DISSERTATION

A DIVERGENT SYNTHESIS OF SECOLOGANIN DERIVED NATURAL PRODUCTS

Submitted by

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ABSTRACT

A DIVERGENT SYNTHESIS OF SECOLOGANIN

DERIVED NATURAL PRODUCTS

This dissertation documents the racemic total synthesis of the natural products oleocanthal, geissoschizol, corynantheidol, dihydrocorynantheol, protoemetinol, and 3-*epi*-protoemetinol from a single synthetic intermediate. Also described are efforts to produce an optically pure supply of the common synthetic intermediate of the above described natural products.

The work described herein represents the first steps toward the development of a general strategy capable of synthesizing several structurally diverse members of the family of compounds derived from secologanin.

ACKNOWLEDGEMENTS

This work and much of my personal and professional development would not have been possible without the support of my colleagues and coworkers. I would like to thank Professor Robert Williams and the rest of the faculty of Colorado State University for providing an environment in which my coworkers and I could attain all that we were capable of. Thanks to every member of the Williams group, past and present. Special thanks go to the Post-Docs whose counsel I most often sought, Dr. Gerald Artman, Dr. Albert Bowers, Dr. Daniel Fishlock, Dr. Thomas Greshock, Dr. Kenneth Miller, and Dr. Aaron Smith, and to my classmates and groupmates whose advice and friendship allowed me to survive graduate school. Specific mention must go to Dr. Dan Gubler and Dr. Jennifer Moore who began this journey with me and provided a great deal of friendship and support.

Without question the people to whom I owe the most are my family. My parents, Mark and Gayle English, have always supported my intellectual development. It was their encouragement that nurtured my curiosity and love of science and their fervent support that allowed me to pursue it. My wife Melissa English has been by my side through all of the good times and hardships that accompany a budding scientific career. Her love, understanding, and humor kept me sane through this process.

DEDICATION

For my parents,

Mark and Gayle

and my wife,

Melissa

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List of Abbreviations

Ac_2O	Acetic anhydride
AcCl	Acetyl Chloride
AcOH or HOAc	Acetic acid
AIBN	Azobisisobutyronitrile
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Boc_2O	Di-*tert*-butyldicarbonate
Dess-Martin or DMP	Triacetoxy *o*-iodoxybenzoic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIBAl-H	Diisobutylaluminium hydride
DMAP	4-(Dimethylamino)-pyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
ee	enantiomeric excess
e.r.	enantiomeric ratio
EtOAc	Ethyl Acetate
Et_2O	Diethyl ether
hex.	Hexanes
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
*i*Bu	isobutyl

*i*Pr	isopropyl
iPr_2NEt	*N*,*N*-Diisopropylethylamine
IBX	*o*-iodoxybenzoic acid
Imid	Imidazole
LDA	Lithium *N*,*N*-diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
*m*CPBA	*m*-Chloroperbenzoic acid
Me	Methyl
MeCN	Acetonitrile
MeI	Methyl iodide
MeOH	Methanol
MsCl	Methanesulfonyl chloride
NaHMDS	Sodium bis(trimethylsilyl)amide
NBS	N-Bromosuccinimide
*n*BuLi	*n*-Butyllithium
NEt_3	Triethylamine
PDC	Pyridinium dichromate
$Pd(OAc)_2$	Palladium(II) acetate
PCC	Pyridinium chlorochromate
Pd/C	Palladium on carbon
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium

Ph	Phenyl
$PhI(OAc)_2$	Iodobenzene diacetate
PPTS	Pyridinium *p*-toluenesulfonate
Py. or Pyr.	Pyridine
No Rxn	No reaction was observed
RT or R.T.	Room temperature
TBAF	Tetrabutyl ammonium fluoride
TBDMSCl or TBSCl	*tert*-Butyldimethylsilyl chloride
TBSOTf	*tert*-Butyldimethylsilyl trifluoromethanesulfonate
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy, free radical
Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
Tf_2O	Trifluoromethanesulfonyl anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSCl	Trimethylsilyl chloride
TMSOK	Potassiumtrimethyl silanoate
TMSOTf	Trimethylsilyl trifluoromethylsulfonate
TsCl	*p*-Toluenesulfonyl chloride
p-TsOH	*p*-Toluenesulfonic acid

Chapter 1: Introduction and Biosynthesis

1.1: Introduction

1.1.1: Background

Secologanin glucoside (**1.1**) has been identified as the common biological precursor to two broad classes of plant derived natural products: the secoiridoids and secologanin tryptamine alkaloids (STAs).[1] The secoiridoids are a diverse class of naturally occurring monoterpenes deriving from elaboration and/or rearrangement of the substituted dihydropyran core of secologanin (**1.1**). The enzyme catalyzed coupling of secologanin with tryptamine (**1.2**) produces strictosidine (**1.3**), which undergoes further biological elaboration and/or rearrangement results in the formation of the STAs (**Figure 1.1**). Taken together these two natural product classes contain an impressively large array of identified structures with diverse functionality, structural frameworks, and biological activities including anti-cancer[2], analgesic[3], anti-inflammatory[4], anti-arthritic[5], anti-allergenic[6], antibacterial[7], and antiviral[8] activities. In addition, several of these natural products including quinine, vinblastine, vincristine, and reserpine have found important clinical applications.

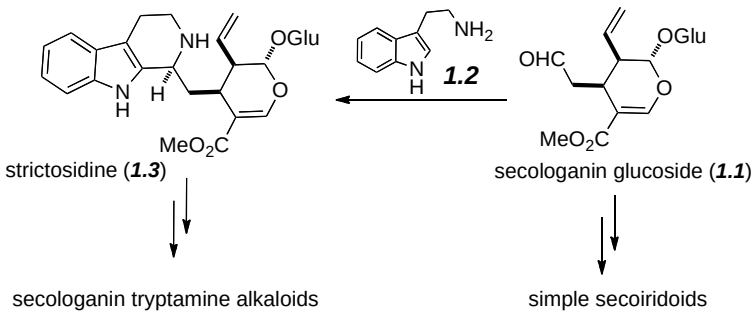


Figure 1.1: Secologanin, the secoiridoids, and secologanin tryptamine alkaloids.

We reasoned that, given the common biological origin of the secologanin-derived natural products, synthetic access to the more complex secoiridoid and secologanin tryptamine alkaloids could be obtained through a divergent synthetic strategy. The synthesis of an optically pure and orthogonally functionalized intermediate, which could be used to access a broad range of natural product frameworks, would grant much more rapid and efficient access to these frameworks than the current strategies, which rely on multiple, independently designed synthetic routes.

1.1.2: Isolation and Classification of Iridoids, Secoiridoids, and STAs

The long and productive history of iridoid and secoiridoid study began with the first reported isolation of a gentiopicroside (**1.4**) by Kromeyer in 1862[9], although, the complete structural assignment of these monoterpenes was not accomplished for nearly a century when Halpern and Schmidt proposed the structure of the iridoid plumieride (**1.5**) (**Figure 1.2**) in 1958[10]. This structural recognition led to the rapid structural assignment of the bulk of the iridoids and secoiridoids known at the time. Since that time more than 1600 unique iridoids and secoiridoids have been structurally identified, screened for biological activity, and compiled by several thorough reviews[11].

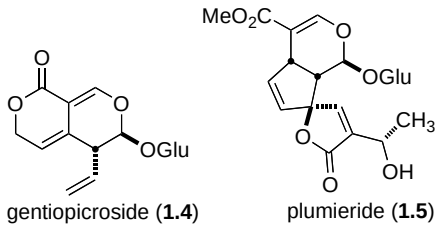


Figure 1.2: Early examples of secoiridoids and iridoids.

The modern numbering scheme of the generic iridoid and secoiridoid skeletons, as presented by Obied and coworkers[12], is illustrated in **Figure 1.3** and reflects the current understanding of the biosynthetic origins of these natural product classes. These origins as will be discussed in the following section. The major structural distinction between the iridoid and secoiridoid generic forms is the C7-C8 bond scission differentiating the 6,5 fused bicycle of the iridoids from the monocyclic pyran core of the secoiridoids. Examples of naturally occurring compounds with modifications to nearly all of the positions of these skeletal forms have been identified accounting for the vast diversity of these natural product classes.

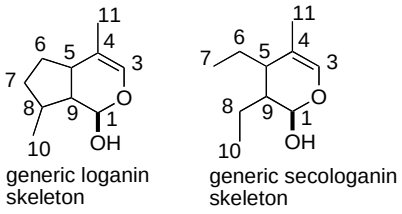


Figure 1.3: The generic iridoid and secoiridoid numbering schemes.

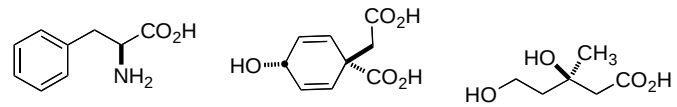
For the purposes of this dissertation, we will distinguish only two secoiridoid subgroups; the secologanin tryptamine alkaloids (STAs), which arise from the conjugation of a secoiridoid with tryptamine (Note: the term secologanin tryptamine alkaloids (STAs) will be used in lieu of the more commonly used term monoterpeneoid tryptamine alkaloids as the latter categorization does not distinguish between tryptamine alkaloids derived from loganin and those derived from secologanin.) and the secologanin dopamine alkaloids. As they are not a focus of our current synthetic interests, the iridoids

and their metabolites retaining the C7-C8 bond, for the purposes of this dissertation, will be considered only as they relate biosynthetically to the secoiridoids.

1.2: Biosynthesis

1.2.1: Biosynthesis of Iridoids and Secoiridoids

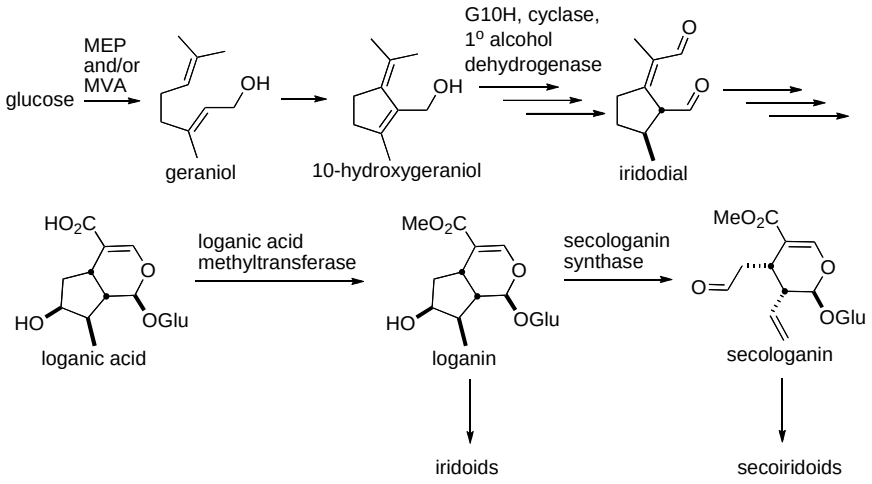
Early hypotheses as to the biosynthetic origin of the iridoids and secoiridoids included phenylalanine (**1.6**)[13] and prephenic acid (**1.7**)[14] (**Figure 1.4**). The terpene origins of the iridoids and their metabolites were first investigated by Money and coworkers[15] who reported the observation of the incorporation of ^{14}C enriched mevalonic acid (**1.8**) into Vinca alkaloids in 1965. In 1998 Contin and coworkers[16] used site specific ^{13}C labeling to show that although the iridoids and their metabolites were terpene derived, they were not produced from mevalonic acid but from 1-deoxy-D-xylulose via the novel triose phosphate/pyruvate pathway first described in higher plants by Lictenthaler and coworkers[17]. Through the characterization of biosynthetic intermediates, the use of feeding studies, the isolation and characterization of key enzymes, the use of selective enzyme inhibitors, and the use of metabolic reconstruction software researchers have produced a detailed map of the biosynthesis of the iridoids and secoiridoids.[18]



phenylalanine (**1.6**) prephenic acid (**1.7**) mevalonic acid (**1.8**)

Figure 1.4: Hypothesized secologanin precursors.

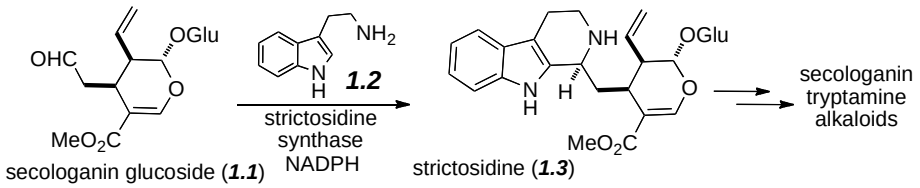
As illustrated in **Scheme 1.1**, iridoid biosynthesis begins with the production of gerianol pyrophosphate (GPP) via the methyl erythritol phosphate (MEP) pathway, which occurs exclusively within the plant organelles known as plastids[19]. Oxidation of GPP and ring closure produces iriodial, which is further oxidized and glycosylated to produce the common biosynthetic precursor to the iridoids and secoiridoids, loganin. Oxidative cleavage of loganin's C7-C8 bond by the cytochrome P450 enzyme secologanin synthase produces secologanin whose further modification produces the secoiridoids[20].



Scheme 1.1: The biosynthesis of iridoids and secoiridoids.

1.2.2: Biosynthesis of Secologanin Tryptamine Alkaloids (STAs)

The reaction of secologanin with tryptamine (produced via the skimate pathway) occurs by a biological Pictet-Spengler reaction catalyzed by strictosidine synthase and exclusively produces 3α-(*S*)-strictosidine, the common biosynthetic precursor of all of the STAs[21] (**Scheme 1.2**). The scores of STAs are produced by various modifications of the strictosidine framework.



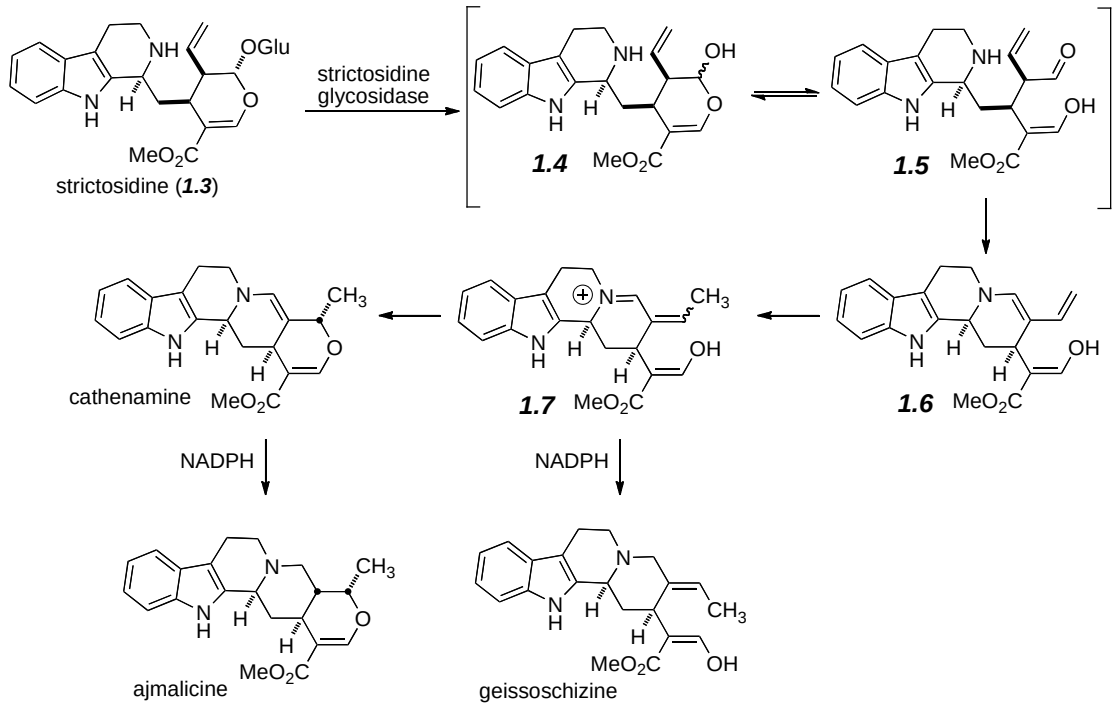
Scheme 1.2: Strictosidine biosynthesis.

The glucose functionalities of secologanin glucoside (**1.1**) and strictosidine glucoside (**1.3**) play a critical role in stabilizing the structure of these natural products. The glucose acetals act as natural "protecting groups" by preventing spontaneous molecular rearrangements. This presents a major synthetic challenge and will be discussed in detail in the following chapter. Nature has evolved a method to avoid or control these rearrangements via enzymatic templating of the molecule in question during the acetal "deprotection".

The natural removal of the strictosidine glucose "protecting group" via deglycosylation is catalyzed by strictosidine glycosidase[22] to produce the unstable strictosidine aglycone (**1.4**). Reversable lactol opening to produce aldehyde **1.5** can result in either condensation of the now revealed C21 aldehyde functionality with the piperidine ring nitrogen giving enamine **1.6** (**Scheme 1.3**) or it can result in the spontaneous reaction of the terpene portion of strictosidine with the strictosidine indole nitrogen (**Scheme 1.4**).

In the case of piperidine nitrogen condensation, the acid catalyzed olefin internalization and iminium formation that follows leads to the next major STA biosynthetic branch point. Either immediate reduction of the iminium ion (**1.7**) by

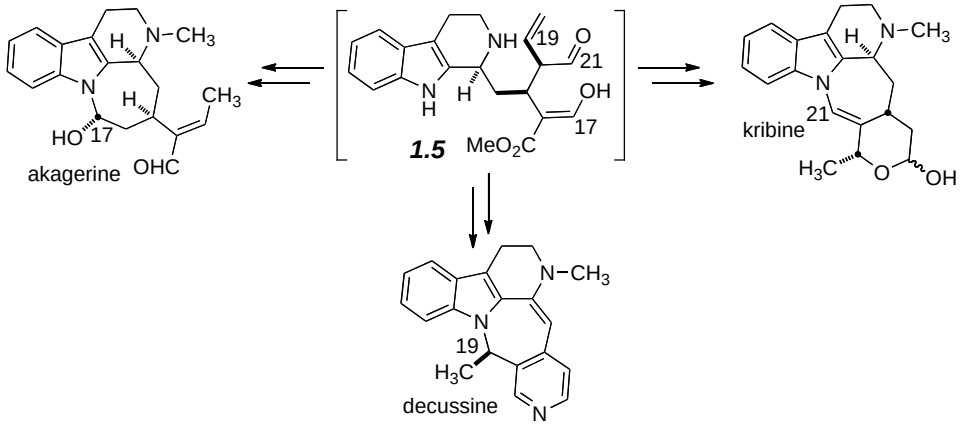
NADPH produces the geissoschizine class of natural products or an initial cyclization occurs forming the dihydropyran ring of cathenamine, which is followed by NADPH reduction of the enamine functionality to produce the ajmalicine class of natural products.[23]



Scheme 1.3: Biosynthesis of ajmalicine and geissoschizine.

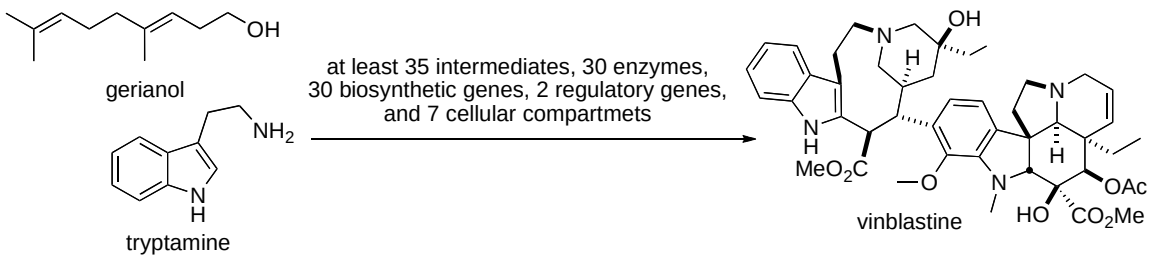
Three unique classes of alkaloids arise from the reaction of the terpene portion of strictosidine aglycone with the tryptamine indole nitrogen depending on which of the carbons forms a bond with the indole nitrogen (**Scheme 1.4**). Decarboxylation of the vinylogous ester functionality of compound **1.5** unmasks a C17 aldehyde, which can react with the indole nitrogen to produce the akagerine alkaloids. Reaction of the C21 aldehyde with the indole nitrogen produces the kribine class of alkaloids. Finally,

isomerization of the olefin functionality of **1.5** produces an α,β-unsaturated aldehyde, which can act as a Michael acceptor forming a bond between the indole nitrogen and C19 giving rise to the decussine class of alkaloids. These three basic skeletons form the basis for the production of the strychnine and vincamine natural product classes.[24]



Scheme 1.4: The biosynthesis of indole alkylated natural products.

Further biosynthetic elaboration of the many of the products discussed above occurs via an extremely complex series of enzymatic steps, which vary by plant species and metabolite and have yet to be fully investigated. These highly varied and rapidly branching biosynthetic pathways account for the diversity of naturally occurring alkaloids deriving from strictosidine. Plant evolution has crafted a beautifully complex machinery for the production of thousands of structurally disparate compounds. As an example of this complexity, consider the production of vinblastine from geraniol and tryptamine in *Catharanthus* species, which includes the participation of, at minimum, 35 intermediates, 30 enzymes, 30 biosynthetic genes, 2 regulatory genes, and 7 cellular compartments (**Scheme 1.5**)[25].



Scheme 1.5: The production of vinblastine by *Catharanthus* species.

Chapter 2: Previous Synthetic Work

2.1: Selected Syntheses of Secoiridoids and Congeners

2.1.1: Synthetic Challenges of the Secoiridoids

The lack of a reported asymmetric total synthesis of secologanin glucoside despite several decades of concerted effort speaks to the substantial synthetic challenges of this seemingly simple terpenoid (**Figure 2.1**). Close inspection of the core dihydropyran of secologanin reveals it to be a vinylogous carbonate arranged as an anomerically glycosylated pseudo-equatorial lactol. The stereogenic center at C9 bears a reactive monosubstituted exocyclic olefin, which exists in a thermodynamically disfavored *cis* relationship to the C5 substituent, a highly reactive primary aldehyde.

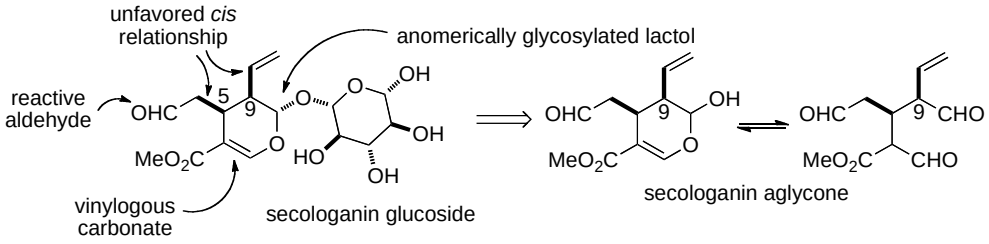
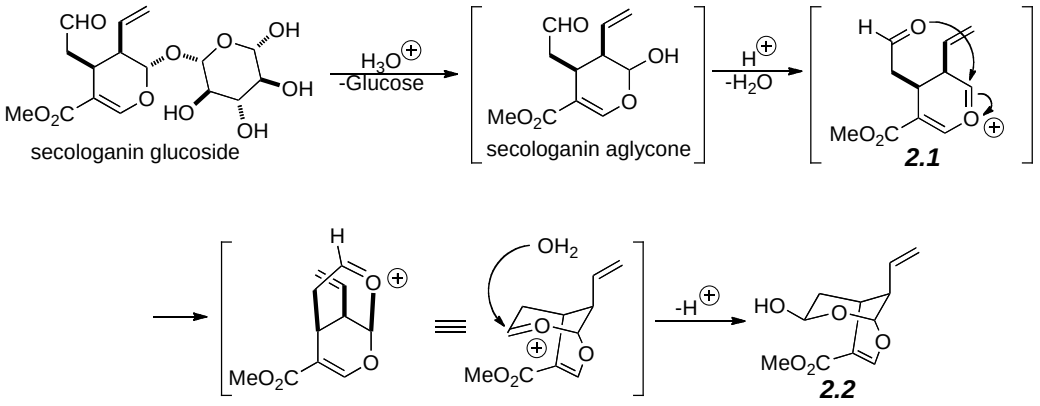


Figure 2.1: Synthetic challenges of secologanin glucoside.

An attractive retrosynthetic disconnection between the C1 dihydropyran lactol carbon and glucose would produce secologanin aglycone and further synthetic challenges. The three reactive aldehydes and methyl ester present in the secologanin aglycone would be difficult to individually manipulate and the C9 stereogenic center would be highly susceptible to epimerization via enolization or olefin migration. Attempted semisynthesis of the aglycone via acidic deglycosylation confirms these fears

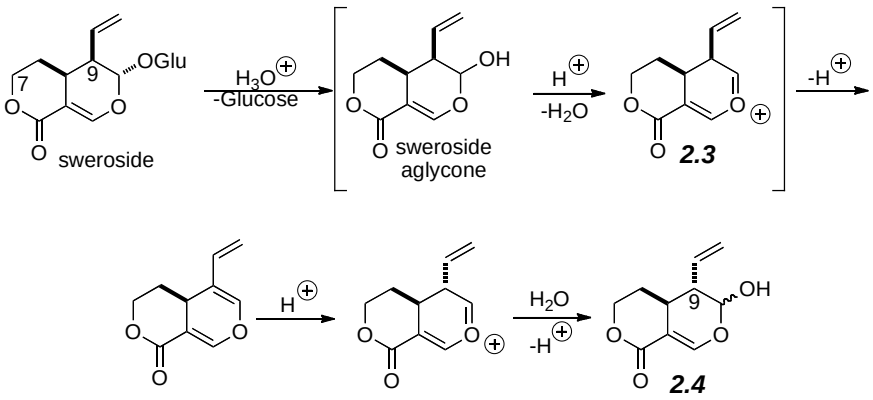
as, upon deglycosilation, an immediate and irreversible rearrangement to bicyclic structure **2.2** is observed[26] (**Scheme 2.1**). Although this bicycle has been utilized in the synthesis of unnatural alkaloids[27], it has found no reported use in the synthesis natural products.



Scheme 2.1: Secologanin aglycone rearrangement.

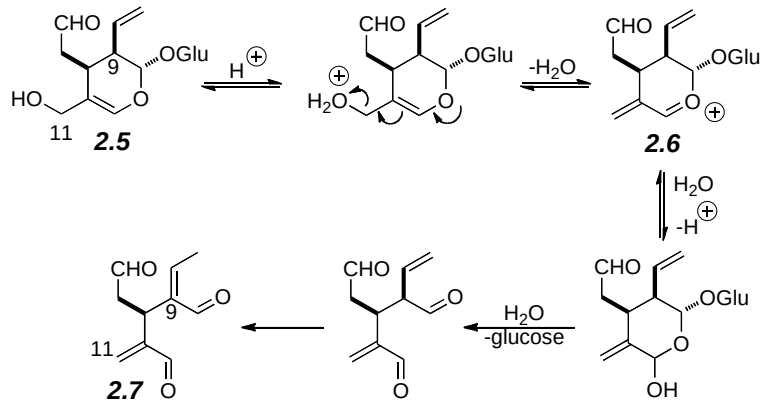
A seemingly obvious solution to the problem of the spontaneous rearrangement of the secologanin aglycone is to mask the C7 aldehyde through protection or other manipulation in order to prevent its reaction with the oxocarbenium ion of compound **2.1**. Unfortunately, as illustrated in **Scheme 2.2**, avoiding the aglycone rearrangement by reducing and cyclizing the C7 aldehyde, thus eliminating the undesired cyclization onto the oxocarbenium functionality, does not avoid undesired rearrangement. Sweroside glucoside is a C7 reduced and lactonized form of secologanin glucoside. Similar to the secologanin glucoside case, upon deglycosilation, sweroside proceeds through an unstable oxocarbenium intermediate (**2.3**) that, rather than participating in bicyclic ring

closure, allows epimerization of the C9 stereogenic center to occur producing the more energetically favorable *trans* diastereomer (**2.4**).



Scheme 2.2: Sweroside aglycone C9 epimerization.

Bianco and coworkers[28] observed a third type of destructive rearrangement of naturally occurring secoiridoids (**Scheme 2.3**), which involves secoiridoids bearing a hydroxide at the C11 position rather than the more common methyl carboxylate functionality. Treatment of alcohol **2.5** with catalytic acid causes acid labile C11 allylic hydroxide to isomerize to oxocarbenium ion **2.6**. This oxocarbenium ion reacts with water causing the subsequent glucose hydrolysis thus allowing the opening of the heterocycle. The exocyclic olefin functionality rapidly isomerizes to the conjugated aldehyde thereby erasing the C9 stereochemistry to give compound **2.7**.



Scheme 2.3: Acid rearrangement of C11 reduced secoiridoids.

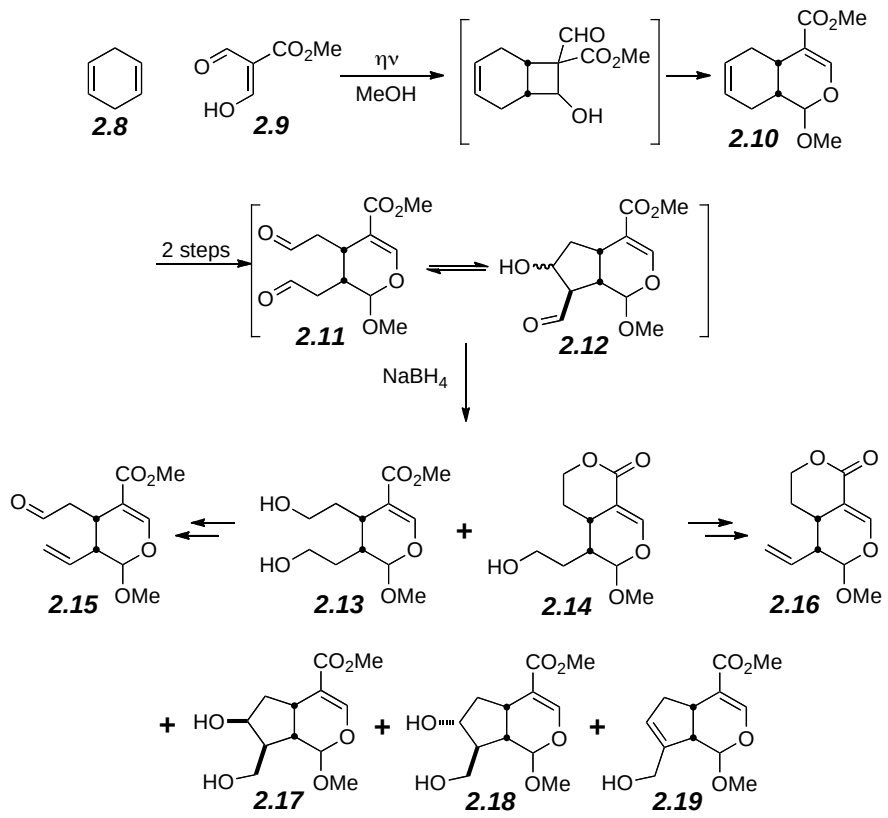
Given the inherent instability of the secologanin aglycone and the extreme synthetic challenges that these instabilities create, it is unsurprising that, to date, no total synthesis of secologanin or any of its glycosilated metabolites has been reported. As outlined in the following section, several syntheses of the protected secologanin aglycone appear throughout the literature, demonstrating that the multitude of other synthetic hurdles can be readily overcome.

2.1.2: Early Aglycone Syntheses by Masamune and Hutchinson

The first syntheses of secoiridoids and their aglycones to appear in the literature[29] involved the fragmentation of other naturally occurring iridoids. Although these early semisyntheses helped to confirm the proposed structures of some of the iridoids and provided valuable information about possible late-stage manipulations of the iridoids, these semisyntheses depended upon stereogenic centers and carbon frameworks isolated from natural sources. Specifically, this limited the production of synthetic iridoids to those bearing similar structural characteristics to those present in the iridoid starting

materials. Additionally, the availability of these naturally occurring starting materials and the fragility of their functionalities further limited the scope of this strategy. A "ground-up" approach was needed in order to have full control over the products produced. This could only be accomplished by total synthesis.

Beginning in the late 1970's concerted efforts by the Tietze, Masamune, and Hutchinson laboratories began to produce total syntheses, which did not rely on molecular complexity isolated from iridoid producing organisms. Hutchinson's original total synthesis of secoiridoid aglycones[30] and its later modification (**Scheme 2.4**)[31] rely on a late stage oxidative carbocycle ring cleavage to install the sensitive C7 and C10 functionality. Both of these syntheses begin with the [2+2] photocyclization of 4-cyclohexadiene (**2.8**) with methyl diformyl acetate (**2.9**) and subsequent rearrangement to yield the secoiridoid dihydropyran core (**2.10**). This strategy elegantly installs all of the required skeletal carbons in a diastereoselective fashion. A two-step oxidative cleavage of carbocycle **2.10** yields a dialdehydic compound **2.11**, which underwent a reversible partial aldol cyclization to produce aldehyde **2.12**. Treatment of this mixture with $NaBH_4$ gave a mixture of iridoids including diol **2.13** and lactone **2.14**, which could be converted to the methyl secologanin (**2.15**) and methyl sweroside (**2.16)** aglycones by published procedures. Along with these compounds were isolated the undesired aldol byproducts: iridoids **2.17**, **2.18**, and the elimination product **2.19**.

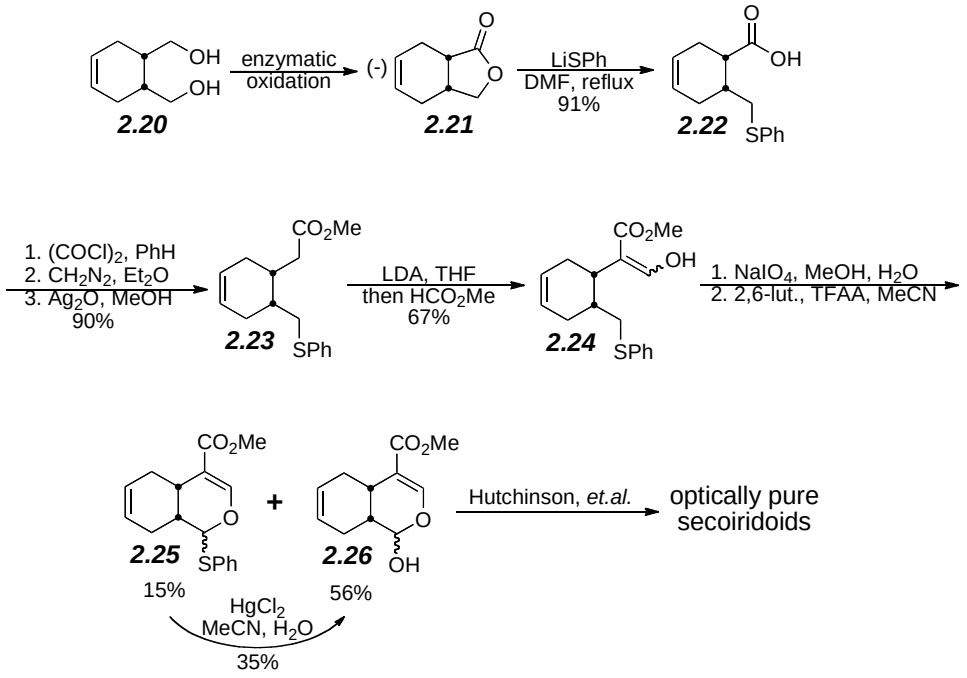


Scheme 2.4: Hutchinson's synthesis of several secoiridoid and iridoid aglycones.

The Hutchinson work represents a short synthesis of a number of secoiridoid and iridoid aglycones and elegantly compliments earlier semisynthetic work. Unfortunately, due to the racemic nature of this work and the inability to control both the aldol cyclization and subsequent reduction, this work could likely not be made amenable to the selective and efficient synthesis of secoiridoid glucosides or complex STAs.

Four years later in 1984, Masamune and coworkers adapted the later portion of the Hutchinson strategy for their synthesis of optically pure methyl sweroside aglycone (**Scheme 2.5**)[32]. Beginning with readily available meso diol **2.20**, conversion to the optically pure lactone **2.21** could be accomplished via an enzymatic oxidation first reported by Jakovic and coworkers[33]. Opening of this lactol with lithium phenylthiolate

gave acid **2.22**, which was modified via single carbon homologation to give ester **2.23**, which was again homologated this time via formylation to produce vinylogous carbonate **2.24**. An intramolecular Pummerer reaction allowed the vinylogous carbonate functionality to cyclize producing the dihydropyran ring of compounds **2.25** and **2.26**. Thiolactol **2.25** was completely converted to lactol **2.26** and then submitted to the above described Hutchinson procedure to produce the optically pure secologanin and sweroside aglycones along with the undesired iridoids.



Scheme 2.5: Masamune's asymmetric adaptation of the Hutchinson aglycone synthesis.

By adapting Hutchinson's previous work, Masamune's synthesis allowed for the first asymmetric total syntheses of several secoiridoid aglycones. Unfortunately the same selectivity problems that plagued the original Hutchinson synthesis were not addressed by this work.

2.1.2: McLean's Synthesis of a Protected Secoxyloganin Aglycone

The secoxyloganin aglycone ether (**2.28**) differs from the secologanin aglycone ether (**2.27**) only in the oxidation state of C7 (**Figure 2.2**). The secoxyloganin aglycone's C7 position is in the carboxylate oxidation state whereas the secologanin aglycone C7 is in the aldehyde oxidation state. Since the synthesis of many STAs would be possible via structures bearing this modification, protected forms of the secoxyloganin aglycone may be desirable synthetic targets. Also, the manipulation of this minor C7 modification should allow access to desired secologanin products.

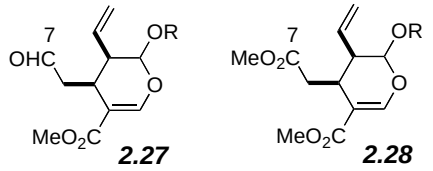
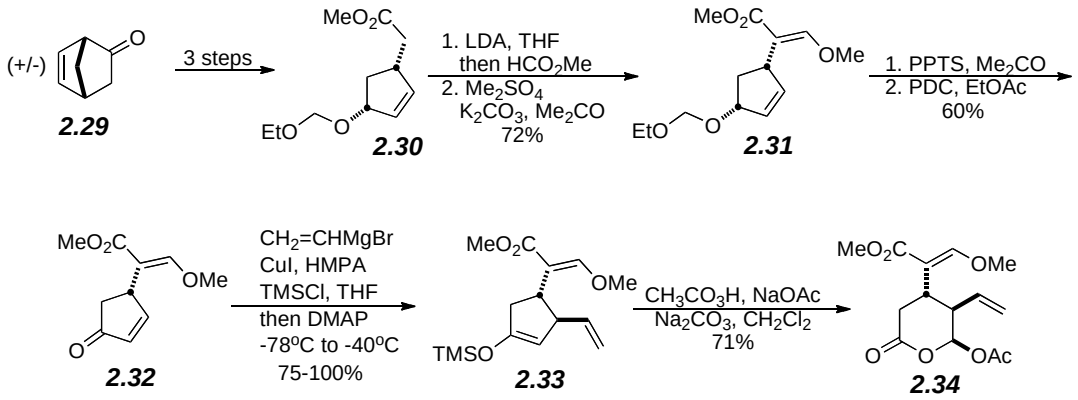


Figure 2.2: Secologanin and secoxyloganin aglycone ethers.

In 1988 Mclean and coworkers reported[34] the diastereoselective synthesis of a protected form of the secoxyloganin aglycone (**Scheme 2.6**), which is theoretically capable of producing optically pure secoiridoids and STAs. The authors begin their synthesis with racemic 5-norboranen-2-one (**2.29**), which they report as being commercially available as either optically pure enantiomer. Conversion of racemic 5-norboranen-2-one to cyclopentene **2.30** was accomplished by Baeyer-Villiger oxidation, ester hydrolysis, and subsequent hydroxide protection utilizing a protocol developed by Greene and coworkers for their synthesis of brefeldin-A[35]. Formylation and subsequent alkylation of the produced vinylagous carbonate gave compound **2.31** in good yield. Deprotection and oxidation of the latent secondary alcohol produced enone **2.32**. The

facially selective conjugate addition of vinyl cuprate to the cyclopentenone functionality of **2.32** and subsequent kinetic enolate trapping gave silyl enol ether **2.33** as a single diastereomer, which was poised for the key tandem oxidation steps. Treatment of **2.33** with peracetic acid in the presence of sodium acetate selectively produced the desired α-acetoxycyclopentanone, which then underwent Baeyer-Villiger oxidation to yield the McLean aglycone **2.34**.



Scheme 2.6: McLean's protected secoxyloganin aglycone synthesis.

Comparison of the McLean aglycone (**2.34**) to the secoxyloganin aglycone (**2.28**) (**Figure 2.3**) reveals full incorporation of all ten of the required skeletal carbons, each of which is in the correct oxidation state and adequately protected from rearrangement. Although not the stated goal of this work, when considering this protected aglycone as an intermediate in the synthesis of secoiridoids or STAs, three major drawbacks of this strategy become apparent. First, the conversion of the McLean aglycone to the dihydropyran core present in many of the secoiridoids would be difficult due to chemoselectivity problems that may arise due the similar reactivity of the lactone, ester, and latent aldehyde functionalities. Next, there is a high likelihood of a secologanin

aglycone and/or sweroside type rearrangement upon removal of the lactol acetate protecting group. Finally, the functionality most likely to need to be immediately accessible for an STA synthesis, the C7 carboxylate, is the least accessible functionality because manipulation of the lactone carboxylate carbon would likely reveal the latent C1 aldehyde, exposing the compound to epimerization or rearrangement.

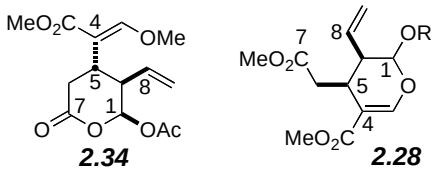
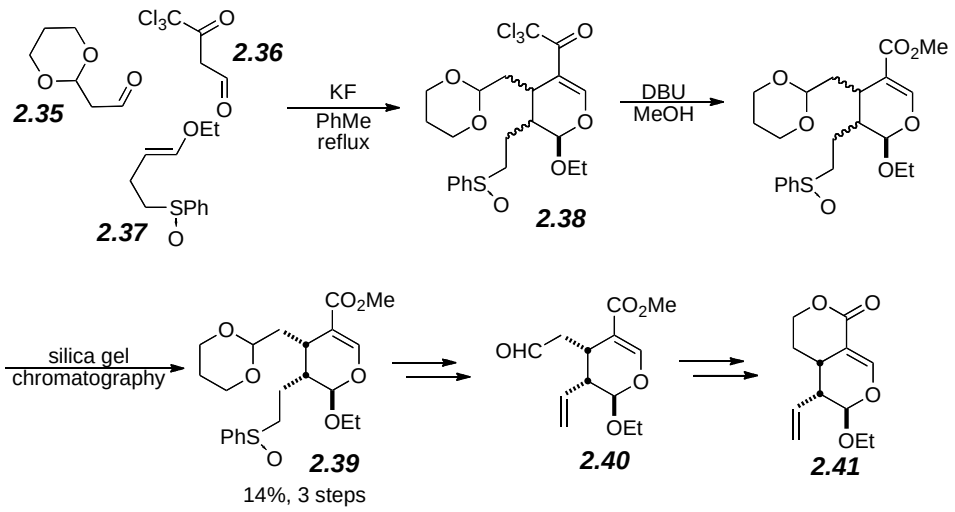


Figure 2.3: Comparison of the secoxyloganin and McLean aglycones.

2.1.3: Tietze's Secologanin Aglycone O-Ethyl Ether Synthesis

The most unique of the early secoiridoid aglycone synthesis was reported by Tietze and coworkers in 1990[36]. This was the first synthesis to directly form the secoiridoid dihydropyran ring without templating its C5 and C9 stereogenic centers with a cis fused carbocycle and then later revealing the C7 and C10 functionality via oxidative ring cleavage (**Scheme 2.7**).



Scheme 2.7: Tietze's tandem Knoevenegel-Diels-Alder strategy.

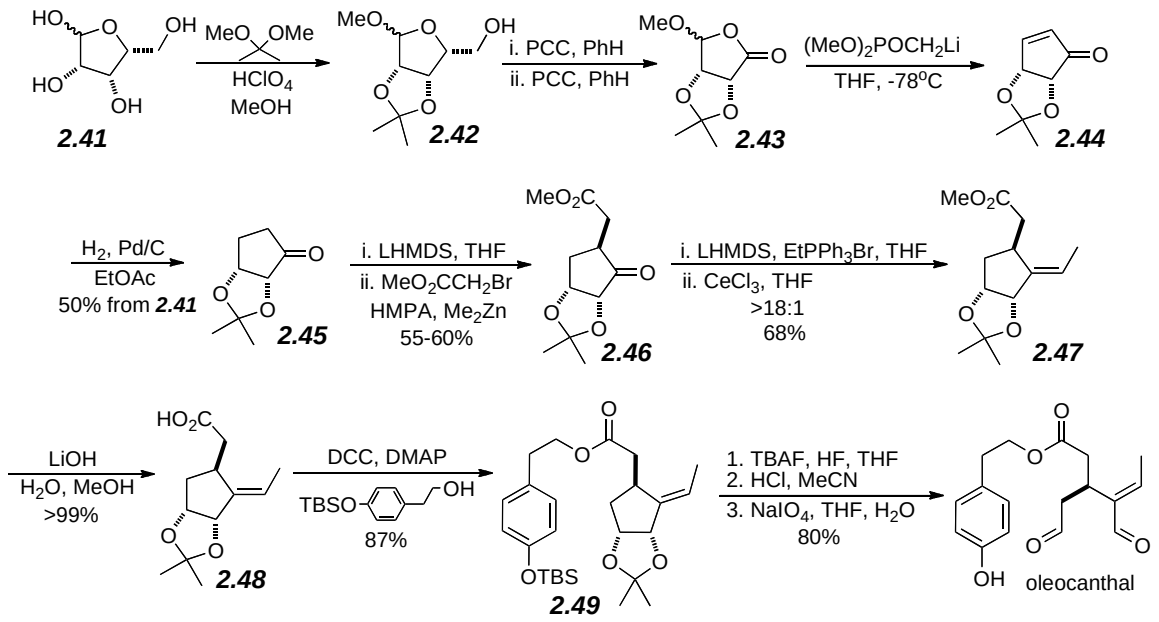
The key three-component tandem Knoevenegel-Diels-Alder reaction was performed early in the synthesis between mono protected dialdehyde **2.35**, 4,4,4-trichloro-3-oxo-butanal (**2.36**), and enol ether **2.37**, which was synthesized in two steps from simple starting materials. Upon heating with KF 4,4,4-trichloro-3-oxo-butanal (**2.36**), and aldehyde **2.35** rapidly condense forming a dynamic mixture of olefin isomers, which undergo hetero Diels-Alder cyclization with enol ether **2.37** to yield compound **2.38**. Treatment of trichloromethyl ketone **2.38** with DBU in methanol produced methyl ester as a mixture of four diastereomers. Separation of the mixture of diastereomers by silica gel chromatography allowed the isolation of the desired diastereomer (**2.39**) in 14% overall yield. Deprotection of the latent aldehyde and thermal sulfoxide elimination gave racemic secologanin aglycone ethyl ether (**2.40**) and, upon further manipulation, sweroside aglycone ethyl ether (**2.41**).

Tietze's ability to selectively synthesize individual secoiridoids represented a great leap forward for the field, however, problems with diastereoselectivity, poor yield,

and the inability to produce optically pure products limit the applicability of this synthetic strategy.

2.1.4: Smith's Oleocanthal Syntheses

In 2007[37] Smith and coworkers published a synthesis of oleocanthal (**Scheme 2.8**) and several analogues, which revised their 2005 first generation oleocanthal synthesis[38]. This work is an excellent example of the state-of-the-art in secoiridoid synthesis. The synthesis began with the protection of commercially available *d*-lyxose (**2.41**) as the corresponding acetonide (**2.42**). The primary alcohol of **2.42** was oxidized with PCC followed by the addition of additional PCC to effect an oxidative C-C bond cleavage producing lactone **2.43**. Treatment of this lactone with lithium trimethyl phosphonate and hydrogenation of the resulting unsaturated cyclopentenone **2.44** produced ketone **2.45** in 50% overall yield from the starting sugar (**2.41**). Two consecutive two carbon homologations installed the methyl carboxylate side-chain giving ester **2.46** and then the olefin side-chain giving compound **2.47**. Quantitative methyl ester hydrolysis gave acid **2.48**, which was primed for the introduction of the tyrosol side-chain. The DCC esterification of acid **2.48** with phenol-protected tyrosol gave ester **2.49** in good yield. Silyl ether and acetonide deprotection followed by oxidative carbocycle cleavage yielded (-)-oleocanthal.



Scheme 2.8: Smith's second-generation oleocanthal synthesis.

In eleven steps and in good overall yield (up to 14%) Smith's second-generation synthesis represents the most efficient and selective published synthesis of optically pure secoiridoids. A testament to the practicality and applicability of this work was the ability of Smith and coworkers to generate more than a dozen structural analogues for biological testing (**Figure 2.4**).

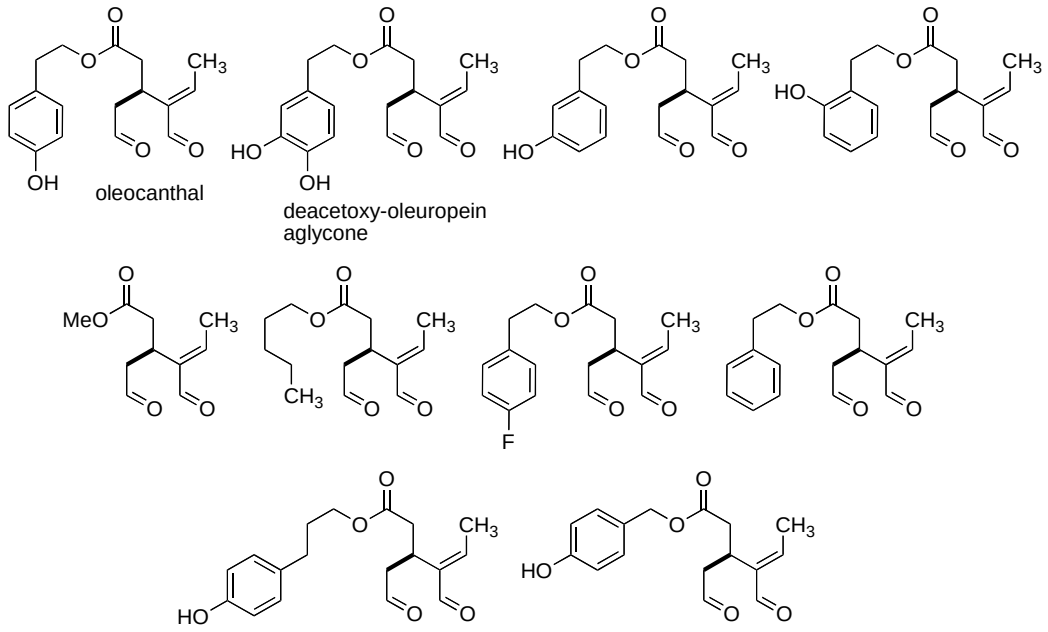


Figure 2.4: Secoiridoid analogues produced for biological testing.

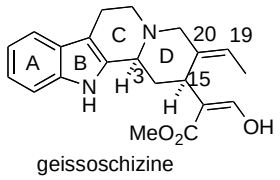
2.2: Selected Secologanin Tryptamine Alkaloid (STA) Syntheses

Due to the their structural complexity, diverse and potent biological activities, and shear number of isolated examples, the STAs have attracted a great deal of attention from synthetic chemists for over a century.[39] The STAs quinine, reserpine, and strychnine inspired the development of modern synthetic chemistry and continuing work to understand and control the production of the cancer fighting alkaloids vinblastine and vincristine is a driving force in the development of the budding field of synthetic biology. Needless to say, it is well beyond the scope of this writing to discuss the literally thousands of publications relating to the synthesis of STAs. The selection of syntheses discussed below is not meant to be a comprehensive review. Discussion is limited to STAs whose skeletal structure is relatively similar to that of strictosidine (i.e. requiring no major carbon-carbon bond rearrangements) and is meant to give a perspective of the

modern strategies for the construction of the natural products whose structures closely resemble those that have been the focus of our work. Additionally, we have strived to include examples of research programs whose broader goals include strategies to access multiple, related structures via a single synthetic strategy. In particular, syntheses of geissoschizine are highlighted because the structure of this STA closely resembles that of our synthetic targets and the general strategies used to approach this alkaloid serve as an excellent benchmark of comparison for our divergent strategy of alkaloid synthesis.

2.2.1: Selected Geissoschizine Alkaloid Syntheses

Geissoschizine has seen a great deal of synthetic attention and, as such, can serve as an excellent illustration of the types of approaches taken toward STAs. The principle synthetic challenges presented by the geissoschizine are the formation of the C and D rings while controlling the absolute and relative stereochemistry of the C3 and C15 stereogenic centers and the control of the *E/Z* geometry of the C19-C20 olefin (**Figure 2.5**).

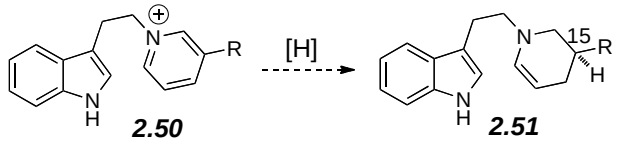


geissoschizine

Figure 2.5: Geissoschizine.

To date, all of the published geissoschizine syntheses introduce the indole potion of the molecule (rings A and B) as an intact heterocycle and these syntheses vary chiefly in their approach to the C and D rings. These approaches can be divided into two types,

those that introduce an intact D ring followed by closure of the C ring to complete the tetracyclic framework and those that first form the C ring and then close the D ring of the tetracycle. Although the former strategy of coupling an intact D ring with an AB portion via C ring closure is the most predominant strategy for the synthesis of more complicated STAs such as reserpine[40], in the past it has proven to be less successful than the C-ring-first strategy for the synthesis of geissoschizine. This is likely due to geissoschizine's lack of additional rings found in more complicated STAs, whose added rigidity helps to control the relative stereochemistry of the C3 stereogenic center during the formation of the C ring.



Scheme 2.9: Deriving the D ring from an N-alkylated pyridine ring.

Wenkert[41] and Lounasmaa[42] derive the geissoschizine D ring from the reduction of a substituted N-alkylated pyridine ring (**Scheme 2.9**, **Figure 2.6**). An immediately apparent drawback of this strategy is that, using currently available techniques, it would be very difficult to adapt this work to produce an asymmetric synthesis of geissoschizine. Deriving the D ring of geissoschizine from a reduced N-alkylated pyridine ring mandates that this synthetic route must pass through a completely achiral pyridinium intermediate (**2.50**). This means that the absolute stereochemistry of the C15 stereogenic center (**2.51**) must be established via the asymmetric reduction this planar pyridinium ring with no

substrate direction available. Asymmetric pyridinium reduction is a difficult synthetic challenge, which has yet to be demonstrated.

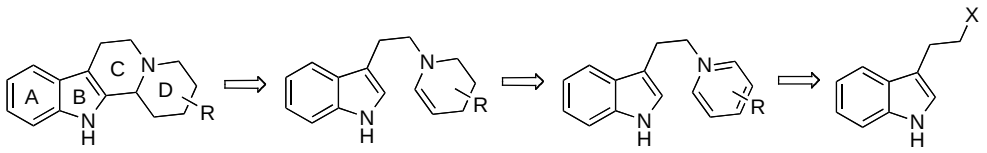
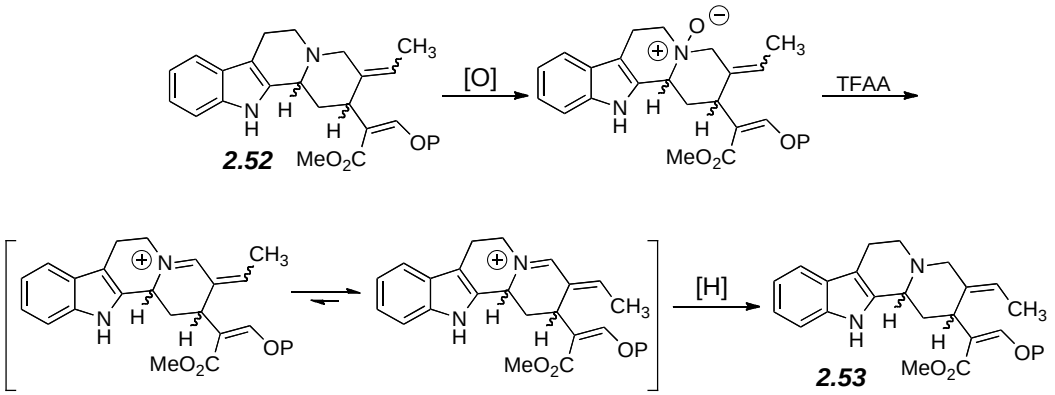


Figure 2.6: The Wenkert, Lounasmaa retrosynthetic analysis.

The apparent difficulty of establishing the correct *E/Z* olefin geometry was addressed by Wenkert and Lounasmaa through the assembly of the tetracycle as a mixture of diastereomers and *E/Z* isomers (**2.52**) followed by the exploitation of a fortunate iminium rearrangement induced by a Polonovski reaction. This rearrangement isomerizes the mixture to exclusively produce the more thermodynamically favorable *Z* olefin isomer (**2.53**) presumably via the generalized pathway illustrated in **Scheme 2.10**. Unfortunately, neither of the groups were able to completely control the relative configurations of the C3 and C15 stereogenic centers and diastereomers had to be separated by crystallization.



Scheme 2.10: Polonovski induced iminium rearrangement.

Bennasar and coworkers also derived the geissoschizine D ring from an N-acylated pyridinium ring in their synthesis of geissoschizine.[43] Unlike the above described Wenkert and Lounasmaa syntheses, the Bennasar synthesis establishes the geissoschizine C3 stereogenic center via alkylation, rather than reduction, of the N-acylated pyridinium ring. This synthesis utilizes a unique series of retrosynthetic disconnections, which allowed for a high degree of control of both the diastereoselectivity and the olefin *E/Z* selectivity and differ greatly from any of the other geissoschizine syntheses described in the literature.

The Bennasar retrosynthetic strategy (**Figure 2.7**) establishes the C ring of geissoschizine precursor **2.54** via late stage closure of the northern half of the ring making a retrosynthetic disconnection between the indole B ring and a substituted ethyl chain appended to the D ring nitrogen (**2.55**). This is the only published geissoschizine synthesis that makes this bond disconnection. The stereochemically defined olefin present in **2.55** derives from a very similar iminium reduction utilized in the Wenkert and Lounasmaa syntheses. Rather than generating the requisite iminium ion via a Polonovski reaction, however, the Bennasar group relied on the decarboxylation of vinylogous

carbamate **2.56** to generate the iminium ion which isomerized before reduction giving the desiered *Z* isomer exclusively. The C3-C15 *cis* stereochemistry of compound **2.56** was established with an intramolecular iminium Friedel-Crafts reaction. The C15 stereogenic center of racemic enamine **2.57** presumably directed this annulation to exclusively produce the observed *cis* relative stereochemistry producing the 6,7-*cis*-fused system. The AB and D portions of compound **2.57** were joined by the alkylation of substituted pyridinium ring **2.59** with N-acetyl indole **2.58** giving 2.57 as a racemic mixture of C15 epimers.

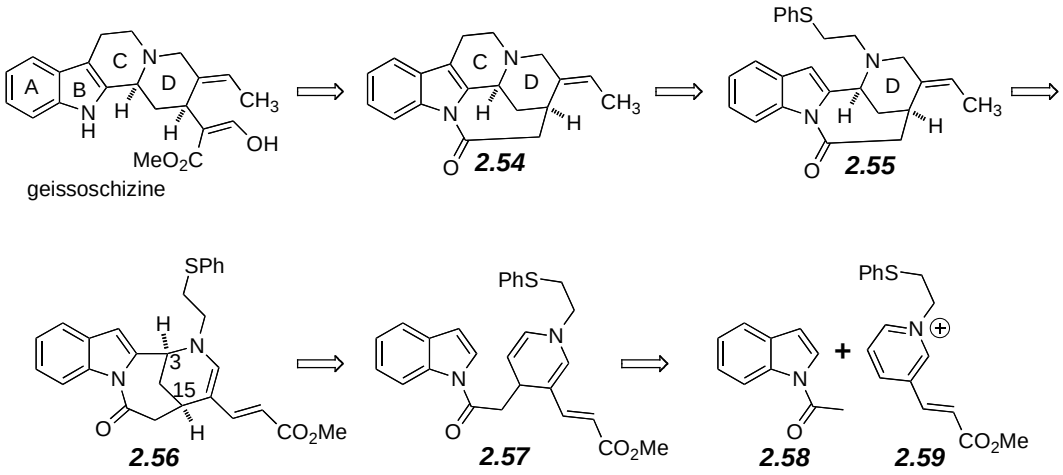


Figure 2.7: The Bennasar retrosynthesis.

Building on the strategies of deriving the geissoschizine D ring from a substituted N-acylated pyridinium ring and establishing the C19-C20 olefin stereochemistry via the reduction of an equilibrated extended iminium ion pioneered by Wenkert and Lounasmaa, Bennasar and coworkers were able to establish the desired *cis* orientation between the C3 and C15 stereogenic centers. The drawbacks of these syntheses include a

lack of absolute stereoselectivity as well as the relative difficulty of adapting these syntheses to easily generate structural analogues of geissoschizine.

In terms of absolute stereoselectivity and adaptability to other synthetic applications, previous geissoschizine syntheses have been more successful if the C-ring-first strategy rather than the D-ring-first strategy, utilized above, is employed. The formation of the geissoschizine C ring followed by D ring formation better facilitates asymmetric syntheses of geissoschizine primarily because the absolute stereochemistry of the C3 stereogenic center can be directed by other substituents on the C ring whose absolute stereochemistry derives from optically pure starting materials such as tryptophan. Once the C3 stereochemistry is established these directing groups are removed and the C3 stereogenic center can be used to establish the stereochemistry of the C15 stereogenic center. All of the published asymmetric geissoschizine syntheses[44] involve the use of an optically pure tryptophan derivative to influence the stereochemistry of the C3 stereogenic center (**Figure 2.8**). Martin takes advantage of the tryptophan carboxylate functionality to facially differentiate the cyclic tryptophan iminium ion for diastereoselective Mannich alkylation. Overman and Cook take advantage of a diastereoselective Pictet-Spengler reaction to establish C3 stereochemistry. The reasons for this diastereoselectivity are discussed below.

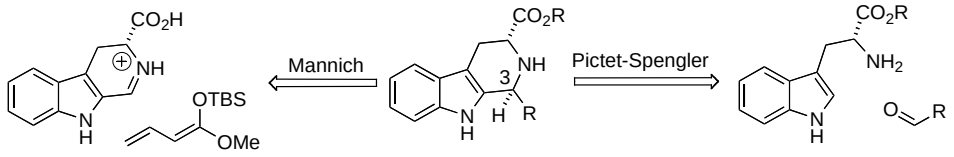


Figure 2.8: Establishing C3 stereochemistry.

All of the reported geissoschizine syntheses which involve the formation of the C ring first, involve the same four major bond disconnections as represented by wavy lines in **Figure 2.9**. The C2-C3 and C3-N4 bonds are formed via Pictet-Spengler or Bischler-Napieralski cyclizations and the N4-C21 bond is formed either by N-acylation or alkylation. The main distinction between the C ring first syntheses is the method of formation of the C15-C20 bond to form the D ring.

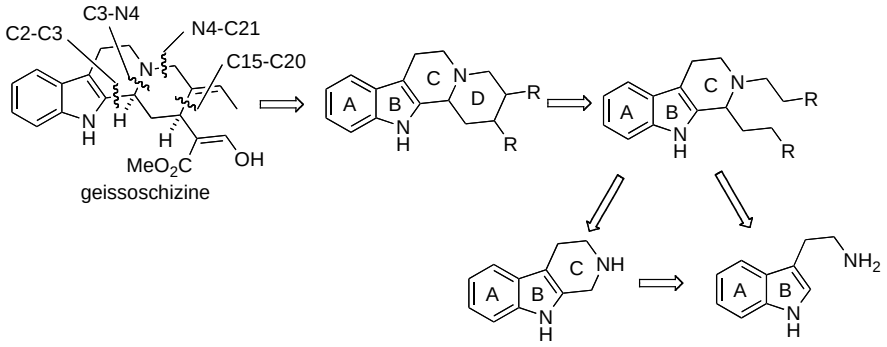
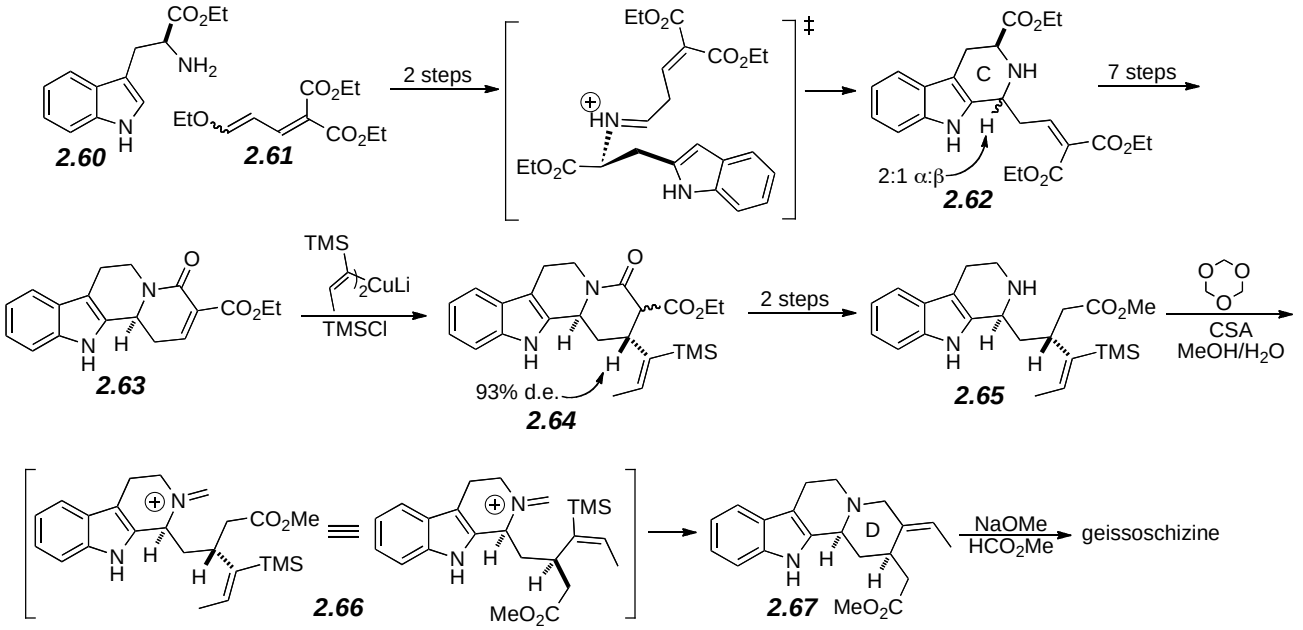


Figure 2.9: The C ring first strategy.

An early use of the C ring first strategy was by Overman and coworkers (**Scheme 2.11**)[45]. The formation of the C ring was accomplished by a stepwise Pictet-Spengler reaction between tryptophan ester **2.60** and enol ether **2.61**. This reaction resulted in a separable 2:1 mixture of C3 epimers (**2.62**) with the desired *cis* isomer, resulting from the pictured transition state, as the major product. After reductive removal of the tryptophan carboxylate and lactamization to yield lactam **2.63** the C15 stereogenic center was installed via vinyl cuprate addition to the less sterically hindered face of **2.63** to afford the desired diastereomer (**2.64**) in 93% diastereomeric excess. By using a stereochemically defined vinyl cuprate, this step also introduced the desired C19-C20 olefin geometry.

Decarboxylation and methanolysis of the lactam ring gave amine **2.65**, which was poised to undergo D ring closure. Treatment of amine **2.65** with paraformaldehyde and catalytic CSA produced iminium ion **2.66**, which underwent nucleophilic attack by the vinyl silane to close the D ring of deformyl geissoschizine (**2.67**). Formylation was accomplished by a method first reported by Winterfeldt and coworkers[46] to give geissoschizine.



Scheme 2.11: Overman's geissoschizine synthesis.

The Overman synthesis adequately addressed each of each of geissoschizine's synthetic challenges, however, the synthesis was plagued with poor diastereoselectivity during installation of the C3 stereogenic center. Additionally this synthesis includes multiple manipulations necessary to diastereoselectivly install the C15 stereogenic center, which do not increase the structural complexity of the intermediate being manipulated. This inefficiency creates a lengthier than necessary synthesis.

Figure 2.10 illustrates the Cook[47], Rawal[48], and Takayama[49] D ring formation strategies. All three of these groups disconnect the C15-C20 bond by reacting an olefin and vinyl iodide. Takayama closes the D ring via vinyl radical cyclization, which exclusively forms the desired C3-C15 *cis* diastereomer as rationalized by a chair-like transition state. Cook and Rawal utilize a Heck reaction followed by facially selective reduction in order to close the D ring. As in the above described Overman synthesis, these three methods allow for the efficient installation exclusively the desired *Z* olefin through the introduction of an externally produced and stereodefined olefin. Unlike the Overman synthesis, the Rawal, Cook, and Takayama strategies rely on an intramolecular C15-C20 bond formation to produce the D ring. This results in a greatly increased step efficiency when compared to the Overman strategy because the lactam annulation and methanolysis sequences that the Overman group required in order to the establish the C15 stereogenic center are unnecessary.

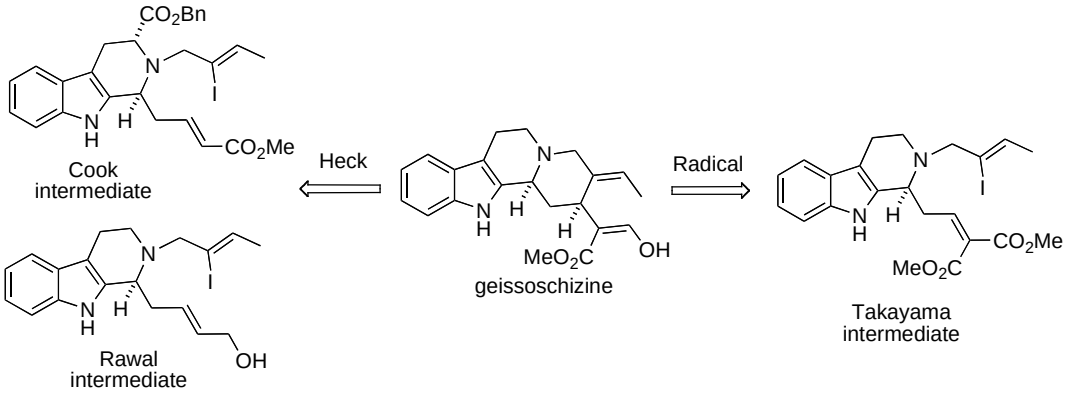


Figure 2.10: The Cook, Rawal, and Takayama C15-C20 bond disconnection.

Despite the similarity in D ring closure amongst these three strategies, their approach to the formation of the C3 stereogenic center differ greatly (**Figure 2.11**).

Rawal and Takayama generate this stereogenic center via N-acyl iminium alkylation and Pictet-Spengler reaction respectively, however, both do so racemicaly and, thus, do not actually address the problem of the C3 stereogenic center. Cook's strategy for defining the C3 stereogenic center involves a diastereoselective Pictet-Spengler reaction directed by a chiral tryptophan carboxylate functionality. This reaction closely resembles work discussed in detail in the following section.

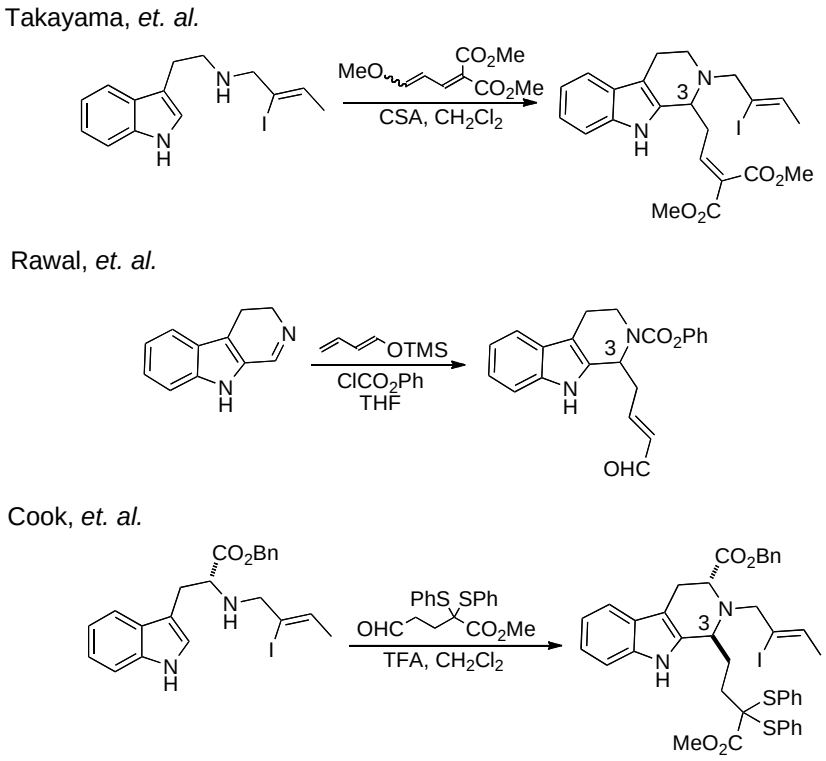
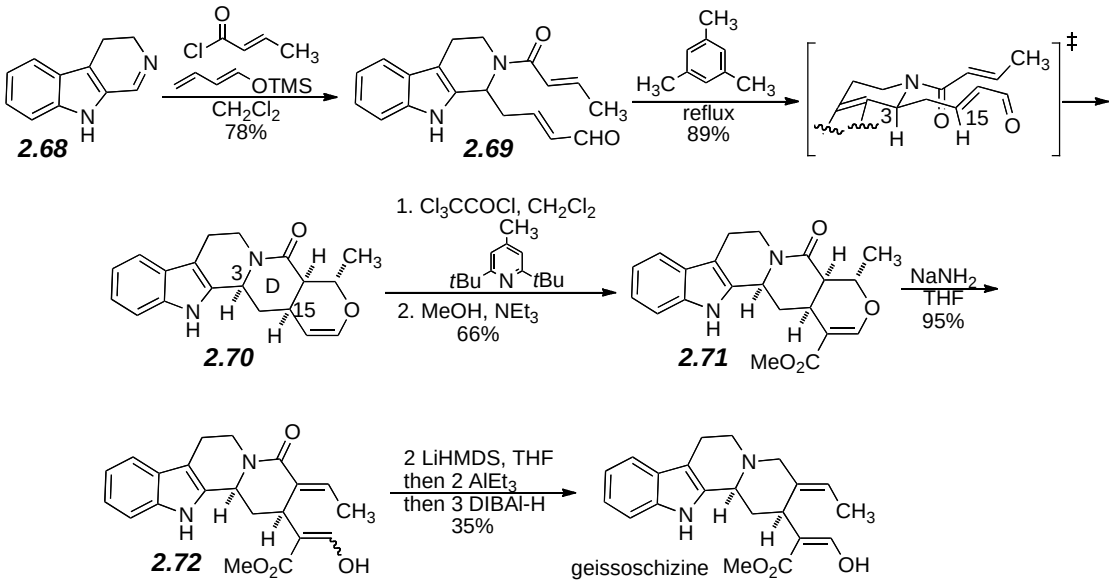


Figure 2.11: The Takayama, Rawal, and Cook C3 installations.

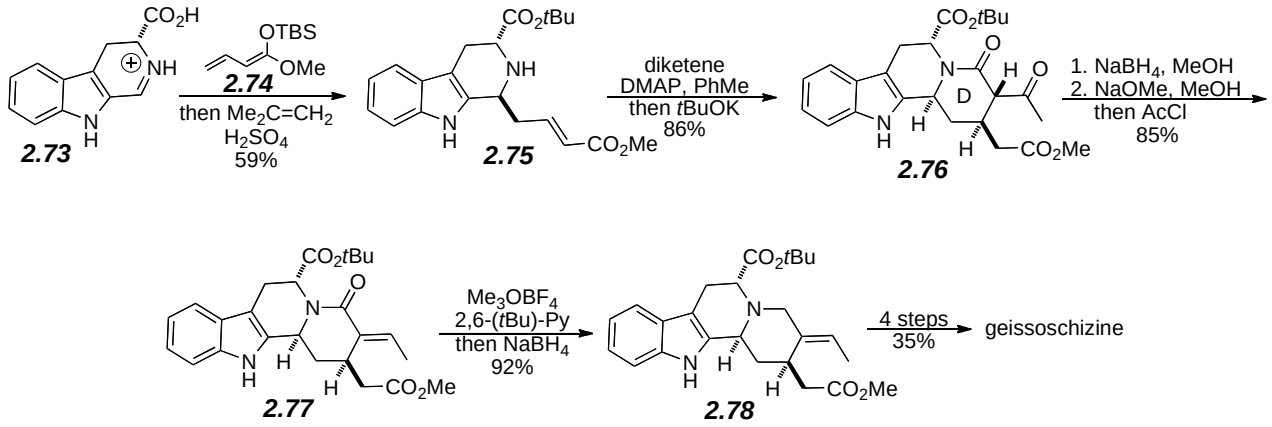
Martin and coworkers employ two distinct C15-C20 bond disconnection strategies for their two unique syntheses of geissoschizine. The earlier racemic strategy[50] (**Scheme 2.12**) evolved from their synthesis of ajmalicine-type alkaloids. This synthesis begins with the one-step acylation and alkylation of imine **2.68** to produce amide **2.69**,

which upon heating undergoes an intramolecular hetero Diels-Alder reaction. This cyclization forms tetracycle **2.70**, which contains the D ring as well as an additional dihydropyran ring. Presumably, the pictured chair-like transition state is responsible for the desired and observed C3-C15 *cis* stereochemistry. Carboxylation of this newly formed dihydropyran ring by a previously developed two-step carboxylation procedure[51] yielded vinylogous carbonate **2.71** in acceptable yield. The final steps of this first generation synthesis involve stereospecific elimination of the dihydropyran oxygen to exclusively generate the desired *E* α,β-unsaturated lactam (**2.72**). The final step of the synthesis should involve a simple lactam reduction, however, a great deal of effort was required to develop a very specific series of reagent additions, which gave geissoschizine in only 35% yield.



Scheme 2.12: Martin's first generation geissoschizine synthesis.

Much like the above described Rawal and Takayama syntheses, the first generation Martin synthesis very efficiently and selectively installs the C19-20 olefin geometry and the C15 stereochemistry relative to the C3 stereogenic center, while neglecting to asymmetrically install the C3 stereogenic center. The more recent geissoschizine synthesis reported by Martin and coworkers[52] solves this problem of asymmetry (**Scheme 2.13**). This second generation synthesis begins with the diastereoselective installation of the C3 stereogenic center via Mannich alkylation of the optically pure, tryptophan derived iminium ion **2.73** with extended enolate **2.74**. This is immediately followed by esterification to give tricycle **2.75** as the only product. The C15 stereogenic center is then established to give the C3-C15 *cis* relative stereochemistry through a diastereoselective intramolecular Michael cyclization. Treatment of amine **2.75** with diketene and catalytic DMAP forms the intermediate β-keto amide, which upon treatment with base immediately cyclizes to form the D ring of tetracycle **2.76**. The desired olefin functionality is then installed via diastereoselective β-keto amide reduction followed by the acylation and stereospecific elimination of the newly formed β-hydroxide to give exclusively the desired *E*-α,β-unsaturated lactam (**2.77**). The problematic unsaturated lactam reduction that was observed in the first generation synthesis was accomplished in vastly improved yield through the use of a reduction protocol reported by Borch and coworkers[53] giving amine **2.78** in excellent yield. The synthesis was concluded with the removal of the tryptophan carboxylate followed by formylation to give geissoschizine in acceptable yield.



Scheme 2.13: Martin's second generation geissoschizine synthesis.

The geissoschizine syntheses discussed above illustrate the evolution of problem solving as applied to the synthesis of this single alkaloid. The most efficient geissoschizine syntheses asymmetrically install the C3 stereogenic center and then use this asymmetry to establish the C15 stereogenic center and C19-C20 stereochemistry. This process is effective and efficient and, if the synthesis of optically pure geissoschizine were the sole objective of a research program, this would likely be considered a solved problem. Our objective has been to approach the synthesis of geissoschizine and its structural analogues as part of a larger strategy aimed at producing a diverse selection of natural products through from a single synthetic intermediate. As the next section will show, this concept of diversity oriented synthesis is not a unique or original concept and can be applied to STAs to vastly increase the number of natural products that can be synthesized from a single synthetic strategy. The Cook STA research program has been chosen as an illustration of this concept because it is fully mature and represents the state of the art for the divergent synthesis of a wide variety of structurally divergent STAs.

2.2.2: Cook's Divergent Syntheses of STAs

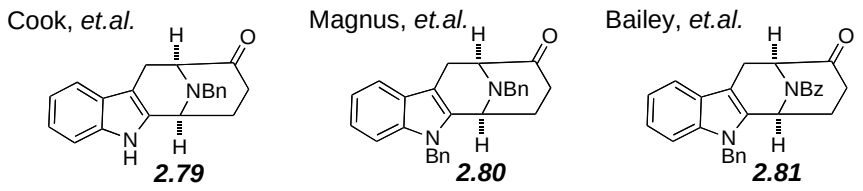
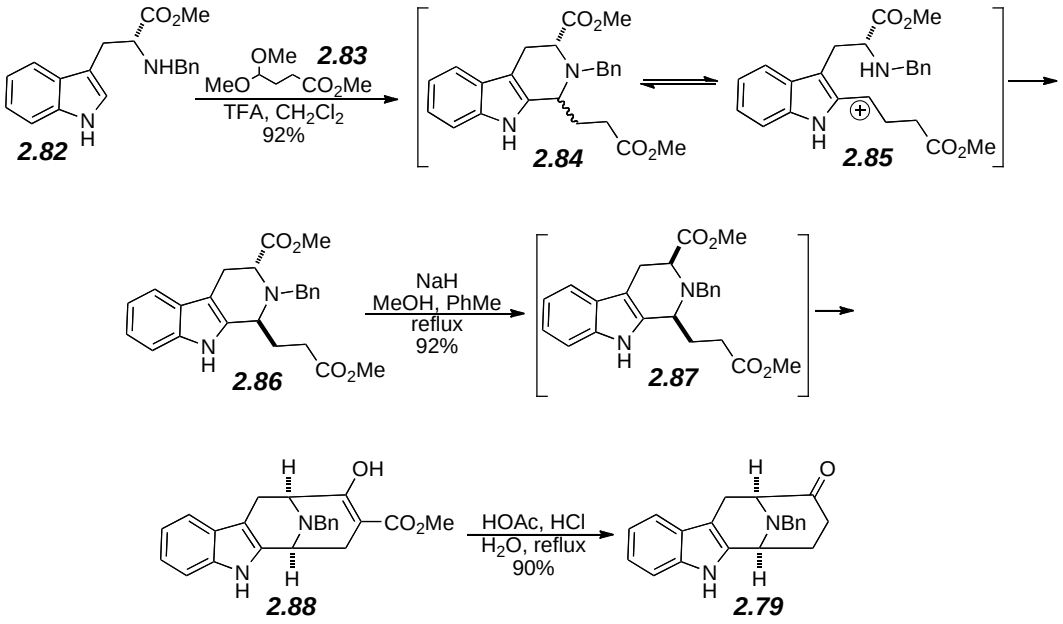


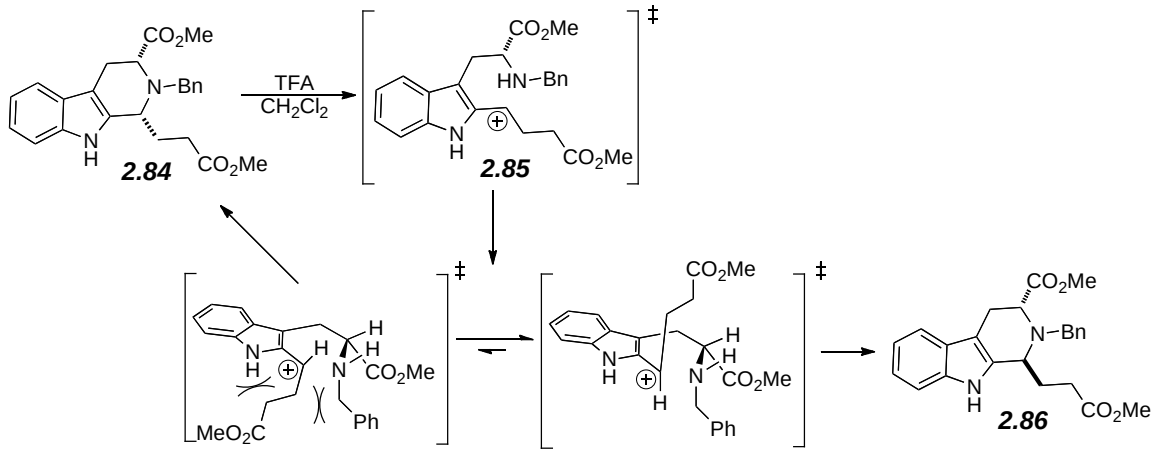
Figure 2.12: The Magnus, Bailey, and Cook substrates.

In 1997 Cook and coworkers reported[54] an efficient and stereoselective synthesis of ketone **2.79** (**Figure 2.12**, **Scheme 2.14**), which would mark the beginning of an impressive and ongoing program of STA synthesis. Magnus[55] and Bailey[56] had previously reported syntheses of a protected version of ketone **2.79** (compounds **2.80**, and **2.81** respectively, **Figure 2.12**), however, these syntheses suffered from poor Pictet-Spengler diastereoselectivities, low yields, and the need for late stage dissolving metal reductions to deprotect the indole nitrogen. Rather than employ the standard aprotic Pictet-Spengler conditions (PhH, 1,4-dioxane, reflux) utilized by Magnus and Bailey to close the C ring, Cook and coworkers performed the Pictet-Spengler reaction between protected tryptophan **2.82** and acetal **2.83** with TFA in CH_2Cl_2 (**Scheme 2.14**). This allowed an acid catalyzed epimerization of the newly formed stereogenic center of **2.84** to occur via the formation of the indole stabilized carbocation **2.85**. This equilibration yielded exclusively the kinetically and thermodynamically favored *trans* product (**2.86**)[57]. Cook supports this analysis with the transition states pictured in **Scheme 2.15**. Treatment of the *trans* product **2.86** with sodium methoxide in refluxing toluene effected a

Dieckmann cyclization presumably via the disfavored *cis* isomer **2.87** to yield enol **2.88**, which readily underwent decarboxylation in refluxing aqueous acid to yield ketone **2.79** as a singe diastereomer and in excellent overall yield after three steps.

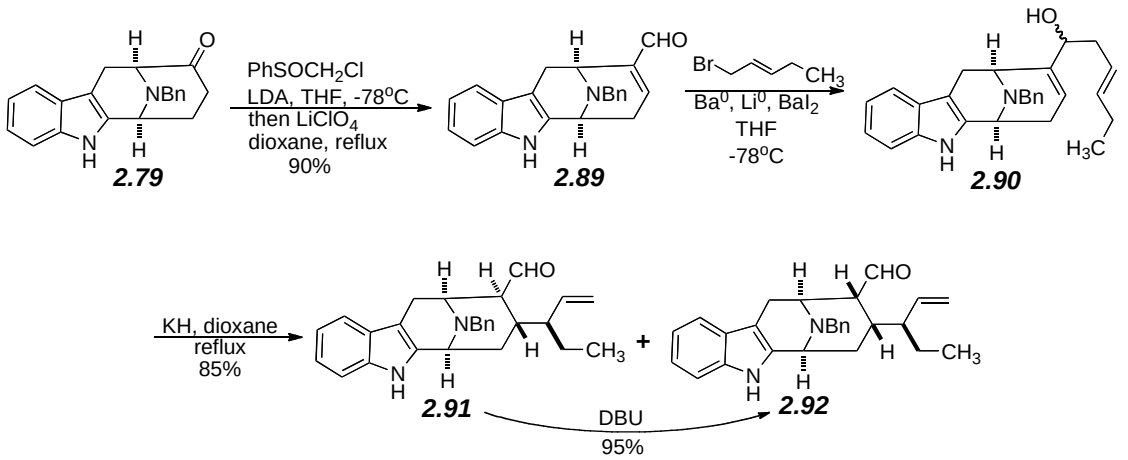


Scheme 2.14: Cook's syntheses of ketone **2.79**.



Scheme 2.15: Cook's analysis of the C3 diastereoselectivity.

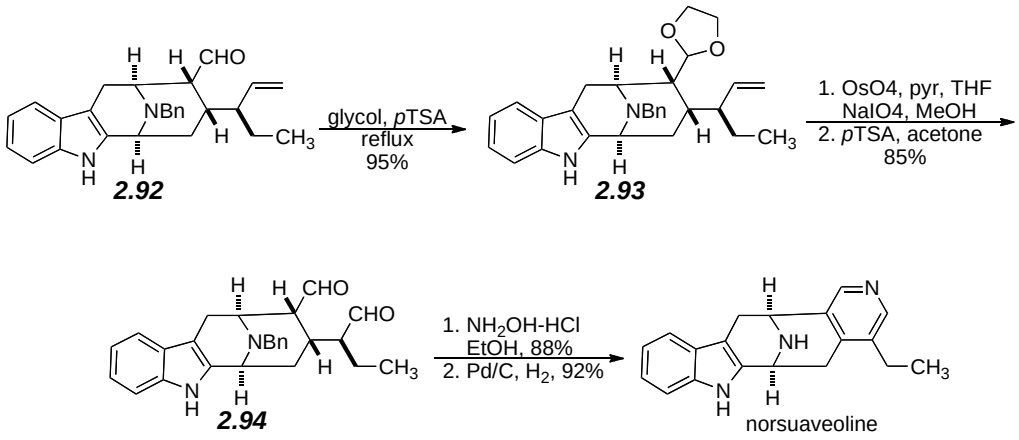
The following year Cook's group reported,[58] "With large amounts of [ketone **2.79**] in hand, the execution of the synthesis of several alkaloids is underway". Treatment of ketone **2.79** with the lithium anion of α-chlorophenylsulfoxide followed by potassium hydroxide gave a 1:1 diastereomeric mixture of spiro phenyl sulfinyloxiranes which upon heating with lithium perchlorate rearranged to provide α,β-unsaturated aldehyde **2.89**. Employing a procedure developed by Yamamoto and coworkers[59], the barium anion derived from 1-bromo-2-pentene was used for alkylation of aldehyde **2.89** in order to avoid allylic rearrangements that were observed with the use of allyl lithium and allyl magnesium anions. Oxy-Cope rearrangement occurred upon treatment of alcohol **2.90** with potassium hydride in refluxing dioxane and gave a mixture of aldehyde epimers **2.90** and **2.91**. Aldehyde 2.90 was efficiently converted to the thermodynamically favored *cis* isomer **2.91** by stirring with DBU.



Scheme 2.16: Synthesis of oxy-Cope product **2.92**.

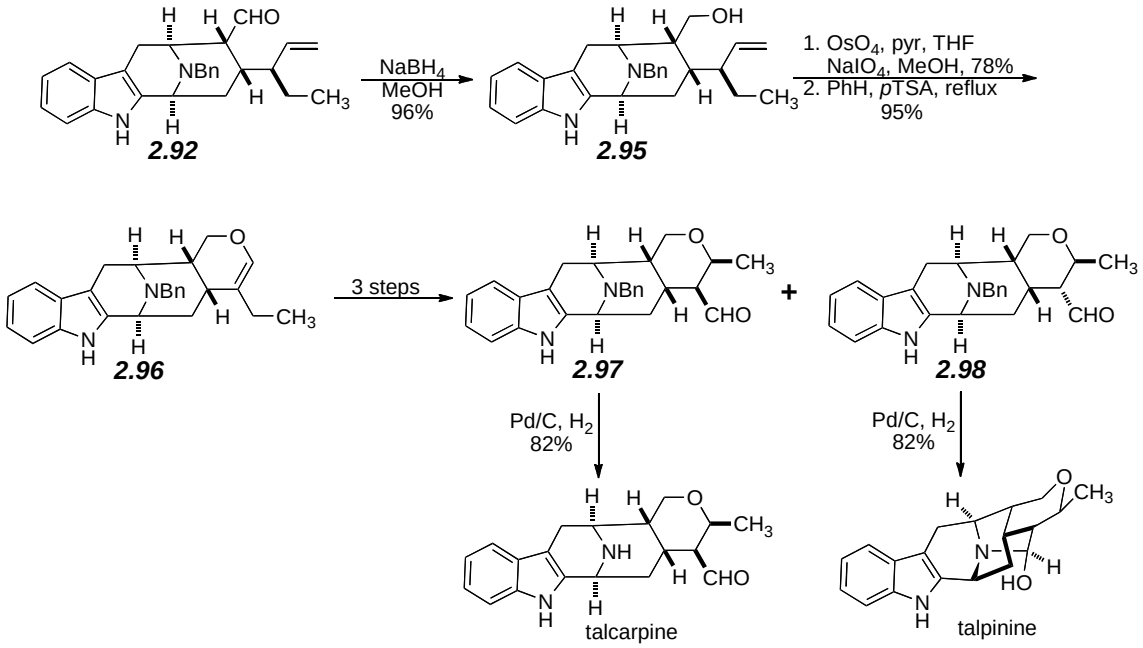
The synthesis of oxy-Cope product **2.92** marks a major synthetic branch point. With all of the required carbon framework and major stereogenic centers in place the

authors were free to complete the final heterocycle formation to selectively and divergently synthesize three structurally distinct natural products; norsuaveoline (**Scheme 2.17**) and in a subsequent publication[60] talcarpine and talpinine (**Scheme 2.18**).



Scheme 2.17: Synthesis of norsuaveoline.

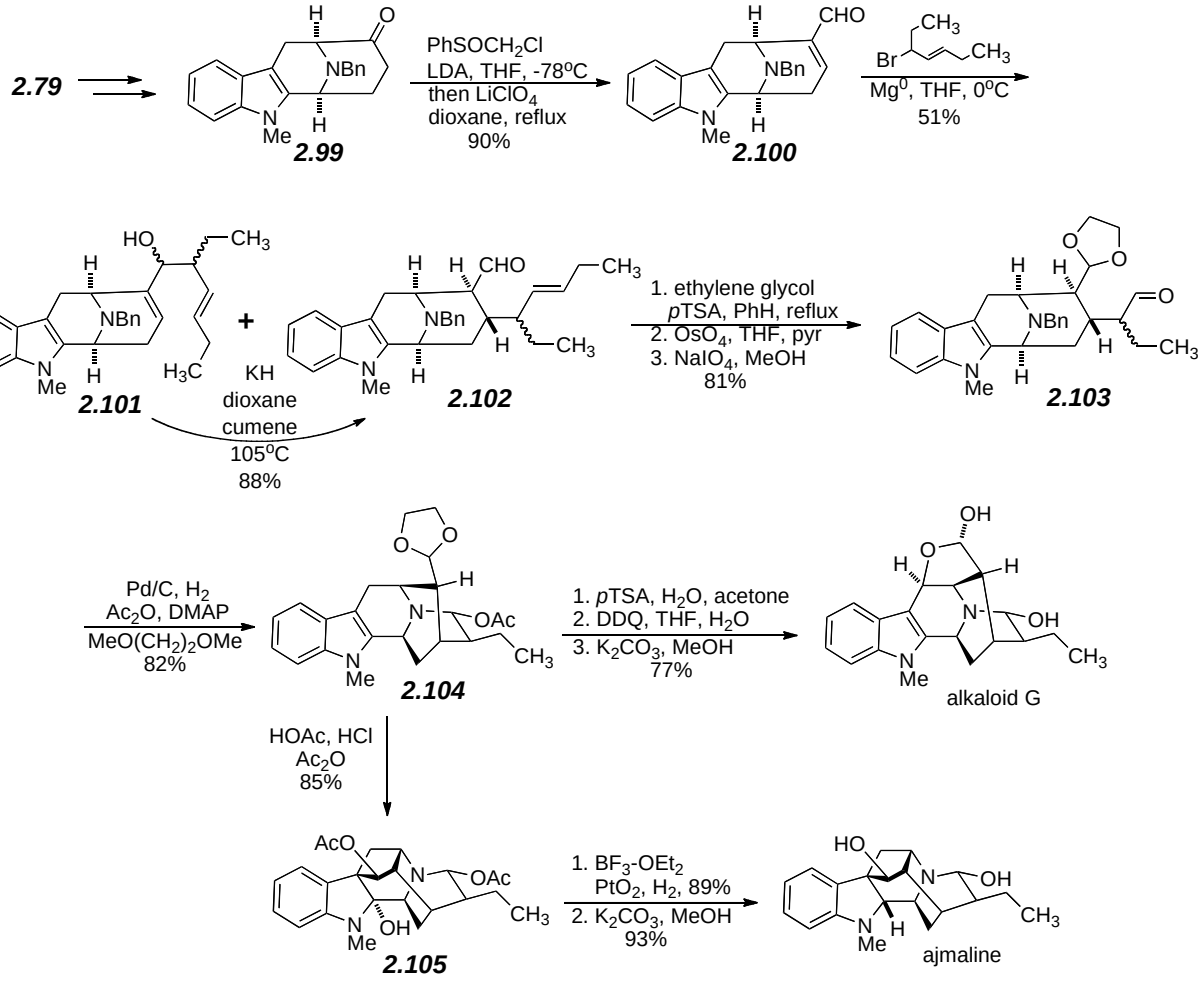
Scheme 2.17 illustrates the synthesis of norsuaveoline from oxy-Cope product **2.92**, which commenced with the protection of aldehyde **2.92** as the corresponding glycol acetal (**2.93**). This was followed by oxidative olefin cleavage and acetal deprotection to yield dialdehyde **2.94**. The pyridine heterocycle of norsuaveoline was completed by treatment of dialdehyde **2.94** with acidic hydroxyl amine followed by hydrogenation conditions, which simultaneously removed the benzyl protecting group completing the synthesis.



Scheme 2.18: Synthesis of talcarpine and talpinine.

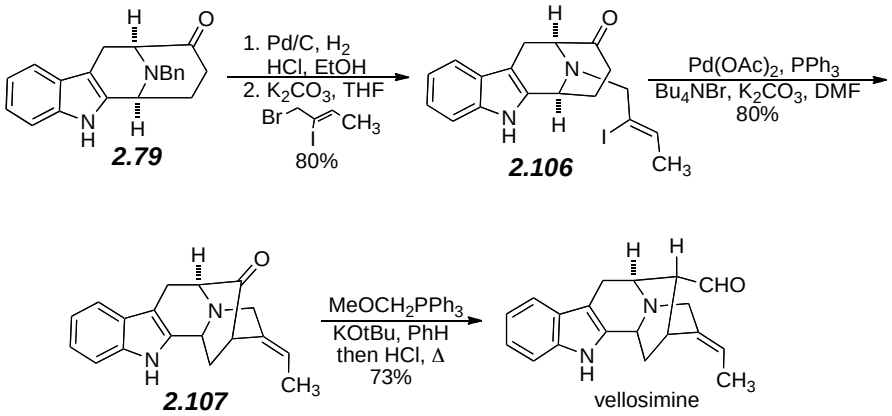
Aldehyde **2.92** was then used to produce two additional naturally occurring alkaloids (**Scheme 2.18**). Reduction of aldehyde **2.92** produced alcohol **2.95**, whose olefin functionality was oxidatively cleaved and rearranged under acidic conditions to provide dihydropyran **2.96**. This dihydropyran ring was oxidized and rearranged to provide a separable mixture of aldehyde epimers **2.97** and **2.98**, which were independently deprotected to yield their respective alkaloids. Hydrogenolysis of compound **2.97** proceeded without further reaction to yield talcarpine, whereas, the hydrogenolysis of the benzyl amine functionality of compound **2.98** resulted in the cyclization of the newly revealed amine functionality onto the aldehyde functionality forming the bridging heterocycle of talpinine. This cyclization was prevented in the previous case by the orientation of the epimeric aldehyde, which was inaccessible to nucleophilic attack by the freed amine.

Cook and coworkers continued their sythetic strategy in a subsequent publication[61]. The divergent strategy employed to synthesize the above alkaloids was adapted to pursue another synthetic branch (**Scheme 2.19**). This process began with ketone **2.99** the indole N-methylated version of ketone **2.79**. The synthesis began with a homologation of ketone **2.99** to produce aldehyde **2.100** utilizing identical conditions to those used to perform the corresponding manipulation of the unprotected ketone **2.79**. Alkylation of aldehyde **2.100** with the anion derived from 5-bromo-3-heptene rather than the anion derived from 1-bromo-2-pentene, which was utilized to produce the oxy-Cope product **2.92** for the norsuaveoline, talcarpine, and talpinine syntheses, was meant as an attempt to directly produce the 1,4-product and avoid the oxy-Cope rearrangement needed to convert the 1,2-product into a useable substrate. Using 5-bromo-3-heptene allowed the generation of the allyl Grignard nucleophile rather than a barium anion. This was acceptable due to the pseudo-symmetry of the anion derived from 5-bromo-3-heptene. Unfortunately, both the 1,2- and 1,4- alkylations of the α,β-unsaturated aldehyde (**2.100**) were observed giving a mixture compounds **2.101** and **2.102** respectively. Fortunately, upon subjection of the 1,2-addition product (**2.101**) to oxy-Cope rearrangement conditions (KH, dioxane, cumene), a single pair of inconsequential epimers was isolated (**2.102**). Aldehyde protection followed by oxidative olefin cleavage produced aldehyde **2.103**, which upon benzyl amine hydrogenolysis in the presence of acetic anhydride, spontaneously formed hemiaminal acetate **2.104**. This synthetic branch point was then exploited to divergently produce alkaloid G via deprotection and oxidation as well as the indolene ajmalicine via cyclopentane cyclization (**2.105**) and subsequent hemiaminal reduction.



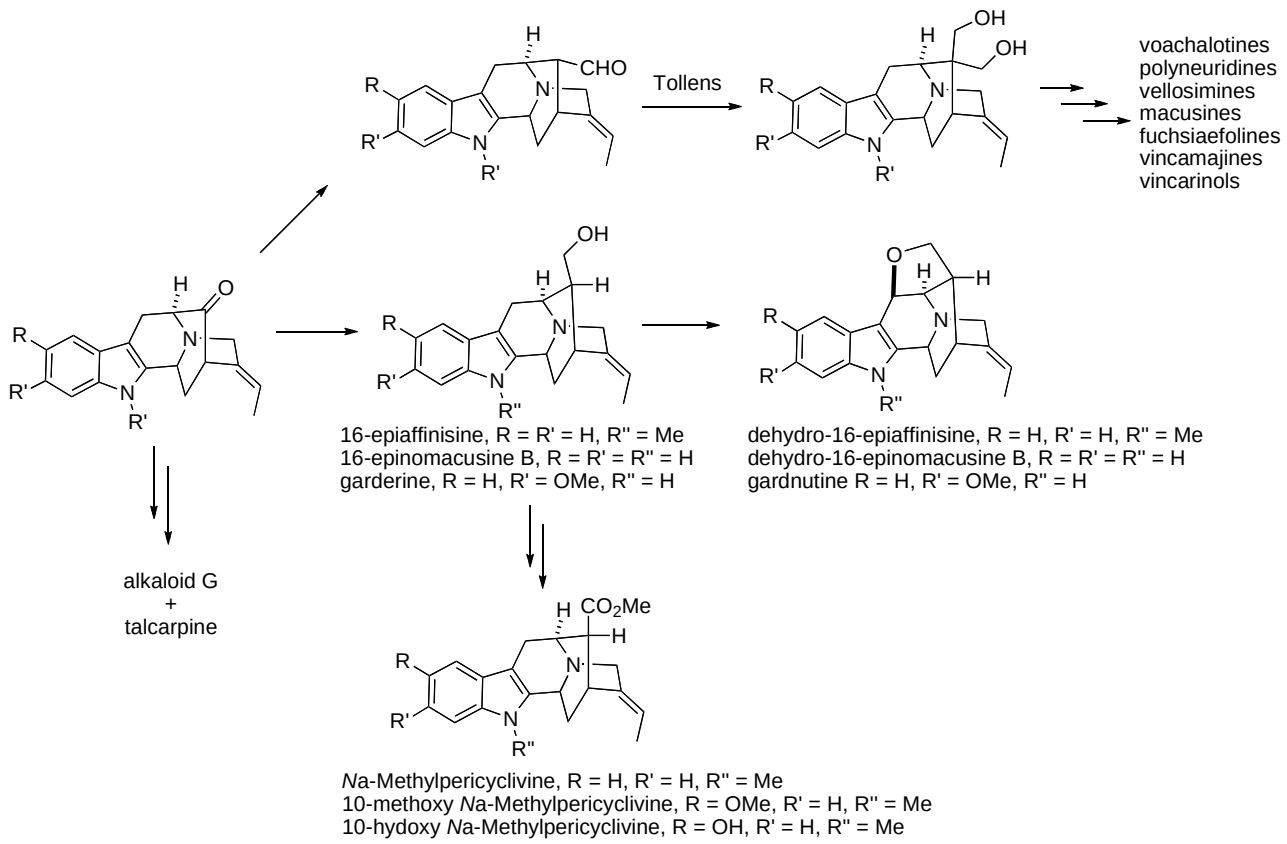
Scheme 2.19: The synthesis of alkaloid G and ajmaline from ketone **2.79**.

The Cook strategy for the divergent synthesis structurally disparate classes of STAs was further improved with the recognition of a new retrosynthetic disconnection[62] (**Scheme 2.20**). Benzyl amine hydrogenolysis of ketone **2.79** followed by alkylation with *Z*-1-bromo-2-iodo-2-butene produced vinyl iodide **2.106**. Palladium catalyzed cyclization of the vinyl iodine with the a-position of the ketone yielded bridged pentacycle **2.107**, which upon homologation with a Wittig ylide gave vellosimine in good overall yield.



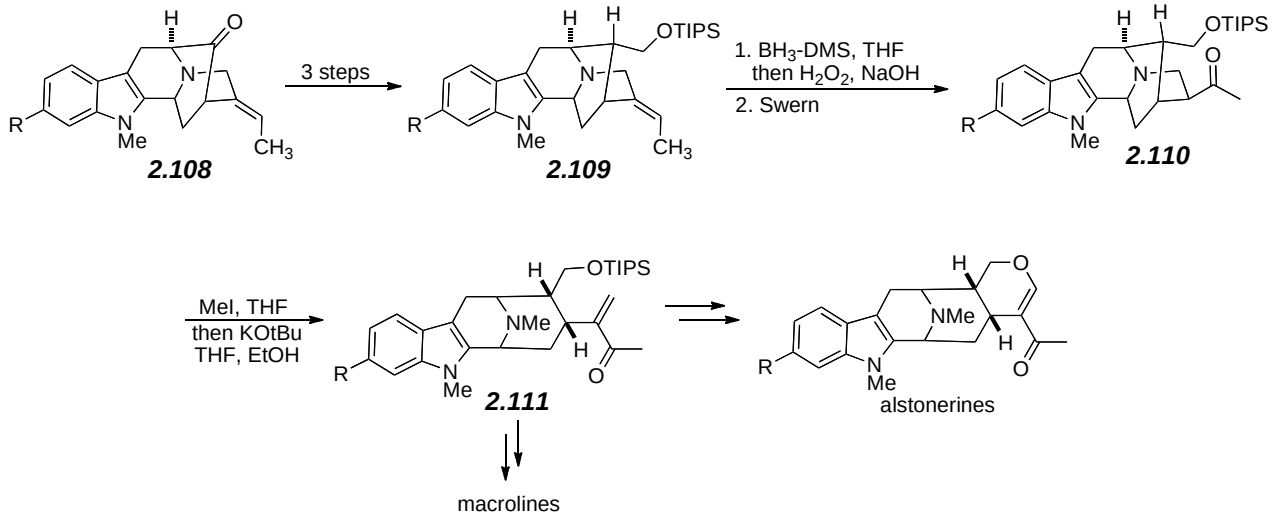
Scheme 2.20: Synthesis of vellosimine.

Beginning with indole substituted tryptophan derivatives and proceeding through an identical series of synthetic manipulations, indole substituted versions of ketone **2.79** have been be synthesized. This allowed for the development of second generation syntheses of alkaloid G and talcarpine as well as the rapid synthesis of literally dozens of additional natural products with high structural diversity (**Scheme 2.21**).[63]



Scheme 2.21: Syntheses of natural products from indole substituted ketone **2.79**.

The latest major synthetic branch point exploited by Cook and coworkers is illustrated in **Scheme 2.22**.[64] Homologation of indole substituted analogues of ketone **2.107** (generic structure **2.108**) by the same method used to produce vellosiminefollowed by reduction and protection produced silyl ethers with general structure **2.109**. Hydroboration and oxidation of the trisubstituted olefin functionality of these compounds gave ketone **2.110**. Nitrogen quaternization with methyl iodide resulted in β-elimination producing tetracycle **2.111**, which could be easily manipulated to produce either the macroline or alstonerine frameworks. Several macroline and alstonerine natural products have been synthesized using this methodology.



Scheme 2.22: Access to the macroline and alstonerine skeletons.

The chief strength of Cook's general strategy for the synthesis of STAs is the ability to convert advanced intermediates into structurally divergent classes of natural products. The efficient, diastereoselective, and large scale synthesis (>100 gram) of ketone **2.79** provides a synthetic intermediate containing enough structural complexity to synthesize any of the target natural products but does not contain structural features only present in some of the targets, which might complicate syntheses of targets not containing such features. Ketone **2.79** contains the indole and pyran heterocycles present in all of the target natural products, with the appropriate stereochemistry installed but does not contain structural features such as pyran and pyridine rings present in some but not all of the target natural products. As synthetic branching occurs and structural complexity is added, it is done in a manner that maximizes the number of natural product targets accessible per synthetic branch. This allows for late stage synthetic branching, minimizing the overall number of synthetic manipulations that must be developed and optimized.

2.3: Chapter Summary

Some of the major synthetic challenges of the secoiridoids and alkaloids derived from secologanin such as the synthesis of many of the glycosilated natural products including the total synthesis of secologanin glucoside itself have yet to be overcome. However, most of the major synthetic challenges of these natural products such as the control of stereochemistry and the installation of various types of functionality have been addressed with a great degree of success. The field of secoiridoid and secologanin alkaloid synthesis has matured to the point that major impacts can be most efficiently made through the pursuit of divergent synthetic strategies that result in the production of The remainder of this dissertation will be dedicated to our efforts to develop a divergent synthetic strategy for the production of secologanin derived natural products.

Chapter 3: A Divergent Strategy for the Synthesis of Secoiridoids and Secologanin Tryptamine Alkaloids

3.1: General Strategy

3.1.1: Goals for this Research Project

The wide variety of biological activities displayed by secoiridoids and STAs outlined in previous chapters combined with the amazing structural diversity of these compounds has initiated a great deal of interest in the total synthesis of scores of secoiridoids and STAs. Total synthesis is the only tool available to the scientific community capable of simultaneously definitively elucidating the structure of these compounds, investigating their complex biosynthesis, and establishing and understanding their biological activities. A single, well-designed synthetic pathway can unambiguously establish absolute stereochemisty and other structural features, produce isotopically labeled intermediates for biosynthetic studies, and produce unnatural analogues critical for establishing structure-activity relationships.

Previous synthetic strategies such as those outlined in previous chapters have concentrated on the synthesis of a small number of closely structurally related natural products. The broadest of these strategies transcend the category of research projects and are better classified as research programs involving decades of study by several successive "generations" of researchers. Although these previous general synthetic strategies have been very fruitful, we believe that a very broad, divergent synthetic strategy can be developed to more efficiently access the thousands of structurally disperate secoiridoids, STAs, and other related compounds.

The chief goal of this research project is the development of a divergent synthetic strategy, which will allow rapid synthetic access to secoiridoids, STAs, unnatural secoiridoid and STA analogues, and isotopically labeled intermediates. This is best accomplished through the development of a late-stage synthetic intermediate, which can be produced asymmetrically and on a large scale. This intermediate should contain independantly manipulable functionality and as much structural complexity as possible, requiring a minimum amount of manipulation to produce the various synthetic targets. This will allow the intermediate to serve as a synthetic branch point. A scalable synthesis of this intermediate will provide a bulk supply of molecular complexity, vastly simplifying the syntheses of target natural products.

Once an appropriate intermediate has been designed and synthesized on large scale, the next project goal is to use this intermediate to synthesize natural products. Our initial efforts focused on two relatively simple and structrally dissimilar natural products in order to demostrate the scope of structural diversity accessible via this strategy.

3.1.2: Designing a Synthetic Intermediate

We looked to nature for inspiration during the design of our planned synthetic intermediate. More than 4 billion years of evolution have produced a complex and enzyme-intensive divergent synthesis of the secoiridoids and STAs, which serves as an excellent model for artificial synthetic methods. As illustrated in previous chapters, secologanin glucoside (**Figure 3.1**) serves as the biosynthetic branchpoint utilized by nature to synthesize all of the secoiridoids and STAs. The compactly functionalized secologanin glucoside most closely matches our requirements for a synthetic intermediate

in that it contains the majority of the molecular complexity required for the rapid production of natural products while remaining general enough to allow access to several disperate classes of compounds. Additionally, the various functionalities are orthogonally functionalized allowing them to be independently manipulated.

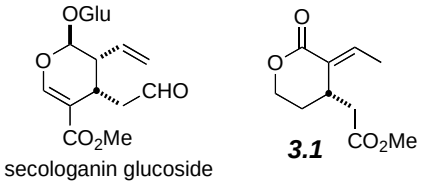


Figure 3.1: Secologanin glucoside and lactone **3.1**.

We chose lactone **3.1** as our ideal synthetic intermediate (**Figure 3.1**) since it contains the requisite stereochemistry, most of the carbon framework, and orthogonal functionality necessary to install the secoiridoid-derived portion of all of our targets without containing superfluous functionality not present in all of our synthetic targets. Initial attempts to asymmetrically synthesize lactone **3.1** proved to be more challenging than anticipated and will be outlined in the next chapter. We chose to develop a racemic synthesis of lactone **3.1** in order to allow the simultaneous investigation of the asymmetric synthesis of lactone **3.1** and the development of late-stage natural product synthetic strategies.

3.1.3: Synthesis of Racemic Lactone 3.1

Our initial retrosythetic analysis (**Figure 3.2**) involved forming the lactone ring of lactone **3.1** via a key intramolecular Michael cyclisation of α,β-unsaturated ester **3.3**

followed by reduction and elimination of the ketone functionality of the resulting β-ketoester (**3.2**) in order to install the olefin functionality. The uncyclized β-ketoester intermediate **3.3** would be accessed via acylation of alcohol **3.4**, which could be synthesized by the Horner-Wadsword-Emmons (HWE) olefination of a protected β-hydroxyaldehyde (**3.5**) utilizing commercially available trimethyl phosphonoacetate followed by silyl ether deprotection. Aldehyde (**3.5**) was envisioned to arise from the monoprotection and oxidation of 1,3-propanediol.

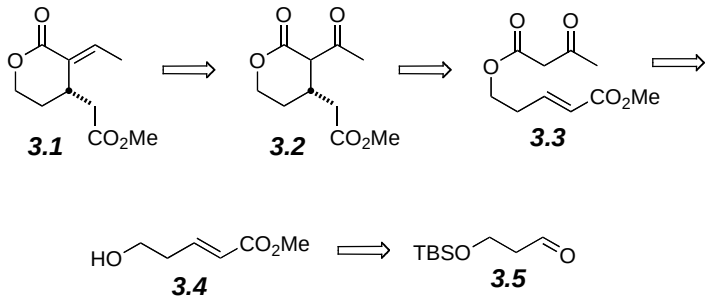
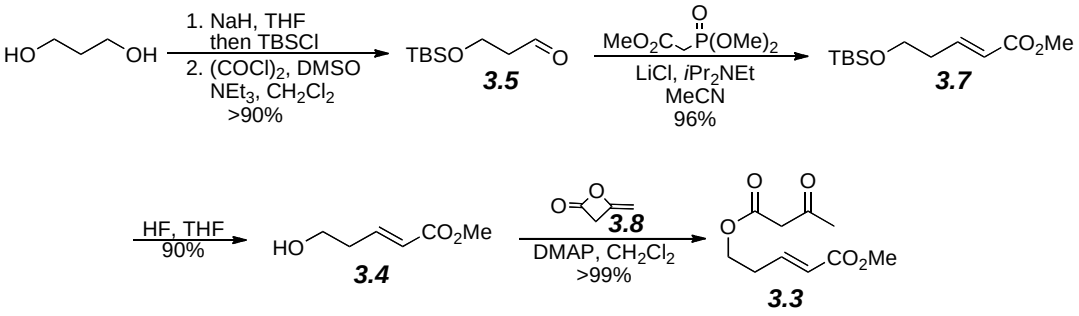


Figure 3.1: Initial retrosynthetic analysis of lactone **3.1**.

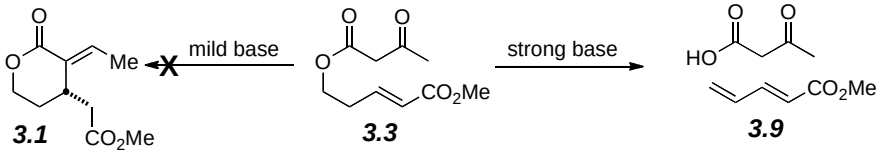
The synthesis of linear intermediate **3.3** (**Scheme 3.1**) began utilizing a method reported by Schaus and coworkers[65] for the synthesis of aldehyde **3.5**. Monoprotection of 1,3-propanediol as the corresponding TBS ether followed by Swern oxidation provided aldehyde **3.5** in excellent yield and on greater than 100g scale after brief optimization efforts. HWE olefination of aldehyde **3.5** proceeded smoothly only under Masamune-Roush conditions, which prevented side reactions and starting material degradation observed when harsher conditions involving stronger bases (KO*t*Bu, LiHMDS, etc.) were employed. Silyl ether deprotection gave alcohol **3.4** which was quantitatively acylated by

treatment with diketene (**3.8**) and DMAP in cold CH_2Cl_2 producing linear intermediate **3.3** in good overall yield (>78% from 1,3-propanediol).



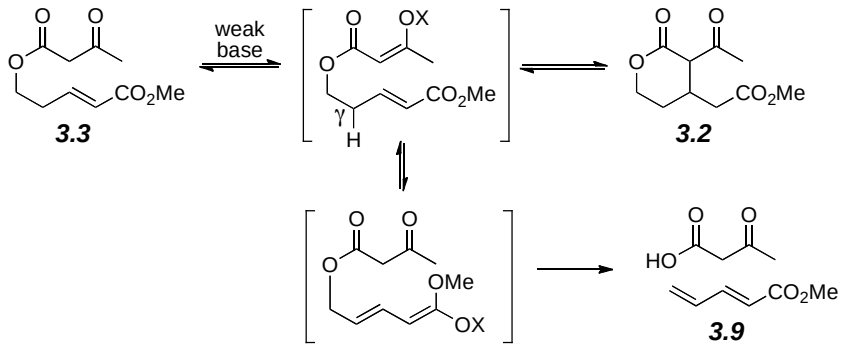
Scheme 3.1: Synthesis of linear intermediate **3.3**.

With linear intermediate **3.3** in hand, we began attempting the key Michael cyclization to form the lactone ring of lactone **3.1** (**Scheme 3.2**). Treatment of linear intermediate **3.3** with strong bases such as LDA, LiHMDS, or KO*t*Bu resulted in immediate and quantitative elimination of the β-ketoacetate functionality to produce diene **3.9**. Treatment of linear intermediate **3.3** with milder bases such as NEt_3, K_2CO_3, Cs_2CO_3, or pyridine at ambient temperature returned only unaltered starting material and upon warming gave only the previously observed elimination product.

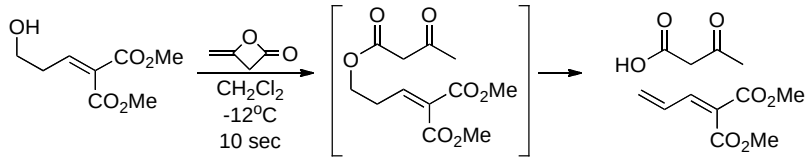


Scheme 3.2: Base initiated elimination of linear intermediate **3.3**.

Our inability to cyclize linear intermediate **3.3** must be due to the fact that the cyclization of the nucleophilic portion of **3.3** onto the α,β-unsaturated ester Michael acceptor was slower than the observed elimination (**Scheme 3.3**) or that the cyclization step is reversible, allowing a steady state concentration of the intermediate to irreversibly eliminate. We reasoned that attempting to force the Michael cyclization by increasing the electrophilicity of the Michael acceptor portion of the molecule would be unlikely to adequately address this problem as an increase in the electrophilicity of the α,β-unsaturated ester in order to accelerate Michael cyclization would likely also increase the rate of β-ketoacetate elimination by increasing the acidity of the protons on the γ-carbon. This hypothesis was supported by observations made during our attempts to perform an asymmetric Michael cyclization. This data will be discussed in detail in the following chapter and is briefly outlined in (**Scheme 3.4**). This left the adjustment of the nucleophilic portion of the cyclization substrate.



Scheme 3.3: Evaluation of the failed Michael cyclization.



Scheme 3.4: Observed elimination of cyclization substrate with additional EWG.

We recognized two separate concerns about the β-ketoester nucleophile that were prudent to consider when choosing a new nucleophilic portion. First was the relatively high acidity of the β-ketoester α-carbon, due to its two adjacent carbonyl electron withdrawing groups. This acidity meant that weak bases could deprotonate this functionality faster than the deprotonation of the Michael acceptor γ-carbon and it was unlikely that the desired enolate was not being formed. In order to retain this property, any modified enolate nucleophiles should be similarly easy to deprotonate.

The second concern involves the electronics of the nucleophile. Because the β-ketoester anion is delocalized across six atoms, its relative nucleophilicity is somewhat diminished. In addition, the geometry of this electron rich π-system may not be able to attain efficient overlap with the electrophilic olefin π-system. We hypothesized that a nucleophilic acetate bearing an exclusively inductive electron withdrawing group may be more competent than the β-ketoester nucleophile.

We decided to substitute a phosphonoacetate ester for the β-ketoacetate portion of the linear cyclization substrate (**Figure 3.2**). This change would require a modified synthetic plan in order to install the desired exocyclic olefin. This functionality would now derive from cyclized phosphonate lactone (**3.10**), which could be transformed into the desired product (**3.1**) via HWE olefination with acetaldehyde. The cyclization

substrate (**3.11**) would be synthesized from alcohol **3.4** by a similar process that provided the β-ketoester cyclization substrate.

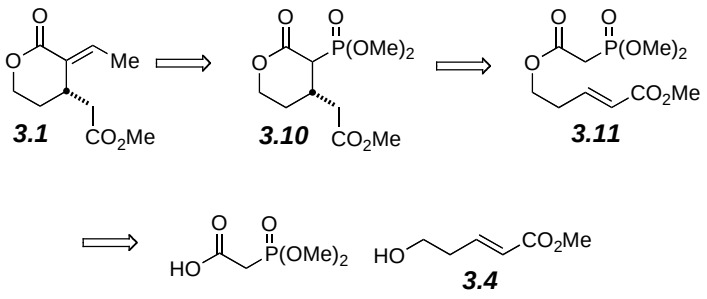
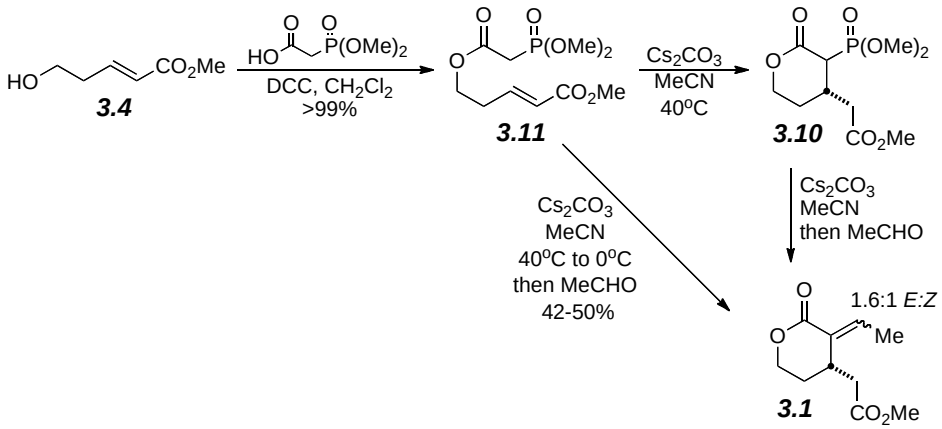


Figure 3.2: An improved retrosynthesis of lactone **3.1**.

As illustrated in **Scheme 3.5**, alcohol **3.4** was synthesized as previously described and quantitatively acylated with dimethyl phosphonoacetate (produced via hydrolysis of trimethyl phosphonoacetate) to yield cyclization precursor **3.11**. After several cyclization attempts involving amine and inorganic bases, we found that treatment of cyclization substrate **3.11** with Cs_2CO_3 in warm MeCN gave the desired cyclization product phosphonate **3.10**. Treatment of the cyclized phosphonate **3.10** with catalytic Cs_2CO_3 in MeCN at ambient temperature followed by the addition of freshly distilled acetaldehyde provided lactone **3.1** as a 1.6 : 1 mixture of *E/Z* isomers. Further optimization allowed for the combination of the cyclization and olefination steps to give a tandem Michael cyclization-HWE olefination, which both decreased the overall step-count and improved the yield of this manipulation to acceptable levels.



Scheme 3.5: Synthesis of lactone **3.1** via tandem Michael cyclization-HWE olefination.

With lactone **3.1** in hand we turned our attention to the synthesis of natural products from this key intermediate.

3.2: The Synthesis of (+/-) Oleocanthal

The aglycone of deacetoxy-oleuropein, later renamed oleocanthal, was first isolated from extra virgin olive oil by Montedoro and coworkers[66] alongside three other previously unknown phenolic secoiridoids (**3.12**-**3.14**) as well as the previously isolated and described ligstroside and oleuropein (**Figure 3.3**). This class of natural products has drawn significant attention due to their presumed role as natural antioxidants, which, it has been suggested, grants them anti-cancer activity[67] and may account for the high degree of oxidative stability of extra virgin olive oils. It has been also been proposed that these compounds may find use as treatments for neurodegenerative disorders such as Alzheimer's disease[68]. These phenolic compounds also are thought to embue extra virgin with many of its organoleptic characteristics such as astringency, bitterness, and pungency[69].

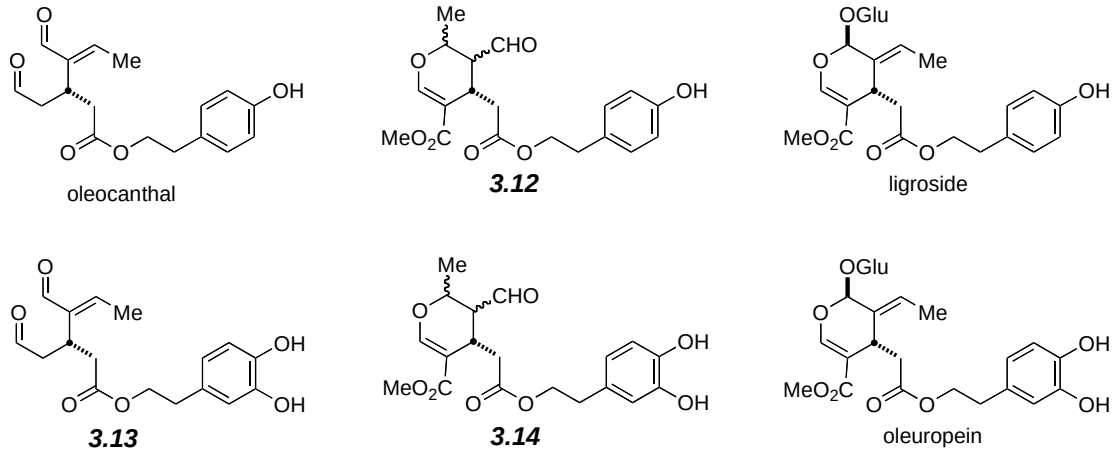


Figure 3.3: Phenolic isolates of extra virgin olive oil.

Oleocanthal has been specifically identified by Smith and coworkers[70] as the source of the "back of the throat irritant (burning) sensation" present in high quality extra virgin olive oil. The Smith syntheses of oleocanthal outlined in the previous chapter also helped establish the ability of oleocanthal to inhibit cyclooxygenases 1 and 2 (COX-1 and COX-2), which are critical enzymes in the tissue inflamation pathway. In fact, the inhibitory concentrations of oleocanthal for COX-1 and COX-2 were nearly identical to those of the popular non-steroidal anti-inflamatory (NSAID) drug ibuprofen. This fact combined with the known cardiovascular and anti-cancer benefits of other COX inhibitors[71], the prevalence of extra virgin olive oil in the so called Mediteranean diet[72], and the observed health benefits of the Mediteranean diet[73] have lead Smith and coworkers to hypothesize a causal relationship between the observed health benefits of the Mediteranean diet and the consumption of oleocanthal. These assertions have been challenged[74], however, and remain an interesting area of debate.

It is this combination of interesting biological activity along with the compact arrangement of sensitive functionality that make oleocanthal an excellent synthetic target with which to demonstrate our ability to rapidly synthesize challenging secoiridoid natural products from lactone **3.1**. Our retrosynthetic analysis (**Figure 3.4**) envisioned a late-stage formation of the sensitive dialdehyde functionality of oleocanthal via reduction and oxidation of a fully functionalized lactone, which could be readily obtained via transesterification of the methyl ester of lactone **3.1** with a phenol protected version of commercially available 4-(2-hydroxyethyl)phenol.

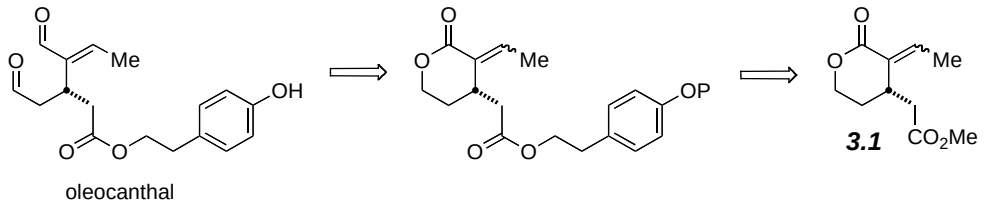
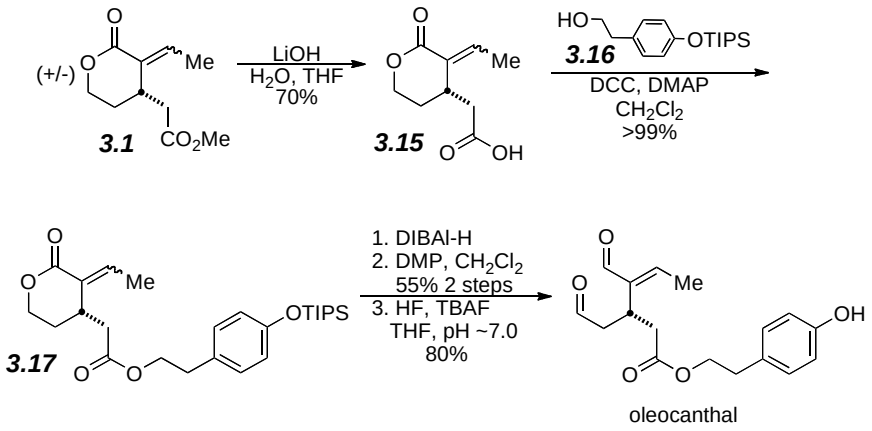


Figure 3.4: Retrosynthetic analysis of oleocanthal.

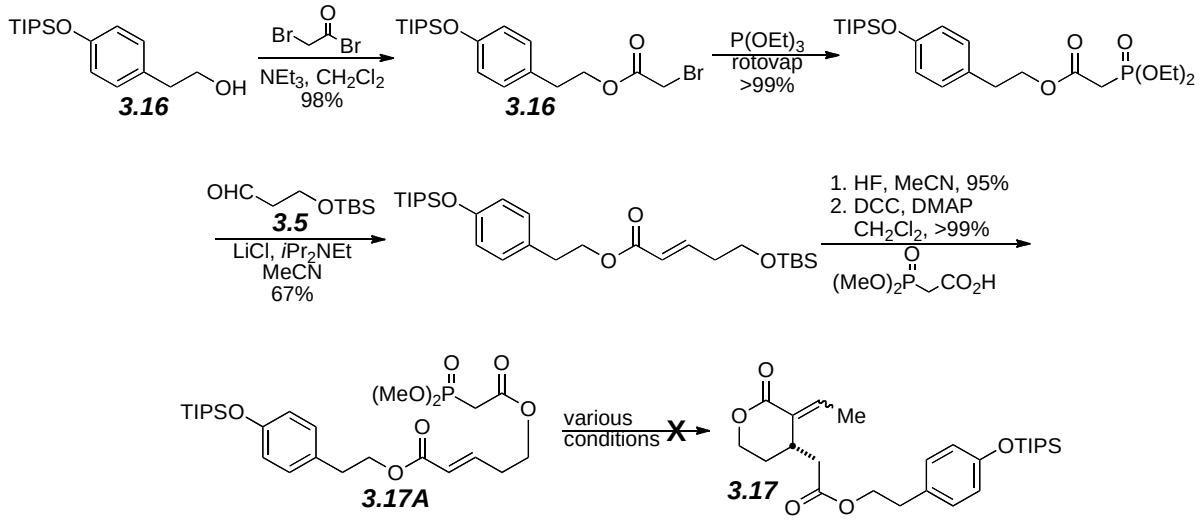
We began the synthesis of oleocanthal[75] (**Scheme 3.6**) with the selective hydrolysis of the methyl ester of lactone **3.1** to give acid **3.15**. This was followed by quantitative esterification with alcohol **3.16**, which was obtained in a single step and in quantitative yield via mono-protection of 4-(2-hydroxyethyl)phenol. The lactone carbonyl of compound **3.17** was then selectively reduced with DIBAl-H to yield a relatively unstable lactol, which spontaneously isomerized to exclusively provide the desired *E* olefin. Immediate oxidation with Dess-Martin periodinane and subsequent *p*H-neutral TIPS ether deprotection provided (+/-)-oleocanthal in good overall yield.



Scheme 3.6: Synthesis of oleocanthal from lactone **3.1**.

The synthesis of oleocanthal from lactone **3.1** was first accomplished in less than one month. This fact combined with our ability to rapidly produce lactone **3.1** from inexpensive starting materials and on a multigram scale is an excellent demonstration of the utility and practicality of this synthetic strategy.

In order to improve the efficiency of this synthesis and as a test of the limitations of our tandem Michael cyclization-HWE olefination, we attempted a shortened synthesis of lactone **3.17** via cyclization substrate **3.17A**, which bears a prefunctionalized ester carbinol (**Scheme 3.6A**). This would obviate the need for the hydrolysis and esterification of lactone **3.1**. Unfortunately, our highly functionalized cyclization substrate (**3.17A**) did not cyclize, presumably due to its vastly increased steric bulk.



Scheme 3.6A: Attempted improvement of lactone **3.17**.

3.3: The Synthesis of (+/-) Geissoschizol

3.3.1: Initial Synthetic Work

The next goal for this project was to demonstrate that our strategy was broadly applicable and capable of synthesizing structurally diverse natural product targets. To this end we chose geissoschizol as at target due to the fact that it is structurally very different from oleocanthal and is relatively structurally simple in comparison to other STAs. Our initial retrosynthesis (**Figure 3.5**) forms the final geissoschizol tetracycle via D ring closure. We hoped that ring closure via reductive amination would not only produce the desired framework but would additionally give the correct olefin geometry. This was predicted since the pictured intermediate iminium ions that our reductive amination must pass through is very similar to the iminium ions whose reduction gave the correct olefin geometry during many of the geissoschizine syntheses described in the previous chapter. As pictured, this selectivity takes advantage of allylic 1,3-strain in the undesired intermediate to force the production of the desired olefin geometry. The

requisite aldehyde would be produced by a method similar method to that described in our oleocanthal synthesis, namely by reduction of a lactone, fused to tryptamine via esterification and Bischler-Napieralski cyclization.

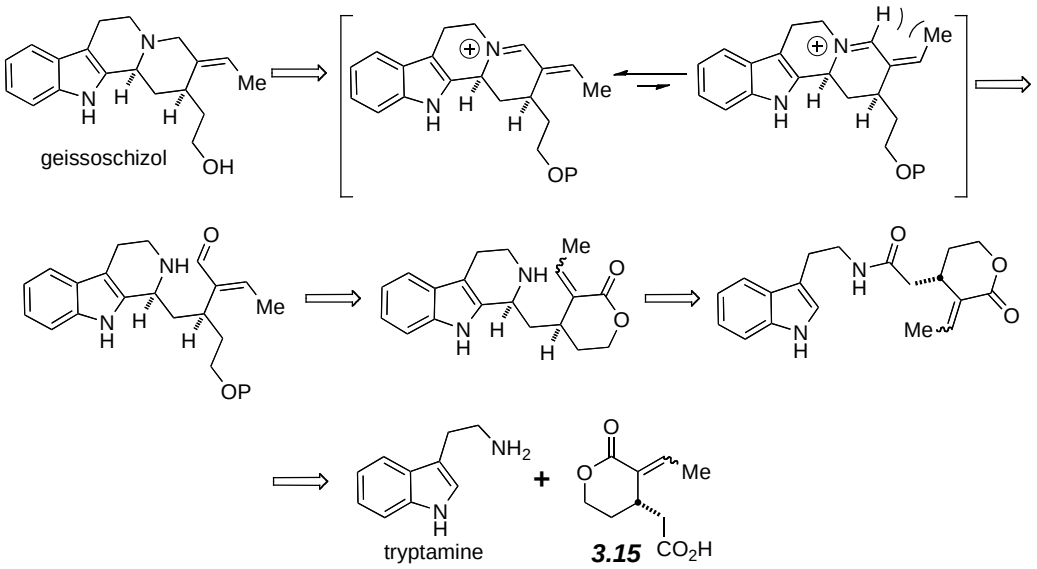
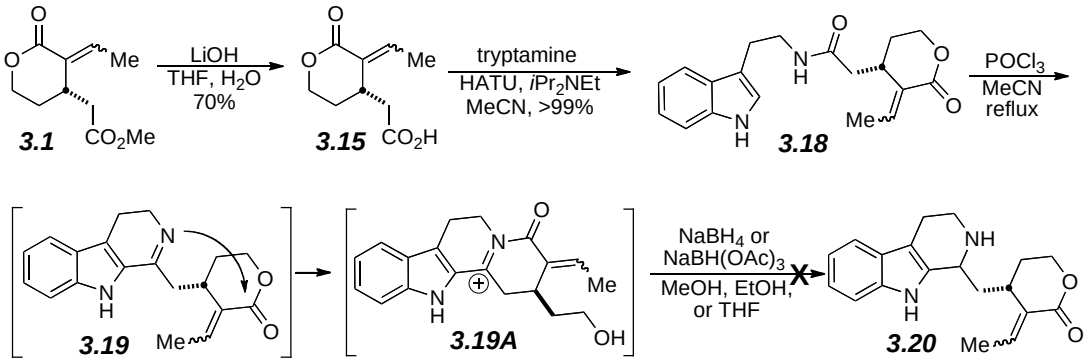


Figure 3.5: Initial geissoschizol retrosynthesis.

We began the synthesis of geissoschizol with the selective hydrolysis of the methyl ester of lactone **3.1** to give acid **3.15** and subsequent formation of the tryptamine amide via HATU coupling to produce amide **3.18** in good yield (**Scheme 3.7**). Treatment of this amide with traditional Bischler-Napieralski cyclization conditions ($POCl_3$, MeCN, reflux) produced a mixture of at least two products, which appeared to be cyclized as evidenced by the disappearance of the indole C2 proton (determined by ^{1}HNMR) as well as the disappearance of the amide carbonyl (determined by IR). This and other evidence lead us to believe that these products were likely the Schiff bases represented by structure **3.19**. Purification or separation of these products was made impossible by their instability to silica gel or air. Treatment of this mixture with $NaBH_4$ or $NaBH(OAc)_3$ in

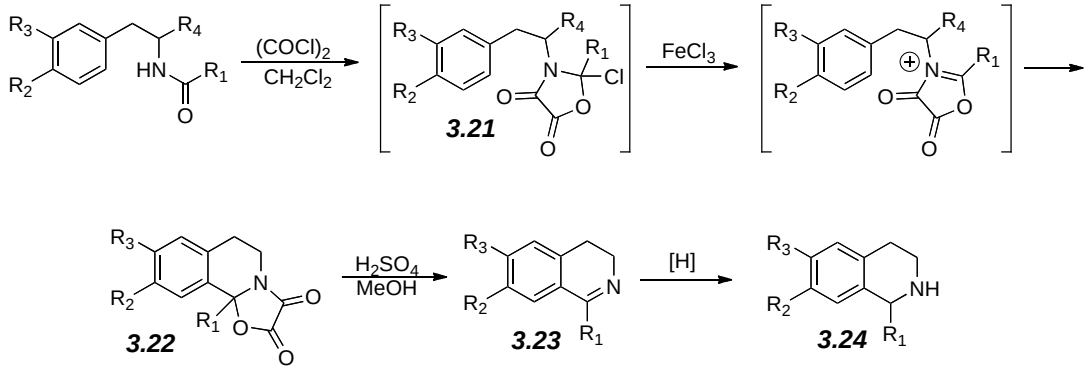
ethanol, methanol, or THF resulted in the production of a complex mixture of decomposition products. We suspected that the reactivity of the intermediate Schiff base **3.19** to produce the likely unstable N-acyl iminium ion **3.19A** may have accounted for the observed decomposition. The desired product mixture **3.20** was never observed.



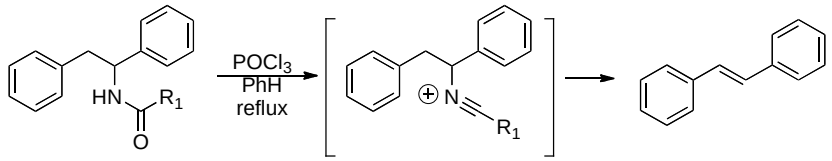
Scheme 3.7: Synthesis of amide **3.18** and attempted Bischler-Napieralski cyclization.

3.3.2: Application of the Modified Bischleri-Napieralski Reaction

In 1991 Reider and coworkers reported[76] a modified Bischler-Napieralski cyclization (**Scheme 3.8**), which they developed as a response to the undesired elimination of nitrilium intermediates that occur during the synthesis of 3-arylisoquinolines (**Scheme 3.9**). The modifications made with this step-wise procedure include the substitution of oxalyl chloride for phosphorous oxychloride. This results in the formation of a 2-chlorooxazolidine-4,5-dione intermediate (**3.21**). Treatment of this cyclic intermediate with a Lewis acid such as $FeCl_3$ results in electrophilic aromatic substitution to give an isolatable tricycle of type **3.22**. Acidic methanol is then used to solvolyze the oxazolidine-4,5-dione heterocycle and the resulting aryl imine (**3.23**) is reduced to yield the desired amine product (**3.24**).



Scheme 3.8: Modified Bischler-Napieralski cyclization.



Scheme 3.9: Observed nitrilium elimination.

We hoped that using the Reider modified Bischler-Napieralski conditions would produce an oxazolidine-4,5-dione intermediate (rather than the more reactive Schiff base intermediate whose nucleophilicity we believed may have been the cause of the product decomposition (**Figure 3.6**). We hoped that treatment of this oxazolidine-4,5-dione with reducing conditions would result in the production of the desired amine product, thus avoiding the reactive Schiff base intermediate.

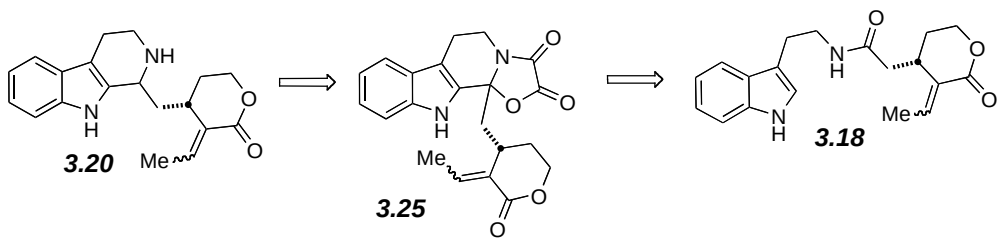
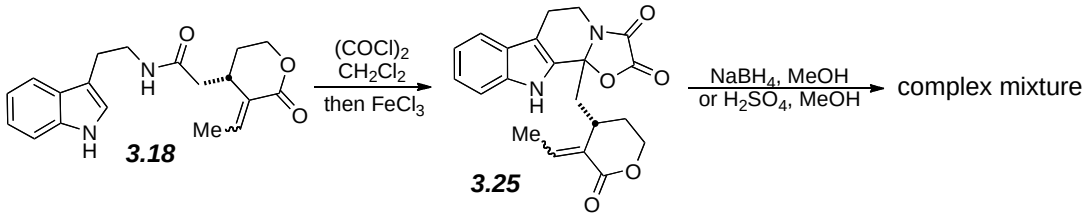


Figure 3.6: Planned application of the Reider modified Bischler-Napieralski conditions.

Treatment of amide **3.18** with oxalyl chloride followed by $FeCl_3$ produced a mixture of four products corresponding to the various combinations of *E/Z* olefin geometries and oxazolidine-4,5-dione epimers (**3.25**) (**Scheme 3.10**). Unfortunately, acid catalyzed solvolysis of these products resulted in the production of a product identical to that produced under traditional Bischler-Napieralski conditions, which rapidly decomposed. Unfortunately, our planned reductive solvolysis gave similar results raising the question of whether the desired amine product (**3.20**) was itself stable.



Scheme 3.10: Application of the Reider modified Bischler-Napieralski conditions.

3.3.3: Redesigned Synthetic Plan

As an alternative to the above described synthetic sequence we developed a synthetic plan, which involved a reversal of the order of bond formation utilized in the above sequence. By first linking tryptamine with the secoiridoid portion of the molecule

via reductive amination rather than by amidation we hoped to avoid the reactive Schiff base and secondary amine compounds that we believed to be the source of earlier problems. **Figure 3.7** illustrates the retrosynthetic analysis of this new plan. We planned to synthesize the geissoschizol tetracycle via Bischler-Napieralski cyclization of lactam **3.26**. By moving this cyclization to the end of the synthesis we could not only avoid the unstable Schiff base and secondary amine intermediates but it should also allow better control of the newly formed stereogenic center. This prediction extrapolates the results reported by Martin and coworkers[77] who observed complete diastereoselectivity during a similar cyclization. Lactam **3.26** could be synthesized though the cyclization of the allyl amine nitrogen of **3.27** onto the methyl ester sidechain. This allyl amine would result from the reductive amination of tryptamine with the aldehyde produced by selective reduction of lactone **3.1**.

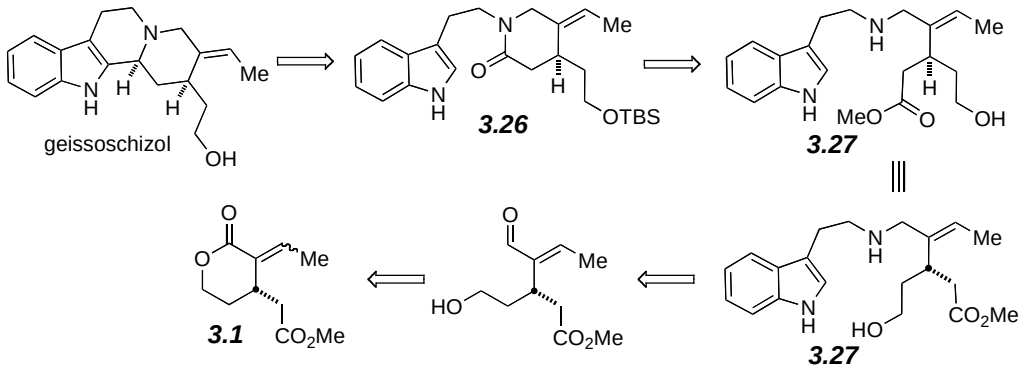
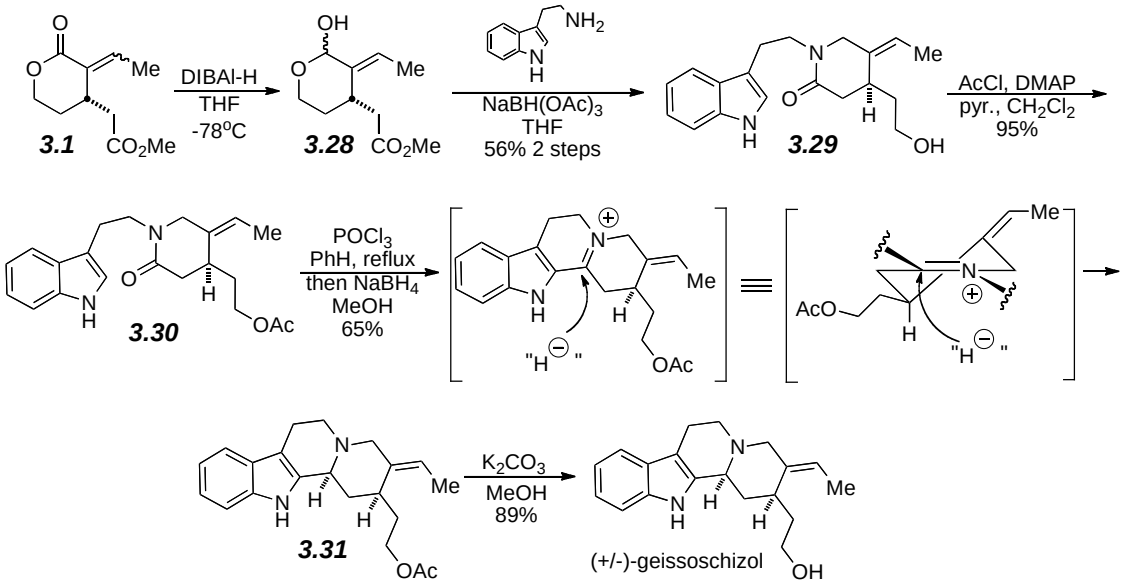


Figure 3.7: Revised retrosynthesis of (+/-)-geissoschizol.

The forward synthesis of (+/-)-geissoschizol (**Scheme 3.11**) proceeded with the selective reduction of the lactone carbonyl of lactone **3.1** with DIBAl-H in cold THF to yield lactol **3.28** as an unstable mixture of isomers that was immediately carried forward.

The reductive amination of crude lactol **3.28** with tryptamine proceeded smoothly after minor reaction optimization. The expected allyl amine product (**3.27**) was not observed, rather, following reductive amination the lactam ring closed spontaneously to yield lactam **3.29** as a single isomer. The alcohol functionality of lactam **3.29** was protected as the TBS ether and was then treated with traditional Bischler-Napieralski conditions ($POCl_3$, PhH, reflux). Unfortunately, these highly acidic conditions resulted in TBS deprotection and reaction of the resulting primary alcohol to produce a mixture of several undesired products. By replacing the TBS ether protecting group with an acetate ester **3.30** we were able to avoid this undesired reactivity. Bischler-Napieralski cyclization produced tetracycle **3.31** as a single isomer. This selectivity is rationalized by the pictured iminium intermediate. The reducing reagent preferentially approaches from the pictured face of the iminium ion in order to access the thermodynamically favorable chair-like transition state. The acetate protecting group was then removed to produce (+/-)-geissoschizol.



Scheme 3.11: Synthesis of (+/-)-geissoschizol

3.4: The Synthesis of (+/-)-Corynantheidol

We next turned our attention to the reduced corynantheine alkaloids (**Figure 3.8**) corynantheidol and dihydrocorynantheol, which, although they appear to be directly accessible via reduction of geissoschizol, must be tackled independently if any product selectivity is desired. A comprehensive study of the catalytic hydrogenation of (+/-)-geissoschizol and its epimers performed by Lounasmaa and coworkers[78] revealed no appreciable product selectivity.

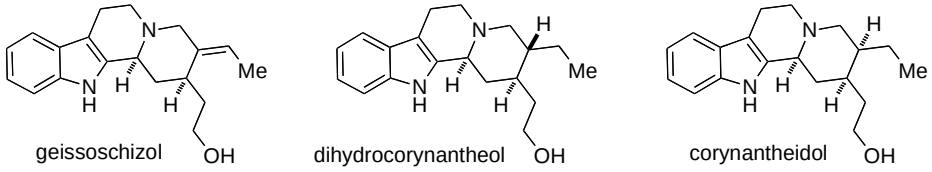


Figure 3.8: Three corynantheine alkaloids.

Our plan for the selective synthesis of these alkaloids involves setting the stereogenic center of the ethyl group sidechain at an early stage followed by a product assembly closely resembling our above described geissoschizol synthesis (**Figure 3.9**). Lactone **3.1** would again serve as our synthetic branch point since, depending on the method employed, it can be preferentially reduced to provide either the *cis* or the *trans* reduction product. We found that hydrogenation of lactone **3.1** proceeded in a facially selective manner, delivering hydrogen from the less sterically encumbered face, producing the *cis* product. Conjugate reduction of lactone **3.1** proceeds through a lactone enolate giving the more thermodynamically stable *trans* product.

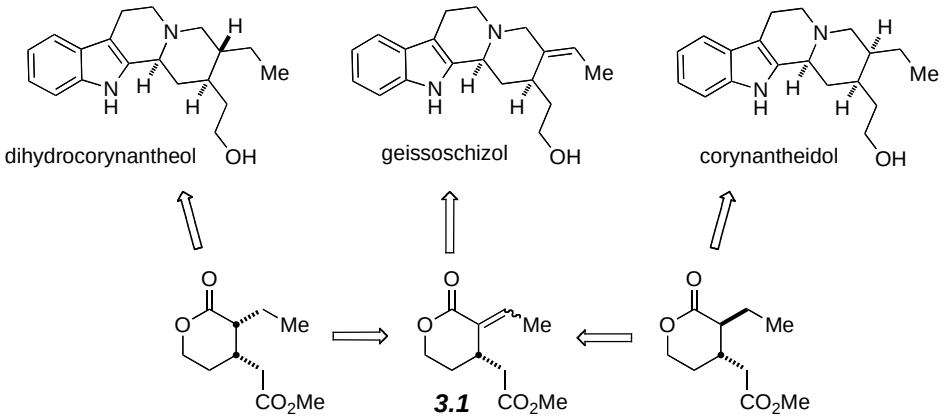
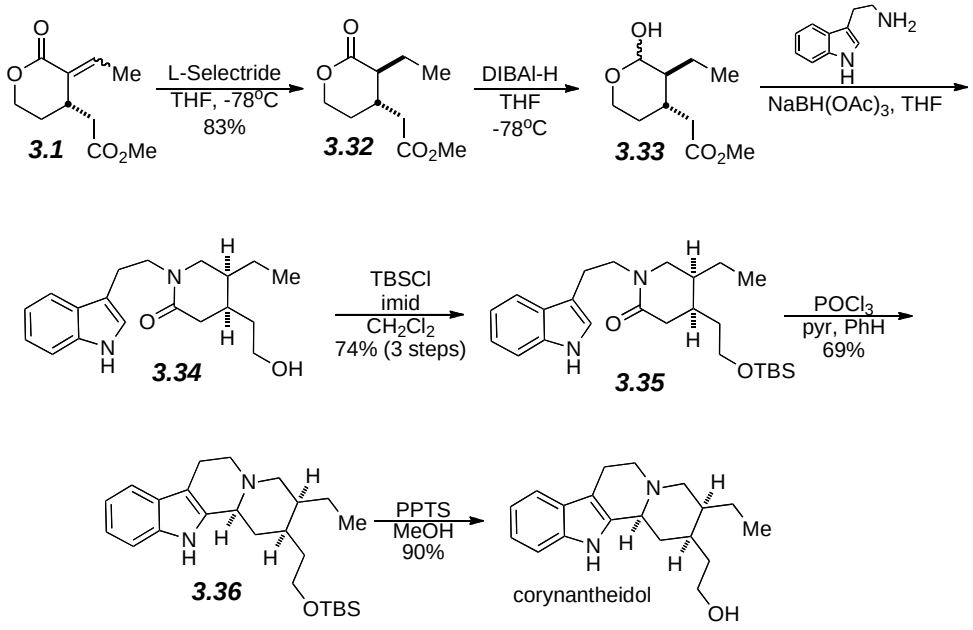


Figure 3.9: Lactone **3.1** as a synthetic branch point for the synthesis of alkaloids.

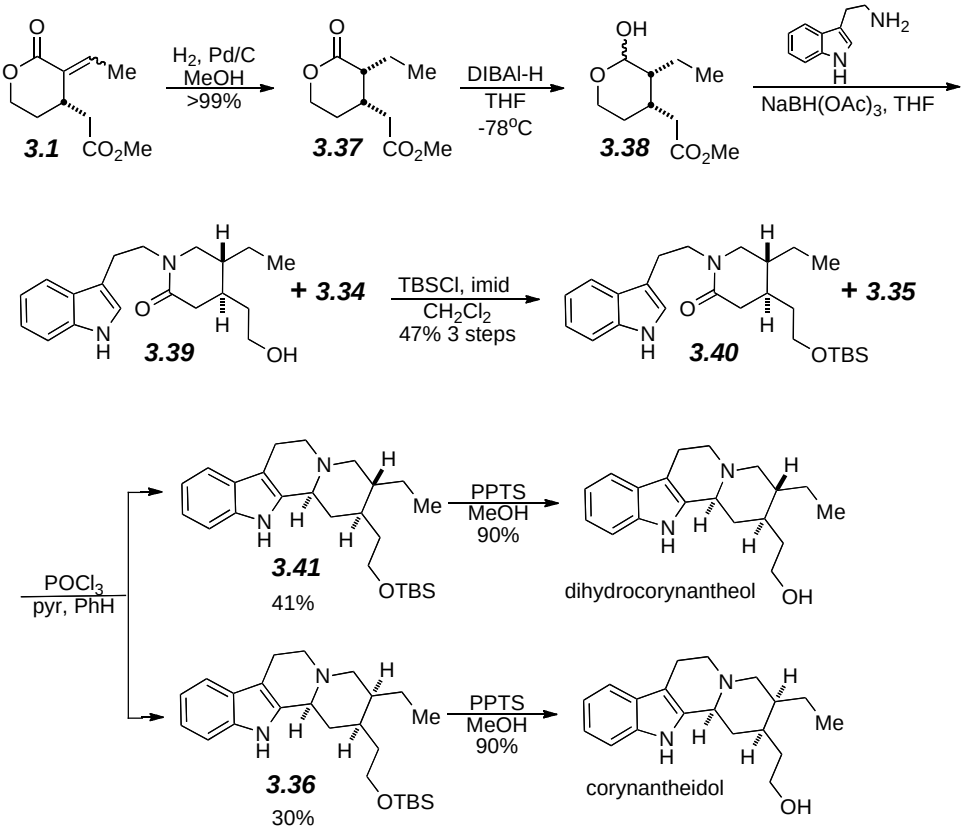
The synthesis of (+/-)-corynantheidol (**Scheme 3.12**) proceeded completely as expected. Conjugate reduction of lactone **3.1** gave the expected *trans* lactone **3.32**, which was reduced to give lactol **3.33**. This crude lactol was then reductively aminated with tryptamine to give lactam **3.34** as a single isomer. Protection of the free hydroxyl group as the TBS ether followed by Bischler-Napieralski cyclization gave the protected natural product (**3.36**) in good yield over three steps. This TBS ether was deprotected to give (+/-)-corynantheidol in good overall yield.



Scheme 3.12: Synthesis of (+/-)-corynantheidol.

3.5: The Synthesis of (+/-)-Dihydrocorynantheol

The synthesis of (+/-)-dihydrocorynantheol (**Scheme 3.13**) commenced with the hydrogenation of lactone **3.1** to give exclusively the desired *cis* isomer (**3.37**). This reduction was followed by selective lactone reduction to produce an unstable mixture of lactol and aldehyde isomers (**3.38**). Reductive amination of this crude mixture with tryptamine gave an inseparable mixture of lactams **3.39** and its undesired ethyl side chain epimer **3.34** (an intermediate in the synthesis of corynantheidol). This mixture was protected as the TBS ether mixture (**3.40** and **3.35**) and cyclized under our previously described basic Bischler-Napieralski conditions to give the now easily separable tetracycles **3.41** and **3.36**. Independent deprotection of these TBS ethers gave (+/-)-dihydrocorynantheol and (+/-)-corynantheidol respectively.

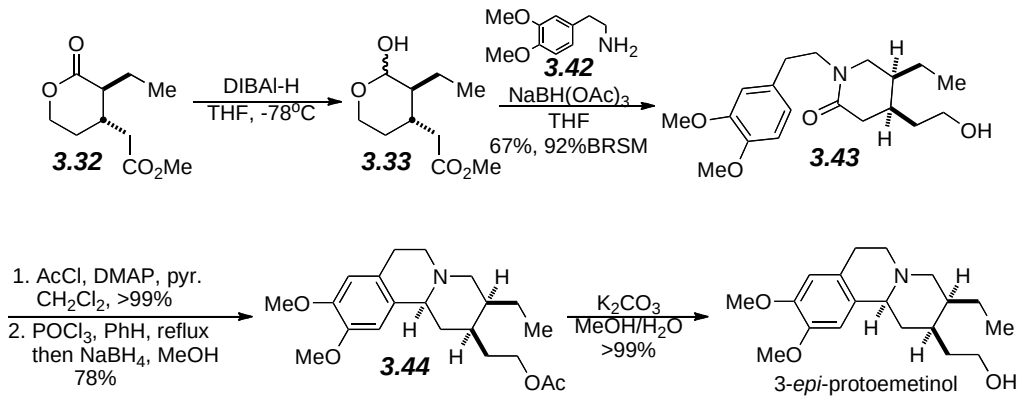


Scheme 3.13: Synthesis of (+/-)-dihydrocorynantheol.

3.6: The Synthesis of (+/-)-3-*epi*-protoemetinol

With our control of the secoiridoid portion of the secologanin-derived alkaloids established, we began our investigation of the secoiridoid alkaloids deriving from dopamine. Fortunately very little modification to our developed procedures was necessary for this purpose. Thus, substituting 2-(3,4-dimethoxyphenyl)ethanamine (**3.42**) for tryptamine and adjusting Bischler-Napieralski reaction temperature to compensate for a slightly less reactive aromatic nucleophile, we could adapt our above described corynantheidol synthesis in order to produce 3-*epi*-protoemetinol. As illustrated in **Scheme 3.14**, this synthesis began with the reduction of lactone **3.32** and subsequent reductive amination of lactol mixture **3.33** with amine **3.42** to give lactam **3.43** as a single

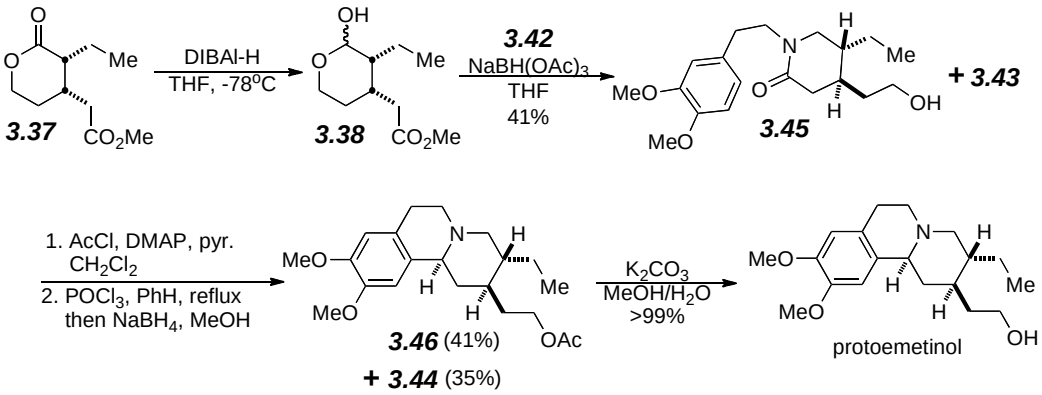
isomer. Because this new aromatic nucleophile had a decreased nucleophilicity relative to indole, harsher Bischler-Napieralski conditions would need to be employed in order to produce the desired tricycle. This meant that the TBS protecting group utilized in our synthesis of corynantheidol and dihydrocorynantheol would likely not survive the cyclization conditions so we decided to exchange this protecting group for an acetate ester. Installation of the acetate followed by Bischler-Napieralski cyclization in refluxing benzene produced tricycle **3.44** as a single isomer and in good yield. Quantitative acetate deprotection produced 3-*epi*-protoemetinol.



Scheme 3.14: Synthesis of (+/-)-3-*epi*-protoemetinol

3.7: The Synthesis of (+/-)-Protoemetinol

Adaptation of our dihydrocorynantheol synthesis to produce protoemetinol proceeded as expected (**Scheme 3.15**). Reductive amination of crude lactol mixture **3.38** with amine **3.42** gave an inseparable mixture of lactams **3.45** and the previously observed **3.43**. Acetylation and cyclization of this mixture produced a separable mixture of acetates **3.46** and **3.44**, which were independently and quantitatively deprotected to yield (+/-)-protoemetinol and (+/-)-3-*epi*-protoemetinol respectively.



Scheme 3.15: Synthesis of (+/-)-protoemetinol.

3.8: Chapter Summary

The work described in this chapter represents the completion of a major portion of our projects goals. The above racemic work was meant to show that our strategy was capable of using a single synthetic intermediate to synthesize a broad selection of natural products. Lactone **3.1** has proven to be very competent in this regard. We were able to install desired functional groups and stereogenic centers relative to the single stereogenic center present in lactone **3.1**. The potential breadth of this strategy can only be implied by this initial foray, however, in a very short time we have completed the total synthesis of six natural products representing four structurally diverse classes of secologanin derived natural products. Only future work can fully elucidate the potential of this strategy.

Two flaws with the above work are apparent. First, an imperfect degree of diastereoselectivity was observed during the synthesis of dihydrocorynantheol and protoemetinol. The relative stereochemistry of the ethyl side chain was only partially controlled. Some stereochemical scrambling occurred during the reductive amination

reaction between lactol mixture **3.38** and the aryl ethylamine. The epimerization of the stereogenic center may have occurred at the lactol or imine stages and is likely unavoidable as long as reductive amination continues to be employed to join these portions of the molecule. It is possible that this new amine bond could be formed by amine alkylation with a fully reduced version of **3.38**, however this would necessitate initial protection of the remaining hydroxyl group in order to avoid its involvement in the coupling step. Our limited efforts in this regard failed completely. Our ability to easily separate the desired and undesired diastereomers produced during these syntheses allowed us to isolate the desired products and will, for now, need to serve as a partial solution to this problem.

The second flaw of our strategy is that we have not demonstrated a method of producing optically pure lactone **3.1**. Our efforts in this regard are detailed in the following chapter.

Chapter 4: Efforts Toward a Synthesis of Optically Pure Secologanin Synthons

4.1: Introduction

As the previous chapter illustrates, lactone **3.1** is an extremely useful substrate for the synthesis of a number of structurally diverse secologanin derived natural products. The chief flaw with the synthesis of lactone **3.1** described in the previous chapter is that it produces racemic product. Because each of the stereogenic centers that we install during the natural product syntheses presented in the previous chapter are established relative to the stereogenic center introduced with lactone **3.1**, a reliable and optically pure supply of either antipode of lactone **3.1** would allow selective access to either optically pure antipode of the above synthesized natural products as well as any newly synthesized derivatives of lactone **3.1**. Concurrent with our above described racemic synthetic efforts, we have been investigating the asymmetric synthesis of lactone **3.1** as well as more complex compounds capable of serving as secologanin synthons.

4.2: Early Efforts Toward the Synthesis of Secologanin Synthons

Prior to our development of lactone **3.1** as our chosen key synthetic intermediate, we investigated the synthesis of more highly functionalized intermediates such as those of type **4.1** pictured in **Figure 4.1**. Intermediates that fit the general form of structure **4.1** possess the entire carbon framework of the terpene core of secologanin, both of the stereogenic centers present in this core, and differentially functionalized side chains allowing the independent manipulation of each of these structurally moieties. Although this strategy would allow the direct synthesis of the more complex secologanin derived

natural products, synthesis of many of the secoiridoids and STAs such as geissoschizol and oleocanthal would involve the late stage *removal* of molecular complexity.

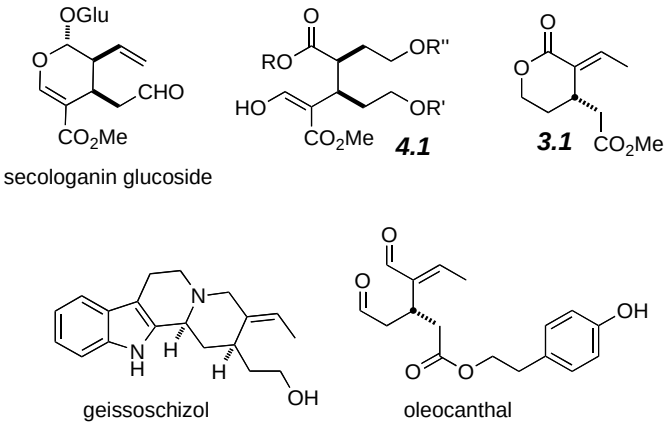
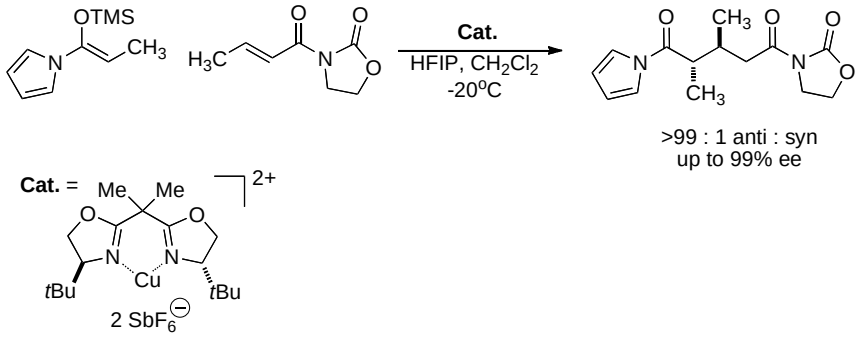


Figure 4.1: Potential synthetic intermediates

4.2.1: Attempted Diastereoselective Intermolecular Michael Additions

Our first attempt to synthesize a secologanin synthon in an asymmetric fashion was inspired by several intermolecular Michael additions of pyrroleamide derived nucleophiles to unsaturated imide electrophiles reported by Evans and coworkers[79] (**Scheme 4.1**). This work was of particular interest because we believed that by extending and functionalizing the terminal methyl groups of the nucleophile and the Michael acceptor we would be able to introduce the two requisite stereogenic centers as well as the majority of the carbon framework of the desired target in a single step.



Scheme 4.1: Asymmetric Michael additions reported by Evans and coworkers.

We planned a retrosynthesis (**Figure 4.2**), which could produce synthon **4.1** by esterification of the pyrroleamide functionality of compound **4.2**. This pyrroleamide intermediate **4.2** could be obtained from the esterification and formylation of compound **4.3**, which is product of the intermolecular Michael addition of a functionalized pyrroleamide nucleophile **4.4** with a functionalized unsaturated imide electrophile **4.5**. We hoped that this intermolecular Michael addition would bring together the bulk of the carbon framework of the desired secologanin synthon (**4.1**) and install both of the required stereogenic centers in a single step.

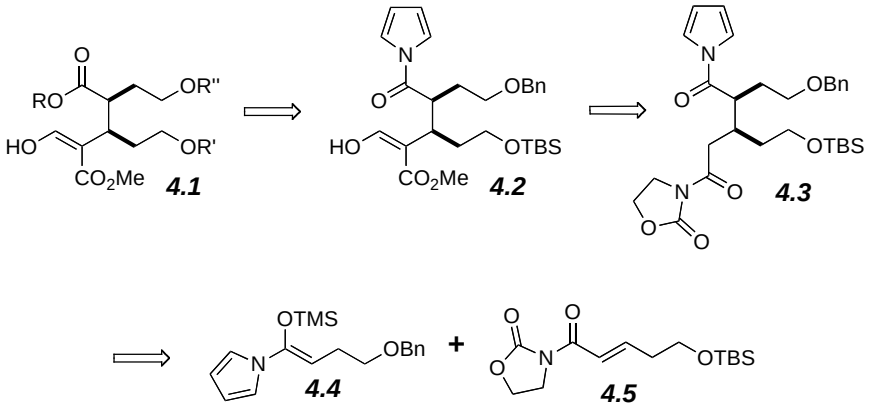
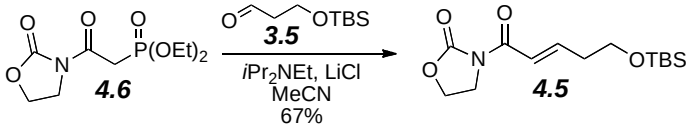
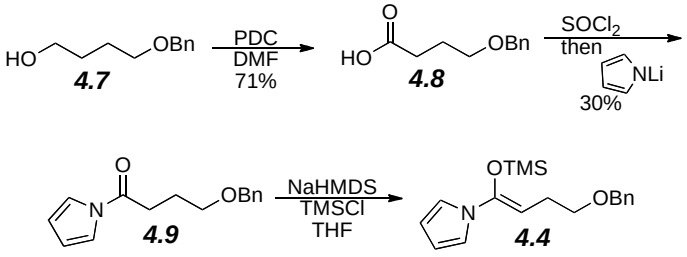


Figure 4.2: Retrosynthesis of synthons of type **4.1**.

We began our efforts toward synthon **4.1** with the synthesis of the unsaturated imide electrophile **4.5** (**Scheme 4.2**). The phosphonate utilized by Evans and coworkers to synthesize their unsaturated imide nucleophiles, phosphonate **4.6**, was used for the HWE olefination of the previously synthesized aldehyde **3.5** to give compound **4.5** in good yield. With this unsaturated imide (**4.5**) in hand we turned to the synthesis of the pyrroleamide nucleophile **4.4** (**Scheme 4.3**). Oxidation of monoprotected diol **4.7**, derived from the benzylation of 1,4-butanediol, produced acid **4.8** in good yield. This acid was converted to the corresponding acid chloride, which was used to acylate *n*BuLi deprotonated pyrrole to give the desired pyrroleamide **4.9** in low yield. The trimethylsilyl enol ether nucleophile **4.4** was formed from the sodium enolate of pyrroleamide **4.9** and then used immediately.

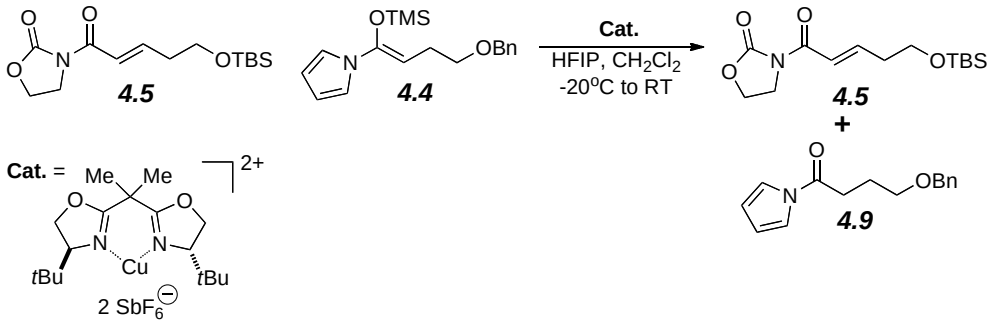


Scheme 4.2: Synthesis of the unsaturated imide electrophile.



Scheme 4.3: Synthesis of the pyrroleamide nucleophile.

With the requisite reaction partners **4.4** and **4.5** in hand we then attempted the asymmetric Michael reaction using the conditions reported by Evans, *et.al.* (**Scheme 4.4**). Unfortunately, despite several attempts and elevated temperatures, no desired product was observed. In each case TLC monitoring indicated that the nucleophile (**4.4**) was rapidly desilylated as evidenced by the formation and then decomposition of pyrroleamide **4.9**. (Two dimensional TLC experiments with pure 4.4 only showed minor starting material decomposition.) We speculate that this lack of reactivity may be caused by the increased steric bulk of both the electrophile and the nucleophile relative to the electrophiles and nucleophiles successfully reacted by Evans, *et.al*.



Scheme 4.4: Attempted Michael reaction.

4.2.2: Attempted Cyclization of Alkylidene Malonimide Substrates

The retrosynthesis pictured in **Figure 4.3** illustrates the redesign of our strategy that followed the failed asymmetric intermolecular Michael reaction described above. An analysis of the structure of target compound **4.1** revealed an opportunity for structural simplification. A lactone of type **4.10** could replace both the ester (-OR) and the alcohol (-OR') protecting groups present in compound **4.1**. This modification would not only

simplify the target structure but would also allow the target to be synthesized by an intramolecular rather than intermolecular Michael reaction. We hoped that the decrease in steric bulk achieved by the removal of the potentially sterically bulky protecting groups and the change in mechanism, from intermolecular to intramolecular, would allow the desired reaction to take place. We planned to access lactone **4.10** by the reduction of a chiral imide such as **4.11** to produce the desired vinylogous carbonate functionality. The chiral auxiliary present in linear cyclization substrate **4.12** would be necessary to control the facial selectivity of the cyclization of the lactone core of **4.11**. This key cyclization step would occur when the tethered nucleophile was activated causing conjugate addition to the chiral alkylidene malonimide. The cyclization substrate **4.12** could be accessed through the esterification of the alkylidene malonimide Michael acceptor portion **4.13** with the nucleophilic portion **4.14**.

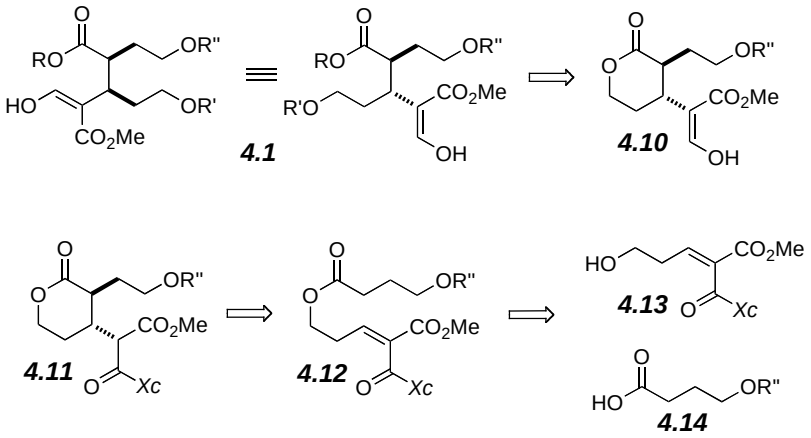
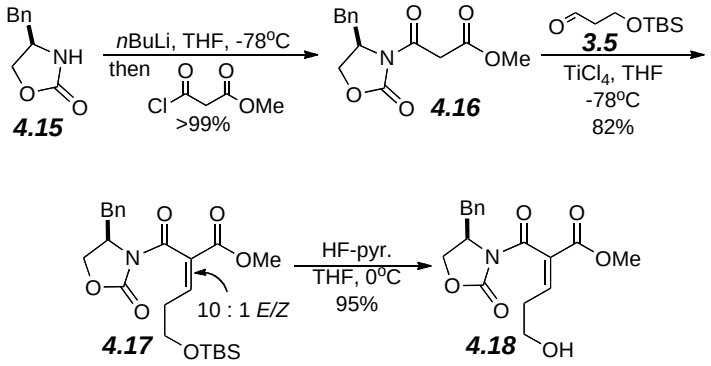


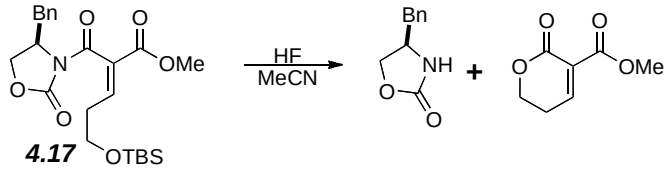
Figure 4.3: A strategic redesign.

As illustrated in **Scheme 4.5**, synthesis of the Michael acceptor portion of the linear cyclization substrate began with the quantitative acylation of chiral auxiliary **4.15**

to produce malonimide **4.16**. Knoevenegel condensation of aldehyde **3.5** with malonimide **4.16** produced alkylidene malonimide **4.17** in good yield. This condensation resulted in a 10 : 1 mixture of olefin isomers. The *E* isomer was formed in large excess presumably due to a diastereoselective alkylation followed by a stereospecific β-hydroxy elimination. The geometry of the major product was determined through ^{1}HNMR and ^{13}CNMR analysis and was further confirmed by the observation of a rapid lactonization upon removal of the TBS protecting group as illustrated in **Scheme 4.6**. Careful TBS removal utilizing the milder HF-pyridine in cold MeCN allowed for the isolation of alcohol **4.18** in excellent overall yield.

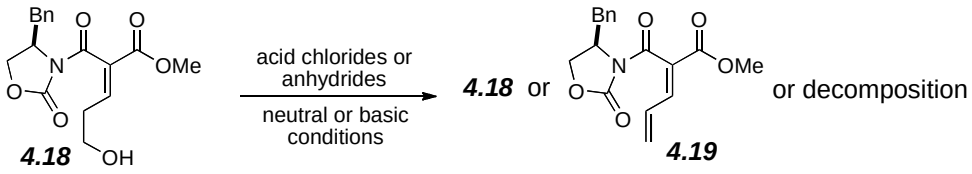


Scheme 4.5: Synthesis of alcohol **4.18**.



Scheme 4.6: Observed lactonization of alkylidene malonimide **4.17**.

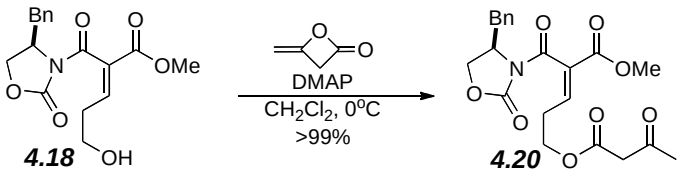
With alcohol **4.18** in hand we turned our attention to the identification and installation of an appropriate tethered nucleophile. Selection criteria that were considered for this portion of the cyclization substrate included both ease of installation and the ability to initiate lactone cyclization under relatively mild conditions. Unfortunately, as illustrated in **Scheme 4.7**, treatment of alcohol **4.18** with most acylating reagents, even under relatively mild conditions, resulted in either the return of unaltered alcohol **4.18**, rapid elimination of the δ-hydroxyl group to produce diene **4.19**, or the formation of a complex mixture of decomposition products.



Scheme 4.7: Unsuccessful esterification attempts.

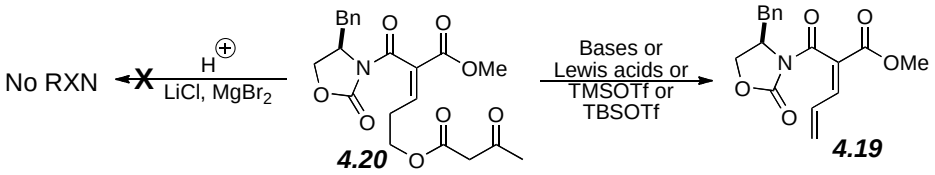
Since free hydroxyl groups are rarely competent leaving groups, we guessed that the observed elimination and possibly the decompositions were likely occurring after the acylation of the δ-hydroxyl functionality because after acylation, the newly formed δ-acyl group would serve as a far superior leaving group. The general base catalysts, which are necessary for the acylation of the δ-hydroxyl moiety, would then catalyze the elimination producing diene **4.19**. It stands to reason that the identification of δ-acylation conditions, which do not involve the addition of a base, would prevent this elimination and allow for the isolation of the desired product. The mild conditions needed to activate diketene allow for the base-free *in situ* generation of an extremely reactive ketene intermediate, capable of alcohol acylation without the need for the addition a base. As illustrated in

Scheme 4.8, acylation of alcohol **4.18** with diketene did not result in elimination and yielded β-ketoester **4.20** in quantitative yield.



Scheme 4.8: Acylation of alcohol **4.18**.

Once having produced a scalable synthesis of the linear cyclization substrate β-ketoester **4.20** we began to screen cyclization conditions (**Scheme 4.9**). The central challenge of this cyclization was the generation of a β-ketoester enolate or enol ether nucleophile in the presence of the fragile δ-acyl alkylidene malonimide. As expected, treating β-ketoester **4.20** with strong bases (LiHMDS, NaH, etc.) resulted in rapid elimination to produce diene **4.19**. Unfortunately even mild bases (K_2CO_3, pyridine, etc.) and Lewis acidic conditions ($SnCl_4$, $TiCl_4$, etc.) also resulted in elimination. Weaker Lewis acids (LiCl, $MgBr_2$, etc.) and Brønsted acids (HOAc, HCl, TsOH) resulted in no reaction, returning unaltered β-ketoester **4.20**. Attempts to generate the silyl enol ether of the β-ketoester portion of cyclization substrate **4.20** resulted in the production of a complex mixture of products when TMSCl or TBSCl were employed and rapid elimination when TMSOTf or TBSOTf were employed **Scheme 4.9**.



Scheme 4.9: Attempted cyclization of β-ketoester.

The fragility of the δ-hydroxy alkylidene malonimide system, as manifested by its rapid elimination when acylated, lead us to redesign our cyclization substrate. We recognized that the problematic characteristics of the alkylidene malonimide system were likely due to the extremely electron deficient nature of the alkylidene malonimide olefin and that a reduction of the electron deficiency of this olefin would likely decrease the rate of the observed and undesired δ-elimination. The inhibition of this side reaction would allow for the use of basic or strongly Lewis acidic conditions needed to both broaden the scope of possible acylation substrates as well as allowing the use of reaction conditions capable of the generation of enolates or enol ethers to act as Michael donors.

4.3: The Development and Attempted Cyclization of Unsaturated Chiral Imides

Our solution to the problems caused by the electron deficiency of the alkylidene malonimide cyclization substrates was to design a cyclization substrate similar to those described above but lacking the methyl carboxylate moiety (**Figure 4.4**). With only a single electron withdrawing group in conjugation with the electrophilic olefin, these new substrates should be less reactive to cyclization but more robust under cyclization conditions. This reduction in molecular complexity also meant that the target secologanin synthon, compound **4.1**, could not be directly synthesized. Fortunately, the unsaturated imide substrates in question could readily be used to intercept lactone **3.1**.

This was not viewed as a problem since by this point in our synthetic efforts racemic lactone **3.1** had begun to prove its utility as an intermediate for the synthesis of racemic natural products and an asymmetric synthesis of this important intermediate would allow us to synthesize optically pure versions of the racemic natural products described in the previous chapter.

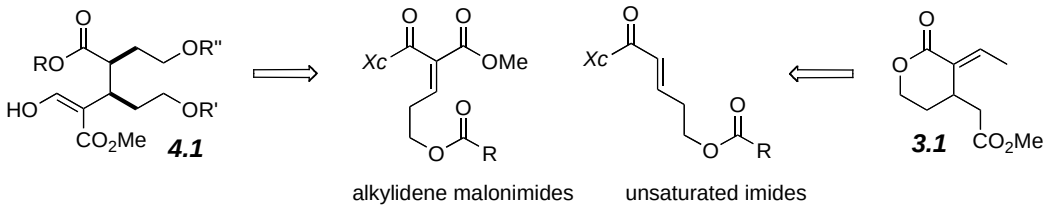
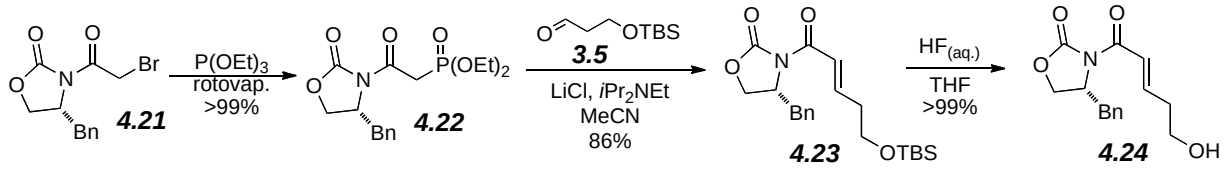


Figure 4.4: The alkylidene malonimide and unsaturated imide cyclization substrates.

4.3.1: Synthesis of the Unsaturated Imide Michael Acceptor

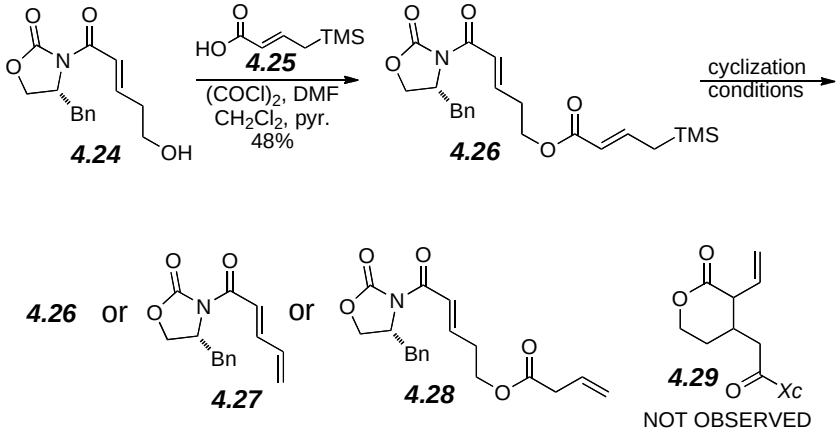
The production of the Michael acceptor portion of the modified cyclization substrate (**Scheme 4.10**) was accomplished by Masamune-Rousch modified Horner-Wadsworth-Emmons olefination of aldehyde **3.5** with phosphonate **4.22**, which was produced by Arbuzov reaction from bromide **4.21**. Removal of the TBS ether of compound 4.23 under acidic conditions gave alcohol **4.44**, which immediately proved to be vastly superior to its alkylidene malonimide counterpart, alcohol **4.19**, because it was more easily produced, bench stable, and readily underwent acylation with a number of potential nucleophiles.



Scheme 4.10: Synthesis of alcohol **4.24**.

4.3.2: Synthesis and Installation of Several Nucleophiles

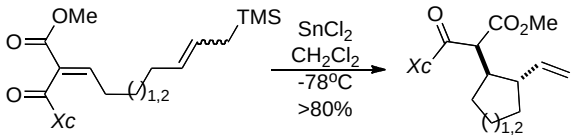
We chose several potential nucleophiles to couple to alcohol **4.24**. The first of these was acid **4.25** (**Scheme 4.11**). This nucleophile possesses an allylsilane moiety, which, once installed, could be triggered to simultaneously cyclize the lactone core and install the desired exocyclic olefin critical to the synthesis of many of the secologanin derived natural products. This strategy was largely inspired by the successful allylsilane cyclizations reported by Tietze and coworkers[80] illustrated in **Scheme 4.12**.



Scheme 4.11: Failed allylsilane cyclizations.

Acylation of alcohol **4.24** with the acid chloride derived from acid **4.25** gave the desired allylsilane cyclization substrate **4.26** in low yield. Unfortunately, treatment of the

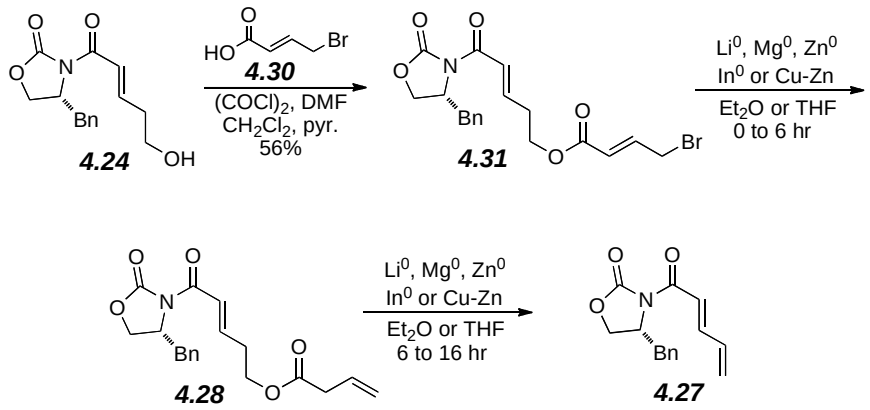
uncyclized allylsilane ester with various Brønsted acids (HCl, TsOH), Lewis acids ($SnCl_4$, $TiCl_4$), and fluoride sources (TBAF, HF), in several solvents (CH_2Cl_2, THF, MeCN), at various temperatures (-78°C to 23°C) resulted in either return of unaltered allylsilane **4.26**, δ-elimination producing diene **4.27**, or production of the uncyclized vinyl acetate ester **4.28**. None of the desired cyclized lactone **4.29** was observed.



Scheme 4.12: Tietze's allylsilane cyclizations.

It appeared that in the above case (**Scheme 4.11**), depending on the cyclization conditions employed, the allylsilane ester was successfully triggered to generate the enolate or enol ether nucleophile. Unfortunately, this nucleophile did not react with the Michael acceptor portion of the molecule before being quenched. Two possible scenarios account for this undesired reactivity: either the allylsilane ester, once triggered, could not react with the unsaturated imide Michael acceptor and was quenched upon the reaction workup or the quenching of the triggered allylsilane ester occurred very quickly on the reaction timescale and hence was prevented from reacting with the unsaturated imide Michael acceptor. We believed the latter scenario to be the most likely due to the highly acidic conditions employed, however, either of these scenarios could theoretically be overcome by an increase in the reactivity of the nucleophile with the unsaturated imide relative to the rate of enolate quenching. Unfortunately, we were unable to identify conditions capable of overcoming this problem.

Our next substrate redesign involved the replacement of the allylsilane-triggered nucleophile with an allylbromide-triggered nucleophile (**Scheme 4.13**). The metal-halogen exchange or radical reactions, which could be used to trigger this new substrate would not require the harsh acids needed to trigger the allylsilane ester nucleophile. Since these harsh acids were likely the cause of the premature nucleophile quenching, their removal should decrease the rate of quenching relative to the rate of cyclization.



Scheme 4.13: Synthesis and attempted cyclization of the allylbromide ester cyclization substrate.

As illustrated in **Scheme 13**, the synthesis and installation of the bromocrotanoic acid ester portion proceeded smoothly. Acylation of alcohol **4.24** with the acid chloride derived from bromocrotanoic acid (**4.30**) gave allyl bromide **4.31** in acceptable yield. Treatment of allylbromide **4.31** with zero valet metals such as Li, Zn, and Mg in THF or Et_2O resulted in rapid metal-halogen exchange as evidenced by the absence of the starting bromide **4.31** in quenched reaction aliquots. At ambient temperature and over short reaction times (less than 6 hours) quenched aliquots contained only the previously

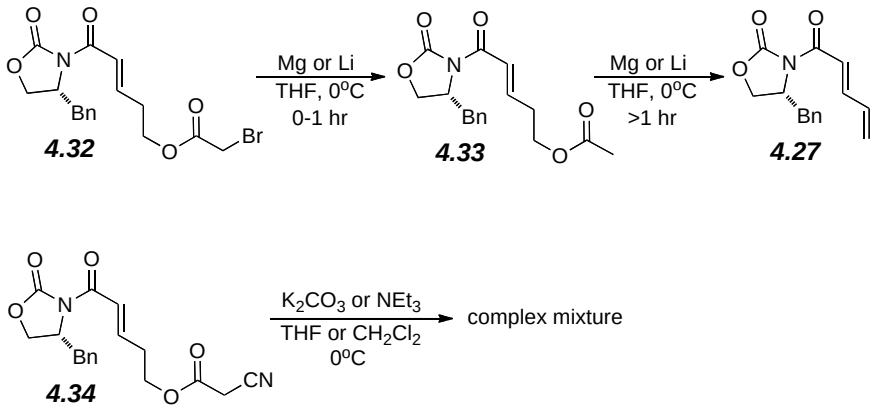
observed vinyl acetate **4.28**. Aliquots taken at longer reaction times of up to 16 hours contained increasing amounts of the δ-elimination product diene **4.27** and no cyclization product was observed. This observation indicates that even the metal enolates are not capable of reacting with the unsaturated imide Michael acceptor under our reaction conditions. This suggests that an extremely slow cyclization, rather than rapid enolate quenching, may be the cause of the reaction failure.

Treatment of the allylbromide ester cyclization substrate **4.31** with In or Cu-Zn couple resulted in returned starting material unless additives such as I_2 or NaI were used or the reaction was subjected to at least 30 minutes of sonication. Unfortunately, these techniques did not result in product formation. As observed with the more reactive zero valent metals, only vinyl acetate **4.28** and/or the δ-elimination product diene **4.27** were isolated.

Unlike the attempted cyclizations of allylsilane substrates, whose failure may be attributed to premature nucleophile quenching by acids present in the reaction mixture, it is unlikely that the metal enolates produced in the allyl bromide case were being quenched prematurely. We concluded that the failure of these cyclizations was probably due to the inability of the nucleophilic portion of these substrates to react with the Michael acceptor portion of the cyclization substrate.

As illustrated in **Scheme 4.14**, attempts to cyclize a similar substrate containing a bromoacetate nucleophile (**4.32**), by treatment with zero valent metals resulted in metal halogen exchange as evidenced by the isolation of acetate **4.33**. Unfortunately no desired product was isolated and on longer reaction times only diene **4.27** was observed.

Cyanoacetate ester **4.33** also failed to produce cyclized products, giving only a complex mixture of products upon treatment with mild base.

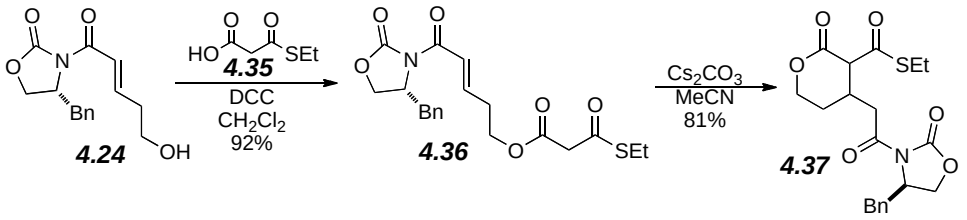


Scheme 4.14: Attempted cyclization of bromoacetate and cyanoacetate substrates.

4.4: Successful Lactone Cyclizations Utilizing a Thioester Nucleophile

Our first successful attempt to synthesize a productive cyclization substrate is illustrated in **Scheme 4.15**. The DCC promoted acylation of alcohol **4.24** with acid **4.25** gave the desired product, cyclization substrate **4.36** in excellent yield. Thankfully, treatment of this cyclization substrate with Cs_2CO_3 in MeCN resulted in the formation of the desired lactone **4.37**. Unfortunately, this lactone was relatively unstable and decomposed within hours when stored neat at low temperature or frozen in benzene. This instability combined with the presence of thioester epimers prevented an accurate quantification of the diastereoselectivity of this reaction using NMR techniques. We decided to attempt to determine the diastereoselectivity of this reaction by carrying lactone **4.37** forward to a more stable intermediate and inferring the diastereoselectivity of the cyclization based on the ratio of intermediate diastereomers. The only substance

identified during an investigation of the decomposition of lactone **4.37** was the chiral auxiliary (*R*)-4-benzyloxazolidin-2-one indicating that the decomposition may be accelerated by the relatively high reactivity of the imide functionality.



Scheme 4.15: Synthesis and cyclization of thioester substrate **4.37**.

Despite its efficient cyclization, one major flaw exists with the use of the thioester nucleophile. Unlike the other nucleophiles that we had previously investigated, the tethered thioester nucleophile introduces only three of the four carbons necessary for the synthesis of lactone **3.1**. This necessitated a redesign of our synthetic plan as well as further manipulations to arrive at the desired carbon framework. **Figure 4.5** illustrates our redesigned retrosynthetic plan. We envisioned that access to the sweroside carbon framework could be gained by the alkylation of lactone **4.38**. This substrate could be accessed by the cyclization of the vinylogous carbonate and carboxylate functionalities of lactone **4.39**. This lactone could be produced by Fukuyama reduction of the cyclized thioester lactone **4.37**. This strategy would necessitate the use of the opposite enantiomer of the cyclized substrate than previous synthetic plans, however, this did not present a problem since we hoped that our strategy would enable the production of either enantiomer depending on the choice of chiral auxiliary antipode.

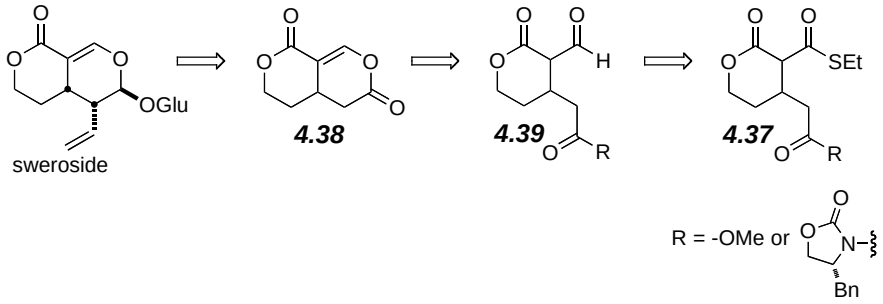
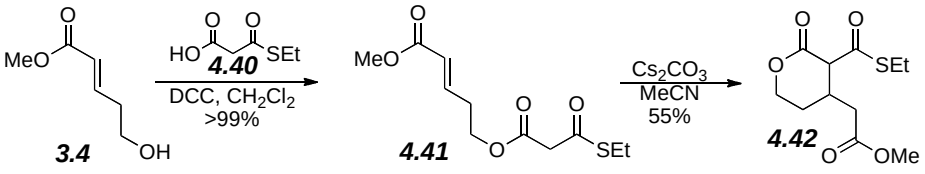


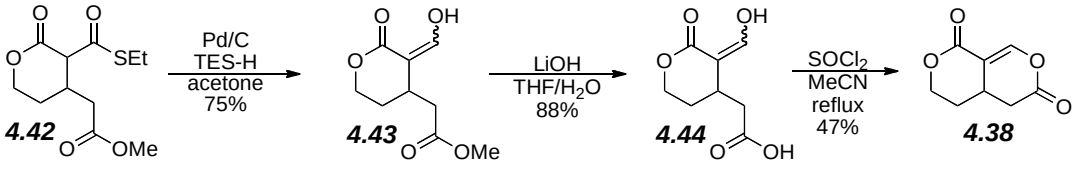
Figure 4.5: Modified retrosynthesis.

We decided to investigate the feasibility of this synthetic redesign using a racemic methyl ester model system (**Scheme 4.16**), in part, because we had already developed alcohol **3.4** as part of our racemic oleocanthal synthesis, but chiefly due to the instability of the cyclized thioester product. Recall that we attributed this instability to the presence of the labile imide moiety not present in this model system. Thus, alcohol **3.4** was acylated with acid **4.40** to produce cyclization substrate **4.41** in quantitative yield. Treatment of this linear substrate with catalytic Cs_2CO_3 in MeCN initiated the desired cyclization to yield lactone **4.42** in acceptable yield. Unlike the lactone bearing the imide moiety (**4.37**), which rapidly decomposed, this newly produced lactone bearing a methyl ester side chain was observed to be stable at ambient temperature for at least several weeks, supporting our contention that the potentially labile imide moiety present in lactone **4.37** may be responsible for its instability.



Scheme 4.16: Cyclization of the racemic thioester substrate.

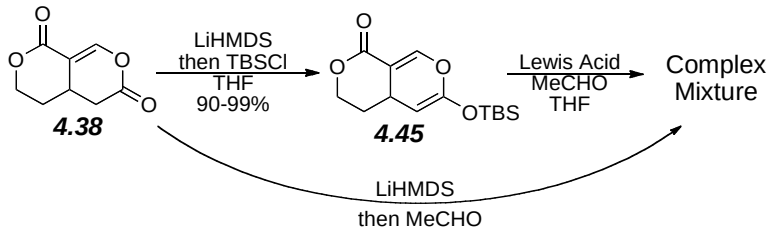
With lactone **4.42** in hand, we turned our attention to the reduction of the thioester moiety and subsequent cyclization. Treatment of lactone **4.42** with Fukuyama's thioester reduction conditions[81] (Pd/C, TESH, acetone) gave the desired vinylogous carbonate **4.43** in good yield (**Scheme 4.17**). Selective hydrolysis of the methyl ester side chain of **4.43** gave acid **4.44**, which was primed for cyclization. Finally, treatment of acid **4.44** with thionyl chloride in refluxing MeCN caused the cyclization of the dihydropyrone ring of lactone **4.38** giving this desired product in acceptable overall yield.



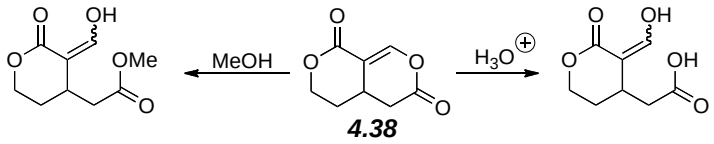
Scheme 4.17: Synthesis of lactone **4.38**.

We began our efforts to elaborate lactone **4.38** by attempting aldol alkylation with acetaldehyde (**Scheme 4.18**). Treatment of lactone **4.38** with LiHMDS produced the desired lithium enolate as evidenced by deuterium quenching. Unfortunately, addition of freshly distilled acetaldehyde returned only a complex mixture of products. Similar results were observed when propanal was employed. We next turned to Mukaiyama aldol conditions. Trapping of the lithium enolate as silyl ketene acetal **4.45** proceeded smoothly and produced a bench stable product. Unfortunately, treatment of this nucleophile with acetaldehyde in the presence of various Lewis acids produced only a complex mixture. The desired alkylated product was not observed. This unfortunate reactivity may be linked to the relative instability of lactone **4.38** to solvolysis under aqueous or alcoholic conditions (**Scheme 4.19**). It is possible that alcohols produced

during the alkylation reactions may be catalyzing the observed decompositions. Despite several attempts to identify an alkylated intermediate and efforts to avoid solvolysis through the elimination of aqueous workup, no alkylated products were identified.



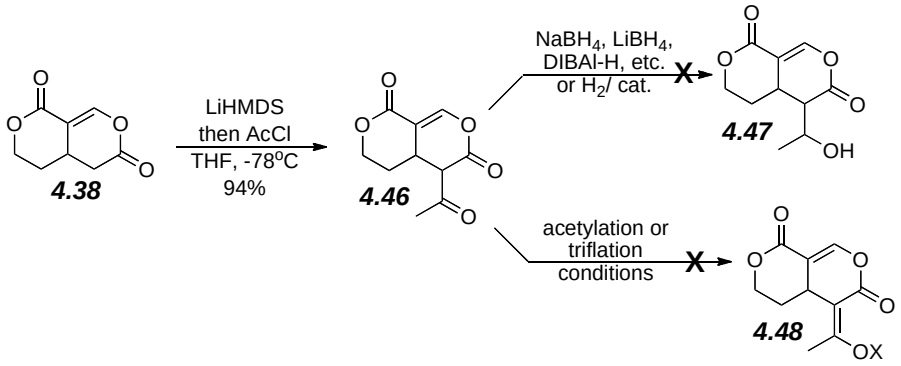
Scheme 4.18: Attempted alkylation of lactone **4.38**.



Scheme 4.19: Observed dihydropyrone solvolysis.

Elaboration of lactone **4.38** was first accomplished by acetylation to provide β-ketoester **4.46** in excellent yield (**Scheme 4.20**). Our next task was to reduce β-ketoester **4.46** in order to access the desired olefin side chain present in the secoiridoid skeleton. Treatment of β-ketoester **4.46** with hydride reducing reagents such as $NaBH_4$, $LiBH_4$, DIBAl-H, or L-Selectride in various solvents resulted in either no observed reaction or the production of a complex product mixture. Catalytic hydrogenation employing various transition metal based catalysts, elevated hydrogen pressures (>40 psi above ambient pressure), and several solvents produced results similar to the hydride reducing conditions so we decided to attempt the reduction of the vinyl triflate or vinyl acetate of

β-ketoester **4.46**. Unfortunately, treatment of β-ketoester **4.46** with NaH and Comins reagent only returned starting material and attempted vinyl triflate formations using triflic anhydride resulted in an intractable polymer. Attempts to form the vinyl acetate by treatment of the sodium enolate of β-ketoester **4.46** with acetyl chloride or acetic anhydride also resulted in a complex mixture of products. Our speculation as to the cause of these difficulties is that the presence of three similarly reactive carbonyls in β-ketoester **4.46** and the potential upon hydrolysis to reveal a fourth, even more reactive, carbonyl raises the probability of poor reduction selectivity resulting in unexpected side reactions, producing undesired alcohols, which may participate in the further degradation of starting materials and any desired products that may have formed. Substrate 4.46 may be too highly functionalized to easily manipulate without the introduction of a series of carbonyl protections.



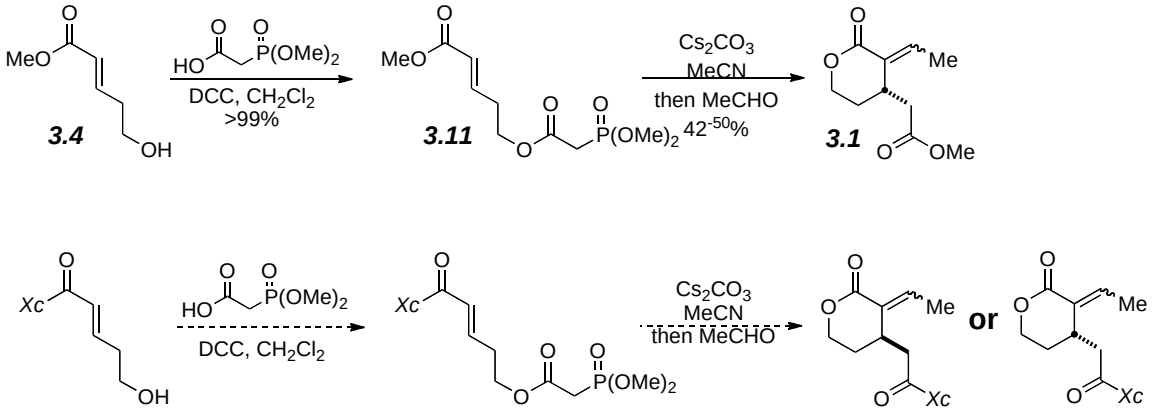
Scheme 4.20: Synthesis and attempted manipulation of β-ketoester **4.46**.

Although the thioester substrates were successfully cyclized, all attempts to further functionalize the products of these cyclizations failed. Fortunately, productive

results were achieved with other systems investigated concurrently with the systems described in this section.

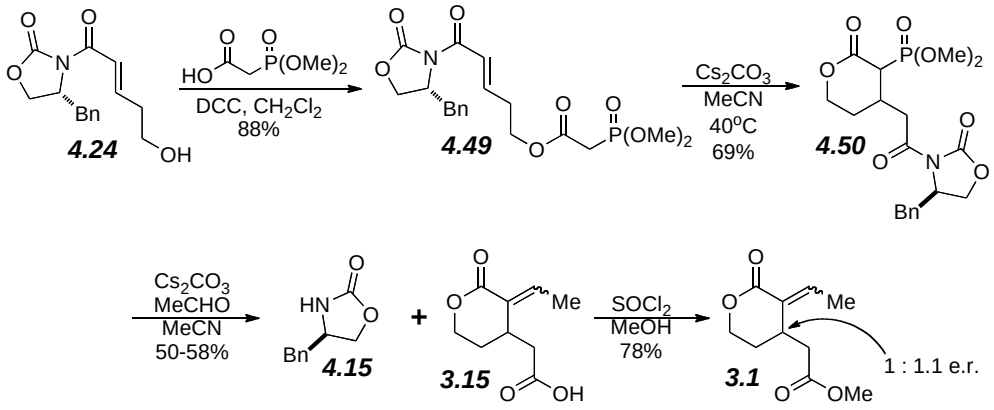
4.5: Cyclization and Manipulation of Phosphonoacetate Substrates

We began to investigate the cyclization of unsaturated imides tethered to phosphonoacetate nucleophiles immediately upon completing our successful synthesis of (+/-)-oleocanthal via tandem Michael cyclization-HWE olefination, which was described in the previous chapter. **Scheme 4.21** shows the key ring forming step of our (+/-)-oleocanthal synthesis. This step not only introduces much of the carbon framework and other important functionality, but it also forms the molecule's only stereogenic center. Thus, it follows that rendering this cyclization step asymmetric, through the use of a chiral auxiliary that could facially bias the Michael acceptor olefin, would grant us selective access to either oleocanthal antipode as well as allowing us to produce optically pure lactone **3.1**, which we have shown in the previous chapter can be used to synthesize several classes of naturally occurring alkaloids. These previously discussed racemic syntheses have demonstrated that the single stereogenic center present in lactone **3.1** can be used to control the relative stereochemistry of the remaining stereogenic centers. Thus control of the absolute configuration of the lactone **3.1** stereogenic center would give us control of the absolute and relative stereochemistry of all of the previously synthesized natural products.



Scheme 4.21: Lactone **3.1** and a proposed asymmetric phosphonoacetate cyclization.

As illustrated in **Scheme 4.22**, the coupling of alcohol **4.24** with phosophonoacetic acid proceeded in excellent yield. Treatment of the newly formed cyclization substrate **4.49** with Cs_2CO_3 in warm MeCN gave the cyclized phosphonate **4.50** in good yield. Unfortunately, reliable diastereoselectivity data for the lactone cyclization reaction could not be obtained at this stage due to the presence of phosphonate epimers and several conformational isomers. It seemed reasonable that following the HWE olefination, a reliable measurement of diastereoselectivity could be obtained. Despite concerted efforts to isolate a HWE olefination product with an intact chiral imide, treatment of phosphonate **4.50** with HWE olefination conditions employing several different aldehydes yielded only the cleaved chiral oxazolidinone **4.15** along with the previously observed carboxylic acid **3.15**. This hydrolysis is only observed upon the addition of and aldehyde, suggesting that imide hydrolysis might be initiated by alkoxides derived from the decomposition of the added aldehydes in the presence of Cs_2CO_3, possibly by and internal displacement of the imide by the HWE alkoxide intermediate.



Scheme 4.22: Cyclization of the chiral phosphonate substrate.

Although inconvenient, the observed hydrolysis does not preclude the determination of the diastereoselectivity of the cyclization reaction. Diastereoselectivity could be implied by the ratio of enantiomers in the isolated product mixture. We were unable to adequately separate the enantiomers of acid **3.15** by chiral HPLC so we decided to form lactone **3.1** from acid **3.15**. Esterification of acid **3.15** with thionyl chloride in methanol gave lactone **3.1** as a mixture of olefin geometries. Thankfully, these isomers were easily separable using standard silica gel chromatography. The enantiomeric ratios of both the *E* and *Z* forms were determined by chiral HPLC using a separation method developed to completely separate the enantiomers of racemically synthesized lactone **3.1**. The obtained enantiomeric ratios were identical for both olefin geometries. As a further test of our method of determining the selectivity of this cyclization, we synthesized the enantiomer of cyclization substrate **4.49** and submitted it to our test conditions. Thankfully, this cyclization showed diastereoselectivity exactly opposite to that of its enantiomer. Unfortunately, however, very poor selectivity (1 : 1.1 e.r.) was observed for

these cyclizations, giving only a slight enantiomeric excess. Although this method cannot definitively conclude the exact diastereoselectivity of this cyclization, it is a reasonable method for implying this selectivity. The identity of the major isomer was not established.

With a successful method for phosphonoacetate cyclization and a method of implying reaction diastereoselectivity, we began our efforts to improve the diastereoselectivity of the cyclization. A search of the literature revealed no previous work on the intramolecular reaction of carbon nucleophiles with chiral unsaturated imides, however, intermolecular reactions of this type were known. Previous work involving intermolecular conjugate additions of carbon nucleophiles to unsaturated chiral imides reported by Koga[82], Nillson[83], Dwight[84], and Williams[85] observed a reversal of diastereoselectivity when Lewis acids capable of *bis*-chelation were substituted for those only capable of *mono*-chelation. **Figure 4.6** illustrates the two models thought to be responsible for the observed selectivity change. The most stable conformer of the *bis*-chelated imide **4.51** contains a 6-membered metallocycle that not only orients the *tert*-butyl blocking group closer to the electrophilic β-carbon, but also orients this large blocking group on the opposite face of the electrophile relative to its position in the *mono*-chelated form (**4.52**). The *mono*-chelated form (**4.52**) lacks the metallocycle present in form **4.51** allowing it to adopt a lower energy imide conformation with opposing carbonyl dipoles. This reversal of blocking group orientation accounts for the reversal of diastereoselectivity reported by Koga, Nillson, Dwight, and Williams.

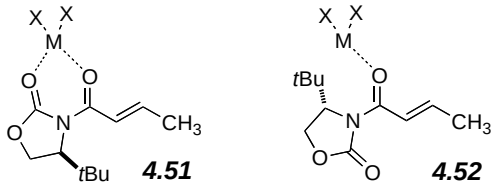
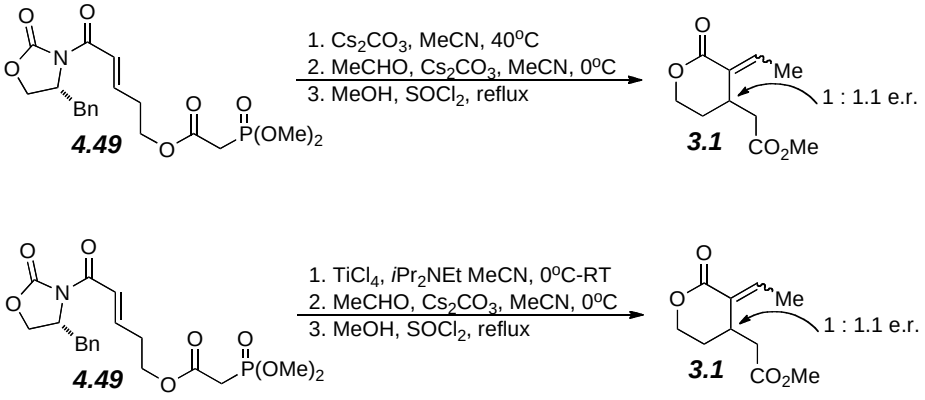


Figure 4.6: Unsaturated imide electrophile models.

While reviewing the above literature we gained a second insight about the diastereoselectivity of Michael additions to unsaturated chiral imides. Generally, better diastereoselectivities were observed with an increase in the size of the blocking group and surprisingly, this increase in steric bulk did not seem to correlate with a corresponding decrease in reactivity or yield. The above observations suggest that through the thoughtful modification of reaction conditions (i.e. screening various monodentate and bidentate Lewis acids) and the modification of the size of the blocking group of our chiral auxiliary we may be able to better control our intramolecular conjugate additions.

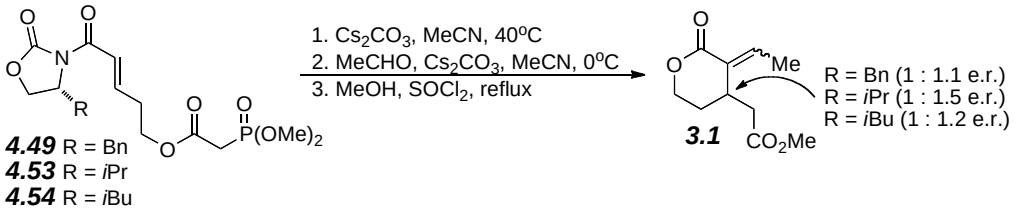
We decided to begin our modification of the intramolecular Michael cyclization of phosphonoacetate nucleophiles tethered to unsaturated chiral imides by investigating the effect of bidentate Lewis acids on the diastereoselectivity of the cyclization. The most common Lewis acids employed for this purpose are $SnCl_4$ and $TiCl_4$. We chose to employ $TiCl_4$ exclusively since treatment of our imides with even catalytic amounts of $SnCl_4$ resulted in rapid decomposition with the diene resulting from δ-elimination (diene **4.27**) as the only identified product. The transition state models discussed above predict that by employing a Lewis acid capable of *bis*-chelation, we should observe both an increase in and a reversal of diastereoselectivity. **Scheme 4.23** illustrates that,

unfortunately, treatment of cyclization substrate **4.49** with $TiCl_4$ and Hünigs base in MeCN at ambient temperature gave an identical ratio of products as the Cs_2CO_3 catalyzed substrate. Neither an increase in diastereoselectivity nor a reversal of diastereoselectivity was observed.



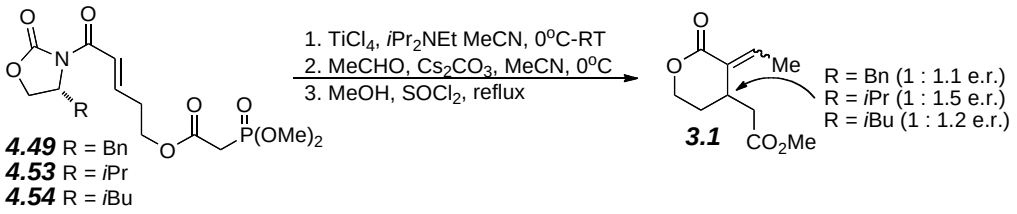
Scheme 4.23: Base and acid catalyzed cyclizations of **4.49**.

Next, we tested the hypothesis that an increase in the steric bulk of the chiral auxiliary would increase the diastereoselectivity of the cyclization. We began by synthesizing cyclization substrates **4.53** and **4.54**, which are similar to the previously discussed cyclization substrate **4.49** varying only in side chain of the chiral auxiliary. Cyclizations were carried out using Cs_2CO_3 in MeCN at 40°C (**Scheme 4.24**). Indeed an increase in steric bulk achieved by switching from the benzyl side chain to the isobutyl side chain did result in a small increase in the ratio of the major product to the minor product. Another slight increase in diastereoselectivity was observed by exchanging the isobutyl side chain for an isopropyl side chain.



Scheme 4.24: Base catalyzed cyclizations of substrates bearing various chiral imides.

The isopropyl and isobutyl cyclization substrates (**4.53** and **4.54**) were also cyclized using the previously described bidentate Lewis acid conditions ($TiCl_4$, iPr_2NEt, MeCN, 0°C) (**Scheme 4.25**). As observed with the benzyl cyclization substrate (**4.49**), no change in product ratio or reversal of diastereoselectivity was observed. This lack of change in diastereoselectivity between the cyclizations utilizing monodentate and bidentate Lewis acids hints that the product ratio in these cases may be under thermodynamic control rather than the kinetic control desired. Efforts to lower the temperature of these cyclizations in order to force kinetic control resulted in the return of unaltered starting materials. Although none of the observed diastereoselectivities are synthetically useful, these results provide an important proof-of-principle demonstrating that the absolute configuration of the intramolecular cyclization of carbon nucleophiles onto tethered unsaturated imides could, in principle, be controlled.



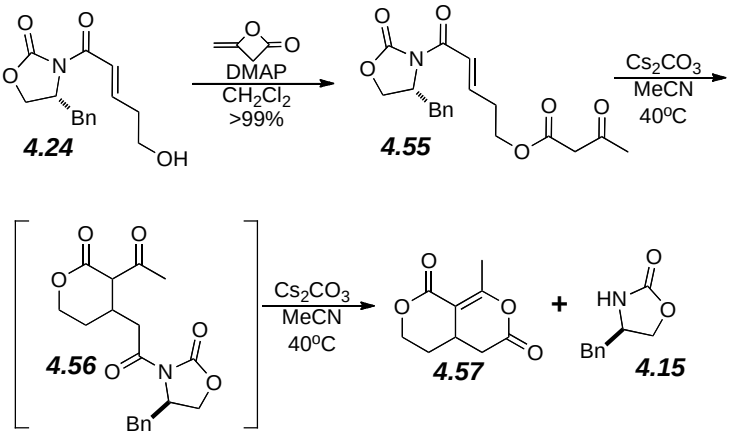
Scheme 4.25: Cylclization of phosphonoacetates under bidentate Lewis acidic conditions.

4.6: Cyclization and Manipulation of β-Ketoester Substrates

Concurrent with our above described investigations of cyclization substrates with tethered thioester and phosphonoacetate nucleophiles, we also investigated similar cyclization substrates bearing tethered β-ketoester nucleophiles.

4.6.1: Formation of an Unexpected Dihydropyrone

Scheme 4.26 illustrates the synthesis of one of these β-ketoesters. Alcohol **4.24**, synthesized as above, was treated with diketene and catalytic DMAP in CH_2Cl_2 to provide the desired β-ketoester **4.55** in quantitative yield. Treatment of cyclization substrate **4.55** with Cs_2CO_3 in dry THF at ambient temperature resulted in a rapid lactone cyclization to presumably produce lactone **4.56**. This cyclization was immediately followed by a second intramolecular cyclization of the ketone oxygen of the β-ketoester moiety onto the imide carbonyl, resulting in the expulsion of the chiral auxiliary **4.15**. Both the newly synthesized dihydropyrone **4.57** and the chiral auxiliary **4.15** were isolated in good yield. The intermediate β-ketoester **4.56** was not isolated or observed under these reaction conditions.

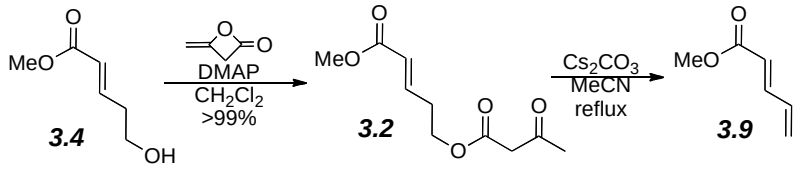


Scheme 4.26: Cyclization of a β-ketoester cyclization substrate.

Given that we could not isolate intermediate **4.56**, the diastereoselectivity of the cyclization reaction would have to be implied by determining the ratio of dihydropyrone **4.57** products. Since the cyclization of the dihydropyrone ring of compound **4.57** displaces the chiral auxiliary, only a single stereogenic center remains in the product. This produces a mixture of enantiomers thus necessitating the use of chiral HPLC to determine the enantiomeric excess of **4.57**, which could be used to imply the diastereoselectivity of the cyclization reaction.

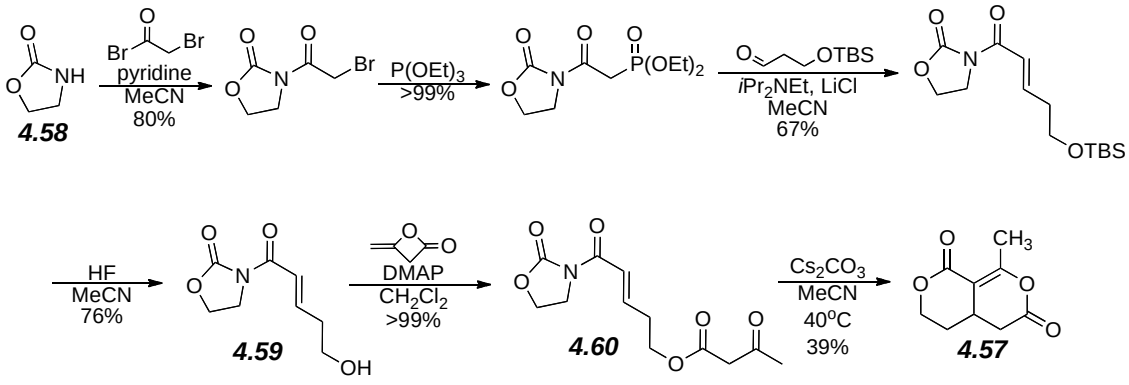
4.6.2: Synthesis of Racemic Dihydropyrone 4.57

In order to properly develop and calibrate our chiral HPLC separation method we needed to produce a sample of racemic **4.57**. This synthesis had the added advantage of providing material that could be used to investigate the transformation of dihydropyrone **4.57** into lactone **3.1** while avoiding the consumption of precious chiral substrates and avoiding the need to painstakingly separate dihydropyrone **4.57** from the co-eluting chiral oxazolidinone **4.15**.



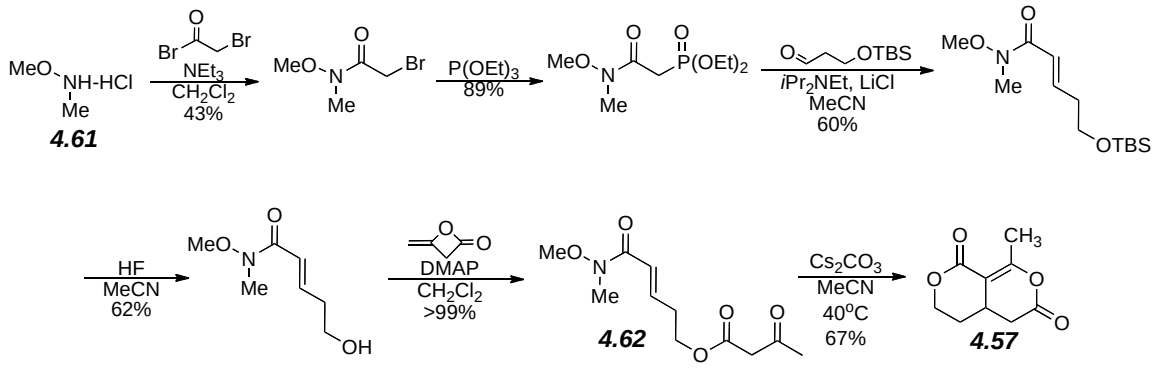
Scheme 4.27: Failed unsaturated methyl ester cyclization.

An obvious strategy to produce racemic dihydropyrone **4.57** involves the cyclization of the achiral methyl ester analog of cyclization substrate **4.55**. **Scheme 4.27** illustrates our previously described results in this area. Recall that the unsaturated methyl ester of compound **3.2** was unreactive under these reaction conditions due to its lack of sufficient elecrophilicity. In order to produce a racemic system which better mimics the electronics of the previously cyclized substituted unsaturated imides we decided to employ the unsubstituted oxazolidinone **4.58** in lieu of the Evan's oxazolidinones. Production of achiral alcohol **4.59** was accomplished by the previously developed sequence. Acetylation with diketene gave the achiral cyclization substrate **4.60**, which upon subjection to cyclization conditions gave dihydropyrone **4.57** in low yield.



Scheme 4.28: Racemic syntheses of dihydropyrone **4.57**.

A second racemic synthesis of dihydropyrone **4.57** was developed concurrently with the above work and proved to be far superior (**Scheme 4.29**). Substituting dimethyl hydroxylamine **4.61** for the oxazolidinone functionalities of the chiral and achiral cyclization substrates gave a cyclization substrate bearing an unsaturated Weireb amide (**4.62**) rather than an unsaturated imide (**4.60**). Although both of these cyclization substrates produced the desired racemic product, the unsaturated Weinreb amide route was chosen for the large scale synthesis of dihydropyrone **4.57** because purification of the final product required only a simple aqueous acid extraction to remove compound **4.61** rather than requiring multiple tedious chromatographic separations to remove the oxazolidinone **4.48** produced upon dihydropyrone cyclization.



Scheme 4.29: Racemic syntheses of dihydropyrone **4.57**.

4.6.3: Conversion of Dihydropyrone 4.57 to Lactone 3.1

Concurrent with our attempts to produce optically pure dihydropyrone, we began to investigate the transformation of dihydropyrone **4.57** into lactone **3.1**. This was necessary since lactone 3.1 served as the lynchpin of our alkaloid and secoiridoid syntheses and must be intercepted during our asymmetric efforts. A comparison of the

structures of dihydropyrone **4.57** and lactone **3.1** (**Figure 4.7**) reveals that these frameworks differ only in the oxidation state of the olefin and in the ester carbinol functionality. Thus, the formal reduction of the carbon-oxygen bond of the dihydropyrone ring of **4.57** should provide acid **3.15**, which we have shown previously could be esterified with thionyl chloride in methanol to provide the desired methyl ester of lactone **3.1**.

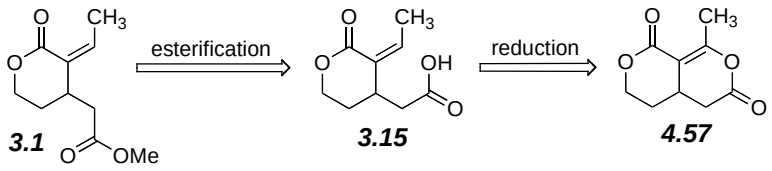
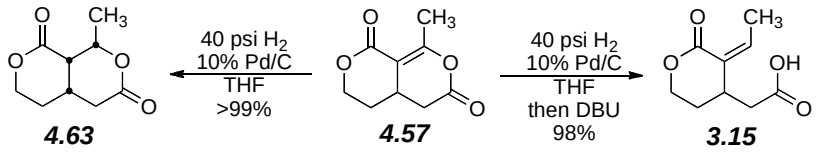


Figure 4.7: Strategy for the conversion of dihydropyrone **4.57** to lactone **3.1**.

Since a direct reduction of the vinyl acetate carbon-oxygen bond was determined to be unlikely to be successful, we decided to attempt a reduction of the dihydropyrone olefin followed by an elimination of the carboxylate side chain thereby effecting a formal, step-wise reduction of the carbon-oxygen bond in question. Stirring dihydropyrone **4.57** in dry THF with catalytic 10% Pd/C overnight under a 40-psi atmosphere of H_2 gave the reduced bicycle **4.63** as a single diastereomer and in quantitative yield (**Scheme 4.30**). If two equivalents of DBU were added to the reaction mixture before product isolation, a nearly quantitative yield of the elimination product, alcohol **3.15**, could be isolated as a single olefin isomer. If even catalytic amounts of DBU were added at the beginning of the reaction only over-reduced product bearing a saturated ethyl side chain was isolated.

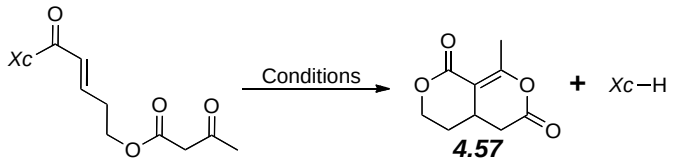


Scheme 4.30: Reduction of dihydropyrone **4.57**.

With confirmation that dihydropyrone **4.57** could be easily converted to lactone **3.1** we continued our efforts to produce optically enriched dihydropyrone **4.57** via cyclization of β-ketoester cyclization precursors.

4.6.4: Synthesis and Base Catalyzed Cyclization of Several Chiral β-Ketoesters

Once chiral HPLC conditions had been identified that could completely and reliably separate the enantiomers of our racemic sample of dihydropyrone **4.57** were identified, we began to attempt the cyclization of various β-ketoesters in an attempt to increase the diastereoselectivity of the reaction. Six distinct cyclization substrates were synthesized by the previously described methods. Each was treated with Cs_2CO_3 in THF at either 0^oC or ambient temperature. The product dihydropyrans were then briefly purified and analyzed by chiral HPLC. The results are summarized in **Table 4.1**.



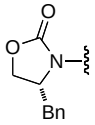
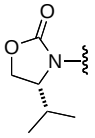
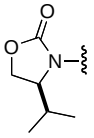
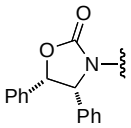
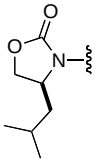
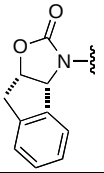
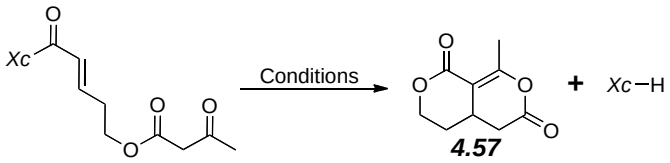
Conditions						
Cs_2CO_3 THF, 0°C	1 : 1.3	1.9 : 1	1 : 2.0	1.3 : 1	1 : 2.1	1 : 2.6
Cs_2CO_3 THF, RT	1 : 1.2	1.2 : 1	1 : 1.2	1.2 : 1	1 : 1.8	1 : 2.5

Table 4.1: Selectivity of various β-ketoester cyclizations. All values represent the enantiomeric ratio (e.r., $t_{r\text{-fast}} : t_{r\text{-slow}}$) of the purified dihydropyrone **4.57** as determined by chiral HPLC. The absolute configurations of the major and minor enantiomers were not identified.

An analysis of the data presented in **Table 4.1** reveals two trends. First, in every case, higher selectivity was obtained at lower temperatures. Secondly, a comparison of the cyclizations of substrates bearing isopropyl auxiliaries of opposite absolute stereochemistry shows that a reversal of the stereochemistry of the chiral auxiliary results in a reversal of the reaction selectivity. Both of these observations are consistent with the results reported by Dwight and Koga for intermolecular conjugate additions to chiral unsaturated imides.

Another observation that should be pointed out is that the cyclizations of the benzyl (first column) and the indene (final column) derived cyclization substrates gave the same product selectivity as substrates bearing chiral auxiliaries with the opposite absolute configuration. This may suggest that substrates bearing these auxiliaries may not proceed through the same *mono*-chelated Lewis acid transition state as the four other cyclization substrates. To further investigate this observation we tested the base

catalyzed reaction of three of the cyclization substrates with a broader solvent selection and at lower temperatures. This data is presented in **Table 4.2**.



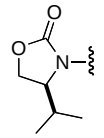
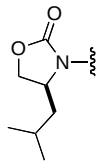
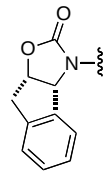
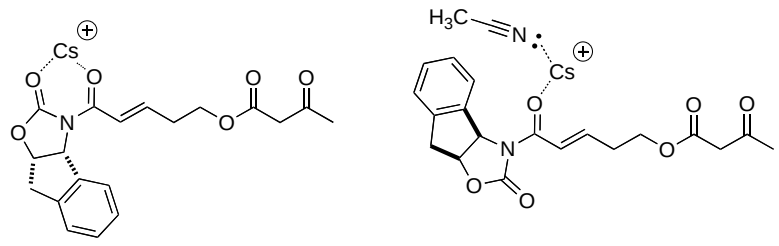
Conditions			
Cs_2CO_3 THF, RT	1 : 1.2	1 : 1.8	1 : 2.5
Cs_2CO_3 THF, 0°C	1 : 2.0	1 : 2.1	1 : 2.6
Cs_2CO_3 THF, -40°C	No Rxn	No Rxn	No Rxn
Cs_2CO_3 MeCN, RT	1 : 1.6	1 : 1.9	1 : 1.6
Cs_2CO_3 MeCN, 0°C	1 : 2.1	1 : 2.1	1.1 : 1
Cs_2CO_3 EtCN, -40°C	No Rxn	1 : 2.8	No Rxn

Table 4.2: Base catalyzed cyclization in THF, MeCN, and EtCN at various temperatures. All values represent the enantiomeric ratio (e.r., $t_{r\text{-fast}} : t_{r\text{-slow}}$) of the purified dihydropyrone as determined by chiral HPLC. The absolute configurations of the major and minor enantiomers were not identified.

As **Table 4.2** illustrates, the isopropyl and isobutyl cyclization substrates (first and second columns respectively) produce expected results. That is, the same enantiomer is favored in every case and lower reaction temperatures result in better reaction selectivity. The results produced from the reaction of the cyclization substrate bearing the indene-derived auxiliary are much more complex. Despite having an absolute configuration opposite to those of the isopropyl and isobutyl substrates, base catalyzed

cyclization of the indene-derived substrate in THF favors the same dihydropyrone enantiomer as the isopropyl and isobutyl substrates. When the cyclization of the indene-derived substrate was performed in cold MeCN rather than THF, a lower selectivity and a reversal of selectivity were observed. We speculated that this might indicate that the extreme steric bulk of the indene-derived imide may prefer to adopt a similar imide rotamer form as the *bis*-chelated transition state rather than the expected *mono*-chelated form when dissolved in relatively nonpolar solvents such as THF (**Figure 4.8**). The more polar MeCN may better solvate the Cs^+ Lewis acid allowing the cyclization substrate to exist in the *mono*-chelated form hence reversing the selectivity of the reaction by blocking the opposite face of the electrophilic olefin.



bis-chelated form *mono*-chelated form

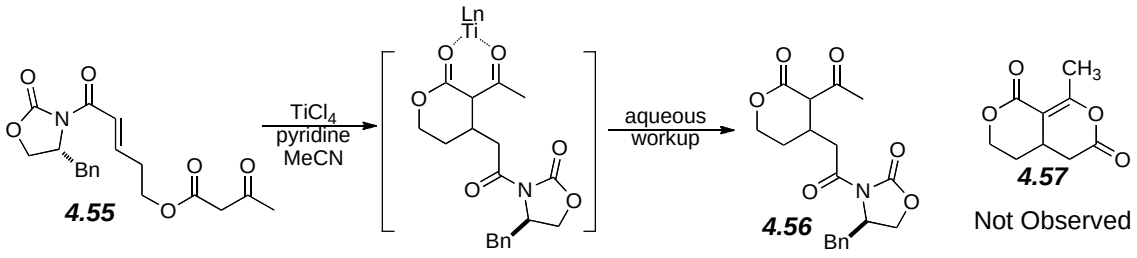
Figure 4.8: Representation of the proposed *mono*- and *bis*-chelated indene-derived cyclization substrates.

4.6.5 $TiCl_4$ Catalyzed Cyclizations of β-Ketoesters

Regardless of the methods or auxiliaries employed, we had yet to meet our goal of developing a cyclization method that would produce a synthetically useful ratio of products. To this end we began to investigate bidentate Lewis acid catalyzed cyclization conditions since, by the formation of a metallocycle in the cyclization transition state

through the chelation of both of the imide carbonyl oxygens, the side chain of the chiral auxiliary would be forced closer to the electrophilic β-carbon, thereby adding a larger bias to the facial selectivity of the reaction. Extrapolation of all of the data obtained indicates that lower reaction temperatures should produce higher product selectivities. We also hoped that the use of an electron deficient Lewis acid might allow cyclizations to occur at lower reaction temperatures and thus increase selectivity.

As observed in the phosphonoacetate series described in the previous section $SnCl_4$ proved to be too harsh for use as our bidentate Lewis acid catalyst since treatment of our β-ketoester substrates with $SnCl_4$ in cold (-78 to 0^oC) THF resulted in rapid elimination of the β-ketoester moiety resulting in the exclusive isolation of the previously observed diene structure. Thankfully our cyclization substrates were stable in the presence of $TiCl_4$ so we began our search for the proper solvent and base combination. Initial experiments in THF resulted in returned starting materials even at ambient temperature so we quickly moved to MeCN as our solvent of choice for these cyclizations.

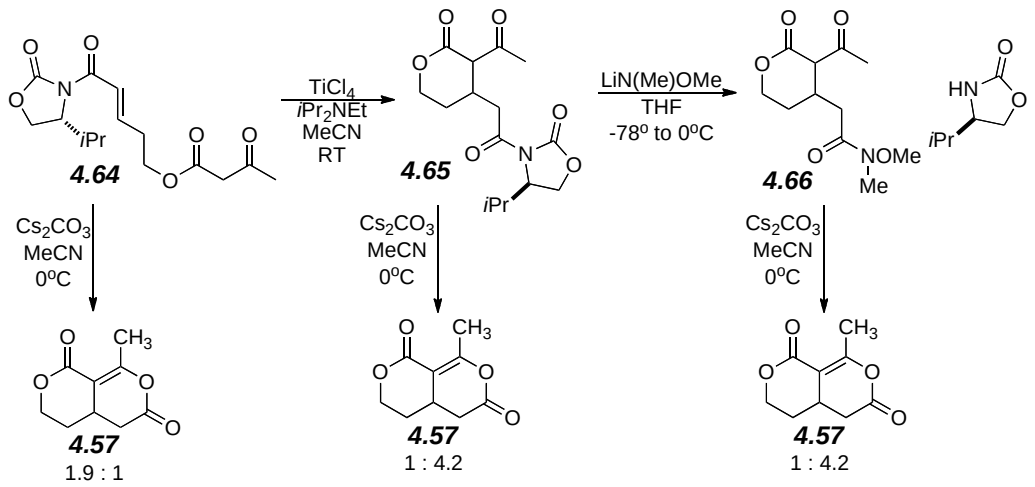


Scheme 4.31: $TiCl_4$ catalyzed cyclization of β-ketoester **4.55**.

As we had hoped, our first successful cyclization of a β-ketoester under bidentate Lewis acidic conditions did not produce dihydropyrone **4.57** (**Scheme 4.31**), rather we were able to isolate the cyclized β-ketolactone intermediate **4.56**. We speculate that after the initial lactone cyclization, the ketone oxygen of the β-ketoester moiety was bound in the pictured 6-membered metallocycle preventing its nucleophilic attack on the imide carbonyl which would the dihydropyrone ring of compound **4.57**. Because the dihydropyrone ring is not formed, the chiral imide remains intact. So, rather than producing a mixture of enantiomers, as in the case of the Cs_2CO_3 catalyzed cyclizations, the $TiCl_4$ catalyzed cyclization produces a mixture of diastereomers, which could potentially be separated prior to the cyclization of the dihydropyrone ring. This could potentially allow access to optically pure lactone **3.1** and thus access to optically pure natural products. Attempts at this separation will be discussed in the next section of this chapter.

In order to determine the diastereoselectivity of the Lewis acid catalyzed cyclizations, we treated the isolated cyclized β-ketoesters with catalytic Cs_2CO_3 to complete the cyclization of the dihydropyrone ring. Since the Cs_2CO_3 and $TiCl_4$ catalyzed cyclization conditions produce opposite diastereoselectivities for the same cyclization substrate we are able to test the reversibility of the Cs_2CO_3 catalyzed cyclizations (**Scheme 4.32**). An ideal test of the reversibility of the Cs_2CO_3 catalyzed cyclization of substrate **4.64** would involve subjecting a single diastereomer of β-ketolactone **4.65** to the Cs_2CO_3 cyclization conditions and determining the enantiomeric ratio of the dihydropyrone **4.57** that was obtained. An erosion of optical purity would indicate that the closure of lactone **4.65** under Cs_2CO_3 conditions was reversible.

Unfortunately, we did not have access to optically pure lactone **4.65** and since the selectivity of the cyclization of lactone **4.65** is inferred after dihydropyrone cyclization, we cannot be sure as to the optical purity of the sample used below. The experiment performed below is less than perfect, however, this undertaking was not meant to definitively investigate this reaction mechanism but to help justify further work attempting to produce optically enriched **4.57** by this method. If the Cs_2CO_3 conditions were found to alter the ratio of diastereomers of lactone **4.65** we would need to find another method of dihydropyran cyclization that does not erode the product selectivity. The isopropyl cyclization substrate **4.64** was chosen for these tests since it performed most closely to the predicted transition state models.

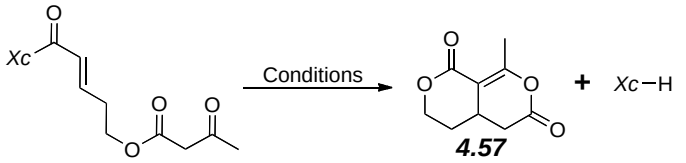


Scheme 4.32: A test of reaction reversibility.

Separate samples of cyclization substrate **4.64** were subjected to the Cs_2CO_3 and $TiCl_4$ cyclization conditions giving dihydropyrone **4.57** and β-ketolactone **4.65** respectively. This β-ketolactone **4.65** sample was then evenly divided into two reactions:

a dihydropyrone cyclization under identical conditions to the Cs_2CO_3 catalyzed cyclization and a displacement of the chiral oxazolidinone to produce Weinreb amide **4.66**, which was subsequently cyclized to dihydropyrone **4.57** under Cs_2CO_3 catalyzed cyclization conditions. The enantiomeric ratios of these three samples of dihydropyrone were then determined to be nearly identical by chiral HPLC. These results suggest that unlike the phosphonoacetate cyclizations, discussed in the previous section of this chapter, the diastereoselectivity of the β-ketoester cyclizations is probably under kinetic rather than thermodynamic control.

Table 4.3 illustrates the results of the attempted cyclization of five chiral β-ketoester substrates in MeCN under Lewis acidic conditions with pyridine as the base. Of note in this data set is the increase in selectivity observed in the cyclizations of the benzyl and isopropyl substrates relative to the Cs_2CO_3 catalyzed cases. Also of note is the reversal in selectivity observed in the isopropyl case relative to its base catalyzed cyclization. This suggests a major change in the geometry of the transition state of this reaction likely from the *mono*-chelated form to the *bis*-chelated form. This switch did not occur in the benzyl case, however. This is likely for the same reason that the substrate bearing the indene-derived chiral auxiliary did invert selectivity when MeCN was substituted for THF. Specifically, because in the relatively nonpolar THF solvent, Cs^+ is capable of chelating both imide carbonyls and thus forcing the transition state to adopt a similar *bis*-chelated geometry to that of the $TiCl_4$ catalyzed transition state.



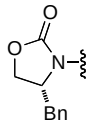
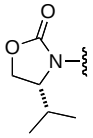
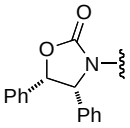
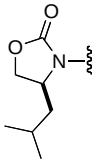
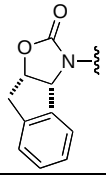
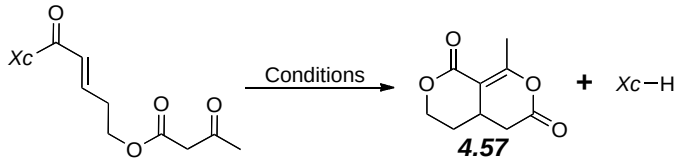
Conditions					
$TiCl_4$, pyridine MeCN, RT then Cs_2CO_3	1 : 2.6	1 : 4.2	No Rxn	No Rxn	No Rxn

Table 4.3: Pyridine as a base for Lewis acid catalyzed cyclizations.

The three failed reactions outlined in **Table 4.3** testify to low reactivity of the cyclization substrates under these conditions. Additionally, no reaction was observed for any of these substrates under these reaction conditions at 0°C. This fact combined with the improved but still not synthetically useful observed diastereoselectivities lead us to investigate new bases in an effort to increase the rate of the reaction at lower temperatures. We hoped that the ability to cyclize these substrates at very low temperatures might also result in improved diastereoselectivities.

Table 4.4 illustrates the results of the $TiCl_4$ catalyzed cyclization of four substrates using Hünig's base rather than pyridine. These conditions allowed the reactions to be performed at a lower temperature likely accounting for the increases in selectivity. We found that it was possible to decrease the temperature of the reaction to as low as -20°C, however no reactions were observed below this temperature under the stated conditions.



4.57

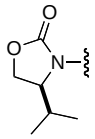
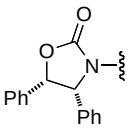
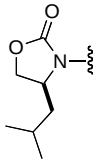
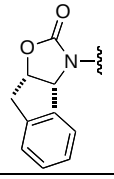
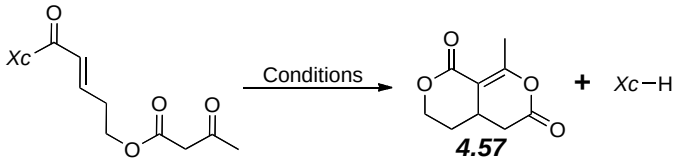
Conditions				
$TiCl_4$, iPr_2NEt MeCN, 0°C then Cs_2CO_3	1.6 : 1	1 : 3.5	1.8 : 1	1 : 6.4

Table 4.4: Hünig's base as a base for Lewis acid catalyzed cyclizations. All values represent the enantiomeric ratio (e.r., $t_{r\text{-fast}} : t_{r\text{-slow}}$) of the purified dihydropyrone as determined by chiral HPLC. The absolute configurations of the major and minor enantiomers were not identified.

4.6.6: Summary of β-Ketoester Cyclizations

Table 4.5 includes all of the reliable data that was accrued during the course of our investigations of the diastereoselectivity of the β-ketoester cyclizations. The best selectivity that was observed was 1 : 7.2 e.r. (76% ee) This selectivity arose from the cyclization of the indene-based substrate under Lewis acidic conditions, employing Hünig's base, and at -20°C.



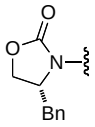
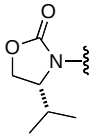
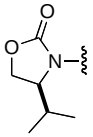
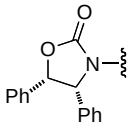
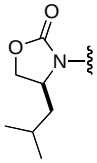
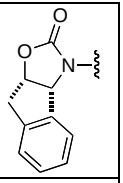
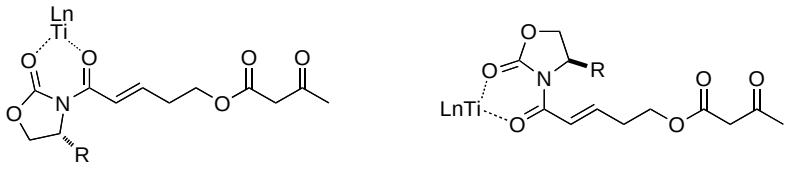
Cyclization Conditions						
Cs_2CO_3, MeCN, RT			1 : 1.6		1 : 1.9	1 : 1.6
Cs_2CO_3, MeCN, 0°C			1 : 2.1		1 : 2.1	1.1 : 1
Cs_2CO_3, EtCN, -40°C			No Rxn		1 : 2.8	No Rxn
Cs_2CO_3, THF, RT	1 : 1.2	1.2 : 1	1 : 1.2	1.2 : 1	1 : 1.8	1 : 2.5
Cs_2CO_3, THF, 0°C	1 : 1.3	1.9 : 1	1 : 2.0	1.3 : 1	1 : 2.1	1 : 2.6
Cs_2CO_3, THF, -40°C			No Rxn	No Rxn	No Rxn	No Rxn
$TiCl_4$, pyr., MeCN, RT	1 : 2.6	1 : 4.2		No Rxn	No Rxn	No Rxn
$TiCl_4$, *i*Pr_2NEt, MeCN, RT			1.3 : 1			
$TiCl_4$, *i*Pr_2NEt, MeCN, 0°C			1.6 : 1	1 : 3.5	1.8 : 1	1 : 6.4
$TiCl_4$, *i*Pr_2NEt, MeCN, -20°C						1 : 7.2
$TiCl_4$, *i*Pr_2NEt, MeCN, -40°C	No Rxn	No Rxn			No Rxn	No Rxn

Table 4.5: Consolidated cyclization selectivity data. All values represent the enantiomeric ratio (e.r., $t_{r\text{-fast}} : t_{r\text{-slow}}$) of the purified dihydropyrone as determined by chiral HPLC. The absolute configurations of the major and minor enantiomers were not identified.

We believe that the reason for the relatively low observed diastereoselectivity relative to the diastereoselectivities reported for intermolecular additions of carbon nucleophiles to unsaturated imides lies in the minimum temperature of reaction. Williams and coworkers attribute their high diastereomeric ratios, at least in part, to their ability to perform their conjugate additions at -78°C. As our results support, lower reaction temperatures of both intermolecular and intramolecular reactions result in more selective conjugate additions. Williams and coworkers explain this observation with the observed presence of higher populations of less stable conformers at higher temperatures

(NMR). **Figure 4.9** illustrates these less stable conformers as applied to our β-ketoester system. The lowest temperature at which we observed cyclization of our substrates was -20°C and to directly quote Williams: "less stable conformers [of type **4.68**] are important contributors to the reactions at -20°C." Cyclization of these less stable conformers results in the production of the opposite epimer to that of the cyclization of the more stable conformer **4.67**. Therefore, higher temperatures lead to higher populations of the less stable conformer and thus erosion of diastereoselectivity. Since our cyclization reactions do not occur below -20°C we cannot decrease the temperature to increase selectivity. Thus, I believe that we have maximized the diastereoselectivity of these cyclizations.



More stable conformer ***4.67*** Less stable conformer ***4.68***

Figure 4.9: Two conformational isomers of the β-ketoester cyclization substrates.

4.6.7 Efforts Toward the Separation of β-Ketoester Diastereomers

Although the above described cyclizations cannot deliver a product of sufficient optical purity for the synthesis of enantiopure natural products, we hoped that through the separation of the diastereomeric β-ketoester intermediates we could produce optically pure dihydropyrone **4.57**. Unfortunately, we were unable to separate the diastereomers of the isolated cyclization intermediates regardless of the chiral auxiliary that was employed. These β-ketoesters were isolated as oils or foams and all attempts at crystallization failed. Efforts to separate these diastereomers by flash chromatography

were hindered by the equilibration of the β-ketoester and vinylogous carbonate tautomers (**Figure 4.10**), resulting in streaking and co-elution regardless of the solid or mobile phases employed. An added hindrance to diastereomer separation was the slow but spontaneous conversion of these β-ketoesters into dihydropyrone **4.57**, even when stored neat or frozen in benzene. In fact, silica gel seemed to accelerate this undesired cyclization.

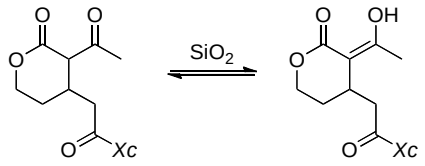
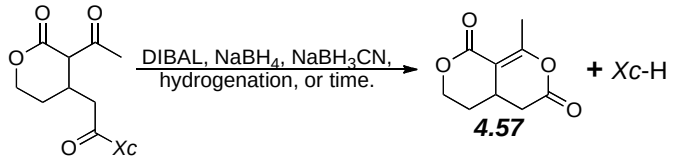


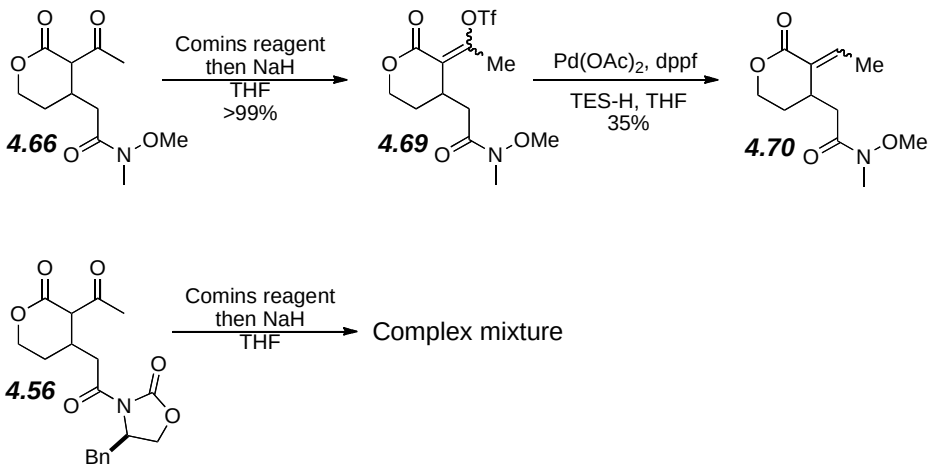
Figure 4.10: Equilibration of the β-ketoester and vinylogous carbonate tautomers.

We planned a solution to these problems involving the immediate modification of the β-ketoester moiety of these compounds followed by separation of the modified diastereomers. Reduction of the ketone carbonyl of β-ketolactone intermediate seemed to be the most logical modification to attempt first since it would eliminate this problematic functionality, which at some stage needed to be reduced in order to access the desired natural product targets. Unfortunately, treatment of the β-ketolactones with hydride reducing reagents such as DIBAl-H, $NaBH_4$, and $NaBH_3CN$ or hydrogenation conditions (H_2, Pd/C, or H_2, PtO_2) resulted in dihydropyrone cyclization (**Scheme 4.33**) often followed by decomposition.



Scheme 4.33: Undesired cyclizations of β-ketoester substrates.

We next attempted to form the vinyl triflate of the enol form of β-ketolactones guessing that we may then be able to directly reduce the product (**Scheme 4.34**). Treatment of β-ketolactone **4.56** or the achiral Weinreb amide **4.66** with NaH resulted in immediate dihydropyrone cyclization. We found that if the Weinreb amide **4.66** was premixed with Comins reagent and then treated with NaH, the desired vinyl triflate **4.69** was delivered in quantitative yield. This vinyl triflate was successfully reduced using transfer hydrogenation conditions to give Weinreb amide **4.70** as a mixture of olefin isomers. Although this strategy worked for the achiral Weinreb amide system, no desired products were isolated when the β-ketoesters bearing chiral imides were subjected to similar conditions. The premixing of these β-ketoesters with Comins reagent followed by treatment with NaH resulted in a complex mixture of compounds. No product or cyclized dihydropyrone **4.57** was observed. Although separation efforts are ongoing, no optically pure intermediates leading to lactone **3.1** have been prepared.



Scheme 4.34: Reduction of Weinreb amide β-ketoester **4.66**.

4.7 Chapter Summary

The stated goal of this chapter was to produce optically pure lactone **3.1**. We first attempted attempted to accomplish this goal by reacting pyrroleamide nucleophiles with an alkylidene malonate electrophile in the presence of a chiral catalyst. We attributed the lack of observed reactivity to the steric encumbrance of substituents near the reactive centers. Intramolecular reactions between an alkylidene malonimide electrophile, similar in structure to the alkylidene malonate electrophile, and tethered nucleophiles also did not produce a cyclized product due to their rapid elimination of the tethered nucleophile. We then switched to a less labile electrophile and concentrated on cyclizing chiral α,β-unsaturated imides tethered to various nucleophiles. Cyclizations were observed for those substrates bearing thioester, phosphonoacetate, and β-ketoester nucleophiles. The thioesters were abandoned due to the instability of the cyclized products and the phosphonoacetates due to poor diastereoselectivity likely resulting from the reversibility of the cyclization.

Cyclizations of substrates bearing β-ketoester nucleophiles proved to be the most successful in terms of product stability and diastereoselectivity. We were also able to show that the product of these cyclizations could be readily converted to lactone **3.1**. Unfortunately, our best results provided the desired product in only 76% enantiomeric excess and we have been unable to separate the intermediate diastereomers. We believe this poor selectivity to be due to an undesired transition state rotamer whose population has previously been demonstrated to increase with temperature. Thus, the inability of our substrates to cyclize below -20^{o}C prevents us from achieving the desired level of optical purity. To date, our goal of producing optically pure lactone **3.1** has not been achieved. Future work in this regard will probably require the development of a new synthetic strategy.

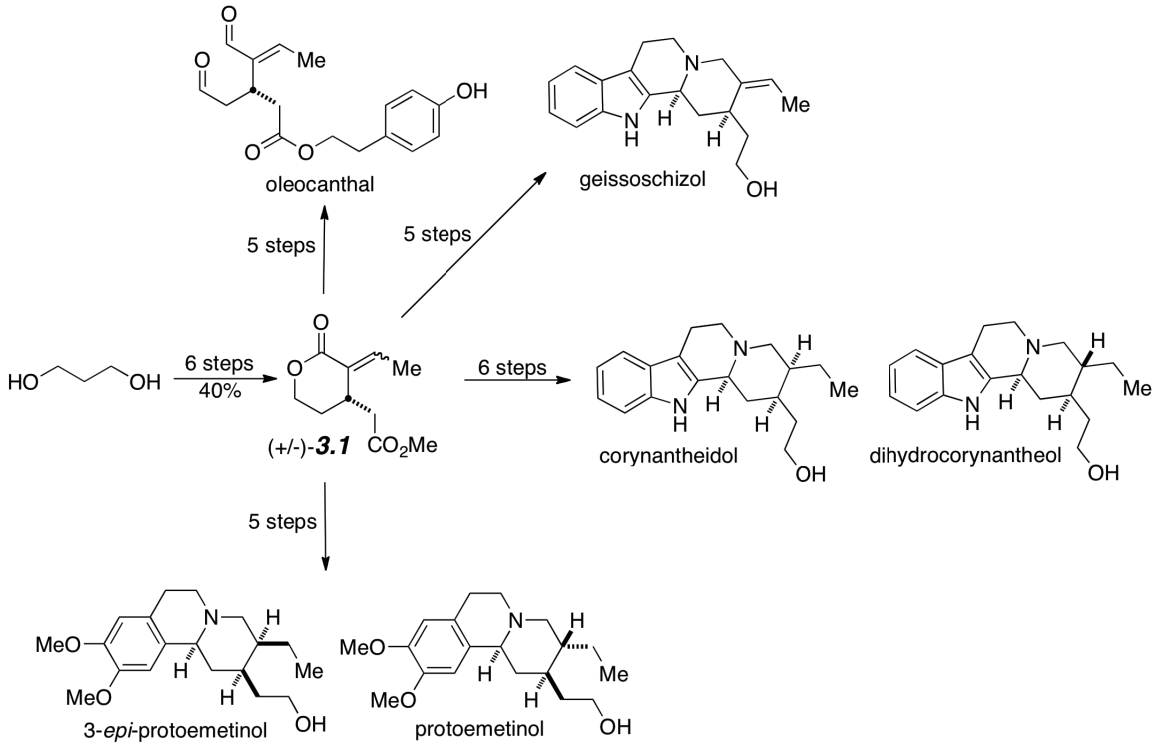
Chapter 5: Concluding Remarks and Future Work

5.1: Concluding Remarks

Our goal for this project was to develop a synthetic strategy that would allow us to rapidly synthesize members of several classes of secologanin derived natural products or their unnatural analogues from a single late-stage intermediate. The reasons that we undertook this goal are no different from the reasons that the total synthesis of natural products remains relevant today. The total synthesis of natural products and their analogues is the only tool available to modern chemists that can simultaneously allow one to confirm or amend the proposed structures of newly isolated natural products, to provide supplies of closely related unnatural analogues and natural product enantiomers for biological testing, to allow the testing of structure-activity hypotheses, to synthesize isotopically labeled intermediates to aid in the elucidation of biosynthetic pathways, and to study the unusual reactivity of complex, naturally occurring structures.

Our approach differs from most of the previously described strategies for the synthesis of secologanin natural products only in its scope. Rather than developing a novel synthetic approach that addresses the synthetic challenges of individual compounds or small classes of compounds, we attempted to mimic the approach of nature and develop an approach that proceeds through a synthetic branch point. Lactone **3.1** is ideal for this purpose since it is relatively densely functionalized while remaining general enough as to not require the removal of structural complexity during the synthesis of the desired structural frameworks. We have shown that lactone **3.1** is a very effective synthetic intermediate allowing access to each of the six natural products that we attempted to synthesize. In addition, racemic lactone **3.1** proved to be relatively easy to

synthesize on large scale providing much needed material for our many synthetic routes. **Scheme 5.1** summarizes our success in this regard.



Scheme 5.1: Summary of synthetic success.

Despite a great deal of effort, we were unable to produce optically pure lactone **3.1**. Our best efforts produced lactone **3.1** in only 76% e.e. and we were unable to separate the intermediate diastereomers. This remains the most important unsolved problem of this project and, unless conditions can be identified to separate these intermediate diastereomers, will likely require a redesigned asymmetric synthesis of lactone **3.1**.

5.2: Future Work

The first problem that should be addressed with future work is the large scale preparation of optically pure lactone **3.1** either through the separation of the diastereomeric mixture of intermediates produced during our asymmetric efforts or through the development of a new synthetic strategy. **Figure 5.1** outlines a redesigned retrosynthesis that may give optically pure lactone **3.1**. This retrosynthesis derives the methyl ester moiety of lactone **3.1** from the oxidative cleavage of the more electron rich olefin of compound **5.1**, which could be synthesized via HWE olefination of phosphonate **5.2**. The lactone ring of phosphonate **5.2** would be derived from the stereospecific S_N^2 displacement of the mesylate moiety of linear substrate **5.3** with the enolate of the phosphonoacetate moiety. This linear substrate could be obtained through esterification of alcohol **5.4**, which could be readily derived from alcohol **5.5** via mesylation and TBS ether deprotection. This chiral alcohol has been previously synthesized as either optically pure antipode by the asymmetric allylation of aldehyde **3.5**[86].

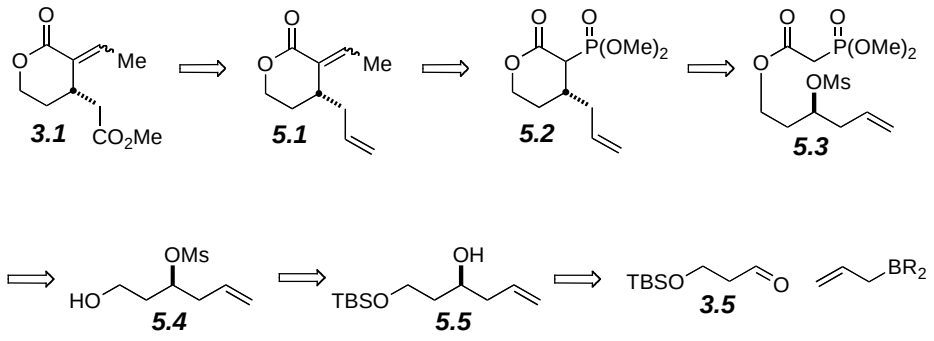


Figure 5.1: Improved retrosynthesis of lactone **3.1**.

A similar retrosynthetic plan, pictured in **Figure 5.2,** utilizes the cyclization of a tethered β-ketoester rather than a phosphonoacetate. We have previously shown that lactone **3.1** can be synthesized from lactone **4.57** by a one-step reduction and elimination followed my esterification of the resulting acid. We have also shown that lactone **4.57** could be derived from acid **4.56** via $SOCl_2$ induced cyclization. This acid could be derived from the oxidative cleavage of the terminal olefin of compound **5.6**, which could be derived via S_N^2 displacement of the mesylate of **5.7**, derived from the esterification of alcohol **5.4** with diketene.

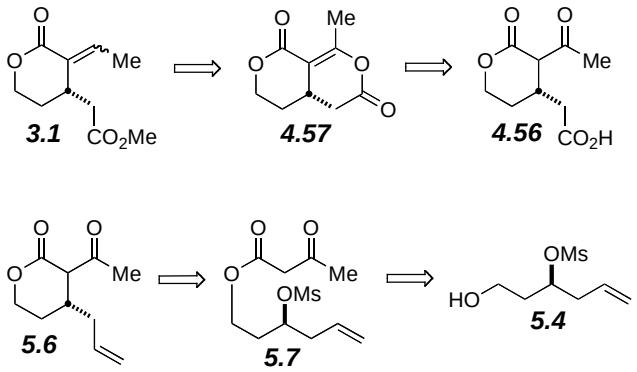


Figure 5.2: A β-ketoester mesylate displacement.

The chief benefit of the above outlined retrosyntheses compared to our previous plans is that the lactone **3.1** stereogenic center is established by the stereospecific displacement of an optically pure alcohol. This eliminates the potential for the poor cyclization selectivities observed during our Michael cyclizations. Additionally, the substitution of an olefin for the unsaturated imide or unsaturated ester Michael acceptors eliminates the possibility of the undesired eliminations observed with these previous substrates allowing for the use of harsh cyclization conditions if necessary.

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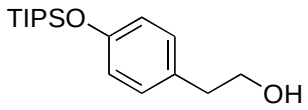
Chapter 6: Experimental Procedures

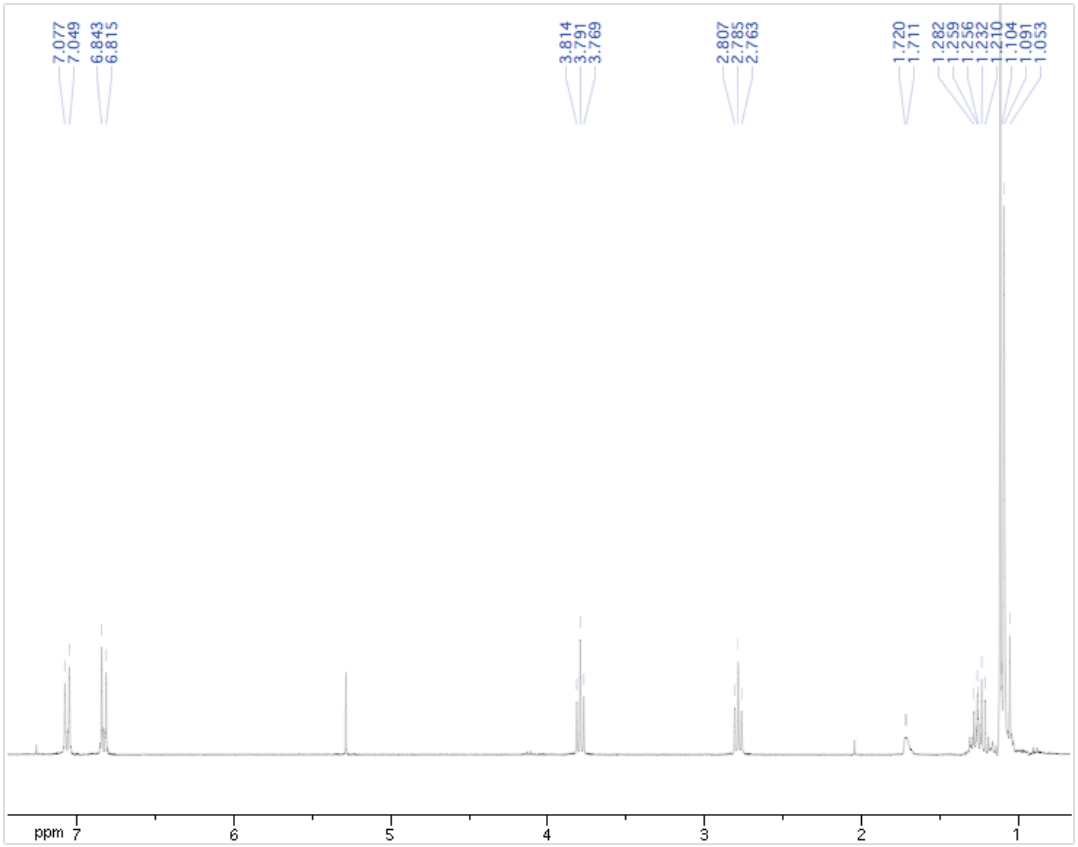
Unless otherwise noted, all reagents were obtained from commercial suppliers and were used without further purification. All air or moisture sensitive reactions were performed under a positive pressured of argon in flame-dried glassware. Tetrahydrofuran (THF), toluene, diethyl ether (Et_2O), dichloromethane, benzene (PhH), acetonitrile (MeCN), triethylamine (NEt_3), pyridine, diisopropyl amine, methanol (MeOH), dimethylsulfoxide (DMSO), and N,N-dimethylformamide (DMF) were obtained from a dry solvent system (Ar degassed solvents delivered through activated alumina columns, positive pressure of argon). Column chromatography was performed on Merck silica gel Kieselgel 60 (230-400 mesh). Melting points were determined in open-end capillary tubes and are uncorrected. ^{1}HNMR and ^{13}CNMR spectra were recorded on Varian 300, or 400 MHz spectrometers. Chemical shifts are reported in ppm relative to $CHCl_3$ at δ 7.27 (^{1}HNMR) and δ 77.23 (^{13}CNMR). Mass spectra were obtained on Fisons VG Autospec. IR spectra were obtained from thin films on a NaCl plate using a Perkin-Elmer 1600 series FT-IR spectrometer. Optical rotations were collected at 589 nm on a Rudolph Research automatic polarimeter Autopol III.



Synthesis of 2-(4-(triisopropylsilyloxy)phenyl)ethanol (3.16): To 2.00 g (14.5 mmol, 1 equiv.) 4-(2-hydroxyethyl)phenol dissolved in 35 mL dry THF at 0^{o}C was added 608 mg (15.2 mmol, 1.05 equiv.) NaH as a 60% suspension in mineral oil. After stirring at 0^{o}C for 30 min 3.10 mL (14.5 mmol, 1equiv.) TIPSCl was added and the reaction was stirred for 4 hr at ambient temperature before being added to brine and extracted thrice with EtOAc. Combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by silica gel flash chromatography eluting with 2 : 1 hex./EtOAc to yield 3.99 g (94%) of the desired product as a colorless oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.06 (dt, *J* = 8.7, 2.1, 2H), 6.83 (dt, *J* = 8.4, 2.1, 2H), 3.80 (t, *J* = 6.6, 2H), 2.79 (t, *J* = 6.6, 2H), 1.72 (bs, 1H), 1.18-1.30 (m, 3H), 1.11 (s, 18H); ^{13}CNMR (75MHz, $CDCl_3$) δ. 154.8, 130.8, 130.7, 120.0, 63.9, 33.5, 18.0, 12.8; IR (NaCl, film) 3334, 1610; HRMS (+TOF) calcd for $C_{17}H_{31}O_2Si$ $[M+H]^+$ 295.20878, found 295.20892; R_f = 0.52 (1:1 hex./EtOAc)

Ref.: BJEIV305, BJEIV314, BJEIV328, **BJEV021**.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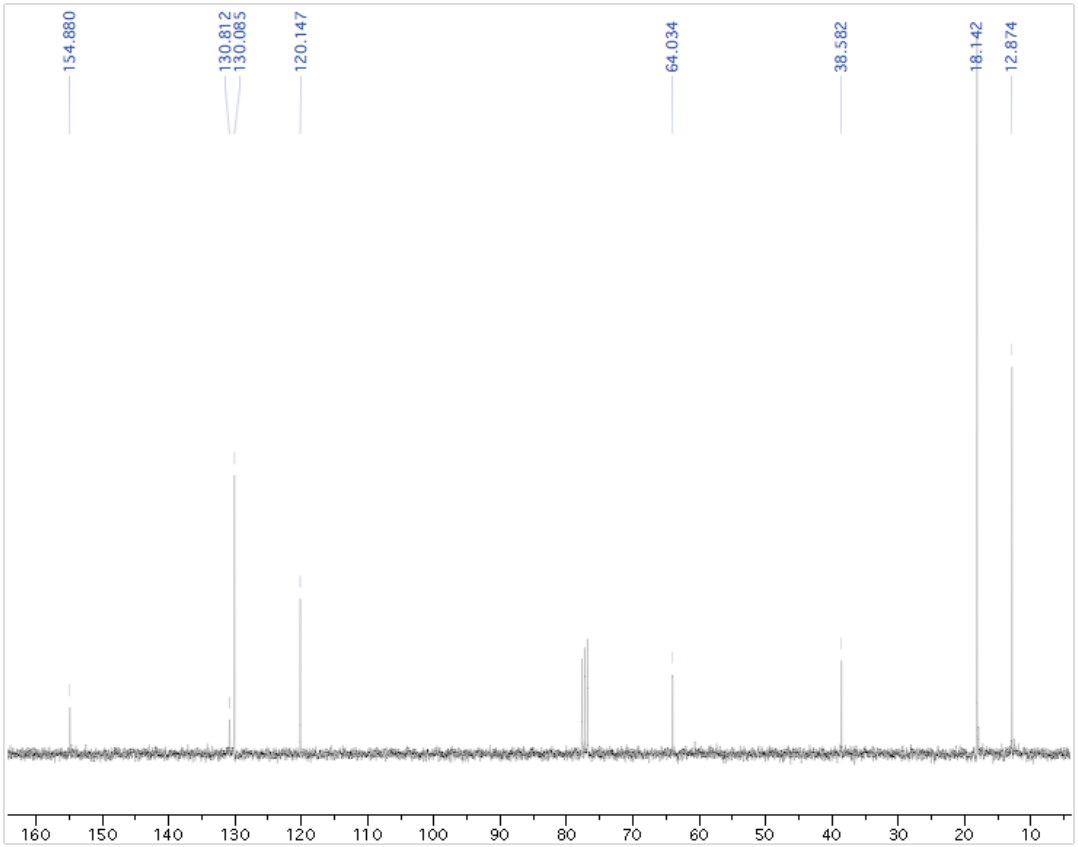
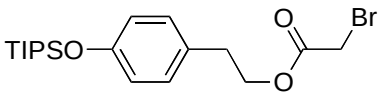


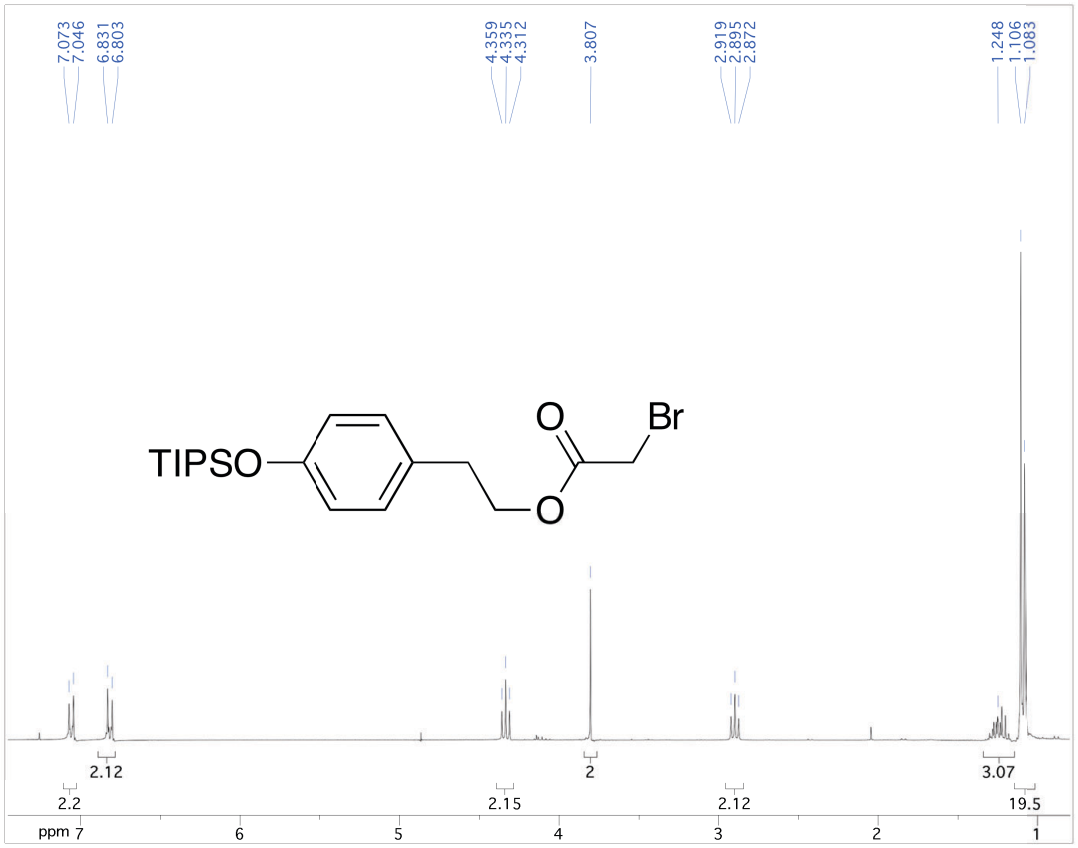


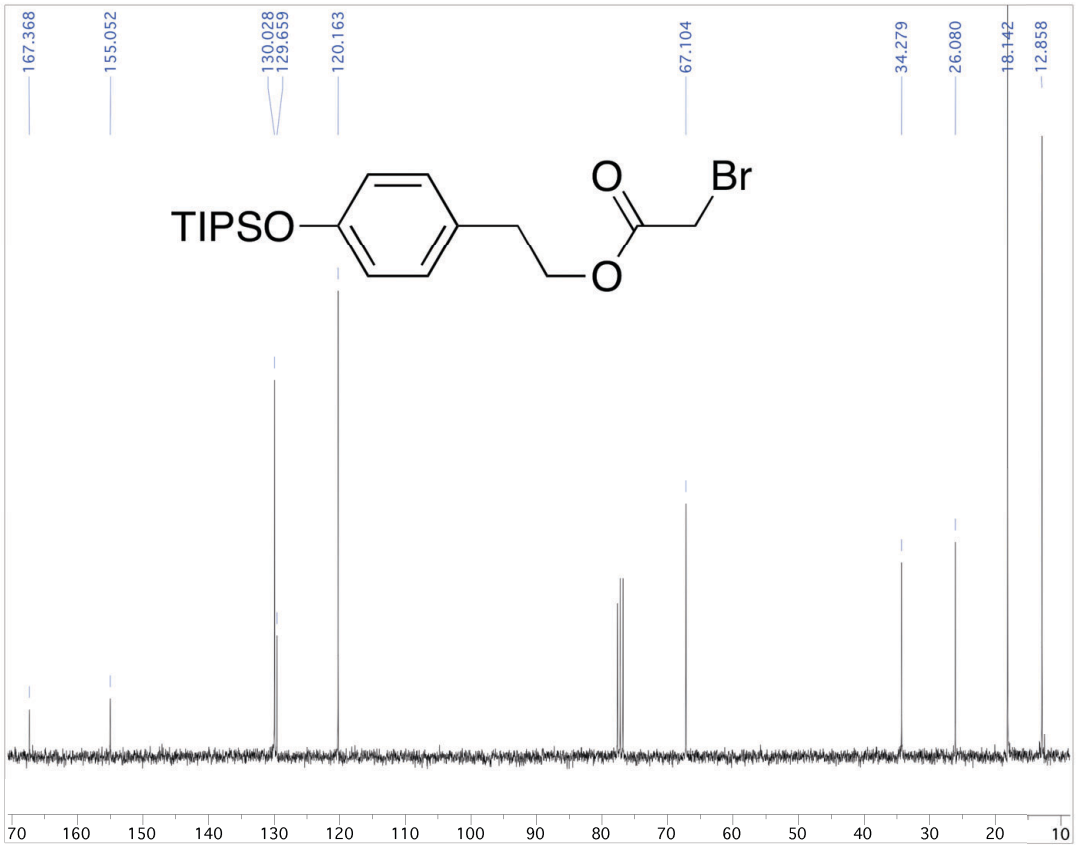
Synthesis of 4-((triisopropylsilyl)oxy)phenethyl 2-bromoacetate : To a 100 mL round-bottomed flask containing 1.45 g (4.92 mmol, 1 equiv.) alcohol **3.16** dissolved in 23 mL dry THF at 0^{o}C was added 516 μL (5.91 mmol, 1.2 equiv.) bromoacetyl bromide followed by 823 μL (5.91 mmol, 1.2 equiv.) dry NEt_3. The reaction was allowed to stir for 1 hr at ambient temperature before being added to $NaHCO_{3(sat.)}$, extracted thrice with EtOAc, dried over Na_2SO_4, and concentrated to yield 1.99 g (98%) of the desired product as a pale yellow oil.

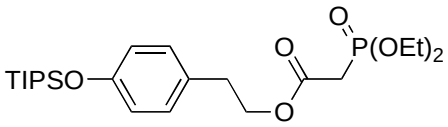
^{1}HNMR (300 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.1, 2H), 6.82 (d, *J* = 8.4, 2H), 4.34 (t, *J* = 7.2, 2H), 3.81 (s, 2H), 2.90 (t, *J* = 7.2, 2H), 1.25 (m, 3H), 1.09 (d, *J* = 6.9, 18H); ^{13}CNMR (75

MHz, $CDCl_3$) δ 167.4, 155.1, 130.0, 129.7, 120.1, 67.1, 34.3, 26.1, 18.1, 12.9; IR (NaCl, film): 1739 cm^{-1}; R_f = 0.78 (1 : 1 hex./EtOAc).

Ref.: **BJEIV458**.





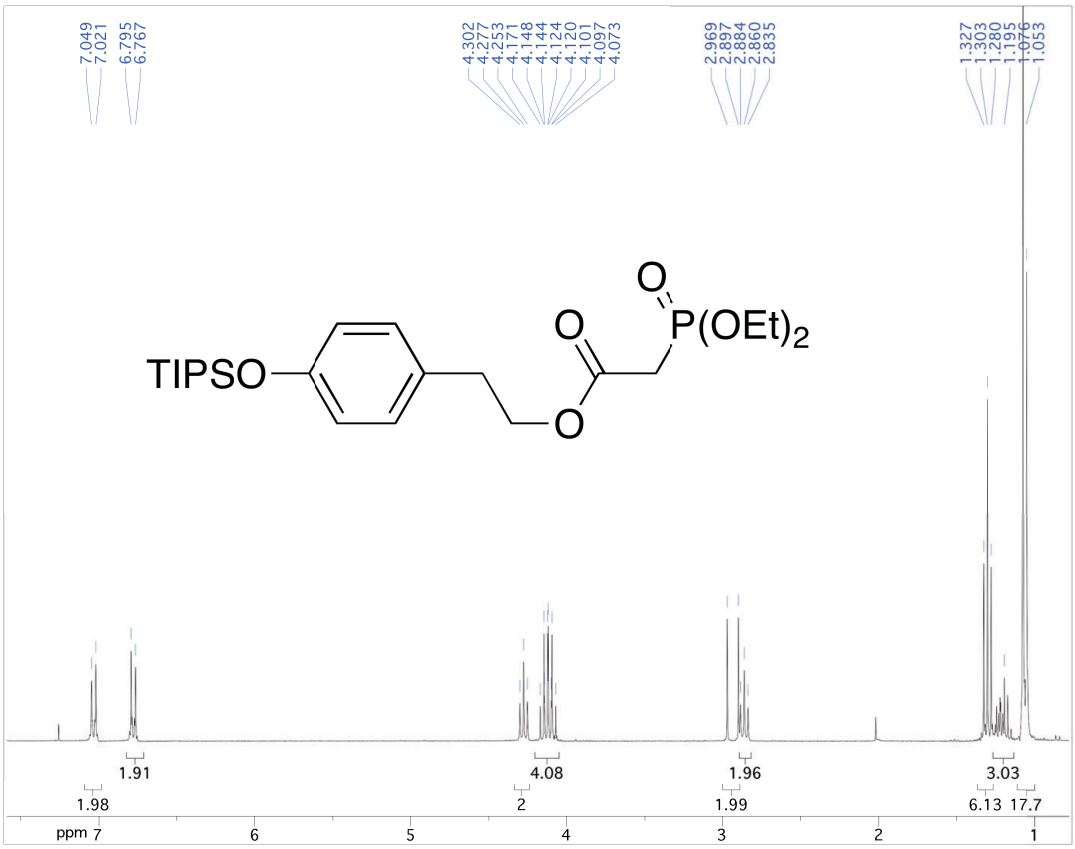


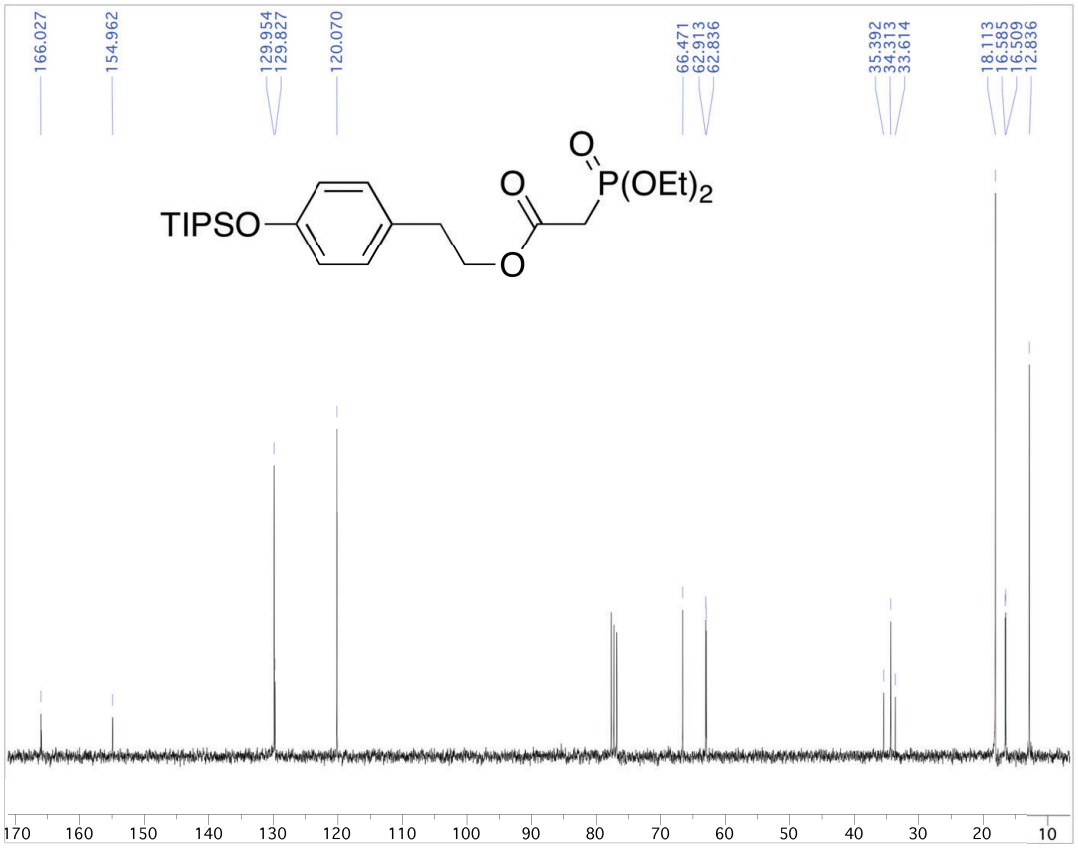
Synthesis of 4-((triisopropylsilyl)oxy)phenethyl 2-(diethoxyphosphoryl)acetate: To a 25 mL round bottomed flask contiaining 1.99 g (4.79 mmol, 1 equiv.) 4-((triisopropylsilyl)oxy)phenethyl 2-bromoacetate was added 2.46 mL (14.37 mmol, 3 equiv.) $P(OEt)_3$. The reaction was heated to 100^{o}C for 15 min and then concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 1 : 2 hex./EtOAc to yield 2.08g (92%) of the desired product as a colorless oil.

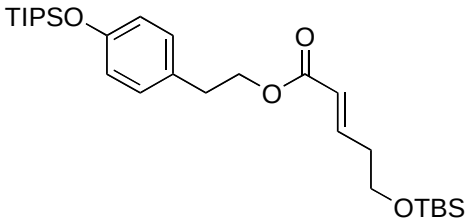
^{1}HNMR (300 MHz, $CDCl_3$) δ 7.03 (d, J = 8.4, 2H), 6.78 (d, J = 8.4, 2H), 4.28 (t, J = 7.5, 2H), 4.12 (m, 4H), 0.93 (d, J_{HP} = 21.6, 2H), 2.86 (t, J = 7.5, 2H), 1.30 (t, J = 7.2, 6H), 1.20 (m, 3H), 1.06 (d, J = 6.9, 18H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 166.0, 155.0, 130.0,

129.8, 120.1, 66.5, 62.9, 62.8, 35.4, 34.3, 33.6, 18.1, 16.6, 16.5, 12.8; IR (NaCl, film): 1739, 1609 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 473.2483 calcd for $C_{23}H_{42}O_6PSi$, found: 473.2479; R_f = 0.32 (1 : 2 hex./EtOAc).

Ref.: **BJEIV459**





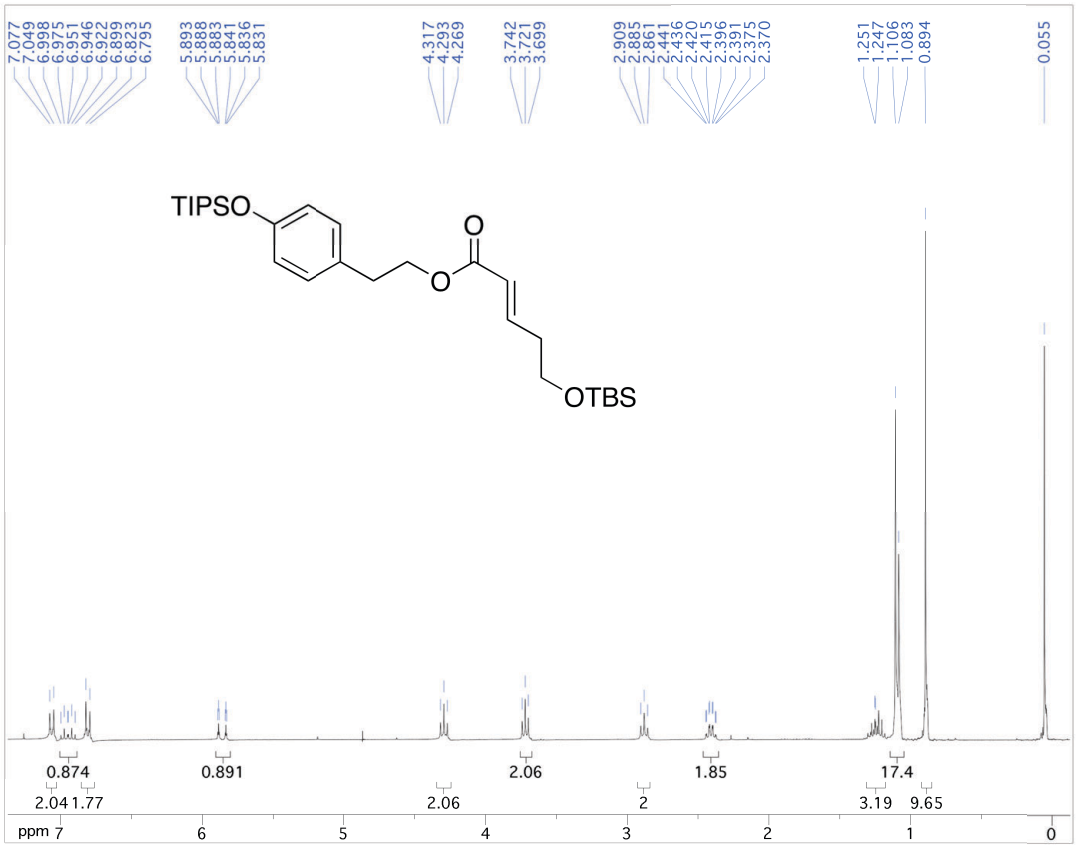


Synthesis of (*E*)-4-((triisopropylsilyl)oxy)phenethyl 5-((*tert*-butyldimethylsilyl)oxy)pent-2-enoate: To a 100 mL round-bottomed flask containing 1.85 g (3.92 mmol, 1 equiv.) 4-((triisopropylsilyl)oxy)phenethyl 2-(diethoxyphosphoryl)acetate and 200 mg (4.70 mmol, 1.2 equiv.) LiCl was added 20 mL dry MeCN followed by 586 μL (3.92 mmol, 1 equiv.) DBU. The reaction was allowed to stir at ambient temperature for 15 min before the addition of 885 mg (3.92 mmol, 1

equiv.) aldehyde **3.5** dissolved in a minimum of dry MeCN. The reaction was stirred for a further 1.5 hr before being added to brine, extracted into EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was taken up in 9 : 1 hex./EtOAc and passed through a short silica gel plug. Concentration yielded 1.343 g (67%) of the desired product as a colorless oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.4, 2H), 6.95 (dt, *J* = 15.9, 6.9, 1H), 7.81 (d, *J* = 8.4, 2H), 5.86 (dt, *J* = 15.6, 1.5, 1H), 4.29 (t, *J* = 7.2, 2H), 3.72 (t, *J* = 6.6, 2H), 2.89 (t, *J* = 7.2, 2H), 2.40 (qd, *J* = 6.3, 1.5, 2H), 1.25 (m, 3H), 1.09 (d, *J* = 6.9, 18H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}CNMR (75MHz, $CDCl_3$) δ 166.6, 154.9, 146.3, 130.4, 130.0, 123.0, 120.1, 65.2, 61.7, 35.9, 34.6, 26.1, 18.1, 12.9 -5.1; IR (NaCl, film): 1721, 1657, 1610, 1510 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 507.3320 calcd for $C_{28}H_{51}O_4Si_2$, found: 507.3307; R_f = 0.35 (9 : 1 hex./EtOAc).

Ref.: BJEIV461, **BJEIV465**.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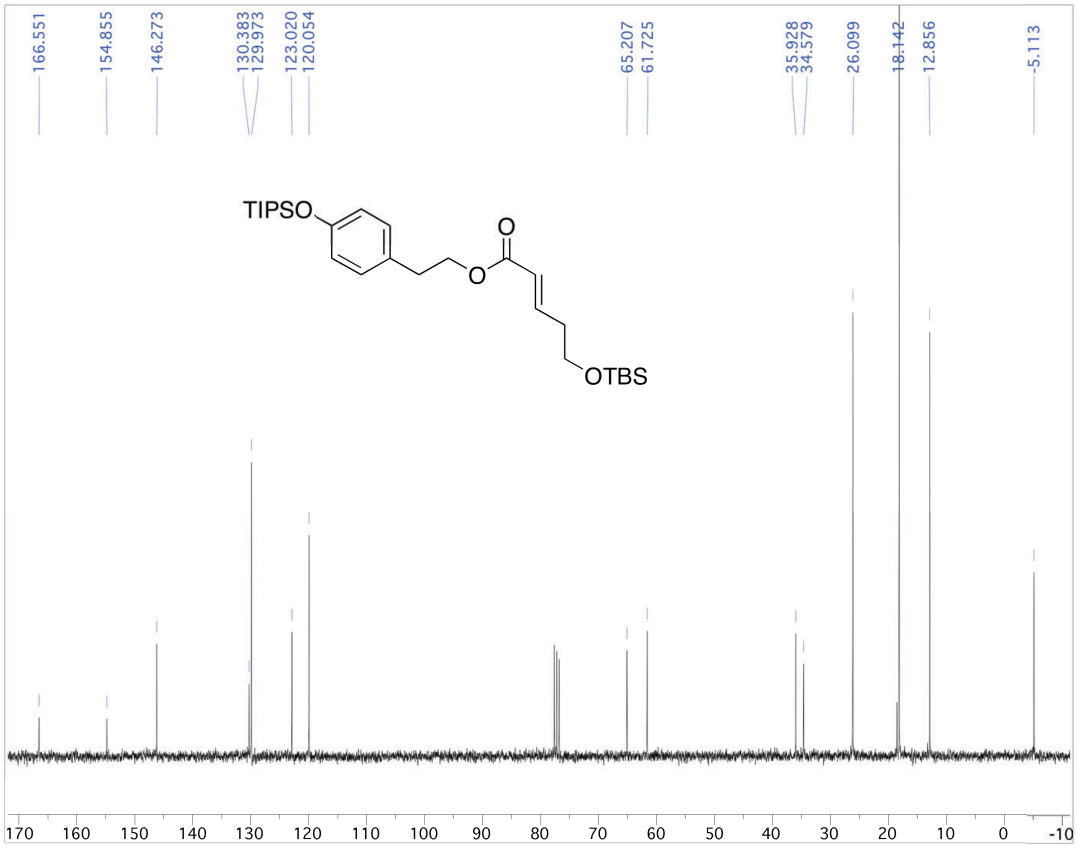
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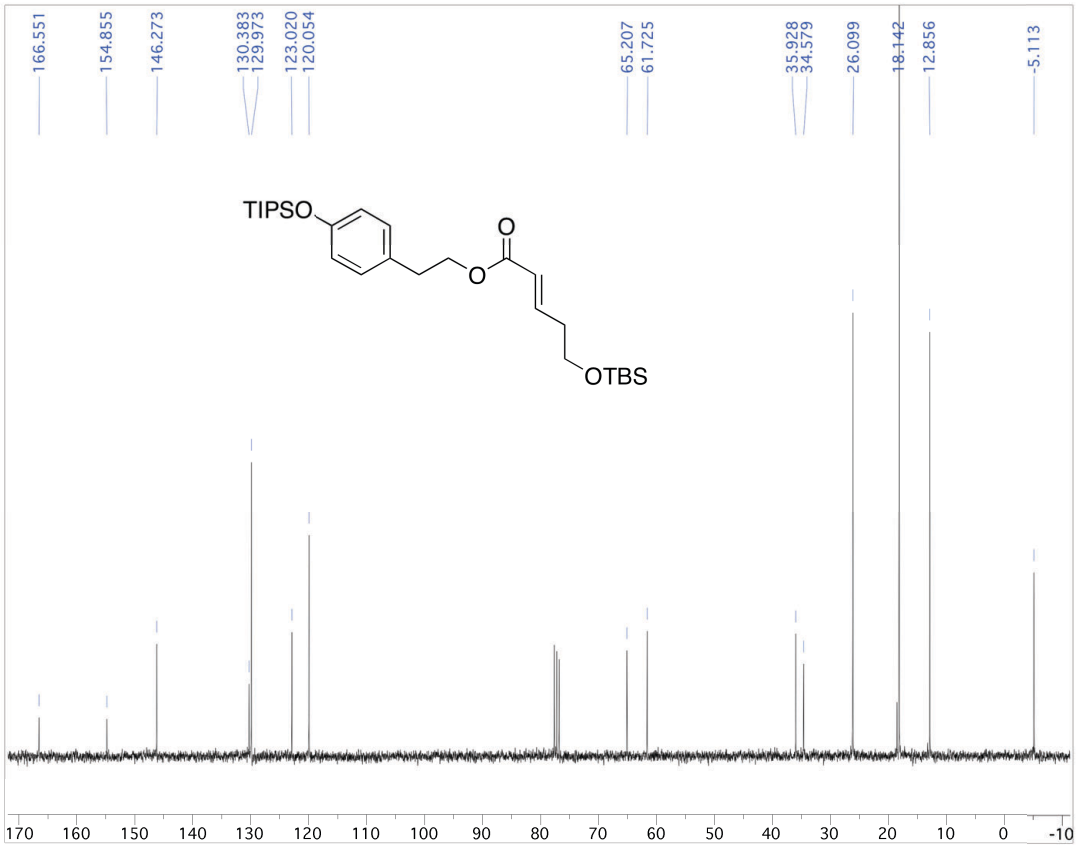
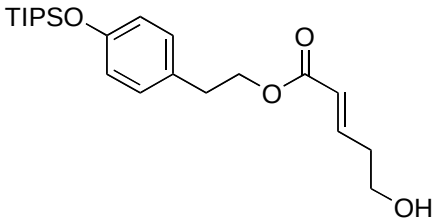


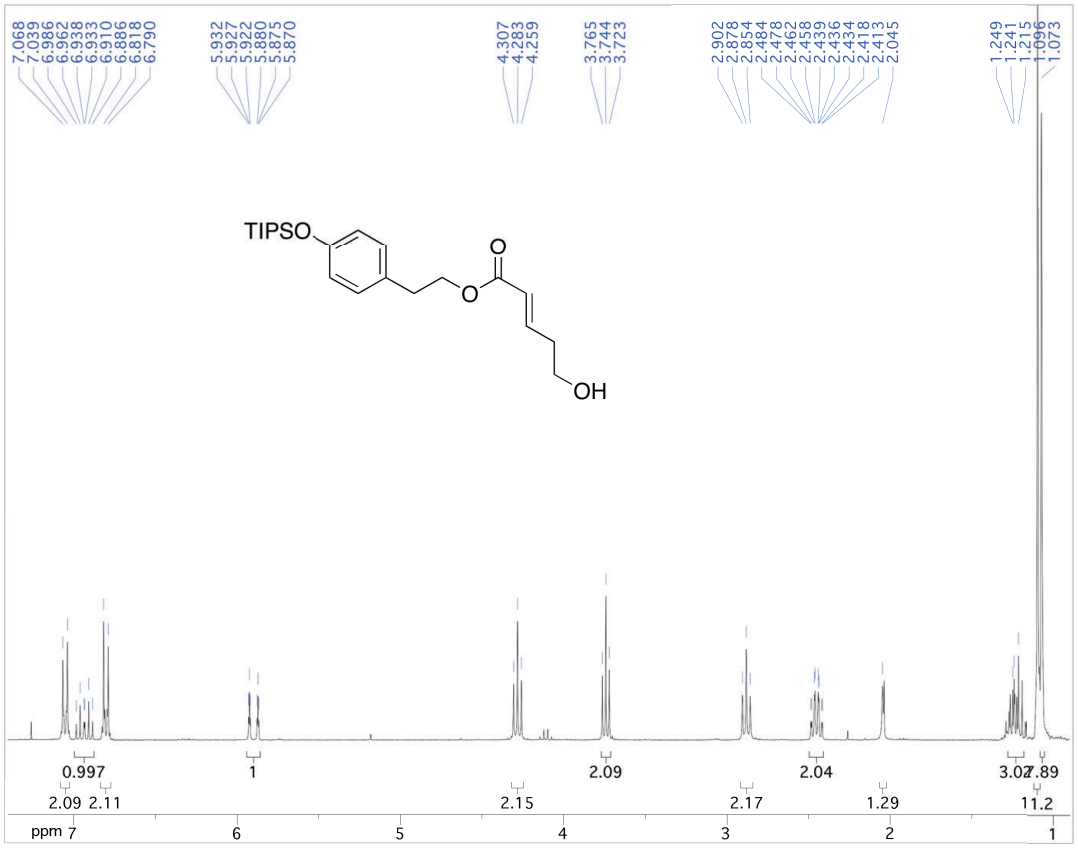


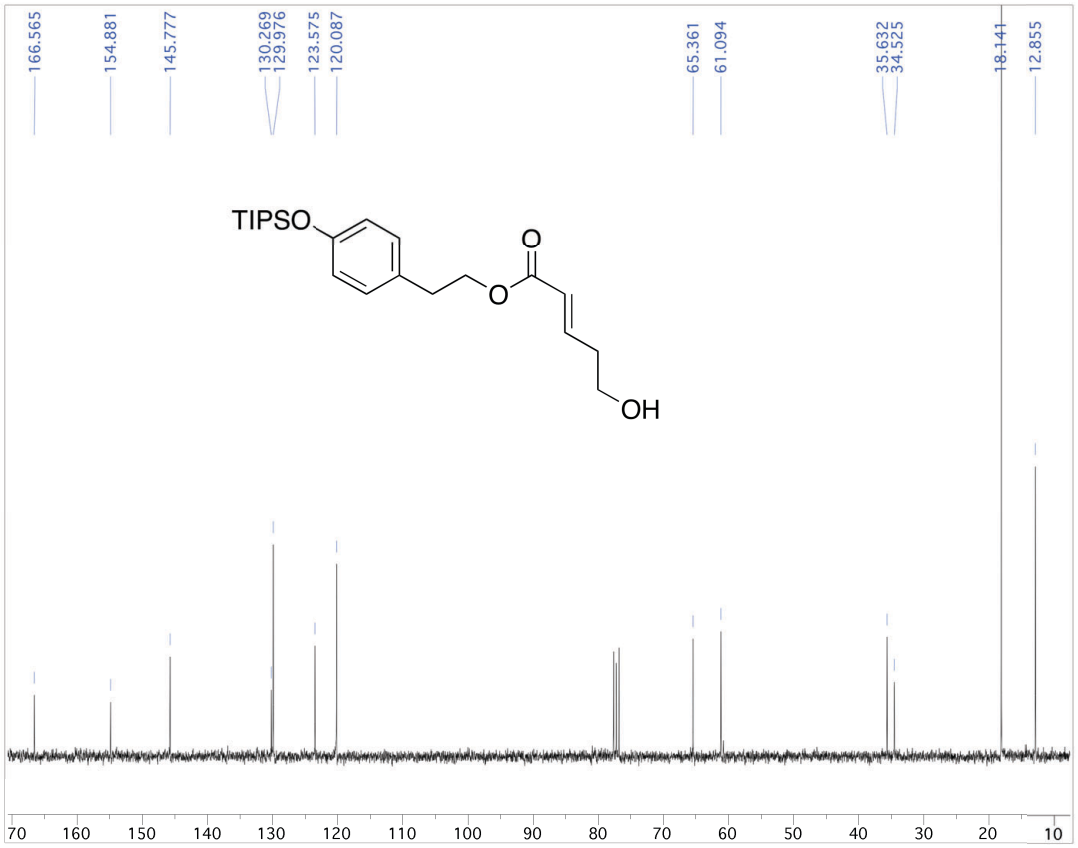
Synthesis of (*E*)-4-((triisopropylsilyl)oxy)phenethyl 5-hydroxypent-2-enoate: To a 100 mL HDPE bottle containing 1.23 g (2.43 mmol, 1 equiv.) (*E*)-4-((triisopropylsilyl)oxy)phenethyl 5-((*tert*-butyldimethylsilyl)oxy)pent-2-enoate was added 729 μL 48% aqueous HF. The reaction was stirred at ambient temperature for 1.5 hr and then was added to $NaHCO_{3(sat.)}$, extracted thrice with EtOAc, dried over Na_2SO_4, and concentrated. The crude residue was purified by silica gel flash chromatography

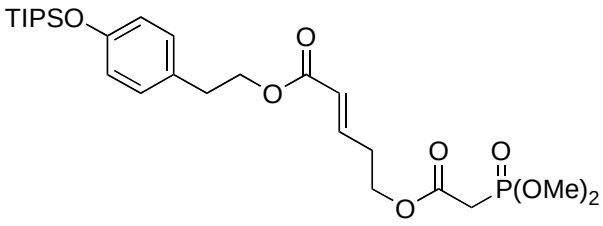
eluting with 2 : 1 to 1 : 1 hex./EtOAc to yield 152 mg of the unaltered starting material along with 795 mg of the desired product as a colorless oil (95% BRSM).

^{1}HNMR (300MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.7, 2H), 6.94 (dt, *J* = 15.6, 7.2, 1H), 6.80 (d, *J* = 8.4, 2H), 5.90 (dt, *J* = 15.6, 1.5, 1H), 4.28 (t, *J* = 7.2, 2H), 3.74 (t, *J* = 6.3, 2H), 2.88 (t, *J* = 7.2, 2H), 2.44 (qd, *J* = 6.6, 1.8, 2H), 2.05 (bs, 1H), 1.24 (m, 3H), 1.08 (d, *J* = 7.0, 18H); ^{13}CNMR (75MHz, $CDCl_3$) δ 166.6, 154.9, 145.8, 130.3, 130.0, 123.6, 120.1, 65.4, 61.1, 35.6, 34.5, 18.1, 12.9; IR (NaCl, film): 3429, 1716, 1653, 1609 cm^{-1}; HRMS (+TOF): $[M+Na]^+$ 415.2281 calcd for $C_{22}H_{36}NaO_4Si$, found: 415.2279; R_f = 0.43 (1 : 1 hex./EtOAc).

Ref.: BJEIV466, **BJEIV471**.

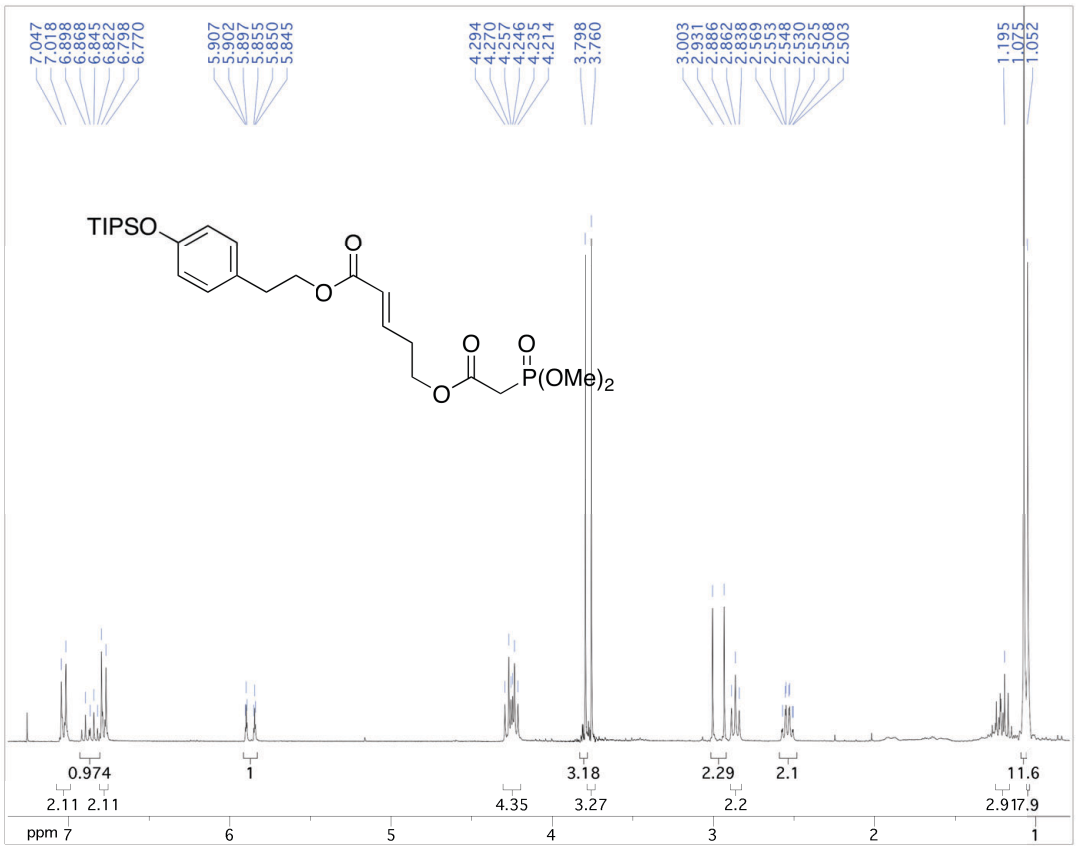


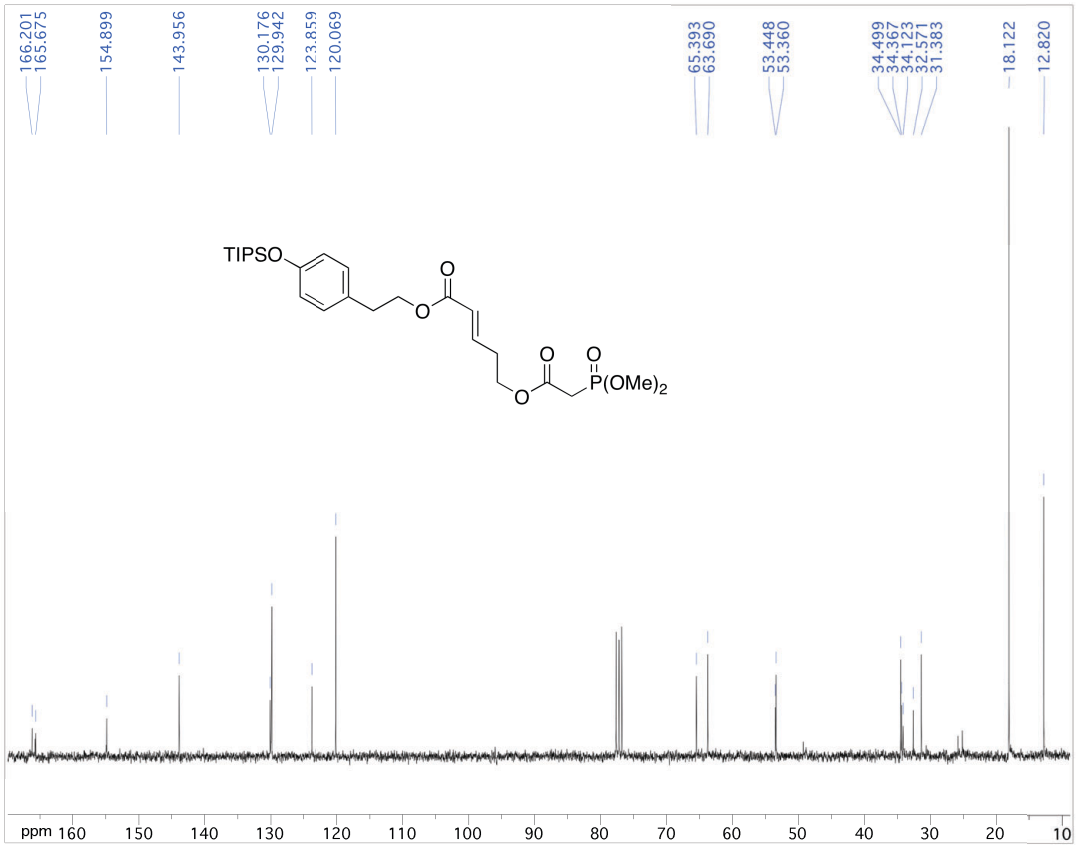


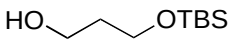


Synthesis of (*E*)-4-((triisopropylsilyl)oxy)phenethyl 5-(2-(dimethoxyphosphoryl)acetoxy)pent-2-enoate (3.17A): To a 10 mL round-bottomed flask charged with 71 mg (0.181 mmol, 1 equiv.) (*E*)-4-((triisopropylsilyl)oxy)phenethyl 5-hydroxypent-2-enoate and 37 mg (0.217 mmol, 1.2 equiv.) 2-(dimethoxyphosphoryl)acetic acid was added 1 mL dry CH_2Cl_2 and then 45 mg DCC. The reaction was stirred for 30 min at ambient temperature before being filtered through celite and concentrated to yield 80 mg of the desired product as a colorless oil.

^{1}HNMR (300MHz, $CDCl_3$): δ 7.03 (d, *J* = 8.7, 2H), 6.85 (dt, *J* = 13.8, 9.0, 1H), 6.78 (d, *J* = 8.4, 2H), 5.88 (dt, *J* = 15.6, 1.5, 1H), 4.27 (t, *J* = 7.2, 2H), 4.24 (t, *J* = 7.2, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 2.97 (d, J_{HP} = 21.6, 2H), 2.86 (t, *J* = 7.2, 2H), 2.54 (qd, *J* = 6.9, 1.5, 2H), 1.20 (m, 3H), 1.06 (d, *J* = 6.9, 18H); ^{13}CNMR (75MHz, $CDCl_3$): δ 166.2, 165.7, 154.9, 144.0, 130.2, 129.9, 123.9, 120.1, 65.4, 63.7, 53.4, 53.4, 34.5, 34.4, 34.1, 32.6, 31.4, 18.1, 12.8; R_f = 0.37 (EtOAc). Ref.: **BJEIV468**, BJEIV479.





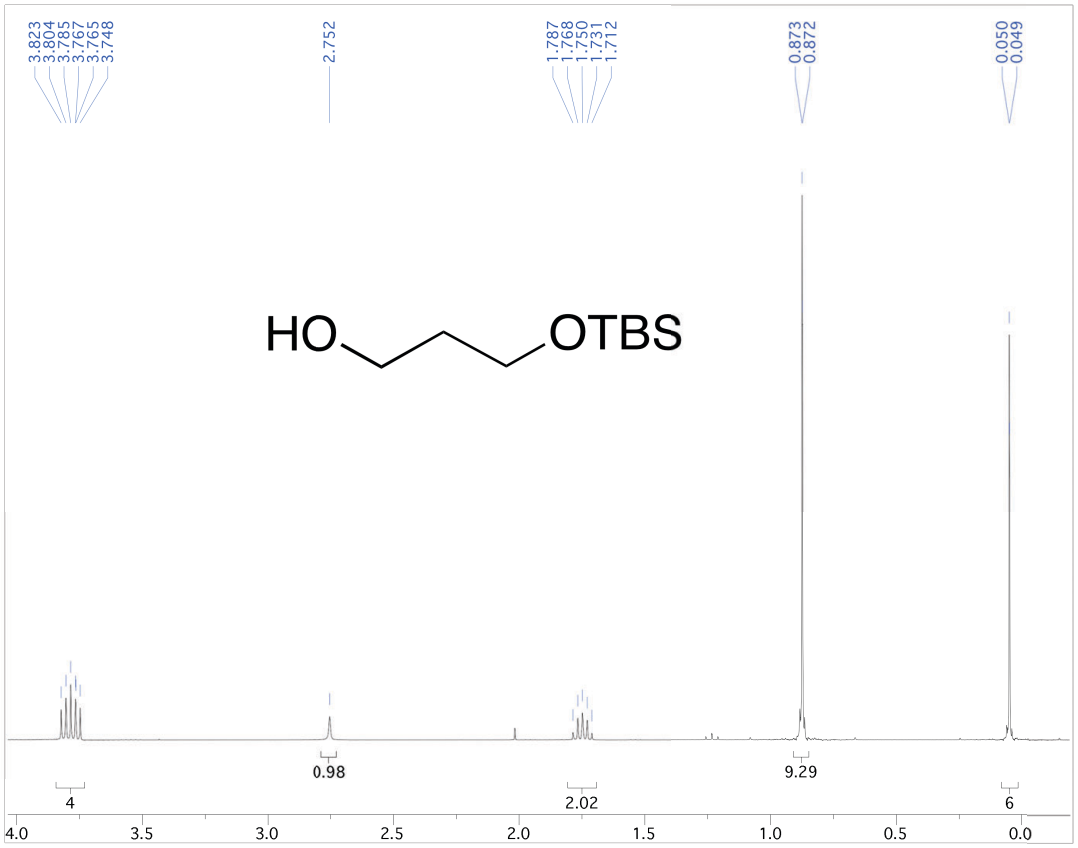


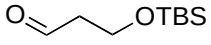
Synthesis of 3-((*tert*-butyldimethylsilyl)oxy)propan-1-ol: To a 3 L oven dried round–bottomed flask containing 26.15 g (653.8 mmol, 1.05 equiv.) of a 60% suspension of NaH in mineral oil was added 1.0 L dry THF. To this suspension was slowly added 45.0 mL (622.7 mmol, 1 equiv.) 1,3-propanediol. The reaction was stirred at ambient temperature for 45 min and then was cooled to 0^{o}C. To the cooled reaction mixture was slowly added 93.88 g (622.7 mmol, 1 equiv.) TBSCl dissolved in 100 mL dry THF via addition funnel. The reaction was allowed to return to ambient temperature over 30 min before being concentrated to ~20% volume, being added to brine, extracted thrice with

EtOAc, dried over Na_2SO_4, and concentrated to yield 113.72 g (97%) of the desired alcohol as a colorless oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 3.77 (m, H), 2.75 (bs, 1H), 1.75 (m, 2H), 1.75 (m, 2H), 0.87 (s, 9H), 0.05 (m, 6H).

Ref. BJEV185, **BJEV246**.



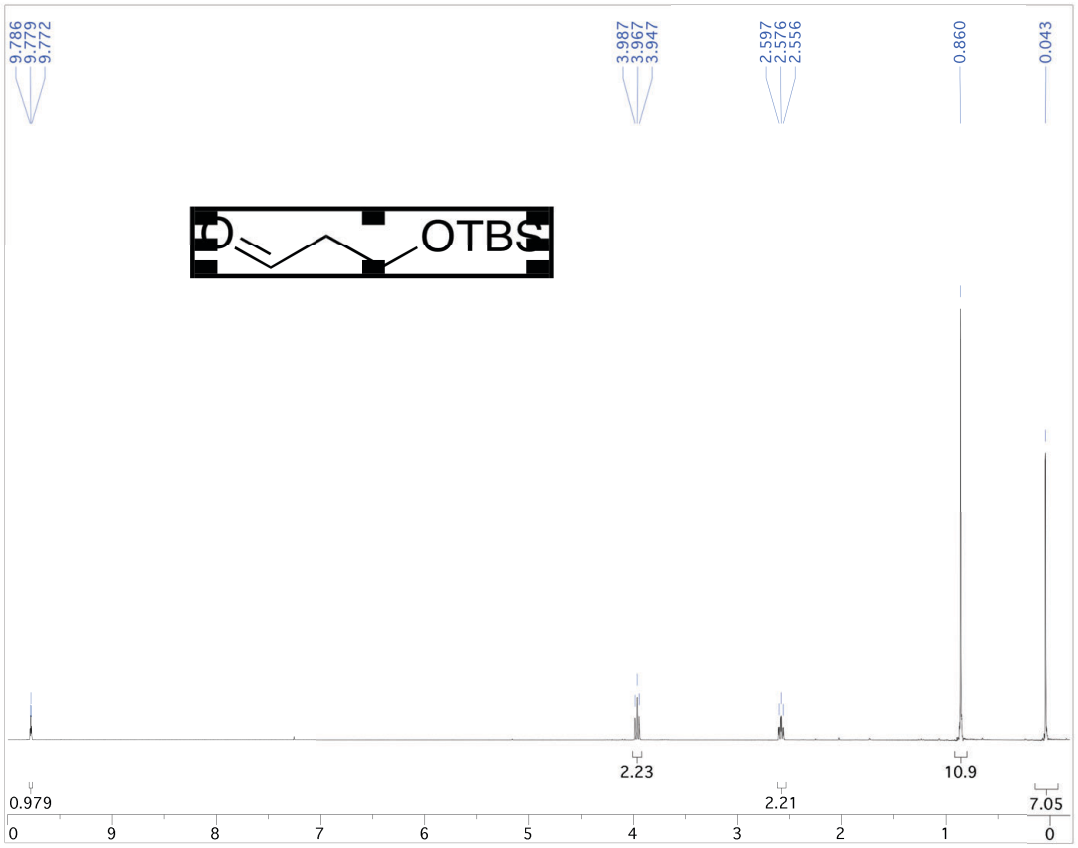


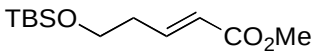
Synthesis of 3-((*tert*-butyldimethylsilyl)oxy)propanal (3.5): To a flame dried 3 L round-bottomed flask containing 64.08 mL (747.0 mmol, 1.25 equiv.) $(COCl)_2$ dissolved in 1.0 L dry CH_2Cl_2 at -78^{o}C was added 106 mL (1.49 mmol, 2.5 equiv.) dry DMSO dissolved in 100 mL dry CH_2Cl_2 at such a rate as to maintain an internal temperature of

less than -65°C. Once the reaction's internal temperature reached -70°C (approx. 30 min), 113.70 g (597.29 mmol, 1 equiv.) 3-((*tert*-butyldimethylsilyl)oxy)propan-1-ol dissolved in 100 mL dry CH_2Cl_2 was added via addition funnel at a rate which maintained an internal temperature of less than -65°C (approx. 1.5 hr). After allowing the reaction to vigorously stir for a further 30 min at -78°C, 500 mL (3.58 mmol, 6 equiv.) dry NEt_3 was added via addition funnel over 30 min and the reaction was allowed to slowly return to ambient temperature before being added to brine, extracted twice with CH_2Cl_2, dried over Na2SO_4, and concentrated. Silica gel flash chromatography eluting with 4 : 1 to 2 : 1 hex./EtOAc yielded 93.77 g (83%) of the desired aldehyde as a pale yellow oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 9.78 (t, *J* = 2.1, 1H), 3.97 (t, *J* = 6.0, 2H), 2.58 (t, *J* = 6.3, 2H), 0.86 (s, 9H), 0.04 (s, 6H).

Ref.: BJEII408, BJEV186, **BJEV247.**



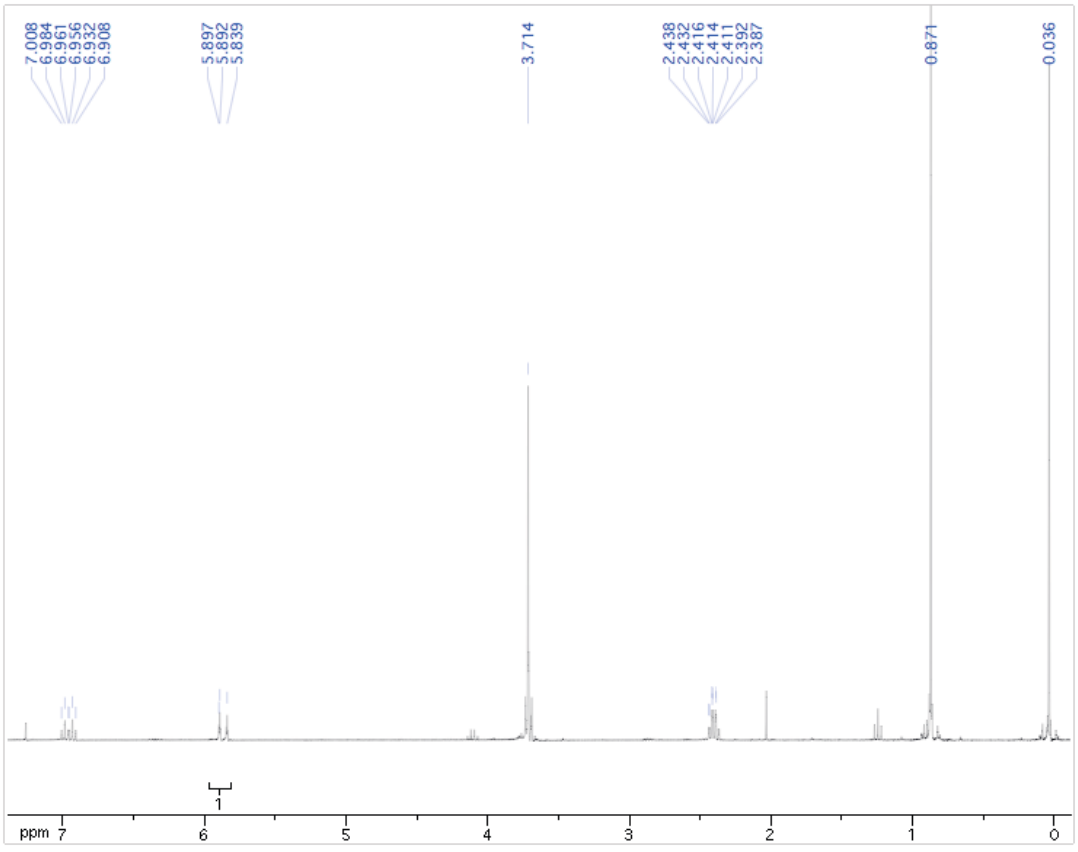


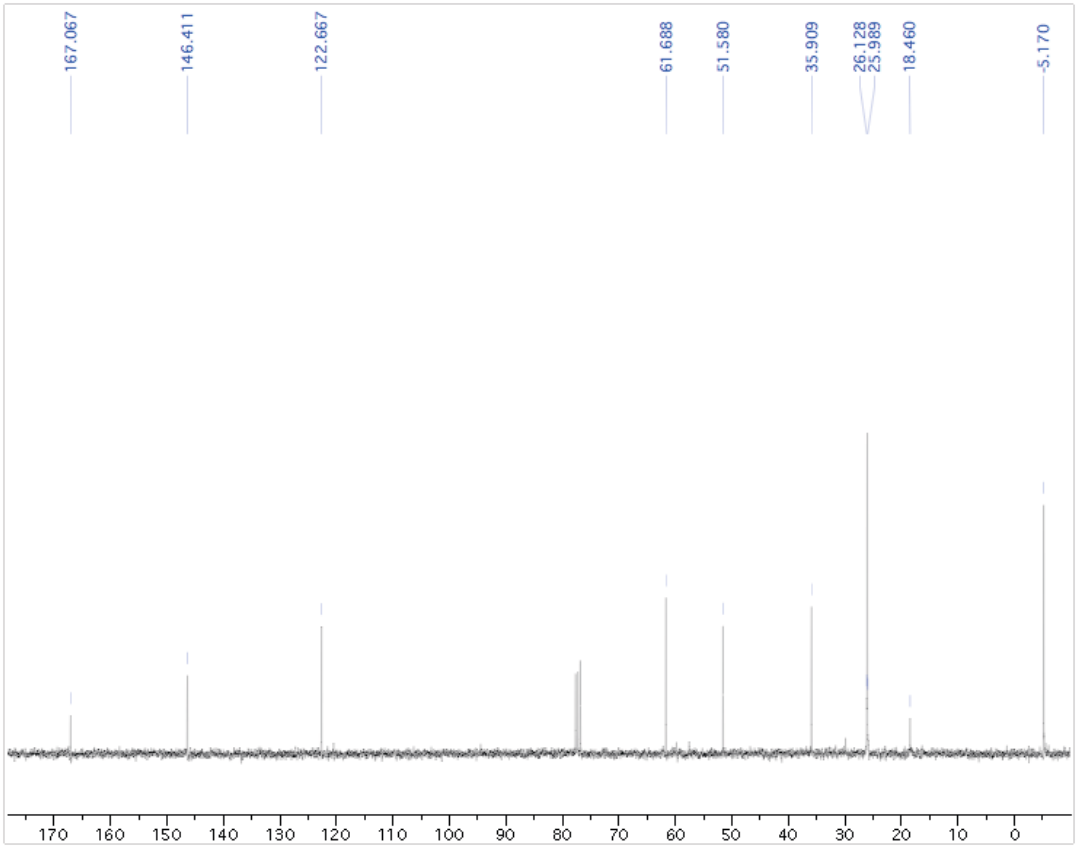
Synthesis of (*E*)-methyl 5-(*tert*-butyldimethylsilyloxy)pent-2-enoate (3.7): To a flame dried 2 L round-bottomed flask charged with 20.98 mL (121.26 mmol, 1.1 equiv.) methyl 2-(dimethoxyphosphoryl)acetate dissolved in 1000 mL dry MeCN was added 6.17 g (145.5 mmol, 1.2 equiv.) LiCl and then 21.12 mL (121.3 mmol, 1.2 equiv.) *i*Pr_2NEt. The reaction was stirred at ambient temperature for 15 min and then 22.84 g (121.3 mmol, 1 equiv.) aldehyde **3.5** dissolved in a minimum of MeCN was added. After stirring for 4 hr the reaction was concentrated to approximately 50% volume, added to brine, and extracted thrice with EtOAc. Combined organic layers were dried over Na_2SO_4,

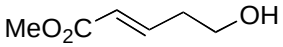
concentrated, and purified by silica gel flash chromatography eluting with 4 : 1 hex./EtOAc to yield 28.56 g (96%) of the title compound as a colorless oil.

^{1}HNMR (300MHz, $CDCl_3$): δ 6.96 (dt, *J* = 15.6, 7.2, 1H), 5.87 (dt, *J* = 15.9, 1.5, 1H), 3.71 (s, 3H), 3.70 (m, 2H), 2.40 (qd, *J* = 6.6, 1.8, 2H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}CNMR (75MHz, $CDCl_3$): δ 167.1, 146.4, 122.7, 61.7, 51.6, 35.9, 26.0, 18.5, -5.2; IR (NaCl, film): 1729, 1660 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 245.1568 calcd for $C_{12}H_{25}O_3Si$, found: 245.1410; R_f = 0.40 (9 : 1 hex./EtOAc).

Ref.: BJEIII403, BJEIII434, **BJEIII449**, BJEIII480, BJEIV085, BJEIV102, BJEIV177, BJEIV213, BJEIV406, BJEV018.





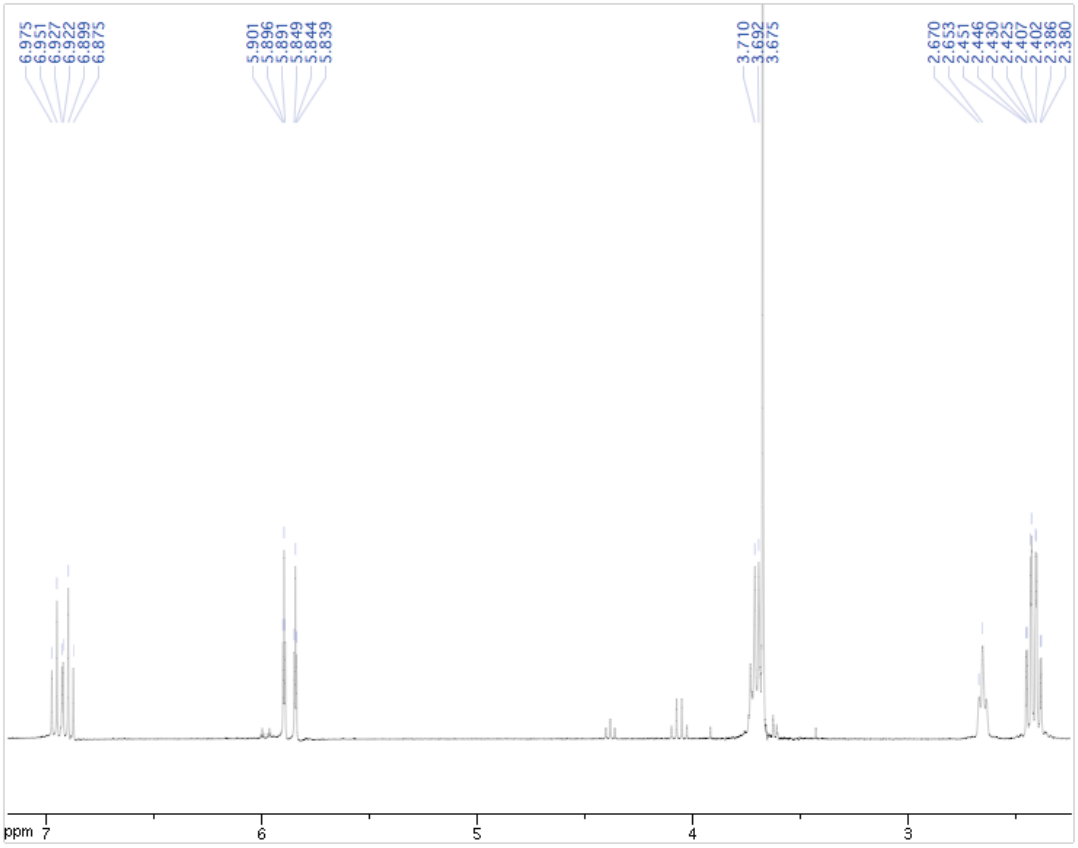


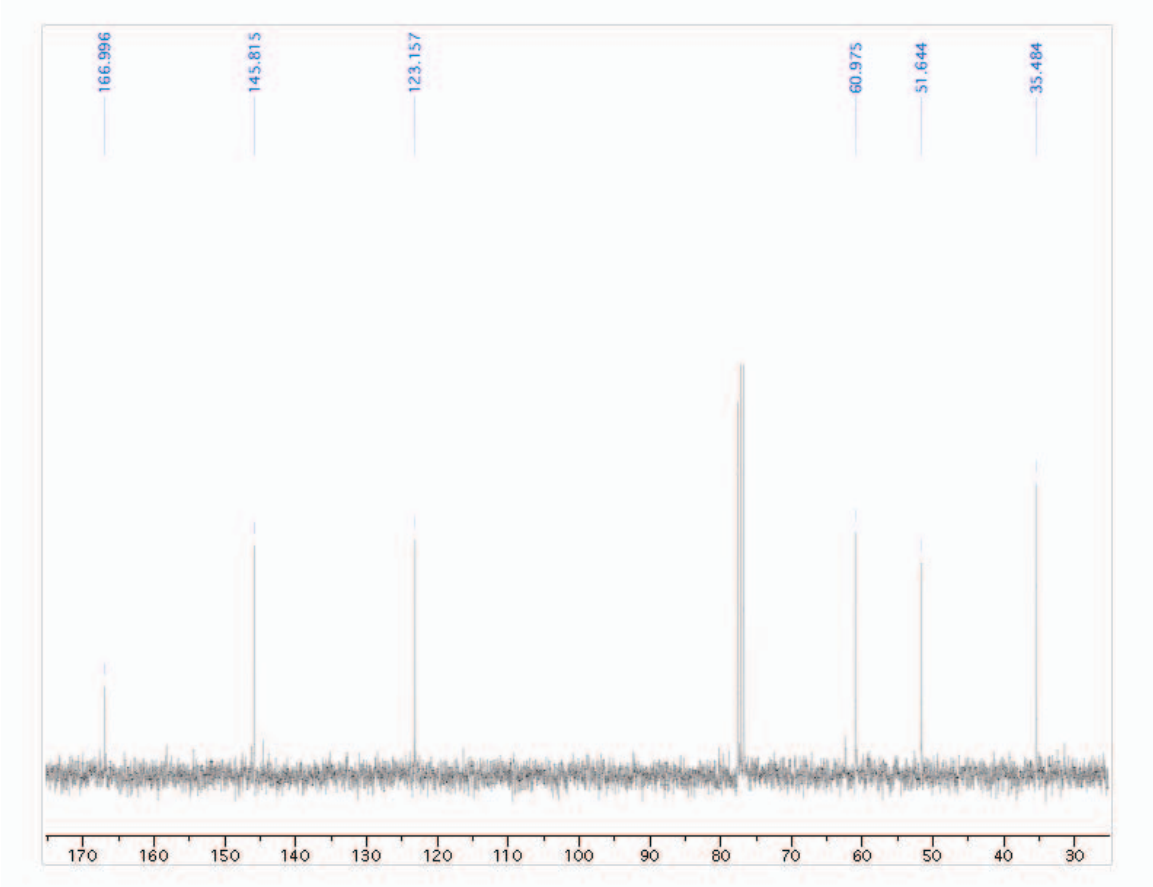
Synthesis of (*Z*)-methyl 5-hydroxypent-2-enoate (3.4): To a 1 L HDPE bottle was added 24.85 g (101.7 mmol, 1 equiv.) silyl ether **3.7** dissolved in 500 mL dry THF followed by 53.0 mL HF as a 48% solution in H_2O. The reaction was stirred for 6 hr at ambient temperature, then slowly added to $NaHCO_{3(sat.)}$, and extracted twice with EtOAc. Combined organic layers were dried over Na_2SO_4 and concentrated. The resulting residue was dissolved in 1 : 1 hex./ EtOAc and filtered through a short silica gel plug. Concentration yielded 11.90 g (90%) of the title compound as a pale yellow oil.

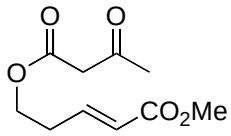
^{1}HNMR (300MHz, $CDCl_3$): δ 6.92 (dt, *J* = 15.6, 7.2, 1H), 5.86 (dt, *J* = 15.6, 1.5, 1H), 3.70 (q, *J* = 5.4, 2H), 3.68 (s, 3H), 2.65 (bt, *J* = 5.1, 1H), 2.41 (qd, *J* = 6.3, 1.5, 2H); ^{13}CNMR (75MHz, $CDCl_3$) δ 167.0, 145.8, 123.2, 61.0, 51.6, 35.5; IR (NaCl, film): 3429,

1721, 1660; HRMS (+TOF): $[M+H]^+$ 131.07027 calcd for $C_6H_{11}O_3$, found: 131.07047; R_f = 0.29 (1:1 hex./EtOAc)

Ref.: BJEIII450, BJEIII451, BJEIII483 BJEIII490, BJEIV089, **BJEIV105**, BJEIV360, BJEIV364, BJEIV409, BJEV020.



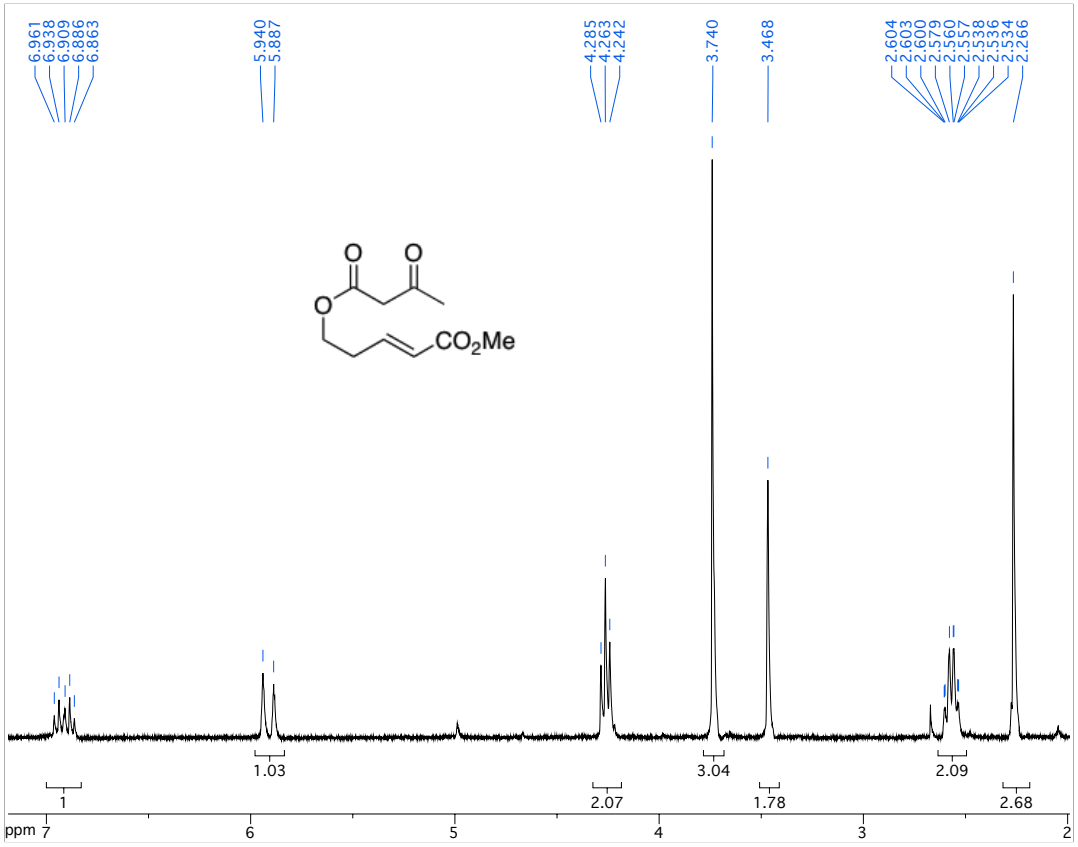


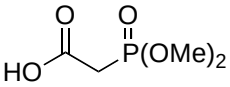


Synthesis of (*E*)-methyl 5-((3-oxobutanoyl)oxy)pent-2-enoate (3.3): To an oven dried 25 mL round bottomed flask containing 430 mg (3.30 mmol, 1 equiv.) alcohol **3.4** dissolved in 15 mL dry CH_2Cl_2 and cooled to 0^oC was added 510 mL (6.61 mmol, 2 equiv.) diketene followed by a single crystal of DMAP. The reaction was stirred for 15 min at 0^oC before being added to $NaHCO_{3(sat.)}$, extracted into CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel chromatography eluting with 4 : 1 to 1 : 1 hex./EtOAc to yield 706 mg (>99%) of the title compound as a pale yellow oil.

^{1}HNMR (300MHz, $CDCl_3$): δ 6.91 (dt, *J* = 15.6, 6.9, 1H), 5.91 (d, *J* = 15.9, 1H), 4.26 (t, *J* = 6.3, 2H), 3.74 (s, 3H), 3.47 (s, 2H), 2.57 (q, *J* = 5.9, 2H), 2.27 (s, 3H); R_f = 0.32 (2 : 1 hex./EtOAc)

Ref.: **BJEIV095**

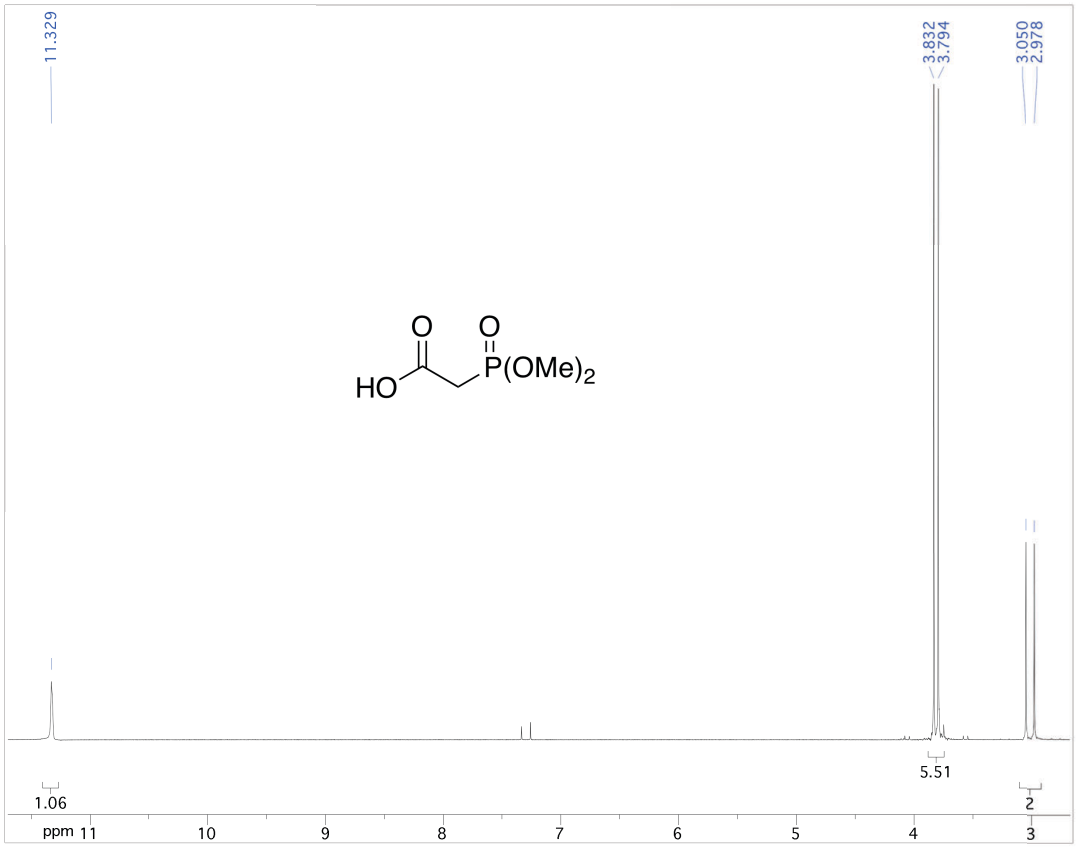


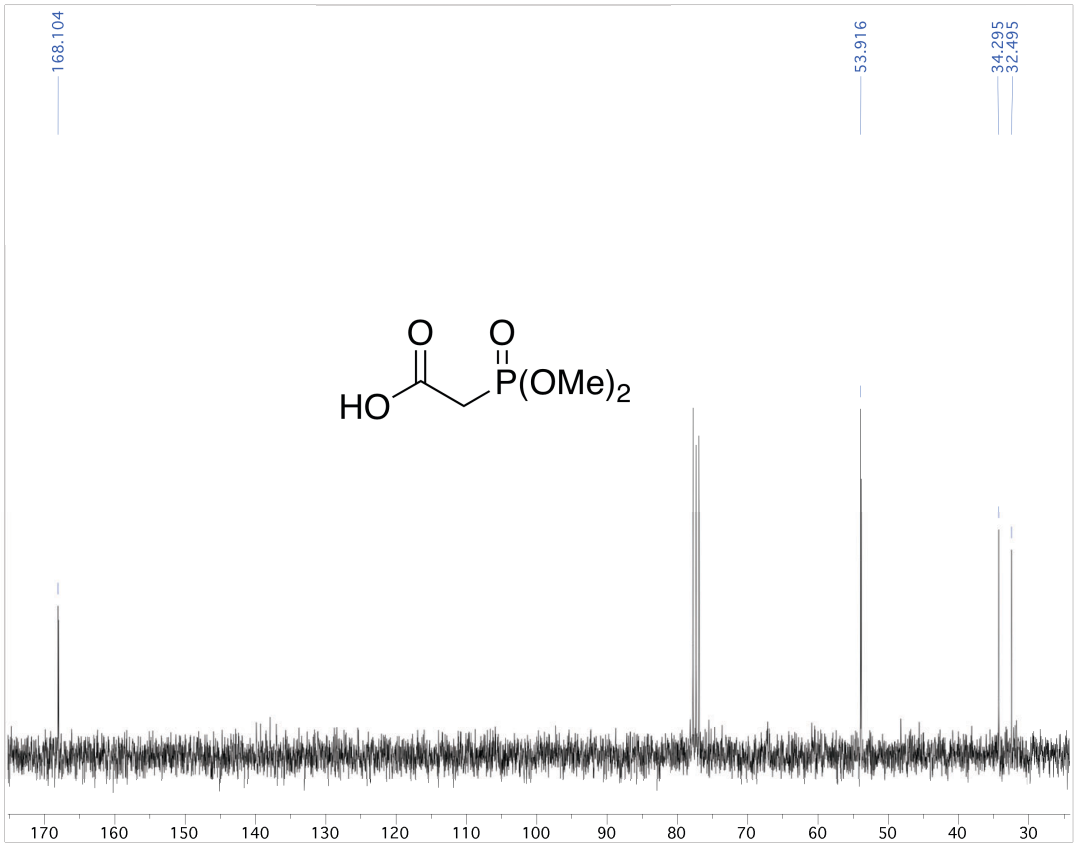


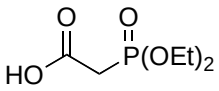
Synthesis of 2-(dimethoxyphosphoryl)acetic acid: To a 200 mL round-bottomed flask containing 20.0 mL (138.7 mmol, 1 equiv.) methyl 2-(dimethoxyphosphoryl)acetate dissolved in 50 mL H_2O was added 15 mL of 10 M $NaOH_{(aq.)}$. The reaction was stirred for 2 hr at ambient temperature before being acidified with $HCl_{(conc.)}$. To this solution was added NaCl to saturation and the solution was extracted thrice with THF. The

resulting residue was taken up in EtOAc and concentrated several times to remove any remaining water. This yielded 14.64 g (63%) of the desired acid as a colorless oil. ^{1}HNMR (300 MHz, $CDCl_3$) δ 11.33 (bs, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.01 (d, J_{HP} = 21.6, 2H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 168.1, 53.9, 34.3, 32.5.

Ref.: BJEIV281, BJEIV301, **BJEIV424**.



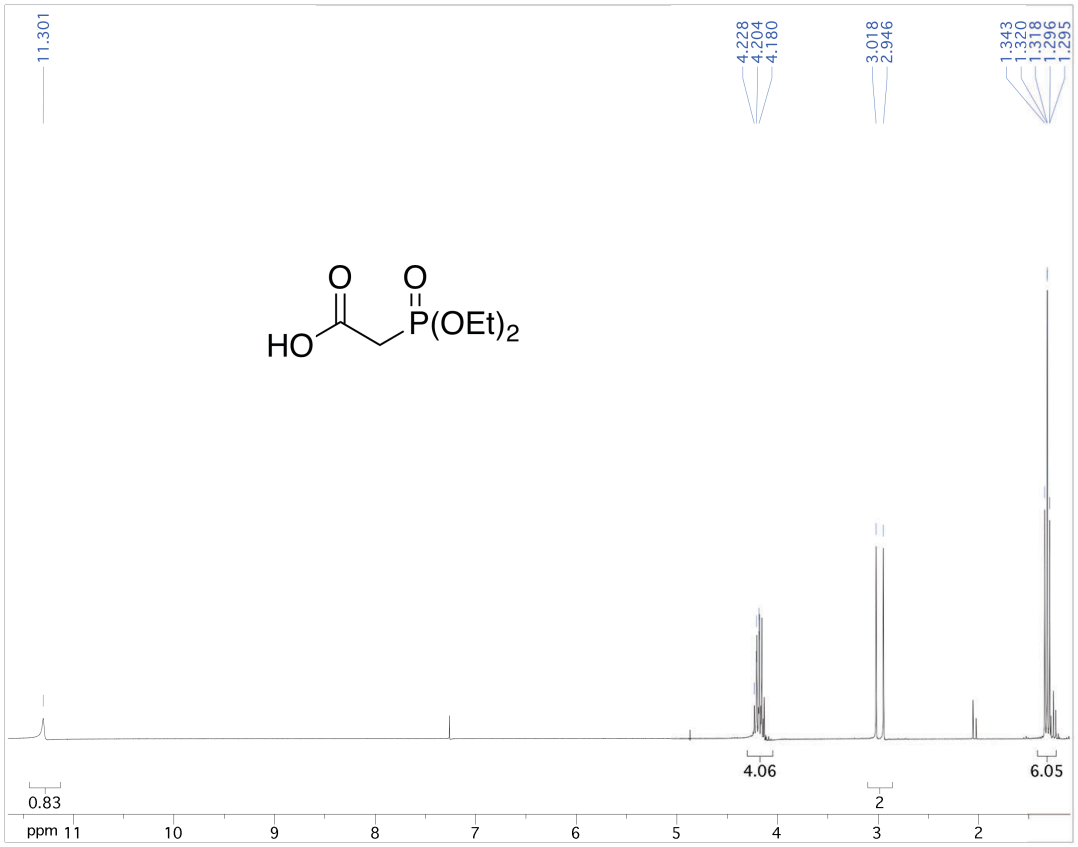


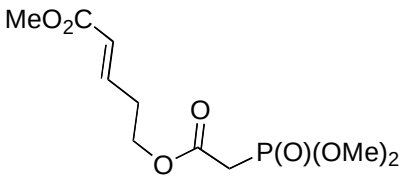


Synthesis of 2-(diethoxyphosphoryl)acetic acid: To a 500 mL round-bottomed flask containing 10.0 mL (50.4 mmol, 1 equiv.) ethyl 2-(diethoxyphosphoryl)acetate dissolved in 250 mL dry Et_2O was added 7.11 g (55.4 mmol, 1.1 equiv.) KOTMS. The reaction was stirred at ambient temperature for 16 hr, acidified with 1 M HCl, extracted into EtOAc, dried over Na_2SO_4, and concentrated to yield 3.82 g (39%) of the desired acid as a colorless oil which was used without further purification.

^{1}HNMR (300 MHz, $CDCl_3$) δ 11.30 (bs, 1H), 4.19 (q, J = 7.2, 4H), 3.00 (d, J_{HP} = 21.6, 2H), 1.32 (t, J = 7.1, 6H).

Ref.: BJEIV163, **BJEIV165**.

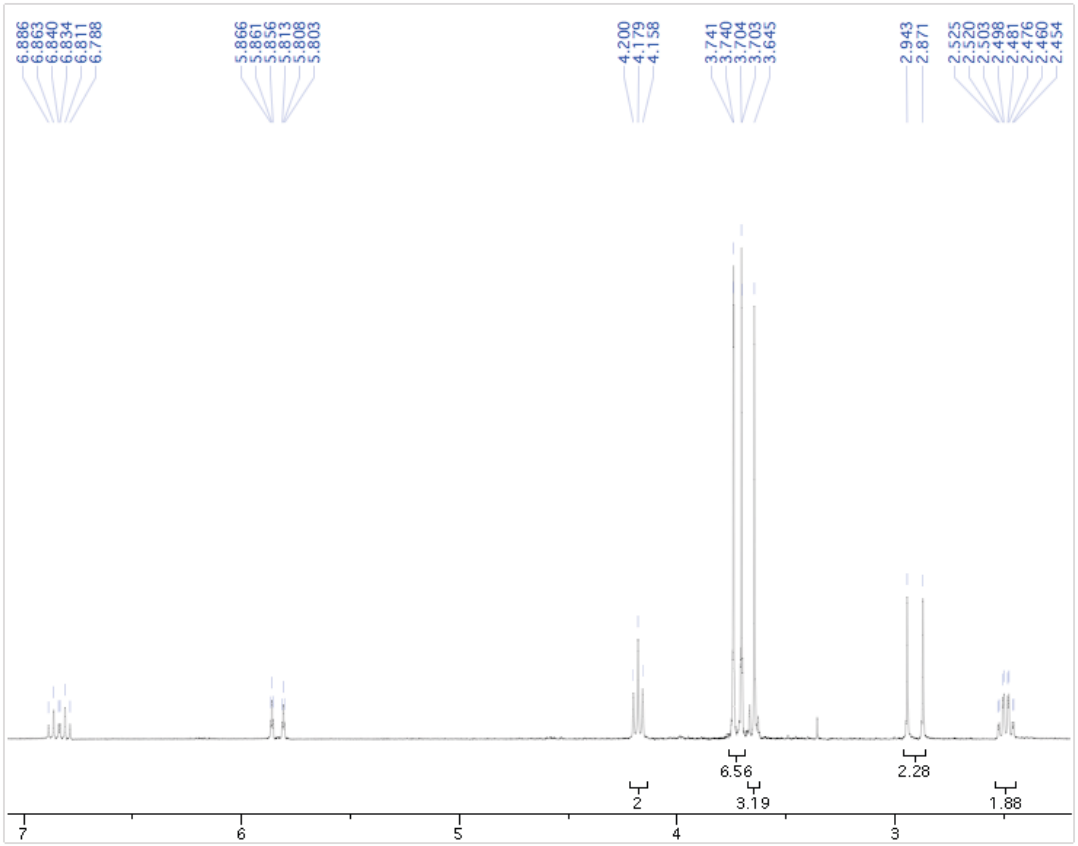


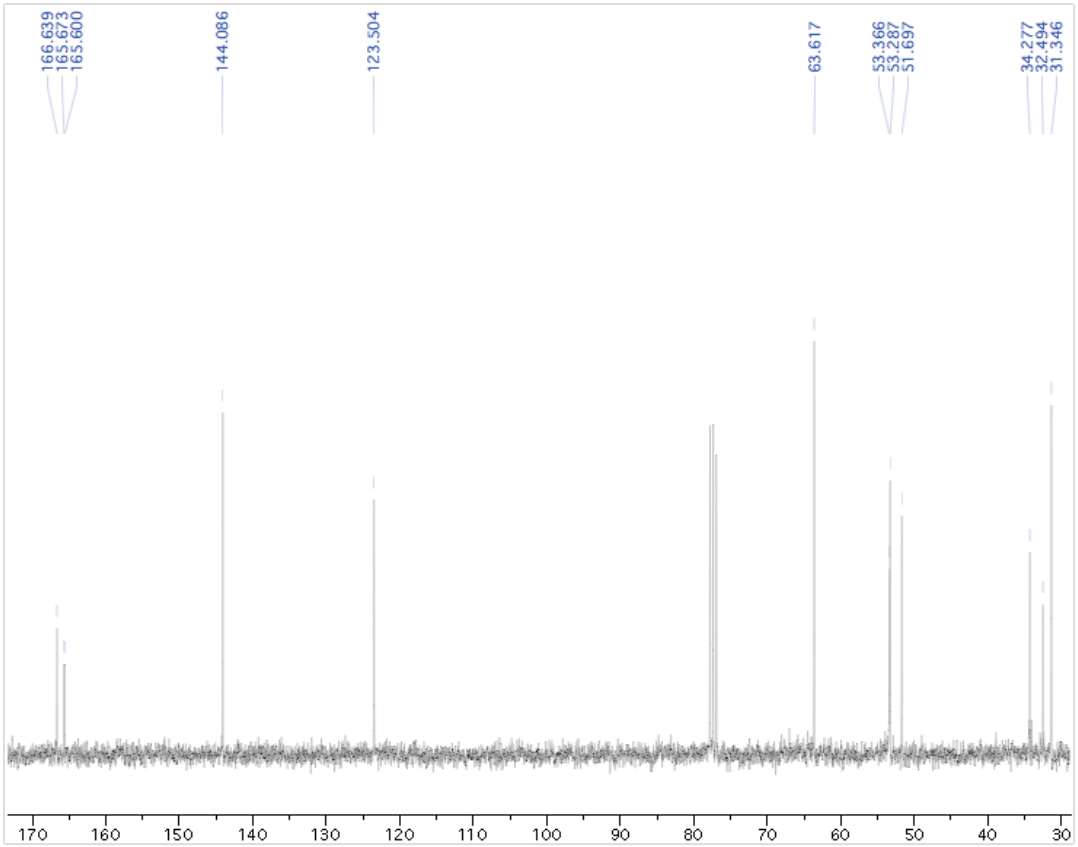


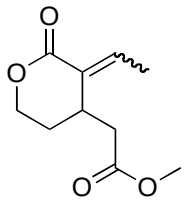
Synthesis of (*Z*)-methyl 5-(2-(dimethoxyphosphoryl)acetoxy)pent-2-enoate (3.11): An oven dried 100 mL round-bottomed flask was charged with 2.94 g (22.6 mmol, 1 equiv.) alcohol **3.4**, 4.56 g (27.1 mmol, 1.2 equiv.) 2-(dimethoxyphosphoryl)acetic acid, and 45 mL dry CH_2Cl_2. To this was added 5.59 g (27.1 mmol, 1.2 equiv.) DCC dissolved in a minimum of CH_2Cl_2. The reaction was stirred for 45 min at ambient temperature before being filtered through a celite pad and concentrated. Purification by flash chromatography eluting with EtOAc yielded 6.31 g (>99%) of the title compound as a colorless solid.

^{1}HNMR (300MHz, $CDCl_3$): δ 6.84 (dt, *J* = 15.6, 6.9, 1H), 5.83 (dt, *J* = 15.9, 1.5, 1H), 4.18 (t, *J* = 6.3, 2H), 3.74 (s, 3H), 3.70 (s, 3H), 3.65 (s, 3H), 2.91 (d, J_{HP} = 21.6, 2H), 2.49 (qd, *J* = 6.6, 1.5, 2H); ^{13}CNMR (75MHz, $CDCl_3$) δ 166.6, 165.7, 144.1, 123.5, 63.6, 53.4, 51.7, 34.3, 32.5, 31.4; IR (NaCl, film): 1724, 1660; HRMS (+TOF) calcd for $C_{10}H_{18}O_7P$ $[M+H]^+$ 281.07847, found: 281.07881; R_f = 0.18 (EtOAc)

Ref.: BJEIII494, BJEIV002, BJEIV010, BJEIV011, BJEIV022, BJEIV083, BJEIV087, BJEIV116, BJEIV353, BJEIV366,BJEIV320, **BJEIV410,** BJEV021.







Synthesis of methyl 2-(3-ethylidene-2-oxotetrahydro-2*H*-pyran-4-yl)acetate (3.1): To 179 mg (0.639 mmol, 1 equiv.) phosphonate **3.11** dissolved in 3.0 mL dry MeCN in an oven dried 25 mL round-bottomed flask was added 416 mg (1.28 mmol, 2 equiv.) Cs_2CO_3. The reaction was heated to reflux for 1.5 hr, cooled to 0^{o}C, and 107 μL (1.92 mmol, 3 equiv.) freshly distilled acetaldehyde was added in a single portion. The reaction was vigarously stirred for 16 hr at ambient temperature and was then acidified with 1N HCl. This mixture was extracted thrice with EtOAc. Combined organic layers were dried over Na_2SO_4, concentrated, and purified by silica gel flash chromatography

eluting with 2 : 1 to 1 : 1 hex./ EtOAc to yield 53 mg (42%) of the title compound (1.6 : 1 E/Z) as a yellow oil. Analytical samples were prepared by successive silica gel chromatography eluting with 2 : 1 to 1 : 1 hex./ EtOAc.

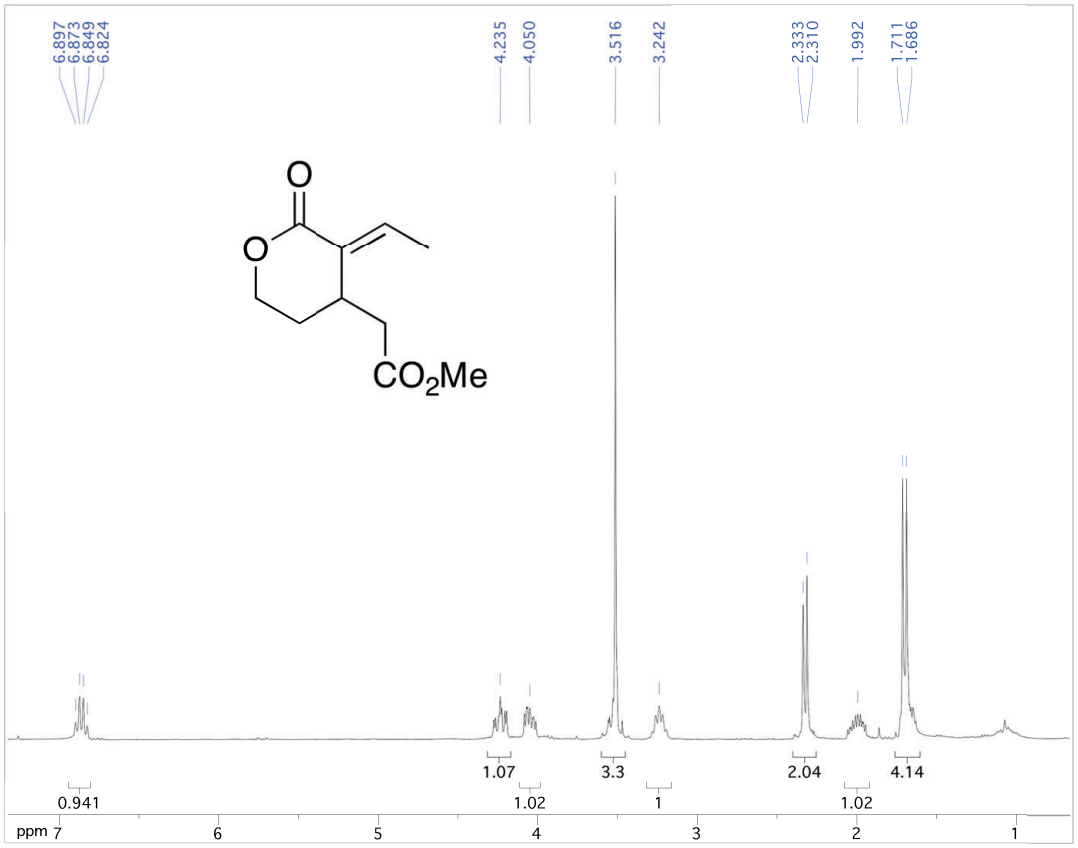
E-isomer :

^{1}HNMR (300MHz, $CDCl_3$) δ 6.86 (q, *J* = 7.2, 1H), 4.24 (m, 1H), 4.05 (m, 1H), 3.52 (s, 3H), 3.24 (m, 1H), 2.32 (d, 7.2, 2H), 1.99 (m, 1H), 1.70 (d, *J* = 7.5, 3H), 1.68 (m, 1H); ^{13}CNMR (75MHz, $CDCl_3$) δ 171.8, 166.9, 141.8, 130.0, 65.1, 51.9, 37.6, 29.5, 27.4, 14.3; IR (NaCl, film) 1732, 1635 cm^{-1}; HRMS (+TOF) calcd for $C_{10}H_{15}O_4$ $[M+H]^+$ 199.0965, found: 199.0963; R_f = 0.19 (2 : 1 hex./ EtOAc).

Z-isomer:

^{1}HNMR (300MHz, $CDCl_3$) δ 6.06 (qd, *J* = 7.2, 1.5, 1H), 4.10 (m, 1H), 3.97 (m, 1H), 3.49 (s, 3H), 2.97 (m, 1H), 2.32 (m, 2H), 1.99 (m, 1H), 1.85 (dd, *J* = 7.2, 0.9, 3H), 1.55 (m, 1H); ^{13}CNMR (75MHz, $CDCl_3$) δ 171.9, 166.1, 141.7, 129.7, 66.1, 51.8, 40.5, 35.4, 28.7, 16.0; IR (NaCl, film) 1732, 1634 cm^{-1}; HRMS (+TOF) calcd for $C_{10}H_{15}O_4$ $[M+H]^+$ 199.0965, found: 199.0963; R_f = 0.26 (2 : 1 hex./ EtOAc).

Ref.: BJEIV011, BJEIV019, BJEIV039, BJEIV090, BJEIV091, BJEIV121, **BJEIV367**, BJEIV404, BJEIV411, BJEIV412, BJEIV421, BJEIV430, BJEIV433, BJEV262.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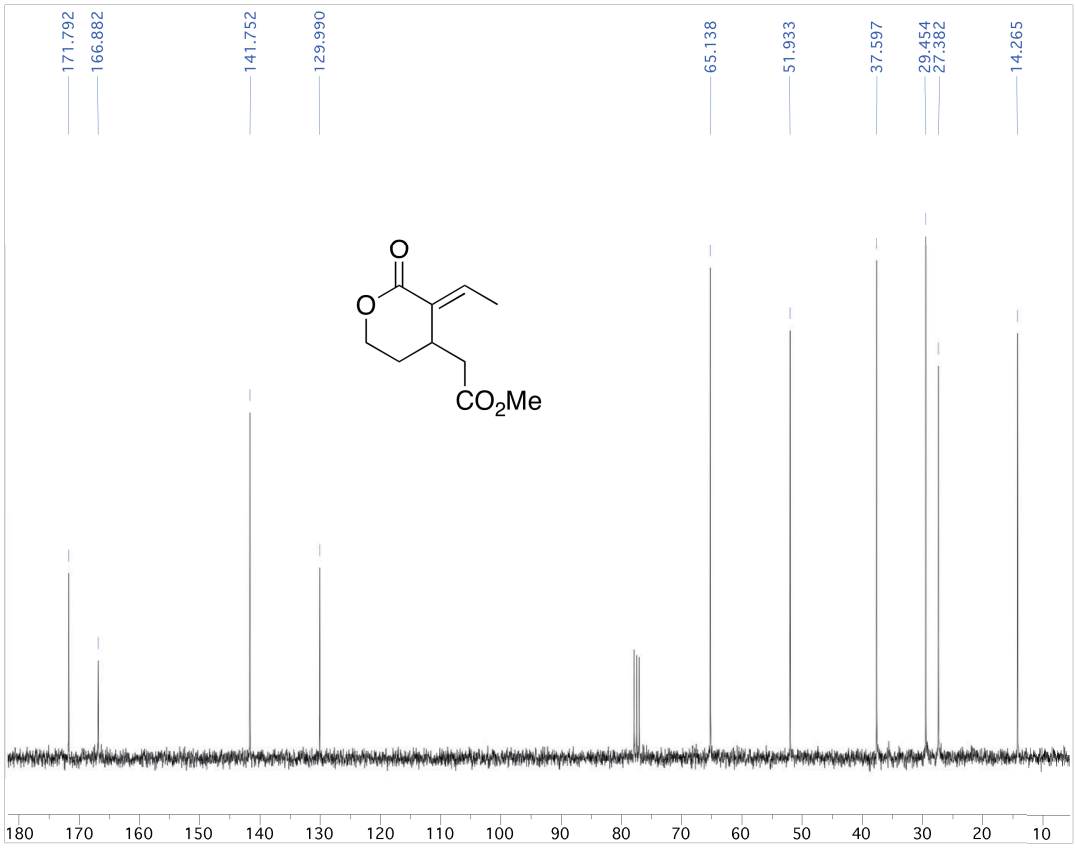
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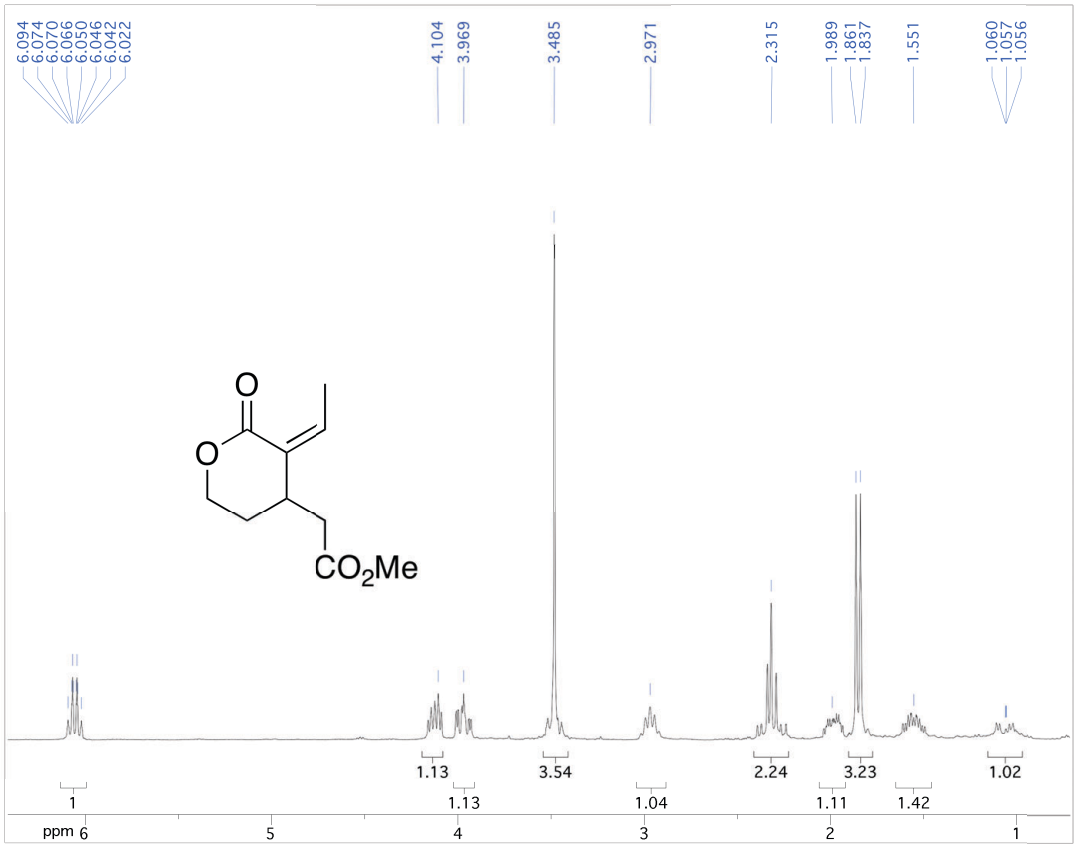
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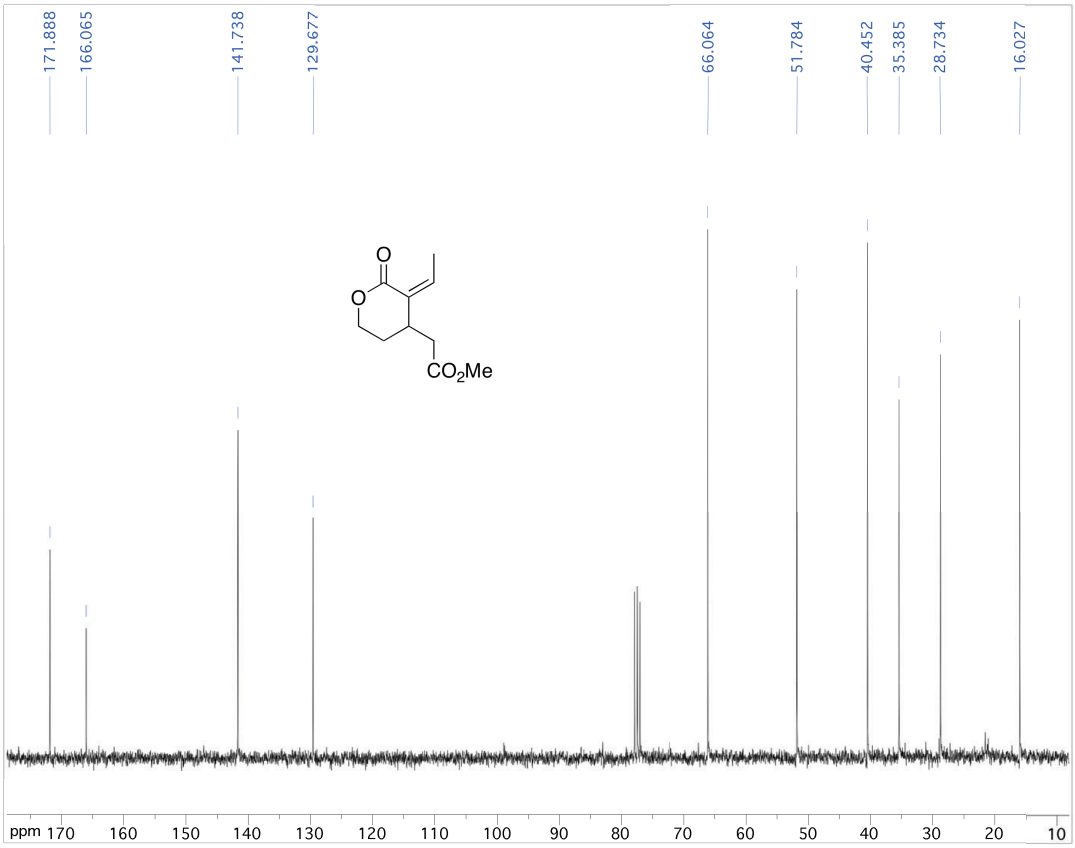
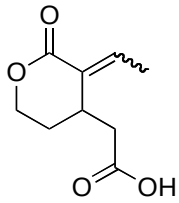


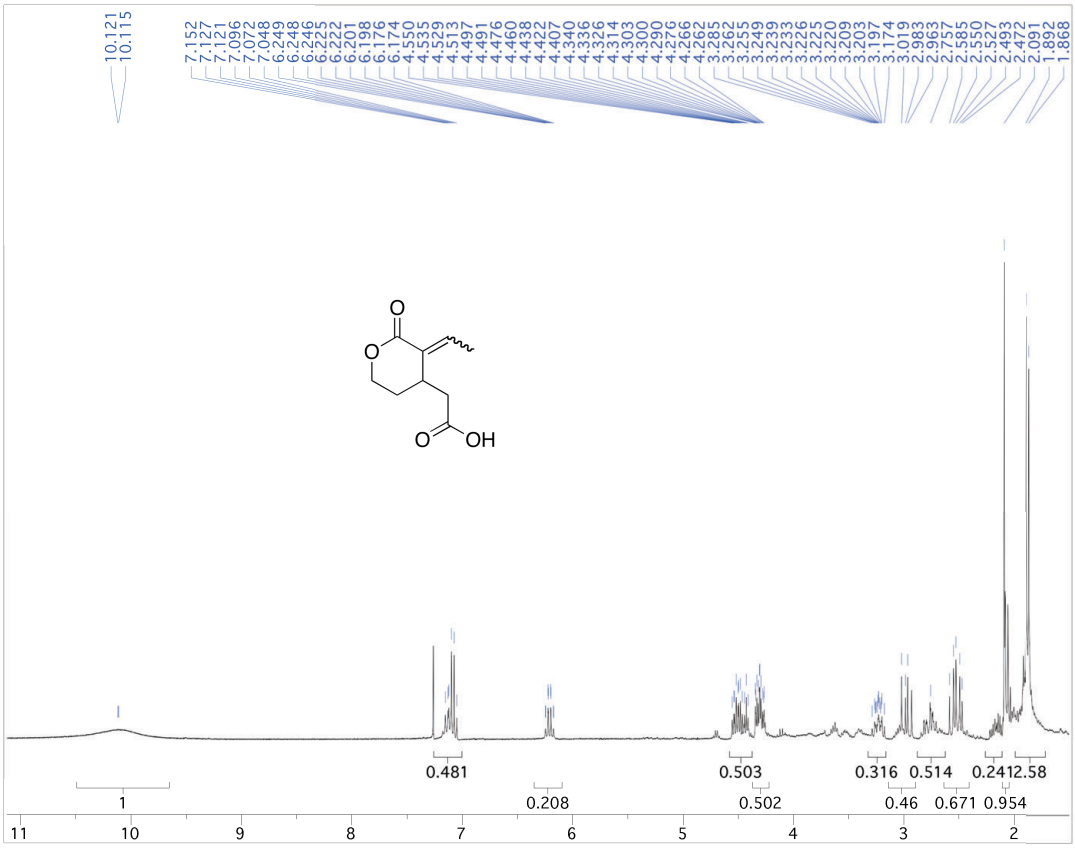


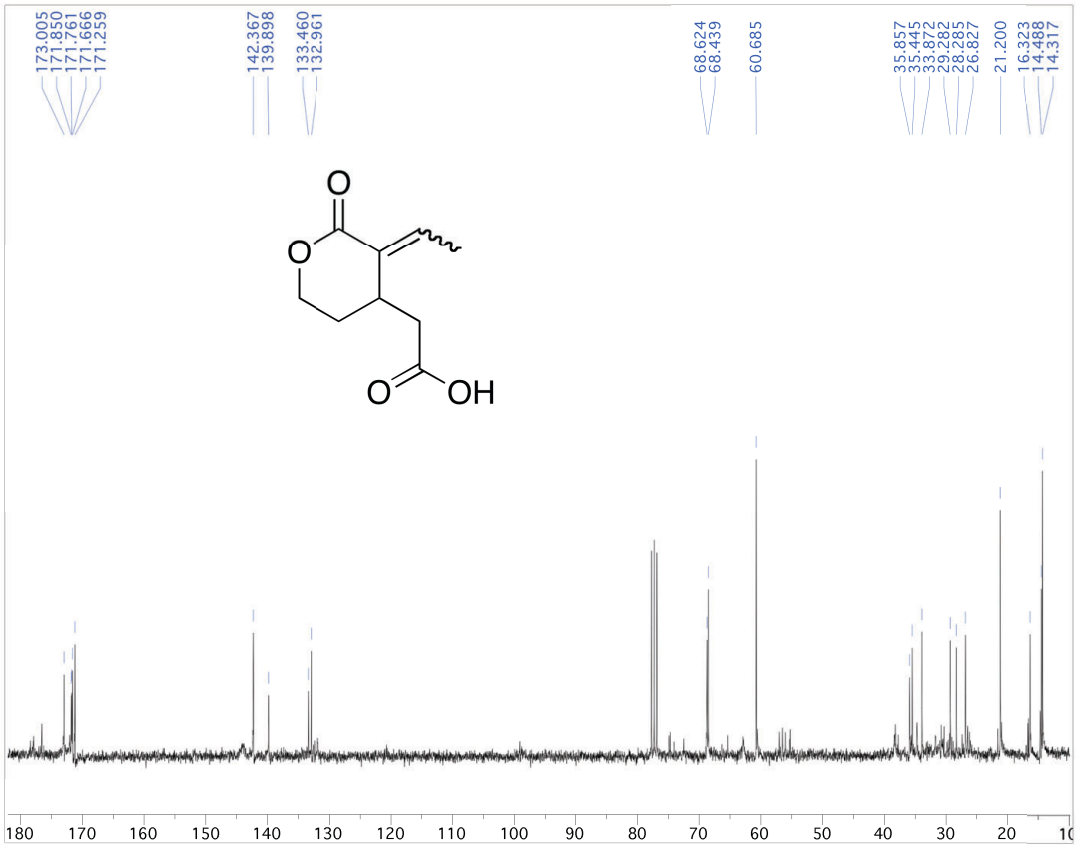
Synthesis of 2-(3-ethylidene-2-oxotetrahydro-2*H*-pyran-4-yl)acetic acid (3.15): To 69 mg (0.345 mmol, 1 equiv.) lactone **3.1** dissolved in 2 mL 3 : 1 THF : H_2O in a 10 mL round-bottomed flask was added 25 mg (1.03 mmol, 3 equiv.) LiOH. The reaction was stirred at ambient temperature for 2 hr and then acidified with 1N HCl. This mixture was extracted thrice with EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 1 : 1 : 0.01 to 0 : 1 : 0

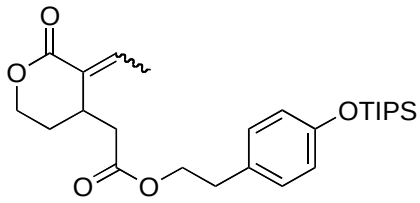
hex./EtOAc/HOAc to yield 44 mg (70%) of the title compound as an inseperable mixture (1.6 : 1 E/Z) of E/Z isomers as a pale yellow oil.

^{1}HNMR (300MHz, $CDCl_3$) Mixture of isomers δ 10.12 (bs, 1H), 7.08 (q, *J* = 7.2, 0.6H), 6.21 (q, *J* = 7.2, 0.4H), 4.55-4.41 (m, 1H), 4.34-4.25 (m, 1H), 3.23 (m, 0.6H), 3.04 (m, 0.4H), 2.97 (dd, *J* = 16.8, 10.8, 1H), 2.22-1.97 (m, 2H), 1.88 (d, *J* = 7.2, 3H); ^{13}CNMR (75MHz, $CDCl_3$) Mixture of isomers δ 172.8, 171.6, 171.5, 171.0, 142.1, 139.7, 133.2, 132.7, 68.4, 68.2, 35.6, 35.2, 33.6, 29.1, 28.1, 26.6; R_f = 0.05 (1 : 1 hex./EtOAc)

Ref.: BJEIV032, **BJEIV100**, BJEIV104, BJEIV109, BJEIV126, BJEIV132, BJEIV138, BJEIV405, BJEIV420, BJEIV436.



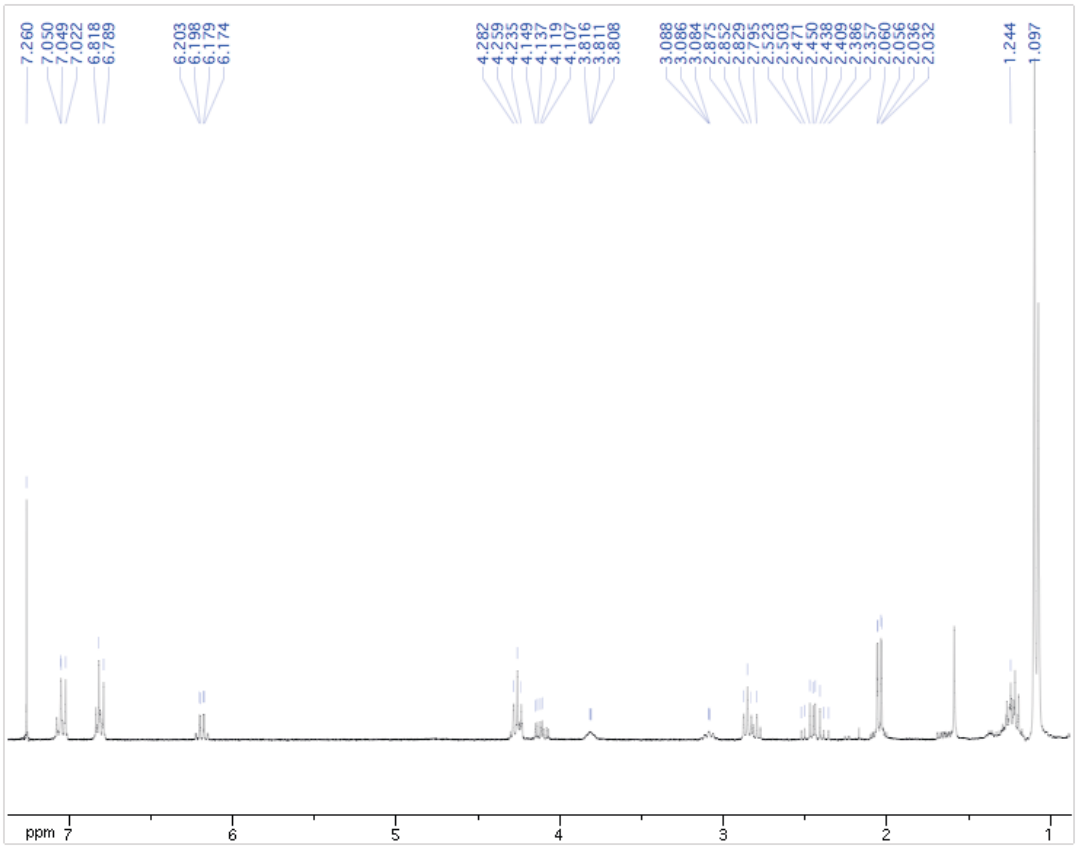


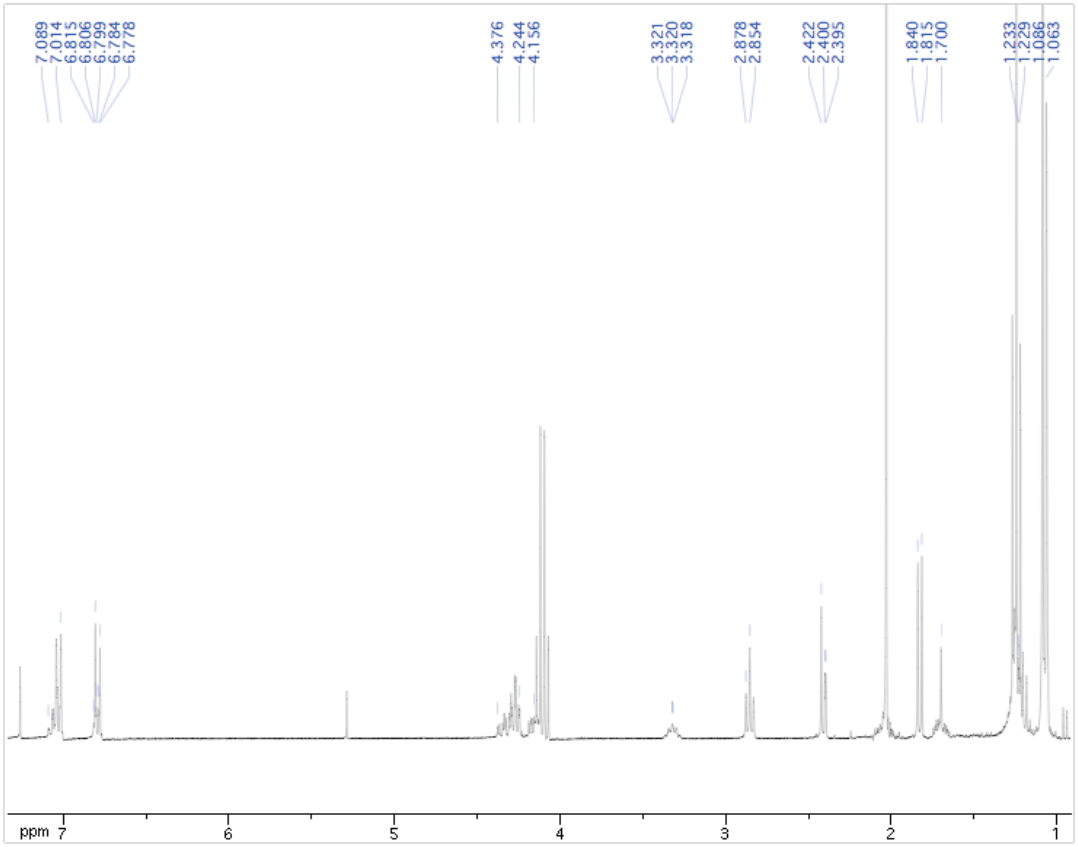


Synthesis of 4-(triisopropylsilyloxy)phenethyl 2-(3-ethylidene-2-oxotetrahydro-2*H*-pyran-4-yl)acetate (3.17): To 36 mg (0.193 mmol, 1 equiv.) acid **3.15** dissolved in 2 mL dry CH_2Cl_2 in an oven dried 10 mL round-bottomed flask and cooled to 0^{o}C was added 85.0 mg (0.290 mmol, 1.5 equiv.) alcohol **3.16** followed by 60 mg (0.290 mmol, 1.5 equiv.) DCC and a spatula tip of DMAP. The reaction was stirred for 16 hr at ambient temperature, filtered through celite, concentrated, and purified by silica gel flash chromatography eluting with 2 : 1 hex./ EtOAc to yield 89.0 mg (>99%) of the title compound as a colorless oil.

^{1}HNMR (300MHz, $CDCl_3$) Z-isomer δ 7.05 (m, 2H), 6.82 (m, 2H), 6.19 (qd, *J* = 7.2, 1.5, 1H), 4.26 (t, *J* = 6.9, 2H), 4.11 (td, *J* = 9.0, 3.6, 1H), 3.81 (m, 1H), 3.09 (m, 1H), 2.84 (dt, *J* = 17.1, 6.9, 3H), 2.44 (ddd, *J* = 15.6, 8.9, 6.3, 2H), 2.04 (dd, *J* = 7.2, 1.2, 3H), 1.24 (m, 3H), 1.10 (s, 18H), E-isomer δ 7.01-7.09 (m, 3H), 6.79 (m, 2H), 4.24-4.38 (m, 3H), 4.16 (m, 1H) 3.32 (m, 1H), 2.85 (t, *J* = 7.2, 2H), 2.41 (m, 2H), 1.83 (d, *J* = 7.5, 3H), 1.70 (m, 2H), 1.22 (m, 3H), 1.07 (m, 18H); ^{13}CNMR (75MHz, $CDCl_3$) mixture of isomers δ 172.4, 171.4, 166.5, 154.9, 142.1, 139.6, 133.8, 130.2, 129.9, 129.8, 120.1, 120.1, 68.2, 65.5, 38.0, 34.4, 34.1, 29.6, 27.4, 27.0, 25.8, 25.2, 18.3, 14.4, 12.8; IR (NaCl, film) 1732, 1511 cm^{-1}; HRMS (+TOF) calcd for $C_{26}H_{41}O_5Si$ $[M+H]^+$ 461.27278, found 461.27215; R_f = 0.24 (2 : 1 hex./EtOAc).

Ref.: BJEIV130, BJEIV135, BJEIV319, **BJEIV331**, BJEIV340, BJEIV427, BJEIV451.

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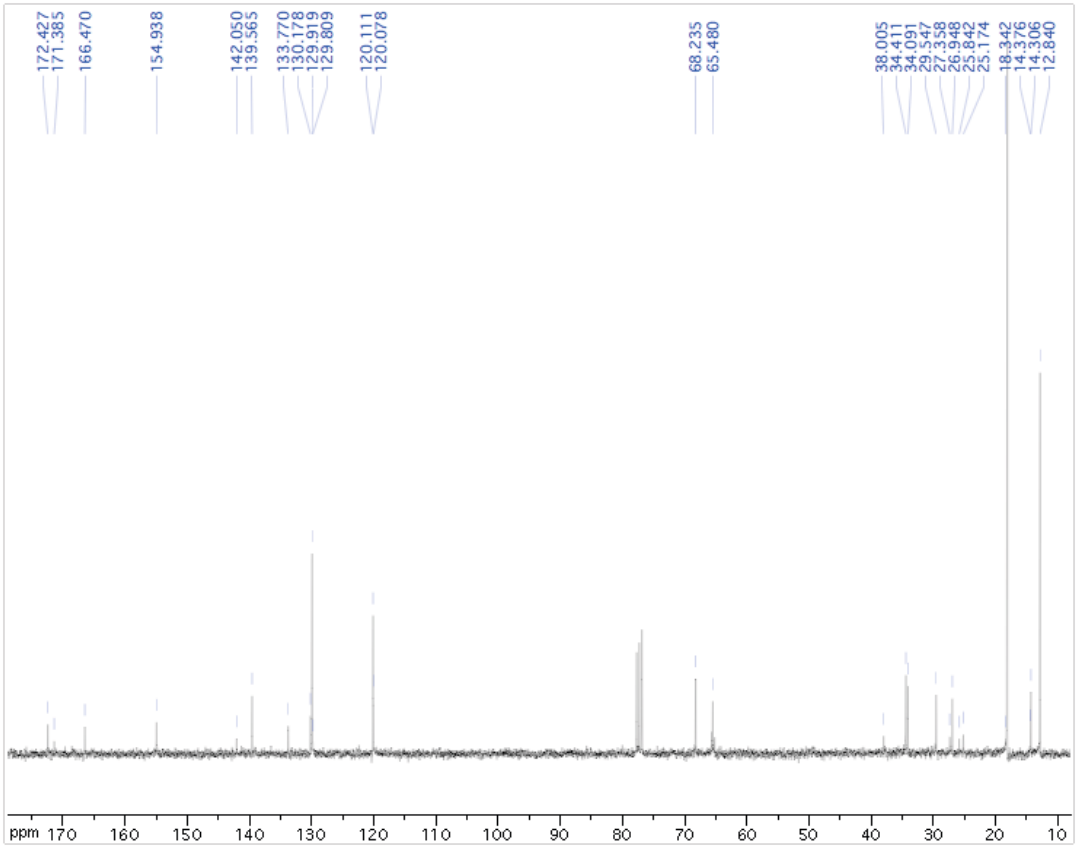
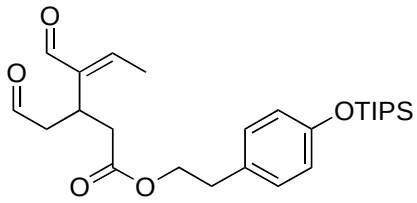




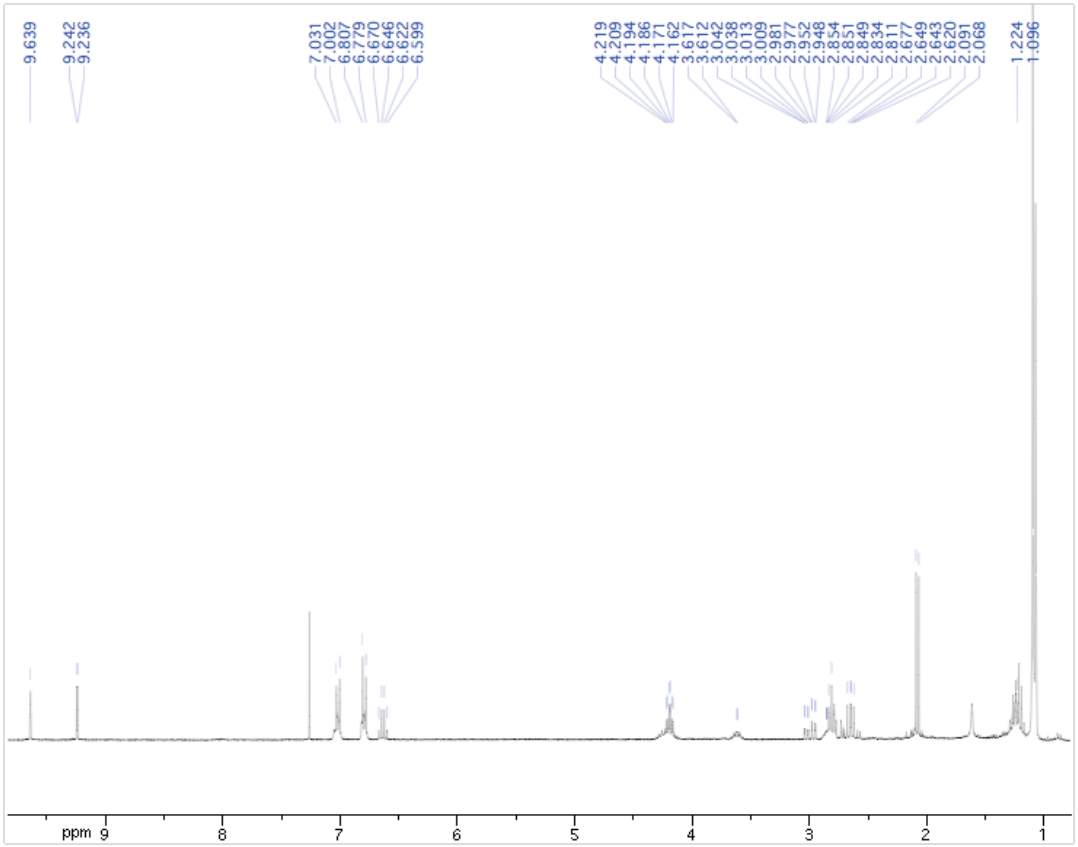
Synthesis of (*E*)-4-(triisopropylsilyloxy)phenethyl 4-formyl-3-(2-oxoethyl)hex-4-enoate: To 47 mg (0.102 mmol, 1 equiv.) lactone **3.17** dissolved in 1 mL dry THF in a 10 mL flame dried round-bottomed flask at -78^{o}C was slowly added 102 μL of a 1.0 M solution of DIBAl-H in PhMe. After stirring the reaction for 1 hr at -78^{o}C 100 μL dry MeOH was added, the reaction was allowed to warm to ambient temperature, and 5 mL saturated Rochelle's salt solution was added. After stirring for 30 min this mixture was extracted thrice with EtOAc, dried over Na_2SO_4, concentrated, and purified by silica gel flash chromatography eluting with 4 : 1 hex./EtOAc to yield 48 mg of the desired alcohol

as a colorless oil. Attempts to further purify this material by silica gel chromatography resulted in decomposition. R_f = 0.18 (4 : 1 hex./EtOAc)

This residue was dissolved in 1 mL dry CH_2Cl_2, charged to a 10 mL oven dried round-bottomed flask, and cooled to 0^oC. To this solution was added 65 mg (0.153 mmol, 1.5 equiv.) Dess-Martin periodinane and the reaction was stirred for 3 hr at ambient temperature before the addition of 5 mL 5 : 1 $Na_2S_2O_{3(sat.)}$: $NaHCO_{3(sat.)}$ solution. This mixture was stirred for 15 min before being extracted thrice with CH_2Cl_2. Combined organic layers were dried over Na_2SO_4 and concentrated. Silica gel flash chromatography eluting with 4 : 1 hex./EtOAc yielded 26 mg (55%) of the desired compound as a colorless oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 9.64 (s, 1H), 9.24 (d, *J* = 1.8, 1H), 7.02 (m, 2H), 6.79 (m, 2H), 6.63 (q, *J* = 7.2, 1H), 4.19 (td, *J* = 7.5, 3.0, 2H), 3.62 (m, 1H), 3.00 (ddd, *J* = 18.3, 8.7, 1.2, 1H), 2.85 (m, 1H) 2.81 (t, *J* = 6.9, 2H), 2.65 (dd, *J* = 10.2, 8.4, 2H), 2.08 (d, *J* = 6.9, 3H), 1.22 (m, 3H), 1.10 (s, 18H); ^{13}CNMR (75MHz, $CDCl_3$) δ 200.6, 195.3, 172.1, 154.6, 150.2, 143.3, 130.0, 129.9, 120.0, 65.3, 46.3, 36.9, 34.3, 27.3, 18.0, 15.4, 12.7; IR (NaCl, film) 2867, 2719, 1732, 1683, 1640, 1610 cm^{-1}; HRMS (+TOF) calcd for $C_{26}H_{41}O_5Si$ $[M+H]^+$ 461.27033, found 461.27069; R_f= 0.29 (4 : 1 hex./EtOAc)

Ref: BJEIV143, **BJEIV324, BJEIV327**, BJEIV329, BJEIV332, BJEIV333, BJEIV356, BJEIV357, BJEV011, BJEV013, BJEV014, BJEV015, BJEV032, BJEV033**.**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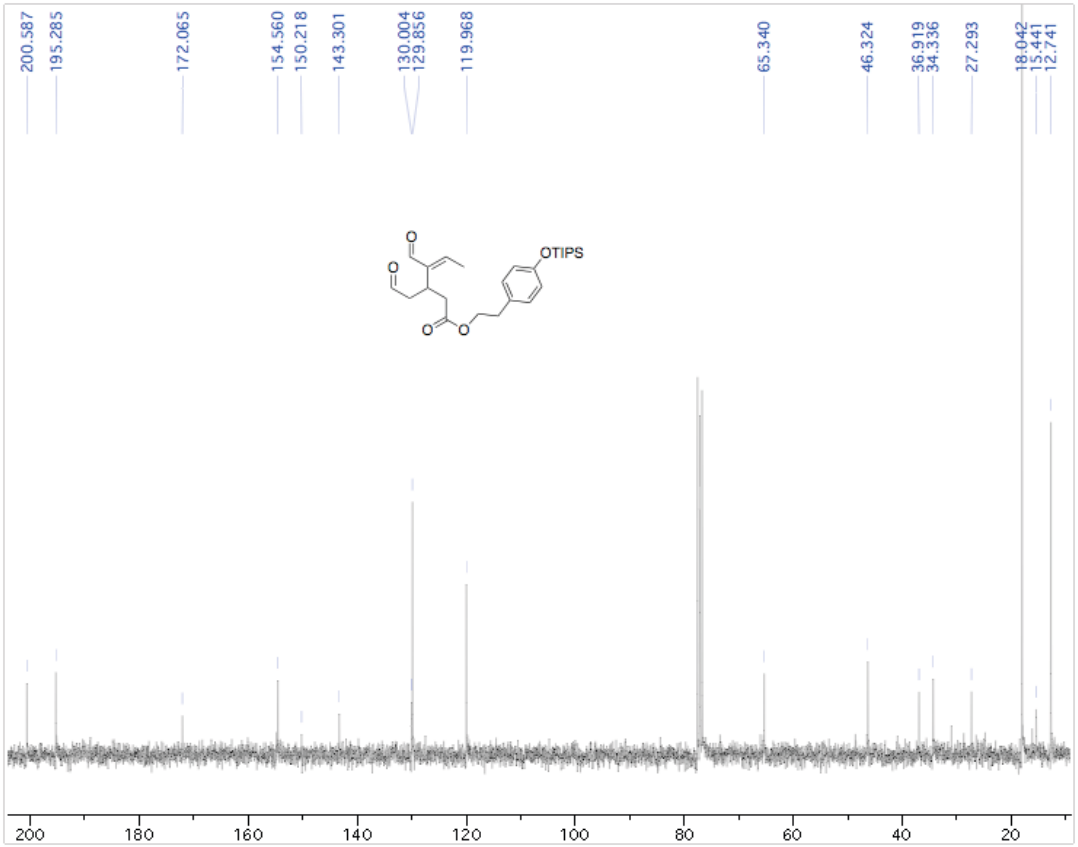
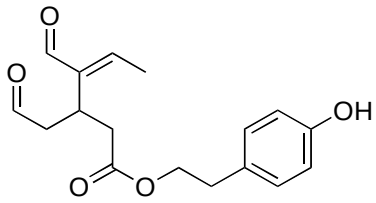


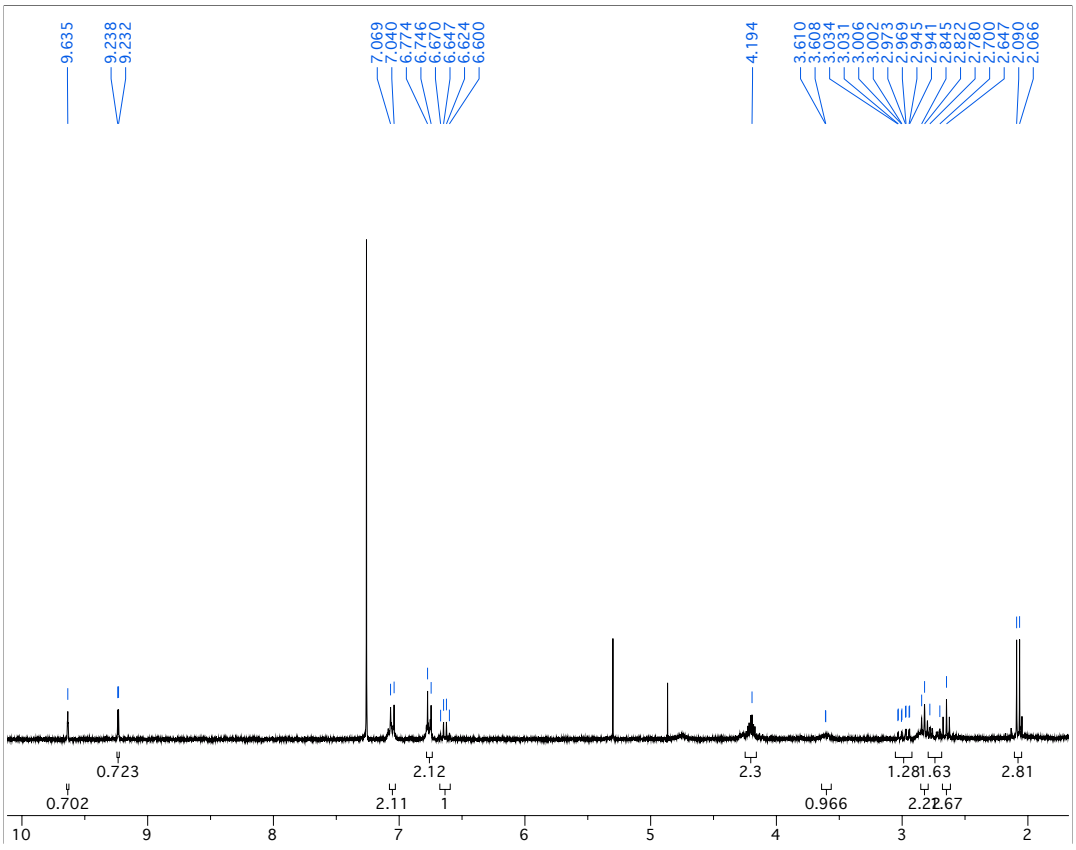


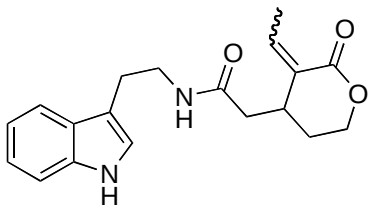
Synthesis of (+/-)-oleocanthal: To a 5 mL round bottomed flask containing 7 mg of the above produced dialdehyde dissolved in 250 µL dry THF at 0°C was added 50 µL of a solution prepared by the addition of 40% $HF_{(aq.)}$ to a 1M THF solution of TBAF until the pH of the resulting solution reached 7 by pH paper. The reaction was stirred for 2 hr at 0°C, added to brine, and extracted thrice with EtOAc. Combined organic layers were dried over Na_2SO_4, concentrated, and taken up in 1 : 2 hex./EtOAc. This solution was filtered through a short plug of silica gel and concentrated to yield 3.7 mg (80%) of (+/-)-

oleocanthal as a colorless film. Spectral properties matched those reported in *J. Org. Chem.* **2007**, 72, 6891.

^{1}HNMR (300MHz, $CDCl_3$) δ 9.64 (s, 1H), 9.23 (d, *J* = 2.1, 1H), 7.05 (d, *J* = 8.7, 2H), 6.75 (d, *J* = 8.4, 2H), 6.63 (q, *J* = 7.2, 1H), 4.19 (m, 2H), 3.61 (m, 1H), 2.97 (m, 1H), 2.82 (t, *J* = 6.9, 2H), 2.78-2.70 (m, 2H), 2.65 (m, 2H), 2.08 (d, *J* = 7.2, 3H); ^{13}CNMR (75MHz, $CDCl_3$) δ 200.4, 195.1, 171.9, 154.3, 154.2, 143.4, 129.5, 130.1, 115.4, 65.2, 46.3, 36.9, 34.2, 27.4, 15.2; IR (NaCl, film) 3340, 1725, 1675 cm^{-1}; HRMS (+TOF) $[M+H]^+$ calcd. for $C_{17}H_{21}O_5$ 305.1389, found 305.1387; R_f = 0.50 (2 : 3 hex./EtOAc)

Ref.: BJEIV145, **BJEIV330**.

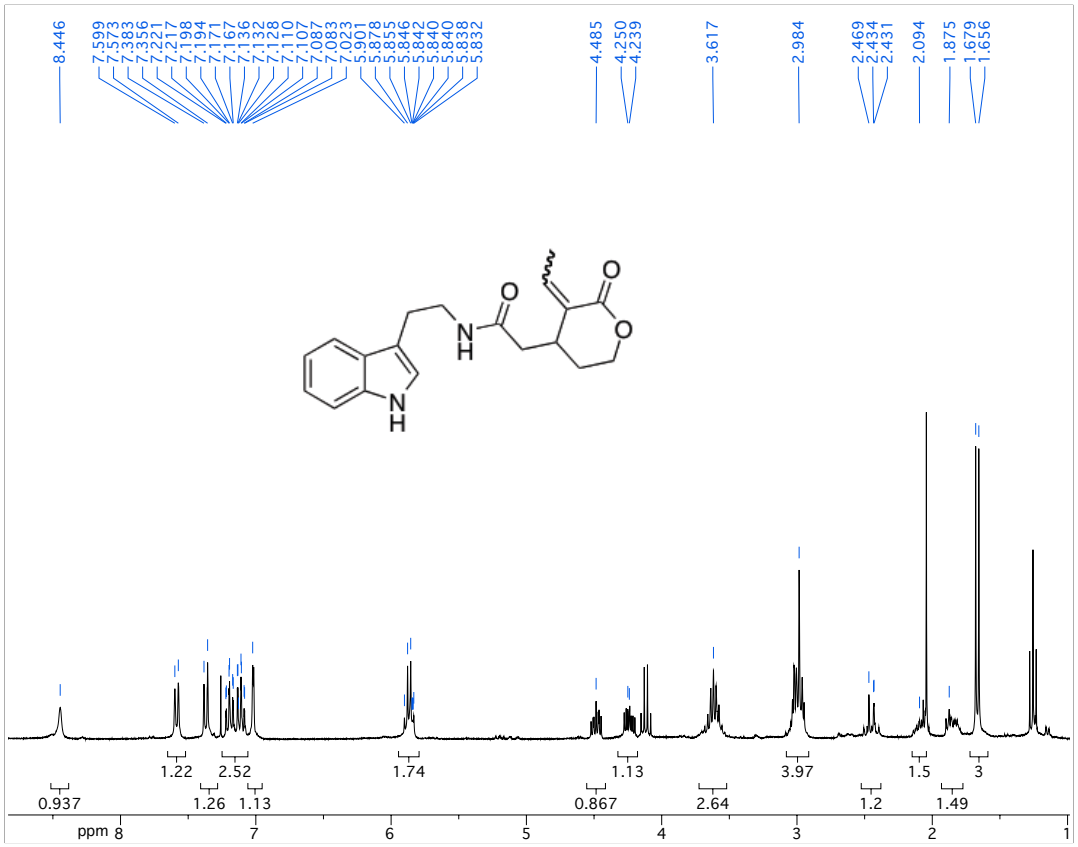




Synthesis of *N*-(2-(1*H*-indol-3-yl)ethyl)-2-(3-ethylidene-2-oxotetrahydro-2*H*-pyran-4-yl)acetamide (3.18): To a 25 mL round-bottomed flask containing 370 mg (1.99 mmol, 1 equiv.) acid **3.15** dissolved in 10 mL dry CH_2Cl_2 was added 433 μL (5.96 mmol, 3 equiv.) $SOCl_2$ and the reaction was heated to reflux for 1 hr before being concentrated. To this crude acid chloride was added 10 mL dry CH_2Cl_2 and the reaction was cooled to 0^oC before the addition of 351 mg (2.19 mmol, 1.1 equiv.) tryptamine followed by 305 μL (2.19 mmol, 1.1 equiv.) dry NEt_3. The reaction was stirred for 30 min at 0^oC and was then allowed to warm to ambient temperature over 2 hr. The reaction mixture was then added to $NH_4Cl_{(sat.)}$, extracted thrice with EtOAc, dried over Na_2SO_4, and concentrated. The crude residue was submitted to silica gel flash chromatography eluting with 1 : 2 to 0 : 1 hex./EtOAc to yield 154 mg of the desired product as a tan foam.

^{1}HNMR (300 MHz, $CDCl_3$) δ 8.45 (bs, 1H), 7.58 (d, *J* = 7.8, 1H), 7.36 (d, *J* = 8.1, 1H), 7.19 (td, *J* = 6.9, 1.2, 1H), 7.11 (td, *J* = 6.9, 1.2, 1H), 7.02 (d, *J* = 2.1, 1H), 5.86 (q, *J* = 6.9, 1H), 4.49 (m, 1H), 4.24 (m, 1H), 3.62 (m, 2H), 2.98 (m, 4H), 2.45 (m, 1H), 2.09 (m, 1H), 1.87 (m, 1H), 1.68 (d, *J* = 6.9, 3H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 172.5, 169.7, 139.7, 136.6, 129.2, 127.5, 122.4, 119.6, 118.8, 112.8, 111.6, 68.6, 39.7, 34.4, 30.5, 27.2, 25.5, 14.4, 13.5; IR (NaCl, film): 1718, 1618 cm^{-1}; HRMS (+TOF): $[M]^+$ 326.16304 calcd for $C_{19}H_{22}N_2O_3$, found: 326.16331; R_f = 0.38 (EtOAc).

Ref.: BJEIV111, BJEIV114, **BJEIV124**, BJEIV146, BJEIV194, BJEV172, BJEV199.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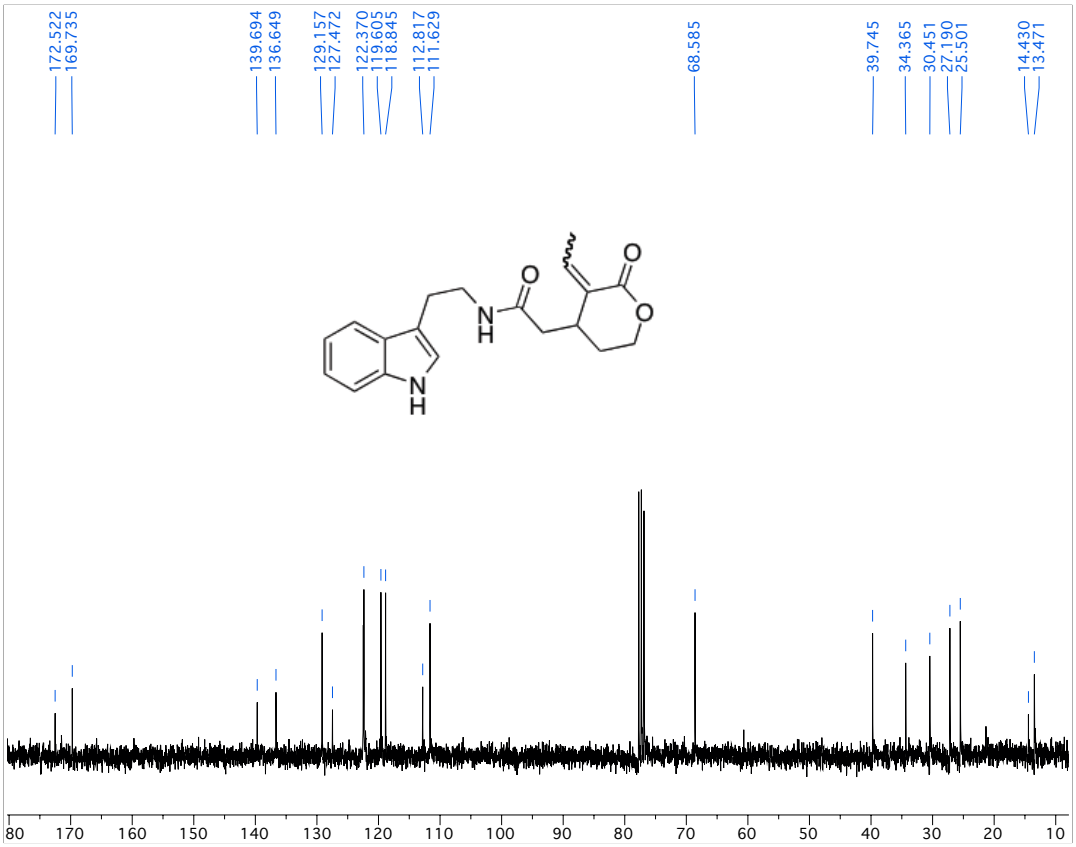
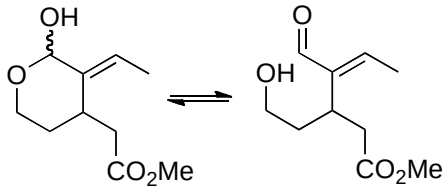
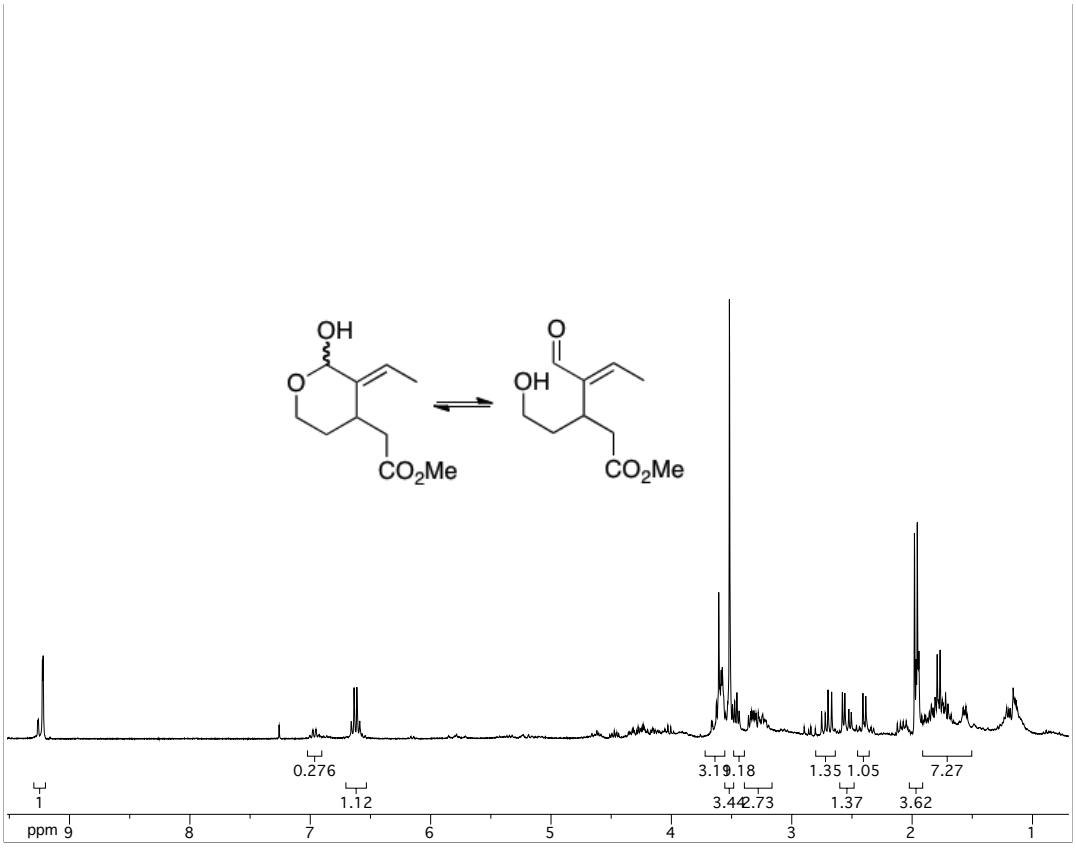
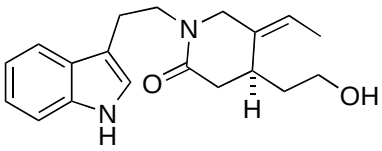




Synthesis of (*E*)-methyl 2-(3-ethylidene-2-hydroxytetrahydro-2*H*-pyran-4-yl)acetate (3.28): To a flame dried 50 mL round-bottomed flask containing 248 mg (1.25 mmol, 1 equiv.) lactone **3.1** was added 20 mL of dry THF and this solution was cooled to -78^{o}C. To this solution was dropwise added 1.5 mL (1.2 equiv.) of a 1.0 M solution of DIBAl-H in THF and the reaction was allowed to stir for 60 min at this temperature before the dropwise addition of 2 mL dry MeOH and warming to ambient temperature. To this reaction mixture was added 25 mL of a saturated aqueous solution of Rochelle's salt and

the mixture was stirred for 30 min at ambient temperature. This mixture was extracted thrice with EtOAc, dried over Na_2SO_4, and concentrated to yield a colorless oil, which was immediately used without purification.



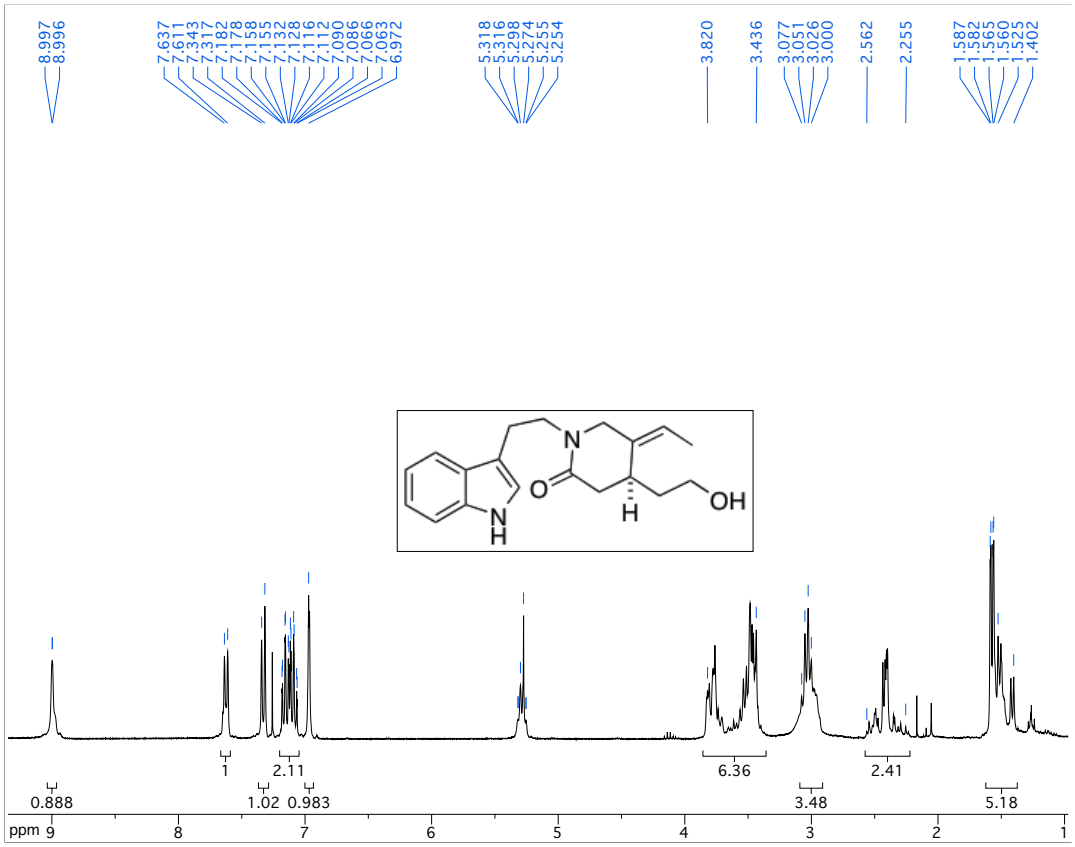


Synthesis of (*E*)-1-(2-(1*H*-indol-3-yl)ethyl)-5-ethylidene-4-(2-hydroxyethyl)piperidin-2-one (3.29): To the above produced residue was added 360 mg (2.25 mmol, 1.5 equiv) tryptamine, 15 mL dry THF, and then 954 mg (4.50 mmol, 3 equiv.) $NaBH(OAc)_3$. After stirring at ambient temperature for 48 hr the reaction was added to $NaHCO_{3(sat.)}$ and

extracted thrice with CH_2Cl_2. Combined organic layers were dried over Na_2SO_4 and concentrated to afford a brown oil which was purified by silica gel chromatography eluting with 5% to 20% MeOH in EtOAc to yield 220 mg (56%, 2 steps) of the title compound as a white foam.

^{1}HNMR (300 MHz, $CDCl_3$): δ 9.00 (brs, 1H), 7.62 (d, *J* = 7.8, 1H), 7.33 (d, *J* = 8.1, 1H) 7.13 (m, 2H), 6.97 (s, 1H), 5.28 (q, *J* = 5.7, 1H), 3.44-3.82 (m, 6H), 3.04 (q, *J* = 7.5, 2H), 2.97 (m, 1H) 2.26-2.56 (m, 2H), 1.57 (dd, *J* = 6.6, 1.5, 3H), 1.40-1.56 (m, 2H); ^{13}CNMR (75 MHz, $CDCl_3$): δ169.7, 136.4, 132.6, 127.4, 122.5, 121.7, 120.8, 119.1, 118.6, 112.3, 111.4, 60.3, 52.5, 47.5, 37.9, 35.2, 29.9, 22.9, 12.8; IR (NaCl, film): 3289, 1620 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 313.1911 calcd for $C_{19}H_{25}N_2O_2$, found: 313.1911; R_f = 0.18 (5% MeOH in EtOAc).

Ref.: BJEV230, BJEV233, BJEV234, BJEV235, BJEV250, BJEV259, BJEV271, BJEV275, BJEV285, BJEV303, BJEV308, **BJEV326, BJEV328.**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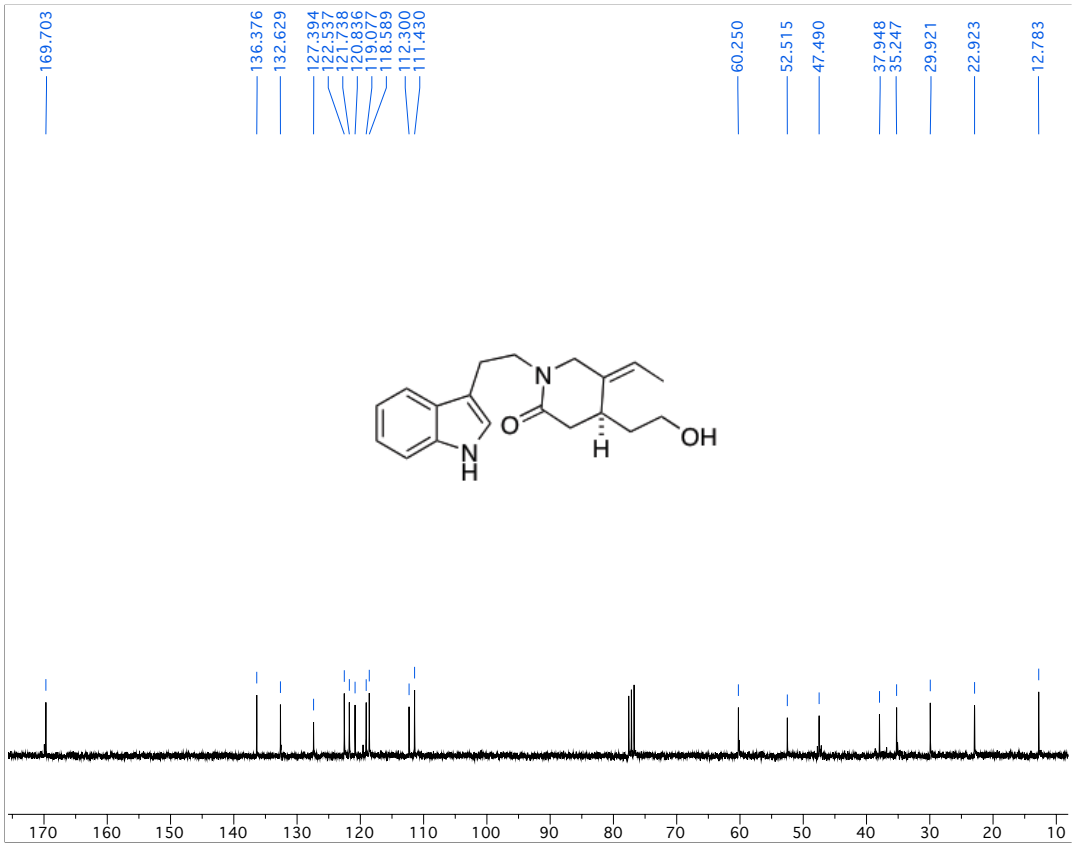
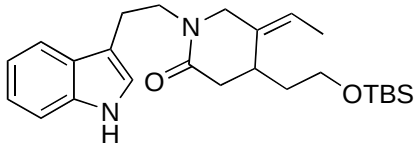


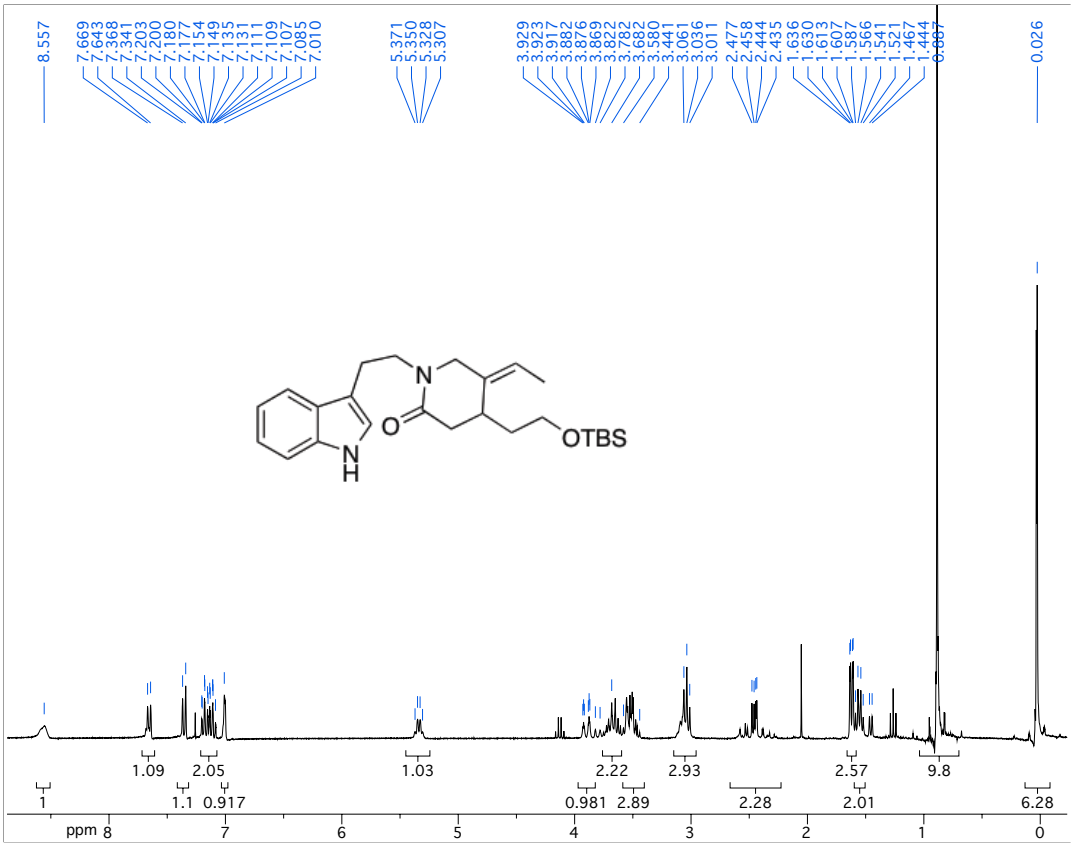


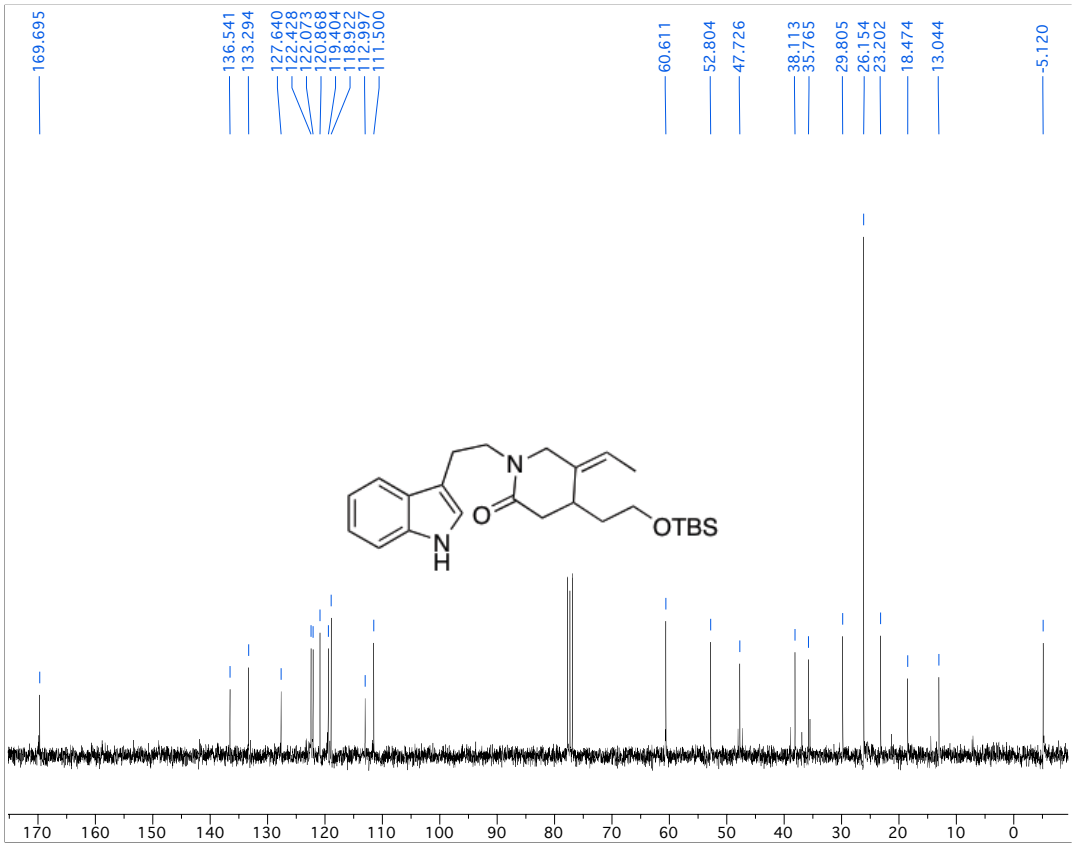
Synthesis of (*E*)-1-(2-(1*H*-indol-3-yl)ethyl)-4-(2-(*tert*-butyldimethylsilyloxy)ethyl)-5-ethylidenepiperidin-2-one (3.30): To 165 mg (0.529 mmol, 1 equiv.) (*E*)-1-(2-(1*H*-indol-3-yl)ethyl)-5-ethylidene-4-(2-hydroxyethyl)piperidin-2-one (**3.29**) dissolved in 5.3 mL dry CH_2Cl_2 was added 96 mg (0.634 mmol, 1.2 equiv.) TBSCl and then 72 mg (1.06 mmol, 2 equiv.) imidazole. The reaction was allowed to stir at ambient temperature for 4 h before being added to brine and extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and purified by silica gel chromatography

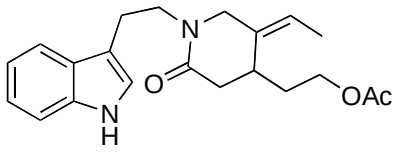
eluting with 1 : 1 hex./EtOAc to yield 226 mg (>99%) of the title compound as a colorless foam.

^{1}HNMR (300 MHz, $CDCl_3$): δ 8.56 (brs, 1H), 7.65 (d, *J* = 7.8, 1H), 7.35 (d, *J* = 7.8, 1H), 7.14 (m, 2H), 7.01 (s, 1H), 5.34 (q, *J* = 6.3, 1H), 3.90 (dt, *J* = 14.1, 1.8, 1H), 3.68 (m, 3H), 3.44-3.58 (m, 3H), 3.05 (m, 1H), 3.04 (t, *J* = 7.5, 2H), 2.45 (m, 2H), 1.62 (dd, *J* = 6.9, 1.8, 3H), 1.55 (q, *J* = 7.5, 2H), 0.89 (s, 9H), 0.03 (s, 6H); ^{13}CNMR (75MHz, $CDCl_3$): δ 169.7, 136.5, 133.3, 127.6, 122.4, 122.1, 120.9, 119.4, 118.9, 113.0, 111.5, 60.6, 52.8, 47.7, 38.1, 35.8, 29.8, 26.2, 23.2, 18.5, 13.0, -5.1; IR (NaCl, film): 3271, 1628 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 427.2775 calcd. for $C_{25}H_{39}N_2O_2Si$, found: 427.2780; R_f = 0.37 (1 : 1 hex./EtOAc).

Ref.: BJEV232, BJEV237, BJEV241, BJEV277, BJEV305, BJEV312, **BJEV335**.



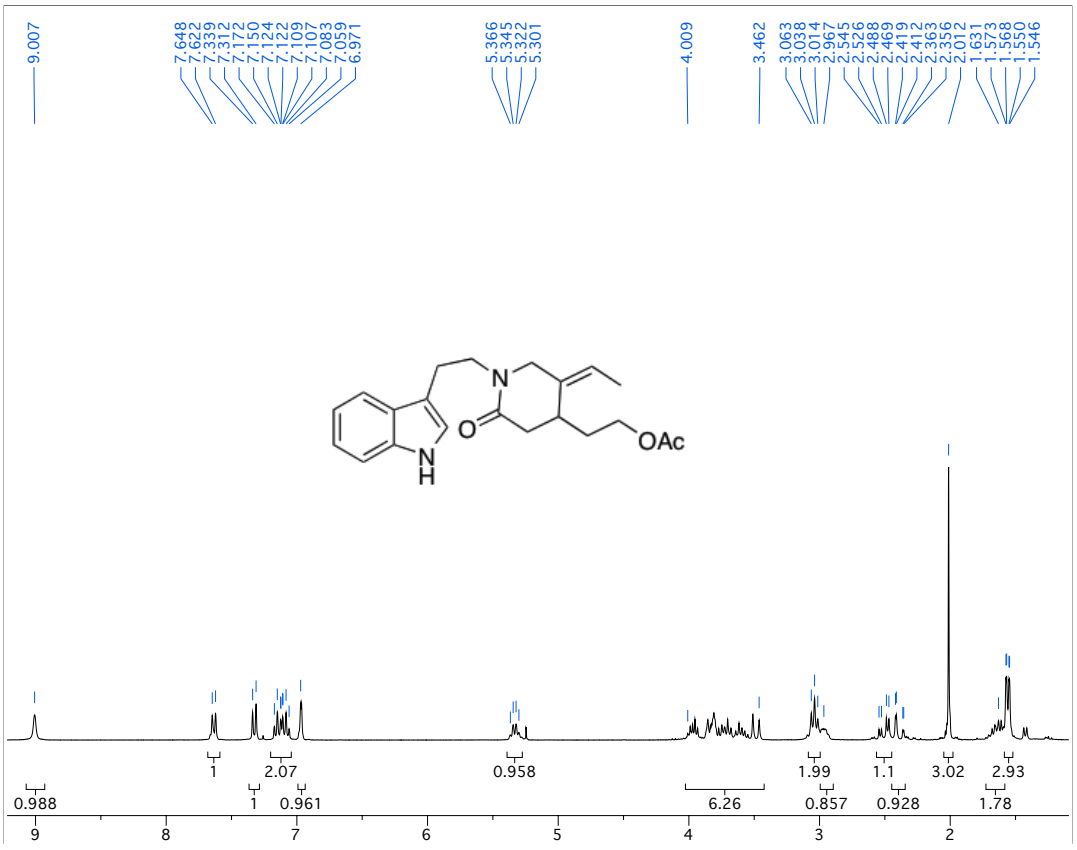


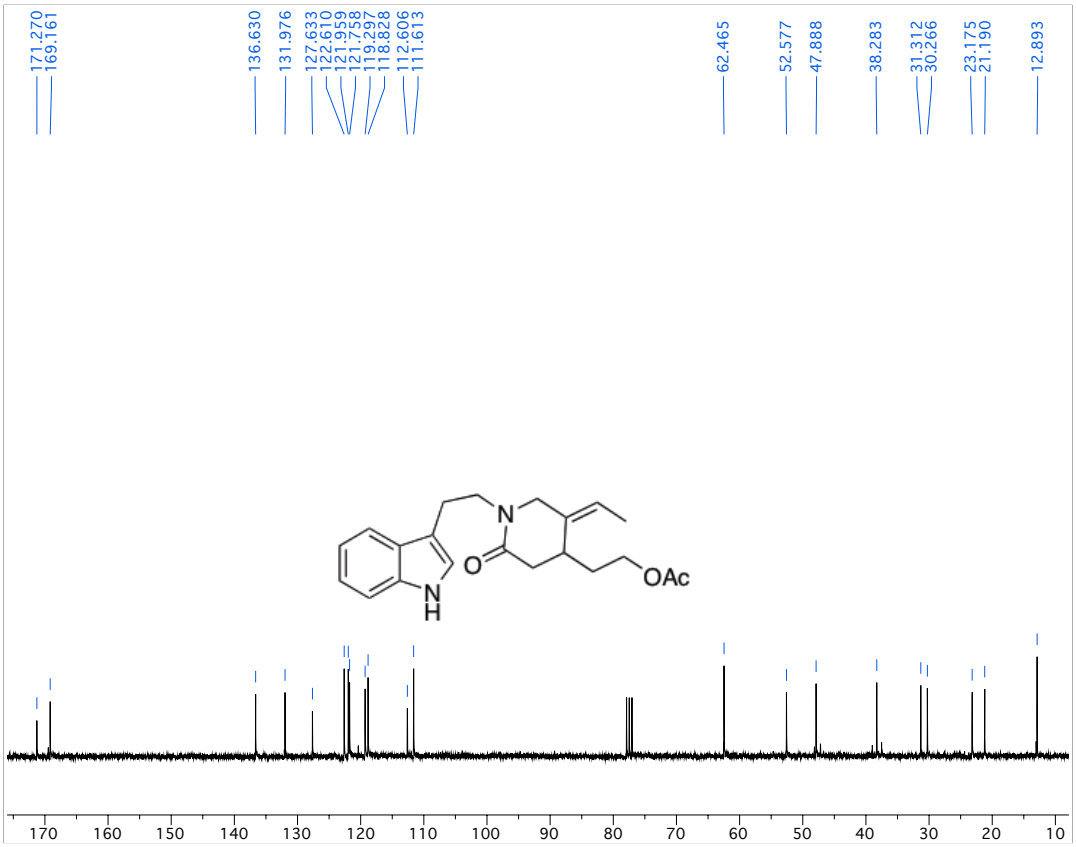


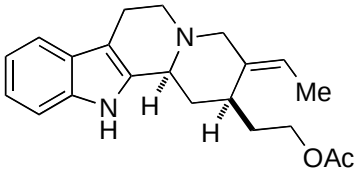
Synthesis of (*E*)-2-(1-(2-(1*H*-indol-3-yl)ethyl)-5-ethylidene-2-oxopiperidin-4-yl)ethyl acetate (3.30): To a 10 mL round bottomed flask containing 65 mg (0.208 mmol, 1 equiv.) alcohol **3.29** dissolved in 1 mL dry CH_2Cl_2 and 1 mL dry pyridine was added 30 µL (0.416 mmol, 2 equiv.) AcCl followed by a single crystal of DMAP. The reaction was stirred at ambient temperature for 1 hr before being added to $NaHCO_{3(sat.)}$, and extracted thrice with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The crude residue was purified by silica gel chromatography eluting with 1% to 10% MeOH in CH_2Cl_2 to yield 70 mg (95%) of the desired product as a pale yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 9.01 (bs, 1H), 7.63 (d, *J* = 7.8, 1H), 7.32 (d, *J* = 8.1, 1H), 7.15 (t, *J* = 6.6, 1H), 7.08 (t, *J* = 7.2, 1H), 6.97 (s, 1H), 5.33 (q, *J* = 6.9, 1H), 4.01-3.46 (m, 6H), 3.04 (t, *J* = 7.5, 2H), 2.97 (m, 1H), 2.50 (dd, *J* = 17.1, 5.7, 1H), 2.39 (dd, *J* = 16.8, 2.1, 1H), 2.01 (s, 3H), 1.63 (m, 2H), 1.56 (dd, *J* = 6.9, 1.5, 3H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 171.3, 169.2, 136.6, 132.0, 127.6, 122.6, 122.0, 121.8, 119.3, 118.8, 112.6, 111.6, 62.5, 52.6, 47.9, 38.3, 31.3, 30.3, 23.2, 21.2, 12.9; IR (NaCl, film): 1736, 1628 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 355.2016 calcd for $C_{21}H_{27}N_2O_3$, found: 355.2014; R_f = 0.27 (5% MeOH in CH_2Cl_2).

Ref.: BJEV352, BJEV381, **BJEV400**





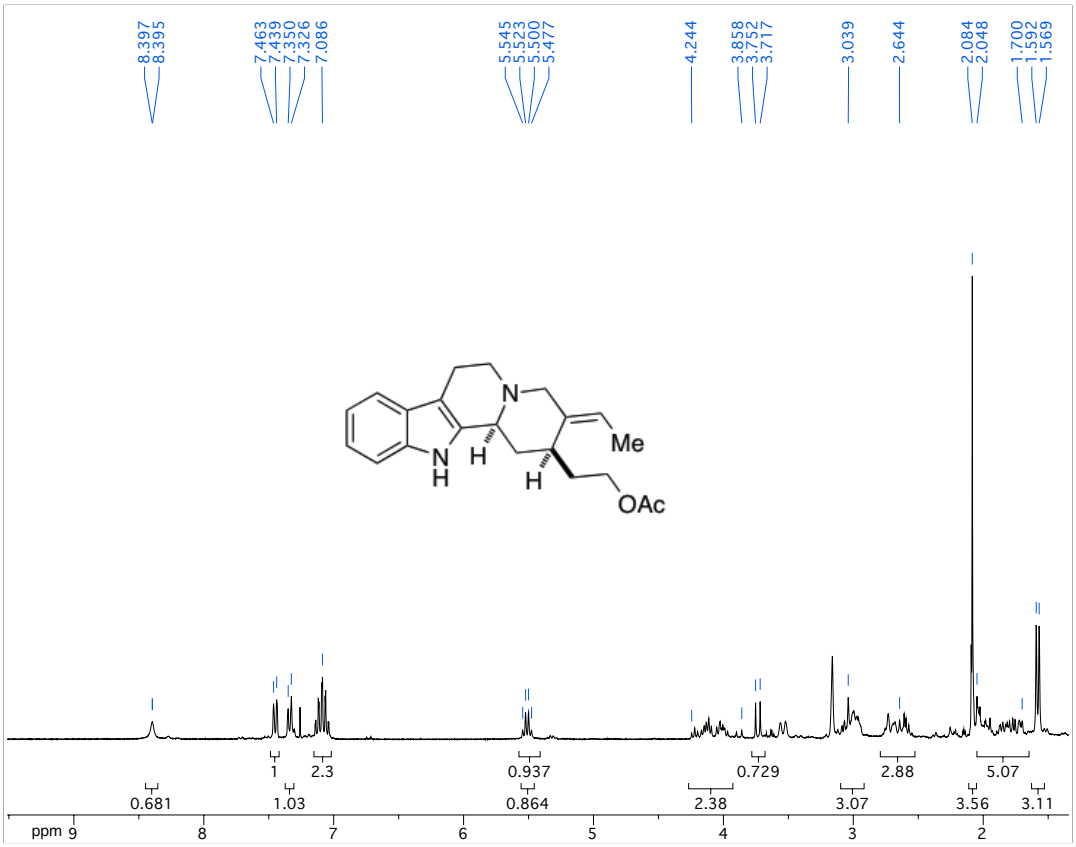


Synthesis of 2-((2*R*,12b*S*,*E*)-3-ethylidene-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-2-yl)ethyl acetate (3.31): To 192 mg (0.542 mmol, 1 equiv.) (*E*)-2-(1-(2-(1*H*-indol-3-yl)ethyl)-5-ethylidene-2-oxopiperidin-4-yl)ethyl acetate (**3.30**) dissolved in 5 mL dry benzene was added 100 μL (1.08 mmol, 2 equiv.) freshly distilled $POCl_3$. The reaction was heated to reflux for 1.5 hr before being concentrated under reduced pressure. The resulting residue was taken up in 5 mL dry MeOH and cooled to 0^oC before 50 mg $NaBH_4$ was added and the reaction was removed from the ice bath and stirred for 15 min.

The reaction was then added to 0.5 M NaOH, extracted thrice with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel chromatography eluting with 5% MeOH in EtOAc to provide 119 mg (65%) of the desired product as a pale yellow foam.

^{1}HNMR (300 MHz, $CDCl_3$) δ 8.40 (bs, 1H), 7.45 (d, *J* = 7.2, 1H), 7.34 (d, *J* = 7.2, 1H), 7.09 (m, 2H), 5.51 (q, *J* = 6.9, 1H), 4.24-3.86 (m, 2H), 3.73 (d, *J* = 10.5, 1H), 3.04 (m, 3H), 2.64 (m, 3H), 2.08 (s, 3H), 2.05-1.70 (m, 5H), 1.58 (d, *J* = 6.9, 3H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 171.5, 136.3, 135.5, 135.0, 127.5, 122.1, 121.4, 119.4, 118.2, 111.1, 108.5, 62.9, 60.1, 55.4, 53.0, 35.3, 31.0, 30.7, 21.9, 21.3, 12.9; IR (NaCl, film): 1735 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 339.2073 calcd for $C_{21}H_{27}N_2O_2$, found: 339.2072; R_f = 0.45 (5% MeOH in EtOAc).

Ref.: BJEV353, BJEV382, **BJEV402**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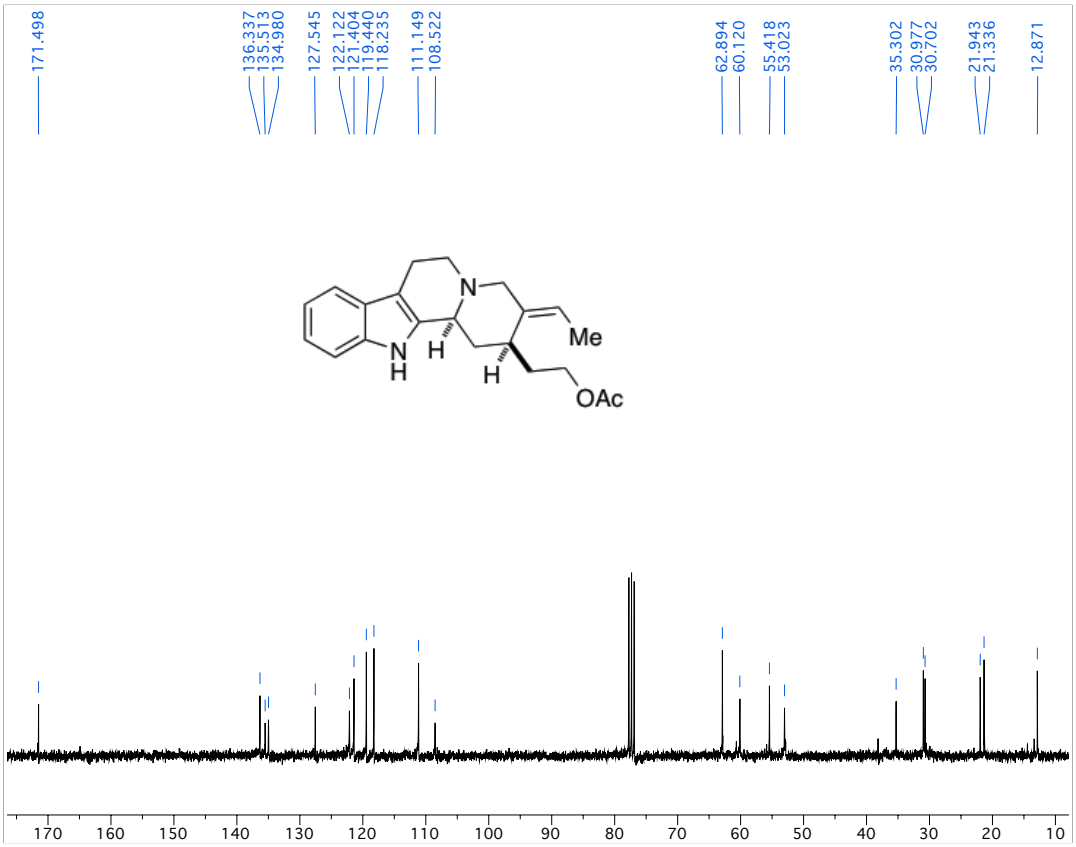
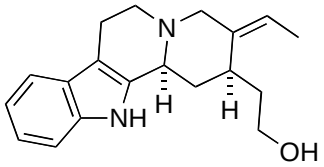
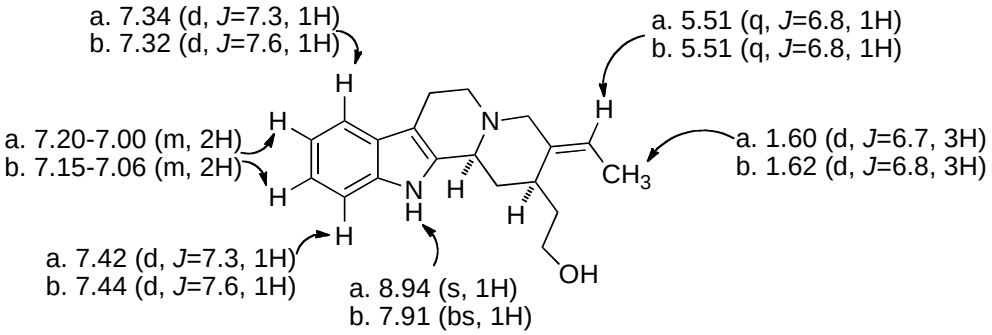




Synthesis of (+/-)-geissoshizol: To a 10 mL round bottomed flask containing 50 mg (0.148 mmol, 1 equiv.) acetate **3.31** dissolved in 1 mL MeOH and 0.5 mL H_2O was added 245 mg (1.77 mmol, 12 equiv.) K_2CO_3. The reaction was stirred at ambient temperature for 2 hr, added to brine, extracted thrice with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting oil was purified by silica gel chromatography eluting with 10% MeOH/CH_2Cl_2 to yield 39 mg (89%) of the desired product as a white solid.

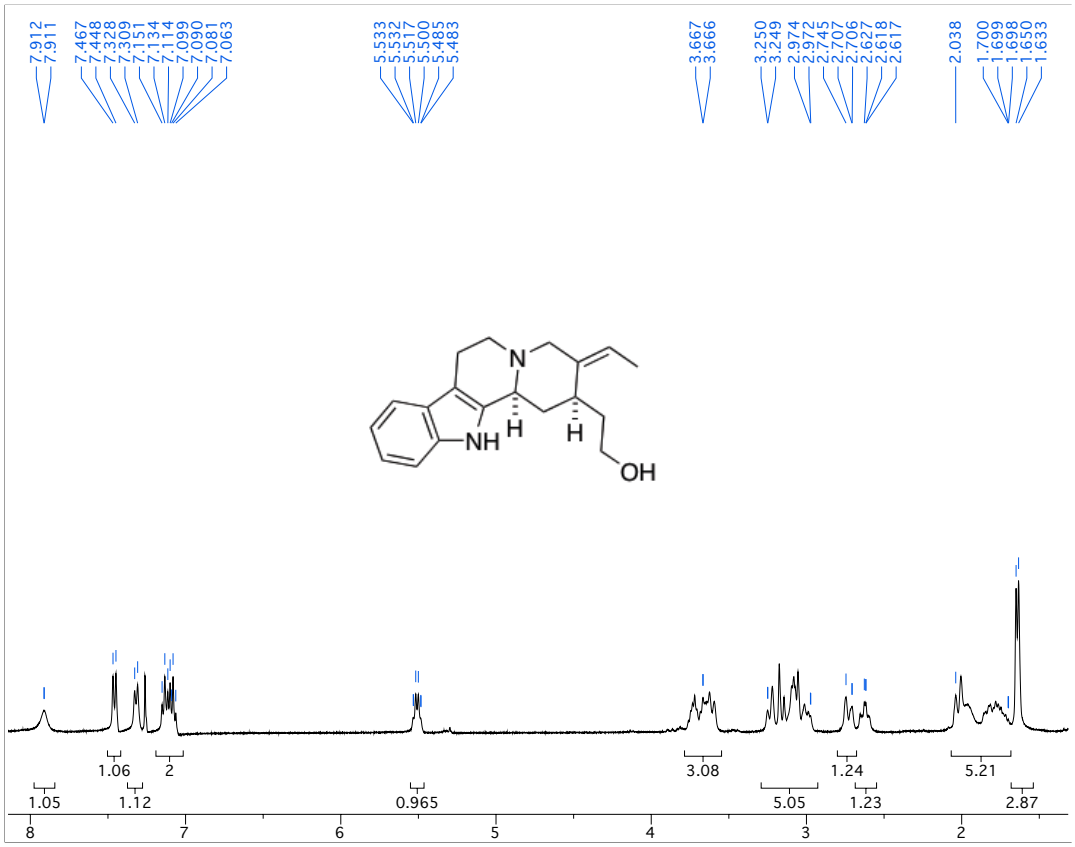
^{1}HNMR (400 MHz, $CDCl_3$) δ 7.91 (bs, 1H), 7.46 (d, *J* = 7.6, 1H), 7.32 (d, *J* = 7.6, 1H), 7.10 (m, 2H), 5.51 (q, *J* = 6.8, 1H), 3.67 (m, 3H), 3.25-2.97 (m, 5H), 2.72 (m, 1H), 2.62 (m, 1H), 2.04-1.70 (m, 5H), 1.64 (d, *J* = 6.8, 3H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 136.4, 136.2, 134.8, 127.5, 121.7, 121.4, 119.5, 118.2, 110.9, 108.6, 61.3, 60.1, 55.3, 52.8, 35.4, 35.2, 31.0, 21.8, 12.9; IR (NaCl, film): 3233, 2851, 2790, 2745 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 297.1961 calcd for $C_{19}H_{25}N_2O$, found: 297.1961; R_f = 0.14 (5% MeOH in EtOAc). Spectroscopic properties agree in all respects with those previously reported: Yu, S.; Berner, M.; Cook, J.M. *J. Am. Chem. Soc.* **2000**, *122*, 7827; Wenkert, E.; Guo, M.; Pestchanker, M.J.; Shi, Y.-J.; Vankar, Y.D. *J. Org. Chem.* **1989**, *54*, 1166.

Comparison of ^{1}HNMR data:



a. Yu, S.; Berner, M.; Cook, J.M. *J. Am. Chem. Soc.* **2000**, *122*, 7827
b. English, B.J.; Williams, R.M.

Ref.: BJEV341, **BJEV384**, BJEV402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H
NH
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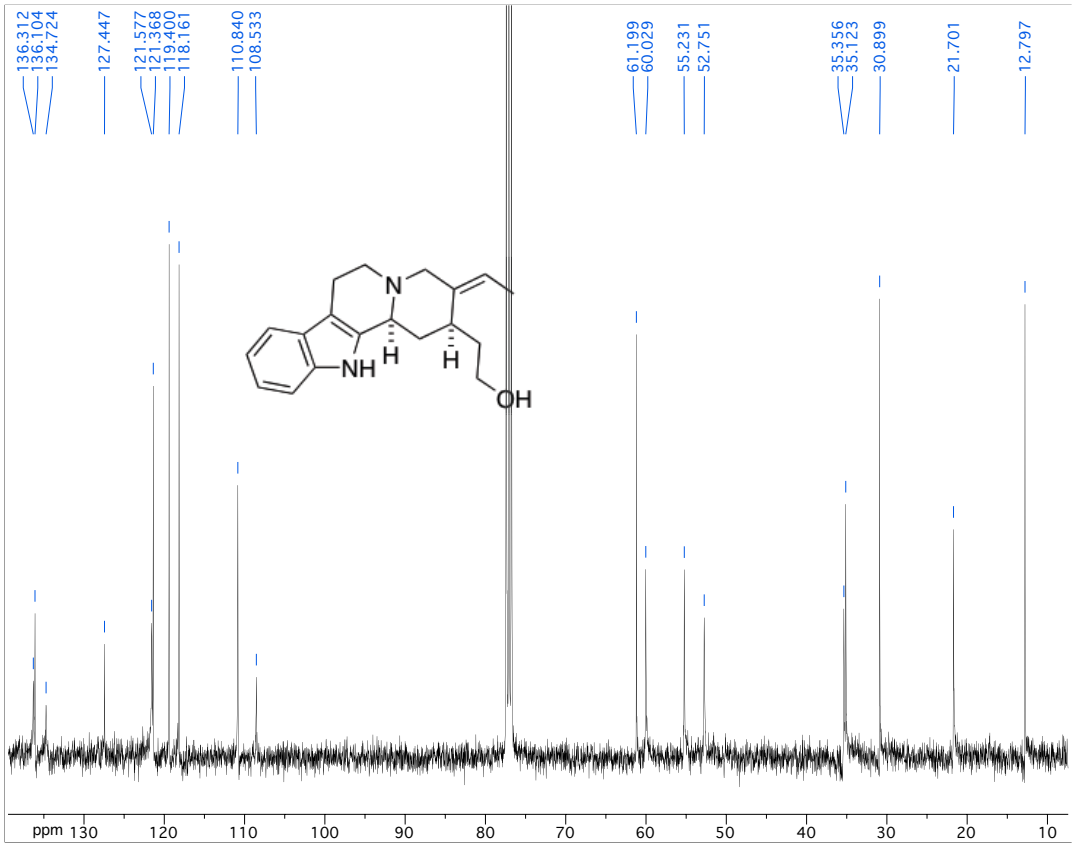
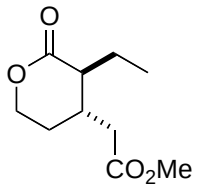
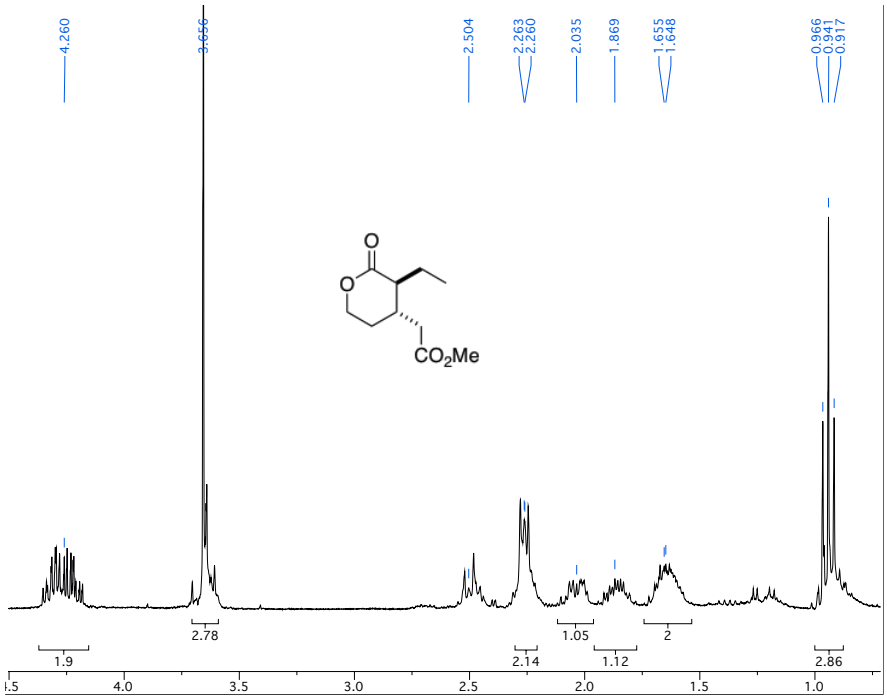


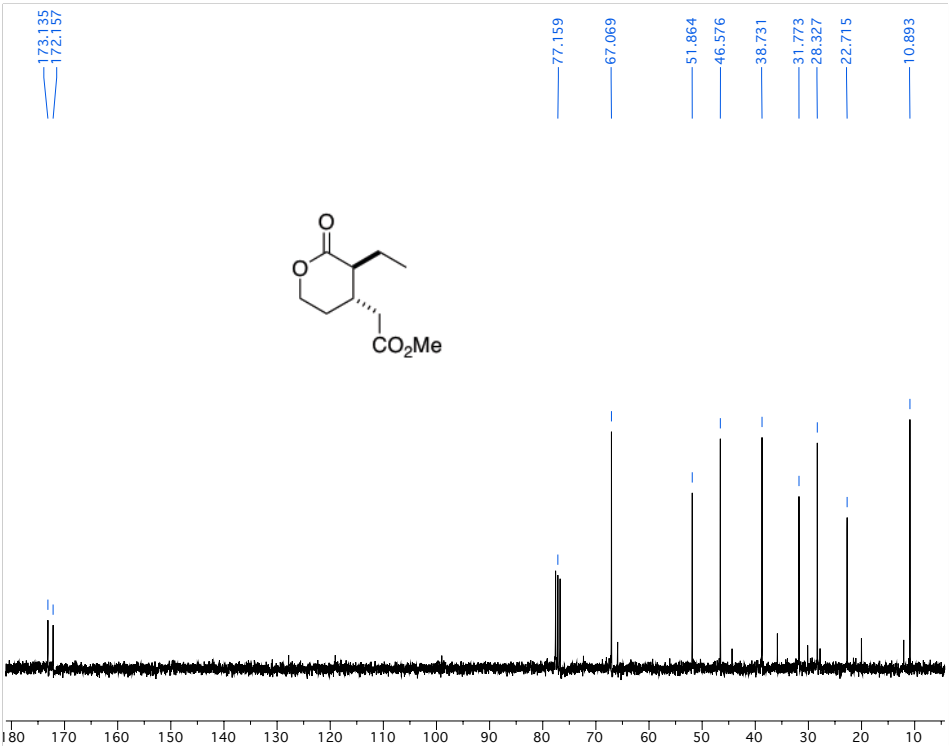


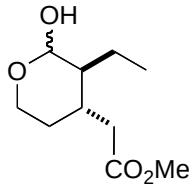
Synthesis of lactone 3.32: To a 250 mL round-bottomed flask contining 1.10 g (5.55 mmol, 1 equiv.) of lactone **3.1** dissolved in 56 mL dry THF at -78°C was added 6.10 mL (1.1 equiv.) of a 1.0 M solution of L-Selectride in THF. The reaction was allowed to stir at -78°C for 60 min and was then added to $NH_4Cl_{(sat.)}$, extracted thrice with EtOAc, dried over Na_2SO_4, concentrated, and purified by silica gel chromatography eluting with 2 : 1 hex./EtOAc to yield 918 mg (83%) of the title compound as a colorless oil.

^{1}HNMR (300 MHz, $CDCl_3$): δ 4.26 (m, 2H), 3.66 (s, 3H), 2.50 (m, 1H), 2.26 (m, 2H), 2.04 (m, 1H), 1.87 (m, 1H), 1.65 (m, 2H), 0.94 (t, *J* = 7.2, 3H) ; ^{13}CNMR (75 MHz, $CDCl_3$) major conformer: δ 173.1, 172.2, 67.1, 51.9, 46.6, 38.7, 31.8, 28.4, 22.7, 10.9; IR (NaCl, film): 1732 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 201.1121 calcd for $C_{10}H_{17}O_4$, found: 201.1123; R_f = 0.52 (1 : 1 hex./EtOAc)

Ref.: BJEIV063, BJEV279, **BJEV291**, BJEV310





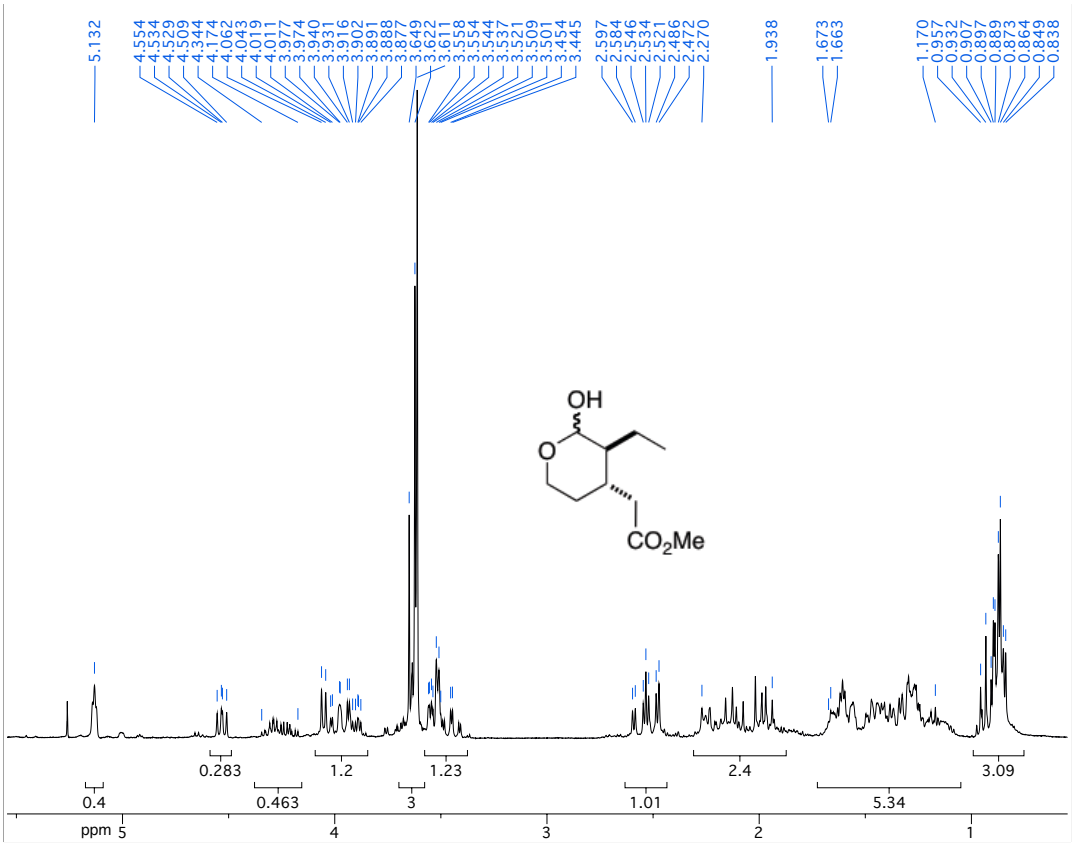


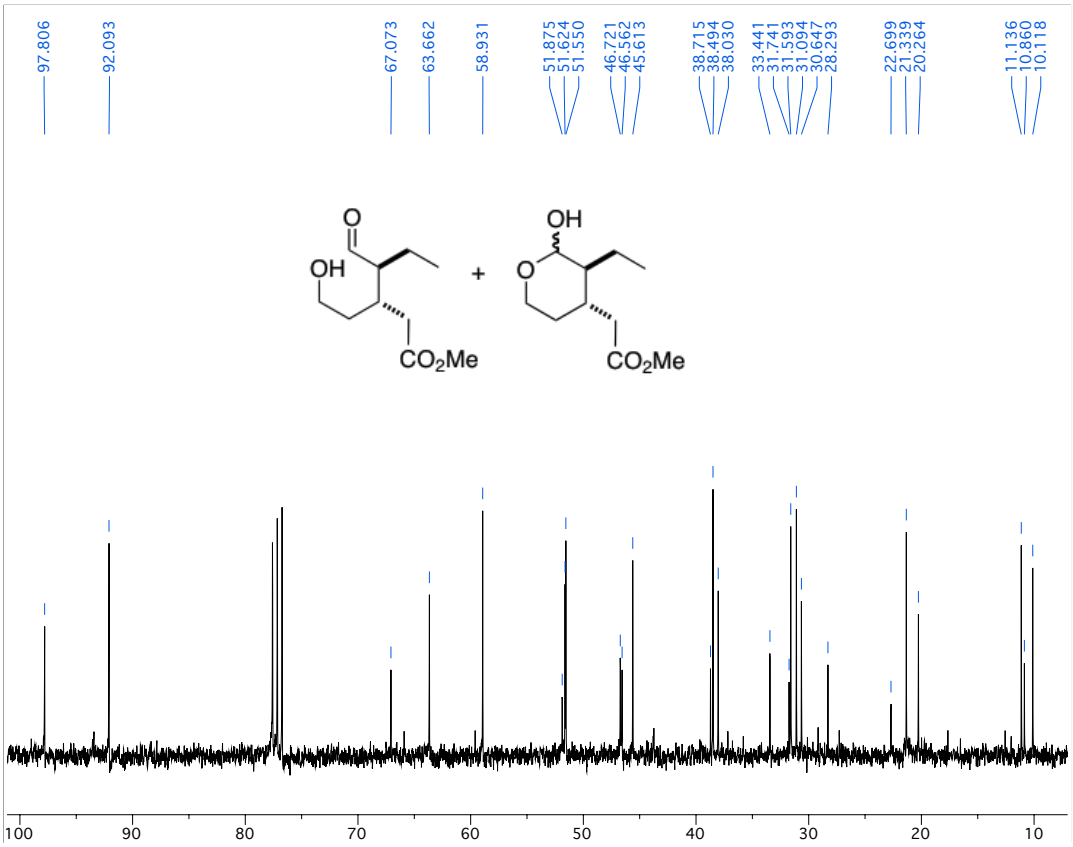
Synthesis of lactol mixture 3.33: A 25 mL round-bottomed flask containing 172 mg (0.859 mmol, 1 equiv.) lactone **3.32** dissolved in 89 mL dry THF was cooled to -78ºC. To this cooled mixture was slowly added 945 μL (0.945 mmol, 1.1 equiv.) of a 1.0 M solution of DIBAL in THF. The reaction was stirred for 30 min at -78ºC followed by the dropwise addition of 2 mL MeOH. The reaction was allowed to warm to ambient temperature and was then added to a saturated aqueous solution of NaK tartrate and extracted thrice with EtOAc. Combined organic layers were dried over Na_2SO_4, and

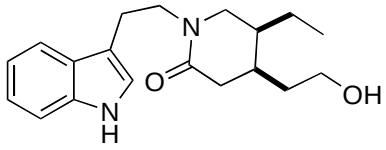
purified by silica gel flash chromatography eluting with 1 : 1 hex./EtOAc to yield 155 mg (90%) of an inseparable mixture of the desired lactol mixture as a colorless oil.

^{13}CNMR (75MHz, $CDCl_3$) mixture of isomers: δ 97.8, 92.1, 67.1, 63.1, 63.7, 58.9, 51.9, 51.6, 51.6, 46.7, 46.6, 45.6, 38.7, 38.5, 38.0, 33.4, 31.7, 31.6, 31.1, 30.6, 28.3, 22.7, 21.3, 20.3, 11.1, 10.9, 10.1; R_f = 0.43 (1:1 hex./EtOAc)

Ref.: **BJEV283**, BJEV294

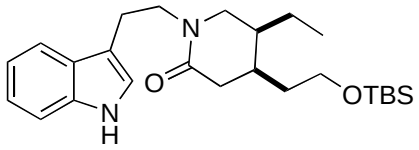






Synthesis of 1-(2-(1*H*-indol-3-yl)ethyl)-5-ethyl-4-(2-hydroxyethyl)piperidin-2-one (3.34): To a 50 mL round-bottomed flask containing 459 mg (2.27 mmol, 1 equiv.) of lactol mixture **3.33** dissolved in 23 mL dry THF was added 546 mg (3.41 mmol, 1.5 equiv.) tryptamine and then 1.44 g (6.81 mmol, 3 equiv.) $NaBH(OAc)_3$. The reaction was allowed to stir at ambient temperature for 48 hr before being added to $NaHCO_{3(sat.)}$, extracted thrice with EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was carried forward without purification.

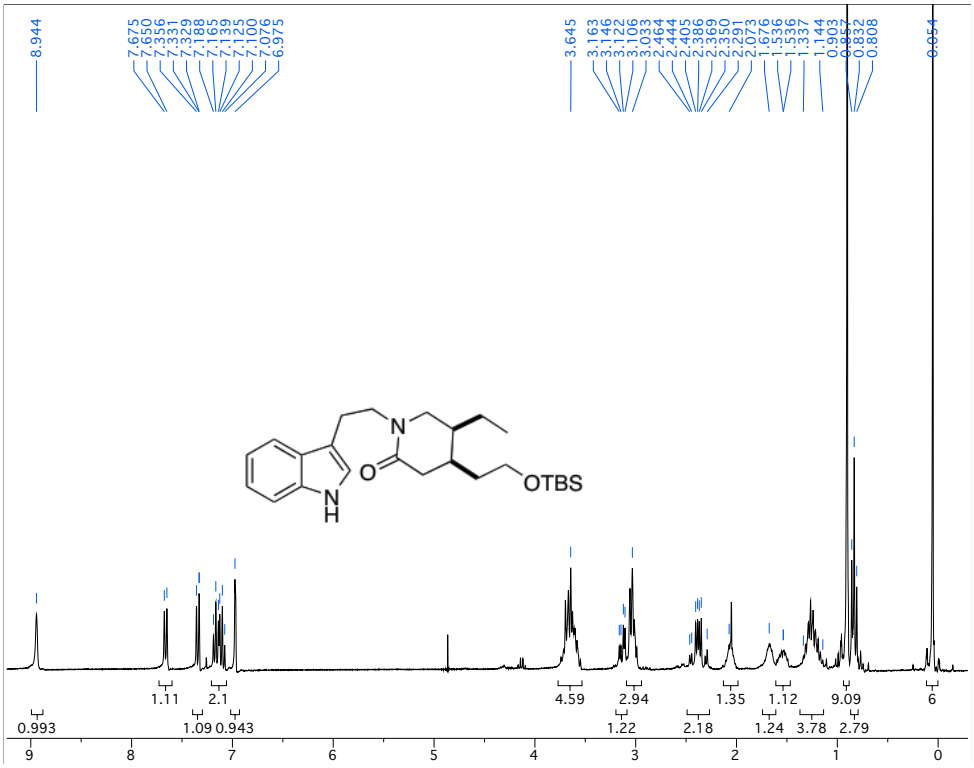
Ref.: **BJEV299**.



Synthesis of 1-(2-(1*H*-indol-3-yl)ethyl)-4-(2-(*tert*-butyldimethylsilyloxy)ethyl)-5-ethylpiperidin-2-one (3.35): To crude alcohol **3.34,** prepared above, in a 50 mL round-bottomed flask was added 22.7 mL dry CH_2Cl_2 followed by 411 mg (2.72 mmol, 1.2 equiv.) TBSCl and then 309 mg (4.54 mmol, 2 equiv.) imidazole. The reaction was allowed to stir at ambient temperature for 12 hr before being added to brine, extracted into CH_2Cl_2, dried over Na_2SO_4 and concentrated. The resultant residue was purified by silica gel flash chromatography eluting with 1 : 1 hex./EtOAc to yield 720 mg (74%, 2 steps) of the desired product as a tan foam.

^{1}HNMR (300 MHz, $CDCl_3$): δ 8.94 (brs, 1H), 7.66 (d, *J* = 7.5, 1H), 7.34 (d, *J* = 7.5, 1H), 7.17 (t, *J* = 7.2, 1H), 7.10 (t, *J* = 7.2, 1H), 6.98 (s, 1H), 3.65 (m, 4H), 3.13 (dd, *J* = 12.3, 5.1, 1H), 3.03 (m, 3H), 2.37 (qd, *J* = 17.7, 6, 2H), 2.07 (m, 1H), 1.68 (m, 1H), 1.54 (m, 1H), 1.14-1.34 (m, 3H), 0.90 (s, 9H), 0.83 (t, *J* = 7.2), 3H), 0.05 (s, 6H); ^{13}CNMR (75MHz, $CDCl_3$): δ 169.5, 136.4, 127.4, 122.3, 121.7, 119.0, 118.6, 112.5, 111.4, 60.6, 50.6, 48.3, 38.3, 36.4, 31.5, 31.1, 26.0, 23.0, 20.5, 18.3, 11.8, –5.3; IR (NaCl, film): 3260, 1622 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 429.2932 calcd for $C_{25}H_{41}N_2O_2Si$, found: 429.2937; R_f = 0.36 (1:1 hex./EtOAc)

Ref.: **BJEV301**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3.146
3.122
3.106
3.033
2.464
2.444
2.405
2.386
2.369
2.350
2.291
2.073
1.676
1.536
1.336
1.337
1.144
0.903
0.832
0.808
0.054
N
O
OTBS
N
H
0.993
1.11
2.1
1.09
0.943
4.59
2.94
1.22
2.18
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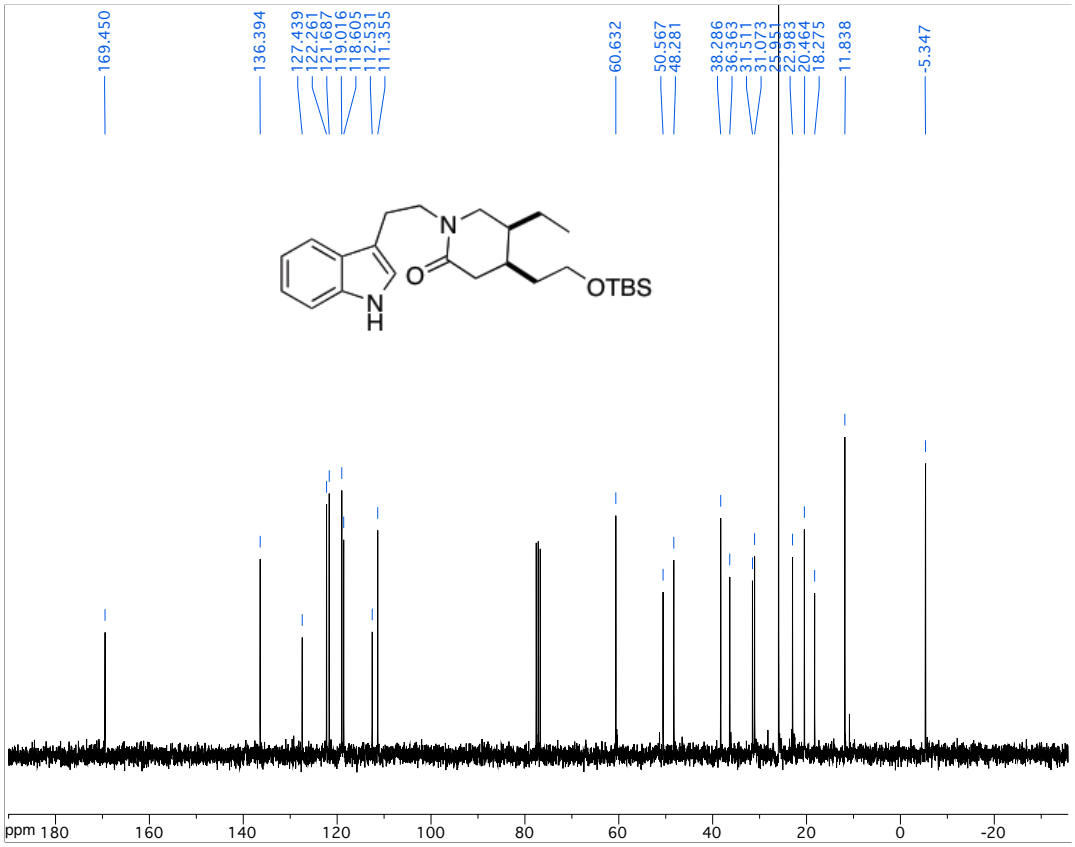
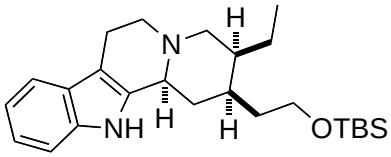


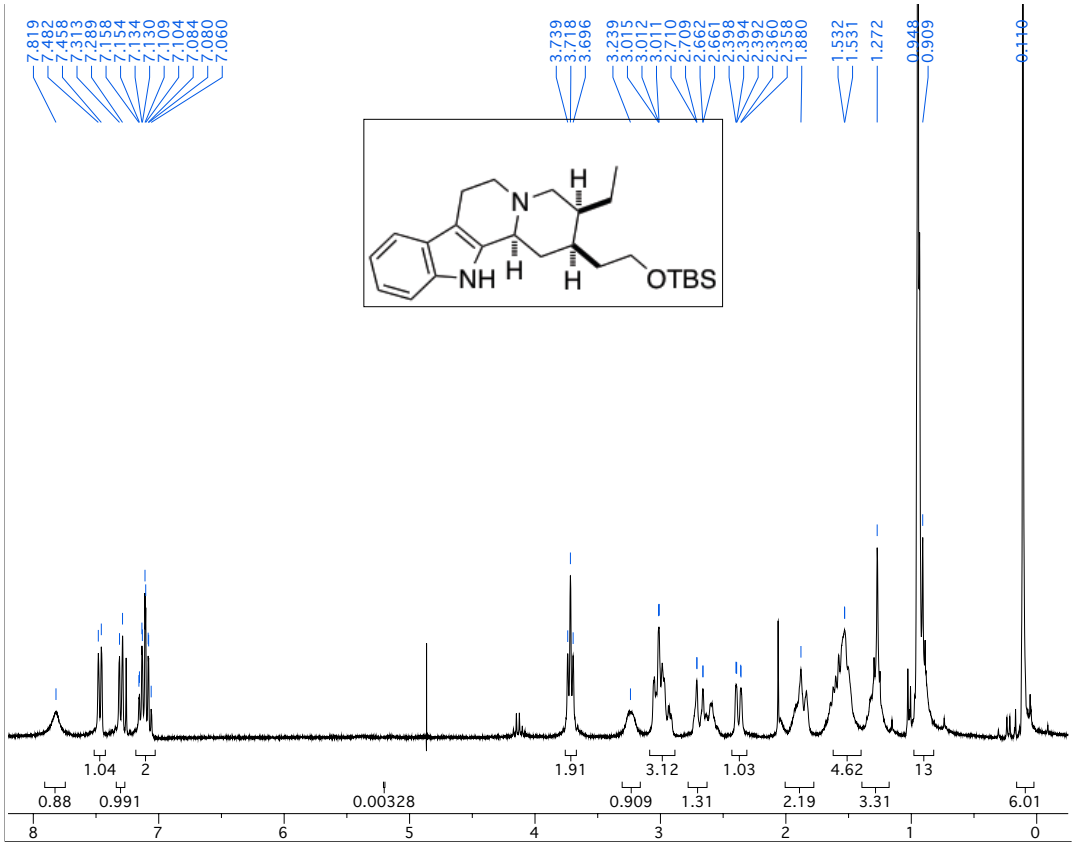


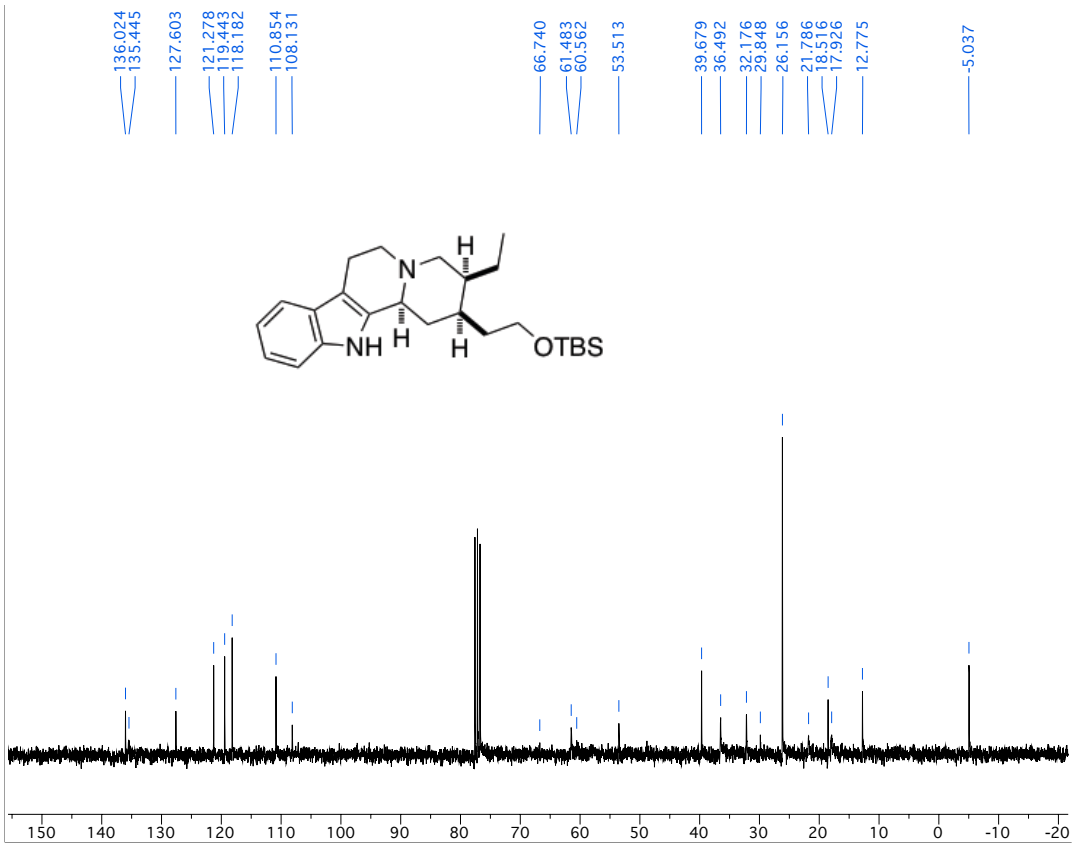
Synthesis of tetracycle 3.36: To 160 mg (0.373 mmol, 1 equiv.) lactam **3.35** dissolved in 4 mL dry MeCN was added 1.21 mL (14.90 mmol, 40 equiv.) dry pyridine followed by 278 μL (2.98 mmol, 8 equiv.) freshly distilled $POCl_3$. The reaction was stirred for 16 hr at 40°C and concentrated under reduced pressure. To the resultant residue was added 4 mL dry MeOH. This solution was cooled to 0°C, 142 mg (3.73 mmol, 10 equiv.) $NaBH_4$ was added, and the reaction was stirred at 0°C 15min before being added to $NaHCO_3$, extracted into CH_2Cl_2, dried over Na_2SO_4, and concentrated. Purification by silica gel

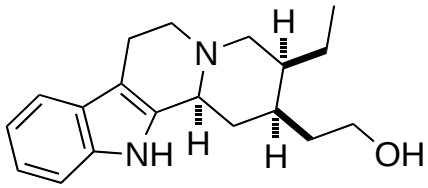
flash chromatography eluting with 2 : 1 hex./EtOAc yielded 107 mg (69%) of the desired product as a pale yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$): δ 7.82 (bs, 1H), 7.47 (d, *J* = 7.2, 1H), 7.30 (d, *J* = 7.2, 1H), 7.11 (m, 2H), 3.72 (t, *J* = 6.6, 2H), 3.24 (m, 1H), 3.01 (m, 3H), 2.68 (m, 1H), 2.38 (d, *J* = 11.4, 1H) 1.88 (m, 2H), 1.53 (m, 4H), 1.27 (m, 3H), 0.95 (s, 9H), 0.91 (m, 3H), 0.11 (s, 6H); ^{13}CNMR (75 MHz, $CDCl_3$): δ 136.0, 135.4, 127.6, 121.3, 119.4, 118.2, 110.9, 108.1, 66.7, 61.5, 60.6, 53.5, 39.7, 36.5, 36.4, 32.2, 29.8, 26.2, 18.5, 17.9, 12.8, –5.1; IR (NaCl, film): 2796, 2747cm^{-1}; HRMS (+TOF): $[M+H]^+$ 413.2951 calcd. for $C_{25}H_{41}N_2O_2Si$, found: 413.2948; R_f = 0.46 (4 : 1 hex./EtOAc)

Ref.: BJEV313, **BJEV320**







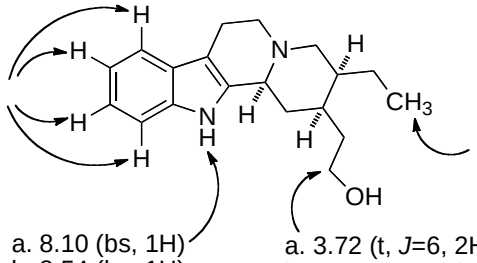
Synthesis of (+/-)-corynantheidol: To a 25 mL round-bottomed flask containing 40 mg (0.097 mmol, 1 equiv.) **3.36** was added 1 mL MeOH followed by 49 mg (0.194 mmol, 2 equiv.) PPTS. The reaction was stirred 12 hr at ambient temperature, added to 1 N NaOH, extracted twice with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 5% to 20% MeOH in CH_2Cl_2 to yield 26 mg (90%) corynantheidol as a white foam.

^{1}HNMR (300 MHz, $CDCl_3$): δ 8.14 (bs, 1H), 7.45 (d, *J* = 6.6, 1H), 7.31 (d, *J* = 7.2, 1H), 7.10 (m, 2H), 3.73 (m, 2H), 3.13 (dd, *J* = 10.8, 0.6, 1H), 2.99 (m, 3H), 2.66 (m, 1H), 2.54

(m, 1H), 2.32 (d, *J* = 9.9, 1H), 1.85 (m, 2H), 1.58-1.48 (m, 5H), 1.26 (m, 2H), 0.91 (t, *J* = 7.2, 3H); ^{13}CNMR (75 MHz, $CDCl_3$): δ 136.1, 135.4, 127.5, 121.2, 119.3, 118.1, 110.9, 107.9, 60.8, 60.5, 57.9, 53.6, 39.7, 36.4, 36.0, 31.9, 21.8, 17.8, 12.8; IR (NaCl, film): 3412, 3277, 2800, 2749 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 299.2118 calcd. for $C_{19}H_{27}N_2O$, found: 299.2120; R_f = 0.25 (5% MeOH in CH_2Cl_2). Spectroscopic properties agree in all respects with those previously reported: Lounasmaa, M.; Jokela, R.; Tirkkonen, B.; Miettinen, J.; Halonen, M. *Heterocycles* **1992**, *34*, 2, 321. Lounasmaa, M.; Jokela, R. *Heterocycles* **1990**, *31*, 7, 1351. Kametani, T.; Kanaya, N.; Honda, T. *Heterocycles* **1981**, *16*, 11, 1937. Yu, S.; Berner, M.; Cook, J.M. *J. Am. Chem. Soc.* **2000**, *122*, 7827. Beard, R. L.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2091.

Comparison of ^{1}HNMR data:

a. 7.50-7.04 (m, 4H)
b. 7.56-6.96 (m, 4H)
c. 7.49-7.05 (m, 4H)
d. 7.44 (d, *J*=7.3, 1H), 7.30 (d, *J*=7.4, 1H) 7.20-7.00 (m, 2H)
e. 7.46 (d, *J*=6.9, 1H) 7.29 (d, *J*=6.9, 1H), 7.10 (m, 2H)
f. 7.45 (d, *J*=6.6, 1H), 7.31 (d, *J*=7.2, 1H), 7.10 (m, 2H)



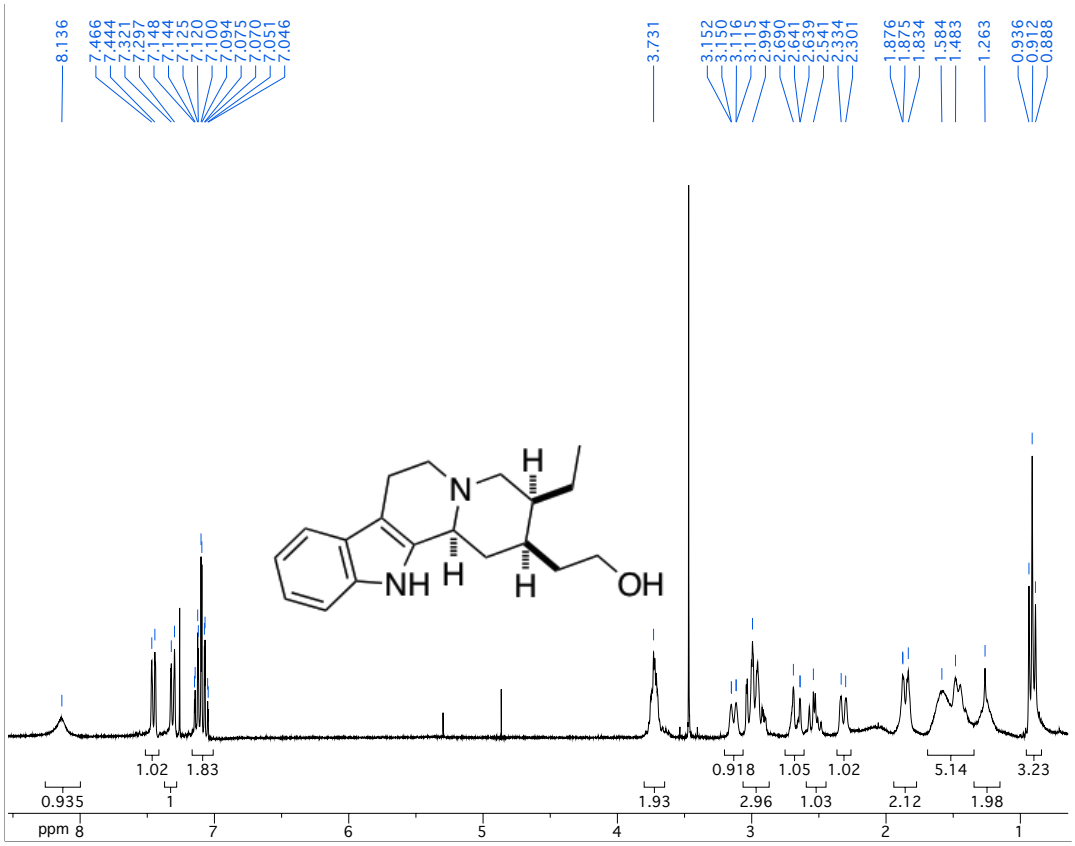
a. 8.10 (bs, 1H)
b. 8.54 (bs, 1H)
c. 7.79 (s, 1H)
d. 7.88 (s, 1H)
e. 7.79 (bs, 1H)
f. 8.14 (bs, 1H)

a. 3.72 (t, *J*=6, 2H)
b. Not Reported
c. 3.76 (t, *J*=6, 2H)
d. 3.85-3.65 (m, 2H)
e. 3.75 (t, *J*=6.5, 2H)
f. 3.73 (m, 2H)

a. 0.91 (t, *J*=7, 3H)
b. 0.88 (t, *J*=7, 3H)
c. 0.92 (t, *J*=6.3, 3H)
d. 0.92 (t, *J*=7.2, 3H)
e. 0.93 (t, *J*=7.2, 3H)
f. 0.91 (t, *J*=7.2, 3H)

a. Lounasmaa, M.; Jokela, R.; Tirkkonen, B.; Miettinen, J.; Halonen, M. *Heterocycles* **1992**, *34*, 2, 321.
b. Lounasmaa, M.; Jokela, R. *Heterocycles* **1990**, *31*, 7, 1351.
c. Kametani, T.; Kanaya, N.; Honda, T. *Heterocycles* **1981**, *16*, 11, 1937.
d. Yu, S.; Berner, M.; Cook, J.M. *J. Am. Chem. Soc.* **2000**, *122*, 7827
e. Beard, R. L.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2091
f. English, B.J.; Williams, R.M.

Ref.: **BJEV322**, BJEV324.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3.116
3.115
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2.690
2.641
2.639
2.541
2.334
2.301
1.876
1.875
1.834
1.584
1.483
1.263
0.936
0.912
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H
NH
H
H
OH
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1.83
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1.02
5.14
3.23
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2.12
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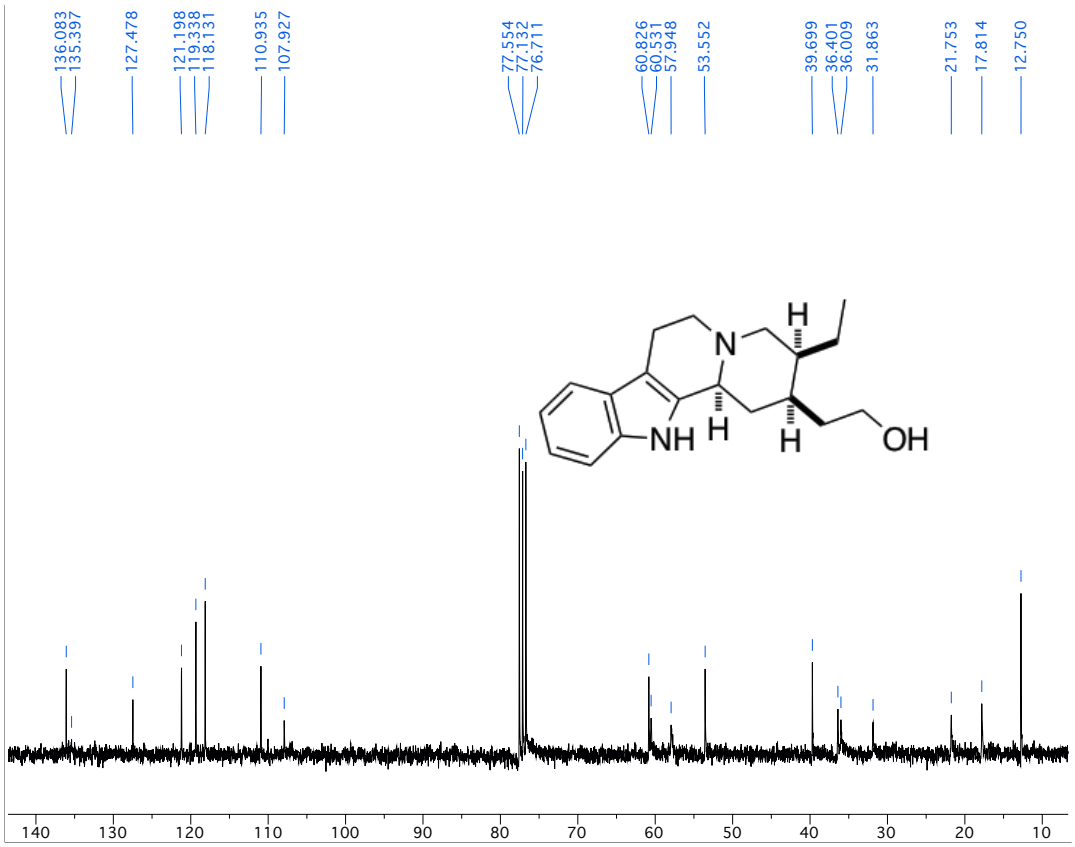
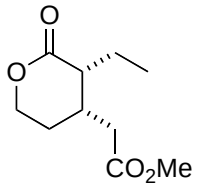
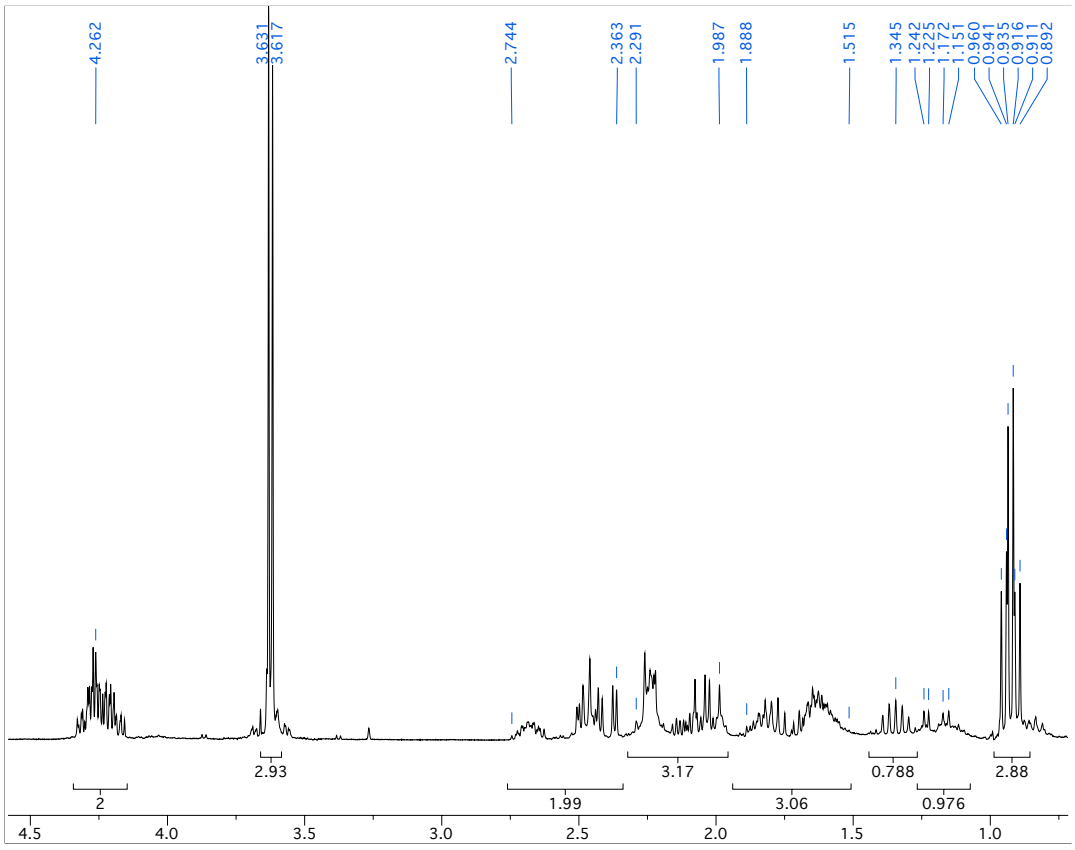


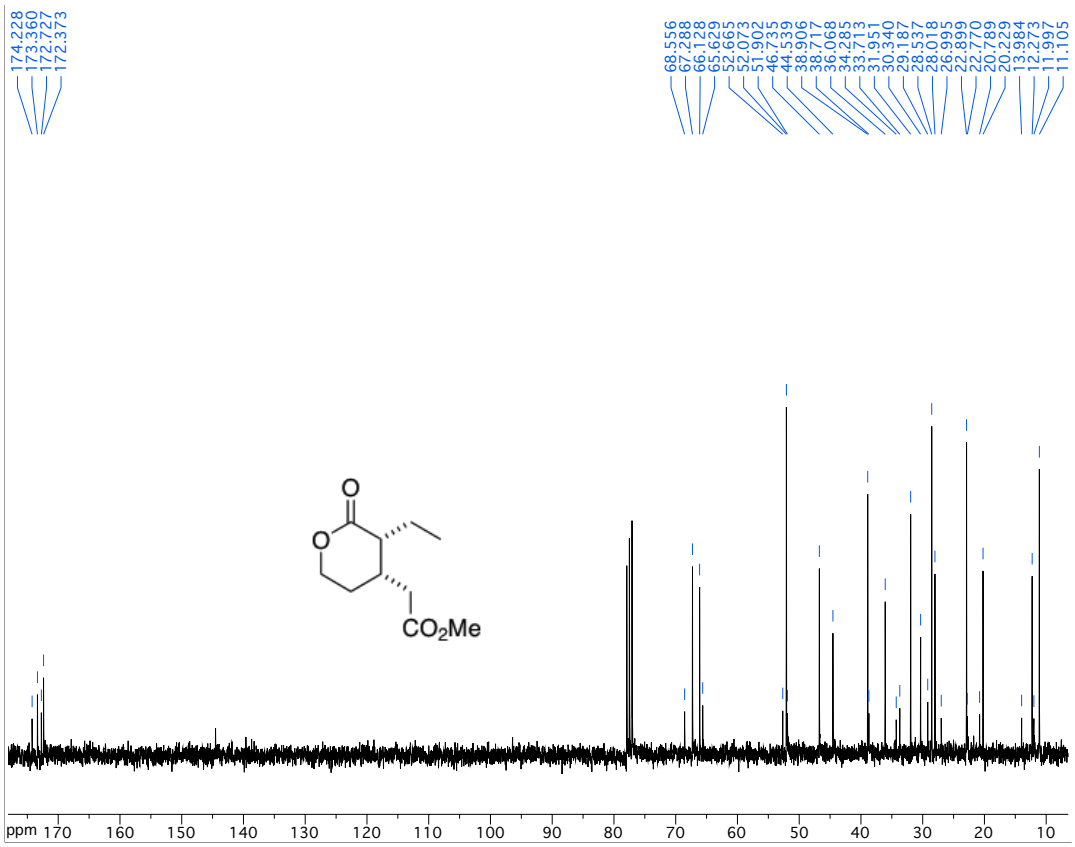


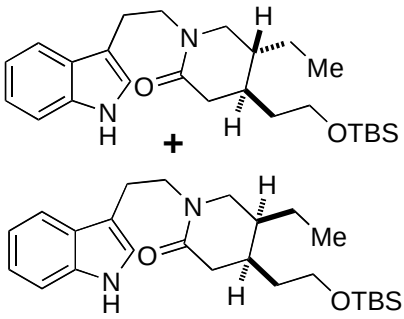
Synthesis of lactone 3.37: To a 100 mL round-bottomed flask containing 1.07 g (5.40 mmol, 1 equiv.) lactone **3.1** was added 25 mL dry MeOH then 574 mg 10% Pd/C. Hydrogen gas was bubbled through this mixture for 5 min and then the reaction was vigorously stirred for 4 hr at ambient temperature under balloon pressure of H_2. The reaction was then filtered through a thin pad of Celite, concentrated, and purified by silica gel flash chromatography eluting with 1 : 1 hex./EtOAc to yield 1.07 g (>99%) of the title compound as a colorless oil. (Note: The *trans* isomer (**3.32**) was not detected by ^{1}HNMR, ^{13}CNMR or TLC.)

^{1}HNMR (300 MHz, $CDCl_3$): (mixture of conformers) δ 4.26 (m, 2H), 3.63 (s, 1.5H), 3.62 (s, 1.5H), 2.74-2.36 (m, 2H), 2.29-1.99 (m, 3H), 1.89-1.52 (m, 3H), 1.35 (m, 1H), 1.20 (m, 1H), 0.94 (t, *J* = 7.5, 1.5H), 0.92 (t, *J* = 7.2, 1.5H); ^{13}CNMR (75 MHz, $CDCl_3$): (mixture of conformers) δ 174.2, 173.4, 172.7, 172.4, 68.6, 67.3, 66.1, 65.6, 52.7, 52.1, 51.9, 46.7, 44.5, 38.9, 38.7, 36.1, 34.3, 33.7, 32.0, 30.3, 29.2, 28.5, 28.0, 27.0, 22.9, 22.8, 20.8, 20.2, 14.0, 12.3, 12.0, 11.1; IR (NaCl, film): 1732 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 201.1121 calcd for $C_{10}H_{17}O_4$, found: 201.1126; R_f = 0.39 (1 : 1 hex./EtOAc).

Ref: BJEIV071, BJEV263, **BJEV290B**, BJEV307







Synthesis of lactams 3.35 and 3.40: To a 100 mL flame dried round bottomed flask was added 1.08 g (5.40 mmol, 1 equiv.) lactone **3.37** dissolved in 25 mL dry THF. This mixture was cooled to -78^{o}C before the slow addition of 5.94 mL (5.94 mmol, 1.1 equiv) of a 1.0 M solution of DIBAl-H in THF. The reaction was stirred at -78^{o}C for 30 min and then 2 mL dry MeOH was added. The reaction was allowed to warm to ambient

temperature before being added to a saturated solution of Rochelle's salt, extracted twice into CH_2Cl_2, dried over Na_2SO_4, and concentrated to yield the desired mixture of lactols **3.38** as colorless oil, which was immediately used without further purification. (Note: The undesired *trans* isomer (**3.33**) was not detected in this crude mixture, however, subjecting this crude mixture to silica gel chromatography did result in the isolation of **3.33**.)

To a 100 mL round bottomed flask containing the above produced lactol mixture (**3.38**) dissolved in 27 mL dry THF was added 649 mg (4.05 mmol, 1.5 equiv.) tryptamine followed by 1.72 g (8.10 mmol, 3 equiv.) $NaBH(OAc)_3$. The reaction was allowed to stir at ambient temperature for 24 hr before being added to $NaHCO_{3(sat.)}$, extracted twice into CH_2Cl_2, dried over Na_2SO_4, and concentrated to yield a mixture of alcohols **3.39** and **3.34** as a tan oil, which was used without further purification.

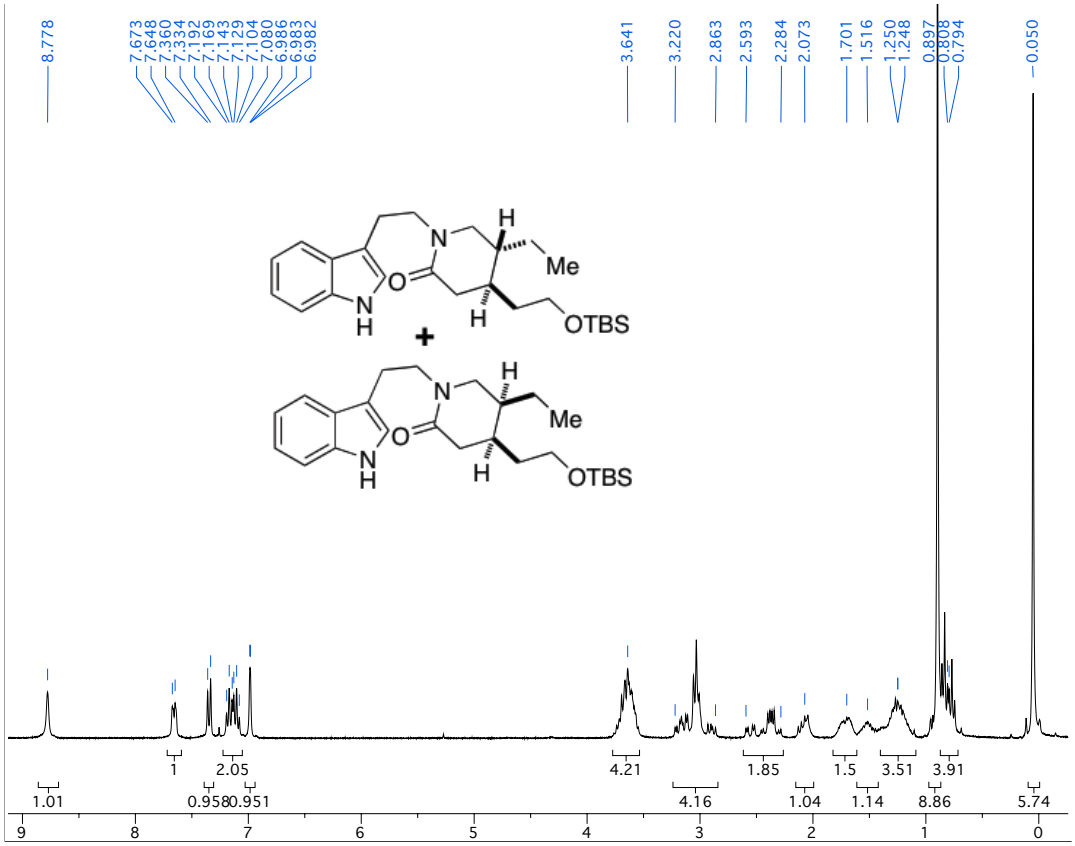
To a 100 mL round bottomed flask containing the above produced crude mixture of alcohols **3.39** and **3.34** dissolved in 27 mL dry CH_2Cl_2 was added 488 mg (3.24 mmol, 1.2 equiv.) TBSCl followed by 368 mg (5.40 mmol, 2 equiv.) imidazole. The reaction was stirred at ambient temperature for 16 hr before being added to brine, extracted twice into CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 1 : 1 to 0 : 1 hex./EtOAc to yield 542 mg (47%, 3 steps) of the desired mixture of isomers as a tan foam.

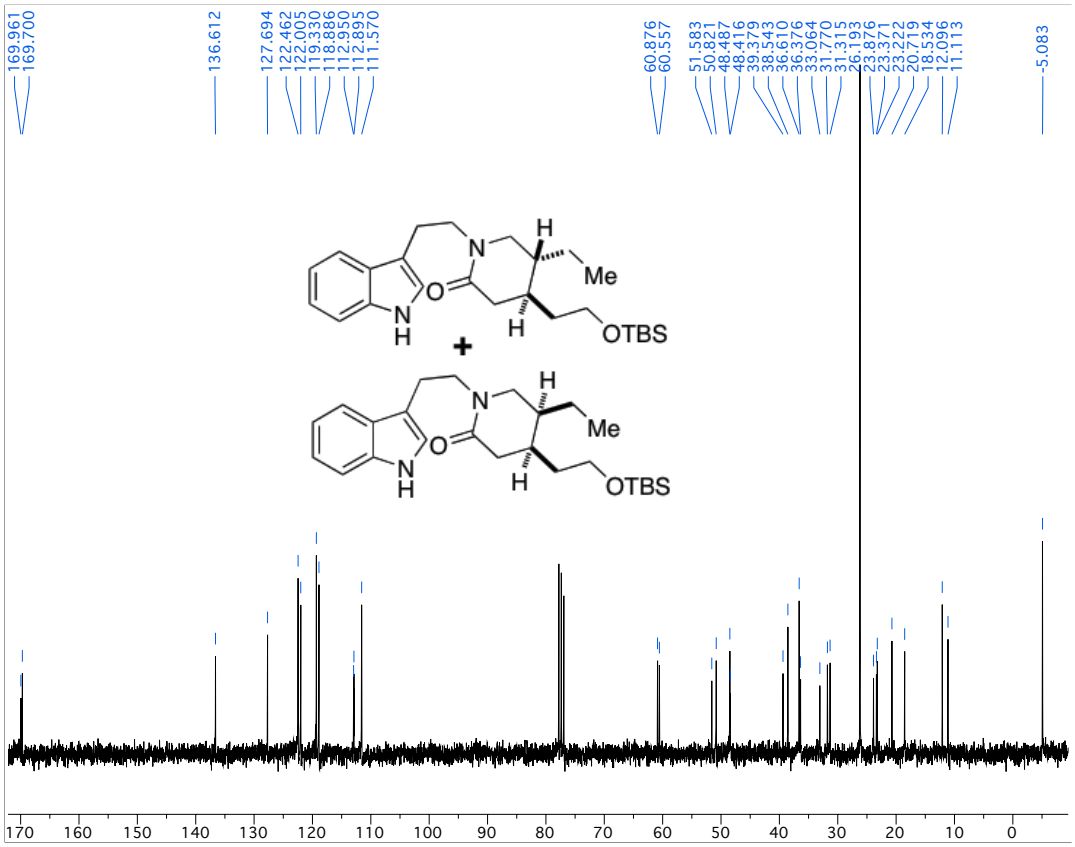
^{1}HNMR (300 MHz, $CDCl_3$): δ 8.78 (bs, 1H), 7.66 (d, J = 7.5, 1H), 7.35 (d, J = 7.8, 1H), 7.13 (m, 2H), 6.98 (s, 1H), 3.64 (m, 4H), 3.22-2.86 (m, 4H), 2.28-2.59 (m, 2H), 2.07 (m,

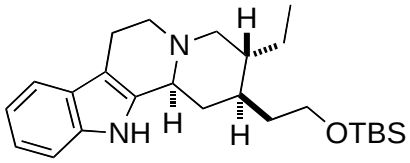
1H), 1.70-1.10 (m, 6H), 0.90 (s, 9H), 0.80 (m, 4H), 0.05 (s, 6H); ^{13}CNMR (75MHz, $CDCl_3$):

δ 170.0, 169.7, 136.6, 127.7, 122.5, 122.0, 119.3, 118.9, 113.0, 112.9, 111.6, 60.9, 60.6, 51.6, 50.8, 48.5, 48.4, 39.4, 38.5, 36.6, 36.4, 33.1, 31.8, 31.3, 26.2, 23.9, 23.4, 23.2, 20.7, 18.5, 12.1, 11.1; IR (NaCl, film): 3254, 1626 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 429.2932 calcd for $C_{25}H_{41}N_2O_2Si$, found: 429.2933; R_f = 0.30 (1 : 1 hex./EtOAc)

Ref.: BJEV264, BJEV330BJEV265, BJEV266, BJEV272, **BJEV293**, **BJEV295**, **BJEV297**, BJEV333, BJEV337.





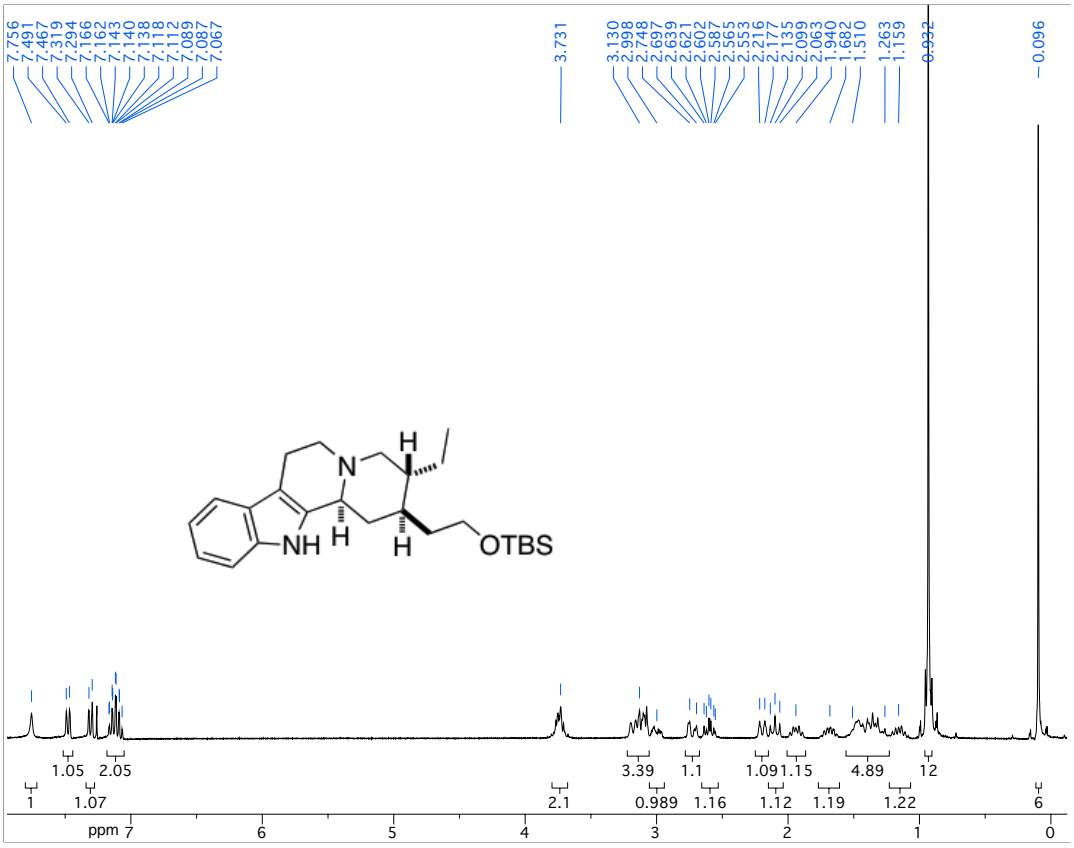


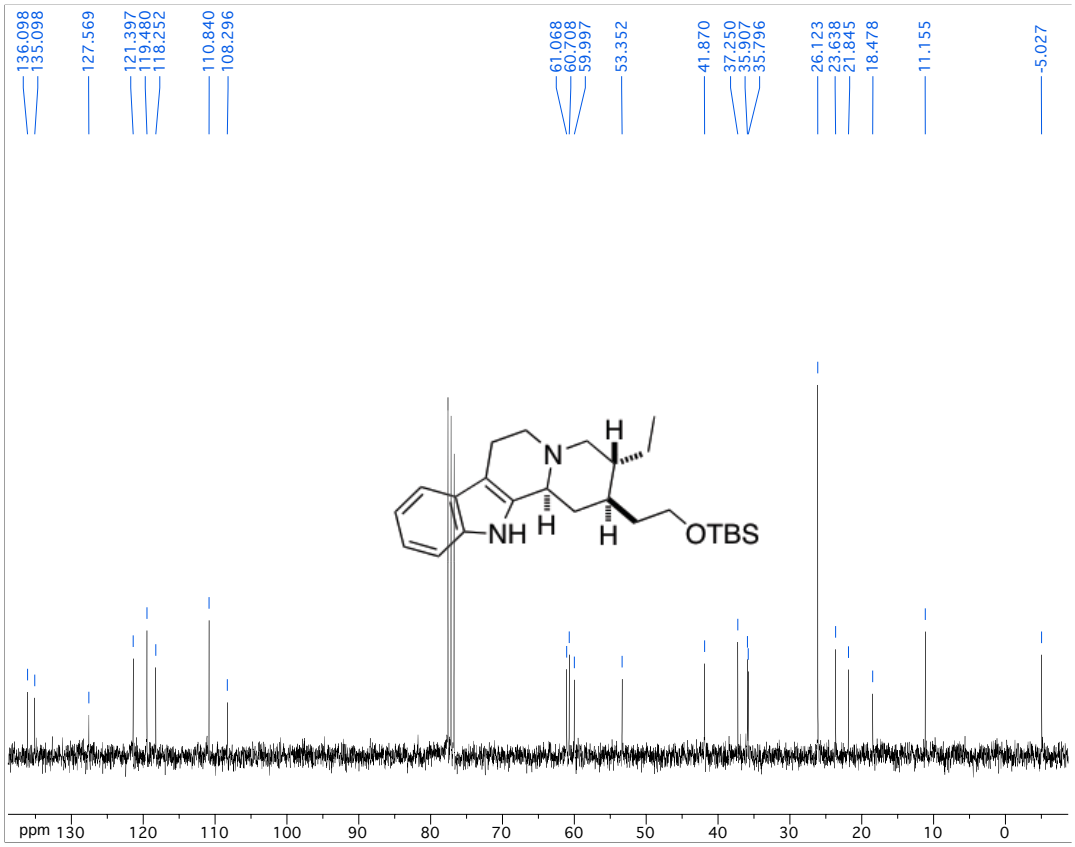
Synthesis of tetracycle 3.41: To a 25 mL round bottomed flask containing 373 mg (0.870 mmol, 1 equiv.) of the above produced mixture of lactams **3.40** and **3.35** dissolved in 9 mL dry MeCN was added 1.40 mL (17.4 mmol, 20 equiv.) dry pyridine followed by 406 μL (4.35 mmol, 5 equiv.) $POCl_3$. The reaction was heated to 40°C for 3 hr before being concentrated, taken up in 9 mL dry MeOH and cooled to 0°C. To this solution was added 33 mg $NaBH_4$ and the reaction was allowed to warm to ambient temperature over 15 min before being added to $NaHCO_{3(sat.)}$, extracted into EtOAc, dried over Na_2SO_4, and concentrated. The crude residue was purified by silica gel flash chromatography eluting

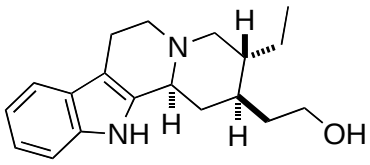
with 4 : 1 to 0 : 1 hex./EtOAc to yield 142 mg (40%) of the desired *trans* product **3.41** as a tan foam along with 113 mg (31%) of the *cis* product **3.36** as a tan foam.

^{1}HNMR (300 MHz, $CDCl_3$): δ 7.76 (bs, 1H), 7.47 (d, *J* = 7.2, 1H), 7.3 (d, *J* = 7.2, 1H), 7.11 (m, 2H), 3.73 (m, 2H), 3.13 (m, 3H), 3.00 (m, 1H), 2.72 (m, 1H), 2.59 (td, *J* = 11.1, 5.4, 1H), 2.19 (d, *J* = 11.7, 1H), 2.10 (t, J = 10.8, 1H), 1.94 (m, 1H), 1.68 (m, 1H), 1.26-1.51 (m, 4H), 1.16 (m, 1H), 0.932 (s, 12H), 0.10 (s, 6H); ^{13}CNMR (75MHz, $CDCl_3$): δ136.1, 135.1, 127.6, 121.4, 119.5, 118.3, 110.8, 108.3, 61.1, 60.7, 60.0, 53.4, 41.9, 37.3, 35.9, 35.8, 26.1, 23.6, 21.8, 18.5, 11.2, -5.0.; HRMS (+TOF): $[M+H]^+$ 413.2983 calcd for $C_{25}H_{41}N_2O_2Si$, found: 413.2985 ; R_f = 0.17 (4 : 1 hex./EtOAc)

Ref.: BJEV292, **BJEV304**, BJEV321.







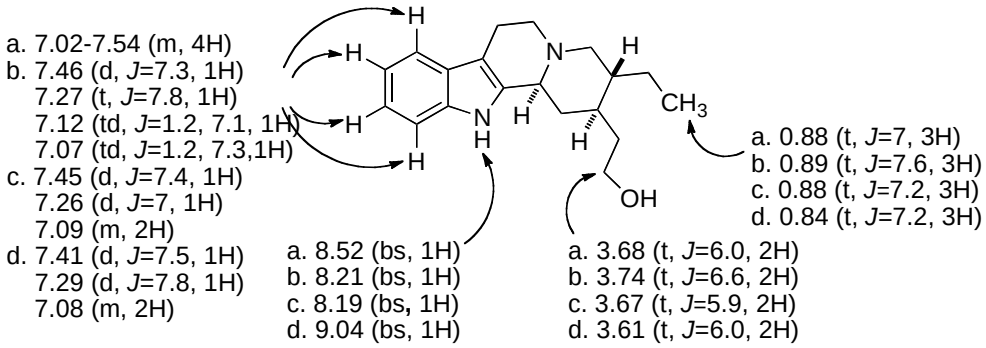
Synthesis of (+/-)-dihydrocorynantheol : To a 25 mL round bottomed flask containing 71 mg (0.171 mmol, 1 equiv.) compound **3.41** was added 1 mL dry MeOH followed by a spatula tip of PPTS. The reaction was heated at reflux for 3 hr, added to 1 M NaOH, extracted twice with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resultant residue was purified by silica gel flash chromatography eluting with 10% to 20% MeOH in CH_2Cl_2 to yield 46 mg (90%) of the title compound as a white foam.

^{1}HNMR (300 MHz, $CDCl_3$): δ 9.04 (bs, 1H), 7.41 (d, J = 7.5, 1H), 7.29 (d, J = 7.8, 1H),

7.08 (m, 2H), 3.61 (t, *J* = 6.0, 2H), 3.58 (bs, 1H), 3.00 (m, 4H), 2.69 (m, 1H), 2.47 (m, 1H), 2.16 (m, 1H), 1.88 (t, *J* = 11.4, 1H), 1.79 (m, 1H), 1.53 (m, 1H), 1.39 (m, 1H), 0.97-1.29 (m, 5H), 0.84 (t, *J* = 7.2, 3H); ^{13}CNMR (75MHz, $CDCl_3$): δ 136.4, 134.5, 127.1, 121.3, 119.3, 118.1, 111.3, 107.3, 60.1, 59.9, 53.1, 50.5, 41.3, 37.0, 35.1, 34.9, 23.4, 21.4, 21.4, 11.0; IR (NaCl, film): 3256, 2813, 2757 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 299.2118 calcd for $C_{19}H_{27}N_2O$, found: 299.2116; R_f = 0.16 (10% MeOH in CH_2Cl_2). Spectroscopic properties agree in all respects with those previously reported:

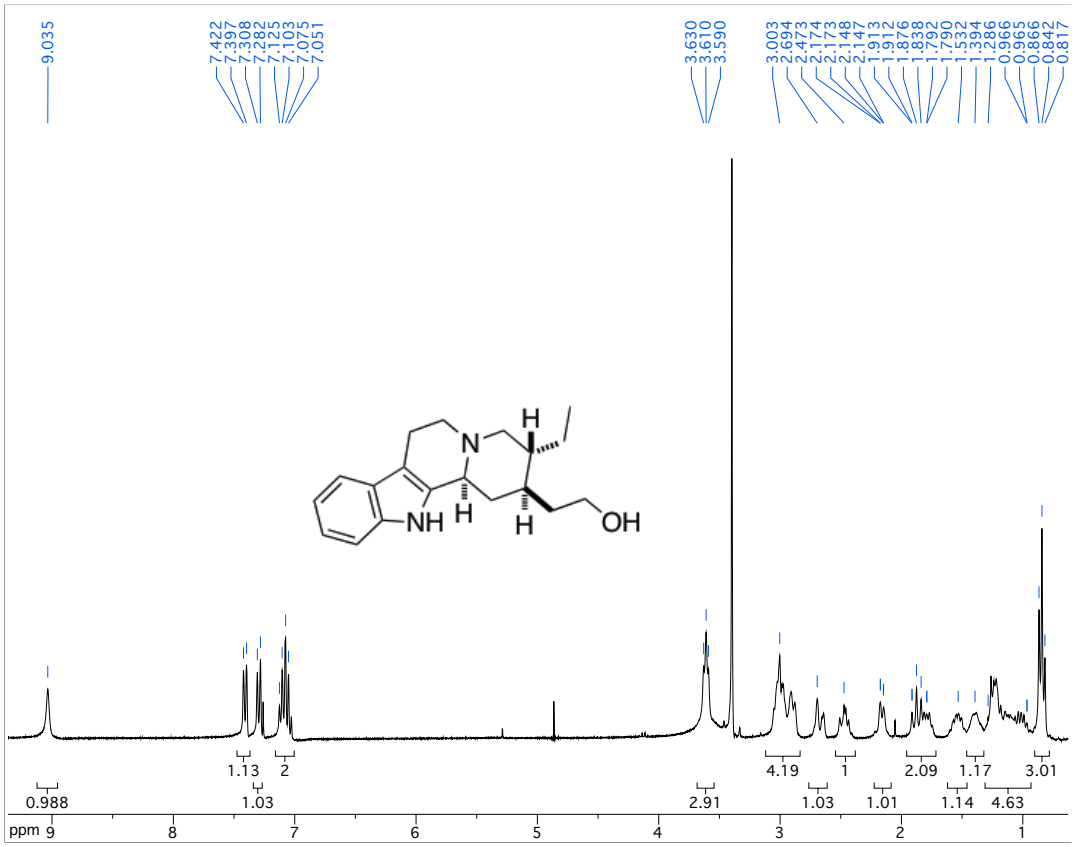
Lounasmaa, M.; Jokela, R.; Tirkkonen, B.; Miettinen, J.; Halonen, M. *Heterocycles* **1992**, *34*, 2, 321. Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. *Org. Lett*. **2006**, *8*, 1533. Beard, R. L.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2091.

Comparison of ^{1}HNMR data:



a. Lounasmaa, M.; Jokela, R.; Tirkkonen, B.; Miettinen, J.; Halonen, M. *Heterocycles* **1992**, *34*, 2, 321.
b. Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. *Org. Lett*. **2006**, *8*, 1533.
c. Beard, R. L.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2091.
d. English, B.J.; Williams, R.M.

Ref.: BJEV292, **BJEV325**, BJEV327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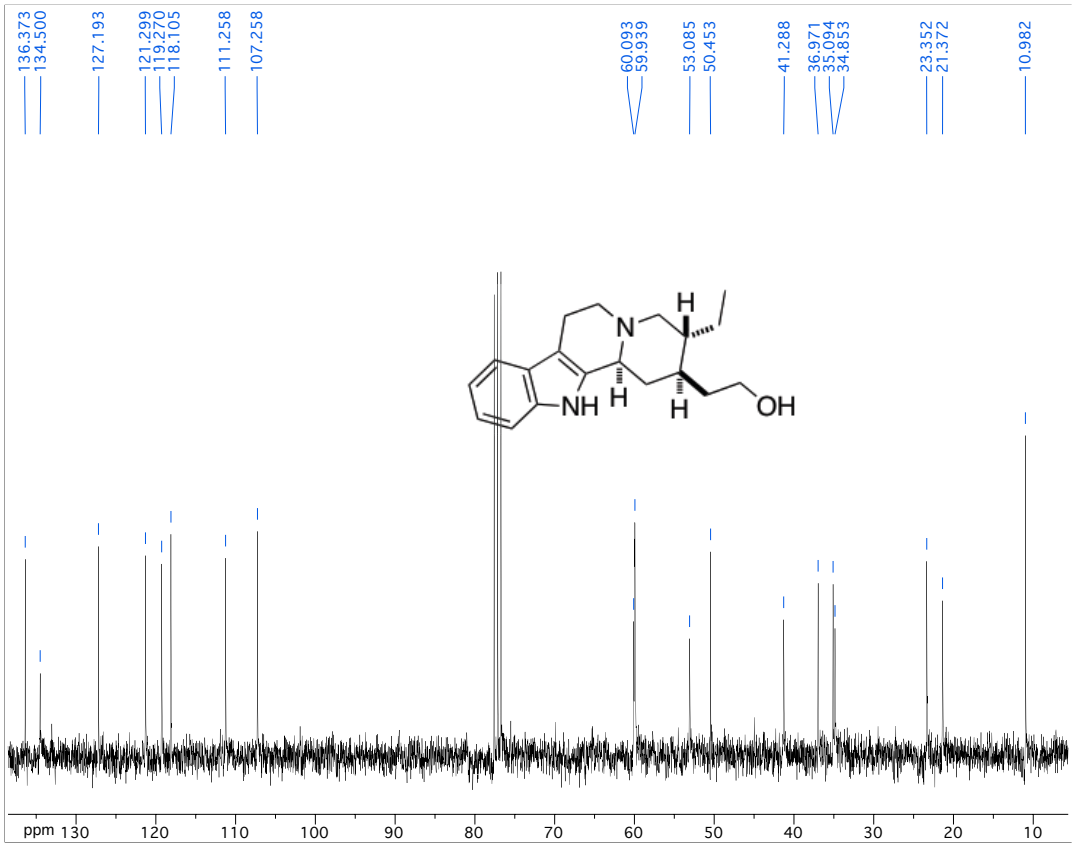
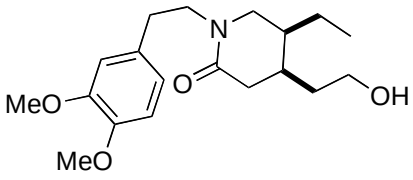


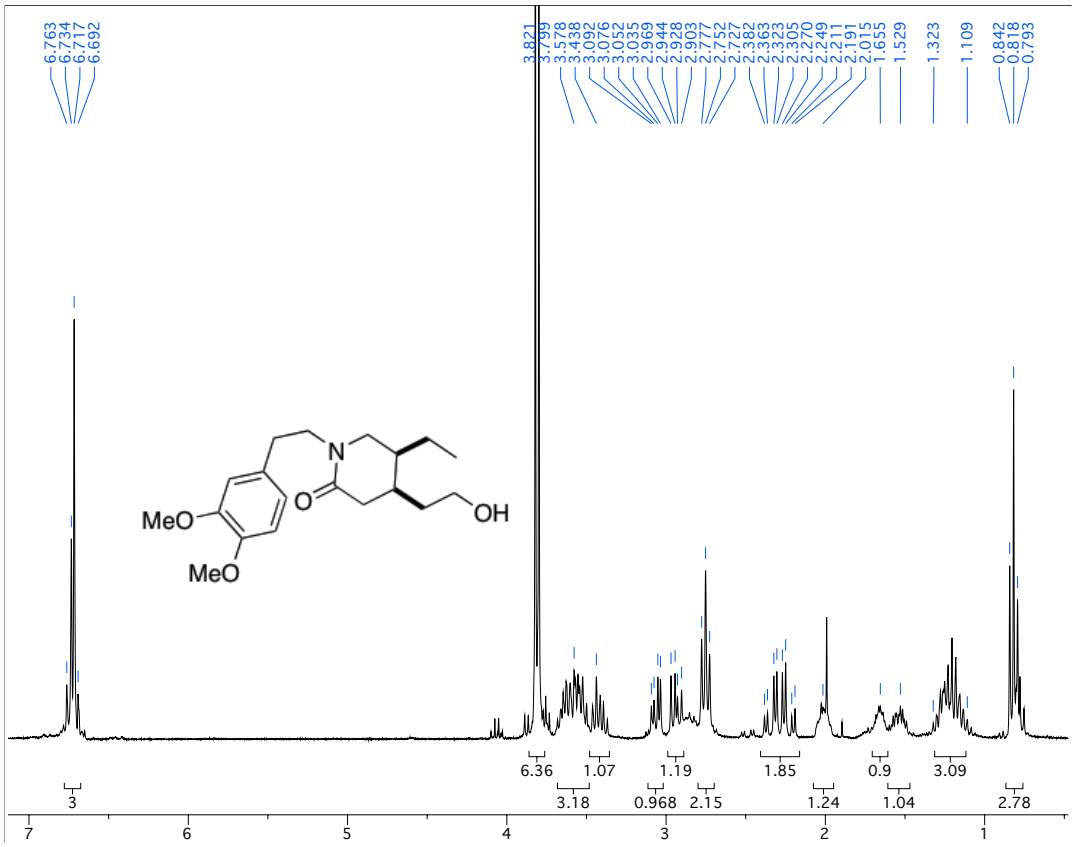


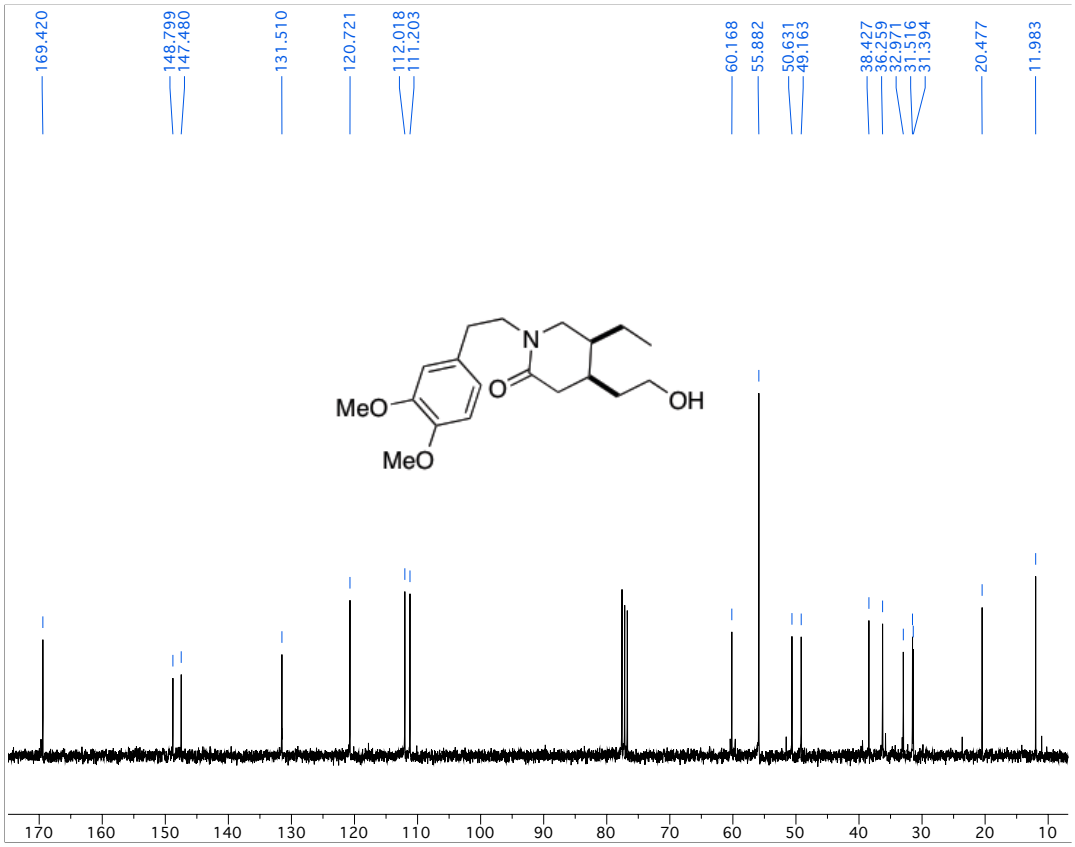
Synthesis of 1-(3,4-dimethoxyphenethyl)-5-ethyl-4-(2-hydroxyethyl)piperidin-2-one (3.43): To a 25 mL round-bottomed flask containing 85 mg (0.420 mmol, 1 equiv.) lactol mixture **3.33** was added 4.2 mL dry THF, 114 mg (0.631 mmol, 1.5 equiv.) 2-(3,4-dimethoxyphenyl)ethanamine (**3.42**), and then 178 mg (0.840 mmol, 2 equiv.) $NaBH(OAc)_3$. The reaction was allowed to stir at ambient temperature for 48 hr before being added to $NaHCO_{3(sat.)}$, extracted thrice with EtOAc, dried over Na_2SO_4, and concentrated. Purification by silica gel flash chromatography eluting with with 5% to

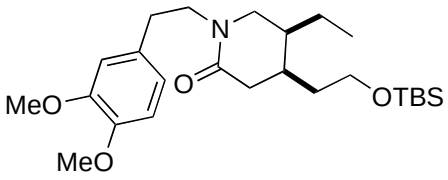
20% MeOH in CH_2Cl_2 to yield 95 mg (67%, 92% BRSM) of the desired product as a colorless oil.

^{1}HNMR (300 MHz, $CDCl_3$): δ 6.69-6.76 (m, 3H), 3.82 (s, 3H), 3.80 (s, 3H) 3.58 (m, 3H), 3.44 (m, 1H), 3.06 (dd, *J* = 12.0, 4.8, 1H), 2.93 (dd, *J* = 12.3, 7.5, 1H), 2.81 (m, 1H), 2.75 (t, *J* = 7.5, 2H), 2.27 (m, 2H), 2.02 (m, 1H), 1.66 (m, 1H), 1.53 (m, 1H), 1.11-1.32 (m, 3H), 0.82 (t, *J* = 7.2, 3H); ^{13}CNMR (75MHz, $CDCl_3$): δ 169.4, 148.8, 147.5, 131.5, 120.7, 112.0, 111.2, 60.2, 55.9, 50.6, 49.1, 38.4, 36.3, 33.0, 31.5, 31.4, 20.5, 12.0; IR (NaCl, film): 3406, 1621 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 336.2169 calcd for $C_{19}H_{30}NO_4$, found: 336.2174 ; R_f = 0.23 (5% MeOH in CH_2Cl_2).

Ref.: BJEV283, **BJEV287**, BJEV294, BJEV300



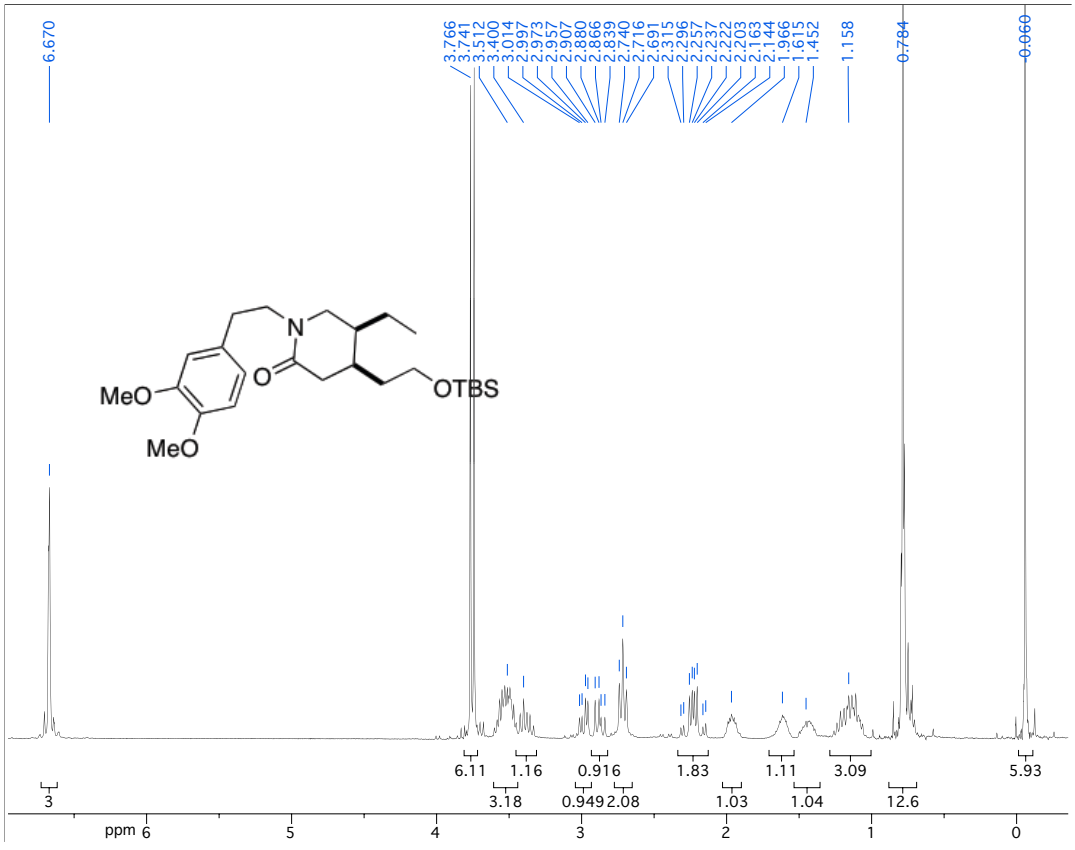


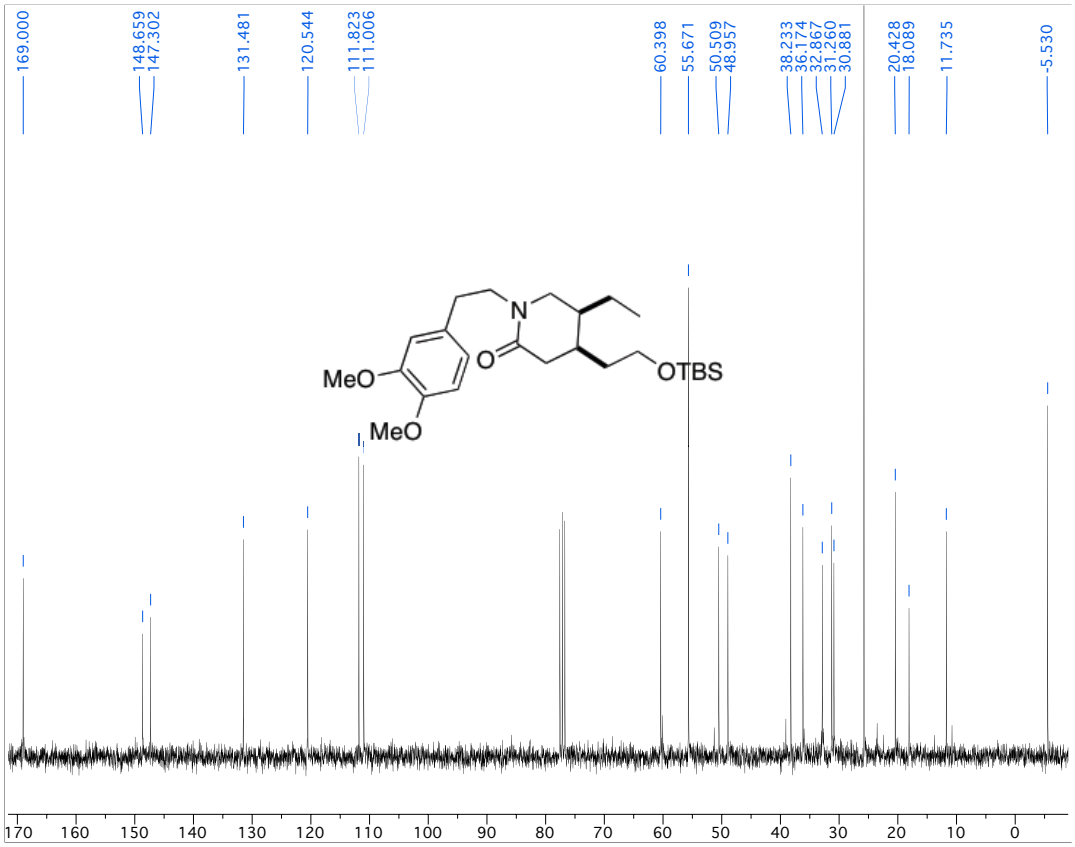


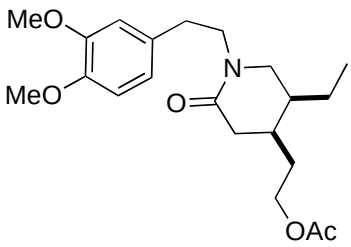
Synthesis of 4-(2-(*tert*-butyldimethylsilyloxy)ethyl)-1-(3,4-dimethoxyphenethyl)-5-ethylpiperidin-2-one: To a 10 mL round bottomed flask containing 95 mg (0.283 mmol, 1 equiv.) alcohol **3.43** dissolved in 3 mL dry CH_2Cl_2 was added 51 mg (0.340 mmol, 1.2 equiv) TBSCl followed by 39 mg (0.566 mmol, 2 equiv.) imidazole. The reaction was stirred for 16 hr at ambient temperature before being added to brine extracted into CH_2Cl_2, dried over Na_2SO_4, and concentrated. Purification by silica gel flash chromatography eluting with 1 : 1 to 1 : 2 hex./EtOAc yielded 114 mg (95%) of the desired product as a colorless oil.

^{1}HNMR (300 MHz, $CDCl_3$): δ 6.67 (m, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 3.33-3.60 (m, 4H), 2.98 (dd, *J* = 12.3, 5.1, 1H), 2.87 (dd, *J* = 12.1, 7.8, 1H), 2.72 (t, *J* = 7.2, 2H), 2.23 (qd, *J* = 17.7, 5.7, 2H), 1.97 (m, 1H), 1.61 (m, 1H), 1.44 (m, 1H), 1.06-1.26 (m, 3H), 0.78 (s, 12H), -0.06 (s, 6H); ^{13}CNMR (75MHz, $CDCl_3$): δ 169.0, 148.7, 147.3, 131.5, 120.5, 111.8, 111.0, 60.4, 55.7, 50.5, 49.0, 38.2, 36.2, 32.9, 31.3, 30.9, 25.8, 20.4, 18.1; IR (NaCl, film): 1642 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 450.3034 calcd for $C_{25}H_{44}NO_4Si$, found: 450.3036; R_f = 0.42 (1 : 1 hex./EtOAc).

Ref.: **BJEV289**, BJEV302





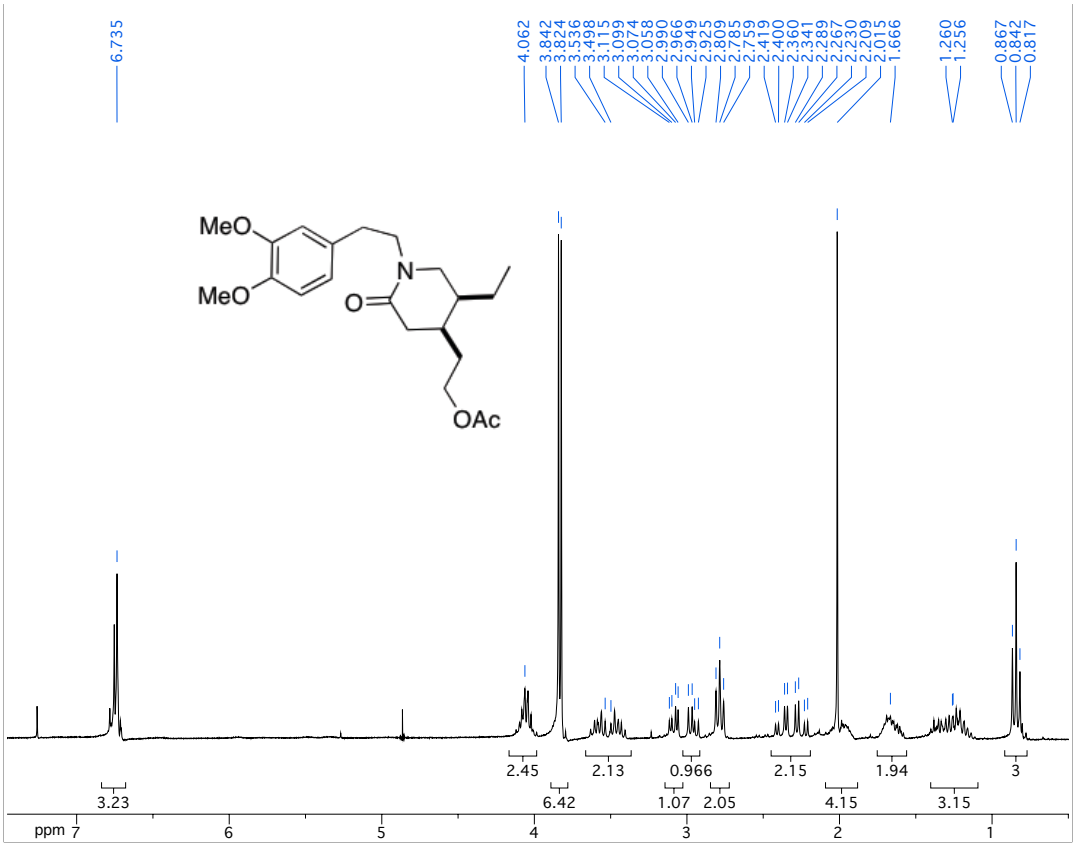


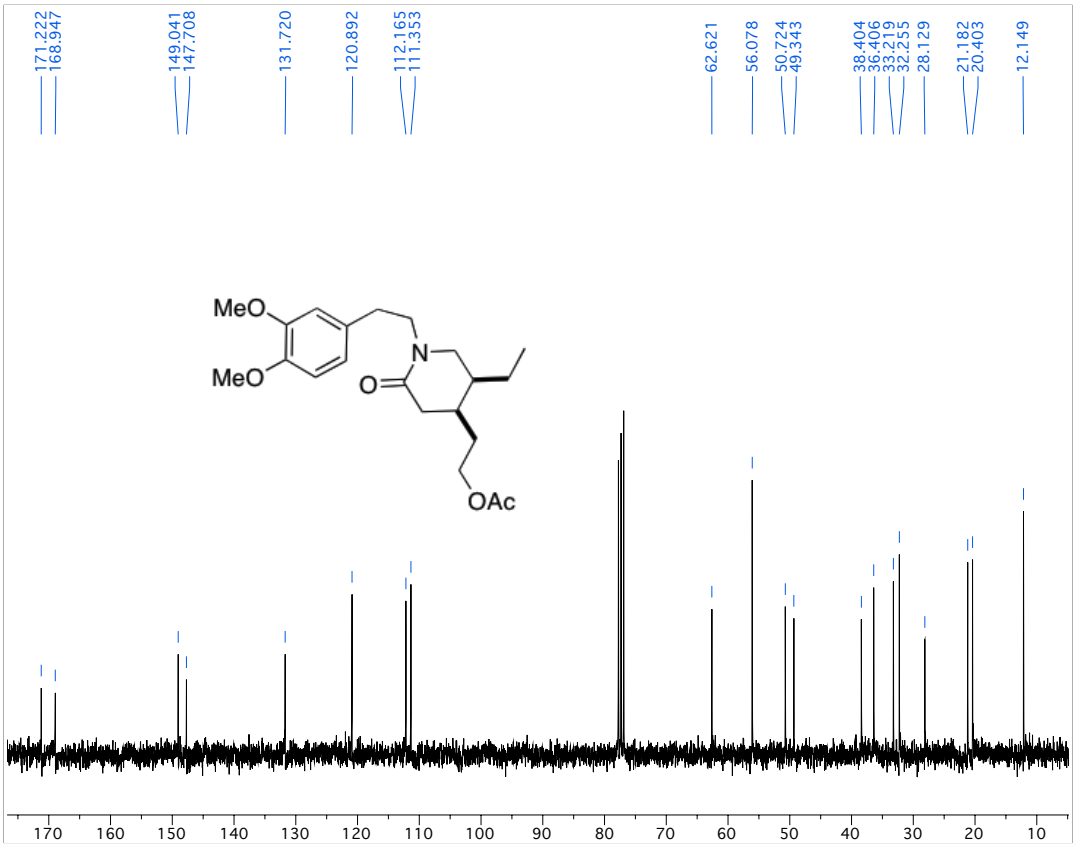
Synthesis of 2-(-1-(3,4-dimethoxyphenethyl)-5-ethyl-2-oxopiperidin-4-yl)ethyl acetate (3.44): To a 10 mL round bottomed flask containing 45 mg (0.134 mmol, 1 equiv.) alcohol **3.43** dissolved in 1 mL dry CH_2Cl_2 and 1 mL pyridine was added 19 μL (0.0.268 mmol, 2 equiv) AcCl followed by a single crystal of DMAP. The reaction was stirred for 30 min at ambient temperature before being added to $NaHCO_{3(sat.)}$, extracted into CH_2Cl_2, dried over Na_2SO_4, and concentrated. Purification by silica gel flash

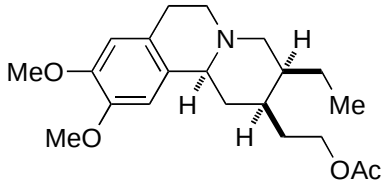
chromatography eluting with 10% MeOH in CH_2Cl_2 yielded 50 mg (99%) of the desired product as a pale yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 6.74 (m, 3H), 4.06 (m, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.52 (m, 2H), 3.08 (dd, *J* = 12.3, 4.8, 1H), 2.96 (dd, *J* = 12.3, 7.2, 1H), 2.79 (t, *J* = 7.8, 2H), 2.31 (qd, *J* = 17.4, 6.3, 2H), 2.02 (s, 3H), 2.00 (m, 1H), 1.67 (m, 2H), 1.26 (m, 3H), 0.84 (t, *J* = 7.5, 3H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 171.2, 168.9, 149.0, 147.7, 131.7, 120.9, 112.2, 111.4, 62.6, 56.1, 50.7, 49.3, 38.4, 36.4, 33.2, 32.3, 28.1, 21.2, 20.4, 12.1; IR (NaCl, film): 1737, 1640 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 378.2275 calcd for $C_{21}H_{32}NO_5$, found: 378.2280.

Ref.: **BJEV346,** BJEV373





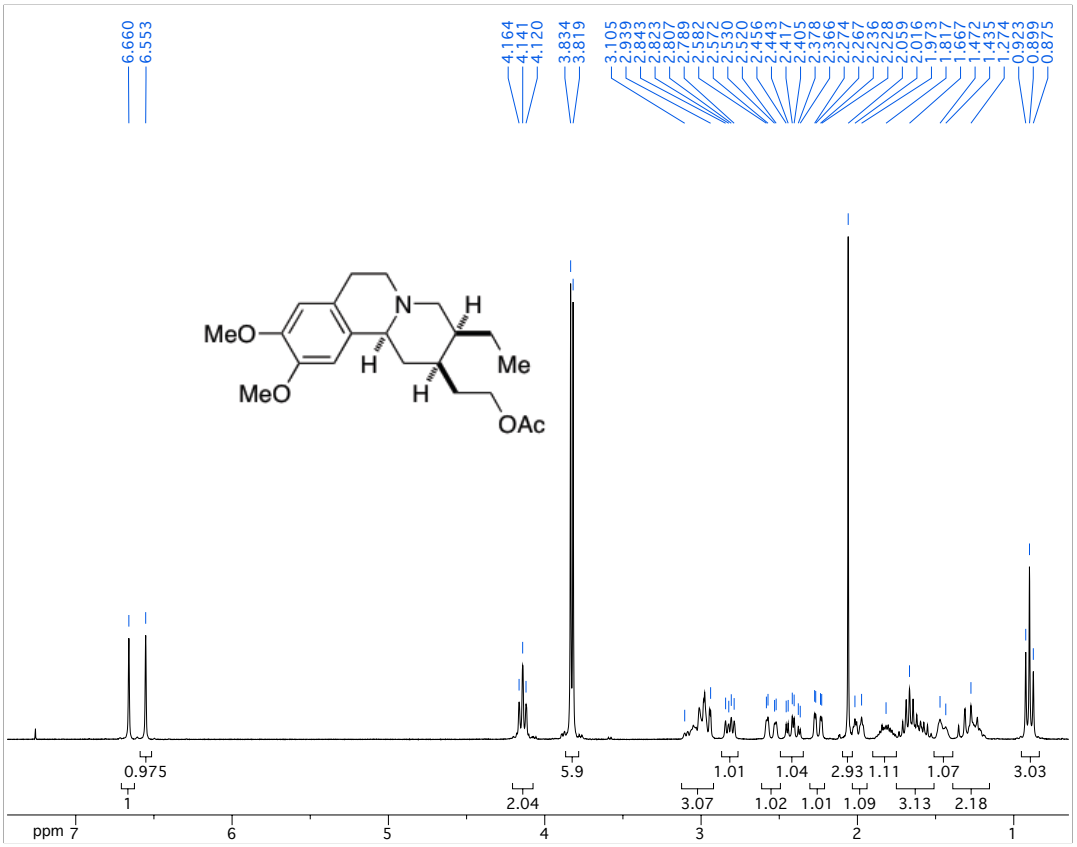


Synthesis of 2-((2*R*,3*S*,11b*S*)-3-ethyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-2-yl)ethyl acetate (3.44): To a 25 mL round bottomed flask containing 190 mg (0.503 mmol, 1 equiv.) acetate **3.43** dissolved in 5 mL dry benzene was added 94.0 μL (1.06 mmol, 2 equiv.) freshly distilled $POCl_3$. The reaction was heated to reflux for 2 hr before being concentrated, taken up in 5 mL dry MeOH, and cooled to 0°C. To this stirred solution was carefully added 19 mg (0.503 mmol, 1 equiv.) $NaBH_4$ and the reaction was allowed to warm to ambient temperature for 15 min. The reaction was added to $NaHCO_{3(sat.)}$, extracted thrice with CH_2Cl_2, dried over Na_2SO_4, and

concentrated. The resulting residue was purified by flash chromatography (10%$_{w/w}$ NEt_3 on silica gel) eluting with 4 : 1 to 0 : 1 hex./EtOAc to yield 142 mg (78%) of the desired product as a colorless oil.

^{1}HNMR (300 MHz, $CDCl_3$): δ 6.66 (s, 1H), 6.55 (s, 1H), 4.16 (t, *J* = 6.3, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.11-2.94 (m, 3H), 2.82 (dd, *J* = 10.8, 6, 1H), 2.55 (dd, *J* = 15.6, 3, 1H), 2.41 (td, *J* = 11.7, 3.9, 1H), 2.25 (dd, *J* = 11.4, 2.4, 1H), 2.06 (s, 3H), 1.99 (m, 1H), 1.82 (m, 1H), 1.67 (m, 3H), 1.45 (m, 1H), 1.27 (m, 2H), 0.90 (t, *J* = 7.2, 3H); ^{13}CNMR (75MHz, $CDCl_3$): δ 171.5, 147.4, 147.2, 130.7, 127.2, 111.6, 108.0, 63.5, 63.1, 59.1, 56.3, 56.0, 53.2, 39.0, 37.5, 34.0, 32.3, 29.6, 21.3, 17.6, 12.8; IR (NaCl, film): 2802, 2748 (Bohlmann bands), 1737 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 362.2326 calcd for $C_{21}H_{32}NO_4$, found: 362.2331.

Ref.: **BJEV378**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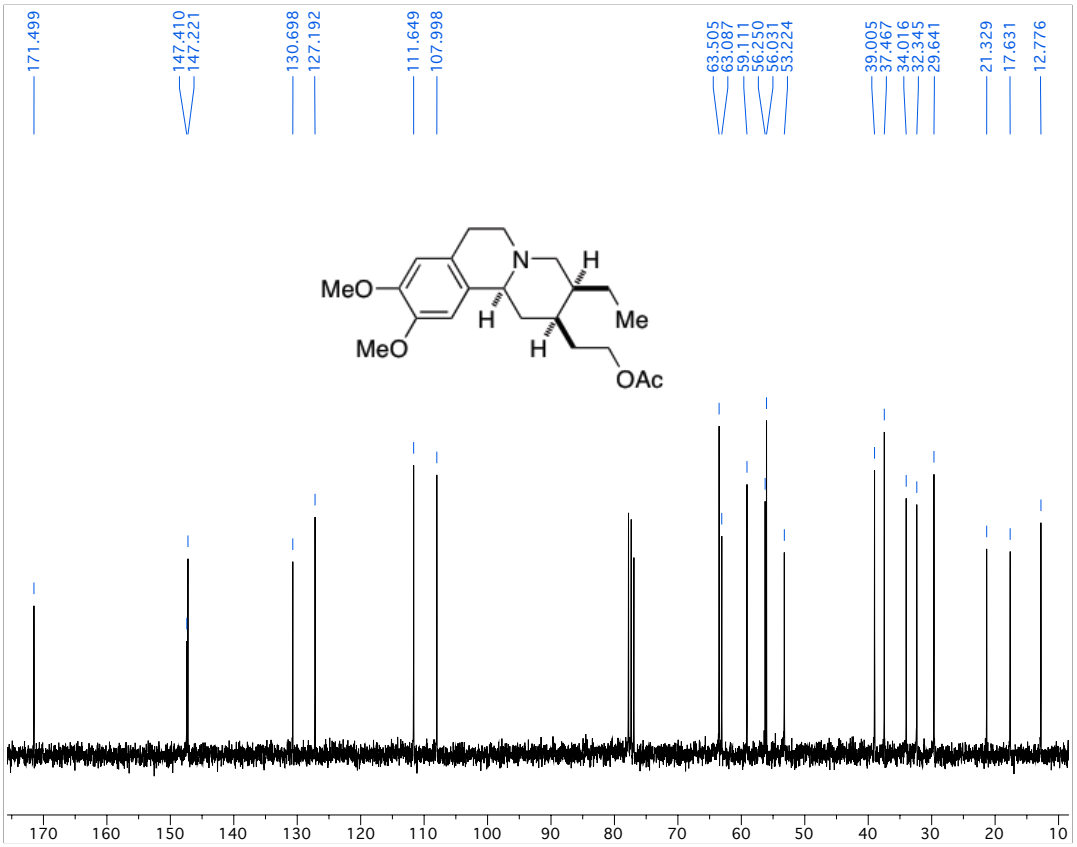
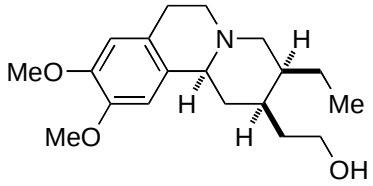


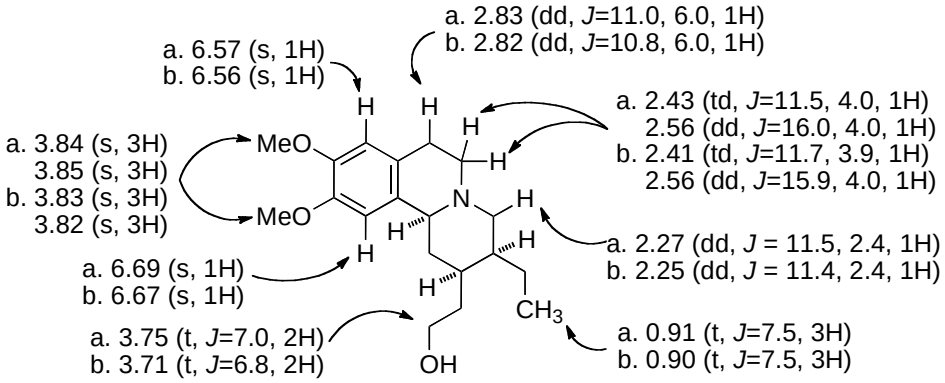


Synthesis of (+/-)-3-*epi*-protoemetinol: To a 10 mL round bottomed flask containing 95.0 mg (0.263 mmol, 1 equiv.) acetate **3.44** was added 2 mL MeOH, 1 mL H_20, and finally 436 mg (3.15 mmol, 12 equiv.) anhydrous K_2CO_3. The reaction was stirred for 2 hr at ambient temperature before being added to brine, extracted thrice into CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 2% to 10% MeOH in CH_2Cl_2 to yield 84 mg (>99%) of the desired product as a white foam.

^{1}HNMR (300 MHz, $CDCl_3$): δ 6.67 (s, 1H), 6.56 (s, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.71 (t, *J* = 6.8, 2H), 3.12-2.94 (m, 3H), 2.82 (dd, *J* = 10.8, 6, 1H), 2.56 (dd, *J* = 15.9, 3, 1H), 2.41 (td, *J* = 11.7, 3.9, 1H), 2.25 (dd, *J* = 11.4, 2.4, 1H), 1.99 (m, 1H), 1.87 (m, 2H), 1.59 (m, 3H), 1.45 (m, 1H), 1.26 (m, 2H), 0.90 (t, *J* = 7.5, 3H); ^{13}CNMR (75MHz, $CDCl_3$): δ 147.5, 147.2, 130.9, 127.3, 111.7, 108.2, 63.6, 61.0, 59.3, 56.3, 56.0, 53.3, 39.2, 36.9, 36.6, 34.0, 29.6, 17.7, 12.9; IR (NaCl, film): 3387, 2803, 2749 cm^{-1}(Bohlmann bands); HRMS (+TOF): $[M+H]^+$ 320.2220 calcd for $C_{19}H_{30}NO_3$, found: 320.2221; R_f = 0.54 (10% MeOH in CH_2Cl_2). All spectral data was in agreement with previous reports:

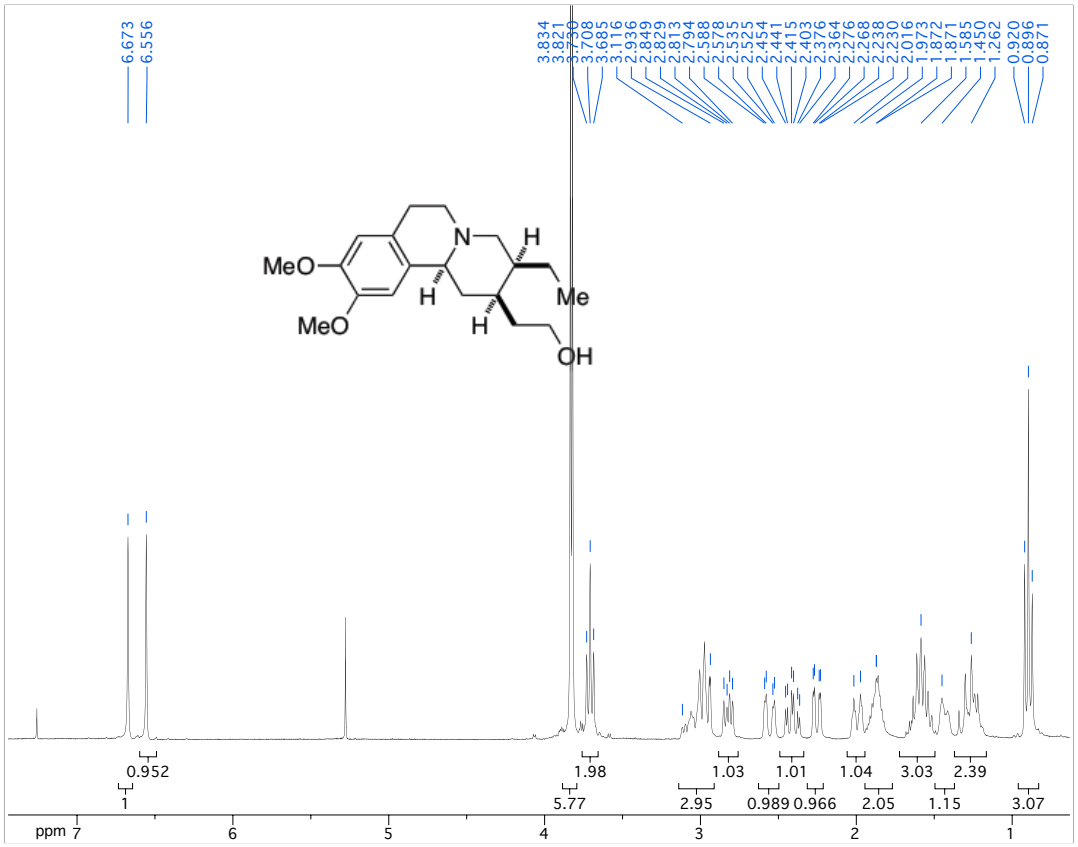
Nuhant, P.; Raikar, S.B.; Wypych, J.-C.; Delpech, B.; Marazano, C. *J. Org. Chem.* **2009**, 74, 9413.

Comparison of ^{1}HNMR data:



a. Nuhant, P.; Raikar, S.B.; Wypych, J.-C.; Delpech, B.; Marazano, C. *J. Org. Chem.* **2009**, 74, 9413.
b. English, B.J.; Williams, R.M.

Ref.: **BJEV387**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2.268
2.238
2.230
2.016
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MeO
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Me
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1.04
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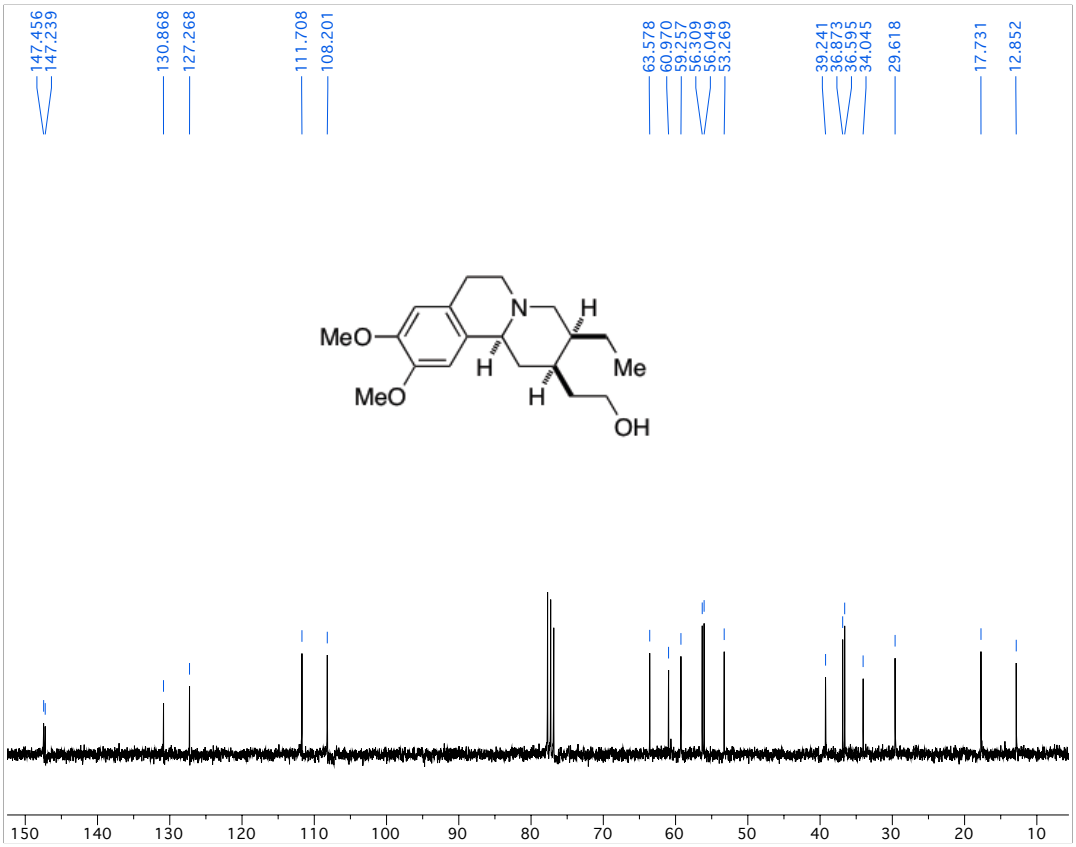
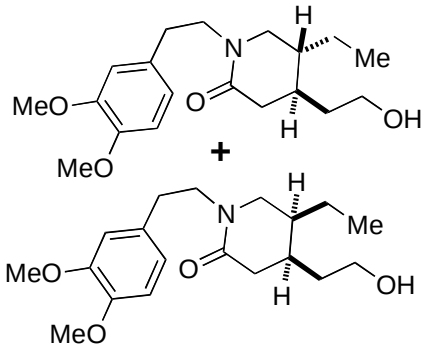




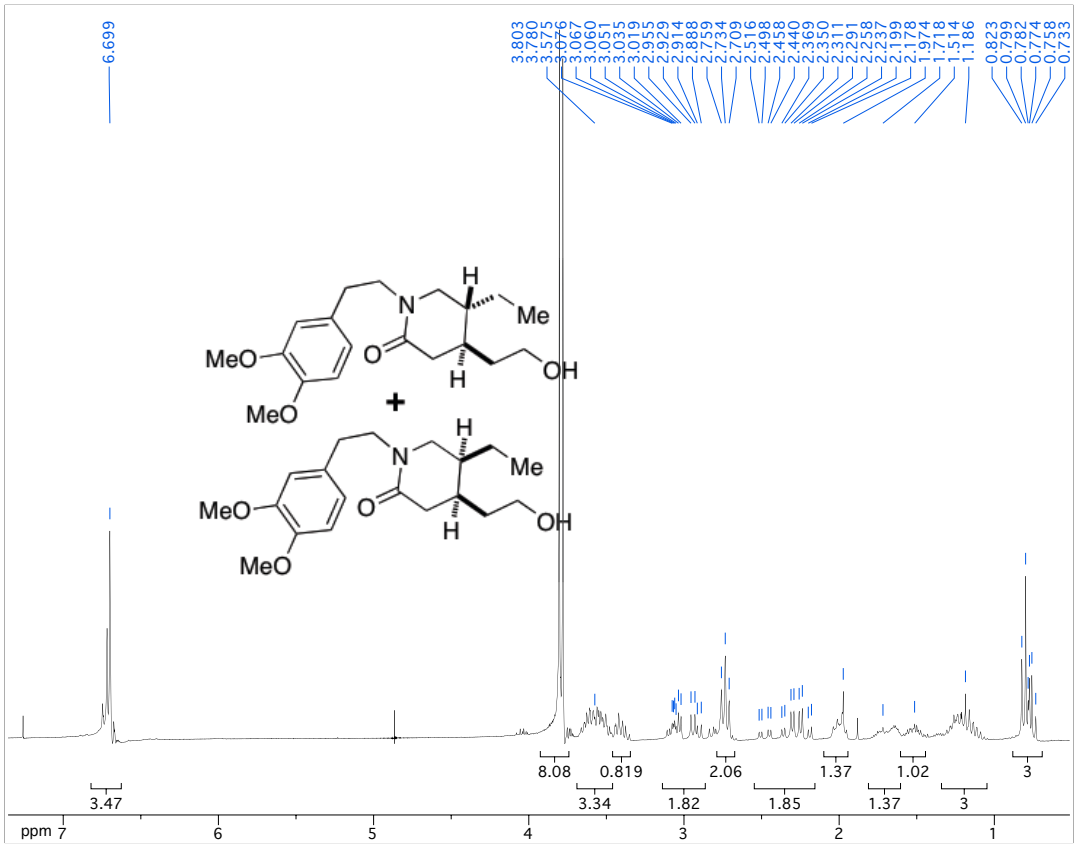
Synthesis of a mixture of alcohols 3.45 and 3.43: To a 25 mL flame dried round bottomed flask containing 410 mg (2.05 mmol, 1 equiv.) lactol **3.37** dissolved in 10 mL dry THF at -78°C was dropwise added 2.15 mL (2.15 mmol, 1.05 equiv.) of a 1.0 M solution of DIBAL-H in THF. The reaction was stirred at -78°C for 30 min before being added to a saturated solution of Rochelle's salt, extracted thrice with CH_2Cl_2, dried over

Na_2SO_4, and concentrated to yield 351 mg (84%) of a mixture of lactol isomers (**3.38**), which was used without further purification.

To a 50 mL round bottomed flash containing 290 mg (1.43 mmol, 1 equiv) of the above produced mixture of lactol isomers (**3.38**) dissolved in 7 mL dry THF was added 390 mg (2.15 mmol, 1.5 equiv.) 2-(3,4-dimethoxyphenyl)ethanamine (**3.42**) dissolved in 7 mL dry THF. To this mixture was added 909 mg (4.29 mmol, 3 equiv.) $NaBH(OAc)_3$ and the reaction was stirred at ambient temperature for 24 hr before being added to $NaHCO_{3(sat.)}$, extracted into CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel chromatography eluting with 5% to 20% MeOH in CH_2Cl_2 to yield 195 mg (41%) of the desired mixture of products.

^{13}CNMR (75MHz, $CDCl_3$): (mixture of epimers) δ 169.9, 169.6 149.0, 147.7, 131.7, 120.9, 120.8, 112.2, 112.0, 111.4, 60.3, 59.8, 56.1, 51.7, 50.8, 49.4, 41.0, 39.6, 38.6, 36.4, 36.0, 35.3, 33.3, 33.2, 31.7, 31.6, 23.8, 20.7, 12.2, 11.2; IR (NaCl, film): 3385, 1621 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 336.2169 calcd for $C_{19}H_{30}NO_4$, found: 336.2174; R_f = 0.33 (5% MeOH in EtOAc).

Ref.: BJEV276, BJEV296, **BJEV356**, **BJEV367.**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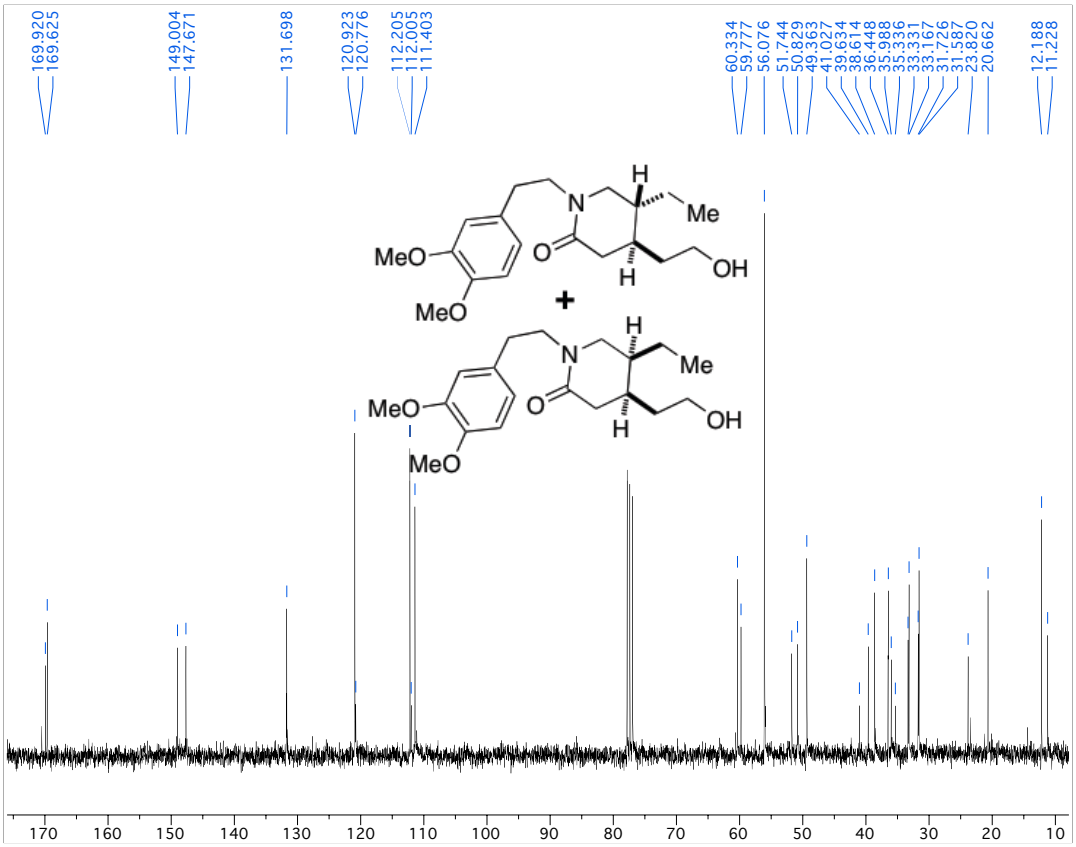
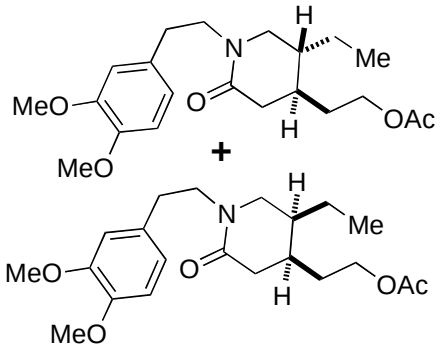
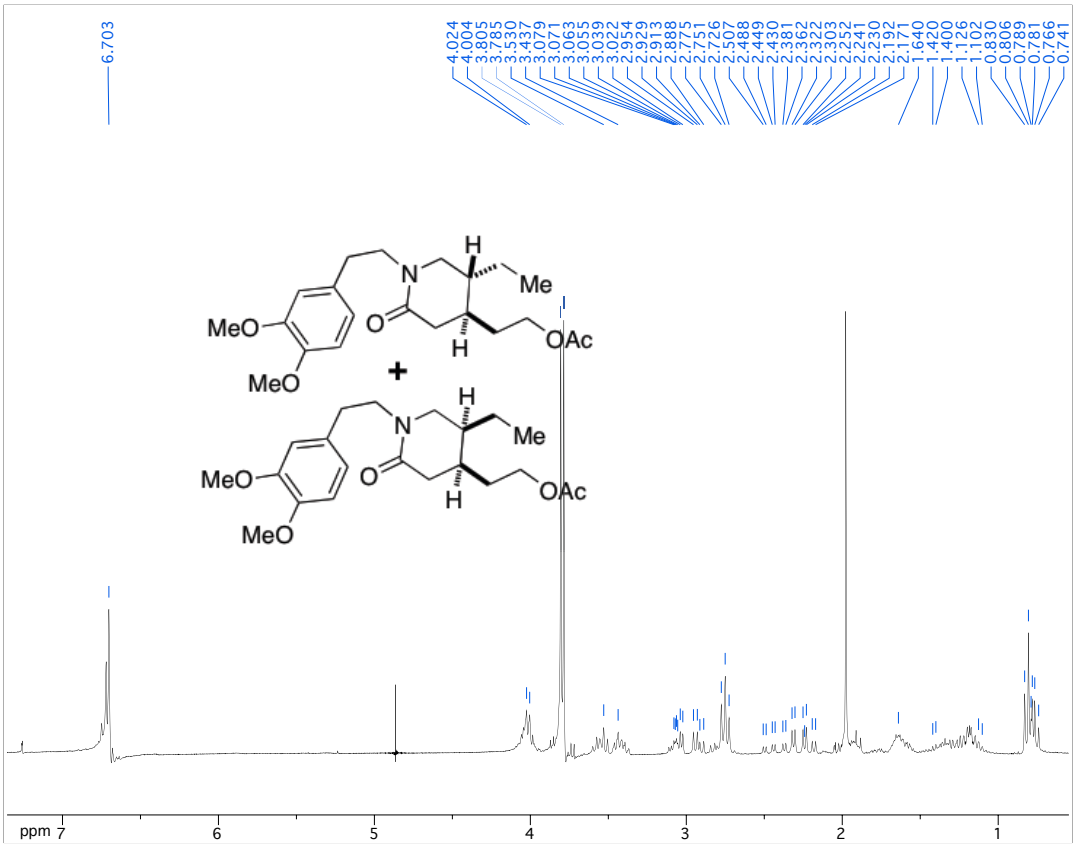


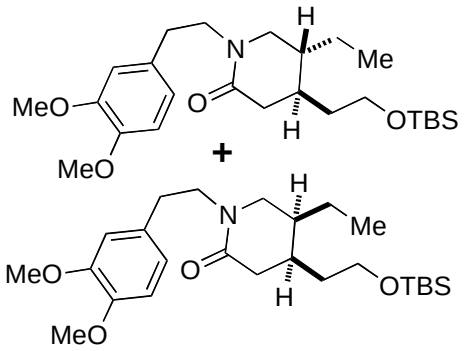


Synthesis of a mixture of 2-((4*S*,5*R*)-1-(3,4-dimethoxyphenethyl)-5-ethyl-2-oxopiperidin-4-yl)ethyl acetate and 2-((4*S*,5*S*)-1-(3,4-dimethoxyphenethyl)-5-ethyl-2-oxopiperidin-4-yl)ethyl acetate: To a 25 mL round bottomed flask containing 195 mg (0.549 mmol, 1 equiv.) of a mixture of alcohols **3.43** and **3.45** dissolved in 5 mL dry CH_2Cl_2 and 1 mL dry pyridine was added 76 mL (1.10 mmol, 2 equiv.) AcCl followed by a single crystal of DMAP. The reaction was stirred at ambient temperature for 30 min

before being added to $NaHCO_{3(sat.)}$, extracted into CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 1% to 10% MeOH in CH_2Cl_2 to yield 204 mg (>99%) of the desired mixture of products.

Ref.: **BJEV374**

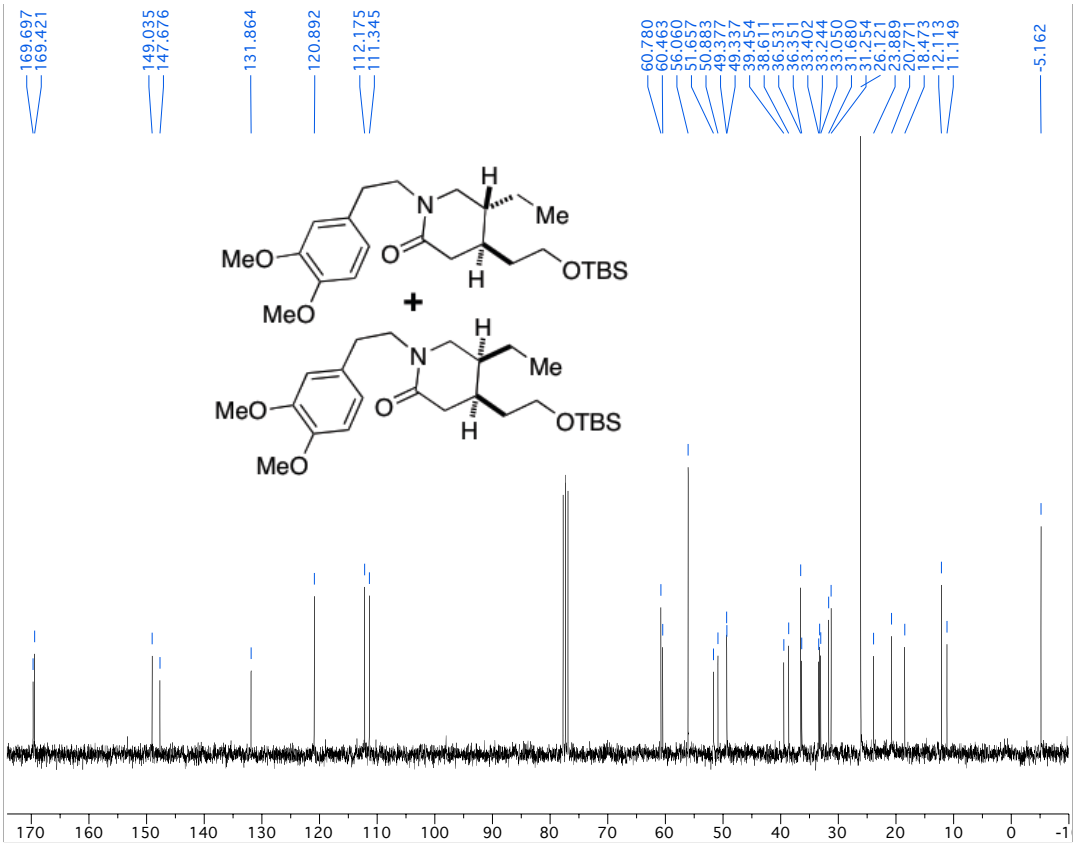


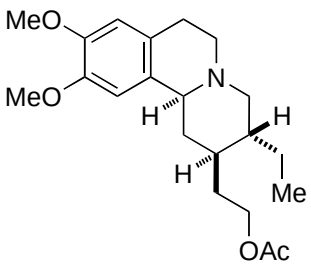


Synthesis of 4-(2-(*tert*-butyldimethylsilyloxy)ethyl)-1-(3,4-dimethoxyphenethyl)-5-ethylpiperidin-2-one: To a 25 mL round bottomed flask containing 105 mg (0.313 mmol, 1 equiv.) alcohols **3.43** and **3.45** dissolved in 3 mL dry CH_2Cl_2 was added 57.0 mg (0.376 mmol, 1.2 equiv.) TBSCl followed by 43.0 mg (0.626 mmol, 2 equiv.) imidazole. The reaction was stirred at ambient temperature for 16 hr before being added to brine and extracted twice with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel chromatography eluting with 1 : 1 to 1 : 2 hex./EtOAc to yield 103 mg (73%) of an inseparable 0.8 : 1 mixture of *cis*/*trans* isomers.

^{13}CNMR (75 MHz, $CDCl_3$): (mixture of epimers) δ 169.7, 169.4, 149.0, 147.7, 131.9, 120.9, 112.2, 111.3, 60.8, 60.5, 56.1, 51.7, 50.9, 49.4, 49.3, 39.5, 38.6, 36.5, 36.4, 33.4, 33.2, 33.1, 31.7, 31.1, 26.1, 23.9, 20.8, 18.5, 12.1, 11.1, -5.2; IR (NaCl, film): 1644 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 450.3034 calcd. for $C_{25}H_{44}NO_4Si$, found: 450.3035.

Ref.: **BJEV280**, BJEV298



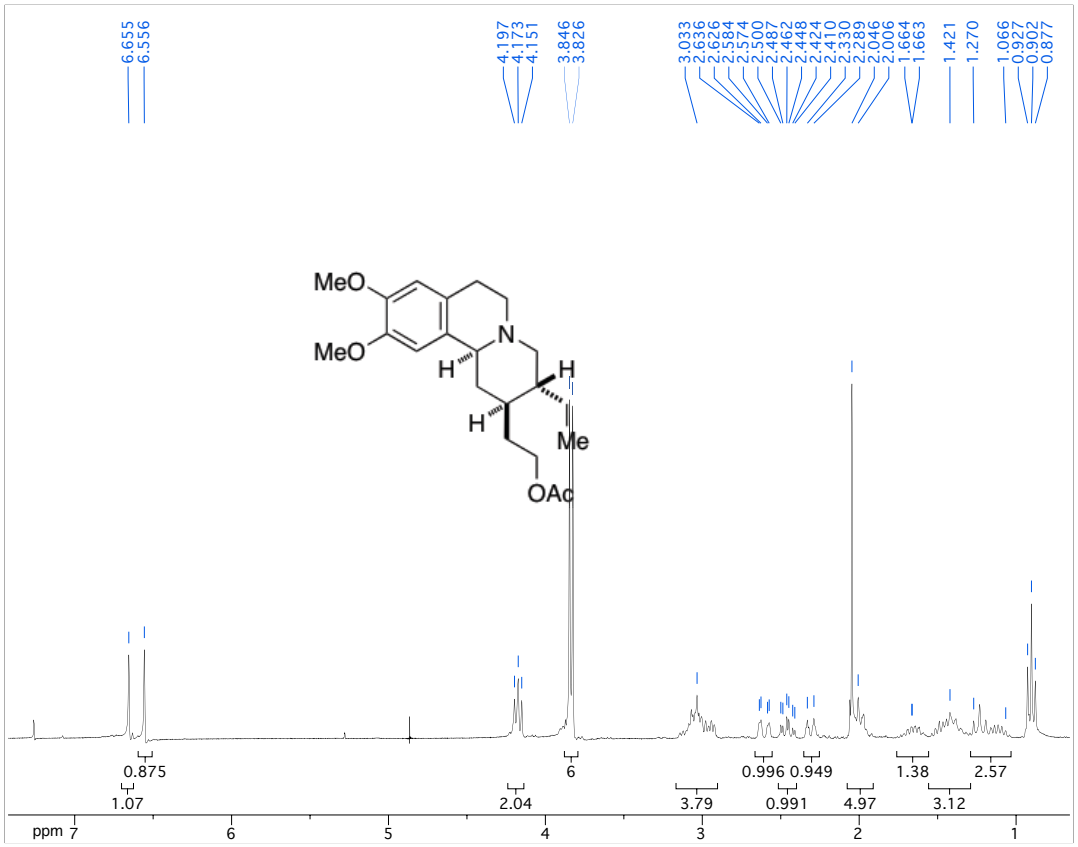


Synthesis of 2-((2*R*,3*R*,11b*S*)-3-ethyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-2-yl)ethyl acetate (3.46): To a 25 mL round bottomed flask containing 164 mg (0.434 mmol, 1 equiv.) of the above produced acetate mixture dissolved in 5 mL dry benzene was added 81.0 μL (0.869 mmol, 2 equiv.) freshly distilled $POCl_3$. The reaction was heated to reflux for 2 hr before being concentrated,

taken up in 5 mL dry MeOH, and cooled to 0°C. To this stirred solution was carefully added 17 mg (0.434 mmol, 1 equiv.) $NaBH_4$ and the reaction was allowed to warm to ambient temperature for 15 min. The reaction was added to $NaHCO_{3(sat.)}$, extracted thrice with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting residue was purified by flash chromatography (10%$_{w/w}$ NEt_3 on silica gel) eluting with 4 : 1 to 0 : 1 hex./EtOAc to yield 64 mg (41%) of the desired product (**3.46**) as a colorless oil as well as 55 mg (35%) of the C3 epimer (**3.44**).

^{1}HNMR (300 MHz, $CDCl_3$): δ 6.66 (s, 1H), 6.56 (s, 1H), 4.17 (t, *J* = 6.3, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.03 (m, 4H), 2.61 (dd, *J* = 15.6, 3, 1H), 2.45 (td, *J* = 11.4, 3.9, 1H), 2.31 (m, 1H), 2.05 (s, 3H), 2.00 (m, 2H), 1.66 (m, 1H), 1.42 (m, 3H), 1.27-1.07 (m, 2H), 0.90 (t, *J* = 7.5, 3H); ^{13}CNMR (75 MHz, $CDCl_3$): δ 171.4, 147.6, 147.3, 130.1, 126.9, 111.6, 108.2, 62.8, 61.6, 56.3, 56.0, 52.7, 41.4, 38.2, 37.4, 31.9, 29.4, 23.7, 21.3, 11.3; IR (NaCl, film): 2802, 2748 (Bohlmann bands), 1737 cm^{-1}; HRMS (+TOF): $[M+Na]^+$ 384.2145 calcd. for $C_{21}H_{31}NNaO_4$, found: 384.2147.

Ref.: **BJEV376**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H
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Me
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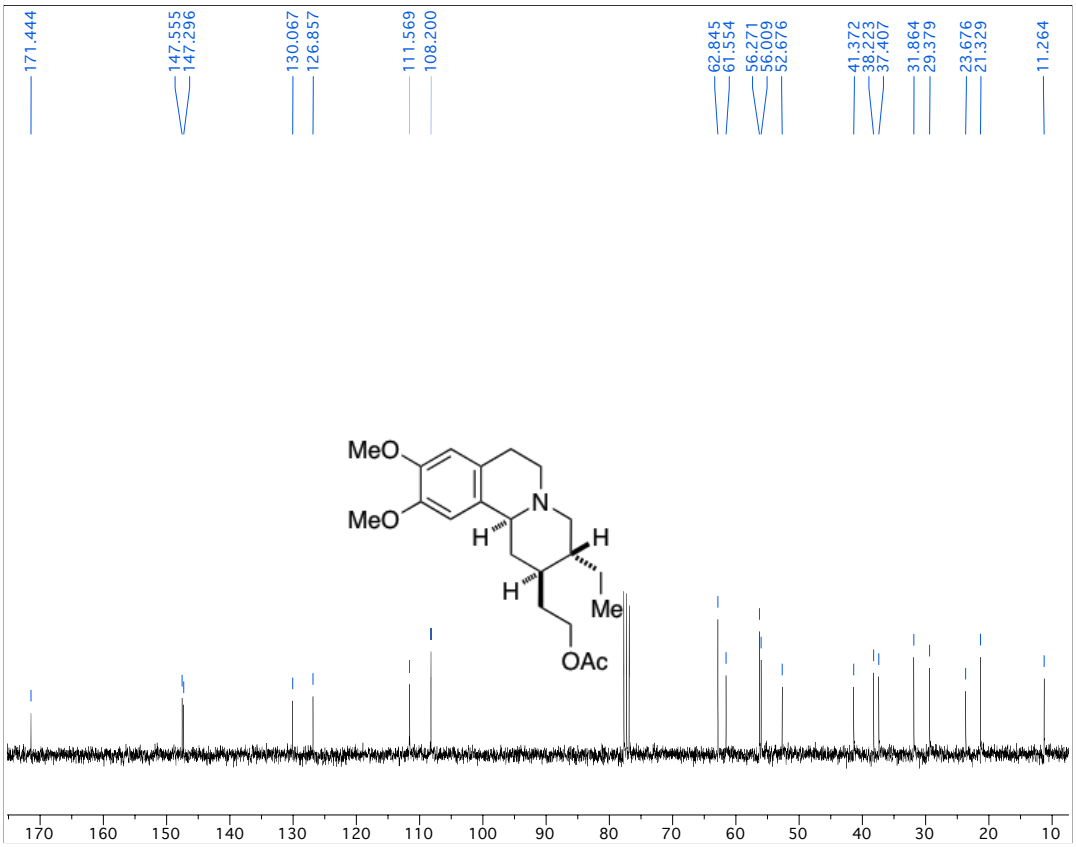
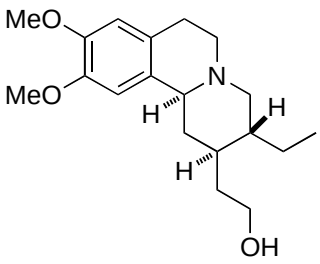


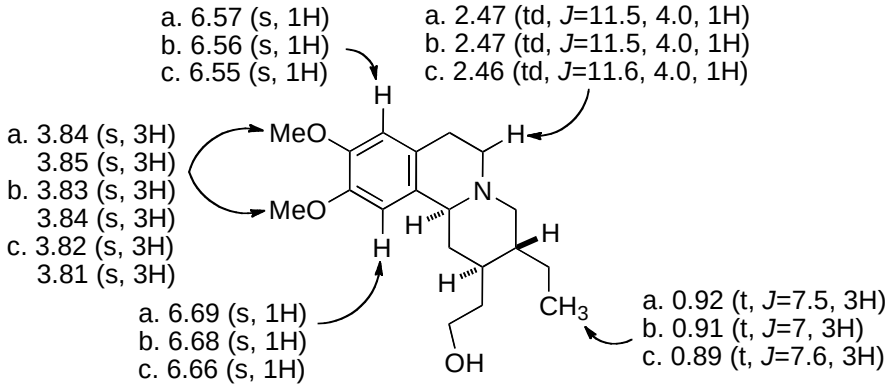


Synthesis of (+/-)-protoemetinol : To a 10 mL round bottomed flask containing 61.0 mg (0.169 mmol, 1 equiv.) acetate **3.46** was added 1 mL MeOH, 0.5 mL H_2O, and finally 280 mg (2.03 mmol, 12 equiv.) anhydrous K_2CO_3. The reaction was stirred for 2 hr at ambient temperature before being added to brine, extracted thrice into CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 2% to 10% MeOH in CH_2Cl_2 to yield 54 mg (>99%) of the desired product as a colorless oil.

^{1}HNMR (400 MHz, $CDCl_3$): δ 6.66 (s, 1H), 6.55 (s, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.72 (m, 2H), 3.14-2.94 (m, 4H), 2.60 (d, *J* = 16.4, 1H), 2.46 (td, *J* = 11.6, 4, 1H), 2.32 (d, *J* = 13.2, 1H), 2.01 (m, 1H), 1.90 (m, 1H), 1.63 (m, 1H), 1.41 (m, 3H), 1.23 (m, 2H), 1.09 (m, 1H), 0.89 (t, *J* = 7.6, 3H); ^{13}CNMR (75MHz, $CDCl_3$): δ 147.5, 147.2, 129.9, 126.7, 111.5, 108.4, 62.8, 61.5, 60.4, 56.2, 55.9, 52.5, 41.2, 37.7, 37.2, 35.9, 29.1, 23.5, 11.2; IR (NaCl, film): 3373, 2801, 2751 cm^{-1} (Bohlmann bands); HRMS (+TOF): $[M+H]^+$ 320.2220 calcd for $C_{19}H_{30}NO_3$, found: 320.2224; R_f = 0.46 (10% MeOH in CH_2Cl_2). All spectral data was in agreement with previous reports:

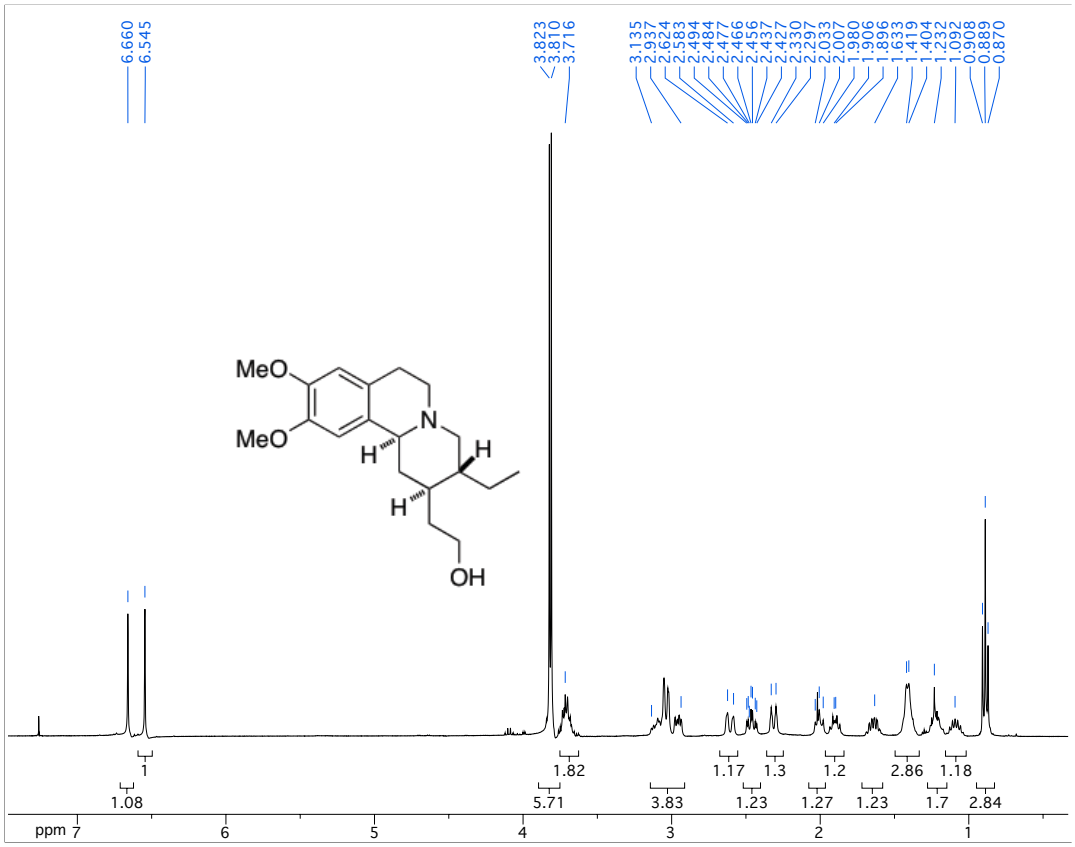
Battersby, A.B.; Kapil, B.S.; Bhakuni, D.S.; Popli, S.P.; Merchant, J. R.; Salgar, S.S. *Tetrahedron Lett.* **1966**, 4965. Chang, J.-K.; Chang, B.-R.; Chuang, Y.-H.; Chang, N.-C. *Tetrahedron* **2008**, *64*, 9685. Nuhant, P.; Raikar, S.B.; Wypych, J.-C.; Delpech, B.; Marazano, C. *J. Org. Chem.* **2009**, 74, 9413.

Comparison of ^{1}HNMR data:



a. Chang, J.-K.; Chang, B.-R.; Chuang, Y.-H.; Chang, N.-C. *Tetrahedron* **2008**, *64*, 9685.
b. Nuhant, P.; Raikar, S.B.; Wypych, J.-C.; Delpech, B.; Marazano, C. *J. Org. Chem.* **2009**, 74, 9413.
c. English, B.J.; Williams, R.M.

Ref.: BJEV386, **BJEV418**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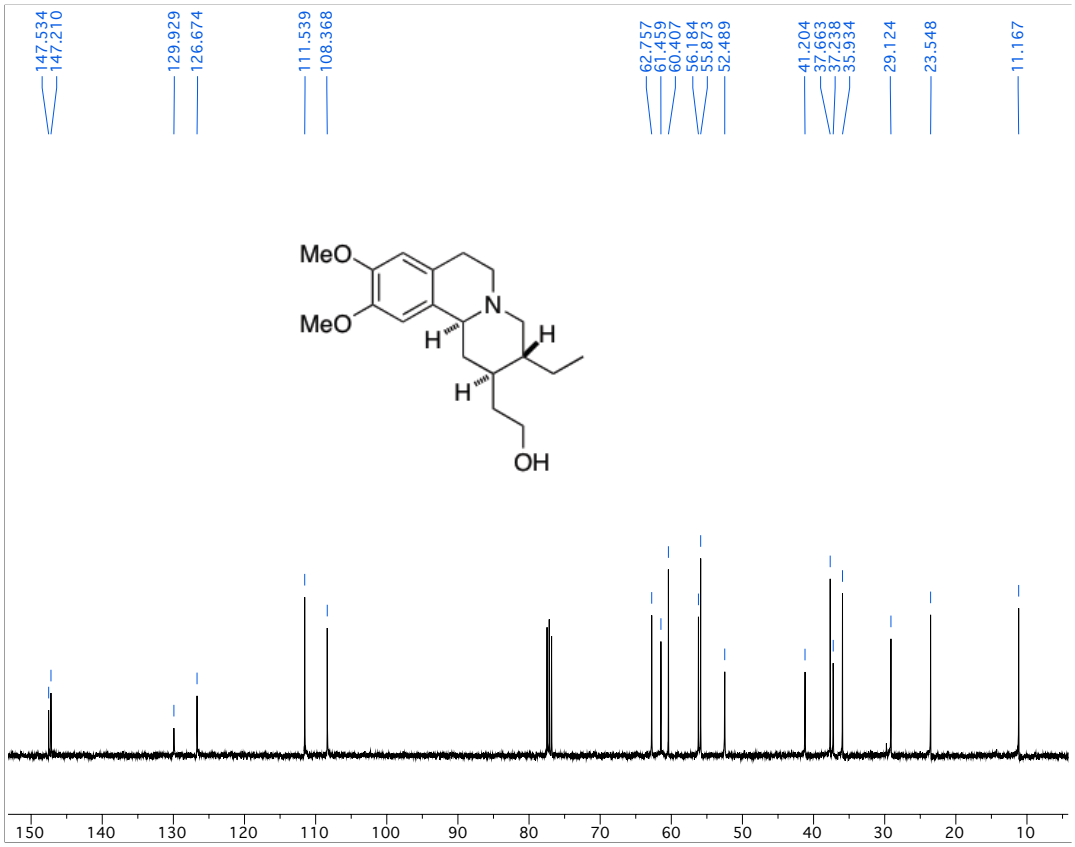
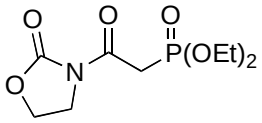
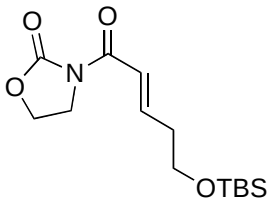




Synthesis of diethyl (2-oxo-2-(2-oxooxazolidin-3-yl)ethyl)phosphonate (4.6): To a 50 mL round-bottomed flask containing 1.91 g (9.22 mmol, 1 equiv.) 3-(2-bromoacetyl)oxazolidin-2-one was added 4.7 mL (27.7 mmol, 3 equiv.) triethyl phosphite. The reaction was heated to 100^{o}C for 20 min and then concentrated to yield 2.46 g (>99%) of the desired product as a red oil which was used without purification.

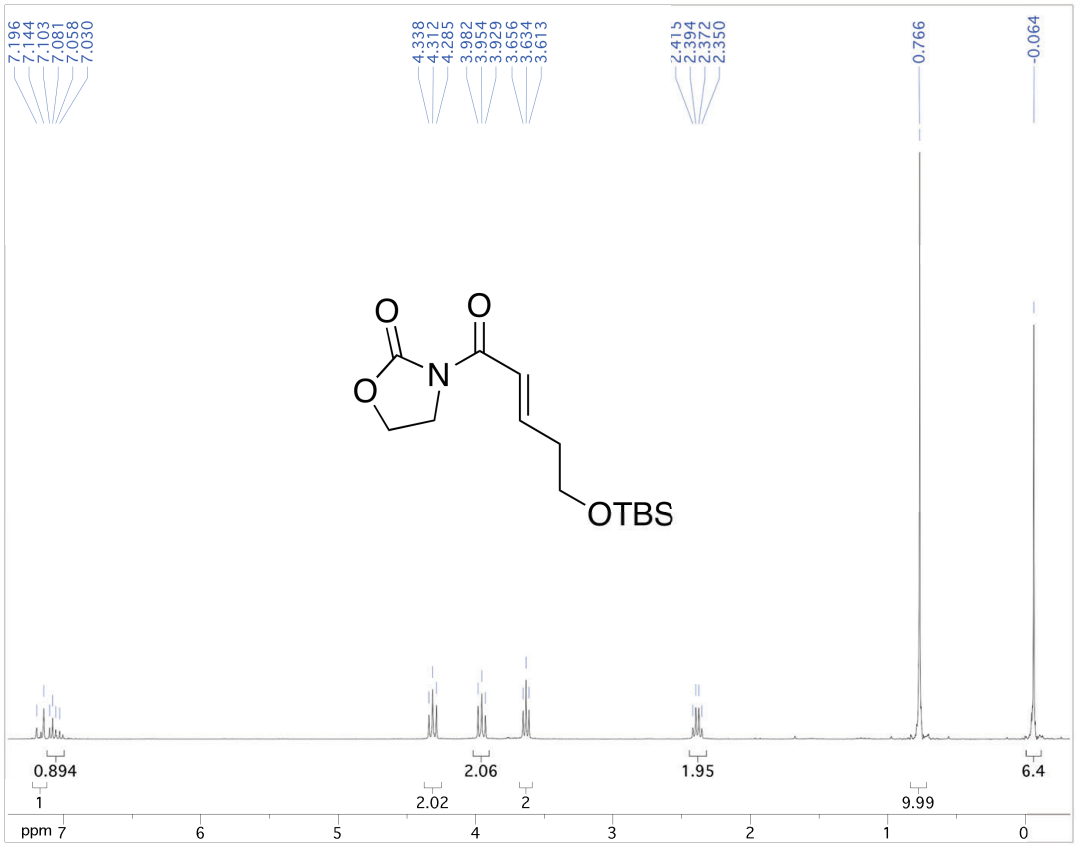
Ref.: **BJEII469**, BJEII479



Synthesis of (*E*)-3-(5-((*tert*-butyldimethylsilyl)oxy)pent-2-enoyl)oxazolidin-2-one (4.5): To a 25 mL round-bottomed flask containing 150 mg (0.566 mmol, 1.2 equiv.) phosphonate **4.6** and 24 mg (0.566 mmol, 1.2 equiv.) LiCl dissolved in 2.5 mL dry MeCN was added 99 μL (0.472 mmol, 1 equiv.) *i*Pr_2NEt. The reaction was stirred for 15 min at ambient temperature before the addition of 89 mg (0.472 mmol, 1 equiv.) aldehyde **3.5** dissolved in 1 mL dry MeCN. The reaction was stirred for 16 hr, added to brine, extracted thrice with EtOAc, dried over Na_2SO_4, and concentrated. The crude residue was purified by silica gel flash chromatography eluting with 4 : 1 to 2 : 1 hex./ EtOAc to yield 95 mg (67%) of the desired product as a colorless oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 7.16 (d, *J* = 15.6, 1H), 7.06 (dt, *J* = 15.3, 6.6, 1H), 4.31 (t, *J* = 8.1, 2H), 3.95 (t, *J* = 7.5, 2H), 3.63 (t, *J* = 6.3, 2H), 2.38 (q, *J* = 6.6, 2H), 0.77 (s, 9H), -0.06 (s, 6H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 165.2, 153.7, 148.6, 121.5, 62.3, 61.8, 42.9, 36.4, 26.1, 18.5, -5.1; R_f = 0.33 (2 : 1 hex./EtOAc)

Ref.: **BJEII483**, BJEII487.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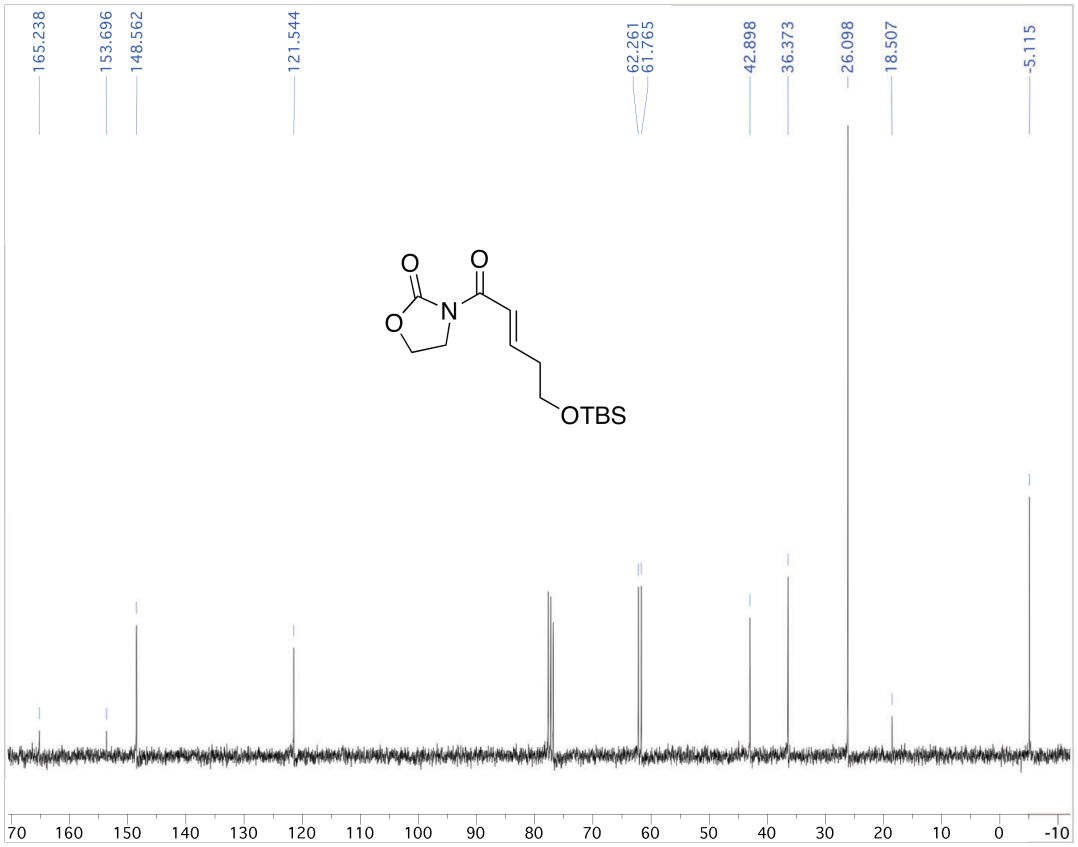
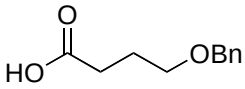
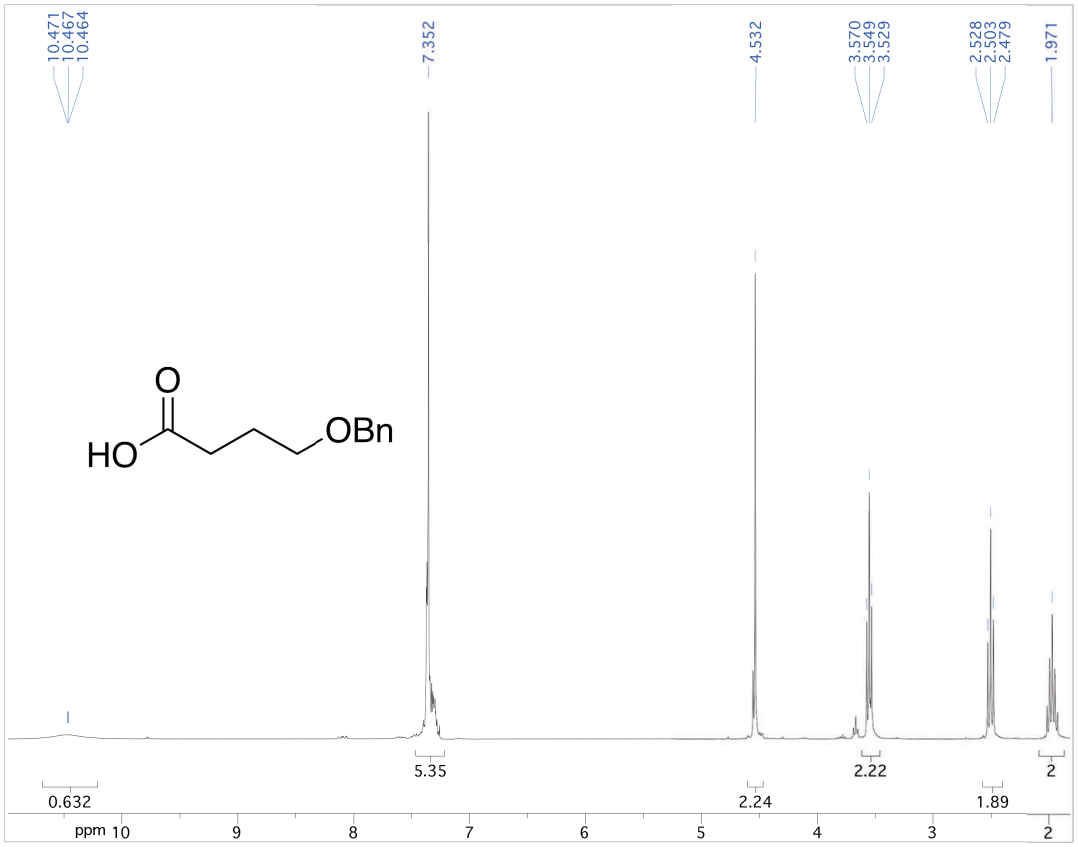


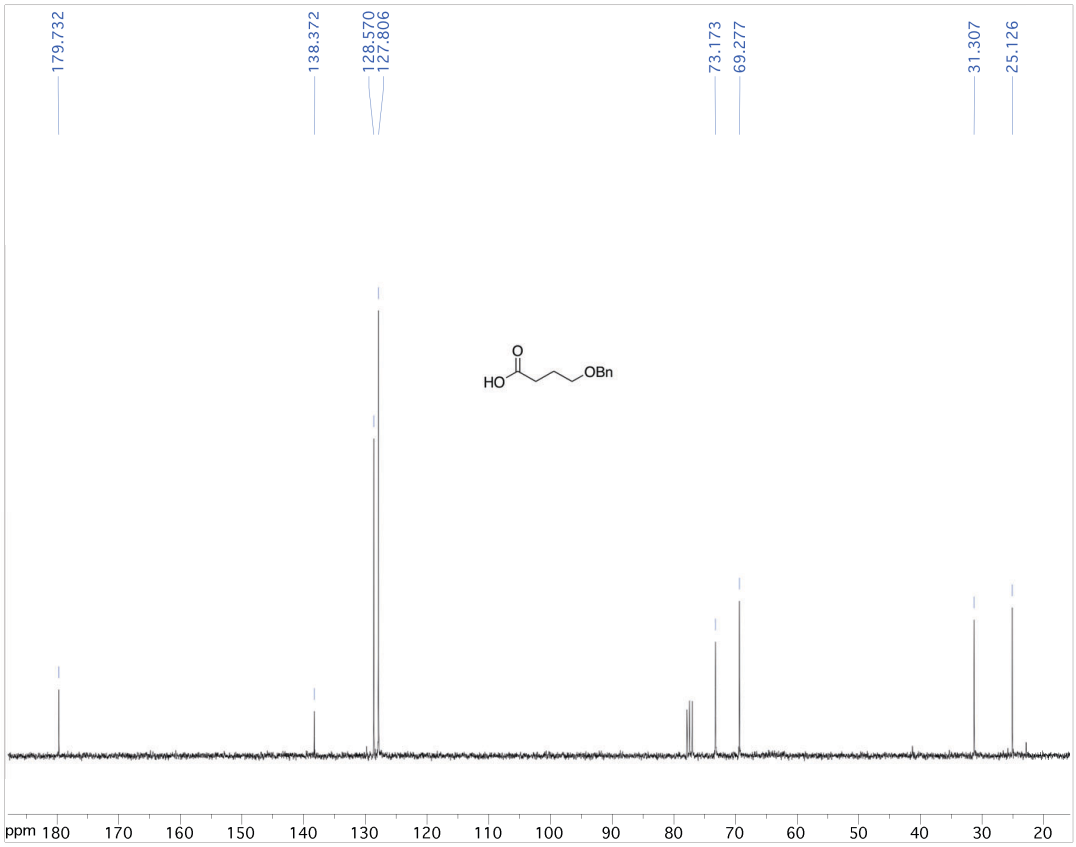


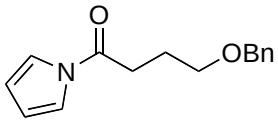
Synthesis of 4-(benzyloxy)butanoic acid (4.8): To a 50 mL round-bottomed flask containing 1.30 g (7.21 mmol, 1 equiv.) 4-(benzyloxy)butan-1-ol (**4.7**) dissolved in 25 mL dry DMF was added 8.14 g (21.6 mmol, 3 equiv.) PDC. The reaction was stirred at ambient temperature for 4 hr, added to H_2O, Extracted twice with EtOAc, dried over $MgSO_4$, and concentrated. The crude acid was purified by silica gel flash chromatography eluting with 2 : 1 to 1 : 1 hex./EtOAc to yield 1.00 g (71%) of the desired product as a colorless oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 10.47 (bs, 1H), 7.35 (m, 5H), 4.53 (s, 2H), 3.55 (t, *J* = 6.0, 2H), 2.50 (t, *J* = 67.2, 2H), 1.97 (m, 2H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 179.7, 138.4, 128.6, 127.8, 73.2, 69.3, 31.3, 25.1; R_f = 0.19 (1 : 1 hex./EtOAc).

Ref.: BJEII035, **BJEII037**, BJEII048, BJEII049





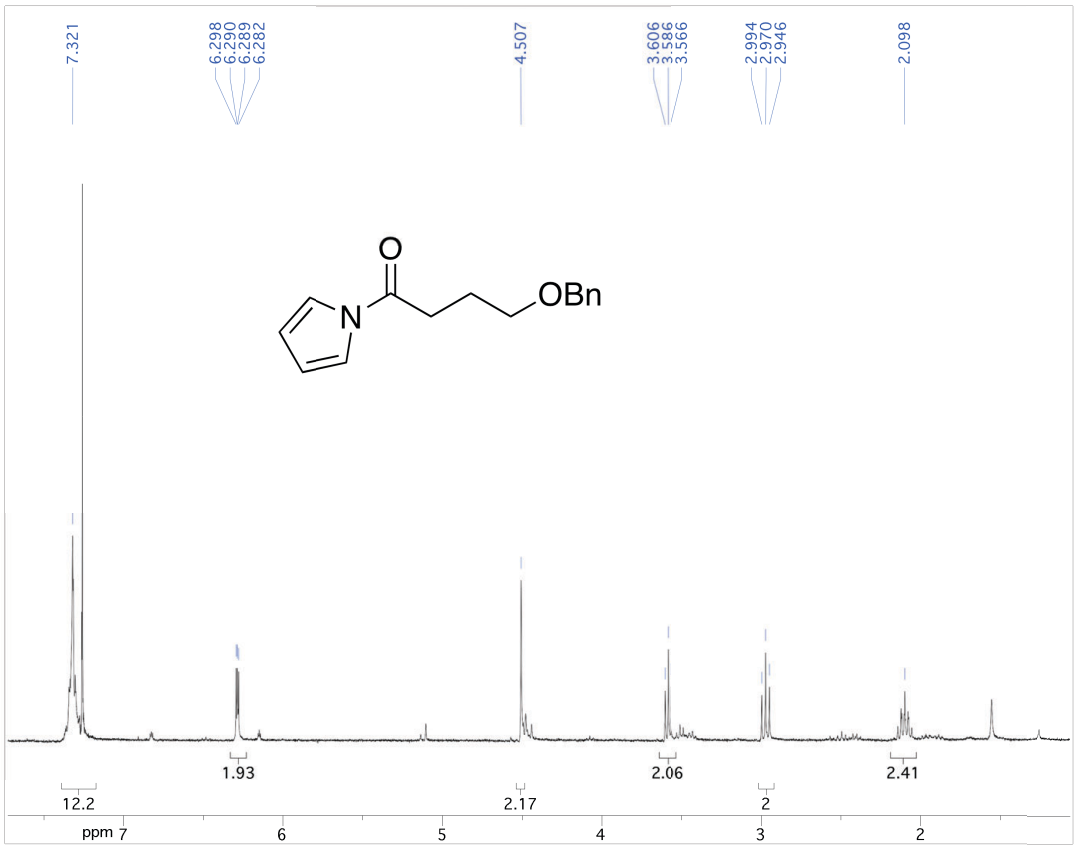


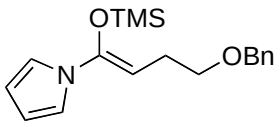
Synthesis of 4-(benzyloxy)-1-(1*H*-pyrrol-1-yl)butan-1-one (4.9): To a 25 mL oven-dried round-bottomed flask containing 188 mg (0.967 mmol, 1 equiv.) acid **4.8** dissolved in 8 mL dry CH_2Cl_2 was added 141 μL (1.93 mmol, 2 equiv.) $SOCl_2$. The reaction was stirred at reflux for 2 hr before being concentrated and then taken up in 1 mL dry THF. To a separate 10 mL flame-dried round-bottomed flask containing 67 μL (0.967 mmol, 1 equiv.) pyrrole dissolved in 2 mL dry THF at -78°C was added 604 μL of a 1.6 M solution (0.967 mmol, 1 equiv.) of *n*BuLi. This soution was stirred at -78°C for 15 min before the addition of the above prepared acid chloride solution. The reaction was stirred for 2 hr at -78°C, added to brine, extracted twice with EtOAc, dried over $MgSO_4$, and

concentrated. The crude material was subjected to silica gel flash chromatography eluting with 9 : 1 to 4 : 1 hex./EtOAc yielding 68 mg (30%) of the desired pyrroleamide as a yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 7.32 (m, 7H), 6.29 (dd, *J* = 2.7, 2.4, 2H), 4.51 (s, 2H), 3.59 (t, *J* = 6.0, 2H), 2.97 (t, *J* = 7.2, 2H), 2.10 (m, 2H); R_f = 0.58 (4 : 1 hex./EtOAc).

Ref.: BJEII040, BJEII041, **BJEII050**, BJEII068

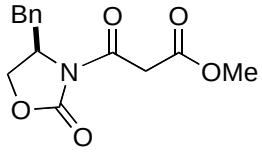




Synthesis of (*Z*)-1-(4-(benzyloxy)-1-((trimethylsilyl)oxy)but-1-en-1-yl)-1*H*-pyrrole (4.4): To a 10 mL flame-dried round-bottomed flask containing 158 μL (0.158 mmol, 1.1 equiv.) of a 1.0 M THF solution of NaHMDS dissolved in 2 mL dry THF at -78^{o}C was

added 35 mg (0.144 mmol, 1 equiv.) pyrroleamide **4.8** dissolved in 1 mL dry THF. The reaction was stirred at -78^{o}C for 20 min before the addition of 26.0 μL (0.202 mmol, 1.4 equiv.) TMSCl. The reaction was stirred for a further 30 in at -78^{o}C before being warmed to ambient emperature over 16 hr, being added to hexanes, washed twice with $CuSO_4$, dried over $MgSO_4$, and concentrated. The crude product was used immediately without purification.

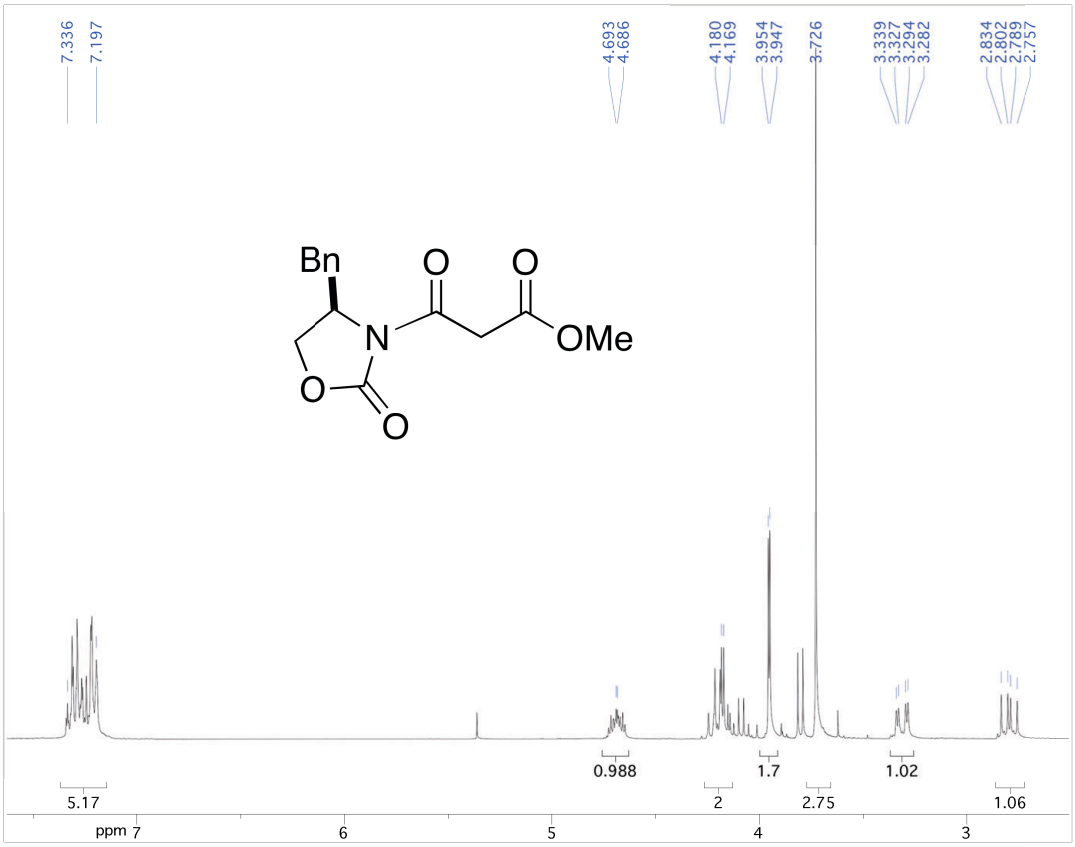
Ref.: BJEII043, **BJEII052**, BJEII054, BJEII056

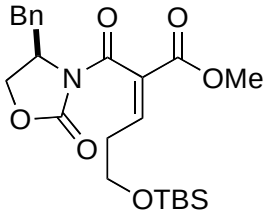


Synthesis of (*R*)-methyl 3-(4-benzyl-2-oxooxazolidin-3-yl)-3-oxopropanoate (4.16): To a 100 mL round-bottomed flask containing 1.74 g (7.91 mmol, 1 equiv.) (*R*)-4-benzyloxazolidin-2-one **4.15** dissolved in 25 mL dry THF at -78^{o}C was slowly added 23.74 mL LiHMDS (1M in THF, 23.74 mmol, 3 equiv.). After stirring for 30 min at -78^{o}C 1.83 mL (23.74 mmol, 3 equiv.) methyl chloroformate was added and the reaction was warmed to 0^{o}C. After stirring for 2 hr at 0^{o}C the reaction was added to $NH_4Cl_{(sat.)}$, extracted into EtOAc, dried over $MgSO_4$, and concentrated. Purification by silica gel flash chromatography eluting with 4 : 1 to 1 : 1 hex./EtOAc yielded 2.18g (>99%) of the desired product as a pale yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 7.20-7.34 (m, 5H), 4.69 (m, 1H), 4.17 (m, 2H), 3.95 (d, *J* = 2.1, 2H), 3.73 (s, 3H), 3.31 (dd, *J* = 13.5, 3.6, 1H), 2.79 (dd, *J* = 13.5, 9.6, 1H); R_f = 0.34 (2 : 1 hex./EtOAc).

Ref.: BJEII165, **BJEII182**.



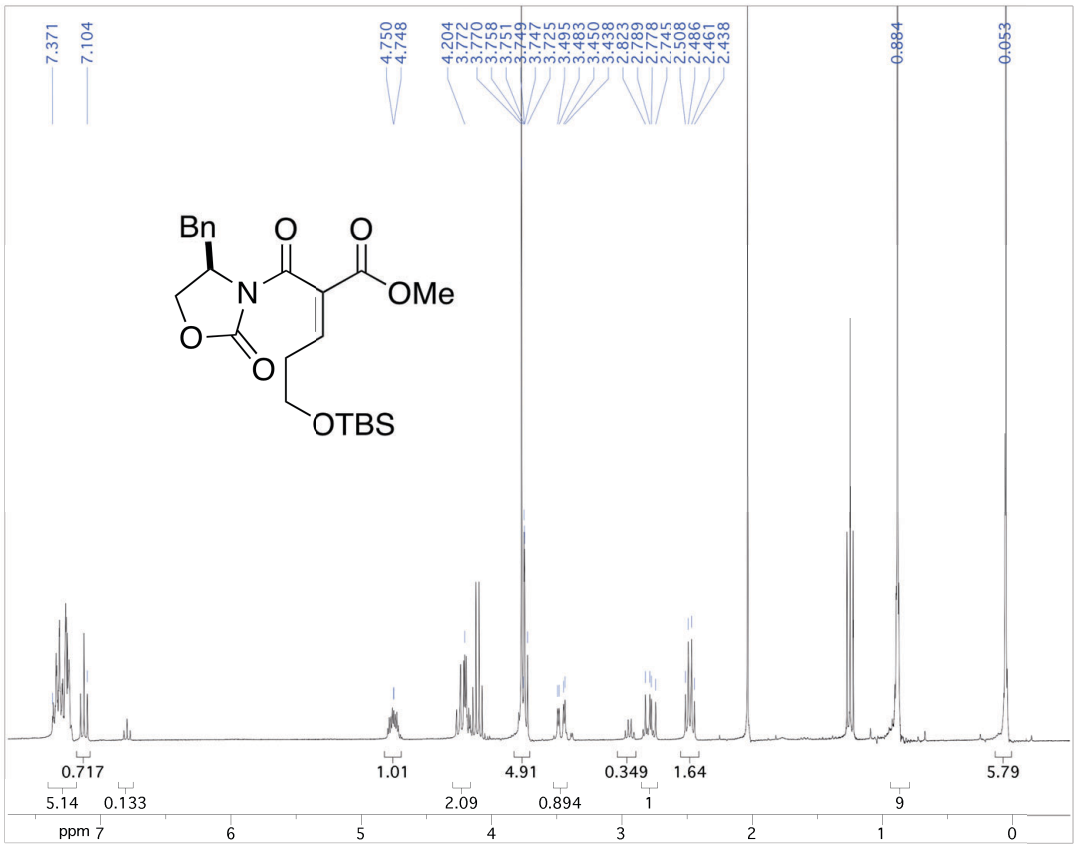


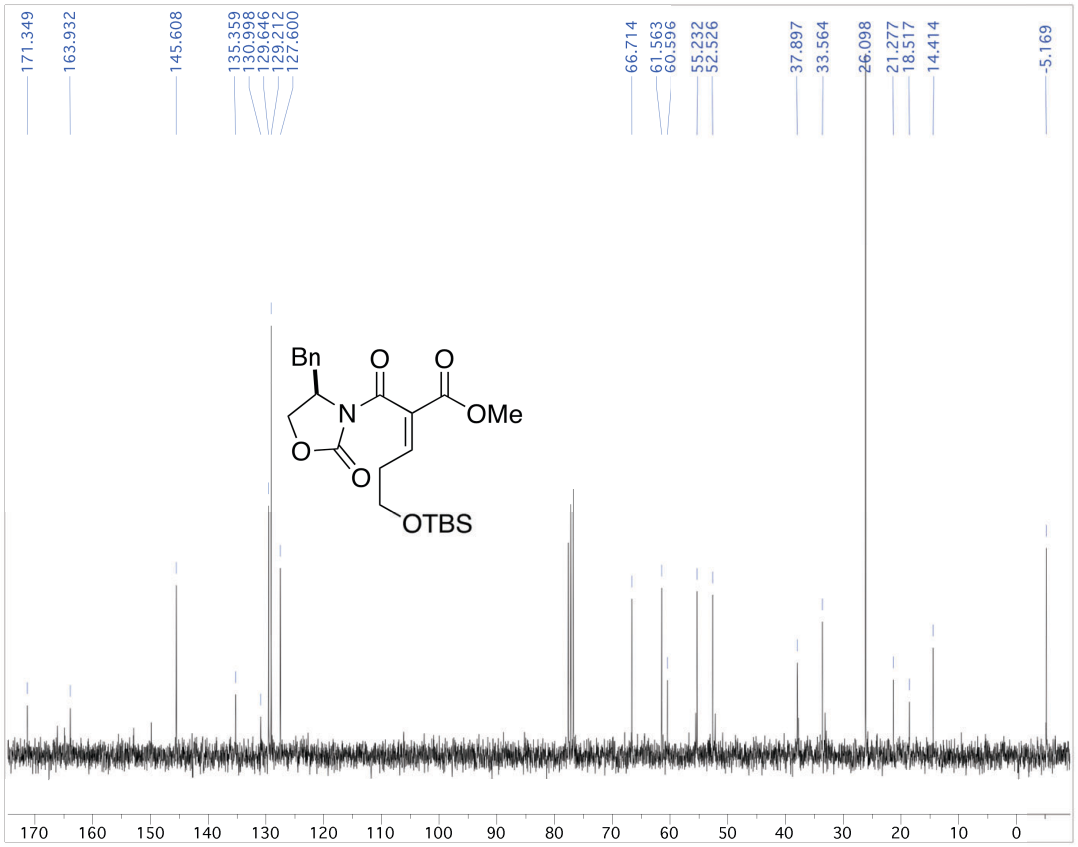
Synthesis of (*R*,*E*)-methyl 2-(4-benzyl-2-oxooxazolidine-3-carbonyl)-5-((*tert*-butyldimethylsilyl)oxy)pent-2-enoate (4.17): To a 100 mL round-bottomed flask containing 560 mg (2.02 mmol, 1 equiv.) compound **4.16** dissolved in 30 mL dry THF at 0°C was added 457 mg (2.42 mmol, 1.2 equiv.) aldehyde **3.5** dissolved in a minimum of THF followed by 444 μL (4.04 mmol, 2 equiv.) $TiCl_4$. After stirring at 0°C for 40 min 654 mL (8.08 mmol, 4 equiv.) dry pyridine was added and the reaction was allowed to return to ambient temperature and was stirred for a further 12 hr before being added to

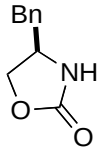
$NaHCO_3$, extracted into EtOAc, dried over $MgSO_4$, and concentrated. The resulting residue was purified by silica gel chromatography eluting with 9 : 1 to 4 : 1 hex./EtOAc to yield 743 mg (82%) of the desired product (10:1 *E/Z*) as a pale yellow oil.

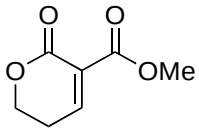
^{1}HNMR (300 MHz, $CDCl_3$) E isomer δ 7.10-7.37 (m, 6H), 4.75 (m, 1H), 4.20 (m, 1H), 3.77 (s, 3H), 3.75 (m, 2H), 3.46 (dd, *J* = 13.5, 3.6, 1H), 2.78 (dd, *J* = 13.5, 10.2, 1H), 2.47 (q, *J* = 6.6, 2H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}CNMR (75 MHz, $CDCl_3$) Mixture of isomers δ 171.3, 163.9, 145.6, 135.4, 131.0, 129.6, 129.2, 127.6, 66.7, 61.6, 60.6, 55.2, 52.5, 37.9, 33.6, 26.1, 21.3, 18.5, 14.4, -5.2; R_f = 0.33 (4 : 1 hex./EtOAc).

Ref.: **BJEII173**.







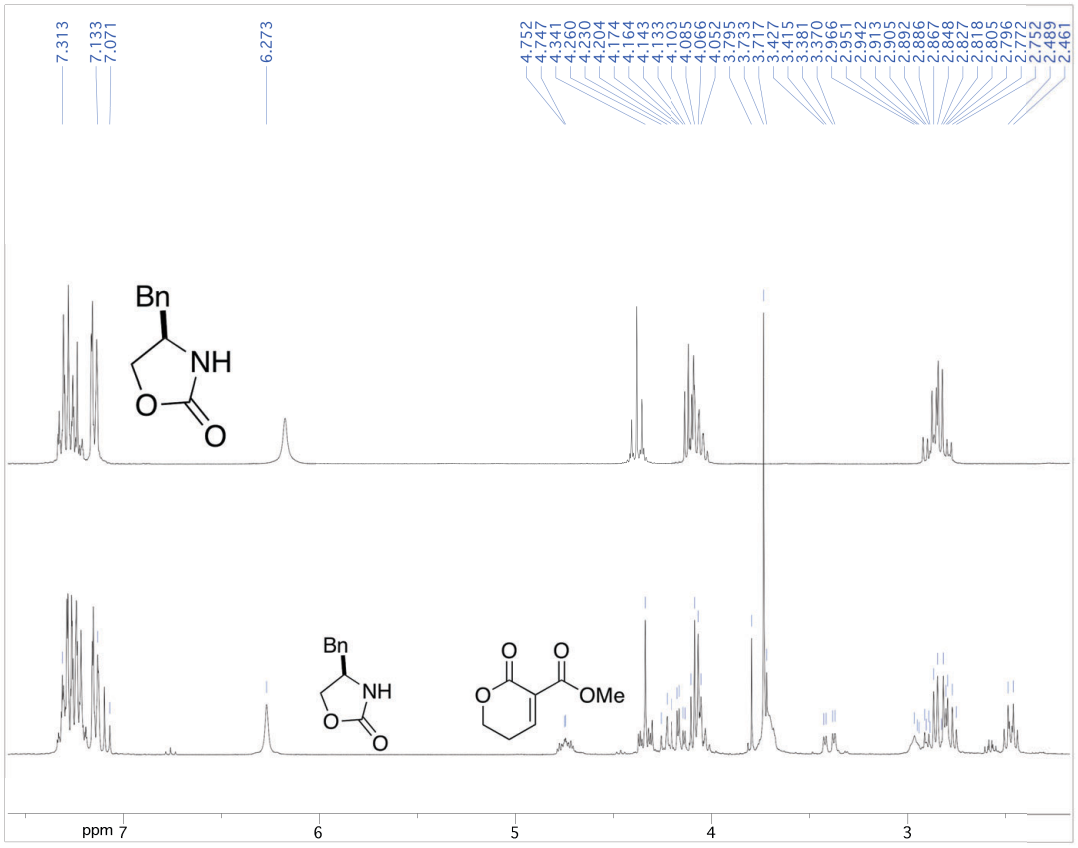


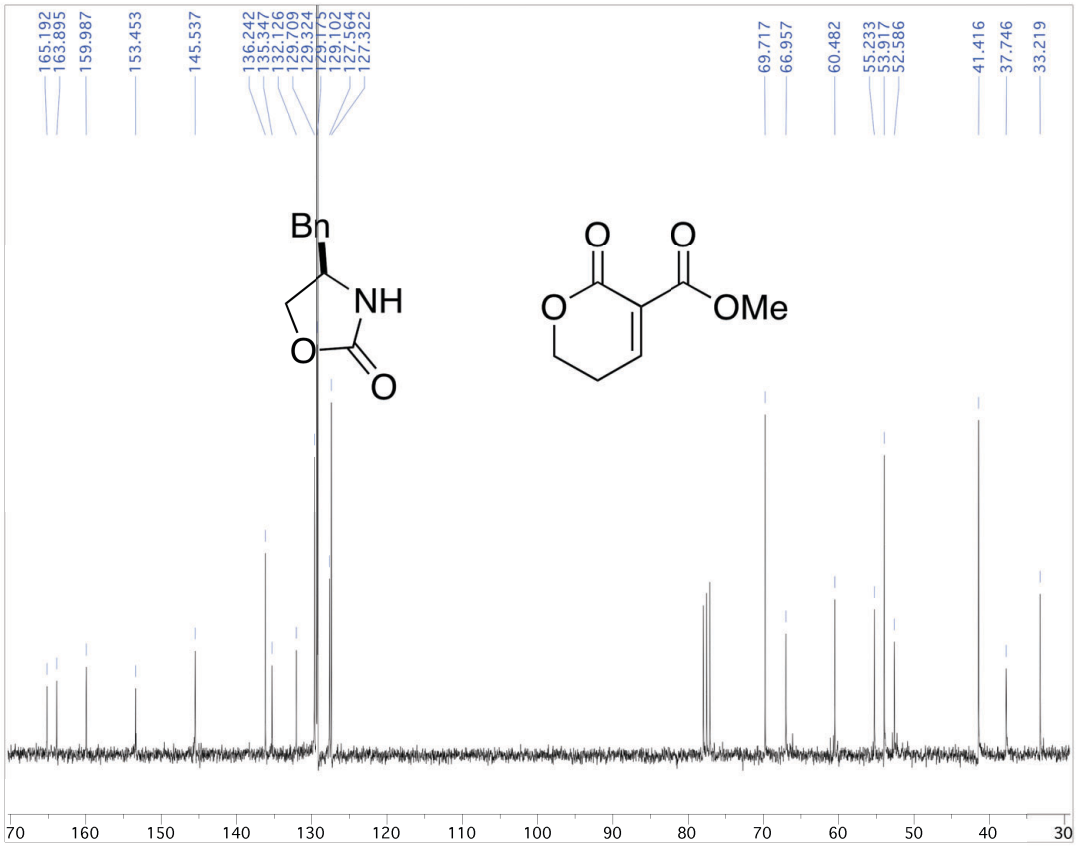
Synthesis of undesired lactone: To a 4 dram vial containing 372 mg (0.831 mmol, 1 equiv.) TBS ether **4.17** dissolved in 4.2 mL dry MeCN was added 250µL 48% aqueous HF and the reaction was allowed to stir for 3 hr at ambient temperature before being added to $NaHCO_{3(sat.)}$, extracted thrice with EtOAc, dried over Na_2SO_4, and concentrated. Silica gel flash chromatography eluting with 1 : 2 to 0 : 1 hex./EtOAc yielded 179 mg above describe product mixture as a colorless oil.

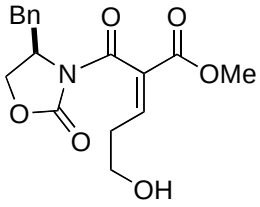
^{1}HNMR (300 MHz, $CDCl_3$) lactone δ 7.16-7.35 (m, 5H), 6.20 (bs, 1H), 4.41 (m, 1H), 4.10 (m, 2H), 2.89 (m, 2H); oxazolinone δ 7.07 (m, 1H), 4.75 (m, 1H), 4.13-4.23 (m,

2H), 3.73 (s, 3H), 3.40 (dd, J = 13.8, 3.6, 1H), 2.47 (m, 1H). ^{13}CNMR (75 MHz, $CDCl_3$) δ 165.2, 163.9, 160.0, 153.5, 145.5, 136.2, 135.3, 132.1, 129.7, 129.3, 129.2, 129.1, 127.6, 127.3, 69.7, 67.0, 60.5, 55.2, 53.9, 52.6, 41.4, 37.7, 33.2; R_f = 0.23 (1 : 2 hex./EtOAc)

Ref.: **BJEV117**.



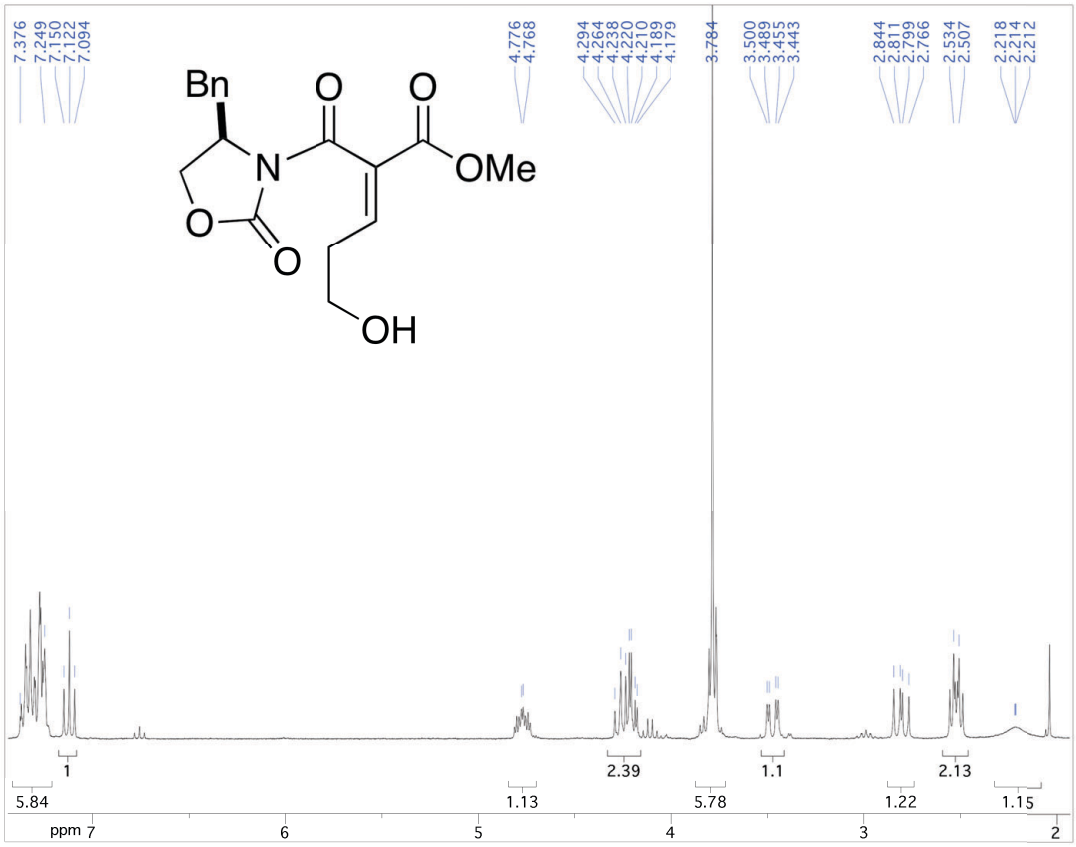


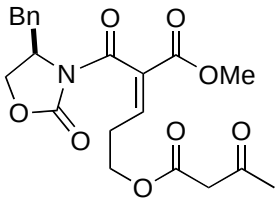


Synthesis of (*R*,*E*)-methyl 2-(4-benzyl-2-oxooxazolidine-3-carbonyl)-5-hydroxypent-2-enoate (4.18): To a 10 mL round-bottomed flask containing 50 mg (0.112 mmol, 1 equiv.) dissolved in 2.5 mL dry THF at 0°C was added 54 μL (0.670 mmol, 6 equiv.) pyridine followed by 1 mL of a 5% solution of HF in MeCN. The reaction was stirred at ambient temperature for 2.5 hr before being concentrated, taken up in EtOAc, washed once with $NaHCO_{3(sat.)}$, and passed through a short silica gel plug. Concentration yielded 35 mg (95%) of the desired product as a pale yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 7.25-7.38 (m, 5H), 7.12 (t, *J* = 8.4, 1H), 4.77 (m, 1H), 4.25 (q, *J* = 9.0, 1H), 4.20 (dd, *J* = 9.3, 3.0, 1H), 3.78 (s, 3H), 3.78 (m, 2H), 3.47 (dd, *J* = 13.5, 3.3, 1H), 2.80 (dd, *J* = 13.5, 9.9, 1H), 2.52 (m, 2H), 2.21 (bs, 1H); R_f = 0.15 (1 : 1 hex./EtOAc)

Ref.: BJEII176, BJEII177, BJEII181, BJEII198, **BJEII250**, BJEV121



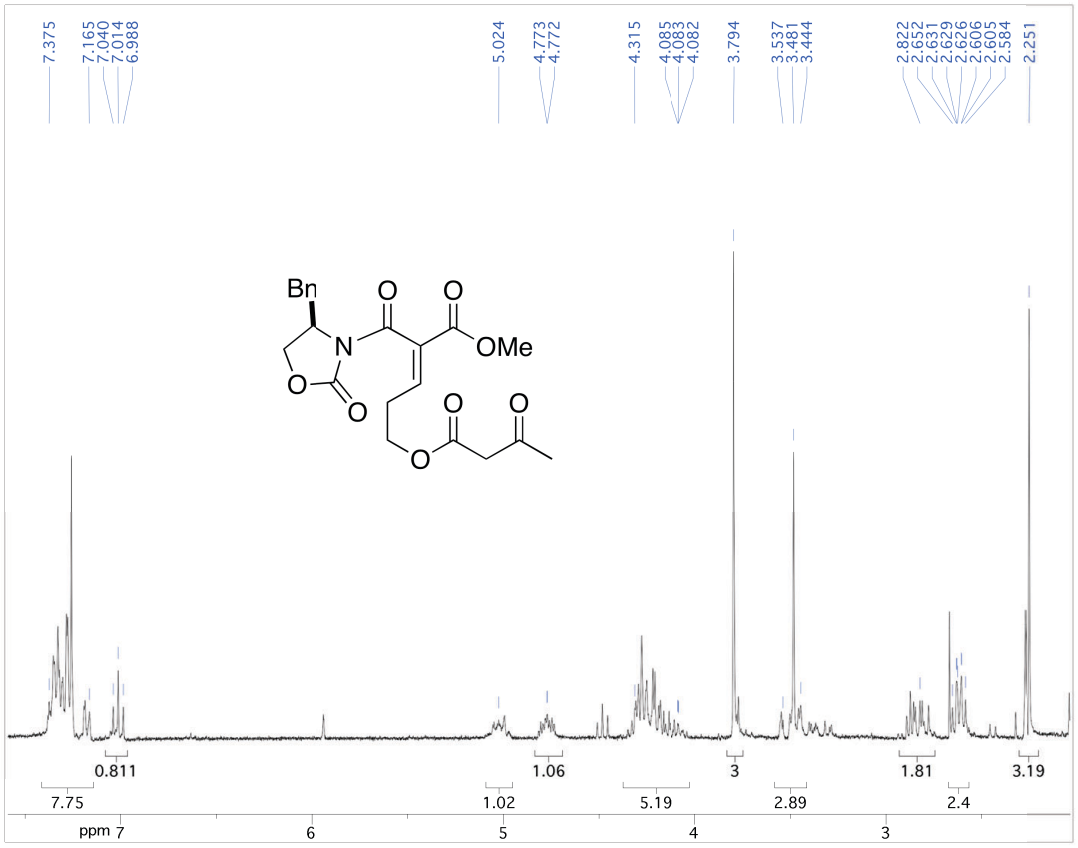


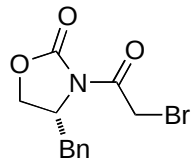
Synthesis **of (*R*,*E*)-methyl 2-(4-benzyl-2-oxooxazolidine-3-carbonyl)-5-((3-oxobutanoyl)oxy)pent-2-enoate (4.20):** To a 25 mL round-bottomed flask containing 375 mg (1.12 mmol, 1 equiv.) alcohol **4.18** dissolved in CH_2Cl_2 at 0^{o}C was added 217 μL

(2.81 mmol, 2.5 equiv.) diketene followed by 14 mg (0.112 mmol, 0.1 equiv.) DMAP. The reaction was stirred at ambient temperature for 1 hr before being added to brine, extracted into CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 1 : 1 to 1 : 2 hex./EtOAc to yield 351 mg (75%) of the desired product as a pale yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 7.17-7.38 (m, 5H), 7.01 (t, *J* = 7.8, 1H), 5.02 (m, 1H), 4.77 (m, 1H), 4.08-4.32 (m, 5H), 3.79 (s, 3H), 3.44-3.54 (m, 1H), 3.48 (s, 2H), 2.82 (m, 1H), 2.61 (q, *J* = 6.3, 2H), 2.25 (s, 3H); R_f = 0.29 (1 : 2 hex./EtOAc).

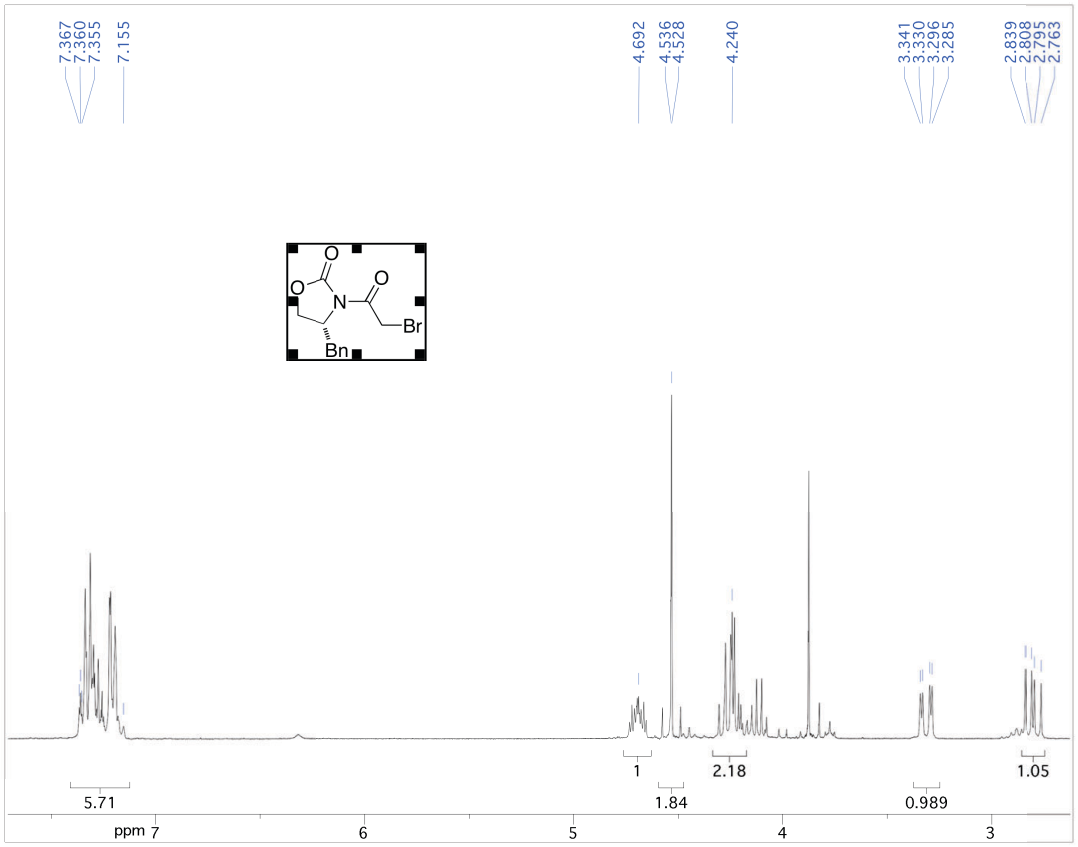
Ref.: **BJEV128**.





Synthesis of (*R*)-4-benzyl-3-(2-bromoacetyl)oxazolidin-2-one (4.21): To a 500 mL flame dried round-bottomed flask was charged 10.81 g (61.00 mmol, 1 equiv.) (*R*)-4-benzyloxazolidin-2-one followed by 240 mL dry THF. The reaction was cooled to -78^{o}C and 48.80 mL (1.6 M in hex., 73.21 mmol, 1.2 equiv.) *n*BuLi was added. The reaction was stirred at -78^{o}C for 45 min before the addition of 7.96 mL (91.50 mmol, 1.5 equiv.) bromoacetyl bromide. The reaction was stirred for a further 6 hr at -78^{o}C and was then allowed to warm to ambient temperature, added to $NH_4Cl_{(sat.)}$, extracted into EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 4 : 1 to 1 : 1 hex./EtOAc to yield 22.35 g (>99%) of the desired product as a red-brwon oil which was used without further purification. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.20-7.37 (m, 5H), 4.70 (m, 1H), 4.53 (d, *J* = 2.1, 2H), 4.25 (m, 2H), 3.32 (dd, *J* = 13.2, 3.3, 1H), 2.80 (dd, *J* = 13.5, 9.6, 1H); ^{13}CNMR (75MHz, $CDCl_3$) δ 166.2, 153.2, 134.9, 129,6, 129.3, 127.8, 66.9, 55.7, 37.7, 28.6; R_f = 0.24 (4 : 1 hex./Et OAc).

Ref.: BJEII275, BJEII278, BJEII281, BJEII471, BJEII453, BJEIV223, **BJEIV267**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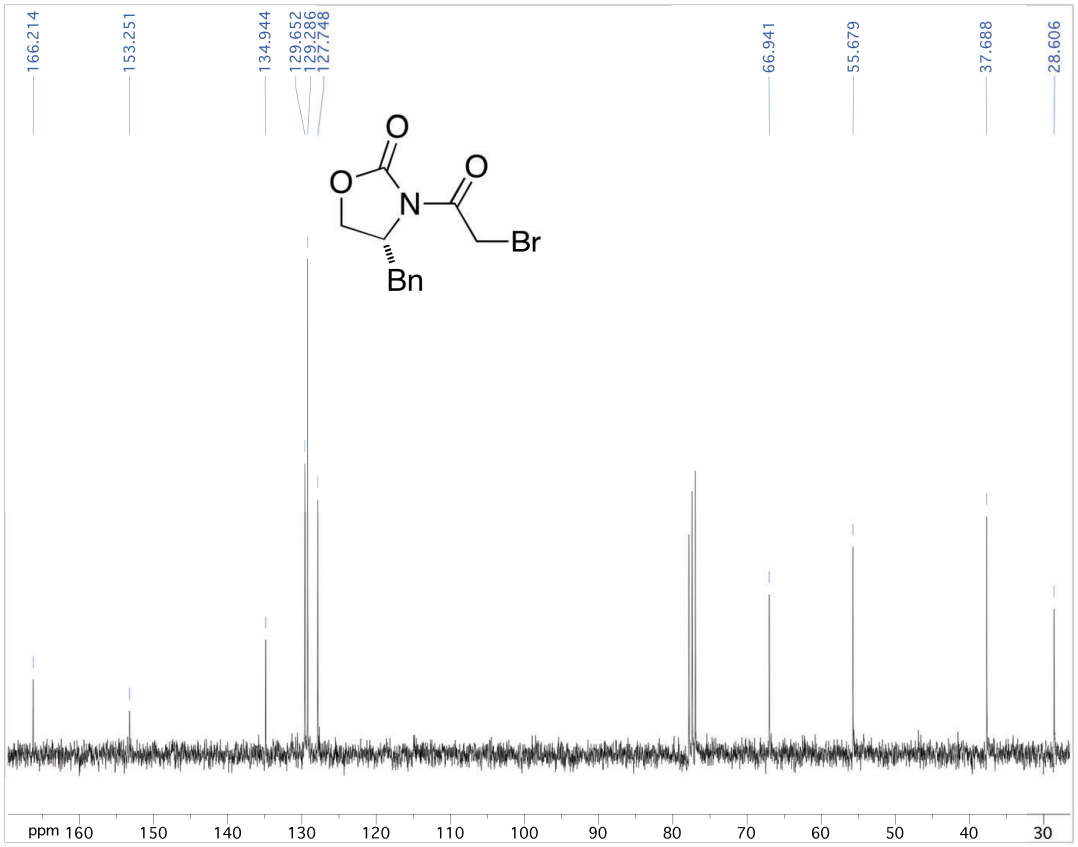
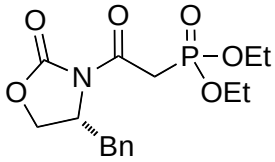


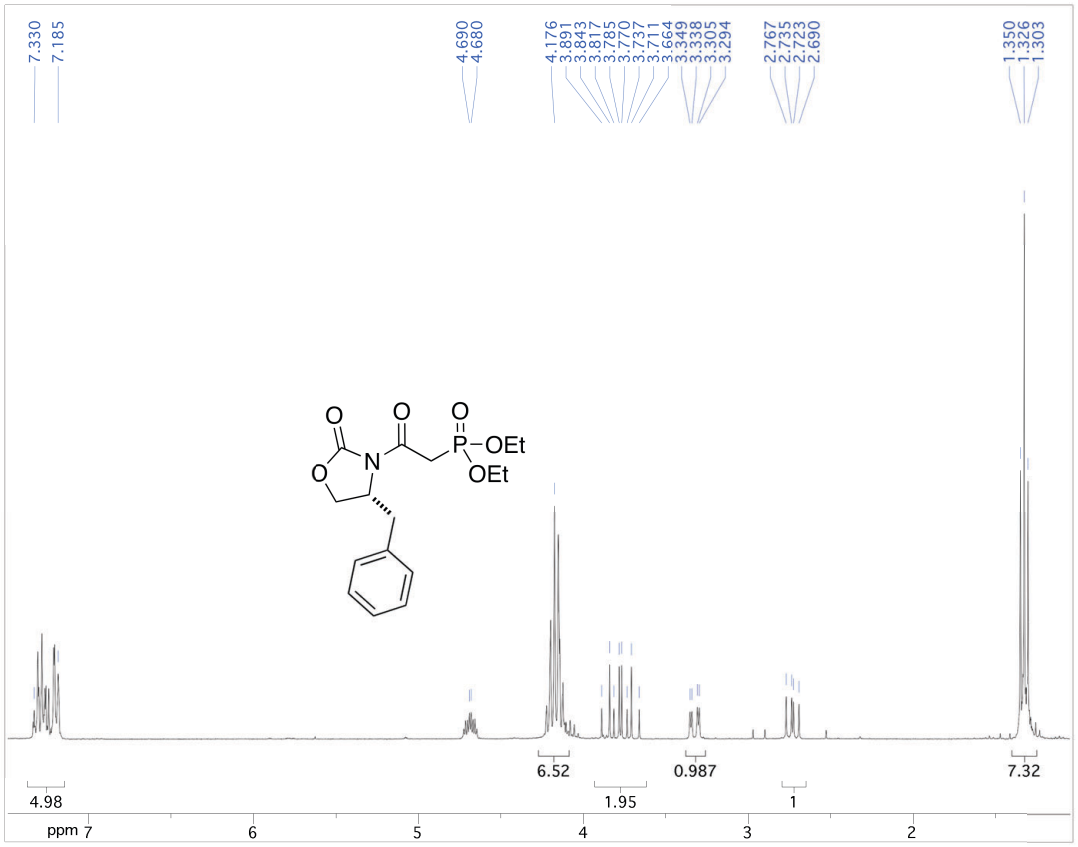


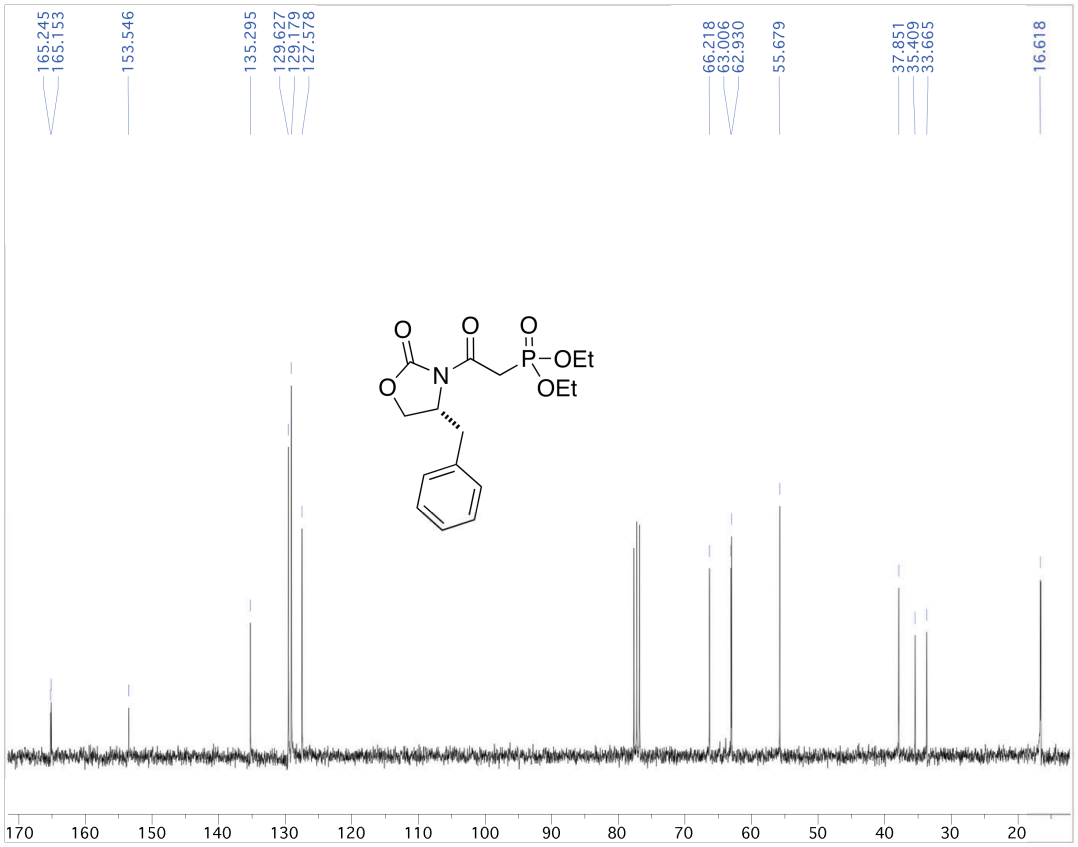
Synthesis of (*R*)-diethyl (2-(4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)phosphonate (4.22): To a 50 mL round bottomed flask containing 3.18 g (10.68 mmol, 1equiv.) bromide **4.21** was added 5.5 mL (32.04 mmol, 3 equiv.) $P(OEt)_3$ and the reaction was heated to 100°C for 15 min and then concentrated to yield 3.83 g (>99%) of the desired product as a thick orange oil which was used without further purification.

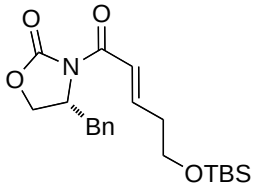
^{1}HNMR (300MHz, $CDCl_3$) δ 7.19-7.33 (m, 5H), 4.69 (m, 1H), 4.18 (m, 6H), 3.78 (m, 2H), 3.32 (dd, *J* = 13.2, 3.3, 1H), 2.73 (dd, *J* = 13.2, 9.76, 1H), 1.33 (t, *J* = 7.2, 6H); ^{13}CNMR (75MHz, $CDCl_3$) δ 165.2, 153.5, 135.3, 129.6, 129.2, 127.6, 66.2, 63.0, 55.7,

37.9, 35.4, 33.7, 16.6; HRMS (+TOF): $[M+H]^+$ 356.1263 calcd for $C_{15}H_{18}NO_4$, found: 356.1272. R_f = 0.40 (EtOAc)

Ref.: **BJEII402**, BJEII455, BJEIV230, BJEIV269





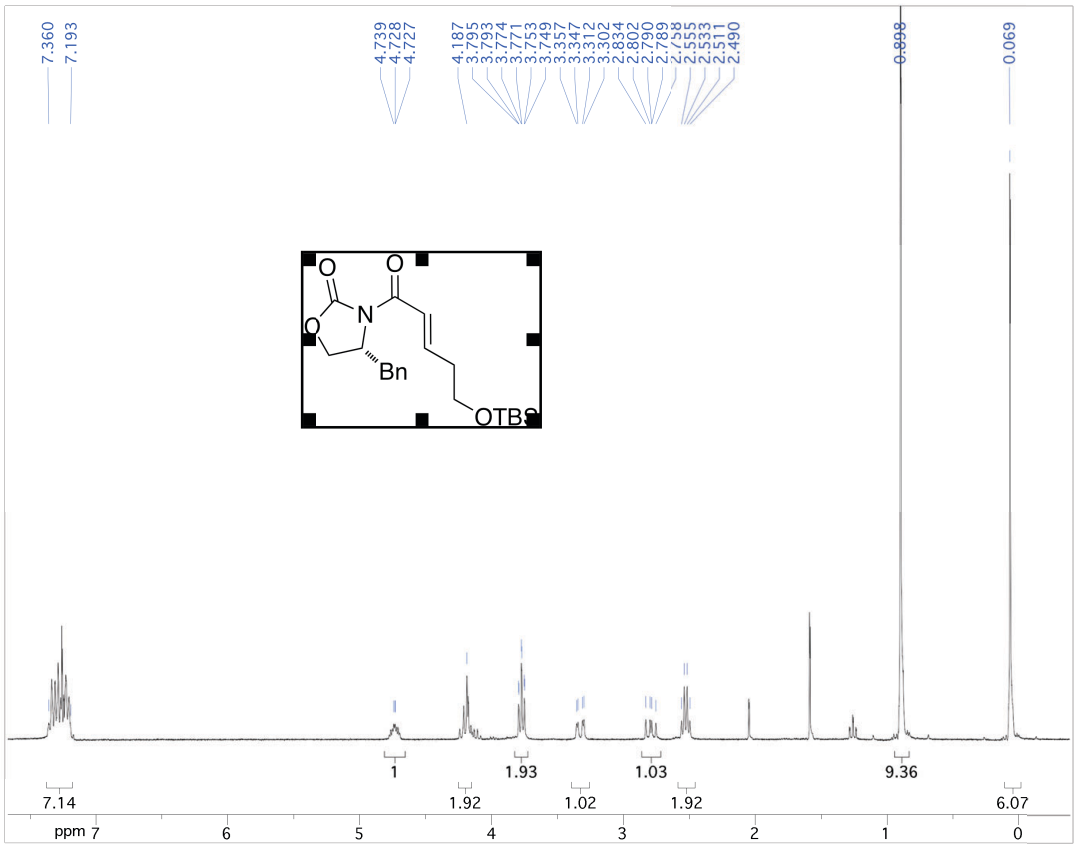


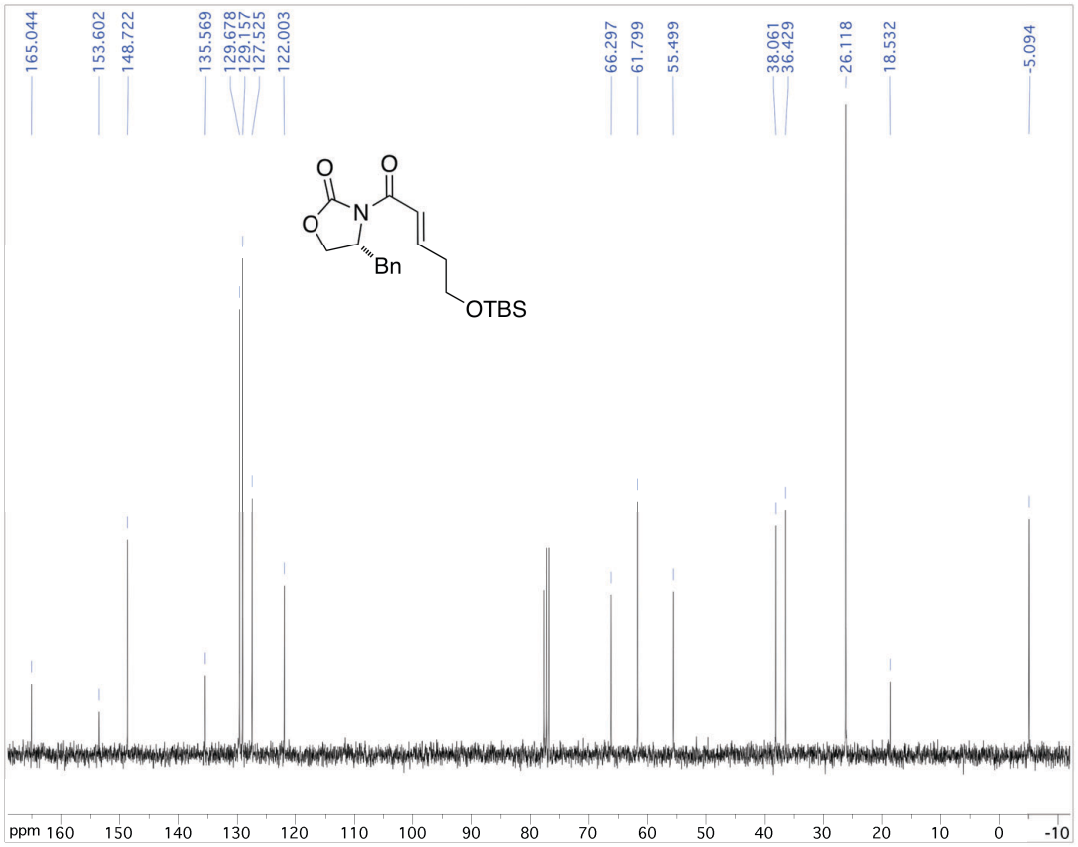
Synthesis of (*R*,*E*)-4-benzyl-3-(5-((*tert*-butyldimethylsilyl)oxy)pent-2-enoyl)oxazolidin-2-one (4.23): To a 250 mL round-bottomed flask containing 2.49 g (7.61 mmol, 1.2 equiv.) phosphonate **4.22** was added 75 mL dry MeCN followed by 323 mg (7.61 mmol, 1.2 equiv.) LiCl and then 1.10 mL (6.34 mmol, 1 equiv.) *i*Pr_2NEt. The reaction was stirred at ambient temperature for 15 min before the addition of 1.19 g (6.34 mmol, 1 equiv.) aldehyde **3.5** dissolved in 5 mL dry MeCN. After stirring at ambient temperature for 12 hr the reaction was added to brine, extracted into EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash

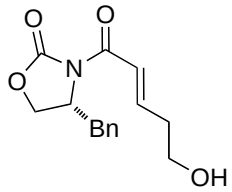
chromatography eluting with 1 : 1 hex./EtOAc to yield 2.12 g (86%) of the desired compound as a pale yellow oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.19-7.36 (m, 7H), 4.73 (m, 1H), 4.19 (m, 2H), 3.77 (t, *J* = 6.3, 2H), 3.33 (dd, *J* = 13.5, 3.0, 1H), 2.80 (dd, *J* = 13.5, 9.6, 1H), 2.52 (q, *J* = 6.6, 2H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}CNMR (75MHz, $CDCl_3$) δ 165.0, 153.6, 148.7, 135.6, 129.7, 129.2, 127.5, 122.0, 66.3, 61.8, 55.5, 38.1, 36.4, 26.1, 18.5, -5.1; R_f = 0.34 (4 : 1 hex./EtOAc).

Ref.: BJEII389, BJEII407, **BJEII423**, BJEIII024, BJEIII275, BJEIII350, BJEIII394, BJEIV418.



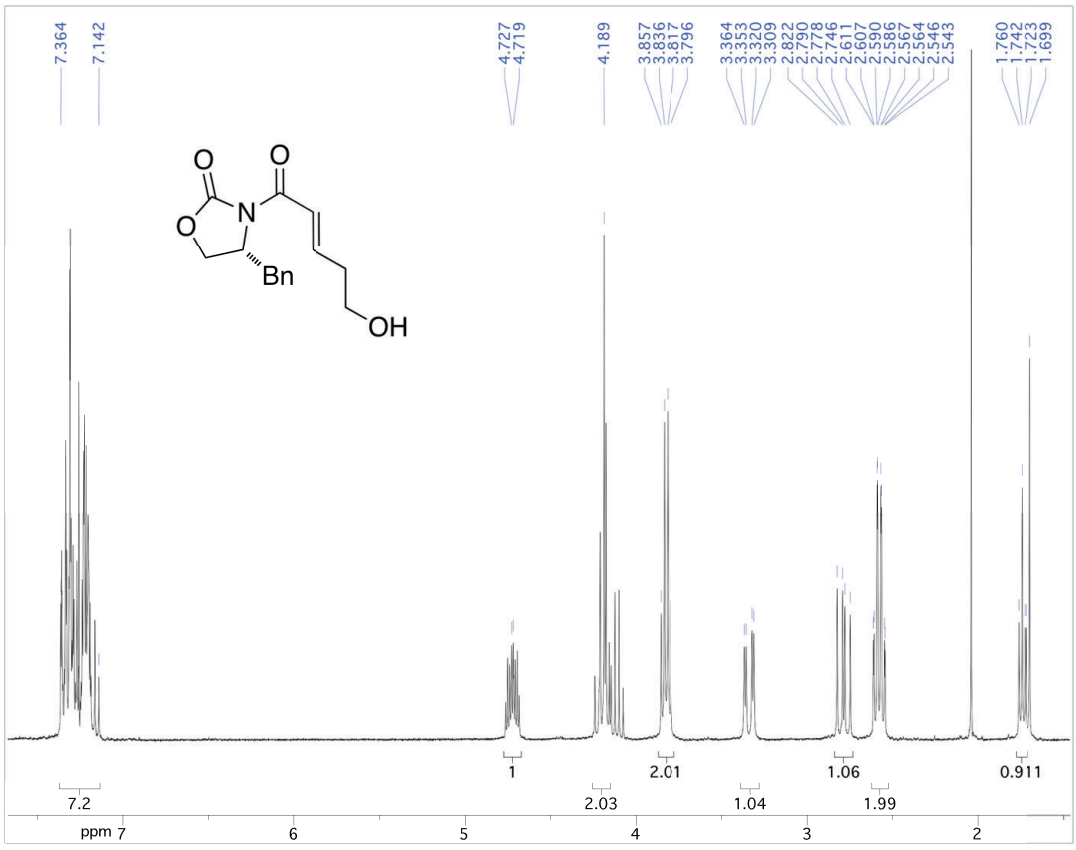


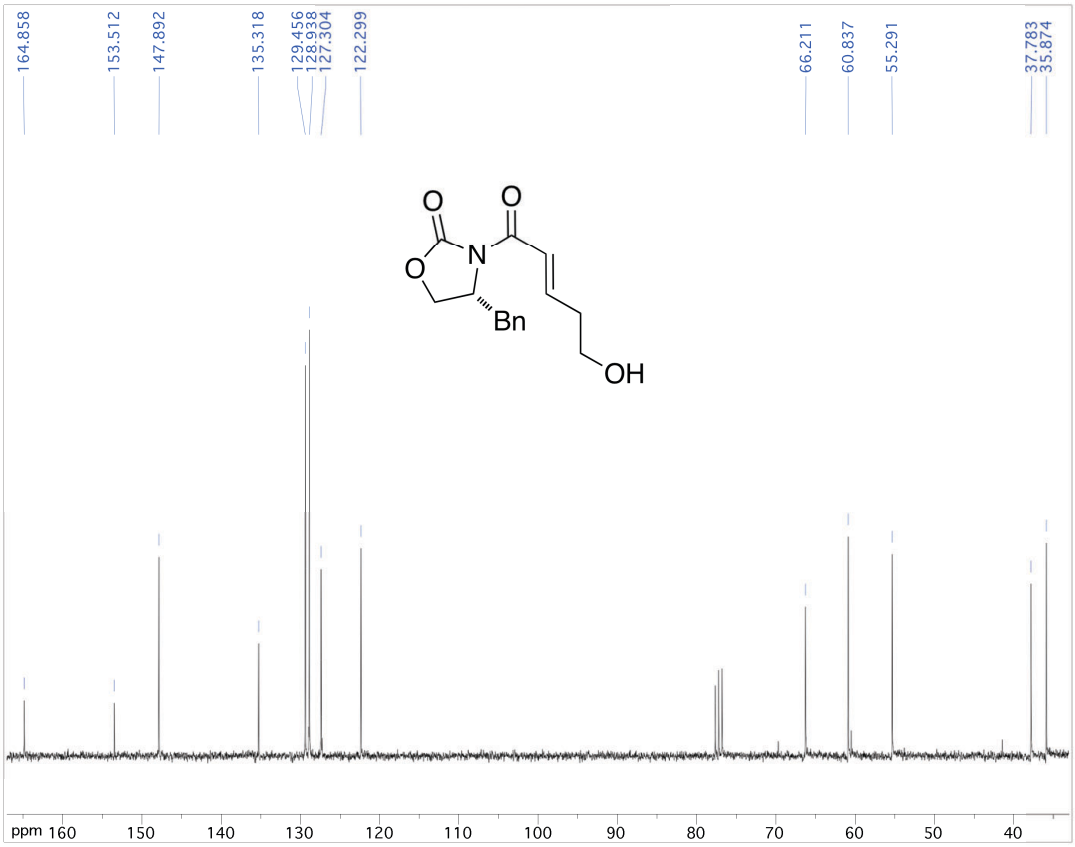


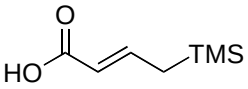
Synthesis of (*R*,*E*)-4-benzyl-3-(5-hydroxypent-2-enoyl)oxazolidin-2-one (4.24): To a 1 L HDPE bottle equipped with a stirbar was added 6.11 g (15.7 mmol, 1 equiv.) (*R*,*E*)-4-benzyl-3-(5-((*tert*-butyldimethylsilyl)oxy)pent-2-enoyl)oxazolidin-2-one (**4.23**) dissolved in 200 mL dry THF. To this solution was slowly added 7.84 mL of a 48% aqueous solution of HF and the reaction was allowed to stir at ambient temperature for 5 hr before being slowly added to $NaHCO_{3(sat.)}$ and extracted into EtOAc, dried over Na_2SO_4, and concentrated. Purification by silica gel flash chromatography eluting with 1 : 1 to 1 : 2 hex./EtOAc yielded 4.30 g (>99%) of the desired alcohol as a colorless oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.14-7.36 (m, 7H), 4.72 (m, 1H), 4.19 (m, 2H), 3.82 (q, *J* = 5.7, 2H), 3.34 (dd, *J* = 13.2, 3.3, 1H), 2.78 (dd, *J* = 13.2, 9.6, 1H), 2.57 (qd, *J* = 6.3, 1.2, 2H), 1.74 (t, *J* = 5.4, 1H), 1.70 (bs, 1H); ^{13}CNMR (75MHz, $CDCl_3$) δ 164.8, 153.5, 147.9, 135.3, 129.5, 128.9, 127.3, 122.3, 66.2, 60.8, 55.3, 37.8, 35.9; IR (NaCl, film): 3426, 1777, 1635 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 276.1236 calcd for $C_{15}H_{18}NO_4$, found: 276.1233; R_f = 0.19 (1 : 1 hex./EtOAc).

Ref.: BJEII403, BJEII442, BJEIII027, BJEIII170, BJEIII247, BJEIII279, BJEIII316, BJEIII352,**BJEIII395,** BJEIV241, BJEV261, BJEIV276, BJEIV277, BJEIV291,





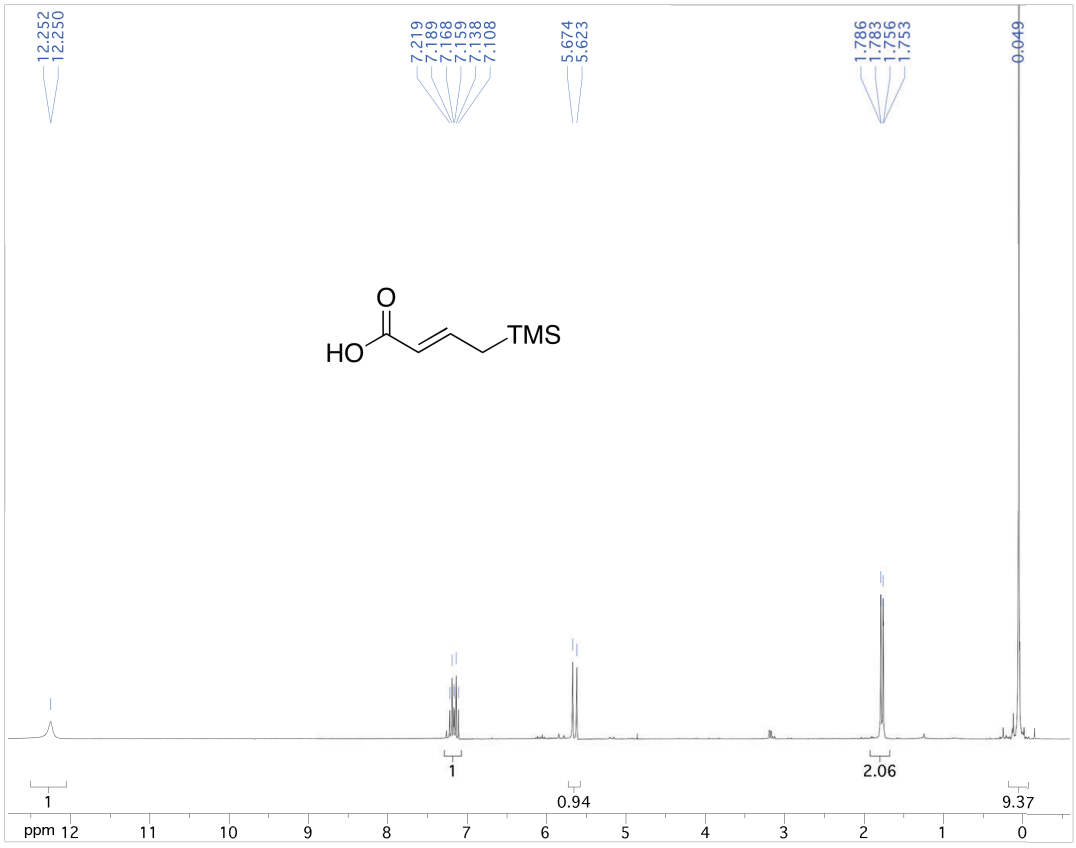


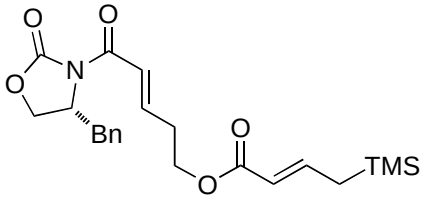
Synthesis of (*E*)-4-(trimethylsilyl)but-2-enoic acid (4.25): To a 250 mL flame dried round-bottomed flask was charged 75 mL dry THF and 24.94 mL of a 1 M solution of LiHMDS in THF (24.94 mmol, 2.2 equiv.) and then the solution was cooled to -78^{o}C. To this solution was added 1 mL (11.34 mmol, 1 equiv.) vinyl acetic acid. The reaction was stirred for 4.5 hr at -78^{o}C followed by the addition of 3.17 mL (24.94 mmol, 2.2 equiv.) TMSCl. After stirring for a further 2 hr at -78^{o}C the reaction was allowed to warm to ambient temperature over 16 hr and was then added to $NH_4Cl_{(sat.)}$, extracted into EtOAc, dried over $MgSO_4$, and concentrated. The crude residue was purified by silica gel flash

chromatography eluting with 9 : 1 to 4 : 1 hex./EtOAc to yield 799 mg (45%) of the desired product as a pale yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 12.25 (bs, 1H), 7.16 (dt, *J* = 15.3, 9.0, 1H), 5.25 (d, *J* = 15.3, 1H), 1.77 (dd, *J* = 9.0, 0.9, 2H), 0.05 (s, 9H); R_f = 0.29 (9 : 1 hex./EtOAc).

Ref.: BJII158, BJEII167, **BJEII195**, BJEII368

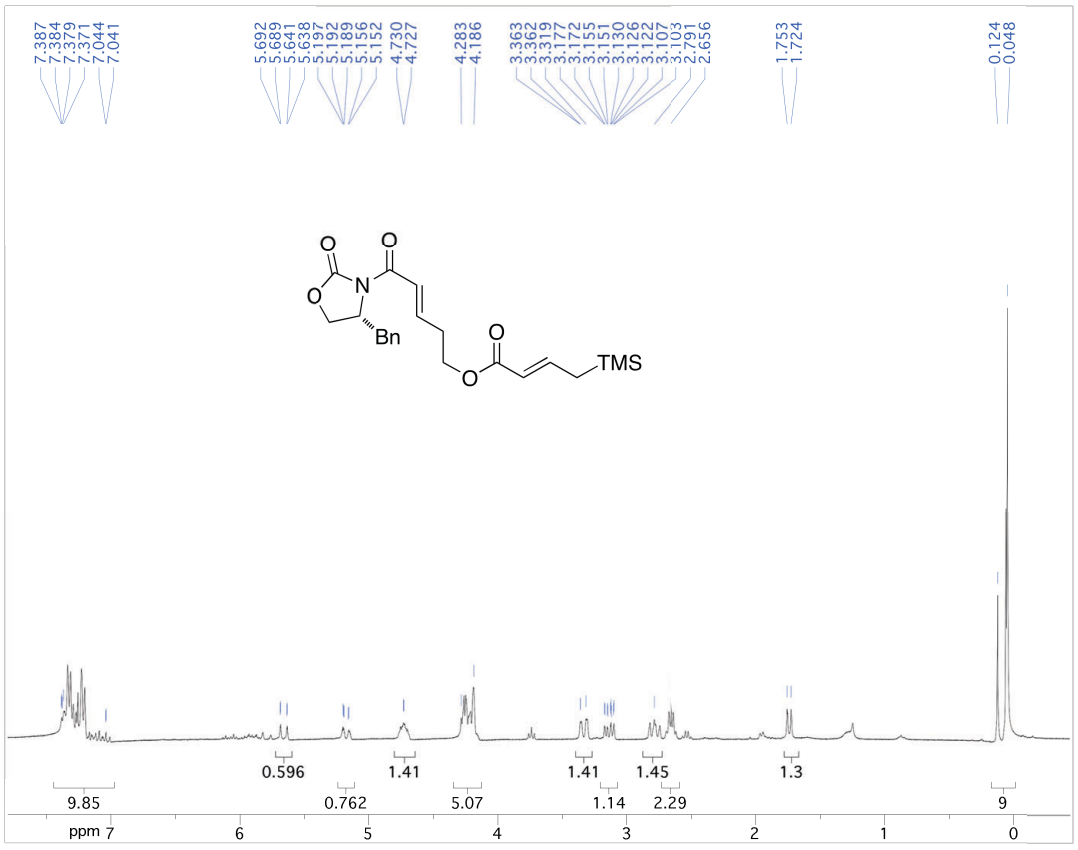


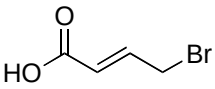


Synthesis of (*E*)-(*E*)-5-((*R*)-4-benzyl-2-oxooxazolidin-3-yl)-5-oxopent-3-en-1-yl 4-(trimethylsilyl)but-2-enoate (4.26): To a 25 mL round-bottomed flask containing 94 mg (0.596 mmol, 4 equiv.) acid **4.25** dissolved in 5 mL dry CH_2Cl_2 was added a single drop

of dry DMF followed by 52 μL (0.596 mmol, 4 equiv.) $(COCl)_2$ and the reaction was stirred for 2 hr at ambient temperature. The reaction was then concentrated to remove any excess $(COCl)_2$. To this crude acid chloride was added 41 mg (0.149 mmol, 1 equiv.) alcohol **4.24** dissolved in 2 mL dry CH_2Cl_2 followed by 13 μL (0.164 mmol, 1.1 equiv.) pyridine. The reaction was allowed to stir at ambient temperature for 6 hr before being added to NaHCO3(sat.), extracted into CH_2Cl_2, dried ove $MgSO_4$, and concentrated. The crude residue was purified by silica gel flash chromatography eluting with 4 : 1 to 1 : 1 hex./EtOAc to yield 30 mg (48%) of the desired product as a pale yellow oil.

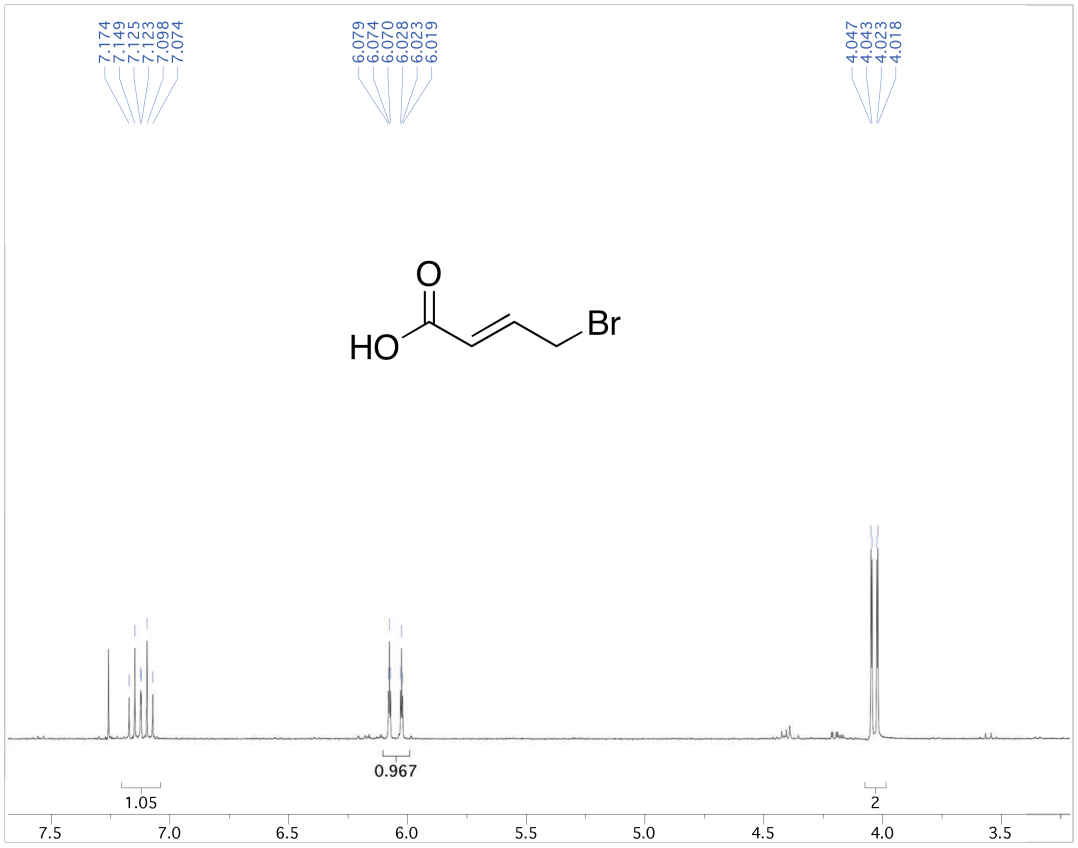
Ref.: BJEII388, **BJEII421**

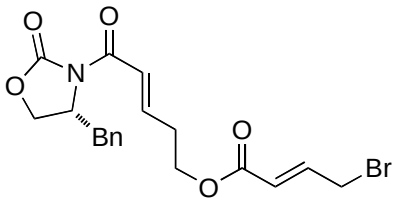




Synthesis of (*E*)-4-bromobut-2-enoic acid (4.30): To a flame dried 250 mL round-bottomed flask was added 50 mL dry toluene, 5.0 mL (37.0 mol, 1 equiv.) (*E*)-ethyl 4-bromobut-2-enoate, and then 38.0 mL (73.9 mmol, 2 equiv.) $(n\text{Bu}_3\text{Sn})_2\text{O}$. The reaction was heated to reflux for 4.5 hr, cooled to ambient temperature, washed thrice with $\text{NaHCO}_{3(\text{sat.})}$, acidified to pH < 1 with 1 M HCl, extracted into EtOAc, dried over MgSO_4, and concentrated to yield 4.38 g (72%) of the desired acid as a pale yellow solid. ^{1}HNMR (300 MHz, CDCl_3) δ 7.12 (dt, *J* = 15.3, 7.5, 1H), 6.05 (dt, *J* = 15.3, 1.2, 1H), 4.03 (dd, *J* = 7.2, 1.2, 2H); R_f = 0.24 (4 : 1 : 1 hex./EtOAc/HOAc)

Ref.: BJEII240, **BJEII244**

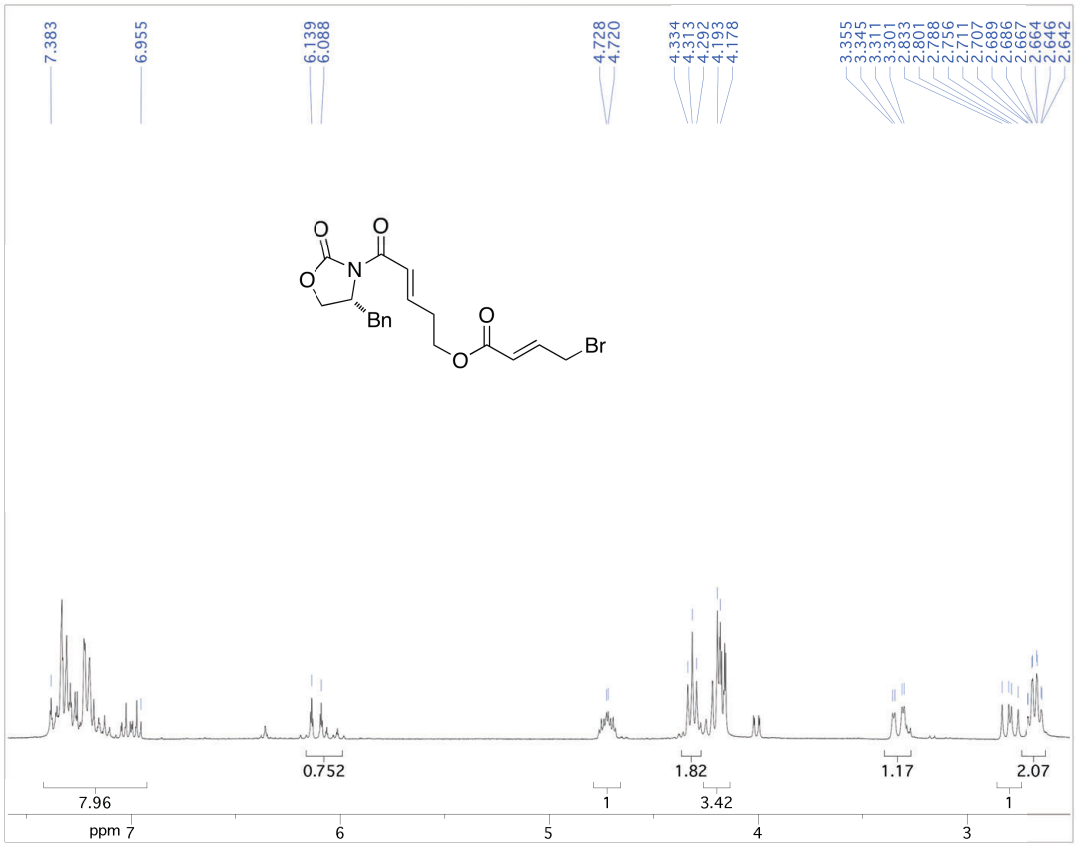




Synthesis of (*E*)-(*E*)-5-((*R*)-4-benzyl-2-oxooxazolidin-3-yl)-5-oxopent-3-en-1-yl 4-bromobut-2-enoate (4.31): To a 50 mL round-bottomed flask containing 196 mg (1.19 mmol, 4 equiv.) acid **4.30** dissolved in 10 mL dry CH_2Cl_2 was added a single drop of dry DMF followed by 104 μL (1.19 mmol, 4 equiv.) $(COCl)_2$ and the reaction was stirred for 2 hr at ambient temperature. The reaction was then concentrated to remove any excess $(COCl)_2$. To this crude acid chloride was added 82 mg (0.298 mmol, 1 equiv.) alcohol **4.24** dissolved in 4 mL dry CH_2Cl_2 followed by 96 μL pyridine. The reaction was allowed to stir at ambient temperature for 6 hr before being added to $NaHCO_{3(sat.)}$, extracted into CH_2Cl_2, dried ove $MgSO_4$, and concentrated. The crude residue was purified by silica gel flash chromatography eluting with 4 : 1 to 2 : 1 hex./EtOAc to yield 49 mg (39%) of the desired product (3.1 : 1 *E/Z* mixture) as a pale yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 6.96-7.38 (m, 8H), 6.11 (d, *J* = 15.3, 1H), 4.72 (m, 1H), 4.31 (t, *J* = 6.3, 2H), 4.18 (m, 3H), 3.32 (dd, *J* = 13.2, 3.0, 1H), 2.79 (dd, *J* = 13.5, 9.6, 1H), 2.67 (qd, *J* = 6.6, 1.2, 2H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 165.6, 164.8, 153.6, 146.3, 142.6, 135.5, 129.7, 129.2, 127.6, 123.8, 123.0, 66.4, 62.8, 55.5, 42.7, 38.0, 32.0; R_f = 0.56 (1 : 1 hex./EtOAc).

Ref.: BJEII398, BJEII405, BJEII409**, BJEII420**, BJEII428, BJEII430, BJEII432.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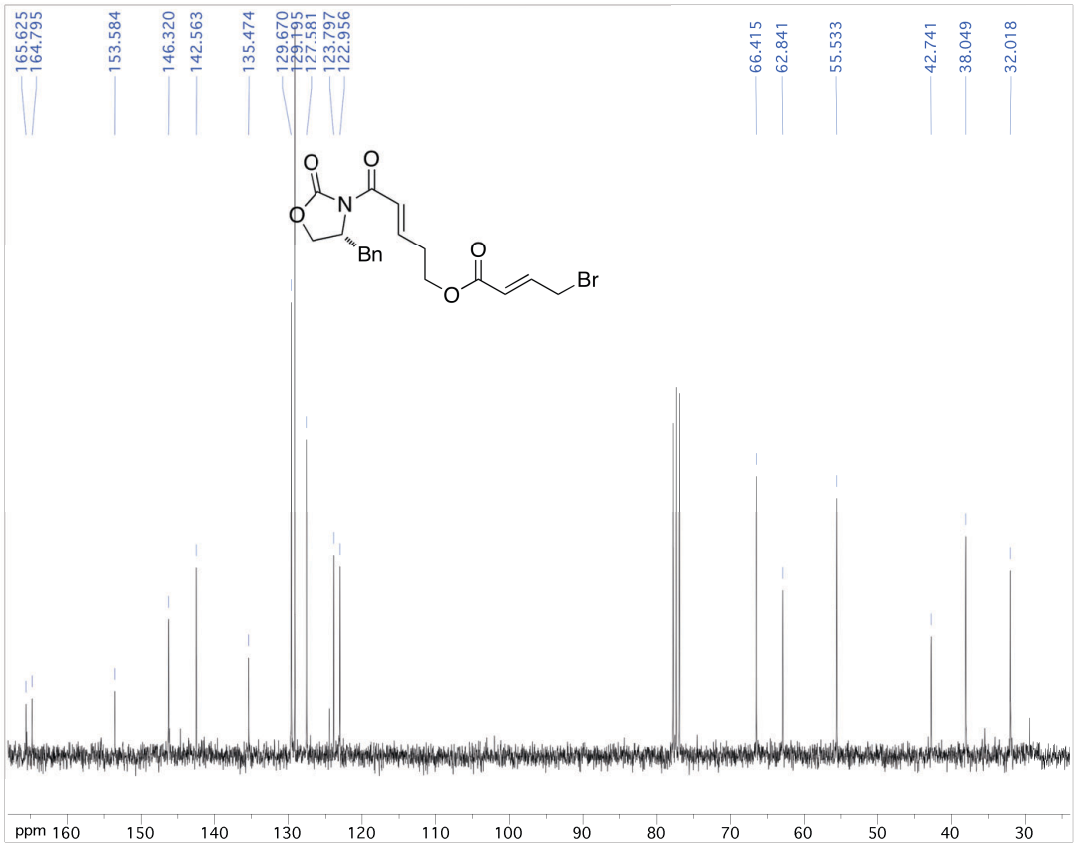
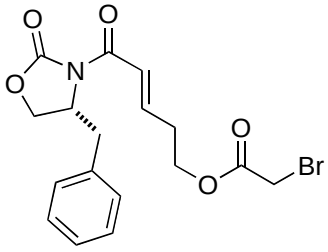


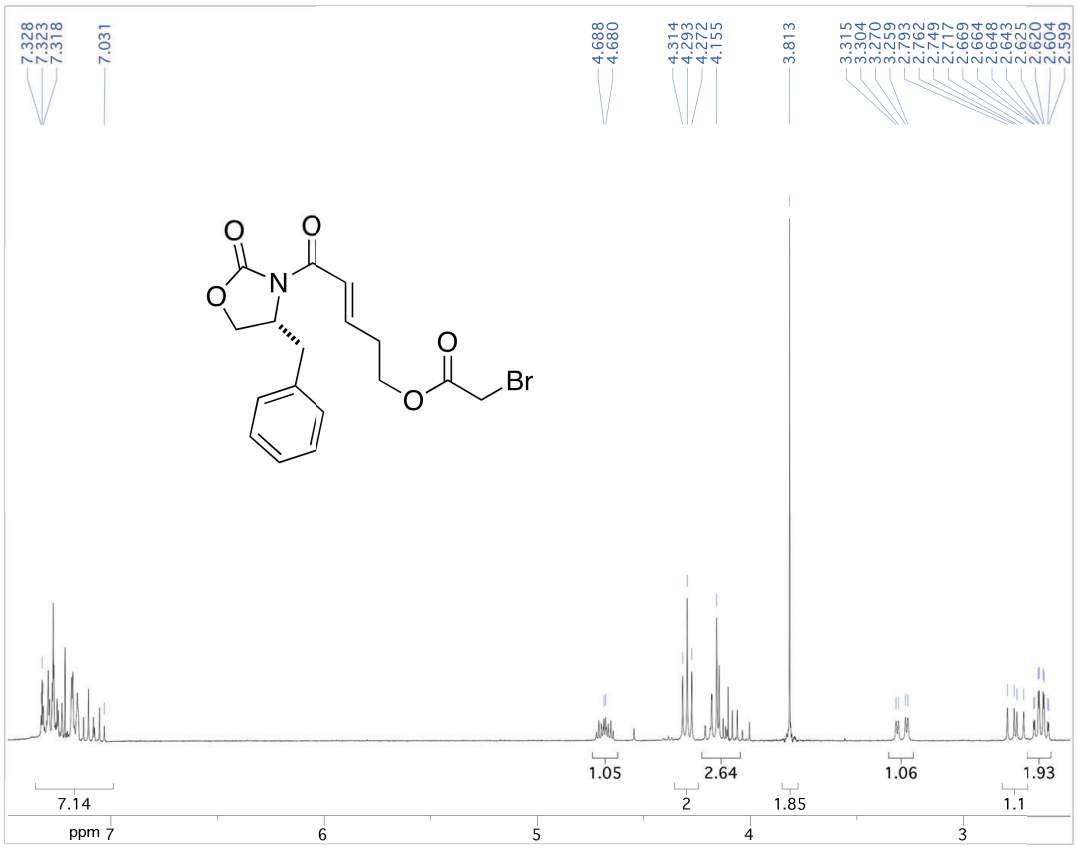


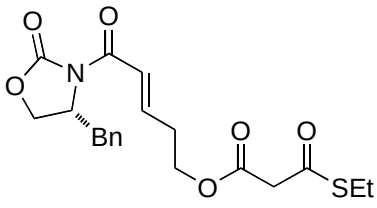
Synthesis of (*R*,*E*)-5-(4-benzyl-2-oxooxazolidin-3-yl)-5-oxopent-3-en-1-yl 2-bromoacetate (4.32): To a 250 mL round-bottomed flask containing 2.95 g (10.72 mmol, 1 equiv.) alcohol **4.24** dissolved in 50 mL dry THF at 0°C was added 1.12 mL (12.86 mmol, 1.2 equiv.) bromoacetyl bromide followed by 1.79 mL (12.86 mmol, 1.2 equiv.) dry NEt_3. The reaction was allowed to stir for 30 min at ambient temperature before being added to $NaHCO_{3(sat.)}$ and extracted thrice with EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was taken up in 1 : 2 hex./EtOAc and passed

through a short silica gel plug. Concentration yielded 4.40 g (95%) of the desired product as a brown oil which was used without further purification.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.03-7.32 (m, 7H), 4.68 (m, 1H), 4.29 (t, *J* = 6.3, 2H), 4.16 (m, 2H), 3.81 (s, 2H), 3.29 (dd, *J* = 13.5, 3.3, 1H), 2.72 (dd, *J* = 13.2, 9.3, 1H), 2.63 (qd, *J* = 6.3, 1.5, 2H).

Ref.: BJEIV278, BJEIV287, **BJEIV294.**



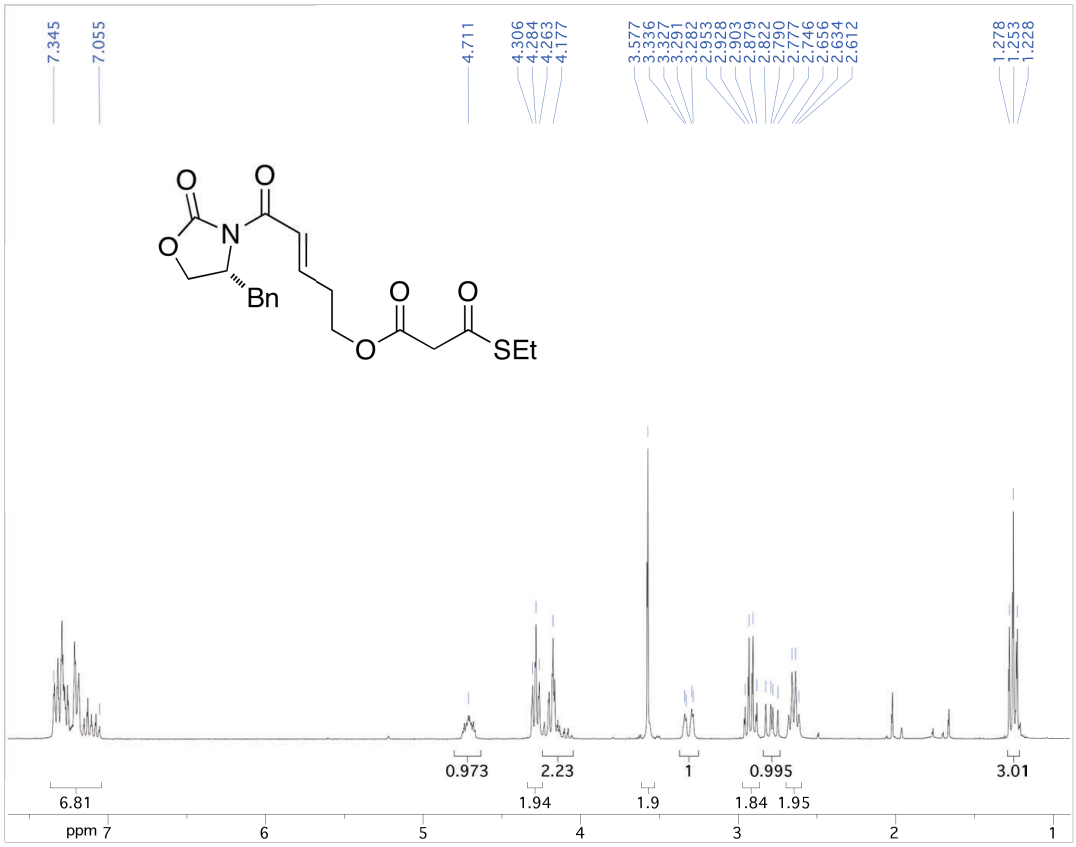


Synthesis of (*R*,*E*)-5-(4-benzyl-2-oxooxazolidin-3-yl)-5-oxopent-3-en-1-yl 3-(ethylthio)-3-oxopropanoate (4.36): To a 100 mL round-bottomed flask containing 550

mg (2.00 mmol, 1 equiv.) alcohol **4.24** and 326 mg (2.20 mmol, 1.1 equiv.) acid **4.35** dissolved in 20 mL dry CH_2Cl_2 was added 454 mg (2.20 mmol, 1.1 equiv.) DCC. The reaction was stirred at ambient temperature for 1.5 hr before being filtered through celite and concentrated. The crude residue was purified by silica gel flash chromatography eluting with 2 : 1 hex./EtOAc to yield 768 mg (92%) of the desired product as a yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 7.06-7.35 (m, 7H), 4.71 (m, 1H), 4.28 (t, *J* = 6.6, 2H), 4.18 (m, 2H), 3.58 (s, 2H), 3.31 (dd, *J* = 13.5, 2.7, 1H), 2.91 (q, *J* = 7.5, 2H), 2.78 (dd, *J* = 13.5, 9.6, 1H), 2.64 (q, *J* = 6.6, 2H), 1.25 (t, *J* = 7.5, 3H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 191.3, 166.2, 164.7, 153.6, 145.8, 135.5, 129.7, 129.2, 127.6, 123.1, 66.4, 63.6, 55.5, 49.6, 38.0, 31.8, 24.2, 14.7; R_f = 0.42 (2 : 1 hex./EtOAc).

Ref.: BJEIII246, **BJEIII248**, BJEIII284, BJEIII354, BJEIII397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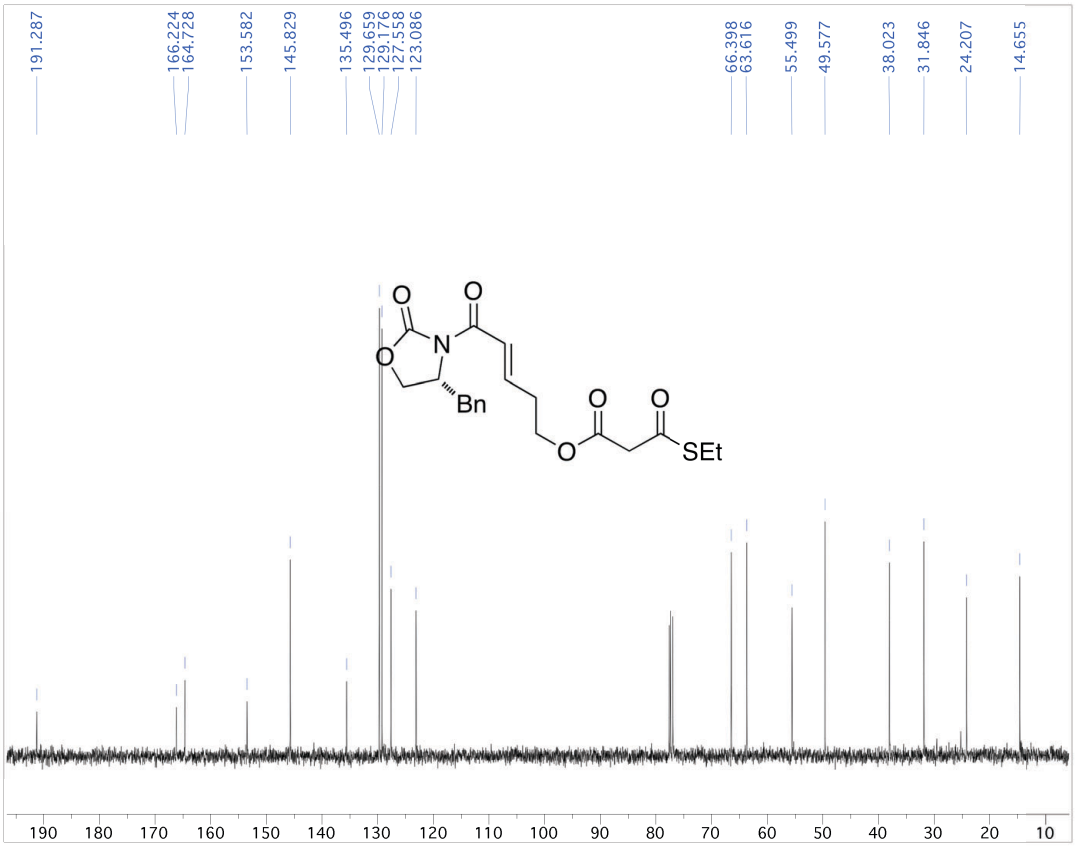
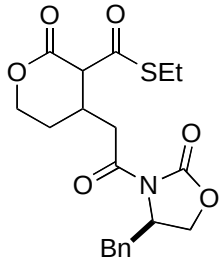


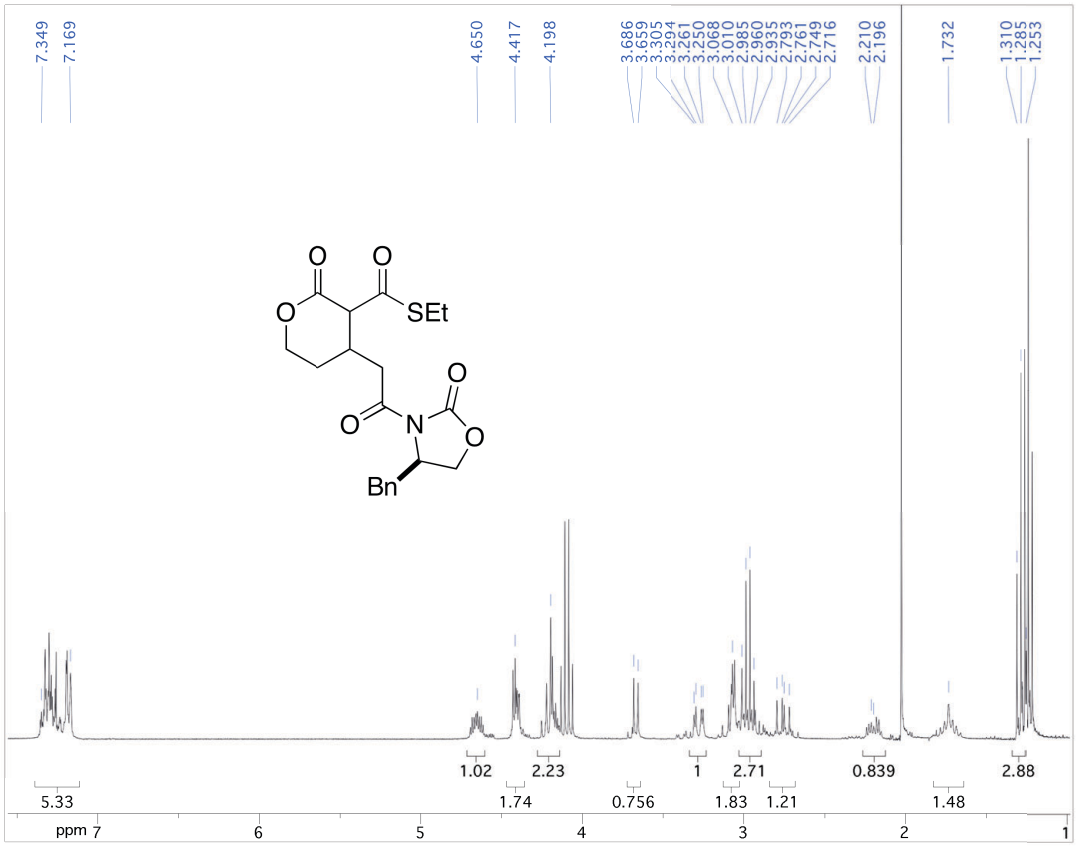


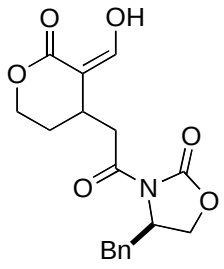
Synthesis of *S*-ethyl 4-(2-((*R*)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)-2-oxotetrahydro-2*H*-pyran-3-carbothioate (4.37): To a 250 mL round-bottomed flask containing 5.67 g (14.0 mmol, 1 equiv.) thioester **4.36** dissolved in 125 mL dry MeCN was added 2.28 g (6.99 mmo, 0.5 equiv.) Cs_2CO_3 and the reaction was stirred for 3 hr at ambient temperature before being concentrated to approximately 33% volume, added to 1 M HCl, extracted thrice with EtOAc, dried over Na_2SO_4, and concentrated. The resulting

residue was purified by silica gel flash chromatography eluting with 2 : 1 to 1 : 1 hex./EtOAc to yield 4.60 g (81%) of the desired product as a yellow foam.

^{1}HNMR (300 MHz, $CDCl_3$) δ 7.17-7.35 (m, 5H), 4.65 (m, 1H), 4.42 (m, 2H), 4.20 (m, 2H), 3.67 (d, *J* = 8.1, 1H), 3.27 (dd, *J* = 13.2, 3.3, 1H), 3.07 (m, 2H), 2.97 (q, *J* = 7.5, 2H), 2.96 (m, 1H), 2.75 (dd, *J* = 13.2, 9.6, 1H), 2.20 (m, 1H), 1.73 (m, 1H), 1.29 (t, *J* = 7.5, 3H); R_f = 0.30 (1 : 1 hex./EtOAc)

Ref.: BJEIII356, **BJEIII401**.

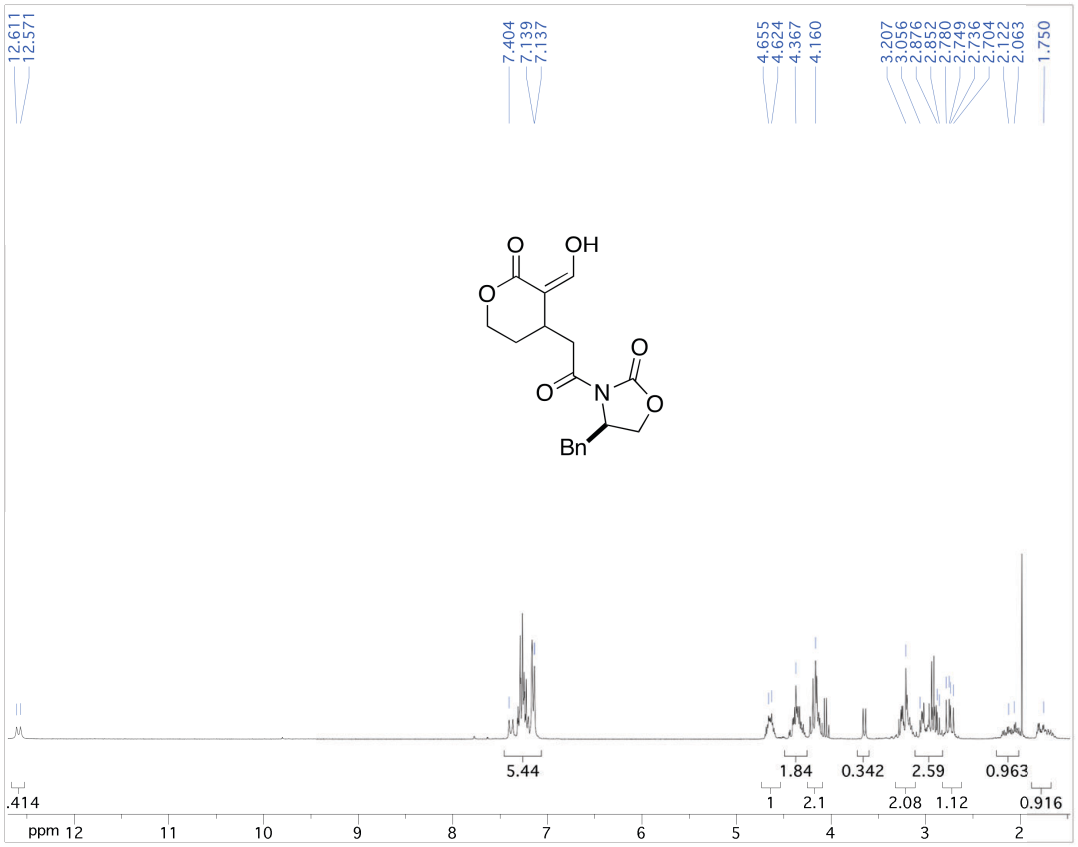




Synthesis of (4*R*)-4-benzyl-3-(2-((*Z*)-3-(hydroxymethylene)-2-oxotetrahydro-2*H*-pyran-4-yl)acetyl)oxazolidin-2-one: To a 250 mL round bottomed flask containing 4.60 g (11.4 mmol, 1 equiv.) thioester **4.37** dissolved in 100 mL acetone was added 6.03 g (5.67 mmol, 0.5 equiv) 10% Pd/C followed by 18.13 mL (113.5 mmol, 10 equiv.) triethylsilane. The reaction was stirred at ambient temperature for 16 hr before being filtered through celite and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 2 : 1 to 1 : 1 hex./EtOAc to yield 3.76 g (96%) of the desired product as a light pink oil.

^{1}HNMR (300 MHz, $CDCl_3$) major tautomer δ 12.59 (d, *J* =12.0, 1H), 7.14-7.40 (m, 5H), 4.64 (m, 1H), 4.37 (m, 2H), 4.16 (m, 2H), 3.21 (m, 2H), 2.85-3.06 (m, 2H), 2.74 (dd, *J* = 13.5, 9.6, 1H), 2.09 (m, 1H), 1.75 (m, 1H); ^{13}CNMR (75 MHz, $CDCl_3$) major tautomer δ 171.7, 171.1, 165.7, 153.7, 135.2, 129.6, 129.2, 127.7, 101.4, 66.7, 65.8, 55.3, 41.2, 38.1, 28.7, 27.4; R_f = 0.29 (1 : 1 hex./EtOAc).

Ref.: BJEIII385, BJEIII365, BJEIII378, **BJEIII402**.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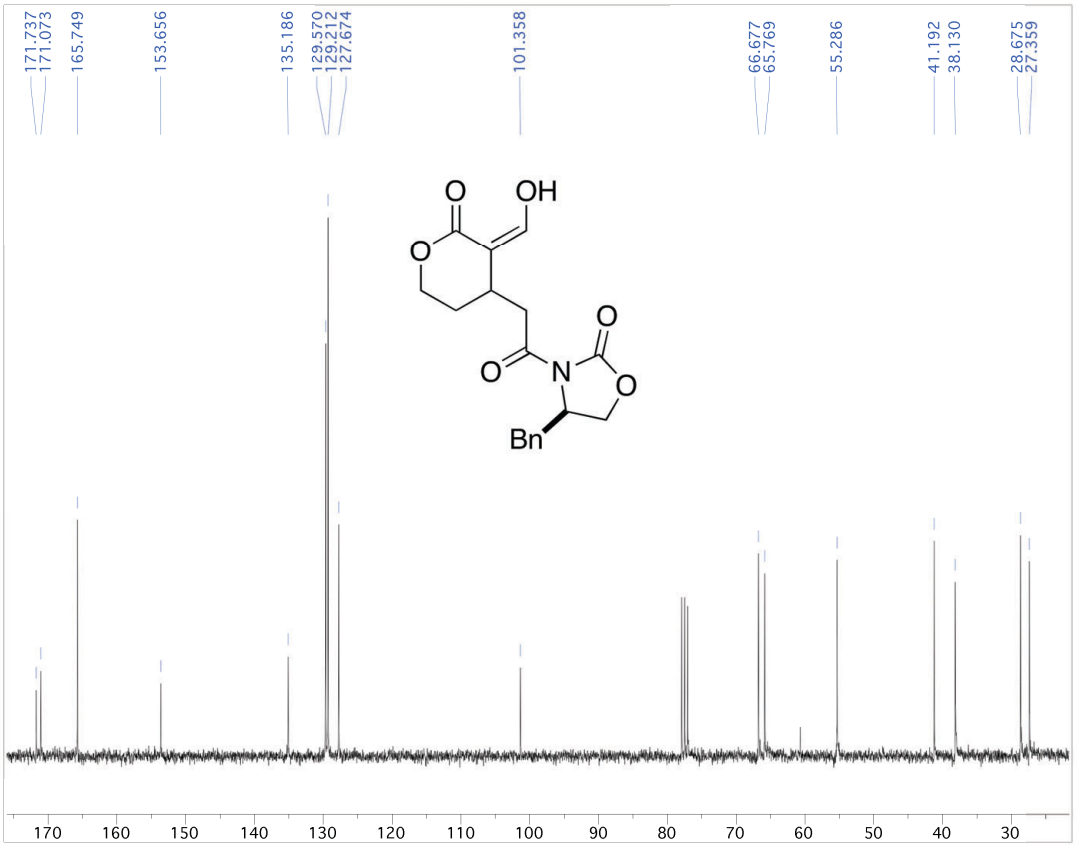
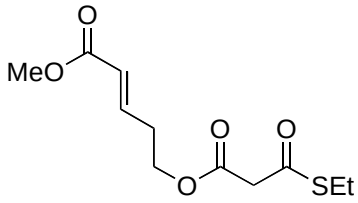


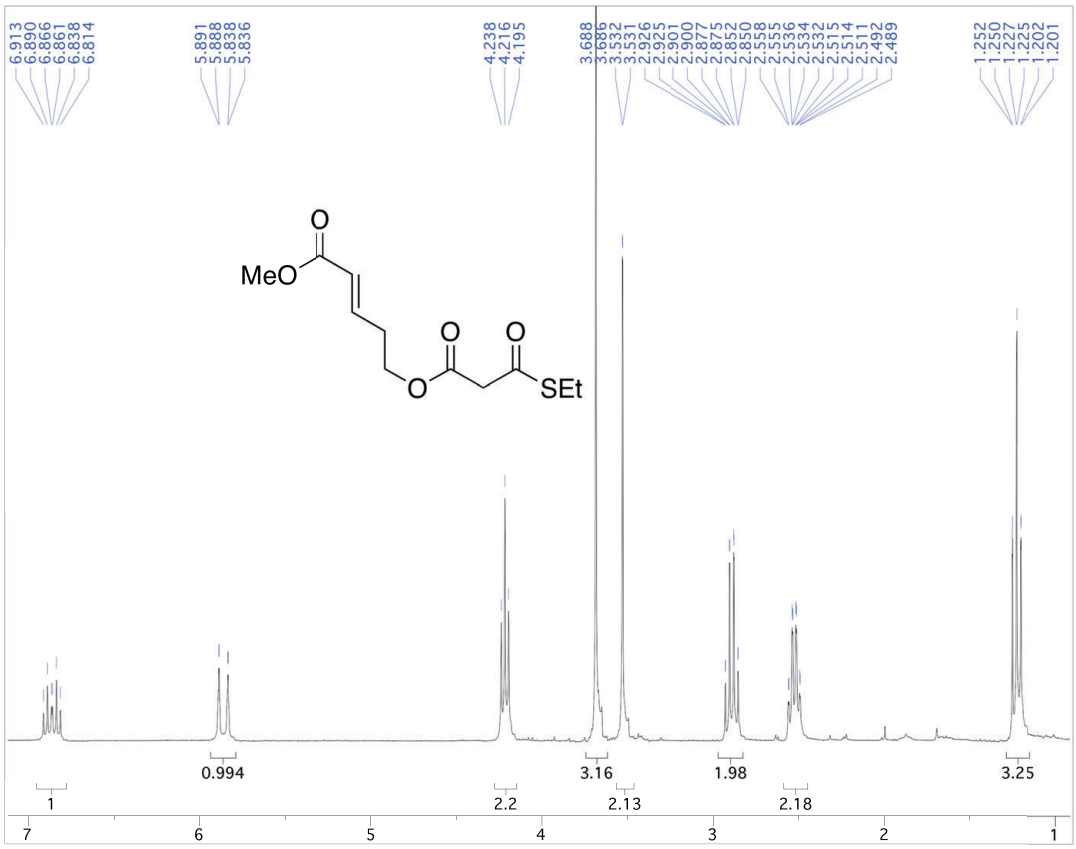


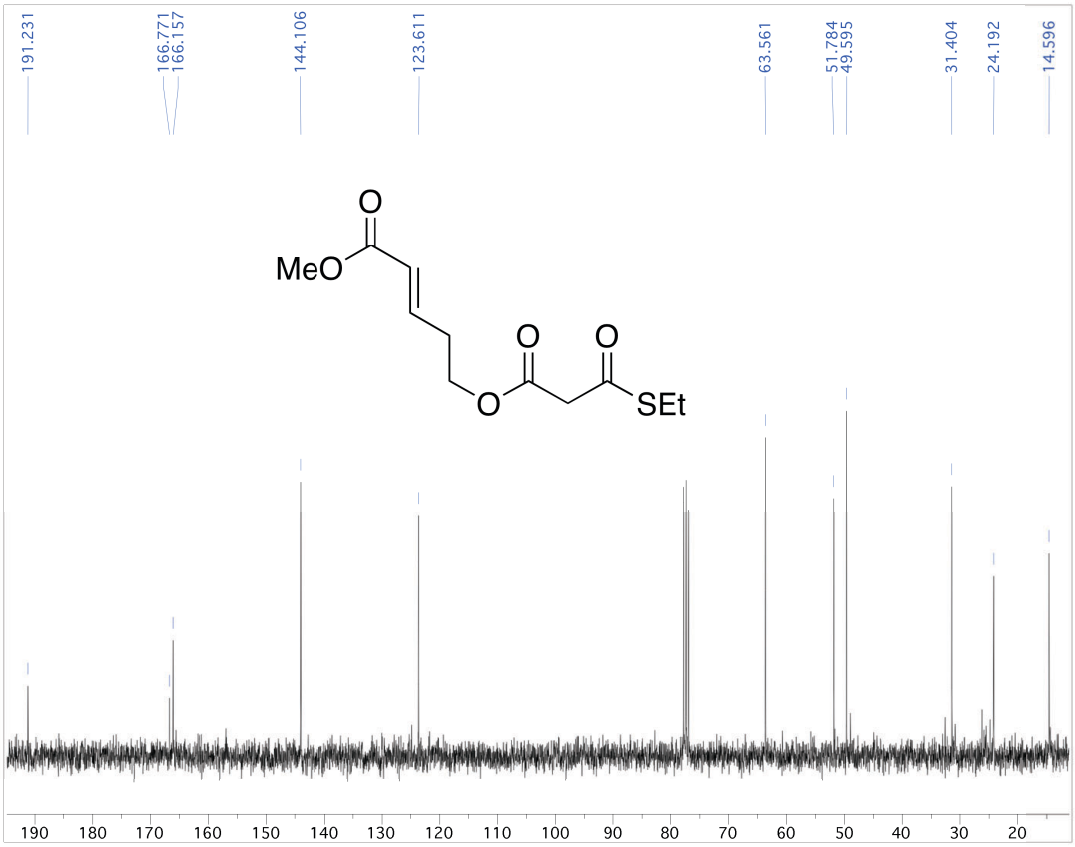
Synthesis of (*E*)-methyl 5-((3-(ethylthio)-3-oxopropanoyl)oxy)pent-2-enoate (4.41): To a 500 mL round-bottomed flask containing 4.55 g (35.0 mmol, 1 equiv.) alcohol **3.4** and 5.70 g (38.5 mmol, 1.1 equiv.) and acid **4.40** dissolved in 175 mL dry CH_2Cl_2 was added 7.94 g (38.5 mmol, 1.1 equiv.) DCC dissolved in 20 mL CH_2Cl_2. The reaction was stirred at ambient temperature for 1 hr before being filtered through celite and concentrated. The crude residue was submitted to silica gel flash chromatography eluting

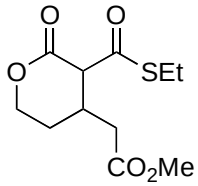
with 9 : 1 to 2 : 1 hex./EtOAc yielding 7.13 g (93%) of the desired product as a yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 6.87 (dt, *J* = 15.6, 6.9, 1H), 5.86 (d, *J* = 15.6, 1H), 4.22 (t, *J* = 6.6, 2H), 3.69 (s, 3H), 3.53 (s, 3H), 2.89 (q, *J* = 7.5, 2H), 2.52 (q, *J* = 7.5, 2H), 1.23 (t, *J* = 7.5, 3H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 191.2, 166.8, 166.2, 144.1, 123.6, 63.6, 51.8, 49.6, 31.4, 24.2, 14.6; R_f = 0.28 (4 : 1 hex./EtOAc).

Ref.: BJEIII268, **BJEIII405**, BJEIII439, BJEIII453



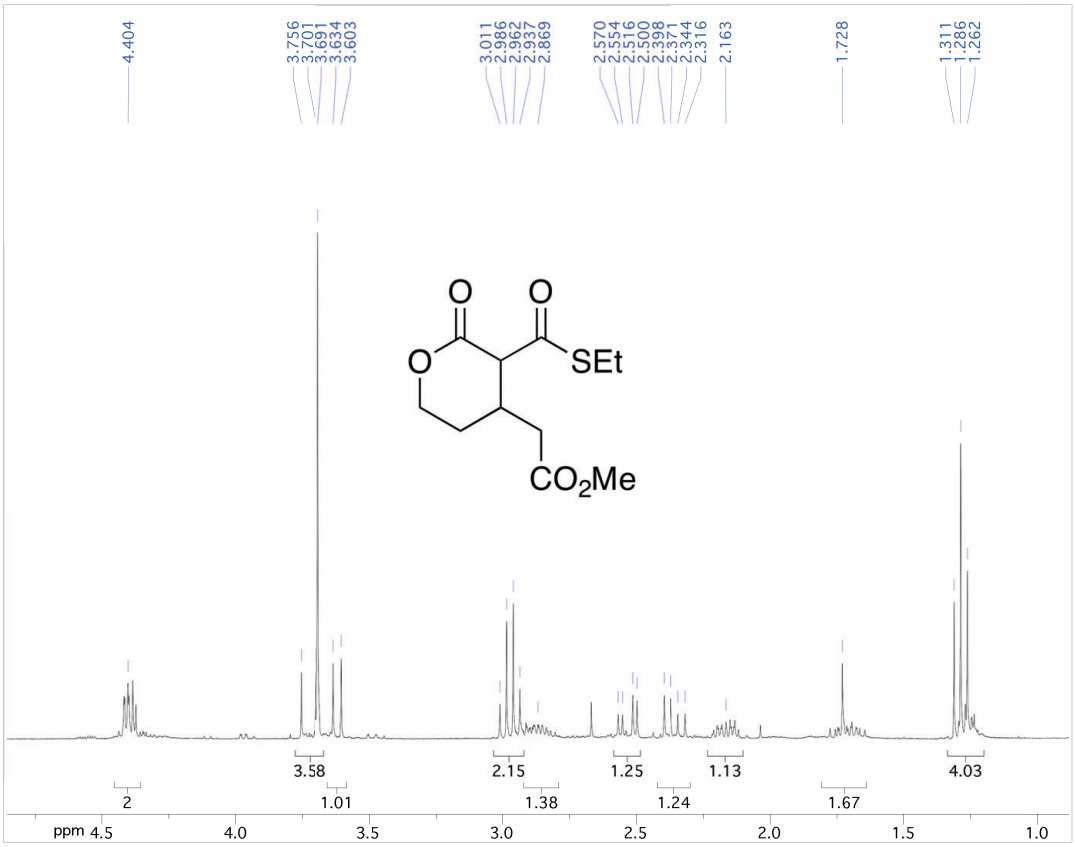


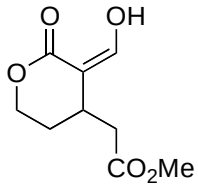


Synthesis of methyl 2-(3-((ethylthio)carbonyl)-2-oxotetrahydro-2*H*-pyran-4-yl)acetate (4.42): To a 500 mL round-bottomed flask containing 11.94 g (45.87 mmol, 1 equiv.) linear substrate **4.41** dissolved in 230 mL dry MeCN was added 29.89 g (91.74 mmol, 2 equiv.) Cs_2CO_3 and the reaction was stirred for 48 hr at ambient temperature before being filtered through celite, added to 1 M HCl, extracted thrice with EtOAc, dried over Na_2SO_4, and concentrated. The crude residue was submitted to silica gel flash chromatography eluting with 4 : 1 to 2 : 1 hex./EtOAc yielding 6.16 g (52%) of the desired compound as a yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 4.40 (m, 2H), 3.69 (s, 3H), 3.62 (d, *J* = 9.3, 1H), 2.97 (q, *J* = 7.5, 2H), 2.87 (m, 1H), 2.53 (dd, *J* = 16.2, 4.8, 1H), 2.36 (dd, *J* = 16.5, 8.4, 1H), 2.16 (m, 1H), 1.72 (m, 1H), 1.29 (t, *J* = 7.5, 3H); R_f = 0.48 (1 : 1 hex./EtOAc).

Ref.: BJEIII407, BJEIII441, **BJEIII459**.



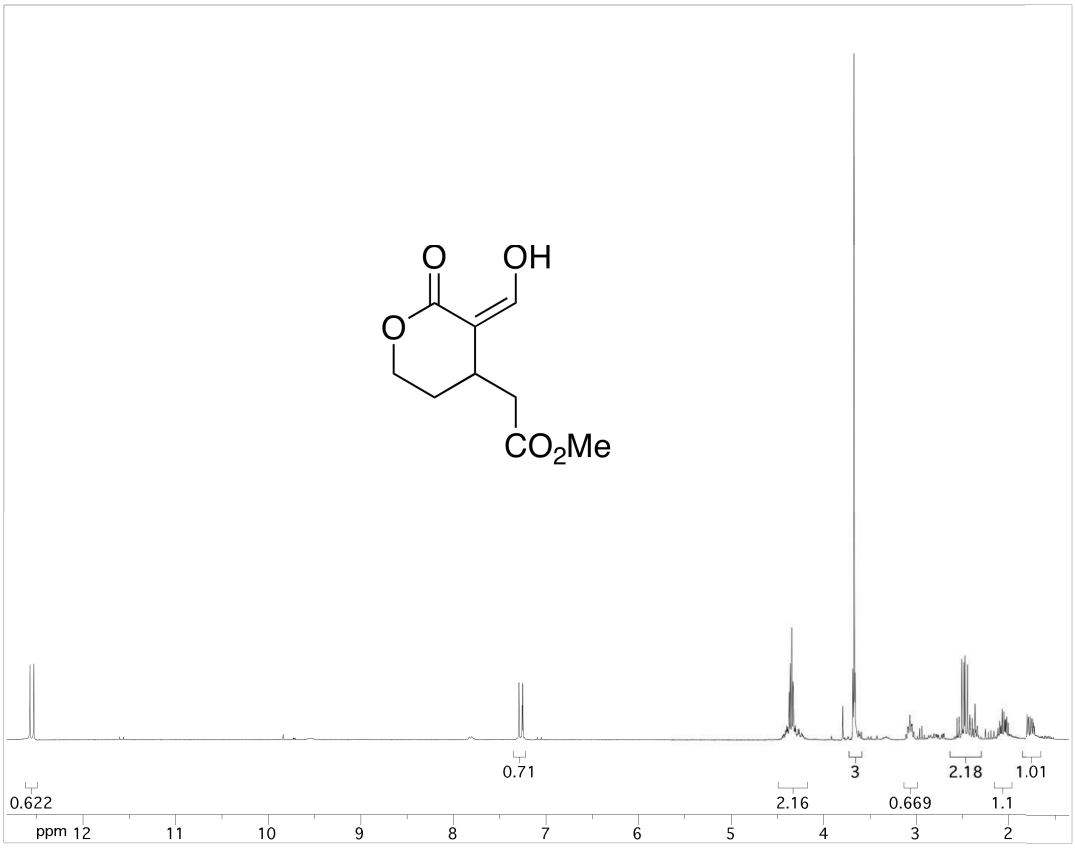


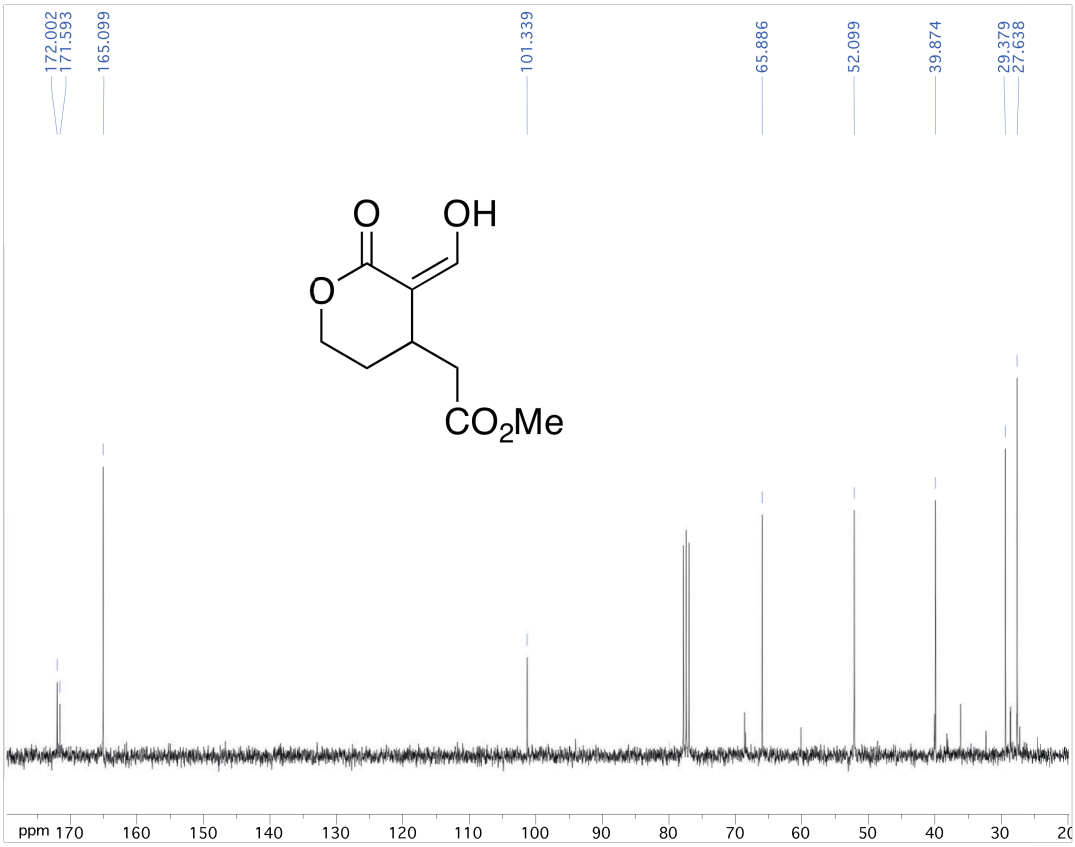
Synthesis of (*Z*)-methyl 2-(3-(hydroxymethylene)-2-oxotetrahydro-2*H*-pyran-4-yl)acetate (4.43): To a 100 mL round bottom charged with 1.38 g (5.30 mmol, 1 equiv.) thioester **4.42** dissolved in 25 mL acetone was added 1.52 g 10% Pd/C (1.43 mmol, 0.25 equiv) followed by the slow addition of 8.47 mL (53.0 mmol, 10 equiv.) triethylsilane.

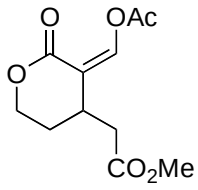
The reaction was stirred at ambient temperature for 16 hr, filtered through celite and concentrated. The resulting residue was submitted to silica gel flash chromatography eluting with 1 : 1 to 1 : 2 hex./EtOAc to yield 881 mg (83%) of the desired product as a pale yellow oil. This inseparable mixture of isomers was used without further purification.

^{1}HNMR (300 MHz, $CDCl_3$) δ 12.55 (dd, *J* = 12.3, 0.9, 1H), 4.34 (m, 2H), 3.67 (s, 3H), 3.07 (m, 1H), 2.47 (dd, *J* = 10.2, 6.9, 2H), 2.07 (m, 1H), 1.77 (m, 1H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 172.0, 171.6, 165.1, 101.3, 65.9, 52.1, 39.9, 29.4, 27.6; HRMS (+TOF): $[M+H]^+$ 201.0763 calcd for $C_9H_{13}O_5$, found: 201.0754; R_f = 0.41 (1 : 2 hex./EtOAc).

Ref.: BJEIII211, BJEIII213, BJEIII239, **BJEIII458**, BJEIII462



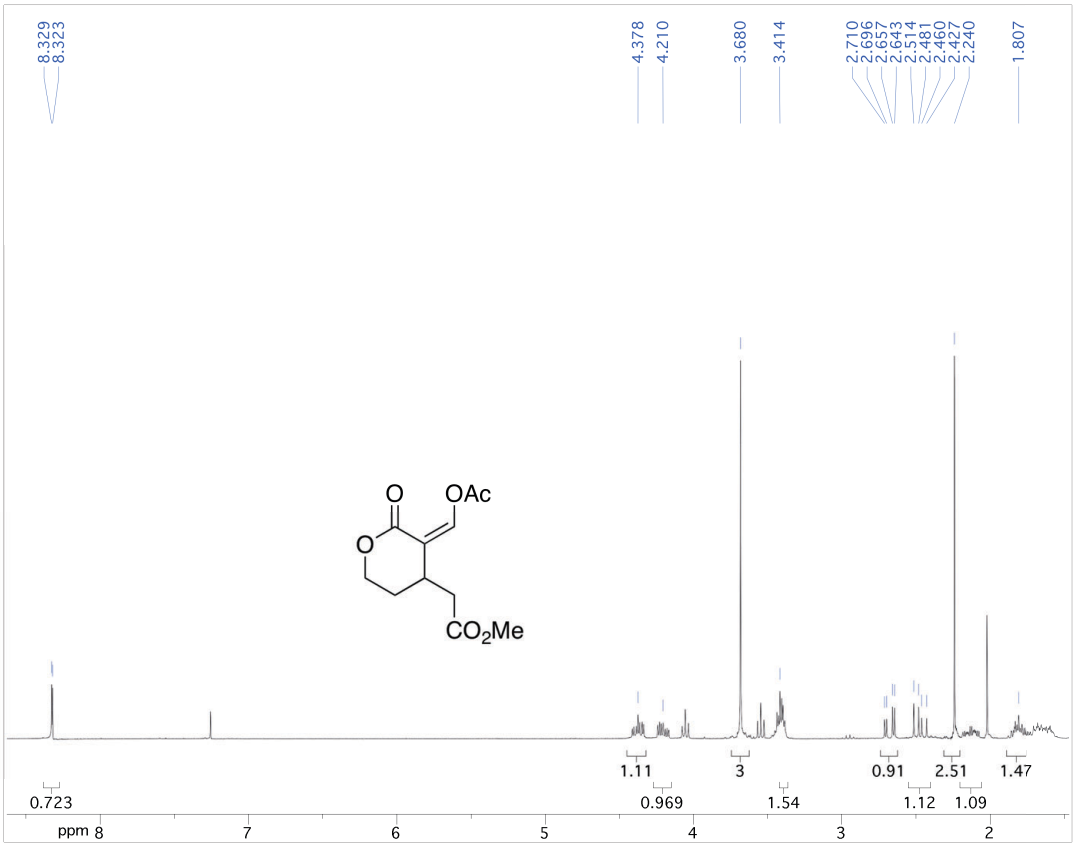


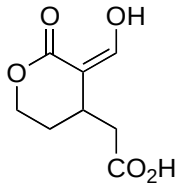


Synthesis of (*Z*)-methyl 2-(3-(acetoxymethylene)-2-oxotetrahydro-2*H*-pyran-4-yl)acetate: To a 10 mL round-bottomed flask containing 66 mg (0.330 mmol, 1 equiv.) compound **4.43** dissolved in 3 mL dry THF was added 1.5 mL AcCl. The reaction was stirred for 1.5 hr at ambient temperature before being added to $NaHCO_{3(sat.)}$, extracted into EtOAc, dried over Na_2SO_4, and concentrated. The crude material was used without purification.

^{1}HNMR (300 MHz, $CDCl_3$) δ 8.32 (d, *J* = 1.8, 1H), 4.38 (m, 1H), 4.21 (m, 1H), 3.68 (s, 3H), 3.41 (m, 1H), 2.67 (dd, *J* = 15.9, 4.2, 1H), 2.47 (dd, *J* = 16.2, 9.9, 1H), 2.24 (s, 3H), 2.10 (m, 1H), 1.81 (m, 1H); R_f = 0.35 (1 : 2 hex./EtOAc).

Ref.: BJEIII242, **BJEIII256**

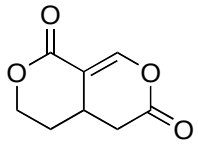




Synthesis of (*Z*)-2-(3-(hydroxymethylene)-2-oxotetrahydro-2*H*-pyran-4-yl)acetic acid (4.44): To a 250 mL round-bottomed flask containing 3.31 g (15.5 mmol, 1 equiv.) compound **4.43** dissolved in 84 mL 3 : 1 THF/H_2O was added 1.19 g (49.6 mmol, 3equiv.) LiOH. The reaction was stirred at ambient temperature for 105 min before being

added to 1 M HCl, extracted in EtOAc, dried over Na_2SO_4, and concentrated. The crude residue was purified by silica gel flash chromatography eluting with 1 : 2 to 0 : 1 hex./EtOAc to yield 2.70 g (88%) of the desired product as a white solid which was used without further purification.

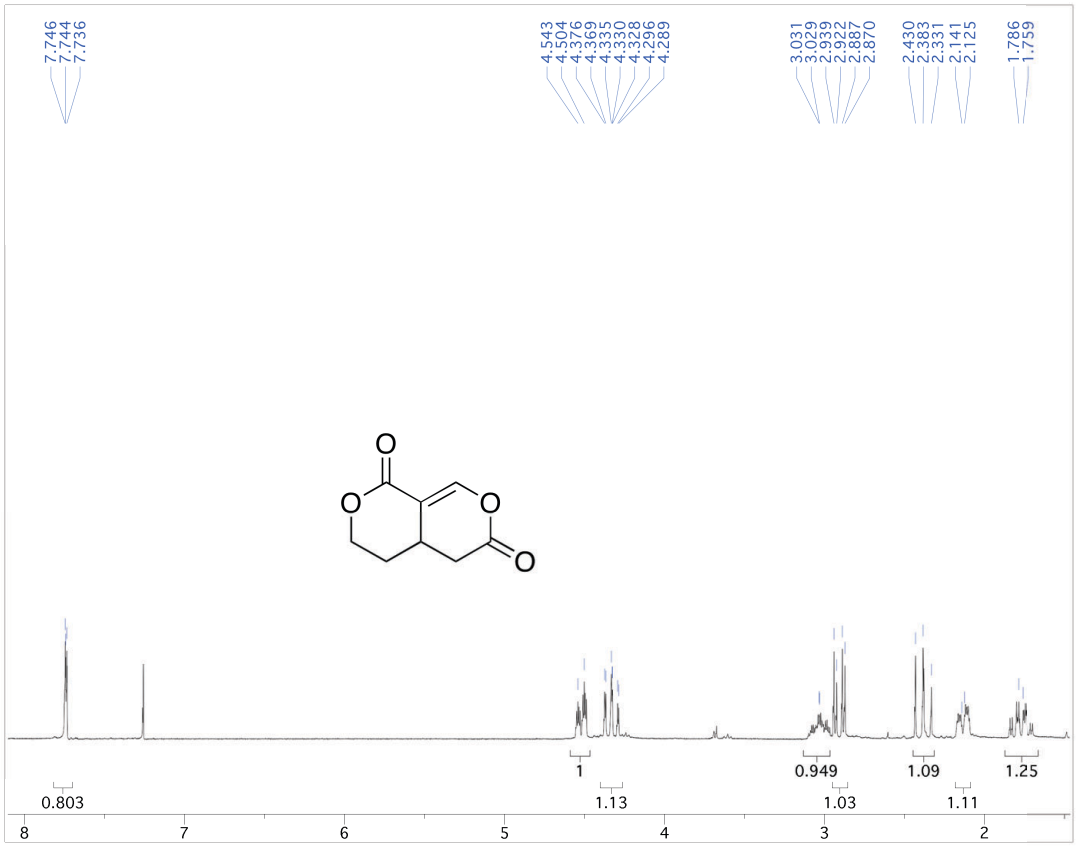
Ref.: BJEIII396, BJEIII398, BJEIII409, BJEIII412, BJEIII460, **BJEIII466**

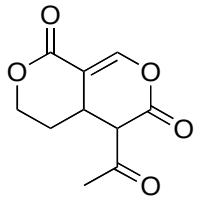


Synthesis of 3,4,4a,5-tetrahydropyrano[3,4-*c*]pyran-1,6-dione (4.38): To a 100 mL round-bottomed flask containing 2.50 g (13.4 mmol, 1 equiv) acid **4.44** dissolved in 45 mL dry MeCN was added 4.90 mL (67.1 mmol, 5 equiv) $SOCl_2$. The reaction was heated to reflux for 2 hr before being concentrated and purified by Davsil flash chromatography eluting with 4 : 1 CH_2Cl_2/EtOAc to yield 1.057 g (47%) of the desired product as a white solid.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.74 (d, *J* = 3.0, 1H), 4.52 (m, 1H), 4.33 (m, 1H), 3.03 (m, 1H), 2.90 (dd, *J* = 15.6, 5.1, 1H), 2.38 (t, *J* = 14.1, 1H), 2.13 (m, 1H), 1.77 (m, 1H); Rf = 0.54 (EtOAc); IR (NaCl, film): 1789, 1732, 1615 cm^{-1};

Ref.: BJEIII411, BJEIII414, BJEIII469, BJEIII472, BJEII474, BJEIII475, BJEIII478, **BJEIII481**.



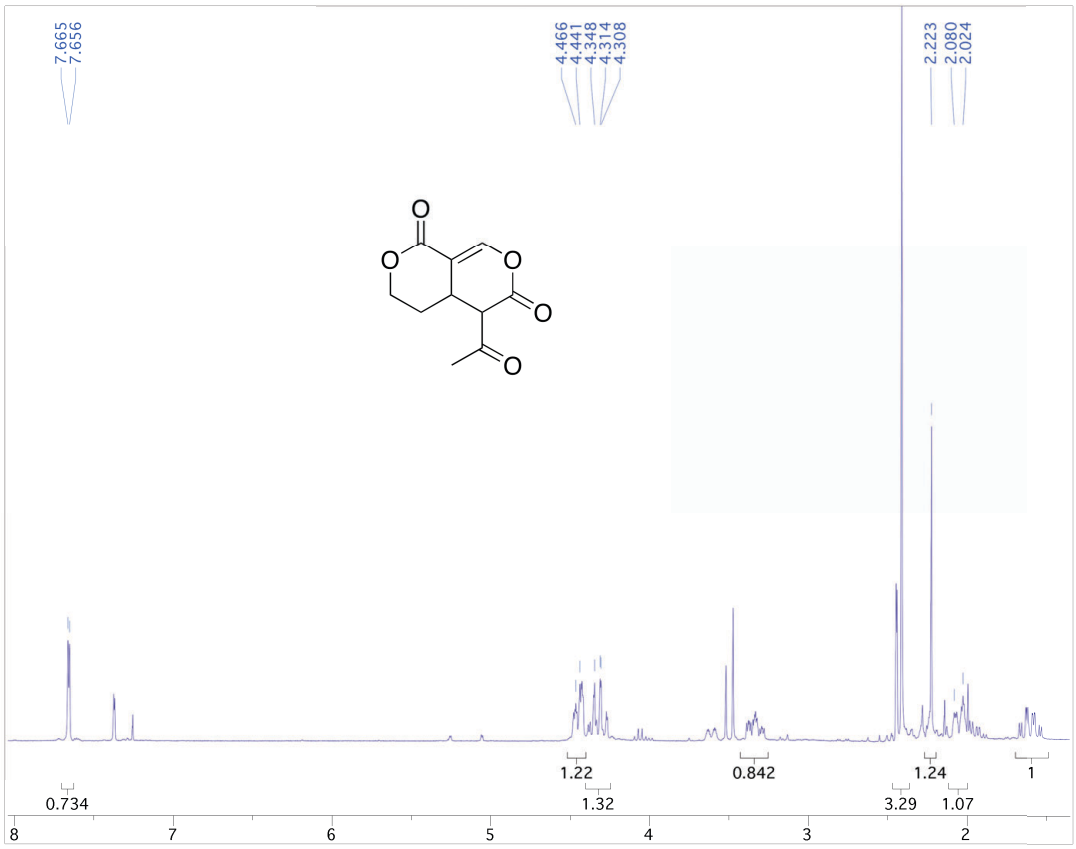


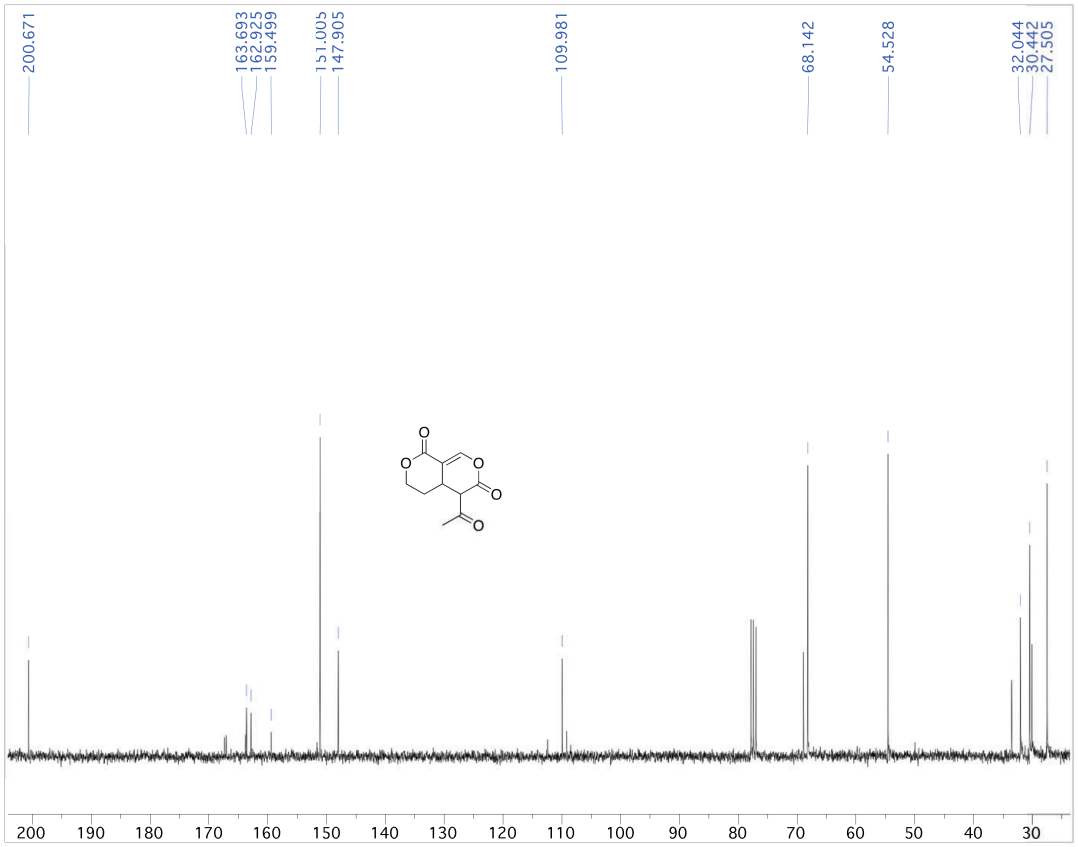
Synthesis of 5-acetyl-3,4,4a,5-tetrahydropyrano[3,4-*c*]pyran-1,6-dione (4.46): To a 10 mL round bottomed flask containing 25 mg (0.149 mmol, 1 equiv.) lactone **4.38** dissolved in 1.5 mL dry THF at -78°C was added 223 μL (0.223 mmol, 1.5 equiv.) of a 1M solution of LiHMDS in THF. The reaction was stirred at -78°C for 1 hr before the addition of 21 μL (0.298 mmol, 2 equiv.) AcCl. The reaction was allowed to warm to ambient temperature over 2 hr before being added to $NH_4Cl_{(sat.)}$, extracted three times with EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was purified by

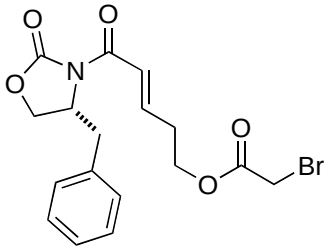
silica gel flash chromatography eluting with 1 : 2 to 0 : 1 hex./EtOAc to yield 29 mg (94%) of the desired product as a pale yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$) major tautomer δ 7.66 (d, *J* = 2.7, 1H), 4.45 (m, 1H), 4.32 (m, 1H), 3.33 (m, 1H), 2.41 (s, 3H), 2.22 (m, 1H), 2.05 (m, 1H), 1.60 (m, 1H); ^{13}CNMR (75 MHz, $CDCl_3$) major tautomer δ 200.7, 163.7, 162.9, 151.0, 110.0, 68.1, 54.5, 32.0, 30.4, 27.5; R_f = 0.20 (1 : 2 hex./EtOAc).

Ref.: **BJEIII418**, BJEIII420, BJEIII430.





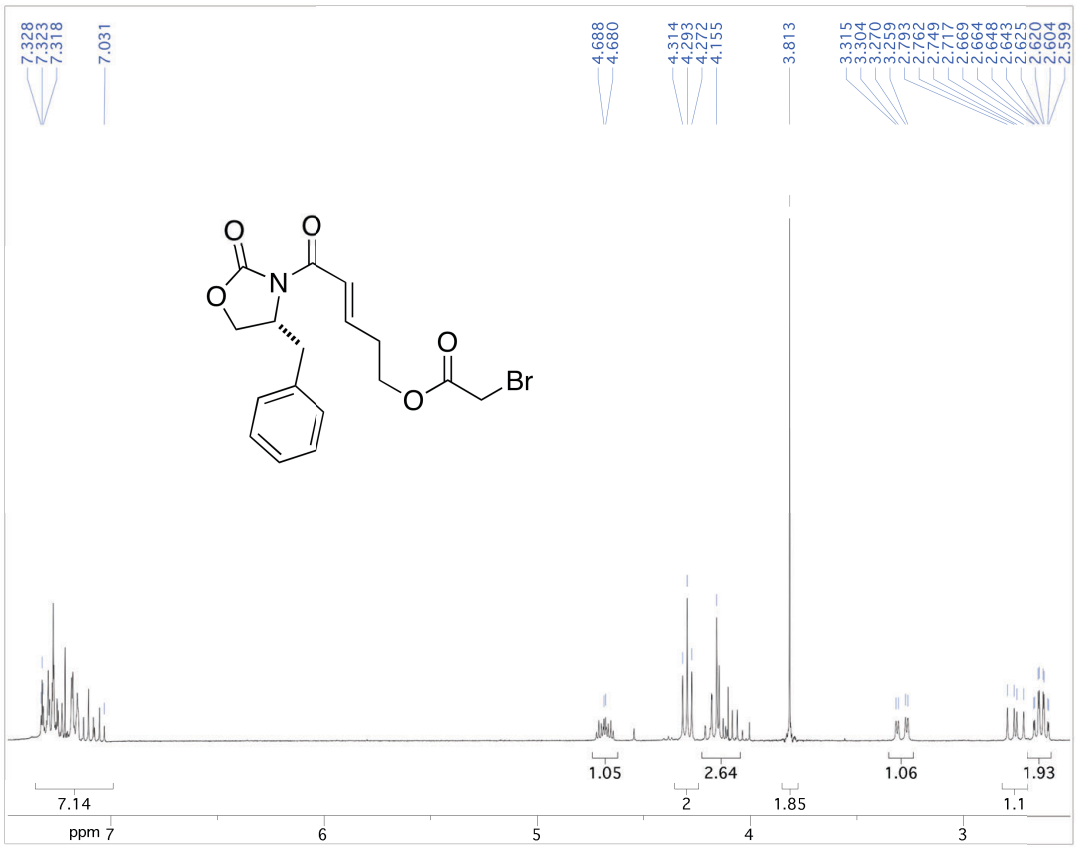


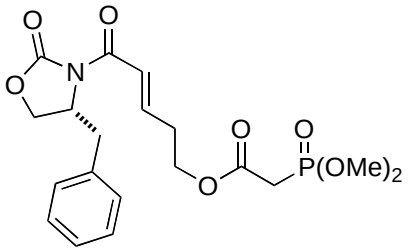
Synthesis of (*R*,*E*)-5-(4-benzyl-2-oxooxazolidin-3-yl)-5-oxopent-3-en-1-yl 2-bromoacetate (4.32): To a 250 mL round-bottomed flask containing 2.95 g (10.72 mmol, 1 equiv.) alcohol **4.24** dissolved in 50 mL dry THF at 0^{o}C was added 1.12 mL (12.86 mmol, 1.2 equiv.) bromoacetyl bromide followed by 1.79 mL (12.86 mmol, 1.2 equiv.) dry NEt_3. The reaction was allowed to stir for 30 min at ambient temperature before being added to $NaHCO_{3(sat.)}$ and extracted thrice with EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was taken up in 1 : 2 hex./EtOAc and passed

through a short silica gel plug. Concentration yielded 4.40 g (95%) of the desired product as a brown oil which was used without further purification.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.03-7.32 (m, 7H), 4.68 (m, 1H), 4.29 (t, *J* = 6.3, 2H), 4.16 (m, 2H), 3.81 (s, 2H), 3.29 (dd, *J* = 13.5, 3.3, 1H), 2.72 (dd, *J* = 13.2, 9.3, 1H), 2.63 (qd, *J* = 6.3, 1.5, 2H).

Ref.: BJEIV278, BJEIV287, **BJEIV294.**

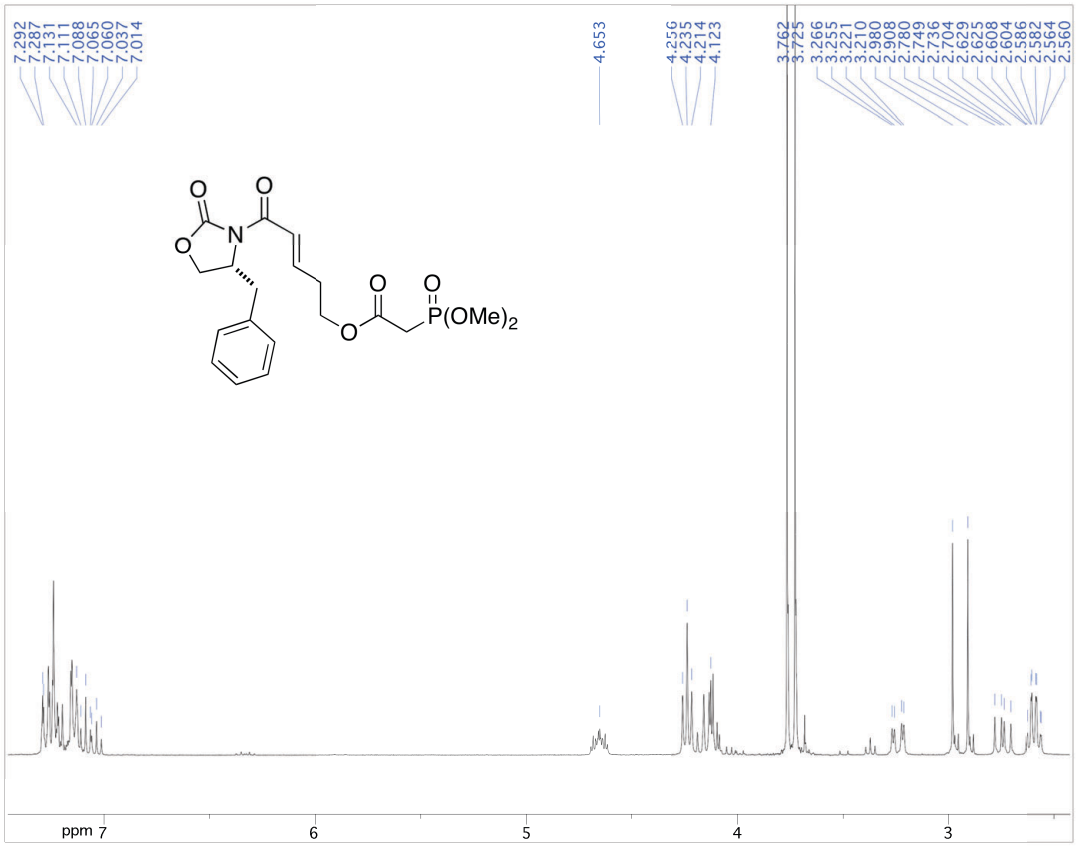




Synthesis of (*R*,*E*)-5-(4-benzyl-2-oxooxazolidin-3-yl)-5-oxopent-3-en-1-yl 2-(dimethoxyphosphoryl)acetate (4.49): To a 25 mL round-bottomed flask containing 4.04 g (10.20 mmol, 1 equiv.) bromoester **4.32** was added 3.60 mL $P(OMe)_3$. The reaction was heated to 100°C for 15min and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 1 : 2 hex./EtOAc to yield 3.83 g (88%) of the desired product as a yellow oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.11-7.27 (m, 6H), 7.04 (dt, *J* = 15.3, 6.9, 1H), 4.63 (m, 1H), 4.21 (t, *J* = 6.3, 2H), 4.10 (m, 2H), 3.74 (s, 3H), 3.70 (s, 3H), 3.21 (dd, *J* = 13.5, 3.3, 1H), 2.92 (d, J_{HP} = 21.6, 2H), 2.72 (dd, *J* = 13.5, 9.3, 1H), 2.57 (qd, *J* = 6.3, 1.2, 2H); ^{13}CNMR (75MHz, $CDCl_3$) δ 165.8, 164.7, 153.6, 145.8, 135.4, 129.6, 129.2, 127.5, 123.0, 66.4, 63.7, 55.5, 53.5, 38.0, 34.3, 32.5, 31.8; IR (NaCl, film): 1777, 1738, 16821639 cm^{-1}; HRMS (+TOF): $[M]^+$ 453.1553 calcd for $C_{21}H_{28}NO_8P$, found: 453.1553; R_f = 0.24 (EtOAc).

Ref.: BJEIV262, BJEIV285, BJEIV288, **BJEIV295**.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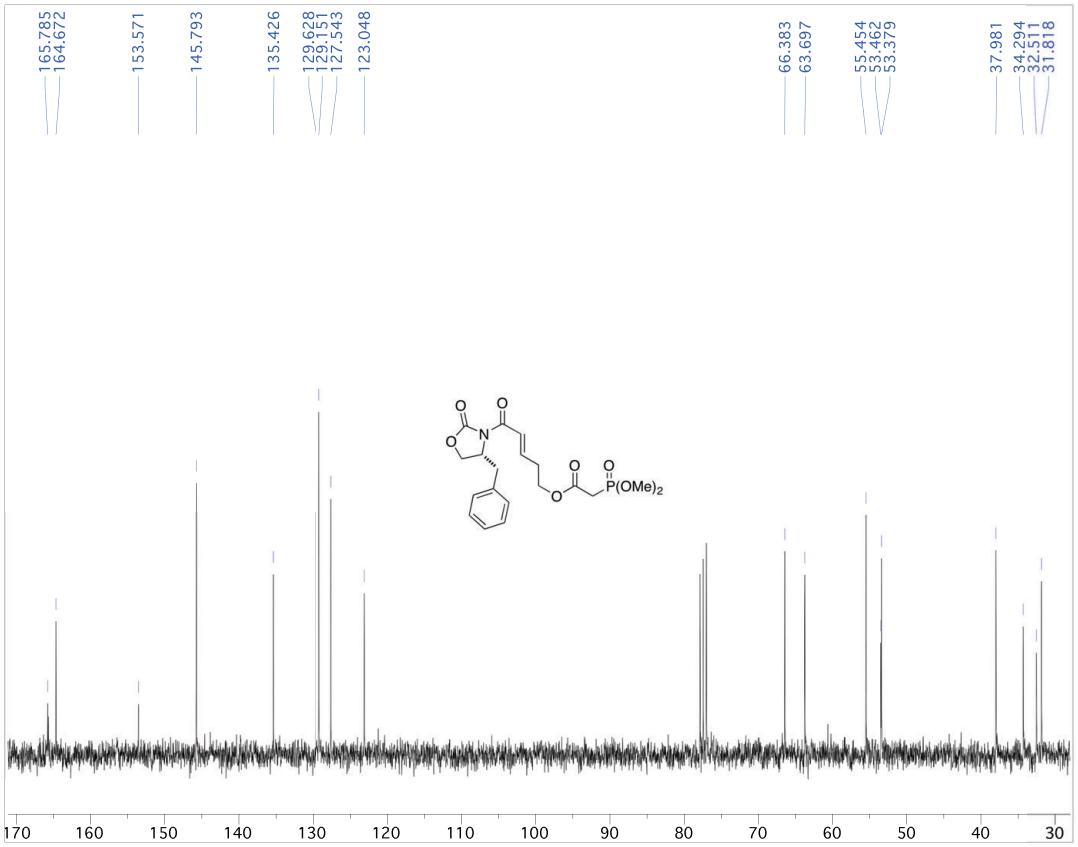
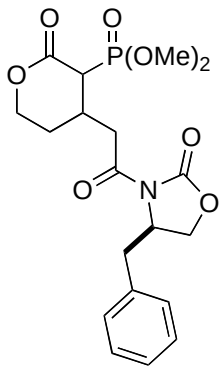


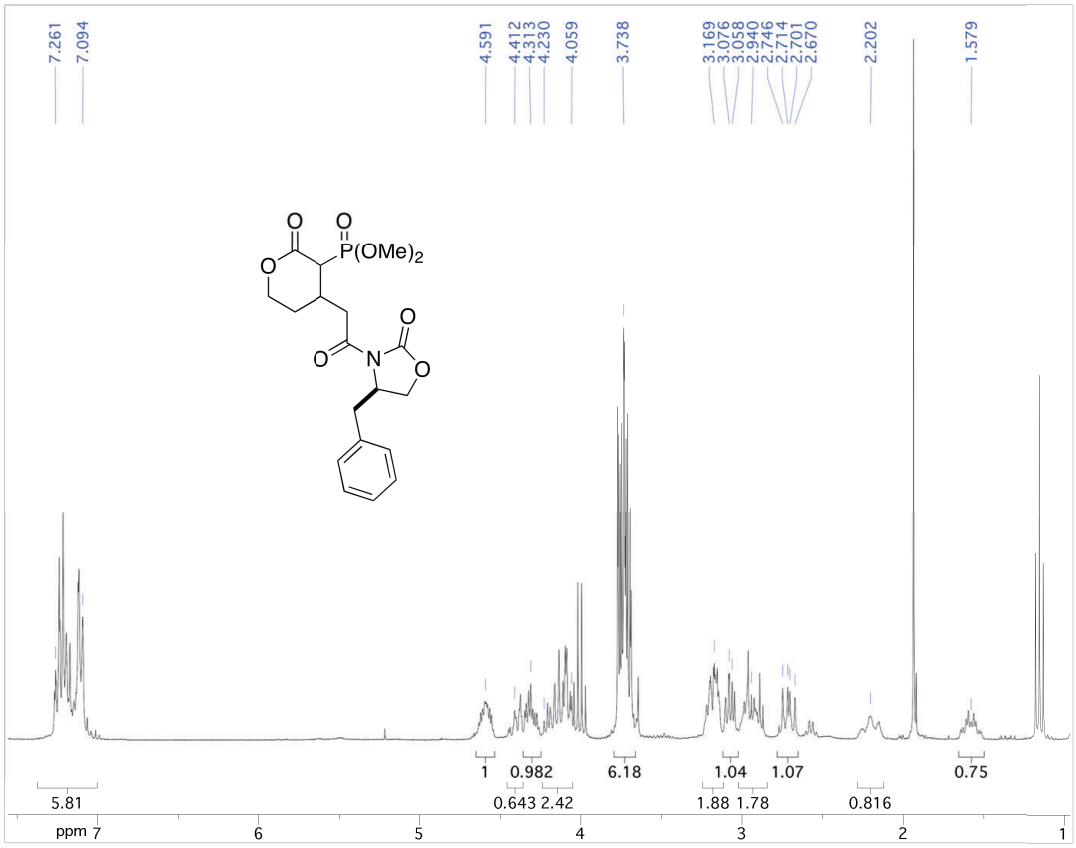


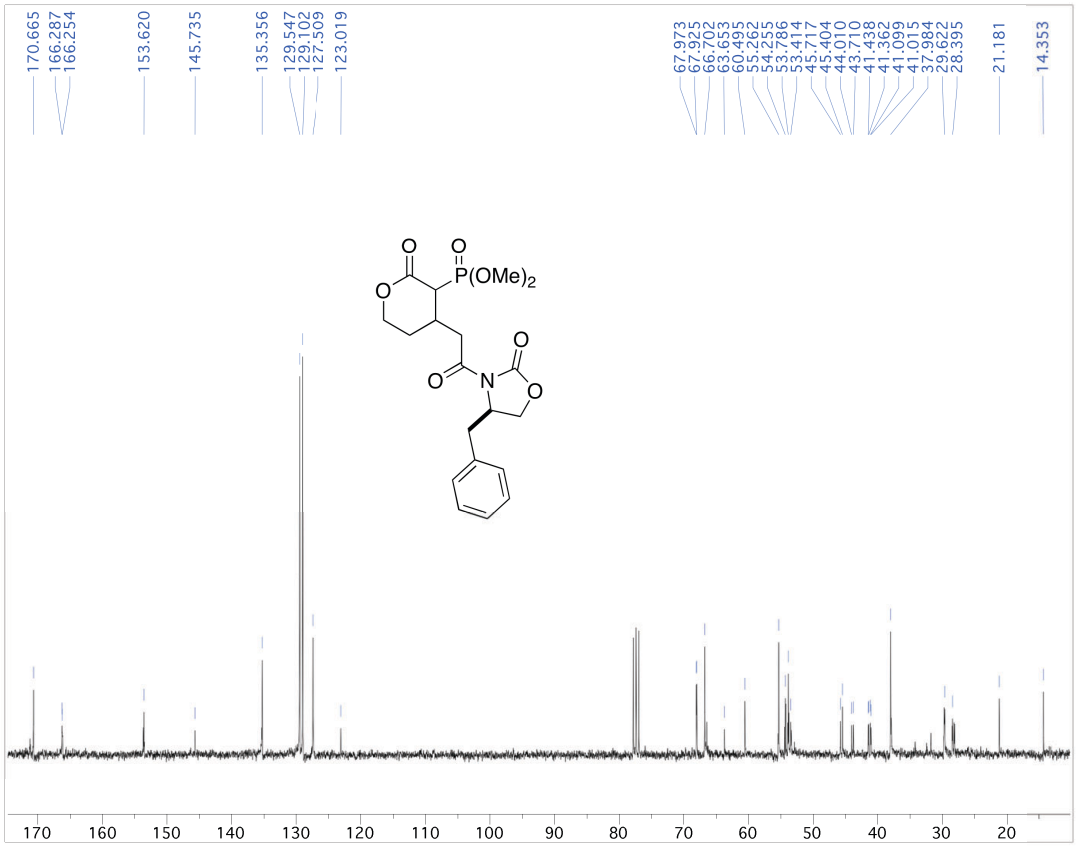
Synthesis of dimethyl (4-(2-((*R*)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)-2-oxotetrahydro-2*H*-pyran-3-yl)phosphonate (4.50): To a 25 mL round-bottomed flask containing 413 mg (0.970 mmol, 1 equiv.) phosphonate **4.49** dissolved in 10 mL dry MeCN was added 632 mg (1.94 mmol, 2 equiv.) Cs_2CO_3 and the reaction was heated to 40^{o}C for 20 min, added to 1 M HCl, extracted thrice with EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography

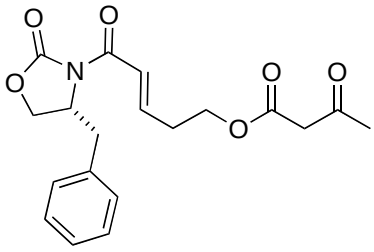
eluting with 0% to 5 % MeOH in EtOAc to yield 286 mg (69%) of the desired product as a pale yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 7.09-7.26 (m, 5H), 4.59 (m, 1H), 4.41 (m, 1H), 4.31 (m, 1H), 4.06-4.23 (m, 2H), 3.74 (m, 6H), 3.17 (m, 2H), 3.06 (m, 1H), 2.94 (m, 2H), 2.71 (dd, *J* = 13.5, 9.6, 1H), 2.20 (m, 1H), 1.58 (m, 1H); ^{13}CNMR (300 MHz, $CDCl_3$) δ 170.7, 166.3, 166.3, 153.6, 145.7, 135.4, 129.5, 129.1, 127.5, 123.0, 68.0, 67.9, 66.7, 63.7, 60.5, 55.3, 54.3, 53.8, 53.4, 45.7, 44.0, 43.7, 41.4, 41.1, 41.0, 38.0, 29.6, 28.4, 21.1, 14.4; R_f = 0.45 (5 % MeOH in EtOAc).

Ref.: BJEIV263, BJEIV286, BJEIV289, BJEIV297, BJEIV299, BJEIV304, BJEIV309, **BJEIV312**.





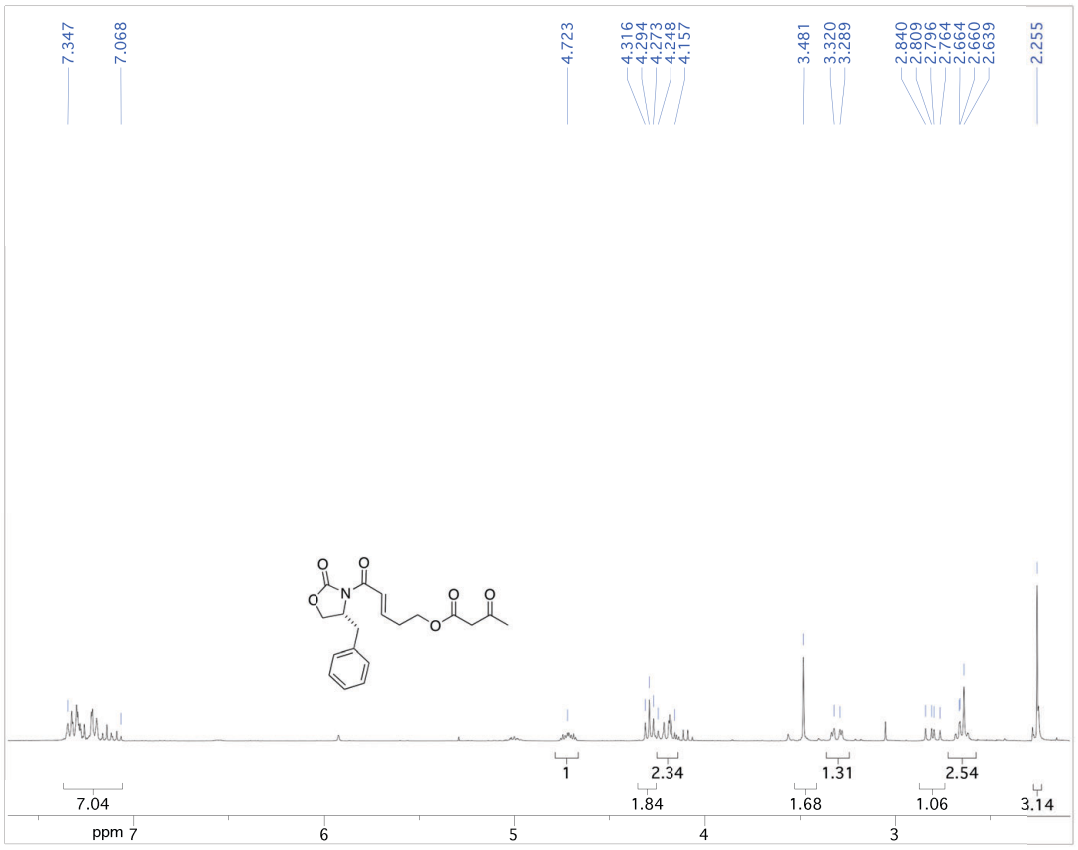


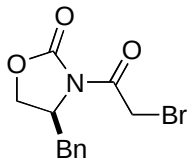
Synthesis of (*R*,*E*)-5-(4-benzyl-2-oxooxazolidin-3-yl)-5-oxopent-3-enyl 3-oxobutanoate (4.55): To 98 mg (0.356 mmol, 1equiv.) alcohol **4.24** in 1.5 mL CH_2Cl_2 at -10^{o}C was added 55 μL diketene then a single crystal of DMAP. The reaction was stirred for 15 min at -10^{o}C and was then diluted with CH_2Cl_2, washed twice with $NaHCO_{3(sat)}$, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was dissolved in 1 : 2 hex. : EtOAc and passed through a short plug of silica gel with copious

1 : 2 hex. : EtOAc washes. Concentration yielded 128 mg (>99%) of the desired product as a pale yellow oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.35-7.07 (m, 7H), 4.72 (m, 1H), 4.30 (t, *J* = 6.3, 2H), 4.25-4.16 (m, 2H), 3.48 (s, 2H), 3.30 (m, 1H), 2.78 (dd, *J* = 15, 9.6, 1H), 2.65 (qd, *J* = 6.6, 1.5, 2H), 2.26 (s, 3H). R_f = 0.43 (1 : 1 hex./EtOAc)

Ref: BJEII446, **BJEII465**, BJEIII029.



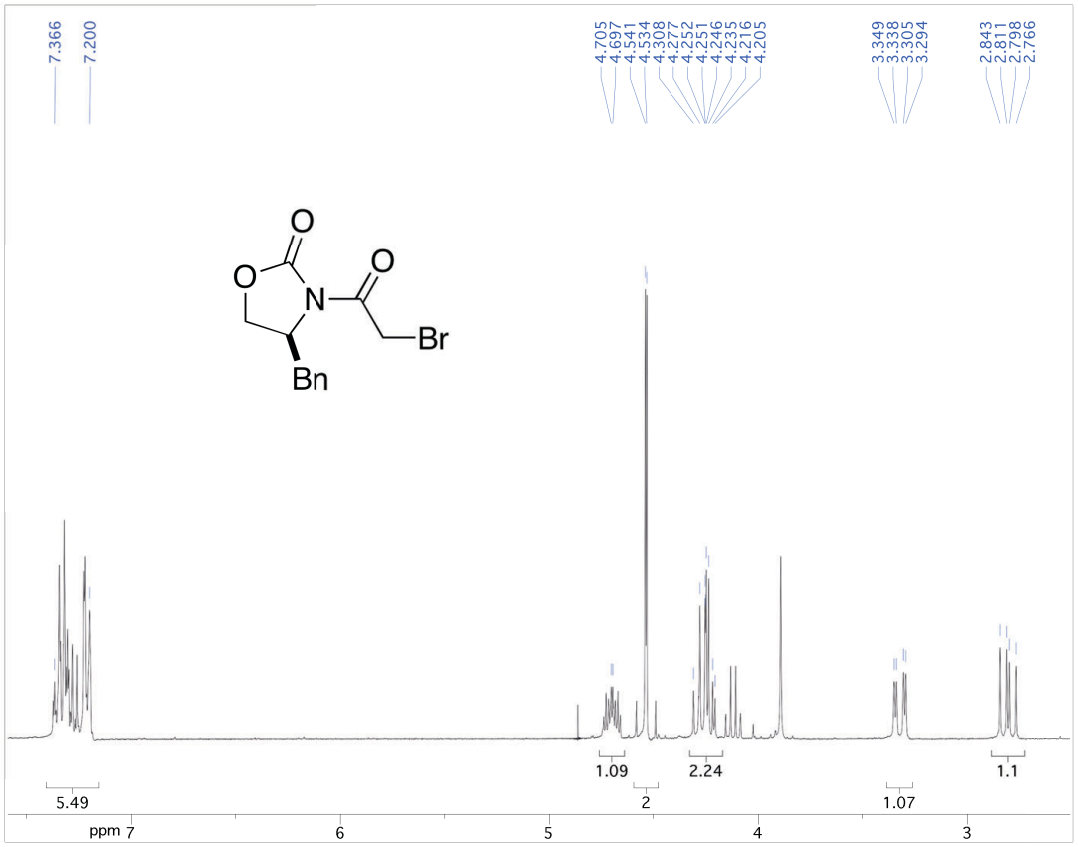


Synthesis of (S)-4-benzyl-3-(2-bromoacetyl)oxazolidin-2-one: To a 250 mL flame dried round-bottomed flask was charged 5.32 g (30.02 mmol, 1 equiv.) (*S*)-4-

benzyloxazolidin-2-one followed by 120 mL dry THF. The reaction was cooled to -78°C and 22.52 mL (1.6 M in hex., 36.03 mmol, 1.2 equiv.) *n*BuLi was added. The reaction was stirred at -78°C for 45 min before the addition of 3.92 mL (45.03 mmol, 1.5 equiv.) bromoacetyl bromide. The reaction was stirred for a further 6 hr at -78°C and was then allowed to warm to ambient temperature, added to $NH_4Cl_{(sat.)}$, extracted into EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 4 : 1 to 1 : 1 hex./EtOAc to yield 9.79 g (>99%) of the desired product as a red oil which was used without further purification.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.20-7.37 (m, 5H), 4.70 (m, 1H), 4.53 (d, *J* = 2.1, 2H), 4.25 (m, 2H), 3.32 (dd, *J* = 13.2, 3.3, 1H), 2.80 (dd, *J* = 13.5, 9.6, 1H); ^{13}CNMR (75MHz, $CDCl_3$) δ 166.2, 153.2, 134.9, 129,6, 129.3, 127.8, 66.9, 55.7, 37.7, 28.6; R_f = 0.24 (4 : 1 hex./Et OAc).

Ref.: BJEIV347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4.205
3.349
3.338
3.305
3.294
2.843
2.811
2.798
2.766
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Bn
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2
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4
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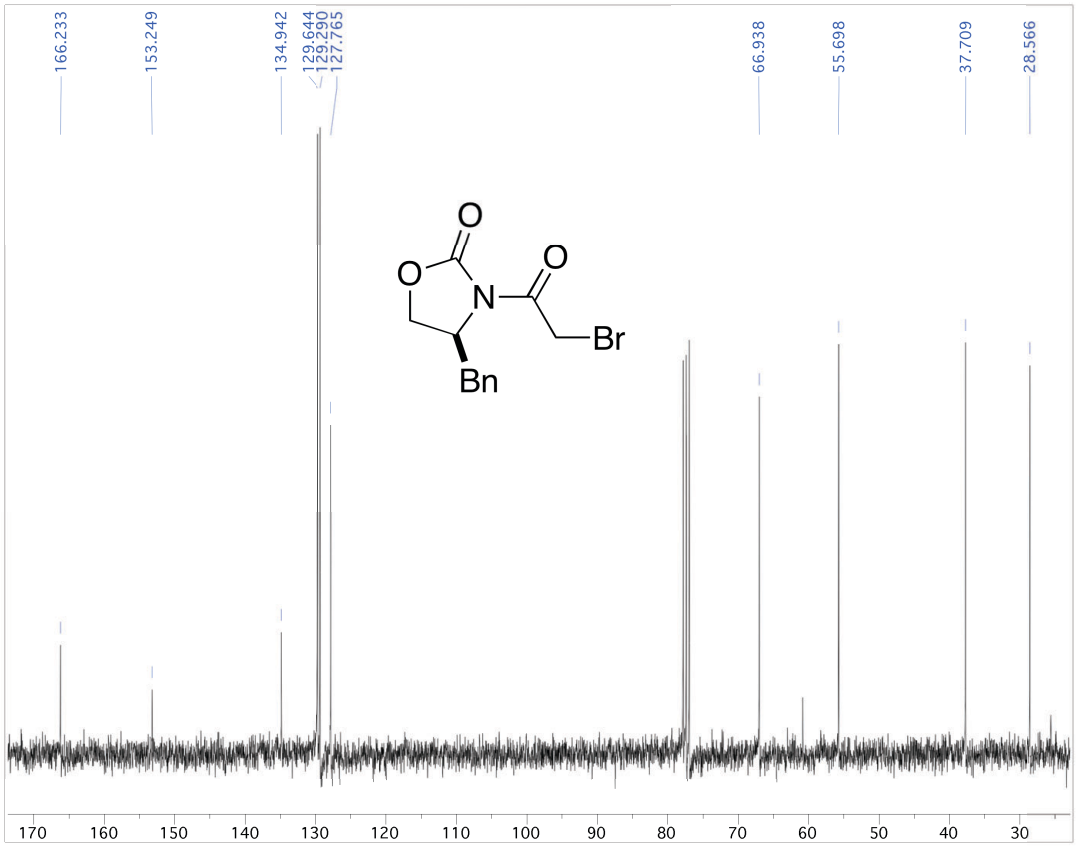
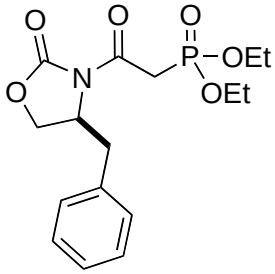
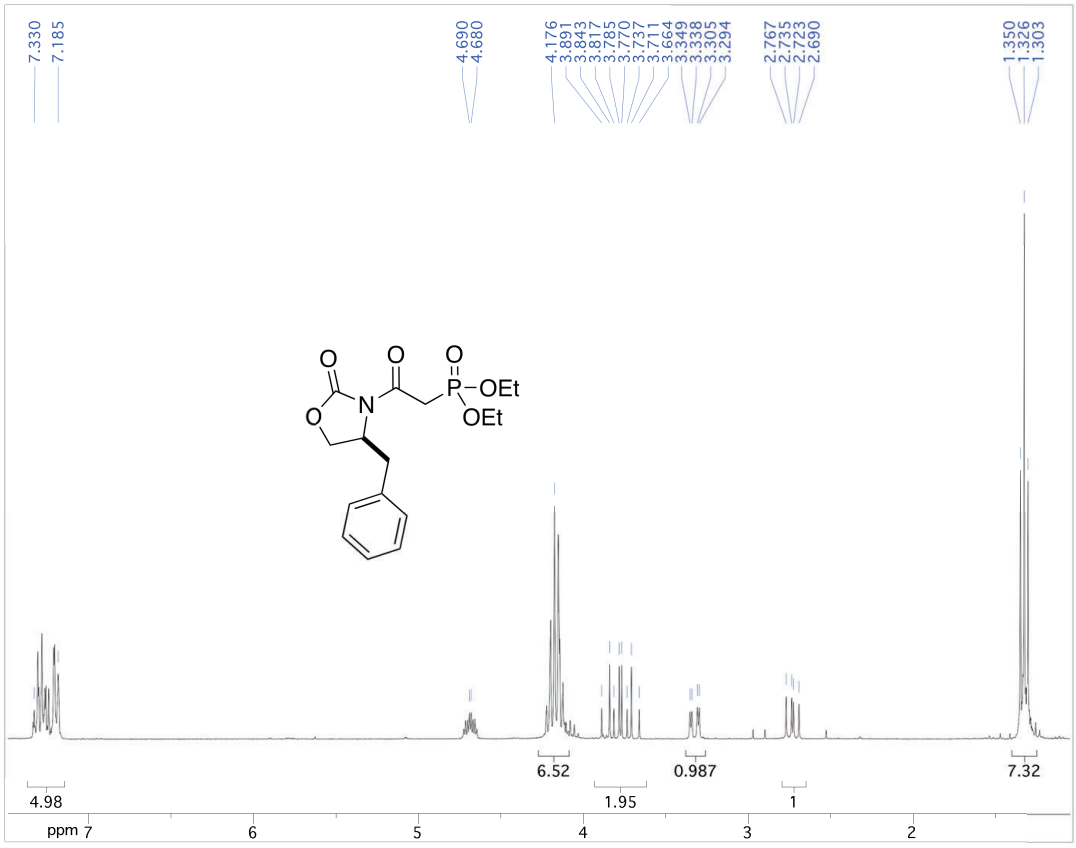


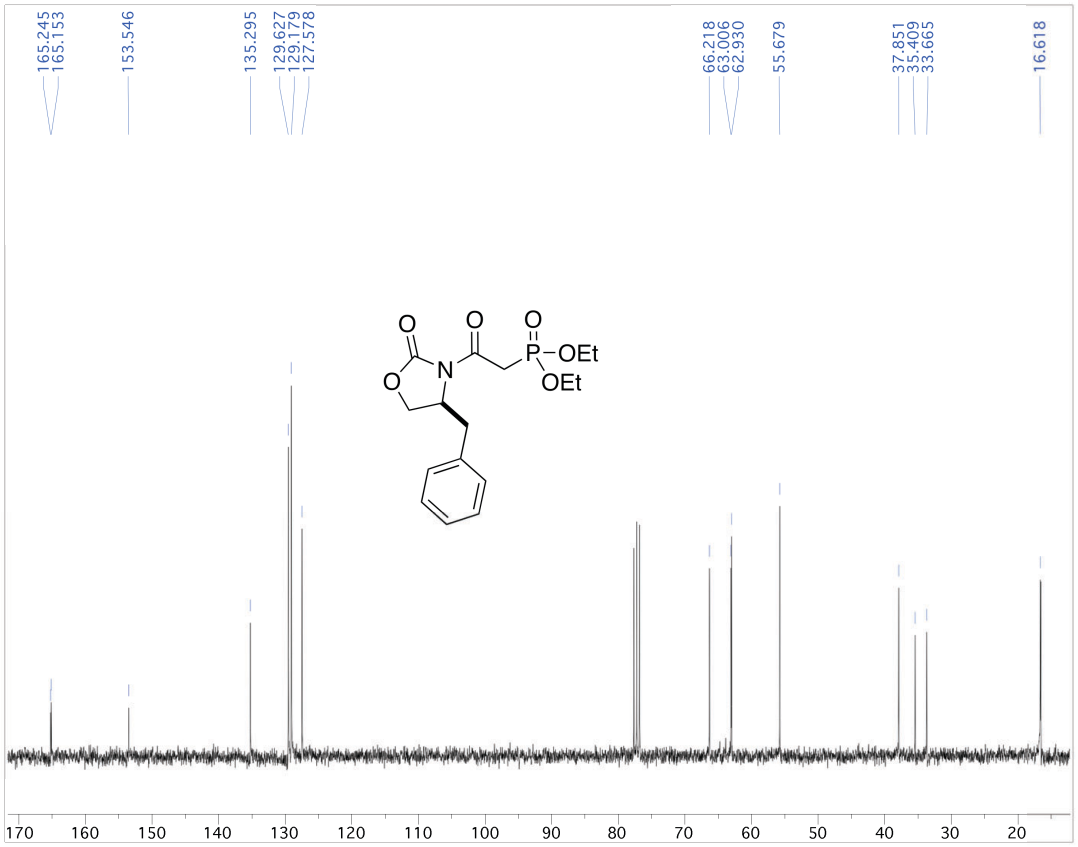


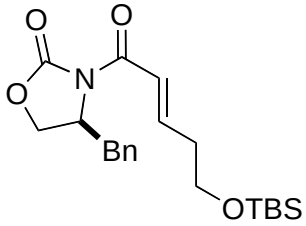
Synthesis of (*S*)-diethyl (2-(4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)phosphonate: To a 50 mL round bottomed flask containing 3.18 g (10.68 mmol, 1equiv.) (S)-4-benzyl-3-(2-bromoacetyl)oxazolidin-2-one was added 5.5 mL (32.04 mmol, 3 equiv.) $P(OEt)_3$ and the reaction was heated to 100^{o}C for 15 min and then concentrated to yield 3.83 g (>99%) of the desired product as a thick orange oil which was used without further purification.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.19-7.33 (m, 5H), 4.69 (m, 1H), 4.18 (m, 6H), 3.78 (m, 2H), 3.32 (dd, *J* = 13.2, 3.3, 1H), 2.73 (dd, *J* = 13.2, 9.76, 1H), 1.33 (t, *J* = 7.2, 6H); ^{13}CNMR (75MHz, $CDCl_3$) δ 165.2, 153.5, 135.3, 129.6, 129.2, 127.6, 66.2, 63.0, 55.7, 37.9, 35.4, 33.7, 16.6; HRMS (+TOF): $[M+H]^+$ 356.1263 calcd for $C_{15}H_{18}NO_4$, found: 356.1272. R_f = 0.41 (EtOAc)

Ref.: **BJEIV350**





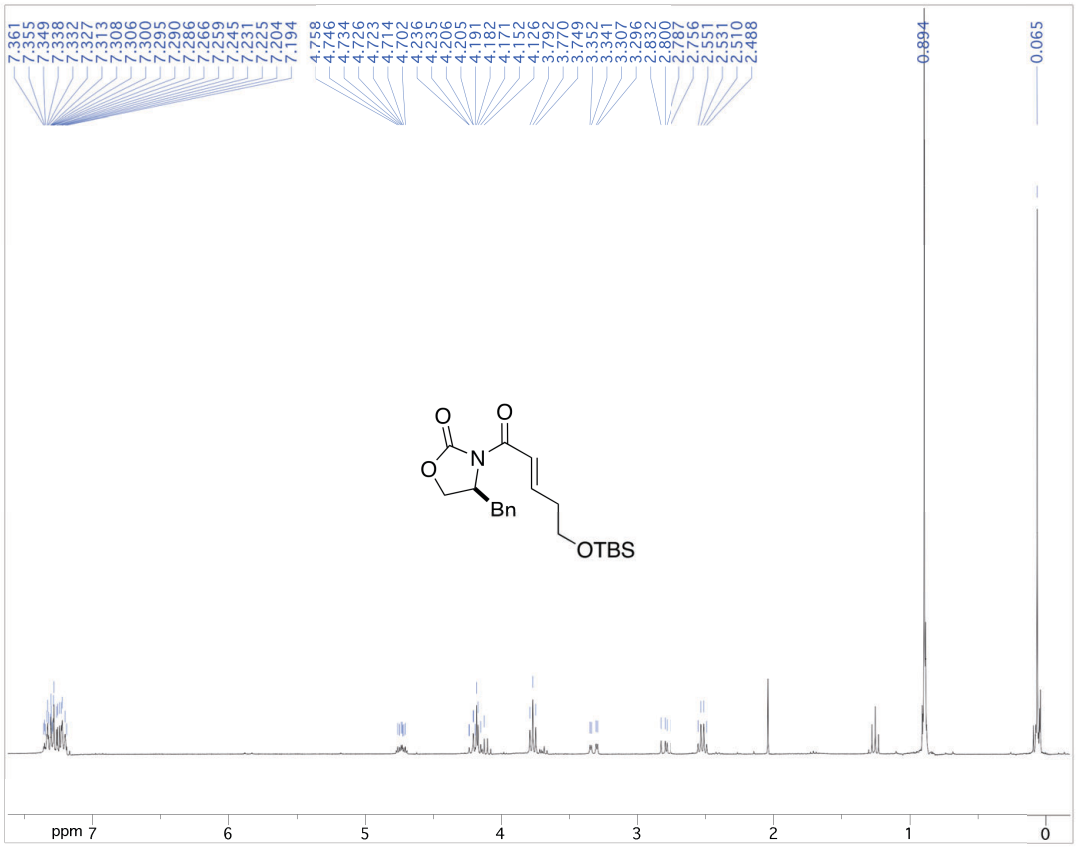


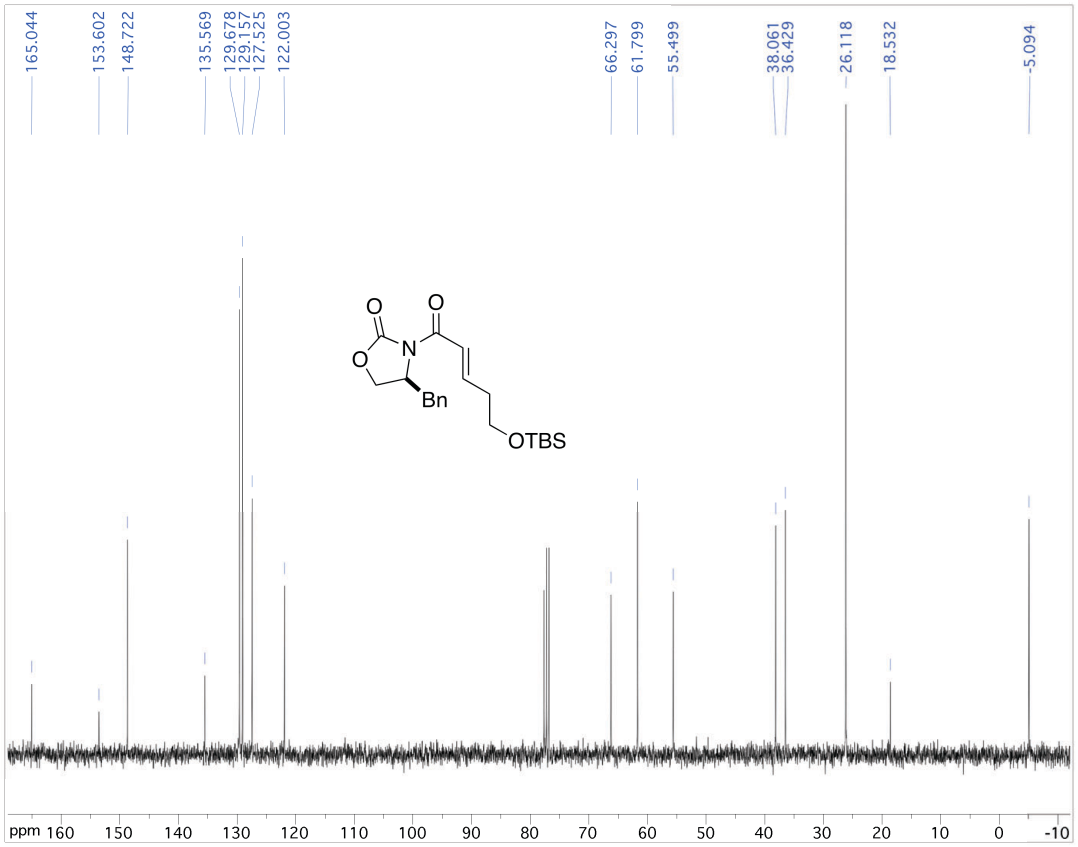
Synthesis of (*S*,*E*)-4-benzyl-3-(5-((*tert*-butyldimethylsilyl)oxy)pent-2-enoyl)oxazolidin-2-one: To a 250 mL round-bottomed flask containing 1.62 g (4.56 mmol, 1.2 equiv.) of (*S*)-diethyl (2-(4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)phosphonate was added 46 mL dry MeCN followed by 232 mg (5.47 mmol, 1.2 equiv.) LiCl and then 0.794 mL (4.56 mmol, 1 equiv.) *i*Pr_2NEt. The reaction was stirred at ambient temperature for 15 min before the addition of 1.03 g (5.47 mmol, 1 equiv.) aldehyde **3.5** dissolved in 5 mL dry MeCN. After stirring at ambient temperature for 12

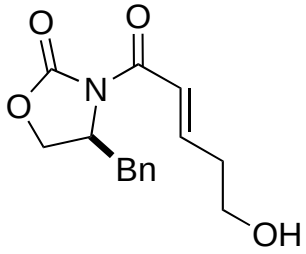
hr the reaction was added to brine, extracted into EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 1 : 1 hex./EtOAc to yield 1.30 g (73%) of the desired compound as a pale yellow oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.19-7.36 (m, 7H), 4.73 (m, 1H), 4.19 (m, 2H), 3.77 (t, *J* = 6.3, 2H), 3.33 (dd, *J* = 13.5, 3.0, 1H), 2.80 (dd, *J* = 13.5, 9.6, 1H), 2.52 (q, *J* = 6.6, 2H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}CNMR (75MHz, $CDCl_3$) δ 165.0, 153.6, 148.7, 135.6, 129.7, 129.2, 127.5, 122.0, 66.3, 61.8, 55.5, 38.1, 36.4, 26.1, 18.5, -5.1; R_f = 0.38 (4 : 1 hex./EtOAc).

Ref.: **BJEIV418**





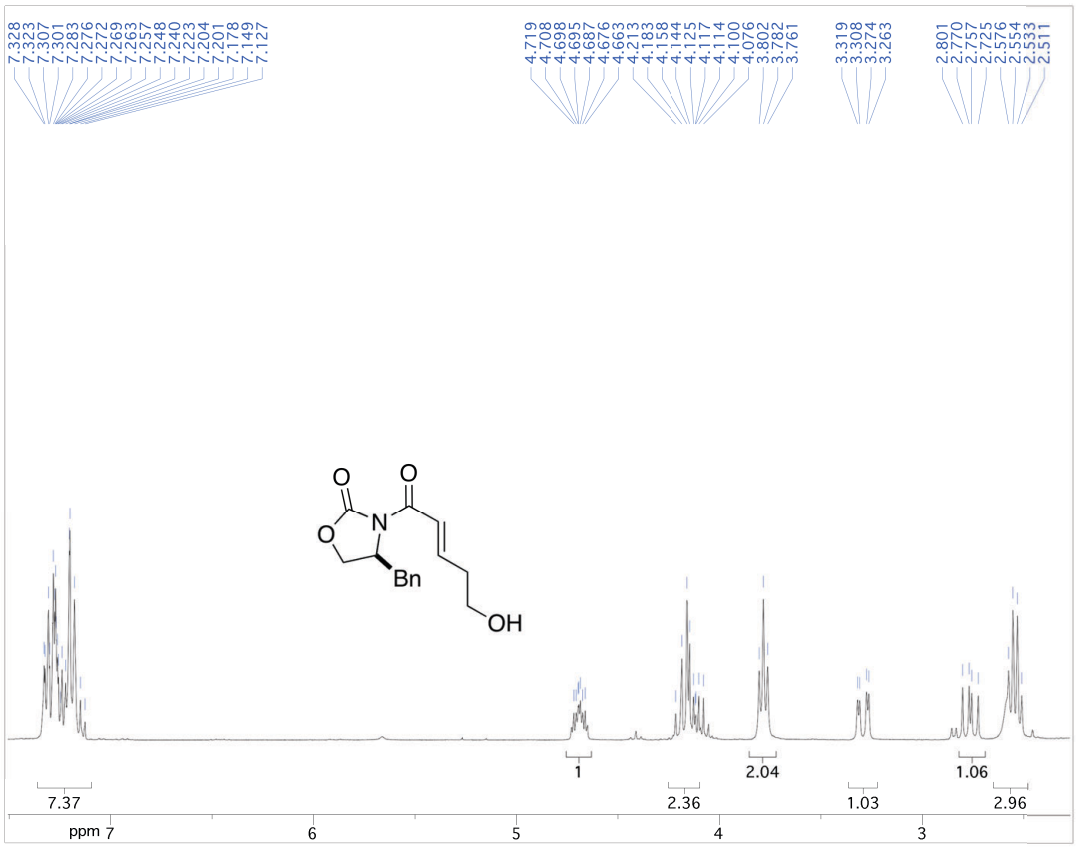


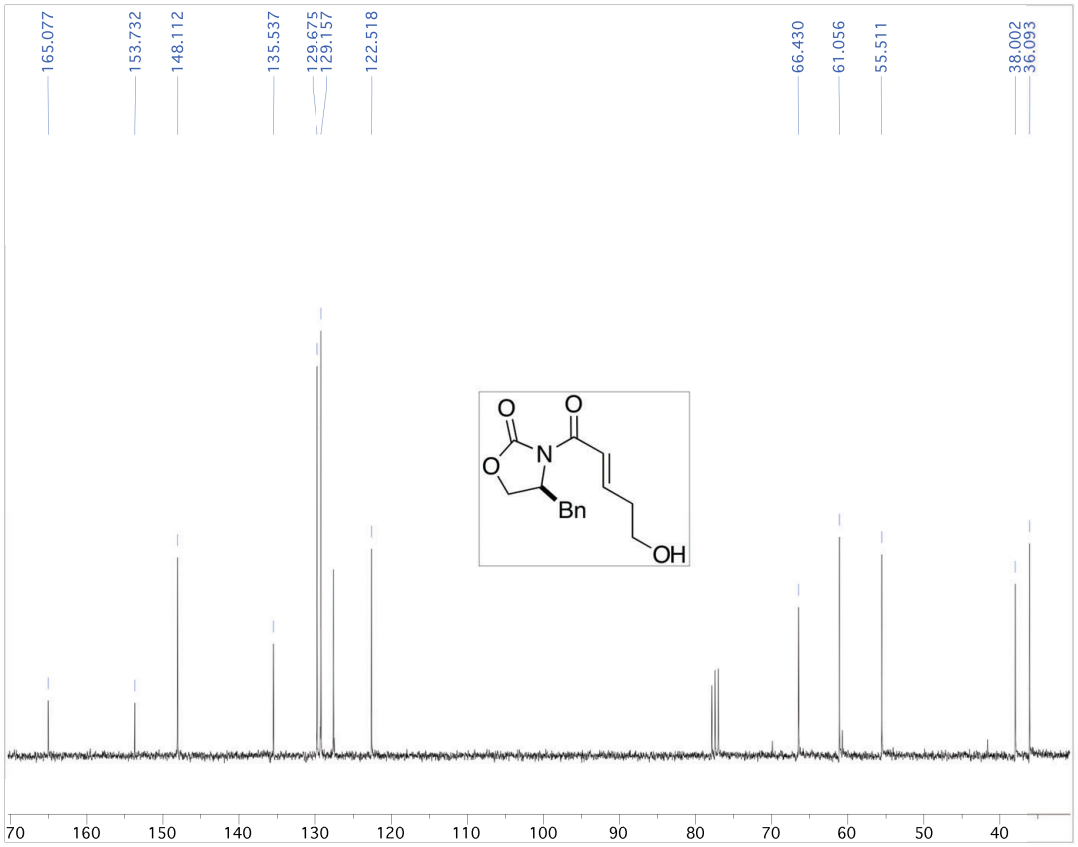
Synthesis of (*S*,*E*)-4-benzyl-3-(5-hydroxypent-2-enoyl)oxazolidin-2-one: To a 1 L HDPE bottle equipped with a stirbar was added 1.30 g (3.34 mmol, 1 equiv.) (*R*,*E*)-4-benzyl-3-(5-((*tert*-butyldimethylsilyl)oxy)pent-2-enoyl)oxazolidin-2-one dissolved in 20 mL dry THF. To this solution was slowly added 1.67 mL of a 48% aqueous solution of HF and the reaction was allowed to stir at ambient temperature for 5 hr before being slowly added to $NaHCO_{3(sat.)}$ and extracted into EtOAc, dried over Na_2SO_4, and

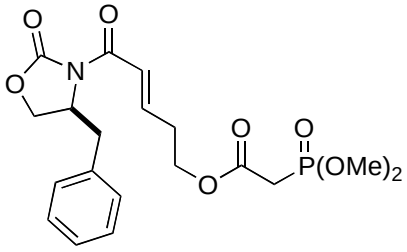
concentrated. Purification by silica gel flash chromatography eluting with 1 : 1 to 1 : 2 hex./EtOAc yielded 901 mg (98%) of the desired alcohol as a colorless oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.14-7.36 (m, 7H), 4.72 (m, 1H), 4.19 (m, 2H), 3.82 (q, *J* = 5.7, 2H), 3.34 (dd, *J* = 13.2, 3.3, 1H), 2.78 (dd, *J* = 13.2, 9.6, 1H), 2.57 (qd, *J* = 6.3, 1.2, 2H), 1.74 (t, *J* = 5.4, 1H), 1.70 (bs, 1H); ^{13}CNMR (75MHz, $CDCl_3$) δ 164.8, 153.5, 147.9, 135.3, 129.5, 128.9, 127.3, 122.3, 66.2, 60.8, 55.3, 37.8, 35.9; IR (NaCl, film): 3426, 1777, 1635 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 276.1236 calcd for $C_{15}H_{18}NO_4$, found: 276.1233; R_f = 0.19 (1 : 1 hex./EtOAc).

Ref.: BJEIV360, **BJEIV422**





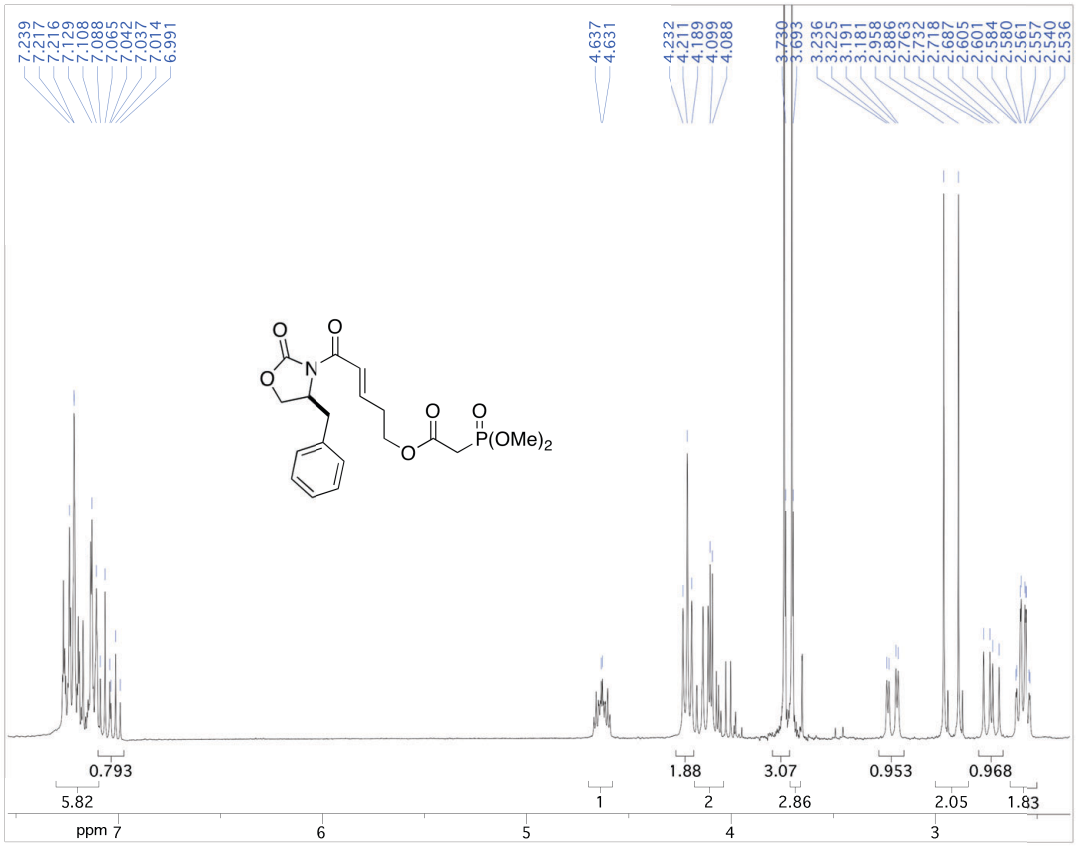


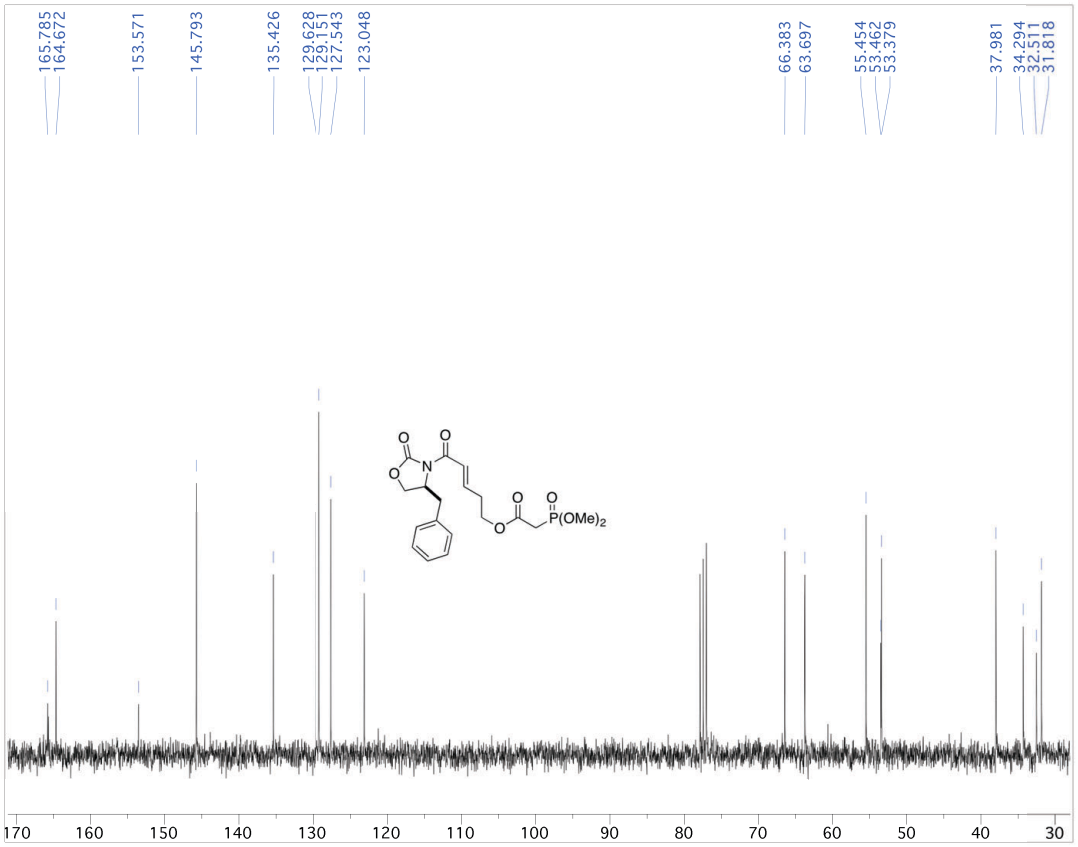
Synthesis of (*S*,*E*)-5-(4-benzyl-2-oxooxazolidin-3-yl)-5-oxopent-3-en-1-yl 2-(dimethoxyphosphoryl)acetate: To a 50 mL round-bottomed flask containing 648 mg (2.35 mmol, 1 equiv.) (*S*,*E*)-4-benzyl-3-(5-hydroxypent-2-enoyl)oxazolidin-2-one was added 12 mL dry CH_2Cl_2 followed by 475 mg (2.82 mmol, 1.2 equiv) 2-(dimethoxyphosphoryl)acetic acid and then 582 mg (2.82 mmol, 1.2 equiv.) DCC dissolved in a minimum of CH_2Cl_2. The reaction was allowed to stir for 30 min at ambient temperature before being filtered through a thin plug of celite and concentrated.

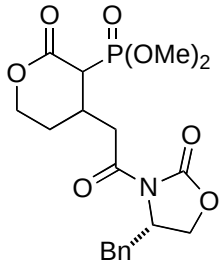
The resulting residue was purified by silica gel flash chromatography eluting with EtOAc to yield 998 mg (>99%) of the desired product as a colorless oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.11-7.27 (m, 6H), 7.04 (dt, *J* = 15.3, 6.9, 1H), 4.63 (m, 1H), 4.21 (t, *J* = 6.3, 2H), 4.10 (m, 2H), 3.74 (s, 3H), 3.70 (s, 3H), 3.21 (dd, *J* = 13.5, 3.3, 1H), 2.92 (d, J_{HP} = 21.6, 2H), 2.72 (dd, *J* = 13.5, 9.3, 1H), 2.57 (qd, *J* = 6.3, 1.2, 2H); ^{13}CNMR (75MHz, $CDCl_3$) δ 165.8, 164.7, 153.6, 145.8, 135.4, 129.6, 129.2, 127.5, 123.0, 66.4, 63.7, 55.5, 53.5, 38.0, 34.3, 32.5, 31.8; IR (NaCl, film): 1777, 1738, 16821639 cm^{-1}; HRMS (+TOF): $[M]^+$ 453.1553 calcd for $C_{21}H_{28}NO_8P$, found: 453.1553; R_f = 0.24 (EtOAc).

Ref.: BJEIV262, BJEIV362, **BJEIV429**





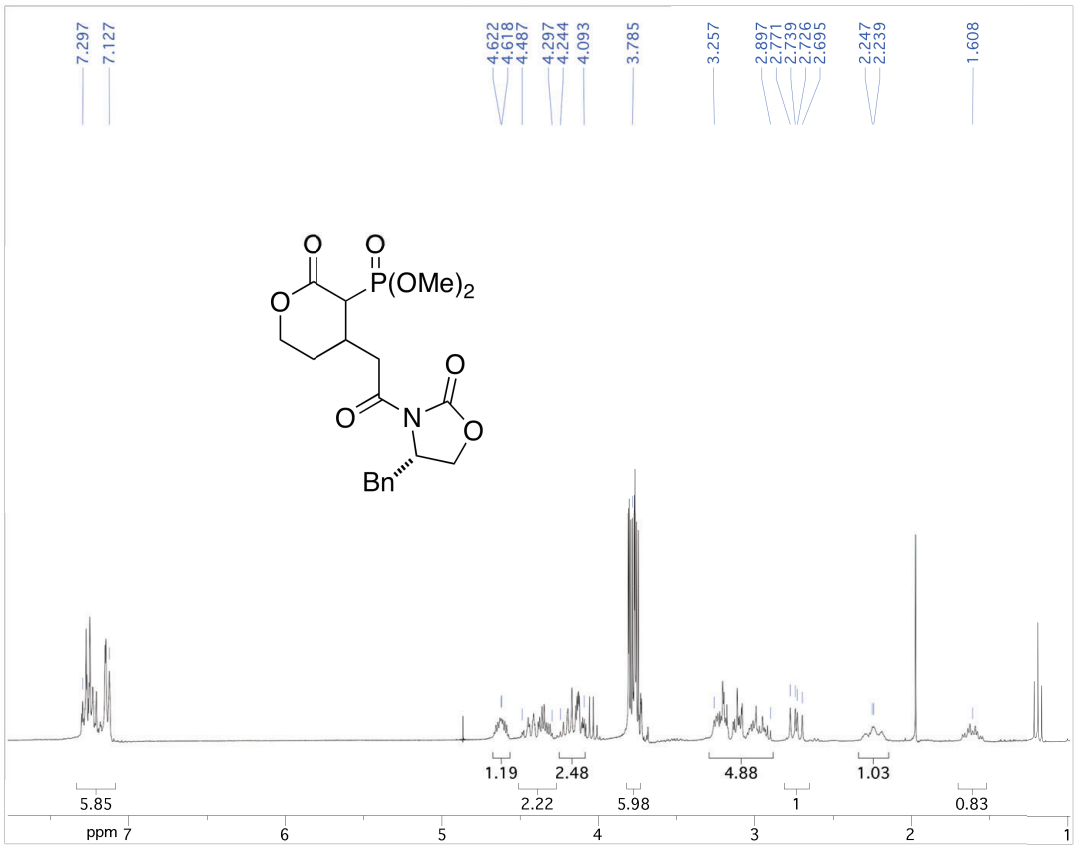


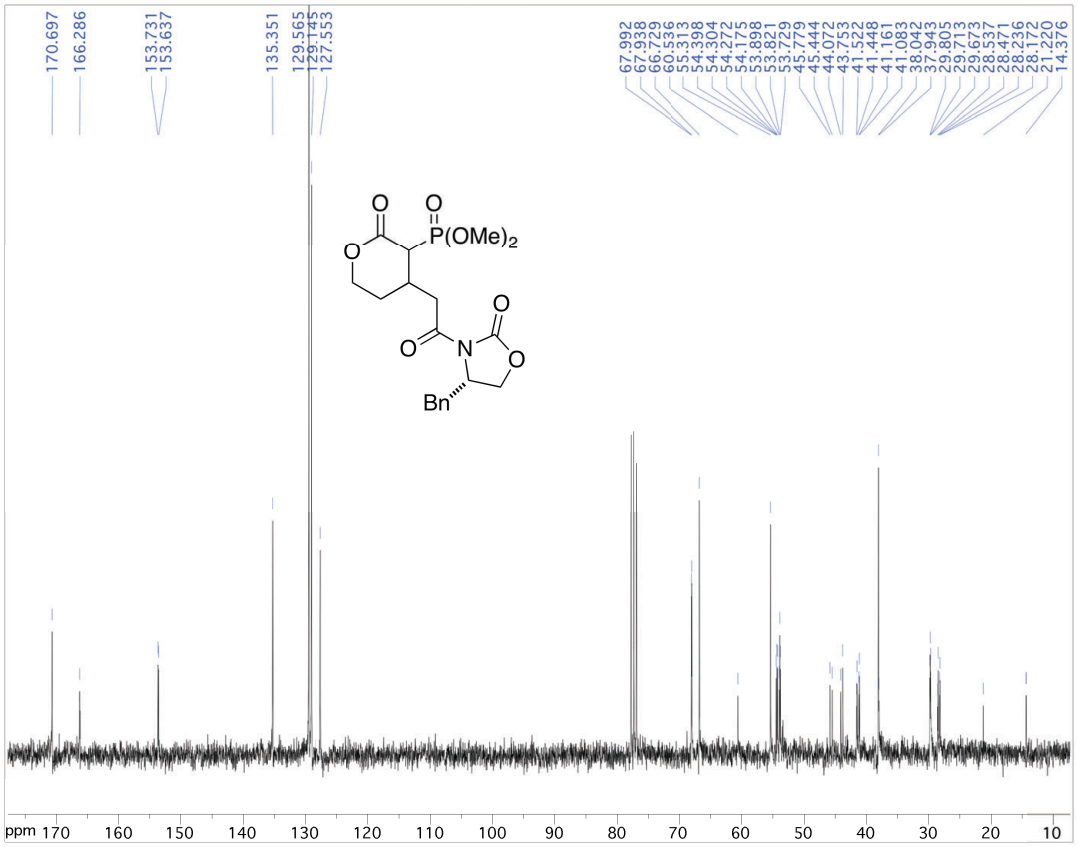
Synthesis of dimethyl (4-(2-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)-2-oxotetrahydro-2*H*-pyran-3-yl)phosphonate: To a 10 mL round-bottomed flask containing 149 mg (0.350 mmol, 1 equiv.) (*S*,*E*)-5-(4-benzyl-2-oxooxazolidin-3-yl)-5-oxopent-3-en-1-yl 2-(dimethoxyphosphoryl)acetate dissolved in 1.75 mL dry MeCN at -15°C was added 77 µL (0.700 mmol, 2 equiv.) $TiCl_4$ followed by 122 µL (0.700 mmol, 2 equiv.) *i*Pr_2NEt. The reaction was stirred at this temperature for 24 hr, added to 1 M HCl,

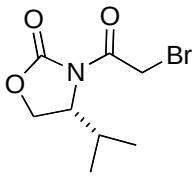
extracted into EtOAc, dried over Na_2SO_4, and concentrated to yield 64 mg (43%) of the desired product as a pale yellow foam.

^{1}HNMR (300 MHz, $CDCl_3$) δ 7.13-7.30 (m, 5H), 4.62 (m, 1H), 4.30-4.49 (m, 2H), 4.09-4.24 (m, 2H), 3.79 (m, 6H), 2.90-3.26 (m, 5H), 2.73 (dd, *J* = 13.5, 9.6, 1H), 2.24 (m, 1H), 1.61 (m, 1H);

Ref.: **BJEIV365**, BJEIV380, BJEIV400, BJEIV419.





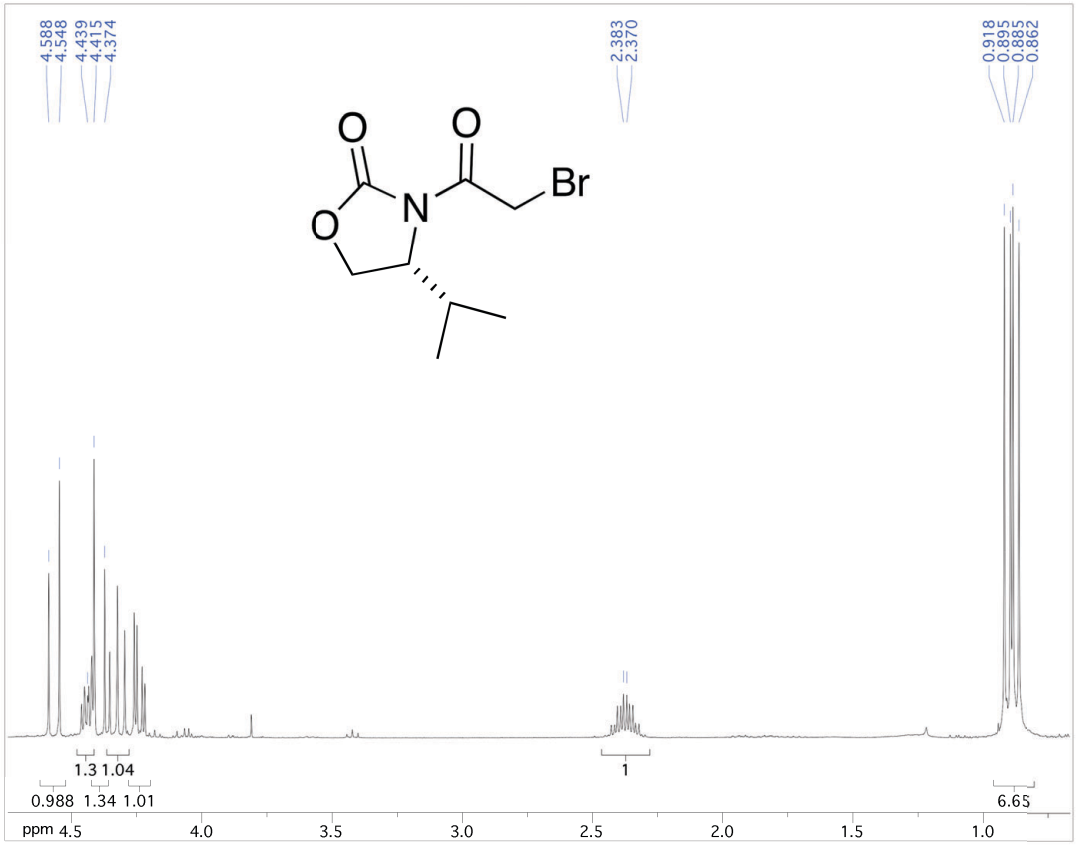


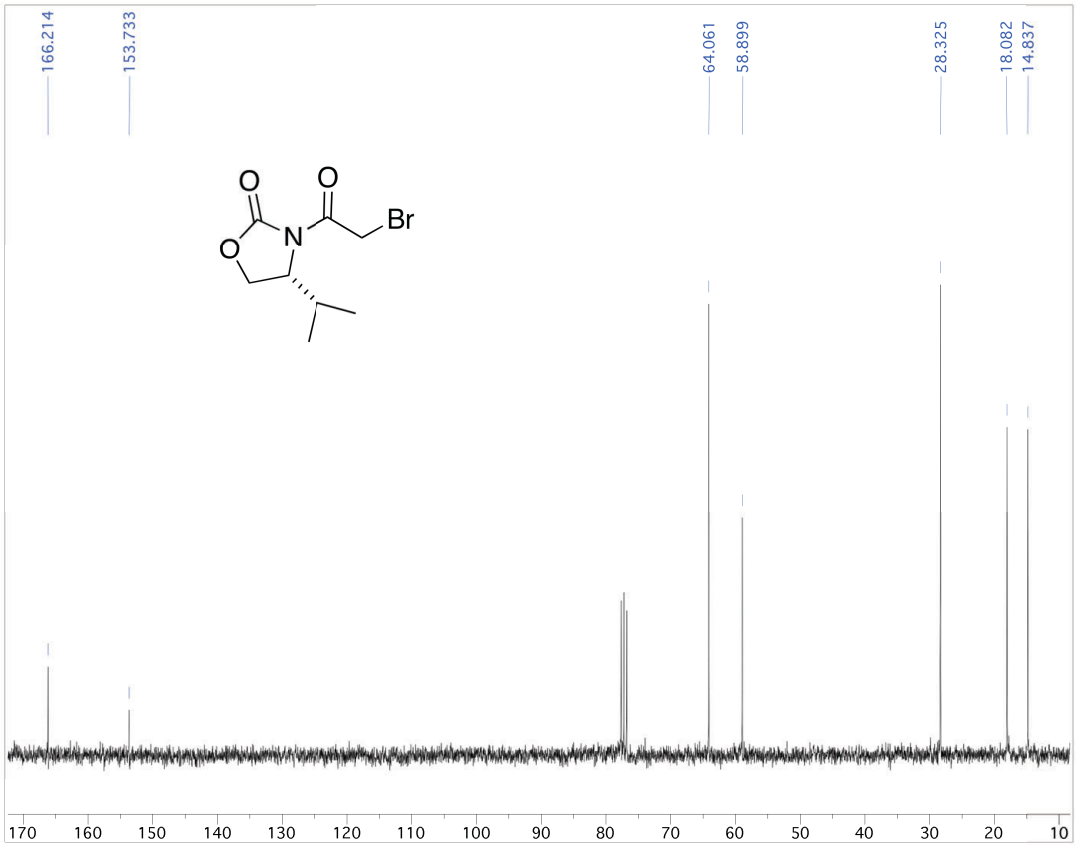
Synthesis of (*R*)-3-(2-bromoethanoyl)-4-isopropyloxazolidin-2-one: To a 50 ml flame dried round-bottomed flask containing 649 mg (5.02 mmol, 1 equiv.) (*R*)-4-isopropyloxazolidin-2-one dissolved in 24 mL dry THF at -78^{o}C was added 3.77 mL (1.6 M in hex, 6.02 mmol, 1.2 equiv.) *n*BuLi and the reaction was stirred at -78^{o}C for 30 min. To the reaction was then added 655 µL (7.53 mmol, 1.5 equiv.) bromoacetyl bromide and the reaction was stirred for 5 h at -78^{o}C and then 12 h at 0^{o}C. The reaction was then

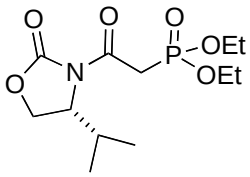
added to $NaHCO_{3(sat)}$, extracted thrice with EtOAc, combined organic layers were dried over Na_2SO_4, and then concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 9 : 1 to 4 : 1 hex./EtOAc to yield 1.25 g (>99%) of the desired product as a brown oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 4.59-4.22 (m, 5H), 2.38 (m, 1H), 0.89 (m, 6H). ^{13}CNMR (75MHz, $CDCl_3$) δ 166.2, 153.7, 64.1, 58.9, 28.3, 18.1, 14.8; IR (NaCl, film): 1779, 1701 cm^{-1}; ; $[\alpha]_D$ = -69.6; R_f = 0.56 (1 : 1 hex./EtOAc).

Ref: BJEII471, **BJEIV341.**





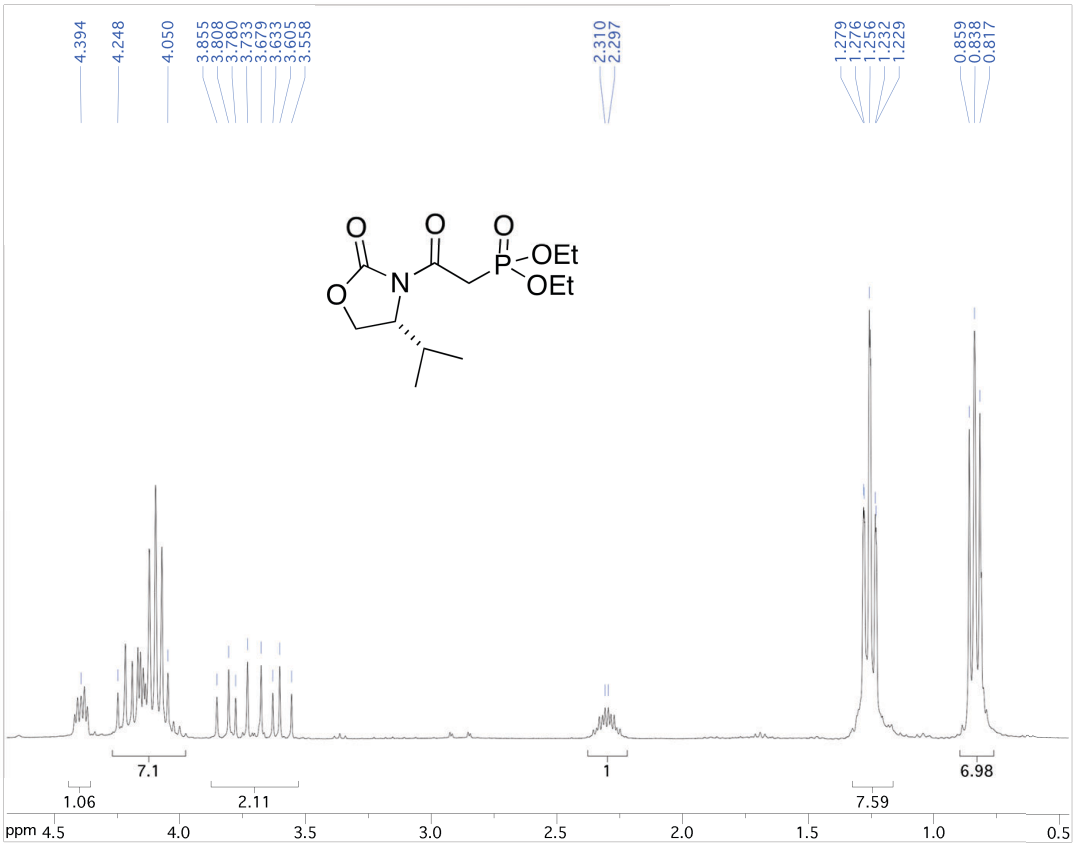


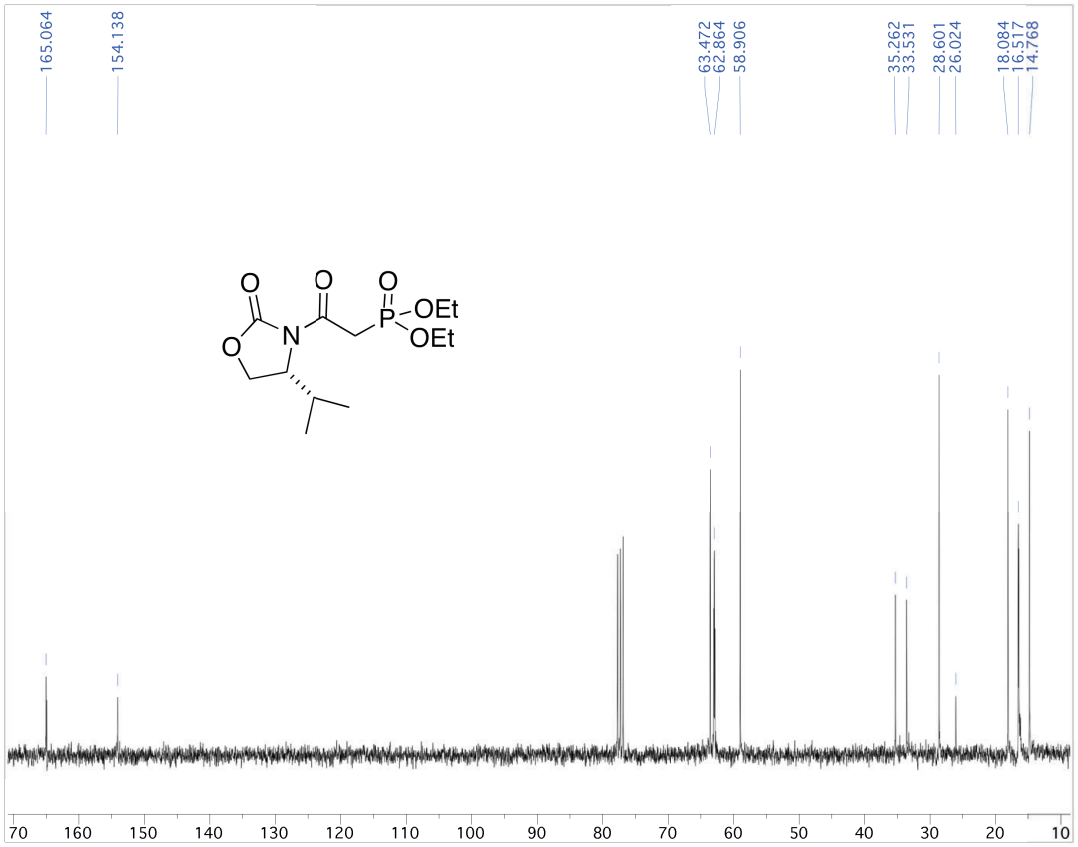
Synthesis of (*R*)-diethyl (2-(4-isopropyl-2-oxooxazolidin-3-yl)-2-oxoethyl)phosphonate: To a 10 mL round bottomed flask was charged 440 mg (1.75 mmol, 1 equiv.) (*R*)-3-(2-bromoethanoyl)-4-isopropyloxazolidin-2-one followed by 900 µL (5.26 mmol, 3 equiv.) $P(OEt)_3$. The reaction was heated to 100°C for 15 min and then concentrated to yield 576 mg (>99%) of the desired phosphonate as a crude red oil which was used without further purification.

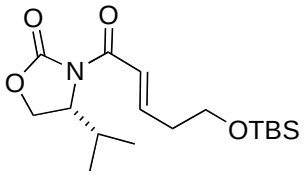
^{1}HNMR (300MHz, $CDCl_3$) δ 4.39 (m, 1H), 4.05-4.25 (m, 7H), 4.70 (m, 2H), 2.30 (m, 1H), 1.26 (t, *J* = 8.1, 6H), 0.84 (t, *J* = 6.3, 6H); ^{13}CNMR (300MHz, $CDCl_3$)δ 165.1, 154.1, 63.5, 62.9, 58.9, 35.3, 33.5, 28.6, 26.0, 18.1, 16.5, 14.8;

165.0, 154.1, 63.5, 62.8, 58.9, 32.3, 33.5, 28.6, 18.1, 16.4, 14.8; IR (NaCl, film): 1778, 1696 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 308.1263 calcd for $C_{12}H_{23}NO_6P$, found: 308.1265; $[\alpha]_D$ = -48.1; R_f = 0.47 (EtOAc.)

Ref: BJEII473, **BJEIII007**, BJEIV344





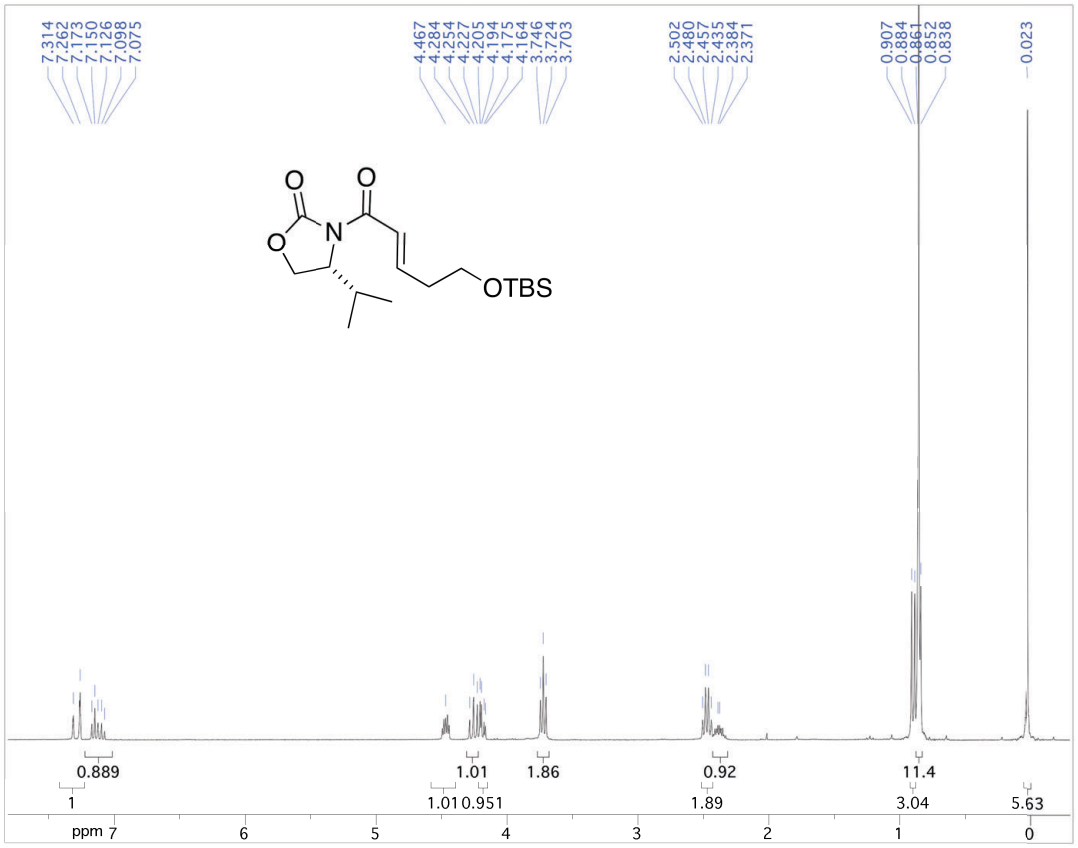


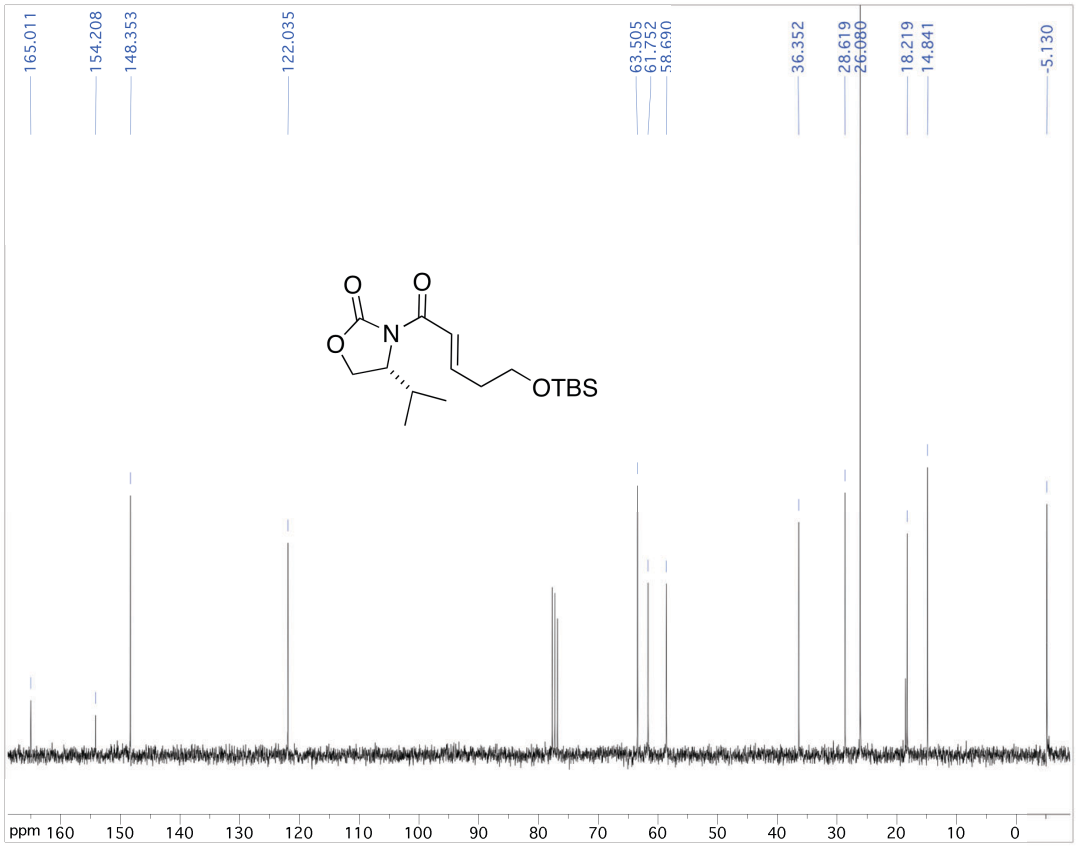
Synthesis of (*R,E*)-3-(5-(*tert*-butyldimethylsilyloxy)pent-2-enoyl)-4-isopropyloxazolidin-2-one: To a 25 mL round-bottomed flask containing 195 mg (0.635 mmol, 1.2 equiv.) (*R*)-diethyl (2-(4-isopropyl-2-oxooxazolidin-3-yl)-2-oxoethyl)phosphonate and 27mg (0.635 mmol, 1.2 equiv.) LiCl dissolved in 3 mL dry MeCN was added 92 μL (0.529 mmol, 1 equiv.) iPr_2NEt. The reaction was stirred at ambient temperature for 30 min then 100mg (0.529 mmol, 1 equiv.) aldehyde **3.5** dissolved in 1 mL dry MeCN was added. The reaction was stirred at ambient temperature for a further 16 hr and was then added to brine and extracted thrice into

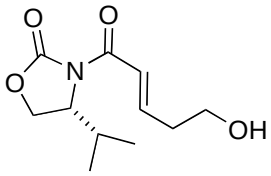
EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated, and purified by flash silica gel chromatography eluting with 9 : 1 to 4 : 1 hex./EtOAc to yield 133 mg (73%) of the desired product as a colorless oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.29 (d, *J* = 15.6, 1H), 7.13 (dt, *J* = 15.6, 6.9, 1H), 4.47 (m, 1H), 4.25 (t, *J* = 9.0, 1H), 4.18 (dd, *J* = 9.0, 3.3, 1H), 3.72 (t, *J* = 6.6, 2H), 2.47 (q, *J* = 6.9, 2H), 2.37 (m, 1H), 0.89 (d, *J* = 6.9, 3H), 0.85 (d, *J* = 6.9, 3H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}CNMR (300MHz, $CDCl_3$)δ 165.0, 154.2, 148.4, 122.0, 63.5, 61.8, 58.7, 36.4, 28.6, 26.0, 18.22, 14.84, –5.1; IR (NaCl, film): 1778, 1683, 1638 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 342.2100 calcd for $C_{17}H_{32}NO_4Si$, found: 342.2100; $[\alpha]_D$ = -55.6; R_f = 0.29 (4 :1 hex./EtOAc).

Ref: **BJEII477**, BJEIII011



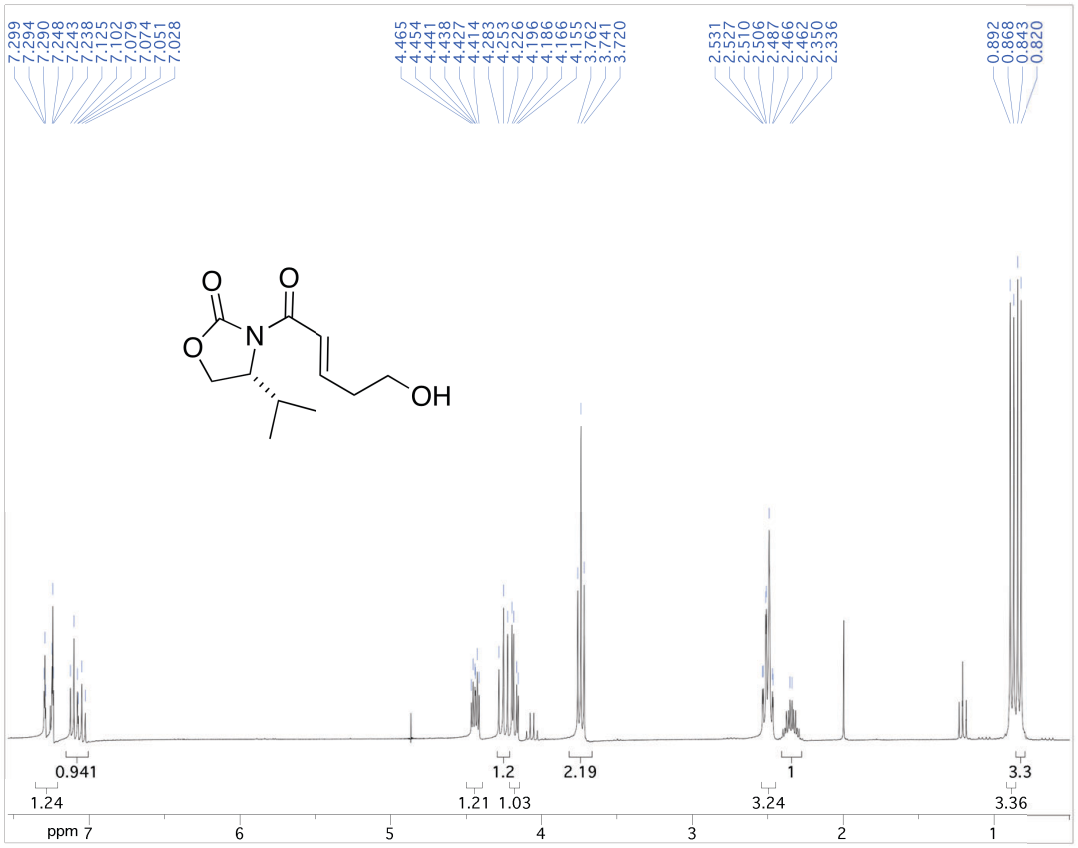


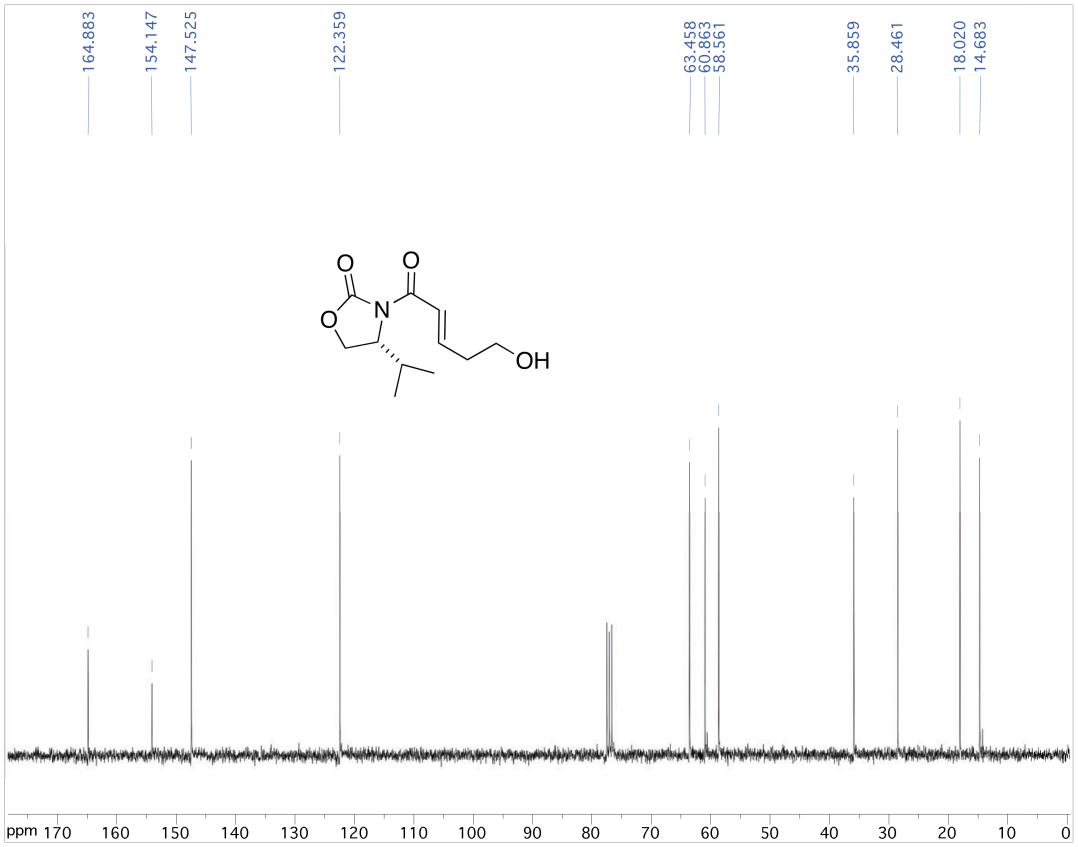


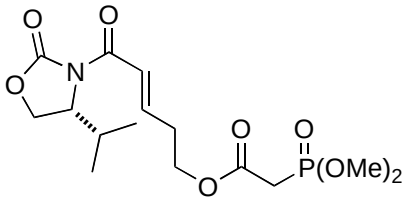
Synthesis of (*R*,*E*)-3-(5-hydroxypent-2-enoyl)-4-isopropyloxazolidin-2-one: To 84 mg (0.246 mmol, 1 equiv.) (*R*,*E*)-3-(5-(*tert*-butyldimethylsilyloxy)pent-2-enoyl)-4-isopropyloxazolidin-2-one in 3mL dry THF was added 132 μL HF (48% in H_2O). After stirring for 5 hr at ambient temperature the reaction was slowly added to $NaHCO_{3(sat)}$ and extacted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated to yield 53mg of the desired alcohol as a (95%) colorless oil. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.30 (dt, *J* = 15.3, 1.5, 1H), 7.10 (dt, *J* = 15.3, 6.9, 1H), 4.44 (dt, *J* = 8.1, 3.3, 1H), 4.16-4.28 (m, 2H), 3.74 (t, *J* = 6.3, 2H), 2.52 (qd, *J* = 6.3, 1.2, 2H), 2.48 (s, 1H), 2.34 (m, 1H),

0.88 (d, *J* = 7.2, 3H), 0.83 (d, *J* = 7.2, 3H); ^{13}CNMR (300MHz, $CDCl_3$) δ 164.9, 154.2, 147.5, 122.4, 63.5, 60.9, 58.6, 35.9, 28.5, 18.0, 14.7; IR (NaCl, film): 3470, 1758, 1674, 1635 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 228.1230 calcd for $C_{11}H_{18}NO_4$, found: 228.1232; $[\alpha]_D$ = -97.4; R_f = 0.14 (1 :1 hex./EtOAc).

Ref: BJEII485, **BJEIII009**, BJEIII014





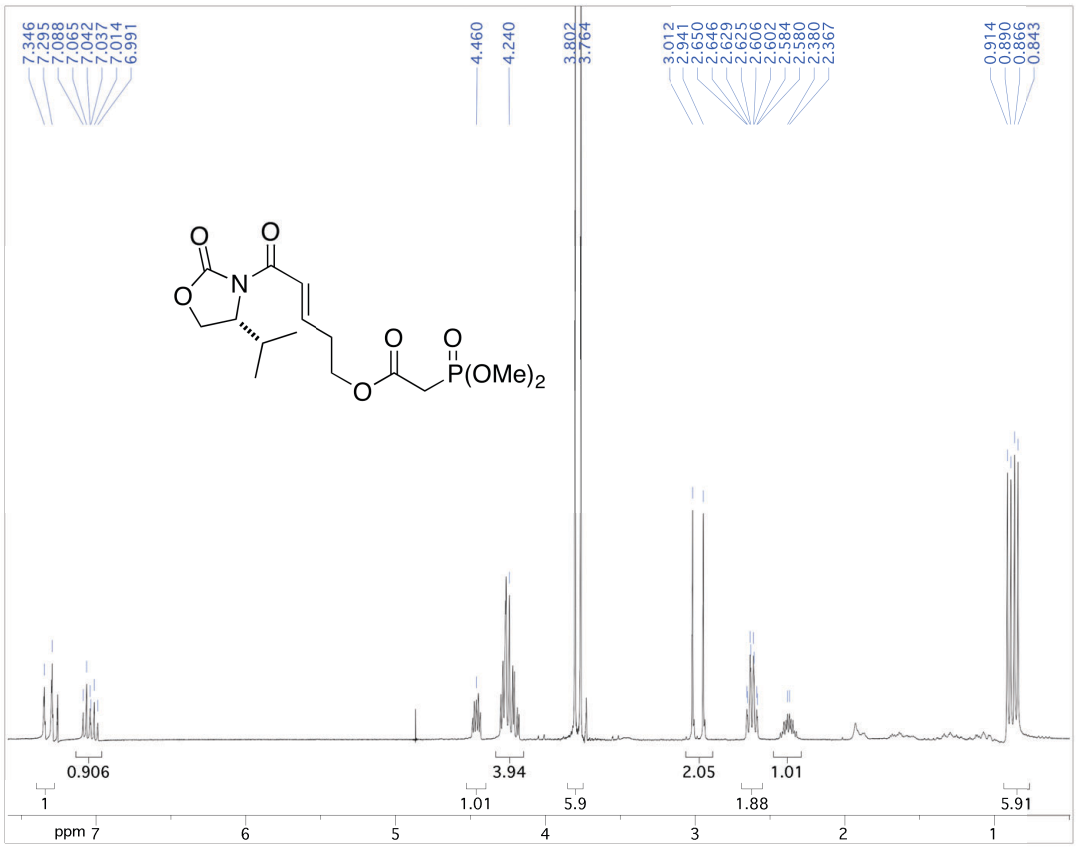


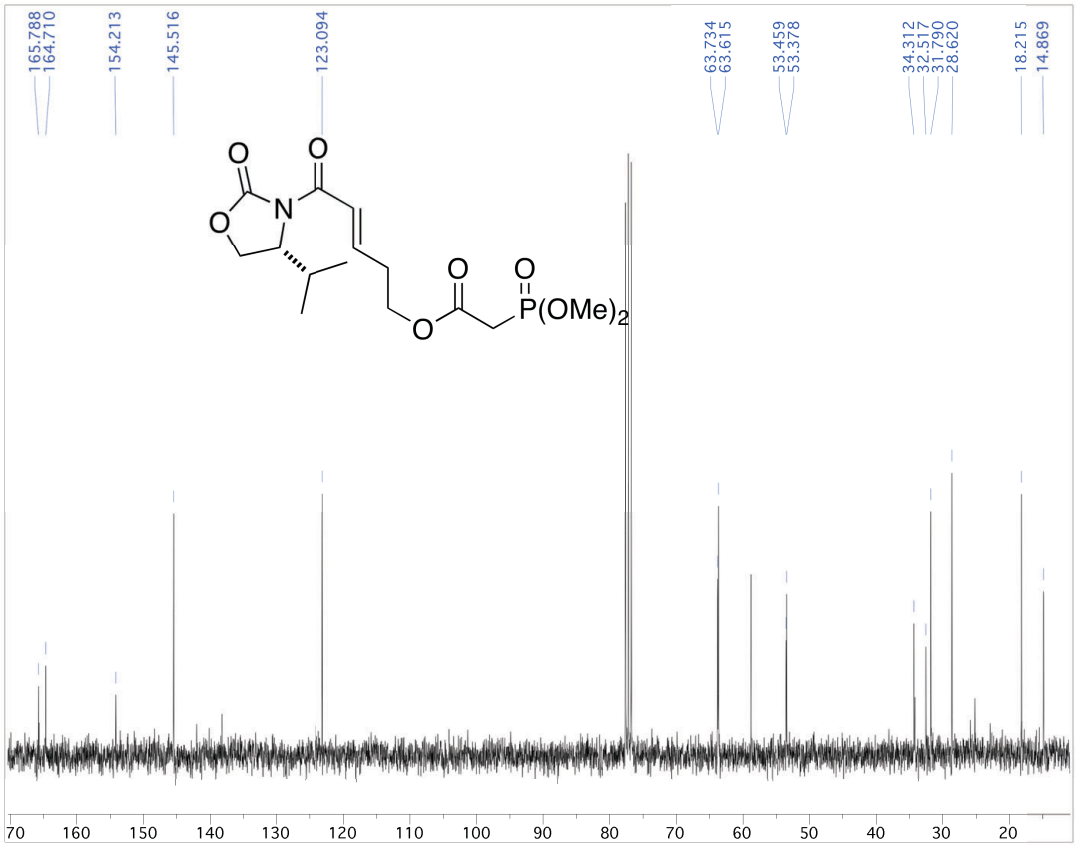
Synthesis of (*R*,*E*)-5-(4-isopropyl-2-oxooxazolidin-3-yl)-5-oxopent-3-en-1-yl 2-(dimethoxyphosphoryl)acetate (4.53): To a 25 mL round-bottomed flask containing 347 mg (1.53 mmol, 1 equiv.) (*R*,*E*)-3-(5-hydroxypent-2-enoyl)-4-isopropyloxazolidin-2-one dissolved in 7.65 mL dry CH_2Cl_2 was added 308 mg (1.83 mmol, 1.2 equiv.) 2-(dimethoxyphosphoryl)acetic acid followed by 378 mg (1.83 mmol, 1.2 equiv.) DCC. The reaction was stirred at ambient temperature for 45 min before being filtered through celite and concentrated. The resulting residue was purified by silica gel flash

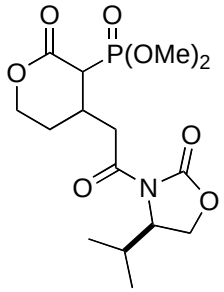
chromatography eluting with EtOAc to yield 579 mg (>99%) of the desired product as a colorless oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.32 (d, J = 15.3, 1H), 7.04 (dt, J = 15.3, 6.9, 1H), 4.46 (m, 1H), 4.24 (m, 4H), 3.80 (s, 3H), 3.76 (s, 3H), 2.97 (d, J_{HP} = 21.3, 2H), 2.61 (qd, J = 6.3, 1.2, 2H), 2.37 (m, 1H), 0.90 (d, J = 7.2, 3H), 0.85 (d, J = 7.2, 3H); ^{13}CNMR (75MHz, $CDCl_3$) δ 165.8, 164.7, 154.2, 145.5, 123.1, 63.7, 63.6, 53.5, 53.4, 34.3, 32.5, 31.8, 28.6, 18.2, 14.9; R_f = 0.28 (EtOAc).

Ref.: **BJEIV353**





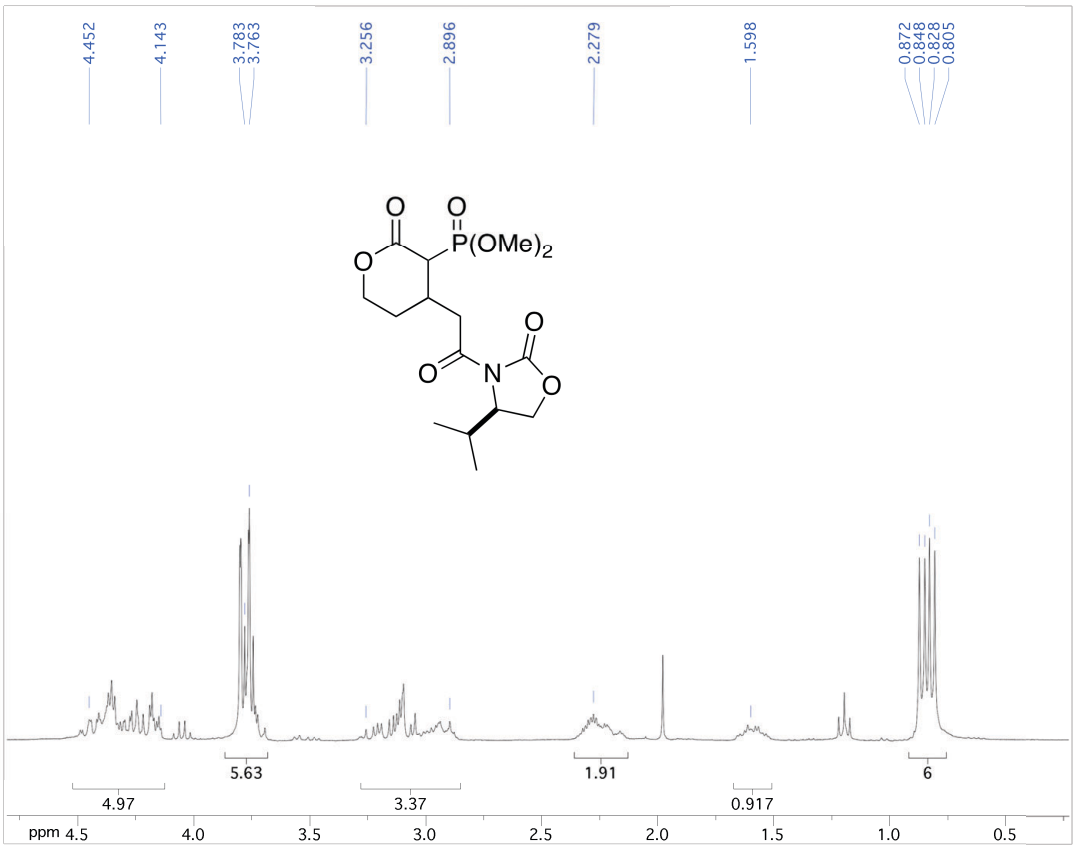


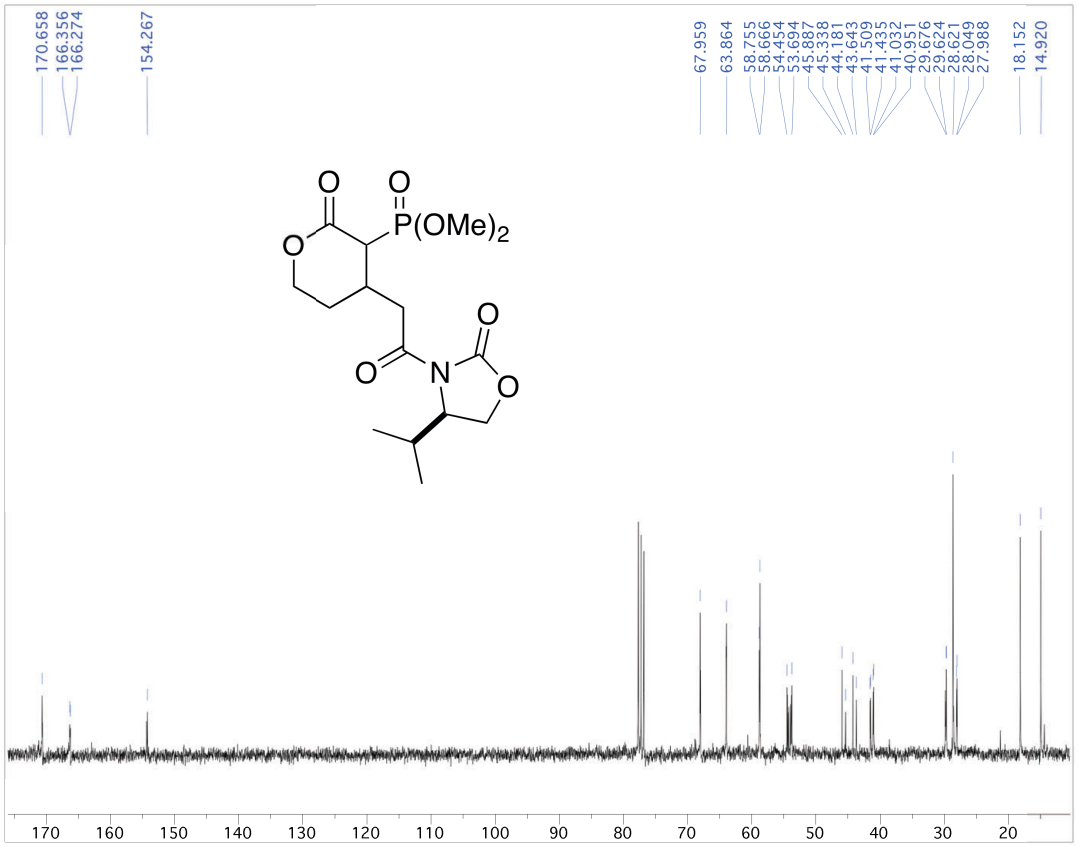
Synthesis of dimethyl (4-(2-((*R*)-4-isopropyl-2-oxooxazolidin-3-yl)-2-oxoethyl)-2-oxotetrahydro-2*H*-pyran-3-yl)phosphonate: To a 10 mL round-bottomed flask containing 239 mg (0.633 mmol, 1 equiv.) linear substrate **4.53** dissolved in 3.5 mL dry MeCN was added 413 mg (1.27 mmol, 2 equiv.) Cs_2CO_3. The reaction was heated to 40^{o}C for 1.5 hr before being added to 1 N HCl, extracted into EtOAc, dried over Na_2SO_4, and concentrated. The crude residue was purified by silica gel flash chromatography

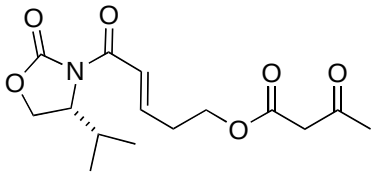
eluting with 1% to 5 % MeOH in EtOAc to yield 93 mg of the desired product as a pale yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 4.14-4.45 (m, 5H), 3.77 (m, 6H), 2.90-3.26 (m, 3H), 2.28 (m, 2H), 1.60 (m, 1H), 0.85 (d, *J* = 7.2, 3H), 0.81 (d, *J* = 7.2, 3H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 170.7, 166.3, 154.3, 68.0, 63.9, 58.7, 54.5, 53.7, 45.9, 44.2, 43.6, 41.5, 41.4, 41.0, 29.7, 29.6, 28.6, 28.0, 18.2, 14.9; R_f = 0.24 (EtOAc)

Ref.: **BJEIV358**.





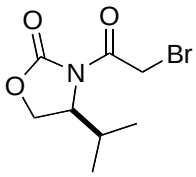


Synthesis of (*R*,*E*)-5-(4-isopropyl-2-oxooxazolidin-3-yl)-5-oxopent-3-enyl 3-oxobutanoate: To a 10 mL round-bottomed flask charged with 32 mg (0.141 mmol, 1 equiv.) (*R*,*E*)-3-(5-hydroxypent-2-enoyl)-4-isopropyloxazolidin-2-one dissolved in 2 mL CH_2Cl_2 at -10°C was added 22 μL (0.299 mmol, 2 equiv.) diketene followed by a spatula tip of DMAP. The reaction was stirred for 15min at -10°C and then 30 min at ambient temperature before being diluted with CH_2Cl_2, washed twice with $NaHCO_{3(sat)}$, dried over Na_2SO_4, and concentrated. The crude residue purified by silica gel flash chromatography

eluting with 2 : 1 to 1 : 1 hex./EtOAc to yield 43 mg (98%) of the desired compound as a pale yellow oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.30 (d, *J* = 15.6, 1H), 7.03 (dt, *J* = 15.3, 6.9, 1H)., 4.47 (m, 1H), 4.26 (m, 4H), 3.45 (s, 2H), 2.61 (q, *J* = 6.3, 2H), 2.37 (m, 1H), 2.23 (s, 3H), 0.90 (d, *J* = 7.2, 3H), 0.85 (d, *J* = 7.2, 3H); R_f = 0.37 (1 : 1 hex:EtOAc).

Ref: BJEII482, **BJEII488**, BJEIII016,

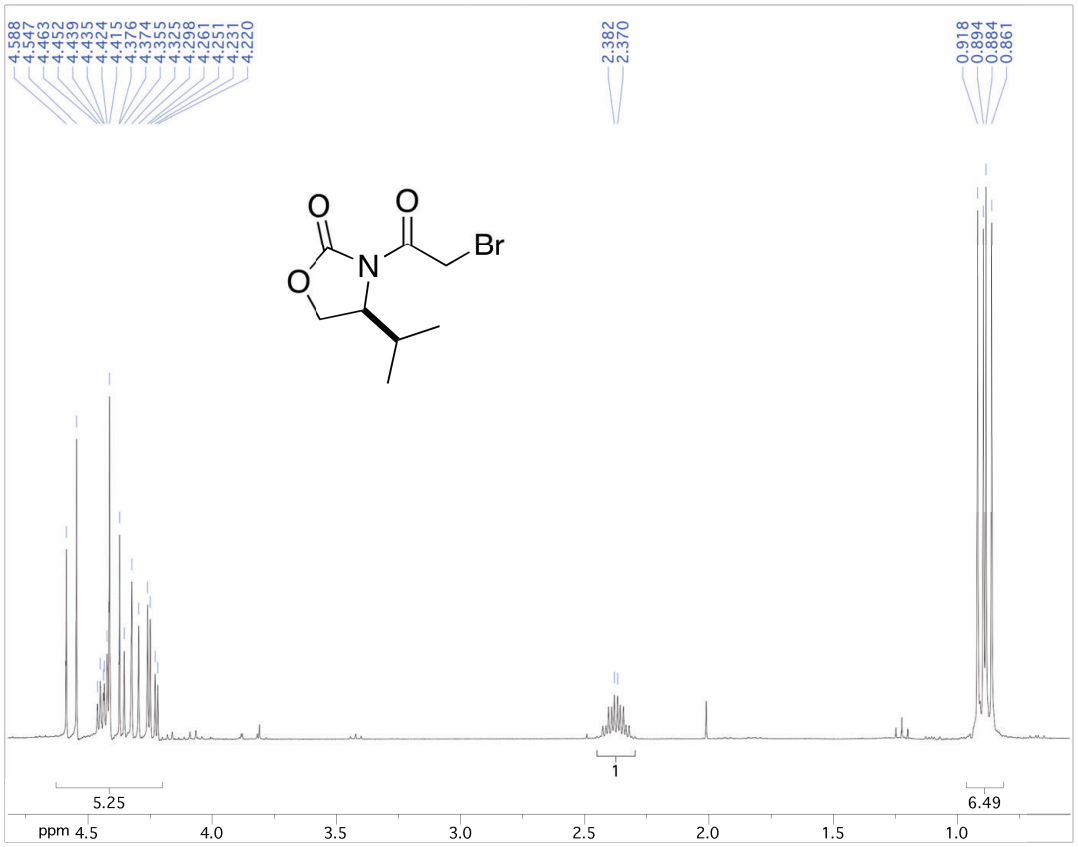


Synthesis of (S)-3-(2-bromoacetyl)-4-isopropyloxazolidin-2-one: To a 250 ml flame dried round-bottomed flask containing 6.25 g (48.4 mmol, 1 equiv.) (*S*)-4-

isopropyloxazolidin-2-onedissolved in 100 mL dry THF at -78^{o}C was added 36.3 mL (1.6 M in hex, 58.1 mmol, 1.2 equiv.) *n*BuLi and the reaction was stirred at -78^{o}C for 30 min. To the reaction was then added 6.31 mL (72.6 mmol, 1.5 equiv.) bromoacetyl bromide and the reaction was stirred for 5 h at -78^{o}C and then 12 h at 0^{o}C. The reaction was then added to $NaHCO_{3(sat)}$, extracted thrice with EtOAc, combined organic layers were dried over Na_2SO_4, and then concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 2 : 1 to 1 : 1 hex./EtOAc to yield 9.76 g (81%) of the desired product as a brown oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 4.59-4.22 (m, 5H), 2.38 (m, 1H), 0.89 (m, 6H). ^{13}CNMR (75MHz, $CDCl_3$) δ 166.2, 153.7, 64.1, 58.9, 28.3, 18.1, 14.8; IR (NaCl, film): 1770, 1699 cm^{-1}; $[\alpha]_D$ = +69.6; R_f = 0.14 (4 : 1 hex./EtOAc).

Ref: BJEII471, BJEIV341, **BJEIV476.**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4.415
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4.261
4.251
4.231
4.220
2.382
2.370
0.918
0.894
0.884
0.861
O
O
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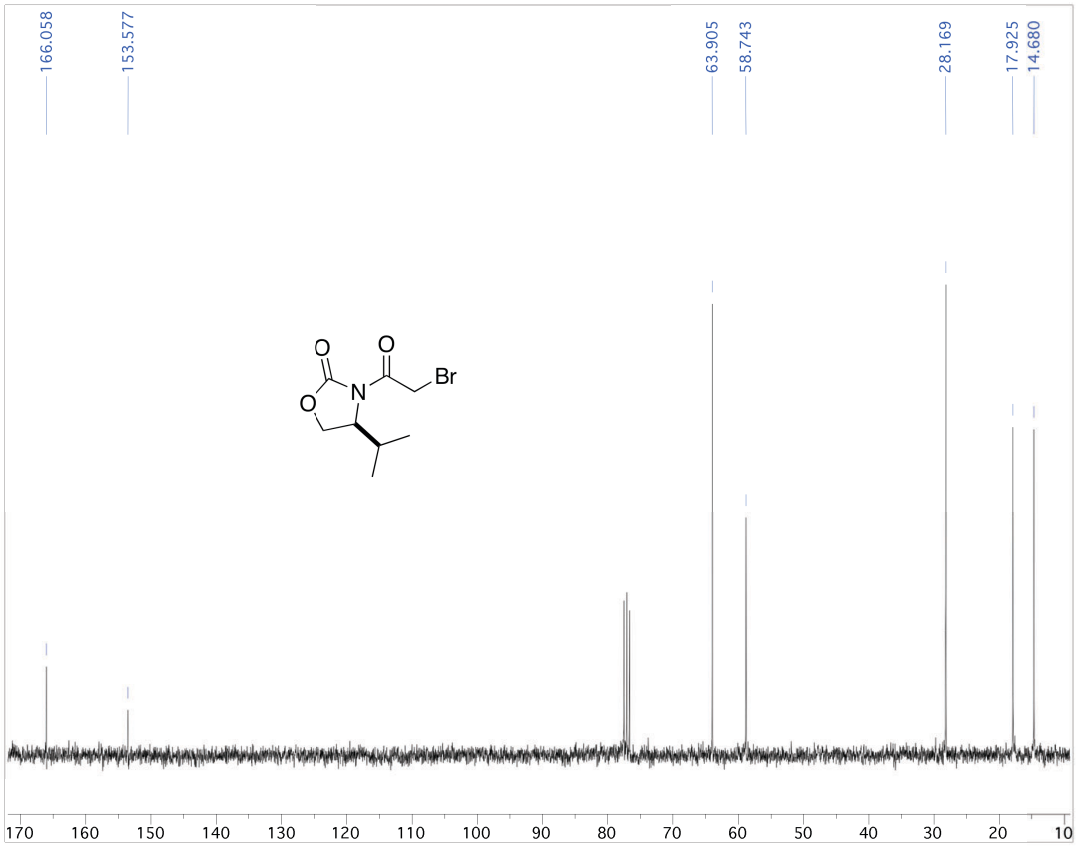
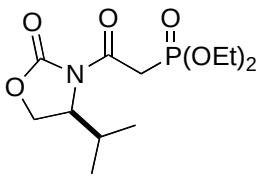


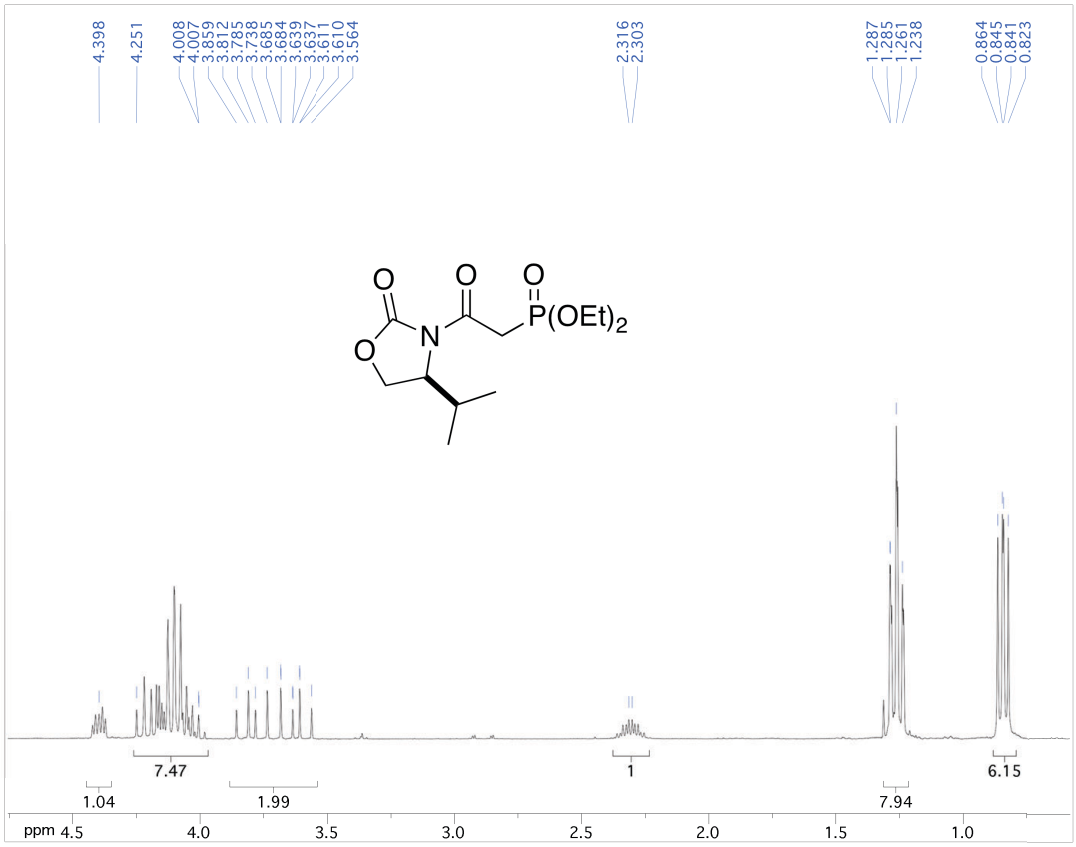


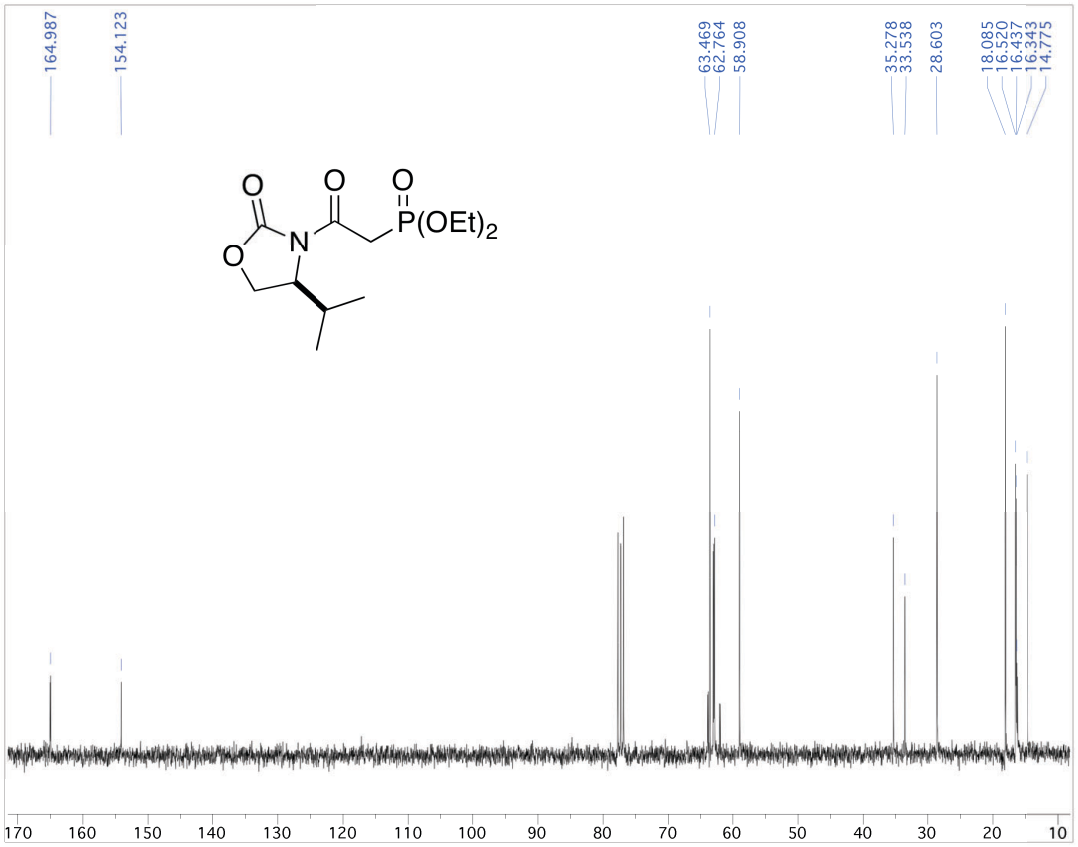
Synthesis of (*S*)-diethyl (2-(4-isopropyl-2-oxooxazolidin-3-yl)-2-oxoethyl)phosphonate: To a 100 mL round bottomed flask was charged 9.76 g (39.0 mmol, 1 equiv.) (S)-3-(2-bromoacetyl)-4-isopropyloxazolidin-2-one followed by 20 mL (117.1 mmol, 3 equiv.) $P(OEt)_3$. The reaction was heated to 100^{o}C for 20 min and then concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 1 : 2 hex./EtOAc to).

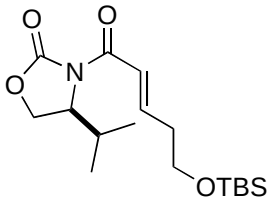
^{1}HNMR (300MHz, $CDCl_3$) δ 4.40 (m, 1H), 4.01-4.25 (m, 6H), 3.56-3.86 (m, 2H), 2.31 (m, 1H), 1.26 (t, *J* = 6.9, 6H), 0.84 (dd, *J* = 6.9, 5.7, 6H); ^{13}CNMR (75MHz,

$CDCl_3$)δ 165.0, 154.1, 63.5, 62.8, 58.9, 32.3, 33.5, 28.6, 18.1, 16.4, 14.8; IR (NaCl, film): 1778, 1696 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 308.1263 calcd for $C_{12}H_{23}NO_6P$, found: 308.1265; $[\alpha]_D$ = +48.5; R_f = 0.27 (1 : 2 hex./EtOAc).

Ref.: **BJEIV480**.





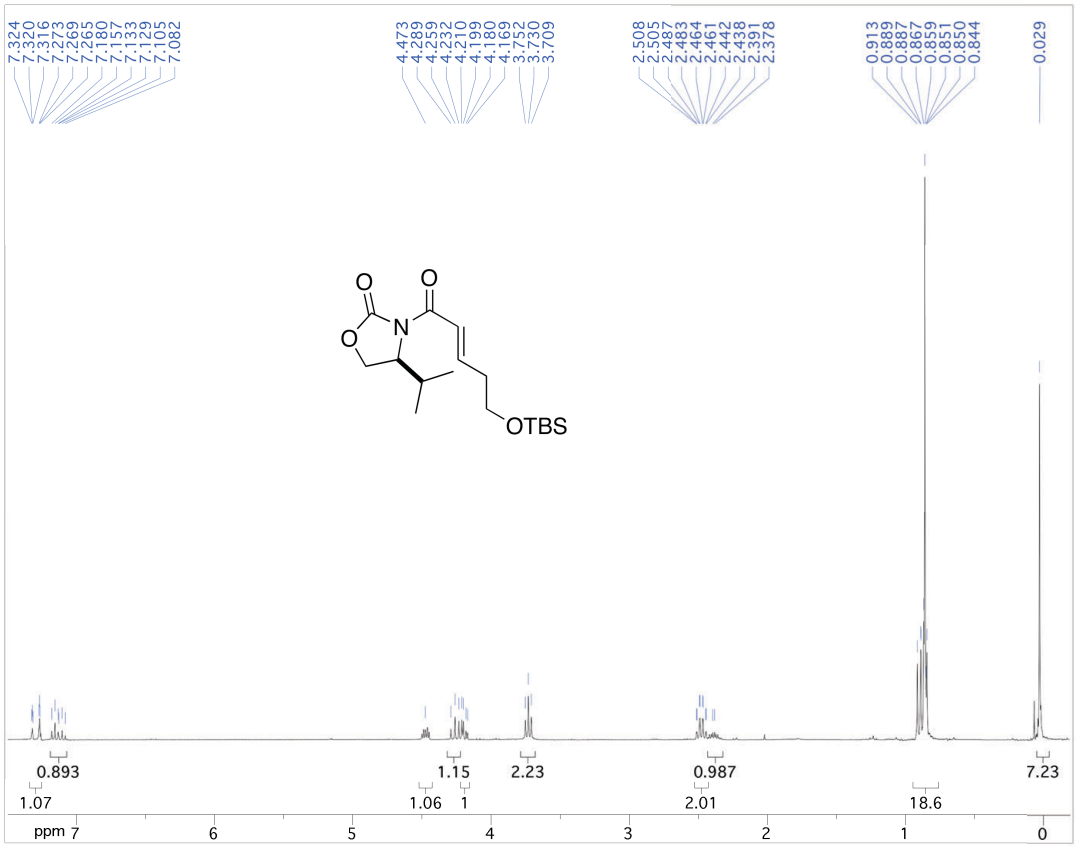


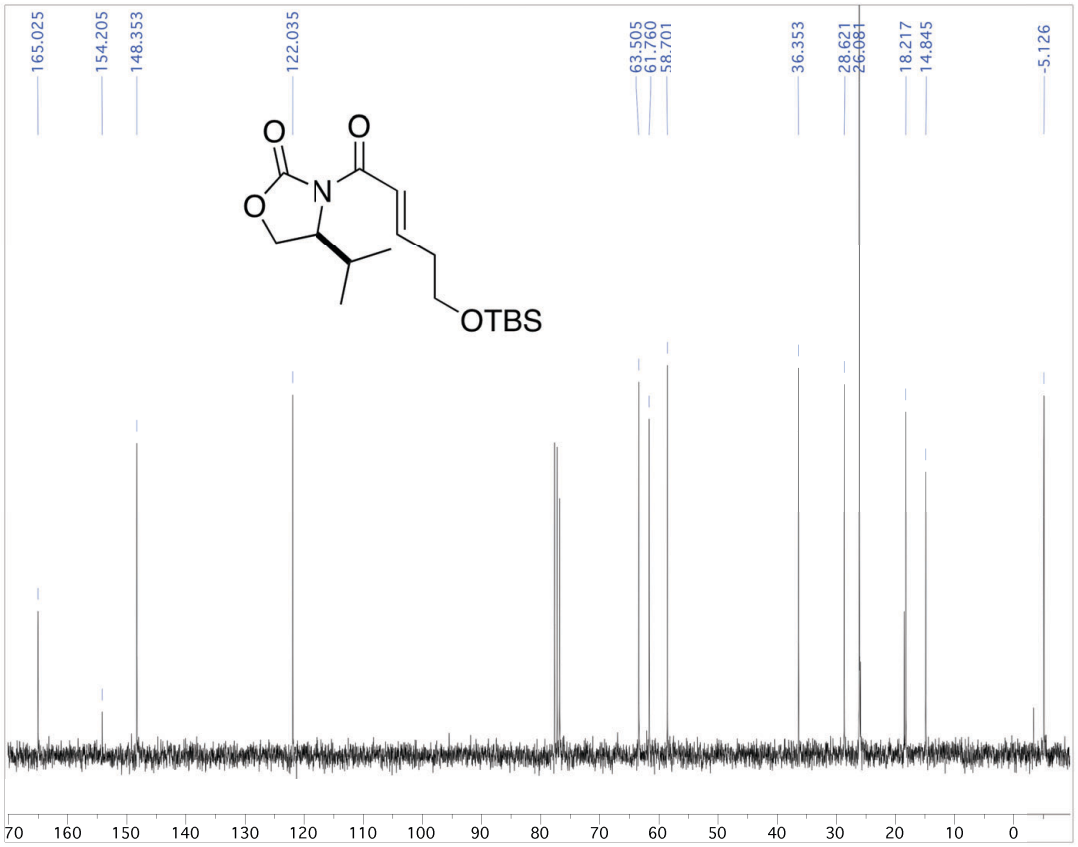
Synthesis of (*S*,*E*)-3-(5-((*tert*-butyldimethylsilyl)oxy)pent-2-enoyl)-4-isopropyloxazolidin-2-one: To a 500 mL round-bottomed flask containing 11.98 g (38.99 mmol, 1 equiv.) (*S*)-diethyl (2-(4-isopropyl-2-oxooxazolidin-3-yl)-2-oxoethyl)phosphonate and 1.98 g (46.78 mmol, 1.2 equiv.) LiCl dissolved in 200 mL dry MeCN was added 6.79 mL (38.99 mmol, 1 equiv.) *i*Pr_2NEt. The reaction was stirred at ambient temperature for 30 min then 8.81 g (46.78 mmol, 1 equiv.) aldehyde **3.5** dissolved in 10 mL dry MeCN was added. The reaction was stirred at ambient temperature for a further 16 hr and was then added to brine and extracted thrice into

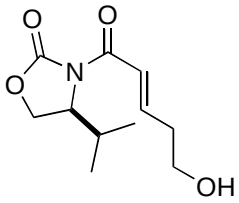
EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated, and purified by flash silica gel chromatography eluting with 9 : 1 to 4 : 1 hex./EtOAc to yield 6.68 g (50%) of the desired product as a colorless oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.29 (d, *J* = 15.6, 1H), 7.13 (dt, *J* = 15.6, 6.9, 1H), 4.47 (m, 1H), 4.25 (t, *J* = 9.0, 1H), 4.18 (dd, *J* = 9.0, 3.3, 1H), 3.72 (t, *J* = 6.6, 2H), 2.47 (q, *J* = 6.9, 2H), 2.37 (m, 1H), 0.89 (d, *J* = 6.9, 3H), 0.85 (d, *J* = 6.9, 3H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}CNMR (300MHz, $CDCl_3$)δ 165.0, 154.2, 148.4, 122.0, 63.5, 61.8, 58.7, 36.4, 28.6, 26.0, 18.22, 14.84, –5.1; IR (NaCl, film): 1778, 1683, 1638 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 342.2101 calcd for $C_{17}H_{32}NO_4Si$, found: 342.2100; $[\alpha]_D$ = +55.9; R_f = 0.29 (4 :1 hex./EtOAc).

Ref.: **BJEIV485**



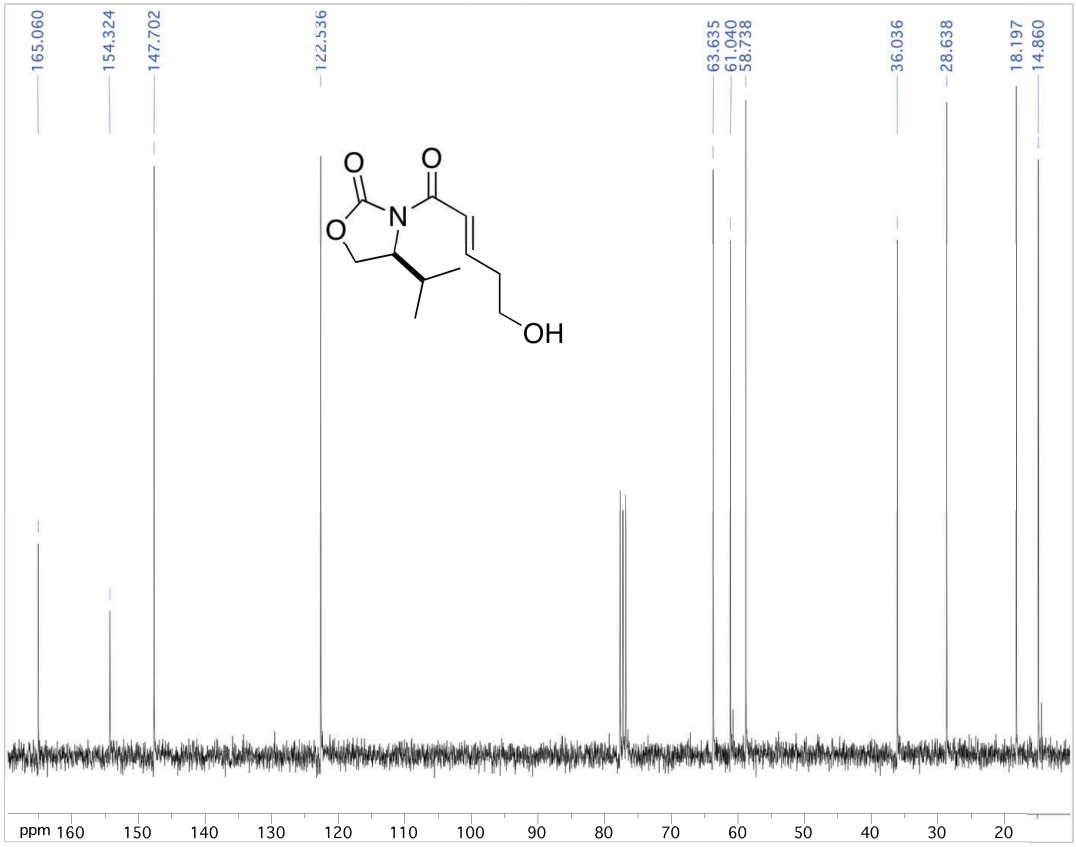


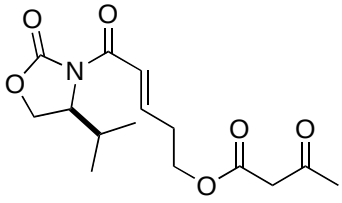


Synthesis of (*S*,*E*)-3-(5-hydroxypent-2-enoyl)-4-isopropyloxazolidin-2-one: To a 1 L HDPE bottle equipped with a stir bar was added 6.68 g (19.58 mmol, 1 equiv.) of (*S*,*E*)-3-(5-((*tert*-butyldimethylsilyl)oxy)pent-2-enoyl)-4-isopropyloxazolidin-2-one dissolved in 200 mL dry MeCN. To this stirred mixture was slowly added 5.87 mL of 48% $HF_{(aq.)}$ and the reaction was allowed to stir at ambient temperature for 2 hr before being slowly added to $NaHCO_{3(sat.)}$, extracted thrice into EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 1 : 2 to 0 : 1 hex./EtOAc to yield 3.80 g (85%) of the desired alcohol as a pale yellow oil.

^{1}HNMR (300MHz, $CDCl_3$) δ ; ^{13}CNMR (300MHz, $CDCl_3$) δ 165.1, 154.3, 147.7, 122.5, 63.6, 61.0, 58.7, 36.0, 28.6, 18.2, 14.9; IR (NaCl, film): 3470, 1759, 1674, 1635 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 228.1230 calcd for $C_{11}H_{18}NO_4$, found: 228.1231; $[\alpha]_D$ = +97.6; R_f = 0.13 (1 : 1 hex./EtOAc).

Ref: **BJEIV490**.

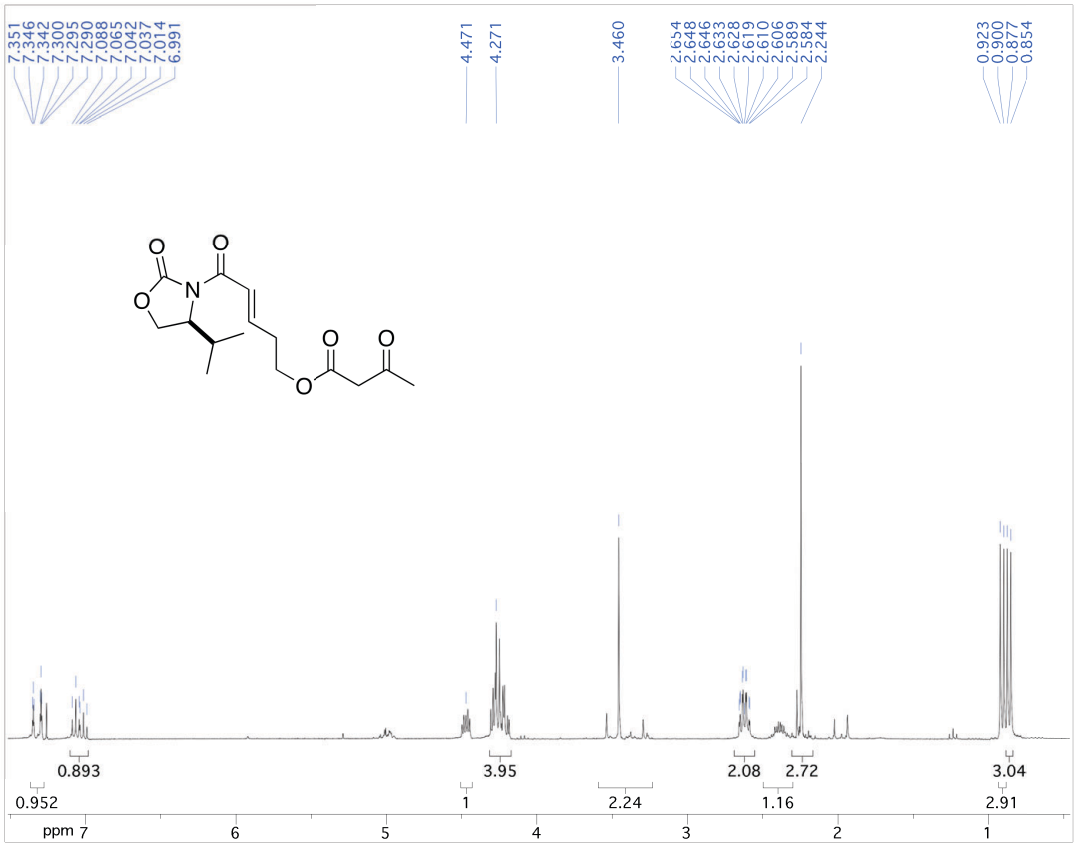


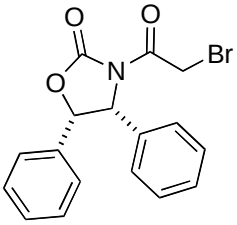


Synthesis of (*S*,*E*)-5-(4-isopropyl-2-oxooxazolidin-3-yl)-5-oxopent-3-en-1-yl 3-oxobutanoate: To a 50 mL round-bottomed flask charged with 380 mg (1.67mmol,

1equiv.) (*S*,*E*)-3-(5-hydroxypent-2-enoyl)-4-isopropyloxazolidin-2-one dissolved in 17 mL CH_2Cl_2 at 0^oC was added 387 μL (5.02 mmol, 3 equiv.) diketene followed by a spatula tip of DMAP. The reaction was stirred for 15min at 0^oC and then 1hr at ambient temperature before being diluted with CH_2Cl_2, washed twicw with $NaHCO_{3(sat)}$, dried over Na_2SO_4, and concentrated. The crude residue was dissolved in 1 : 2 hex./EtOAc and passed through a short plug of silica gel with copious 1 : 2 hex./EtOAc washes. Concentration yielded 503mg (98%) of the desired compound as a pale yellow oil. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.33 (dt, 1H, *J* = 15.3, 1.5), 7.05 (dt, 1H, *J* = 15.3, 6.9), 4.48 (m, 1H), 4.31-4.19 (m, 4H), 3.47 (s, 2H), 2.63 (qd, 2H, *J* = 6.3, 1.5), 2.40 (m, 1H), 2.25 (s, 3H), 0.91 (d, *J* = 6.9, 3H), 0.86 (d, *J* = 6.9, 3H). ^{13}CNMR (300MHz, $CDCl_3$) δ 200.7, 167.2, 164.8, 154.2, 145.5, 123.1, 63.6, 63.3, 58.7, 50.1, 31.8, 30.5, 28.6, 18.2, 14.9; IR (NaCl, film): 1770, 1743, 1716, 1682, 1639 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 312.1442 calcd for $C_{15}H_{22}NO_6$, found: 312.1448; $[\alpha]_D$ = +62.0; R_f = 0.51 (1:2 hex:EtOAc).

Ref: **BJEIV492**, BJEV019.



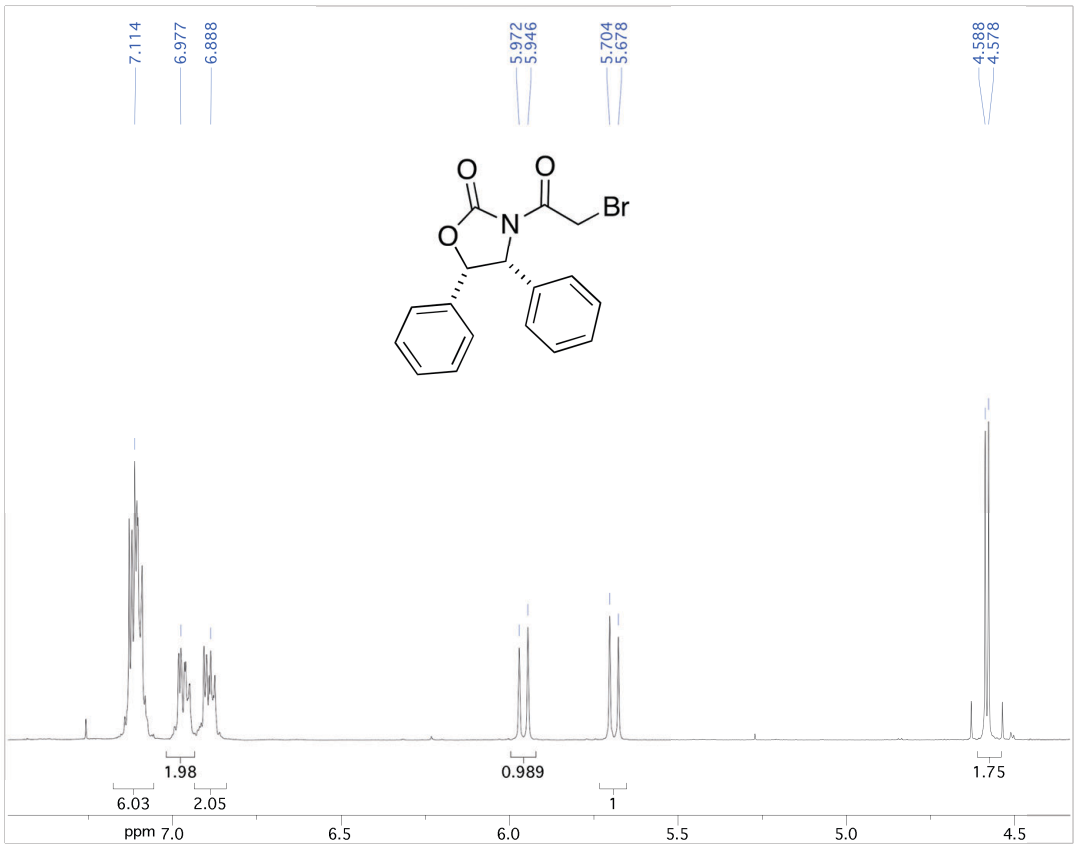


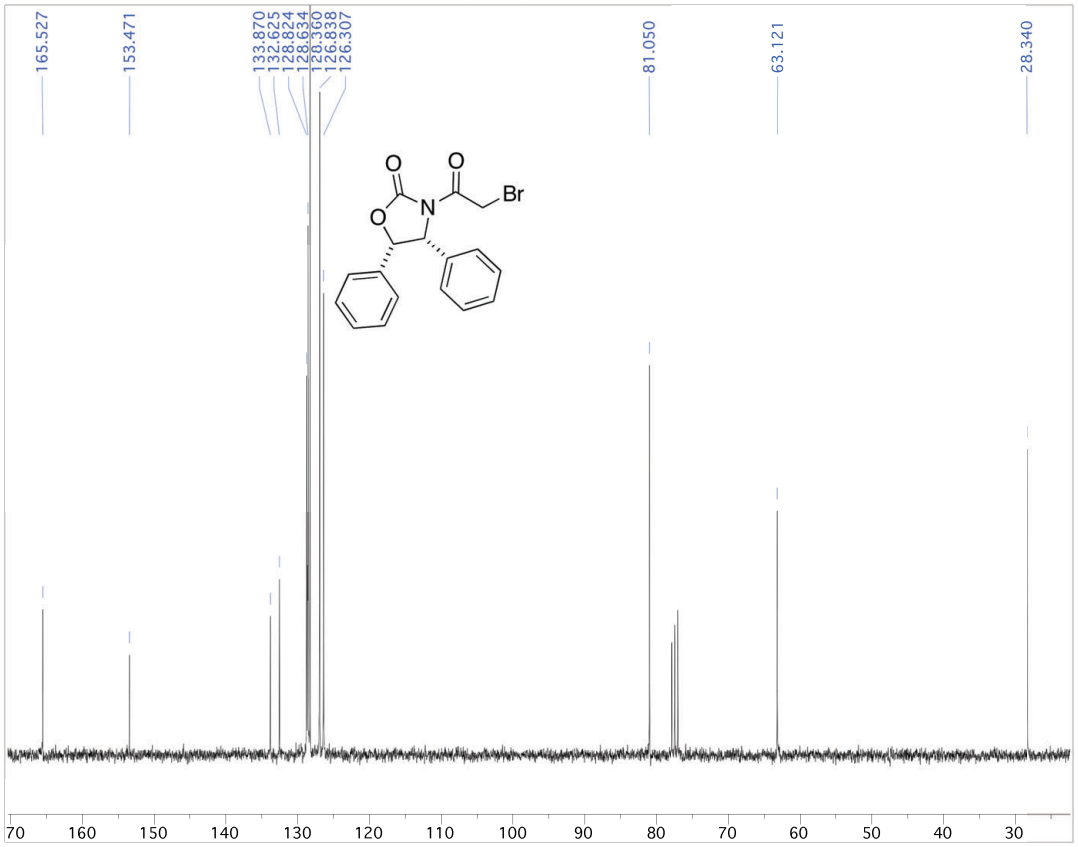
Synthesis of (4*R*,5*S*)-3-(2-bromoethanoyl)-4,5-diphenyloxazolidin-2-one: To a 25 mL round bottomed flask containing 830 mg (3.47 mmol, 1equiv.) (4*R*,5*S*)-4,5-diphenyloxazolidin-2-one dissolved in 13mL dry THF at -78^{o}C was added 2.60 mL (1.6M in hex, 4.16 mmol, 1.2eq.) *n*BuLi and the reaction was stirred at -78^{o}C for 30 min. To the reaction was then added 453 µL (5.21 mmol, 1.5 equiv.) bromoacetyl bromide and the reaction was stirred for 5 hr at -78^{o}C and then allowed to slowly return to ambient temperature. The reaction was then added to $NaHCO_{3(sat)}$, extracted thrice with EtOAc,

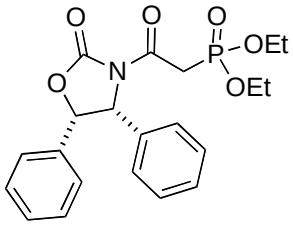
dried over $MgSO_4$, and then concentrated. Silica gel flash chromatography eluting with 4 : 1 to 2 : 1 hex:EtOAc of the crude residue yielded 819 mg (66%) of the desired bromide as a yellow crunchy foam.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.11 (m, 6H), 6.98-6.88 (m, 4H), 5.96 (d , *J* = 7.8, 1H), 5.69 (d , *J* = 7.8, 1H), 4.58 (d, *J* = 3.0, 2H); ^{13}CNMR (75MHz, $CDCl_3$) δ 165.5, 153.5, 133.9, 132.6, 128.8, 128.6, 128.4, 126.8, 126.3, 81.1, 63.1, 28.34; R_f = 0.45 (2 : 1 hex./EtOAc).

Ref: BJEIII037, **BJEIII046**, BJEIII054



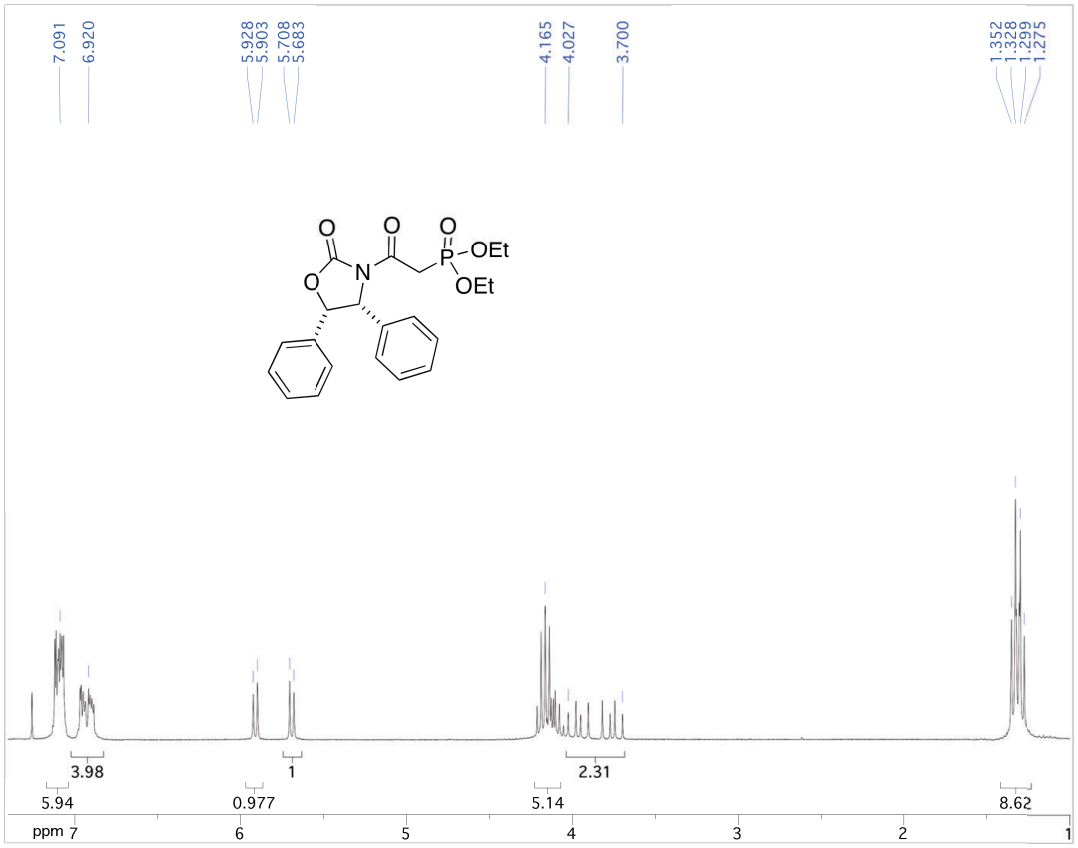


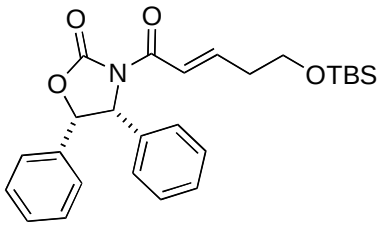


Synthesis of diethyl 2-oxo-2-((4*R*,5*S*)-2-oxo-4,5-diphenyloxazolidin-3-yl)ethylphosphonate: To 819 mg (2.27 mmol, 1equiv.) (4*R*,5*S*)-3-(2-bromoethanoyl)-4,5-diphenyloxazolidin-2-one was added 2 mL $P(OEt)_3$. The reaction was heated to 100°C for 15 min and then concentrated to yield 950 mg (>99%) of the desired product as a yellow oil which was used without purification.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.09 (m, 6H), 6.92 (m, 4H), 5.91 (d, *J* = 7.5, 1H), 5.69 (d, *J* = 7.5, 1H), 4.17 (m, 4H), 3.70-4.03 (m, 2H), 1.33 (t, *J* = 7.2, 6H).

Ref: BJEIII022, BJEIII039, **BJEIII048**

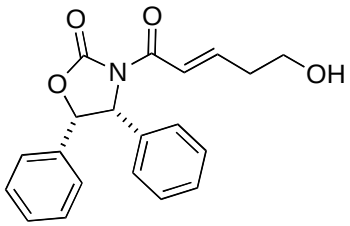




Synthesis of (4*R*,5*S*)-3-((*E*)-5-(*tert*-butyldimethylsilyloxy)pent-2-enoyl)-4,5-diphenyloxazolidin-2-one: To a 10 mL round bottomed flask containing 60 mg (0.144 mmol, 1.2 equiv.) diethyl 2-oxo-2-((4*R*,5*S*)-2-oxo-4,5-diphenyloxazolidin-3-

yl)ethylphosphonate and 6 mg (0.144 mmol, 1.2 equiv.) LiCl dissolved in 1.5 mL dry MeCN was added 21 μL (0.120 mmol, 1equiv.) *i*Pr_2NEt. The reaction was stirred at ambient temperature for 30 min then 23 mg (0.120 mmol, 1equiv.) aldehyde **3.5** dissolved in 1 mL dry MeCN was added. The reaction was stirred for a further 16h and was then added to brine and extracted thrice with EtOAc, dried over $MgSO_4$, and concentrated. The crude residue was taken up in 2:1 hex./EtOAc, filtered through silica gel and concentrated to yield 35mg (65%) of the desired product as a white solid. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.46-6.85 (m, 12H), 5.91 (d, *J* = 7.8, 1H), 5.72 (d, *J* = 7.8, 1H), 3.75 (t, *J* = 6.6, 2H), 2.52 (qd, *J* = 6.6, 1.2, 2H), 0.88 (s, 9H), 0.05 (s, 6H). R_f = 0.43 (4 : 1 hex./EtOAc).

Ref: **BJEIII026**, BJEIII041, BJEIII051

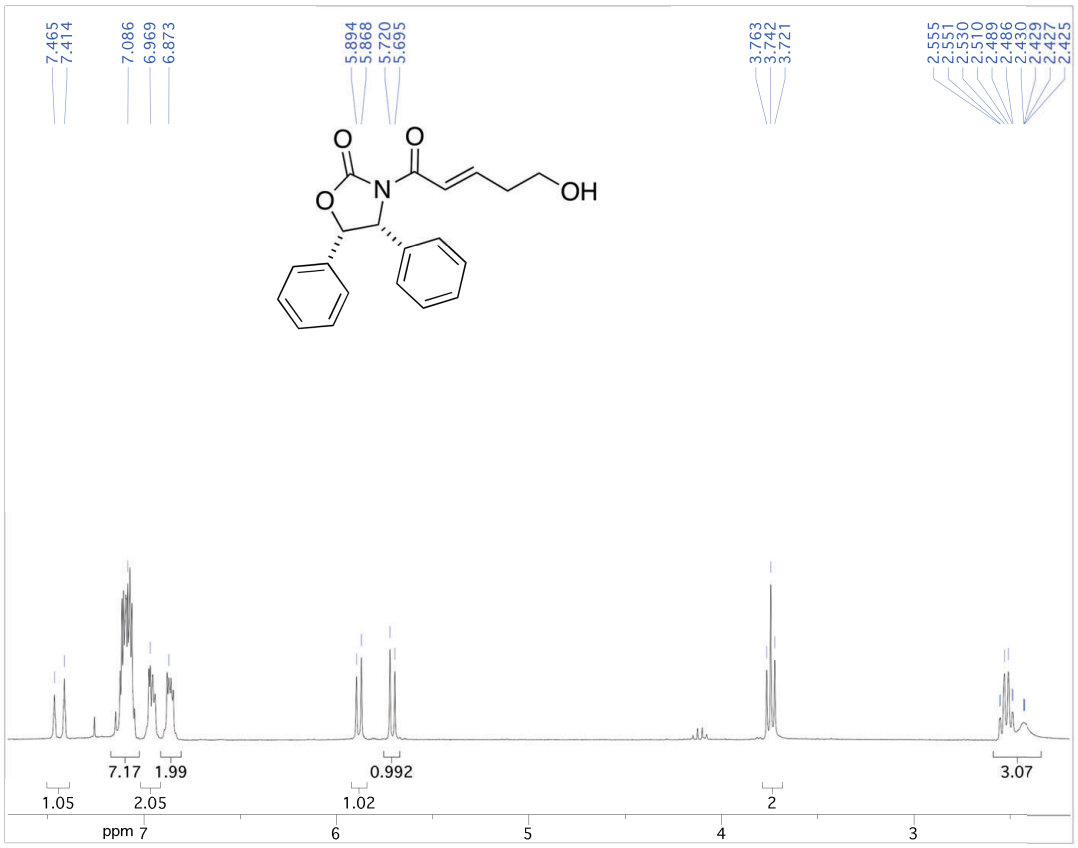


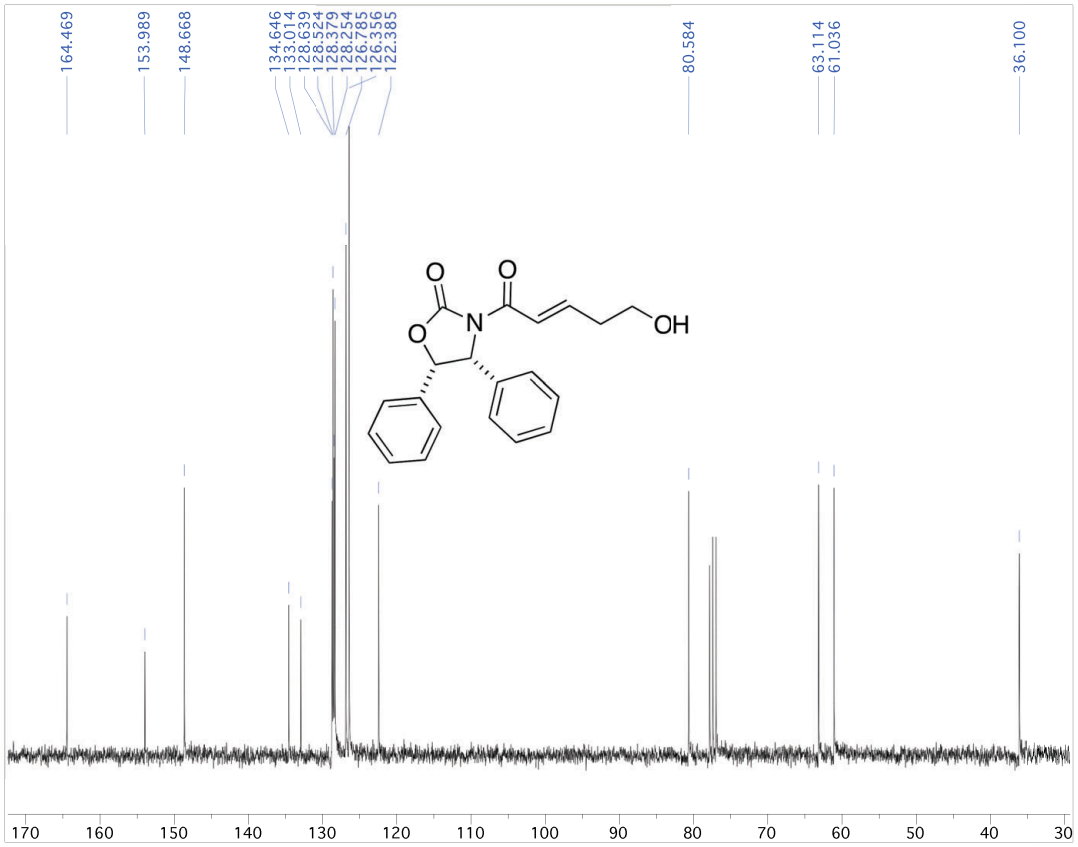
Synthesis of (4*R*,5*S*)-3-((*E*)-5-hydroxypent-2-enoyl)-4,5-diphenyloxazolidin-2-one: To a 4 dram vial containing 408 mg (0.903 mmol, 1 equiv.) (4*R*,5*S*)-3-((*E*)-5-(*tert*-butyldimethylsilyloxy)pent-2-enoyl)-4,5-diphenyloxazolidin-2-one dissolved in 9 mL dry THF was added 481 μL HF (48% in H_2O). After stirring for 5 hr at ambient temperature the reaction was slowly added to $NaHCO_{3(sat)}$, diluted with CH_2Cl_2, dried over $MgSO_4$ and concentrated to yield 305mg (>99%) of the desired product as a white solid.

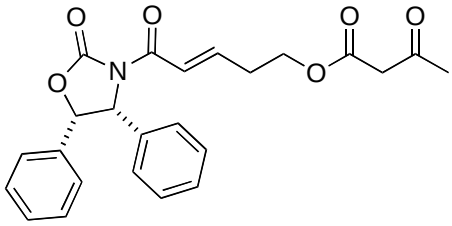
^{1}HNMR (300MHz, $CDCl_3$) δ 7.47-6.85 (m, 12H), 5.88 (d, *J* = 7.8, 1H), 5.71 (d, *J* = 7.8, 1H), 3.74 (t, *J* = 6.3, 2H), 2.52 (q, *J* = 6.0, 2H), 2.43 (bs, 1H); ^{13}CNMR (75MHz, $CDCl_3$)

δ 164.5, 154.0, 148.7, 134.7, 133.0, 128.6, 128.5, 128.4, 128.3, 126.8, 126.4, 122.4, 80.6, 63.1, 61.0, 36.1.

Ref: BJEIII028, **BJEIII044**, BJEIII055





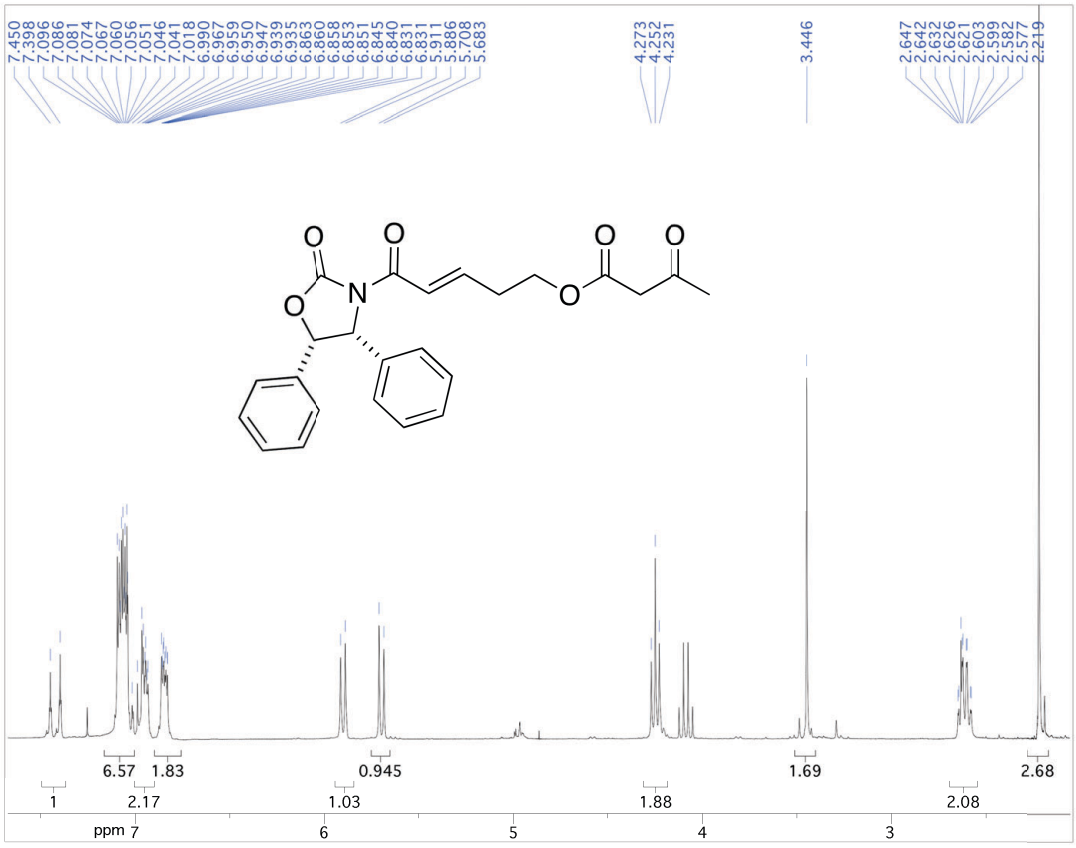


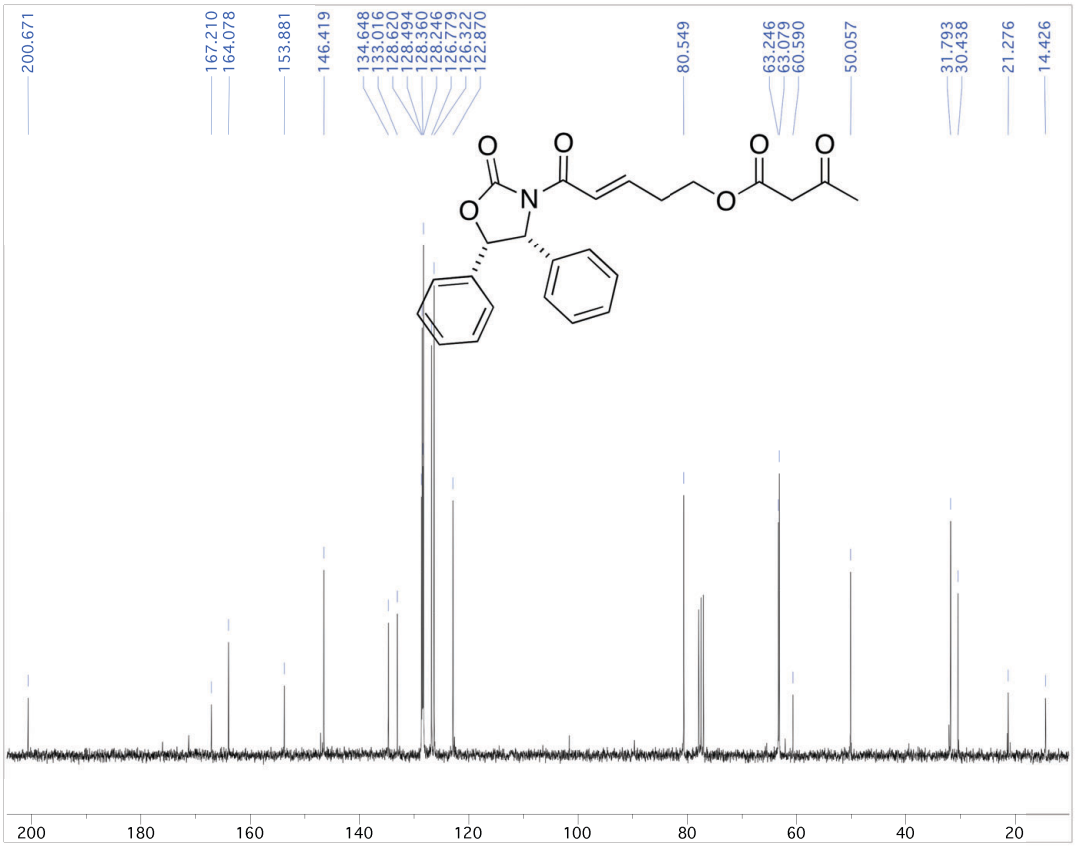
Synthesis of (*E*)-5-oxo-5-((4*R*,5*S*)-2-oxo-4,5-diphenyloxazolidin-3-yl)pent-3-enyl 3-oxobutanoate: To a 10 mL round-bottomed flask containing 26 mg (0.077 mmol, 1equiv.) (4*R*,5*S*)-3-((*E*)-5-hydroxypent-2-enoyl)-4,5-diphenyloxazolidin-2-one dissolved in 1 mL CH_2Cl_2 at -10^{o}C was added 12 μL (0.154 mmol, 2 equiv.) diketene then a single crystal of DMAP. The reaction was stirred for 15 min at -10^{o}C and was then diluted with CH_2Cl_2, washed twice with $NaHCO_{3(sat)}$, dried over $MgSO_4$, and concentrated. The crude

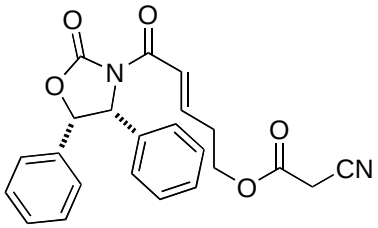
residue was dissolved in 1 : 1 hex./EtOAc and passed through a short plug of silica gel with copious 1 : 1 hex./EtOAc washes. Concentration yielded 32 mg (>99%) of the desired product as a pale yellow oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.45-6.83 (m, 12H), 5.90 (d, 1H, *J* = 7.8), 5.69 (d, 1H, *J* = 7.8), 4.25 (t, 2H, *J* = 6.3), 3.45 (s, 3H), 2.61 (qd, 2H, *J* = 6.9, 1.5), 2.22 (s, 3H); ^{13}CNMR(75MHz,$CDCl_3$)δ 200.67, 167.21, 164.08, 153.88, 146.42, 134.65, 133.02, 128.62, 128.49, 128.36, 128.25, 126.78, 126.32, 122.87, 80.55, 63.25, 63.08, 50.06, 31.79, 30.44; R_f = 0.45 (1 : 1 hex/EtOAc).

Ref: BJEIII045, **BJEIII031**, BJEIII029

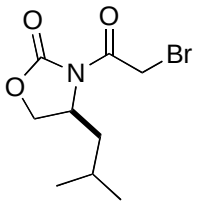






Synthesis of (*E*)-5-oxo-5-((4*R*,5*S*)-2-oxo-4,5-diphenyloxazolidin-3-yl)pent-3-en-1-yl 2-cyanoacetate: To a 10 mL round-bottomed flask containing 15 mg (0.044 mmol, 1 equiv.) (4*R*,5*S*)-3-((*E*)-5-hydroxypent-2-enoyl)-4,5-diphenyloxazolidin-2-one and 8 mg (0.089 mmol, 2 equiv.) cyanoacetic acid dissolved in 0.5 mL dry CH_2Cl_2 was added a spatula tip of DCC and a single pellet of DMAP. The reaction was stirred for 15 min at ambient temperature, filtered through celite and concentrated to yield 19 mg of crude material which was used without purification.

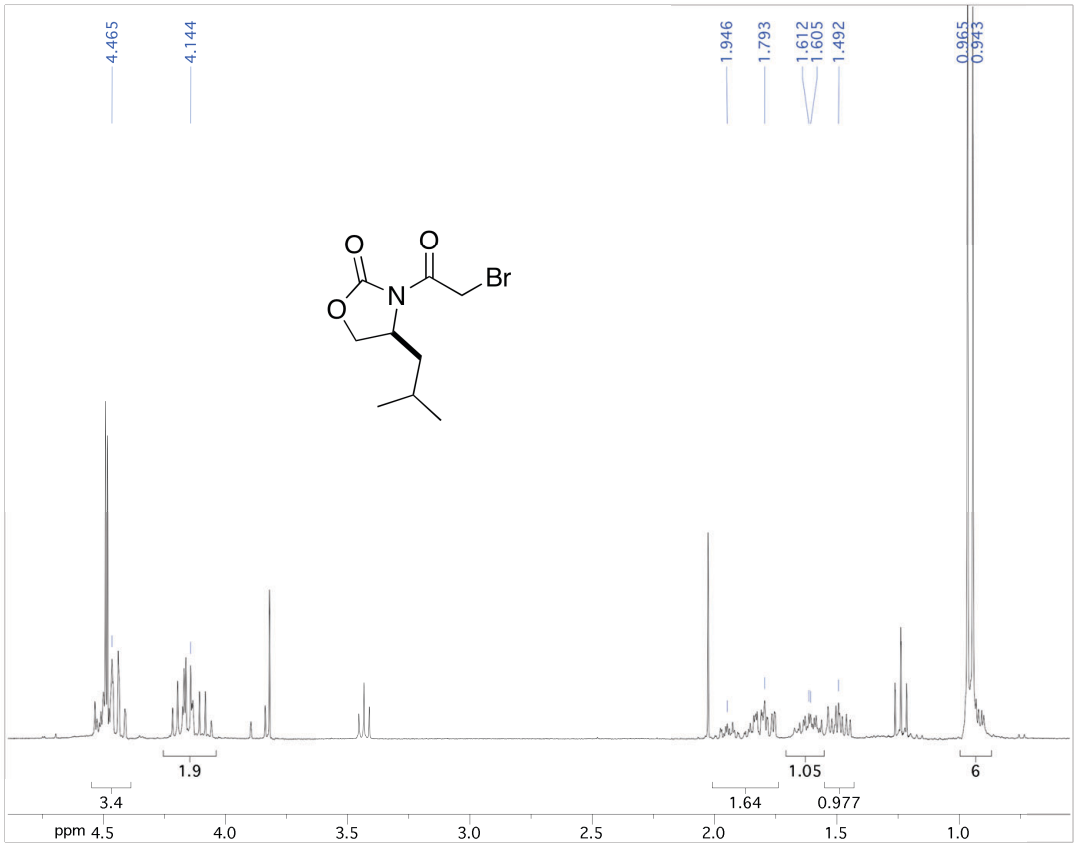
Ref.: **BJEIII062**.

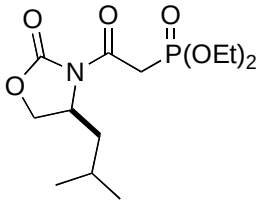


Synthesis of (*S*)-3-(2-bromoacetyl)-4-isobutyloxazolidin-2-one: To a 500 mL flame dried round-bottomed flask containing 10.36 g (72.36 mmol, 1 equiv.) (*S*)-4-isobutyloxazolidin-2-one dissolved in 150 mL dry THF at -78^{o}C was added 54.27 mL (1.6 M in hex., 86.83 mmol, 1.2 equiv.) *n*BuLi. The reaction was stirred at -78^{o}C for 40 min before the addition of 9.44 mL (108.54 mmol, 1.5 equiv) bromoacetyl bromide. The reaction was allowed to slowly return to ambient temperature over 12 hr and was then added to $NH_4Cl_{(sat.)}$, extracted twice with EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 9 : 1 to 2 : 1 hex./EtOAc to yield 17.12 g of the desired product as a brown oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 4.65 (m, 3H), 4.14 (m, 2H), 1.95 (m, 1H), 1.79 (m, 1H), 1.49 (m, 1H), 0.95 (d, J = 6.6, 6H); R_f = 0.33 (4 : 1 hex./EtOAc).

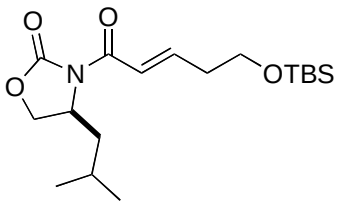
Ref.: **BJEV382**.





Synthesis of (*S*)-diethyl (2-(4-isobutyl-2-oxooxazolidin-3-yl)-2-oxoethyl)phosphonate: To a 100 mL round-bottomed flask containing 8.00 g (30.3 mmol, 1 equiv.) (*S*)-3-(2-bromoacetyl)-4-isobutyloxazolidin-2-one was added 15.7 mL (90.9 mmol, 3 equiv.) $P(OEt)_3$ and the reaction was heated to 100^{o}C for 20 min before being concentrated. The resulting residue was purified by silica gel chromatography eluting with 1 : 1 to 0 : 1 hex./EtOAc to yield 9.71 g (>99%) of the desired product as a brown oil which was used without further purification. R_f = 0.45 (EtOAc).

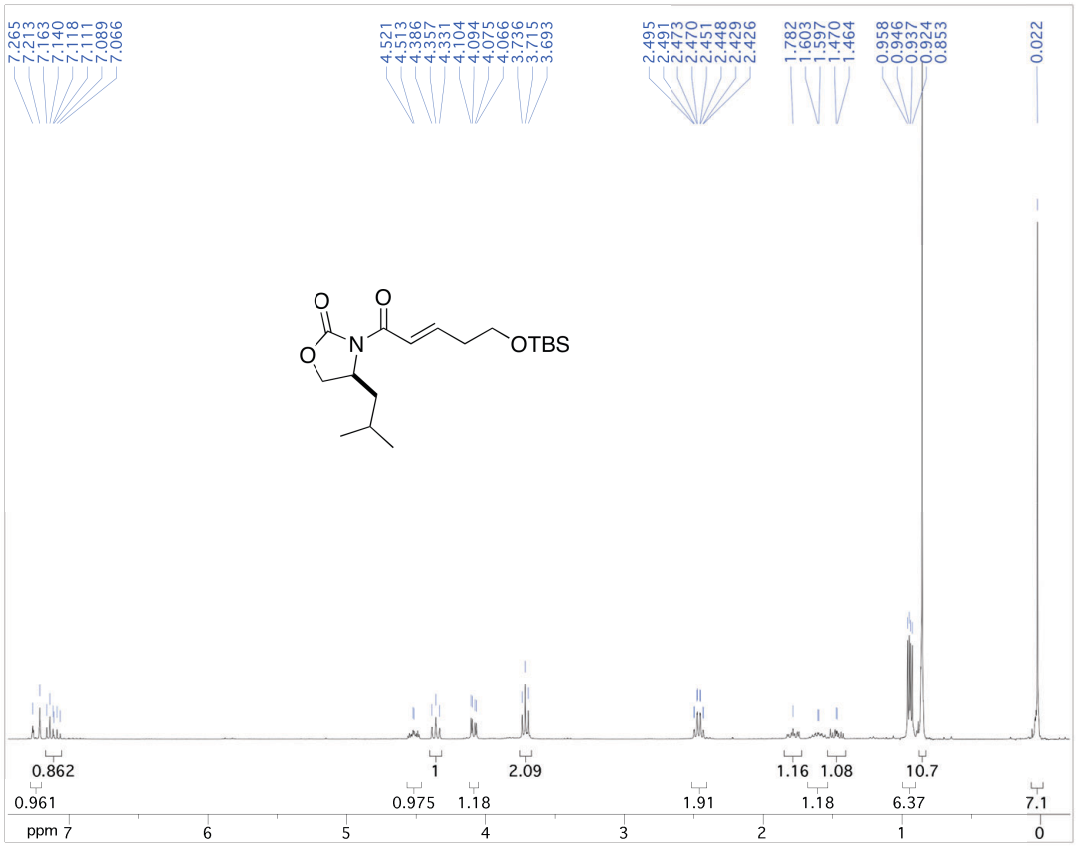
Ref.: **BJEIV383**.



Synthesis of (*S*,*E*)-3-(5-((*tert*-butyldimethylsilyl)oxy)pent-2-enoyl)-4-isobutyloxazolidin-2-one: To a 250 mL round-bottomed flask containing 4.26 g (13.3 mmol, 1 equiv.) (*S*)-diethyl (2-(4-isobutyl-2-oxooxazolidin-3-yl)-2-oxoethyl)phosphonate and 675 mg (15.9 mmol, 1.2 equiv.) LiCl dissolved in 66 mL dry MeCN was added 2.31 mL (13.3 mmol, 1 equiv.) *i*Pr_2NEt. The reaction was stirred at ambient temperature for 15 min before the addition of 3.00 g (15.9 mmol, 1.2 equiv.) aldehyde **3.5** dissolved in 5 mL dry MeCN. The reaction was stirred for a further 16 hr and then added to brine, extracted twice with EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 9 : 1 to 4 : 1 hex./EtOAc to yield 3.28 g (69%) of the desired product as a colorless oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.25 (d, *J* = 15.6, 1H), 7.11 (dt, 15.3, 6.9, 1H), 4.52 (m, 1H), 4.36 (t, *J* = 7.8, 1H), 4.08 (dd, *J* = 8.7, 3.0, 1H), 3.72 (t, *J* = 6.3, 2H), 2.46 (qd, *J* = 6.6, 1.2, 2H), 1.78 (m, 1H), 1.60 (m, 1H), 1.46 (m, 1H), 0.95 (d, *J* = 3.6, 3H), 0.93 (d, *J* = 3.6, 3H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}CNMR (75MHz, $CDCl_3$) δ 164.9, 153.8, 148.2, 122.1, 67.8, 61.8, 53.3, 41.7, 36.4, 26.1, 25.1, 23.6, 21.8, 18.5, –5.1; IR (NaCl, film): 1770, 1721, 1685, 1638 cm^{-1}; $[\alpha]_D$ = +57.9^o; R_f = 0.52 (4 : 1 hex./EtOAc).

Ref.: **BJEIV416**, BJEIV469.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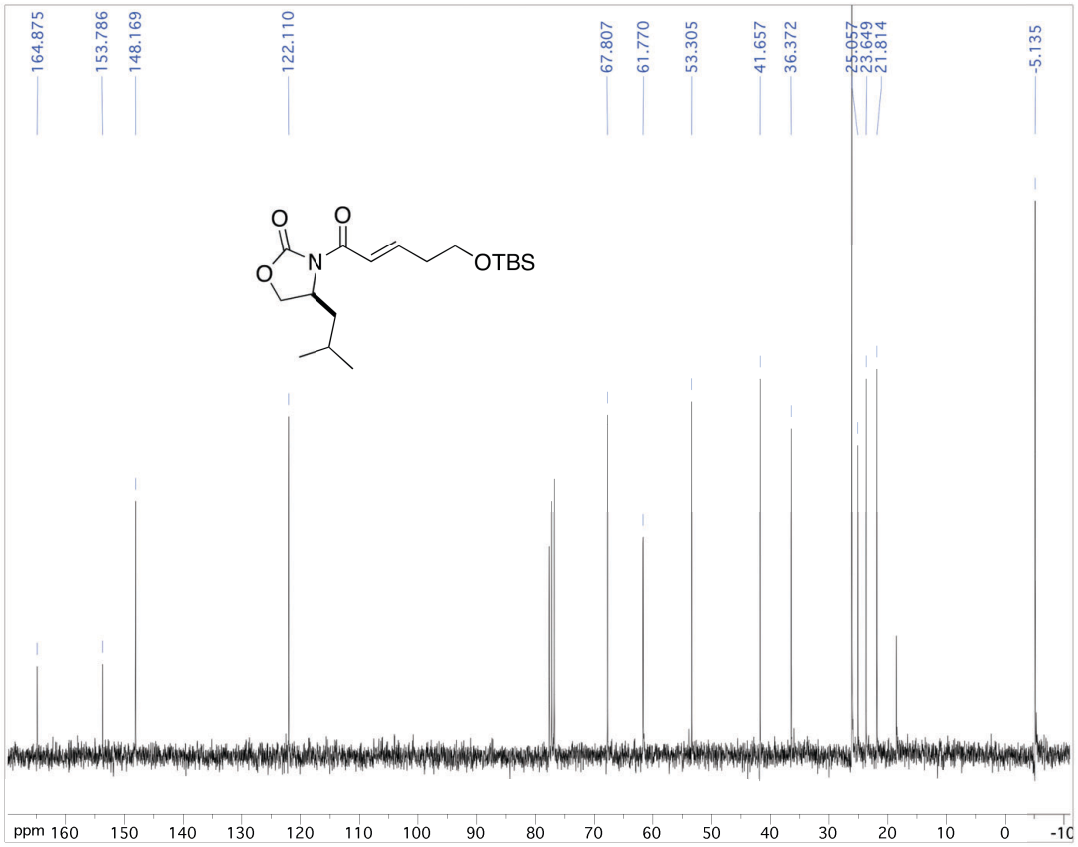
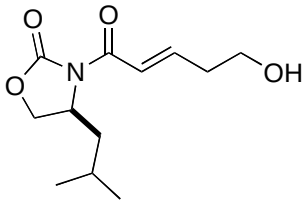
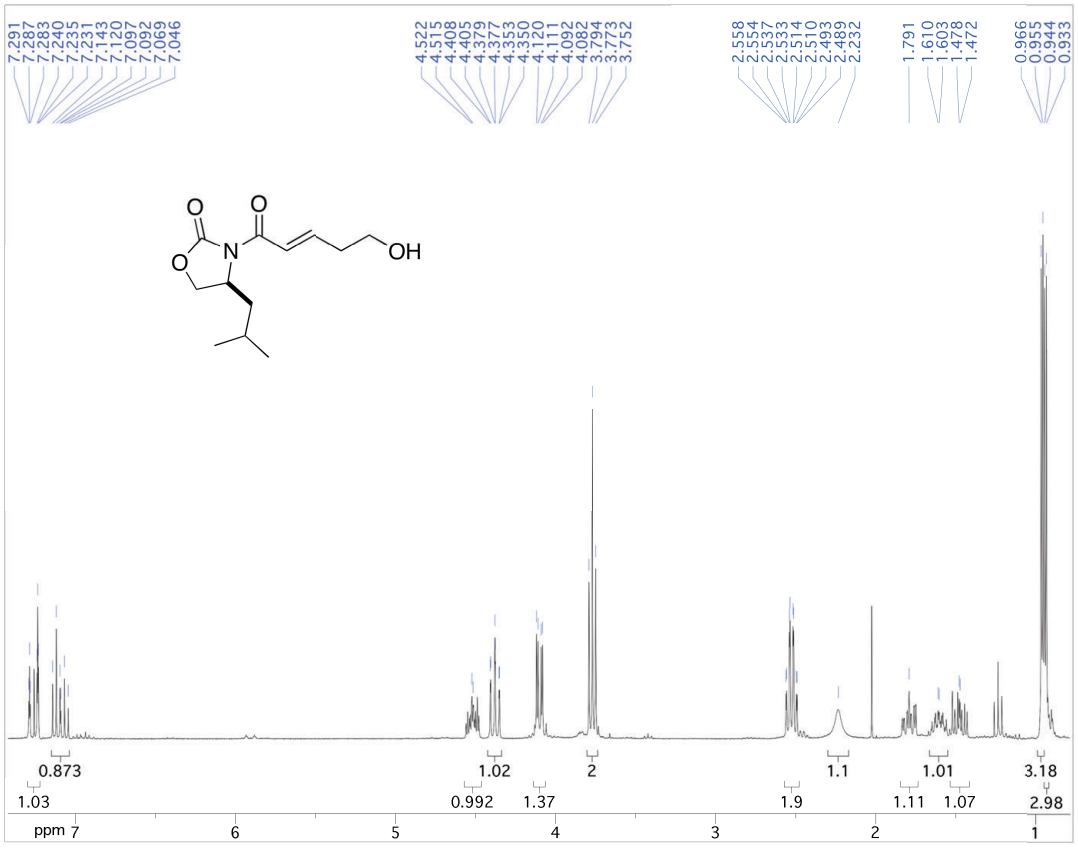


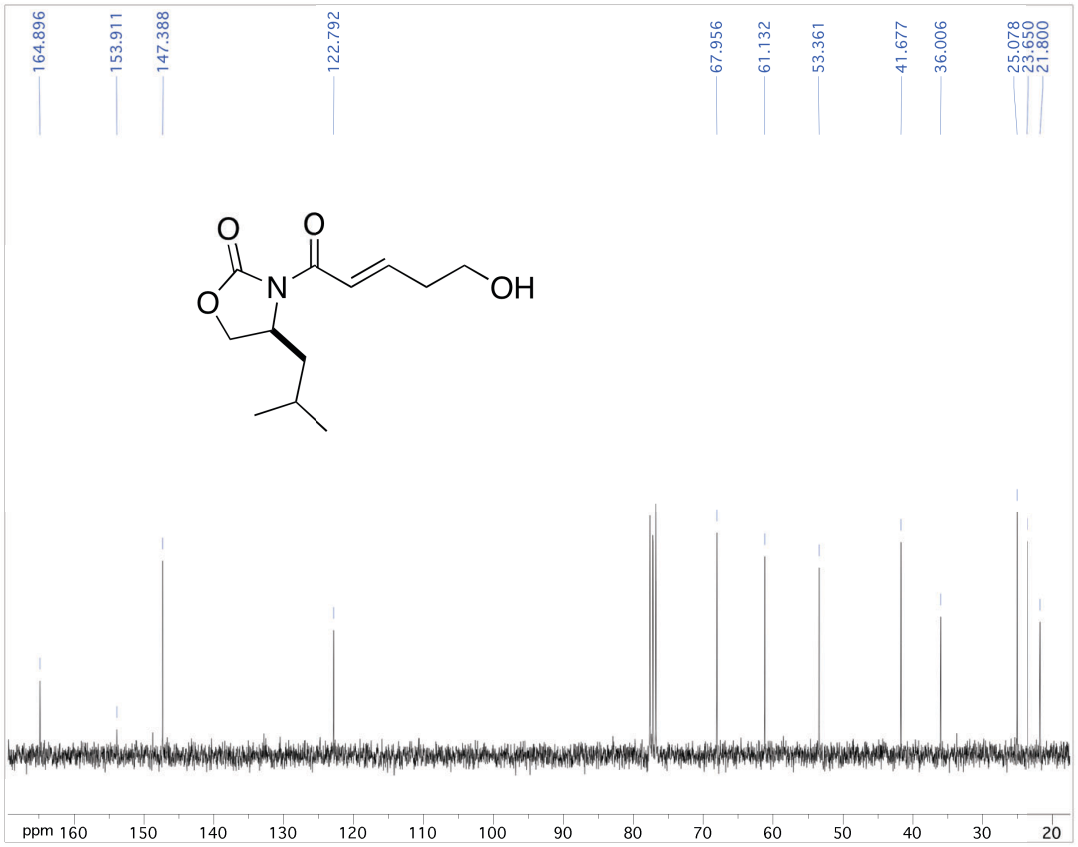


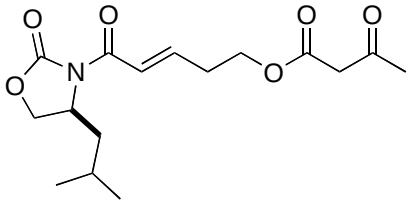
Synthesis of (*S*,*E*)-3-(5-hydroxypent-2-enoyl)-4-isobutyloxazolidin-2-one: To a 250 mL HDPE bottle containing 1.00 g (2.81 mmol, 1 equiv.) (*S*,*E*)-3-(5-((*tert*-butyldimethylsilyl)oxy)pent-2-enoyl)-4-isobutyloxazolidin-2-one dissolved in 28 mL dry MeCN was added 843 μL 48% aqueous HF. The reaction was allowed to stir at ambient temperature for 2.5 hr before being added to $NaHCO_{3(sat.)}$, extracted into EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 1 : 1 hex./EtOAc to yield 676 mg (>99%) of the desired alcohol as a colorless oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.26 (dt, *J* = 15.6, 1.2 1H), 7.09 (dt, *J* = 15.3, 6.9, 1H), 4.52 (m, 1H), 4.38 (td, *J* = 8.7, 0.9, 1H), 4.10 (dd, *J* = 8.4, 2.7, 1H), 3.77 (t, *J* = 6.3, 2H), 2.52 (qd, *J* = 6.3, 1.2, 2H), 2.32 (bs, 1H), 1.79 (m, 1H), 1.61 (m, 1H), 1.47 (m, 1H), 0.96 (d, *J* = 3.3, 3H), 0.94 (d, *J* = 3.3, 3H); ^{13}CNMR (75MHz, $CDCl_3$) δ 164.9, 153.9, 147.4, 122.8, 68.0, 61.1, 53.4, 41.7, 36.0, 25.1, 23.7, 21.8; IR (NaCl, film): 3093, 1771, 1682, 1635 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 242.1387 calcd for $C_{12}H_{20}NO_4$, found: 242.1385; $[\alpha]_D$ = +88.1°; R_f = 0.25 (1 : 1 hex./EtOAc).

Ref.: **BJEIV475**



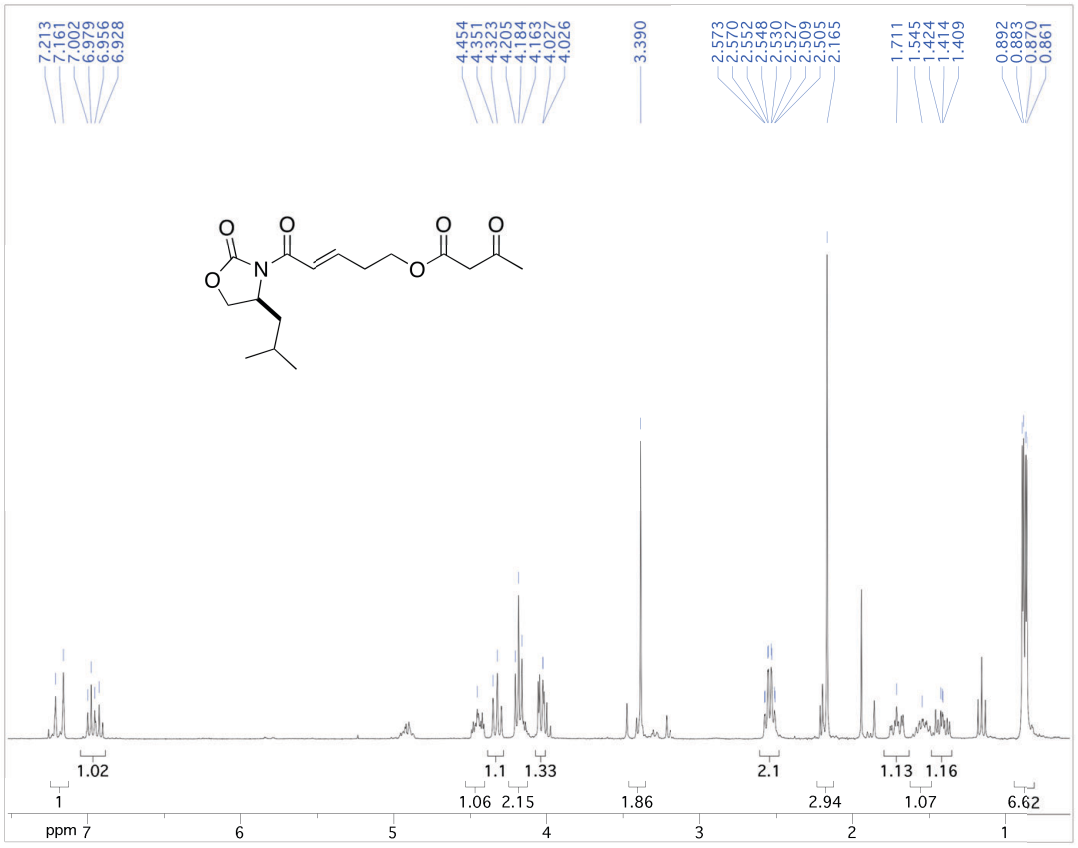


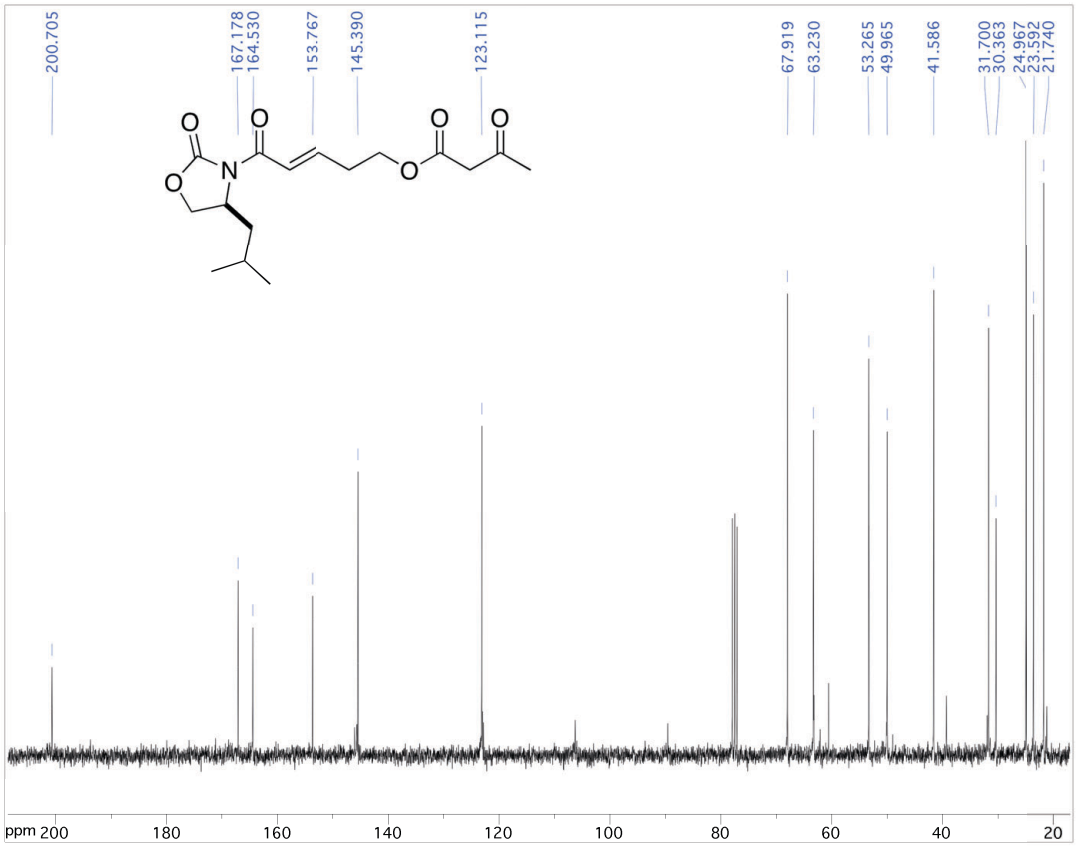


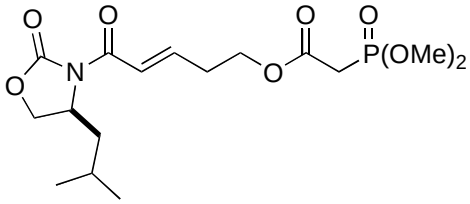
Synthesis of (*S*,*E*)-5-(4-isobutyl-2-oxooxazolidin-3-yl)-5-oxopent-3-en-1-yl 3-oxobutanoate: To a 250 mL round-bottomed flask containing 305 mg (1.26 mmol, 1 equiv.) (*S*,*E*)-3-(5-hydroxypent-2-enoyl)-4-isobutyloxazolidin-2-one dissolved in 65 mL dry CH_2Cl_2 at -10^oC was added 292 μL (3.79 mmol, 3 equiv.) diketene and then a single pellet of DMAP. The reaction was stirred at -10^oC for 30 min before being added to $NaHCO3_{(sat.)}$, extracted into CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 2 : 1 to 1 : 1 hex./EtOAc to yield 312 mg (76% of the desired product as a pale yellow oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.19 (d, *J* = 15.6,1H), 6.96 (dt, *J* = 15.3, 6.9, 1H), 4.45 (m, 1H), 4.32 (t, *J* = 8.4, 1H), 4.18 (t, *J* = 6.3, 2H), 4.03 (m, 1H), 3.39 (s, 2H), 2.54 (qd, *J* = 6.3, 0.9, 2H), 2.17 (s, 3H), 1.71 (m, 1H), 1.55 (m, 1H), 1.41 (m, 1H), 0.89 (d, *J* = 2.7, 3H), 0.87 (d, *J* = 2.7, 3H); ^{13}CNMR (75MHz, $CDCl_3$) δ 200.7, 167.2, 164.5, 153.8, 145.4, 123.1, 67.9, 63.2, 53.3, 50.0, 41.6, 31.7, 30.4, 25.0, 22.6, 21.7; IR (NaCl, film): 1775, 1739, 1684, 1639cm^{-1}; HRMS (+TOF): $[M+H]^+$ 326.1598 calcd for $C_{16}H_{24}NO_6$, found: 326.1603; $[\alpha]_D$ = +69.6^o; R_f = 0.23 (2 : 1 hex./EtOAc).

Ref.: BJEIV478, **BJEIV511**





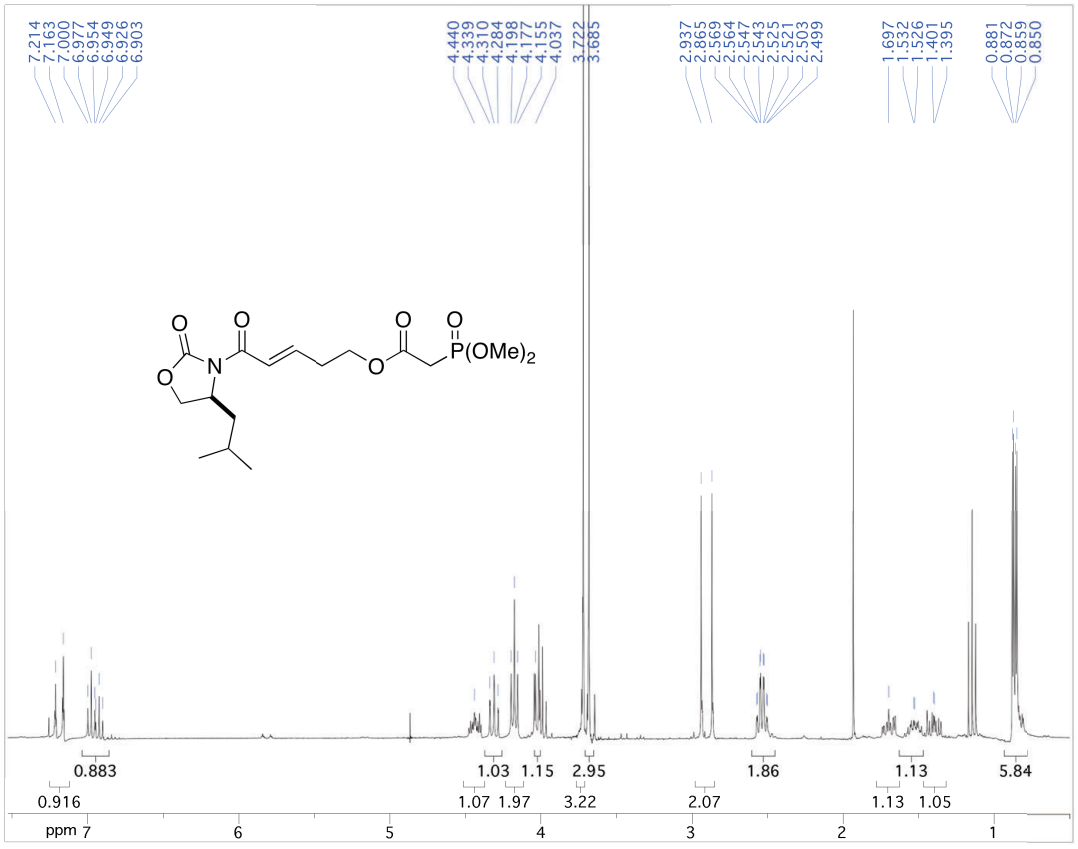


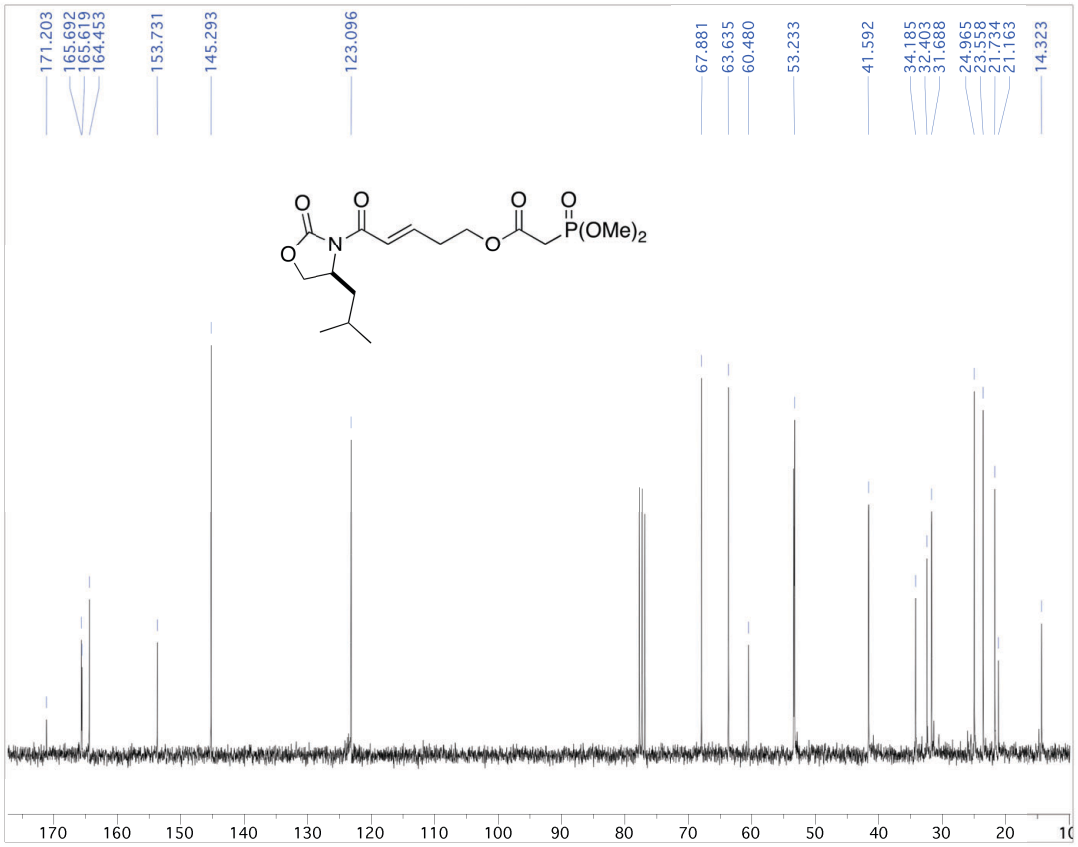
Synthesis of (*S*,*E*)-5-(4-isobutyl-2-oxooxazolidin-3-yl)-5-oxopent-3-en-1-yl 2-(dimethoxyphosphoryl)acetate: To a 100 mL round-bottomed flask containing 1.12 g (4.64 mmol, 1 equiv.) (*S*,*E*)-3-(5-hydroxypent-2-enoyl)-4-isobutyloxazolidin-2-one dissolved in 23 mL CH_2Cl_2 was added 936 mg (5.57 mmol, 1.2 equiv.) 2-(dimethoxyphosphoryl)acetic acid followed by 1.15 g (5.57 mmol, 1.2 equiv.) DCC dissolved in a minimum of CH_2Cl_2. The reaction was stirred at ambient temperature for 30 min before being filtered through celite and concentrated. The resulting residue was

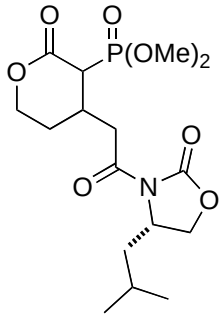
purified by silica gel flash chromatography eluting with 5% MeOH in EtOAc to yield 1.82 g (>99%) of the desired product as a colorless oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.18 (d, *J* = 15.3, 1H), 6.95 (dt, *J* = 15.3, 6.9, 1H), 4.44 (m, 1H), 4.31 (t, *J* = 8.7, 1H), 4.04 (m, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 2.90 (d, J_{HP} = 21.6, 2H), 2.53 (qd, *J* = 6.6, 1.5, 2H), 1.70 (m, 1H), 1.53 (m, 1H), 1.40 (m, 1H), 0.88 (s, 3H), 0.85 (s, 3H); ^{13}CNMR (300MHz, $CDCl_3$) δ 171.2, 165.7, 164.5, 153.7, 145.3, 123.1, 67.9, 63.6, 60.5, 53.2, 41.6, 34.2, 32.4, 31.7, 25.0, 23.6, 21.7, 21.2, 14.3; IR (NaCl, film): 1778, 1739, 1684, 1640 cm^{-1}; R_f = 0.24 (EtOAc).

Ref.: BJEIV395, **BJEIV428**.





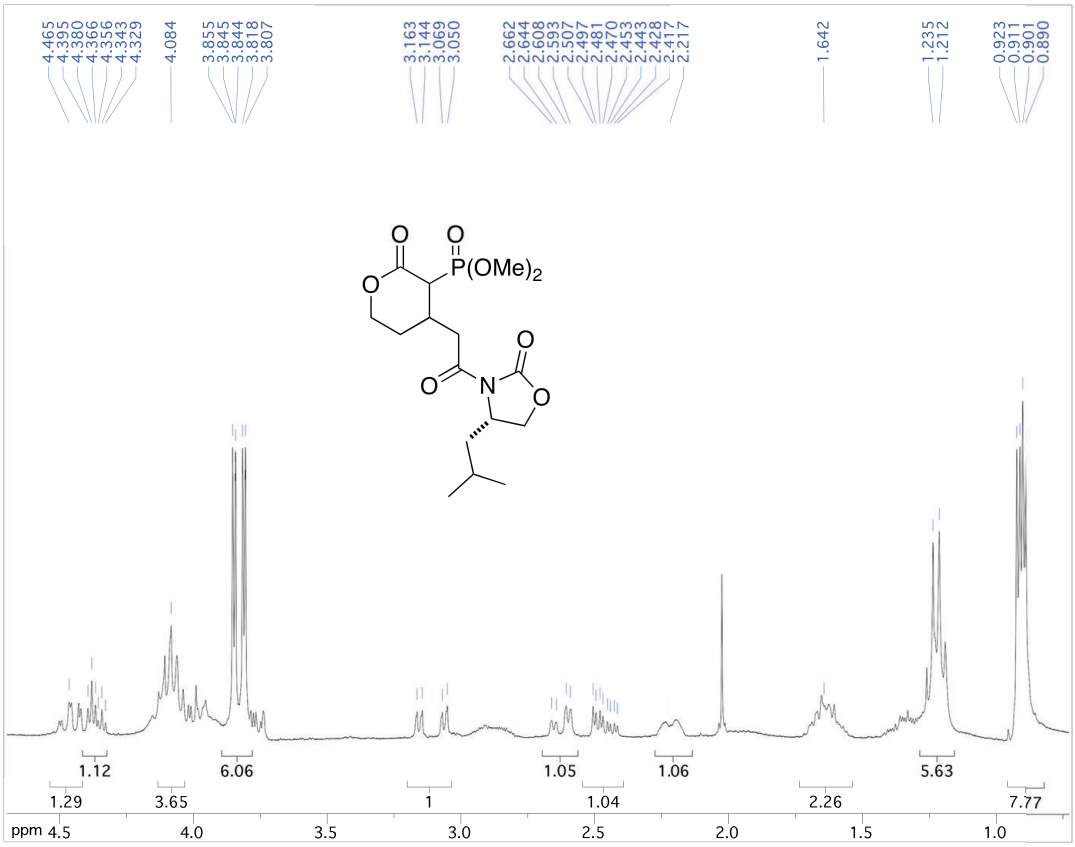


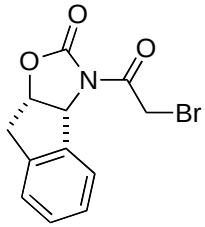
Synthesis of dimethyl (4-(2-((*S*)-4-isobutyl-2-oxooxazolidin-3-yl)-2-oxoethyl)-2-oxotetrahydro-2*H*-pyran-3-yl)phosphonate: To a 25 mL round-bottomed flask containing 196 mg (0.501 mmol, 1 equiv.) (*S*,*E*)-5-(4-isobutyl-2-oxooxazolidin-3-yl)-5-oxopent-3-en-1-yl 2-(dimethoxyphosphoryl)acetate dissolved in 5 mL MeCN was added 326 mg (1.00 mmol, 2 equiv.) Cs_2CO_3. The reaction was heated to 40^{o}C for 20 min, added to 1 M HCl, extracted thrice with EtOAc, dried over Na_2SO_4, concentrated.

Purification by silica gel flash chromatography eluting with 1% to 5% MeOH in EtOAc yielded 38 mg (19%) of the desired product as a pale yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 4.47 (m, 1H), 4.36 (dt, *J* = 11.7, 4.5, 1H), 4.08 (m, 3H), 3.85 (d, *J* = 3.3, 3H), 3.81 (d, *J* = 3.3, 3H), 3.10 (dd, J_{HP} = 28.2, *J* = 5.7, 1H), 2.62 (dd, *J* = 16.2, 5.4, 1H), 2.46 (ddd, *J* = 16.2, 7.8, 3.0, 1H), 2.22 (m, 1H), 1.64 (m, 2H), 1.22 (m, 3H), 0.92 (d, *J* = 3.3, 3H), 0.89 (d, *J* = 3.3, 3H); R_f = 0.25 (EtOAc)

Ref.: **BJEIV355**.

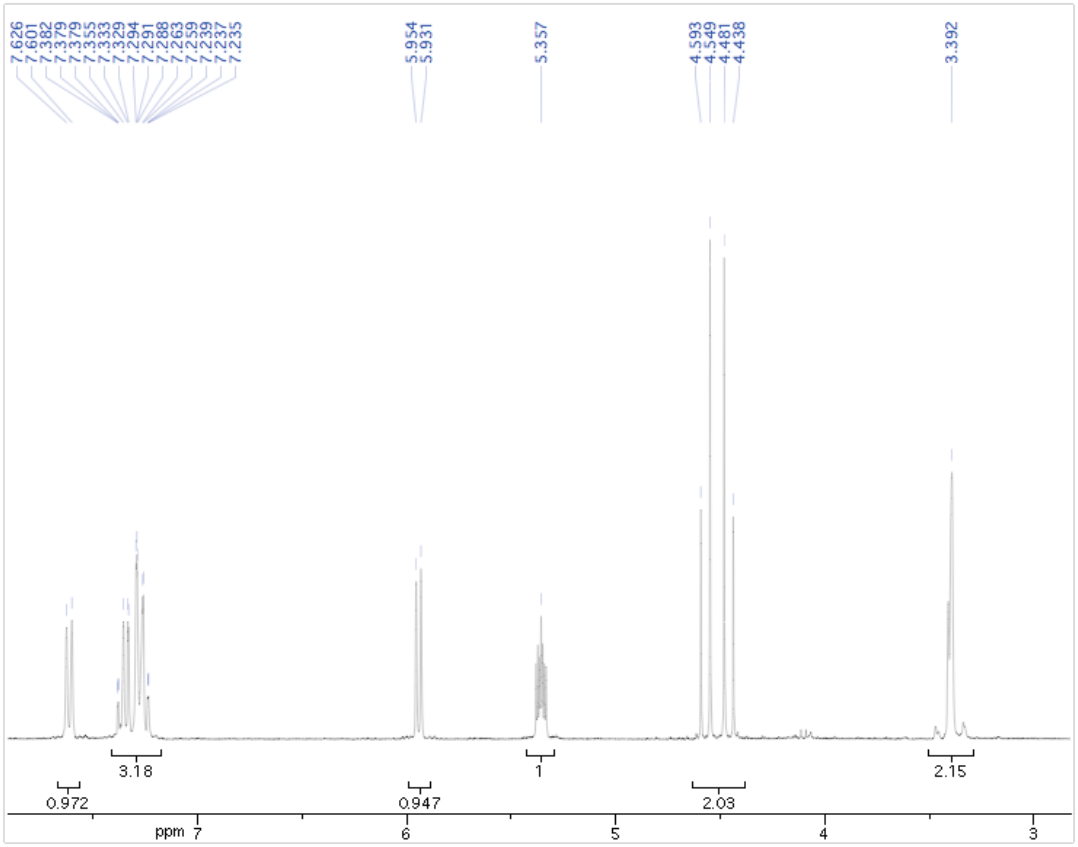




Synthesis of (3a*R*,8a*S*)-3-(2-bromoacetyl)-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one: To a 500 mL flame dried round-bottomed flask was charged 5.51 g (31.5 mmol, 1equiv.) (3a*R*,8a*S*)-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one dissolved in 150 mL dry THF. The solution was cooled to 0^{o}C before the addition of 23.6 mL (1.6M in hex, 4.65 mmol, 1.2 equiv.) *n*BuLi. After stirring 30 min at 0^{o}C the reaction was cooled to -78^{o}C, 3.56 mL (37.7 mmol, 1.3 equiv.) bromoacetyl bromide was added dropwise, and the reaction was stirred for 4 hr at -78^{o}C and then allowed to return to ambient temperature. The reaction was then added to $NaHCO_{3(sat)}$, extracted thrice with EtOAc, combined organic layers were dried over Na_2SO_4, and then concentrated. Silica gel flash chromatography eluting with 2 : 1 hex./EtOAc yielded 8.10 g (87%) of the desired compound as an off-white solid.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.61 (d, 1H, *J* = 7.5), 7.24-7.38 (m, 3H), 5.94 (d, 1H, *J* = 6.9), 5.36 (m, 1H), 4.52 (dd, 2H, *J* = 33.2, 13.2), 3.39 (m, 2H); ^{13}CNMR (300MHz, $CDCl_3$) δ 166.31, 152.65, 139.50, 138.36, 130.19, 128.34, 127.24, 125.33, 78.93, 63.40, 37.98, 28.72; IR (NaCl, film): 1690 cm^{-1}; $[\alpha]_D$ = -208.3^{o}; R_f = 0.37 (2 : 1 hex./EtOAc)

Ref: BJEIV477, BJEIV535, **BJEIV538**, BJEV030, BJEV149.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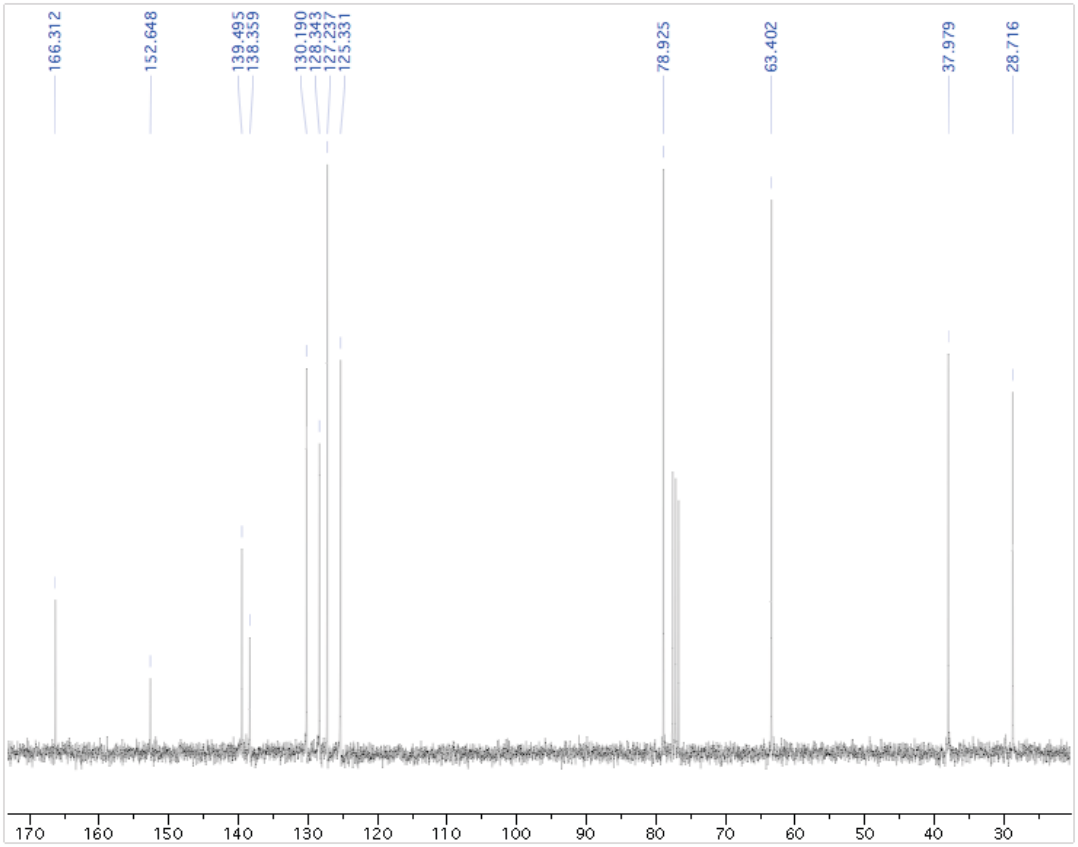
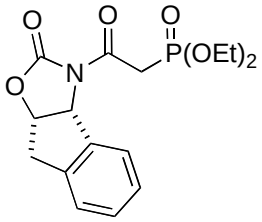


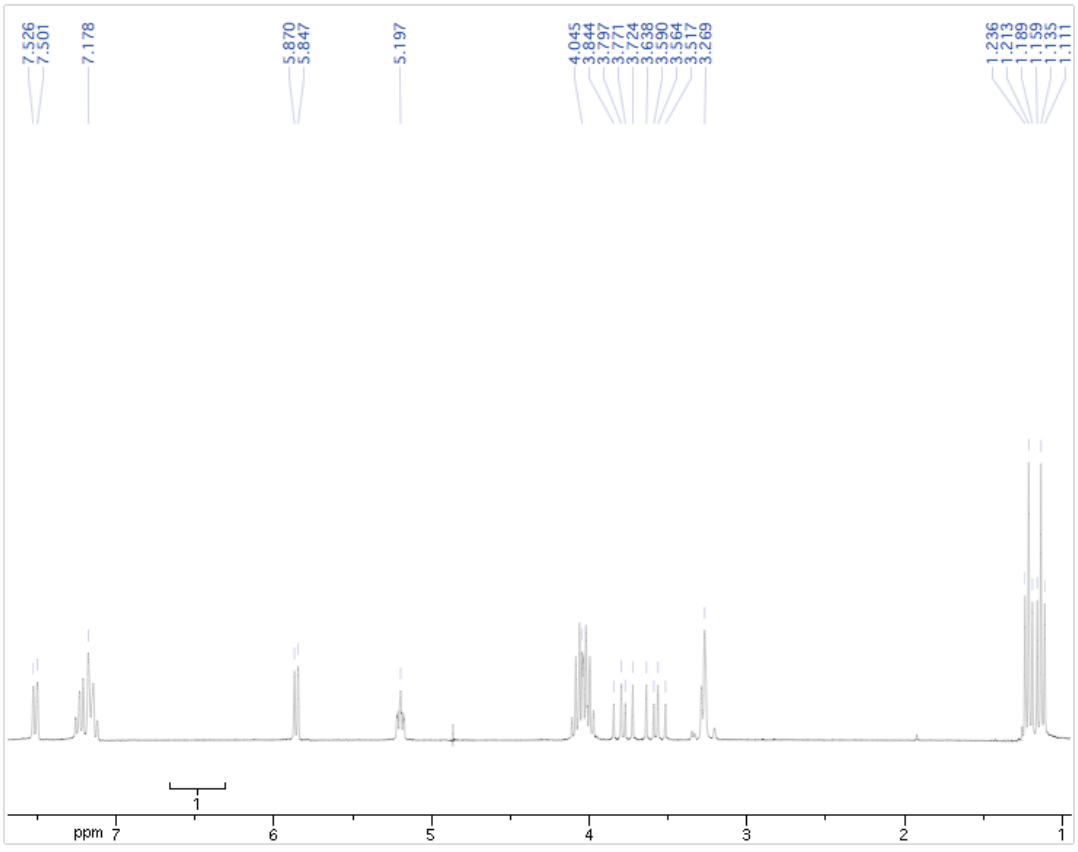


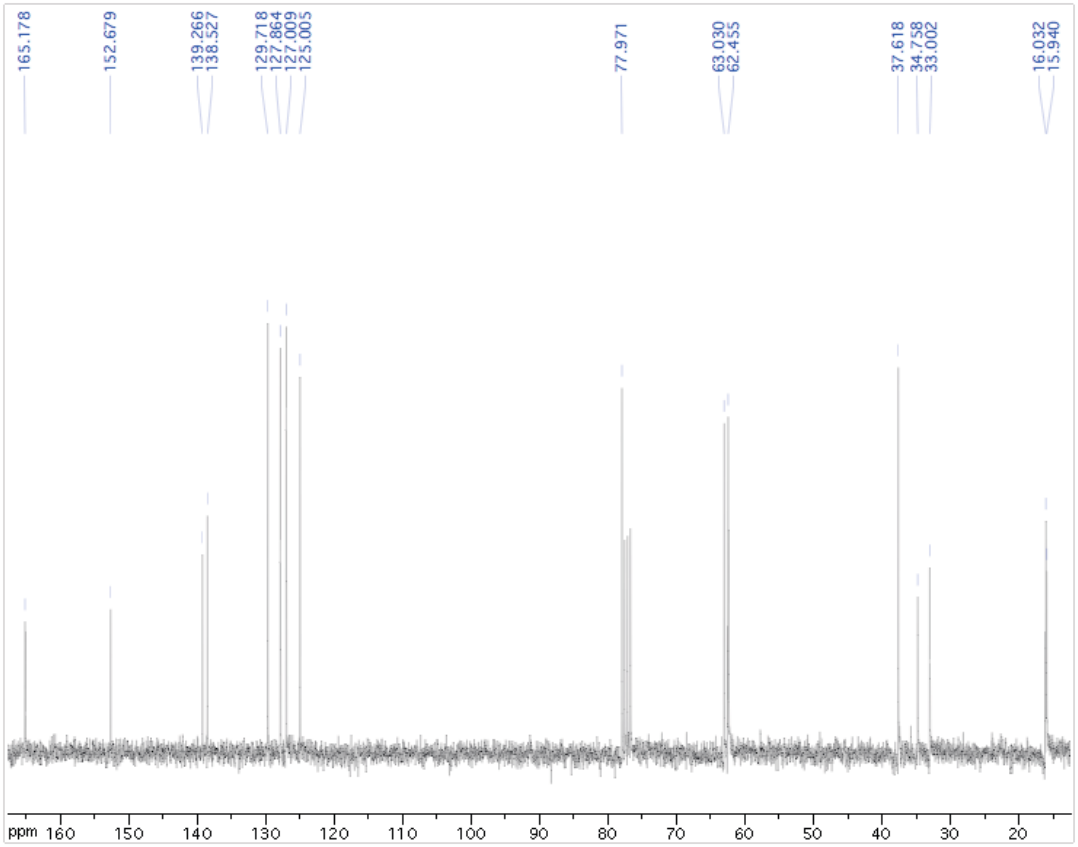
Synthesis of diethyl 2-oxo-2-((3a*R*,8a*S*)-2-oxo-2*H*-indeno[1,2-*d*]oxazol-3(3a*H*,8*H*,8a*H*)-yl)ethylphosphonate: An oven dried 100 mL round-bottomed flask was charged with 12.85 g (43.39 mmol, 1equiv.) (3a*R*,8a*S*)-3-(2-bromoacetyl)-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one and 18.6 mL (108.49 mmol, 2.5 equiv.) triethyl phosphite. The reaction was stirred at 100^{o}C for 20 min and then partially concentrated via rotary evaporation while heating in a 60^{o}C water bath for 30 min. The resulting residue was taken up in 250 mL MeCN and washed 4 x 200 mL hexanes. Concentration

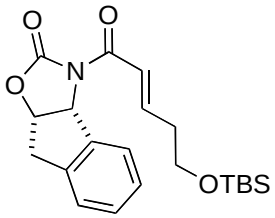
and purification of the MeCN layer by silica gel flash chromatography eluting with EtOAc yielded 15.34 g (>99%) of the desired product as a white solid.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.53 (d, 1H, *J* = 7.5), 7.18 (m, 3H), 5.86 (d, 1H, *J* = 6.9), 5.20 (m, 1H), 4.05 (m, 4H), 3.78 (dd, 1H, *J* = 21.9, 14.4), 3.57 (dd, 1H, *J* = 22.2, 14.4), 3.27 (m, 2H), 1.21 (t, 3H, *J* = 7.2), 1.135 (t, 3H, *J* = 7.2); ^{13}CNMR (300MHz, $CDCl_3$) δ 165.2, 152.7, 139.3, 138.5, 129.7, 127.9, 127.0, 125.0, 78.0, 63.0, 62.5, 37.6, 34.8, 33.0, 16.0, 15.9; IR (NaCl, film): 1780, 1697 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 353.1028 calcd for $C_{16}H_{20}NO_6P$, found: 353.1030; $[\alpha]_D$ = -157.6°; R_f = 0.25 (EtOAc).

Ref: BJEIV488, BJEIV537, BJEV002, **BJEV031**, BJEV152.





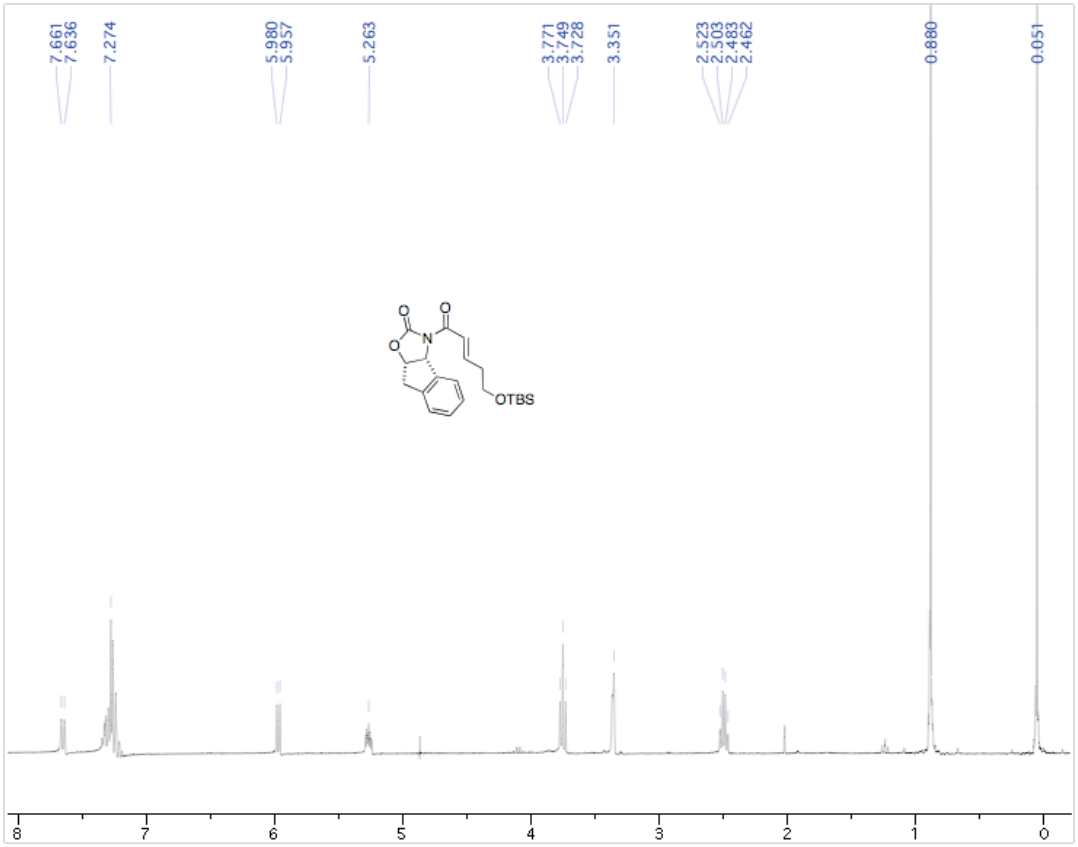


Synthesis of (3a*R*,8a*S*)-3-((*E*)-5-(*tert*-butyldimethylsilyloxy)pent-2-enoyl)-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one: A 1 L oven dried round-bottomed flask was charged with 15.34 g (43.42 mmol, 1equiv.) diethyl 2-oxo-2-((3a*R*,8a*S*)-2-oxo-2*H*-indeno[1,2-*d*]oxazol-3(3a*H*,8*H*,8a*H*)-yl)ethylphosphonate, 2.21 g (52.10 mmol, 1.2 equiv.) LiCl, and 220 mL dry MeCN. To this suspension was added 7.56 mL (43.42 mmol, 1equiv.) *i*Pr_2NEt and the reaction was stirred for 15 min at ambient temperature before 9.81 g (52.10 mmol, 1.2 equiv.) of aldehyde **3.5** dissolved in 5 mL MeCN was

added. Stirring was continued at ambient temperature for 16 hr and then the reaction was concentrated to ~30% volume, added to brine, and extracted twice with EtOAc. Combined organic layers were dried over Na_2SO_4 and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 4 : 1 hex./EtOAc to yield 14.83 g (88%) of the desitred compound as a colorless oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.5, 1H), 7.27 (m, 5H), 5.97 (d, *J* = 6.9, 1H), 5.26 (m, 1H), 3.75 (t, *J* = 6.6, 2H), 3.35 (m, 2H), 2.49 (q, *J* = 6.0, 2H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}CNMR (75MHz, $CDCl_3$) δ 165.2, 153.0, 148.5, 139.5, 139.3, 129.8, 128.1, 127.4, 125.2, 121.8, 78.1, 63.2, 61.7, 60.4, 38.0, 36.3, 26.0, 21.1, 18.4, 14.3, -5.3; IR (NaCl, film): 1778, 1683, 1635 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 388.19386 calcd for $C_{21}H_{30}NO_4Si$, found: 388.1938; $[\alpha]_D$ = -247.9^o; R_f = 0.38 (4 : 1 hex./EtOAc).

Ref: BJEIV489, BJEV001, BJEV003, **BJEV034**, BJEV157.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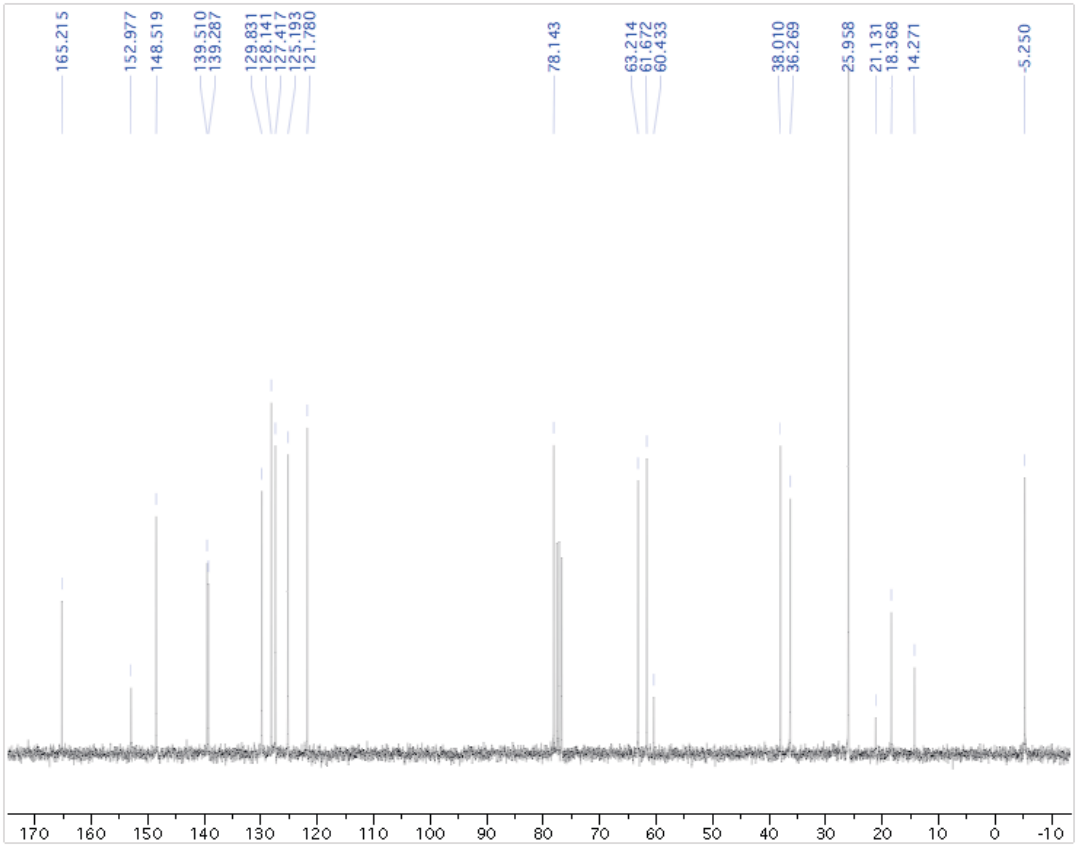
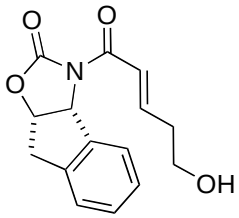


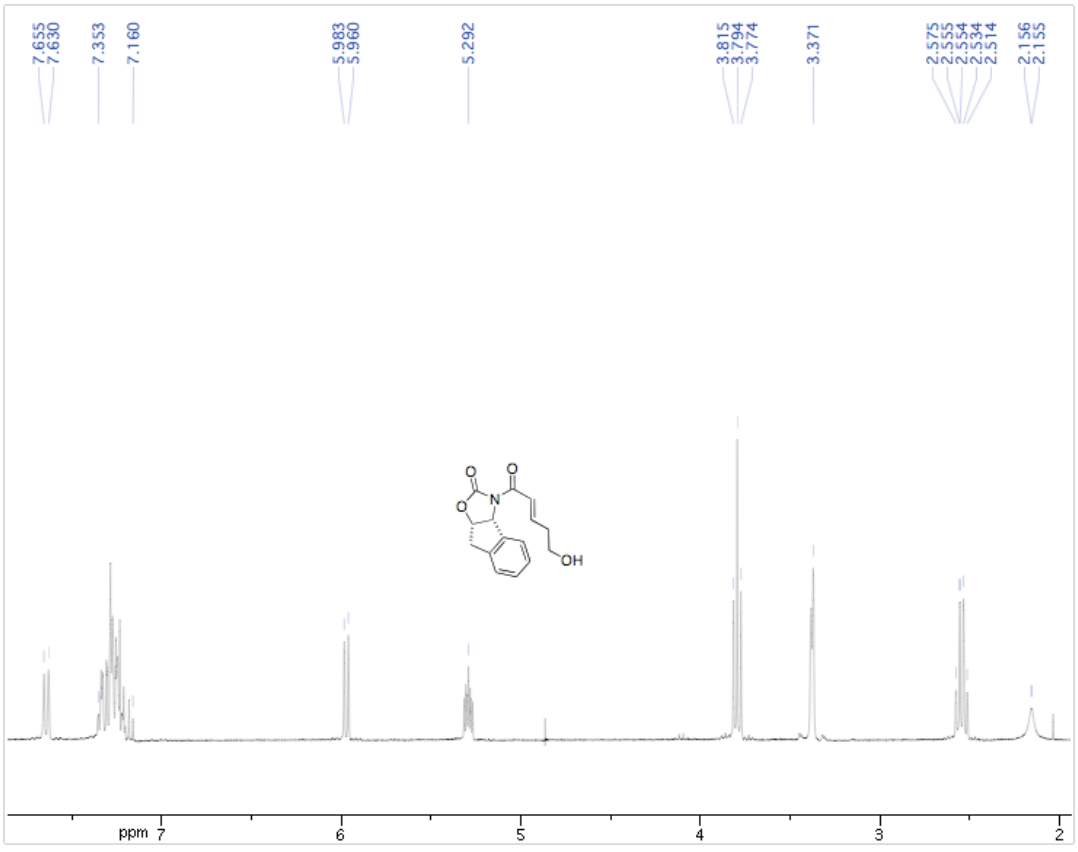


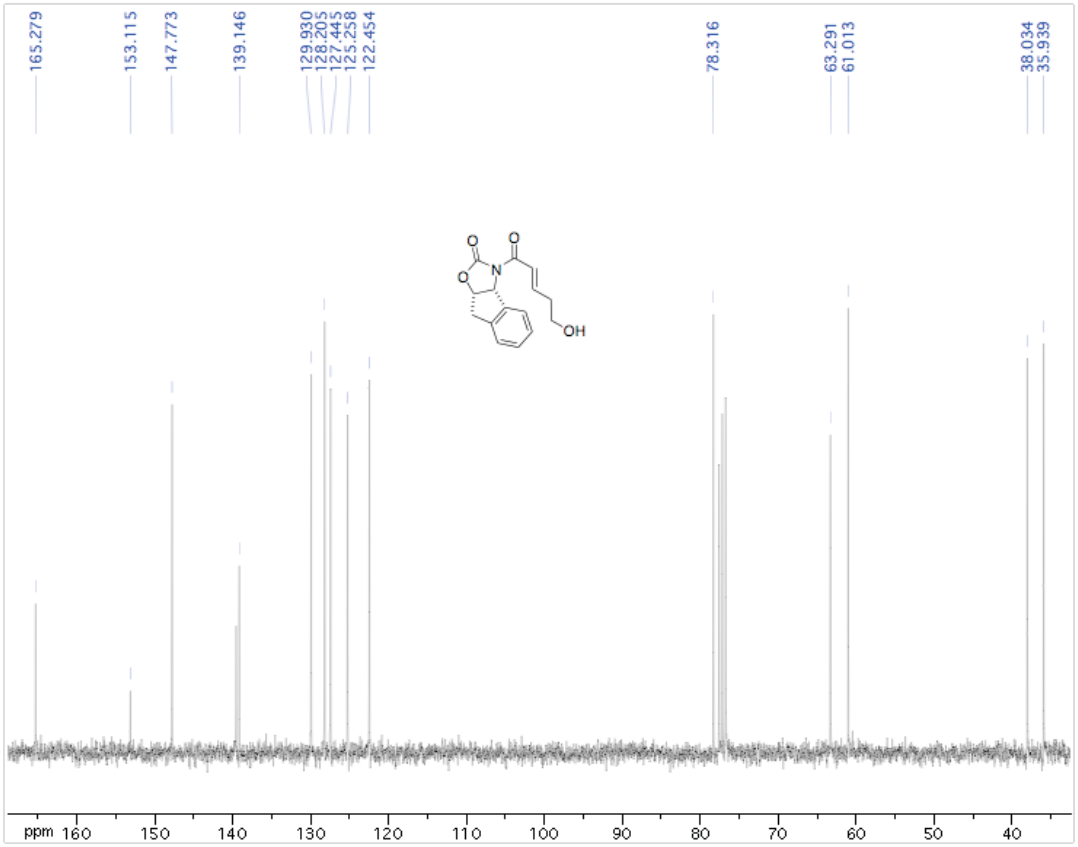
Synthesis of (3a*R*,8a*S*)-3-((*E*)-5-hydroxypent-2-enoyl)-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one: A 50 mL HDPE bottle was charged with 471 mg (1.22 mmol, 1equiv.) (3a*R*,8a*S*)-3-((*E*)-5-(*tert*-butyldimethylsilyloxy)pent-2-enoyl)-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one dissolved in 12 mL dry MeCN. To this solution was added 365 μL of 48% aqueous HF and the reaction was stirred at ambient temperature for 3 hr before the slow addition of $NaHCO_{3(sat.)}$. This mixture was extracted thrice with EtOAc, combined organic layers were dried over Na_2SO_4, and concentrated.

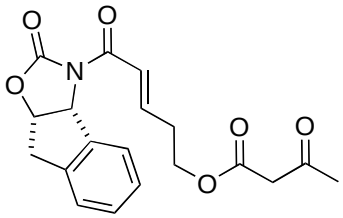
The resulting residue was purified by silica gel flash chromatography eluting with 1 : 2 hex./EtOAc to yield 334 mg (>99%) of the title compound as a white solid.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.5, 1H), 7.16-7.35 (m, 5H), 5.97 (d, *J* = 6.9, 1H), 5.29 (m, 1H), 3.79 (t, *J* = 6.6, 2H), 3.37 (m, 2H), 2.54 (q, *J* = 6.0, 2H), 2.16 (brs, 1H); ^{13}CNMR (75MHz, $CDCl_3$) δ 165.3, 153.1, 147.8, 139.5, 139.2, 129.9, 128.2, 127.5, 125.3, 122.5, 78.3, 63.3, 61.0, 38.0, 35.9; IR (NaCl, film): 3412, 1766, 1682, 1634 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 274.1074 calcd for $C_{15}H_{16}NO_4$, found: 274.1077; $[\alpha]_D$ = -341.4°; R_f = 0.17 (1 : 1 hex./EtOAc).

Ref: BJEIV491, **BJEV004**, BJEV006, BJEV035.



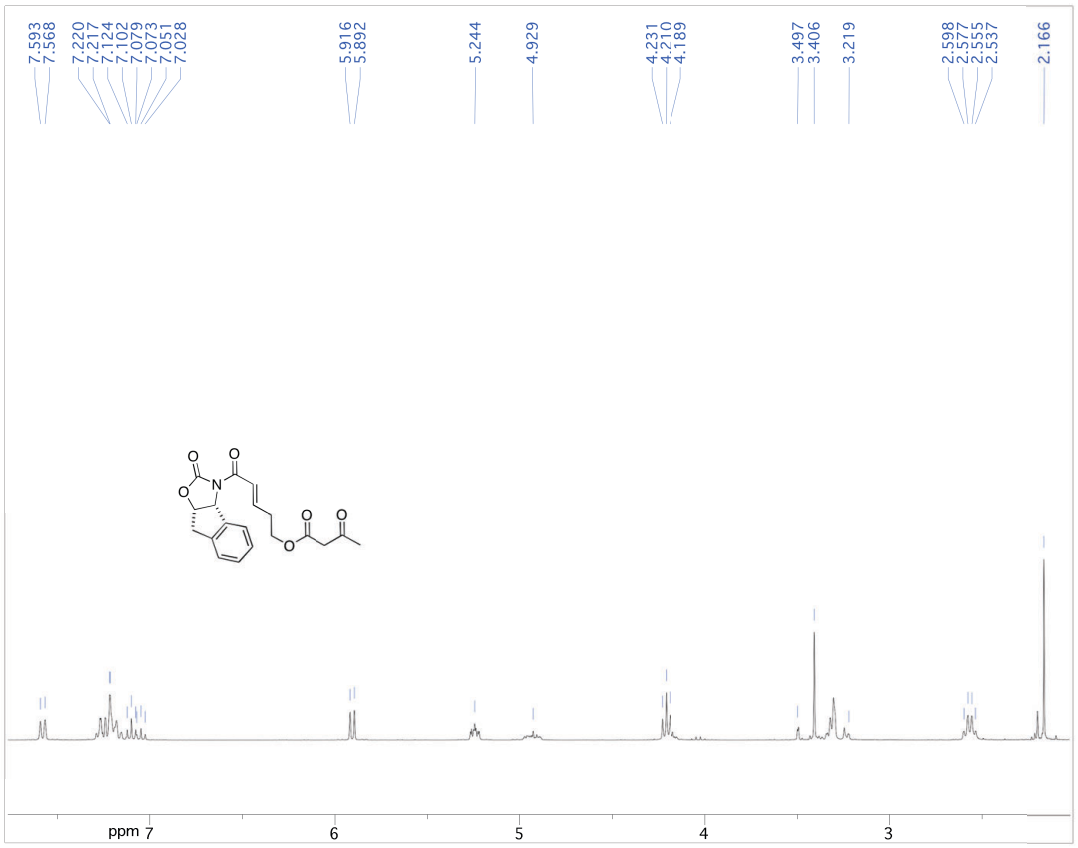


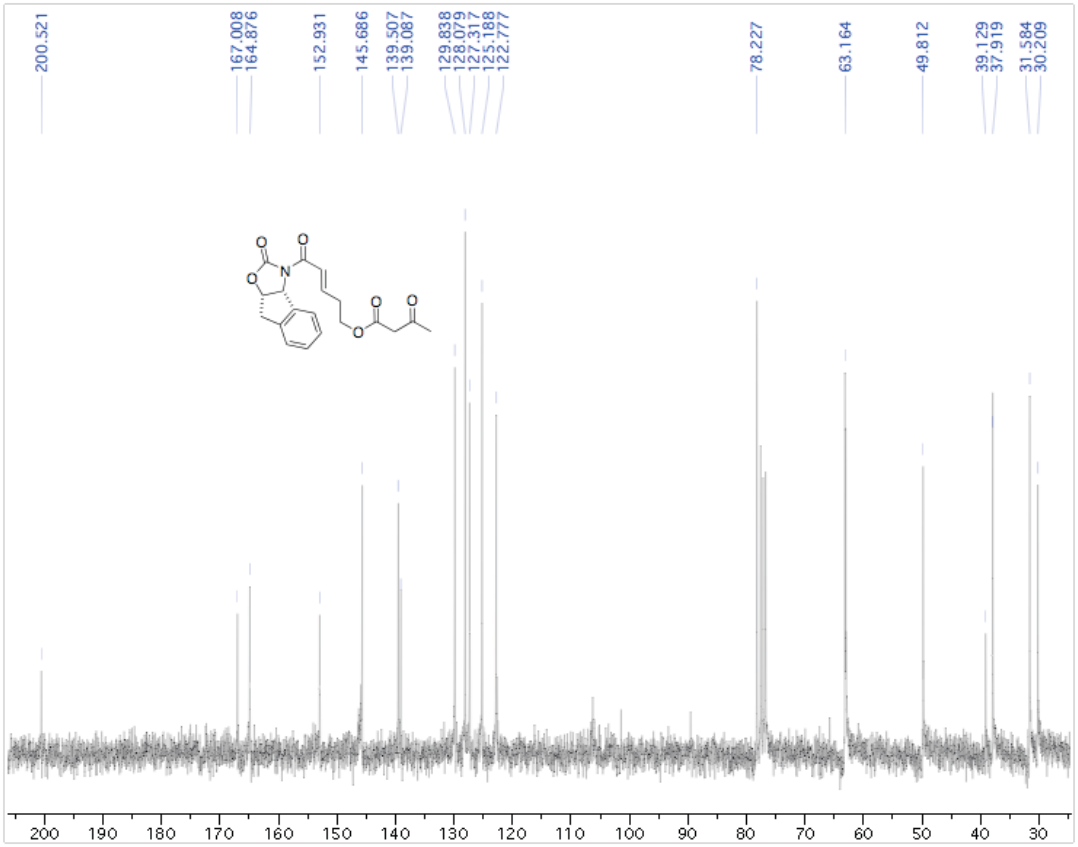


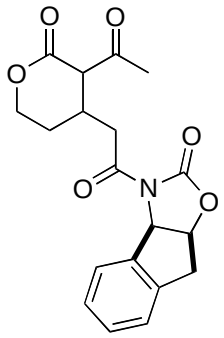
Synthesis of (*E*)-5-oxo-5-((3a*R*,8a*S*)-2-oxo-2*H*-indeno[1,2-*d*]oxazol-3(3a*H*,8*H*,8a*H*)-yl)pent-3-enyl 3-oxobutanoate: To a 1L flame dried round-bottomed flask containing 6.34 g (23.2 mmol, 1 equiv.) (3a*R*,8a*S*)-3-((*E*)-5-hydroxypent-2-enoyl)-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one dissolved in 230 mL dry CH_2Cl_2 at 0^oC was added 4.47 g (58.0 mmol, 2.5 equiv.) diketene and then 283 mg (2.32 mmol, 0.1 equiv.) DMAP. Te reaction was stirred for 1.5 hr at ambient temperature, added to $NaHCO_{3(sat.)}$, and extracted thrice with CH_2Cl_2. Combined organic layers were dried over Na_2SO_4,

concentrated, and purified by silica gel flash chromatography eluting with 1 : 1 hex./EtOAc to yield 8.28 g (>99%) of the desired compound as a pale yellow oil. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.5, 1H), 7.22 (m, 4H), 7.08 (dt, *J* = 15.3, 6.6, 1H), 5.90 (d, *J* = 7.2, 1H), 5.24 (m, 1H), 4.93 (m, 1H), 4.21 (t, *J* = 6.3, 2H), 3.22-3.50 (m, 4H), 3.41 (s, 2H), 2.57 (q, *J* = 6.6, 2H), 2.17 (s, 3H); ^{13}CNMR (75MHz, $CDCl_3$) δ 200.5, 167.0, 164.9, 152.9, 145.7, 139.5, 139.1, 129.8, 128.1, 127.3, 125.2, 122.8, 78.2, 63.2, 49.8, 39.1, 37.9, 31.6, 30.2; IR (NaCl, film): 1744, 1770, 1714, 1681, 1638 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 358.1285 calcd for $C_{19}H_{20}NO_6$, found: 358.1284; $[\alpha]_D$ = -270.3°; R_f = 0.28 (1 : 1 hex./EtOAc).

Ref: BJEIV495, BJEV005, BJEV007, **BJEV036**.



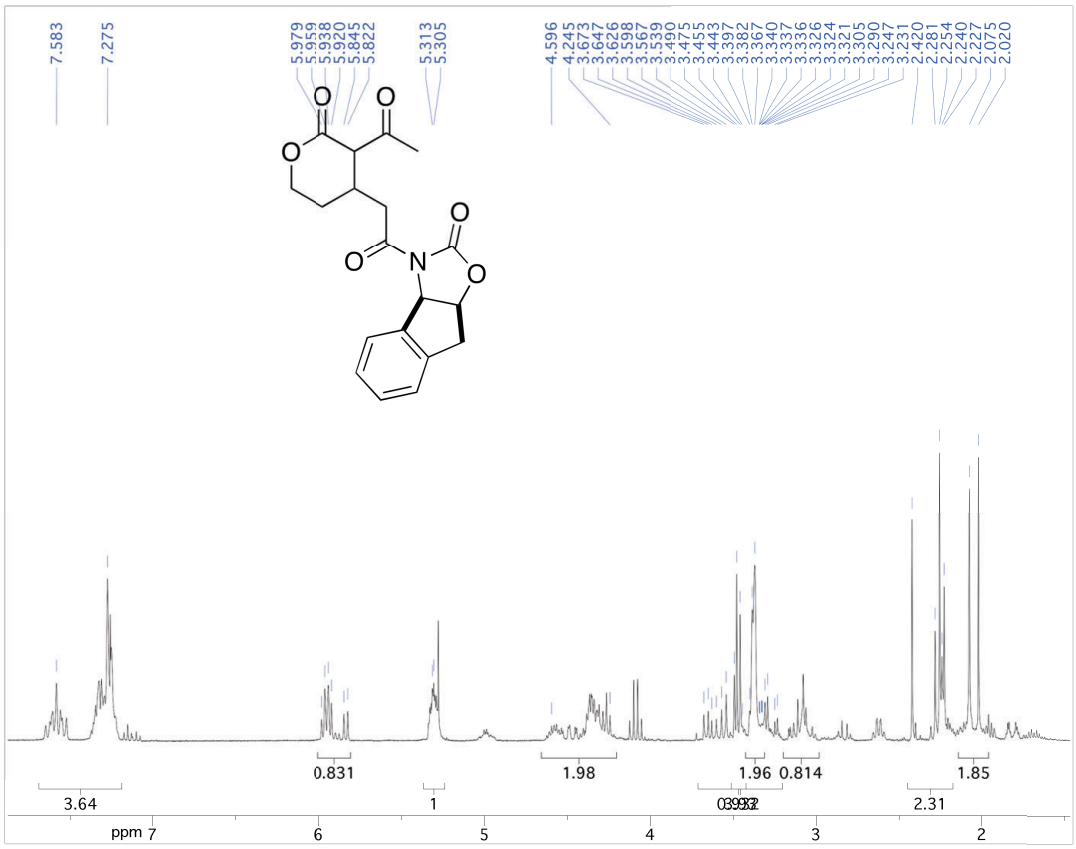


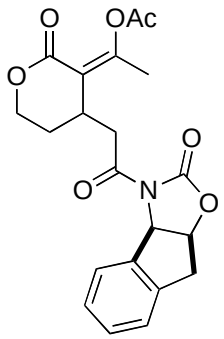


Synthesis of (3a*R*,8a*S*)-3-(2-(3-acetyl-2-oxotetrahydro-2*H*-pyran-4-yl)acetyl)-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one: To a 200 mL round-bottomed flask containing 4.71 g (13.2 mmol, 1 equiv.) (*E*)-5-oxo-5-((3a*R*,8a*S*)-2-oxo-2*H*-indeno[1,2-*d*]oxazol-3(3a*H*,8*H*,8a*H*)-yl)pent-3-enyl 3-oxobutanoate dissolved in 65 mL dry MeCN at -15^{o}C was added 2.90 mL (26.3 mmol, 2 equiv.) $TiCl_4$ and then 460 μL

(2.63 mmol, 0.2 equiv.) *i*Pr_2NEt. The reaction was stirred for 72 hr before being added to $NaHCO_3$, extracted into EtOAc, dried over Na_2SO_4, and concentrated to yield the desired mixture of isomers as a tan oil which was used without further purification.

Ref.: BJEV009, **BJEV039**, BJEV072.



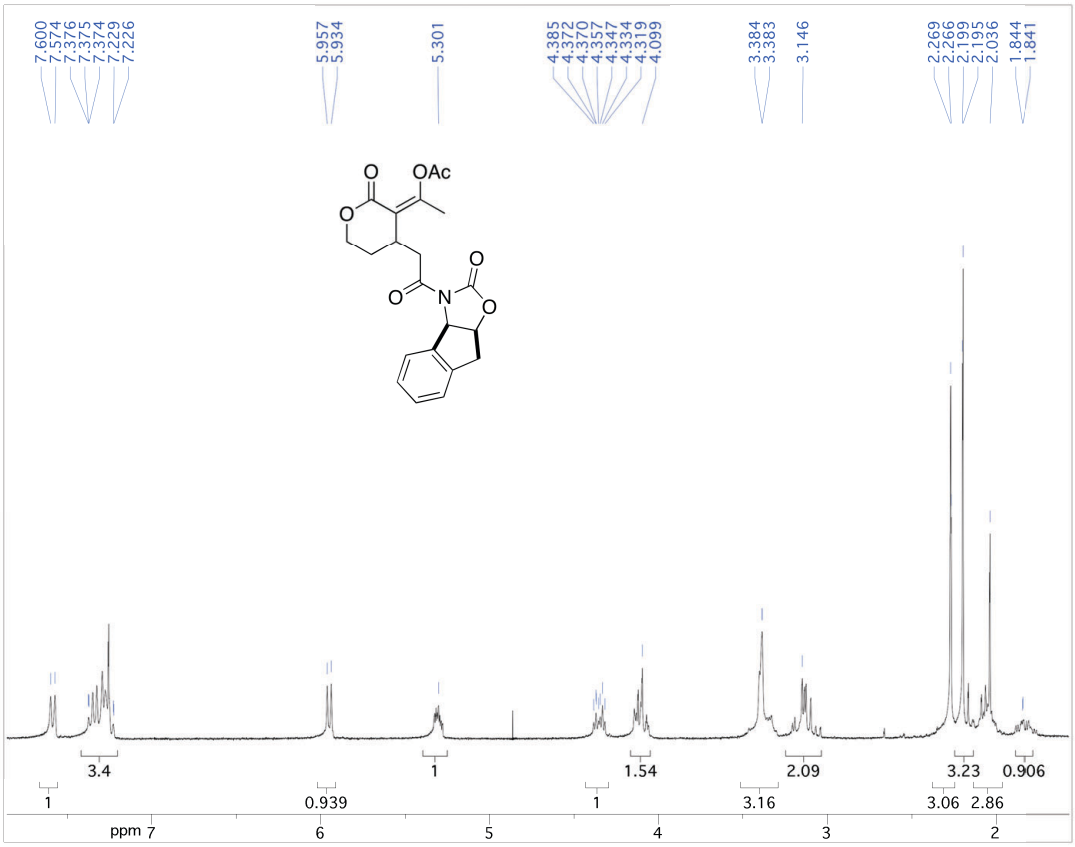


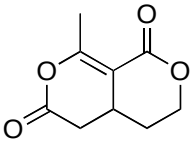
Synthesis of (*Z*)-1-(2-oxo-4-(2-oxo-2-((3a*R*,8a*S*)-2-oxo-8,8a-dihydro-2*H*-indeno[1,2-*d*]oxazol-3(3a*H*)-yl)ethyl)dihydro-2*H*-pyran-3(4*H*)-ylidene)ethyl acetate: To a 10 mL

round-bottomed flask containing 35 mg (0.098 mmol, 1 equiv.) of **(**3a*R*,8a*S*)-3-(2-(3-acetyl-2-oxotetrahydro-2*H*-pyran-4-yl)acetyl)-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one dissolved in 1 mL CH_2Cl_2 was added 46 μL (0.490 mmol, 5 equiv.) Ac_2O, 68 μL (0.490 mmol, 5 equiv.) NEt_3, and then 2 mg (0.02 mmol, 0.2 equiv.) DMAP. The reaction was stirred for 16 hr at ambient temperature before being added to 1 M HCl, extracted into EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel chromatography eluting with 2 : 1 to 1 : 2 hex./EtOAc to yield 19 mg (49%) of the desired product as a pale yellow oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 7.58 (d, J = 7.8, 1H), 7.23-7.38 (m, 3H), 5.94 (d, *J* = 6.9, 1H), 5.30 (m, 1H), 4.34 (dt, *J* = 11.4, 4.5, 1H), 3.38 (m, 3H), 3.15 (m, 2H), 2.27 (s, 3H), 2.20 (s, 3H), 2.04 (m, 2H), 1.84 (m, 1H); Rf = 0.22 (1 : 1 hex./EtOAc).

Ref.: **BJEV101**, BJEV106.

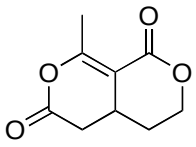




General procedure for the synthesis of 8-methyl-3,4,4a,5-tetrahydropyrano[3,4-*c*]pyran-1,6-dione (4.57) under basic conditions: To 1 equiv. β-ketoester substrate dissolved in dry MeCN (0.1-0.2M) was added 2 equiv Cs_2CO_3 and the reaction was stirred at 40^{o}C until all starting material had been consumed (TLC 1 : 1 hex./EtOAc). The reaction was then filtered through celite with THF or EtOAc washes and

concentrated. The crude residue was purified by silica gel chromatography eluting with 1 : 1 to 0 : 1 hex./EtOAc. All e.r. data was determined by chiral HPLC.

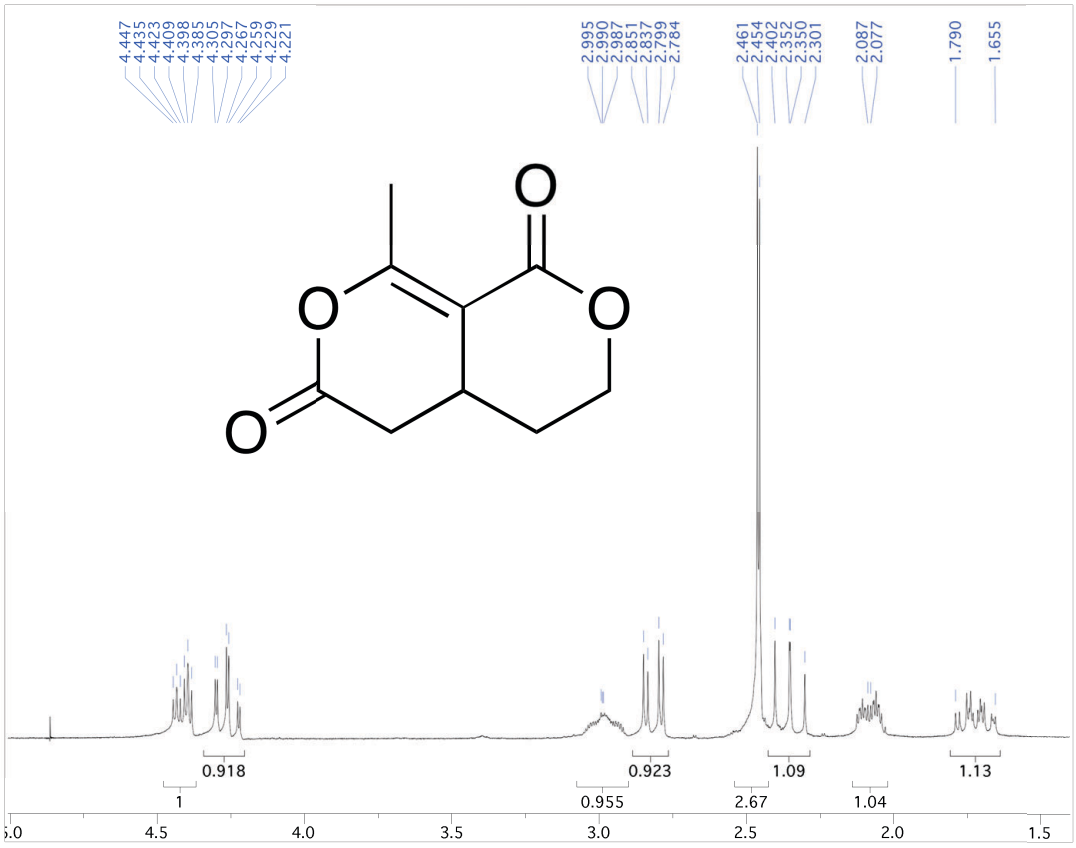
Ref.: BJEV040, BJEV025, BJEV081, BJEV094, BJEV156

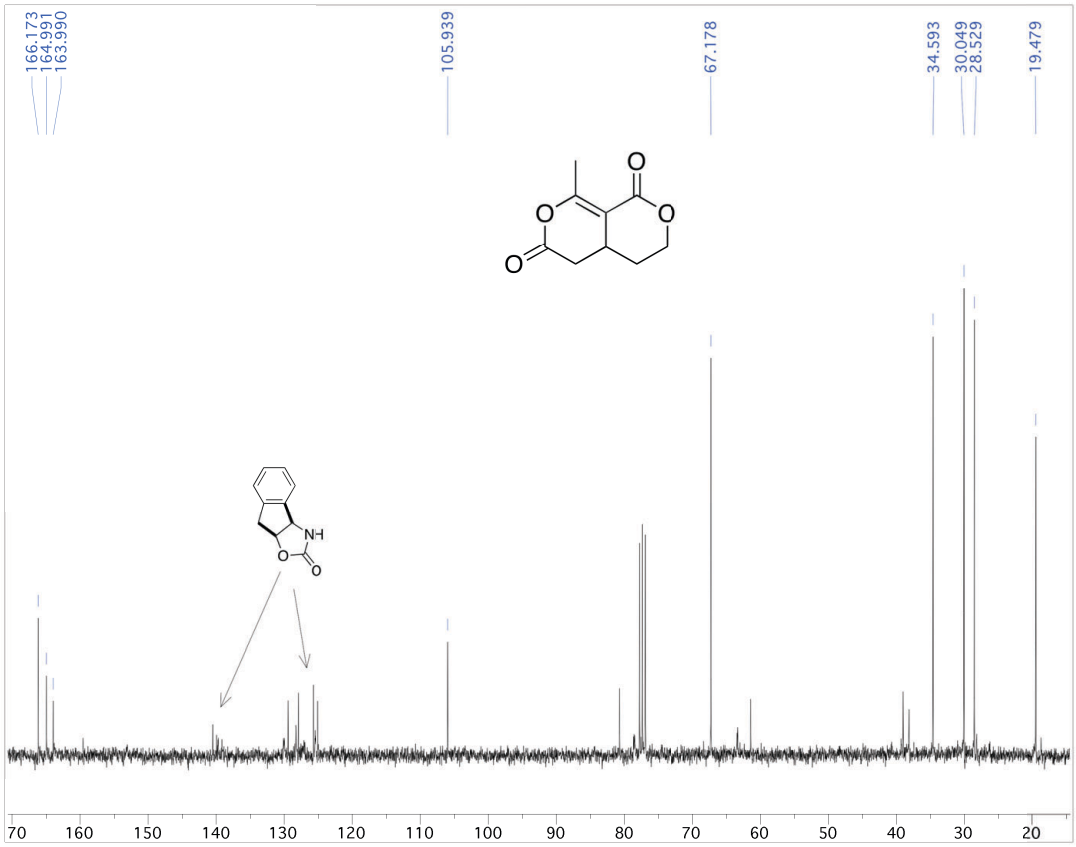


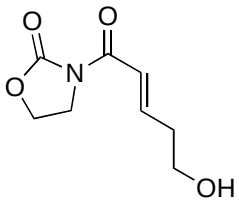
General procedure for the synthesis of 8-methyl-3,4,4a,5-tetrahydropyrano[3,4-*c*]pyran-1,6-dione (4.57) under Lewis acidic conditions: To 1 equiv. β-ketoester substrate dissolved in dry MeCN (0.1-0.2M) at -15°C was added 2 equiv. $TiCl_4$ and the reaction was stirred at this temperature for 15 min before the addition of 2 equiv. *i*Pr_2NEt. The reaction was stirred at -15°C until all starting material had been consumed (TLC 1:1 hex/EtOAc). The reaction was then added to $NaHCO_{3(sat)}$ and extracted 3 x EtOAc, dried over $MgSO_4$ and concentrated. This residue was taken up in dry MeCN and catalytic Cs_2CO_3 was added. The reaction was stirred at ambient temperature until all starting material had been consumed (TLC 1 : 1 hex./EtOAc). The reaction was then filtered through celite with THF or EtOAc washes and concentrated. The crude residue was purified by silica gel chromatography eluting with 1 : 1 to 0 : 1 hex./EtOAc. All e.r. data was determined by chiral HPLC.

^{1}HNMR (300 MHz, $CDCl_3$) δ 4.41 (dt, *J* = 11.4, 3.3, 1H), 4.23 (td, *J* = 11.4, 2.4, 1H), 2.99 (m, 1H), 2.81 (dd, *J* = 15.6, 4.5, 1H), 2.46 (d, *J* = 2.4, 3H), 2.35 (dd, *J* = 15.6, 15.0, 1H), 2.08 (m, 1H), 1.74 (m, 1H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 166.2, 165.0, 105.9, 67.2, 34.6, 30.0, 28.5, 19.5; IR (NaCl, film): 1784, 1705, 1630 cm^{-1}; R_f = 0.20 (1 : 1 hex./EtOAc)

Ref.: BJEV039, BJEV072, BJEV074.

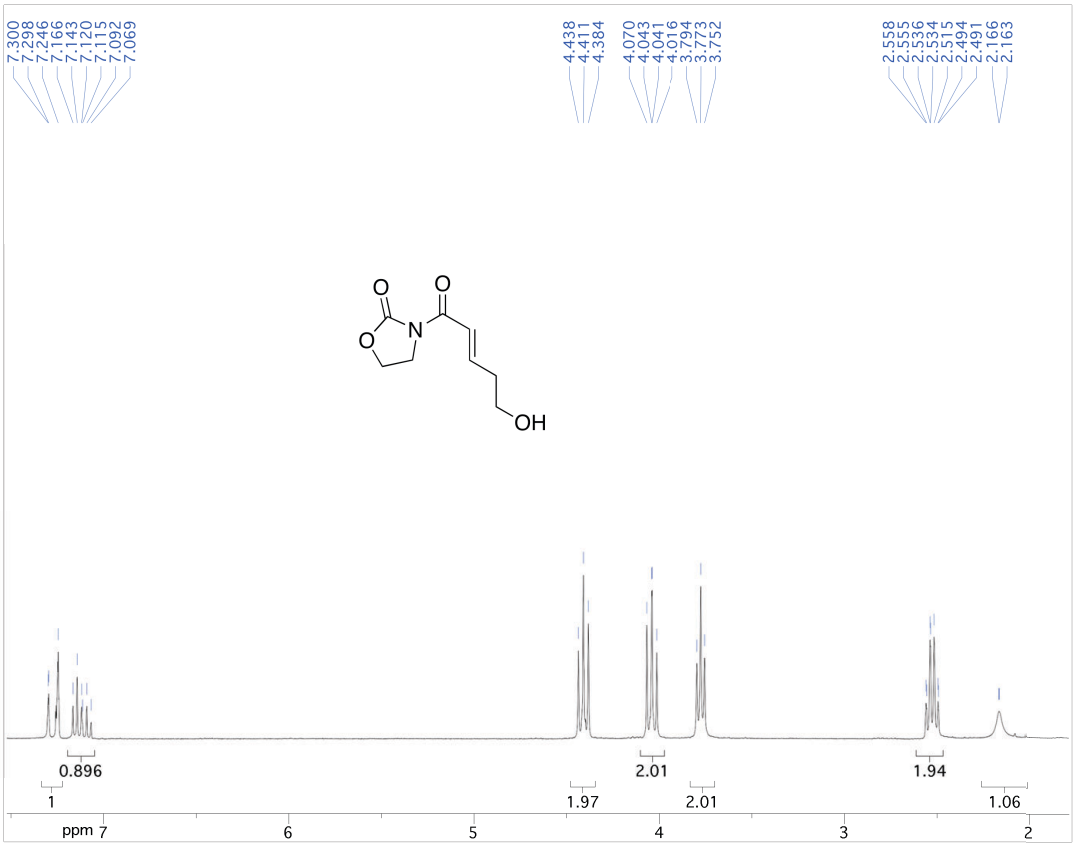


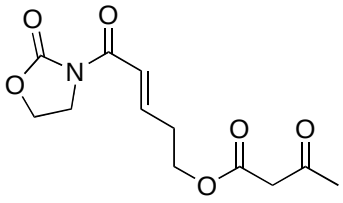




Synthesis of (*E*)-3-(5-hydroxypent-2-enoyl)oxazolidin-2-one (4.59): To a 4 dram vial containing 95 mg (0.32 mmol, 1 equiv.) TBS ether **4.5** dissolved in 4 mL THF was added 200 μL 48% $HF_{(aq.)}$. The reaction was stirred at ambient temperature for 6 hr, added to $NaHCO_{3(sat.)}$, extracted into EtOAc, dried over Na_2SO_4, and concentrated to yield 45 mg (76%) of the desired product as a pale yellow oil which was used without purification. ^{1}HNMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 15.9, 1H), 7.12 (dt, *J* = 15.3, 6.9, 1H), 4.41 (t, *J* = 8.1, 2H), 4.04 (t, *J* = 8.1, 2H), 3.77 (t, *J* = 6.3, 2H), 2.52 (qd, *J* = 6.6, 0.9, 2H), 2.16 (bs, 1H); R_f = 0.39 (1 : 2 hex./EtOAc).

Ref.: **BJEII486**, BJEII493.

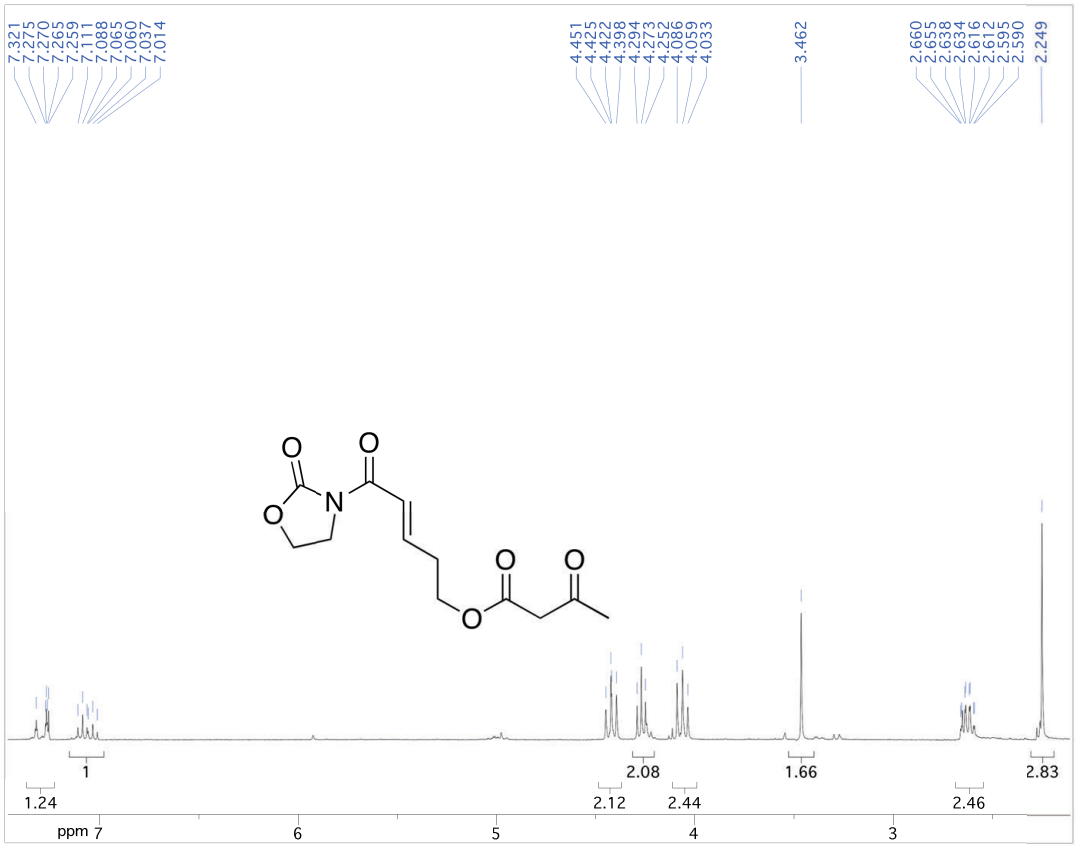


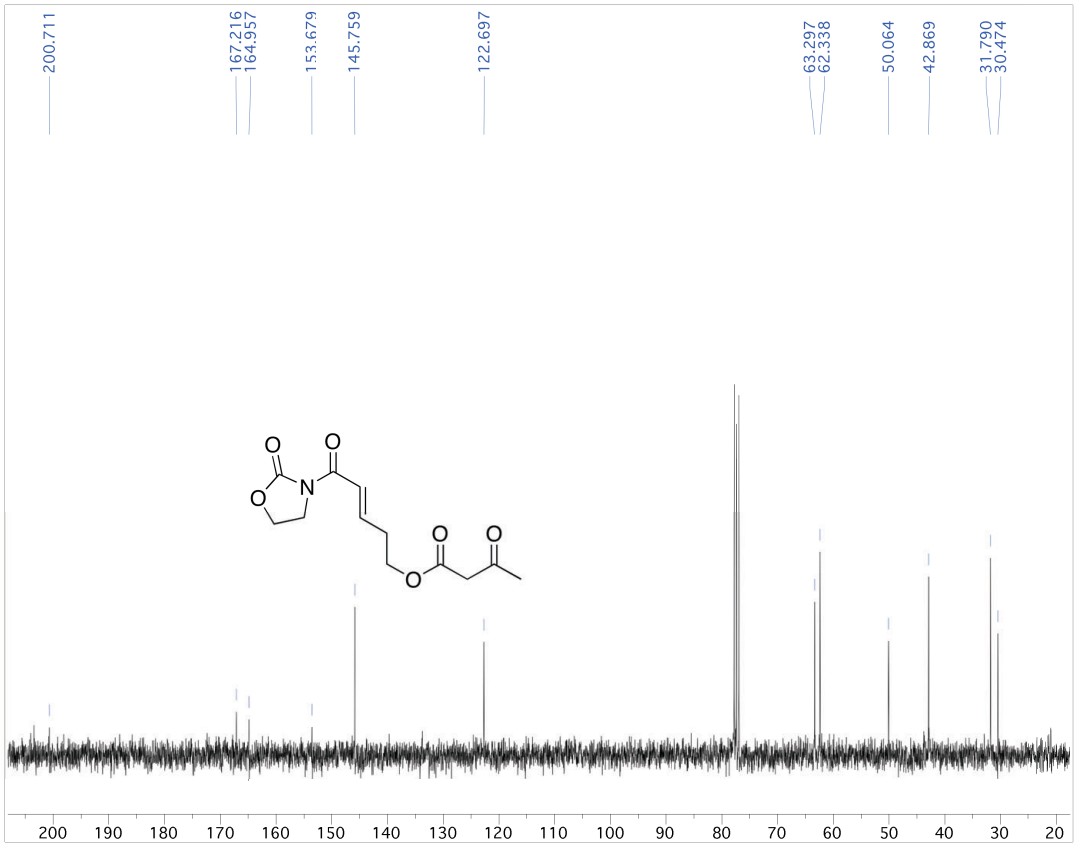


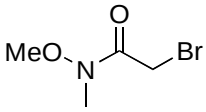
Synthesis of (*E*)-5-oxo-5-(2-oxooxazolidin-3-yl)pent-3-en-1-yl 3-oxobutanoate (4.60): To a 10 mL round-bottomed flask containing 148 mg (0.799 mmol, 1 equiv.) alcohol **4.59** dissolved in 3 mL dry CH_2Cl_2 at -10°C was added 123 μL (1.60 mmol, 2 equiv.) diketene followed by a single pellet of DMAP. The reaction was stirred for 20 min at -10°C before being added to $NaHCO_{3(sat.)}$, extracted into EtOAc, dried over Na_2SO_4, and concentrated. The crude residue was used without purification.

^{1}HNMR (300 MHz, $CDCl_3$) δ 7.30 (m, 1H), 7.06 (dt, *J* = 15.3, 6.9, 1H), 4.42 (t, *J* = 7.8, 2H), 4.27 (t, *J* = 6.3, 2H), 4.06 (t, *J* = 7.8, 2H), 3.46 (s, 2H), 2.62 (qd, *J* = 6.6, 1.2, 2H), 2.25 (s, 3H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 200.7, 167.2, 165.0, 153.7, 145.8, 122.7, 63.3, 62.3, 50.1, 42.9, 31.8, 30.5; R_f = 0.37 (1 : 1 hex./EtOAc)

Ref.: BJEII489, **BJEII494**.





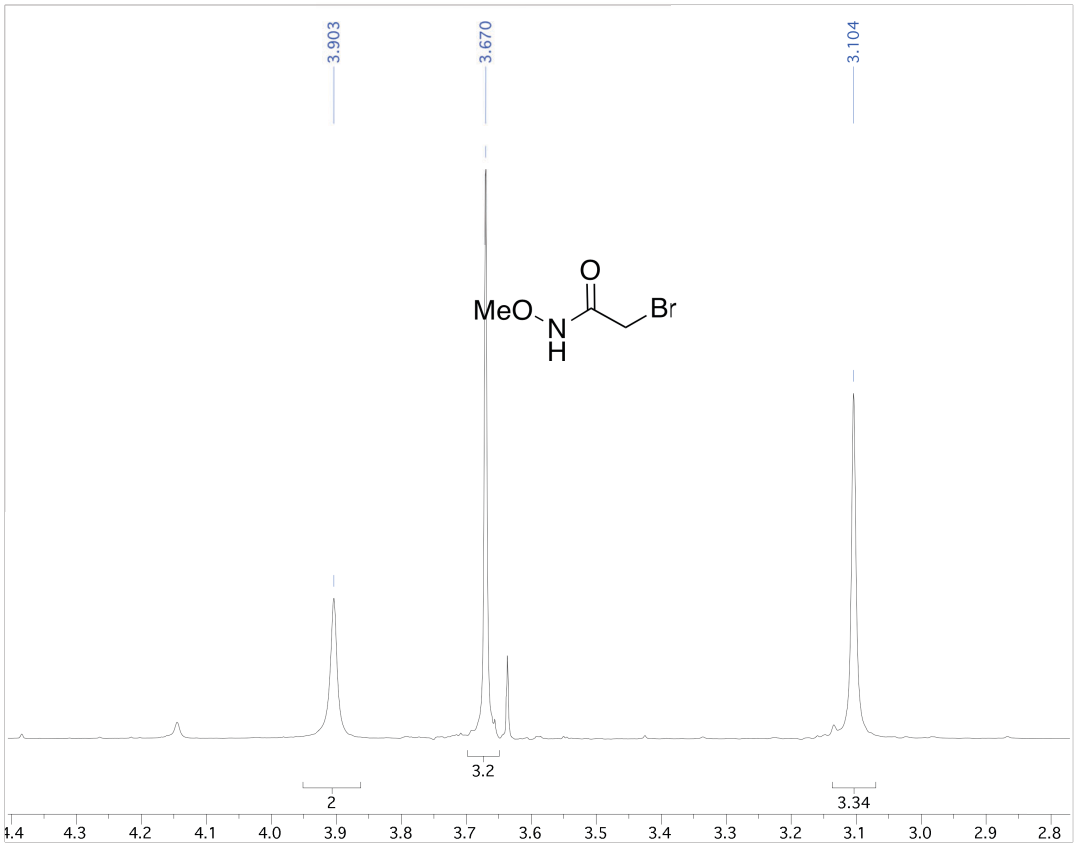


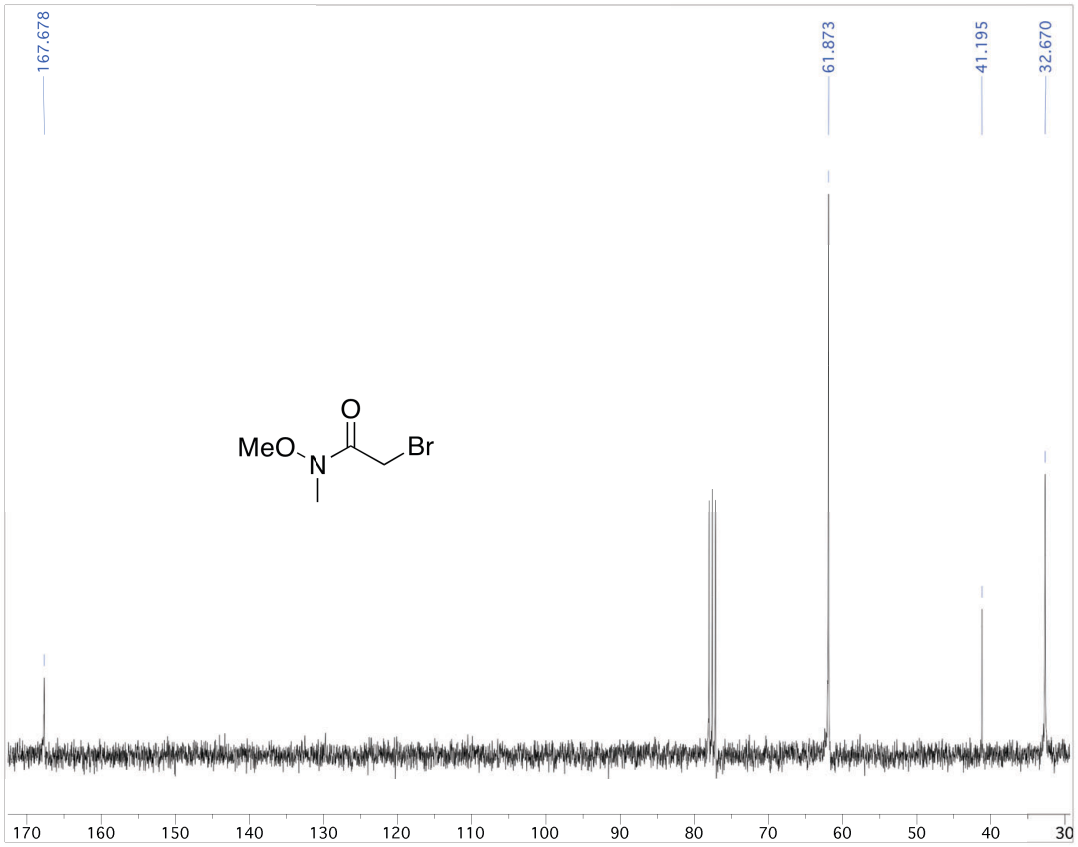
Synthesis of 2-bromo-*N*-methoxy-*N*-methylacetamide: To a 500 mL round-bottomed flask containing 5.20 g (53.3 mmol, 1 equiv.) *N*,*O*-dimethylhydroxylammonium chloride **4.61** dissolved in 250 mL CH_2Cl_2 at 0°C was added 4.87 mL (56.0 mmol, 1.05 equiv.) bromacetyl bromide followed by 18.58 mL (133.3 mmol, 2.5 equiv.) dry NEt_3. The reaction was allowed to warm to ambient temperature over 30 min and was then added to 1 M HCl, extracted into CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting

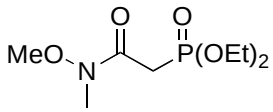
residue was purified by silica gel flash chromatography eluting with 2 : 1 to 1 : 1 hex./EtOAc to yield 4.18 g (43%) of the desired bromide as a yellow oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 3.90 (s, 2H), 3.67 (s, 3H), 3.10 (s, 3H); ^{13}CNMR (75MHz, $CDCl_3$) 167.7, 61.9, 41.2, 32.7; IR (NaCl, film): 1671 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 181.9811 calcd for $C_4H_9BrNO_2$, found: 181.9814; R_f = 0.35 (2 : 1 hex./EtOAc).

Ref: **BJEV073**.

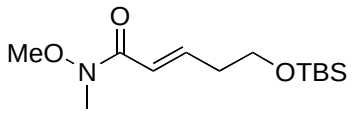






Synthesis of diethyl (2-(methoxy(methyl)amino)-2-oxoethyl)phosphonate: To a 25 mL round-bottomed flask containing 4.18 g (22.96 mmol, 1 equiv.) 2-bromo-*N*-methoxy-*N*-methylacetamide was added 9.85 mL (57.41 mmol, 2.5 equiv.) $P(OEt)_3$. The reaction was heated to 100°C for 20 min before being concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 5% MeOH in EtOAc to yield 4.91 g (89%) of the desired product as a pale yellow oil. R_f = 0.20 (5% MeOH in EtOAc).

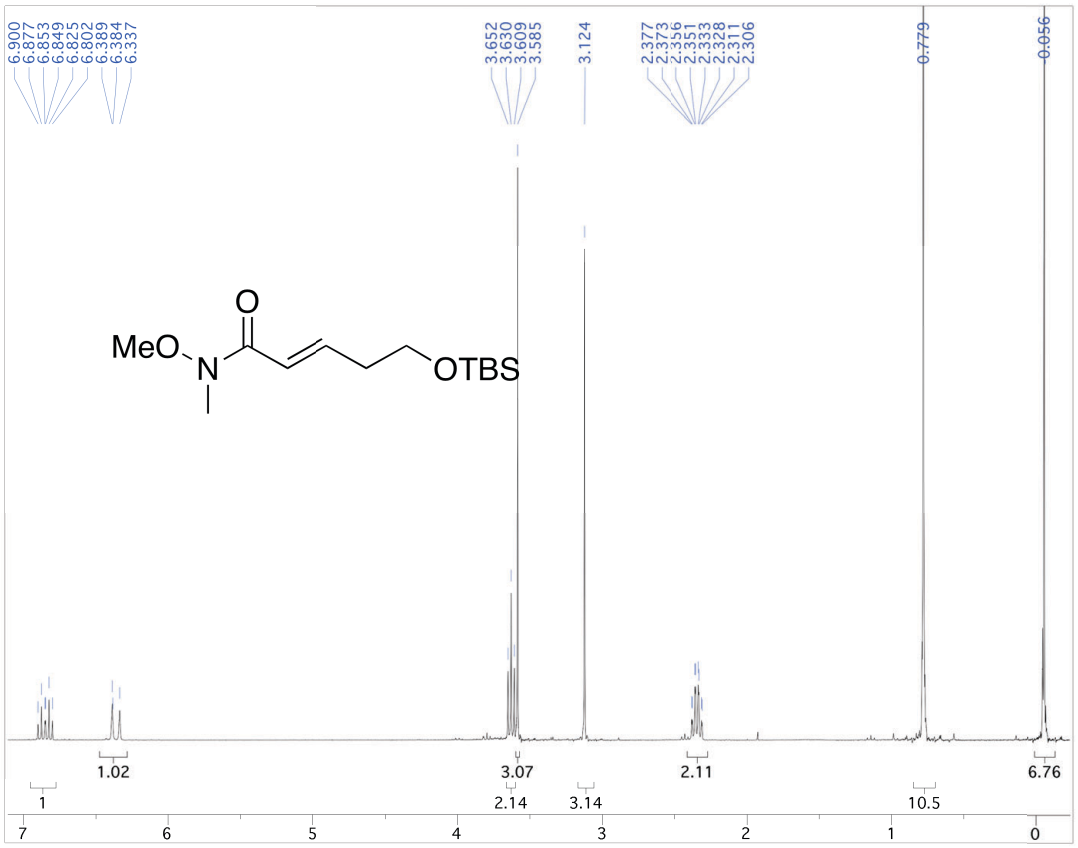
Ref: **BJEV075**.



Synthesis of (*E*)-5-((*tert*-butyldimethylsilyl)oxy)-*N*-methoxy-*N*-methylpent-2-enamide: To a 250 mL round-bottomed flask containing 4.91 g (20.5 mmol, 1 equiv.) diethyl (2-(methoxy(methyl)amino)-2-oxoethyl)phosphonate and 1.04 g (24.6 mmol, 1.2 equiv.) LiCl dissolved in 100 mL dry MeCN was added 3.58 mL (20.5 mmol, 1 equiv.) *i*Pr_2NEt. The reaction was stirred at ambient temperature for 15 min before the addition of 4.64 g (24.6 mmol, 1.2 equiv.) aldehyde **3.5** dissolved in a minimum of dry MeCN. The reaction was stirred for a further 4 hr at ambient temperature and was then added to brine and extracted thrice with EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 4 : 1 to 1 : 1 hex./EtOAc to yield 3.38 g (60%) of the desired product as a pale yellow oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 6.85 (dt, *J* = 15.6, 6.9, 1H), 6.35 (d, *J* = 14.1, 1H), 3.63 (t, *J* = 6.6, 2H), 3.59 (s, 3H), 3.12 (s, 3H), 2.34 (qd, 6.3, 1.2, 2H), 0.78 (s, 9H), 0.06 (s, 6H); ^{13}CNMR (75MHz, $CDCl_3$) δ 166.9, 144.3, 120.5, 61.8, 36.1, 32.4, 25.8, 18.4, -5.2; IR (NaCl, film): 1668, 1638 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 274.1833 calcd for $C_{13}H_{28}NO_3Si$, found: 274.1840; R_f = 0.21 (4 : 1 hex./EtOAc).

Ref: **BJEV076**.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2.377
2.373
2.356
2.351
2.333
2.328
2.311
2.306
0.779
0.056
MeO
N
O
OTBS
1.02
3.07
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7
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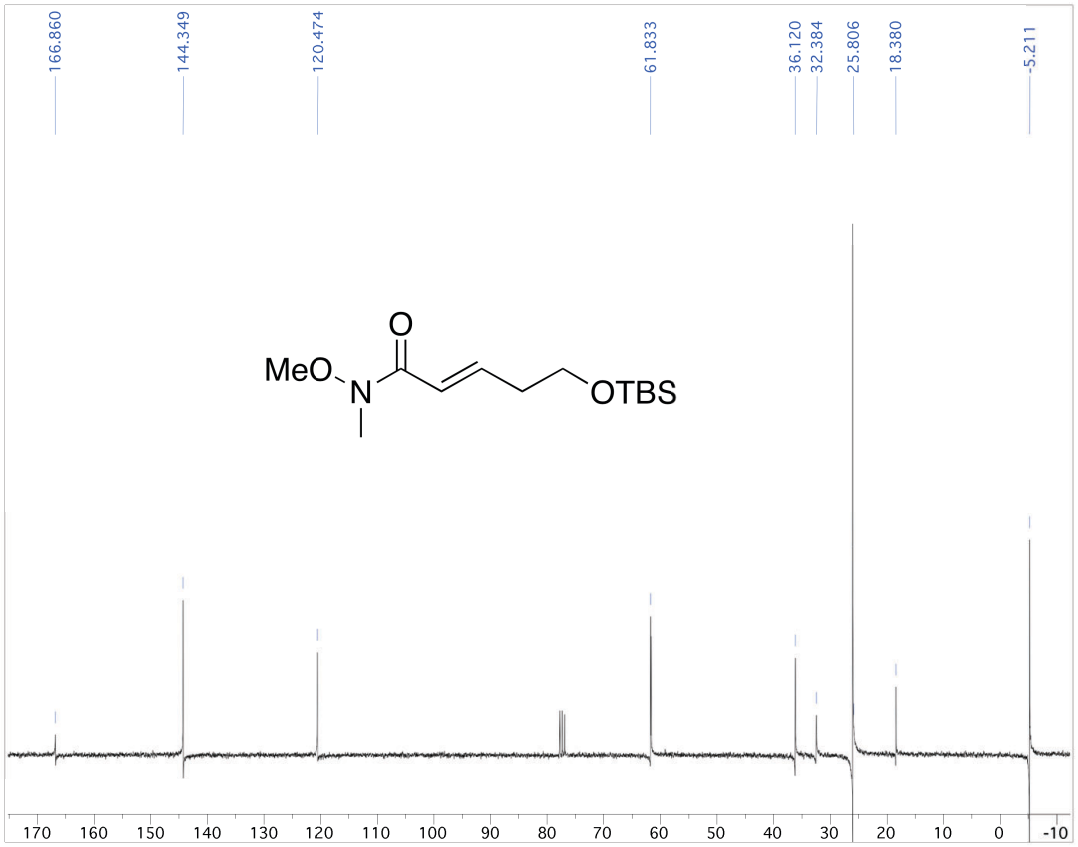
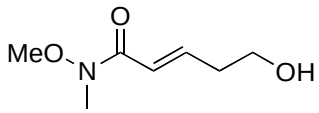


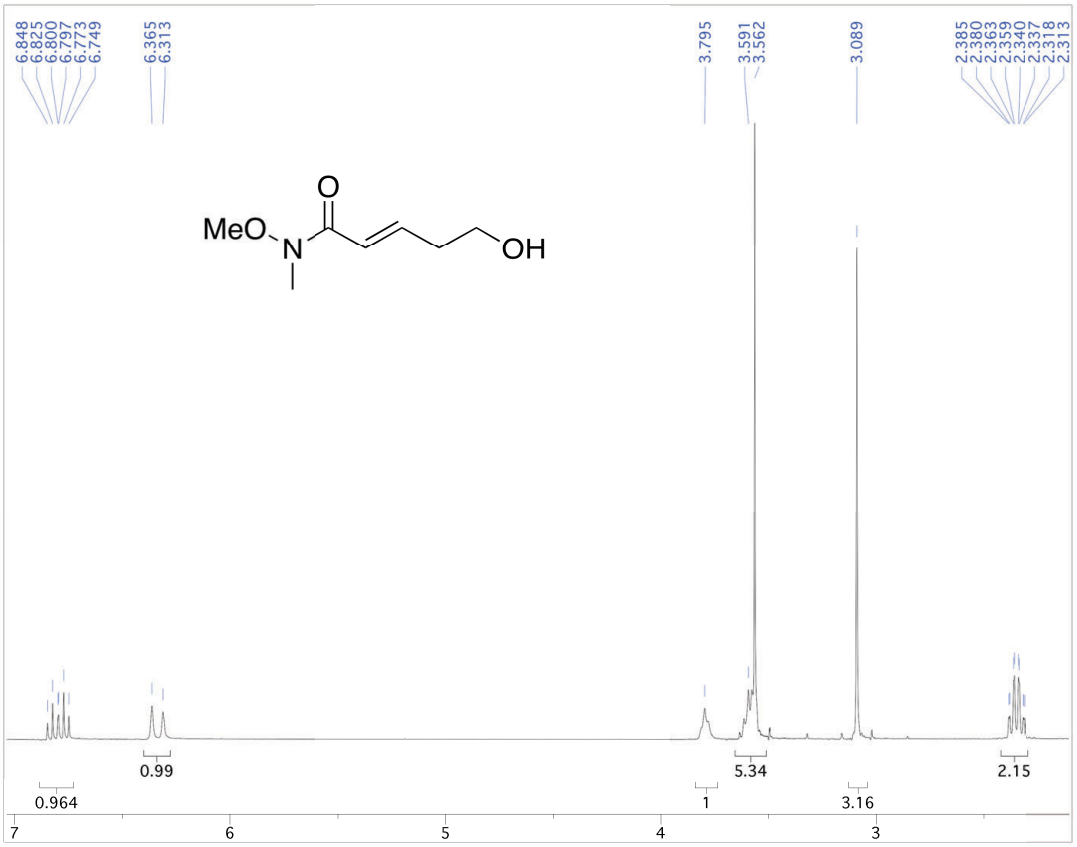


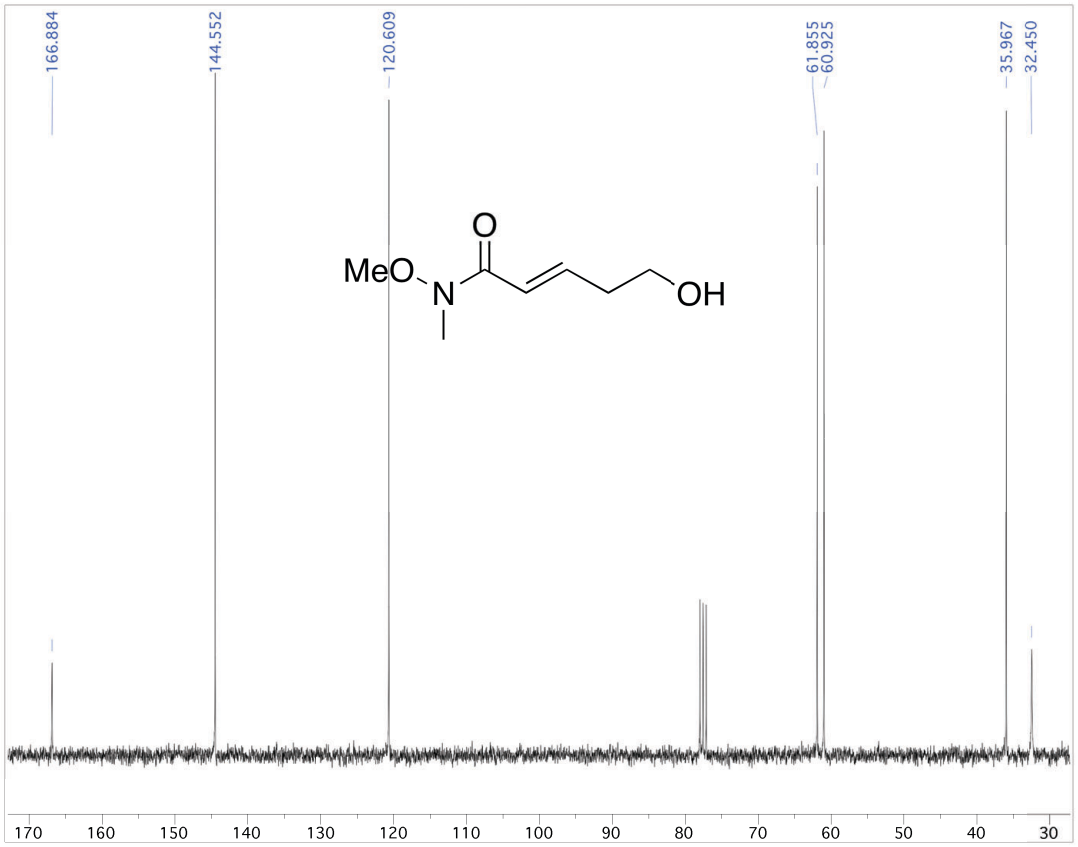
Synthesis of (*E*)-5-hydroxy-*N*-methoxy-*N*-methylpent-2-enamide: To a 1 L HDPE bottle containing 3.38 g (12.4 mmol, 1 equiv.) (*E*)-5-((*tert*-butyldimethylsilyl)oxy)-*N*-methoxy-*N*-methylpent-2-enamide dissolved in 62 mL dry MeCN was added 3.71 mL 48% aqueous HF. The reaction was stirred at ambient temperature for 3 hr before being added to $NaHCO_{3(sat.)}$, extracted thrice with EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 1 : 2 hex./EtOAc to yield 1.23 g (62%) of the desired alcohol as a pale yellow oil.

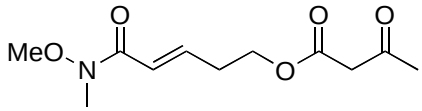
^{1}HNMR (300MHz, $CDCl_3$) δ 6.80 (dt, *J* = 15.6, 6.9, 1H), 6.33 (d, *J* = 15.6, 1H), 3.80 (bs, 1H), 3.59 (m, 2H), 3.59 (s, 3H), 3.09 (s, 3H), 2.34 (qd, *J* = 6.6, 1.6, 2H); ^{13}CNMR (75MHz, $CDCl_3$) δ166.9, 144.6, 120.6, 61.9, 60.9, 36.0, 32.5; IR (NaCl, film): 3417,

1661, 1614 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 160.0968 calcd for $C_7H_{14}NO_3$, found: 160.0970; R_f = 0.18 (EtOAc).

Ref: **BJEV077**.



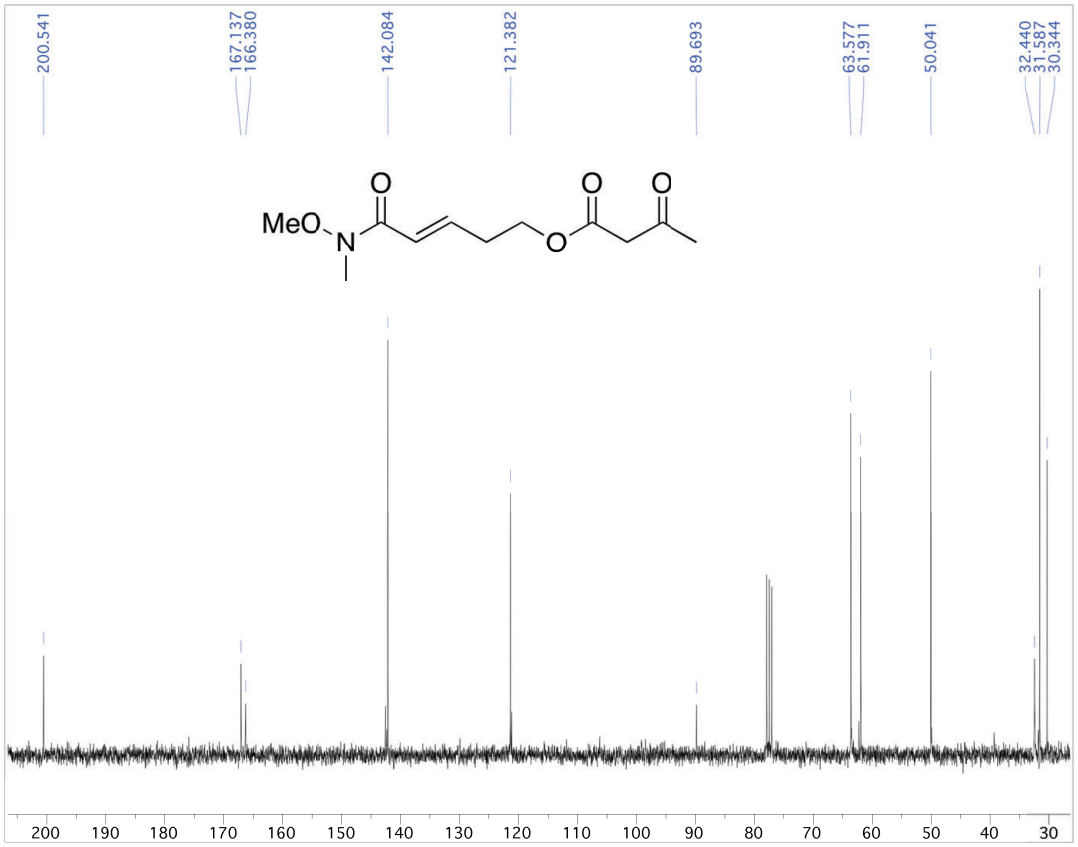


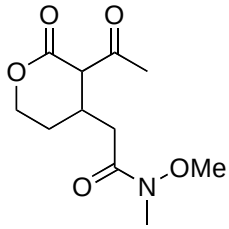


Synthesis of (*E*)-5-(methoxy(methyl)amino)-5-oxopent-3-en-1-yl 3-oxobutanoate (4.62): To a 100 mL round bottomed flask containing 1.23 g (7.73 mmol, 1 equiv.) (*E*)-5-hydroxy-*N*-methoxy-*N*-methylpent-2-enamide dissolved in 40 mL dry CH_2Cl_2 was added 1.49 mL (19.3 mmol, 2.5 equiv.) diketene followed by 94 mg (0.773 mmol, 0.1 equiv.) DMAP. The reaction was allowed to stir at ambient temperature for 1.5 hr before being added to $NaHCO_{3(sat.)}$, extracted twice with EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 1 : 2 hex./EtOAc to yield 1.87 g (99%) of the desired product as a pale yellow oil.

^{1}HNMR (300MHz, $CDCl_3$) δ 6.81 (dt, *J* = 15.3, 6.9, 1H), 6.40 (d, *J* = 15.6, 1H), 4.18 (t, *J* = 6.6, 2H), 3.62 (s, 3H), 3.37 (s, 2H), 3.14 (s, 3H), 2.51 (qd, *J* = 6.6, 1.5, 2H), 2.16 (s, 3H); ^{13}CNMR (75MHz, $CDCl_3$) δ200.5, 167.1, 166.4, 142.0, 121.4, 89.7, 63.6, 61.9, 50.0, 32.4, 31.6, 30.3; IR (NaCl, film): 1743, 1717, 1665, 1633 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 244.1179 calcd for $C_{11}H_{18}NO_5$, found: 244.1182; R_f = 0.13 (1 : 1 hex./EtOAc).

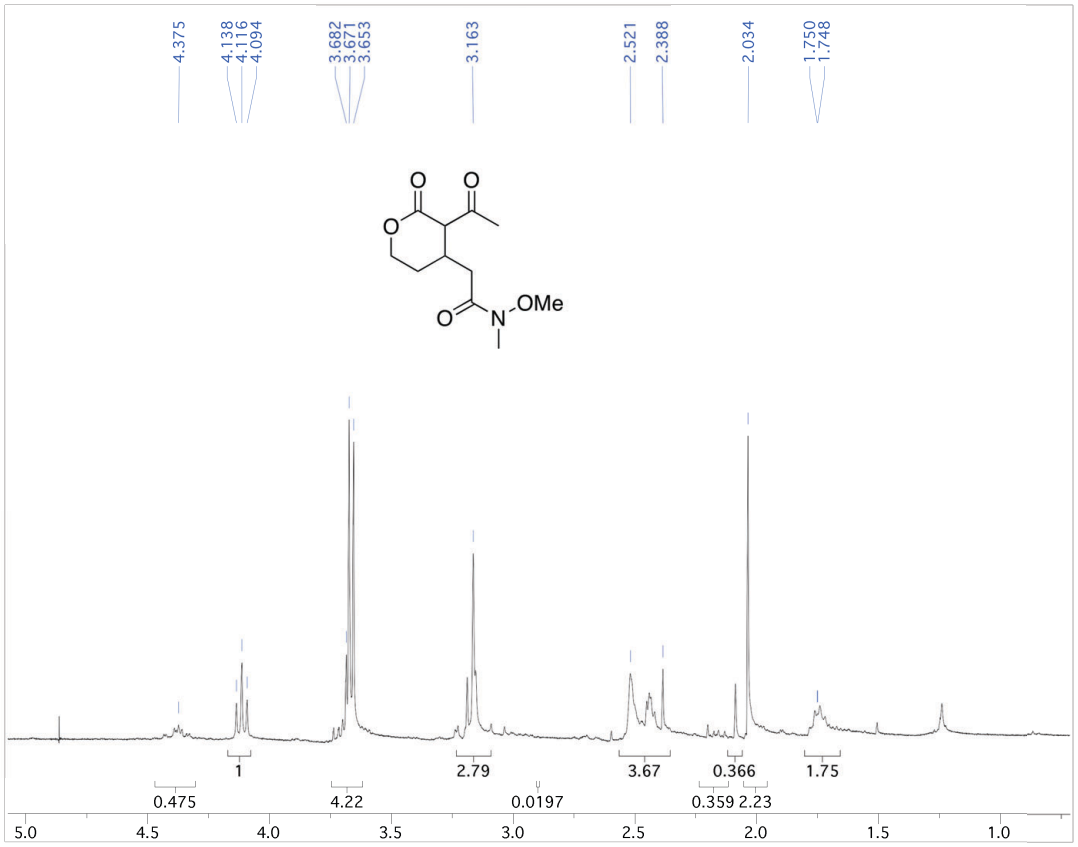
Ref: **BJEV078**.

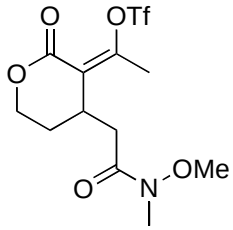




Synthesis of 2-(3-acetyl-2-oxotetrahydro-2*H*-pyran-4-yl)-*N*-methoxy-*N*-methylacetamide (4.66): To a 50 mL round-bottomed flask containing 1.20 g (4.93 mmol, 1 equiv.) β-ketoester **4.62** dissolved in 25 mL MeCN was added 3.21 g (9.86 mmol, 2 equiv.) Cs_2CO_3. The reaction was stirred at reflux for 3 hr, added to 1 M HCl, extracted thrice with EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 1 : 2 to 0 : 1 hex./EtOAc to yield 338 mg (28%) of the desired product as a mixture of isomers.

Ref.: BJEV090, BJEV098, BJEV104, **BJEV132**

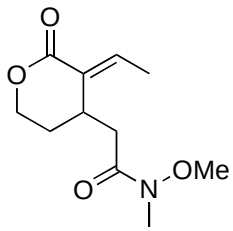




Synthesis of (*Z*)-1-(4-(2-(methoxy(methyl)amino)-2-oxoethyl)-2-oxodihydro-2*H*-pyran-3(4*H*)-ylidene)ethyl trifluoromethanesulfonate (4.69): To a 50 mL round bottomed flask containing 337 mg (1.39 mmol, 1 equiv.) β-ketoester **4.66** and 653 mg (1.66 mmol, 1.2 equiv.) Comins reagent dissolved in 14 mL dry THF at 0^{o}C was added 72 mg NaH (60% suspension in mineral oil, 1.81 mmol, 1.3 equiv.). The reaction was

stirred at ambient temperature for 1 hr, added to brine, extracted thrice with EtOAc, dried over Na_2SO_4, and concentrated to yield 522 mg (>99%) of the desired product as a pale yellow oil which was immediately carried forward without further purification.

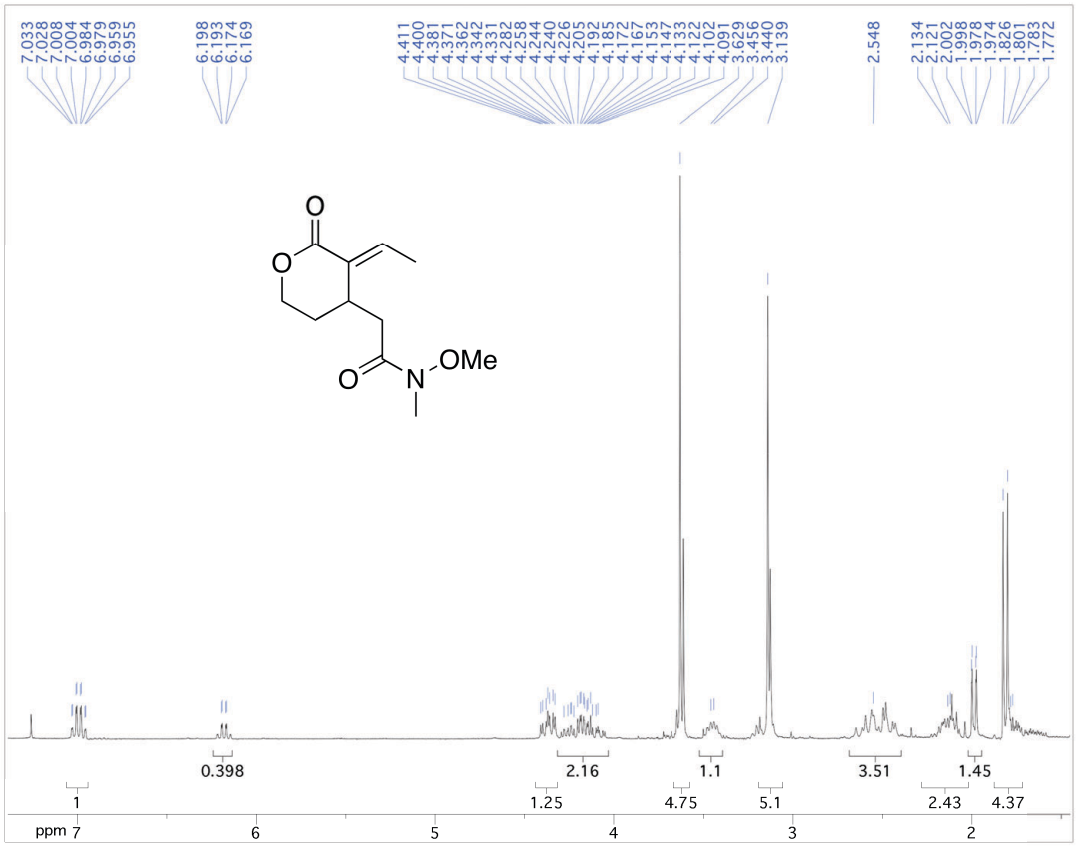
Ref.: BJEV129, **BJEV138**.

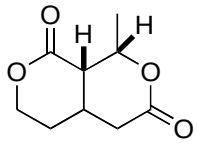


Synthesis of (*E*)-2-(3-ethylidene-2-oxotetrahydro-2*H*-pyran-4-yl)-*N*-methoxy-*N*-methylacetamide (4.70): To a 50 mL flame dried round bottomed flask charged with Ar was added 522 mg (1.39 mmol, 1 equiv.) vinyl triflate **4.69**, 156 mg (0.695 mmol, 0.5 equiv.) $Pd(OAc)_2$, 424 mg (0.765 mmol, 0.55 equiv.) dppf, and then 14 mL dry THF. This solution was vigorously degassed with Ar before the addition of 666 μL (4.17 mmol, 3 equiv.) triethylsilane. The reaction was stirred at ambient temperature for 3 hr and was then added to $NaHCO_{3(sat.)}$, extracted into EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 5% MeOH in EtOAc to yield 75 mg of a 2.5 : 1 E/Z mixture the desired products as a pale yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$) major isomer δ 7.05 (q, *J* = 7.2, 1H), 4.42 (m, 1H), 4.22 (m, 1H), 3.67 (s, 3H), 3.51 (m, 1H), 3.19 (s, 3H), 2.64 (m, 1H), 2.50 (dd, *J* = 15.6, 4.5, 1H), 2.18 (m, 1H), 1.86 (d, *J* = 7.2, 3H), 1.81 (m, 1H); R_f = 0.31 (5% MeOH in EtOAc).

Ref.: BJEV135, **BJEV142.**

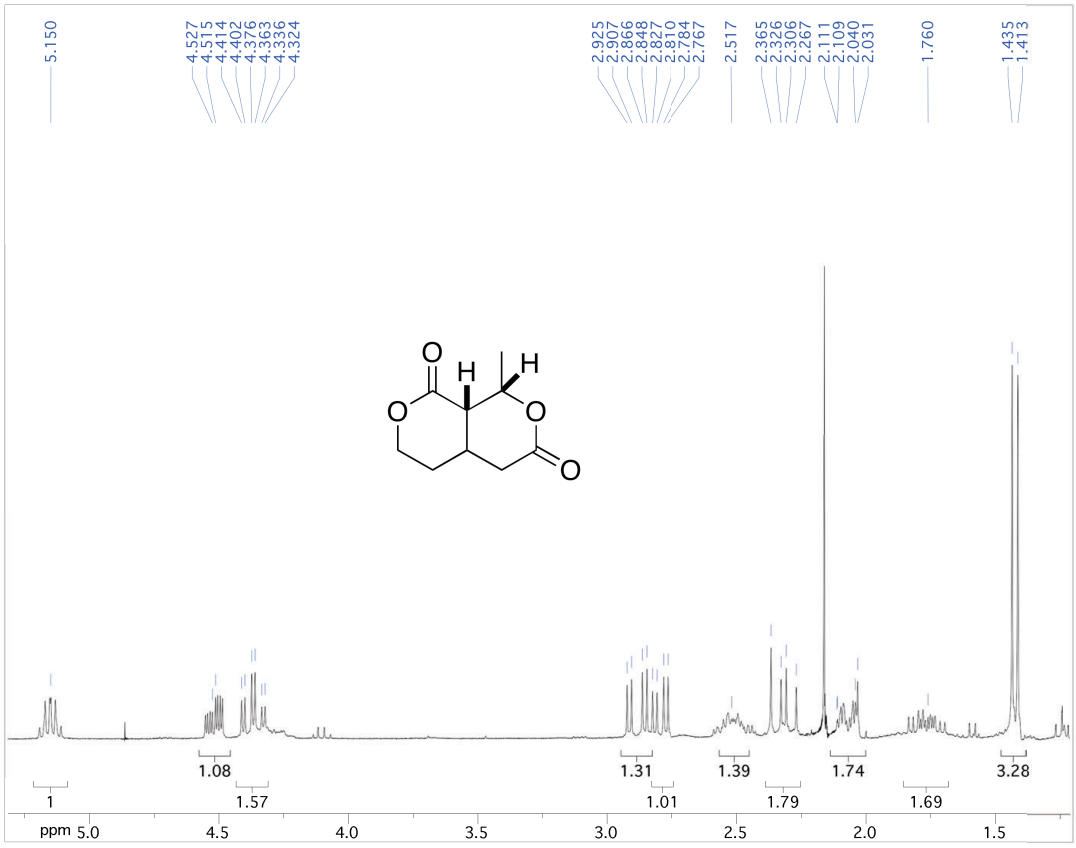


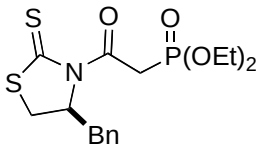


Synthesis of (+/-)-(8-methylhexahydropyrano[3,4-*c*]pyran-1,6-dione (4.63): To a 10 mL round-bottomed flask containing 24 mg (0.132 mmol, 1 equiv.) lactone **4.57** dissolved in 1 mL dry THF was added 14 mg (0.026 mmol, 0.2 equiv) 10% Pd/C. The reaction was stirred for 16 hr under a 40 psi H_2 atmosphere. Solids were removed by filtration through celite and the reaction was concentrated to yield 14 mg (>99%) of the desired product as a colorless film.

^{1}HNMR (300 MHz, $CDCl_3$) δ 5.15 (m, 1H), 4.52 (m, 1H), 4.37 (td, *J* = 11.4, 3.6, 1H), 2.89 (dd, *J* = 17.7, 5.4, 1H), 2.80 (dd, *J* = 12.9, 5.1, 1H), 2.52 (m, 1H), 2.31 (dd, *J* = 17.7, 11.7, 1H), 2.03-2.11 (m, 1H), 1.76 (m, 1H), 1.42 (d, *J* = 6.6, 3H);

Ref.: **BJEV079**



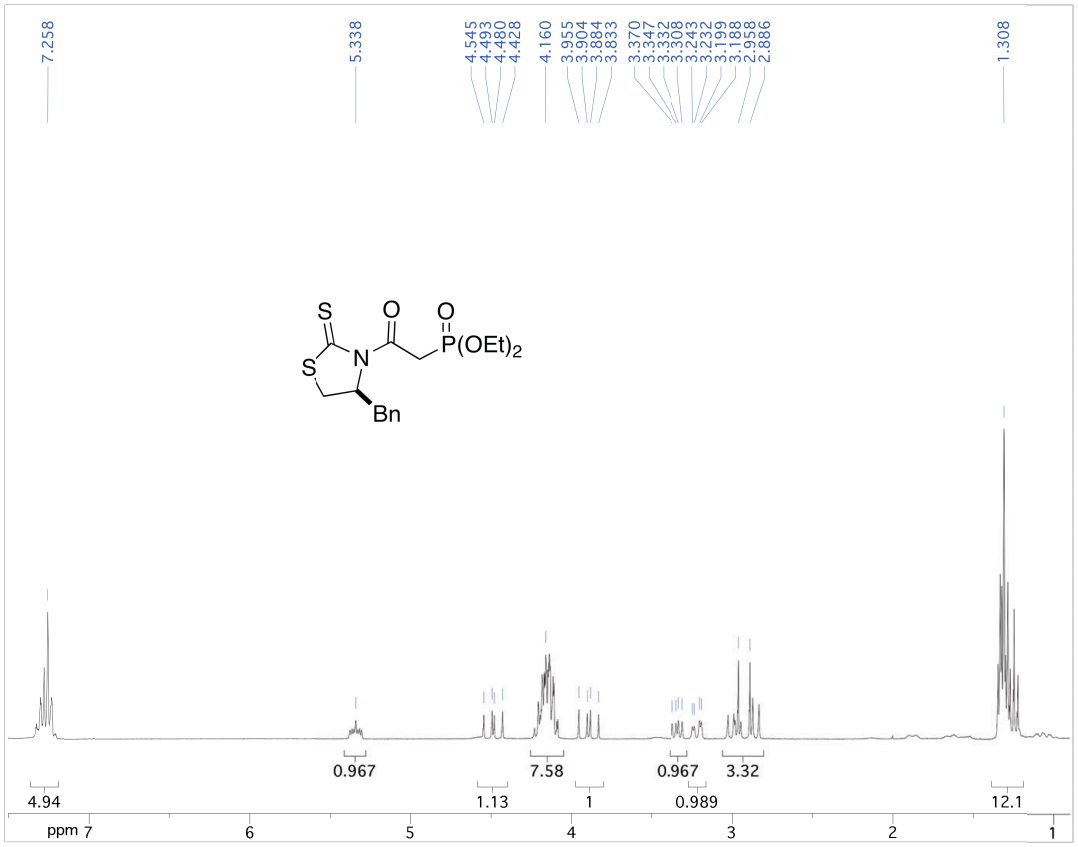


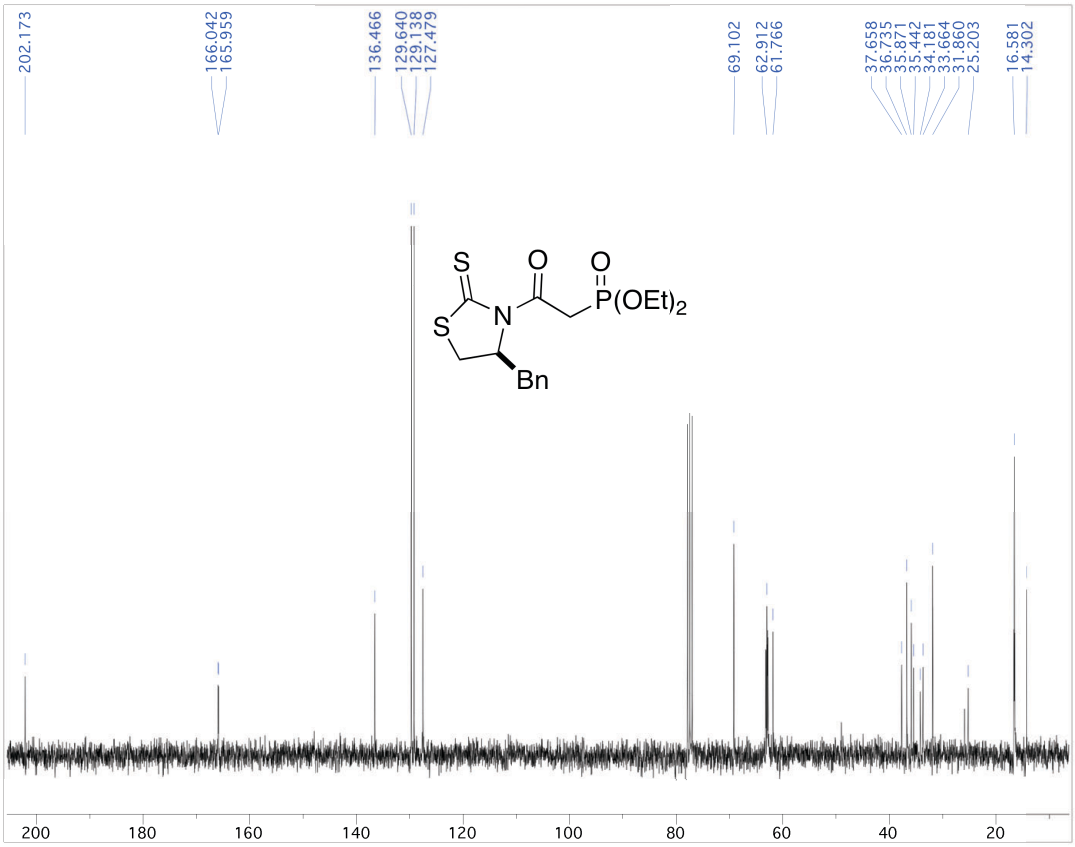
Synthesis of (*S*)-diethyl (2-(4-benzyl-2-thioxothiazolidin-3-yl)-2-oxoethyl)phosphonate: To a 25 mL round-bottomed flask containing 95 mg (0.487 mmol, 1.1 equiv.) 2-(diethoxyphosphoryl)acetic acid and 93 mg (0.442 mmol, 1 equiv.)

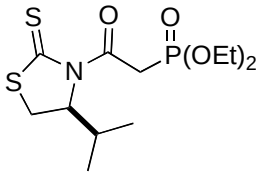
(*S*)-4-benzylthiazolidine-2-thione dissolved in 2.5 mL dry CH_2Cl_2 was added 100 mg (0.487 mmol, 1.1 equiv.) DCC and 3 pellets DMAP dissolved in CH_2Cl_2. The reaction was stirred at ambient temperature for 5 hr, filtered through celite, and concentrated. The crude residue was purified by silica gel flash chromatography eluting with 1 : 1 to 1 : 2 hex./EtOAc to yield 103 mg (60%) of the desired product as a yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5H), 5.34 (m, 1H), 4.49 (dd, *J* = 19.5, 15.6, 1H), 4.16 (m, 4H), 3.89 (dd, *J* = 21.3, 15.3, 1H), 3.33 (dd, *J* = 11.4, 6.9, 1H), 3.21 (dd, J = 13.2, 3.3, 1H), 2.91 (m, 2H), 1.31 (m, 6H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 202.2, 166.0, 166.0, 136.5, 129.6, 129.1, 127.5, 69.1, 62.9, 61.8, 37.7, 36.7, 35.9, 35.4, 34.2, 33.7, 31.9, 25.2, 16.6, 14.3; R_f = 0.21 (1 : 1 hex./EtOAc).

Ref.: **BJEIV178**



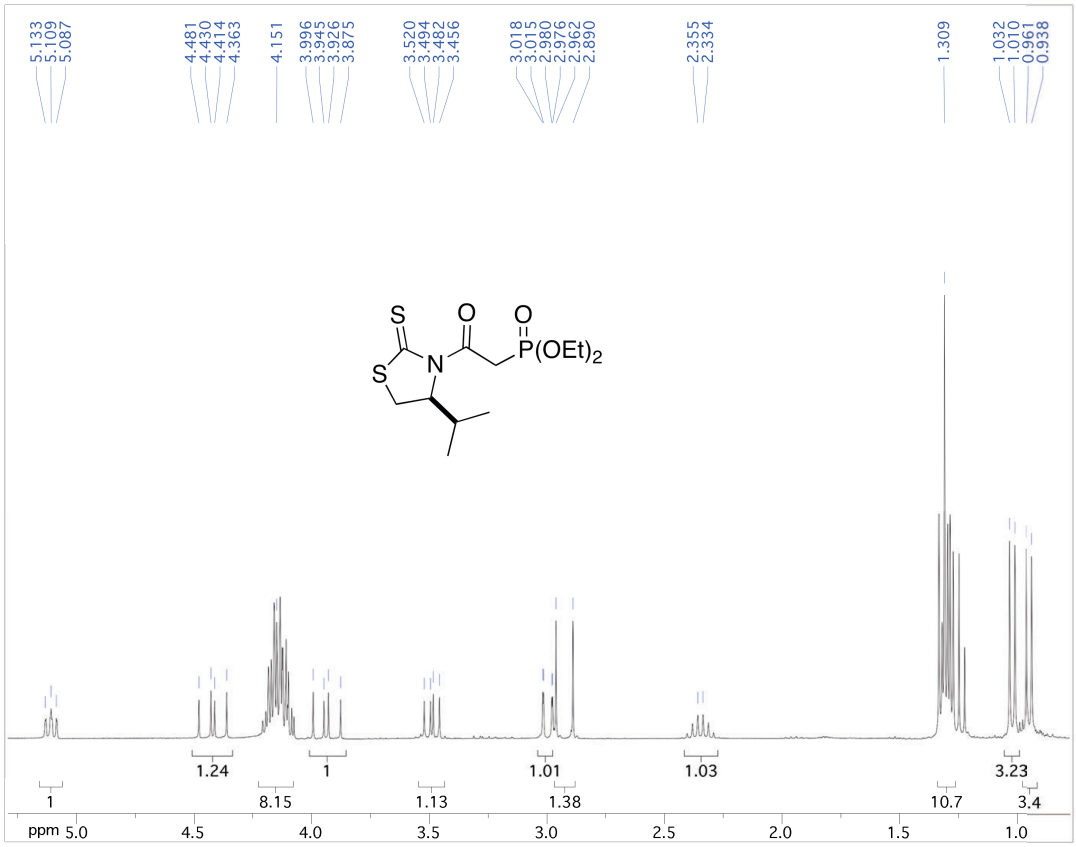


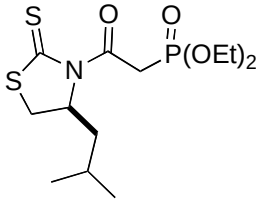


Synthesis of (*S*)-diethyl (2-(4-isopropyl-2-thioxothiazolidin-3-yl)-2-oxoethyl)phosphonate: To a 25 mL round-bottomed flask containing 125 mg (0.640 mmol, 1.1 equiv.) 2-(diethoxyphosphoryl)acetic acid and 94 mg (0.582 mmol, 1 equiv.) (*S*)-4-isopropylthiazolidine-2-thione dissolved in 2.5 mL dry CH_2Cl_2 was added 120 mg (0.582 mmol, 1.1 equiv.) DCC and 3 pellets DMAP dissolved in CH_2Cl_2. The reaction was stirred at ambient temperature for 12 hr, filtered through celite, and concentrated. The crude residue was purified by silica gel flash chromatography eluting with 1 : 2 to 0 : 1 hex./EtOAc to yield 84 mg of the desired product as a yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 5.13 (t, *J* = 7.2, 1H), 4.42 (dd, *J* = 20.1, 15.3, 1H), 4.25 (m, 4H), 3.94 (dd, *J* = 21.0, 15.3, 1H), 3.49 (dd, *J* = 11.4, 7.8, 1H), 2.99 (dd, *J* = 11.4, 0.9, 1H), 2.93 (d, J_{HP} = 21.6, 2H), 2.34 (m, 1H), 1.31 (m, 6H), 1.02 (d, *J* = 6.6, 3H), 0.95 (d, *J* = 6.6, 3H); R_f = 0.29 (EtOAc).

Ref.: **BJEIV170**, BJEIV171.

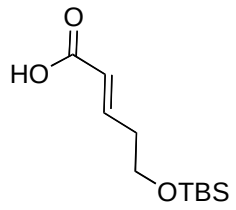




Synthesis of (*S*)-diethyl (2-(4-isobutyl-2-thioxothiazolidin-3-yl)-2-oxoethyl)phosphonate: To a 25 mL round-bottomed flask containing 390 mg (2.22 mmol, 1 equiv.) (*S*)-4-isobutylthiazolidine-2-thione and 521 mg (2.67 mmol, 1.2 equiv.)

2-(diethoxyphosphoryl)acetic acid dissolved in 11 mL dry CH_2Cl_2 was added 550 mg (2.67 mmol, 1.2 equiv.) DCC followed by 27 mg (0.222 mmol, 0.1 equiv.) DMAP. The reaction was stirred 16 hr at ambient temperature, filtered through celite, and concentrated to yield 350mg (44%) of the desired product as a yellow oil which was used without purification.

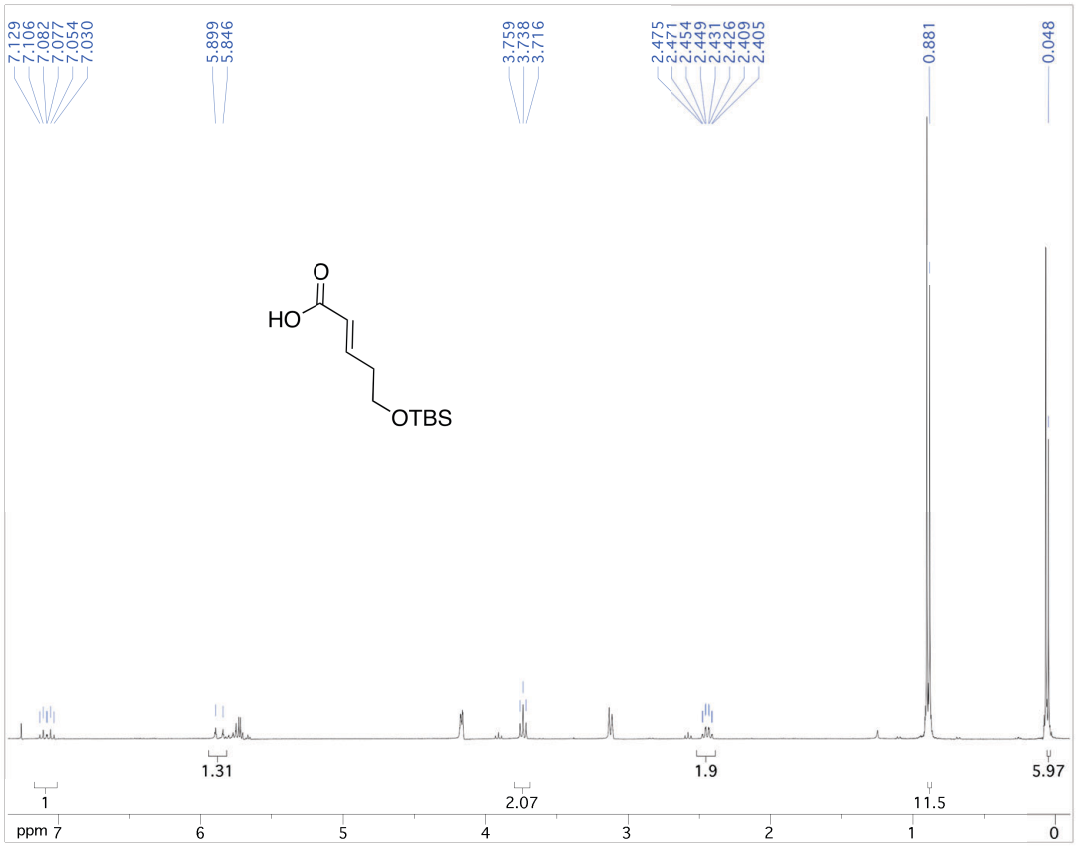
Ref.: **BJEIV188**.

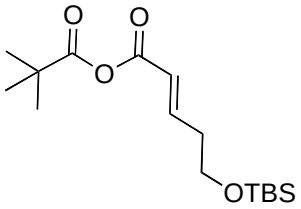


Synthesis of (*E*)-5-((*tert*-butyldimethylsilyl)oxy)pent-2-enoic acid: To a 25 mL round-bottomed flask charged with 63 mg (0.258 mmol, 1 equiv.) ester **3.7** dissolved in 2 mL THF, 2 mL H_2O, and 2 mL MeOH was added 31 mg (1.29 mmol, 5 equiv.) LiOH. The reaction was stirred at ambient temperature for 72 hr before being added to 1 M HCl, extracted into EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 9 : 1 to 4 : 1 hex./EtOAc to yield 38 mg (64%) of the desired product as a colorless oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 7.08 (dt, *J* = 15.6, 6.9, 1H), 5.87 (d, *J* = 15.9, 1H), 3.74 (t, *J* = 6.3, 2H), 2.44 (qd, *J* = 6.3, 1.2, 2H), 0.88 (s, 9H), 0.05 (s, 6H).

Ref.: **BJEIV191**, BJEIV195.

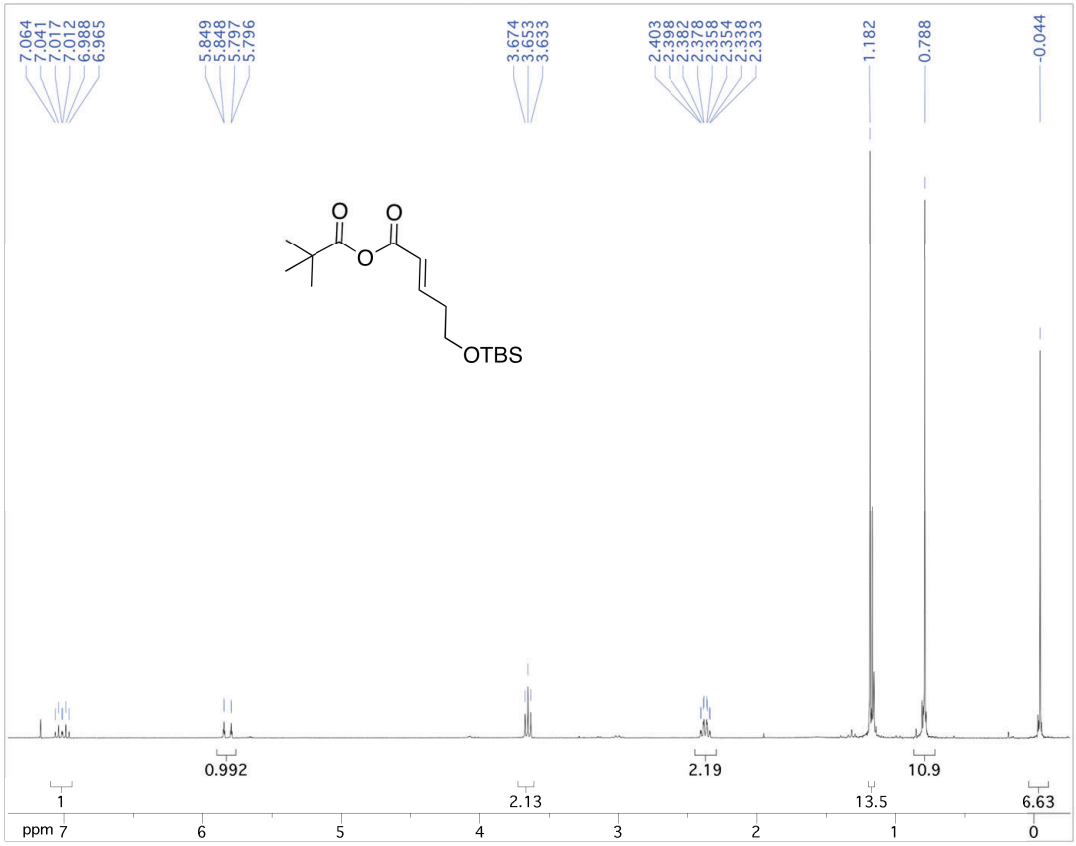


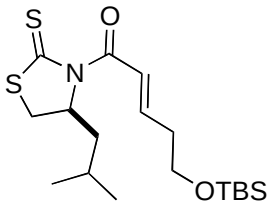


Synthesis of (*E*)-5-((*tert*-butyldimethylsilyl)oxy)pent-2-enoic pivalic anhydride: To a 10 mL round-bottomed flask containing 20 mg (0.087 mmol, 1 equiv.) (*E*)-5-((*tert*-butyldimethylsilyl)oxy)pent-2-enoic acid dissolved in 900 µL dry THF at 0°C was added 16 µL (0.174 mmol, 2 equiv.) dry NEt_3 followed by 16 µL (0.130 mmol, 1.5 equiv.) PivCl. The reaction was stirred for 1 hr at 0°C, added to $NaHCO_{3(sat.)}$, extracted into EtOAc, dried over Na_2SO_4, and concentrated to yield 29 mg (>99%) of the desired product as a yellow oil which was used without purification.

^{1}HNMR (300 MHz, $CDCl_3$) δ 7.01 (dt, *J* = 15.9, 6.9, 1H), 5.82 (d, *J* = 15.6, 1H), 3.65 (t, *J* = 6.3, 2H), 2.36 (qd, *J* = 7.2, 1.2, 2H), 1.18 (s, 9H), 0.79 (s, 9H), 0.04 (s, 6H); R_f = 0.95 (2 : 1 hex./EtOAc).

Ref.: **BJEIV199**.



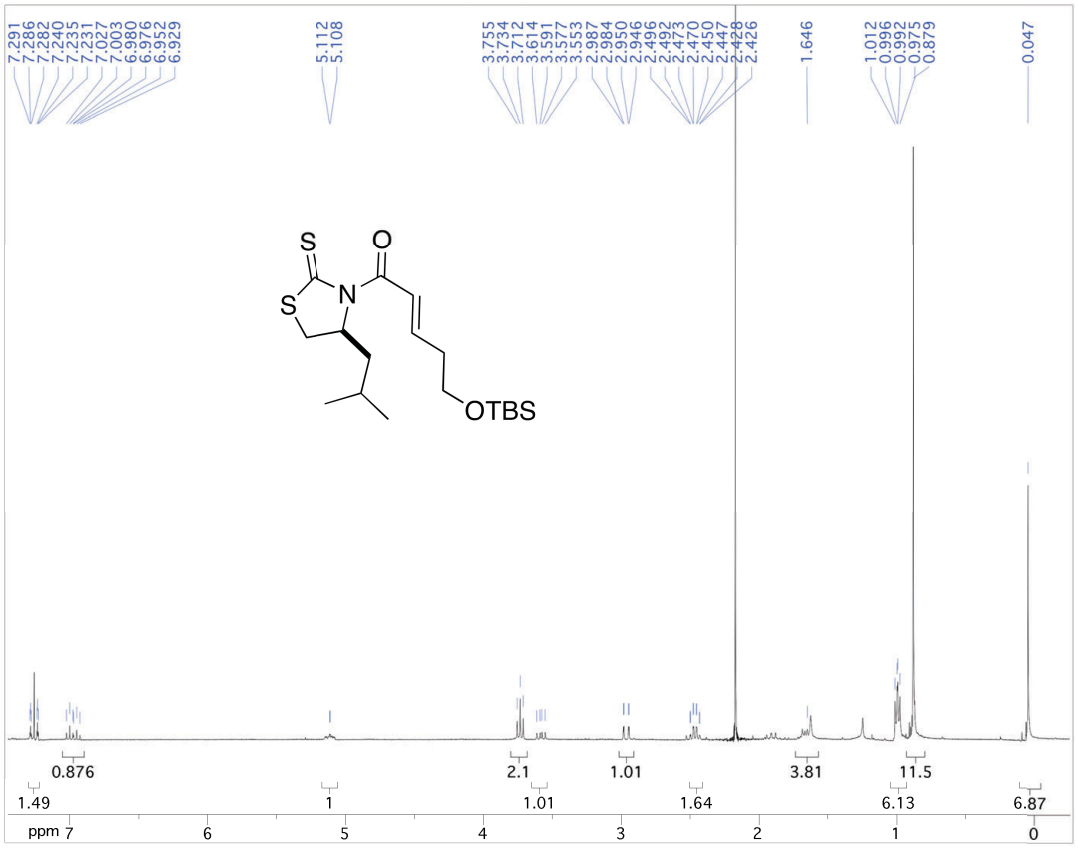


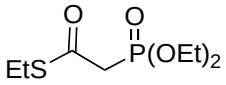
Synthesis of (*S*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-1-(4-isobutyl-2-thioxothiazolidin-3-yl)pent-2-en-1-one : To a 10 mL round-bottomed flask containing 27 mg (0.087 mmol, 1.1 equiv.) (*E*)-5-((*tert*-butyldimethylsilyl)oxy)pent-2-enoic pivalic anhydride and 14 mg (0.079 mmol, 1 equiv.) (*S*)-4-isobutylthiazolidine-2-thione dissolved in 900 μL dry THF

was added 16 μL (0.119 mmol, 1.5 equiv.) pyridine followed by a single tablet of DMAP. The reaction was stirred at ambient temperature for 24 hr, added to brine, extracted twice with EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 1 : 0 to 9 : 1 hex./EtOAc to yield 11 mg (35%) of the desired product as a pale yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 7.26 (dt, *J* = 15.3, 1.5, 1H), 6.98 (dt, *J* = 15.3, 7.2, 1H), 5.11 (m, 1H), 3.73 (t, *J* = 6.3, 2H), 3.58 (dd, *J* = 11.1, 6.9, 1H), 2.97 (dd, *J* = 11.1, 0.9, 1H), 2.46 (qd, *J* = 6.9, 0.9, 2H), 1.65 (m, 4H), 0.99 (dd, *J* = 6.0, 4.8, 6H), 0.88 (s, 9H), 0.05 (s, 6H); R_f = 0.43 (9 : 1 hex./EtOAc).

Ref.: **BJEIV200**.

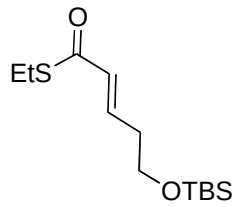




Synthesis of *S*-ethyl 2-(diethoxyphosphoryl)ethanethioate: To a 100 mL round-bottomed flask containing 11.37 g (62.11 mmol, 1 equiv.) *S*-ethyl 2-bromoethanethioate was added 26.62 mL (155.3 mmol, 2.5 equiv.) $P(OEt)_3$. The reaction was heated to 100°C for 20 min and then concentrated to yield 15.10 g (>99%) of the desired product as a yellow oil which was used without purification.

^{1}HNMR (300 MHz, $CDCl_3$) δ 4.11 (m, 4H), 3.15 (d, J_{HP} = 21.3, 2H), 2.86 (q, J = 7.5, 2H), 1.28 (t, J = 6.9, 6H), 1.20 (t, J = 7.5, 3H).

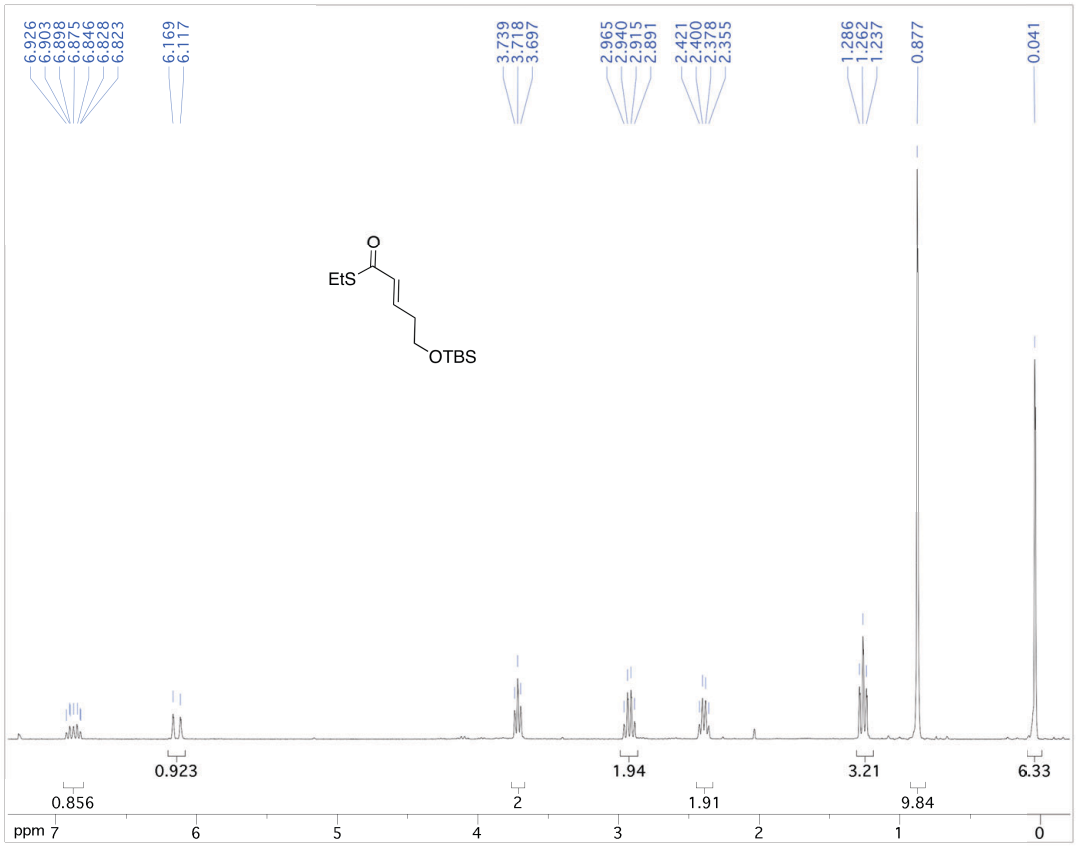
Ref.: **BJEIV036**



Synthesis of (*E*)-*S*-ethyl 5-((*tert*-butyldimethylsilyl)oxy)pent-2-enethioate: To a 250 mL round-bottomed flask containing 9.54 g (39.7 mmol, 1.2 equiv.) *S*-ethyl 2-(diethoxyphosphoryl)ethanethioate and 1.68 g (39.7 mmol, 1.2 equiv.) LiCl dissolved in 125 mL dry MeCN was added 5.76 mL (33.1 mmol, 1 equiv.) *i*Pr_2NEt. The reaction was stirred for 15 min at ambient temperature before the addition of 6.23 g (33.1 mmol, 1 equiv.) aldehyde **3.5** dissolved in 10 mL dry MeCN. The reaction was stirred at ambient temperature for a further 16 hr before being added to brine, extracted thrice with EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 9 : 1 hex./EtOAc to yield 8.13 g (90%) of the desired product as a pale yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 6.88 (m, 1H), 6.16 (d, *J* = 15.6, 1H), 3.72 (t, *J* = 6.3, 2H), 2.93 (q, *J* = 7.5, 2H), 2.39 (q, *J* = 6.6, 2H), 1.26 (t, *J* = 7.5, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 190.1, 142.0, 130.4, 61.6, 35.8, 26.1,23.2, 18.5, 15.0, -5.2; HRMS (+TOF): $[M+H]^+$ 275.1501 calcd for $C_{13}H_{27}O_2SSi$, found: 275.1502; R_f = 0.44 (9 : 1 hex./EtOAc).

Ref.: BJEIV038, **BJEIV046**.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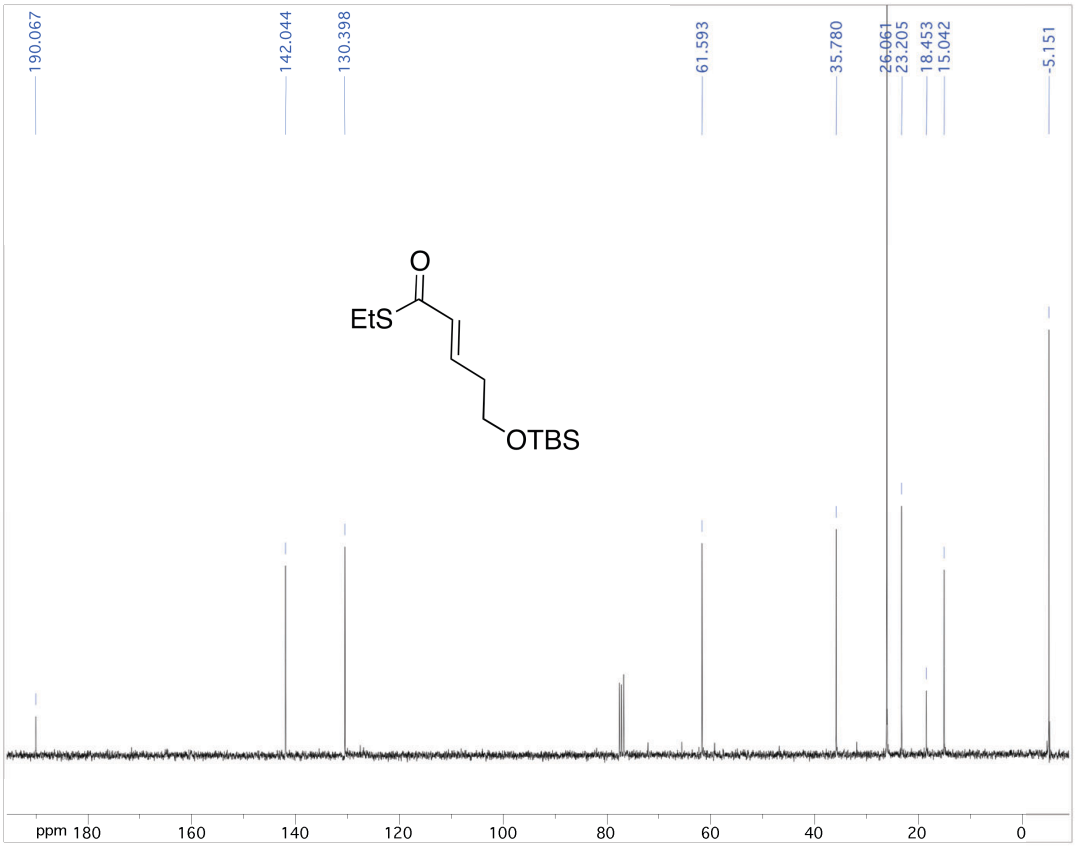
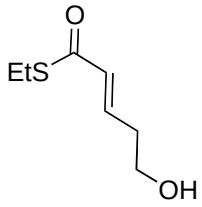
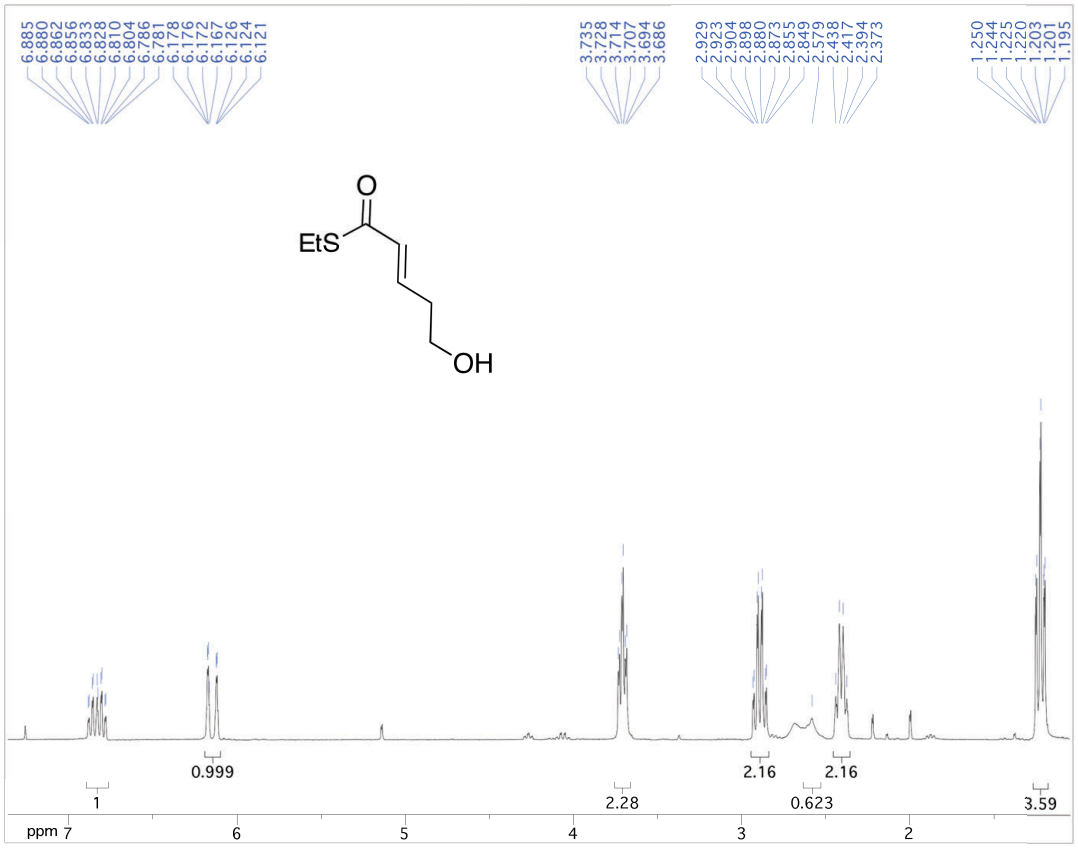


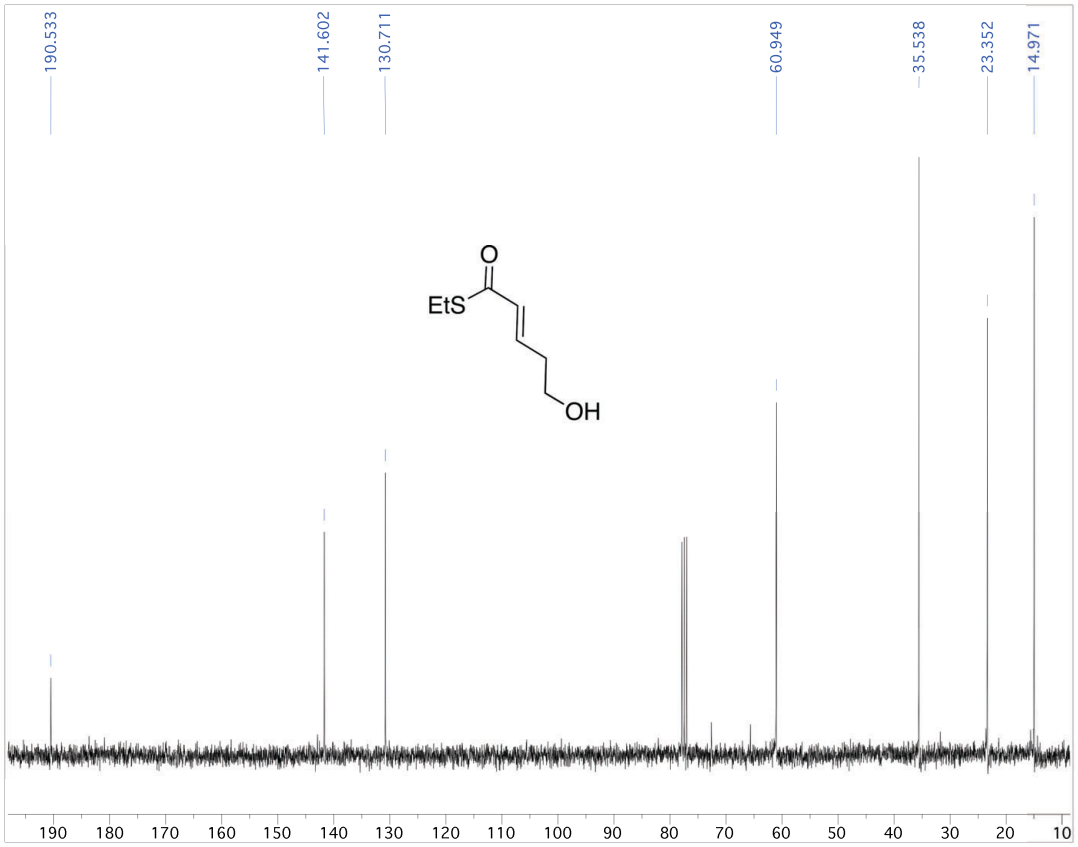


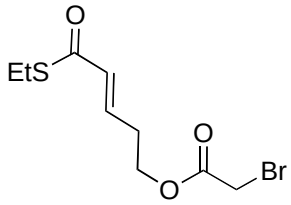
Synthesis of (*E*)-*S*-ethyl 5-hydroxypent-2-enethioate: To a 4 dram vial containing 391 mg (1.42 mmol, 1 equiv.) (*E*)-*S*-ethyl 5-((*tert*-butyldimethylsilyl)oxy)pent-2-enethioate dissolved in 7 mL dry THF was added 740 μL of 48% $HF_{(aq.)}$. The reaction was stirred for 3 hr at ambient temperature before being added to $NaHCO_{3(sat.)}$, extracted thrice with EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was taken up in 2 : 1 hex./EtOAc, passed though a short plug of silica gel, and concentrated to yield 215 mg (94%) of the desired alcohol as a pale yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 6.83 (m, 1H), 6.14 (m, 1H), 3.71 (td, *J* = 6.3, 2.1, 2H), 2.89 (qd, *J* = 7.5, 1.8, 2H), 2.58 (bs, 1H), 2.40 (q, *J* = 6.9, 2H), 1.22 (td, *J* = 7.2, 3.0, 3H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 190.5, 141.6, 130.7, 60.9, 35.5, 23.4, 15.0.; R_f = 0.46 (1 : 1 hex./EtOAc).

Ref.: **BJEIV040**, BJEIV049.



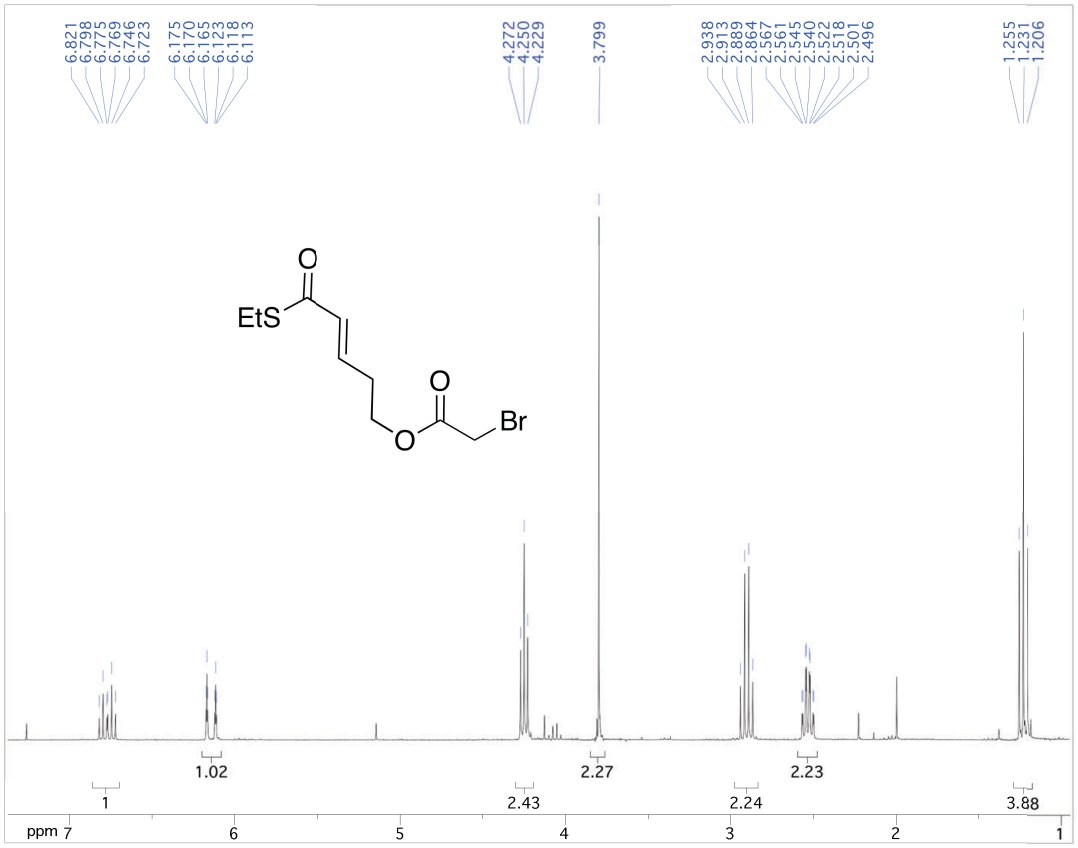


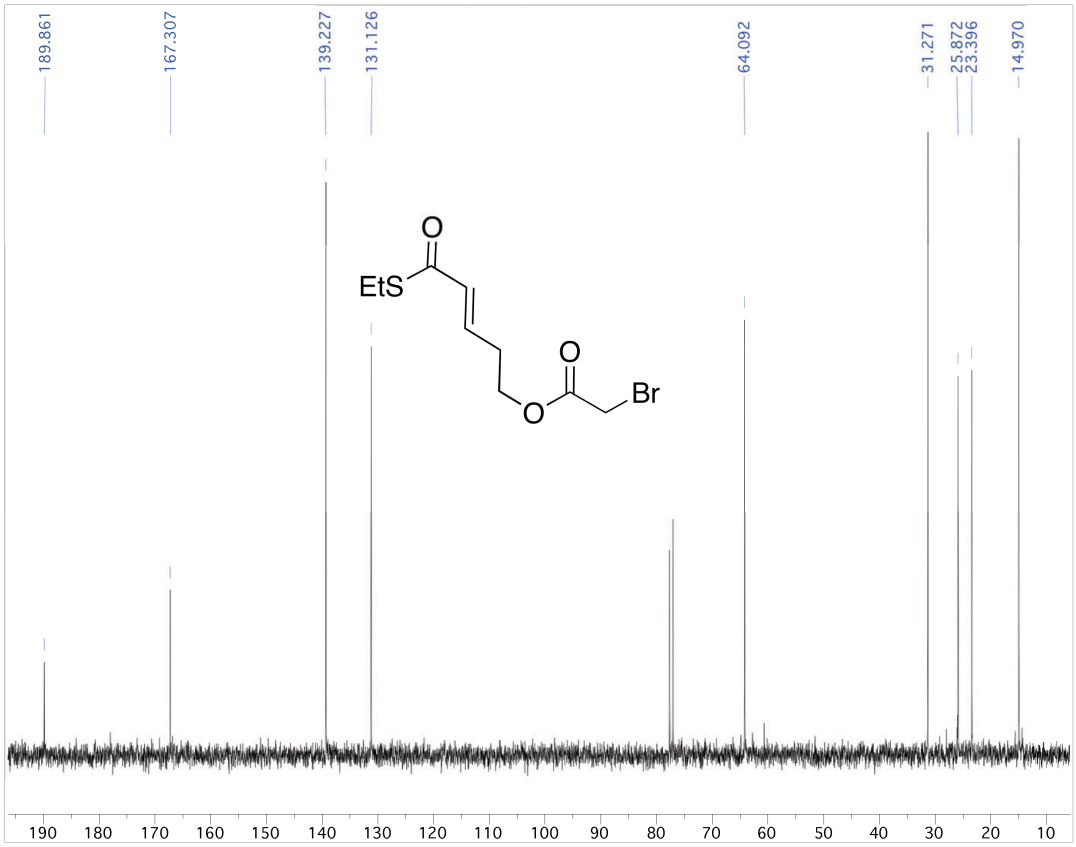


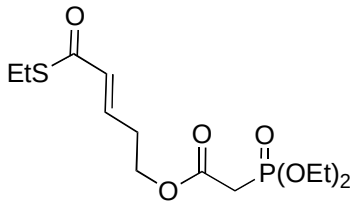
Synthesis of (*E*)-5-(ethylthio)-5-oxopent-3-en-1-yl 2-bromoacetate: To a 25 mL round-bottomed flask containing 215 mg (1.34 mmol, 1 equiv.) (*E*)-*S*-ethyl 5-hydroxypent-2-enethioate dissolved in 6.7 mL dry THF at 0^{o}C was added 141 μL (1.61 mmol, 1.2 equiv.) bromoacetyl bromide followed by 224 μL (1.61 mmol, 1.2 equiv.) dry NEt_3. The reaction was stirred for 30 min at ambient temperature, added to $NaHCO_{3(sat.)}$, extracted into EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was taken up in 1 : 2 hex./EtOAc, passed through a short plug of silica gel, and concentrated to yield 373 mg (99%) of the desired product as a pale yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 6.80 (dt, *J* = 15.6, 6.9, 1H), 6.14 (dt, *J* = 15.6, 1.5, 1H), 4.25 (t, *J* = 6.6, 2H), 3.80 (s, 2H), 2.90 (q, *J* = 7.2, 2H), 2.53 (qd, *J* = 6.6, 1.8, 2H), 1.23 (t, *J* = 7.5, 3H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 189.9, 167.3, 139.2, 131.1, 64.1, 31.3, 25.9, 23.4, 15.0; R_f = 0.68 (2 : 1 hex./EtOAc).

Ref.: **BJEIV041**, BJEIV051.





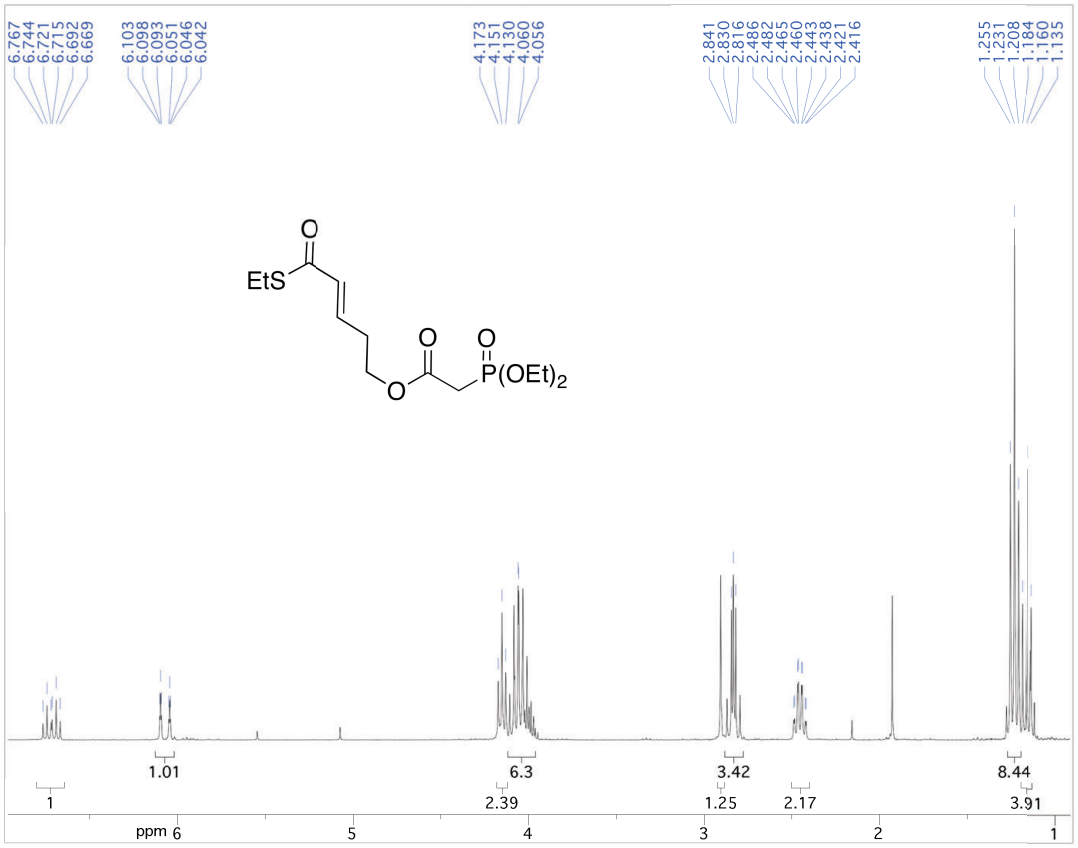


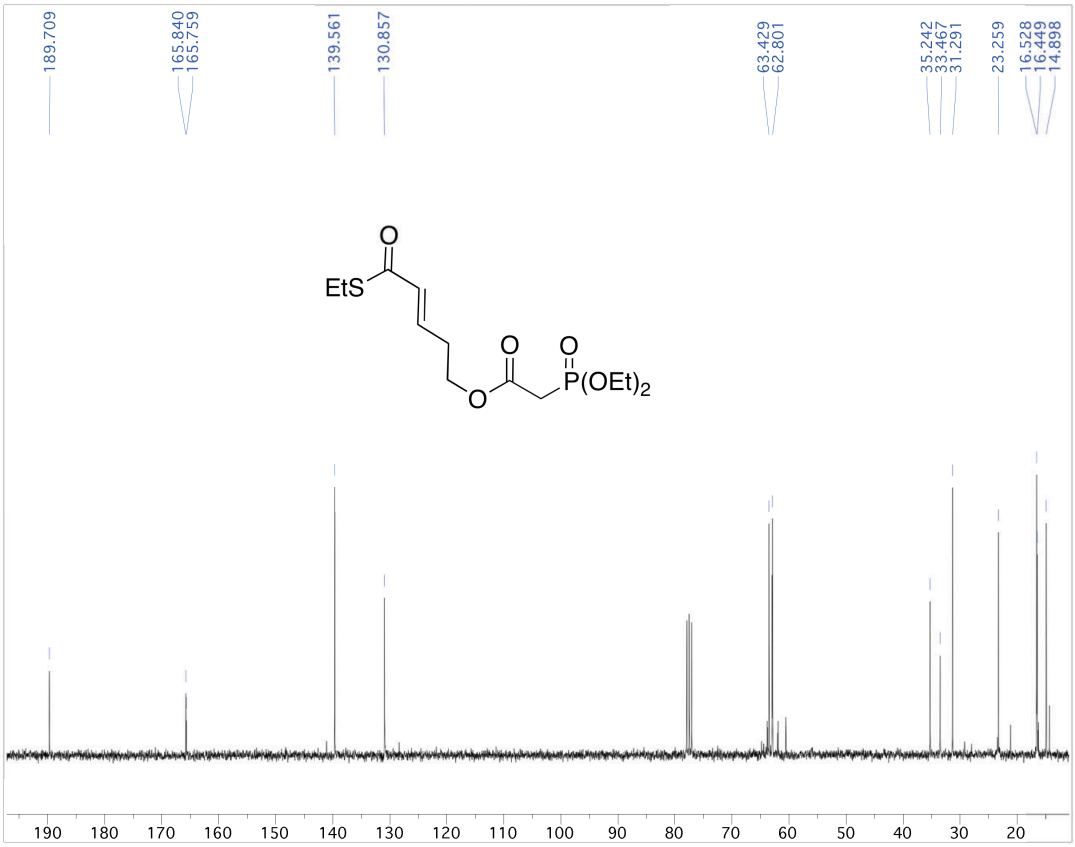
Synthesis of (*E*)-5-(ethylthio)-5-oxopent-3-en-1-yl 2-(diethoxyphosphoryl)acetate: To a 100 mL round-bottomed flask containing 5.46 g (19.4 mmol, 1 equiv.) (*E*)-5-(ethylthio)-5-oxopent-3-en-1-yl 2-bromoacetate was added 6.66 mL (38.8 mmol, 2 equiv.) $P(OEt)_3$. Th reaction was heated to 100^{o}C for 20 min and was then concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 1 : 2 to 0 : 1 hex./EtOAc to yield 6.60 g (>99%) of the desired product as a pale yellow oil.

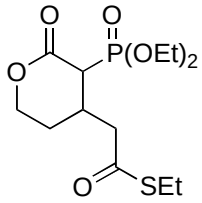
^{1}HNMR (300 MHz, $CDCl_3$) δ 6.72 (dt, *J* = 15.6, 6.9, 1H), 6.07 (td, *J* = 15.6, 1.5, 1H), 4.15 (t, *J* = 6.6, 2H), 4.06 (m, 4H), 2.83 (m, 4H), 2.45 (qd, *J* = 6.3, 1.2, 2H), 1.23 (t, *J* =

7.2, 6H) .23 (t, *J* = 7.5, 3H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 189.7, 165.8, 139.6, 130.9, 63.4, 62.8, 35.2, 33.5, 31.3, 23.3, 16.5, 16.4, 14.9; R_f = 0.38 (EtOAc).

Ref.: BJEIV042, **BJEIV052**



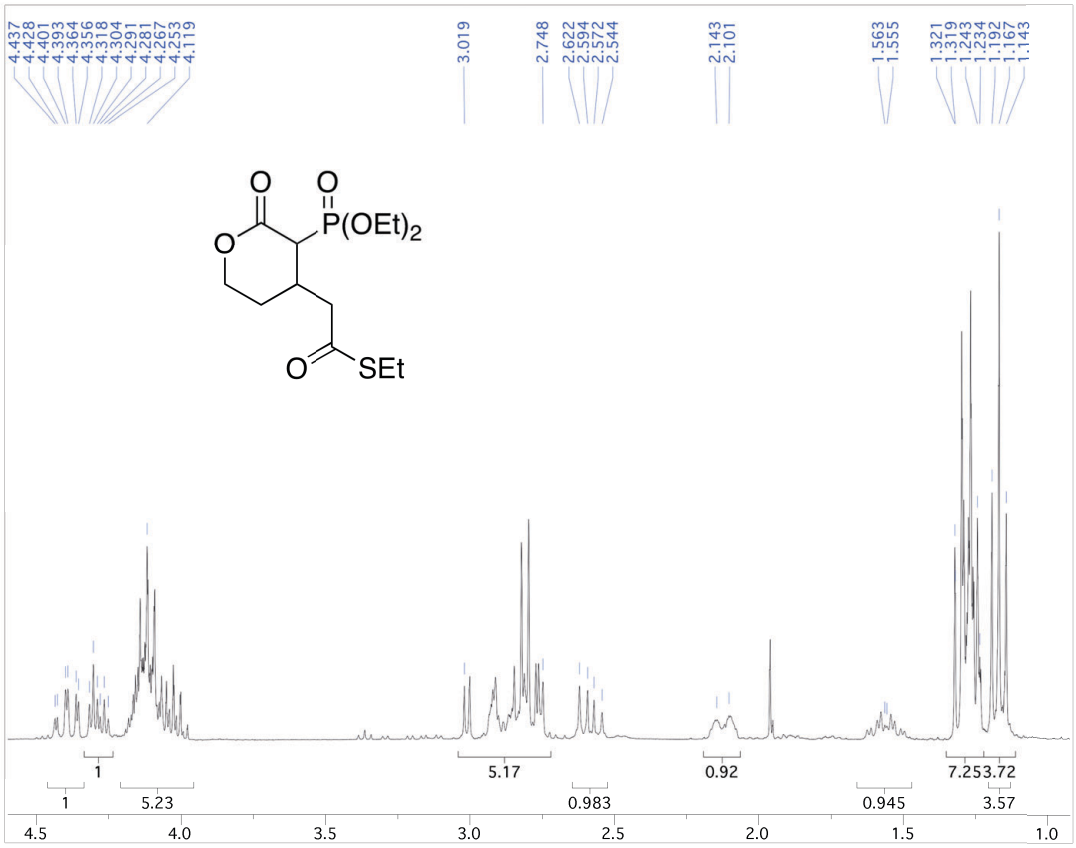


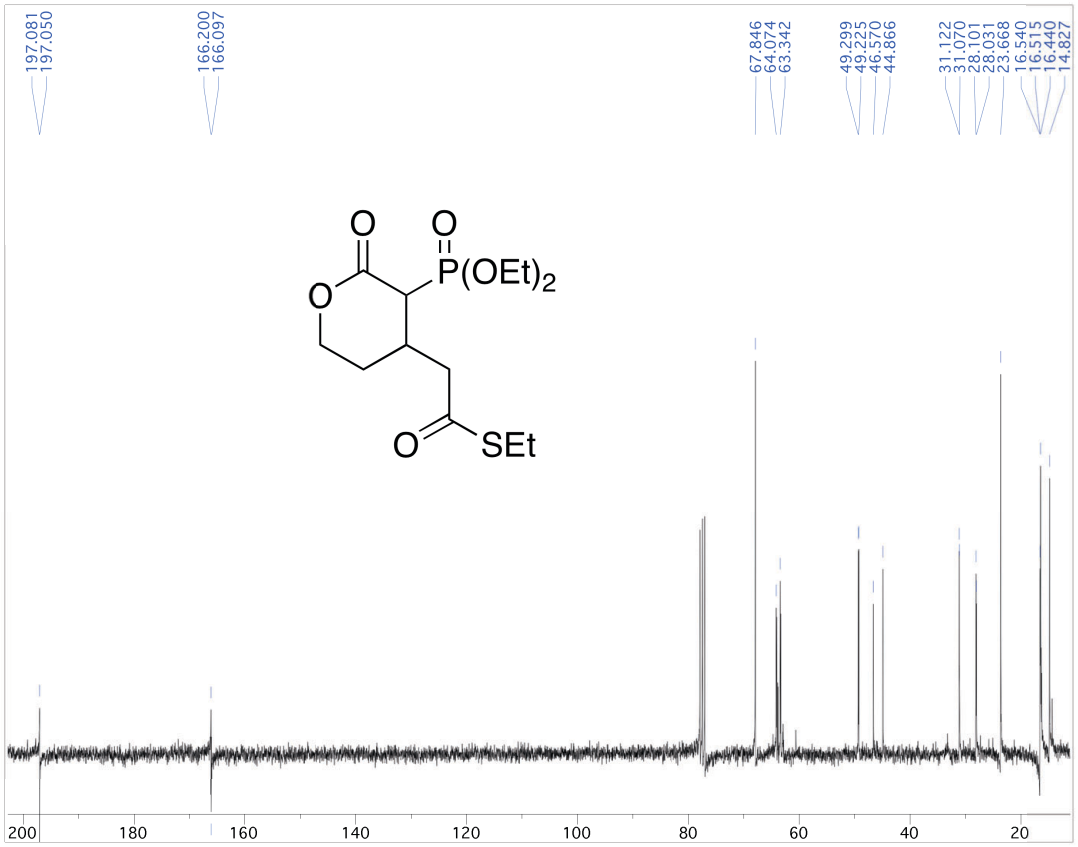


Synthesis of *S*-ethyl 2-(3-(diethoxyphosphoryl)-2-oxotetrahydro-2*H*-pyran-4-yl)ethanethioate: To a 25 mL round-bottomed flask containing 350 mg (1.03 mmol, 1 equiv.) (*E*)-5-(ethylthio)-5-oxopent-3-en-1-yl 2-(diethoxyphosphoryl)acetate dissolved in 5.2 mL dry CH_2Cl_2 was added 674 mg (2.06 mmol, 2 equiv.) Cs_2CO_3. The reaction was stirred for 16hr at ambient temperature before being added to 1 M HCl, extracted thrice with EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was purifed by silica gel flash chromatography eluting with 1 : 2 to 0 : 1 hex./EtOAc to yield 127 mg (36%) of the desired product as a pale yellow oil.

^{1}HNMR (300 MHz, $CDCl_3$) δ 4.40 (td, *J* = 10.8, 2.7, 1H), 4.29 (dt, *J* = 11.1, 4.2, 1H), 4.12 (m, 5H), 2.75-3.02 (m, 4H), 2.58 (dd, *J* = 15.0, 8.4, 1H), 2.12 (m, 1H), 1.56 (m, 1H), 1.23-1.32 (m, 6H), 1.17 (t, *J* = 7.5, 3H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 197.1, 166.1, 67.8, 64.1, 63.3, 49.3, 49.2, 46.6, 44.9, 31.3, 28.1, 23.7, 16.5, 16.4, 14.8; R_f = 0.39 (EtOAc).

Ref.: BJEIV053, **BJEIV062**.

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40
20

Appendix A: Publications

Tetrahedron Letters 50 (2009) 2713–2715

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of (±)-oleocanthal via a tandem intramolecular Michael cyclization–HWE olefination

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ABSTRACT

A synthesis of racemic oleocanthal has been accomplished in 11 steps from 1,3 propanediol by a key tandem intramolecular Michael cyclization–Horner–Wadsworth–Emmons olefination.

The secoiridoids are a class of plant-derived monoterpenes containing the substituted pyran core of secologanin (**1**). This class of natural products arises in biological systems from the oxidative cleavage of the loganin skeleton (**2**) by the cytochrome P450 enzyme secologanin synthase (Fig. 1).[1] Secologanin then undergoes various modifications to produce a wide array of structures displaying diverse biological activities including analgesic[2], anti-inflammatory[3], anti-arthritic[4], anti-allergenic[5], antibacterial[6], and antiviral[7] activities. Coupling of the simple secoiridoids with tryptamine gives rise to a large class (>250 examples) of indole and oxindole alkaloids including geissoschizine, strychnine, reserpene, ajmaline, and the Vinca alkaloids with highly varied carbon frameworks and biological profiles.

We reasoned that, given the structural similarities of the secologanin-derived natural products, synthetic access to the more complex secoiridoid and secologanin tryptamine alkaloids could be obtained through a single strategically functionalized intermediate. As a test case for our strategy, our attention focused on the secoiridoid oleocanthal (**3**) for both its relative structural simplicity that retains the compact arrangement of functionality of the secoiridoids and its demonstrated potency as an inhibitor of the COX-1 and COX-2 enzymes[3,8], making it an ideal entry point into the synthesis of this class of natural products. Important to our retrosynthetic analysis was proceeding through an intermediate with functionalities that could be independently manipulated allowing for future adaptation of this synthesis to produce a diverse selection of natural product targets. Lactone **5** appeared ideal for this purpose as it contained the requisite carbon backbone as well as properly situated synthetic handles with orthogonal reactivities.

We envisioned the dialdehyde moiety of **3** arising from the reduction and oxidation of lactone **5** whose carbon framework could be assembled through a key tandem Michael cyclization and Horner–Wadsworth–Emmons (HWE) olefination[9] of phosphonoacetic ester **6** (Scheme 1). This allows for the simultaneous assembly of the desired lactone core, the addition of the two-carbon olefin sidechain, and the introduction of a stereogenic center. Studies to control the absolute configuration of this new stereogenic center through the introduction of chiral auxiliaries are currently underway.

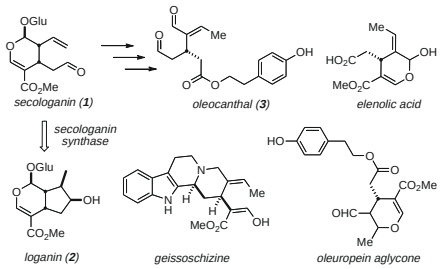
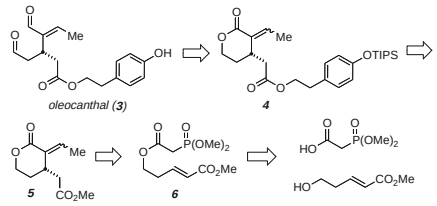


Figure 1. Structures of several secologanin derivatives.



Scheme 1. Retrosynthetic analysis.

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E-mail address: rmw@lamar.colostate.edu (R.M. Williams).

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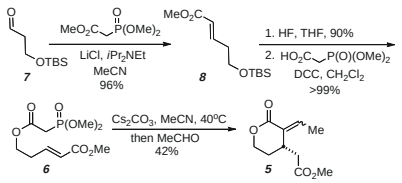


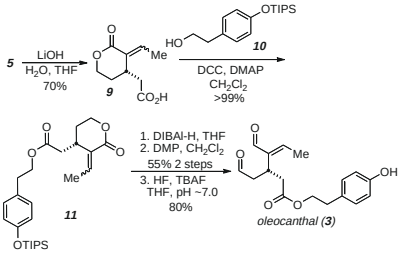
Scheme 2. Synthesis of lactone **5**.

Assembly of lactone **5** began with the synthesis of aldehyde **7** from 1,3-propanediol utilizing the method reported by Schaus and coworkers.[10] Reaction of **7** with commercially available trimethyl acetophosphonate under Masamune-Roush conditions produced the unsaturated ester **8** as a single isomer and in good yield (Scheme 2). Deprotection and subsequent esterification gave the desired substrate **6**, which upon treatment with Cs_2CO_3 and acetaldehyde in warm acetonitrile underwent sequential intramolecular Michael cyclization and HWE olefination to yield lactone **5** as an inconsequential 1.6:1 mixture of *E*/*Z* isomers.

Selective hydrolysis of the methyl ester of **5** yielded acid **9** that was esterified with protected tyrosol **10** affording lactone **11**, which upon reduction and Dess–Martin oxidation gave the dialdehyde precursor to oleocanthal as a single isomer (Scheme 3). This sensitive dialdehyde rapidly decomposed when treated with standard deprotection conditions (HF, HF-pyr, and TBAF) but underwent clean deprotection to furnish (±)-oleocanthal when the neutral conditions described in the literature by Smith et al. were employed (HF, TBAF aqueous THF at pH 7).[2]

We have demonstrated a short and scalable synthesis of (±)-oleocanthal, which can be readily adapted to allow access to a diverse selection of secoiridoid natural products. Current efforts are underway both to control the absolute stereochemistry of the key intramolecular Michael cyclization step of this approach and then to employ this method to synthesize several secoiridoids and secologanin tryptamine alkaloids.

Synthesis of ester **8**: To a flame dried 2 L round-bottomed flask (RBF) charged with 20.98 mL (121.3 mmol, 1.1 equiv) methyl 2-(dimethoxyphosphoryl)acetate dissolved in 1000 mL dry MeCN were added 6.170 g (145.5 mmol, 1.2 equiv) LiCl and then 21.12 mL (121.3 mmol, 1.2 equiv) iPr$_2$NEt. The reaction was stirred at ambient temperature for 15 min and then 22.84 g (121.3 mmol, 1 equiv) aldehyde **7** dissolved in a minimum of MeCN was added. After stirring for 4 h the reaction was concentrated to approximately 50% volume, added to brine, and extracted thrice with EtOAc. Combined organic layers were dried over Na_2SO_4, concentrated, and purified by silica gel chromatography eluting with 4:1 hex./EtOAc to yield 28.56 g (96%) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 (dt, J = 15.6, 7.2 Hz, 1H), 5.87 (dt, J = 15.9, 1.5 Hz, 1H), 3.71 (s, 3H), 3.70 (m, 2H), 2.40 (qd, J = 6.6, 1.8 Hz, 2H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}CNMR (75 MHz, $CDCl_3$): δ 167.1, 146.4, 122.7, 61.7, 51.6, 35.9, 26.0, 18.5, −5.2; IR (NaCl, film): 1729, 1660 cm^{-1}; HRMS (+TOF): [M+H]$^+$ 245.1568 calcd for $C_{12}H_{25}O_3Si$, found: 245.1571; R_f = 0.40 (9:1 hex./EtOAc).



Scheme 3. Synthesis of (±)-oleocanthal.

Synthesis of phosphonate **6**: To a 1 L HDPE bottle was added 24.85 g (101.7 mmol, 1 equiv) (*E*)-methyl 5-(*tert*-butyldimethylsilyloxy)pent-2-enoate (**8**) dissolved in 500 mL dry THF followed by 53 mL HF as a 48% solution in H_2O. The reaction was stirred for 6 h at ambient temperature, then slowly added to $NaHCO_{3(satd)}$, and extracted twice with EtOAc. Combined organic layers were dried over Na_2SO_4 and concentrated. The resulting residue was dissolved in 1:1 hex./EtOAc and filtered through a short silica gel plug. Concentration yielded 11.90 g (90%) of the desired alcohol as a pale yellow oil.

An oven-dried 100 mL RBF was charged with 2.940 g (22.58 mmol, 1 equiv) of the above alcohol, 4.560 g (27.11 mmol, 1.2 equiv) 2-(dimethoxyphosphoryl)acetic acid, and 45 mL dry CH_2Cl_2. To this was added 5.590 g (27.11 mmol, 1.2 equiv) DCC dissolved in a minimum volume of CH_2Cl_2. The reaction was stirred for 45 min at ambient temperature before being filtered through a Celite pad and concentrated. Purification by flash chromatography eluting with EtOAc yielded 6.310 g (>99%) of **6** as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.84 (dt, J = 15.6, 6.9 Hz, 1H), 5.83 (dt, J = 15.9, 1.5 Hz, 1H), 4.18 (t, J = 6.3 Hz, 2H), 3.74 (s, 3H), 3.70 (s, 3H), 3.65 (s, 3H), 2.91 (d, J_{HP} = 21.6 Hz, 2H), 2.49 (qd, J = 6.6, 1.5 Hz, 2H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 166.6, 165.7, 144.1, 123.5, 63.6, 53.4, 51.7, 34.3, 32.5, 31.4; IR (NaCl, film): 1724, 1660; HRMS (+TOF) calcd for $C_{10}H_{18}O_7P$ [M+H]$^+$ 281.0785, found 281.0788; R_f = 0.18 (EtOAc).

Synthesis of lactone **5**: To 179 mg (0.639 mmol, 1 equiv) (*E*)-methyl 5-(2-(diethoxyphosphoryl)acetoxy)pent-2-enoate (**6**) dissolved in 3 mL dry MeCN in an oven-dried 25 mL RBF was added 416 mg (1.28 mmol, 2 equiv) Cs_2CO_3. The reaction was heated to reflux for 1.5 h, cooled to 0 °C, and 107 μL (1.92 mmol, 3 equiv) freshly distilled acetaldehyde was added in a single portion. The reaction was vigorously stirred for 16 h at ambient temperature and was then acidified with 1 N HCl. This mixture was extracted thrice with EtOAc. Combined organic layers were dried over Na_2SO_4, concentrated, and purified by silica gel flash chromatography eluting with 2:1 to 1:1 hex./EtOAc to yield 53.0 mg (42%) of **5** (1.6:1 *E*/*Z*) as a yellow oil.

Synthesis of lactone **11**: To 69.0 mg (0.345 mmol, 1 equiv) crude lactone **5** dissolved in 2 mL 3:1 THF:H_2O in a 10 mL RBF was added 25.0 mg (1.03 mmol, 3 equiv) LiOH. The reaction was stirred at ambient temperature for 2 h and then acidified with 1 N HCl. This mixture was extracted thrice with EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 1:1:0.01 to 0:1:0 hex./EtOAc/HOAc to yield 44.0 mg (70%) of the desired acid as an inseparable mixture (1.6:1 *E*/*Z*) of *E*/*Z* isomers as a pale yellow oil.

To 36.0 mg (0.193 mmol, 1 equiv) of the above acid dissolved in 2 mL dry CH_2Cl_2 in an oven-dried 10 mL RBF and cooled to 0 °C was added 85.0 mg (0.290 mmol, 1.5 equiv) 2-(4-(triisopropylsilyloxy)phenyl)ethanol (**10**) followed by 60.0 mg (0.290 mmol, 1.5 equiv) DCC and a spatula tip of DMAP. The reaction was stirred for 16 h at ambient temperature, filtered through Celite, concentrated, and purified by silica gel flash chromatography eluting with 2:1 hex./EtOAc to yield 89.0 mg (>99%) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): *Z*-isomer δ 7.05 (m, 2H), 6.82 (m, 2H), 6.19 (qd, J = 7.2, 1.5 Hz, 1H), 4.26 (t, J = 6.9 Hz, 2H), 4.11 (td, J = 9.0, 3.6 Hz, 1H), 3.81 (m, 1H), 3.09 (m, 1H), 2.84 (dt, J = 17.1, 6.9 Hz, 3H), 2.44 (ddd, J = 15.6, 8.9, 6.3 Hz, 2H), 2.04 (dd, J = 7.2, 1.2 Hz, 3H), 1.24 (m, 3H), 1.10 (s, 18H), *E*-isomer δ

7.01–7.09 (m, 3H), 6.79 (m, 2H), 4.24–4.38 (m, 3H), 4.16 (m, 1H) 3.32 (m, 1H), 2.85 (t, J = 7.2 Hz, 2H), 2.41 (m, 2H), 1.83 (d, J = 7.5 Hz, 3H), 1.70 (m, 2H), 1.22 (m, 3H), 1.07 (m, 18H); ^{13}CNMR (75 MHz, $CDCl_3$) mixture of isomers δ 172.4, 171.4, 166.5, 154.9, 142.1, 139.6, 133.8, 130.2, 129.9, 129.8, 120.1, 120.1, 68.2, 65.5, 38.0, 34.4, 34.1, 29.6, 27.4, 27.0, 25.8, 25.2, 18.3, 14.4, 12.8; IR (NaCl, film) 1732, 1511 cm^{-1}; HRMS (+TOF) calcd for $C_{26}H_{41}O_5Si$ $[M+H]^+$ 461.2728, found 461.2722; R_f = 0.24 (2:1 hex./EtOAc).

*Synthesis of oleocanthal (***3***)*: To 47.0 mg (0.102 mmol, 1 equiv) (*S*)-4-(triisopropylsilyloxy)phenethyl 2-(3-ethylidene-2-oxotetrahydro-2*H*-pyran-4-yl)acetate (**11**) dissolved in 1 mL dry THF in a 10 mL flame-dried RBF at −78 °C was slowly added 102 μL of a 1 M solution of DIBAL in toluene. After stirring the reaction for 1 h at −78 °C 100 μL dry MeOH was added, the reaction was allowed to warm to ambient temperature, and 5 mL saturated Rochelle's salt solution was added. After stirring for 30 min this mixture was extracted thrice with EtOAc, dried over Na_2SO_4, concentrated, and purified by silica gel flash chromatography eluting with 4:1 hex./EtOAc to yield 48 mg of the desired alcohol as a colorless oil.

This residue was dissolved in 1 mL dry CH_2Cl_2, charged to a 10 mL oven-dried RBF, and cooled to 0 °C. To this solution was added 65.0 mg (0.153 mmol, 1.5 equiv) Dess–Martin periodinane and the reaction was stirred for 3 h at ambient temperature before the addition of 5 mL 5:1 $Na_2S_2O_{3(satd)}$:$NaHCO_{3(satd)}$ solution. This mixture was stirred for 15 min before being extracted thrice with CH_2Cl_2. Combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography eluting with 4:1 hex./EtOAc yielded 26.0 mg (55%) of the desired dialdehyde as a colorless oil.

To 7.0 mg of the above dialdehyde dissolved in 250 μL dry THF at 0 °C was added 50 μL of a solution prepared by the addition of 40% $HF_{(aq)}$ to a 1 M THF solution of TBAF until the pH of the resulting solution reached 7 as evidenced by pH paper. The reaction was stirred for 2 h at 0 °C, added to brine, and extracted thrice with EtOAc. Combined organic layers were dried over Na_2SO_4, concentrated, and taken up in 1:2 hex./EtOAc. This solution was filtered through a short plug of silica gel and concentrated to yield 3.7 mg (80%) of (±)-oleocanthal as a colorless film. All spectral properties matched data reported in the literature.[8]

Acknowledgments

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Appendix B:

Research Proposal

An Asymmetric Organocatalytic Method for 1,3-Dipolar Cycloadditions and Inverse Electron Demand Hetero Diels-Alder Reactions

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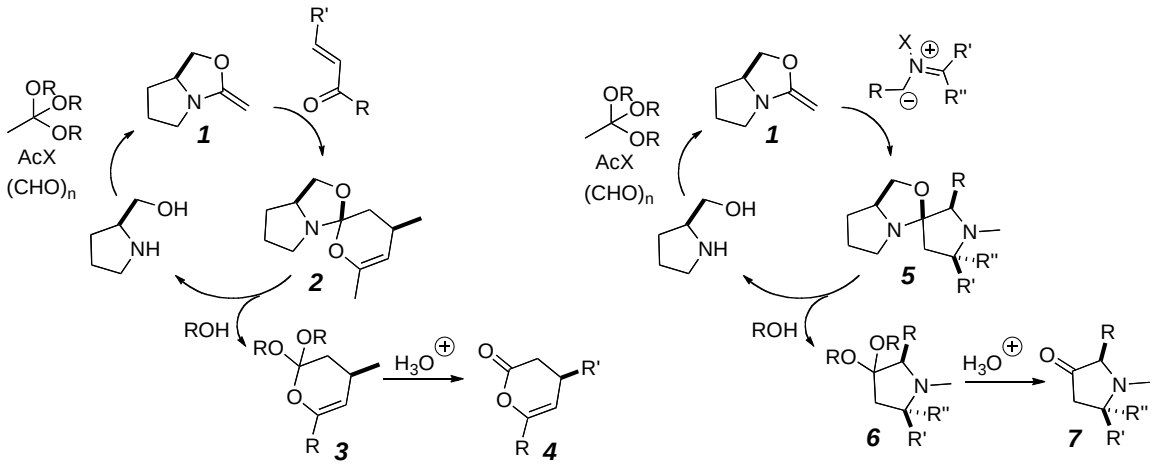
Robert M. Williams

Colorado State University

May, 2009

Abstract/ Specific Aims

The aim of this proposal is to develop an organocatalytic strategy for the use of prolinol based ketene hemiaminal ether intermediates, derived from simple and readily available feedstocks, as asymmetric ketene synthons for cycloaddition reactions, using methods which are accessible to undergraduate researchers. The stable, isolable, and, to date, unreported prolinol ketene hemiaminal ether (**1**) is an interesting substrate for use as a dipolarophile for 1,3-dipolar cycloadditions, and as a dieneophile for inverse electron demand hetero Diels-Alder (HDA) reactions (**Scheme 1**). Simple starting materials such as paraformaldehyde, acetyl chloride, acetic anhydride, or trialkyl orthoacetates, which are otherwise unreactive to the specific reaction conditions, will be activated by reaction with the prolinol catalyst to form **1**. Ketene hemiaminal ether **1** will then undergo cycloaddition with either the heterodiene or 1,3-dipole to form the respective hemi orthoamide ether (**2**) or hemi ketal ether (**5**). Upon solvolysis, the prolinol catalyst is released and the desired optically enriched 3,4-dihydropyran-2-ones (**4**) or *cis*-2,5-disubstituted pyrrolidines (**7**) are produced.



Scheme 1: Proposed catalytic cycles.

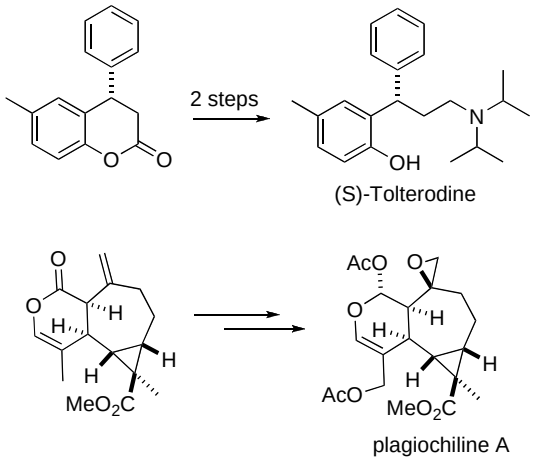
<u>The Specific Aims for this Proposal are the Following</u>:

1. To examine the scope of prolinol ketene hemiaminal ether **1** as a chiral dipolarophile for use in asymmetric 1,3-dipolar cycloadditions and as a chiral dienophile for use in asymmetric [4 + 2] cycloadditions.
2. To identify a 2-carbon feedstock which is unreactive to cycloaddition unless activated by prolinol.
3. To identify reaction conditions under which **1** is efficiently formed, cycloaddition occurs in good yield and high diastereoselectivity, and prolinol solvolysis occurs releasing the desired product and the prolinol catalyst.
4. To utilize the above described methodology for the synthesis of simple natural product targets.

Background and significance

Existing syntheses of 3,4-dihydropyran-2-ones.

Optically enriched, highly substituted 3,4-dihydropyran-2-ones have been demonstrated to be useful intermediates for the synthesis of a wide variety of useful structures such as cyclic enamines[i] and γ-lactones[ii] as well as for the synthesis of natural products ranging in complexity from simple coumarins such as (*s*)-Tolterodine[iii] to more complex structures such as plagiochiline A[iv] (**Scheme 2**).

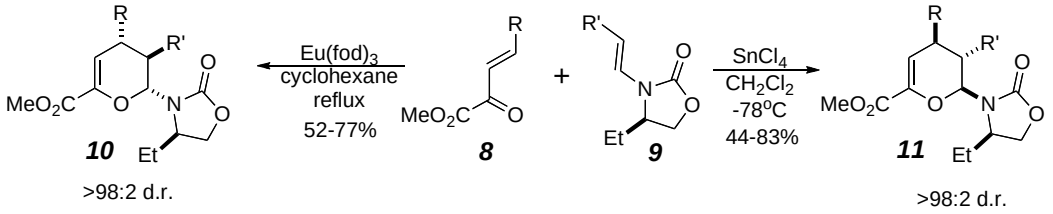


Scheme 2: Examples of 3,4-dihydropyran-2-ones in natural product synthesis.

Several stereoselective multistep methods have been developed for the synthesis of 3,4-dihydropyran-2-ones, however, these methods do not surpass modern single-step cycloaddition methods in scope, yield, or stereoselectivity. This fact, combined with the multistep nature of these methods renders them obsolete.

Stereoselective cycloadditions have found great utility as methods for the preparation of stereodefined heterocycles, natural products, drugs, and fine chemicals due to the ability of these reactions to efficiently and controllably introduce several atoms, one or more rings, and several defined stereogenic centers in a single synthetic manipulation. Critical to the production of desired, stereodefined products is the control of the reaction regioselectivity, the endo/ exo selectivity of the cycloaddition, and control of facial selectivity.

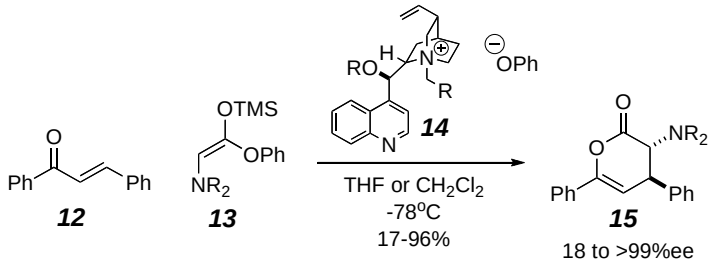
The use of chiral auxiliaries for asymmetric induction has provided mixed results. Dhal and coworkers[v] have demonstrated the ability to produce highly substituted dihydropyrans (**10** and **11**) with a high degree of diastereoselectivity by the inverse electron demand hetero Diels-Alder (HDA) cyclization of achiral α,β-unsaturated pyruvate esters (**8**) with chiral *N*-vinyloxazolidinones (**9**) (**Scheme 3**). As with most inverse electron demand HDA cyclizations, regioselectivity is determined by the most efficient overlap of the electronically biased diene LUMO and dienophile HOMO. Effective transition state FMO overlap favors a single regioisomer. The orientation of the chiral auxiliary, as controlled by varying the Lewis acid used, provides the dienophile facial bias allowing for the production of the desired dihydropyran core with excellent diastereoselectivity and in moderate yield. Unfortunately, hydrolysis and oxidation are required to produce the final dihydropyranone heterocycle.



Scheme 3: Dhal's chiral auxilliary method.

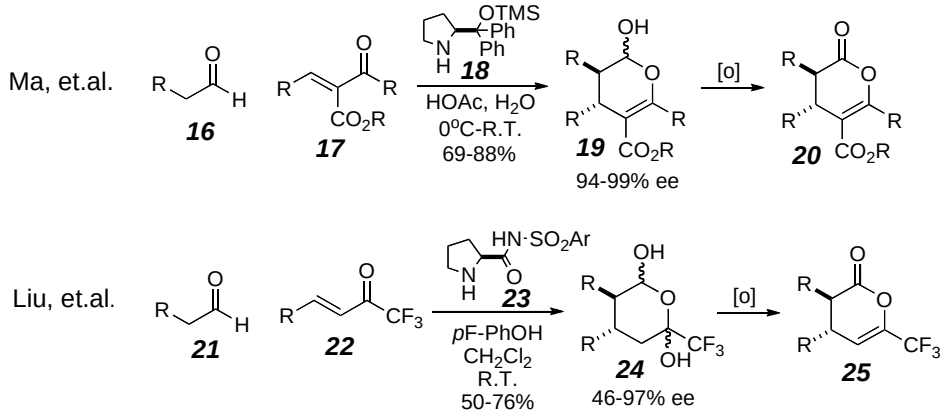
Reaction control through the use of asymmetric catalysis overcomes the limitations inherent in the use of chiral auxiliaries by allowing for the direct use of more simple and widely available achiral starting materials, rather than relying on asymmetry present in more costly and structurally limited chiral pool reagents or necessitating the introduction, removal, and recovery of chiral auxiliaries.

Mukaiyama and coworkers[vi] have developed quaternary ammonium salts (**14**) derived from Cinchona alkaloids as effective catalysts for the synthesis of a variety of highly substituted 3,4-dihydropyran-2-ones (**15**) (**Scheme 4**). Unfortunately this strategy is plagued with highly variable yields, an extremely limited substrate scope, an inability to form the opposite enantioform of the product shown (**15**) due to lack of naturally occurring Chinchona alkaloid antipodes, and the need to prepare the silyl enolate starting material (**13**).



Scheme 4: Mukaiyama's Chinchona catalyst.

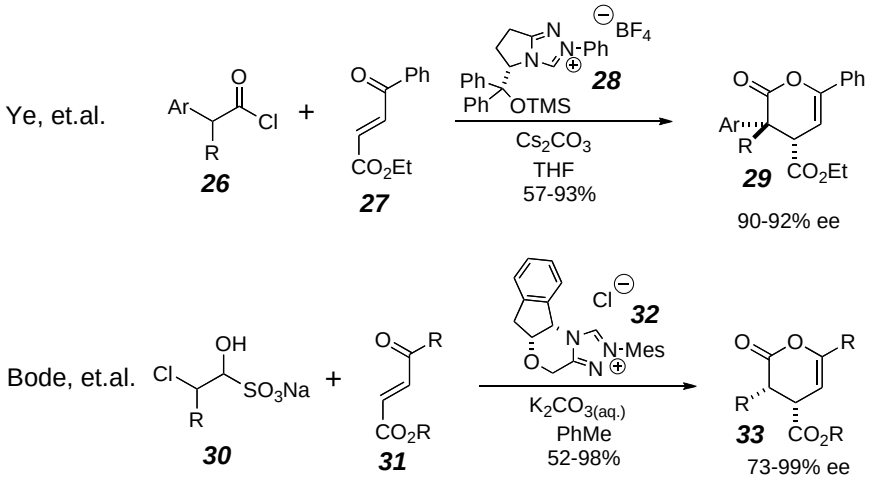
Several methods utilizing proline derived organocatalysts (**18** and **23**) to produce substituted 3,4-dihydropyran-2-ones (**20** and **25**) such as those reported by Liu[vii] and Ma[viii] (**Scheme 5**) have demonstrated the potential of organocatalysis in this field. Although good yields and high enantioselectivity generally characterize these methods, major drawbacks exist. Since these transformations are essentially tandem asymmetric Michael addition-cyclization reactions, the heterodiene substrates (**17** and **22**) must possess extremely electron deficient ketones capable of existing, to a significant degree, as the corresponding enol tautomer necessary for cyclization to the product lactol. This extremely limits the possible substrate scope of this method. For instance, aldehydes and ketones without an adjacent electron withdrawing group are not reported. The need to oxidize the product lactol (**19** and **24**) to the desired pyranone further complicates these methods.



Scheme 5: Proline based catalysts.

The most convenient modern methods for the asymmetric synthesis of 3,4-dihydropyran-2-ones involve *N*-heterocyclic carbene (NHC) catalyzed cycloadditions. Bode[ix] and Ye[x] have recently reported synthetic methods which utilize NHCs (**28** and **32**) to catalyze the [4+2] asymmetric cyclization of ketenes and α,β-unsaturated ketones to produce 3,4-dihydropyran-2-ones (**Scheme 6**). Due to their inherent instability, the ketenes are generated in situ from either chloroaldehyde acid chlorides (**26**) or bisulfite salts (**30**). Reaction of these ketenes with the NHC catalyst produces a Breslow intermediate, which undergoes cycloaddition and releases the NHC catalyst along with the 3,4-dihydropyran-2-one product. These cycloadditions produce the desired products in good yield and with high diastereo- and enantioselectivities. Inherent limitations of these cyclizations include the limited heterodiene substrate (**27** and **31**) scope, which cannot include unsaturated aldehydes due to side reactions resulting from their reaction with the

NHC catalyst, the complexity of, and need to synthesize, the NHC catalyst, and the need to use relatively complex ketene precursors.



Scheme 6: NHC based catalytic methods.

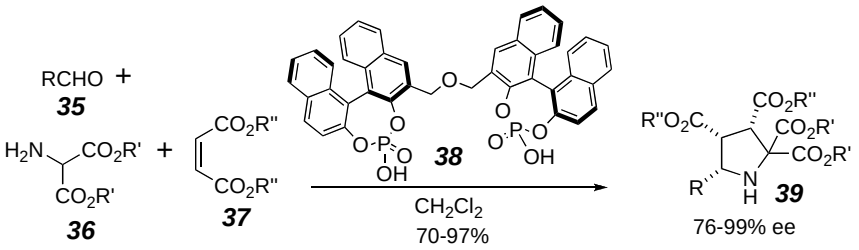
Existing syntheses of *cis*-2,5-disubstituted pyrrolidines.

The synthesis of optically active *cis*-2,5-disubstituted pyrrolidines has garnered a great deal of interest due to the prevalence of this heterocyclic residue in natural products, pharmaceuticals, and organocatalysts. Although several multi-step asymmetric syntheses of *cis*-2,5-disubstituted pyrrolidines have been reported[xi], the catalytic asymmetric, single-step installation of the 2,5-*cis* arrangement of substituents remains the gold standard for the field. To date, this has been most efficiently accomplished via 1,3-dipolar cycloaddition of unsaturated substrates with azomethine ylides. This is the most logical disconnection as it

convergently and diastereospecifically installs the requisite substituents in a single step, with control of stereochemistry.

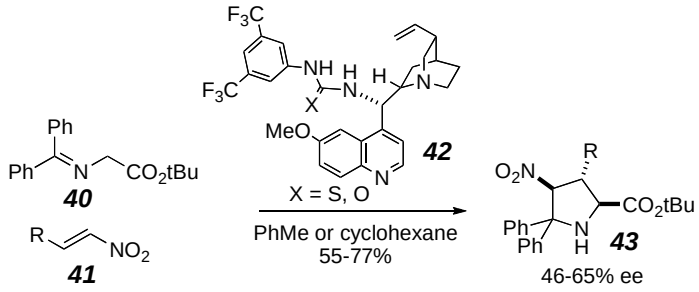
A number of successful methods for controlling the absolute stereochemistry of 1,3-dipolar cycloadditons of azomethine ylides have been reported using Lewis acidic metal catalysts (mainly Cu, Zn, and Ag) bound to chiral ligands[xii], however, the problems endemic to traditional metal-based catalysis such as moisture and air sensitivity, expense, toxicity, ligand complexity, and problems with product purification have recently motivated the investigation of organocatalysis of 1,3-dipolar cycloadditons of azomethine ylides as an alternative to the traditional methods.

Gong and coworkers[xiii] have utilized a three-component chiral Brønsted-acid catalyzed strategy to produce chiral 2,5-disubstituted pyrrolidines (**39**) in excellent yield and enantiomeric excess (**Scheme 7**), however, not without major drawbacks. The complexity and expense of the binol derived phosphonate catalyst (**38**), a very limited substrate scope, and the inability to introduce a C2 stereocenter extremely limit the possible synthetic applications of this method.



Scheme 7: Gong's chiral Brønsted-acid catalyst.

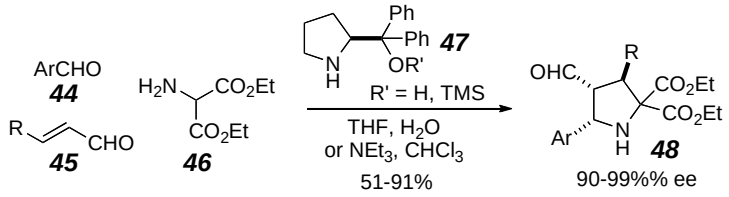
A second strategy developed by Gong and coworkers[xiv] involves the use of modified Chinchona alkaloids bearing urea or thiourea sidechains capable of hydrogen bonding with nitroalkene dipolarophiles (**42**), thus inducing cycloaddition asymmetry (**Scheme 8**). The extremely limited substrate scope combined with low yields, high catalyst complexity, poor enantioselectivity, and only moderate diastereoselectivity reported for this strategy render it unlikely to be applicable to total synthesis.



Scheme 8: Gong's Chinchona-based catalysts.

The most successful organocatalytic azomethine ylide [3 + 2] cycloadditions have been reported by the Vicario[xv] and Cordova[xvi] groups who utilize proline-derived organocatalysts (**47**) (**Scheme 9**). Although these methods provide high yields and stereoselectivities, C5 substituents are limited to aryl groups and only a

single amine (**46**) has been employed, which, due to its lack of a chiral or prochiral α-position, cannot produce a pyrrolidine C2 stereogenic center.



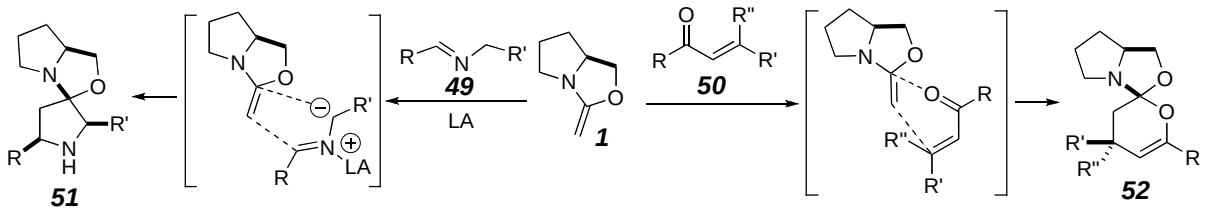
Scheme 9: Proline based catalysts for [3 + 2] cycloadditions.

Research Design and Methods

We envision the development of a general method for the synthesis of highly substituted, optically active 3,4-dihydropyran-2-ones and 2,5-disubstituted pyrrolidines via asymmetric cycloadditions between chiral ketene synthon **1** and either azomethine ylides (**49**) or α,β-unsaturated carbonyl compounds (**50**). The accessibility and robustness of this strategy combined with the progressive development plan described below make this an ideal project for undergraduate researchers.

Initially, investigations using pre-synthesized and purified ketene synthon **1** will be employed to identify reaction conditions ideal for HDA and dipolar

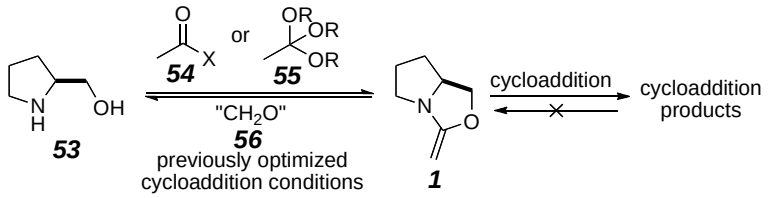
cycloadditions (**Scheme 10**). Commercially available or readily synthesized heterodienes (**50**) and azomethine ylides (**49**) whose asymmetric cycloaddition reactivites have been previously demonstrated by literature precedent will be initially employed to simplify product characterization and to facilitate direct comparison of our methods to the existing state-of-the-art.



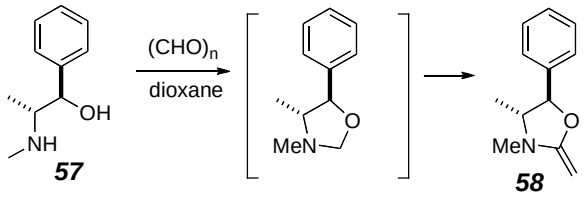
Scheme 10: Proposed cycloaddition reactions.

Upon the establishment of conditions ideal for stoichiometric, asymmetric cycloadditions, work toward a catalytic version of these cycloadditions will commence by addressing two necessary concerns: identifying a two-carbon ketene feedstock and identifying conditions to solvolyze the immediate cycloaddition products to regenerate the prolinol catalyst. Potential two-carbon feedstocks (**Scheme 11**) include acetic acid and its many derivatives (**54**), orthoacetates (**55**), and, based on an interesting observation by Gazaliev and coworkers[xvii] (**Scheme 12**), formaldehyde derivatives (**56**). It is important to note that, although the formation of **1** may be a reversible process under the reaction conditions, only a

steady-state concentration of **1** is necessary for the catalytic cycle to continue because the [4 + 2] and [3 + 2] cycloadditons are predicted to be irreversible.



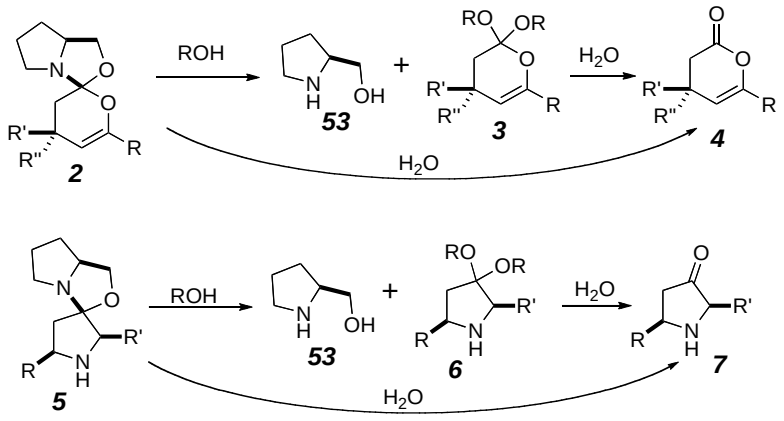
Scheme 11: Potential 2-carbon feedstocks.



Scheme 12: Gazaliev's double paraformaldehyde condensation.

Upon generation of the immediate cycloaddition products (**2** and **5**), solvolysis to regenerate the prolinol catalyst (**53**) (**Scheme 13**) is critical both to continue the catalytic cycle as well as to prevent retro-cycloaddition. In the case of HDA cyclizations, that will likely proceed through a rapid stepwise, rather than truly concerted mechanism, reversability of the reaction may result in partial loss of enantioselectivity. This solvolysis is likely best accomplished through the use of

water or alcoholic cosolvents such as those employed by the majority of the methods discussed in the above section.

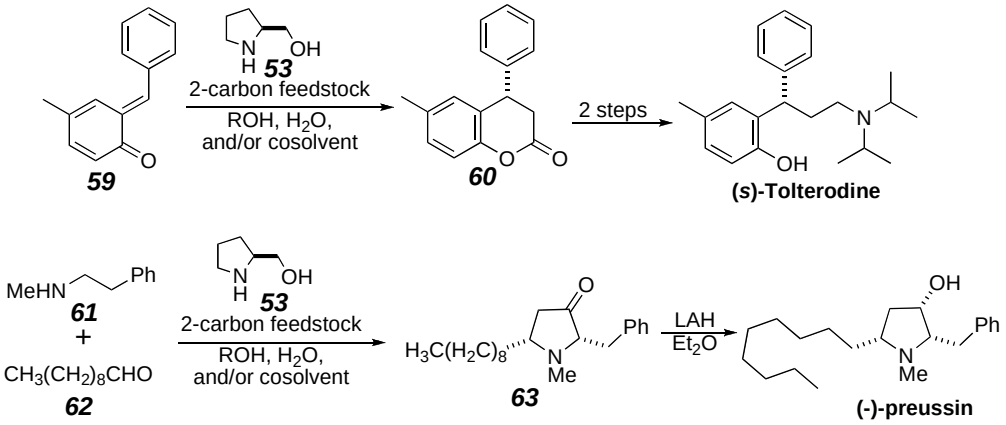


Scheme 13: Solvolysis to regenerate prolinol catalyst.

Once optimized catalytic conditions have been developed, the scope of these cycloadditions can be examined. Due to the simplicity of this method, the scope of heterodienes and azomethine ylides which can be employed should far exceed that of previous precedents. For example, as opposed to the methods of Ma and Liu detailed above (**Scheme 5**), which require the use of electron deficient ketones as heterodienes in order to form the product lactol, and the NHC methods of Ye and Bode (**Scheme 6**), which also cannot accommodate aldehydic heterodienes due to their reactivity with the NHC catalyst, our method is fully compatible with the use of α,β-unsaturated aldehydes as heterodienes. This would be a major expansion of the

scope of this type of transformation, allowing for the production of C2 unsubstituted dihydropyranones.

The final goal of this proposal is to utilize our methods for the synthesis of optically active natural products (**Scheme 14**). The specific targets chosen will largely depend on the scope and limitations of our methods. Special attention will be paid to structures which are sufficiently simple as to allow them to be reasonably accessed by undergraduate researchers on a short timeframe. Potential targets include simple coumarins such as (*s*)-Tolterodine, accessible via cycloaddition of **1** with known orthoquinone methide heterodienes (**59**), as well as, *cis*-2,5-disubstituted pyrrolidines such as (-)-preussin.



Scheme 14: Potential applications to natural product synthesis.

Potential Difficulties and Limitations:

Difficulties, both anticipated and not, are a part of every research program. Below are listed the potential difficulties and limitations of this proposal and our contingency plans to overcome these difficulties.

1. It is possible that the ketene hemiaminal ether derived from prolinol (**1**) will either not undergo cycloaddition or will not do so with sufficient stereoselectivity. This would necessitate redesign of the catalyst. A number of commercially available amino alcohols derived from corresponding amino acids or ephedrine-type substrates could be investigated to overcome these problems without altering the general concept of this method.
2. It is possible that problems with the formation of **1** or the solvolysis of the cycloaddition products in a single reaction vessel will not allow for the development of a catalytic method. A stoichiometric version of this method involving the introduction of pre-formed **1** followed by cycloaddition and hydrolysis would remain a useful technique for the synthesis of these chiral heterocycles due to the simplicity of manufacturing **1** on large scale and the inexpensive nature of its starting materials.
3. The substrate scope of these cycloadditions will inevitably vary from that anticipated. This is the nature of empirical science and is critical for the identification of unanticipated and serendipitous reactivity.
4. A major limitation of this method is the inability to introduce substituents at the C3 position of 3,4-dihydropyran-2-ones or the C2 or C3 positions of 2,5-

disubstituted pyrrolidines. Fortunately, this method introduces a carbonyl synthetic handle at these positions allowing for facile substitution via multiple established methods.

Concluding Remarks:

This proposal details our plan to develop an asymmetric organocatalytic method for the synthesis of 3,4-dihydropyran-2-ones and 2,5-disubstituted pyrrolidines via cycloaddition of catalytically generated ketene hemiaminal ether **1** with heterodienes and azomethine ylides. This method has several benefits over the current state-of-the-art:

1. The catalytic system is simple, commercially available as either antipode, and inexpensive.
2. The potential 2-carbon dipolarophile/dienophile feedstocks are simple, commercially available, inexpensive, and much more stable than currently reported ketene synthons.
3. No portion of this method is incompatible with air or moisture, providing reaction robustness.

The progressive plan described above neatly divides this proposal into smaller goals, which, taken individually, are sufficiently accessible to allow them to be accomplished by undergraduate researchers on a compressed schedule. Many of these smaller goals are designed to be developed in parallel, allowing each individual researcher within the group to work on a personalized project, closely

related to, but still distinct from, those of their colleagues. This personal responsibility will both maximize productivity and allow each researcher to work at his or her own pace, maximizing learning potential.

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