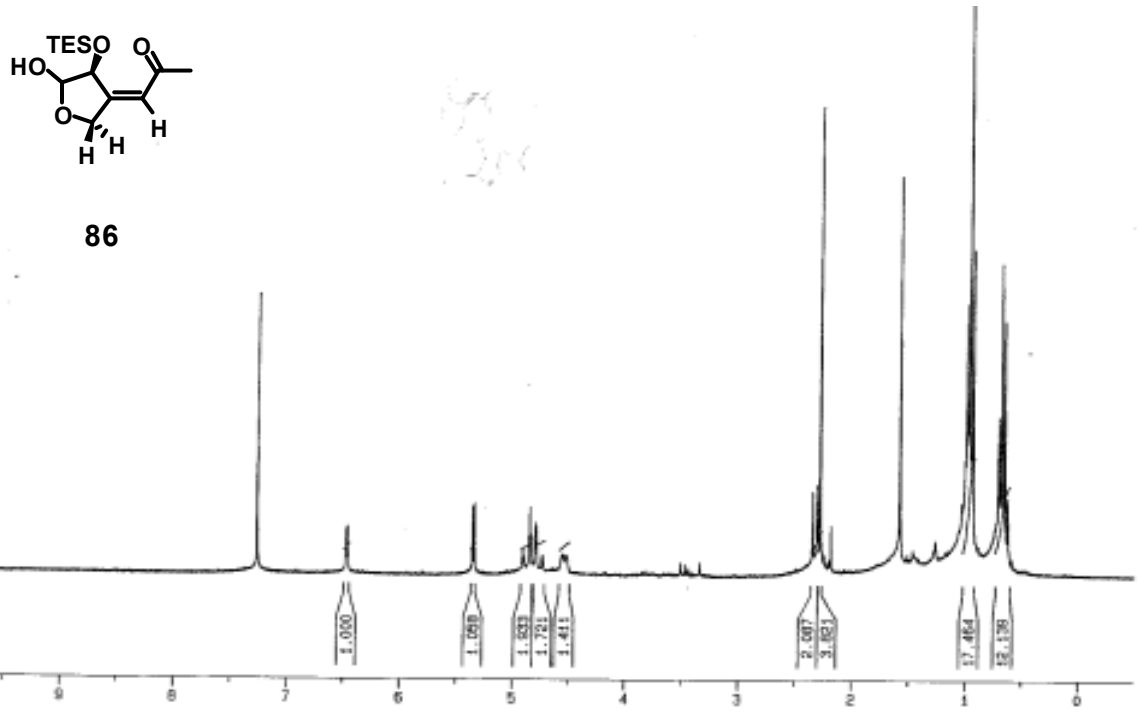
[1]**H NMR of 85**: $CDCl_3$, 293 K, 300 MHz



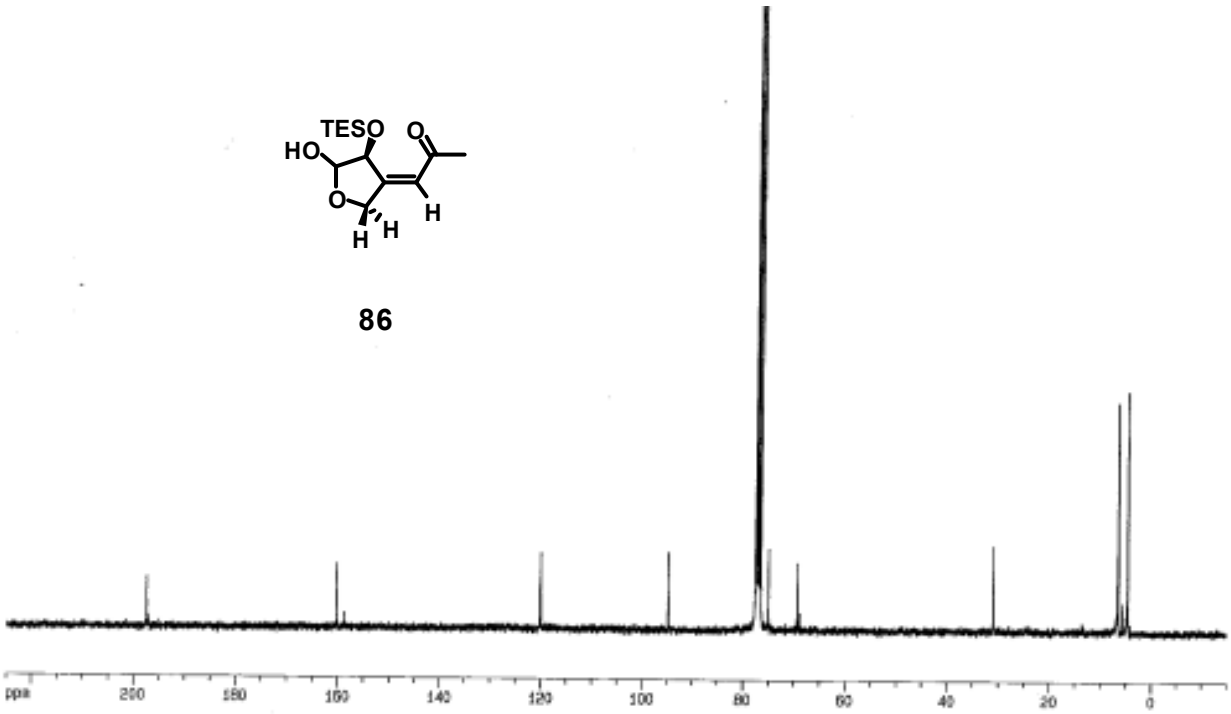
[13]**C NMR of 85**: C_6D_6, 293 K, 75 MHz



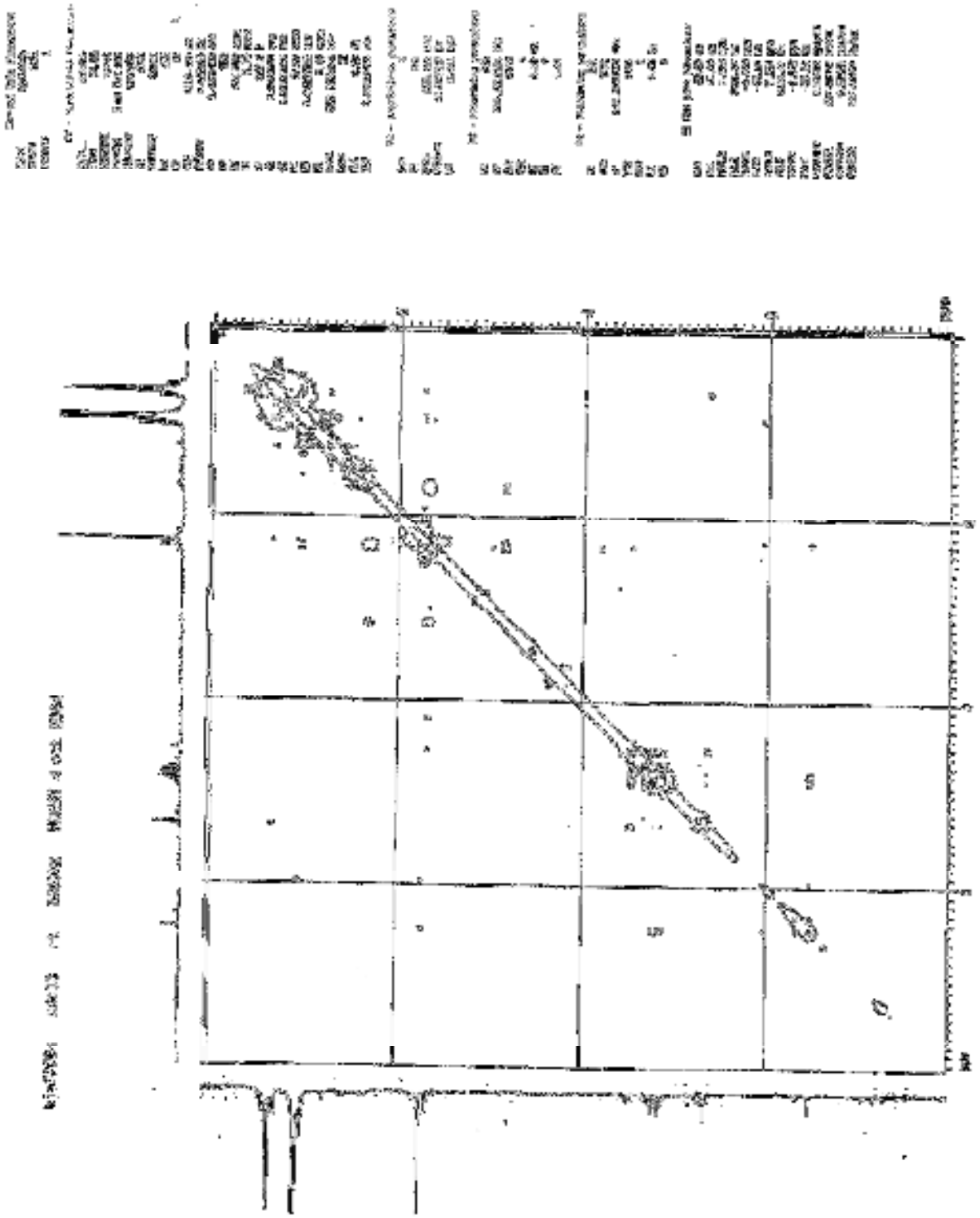
[1]**H NMR of 86**: $CDCl_3$, 293 K, 300 MHz



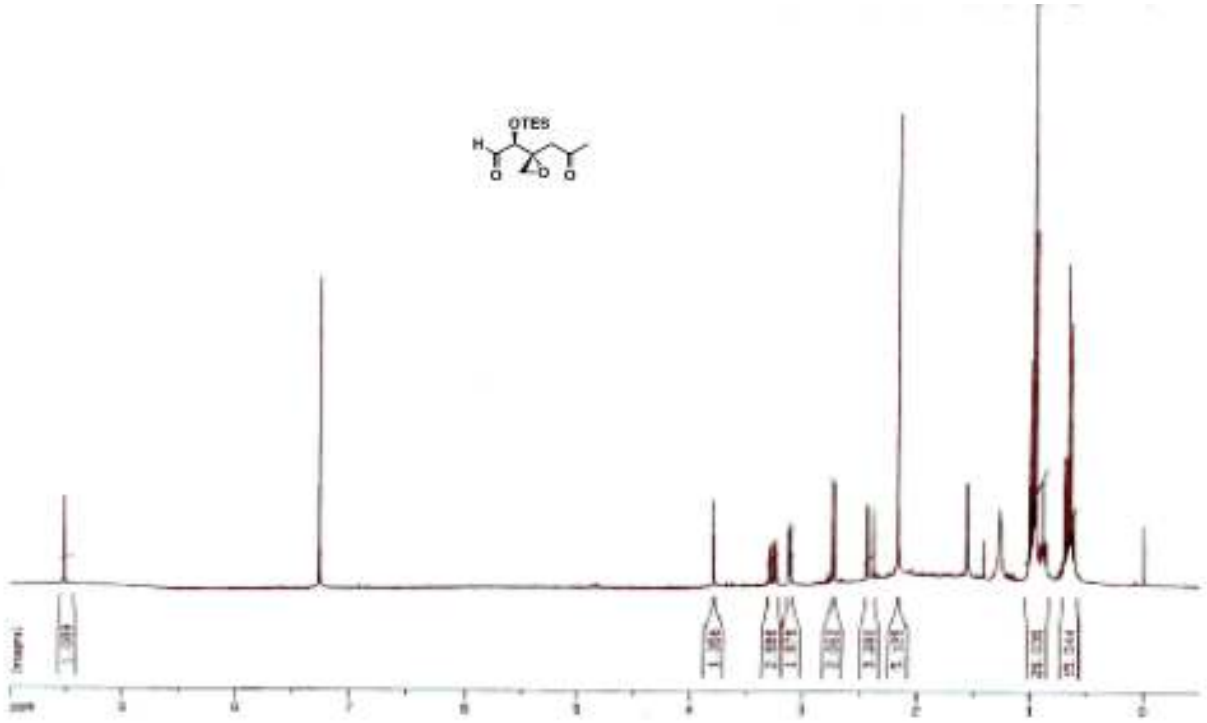
[13]**C NMR of 86**: C_6D_6, 293 K, 75 MHz



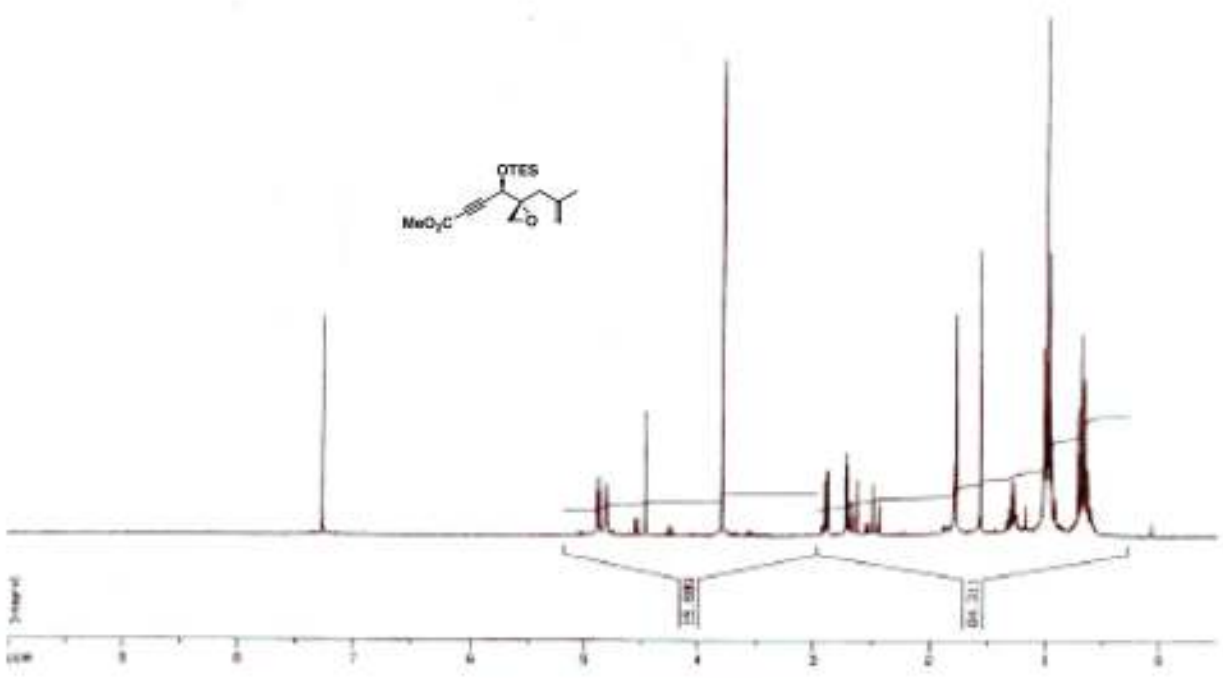
NOESY of 86: $CDCl_3$, 293 K, 500 MHz



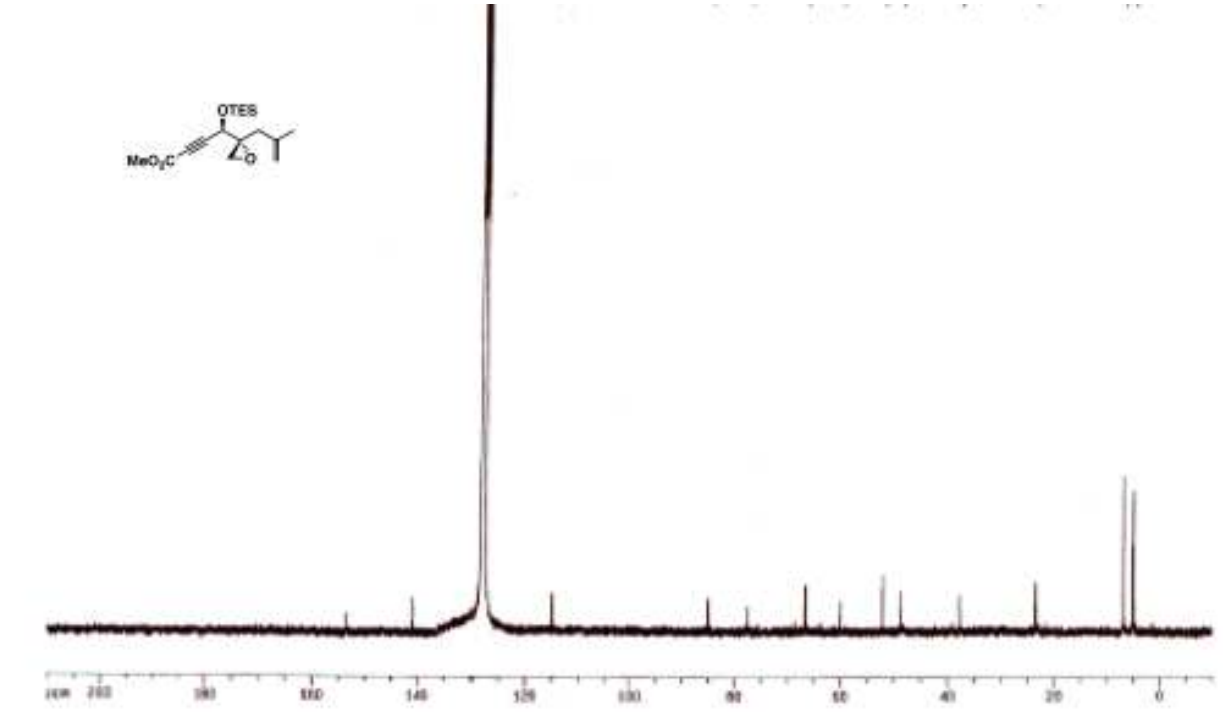
[1]**H NMR of 26**: $CDCl_3$, 293 K, 300 MHz



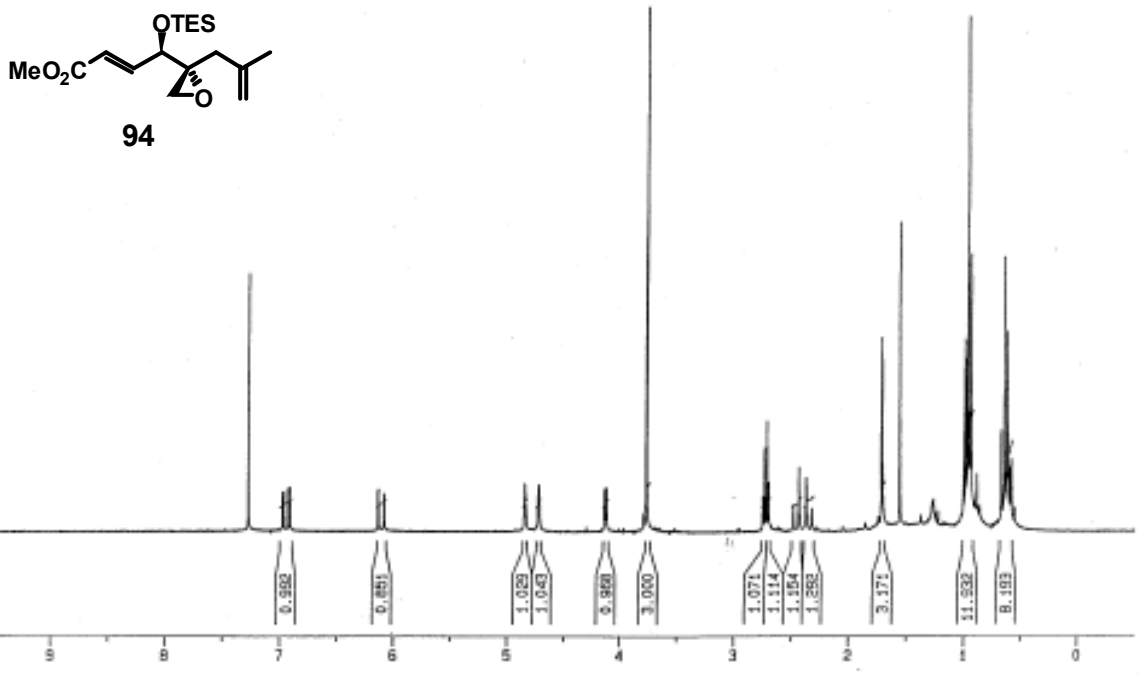
[1]**H NMR of 90**: $CDCl_3$, 293 K, 300 MHz



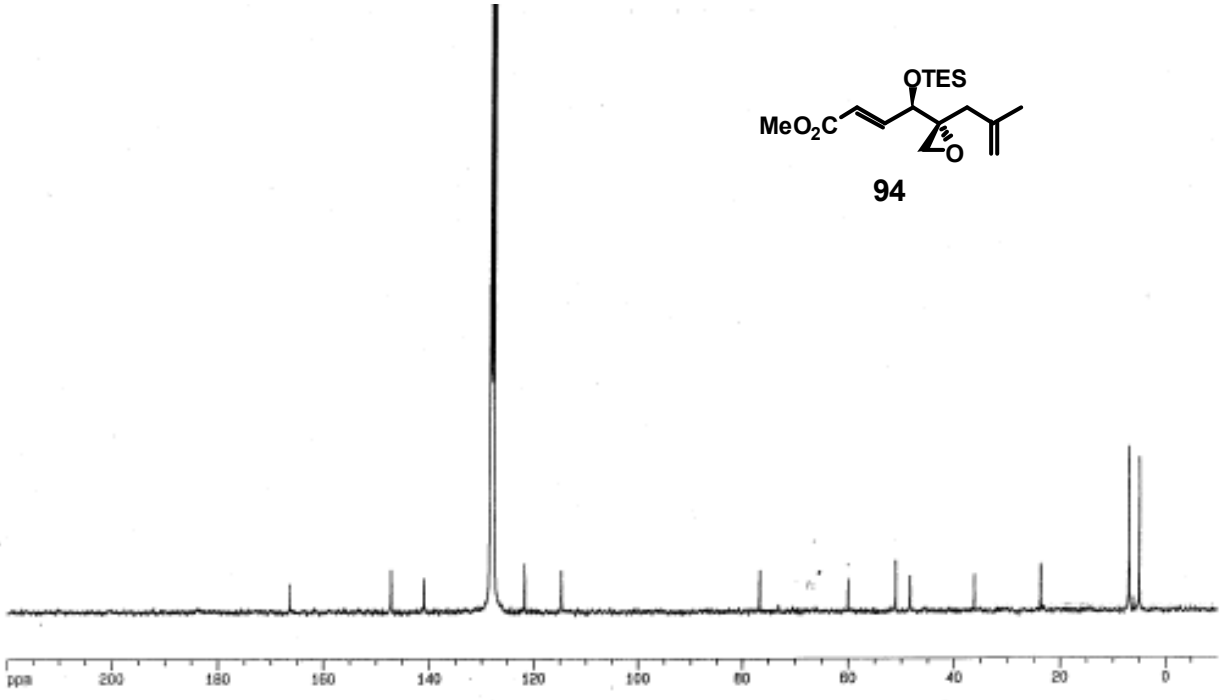
[13]**C NMR of 90**: C_6D_6, 293 K, 75 MHz



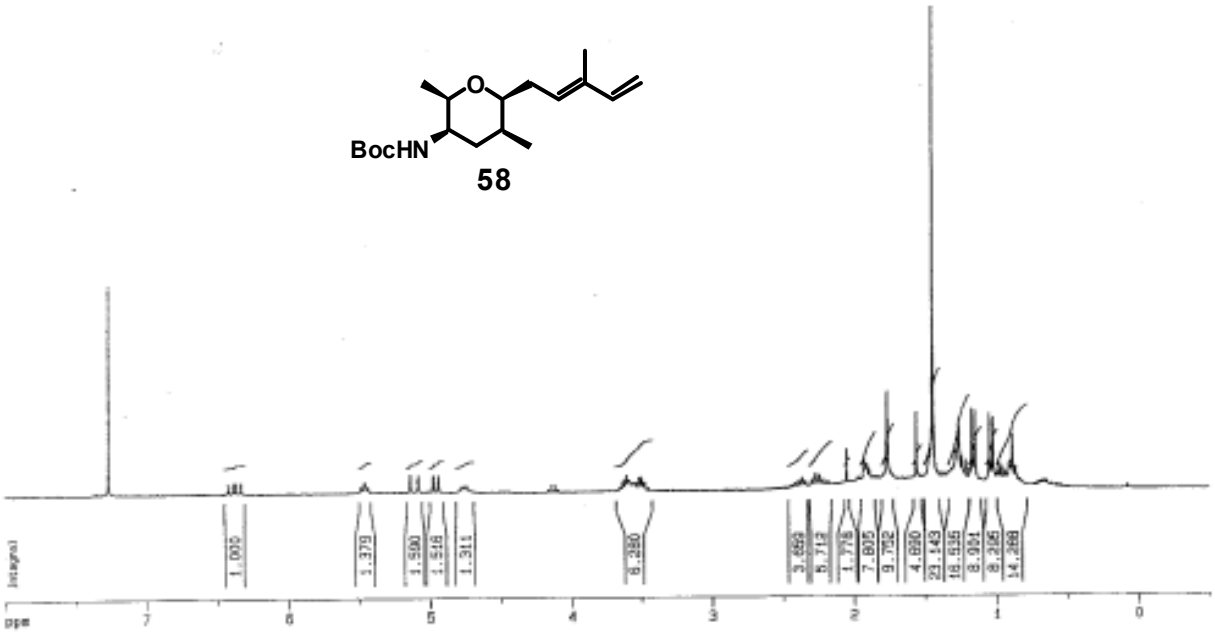
[1]**H NMR of 94**: $CDCl_3$, 293 K, 300 MHz



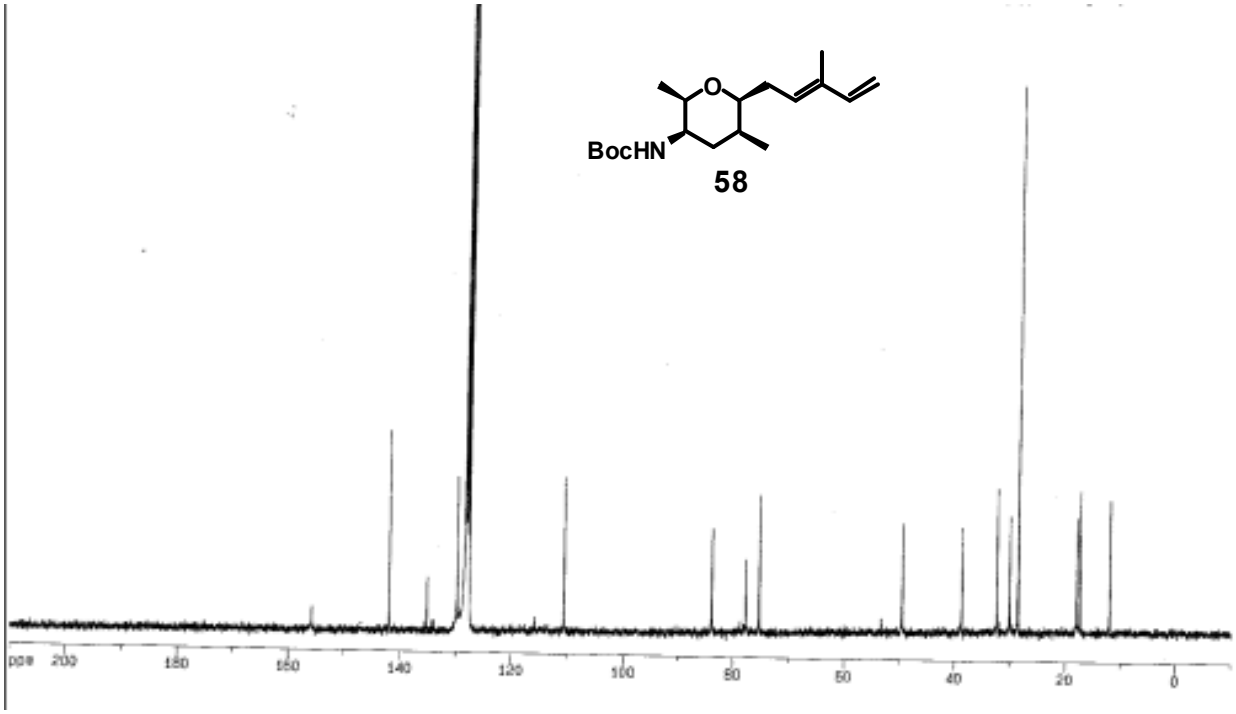
[13]**C NMR of 94**: C_6D_6, 293 K, 75 MHz



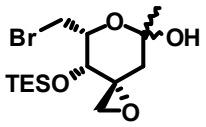
[1]**H NMR of 58**: $CDCl_3$, 293 K, 300 MHz



[13]**C NMR of 58**: C_6D_6, 293 K, 75 MHz

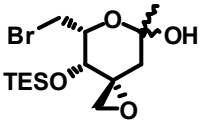


[1]**H NMR of 106**: $CDCl_3$, 293 K, 300 MHz



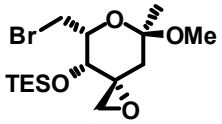
106

[13]**C NMR of 106**: $CDCl_3$, 293 K, 75 MHz



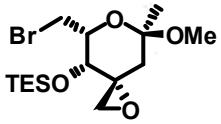
106

[1]**H NMR of 107**: $CDCl_3$, 293 K, 300 MHz



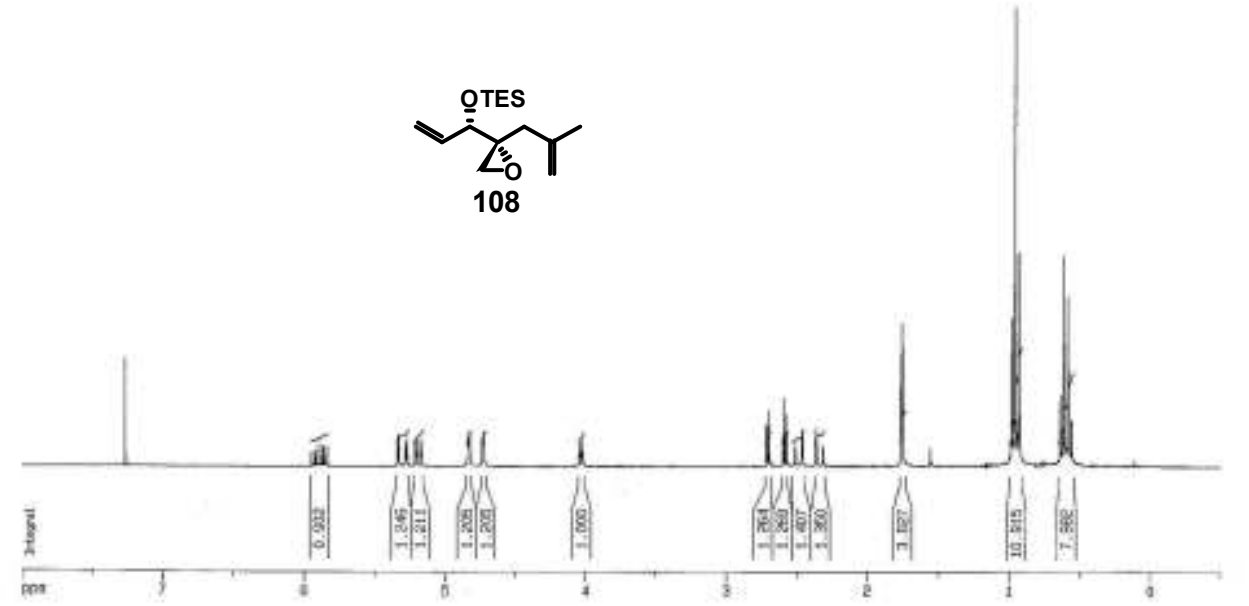
107

[13]**C NMR of 107**: C_6D_6, 293 K, 75 MHz

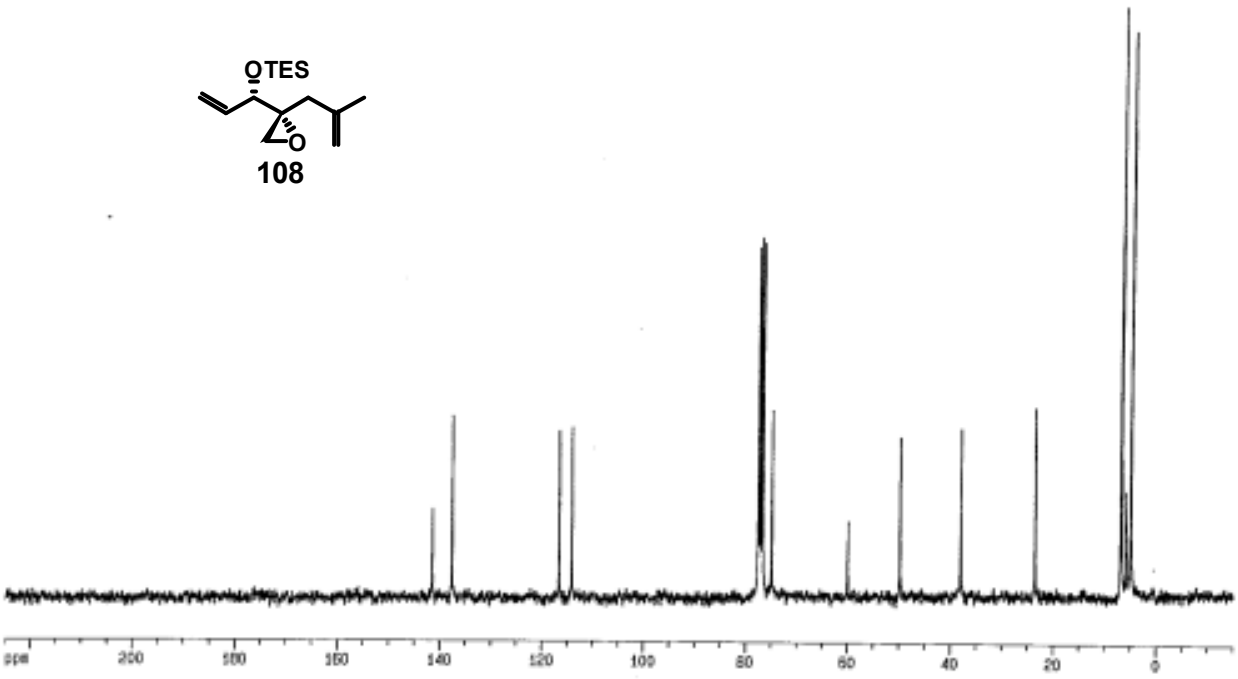


107

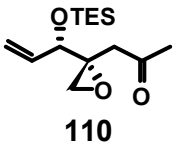
[1]**H NMR of 108**: $CDCl_3$, 293 K, 300 MHz



[13]**C NMR of 108**: $CDCl_3$, 293 K, 75 MHz

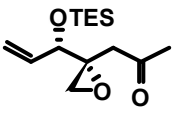


[1]**H NMR of 110**: $CDCl_3$, 293 K, 300 MHz



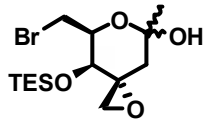
110

[13]**C NMR of 110**: $CDCl_3$, 293 K, 75 MHz



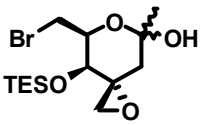
110

[1]**H NMR of 111**: $CDCl_3$, 293 K, 300 MHz



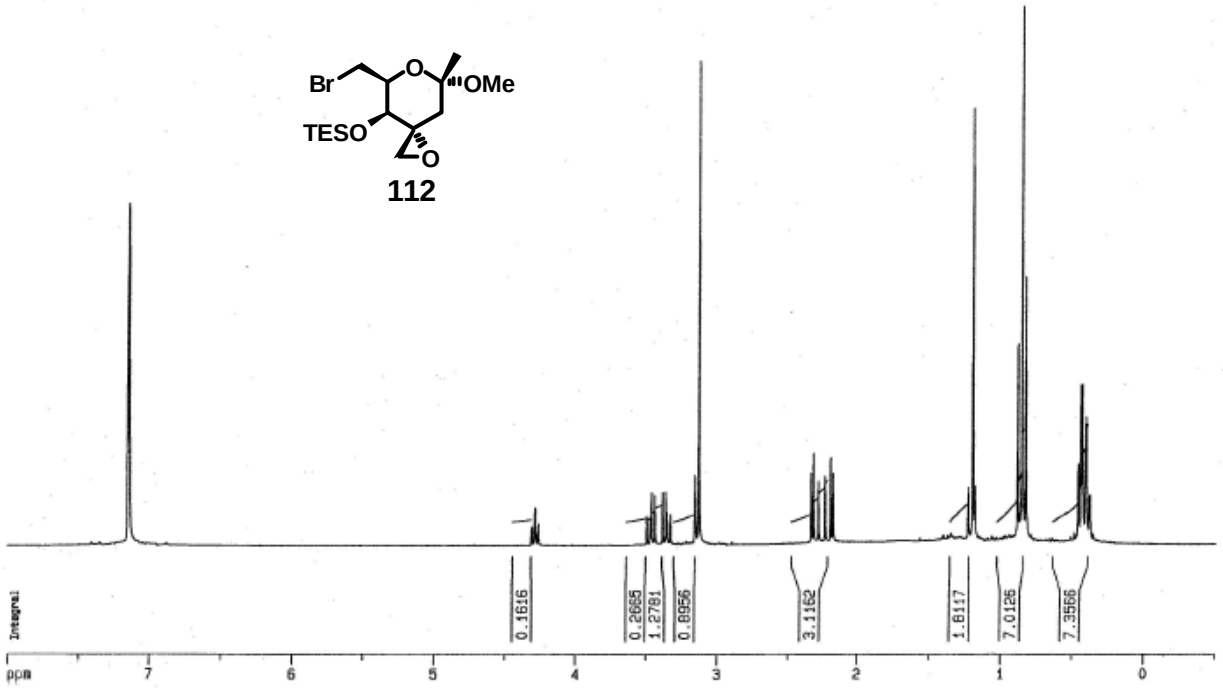
111

[13]**C NMR of 111**: $CDCl_3$, 293 K, 75 MHz

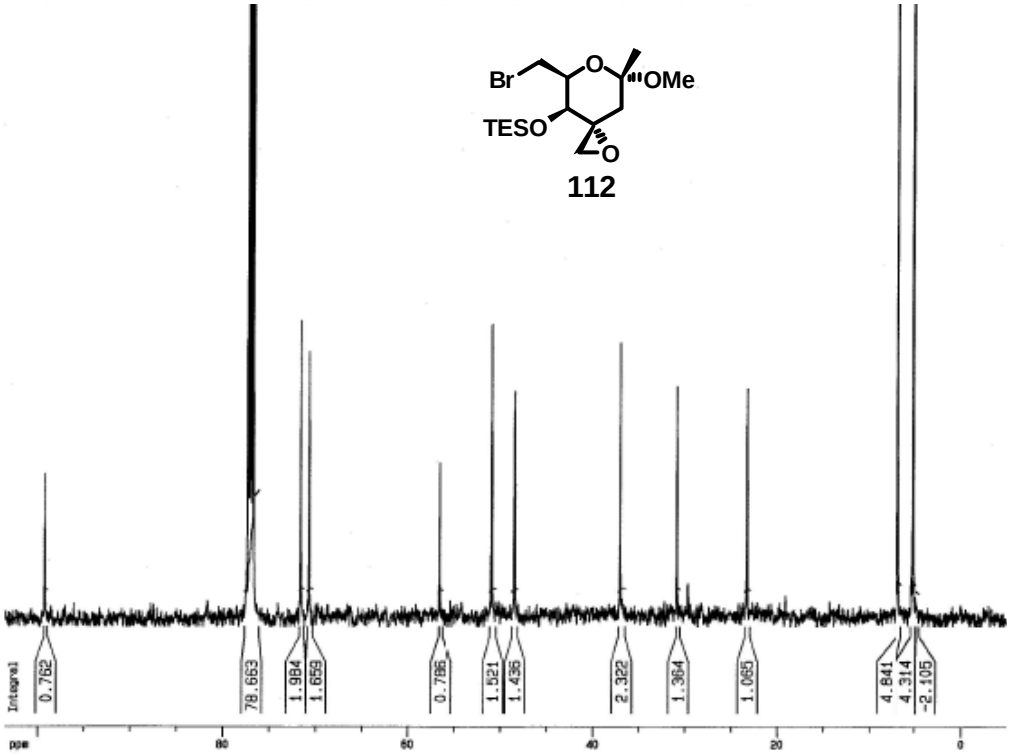


111

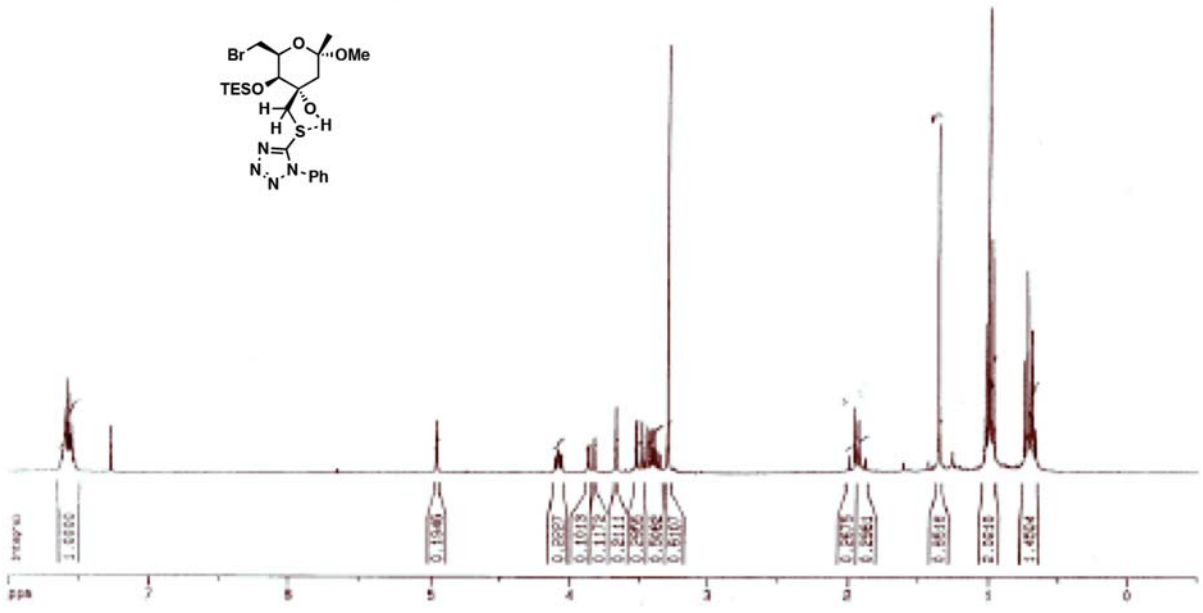
[1]**H NMR of 112**: C_6D_6, 293 K, 300 MHz



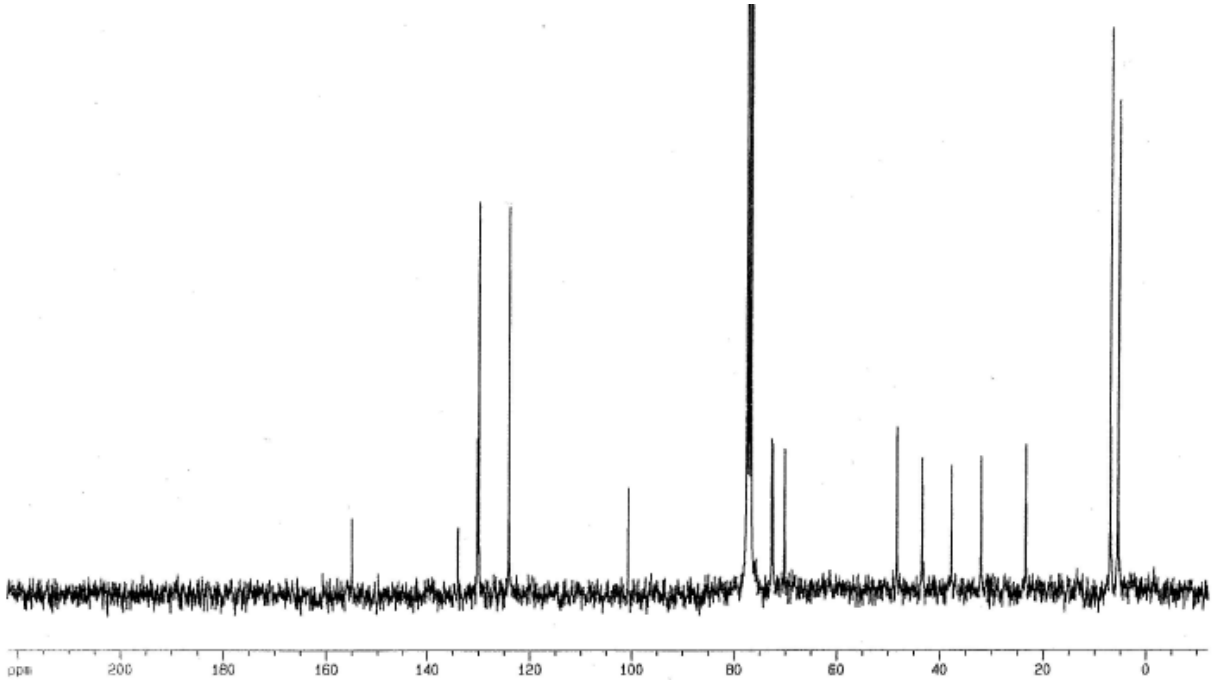
[13]**C NMR of 112**: $CDCl_3$, 293 K, 125 MHz



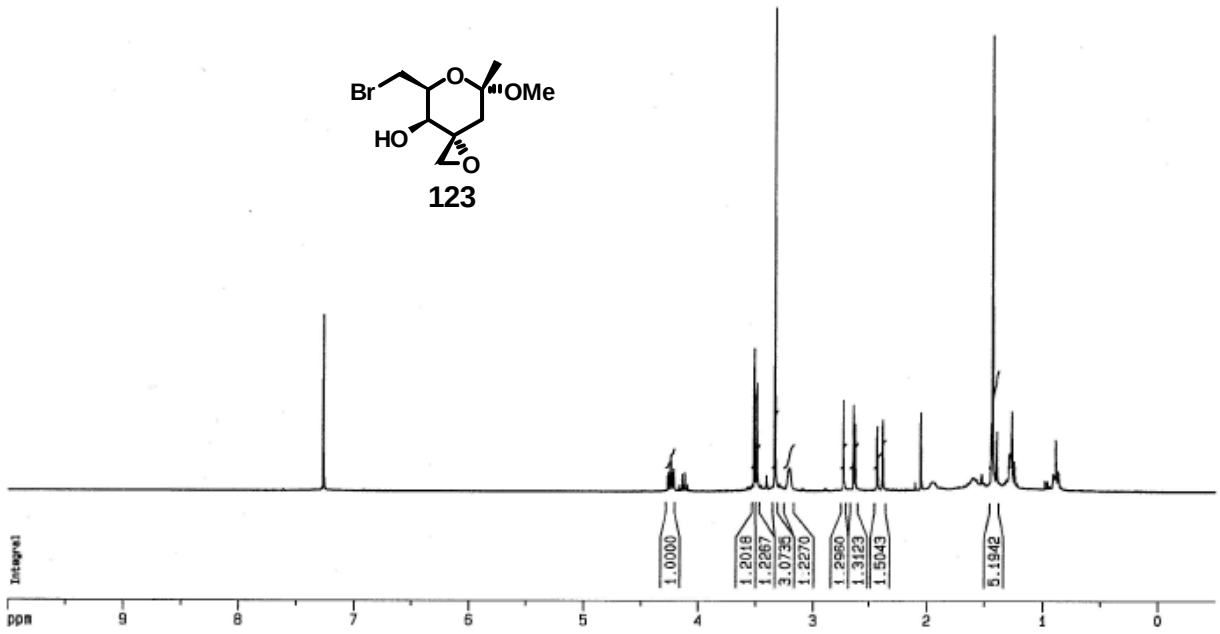
[1]**H NMR of 125**: $CDCl_3$, 293 K, 300 MHz



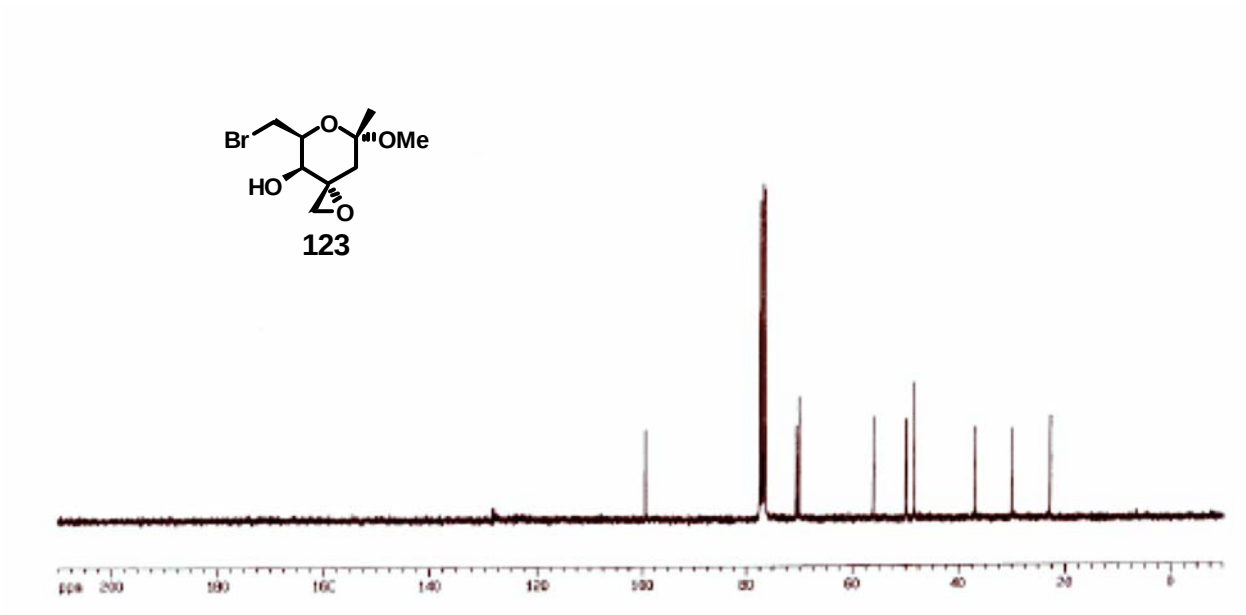
[13]**C NMR of 125**: $CDCl_3$, 293 K, 75 MHz



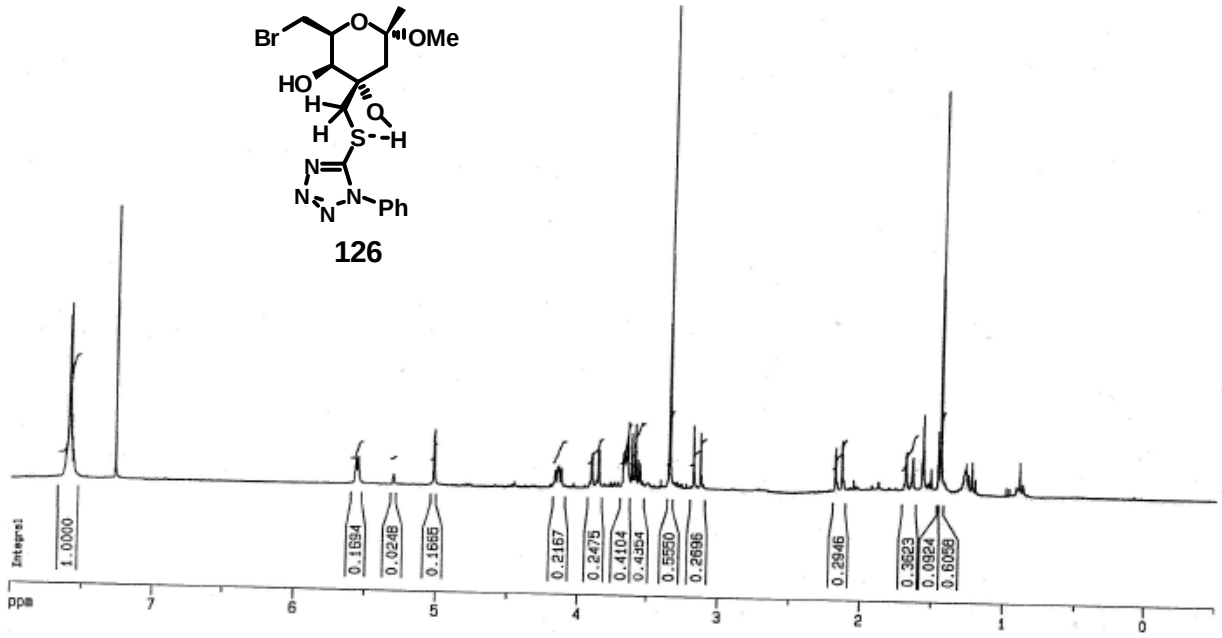
[1]**H NMR of 123**: $CDCl_3$, 293 K, 300 MHz



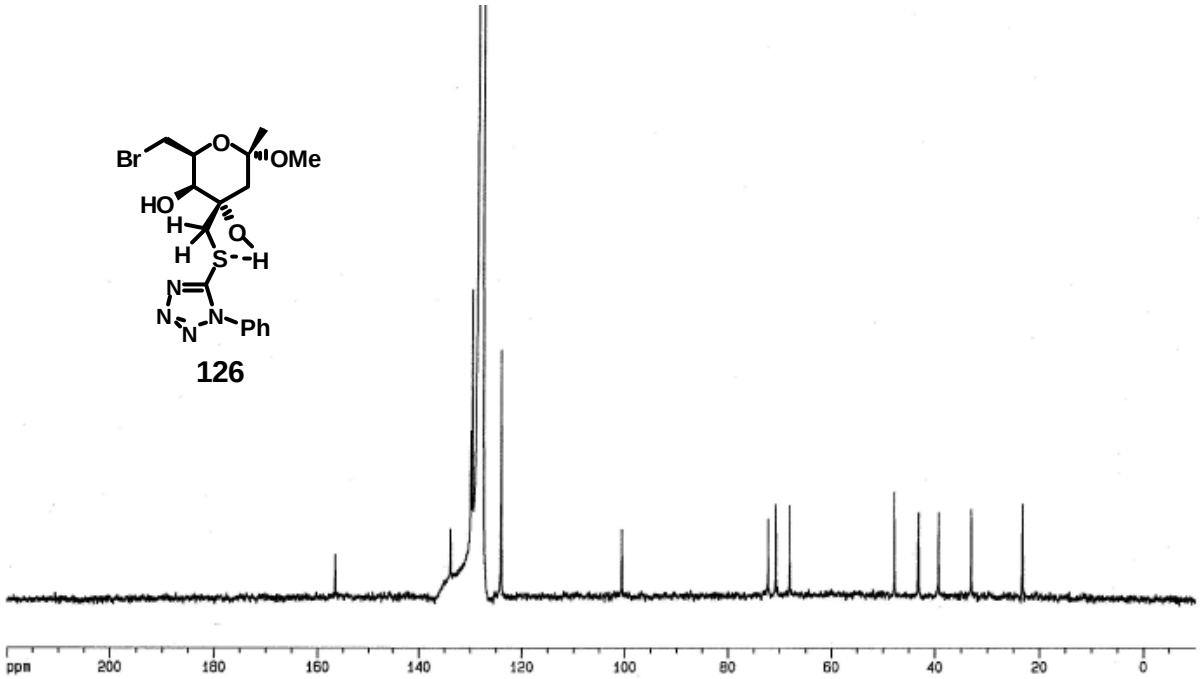
[13]**C NMR of 123**: $CDCl_3$, 293 K, 75 MHz



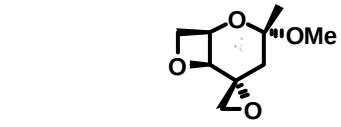
[1]**H NMR of 126**: C_6D_6, 293 K, 300 MHz



[13]**C NMR of 126**: C_6D_6, 293 K, 75 MHz

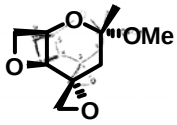


[1]**H NMR of 127**: $CDCl_3$, 293 K, 300 MHz



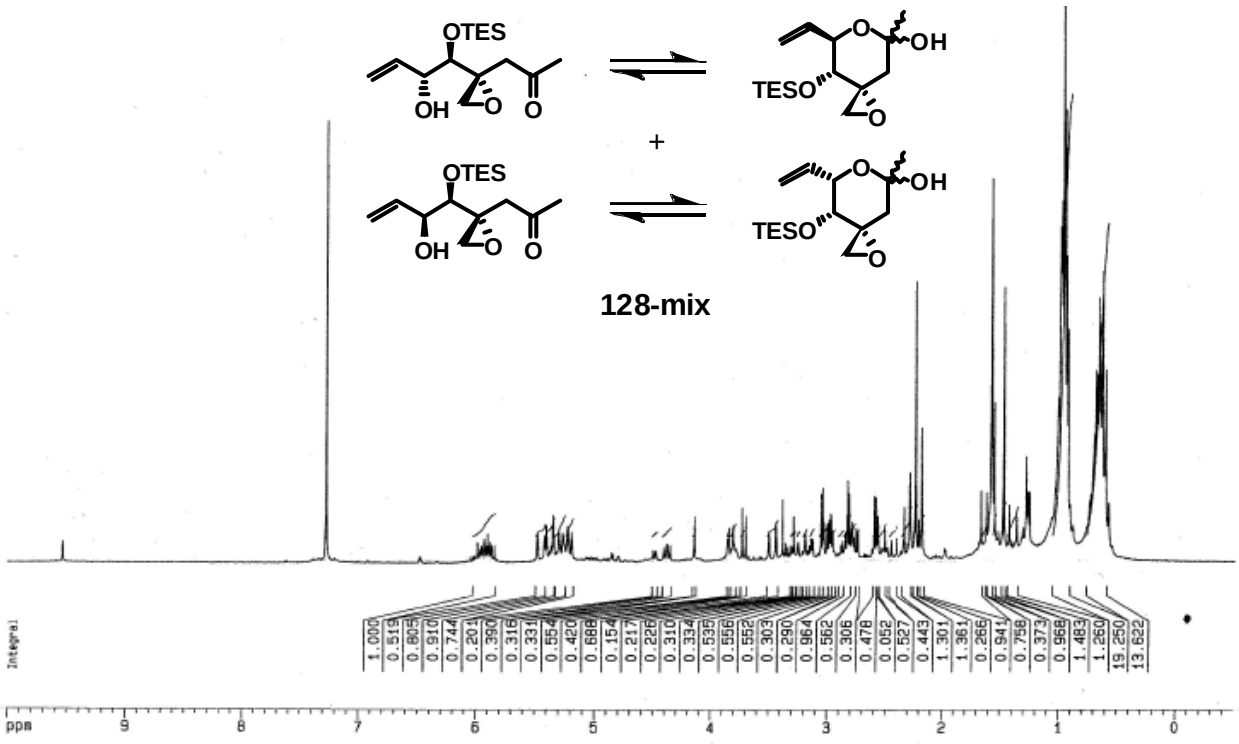
127

[13]**C NMR of 127**: C_6D_6, 293 K, 75 MHz

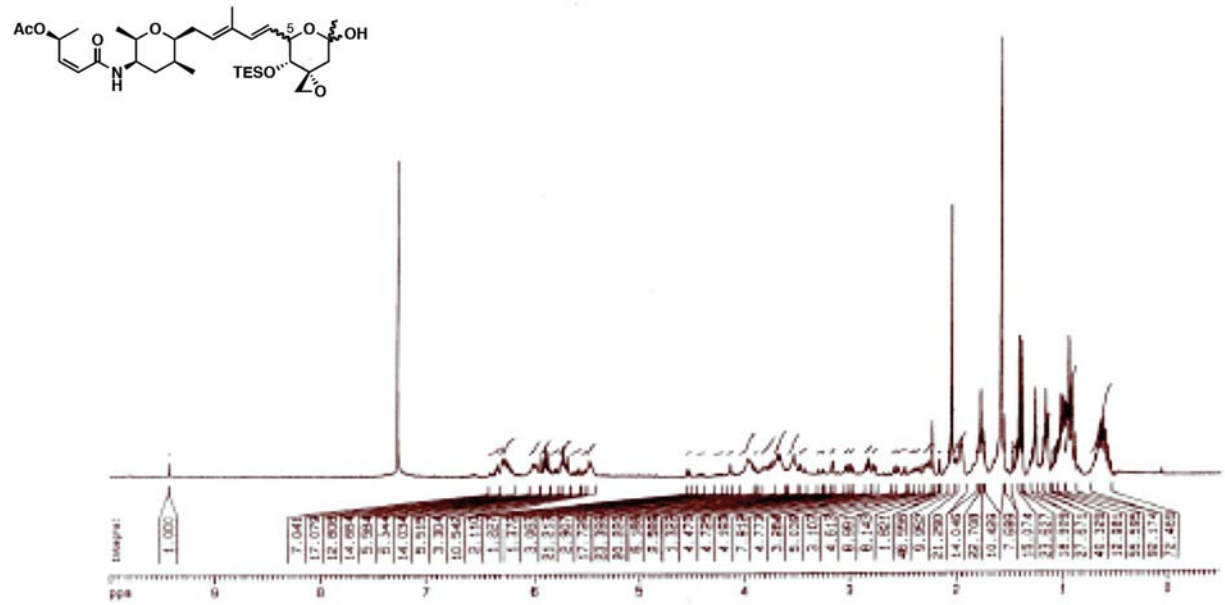


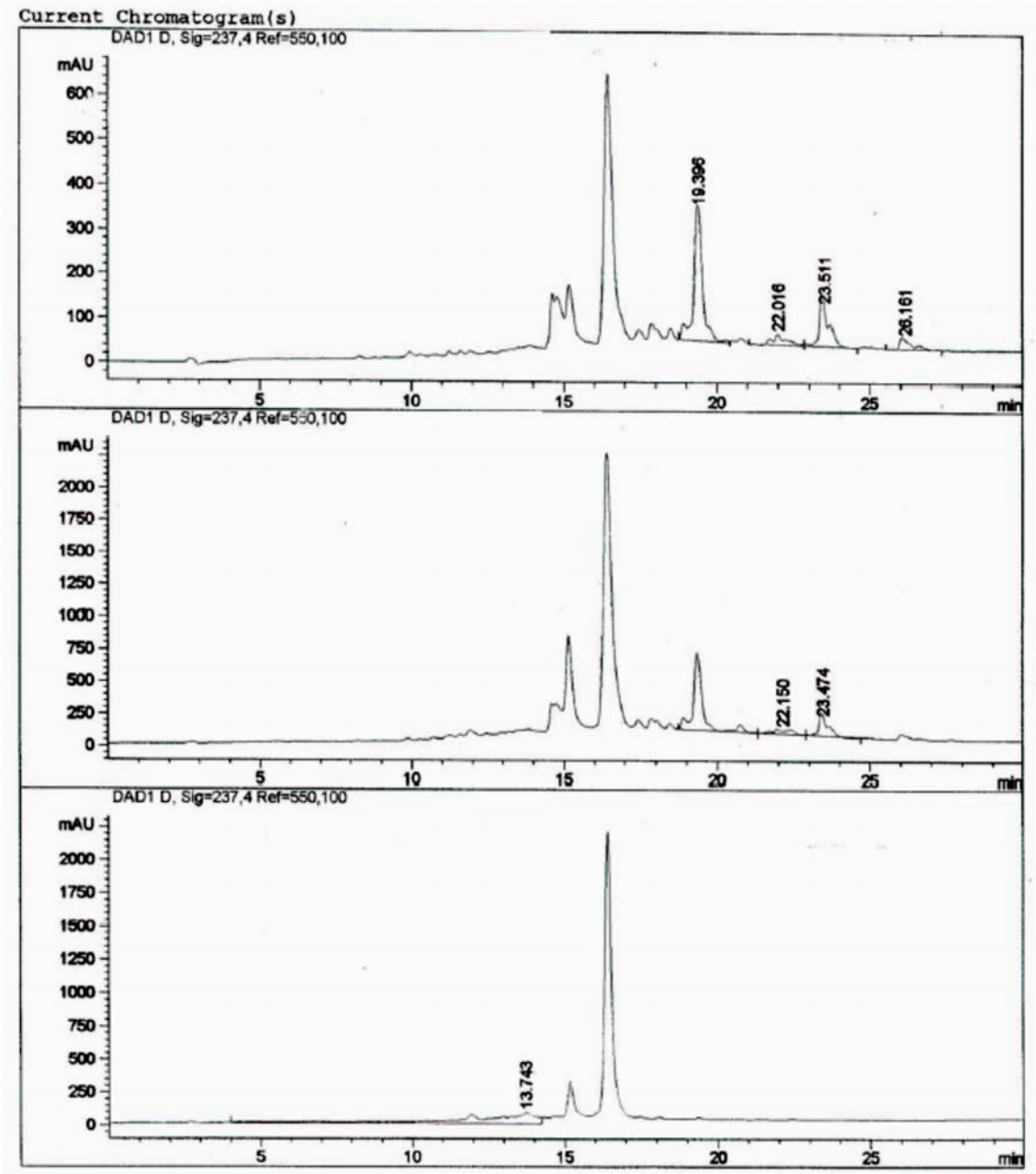
127

^{1}**H NMR of 128-mixture**: $CDCl_3$, 293 K, 300 MHz



^{1}**H NMR of 129**: $CDCl_3$, 293 K, 300 MHz





HPLC comparison of crude and authentic FR901464

HPLC conditions: Varian Chrompack Microsorb 100 C18 column (5 μm packing; 2 mm × 250 mm); 5 → 95% MeCN in H_2O (containing 0.05% HCO_2H); 0.8 mL/min; 237 nm.

A: crude (reaction mixture after a small silica plug) synthetic FR901464

B: co-injection of **A** and **C**

C: authentic FR901464 obtained from Fujisawa Pharmaceutical Co.

HPLC-MS (ESI) for 16.4 min

A: crude (reaction mixture after a small silica plug) synthetic FR901464

B: co-injection of **A** and **C**

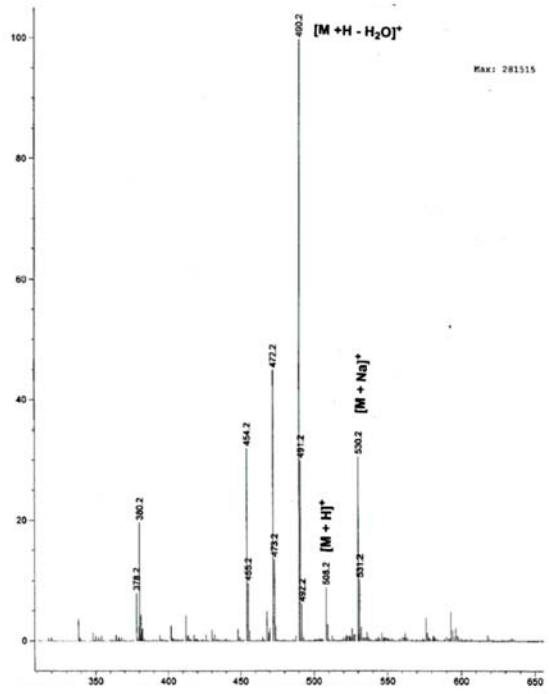
C: authentic FR901464 obtained from Fujisawa Pharmaceutical Co.

Calculated Masses:

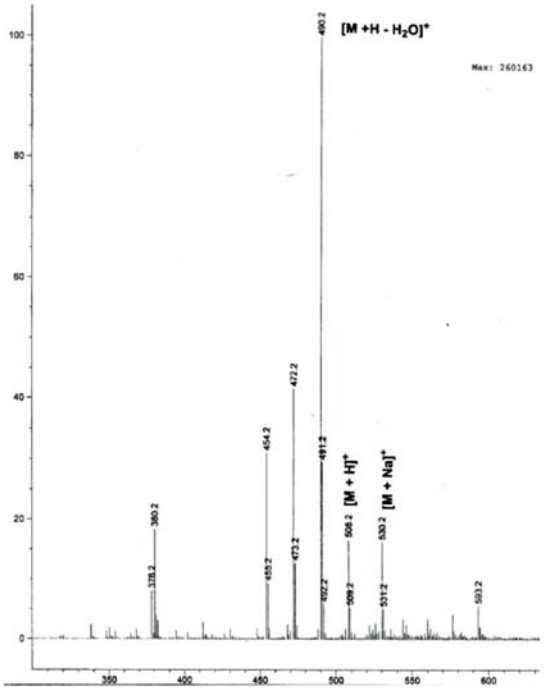
$C_{27}H_{40}NO_7$ $[M+H-H_2O]^+ = 490.3$

$C_{27}H_{42}NO_8$ $[M+H]^+ = 508.3$

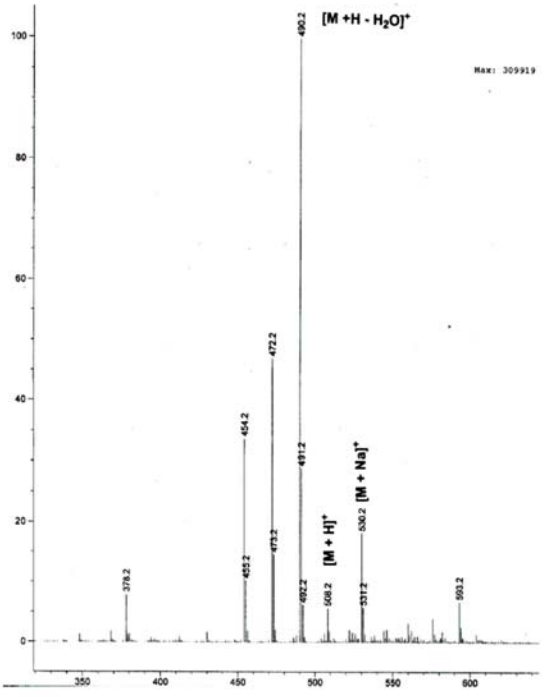
$C_{27}H_{41}NNaO_8$ $[M+Na]^+ = 530.3$



A

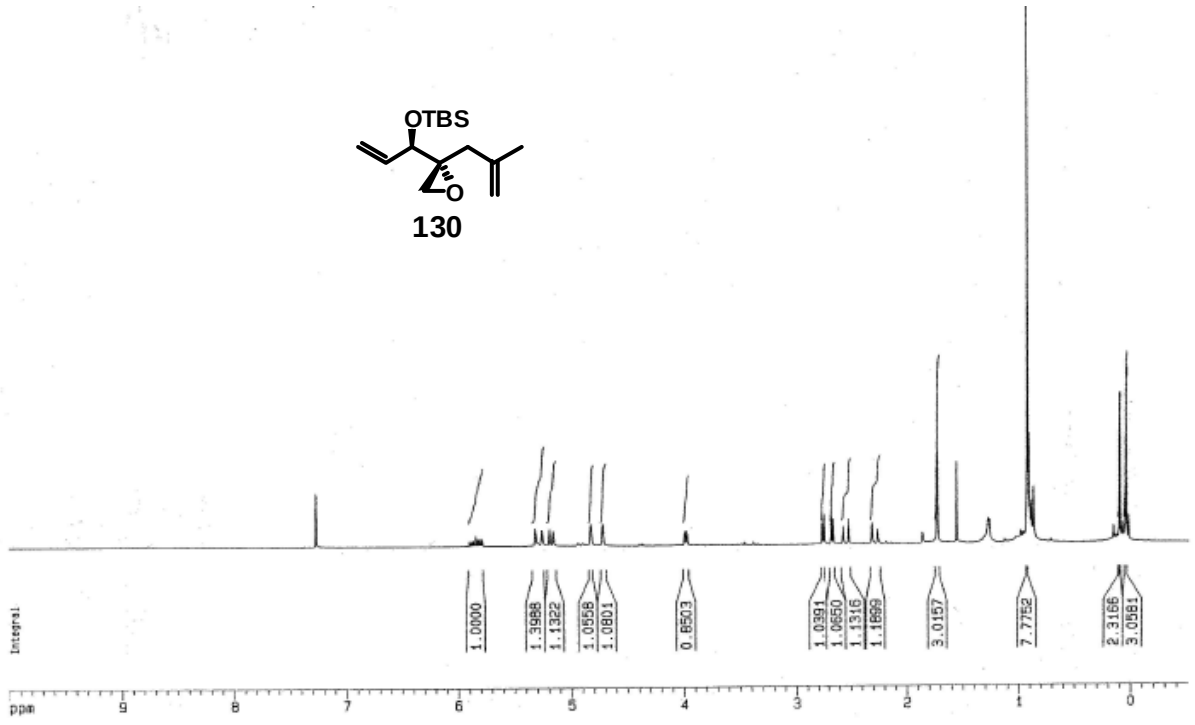


B

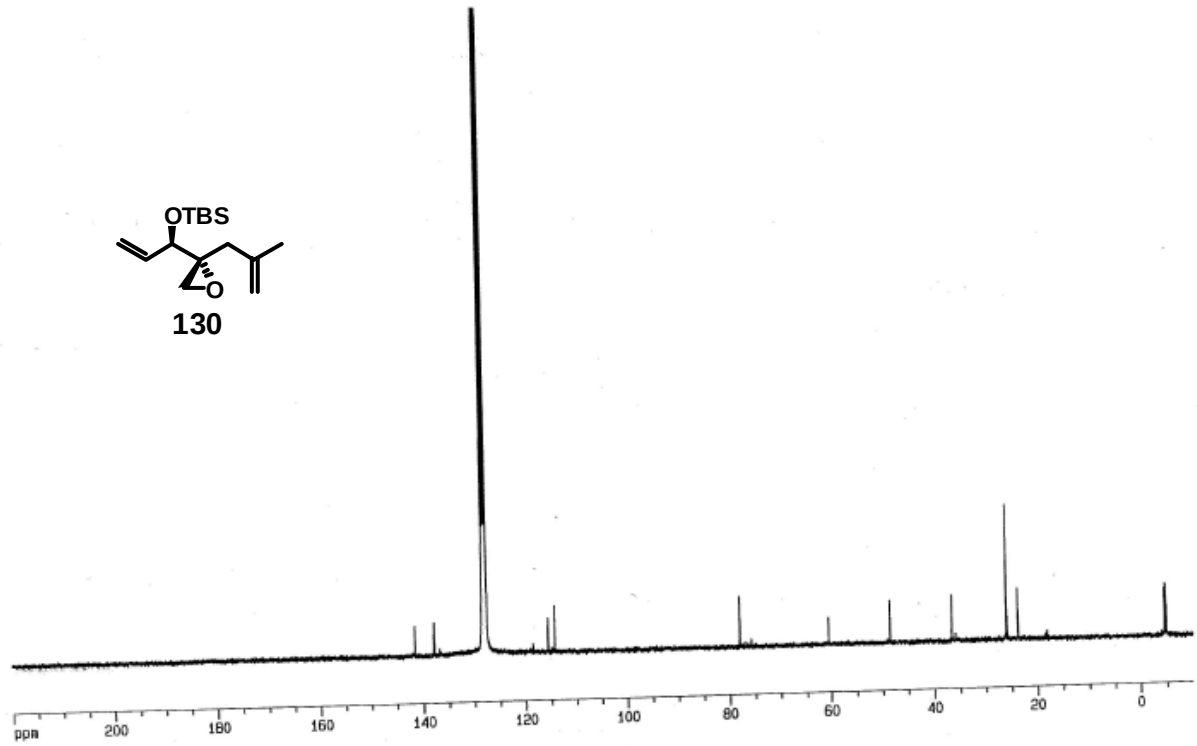


C

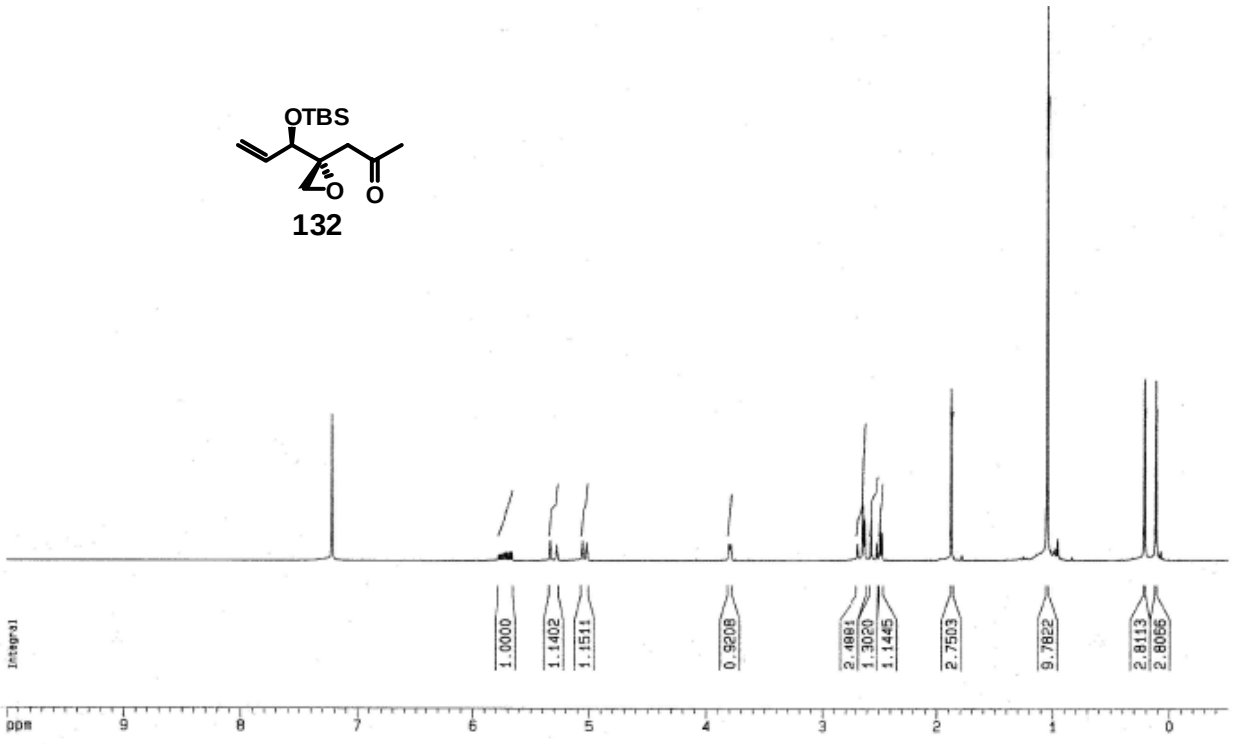
[1]**H NMR of 130**: $CDCl_3$, 293 K, 300 MHz



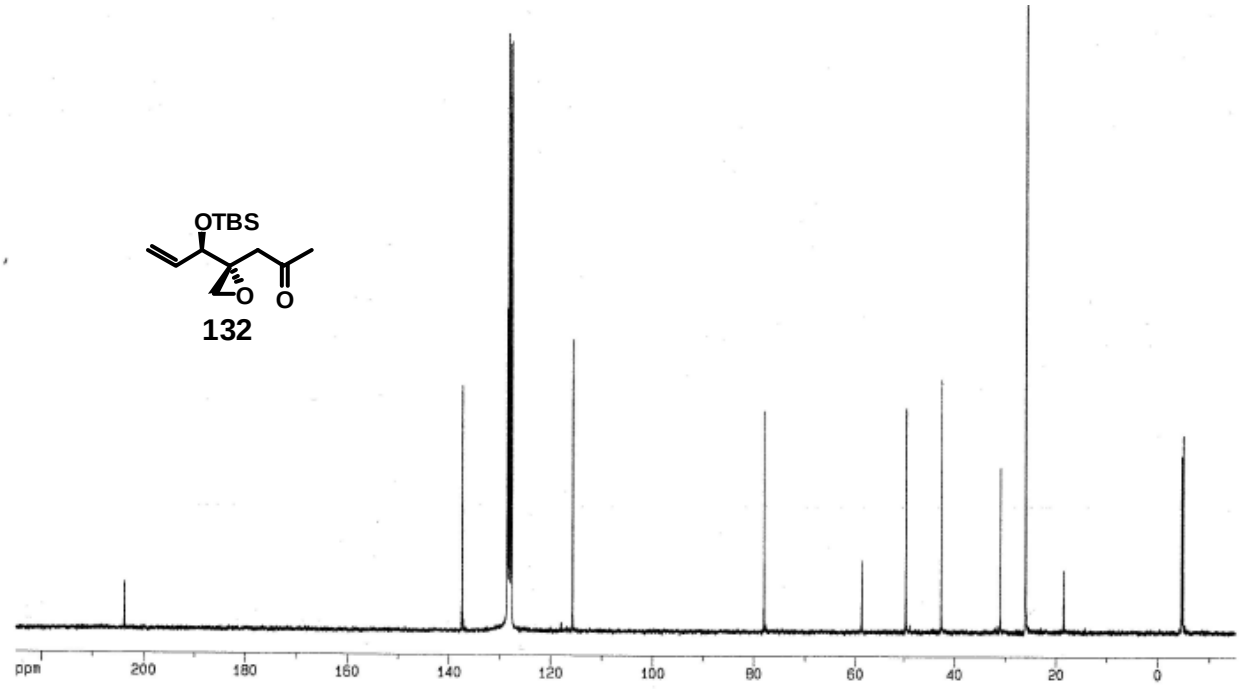
[13]**C NMR of 130**: C_6D_6, 293 K, 75 MHz



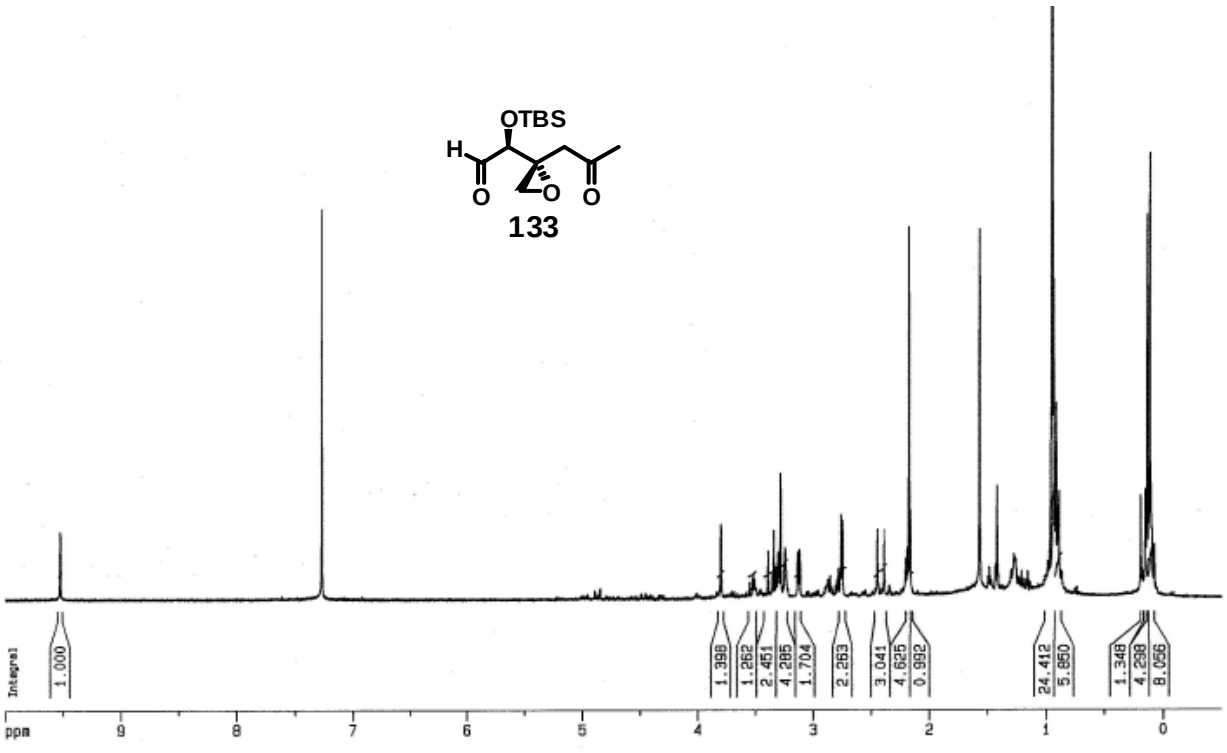
[1]**H NMR of 132**: $CDCl_3$, 293 K, 300 MHz



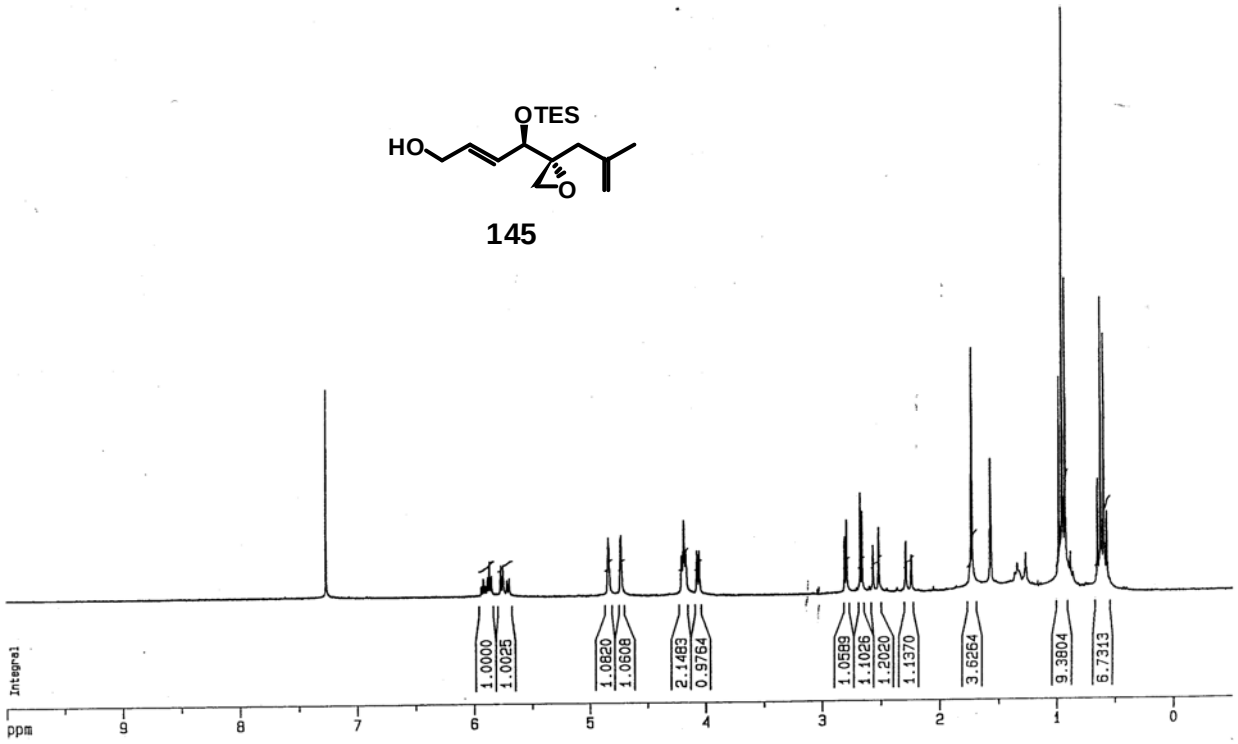
[13]**C NMR of 132**: C_6D_6, 293 K, 75 MHz



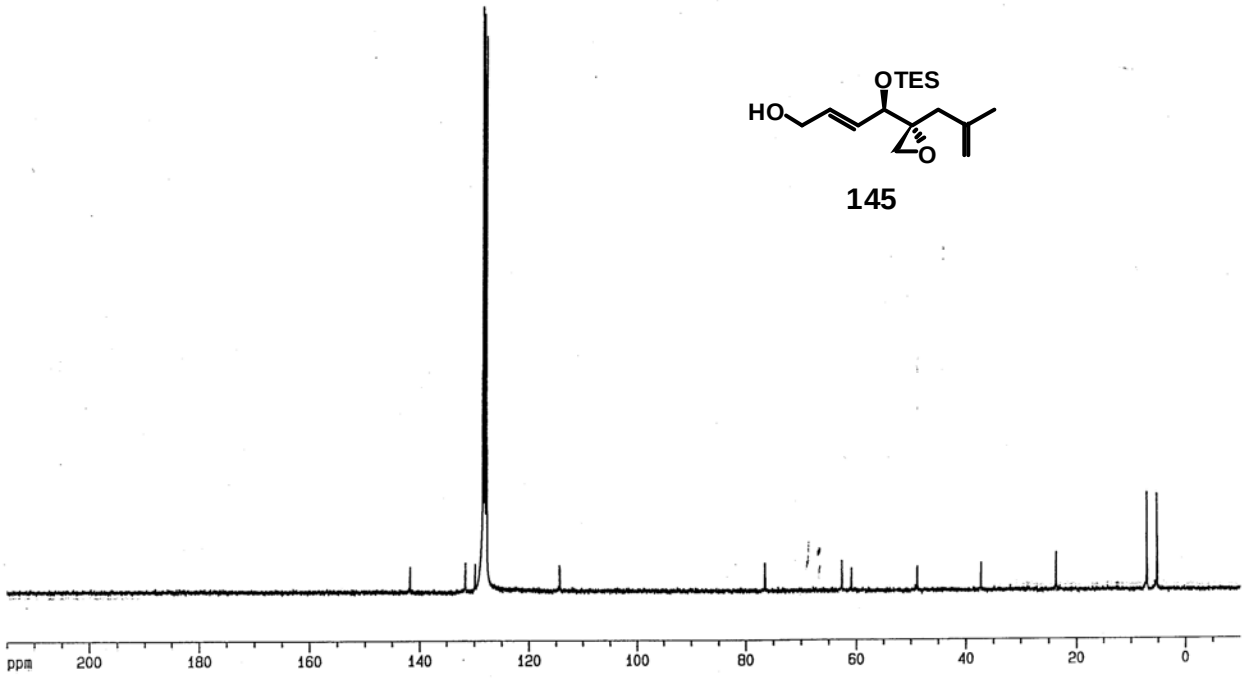
[1]**H NMR of 133**: $CDCl_3$, 293 K, 300 MHz



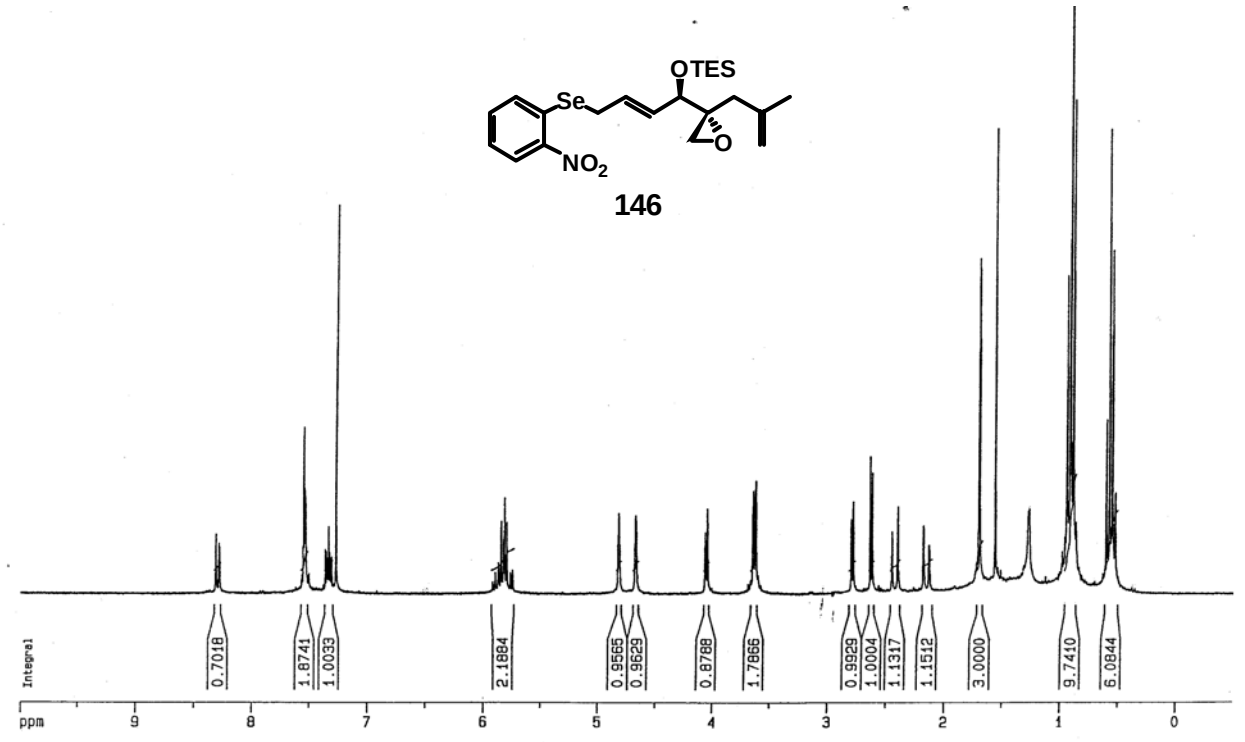
[1]**H NMR of 145**: $CDCl_3$, 293 K, 300 MHz



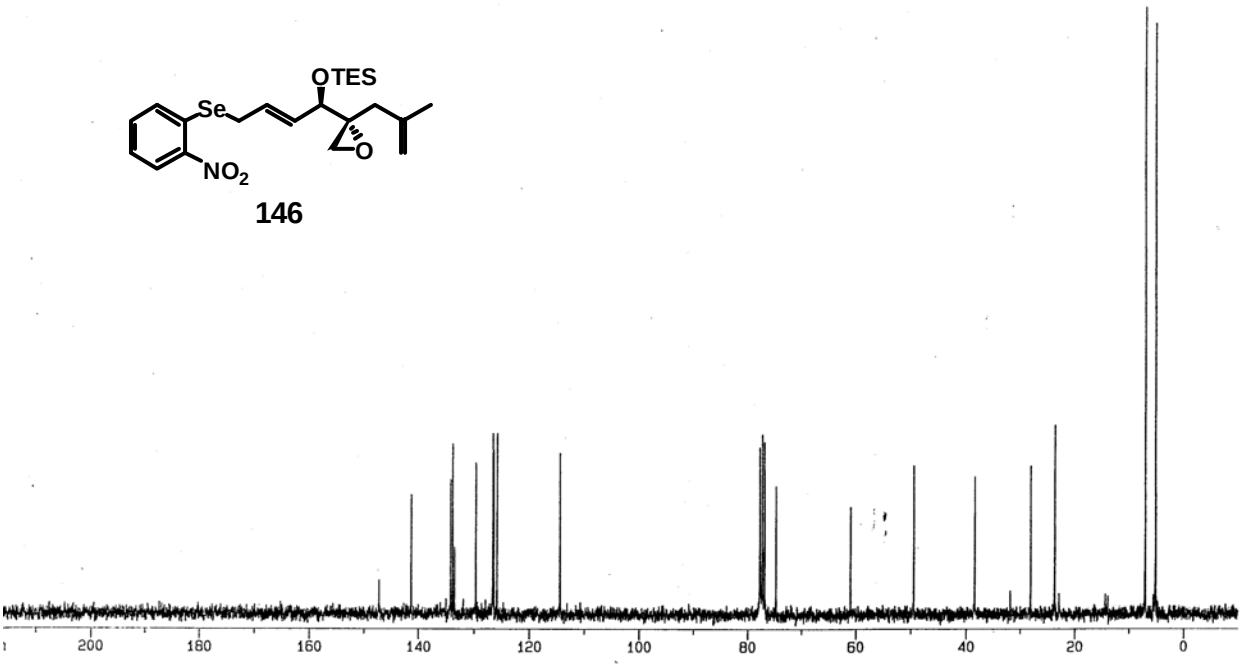
[13]**C NMR of 145**: C_6D_6, 293 K, 75 MHz



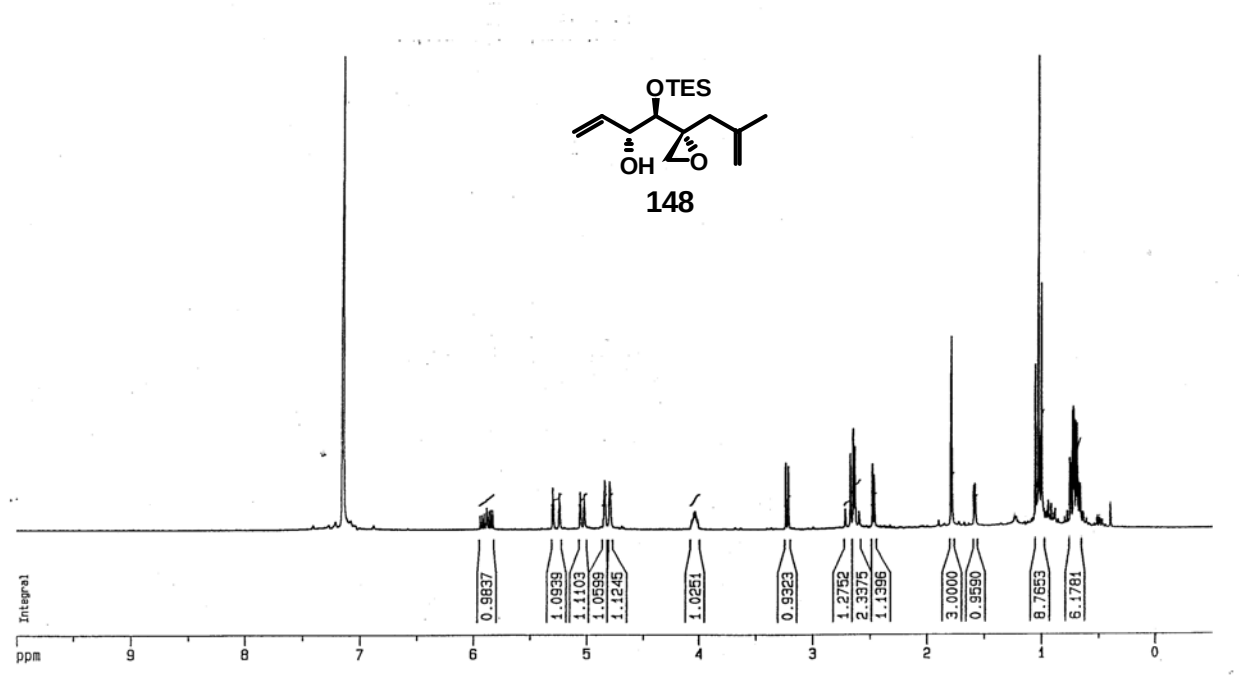
[1]**H NMR of 146**: $CDCl_3$, 293 K, 300 MHz



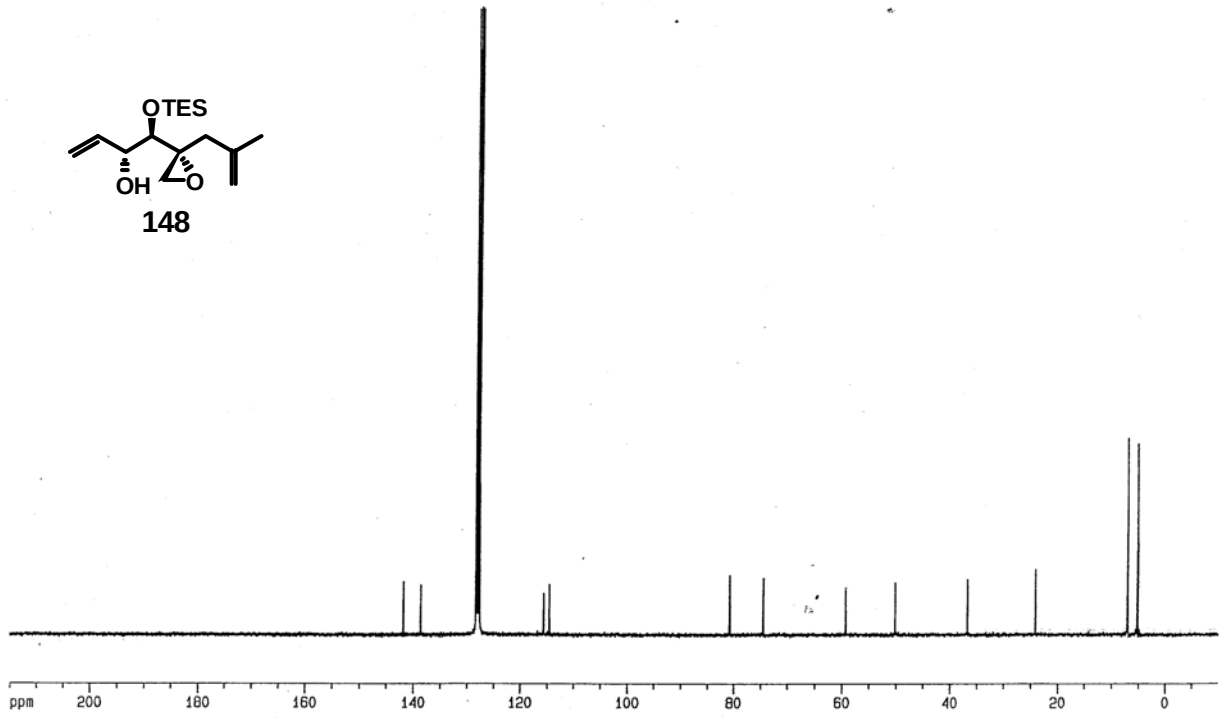
[13]**C NMR of 146**: $CDCl_3$, 293 K, 75 MHz



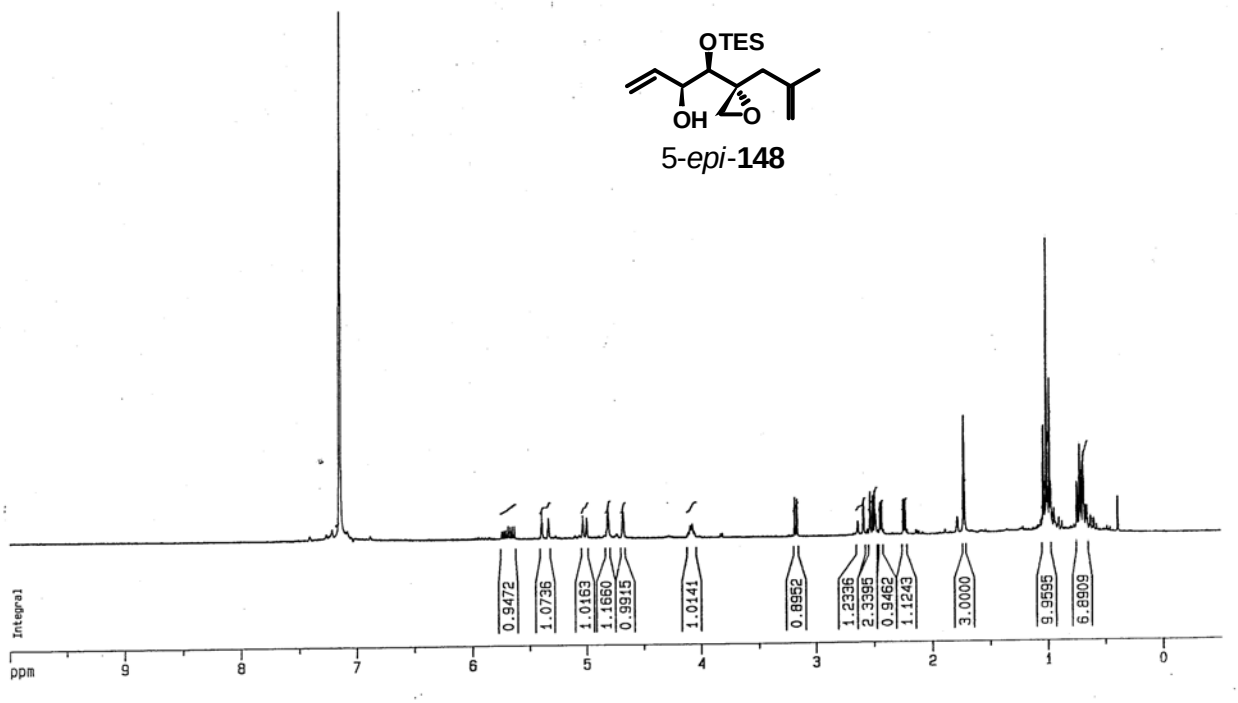
[1]**H NMR of 148**: C_6D_6, 293 K, 300 MHz



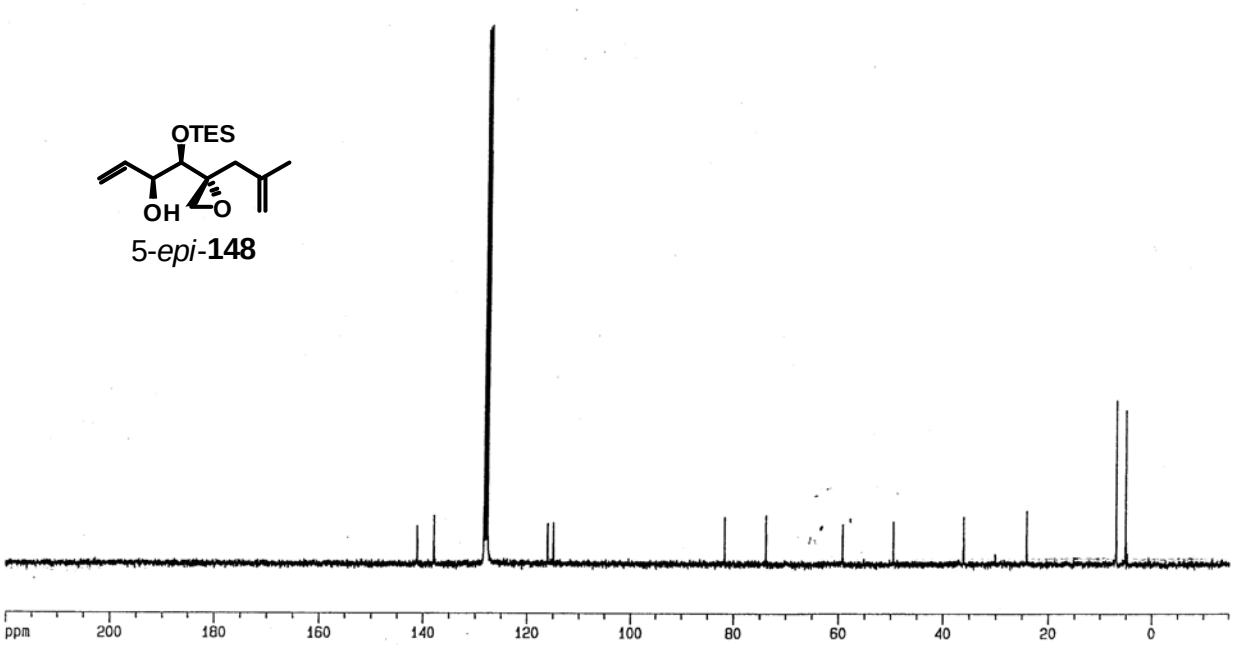
[13]**C NMR of 148**: C_6D_6, 293 K, 75 MHz



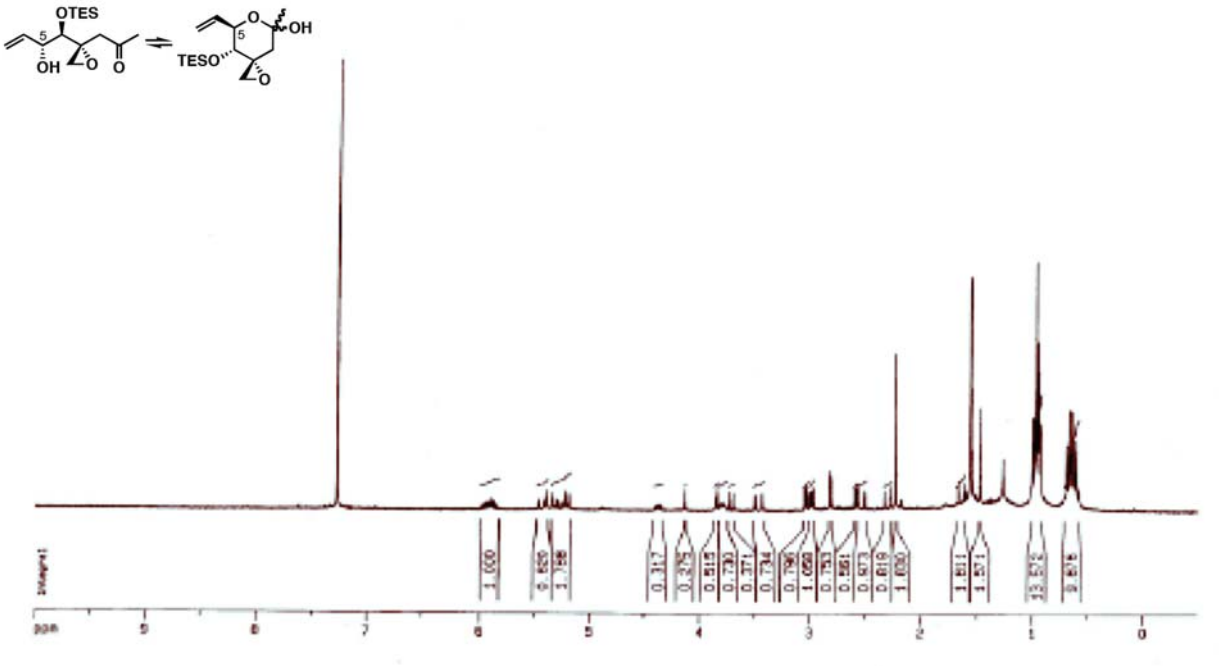
[1]**H NMR of 5-*epi*-148**: C_6D_6, 293 K, 300 MHz



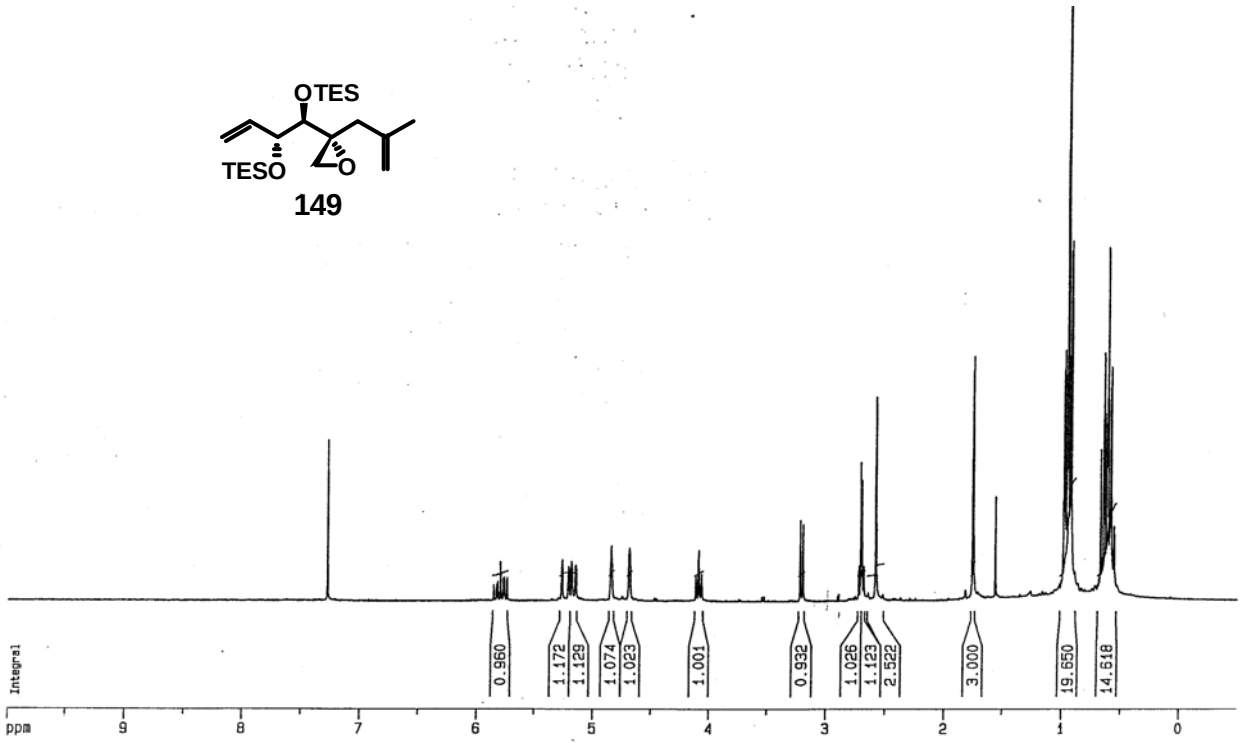
[13]**C NMR of 5-*epi*-148**: C_6D_6, 293 K, 75 MHz



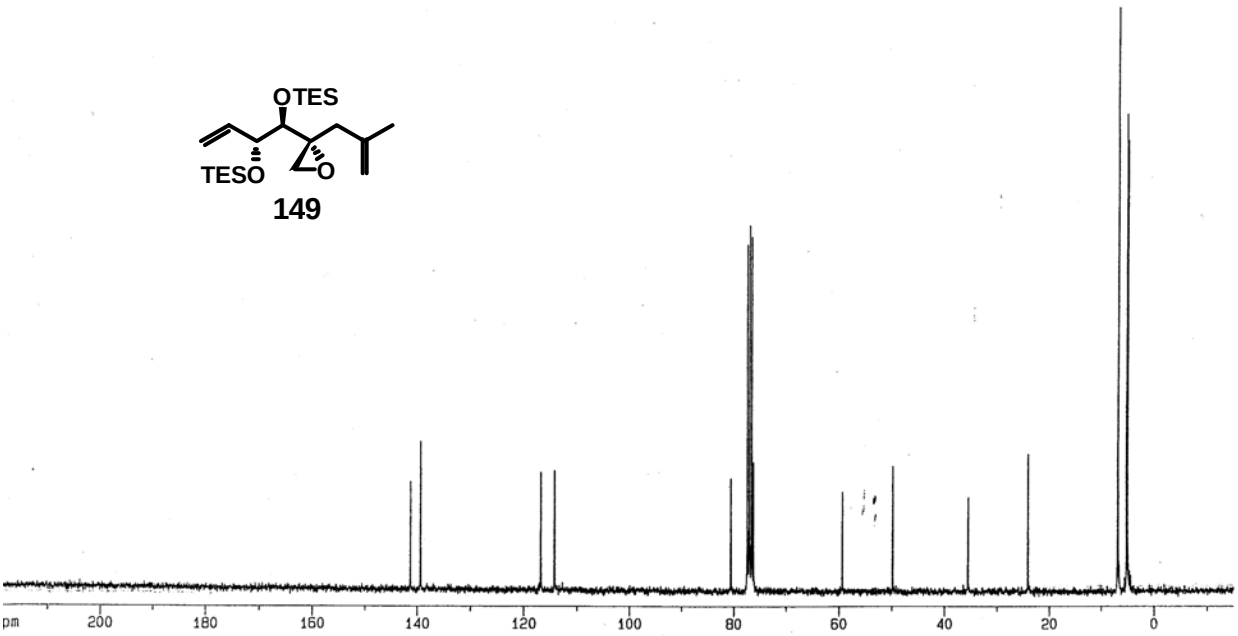
^{1}**H NMR of 128**: $CDCl_3$, 293 K, 300 MHz



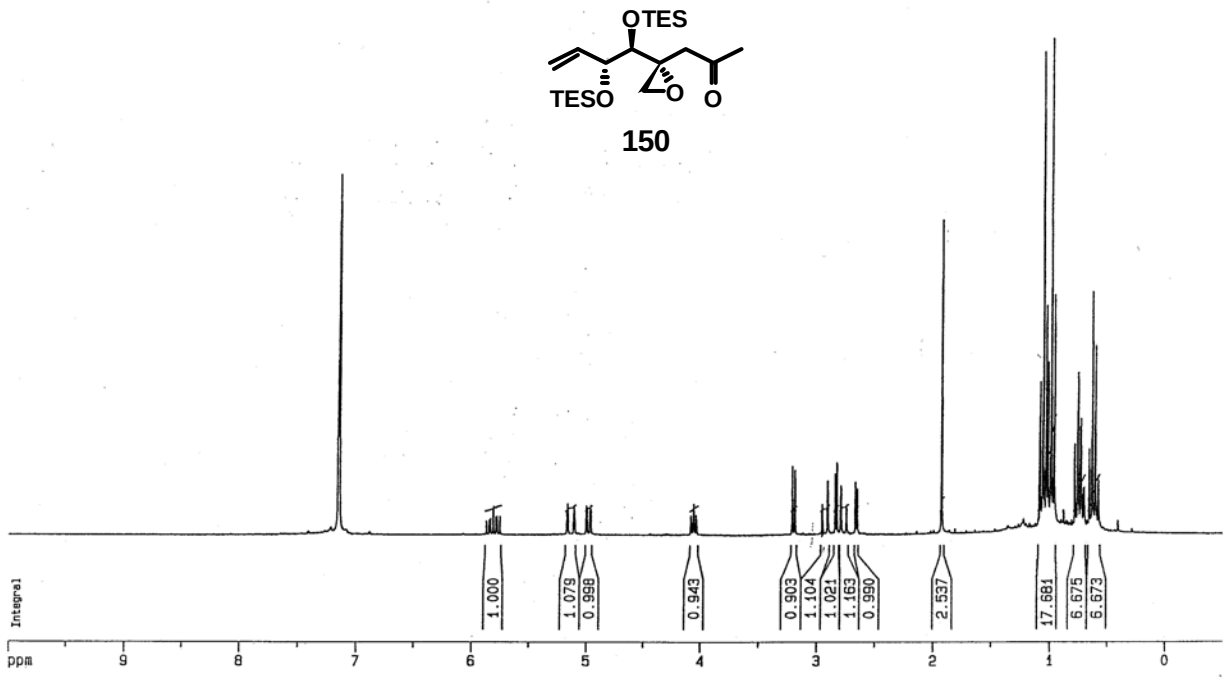
[1]**H NMR of 149**: $CDCl_3$, 293 K, 300 MHz



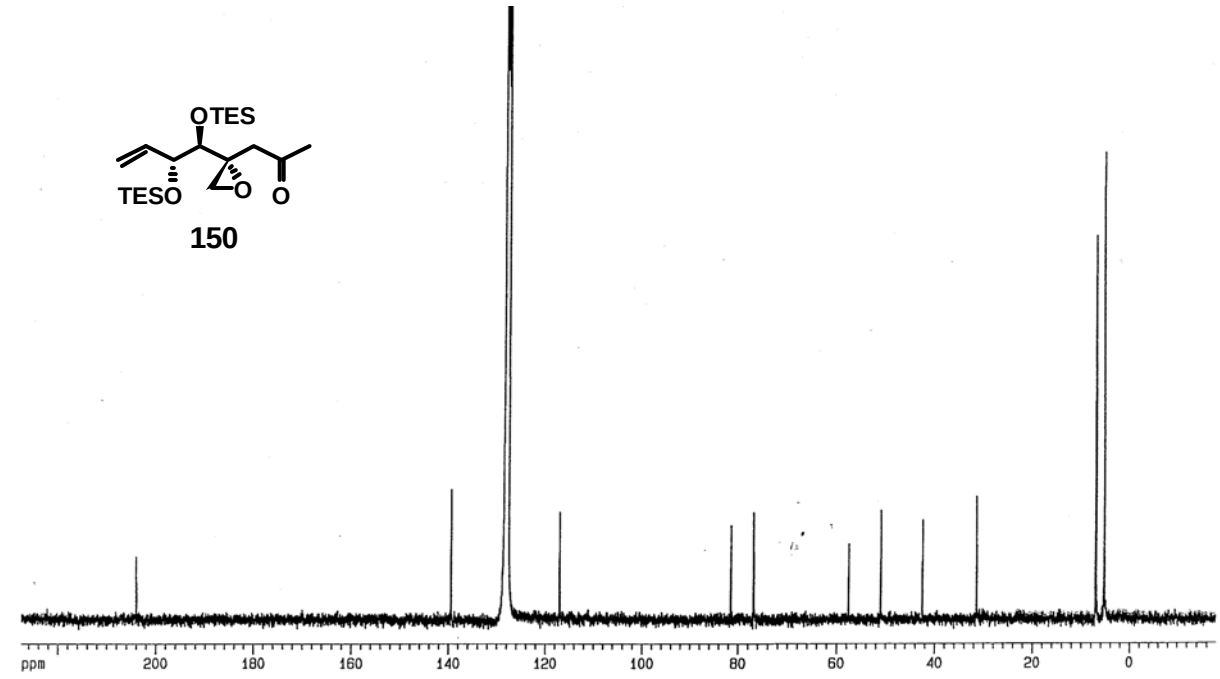
[13]**C NMR of 149**: $CDCl_3$, 293 K, 75 MHz



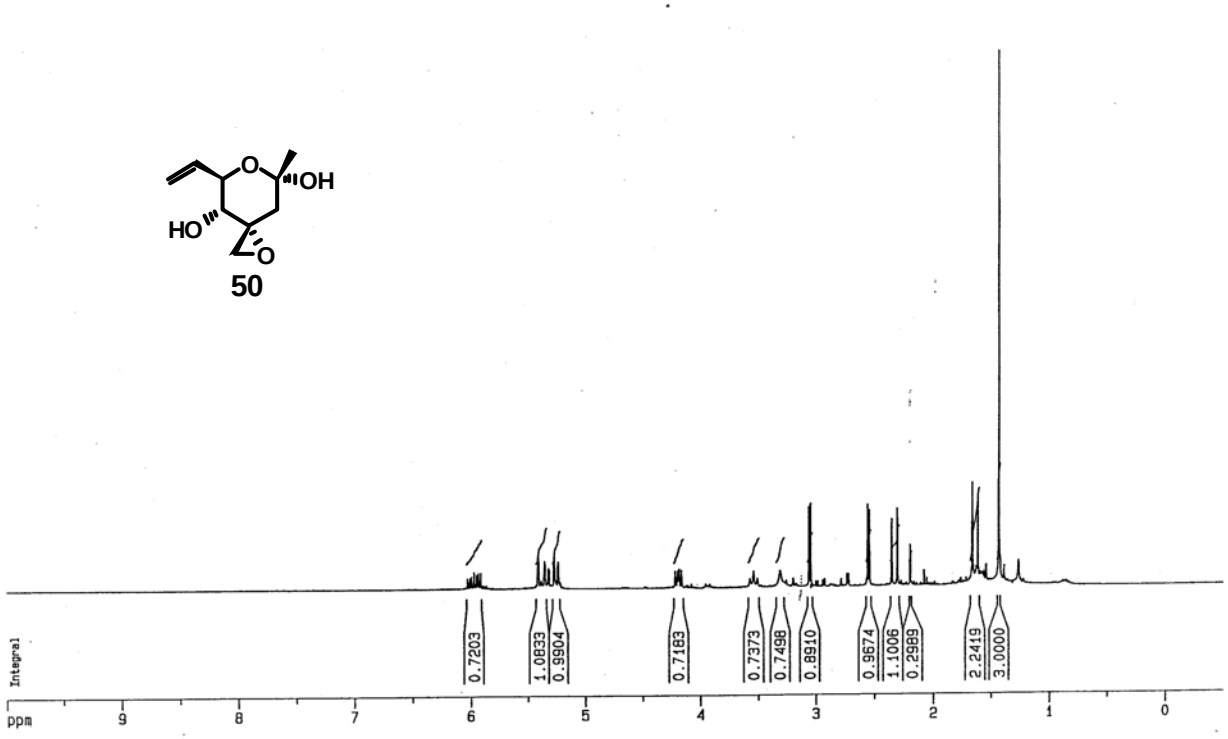
[1]**H NMR of 150**: C_6D_6, 293 K, 300 MHz



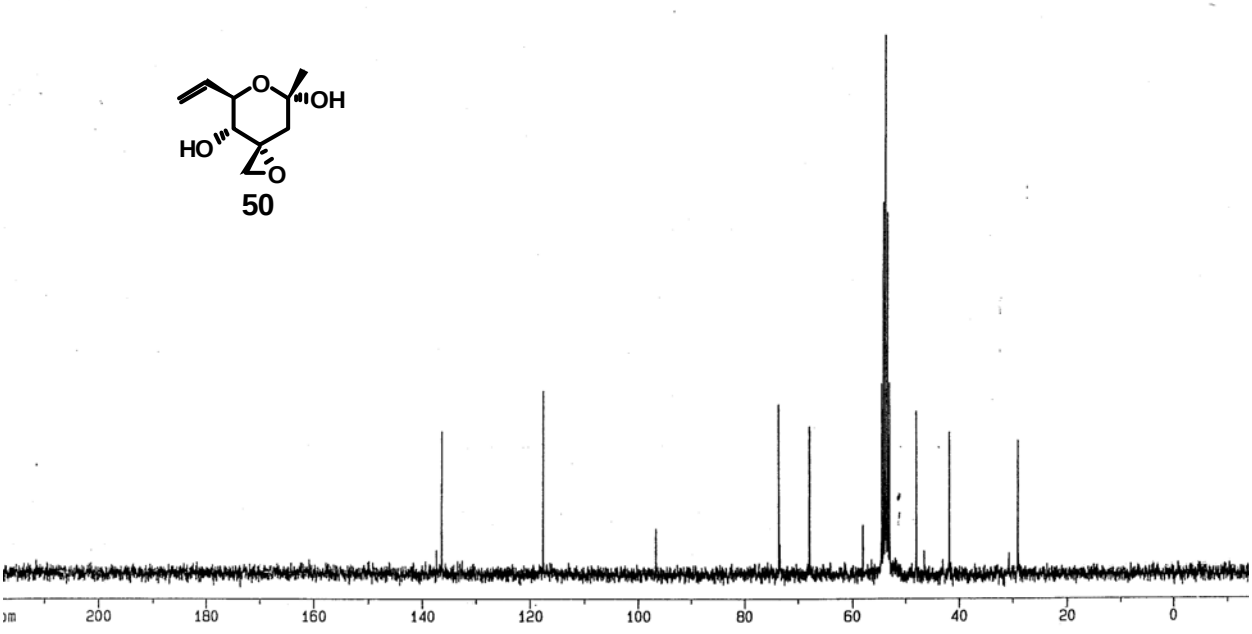
[13]**C NMR of 150**: C_6D_6, 293 K, 75 MHz



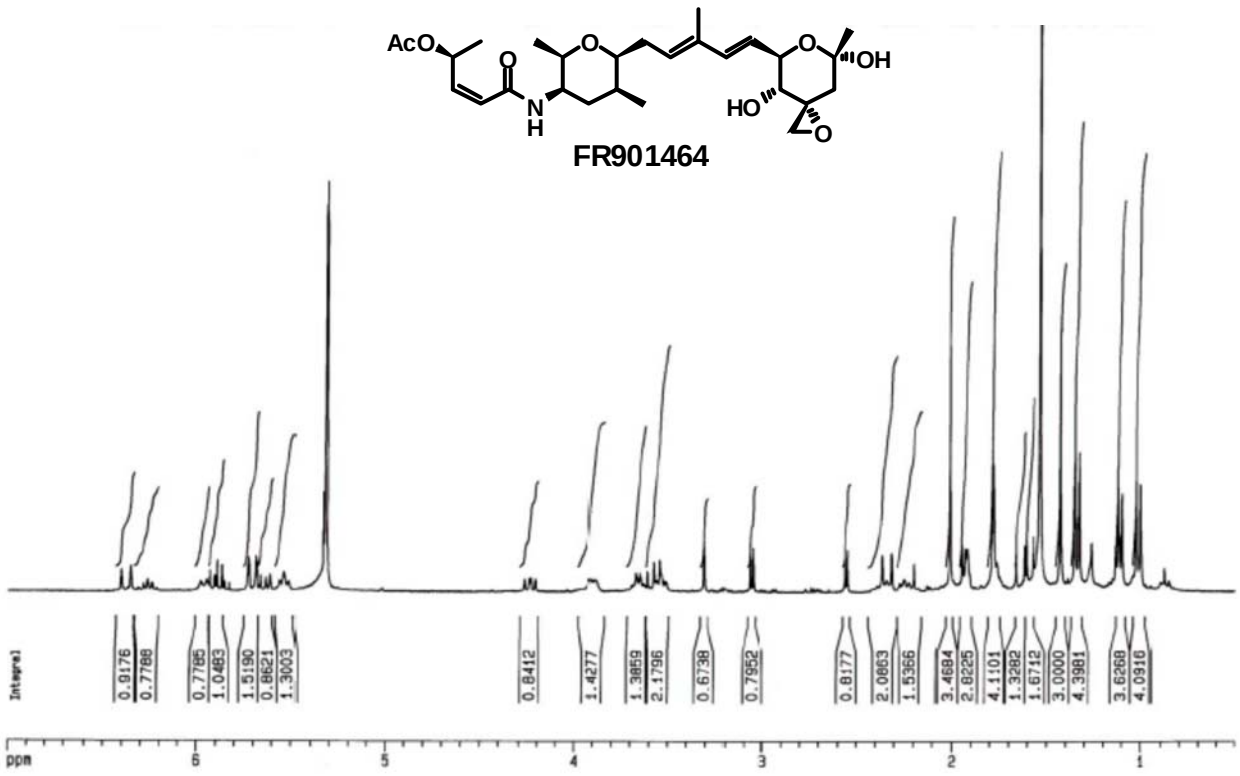
[1]**H NMR of 50**: CD_2Cl_2, 293 K, 300 MHz



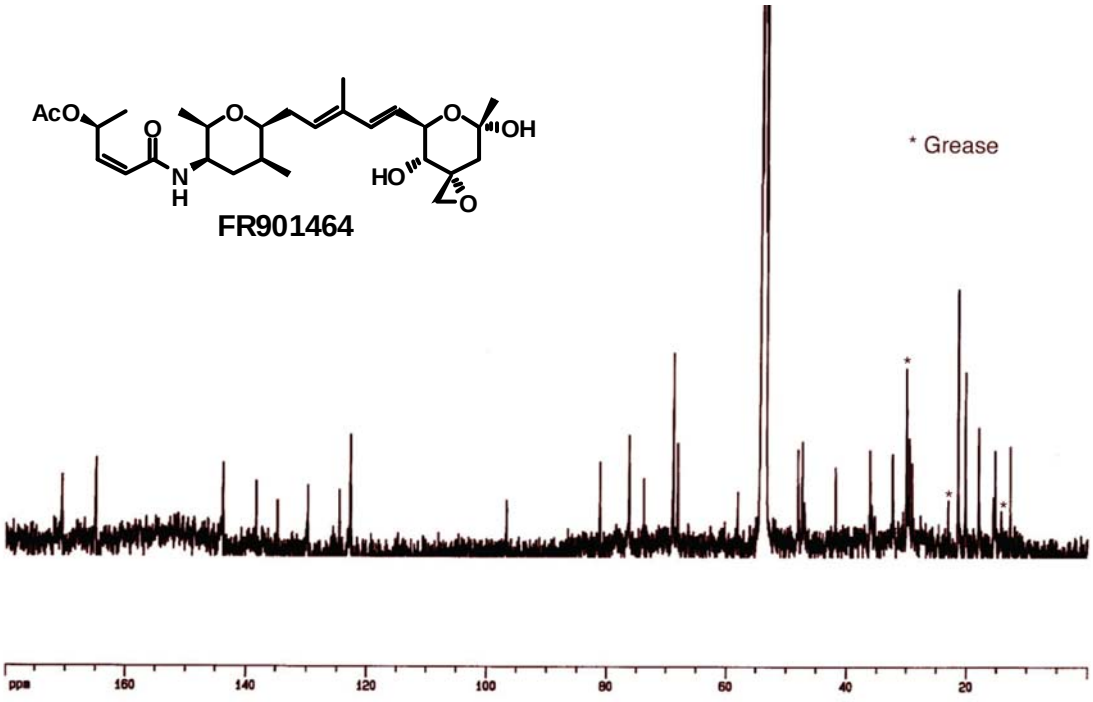
[13]**C NMR of 50**: CD_2Cl_2, 293 K, 75 MHz



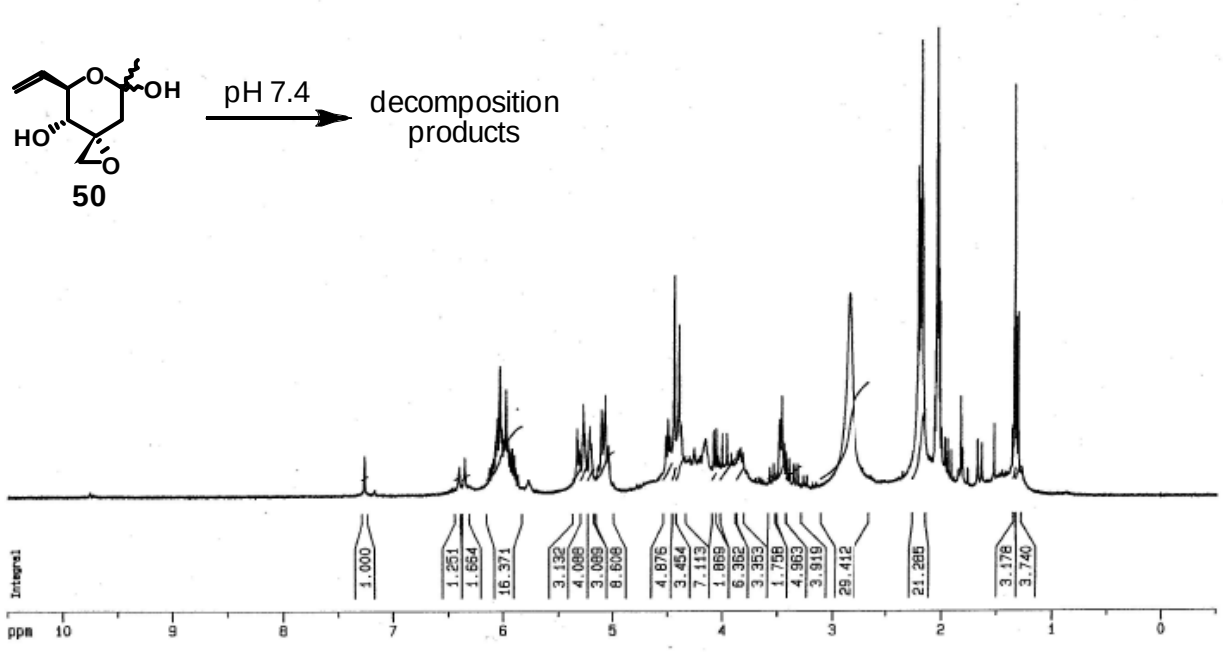
[1]**H NMR of FR901464**: CD_2Cl_2, 293 K, 500 MHz



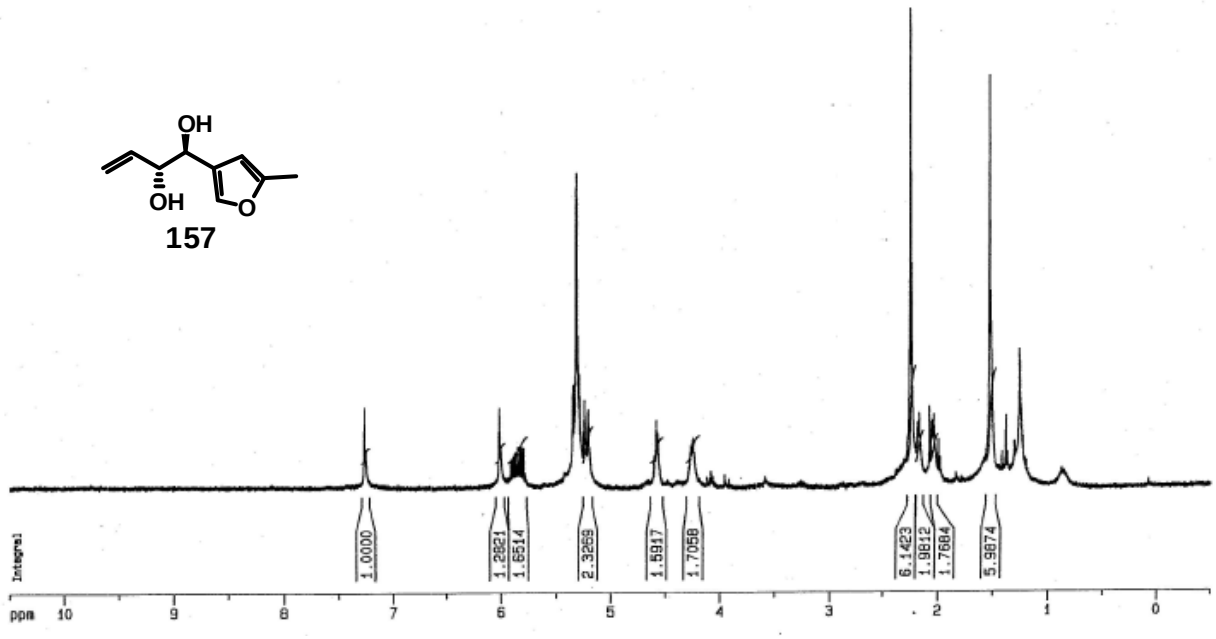
[13]**C NMR of FR901464**: CD_2Cl_2, 293 K, 125 MHz



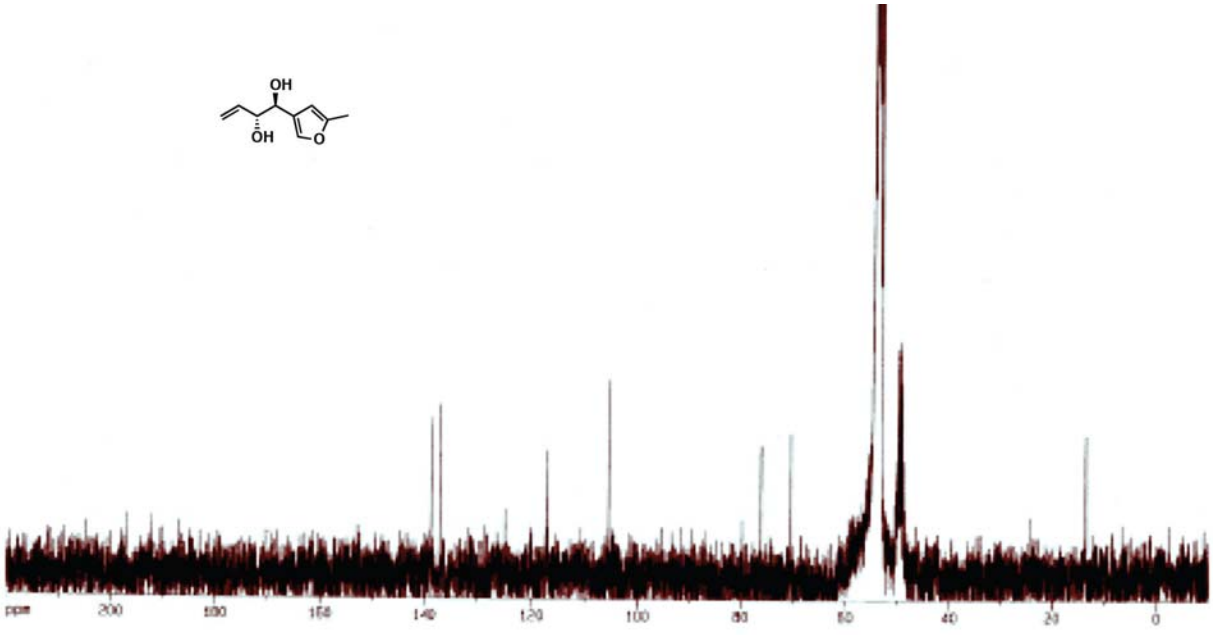
Crude ^{1}H NMR of the decomposition of 50: acetone-d_6, 293 K, 300 MHz



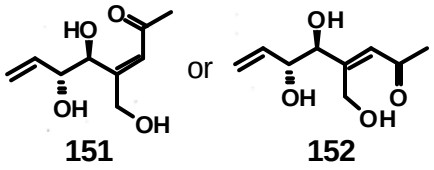
[1]**H NMR of 157**: CD_2Cl_2, 293 K, 300 MHz



[13]**C NMR of 157**: CD_2Cl_2, 293 K, 75 MHz

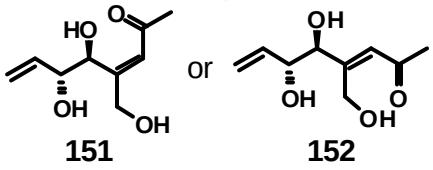


[1]**H NMR of 151 or 152 (B)**: CD_2Cl_2, 293 K, 300 MHz



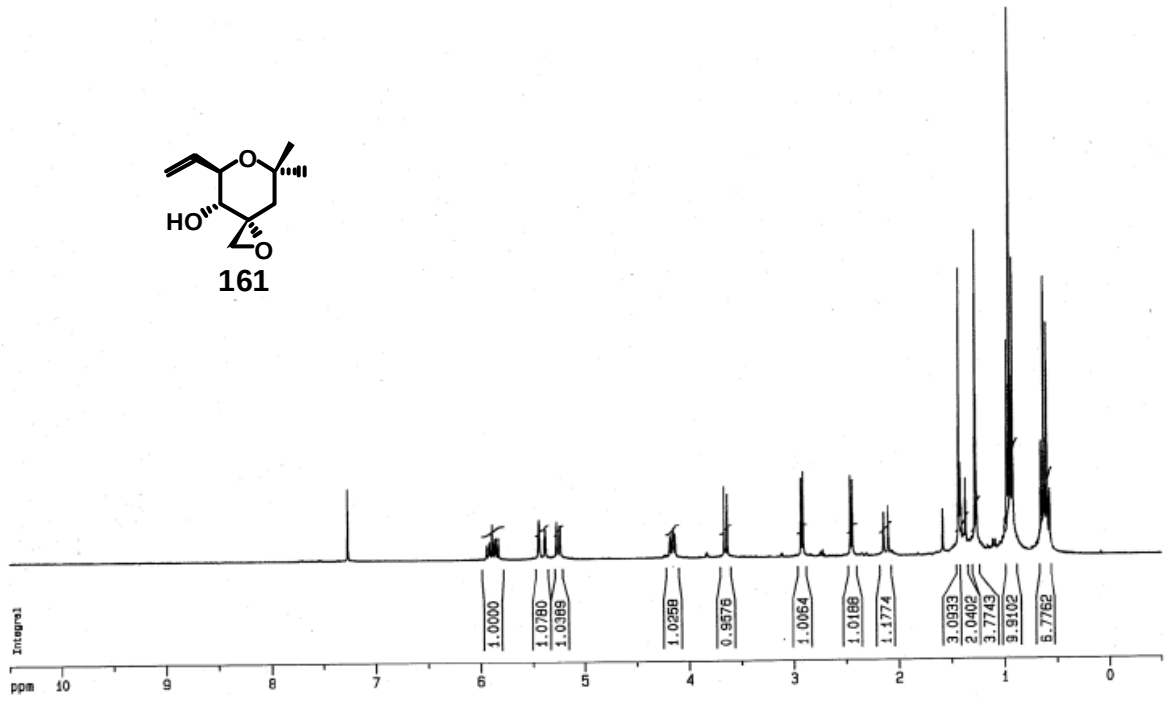
151 **152**

[1]**H NMR of 151 or 152 (C)**: CD_2Cl_2, 293 K, 300 MHz

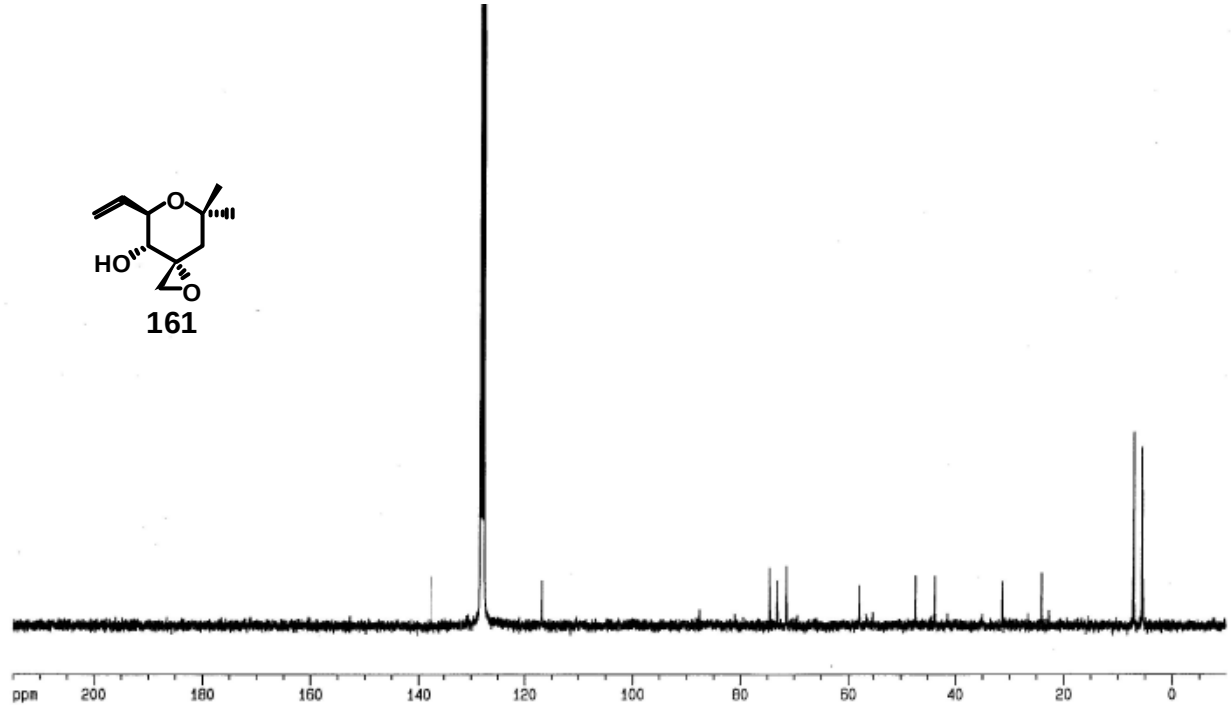


151 **152**

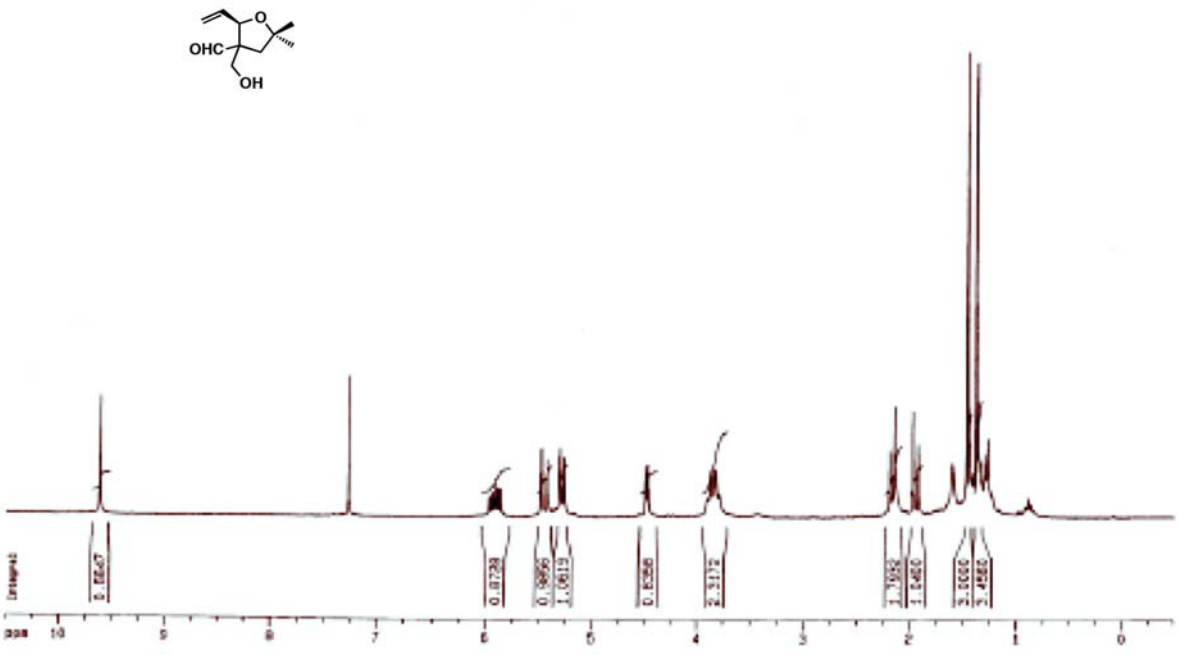
[1]**H NMR of 161**: $CDCl_3$, 293 K, 300 MHz



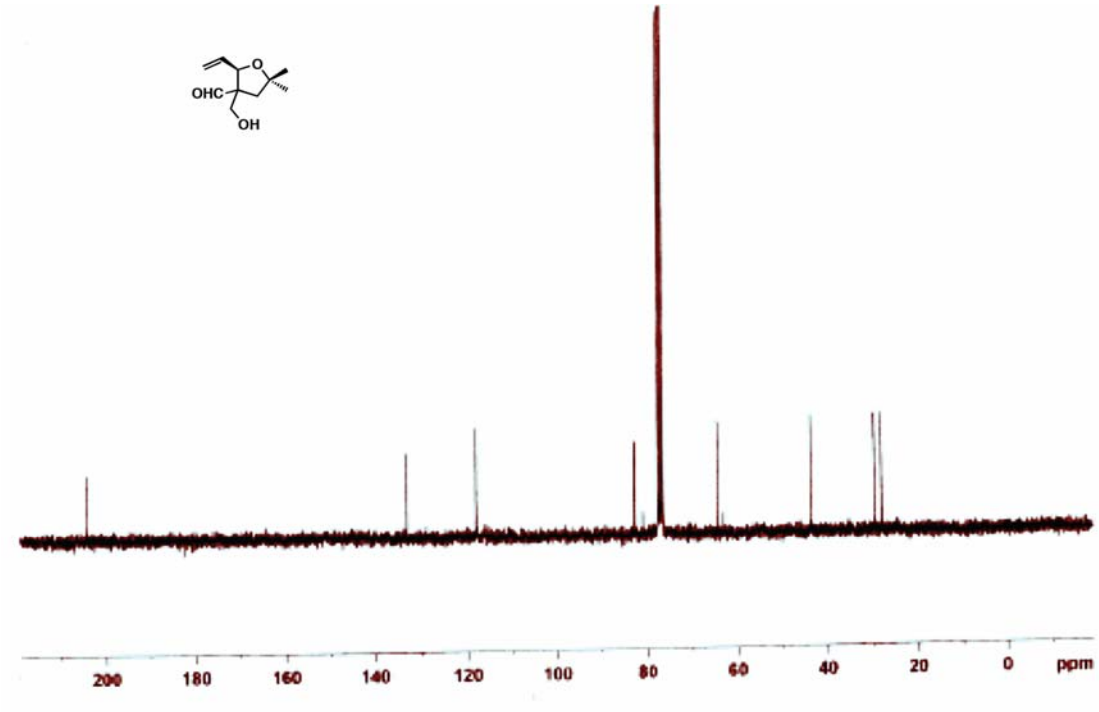
[13]**C NMR of 161**: C_6D_6, 293 K, 75 MHz



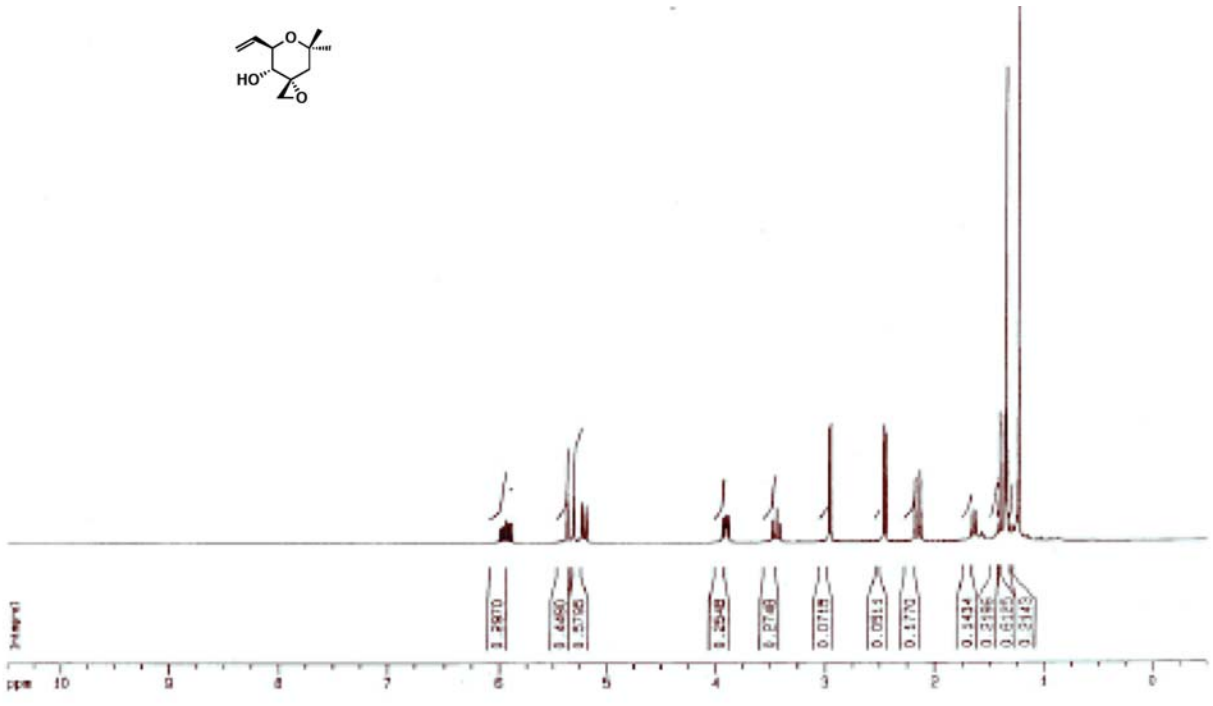
[1]**H NMR of 163**: $CDCl_3$, 293 K, 300 MHz



[13]**C NMR of 163**: $CDCl_3$, 293 K, 75 MHz

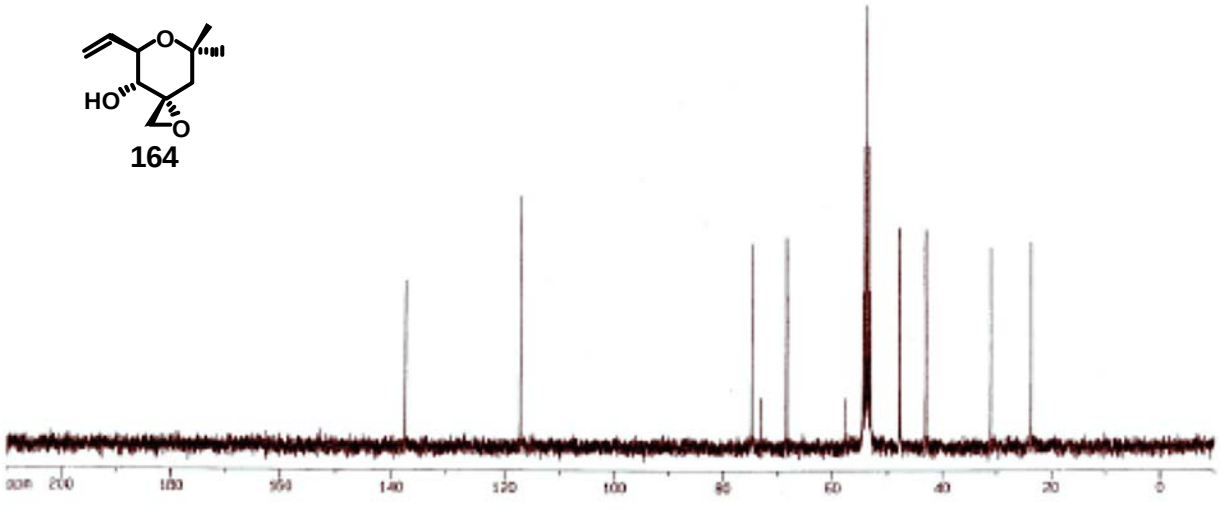


[1]**H NMR of 164**: CD_2Cl_2, 293 K, 300 MHz

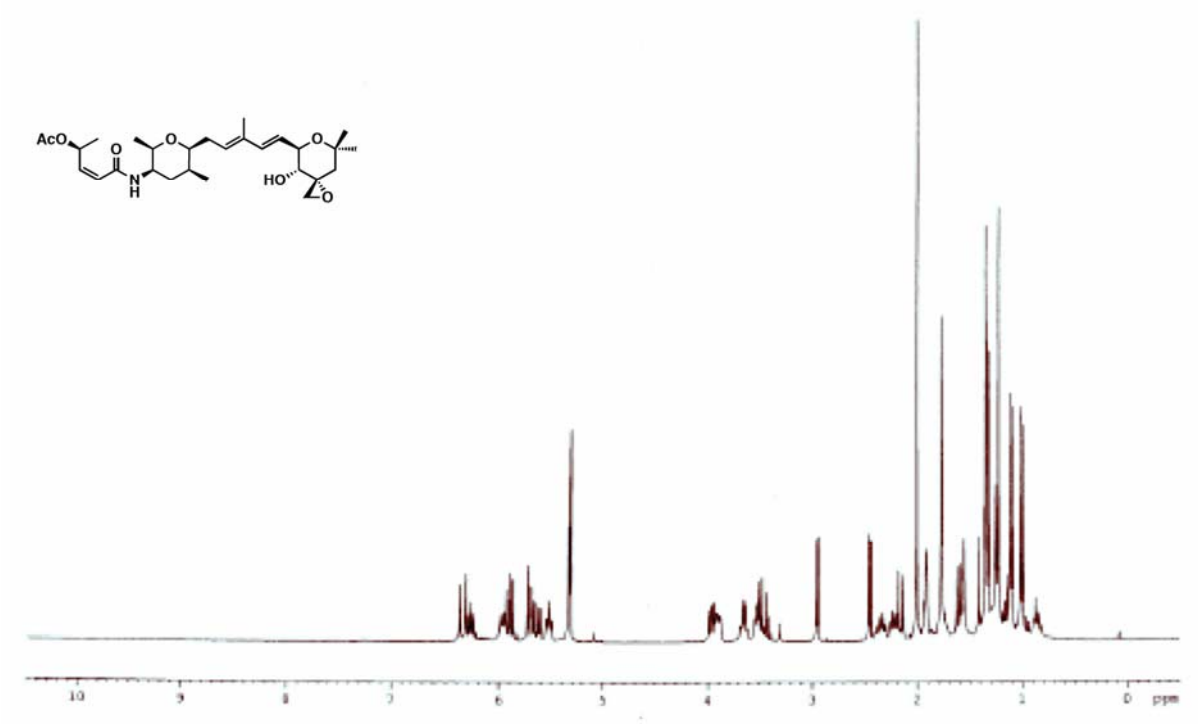


[13]**C NMR of 164**: CD_2Cl_2, 293 K, 75 MHz

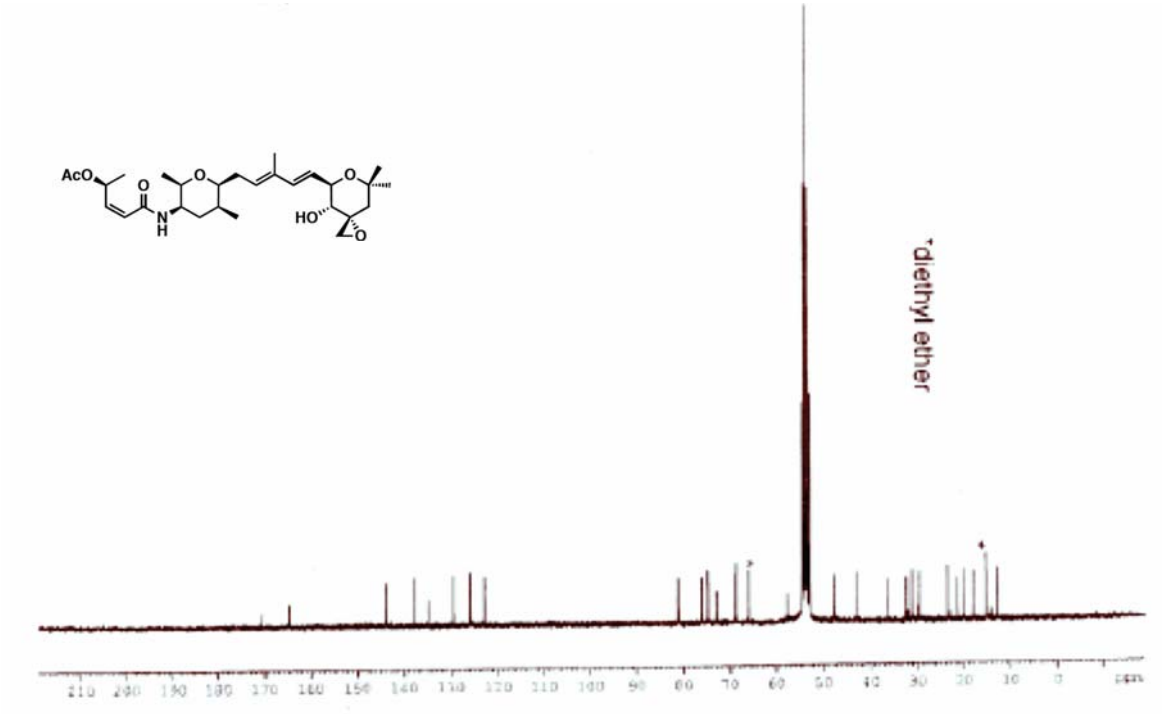
164



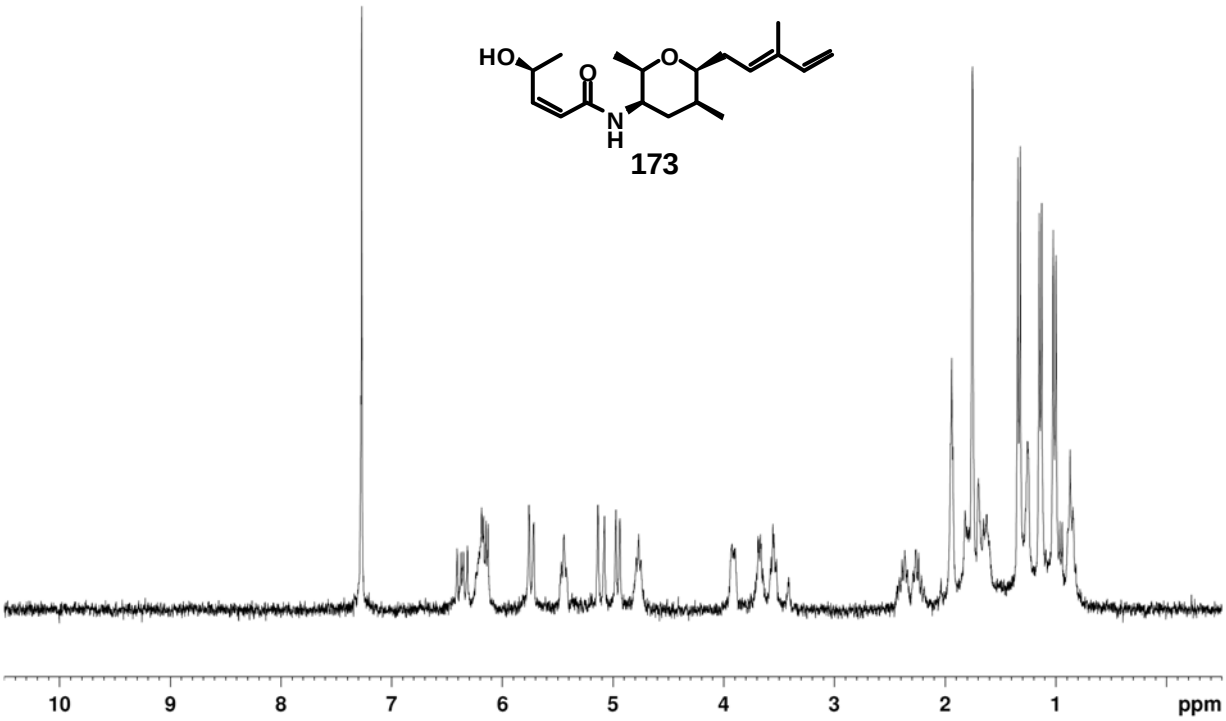
^{1}H NMR of 165 (meayamycin): CD_2Cl_2, 293 K, 300 MHz



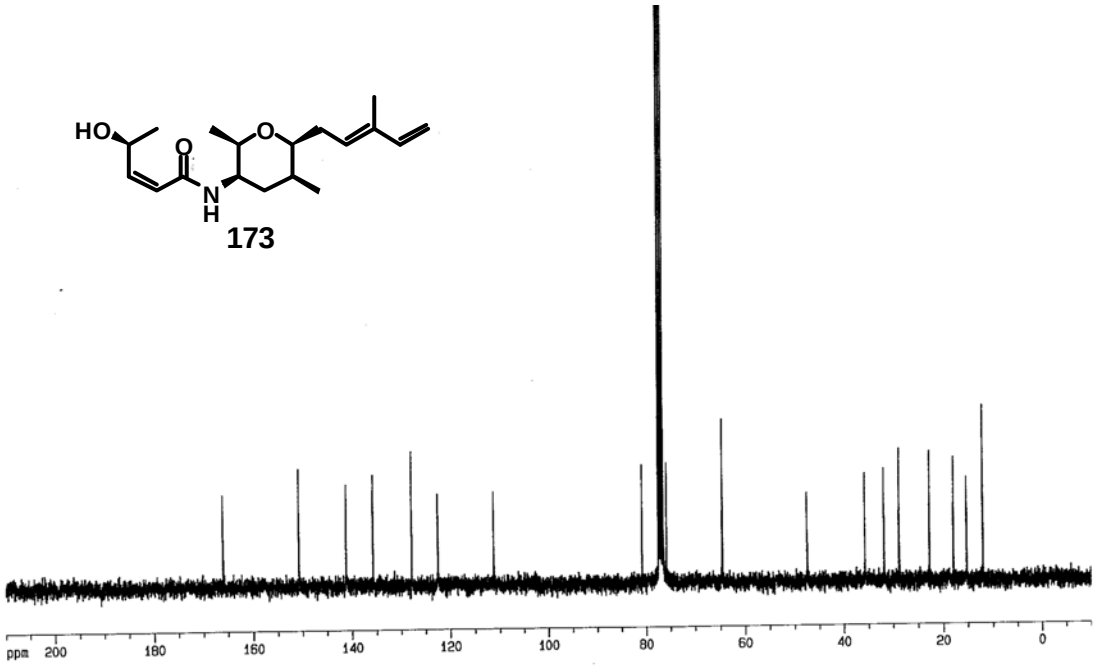
^{13}C NMR of 165 (meayamycin): CD_2Cl_2, 293 K, 75 MHz



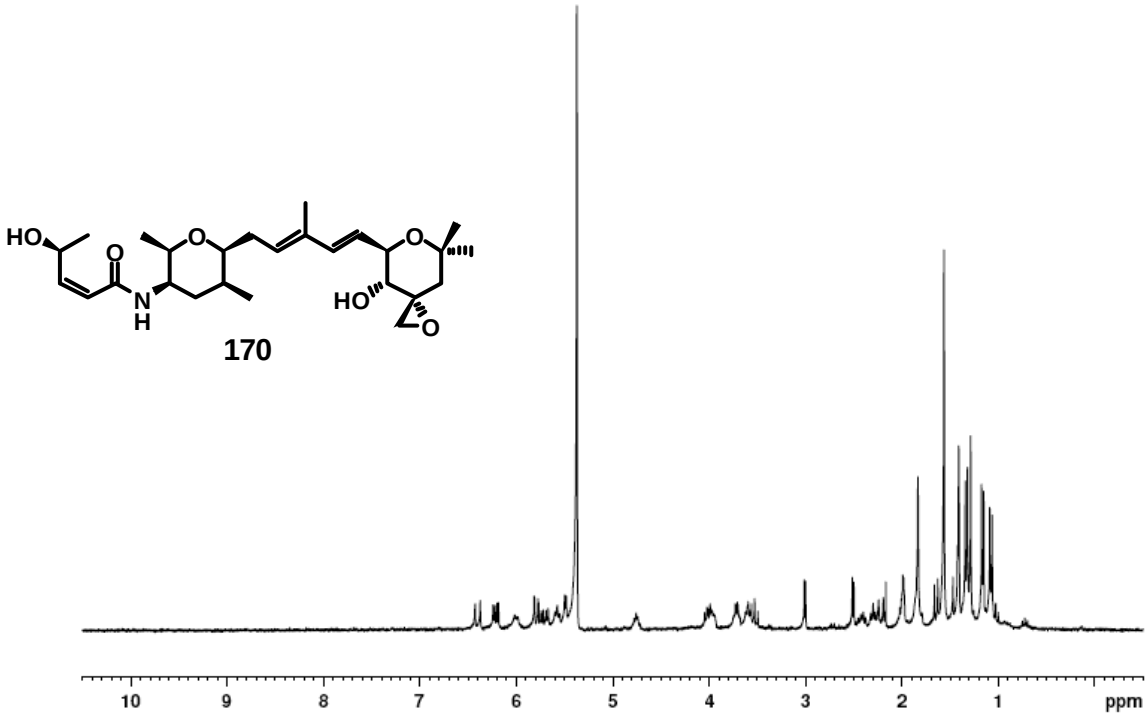
[1]**H NMR of 173**: 1% CD_3OD in $CDCl_3$, 293 K, 300 MHz



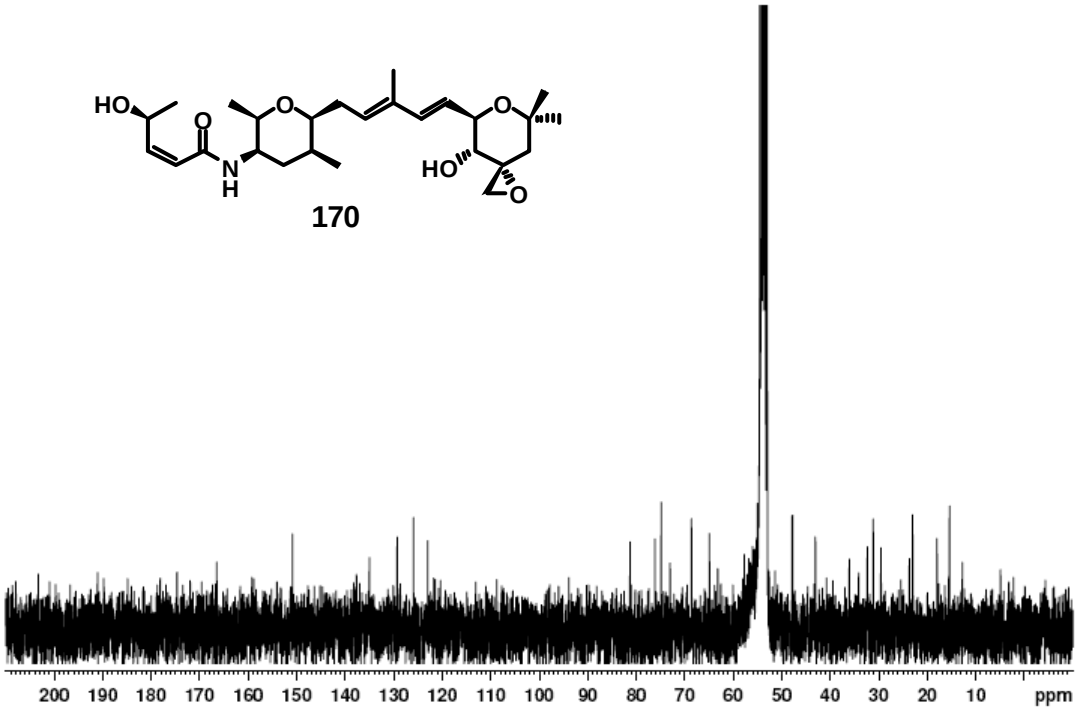
[13]**C NMR of 173**: $CDCl_3$, 293 K, 125 MHz



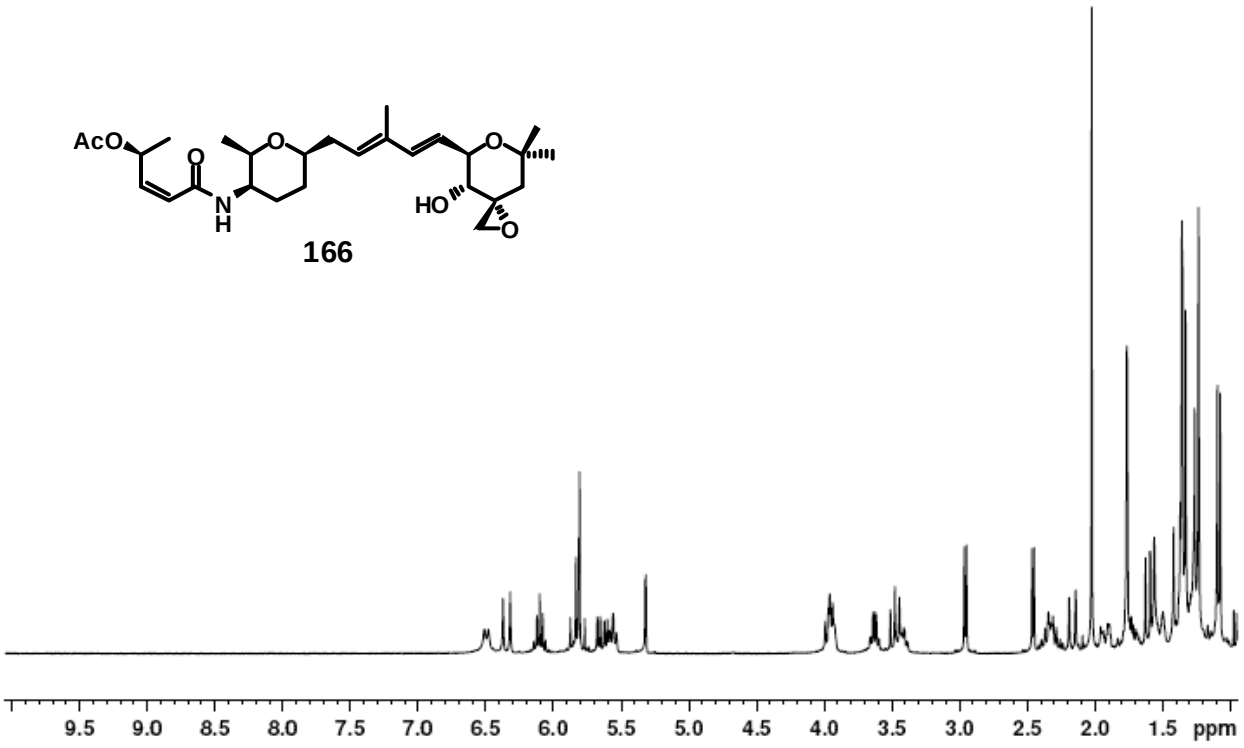
[1]**H NMR of 170**: CD_2Cl_2, 293 K, 300 MHz



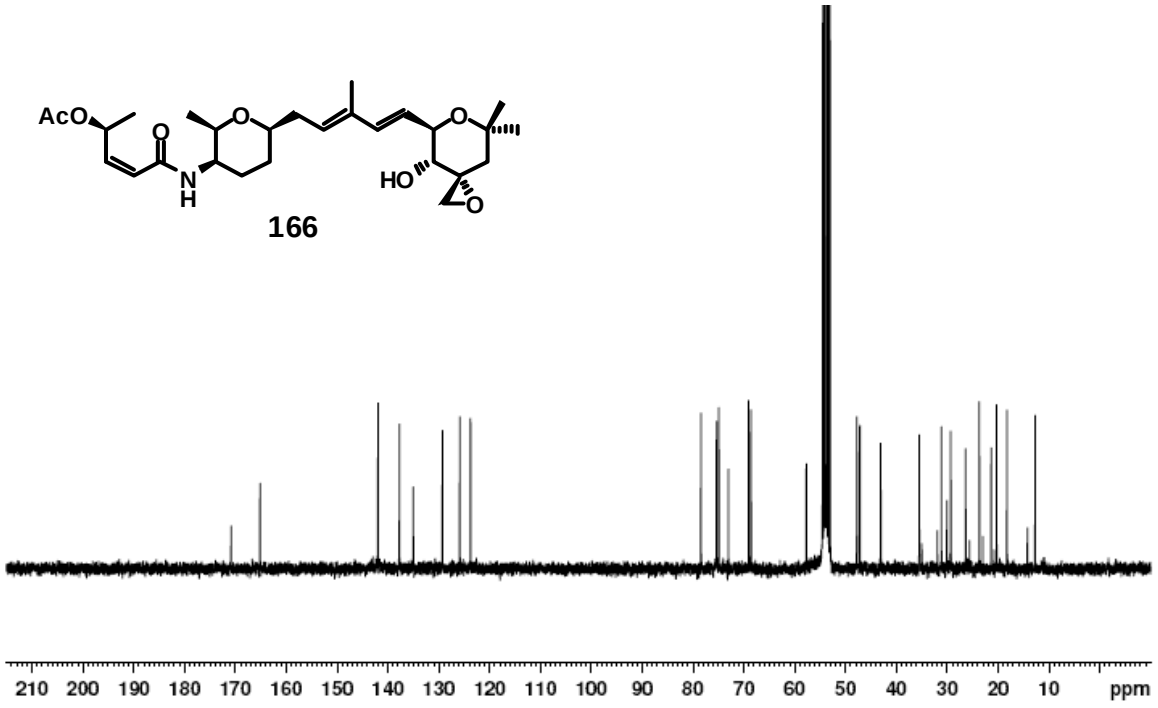
[13]**C NMR of 170**: CD_2Cl_2, 293 K, 125 MHz



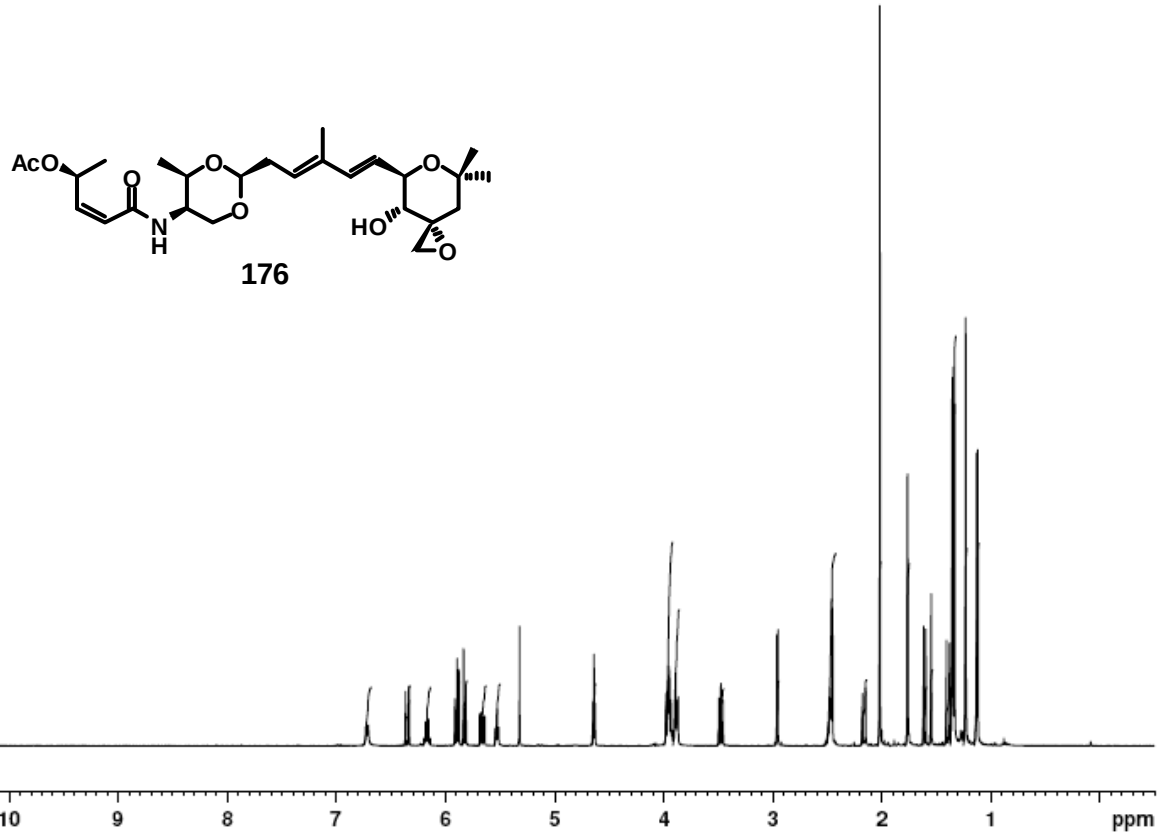
[1]**H NMR of 166**: CD_2Cl_2, 293 K, 500 MHz



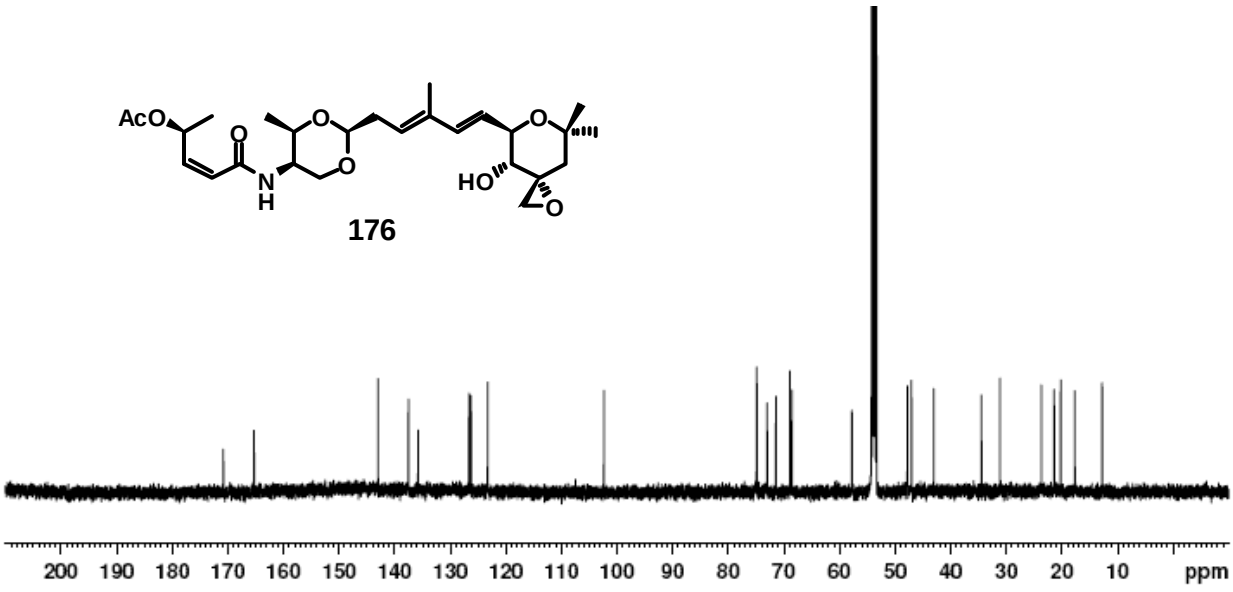
[13]**C NMR of 166**: CD_2Cl_2, 293 K, 125 MHz



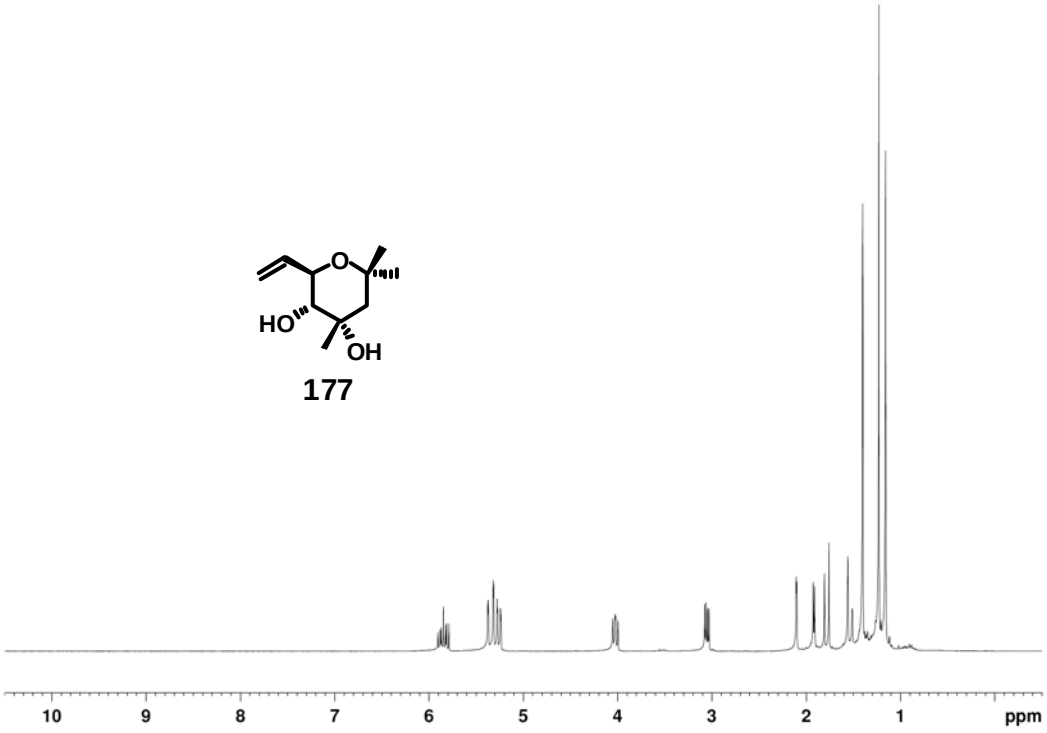
[1]**H NMR of 176**: CD_2Cl_2, 293 K, 500 MHz



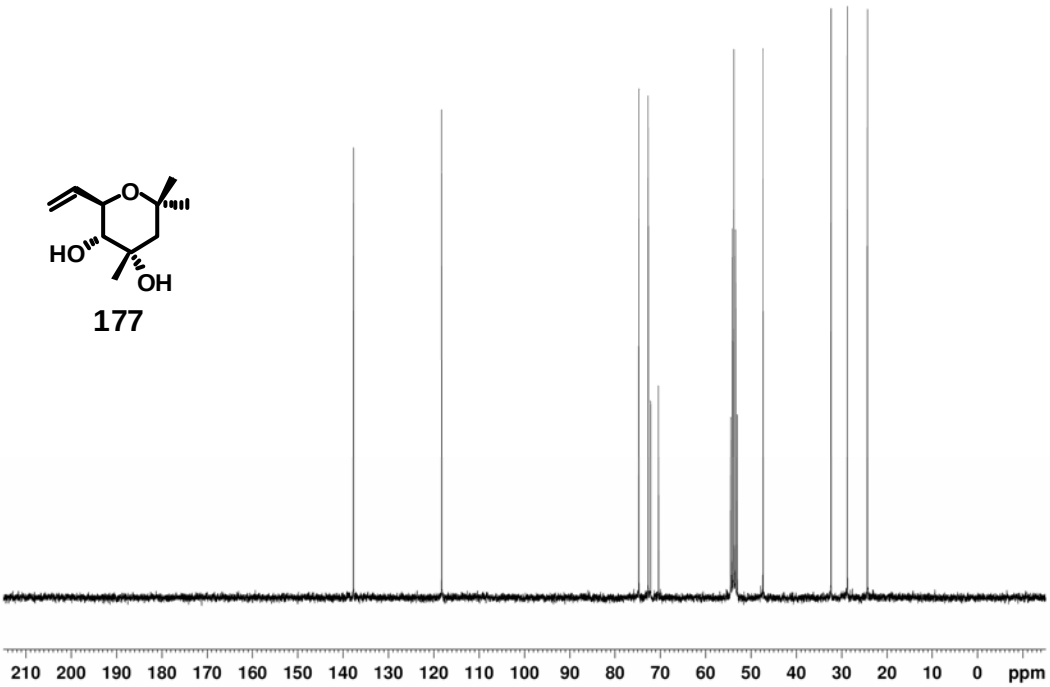
[13]**C NMR of 176**: CD_2Cl_2, 293 K, 125 MHz



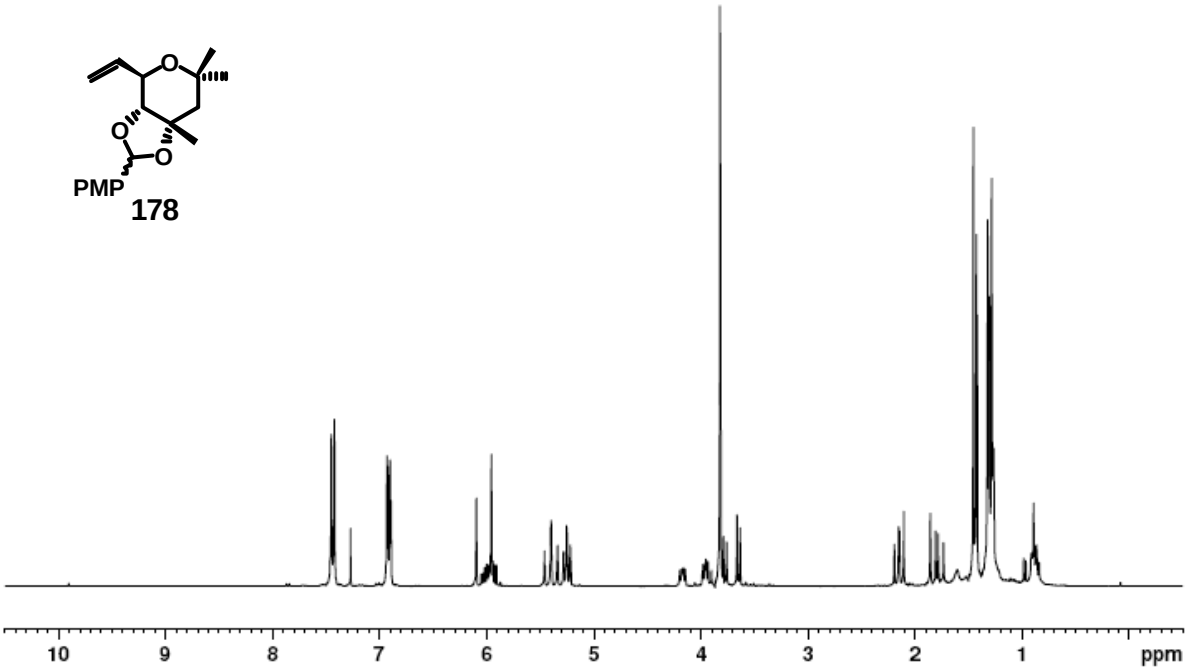
[1]**H NMR of 177**: CD_2Cl_2, 293 K, 300 MHz



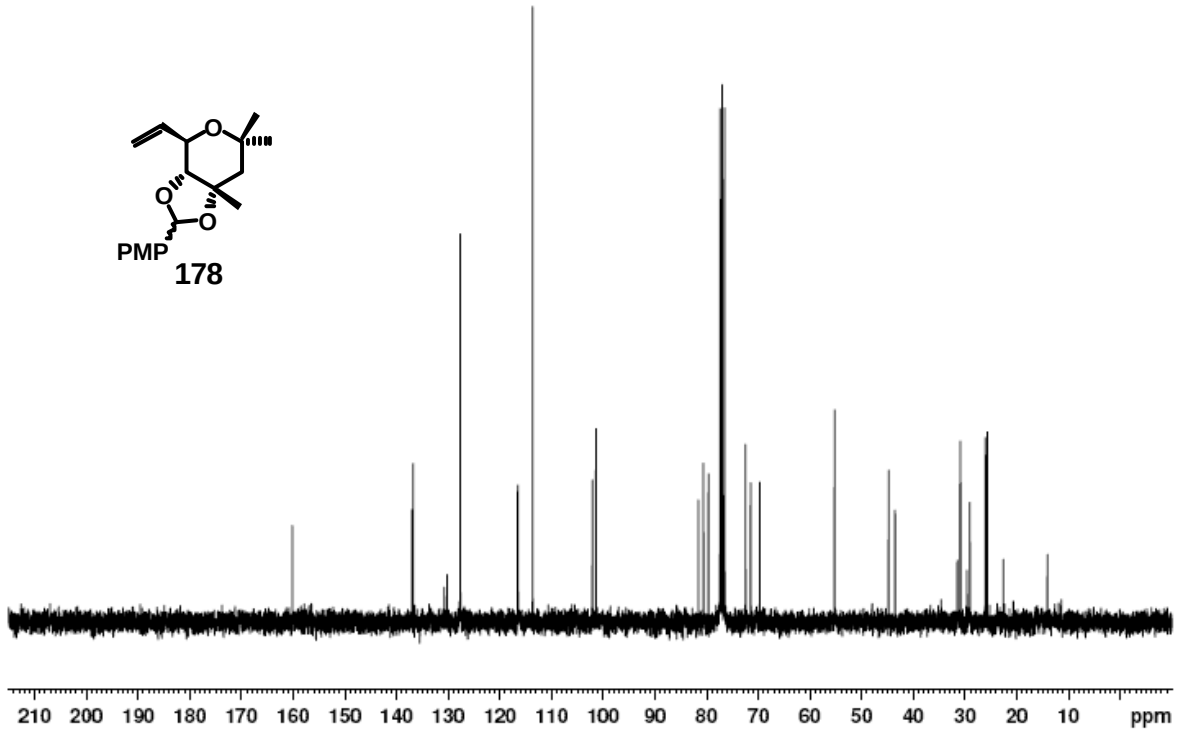
[13]**C NMR of 177**: CD_2Cl_2, 293 K, 75 MHz



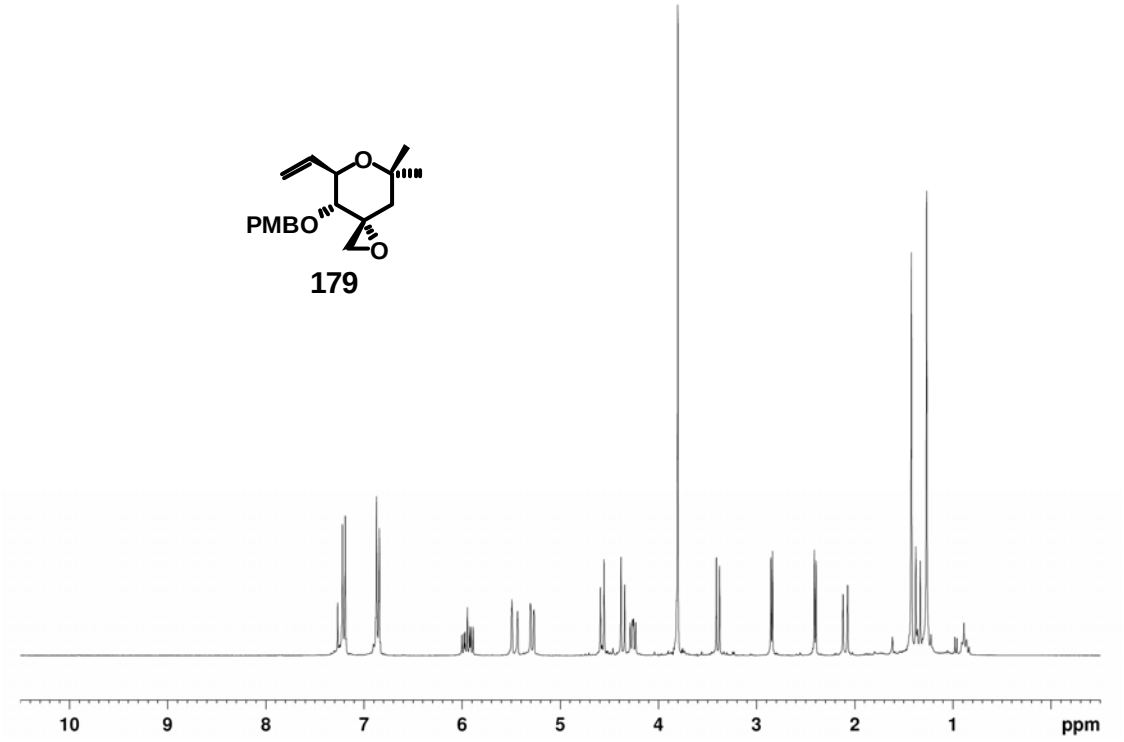
[1]**H NMR of 178**: $CDCl_3$, 293 K, 300 MHz



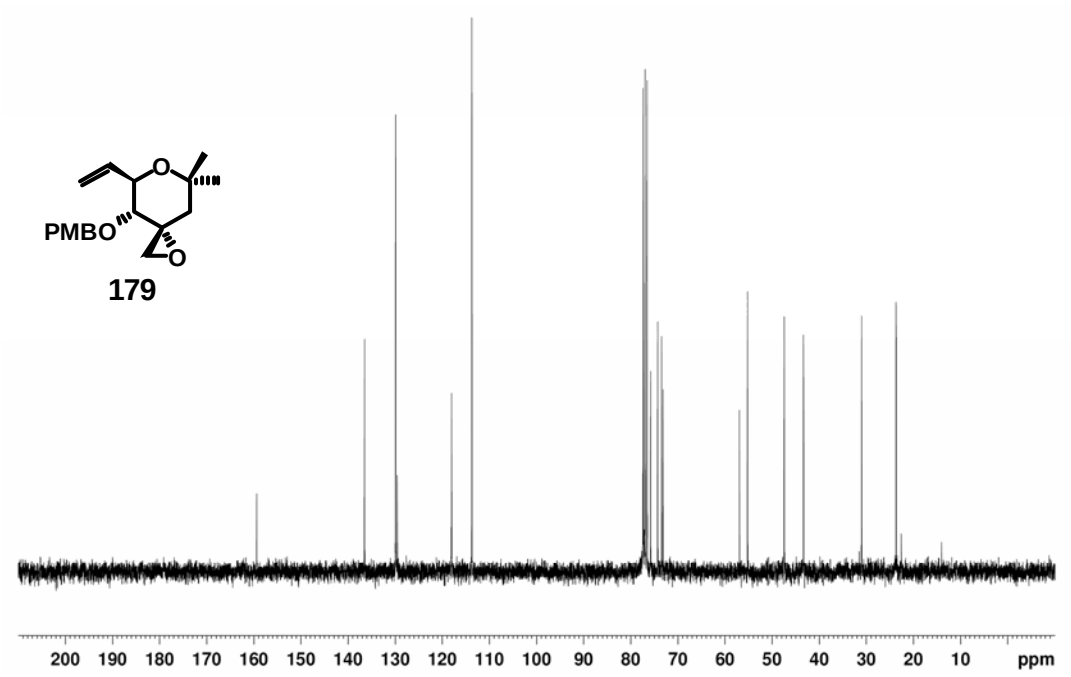
[13]**C NMR of 178**: $CDCl_3$, 293 K, 75 MHz



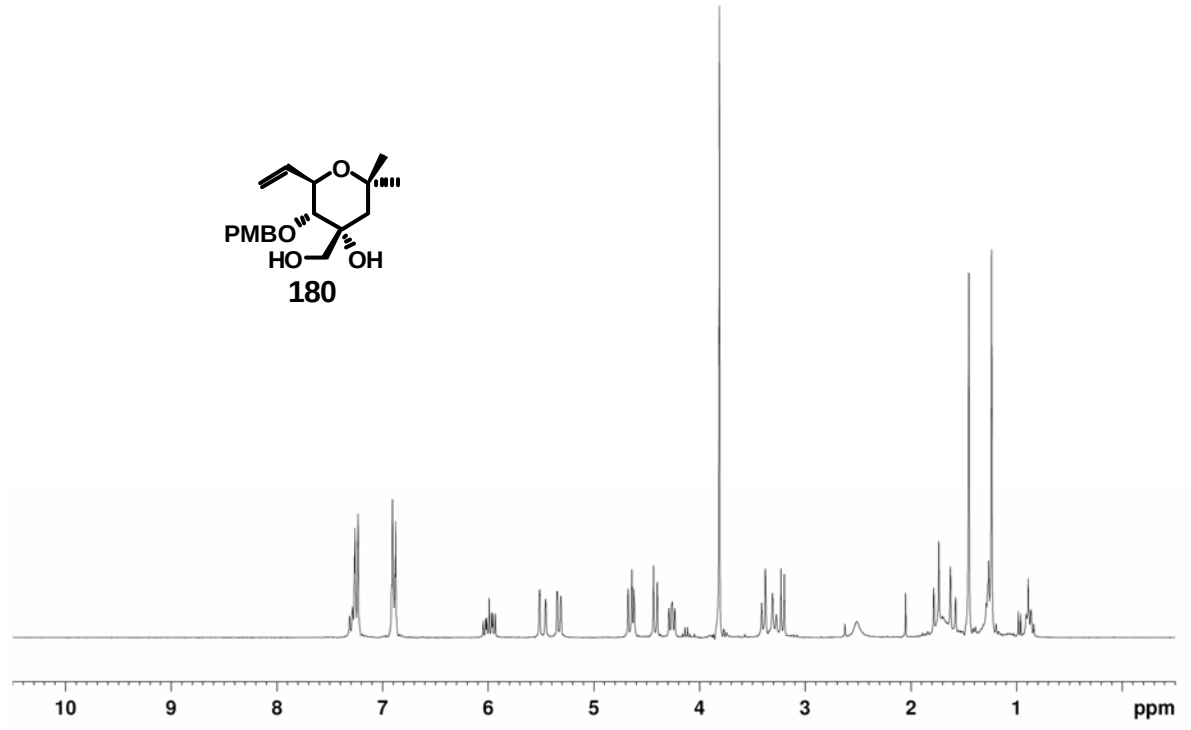
[1]**H NMR of 179**: $CDCl_3$, 293 K, 300 MHz



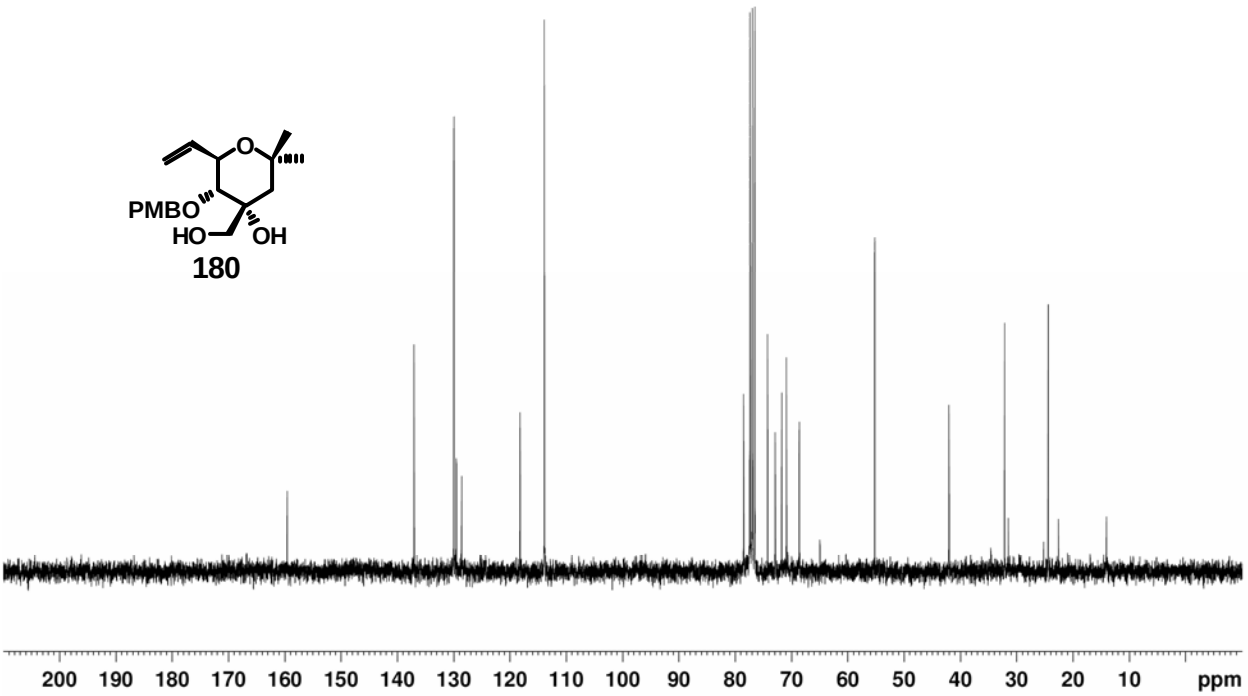
[13]**C NMR of 179**: $CDCl_3$, 293 K, 75 MHz



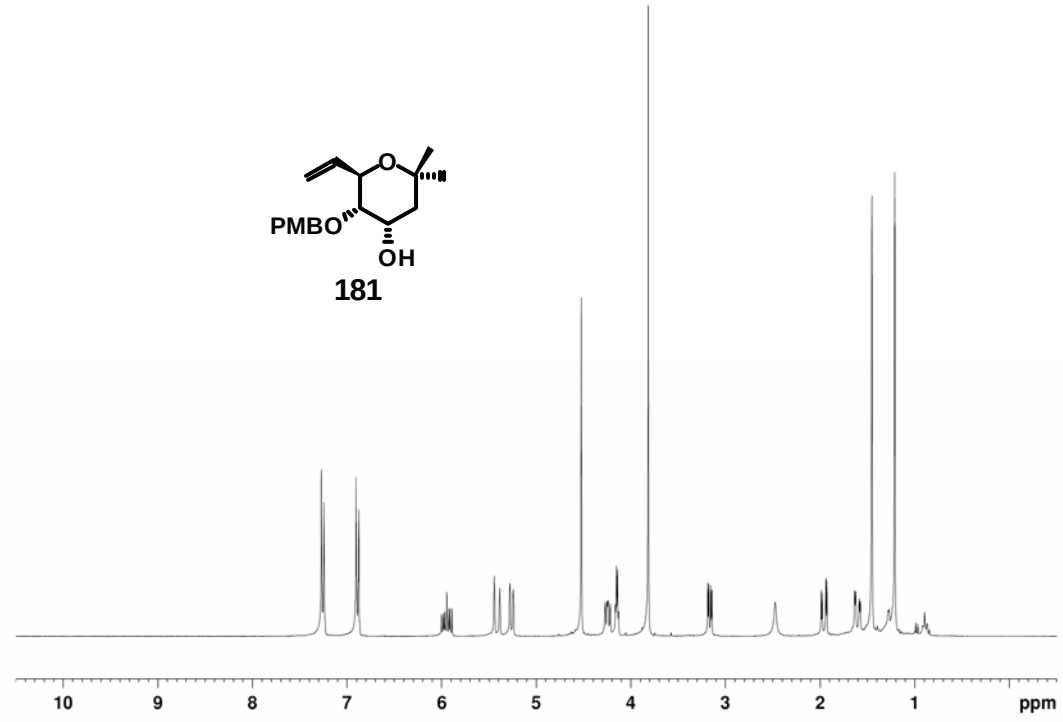
[1]**H NMR of 180**: $CDCl_3$, 293 K, 300 MHz



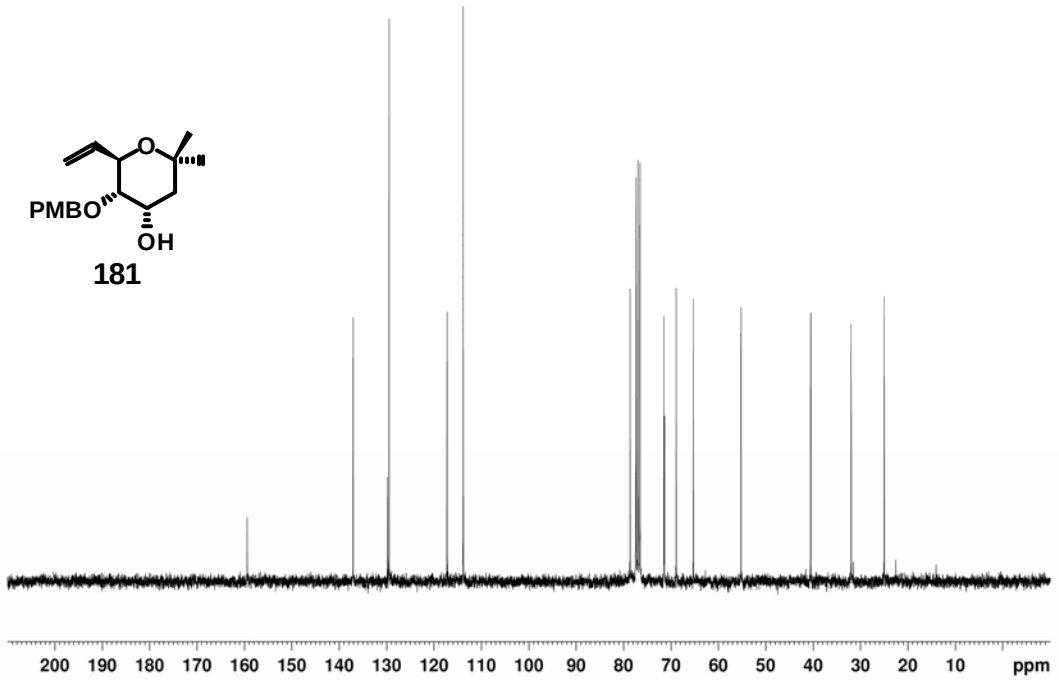
[13]**C NMR of 180**: $CDCl_3$, 293 K, 75 MHz



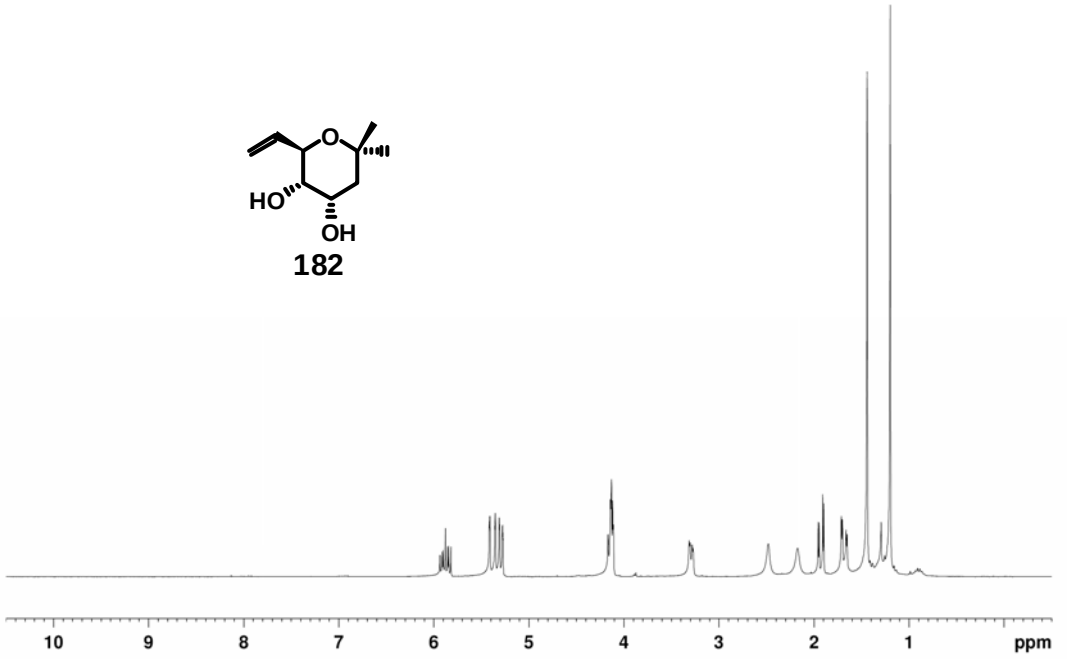
[1]**H NMR of 181**: $CDCl_3$, 293 K, 300 MHz



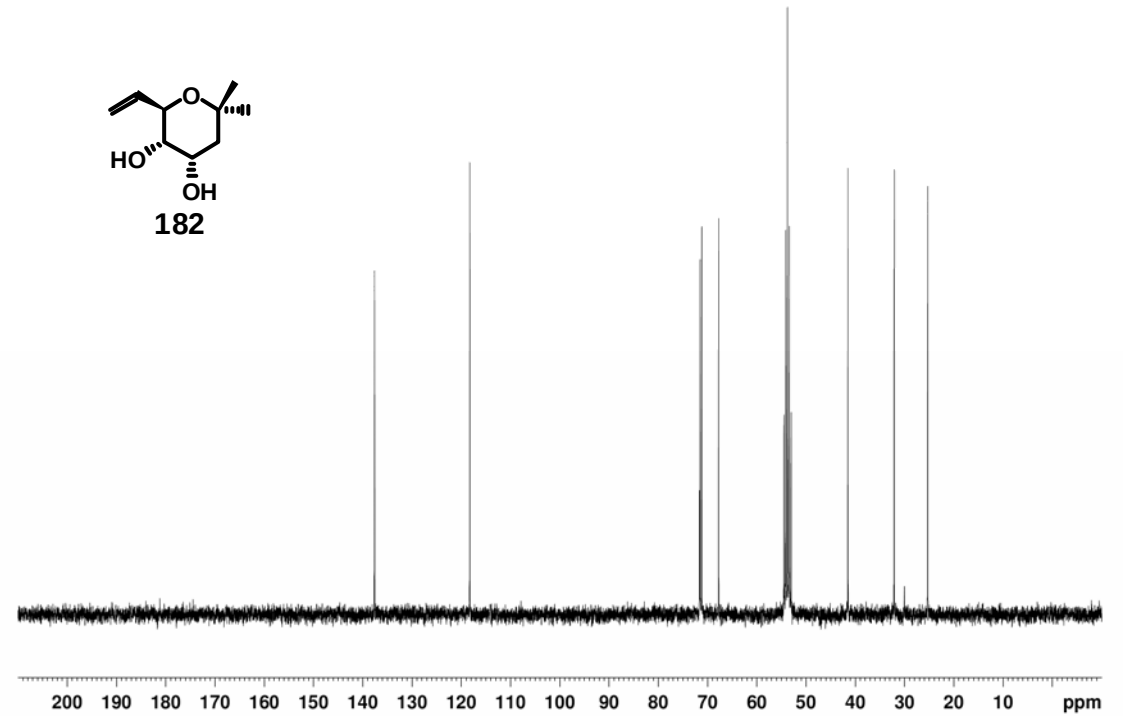
[13]**C NMR of 181**: CD_2Cl_2, 293 K, 75 MHz



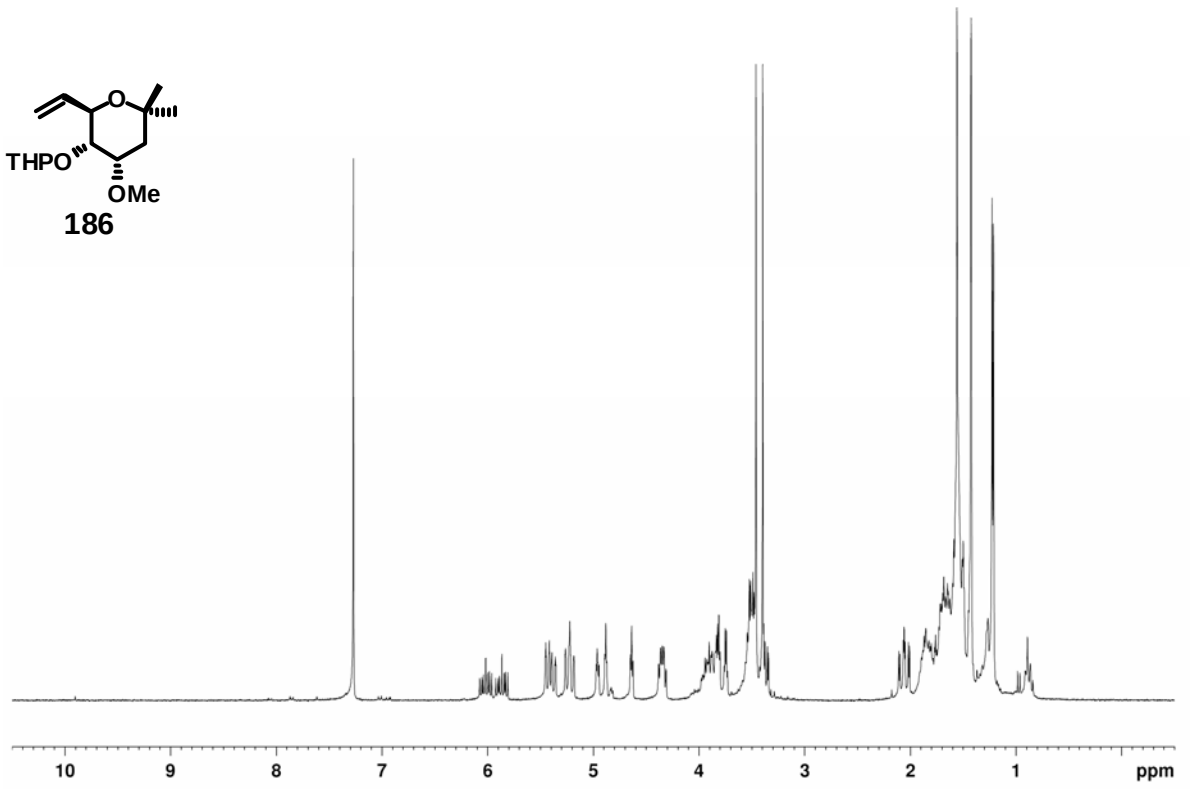
^{1}H NMR of 182: CD_2Cl_2, 293 K, 300 MHz



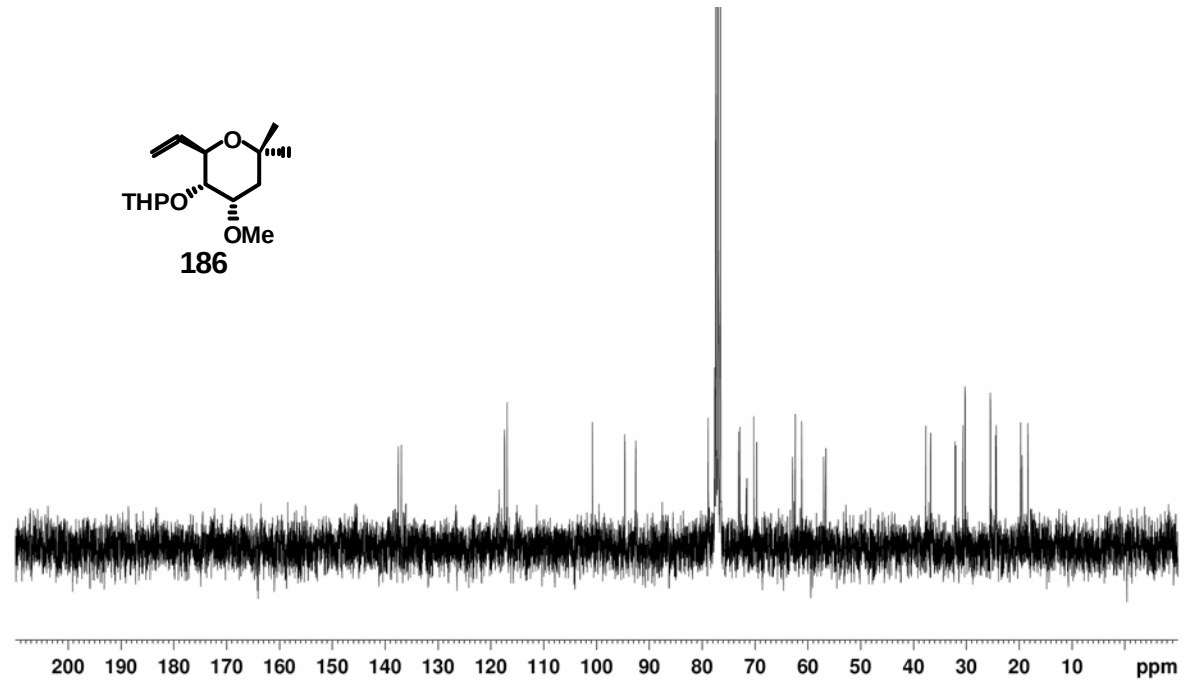
^{13}C NMR of 182: CD_2Cl_2, 293 K, 75 MHz



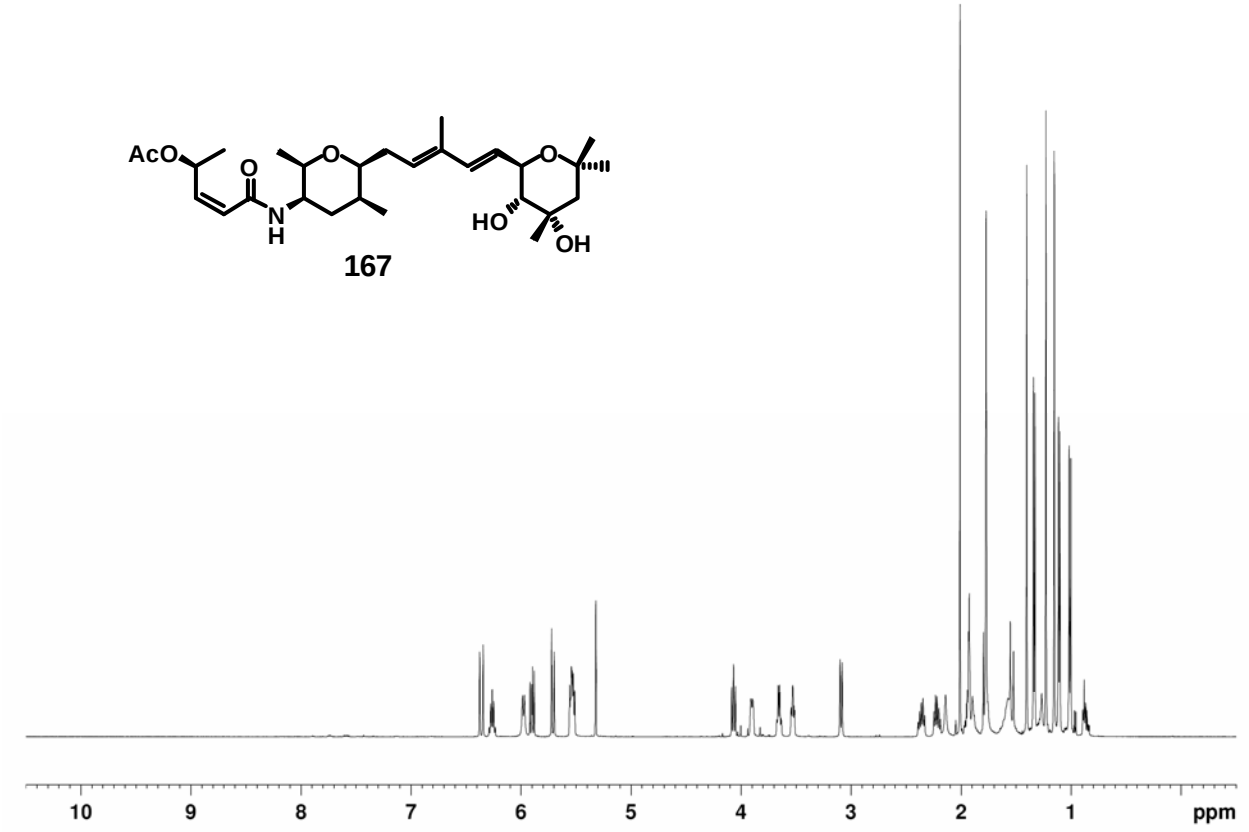
^{1}H NMR of 186: $CDCl_3$, 293 K, 300 MHz



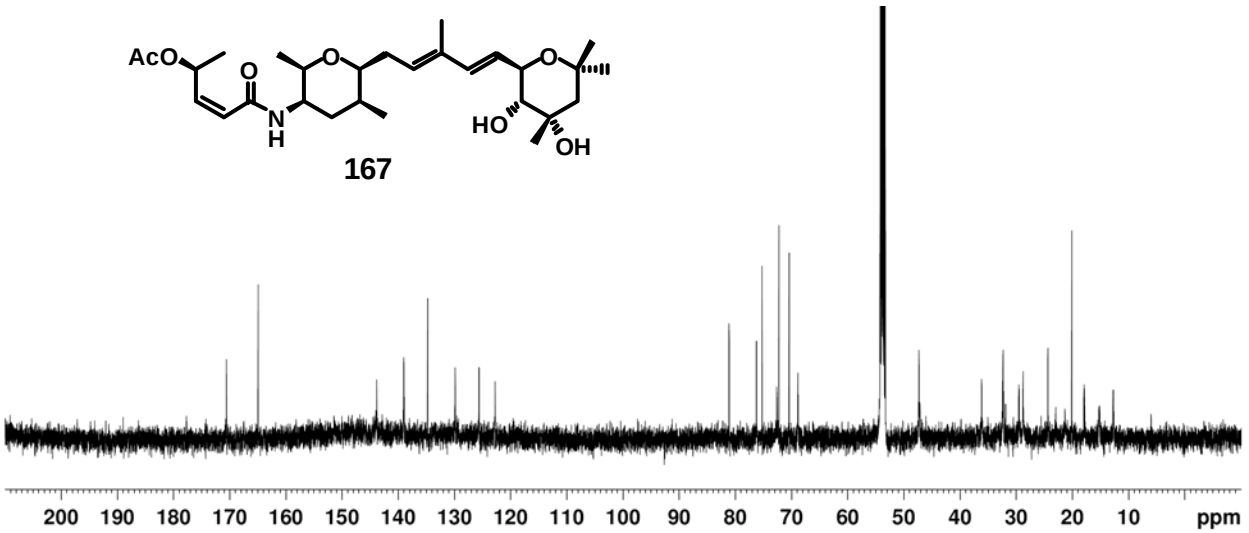
^{13}C NMR of 186: $CDCl_3$, 293 K, 75 MHz



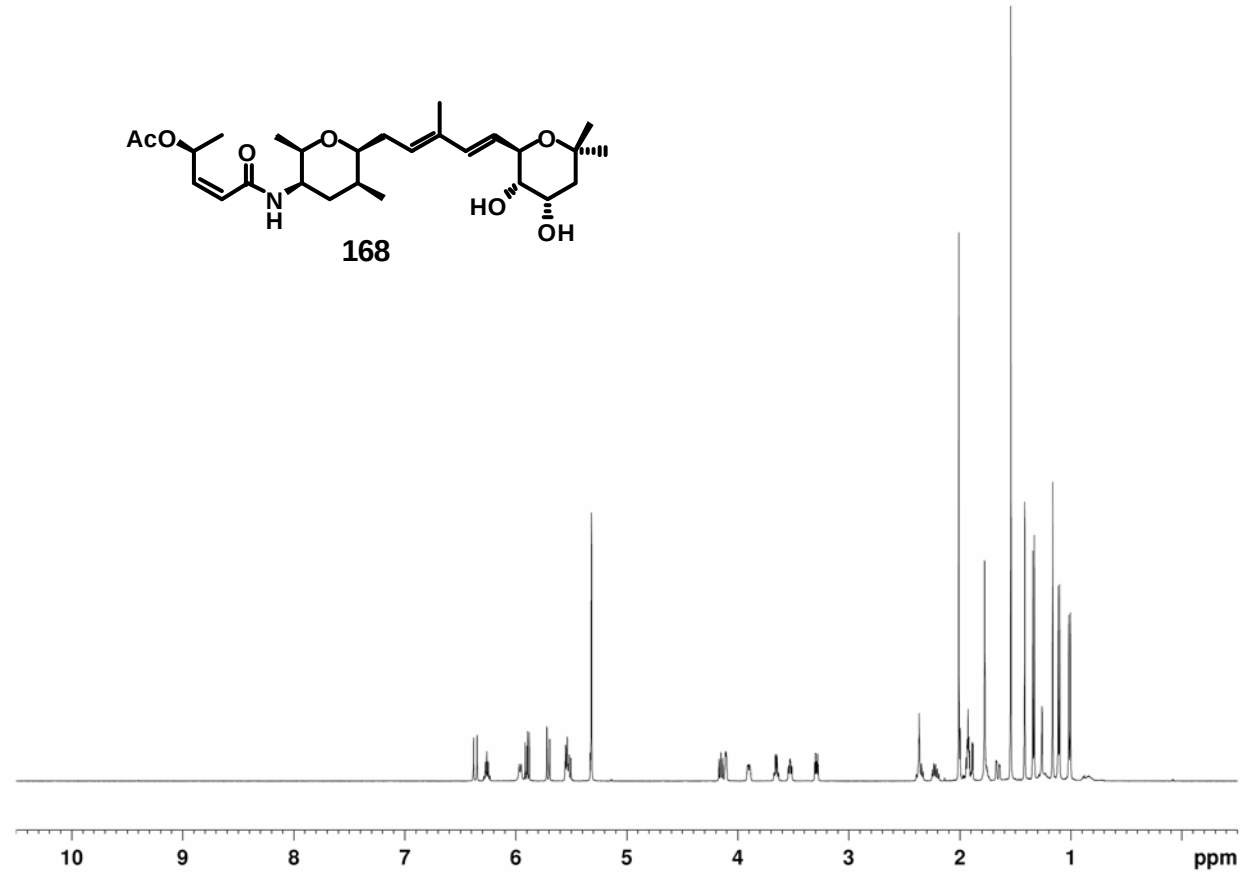
[1]**H NMR of 167**: CD_2Cl_2, 293 K, 500 MHz



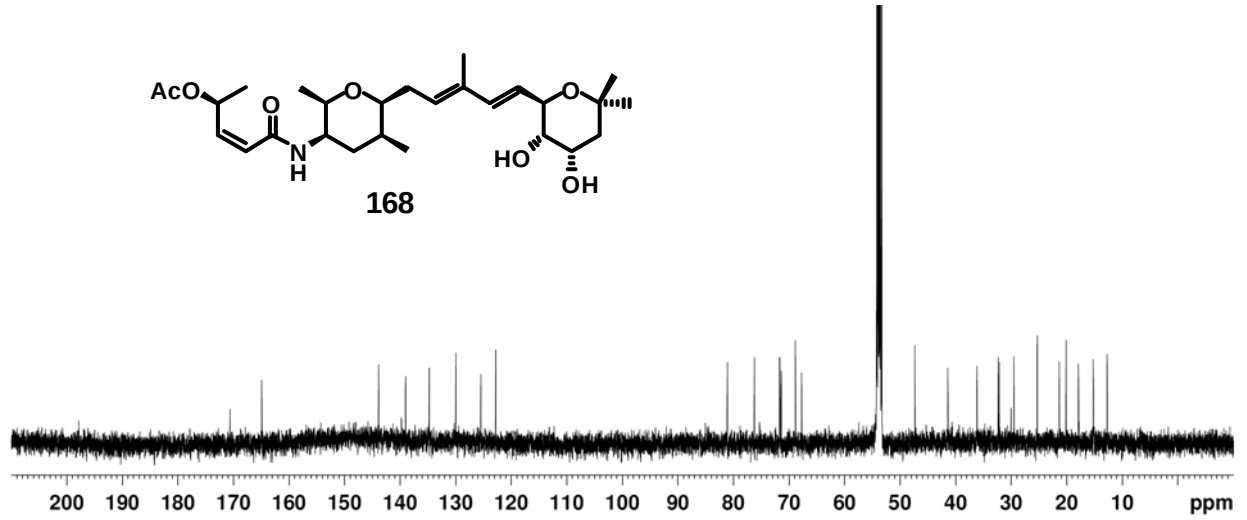
[13]**C NMR of 167**: CD_2Cl_2, 293 K, 125 MHz



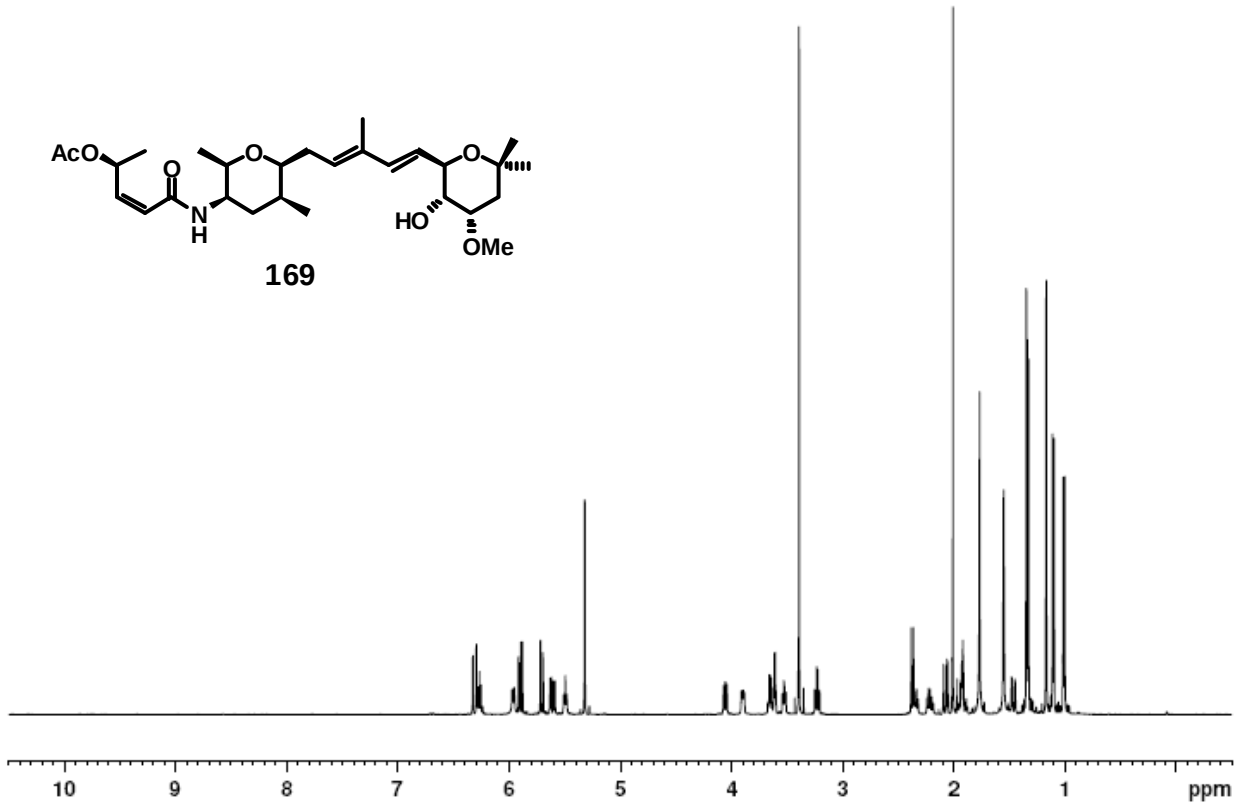
[1]**H NMR of 168**: CD_2Cl_2, 293 K, 500 MHz



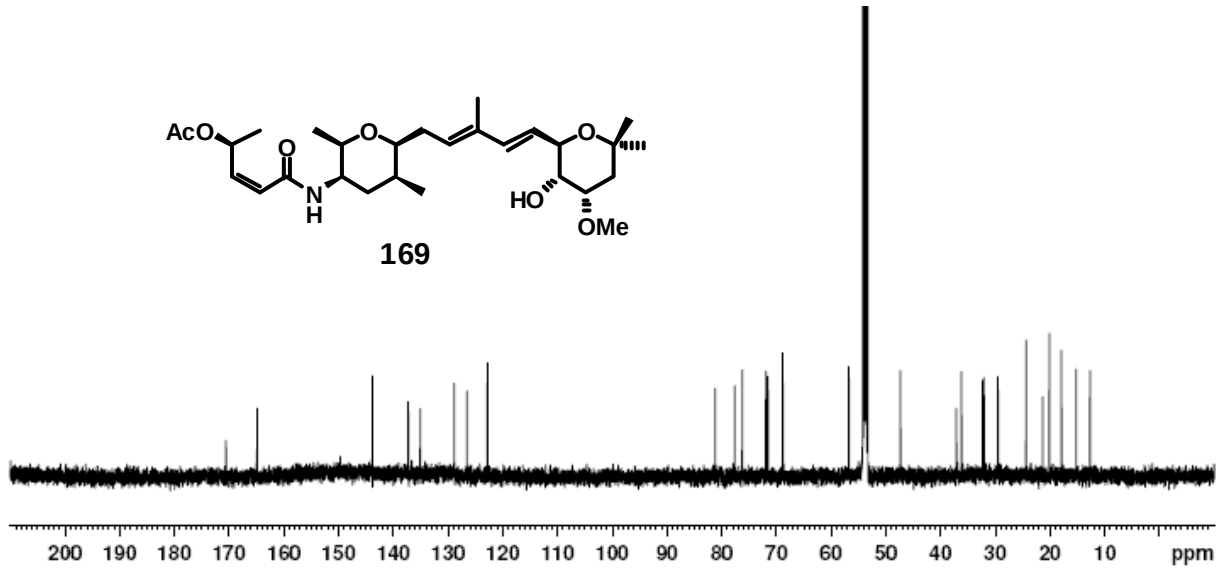
[13]**C NMR of 168**: CD_2Cl_2, 293 K, 125 MHz



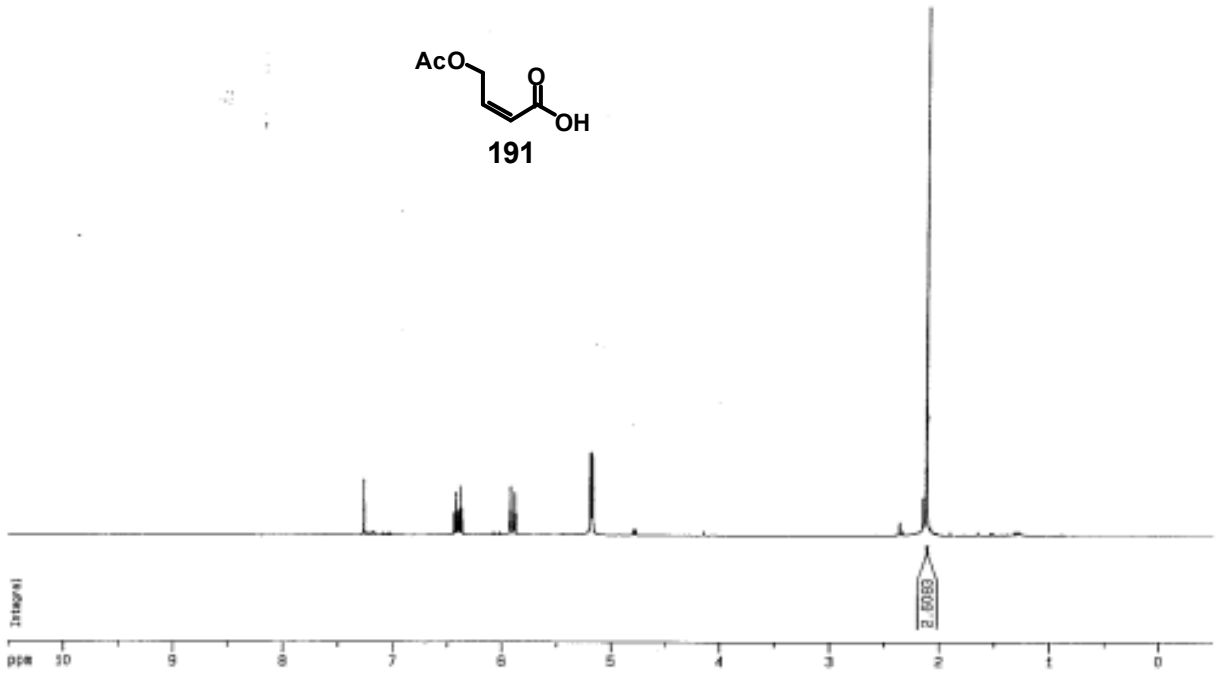
[1]**H NMR of 169**: CD_2Cl_2, 293 K, 500 MHz



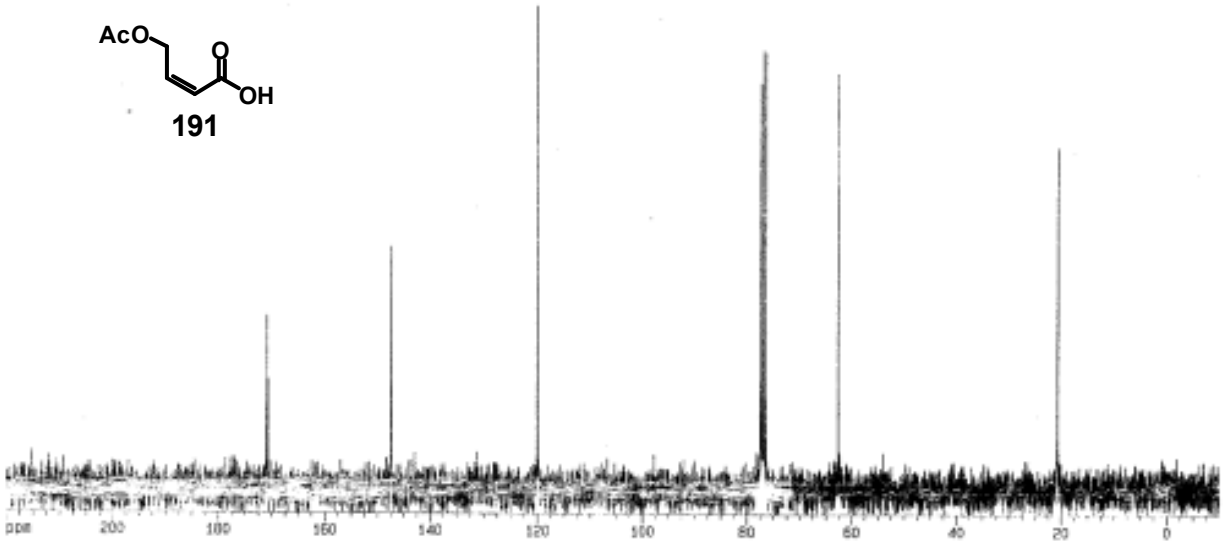
[13]**C NMR of 169**: CD_2Cl_2, 293 K, 125 MHz



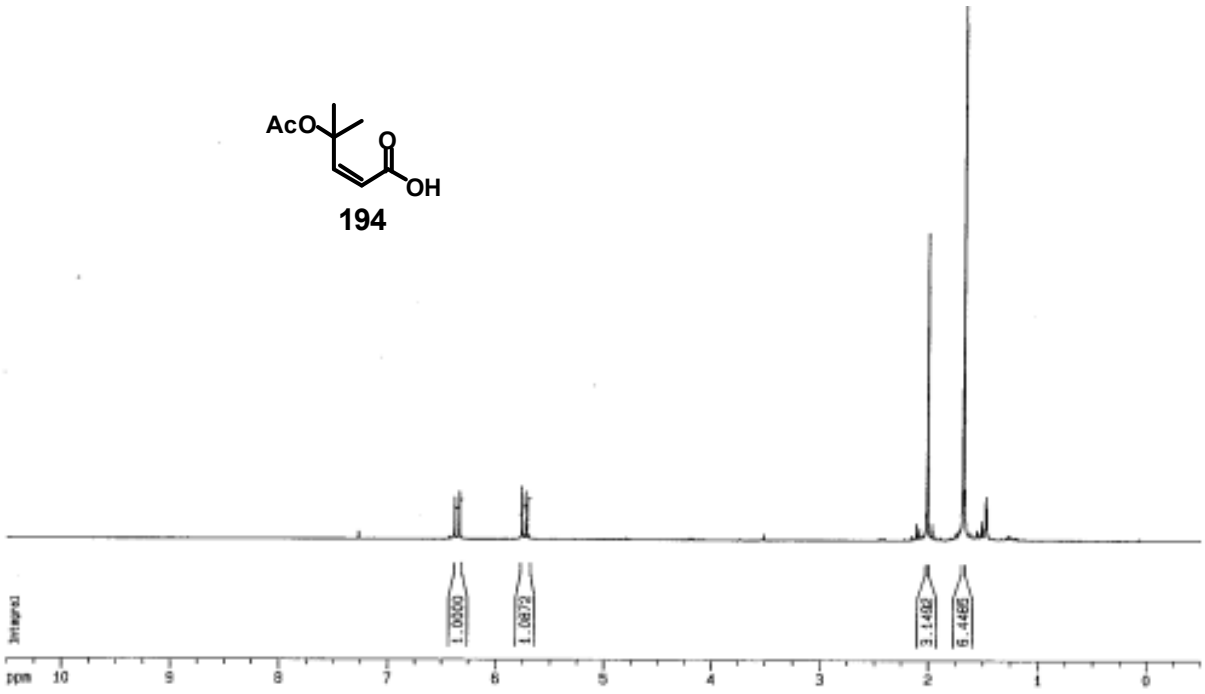
[1]**H NMR of 191**: $CDCl_3$, 293 K, 300 MHz



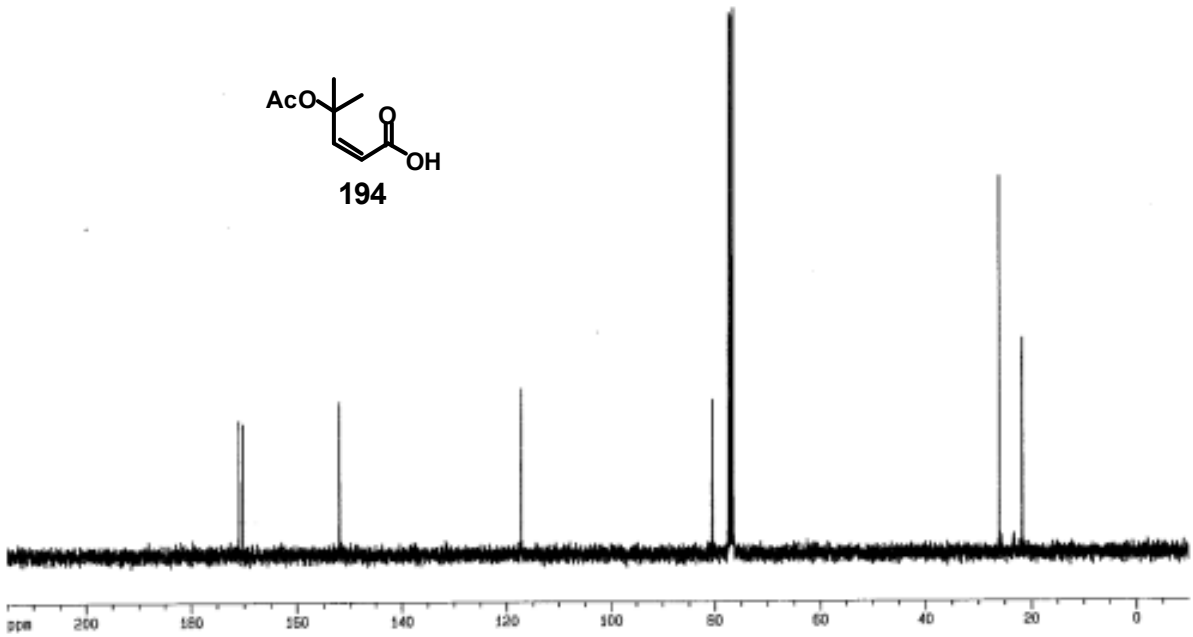
[13]**C NMR of 191**: $CDCl_3$, 293 K, 75 MHz



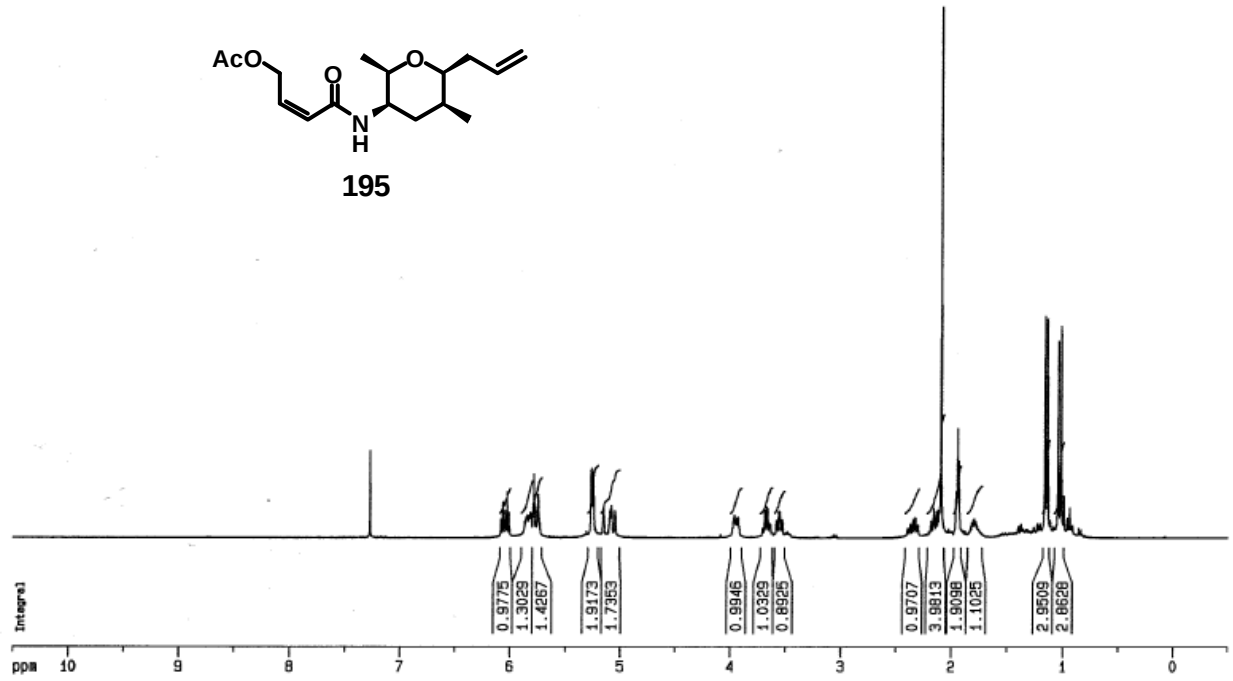
[1]**H NMR of 194**: $CDCl_3$, 293 K, 300 MHz



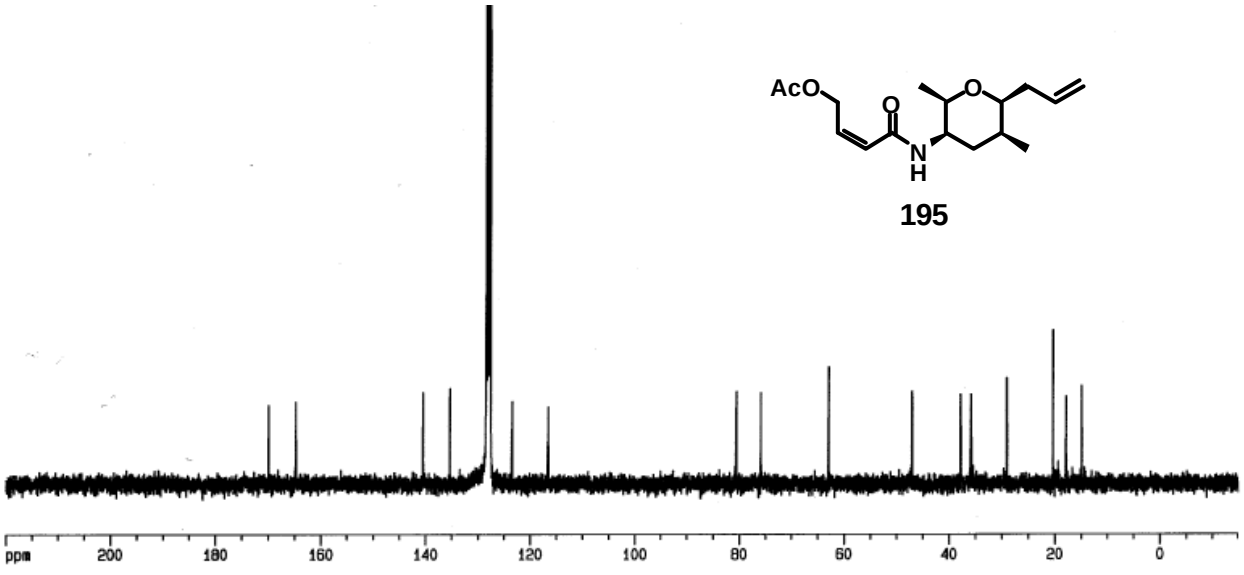
[13]**C NMR of 194**: $CDCl_3$, 293 K, 75 MHz



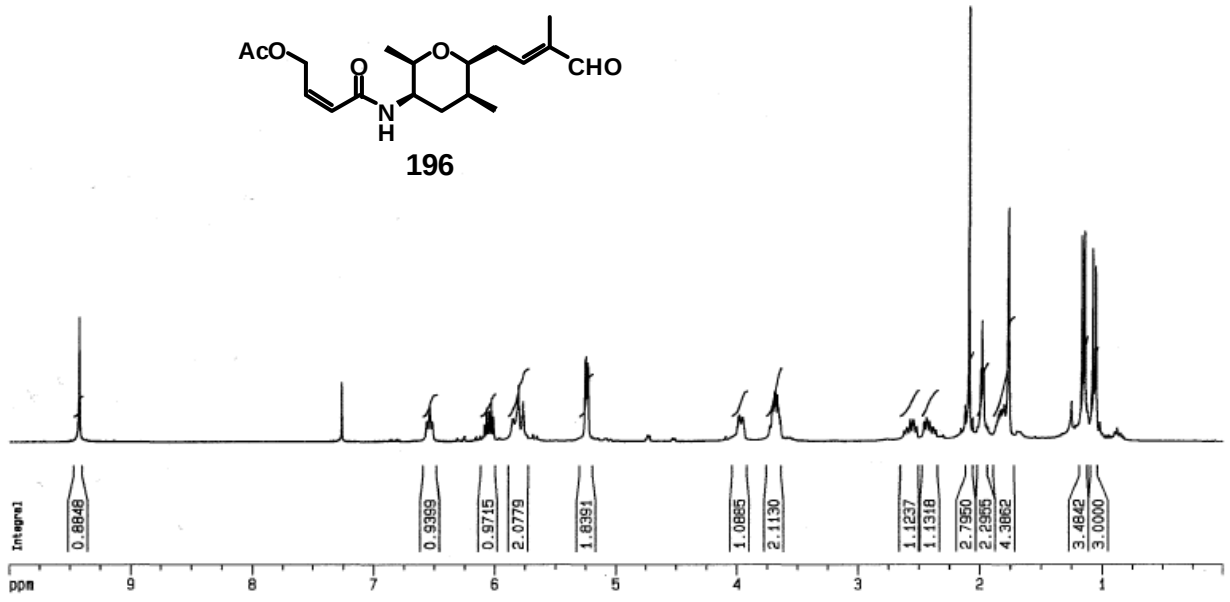
[1]**H NMR of 195**: $CDCl_3$, 293 K, 300 MHz



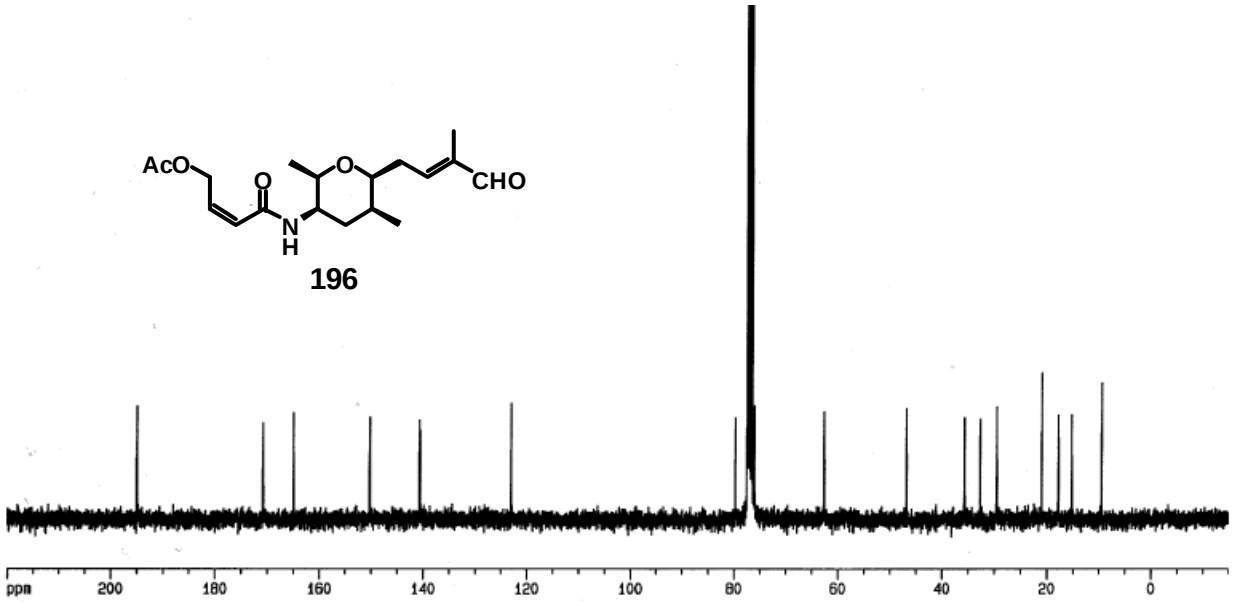
[13]**C NMR of 195**: C_6D_6, 293 K, 75 MHz



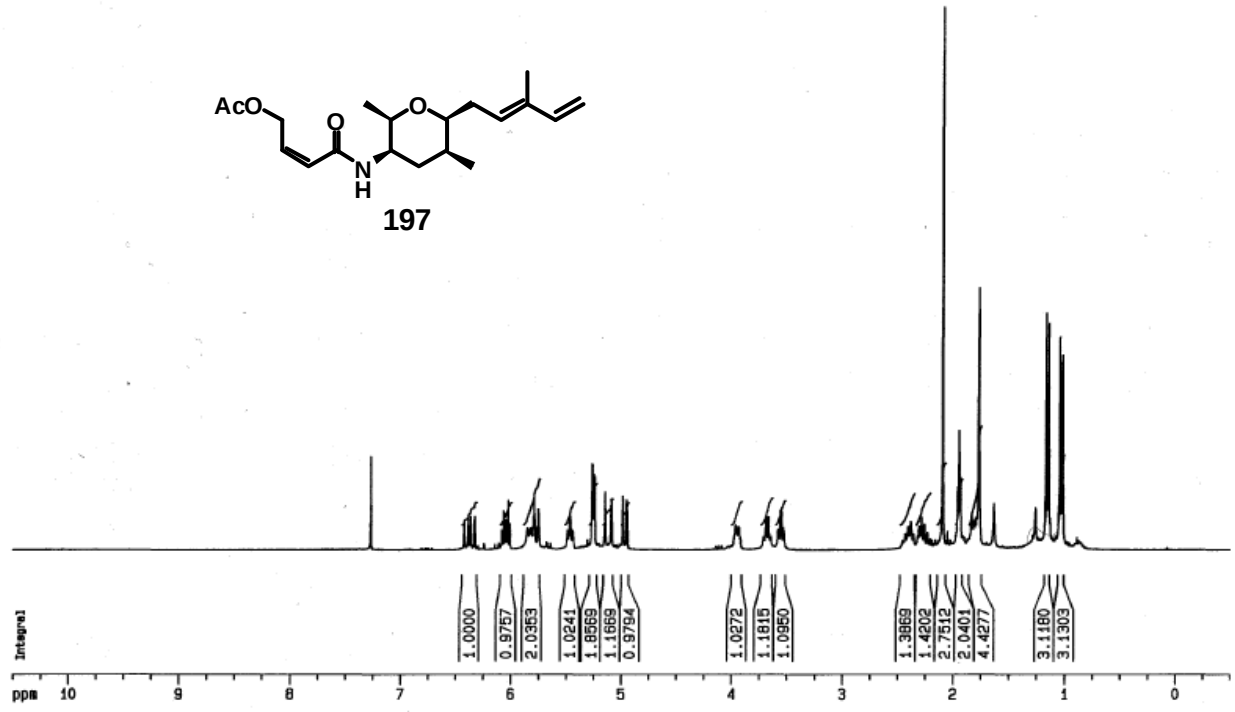
[1]**H NMR of 196**: $CDCl_3$, 293 K, 300 MHz



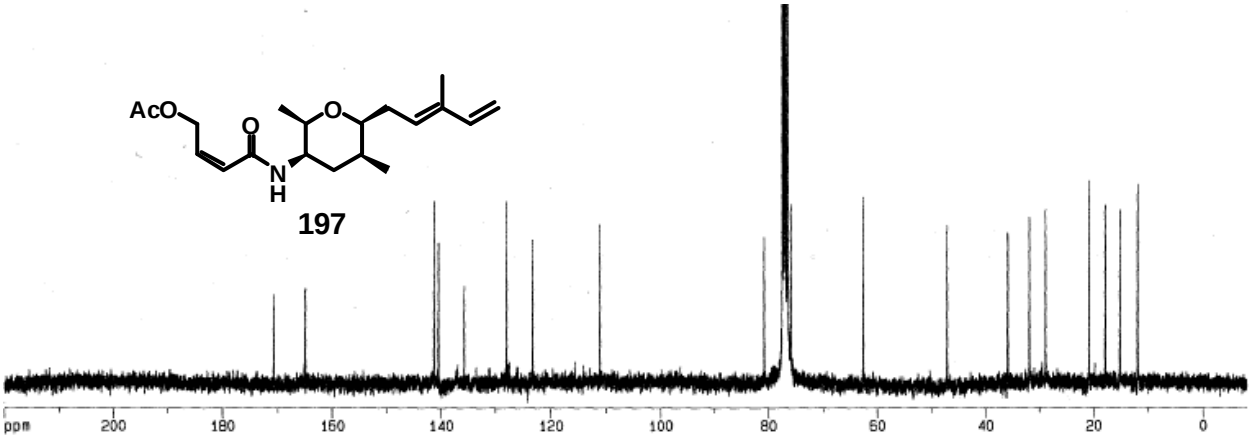
[13]**C NMR of 196**: $CDCl_3$, 293 K, 75 MHz



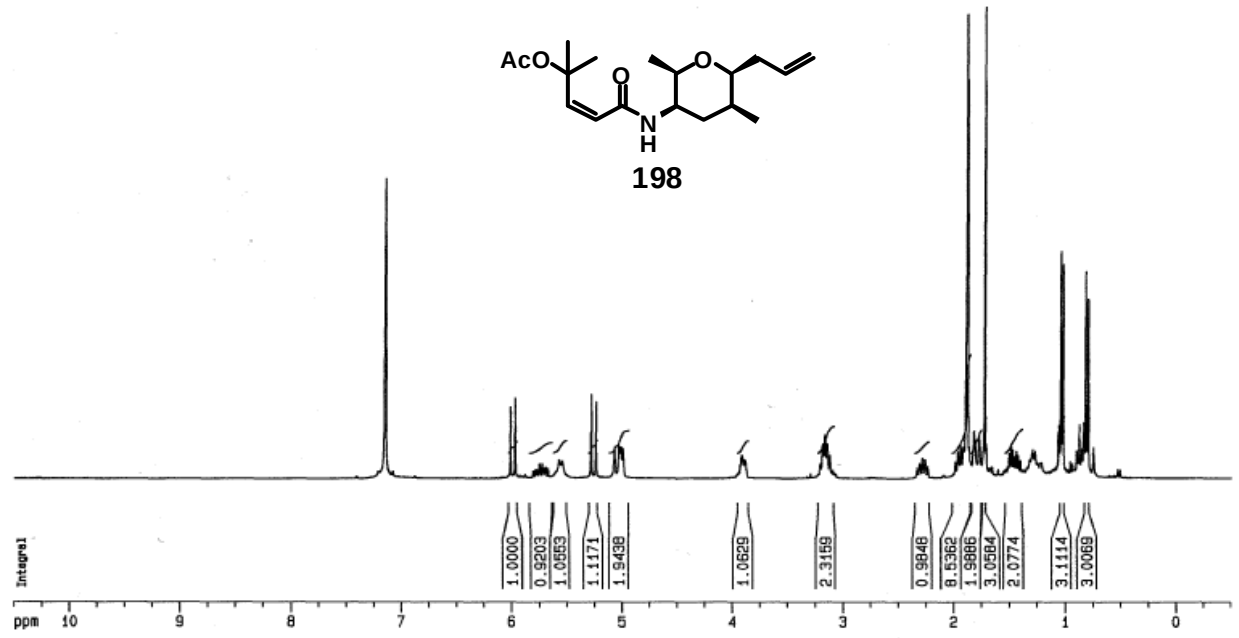
[1]**H NMR of 197**: $CDCl_3$, 293 K, 300 MHz



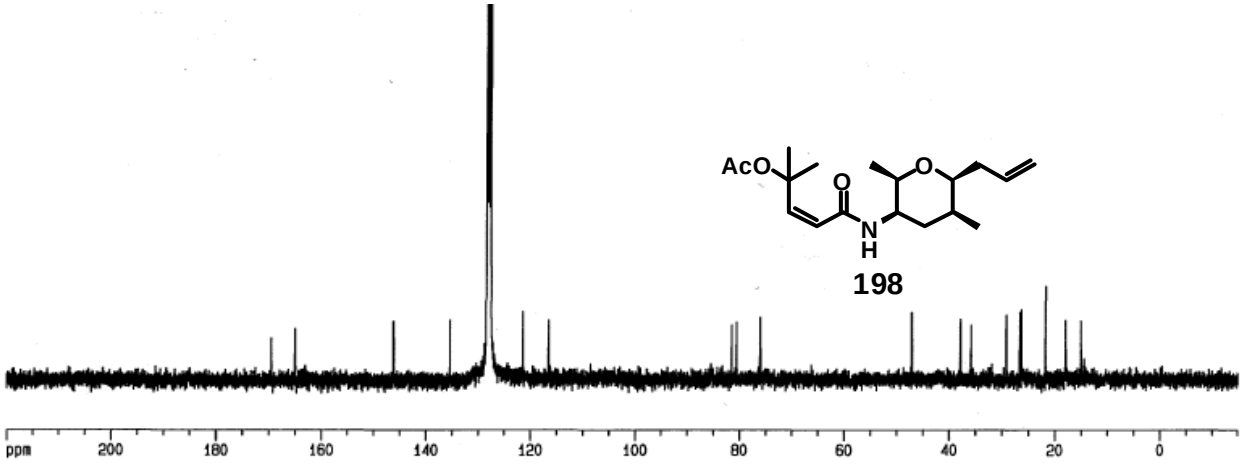
[13]**C NMR of 197**: $CDCl_3$, 293 K, 75 MHz



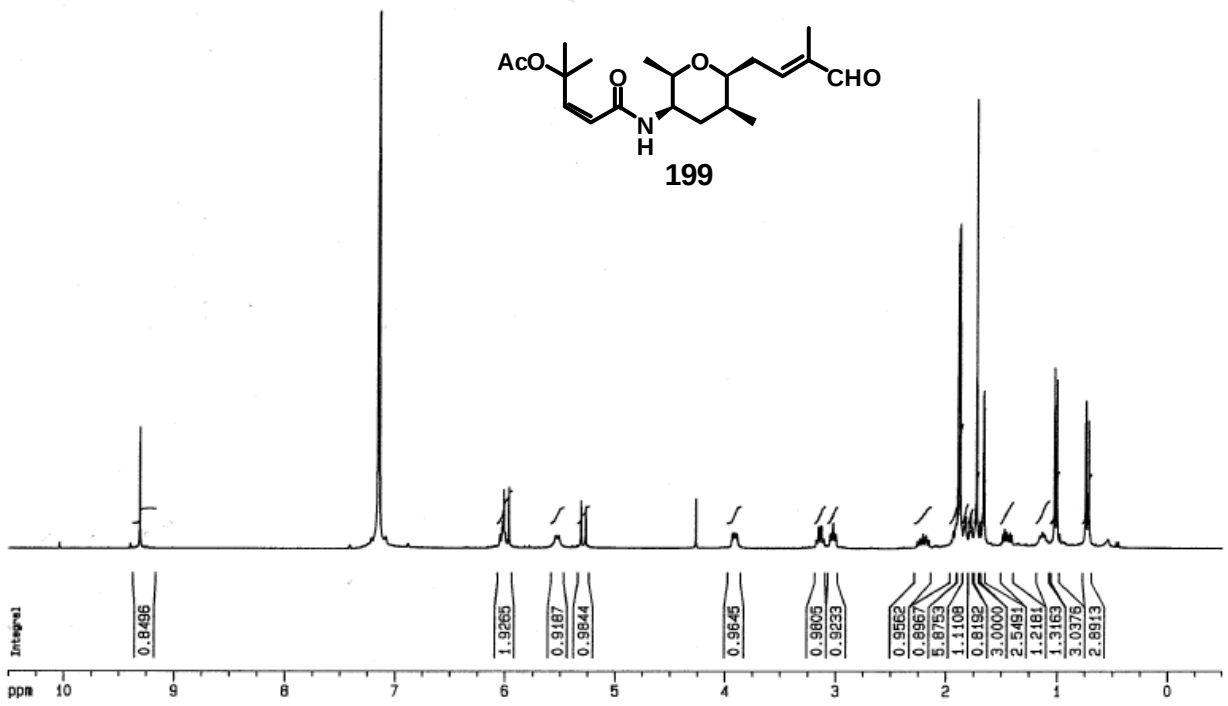
[1]**H NMR of 198**: C_6D_6, 293 K, 300 MHz



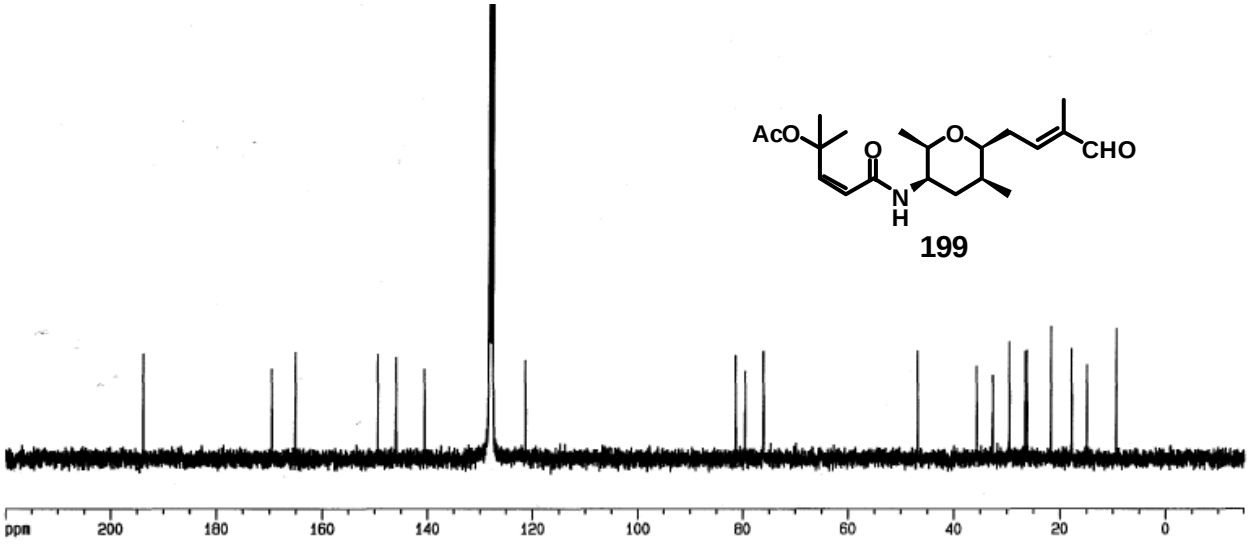
[13]**C NMR of 198**: C_6D_6, 293 K, 75 MHz



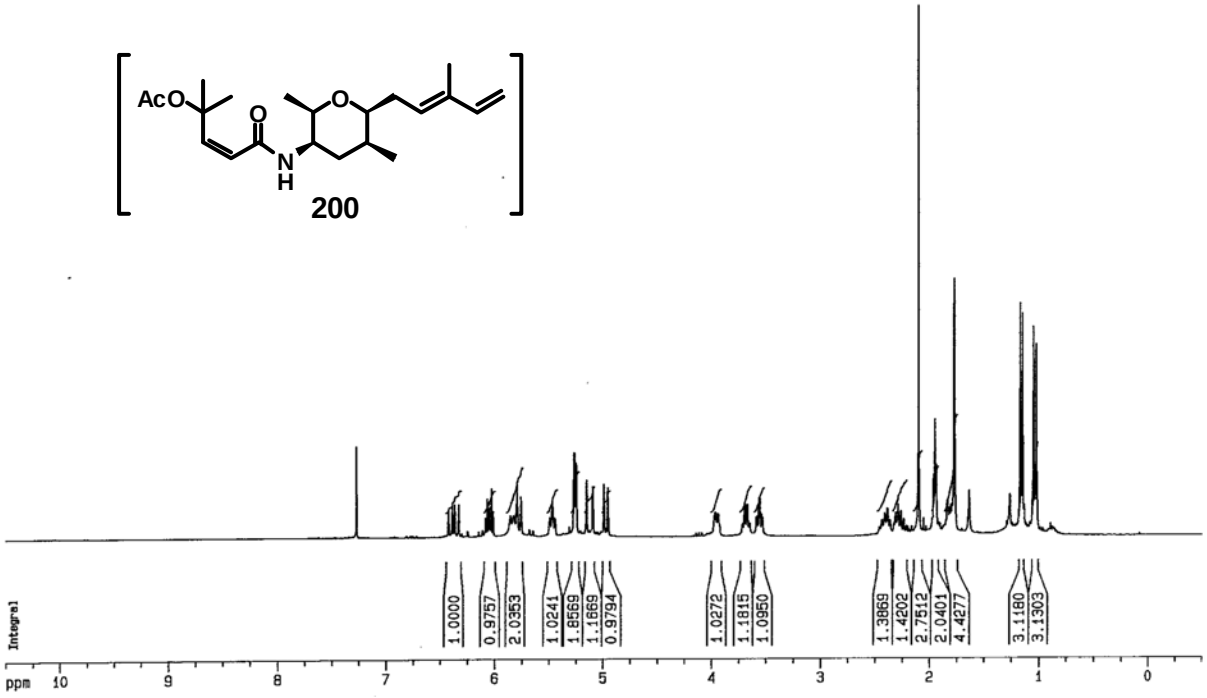
[1]**H NMR of 199**: C_6D_6, 293 K, 300 MHz



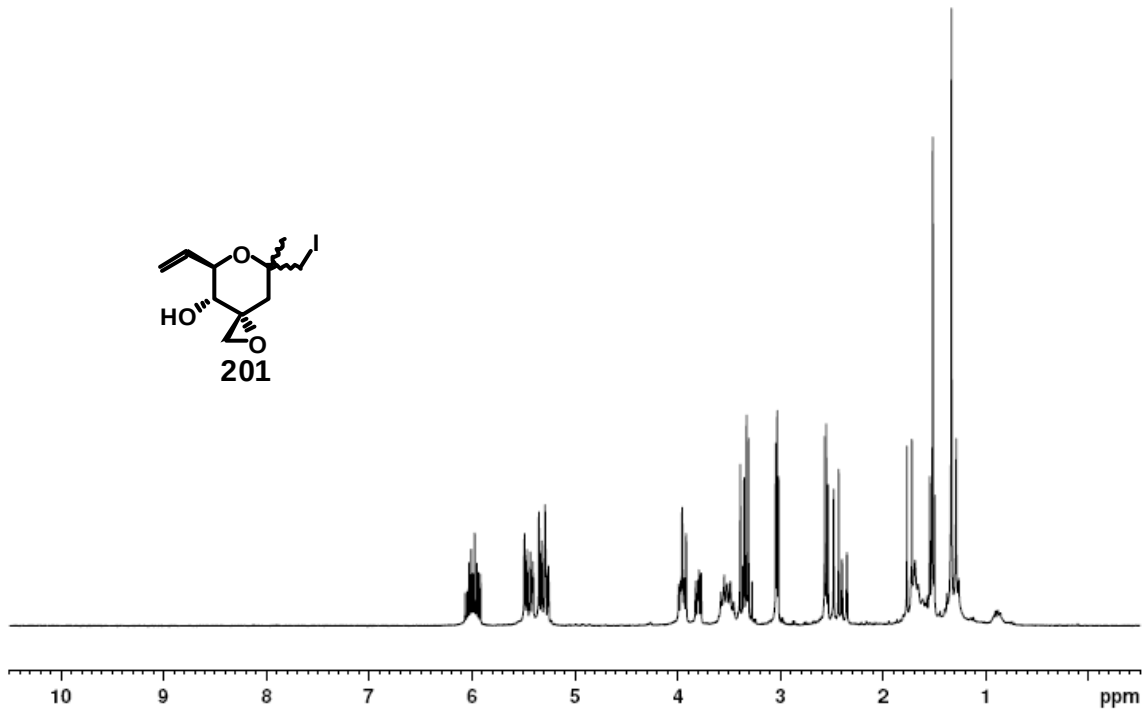
[13]**C NMR of 199**: CD_6D_6, 293 K, 75 MHz



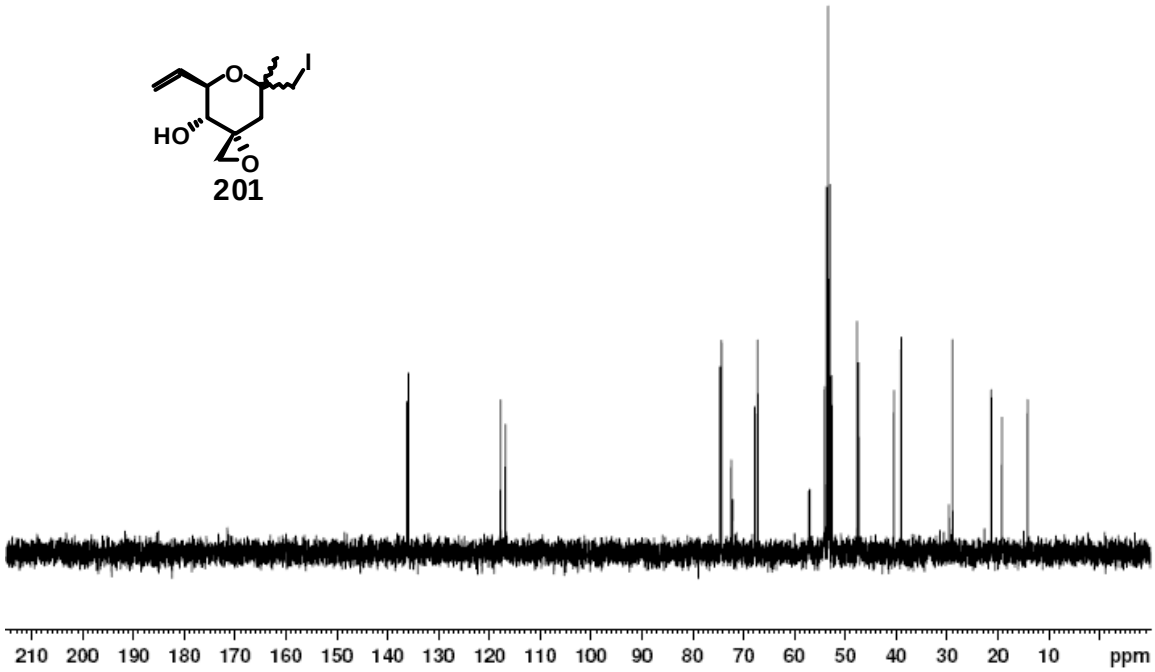
[1]**H NMR of 200**: C_6D_6, 293 K, 300 MHz



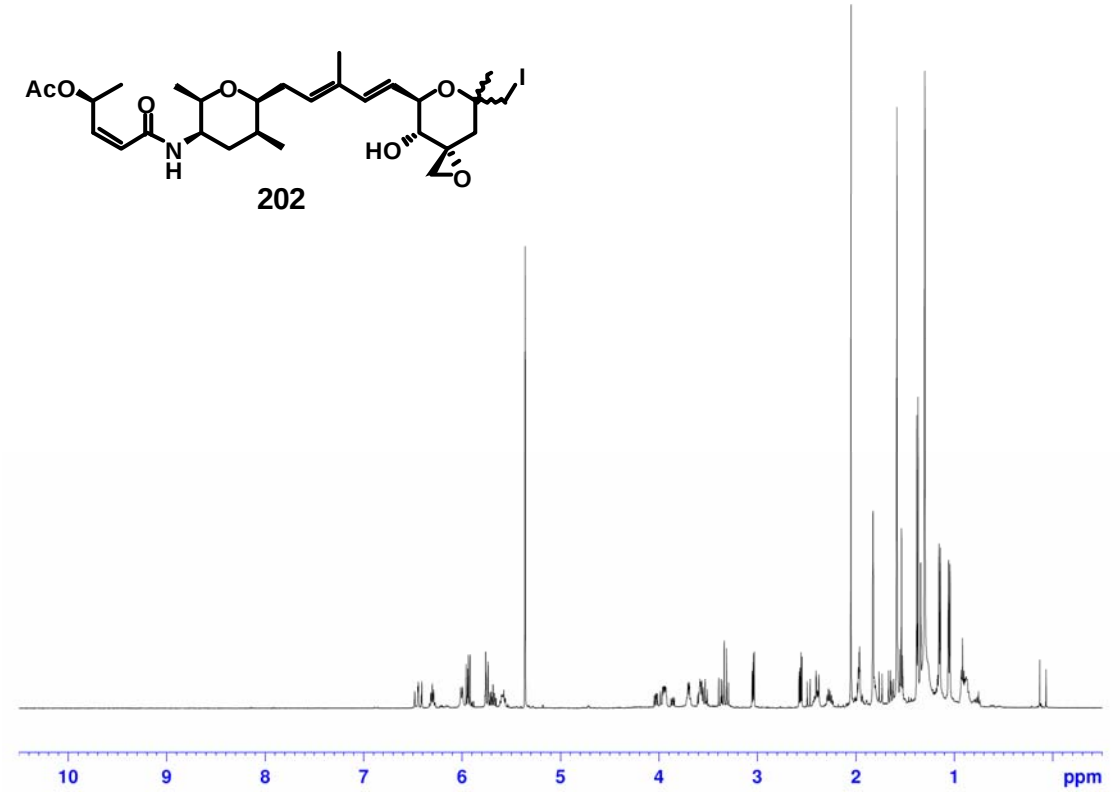
[1]**H NMR of 201**: CD_2Cl_2, 293 K, 300 MHz



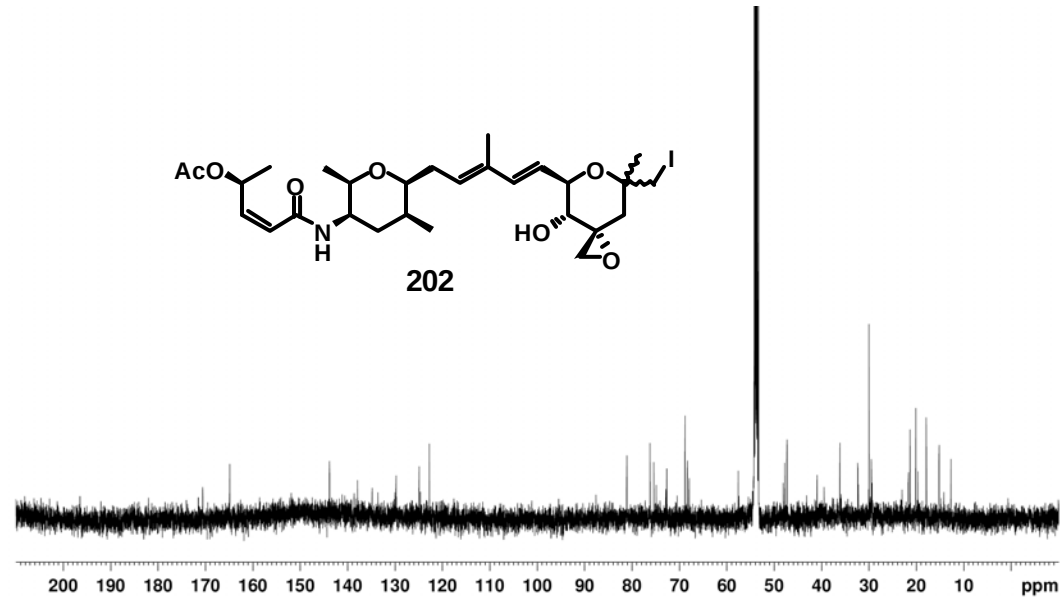
[13]**C NMR of 201**: CD_2Cl_2, 293 K, 75 MHz



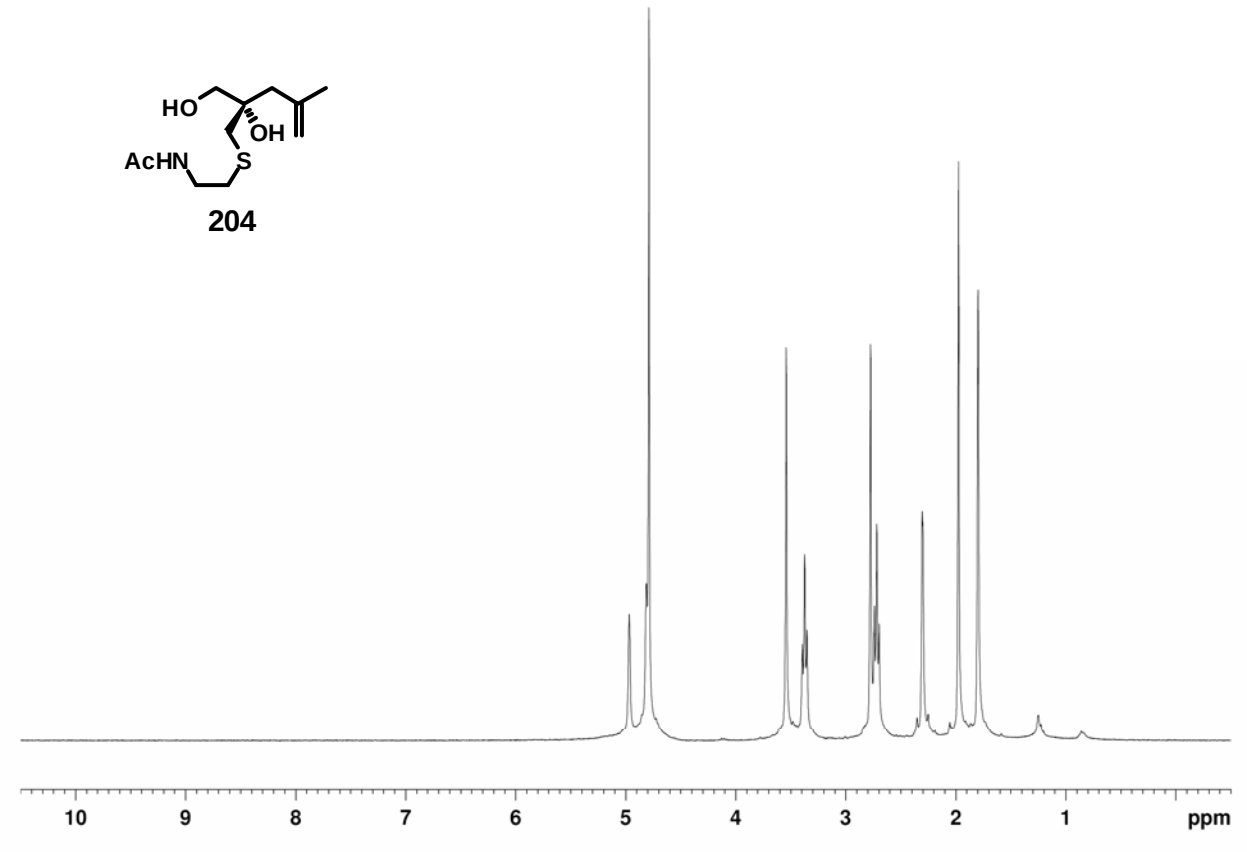
[1]**H NMR of 202**: CD_2Cl_2, 293 K, 500 MHz



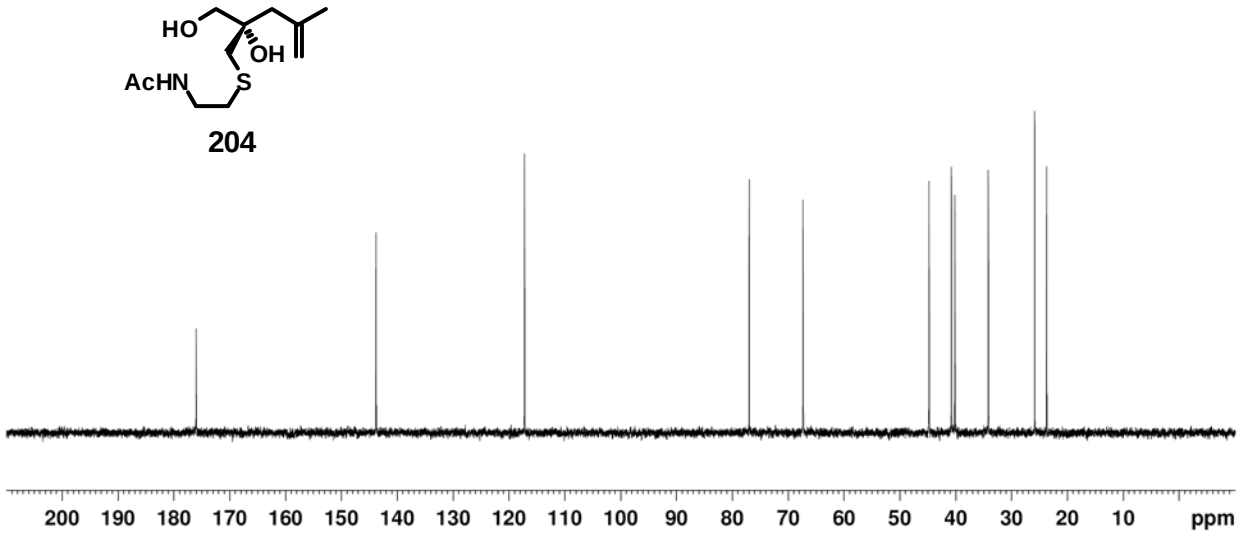
[13]**C NMR of 202**: CD_2Cl_2, 293 K, 125 MHz



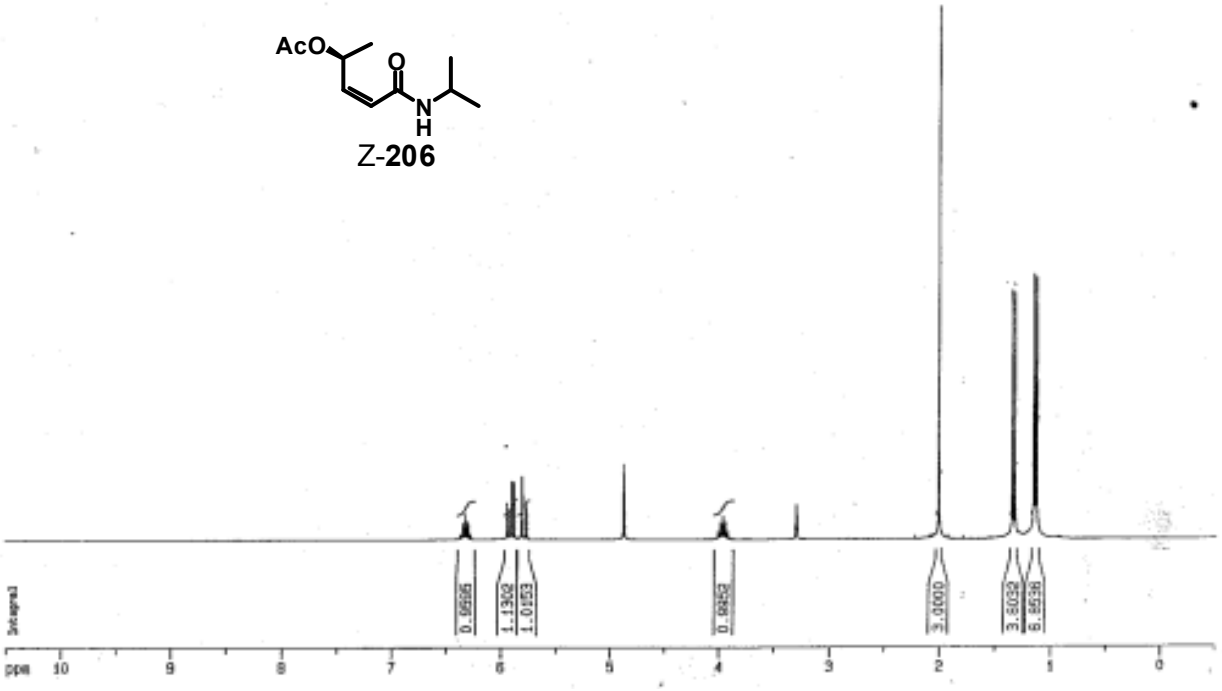
[1]**H NMR of 204**: D_2O, 293 K, 300 MHz



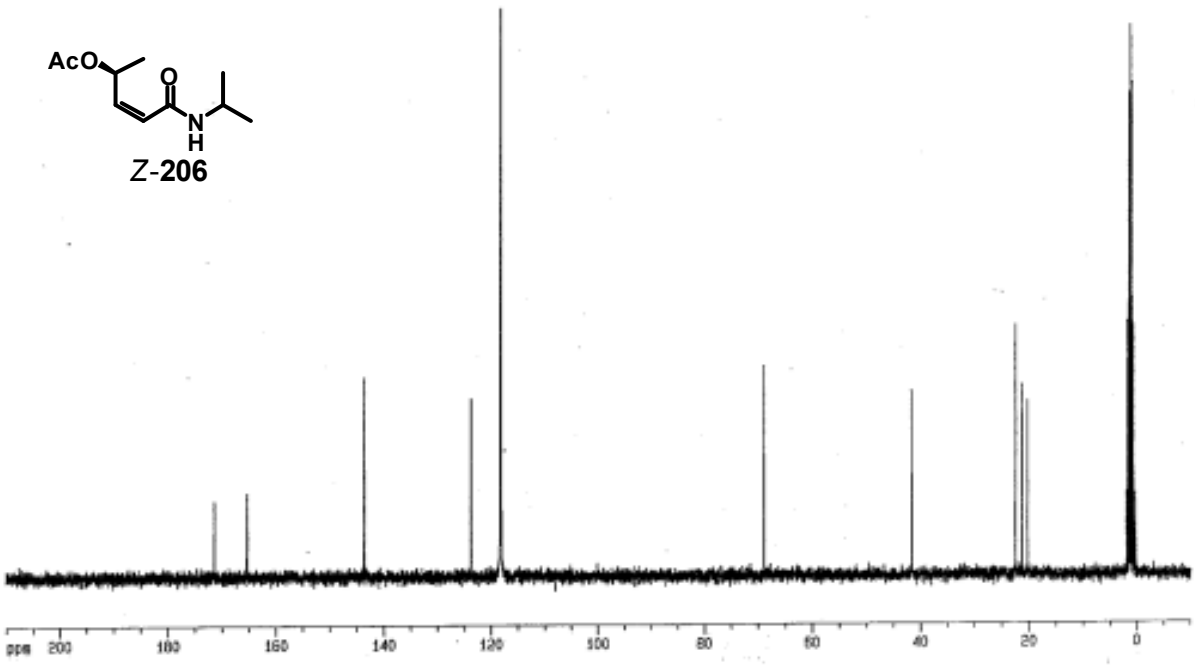
[13]**C NMR of 204**: D_2O, 293 K, 75 MHz



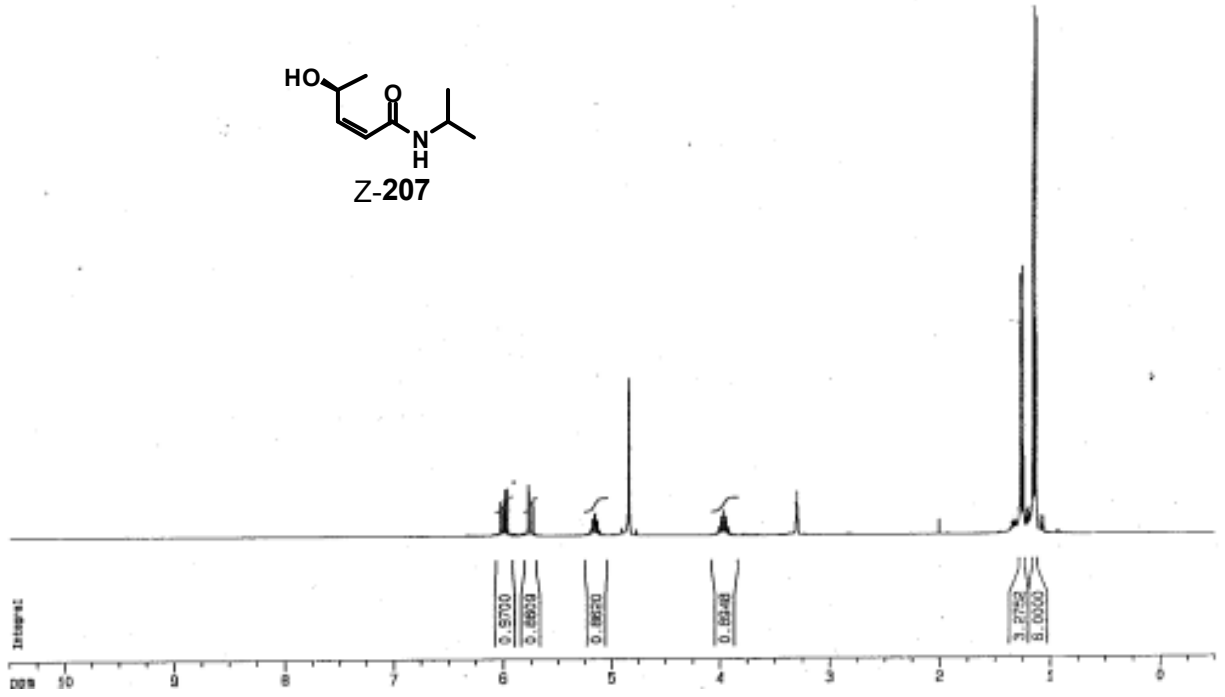
[1]**H NMR of 206**: CD_3OD, 293 K, 300 MHz



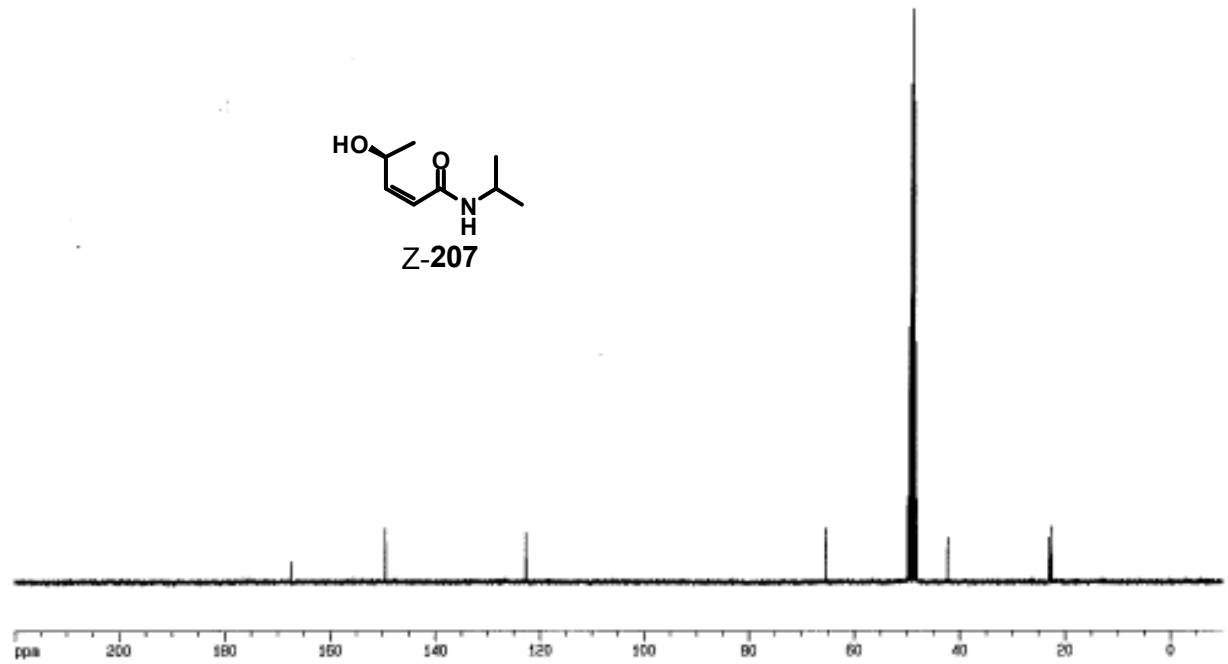
[13]**C NMR of 206**: CD_3CN, 293 K, 75 MHz



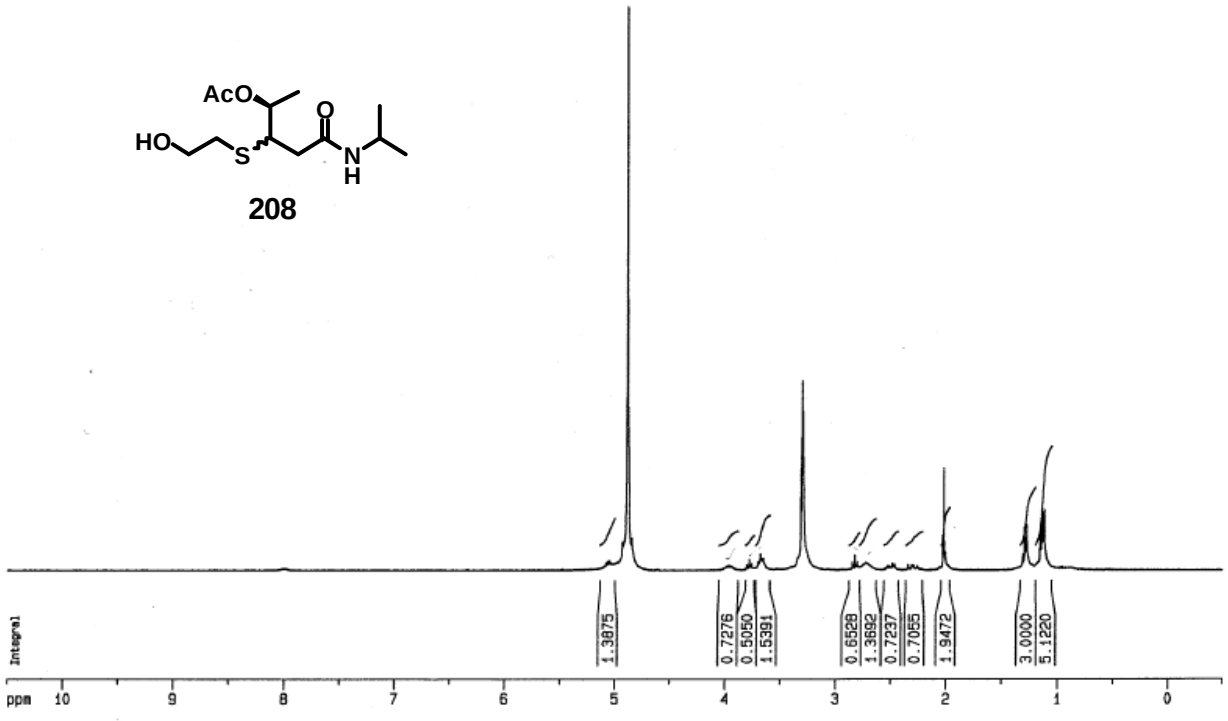
[1]**H NMR of 207**: CD_3OD, 293 K, 300 MHz



[13]**C NMR of 207**: CD_3OD, 293 K, 125 MHz



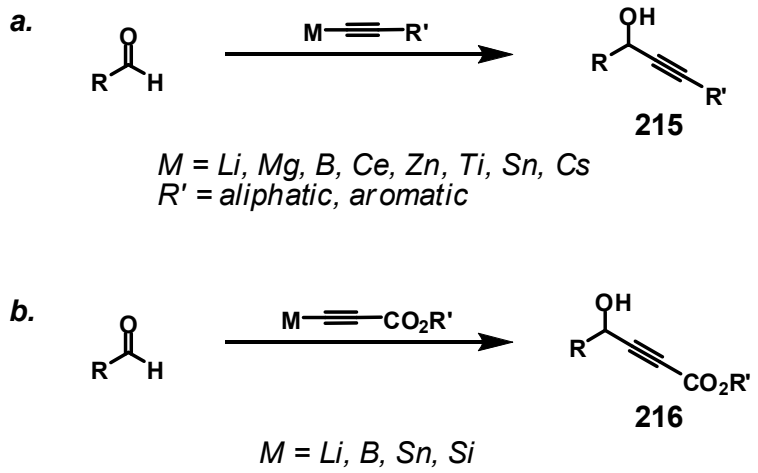
^{1}H NMR of 208: CD_3OD, 293 K, 300 MHz



2.0 SILVER AND ZIRCONIUM PROMOTED ALKYNYL ADDITIONS TO ALDEHYDES AND EPOXIDES

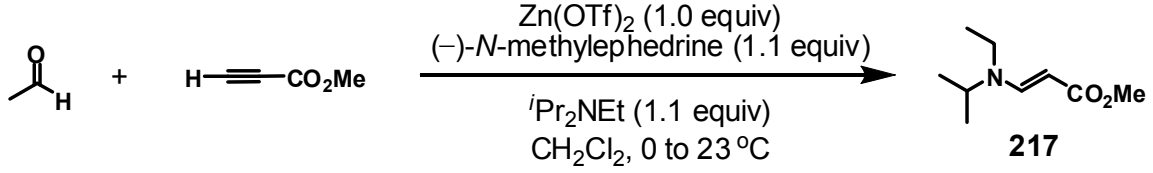
2.1 METHODS FOR ALKYNYL ADDITIONS TO ALDEHYDES

Methods to give addition of alkynes to aldehydes have tremendously impacted synthetic organic chemistry because the products are highly versatile propargylic alcohols **215** (Scheme 49).[174] When the R' group of the alkyne is an aliphatic or aromatic group, the terminus of the alkyne may be deprotonated and substituted with a variety of metals (Scheme 49*a*). These metals may be Li, Mg, B, Ce, Ti, Sn, and Cs. When propiolate esters are used as the nucleophiles the products are γ-hydroxy-α,β-unsaturated ynoates **216**, which are highly versatile compounds that have been exploited in complex molecule synthesis (Scheme 49*b*).[175-184] To prepare the lithium acetylides from propiolate esters, the most common metal used is Li (although B, Sn, and Si can be used).[185] To generate these lithium acetylides, typically a strong base such as ^{n}BuLi is employed, and therefore base-stable substrates must be employed to tolerate the highly basic conditions. Morever, ^{n}BuLi is also nucleophilic towards aldehydes and ketones, and thus the stoichiometry of reagents must be carefully controlled.



Scheme 49. (*a*) Preparation of propargylic alcohols from aldehydes; (*b*) Preparation of γ-hydroxy-α,β-unsaturated ynoates from aldehydes.

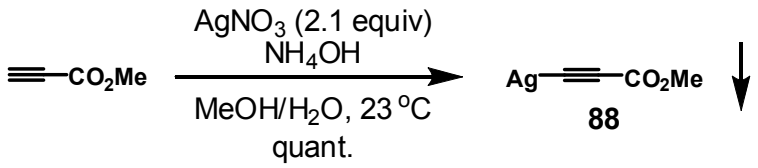
In 2002, the Koide group became interested in the preparation of γ-hydroxy-α,β-unsaturated ynoates from aldehydes under milder conditions. In 2000, a new alkynyl addition method was developed in the Carreira laboratories involving the in situ preparation of zinc acetylides, from terminal alkynes, $Zn(OTf)_2$, and tertiary amines, and their subsequent additions to aldehydes.[83,186-189] However, these reaction conditions proved to be incompatible with methyl propiolate and acetaldehyde giving **217** in 10–30% yields with no formation of the desired ynoate (Scheme 50).[190] This called for the development of a more robust, general, and mild method to form γ-hydroxy-α,β-unsaturated ynoates from aldehydes and ynoates.



Scheme 50. Unexpected formation of **217**

2.2 DEVELOPMENT OF THE SILVER AND ZIRCONIUM PROMOTED ALKYNYL ADDITION TO ALDEHYDES

Due to the difficulty in preparing γ-hydroxy-α,β-unsaturated ynoates using lithium and zinc acetylides, a different strategy was envisioned. The preparation of other terminally-protected alkynes (B, Sn, Si) also requires the use of strong bases which is undesirable (Scheme 49*b*). In contrast, silver acetylide **88** is readily prepared in excellent yields employing a known protocol using $AgNO_3$ and aqueous ammonia (Scheme 51).[191] Moreover, this method was shown to be an effective method to prepare several other silver acetylides. These reagents are H_2O stable, of low basicity and nucleophilicity.[191-193]

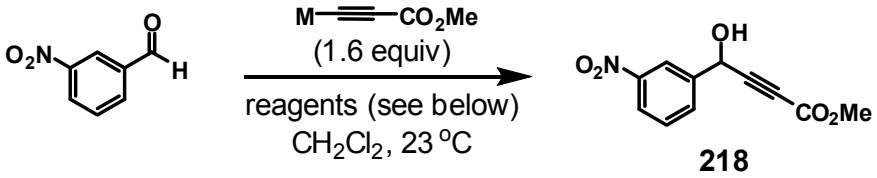


Scheme 51. Preparation of silver acetylide **88**

The condensation of silver acetylide **88** and *m*-O_2NPhCHO was chosen for the model system (Table 15). No condensation occurs between **88** and *m*-O_2NPhCHO (entry 1), and therefore Lewis acid additives were screened. Addition of BF_3•OEt_2 or $Cu(OTf)_2$ to the reaction mixture did promote the generation of ynoate **218** (entries 2 and 3). Addition of $ZnBr_2$ and Cp_2TiCl_2 to the reaction mixture afforded this ynoate in 4% and 30% yields, respectively (entries 4 and 5). However, the use of $ZrCl_4$ and Cp_2ZrCl_2 gave **218** in 51% and 73% yields, respectively (entries 6 and 7). Therefore, zirconium appeared to be the metal of choice, and the reaction was optimized using Cp_2ZrCl_2. The Jordan, Suzuki, and Wipf groups observed that silver salts can

promote the couplings of organozirconium species and aldehydes.[194-197] Addition of a substoichiometric amount of AgOTf gave **218** in 95% yield, in only 5 h (entry 8). As a control reaction, this reaction was attempted using Cp_2HfCl_2 which gave no formation of this ynoate (entry 9). Moreover, the use of methylpropiolate in combination with Cp_2ZrCl_2 led to no formation of **218** (entry 10).[121] Therefore, the use of Cp_2ZrCl_2 in combination with a substoichiometric amount of AgOTf was optimal to form **218**. The role of the Cp_2ZrCl_2 appeared

Table 15. Development of the Cp_2ZrCl_2-promoted alkynlation reaction



218

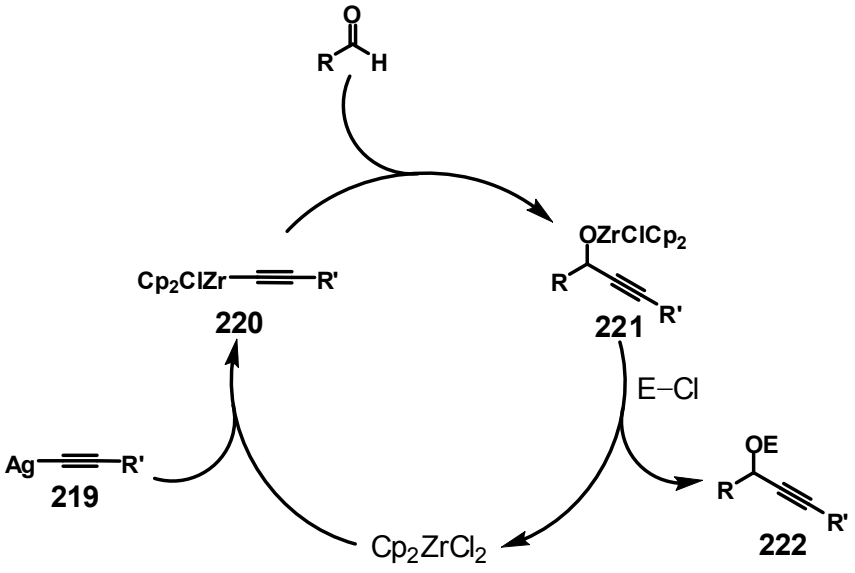
entry	M	reagents	time (h)	yield (%)
1	Ag	none	30	0
2	Ag	$BF_3 \bullet OEt_2$ (1.2 equiv)	30	0
3	Ag	$Cu(OTf)_2$ (1.2 equiv)	7	0
4	Ag	$ZnCl_2$ (1.2 equiv)	15	4
5	Ag	Cp_2TiCl_2 (1.2 equiv)	24	30
6	Ag	$ZrCl_4$ (1.2 equiv)	27	51
7	Ag	Cp_2ZrCl_2 (1.2 equiv)	30	73
8	Ag	Cp_2ZrCl_2 (1.2 equiv) + AgOTf (0.2 equiv)	5	95
9	Ag	Cp_2HfCl_2 (1.2 equiv) + AgOTf (0.2 equiv)	18	0
10	H	Cp_2ZrCl_2 (1.2 equiv)	30	0

to be more than that of a simple Lewis acid as demonstrated in entry 2, presumably generating a zirconium acetylide in situ by transmetallation and precipitation of AgCl.[198]

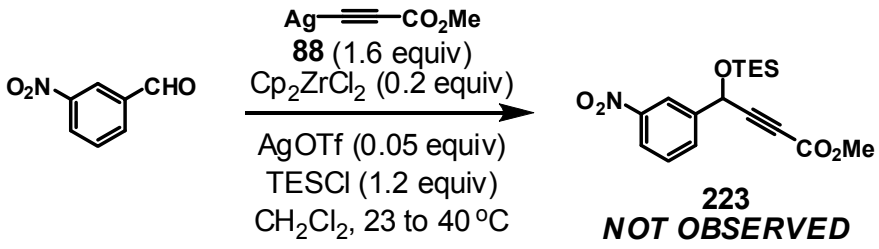
This potentially valuable methodology was then further explored, and 13 successful reactions were described yielding ynoates in 59–95% yields.[121] The reaction conditions were found to be compatible with a variety of functional groups including variously substituted aromatic aldehydes, enolizable aliphatic aldehydes, acid labile ^{t}butyl carbamates bearing an acidic N-H bond, base labile Fmoc carbamates, epoxides, and acid labile ketals. Moreover, this method proved to be higher yielding and gave higher diastereoselectivities for two chiral aldehydes than the method described by Midland.[121,185]

Later, a catalytic version of this Ag/Zr-promoted reaction of aldehydes and silver acetylides **219** was desired to eliminate the need for a stoichiometric amount of Cp_2ZrCl_2 (Scheme 52). This catalytic cycle would require an electrophile, E–Cl, to break the Zr–O bond in **221**, to regenerate Cp_2ZrCl_2 and give **222** as the product. Carreira's catalytic method involved protonolysis of the putative Zn–O bond from a protonated amine using heat to achieve the activation barrier for this reaction. However, HCl would be required for protonolysis of Koide's alkynyl addition reaction and thus too harsh of conditions. Alternatively, chlorotriethylsilane could serve the role as regenerating Cp_2ZrCl_2 and promoting the formation of **222**.[199] This would require that the sum of the bond enthalpy of the Zr–Cl and O–Si bonds be greater than that of Zr–O and Cl–Si bonds to drive this reaction, and that the activation barrier is low. Although some of these bond enthalpies are unknown, this reaction was still deemed reasonable. Towards this end, treatment of *m*-O_2NPhCHO to a substiochiometric amount of Cp_2ZrCl_2 and AgOTf, and a stoichiometric amount of **88** and TESCl did not afford ynoate **223** (Scheme 53). Furthermore,

heating of this reaction mixture to 40 °C did not promote the desired reaction, and therefore this strategy was temporarily abandoned.



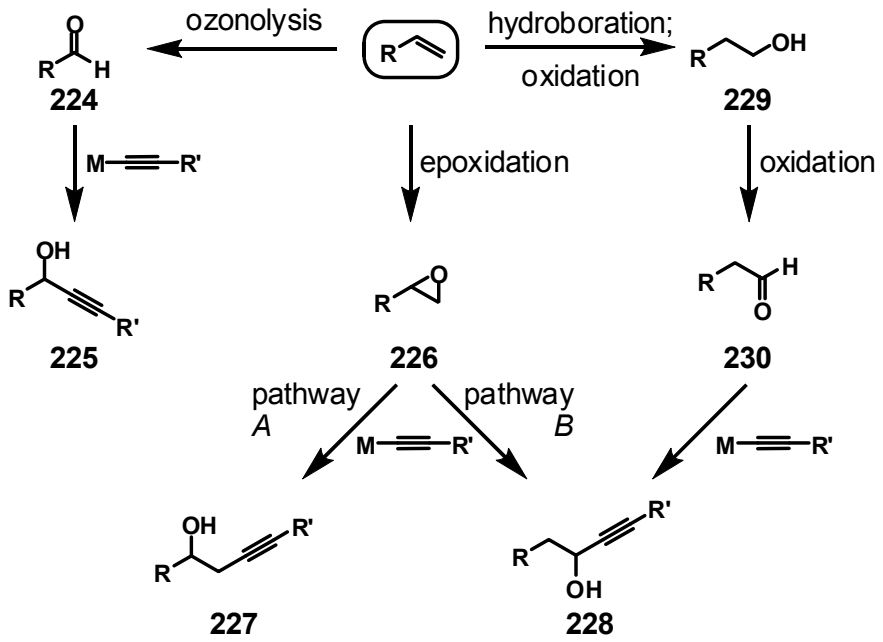
Scheme 52. Proposed catalytic cycle for the alkynyl addition



Scheme 53. Unsuccessful catalytic alkynylation

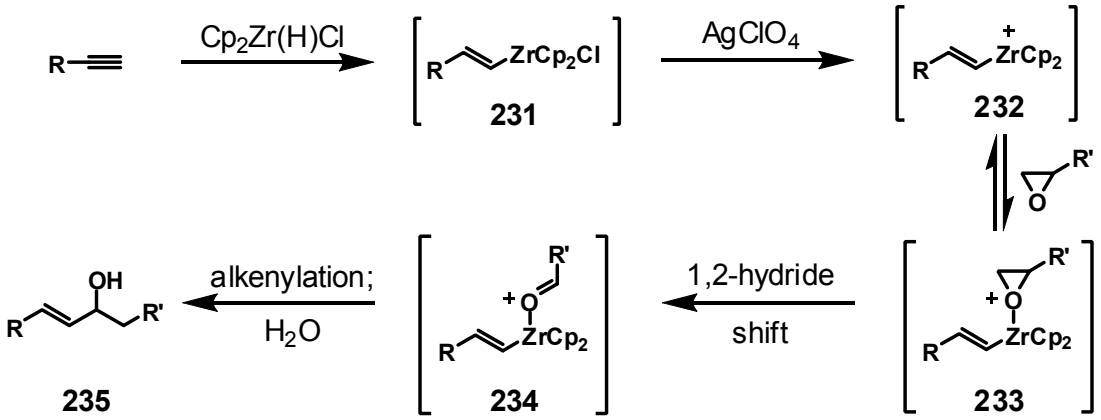
2.3 METHODS FOR ALKYNYL ADDITIONS TO EPOXIDES

A complementary reaction to the alkynyl addition to aldehydes is to epoxides (Scheme 54). Alkenes are a common precursor to both aldehydes **224** and epoxides **226** by ozonolysis and epoxidation reactions, respectively. The subsequent alkynyl addition to aldehyde **224** with metallated alkyne **219** giving **225** as products has been discussed previously. However, alkynyl addition to epoxide **226** can proceed by either pathway A to afford homopropargylic alcohols **227** or by pathway B to afford propargylic alcohols **228**. Pathway A is a widely used method to add alkynes to enantioenriched epoxides stereospecifically, and therefore has been oft-employed in organic synthesis.[200-204] Typically, pathway A can be accomplished when M = Li and highly Lewis-acidic BF_3•OEt_2 is added to the reaction mixture.[202] Pathway B is complementary to the alkynyl addition of aldehyde **224** because **228** contains one extra carbon not removed by the ozonolysis reaction. Although pathway B should be of importance, there remained no general method for this transformation, only scarce examples in the literature.[205,206] Alternatively, **228** can be obtained by hydroboration of an alkene to give **229**, subsequent oxidation to aldehyde **230**, and finally alkynyl addition. However, this strategy requires one more synthetic step than the epoxidation/alkynyl addition strategy.



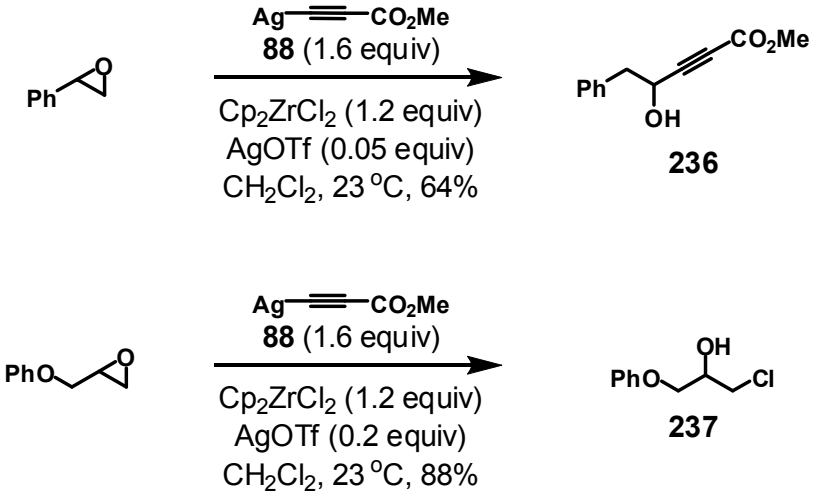
Scheme 54. Alkynyl addition reactions

The utility of pathway B (Scheme 54) has been neglected with respect to alkynyl addition, but other nucleophilic addition reactions have been exploited. Rose and coworkers developed methods to selectively add phenyl groups to butadienemonoxide to give propargylic and homopropargylic alcohols.[207] More recently, the Wipf group developed a method to add alkenyl groups to epoxides to give allylic alcohols (Scheme 55).[196] It was postulated that addition of Schwartz's reagent [$Cp_2Zr(H)Cl$] across an alkyne to generate alkenylzirconocene **231**, and subsequent reaction with $AgClO_4$ would give cationic complex **232**.[195] Coordination of an epoxide would give **233**, which could undergo a 1,2-hydride shift to complex **234**, and subsequent intramolecular alkenyl addition would give alcohol **235** upon aqueous workup. Therefore, it is possible that the aldehyde alkynyl addition method developed in the Koide group could function similarly.



Scheme 55. Wipf's alkenyl addition method

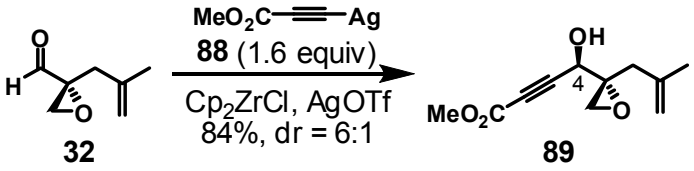
With the goal of alkynyl addition to epoxides via pathway B (Scheme 54), initial experimentation was undertaken in the Koide laboratories. It was demonstrated that styrene oxide smoothly reacts with silver acetylide **88** to give ynoate **236** in 64% yield (Scheme 55). However, 1,2-epoxy-3-phenoxypropane under similar reaction conditions gave chlorohydrin **237** in 88% yield. Due some to initial success with this methodology and the scarcity for this method in the literature it warranted further investigation.



Scheme 56. Initial alkynylation experiments

2.4 PREPARATION OF SILVER ACETYLIDE 88

The reaction of epoxyaldehyde **32** and silver acetylide **88** was crucial in the total synthesis of FR901464, but inconsistent yields (20–84%) beset scale-up efforts, and **88** was thought to be the cause of the irreproducibility (Scheme 57). Due to these unpredictable yields, the preparation of **88** was studied thoroughly. The source of methyl propiolate and silver nitrate were found to be inconsequential to the yield of **88** or to the alkynyl addition reaction. To determine the quantity of NH_4OH required for the preparation of **88**, a solution of 1.00 N NH_4OH was employed, which determined that 2.0 molar equivalents of NH_4OH (relative to $AgNO_3$) were required to generate a clear solution of aqueous $AgNO_3$. The source of NH_4OH was also shown to be inconsequential for the alkynyl addition reaction. Finally, the purity of methanol and H_2O (tap, deionized, and Millipore) were examined, but displayed no difference in the subsequent alkynyl addition reaction. From these experiments it was determined that the quality of the reagents used for the preparation of silver acetylide **88** were not responsible for the poor alkynyl addition results, and other variables would have to be investigated.



Scheme 57. Alkynyl addition to **88**

The first variable that was examined was the exposure to light during the preparation of **88** (possibly light-sensitive as is $AgNO_3$). Separate preparations of **88**, with one being exposed to ambient light, and the other protected from light with aluminum foil gave no difference in the

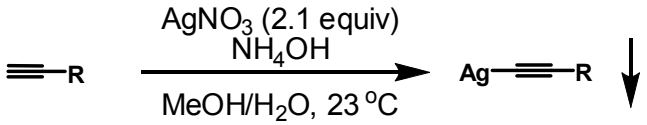
physical appearance of this silver acetylide. More importantly, the subsequent alkynyl addition reaction gave low yields in forming **218** (~30% yield). The second variable examined was residual H_2O. Drying for several days under high vacuum while drying over P_2O_5 gave no improvement in yield of **218**. Cationic silver coordinates well with phosphines and amines, but no phosphines were present in the preparation of **88**. However, it was possible that the washing process of **88** was inefficiently removing all of the ammonia. Therefore, a sample of **88** that was found to afford **218** in 30% yield for the alkynyl addition reaction to *m*-O_2NPhCHO was rewashed with H_2O thoroughly and dried under high vacuum overnight. The resulting silver acetylide was used in the alkynyl addition reaction of *m*-O_2NPhCHO to yield **218** in 64% yield! This experiment was validated by using this washing procedure to prepare **88**, and consistently giving high yields in the subsequent alkynyl addition reaction. It was concluded that residual H_2O-soluble materials poisons for the Ag/Zr-promoted alkynyl addition reaction, but can be easily removed by thorough washing of the silver acetylides with H_2O.

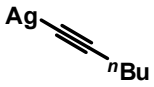
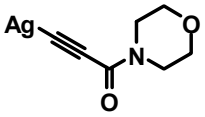
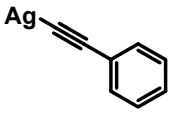
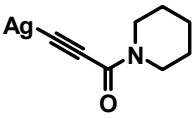
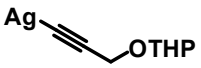
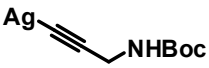
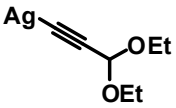
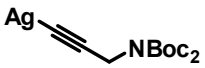
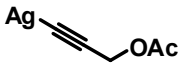
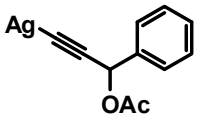
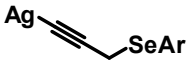
2.5 PREPARATION, APPEARANCE, AND REACTIVITY OF SILVER ACETYLIDES

With a well understood process to prepare **88** from methyl propiolate, the generality of the procedure was explored (Table 16). Simple aliphatic and aromatic terminal alkynes are compatible with the reaction conditions as demonstrated with the quantitative preparations of **238** from 1-hexyne and **239** from phenylacetylene (entries 1 and 2). Protected acid-labile propargylic substituted alkynes gave **240** and **241** in 45% and quantitative yields, respectively (entries 3 and 4). However, the low yield of **240** was attributed to its solubility in CH_2Cl_2 during

the washing process, which is discussed below. Base-labile acetate-protected hydroxy-groups are compatible with the reaction conditions, and were used to prepare acetylides **242** and **248** in 79–97 and 81% yields, respectively (entries 5 and 11). These are remarkable results since the pK_a of the α-hydrogen of an ester and the acetylenic hydrogen are both ~25, which demonstrates the selective activation of the terminal alkynes in the presence of similarly acidic hydrogen atoms. Moreover, in the presence of excess ammonia, the deacetylations of **242**, **248**, and their respective hydrocarbon starting materials appear to be minor. The preparation of **243** was accomplished in the presence of a selenium atom in 90% (entry 6). Preparations of **244** and **245** were accomplished in 76 and 86% yields respectively showing the tolerance of amides (entries 7 and 8). Finally, preparation of **246** and **247** were accomplished in 95 and 52% yields, respectively, demonstrating the compatibility of protected amines (entries 9 and 10). Therefore, the preparation of silver acetylides is broadly applicable to a variety of aliphatic, conjugated, acid-labile, and base-labile terminal alkynes.

Table 16. Preparation of silver acetylides



entry	product	yield (%)	entry	product	yield (%)
1	 **238**	quant.	7	 **244**	76
2	 **239**	quant.	8	 **245**	86
3	 **240**	45	9	 **246**	95
4	 **241**	quant.	10	 **247**	52
5	 **242**	79–97	11	 **248**	81
6	 **243**: Ar = *o*-O_2NPh	90			

Typically, silver acetylides are off-white powders, as shown with silver acetylide **88** (Figure 25*a*). After 10 d of exposure of thoroughly washed **88** to ambient air, the appearance slowly changes to a light tan solid (Figure 25*b*). Moreover, exposure of **88** to ambient air and light causes no further change in the appearance of this silver acetylide (Figure 25*c*). To test the efficacy of these samples of **88**, they were subjected to the alkynyl addition conditions using *m*-

O_2NPhCHO as the electrophile to give **218** in 76 and 75% yields respectively (compared to 81% for freshly prepared **88** from the same batch). However, insufficient washing of **88** with H_2O gives a tan material that rapidly decomposes to a dark brown solid that gives adverse effects on the subsequent alkynyl addition reaction. Although this silver acetylide is fairly insensitive towards air, light, and moisture,[191,192] silver acetylides are typically stored in amber vials/bottles as a precaution.

Figure 25. Appearances of **88**: (*a*) freshly prepared; (*b*) exposed to air for 10 d; (*c*) exposed to air and ambient light for 10 d

The solubility of these silver acetylides in organic solvents is not always predictable, but generally are more soluble in CH_2Cl_2 with more hydrophobic character. Since silver acetylide **88** was found to be poorly soluble in CH_2Cl_2, the final washing would be with 9:1 CH_2Cl_2/MeOH to dry the solid and remove organic impurities. However, this procedure is usually omitted since silver acetylides **238**, **240**, **241**, **242**, **245**, **247**, and **248** were found to be soluble in CH_2Cl_2. Silver acetylide **246** was approximately soluble at 0.1 M in CH_2Cl_2 at 23 °C, while **239**, **243**, and **244** were poorly soluble. Therefore, it remains inconclusive what molecular alterations give the bulk properties of these silver acetylides. Although a common bulk property of these reagents is the insolubility in H_2O and MeOH.

Koide and Naka demonstrated that **88** slowly decomposed when the neat material was heated to 150 °C, without explosion.[190] However, the safety of using silver acetylides was further examined partially because of two safety concerns in the literature.[121,208,209] A falling hammer test, an industrial standard for safety, was performed to examine the stability of silver acetylide **88** towards shock. The off-white powder was placed on aluminum foil (Figure 26*a*), and subsequently struck with a hammer, but neither an explosion of **88** nor physical change in appearance was observed (Figure 26*b*). Moreover, this silver acetylide was prepared for the total synthesis of FR901464 in 140 mmol scale, and used for the alkynyl addition of epoxyaldehyde **88** (90 mmol) in the same scale without precaution or incident.

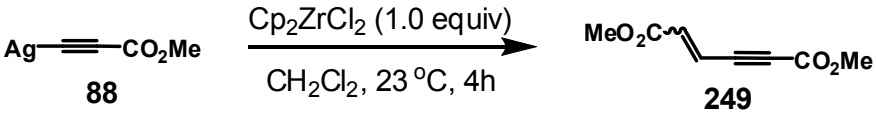
a.  ***b***. 

Figure 26. Falling hammer test of **88**: (*a*) appearance of **88** before striking with a hammer; (*b*) appearance of **88** after being struck with a hammer

To examine why less silver acetylide **88** than Cp_2ZrCl_2 was detrimental for the alkynyl addition of aldehydes and to confirm some trace impurities, the following control reactions were performed (Table 17). Treatment of Cp_2ZrCl_2 with 0.45 equiv of silver acetylide **88** gave only 6% of exclusively E-**249** (entry 1). Increasing the amount of **88** to 1.1 equiv caused a decrease in the already low yield of **249** to 3% in a 1:1 E/Z ratio. Further increasing of **88** to 2.1 equiv gave enyne **249** in 4% yield in a 1:1 E/Z ratio. The low yields of **249** did not increase by the addition

of more **88**, and thus are likely intermediates of a polymerization process, since Zr-species are excellent polymerization catalysts.[210-213] This explains why an excess of **88** is beneficial to the alkynyl addition yield, and why it is better to add it to the reaction mixture after the aldehyde and Cp_2ZrCl_2.

Table 17. Formation of enynes **249**



entry	equiv of **88**	yield (%)	*E*/*Z*[a]
1	0.45	6	1:0
2	1.1	3	1:1
3	2.1	4	1:1

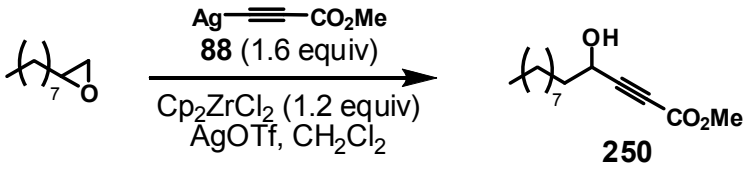
[a] Based on isolated yields

2.6 BROADENING THE SCOPE OF THE EPOXIDE OPENING METHODOLOGY

With an understanding of the Ag/Zr-promoted alkynyl addition of aldehydes, the successful implementation in the addition to styrene oxide, and an arsenal of silver acetylides, the epoxide alkynyl addition generality was further explored (Table 18). The model epoxide chosen was 1,2-epoxydecane, and the model silver acetylide was **88**. Reaction of these reagents to the standard alkynyl addition reaction conditions gave ynoate **250** in 44% yield (entry 1). Simply increasing the temperature of the reaction to 40 °C improved the yield to 57% (entry 2). Alternatively, implementation of 0.5 equiv of AgOTf increased the yield of **250** to 58% (entry 3), but

increasing the amount of AgOTf to 1.0 equiv had a deleterious effect giving this ynoate in only 43% yield (entry 4). Therefore, either by heating or adding 0.5 equiv AgOTf to the reaction mixture was effective in preparing **250**, but heating of the reaction mixture proved not to be a general method (see below).

Table 18. Optimization for the alkynyl addition to 1,2-epoxydecane

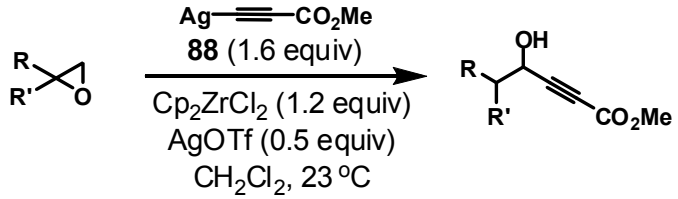


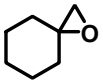
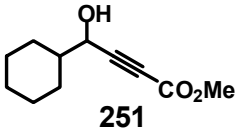
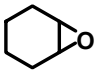
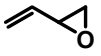
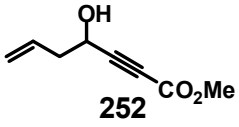
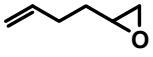
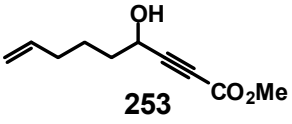
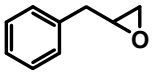
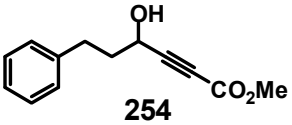
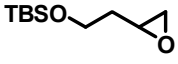
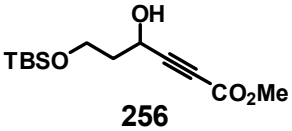
entry	AgOTf (equiv)	temp (^{o}C)	% yield
1	0.2	23	44
2	0.2	40	57
3	0.5	23	58
4	1.0	23	43

With optimized epoxide alkynyl addition reaction conditions in hand, the epoxide scope was explored (Table 19). Reaction of 1-oxaspiro[2.5]octane (**205**) to the alkynyl addition conditions gave **251** in 43% yield. However, lowering the amount of AgOTf to 0.2 equiv in this reaction gave **251** in 54% yield (entry 1). Subjection of cyclohexene oxide or cyclopentene oxide to the alknylation conditions generated intractable mixtures consisting of the desired products, ring-contracted products, and chlorohydrins (entries 2 and 3). Butadienemonoxide gave **252** in 9% yield under the alkynyl addition conditions (entry 4). Treatment of 1,2-epoxy-5-hexene to the alkynyl addition conditions gave **253** in 33% yield, and interestingly only 12% of this ynoate was formed when the reaction was conducted with 0.2 equiv AgOTf and at 40 °C (entry 5). Similarly,

1,2-epoxy-3-phenylpropane gave **254** in 22% yield, but afforded no product when treated with 0.2 equiv AgOTf and at 40 °C (entry 6). Finally, epoxide **255** afforded **256** in 35% yield under the reaction conditions (entry 7). These results show that monosubstituted and 1,1-

Table 19. Epoxide scope with silver acetylide **88**



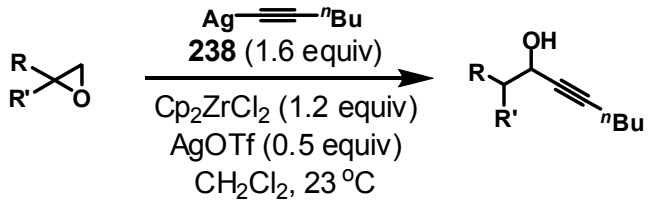
entry	epoxide	time (h)	product	yield (%)
1		6, 3[a]	 **251**	43, 54[a]
2		8	intractable mixture	NA
3		6	intractable mixture	NA
4		6	 **252**	9
5		8	 **253**	33, 12[a,b]
6		8	 **254**	22, 0[a,b]
7	 **255**	6.5	 **256**	35

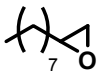
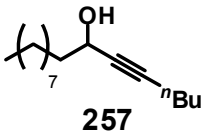
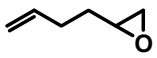
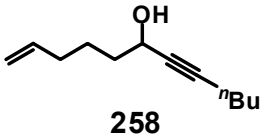
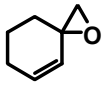
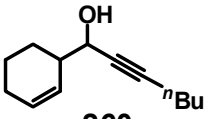
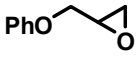
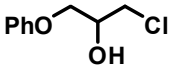
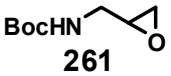
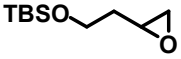
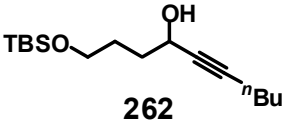
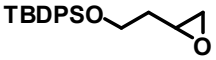
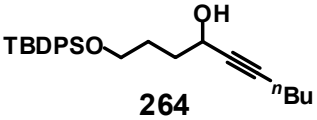
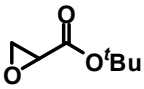
[a] 0.2 equiv AgOTf employed; [b] 40 °C reaction temperature

disubstituted epoxides are compatible for this reaction, and that additional oxygen atoms are tolerated on the epoxide. However, cyclic 1,2-disubstituted epoxides suffer from poor selectivity in 1,2-alkyl vs. -hydrogen atom shifts, and sensitive allylic epoxides may be challenging substrates to add electron deficient alkynyl groups under these reaction conditions.

Since silver acetylide **88** is electron poor from the inductively electron withdrawing ester moiety, a more electron rich alkyne could perform better in this alkynyl addition reaction. The results from this hypothesis using silver acetylide **238** are shown in Table 20. Treatment of 1,2-epoxydecane gave **257** in 69% yield (entry 1). Somewhat surprisingly, 1,2-epoxy-5-hexene gave **258** in 59% yield (entry 2), a rather large increase in yield (26%) as compared to the yield in forming **253**. Allylic spiroepoxide **259** generated **260** in 53% yield and a 2:1 unassigned diastereomeric ratio under the reaction conditions (entry 3). This was a surprising result due to the instability of this epoxide, and because the alkene avoided migration during the reaction conditions. When 1,2-epoxy-3-pheoxypropane was subjected to the same reaction conditions again chlorohydrin **237** was the major product (entry 4). Carbamate **261** when subjected to the alkynyl addition conditions generated an intractable mixture (entry 5). Silyl ethers **255** and **263** react similarly under the reaction conditions to afforded **262** and **264** in 52 and 55% yields, respectively (entries 6 and 7). Finally, *t*butylacrylate oxide when subjected to these reaction conditions somewhat surprisingly gave no reaction (entry 8). This table verifies our hypothesis that more electron rich silver acetylide **238** gives products in higher yields as shown in entries 1, 2, and 6. Moreover, highly acid-sensitive allylic epoxides are compatible with the reaction conditions and avoid isomerization of the putative aldehyde to the thermodynamically favored α,β-unsaturated enal.

Table 20. Epoxide scope with silver acetylide **238**

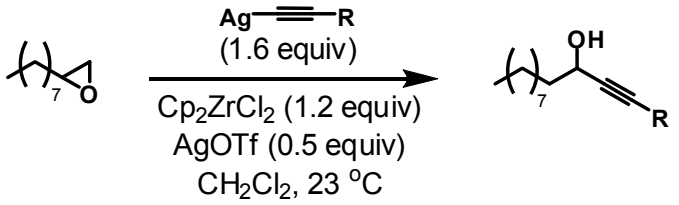


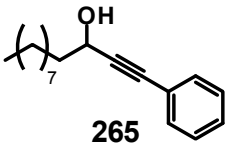
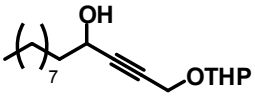
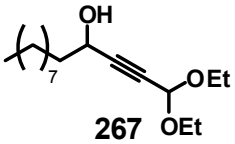
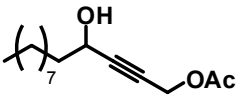
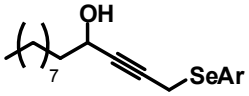
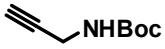
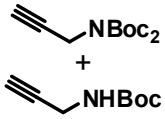
entry	epoxide	time (h)	product	yield (%)
1		8.5	 **257**	69
2		8	 **258**	59
3	 **259**	4	 **260**	53[a]
4		8	 **237**	NA
5	 **261**	10.5	intractable mixture	NA
6	 **255**	8	 **262**	52
7	 **263**	9	 **264**	55
8		8	no reaction	NA

[a] Unassigned dr = 2:1

With an understanding of the limitations of the epoxide for the alkynyl addition reaction, the scope of the alkynes was then examined (Table 21). Silver acetylide derived from phenylacetylene afforded **265** in 82% yield under the reaction conditions (entry 1). Acid labile silver acetylides **240** and **241** remarkably gave propargylic alcohols **266** and **267** in 82 and 81% respectively despite the Lewis acidic reaction conditions (entries 2 and 3). Moreover, the reaction utilizing **241** proved to be mildly sensitive to H_2O, giving **267** in 66% yield in non-distilled CH_2Cl_2, and in 57% yield in non-distilled CH_2Cl_2 and under a wet air atmosphere (entry 3). Base-labile **242** generated propargylic alcohol **268** in 57% yield under the reaction conditions (entry 4). This compound is of synthetic importance by simple conversions to give versatile γ-hydroxy α,β-unsaturated aldehydes as demonstrated by the Carreira group.[214] The alkynyl addition of epoxydecane with **243** gave **269** in 52% yield, showing that selenium atoms are compatible with the reaction conditions (entry 5). Amide-derived silver acetylides **244** and **245** gave no reaction with 1,2-epoxydecane, even upon heating to 40 °C (entries 6 and 7). Quenching of entry 7 with D_2O suppressed the acetylenic proton in the crude ^1H NMR, thereby demonstrating that transmetallation had indeed occurred, and that ambient H_2O was not the reason for the failed alkynyl addition. Propargylic amine-derived silver acetylide **246** gave no desired alkynyl addition, and when quenched with D_2O showed no deuterium incorporation in *N*-(^{t}butoxycarbonyl)propargylamine, implying intermolecular protonation from the acidic N-H moiety (entry 8). Therefore acetylide **247** was prepared and under the alkynyl addition conditions gave only *N*-(^{t}butoxycarbonyl)propargylamine and bis-*N*-(^{t}butoxycarbonyl)propargylamine (entry 9). From these results, acid and base-labile protected hydroxy groups, conjugated alkynes, and selenium atoms are all tolerated, but nitrogen atoms appear to be incompatible with the reaction conditions.

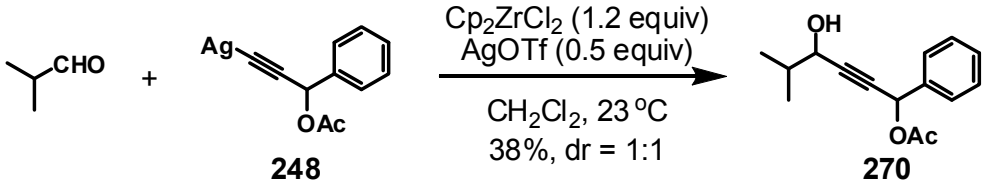
Table 21. Alkyne scope with 1,2-epoxydecane



entry	alkyne	time (h)	product	yield (%)
1	**239**	6.5	 **265**	82
2	**240**	8.5	 **266**	82
3	**241**	7	 **267**	81, 66[a], 57[a,b]
4	**242**	10	 **268**	57
5	**243**	10	 **269**	52
6	**244**	30	no reaction	---
7	**245**	10[c]	no reaction	---
8	**246**	30		---
9	**247**	30		---

[a] Performed in non-distilled CH_2Cl_2; [b] Performed under an air atm; [c] Heated to reflux

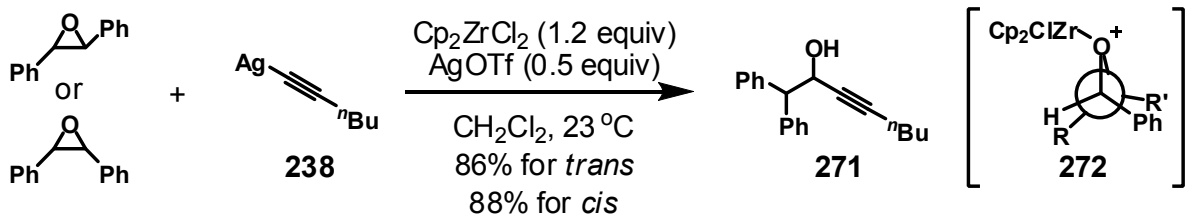
Substrate control is a common method to induce stereoselectivity in condensation reactions when one of the components contains a stereocenter. Towards this end, chiral silver acetylide **248** was prepared and tested under the alkynyl addition conditions to examine whether the propargylic position of this alkyne could direct the forming hydroxy group stereocenter (Scheme 58). This silver acetylide was treated with ^{i}butyraldehyde under the alkynyl addition conditions and afforded the desired adduct **270** in 38% yield but without diastereoselectivity. Therefore, this method to induce stereoelectivity was temporarily abandoned.



Scheme 58. Examining the stereoinduction of a chiral alkyne

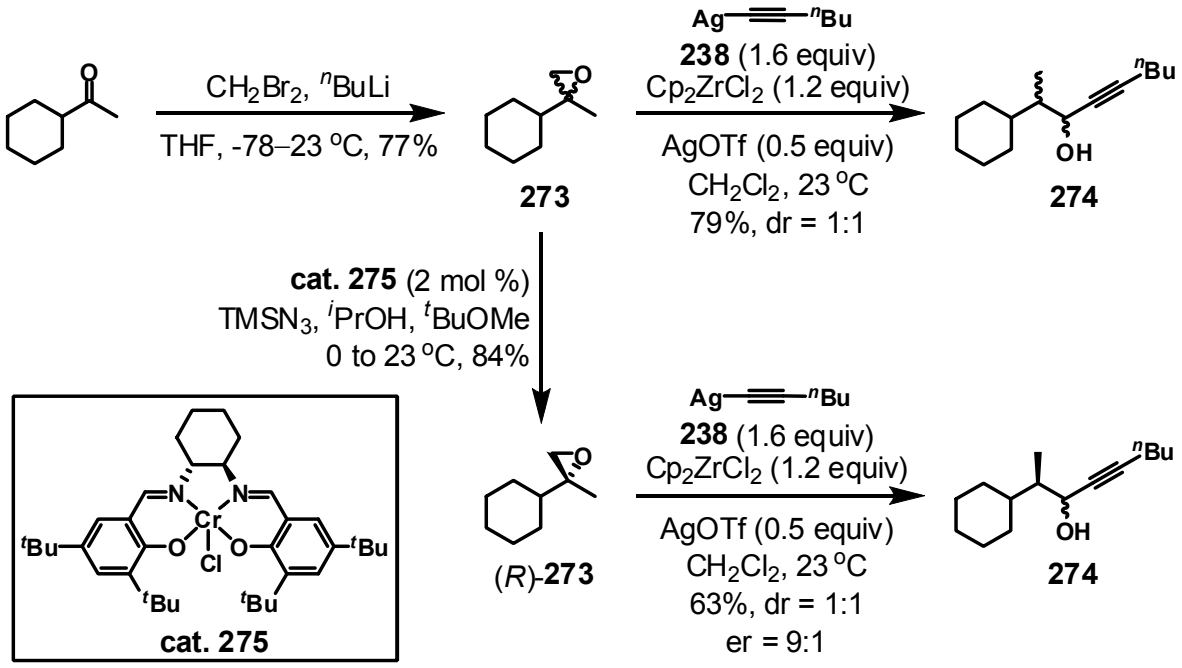
To determine the relationship between *cis* and *trans* disubstituted epoxides and their role in the formation of products, *cis*- and *trans*-stilbene oxide were treated with **238** under the alkynyl addition conditions (Scheme 59). Treatment of *trans*- and *cis*-stilbene oxide to the alkynyl addition conditions with **238** both gave phenyl group migration affording alcohol **271** in 86 and 88% yields, respectively. Inspection of Newman projection **272**, of the Zr-coordinated epoxides, shows that when R = H there will be a clear prefence for the zirconium atom to coordinate away from the bulky phenyl rings. However, when R = Ph, there is no preferential face since *trans*-stilbene oxide is symmetrical. These were somewhat surprising results since in related systems, there have been precedence for *syn* migrations where bulky groups shield one lone pair of the epoxide oxygen atom.[215] However, for *cis*-stilbene oxide no formation of a

ketone via a syn-hydride shift was observed. Therefore, the dominant factor in determining the migrating group is the migratory ability of these possible groups.



Scheme 59. Examining the stereospecificity in 1,2-migration

To determine if a chiral, enantioenriched 1,1-disubstituted epoxide would give enantioenriched products, (*R*)-**273** was synthesized (Scheme 60). Cyclohexyl methyl ketone was transformed to racemic epoxide **273** in 77% yield. This racemic epoxide was then resolved using Jacobsen's catalyst **275** to give (*R*)-**273** in 84% yield (based on $TMSN_3$).[216] Condensation of this enriched epoxide with (*R*)-(+)-α-methylbenzylamine showed a >40:1 ratio of diastereomers when compared to the reaction with racemic **273**, showing the high enantiopurity of (*R*)-**273**. Treatment of **273** with silver acetylide **238** under the reaction conditions gave **274** in 79% yield as a 1:1 mixture of diastereomers. Accordingly, exposure of (*R*)-**273** with **238** under the alkynyl addition conditions afforded enriched-**274** in 63% yield again in a 1:1 diastereomeric ratio. Preparation of the Mosher esters revealed that the enantiomeric ratios of *syn*-**274** and *anti*-**274** were 9:1 as determined by preparation of their Mosher esters and subsequent HPLC analyses. The stereochemistry of enriched-**274** was tentatively assigned based on the literature.[217-219]

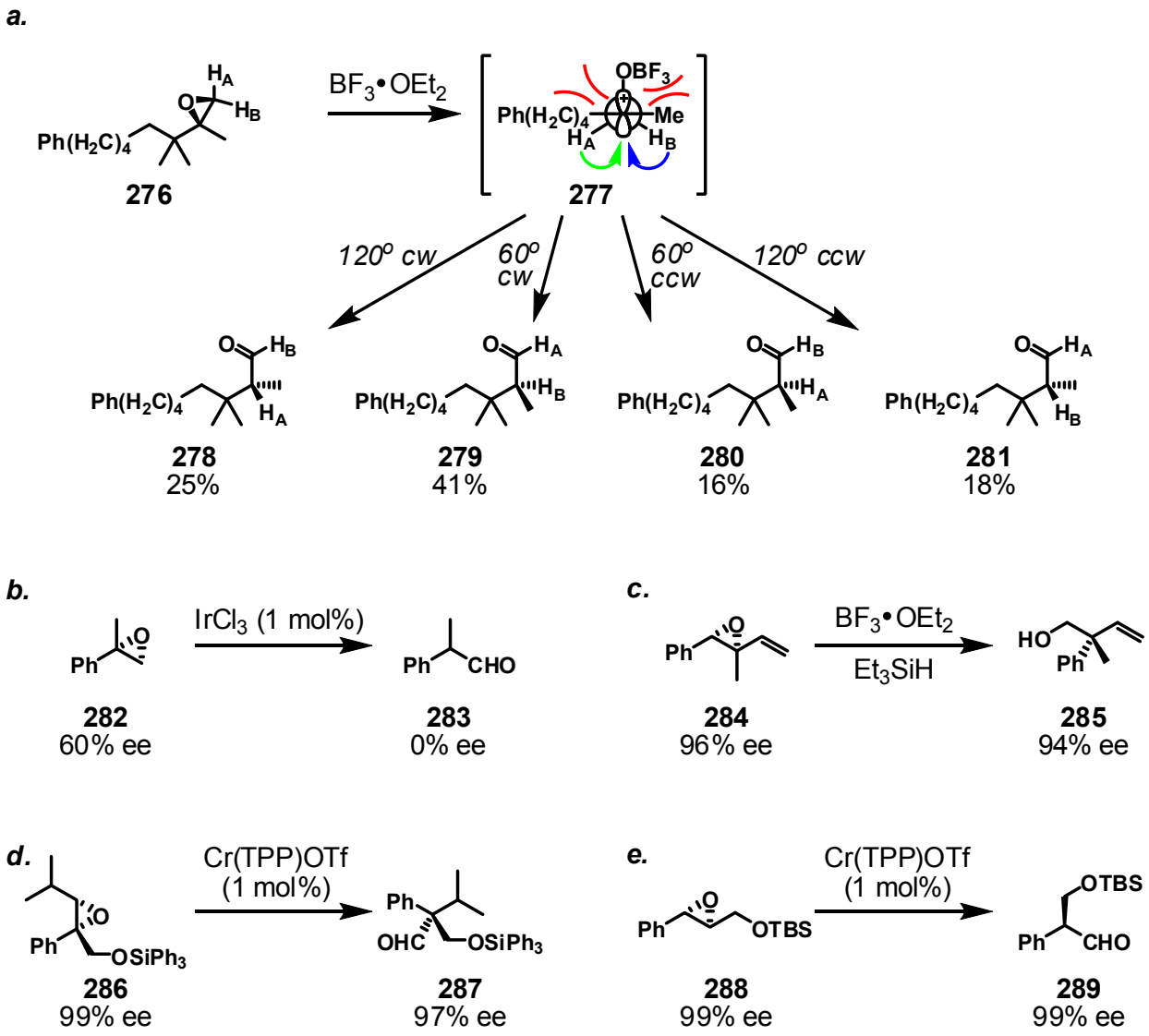


Scheme 60. Examining the enantiospecificity of the 1,2-hydride shift

The stereospecific 1,2-hydride shift observed in (*R*)-**273** could occur via a short- or a long-lived carbocation intermediate, but hydride shift via a long-lived carbocation could allow for free rotation and significant loss of enantiopurity. A long-lived carbocation was suggested by Fujimoto with their results in the epoxide rearrangement of **276** (Scheme 61*a*).[220] Treatment of this epoxide with BF_3•OEt_2 would give putative carbocation **277**. Rotation of this carbocation 60° clockwise would give overlap of H_B with the empty p-orbital of **277** to give **279** in 41% yield after 1,2-hydride shift. Additional 60° clockwise rotation would give overlap of H_A with the empty p-orbital to give **278** in 25% yield. Alternatively, 60° counterclockwise rotation of **277** would give overlap of H_A with the empty p-orbital, producing **280** in 16% yield after 1,2-hydride shift. Additional 60° counterclockwise rotation of **277** would give overlap of H_B with carbocation and lead to the formation of **281** observed in 18% yield. The authors suggested that clockwise rotations were preferred to avoid the steric repulsion of the $–OBF_3$ group with the

bulky $-C(CH_3)_2-(CH_2)_4Ph$ group. Lemaire and coworkers found that the rearrangement of enriched epoxide **282** with $IrCl_3 \bullet \times H_2O$ gave aldehyde **283** in racemic form (Scheme 61*b*).[221] This result may be consistent with Fujimoto's assuming that the lifetime of the putative carbocation allows for 60 and/or 120° rotations in either direction. Since Lemaire's tertiary benzylic carbocation should be more stable than Fujimoto's teriary carbocation, the requisite 120° rotation should be feasible to give a racemic product. Jung found the rearrangement of **284** (96% ee) in the presence of $BF_3 \bullet OEt_2$ and Et_3SiH to give **285** in 70% yield and 94% ee (Scheme 61*c*).[218] The authors explained this result by inferring the greater stability of the putative tertiary allylic carbocation as compared to the secondary benzylic cation, since the migratory abilities of a phenyl and vinyl group are similar. Moreover, this rearrangement would require a 60° rotation that would create only a vinyl-hydrogen atom eclipsing interaction, and thus nearly complete retention of the stereochemical information. Suda and coworkers found the rearrangement of epoxides **286** and **288** to give aldehydes **287** and **289**, respectively, in high yields and with retentions of enantiopurity (Scheme 61*d* and *e*).[222] Both of these rearrangements can be explained by 60° rotations that would create only a carbon-hydrogen atom eclipsing interactions and subsequent aliphatic migration.

The observed stereospecificity is for the rearrangement of (*R*)-**273** is remarkable because no related 1,1-disubstituted epoxides gave any appreciable specificity under these different reaction conditions.[223,224] Moreover, this result could indicate that the lifetime of the putative tertiary carbocation from epoxide (*R*)-**273** is short, and a 60° rotation is strongly preffered (presumably generating a H–Me eclipsing interaction, rather than the H–*c*-Hex eclipsing interaction). Thus, the stereochemical information in (*R*)-**273** is highly conserved as seen in propargylic alcohol **274**.



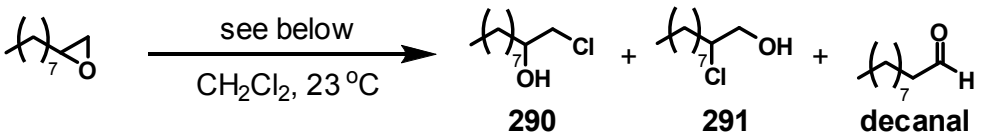
Scheme 61. Rearrangements of chiral epoxides

2.7 MECHANISTIC STUDIES AND PROPOSED MECHANISM

To understand the processes occurring other than the desired alkynyl addition, the roles of all additives were determined (Table 22). Treatment of 1,2-epoxydecane with an excess of Cp_2ZrCl_2 gave a mixture of chlorohydrins **290** and **291** in a 5.0:1 ratio, respectively, without formation of

decanal. Interestingly, treatment of 1,2-epoxydecane with AgOTf gave no rearrangement to decanal. Although, Wipf reported the rearrangement of highly activated styrene oxide under similar conditions.[196] The combination of Cp_2ZrCl_2 and AgOTf generated chlorohydrins **290** and **291** in 87% yield in a 0.8:1 ratio respectively with trace formation of decanal. The combination of these reagents presumably generates $Cp_2ZrCl(OTf)$ in situ and allows for the 1,2-hydride shift to occur, but chlorohydrin formation promoted by Cp_2ZrCl_2 and/or $Cp_2ZrCl(OTf)$ is strongly preferred. Finally, treatment of 1,2-epoxydecane with Cp_2ZrCl_2 and silver acetylide **88** gave chlorohydrins **290** and **291** in 22% yield in a 2.5:1 ratio, respectively, with no formation of decanal. Presumably this reagent combination generates $[Cp_2ClZr–C{\equiv}C–CO_2Me]$ in situ, and is not responsible for the neither the alkynyl addition reaction nor aldehyde formation, but suppresses the formation of chlororhydrins to some extent. From these results, the presumed electronic nature of the zirconium atom plays a crucial role in formation of chlorohydrins, and the propensity for promoting the 1,2-shift. Chlorohydrin formation possibly occurs by different mechanisms due to the wide range of ratios observed in the formation of the two regiomeric products.

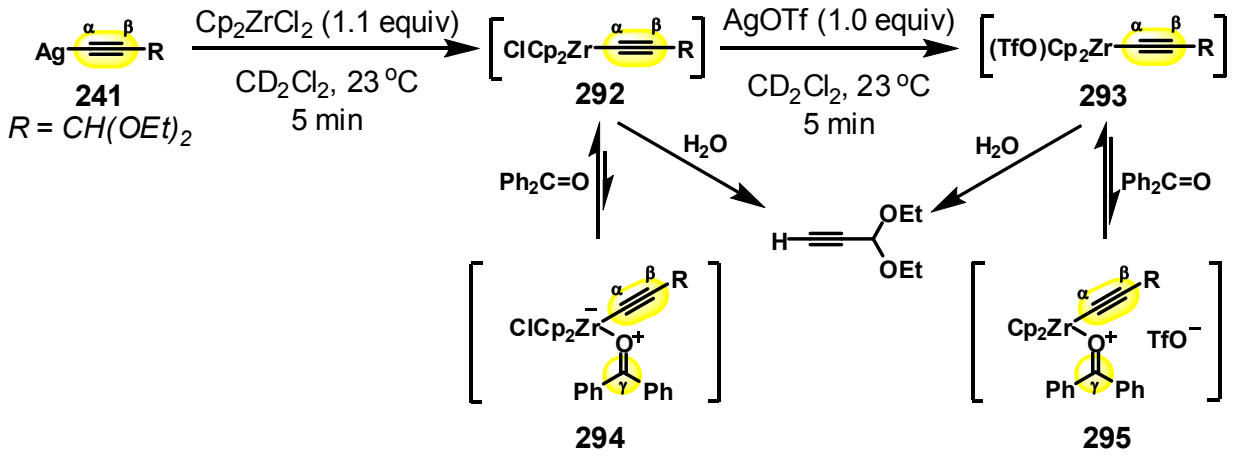
Table 22. Control experiments



entry	reagents (equiv)	**290**:**291** (% yield)	decanal
1	Cp_2ZrCl_2 (1.6)	5.0:1 (83)	none
2	AgOTf (0.5)	none	none
3	Cp_2ZrCl_2 (1.2) + AgOTf (0.5)	0.8:1 (87)	trace
4	Cp_2ZrCl_2 (1.2) + **88** (1.6 equiv)	2.5:1 (22)	none

In order to probe the electronic nature of the zirconium atom in this alkynyl addition reaction NMR experiments were conducted (Scheme 62). Silver acetylide **241** was chosen as a model due to its solubility in CH_2Cl_2, and was then characterized by ^1H and ^{13}C NMR (selected ^{13}C data in Table 23, see experimental section for all data). To an NMR tube was added **241** and Cp_2ZrCl_2 which rapidly formed **292** via transmetallation which was again characterized by ^1H and ^{13}C NMR. Treatment of this zirconium acetylide with a stoichiometric amount of AgOTf rapidly generated a new species showing downfield chemical shifts of the alkyne compared to **292**, which was assigned as **293**. Both **292** and **293** were sensitive to H_2O, and could not be isolated after aqueous workups, only yielding 3,3-diethoxypropyne. To probe the Lewis acidities of these zirconium acetylides, benzophenone was employed as a Lewis base for its attenuated reactivity to towards these species. Treatment of complex **292** with benzophenone showed slight upfield chemical shifts in benzophenone and the alkynyl carbons in the ^{13}C spectra. This was interpreted as an equilibrium existing between the starting materials and ate-complex **294**. However, it is possible that this could imply that the equilibrium is between the starting materials

and an α-chlorohydrin. However, no zirconium α-chlorohydrins have been characterized in the literature and therefore its formation is unlikely. Treatment of **293** with benzophenone gave ^{13}C chemical shifts slightly downfield relative to the starting materials which were interpreted as complex **295**. These results demonstrate that the zirconium atoms in both **292** and **293** are Lewis-acidic, and that **295** exists in a higher population than **294**. Moreover, this is consistent with the observation that AgOTf is required to induce a 1,2-hydride shift in 1,2-epoxydecane.



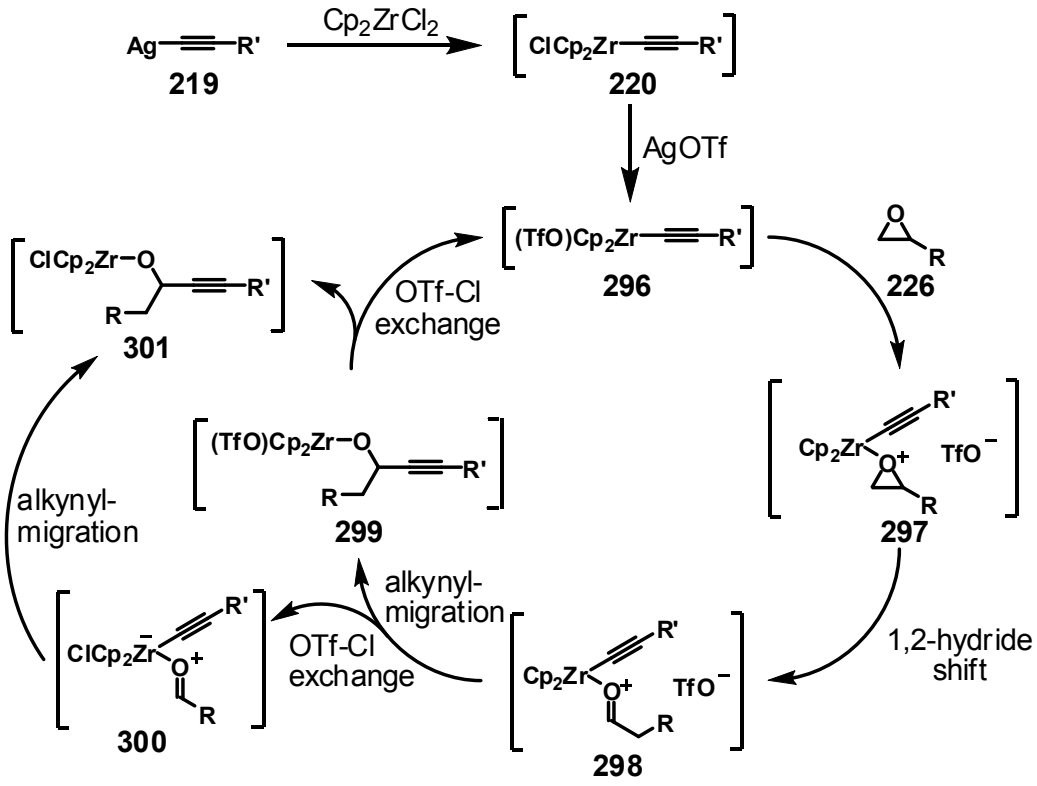
Scheme 62. Spectroscopically characterized species

Table 23. Selected ^{13}C NMR data for **241**, **292**, **293**, **294**, and **295**

compound	^{13}C NMR δ (75 MHz, 293K, CD_2Cl_2)		
	α	β	γ
3,3-diethoxypropyne	73.35	79.60	NA
241 [a]	117.93	93.65	NA
292	114.41	113.77	NA
293 [b]	115.81	114.70	NA
benzophenone	NA	NA	198.68
294	114.42	113.72	198.63
295 [b]	115.82	114.70	196.83

[a] Determined by an HMBC experiment; [b] Contaminated by hydrolysis products.

Based on the understanding of the mechanistic roles of all components involved in the alkynylation methodology, and the spectroscopic characterization of reaction intermediates, the following mechanism is proposed (Scheme 62). Treatment of silver acetylide **219** with Cp_2ZrCl_2 rapidly generates zirconium acetylide **220** that could reversibly coordinate an epoxide and/or lead to chlorohyrin formations. However, in the presence of AgOTf, this compound rapidly generates a more Lewis acidic zirconium acetylide, **296**. This complex can reversibly coordinate epoxide **226** to give **297**, which then is electronically tuned for the 1,2-hydride shift giving aldehyde-zirconium complex **298**. Complex **298** could be responsible for the alkynyl addition to give **299**, or could undergo triflate-chloride exchange to ate complex **300**. This ate complex could enhance the alkynyl addition to give **301**, which may explain why using a stoichiometric amount of AgOTf gave **250** in lower yield due to the lack of chloride ions. Finally, alkoxide-zirconium complex **299** could undergo triflate-chloride exchange to give **301**, explaining why a sub-stoichiometric amount of AgOTf is needed for the reaction.



Scheme 63. Proposed mechanism for the Ag/Zr-promoted alkynyl addition to epoxides

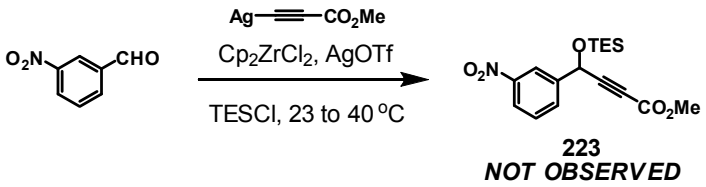
2.8 SUMMARY

There was a need for a general method for the alkynyl addition to epoxides to give propargylic alcohols as products. Towards this end, the Ag/Zr-promoted alkynyl addition methodology discovered in the Koide laboratories was successfully applied. These studies began with the preparation of 11 silver acetylides and examining their safety as reagents for organic synthesis. Subsequently, these silver acetylides were shown to add to epoxides via 1,2-shifts to give propargylic alcohols in the presence of Cp_2ZrCl_2 and AgOTf. The scope and limitations of both the epoxide and alkyne were realized and was demonstrated in over 20 successful reactions. Moreover, the 11 new silver acetylides used in the epoxide alkynyl addition methodology should

be readily applicable to the aldehyde alkynyl addition methodology. Finally, mechanistic studies were undertaken and were crucial in understanding the roles of all additives necessary for this alkynyl addition reaction to be successful, culminating in the generating of the proposed mechanism seen in Scheme 62.

2.9 EXPERIMENTAL SECTION

General techniques. All reactions were carried out with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone, and methylene chloride (CH_2Cl_2) was distilled from calcium hydride. Acetonitrile was distilled over CaH_2 and stored over 3Å molecular sieves. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogenous materials, unless otherwise stated. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25-mm Merck silica gel plates (60F-254) using UV-light (254 nm), 2.4% phosphomolybdic acid/1.4% phosphoric acid/5% sulfuric acid in H_2O, anisaldehyde in ethanol, or 0.2% ninhydrin in ethanol and heat as developing agents. TSI silica gel (230-400 mesh) was used for flash column chromatography. NMR spectra were recorded on AM300 or AM500 (Bruker) instruments and calibrated using a solvent peak or tetramethylsilane as an internal reference. The following abbreviations are used to indicate the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. High resolution mass spectra were obtained by using EBE geometry.

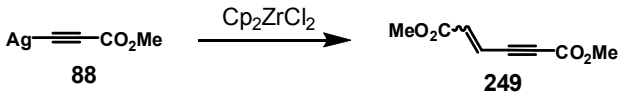


223
NOT OBSERVED

Procedure used in the failed catalytic alkynylation reaction. To a stirred solution silver acetylide **88** (153 mg, 0.801 mmol) and 3-nitrobenzaldehyde (75.8 mg, 0.502 mmol) in CH_2Cl_2 was added Cp_2ZrCl_2 (29.6 mg, 0.101 mmol), AgOTf (6.6 mg, 0.026 mmol), and chlorotriethylsilane (100 μL, 0.600 mmol) at 23 °C under a nitrogen atmosphere. After 5 h at the same temperature, the reaction vessel was sealed and heated to 43 °C. After an additional 5 h at this temperature the reaction mixture was cooled to 23 °C, and subsequently quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). The resulting mixture was filtered through a pad of Celite 545®, rinsed with EtOAc (3 × 5 mL), and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (2.5 → 20% EtOAc/hexanes) on silica gel (8 mL) to no desired adducts.

General procedure for the preparation of the silver acetylides. To a stirred solution of $AgNO_3$ (2.1–283 mmol, 2.1 equiv) in deionized H_2O (1.0–84 mL) and MeOH§ (0.4–50 mL) was added NH_4OH (28–30%, 0.4–54 mL) until the solution became clear again at 23 °C under ambient light. After 30 min at the same temperature, terminal alkynes (1.0–138 mmol, 1 equiv) in MeOH (0.3–6 mL) were added dropwise. After an additional 10–30 min of vigorous stirring at the same temperature, the reaction mixture was filtered through a frit, thoroughly rinsed with deionized H_2O (8 × 5–250 mL), and MeOH (5–250 mL). The resulting solids were dried under high vacuum overnight over P_2O_5 to give the appropriate silver acetylides (79%–quant. yield) as powders.

[§] EtOH was used instead of MeOH for the preparation of the silver acetylide **20** from 3,3-diethoxypropyne.



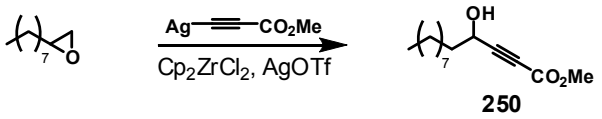
Representative procedure for the isolation of enynes 249. To a stirred solution of **88** (211 mg, 1.11 mmol) in CH_2Cl_2 (4 mL) was added Cp_2ZrCl_2 (292 mg, 1.00 mmol) in one portion at 23 °C. The resulting mixture was vigorously stirred for 4 h at the same temperature, then quenched with H_2O (5 mL), filtered through a pad of Celite 545®, rinsed with EtOAc (3 × 5 mL) and H_2O (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 → 40% EtOAc/hexanes) on silica gel (20 mL) to afford E-**249** (1.5 mg, 1.6%) as a white solid and Z-**249** (1.2 mg, 1.3%) as a pale yellow oil.

Data for E-**249**: See C. S. Yi, N. Liu *Organometallics* **1997**, *16*, 3910–3913.

Data for Z-**249**: R_f = 0.36 (30% EtOAc in hexanes); ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 6.36 (d, 1H, J = 11.6 Hz), 6.22 (d, 1H, J = 11.6 Hz), 3.83 (s, 3H), 3.81 (s, 3H).

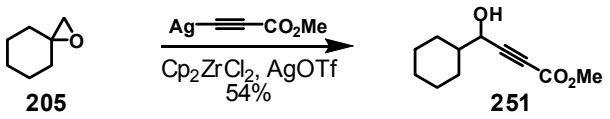
General procedure for the addition of silver acetylides to epoxides. To a stirred solution or suspension of silver acetylide (0.8–16 mmol, 1.6 equiv) in CH_2Cl_2 (1.8–30 mL) was added epoxide (0.5–9.9 mmol, 1 equiv) followed by the addition of Cp_2ZrCl_2 (0.6–12 mmol, 1.2 equiv) and AgOTf (0.025–5.0 mmol, 0.05–0.5 equiv) in one portion at 23 °C under ambient light. After vigorous stirring at the same temperature for 1–10 h the solution was quenched with

saturated aqueous NH_4Cl or saturated aqueous $NaHCO_3$ (0.5–6 mL). After stirring for 15–30 min at the same temperature, the reaction mixture was filtered through a pad of Celite 545® and Na_2SO_4, rinsed with Et_2O (2 × 5–30 mL), and concentrated under reduced pressure. The resulting residues were purified by flash chromatography (EtOAc/hexanes) on silica gel to afford the corresponding alcohols.



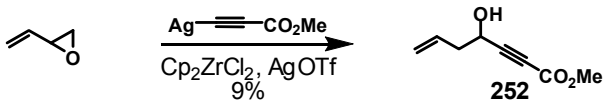
250

Data for **250**: colorless oil; R_f = 0.29 (20% EtOAc in hexanes); IR (neat): 3419 (br, O-H), 2924, 2855, 2237, 1717, 1436, 1251, 1065, 752 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 4.50 (br app q, 1H, *J* = 6.4 Hz), 3.80 (s, 3H), 1.91 (d, 1H, *J* = 5.8 Hz), 1.82–1.73 (m, 2H), 1.53–1.22 (m, 14H), 0.89 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 153.8, 88.4, 76.1, 62.1, 52.8, 36.8, 31.8, 29.44, 29.39, 29.2, 29.1, 24.9, 22.6, 14.0; HRMS (EI+) calcd. for $C_{14}H_{24}O_3$ $[M]^+$ 240.1725, found 240.1735.



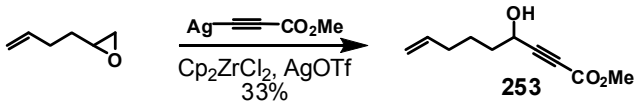
205 **251**

Data for **251**: See S. P. Shahi, K. Koide *Angew. Chem., Int. Ed.* **2004**, *43*, 2525–2527.

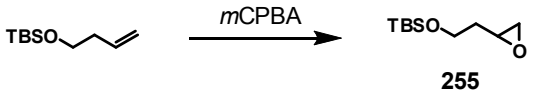


252

Data for **252**: See C. T. Meta "Stereoselective Preparation of Highly Substituted Olefins and Synthetic Studies Toward Stresgenin B," Univ. of Pittsburgh.

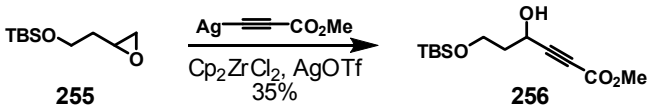


Data for **253**: colorless oil; R_f = 0.40 (30% EtOAc in hexanes); IR (neat): 3412 (br, O-H), 2952, 2237, 1718, 1436, 1254, 1068, 914, 752 cm^{-1}; ^1H NMR (300 MHz, 293K, 1% CD_3OD in $CDCl_3$) δ 5.79 (dddd, 1H, *J* = 16.8, 10.2, 6.6, 6.6 Hz), 5.06–4.94 (m, 2H), 4.46 (app t, 1H, *J* = 6.6 Hz), 3.78 (s, 3H), 2.13–2.04 (m, 2H), 1.80–1.51 (m, 4H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 153.9, 138.0, 115.0, 88.6, 75.9, 61.6, 52.7, 36.1, 33.1, 24.0; LRMS (EI+) $C_{10}H_{11}O_2$ $[M - H_3O]^+$ 163 (58%), $C_9H_9O_2$ $[M - CH_5O]^+$ 149 (14%), $C_7H_{11}O$ $[M - C_2H_4O_2]^+$ 122 (26%).

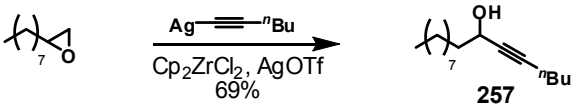


Procedure for the preparation of 255. To a stirred solution of 1-*t*butyldimethylsiloxy-3-butene (935 mg, 5.02 mmol) in CH_2Cl_2 (17 mL) was added *m*CPBA (70%, 2.47 g, 10.0 mmol) at 0 °C. After 10 min at the same temperature, the reaction was allowed to warm to 23 °C. After 14 h at the same temperature, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous Na_2SO_3 (10 mL). The reaction mixture was then vigorously stirred for an additional 15 min, then diluted with hexanes (25 mL), and the layers were separated. The organic layer was then washed with saturated aqueous $NaHCO_3$ (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1–5% EtOAc in hexanes) on silica gel (50 mL) to afford **255** (964 mg, 95%) as a colorless oil.

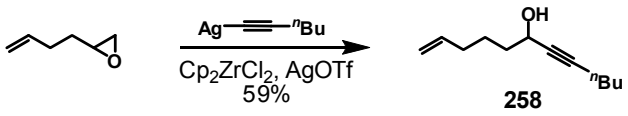
Data for **255**: See E. N. Lawson, J. F. Jamie, W. Kitching *J. Org. Chem.* **1992**, *57*, 353–358.



Data for **256**: pale yellow oil; R_f = 0.30 (20% EtOAc in hexanes); IR (neat): 3411 (br O-H), 2954, 2858, 2237, 1720 (C=O), 1436, 1255, 1100, 837 cm^{-1}; ^1H NMR (300 MHz, 293K, 1% CD_3OD in $CDCl_3$) δ 4.53 (br app t, 1H, *J* = 5.3 Hz), 3.77 (s, 3H), 3.76–3.60 (m, 2H), 1.96–1.64 (m, 4H), 0.90 (s, 9H), 0.083 (s, 3H), 0.079 (s, 3H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 153.9, 88.6, 76.0, 63.0, 61.5, 52.6, 34.5, 28.3, 25.8, 18.3, –5.48, –5.53; HRMS (ESI+) calcd. for $C_{14}H_{27}O_4Si$ $[M + H]^+$ 287.1679, found 287.1675.

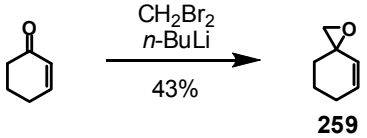


Data for **257**: colorless oil; R_f = 0.40 (15% EtOAc in hexanes); IR (neat): 3384 (br, O-H), 2926, 2855, 2233, 1466, 1379, 1026, 722 cm^{-1}; ^1H NMR (300 MHz, 293K, 1% CD_3OD in $CDCl_3$) δ 4.35 (br app t, 1H, *J* = 6.4 Hz), 2.22 (app td, 2H, *J* = 6.9, 1.8 Hz), 1.72–1.60 (m, 2H), 1.55–1.24 (m, 18H), 0.96–0.85 (m, 6H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 85.4, 81.4, 62.8, 38.2, 31.9 30.8, 29.52, 29.48, 29.27, 29.26, 25.2, 22.7, 21.9, 18.4, 14.1, 13.5; HRMS (EI+) calcd. for $C_{16}H_{30}O$ $[M]^+$ 238.2297, found 238.2288.



258

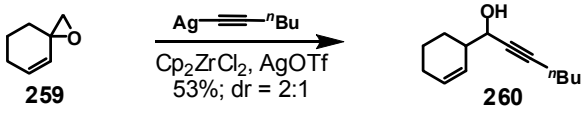
Data for **258**: colorless oil; R_f = 0.27 (15% EtOAc in hexanes); IR (neat): 3345 (br O-H), 2933, 2863, 2232, 1641, 1459, 996, 911 cm^{-1}; ^1H NMR (300 MHz, 293K, 1% CD_3OD in $CDCl_3$) δ 5.79 (dddd, 1H, *J* = 17.2, 10.0, 6.5, 6.5 Hz), 4.99 (dddd, 1H, *J* = 17.2, 1.5, 1.5, 1.5 Hz), 4.93 (br d, 1H, *J* = 10.0 Hz), 4.31 (br app t, 1H, *J* = 3.9 Hz), 2.18 (app td, 2H, *J* = 7.0, 2.0 Hz), 2.06 (br app q, 2H, *J* = 7.5 Hz), 1.71–1.58 (m, 2H), 1.56–1.33 (m, 6H), 0.88 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, 293K, $CDCl_3$) δ 138.5, 114.6, 85.3, 81.1, 62.2, 37.4, 33.2, 30.7, 24.4, 21.8, 18.2, 13.5; LRMS (EI+) $C_{12}H_{19}O$ $[M - H]^+$ 179 (5%), $C_9H_{13}O$ $[M - C_3H_7]^+$ 137 (75%), $C_7H_{11}O$ $[M - C_5H_9]^+$ 111 (100%).



259

Procedure for the preparation of 259: See T. J. Michnik, D. S. Matteson *Synlett* **1991**, 631–632.

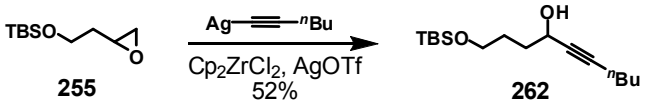
Data for **259**: See S. P. Tanis, M. C. McMills, P. M. Herrington *J. Org. Chem.* **1985**, *50*, 5587–5589.



259 260

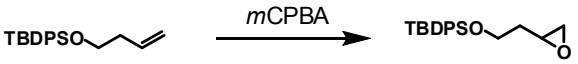
Data for **260**: colorless oil; R_f = 0.28 (15% EtOAc in hexanes); IR (neat): 3360 (br O-H), 2931, 2862, 2224, 1451, 1379, 1140, 1047, 725 cm^{-1}; ^1H NMR (300 MHz, 293K, 1% CD_3OD in $CDCl_3$) δ 5.90–5.66 (m, 2H), 4.19 (br app s, 1H), 2.40–2.28 (m, 1H), 2.21 (app t, 2H, *J* = 6.5

Hz), 2.06–1.94 (m, 2H), 1.92–1.73 (m, 2H), 1.64–1.35 (m, 6H), 0.90 (t, 3H, J = 7.1 Hz); ^{13}C NMR (125 MHz, 293K, CD_2Cl_2) δ 130.1, 129.9, 127.2, 126.5, 86.2, 86.1, 80.2, 80.0, 66.2, 66.0, 42.4, 30.7, 25.18, 25.16, 24.5, 21.8, 21.4, 21.0, 18.3, 13.5; HRMS (EI+) calcd. for $C_{13}H_{20}O$ $[M]^+$ 192.1514, found 192.1508.



255 **262**

Data for **262**: colorless oil; R_f = 0.31 (15% EtOAc in hexanes); IR (neat): 3385 (br O-H), 2931, 2859, 2235, 1468, 1387, 1254, 1103, 837 cm^{-1}; ^{1}H NMR (300 MHz, 293K, 1% CD_3OD in $CDCl_3$) δ 4.39 (br s, 1H), 3.71–3.63 (m, 2H), 2.24–2.16 (m, 2H), 1.82–1.64 (m, 4H), 1.51–1.23 (m, 4H), 0.93–0.87 (m, 12H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, 293K, CD_2Cl_2) δ 85.2, 81.1, 63.2, 62.2, 35.5, 30.7, 28.5, 25.9, 21.9, 18.34, 18.27, 13.5, –5.4; HRMS (ESI+) calcd. for $C_{16}H_{32}O_2NaSi$ $[M + Na]^+$ 307.2069, found 307.2070.

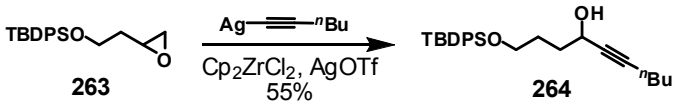


263

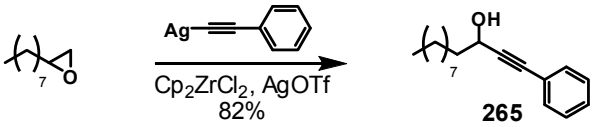
Procedure for the preparation of 263. To a stirred solution of 1-^{t}butyldiphenylsiloxy-3-butene (1.24 g, 3.99 mmol) in CH_2Cl_2 (14 mL) was added *m*CPBA (70%, 2.47 g, 6.0 mmol) at 0 °C. After 10 min at the same temperature, the reaction was allowed to warm to 23 °C. After 14 h at the same temperature, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous Na_2SO_3 (10 mL). The reaction mixture was then vigorously stirred for an additional 15 min, then diluted with hexanes (20 mL), and the layers were separated. The organic layer was then washed with saturated aqueous $NaHCO_3$ (20 mL),

dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (2.5–15% EtOAc in hexanes) on silica gel (60 mL) to afford **263** (1.18 g, 91%) as a colorless oil.

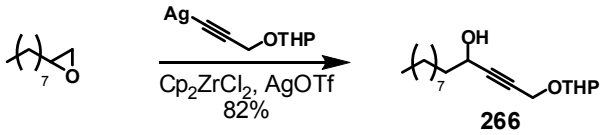
Data for **263**: See R. Hanessian, A. Tehim, P. Chen *J. Org. Chem.* **1993**, *58*, 7768–7781.



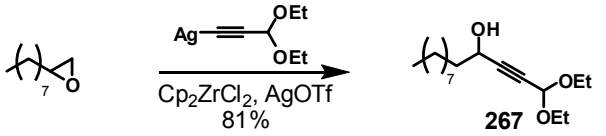
Data for **264**: colorless oil; R_f = 0.27 (15% EtOAc in hexanes); IR (neat): 3383 (br O-H), 2932, 2856, 2235, 1469, 1428, 1389, 1189, 1110, 702 cm^{-1}; ^1H NMR (300 MHz, 293K, 1% CD_3OD in $CDCl_3$) δ 7.74–7.62 (m, 4H), 7.46–7.33 (m, 6H), 4.40 (br s, 1H), 3.72–3.67 (m, 2H), 2.21 (app td, 2H, *J* = 6.9, 1.5 Hz), 1.80–1.35 (m, 8H), 1.05 (s, 9H), 0.92 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, 293K, CD_2Cl_2) δ 135.5, 133.6, 129.6, 127.6, 85.3, 81.1, 63.9, 62.3, 35.2, 30.7, 28.2, 26.7, 21.9, 19.1, 18.3, 13.5; HRMS (ESI+) calcd. for $C_{26}H_{37}O_2Na$ $[M + H]^+$ 409.2563, found 409.2556.



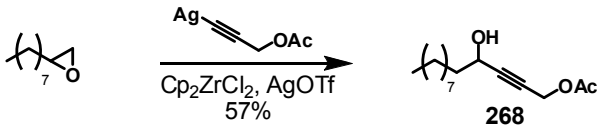
Data for **265**: pale yellow oil; R_f = 0.31 (15% EtOAc in hexanes); IR (neat): 3329 (br, O-H), 2924, 2855, 2229, 1599, 1490, 1070, 1027, 755 cm^{-1}; ^1H NMR (300 MHz, 293K, 1% CD_3OD in $CDCl_3$) δ 7.45–7.39 (m, 2H), 7.34–7.28 (m, 3H), 4.57 (app t, 1H, *J* = 6.6 Hz), 1.83–1.74 (m, 2H), 1.57–1.23 (m, 14H), 0.87 (t, 3H, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 131.7, 128.3, 128.2, 122.7, 90.3, 84.8, 63.0, 37.9, 31.9, 29.5, 29.3, 25.2, 22.7, 14.1; HRMS (EI+) calcd. for $C_{18}H_{26}O$ $[M]^+$ 258.1984, found 258.1975.



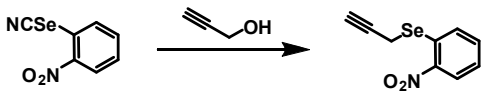
Data for **266**: colorless oil; R_f = 0.14 (15% EtOAc in hexanes); IR (neat): 3423 (br, O-H), 2924, 2854, 1466, 1343, 1201, 1120, 1024, 902 cm^{-1}; ^1H NMR (300 MHz, 293K, 1% CD_3OD in $CDCl_3$) δ 4.81 (br s, 1H), 4.40–4.33 (m, 1H), 4.33 (dd, 1H, *J* = 15.6, 1.5 Hz), 4.25 (dd, 1H, *J* = 15.6, 1.2 Hz), 3.88–3.79 (m, 1H), 3.56–3.49 (m, 1H), 1.88–1.20 (m, 22H), 0.87 (t, 3H, *J* = 5.9 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 96.9, 87.4, 80.2, 62.1, 62.0, 54.3, 37.6, 31.8, 30.1, 29.47, 29.45, 29.22, 29.21, 25.2, 25.1, 22.6, 18.9, 14.0; HRMS (ESI+) calcd. for $C_{18}H_{32}O_3$ $[M + Na]^+$ 319.2249, found 319.2250.



Data for **267**: colorless oil; R_f = 0.22 (15% EtOAc in hexanes); IR (neat): 3425 (br, O-H), 2925, 2856, 2241, 1467, 1328, 1145, 1054, 1012 cm^{-1}; ^1H NMR (300 MHz, 293K, 1% CD_3OD in $CDCl_3$) δ 5.29 (d, 1H, *J* = 1.2 Hz), 4.39 (br app t, 1H, *J* = 6.6 Hz), 3.81–3.68 (m, 2H), 3.63–3.56 (m, 2H), 1.75–1.66 (m, 2H), 1.52–1.18 (m, 20H), 0.87 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 91.2, 86.5, 80.0, 62.2, 60.9, 60.8, 37.4, 31.8, 29.5, 29.3, 29.2, 25.1, 22.6, 15.0, 14.1; HRMS (EI+) calcd. for $C_{15}H_{27}O_2$ $[M – OEt]^+$ 239.2011, found 239.2007.



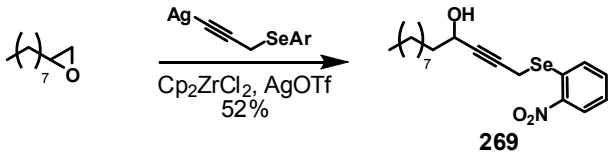
Data for **268**: colorless oil; R_f = 0.24 (20% EtOAc in hexanes); IR (neat): 3424 (br, O-H), 2925, 2855, 1750, 1457, 1379, 1226, 1028 cm^{-1}; ^1H NMR (300 MHz, 293K, 1% CD_3OD in $CDCl_3$) δ 4.73 (d, 1H, *J* = 18.2 Hz), 4.67 (d, 1H, *J* = 18.2 Hz), 4.37 (br app t, 1H, *J* = 6.3 Hz), 2.10 (s, 3H), 1.73–1.64 (m, 2H), 1.48–1.21 (m, 14H), 0.87 (t, 3H, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 170.3, 88.0, 78.6, 62.3, 62.2, 53.3, 37.5, 31.8, 29.5, 29.3, 29.2, 25.1, 22.6, 20.7, 14.1; HRMS (ESI+) calcd. for $C_{15}H_{26}O_3$ $[M + Na]^+$ 277.1780, found 277.1829.



Procedure for the preparation of 2-nitrophenyl propargyl selenide. To a stirred solution of 2-nitrophenylselenocyanate (2.27 g, 10.0 mmol) and propargyl alcohol (650 μL, 11.2 mmol) in THF (35 mL) was added $^nBu_3P$ (3.0 mL, 12 mmol) dropwise at 0 °C. After 40 min at the same temperature, the reaction was poured onto saturated aqueous $NaHCO_3$ (300 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (1 → 5% Et_2O in hexanes) on silica gel (250 mL) to afford **2-nitrophenyl propargyl selenide** (1.90 g, 79%) as a yellow solid.

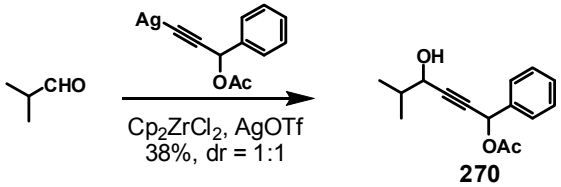
Data for **2-nitrophenyl propargyl selenide**: yellow solid; m.p. = 85–86 °C; R_f = 0.29 (15% EtOAc in hexanes); IR (KBr pellet): 3272, 3088, 2925, 1589, 1565, 1497, 1352, 1306, 1100, 1038, 731 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 8.37 (dd, 1H, *J* = 8.4, 1.2 Hz), 7.69

(dd, 1H, *J* = 8.1, 1.2 Hz), 7.62 (ddd, 1H, *J* = 8.1, 6.9, 1.5 Hz), 7.39 (ddd, 1H, *J* = 8.4, 6.9, 1.5 Hz), 3.55 (d, 2H, *J* = 2.7 Hz), 2.28 (t, 1H, *J* = 2.7 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 146.0, 134.0, 132.9, 128.8, 126.4, 125.9, 79.5, 72.1, 11.4; HRMS (EI+) calcd. for $C_9H_7NO_2{}^{80}Se$ $[M]^+$ 240.9642, found 240.9633.



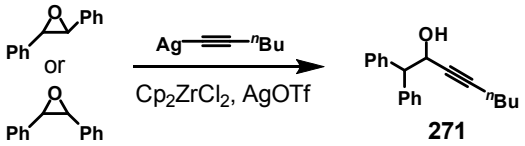
269

Data for **269**: pale yellow solid; m.p. = 71–72 °C; R_f = 0.34 (30% EtOAc in hexanes); IR (KBr pellet): 3332 (br, O-H), 2923, 2850, 1589, 1567, 1503, 1330, 1306, 1038, 729 cm^{-1}; ^{1}H NMR (300 MHz, 293K, 1% CD_3OD in $CDCl_3$) δ 8.34 (dd, 1H, *J* = 8.3, 1.3 Hz), 7.65 (dd, 1H, *J* = 8.1, 1.3 Hz), 7.58 (ddd, 1H, *J* = 8.1, 7.2, 1.5 Hz), 7.36 (ddd, 1H, *J* = 8.3, 7.2, 1.5 Hz), 4.33 (br app t, 1H, *J* = 6.6 Hz), 3.62–3.55 (m, 2H), 1.71–1.15 (m, 16H), 0.87 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 146.2, 133.9, 133.2, 129.0, 126.4, 125.8, 85.2, 80.2, 62.6, 37.8, 31.8, 29.5 (two overlapping carbons), 29.25, 29.20, 25.1, 22.6, 14.1, 12.0; HRMS (EI+) calcd. for $C_{19}H_{27}NO_3{}^{80}Se$ $[M]^+$ 397.1156, found 397.1141.



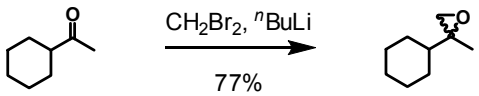
270

Data for **270**: See X. Ariza, J. Garcia, Y. Georges, M. Vicente *Org. Lett.* **2006**, *8*, 4501–4504.



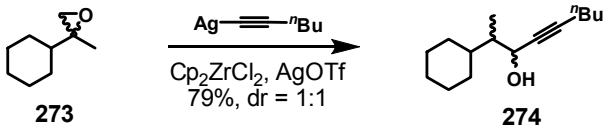
271

Data for **271**: R_f = 0.40 (20% EtOAc in hexanes); IR (neat): 3420 (br, O-H), 3028, 2931, 2228, 1495, 1452, 1032, 746 cm^{-1}; ^1H NMR (300 MHz, 293K, 1% CD_3OD in $CDCl_3$) δ 7.42–7.18 (m, 10H), 5.02 (ddd, 1H, *J* = 7.2, 1.8, 1.8 Hz), 4.20 (br d, 1H, *J* = 7.2 Hz), 2.16–1.95 (m, 3H), 1.40–1.16 (m, 4H), 0.82 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, 293K, 1% CD_3OD in $CDCl_3$) δ 141.2, 140.6, 128.9, 128.8, 128.3, 128.1, 126.7, 126.6, 87.6, 79.9, 65.2, 58.2, 30.4, 21.6, 18.2, 13.4; HRMS (ESI+) calcd. for $C_{20}H_{22}ONa$ $[M + Na]^+$ 301.1568, found 301.1579.

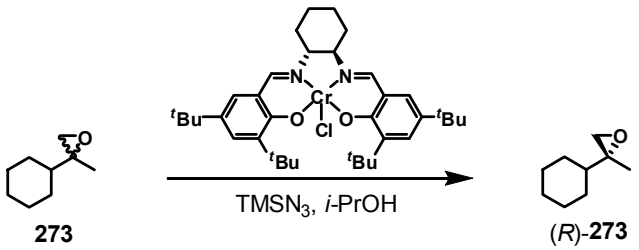


273

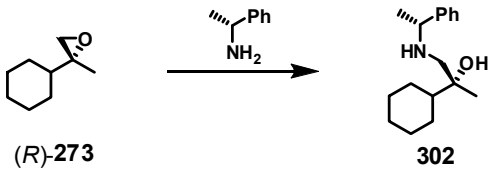
Procedure for the preparation of racemic-273. To a stirred solution of cyclohexylmethyl ketone (1.4 mL, 10 mmol) and CH_2Br_2 in THF (30 mL) was added ^{n}BuLi (1.6 M in hexanes, 7.0 mL) down the flask side over 15 min at –78 °C. After an additional 30 min at the same temperature, the reaction was warmed to 23 °C. After 2.75 h at the same temperature, the reaction mixture was poured onto saturated aqueous NH_4Cl (40 mL) and concentrated under reduced pressure to remove most of the THF. The resulting aqueous residue was extracted with Et_2O (2 × 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (2 → 4% EtOAc in hexanes) on silica gel (50 mL) to afford **racemic-273** (1.08 g, 77%) as a colorless oil.



Data for **274**: R_f = 0.27 (10% EtOAc in hexanes); IR (neat): 3417 (br, O-H), 2924, 1637, 1490, 1447, 1000, 755 cm^{-1}; ^1H NMR (300 MHz, 293K, 1% CD_3OD in $CDCl_3$) δ 7.41–7.38 (m), 7.33–7.28 (m), 4.61 (d, *J* = 5.7 Hz), 1.82–1.52 (m), 1.36–1.10 (m), 1.06 (t, *J* = 6.6 Hz), 1.03 (t, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 131.7, 131.6, 128.3, 122.8, 90.2, 89.2, 85.9, 85.3, 65.40, 65.35, 45.0, 44.8, 39.5, 35.0, 31.6, 31.4, 29.2, 28.7, 26.71, 26.64, 26.59, 26.47, 11.43, 11.40; HRMS (EI+) calcd. for $C_{17}H_{22}O$ $[M]^+$ 242.1671, found 242.1676.

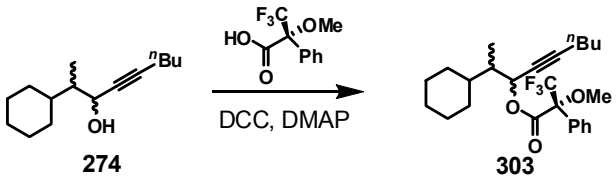


Procedure and data for the preparation of (*R*)-273: See H. Lebel, E. N. Jacobsen *Tetrahedron Lett*. **1999**, *40*, 7303–7306.



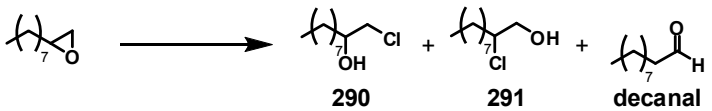
General procedure for the determination of the enantiomeric ratio of 273. To a stirred solution of **273** (9.2 mg, 0.066 mmol) and (*R*)-(+)-α-methylbenzylamine (25 μL, 0.19 mmol) in MeOH (0.3 mL) was added KI (2.2 mg, 0.013 mmol) in one portion at 23 °C. After 5 min at the same temperature, the reaction mixture was heated to 55 °C. After an additional 2 d at

the same temperature, the reaction mixture was cooled and concentrated under reduced pressure. The resulting crude residue was analyzed by ^{1}H NMR spectroscopy revealing the diastereomeric ratio of **302** to be >40:1 by comparison with **302** prepared from racemic-**273**.



274 **303**

General procedure for the determination of the enantiomeric ratios of 274 by Mosher ester synthesis. To a stirred solution of **274** (9.9 mg, 0.041 mmol) and (*R*)-(+)-α-methoxy-(trifluoromethyl)phenylacetic acid (40 mg, 0.17 mmol) in CH_2Cl_2 was added DCC (34 mg, 0.17 mmol) followed by DMAP (12 mg, 0.098 mmol) in one portion at 0 °C. After 10 min at the same temperature, the reaction was warmed to 23 °C. After an additional 20 min at the same temperature, the reaction mixture was filtered through a pad of Florisil (3 mL), rinsed with 15% EtOAc in hexanes (3 × 5 mL), and concentrated under reduced pressure. The resulting crude residue was analyzed by ^{1}H NMR spectroscopy and reverse phase HPLC revealing the diastereomeric ratio of **303** to be 9:9:1:1 by comparison with **303** prepared from **racemic-274**.

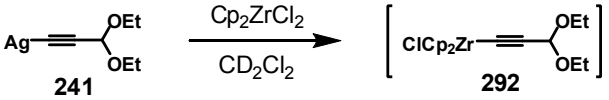


290 **291** **decanal**

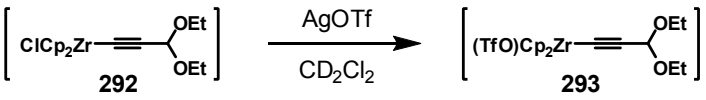
General procedure for the preparation of 290, 291, and decanal from 1,2-epoxydecane. To a stirred solution of 1,2-epoxydecane (45 μL, 0.24 mmol) in CH_2Cl_2 (1.0 mL) were added the other reaction components (equivalents based on optimized alkynylation reaction conditions) at 23 °C. After 3.5–19 h at the same temperature, the reaction was quenched by the

addition of saturated aqueous $NaHCO_3$ (0.3 mL). After stirring for 15–30 min at the same temperature, the reaction mixture was filtered through a pad of Celite 545® and Na_2SO_4, rinsed with Et_2O (3 × 5 mL), and concentrated under reduced pressure. The resulting residues were purified by flash chromatography (EtOAc/hexanes) on silica gel to afford the corresponding products.

Data for **290** and **291**: See Barry, C. N.; Evans, S. A., Jr. *J. Org. Chem.* **1983**, *48*, 2825–2828



Procedure for the preparation of 292 and 294 from 241. To an NMR tube was added **241** (35–49 mg, 0.15–0.20 mmol) followed by CD_2Cl_2 (0.8 mL) under Ar at 23 °C. To the homogeneous solution was added Cp_2ZrCl_2 (1.1 equiv) and the resulting mixture was vortexted for 5 min. NMR experiments were then performed on the rapidly generated acetylide **292**. To this solution was added benzophenone (1.0 equiv) and the mixture was vortexed for 2 min. NMR experiments were then performed on equilibrium between **292** and **294**. See Tables 24 and 25 for complete NMR data.



Procedure for the preparation of 293 and 295 from 292. To an NMR tube containing **292** (0.15–0.20 mmol) in CD_2Cl_2 (0.8 mL) was added AgOTf (1.0 equiv) under Ar at 23 °C, and the mixture was then vortexed for 5 min. NMR experiments were immediately performed on the rapidly generated acetylide **293**. To this solution was added benzophenone (1.0 equiv) and the

mixture was vortexed for 2 min. NMR experiments were then performed on equilibrium between **293** and **295** (see Tables 24 and 25 for spectral data).

Table 24. Complete ^{1}H NMR data for **241**, **292**, **293**, **294**, and **295**

Compound	^{1}H NMR (300 MHz, 293K, CD_2Cl_2)
3,3-diethoxypropyne	5.22 (d, 1H, *J* = 1.8 Hz), 3.72 (q, 1H, *J* = 7.1 Hz), 3.69 (q, 1H, *J* = 7.1 Hz), 3.56 (q, 1H, *J* = 7.0 Hz), 3.53 (q, 1H, *J* = 7.1 Hz), 2.57 (d, 1H, *J* = 1.8 Hz), 1.19 (t, 6H, *J* = 7.1 Hz)
241	5.32 (br s, 1H), 3.77–3.71 (m, 2H), 3.66–3.55 (m, 2H), 1.23 (t, 6H, *J* = 7.1 Hz)
292	6.48 (br s, 10 H), 5.32 (br s, 1H), 3.79–3.71 (m, 2H), 3.68–3.56 (m, 2H), 1.22 (t, 6H, *J* = 7.1 Hz)
293†	6.67 (br s, 10 H), 5.34 (br s, 1H), 3.84–3.72 (m, 2H), 3.70–3.55 (m, 2H), 1.27 (t, 6H, *J* = 7.1 Hz)
benzophenone	7.83–7.77 (m, 4H), 7.65–7.58 (m, 2H), 7.55–7.47 (m, 4H)
294	7.82–7.77 (m, 4H), 7.64–7.58 (m, 2H), 7.55–7.47 (m, 4H), 6.64 (br s, 10H), 5.35 (br s, 1H), 3.84–3.74 (m, 2H), 3.71–3.56 (m, 2H), 1.27 (t, 6H, *J* = 7.1 Hz)
295†	7.82–7.77 (m, 4H), 7.65–7.58 (m, 2H), 7.55–7.47 (m, 4H), 6.50 (br s, 10H), 5.36 (br s, 1H), 3.83–3.73 (m, 2H), 3.69–3.58 (m, 2H), 1.25 (t, 6H, *J* = 7.1 Hz)

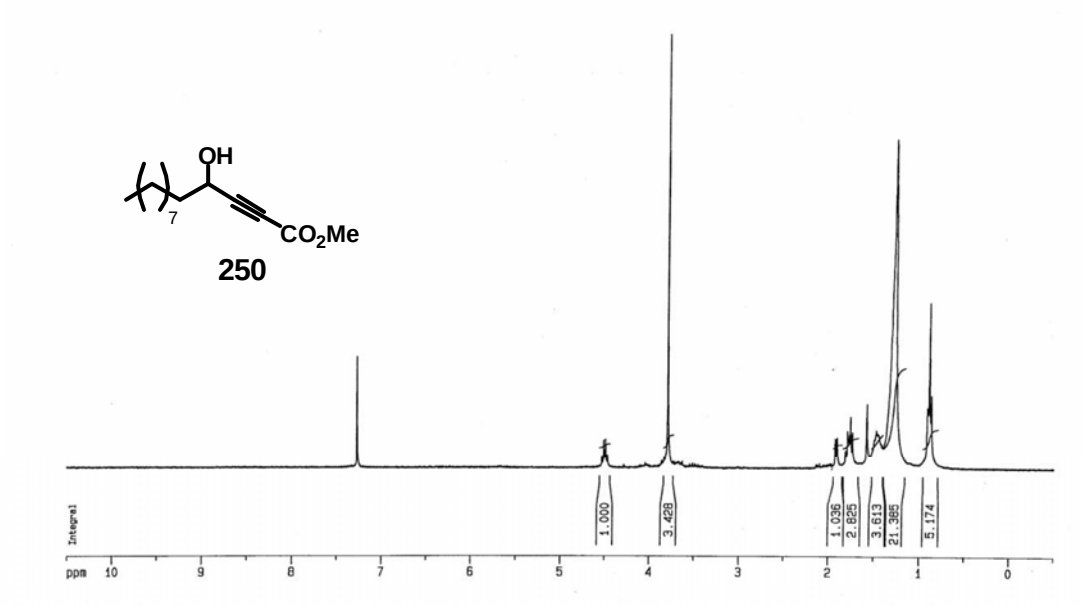
Table 25. Complete ^{13}C NMR data for **241**, **292**, **293**, **294**, and **295**

Compound	^{13}C NMR (75 MHz, 293K, CD_2Cl_2)
3,3-diethoxypropyne	91.31, 79.60, 73.35, 61.24, 15.18
241	117.93 (C≡*C*–Ag),‡ 93.65(C≡*C*–CH(OEt)$_2$),‡ 91.86(–*C*H(OEt)$_2$),‡ 61.40, 15.35
292	116.44, 114.41, 113.77, 92.00, 61.48, 15.33
293†	119.40 (q), 117.62, 116.46, 115.81, 91.78, 61.93, 15.28
benzophenone	198.68, 138.00, 132.71, 130.29, 128.62
294	198.63, 137.94, 132.69, 130.24, 128.59, 116.44, 113.72, 92.01, 61.52, 15.35
295†	196.83, 137.90, 132.76, 130.30, 119.43 (q), 117.60, 116.46, 115.82, 91.79, 61.94, 15.29

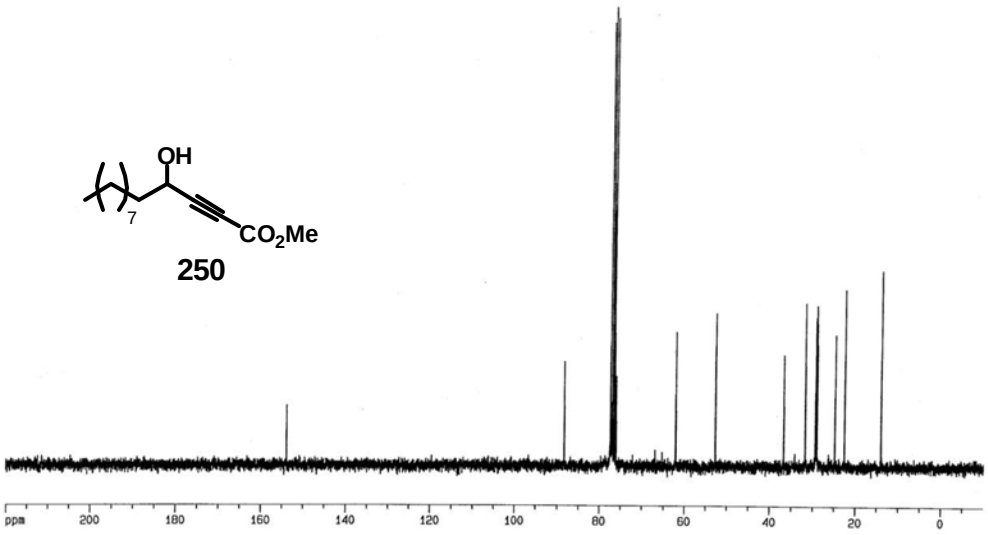
† Contaminated by hydrolysis products; ‡ Determined by an HMBC experiment

2.10 ^{1}H AND ^{13}C SPECTRA

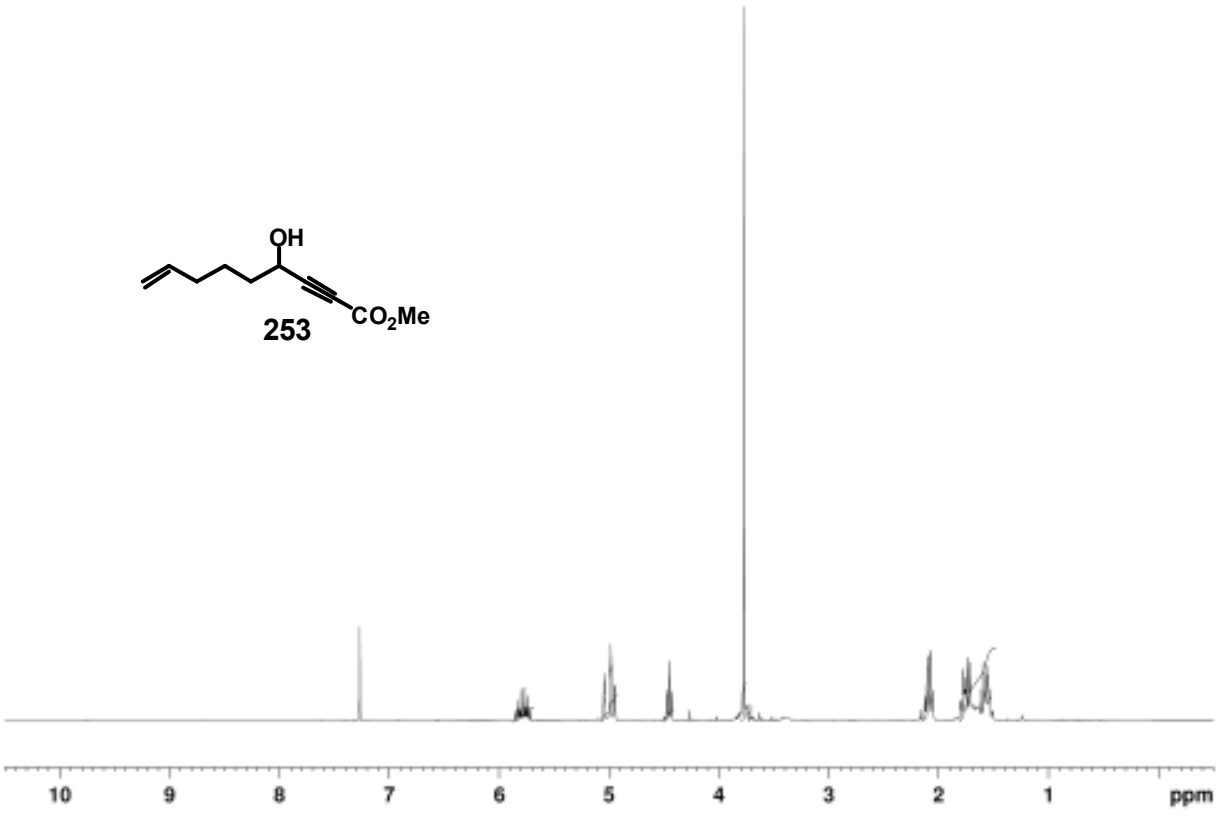
^{1}H NMR of 250: 1% CD_3OD in $CDCl_3$, 293 K, 300 MHz



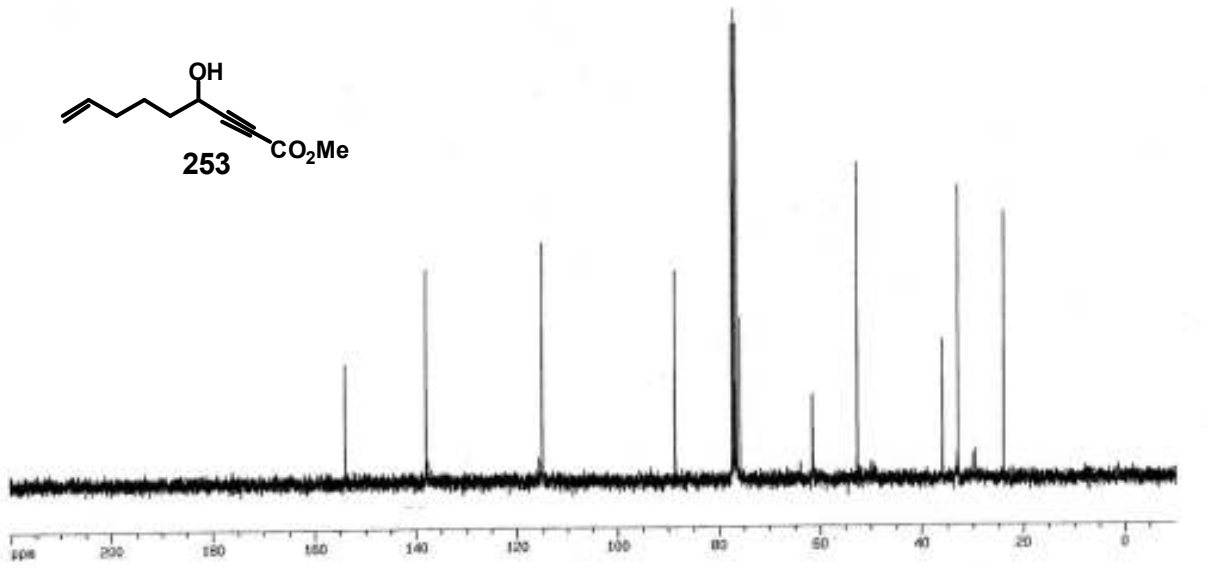
^{13}C NMR of 250: $CDCl_3$, 293 K, 75 MHz



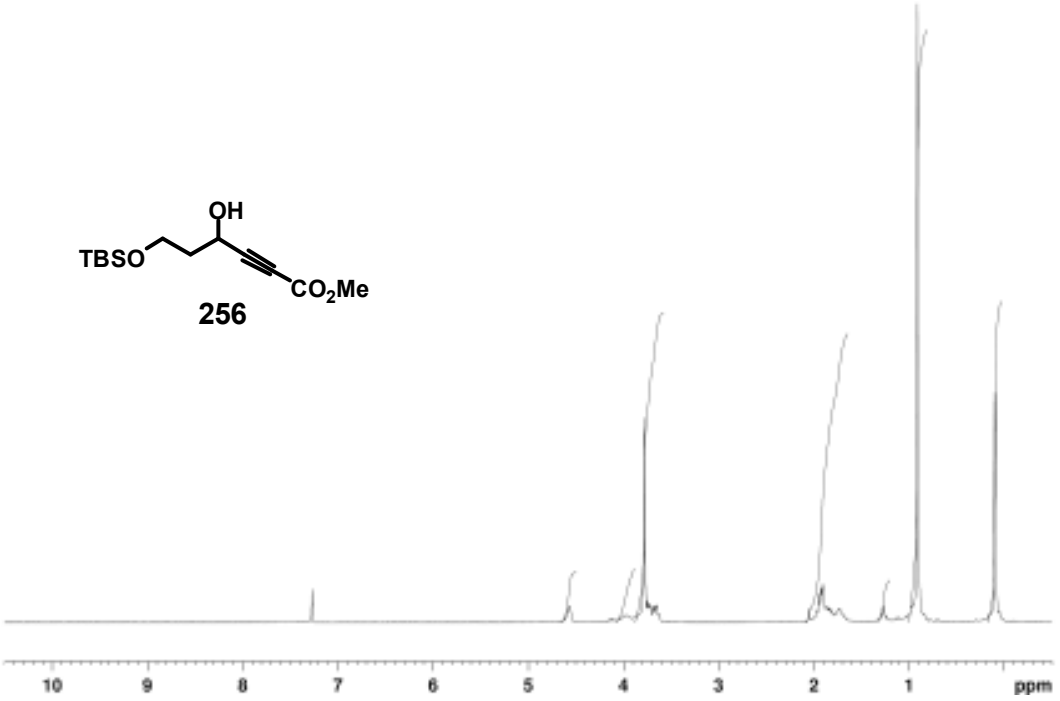
[1]**H NMR of 253**: 1% CD_3OD in $CDCl_3$, 293 K, 300 MHz



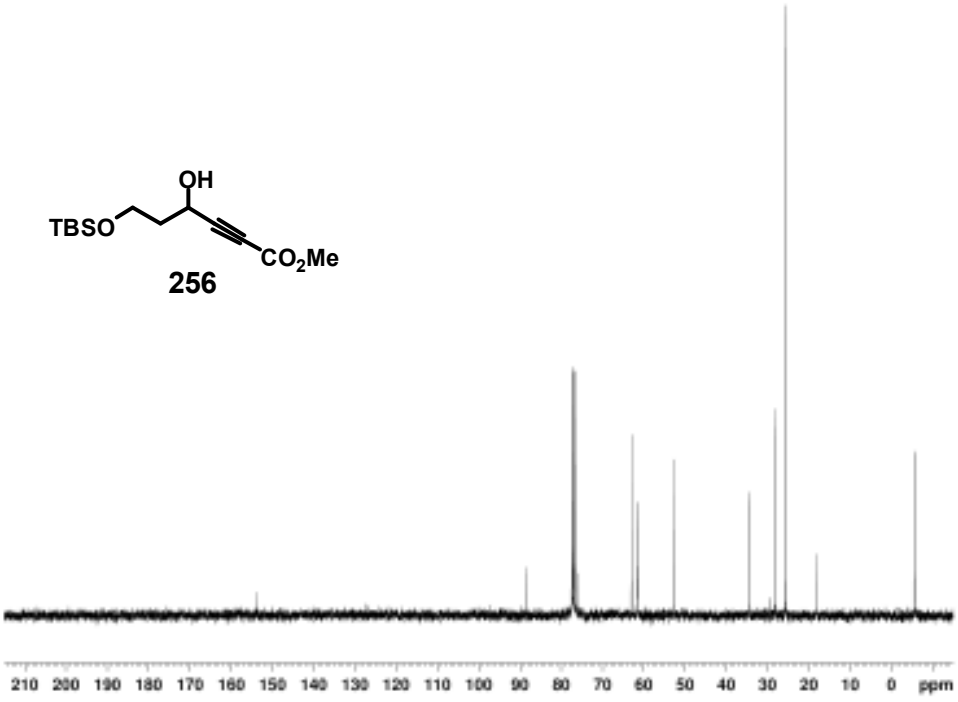
[13]**C NMR of 253**: $CDCl_3$, 293 K, 75 MHz



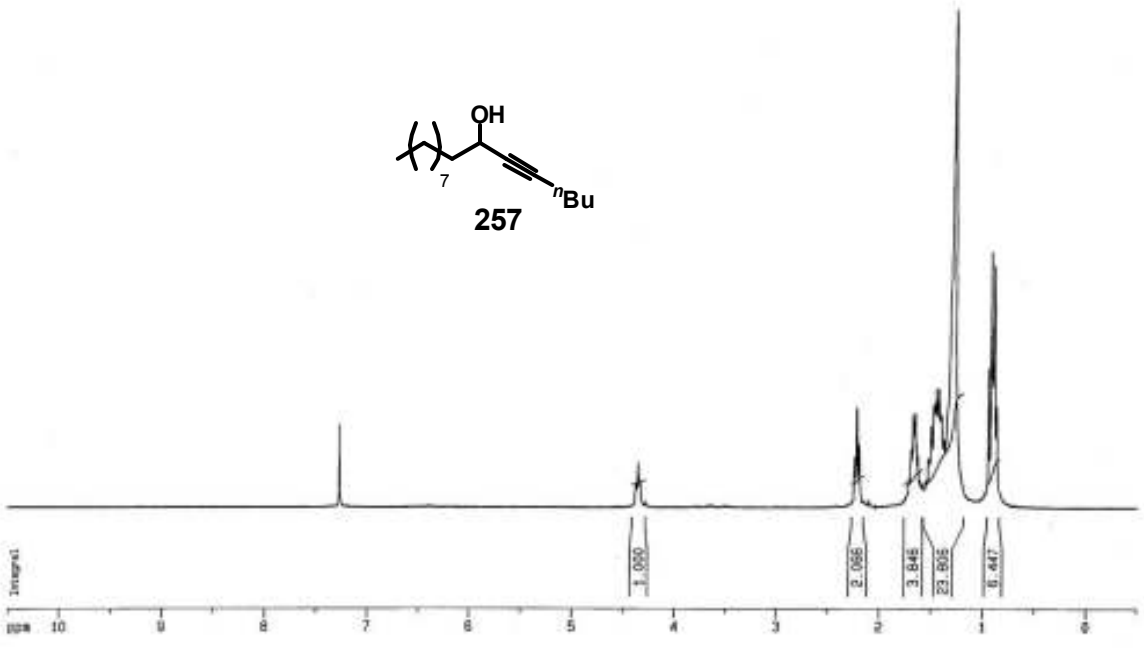
[1]**H NMR of 256**: 1% CD_3OD in $CDCl_3$, 293 K, 300 MHz



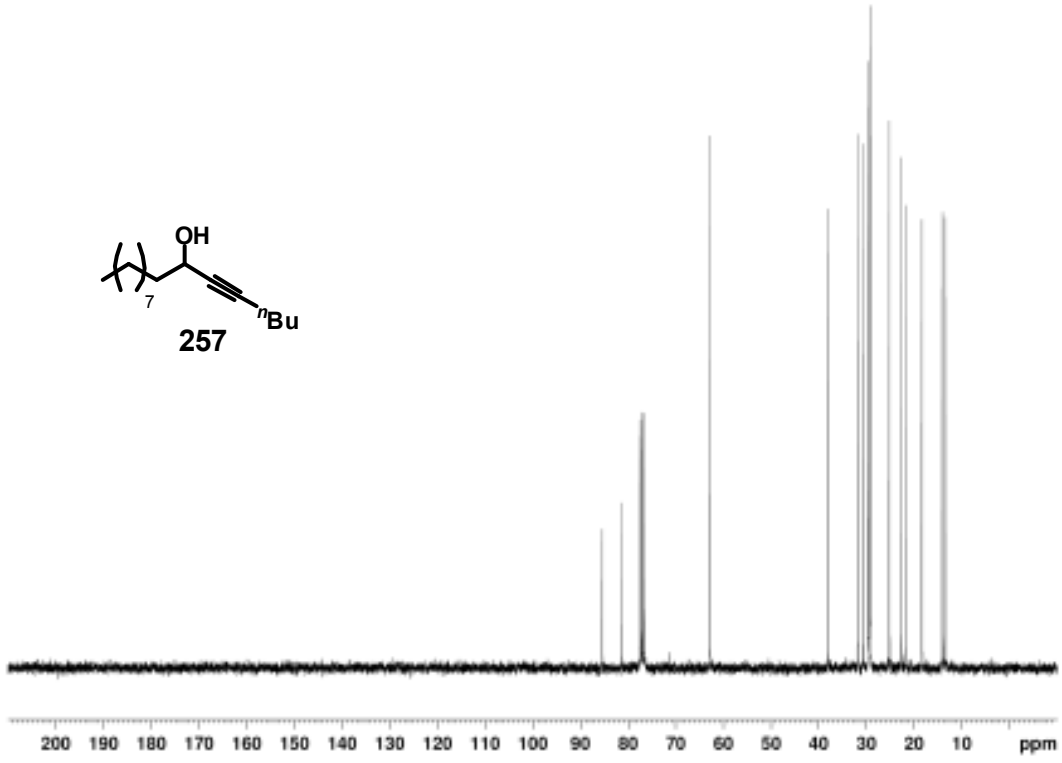
[13]**C NMR of 256**: $CDCl_3$, 293 K, 75 MHz



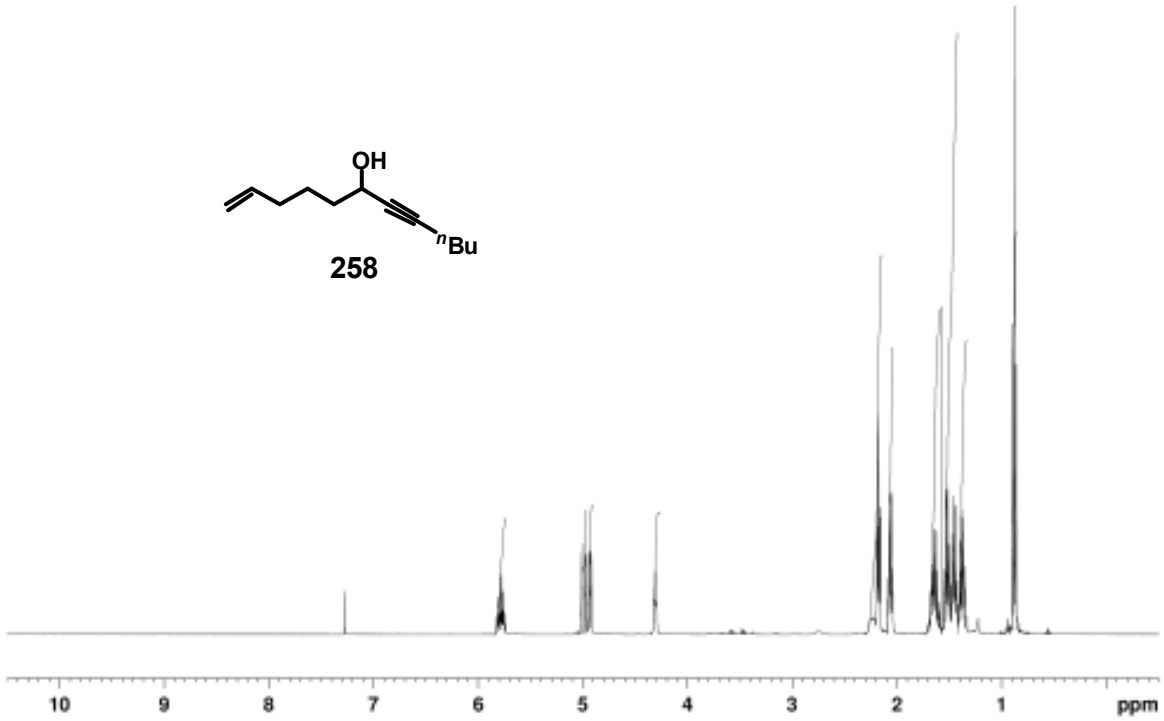
[1]**H NMR of 257**: 1% CD_3OD in $CDCl_3$, 293 K, 300 MHz



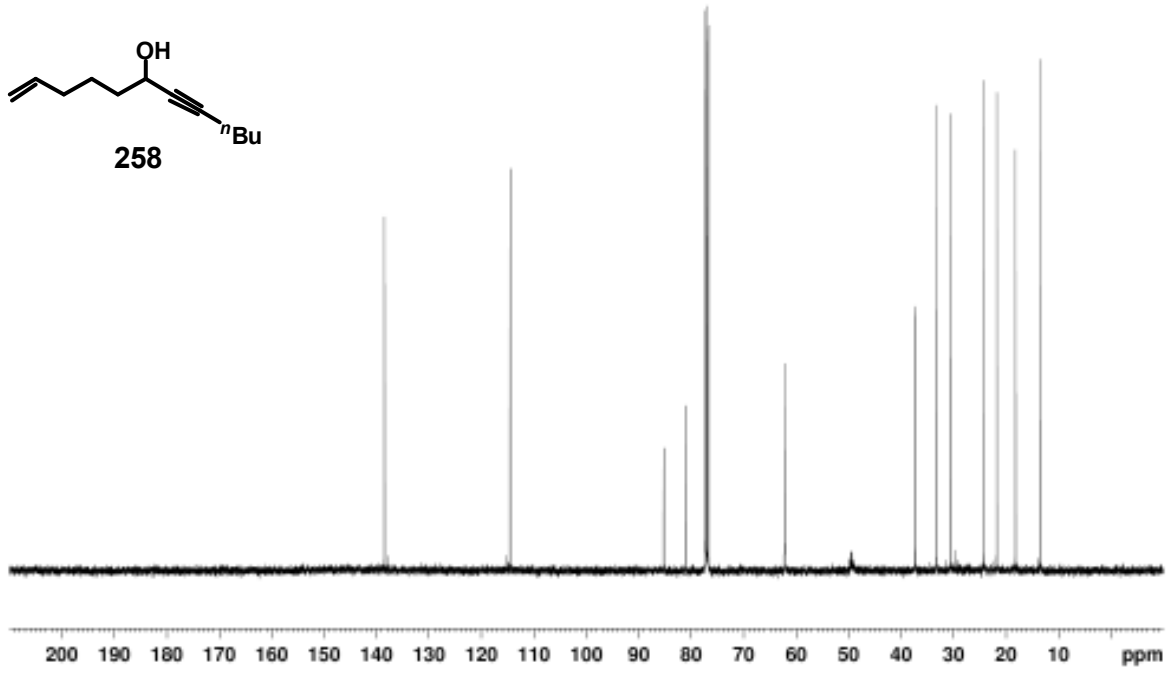
[13]**C NMR of 257**: $CDCl_3$, 293 K, 75 MHz



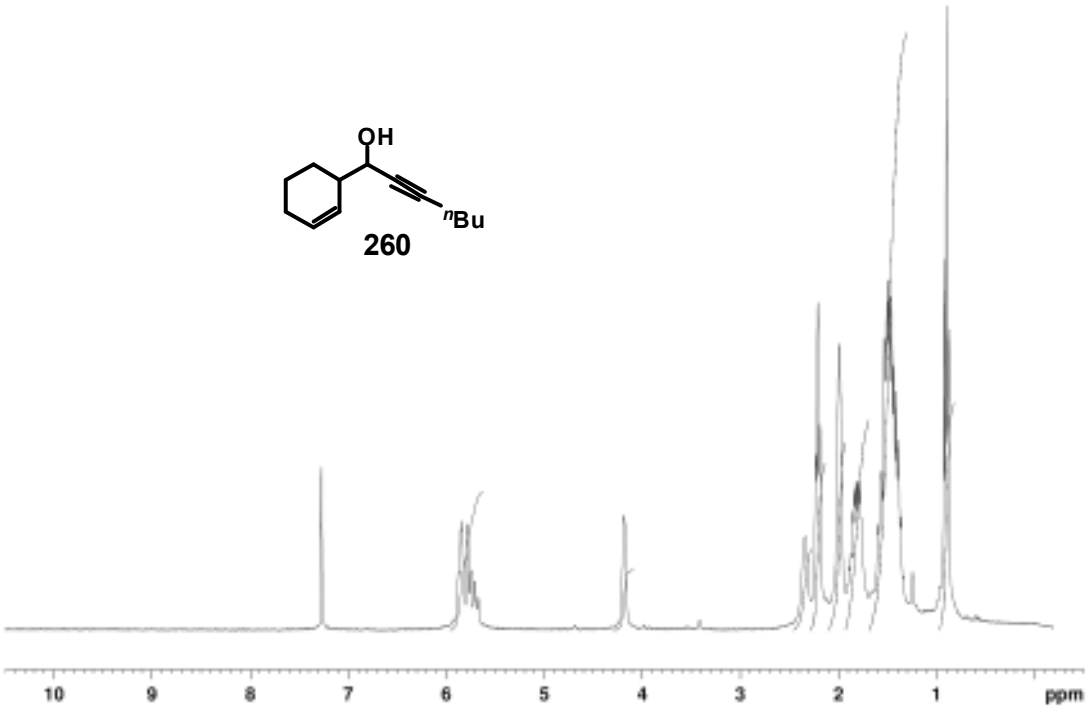
[1]**H NMR of 258**: 1% CD_3OD in $CDCl_3$, 293 K, 300 MHz



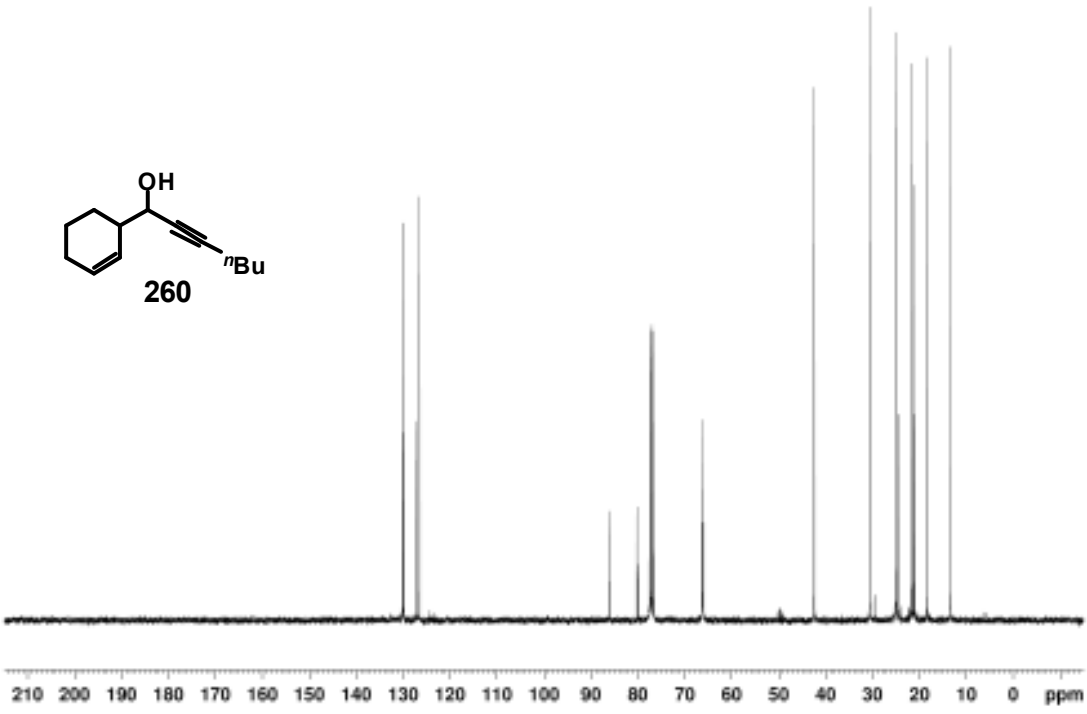
[13]**C NMR of 258**: $CDCl_3$, 293 K, 75 MHz



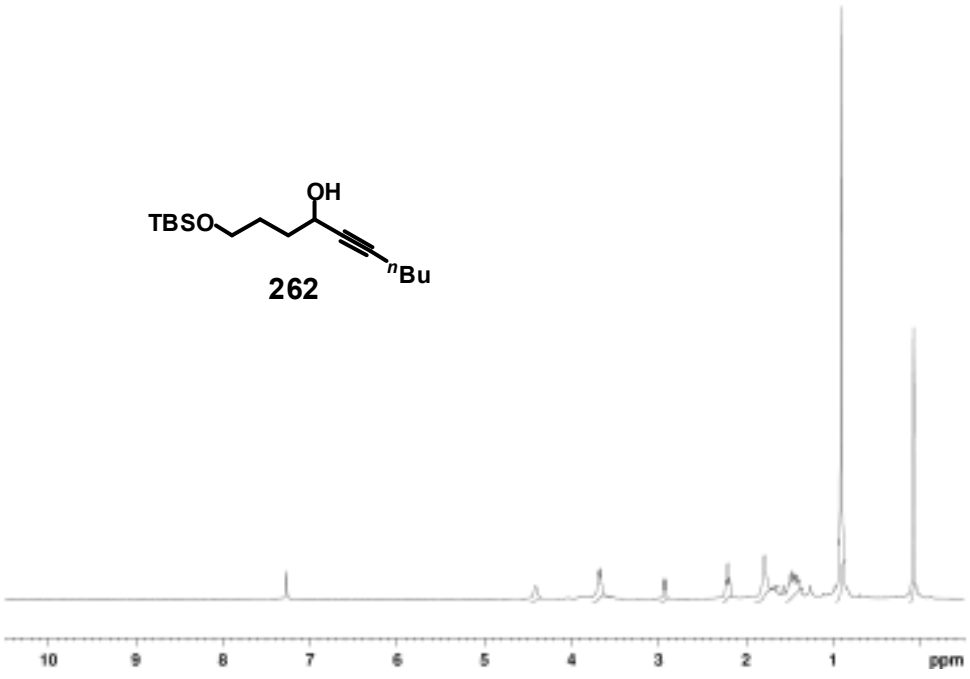
[1]**H NMR of 260**: 1% CD_3OD in $CDCl_3$, 293 K, 300 MHz



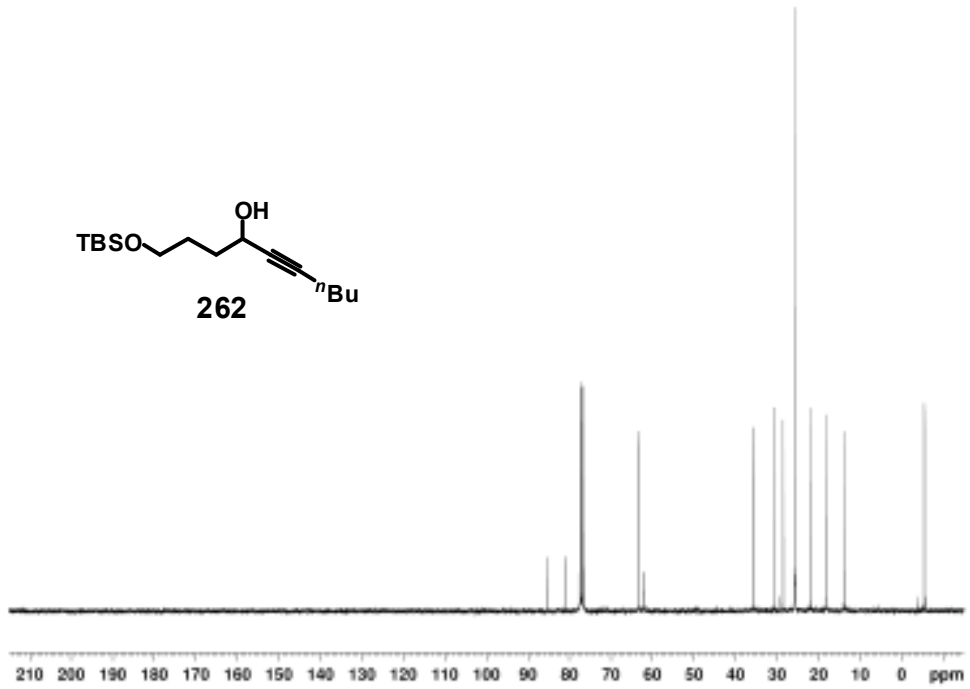
[13]**C NMR of 260**: $CDCl_3$, 293 K, 75 MHz



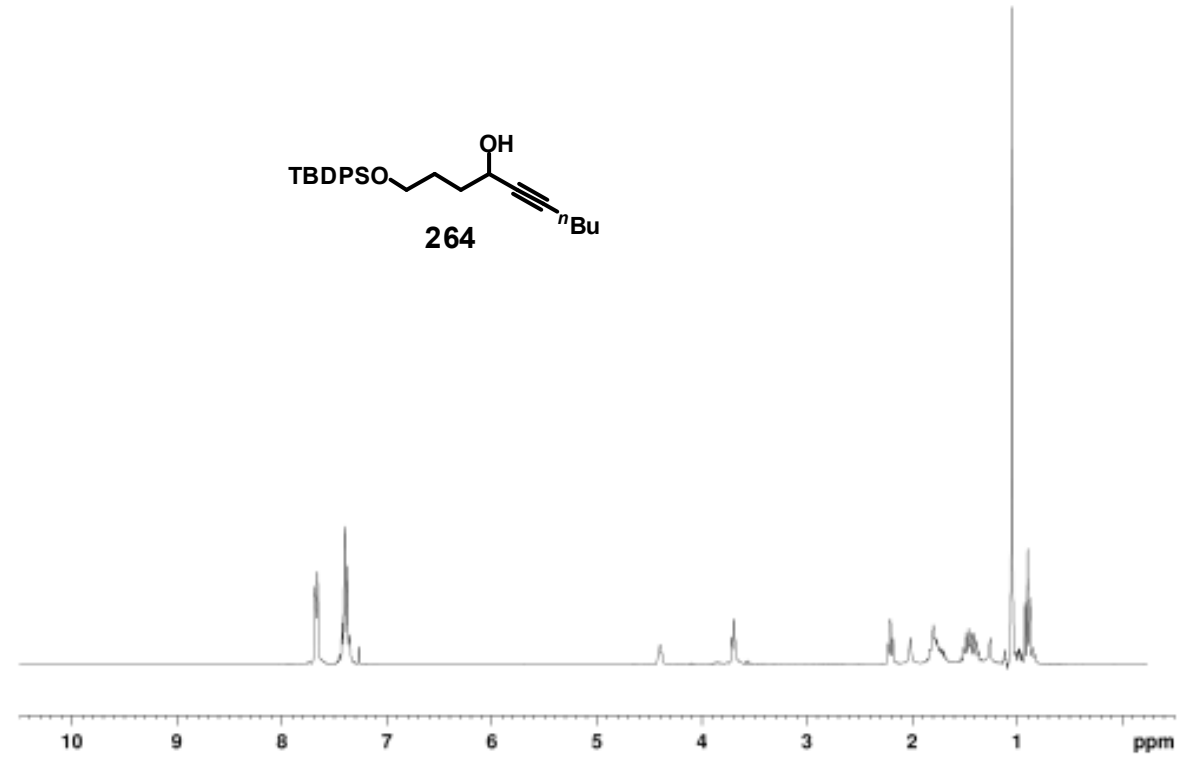
[1]**H NMR of 262**: 1% CD_3OD in $CDCl_3$, 293 K, 300 MHz



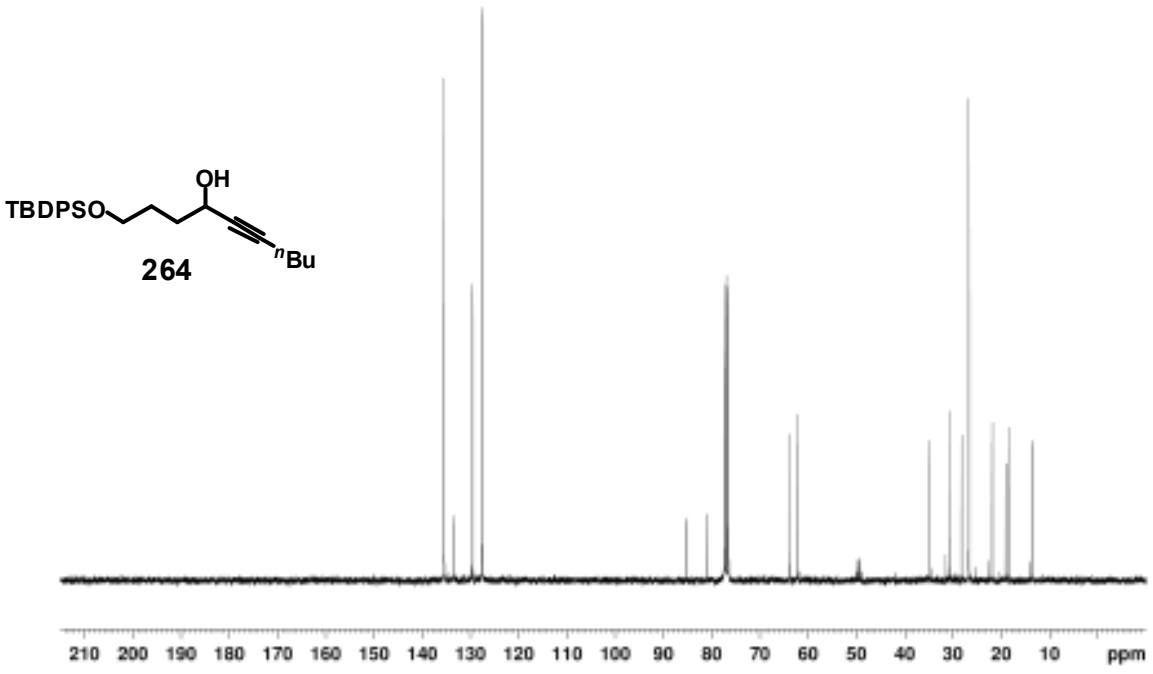
[13]**C NMR of 262**: $CDCl_3$, 293 K, 75 MHz



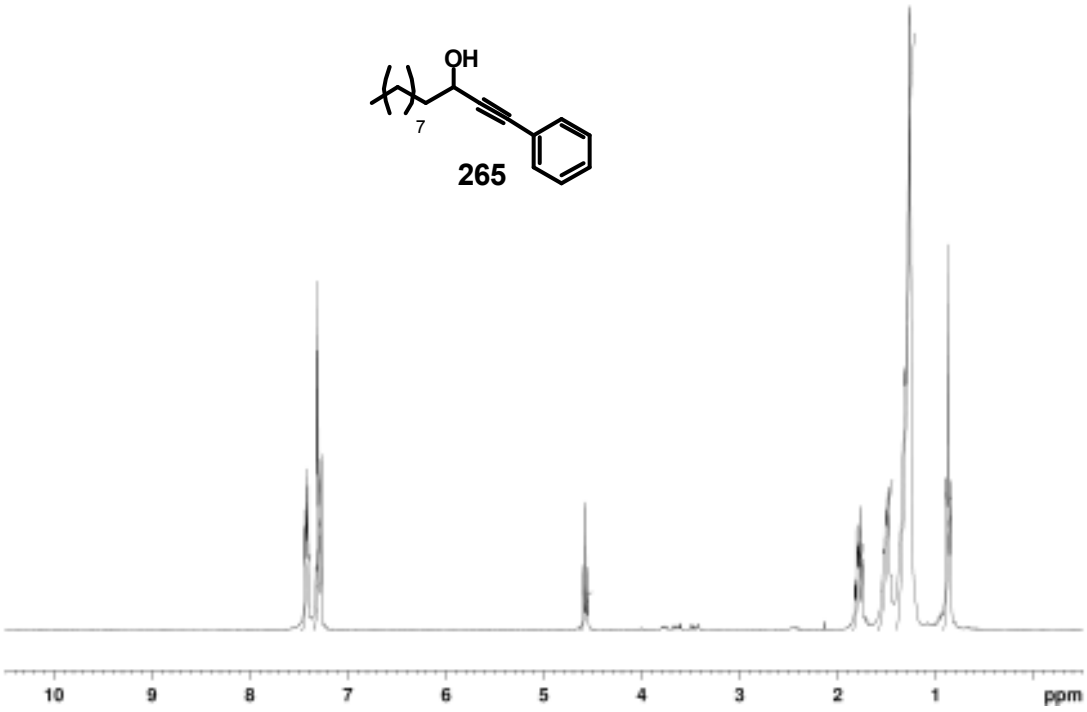
[1]**H NMR of 264**: 1% CD_3OD in $CDCl_3$, 293 K, 300 MHz



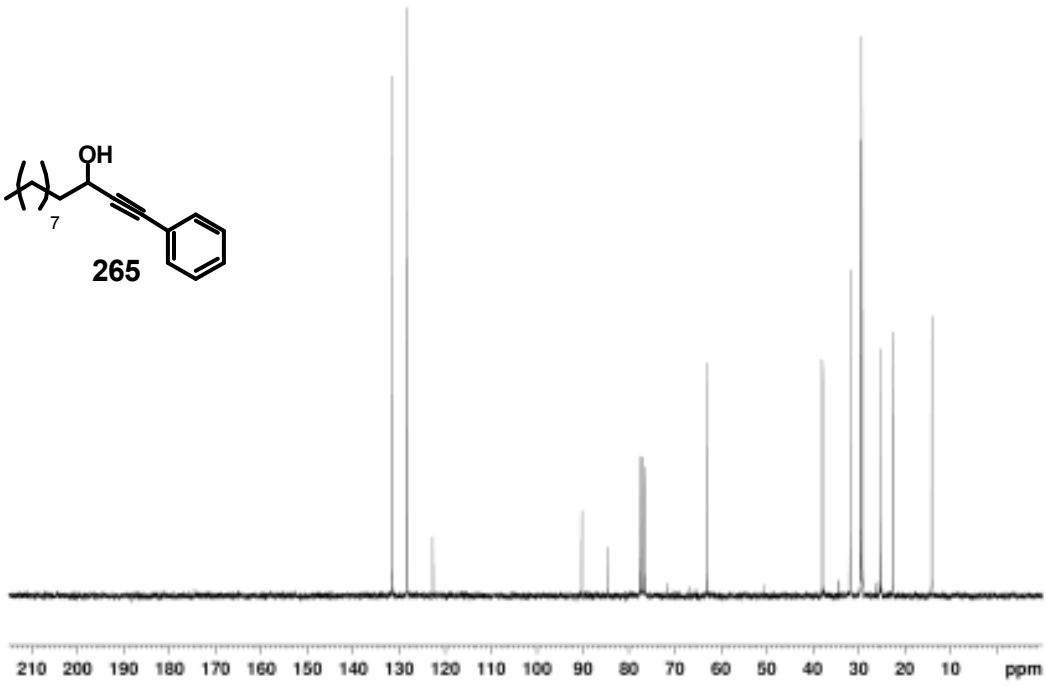
[13]**C NMR of 264**: $CDCl_3$, 293 K, 75 MHz



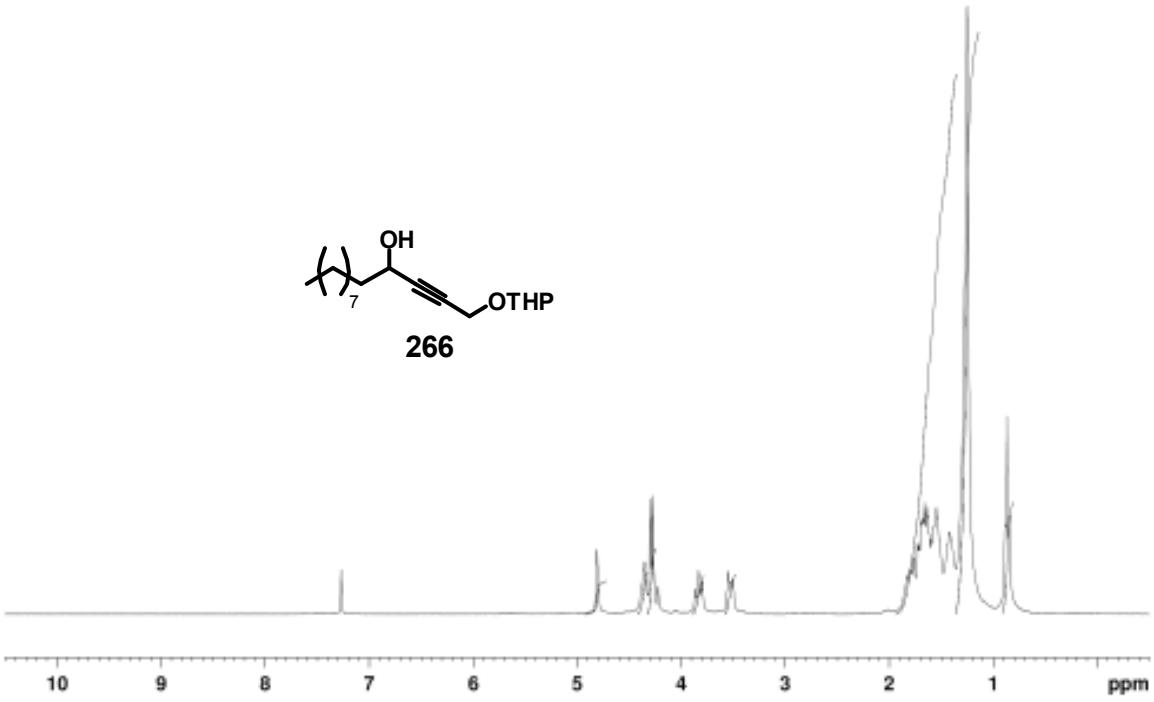
[1]**H NMR of 265**: 1% CD_3OD in $CDCl_3$, 293 K, 300 MHz



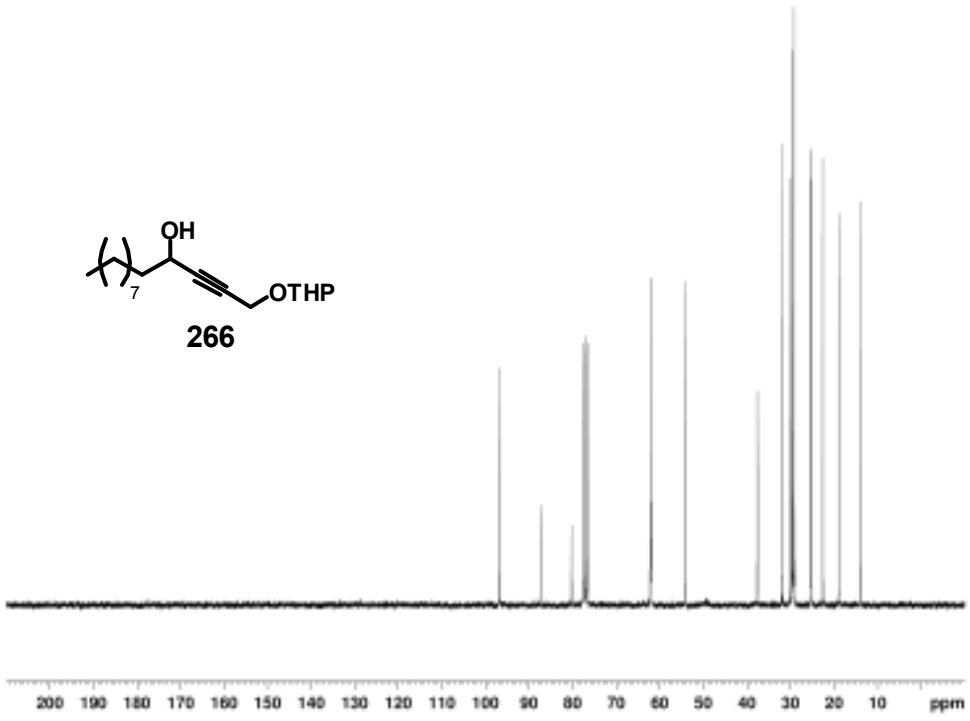
[13]**C NMR of 265**: $CDCl_3$, 293 K, 75 MHz



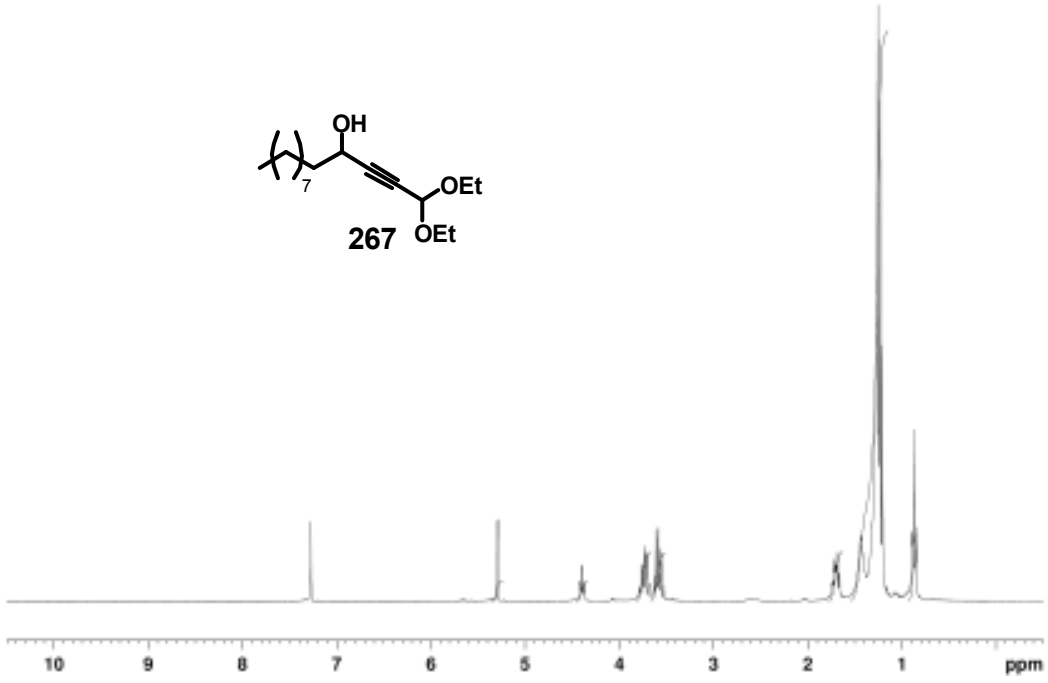
^{1}H NMR of 266: 1% CD_3OD in $CDCl_3$, 293 K, 300 MHz



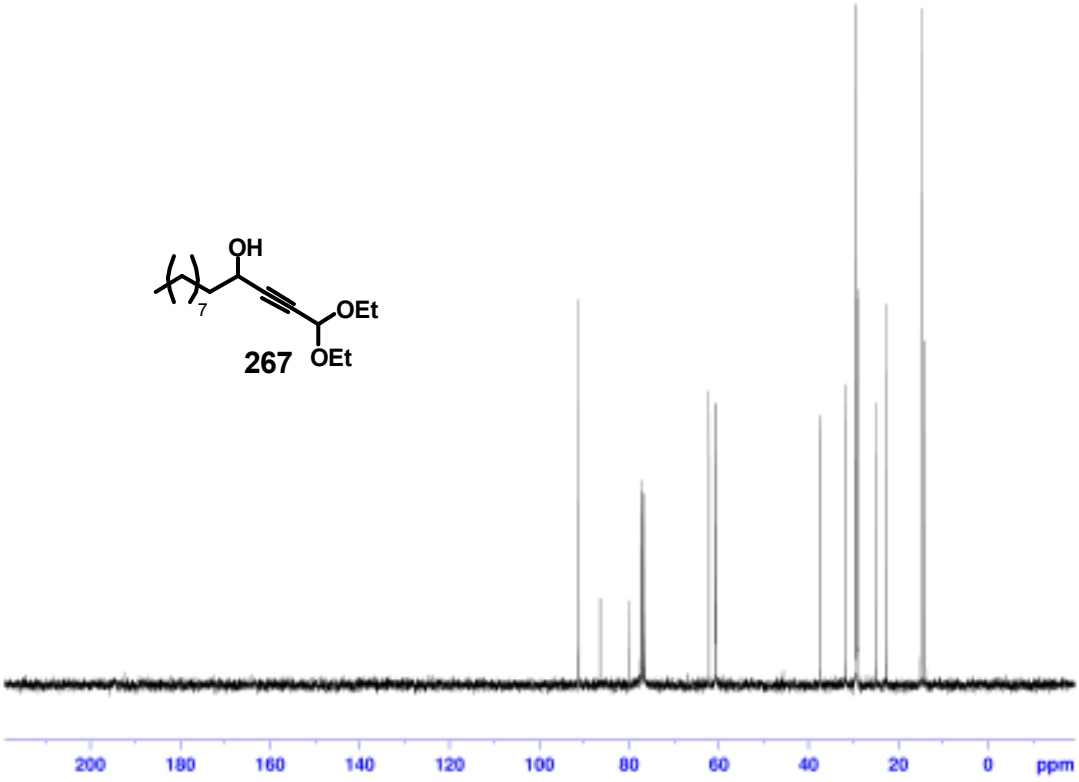
^{13}C NMR of 266: $CDCl_3$, 293 K, 75 MHz



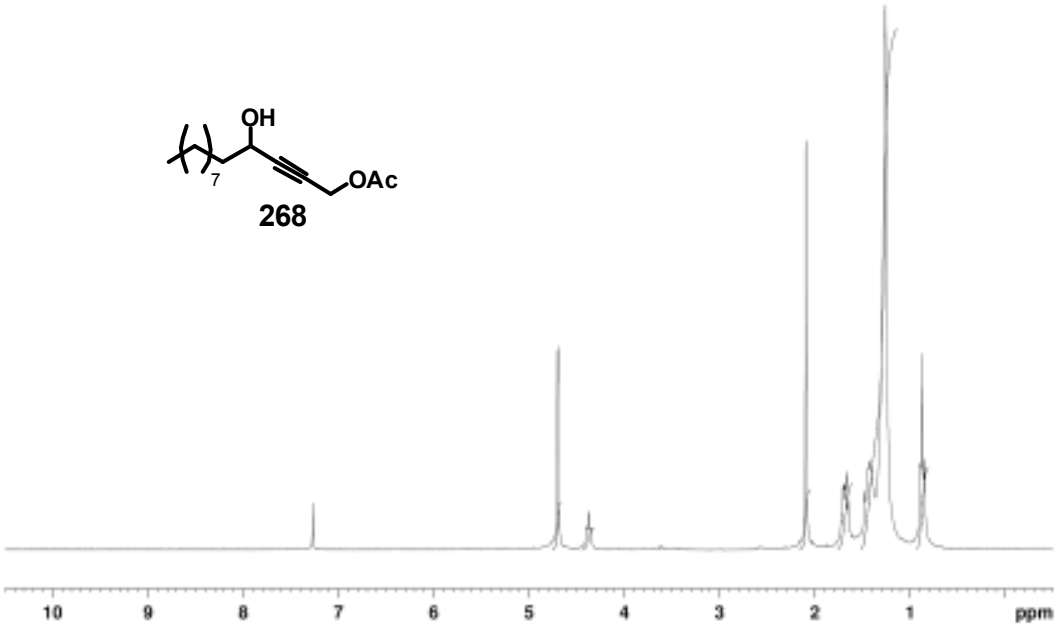
[1]**H NMR of 267**: 1% CD_3OD in $CDCl_3$, 293 K, 300 MHz



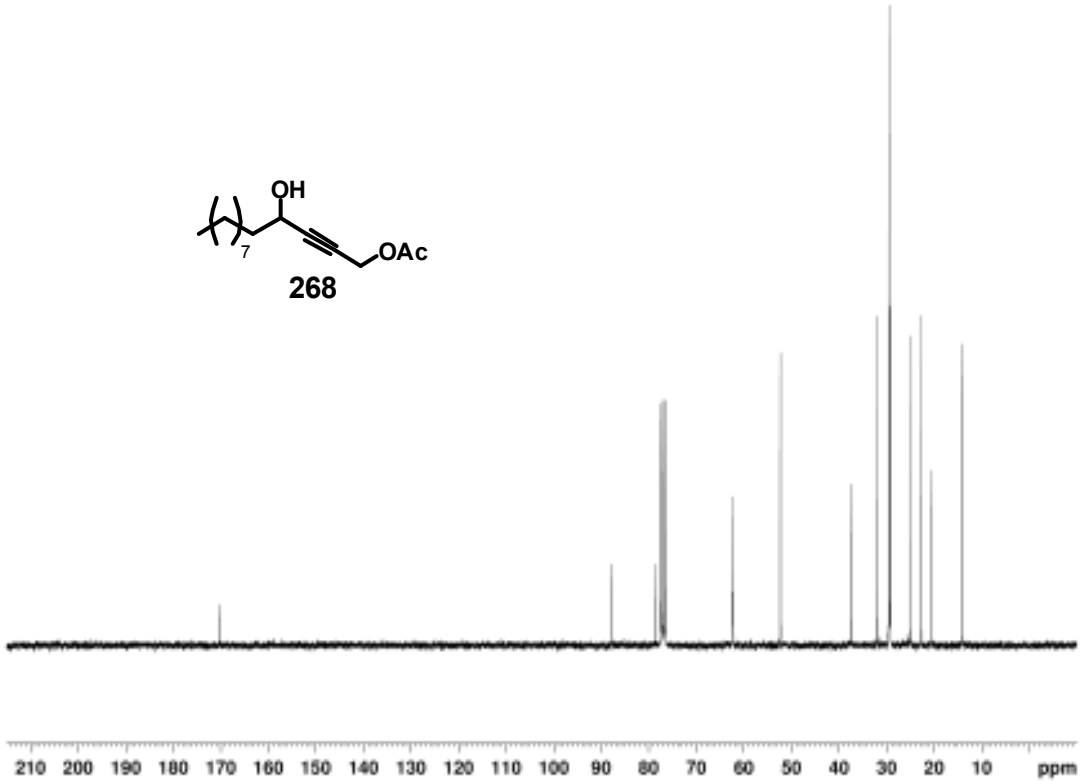
[13]**C NMR of 267**: $CDCl_3$, 293 K, 75 MHz



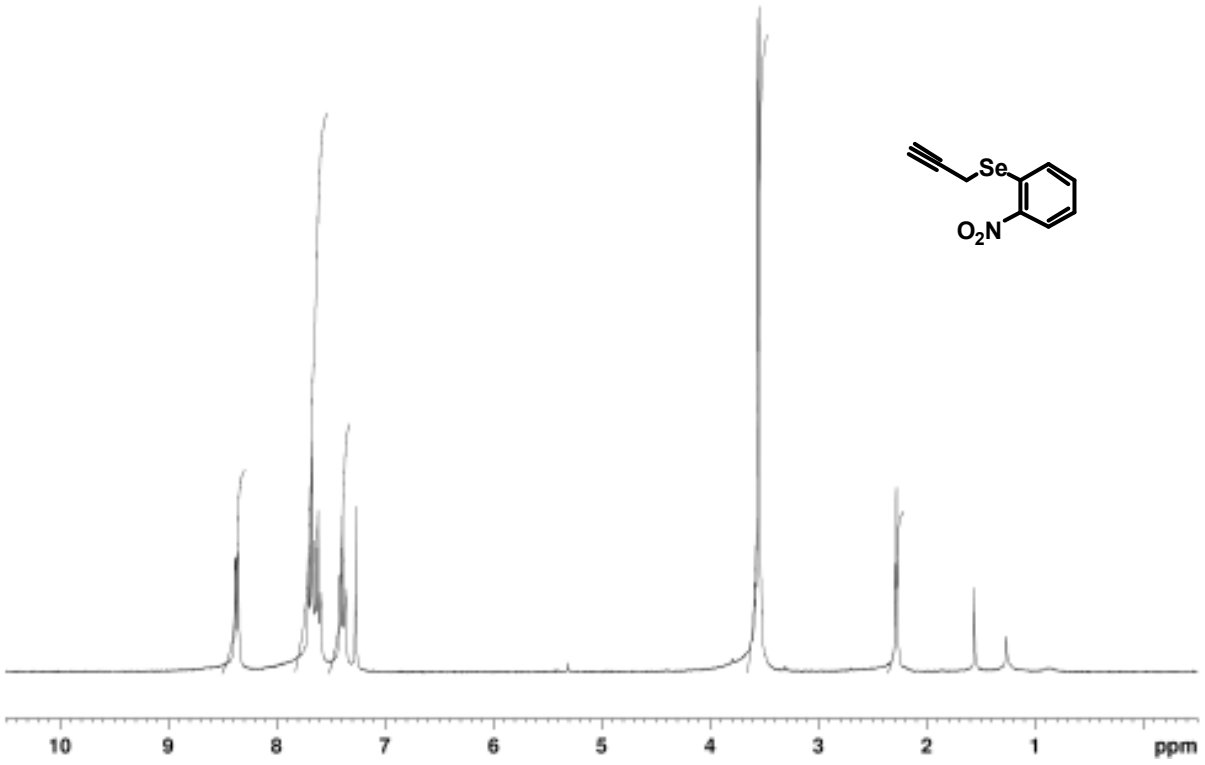
[1]**H NMR of 268**: 1% CD_3OD in $CDCl_3$, 293 K, 300 MHz



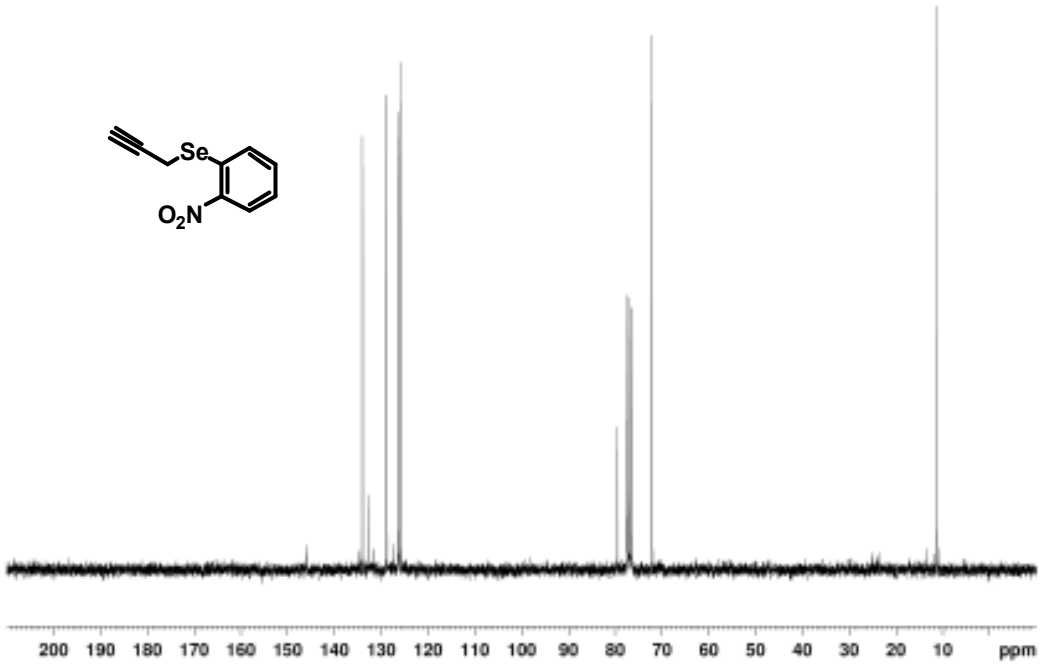
[13]**C NMR of 268**: $CDCl_3$, 293 K, 75 MHz



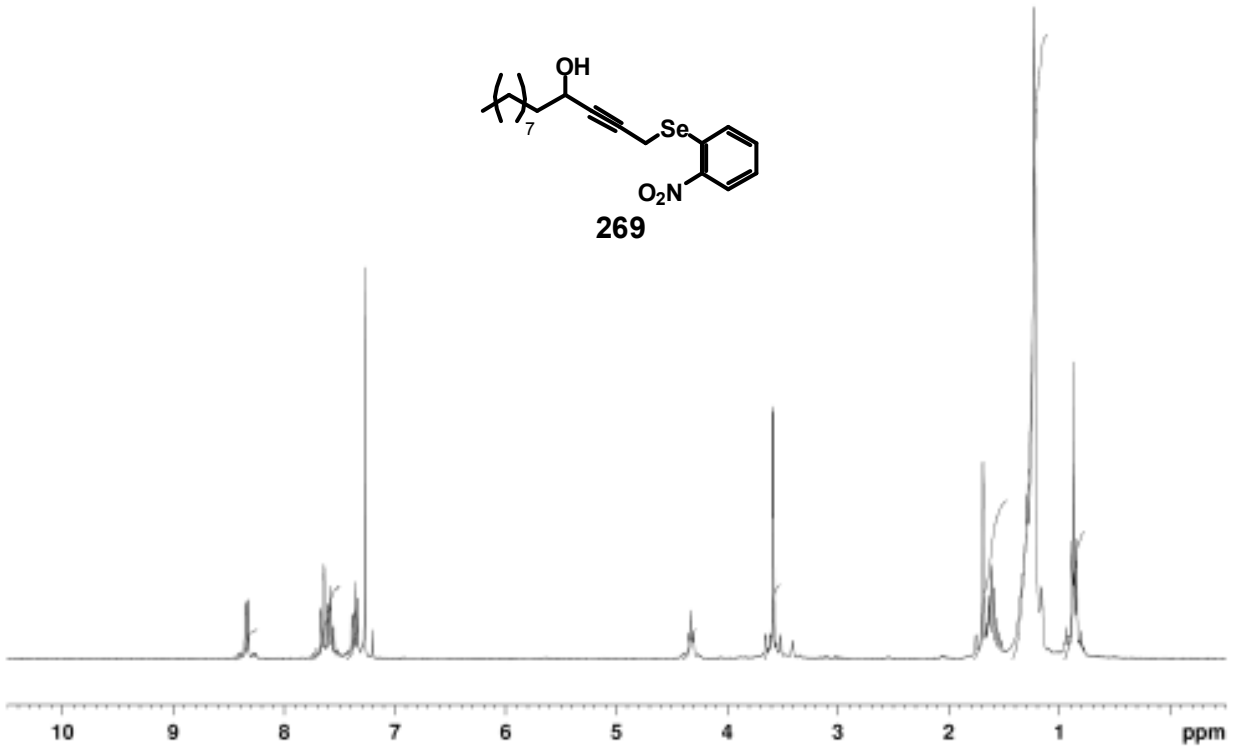
[1]**H NMR of 2-nitrophenyl propargyl selenide**: $CDCl_3$, 293 K, 300 MHz



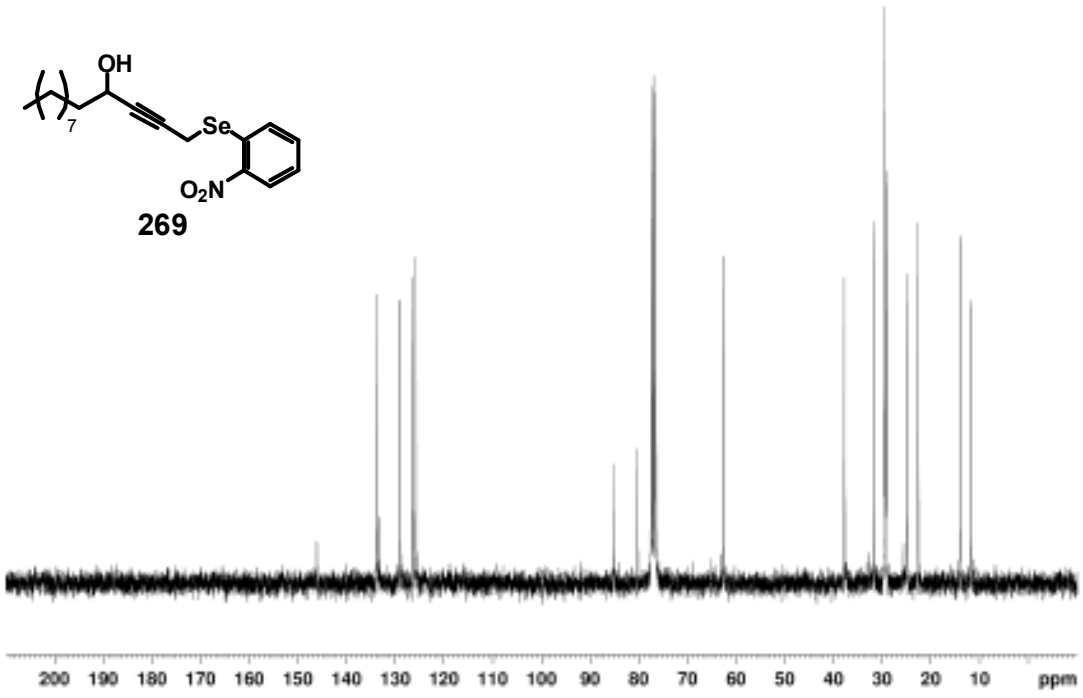
[13]**C NMR of 2-nitrophenyl propargyl selenide**: $CDCl_3$, 293 K, 75 MHz



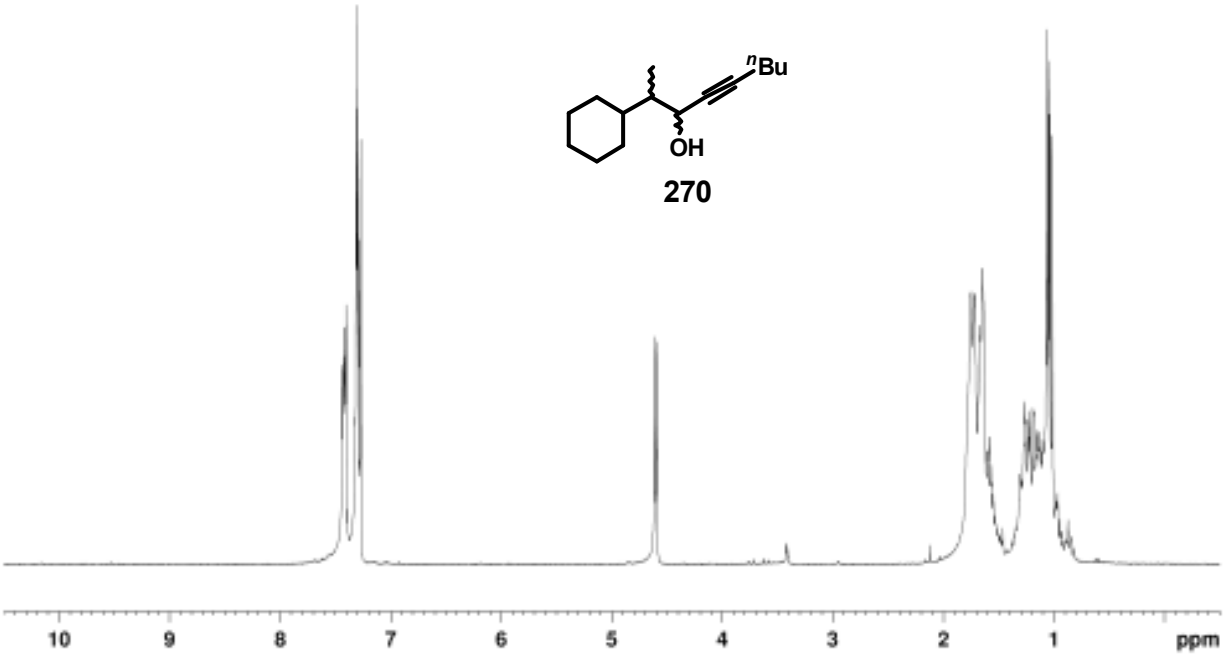
[1]**H NMR of 269**: 1% CD_3OD in $CDCl_3$, 293 K, 300 MHz



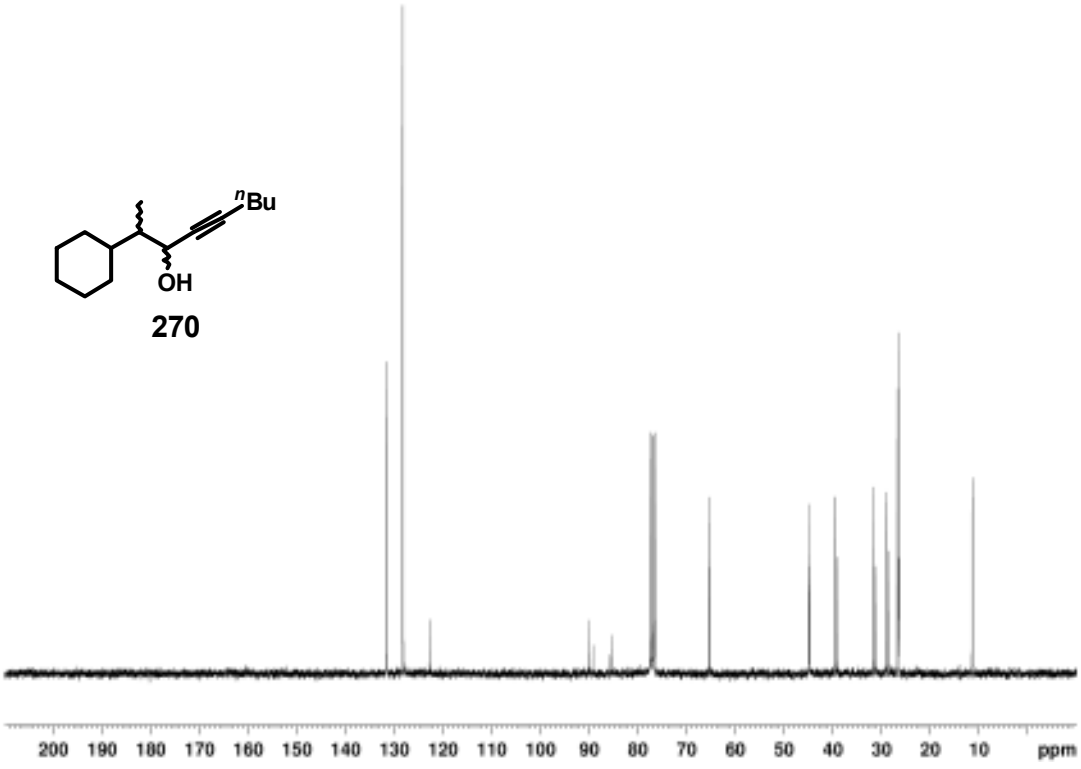
[13]**C NMR of 269**: $CDCl_3$, 293 K, 75 MHz



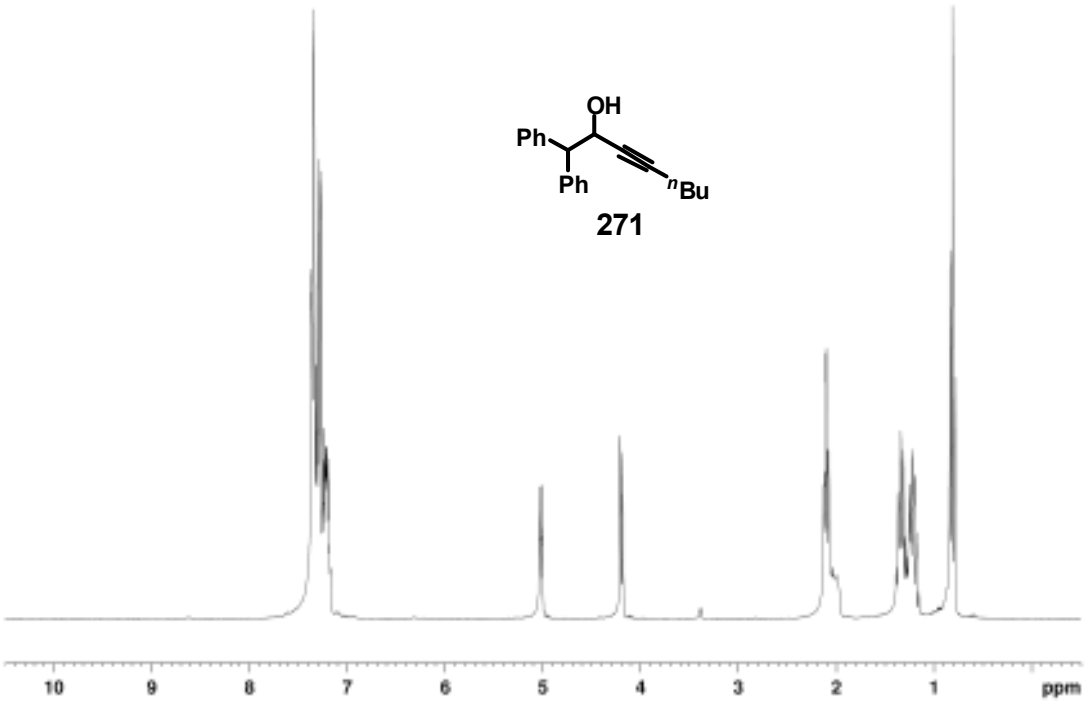
[1]**H NMR of 270**: 1% CD_3OD in $CDCl_3$, 293 K, 300 MHz



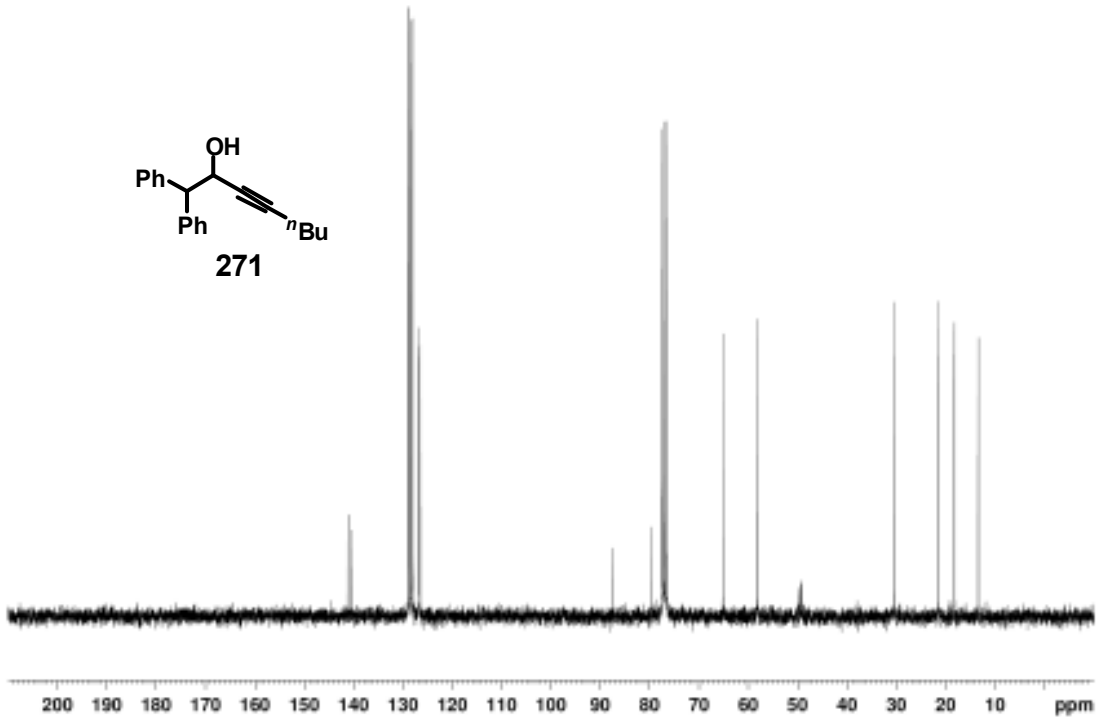
[13]**C NMR of 270**: $CDCl_3$, 293 K, 75 MHz



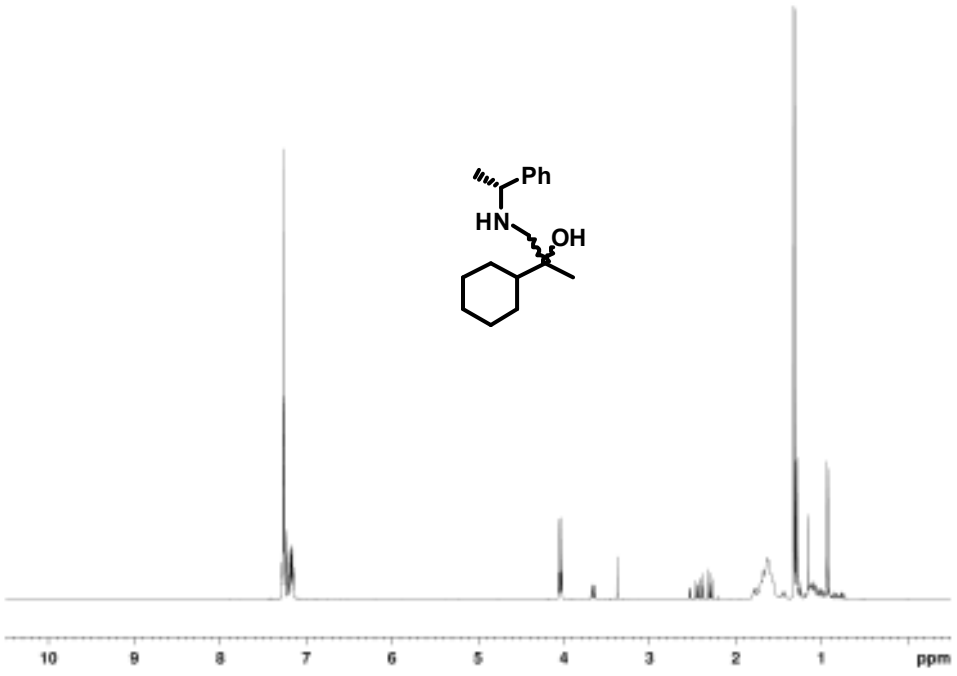
[1]**H NMR of 271**: 1% CD_3OD in $CDCl_3$, 293 K, 300 MHz



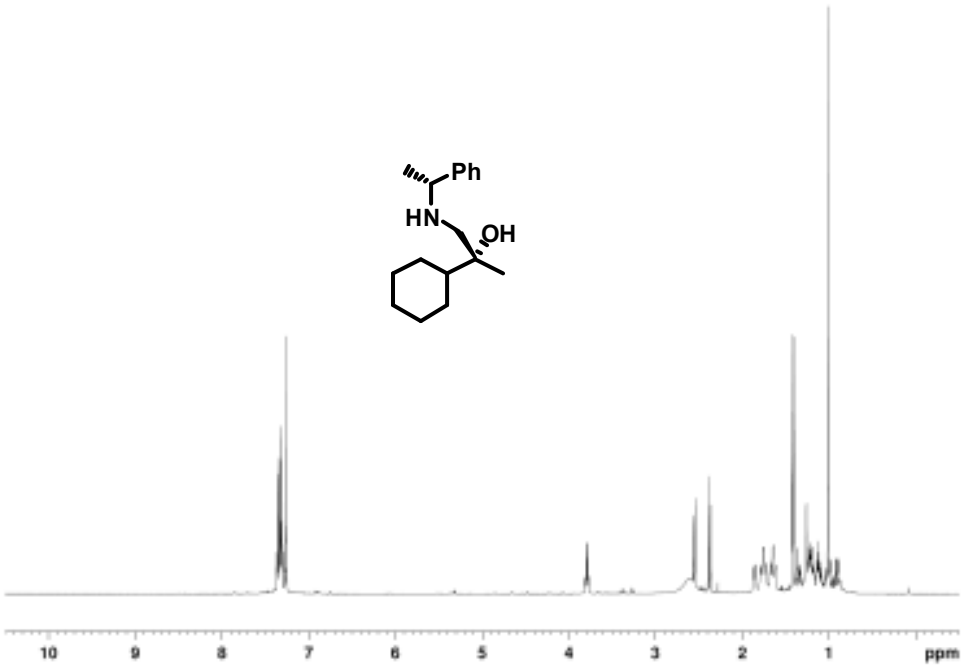
[13]**C NMR of 271**: $CDCl_3$, 293 K, 75 MHz



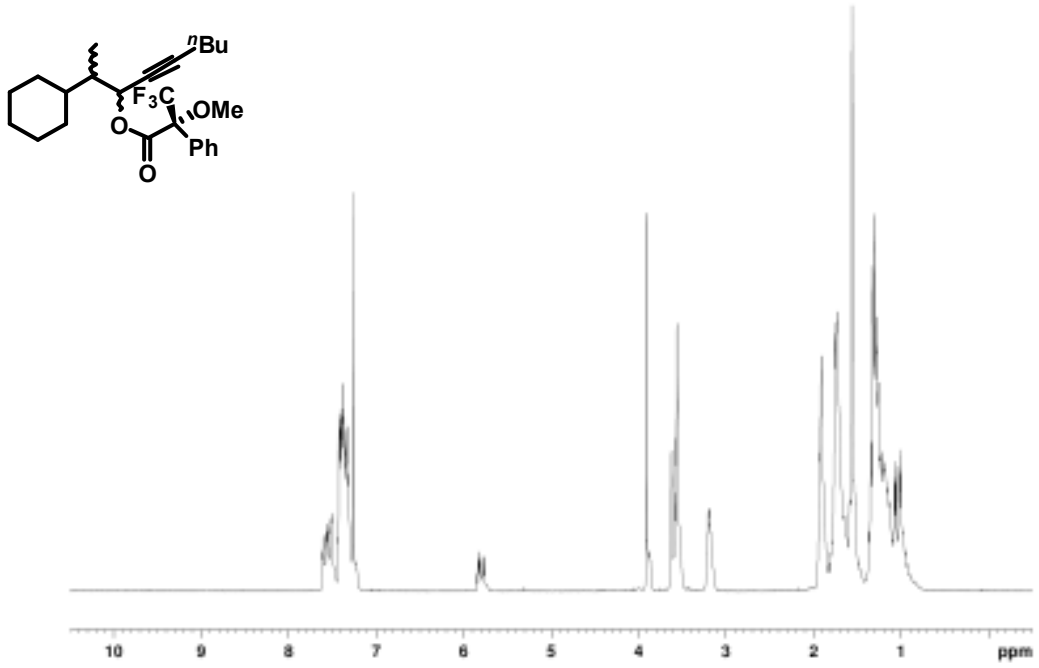
[1]**H NMR of 302**: 1% CD_3OD in $CDCl_3$, 293 K, 300 MHz



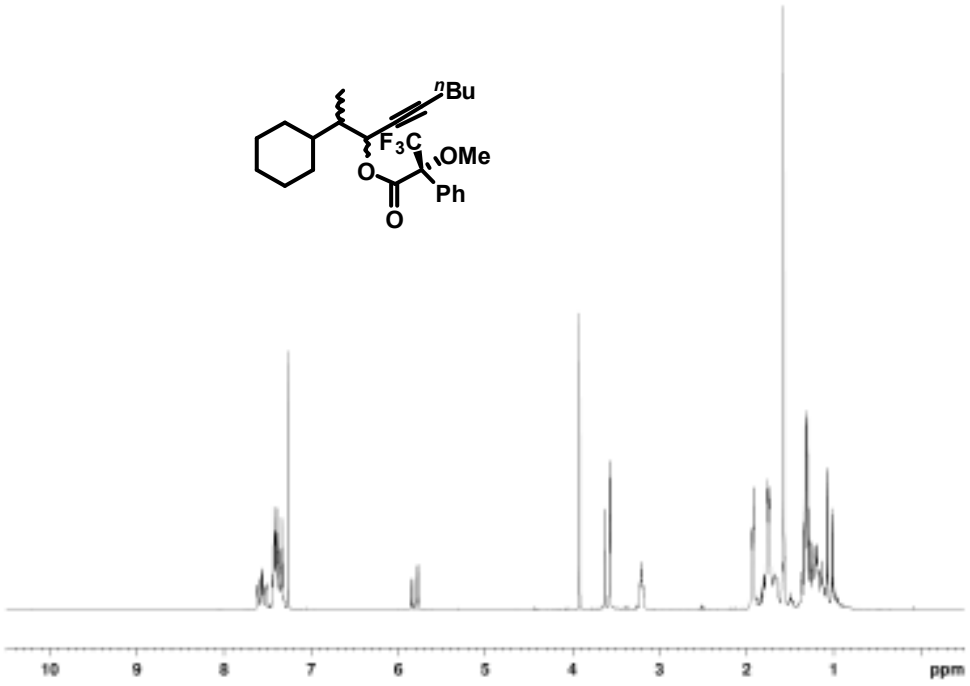
[1]**H NMR of 302 – prepared from (*R*)-273**: 1% CD_3OD in $CDCl_3$, 293 K, 300 MHz



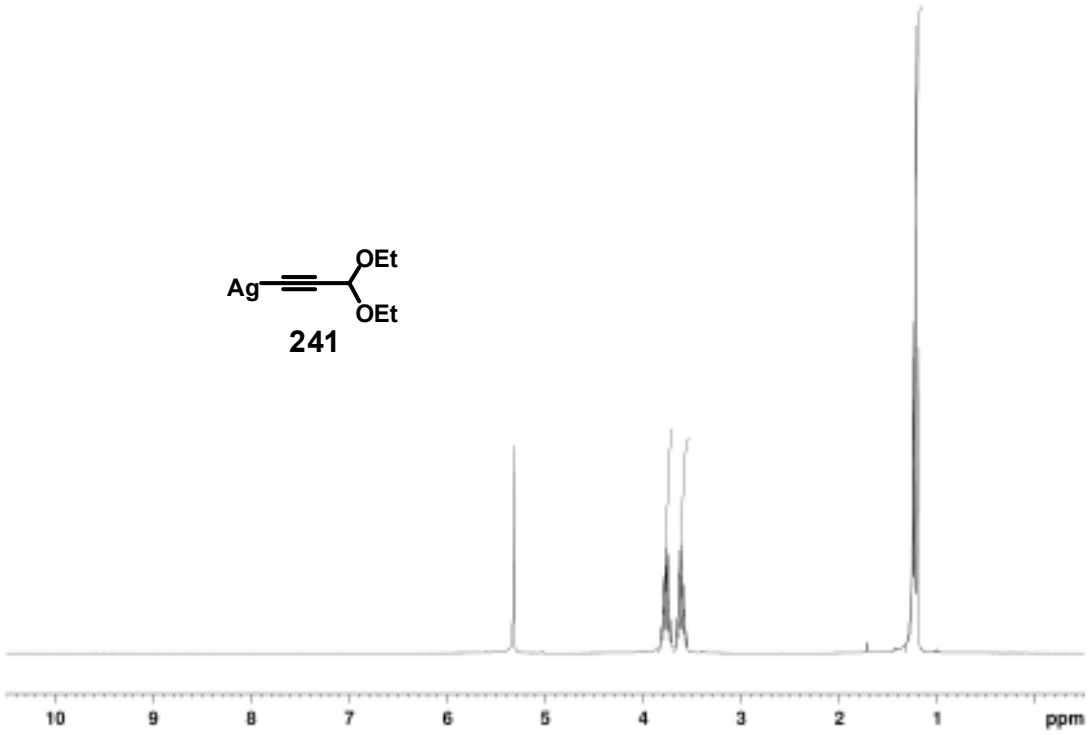
^{1}H NMR of 303 – prepared from 274: $CDCl_3$, 293 K, 300 MHz



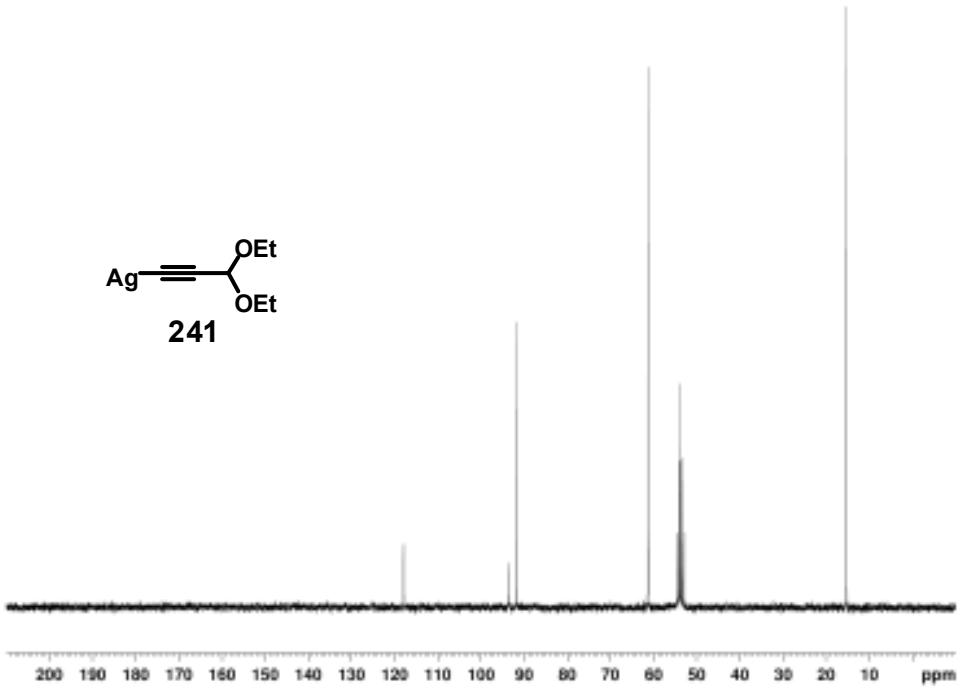
^{1}H NMR of 303 – prepared from enantioenriched-274: $CDCl_3$, 293 K, 300 MHz



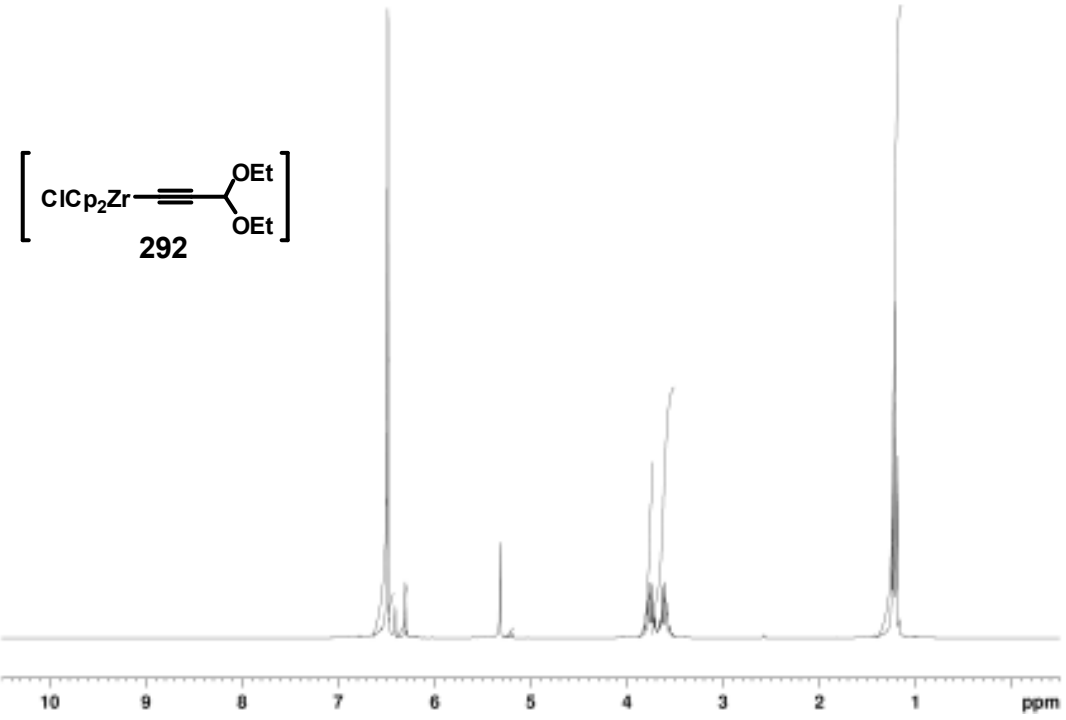
[1]**H NMR of 241**: CD_2Cl_2, 293 K, 300 MHz



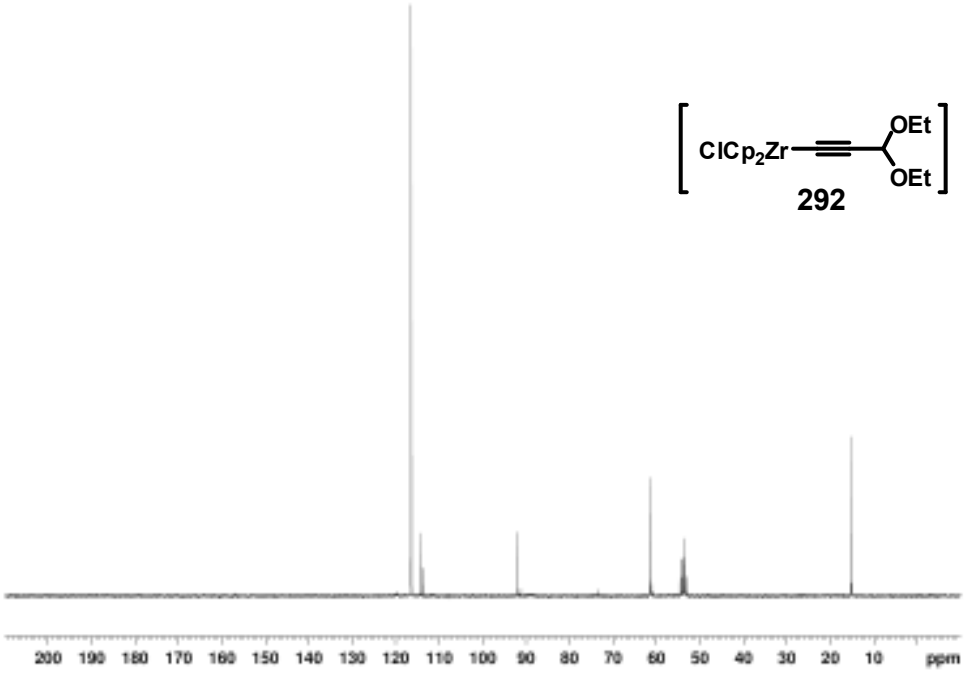
[13]**C NMR of 241**: $CDCl_3$, 293 K, 75 MHz



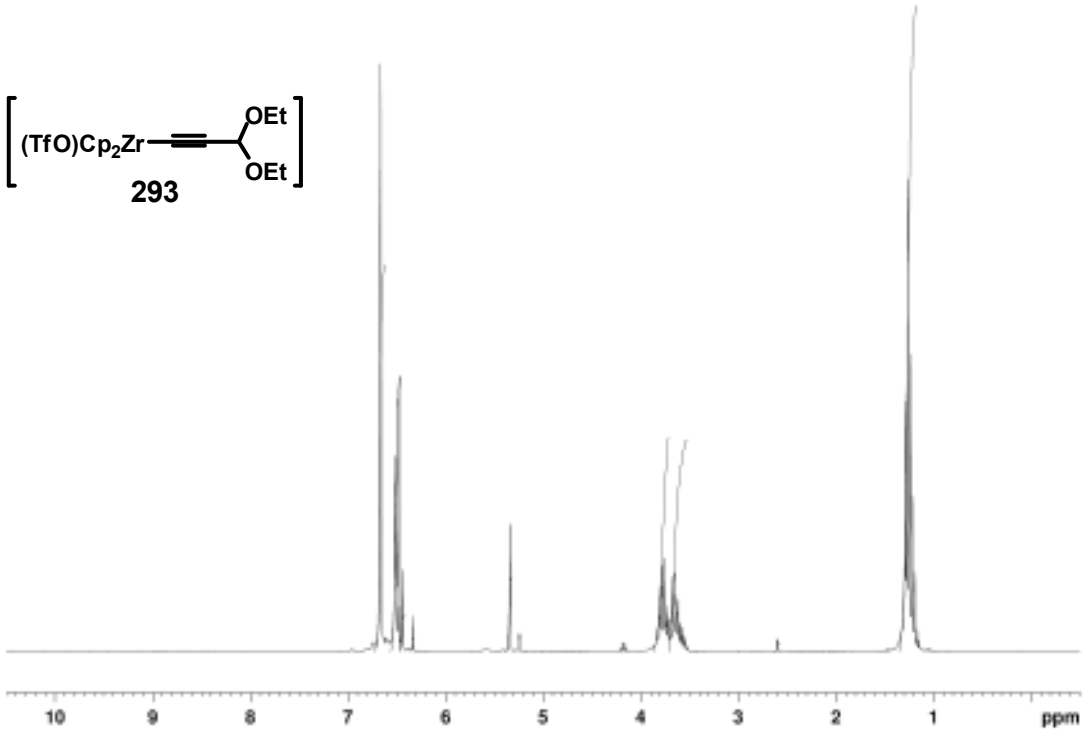
[1]**H NMR of 292**: CD_2Cl_2, 293 K, 300 MHz



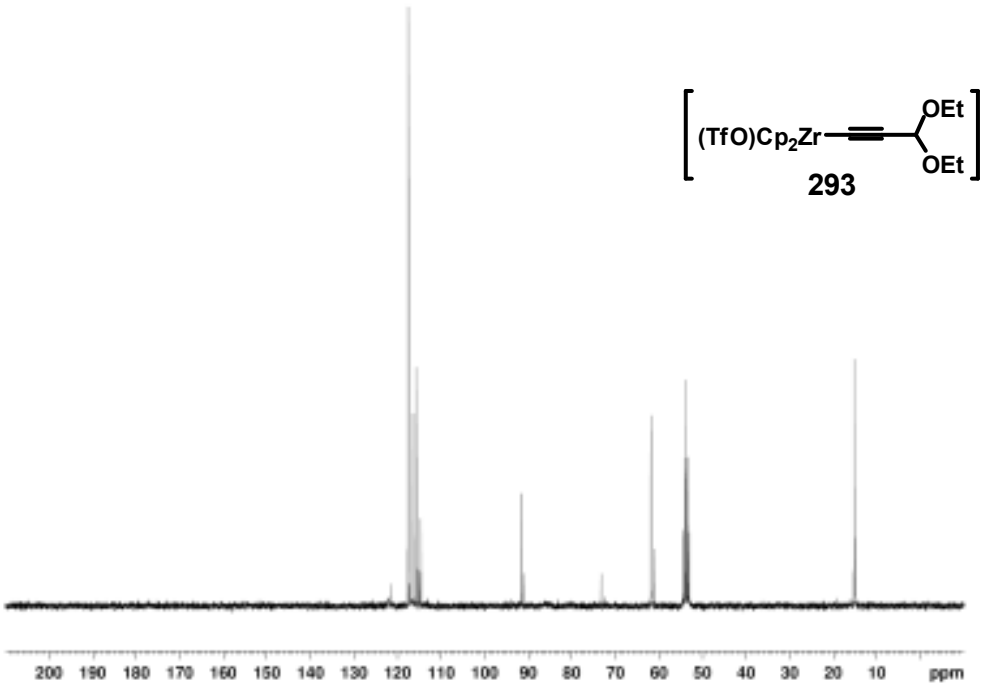
[13]**C NMR of 292**: CD_2Cl_2, 293 K, 75 MHz



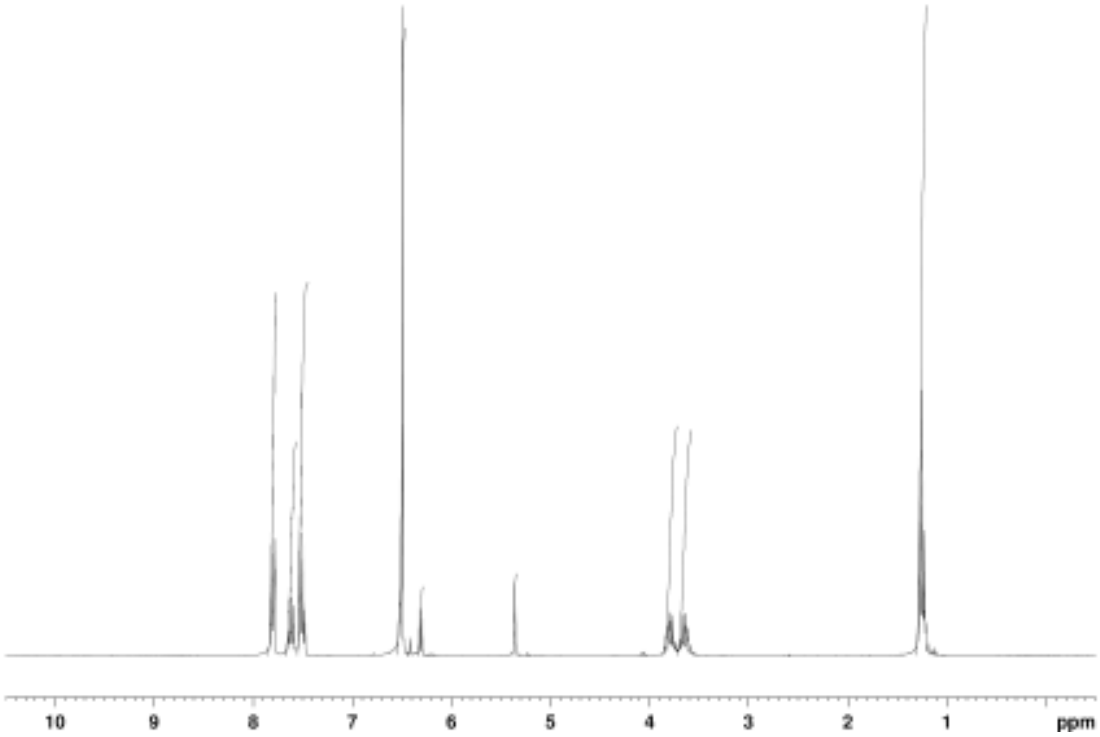
[1]**H NMR of 293**: CD_2Cl_2, 293 K, 300 MHz



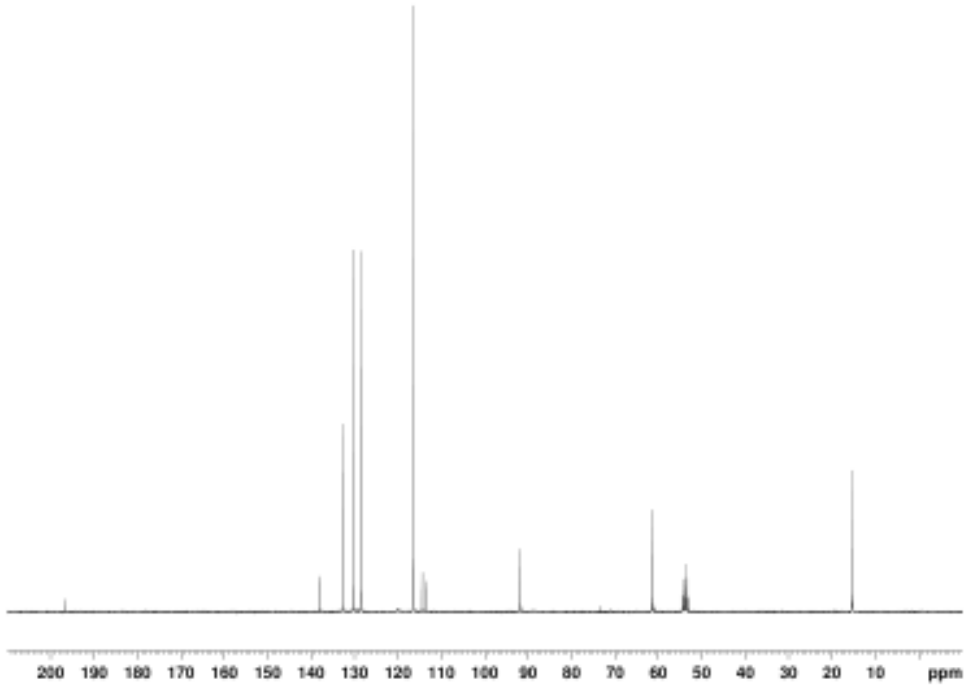
[13]**C NMR of 293**: CD_2Cl_2, 293 K, 75 MHz



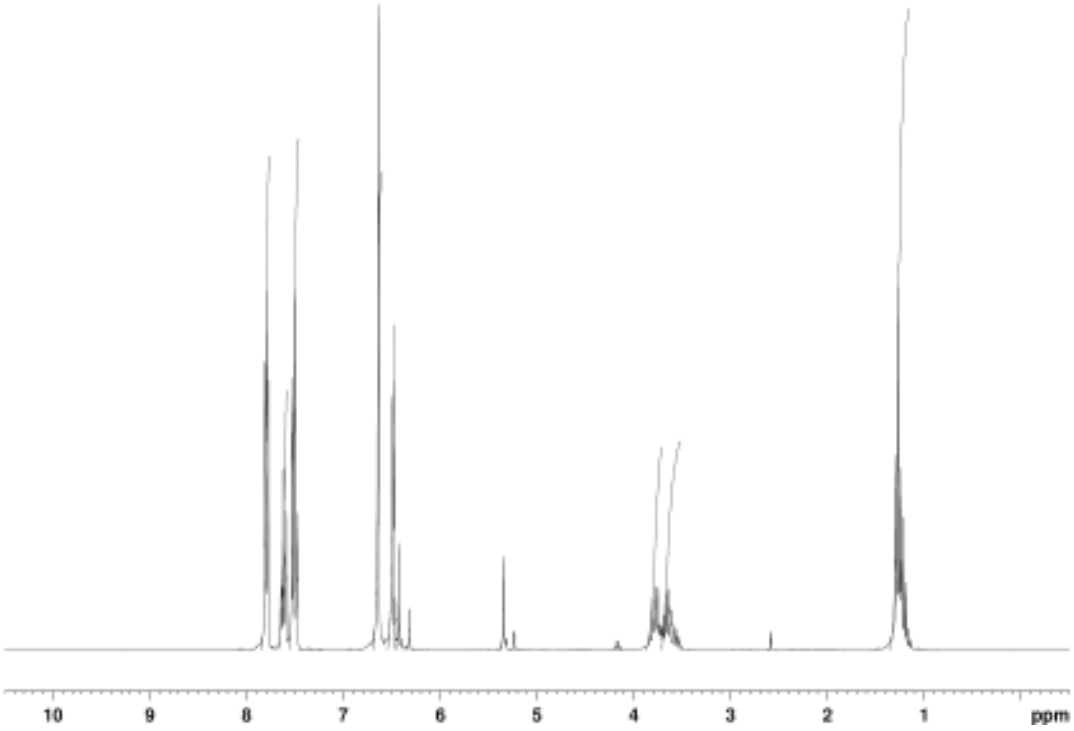
^{1}H NMR of 292 + benzophenone: CD_2Cl_2, 293 K, 300 MHz



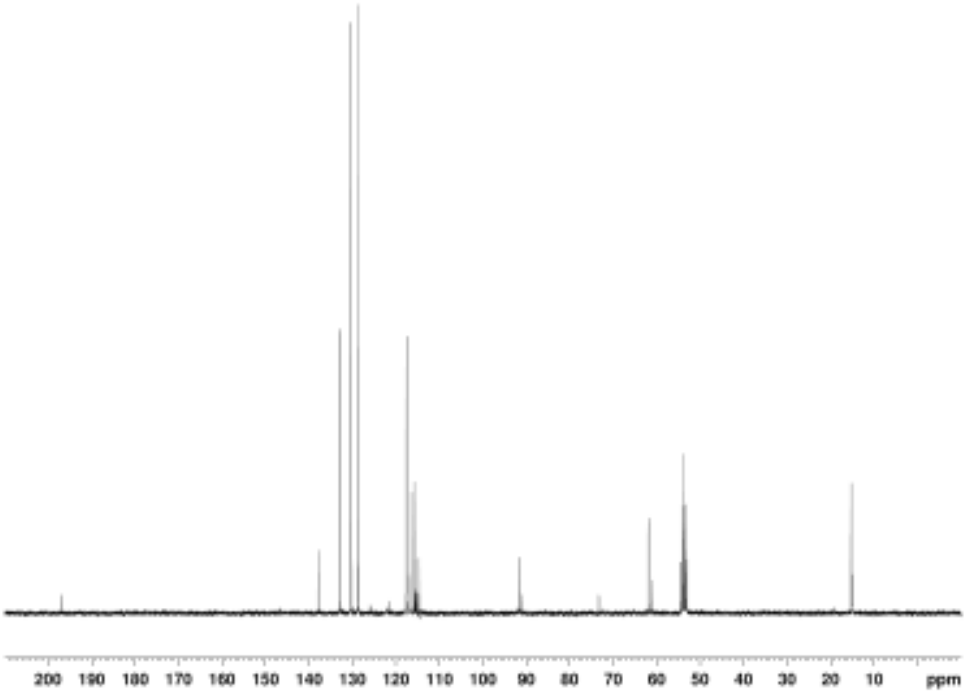
^{13}C NMR of 292 + benzophenone: CD_2Cl_2, 293 K, 75 MHz



^{1}H NMR of 293 + benzopehenone: CD_2Cl_2, 293 K, 300 MHz



^{13}C NMR of 293 + benzophenone: CD_2Cl_2, 293 K, 75 MHz



3.0 APPENDIX

A.1 SPECTRAL COMPARISON OF FR901464

Table 26. ^{1}H NMR assignments for FR901464

Position	Synthetic FR901464 - our material: δ_H (mult, *J* (Hz))	Natural FR901464: δ_H (mult, *J* (Hz))	Synthetic FR901464 – Jacobsen's: δ_H (mult, *J* (Hz))
1-OH	3.31 (s)	3.38 (s)	3.40 (s)
2_{axial}	2.34 (d, 14.4)	2.36 (d, 14)	2.34 (d, 14.5)
$2_{equitorial}$	1.64 (d, 14.4)	1.66 (d, 14)	1.64 (d, 14)
4	3.57 (app t, 10.0)	3.58 (dd, 10, 10)	3.57 (dd, 10, 10)
4-OH	1.59 (10.3)	1.66 (d, 10)	1.67 (d, 10)
5	4.24 (dd, 9.3, 7.0)	4.25 (10, 7)	4.24 (dd, 9, 7)
6	5.65 (dd, 15.7, 7.0)	5.66 (dd, 7, 16)	5.66 (dd, 7, 16)
7	6.38 (d, 15.7)	6.37 (d, 16)	6.37 (d, 15.5)
9	5.54 (br app t, 7.0)	5.53 (br t, 7)	5.53 (br t, 7)
10	2.40–2.30 (m)	2.36 (m)	2.35 (m)
	2.28–2.20 (m)	2.24 (m)	2.22 (m)
11	3.57–3.50 (m)	3.53 (m)	3.53 (m)
12	1.77 (m)	1.77 (m)	1.77 (m)
13	1.95–1.93 (m)	1.94 (m)	1.93 (m)
	1.93–1.91 (m)	1.91 (m)	1.92 (m)
14	3.94–3.88 (m)	3.90 (m)	3.90 (m)
14-NH	5.96 (br d, 8.9)	5.99 (d, 9)	6.00 (d, 9)
15	3.66 (qd, 6.5, 2.2)	3.66 (qd, 7, 2)	3.65 (qd, 6.5, 2.5)
16	1.11 (3H, d, 6.4)	1.11 (3H, d, 7)	1.11 (3H, d, 6.5)
17	1.43 (3H, s)	1.43 (3H, s)	1.42 (3H, s)
18	3.06 (d, 4.5)	3.07 (d, 4.5)	3.05 (d, 4.5)
	2.55 (d, 4.5)	2.55 (d, 4.5)	2.55 (d, 4.5)
19	1.78 (3H, br s)	1.78 (3, s)	1.78 (3H, s)
20	1.01 (3H, d, 7.3)	1.01 (3H, d, 7)	1.01 (3H, d, 7.5)
2'	5.71 (dd, 11.6, 1.3)	5.71 (dd, 11.5, 1)	5.71 (dd, 12, 1.5)
3'	5.90 (dd, 11.6, 7.8)	5.90 (11.5, 8)	5.90 (dd, 11, 8)
4'	6.26 (m)	6.26 (m)	6.26 (m)
5'	1.34 (3H, d, 6.5)	1.33 (3H, d, 6.5)	1.33 (3H, d, 8.5)
2"	2.01 (3H, s)	2.02 (3H, s)	2.01 (3H, s)

Table 27. ^{13}C NMR assignments for FR901464

Position	Natural FR901464: δ_C	Synthetic FR901464 - our material: δ_C	Synthetic FR901464 - Jacobsen's: δ_C
1	96.7	96.7	96.6
2	41.8	41.8	41.8
3	58.1	58.1	58.1
4	68.1	68.1	68.1
5	73.8	73.9	73.8
6	124.7	124.6	124.6
7	138.3	138.3	138.2
8	134.8	134.8	134.7
9	129.8	129.9	129.7
10	32.4	32.4	32.4
11	81.2	81.2	81.1
12	29.6	29.6	29.6
13	36.3	36.2	36.2
14	47.4	47.4	47.4
15	76.3	76.3	76.2
16	17.9	17.9	18.0
17	29.1	29.1	29.1
18	48.0	48.1	48.1
19	12.7	12.7	12.8
20	15.2	15.2	15.3
1'	165.0	165.0	164.8
2'	122.8	122.8	122.7
3'	143.9	143.9	143.7
4'	68.9	68.9	68.9
5'	20.2	20.1	20.2
1"	170.6	170.6	170.4
2"	21.4	21.4	21.4

A.2 X-RAY DATA FOR METHYL GLYCOSIDE 112

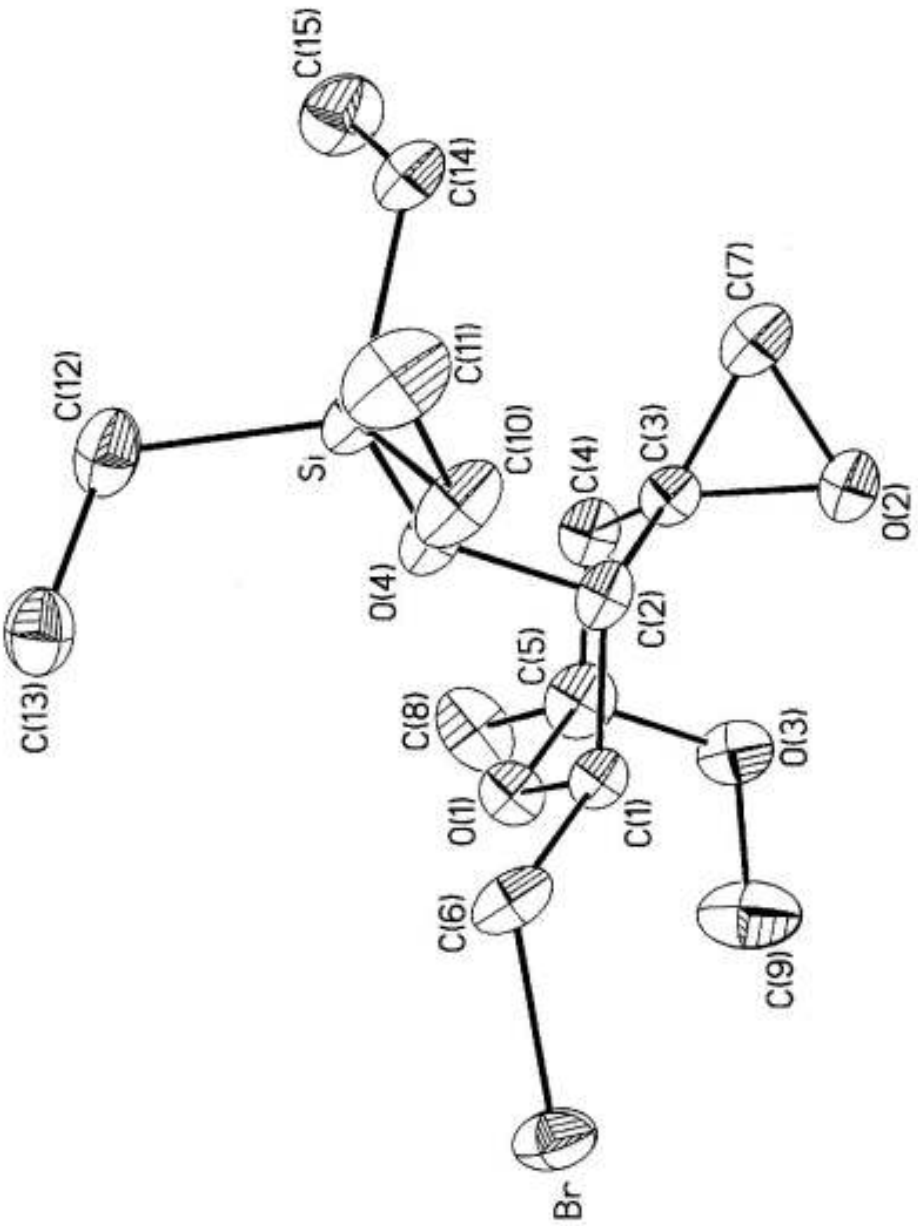


Figure 27. X-ray structure of **112**

Table 28. Crystal data and structure refinement for **112**

Identification code	**112**	
Empirical formula	C15 H26 Br O4 Si	
Formula weight	378.36	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 8.7770(19) Å	□= 90°.
	b = 20.887(5) Å	□= 101.429(4)°.
	c = 10.432(2) Å	□ = 90°.
Volume	1874.5(7) $Å^3$	
Z	4	
Density (calculated)	1.341 Mg/m^3	
Absorption coefficient	2.268 mm^{-1}	
F(000)	788	
Crystal size	0.06 x 0.06 x 0.21 mm^3	
Theta range for data collection	1.95 to 33.18°.	
Index ranges	-13<=h<=12, -30<=k<=31, -15<=l<=15	
Reflections collected	22623	
Independent reflections	12241 [R(int) = 0.1181]	
Completeness to theta = 33.18°	91.9 %	
Absorption correction	Sadabs	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	12241 / 1 / 380	
Goodness-of-fit on F^2	0.639	
Final R indices [I>2sigma(I)]	R1 = 0.0506, wR2 = 0.0994	
R indices (all data)	R1 = 0.1382, wR2 = 0.1173	
Absolute structure parameter	0.033(8)	
Largest diff. peak and hole	0.670 and -0.634 $e.Å^{-3}$	

Table 29. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **112**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

x	y	z	U(eq)
Br	5172(1)	5913(1)	16867(1)	50(1)
Si	5088(1)	3289(1)	14865(2)	34(1)
O(1)	7931(3)	5076(1)	16082(3)	34(1)
C(1)	6445(4)	5050(2)	15220(5)	28(1)
O(2)	7339(3)	4808(2)	12449(4)	38(1)
C(2)	6265(5)	4467(2)	14339(5)	31(1)
O(3)	9117(4)	5647(2)	14612(4)	46(1)
C(3)	7602(5)	4447(2)	13648(5)	31(1)
O(4)	6291(3)	3907(1)	15138(4)	35(1)
C(4)	9168(5)	4531(2)	14526(6)	36(1)
C(5)	9224(5)	5089(3)	15409(6)	45(2)
C(6)	5243(5)	5077(2)	16065(6)	38(1)
C(7)	7412(5)	4132(2)	12394(6)	42(1)
C(8)	10666(5)	5082(3)	16502(6)	59(2)
C(9)	9078(8)	6248(3)	15306(8)	76(2)
C(10)	3050(5)	3572(2)	14333(7)	44(2)
C(11)	1850(5)	3024(2)	14007(7)	56(2)
C(12)	5379(6)	2878(3)	16468(6)	48(2)
C(13)	4619(9)	3195(4)	17439(9)	47(3)
C(13")	4907(17)	2234(7)	16591(17)	40(5)
C(14)	5619(5)	2739(2)	13622(6)	41(1)
C(15)	7326(6)	2496(3)	13959(7)	57(2)
Br'	-1844(1)	4089(1)	-1021(1)	47(1)
Si'	-235(2)	6783(1)	575(2)	43(1)
O(1')	1426(3)	4834(1)	-253(3)	35(1)
C(1')	327(5)	4922(2)	595(6)	35(1)
C(2')	645(5)	5537(2)	1367(5)	30(1)
O(2')	2475(4)	5135(1)	3332(4)	43(1)
C(3')	2292(5)	5503(2)	2151(5)	34(1)
O(4')	3230(3)	4256(1)	1265(4)	36(1)

C(4')	3453(4)	5376(2)	1304(5)	38(1)
O(4')	510(3)	6062(1)	492(3)	36(1)
C(5')	3013(5)	4797(2)	436(5)	34(1)
C(6')	-1276(4)	4924(2)	-282(5)	33(1)
C(7')	2699(6)	5816(2)	3416(6)	50(2)
C(8')	3929(5)	4756(3)	-651(6)	53(2)
C(9')	2835(6)	3655(2)	646(7)	50(2)
C(10')	649(7)	7274(2)	-592(6)	56(2)
C(11')	2433(7)	7292(3)	-291(8)	81(2)
C(12')	299(6)	7084(2)	2283(7)	56(2)
C(13')	-361(8)	7760(3)	2470(8)	75(2)
C(14')	-2363(6)	6772(3)	32(9)	88(3)
C(15')	-3273(7)	6466(3)	949(13)	161(6)

Table 30. Bond lengths [Å] and angles [°] for **112**

Br-C(6)	1.941(4)
Si-O(4)	1.657(3)
Si-C(12)	1.851(6)
Si-C(14)	1.859(5)
Si-C(10)	1.861(5)
O(1)-C(1)	1.431(5)
O(1)-C(5)	1.448(6)
C(1)-C(6)	1.505(6)
C(1)-C(2)	1.516(6)
O(2)-C(7)	1.416(6)
O(2)-C(3)	1.440(6)
C(2)-O(4)	1.433(5)
C(2)-C(3)	1.494(6)
O(3)-C(5)	1.424(6)
O(3)-C(9)	1.452(6)
C(3)-C(7)	1.445(7)
C(3)-C(4)	1.503(6)
C(4)-C(5)	1.480(7)
C(5)-C(8)	1.526(7)
C(10)-C(11)	1.547(7)
C(12)-C(13)	1.475(10)
C(14)-C(15)	1.555(7)
Br'-C(6')	1.932(4)
Si'-O(4')	1.652(3)
Si'-C(14')	1.842(5)
Si'-C(12')	1.860(7)
Si'-C(10')	1.874(6)
O(1')-C(5')	1.437(5)
O(1')-C(1')	1.444(6)
C(1')-C(2')	1.512(6)
C(1')-C(6')	1.519(6)
C(2')-O(4')	1.416(5)
C(2')-C(3')	1.515(6)

O(2')-C(3')	1.433(6)
O(2')-C(7')	1.437(5)
C(3')-C(7')	1.452(7)
C(3')-C(4')	1.499(7)
O(4')-C(5')	1.414(5)
O(4')-C(9')	1.422(6)
C(4')-C(5')	1.514(7)
C(5')-C(8')	1.517(7)
C(10')-C(11')	1.535(8)
C(12')-C(13')	1.552(7)
C(14')-C(15')	1.505(11)
O(4)-Si-C(12)	103.7(2)
O(4)-Si-C(14)	111.2(2)
C(12)-Si-C(14)	109.6(3)
O(4)-Si-C(10)	110.19(18)
C(12)-Si-C(10)	111.7(3)
C(14)-Si-C(10)	110.3(3)
C(1)-O(1)-C(5)	113.6(4)
O(1)-C(1)-C(6)	106.7(4)
O(1)-C(1)-C(2)	112.6(3)
C(6)-C(1)-C(2)	112.6(3)
C(7)-O(2)-C(3)	60.8(3)
O(4)-C(2)-C(3)	109.5(3)
O(4)-C(2)-C(1)	108.4(4)
C(3)-C(2)-C(1)	108.5(3)
C(5)-O(3)-C(9)	114.9(5)
O(2)-C(3)-C(7)	58.8(3)
O(2)-C(3)-C(2)	113.4(4)
C(7)-C(3)-C(2)	119.3(4)
O(2)-C(3)-C(4)	115.9(4)
C(7)-C(3)-C(4)	122.2(4)
C(2)-C(3)-C(4)	114.5(5)
C(2)-O(4)-Si	126.9(3)
C(5)-C(4)-C(3)	112.7(4)
O(3)-C(5)-O(1)	109.3(4)
O(3)-C(5)-C(4)	106.9(5)

O(1)-C(5)-C(4)	110.8(4)
O(3)-C(5)-C(8)	113.2(4)
O(1)-C(5)-C(8)	104.5(5)
C(4)-C(5)-C(8)	112.2(4)
C(1)-C(6)-Br	111.9(3)
O(2)-C(7)-C(3)	60.4(3)
C(11)-C(10)-Si	113.8(3)
C(13)-C(12)-Si	114.3(4)
C(15)-C(14)-Si	114.0(4)
O(4')-Si'-C(14')	111.1(2)
O(4')-Si'-C(12')	109.3(2)
C(14')-Si'-C(12')	110.3(3)
O(4')-Si'-C(10')	104.3(2)
C(14')-Si'-C(10')	109.4(3)
C(12')-Si'-C(10')	112.3(3)
C(5')-O(1')-C(1')	113.5(4)
O(1')-C(1')-C(2')	111.0(3)
O(1')-C(1')-C(6')	106.5(4)
C(2')-C(1')-C(6')	111.7(3)
O(4')-C(2')-C(1')	109.4(4)
O(4')-C(2')-C(3')	109.5(3)
C(1')-C(2')-C(3')	107.7(4)
C(3')-O(2')-C(7')	60.8(3)
O(2')-C(3')-C(7')	59.7(3)
O(2')-C(3')-C(4')	116.0(4)
C(7')-C(3')-C(4')	122.8(4)
O(2')-C(3')-C(2')	115.0(4)
C(7')-C(3')-C(2')	120.4(4)
C(4')-C(3')-C(2')	112.1(4)
C(5')-O(4')-C(9')	116.0(4)
C(3')-C(4')-C(5')	111.7(3)
C(2')-O(4')-Si'	131.0(3)
O(4')-C(5')-O(1')	110.4(3)
O(4')-C(5')-C(8')	112.6(4)
O(1')-C(5')-C(8')	103.5(4)
O(4')-C(5')-C(4')	106.6(4)

O(1')-C(5')-C(4')	111.3(3)
C(8')-C(5')-C(4')	112.5(4)
C(1')-C(6')-Br'	111.9(3)
O(2')-C(7')-C(3')	59.5(3)
C(11')-C(10')-Si'	114.7(4)
C(13')-C(12')-Si'	113.5(5)
C(15')-C(14')-Si'	116.4(6)

Symmetry transformations used to generate equivalent atoms

Table 31. Anisotropic displacement parameters ($Å^2 \times 10^3$) for **112**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br	53(1)	34(1)	71(1)	-6(1)	27(1)	-2(1)
Si	23(1)	27(1)	54(1)	7(1)	11(1)	2(1)
O(1)	15(1)	46(2)	41(2)	-2(2)	8(1)	-5(1)
C(1)	14(2)	32(2)	37(3)	2(2)	3(2)	1(2)
O(2)	26(2)	40(2)	48(3)	11(2)	11(2)	-1(1)
C(2)	17(2)	31(2)	43(4)	9(2)	3(2)	-1(2)
O(3)	36(2)	39(2)	68(3)	-5(2)	24(2)	-13(1)
C(3)	20(2)	32(2)	42(4)	2(2)	12(2)	0(2)
O(4)	21(1)	31(2)	53(3)	9(2)	9(2)	1(1)
C(4)	14(2)	45(3)	49(4)	8(2)	9(2)	2(2)
C(5)	13(2)	55(3)	66(5)	5(3)	9(2)	-7(2)
C(6)	17(2)	25(2)	73(5)	-1(2)	12(2)	-3(2)
C(7)	27(2)	35(3)	68(4)	9(3)	19(2)	-1(2)
C(8)	23(2)	101(5)	52(5)	-5(4)	2(3)	-14(3)
C(9)	76(4)	55(4)	112(7)	-27(4)	53(5)	-30(3)
C(10)	20(2)	32(3)	78(5)	10(3)	11(2)	0(2)
C(11)	27(3)	50(3)	90(6)	-1(3)	8(3)	-10(2)
C(12)	41(3)	48(3)	57(5)	19(3)	13(3)	7(2)
C(13)	39(4)	52(5)	50(7)	13(4)	9(4)	0(4)
C(14)	37(3)	29(2)	56(4)	6(2)	11(3)	4(2)
C(15)	44(3)	56(4)	75(6)	5(3)	22(3)	17(3)
Br'	31(1)	40(1)	68(1)	-5(1)	6(1)	-6(1)
Si'	26(1)	29(1)	71(1)	5(1)	1(1)	2(1)
O(1')	19(2)	39(2)	48(3)	6(2)	10(2)	5(1)
C(1')	20(2)	27(2)	62(4)	8(2)	16(2)	-1(2)
C(2')	21(2)	30(2)	39(3)	6(2)	6(2)	3(2)
O(2')	32(2)	30(2)	65(3)	7(2)	6(2)	4(1)
C(3')	21(2)	29(2)	49(4)	8(2)	0(2)	-2(2)
O(4')	24(2)	32(2)	50(3)	4(2)	5(2)	1(1)
C(4')	15(2)	39(3)	56(4)	13(3)	0(2)	-3(2)

C(5')	17(2)	36(3)	51(4)	8(2)	9(2)	3(2)
C(6')	18(2)	39(3)	40(4)	-2(2)	4(2)	5(2)
C(7')	35(2)	28(3)	81(5)	-1(3)	0(3)	0(2)
C(8')	30(3)	71(4)	63(5)	19(3)	19(3)	5(3)
C(9')	43(3)	39(3)	67(5)	1(3)	8(3)	5(2)
C(10')	86(4)	31(3)	47(4)	11(3)	8(3)	2(3)
C(11')	69(4)	76(5)	106(7)	34(4)	40(4)	-13(4)
C(12')	36(3)	40(3)	99(6)	3(3)	29(3)	2(2)
C(13')	93(5)	46(4)	90(7)	7(4)	32(5)	22(3)
C(14')	25(3)	46(4)	180(9)	7(5)	-11(4)	-1(3)
C(15')	37(4)	59(4)	400(19)	66(7)	76(7)	3(3)

Table 32. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for **112**

	x	y	z	U(eq)
H(1A)	6330	5441	14655	34
H(2A)	5262	4490	13689	37
H(4A)	9429	4139	15057	43
H(4B)	9962	4586	13980	43
H(6A)	5484	4748	16759	46
H(6B)	4209	4978	15526	46
H(7A)	8345	3938	12151	50
H(7B)	6431	3897	12076	50
H(8A)	10654	5457	17064	89
H(8B)	11600	5093	16120	89
H(8C)	10670	4691	17022	89
H(9A)	9006	6605	14687	115
H(9B)	10029	6291	15975	115
H(9C)	8172	6253	15725	115
H(10A)	2772	3839	15036	52
H(10B)	2988	3846	13550	52
H(11A)	807	3206	13734	84
H(11B)	1881	2757	14783	84
H(11C)	2101	2763	13297	84
H(12A)	4975	2436	16331	58
H(12B)	6509	2850	16830	58
H(13A)	4825	2951	18257	71
H(13B)	3495	3215	17103	71
H(13C)	5031	3630	17602	71
H(14A)	4912	2365	13522	49
H(14B)	5454	2964	12770	49
H(15A)	7521	2210	13264	86
H(15B)	7495	2262	14790	86
H(15C)	8038	2862	14037	86
H(1'A)	406	4553	1215	42

H(2'A)	-106	5585	1966	36
H(4'A)	4489	5306	1864	45
H(4'B)	3523	5756	751	45
H(6'A)	-1292	5236	-999	39
H(6'B)	-2052	5062	232	39
H(7'A)	3775	5977	3692	60
H(7'B)	1891	6077	3709	60
H(8'A)	3601	4376	-1186	80
H(8'B)	5040	4725	-270	80
H(8'C)	3737	5140	-1199	80
H(9'A)	3020	3313	1303	75
H(9'B)	3479	3581	-7	75
H(9'C)	1736	3656	217	75
H(10C)	295	7102	-1485	67
H(10D)	256	7718	-587	67
H(11D)	2800	7554	-949	121
H(11E)	2839	6856	-308	121
H(11F)	2799	7479	578	121
H(12C)	-89	6780	2871	67
H(12D)	1447	7098	2545	67
H(13D)	-41	7890	3387	112
H(13E)	-1498	7748	2234	112
H(13F)	39	8067	1909	112
H(14C)	-2726	7219	-126	106
H(14D)	-2612	6544	-816	106
H(15D)	-4385	6485	565	241
H(15E)	-3071	6695	1785	241
H(15F)	-2955	6018	1094	241

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