# Synthetic Studies on Bielschowskysin

By

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**To my family:**

the chemists and

the non-chemists

alike.

“I try all things; I achieve what I can.”

-*Moby Dick* by Herman Melville

**Acknowledgements**

First and foremost, I need to thank my advisor, Professor Gary Sulikowski. As he is fond of reminding me, I would not have even been accepted to the PhD program at Vanderbilt had he not pulled my file out of the rejection pile. I certainly hope he feels that he made the right decision. He has been incredibly supportive during the best of times and during the worst of times and, for that support, I will be forever grateful. Although I have not always agreed with Gary, he has given me a great deal of independence in order for me to fully grow as a synthetic chemist. With that said, he has also always been there to steer me back on course when I would begin to wonder around aimlessly in the forest.

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me more support than I could have ever imagined — in sickness and in health, indeed. I will always be grateful to her and, fortunately, I have the rest of my life to return the favor.

I would also like to thank my Mom and my Dad. Not only have they raised me into the person I am today, but they also instilled my love of chemistry in me from a very young age. They have always been willing to listen to any problems that I had, either chemistry related or otherwise. My Dad has always been very interested in my chemistry, and I'm sure that the results presented here are, at least in some way, shaped by his input. I am also very thankful for their helpful comments, suggestions, and corrections in putting together this dissertation. I know that it wasn't an easy task to read through the whole thing. In all, there are not enough words for me to express my gratitude to my parents but I can easily say that I would not be where I am now without their love, support, and guidance.

My extended family, too, has been incredibly supportive of this monumental challenge. My in-laws, Marc and Carine, as well as An, Kim, and Baby Xander, have been a huge help, even if we can't visit as often as we would have liked. They always made me feel at home and relaxed during our visits and I am so much looking forward to future visits once the pandemic is over.

Finally, I want to thank Korey Bedard and Tomas Hudlicky at Brock University for the generous donation of some starting materials at a time when circumstances kept me from operating at full efficiency.

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## List of Abbreviations

| | |
|---|---|
| Ac | acetyl |
| acac | acetylacetonate |
| AIBN | azobisisobutyronitrile |
| atm | atmosphere(s) |
| 9-BBN | 9-borabicyclo[3.3.1]nonane |
| BINOL | 1,1′-bi-2-naphthol |
| Bn | benzyl |
| BOM | benzyloxymethyl |
| bp | boiling point |
| brsm | based on recovered starting material |
| Bu | butyl |
| Bz | benzoyl |
| ° C | degrees Celsius |
| CAN | cerium ammonium nitrate |
| Cp | cyclopentadienyl |
| CSA | 10-camphorsulfonic acid |
| cy | cyclohexane, cyclohexyl |
| Δ | reflux |
| ∂ | chemical shift in parts per million |
| DABCO | 1,4-diazabicyclo[2.2. 2]octane |
| dba | dibenzylideneacetone |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCC | N,N′-dicyclohexylcarbodiimide |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DET | diethyltartrate |
| DHP | 3,4-dihydropyran |
| DIAD | diisopropyl azodicarboxylate |
| DIBAL | diisobutylaluminum hydride |
| DMAP | 4-dimethylaminopyridine |
| DMB | dimethoxybenzyl |
| DMDO | dimethyldioxirane |
| DME | dimethoxyethane |
| DMF | N,N-dimethylformamide |
| 2,2-DMP | 2,2-dimethoxypropane |
| DMP | Dess–Martin periodinane |
| DMSO | dimethyl sulfoxide |
| DMVS | dimethylvinylsilyl |
| DNBz | 3,5-dinitrobenzoyl |
| dppf | 1,1'-bis(diphenylphosphino)ferrocene |
| dr | diastereomeric ratio |
| EDA | ethylenediamine |
| EDCI | 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide |
| ee | enantiomeric excess |
| eq. | equivalent(s) |
| er | enantiomeric ratio |
| Et | ethyl |
| g | gram(s) |
| GI | Grubbs' 1st generation catalyst |
| GII | Grubbs' 2nd generation catalyst |
| $GI_{50}$ | half maximal growth concentration |

| | |
|---|---|
| h | hour(s) |
| HFIP | hexafluoro-2-propanol |
| HMPA | hexamethylphosphoramide |
| hv | irradiation |
| IBX | 2-iodoxybenzoic acid |
| $IC_{50}$ | half maximal inhibitory concentration |
| ImH | imidazole |
| kcal | kilocalorie(s) |
| KHMDS | potassium bis(trimethylsilyl)amide |
| L | liter(s) |
| LDA | lithium diisopropylamide |
| LHMDS | lithium bis(trimethylsilyl)amide |
| m | meter(s) |
| M | molar |
| mCPBA | meta-chloroperoxybenzoic acid |
| Me | methyl |
| MEM | 2-methoxyethoxymethyl |
| Mes | mesityl |
| mg | milligram(s) |
| MHz | megahertz |
| min | minute(s) |
| mL | milliliter(s) |
| mmol | millimole(s) |
| MMTr | 4-methoxytrityl, 4-methoxytriphenylmethyl |
| mol | mole(s) |
| MOM | methoxymethyl |
| mp | melting point |
| MPTA | α-methoxy-α-trifluoromethylphenylacetic acid, Mosher's acid |
| Ms | methansulfonyl |
| MS | molecular sieves |
| N | normal |
| NaHMDS | sodium bis(trimethylsilyl)amide |
| nbd | norbornadiene |
| NBS | *N*-bromosuccinimide |
| nm | nanometer(s) |
| NMI | N-methylimidazole |
| NMO | N-methylmorpholine N-oxide |
| NMR | nuclear magnetic resonance |
| nOESY | nuclear Overhauser effect spectroscopy |
| OPP | pyrophosphate |
| PAD | potassium azodicarboxylate |
| PDC | pyridinium dichromate |
| PCC | pyridinium chlorochromate |
| Ph | phenyl |
| PIDA | (diacetoxyiodo)benzene |
| Piv | pivaloyl, trimethylacetyl |
| PMB | *para*-methoxybenzyl |
| PPTS | pyridinium *para*-toluenesulfonate |
| Pr | propyl |
| pyr | pyridine |
| RedAl | sodium bis(2-methoxyethoxy)aluminium hydride |
| SEM | trimethylsilylethoxymethyl |
| TASF | tris(dimethylamino)sulfonium difluorotrimethylsilicate |

| | |
|---|---|
| TBAI | tetrabutylammonium iodide |
| TBAF | tetrabutylammonium fluoride |
| TBDPS | *tert*-butyldiphenylsilyl |
| TBS | *tert*-butyldimethylsilyl |
| TBSal | *tert*-butylsalicylimide |
| TCA | trichloroacetimidate |
| TEMPO | (2,2,6,6-tetramethylpiperidin-1-yl)oxyl |
| TES | triethylsilyl |
| Tf | trifluoromethanesulfonyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| THP | tetrahydropyranyl |
| TIPS | triisopropylsilyl |
| TMEDA | tetramethylethylenediamine |
| TMP | tetramethylpiperidine |
| TMS | trimethylsilyl |
| TPAP | tetrapropylammonium perruthenate |
| Tr | trityl, triphenylmethyl |
| Ts | *para*-toluenesulfonyl |
| UV | ultraviolet |
| W | watt |
| μ | micro |
| ))) | ultrasonication |

# Chapter 1

## Introduction

The research presented in this dissertation covers recent efforts in the Sulikowski laboratory toward the total synthesis of bielschowskysin (**1**), a bioactive diterpene isolated in 2004 from the gorgonian coral, *Pseudopterogorgia kallos*. Since then, arguably, no natural product has gripped the imaginations of the synthetic community as much as this one. Our group was the first to publish, in 2006, a synthetic approach to **1**, that culminated in a stereoselective [2+2] photocycloaddition between a γ-alkylidine butenolide and a butenolide to furnish the tetracyclic core (highlighted in blue in **Figure 1.1**). Since then, nine other research groups around the world have published efforts toward the total synthesis of **1**, resulting in an additional 18 publications. To date, no one has yet completed the total synthesis of this unique compound.

The challenges of a successful total synthesis of **1** are many. The structure features a total of eleven total stereogenic centers, including four contiguous centers located at the periphery of the cyclobutane core. Thus, the stereoselective synthesis of the cyclobutane moiety poses a significant challenge. Furthermore, the closure of the eight-membered ring is, ostensibly, quite difficult, as there exists no obvious bond disconnections to ring formation. Indeed, the fact that there is no other known structure bearing any resemblance to the carbon framework of **1** also means that there is scant literature precedence for many of the transformations. This is especially true for any incipient maneuvers that may be required as the synthesis progresses.

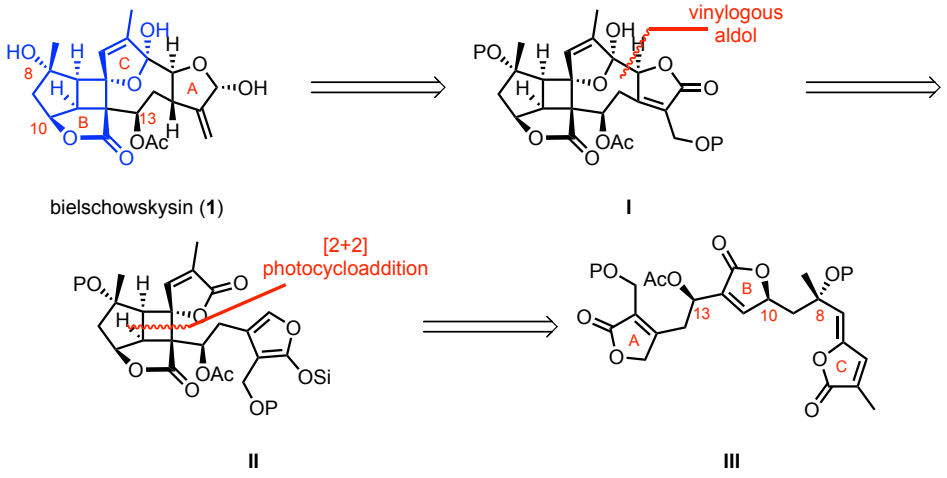



**Figure 1.1**: Synthetic analysis of bielschowskysin.

Our strategy towards a successful synthesis of **1** is outlined in **Figure 1.1**. We envisage that the eight-membered ring might be formed via a vinylogous Mukaiyama aldol reaction between the hypothetical silyloxyfuran and the spirocyclic butenolide of intermediate **II**. Intermediate **II**, in turn, would be accessed via the stereoselective [2+2] photocycloaddition between the central butenolide and the enol ether moiety in the linear precursor **III**. There are six components of this hypothetical structure that must be considered: the α,ß-substituted butenolide A-ring, the α,γ-substituted butenolide B-ring, the γ-alkylidine butenolide C-ring as well as the C8, C10, and C13 stereogenic centers. Thus, our sights are set on the synthesis of linear precursor **III**, focusing specifically on efficient control of the six aforementioned components.

Before the discussion of research results, I will first provide an overview of diterpene secondary metabolites of gorgonian corals. To keep the discussion focused, I will cover only metabolites isolated from *Pseudopterogorgia kallos*, the organism from which bielschowskysin originates. I include the isolation and any reported biological activity, proposed biosynthesis, and any attempts at the chemical synthesis of these compounds. Furthermore, I also provide a brief discussion of the speculations concerning the biological function of marine diterpenes and whether or not a symbiont is involved in the biosynthesis. Finally, I offer a comprehensive report of my efforts toward the total synthesis of **1**. With a determined and strategic effort, and a little bit of luck, I hope to disclose the first total synthesis of bielschowskysin.

# Chapter 2

## Background and Significance

Gorgonian corals, found around the world's tropical and subtropical oceans and commonly known as sea fans or sea whips, belong to the order of soft corals known as Alcyonacea, *viz*., organisms that do not produce a calcium carbonate skeleton. They produce a rich source of secondary metabolites that reportedly display a diverse array of biological attributes including anti-cancer, anti-inflammatory, and anti-microbial activities. The first report of anti-microbial activity in gorgonian coral extracts was published in 1958 by Burkholder.[1] Since then, a series of reviews have been published documenting the scope of diterpenes isolated from gorgonian corals and their associated biological activities.[2-4] Between 2008 and 2014, 244 new diterpenoids were isolated from the various species of these corals that add to the hundreds of metabolites that had been documented prior to 2008.[4] The extent of structural variation amongst these metabolites will be detailed later in this chapter.

Shown in **Figure 2.1** are examples of the variety of carbon frameworks that have been documented; these include carbocycles of all sizes ranging from three-membered rings to 14-membered rings. Although diterpenoids have been isolated from approximately 15 different genera of gorgonians, the genus *Pseudopterogorgia* produces by far the most structurally diverse with 28 of the 40 skeletal classes represented.[3] In the interest of brevity, this chapter will focus solely on compounds isolated from *P. kallos*, their biosynthesis, chemical syntheses, and associated biological activities.

### 2.1 Isolation of Bielschowskysin

Bielschowskysin (**1**) was isolated in 2004 from the extracts of *P. kallos*, which was collected off the coast of Old Providence Island in the southwestern Caribbean Sea.[5] Rodríguez reported isolating 39.6 mg of **1** and as colorless crystals. The structure, featuring the previously undescribed [9.3.0.0] tricyclic ring system, was assigned primarily by a series NMR experiments and confirmed by single-crystal x-ray diffraction analysis. When the authors evaluated bielschowskysin for antiplasmodial activity against *Plasmodium falciparum*, they found it to exhibit an $IC_{50}$ of 10 μg/mL. On the basis of these results, bielschowskysin was also subjected to the National Cancer Institute's (NCI) *in vitro* antitumor screen, where it displayed cytotoxic activity against EKVX nonsmall cell lung cancer ($GI_{50}$ < 0.01 μM) and CAKI-1 renal cancer ($GI_{50}$ = 0.51 μM). These assays represent the extent of biological study of

bielschowskysin with no further knowledge of its mechanism of action or cellular target. The limited quantity of material and the scope of biological significance underscores the necessity to access **1** by means of total synthesis.

## 2.2 Related Natural Products

As mentioned in the introduction to this chapter, there is an abundance of secondary metabolites that have been isolated from gorgonians. To date, 28 different metabolites have been isolated from *P. kallos*, shown in **Figure 2.2**. In 1985, the groups of Fenical and Clardy were the first to report diterpenoid secondary metabolites isolated from extracts of *P. kallos*.[6] The authors identified four compounds, bearing the pseudopterane skeleton. Kallolide A (**2**, 850 mg), kallolide A acetate (**3**, 300 mg), kallolide B (**4**, 100 mg), and kallolide C (**5**, 250 mg) were identified, with kallolide A (**2**) being the most abundant. Furthermore, kallolide A (**2**) was found to exhibit moderate anti-inflammatory activity at concentrations comparable to indomethacin, a potent nonsteroidal anti-inflammatory drug (NSAID). Interestingly, the publication by Fenical and Clardy was the only report of compounds isolated from *P. kallos* until the Rodríguez group began a systematic study of extracts nearly two decades later.

In 2003, Rodríguez isolated a new compound, kallosin A (**6**), as a minor metabolite (6.1 mg) alongside kallolide A (**2**, 359 mg) from *P. kallos*.[7] Kallosin A bears a rearranged kallane skeleton which presumably results from a C2–C3 σ-bond migration (see **Scheme 2.6**). Further insight into the biogenesis of these compounds will be explored in the next section. Kallosin was tested at a concentration of 500 μg/mL in the brine shrimp lethality bioassay but showed no *in vivo* cytotoxicity. Meanwhile, at the same concentration, kallolide A showed a 64% death response after a 24 h period. The authors speculate that, like kallolide A (**2**), kallosin A (**6**) has anti-inflammatory activity; however, there was not sufficient natural product to carry out further bioassays.

Another unique diterpenoid was isolated from *P. kallos* in 2003 by the same group, and named providencin (**7**, 20 mg).[8] In cell culture cytotoxicity screens at the NCI, it displayed modest activity against MCF7 breast cancer (57% growth inhibition compared to the untreated control), NCI-H460 nonsmall cell lung cancer (39% growth inhibition), and SF-268 CNS cancer (94% growth inhibition).

Ciereszkolide (**8**, 4.5 mg) was isolated from the same batch of *P. kallos* obtained from an animal specimen collected off the coast of Old Providence Island.[9] Ciereszkolide (**8**) possesses yet another novel ring system that likely arises from a C2 to C3 σ-bond migration from the cembrane skeleton, analogous to the ring contraction postulated in the biosynthesis of kallosin

A. Ciereszkolide showed no cytotoxic activity in the brine shrimp lethality bioassay at concentrations up to 500 μg/mL and did not inhibit growth of *Mycobacterium tuberculosis* H37Rv at 6.25 μg/mL.

In 2005, another unprecedented carbocyclic skeleton was identified from the extracts of *P. kallos*.[10] Intricarene (**9**, 4.0 mg) is derived from a cembrane skeleton that is quite common among *Pseutopterogorgia* metabolites; however, it differs by undergoing sequential C6–C11 and C2–C12 cyclizations. It was tested for growth inhibition of *Mycobacterium tuberculosis*, but only showed weak activity (15%) at a concentration of 128 μg/mL.

The following year, Rodríguez undertook an exhaustive study of the lipophilic extracts of *P. kallos*, and isolated fourteen metabolites.[11] Of the compounds isolated, kallolide A (**2**, 702.2 mg), kallolide A acetate (**3**, 213.4 mg), and kallolide C (**5**, 56 mg) had been previously identified in extracts of *P. kallos*.[6] Furthermore, 2-*O*-ethylkallolide A (**10**, 11.3 mg)[12], gersemolide (**11**, 27.1 mg)[13], bipinnapterolide A (**12**, 12.2 mg)[14], pinnatin B (**13**, 55.3 mg)[15], pinnatin D (**14**, 8.6 mg)[15], and gersolide (**15**, 5.3 mg)[16] had previously been isolated from other gorgonian corals. Five new, but related, pseudopterane metabolites were characterized: kallolide C acetate (**16**, 26.4 mg), kallolide E (**17**, 4.2 mg), kallolide G (**18**, 6.1 mg), kallolide H (**19**, 12.1 mg), kallolide I (**20**, 5.1 mg). The isolated compounds were tested for growth inhibition of *Mycobacterium tuberculosis* and *Plasmodium falciparum*. The most active anti-mycobacterial compounds were 2-*O*-ethylkallolide A (**10**) and gersemolide (**11**), showing 30.0% and 41.7% growth inhibition at 64 μg/mL, respectively. Gersemolide (**11**) and pinnatin B (**13**) were also most active in a DNA-based microfluorimetric anti-plasmodial assay with $IC_{50}$ values of 21.3 μM and 23.3 μM, respectively.

The most recent report of new compounds identified in extracts of *P. kallos* came in 2008, when the Rodríguez group identified seven new cembrane metabolites, named bipinnatin K (**21**, 7.5 mg), bipinnatin L (**22**, 4.4 mg), bipinnatin M (**23**, 140.9 mg), bipinnatin N (**24**, 22 mg), bipinnatin O (**25**, 27.8 mg), bipinnatin P (**26**, 2.7 mg), and bipinnatin Q (**27**, 27.1 mg), as well as known metabolite bipinnatin E (**28**, 6.1 mg).[17] The isolated compounds showed no appreciable anti-mycobacterial or anti-plasmodial activity; however, bipinnatin Q (**27**) displayed cytotoxic activity against various leukemia cell lines with $GI_{50}$ values of 2.6–5.8 μM. Bipinnatin E (**28**) was also shown to be a potent inhibitor of the acetylcholine-binding protein (AChBP) from *Aplysia californica* (Californian sea hare), with an $IC_{50}$ value of 0.23 μM.

Since the Rodríguez group had undertaken an exhaustive study of diterpene secondary metabolites in *P. kallos* between 2003 and 2008, no new compounds have been identified. There has been, however, a considerable effort to identify the biosynthetic pathways by which

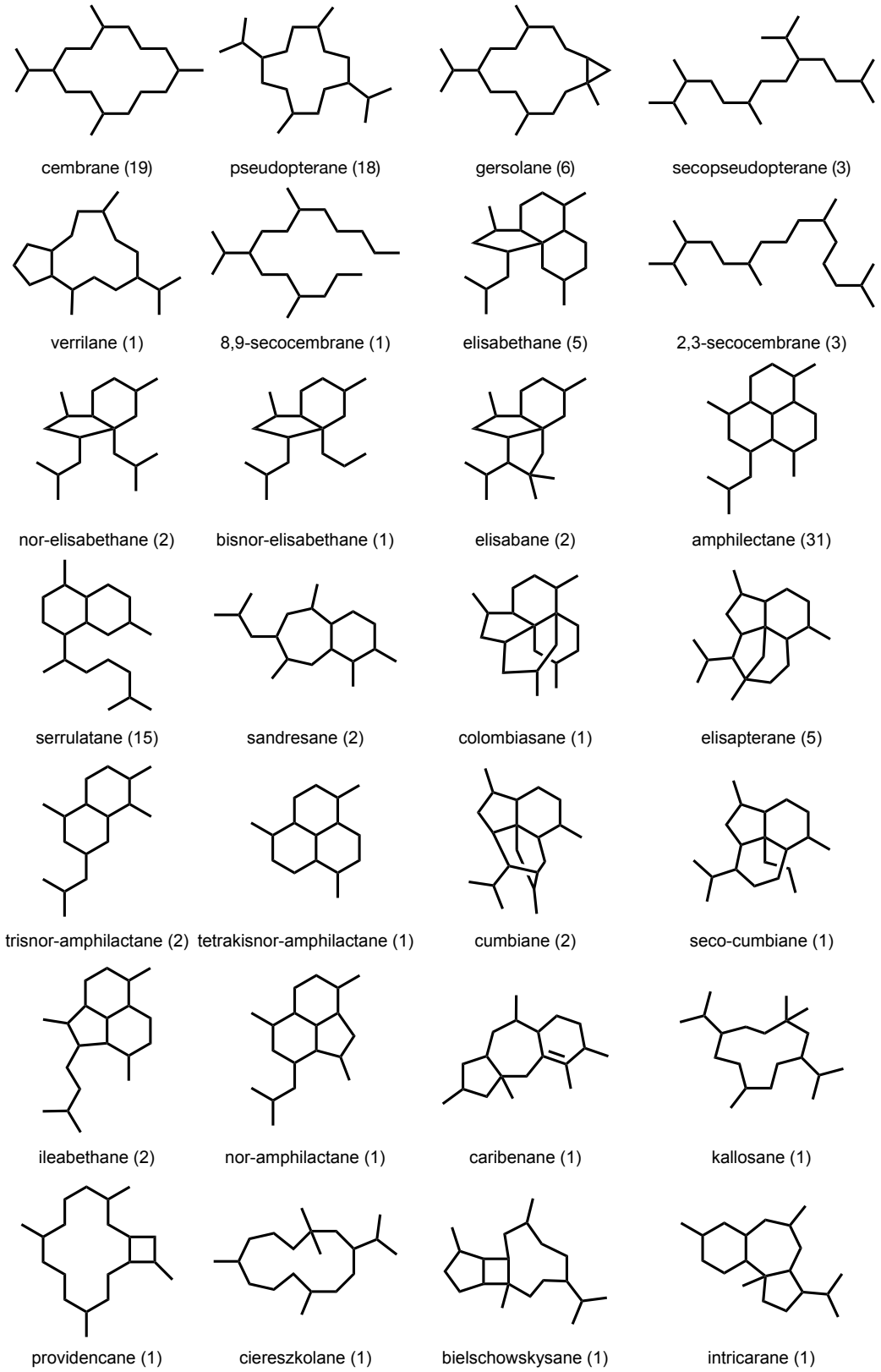
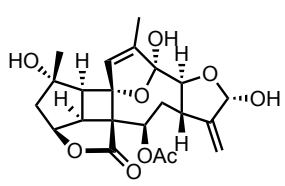
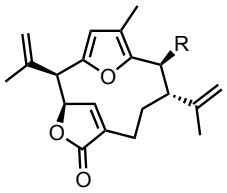


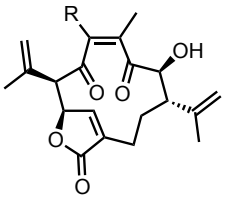

**Figure 2.1**: Skeletal classes of diterpenes isolated from genus *Pseudopterogorgia.* The frequency of occurrence of each class are shown in parentheses (1995-2008).[3]



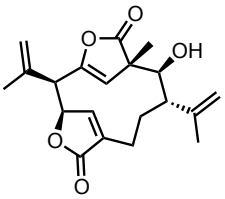
bielschowskysin (**1**)



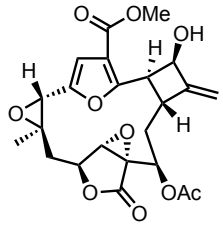
R = OH kallolide A (**2**)
R = OAc kallolide A acetate (**3**)
R = H kallolide B (**4**)
R = OEt 2-*O*-ethylkallolide A (**10**)



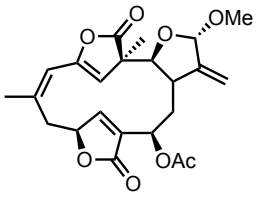
R = OH kallolide C (**5**)
R = OAc kallolide C acetate (**16**)



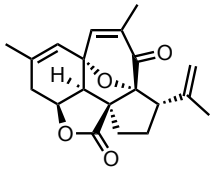
kallosin A (**6**)



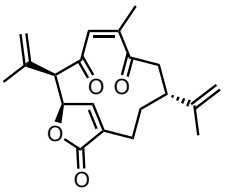
providencin (**7**)



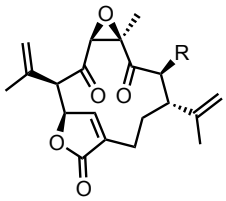
ciereszkolide (**8**)



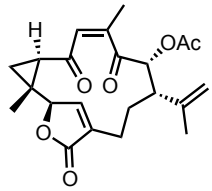
intricarene (**9**)



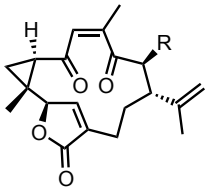
gersemolide (**11**)



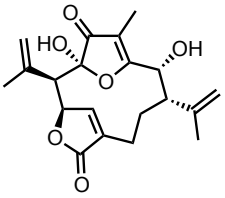
R = OH bipinnapterolide A (**12**)
R = OAc kallolide I (**20**)



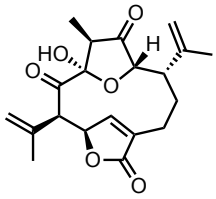
pinnatin B (**13**)



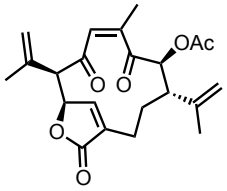
R = OH pinnatin D (**14**)
R = H gersolide (**15**)



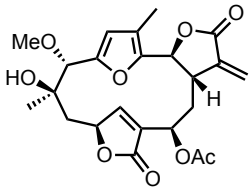
kallolide E (**17**)



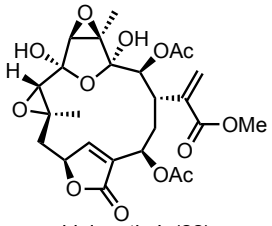
kallolide G (**18**)



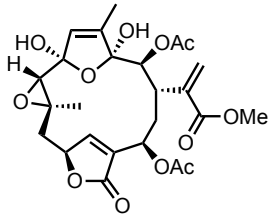
kallolide H (**19**)



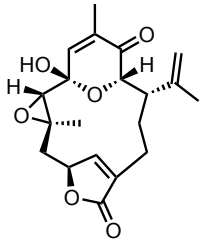
bipinnatin K (**21**)



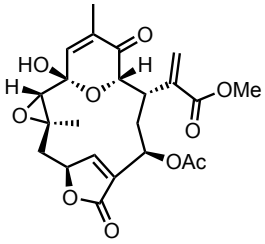
bipinnatin L (**22**)



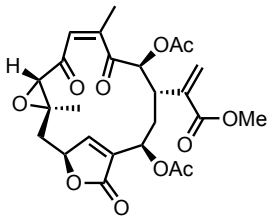
bipinnatin M (**23**)



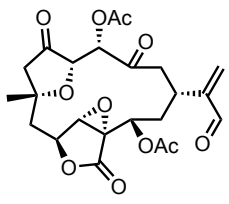
bipinnatin N (**24**)



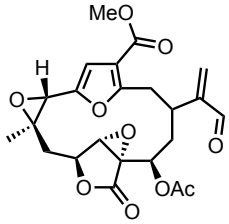
bipinnatin O (**25**)



bipinnatin P (**26**)



bipinnatin Q (**27**)



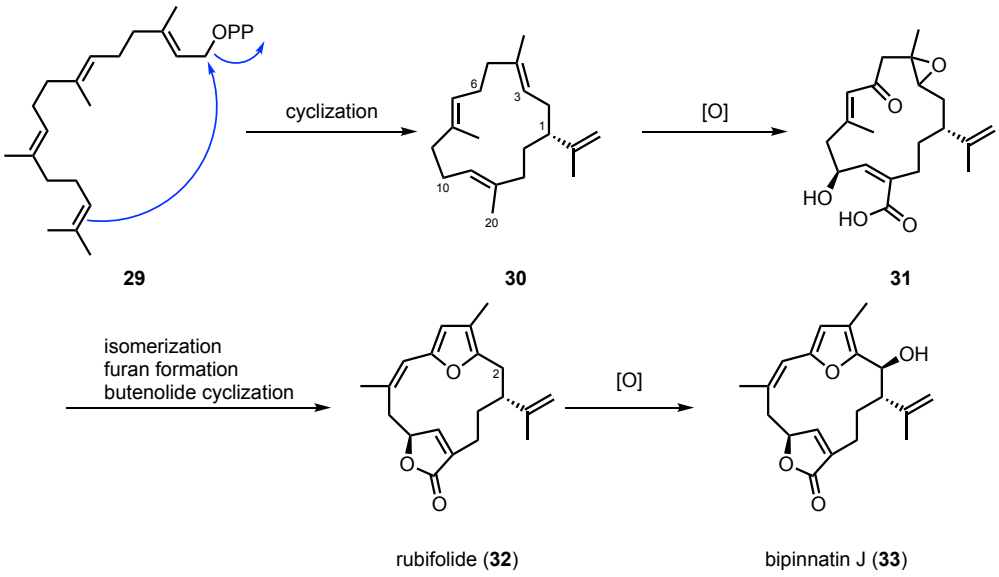
bipinnatin E (**28**)

**Figure 2.2**: Diterpenes isolated from *Pseudopterogorgia kallos.*

such a structurally diverse series of compounds arise. Furthermore, knowledge of the extent of related metabolites may give additional insight into the biogenic origin.

## 2.3 Biosynthesis

The first step for all diterpene biosyntheses starts with geranylgeranyl diphosphate (**29**, **Scheme 2.1**) and the subsequent C1–C2 cyclization to form a 14-membered ring that, upon loss of a proton and quenching of the carbocation, affords the macrocyclic natural product neo-cembrene (**30**, also known as cembrene A). It is interesting that, the C1 stereochemistry from the cyclization is conserved among nearly all furanocembrane natural products. A series of site-selective oxidations, presumably mediated by P450 monooxygenases, occur at C3, C6, C10, and C20 to yield the putative biosynthetic precursor **31**. Cyclization of the γ-hydroxy acid would form the butenolide ring and cyclodehydration of the epoxy-ketone moiety, in a manner analogous to the Paal–Knorr reaction, leading to pyrrole heterocycles, would furnish the furan unit of rubifolide (**32**). (The concomitant *Z–E* alkene isomerization is discussed below.) One can imagine yet another enzyme-mediated oxidation at C2 to provide bipinnatin J (**33**). It is worthwhile to note that neither rubifolide (*Gersemia rubiformis*) nor bipinnatin J (*Pseudopterogorgia bipinnata*) has been isolated from *P. kallos*.




**Scheme 2.1**: Biosynthesis of rubifolide and bipinnatin J.

One might recall that the first compounds isolated from *P. kallos*, the kallolides, do not bear the canonical cembrane skeleton. Rather, they contain the pseudopterolide skeleton,

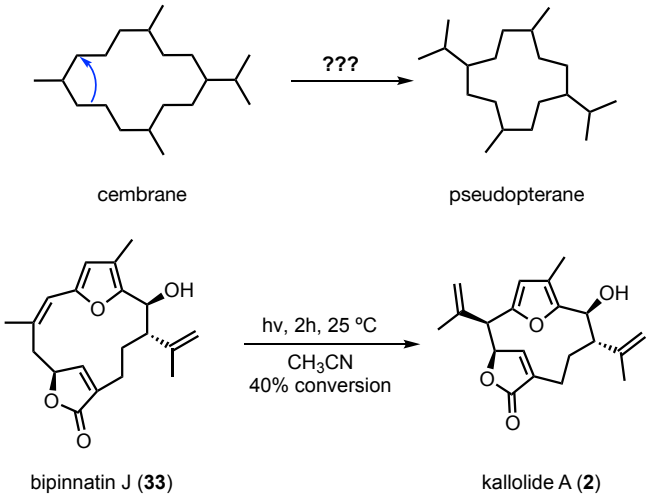
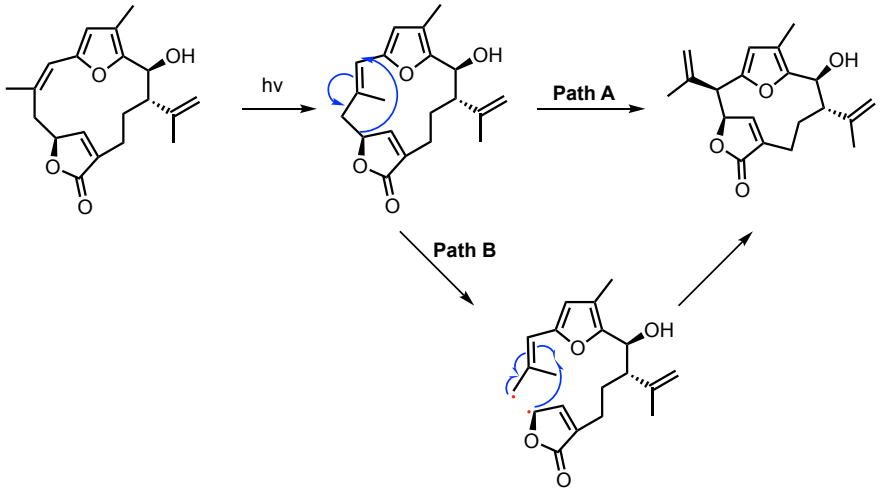
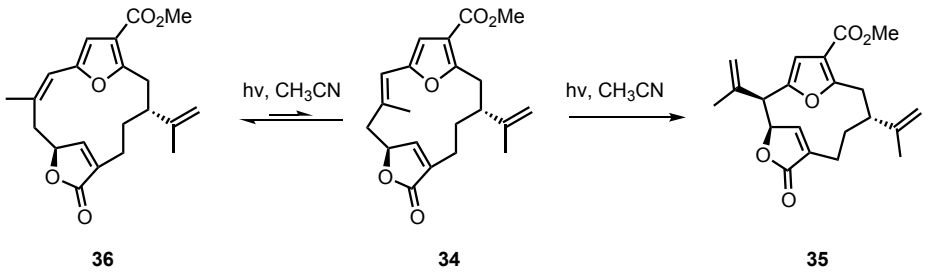



**Figure 2.3**: Cembrane-pseudopterane ring contraction.

which, as speculated by Fenical, could be the result of a ring contraction as shown in **Figure 2.3**.[18] Indeed, in 1998, Rodríguez and Shi demonstrated that the ring contraction of bipinnatin J (**33**) to kallolide A (**2**) readily occurs under photochemical conditions.[19] The rearrangement appears to be irreversible, as irradiation of **2** resulted only in decomposition, not ring expansion. Furthermore, that the stereochemistry at C10 is conserved throughout the process, led the authors to speculate that the reaction mechanism proceeds through a [1,3]-sigmatropic rearrangement rather than through a diradical intermediate. It is possible, however, that the mechanism of this rearrangement is stepwise, as shown in **Scheme 2.2**. Perhaps under photochemical conditions, bipinnatin J (**33**) could undergo *Z–E* isomerization, at which point the more strained E-isomer would then undergo either a thermal [$\pi^2 + \sigma^2$] rearrangement (Path A) or homolytic cleavage of the bis-allylic σ-bond followed by recombination (Path B).



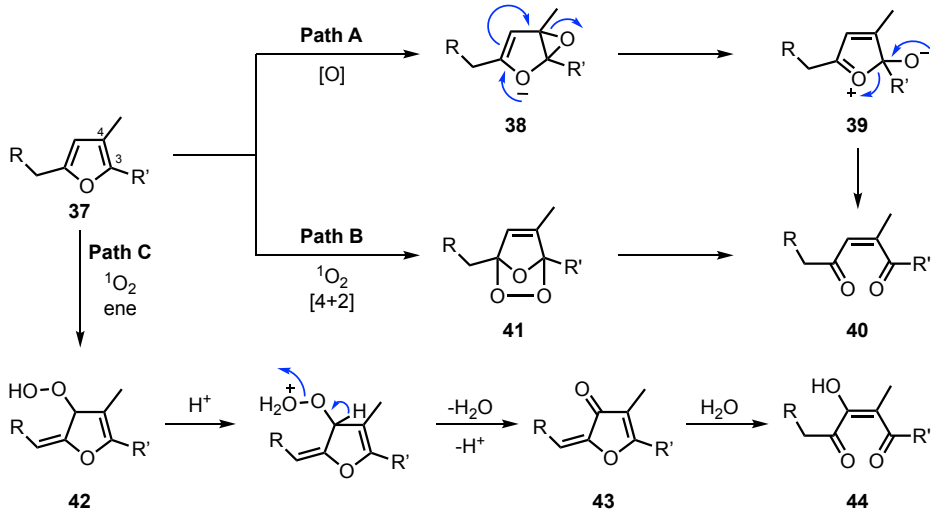

**Scheme 2.2**: Stepwise mechanisms of cembrane-pseudopterane ring contraction.




**Scheme 2.3**: Pattenden's synthesis of *E*-deoxypukalide and deoxypseudopterolide.

Indeed, the *Z–E* isomerzation of the C7–C8 π-bond has been documented. In 2010, the Pattenden group reported on the synthesis of *E*-deoxypukalide (**34**) and deoxypseudopterolide (**35**) from *Z*-deoxypukalide (**36**).[20] As shown in **Scheme 2.3**, irradiation of a solution of **36** in acetonitrile for 20 minutes led to a mixture of **34** and **36**, which were recovered in a 1:3.5 ratio. After iterative separation and irradiation, Pattenden and coworkers isolated E-deoxypukalide (**34**) in 60% yield, as an unstable product. After further irradiation of a solution of **34**, deoxypseudopterolide (**35**) was isolated in 90% yield. These results seem to lend credence to the stepwise mechanism mentioned above.

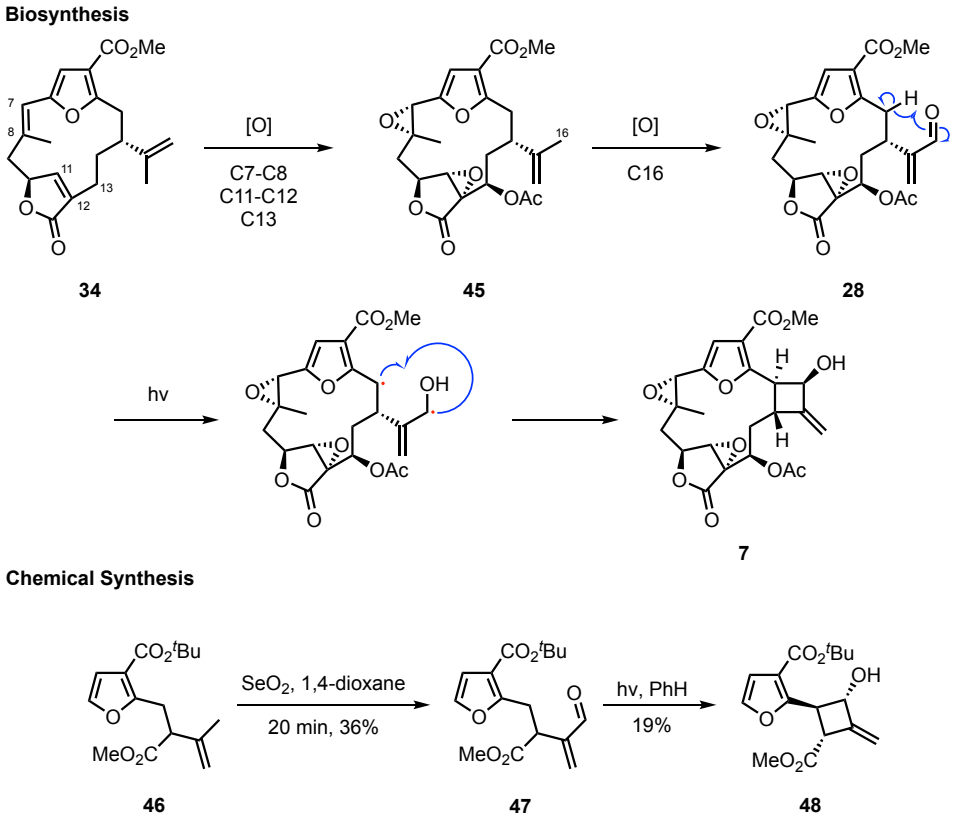
Of the large number of furanocembrane natural products that have been isolated from numerous species, only four compounds bearing the *E*-configuration at C7–C8 were reported as of 2011. It is noteworthy that many compounds that contain the C7–C8 epoxide would be derived from stereospecific oxidation of *E*-configured alkene precursors. Furthermore, the *in vivo* epoxidations are selective and lead almost exclusively to epoxidations from the α-face, leading to 7*S*-8*R* configurations.[21] The authors put forth two possibilities for the observed distribution of natural products: (1) the *Z*-alkene-derived epoxides are produced *in vivo*, but are




**Scheme 2.4**: Mechanisms of furan oxidation in furanocembranoids.

much more labile than the corresponding *E*-alkene-derived epoxides and thus are metabolized faster; or (2) the *E*-alkene natural products are generally less stable than the *Z*-alkene counterparts, and this instability has prevented isolation and characterization.

Besides alkene geometry, furanocembrane natural products diverge by variable furan oxidation state, which has been shown to exist in at least two different forms. As shown in **Scheme 2.4**, there are three possible mechanisms by which the initial furan oxidation can occur. In **Path A**, the furan ring (**37**) could undergo regioselective epoxidation at C3–C4 (likely an enzymatic process). The resulting epoxide (**38**) would then undergo intramolecular epoxide opening and ring cleavage via **39** to afford the commonly observed ene–dione moiety (**40**). Alternatively (**Path B**), the furan ring may be subjected to singlet oxygen [4+2] cycloaddition reaction to afford endoperoxide intermediate **41**. Peroxide cleavage then leads directly to ene–dione **40**. In the context of kallolide C (**5**), Fenical and Clardy[6] proposed a third possible mechanism by which the ene–dione moiety could be formed, albeit in a higher oxidation state (**Path C**). This mechanism, which proceeds via an ene reaction with singlet oxygen affords allylic hydroperoxide **42**. The hydroperoxide, after protonation, then undergoes fragmentation via 3(2H)-furanone intermediate **43** to the requisite ene–dione (**44**). This latter mechanism may

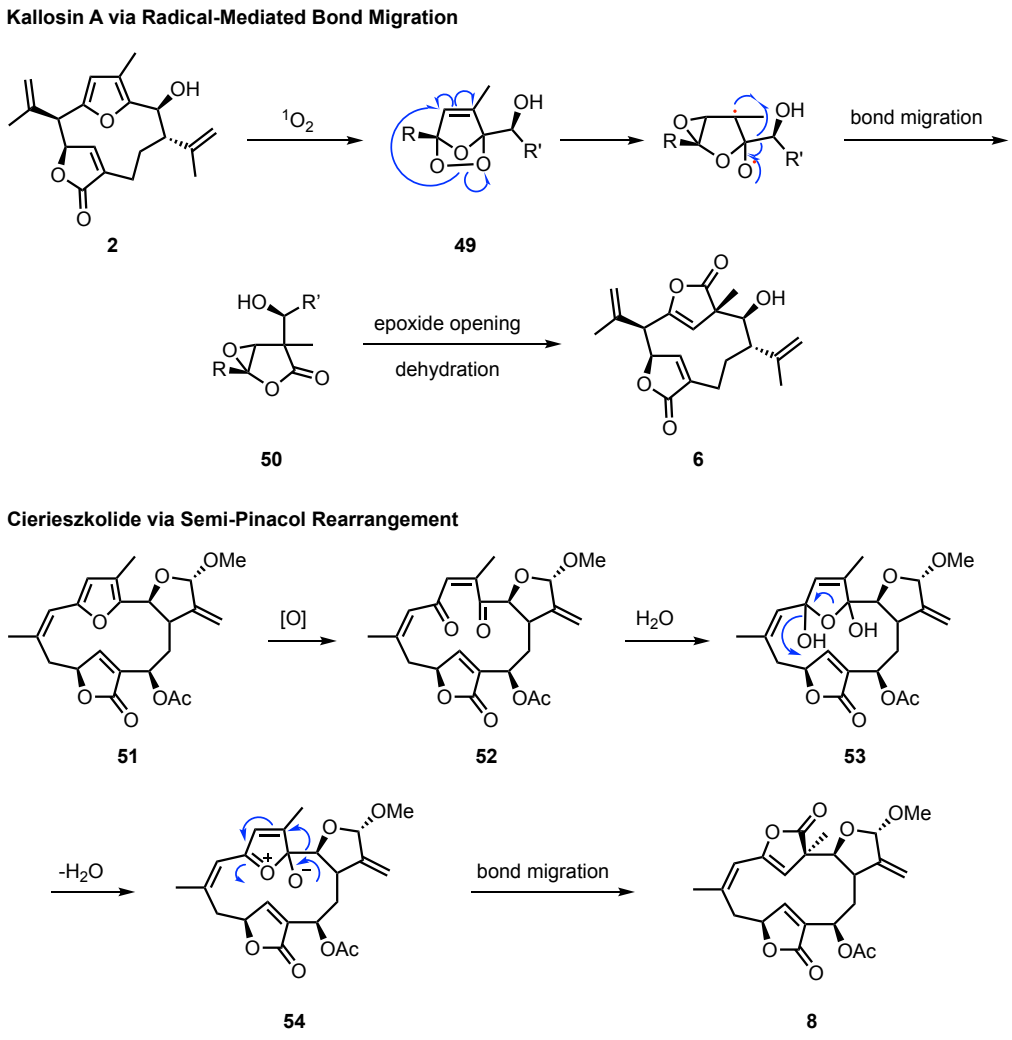



**Scheme 2.5:** Biosynthesis of providencin (**7**).

have some validity; Rodríguez later isolated structures containing this very moiety, trapped as the hemiketal (e.g., kallolide E, **17**).[11]

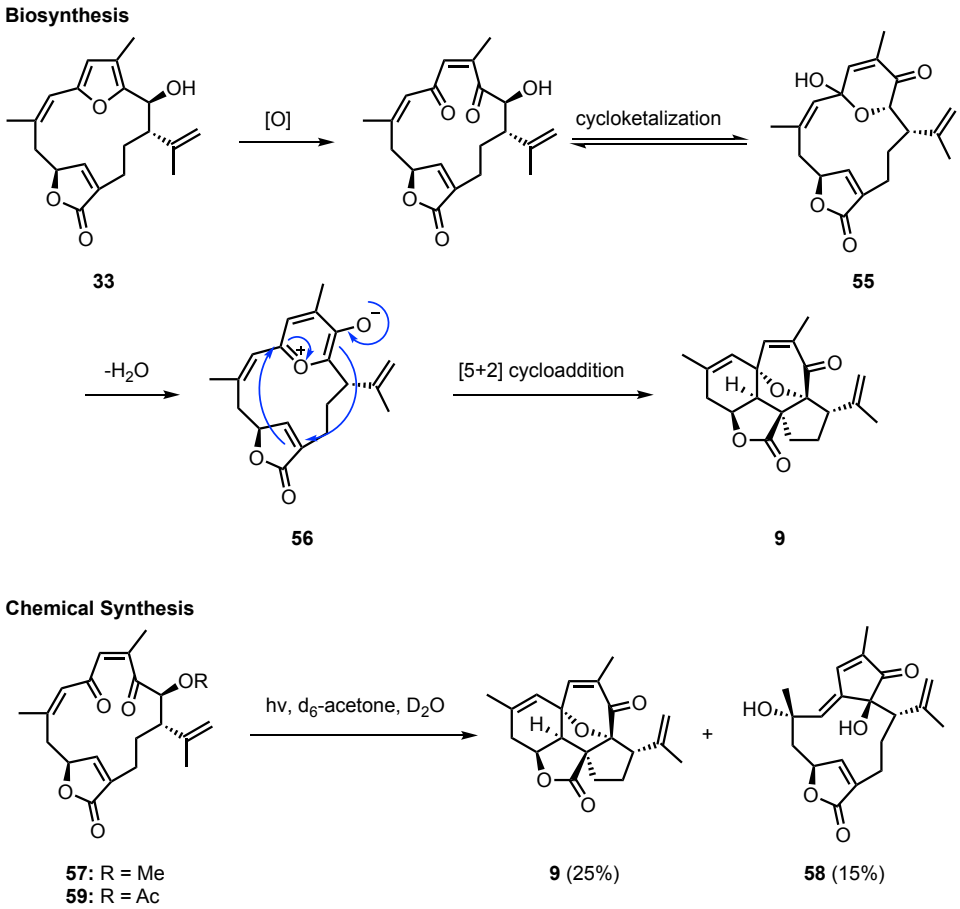
Providencin (**7**), one of the first of the metabolites of *P. kallos* to be isolated, bears a distinctly unique ring skeleton. Both Pattenden[21] and Trauner[22] have proposed that providencin is formed photochemically by a Norrish type II reaction of bipinnatin E (**28**), which, in turn, is generated from *E*-deoxypukalide (**34**) via lopholide (**45**) through a series of oxidations (**Scheme 2.5**). Bipinnatin E (**28**) has been found in extracts of *P. kallos* and the hypothesis has been supported by a synthetic study in the Pattenden group.[23] As shown in **Scheme 2.5**, furan **46** undergoes allylic oxidation to provide aldehyde **47,** which, upon irradiation, forms cyclobutanol **48** in a Norrish type II process.

Both ciereszkolide (**8**) and kallosin A (**6**) arise from a ring contraction of the cembrane and pseudopterane skeletons, respectively, through a migration of the C2–C3 σ-bond. In the




**Scheme 2.6:** Biosynthetic proposals of kallosin A (**6**) and ciereszkolide (**8**).

initial report on the isolation of **6**, Rodríguez proposed a radical mechanism for the bond migration.[7] As shown in **Scheme 2.6**, after oxidation of the furan ring with singlet oxygen, endoperoxide **49** is homolytically cleaved with concomitant bond migration to yield a hypothetical precursor **50**. Epoxide opening and subsequent dehydration would produce the 2(3H)-furanone of **6**. In the biosynthesis of ciereszkolide (**8**), Trauner[22] and Pattenden[21] have both invoked a semipinacol rearrangement, which could arise from the canonical oxidation of the furan ring of hypothetical precursor **51** to ene–dione **52**. Hydration of **52** would lead to **53**, which can undergo the requisite semipinacol rearrangement via oxonium **54** to lead to ciereszkolide (**8**) and furnish the 2(3H)-furanone ring system.

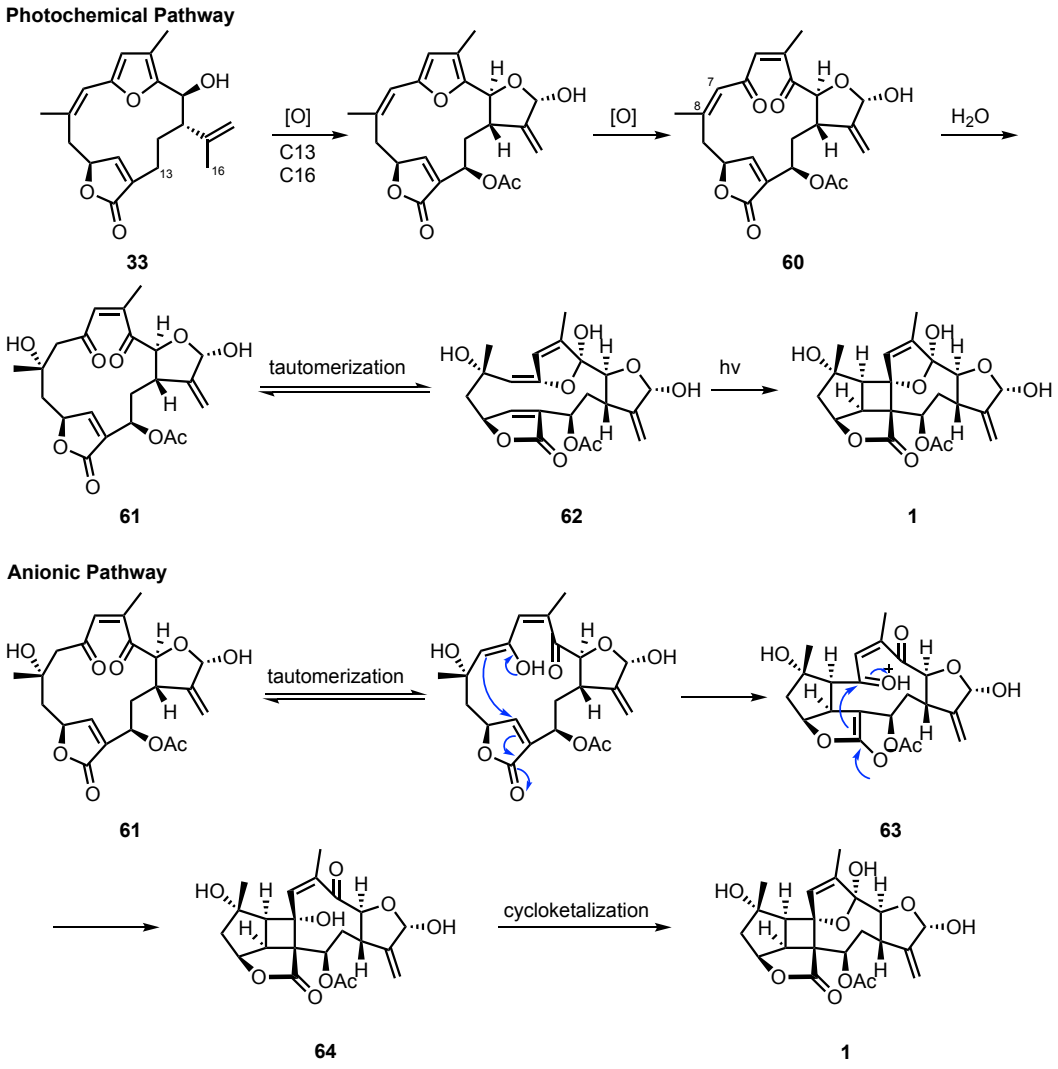



**Scheme 2.7:** Biosynthesis of intricarene (**9**).

The initial biosynthetic hypothesis for intricarene (**9**), shown in **Scheme 2.7**, put forth by Trauner[22] and Pattenden,[21] invokes bipinnatin J (**33**) as the biogenic precursor. After initial oxidative cleavage of the furan ring and tautomerization to hydroxypyranone **55**, dehydration would lead to the oxidopyrylium ion **56** as the cycloaddition precursor. A transannular [5+2]

cycloaddition between the oxidopyrylium ion and butenolide would produce (**9**). Both Trauner[24] and Pattenden[25,26] validated this hypothesis by way of total synthesis (see section 2.5.2 and 2.5.3), although the final cycloaddition required harsh conditions and was low yielding. Two years after Trauner's and Pattenden's reported syntheses, Tantillo published calculations exploring the possibility of whether or not this cycloaddition could be accomplished non-enzymatically.[27] It was determined that the cycloaddition itself had an activation barrier of ~20 kcal/mol in both polar and nonpolar environments, indicating that once generated, the oxidopyrylium ion would cyclize quite readily and without enzymatic aid. The dehydrative formation of the cycloaddition substrate, however, may not be as easy and might explain the harsh conditions needed to complete the synthesis *ex vivo*. It is noteworthy that, in 2008, bipinnatins N (**24**) and O (**25**), which bear the requisite pyranone precursor were isolated from *P. kallos*.[12] More recently, Trauner explored the possibility that **9** may be formed photochemically.[28] Indeed, upon irradiation with a reptile lamp, **57** yielded **9** in 25% yield (along with cyclopentenone **58** in 15% yield). The C2 acetate (**59**) and the pyranone precursor (**55**) failed to cyclize to **9** under identical conditions. Thus, while thermal cycloaddition is the likely pathway by which **9** is formed in nature, it cannot be ruled out that **9** is produced by a photochemical pathway either *in vivo* or as an artifact of the isolation procedure.

Speculation on the biosynthetic provenance of bielschowskysin (**1**) is interesting, as this compound is one of only a handful of cyclobutane-containing furanocembrane natural products. There are two prevailing hypotheses as to the mechanism of cyclobutane formation, both invoking bipinnatin J (**33**) as the biosynthetic precursor. The first proposal, put forth by Trauner[22] and elaborated upon by Pattenden,[21] involves a light-mediated transannular [2+2] cycloaddition (**Scheme 2.8**). After site-specific oxidations of C13 and C16 of **33**, the furan ring is thought to undergo oxidative cleavage, seen also in other natural products, to the ene–dione moiety (**60**). Hydration of the C7–C8 double bond to **61** and tautomerization would produce the cyclic enol ether as the putative cycloaddition substrate **62**. Subsequent [2+2] cycloaddition would lead directly to bielschowskysin (**1**). Alternatively, Pattenden suggested that the cyclobutane may be generated via an anionic mechanism.[21] From the same ene–dione intermediate **61**, a Michael reaction may be responsible for the C7–C11 bond, forming intermediate **63**, which is followed by an aldol reaction to form the C6–C12 bond and complete the cylcobutane **64**. Cycloketalization would then complete the biosynthesis of (**1**). Additional speculation regarding which of the two pathways is more plausible was added by Paton, who published the results of calculations exploring each possibility in 2015.[29] Although not working directly from ene–dione intermediate **61**, the authors explored the possibility of *5-exo-trig*




**Scheme 2.8:** Biosynthesis of bielschowskysin (**1**).

cyclization of cyclic enol ether **62**. They concluded that, in the case of the thermal (anionic) mechanism, the transformation has an activation barrier of ~22 kcal/mol in water, and thus it is possible that the ring formation may occur spontaneously. The thermal ring closure is also predicted to be 3–4 kcal/mol lower in the presence of enzyme catalysis. On the other hand, if exposed to light at ~280 nm, it is predicted that sensitization of the cyclic enol ether moiety would occur, resulting in a straightforward cyclization in the absence of enzymatic catalysis.

The findings above beg the question of whether light of the appropriate wavelength is accessible and can penetrate through the water to where the organisms were collected—the specimen of *P. kallos* from which bielschowskysin (**1**) was isolated was found at a depth of 25–28 meters.[5] In 1989, Fleischmann conducted studies to quantify the absorption of UV light in tropical seawater.[30] By using the photochemical isomerization of *o*-nitrobenzaldehyde (**Figure**

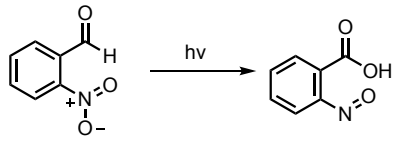



**Figure 2.4**: Photoisomerization of *o*-nitrobenzaldehyde.

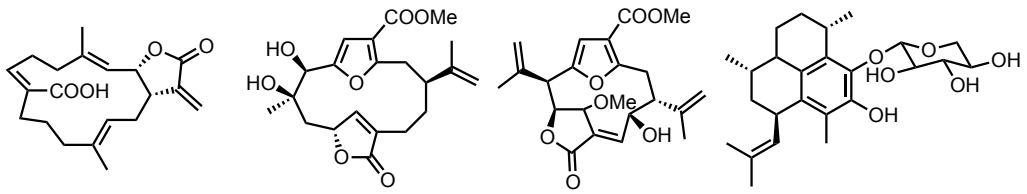
**2.4**), Fleischmann found that, at a depth of 25 meters, 10% of the surface intensity was still present. Furthermore, in Trauner's photochemical synthesis of intricarene (**9**), it was estimated that at a depth of 25 m, the total irradiance between 300 nm and 450 nm is approximately 90 W/m$^2$.[28] Compared to the integrated solar irradiance of ~1000 W/m$^2$ at the surface,[31] this is in agreement with the findings of Fleischmann. Thus, given that sensitization of the putative biosynthetic precursor **62** at 280 nm, it is likely that sufficient UV irradiation reaches the organism, resulting in production of **1** *in vivo*.

## 2.4 Symbiosis & Biological Function

The presence of such a diverse trove of diterpene secondary metabolites certainly makes one wonder about their function of these compounds *in vivo*. Although *P. kallos* has not been described other than the isolation reports of Fenical, Clardy,[6] and Rodríguez,[5,7–11,17] other species of the genus *Pseudopterogorgia* have been studied. One can make an extrapolation can be made, to some extent, as to the biological function of naturally occurring diterpenes.

In an earlier communication, Fenical summarized some of the anti-inflammatory and analgesic activity of diterpenes isolated from various *Pseudopterogorgia* gorgonians, including kallolides **2**, **4**, and **5**.[18] Fenical concludes that the diterpenes function primarily as a chemical defense system for the corals in their natural habitat. However, he goes on to speculate that, based on the preponderance of unique prostaglandin derivatives in other species of gorgonian corals, it is possible that the function of some of these diterpenoids has evolved to regulate arachidonic acid metabolism.

In 2015, Fernandez published a review of marine diterpenoids as potential anti-inflammatory agents.[32] Although none of the compounds discussed here are found in *Pseudopterogorgia* species, several members of the cembrane class of diterpenoids (e.g. **65, 66**, **Figure 2.5**) have been shown to inhibit the expression of iNOS and/or COX-2 while other cembranes have been shown to modulate the NFκB signaling pathway. Furthermore, it was shown that some pseudopterane derivatives (**67**) inhibit either the secretion or the mRNA expression of various inflammatory mediators, including TNF-α, iNOS, and COX-2. The authors suspect that this was because of the inhibition of IκBα phosphorylation and, as a result, the




lobohedleolide (**65**) sinumaximol B (**66**) **67** pseudopterosin A (**68**)

**Figure 2.5**: Selected anti-inflammatory marine diterpenes.

activation of NFκB was suppressed. Pseudopterosin A (**68**) is a glycosylated tricyclic diterpene that has been shown to to inhibit prostaglandin $E_2$ and leukotriene $C_4$ secretion.

Perhaps more significant than the anti-inflammatory activity of gorgonian-derived diterpenes is the modestly potent cytotoxicity that many of the compounds display. This observed phenotype certainly lends credence to Fenical's initial conclusion that these compounds serve primarily as a defense mechanism. In a seminal publication, Randall reported that only eleven of 212 species of reef fish consumed gorgonians (via analysis of gut contents) and that only one consumed gorgonians in excess of 5% of its total diet.[33] This disparity is indeed surprising, as gorgonian corals are among the most abundant organisms in the Caribbean reefs.[34] Pawlik has noted that there are three possibilities for this disparity:[35] (1) the presence of secondary metabolites providing chemical defense systems, (2) the presence calcitic sclerites providing physical defense systems, or (3) the lack of sufficient nutrition. Pawlik concluded that, when fed with food pellets containing crude organic extracts of gorgonian corals, the pellets from all species (32 in total, including six *Pseudoptorogorgia* species) were considered deterrent to the assay organism (*Thalassoma bifasciatum*, one of the most abundant reef fishes throughout the Caribbean). To test whether or not the sclerites act as a physical defense system, pellets were imbued with spicules of gorgonians and fed to the assay organism. Pellets made from all but two species were not considered deterrent. Furthermore, the authors found that there was not a relationship between deterrence and the nutritional quality of the gorgonians. Thus, based on these results, it appears that the chemistry of secondary metabolites is the most operative defense system for gorgonians.

Another major question about these marine diterpenes concerns their production *in vivo*. Namely, are these compounds truly secondary metabolites of gorgonian corals? Or, as has been more recently speculated, are they produced by a different organism, living in symbiosis with the coral? The symbiosis between invertebrates and algae has been known for quite some time.[36] More recently, studies were undertaken to determine which species is responsible for the biosynthesis of interesting compounds, including diterpenes.

To the best of my knowledge, the first definitive report on diterpene biosynthesis by a symbiont of *Psuedopterogorgia* appeared in 2003, when Jacobs published a study of the

biosynthesis of pseudopterosin.[37] The authors found that regions of the coral (*P. elisabethae*) where there was a greater distribution of symbiont (*Symbiodinium* sp.) cells correlated with the concentration of pseudopterosins (e.g. **68**) per coral weight. Furthermore, the concentration of pseudopterosins was found to be greater in the purified *Symbiodinium* sp. cells (11%) when compared to the lipid extract of *P. elisabethae* (5%). To confirm the hypothesis that *Symbiodinium* sp. is responsible for pseudopterosin biosynthesis, the authors incubated purified cells in the presence of $^{14}$C-labeled sodium bicarbonate ($NaH^{14}CO_3$) under ambient light, and they were able to isolate $^{14}$C-labeled pseudopterosins. When incubated with $NaH^{14}CO_3$ either in the dark or in the presence of mevastatin sodium (a known inhibitor of the mevalonic acid pathway), radio-labeled pseudopterosin incorporation did not occur. Furthermore, when purified cells were incubated in the presence of $^{3}$H-GGPP, tritium-labeled pseudopterosins and diterpene precursors were observed. These observations indicate clearly that *Symbiodinium* sp. is capable of—and likely responsible for—pseudopterosin biosynthesis and that it is dependent on the photosynthetic processes of the algal cells. Similar results were observed in a later examination of kallolide A (**2**) biosynthesis in *P. bipinnata*.[38] The hypothesis was further substantiated when Kerr induced pseudopterosin biosynthesis in purified *Symbiodinium sp*. after treatment with methyl jasmonate, a compound known to induce *de novo* terpene biosynthesis in plants.[39]

Thus, it appears that there does in fact exist a symbiotic relationship between dinoflagellates and various species of gorgonian corals. The tradeoff ostensibly seems quite simple: the gorgonian corals grow in areas where they are exposed to at least partial sunlight for the photosynthetically dependent symbionts, and, in exchange for growing in such a vulnerable location, they are imbued with a chemical defense system in the form of, for example, a variety of diterpenes. Furthermore, this can explain why photochemical transformations may be invoked in the biosynthesis of many of these compounds (e.g., **1**).

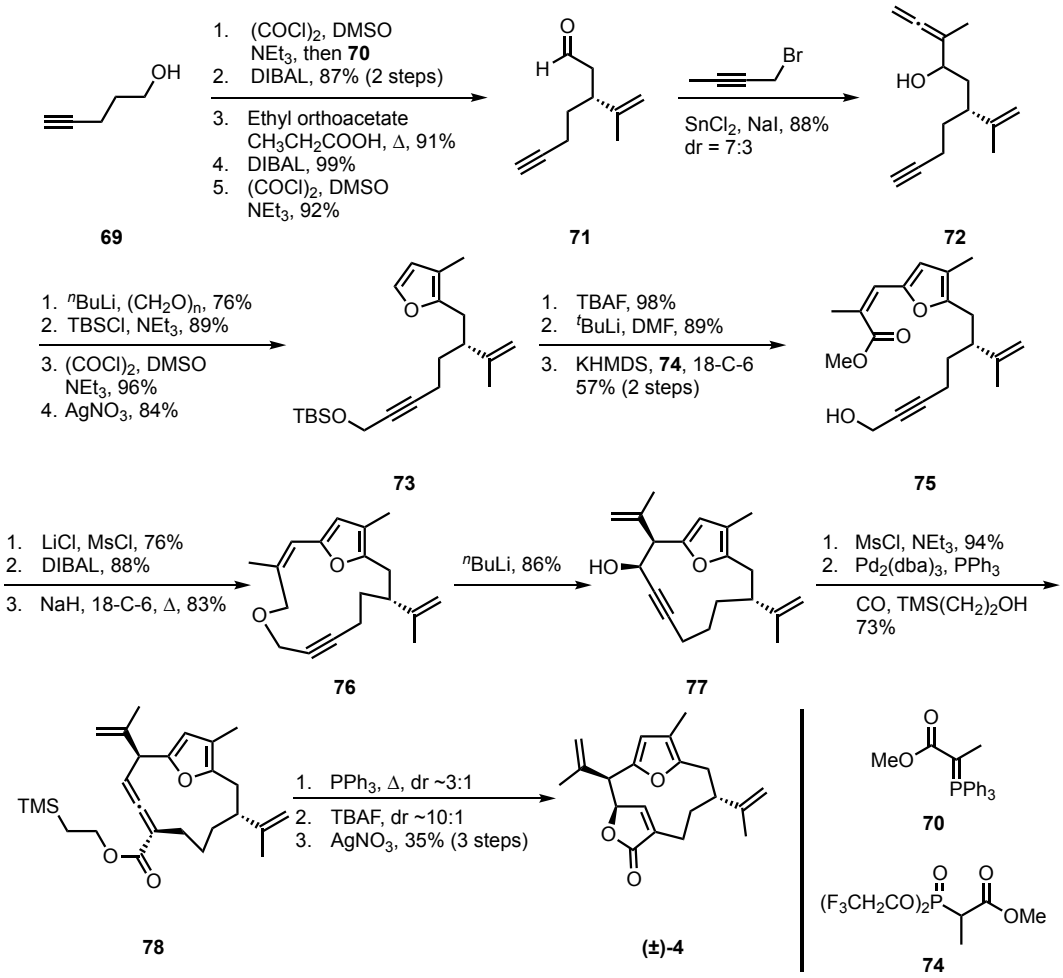
### 2.5 Synthetic Efforts Toward Related Natural Products

There has also been considerable interest from the synthetic community in the diterpene secondary metabolites of gorgonian corals. The interest is mainly because of the unique ring systems featured in many of these natural products, but the interesting biological activity paired with the relative scarcity from natural sources could also be a factor in the pursuits of total synthesis. Despite the interest, only three (**2**, **4**, and **9**) of the 28 known metabolites of *P. kallos*, have been prepared by chemical synthesis. Fragments or advanced

intermediates of two compounds (**1** and **7**) have been synthesized, but their total synthesis remains elusive.

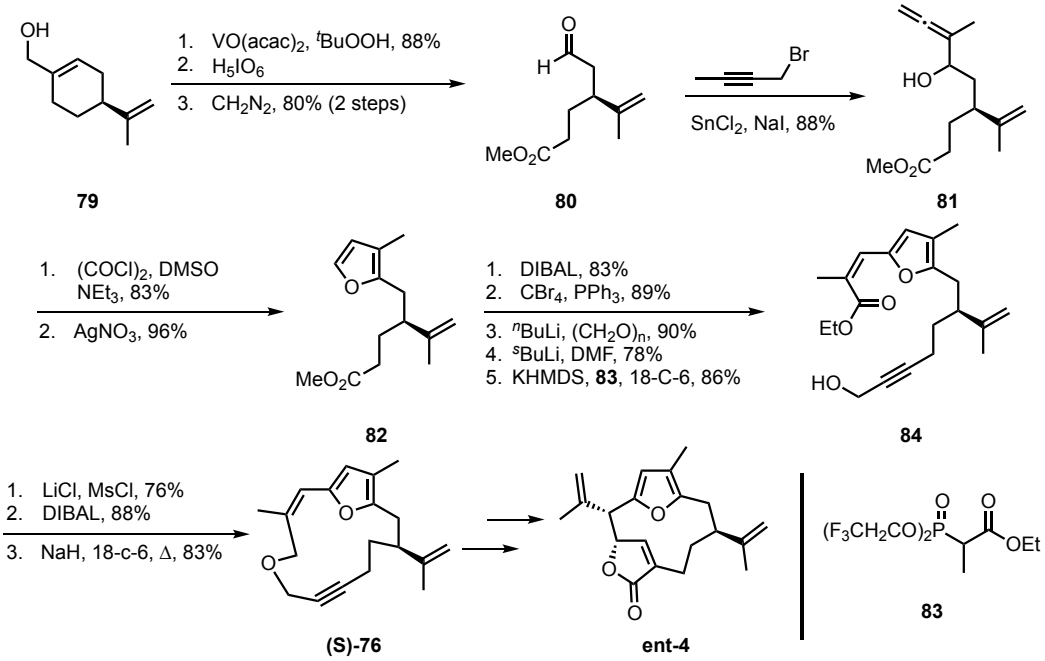
### 2.5.1 Marshall's Synthesis of Kallolides A & B

The first total synthesis of a diterpene metabolite of *P. kallos* was reported by Marshall in 1995, with the synthesis of (±)-kallolide B [**(±)-4**].[40] As shown in **Scheme 2.9**, the synthesis began with 4-pentynol (**69**), which was converted to aldehyde **71** in five steps. Tin(II)-mediated addition of the propargylic bromide afforded allenic alcohol **72**, which, after hydroxymethylation of the terminal alkyne and selective silylation of the propargylic alcohol, enabled selective Swern oxidation of the allenic alcohol to the corresponding ketone. Silver(I)-catalyzed cycloisomerization then yielded furan **73**. Desilylation followed by furan metallation and formylation afforded an intermediate furfural derivative which was then homologated with by a




**Scheme 2.9**: Marshall's synthesis of (±)-kallolide B.

Still-Gennari olefination with phosphonate **74** to produce *Z*-enoate **75**. After functional group interconversion leading to the propargylic chloride and reduction of the methyl ester, the macrocycle **76** was formed upon treatment of the primary allylic alcohol with NaH and 18-C-6. Upon exposure to $^{n}$BuLi, ether **76** underwent a [2,3]-Wittig ring contraction to afford propargylic alcohol **77** as the sole diastereomer. Mesylation of the resulting secondary alcohol and subsequent treatment with Pd(0) in the presence of CO furnished allenic ester **78**. The α-carbon of alleneoate **78** was epimerized with a catalytic amount of $PPh_3$, and the stereochemistry was further enriched by TBAF-mediated cleavage of the ester. Finally, cyclization of the free acid onto the allene furnished the butenolide and completed the synthesis of **(±)-4**.

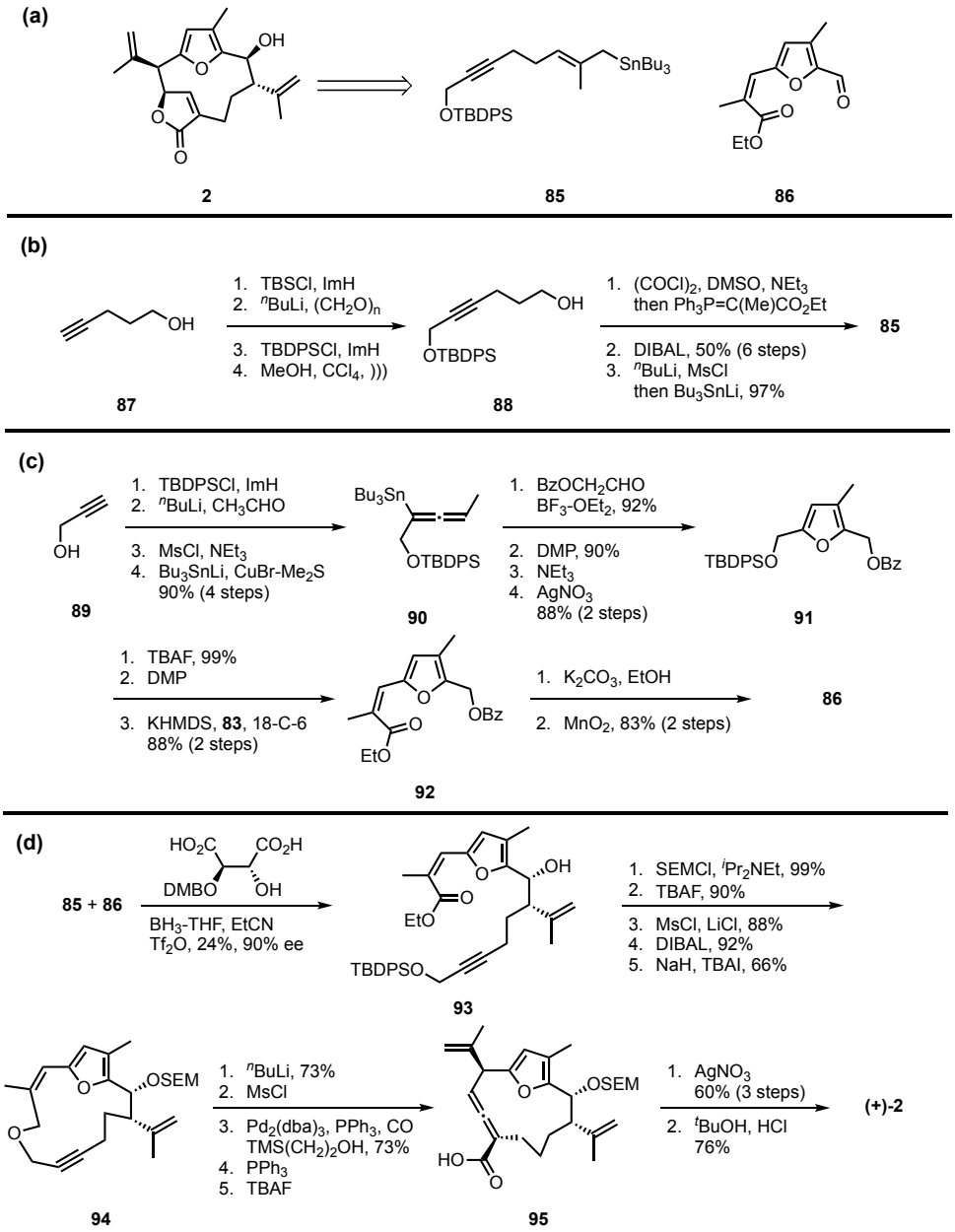



**Scheme 2.10**: Marshall's synthesis of *ent*-kallolide B.

Marshall was able to achieve a enantioselective synthesis the following year by choosing (*S*)-(–)-perillyl alcohol (**79**) as the starting material.[41] Thus, hydroxyl-directed epoxidation of **79** followed by oxidative cleavage and esterification afforded enantiopure aldehyde **80** (**Scheme 2.10**). From this point on, the synthesis followed roughly the same path as that of the previous route, which produced the racemate, differing only in the way in which the propargylic alcohol was installed. The methyl ester of **82** was semi-reduced and the resulting aldehyde was first homologated using $CBr_4$ and $PPh_3$. The corresponding dibromoolefin was then homologated once again by treatment with $^{n}$BuLi and quenching with

paraformaldehyde. Five additional steps that were analogous to those in the earlier synthesis afforded enantiopure macrocyclic ether **(S)-76**. Following the previous route, they completed the synthesis of *ent*-(**4**). It is noteworthy that upon exposure to air (13 days) or oxygen (3 days), no oxidation of the furan ring was observed. It is thus unlikely that natural products bearing an ene–dione moiety, such as **5** or **11**, are artifacts of oxidation during their isolation.

Marshall's synthetic studies of the kallolides concluded with a stereoselective synthesis of kallolide A (**2**).[42] The synthesis borrowed some features from their earlier work on **4**, including the [2,3]-Wittig ring contraction and stereoselective installation of the butenolide ring from a

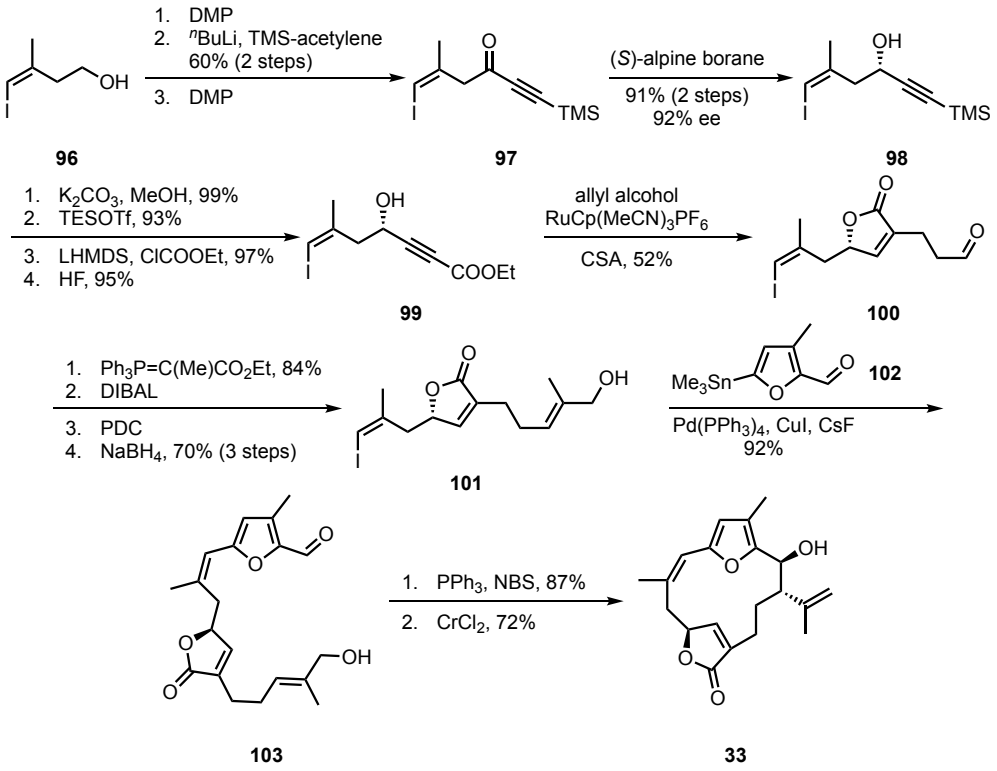



**Scheme 2.11**: Marshall's synthesis of kallolide A.

chiral allene. As shown in **Scheme 2.11(a)**, Marshall opted to use a convergent approach, employing an enantioselective addition of allylstannane **85** to aldehyde **86**. Allylstannane **85**, in turn, was prepared in seven steps from 4-pentyn-1-ol (**87, Scheme 2.11(b)**). Of note in this sequence is the chemoselective desilylation of the primary TBS group by using a mixture of MeOH and $CCl_4$ under ultrasound conditions to afford alcohol **88**. Finally, after oxidation, Wittig homologation, and reduction, the allylstannane was prepared by displacement of mesylate, generated the *in situ* with $Bu_3SnLi$. Shown in **Scheme 2.11(c)**, the synthesis of aldehyde **86** began with protection and homologation of propargyl alcohol (**89**). The resulting secondary alcohol was converted to the corresponding mesylate and displaced with $Bu_3SnLi$ in an $S_N2'$ fashion to afford allenylstannane **90**, which was then added to α-(benzoyloxy)-acetaldehyde in a $BF_3{\bullet}Et_2O$-mediated $S_E2'$ reaction. The resulting secondary propargylic alcohol was then oxidized with Dess–Martin periodinane and, upon treatment with $NEt_3$, the propargyl ketone was isomerized to the corresponding allenyl ketone. Silver(I)-mediated cycloisomerization then produced furan **91**. Desilylation, oxidation, and Still–Gennari olefination furnished ester **92**. Finally, ethanolysis of the benzoate followed by oxidation produced aldehyde **86**. The addition of allylstannane **85** proceeded smoothly under Lewis acid conditions ($BF_3{\bullet}OEt_2$) to afford **(±)-93** in 99% yield. However, when the reaction was attempted under asymmetric conditions (**Scheme 2.11(d)**) with the tartrate-derived ligand shown, the yield dropped considerably, albeit with good enantioselectivity. Thus, protection of the resulting secondary alcohol in **93**, followed by desilylation of the primary alcohol, conversion to the propargyllic chloride, reduction of the ester, and treatment with NaH produced macrocycle **94**. The [2,3]-Wittig rearrangement proceeded in a manner analogous to the synthesis of **4** with excellent diastereoselectivity. The remainder of the synthesis followed the same path as the previous route, including palladium(0)-catalyzed carbonylation, and $PPh_3$-mediated isomerization of the allene to afford, after deprotection, carboxylic acid **95**. The butenolide was formed by silver(I)-catalyzed cycloisomerization and, finally, the secondary alcohol was solvolyzed in acidic media to afford **2**. Marshall also reported the synthesis of kallolide A acetate (**3**) when the solvolysis was performed in the presence of acetic acid. Thus, the absolute configurations of **2** and **3** were confirmed by total synthesis.

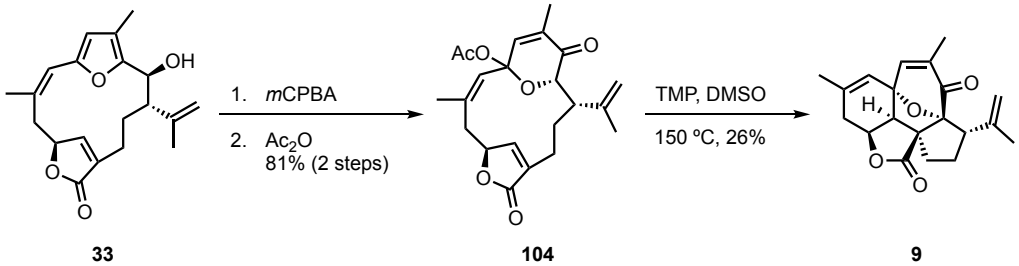
### 2.5.2 Trauner's Synthesis of Intricarene

Trauner's approach to the total synthesis of intricarene (**9**) stems from the biosynthetic hypothesis that assumes it is derived from bipinnatin J (**33**). Thus, his synthetic goal was




**Scheme 2.12**: Trauner's synthesis of bipinnatin J.

initially directed toward the total synthesis of **33**.[24] As shown in **Scheme 2.12**, he developed a concise asymmetric synthesis of **33**, starting from vinyl iodide **96**. Oxidation of the primary alcohol followed by the nonselective addition of lithium (trimethylsilyl)acetylide to the aldehyde and oxidation furnished alkynone **97**. The asymmetry was induced via a reagent-controlled Midland reduction to afford propargyllic alcohol **98** in good yield and with a high level of enantioselectivity. The butenolide ring was then created using a ruthenium-catalyzed Alder–ene reaction. Aldehyde **100** was then subjected to Wittig olefination and reduction with DIBAL. Under the reported reduction conditions, the butenolide ring underwent partial reduction to the lactol, thus the need for reoxidation and a milder $NaBH_4$ reduction to produce allylic alcohol **101**. Stille coupling of the vinyl iodide with furylstannane **102** furnished alcohol **103**, which,

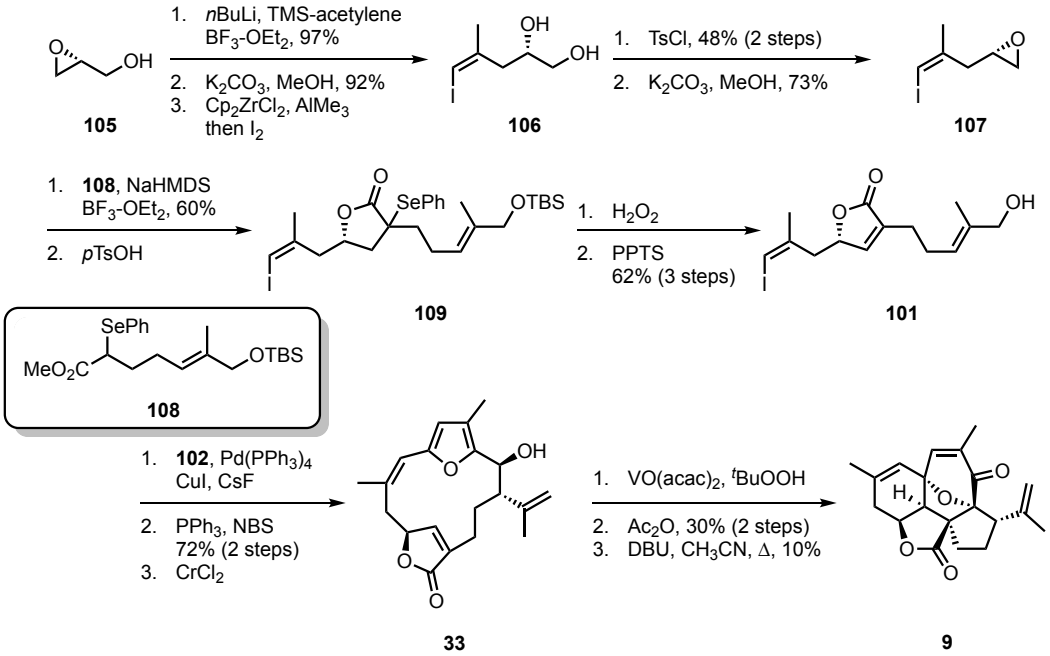



**Scheme 2.13**: Conversion of bipinnatin J into intricarene.

after conversion to the bromide and macrocyclization under Nozaki–Hiyama–Kishi (NHK) conditions, afforded bipinnatin J (**33**) as a single diastereomer and with retention of the sensitive stereocenter in the butenolide ring. With **33** in hand, the conversion to intricarene (**9**) was rather uneventful (**Scheme 2.13**). By incorporation of the Achmatowicz strategy, **33** was treated with *m*CPBA and underwent smooth oxidative rearrangement to furnish, after acylation, pyranone **104**. The final, biomimetic, cycloaddition (cf. **Scheme 2.7**) occurred upon treatment with tetramethylpiperidine to generate the oxidopyrylium intermediate, through the elimination of acetic acid, and complete the synthesis of intricarene (**9**). Later, Trauner was also able to synthesize **9** photochemically,[28] demonstrating that such harsh conditions (base, 150 ºC) may not be necessary to form **9** *in vivo* (see section 2.3).

### 2.5.3 Pattenden's Synthesis of Intricarene

Concurrent with Trauner's initial communication on the total synthesis of intricarene (**9**), the Pattenden group independently published their own total synthesis of (**9**). Like Trauner's approach, Pattenden's strategy relies on a late-stage, biomimetic [5+2] cycloaddition from a pyranone intermediate that can be accessed from bipinnatin J (**33**).[25, 26] As shown in **Scheme 2.14**, Pattenden opted to begin the synthesis with (+)-glycidol (**105**) as a means to set the initial stereochemistry, thus avoiding the need for reagent-controlled induction of stereochemistry as

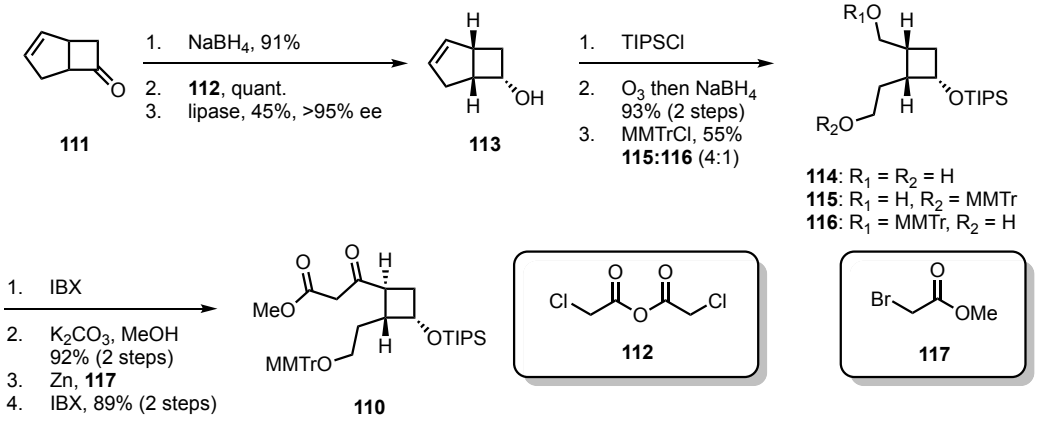



**Scheme 2.14**: Pattenden's synthesis of intricarene.

was done Trauner's synthesis. Opening of the epoxide with the lithium acetylide followed by desilylation afforded a terminal alkyne that was then carbometallated and isomerized to afford, after quenching with $I_2$, (*Z*)-iodoalkene **106**. Conversion of the diol into epoxide **107** via the intermediate primary tosylate was straightforward. The epoxide was then opened with the α-selenyl enolate derived from **108** to produce, after acid-catalyzed lactonization, lactone **109**. Oxidative selenoxide elimination followed by deprotection of the primary allylic alcohol afforded butenolide **101**, which intersected with Trauner's synthesis shown above, albeit in four fewer steps. In a similar manner, bipinnatin J (**33**) was prepared by Stille coupling, Appel reaction, and chromium(II)-mediated NHK macrocyclization. Finally, furan oxidation, acetylation, and [5+2]-cycloaddition through the same oxidopyrylium intermediate completed the synthesis of **9**.

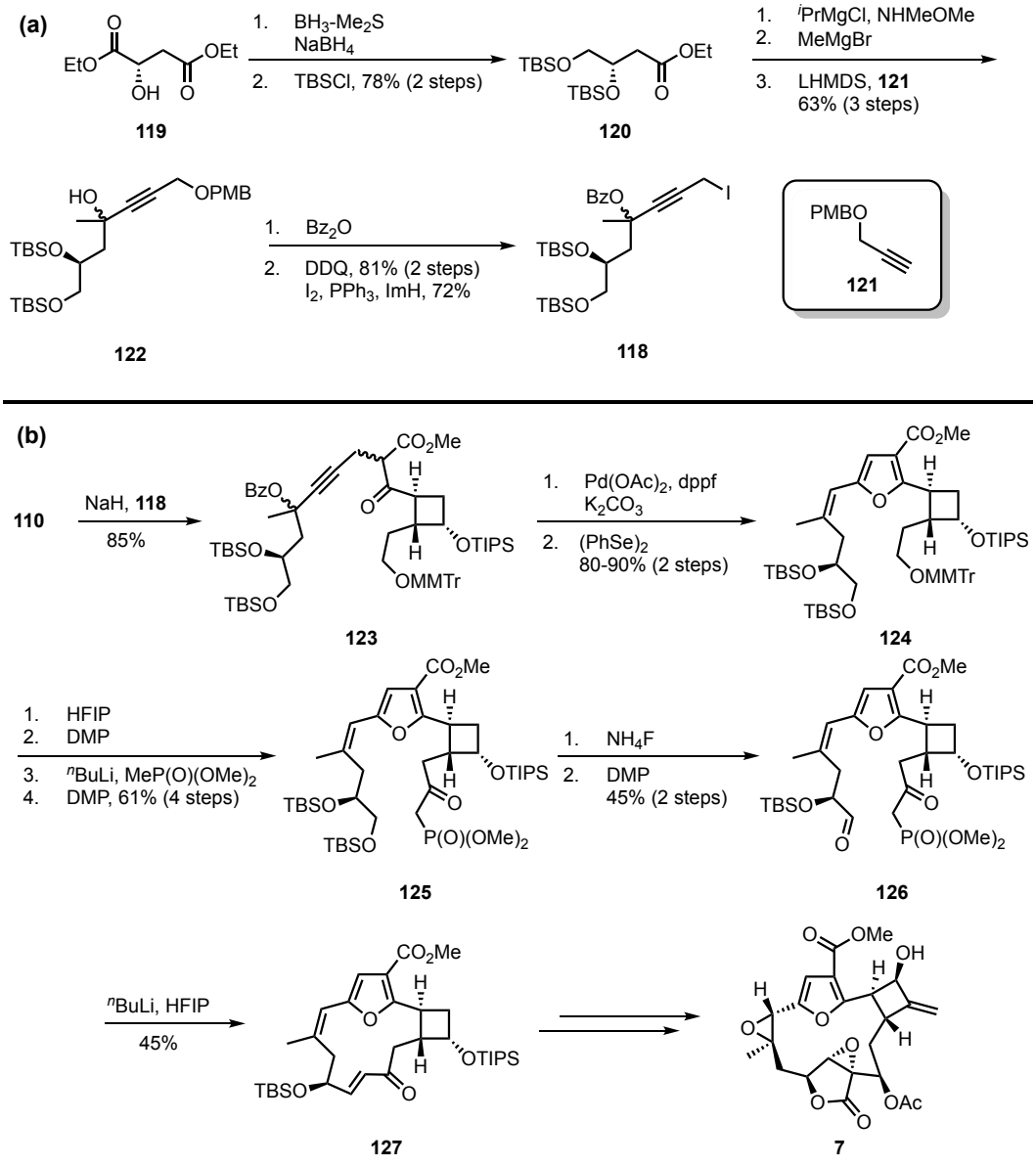
### 2.5.4 Mulzer's Approach Toward Providencin

The first published report on the synthesis of providencin (**7**) came from the Pattenden lab in 2006, although the extent of the report is a biomimetic approach to the substituted cyclobutane moiety (see **Scheme 2.5**).[23] The Mulzer lab then embarked on a thorough synthetic program during which they were able to access several advanced intermediates, although they were never able to complete the synthesis of **7**. The initial communication by Mulzer described an asymmetric approach to the cylobutane fragment (**110**, **Scheme 2.15**), developing methodology that would form the base of his future synthetic efforts.[43] The following year Mulzer published the full scope of his group's efforts.[44] All attempts began with the synthesis of cyclobutane **110**, which was prepared as shown in **Scheme 2.15**. The synthesis commenced with the non-selective reduction of racemic ketone **111**, which was then acetylated as the chloroacetate. This choice of ester was crucial for the subsequent lipase-



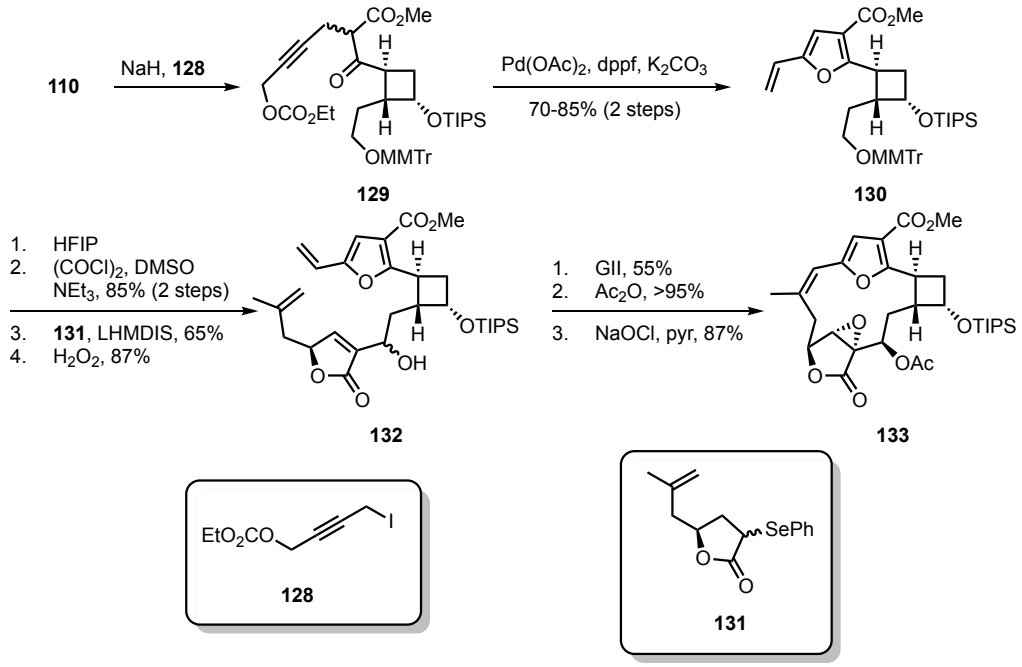

**Scheme 2.15**: Mulzer's synthesis of key intermediate **110**.

mediated hydrolytic resolution as the simple acetate required 14 days of reaction time as opposed to 24 hours with the chloroacetate. The resulting alcohol was then protected as the silyl ether and ozonolysis furnished diol **114** following a reductive workup of the secondary ozonide. Differentiation of the two hydroxyl groups was found to be easiest by treatment with one equivalent of MMTrCl which afforded a 4:1 ratio of **115** (desired) and **116** (undesired, recycled). Finally, oxidation of the primary alcohol followed by epimerization to the desired *trans* diastereomer and a Reformatsky reaction yielded, after reoxidation, cyclobutane **110**.




**Scheme 2.16**: Mulzer's first-generation approach towards providencin.

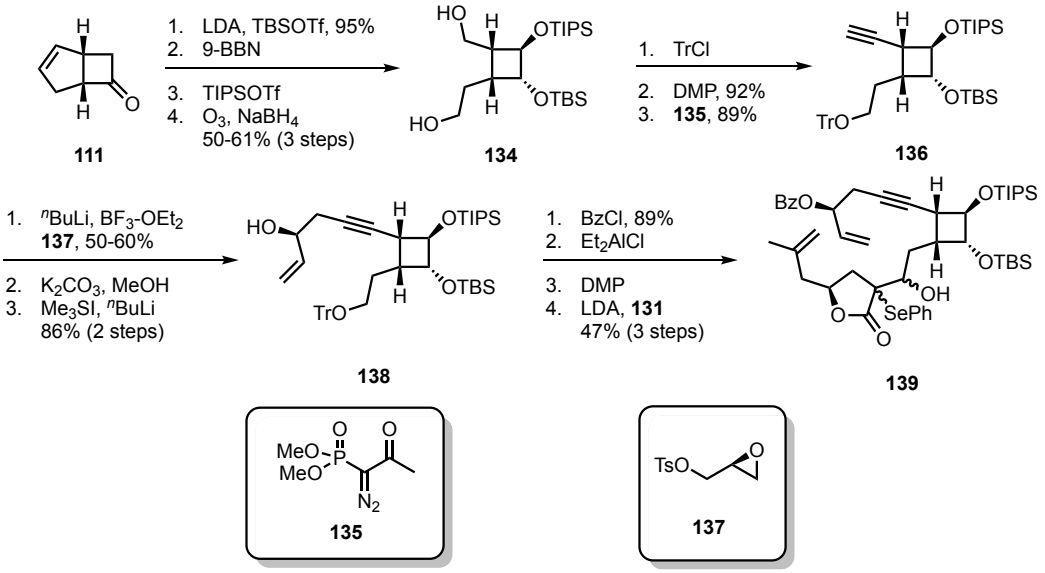
The first-generation synthesis involved the alkylation of **110** with propargyl iodide **118**, which was prepared as shown in **Scheme 2.16(a)**. The synthesis began with selective reduction of the bis-ethyl ester of (*S*)-malic acid (**119**) and silyl protection to arrive at ester **120**. The ester was converted to the corresponding Weinreb amide before being treated with MeMgBr and the lithium acetylide of **121** to arrive at tertiary alcohol **122** as an inconsequential mixture of diastereomers. The tertiary alcohol was protected as the benzoate ester and oxidative removal of the PMB group followed by Appel reaction afforded propargyl iodide **118**. The ß-ketoester of **110** was then deprotonated with NaH and alkylated with propargyl iodide **118** (**Scheme 2.16(b)**). Wipf cyclization of **123** then afforded furan **124** as a 1:1 mixture of *E*- and *Z*-isomers of the newly formed olefin. Upon treatment with $(PhSe)_2$, the mixture of isomers was equilibrated to the desired *E*-olefin. After removal of the MMTr protecting group, furan **124** was converted into phosphonate **125** in three steps. Removal of the primary TBS group followed by oxidation afforded aldehyde **126** as the substrate for the Horner–Wadsworth–Emmons macrocyclization, which occurred upon treatment of a dilute solution of **126** in HFIP with $^{n}$BuLi to afford enone **127**. Mulzer was unable to complete the synthesis of **7** from this point, although the vast majority of the carbon framework was installed.




**Scheme 2.17**: Mulzer's second-generation approach towards providencin.

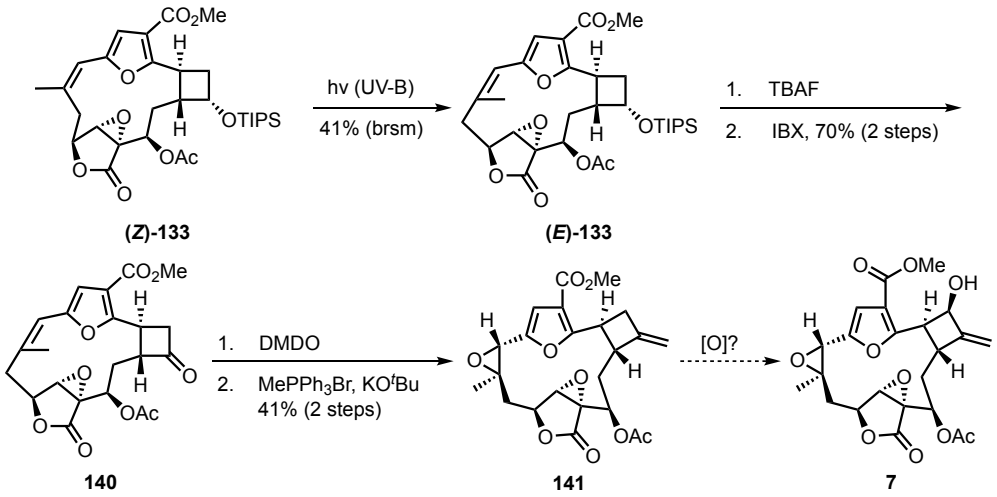
The second-generation synthesis involved the use of ring-closing metathesis in order form the macrocyclic ring, although the strategy to form the furan ring remained the same.

Shown in **Scheme 2.17**, intermediate **110** was alkylated with propargyl iodide **128**. As in their first-generation approach, Wipf cyclization of alkyne **129** afforded vinylfuran **130**, bearing the terminal olefin requisite for the ring-closing metathesis. Deprotection of the MMTr group, Swern oxidation, and aldol reaction with α-selenyl lactone **131** (prepared in five steps from (*R*)-glycidol) resulted, after oxidative elimination, in butenolide **132**, obtained a mixture of diastereomers. Ring-closing metathesis proceeded smoothly and provided only the (*Z*)-isomer. After acetylation and basic epoxidation, the synthesis was terminated at epoxide **133** because of the lack of success in isomerization of the olefin to the required (*E*)-isomer under a variety of conditions.




**Scheme 2.18**: Mulzer's third-generation approach towards providencin.

The third-generation synthesis focused on the problem of installing the C17 hydroxyl, which required a complete change in strategy, as shown in **Scheme 2.18**. Beginning from **(±)-111**, formation of the silyl enol ether followed by hydroboration and oxidation generated, after TIPS protection and ozonolysis, diol **134**. As in previous generations, monotritylation produced a separable mixture of regioisomers, and the desired isomer was carried forward to alkyne **136**. Deprotonation of the terminal alkyne followed by quenching with epoxide **137** afforded, after one-carbon homologation, allylic alcohol **138**. After four additional steps, diene **139** was attained; however, all attempts to close the macrocycle by ring-closing metathesis failed. It is unclear why no attempt was made to form the macrocycle by the use of the methods employed in the previous two generations.

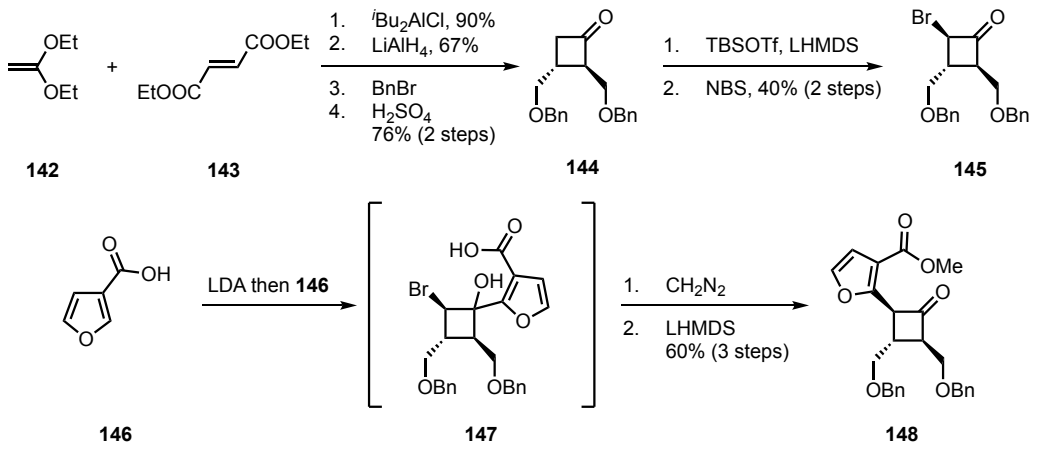



**Scheme 2.19**: Mulzer's synthesis of 17-deoxyprovidencin.

Some years later, the Mulzer group published the final communication of their work on the synthesis of providencin (**7**).[45] Continuing where they left off at the end of the second generation, with epoxide **133**, they observed that under photochemical conditions (UV-B), the olefin could be isomerize to the desired (*E*) geometry, albeit in relatively low yields (**Scheme 2.19**). Desilylation and oxidation cleanly produced cyclobutanone **140**, and DMDO epoxidation followed by Wittig olefination completed the synthesis of 17-deoxyprovidencin (**141**). The authors speculate that the synthesis of **7** may be completed either by allylic or enzymatic oxidation at C17; however, to date no results to this end have been published.

### 2.5.5 Wood's Approach Toward Providencin

In 2011, Wood published an approach toward the furanyl cyclobutanone of providencin (**7**).[46] As shown in **Scheme 2.20**, the synthesis began with the Lewis acid promoted [2+2] cycloaddition between ketene acetal **142** and diethyl fumarate (**143**). Reduction of the diester, protection of the resulting alcohol as the benzyl ether, and hydrolysis of the ketal provided rapid access to cyclobutanone **144**. Installation of the bromide proved to be straightforward by employing the silyl enol ether generated from **144** and quenching it with NBS to afford bromide **145** as a 6:1 mixture of diastereomers, favoring the desired trans–trans relationship. Finally, metallation of 3-furoic acid (**146**) and addition to the ketone in **145** led to the tertiary alcohol **147**. This compound was immediately converted to the methyl ester and, after treatment with an additional equivalent of LHMDS, a 1,2-shift occurred to arrive at furanyl cyclobutanone **148**.

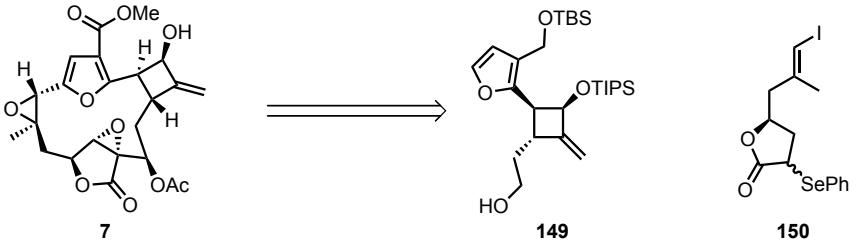



**Scheme 2.20**: Wood's synthesis of furanyl-cyclobutanone moiety.

The mechanism of such a migration is not clear; it could proceed by a 1,2-shift of the furan moiety or through an epoxide intermediate accompanied by a 1,2-hydride shift.

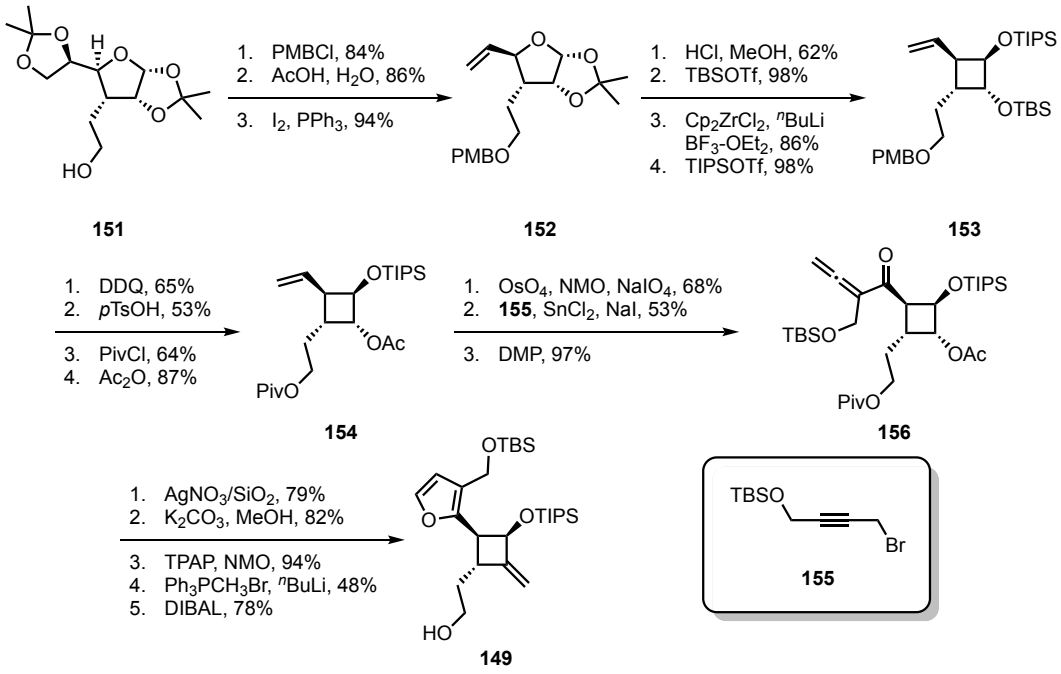
### 2.5.6 White's Approach Toward Providencin

The most recent reports of efforts towards the total synthesis of providencin (**7**) came from the White research group in 2009[47] and again in 2014.[48] White employed a convergent approach, as shown in **Scheme 2.21**, in which providencin could be divided into two roughly equal subunits, namely cyclobutane **149** and lactone **150**. The synthesis of the fully substituted cyclobutane made use of a methodology for a zirconicene-mediated ring contraction of furans to tetrasubstituted cyclobutanols. As shown in **Scheme 2.22**, the synthesis of **149** began with alcohol **151** (available in four steps from (D)-glucose). Protection of the primary alcohol, hydrolysis of the exocyclic acetonide, and treatment of the resulting diol with $I_2$ and $PPh_3$



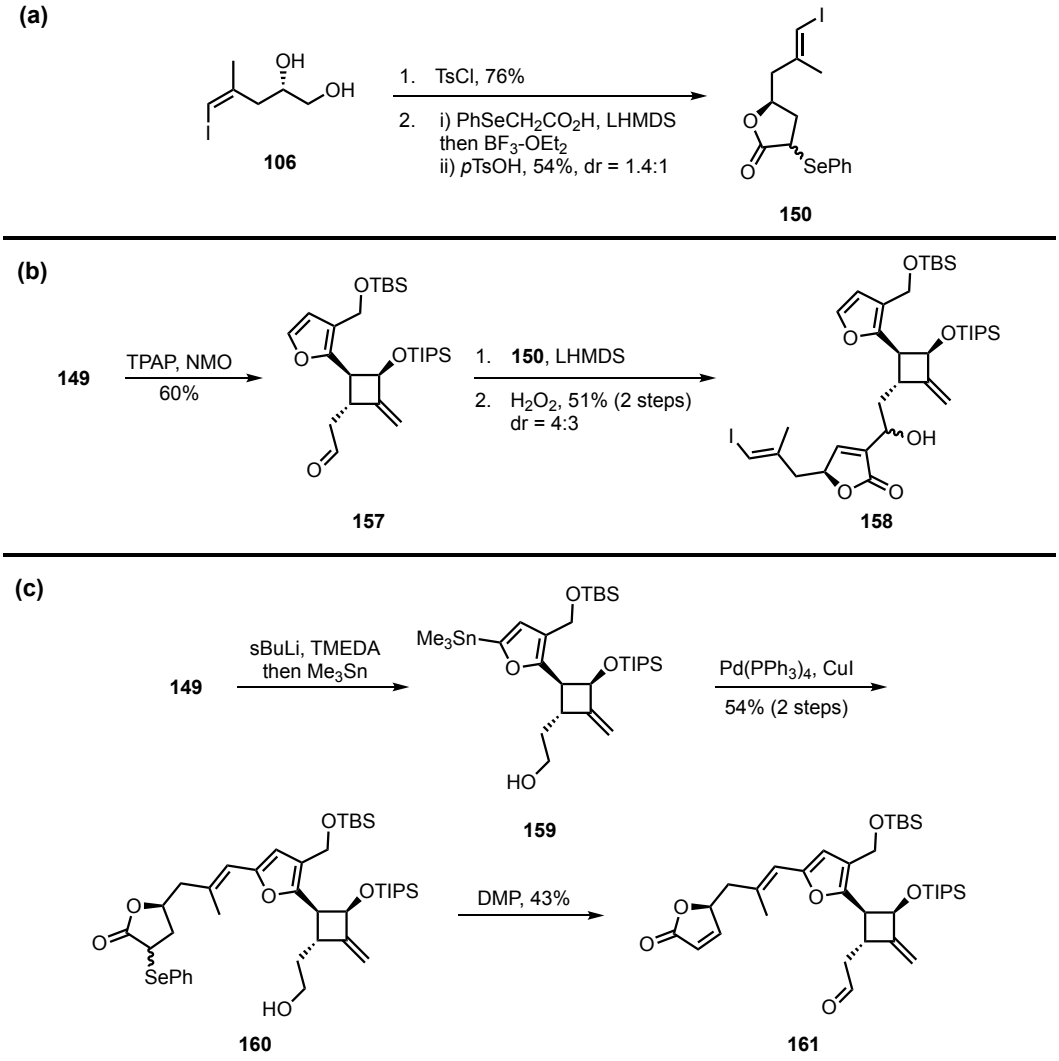

**Scheme 2.21**: White's analysis of providencin.

afforded furan **152**. Methanolysis of the remaining acetonide and protection of the alcohol set the stage for the oxygen atom abstraction reaction, which proceeded with full retention of configuration around the cyclobutanol core. After protection of the alcohol, fully substituted




**Scheme 2.22**: White's synthesis of furanyl cyclobutane **149**.

cyclobutane **153** was produced. Following selective protecting group manipulations, compound **154** was obtained. After oxidative cleavage of the olefin, the resulting aldehyde was alkylated with propargyl bromide **155** to afford, after oxidation, allene **156**. Finally, silver(I)-mediated cycloisomerization and Wittig homologation afforded cyclobutane **149**, which contains all of the requisite functionality required to proceed with the synthesis of **7**. The synthesis of lactone **150** was rather straightforward and proceeded through diol **106** (available in three steps from (*R*)-glycidol, cf. **Scheme 2.14**). Conversion of the primary alcohol to the tosylate followed by opening of the resulting epoxide (generated *in situ*) with the dianion phenylselenoacetic acid produced lactone **150** upon treatment with *p*TsOH (**Scheme 2.23(a)**). From this point, White explored two options to couple the two fragments. Shown in **Scheme 2.23(b)**, aldol reaction between lactone **150** and aldehyde **157** afforded, after oxidative elimination, butenolide **158**. All attempts to close the macrocycle between the vinyl iodide and the furan were unsuccessful. As shown in **Scheme 2.23(c)**, an attempt was made to subvert this problem by coupling the vinyl iodide (**150**) with furylstannane **159** first, followed by closure of the macrocycle via an aldol reaction. Unfortunately, selenoxide elimination could not be suppressed during oxidation of alcohol **160**, and the synthesis was not pursued any further.



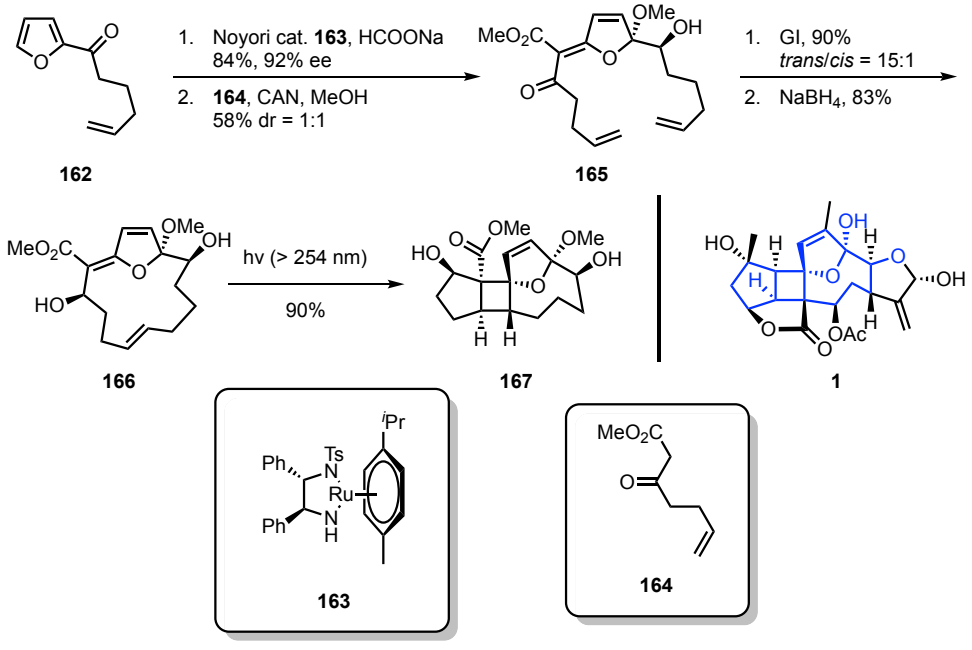

**Scheme 2.23**: White's synthesis of **150** and end-game approaches.

## 2.6 Synthetic Efforts Toward Bielschowskysin

The previous section will have demonstrated to the reader that the synthetic pursuits of these natural products can be extremely challenging; nevertheless, their pursuit can also be quite attractive. There is, arguably, no any known natural product that has generated more attention than bielschowskysin (**1**) over the past two decades. This section will describe the synthetic efforts that have been published by ten research groups around the world, beginning with some of the model systems that have been developed to access key components of the core structure of **1**. It is worth repeating that, to date, no one has completed the total synthesis of **1**.

### 2.6.1 Nicolaou (2011)

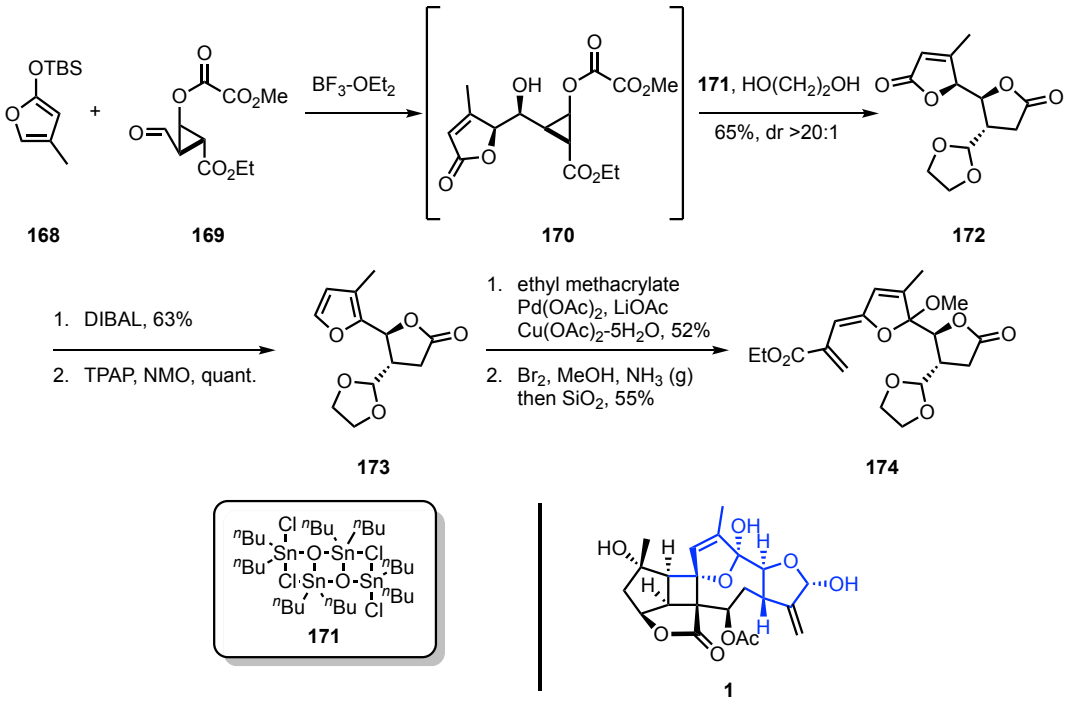
The first model system dealing with access to the polycyclic core of **1** was published by the Nicolaou group in 2011, although it is worth mentioning that a number of progress reports on the total synthesis had appeared in the years prior. Nicolaou describes an efficient synthesis of a tetracyclic structure that bears the core ring system of **1** (including the cyclobutane core and the challenging eight-membered ring).[49] As depicted in **Scheme 2.24**, the synthetic efforts began with Noyori reduction of furanone **162**, followed by an elegant oxidative coupling between ß-ketoester **164** and the furan ring to furnish **165** to form the *exo*-enol ether moiety necessary for photochemistry. A mixture of diastereomers were formed and carried through the sequence, but for clarity only one is being shown. Following the coupling reaction, diene **165** was treated with Grubbs' first generation catalyst to close the macrocycle. Reduction of the ketone, necessary to effect the desired photochemical transformation, was performed with $NaBH_4$ to afford alcohol **166** as a single diastereomer. Finally, upon irradiation, the cyclobutane core was formed by a transannular [2+2] cycloaddition, again as a single diastereomer, to rapidly complete the synthesis in of the tetracyclic core of **1**. As can be seen in the highlighted structure, however, this methodology is not easily amenable to installing the full functionality present in the natural product.




**Scheme 2.24**: Nicolaou's approach to the bielschowskysin core.

### 2.6.2 Reiser (2012)

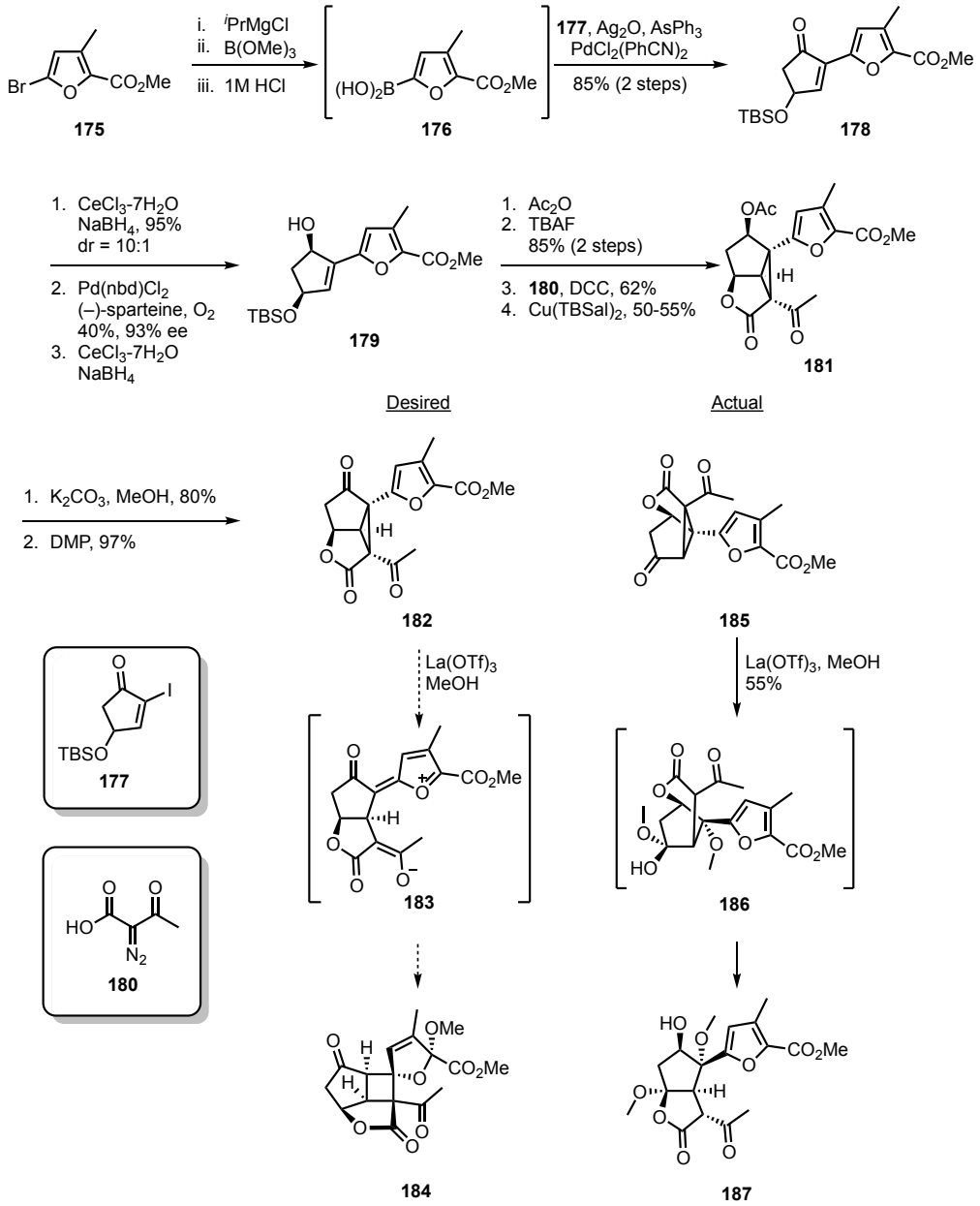
The methodology developed in Reiser's laboratory in 2012 focused on forming a functionalized "eastern" portion of the molecule, rather than the polycyclic core.[50] As shown in **Scheme 2.25**, the key sequence began with a Mukaiyama vinylogous aldol addition of silyloxyfuran **168** to cyclopropane **169**. The reaction proceeded smoothly under Lewis acid conditions to afford intermediate **170**, which was then treated with Otera's catalyst (**171**) and ethylene glycol to induce a lactonization retro-aldol cascade to produce γ-butenolide-butyrolactone **172** in 65% yield and excellent diastereoselectivity. The butenolide was reduced to furan **173** (after reoxidation of the resulting lactol), and a Heck reaction with ethyl methacrylate enabled functionalization of the C5 position of the furan ring. Finally, the furan was oxidized with bromine in methanol, and, upon column chromatography, an equivalent of methanol was eliminated to afford *exo*-enol ether **174**. The methodology developed by Reiser sets the *trans*-relationship on the easternmost lactol of **1** as well as providing a handle for the necessary photochemical cycloaddition. Installing the remainder of the molecule, however, would pose a significant challenge.




**Scheme 2.25**: Reiser's approach to the eastern half of bielschowskysin.

### 2.6.3 Stoltz (2013)

In 2013, the Stoltz group published an elegant approach to the core of **1**, depicted in **Scheme 2.26**.[51] Beginning from furan **175**, magnesium–halogen exchange followed by borylation produced boronic acid **176**, which was immediately coupled with iodoenone **177** to afford enone **178**. Diastereoselective Luche reduction provided the corresponding allylic alcohol with excellent (10:1) *syn* selectivity. The two enantiomers were then resolved using a

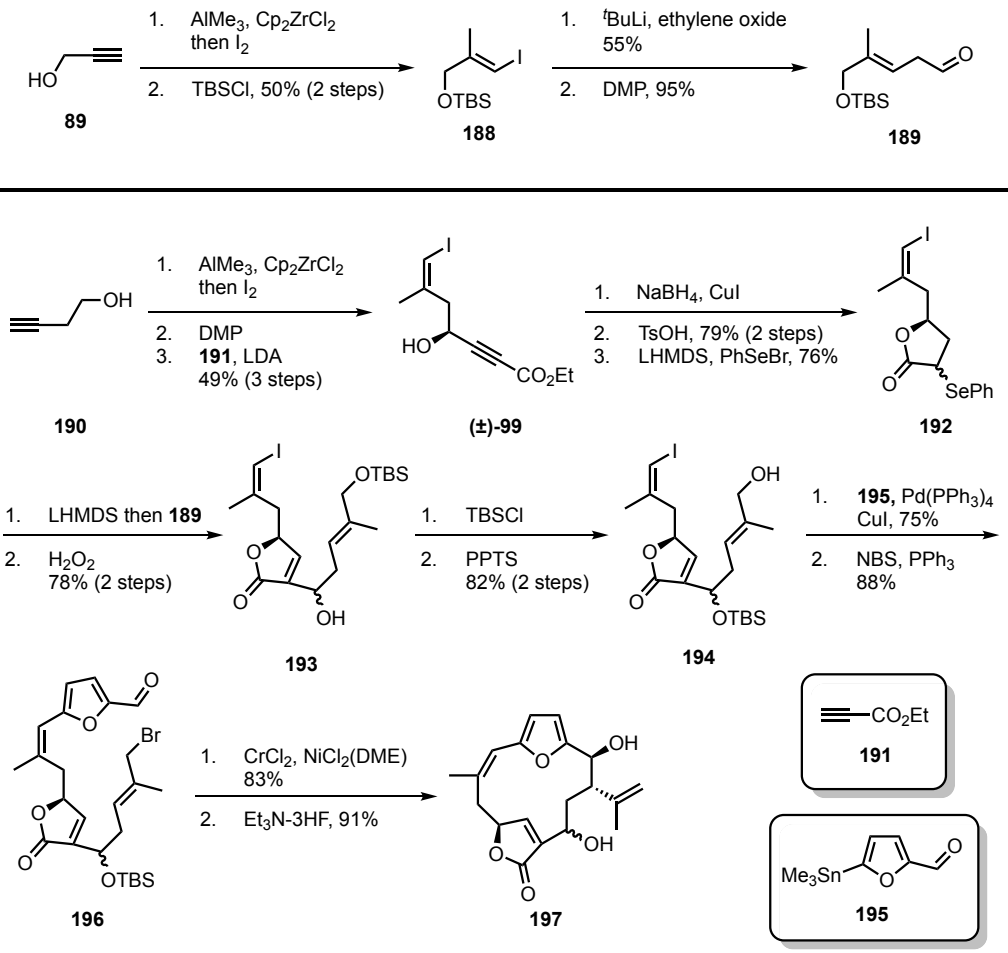



**Scheme 2.26**: Stoltz's failed approach to the core of bielschowskysin.

palladium-mediated oxidation in the presence of (–)-sparteine to arrive at enantiopure enone **178**. The authors then envisioned that Luche reduction would generate enantiopure alcohol **179**, although it should be noted that they carried out the remainder of the synthesis with racemic material. Acetylation, desilylation and esterification with α-diazoacetoacetic acid then set the stage for copper(II)-catalyzed intramolecular cyclopropanation to provide tricycle **181**. The authors hoped that after deacetylation and oxidation, they would arrive at ketone **182**. Upon treatment with a Lewis acid ($La(OTf)_3$), the cyclopropane would fragment to intermediate **183** and recombination via an intramolecular Michael addition would generate the fully substituted cyclobutane core of **1**. Unfortunately, when the acetate in **181** was removed, the resulting alcohol underwent an intramolecular translactonization to afford, after oxidation, ketone **185**. Hoping that the cyclopropane fragmentation would still occur, **185** was treated with $La(OTf)_3$. However, after the cyclopropane fragmentation, two equivalents of MeOH were incorporated to arrive at hemiketal intermediate **186**, which then underwent another translactonization to generate bicyclic lactone **187**. Unfortunately, Stoltz and his group were not able to subvert the initial translactonization, as ketone **185** seems to be the thermodynamically favored isomer, and no further results were reported. However, had the desired transformation taken place, these results would represent a remarkably fast (and non-photochemical) synthetic strategy to access the cyclobutane core of **1**.

### 2.6.4 Theodorakis (2013)

The same year, Theodorakis published an approach to the macrocyclic structure of several of the C13-oxidized furanocembranes, including **1**.[52] As shown in **Scheme 2.27**, the approach began with the synthesis of **(±)-99** from 3-butyn-1-ol (**190**) followed by CuH mediated alkyne reduction, lactonization, and α-selenation to arrive at lactone **192**. The lactone was then further reacted with aldehyde **189** (prepared in four simple steps from **89**) in an aldol reaction to afford, after selenoxide elimination, butenolide **193** as a 1:1 mixture of diastereomers. Protecting group manipulation resulted in allylic alcohol **194** and Stille coupling with furylstannane **195** followed by Appel reaction afforded allyl bromide **196**. The macrocycle was formed via Nozaki–Hiyama–Kishi reaction to produce, after desilylation, diol **197**. The chemistry of this diol was explored further, including deoxygenation, butenolide epoxidation, and furan oxidation, although nothing could be considered productive toward the synthesis of **1**. Nevertheless, Theodorakis expanded upon existing methodologies employed in the



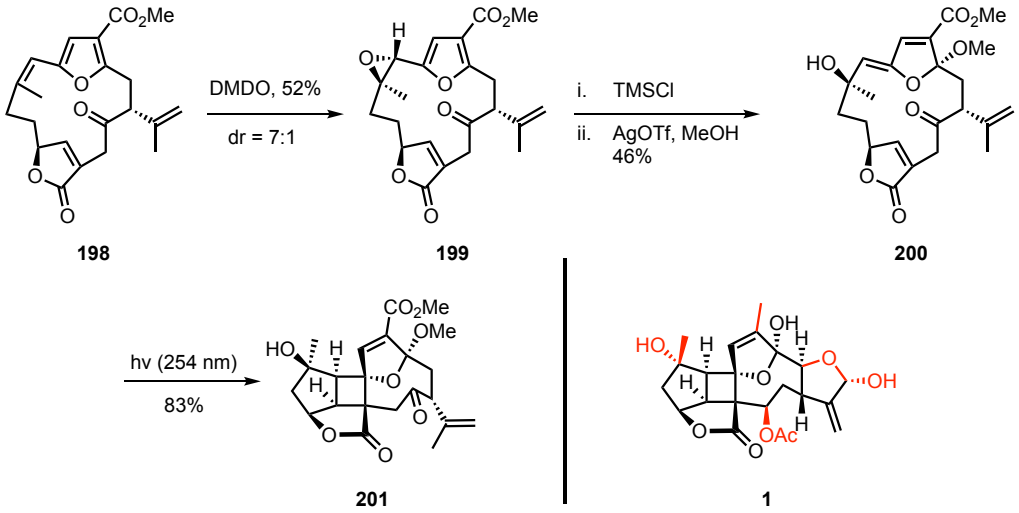

**Scheme 2.27**: Theodorakis' approach to the macrocyclic structure of bielschowskysin.

synthesis of bipinnatin J (**33**, see **Scheme 2.12**), while incorporating the key C13 hydroxyl group that is present in many related diterpenes.

### 2.6.5 West and Roche (2018)

One of the more recent synthetic studies of **1**, which from the West and Roche groups in 2018, made use of a very different approach.[53] Rather than starting from scratch, they opted for a semi-synthetic approach in beginning from a known natural product, acerosolide (**198**), which was been isolated from *P. acerosa*. As shown in **Scheme 2.28**, diastereoselective epoxidation led to epoxide **199**, which would serve as the substrate for the key oxidative dearomatization reaction. Indeed, treatment of epoxide **199** with TMSCl afforded the intermediate chlorohydrin, which, after silver(I)-mediated abstraction of the halogen, was

trapped with methanol to afford *exo*-enol ether **200**. Furthermore, upon irradiation of this compound, the desired [2+2] cycloaddition proceeded cleanly in 83% yield to produce cyclobutane **201**. Significantly, this reaction serves as a proof-of-concept for the biosynthetic hypothesis discussed in **Scheme 2.8** (via intermediate **62**). While the synthesis of **201** has addressed many of the challenges present in the synthetic efforts toward **1**, many components are not easily addressed (e.g., C13 hydroxyl, C2 hydroxyl, C18 methyl). It remains to be seen if this clever synthetic sequence can be applied to the total synthesis of **1**.

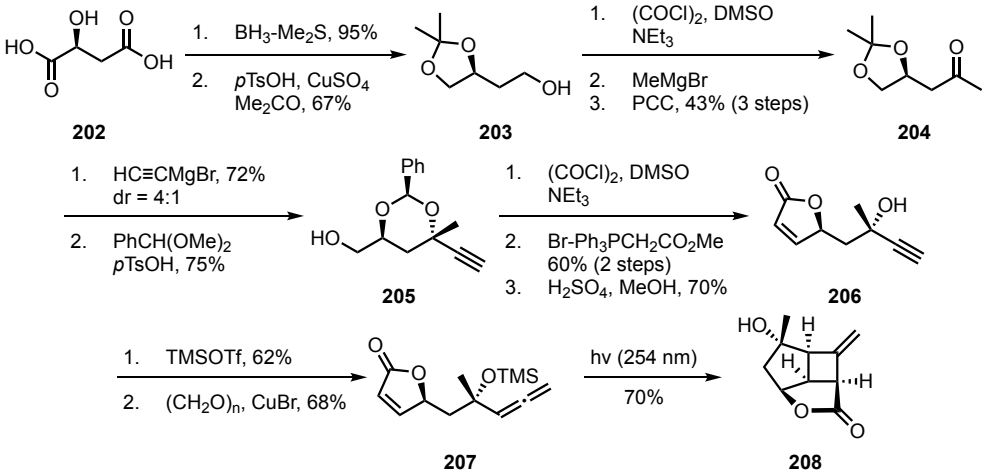



**Scheme 2.28**: Approach to bielschowskysin skeleton by West and Roche.

### 2.6.6 Lear (2009–2013)

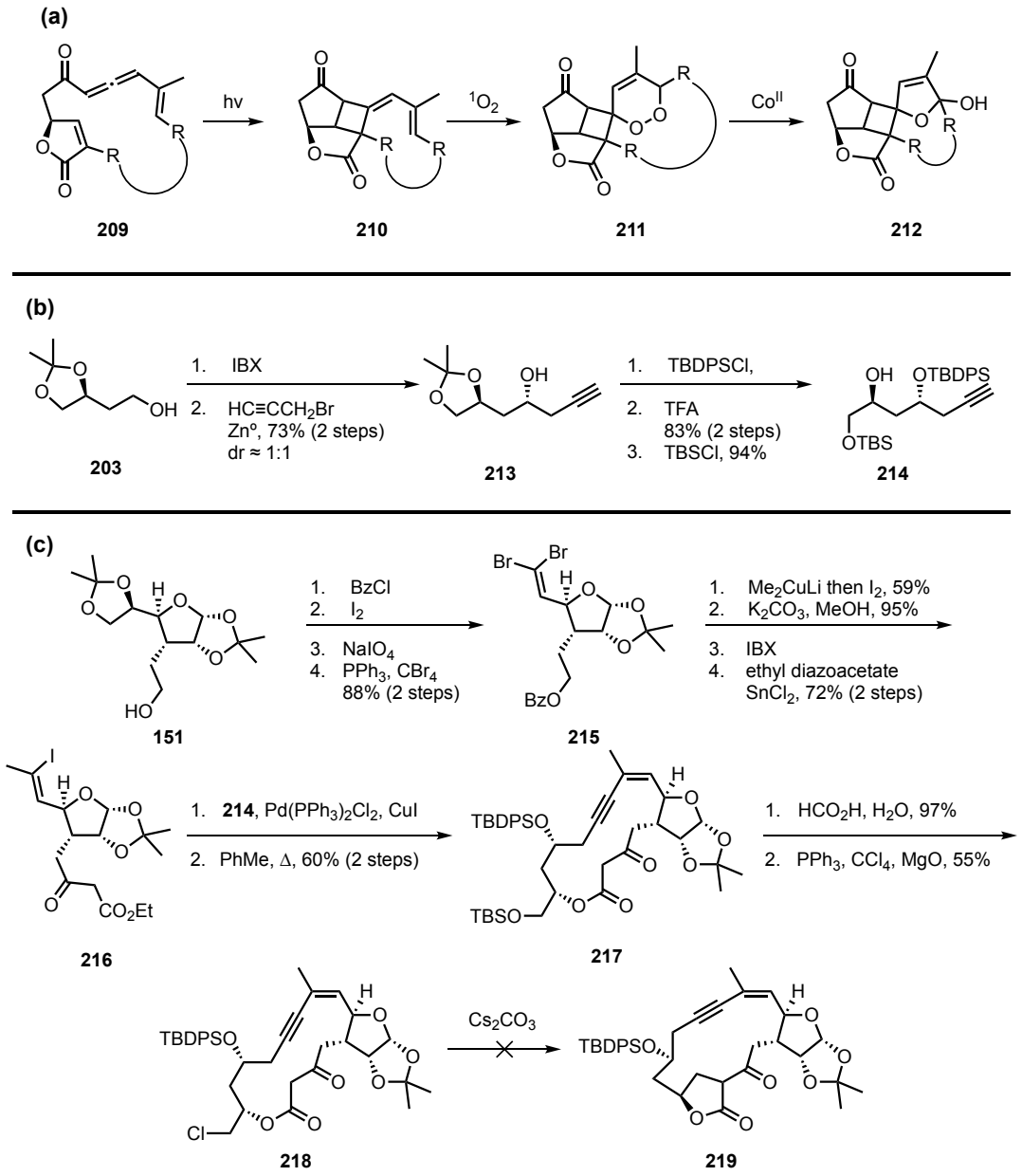
One of the first concerted efforts to complete the total synthesis of **1** stemmed from the Lear group beginning in 2009.[54] The earliest efforts by Lear focused on rapid formation of the cyclobutane core, following a similar route to that developed by the Sulikowski group three years prior (see Section 2.7). Beginning from L-malic acid (**202**, **Scheme 2.29**) to set the initial C10 stereochemistry, reduction to the triol followed by acetonide protection led to alcohol **203**. A series of manipulations about the primary alcohol resulted in ketone **204**, which would serve as the substrate for a diastereoselective Grignard addition. Transketalization to the 1,3-benzylidine afforded alcohol **205**, which was converted to butenolide **206** by oxidation, Wittig olefination, and hydrolysis of the acetal protecting group. The resulting tertiary alcohol was capped as the TMS ether before homologation of the acetylene to arrive at allene butenolide **207**. Upon irradiation, this compound underwent the desired [2+2] cycloaddition to afford

cyclobutane **208** as a single diastereomer. Lear and his group were able to synthesize multiple grams of **207**, however without an easy route to elaborate the eastern half of the molecule, they opted to abandon the early installation of the cyclobutane in favor of the transannular approach depicted in **Scheme 2.30(a)**.




**Scheme 2.29**: Lear's first-generation approach to bielschowskysin.

Lear's second-generation approach would feature the allene butenolide cycloaddition and the resulting diene **210** would then be trapped by singlet oxygen and a Co(II)-mediated rearrangement of endoperoxide **211** would furnish the spirocyclic cyclobutane (**212**).[55] Thus, Lear set his sights on the synthesis of macrocyclic allene **209**. The synthesis commenced with the preparation of alkyne **215**, which can be easily accessed from alcohol **203** (**Scheme 2.30(b)**). Propargylation of the resulting aldehyde afforded a separable mixture of diastereomers, the undesired of which could be converted into **213** by Mitsunobu inversion. Finally, installation of appropriate protecting groups furnished alkyne **214**. The synthesis of the other fragment, namely **216**, started from alcohol **151**. Acylation of the primary alcohol followed by selective hydrolysis of the exocyclic acetonide, oxidative cleavage of the resulting diol, and finally Ramirez dibromoolefination afforded dibromide **215**. The *Z*-vinyl iodide was installed by treatment with $Me_2CuLi$ followed by quenching with iodine. Debenzoylation and homologation afforded ß-ketoester **216**. Following Sonogashira coupling with alkyne **214**, heating the resulting enyne produced macrocyclic lactone **217** via the corresponding ketene generated *in situ*. Desilylation and a surprisingly challenging Appel reaction afforded primary chloride **218**. The authors expected that, upon exposure to base, the ß-ketoester would be alkylated to afford γ-lactone **219**. However, when treated with $Cs_2CO_3$, only hydrolysis of the chloride occurred, resulting in reformation of the corresponding alcohol. The authors speculate that the

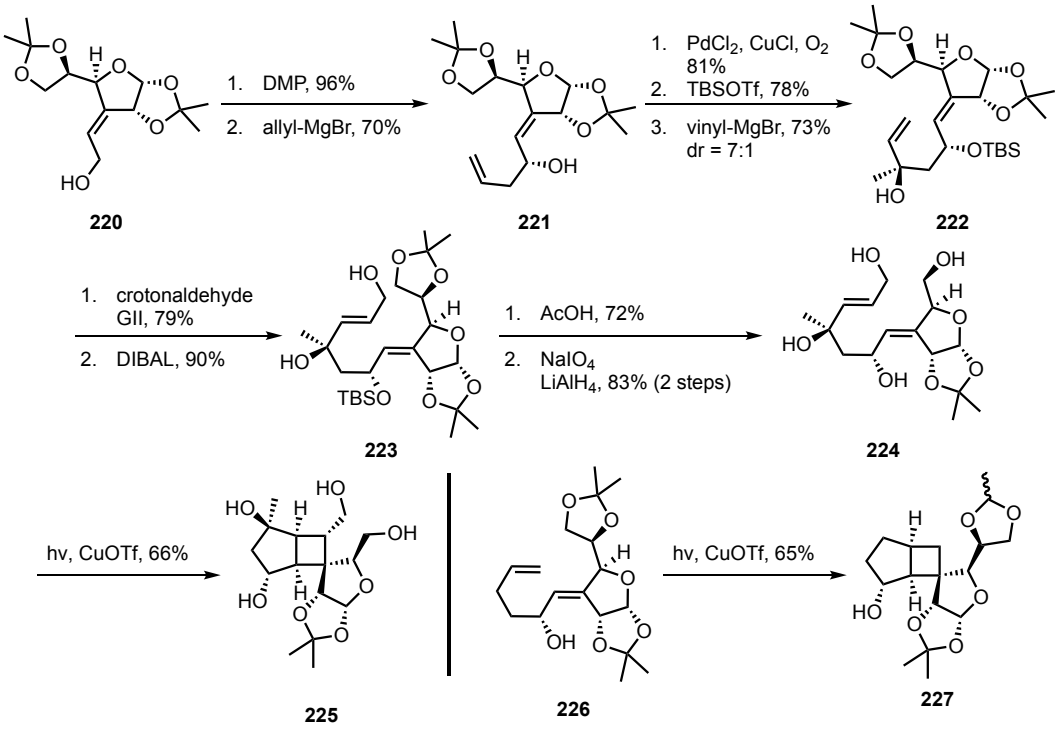



**Scheme 2.30**: Lear's second-generation approach to bielschowskysin.

hydrolysis proceeded through O-alkylation of the ß-ketoester. Unfortunately, they were unable to solve this problem, so this marks the last published progress by the Lear group towards the synthesis of **1**.

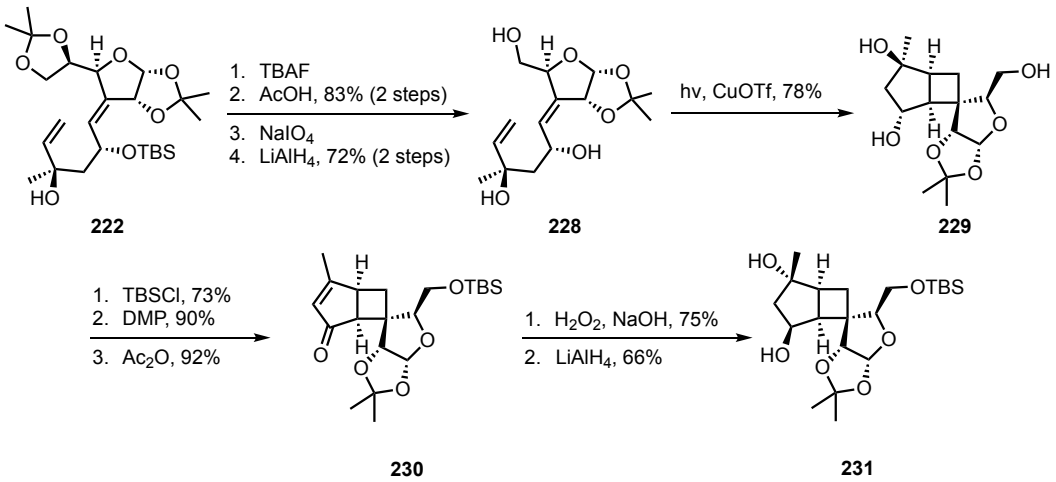
### 2.6.7 Ghosh (2012–2016)

The Ghosh laboratory has published three reports on their approaches towards the synthesis of **1**, which features a unique strategy to access the cyclobutane core.[56,57,58] As




**Scheme 2.31**: Ghosh's approach to bielschowskysin.

shown in **Scheme 2.31**, glucose-derived allylic alcohol **220** was chosen as the starting point. Note that hydrogenation of this material generates alcohol **151**, that was used by Lear (**Scheme 2.30(c)**) and White (**Scheme 2.22**). Ghosh's approach begins with oxidation of the allylic alcohol to the corresponding aldehyde followed by Grignard addition to afford alcohol **221**. Wacker oxidation followed by silyl protection and chelate-controlled addition of vinylmagnesium bromide led to tertiary alcohol **222**. Cross metathesis and subsequent reduction produced diol **223**, which was then converted to **224** by a sequence of deprotection, oxidative cleavage, and reduction. At this point, the resulting diene underwent a copper(I)-catalyzed photocycloaddition to afford cyclobutane **225** as a single diastereomer. It is interesting to note that when acetonide **226** was subjected to the same photochemical conditions, acetal **227** was produced with an inexplicable loss of a methyl group. Furthermore, it should be noted that the C8 and C10 hydroxyl groups of **225** possess the incorrect stereochemistry for **1**. Thus, Ghosh explored the possibility of correcting the two stereocenters, albeit on a simpler substrate, as shown in **Scheme 2.32**. From alcohol **222**, deprotection, oxidative cleavage, and reduction of the resulting aldehyde led to triol **228**, which would serve as the substrate for the copper(I)-catalyzed photocycloaddition. With cyclobutane **229** in hand and after selective protection of the primary alcohol and oxidation of the secondary alcohol,

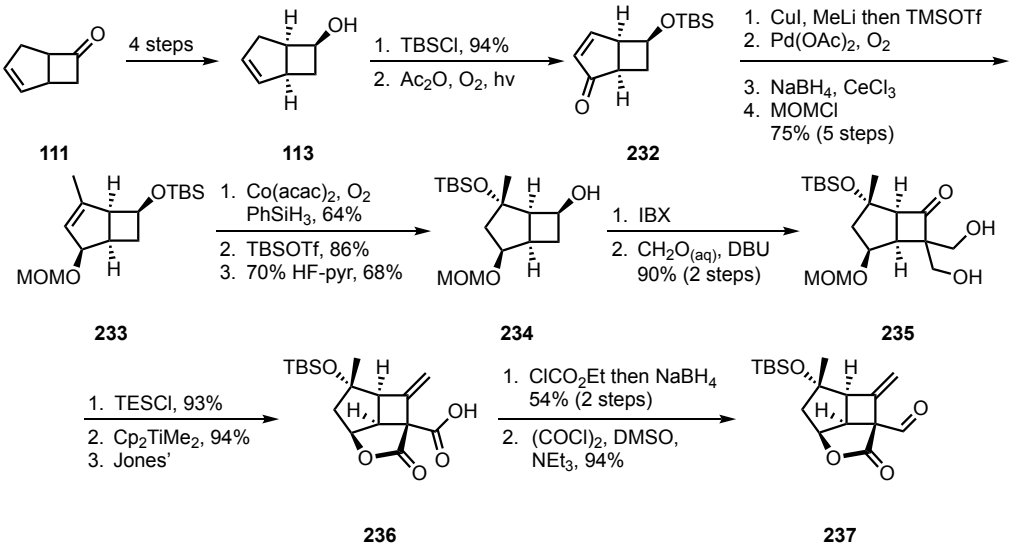



**Scheme 2.32**: Ghosh's stereochemical inversions.

the tertiary alcohol was eliminated as the acetate to afford enone **230**. Finally epoxidation under basic conditions from the *exo* face of the bicycle followed by reduction of the ketone (again from the *exo* face) and hydroxyl-directed reductive epoxide opening led to diol **231**, bearing the corrected stereochemistry at C8 and C10. Unfortunately, all attempts to remove the acetonide were unsuccessful and the synthesis of **1** could not be advanced further.

### 2.6.8 Mulzer (2012–2016)

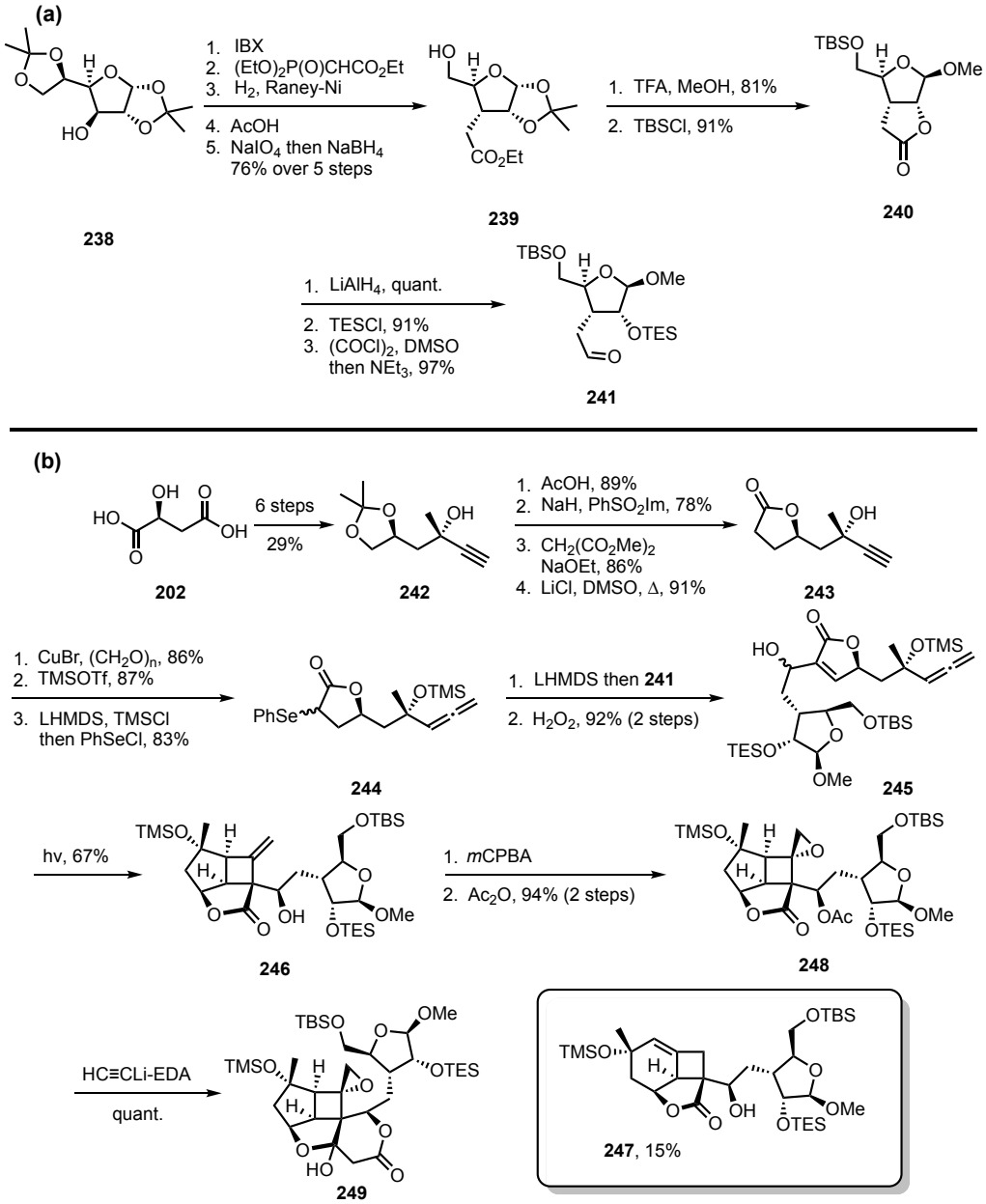
The Mulzer group has published the most extensive studies, by far, towards the total synthesis of **1**, resulting in six publications and at least six different approaches to the polycyclic core. They reported two different approaches to the cyclobutane core, the first of which, a "non-photochemical" approach, was reported in 2012.[59,60] As shown in **Scheme 2.33**, the synthesis begins with the same enzymatic resolution of cyclobutanone **111** used in his approach to providencin (cf. **Scheme 2.15**) to arrive at enantiopure alcohol **113**. After silylation of the secondary alcohol, a singlet oxygen-mediated oxidation led to enone **232**. Cuprate addition and Saegusa oxidation of the resulting silyl enol ether afforded, after Luche reduction and protection, bicycle **233**. Cobalt-mediated hydration of the olefin followed by selective manipulation of the protecting groups led to alcohol **234**, which was then then oxidized and bis-alkylated with formaldehyde form diol **235**. Bis-TES protection and Petasis olefination afforded the exocyclic methylene before exposure to Jones reagent resulted in a deprotection, oxidation, and lactonization cascade to arrive at lactone **236**. Finally, formation of the mixed




**Scheme 2.33**: Mulzer's "non-photochemical" approach to the bielschowskysin core.

anhydride enabled selective reduction of the carboxylic acid, and Swern oxidation afforded aldehyde **237**, which possesses the fully functionalized tricyclic core of **1**.

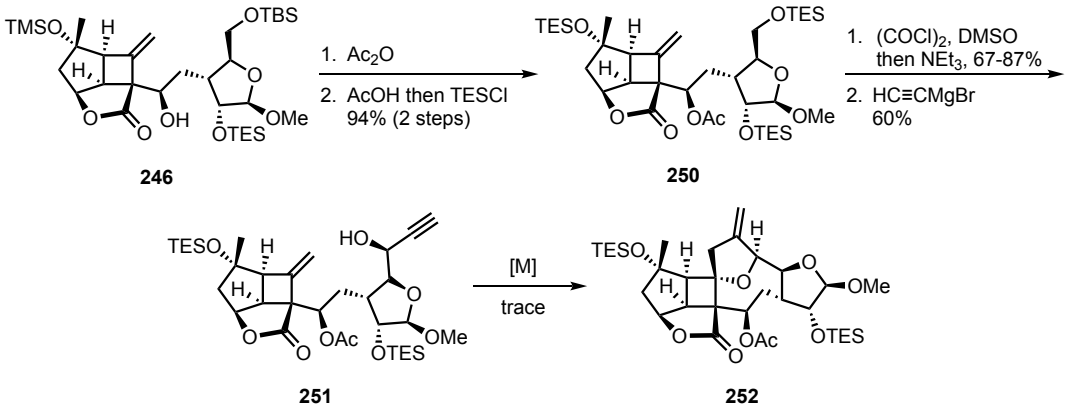
At the same time, Mulzer was also working on a photochemical approach (**Scheme 2.34**) employing an allene butenolide cycloaddition.[61] Shown in **Scheme 2.34(a)** is the synthesis of the eastern half of **1**, beginning from the glucose-derived acetonide **238**. A five-step sequence led to primary alcohol **239**, and methanolysis of the acetonide provided lactone **240**, following the protection of the primary alcohol as the TBS ether. After reduction of the lactone and bis-silylation, Swern conditions effected selective oxidation of the primary silyl ether to arrive at aldehyde **241**. To attain the "western" portion of the molecule, L-malic acid (**202**) was converted into alkyne **242** in six steps (see **Scheme 2.29**). Hydrolysis of the acetonide was followed by conversion of the 1,2-diol into an epoxide, which was then opened with dimethylmalonate to afford, after decarboxylation, lactone **243**. Homologation of the alkyne to the allene, TMS protection, and installation of the α-selenide led to allene **244**. The two fragments were then coupled in an aldol reaction to afford, after selenoxide elimination, allene butenolide **245**. Irradiation of **245** led to the desired [2+2] cycloaddition and formation of cyclobutane **246**. As well, a reaction at the terminus of the allene formed cyclohexene **247** as a minor byproduct. At this stage, the undesired C13 epimer was oxidized and selectively reduced by use of the CBS catalyst. Epoxidation of the exocyclic olefin and acetylation of the secondary alcohol afforded **248**. Unfortunately, the numerous attempts to open the epoxide with a variety of nucleophiles resulted, for the most part, only in recovery of starting material. The only significant reactivity observed was, upon treatment with lithium acetylide ethylene




**Scheme 2.34**: Mulzer's "photochemical" approach to the bielschowskysin core and failed epoxide opening.

diamine complex, an aldol reaction between the C13 acetate and the adjacent butenolide to form hemiketal **249**.

The second attempt to close the eight-membered ring began with cycloadduct **246** (**Scheme 2.35**). Protecting group manipulations led to tris-silylated intermediate **250**, and Swern conditions selectively oxidized the primary silyl ether to the corresponding aldehyde. Addition of ethynylmagnesium bromide resulted in propargylic alcohol **251**. At this point, several different metal catalysts (e.g., Au(I), Pt(II), and Cu(I)) were employed in order to effect



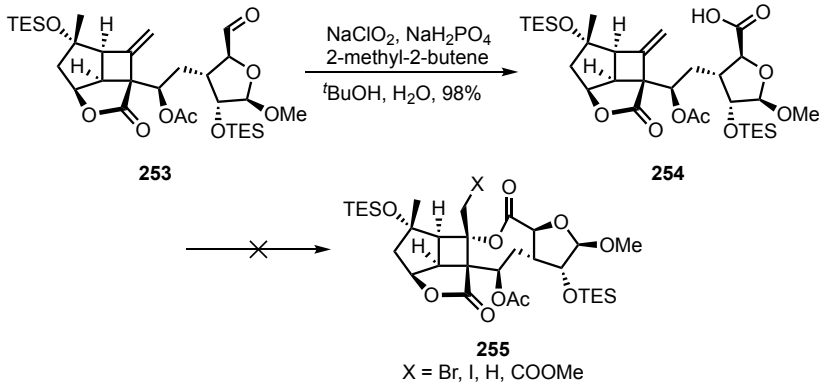

246 250 251 252

**Scheme 2.35**: Mulzer's cycloisomerization approach.

the desired cycloisomerization to arrive at **252**, which possesses nearly the entire carbon framework of **1**. Only trace amounts of the desired product were observed, with global desilylation as the only outcome and the major product.

After abandoning the cycloisomerization strategy, Mulzer opted to try a halo-lactonization approach to form the macrocyclic ether moiety (**Scheme 2.36**). The carboxylic acid substrate (**254**) was readily accessible from aldehyde **253** via a high-yielding Pinnick oxidation. Despite several attempts to effect the desired cyclization, they resulted only in decomposition or recovery of starting material. Similarly, palladium-catalyzed cyclization methods were also unproductive and nothing resembling **255** was observed.

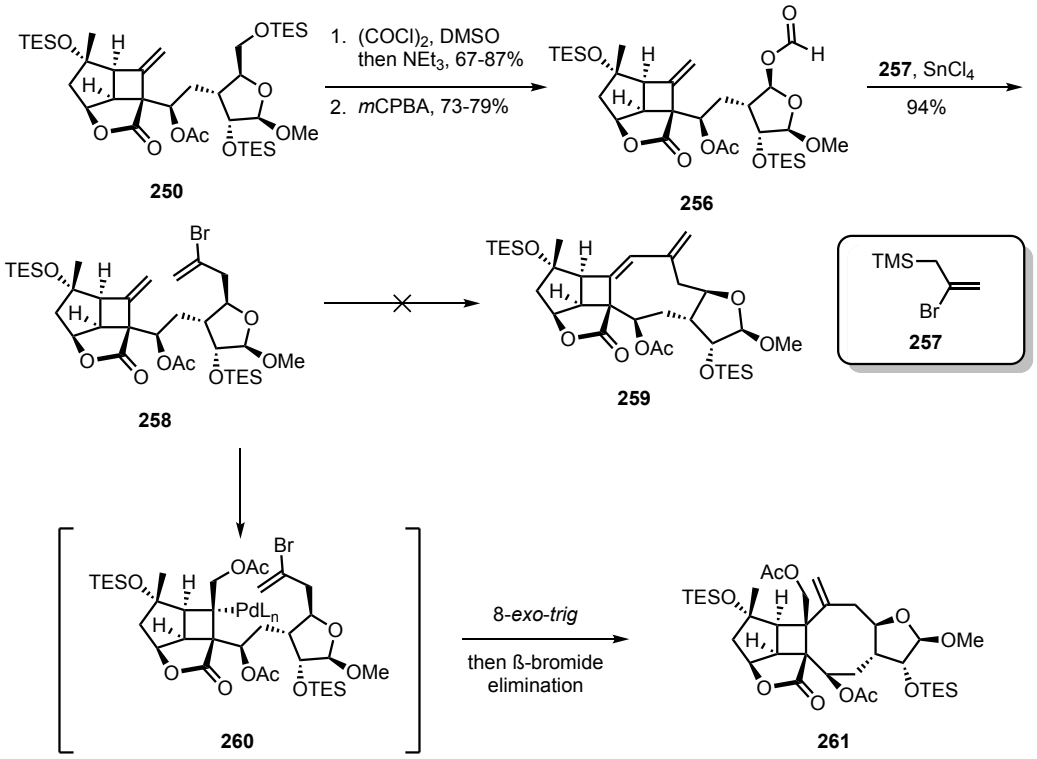
At this point, rather than forming a macrocyclic ether, Mulzer decided to form the macrocycle via a variety of metal-catalyzed approaches to form carbon–carbon bonds. The first attempt was by means of a Heck cyclization strategy, beginning from acetate **250** (**Scheme 2.37**).[62] Swern oxidation followed by Baeyer–Villiger oxidation afforded formate **256**, which then underwent tin(II)-catalyzed alkylation with allylsilane **257**. With macrocyclization




253 254

**Scheme 2.36**: Mulzer's failed halo-lactonization approach.

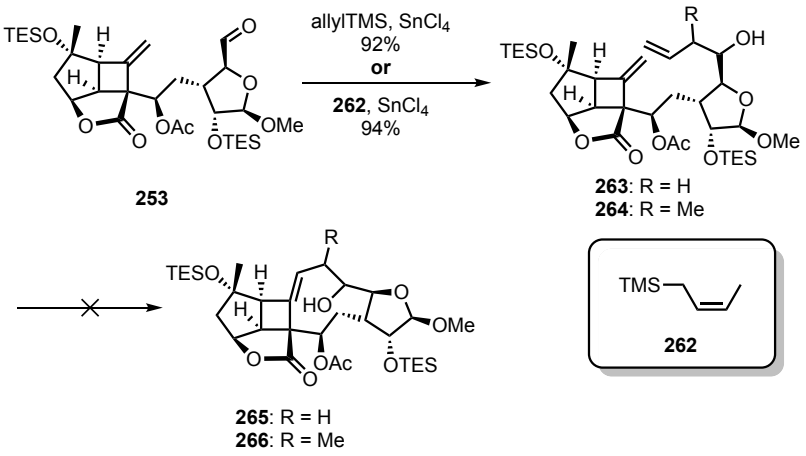
precursor **258** in hand, they attempted a variety of conditions to effect the ring closure, however only trace amounts of the desired diene **259** were observed by HRMS. Meanwhile, the major product isolated (in up to 55% yield) was acetate **261**, which was presumably formed via intermediate **260**, via initial acetoxy-palladation of the exocyclic methylene.



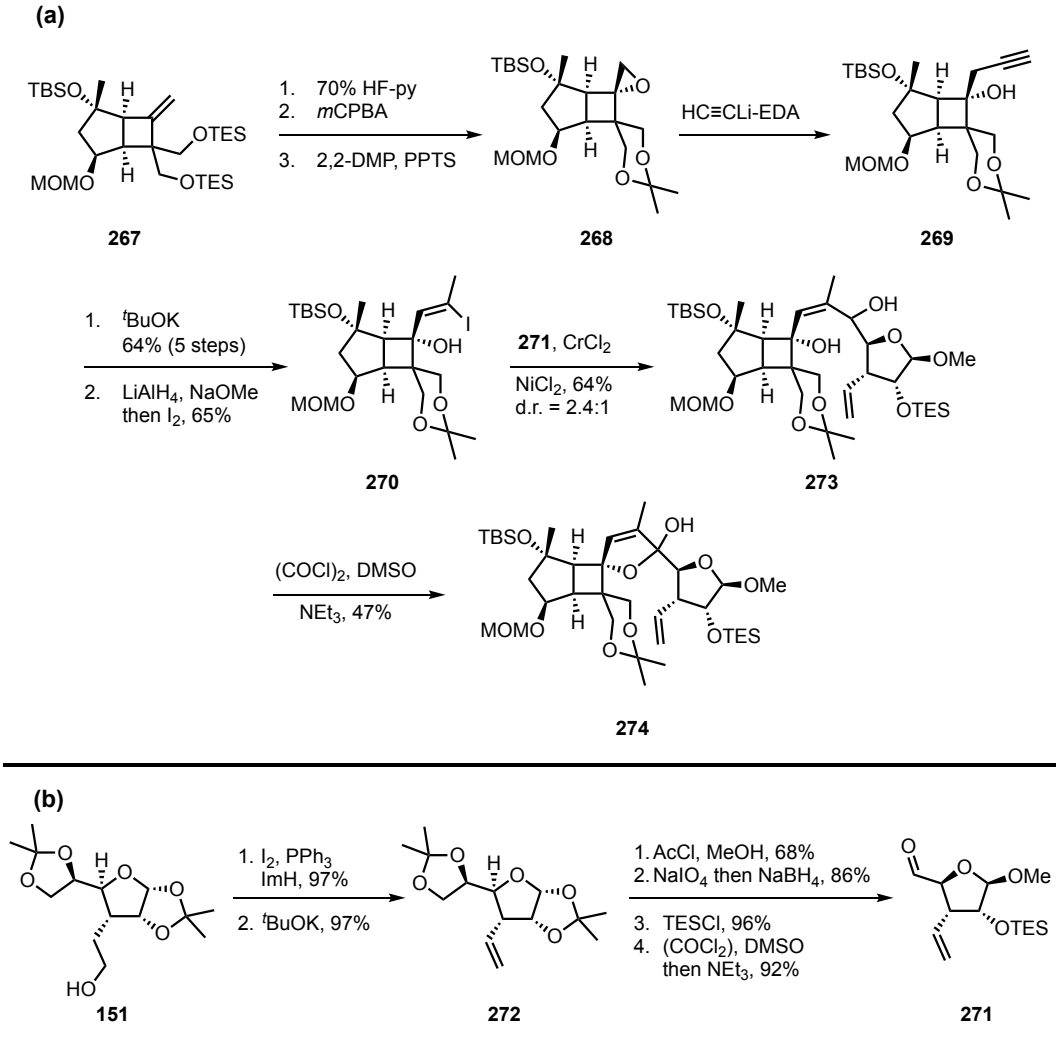

**Scheme 2.37**: Mulzer's attempted Heck cyclization.

Mulzer was also working on a ring-closing metathesis strategy toward the macrocyclization problem, as shown in **Scheme 2.38**. Beginning again from aldehyde **253**, allylation with either allyltrimethylsilane or allyl silane **262** afforded dienes **263** and **264**, respectively. At this point, several metathesis catalysts were tried, and the use of most of them resulted in a complex mixture of products, with only traces of the desired macrocycle present by MS. A major byproduct was homodimerization at the terminal allyl functionality. Cross-metathesis and protection of the free hydroxyl as a silyl ether also proved unsuccessful.

The Mulzer group also described a strategy to close the macrocycle at the "southern" junction rather than at the spirocyclic furan moiety as had been reported up to this point.[63] This route is derived from their "non-photochemical" strategy to access the cyclobutane core, described in **Scheme 2.33**. Here, beginning from bicycle **267**, desilylation, epoxidation, and acetonide protection afforded epoxide **268**. The epoxide was easily opened with lithium



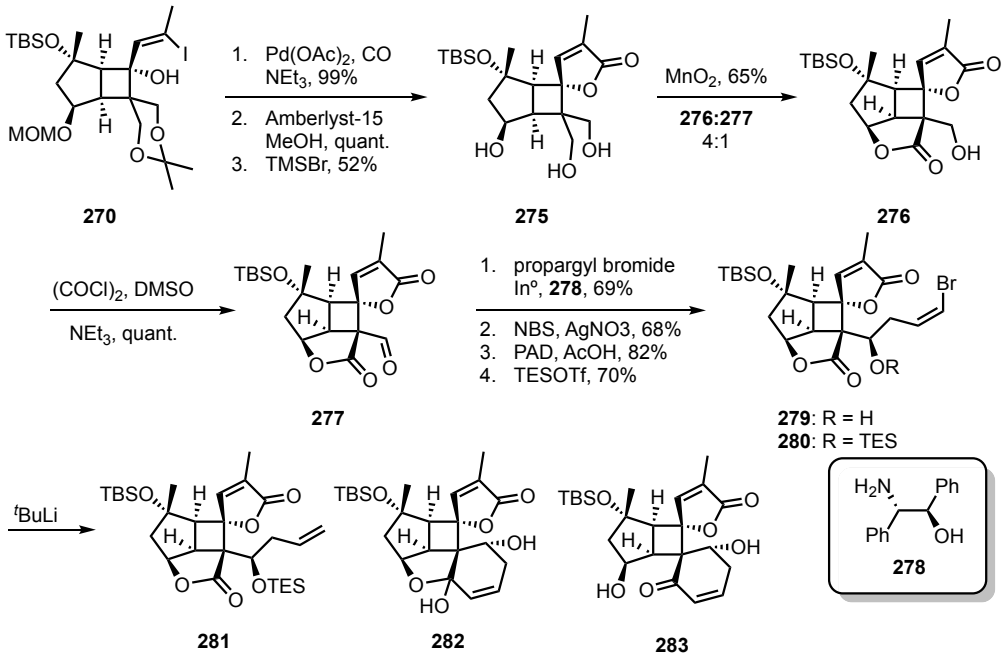

**Scheme 2.38**: Mulzer's ring-closing metathesis strategy.




**Scheme 2.39**: Mulzer's NHK coupling approach.

acetylide to furnish homopropargylic alcohol **269**. The alkyne could be isomerized under basic conditions to the internal alkyne, which was then hydroaluminated and iodinated to afford vinyl iodide **270**. The vinyl iodide was then coupled to aldehyde **271** (prepared via intermediate **272**, **Scheme 2.39(b)**) under NHK conditions to afford diol **273**. Oxidation of the secondary alcohol then induced cyclization to afford hemiketal **274**. Nothing further was attempted, although the authors do describe an end-game approach to **1**.

In their most recent report in 2016, the Mulzer group abandoned the previously described NHK approach in favor of a simpler substrate.[64] As shown in **Scheme 2.40**, vinyl iodide **270** underwent palladium-catalyzed carbonylation to generate, after deprotections, butenolde **275**. When a of oxidation conditions were, screened and it was found that upon treatment with $MnO_2$, the diol moiety was oxidized to alcohol **276** and aldehyde **277** in a 4:1 ratio. The remaining alcohol **276** was further oxidized to **277** under Swern conditions. Asymmetric propargylation of the aldehyde, by an *in situ* generated propargyl indium species and chiral amino alcohol **278**, furnished, after bromination and diimide reduction, vinyl bromide **279**. Attempts to close the the macrocycle by lithium–halogen exchange either as the free alcohol or as silyl ether **280** were unproductive and resulted primarily in protonation of the vinyl lithium species to generate **281**. Small amounts of **282** and **283** were observed by NMR analysis, although these compounds were never isolated.

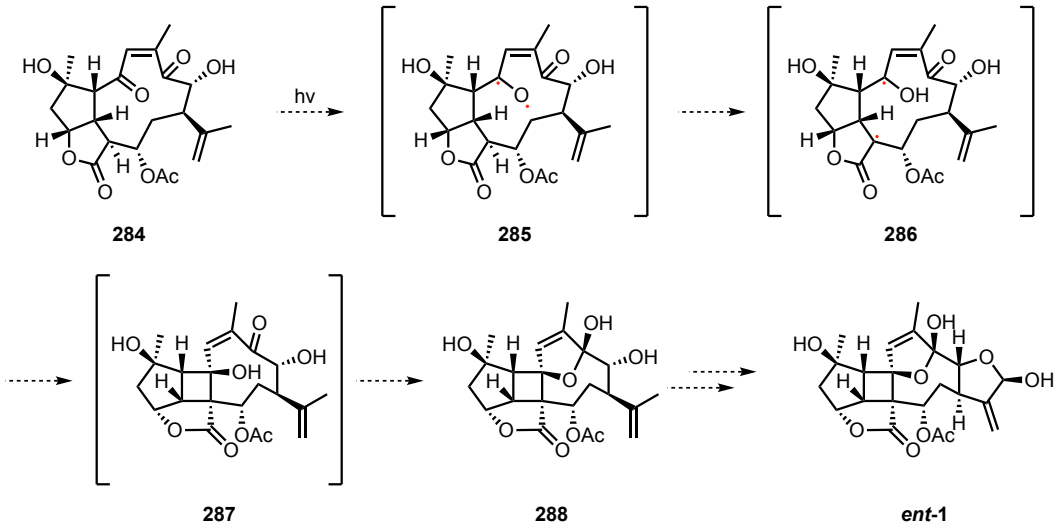



**Scheme 2.40**: Mulzer's lithium–halogen approach.

Thus concluded Mulzer's efforts to complete the total synthesis of **1**. He was able to access numerous advanced intermediates however, in all cases, closure of the final eight-membered ring remained elusive.

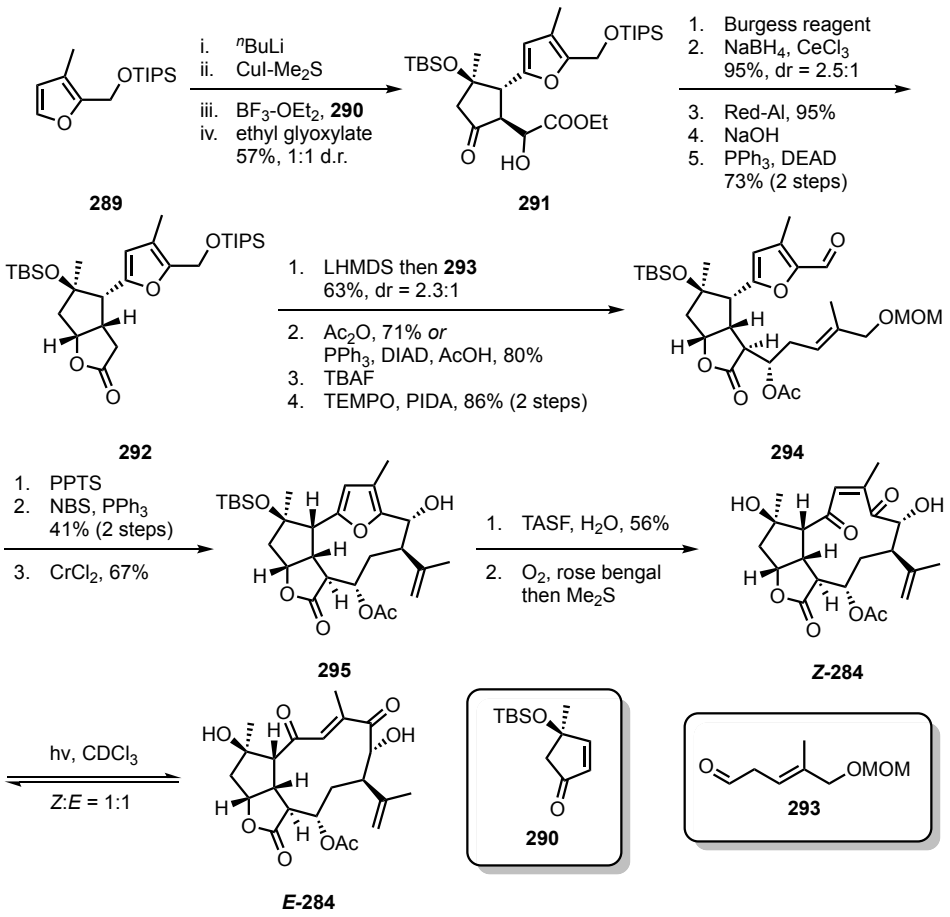
### 2.6.9 Sarlah (2020)

Most recently, the Sarlah group published an approach to ***ent*-1** in which they were able to arrive at macrocyclic ene–dione intermediate **284**, with the expectation that the full carbon framework could be installed by the Norrish–Yang cyclization shown in **Scheme 2.41**.[65] The synthesis began with addition of the cuprate derived from furan **289** to cyclopentenone **290** (prepared from (*R*)-linalool), followed by trapping with ethyl glyoxylate, shown in **Scheme 2.42**. Dehydration of alcohol **291** was mediated by Burgess reagent and followed by sequential reductions of the ketone and the α,ß-unsaturated ester. The resulting saturated ester was




**Scheme 2.41**: Sarlah's Norrish–Yang cyclization strategy.

saponified and cyclized under Mitsunobu conditions to afford lactone **292**. Aldol reaction between the lactone and aldehyde **293** afforded a mixture of diastereomers, which were separated and protected as the acetate under Mitsunobu (undesired diastereomer) or standard (desired) conditions. Selective removal of the TIPS group and oxidation of the primary alcohol provided aldehyde **294**. Deprotection of the MOM ether and the resulting alcohol was converted to the allylic bromide under Appel conditions. The macrocycle was formed using the NHK reaction to generate alcohol **295** as a single diastereomer. Finally, deprotection of the tertiary TBS group and oxidative cleavage of the furan ring afforded ene–dione **284** as the key

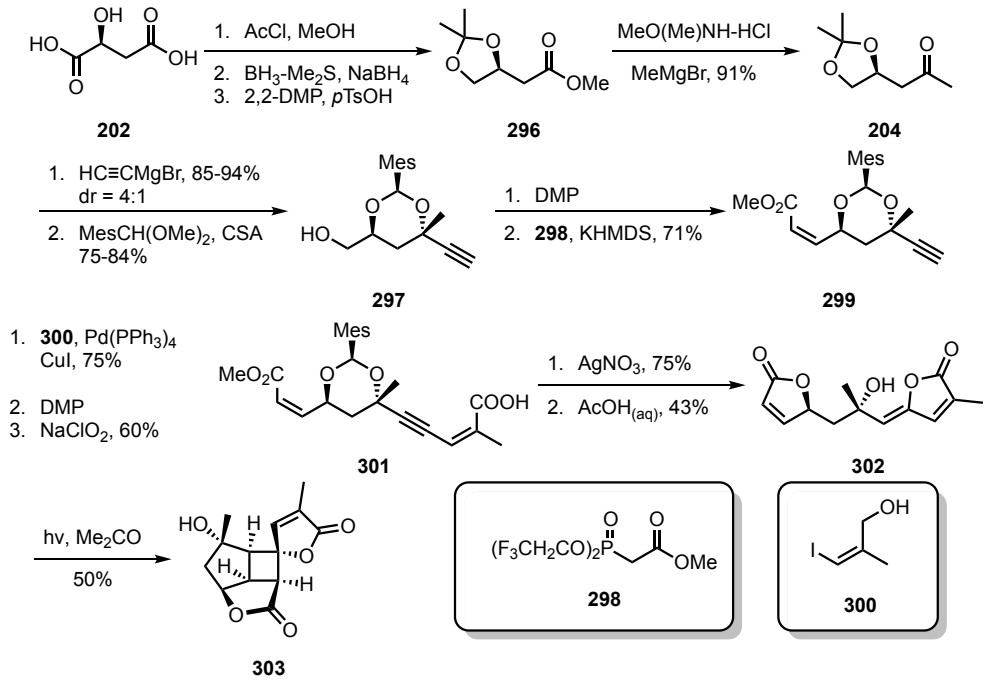



**Scheme 2.42**: Sarlah's approach to *ent*-bielschowskysin.

precursor to the proposed Norrish–Yang cyclization. Unfortunately, upon irradiation of **284**, the desired cyclization was not observed — only isomerization of the double bond occurred to result in an equilibration of *E* and *Z* isomers.

## 2.7 Sulikowski's Approach Toward Bielschowskysin (2006–present)

The Sulikowski research group was the first to publish on efforts towards the total synthesis of bielschowskysin (**1**). In 2006, two years after its isolation, Sulikowski published a report that details the rapid synthesis of the tetracyclic core of **1**, featuring an intramolecular [2+2] cycloaddition between a butenolide and a γ-alkylidine butenolide.[66] Beginning from (L)-malic acid (**202**, **Scheme 2.43**), Fischer esterification and hydroxyl-directed reduction afforded, after acetonide protection, ester **296**. *In situ* formation of the corresponding Weinreb amide and subsequent addition of methylmagnesium bromide afforded ketone **204**. Chelation-controlled alkynylation of the ketone produced the tertiary alcohol in a 4:1 diastereomeric ratio and




**Scheme 2.43**: Sulikowski's first-generation approach.

selective protection of the 1,3-diol moiety afforded alcohol **297**. The primary alcohol was then oxidized, and the resulting aldehyde was subjected to Still–Gennari olefination to generate selectively *Z*-olefin **299**. Sonogashira coupling with vinyl iodide **300** and sequential oxidations led to acid **301**, which underwent a smooth cycloisomerization to the desired γ-alkylidine butenolide. Acidic hydrolysis of the benzylidine acetal and concomitant cyclization afforded bis-butenolide **302**. Finally, irradiation of a solution of **302** in acetone induced the desired photocycloaddition to yield cycloadduct **303** as a 5:1 mixture of diastereomers. It is interesting that acetone proved necessary for this transformation, as irradiation of a solution of **302** in chloroform resulted in a simple isomerization of the chromophore to ***E*-302**. Thus, acetone likely served as a triplet sensitizer in the mechanism of the cycloaddition, described in **Figure 2.6**. Photosensitization of the enol ether moiety occurs to generate the 1,2-diradical species **$^1$[302]*** which, in the presence of **$^3$[Me$_2$CO]***, undergoes spin exchange to generate the triplet 1,2-diradical (**$^3$[302]***). In accordance with the rule-of-five,[67] formation of the five-membered ring occurs first, resulting in the formation of intermediate **$^3$[304]*** or **$^3$[*epi*-304]***, which are interchangeable via bond rotation. Combination of the resulting 1,4-diradical then completes the formation of the cyclobutane, resulting in either **303** or ***epi*-303**. The observed selectivity for **303** can likely be explained through dipole minimization that occurs in intermediate **$^3$[304]***.

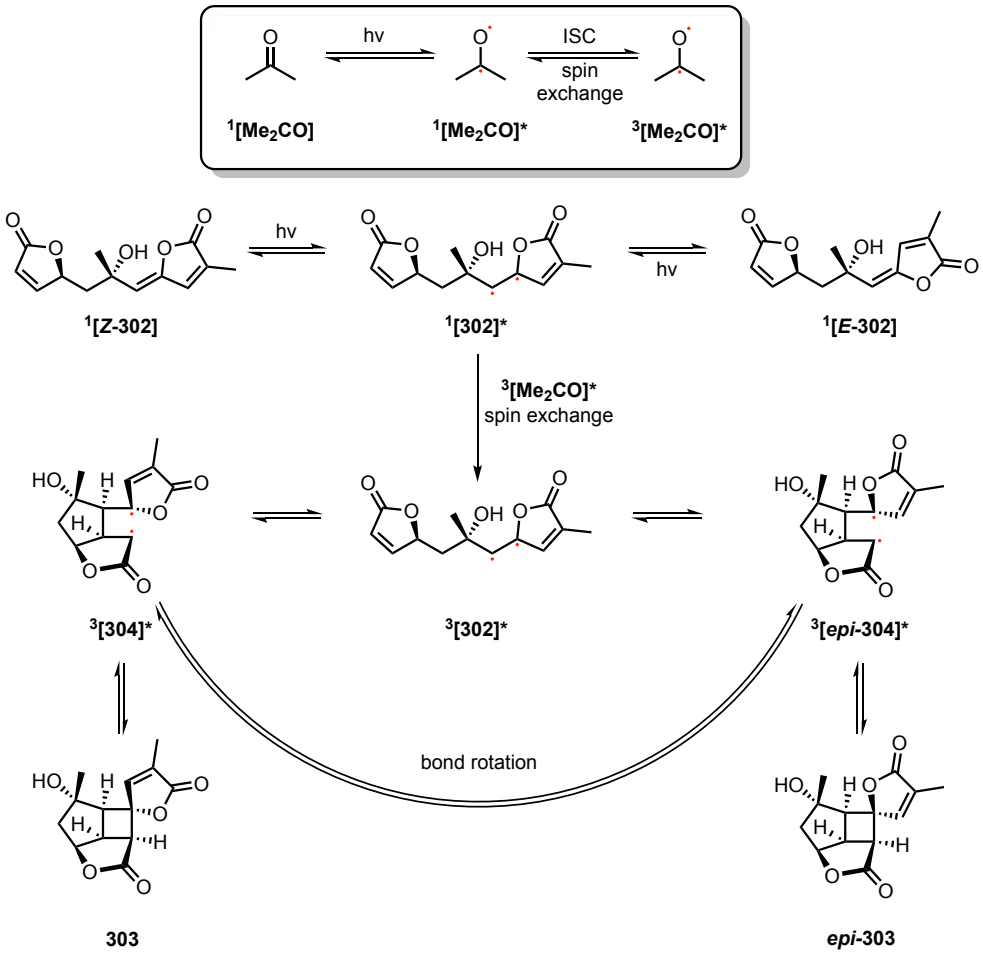
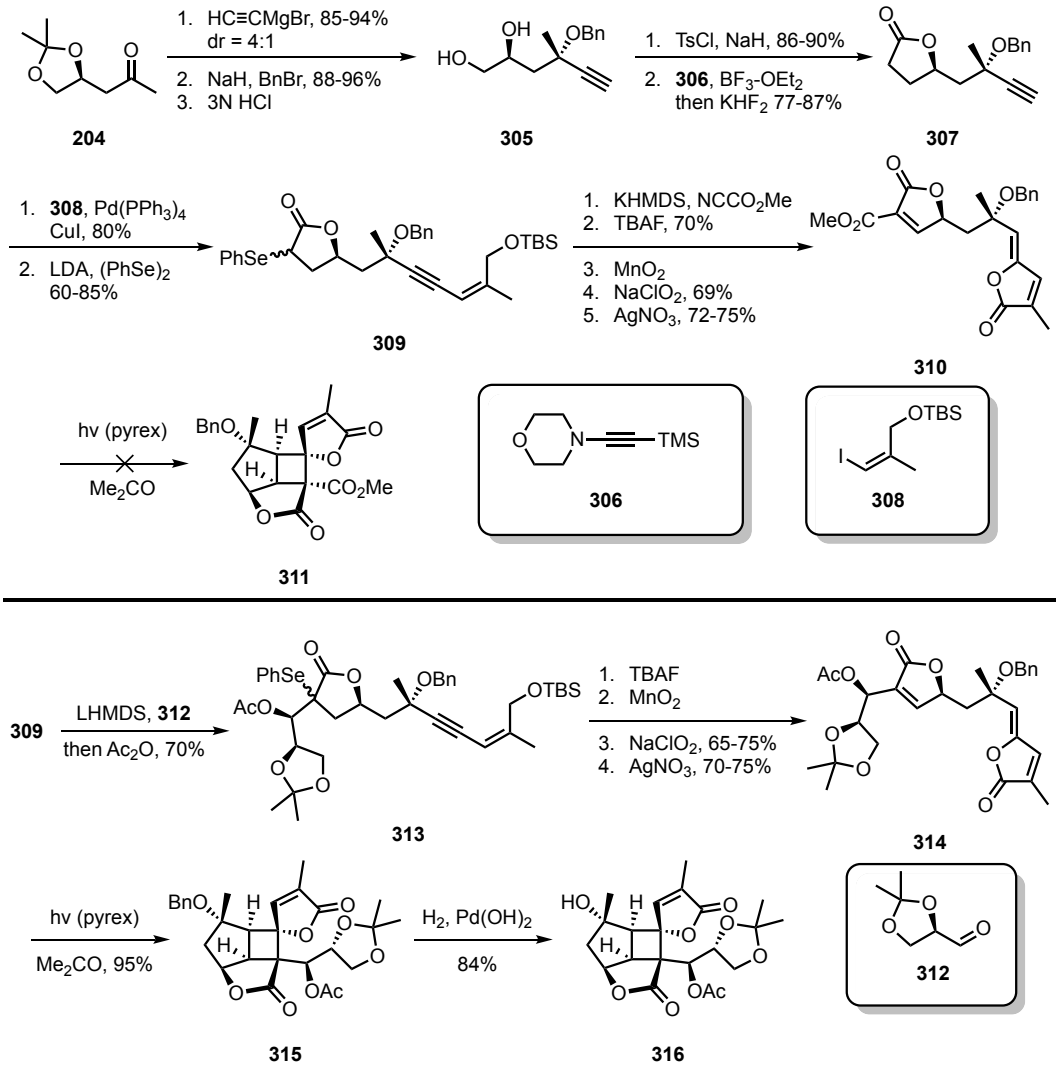



**Figure 2.6**: Mechanistic rationale for observed stereoselectivity.

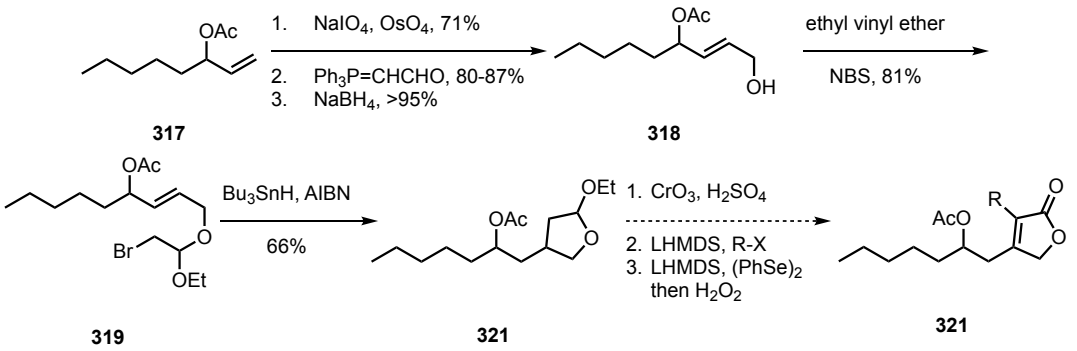
Initial attempts to build off of **303** by deprotonation at the α-position of the lactone were unsuccessful, presumably because of the extremely strained nature of the resulting enolate. Thus, Sulikowski decided to approach the synthesis via a second-generation attempt, in which the side chain was installed prior to the photochemical cycloaddition.[68] As shown in **Scheme 2.44**, this re-imagined synthesis began with the same alkynylation of ketone **204**. After protection of the tertiary alcohol as its benzyl ether and hydrolysis of the acetonide, diol **305** was converted into the corresponding epoxide by selective conversion of the primary alcohol to the tosylate and subsequent intramolecular displacement. Ring expansion of the epoxide to lactone **307** was achieved by reaction with yneamide **306** under Lewis acidic conditions. After Sonogashira coupling with vinyl iodide **308**, the α-selenide was introduced by deprotonation with LDA to furnish lactone **309**. Following installation of the methyl ester and desilylation, sequential oxidations with concomitant selenoxide elimination and silver(I)-catalyzed cycloisomerization produced the photochemical substrate with the desired substitution




**Scheme 2.44**: Sulikowski's second-generation approach.

pattern. Unfortunately, irradiation of bis-butenolide **310** resulted only in isomerization of the enol ether moiety; no cyclization to **311** occurred. This was explained by the stabilizing effect of the methyl ester on the 1,4-diradical intermediate (cf. $^3$**[304]***) and, thus, a side chain bearing a lower oxidation state would be necessary. Aldol reaction between lactone **309** and glyceraldehyde derivative **312** afforded, after acetylation, lactone **313**. A similar sequence of deprotection, oxidations, and cycloisomerization furnished bis-butenolide **314**. The photochemical cycloaddition of **314** proceeded smoothly and formed cycloadduct **315** as a single diastereomer. Hydrogenolysis of the benzyl protecting group was straightforward with Pearlman's catalyst to afford **316**.

Because of time constraints, **316** was the most advanced intermediate reached in the Sulikowski group; however, a model system was developed to explore the possibility of




**Scheme 2.45**: Model system for proposed end-game approach.

elaborating the acetonide moiety into the butenolide necessary for the final ring closure (cf. **Scheme 1.1**).[69] The model system, shown in **Scheme 2.45**, features a radical cyclization to form the oxygenated heterocycle which can then be further alkylated as necessary. Thus, oxidative cleavage of olefin **317** (this can be considered as a mimetic of the oxidative cleavage of the hypothetical diol from **316**) and Wittig homologation afforded, after reduction, alcohol **318**. Treatment of the primary alcohol with ethyl vinyl ether in the presence of NBS afforded bromoacetal **319**, which, after exposure to $Bu_3SnH$ and AIBN, underwent the desired 5-*exo*-*trig* cyclization to form acetal **320**. Jones oxidation and appropriate α-functionalization should then form the desired α,ß-substituted butenolide as in **321**. Thus concluded the efforts of the Sulikowski laboratory towards the total synthesis of **1**. Although the synthesis was not completed, considerable progress was made towards the development of an efficient attainment of the key tetracyclic intermediate **316**.

## 2.8 Significance

It is hoped from this chapter is that the importance of Gorgonian-derived diterpenes has been sufficiently and adequately communicated to the reader. Many of the natural products discussed here possess significant biological activities, whether anti-plasmodial, anti-inflammatory, or cytotoxic. Many of the compounds have not been isolated in sufficient quantities to enable exhaustive biological studies. It is imperative that as many compounds as possible be prepared via total synthesis such that the full scope of their biological significance may be explored without harvesting, and in the process, harming, the natural sources in the world's coral reefs. In addition to posing a practical need for total synthesis, there is also an academic need. Many of the diterpenes discussed here contain distinctly unique structural motifs and the synthetic pursuit of these motifs has given rise to some interesting and creative

solutions. Furthermore, the difficulty in accessing these compounds by total synthesis can be illustrated in the fact that, to date, the total synthesis of only three compounds has been achieved. It is a pursuit that requires patience but, with some skill and a little bit of luck, a completed total synthesis may reveal unprecedented biological or chemical significance.

## Chapter 3

### The C8–C10 Stereochemical Problem

In January of 2015, I inherited a project that already had some history in our laboratory. Considerable work had been done to access the fully substituted cyclobutane core of **1** (see Section 2.7). Synthetic efforts were subsequently directed towards the development of a substituted cycloadduct that could be more amenable to closure of the eight-membered ring and, in turn, to the completion of the total synthesis. As shown in **Figure 3.1**, I sought to access a linear precursor to the photochemical cycloaddition (**III**, cf. **Figure 1.1**) containing three different butenolide rings. A synthetic route to access the B-ring butenolide and the C-ring butenolide had been developed, but an efficient strategy to access the α,ß-subtituted A-ring butenolide remained elusive. I envisioned that this intermediate could be accessed via an aldol reaction between α-selenolactone **309** (prepared as described in **Scheme 2.42**) and a butenolide-containing aldehyde, such as **IV**. It should be pointed out that without the glyceraldehyde-derived aldehyde used in the previous synthesis, control of the C13 stereocenter is lost. I conceded that the aldol reaction between lactone **309** and aldehyde **IV** would converge upon acetylation of the undesired epimer via Mitsunobu reaction, and the desired by a standard acetylation. Thus, my initial efforts were directed towards the synthesis of multigram quantities of lactone **309** and the development of a synthesis to efficiently prepare the requisite α,ß-disubstituted butenolide **IV** (**Figure 3.1)**. The remainder of this chapter will discuss the progress towards those goals.

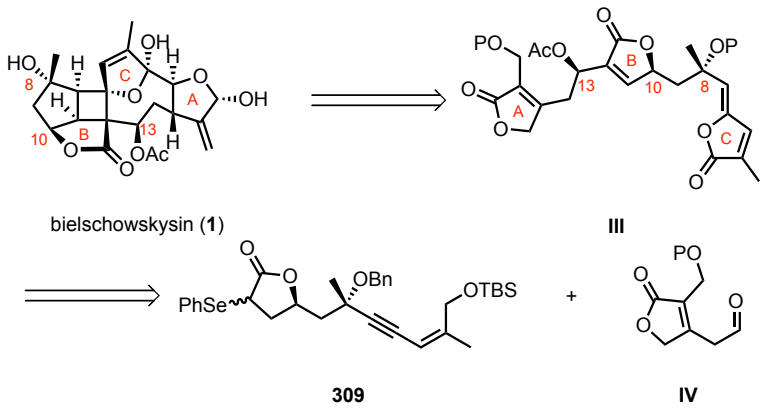
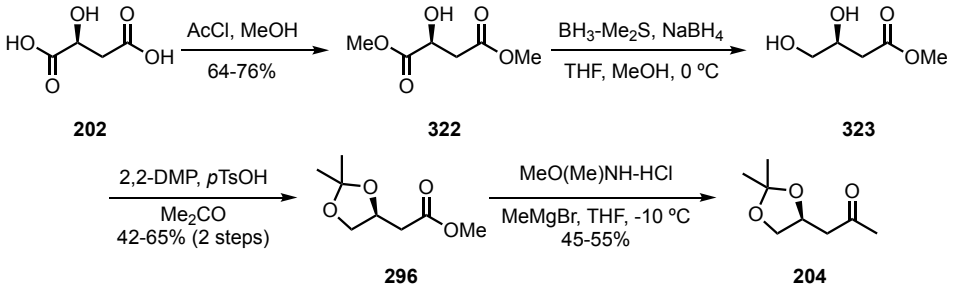


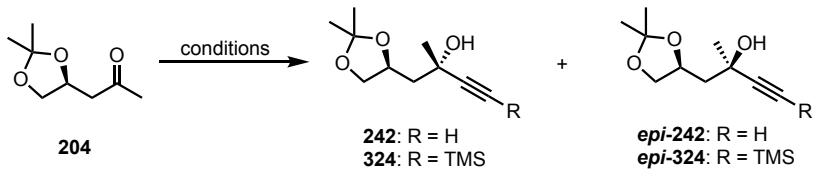

**Figure 3.1**: Revised synthetic analysis.

## 3.1 Problems with the First-Generation Approach

When I first began work on this project, I set out to familiarize myself with the established chemistry, at the same time, working towards the synthesis of sufficient quantities lactone **309** (**Figure 3.1**). The synthetic route started from L-malic acid (**202**) in order to incorporate the C10 stereocenter. Fischer esterification of the diacid was straightforward, so I was able to perform the reaction on 20-gram scales (**Scheme 3.1**). Chemoselective reduction of the ester adjacent to the free hydroxyl group[70] afforded diol **323**, which was immediately protected as acetonide **296**. Ester **296** was converted to methyl ketone **204** via *in situ* formation of the Weinreb amide and subsequent addition of methylmagnesium bromide.[71] Although the yield for this four-step sequence was modest (at best 12%-27%), it was possible to prepare several grams of ketone **204** relatively quickly. As was reported in the previous route (**Section 2.7**), I hoped to use the existing C10 alkoxy moiety to induce a diastereoselective addition of acetylene to the methyl ketone, thereby setting the C8–C10 relative stereochemistry. Unfortunately, despite many attempts, I was unable to reproduce the reported 4:1 diastereoselectivity.[54,66,68] The results of the conditions screened are summarized in **Table 3.1**. A screen of solvents and concentrations revealed that THF was the optimal solvent. Interestingly, use of $CH_2Cl_2$ or high dilution (entries 2 and 6, respectively) resulted in a modest reversal of diastereoselectivty, favoring the formation of ***epi*-242**. All attempts at employing a Lewis acid additive with the Grignard reagent resulted in decomposition of the starting material. A switch of alkyne source to the lithium acetylide derived from trimethylsilyl acetylene resulted in a significant improvement in yields without sacrificing selectivity (entry 11). The addition of $TiCl_4$ resulted in decomposition (entry 12). Attempts to transmetallate to the zinc acetylide (entry 13) or the magnesium acetylide (entry 16) led to the recovery of starting material. I thought that the addition of trimethylsilyl acetylene could be catalyzed by TBAF following Kuwajima's protocol;[72] however, the reaction was extremely sluggish, ultimately resulting in decomposition of the methyl ketone. Inspired by the use of cerium(III) as an additive




**Scheme 3.1**: Synthesis of methyl ketone **204**.




**204**

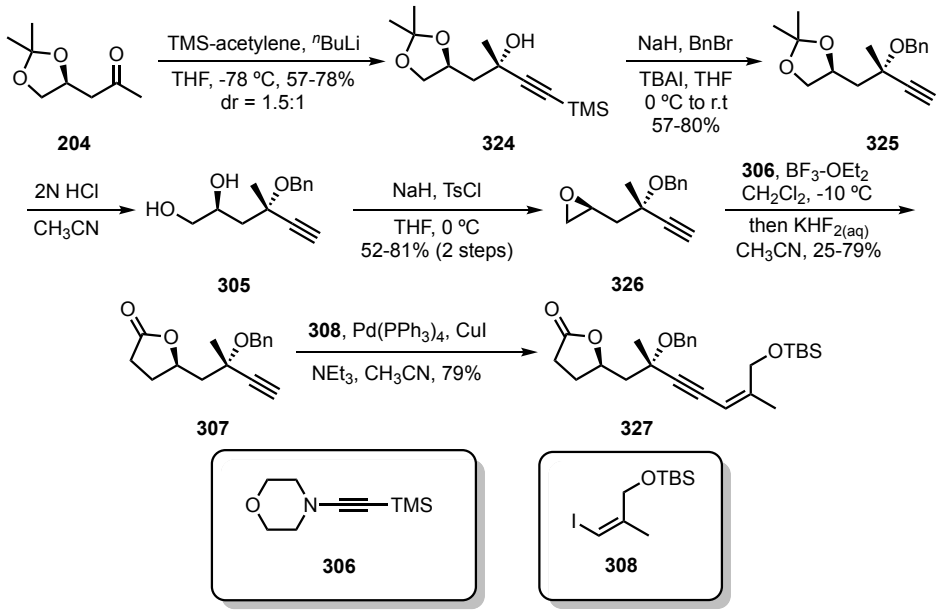
**242**: R = H
**324**: R = TMS

***epi*-242**: R = H
***epi*-324**: R = TMS

| Entry | Alkyne (eq.) | Solvent (Concentration) | Additive (eq.) | dr | Results |
|---|---|---|---|---|---|
| **1** | HC≡CMgBr (3.0) | THF (0.1 M) | None | 2:1 | n/a |
| **2** | HC≡CMgBr (3.0) | $CH_2Cl_2$ (0.1 M) | None | 1:1.2 | n/a |
| **3** | HC≡CMgBr (3.0) | PhMe (0.1 M) | None | 1.6:1 | n/a |
| **4** | HC≡CMgBr (3.0) | THF (0.1 M) | None | 1.2:1 | n/a |
| **5** | HC≡CMgBr (3.0) | THF (0.5 M) | None | 2:1 | n/a |
| **6** | HC≡CMgBr (3.0) | THF (0.05 M) | None | 1:2.6 | n/a |
| **7** | HC≡CMgBr (3.0) | THF (0.1 M) | $TiCl_4$ (1.1) | N/A | Decomposition |
| **8** | HC≡CMgBr (3.0) | THF (0.1 M) | $ZnCl_2$ (1.1) | N/A | Decomposition |
| **9** | HC≡CMgBr (3.0) | THF (0.1 M) | LiCl (1.1) | N/A | Decomposition |
| **10** | HC≡CMgBr (3.0) | THF (0.1 M) | $SnCl_4$ (1.1) | N/A | Decomposition |
| **11** | TMS-acetylene (1.5) $^n$BuLi (1.4) | THF (0.1 M) | None | 1.4:1 | 56% yield |
| **12** | TMS-acetylene (1.5) $^n$BuLi (1.4) | THF (0.1 M) | $TiCl_4$ (2.0) | N/A | Decomposition |
| **13** | TMS-acetylene (1.5) $^n$BuLi (1.4) | THF (0.1 M) | $ZnMe_2$ (1.5) | N/A | Recovered starting material |
| **14**[71] | TMS-acetylene (1.5) $^n$BuLi (1.4) | THF (0.1 M) | TBAF (0.1) | N/A | Decomposition |
| **15** | TMS-acetylene (1.5) $^n$BuLi (1.4) | PhMe (0.1 M) | None | N/A | Decomposition |
| **16** | TMS-acetylene (1.5) $^n$BuLi (1.4) | THF (0.1 M) | $MgBr_2$-$Et_2O$ (2.0) | N/A | Recovered starting material |
| **17**[72] | TMS-acetylene (1.5) $^n$BuLi (1.4) | THF (0.1 M) | $CeCl_3$ (2.0) | 1:2.6 | 27% yield |

**Table 3.1**: Summary of optimization efforts of diastereoselective alkynylation.

in Trost's total synthesis of pseudolaric acid B,[73] I attempted addition of the cerium acetylide (entry 17), but the yield was low, and the addition actually favored the undesired diastereomer.

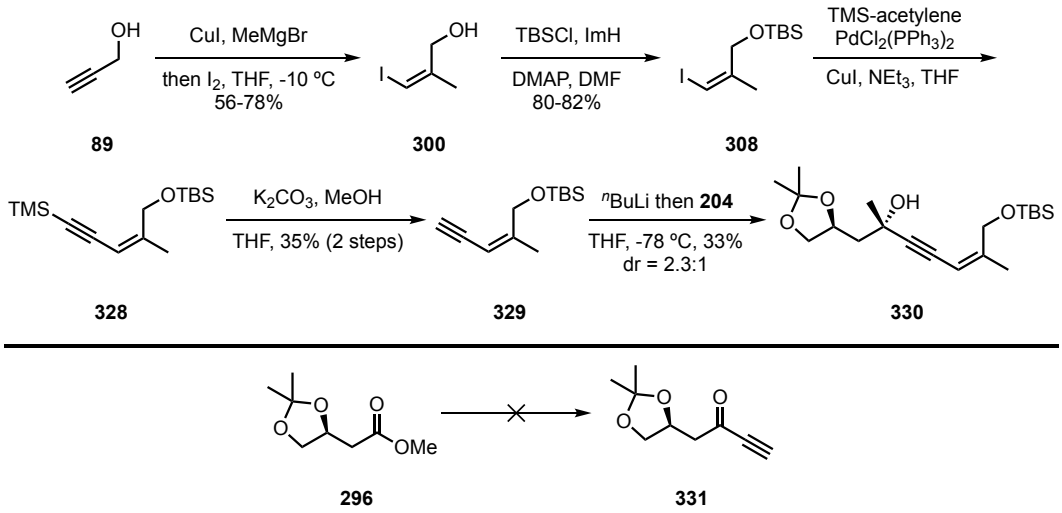



**Scheme 3.2**: Synthesis of enyne **327**.

With these results in hand, I decided to continue the synthesis with the simple lithium acetylide, despite the modest yield and relatively poor selectivity.

As shown in **Scheme 3.2**, the resulting tertiary alcohol **324** was protected as the benzyl ether with concomitant desilylation to afford alkyne **325**. Hydrolysis of the acetonide with aqueous HCl proceeded quite cleanly and the crude diol (**305**) was then converted into the terminal epoxide (**326**) in a one-pot process involving tosylation of the primary alcohol followed by displacement by the secondary alkoxide.[74] The epoxide was then converted into the corresponding γ-butyrolactone following a procedure developed by Jacobsen.[75] This reaction proved to be quite difficult to reproduce, because of the instability of the ynamide reagent (**306**) and resulted in the extremely varied yields, as shown in **Scheme 3.2**. I had noticed that higher yields occurred when **306** was either obtained from a freshly opened bottle from a commercial source — the reagent was very expensive — or when it was freshly distilled via bulb-to-bulb distillation *in vacuo*. Interestingly, neither the original communication nor the previous experimental procedure for this transformation mentioned this instability — in fact, the former notes that the **306** is stable at 0 ºC for months! With lactone **307** in hand, the terminal alkyne moiety was then extended by Sonogashira coupling[76] with vinyl iodide **308** to afford enyne **327** (**Scheme 3.2**).

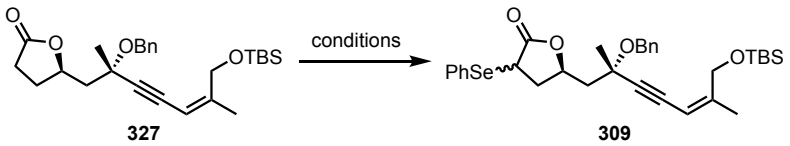
The synthesis of vinyl iodide **308** was quite straightforward, as shown in **Scheme 3.3**. Following a procedure reported by Duboudin in 1979, propargyl alcohol (**89**) underwent a hydroxyl-directed carbometallation, which, upon quenching with $I_2$, afforded vinyl iodide **300** A




**Scheme 3.3**: Synthesis of vinyl iodide **308** & alternate alkynylations.

simple silyl protection followed to afford vinyl iodide **308**. With this compound in hand, I decided to explore the possibility of performing the Sonogashira coupling first, before addition of the alkyne moiety to ketone **204**. Thus, coupling with trimethylsilyl acetylene and desilylation furnished enyne **329** in an unoptimized yield of 35% over two steps, as shown in **Scheme 3.3**. The terminal alkyne was then deprotonated with $^{n}$BuLi, and the resulting lithium acetylide was quenched by the addition of ketone **204**. Although the desired tertiary alcohol **330** was obtained, the yield was poor, and the diastereoselectivity was not significantly better than the earlier established alkynylations (see **Table 3.1**). However, I began to consider the possibility of an alternative approach to the introduction of the C8–C10 relative stereochemistry by starting with ketone **331** followed by the addition of methylmagnesium bromide. In 1986, the Yamaguchi group had published a method for the direct conversion of esters to alkynyl ketones promoted by $BF_3$•$OEt_2$.[78] Unfortunately, when this protocol was applied to ester **296**, the reaction did not proceed smoothly with only trace amounts of the desired **331** observed. Similarly, *in situ* formation of the Weinreb amide did not produce **331** efficiently enough to warrant further efforts.

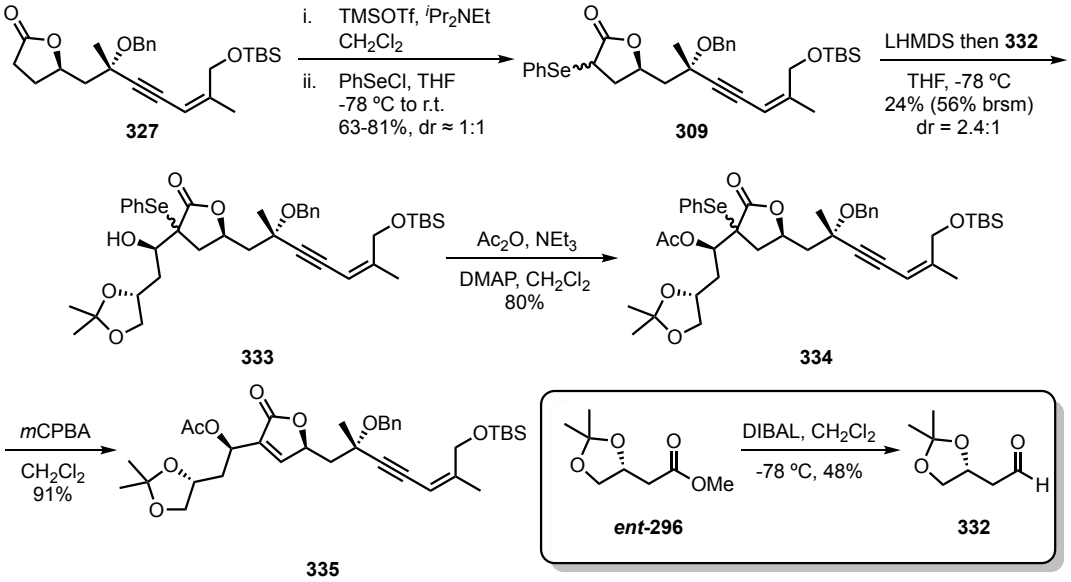
With lactone **327** in hand and efforts to further improve the C8–C10 stereoselectivity thoroughly abandoned, my focus then shifted to the installation of the phenylselenide moiety at the α-position of the lactone. Following the established procedure (see **Section 2.7**), the reaction was unsuccessful in my hands; the efforts to optimize this reaction are summarized in **Table 3.2**. Initially, the reaction was run at a higher dilution than normal. While the reaction worked with LHDMS as the base, yields and conversion were poor. The use of LDA and $(PhSe)_2$, as previously reported (**Section 2.7**), resulted only in the recovery of starting material




327 309

| Entry | Base (eq.) | Additive | Electrophile (eq.) | Solvent (Concentration) | Result |
|---|---|---|---|---|---|
| **1** | LHMDS (1.1) | HMPA (25%) | $(PhSe)_2$ (1.5) | THF (0.05 M) | 24% |
| **2** | LDA (1.1) | HMPA (25%) | $(PhSe)_2$ (1.5) | THF (0.05 M) | Recovered starting material |
| **3** | LHMDS (1.1) | HMPA (10%) | $(PhSe)_2$ (1.5) | THF (0.05 M) | 40% (52% brsm) |
| **4** | LHMDS (1.1) | HMPA (10%) | PhSeBr (3.0) | THF (0.05 M) | 19% (36% brsm) |
| **5** | LDA (1.2) | HMPA (10%) | $(PhSe)_2$ (1.5) | THF (0.05 M) | Recovered starting material |
| **6** | LDA (1.2) | HMPA (20%) | $(PhSe)_2$ (1.5) | THF (0.1 M) | 40% (59% brsm) |
| **7** | LDA (1.5) | HMPA (30%) | $(PhSe)_2$ (1.5) | THF (0.5 M) | 20% (36% brsm) |
| **8** | LDA (1.2) | None | PhSeCl (1.5) | THF (0.5 M) | 5% (17% brsm) |
| **9** | $^{i}Pr_2NEt$ (18.6) | TMSOTf (5.4) | PhSeCl (5.4) | $CH_2Cl_2$ (0.1 M) THF (0.1 M) | Decomposition on workup |
| **10** | $^{i}Pr_2NEt$ (18.6) | TMSOTf (5.4) | PhSeCl (5.4) | $CH_2Cl_2$ (0.1 M) THF (0.1 M) | 32% |
| **11** | $^{i}Pr_2NEt$ (18.6) | TMSOTf (5.4) | PhSeCl (1.2) | $CH_2Cl_2$ (0.1 M) THF (0.1 M) | 63% |

**Table 3.2**: Summary of optimization efforts of selenation.

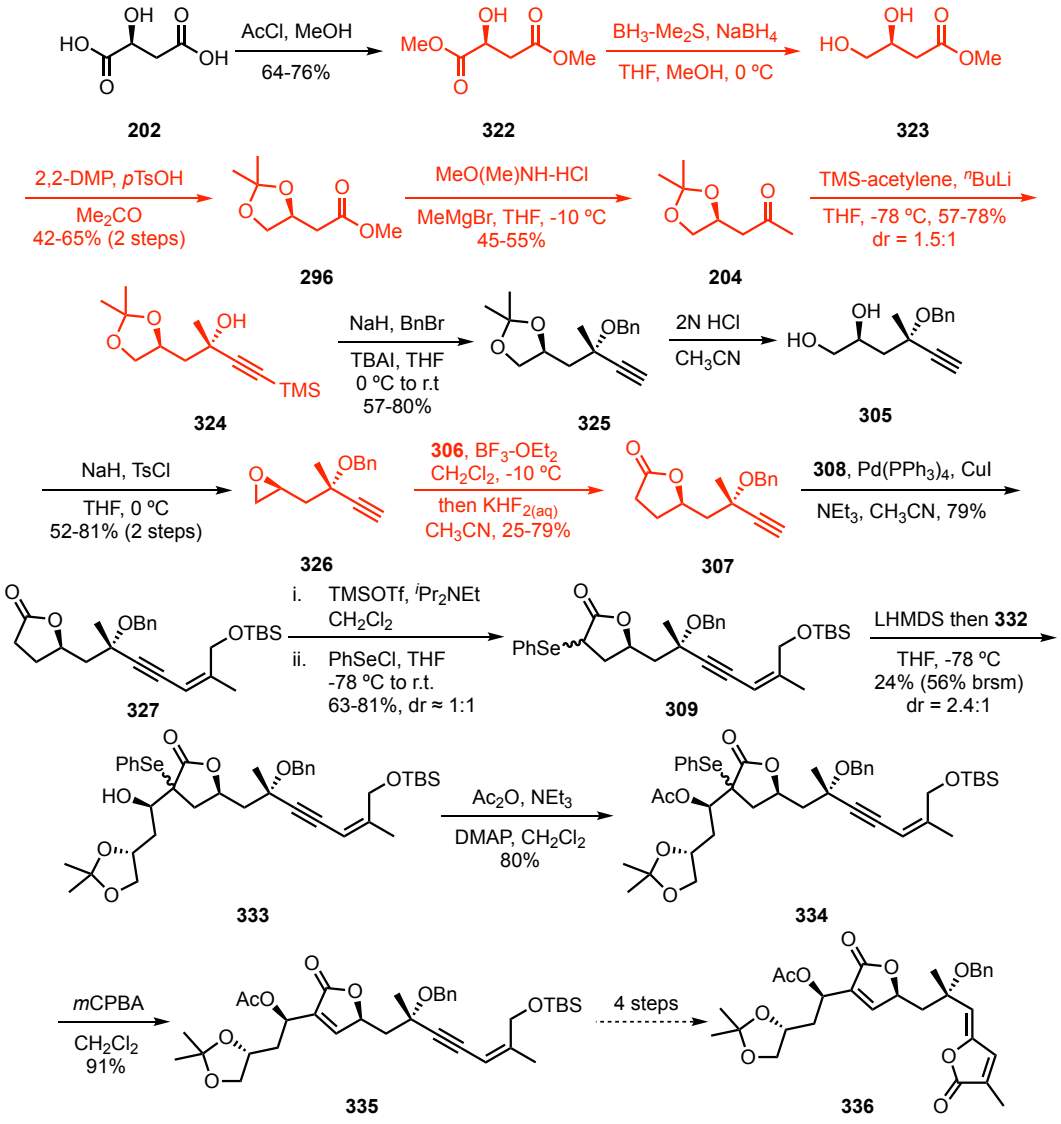



327 309 333 334 335 *ent*-296 332

**Scheme 3.4**: Synthesis of butenolide **335**.

at 0.05M concentration. Increasing the concentration improved conversion when LDA was used; however, the yields remained poor. After repeated failure at using a strong base to generate the enolate, I opted for an approach that had been used in the past to prepare α-selenolactones.[79] Generation of the silyl ketene acetal with Hünig's base and TMSOTf, followed by treatment with PhSeCl afforded, after some further optimization, the desired α-selenolactone **309** in a reproducible 63% yield and as an inconsequential mixture of diastereomers (dr ≈ 1:1).

During the course of the optimization of the phenylselenation reaction, my confidence in this route began to waver and material throughput became exceedingly difficult. Nevertheless, once sufficient quantities of phenylselenide **309** were generated, it was subjected to an aldol reaction with aldehyde **332** (derived from ***ent*-296**). This choice of aldehyde is crucial, as it




**Scheme 3.5**: Summary of first-generation synthesis.

would serve as a synthetic precursor to the A-ring butenolide (see Section 3.2). As shown in **Scheme 3.4**, alcohol **333** was generated in poor yield and with modest selectivity. Although the absolute configuration of the newly formed stereocenter was not determined, the model for aldol additions to ß-alkoxy aldehydes suggests that the configuration favors the desired 1,3-*anti* relationship.[80] Acetylation and oxidative selenoxide elimination afforded butenolide **335**.

At this point, I decided to abandon this synthetic route. The problems with the synthesis became quite apparent and I was never able to synthesize gram-quantities of lactone **327** — only 20 mg of butenolide **335** had been prepared. Shown in **Scheme 3.5** is a summary of the first-generation synthesis, with the problems highlighted in red. The main issues with this route, then, are the poor yields in each of the first four steps, the poor asymmetric induction in setting the C8 stereocenter, and the inconsistent ring expansion of epoxide **326**. Furthermore, an additional four steps would be required to synthesize bis-butenolide **336**, the substrate for the photochemical cycloaddition. That would bring the overall step count to 18 steps to reach the key intermediate — this seemed too high and did not bode well for a successful total synthesis. However, the work completed on this first-generation had highlighted some features that would serve as the focal points in the development of any subsequent generations. First, efficient control of the C8–C10 relative stereochemistry is crucial — whether accessed via reagent control or substrate control, non-selective or poorly selective reactions are unacceptable. Second, a new method is needed to reliably prepare what would become the B-ring butenolide. Finally, the beginning of the synthesis must be reproducible, high-yielding, and amenable to multigram scales. But before discussing how these considerations were addressed in the second-generation synthesis, I want to first shift attention to the synthesis of a compound resembling aldehyde **IV** (**Figure 3.1**).

## 3.2 Initial Attempts at the Synthesis of α,ß-Disubstituted Butenolide

Although there are many methods by which to prepare monosubstituted butenolides, the synthesis of α,ß-disubstituted butenolides is considerably more challenging. Inspired by a 1996 report from the Welzel group (see **Figure 3.2**),[81] in which digitoxigenin (**337**) was be selectively allylated in the α-position to produce disubstituted butenolide **338**, I decided to first attempt to prepare the desired ß-substituted butenolide **339**, **Scheme 3.6**. This could be accomplished using an olefination reaction of the corresponding α-hydroxyketone **340**, which could ostensibly come from the corresponding diol; however, it was desirable to avoid excessive protecting group manipulations. Therefore, I decided to start from alcohol **341**, which was prepared from L-malic acid (**202**) in two steps (**Scheme 3.6**).[82] Benzyl protection followed

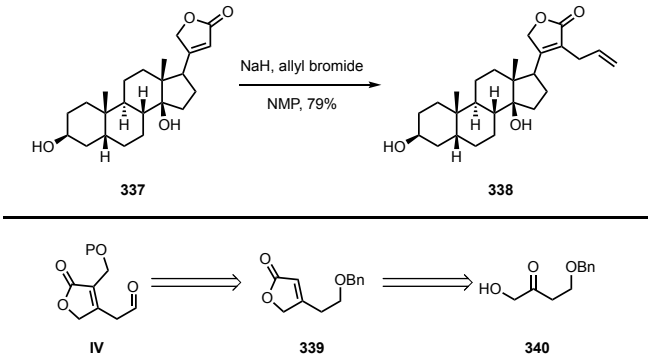
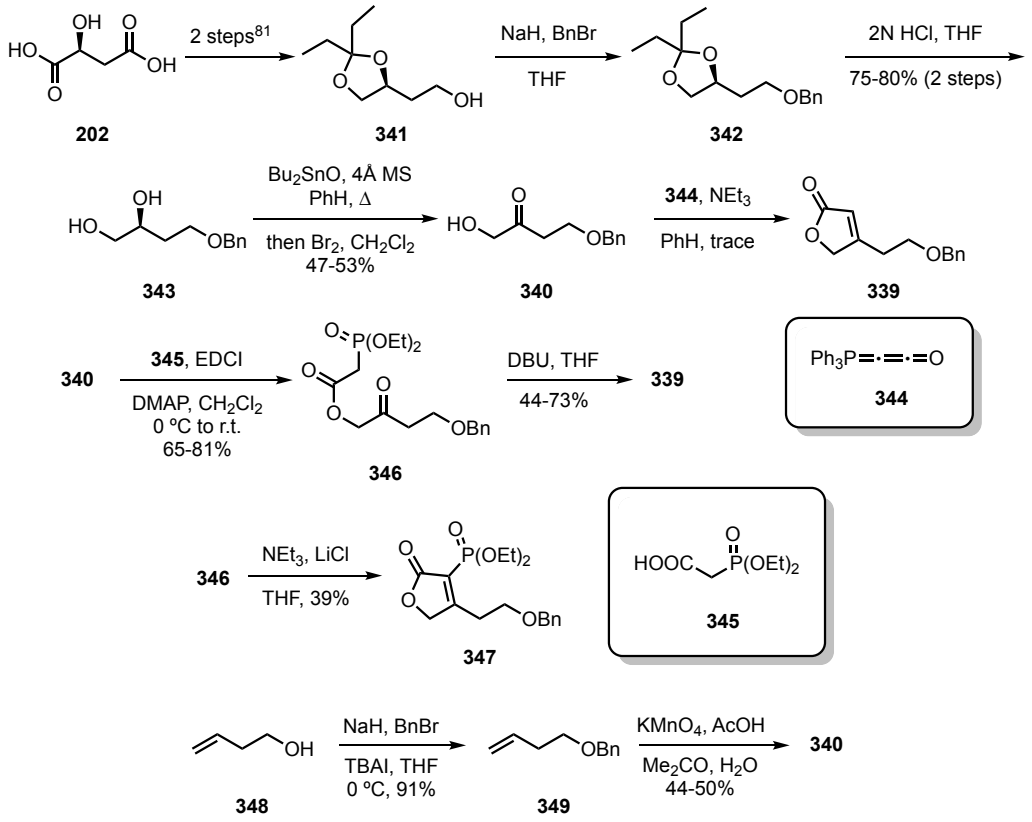



**Figure 3.2**: Inspiration for synthesis of α,ß-disubstituted butenolide.

by hydrolysis of the ketal afforded diol **343** in good yields. It was then necessary to oxidize the secondary alcohol selectively, ideally in a manner in which protection of the remaining primary alcohol would be unnecessary. Fortunately, there is a method for the regioselective manipulation of diols via an intermediate stannylene ketal.[83,84] Thus, treatment of the diol with dibutyltin oxide in refluxing benzene followed by the addition of bromine resulted in clean conversion to **340**. Although the yields were modest, no aldehyde byproducts were observed,

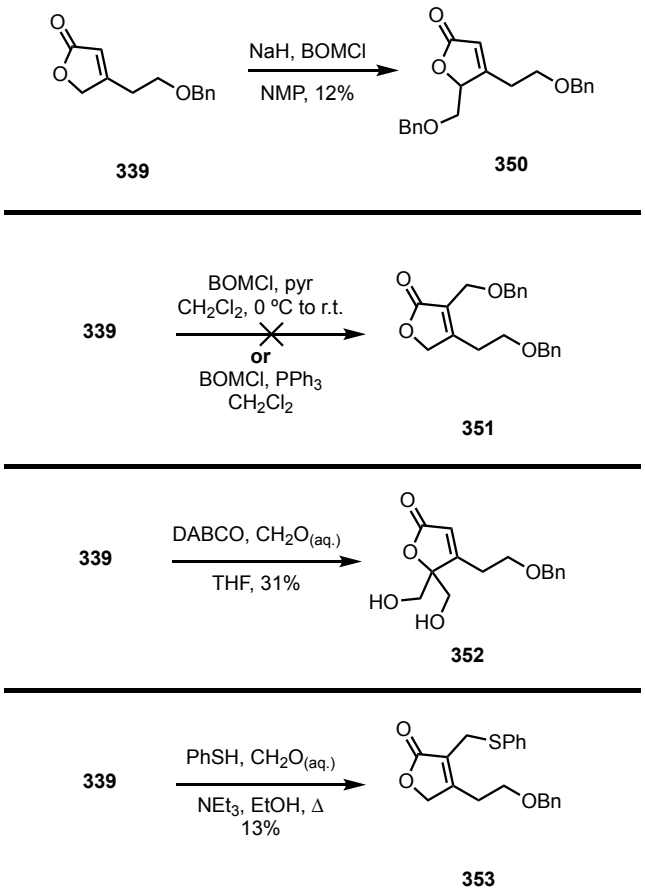



**Scheme 3.6**: Synthesis of ß-substituted butenolide **339**.

indicating a completely regioselective oxidation. This transformation may also be performed with NBS as the oxidant;[85] however, the significantly lower yields and the difficulty with removal of succinimide byproducts proved it to be inferior.

With ketone **340** in hand, efforts then shifted towards fashioning the butenolide ring to generate **339**. The first attempts at this transformation involved a one-step process using the ylide **344**, first developed by Bestmann.[86,87] Unfortunately, under these conditions only trace amounts of the desired butenolide **339** were observed, and I opted to pursue a more reliable, two-step procedure. Thus, esterification of the primary alcohol with diethylphosphonoacetic acid (**345**) afforded phosphonate ester **346**. When treated with DBU, ester **346** underwent the desired intramolecular Horner–Wadsworth–Emmons reaction to afford butenolide **339**. It should be noted that the yields of this reaction were lower when performed at larger scale. Interestingly, when ester **346** was treated with $NEt_3$ and LiCl, no phosphonate elimination occurred, resulting in the isolation of vinyl phosphonate **347** as the major product.

At the same time I had developed a more concise route to hydroxyketone **340**, based on the report that terminal olefins could selectively be oxidized with $KMnO_4$ to the




**Scheme 3.7**: Attempted alkylation of butenolide **339**.

corresponding hydroxyketone.[88] Indeed, when exposed to the reported conditions, olefin **349** was oxidized to hydroxyketone **340** in modest yields. Although the yield was comparable to the tin-mediated oxidation, this new method enabled the synthesis of **340** in just two steps from a commercially available starting material (as opposed to five steps from **202**).

Now that sufficient quantities of **339** had been synthesized, it was time to begin exploring the possibility of functionalization at the α-position. As shown in **Scheme 3.7**, attempts to reproduce the reported allylation (see **Figure 3.2**) with BOMCl as the electrophile resulted in trace amounts of the γ-alkylated product **350** as the only identifiable product. Alkylation with BOMCl at the α-position under Morita–Baylis–Hillman conditions ($PPh_3$ or pyridine) did not show even traces of the desired product (**351**), and starting material was recovered. However, when formaldehyde was used as the electrophile, bis-alkylation at the γ-position occurred to provide diol **352** as the major product, along with 18% recovered starting material. Finally, the Kirk–Petrow[89] method for installation of a thiomethyl moiety afforded only 13% of the desired α-substituted butenolide **353**, with the remainder of the material decomposing. With these results in mind, I realized that that it would be more practical to incorporate the full substitution before installation of the butenolide moiety. Those efforts will be discussed in Section 3.4.

## 3.3 Second Generation: Convergent Synthesis of Enyne

The second-generation approach to lactone **309** was designed to address the problems with the first generation directly; these were brought up at the end of Section 3.1. The analysis, shown in **Figure 3.3**, is centered on a chelation-controlled addition of stannylacetylene **354** to methyl ketone **355**. This approach was inspired by two publications by Evans that reported high diastereoselectivities in the addition of stannylacetylenes to ß-silyloxy- or ß-alkoxyaldehydes, mediated by dimethylaluminium chloride.[90,91] Thus, I had hoped that this

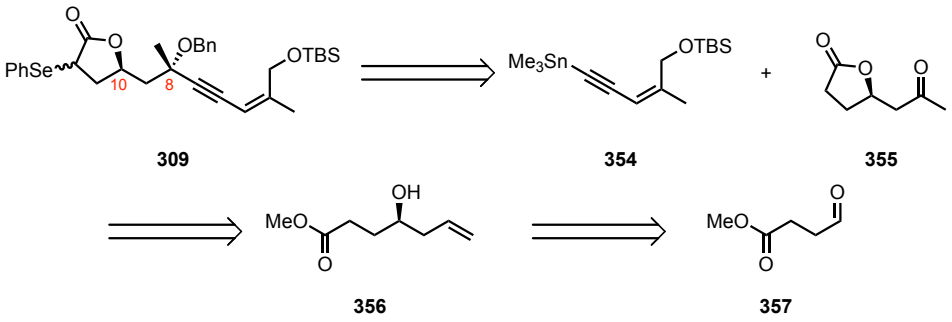
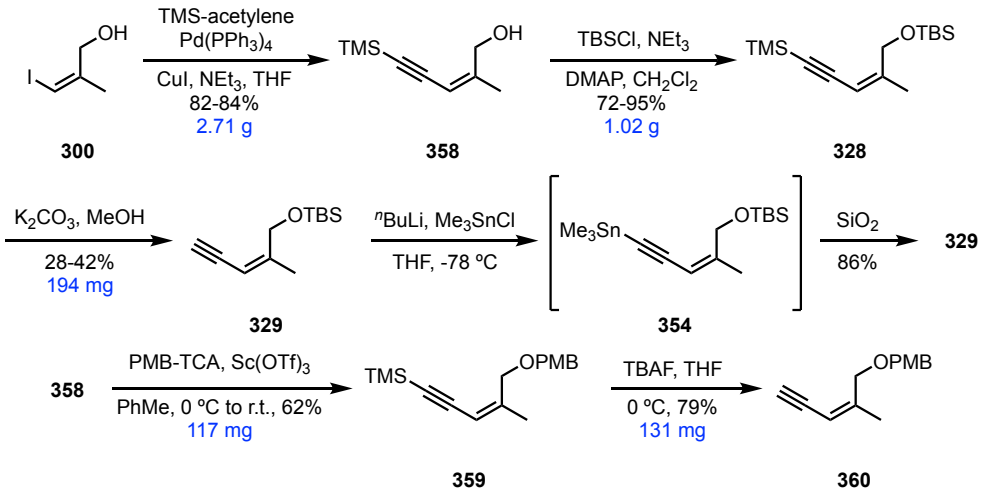



**Figure 3.3**: Second-generation approach to lactone **309**.

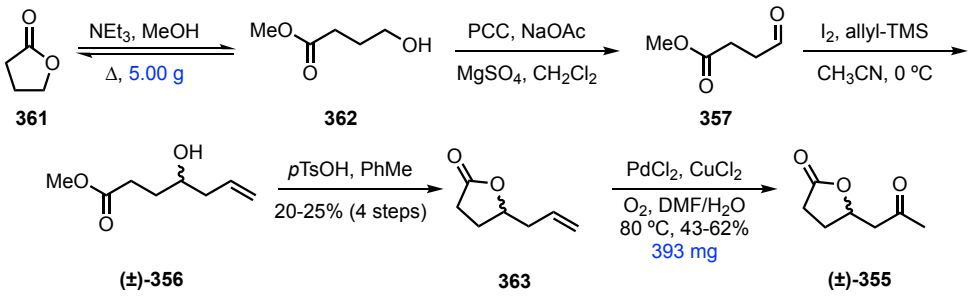
methodology could be extended to the ß-alkoxyketone (**355**) with only a modest decrease in diastereoselectivity, apparently solving the previous problems in setting the C8 stereocenter. The synthesis of **354** would be rather straightforward and require only slight modifications of the route shown in **Scheme 3.3**. The synthesis of **355**, however, would require a considerable adjustment in order to set the C10 stereocenter efficiently and provide a robust method for the construction of the lactone ring. I had envisioned that the lactone ring could simply arise from the acid-catalyzed cyclization of γ-hydroxy ester **356** and that the corresponding homoallylic alcohol could be introduced by an asymmetric allylation reaction of aldehyde **357** to set the C10 stereocenter. If the synthesis went according to plan, not only would it be two steps shorter in comparison to the first generation synthesis, but also the C8–C10 relative stereochemistry problem would be addressed, and lactonization would be straightforward, avoiding the need for sensitive and expensive reagents. However, as any practitioner of organic synthesis knows quite well, syntheses rarely, if ever, go according to plan.




**Scheme 3.8**: Attempted synthesis of stannane **354**.

The synthesis of alkynylstannane **354** (**Scheme 3.8**) was inspired by the previous work discussed in Section 3.1. Initially, Sonogashira coupling of vinyl iodide **300** with TMS-acetylene afforded allylic alcohol **358** in good yields. In order to intersect with the previous enyne intermediate **328**, the allylic alcohol was protected as the TBS ether. Desilylation continued to be problematic under standard conditions ($K_2CO_3$/MeOH) resulting in low yields and poor mass recovery. The use of DBU in aqueous acetonitrile reported by Kim[92] did not show any improvement in yields and the attempted alkyne desilylation of **358** was unsuccessful. However, despite the low yields, I was able to prepare sufficient quantities of the alkyne to

attempt the stannylation. Deprotonation of alkyne **329** with $^{n}$BuLi followed by quenching with $Me_3SnCl$ afforded the desired stannane **354** (observed by crude NMR); however, upon filtration through a plug of $SiO_2$, protodestannylation occurred, and **329** was recovered as the sole product. At the same time, I sought to optimize the desilylation by simply switching the protecting group on the allylic alcohol. The use of a PMB group, rather than a silicon-based protecting group, enabled the TBAF-mediated desilylation of **359** with markedly improved yields. Stannylation of **360** in a similar manner appeared promising (TLC analysis); however, upon purification on basic $SiO_2$, it similarly resulted in destannylation and led to the recovery of alkyne **360**. The purification of the stannane would require significant optimization in order to attempt the diastereoselective addition to ketone **355**.

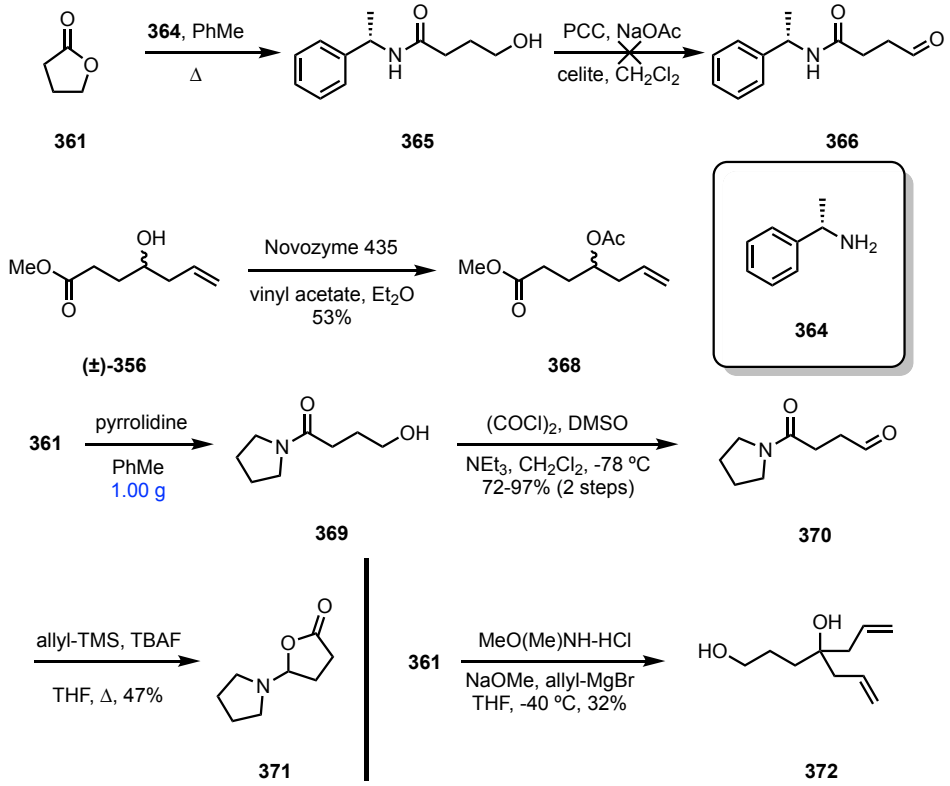



**Scheme 3.9**: Synthesis of ketone **355**.

The synthesis of **355** was somewhat more straightforward, and it was rapidly scaled up to multigram quantities. As shown in **Scheme 3.9**, the synthesis of **355** started from commercially available (although restricted) γ-butyrolactone (**361**). Methanolysis of the lactone ring was straightforward; however, the reaction was reversible and seemed to equilibrate to a 2:1 ratio of **362**:**361**. The resulting alcohol was then oxidized to afford the desired aldehyde **357**. Although I initially wanted to set the C10 stereocenter via enantioselective allylation of this aldehyde, I had decided to move forward using the racemic series as a model system. Thus, allylation was accomplished using the allyltrimethylsilane and a catalytic amount of $I_2$, following the method of Yadav,[93] to generate homoallylic alcohol **(±)-356** in just five minutes. Interestingly, **(±)-344** was reluctant to lactonize, even when exposed to $SiO_2$ for two hours. Finally, acid-catalyzed cyclization afforded the lactone **363** in 20–25% yields over the four steps. Wacker oxidation[94,95] of the terminal olefin completed the synthesis of **(±)-355** in just five steps. There are a couple of issues with this sequence, however, that should be pointed out. First, the incomplete methanolysis of **361**, resulting in a 3:1 mixture of product and starting material, inherently inhibits the production of quantitative amounts of alcohol **362**, which is probably the primary reason that the yield of this four-step sequence is so low. Second,

purification of both aldehyde **357** and alcohol **356** was quite challenging. Finally, as the synthesis, as shown, produces a racemate, the enantioselective allylation had to be thoroughly vetted.

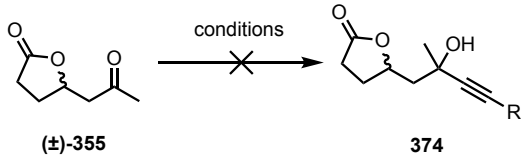
In addressing these concerns, the first problem to tackle was the most important, namely, the question of enantioselective allylation. Unfortunately, the attempted asymmetric allylations using either Kriche's iridium-catalyzed allylations[96] or Keck's titanium-promoted addition of allylstannanes[97] did not prove fruitful. Shifting attention away from asymmetric allylation, I thought that perhaps the initial opening of **361** might be performed with a chiral alcohol and that later the diastereomers could be separated before re-lactonization. I chose menthol, because of its derivatives having a long history of use as chiral auxiliaries;[98] however, when a mixture of **361** and excess menthol was heated in neat $NEt_3$, no ring-opening occurred. Perhaps, then, the question of thermodynamics could be addressed by using an amine-based nucleophile, as the resulting amide would be more reluctant to cyclize under standard conditions. Indeed, when the chiral α-methyl-N-benzylamine (**364**) was used, as shown in **Scheme 3.10**, the ring-opening reaction proceeded smoothly to afford the chiral amido alcohol **365**. Unfortunately, oxidation of the primary alcohol did not result in the desired aldehyde **366**. Although it was not clear what had happened, the $^1H$ NMR spectrum of the crude reaction




**Scheme 3.10**: Miscellaneous failed reactions of **361**.

mixture indicated a loss of the three sets of methylene protons between the alcohol and the amide functionalities. Thinking that it might be more successful to use a secondary amine, I attempted the ring opening, unsuccessfully, with the methyl ester of proline. In a final effort to produce the chiral secondary alcohol, an enzymatic resolution of alcohol **(±)-356** was attempted. Indeed, it was been reported in 2009 that the secondary alcohols bearing a similar substitution pattern were good substrates for the Novozyme 435-mediated resolution.[99] Although conversion to the corresponding acetate (**368**) was observed, the reaction was sluggish and inefficient. The full characterization of the acetate **368** was not pursued further.

Deciding to abandon, for the time being, the desire to impart enantioselectivity, I refocused my attention on improving the yields of the four-step sequence leading to **363** (**Scheme 3.9**). The use of pyrrolidine as the nucleophile in the ring-opening reaction led to alcohol **369** and subsequent Swern oxidation[100] cleanly afforded aldehyde **370** in a high-yielding, two-step process. Once again, the amide functionality proved problematic, however, when the aldehyde was exposed to Hosomi-Sakurai conditions[101] in order to effect the desired allylation. The major product isolated was amino lactone **371**, with only small amounts of the desired homoallylic alcohol **372** produced. I then attempted to directly allylate lactone **361** directly via *in situ* formation of the Weinreb amide, hoping to obtain the γ-hydroxy ketone.[102]




**(±)-355** **374**

| Entry | Alkyne (eq.) | Conditions | Solvent (Concentration) | Temperature | Results |
|---|---|---|---|---|---|
| **1** | **328** (1.2) | $Me_2AlCl$ (5.0 eq.) | PhMe (0.1 M) | -78 ºC | Recovered starting material |
| **2** | **359** (1.9) | $Me_2AlCl$ (3.0 eq.) TBAF (0.2 eq.) | $CH_2Cl_2$ (0.1 M) | -78 ºC | Recovered starting material |
| **3** | TMS-acetylene (1.2) | $Me_2AlCl$ (5.0 eq.) TBAF (0.2 eq.) | $CH_2Cl_2$ (0.1 M) | -78 ºC | Recovered starting material |
| **4** | TMS-acetylene (1.2) | $Me_2AlCl$ (3.0 eq.) TBAF (0.2 eq.) | $CH_2Cl_2$ (0.1 M) | -78 ºC to r.t. | Recovered starting material |
| **5** | TMS-acetylene (1.2) | $Me_2AlCl$ (3.0 eq.) TBAF (1.1 eq.) | $CH_2Cl_2$ (0.1 M) | -78 ºC to r.t. | Recovered starting material & unidentified byproduct |

**Table 3.3**: Attempted addition of alkynes to ketone **355**.

Redox manipulations would then lead to the desired γ-allylated lactone **363**. Under the reported conditions, however, the only identifiable product was the tertiary alcohol **373**, resulting from bis-allylation of the ester moiety.

At the same time, I was questioning my inability to form the requisite alkynylstannane (e.g., **354**) and began to think of some alternatives — could it be possible to effect the desired transformation from the alkynylsilane instead? Indeed, Verkade recently reported the addition of alkynylsilanes to carbonyl compounds promoted by a catalytic amount of TBAF.[103] My attempts at this transformation are shown in **Table 3.3**. The addition of either alkyne **328** or **359** to ketone **355** proved unsuccessful, resulting in only recovered starting material, although in the case of the former, mass recovery was quite poor. The addition was also attempted with a simpler alkyne, but the desired product (**374**) was never observed. The primary observation of these studies was recovery of ketone **355**.

The results presented in this section indicate that the second-generation attempts to set the C8–C10 relative stereochemistry were unsuccessful and that yet a different approach was required. However, the synthesis of the lactone ring was shown to be quite facile under acid-catalyzed cyclization conditions and demonstrated a great improvement over the ring-expansion method from the previous generation. Before moving onto the third-generation analysis, I would like to discuss contemporaneous efforts toward a second generation synthesis of aldehyde **IV**.

### 3.4 Diels–Alder Approach to α,ß-Substituted Butenolides

The second-generation synthesis of the α,ß-substituted butenolide moiety was inspired by a rather fortuitous discovery in the literature. In 1962, a group from Merck reported a new synthesis of pyridoxine (**379**) — also known as vitamin B6 — that began from a Diels–Alder reaction between oxazole **375** and diethyl maleate (**376**), as shown in **Figure 3.4**.[104,105] Upon treatment with acid, the resulting bicyclic hemiketal underwent a fragmentation to afford the highly substituted pyridine **378**. A simple reduction of the diester moiety completed the synthesis of **379**. Some years later, the Yadav group reported that, when an acetylene such as **380** was used as the dienophile, the resulting adduct would undergo a retro [4+2] cycloreversion with the expulsion of acetonitrile to afford the 3,4-disubstituted-2-ethoxyfuran (**382**).[106] Upon hydrolysis in the presence of an oxidant, the desired γ-hydroxybutenolide **383** was obtained. Notably, the cycloaddition was highly regioselective and furnished the electron-withdrawing group in the α-position of the resulting butenolide. I surmised that perhaps the use of an α,ß-acetylenic aldehyde could perform similarly in the Diels–Alder reaction sequence and

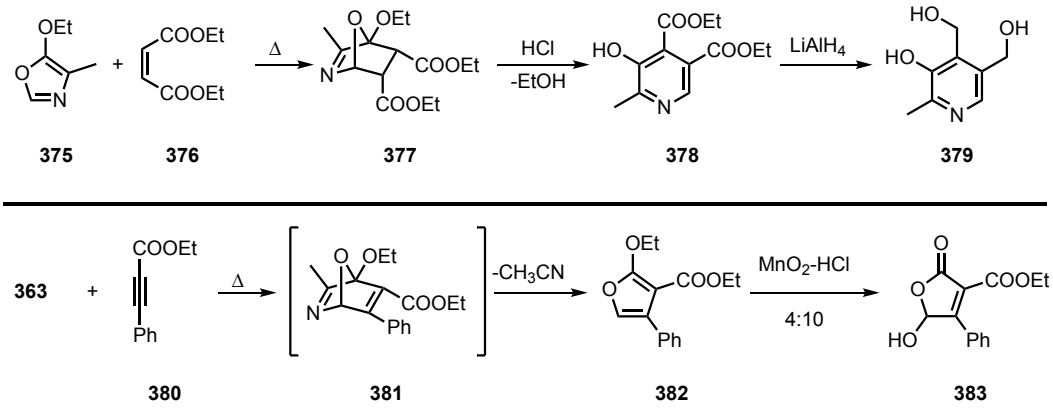
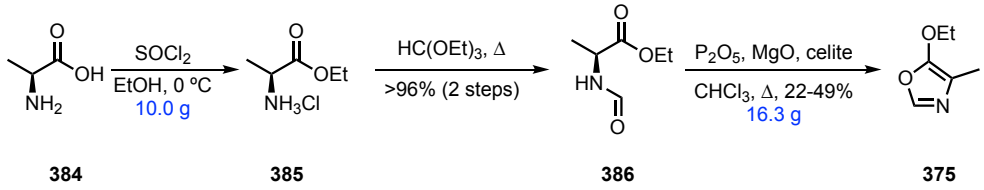



**Figure 3.4**: Inspiration for α,ß-substituted butenolide synthesis.

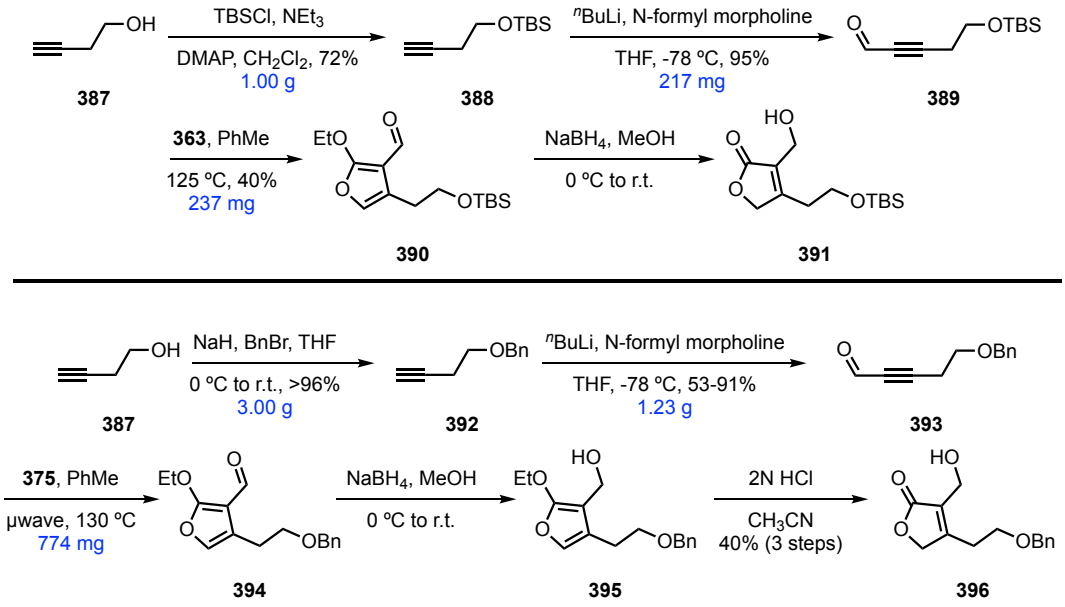
that subsequent chemoselective reduction would result in the desired α-hydroxymethyl moiety in aldehyde **IV** (**Figure 3.1**).




**Scheme 3.11**: Synthesis of oxazole **375**.

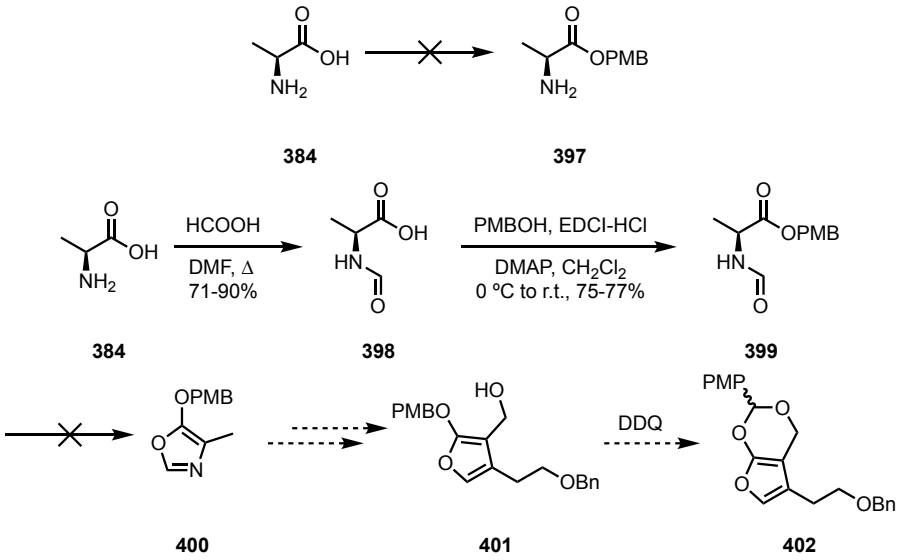
The synthesis of oxazole **375**, shown in **Scheme 3.11**, followed from a known literature procedure starting from the readily available L-alanine (**384**).[107] Esterification of the carboxylic acid proceeded smoothly to afford the corresponding ethyl ester as the HCl salt (**385**). The crude salt was then refluxed in neat triethyl orthoformate to afford *N*-formyl alanine ethyl ester (**386**). Finally, upon treatment with $P_2O_5$ in refluxing $CHCl_3$, aldehyde **386** underwent a cyclodehydration to yield oxazole **375**. There are a couple of things that are worth mentioning regarding the cyclodehydration. The yields of this reaction were quite low. I suspect that the reason for that is two-fold: first, because of the heterogeneous nature of the reaction (and the large quantities of the reactive $P_2O_5$), the quench and workup was often quite challenging, particularly on larger scales. Secondly, the oxazole product was volatile, and, though it could be purified easily by distillation, some quantities were likely lost during removal of the solvents. Nevertheless, the reaction could be performed on large scales, resulting in the isolation of multigram quantities of oxazole **375**.

The alkyne component was prepared in a three-step sequence, starting from butyn-1-ol (**387**). Initially, I opted for a TBS protecting group for the primary alcohol. Subsequent



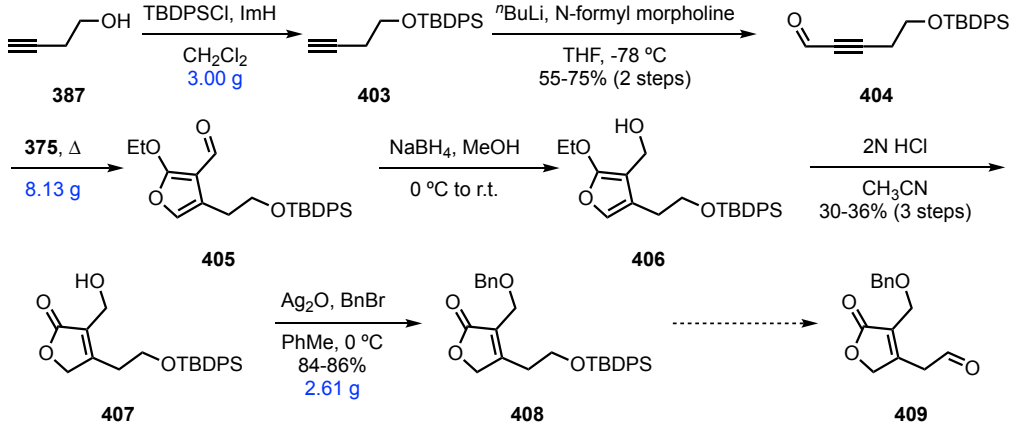

**Scheme 3.12**: Synthesis of alkyne and initial Diels–Alder results.

formylation of the alkyne by a sequence of deprotonation and quenching with *N*-formyl morpholine afforded aldehyde **389**. The Diels–Alder reaction occurred by refluxing aldehyde **389** and oxazole **375** in toluene to yield ethoxyfuran **390**. Reduction of the aldehyde presumably led to the corresponding alcohol; however, the ethoxyfuran moiety appeared to hydrolyze upon purification resulting in the isolation of butenolide **391**. It seemed that the electron-withdrawing nature of the aldehyde had a considerable stabilizing effect on the electron-rich furan ring. At this point, I had not given much thought to the nature of the protecting group on the α side chain and assumed it would be most prudent to employ a silyl group. However, that necessitated a change of the protecting group on the ß side chain; therefore, the formyl acetylene was prepared with a benzyl protecting group to provide aldehyde **393**. During this effort, the reaction sequence was scaled up and further optimized. It was noted that the yields of the formylation had become quite variable, and the efficacy of the reaction was apparently highly dependent upon the nature of the quench. A group from Merck's process department, who studied this reaction in some detail in the late 1990s, reported that, when a standard acidic quench was used, isolated yields of the desired aldehydes were unacceptably low.[108] This was because of a series of Michael additions of the amine byproduct (morpholine, in this case) to the acetylene moiety, resulting in the loss of products as the corresponding ammonium salts. Performing a reverse quench into cold 10% aqueous $KH_2PO_4$ alleviated these side reactions, and, when applied to the synthesis of **393**, isolated yields were consistently >70%.




**Scheme 3.13**: Alternative protecting group methods.

Moving forward, the Diels–Alder reaction was further scaled up, and it was determined that the optimal sequence was to carry the crude cycloadduct **394** on to the reduction and subsequent hydrolysis so that the significantly more stable butenolide **396** could be isolated. Base-promoted protections of the resulting primary alcohol were unsuccessful, and it was thought if oxazole **400** (**Scheme 3.13**) was prepared from the corresponding PMB ester, perhaps the primary alcohol could be trapped upon treatment of benzyloxyfuran **401** with anhydrous DDQ. I then set out to attempt to synthesize oxazole **400**. Analogous esterification of alanine (**384**) with PMBOH was unsuccessful; however, performing the formylation first, following the method reported by Palomo,[109] proved effective in synthesizing acid **398**. Esterification with EDCI then afforded compound **399**; however, the subsequent




**Scheme 3.14**: Final route to aldehyde **409**.

cyclodehydration failed and resulted in decomposition of the substrate. This strategy for protection was abandoned.

The third and final, optimized route to the desired α,ß-substituted butenolide is shown in **Scheme 3.14**. I had settled on going back to a silyl-based protecting group on the ß side chain (opting for the more hindered TBDPS ether in order to suppress the volatility of aldehyde **389**) and installing a benzyl ether as the protecting group on the α side chain. Although both acidic conditions [BnTCA, $Sc(OTf)_3$] and basic conditions (NaH, BnBr) were unsuccessful for installing the benzyl ether, the use of benzyl bromide in the presence of silver(I) oxide afforded benzyl ether **408** in good yields and on multigram scales. It is noteworthy that the yields were considerably higher when freshly prepared silver(I) oxide was used rather than the commercial reagent. Although aldehyde **409** was never prepared, one can imagine that desilylation (TBAF or HF) followed by oxidation would afford **409** in two simple operations from **408**. With an efficient route to multigram quantities of **408** developed, this work was set aside in favor of devoting my full attention towards a synthesis of the required lactone coupling partner.

## 3.5 Barbier Approach to Alkyne 307

The failed attempt at setting the C8 stereocenter via a diastereoselective alkyne addition was incredibly frustrating, and the synthesis of lactone **309** clearly required a substantially different approach. As shown in **Figure 3.5**, I reasoned that perhaps I could still make use of the efficient Sonogashira coupling between vinyl iodide **308** and alkyne **307**. I thus began to rethink the synthesis of **307**. Rather than installing the alkyne by means of the addition of an alkynyl metal species to a methyl ketone, I thought that it could be installed via a homologation of aldehyde **410**, which, in turn, would arise from a Sharpless dihydroxylation of olefin **411**. By making use of reagent control to set the C8 stereocenter, I would no longer need

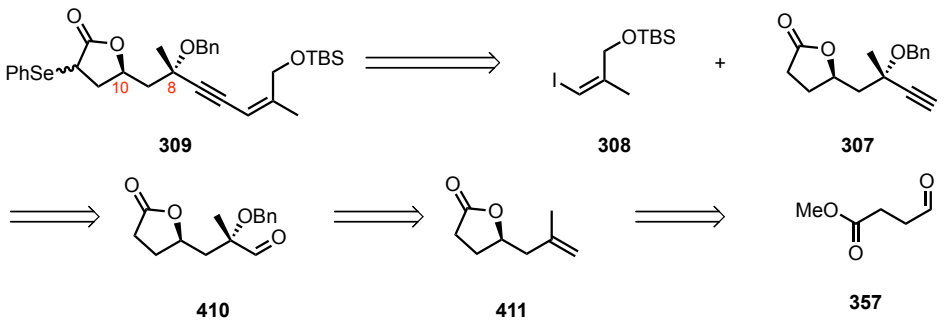
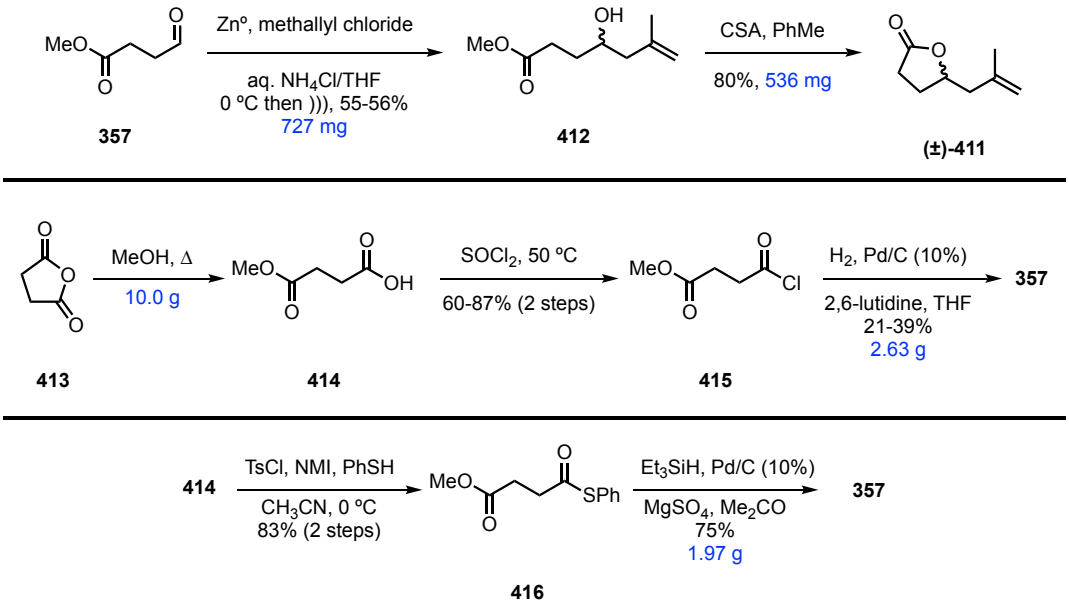



**Figure 3.5**: Third generation approach to lactone **309**.

to rely on the inefficient asymmetric induction from the C10 stereocenter. Finally, olefin **411** would be similarly accessible from the previously prepared aldehyde **357** in two simple steps.

Starting from aldehyde **357**, which was initially prepared as shown in **Scheme 3.9**, a zinc-mediated Barbier reaction using methallyl chloride afforded the substituted homoallylic alcohol **412** (**Scheme 3.15**).[110,111] A rapid screen of conditions for the lactonization was then undertaken. It was determined that the treatment of alcohol **412** with a catalytic amount (0.3 eq.) of CSA was found to effect the desired reaction in just two hours and in good yields.

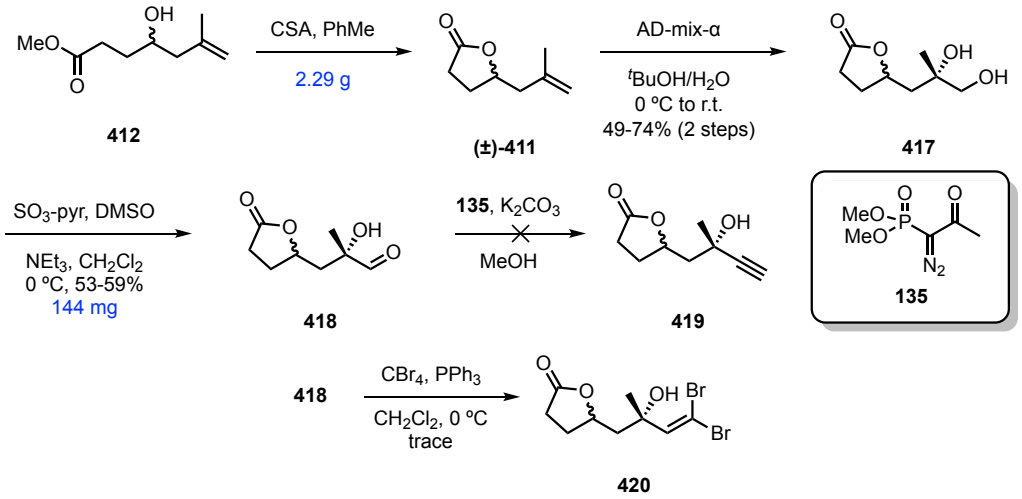
At this point, the material throughput for aldehyde **357** became quite difficult because of the thermodynamic mixture produced upon methanolysis of γ-butyrolactone (**361**). What was required was a ring-opening reaction that was, in effect, irreversible. While the amine-based nucleophiles used in **Section 3.3** led to irreversibility, there were problems with unwanted reactivity that occurred once the primary alcohol had been oxidized to the corresponding aldehyde (see **Scheme 3.10**). However, the methanolysis of succinic anhydride (**413**) should be rather simple and the lower nucleophilicity of the corresponding carboxylic acid should presumably prevent reversion to the starting material. Indeed, when a methanolic solution of **413** was heated to reflux, the half-ester **414** was obtained in nearly quantitative yields. Conversion of carboxylic acid **414** to the acid chloride **415** was also straightforward, and the product could be easily distilled on multigram scale. Semi-reduction of the acid chloride by Rosenmund reaction[112] proceeded cleanly to give aldehyde **357**; however, yields were consistently low. I surmised that the low yields were due to the sensitive nature of the acid chloride functionality, so I sought to avoid this compound as an intermediate. Thinking about




**Scheme 3.15**: Various syntheses of aldehyde **357**.

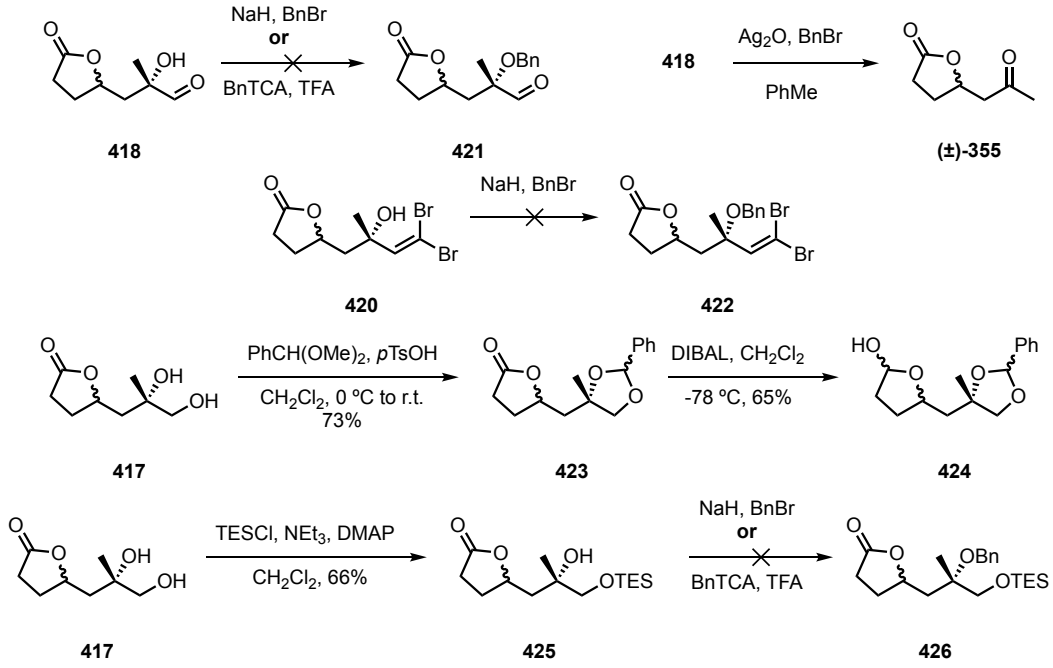
alternative methods to semi-reduce carbonyls from the carboxylic acid oxidation state to that of an aldehyde, I turned to the preparation of the corresponding thioester, by using the methodology developed by Tanabe.[113] Thioester **416** was thus prepared on multigram scale and in 83% yield from succinic anhydride (**413**). The thioester could then be cleanly reduced to the corresponding aldehyde using a mixture of triethylsilane and palladium on carbon as described by Fukuyama.[114]

With an acceptable route to the racemic lactone **411** established, I began efforts toward installation of the tertiary alcohol and subsequent homologation of the primary alcohol, shown in **Scheme 3.16**. I decided to go ahead and employ Sharpless' asymmetric dihydroxylation to install the tertiary alcohol.[115] The reaction was quite effective at leading to the desired dihydroxylation and affording diol **417** as an inseparable mixture of diastereomers. At this time, the enantioselectivity of the dihydroxylation was not determined, and I assumed that the selectivity was aligned with the model previously described by Sharpless, as well as examples of asymmetric dihydroxylations of some analogous 1,1-disubstituted olefins.[116] With diol **417** in hand, I moved forward to the oxidation, continuing to work with the mixture of diastereomers. Cognizant of the issues associated with the oxidation of 1,2-diols, a small screen of mild oxidants (DMP, TEMPO, activated DMSO) was undertaken to determine the optimum conditions for this transformation. Both DMP[117] and TEMPO[118] afforded mixtures of the desired aldehyde **418** and the product of oxidative cleavage, ketone **355**, despite the authors reporting that 1,2-diols could be oxidized to the corresponding aldehyde in 95% yields with TEMPO. Nevertheless, the Parikh–Doering[119] oxidation proved effective, and no traces of ketone **355** were detected. Unfortunately, the homologation of aldehyde **418** was unsuccessful with the Ohira–Bestmann reagent,[120] and homologation to the *gem*-dibromide according to the method




**Scheme 3.16**: Dihydroxylation and attempted homologations of aldehyde **418**.

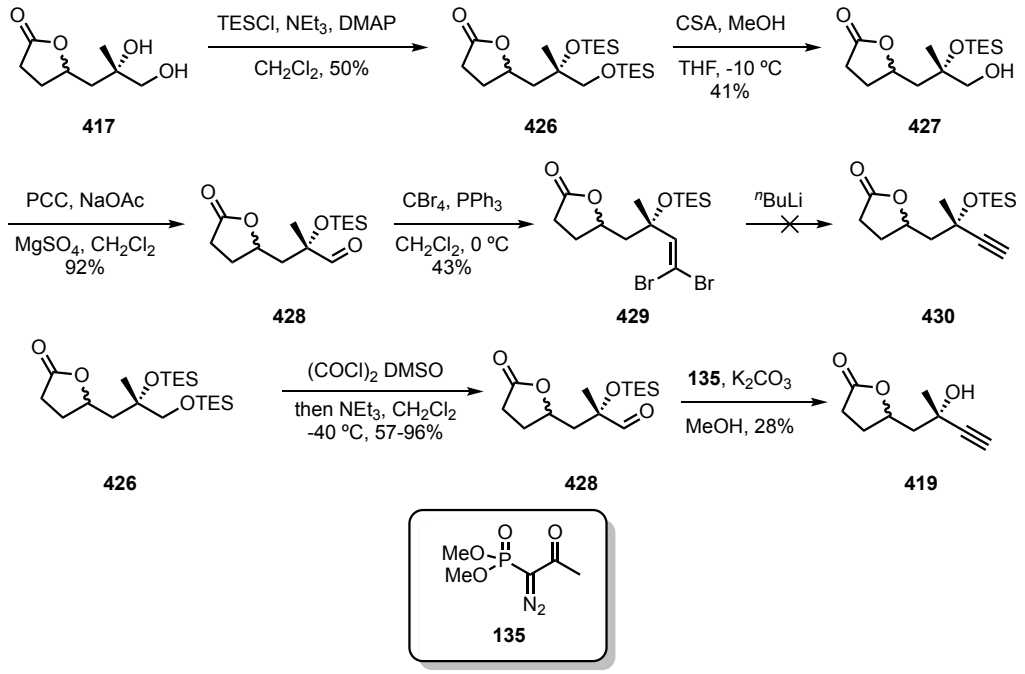
of Corey and Fuchs[121] only afforded trace amounts of the desired product (**420**), **Scheme 3.17**. The elimination step was not attempted, and I reasoned that protection of the tertiary alcohol might be necessary.




**Scheme 3.17**: Attempted benzyl protections of the tertiary alcohol.

In order to intersect with the first-generation route, I sought to install a benzyl ether protecting group, particularly in such a way that excessive protecting group manipulations would be avoided. As shown in **Scheme 3.17**, initial attempts focused on installing the benzyl ether on aldehyde **418**. Not surprisingly, these attempts resulted, for the most part, in decomposition of the aldehyde. It is interesting that the use of $Ag_2O$ and BnBr resulted in oxidative cleavage to ketone **355** as the only identifiable product. Similarly, protection of the alcohol in dibromide **420** was also unsuccessful. Some success was achieved when diol **417** was converted directly into the benzylidene acetal (**423**); however, the lactone carbonyl proved more susceptible to reduction with DIBAL than the benzylidene and only lactol **424** was observed. Monoprotection of the primary alcohol as its triethylsilyl ether was, likewise, successful; however, all attempts at protection of the remaining tertiary alcohol resulted in either recovery of starting material or decomposition. Evidently, the tertiary alcohol was too hindered to react with BnBr.

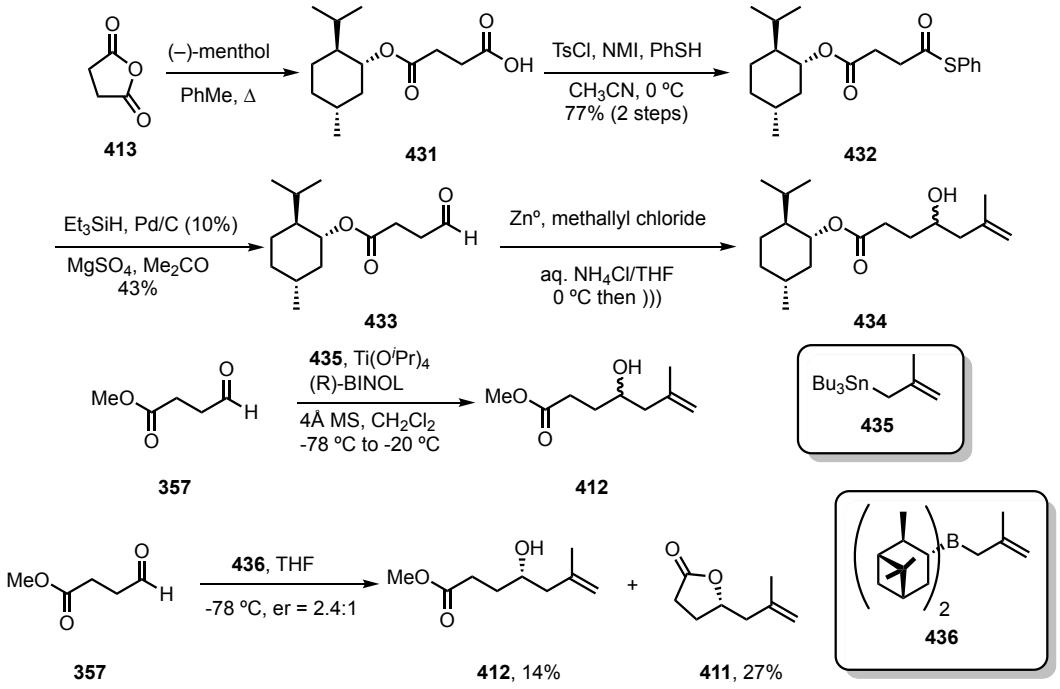
Fortune turned when I opted to protect both alcohols as the corresponding triethylsilyl ethers, as shown in **Scheme 3.18**. Furthermore, chemoselective deprotection of the primary




**Scheme 3.18**: Successful protection and homologation.

silyl ether afforded alcohol **427** and subsequent oxidation with PCC led to aldehyde **428** in good yields. Homologation of the aldehyde to the corresponding dibromide was effective, albeit in low yields; however, the elimination with $^{n}$BuLi did not produce the desired alkyne **430**. At around the same time, I noticed that it was, indeed, possible to perform a direct oxidation of the primary silyl ether of **426** to aldehyde **428**.[122] During the course of the reaction, it was crucial to ensure that the primary silyl group was removed before addition of the $NEt_3$. Following the oxidation, the Ohira–Bestmann homologation was attempted once more, and to my delight, alkyne **419**, **Scheme 3.18**, was isolated, albeit with concomitant complete removal of the tertiary silyl ether. Although the yield was poor, I was encouraged by these results and set my sights on the installation of the correct stereochemistry at C10.

In order to impart the stereochemistry required at the secondary alcohol, I first attempted the ring opening of succinic anhydride (**413**) with menthol. My thought process was that, in the best-case scenario, the chiral ester moiety would afford some level of diastereoselection in the subsequent Barbier reaction. In the worst-case scenario, there would be no influence of the remote chiral centers, and the mixture of diastereomers could then be separated into enantiopure secondary alcohols. Unfortunately, as shown in **Scheme 3.19**, neither one of these occurred, and what ultimately resulted was an approximately 1:1 mixture of inseparable diastereomers (**434**). Fortunately, this was not the only way to create a chiral homoallylic alcohol as there exist a handful of asymmetric methallylation methods. I first




**Scheme 3.19**: Attempted introduction of C10 stereochemistry.

attempted to try the Keck asymmetric methallylation using the titanium-mediated addition of an allylstannane (**435**).[123,124] The reaction did not proceed to completion, even after being allowed to react for 48 hours. Although some product was obtained, the reaction was not efficient enough to move forward with it. The next attempt was made by means of the pinene derived borane **436** following Brown's allylation conditions.[125] In this case, the desired methallylation also occurred, resulting even in some lactonization to **411**, presumably promoted by the Lewis acid nature of the borane, although both the yield and the enantioselectivity was poor (41% overall, 2.4:1 er). Furthermore, the absolute stereochemistry was determined to be that of the undesired epimer, by analysis of Mosher's esters.[126,127] Although this could be remedied either by Mitsunobu inversion or by use of the opposite enantiomer of pinene, the poor selectivity meant that this route would ultimately be abandoned.

The reasons for the termination of this third-generation route are many, from the lack of success with imparting the desired stereochemistry at C10 to the poor yielding alkynylation reaction. In developing a new synthesis, I had hoped that the new route would be shorter than the original one; however, as designed here the route to alkyne **307** would require ten steps from commercially available succinic anhydride (**413**). By comparison, the first-generation synthesis beginning from L-malic acid (**202**) was only a nine-step sequence. Although many of the operations of this generation were simpler and more efficient, the lack of stereochemical

control constituted a major problem. Thus, in the subsequent iterations, installation of the desired stereochemistry at C8 and C10 would be at the forefront of the effort.

### 3.6 Fourth Generation: Back to the Chiral Pool

The most obvious way to solve a stereochemical problem is to turn to where stereochemistry is most readily available, that is, in natural sources. Indeed, after two generations of struggle with inefficient reagent-controlled induction of stereochemistry, the launching point for the fourth-generation synthesis would be from the so-called "chiral pool." The question became: how might enantiopure lactone **411** be prepared? As shown in **Figure 3.6**, one could certainly imagine that the corresponding alcohol might be accessed by the opening of epoxide **437** with an appropriate nucleophile. Epoxide **437** could arise from γ-hydroxymethyl-γ-butyrolactone (**438**), which in turn is prepared in two steps from D-glutamic acid (**439**). The synthesis of both enantiomers of **438** is well-precedented,[128,129] as well as the

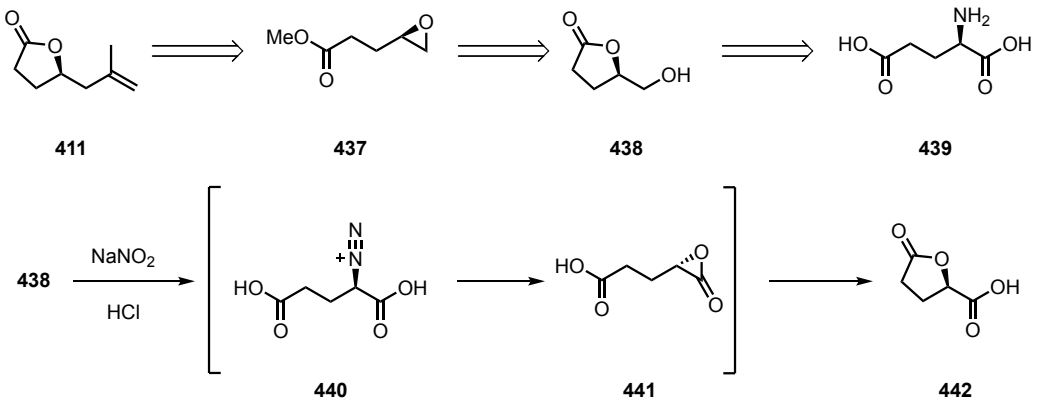
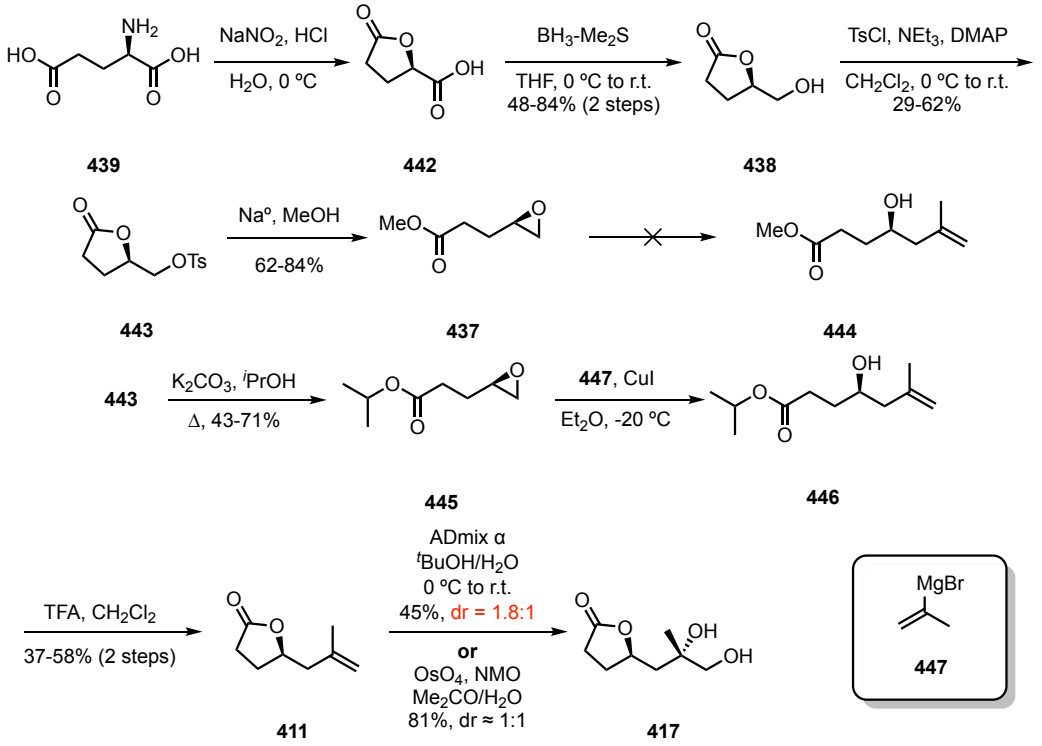



**Figure 3.6**: Fourth-generation analysis.

synthesis of **438** starting from the cheaper, natural enantiomer of glutamic acid.[130] Conversion of lactone **438** to epoxide **437** is also known to proceed through methanolysis of the lactone and subsequent displacement of the corresponding tosylate derived from **438**.[131] Finally, the initial reaction of glutamic acid has been demonstrated to proceed with full retention of stereochemistry.[132] After initial diazotization of the amine, the subsequent displacement of the diazonium **440** occurs from the adjacent carboxylic acid to furnish α-lactone **441**. Complete isomerization to the less strained γ-lactone then occurs to arrive at **442**. Thus, with a well precedented route to epoxide **437**, all that remained would be the relatively straightforward epoxide-opening and lactonization to arrive at the desired enantiomer of **411**. As will be seen, however, the opening of epoxide **437** would be anything but straightforward.




**Scheme 3.20**: Initial epoxide opening and dihydroxylations.

As shown in **Scheme 3.20**, the synthesis of lactone **438** was rather uneventful. After conversion to the tosylate, methanolysis and epoxide closure was effected using freshly prepared sodium methoxide. Opening of the epoxide moiety with 2-propenylmagnesium bromide was unsuccessful, resulting mostly in the recovery of starting material. When the isopropyl ester was used instead, the epoxide opening proceeded with minimal side reactions to afford, after acid-catalyzed lactonization, enantiopure lactone **411**. Although the yields were not exceptional, they were sufficient to proceed further with the synthesis. At this point, I had intersected with the route described in Section 3.5, and it would be possible to determine the selectivity of the Sharpless asymmetric dihydroxylation. Although the diastereomers were not

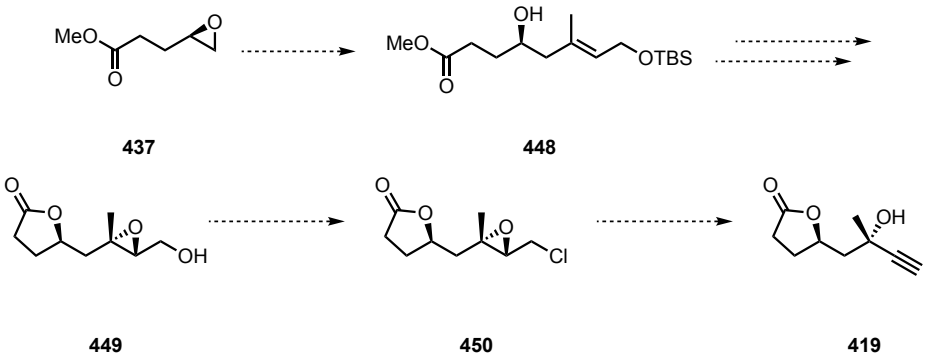
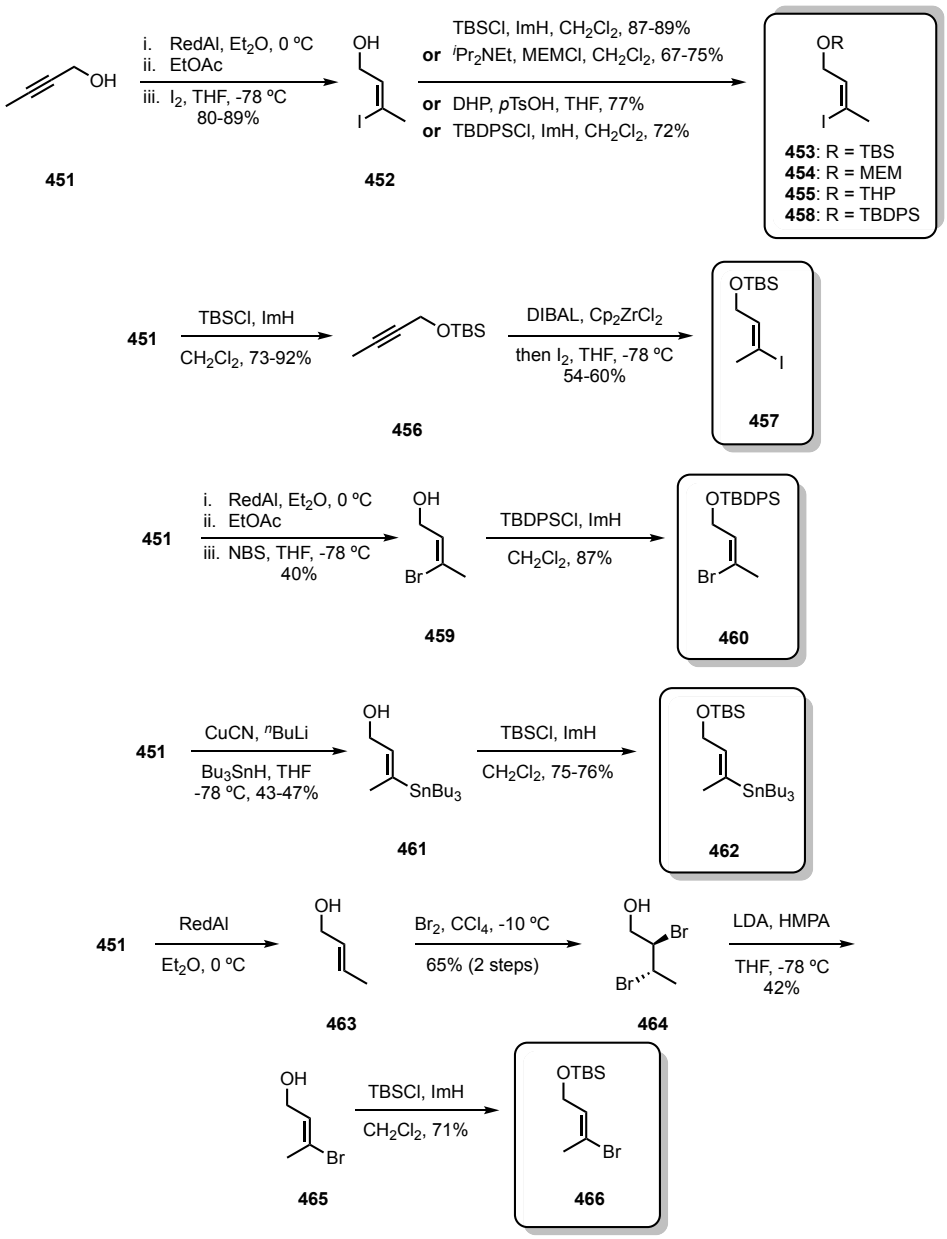



**Figure 3.7**: Revised approach to alkyne **419**.

distinguishable by $^{1}H$ NMR, the ratio of the two diastereomers was estimated to be 1.8:1 by $^{13}C$ NMR. To test whether the existing stereocenter had any effect on the selectivity dihydroxylation, I also performed the reaction using the Upjohn procedure.[133] Since this dihydroxylation was completely non-selective, it was determined that **411** was simply a poor substrate for Sharpless dihydroxylations. A new method to install the C8 stereocenter would be required.

It is possible that by judicious choice of nucleophile for the epoxide-opening reaction, I might be able to take advantage of an asymmetric epoxidation reaction of the resulting olefin.




**Scheme 3.21**: Synthesis of various alkene proto-nucleophiles.

Indeed, Pattenden had prepared homoallylic alcohol **448** by opening of epoxide **437** in his synthesis of bis-deoxylophotoxin.[134] Thus, after lactonization, deprotection, and asymmetric epoxidation, I would arrive at epoxide **449**, as shown in **Figure 3.7**. Then, treatment of the corresponding chloride **450** with two equivalents of LDA, as first reported by Takano,[135] would induce a rearrangement to the desired propargylic alcohol **419**. Thus, a series of suitable alkenes were synthesized, as shown in **Scheme 3.21**. The range of alkenes that were prepared covered vinyl iodides as well as vinyl bromides and a vinyl stannane, both *E* and *Z* isomers, and a variety of protecting groups on the primary alcohol.

| Entry | Epoxide | Nucleophile | Conditions | Compound(s) (Figure 3.8) |
|---|---|---|---|---|
| **1** | **445** (1.0 eq.) | **447** (2.2 eq.) | CuI (1.1 eq.), $Et_2O$ (0.1 M), -20 °C | **411**: 38% (2 steps) |
| **2** | **445** (1.0 eq.) | **453** (1.5 eq.)<br>$^t$BuLi (2.0 eq.) | CuCN (0.5 eq.), $BF_3OEt_2$ (3.0 eq.),<br>THF (0.2 M), -78 °C | **467**: 77%<br>**468**: n.d. |
| **3** | **445** (1.0 eq.) | **453** (1.5 eq.)<br>$^t$BuLi (2.0 eq.) | CuCN (0.5 eq.), THF (0.2 M),<br>-78 °C | **445**: n.d.<br>**468**: n.d. |
| **4** | **445** (1.3 eq.) | **454** (1.0 eq.)<br>$^t$BuLi (2.0 eq.) | CuCN (0.5 eq.), THF (0.2 M),<br>-78 °C | **445**: n.d.<br>**468**: n.d. |
| **5** | **437** (1.5 eq.) | **455** (1.0 eq.)<br>$^t$BuLi (2.0 eq.) | CuCN (0.5 eq.), $BF_3OEt_2$ (3.0 eq.),<br>THF (0.4 M), -78 °C | **470**: n.d.<br>**471**: n.d. |
| **6** | **437** (1.5 eq.) | **457** (1.0 eq.)<br>$^t$BuLi (2.0 eq.) | CuCN (0.5 eq.), THF (0.4 M),<br>-78 °C | **437**: n.d.<br>**472**: n.d. |
| **7** | **437** (1.0 eq.) | **456** (1.1 eq.)<br>DIBAL (1.1 eq.)<br>MeLi (1.1 eq.) | $BF_3OEt_2$ (1.0 eq.),<br>hexanes/$Et_2O$ (0.1 M), -78 °C | **437:** n.d.<br>**473**: 28% |
| **8** | **437** (1.0 eq.) | **457** (2.0 eq.)<br>$^n$BuLi (2.1 eq.) | CuCN (1.0 eq.), $BF_3OEt_2$ (3.0 eq.),<br>THF (0.2 M), -78 °C | **474**: 29%<br>**470**: 73% |
| **9** | **437** (1.0 eq.) | **457** (2.0 eq.)<br>$^t$BuLi (4.0 eq.) | CuCN (1.0 eq.), $BF_3OEt_2$ (1.5 eq.),<br>THF (0.2 M), -78 °C | **470**: 26%<br>**475**: 28% |
| **10** | **437** (1.0 eq.) | **458** (1.5 eq.)<br>$^t$BuLi (3.1 eq.) | CuCN (0.8 eq.), HMPA (2.0 eq.),<br>TMSCl (2.0 eq.), THF (0.2 M),<br>-78 °C to -40 °C | **477**: 68% |
| **11** | **437** (1.0 eq.) | **460** (2.0 eq.)<br>Mg° (2.1 eq.) | CuCN (1.0 eq.), $BF_3OEt_2$ (3.0 eq.),<br>THF (0.4 M), -40 °C | **437**: n.d. |
| **12** | **437** (1.0 eq.) | **462** (1.2 eq.)<br>$^n$BuLi (1.2 eq.) | CuCN (0.6 eq.), $BF_3OEt_2$ (3.0 eq.),<br>THF (0.7 M), -10 °C | **475**: 12% |
| **13** | **437** (1.5 eq.) | **466** (1.0 eq.)<br>$^t$BuLi (2.0 eq.) | CuCN (0.5 eq.), $BF_3OEt_2$ (3.0 eq.),<br>THF (0.7 M), -78 °C to -10 °C | **476**: 92% |

**Table 3.4**: Summary of selected epoxide openings.

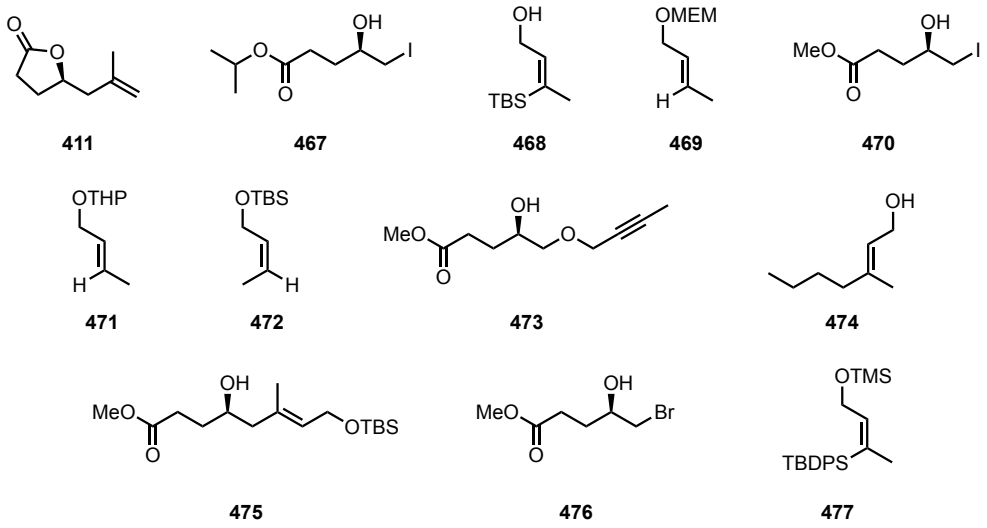



**Figure 3.8**: Various products observed in epoxide opening.

The outcomes of the attempted epoxide openings are summarized in **Table 3.3** and are somewhat representative of the results with each of the alkene nucleophiles that were prepared above. One of the major side products (shown in **Figure 3.8**) was the formation of the halohydrin (**467**, **470**, or **476**); however this compound was formed only when $BF_3$•$OEt_2$ was used. When the Lewis acid additive was omitted from the reaction, no epoxide opening occurred, and only starting material was recovered. In the case of the *Z*-vinyl halides bearing a silyl protecting group (**453** and **458**), a retro-Brook[136] rearrangement rapidly took place, preventing the desired ring opening from occurring and only a mixture of starting material and vinyl silane was recovered. The rearrangement could be prevented when the corresponding *E*-vinyl halides (**457** and **466**) were used. In fact, these proved to be the most successful (28% yield, Entry 9). In the best-case scenario, however, formation of the halohydrin could not be suppressed. Even when following the exact conditions reported by Pattenden (Entry 13),[134] the halohydrin **476** was isolated as the only product, in 92% yield. While halohydrin formation could be mitigated by employing vinyl stannane **462** (Entry 12), the yield and mass recovery was extremely poor. Some unexpected reactivity was also observed. Entry 7 shows the attempted hydroalumination of alkyne **456** with DIBAL, followed by transmetallation to the vinyl lithium, as reported by Knight and co-workers.[137] However the initial step, which required heating alkyne **456** with DIBAL to 60 ºC, simply deprotected the primary alcohol, and, when the epoxide was introduced, *O*-alkylation occurred to lead to propargyl ether **473**. In one scenario (Entry 8), a coupling between the butyl group of $^{n}$BuLi and the vinyl iodide occurred. I would expect this was due to the presence of a small amount of Cu(II) impurities in the reaction mixture.

In total, the epoxide-opening reaction was attempted, in some form or another, 67 times over the course of five-and-a-half months. Once I had shifted away from 2-propenylmagnesium bromide as the nucleophile, the desired product was obtained in only ten of the trials, with a maximum yield of 28%. In some cases, the undesired halohydrin was formed almost quantitatively, and I was unable suppress this reactivity without also sacrificing the formation of the desired product. The failure of this transformation, in particular, would lead to a massive departure from my synthetic analysis and resulted, as I will discuss in Chapter 4, in a completely different approach.

I would like to offer a personal aside at this point. The repeated failure of this reaction provided a test of will that I had not yet experienced during my short career as a synthetic chemist. During what became known as “epoxide hell”, there were days when I wanted to try a new idea or route, there were days when I did not want to go to lab, and there were days when I wanted to quit altogether. I did not give up until it had become abundantly clear that this synthetic route was no longer viable. It is still a mystery to me how Pattenden’s group was able to open the epoxide in 70% yield without a mention of the ubiquitous halohydrin side product. Nevertheless, the work presented in this section taught me a considerable amount about the perseverance and mental fortitude required during the course of a challenging total synthesis.

## 3.7 Conclusions

In this chapter, I have described the course of the synthetic efforts toward the hypothetical linear precursor **III** (**Figure 3.1**), beginning with the first-generation synthesis that I inherited when I joined the lab. The problems associated with the first generation of effort, outlined in Section 3.1, highlighted what would become the focus in any future synthetic generations, specifically the incorporation of the correct stereochemistry at C8 and at C10. The following three generations would be centered on lactone **309** (**Figure 3.1**) as a target to intersect with the first generation. Unfortunately, in each generation the required stereocenters could not be efficiently incorporated either by substrate-controlled asymmetric induction or by reagent-controlled asymmetric reactions. However, despite the failures in developing a more efficient synthesis of lactone **309**, I was able to develop a reasonable synthesis of the requisite α,ß-substituted butenolide using a Diels–Alder approach to highly substituted 2-alkoxyfurans. In the end, the failure of one key step would lead to a departure from the planned route and, eventually, a complete shift in synthetic strategy.

# Chapter 4

## The Path to Photochemistry

After the failures of the epoxide opening route described Section 3.6, I decided to take a step back and reassess the direction of the project. The goal would remain to achieve an efficient synthesis of tris-butenolide **III** (see **Figure 4.1**); however, a radically different approach would be required. The challenges were the same, namely the synthesis of three different butenolide rings — only one of which would originate in my previous work — and the stereocontrolled introduction of the three key stereocenters. **Figure 4.1** compares the approach of the first four generations as it with the new approach. One aspect of the synthetic analysis that each of the first four generations had in common was the so-called "left-to-right" approach to the relative *anti* relationship between the secondary alcohol at C10 and the tertiary alcohol at C8. In the first-generation synthesis, the correct configuration at C10 was obtained from L-malic acid (**202**), and I expected that the existing stereocenter would then be induced by substrate-controlled addition to the C8 ketone (**VII**, X = O). The three subsequent generations began with the assumption that the C10 stereocenter would be introduced first and that the C8 stereocenter would follow, under the control of either the substrate or an appropriate reagent. In all cases, the synthesis proceeded through some form of intermediate **VII**.

Beginning the fifth generation, inspired in part by repeated failures in the "left-to-right" approach, I began to think about the synthesis in a different way. Namely, would it be possible

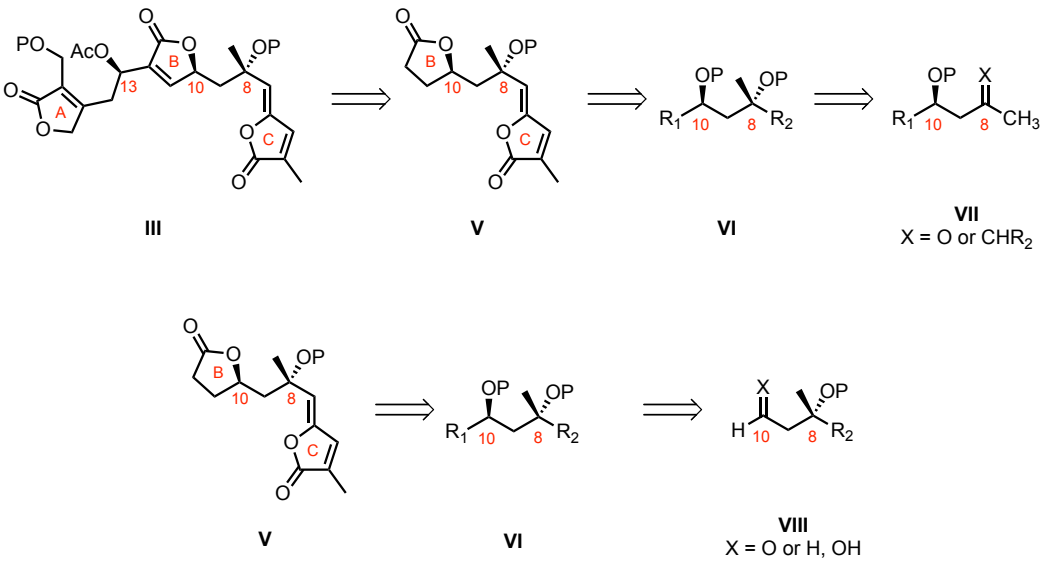


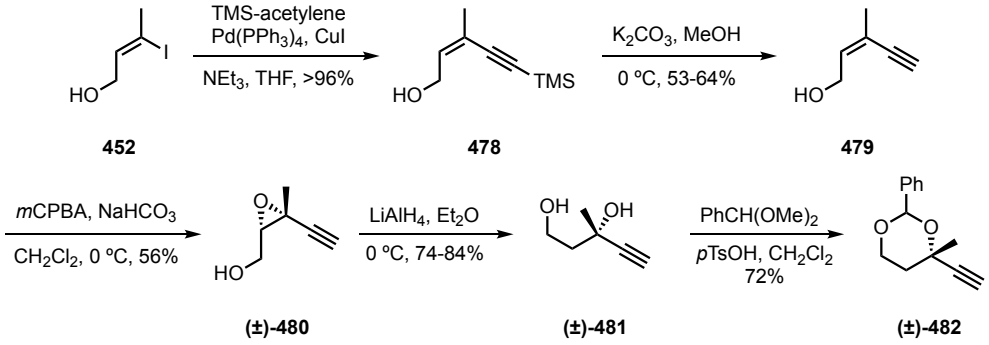

**Figure 4.1**: Shifting approaches toward the stereochemical problem.

to set the C8 stereocenter first using reagent control — there are very few examples of tertiary alcohols in the chiral pool — to synthesize intermediate **VIII**? One could then incorporate the C10 stereocenter either using substrate-controlled induction or reagent control to intersect, once again, with intermediate **VI**.

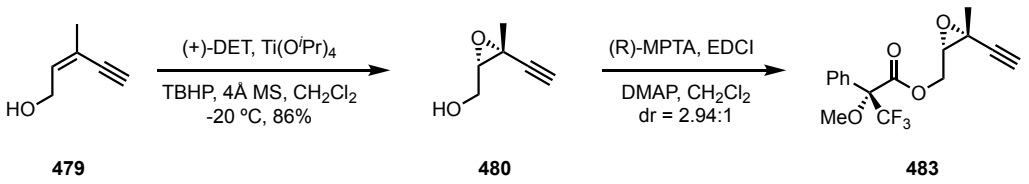
Chapter 4 will focus on the attempted synthesis of an appropriately substituted compound **VI** by first installing the C8 stereocenter, then the C10 stereocenter, and finally focusing on the construction of the B-ring butenolide and the appropriate side chain.

## 4.1 Fifth Generation: Enyne Approach and Asymmetric Epoxidation

With the shift in synthetic strategy, the new question became whether or not I could prepare enantiopure intermediate **VIII**. Of course, the 1,3-diol moiety is quite common, and one could imagine a number of ways to prepare it. Inspired by a literature search, I imagined that the diol could arise from the hydroxyl-directed opening of an epoxide, formed from the corresponding allylic alcohol. Indeed, in the previous generation, I prepared allylic alcohol **452**, which could be coupled with TMS-acetylene to yield the desired enyne fragment **478**, as shown in **Scheme 4.1**. After desilylation, I decided to test this approach on racemic material, once again. Epoxidation under basic conditions yielded the desired epoxide in modest yields and, fortunately, upon exposure to $LiAlH_4$, the epoxide was reduced in a regioselective manner to yield diol **(±)-481**. In order to protect the tertiary alcohol selectively, I opted to use the benzyilidene protecting group for the diol **(±)-482**, which could then be regioselectively opened to afford the tertiary benzyl ether, leaving the primary alcohol available for further manipulations. This strategy would, hopefully, allow for the protecting group of the tertiary alcohol to remain constant. I could thus take advantage of the conditions previously developed for benzyl deprotection after the [2+2] cycloaddition.




**Scheme 4.1**: Approach to the racemic 1,3-diol moiety.




**479** **480** **483**

**Scheme 4.2**: Enantioselective epoxidation.

With a relatively concise route to the 1,3-diol, the incorporation of the required stereochemistry was the next hurdle to be crossed. Fortunately, the allylic alcohol moiety **479** appeared to be a canonical substrate for the Sharpless asymmetric epoxidation.[138] Indeed, as the Ghosh research group reported, in 2003, the asymmetric epoxidation of enyne **479** to produce the desired stereoisomer with 98% ee![139] With this in mind, I was quite enthusiastic to attempt this reaction and solve the C8 stereocenter on the first attempt. Although the reaction was sluggish (72 hours), the desired epoxide **480** was formed in 86% yield. In order to determine the enantioselectivity, the corresponding Mosher ester **483** was formed and the dr was measured by $^{19}F$ NMR. Needless to say, I was disappointed to learn that the diasteomeric ratio (dr) was found to be 2.94:1 (48% ee), exactly half of what was reported by Ghosh. Why this reaction failed to give the reported enantioselectivity is, once again, a mystery, as one would expect that following a published protocol would yield similar, if not identical, results. With this in mind, optimization of this reaction was not pursued, although diol **481** would prove to be a crucial compound.

## 4.2 Sixth Generation: Acetyl Aldol Solves the C8 Problem

Now that I had identified diol **481** as a potential source for the C8 stereocenter, I undertook a search through the literature to see if it had been made by another method. Buried within Fürstner's total synthesis of the amphidinolides was the diastereoselective aldol reaction shown at the top of **Figure 4.2**.[140] By employing the acetyl derivative of Evans's phenylalanine-derived auxiliary ***(R)*-485**,[141] Fürstner was able to prepare tertiary alcohol **(–)-486** in moderate yield. Although the selectivity is not as high as one would expect with the corresponding propionate aldol reaction (dr = 7.2:1), it was certainly a promising lead to the incorporation of the correct stereochemistry at C8. The diastereomers could be, moreover, separated after the first step, and enantiopure material could be carried on for the remainder of the synthesis.

The revised synthetic strategy to access intermediate **III** is shown in **Figure 4.2**. The known cycloisomerization approach from the allylic alcohol in **IX** approach furnish the C-ring butenolide. The Diels–Alder reaction with an ethoxyoxazole (see Section 3.4) would produce

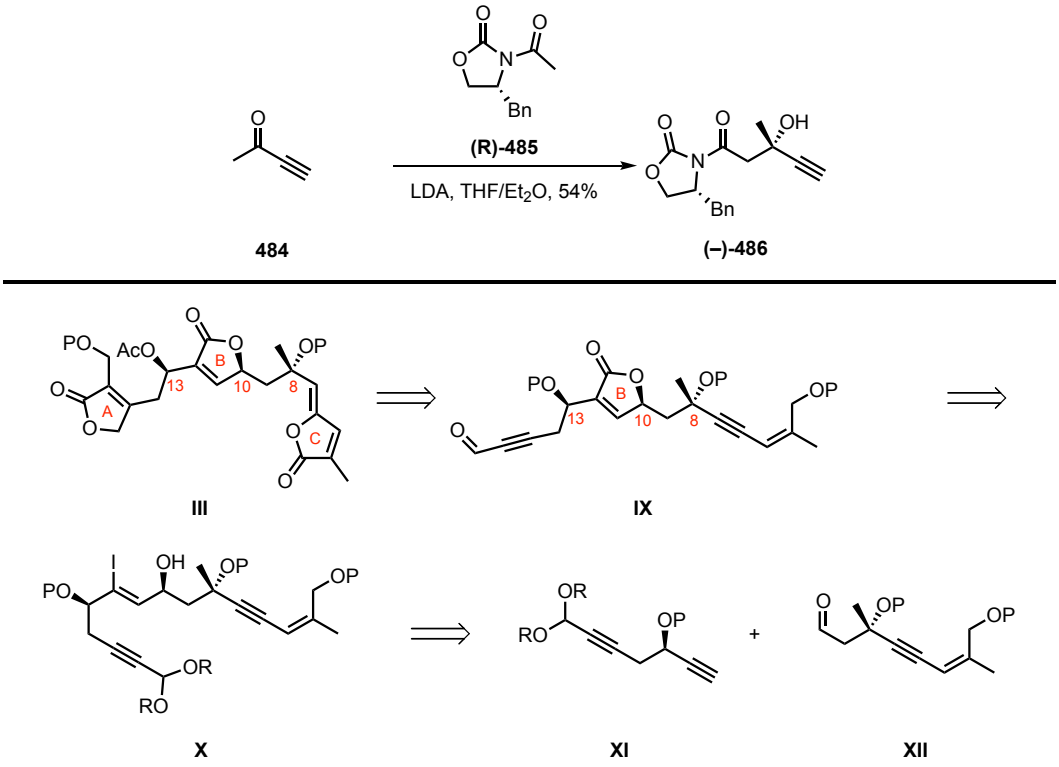
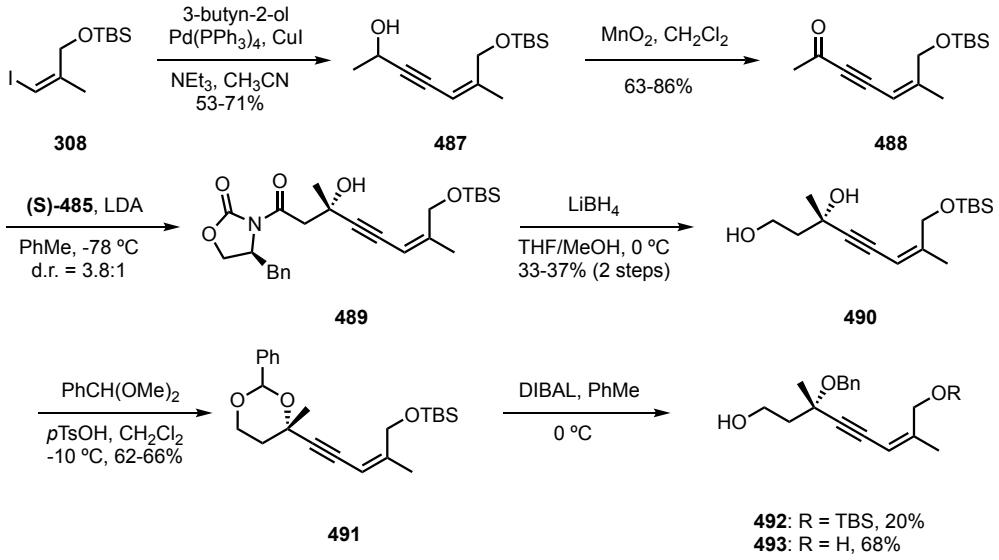



**Figure 4.2**: Reported aldol reaction and sixth-generation analysis.

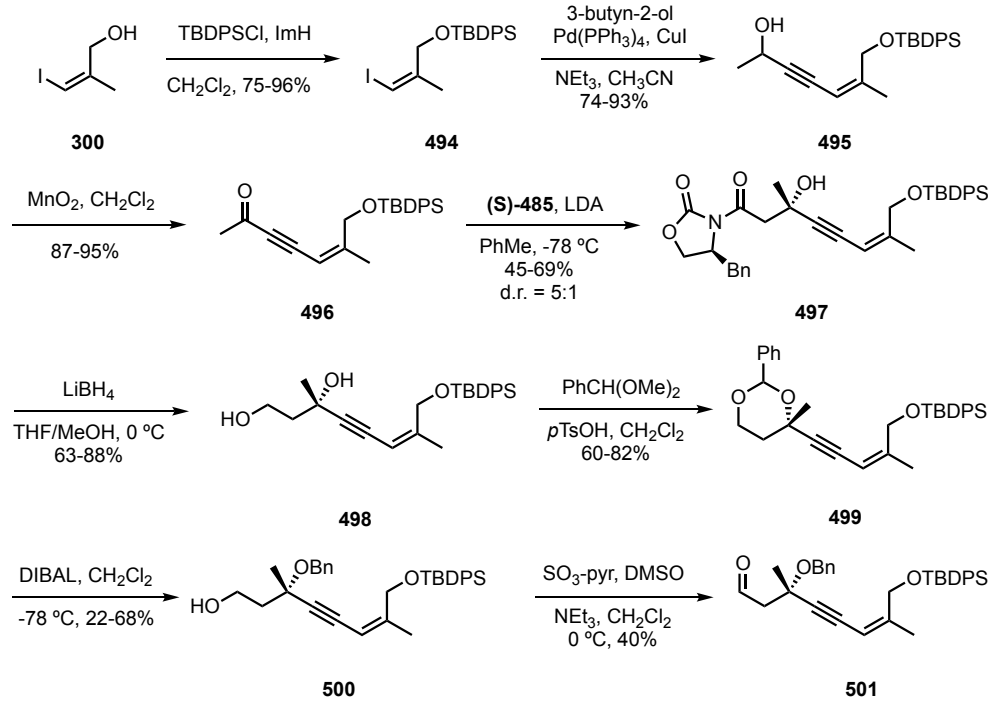
the A-ring butenolide. This would require the incorporation of a propargyl aldehyde, as shown in intermediate **IX**. It was reasoned that the B-ring butenolide could then be formed using a palladium-catalyzed carbonization of a vinyl iodide, which, in turn, could be synthesized from the corresponding propargylic alcohol. Using this approach, then, would necessitate the preparation of two fragments, diyne **XI** and aldehyde **XII**, which could be accessed via the newly found diastereoselective aldol reaction.

I reasoned that I could begin the synthesis of aldehyde **XII** from the olefin moiety, beginning with vinyl iodide **308**, which had already been used in previous generations. As shown in **Scheme 4.3**, the Sonogashira coupling with 3-butyn-2-ol was effective and afforded enyne **487**. It is worth noting that the choice of solvent was crucial to obtaining reasonable yields in the cross-coupling reaction — the use of THF instead of $CH_3CN$ resulted in consistently low yields of <30%. After mild oxidation of the propargylic alcohol, the stage was set for the aldol reaction, which proceeded smoothly, and, although the diastereoselectivity was not as high as reported by Fürstner, the diastereomers were readily separable. The excess auxiliary [**(*S*)-485**], however, could not be separated from alcohol **489** and the yield was determined over two steps after reductive removal of the chiral auxiliary. Attempts to protect the tertiary alcohol as its benzyl ether immediately following the aldol reaction were



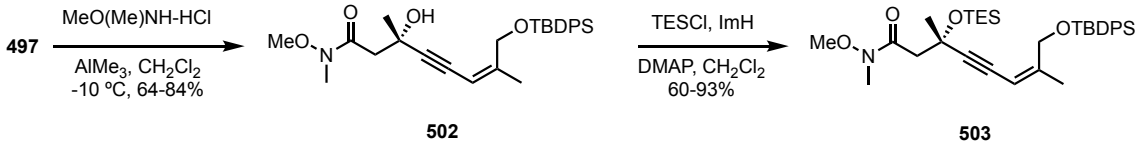

**Scheme 4.3**: First attempt at aldol reaction.

unsuccessful. Under basic conditions (BnBr, NaH) the resulting alkoxide underwent a retro-aldol reaction, reverting to ketone **488**. Acidic (BnTCA, PPTS) or neutral (BnBr, $Ag_2O$) conditions did not show any signs of progress, presumably because of the extremely hindered nature of the alcohol. Thus, the benzyl ether was installed by first protecting diol **490** as the benzylidene acetal **491** and followed by its subsequent reductive cleavage. Upon treatment of




**Scheme 4.4**: Synthesis of aldehyde with new protecting group.

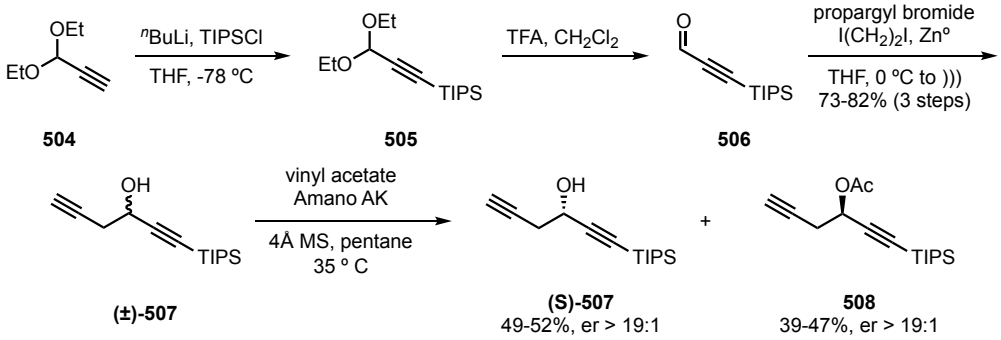
benzylidene **491** with DIBAL, the acetal underwent the desired regioselective cleavage to liberate the primary alcohol 480; however, the in most of the material, the TBS group was also lost. Rather than face the challenge of differentiating the two primary alcohols in order to reprotect the allylic alcohol, I decided to change protecting groups to the less labile TBDPS ether. As shown in **Scheme 4.4**, I was able to access aldehyde **501** using the same sequence, and, in many cases, the yields and stereoselectivity were improved. The oxidation of alcohol **500**, however, was low-yielding and only attempted once before I decided to pursue a different approach.



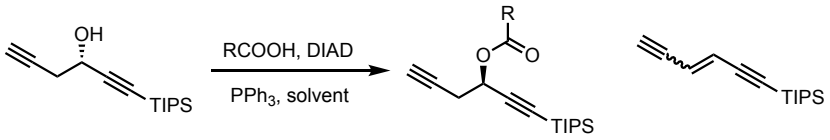

**Scheme 4.5**: Synthesis of Weinreb amide fragment.

Rather than relying on what might invariably be poor asymmetric induction of the tertiary alcohol on any nucleophilic additions to aldehyde **501**, I decided to pursue the synthesis of the corresponding Weinreb amide.[142] The resulting alkynyl ketone should then be a good substrate for an asymmetric reduction to set the C10 stereocenter. Thus, the aldol adduct **497** was converted to Weinreb amide **502** using $AlMe_3$, as shown in **Scheme 4.5**. Once again, I attempted to install the benzyl ether, but the alcohol remained unreactive under acidic conditions and continued to revert to ketone **496** under strongly basic conditions. As I noticed that under mildly basic conditions, such as those required for silylation, the compound was stable, I opted to protect the tertiary alcohol as the corresponding TES ether (**503**) moving forward.

With Weinreb amide **503** in hand, my attention shifted to the synthesis of the second fragment, diyne **XI**. As shown in **Scheme 4.6**, the synthesis commenced with 1,1-




**Scheme 4.6**: Enzymatic resolution sets C13 stereocenter.



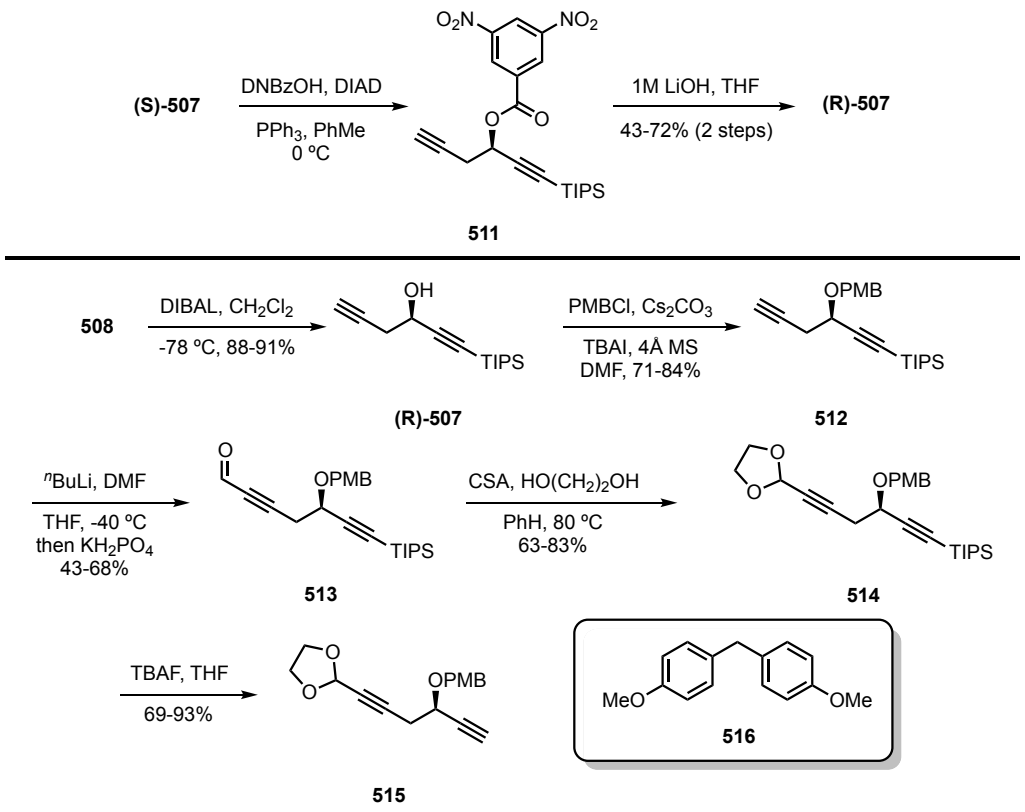

(S)-507 509 510

| Entry | R-COOH | Solvent | 497:498 |
|---|---|---|---|
| **1** | BzOH | THF | 1:1.3 |
| **2** | 4-OMeBzOH | THF | 1:1.9 |
| **3** | 3,5-$(NO_2)_2$BzOH | THF | 1:0.3 |
| **4** | *trans*-crotonic acid | THF | 1:1.2 |
| **5** | 3,5-$(NO_2)_2$BzOH | PhMe | 1:0.1 |

**Table 4.1**: Optimization of Mitsunobu inversion.

diethoxypropyne. Marshall had previously demonstrated that propargylic alcohol **(±)-507** is a suitable substrate for an enzymatic resolution in his total synthesis of callipeltoside aglycone.[143] Indeed, I was able to access enantiopure acetate **508** as well as alcohol **(*S*)-507**, which could be converted to the desired enantiomer by Mitsunobu reaction[144] and subsequent hydrolysis. The Mitsunobu reaction was not as straightforward as it might initially appear, as elimination of either the intermediate phosphonium or the benzoate product resulted in the highly conjugated ene–diyne **510**. As shown in **Table 4.1**, with a suitable choice of acid and solvent, this side reaction could be suppressed almost entirely as it appeared to be influenced both by the electronics of aromatic ring and solvent polarity. Thus, the C13 stereocenter could be set efficiently without the significant loss of material that often happens with resolutions.

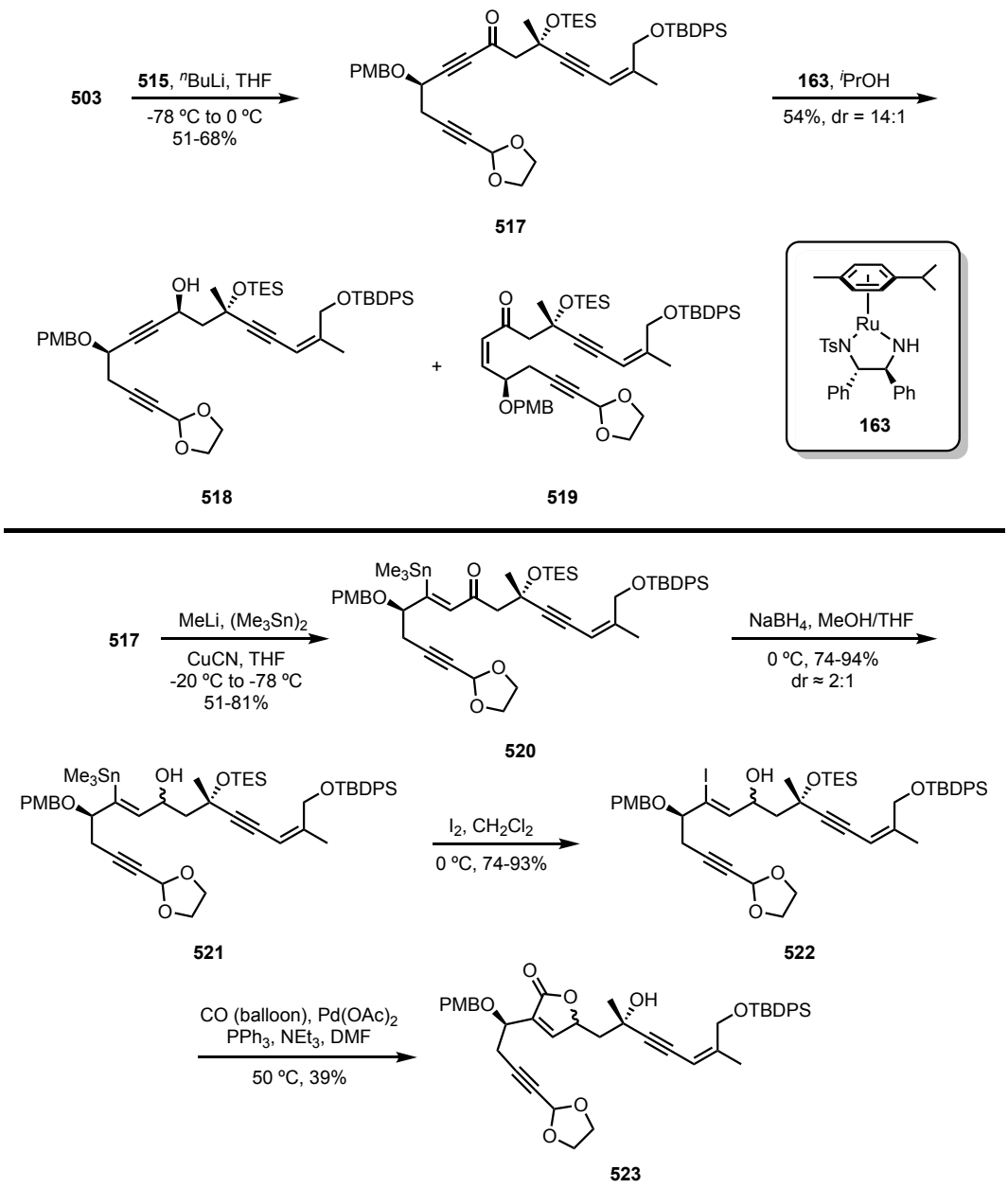
With an efficient route to **(*R*)-507** established — I could quickly prepare up to 5 g of the enantiopure alcohol — the completion of the synthesis of the desired diyne fragment would be a matter of a couple of steps. The secondary alcohol was protected as the PMB ether because of the planned late-stage removal and orthogonality to all other protecting groups in the synthesis. Initial attempts to protect the alcohol using standard conditions (NaH, PMBCl) were unsuccessful; however, acidic conditions (PMB-TCA, CSA) successfully installed the PMB ether. I noted during this reaction that a byproduct containing the *para*-methoxybenzyl moiety contaminated the product and could not be removed by means of standard chromatography. When the trichloroacetimidate was treated with CSA in the absence of an alcohol, the pseudo-dimer **516** was isolated, as shown in **Scheme 4.7**. This compound is presumably formed through generation of the intermediate *p*-quinone methide, *para*-alkylation, and subsequent




**Scheme 4.7**: Completing the synthesis of the diyne fragment.

loss of formaldehyde and trichloroacetonitrile. Fortunately, the propargyl alcohol could be alkylated using $Cs_2CO_3$ as the base in good yields. After formylation, protection of the resulting aldehyde, and desilylation, the desired diyne **515** was prepared in eleven total synthetic operations from 1,1-diethoxypropyne.

The addition of alkyne **515** to Weinreb amide **503** proceeded smoothly and in good yields to arrive at α,ß-acetylenic ketone **517**, as shown in **Scheme 4.8**. It should be pointed out that this compound bears all but four of the 22 carbons present in bielschowskysin (**1**) — only the acetate and the two carbons to be introduced via the Diels–Alder reaction — although none of the rings in the final target are yet formed. Focus shifted towards setting the stereochemistry at C10 and the formation the B-ring butenolide by functionalization of the alkyne. The ketone was reduced with excellent (14:1) selectivity using Noyori's asymmetric transfer hydrogenation.[145] Unfortunately, in what should be an extremely high-yielding reaction, only 54% of the desired propargylic alcohol **519** was obtained. The remainder of the material was isolated as a mixture of starting ketone **517** and semi-reduced enone **520**. The enone is a product of a known side reaction that arises through a hydrometallation of the alkyne rather than the carbonyl moiety, shutting down the catalytic cycle. Noyori noted that this unproductive




**Scheme 4.8**: Late stage stereochemical difficulties.

pathway may be subverted by using lower catalyst loading; however, in the case of ketone **517**, lower catalyst loading resulted only in lower yields (<15%). Furthermore, I was unable to convert the propargylic alcohol to the vinyl iodide by RedAl-mediated hydroiodination.

I then focused on ß-functionalization of the ketone, a transformation that is well-precedented by means of the stannylcupration method of Piers.[146,147] Vinyl stannane **520** was thus obtained as a single isomer (**Scheme 4.8**). Reduction of the resulting ketone with sodium borohydride afforded allylic alcohol **521** as an inseparable mixture of diastereomers (dr = 2:1).

| Entry | Reductant | dr | Notes |
|---|---|---|---|
| **1** | $NaBH_4$ | 2:1 | — |
| **2** | (*R*)-CBS, $BH_3$•$Me_2S$ | N/A | No reduction |
| **3** | **163**, $^{i}$PrOH | N/A | No reduction |
| **4** | L-selectride | 2.5:1 | — |
| **5** | DIBAL | 1:1.3 | — |
| **6** | $LiBH_4$ | 2.6:1 | — |
| **7** | $LiAl(O^{t}Bu)_3H$ | N/A | No reduction |
| **8** | RedAl | 1.5:1 | — |

**Table 4.2**: Attempted reductions of ketone **509**.

As shown in **Table 4.2**, a small screen of reducing agents was undertaken to probe the diastereoselectivity of the reduction with no noticeable improvement in selectivity; furthermore, the use of reagent-controlled reductions (Entries 2 and 3) did not afford any of the desired product. Nevertheless, I proceeded with the synthesis with the hope that the two diastereomers would be separable at a later stage. Tin–iodine exchange was unproblematic and accompanied by a remarkable change in polarity. It was the first time I ran the reaction that I did not notice that the product had formed at the baseline of the TLC plate. Unfortunately, the carbonylation of the allylic alcohol was not efficient, and, with concomitant loss of the silyl protecting group, the compound became increasingly difficult to handle.

It was at this point that I had reached an impasse regarding the direction of this synthesis. I could either have moderate control over the C10 stereocenter *or* functionlization of the alkyne but the combination of the two remained elusive. As the situation was compounded by the fact that the carbonylation reaction was inefficient, I opted to take a different approach toward the formation of the B-ring butenolide. Nevertheless, the sixth-generation synthesis offered a marked step forward in my pursuit of **1**, beginning with the successful incorporation of the C8 stereochemistry. As will become apparent throughout the remainder of this chapter, Weinreb amide **503** (**Scheme 4.5**) would become a key intermediate in the synthesis as I sought to incorporate the rest of the required functionality.

## 4.3 Seventh Generation: Ring-Closing Metathesis Approach

The failure of the previous generation was two-fold: first, the C10 stereocenter could not be set efficiently, and, second, there was not a straightforward route to the B-ring butenolide. While the previous generation was centered around the premise of a carbonylative cyclization of a ß-iodoallylic alcohol (cf. **522**), another approach based on ring-closing metathesis might arise from a disconnection across the olefin of the butenolide moiety, as shown in **Figure 4.3**, by the use a ring-closing metathesis approach.[148] This approach would necessitate the preparation of two fragments: allylic alcohol **XIV** and α,ß-unsaturated carboxylic acid **XV**. Furthermore, one could imagine that alcohol **XIV** and acid **XV** could be synthesized from the previously prepared compounds **503** and **515**, respectively. With that in mind, I set out to modify the syntheses developed in the previous section to access the two components necessary for a ring-closing metathesis reaction.

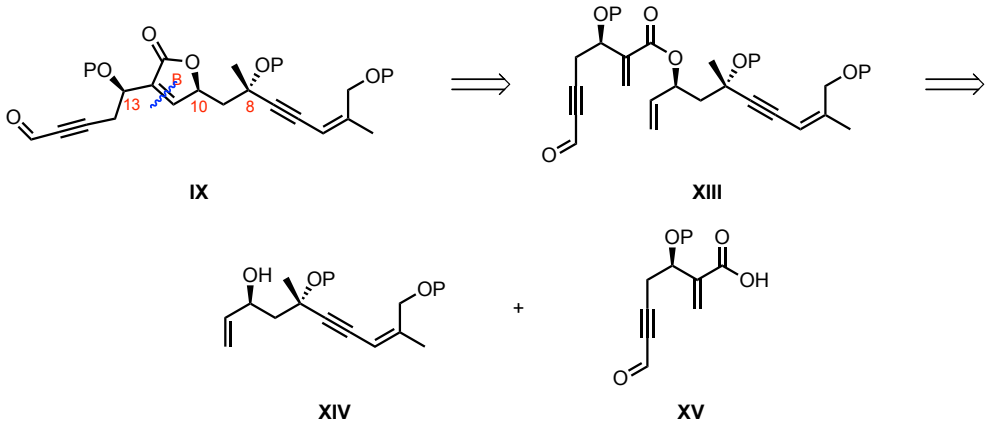
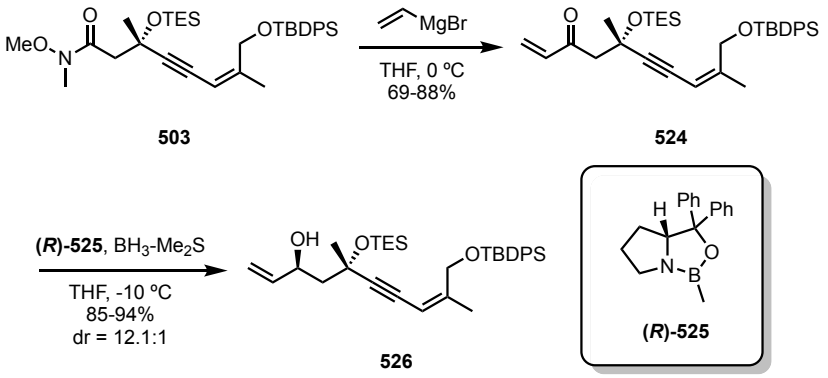


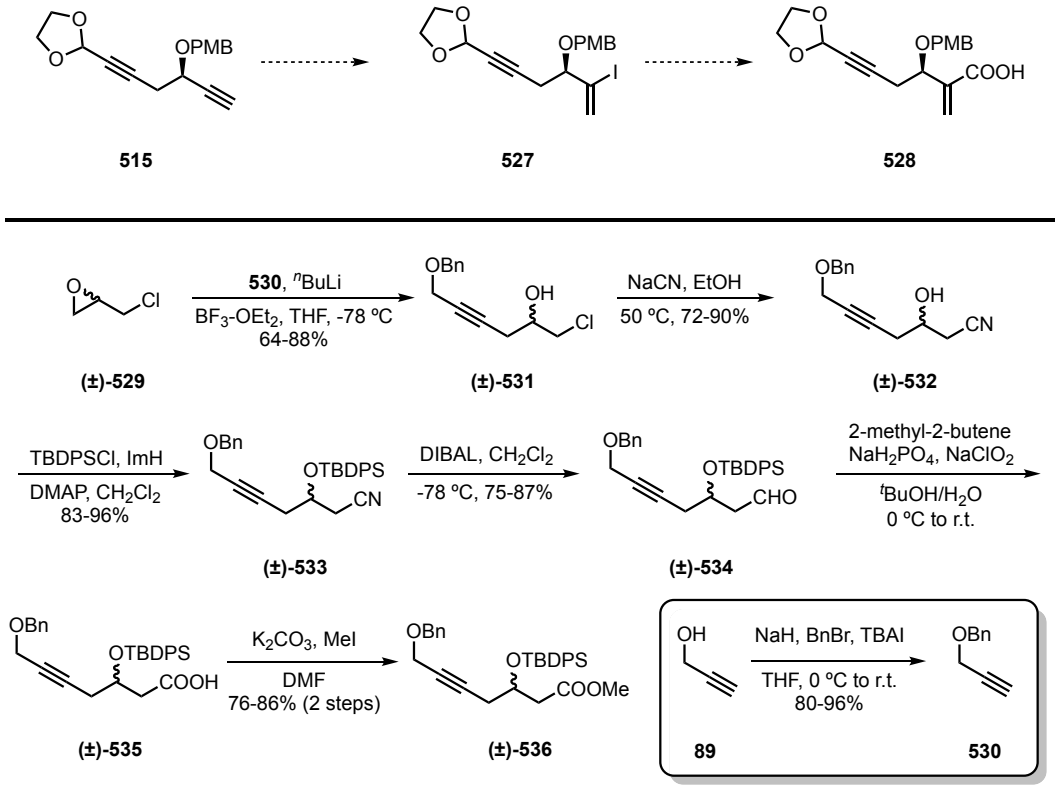

**Figure 4.3**: Seventh-generation analysis.

As shown in **Scheme 4.9**, Weinreb amide **503** could be easily converted to enone **524** by treatment with vinylmagnesium bromide. This enone ostensibly seemed like it would be an excellent substrate for substrate-controlled reduction using the Corey–Itsuno method (CBS).[149-151] Thus, treatment of enone **524** with the (*R*)-CBS catalyst (**(*R*)-525**) and borane–dimethylsulfide complex afforded allylic alcohol **526** in excellent yields, with quite good diastereoselectivity. The configuration was confirmed by NMR analysis of the corresponding Mosher esters and found to be in agreement with the model initially put forth by Corey.[150] I was thus able to prepare up over three grams of enantiopure alcohol **526** at a time, and I shifted my attention toward an equally efficient synthesis of acrylate **XV**, in anticipation of the coupling of the two moieties and the closure of the B-ring butenolide.



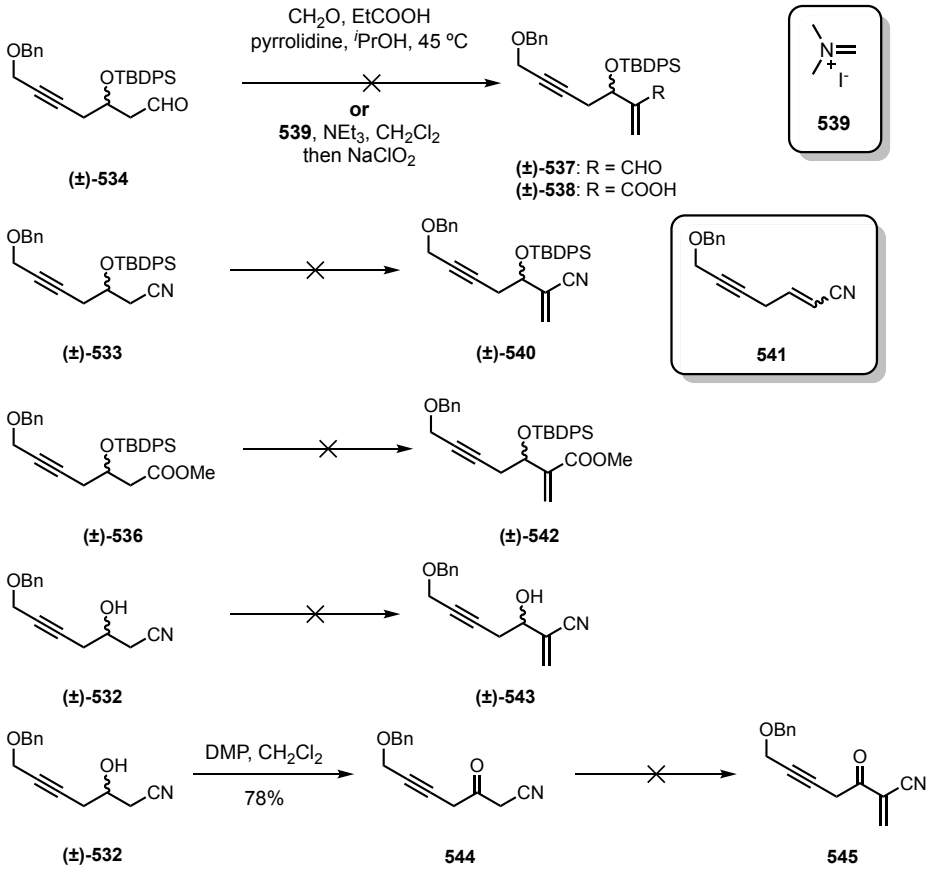

**Scheme 4.9**: Synthesis of enantiopure allylic alcohol **526**.

I initially thought that installation of the acrylate moiety could arise from functionalization of the terminal alkyne of compound **515** (**Scheme 4.10**). Because hydrometallation of terminal alkynes in the internal position is often difficult to achieve selectively, I anticipated that there might be a degree of competing reactivity at the internal alkyne. It seemed prudent to develop a new synthesis of **528** with these difficulties in mind. I envisioned that the C13 stereocenter could arise from epichlorohydrin (**529**), which is readily available in both racemic and enantiopure forms. The synthesis was initially developed with the



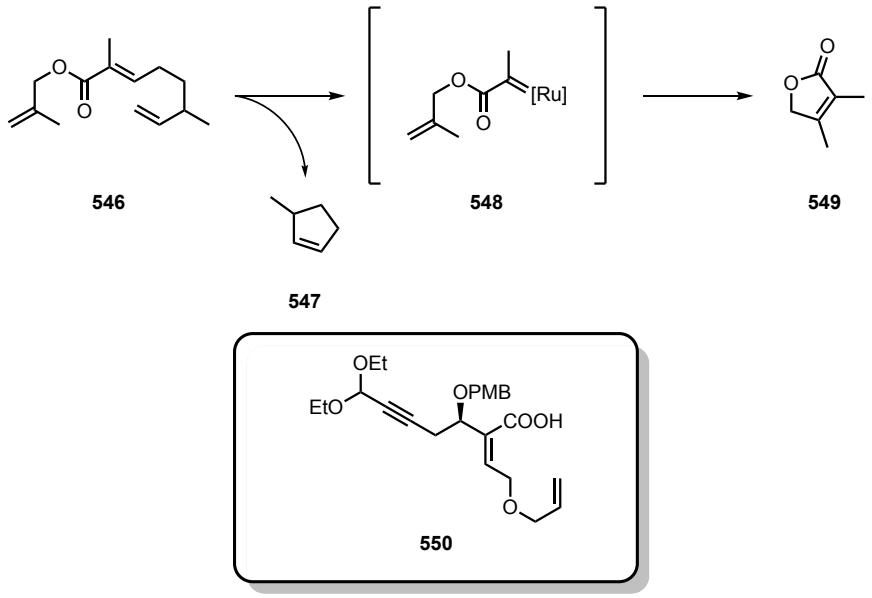

**Scheme 4.10**: Synthesis of ester **536**.

racemic material, as shown in **Scheme 4.10**. If successful, the route would be applied to (*R*)-epichlorohydrin to move forward with enantiopure material. Opening of the epoxide with alkyne **530** installed the internal alkyne, and displacement of the chloride with sodium cyanide afforded the homologated nitrile **(±)-532** in the correct oxidation state. Protection of the alcohol and conversion of the nitrile to the corresponding ester via the intermediate aldehyde **(±)-523** led to methyl ester **(±)-536** in a short and scalable synthesis. The only transformation that remained was the installation of the α-methylene unit. Initially, I envisioned that this could be accomplished either by a Mannich reaction with Eschenmoser's salt[152] or by using a more recent, organocatalytic method[153] on aldehyde **(±)-534**. Unfortunately, the organocatalytic method (see **Scheme 4.11**) led to decomposition with none of aldehyde **(±)-537** was observed. Upon treatment with Eschenmoser's salt, a trace amount of the desired aldehyde was observed by NMR; however, Pinnick oxidation[154,155] of the putative aldehyde failed to produced acid **(±)-538** (**Scheme 4.11**). I suspected that perhaps the α,ß-unsaturated aldehyde moiety of **(±)-537** was too labile; therefore, I attempted to install the methylene at on either nitrile **(±)-533** or ester **(±)-536**. The problem with the higher oxidation states is that α-functionalization would




**Scheme 4.11**: Attempted α-functionalization.

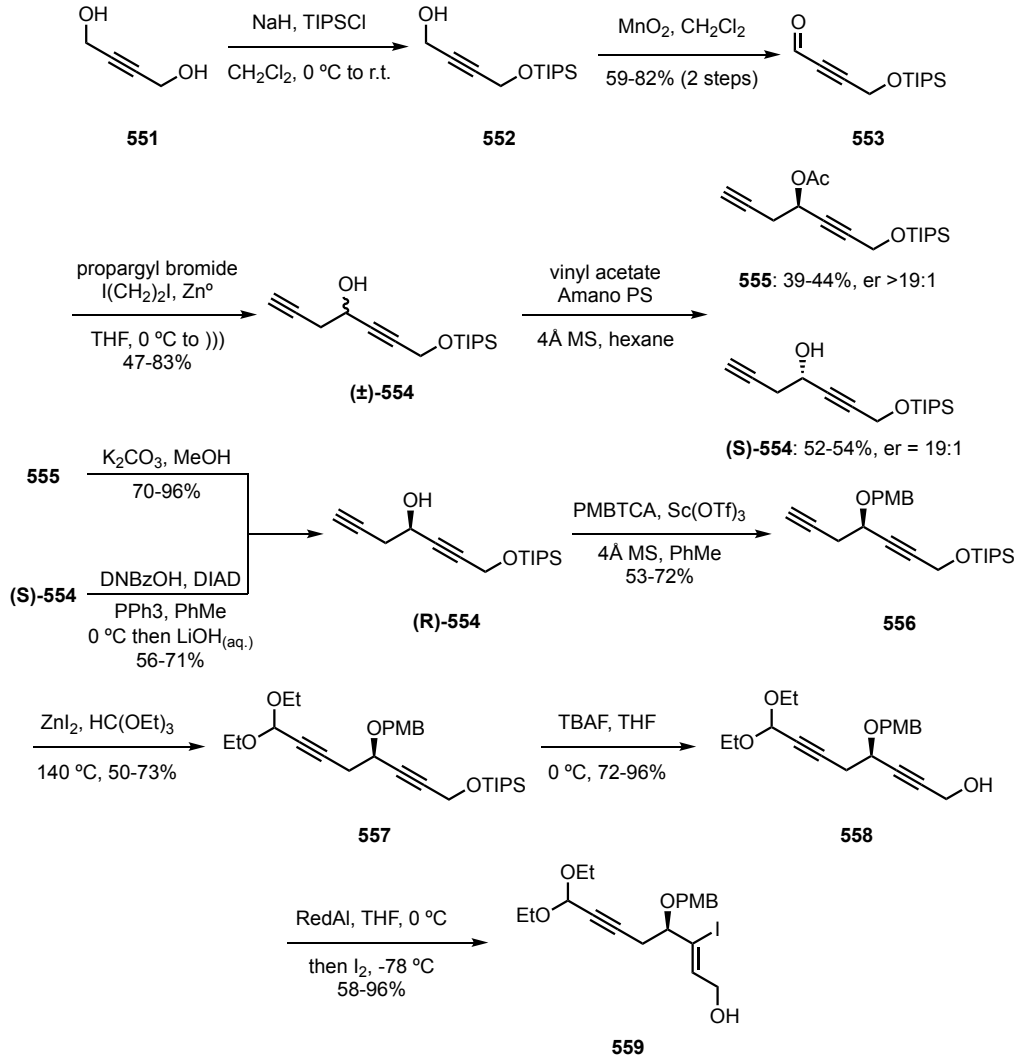
involve the application of a strong base. This problem became evident, as confirmed by $D_2O$ quenches, and upon treatment of nitrile **(±)-533** with LHMDS, the deprotonation was accompanied by approximately 30% ß-elimination of the silyloxy moiety to alkene **541**. I thought that alkylation of alcohol **(±)-532** might suppress the elimination via the *in situ* generated dianion. Indeed, although no elimination products were observed, no α-functionalization was achieved, and only starting material was recovered. Finally, oxidation of the alcohol to ketone **544** was successful, but all attempts at condensation of the resulting ß-ketonitrile with formaldehyde led to decomposition with no trace of nitrile **545** observed.




**Scheme 4.12**: Relay ring-closing metathesis strategy.

The failure to install the required acrylate moiety was concurrent with the realization that perhaps a simple acrylate was not effective in the ring-closing metathesis reaction because of a combination of steric effects and the electron deficiency of the olefin (see **Table 4.3** for model studies). One way to overcome such a problem would be to use the relay ring-closing metathesis method reported by Hoye.[156] In this method, the metal center is directed to traditionally difficult-to-activate olefins (i.e., hindered and/or electron-poor) by performing the more straightforward metathesis first. As shown in **Scheme 4.12**, the disubstituted butenolide **549** was prepared starting from triene **546**. The initial ring-closure occurred with the expulsion of cyclopentene **547**, leaving the Ru catalyst attached at the desired site in **548**. A second ring-closure then occurred to provide the product and regenerate the catalyst. Thus, I sought to prepare a substrate resembling allyl ether **550**.

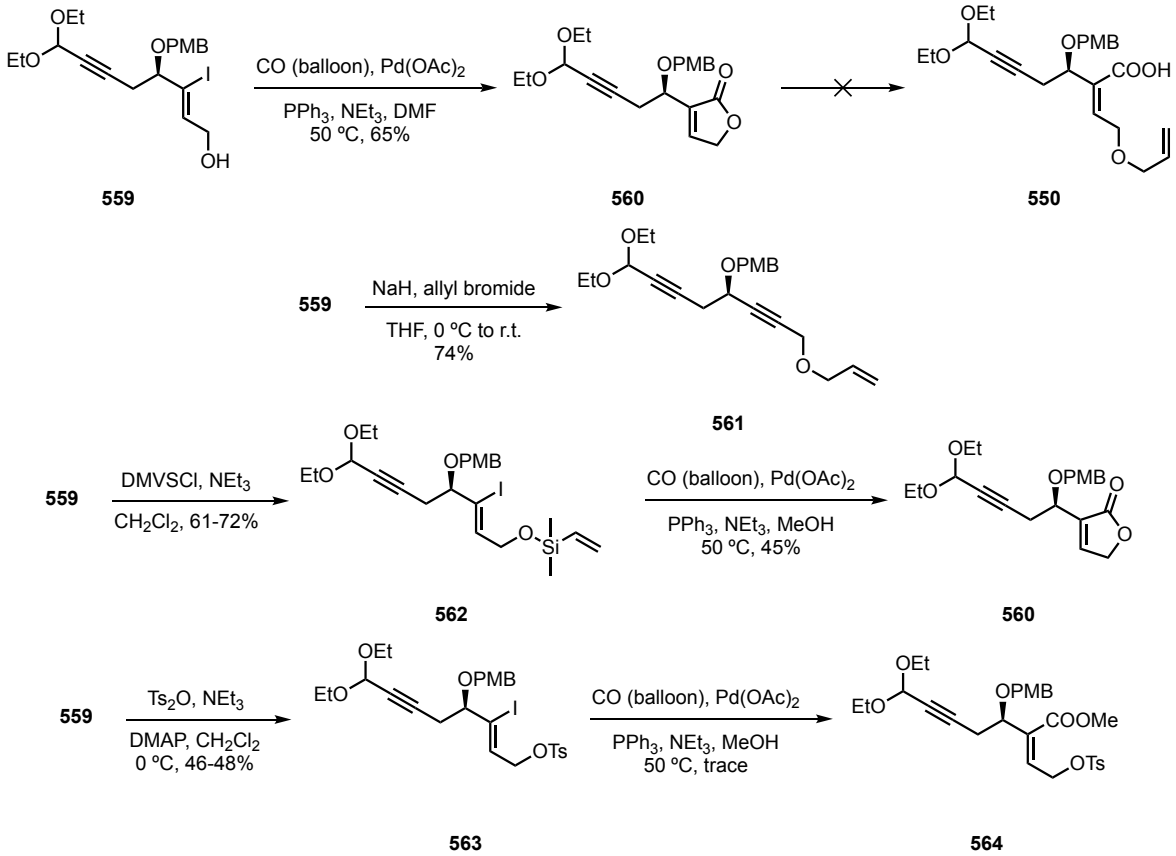
The synthesis of the allylic alcohol precursor to **550** was quite straightforward and followed roughly the same approach to alkyne **515** (see **Scheme 4.6-7**), with a couple of key modifications. It is worth mentioning that homologation of alkyne **515** by deprotonation of the alkyne was inefficient because of the propensity for elimination of the *p*-methoxybenzyl ether. Thus, a modified synthesis, shown in **Scheme 4.13**, was developed by incorporating the hydroxymethyl moiety from the outset with 1,4-butyndiol (**551**) as the starting material. Monoprotection as the TIPS ether and oxidation of the remaining alcohol led to aldehyde **553**. The Barbier propargylation, enzymatic resolution, and PMB protection remained consistent with the previous route. Notably, the minor change in substrate for the enzymatic resolution of propargyl alcohol **(±)-554** did not impact the selectivity of the resolution, and both enantiomers were obtained in high enantiopurity, although a slightly different enzyme was required to obtain




**Scheme 4.13**: Synthesis of vinyl iodide precursor.

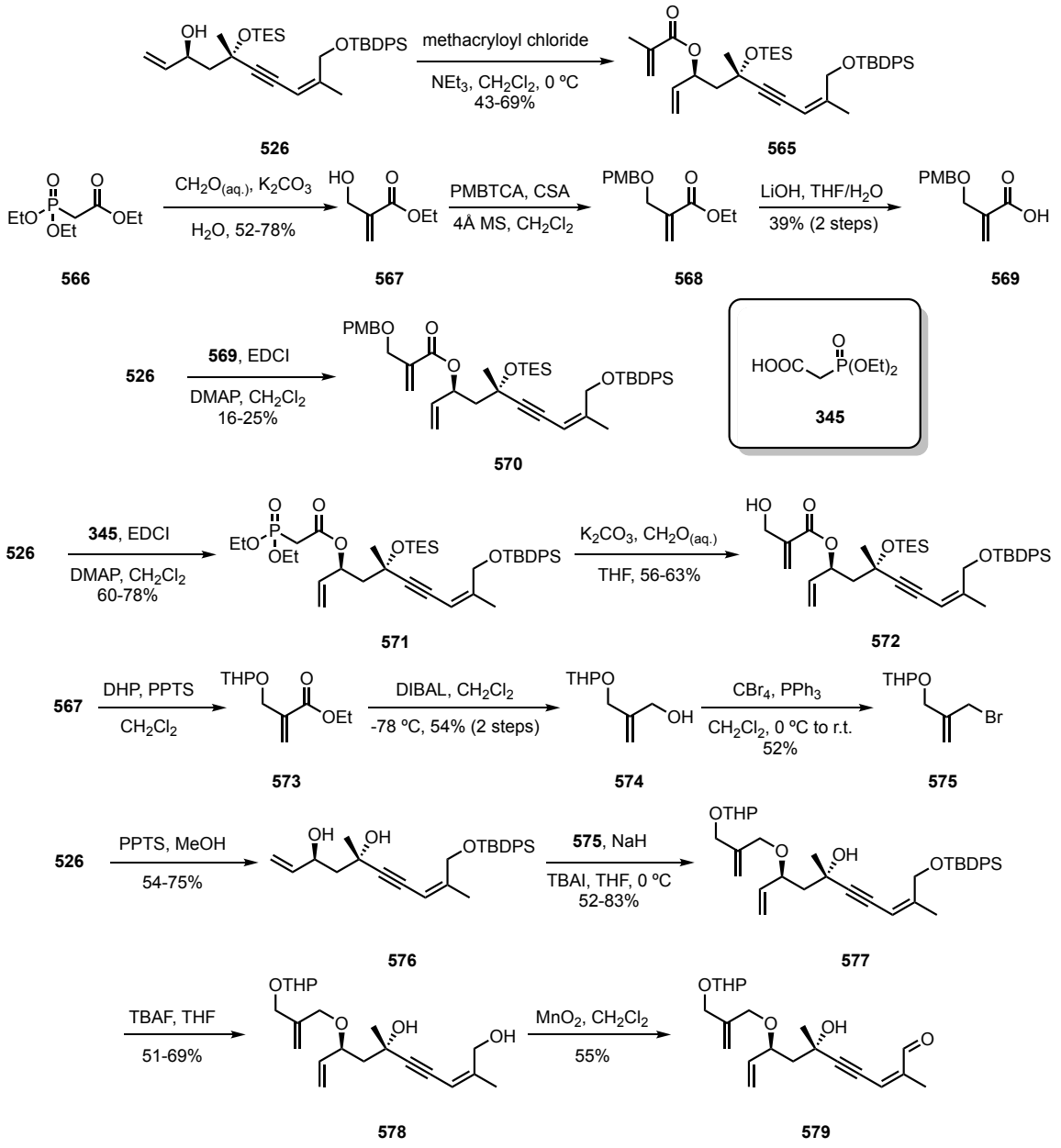
optimal results. One key difference in this synthesis was the ability to homologate the terminal alkyne directly to the diethyl acetal by means of the method first reported by Howk and Sauer in 1958.[157] Although the yields were not exceptionally high, they were certainly an improvement over the two-step procedure of formylation and protection. Following deprotection and hydroxyl-directed hydroiodination of the alkyne, I arrived at vinyl iodide **559** (**Scheme 4.13**). Ostensibly, only two transformations remained to access bis-allyl ether **550**: carbonylation of the vinyl iodide to install the carboxylate moiety and allylation of the free alcohol.

The efforts to continue the synthesis from vinyl iodide **559** are shown in **Scheme 4.14**. Initially, I attempted to perform the carbonylation first. Expecting that the intramolecular butenolide formation would predominate, I had hoped that the butenolide could be hydrolyzed to enable further functionalization. Unfortunately, while the carbonylation was successful, I could not further functionalize the product, so the butenolide represented a dead end. It became evident that functionalization of the allylic alcohol must be the first operation. Surprisingly, upon treatment of vinyl iodide **559** with sodium hydride and allyl bromide did not lead to the expected allylation; instead, the iodine was efficiently eliminated to alkyne **561**, with the alcohol converted to its allyl ether. It became evident that a weaker base would be




**Scheme 4.14**: Attempted functionalization of vinyl iodide **559**.

necessary to "protect" the alcohol. This could be achieved using a silyl derivative — the dimethylvinyl silyl ether — as an allyl surrogate. Indeed, silylation of the allylic alcohol furnished silyl ether **562**; however, upon exposure to carbonylation conditions, desilylation occurred and the resulting alcohol rapidly cyclized to butenolide **560**. Unfortunately, none of the desired methyl ester was obtained. Finally, I hoped to be able to convert the alcohol to the corresponding tosylate **563**. I hoped that this *de facto* alcohol protecting group could be displaced with allyl alcohol once the carboxylate moiety was installed. Exposure of vinyl iodide




**Scheme 4.15**: Preparation of various ring-closing metathesis substrates.

**564** to the standard carbonylation conditions, however, produced only trace amounts of methyl ester **564** accompanied by a significant amount of decomposition.

As I was unable to synthesize either acrylate **528** or relay ring-closing metathesis substrate **550**, I shifted my attention to a simpler substrate without the propargyl side chain. A variety of α-hydroxymethyl acrylates were synthesized, as shown in **Scheme 4.15**. In anticipation of the difficulties associated with ring-closing metathesis with acrylates, I also prepared allyl ether derivative **577**, with the expectation that the resulting dihydrofuran could later be oxidized to the corresponding butenolide. It is worth mentioning that deprotection of the tertiary silyl ether in alcohol **526** was necessary prior to alkylation as silyl migration occurred upon deprotonation of the secondary alcohol. Aldehyde **579** was also prepared because, as will be seen, the enyne moiety would become problematic during the ring-closing metathesis reaction. I surmised that removing electron density from the enyne would better promote the desired reactivity. Thus, five different substrates were prepared for trials in forming the B-ring butenolide by the ring-closing metathesis reaction.

The results of selected ring-closing metathesis attempts are shown in **Table 4.3**. Entries 1–3 represent efforts at the simplest acrylate **565**. That only starting material was recovered when using low-catalyst loadings is not in agreement with the report by Fürstner that claims ring-closing metathesis to form similar α,γ-substituted butenolides proceeds in 92% yield.[158] Increasing the catalyst loading from 5% to 30% resulted in a mixture of unidentified compounds lacking many of the characteristic NMR peaks of the desired product. Fürstner also reported the use of mild Lewis acid additives that may improve the reactivity of acrylates in ring-closing metathesis, such as $Ti(O^iPr)_4$.[159,160] After the catalytic cycle is initiated and the substrate is bound to the ruthenium catalyst, the Lewis basic oxygen of the carbonyl coordinates to the metal center, forming a stabilized chelate and preventing further reactivity. This complex is disrupted by the addition of Lewis acids, allowing for the reaction to proceed as expected. When I used $Ti(O^iPr)_4$, I observed an increase in reactivity and, for the first time, complete and clean consumption of starting material. I was unable, however, to fully characterize this product completely. I suspect that after initiation at the terminal olefin, the complex reacted further at the enyne terminus of the molecule as the acrylate moiety was unchanged according to NMR analysis. The pattern of reactivity at the more electron-rich enyne became more evident throughout the trials and I was never able to isolate the desired product in amounts sufficient for full characterization. The attempt to reduce electron density of the enyne by oxidation of the allylic alcohol (entry 10) was unsuccessful — the metathesis catalysts continued to react with the undesired π-system. Once it became apparent that the

| Entry (Substrate) | Catalyst | Additive | Solvent (Concentration) | Temperature | Result |
|---|---|---|---|---|---|
| **1 (565)** | Grubbs' II (5%) | — | PhMe (0.01 M) | 80 °C | Starting material |
| **2 (565)** | Hoveyda-Grubbs' II (5%) | — | PhMe (0.01 M) | 80 °C | Starting material |
| **3 (565)** | Hoveyda-Grubbs' II (30%) | — | PhMe (0.01 M) | 80 °C | Enyne reactivity (mixture) |
| **4 (570)** | Grubbs' II (20%) | $Ti(O^iPr)_4$ | $CH_2Cl_2$ (0.01 M) | 40 °C | Unknown product (enyne) |
| **6 (572)** | Grubbs' II (10%) | $Ti(O^iPr)_4$ | $CH_2Cl_2$ (0.1 M) | 40 °C | Ester hydrolysis then enyne reactivity |
| **6 (572)** | Grubbs' II (10%) | $Cy_2BCl$ | $CH_2Cl_2$ (0.1 M) | 40 °C | Starting material and decomposition |
| **7 (577)** | Grubbs' II (20%) | — | $CH_2Cl_2$ (0.05 M) | 40 °C | Starting material and unknown product |
| **8 (577)** | Grubbs' II (10%) | — | $CH_2Cl_2$ (0.3 M) | 40 °C | Starting material and unknown product |
| **9 (577)** | Hoveyda-Grubbs' II (10%) | — | PhH (0.05 M) | 80 °C | Enyne reactivity |
| **10 (579)** | Hoveyda-Grubbs' II (10%) | — | PhH (0.05 M) | 80 °C | Enyne reactivity |

**Table 4.3**: Selected attempts at ring-closing metathesis.

enyne moiety was the cause of the problem, I began to think about ways in which the enyne might be modified to suppress this problematic side reaction.

One solution that occurred to me was to protect the alkyne as the TIPS derivative. The loss of conjugation combined with the large steric environment of the TIPS group should prevent metathesis at the wrong end of the molecule. Unfortunately, installation of the TIPS group prior to the aldol reaction led to a complete loss of diastereoselectivity. The sensitivity of the ß-silyloxy carbonyl moiety (cf. **497**, **503**, **515**) to base meant the alkyne had to be protected after reduction of the ketone; however, the presence of a terminal alkyne interfered with the CBS reduction, apparently via a hydroboration process. As a result of these difficulties, I was unable to prepare the necessary substrates which lacked the problematic enyne functionality, and the ring-closing metathesis reaction was not attempted. After a total of 28 attempts to form the B-ring butenolide by this method, I decided to move on from the ring-closing metathesis approach.

## 4.4 Eighth Generation: Back to Epoxide Openings

The dependence of the CBS stereoselective reduction on the nature of the substrate meant that the CBS protocol could not serve as a general method by which to set the stereochemistry at C10. I therefore had to explore alternate methods, preferably under reagent-controlled conditions, to incorporate the correct configuration. While I was exploring the possibility of advancing the terminal alkyne through the ring-closing metathesis reaction, I happened to stumble upon alkene **580**, shown in **Figure 4.4**, which happened to be a known compound.[161] When they subjected alkyne **580** to Sharpless dihydroxylation conditions, they obtained four diastereomers as they did not use enantiopure material. They were able to assign which combinations of substrate and reagent represented the matched case, and which represented the mismatched case (**Figure 4.4**). Thus, the major enantiomer of **580** was found to be mismatched with the reagent (AD-mix-ß), offering very little selectivity for the newly formed secondary alcohol center. However, the minor enantiomer was a matched case, and favored the 1,3-anti product **(2*R*,4*R*)-581** in a diastereomeric ratio of 14:1. An observant reader will note that **(2*R*,4*R*)-581** is the enantiomer of what would be required for the synthesis of bielschowskysin (**1**). It stands to reason that treatment of enantiopure **580** with AD-mix-α, the desired **(2*S*,4*S*)-581** should be formed with a high degree of selectivity.

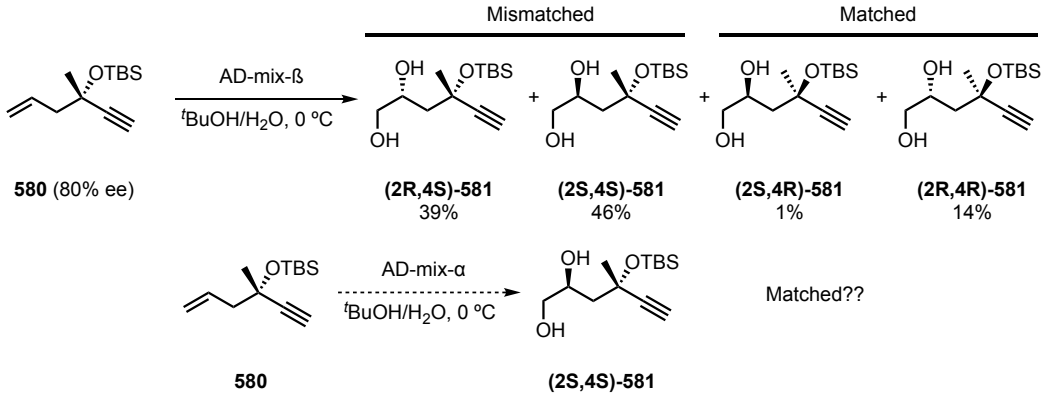
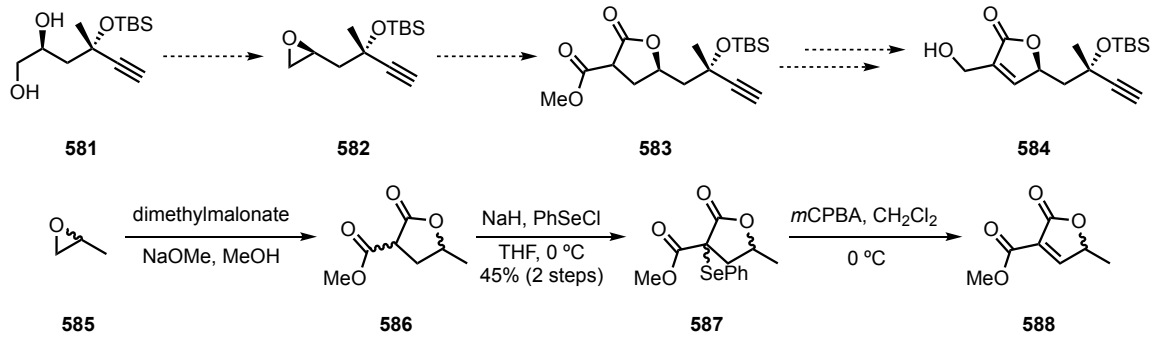


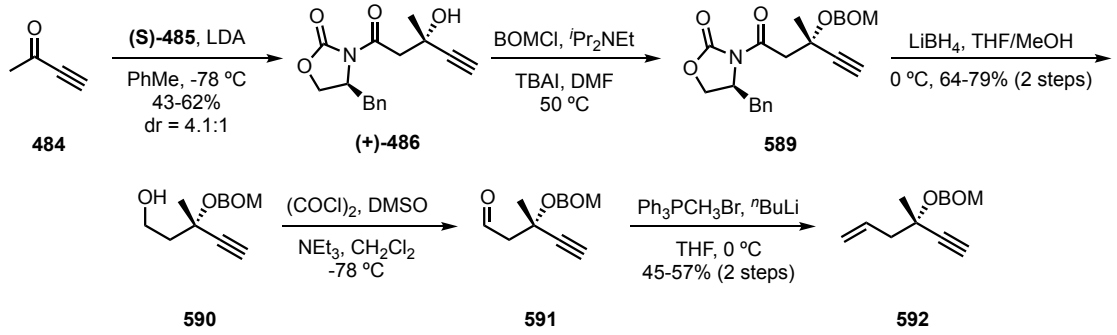

**Figure 4.4**: Dihydroxylation analysis.

With these observations in mind, I developed a revised approach, shown in **Scheme 4.16**. I had hoped to convert diol **581** into the corresponding epoxide **582**, which could then be opened with a malonate to afford lactone **583**. There are two key points about this revision. First, one might recall that this approach mirrors the first-generation approach in which ynamide **306** was used to open epoxide **326**, which differs only in the nature of the protecting group. I planned, however, to use a much more efficient route to epoxide **582**. The opening of



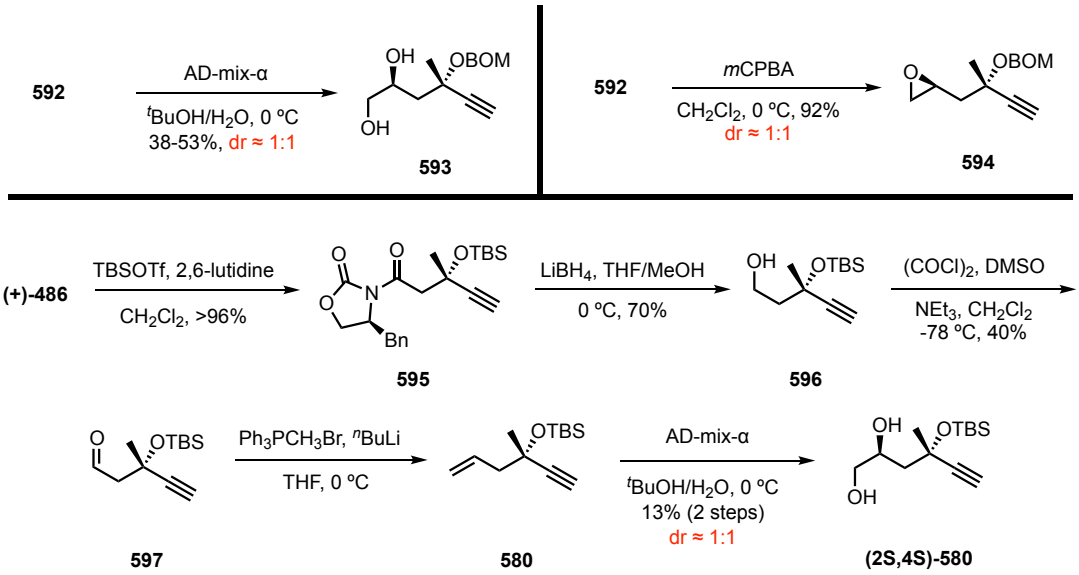

**Scheme 4.16**: Revised approach and model studies.

the epoxide under thermodynamic conditions would be significantly more reproducible. To that end, I attempted the epoxide opening with malonate on a model system and, indeed, I was able to access, after selenation and oxidative elimination, the corresponding butenolide **577** effectively. The second consideration, and this was indeed a gamble, is that the endocyclic carbonyl could be differentiated, in some way, from the exocyclic carbonyl in order to access alcohol **584**.




**Scheme 4.17**: Synthesis of dihydroxylation substrate.

In order to intersect as closely as possible with the substrate reported by Laschat,[161] I performed the aldol reaction, shown in **Scheme 4.17**, on the simple alkyne **484** to produce **(+)-486**, the exact enantiomer of what had been initially reported by Fürstner.[140] The protecting group, however, was modified as it was important to retain, if possible, the benzyl functionality on the tertiary alcohol because it had been demonstrated previously that late-stage removal was not problematic.[68] The BOM group, then, was advantageous as it could be installed without the direct formation of the oxyanion, which in the past had led to retro-aldol reactions. Straightforward reductive removal of the auxiliary followed by oxidation and Wittig homologation afforded olefin **592** in a short and scalable synthesis.

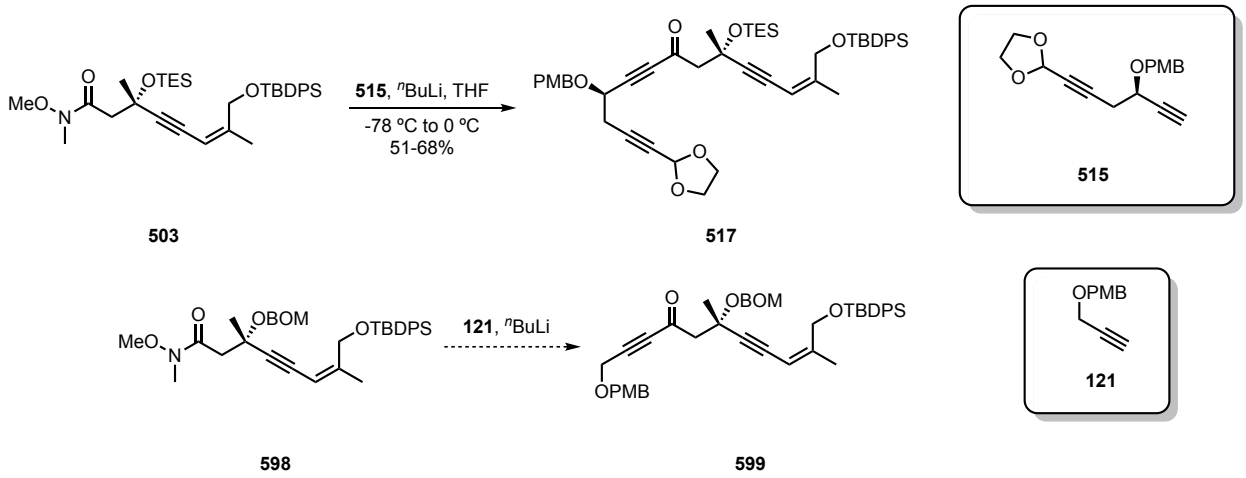



**Scheme 4.18**: Stereochemical outcomes of olefin oxidation.

The attempted oxidations of olefin **592** are shown in **Scheme 4.18**. Dihydroxylation using the Sharpless catalytic system AD-mix-α resulted in no observed diastereoselectivity, and diol **593** was obtained as a 1:1 mixture of diastereomers. Furthermore, simple epoxidation with *m*CPBA also produced epoxide **594** as a 1:1 mixture of diastereomers, indicating that the existing chiral center had minimal influence on the stereochemical outcome at the ß-position. The failure of the Sharpless asymmetric dihydroxylation should not have come as a complete surprise, as Laschat noted parenthetically that adjacent π-systems such as a phenyl ring might negate any stereoselectivity through unfavorable π-π interactions. Thinking that perhaps the TBS ether would overcome these challenges, I prepared olefin **580** following the same general procedure, albeit in unoptimized yields. Much like the benzyloxymethyl ether, however, dihydroxylation of the olefin with AD-mix-α generated no diastereoselectivity. Once again, the failure to incorporate the correct configuration at C10 signified the dead end of this route. Although this particular synthetic route was relatively short-lived, I decided to abandon the approach to the B-ring butenolide via epoxide **594** or **582** in favor of an approach that I had already had some success with previously.

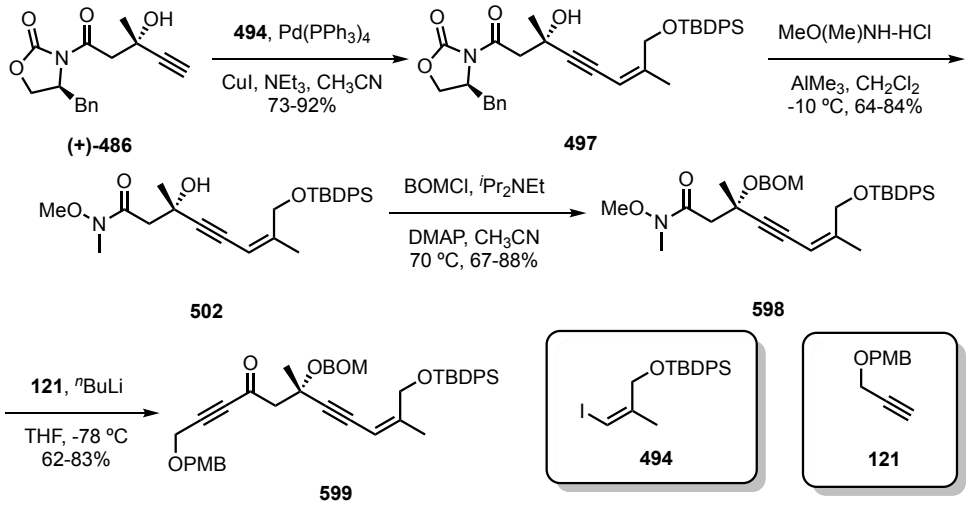
## 4.5 1

In Section 4.2, I described the addition of alkyne **515** to Weinreb amide **503** and the subsequent efforts to reduce the ketone diastereoselectively and to functionlize the alkyne in order to construct the central butenolide ring using a palladium-catalyzed carbonylation. At this




**Scheme 4.19**: Ninth-generation approach.

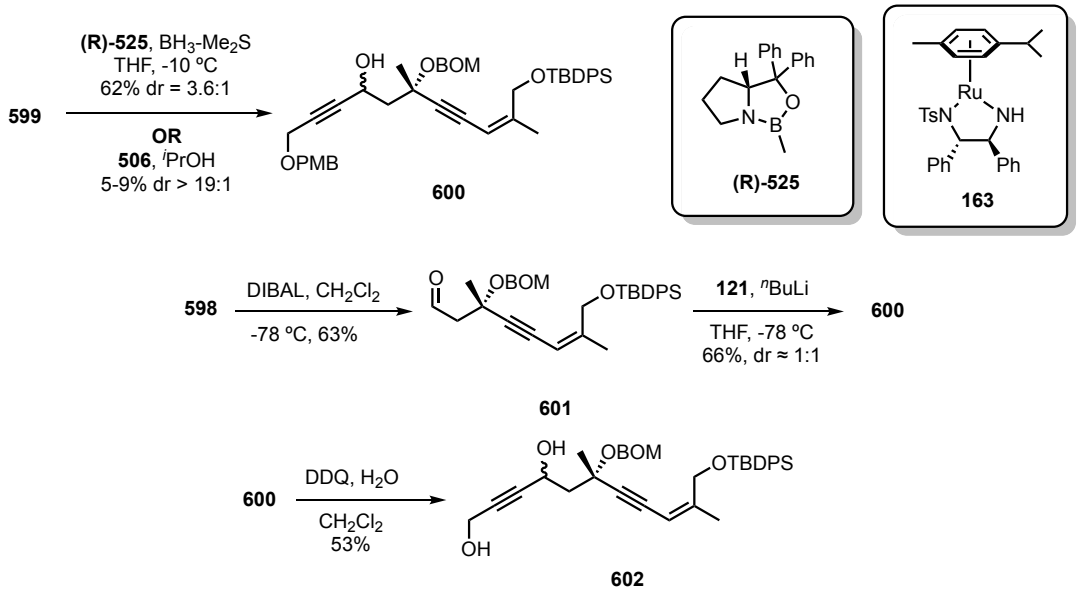
point, I chose to return to this strategy but, in doing so, to incorporate two key features that I worked out since then. First, as described in Section 4.3, I could efficiently set the C10 stereocenter using a CBS reduction *if* the substituent was small (e.g., vinyl or ethynyl). Second, as described in Section 4.4, the tertiary alcohol could be protected as the BOM ether, which proved considerably less labile than the silyl ether initially used. Thus, I chose to pursue the approach shown in **Scheme 4.19**, in which the simpler alkyne **121** would be added to Weinreb amide **598**, in the hope that the resulting alkynone **599** would prove a suitable substrate for asymmetric reduction.




**Scheme 4.20**: Synthesis of alkynone **599**.

As shown in **Scheme 4.20**, the synthesis of alkynone **599** followed roughly the same path as I had used in the earlier sections of this chapter, although the order of operations had

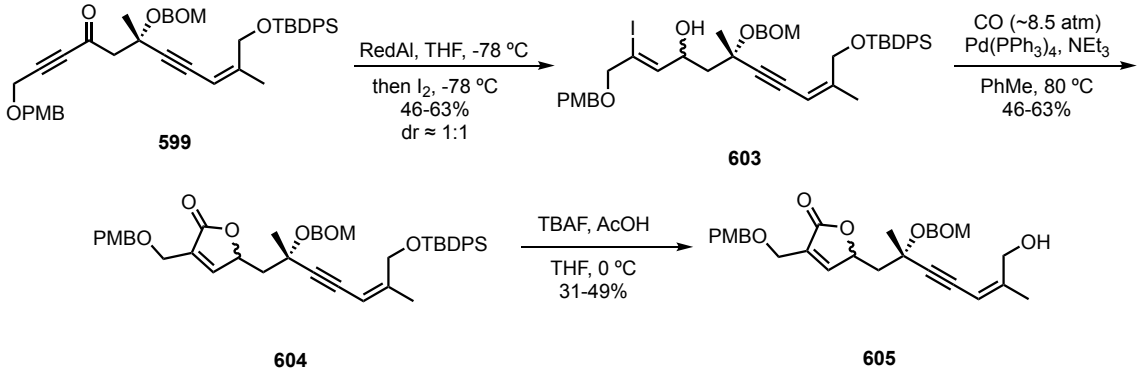
to be optimized. Performing the aldol reaction first, followed by Sonogashira coupling with the previously used vinyl iodide **494** led to tertiary alcohol **497**. After transamidation and protection of the tertiary alcohol, I arrived at the desired Weinreb amide **598**. The addition of alkyne **121** proved somewhat challenging and required considerable optimization. For example, because the lithium acetylide of **121** proved unstable at higher temperatures (e.g., 0 ºC) and Weinreb amide **598** was not overly reactive at lower temperatures, significant amounts of starting material were recovered initially. This problem was overcome by using a large excess of the acetylide. Furthermore, the relatively low electrophilicity of the carbonyl moiety had to be balanced with the relatively high acidity of the α-protons, deprotonation of which had led to elimination of the benzyloxymethyl ether in the past. Ultimately, these issues were overcome and I was able to access alkynone **599** in gram quantities and with quite good yields.




**Scheme 4.21**: Failure to establish C10 stereocenter.

In terms of establishing the stereochemistry at C10, a gamut of approaches was attempted, as shown in **Scheme 4.21**. CBS reduction afforded propargyl alcohol **600** in moderate yields, although the diastereoselectivity was not great. It should also be noted that the absolute configuration of the product was not determined. Noyori asymmetric transfer hydrogenation did produce the propargyl alcohol with excellent diastereoselectivity, although in this case the yields were abysmal. Either starting material was recovered or the alkyne was reduced to the corresponding olefin. Midland reduction[162] resulted in decomposition of the substrate. Semireduction of the Weinreb amide moiety followed by addition of the lithium acetylide of **121** to the corresponding aldehyde produced propargyl alcohol **600** with almost no

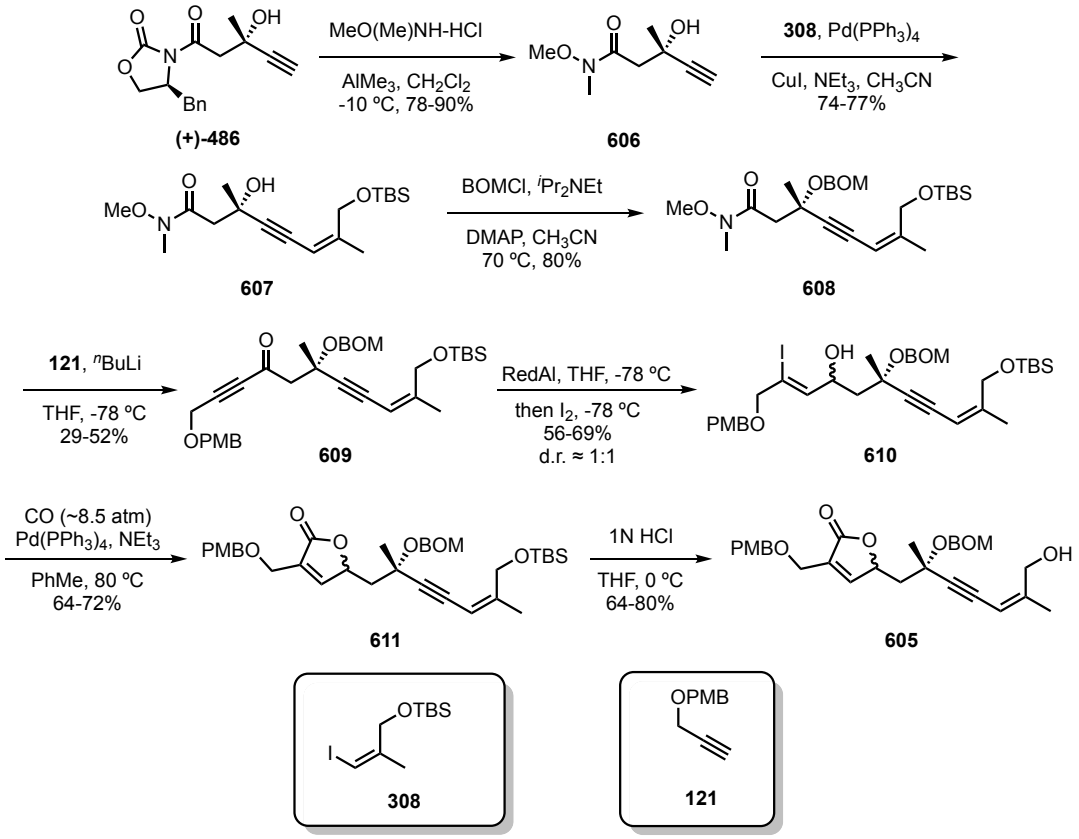
diastereoselectivity. Finally, the two epimers could not be resolved with lipase either as alcohol **600** or as diol **602**, as reported by Princival.[163] Furthermore, the two C10 epimers were inseparable by traditional chromatographic methods. Although it was desirable to separate the epimers at this stage in order to recycle the undesired epimer by Mitsunobu inversion, I made the decision to continue the synthesis with the mixture, expecting that they could be separated at a later stage.




**Scheme 4.22**: Synthesis of B-ring butenolide.

Under ideal circumstances, the diastereomerically pure alcohol **600** would be hydrometalated with RedAl in a hydroxyl-directed fashion. Since the diastereomeric ratio became inconsequential, I found that alkynone **599** could be converted directly to vinyl iodide **603** using identical conditions, shown in **Scheme 4.22**. Palladium-catalyzed carbonylation of the vinyl iodide under a balloon atmosphere of CO afforded butenolide **604** in only 20–29% yields. When performing the reaction in a Parr apparatus at elevated temperature and pressure (~8.5 atm), however, the yield of the transformation increased up to three-fold. Interestingly, the diastereomers of both vinyl iodide **603** and butenolide **604** remained inseparable and, moreover, **603** and **604** could not be separated from each other. Thus, it was imperative that the carbonylation reaction proceed to completion. With the desired B-ring butenolide formed for the first time since the first generation, what remained was to fashion the C-ring butenolide by the established silver-catalyzed cycloisomerization strategy. Unfortunately, as fluoride-mediated desilylation was unacceptably low-yielding and I was unable to access to access sufficient quantities of allylic alcohol **605**, I made the decision to switch to a more labile protecting group that could be removed under acidic conditions.

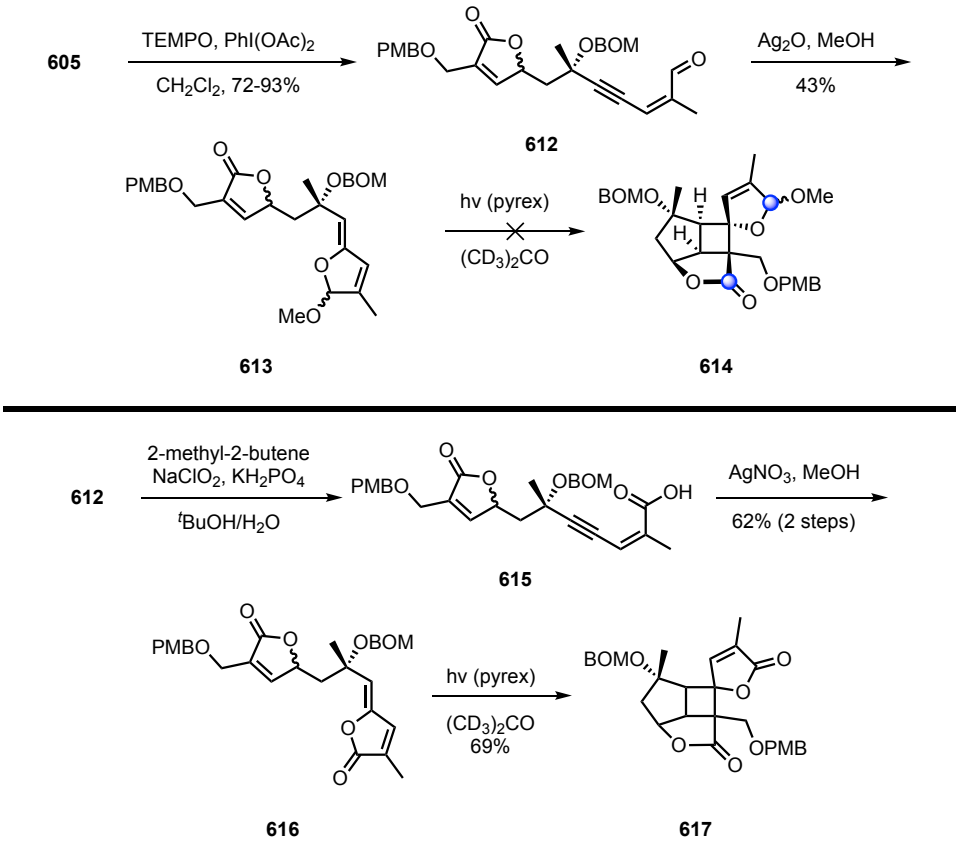
As shown in **Scheme 4.23**, the synthetic route with the TBS-protected allylic alcohol was nearly identical, with one key exception. If the Sonogashira coupling was performed on **(+)-486** with vinyl iodide **308** and if I continued through to the transamidation, the product could not be separated from the auxiliary byproduct. Thus, the order of operations was




**Scheme 4.23**: Revised synthesis of allylic alcohol **605**.

reversed and the transamidation was performed first to afford Weinreb amide **606**. From there, the previous route was unchanged to butenolide **611**, at which time the silyl protecting group was removed with 1N HCl to afford alcohol **605** in much improved yields.

After oxidation of the primary alcohol, it became clear that, from aldehyde **612**, there were two possible routes to take. The first involved silver-catalyzed cycloisomerization of the aldehyde moiety, leading directly to cyclic acetal **613** (**Scheme 4.24**). Indeed, this type of transformation is known with aromatic substrates,[164] and it stood to reason that I should have some degree of success with aldehyde **612**. Although the reaction was extremely sluggish (it took three days), acetal **613** was formed in 43% yield. I had hoped that irradiation of this compound would produce cycloadduct **614** with the key feature that the two carbonyls (highlighted in **Scheme 4.24**) exist in different oxidation states. This could be advantageous when completing the total synthesis, namely in the closure of the eight-membered ring. Irradiation of **613**, however, did not produce the desired cycloadduct but instead resulted in decomposition of the substrate. It was not clear whether photoexcitation of the diene moiety actually occurred. Furthermore, the cycloisomerization reaction could not be optimized beyond

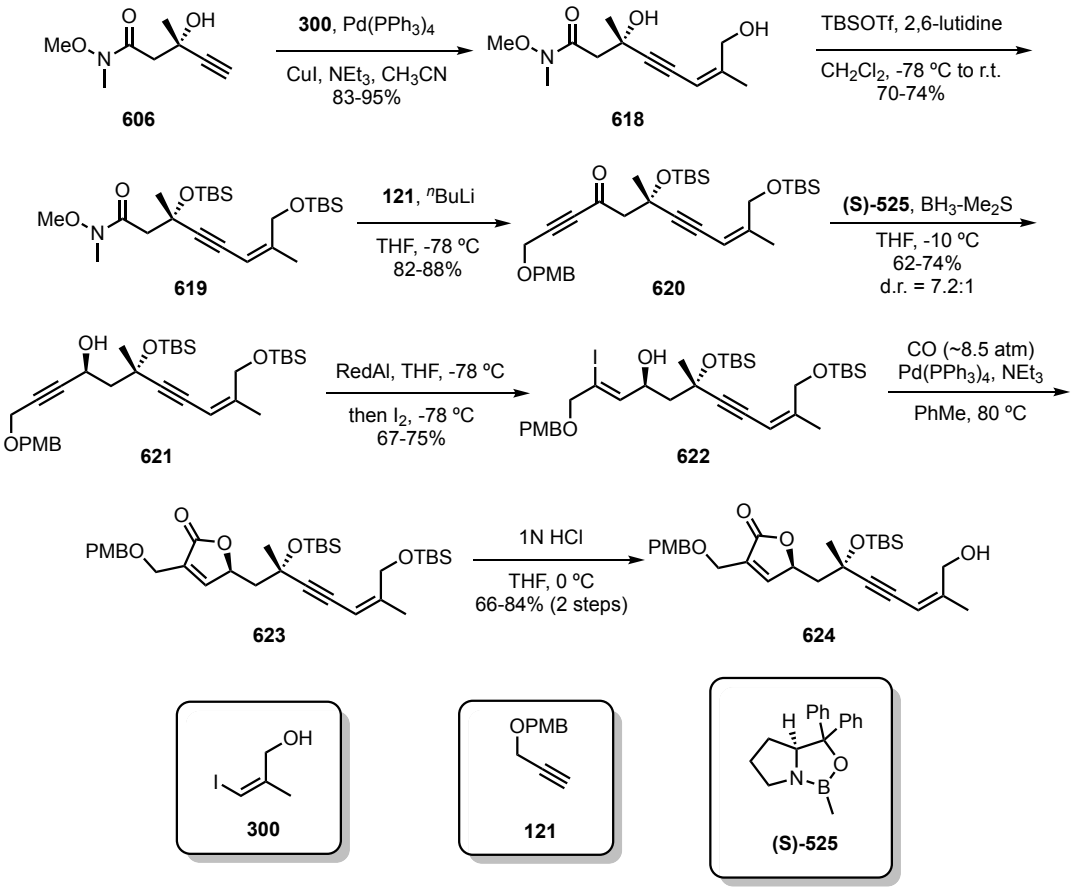



**Scheme 4.24**: First forays into photochemistry.

the initial slow, low-yielding result. I decided that it might be more prudent to simply follow the initial plan, and, indeed, further oxidation of the aldehyde to the corresponding carboxylic acid and silver-catalyzed cycloisomerization afforded bis-butenolide **616**. Finally, four-and-a-half years after beginning my journey of total synthesis, I was able to prepare cyclobutane **617** after irradiation of the bis-butenolide. As the reader has surely noticed, however, the stereochemistry is not drawn in **Scheme 4.24** because, to my surprise, the diastereomers were still not separable. This highlighted the absolute necessity that the C10 stereocenter must be established from the outset. As I will explain in the following section, this problem was not quite so daunting as it initially seemed.

## 4.6 Tenth Generation: CBS Reduction (Finally) Establishes C10 Stereocenter

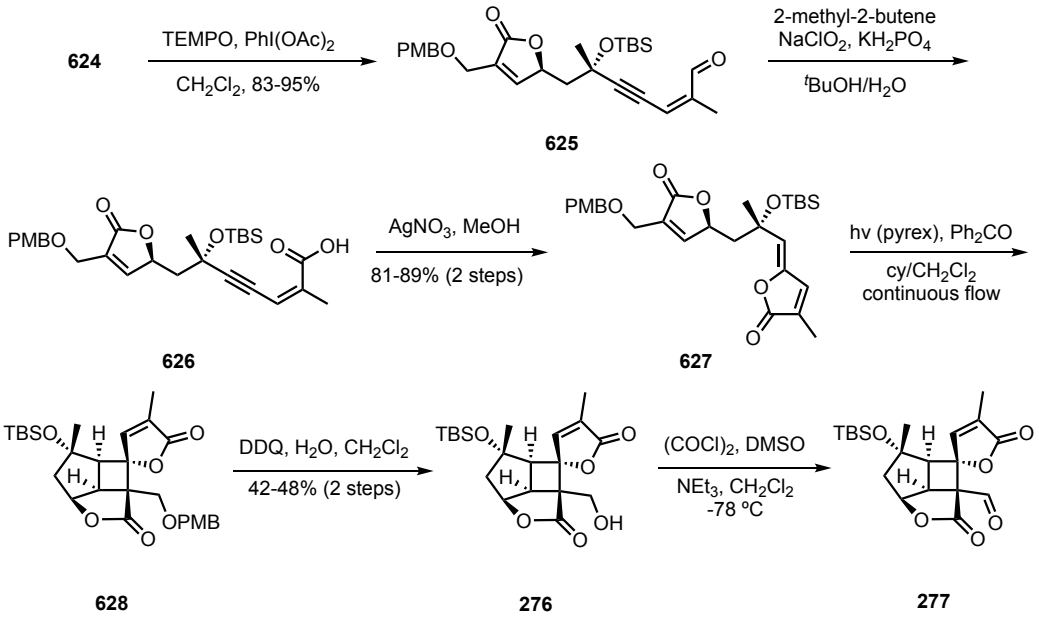
Although I was delighted at the fact that the photochemical reaction had proceeded so smoothly, it was unfortunate that the C10 stereocenter still constituted a major problem. I recalled that perhaps the BOM group was the culprit of the low selectivity of the CBS reduction (see **Scheme 4.21**) based on the similar hypothesis voiced in Section 4.4.[161] Thus, in order to




**Scheme 4.25**: Diastereoselective synthesis of B-ring butenolide.

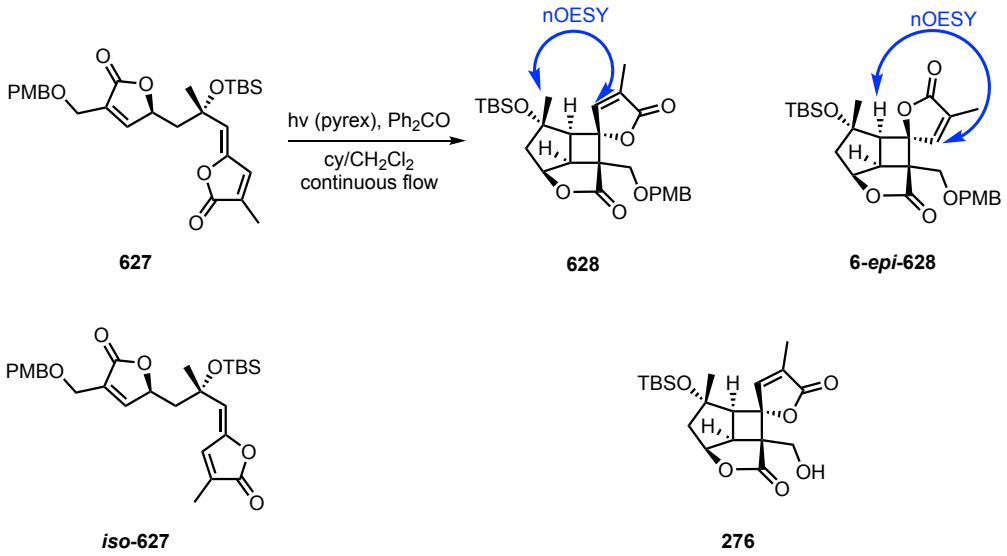
solve the stereochemical problem once and for all, I made the decision to switch the protecting group on the C8 tertiary alcohol to a TBS group. This required only a slight modification of the synthesis, shown in **Scheme 4.25**. Rather than perform the Sonogashira coupling with the TBS-protected vinyl iodide (**308**, **Scheme 4.23**), it seemed more prudent to use the free alcohol **300** and protect both hydroxyl moieties later in a single step. The addition of the lithium acetylide of alkyne **121** to Weinreb amide **619** proceeded smoothly, and the reaction was optimized to afford alkynone **620** in excellent yields. It is worth noting that alkynone **620** and alkyne **121** proved to be inseparable by chromatographic methods, although the purity of **620** did not influence the efficacy of the diastereoselective reduction. The reduction of the ketone moiety afforded propargylic alcohol **611** in good yields and with good diastereoselectivities. Although the reaction was not as efficient as the reduction of enone **524** (see **Scheme 4.9**), the reduction proceeded quite well when following the procedure reported by Parker.[165] A key modification of this procedure is the use of two full equivalents of oxazaborolidine **525**, as opposed to the catalytic amount reported by Corey[150] or the one equivalent used in the case of

enone **524**. Whether or not the change in procedure or the change in protecting groups was responsible for the success of this reaction was not determined; nevertheless, I was finally able to continue the synthesis in a diastereomerically pure fashion. After hydroiodination of the alkyne, vinyl iodide **622** was subjected to the carbonylation conditions previously used (see **Scheme 4.23**). I noticed that if more than one equivalent of base was used in the reaction, or if the reaction was allowed to continue for longer times, partial epimerization of the C10 position occurred. The use of inorganic bases such as $K_2CO_3$ did not suppress this undesired reactivity; however, under the somewhat optimized conditions, there was only a minimal loss of diastereomeric purity.




**Scheme 4.26**: Accessing the cycloadduct.

With allylic alcohol **624** in hand, a series of sequential oxidations followed by the silver-catalyzed cycloisomerization reaction afforded bis-butenolide **627**, as shown in **Scheme 4.26**. Upon irradiation of butenolide **627** with a medium-pressure Hg lamp and a Pyrex filter, the desired [2+2] cycloaddition proceeded smoothly and cleanly to afford cyclobutane **628**. There are a couple of things worth mentioning about this reaction. A major problem with doing the reaction is the necessity of quartz glass rather than standard borosilicate glass as the material for the reaction vessel. Thus, it would become difficult to perform this reaction on scales that exceeded what could fit in one or two quartz test tubes without significant investment in a full set of quartz glassware. I decided, based on the protocol reported by Danheiser, to attempt the reaction using a continuous flow apparatus.[166] All materials required for the flow apparatus could be obtained for less than the price of a single 50 mL quartz round-bottom flask!




| Entry | Additive | Solvent | Flow Rate | 627:*iso*-627 | 628:6-*epi*-628 | 276 |
|---|---|---|---|---|---|---|
| **1** | $Ph_2CO$ | $CH_2Cl_2$ (0.05 M) | 3 mL/h | 0% | 0% | 41% |
| **2** | $Ph_2CO$ | $CH_2Cl_2$ (0.05 M) | 12 mL/h | 24% (1.2:1) | 27% (3.7:1) | 0% |
| **3** | $Ph_2CO$ | $CH_3CN$ (0.05 M) | 6 mL/h | 0% | 54% (2.2:1) | 0% |
| **4** | None | $(CH_3)_2CO$ (0.05 M) | 6 mL/h | 0% | 61% (1.4:1) | 0% |
| **5** | $Ph_2CO$ | cyclohexane/$CH_2Cl_2$ (13:1, 0.05 M) | 6 mL/h | 0% | 54% (6.8:1) | 0% |
| **6** | $Ph_2CO$ | cyclohexane/$CH_2Cl_2$ (19:1, 0.05 M) | 5 mL/h | 0% | 57% (13:1) | 0% |
| **7** | $Ph_2CO$ | cyclohexane/$CH_2Cl_2$ (19:1, 0.05 M) | 3 mL/h | 0% | 55% (>19:1) | 0% |

**Table 4.4**: Optimization of photochemical cycloaddition in continuous flow.

Furthermore, because the path length of the flow apparatus is much smaller than the size of a flask, the attenuation of light becomes negligible and much more uniform irradiation is achieved.[167] Using the photochemical setup in continuous flow enabled the synthesis of gram quantities of cyclobutane **628**. During the course of optimizing of this reaction, I noticed that there was a strong correlation between the configuration of the C6 spirocyclic stereocenter and the solvent polarity. The results, summarized in **Table 4.4**, lend credence to the hypothesis that dipole minimization plays a role in the stereochemical outcome of the reaction (see **Figure 2.6**, Section 2.7). Interestingly, the PMB ether was photochemically removed upon longer exposure in $CH_2Cl_2$. This photochemical deprotection of PMB ethers does have some precedent.[168] The reaction, however, was not particularly reproducible, and I decided to attempt to minimize this

side reaction instead. The use of a 5% solution of $CH_2Cl_2$ (for solubility) in cyclohexane afforded the best results, producing cyclobutane **628** as the sole product with no detectable presence of **6-*epi*-628** by $^1H$ NMR. Ultimately, a flow rate of 6 mL/h was the used to improve the practicality of the reaction (on multi-gram scales, a flow rate of 3 mL/h would necessitate irradiation times of more than 25 hours!), and the consequent decrease in diastereoselectivity was negligible. The configuration of the major diastereomer was confirmed by NMR-nOESY analysis. Finally, oxidative removal of the PMB group with DDQ and Swern oxidation of the primary alcohol afforded aldehyde **277** (which will be discussed further in the next chapter).

In addition to enabling the diastereoselective reduction at C10, the installation of the TBS protecting group at C8 had another serendipitous consequence, namely, that aldehyde **277** had been previously prepared by the Mulzer group in their efforts toward the synthesis of bielschowskysin (**1**). I was thus able to confirm all stereochemical assignments with what had been reported previously (see Section 2.6).[64] Furthermore, while it took the Mulzer group 29 steps from a commercially available starting material to access aldehyde **277**, this tenth-generation synthesis only required 15 steps .

## 4.7 Conclusions

I have described in this chapter how a dramatic shift in thinking enabled the advancement of the synthesis. I began with a new analysis of the relative stereochemistry between C8 and C10 and looking at the possibility of establishing the tertiary alcohol center at C8 before the secondary alcohol center at C10. This new approach led to my discovery of the known acetyl aldol reaction highlighted in **Figure 4.2**. With the tertiary alcohol center set by Evans's aldol, the secondary alcohol was ultimately established by means of CBS reduction. With both stereocenters firmly established, the problem then shifted to forming of the central butenolide. My initial attempts to form the butenolide ring by palladium-catalyzed carbonylation or ring-closing metathesis were entirely unsuccessful, but I was finally able to form the butenolide ring by high-pressure carbonylation of a much simpler vinyl iodide substrate (**622**). Now that the problems that I had identified from the outset were solved, I was able (finally) to advance the synthesis to the key photochemical [2+2] cycloaddition. With the ability to prepare gram quantities of the cycloadduct, my attention then shifted toward the potential end-game strategies to complete the total synthesis of **1**. These are discussed in the following chapter.

# Chapter 5

## Beyond Photochemistry: End-Game Strategies

Now that I am able to prepare large quantities of alcohol **276** (see **Scheme 4.26**), I have finally solved many of the problems outlined in Chapter 3. The stereochemistry of C8 and C10 was efficiently established, the formation of the B-ring butenolide was straightforward under palladium-catalyzed carbonylation conditions, and, most importantly, the synthesis of alcohol **276** was reproducible and scalable. To illustrate, I can begin with five grams of methyl ethynyl ketone (**484**) and, over the course of three weeks, the 14-step sequence will yield 600-800 mg of alcohol **276**. The end certainly felt achievable with the route which I had developed.

My attention then shifted to developing a strategy by which the total synthesis of **1** could be completed. Fortunately, Mulzer's publication[64] provided a degree of insight into what sorts of chemistry was achievable with alcohol **276**. As shown in **Figure 5.1**, I envisioned that the 8-membered ring could be formed by a vinylogous aldol reaction of bis-butenolide **IX**. The task at hand then became the development of an efficient route from alcohol **276** to the elaborated butenolide side chain of **IX**. Those efforts are the focus of this chapter.

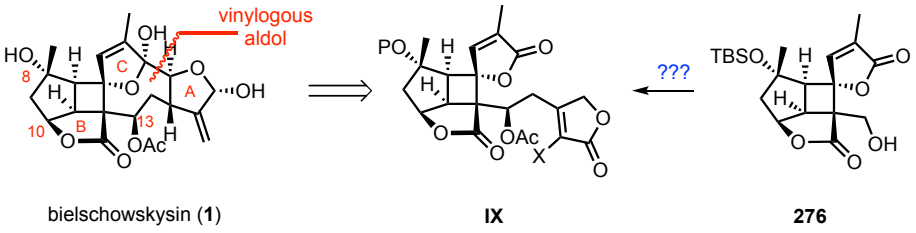
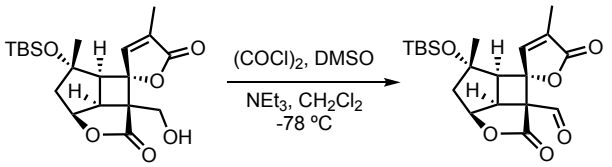


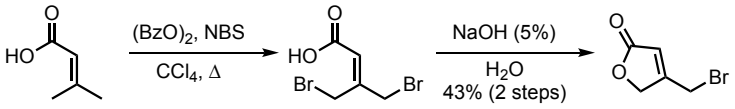

**Figure 5.1**: End-game strategy to bielschowskysin (**1**).

### 5.1 Exploration of Additions to Aldehyde 277

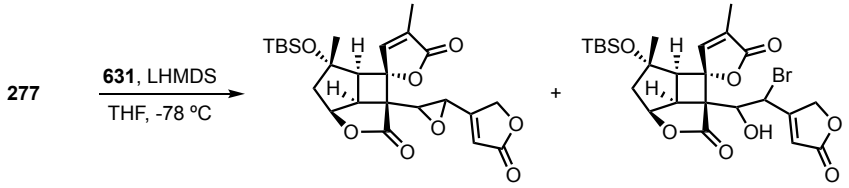
Once I had prepared sufficient quantities of alcohol **276**, my initial efforts were devoted to exploring the conversion of the hydroxymethyl group of **276** into a functionality suitable for butenolide synthesis. The logical first step, shown in **Scheme 5.1**, was an oxidation of the alcohol to aldehyde **277**, which was accomplished using Swern conditions. It is worth noting that the aldehyde was never purified, but the reaction was quantitative by $^{1}$H NMR analysis. From this point on, I began to identify the scope and limitations of the reactivity of the aldehyde. I quickly realized that nucleophilic additions to the aldehyde would be far from trivial. My initial attempts focused on a Darzens reaction[169] between aldehyde **277** and bromo




**276** **277**

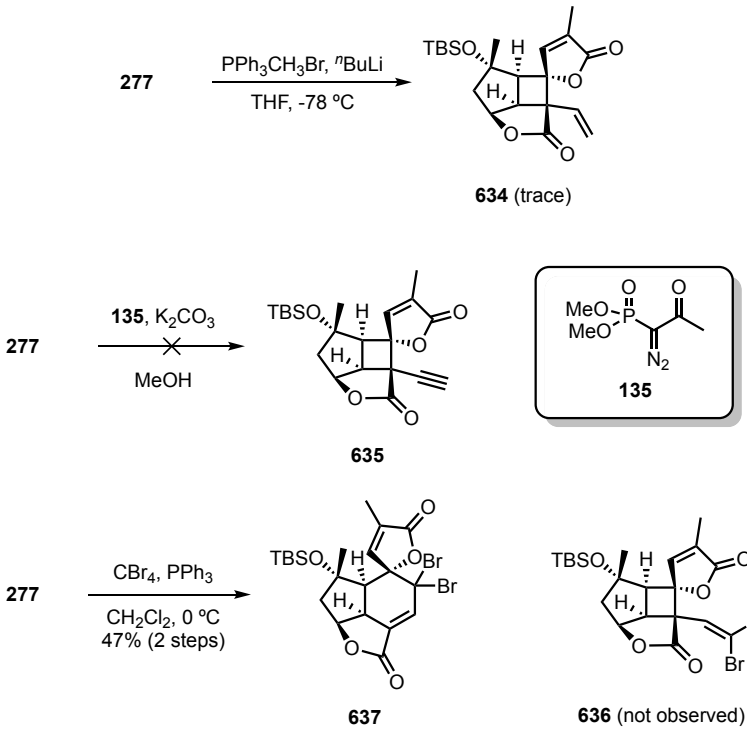



**629** **630** **631**




**632** (trace) **633** (trace)

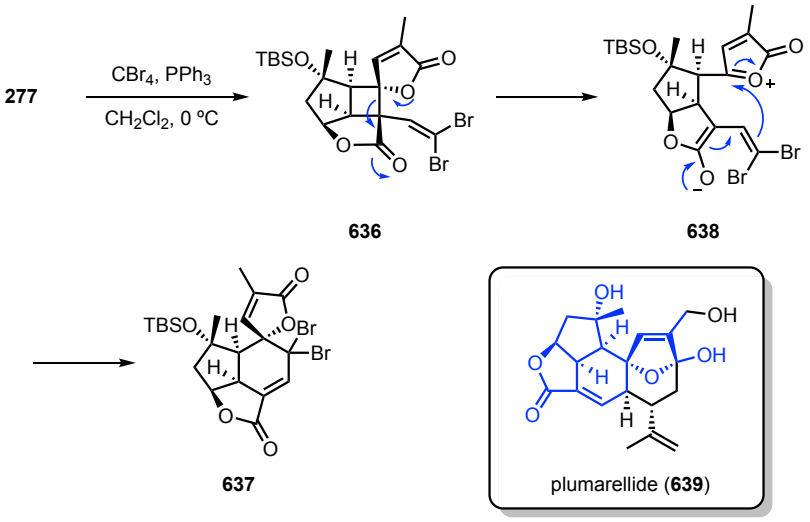
**Scheme 5.1**: First foray into reactivity of aldehyde **277**.




**Scheme 5.2**: Attempted homologations of aldehyde **277**.

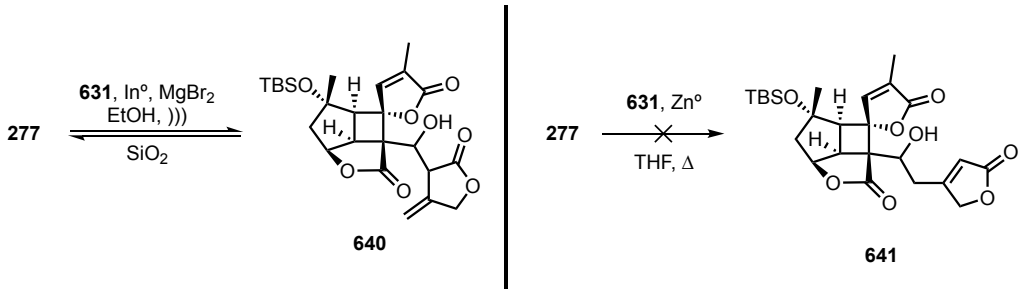
butenolide **631** (prepared in two steps from **629**[170]). As I will discuss in detail in Section 5.2, the epoxide that would result from the Darzens reaction would be favorable to promote the proposed vinylogous aldol reaction. Unfortunately, only trace amounts of the epoxide **632** were observed along with halohydrin **633**. When I attempted to reproduce the result, I was unable to isolate appreciable amounts of epoxide **632**, and the reaction was not pursued further.

I then began to examine whether or not the aldehyde could be homologated by either a simple Wittig olefination[171] or Ohira–Bestmann[120] reaction. As shown in **Scheme 5.2**, the Wittig reaction with methyltriphenylphosphonium bromide produced only trace amounts of the homologated olefin **634**. Upon subjecting aldehyde **277** to Ohira–Bestmann conditions, I observed complete decomposition in just 20 minutes, leading me to speculate that the **277** might be base sensitive. An interesting rearrangement did occur upon exposure to the Ramirez reagent.[172] Rather than forming the expected *gem*-dibromoolefin **636**, I observed ring expansion of the cyclobutane to produce dibromide **637**. The proposed mechanism for this transformation is shown in **Scheme 5.3**. After initial formation of the dibromoolefin (**635**), fragmentation of the cyclobutane occurs via oxonium **638**. Recombination then occurs in a vinylogous aldol to form the new cyclohexene ring of **637**. Interestingly, this rearranged carbon skeleton bears the most of the functionality of plumarellide (**639**), highlighted in **Scheme 5.3**, which is a diterpene natural product isolated from the gorgonian coral *Plumarella* sp. in the northwestern Pacific Ocean.[173] One might imagine exploiting this rearrangement as a means to access a large portion of the carbon framework of **639**. Since it was unproductive for the purposes of the total synthesis of **1**, the rearrangement was not explored further.



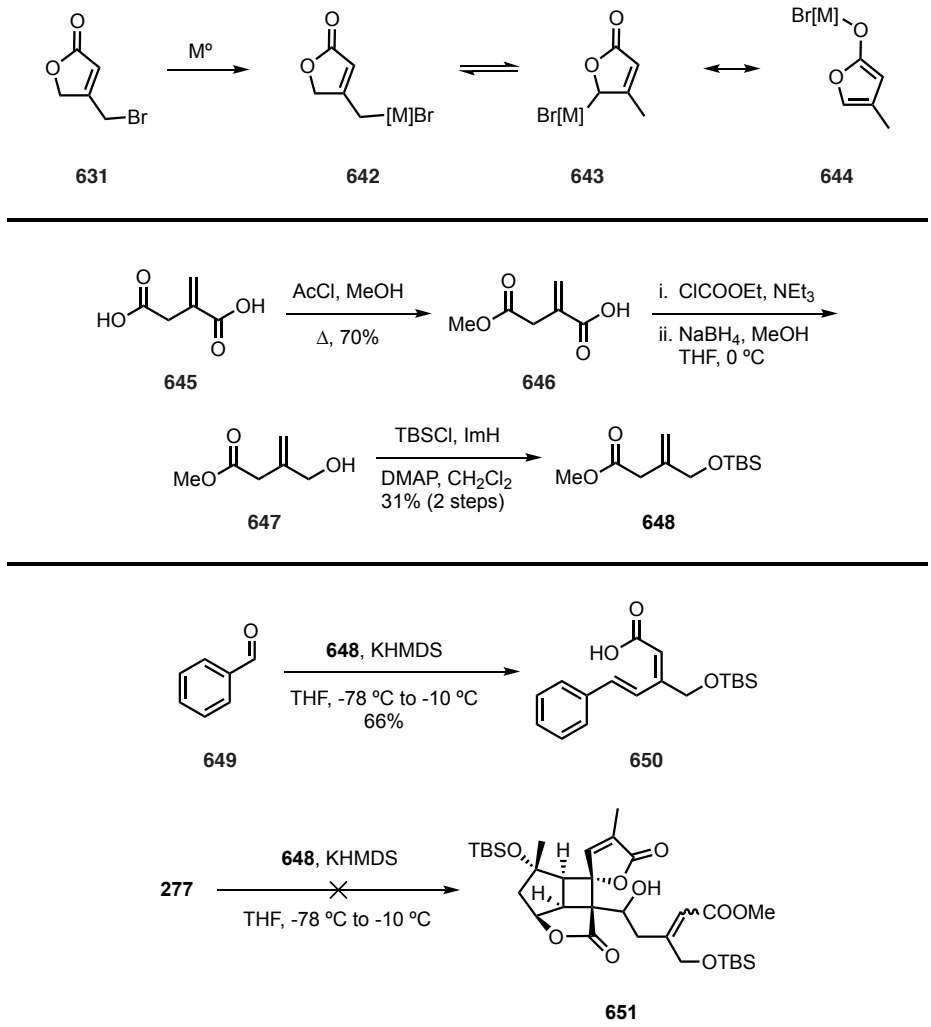

**Scheme 5.3**: Possible mechanism of ring expansion.

Given the concern that aldehyde **277** is base-sensitive, I began to explore the possibility of adding the bromo butenolide **633** moiety in a way that would mitigate the basicity of the nucleophilic reagent, shown in **Scheme 5.4**. Upon formation of the allylindium complex of bromide **631**, addition to the aldehyde did seem to occur to form alcohol **640**, albeit with the incorrect regiochemistry. Moreover, it appeared that the product underwent partial decomposition in a retro-aldol pathway upon purification on silica. Formation of the allylzinc in order to effect a vinylogous Reformatsky reaction[174] was unsuccessful and did not result in the production of the desired product **641**. Although the starting material was consumed in the reaction, I was unable to complete the structural assignment of any of the products by NMR analysis.




**Scheme 5.4**: Unsuccessful additions of bromide **631**.

At this time, I began to explore the possibility that an isomerization of the allylmetal species might be occurring, as shown in **Scheme 5.5**. This isomerization could likely be avoided by using an acyclic enolate, thereby surpassing the formation of the supposed alkoxyfuran intermediate (**644**). The synthesis of the acyclic compound began with the selective mono-esterification of itaconic acid (**645**).[175] Selective reduction of the carboxylic acid via the intermediate anhydride was accomplished with sodium borohydride in methanol,[176] and the resulting allylic alcohol (**647**) was immediately protected as its TBS ether **648**. The aldol reaction was first attempted on a model system with benzaldehyde (**649**), and the desired vinylogous aldol occurred, albeit with concomitant dehydration and ester hydrolysis, to yield diene acid **650** in 66% yield and as the sole regioisomer. The carboxylic acid was likely formed via the intermediate unsaturated ∂-lactone, which underwent a base-mediated elimination to the diene. With this result in mind, I was excited to replicate this transformation with aldehyde **277**. Unfortunately, under the reaction conditions, apparent decomposition occurred and no characterizable products were isolated. It is worth noting that I was able to recover the ester, albeit with the olefin isomerized into conjugation, confirming that deprotonation did occur.

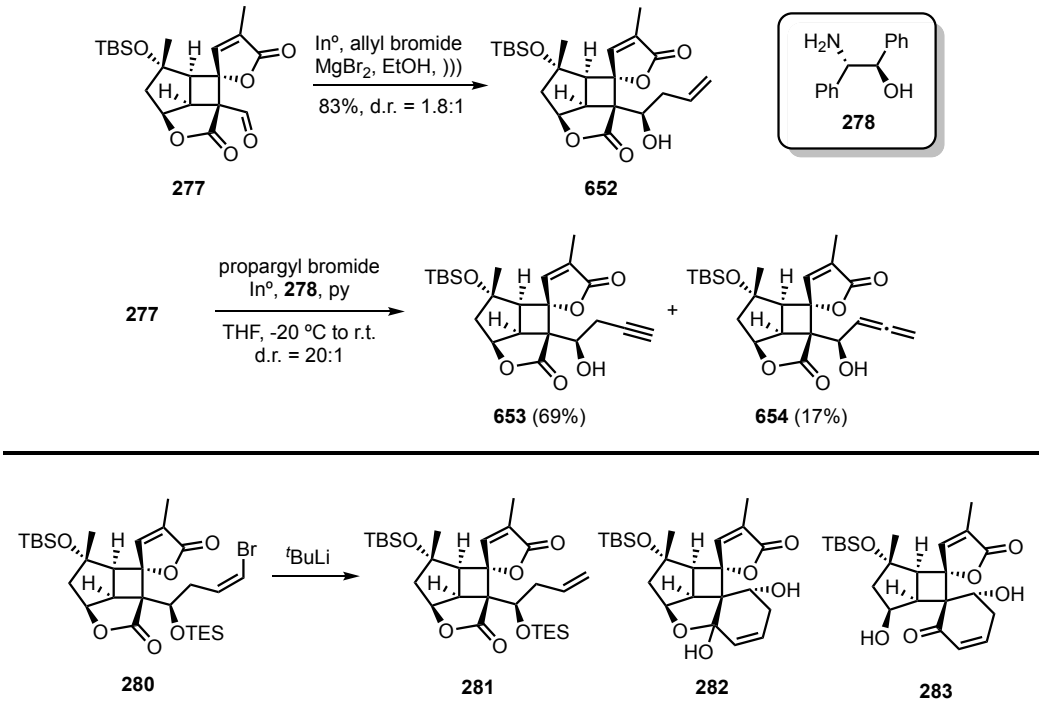



**Scheme 5.5**: Attempted additions with acyclic nucleophile.

The results summarized in this section seemed to confirm my suspicion that aldehyde **277** was unstable to basic conditions (both kinetic and thermodynamic). In my future attempts, I would seek to suppress the base-mediated decomposition with the hope that a suitable side-chain could be installed.

## 5.2 12

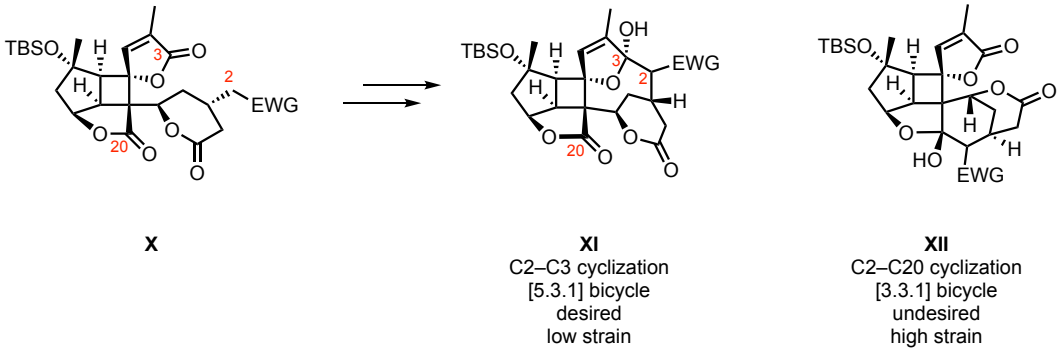
In addition to a confirmation of stereochemical assignments, another benefit to the intersection of my synthetic route with Mulzer's is my deeper understanding of the reactivity of aldehyde **277**. In hindsight, it should have been obvious that **277** is sensitive to an array of conditions as Mulzer reported only indium-mediated additions of simple nucleophiles (**Scheme 5.6**). Allylation was achieved in a surprisingly non-selective manner to afford a 1.8:1 mixture of




**Scheme 5.6**: Lessons from Mulzer.

epimers of homoallylic alcohol **652**, in 83% yield. The more productive route with respect to diastereoselectivity, was the indium-mediated propargylation in the presence of the amino alcohol ligand **278**. Under these conditions, homopropargyl alcohol **653** was obtained in 69% yield with a diastereoselectivity greater than 20:1. The pitfall with this approach, however, was the formation of a considerable amount of the corresponding allene (17%, **654**), which arose from the addition occurring in an $S_E2'$ manner. Moreover, Mulzer sought to close the eight-membered ring by the same carbon–carbon bond disconnection that I had planned (from vinyl bromide **280**). It was problematic, then, that Mulzer had observed trace amounts of reactivity at the adjacent lactone (**282** and **283**), which resulted in the formation of the (much more favorable) six-membered ring (see Section 2.6.7 for more details).

It was with these observations in mind that I reanalyzed my strategy for this crucial ring-closure. As shown in **Figure 5.2**, I envisioned I could make use of conformational strain to inhibit the formation of the undesired six-membered ring (C2–C20 cyclization, **XI**) and force the reactivity, if any was to be had, at the desired carbonyl at C3 (**XII**, **Figure 5.2**). Furthermore, the 1,3-trans stereochemical relationship of the ∂-lactone corresponds to the correct stereochemistry in the natural product. The task at hand then became the procurement of the ∂-lactone — preferably with the correct stereochemistry and a suitable substituent at C2 — from aldehyde **277**.

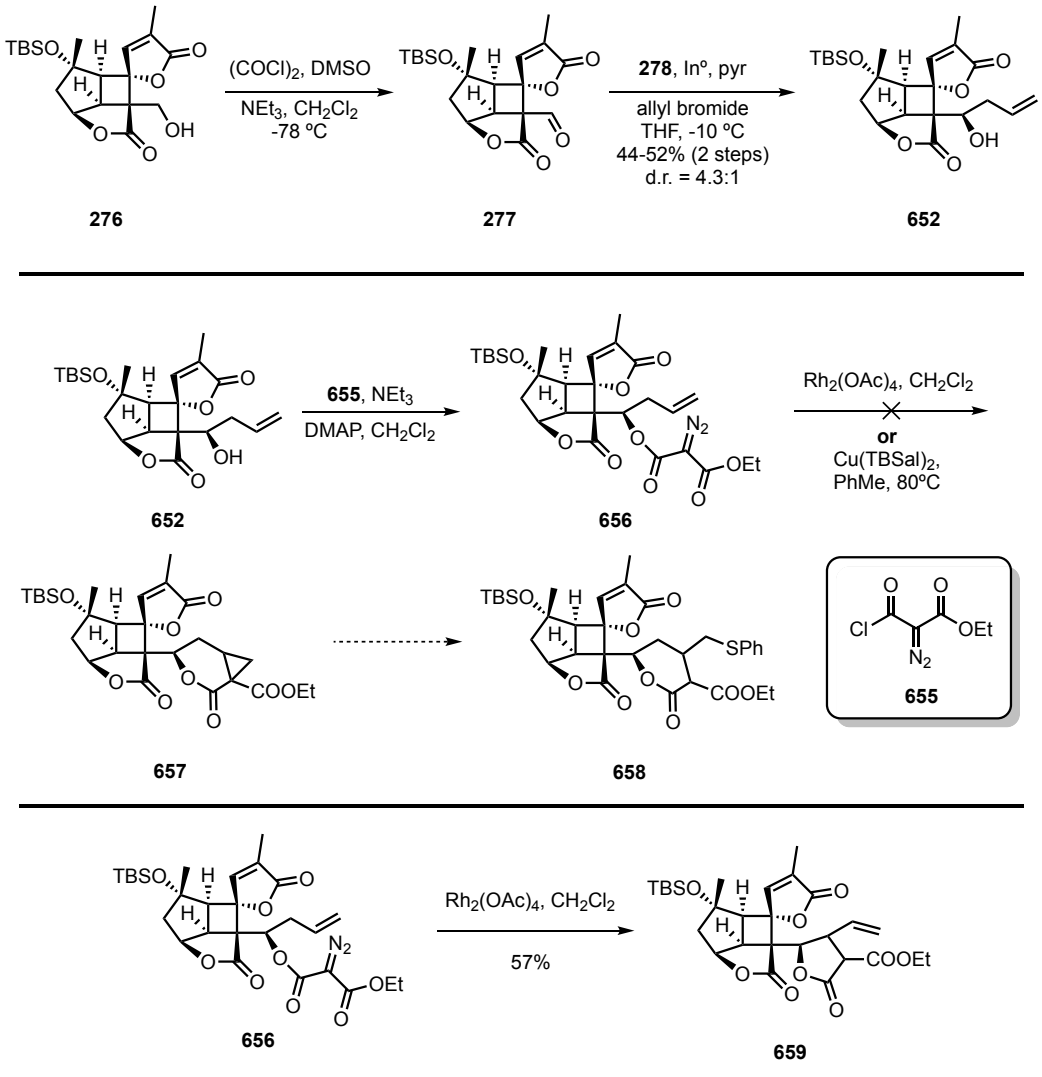



**X**

**XI**
C2–C3 cyclization
[5.3.1] bicycle
desired
low strain

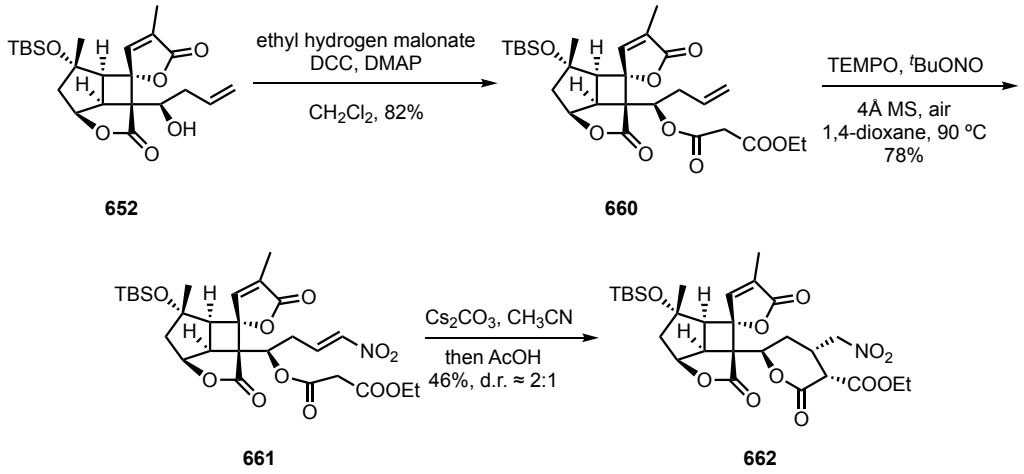
**XII**
C2–C20 cyclization
[3.3.1] bicycle
undesired
high strain

**Figure 5.2**: Analysis of ∂-lactone cyclization.




**Scheme 5.7**: Cyclopropanation strategy.

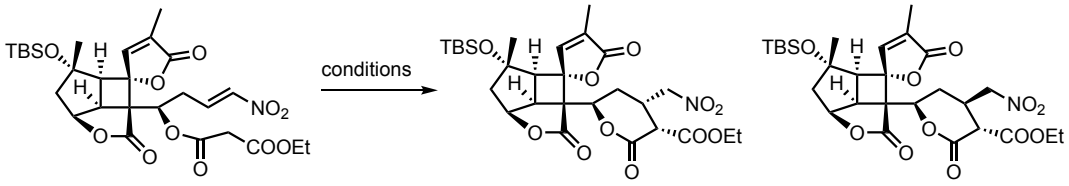
To that end and based on what I had learned about the sensitivity of aldehyde **277**, I opted to borrow from Mulzer's route once more. Indium-mediated allylation in the presence of amino alcohol ligand **278** afforded the desired homoallylic alcohol **652** with selectivities of 4.3:1 (**Scheme 5.7**). As the diastereomers were readily separable, the modest selectivity was considered good enough and other ligands were not screened. Unsurprisingly, the undesired epimer was inert to Mitsunobu conditions and could not be recycled. From alcohol **652**, my initial attempts were focused on the forming a cyclopropane via the intramolecular cyclopropanation shown in **Scheme 5.7**. The esterification with diazomalonyl chloride (**655**) was not straightforward, although I was able to obtain enough of diazomalonate **656** to try the key cyclopropanation reaction. Exposure of diazomalonate **656** to either $Rh_2(OAc)_4$ or copper (*tert*-butylsalicylimide )$_2$ ($Cu(TBSal)_2$)[177,178] did not yield the desired cyclopropanation, and starting material was recovered, in some experiments with the loss of the diazo functionality. The only one that resulted in any reactivity was one performed with the slow addition of **656** to a dilute solution of $Rh_2(OAc)_4$ (over 14 hours with a syringe pump). In this case, lactone **659** was identified in 57% yield as the product of C–H insertion at the allylic position. This should not have come as a surprise, as this is a known reaction of metal carbenoid species.[179] With these results in mind, I opted to move away from the cyclopropanation approach in favor of a simpler tactic.




**Scheme 5.8**: Formation of ∂-lactone **662**.

The thought process became quite simple: if I could install an appropriate electron-withdrawing group at the terminus of the olefin — either by cross-metathesis or some other method — then a base-mediated Michael addition of the malonate should form the desired ∂-lactone. Since metathesis often proceeds poorly with electron-deficient olefins (cf. Section 4.3),

I opted to install a nitro group, as shown in **Scheme 5.8**. The nitration of olefins can be achieved under mild conditions and in a highly regioselective manner.[180] Thus, after esterification of alcohol **652** with ethyl hydrogen malonate, the nitration proceeded smoothly to afford nitroalkene **661** in 78% yield. The Michael addition was not as efficient as I would have liked, but after some screening of conditions (see **Table 5.1**), I was able to obtain ∂-lactone **662** in 46% yield as a 2:1 mixture of diastereomers. Crucially, longer reaction times and the addition of an extra equivalent of base led to the desired diastereomer to predominate, although the diastereoselectivity of the addition never exceeded 2.5:1.

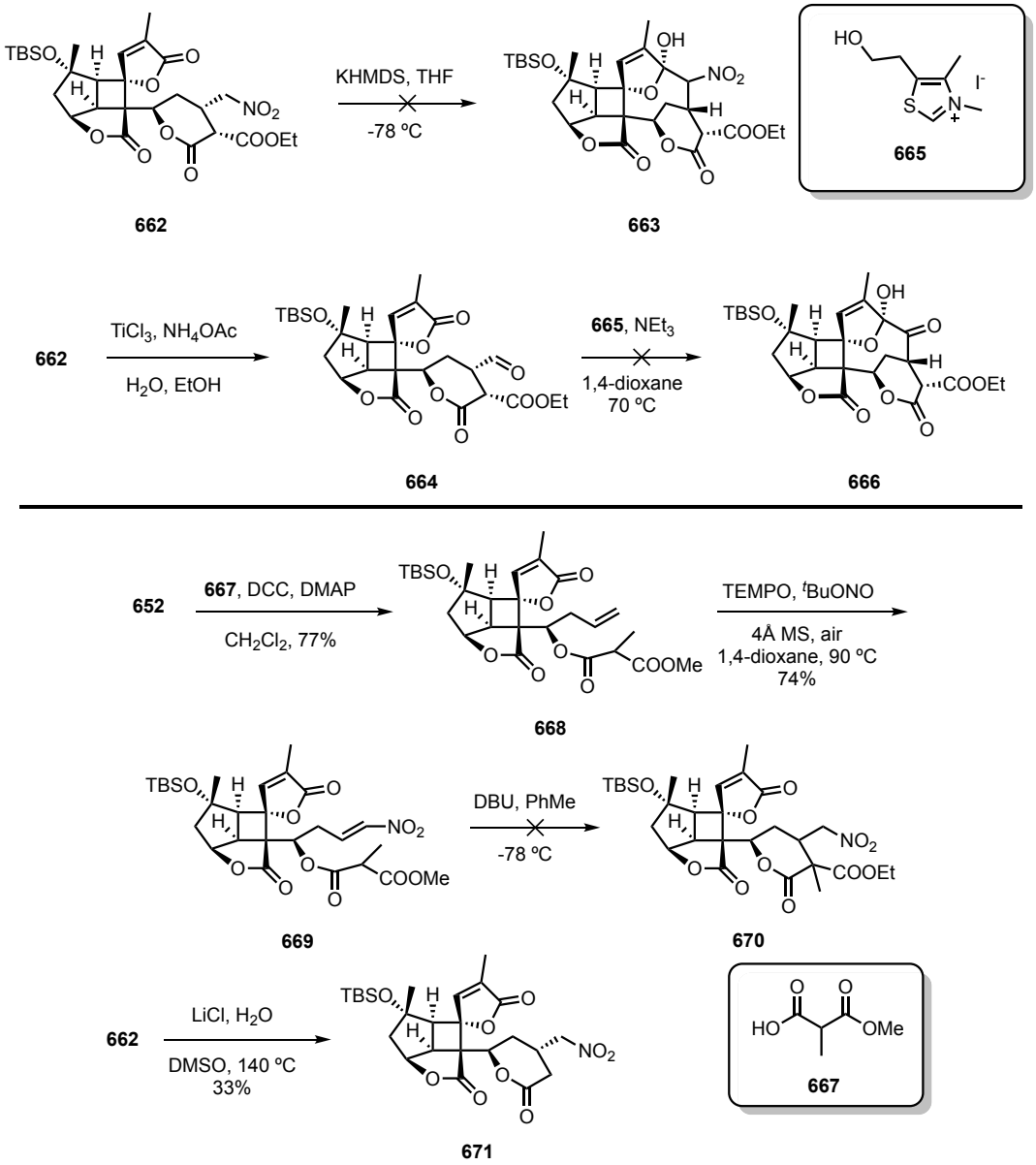



**661** **662** ***epi*-662**

| Entry | Base (eq.) | Solvent | Time | Temperature | Yield | (662:*epi*-662) |
|---|---|---|---|---|---|---|
| **1** | $Cs_2CO_3$ (1.2) | PhMe | 1.5 h | 0 ºC | 18% | 1:19 |
| **2** | $Cs_2CO_3$ (1.2) | $CH_3CN$ | 1 h | 0 ºC | 77% | 1:9 |
| **3** | $Cs_2CO_3$ (1.2) | $CH_3CN$ | 24 h | r.t. | 52% | 1.5:1 |
| **4** | $Cs_2CO_3$ (1.2) | $CH_3CN$ | 17 h | 45 ºC | decomposition | N/A |
| **5** | $Cs_2CO_3$ (1.2) | $CH_3CN$ | 44 h | -78 ºC to -20 ºC | 37% | 1:18 |
| **6** | DBU (1.2) | $CH_3CN$ | 23 h | 0 ºC to r.t. | 35% | 1:1.7 |
| **7** | NaH (1.2) | $CH_3CN$ | 25 h | 0 ºC to r.t. | 58% | 1:2.5 |
| **8** | $Cs_2CO_3$ (1.2) | $CH_3CN$ | 10 d | 0 ºC to r.t. | decomposition | N/A |
| **9** | $Cs_2CO_3$ (2.2) | $CH_3CN$ | 24 h | r.t. | 38% | 2.7:1 |
| **10** | $Cs_2CO_3$ (5.0) | $CH_3CN$ | 24 h | r.t. | 24% | 1.9:1 |

**Table 5.1**: Diastereoselectivity of Michael addition.

With lactone **662**, I began to explore a couple of different paths toward the ring closure. The overall transformation would be the same two-step process: closure of the ring and a Nef[181] reaction to convert the nitro group into a carbonyl. As shown in **Scheme 5.9**, initial formation of the nitronate anion of **662** with KHMDS produced no detectable amounts of hemiketal **663**, although starting material was consumed during the course of the reaction. Conversion of the nitro group to the corresponding aldehyde (**664**) did proceed under




**Scheme 5.9**: Reactions of lactone **662**.

McMurray's $TiCl_3$-mediated conditions.[182] Attempts at the ring closure using thiazolium catalysis, however, were unsuccessful as well. Because both the attempted closure of **662** and of **664** were performed under basic conditions, I began to suspect that the culprit of the failed reactivity was the acidic malonate proton — both nitroalkanes and malonates have $pK_a$ values of approximately 10.

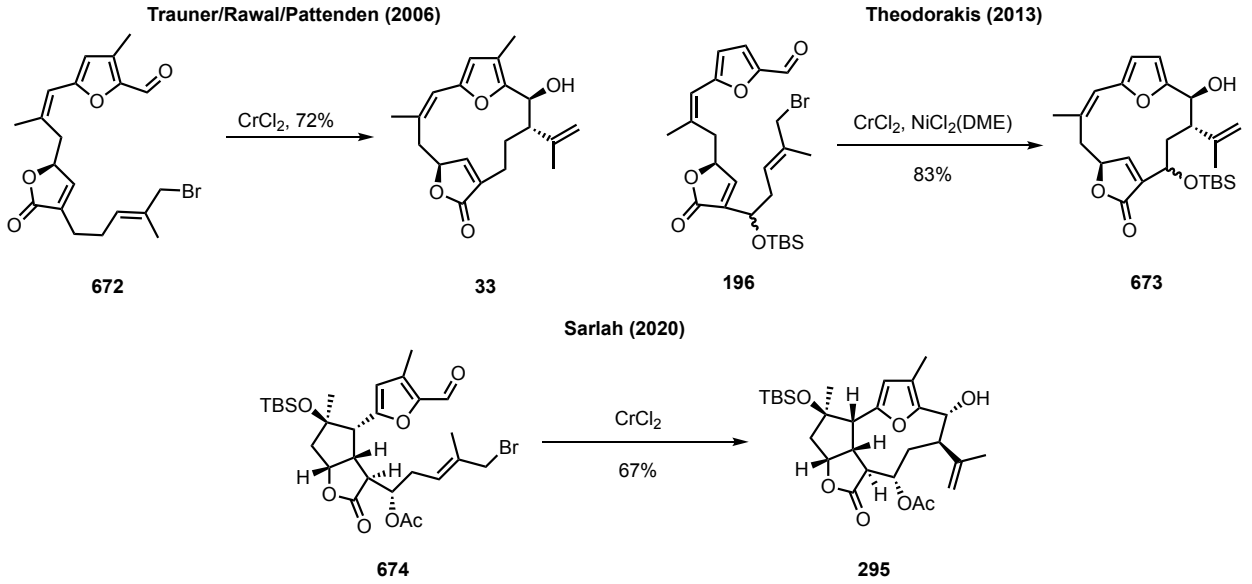
To solve this problem, I initially attempted the same sequence with a methyl group instead of a proton at the malonate position. I was able to successfully prepare ester **668** and nitroalkene **669**; however, the Michael addition of the substituted malonate failed to yield

appreciable amounts of lactone **670**, presumably because of the increased steric environment. Decarboxylation of the ethyl ester moiety did produce lactone **671**, but this route was not pursued further because I did not have enough material to optimize the reactions.

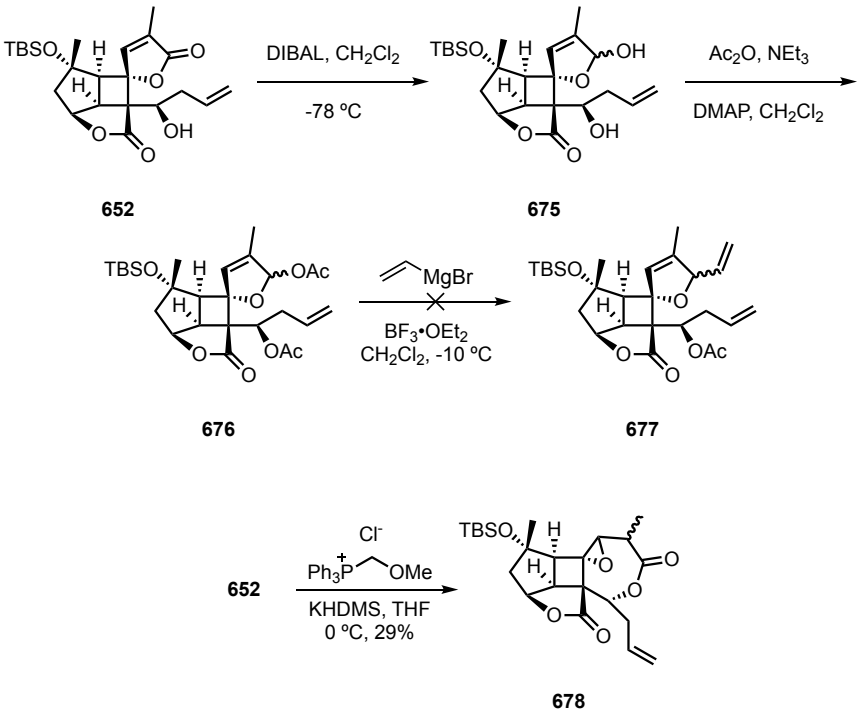
At the time, I had to take a pause from the so-called "frontline" chemistry to bring up another batch of alcohol **652**. I began to reconsider the route, one final time, as a result of poor yields and a sense of impending hopelessness at the key ring-closure. Even if I were able to access sufficient amounts of a cyclization substrate, which lacked the acidic proton, I was not optimistic that the butenolide ring would be sufficiently reactive. If I could, perhaps, homologate the butenolide carbonyl by one carbon to the corresponding aldehyde, then the increased reactivity could prove useful in forming the eight-membered ring.

## 5.3 Final Change in Strategy

Although the homologation of the butenolide has zero precedence in the literature, it would set the stage for a much safer attempt at the closure of the eight-membered ring. Indeed, establishing an aldehyde at C2, widely used in the total synthesis of C2-oxygenated furanocembranes, enables macrocycle formation by an NHK coupling. As shown in **Scheme 5.10**, this reaction was first used in 2006 in Trauner's synthesis of bipinnatin J (**33**, see Section 2.5.2)[24,183] and the same reaction has since been employed by Rawal[184] and Pattenden (Section 2.5.3).[25,26] More recently, Theodorakis and Sarlah also published a late-stage NHK cyclization in efforts toward the total synthesis of **1** (see Sections 2.6.4 and 2.6.8,




**Scheme 5.10**: Reported NHK macrocyclizations.



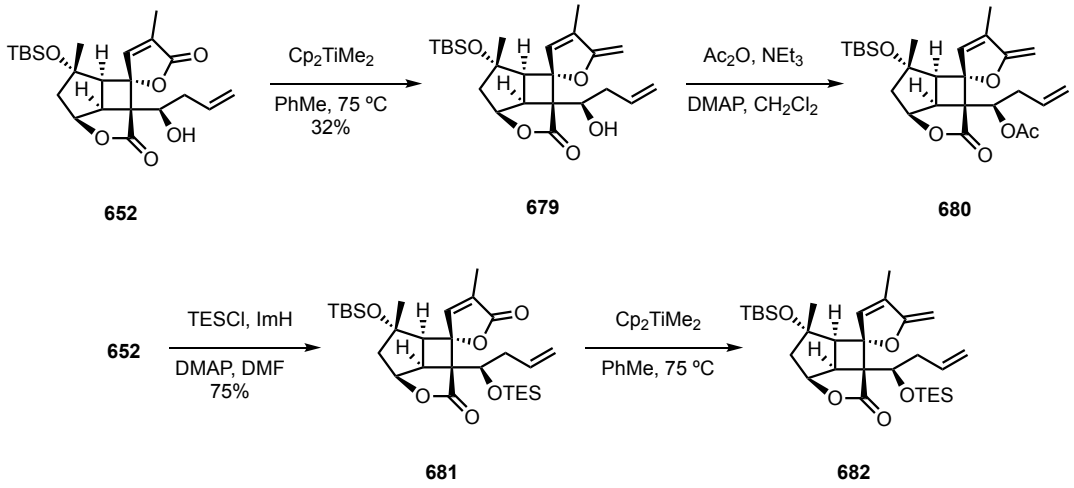

**Scheme 5.11**: Surprising reactivity of the butenolide carbonyl.

respectively).[65] I hoped to adopt this same strategy, but the question remained: could the butenolide be functionalized, or was it simply too inert?

In the spirit of true research, I treated alcohol **652** (**Scheme 5.11**) with DIBAL (2.5 eq.) to see what happened. Much to my delight, the butenolide carbonyl was selectively reduced and the lactone carbonyl at C20 remained, to the best of my knowledge, untouched. Although the reaction was not clean (as well as producing a mixture of diastereomers), the selectivity was confirmed, upon acetylation of the resulting lactol, by the expected upfield shift of the butenolide ß-proton. The attempted Lewis acid mediated Grignard displacement resulted in decomposition rather than olefin **677**; nevertheless, I was once again excited about probing this surprising selectivity further.

Treatment of alcohol **652** with methoxymethyltriphenylphosphonium chloride, in the attempt to homologate directly to the aldehyde, resulted in the formation of epoxide **678** rather than the desired Wittig reaction, as shown in **Scheme 5.11**. This presumably occurred by base-induced transesterification between the alcohol and butenolide carbonyl, followed by an oxy-Michael reaction to form the epoxide. Although functionally a useless compound for further applications, this rearrangement confirmed that the butenolide carbonyl is, in fact, reactive.

I finally had success when treating alcohol **652** with the Petasis reagent.[185] The butenolide was selectively homologated to give enol ether **679**, as shown in **Scheme 5.12**. At




**Scheme 5.12**: Successful homologation of the butenolide carbonyl.

higher temperatures and with more equivalents of the Petasis reagent, bis-olefination, but none of the undesired mono-olefin, was observed. The yield of the subsequent acetylation to **680** was poor, presumably because of the difficulty I had in purifying the enol ether from the titanocene byproducts of the Petasis reaction. I made the decision to protect the alcohol first as the silyl ether — the required acetate would likely react in the Petasis reaction. Fortunately, once the free alcohol was protected, the Petasis reaction proceeded smoothly and without the observation of bis-olefination to yield enol ether **682**. Further optimization of this sequence is ongoing.

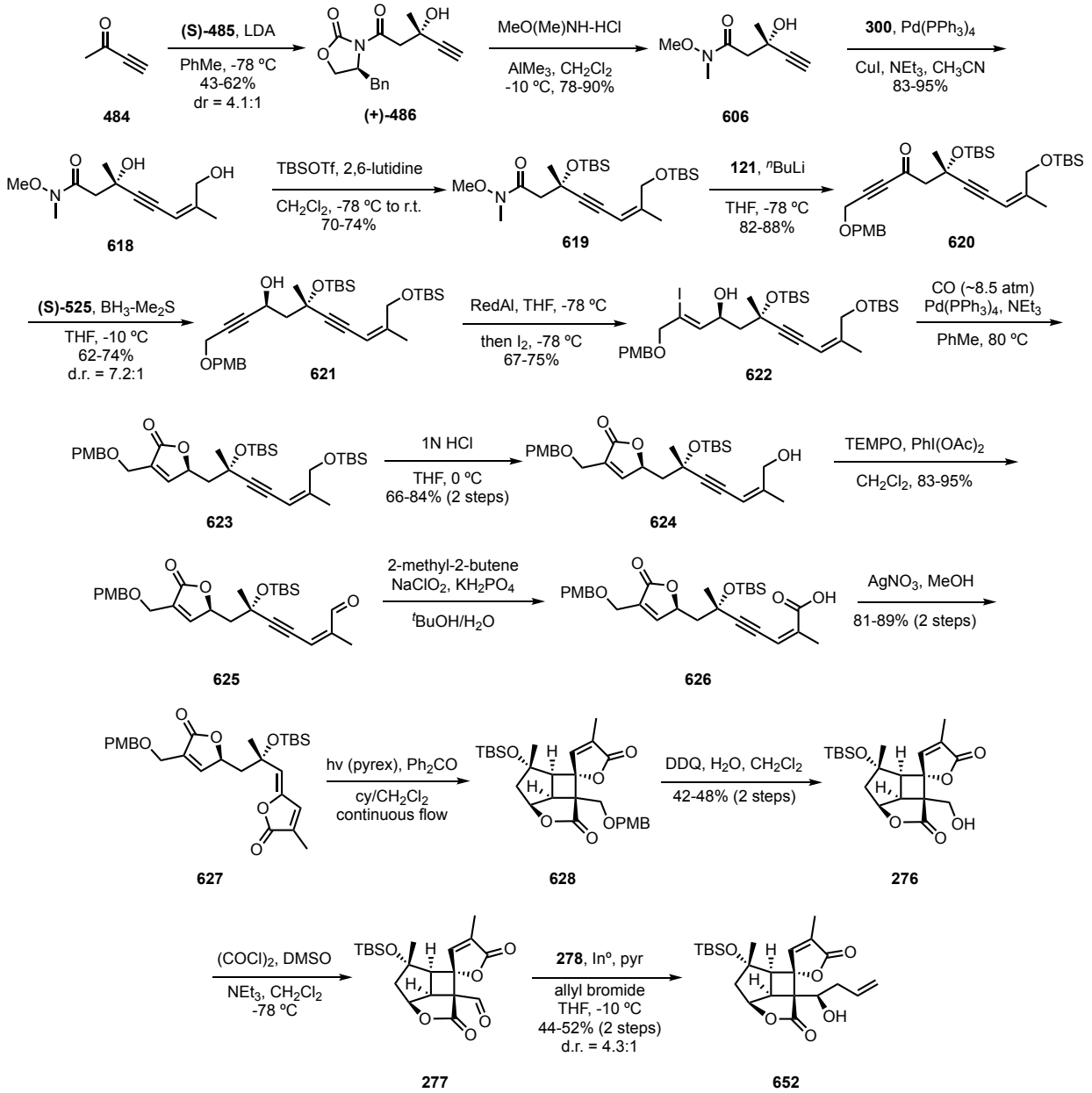
## 5.4 Conclusions

As of the time of this writing, optimization of the olefination reaction, as well as further studies into the reactivity of enol ether **682**, are ongoing in the laboratory. While it is disappointing to be unable to report the completed total synthesis of **1** in my dissertation, the results discussed in this chapter have shown a great deal of progress towards that goal. Although the initial efforts to push beyond the photochemical cycloadduct were unsuccessful, I found a great deal of promise with the serendipitous discovery that the butenolide carbonyl may be selectively manipulated to advance the synthesis ever so slightly forward. The last chapter of my discussion will address my plans to convert **682** into **1.**

# Chapter 6

## Future Directions and Conclusions

In the previous three chapters, I have described my efforts toward the total synthesis of bielschowskysin (**1**). Although I have not yet realized the goal, I have developed, through ten generations of synthetic approaches, a robust and scalable process by which I am able to

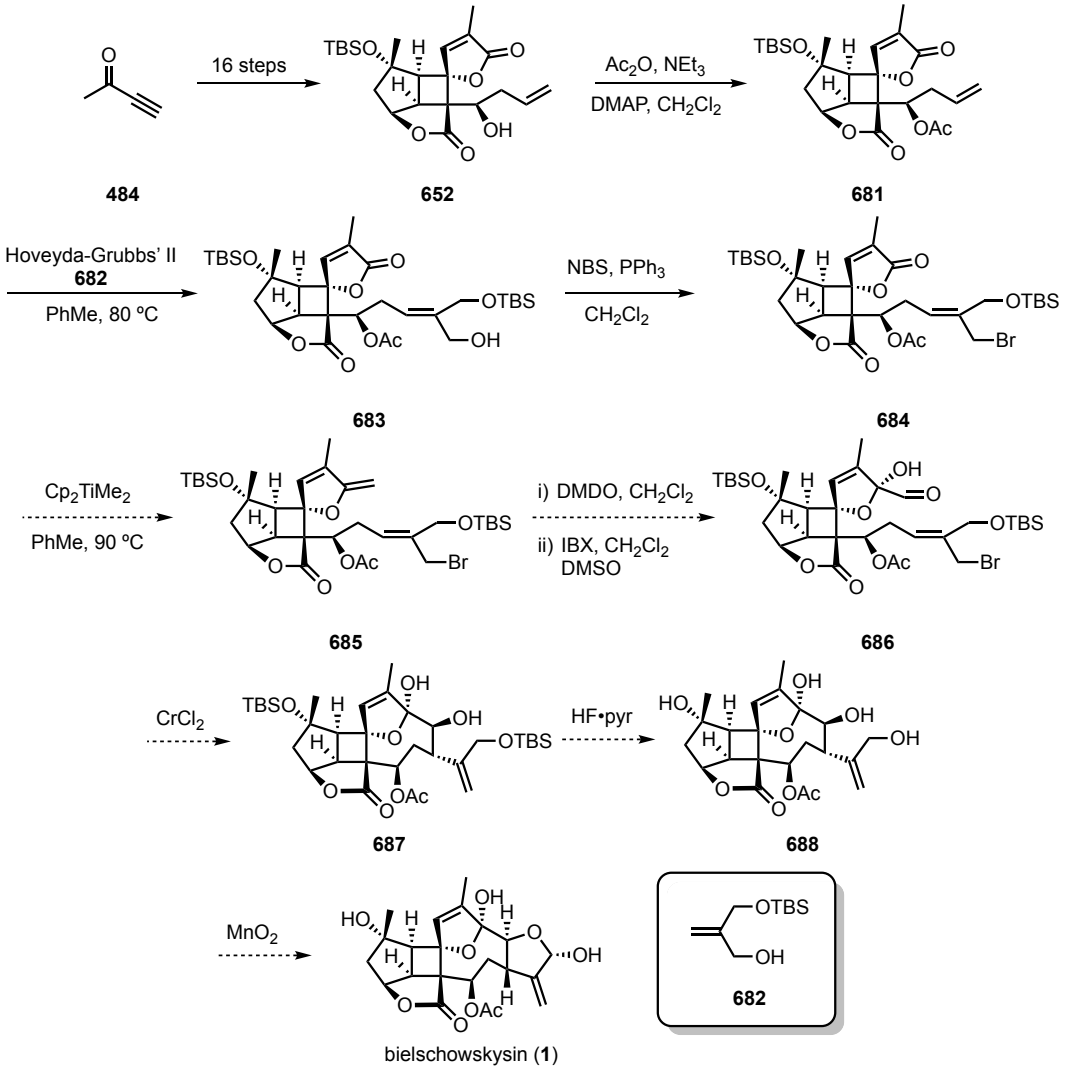



**Scheme 6.1**: 13.

prepare gram quantities of advanced materials (**Scheme 6.1**). In this chapter, I outline the necessary steps to complete the total synthesis.

## 6.1 Future Directions

Chapter 5 concluded with a description of my relatively recent result of the successful Petasis reaction of butenolide **652** (**Scheme 6.2**). In order to ease the purification of the Petasis reaction, acetylation of alcohol **652** and cross metathesis with 1,1,-disubstituted olefin **682** would provide alcohol **683**. After Appel reaction to convert the allylic alcohol to bromide **684**, the previously described Petasis reaction should continue to favor the butenolide carbonyl. Sequential oxidation of the exocyclic enol ether, first by DMDO, then by IBX, would erode the




**Scheme 6.2**: Path for completion of **1**.

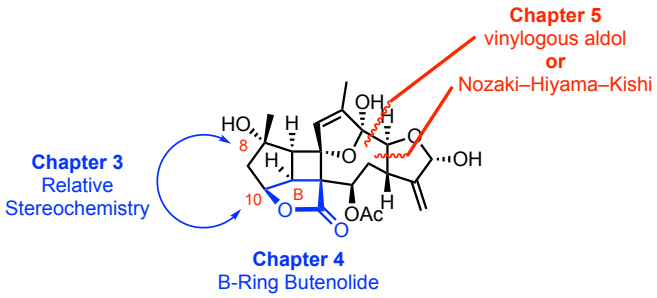



**Figure 6.1**: Summary of major problems.

desired aldehyde hemiketal and set the stage for the key NHK ring closure to alcohol **687**. After the ring closure, desilylation would afford triol **688** and a mild oxidation of the primary, allylic alcohol should complete the synthesis of **1**. In total, the synthesis could be completed in 24 steps from ketone **484**, with just five steps remaining. Should the synthesis of **1** be realized with sufficient quantity, it will be worthwhile to validate the cytotoxicity that was initially reported.[5]

Should the proposed route fail, the solution to this challenging problem will likely require a total redesign of the synthesis. Perhaps the transannular [2+2] that was reported by Nicolaou a decade ago (Section 2.6.1) could be further exploited to that end. As it stands now, the synthesis of **1** remains one of the few unconquered frontiers of synthetic chemistry.

## 6.2 Conclusion

It is with great disappointment that I conclude this dissertation not with the triumph that I had expected when I first set out on this journey, but with the sting of defeat. As I write this, there are but a mere eight weeks before the clock expires on my efforts to complete the synthesis. There is certainly enough time to work out the remaining eight steps but, as with most things, an immense amount of luck is required.

Despite all of this, I have solved many problems along the way. In Chapter 3, I describe the state of efforts from my group toward the synthesis of bielschowskysin before I began the project six-and-a-half years ago. I identified several key problems that had inhibited the progress of the synthesis. Over the course of the first four generations of my efforts, problems were not solved but exacerbated. The failures of those generations highlighted the importance of establishing the correct stereochemistry at C8 and C10 (**Figure 6.1**). One might argue that these failures were necessary for the course correction described in Chapter 4.

The decision to establish the C8 stereocenter first proved a launching point from which the rest of the synthesis began to unfold. In Chapter 4, I describe my pursuit of that change in strategy, which led to new problems, although the stereochemical problems presented in Chapter 3 had been solved. The synthesis of the B-ring butenolide became problematic as it proved inaccessible by a ring-closing metathesis strategy. It was not until the ninth generation, when I found that formation of the ring under palladium-catalyzed carbonylative conditions required both high temperature (80 °C) and high pressure (~8 atm). With that problem solved, the path was clear to access the photochemical substrate that I had spent five-and-a-half years trying to reach. Ultimately, the work communicated in Chapter 4 can be viewed as a triumph of sorts and the fact that I was able to access nearly 2 g of photochemical cycloadduct was an immense accomplishment in itself.

But it was a false summit, and the results presented in Chapter 5 demonstrate that. Often times, it is the first peak that is the easiest even if it does not seem so at the time. In Chapter 5, I describe the efforts that I made to close the eight-membered ring and, in doing so, stumbled upon a new bond disconnection that could prove fruitful in reaching the summit. The path outlined in Section 6.1 is clear, but I am no longer so naïve to think that there are no hidden obstacles on the way.

To conclude, once and for all, I am humbled. This dissertation represents both a triumph and a failure. A triumph, to be sure, as over the past six years I have become an accomplished synthetic chemist. I have learned more chemistry than I would have had I been working on *any* other project. I have learned to be creative in finding solutions to problems that are evident, and to those which have not yet been revealed. Moreover, I have learned a lot about myself and the dedication and drive that is required to complete such a monumental task. But, the results presented here are also a failure, of sorts, even though I have been dissuaded by many people from that line of thinking. In Chapter 1, I outlined a target and, more than a hundred pages later, I am now writing about how I did not reach that target. If I cannot finish this total synthesis in the next few weeks, many questions will remain in my mind as I move on to new challenges. What if I had not spent so much time on the earlier generations, ones, in hindsight, doomed to fail? What if the global pandemic had not shut me out of the lab for over two months? What if other, more serious obstacles had not prevented me from making progress at a time when I was just beginning to regain momentum? Ultimately, those questions, of course, are pointless, as the circumstances were out of my control. That, specifically, is one of the biggest lessons I have learned: no matter how much desire, how much devotion, how much work one puts in, it does not guarantee success without luck. And that stings.

# Chapter 7

## Experimental

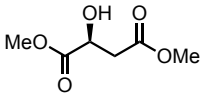
### General:

All glassware used for non-aqueous reactions was either flame dried under vacuum or oven-dried (130 °C) overnight. All reagents and solvents were commercial grade and purified prior to use when necessary. All reactions were performed under an argon atmosphere unless otherwise stated. Dichloromethane ($CH_2Cl_2$) and toluene (PhMe) were dried by passage through a column of activated alumina using an MBraun MB-SPS dry solvent system. Tetrahydrofuran (THF) in quantities less than 50 mL was freshly distilled from sodium-benzophenone ketyl prior to use. THF in quantities greater than 50 mL was dried by passage through a column of activated alumina using an MBraun MB-SPS dry solvent system. All workup solutions are aqueous unless otherwise noted.

All reactions were monitored by analytical thin-layer chromatography performed on Merck silica gel 60 $F_{254}$ plates. The plates were visualized with UV light (254 nm) and either iodine, potassium permanganate, ceric ammonium molybdate (CAM), or *p*-anisaldehyde-sulfuric acid (PAA) followed by charring with a heat gun. Flash column chromatography was performed on 230-400 mesh SiliaFlash® P60 silica from SiliCycle or Silica RediSep $R_f$ flash columns on a CombiFlash $R_f$ automated flash chromatography system (ISCO). Solvents for extraction, washing, and chromatography were HPLC grade.

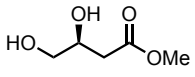
Nuclear magnetic resonance (NMR) spectra were acquired on a 400 MHz Bruker AV-400 FT-NMR spectrometer at ambient temperature. $^1H$ and $^{13}C$ NMR data are reported as values relative to $CDCl_3$ and chemical shifts are reported in ∂ values in ppm. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet), integration, coupling constant (Hz). Infrared spectra were acquired on a Thermo IR100 spectrometer. Optical rotations were recorded on an Autopol III automatic polarimeter. Melting points were recorded on an SRS OptiMelt melting point apparatus and are uncorrected.

**Experimental Procedures: Section 3.1**



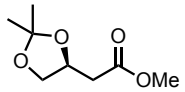
**Dimethyl (*S*)-2-hydroxysuccinate (322):** AcCl (5.28 mL, 74.3 mmol, 0.6 eq.) was added to MeOH (100 mL) at room temperature. After 45 minutes, L-malic acid (**202**, 16.6 g, 124 mmol, 1.0 eq.) was added and the resulting solution was stirred at room temperature for 18 h. The reaction mixture was then concentrated *in vacuo* and the residue was purified by vacuum distillation (P ≈ 0.01 mmHg, T = 68-75 ºC) to yield ester **322** (15.3 g, 76%). Spectral data matched reported values.[187]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 4.50 (br d, *J* = 3.6 Hz, 1H), 3.81 (s, 3H), 3.71 (s, 3H), 3.23 (br s, 1H), 2.83 (qd, *J* = 16.5, 4.3 Hz).



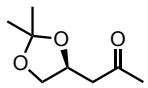
**Methyl (*S*)-3,4-dihydroxybutanoate (323):** To a solution of ester **322** (15.3 g, 94.5 mmol, 1.0 eq.) in THF (100 mL) was added $BH_3$•$Me_2S$ (9.86 mL, 104 mmol, 1.1 eq.) dropwise over 15 min. After 3 h, the reaction mixture was cooled to 0 ºC and $NaBH_4$ (179 mg, 4.72 mmol, 0.05 eq.) was added. After stirring for an additional 3 h, the reaction mixture was quenched by the slow addition of MeOH (100 mL) and concentrated *in vacuo* to afford diol **323**, which was used directly in the next step. Spectral data matched reported values.[188]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 4.12 (br s, 1H), 3.71 (s, 3H), 3.57-3.49 (m, 2H), 2.74 (br s, 1H), 2.58-2.46 (m, 2H).



**Methyl (*S*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetate (296):** To a solution of crude diol **323** (95 mmol, 1.0 eq.) and 2,2,-DMP (12.8 mL, 104 mmol, 1.1 eq.) in $Me_2CO$ (95 mL) was added *p*TsOH-$H_2O$ (1.80 g, 9.45 mmol, 0.1 eq.). The reaction mixture was stirred at room temperature for 15 h before quenching with solid $NaHCO_3$ (~1.5 g). The resulting slurry was filtered through a plug of celite and concentrated *in vacuo*. The crude residue was purified by vacuum distillation (P ≈ 0.1 mmHg, T = 62-65 ºC) to yield ester **296** (6.99 g, 42% over two steps). Spectral data matched reported values.[189]

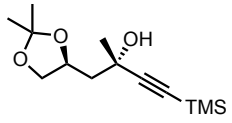
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 4.46 (p, *J* = 6.2 Hz, 1H), 4.15 (dd, *J* = 8.1, 6.2 Hz, 1H), 3.69 (s, 3H), 3.64 (dd, *J* = 8.1, 6.2 Hz, 1H), 2.71 (dd, *J* = 16.2, 6.2 Hz, 1H), 2.52 (dd, *J* = 16.2, 6.9 Hz, 1H), 1.41 (s, 3H), 1.35 (s, 3H).



**(*S*)-1-(2,2-Dimethyl-1,3-dioxolan-4-yl)propan-2-one (204):** A solution of ester **296** (6.99 g, 37.9 mmol, 1.0 eq.) in THF (35 mL) was cooled to -10 ºC (acetone/ice) and

MeO(Me)NH-HCl (4.62 g, 47.4 mmol, 1.25 eq.) was added. After 4 h, MeMgBr (64 mL, 190 mmol, 5 eq., 3.0 M solution in $Et_2O$) was added dropwise over 2 h. The resulting mixture was allowed to warm slowly to room temperature and was stirred for an additional 16 h. The reaction mixture was then cooled back to -10 ºC and quenched with saturated $NH_4Cl$ (30 mL). The resulting biphasic mixture was diluted with $Et_2O$ (150 mL) and the layers were separated. The organic phase was washed with $H_2O$ (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by vacuum distillation (P ≈ 0.1 mmHg, T = 60-65 ºC) to yield methyl ketone **204** (3.30 g, 55%). Spectral data matched reported values.[54]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 4.44 (p, *J* = 6.5 Hz, 1H), 4.18 (dd, *J* = 8.4, 6.5 Hz, 1H), 3.54 (dd, *J* = 8.5, 6.4 Hz, 1H), 2.92 (dd, *J* = 16.8, 5.6 Hz, 1H), 2.62 (dd, *J* = 16.8, 6.5 Hz, 1H), 2.18 (s, 3H), 1.39 (s, 3H), 1.34 (s, 3H).




**(*S*)-1-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-methyl-4-(trimethylsilyl)but-3-yn-2-ol (324):** A solution of TMS-acetylene (14.5 mL, 102 mmol, 1.5 eq.) in THF (500 mL) was cooled to -78 ºC and $^n$BuLi (48 mL, 95.5 mmol, 1.4 eq., 2.0 M solution in hexanes) was added dropwise over 30 minutes. After stirring for an additional 1 h at -78 ºC, a solution of methyl ketone **204** (10.8 g, 68.2 mmol, 1.0 eq.) in THF (50 mL) was added dropwise via addition funnel over 2 h. The temperature was maintained for 1 h, at which time the reaction mixture was quenched with saturated $NH_4Cl$ (50 mL) and warmed to room temperature. The biphasic mixture was extracted with EtOAc (3 x 150 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1 to 8:1 to 7:1) to yield alcohols **324** (3.38 g, 19%), ***epi*-324** (1.10 g, 6%) and a mixture of **324**:***epi*-324** (9.30 g, 53%, dr = 1.3:1).

Data for **324**:

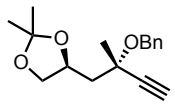
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 4.66-4.60 (m, 1H), 4.15 (dd, *J* = 8.1, 6.1 Hz, 1H), 3.97 (s, 1H), 3.60 (dd, *J* = 7.4, 6.8 Hz, 1H), 1.85 (m, 2H), 1.49 (s, 3H), 1.43 (s, 3H), 1.38 (s, 3H), 0.16 (s, 9H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 109.5, 108.5, 87.8, 74.2, 69.5, 67.5, 45.4, 30.4, 26.9, 25.6, -0.1.

Data for ***epi*-324**:

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 4.40-4.33 (m, 1H), 4.14 (dd, *J* = 8.6, 6.0 Hz, 1H), 3.68 (t, *J* = 8.0, 1H), 2.68 (s, 1H), 2.10 (dd, *J* = 14.5, 6.1 Hz, 1H), 1.91 (dd, *J* = 14.5, 6.8 Hz, 1H), 1.54 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H), 0.16 (s, 9H).

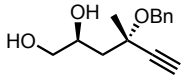
$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 108.8, 108.6, 87.7, 73.4, 69.9, 66.9, 45.8, 30.3, 26.7, 25.7, -0.2.



**(*S*)-4-((*S*)-2-(Benzyloxy)-2-methylbut-3-yn-1-yl)-2,2-dimethyl-1,3-dioxolane (325):** A suspension of NaH (577 mg, 24.0 mmol, 2.2 eq.) in THF (60 mL) was cooled to 0 ºC and alcohol **324** (2.80 g, 10.9 mmol, 1.0 eq.) in THF (6 mL) was added dropwise. After 1.5 h, BnBr (3.25 mL, 27.3 mmol, 2.5 eq.) and TBAI (spatula tip) were added and the resulting solution was stirred for 18 h. The reaction mixture was then quenched with saturated $NH_4Cl$ (15 mL) and the resulting mixture was extracted with EtOAc (100 mL). The organic extracts were washed with $H_2O$ (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, hexanes to 9:1) to yield alkyne **325** (2.51 g, 80%). Spectral data matched reported values.[68]

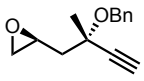
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.33-7.27 (m, 5H), 4.69 (d, *J* = 11.3 Hz, 1H), 4.59 (d, *J* = 11.3 Hz, 1H), 4.43-4.36 (m, 1H), 4.14 (dd, *J* = 7.9, 5.6 Hz, 1H), 3.64 (t, *J* = 7.9 Hz, 1H), 2.53 (s, 1H), 2.26 (dd, *J* = 14.0, 4.7 Hz, 1H), 2.07 (dd, *J* = 14.0, 7.8 Hz, 1H), 1.57 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 138.7, 128.2, 127.4, 127.3, 107.9, 84.9, 73.9, 72.3, 71.4, 70.2, 66.2, 45.6, 26.8, 26.4, 25.9.



**(2*S*,4*S*)-4-(Benzyloxy)-4-methylhex-5-yne-1,2-diol (305):** To a solution of acetonide **325** (3.40 g, 12.4, 1.0 eq.) in $CH_3CN$ (140 mL) was added 2N $HCl_{(aq.)}$ (70 mL) and the reaction mixture was stirred at room temperature. After 1 h, the reaction mixture was quenched with saturated $NaHCO_3$ (50 mL) and diluted with EtOAc (200 mL). The layers were separated and the organic phase was washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL). The organic phase was then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford crude diol **305**, which was used directly in the next step. Spectral data matched reported values.[68]

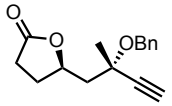
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.37-7.27 (m, 5H), 4.79 (d, *J* = 10.8 Hz, 1H), 4.56 (d, *J* = 10.8 Hz, 1H), 4.35-4.31 (m, 1H), 3.83 (s, 1H), 3.63 (bd, *J* = 11.0 Hz, 1H), 3.49 (bs, 1H), 2.64 (s, 1H), 2.18 (bs, 1H), 2.04 (dd, *J* = 14.6, 9.9 Hz, 1H), 1.80 (dd, *J* = 14.7, 1.5 Hz, 1H), 1.59 (s, 3H).



**(*S*)-2-((*S*)-2-(Benzyloxy)-2-methylbut-3-yn-1-yl)oxirane (326):** A solution of crude diol **305** (2.81 g, 12.0 mmol, 1.0 eq.) in THF (120 mL) was cooled to 0 ºC and NaH (864 mg, 35.9 mmol, 3.0 eq.) was added. TsCl (2.52 g, 13.2 mmol. 1.1 eq.) was then added in three portions over 20 minutes and the resulting mixture was stirred for 75 min. The reaction mixture was quenched with saturated $NH_4Cl$ (30 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$,

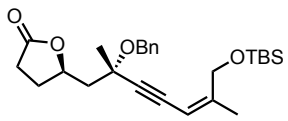
filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to yield epoxide **326** (1.99 g, 77% over two steps). Spectral data matched reported values.[68]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.40-7.26 (m, 5H), 4.74 (d, *J* = 11.1 Hz, 1H), 4.66 (d, *J* = 11.3 Hz, 1H), 3.28-3.24 (m, 1H), 2.82 (t, *J* = 4.7 Hz, 1H), 2.58 (s, 1H), 2.56 (dd, *J* = 5.1, 2.7 Hz, 1H), 2.09 (dd, *J* = 14.2, 6.1 Hz, 1H), 2.00 (dd, *J* = 14.2, 5.4 Hz, 1H), 1.63 (s, 3H).




**(*R*)-5-((*S*)-2-(Benzyloxy)-2-methylbut-3-yn-1-yl)dihydrofuran-2(3*H*)-one (307):** A solution of freshly purified ynamide **306** (4.30 mL, 21.8 mmol, 2.4 eq.) in $CH_2Cl_2$ (80 mL) was cooled to -10 ºC and $BF_3$-$OEt_2$ (3.41 mL, 27.6 mmol, 3.0 eq.) was added. Epoxide **326** (1.99 g, 9.21 mmol, 1.0 eq.) was then added as a solution in $CH_2Cl_2$ (2 mL) over 5 min. After 1 h, $CH_3CN$ (11 mL) was added followed by $KHF_2$ (3.59 g, 46.0 mmol, 5.0 eq.) as a solution in $H_2O$ (18 mL). The resulting mixture was stirred for an additional 2 h, at which time the reaction mixture was quenched with 1N HCl (15 mL). The layers were separated and the aqueous phase was extracted with $CH_2Cl_2$ (3 x 80 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to afford alkyne **307** (1.19 g, 50%). Spectral data matched reported values.[68]

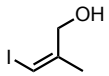
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.35-7.27 (m, 5H), 4.87-4.81 (m, 1H), 4.69 (d, *J* = 11.2 Hz, 1H), 4.60 (d, *J* = 11.2 Hz, 1H), 2.56 (s, 1H), 2.53-2.48 (m, 1H), 2.44-2.36 (m, 1H), 2.31 (dd, *J* = 14.7, 6.4 Hz, 1H), 2.16 (dd, *J* = 14.6, 5.4 Hz, 1H), 2.04-1.94 (m, 1H), 1.61 (s, 3H).




**(*R*)-5-((*S*,*Z*)-2-(Benzyloxy)-7-((*tert*-butyldimethylsilyl)oxy)-2,6-dimethylhept-5-en-3-yn-1-yl)dihydrofuran-2(3*H*)-one (327):** A solution of alkyne **307** (1.19 g, 4.61 mmol, 1.0 eq.) and vinyl iodide **308** (1.73 g, 5.53 mmol, 1.2 eq.) in $CH_3CN$ (50 mL) was degassed with three freeze-pump-thaw cycles. After the final cycle, $Pd(PPh_3)_4$ (532 mg, 0.461 mmol, 0.1 eq.), CuI (87 mg, 0.461 mmol, 0.1 eq.) and $NEt_3$ (1.61 mL, 11.5 mmol, 2.5 eq.) were added sequentially. The resulting orange solution was stirred at room temperature for 24 h before being filtered through a plug of celite. The filtrate was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (hexanes/EtOAc, 6:1 to 4:1) to afford enyne **327** (1.62 g, 79%). Spectral data matched reported values.[68]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.35-7.24 (m, 5H), 5.36 (d, *J* = 1.2 Hz, 1H), 4.88-4.81 (m, 1H), 4.68 (d, *J* = 11.1 Hz, 1H), 4.60 (d, *J* = 11.1 Hz, 1H), 4.38 (s, 2H), 2.52-2.48 (m, 2H), 2.42-2.29 (m, 2H),

2.16 (dd, *J* = 14.8, 5.8 Hz, 1H), 2.03-1.93 (m, 1H), 1.87 (d, *J* = 1.3 Hz, 3H), 1.62 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H).

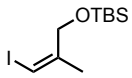


**(*Z*)-3-Iodo-2-methylprop-2-en-1-ol (300):** A suspension of CuI (1.70 g, 8.92 mmol, 0.1 eq.) in THF (100 mL) was cooled to -10 ºC (acetone/ice) and propargyl alcohol (**89**, 5.00 g, 89.2 mmol, 1.0 eq.) was added neat via syringe. After 1 h, a solution of MeMgBr (59.5 mL, 178 mmol, 2.0 eq., 3.0 M in $Et_2O$) was added dropwise over 25 min. The resulting dark solution was stirred at that temperature for an additional 1 h, at which time a solution of $I_2$ (33.96 g, 134 mmol, 1.5 eq.) in THF (150 mL) was added via cannula over 1 h. The cooling bath was removed and the resulting thick suspension was allowed to warm to room temperature. After 2 h, the reaction mixture was quenched with saturated $NH_4Cl$ (60 mL). The aqueous layer was extracted with $Et_2O$ (3 x 100 mL). The combined organic extracts were washed with saturated $Na_2S_2O_3$ (120 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1) to yield vinyl iodide **300** (11.0 g, 62%) as a yellow oil. Spectral data matched reported values.[190]

$R_f$ 0.30 (4:1 hexanes/ethyl acetate, UV/$KMnO_4$)

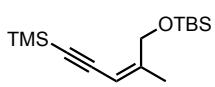
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.98 (t, *J* = 0.7 Hz, 1H), 4.25 (d, *J* = 6.1 Hz, 2H), 2.53 (bm, exchanges w/ $D_2O$, 1H), 1.98 (d, *J* = 1.5 Hz, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 146.0, 74.8, 67.9, 21.6.



**(*Z*)-*tert*-Butyl((3-iodo-2-methylallyl)oxy)dimethylsilane (308):** To a solution of vinyl iodide **300** (6.87 g, 34.7 mmol, 1.0 eq.) in DMF (100 mL) was added TBSCl (5.75 g, 38.2 mmol, 1.1 eq.), ImH (2.60 g, 38.2 mmol, 1.1 eq.) and DMAP (spatula tip). The reaction mixture was protected from light and stirred for 5 h at which time an additional portion of TBSCl (5.23 g, 34.7 mmol. 1.0 eq.) and ImH (4.72 g, 69.3 mmol, 2.0 eq.) was added. After 1 h, the reaction mixture was poured into a separatory funnel containing hexanes (350 mL) and washed with $H_2O$ (2 x 50 mL), and brine (50 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude residue was further purified by vacuum distillation (P ≈ 1.9 mmHg, T = 71 ºC) to yield vinyl iodide **308** (8.76 g, 81%). Spectral data matched reported values.[191]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.86-5.85 (m, 1H), 4.24 (d, *J* = 0.5 Hz, 2H), 1.91 (d, *J* = 1.5 Hz, 3H), 0.92 (s, 9H), 0.10 (s, 6H).

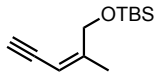


**(*Z*)-*tert*-Butyldimethyl((2-methyl-5-(trimethylsilyl)pent-2-en-4-yn-1-yl)oxy)silane (328):** A solution of vinyl iodide **308** (500 mg, 1.60 mmol, 1.0 eq.) and TMS-

acetylene (0.45 mL, 3.20 mmol, 2.0 eq.) in THF (8 mL) was degassed with three freeze-pump-thaw cycles. After the final cycle, $PdCl_2(PPh_3)_2$ (23 mg, 0.032 mmol, 0.02 eq.), CuI (30 mg, 0.160 mmol, 0.1 eq.), and $NEt_3$ (1.56 mL, 11.2 mmol, 7.0 eq.) was added and the resulting dark solution was sonicated for 1 h. The reaction mixture was then quenched by the addition of saturated $NaHCO_3$ (10 mL) and the resulting mixture was extracted with EtOAc (3 x 80 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was filtered through a plug of $SiO_2$ (hexanes/ EtOAc, 9:1) to afford enyne **328**, which was used immediately in the next step. Spectral data matched reported values.[192]

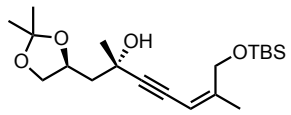
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.32 (d, *J* = 0.8 Hz, 1H), 4.39 (s, 2H), 1.84 (d, *J* = 1.2 Hz, 3H), 0.91 (s, 9H), 0.18 (s, 9H), 0.09 (s, 6H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 152.4, 105.4, 101.9, 97.6, 63.9, 25.8, 19.7, 18.2, -0.1, -5.4.




**(*Z*)-*tert*-Butyldimethyl((2-methylpent-2-en-4-yn-1-yl)oxy)silane (329):** To a solution of crude enyne **328** (1.60 mmol, 1.0 eq.) in MeOH (2 mL) and THF (2 mL) was added $K_2CO_3$ (221 mg, 1.60 mmol, 1.0 eq.) and the resulting mixture was stirred at room temperature for 19 h. The resulting suspension was filtered through a plug of $SiO_2$ and concentrated *in vacuo*. The crude residue was further purified by flash column chromatography (hexanes to hexanes/EtOAc 20:1) to yield enyne **329** (119 mg, 35% over two steps).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.30 (d, *J* = 0.9 Hz, 1H), 4.40 (s, 2H), 3.04 (d, *J* = 2.1 Hz, 1H), 1.85 (d, *J* = 0.8 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 6H).



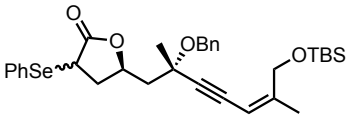

**(*S*,*Z*)-7-((*tert*-Butyldimethylsilyl)oxy)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,6-dimethylhept-5-en-3-yn-2-ol (330):** A solution of enyne **329** (119 mg, 0.566 mmol, 1.3 eq.) in THF (3 mL) was cooled to -78 ºC and $^n$BuLi (0.24 mL, 0.528 mmol, 1.2 eq., 2.2 M solution in hexanes) was added dropwise. After 1 h, a solution of ketone **204** (70 mg, 0.442 mmol, 1.0 eq.) in THF (3 mL) was added dropwise over 10 min. The reaction mixture was stirred at -78 ºC for 3 h before being quenched with saturated $NH_4Cl$ (4 mL). The reaction mixture was then extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes to hexanes/EtOAc, 7:1) to yield alcohols **330** (36 mg, 23%) and ***epi*-330** (16 mg, 10%).

Data for **330**:

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.33 (d, *J* = 1.3 Hz, 1H), 4.67-4.61 (m, 1H), 4.36 (s, 2H), 4.14-4.08 (m, 3H), 3.60 (dd, *J* = 8.2, 6.7 Hz, 1H), 1.88-1.83 (m, 5H), 1.52 (s, 3H), 1.43 (s, 3H), 1.37 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H).

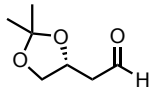
Data for ***epi*-330**:

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.31 (d, *J* = 1.3 Hz, 1H), 4.40-4.35 (m, 3H), 4.16-4.11 (m, 1H), 3.66 (t, *J* = 7.7 Hz, 1H), 2.13 (dd, *J* = 14.2, 6.5 Hz, 1H), 1.93 (dd, *J* = 13.6, 5.9 Hz, 1H), 1.84 (d, *J* = 1.4 Hz, 3H), 1.58 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H).




**(5*S*)-5-((*S*,*Z*)-2-(Benzyloxy)-7-((*tert*-butyldimethylsilyl)oxy)-2,6-dimethylhept-5-en-3-yn-1-yl)-3-(phenylselanyl)dihydrofuran-2(3*H*)-one (309):** To a solution of lactone **327** (218 mg, 0.492 mmol, 1.0 eq.) in $CH_2Cl_2$ (5 mL) was added $^i$Pr$_2$NEt (1.60 mL, 9.16 mmol, 18.6 eq.) followed by TMSOTf (0.48 mL, 2.66 mmol, 5.4 eq.). The reaction mixture was stirred at room temperature for 2 h, before being concentrated *in vacuo*. The crude residue was immediately taken up in THF (5 mL) and cooled to -78 ºC. A solution of PhSeCl (113 mg, 0.590, 1.2 eq.) in THF (1 mL) was then added dropwise. After stirring at -78 ºC for 2 h, the reaction mixture was quenched with ~3 mL of $SiO_2$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes to hexanes/EtOAc, 9:1) to yield selenide **309** (239 mg, 81%) as a 2:1 mixture of diastereomers. Spectral data matched reported values.[68]

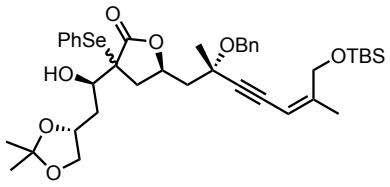
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.66-7.63 (m, 2H), 7.36-7.26 (m, 8H), 5.31 (m, 1H), 4.79-4.72 (m, 1H, major), 4.66-4.61 (m, 1H, minor), 4.62 (d, *J* = 11.3 Hz, 1H), 4.55 (d, *J* = 11.2 Hz, 1H), 4.35 (s, 2H), 3.98 (dd, *J* = 9.9, 9.2 Hz, 1H, major), 3.91-3.89 (m, 1H, minor), 2.80-2.72 (m, 1H, minor), 2.44-2.40 (m, 1H, major), 2.28-2.16 (m, 1H), 2.11-2.08 (m, 1H), 1.98, (dd, *J* = 14.6, 5.7 Hz, 1H), 1.86 (s, 3H), 1.56 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H).




**(*R*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)acetaldehyde (332)**: A solution of ester ***ent*-296** (131 mg, 0.752 mmol, 1.0 eq.) in $CH_2Cl_2$ (8 mL) was cooled to -78 ºC and DIBAL (0.9 mL, 0.903 mmol, 1.2 eq., 1.0 M solution in hexanes) was added dropwise over 5 min. The reaction mixture was maintained at that temperature for 3 h, before being quenched by the slow addition of MeOH (2 mL) at -78 ºC. Rochelle's salt solution (10 mL) was added and the resulting biphasic mixture was allowed to warm to room temperature. The phases were then separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 30 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in*

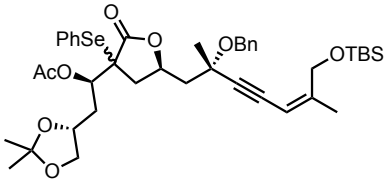
*vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1 to 4:1) to yield aldehyde **332** (52 mg, 48%). Spectral data matched reported values.[193]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 9.79 (s, 1H), 4.51 (p, *J* = 6.3 Hz, 1H), 4.17 (dd, *J* = 8.1, 6.3 Hz, 1H), 3.57 (dd, *J* = 8.8, 6.9 Hz, 1H), 2.83 (ddd, *J* = 17.1, 6.3, 1.7, 1H), 2.63 (ddd, *J* = 17.1, 5.9, 1.0 Hz, 1H), 1.40 (s, 3H), 1.34 (s, 3H).




**(5*S*)-5-((*S*,*Z*)-2-(Benzyloxy)-7-((*tert*-butyldimethylsilyl) oxy)-2,6-dimethylhept-5-en-3-yn-1-yl)-3-((*R*)-2-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-hydroxyethyl)-3-(phenylselanyl)dihydrofuran-2(3*H*)-one (333)**: A solution of selenide **309** (186 mg, 0.311 mmol, 1.0 eq.) in THF (3 mL) was cooled to -78 ºC and LHMDS (0.36 mL, 0.360 mmol, 1.2 eq., 1.0 M solution in THF) was added dropwise. After 1 h, a solution of aldehyde **332** (52 mg, 0.360 mmol, 1.2 eq.) in THF (0.5 mL) was added dropwise. After stirring at -78 ºC for an additional 1.5 h, the reaction mixture was quenched by pouring into an Erlenmeyer flask containing $Et_2O$ (20 mL) and saturated $NH_4Cl$ (10 mL). The biphasic mixture was further diluted with $Et_2O$ (20 mL) and the layers were separated. The organic phase was washed with $H_2O$ (2 x 5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to yield recovered selenide **309** (106 mg, 57%) and alcohol **333** (57 mg, 24%) as a mixture of diastereomers.

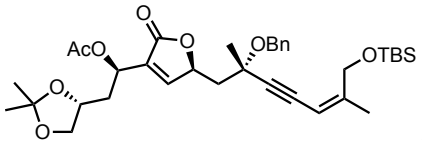
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.67-7.65 (m, 2H), 7.44-7.40 (m, 1H), 7.36-7.23 (m, 7H), 5.34 (s, 1H), 4.85-4.80 (m, 1H), 4.65-4.53 (m, 2H), 4.37 (s, 2H), 4.33-4.29 (m, 1H), 4.10-4.01 (m, 2H), 3.64-3.56 (m, 1H), 2.96 (dd, *J* = 14.4, 8.5 Hz, 1H, minor), 2.71 (dd, *J* = 14.8, 8.5 Hz, 1H, major), 2.41-2.07 (m, 3H), 2.02-1.95 (m, 1H), 1.90-1.78 (m, 4H), 1.56 (s, 3H, minor), 1.52 (s, 3H, major), 1.42 (s, 3H, minor), 1.39 (s, 3H, major), 1.36 (s, 3H, minor), 1.33 (s, 3H, major), 0.90 (s, 9H), 0.07 (s, 6H).




**(1*R*)-1-((5*S*)-5-((*S*,*Z*)-2-(Benzyloxy)-7-((*tert*-butyldimethylsilyl)oxy)-2,6-dimethylhept-5-en-3-yn-1-yl)-2-oxo-3-(phenylselanyl) tetrahydrofuran-3-yl)-2-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl acetate (334)**: To a solution of alcohol **333** (57 mg, 0.075 mmol, 1.0 eq.) in $CH_2Cl_2$ (1 mL) was added $NEt_3$ (0.01 mL, 0.113 mmol, 1.5 eq.), $Ac_2O$ (0.02 mL, 0.151 mmol, 2.0 eq.) and DMAP (spatula tip). The

resulting mixture was stirred at room temperature for 20 h, before being quenched with saturated $NH_4Cl$ (2 mL). The reaction mixture was then extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic extracts were washed with brine (2 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to yield acetate **334** (48 mg, 80%) as a mixture of diastereomers.

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.69-7.62 (m, 2H), 7.44-7.28 (m, 8H), 5.56 (dd, *J* = 9.9, 2.2 Hz, 1H, major), 5.35-5.29 (m, 1H), 5.12 (dd, *J* = 11.2, 1.7 Hz, 1H, minor), 4.92-4.87 (m, 1H, minor), 4.69-4.50 (m, 3H), 4.39-4.35 (m, 2H), 4.02-3.96 (m, 2H), 3.57-3.53 (m, 1H, major), 3.47-3.42 (m, 1H, minor), 2.91 (dd, *J* = 14.5, 8.8 Hz, 1H, minor), 2.56 (dd, *J* = 14.5, 7.4 Hz, 1H, major), 2.38-2.23 (m, 2H), 2.16-2.04 (m, 3H), 1.93 (s, 3H, minor), 1.91 (s, 3H, major), 1.87 (s, 3H), 1.79 (dd, *J* = 14.4, 5.9 Hz, 1H), 1.59 (s, 3H, minor), 1.52 (s, 3H, major), 1.42 (s, 3H), 1.31 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H, minor), 0.06 (s, 6H, major).

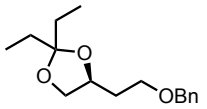



**(*R*)-1-((*S*)-5-((*S*,*Z*)-2-(Benzyloxy)-7-((*tert*-butyldimethylsilyl) oxy)-2,6-dimethylhept-5-en-3-yn-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)-2-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl acetate (335)**: To a solution of acetate **334** (27 mg, 0.034 mmol, 1.0 eq.) in $CH_2Cl_2$ (0.5 mL) was added *m*CPBA (8 mg, 0.034 mmol, 1.0 eq., 77%). The reaction mixture was stirred at room temperature for 6 h, before being quenched with saturated $Na_2S_2O_3$ (1 mL). The resulting mixture was further extracted with $CH_2Cl_2$ (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to yield butenolide **335** (20 mg, 91%) as a mixture of diastereomers.

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.41 (s, 1H, major), 7.39 (s, 1H, minor), 7.34-7.28 (m, 5H), 5.73-5.67 (m, 1H), 5.34 (s, 1H), 5.31-5.27 (m, 1H), 4.69-4.66 (m, 1H), 4.62-4.59 (m, 1H), 4.40-4.33 (m, 2H), 4.12 (m, 1H, overlap with EtOAc), 4.06-4.01 (m, 1H), 3.59-3.54 (m, 1H), 2.29-2.22 (m, 1H), 2.20-2.12 (m, 2H), 2.10-2.08 (m, 1H), 2.05 (s, 3H, minor), 2.04 (s, 3H, major), 1.87 (s, 3H), 1.65 (s, 3H, minor), 1.64 (s, 3H, major), 1.39 (s, 3H, major), 1.37 (s, 3H, minor), 1.32 (s, 3H, major), 1.31 (s, 3H, minor), 0.89 (s, 9H), 0.06 (s, 6H).

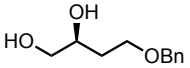
$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 170.6, 169.6, 152.2, 151.3 (major), 150.8 (minor), 138.4, 132.1, 128.3, 127.5, 127.4, 109.0, 104.0, 92.9, 83.3, 78.0, 72.4 (minor), 72.2 (major), 71.7, 69.2, 66.5, 66.3, 63.8, 45.1 (major), 44.9 (minor), 36.7, 29.6, 26.9, 26.6, 25.8 (major), 25.6 (minor), 20.8, 19.8, 18.2, -5.3.

**Experimental Procedures: Section 3.2**



**(*S*)-4-(2-(Benzyloxy)ethyl)-2,2-diethyl-1,3-dioxolane (342):** To a solution of alcohol **341** (2.90 g, 16.6 mmol, 1.0 eq.) in THF (120 mL) was added NaH (1.20 g, 49.9 mmol, 3.0 eq.) followed by BnBr (5.94 mL, 49.9 mmol, 3.0 eq.). The reaction mixture was stirred at room temperature for 20 h, then quenched with the slow addition of $H_2O$ (20 mL). The reaction mixture was diluted with EtOAc (150 mL) and the layers were separated. The organic phase was washed with $H_2O$ (3 x 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford crude benzyl ether **342**, which was used without further purification.

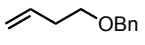
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.43-7.30 (m, 5H), 4.53 (s, 2H), 4.28-4.21 (m, 1H), 4.11 (dd, *J* = 7.9, 6.1 Hz, 1H), 3.64-3.60 (m, 2H), 3.57 (t, *J* = 7.9 Hz, 1H), 2.03-1.85 (m, 2H), 1.67 (p, *J* = 7.2 Hz, 4H), 0.95 (t, *J* = 7.2 Hz, 6H).



**(*S*)-4-(Benzyloxy)butane-1,2-diol (343):** To a solution of crude ether **342** (16.6 mmol, 1.0 eq.) in THF (180 mL) was added 2N HCl (90 mL). A slight exotherm was observed. The reaction mixture was stirred at room temperature for 4 h, then quenched with saturated $NaHCO_3$ (75 mL). The THF was removed *in vacuo* and the aqueous residue was extracted with EtOAc (3 x 150 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 1:1 to EtOAc) to yield diol **343** (2.63 g, 80% over two steps). Spectral data matched reported values.[194]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.38-7.30 (m, 5H), 4.53 (s, 2H), 3.96-3.90 (m, 1H), 3.73-3.67 (m, 2H), 3.64 (dd, *J* = 11.2, 3.7 Hz, 1H), 3.51 (dd, *J* = 11.0, 6.2 Hz, 1H), 3.04 (bs, 1H), 2.13 (bs, 1H), 1.88-1.81 (m, 1H), 1.78-1.71 (m, 1H).

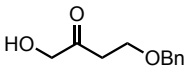
$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 128.4, 128.2, 127.8, 127.7, 73.3, 71.4, 68.3, 66.5, 32.7.



**((But-3-en-1-yloxy)methyl)benzene (349):** A solution of alcohol **348** (500 mg, 6.93 mmol, 1.0 eq.) in THF (50 mL) was cooled to 0 ºC and NaH (333 mg, 13.9 mmol, 2.0 eq.) was added. After 15 min, TBAI (spatula tip) and BnBr (1.24 mL, 10.4 mmol, 1.5 eq.) were added and the resulting mixture was stirred at room temperature for 19 h. The reaction mixture was quenched with saturated $NH_4Cl$ (25 mL) and diluted with EtOAc (100 mL). The layers were separated and the organic phase was washed with $H_2O$ (2 x 25 mL) and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by

flash column chromatography (hexanes) to yield benzyl ether **349** (1.54 g contaminated with ~510 mg excess BnBr, 91%). Spectral data matched reported values.[195]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.41-7.27 (m, 5H), 5.91-5.80 (m, 1H), 5.11 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.07-5.04 (m, 1H), 4.53 (s, 2H), 3.54 (t, *J* = 6.7 Hz, 2H), 2.39 (q, *J* = 6.7 Hz, 2H).



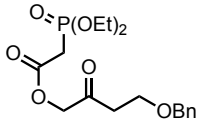

**4-(Benzyloxy)-1-hydroxybutan-2-one (340):**

**From 343:** To a solution of diol **343** (2.63 g, 13.4 mmol, 1.0 eq.) in PhH (150 mL) over activated 4Å molecular sieves (~1.0 g) was added $Bu_2SnO$ (6.67 g, 26.8 mmol, 2.0 eq.) and the resulting suspension was heated to reflux. After 20 h at reflux, the reaction mixture was cooled to room temperature and a 1M solution of $Br_2$ in $CH_2Cl_2$ was added dropwise until the yellow color persisted (~8.5 mL). The resulting suspension was filtered through a plug of celite and the filtrate was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to yield ketone **340** (1.21 g, 47%).

**From 349:** To a solution of ether **349** (500 mg, 3.08 mmol, 1.0 eq.) in a mixture of AcOH (1.2 mL), $H_2O$ (4.9 mL), and $Me_2CO$ (25 mL) was added $KMnO_4$ (779 mg, 4.93 mmol, 1.6 eq.) as a solution in $Me_2CO$ (9 mL) and $H_2O$ (3 mL). The reaction mixture was stirred at room temperature for 2 h, before being quenched with EtOH (5 mL), filtered through a plug of celite, and concentrated *in vacuo*. The residue was taken up in $Et_2O$ (75 mL) and washed with saturated $NaHCO_3$ (3 x 10 mL) and brine (10 mL). The organic phase was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 1:1) to yield ketone **340** (301 mg, 50%). Spectral data matched reported values.[196]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.36-7.27 (m, 5H), 4.50 (s, 2H), 4.28 (d, *J* = 2.1 Hz, 2H), 3.77 (t, *J* = 6.3 Hz, 2H), 3.14 (bs, 1H), 2.68 (t, *J* = 6.3 Hz, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 208.4, 137.6, 128.4, 127.8, 127.6, 73.3, 68.8, 64.9, 39.0.



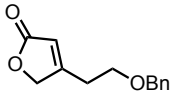

**4-(Benzyloxy)-2-oxobutyl 2-(diethoxyphosphoryl)acetate (346):** To a solution of alcohol **340** (773 mg, 3.98 mmol, 1.0 eq.) in $CH_2Cl_2$ (40 mL) was added acid **345** (1.56 g, 7.96 mmol, 2.0 eq.) and DMAP (1.46 g, 11.9 mmol, 3.0 eq.). The resulting solution was cooled to 0 ºC and EDCI-HCl (1.53 g, 7.96 mmol, 2.0 eq.) was added. The reaction mixture was allowed to warm slowly to room temperature and stirred for 20 h, at which time it was quenched with saturated $NaHCO_3$ (10 mL). The mixture was then extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic extracts were then washed with 1N HCl (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash

column chromatography (hexanes/EtOAc, 1:1 to EtOAc) to yield phosphonate **346** (1.20 g, 81%).

$^{1}$H NMR (400 MHz, $CDCl_3$) ∂ 7.36-7.28 (m, 5H), 4.75 (s, 2H), 4.50 (s, 2H), 4.23-4.15 (m, 4H), 3.75 (t, *J* = 6.6 Hz, 2H), 3.08 (d, *J* = 20.8 Hz, 2H), 2.72 (t, *J* = 6.6 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 6H).

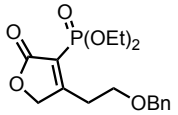
$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 201.6, 165.0 (2), 73.2, 69.2, 64.7, 62.8 (2), 49.2, 39.4 35.7 (d, *J* = 70.1), 33.1, 25.2 (d, *J* = 70.1), 16.2 (2).

$^{31}$P NMR (160 MHz, $CDCl_3$) ∂ 18.8.




**4-(2-(Benzyloxy)ethyl)furan-2(5*H*)-one (339):** To a solution of phosphonate **346** (226 mg, 0.607 mmol, 1.0 eq.) in THF (60 mL) was added DBU (0.91 mL, 6.07 mmol, 10.0 eq.). The reaction mixture was stirred at room temperature for 17 h, then quenched with the slow addition of 1N HCl (8 mL). The reaction mixture was extracted with EtOAc (2 x 50 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 2:1 to 1:1) to yield butenolide **339** (84 mg, 64%).

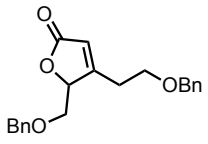
$^{1}$H NMR (400 MHz, $CDCl_3$) ∂ 7.39-7.29 (m, 5H), 5.90 (t, *J* = 1.5 Hz, 1H), 4.78 (m, 2H), 4.52 (s, 2H), 3.67 (t, *J* = 5.9 Hz, 2H), 2.72 (t, *J* = 5.9 Hz, 2H).




**diethyl (4-(2-(Benzyloxy)ethyl)-2-oxo-2,5-dihydrofuran-3-yl)phosphonate (347):** To a solution of phosphonate **346** (59 mg, 0.158 mmol, 1.0 eq.) and LiBr (16 mg, 0.190 mmol, 1.2 eq.) in THF (3 mL) was added $NEt_3$ (0.03 mL, 0.174 mmol, 1.1 eq.) and the resulting cloudy solution was stirred at room temperature for 4 h. The reaction mixture was quenched with 1N HCl (2 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 1:1) to yield undesired phosphonate **347** (22 mg, 39%).

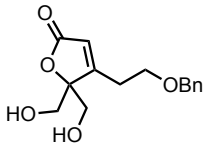
$^{1}$H NMR (600 MHz, $CDCl_3$) ∂ 7.35-7.27 (m, 5H), 4.90 (d, *J* = 1.7 Hz, 2H), 4.49 (s, 2H), 4.20-4.12 (m, 4H), 3.70 (t, *J* = 5.6 Hz, 2H), 3.21 (bs, 2H), 1.33 (t, *J* = 7.0 Hz, 6H).

$^{13}$C NMR (150 MHz, $CDCl_3$) ∂ 181.5 (2), 170.9 (2), 137.4, 128.5, 127.9, 127.7, 118.8, 117.4, 74.1 (2), 73.2, 67.7, 63.0 (2), 29.4, 16.2 (2).



**4-(2-(Benzyloxy)ethyl)-5-((benzyloxy)methyl)furan-2(5*H*)-one (350):** To a solution of butenolide **349** (89 mg, 0.385 mmol, 1.0 eq.) in NMP (4 mL) was added NaH (14 mg, 0.577 mmol, 1.5 eq.). The resulting rose-colored solution was stirred for 5 min before the addition of BOMCl (0.08 mL, 0.500 mmol, 1.3 eq., 85% purity). The color slowly dissipated over the course of the addition. The reaction mixture was stirred for 22 h, then quenched with saturated $NH_4Cl$ (2 mL) and extracted with EtOAc (50 mL). The organic extract was washed with $H_2O$ (3 x 5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1) to yield impure butenolide **350** (16 mg, 12%).

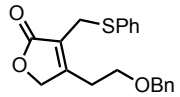
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.36-7.28 (m, 10H), 6.79 (d, *J* = 0.8 Hz, 1H), 5.37 (s, 1H), 5.19 (s, 2H), 4.75 (s, 2H), 4.54 (s, 2H), 3.63 (t, *J* = 7.0 Hz, 2H), 2.68 (t, *J* = 7.0 Hz, 2H).



**4-(2-(Benzyloxy)ethyl)-5,5-bis(hydroxymethyl)furan-2(5*H*)-one (352):** To a solution of butenolide **339** (96 mg, 0.440 mmol, 1.0 eq.) and DABCO (spatula tip) in THF (5 mL) was added aqueous 37% $CH_2O$ (0.06 mL, 0.660 mmol, 1.5 eq.). The reaction mixture was stirred at room temperature for 5 h, then heated to reflux for an additional 18 h. Upon cooling back to room temperature, the reaction mixture was quenched with 1N HCl (2 mL) and extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1) to yield impure diol **352** (38 mg, 31%) and recovered butenolide **339** (17 mg, 18%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.37-7.28 (m, 5H), 5.93 (s, 1H), 4.52 (s, 2H), 3.86-3.73 (m, 4H), 3.15 (t, *J* = 7.1 Hz, 2H), 2.64 (td, *J* = 5.8, 1.1 Hz).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 172.5, 169.5, 136.8, 128.5, 128.1, 128.0, 118.9, 93.2, 73.5, 67.9, 62.3 (2C), 27.7.

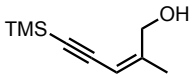


**4-(2-(Benzyloxy)ethyl)-3-((phenylthio)methyl)furan-2(5*H*)-one (353):** A solution of butenolide **339** (107 mg, 0.490 mmol, 1.0 eq.), PhSH (0.08 mL, 0.735 mmol, 1.5 eq.), aqueous 37% $CH_2O$ (0.05 mL, 0.799 mmol, 1.6 eq.), and $NEt_3$ (0.09 mL, 0.618 mmol, 1.3 eq.) in EtOH (1 mL) was heated to reflux and stirred for 96 h. Upon cooling to room temperature, the

reaction mixture was quenched with 1N NaOH (2 mL) and extracted with $Et_2O$ (25 mL). The organic extract was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to yield butenolide **353** (22 mg, 13%).

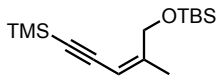
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.41-7.24 (m, 10H), 4.69 (s, 2H), 4.43 (s, 2H), 3.72 (s, 2H), 3.40 (t, *J* = 5.8 Hz, 2H), 2.46 (t, *J* = 5.8 Hz, 2H).

**Experimental Procedures: Section 3.3**

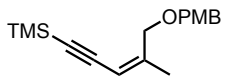



**(*Z*)-2-Methyl-5-(trimethylsilyl)pent-2-en-4-yn-1-ol (358)**: A solution of vinyl iodide **300** (2.71 g, 13.7 mmol, 1.0 eq.) and TMS-acetylene (3.87 mL, 27.4 mmol, 2.0 eq.) in THF (65 mL) was degassed with two freeze-pump-thaw cycles. $NEt_3$ (13.4 mL, 95.8 mmol, 7.0 eq.) was added and the resulting solution was degassed once more before the addition of CuI (261 mg, 1.37 mmol, 0.1 eq.) and $Pd(PPh_3)_4$ (316 mg, 0.274 mmol, 0.02 eq.) were added sequentially. The resulting solution was stirred at room temperature for 3 h then filtered through a plug of celite and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to yield enyne **358** (1.39 g, 82%). Spectral data matched reported values.[197]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.42-5.41 (m, 1H), 4.36 (d, *J* = 6.0 Hz, 2H), 1.87 (d, *J* = 1.6 Hz, 3H), 1.75 (bt, *J* = 6.0 Hz, 1H), 0.18 (s, 9H).



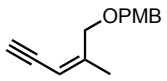

**(*Z*)-*tert*-Butyldimethyl((2-methyl-5-(trimethylsilyl)pent-2-en-4-yn-1-yl)oxy)silane (328):** To a solution of enyne **358** (1.02 g, 6.06 mmol, 1.0 eq.) and DMAP (spatula tip) in $CH_2Cl_2$ (50 mL) was added TBSCl (1.37 g, 9.09 mmol, 1.5 eq.) then $NEt_3$ (1.69 mL, 12.1 mmol, 2.0 eq.). The reaction mixture was stirred at room temperature for 21 h, then quenched with saturated $NH_4Cl$ (10 mL) and extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to yield silyl ether **328** (1.34 g, 78%). Spectral data matches previously prepared sample.




**(*Z*)-(5-((4-Methoxybenzyl)oxy)-4-methylpent-3-en-1-yn-1-yl)trimethylsilane (359):** A solution of PMB-TCA (589 mg, 2.08 mmol, 3.o eq.) in PhMe (7 mL) was cooled to 0 ºC and a solution of enyne **358** (117 mg, 0.695 mmol, 1.0 eq.) in PhMe (1 mL)

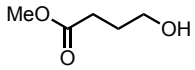
was added followed immediately by $Sc(OTf)_3$ (34 mg, 0.070 mmol, 0.1 eq.). The reaction mixture was allowed to warm to room temperature and stirred for 18 h before a second portion of $Sc(OTf)_3$ (34 mg, 0.070 mmol, 0.1 eq.) was added. The reaction mixture was stirred for an additional 3 h, then concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 20:1) to yield PMB ether **359** (124 mg, 62%, ~50% purity).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.29 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.49 (s, 1H), 4.40 (s, 2H), 4.25 (s, 2H), 3.80 (s, 3H), 1.88 (d, *J* = 1.1 Hz, 3H), 0.17 (s, 9H).



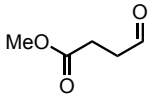

**(*Z*)-1-Methoxy-4-(((2-methylpent-2-en-4-yn-1-yl)oxy)methyl)benzene (360):** A solution of PMB ether **359** (131 mg, 0.454 mmol, 1.0 eq.) in THF (5 mL) was cooled to 0 ºC and TBAF (0.5 mL, 0.499 mmol, 1.1 eq., 1.0 M solution in THF) was added dropwise. The resulting dark brown solution was stirred for 30 min, then quenched with $H_2O$ (2 mL) and extracted with $Et_2O$ (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1) to yield alkyne **360** (77 mg, 79%, ~70% purity).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.30 (d, *J* = 8.5 Hz, 2H), 6.91-6.89 (m, 2H), 5.47 (m, 1H), 4.43 (s, 2H), 4.28 (s, 2H), 3.81 (s, 3H), 3.06 (d, *J* = 2.1 Hz, 1H), 1.91 (d, *J* = 1.2 Hz, 3H).



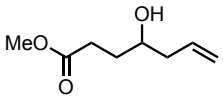

**Methyl 4-hydroxybutanoate (362):** To a solution of γ-butyrolactone **361** (0.88 mL, 11.6 mmol, 1.0 eq.) in MeOH (50 mL) was added $NEt_3$ (9.71 mL, 69.7 mmol, 6.0 eq.) and the resulting solution was heated at reflux for 12 h. Once cooled back to room temperature, the solvents were removed *in vacuo* to afford crude alcohol **362** and starting lactone **361** in a 3:1 ratio. The material was used immediately in the following step without further purification. Spectral data matched reported values.[198]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 3.69-3.66 (m, 5H), 2.44 (t, *J* = 7.1 Hz, 2H), 1.93 (bs, 1H), 1.91-1.86 (m, 2H).



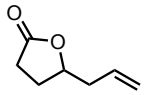

**Methyl 4-oxobutanoate (357):** To a solution of crude alcohol **362** (11.6 mmol, 1.0 eq.) in $CH_2Cl_2$ (30 mL) containing a scoop of $MgSO_4$ was added PCC (3.76 g, 17.4 mmol, 1.5 eq.) and NaOAc (256 mg, 3.49 mmol, 0.3 eq.). The resulting suspension was stirred at room temperature for 3 h, then diluted with $Et_2O$ (100 mL) and filtered through a plug of celite. The filtrate was concentrated *in vacuo* to yield crude aldehyde **357** contaminated with ~30% lactone **361**. The material was used immediately in the following step without further purification. Spectral data matched reported values.[199]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 9.81 (s, 1H), 3.69 (s, 3H), 2.80 (t, *J* = 6.6 Hz, 2H), 2.63 (t, *J* = 6.6 Hz, 2H).



**Methyl 4-hydroxyhept-6-enoate ((±)-356):** A solution of aldehyde **357** (11.6 mmol, 1.0 eq.) and allyltrimethylsilane (2.22 mL, 13.9 mmol, 1.2 eq.) in $CH_3CN$ (30 mL) was cooled to -10 ºC (acetone/ice) and $I_2$ (590 mg, 2.32 mmol, 0.2 eq.) was added. The reaction mixture was stirred at that temperature for 10 min, then quenched by the addition of saturated $Na_2S_2O_3$ (15 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL) and the combined organic extracts were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield crude **(±)-356**, which was used immediately in the following step without further purification.

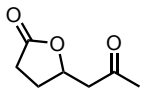
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.87-5.76 (m, 1H), 5.14 (d, *J* = 12.5 Hz, 2H), 3.68 (s, 3H), 2.51-2.46 (m, 2H), 2.22-2.17 (m, 1H), 2.00-1.93 (m, 1H), 1.90-1.84 (m, 1H), 1.77-1.70 (m, 1H).



**5-Allyldihydrofuran-2(3*H*)-one (363):** To a solution of crude **(±)-356** (11.6 mmol, 1.0 eq.) in PhMe (120 mL) was added *p*TsOH-$H_2O$ (221 mg, 1.16 mmol, 0.1 eq.). The reaction mixture was stirred at room temperature for 16 h, then concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to yield lactone **363** (297 mg, 20% over four steps). Spectral data matched reported values.[200]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.84-5.74 (m, 1H), 5.20-5.15 (m, 2H), 4.59-4.53 (m, 1H), 2.55-2.47 (m, 3H), 2.44-2.37 (m, 1H), 2.35-2.26 (m, 1H), 2.00-1.88 (m, 1H).

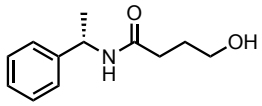
$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 176.9, 132.0, 118.7, 79.6, 39.3, 28.5, 26.9.



**5-(2-Oxopropyl)dihydrofuran-2(3*H*)-one ((±)-355):** To a solution of lactone **363** (393 mg, 3.12 mmol, 1.0 eq.) in DMF (40 mL) and $H_2O$ (3 mL) was added $CuCl_2$ (503 mg, 3.74 mmol, 1.2 eq.) and $PdCl_2$ (110 mg, 0.623 mmol, 0.1 eq.). The reaction flask was quickly evacuated and backfilled with an atmosphere of $O_2$ then heated to 80 ºC. The reaction mixture was stirred at that temperature under a balloon atmosphere of $O_2$ for 18 h. Upon cooling to room temperature, the solvents were removed *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 1:1) to yield ketone **(±)-355** (190 mg, 43%). Spectral data matched reported values.[201]

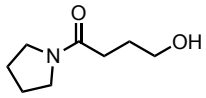
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 4.91-4.87 (m, 1H), 3.00 (dd, *J* = 17.4, 6.2 Hz, 1H), 2.71 (dd, *J* = 17.2, 6.5 Hz, 1H), 2.58-2.46 (m, 3H), 2.21 (s, 3H), 1.90-1.84 (m, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 204.8, 176.6, 76.0, 48.4, 30.6, 28.4, 27.9.



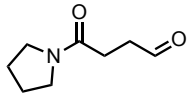
**(*S*)-4-Hydroxy-*N*-(1-phenylethyl)butanamide (365):** A solution of lactone **361** (500 mg, 5.61 mmol, 1.0 eq.) and amine **364** (3.62 mL, 28.1 mmol, 5.0 eq.) in PhMe (5 mL) was heated to reflux for 20 h. Upon cooling to room temperature, the reaction mixture was diluted with EtOAc (100 mL) and washed with 1N HCl (10 mL) and brine (10 mL). The organic phase was then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield alcohol **365**, which was used in the next step without further purification.

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.36-7.27 (m, 5H), 5.91 (bs, 1H), 5.12 (p, *J* = 7.2 Hz, 1H), 3.68 (t, *J* = 5.8 Hz, 2H), 2.39-2.34 (m, 2H), 1.90-1.84 (m, 2H), 1.49 (d, *J* = 6.9 Hz, 3H).



**4-Hydroxy-1-(pyrrolidin-1-yl)butan-1-one (369):** A solution of lactone **361** (1.00 g, 11.6 mmol, 1.0 eq.) and pyrrolidine (2.86 mL, 34.9 mmol, 3.0 eq.) in PhMe (10 mL) was stirred at room temperature for 19 h. Upon completion of the reaction, the solvent was removed *in vacuo* to afford crude alcohol **369**, which was used immediately in the next step without further purification. Spectral data matched reported values.[202]

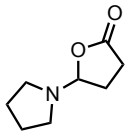
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 3.70 (t, *J* = 5.4 Hz, 2H), 3.47 (t, *J* = 6.8 Hz, 2H), 2.42 (t, *J* = 6.8 Hz, 2H), 2.46 (t, *J* = 6.5 Hz, 2H), 1.99-1.82 (m, 6H).



**4-Oxo-4-(pyrrolidin-1-yl)butanal (370):** A solution of freshly distilled $(COCl)_2$ (1.60 mL, 18.5 mmol, 1.6 eq.) in $CH_2Cl_2$ (50 mL) was cooled to -78 ºC and DMSO (2.64 mL, 37.2 mmol, 3.2 eq.) was added dropwise. After stirring for 20 min at -78 ºC, a solution of crude alcohol **369** (11.6 mmol, 1.0 eq.) in $CH_2Cl_2$ (10 mL) was added dropwise. After an additional 20 min, $NEt_3$ (8.10 mL, 58.1 mmol, 5.0 eq.) was added. The cooling bath was removed after 40 min, and the reaction mixture was allowed to warm over 30 min, before quenching with $H_2O$ (10 mL). The layers were separated and the aqueous phase was extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to yield aldehyde **370** (1.74 g, 97%). Spectral data matched reported values.[203]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 9.85 (s, 1H), 3.44 (t, *J* = 6.8 Hz, 4H), 2.82 (t, *J* = 6.5 Hz, 2H), 2.57 (t, *J* = 6.5 Hz, 2H), 1.99-1.93 (m, 2H), 1.88-1.81 (m, 2H).

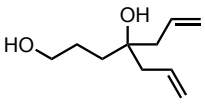
$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 201.2, 169.4, 46.4, 45.7, 38.4, 27.0, 26.0, 24.3.



**5-(Pyrrolidin-1-yl)dihydrofuran-2(3*H*)-one (371):** To a flask containing THF (30 mL) was added TBAF (1.02 mL, 1.02 mmol, 0.1 eq., 1.0 M in THF) followed by a solution of aldehyde **370** (1.58 g, 10.2 mmol, 1.0 eq.) and allyltrimethylsilane (1.78 mL, 11.2 mmol, 1.1 eq.) in THF (10 mL). The resulting solution was then stirred at reflux for 11 h. Upon cooling to room temperature the reaction mixture was quenched with 1N HCl (8 mL) and extracted with $Et_2O$ (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (EtOAc) to yield lactone **371** (743 mg, 47%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 4.10 (dd, *J* = 9.9, 2.6 Hz, 1H), 3.52-3.46 (m, 2H), 3.43 (t, *J* = 6.7 Hz, 2H), 2.70 (ddd, *J* = 17.4, 7.9, 3.1 Hz, 1H), 2.50 (ddd, *J* = 17.4, 9.8, 3.1 Hz, 1H), 2.42-2.35 (m, 1H), 2.23-2.14 (m, 1H), 2.02-1.96 (m, 2H), 1.92-1.85 (m, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 171.9, 82.9, 46.7, 46.0, 30.9, 26.1, 26.0, 24.3.

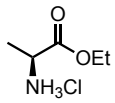


**4-Allylhept-6-ene-1,4-diol (372):** A suspension of lactone **361** (86 mg, 1.00 mmol, 1.0 eq.), NaOMe (0.05 mL, 0.25 mmol, 0.25 eq., 5.4 M in MeOH), and MeO(Me)NH-HCl (116 mg, 1.20 mmol, 1.2 eq.) in THF (20 mL) was cooled to -40 ºC and allylmagnesium bromide (8.0 mL, 8.00 mmol, 8.0 eq., 1.0 M in THF) was added dropwise. After stirring for 45 min at that temperature, the reaction mixture was quenched with 1N HCl (5 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 1:1) to yield diol **372** (55 mg, 32%). Spectral data matched reported values.[204]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.88-5.77 (m, 2H), 5.13-5.07 (m, 4H), 3.61 (t, *J* = 6.0 Hz, 2H), 2.67 (bs, 2H), 2.28-2.18 (m, 4H), 1.68-1.61 (m, 2H), 1.55-1.52 (m, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 133.6, 118.6, 73.1, 63.0, 43.6, 35.8, 26.4.

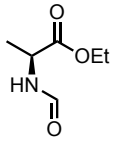
**Experimental Procedures: Section 3.4**



**Ethyl-*L*-alaninate hydrochloride (385):** A solution of (L)-alanine (**384**, 10.0 g, 112 mmol, 1.0 eq.) in EtOH (200 mL) was cooled to 0 ºC and $SOCl_2$ (12.3 mL, 168 mmol, 1.5 eq.) was added dropwise. The cooling bath was removed and the resulting solution was stirred

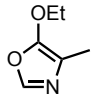
at room temperature for 48 h. Upon completion of the reaction, the solvent was removed *in vacuo* to yield crude ester **385**, which was used without further purification. Spectral data matched reported values.[205]

$^1$H NMR (400 MHz, $CD_3OD$) ∂ 4.30 (q, *J* = 6.9 Hz, 2H), 4.08 (q, *J* = 7.3 Hz, 1H), 1.54 (d, *J* = 7.2 Hz, 3H), 1.32 (t, *J* = 7.2 Hz, 3H).



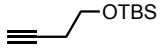

**Ethyl formyl-*L*-alaninate (386):** A solution of crude ester **385** (112 mmol, 1.0 eq.) in triethyl orthoformate (56 mL, 337 mmol, 3.0 eq.) was heated to reflux for 1 h, then cooled back to room temperature. Once the reaction mixture had cooled, the excess triethyl orthoformate was removed *in vacuo*. The crude residue was then purified by flash column chromatography (EtOAc) to yield formamide **386** (15.9 g, 97%). Spectral data matched reported values.[206]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 8.18 (s, 1H), 6.27 (bs, 1H), 4.65 (p, *J* = 7.1 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 1.44 (d, *J* = 7.0 Hz, 3H), 1.28 (t, *J* = 7.0 Hz, 3H).




**5-Ethoxy-4-methyloxazole (375):** A three-neck flask fitted with a condenser, mechanical stirrer, and an addition funnel was charged with MgO (24.3 g), celite (24.3 g), and $CHCl_3$ (470 mL). The resulting heterogeneous mixture was stirred and $P_2O_5$ (80.5 g) was added. A solution of formamide **386** (15.9 g, 109 mmol, 1.0 eq.) in $CHCl_3$ (40 mL) was then added dropwise via the addition funnel. Once the addition was complete, the reaction mixture was heated to reflux and stirred at that temperature for 18 h. When the reaction had cooled down to room temperature, the liquids were decanted and the residue was quenched with the slow addition of saturated $NaHCO_3$ (100 mL) at 0 ºC. After 30 min of vigorous stirring, the solids were filtered off. The filtrate was then extracted with $CH_2Cl_2$ (2 x 200 mL) and the extracts were combined with the initially decanted organics. The combined organic extracts were washed with saturated $NaHCO_3$ (100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by vacuum distillation (P ≈ 50 mmHg, T = 70-75 ºC) to yield oxazole **375** (3.35 g, 24%). Spectral data matched reported values.[207]

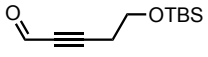
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.34 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.01 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H).




**(But-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane (388):** To a solution of but-3-yn-1-ol (1.00 g, 14.3 mmol, 1.0 eq.), TBSCl (3.23 g, 21.4 mmol, 1.5 eq.), and DMAP (spatula tip) in

$CH_2Cl_2$ (15 mL) was added $NEt_3$ (3.98 mL, 28.5 mmol, 2.0 eq.). The resulting mixture was stirred at room temperature for 24 h, then quenched with saturated $NH_4Cl$ (10 mL). The layers were separated and the aqueous phase was further extracted with $CH_2Cl_2$ (2 x 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes) to yield silyl ether **388** (1.89 g, 72%). Spectral data matched reported values.[208]

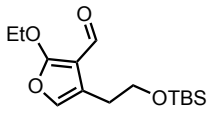
$^1H$ NMR (400 MHz, $CDCl_3$) ∂ 3.74 (t, *J* = 7.1 Hz, 2H), 2.40 (td, *J* = 7.0, 2.6 Hz, 2H), 1.96 (t, *J* = 2.6 Hz, 1H), 0.90 (s, 9H), 0.08 (s, 6H).




**5-((*tert*-Butyldimethylsilyl)oxy)pent-2-ynal (389):** A solution of alkyne **388** (217 mg, 1.17 mmol, 1.0 eq.) in THF (8 mL) was cooled to -78 °C and $^n$BuLi (0.71 mL, 1.41 mmol, 1.2 eq., 2.0 M solution in hexanes) was added dropwise. After 45 min, N-formyl morpholine (0.17 mL, 1.65 mmol, 1.4 eq.) was added dropwise and the cooling bath was removed immediately following the addition. After stirring at room temperature for 2 h, the reaction mixture was poured into 10% $KH_2PO_4$ solution (5 mL) at 0 °C. The resulting biphasic mixture was extracted with $Et_2O$ (30 mL) and the organic extract was further washed with brine (5 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* at 0 °C. The crude residue was further purified by flash column chromatography (petroleum ether) to yield aldehyde **389** (237 mg, 95%). Spectral data matched reported values.[209]

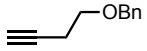
$^1H$ NMR (400 MHz, $CDCl_3$) ∂ 9.17 (s, 1H), 3.80 (t, *J* = 6.9 Hz, 2H), 2.62 (t, *J* = 6.9 Hz, 2H), 0.89 (s, 9H), 0.08 (s, 6H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) ∂ 176.9, 96.1, 82.2, 60.5, 25.7, 23.5, 18.2, -5.4.



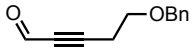

**4-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-ethoxyfuran-3-carbaldehyde (390):** A solution of aldehyde **389** (237 mg, 1.12 mmol, 1.0 eq.) and oxazole **375** (142 mg, 1.12 mmol, 1.0 eq.) in PhMe (0.75 mL) was deoxygenated by bubbling argon through the stirring solution for 15 min. The reaction vessel was sealed and heated to 125 °C for 13 h. The reaction mixture was then cooled to room temperature and loaded directly onto a column for purification via flash column chromatography (hexanes to hexanes/EtOAc, 9:1) to yield furan **390** (132 mg, 40%).

$^1H$ NMR (400 MHz, $CDCl_3$) ∂ 9.79 (s, 1H), 6.75 (d, *J* = 0.6 Hz, 1H), 4.44 (q, *J* = 7.4 Hz, 2H), 3.80 (t, *J* = 6.4 Hz, 2H), 2.80 (td, *J* = 6.3, 0.9 Hz, 2H), 1.45 (t, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H).



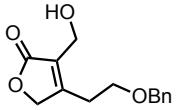
**((But-3-yn-1-yloxy)methyl)benzene (392):** To a solution of but-3-yn-1-ol (1.00 g, 14.3 mmol, 1.0 eq.) in THF (15 mL) was added NaH (514 mg, 21.4 mmol, 1.5 eq.). The resulting suspension was stirred for 40 min before the addition of BnBr (1.87 mL, 15.7 mmol, 1.1 eq.). The reaction mixture was stirred at room temperature for 17 h, then quenched by the addition of saturated $NH_4Cl$ (10 mL). The mixture was extracted with $Et_2O$ (100 mL) and the organic extract was washed with $H_2O$ (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to yield alkyne **392** (2.28 g, >96%). Spectral data matched reported values.[210]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.39-7.27 (m, 5H), 4.57 (s, 2H), 3.61 (t, *J* = 7.2 Hz, 2H), 2.51 (td, *J* = 7.0, 2.7 Hz, 2H), 2.00 (t, *J* = 2.7 Hz, 1H).



**5-(Benzyloxy)pent-2-ynal (393):** A solution of alkyne **392** (1.08 g, 6.74 mmol, 1.0 eq.) in THF (60 mL) was cooled to -78 ºC and $^n$BuLi (3.85 mL, 8.09 mmol, 1.2 eq., 2.1 M solution in hexanes) was added dropwise. After 1 h, N-formyl morpholine (0.95 mL, 9.44 mmol, 1.4 eq.) was added dropwise and the cooling bath was removed immediately following the addition. After stirring at room temperature for 1.5 h, the reaction mixture was poured into 10% $KH_2PO_4$ solution (25 mL) at 0 ºC. The resulting biphasic mixture was extracted with $Et_2O$ (2 x 100 mL) and the organic extract was further washed with brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was further purified by flash column chromatography (hexanes/EtOAc, 9:1) to yield aldehyde **393** (911 mg, 72%, ~70% purity). Spectral data matched reported values.[211]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 9.18 (s, 1H), 7.36-7.28 (m, 5H), 4.56 (s, 2H), 3.65 (t, *J* = 6.5 Hz, 2H), 2.72 (t, *J* = 6.5 Hz, 2H).

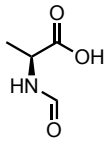


**4-(2-(Benzyloxy)ethyl)-3-(hydroxymethyl)furan-2(5*H*)-one (396):** A solution of aldehyde **381** (774 mg, 4.11 mmol, 1.0 eq.) and oxazole **375** (575 mg, 4.52 mmol, 1.1 eq.) in PhMe (0.5 mL) was heated in a microwave at 130 ºC for 1 h to yield crude furan **394** [$^1$H NMR (400 MHz, $CDCl_3$) ∂ 9.90 (s, 1H), 7.50-7.28 (m, 5H), 6.89 (d, *J* = 0.8 Hz, 1H), 4.65 (s, 2H), 4.56 (q, *J* = 7.1 Hz, 2H), 3.83 (t, *J* = 6.5 Hz, 2H), 3.05 (td, *J* = 6.5, 1.0 Hz, 2H), 1.57 (t, *J* = 7.0 Hz, 3H)]. The crude furan **394** thus obtained was dissolved in MeOH (40 mL) and cooled to 0 ºC and $NaBH_4$ (311 mg, 8.22 mmol, 2.0 eq.) was added slowly. The reaction mixture was stirred at 0 ºC for 1 h before the solvent was removed *in vacuo* to yield crude alcohol **395** [$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.38-7.28 (m, 5H), 6.75 (s, 1H), 4.53 (s, 2H), 4.34 (s, 2H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.64 (t, *J* = 5.8 Hz, 2H), 2.68 (t, *J* = 5.8 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H)]. The crude residue was

dissolved in $CH_3CN$ (48 mL) and 2N HCl (24 mL) was added dropwise. The resulting solution was stirred at room temperature for 45 min, then diluted with EtOAc (150 mL) and washed with saturated $NaHCO_3$ (2 x 30 mL) and brine (30 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc 1:1 to EtOAc) to yield butenolide **396** (413 mg, 40% over three steps).

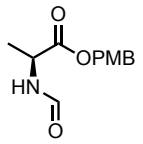
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.38-7.28 (m, 5H), 4.73 (s, 2H), 4.51 (s, 2H), 4.37 (d, *J* = 1.3 Hz, 2H), 3.63 (t, *J* = 6.0 Hz, 2H), 2.79 (t, *J* = 6.0 Hz, 2H), 2.74 (bs, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 160.5, 137.0, 128.5, 128.1, 127.8, 127.2, 73.4, 72.2, 67.0, 55.1, 27.6.



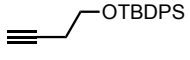
**Formyl-*L*-alanine (398):** To a solution of (L)-alanine (**384**, 500 mg, 5.61 mmol, 1.0 eq.) in DMF (3 mL) was added HCOOH (0.36 mL, 8.54 mmol, 1.7 eq.) and the resulting solution was heated to reflux for 3 h. Once the reaction had cooled back to room temperature, the solvent was removed *in vacuo* and the residue was recrystallized from PhMe to yield aldehyde **398** (464 mg, 71%, ~70% purity). Spectral data matched reported values.[212]

$^1$H NMR (400 MHz, DMSO-$d_6$) ∂ 8.36 (bd, *J* = 6.6 Hz, 1H), 7.99 (s, 1H), 4.27 (p, *J* = 7.3 Hz, 1H), 1.26 (d, *J* = 7.2 Hz, 3H).



**4-Methoxybenzyl formyl-*L*-alaninate (399):** A solution of acid **398** (150 mg, 1.28 mmol, 1.0 eq.), PMBOH (0.17 mL, 1.41 mmol, 1.1 eq.) and DMAP (469 mg, 3.84 mmol, 3.0 eq.) in $CH_2Cl_2$ (13 mL) was cooled to 0 ºC and EDCI-HCl (491 mg, 2.56 mmol, 2.0 eq.) was added. The reaction mixture was allowed to slowly warm to room temperature and stirred for 23 h. The reaction mixture was then quenched with 1N HCl (10 mL) and extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 2:1 to EtOAc) to yield ester **399** (235 mg, 77%).

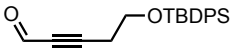
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 8.18 (s, 1H), 7.29 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.18 (bs, 1H), 5.16-5.09 (m, 2H), 4.73-4.66 (m, 1H), 3.81 (s, 3H), 1.43 (d, *J* = 7.2 Hz, 3H).



**(But-3-yn-1-yloxy)(*tert*-butyl)diphenylsilane (403):** To a solution of but-3-yn-1-ol (3.00 g, 42.8 mmol, 1.0 eq.) in $CH_2Cl_2$ (240 mL) was added ImH (3.21 g, 47.1

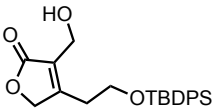
mmol, 1.1 eq.) followed by TBDPSCl (12.2 mL, 47.1 mmol, 1.1 eq.) and the resulting mixture was stirred at room temperature for 48 h. Upon completion, the reaction mixture was filtered through a plug of $SiO_2$ (eluting with $CH_2Cl_2$) and the solvent was removed *in vacuo* to yield crude alkyne **403**, which was used without further purification. Spectral data matched reported values.[213]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.70-7.67 (m, 4H), 7.44-7.37 (m, 6H), 3.79 (t, *J* = 7.2 Hz, 2H), 2.46 (td, *J* = 7.1, 2.6 Hz, 2H), 1.95 (t, *J* = 2.5 Hz, 1H), 1.06 (s, 9H).




**5-((*tert*-Butyldiphenylsilyl)oxy)pent-2-ynal (404):** A solution of crude alkyne **403** (42.8 mmol, 1.0 eq.) in THF (400 mL) was cooled to -78 ºC and $^n$BuLi (21.4 mL, 51.4 mmol, 1.2 eq., 2.4 M solution in hexanes) was added dropwise. After 1 h, N-formyl morpholine (6.02 mL, 59.9 mmol, 1.4 eq.) was added rapidly and the cooling bath was removed immediately following the addition. After stirring at room temperature for 50 min, the reaction mixture was poured into 10% $KH_2PO_4$ solution (200 mL) at 0 ºC. The resulting biphasic mixture was extracted with $Et_2O$ (2 x 250 mL) and the organic extract was further washed with brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was further purified by flash column chromatography (hexanes) to yield aldehyde **404** (10.8 g, 75% over two steps, ~85% purity). Spectral data matched reported values.[214]

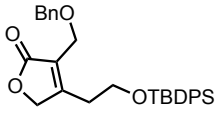
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 9.15 (s, 1H), 7.69-7.66 (m, 4H), 7.45-7.38 (m, 6H), 3.84 (t, *J* = 6.6 Hz, 2H), 2.67-2.64 (m, 2H), 1.07 (s, 9H).




**4-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-3-(hydroxymethyl)furan-2(5*H*)-one (407):** A mixture of aldehyde **404** (8.13 g, 26.4 mmol, 1.0 eq.) and oxazole **375** (3.35 g, 26.4 mmol, 1.0 eq.) was heated neat in a sealed tube at 100 ºC for 11 h to yield crude furan **405** [1H NMR (400 MHz, $CDCl_3$) ∂ 9.71 (s, 1H), 7.63-7.61 (m, 4H), 7.41-7.33 (m, 6H), 6.74, (d, *J* = 0.5 Hz, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 3.88 (t, *J* = 6.2 Hz, 2H), 2.87-2.84 (m, 2H), 1.45 (t, *J* = 7.4 Hz, 3H), 1.03 (s, 9H)]. The crude furan **405** thus obtained was dissolved in MeOH (150 mL) and cooled to 0 ºC and $NaBH_4$ (1.99 mg, 26.4 mmol, 2.0 eq.) was added slowly. The reaction mixture was stirred at 0 ºC for 20 min before the solvent was removed *in vacuo* to yield crude alcohol **406** [1H NMR (400 MHz, $CDCl_3$) ∂ 7.63-7.61 (m, 4H), 7.42-7.34 (m, 6H), 6.72 (s, 1H), 4.29 (s, 2H), 4.20-4.11 (m, 2H), 3.80 (t, *J* = 6.7 Hz, 2H), 2.64 (t, *J* = 6.7 Hz, 2H), 1.37-1.32 (m, 3H), 1.03 (s, 9H)]. The crude residue was dissolved in $CH_3CN$ (100 mL) and 2N HCl (50 mL) was added dropwise. The resulting solution was stirred at room temperature for 30 min, then diluted with EtOAc (250 mL) and washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL). The organic

phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc 2:1 to 1:1) to yield butenolide **407** (3.71 g, 36% over three steps).

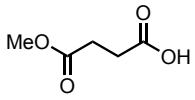
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.61-7.59 (m, 4H), 7.48-7.38 (m, 6H), 4.73 (s, 2H), 4.35 (s, 2H), 3.81 (t, *J* = 6.1 Hz, 2H), 2.71 (t, *J* = 5.8 Hz, 2H), 1.05 (s, 9H).




**3-((Benzyloxy)methyl)-4-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl) furan-2(5*H*)-one (408):** A solution of butenolide **407** (2.61 g, 6.58 mmol, 1.0 eq.) in PhMe (75 mL) was cooled to 0 ºC and $Ag_2O$ (1.83 g, 7.90 mmol, 1.2 eq.) was added followed by BnBr (1.01 mL, 9.21 mmol, 1.4 eq.). After the addition, the cooling bath was removed and the flask was shielded from light. After 48 h, an additional portion of $Ag_2O$ (1.83 g, 7.90 mmol, 1.2 eq.) and BnBr (1.01 mL, 9.21 mmol, 1.4 eq.) and the reaction mixture was stirred at room temperature for an additional 24 h. Once the reaction mixture was complete, the heterogeneous mixture was filtered through a plug of celite and the filtrate was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 6:1 to 4:1) to yield benzyl ether **408** (2.76 g, 86%).

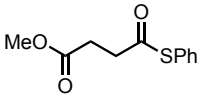
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.60-7.58 (m, 4H), 7.44-7.36 (m, 6H), 7.31-7.28 (m, 5H), 4.77 (s, 2H), 4.50 (s, 2H), 4.20 (s, 2H), 3.81 (t, *J* = 5.6 Hz, 2H), 2.74 (t, *J* = 5.9 Hz, 2H), 1.03 (s, 9H).

**Experimental Procedures: Section 3.5**




**4-Methoxy-4-oxobutanoic acid (414):** A solution of succinic acid (**413**, 10.0 g, 99.9 mmol, 1.0 eq.) in MeOH (10 mL) was heated to reflux until the solution had become homogeneous, approximately 1 h. The reaction mixture was cooled back to room temperature and stirred for 15 h. The solvents were then removed *in vacuo* to yield crude acid **414** which was used without further purification. Spectral data matched reported values.[215]

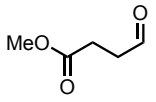
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 10.4 (bs, 1H), 3.70 (s, 3H), 2.71-2.67 (m, 2H), 2.64-2.60 (m, 2H).



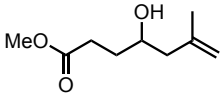

**Methyl 4-oxo-4-(phenylthio)butanoate (415):** A solution of crude acid **414** (99.9 mmol, 1.0 eq.), NMI (23.9 mL, 300 mmol, 3.0 eq.) in $CH_3CN$ (60 mL) was cooled to 0 ºC and to the cooled solution was added a solution of TsCl (22.9 g, 120 mmol, 1.2 eq.) in $CH_3CN$ (30 mL) via cannula over 30 min. The flask was washed with an additional portion of

$CH_3CN$ (25 mL). The reaction mixture was stirred for an additional 30 min and to the resulting thick white slurry, PhSH (10.2 mL, 99.9 mmol, 1.0 eq.) was added as the reaction became more homogeneous. After stirring for an additional 1.5 h, the reaction mixture was quenched by the addition of $H_2O$ (30 mL) and extracted with EtOAc (3 x 150 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1) to yield thioester **415** (18.5 g, 83% over two steps). Spectral data matched reported values.[216]

$^1H$ NMR (400 MHz, $CDCl_3$) ∂ 7.43-7.39 (m, 5H), 3.70 (s, 3H), 3.00 (t, *J* = 7.2 Hz, 2H), 2.69 (t, *J* = 7.2 Hz, 2H).



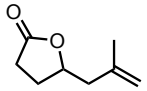

**Methyl 4-oxobutanoate (357):** To a suspension of thioester **415** (1.97 g, 8.78 mmol, 1.0 eq.) and $MgSO_4$ (spatula tip) in $Me_2CO$ (25 mL) was added 10% Pd/C (280 mg, 0.264 mmol, 0.03 eq.) and the resulting vigorously stirred suspension was cooled to 0 ºC before the addition of $Et_3SiH$ (4.21 mL, 26.4 mmol, 3.0 eq.) dropwise. The reaction mixture was stirred for an additional 1.5 h, then filtered through a plug of celite. The filtrate was concentrated *in vacuo* and the resulting crude residue was purified by flash column chromatography (pet. ether/$Et_2O$, 4:1) to yield aldehyde **357** (760 mg, 75%). Spectral data matches previously prepared sample.




**Methyl 4-hydroxy-6-methylhept-6-enoate (412):** A biphasic mixture of aldehyde **357** (727 mg, 6.26 mmol, 1.0 eq.) and methallyl chloride (1.13 g, 12.5 mmol, 2.0 eq.) in saturated $NH_4Cl$ (8 mL) and THF (2 mL) was cooled to 0 ºC before the slow addition of Zn dust (1.28 g, 18.8 mmol, 3.0 eq.). After the addition, the reaction flask was removed form the cooling bath and placed in an ultrasound bath for 3 h. The reaction mixture was stopped by the addition of $H_2O$ (15 mL) and then filtered through a cotton plug. The filtrate was extracted with $CH_2Cl_2$ (3 x 60 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 3:1) to yield alcohol **412** (596 mg, 55%).

$^1H$ NMR (400 MHz, $CDCl_3$) ∂ 4.88 (m, 1H), 4.79 (s, 1H), 3.79-3.73 (m, 1H), 3.68 (s, 3H), 2.52-2.47 (m, 2H), 2.22-2.10 (m, 2H), 1.90-1.82 (m, 2H), 1.75 (s, 3H), 1.72-1.67 (m, 1H).

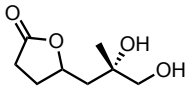
$^{13}C$ NMR (100 MHz, $CDCl_3$) ∂ 171.2, 140.6, 113.9, 79.3, 51.0, 43.6, 28.8, 27.8, 23.0.



**5-(2-Methylallyl)dihydrofuran-2(3*H*)-one ((±)-411):** To a solution of alcohol **412** (1.38 g, 8.01 mmol, 1.0 eq.) in PhMe (120 mL) was added CSA (558 mg, 2.40 mmol, 0.3 eq.) and the resulting solution was stirred at room temperature for 2 h. The reaction mixture was then quenched with saturated $NaHCO_3$ (20 mL) and extracted with EtOAc (100 mL). The organic extract was washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield crude lactone **(±)-411**, which was used without further purification. Spectral data matched reported values.[217]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 4.87-4.86 (m, 1H), 4.79 (m, 1H), 4.68-4.62 (m, 1H), 2.55-2.47 (m, 3H), 2.36-2.26 (m, 2H), 1.95-1.87 (m, 1H), 1.77 (s, 3H).

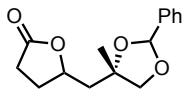
$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 177.1, 140.6, 113.9, 79.3, 43.6, 28.7, 27.8, 23.0.



**5-((*S*)-2,3-Dihydroxy-2-methylpropyl)dihydrofuran-2(3*H*)-one (417):** A solution of crude lactone **(±)-411** (8.01 mmol, 1.0 eq.) in $^t$BuOH (50 mL) and $H_2O$ (50 mL) was cooled to 0 ºC and AD mix α (11.2 g) was added. The resulting biphasic solution was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was quenched by the addition of $Na_2SO_3$ (1.11 g, 1.1 eq.) and stirred for 1 h. Brine (30 mL) was then added and the reaction mixture was extracted with EtOAc (4 x 100 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to yield diol **417** (1.03 g, 74% over two steps) as an inseparable mixture of diastereomers.

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 4.83-4.73 (m, 1H), 3.55-3.46 (m, 2H), 2.56-2.51 (m, 2H), 2.43-2.35 (m, 1H), 2.02-1.79 (m, 5H), 1.26 (s, 3H).

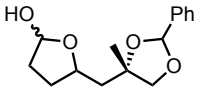
$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 177.5/177.2, 78.0/77.7, 71.8 (2), 69.9/69.3, 44.2/43.9, 29.3/29.2, 28.7/28.6, 24.6/23.5.



**5-(((4*S*)-4-Methyl-2-phenyl-1,3-dioxolan-4-yl)methyl)dihydrofuran-2(3*H*)-one (423):** A solution of diol **417** (215 mg, 1.23 mmol, 1.0 eq.) $CH_2Cl_2$ (4 mL) was cooled to 0 ºC and $PhCH(OMe)_2$ (207 mg, 1.36 mmol, 1.1 eq.) and *p*TsOH (23 mg, 0.123 mmol, 0.1 eq.) was added. The reaction mixture was allowed to warm to room temperature and after 6 h, an additional portion of $PhCH(OMe)_2$ (94 mg, 0.618, 0.5 eq.) was added. The reaction mixture was stirred at room temperature for an additional 20 h, then quenched with $NEt_3$ (5 drops). The solvents were removed *in vacuo* and the crude residue was purified by flash

column chromatography (hexanes/EtOAc, 4:1 to 2:1) to yield benzylidene **423** (235 mg, 73%) as an inseparable mixture of 4 diastereomers.

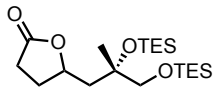
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.50-7.35 (m, 5H), 5.94-5.74 (s, 1H), 4.84-4.70 (m, 1H), 4.27-3.76 (m, 2H), 2.49-2.30 (m, 3H), 2.16-1.85 (m, 3H), 1.49-1.39 (s, 3H).




**5-(((4*S*)-4-Methyl-2-phenyl-1,3-dioxolan-4-yl)methyl)tetrahydrofuran-2-ol (424):** A solution of benzylidene **423** (235 mg, 0.896 mmol, 1.0 eq.) in $CH_2Cl_2$ (5 mL) was cooled to -78 ºC and a solution of DIBAL (2.69 mL, 2.69 mmol, 3.0 eq., 1.0 M solution in hexanes) was added dropwise. After 3 h at -78 ºC, the reaction mixture was quenched with MeOH (4 mL) and poured on to a vigorously stirred solution of Rochelle's salt (10 mL). After 2 h, the biphasic mixture was extracted with $CH_2Cl_2$ (3 x 30 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to yield lactol **424** (154 mg, 65%) as a mixture of diastereomers.

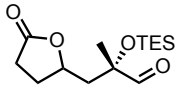
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.52-7.36 (m, 5H), 5.93-5.87 (m, 1H), 5.58-5.46 (m, 1H), 4.48-4.26 (m, 1H), 4.23-3.27 (m, 2H), 2.47-2.39 (bs, 1H), 2.46-1.75 (m, 5H), 1.61-1.58 (m, 1H), 1.46-1.44 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 138.3-137.7, 129.2, 128.3, 126.7-126.6, 104.0-103.3, 102.8-102.5, 98.4-98.3, 80.9-80.4, 77.3-76.2, 75.2-74.3, 47.4-44.0, 33.8, 33.0-32.9, 31.3, 30.8-30.3, 25.0-24.5, 22.8-22.7.



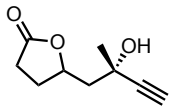

**5-((*S*)-2-Methyl-2,3-bis((triethylsilyl)oxy)propyl)dihydrofuran-2(3*H*)-one (426):** To a solution of diol **417** (394 mg, 2.26 mmol, 1.0 eq.), DMAP (spatula tip), and ImH (385 mg, 5.65 mmol, 2.5 eq.) in DMF (5 mL) was added TESCl (0.80 mL, 4.75 mmol, 2.1 eq.). The reaction mixture was stirred at room temperature 17 h, then heated to 40 ºC for an additional 20 h. The reaction mixture was quenched with $H_2O$ (10 mL) and extracted with $Et_2O$ (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1) to yield silyl ether **426** (457 mg, 50%) as an inseparable mixture of diastereomers.

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 4.80-4.69 (m, 1H), 3.52-3.34 (m, 2H), 2.52-2.47 (m, 2H), 2.37-2.29 (m, 1H), 2.10-2.05 (m, 1H), 1.98-1.86 (m, 1H), 1.80-1.68 (m, 1H), 1.26/1.24 (s, 3H), 0.94 (t, $J$ = 7.9 Hz, 9H), 0.59 (t, $J$ = 8.0 Hz, 6H).



**(2*S*)-2-Methyl-3-(5-oxotetrahydrofuran-2-yl)-2-((triethylsilyl)oxy) propanal (428):** A solution of $(COCl)_2$ (0.29 mL, 3.33 mmol, 5.0 eq.) in $CH_2Cl_2$ (4 mL) was cooled to -40 ºC and DMSO (0.47 mL, 6.65 mmol, 10.0 eq.) was added dropwise. After 10 min, a solution of silyl ether **426** (268 mg, 0.665 mmol, 1.0 eq.) in $CH_2Cl_2$ (2 mL) was added dropwise. The reaction mixture was stirred at -40 ºC for 5 h at which time TLC analysis indicated the consumption of starting material. $NEt_3$ (1.86 mL, 13.3 mmol, 20.0 eq.) was then added and the reaction mixture was slowed to warm to room temperature and stirred for an additional 1 h. The reaction mixture was quenched with $H_2O$ (5 mL) and extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to yield aldehyde **428** (185 mg, >96%) as an inseparable mixture of diastereomers..

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 9.66/9.55 (s, 1H), 4.74-4.69 (m, 1H), 2.53-2.49 (m, 2H), 2.36-2.30 (m, 1H), 2.09-1.82 (m, 3H), 1.39/1.34 (s, 3H), 0.99-0.94 (m, 9H), 0.67-0.58 (m, 6H).



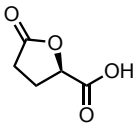
**5-((*S*)-2-Hydroxy-2-methylbut-3-yn-1-yl)dihydrofuran-2(3*H*)-one (418):**

To a suspension of aldehyde **428** (78 mg, 0.272 mmol, 1.0 eq.) and $K_2CO_3$ (75 mg, 0.545 mmol, 2.0 eq.) in MeOH (4 mL) was added phosphonate **135** (78 mg, 0.405 mmol, 1.5 eq.) as a solution in MeOH (0.2 mL). The reaction mixture was stirred at room temperature for 3 h, then diluted with $Et_2O$ (20 mL) and washed with saturated $NaHCO_3$ (5 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1 to 2:1) to yield alkyne **419** (13 mg, 28%) as an inseparable mixture of diastereomers.

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.05-4.98/4.87-4.80 (m, 1H), 2.57-2.39 (m, 4H), 2.21-1.92 (m, 3H), 1.60/1.56 (s, 3H).

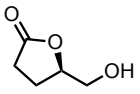
$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 176.8, 86.3, 78.3/78.1, 72.6/72.5, 66.7/66.6, 48.0/47.9, 30.8/30.2, 29.6/29.2, 28.6/28.1.

**Experimental Procedures: Section 3.6**



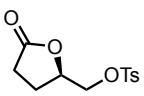
**(*R*)-5-Oxotetrahydrofuran-2-carboxylic acid (442):** A solution of D-glutamic acid (30.0 g, 204 mmol, 1.0 eq.) in $H_2O$ (120 mL) was cooled to 0 ºC and concentrated HCl (60 mL) was added slowly. To the resulting solution, $NaNO_2$ (21.1 g, 306 mmol, 1.5 eq.) was added as a solution in $H_2O$ (60 mL) dropwise via addition funnel over 45 min. The resulting solution was allowed to warm to room temperature and stirred for 24 h. The solvent was then removed *in vacuo* and the resulting white paste was taken up in EtOAc (200 mL) and filtered. The filtrate was dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was taken up in PhMe (50 mL) and concentred *in vacuo* once more to yield crude acid **442**, which was used without further purification. Spectral data matched reported values.[218]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 10.47 (bs, 1H), 5.02-4.99 (m, 1H), 2.70-2.53 (m, 3H), 2.46-2.35 (m, 1H).



**(*R*)-5-(Hydroxymethyl)dihydrofuran-2(3*H*)-one (438):** A solution of crude acid **442** (204 mmol, 1.0 eq.) in THF (200 mL) was cooled to 0 ºC and $BH_3$•$Me_2S$ (24.0 mL, 255 mmol, 1.25 eq.) was added dropwise over 10 min. The resulting solution was allowed to warm slowly to room temperature and stirred for 15 h. The reaction mixture was then cooled back to 0 ºC and quenched by the slow addition of MeOH (50 mL). The solvent was removed *in vacuo*, an additional portion of MeOH (100 mL) was added, and the resulting solution was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 1:1) to yield alcohol **438** (11.3 g, 48% over two steps) as a colorless oil. Spectral data matched reported values.[219]

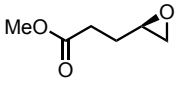
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 4.66-4.60 (m, 1H), 3.91 (dd, *J* = 12.5, 2.9 Hz, 1H), 3.65 (dd, *J* = 12.5, 4.3 Hz, 1H), 2.67-2.50 (m, 2H), 2.33-2.24 (m, 2H), 2.19-2.10 (m, 1H).



**(*R*)-(5-Oxotetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate (443):** A solution of alcohol **438** (11.3 g, 97.5 mmol, 1.0 eq.) in $CH_2Cl_2$ (160 mL) was cooled to 0 ºC before the addition $NEt_3$ (27.0 mL, 195 mmol, 2.0 eq.) and DMAP (1.19 g, 9.75 mmol, 0.1 eq.). TsCl (20.4 g, 107 mmol, 1.1 eq.) was then added in four portions over 15 min and the resulting solution was allowed to warm to room temperature and stirred for 14 h. The reaction mixture was then poured into $H_2O$ (50 mL) and extracted with $CH_2Cl_2$ (2 x 150 mL). The combined

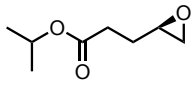
organic extracts were washed with $H_2O$ (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude tosylate was recrystallized from MeOH to yield pure tosylate **443** (16.1 g, 61%) as white crystals. Spectral data matched reported values.[220]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.76 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 4.69-4.64 (m, 1H), 4.17 (dd, *J* = 11.1, 3.3 Hz, 1H), 4.10 (dd, *J* = 11.1, 4.3 Hz, 1H), 2.60-2.45 (m, 2H), 2.43 (s, 3H), 2.36-2.28 (m, 1H), 2.13-2.03 (m, 1H).



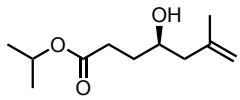
**Methyl (*R*)-3-(oxiran-2-yl)propanoate (437):** Tosylate **443** (500 mg, 1.11 mmol, 1.0 eq.) was added to a solution of freshly prepared NaOMe (2.22 mmol, 2.0 eq.) in MeOH (2 mL) and the resulting solution was stirred at room temperature for 30 min. The reaction mixture was quenched by the addition of AcOH (0.05 mL), diluted with $Et_2O$ (50 mL) and washed with saturated $NaHCO_3$ (5 mL) and brine (5 mL). The organic phase was dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (pet. ether/$Et_2O$, 2:1) to yield epoxide **437** (116 mg, 81%) as a colorless oil. Spectral data matched reported values of enantiomer.[130]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 3.69 (s, 3H), 3.00-2.96 (m, 1H), 2.76 (t, *J* = 4.4 Hz, 1H), 2.50 (dd, *J* = 4.9, 2.7 Hz, 1H), 2.47 (t, *J* = 7.3 Hz, 2H), 2.02-1.94 (m, 1H), (sextet, *J* = 7.2 Hz, 1H).



**Isopropyl (*R*)-3-(oxiran-2-yl)propanoate (445):** A solution of tosylate **443** (811 mg, 3.00 mmol, 1.0 eq.) in $^i$PrOH (9 mL) was heated to reflux before the addition of $K_2CO_3$ (415 mg, 3.00 mmol, 1.0 eq.) and the reaction mixture was stirred at reflux for 18 h. Upon cooling to room temperature, the crude reaction mixture was loaded directly onto $SiO_2$ and purified by flash column chromatography (pet. ether/$Et_2O$, 4:1) to yield epoxide **445** (338 mg, 71%) as a colorless oil.

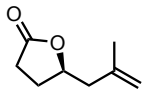
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.02 (septet, *J* = 6.3 Hz, 1H), 3.00-2.96 (m, 1H), 2.76 (t, *J* = 4.9 Hz, 1H), 2.50 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.42 (t, *J* = 7.2 Hz, 2H), 2.00-1.91 (m, 1H), 1.78 (sextet, *J* = 6.7 Hz, 1H), 1.23 (d, *J* = 6.2 Hz, 6H).



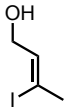
**Isopropyl (*R*)-4-hydroxy-6-methylhept-6-enoate (446):** To a suspension of CuI (329 mg, 1.73 mmol, 1.2 eq.) in $Et_2O$ (5 mL) at -20 ºC was added isopropenylmagnesium bromide (6.34 mL, 3.17 mmol, 2.2 eq., 0.5 M solution in THF) and the resulting mixture was stirred for 45 min. A solution of epoxide **445** (228 mg, 1.44 mmol, 1.0 eq.) in $Et_2O$ (3 mL) was then added dropwise via addition funnel. After stirring for an additional 10 min, the reaction mixture was quenched with saturated $NH_4Cl$ (4 mL) and extracted with $Et_2O$

(3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield crude alcohol **446**, which was used without further purification.

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.04-4.98 (m, 1H), 4.87 (m, 1H), 4.79 (m, 1H), 2.47-2.42 (m, 2H), 2.19-2.13 (m, 2H), 1.87-1.83 (m, 2H), 1.75 (s, 3H), 1.23 (d, *J* = 6.3 Hz, 6H).

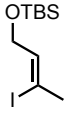


**(*R*)-5-(2-Methylallyl)dihydrofuran-2(3*H*)-one (411):** To a solution of crude alcohol **446** (1.44 mmol, 1.0 eq.) in $CH_2Cl_2$ (60 mL) was added TFA (3 drops) and the resulting mixture was stirred for 13 h. After removal of the solvents *in vacuo*, the crude residue was purified by flash column chromatography (pet. ether/$Et_2O$, 2:1) to yield lactone **411** (118 mg, 58% over two steps). Spectral data is consistent with the previously prepared racemic sample.



**(*Z*)-3-Iodobut-2-en-1-ol (452):** A solution of RedAl (7.21 mL, 21.4 mmol, 1.5 eq., 60% wt. in PhMe) in $Et_2O$ (16 mL) was cooled to 0 ºC and a solution of 2-butyn-1-ol (1.00 g, 14.3 mmol, 1.0 eq.) in $Et_2O$ (16 mL) was added dropwise via addition funnel. After the addition was complete, the addition funnel was rinsed with $Et_2O$ (2 mL) and the reaction mixture was allowed to warm slowly to room temperature. The resulting mixture was stirred at room temperature for 15 h before cooling back to 0 ºC. The excess RedAl was quenched with EtOAc (10 mL, dried over $Na_2SO_4$ prior to addition) and stirred for 30 min. The resulting solution was then cooled further to -78 ºC and a solution of $I_2$ (5.43 g, 21.4 mmol, 1.5 eq.) in THF (16 mL) was added dropwise via the addition funnel over 30 min. After the addition was complete, the cooling bath was removed and the reaction mixture was stirred for an additional 45 min, at which time the reaction mixture was poured into a vigorously stirred solution of Rochelle's salt (16 mL) and saturated $Na_2S_2O_3$ (16 mL) and stirred for 2 h. The layers were then separated and the aqueous phase was extracted with EtOAc (80 mL). The combined organic phases were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to yield iodide **452** (2.52 g, 89%). Spectral data matched reported values.[221]

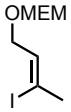
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.80-5.76 (m, 1H), 4.17 (m, 2H), 2.54 (m, 3H).



**(*Z*)-*tert*-Butyl((3-iodobut-2-en-1-yl)oxy)dimethylsilane (453):** To a solution of alcohol **452** (1.51 g, 7.63 mmol, 1.0 eq.) in $CH_2Cl_2$ (75 mL) was added ImH (779 mg, 11.4 mmol, 1.5 eq.) followed by TBSCl (1.26 g, 8.39 mmol, 1.1 eq.). After stirring for 17 h, the reaction

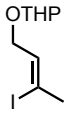
mixture was quenched with $H_2O$ (10 mL) and diluted with $CH_2Cl_2$ (75 mL). The layers were separated and the organic phase was washed with 2N HCl (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes to hexanes/EtOAc, 19:1) to yield silyl ether **453** (2.07 g, 87%). Spectral data matched reported values.[222]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.70-5.67 (m, 1H), 4.19-4.17 (m, 2H), 2.51 (q, *J* = 1.4 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 6H).



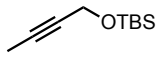

**(*Z*)-3-Iodo-1-((2-methoxyethoxy)methoxy)but-2-ene (454):** A solution of alcohol **452** (532 mg, 2.69 mmol, 1.0 eq.) and $^i$Pr$_2$NEt (1.40 mL, 8.06 mmol, 3.0 eq.) in $CH_2Cl_2$ (20 mL) was cooled to 0 ºC and MEMCl (0.61 mL, 5.37 mmol, 2.0 eq.) was added. The resulting solution was allowed to warm to room temperature and stirred for 26 h. The reaction mixture was quenched by the addition of $NEt_3$ (0.2 mL) and stirred for an additional 50 min before the solvent was removed *in vacuo*. The residue was taken up in $Et_2O$ (100 mL) and washed with saturated $NH_4Cl$ (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to yield iodide **454** (581 mg, 75%). Spectral data matched reported values.[223]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.74 (tq, *J* = 5.9, 1.5 Hz, 1H), 4.34 (s, 2H), 4.12-4.11 (m, 2H), 3.73-3.71 (m, 2H), 3.59-3.57 (m, 2H), 3.40 (s, 3H), 2.54 (q, *J* = 1.4 Hz, 3H).




**(*Z*)-2-((3-Iodobut-2-en-1-yl)oxy)tetrahydro-2*H*-pyran (455):** To a solution of alcohol **452** (1.17 g, 5.91 mmol, 1.0 eq.) and DHP (0.59 mL, 6.50 mmol, 1.1 eq.) in THF (10 mL) was added *p*TsOH (112 mg, 0.591 mmol, 0.1 eq.). The resulting solution was stirred at room temperature for 3 h, then quenched with saturated $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 6:1) to yield iodide **455** (1.29 g, 77%). Spectral data matched reported values.[224]

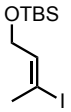
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.77-5.73 (m, 1H), 4.65-4.63 (m, 1H), 4.29-4.23 (m, 1H), 4.05-4.00 (m, 1H), 3.92-3.86 (m, 1H), 3.56-3.51 (m, 1H), 2.54 (q, *J* = 1.4 Hz, 3H), 1.86-1.79 (m, 1H), 1.76-1.69 (m, 1H), 1.63-1.51 (m, 4H).




**(But-2-yn-1-yloxy)(*tert*-butyl)dimethylsilane (456):** To a solution of 2-butyn-1-ol (5.00 g, 71.3 mmol, 1.0 eq.) in $CH_2Cl_2$ (300 mL) was added ImH (7.28 g, 107 mmol, 1.5 eq.)

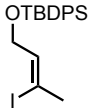
and TBSCl (11.8 g, 78.5 mmol, 1.1 eq.). The resulting solution was stirred at room temperature for 17 h, then diluted further with $CH_2Cl_2$ (100 mL) and washed with 2N HCl (40 mL) and brine (40 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes) to yield alkyne **456** (12.1 g, 92%). Spectral data matched reported values.[225]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 4.27 (q, *J* = 2.4 Hz, 2H), 1.83 (t, *J* = 2.4 Hz, 3H), 0.91 (s, 9H), 0.11 (s, 6H).



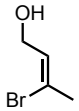

**(*E*)-*tert*-Butyl((3-iodobut-2-en-1-yl)oxy)dimethylsilane (457):** A suspension of $Cp_2ZrCl_2$ (2.38 g, 8.14 mmol, 1.5 eq.) in THF (14 mL) was cooled to 0 ºC and DIBAL (8.10 mL, 8.14 mmol, 1.5 eq., 1.0 M solution in hexanes) was added dropwise. After 30 min, alkyne **456** (1.00 g, 5.42 mmol, 1.0 eq.) was added as a solution in THF (3 mL) and the resulting suspension was stirred for an additional 45 min. The reaction mixture was then cooled to -78 ºC and solution of $I_2$ (1.79 g, 7.05 mmol, 1.3 eq.) in THF (7 mL) was added dropwise. After stirring at -78 ºC for 1 h, the reaction mixture was quenched with 2N HCl (5 mL) and warmed to room temperature. The reaction mixture was extracted with $Et_2O$ (100 mL) and the organic extracts were washed with saturated $Na_2S_2O_3$ (10 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes) to yield iodide **457** (1.02 g, 60%). Spectral data matched reported values.[226]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 6.31-6.28 (m, 1H), 4.12 (dd, *J* = 6.5, 0.6 Hz, 2H), 2.41 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H).



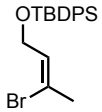

**(*Z*)-*tert*-Butyl((3-iodobut-2-en-1-yl)oxy)diphenylsilane (458):** To a solution of alcohol **452** (2.52 g, 12.7 mmol, 1.0 eq.) in $CH_2Cl_2$ (70 mL) was added ImH (1.30 g, 19.1 mmol, 1.5 eq.) followed by TBDPSCl (3.48 mL, 13.4 mmol, 1.05 eq.). After stirring for 17 h, the reaction mixture was quenched with $H_2O$ (25 mL) and diluted with $CH_2Cl_2$ (100 mL). The layers were separated and the organic phase was washed with 2N HCl (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes) to yield silyl ether **458** (4.01 g, 72%). Spectral data matched reported values.[227]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.69-7.67 (m, 4H), 7.43-7.37 (m, 6H), 5.79-5.75 (m, 1H), 4.24-4.22 (m, 2H), 2.48 (q, *J* = 1.5 Hz, 3H), 1.06 (s, 9H).



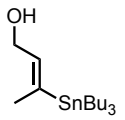
**(*Z*)-3-Bromobut-2-en-1-ol (459):** A solution of RedAl (7.21 mL, 21.4 mmol, 1.5 eq., 60% wt. in PhMe) in $Et_2O$ (16 mL) was cooled to 0 ºC and a solution of 2-butyn-1-ol (1.00 g, 14.3 mmol, 1.0 eq.) in $Et_2O$ (16 mL) was added dropwise via addition funnel over 15 min. After the addition was complete, the addition funnel was rinsed with $Et_2O$ (2 mL) and the reaction mixture was allowed to warm slowly to room temperature. The resulting mixture was stirred at room temperature for 15 h before cooling back to 0 ºC. The excess RedAl was quenched with EtOAc (10 mL, dried over $Na_2SO_4$ prior to addition) and stirred for 15 min. NBS (3.81 g, 21.4 mmol, 1.5 eq.) was then added in 500 mg portions at 5 min intervals. After the final portion was added, the resulting solution was stirred for an additional 15 min, then poured into a vigorously stirred solution of Rochelle's salt (16 mL) and saturated $Na_2S_2O_3$ (16 mL) and stirred for 2 h. The layers were then separated and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to yield bromide **459** (866 g, 40%, ~90% purity). Spectral data matched reported values.[228]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.91 (tq, *J* = 6.1, 1.4 Hz, 1H), 4.24 (m, 2H), 2.32 (q, *J* = 1.3, 3H).



**(*Z*)-((3-Bromobut-2-en-1-yl)oxy)(*tert*-butyl)diphenylsilane (460):** To a solution of alcohol **459** (620 mg, 4.11 mmol, 1.0 eq.) in $CH_2Cl_2$ (40 mL) was added ImH (419 mg, 6.16 mmol, 1.5 eq.) followed by TBDPSCl (1.12 mL, 4.31 mmol, 1.05 eq.). After stirring for 21 h, the reaction mixture was quenched with $H_2O$ (10 mL) and diluted with $CH_2Cl_2$ (150 mL). The layers were separated and the organic phase was washed with 2N HCl (25 mL), $H_2O$ (25 mL), and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes) to yield silyl ether **460** (1.36 g, 87%). Spectral data matched reported values.[228]

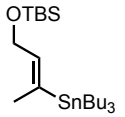
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.69-7.67 (m, 4H), 7.43-7.37 (m, 6H), 5.88 (tq, *J* = 5.4, 1.4 Hz, 1H), 4.31 (dq, *J* = 5.4, 1.4 Hz, 2H), 2.26 (q, *J* = 1.5 Hz, 3H), 1.06 (s, 9H).



**(*E*)-3-(Tributylstannyl)but-2-en-1-ol (461):** To a suspension of CuCN (1.28 g, 14.3 mmol, 2.0 eq.) in THF (56 mL) at -78 ºC was added $^n$BuLi (13.0 mL, 30.0 mmol, 4.2 eq., 2.3 M solution in hexanes) dropwise over 8 min. After stirring for an additional 5 min at -78 ºC, $Bu_3SnH$ (8.06 mL, 30.0 mmol, 4.2 eq.) was added dropwise and the resulting solution was

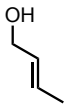
stirred for 1 h before MeOH (28 mL) was added dropwise via an addition funnel. The resulting solution was stirred further for 30 min then a solution of 2-butyn-1-ol (500 mg, 7.13 mmol, 1.0 eq.) in THF (7 mL) was added. After stirring for an additional 1.5 h, the reaction mixture was quenched by the addition of saturated $NH_4Cl/NH_4OH$ (9:1, 15 mL) and extracted with $Et_2O$ (100 mL). The organic phase was washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10:1 $SiO_2/K_2CO_3$, hexanes to hexanes/EtOAc, 9:1) to yield vinyl stannane **461** (1.22 g, 47%). Spectral data matched reported values.[229]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.77-5.73 (m, 1H), 4.26 (t, *J* = 5.4 Hz, 2H), 1.89 (m, 3H), 1.52-1.45 (m, 6H), 1.34-1.28 (m, 6H), 0.90-0.87 (m, 15H).



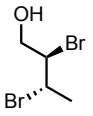

**(*E*)-*tert*-Butyldimethyl((3-(tributylstannyl)but-2-en-1-yl)oxy)silane (462):** To a solution of stannane **461** (1.22 g, 3.38 mmol, 1.0 eq.) in $CH_2Cl_2$ (40 mL) was added ImH (345 mg, 5.07 mmol, 1.5 eq.) and TBSCl (560 mg, 3.72 mmol, 1.1 eq.). The resulting reaction mixture was stirred at room temperature for 1.5 h, then diluted with $CH_2Cl_2$ (40 mL), washed with $H_2O$ (2 x 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10:1 $SiO_2/K_2CO_3$, hexanes to hexanes/EtOAc, 9:1) to yield vinyl stannane **462** (1.20 g, 75%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.67-5.64 (m, 1H), 4.30 (dd, *J* = 5.5, 0.5 Hz, 2H), 1.83 (m, 3H), 1.53-1.45 (m, 6H), 1.35-1.26 (m, 6H), 0.91-0.86 (m, 24H), 0.08 (s, 6H).



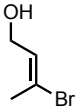

**(*E*)-But-2-en-1-ol (463):** A solution of RedAl (3.61 mL, 10.7 mmol, 1.5 eq., 60% wt. in PhMe) in $Et_2O$ (8 mL) was cooled to 0 ºC and a solution of 2-butyn-1-ol (500 mg, 7.13 mmol, 1.0 eq.) in $Et_2O$ (8 mL) was added dropwise and the reaction mixture was allowed to warm slowly to room temperature. The resulting mixture was stirred at room temperature for 15 h before cooling back to 0 ºC and the reaction mixture was quenched with 2N HCl (4 mL). The resulting solution vigorously stirred solution of Rochelle's salt (8 mL) and stirred for 30 min. The layers were then separated and the aqueous phase was extracted with EtOAc (2 x 30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo* at 0 ºC. The crude alkene **463** was used without further purification. Spectral data matched reported values.[230]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.75-5.64 (m, 2H), 4.09-4.06 (m, 2H), 1.72-1.71 (m, 3H).



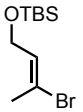
**2,3-Dibromobutan-1-ol (464):** To a solution of crude **463** (7.13 mmol, 1.0 eq.) in $CCl_4$ (4 mL) at -10 ºC was added $Br_2$ (0.37 mL, 7.13 mmol, 1.0 eq.) as a solution in $CCl_4$ (2 mL). The resulting mixture was stirred for 2 h, then diluted with $CH_2Cl_2$ (80 mL) and washed with saturated $Na_2S_2O_3$ (2 x 6 mL) and brine (6 mL). The organic phase was dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc) to yield dibromide **464** (1.07 g, 65% over two steps). Spectral data matched reported values.[231]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 4.41-4.34 (m, 1H), 4.27-4.22 (m, 1H), 4.10-4.07 (m, 2H), 1.91 (d, *J* = 6.6 Hz, 3H).



**(*E*)-3-Bromobut-2-en-1-ol (465):** To a solution of freshly distilled (from KOH) $^{i}Pr_2NH$ (1.55 mL, 11.1 mmol, 2.4 eq.) in THF (9 mL) at -78 ºC was added $^{n}$BuLi (4.8 mL, 11.1 mmol, 2.4 eq., 2.3 M solution in hexanes). After the addition was complete, the cooling bath was removed and the resulting solution was stirred at room temperature for 15 min. The solution of LDA thus formed was cooled back to -78 ºC and HMPA (0.40 mL, 2.30 mmol, 0.5 eq.) was added. Dibromide **464** (1.07 g, 4.61 mmol, 1.0 eq.) was then added via syringe pump (2.5 mL/hr) as a solution in THF (1.5 mL). The reaction mixture was stirred for an additional 4 h, then quenched with $H_2O$ (10 mL) and extracted with EtOAc (100 mL). The organic extract was dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to yield vinyl bromide **465** (294 mg, 42%). Spectral data matched reported values.[231]

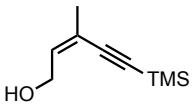
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 6.12-6.08 (m, 1H), 4.15-4.09 (m, 2H), 2.30 (s, 3H), 1.38 (bs, 1H).



**(*E*)-((3-Bromobut-2-en-1-yl)oxy)(*tert*-butyl)dimethylsilane (466):** To a solution of alcohol **465** (294 mg, 1.95 mmol, 1.0 eq.) in $CH_2Cl_2$ (20 mL) was added ImH (199 mg, 2.92 mmol, 1.5 eq.) followed by TBSCl (323 mg, 2.14 mmol, 1.1 eq.). After stirring for 18 h, the reaction mixture was diluted with $CH_2Cl_2$ (50 mL), washed with 2N HCl (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes to hexanes/EtOAc, 9:1) to yield silyl ether **466** (364 mg, 71%). Spectral data matched reported values.[134]

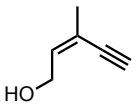
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 6.02-5.98 (m, 1H), 4.13 (dd, *J* = 6.7, 0.7 Hz, 2H), 2.26 (d, *J* = 0.8 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H).

**Experimental Procedures: Section 4.1**



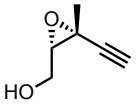

**(*Z*)-3-Methyl-5-(trimethylsilyl)pent-2-en-4-yn-1-ol (478):** A solution of vinyl iodide **452** (1.00 g, 5.05 mmol, 1.0 eq.), TMS-acetylene (1.43 mL, 10.1 mmol, 2.0 eq.) in THF (30 mL) was deoxygenated with a stream of Ar for 5 min. $NEt_3$ (4.93 mL, 35.4 mmol, 7.0 eq.) was added and the stream was continued for an additional 5 min before CuI (96 mg, 0.505 mmol, 0.1 eq.) and $Pd(PPh_3)_4$ (117 mg, 0.101 mmol, 0.02 eq.) were added sequentially. The resulting solution was stirred at room temperature for 15 h. The reaction mixture was then filtered through a plug of celite and the filtrate was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) and the combined fractions were then treated with activated charcoal and filtered through a plug of celite. The filtrate was concentrated *in vacuo* to yield enyne **478** (820 mg, 96%). Spectral data matched reported values.[232]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.90 (tq, *J* = 6.6, 1.4 Hz, 1H), 4.33 (t, *J* = 5.7 Hz, 2H), 1.87 (d, *J* = 1.3 Hz, 3H), 1.52 (t, *J* = 5.8 Hz, 1H), 0.20 (s, 9H).




**(*Z*)-3-Methylpent-2-en-4-yn-1-ol (479):** To a cooled of enyne **478** (174 mg, 1.03 mmol, 1.0 eq.) in MeOH (2 mL) at 0 ºC was added $K_2CO_3$ (14 mg, 0.103 mmol, 0.1 eq.) and the resulting suspension was stirred for 3 h. The reaction mixture was then diluted with $Et_2O$ (20 mL) and washed with $H_2O$ (2 mL) and brine (2 mL). The organic phase was dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/$Et_2O$, 2:1) to yield enyne **479** (63 mg, 64%). Spectral data matched reported values.[233]

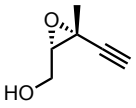
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.96 (t, *J* = 6.5 Hz, 1H), 4.34 (s, 2H), 3.17 (s, 1H), 1.90 (s, 3H), 1.49 (bs, 1H).



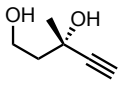

**(3-Ethynyl-3-methyloxiran-2-yl)methanol ((±)-480):** To a cooled suspension of enyne **479** (1.00 g, 10.4 mmol, 1.0 eq.) and $NaHCO_3$ (2.62 g, 31.2 mmol, 3.0 eq.) in $CH_2Cl_2$ (80 mL) at 0 ºC was added *m*CPBA (4.66 g, 20.8 mmol, 2.0 eq., 77%) as a solution in $CH_2Cl_2$ (40

mL) dropwise via addition funnel. The reaction mixture was allowed to warm slowly to room temperature and stirred for 17 h. The reaction mixture was then quenched with $H_2O$ (30 mL) and diluted further with $CH_2Cl_2$ (100 mL). The organic phase was washed with saturated $NaHCO_3$ (30 mL) and dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 6:1 to 2:1) to yield racemic epoxide **480** (651 mg, 56%). Spectral data matched reported values.[234]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 3.93 (dd, *J* = 12.3, 4.8 Hz, 1H), 3.85 (dd, *J* = 12.3, 6.0 Hz, 1H), 3.11 (t, *J* = 5.4 Hz, 1H), 2.40 (s, 1H), 1.59 (s, 3H).

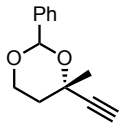


**((2*S*,3*R*)-3-Ethynyl-3-methyloxiran-2-yl)methanol (480):** A suspension of powdered, activated 4Å molecular sieves (150 mg) in $CH_2Cl_2$ (6 mL) was cooled to -20 ºC and (+)-DET (0.05 mL, 0.281 mmol, 0.18 eq.) was added followed by $Ti(O^iPr)_4$ (0.07 mL, 0.234 mmol, 0.15 eq.). The reaction mixture was stirred for 20 min before a solution of enyne **479** (150 mg, 1.56 mmol, 1.0 eq.) in $CH_2Cl_2$ (1 mL) was added dropwise. After 20 min, TBHP (0.62 mL, 3.43 mmol, 2.2 eq., 5.5 M solution in nonane) was added and the reaction flask was placed in a freezer at -20 ºC for 72 h. Upon removal from the freezer, the reaction mixture was warmed to 0 ºC and quenched with 6M NaOH (2 mL) and stirred for 1 h. The suspension was filtered through a plug of celite and $H_2O$ (4 mL) and EtOAc (40 mL) were added to the filtrate. The layers were separated and the aqueous phase was extracted with EtOAc (40 mL). The combined organic phases were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to yield epoxide **480** (151 mg, 86%). Spectral data matches **(±)-480**.



**(*S*)-3-Methylpent-4-yne-1,3-diol (481):** A solution of epoxide **(±)-480** (613 mg, 5.47 mmol, 1.0 eq.) in $Et_2O$ (20 mL) was cooled to 0 ºC and $LiAlH_4$ (415 mg, 10.9 mmol, 2.0 eq.) was added. After 35 min, the reaction mixture was diluted with $Et_2O$ (20 mL) and quenched by the careful addition of $H_2O$ (0.4 mL) followed by 15% NaOH (0.4 mL) and $H_2O$ (1.2 mL). The reaction mixture was warmed to room temperature and stirred vigorously for 15 min before the addition of $MgSO_4$. After the suspension was stirred further for 15 min, the mixture was filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 1:1) to yield diol **481** (525 mg, 84%, ~90% purity). Spectral data matched reported values.[235]

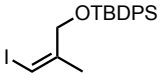
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 4.23-4.16 (m, 1H), 3.97-3.91 (m, 1H), 3.52 (s, 1H), 2.50 (s, 1H), 2.22 (bs, 1H), 2.02-1.98 (m, 1H), 1.88-1.81 (m, 1H), 1.55 (s, 3H).




**(4*S*)-4-Ethynyl-4-methyl-2-phenyl-1,3-dioxane (482):** To a solution of diol **481** (525 mg, 4.60 mmol, 1.0 eq.) and $PhCH(OMe)_2$ (0.76 mL, 5.06 mmol, 1.1 eq.) in $CH_2Cl_2$ (40 mL) was added *p*TsOH (spatula tip). The resulting solution was stirred at room temperature for 24 h, then quenched with saturated $NaHCO_3$ (10 mL) and extracted with $CH_2Cl_2$ (2 x 40 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 6:1) to yield benzylidene **482** (807 mg, 72%, ~70% purity, contaminated with PhCHO) as a single diastereomer.

$^1H$ NMR (400 MHz, $CDCl_3$) ∂ 7.54-7.45 (m, 2H), 7.38-7.32 (m, 3H), 5.99 (s, 1H), 4.27 (td, *J* = 12.0, 2.1 Hz, 1H), 4.17-4.11 (m, 1H), 2.63 (s, 1H), 2.10-2.02 (m, 1H), 1.72-1.69 (m, 1H), 1.61 (s, 3H).

**Experimental Procedures: Section 4.2**

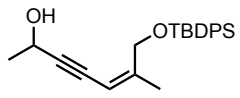



**(*Z*)-*tert*-Butyl((3-iodo-2-methylallyl)oxy)diphenylsilane (494):** To a solution of vinyl iodide **300** (11.0 g, 55.6 mmol, 1.0 eq.) in $CH_2Cl_2$ (150 mL) was added TBDPSCl (14.5 mL, 55.6 mmol, 1.0 eq.) followed by ImH (5.67 g, 83.3 mmol, 1.5 eq.) and the resulting mixture was stirred at room temperature for 16 h. Upon completion of the reaction, the resulting suspension was poured into a separatory funnel containing hexanes (400 mL). The organic mixture was washed with $H_2O$ (2x50 mL), brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes) to yield vinyl iodide **494** (23.4 g, 96%) as a colorless oil. Spectral data matched reported values.[236]

$R_f$ 0.80 (9:1 hexanes/ethyl acetate, UV/$KMnO_4$)

$^1H$ NMR (400 MHz, $CDCl_3$) ∂ 7.66-7.71 (m, 4H), 7.38-7.44 (m, 6H), 5.87 (q, *J* = 1.39 Hz, 1H), 4.30 (d, *J* = 0.67 Hz, 2H), 2.01 (d, *J* = 1.39 Hz, 3H), 1.07 (s, 9H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) ∂ 146.3, 135.6, 133.3, 129.7, 127.7, 72.7, 69.2, 26.8, 22.3, 21.7, 19.3.




**(*Z*)-7-((*tert*-Butyldiphenylsilyl)oxy)-6-methylhept-5-en-3-yn-2-ol (495):** A solution of vinyl iodide **494** (23.4 g, 53.5 mmol, 1.0 eq.) and 3-butyn-2-ol (4.50 g, 64.2 mmol, 1.2 eq.) in $CH_3CN$ (350 mL) was deoxygenated for 10 min with a stream of Ar. $NEt_3$ (22.4 mL,

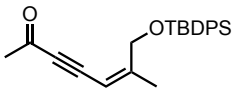
161 mmol, 3.0 eq.) was added and the stream was continued for an additional 5 min. The stream was discontinued and CuI (1.02 g, 5.35 mmol, 0.1 eq.) then $Pd(PPh_3)_4$ (1.24 g, 1.07 mmol, 0.02 eq.) was added. The reaction mixture was stirred for 2.5 h at room temperature. The reaction mixture was then concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes to hexanes/ethyl acetate, 9:1). The combined fractions were concentrated and the residue was triturated with $Et_2O$, filtered, and concentrated to yield alcohol **495** (18.9 g, 93%) as an orange oil.

$R_f$ 0.20 (9:1 hexanes/ethyl acetate, UV/PAA)

IR (NaCl) ν 3356, 1443, 1089, 822, 704 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$) ∂ 7.69-7.71 (m, 4H), 7.37-7.44 (m, 6H), 5.31 (s, 1H), 4.43-4.46 (m, 1H), 4.41 (s, 2H), 1.96 (d, *J* = 1.16 Hz, 3H), 1.46 (d, *J* = 5.20 Hz, exchanges w/ $D_2O$, 1H), 1.27 (d, *J* = 6.59 Hz, 3H), 1.06 (s, 9H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) ∂ 150.8, 135.6, 133.6, 129.6, 127.6, 104.8, 94.4, 80.4, 64.6, 58.6, 26.8, 24.2, 19.9, 19.3.



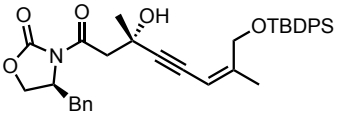

**(*Z*)-7-((*tert*-Butyldiphenylsilyl)oxy)-6-methylhept-5-en-3-yn-2-one (496):** To a solution of alcohol **495** (18.9 g, 50.0 mmol, 1.0 eq.) in $CH_2Cl_2$ (450 mL) was added $MnO_2$ (41.1 g, 412 mmol, 8.4 eq., 90%) in one portion. The black suspension was stirred at room temperature for 12 h. Upon completion of the reaction, the suspension was filtered through a plug of celite and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/ethyl acetate, 9:1) to yield ketone **496** (16.4 g, 87%) as an orange oil.

$R_f$ 0.54 (4:1 hexanes/ethyl acetate, UV/PAA)

IR (NaCl) ν 2182, 1671, 1429, 1240, 1100, 824, 703 $cm^{-1}$.

1H NMR (400 MHz, $CDCl_3$) ∂ 7.67-7.70 (m, 4H), 7.37-7.46 (m, 6H), 5.44 (d, *J* = 1.22 Hz, 1H), 4.46 (s, 2H), 2.09 (s, 3H), 2.04 (d, *J* = 1.27 Hz, 3H), 1.07 (s, 9H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) ∂ 184.2, 159.0, 135.5, 133.1, 129.7, 127.7, 103.2, 92.2, 87.3, 64.6, 32.4, 26.7, 20.6, 19.2.




**(*S*)-4-Benzyl-3-((*S*,*Z*)-8-((*tert*-butyldiphenylsilyl)oxy)-3-hydroxy-3,7-dimethyloct-6-en-4-ynoyl)oxazolidin-2-one (497):** To a solution of freshly distilled (from KOH) $^iPr_2NH$ (3.16 mL, 22.57 mmol, 1.7 eq.) in PhMe (20 mL) at 0 ºC was added a solution of $^n$BuLi (10.7 mL, 22.57 mmol, 1.7 eq., 2.1 M in hexanes) dropwise. After 30 min, the

solution was transferred via cannula to a suspension of auxiliary **(*S*)-485** (4.93 g, 22.57 mmol, 1.7 eq.) in PhMe (60 mL) at -78 ºC. The yellow solution was stirred at that temperature for 1 h, after which a solution of ketone **496** (5.00 g, 13.28 mmol, 1.0 eq.) in PhMe (50 mL) was added dropwise via addition funnel over 45 min. After 1 h, the reaction mixture was quenched with saturated $NH_4Cl$ solution (50 mL). The layers were separated and the aquoeous phase was further extracted with EtOAc (3x150 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/ethyl acetate, 9:1 to 6:1 to 4:1) to yield alcohol **497** (5.13 g, 65%):

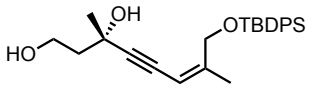
$R_f$ 0.26 (2:1 hexanes/ethyl acetate, UV/PAA)

$[\alpha]^{20}_D$ 45.2 (c = 1.0, $CHCl_3$)

IR (NaCl) v 3503, 2944, 1783, 1689, 1378, 1217, 1097 $cm^{-1}$.

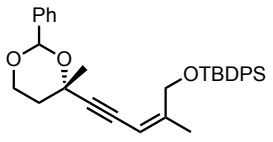
$^1H$ NMR (400 MHz, $CDCl_3$) ∂ 7.62-7.65 (m, 4H), 7.20-7.38 (m, 9H), 7.09-7.11 (m, 2H), 5.26 (d, *J* = 0.96 Hz, 1H), 4.57-4.62 (m, 1H), 4.38 (s, 2H), 4.07-4.15 (m, 3H), 3.55 (d, *J* = 17.36 Hz, 1H), 3.10 (dd, *J* = 3.38, 13.50 Hz, 1H), 2.85 (d, *J* = 16.88 Hz, 1H), 2.62 (dd, *J* = 9.16, 13.50 Hz, 1H), 1.86 (s, 3H), 1.37 (s, 3H), 1.01 (s, 9H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) ∂ 171.7, 153.1, 151.1, 135.5, 134.8, 133.5, 129.6, 129.4, 128.9, 127.6, 127.4, 104.6, 95.2, 79.3, 66.1, 65.8, 64.5, 54.8, 47.1, 37.5, 29.5, 26.8, 19.9, 19.2.




**(*S*,*Z*)-8-((*tert*-Butyldiphenylsilyl)oxy)-3,7-dimethyloct-6-en-4-yne-1,3-diol (498):** A solution of alcohol **497** (2.83 g, 4.83 mmol, 1.0 eq.) in THF (32 mL) and MeOH (8 mL) was cooled to 0 ºC and a solution of $LiBH_4$ (7.25 mL, 14.5 mmol, 2.0 eq., 2.0 M in THF) was added dropwise. The reaction mixture was allowed to warm slowly to room temperature and stirred for an additional 17 h. The reaction mixture was then quenched with EtOAc (10 mL) then $H_2O$ (10 mL). After 15 min, the layers were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to yield diol **498** (1.71 g, 84%).

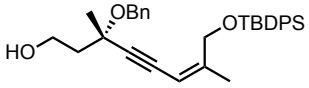
$^1H$ NMR (400 MHz, $CDCl_3$) ∂ 7.71-7.68 (m, 4H), 7.43-7.37 (m, 6H), 5.32 (m, 1H), 4.43 (s, 2H), 3.83 (t, *J* = 10.3 Hz, 1H), 3.65-3.61 (m, 1H), 3.03 (s, 1H), 1.97 (d, *J* = 1.4 Hz, 3H), 1.89 (bs, 1H), 1.87-1.80 (m, 1H), 1.62-1.56 (m, 1H), 1.35 (s, 3H), 1.06 (s, 9H).




***tert*-Butyl(((*Z*)-2-methyl-5-((4*S*)-4-methyl-2-phenyl-1,3-dioxan-4-yl)pent-2-en-4-yn-1-yl)oxy)diphenylsilane (499):** To a solution of diol **498** (1.33 g, 3.15 mmol,

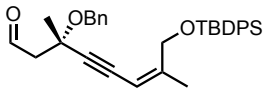
1.0 eq.) and $PhCH(OMe)_2$ (0.65 mL, 4.72 mmol, 1.5 eq.) in PhMe (40 mL) was added powdered activated 4Å MS (1.57 g) and CSA (365 mg, 1.57 mmol, 0.5 eq.). The resulting heterogeneous mixture was heated to reflux and stirred for 15 h. Once the reaction had cooled back to room temperature, EtOAc (50 mL) was added and the mixture was washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1) to yield benzylidene **499** (1.31 g, 82%) as a mixture of diastereomers.

$^1H$ NMR (400 MHz, $CDCl_3$) ∂ 7.70-7.66 (m, 4H), 7.46-7.29 (m, 11H), 5.73/5.67 (s, 1H), 5.38/5.31 (m, 1H), 4.49/4.43 (s, 2H), 4.07-3.86 (m, 2H), 2.27-2.20/1.96-1.88 (m, 1H), 1.99/1.94 (s, 3H), 1.58/1.45 (s, 3H), 1.43-1.40 (m, 1H), 1.06 (s, 9H).




**(*S*,*Z*)-3-(Benzyloxy)-8-((*tert*-butyldiphenylsilyl)oxy)-3,7-dimethyloct-6-en-4-yn-1-ol (500):** A solution of benzylidene **499** (477 mg, 0.934 mmol, 1.0 eq.) in $CH_2Cl_2$ (9 mL) was cooled to -78 ºC and DIBAL (9.34 mL, 9.34 mmol, 10.0 eq., 1.0 M in hexanes) was added dropwise. The resulting solution was allowed to warm slowly to room temperature. After 5.5 h, the excess DIBAL was quenched by the slow addition of MeOH (5 mL) and poured into saturated Rochelle's salt solution (10 mL). The biphasic mixture was stirred vigorously for 2 h, then extracted with $CH_2Cl_2$ (3 x 40 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to yield alcohol **500** (328 mg, 68%).

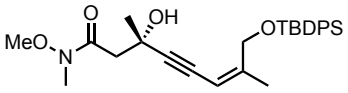
$^1H$ NMR (400 MHz, $CDCl_3$) ∂ 7.69-7.67 (m, 4H), 7.42-7.34 (m, 6H), 7.29-7.18 (m, 5H), 5.37 (m, 1H), 4.50-4.47 (m, 3H), 4.34 (d, *J* = 10.9 Hz, 1H), 3.89-3.84 (m, 1H), 3.66-3.62 (m, 1H), 2.62 (bs, 1H), 1.99 (d, *J* = 1.2 Hz, 3H), 1.97-1.92 (m, 1H), 1.80 (ddd, *J* = 14.4, 6.1, 3.7 Hz, 1H), 1.39 (s, 3H), 1.07 (s, 9H).




**(*S*,*Z*)-3-(Benzyloxy)-8-((*tert*-butyldiphenylsilyl)oxy)-3,7-dimethyloct-6-en-4-ynal (501):** To a solution of alcohol **500** (187 mg, 0.365 mmol, 1.0 eq.) in $CH_2Cl_2$ (2 mL) was added DMSO (0.09 mL, 1.28 mmol, 3.5 eq.) and $NEt_3$ (0.18 mL, 1.28 mmol, 3.5 eq.) and the resulting solution was cooled to 0 ºC before the addition of $SO_3$-pyr (145 mg, 0.912 mmol, 2.5 eq.). The reaction mixture was stirred for 3 h, then quenched with saturated $NH_4Cl$ (5 mL) and extracted with $CH_2Cl_2$ (3 x 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column

chromatography (hexanes/EtOAc, 9:1 to 6:1) to yield aldehyde **501** (75 mg, 40%) along with unreacted alcohol **500** (15 mg, 8%).

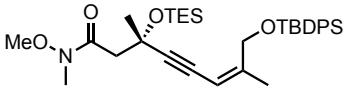
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 9.72 (t, *J* = 2.9 Hz, 1H), 7.68-7.65 (m, 4H), 7.42-7.33 (m, 6H), 7.29-7.21 (m, 3H), 7.18-7.16 (m, 2H), 5.35 (m, 1H), 4.48 (d, *J* = 11.1 Hz, 1H), 4.44 (s, 2H), 4.38 (d, *J* = 11.1 Hz, 1H), 2.59 (dd, *J* = 15.5, 3.1 Hz, 1H), 2.51 (dd, *J* = 15.5, 2.6 Hz, 1H), 1.98 (d, *J* = 1.3 Hz, 3H), 1.41 (s, 3H), 1.06 (s, 9H).




**(*S*,*Z*)-8-((*tert*-Butyldiphenylsilyl)oxy)-3-hydroxy-*N*-methoxy-*N*,3,7-trimethyloct-6-en-4-ynamide (502):** A suspension of MeO(Me)NH-HCl (6.12 g, 63.4 mmol, 7.0 eq.) in $CH_2Cl_2$ (75 mL) was cooled to -10 ºC (ice/acetone) and a solution of $AlMe_3$ (32.0 mL, 63.4 mmol, 7.0 eq., 2.0 M in toluene) was added. After addition, the resulting solution was removed from the cooling bath and stirred at room temperature for 1 h, at which time the reaction mixture was cooled back to -10 ºC and amide **497** (5.44 g, 9.13 mmol, 1.0 eq.) was added as a solution in $CH_2Cl_2$ (75 mL) via cannula over 20 min. The reaction mixture was then stirred at that temperature for 1 h. After the reaction mixture was judged to be complete by TLC, the yellow solution was cannulated onto a saturated Rochelle's salt solution (150 mL) and stirred vigorously for 16 h. The biphasic mixture was then transferred to a separatory funnel and the layers were separated. The aqueous phase was extracted with $CH_2Cl_2$ (3 x 150 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/ethyl acetate, 2:1) to yield Weinreb amide **502** (3.34 g, 76%) as a pale yellow oil.

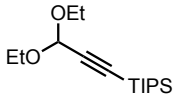
$R_f$ 0.23 (2:1 hexanes/ethyl acetate, UV/PAA)

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.71-7.69 (m, 4H), 7.43-7.36 (m, 6H), 5.36 (s, 1H), 5.31 (s, 1H), 4.44 (s, 2H), 3.52 (s, 3H), 3.08 (s, 3H), 2.89 (d, *J* = 16.0 Hz, 1H), 2.45 (d, *J* = 16.0 Hz, 1H), 1.93 (s, 3H), 1.39 (s, 3H), 1.06 (s, 9H).




**(*S*,*Z*)-8-((*tert*-Butyldiphenylsilyl)oxy)-*N*-methoxy-*N*,3,7-trimethyl-3-((triethylsilyl)oxy)oct-6-en-4-ynamide (503):** To a solution of alcohol **502** (1.99 g, 4.15 mmol, 1.0 eq.) in $CH_2Cl_2$ (20 mL) was added ImH (565 mg, 8.30 mmol, 2.0 ), DMAP (spatula tip), and TESCl (1.04 mL, 6.22 mmol, 1.5 eq.). The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was then diluted with $CH_2Cl_2$ (100 mL), washed with $H_2O$ (10 mL) and brine (10 mL). The organic phase was dried dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/ethyl acetate, 9:1 to 6:1) to yield Weinreb amide **503** (2.17 g, 88%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.68-7.66 (m, 4H), 7.43-7.34 (m, 6H), 5.30 (m, 1H), 4.45 (d, *J* = 3.8 Hz, 2H), 3.56 (s, 3H), 3.07 (s, 3H), 2.69 (s, 2H), 1.92 (d, *J* = 0.7 Hz, 3H), 1.52 (s, 3H), 1.05 (s, 9H), 0.86 (t, *J* = 7.9 Hz, 9H), 0.60-0.52 (m, 6H).

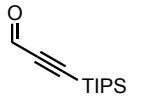



**(3,3-Diethoxyprop-1-yn-1-yl)triisopropylsilane (505)**: A solution of 3,3-diethoxyprop-1-yne (8.00 g, 62.40 mmol) in THF (250 mL) was cooled to -78 ºC (dry ice/acetone) and $^n$BuLi (27.1 mL, 62.40 mmol, 1.0 eq., 2.3 M in hexanes) was added dropwise via addition funnel over 7 min. The resulting yellow solution was stirred at that temperature for 1 h, at which time TIPSCl (13.4 mL, 62.40 mmol, 1.0 eq.) was added in one portion. After addition, the reaction mixture was allowed to warm slowly to room temperature in the bath. After 2.5 h, starting material ($R_f$ 0.46) was consumed as judged by TLC (9:1 hexanes/ethyl acetate) and the reaction mixture was quenched by addition of saturated $NH_4Cl$ (50 mL). The mixture was then extracted with ethyl acetate (3 x 150 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield crude **505** (20.2 g) as a yellow oil which was used without further purification.

$R_f$ 0.68 (9:1 hexanes/ethyl acetate, $KMnO_4$)

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.26 (s, 1H), 3.70-3.78 (m, 2H), 3.55-3.63 (m, 2H), 1.22 (t, 6H, *J* = 7.1 Hz), 1.07 (s, 21H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 102.3, 91.2, 86.4, 60.7, 18.5, 15.1, 11.1.

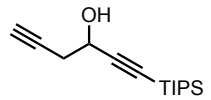



**3-(Triisopropylsilyl)propiolaldehyde (506)**: To a solution of crude **505** (62.40 mmol) in $CH_2Cl_2$ (350 mL) was added TFA (35 mL) and the resulting dark red solution was stirred at room temperature for 3.5 h, after which time the reaction mixture was transferred to a separatory funnel and washed successively with $H_2O$ (2 x 75 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by vacuum distillation (P ≈ 8 mmHg, T = 92-96 ºC) to yield aldehyde **506** (5.19 g, 40% over two steps) as a colorless oil. Spectral data matched reported values.[237]

$R_f$ 0.35 (99:1 hexanes/ethyl acetate, $KMnO_4$)

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 9.19 (s, 1H), 1.10 (m, 21H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 176.4, 104.4, 100.6, 18.3, 10.8.



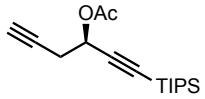

**1-(Triisopropylsilyl)hexa-1,5-diyn-3-ol ((±)-507)**: To a solution of aldehyde **506** (5.19 g, 24.67 mmol) and propargyl bromide (3.99 mL, 37.00 mmol, 1.5 eq., 80%

wt. in toluene) in THF (150 mL) was added successively $I(CH_2)_2I$ (6.95 g, 24.67 mmol, 1.0 eq.) and Zn powder (10.62 g, 123.3 mmol, 5.0 eq.). The resulting grey slurry was stirred at room temperature for 10 min before being placed in an ultrasound bath for 1.5 h. The reaction mixture was then removed from the ultrasound bath, cooled to 0 ºC, and quenched with 2N HCl (50 mL). The mixture was then extracted with $Et_2O$ (2 x 150 mL). The combined organic extracts were washed with saturated $Na_2S_2O_3$ (50 mL) and brine (50 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes to hexanes/EtOAc, 19:1 to 9:1) to yield **(±)-507** (5.56 g, 90%) as a yellow oil. Spectral data matched reported values.[238]

$R_f$ 0.32 (9:1 hexanes/ethyl acetate, $KMnO_4$)

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 4.51 (q, 1H, *J* = 6.0 Hz), 2.63-2.60 (m, 2H), 2.45 (d, 1H, *J* = 6.4 Hz, exchanges w/ $D_2O$), 2.07 (t, 1H, *J* = 2.8 Hz), 1.06 (s, 21H).

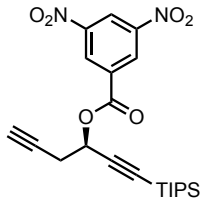
$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 106.6, 86.4, 79.3, 71.1, 28.7, 18.4, 11.0.




**(*R*)-1-(Triisopropylsilyl)hexa-1,5-diyn-3-yl acetate (508):** To a solution of **(±)-507** (9.65 g, 38.5 mmol, 1.0 eq.) and vinyl acetate (28.4 mL, 308 mmol, 8.0 eq.) in pentane (77 mL) was added powdered activated 4Å MS (2.41 g) followed by Amano AK lipase (4.83 g). The flask was sealed with a rubber septum and heated to 35 ºC for 112 h. After the reaction mixture was cooled back to room temperature, the suspension was filtered through a plug of celite and the filtrate was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 19:1) to yield acetate **508** (5.32 g, 47%, er > 19:1) and alcohol **(*S*)-507** (4.70 g, 49%, er > 19:1).

Data for acetate **508**:

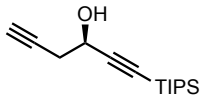
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.52 (t, *J* = 6.6 Hz, 1H), 2.68 (dd, *J* = 6.4, 2.7 Hz, 2H), 2.10 (s, 3H), 2.03 (t, *J* = 2.7 Hz, 1H), 1.08-1.07 (m, 21H).




**(*R*)-1-(Triisopropylsilyl)hexa-1,5-diyn-3-yl 3,5-dinitrobenzoate (511):** A solution of 3,5-dinitrobenzoic acid (4.84 g, 22.8 mmol, 1.5 eq.) and $PPh_3$ (5.98 g, 22.8 mmol, 1.5 eq.) in PhMe (73 mL) was cooled to 0 ºC and DIAD (4.2 mL, 21.3 mmol, 1.4 eq.) was added dropwise. After 5 min, a solution of alcohol **(*S*)-507** (3.81 g, 15.2 mmol, 1.0 eq.) in PhMe (15 mL) was added and the resulting solution was stirred at room temperature for 1.5 h before the solvent was then removed *in vacuo*. The residue was taken up in $CH_2Cl_2$ (160 mL) and washed

with 15% $H_2O_2$ (160 mL), saturated $Na_2S_2O_3$ (80 mL), and $H_2O$ (80 mL). The organic phase was dried over $MgSO_4$, filtered through a plug of $SiO_2$, and concentrated *in vacuo* to yield crude benzoate **511** which was used without further purification.

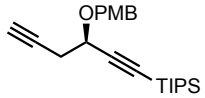
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 9.25 (t, *J* = 2.1 Hz, 1H), 9.19 (d, *J* = 2.1 Hz, 1H), 5.82 (t, *J* = 6.6 Hz, 1H), 2.93-2.90 (m, 2H), 2.08 (t, *J* = 2.6 H, 1H), 1.10-1.05 (m, 21H).




**(*R*)-1-(Triisopropylsilyl)hexa-1,5-diyn-3-ol ((*R*)-507):**

From **511**: To a solution of crude benzoate **511** (15.2 mmol, 1.0 eq.) in THF (120 mL) was added 1M LiOH (22.8 mL, 22.8 mmol, 1.5 eq.) and the resulting mixture was stirred at room temperature for 2.5 h before an additional portion of 1M LiOH (10.0 mL, 10.0 mmol, 0.7 eq.) was added. After 30 min, the reaction mixture was poured into a separatory funnel containing 1N HCl (50 mL) and extracted with EtOAc (150 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 19:1) to yield alcohol **(*R*)-507** (2.54 g, 67% over two steps). Spectral data matches **(±)-507**.

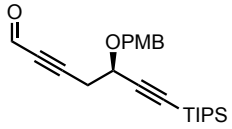
From **508**: A solution of acetate **508** (3.02 g, 10.3 mmol, 1.0 eq.) in $CH_2Cl_2$ (100 mL) was cooled to -78 ºC and DIBAL (25.8 mL, 25.8 mmol, 2.5 eq., 1.0 M in hexanes) was added dropwise over 5 min. The reaction mixture was stirred at that temperature for 1 h. The reaction mixture was then poured into a vigorously stirred Rochelle's salt solution (50 mL). The biphasic mixture was stirred for an additional 4 h before then layers were separated and the aqueous phase was extracted with $CH_2Cl_2$ (100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 19:1 to 9:1) to yield alcohol **(*R*)-507** (2.34 g, 91%). Spectral data matches **(±)-507**.




**(*R*)-Triisopropyl(3-((4-methoxybenzyl)oxy)hexa-1,5-diyn-1-yl)silane (512):** To a suspension of alcohol **(*R*)-507** (3.62 g, 14.5 mmol, 1.0 eq.) and powdered activated 4Å MS (1.81 g) in DMF (16 mL) was added $Cs_2CO_3$ (14.1 g, 43.4 mmol, 3.0 eq.) and TBAI (spatula tip) before the addition of PMBCl (3.92 mL, 28.9 mmol, 2.0 eq.). The reaction mixture was stirred at room temperature for 16 h, diluted with EtOAc (100 mL), and washed with $H_2O$ (2 x 10 mL) and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 19:1) to yield ether **512**, which was contaminated with PMBCl. The mixture

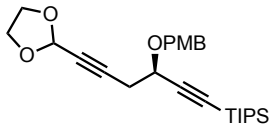
was further purified by bulb-to-bulb distillation (P ~ 0.02 mmHg, T = 130-135 ºC) to remove most of the PMBCl to yield a mixture of ether **512** (3.96 g, 74%) and PMBCl (200 mg).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.31-7.29 (m, 2H), 6.89-6.87 (m, 2H), 4.77 (d, *J* = 11.8 Hz, 1H), 4.53 (d, *J* = 11.2 Hz, 1H), 3.81 (s, 3H), 2.63 (ddd, *J* = 6.5, 2.6, 1.2 Hz, 2H), 2.02 (t, *J* = 2.7 Hz, 1H), 1.11-1.09 (m, 21H).



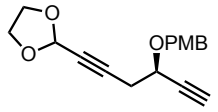

**(*R*)-5-((4-Methoxybenzyl)oxy)-7-(triisopropylsilyl)hepta-2,6-diynal (513):** A solution of alkyne **512** (3.96 g, 10.7 mmol, 1.0 eq.) in THF (30 mL) was cooled to -40 ºC and $^n$BuLi (5.11 mL, 11.8 mmol, 1.1 eq., 2.3 M solution in hexanes) was added dropwise. Immediately following the addition, DMF (1.65 mL, 21.4 mmol, 2.0 eq.) was added rapidly and the cooling bath was removed. After 30 min, the reaction mixture was poured into a 0 ºC solution of $KH_2PO_4$ (53 mL, 42.7 mmol, 4.0 eq., 10% aqueous). The reaction mixture was diluted with EtOAc (120 mL) and washed with $H_2O$ (2 x 15 mL) and brine (15 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 19:1) to yield aldehyde **513** (2.40 g, 56%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 9.17 (s, 1H), 7.30-7.28 (m, 2H), 6.90-6.88 (m, 2H), 4.78 (d, *J* = 11.5 Hz, 1H), 4.52 (d, *J* = 11.5 Hz, 1H), 4.28 (t, *J* = 6.5 Hz, 1H), 3.81 (s, 3H), 2.84 (d, *J* = 6.4 Hz, 2H), 1.10 (m, 21H).



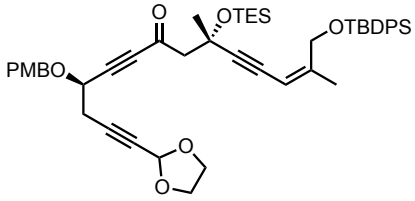

**(*R*)-(6-(1,3-Dioxolan-2-yl)-3-((4-methoxybenzyl)oxy)hexa-1,5-diyn-1-yl)triisopropylsilane (514):** To a solution of aldehyde **513** (2.40 g, 6.03 mmol, 1.0 eq.) and ethylene glycol (6.73 mL, 120 mmol, 20.0 eq.) in PhH (30 mL) was added CSA (699 mg, 3.01 mmol, 0.5 eq.). The resulting solution was heated to 80 ºC for 14 h before the reaction mixture was removed from the heat and cooled to room temperature. The solution was diluted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ (15 mL) and brine (15 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1) to yield acetal **514** (1.76 g, 66%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.30-7.28 (m, 2H), 6.89-6.86 (m, 2H), 5.64 (s, 1H), 4.75 (d, *J* = 11.9 Hz, 1H), 4.51 (d, *J* = 11.4 Hz, 1H), 4.22 (t, *J* = 6.9 Hz, 1H), 4.05-4.01 (m, 2H), 3.92-3.88 (m, 2H), 3.81 (s, 3H), 2.67 (dt, *J* = 6.8, 1.4 Hz, 2H), 1.10 (m, 21H).




**(*R*)-2-(4-((4-Methoxybenzyl)oxy)hexa-1,5-diyn-1-yl)-1,3-dioxolane (515):** To a solution of acetal **514** (1.76 g, 3.98 mmol, 1.0 eq.) in THF (90 mL) was added TBAF (7.95 mL, 7.95 mmol, 2.0 eq., 1.0 M solution in THF). The resulting solution was stirred at room temperature for 1.5 h then quenched with saturated $NH_4Cl$ (10 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 6:1 to 4:1) to yield alkyne **515** (954 mg, 84%).

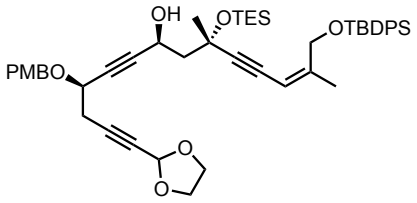
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.31-7.29 (m, 2H), 6.89-6.87 (m, 2H), 5.65 (s, 1H), 4.74 (d, *J* = 11.4 Hz, 1H), 4.49 (d, *J* = 11.7 Hz, 1H), 4.20 (td, *J* = 6.7, 2.0 Hz, 1H), 4.07-4.01 (m, 2H), 3.96-3.90 (m, 2H), 3.81 (s, 3H), 2.74-2.63 (m, 2H), 2.51 (d, *J* = 2.0 Hz, 1H).




**(4*R*,9*S*,*Z*)-14-((*tert*-Butyldiphenylsilyl)oxy)-1-(1,3-dioxolan-2-yl)-4-((4-methoxybenzyl)oxy)-9,13-dimethyl-9-((triethylsilyl)oxy)tetradeca-12-en-1,5,10-triyn-7-one (517):** To a cooled solution of alkyne **515** (954 mg, 3.33 mmol, 1.8 eq.) in THF (9 mL) at -78 ºC was added $^n$BuLi (1.45 mL, 3.33 mmol, 1.8 eq., 2.3 M solution in hexanes). The reaction mixture was stirred at that temperature for 10 min, warmed to 0 ºC for 5 min, and cooled back to -78 º before the addition of Weinreb amide **503** (1.10 g, 1.85 mmol, 1.0 eq.) as a solution in THF (2 mL). After 1.5 h, the reaction mixture was warmed to 0 ºC and stirred at that temperature for an additional 1.5 h. The reaction mixture was quenched with saturated $NH_4Cl$ (5 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1) to yield ketone **517** (901 mg, 59%).

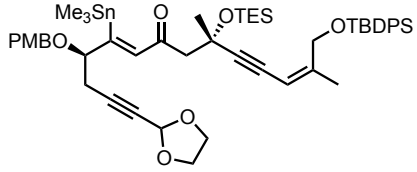
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.68-7.66 (m, 4H), 7.42-7.35 (m, 6H), 7.28-7.27 (m, 2H), 6.88-6.86 (m, 2H), 5.63 (s, 1H), 5.29 (m, 1H), 4.71 (d, *J* = 11.3 Hz, 1H), 4.47-4.39 (m, 3H), 4.31 (t, *J* = 6.6 Hz, 1H), 4.05-4.01 (m, 2H), 3.94-3.88 (m, 2H), 3.80 (s, 3H), 2.86 (d, *J* = 13.6 Hz, 1H), 2.75 (d, *J* = 13.6 Hz, 1H), 2.74-2.62 (m, 2H), 1.93 (d, *J* = 1.3 Hz, 3H), 1.44 (s, 3H), 1.06 (s, 9H), 0.87 (t, *J* = 7.6 Hz, 9H), 0.59-0.53 (m, 6H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 183.3, 159.4, 151.5, 135.4(7), 135.4(5), 133.4, 129.6(4), 129.5(7), 128.7, 127.6, 113.8, 104.3, 95.6, 92.9, 80.8, 70.8, 67.4, 66.3, 66.2, 64.6, 64.3, 58.6, 55.2, 31.1, 31.0, 26.8, 25.7, 22.3, 19.9, 19.3, 14.0, 6.8, 5.8.




**(4*R*,7*S*,9*S*,*Z*)-14-((*tert*-Butyldiphenylsilyl)oxy)-1-(1,3-dioxolan-2-yl)-4-((4-methoxybenzyl)oxy)-9,13-dimethyl-9-((triethylsilyl)oxy)tetradeca-12-en-1,5,10-triyn-7-ol (518):** A solution of ketone **517** (172 mg, 0.210 mmol, 1.0 eq.) in $^{i}$PrOH (2 mL) was added to a flask containing freshly prepared Ru catalyst **163** (31 mg, 0.0545 mmol, 0.25 eq.). The resulting solution was stirred at room temperature for 32 h before the solvents were removed *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 6:1) to yield alcohol **518** (98 mg, 57%, dr = 14:1).

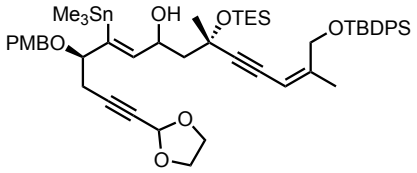
$^{1}$H NMR (400 MHz, $CDCl_3$) ð 7.69-7.66 (m, 4H), 7.43-7.37 (m, 6H), 7.30-7.28 (m, 2H), 6.88-6.85 (m, 2H), 5.64 (s, 1H), 5.33 (s, 1H), 4.89-4.87 (m, 1H), 4.72 (d, *J* = 11.8 Hz, 1H), 4.47-4.39 (m, 3H), 4.25-4.22 (m, 1H), 4.05-3.99 (m, 2H), 3.90-3.87 (m, 2H), 3.80 (s, 3H), 2.72-2.56 (m, 2H), 2.11-2.07 (m, 1H), 1.96 (s, 3H), 1.86 (d, *J* = 14.2 Hz, 1H), 1.37 (s, 3H), 1.07 (s, 9H), 0.90-0.86 (m, 9H), 0.62-0.54 (m, 6H).




**(4*R*,5*Z*,9*S*,12*Z*)-14-((*tert*-Butyldiphenylsilyl)oxy)-1-(1,3-dioxolan-2-yl)-4-((4-methoxybenzyl)oxy)-9,13-dimethyl-9-((triethylsilyl)oxy)-5-(trimethylstannyl)tetradeca-5,12-dien-1,10-diyn-7-one (520):** A solution of $(Me_3Sn)_2$ (1.08 g, 3.30 mmol, 3.0 eq.) in THF (30 mL) was cooled to -20 ºC and MeLi (2.75 mL, 3.30 mmol, 3.0 eq., 1.2 M solution in $Et_2O$) was added dropwise. After 25 min, the reaction mixture was cooled to -60 ºC and CuCN (296 mg, 3.30 mmol, 3.0 eq.) was added in one portion and the resulting suspension was allowed to warm to -45 ºC over 10 min. After an addition 5 min at that temperature, the reaction mixture was cooled to -78 ºC before the addition of ketone **517** (905 mg, 1.10 mmol, 1.0 eq.) as a solution in THF (3 mL). The resulting mixture was stirred at -78 ºC for 2 h, then quenched with saturated $NH_4Cl/NH_4OH$ (9:1, 10 mL) and allowed to warm to room temperature. The reaction mixture was diluted with EtOAc (75 mL) and the layers were separated. The organic phase was washed with brine (10 mL) and the combined aqueous layers were re-extracted with EtOAc (75 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1) to yield vinyl stannane **520** (876 mg, 81%).

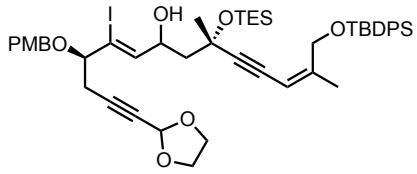
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.68-7.65 (m, 4H), 7.41-7.35 (m, 6H), 7.24-7.22 (m, 2H), 7.10 (d, *J* = 0.9 Hz, 1H), 6.87-6.85 (m, 2H), 5.60 (s, 1H), 5.27 (m, 1H), 4.46-4.43 (m, 3H), 4.26-4.24 (m, 2H), 4.01-3.98 (m, 2H), 3.89-3.86 (m, 2H), 3.80 (s, 3H), 2.83 (d, *J* = 12.5 Hz, 1H), 2.60 (d, *J* = 12.5 Hz, 1H), 2.54 (ddd, *J* = 16.8, 7.1, 1.5 Hz, 1H), 2.40 (ddd, *J* = 16.8, 5.8, 1.5 Hz, 1H), 1.93 (s, 3H), 1.37 (s, 3H), 1.06 (s, 9H), 0.85 (t, *J* = 7.8 Hz, 9H), 0.57-0.51 (m, 6H), 0.15 (s, 9H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 196.8, 171.7, 159.1, 151.4, 137.3, 135.5, 133.4, 130.1, 129.6, 129.1, 127.6, 113.7, 104.3, 96.3, 93.0, 82.7, 82.6, 81.0, 77.8, 70.8, 67.9, 64.6, 64.3, 60.3, 57.0, 55.2, 34.1, 30.7, 26.8, 26.1, 22.3, 21.0, 19.9, 19.3, 14.1, 14.0, 6.9, 5.9, -6.5.




**(4*R*,5*Z*,9*S*,12*Z*)-14-((*tert*-Butyldiphenylsilyl)oxy)-1-(1,3-dioxolan-2-yl)-4-((4-methoxybenzyl)oxy)-9,13-dimethyl-9-((triethylsilyl)oxy)-5-(trimethylstannyl)tetradeca-5,12-dien-1,10-diyn-7-ol (521):** To cooled a solution of ketone **520** (277 mg, 0.281 mmol, 1.0 eq.) in MeOH (8 mL) and THF (2 mL) at 0 ºC was added $NaBH_4$ (11 mg, 0.281 mmol, 1.0 eq.). The reaction mixture was allowed to warm to room temperature slowly and stirred for 4.5 h before the solvents were removed *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1) to yield alcohol **521** (261 mg, 94%) as an inseparable mixture of diastereomers (~2:1).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.67-7.66 (m, 4H), 7.42-7.35 (m, 6H), 7.25-7.23 (m, 2H), 6.86-6.84 (m, 2H), 6.13-6.09 (m, 1H), 5.61/5.57 (s, 1H), 5.32/5.30 (s, 1H), 4.66 (d, *J* = 8.8, 5.7 Hz, 1H, major), 4.49-4.42 (m, 4H), 4.31-4.21 (m, 2H), 4.04-3.97 (m, 2H), 3.89-3.81 (m, 2H), 3.79 (s, 3H), 2.59-2.52 (m, 1H), 2.41-2.32 (m, 1H), 1.96 (s, 3H), 1.76-1.53 (m, 2H), 1.42/1.35 (s, 3H), 1.06 (s, 9H), 0.89 (t, *J* = 8.4 Hz, 9H), 0.64-0.55 (m, 6H), 0.21/0.16 (s, 9H).

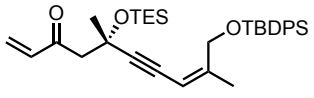



**(4*R*,5*Z*,9*S*,12*Z*)-14-((*tert*-Butyldiphenylsilyl)oxy)-1-(1,3-dioxolan-2-yl)-5-iodo-4-((4-methoxybenzyl)oxy)-9,13-dimethyl-9-((triethylsilyl)oxy) tetradeca-5,12-dien-1,10-diyn-7-ol (522):** A solution of alcohol **521** (261 mg, 0.265 mmol, 1.0 eq.) in $CH_2Cl_2$ (3 mL) was cooled to 0 ºC before a $I_2$ (67 mg, 0.265 mmol, 1.0 eq.) was added as a solution in $CH_2Cl_2$ (5 mL). The reaction mixture was stirred at 0 ºC for 30 min, then quenched with saturated $Na_2S_2O_3$ (2 mL), and extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was

purified by flash column chromatography (hexanes/EtOAc, 1:1) to yield vinyl iodide **522** (204 mg, 81%).

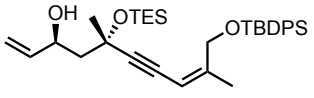
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.67-7.65 (m, 4H), 7.42-7.30 (m, 8H), 6.89-6.86 (m, 2H), 6.40-6.32 (m, 1H), 5.66/5.59 (s, 1H), 5.33/5.28 (s, 1H), 4.81-4.74 (m, 1H), 4.53-4.45 (m, 2H), 4.40/4.38 (s, 2H), 4.05-3.98 (m, 2H), 3.91-3.82 (m, 2H), 3.80/3.79 (s, 3H), 2.80-2.71 (m, 1H), 2.60-2.48 (m, 1H), 1.98 (s, 3H), 1.77-1.46 (m, 2H), 1.42/1.38 (s, 3H), 1.06 (s, 9H), 0.89 (t, *J* = 7.9 Hz, 9H), 0.67-0.54 (m, 6H).

**Experimental Procedures: Section 4.3**




**(*S*,*Z*)-10-((*tert*-Butyldiphenylsilyl)oxy)-5,9-dimethyl-5-((triethylsilyl)oxy)deca-1,8-dien-6-yn-3-one (524):** A solution of Weinreb amide **503** (3.26 g, 5.49 mmol, 1.0 eq.) in THF (32 mL) was cooled to 0 ºC and vinylmagnesium bromide (11 mL, 11.0 mmol, 2.0 eq., 1.0 M solution in THF) was added dropwise. After 1 h, the cooling bath was removed and the reaction mixture was allowed to reach room temperature. The reaction mixture was stirred for an additional 5 h and quenched by the slow addition of 1N HCl (10 mL). The reaction mixture was extracted with EtOAc (3 x 50 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1) to yield enone **524** (2.36 g, 77%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.68-7.66 (m, 4H), 7.42-7.35 (m, 6H), 6.38 (dd, *J* = 17.5, 10.8 Hz, 1H), 6.09 (dd, *J* = 17.5, 1.3 Hz, 1H), 5.62 (dd, *J* = 10.8, 1.3 Hz, 1H), 5.30 (s, 2H), 4.42 (s, 2H), 2.78 (d, *J* = 12.8 Hz, 1H), 2.66 (d, *J* = 13.4 Hz, 1H), 1.94 (d, *J* = 1.6 Hz, 3H), 1.39 (s, 3H), 1.06 (s, 9H), 0.88-0.84 (m, 9H), 0.58-0.51 (m, 6H).

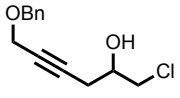



**(3*S*,5*S*,*Z*)-10-((*tert*-Butyldiphenylsilyl)oxy)-5,9-dimethyl-5-((triethylsilyl)oxy)deca-1,8-dien-6-yn-3-ol (526):** A solution of enone **524** (1.40 g, 2.50 mmol, 1.0 eq.) and (*R*)-CBS catalyst **525** (692 mg, 2.50 mmol, 1.0 eq.) in THF (25 mL) was cooled to -10 ºC (acetone/ice). $BH_3$•$Me_2S$ (0.26 mL, 2.75 mmol, 1.1 eq.) was then added dropwise and the reaction mixture was stirred at that temperature for 30 min. The reaction mixture was quenched with MeOH (4 mL) and the solvents were then removed *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1) to yield allylic alcohol **526** (1.28 g, 91%) as a 13.7:1 mixture of inseparable diastereomers.

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.68-7.65 (m, 4H), 7.42-7.35 (m, 6H), 5.66 (ddd, *J* = 17.2, 10.5, 5.1 Hz, 1H), 5.32 (m, 1H), 5.17 (dt, *J* = 17.1, 1.9 Hz, 1H), 4.98 (dt, *J* = 10.4, 1.6 Hz, 1H), 4.54-4.50 (m, 1H), 4.43 (s, 2H), 3.97 (s, 1H), 1.96 (s, 3H), 1.72 (dd, *J* = 14.0, 9.9 Hz, 1H), 1.59-1.54 (m, 1H), 1.35 (s, 3H), 1.06 (s, 9H), 0.89 (t, *J* = 8.2 Hz, 9H), 0.66-0.55 (m, 6H).

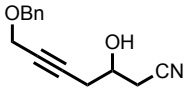

**((Prop-2-yn-1-yloxy)methyl)benzene (530):** A suspension of NaH (4.28 g, 107 mmol, 1.2 eq., 60% dispersion in mineral oil) in THF (150 mL) was cooled to 0 ºC and propargyl alcohol (**89**, 5.14 mL, 89.2 mmol, 1.0 eq.) was added dropwise over 5 min. The resulting slurry was stirred for 1 h before the addition of TBAI (spatula tip) and BnBr (15.9 mL, 134 mmol, 1.5 eq.). The reaction mixture was allowed to warm slowly to room temperature and stirred for 20 h before quenching with $H_2O$ (25 mL). The biphasic mixture was extracted with EtOAc (3 x 100 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by ISCO (120 g, gradient: 0% to 20% EtOAc in hexanes over 35 min) to yield alkyne **530** (12.8 g, >96%). Spectral data consistent with reported values.[239]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.30-7.27 (m, 5H), 4.61 (s, 2H), 4.17 (d, *J* = 2.5 Hz, 2H), 2.46 (t, *J* = 2.5 Hz, 1H).




**6-(Benzyloxy)-1-chlorohex-4-yn-2-ol ((±)-531):** To a cooled solution of alkyne **530** (4.74 g, 32.4 mmol, 1.5 eq.) in THF (80 mL) at -78 ºC was added $^n$BuLi (14.4 mL, 30.3 mmol, 1.4 eq., 2.1 M solution in hexanes) dropwise. After stirring for an additional 30 min at -78 ºC, $BF_3$-$OEt_2$ (4.00 mL, 32.4 mmol, 1.5 eq.) was added then after 10 min, (±)-epichlorohydrin (**(±)-529**, 2.00 g, 21.6 mmol, 1.0 eq.) was added as a solution in THF (24 mL) dropwise. The resulting solution was allowed to warm slowly and stirred for 3 h. The reaction mixture was quenched with saturated $NH_4Cl$ (40 mL) and extracted with EtOAc (3 x 80 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by ISCO (80 g, gradient: 15% to 50% EtOAc in hexanes over 30 min) to yield alcohol **(±)-531** (3.58 g, 69%). Spectral data consistent with reported values.[240]

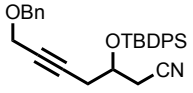
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.38-7.29 (m, 5H), 4.58 (s, 2H), 4.17 (t, *J* = 2.1 Hz, 2H), 4.03-3.96 (m, 1H), 3.72 (dd, *J* = 11.1, 4.5 Hz, 1H), 3.64 (dd, *J* = 11.5, 6.1 Hz, 1H), 2.67-2.55 (m, 2H), 2.33 (d, *J* = 5.7 Hz, 1H).




**7-(Benzyloxy)-3-hydroxyhept-5-ynenitrile ((±)-532):** To a solution of alcohol **(±)-531** (3.20 g, 13.4 mmol, 1.0 eq.) in EtOH (27 mL) was added NaCN (1.64 g, 33.5, 2.5 eq.) and the resulting mixture was heated to 50 ºC. After stirring at that temperature for 13 h, the suspension was filtered through a plug of celite and the filtrate was concentrated *in vacuo*. The crude residue was purified by ISCO (40 g, gradient: 20% to 50% EtOAc in hexanes over 18 min) to yield nitrile **(±)-532** (2.54 g, 88%).

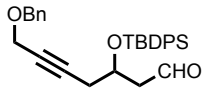
$^{1}$H NMR (400 MHz, $CDCl_3$) ∂ 7.39-7.28 (m, 5H), 4.57 (s, 2H), 4.17 (t, *J* = 2.2 Hz, 2H), 4.04-4.00 (m, 1H), 3.17 (d, *J* = 4.8 Hz, 1H), 2.67-2.59 (m, 2H), 2.56-2.53 (m, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 137.1, 128.5, 128.1, 128.0, 117.3, 81.2, 79.7, 71.9, 66.0, 57.6, 26.8, 24.7.



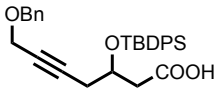

**7-(Benzyloxy)-3-((tert-butyldiphenylsilyl)oxy)hept-5-ynenitrile ((±)-533):** To a solution of nitrile **(±)-532** (3.58 g, 15.6 mmol, 1.0 eq.) in $CH_2Cl_2$ (75 mL) was added TBDPSCl (4.06 mL, 15.6 mmol, 1.0 eq.) followed immediately by ImH (1.59 g, 23.4 mmol, 1.5 eq.) and DMAP (spatula tip). The reaction mixture was stirred at room temperature for 48 h and, upon completion, was diluted with $CH_2Cl_2$ (100 mL) and washed with $H_2O$ (25 mL) and brine (25 mL). The organic layer was separated and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1) to yield nitrile **(±)-533** (7.23 g, >96%).

$^{1}$H NMR (400 MHz, $CDCl_3$) ∂ 7.72-7.66 (m, 4H), 7.48-7.38 (m, 6H), 7.36-7.28 (m, 5H), 4.53 (s, 2H), 4.09 (t, *J* = 2.0 Hz, 2H), 4.07-4.01 (m, 1H), 2.64-2.49 (m, 4H), 1.09 (s, 9H).



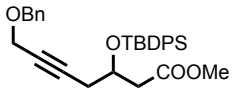

**7-(Benzyloxy)-3-((tert-butyldiphenylsilyl)oxy)hept-5-ynal ((±)-534):** A solution of nitrile **(±)-533** (610 mg, 1.30 mmol, 1.0 eq.) in $CH_2Cl_2$ (2.5 mL) was cooled to -78 ºC and DIBAL (1.96 mL, 1.96 mmol, 1.5 eq., 1.0 M solution in hexanes) was added dropwise. The reaction mixture was stirred at that temperature for 4 h before being quenched by the slow addition of MeOH (1 mL). The reaction mixture was poured into Rochelle's salt solution (10 mL) and stirred vigorously for 3 h. The resulting biphasic mixture was extracted with $CH_2Cl_2$ (3 x 30 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 6:1) to yield aldehyde **(±)-534** (458 mg, 75%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 9.73 (t, *J* = 2.2 Hz, 1H), 7.73-7.65 (m, 4H), 7.45-7.35 (m, 6H), 7.34-7.28 (m, 5H), 4.53 (s, 2H), 4.34 (p, *J* = 6.1 Hz, 1H), 4.10 (t, *J* = 2.1 Hz, 2H), 2.71-2.68 (m, 2H), 2.47-2.45 (m, 2H), 1.05 (s, 9H).



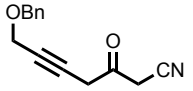

**7-(Benzyloxy)-3-((*tert*-butyldiphenylsilyl)oxy)hept-5-ynoic acid ((±)-535):** A solution of aldehyde **(±)-534** (458 mg, 0.973 mmol, 1.0 eq.) and 2-methyl-2-butene (10.3 mL, 97.3 mmol, 100.0 eq.) in $^t$BuOH (30 mL) and $H_2O$ (30 mL) was cooled to 0 ºC and $NaH_2PO_4$ (1.17 g, 9.73 mmol, 10.0 eq.) and $NaClO_2$ (1.10 g, 9.73 mmol, 10.0 eq., 80%) were added. The reaction mixture was allowed to warm slowly to room temperature and stirred for 3 h. The solution was diluted with EtOAc (75 mL) and washed with $H_2O$ (2 x 15 mL). The combined aqueous washes were further extracted with EtOAc (2 x 75 mL) and the combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo* to yield crude acid **(±)-535** which was used without further purification.

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.73-7.66 (m, 4H), 7.43-7.35 (m, 6H), 7.33-7.27 (m, 5H), 4.53 (s, 2H), 4.30-4.24 (m, 1H), 4.09 (t, *J* = 2.0 Hz, 2H), 2.75-2.63 (m, 2H), 2.50- 2.37 (m, 2H), 1.05 (s, 9H).




**Methyl 7-(benzyloxy)-3-((tert-butyldiphenylsilyl)oxy)hept-5-ynoate ((±)-536):** To a suspension of crude acid **(±)-535** (0.973 mmol, 1.0 eq.) and $K_2CO_3$ (269 mg, 1.95 mmol, 2.0 eq.) in DMF (7 mL) was added MeI (0.12 mL, 1.95 mmol, 2.0 eq.). The reaction mixture was stirred at room temperature for 1.5 h, then diluted with EtOAc (75 mL) and washed with $H_2O$ (15 mL) and brine (15 mL). The layers were separated and the organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by ISCO (24 g, gradient: 10% to 20% EtOAc in hexanes over 15 min) to yield methyl ester **(±)-536** (417 mg, 86% over two steps).

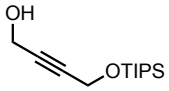
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.73-7.65 (m, 4H), 7.43-7.28 (m, 11H), 4.53 (s, 2H), 4.32-4.27 (m, 1H), 4.09 (t, *J* = 2.1 Hz, 2H), 3.57 (s, 3H), 2.72-2.61 (m, 2H), 2.48-2.35 (m, 2H), 1.04 (s, 9H).




**7-(Benzyloxy)-3-oxohept-5-ynenitrile (544):** To a solution of alcohol **(±)-532** (799 mg, 3.48 mmol, 1.0 eq.) in $CH_2Cl_2$ (12 mL) was added Dess-Martin periodinane (2.22 g, 5.23 mmol, 1.5 eq.) and the resulting mixture was stirred at room temperature for 30 min. The reaction mixture was quenched by the addition of saturated $NaHCO_3$ (4 mL) and saturated $Na_2S_2O_3$ (4 mL) and extracted with $CH_2Cl_2$ (80 mL). The organic extract was washed with saturated $NaHCO_3$ (2 x 8 mL) and brine (8 mL), dried over $MgSO_4$, filtered, and

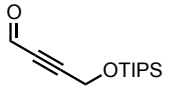
concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to yield ketone **544** (620 mg, 78%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.39-7.31 (m, 5H), 5.98-5.92 (m, 1H, enol), 4.59/4.58 (s, 2H), 4.23-4.20 (m, 2H), 3.72/3.64 (s, 2H), 3.48 (t, *J* = 2.1 Hz, 1H, keto).



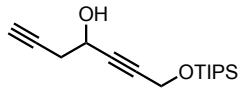

**4-((Triisopropylsilyl)oxy)but-2-yn-1-ol (552):** A solution of 1,4-butynediol (925 mg, 10.4 mmol, 2.0 eq.) in THF (15 mL) was cooled to 0 ºC and NaH (311 mg, 7.79 mmol, 1.5 eq., 60% dispersion in mineral oil) was added. After 30 min, TIPSCl (1.11 mL, 5.19 mmol, 1.0 eq.) was added and the resulting mixture was allowed to warm slowly to room temperature and stirred for an additional 15 h. The reaction mixture was then quenched with $H_2O$ (10 mL) and diluted with EtOAc (100 mL). The layers were separated and the organic phase was washed with $H_2O$ (2 x 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was taken up in hexanes/EtOAc (9:1), filtered through a plug of $SiO_2$, and concentrated *in vacuo* to yield alcohol **552**, which was used without further purification. Spectral data consistent with reported values.[241]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 4.43-4.41 (m, 2H), 4.30 (t, *J* = 1.7 Hz, 2H), 1.16-1.05 (m, 21H).



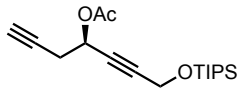

**4-((Triisopropylsilyl)oxy)but-2-ynal (553):** To a solution of alcohol **552** (5.19 mmol, 1.0 eq.) in $CH_2Cl_2$ (40 mL) was added $MnO_2$ (4.15 g, 41.5 mmol, 8.0 eq., 90%). The resulting black suspension was stirred at room temperature for 22 h before the addition of an additional portion of $MnO_2$ (2.08 g, 20.8 mmol, 4.0 eq., 90%). After an additional 30 min at room temperature, the reaction mixture was filtered through a plug of $SiO_2$ and the solvents were removed *in vacuo* to yield crude aldehyde **553**, which was used without further purification.

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 9.24 (s, 1H), 4.58 (s, 2H), 1.15-1.05 (m, 21H).




**7-((Triisopropylsilyl)oxy)hepta-1,5-diyn-4-ol ((±)-554):** To a solution of aldehyde **553** (5.19 mmol, 1.0 eq.) and propargyl bromide (1.16 mL, 7.79 mmol, 1.5 eq., 80% wt. in PhMe) in THF (25 mL) was added Znº (2.23 g, 26.0 mmol, 5.0 eq.). The resulting suspension was stirred at room temperature for 10 min before being placed in an ultrasound bath for 30 min. Upon completion, the reaction mixture was quenched with 1N HCl (10 mL) and extracted with EtOAc (3 x 75 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1) to yield alcohol **(±)-554** (1.12 g, 77% over three steps).

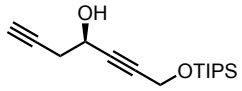
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 4.57-4.55 (m, 1H), 4.42 (d, *J* = 1.7 Hz, 2H), 2.68-2.56 (m, 2H), 2.18 (d, *J* = 5.9 Hz, 1H), 2.10 (t, *J* = 2.7 Hz, 1H), 1.16-1.05 (m, 21H).




**(*R*)-7-((Triisopropylsilyl)oxy)hepta-1,5-diyn-4-yl acetate (555):** To a solution of alcohol **(±)-554** (5.21 g, 18.6 mmol, 1.0 eq.) and vinyl acetate (6.85 mL, 74.3 mmol, 4.0 eq.) in hexane (150 mL) was added powdered 4Å MS (2.61 g) and AmanoPS (2.61 g). The resulting suspension was stirred at room temperature for 18 h, then filtered through a plug of celite and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 19:1 to 9:1) to yield acetate **555** (2.33 g, 39%, er > 19:1) and **(*S*)-554** (2.82 g, 54%, er = 19:1).

Data for acetate **555**:

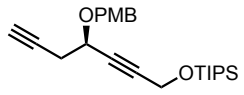
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.54 (tt, *J* = 6.5, 1.7 Hz, 1H), 4.42 (d, *J* = 1.7 Hz, 2H), 2.68 (dd, *J* = 6.4, 2.6 Hz, 2H), 2.10 (s, 3H), 2.04 (t, *J* = 2.8 Hz, 1H), 1.15-1.04 (m, 21H).




**(*R*)-7-((Triisopropylsilyl)oxy)hepta-1,5-diyn-4-ol ((*R*)-554):**

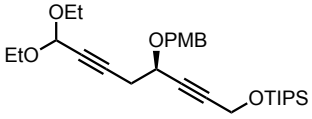
From **555**: To a solution of acetate **555** (2.33 g, 7.22 mmol, 1.0 eq.) in MeOH (50 mL) was added $K_2CO_3$ (999 mg, 7.22 mmol, 1.0 eq.) and the resulting suspension was stirred at room temperature for 1.5 h. The solvents were then removed *in vacuo* and the resulting crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1) to yield alcohol **(*R*)-554** (2.00 g, >96%).

From **(*S*)-554**: A solution of DNBzOH (3.20 g, 15.1 mmol, 1.5 eq.) and $PPh_3$ (3.96 g, 15.1 mmol, 1.5 eq.) in PhMe (40 mL) was cooled to 0 ºC before the addition of **(*S*)-554** (2.82 g, 10.1 mmol, 1.0 eq.) as a solution in PhMe (8 mL) followed immediately by the dropwise addition of DIAD (2.77 mL, 14.1 mmol, 1.4 eq.). The reaction mixture was stirred at 0 ºC for 1 h, before the solvents were removed *in vacuo*. The residue was taken up in THF (40 mL) and 1N LiOH (30 mL) was added. The resulting mixture was stirred at room temperature for 2 h then poured into a separatory funnel containing 1N HCl (30 mL). The biphasic mixture was diluted with EtOAc (120 mL) and the aqueous layer was removed. The organic phase was further washed with brine (30 mL), dried over $Na_2SO_4$, filtered, and concentrated onto $SiO_2$ (~10 g). The crude mixture was purified by flash column chromatography (hexanes/EtOAc, 9:1) to yield **(*R*)-554** (1.99 g, 71%). Spectral data matches **(±)-554**.



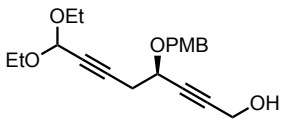

**(*R*)-Triisopropyl((4-((4-methoxybenzyl)oxy)hepta-2,6-diyn-1-yl)oxy) silane (556):** A solution of **(*R*)-554** (2.73 g, 9.73 mmol, 1.0 eq.) and PMBTCA (8.25 g, 29.2 mmol, 3.0 eq.) in PhMe (47 mL) was cooled to 0 ºC and powdered 4Å MS (1.37 g) and $Sc(OTf)_3$ (479 mg, 0.973 mmol, 0.1 eq.) were added sequentially. The resulting suspension was allowed to warm slowly to room temperature and stirred for 14 h. The reaction mixture was then poured into a separatory funnel containing saturated $NaHCO_3$ (20 mL) and extracted with EtOAc (120 mL). The organic extract was further washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by ISCO (80 g, gradient: 0% to 5% EtOAc in hexanes over 30 min) to yield PMB ether **556** (2.82 g, 72%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.31-7.29 (m, 2H), 6.88-6.86 (m, 2H), 4.74 (d, *J* = 11.6 Hz, 1H), 4.51-4.47 (m, 3H), 4.25 (tt, *J* = 6.5, 1.5 Hz, 1H), 3.80 (s, 3H), 2.67-2.56 (m, 2H), 2.03 (t, *J* = 2.6 Hz, 1H), 1.18-1.07 (m, 21H).




**(*R*)-((8,8-Diethoxy-4-((4-methoxybenzyl)oxy)octa-2,6-diyn-1-yl)oxy)triisopropylsilane (557):** To a solution of alkyne **556** (2.82 g, 7.04 mmol, 1.0 eq.) in $HC(OEt)_3$ (14 mL) was added $ZnI_2$ (1.12 g, 3.52 mmol, 0.5 eq.) and the resulting mixture was heated to 140 ºC. After 16 h, the reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 19:1 to 9:1) to yield acetal **557** (2.59 g, 73%, contaminated with ~25% $HC(OEt)_3$).

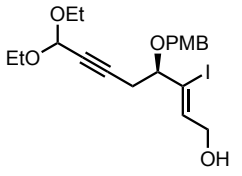
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.29-7.27 (m, 2H), 6.87-6.85 (m, 2H), 5.24 (t, *J* = 1.6 Hz, 1H), 4.72 (d, *J* = 11.3 Hz, 1H), 4.48-4.43 (m, 3H), 4.27-4.20 (m, 1H), 3.80 (s, 3H), 3.75-3.69 (m, 2H), 3.60-3.48 (m, 2H), 2.74-2.62 (m, 2H), 1.26-1.20 (m, 6H), 1.17-1.07 (m, 21H).




**(*R*)-8,8-Diethoxy-4-((4-methoxybenzyl)oxy)octa-2,6-diyn-1-ol (558):** A solution of acetal **557** (3.29 g, 6.54 mmol, 1.0 eq.) in THF (65 mL) was cooled to 0 ºC and TBAF (13.1 mL, 13.1 mmol, 2.0 eq., 1.0 M solution in THF) was added dropwise. The reaction mixture was stirred at that temperature for 1.5 h before quenching with saturated $NH_4Cl$ (15 mL). The reaction mixture was extracted with EtOAc (3 x 75 mL) and the combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude

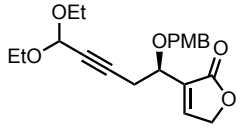
residue was purified by ISCO (40 g, gradient: 20% to 50% EtOAc in hexanes over 18 min) to yield alcohol **558** (2.47 g, >96%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.29-7.27 (m, 2H), 6.89-6.85 (m, 2H), 5.26 (t, *J* = 1.5 Hz, 1H), 4.71 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.32 (d, *J* = 1.4 Hz, 2H), 4.28-4.25 (m, 1H), 3.80 (s, 3H), 3.78-3.70 (m, 2H), 3.61-3.53 (m, 2H), 2.70-2.63 (m, 2H), 1.30-1.21 (m, 6H).




**(*R*,*Z*)-8,8-Diethoxy-3-iodo-4-((4-methoxybenzyl)oxy)oct-2-en-6-yn-1-ol (559):** A solution of RedAl (1.04 mL, 3.09 mmol, 1.5 eq., 60% wt. in PhMe) in THF (5 mL) was cooled to 0 ºC and alcohol **558** (713 mg, 2.06 mmol, 1.0 eq.) was added dropwise as a solution in THF (1 mL). After 45 min, the cooling bath was removed and the resulting solution was stirred at room temperature for an additional 45 min. The excess RedAl was quenched with EtOAc (1.5 mL) and the reaction mixture was cooled to -78 ºC before the dropwise addition of $I_2$ (783 mg, 3.09 mmol, 1.5 eq.) in THF (2 mL). The resulting dark solution was stirred at -78 ºC for 20 min, the cooling bath was removed, and the reaction mixture was stirred for an additional 15 min. The reaction mixture was poured into a mixture of saturated $Na_2S_2O_3$ (8 mL) and Rochelle's salt (8 mL) and stirred vigorously for 30 min. The biphasic mixture was transferred to a separatory funnel and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by ISCO (24 g, gradient: 20% to 50% EtOAc in hexanes over 18 min) to yield vinyl iodide **559** (913 mg, 94%).

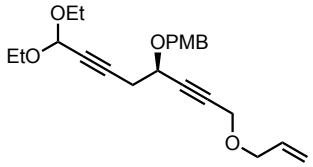
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.28-7.26 (m, 2H), 6.89-6.86 (m, 2H), 6.33 (t, *J* = 5.5 Hz, 1H), 4.53 (d, *J* = 11.2 Hz, 1H), 4.34-4.31 (m, 1H), 4.21 (d, *J* = 11.8 Hz, 1H), 3.81 (s, 3H), 3.74-3.66 (m, 2H), 3.60-3.53 (m, 2H), 2.63-2.49 (m, 2H), 1.97 (t, *J* = 6.1 Hz, 1H), 1.28-1.20 (m, 6H).




**(*R*)-3-(5,5-Diethoxy-1-((4-methoxybenzyl)oxy)pent-3-yn-1-yl)furan-2(5*H*)-one (560):** A microwave vial was charged with $Pd(OAc)_2$ (4 mg, 0.0169 mmol, 0.1 eq.) and $PPh_3$ (9 mg, 0.0337 mmol, 0.2 eq.). Vinyl iodide **559** (80 mg, 0.169 mmol, 1.0 eq.) was then added as a solution in DMF (4 mL) followed by $NEt_3$ (0.05 mL, 0.337 mmol, 2.0 eq.). CO was bubbled through the solution as the solution turned from green to dark red. After 1 h, the stream of CO was stopped, replaced with a balloon of CO, and the reaction mixture was heated to 50 ºC. The reaction mixture was stirred at that temperature for 18 h, then cooled to room temperature. The resulting solution was poured into a separatory funnel containing EtOAc

(50 mL) and washed with brine (3 x 5 mL). The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to yield butenolide **560** (41 mg, 65%).

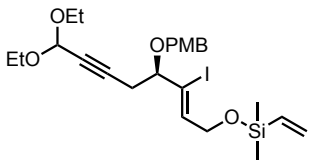
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.47 (d, *J* = 1.1 Hz, 1H), 7.28-7.27 (m, 2H), 6.88-6.86 (m, 2H), 5.22 (t, *J* = 1.6 Hz, 1H), 4.83 (t, *J* = 1.6 Hz, 2H), 4.54 (s, 2H), 4.44-4.41 (m, 1H), 3.80 (s, 1H), 3.72-3.67 (m, 2H), 3.58-3.52 (m, 2H), 2.85 (ddd, *J* = 17.0, 5.3, 1.6 Hz, 1H), 2.68 (ddd, *J* = 17.1, 5.7, 1.7 Hz, 1H), 1.27-1.19 (m, 6H).




**(*R*)-1-(((1-(Allyloxy)-8,8-diethoxyocta-2,6-diyn-4-yl)oxy)methyl) -4-methoxybenzene (561):** A solution of vinyl iodide **559** (90 mg, 0.190 mmol, 1.0 eq.) in THF (1 mL) was cooled to 0 ºC in a flask protected from light and NaH was added (11 mg, 0.285 mmol, 1.5 eq., 60% dispersion in mineral oil). The reaction mixture was stirred at that temperature for 30 min before the addition of allyl bromide (0.05 mL, 0.569 mmol, 3.0 eq.). The resulting solution was allowed to warm slowly to room temperature and stirred for an additional 14 h. The reaction mixture was then quenched with saturated $NH_4Cl$ (2 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 6:1) to yield ether **561** (54 mg, 74%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.30-7.27 (m, 2H), 6.89-6.85 (m, 2H), 5.97-5.87 (m, 1H), 5.35-5.30 (m, 1H), 5.26-5.21 (m, 2H), 4.73 (d, *J* = 11.2 Hz, 1H), 4.47 (d, *J* = 11.2 Hz, 1H), 4.29-4.25 (m, 1H), 4.23 (d, *J* = 1.6 Hz, 2H), 4.08 (dt, *J* = 5.8, 1.3 Hz, 2H), 3.80 (s, 3H), 3.77-3.69 (m, 2H), 3.60-3.53 (m, 2H), 2.75-2.64 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 6H).

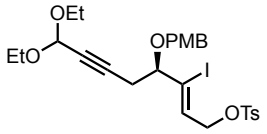
$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 159.3, 133.7, 129.6, 129.3, 117.8, 113.7, 91.3, 84.0, 82.4, 81.6, 77.7, 70.5, 70.3, 66.5, 66.6(0), 60.5(7), 57.2, 55.2, 26.4, 15.0.




**(*R*,*Z*)-((8,8-Diethoxy-3-iodo-4-((4-methoxybenzyl)oxy)oct-2-en-6-yn-1-yl)oxy)dimethyl(vinyl)silane (562):** To a solution of vinyl iodide **559** (243 mg, 0.512 mmol, 1.0 eq.), $NEt_3$ (0.11 mL, 0.768 mmol, 1.5 eq.), and DMAP (spatula tip) in $CH_2Cl_2$ (2 mL) was added DMVSCl (0.09 mL, 0.665 mmol, 1.3 eq.). The resulting solution was stirred at room temperature for 1.5 h, then quenched with saturated $NaHCO_3$ (5 mL) and extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated

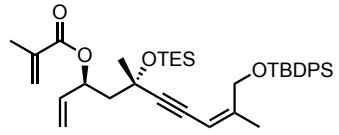
*in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 6:1) to yield silyl ether **562** (175 mg, 61%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.28-7.26 (m, 2H), 6.88-6.86 (m, 2H), 6.28 (t, *J* = 4.9 Hz, 1H), 6.19-6.03 (m, 2H), 5.83 (dd, *J* = 20.2, 4.0 Hz, 1H), 5.21 (t, *J* = 1.6 Hz, 1H), 4.51 (d, *J* = 11.3 Hz, 1H), 4.35-4.23 (m, 2H), 4.18 (d, *J* = 11.3 Hz, 1H), 3.80 (s, 3H), 3.73-3.65 (m, 2H), 3.58-3.50 (m, 2H), 2.55 (dd, *J* = 6.8, 1.5 Hz, 2H), 1.23-1.19 (m, 6H), 0.23 (s, 6H).



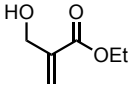

**(*R*,*Z*)-8,8-Diethoxy-3-iodo-4-((4-methoxybenzyl)oxy)oct-2-en-6-yn-1-yl 4-methylbenzenesulfonate (563):** To a cooled solution of vinyl iodide **559** (231 mg, 0.487 mmol, 1.0 eq.), $NEt_3$ (0.14 mL, 0.974 mmol, 2.0 eq.), and DMAP (spatula tip) in $CH_2Cl_2$ (1.5 mL) at 0 ºC was added $Ts_2O$ (238 mg, 0.730 mmol, 1.5 eq.). The resulting solution was stirred at that temperature for 3.5 h, then quenched with 1N HCl (5 mL) and extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to yield tosylate **563** (146 mg, 48%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.84 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 2H), 6.27 (t, *J* = 6.3 Hz, 1H), 5.19 (s, 1H), 4.73 (dd, *J* = 13.3, 6.1 Hz, 1H), 4.64 (dd, *J* = 13.3, 5.3 Hz, 1H), 4.43 (d, *J* = 11.4 Hz, 1H), 4.13 (d, *J* = 11.4 Hz, 1H), 3.81 (s, 3H), 3.71-3.63 (m, 2H), 3.56-3.49 (m, 2H), 2.50 (dd, *J* = 6.7, 1.4 Hz, 2H), 2.44 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 6H).



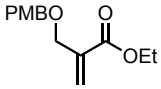

**(3*S*,5*S*,*Z*)-10-((*tert*-Butyldiphenylsilyl)oxy)-5,9-dimethyl-5-(triethylsilyl)deca-1,8-dien-6-yn-3-yl methacrylate (565):** A solution of allylic alcohol **526** (371 mg, 0.678 mmol, 1.0 eq.) in $CH_2Cl_2$ (7 mL) was cooled to 0 ºC and $NEt_3$ (0.47 mL, 3.39 mmol, 5.0 eq.) and methacryloyl chloride (0.27 mL, 2.71 mmol, 4.0 eq.) were added sequentially. The reaction mixture was allowed to warm slowly to room temperature and stirred for 18 h. The reaction mixture was then quenched with 1N HCl (5 mL) and extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 19:1) to yield ester **565** (186 mg, 43%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.68-7.66 (m, 4H), 7.43-7.35 (m, 6H), 6.09 (s, 1H), 5.82-5.74 (m, 1H), 5.56-5.50 (m, 2H), 5.28 (m, 1H), 5.16-5.12 (m, 1H), 5.06-5.04 (m, 1H), 4.41 (s, 2H), 2.00-1.84 (m, 8H), 1.30 (s, 3H), 1.06 (s, 9H), 0.86 (t, *J* = 7.7 Hz, 9H), 0.54 (q, *J* = 7.7 Hz, 6H).



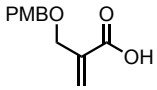

**Ethyl 2-(hydroxymethyl)acrylate (567):** To a solution of phosphonate **566** (5.00 g, 22.3 mmol, 1.0 eq.) in $CH_2O$ (23 mL, 37% aq. solution) was added $K_2CO_3$ (6.16 g, 44.6 mmol, 2.0 eq.) as a solution in $H_2O$ (23 mL) dropwise via addition funnel over 20 min. The reaction mixture was stirred at room temperature for 30 min, then quenched with saturated $NH_4Cl$ (20 mL) and extracted with $Et_2O$ (180 mL). The organic extract was washed with brine (20 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/$Et_2O$, 2:1) to yield alcohol **567** (2.26 g, 78%). Spectral data consistent with reported values.[242]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 6.25 (s, 1H), 5.82 (d, *J* = 1.3 Hz, 1H), 4.33 (s, 2H), 4.25 (q, *J* = 7.2 Hz, 2H), 2.28 (bs, 1H), 1.32 (t, *J* = 7.2 Hz, 3H).



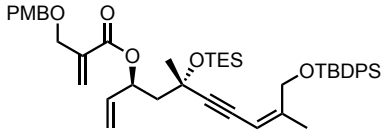

**Ethyl 2-(((4-methoxybenzyl)oxy)methyl)acrylate (568):** To a solution of alcohol **567** (2.26 g, 17.4 mmol, 1.0 eq.), PMBTCA (9.81 g, 34.7 mmol, 2.0 eq.) in $CH_2Cl_2$ (18 mL) was added powdered 4Å MS (2.30 g) and CSA (2.02 g, 8.68 mmol, 0.5 eq.). The resulting suspension was stirred at room temperature for 4 h, then quenched with saturated $NaHCO_3$ (10 mL) and extracted with $CH_2Cl_2$ (3 x 75 mL). The organic extract was washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield crude ester **568** which was used without further purification. Spectral data consistent with reported values.[243]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.29-7.26 (m, 2H), 6.89-6.87 (m, 2H), 6.31-6.30 (m, 1H), 5.90-5.89 (m, 1H), 4.51 (s, 2H), 4.25-4.19 (m, 4H), 3.80 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H).



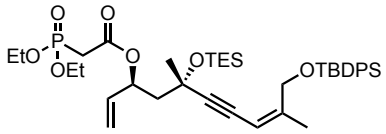

**2-(((4-Methoxybenzyl)oxy)methyl)acrylic acid (569):** To a solution of crude ester **568** (17.4 mmol, 1.0 eq.) in THF (20 mL) and $H_2O$ (20 mL) was added LiOH (2.92 g, 69.6 mmol, 4.0 eq.). The resulting solution was stirred at room temperature for 12 h, then acidified with concentrated HCl (8 mL) and extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (3 x 20 mL) and the combined washes were carefully acidified to ~pH 2 with concentrated HCl and re-extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic extracts were dried over $Na_2SO_4$ , filtered, and concentrated *in vacuo*. The crude residue was recrystallized from PhMe to yield acid **569** (1.52 g, 39% over two steps). Spectral data consistent with reported values.[243]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.77 (bs, 1H), 7.29-7.27 (m, 2H), 6.90-6.88 (m, 2H), 6.47 (m, 1H), 6.04 (m, 1H), 4.54 (s, 2H), 4.22 (s, 2H), 3.81 (s, 3H).



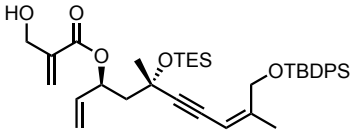

**(3*S*,5*S*,*Z*)-10-((*tert*-Butyldiphenylsilyl)oxy)-5,9-dimethyl-5-(triethylsilyl)deca-1,8-dien-6-yn-3-yl 2-(((4-methoxybenzyl)oxy)methyl)acrylate (570):** To a solution of alcohol **526** (152 mg, 0.270 mmol, 1.0 eq.) and acid **569** (240 mg, 1.08 mmol, 4.0 eq.) in $CH_2Cl_2$ (2 mL) was added DMAP (132 mg, 1.08 mmol, 4.0 eq.) and EDCI-HCl (207 mg, 1.08 mmol, 4.0 eq.). The resulting solution was stirred at room temperature for 15 h, then quenched with $H_2O$ (5 mL) and extracted with $CH_2Cl_2$ (3 x 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 19:1) to yield ester **570** (51 mg, 25%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.68-7.65 (m, 4H), 7.41-7.34 (m, 6H), 7.28-7.26 (m, 2H), 6.89-6.86 (m, 2H), 6.29 (d, *J* = 1.4 Hz, 1H), 5.90 (d, *J* = 1.4 Hz, 1H), 5.81-5.72 (m, 1H), 5.58-5.54 (m, 1H), 5.27 (m, 1H), 5.14 (d, *J* = 17.1 Hz, 1H), 5.05 (d, *J* = 10.5 Hz, 1H), 4.50 (s, 2H), 4.40 (s, 2H), 4.20 (s, 2H), 3.80 (s, 3H), 1.99-1.91 (m, 4H), 1.86 (dd, *J* = 14.5, 4.0 Hz, 1H), 1.29 (s, 3H), 1.05 (s, 9H), 0.85 (t, *J* = 8.0 Hz, 9H), 0.53 (q, *J* = 8.0 Hz, 6H).



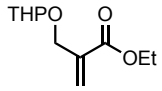

**(3*S*,5*S*,*Z*)-10-((*tert*-Butyldiphenylsilyl)oxy)-5,9-dimethyl-5-((triethylsilyl)oxy)deca-1,8-dien-6-yn-3-yl 2-(diethoxyphosphoryl)acetate (571):** To a solution of alcohol **526** (339 mg, 0.602 mmol, 1.0 eq.) and acid **345** (472 mg, 2.41 mmol, 4.0 eq.) in $CH_2Cl_2$ (3 mL) was added DMAP (294 mg, 2.41 mmol, 4.0 eq.) and EDCI-HCl (462 mg, 2.41 mmol, 4.0 eq.). The resulting solution was stirred at room temperature for 13 h, then quenched with $H_2O$ (10 mL) and extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic extracts were washed with 1N HCl (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by ISCO (12 g, gradient: 20% to 50% EtOAc in hexanes over 15 min) to yield phosphonate **571** (300 mg, 67%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.68-7.66 (m, 4H), 7.42-7.35 (m, 6H), 5.79-5.71 (m, 1H), 5.54-5.50 (m, 1H), 5.29-5.28 (m, 1H), 5.24 (dt, *J* = 17.3, 1.2 Hz, 1H), 5.08-5.05 (m, 1H), 4.41 (s, 2H), 4.19-4.11 (m, 4H), 3.00-2.85 (m, 2H), 1.98-1.93 (m, 4H), 1.85 (dd, *J* = 14.5, 4.7 Hz, 1H), 1.34-1.30 (m, 9H), 1.06 (s, 9H), 0.86 (t, *J* = 7.9 Hz, 9H), 0.54 (q, *J* = 7.9 Hz, 6H).



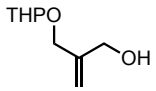

**(3*S*,5*S*,*Z*)-10-((*tert*-Butyldiphenylsilyl)oxy)-5,9-dimethyl-5-((triethylsilyl)oxy)deca-1,8-dien-6-yn-3-yl 2-(hydroxymethyl)acrylate (572):** To a solution of phosphonate **571** (300 g, 0.405 mmol, 1.0 eq.) in $CH_2O$ (0.5 mL, 37% aq. solution) and THF (0.5 mL) was added $K_2CO_3$ (112 mg, 0.810 mmol, 2.0 eq.). The reaction mixture was stirred at room temperature for 17 h, then quenched with saturated $NH_4Cl$ (5 mL) and extracted with $CH_2Cl_2$ (3 x 30 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by ISCO (12 g, gradient: 10% to 40% EtOAc in hexanes over 15 min) to yield alcohol **572** (153 mg, 58%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.67-7.65 (m, 4H), 7.42-7.34 (m, 6H), 6.22 (s, 1H), 5.80-5.72 (m, 2H), 5.59-5.55 (m, 1H), 5.27 (m, 1H), 5.14 (dt, *J* = 17.4, 1.2 Hz, 1H), 5.06 (dt, *J* = 10.6, 1.2 Hz, 1H), 4.40 (s, 2H), 4.30 (d, *J* = 5.5 Hz, 2H), 2.22 (t, *J* = 5.6 Hz, 1H), 1.98 (dd, *J* = 14.6, 7.4 Hz, 1H), 1.93-1.91 (m, 3H), 1.85 (dd, *J* = 14.6, 3.7 Hz, 1H), 1.29 (s, 3H), 1.05 (s, 9H), 0.85 (t, *J* = 8.0 Hz, 9H), 0.56-0.50 (m, 6H).




**Ethyl 2-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)acrylate (573):** To a solution of alcohol **567** (4.44 g, 34.1 mmol, 1.0 eq.) and PPTS (1.71 g, 6.82 mmol, 0.2 eq.) in $CH_2Cl_2$ (50 mL) was added DHP (9.34 mL, 102 mmol, 3.0 eq.). The resulting solution was stirred at room temperature for 22 h, then quenched with saturated $NaHCO_3$ (20 mL) and extracted with $CH_2Cl_2$ (100 mL). The organic extract was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield crude ester **573**, which was used without further purification. Spectral data consistent with reported values.[244]

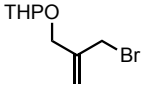
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 6.29 (q, *J* = 1.4 Hz, 1H), 5.88 (q, *J* = 1.7 Hz, 1H), 4.69 (t, *J* = 3.5 Hz, 1H), 4.45 (dt, *J* = 14.3, 1.6 Hz, 1H), 4.25-4.17 (m, 3H), 3.97 (t, *J* = 5.3 Hz, 1H), 3.90-3.84 (m, 1H), 3.55-3.50 (m, 1H), 1.88-1.50 (m, 6H, overlapped with excess DHP), 1.30 (t, *J* = 7.0 Hz, 3H).




**2-(((Tetrahydro-2*H*-pyran-2-yl)oxy)methyl)prop-2-en-1-ol (574):** To a solution of crude ester **573** (34.1 mmol, 1.0 eq.) in $CH_2Cl_2$ (68 mL) at -78 °C was added DIBAL (18.2 mL, 102 mmol, 3.0 eq.) dropwise. The reaction mixture was stirred at that temperature for 5 h, then quenched by the careful addition of MeOH (5 mL). Once the reaction had been quenched, the resulting solution was poured into Rochelle's salt (50 mL) and stirred vigorously for 15 h. The biphasic mixture was then extracted with $CH_2Cl_2$ (3 x 100 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by

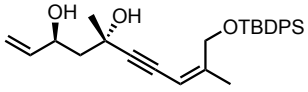
flash column chromatography (hexanes/$Et_2O$, 3:1 to 1:1) to yield alcohol **574** (3.16 g, 54% over two steps). Spectral data consistent with reported values.[245]

$^1H$ NMR (400 MHz, $CDCl_3$) ∂ 5.16 (s, 1H), 5.14 (s, 1H), 4.64-4.62 (m, 1H), 4.33 (d, *J* = 12.3 Hz, 1H), 4.23-4.15 (m, 2H), 4.07 (d, *J* = 12.3 Hz, 1H), 3.91-3.86 (m, 1H), 3.55-3.50 (m, 1H), 1.86-1.49 (m, 6H).



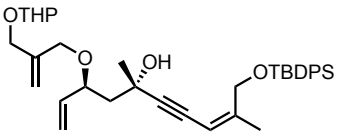

**2-((2-(Bromomethyl)allyl)oxy)tetrahydro-2*H*-pyran (575):** A solution of alcohol **574** (3.16 g, 18.3 mmol, 1.0 eq.) in $CH_2Cl_2$ (50 mL) was cooled to 0 ºC and $PPh_3$ (4.98 g, 22.0 mmol, 1.2 eq.) was added. After 1 min, $CBr_4$ (9.13 g, 27.5 mmol, 1.5 eq.) was added and the resulting solution was allowed to warm slowly to room temperature. The reaction mixture was stirred for 21 h, then quenched with saturated $NaHCO_3$ (20 mL) and extracted with $CH_2Cl_2$ (3 x 75 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by ISCO (40 g, gradient: 0% to 20% $Et_2O$ in hexanes over 18 min) to yield allylic bromide **575** (2.25 g, 52%). Spectral data consistent with reported values.[246]

$^1H$ NMR (400 MHz, $CDCl_3$) ∂ 5.32 (s, 1H), 5.26 (d, *J* = 1.3 Hz, 1H), 4.66 (t, *J* = 3.0 Hz, 1H), 4.37 (d, *J* = 12.7 Hz, 1H), 4.10 (d, *J* = 13.3 Hz, 1H), 4.04 (s, 2H), 3.91-3.86 (m, 1H), 3.56-3.51 (m, 1H), 1.88-1.80 (m, 1H), 1.77-1.70 (m, 1H), 1.66-1.51 (m, 4H).




**(3*S*,5*S*,*Z*)-10-((*tert*-Butyldiphenylsilyl)oxy)-5,9-dimethyldeca-1,8-dien-6-yne-3,5-diol (576):** To a solution of alcohol **526** (663 mg, 1.18 mmol, 1.0 eq.) in MeOH (17 mL) was added PPTS (296 mg, 1.18 mmol, 1.0 eq.). The resulting solution was stirred at room temperature for 10 min before the solvents were removed *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 6:1 to 4:1) to yield diol **576** (312 mg, 59%).

$^1H$ NMR (400 MHz, $CDCl_3$) ∂ 7.69-7.67 (m, 4H), 7.44-7.36 (m, 6H), 5.72-5.64 (m, 1H), 5.34 (m, 1H), 5.06 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.00 (dt, *J* = 10.5, 1.4 Hz, 1H), 4.47-4.43 (m, 3H), 1.97 (d, *J* = 1.4 Hz, 3H), 1.66 (dd, *J* = 14.4, 10.5 Hz, 1H), 1.57 (dd, *J* = 14.4, 2.5 Hz, 1H), 1.34 (s, 3H), 1.05 (s, 9H).

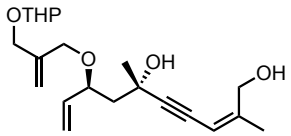



**(3*S*,5*S*,*Z*)-10-((*tert*-Butyldiphenylsilyl)oxy)-5,9-dimethyl-3-((2-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)allyl)oxy)deca-1,8-dien-6-yn-5-ol (577):** To a

solution of diol **576** (242 mg, 0.540 mmol, 1.0 eq.) in THF (1.1 mL) at 0 ºC was added NaH (24 mg, 0.593 mmol, 1.1 eq., 60% dispersion in mineral oil). The resulting suspension was stirred at that temperature for 40 min before the addition of allyl bromide **575** (380 mg, 1.62 mmol, 3.0 eq.) and TBAI (spatula tip). The reaction mixture was stirred for 1 h, then quenched with saturated $NH_4Cl$ (4 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by ISCO (24 g, gradient: 0% to 20% EtOAc in hexanes over 18 min) to yield diene **577** (246 mg, 76%) as a mixture of diastereomers.

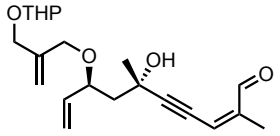
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.69-7.67 (m, 4H), 7.43-7.35 (m, 6H), 5.61-5.52 (m, 1H), 5.37-5.36 (m, 1H), 5.15-5.01 (m, 4H), 4.65 (s, 1H), 4.58 (s, 1H), 4.49-4.42 (m, 2H), 4.22-4.16 (m, 2H), 4.03-3.92 (m, 2H), 3.86-3.75 (m, 2H), 3.50-3.46 (m, 1H), 1.95 (s, 3H), 1.86-1.80 (m, 2H), 1.71-1.49 (m, 6H), 1.30 (s, 3H), 1.06 (s, 9H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 150.1, 142.1/141.9, 142.0(9)/141.9(4), 137.2(1)/137.1(7), 135.4(5)/135.4(3), 133.5/133.4, 129.6, 127.6, 117.4/117.3, 114.5/114.3, 104.9, 97.8/96.6, 96.2, 80.1/79.9, 79.8(2)/79.7(9), 68.8(9)/68.8(4), 67.8, 67.6/67.5, 64.6, 62.0(4)/62.0(1), 47.3, 30.5, 30.4(5)/30.4(1), 26.7, 25.4, 19.8, 19.3/19.2.




**(6*S*,8*S*,*Z*)-2,6-Dimethyl-8-((2-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)allyl)oxy)deca-2,9-dien-4-yne-1,6-diol (578):** To a solution of diene **577** (144 mg, 0.239 mmol, 1.0 eq.) in THF (2.5 mL) at 0 ºC was added TBAF (0.48 mL, 0.478 mmol, 1.0 eq., 1.0 M solution in THF) and the resulting solution was stirred at 0 ºC for 3.5 h. The cooling bath was then removed and an additional portion of TBAF (0.48 mL, 0.478 mmol, 1.0 eq., 1.0 M solution in THF) was added and the reaction mixture was stirred for 1 h, then quenched with saturated $NH_4Cl$ (4 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to yield diol **578** (60 mg, 69%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.75-5.66 (m, 1H), 5.42 (s, 1H), 5.32-5.18 (m, 5H), 4.81 (d, *J* = 10.2 Hz, 1H), 4.65-4.63 (m, 1H), 4.44-4.22 (m, 5H), 4.16-3.82 (m, 5H), 3.53-3.49 (m, 1H), 2.35/2.23 (bs, 1H), 2.00-1.88 (m, 5H), 1.86-1.68 (m, 4H), 1.62-1.50 (m, 6H), 1.48 (s, 3H).



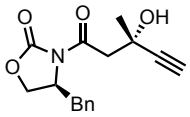

**(6*S*,8*S*,*Z*)-6-Hydroxy-2,6-dimethyl-8-((2-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)allyl)oxy)deca-2,9-dien-4-ynal (579):** To a solution of diol **578** (75 mg, 0.206 mmol, 1.0 eq.) in $CH_2Cl_2$ (2 mL) was added $MnO_2$ (247 mg, 2.47 mmol, 12.0 eq., 90%)

and the resulting suspension was stirred at room temperature for 24 h. The reaction mixture was then filtered through a plug of celite and the solvents were removed *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to yield aldehyde **579** (41 mg, 55%) as a mixture of diastereomers.

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 10.23 (s, 1H), 6.61-6.60 (m, 1H), 5.75-5.67 (m, 1H), 5.30-5.17 (m, 4H), 4.94 (bs, 1H), 4.61 (s, 1H), 4.36 (t, *J* = 8.9 Hz, 1H), 4.26 (dd, *J* = 13.1, 4.2 Hz, 1H), 4.17-4.11 (m, 1H), 4.05-3.99 (m, 1H), 3.94-3.81 (m, 2H), 3.51-3.49 (m, 1H), 2.05-1.98 (m, 1H), 1.88 (s, 3H), 1.86-1.79 (m, 2H), 1.74-1.68 (m, 1H), 1.61-1.52 (m, 7H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 191.9, 145.9, 141.8, 137.0, 125.3, 118.2/118.1, 114.9/114.7, 103.1, 97.9/97.7, 80.2/80.1, 77.1, 69.0/68.9, 68.1, 67.7/67.5, 62.1, 47.2, 30.4(2)/30.3(5), 25.3, 19.3, 15.1.

**Experimental Procedures: Section 4.4**




**(S)-4-Benzyl-3-((S)-3-hydroxy-3-methylpent-4-ynoyl)oxazolidin-2-one ((+)-486):** A solution of freshly distilled (from KOH) $^i$Pr$_2$NH (7.0 mL, 49.9 mmol, 1.7 eq.) in PhMe (50 mL) was cooled to 0 ºC and $^n$BuLi (25 mL, 49.9 mmol, 1.7 eq., 2.0 M in hexanes) was added dropwise. The resulting yellow solution was allowed to stir at that temperature for 30 min. The thus formed LDA was then transferred via cannula to a thick slurry of **(*S*)-485** (10.9 g, 49.9 mmol, 1.7 eq.) in PhMe (120 mL) at -78 ºC. The resulting mixture was allowed to stir at -78 ºC as stirring became gradually more facile. After 1 h, 3-butyn-2-one (2.00 g, 29.4 mmol, 1.0 eq.) was added rapidly. The yellow reaction mixture immediately turned deep orange. After 30 min, saturated $NH_4Cl_{(aq.)}$ (100 mL) was added and the reaction mixture was allowed to warm to room temperature. The mixture was then extracted with EtOAc (3 x 100 mL) and the combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was adsorbed onto $SiO_2$ (45 g) and purified by ISCO (330 g, gradient: 20% to 35% EtOAc in hexanes over 35 min) to afford ***epi*-(+)-486** (1.28 g, 15%, d.r. = 14:86) as a thick yellow oil and **(+)-486** (5.22 g, 62%, d.r. > 95:5) as an off-white solid. Spectral data consistent with reported values of enantiomer.[140]

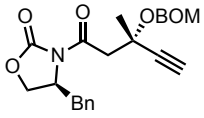
$R_f$ 0.24 (2:1 hexanes/ethyl acetate, UV/PAA (orange))

m.p. 116-119 ºC ($Et_2O$, white needles)

$[\alpha]^{20}_D$ 85.1 (c = 1.0, $CHCl_3$)

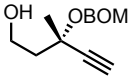
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.36-7.22 (m, 5H), 4.76-4.71 (m 1H), 4.43 (s, 1H, exchanges w/ $D_2O$), 4.27-4.19 (m, 2H), 3.78 (d, *J* = 17.6 Hz, 1H), 3.31 (dd, *J* = 13.4, 2.8 Hz, 1H), 2.96 (d, *J* = 17.6 Hz, 1H), 2.87 (dd, *J* = 13.4, 9.2 Hz, 1H), 2.46 (s, 1H), 1.61 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 171.9, 153.1, 134.7, 129.4, 129.0, 127.4, 86.5, 70.9, 66.2, 65.3, 54.9, 37.7, 29.5.



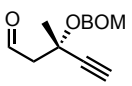

**(*S*)-4-Benzyl-3-((*S*)-3-((benzyloxy)methoxy)-3-methylpent-4-ynoyl)oxazolidin-2-one (589):** To a solution of **(+)-486** (1.32 g, 4.59 mmol, 1.0 eq.) and TBAI (spatula tip) in DMF (10 mL) was added $^i$Pr$_2$NEt (2.40 mL, 13.8 mmol, 3.0 eq.) and BOMCl (1.92 mL, 13.8 mmol, 3.0 eq.). The resulting solution was heated to 50 ºC and stirred at that temperature for 15 h. Once the reaction had cooled back to room temperature, EtOAc (100 mL) was added and the organic phase was washed with $H_2O$ (2 x 10 mL) and brine (10 mL). The organic layer was then dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The crude residue was filtered through a plug of $SiO_2$ (hexanes/EtOAc, 2:1) to afford alkyne **589**, which was used without further purification.

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.38-7.20 (m, 10H), 5.17 (d, *J* = 7.6 Hz, 1H), 5.04 (d, *J* = 7.6 Hz, 1H), 4.72-4.61 (m, 3H), 4.11-4.09 (m, 2H), 3.70 (d, *J* = 16.1 Hz, 1H), 3.39 (d, *J* = 16.1 Hz, 1H), 3.32 (dd, *J* = 13.2, 2.9 Hz, 1H), 2.69 (dd, *J* = 12.8, 9.7 Hz, 1H), 2.63 (s, 1H), 1.76 (s, 3H).




**(*S*)-3-((Benzyloxy)methoxy)-3-methylpent-4-yn-1-ol (590):** To a solution of alkyne **589** (4.59 mmol, 1.0 eq.) in THF (55 mL) and MeOH (14 mL) at 0 ºC was added $LiBH_4$ (6.9 mL, 13.8 mmol, 3.0 eq., 2.0 M solution in THF). The reaction mixture was stirred at that temperature for 2 h, then quenched by the sequential addition of EtOAc (5 mL) and $H_2O$ (10 mL) and finally extracted with EtOAc (3 x 75 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to yield alcohol **590** (841 mg, 78% over two steps).

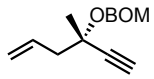
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.38-7.28 (m, 5H), 5.19 (d, *J* = 7.3 Hz, 1H), 4.93 (d, *J* = 7.3 Hz, 1H), 4.72 (d, *J* = 11.7 Hz, 1H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.03-3.97 (m, 1H), 3.87-3.81 (m, 1H), 2.57 (s, 1H), 2.10 (ddd, *J* = 14.5, 7.9, 4.6 Hz, 1H), 1.97 (ddd, *J* = 14.5, 6.1, 4.2 Hz, 1H), 1.60 (s, 3H).




**(*S*)-3-((Benzyloxy)methoxy)-3-methylpent-4-ynal (591):** A solution of $(COCl)_2$ (0.09 mL, 1.02 mmol, 1.6 eq.) in $CH_2Cl_2$ (2.5 mL) was cooled to -78 ºC and DMSO (0.15 mL,

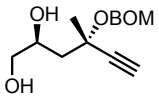
2.05 mmol, 3.2 eq.) was added dropwise. After 15 min, alcohol **590** (150 mg, 0.640 mmol, 1.0 eq.) was added as a solution in $CH_2Cl_2$ (0.5 mL). After stirring at -78 ºC for an additional 15 min, $NEt_3$ (0.45 mL, 3.20 mmol, 5.0 eq.) was added and stirring was continued for 1 h. The reaction mixture was then quenched with $H_2O$ (4 mL) and extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield crude aldehyde **591**, which was used without further purification.

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 9.86 (t, *J* = 2.7 Hz, 1H), 7.36-7.27 (m, 5H), 5.14 (d, *J* = 7.6 Hz, 1H), 5.01 (d, *J* = 7.6 Hz, 1H), 4.67 (d, *J* = 11.9 Hz, 1H), 4.58 (d, *J* = 11.9 Hz, 1H), 2.78-2.67 (m, 3H), 1.64 (s, 3H).




**(*S*)-((((3-Methylhex-5-en-1-yn-3-yl)oxy)methoxy)methyl)benzene (592):** A suspension of methyltriphenylphosphonium bromide (274 mg, 0.768 mmol, 1.2 eq.) in THF (6 mL) was cooled to 0 ºC before the dropwise addition of $^n$BuLi (0.32 mL, 0.704 mmol, 1.1 eq., 2.2 M solution in hexanes). The resulting orange solution was stirred at that temperature for 30 min and aldehyde **591** (0.640 mmol, 1.0 eq.) was then added as a solution in THF (1.5 mL). The reaction mixture was stirred for 30 min, quenched with saturated $NH_4Cl$ (6 mL), and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 6:1) to yield olefin **592** (84 mg, 57% over two steps).

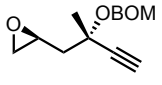
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.37-7.27 (m, 5H), 5.98-5.88 (m, 1H), 5.17-5.10 (m, 3H), 5.01 (d, *J* = 7.4 Hz, 1H), 4.69 (d, *J* = 11.5 Hz, 1H), 4.62 (d, *J* = 11.5 Hz, 1H), 2.61-2.45 (m, 3H), 1.53 (s, 3H).




**(2*S*,4*S*)-4-((Benzyloxy)methoxy)-4-methylhex-5-yne-1,2-diol (593):** A solution of olefin **592** (84 mg, 0.365 mmol, 1.0 eq.) in $^t$BuOH (2.5 mL) and $H_2O$ (2.5 mL) was cooled to 0 ºC and AD-mix-α (510 mg) was added. The resulting biphasic mixture was allowed to warm slowly to room temperature and stirred vigorously for 88 h. The reaction mixture was quenched with solid $Na_2S_2O_3$-$5H_2O$ (100 mg, 0.402 mmol, 1.1 eq.) and stirred for 1 h at room temperature. The reaction mixture was then extracted with EtOAc (3 x 50 mL) and the combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 1:1 to EtOAc) to yield diol **593** (51 mg, 53%, dr ≈ 1:1).

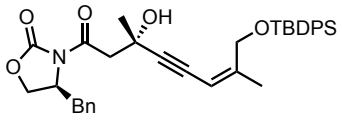
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.38-7.27 (m, 5H), 5.23/5.18 (d, *J* = 7.4 Hz, 1H), 4.94 (t, *J* = 7.4 Hz, 1H), 4.74/4.71 (d, *J* = 11.8 Hz, 1H), 4.59/4.57 (d, *J* = 11.8 Hz, 1H), 4.30-4.25/4.16-4.10 (m, 1H),

3.67/3.64 (t, *J* = 3.2 Hz, 1H), 3.54-3.49 (m, 1H), 2.61/2.59 (s, 1H), 2.09-2.01 (m, 1H), 1.88-1.75 (m, 1H), 1.63/1.62 (s, 3H).

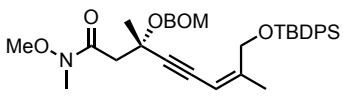



**(*S*)-2-((*S*)-2-((Benzyloxy)methoxy)-2-methylbut-3-yn-1-yl)oxirane (594):** To a solution of olefin **592** (116 mg, 0.504 mmol, 1.0 eq.) in $CH_2Cl_2$ at 0 ºC was added mCPBA (169 mg, 0.756 mmol, 1.5 eq., 77%). The resulting solution was allowed to warm slowly to room temperature and stirred for 17 h. The reaction mixture was then diluted with EtOAc (75 mL) and washed with saturated $NaHCO_3$ (2 x 15 mL) and brine (15 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 6:1) to yield epoxide **594** (114 mg, 92%, dr ≈ 1:1).
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.35-7.27 (m, 5H), 5.16-5.12 (m, 1H), 5.01 (d, *J* = 7.4 Hz, 1H), 4.71/4.69 (d, *J* = 11.8 Hz, 1H), 4.63/4.62 (d, *J* = 11.8 Hz, 1H), 3.24-3.18 (m, 1H), 2.81-2.79 (m, 1H), 2.59/2.56 (s, 1H), 2.55-2.53 (m, 1H), 2.12-2.01 (m, 1H), 1.99-1.86 (m, 1H), 1.64/1.63 (s, 3H).

**Experimental Procedures: Section 4.5**




**(*S*)-4-Benzyl-3-((*S*,*Z*)-8-((*tert*-butyldiphenylsilyl)oxy)-3-hydroxy-3,7-dimethyloct-6-en-4-ynoyl)oxazolidin-2-one (497):** A solution of **(+)-486** (2.10 g, 7.31 mmol, 1.0 eq.) and vinyl iodide **494** (3.83 g, 8.77 mmol, 1.2 eq.) in $CH_3CN$ (36 mL) was deoxygenated with a stream of Ar for 15 min before $NEt_3$ (3.06 mL, 21.9 mmol, 3.0 eq.) was added. The stream was continued for an additional 5 min and CuI (139 mg, 0.731 mmol, 0.1 eq.) and $Pd(PPh_3)_4$ (169 mg, 0.146 mmol, 0.02 eq.) were added sequentially. The stream of Ar was stopped and the resulting orange solution was stirred at room temperature for 3 hr. Upon completion of the reaction, the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1 to 2:1) to yield alcohol **497** (4.03 g, 92%, >90% purity) as an orange oil. Spectral data consistent with previously prepared sample.



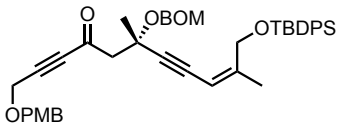

**(*S*,*Z*)-3-((Benzyloxy)methoxy)-8-((*tert*-butyldiphenylsilyl)oxy)-*N*-methoxy-*N*,3,7-trimethyloct-6-en-4-ynamide (598):** To a solution of alcohol **502** (6.42 g, 13.4 mmol, 1.0 eq.) and DMAP (spatula tip) in $CH_3CN$ (28 mL) was added BOMCl (3.72 mL, 26.8 mmol, 2.0 eq.) followed by $^i Pr_2NEt$ (4.66 mL, 26.8 mmol, 2.0 eq.). The resulting solution

was heated to 70 ºC and stirred at that temperature for 3 h. The reaction mixture was then cooled back to room temperature and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1 to 2:1) to yield Weinreb amide **598** (7.10 g, 88%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.68-7.65 (m, 4H), 7.39-7.27 (m, 11H), 5.32 (m, 1H), 4.88 (d, *J* = 7.3 Hz, 1H), 4.84 (d, *J* = 7.3 Hz, 1H), 4.58 (d, *J* = 11.8 Hz, 1H), 4.53 (d, *J* = 11.8 Hz, 1H), 4.47-4.40 (m, 2H), 3.51 (s, 3H), 3.07 (s, 3H), 2.86 (d, *J* = 15.1 Hz, 1H), 2.78 (d, *J* = 15.1 Hz, 1H), 1.93 (d, *J* = 1.2 Hz, 3H), 1.60 (s, 3H), 1.05 (s, 9H).

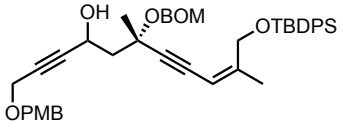

**1-Methoxy-4-((prop-2-yn-1-yloxy)methyl)benzene (121):** A suspension of NaH (6.51 g, 163 mmol, 1.5 eq., 60% dispersion in mineral oil) in THF (150 mL) was cooled to 0 ºC before the careful addition of *p*-methoxybenzyl alcohol (13.5 mL, 109 mmol, 1.0 eq.). After stirring for 30 min, propargyl bromide (32.3 mL, 217 mmol, 2.0 eq., 80% wt. solution in PhMe) was added. The resulting dark brown solution was allowed to warm to room temperature and stirred for 17 h. The reaction mixture was then carefully quenched with saturated $NH_4Cl$ (50 mL) and extracted with EtOAc (200 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by vacuum distillation (P ≈ 1.0 mmHg, T = 117-121 ºC) to yield ether **121** (16.4 g, 86%) as a pale yellow oil. Spectral data matched reported values.[247]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.30-7.28 (m, 2H), 6.91-6.89 (m, 2H), 4.55 (s, 3H), 4.15 (d, *J* = 2.6 Hz, 2H), 3.80 (s, 3H), 2.48 (t, *J* = 2.3 Hz, 1H).



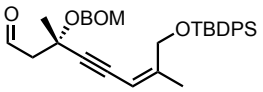

**(*S*,*Z*)-6-((Benzyloxy)methoxy)-11-((*tert*-butyldiphenylsilyl)oxy)-1-((4-methoxybenzyl)oxy)-6,10-dimethylundeca-9-en-2,7-diyn-4-one (599):** A solution of alkyne **121** (1.97 g, 11.2 mmol, 4.0 eq.) in THF (22 mL) was cooled to -78 ºC and $^n$BuLi (4.4 mL, 10.9 mmol, 3.9 eq., 2.5 M solution in hexanes) was added dropwise over 7 min. The resulting dark purple solution was stirred for 10 min before the rapid addition of Weinreb amide **598** (1.68 g, 2.80 mmol, 1.0 eq.) as a solution in THF (2.8 mL). The reaction mixture was stirred at -78 ºC for 80 min before warming to -10 ºC. After an additional 30 min at that temperature, the reaction mixture was quenched by the addition of 1N HCl (20 mL). The mixture was extracted with EtOAc (3 x 50 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1 to 6:1) to yield alkynone **599** (1.66 g, 83%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.67-7.65 (m, 4H), 7.39-7.23 (m, 13H), 6.88-6.86 (m, 2H), 5.30 (s, 1H), 4.86 (d, *J* = 7.4 Hz, 1H), 4.81 (d, *J* = 7.4 Hz, 1H), 4.58-4.49 (m, 4H), 4.41 (s, 2H), 4.21 (s, 2H), 3.80 (s, 3H), 2.91 (s, 2H), 1.93 (s, 3H), 1.52 (s, 3H), 1.05 (s, 9H).



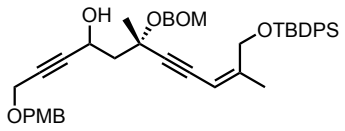

**(6*S*,*Z*)-6-((Benzyloxy)methoxy)-11-((*tert*-butyldiphenylsilyl)oxy)-1-((4-methoxybenzyl)oxy)-6,10-dimethylundeca-9-en-2,7-diyn-4-ol (600):** To a solution of alkynone **599** (53 mg, 0.0741 mmol, 1.0 eq.) and **(*R*)-525** (21 mg, 0.0741 mmol, 1.0 eq.) in THF (1 mL) at -10 ºC was added $BH_3$•$Me_2S$ (0.01 mL, 0.0815 mmol, 1.1 eq.). The reaction mixture was stirred at that temperature for 1 h at which time it was judged to be complete by TLC. The reaction mixture was quenched with MeOH (0.1 mL) and the solvents were removed *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1 to 6:1) to yield alcohol **600** (33 mg, 62%, dr = 3.6:1).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.67-7.65 (m, 4H), 7.40-7.28 (m, 13H), 6.88-6.86 (m, 2H), 5.30 (s, 1H), 4.91 (d, *J* = 6.6 Hz, 1H), 4.74-4.68 (m, 2H), 4.61-4.58 (m, 1H), 4.51 (s, 2H), 4.48-4.45 (m, 1H), 4.39 (s, 2H), 4.17 (m, 2H), 3.80 (s, 3H), 2.19-2.13 (m, 1H), 2.04-2.00 (m, 1H), 1.95 (s, 3H), 1.44/1.41 (s, 3H), 1.05 (s, 9H).

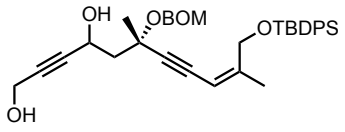



**(*S*,*Z*)-3-((Benzyloxy)methoxy)-8-((*tert*-butyldiphenylsilyl)oxy)-3,7-dimethyloct-6-en-4-ynal (601):** To a solution of Weinreb amide **598** (151 mg, 0.252 mmol, 1.0 eq.) in $CH_2Cl_2$ (0.5 mL) at -78 ºC was added DIBAL (1.01 mL, 1.01 mmol, 4.0 eq., 1.0 M solution in PhMe) dropwise. The reaction mixture was stirred at that temperature for 1 h, then quenched with MeOH (1 mL). The reaction mixture was then poured into 10% Rochelle's salt solution (5 mL) and stirred vigorously for 2.5 h. The layers were separated and the aqueous layer was further extracted with $CH_2Cl_2$ (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 6:1) to yield aldehyde **601** (86 mg, 63%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 9.65 (t, *J* = 2.6 Hz, 1H), 7.67-7.64 (m, 4H), 7.40-7.28 (m, 11H), 5.31 (s, 1H), 4.90 (d, *J* = 7.8 Hz, 1H), 4.76 (d, *J* = 7.8 Hz, 1H), 4.57 (d, *J* = 11.7 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.39 (s, 2H), 2.57 (dd, *J* = 15.6, 3.1 Hz, 1H), 2.48 (dd, *J* = 15.6, 2.6 Hz, 1H), 1.96 (s, 3H), 1.44 (s, 3H), 1.05 (s, 9H).

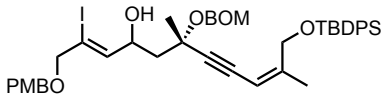



**(6*S*,*Z*)-6-((Benzyloxy)methoxy)-11-((*tert*-butyldiphenylsilyl)oxy)-1-((4-methoxybenzyl)oxy)-6,10-dimethylundeca-9-en-2,7-diyn-4-ol (600):** A solution of alkyne **121** (31 mg, 0.175 mmol, 1.1 eq.) in THF (1 mL) was cooled to -78 ºC and $^{n}$BuLi (0.07 mL, 0.175 mmol, 1.1 eq., 2.5 M solution in hexanes) was added dropwise. The resulting dark purple solution was stirred for 5 min, then transferred via cannula to a -78 ºC solution of aldehyde **591** (86 mg, 0.159 mmol, 1.0 eq.) in THF (2 mL). The reaction mixture was stirred at that temperature for 2 h, then quenched with saturated $NH_4Cl$ (2 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to yield alcohol **600** (75 mg, 66%, dr ≈ 1:1). Spectral data consistent with previously prepared sample.




**(6*S*,*Z*)-6-((Benzyloxy)methoxy)-11-((*tert*-butyldiphenylsilyl)oxy)-6,10-dimethylundeca-9-en-2,7-diyne-1,4-diol (602):** To a solution of alcohol **600** (75 mg, 0.105 mmol, 1.0 eq.) in $CH_2Cl_2$ (1.2 mL) and $H_2O$ (0.06 mL) was added DDQ (36 mg, 0.157 mmol, 1.5 eq.). The reaction mixture was stirred at room temperature for 3 h, then quenched with saturated $NaHCO_3$ (2 mL). The layers were separated and the aqueous layer was further extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to yield diol **602** (33 mg, 53%).

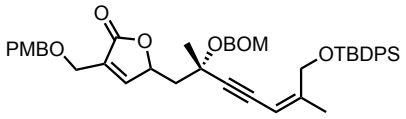
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.68-7.65 (m, 4H), 7.41-7.27 (m, 11H), 5.31-5.30 (m, 1H), 4.95-4.91 (m, 1H), 4.84-4.82/4.63-4.58 (m, 1H), 4.71-4.69 (m, 1H), 4.63-4.58 (m, 1H), 4.48-4.39 (m, 3H), 4.28-4.25 (m, 2H), 3.55/3.02 (m, 1H), 2.20-2.10 (1H), 2.03-1.87 (m, 4H), 1.43/1.41 (s, 3H), 1.06/1.05 (s, 9H).




**(2*Z*,6*S*,9*Z*)-6-((Benzyloxy)methoxy)-11-((*tert*-butyldiphenylsilyl)oxy)-2-iodo-1-((4-methoxybenzyl)oxy)-6,10-dimethylundeca-2,9-dien-7-yn-4-ol (603):** A solution of RedAl (0.83 mL, 2.91 mmol, 2.0 eq., 3.5 M solution in PhMe) in THF (5 mL) was cooled to -78 ºC and a solution of alkynone **599** (1.04 g, 1.45 mmol, 1.0 eq.) in THF (4 mL) was added dropwise via addition funnel. The addition funnel was further washed with THF (0.5 mL), and the reaction mixture was allowed to warm slowly to room temperature and

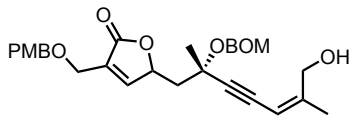
stirred for 17 h. The excess RedAl was quenched by addition of EtOAc (0.28 mL, 2.84 mmol, 1.95 eq.) and the resulting solution was cooled back to -78 ºC. A solution of $I_2$ (554 mg, 2.18 mmol, 1.5 eq.) in THF (2.2 mL) was then added via addition funnel. The resulting dark red solution was stirred at -78 ºC for 15 min before the cooling bath was removed. After an additional 20 min, the reaction mixture was quenched by pouring onto saturated $Na_2S_2O_3$ (10 mL) and 10% Rochelle's salt (10 mL) and stirred vigorously for 1 h, until the color dissipated. The aqueous layer was then extracted with EtOAc (3 x 50 mL) and the combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to yield vinyl iodide **603** (636 mg, 52%, dr ≈ 1:1) as a colorless oil.

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.67-7.65 (m, 4H), 7.39-7.27 (m, 13H), 6.89-6.87 (m, 2H), 6.07/6.03 (d, *J* = 7.7 Hz, 1H), 5.35/5.29 (m, 1H), 4.96 (t, *J* = 7.7 Hz, 1H), 4.71-4.60 (m, 3H), 4.49-4.39 (m, 5H), 4.15-4.07 (m, 2H), 3.80 (s, 3H), 3.64/3.40 (s, 1H), 2.00-1.92 (m, 4H), 1.79-1.71 (m, 1H), 1.54/1.42 (s, 3H), 1.05 (s, 9H).




**5-((*S*,*Z*)-2-((Benzyloxy)methoxy)-7-((*tert*-butyldiphenylsilyl)oxy)-2,6-dimethylhept-5-en-3-yn-1-yl)-3-(((4-methoxybenzyl)oxy)methyl)furan-2(5*H*)-one (604):** A solution of vinyl iodide **603** (147 mg, 0.174 mmol, 1.0 eq.), $NEt_3$ (0.05 mL, 0.348 mmol, 2.0 eq.), and $Pd(PPh_3)_4$ (10 mg, 0.00870 mmol, 0.05 eq.) in PhMe (5 mL) was added to a Parr High Pressure Reactor. The reactor was pressurized with CO gas to ~8.0 atm and heated to 80 ºC. The reaction mixture was stirred under those conditions for 4 h, before cooling back to room temperature. Once the reaction had cooled, the vessel was depressurized and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to yield butenolide **604** (82 mg, 63%, dr ≈ 1:1).

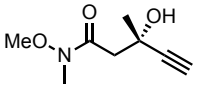
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.65-7.63 (m, 5H), 7.38-7.21 (m, 13H), 6.88-6.86 (m, 2H), 5.32/5.28 (s, 1H), 5.11/5.00-4.96 (m, 1H), 4.77-4.68 (m, 1H), 4.60-4.33 (m, 7H), 4.18 (m, 2H), 3.80 (s, 3H), 2.00-1.81 (m, 5H), 1.44/1.43 (s, 3H), 1.04 (s, 9H).




**5-((*S*,*Z*)-2-((Benzyloxy)methoxy)-7-hydroxy-2,6-dimethylhept-5-en-3-yn-1-yl)-3-(((4-methoxybenzyl)oxy)methyl)furan-2(5*H*)-one (605):** A solution of butenolide **604** (116 mg, 0.156 mmol, 1.0 eq.) in THF (1.6 mL) was cooled to -30 ºC. AcOH (0.05 mL, 0.794 mmol, 5.1 eq.) and TBAF (0.78 mL, 0.779 mmol, 5.0 eq., 1.0 M solution

in THF) were then added sequentially and the reaction mixture was warmed to -20 ºC. After 2 h at -20 ºC, the reaction mixture was warmed to room temperature and stirred for an additional 3 h. The reaction mixture was then quenched with saturated $NH_4Cl$ (2 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to yield alcohol **605** (35 mg, 44%, dr ≈ 1:1).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.48/7.40 (d, *J* = 2.0 Hz, 1H), 7.34-7.25 (m, 8H), 6.89-6.87 (m, 2H), 5.39/5.36 (s, 1H), 5.34-5.24 (m, 1H), 5.15/5.08 (d, *J* = 7.3 Hz, 1H), 4.96/4.95 (d, *J* = 7.3 Hz, 1H), 4.71-4.67 (m, 1H), 4.61-4.57 (m, 1H), 4.53/4.52 (s, 2H), 4.38-4.19 (m, 4H), 3.80 (s, 3H), 2.40-2.31 (m, 1H), 2.24-2.00 (m, 2H), 1.90/1.86 (d, *J* = 1.4 Hz, 3H), 1.63/1.62 (s, 3H).




**(*S*)-3-Hydroxy-*N*-methoxy-*N*,3-dimethylpent-4-ynamide (606):** A suspension of Me(MeO)NH•HCl (8.90 g, 91.2 mmol, 2.0 eq.) in $CH_2Cl_2$ (140 mL) was cooled to -10 ºC (ice/acetone bath) and $AlMe_3$ (45.6 mL, 91.2 mmol, 2.0 eq., 2.0 M solution in PhMe) was added slowly. After addition, the cooling bath was removed and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was then cooled back to -10 ºC and a solution of **(+)–486** (13.1 g, 45.6 mmol, 1.0 eq.) in $CH_2Cl_2$ (140 mL) was introduced by cannula. The reaction mixture was allowed to slowly warm to room temperature and stirred for 1.5 h. The reaction mixture was then quenched by careful transfer via cannula to a vigorously stirred 10% Rochelle's salt solution (200 mL) and the resulting mixture was stirred for 20 h. The layers were then separated and the aqueous layer was further extracted with $CH_2Cl_2$ (3 x 250 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to yield Weinreb amide **606** (6.96 g, 89%) as a pale yellow oil.

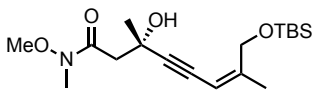
$R_f$ 0.23 (2:1 hexanes/ethyl acetate, PAA (brown))

$[\alpha]^{20}_D$ 65.2 (c = 1.0, $CHCl_3$)

IR (NaCl) v 3277, 2970, 1638, 1400, 1176, 1002 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.52 (s, 1H, exchanges w/ $D_2O$), 3.68 (s, 3H), 3.20 (s, 3H), 3.03 (d, *J* = 17.3 Hz, 1H), 2.50 (d, *J* = 17.3 Hz, 1H), 2.37 (s, 1H), 1.52 (s, 3H).

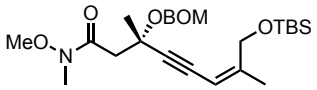
$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 172.5, 87.0, 70.4, 65.3, 61.4, 42.4, 31.6, 29.7.




**(*S*,*Z*)-8-((*tert*-Butyldimethylsilyl)oxy)-3-hydroxy-*N*-methoxy-*N*,3,7-trimethyloct-6-en-4-ynamide (607):** A solution of amide **606** (2.34 g, 13.7 mmol, 1.0 eq.) and vinyl iodide **308** (5.12 g, 16.4 mmol, 1.2 eq.) in $CH_3CN$ (68 mL) was deoxygenated with

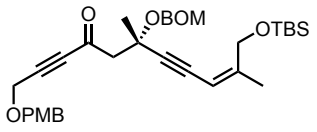
a stream of Ar for 10 min. $NEt_3$ (3.81 mL, 27.3 mmol, 2.0 eq.) was added and the stream was continued for an additional 5 min before the sequential addition of CuI (260 mg, 1.37 mmol, 0.1 eq.) and $Pd(PPh_3)_4$ (316 mg, 0.273 mmol, 0.02 eq.). The resulting orange solution was stirred at room temperature for 4 h before the solvents were removed *in vacuo*. The residue was taken up in $Et_2O$ (150 mL) and washed with brine (25 mL). The organic layer was dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 6:1 to 4:1) to yield Weinreb amide **607** (3.73 g, 77%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.47 (s, 1H), 5.28 (m, 1H), 4.38-4.31 (m, 2H), 3.70 (s, 3H), 3.22 (s, 3H), 3.07 (d, *J* = 15.4 Hz, 1H), 2.57 (d, *J* = 15.4 Hz, 1H), 1.82 (d, *J* = 1.5 Hz, 3H), 1.57 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H).




**(*S*,*Z*)-3-((Benzyloxy)methoxy)-8-((*tert*-butyldimethylsilyl)oxy)-*N*-methoxy-*N*,3,7-trimethyloct-6-en-4-ynamide (608):** To a solution of alcohol **607** (3.73 g, 10.5 mmol, 1.0 eq.) and DMAP (spatula tip) in $CH_3CN$ (21 mL) was added BOMCl (2.92 mL, 21.0 mmol, 2.0 eq.) followed by $^i Pr_2NEt$ (3.65 mL, 21.0 mmol, 2.0 eq.). The resulting solution was heated to 70 ºC and stirred at that temperature for 6.5 h. The reaction mixture was then cooled back to room temperature and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 6:1 to 4:1) to yield Weinreb amide **608** (3.97 g, 80%).

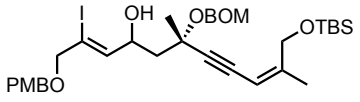
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.38-7.27 (m, 5H), 5.33-5.32 (m, 1H), 5.11 (d, *J* = 7.3 Hz, 1H), 5.06 (d, *J* = 7.3 Hz, 1H), 4.69-4.61 (m, 2H), 4.37 (s, 2H), 3.63 (s, 3H), 3.16 (s, 3H), 3.04 (d, *J* =15.0 Hz, 1H), 2.91 (d, *J* = 15.0 Hz, 1H), 1.84 (d, *J* = 1.4 Hz, 3H), 1.77 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H).




**(*S*,*Z*)-6-((Benzyloxy)methoxy)-11-((*tert*-butyldimethylsilyl)oxy)-1-((4-methoxybenzyl)oxy)-6,10-dimethylundeca-9-en-2,7-diyn-4-one (609):** A solution of alkyne **121** (4.40 g, 25.0 mmol, 4.0 eq.) in THF (25 mL) was cooled to -78 ºC and $^n$BuLi (12.2 mL, 24.3 mmol, 3.9 eq., 2.0 M solution in hexanes) was added dropwise over 8 min. The resulting dark purple solution was stirred for 10 min before the addition of Weinreb amide **608** (2.97 g, 6.24 mmol, 1.0 eq.) as a solution in THF (6.3 mL). The reaction mixture was warmed slowly to 0 ºC over 3 h, then quenched by the addition of 1N HCl (40 mL). The mixture was extracted with EtOAc (3 x 100 mL) and the combined organic extracts were dried over $MgSO_4$,

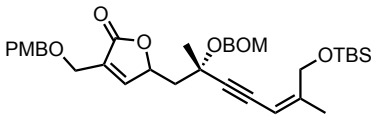
filtered, and concentrated *in vacuo*. The crude residue was purified by ISCO (80 g, gradient: 0% to 10% EtOAc in hexanes over 30 min) to yield alkynone **609** (1.35 g, 37%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.33-7.24 (m, 7H), 6.89-6.86 (m, 2H), 5.31 (s, 1H), 5.10 (d, *J* = 7.2 Hz, 1H), 5.02 (d, *J* = 7.2 Hz, 1H), 4.67 (d, *J* = 11.7 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.52 (s, 2H), 4.35 (s, 2H), 4.26 (s, 2H), 3.80 (s, 3H), 3.13 (d, *J* = 15.3 Hz, 1H), 3.03 (d, *J* = 15.3 Hz, 1H), 1.83 (s, 3H), 1.71 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H).




**(2*Z*,6*S*,9*Z*)-6-((Benzyloxy)methoxy)-11-((*tert*-butyldimethylsilyl) oxy)-2-iodo-1-((4-methoxybenzyl)oxy)-6,10-dimethylundeca-2,9-dien-7-yn-4-ol (610):** A solution of RedAl (0.81 mL, 2.84 mmol, 1.5 eq., 3.5 M solution in PhMe) in THF (9 mL) was cooled to -78 ºC and a solution of alkynone **609** (1.12 g, 1.90 mmol, 1.0 eq.) in THF (4.5 mL) was added dropwise. The reaction mixture was allowed to warm slowly to room temperature and stirred for 13 h. The excess RedAl was quenched by addition of EtOAc (0.28 mL, 2.82 mmol, 1.49 eq.) and the resulting solution was cooled back to -78 ºC. A solution of $I_2$ (722 mg, 2.84 mmol, 1.5 eq.) in THF (2.9 mL) was then added. The resulting dark red solution was stirred at -78 ºC for 20 min before the cooling bath was removed. After an additional 25 min, the reaction mixture was quenched by pouring onto saturated $Na_2S_2O_3$ (10 mL) and 10% Rochelle's salt (10 mL) and stirred vigorously for 1.5 h, until the color dissipated. The aqueous layer was then extracted with EtOAc (3 x 50 mL) and the combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 6:1 to 4:1) to yield vinyl iodide **610** (961 mg, 69%, dr ≈ 1:1) as a colorless oil.

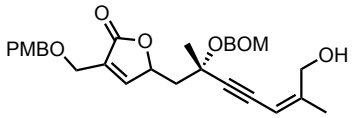
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.38-7.27 (m, 7H), 6.91-6.87 (m, 2H), 6.13-6.10 (m, 1H), 5.37-5.31 (m, 1H), 5.26-5.18 (m, 1H), 4.97-4.81 (m, 2H), 4.76-4.72 (m, 1H), 4.63-4.56 (m, 1H), 4.44-4.34 (m, 4H), 4.15-4.13 (m, 2H), 3.81 (s, 3H), 2.20-1.95 (m, 2H), 1.86/1.85 (d, *J* = 1.3 Hz, 3H), 1.73/1.63 (s, 3H), 0.90/0.89 (s, 9H), 0.07-0.06 (m, 6H).



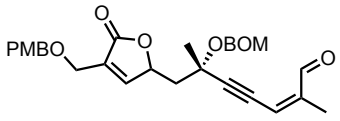

**5-((*S*,*Z*)-2-((Benzyloxy)methoxy)-7-((*tert*-butyldimethylsilyl) oxy)-2,6-dimethylhept-5-en-3-yn-1-yl)-3-(((4-methoxybenzyl)oxy)methyl)furan-2(5*H*)-one (611):** A solution of vinyl iodide **610** (951 mg, 1.32 mmol, 1.0 eq.), $NEt_3$ (0.37 mL, 2.64 mmol, 2.0 eq.), and $Pd(PPh_3)_4$ (76 mg, 0.0660 mmol, 0.05 eq.) in PhMe (13 mL) was added to a Parr High Pressure Reactor. The reactor was pressurized with CO gas to ~8.0 atm and heated to 80 ºC. The reaction mixture was stirred under those conditions for 4 h, before cooling back to

room temperature. Once the reaction had cooled, the vessel was depressurized and the solvent was removed *in vacuo*. The crude residue was purified by ISCO (24 g, gradient: 0% to 20% EtOAc in hexanes over 18 min) to yield butenolide **611** (521 mg, 64%, dr ≈ 1:1).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.45/7.36 (m, 1H), 7.33-7.25 (m, 7H), 6.89-6.86 (m, 2H), 5.34-5.26 (m, 2H), 5.14/5.10 (d, *J* = 7.1 Hz, 1H), 5.00/4.93 (d, *J* = 7.1 Hz, 1H), 4.71-4.67 (m, 1H), 4.61-4.55 (m, 1H), 4.53/4.51 (s, 2H), 4.35/4.32 (s, 2H), 4.23/4.22 (t, *J* = 1.9 Hz, 2H), 3.81/3.80 (s, 3H), 2.21-2.07 (m, 2H), 1.85/1.84 (d, *J* = 1.2 Hz, 3H), 1.65/1.64 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

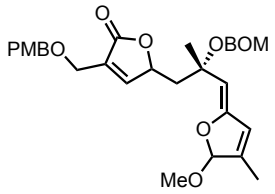



**5-((*S*,*Z*)-2-((Benzyloxy)methoxy)-7-hydroxy-2,6-dimethylhept-5-en-3-yn-1-yl)-3-(((4-methoxybenzyl)oxy)methyl)furan-2(5*H*)-one (605):** A solution of butenolide **611** (327 mg, 0.527 mmol, 1.0 eq.) in THF (5.2 mL) was cooled to 0 ºC and 1N HCl (5.2 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for 11 h. The reaction mixture was then quenched by addition to a separatory funnel containing saturated $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined aqueous layers were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to yield alcohol **605** (214 mg, 80%, dr ≈ 1:1). Spectral data consistent with previously prepared sample.



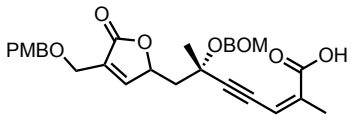

**(6*S*,*Z*)-6-((Benzyloxy)methoxy)-7-(4-(((4-methoxybenzyl)oxy)methyl)-5-oxo-2,5-dihydrofuran-2-yl)-2,6-dimethylhept-2-en-4-ynal (612):** To a solution of alcohol **605** (214 mg, 0.422 mmol, 1.0 eq.) in $CH_2Cl_2$ (4.2 mL) was added $PhI(OAc)_2$ (150 mg, 0.465 mmol, 1.1 eq.) followed by TEMPO (4 mg, 0.0211 mmol, 0.05 eq.). The resulting orange solution was stirred at room temperature for 5 h, at which time it was judged complete by TLC. The reaction mixture was loaded directly on a column and purified by flash column chromatography (hexanes/EtOAc, 2:1) to yield aldehyde **612** (198 mg, 93%, d.r. ≈ 1:1).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 10.19/10.15 (s, 1H), 7.41-7.24 (m, 8H), 6.89-6.86 (m, 2H), 6.54/6.49 (m, 1H), 5.25-5.23 (m, 1H), 5.11/5.06 (d, *J* = 7.3 Hz, 1H), 5.00/4.96 (d, *J* = 7.3 Hz, 1H), 4.70-4.51 (m, 4H), 4.23/4.21 (t, *J* = 2.0 Hz, 2H), 3.80 (s, 3H), 2.27-2.08 (m, 2H), 1.87/1.85 (d, *J* = 1.5 Hz, 3H), 1.69/1.67 (s, 3H).



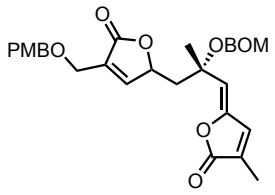

**5-((2*S*,*Z*)-2-((Benzyloxy)methoxy)-3-(5-methoxy-4-methylfuran-2(5*H*)-ylidene)-2-methylpropyl)-3-(((4-methoxybenzyl)oxy)methyl)furan-2(5*H*)-one (613):** To a solution of aldehyde **612** (20 mg, 0.0396 mmol, 1.0 eq.) in MeOH (0.8 mL) was added a spatula tip of $Ag_2O$. The resulting suspension was stirred at room temperature for 4 d before being diluted with EtOAc (30 mL). The organic layer was washed with saturated $NaHCO_3$ (3 x 5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to yield methyl acetal **613** (9 mg, 43%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.46-7.25 (m, 8H), 6.89-6.86 (m, 2H), 5.93/5.90 (s, 1H), 5.77/5.76 (m, 1H), 5.28-5.11 (m, 1H), 4.92-4.84 (m, 2H), 4.70-4.42 (m, 4H), 4.23-4.21 (m, 2H), 3.80 (s, 3H), 3.34-3.33 (m, 3H), 2.36-1.99 (m, 2H), 1.85 (s, 3H), 1.62-1.59 (s, 3H).




**(6*S*,*Z*)-6-((Benzyloxy)methoxy)-7-(4-(((4-methoxybenzyl)oxy)methyl)-5-oxo-2,5-dihydrofuran-2-yl)-2,6-dimethylhept-2-en-4-ynoic acid (615):** To a solution of aldehyde **612** (81 mg, 0.161 mmol, 1.0 eq.) in $^t$BuOH (3 mL) and $H_2O$ (3 mL) was added 2-methyl-2-butene (1.70 mL, 16.1 mmol, 100.0 eq.) followed by $KH_2PO_4$ (218 mg, 1.61 mmol, 10.0 eq.) and $NaClO_2$ (181 mg, 1.61 mmol, 10.0 eq., 80%). The resulting biphasic mixture was vigorously stirred for 2.5 h before the addition of 1N HCl (10 mL). The organic phase was then extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo* to yield crude acid **615**, which was used without further purification.

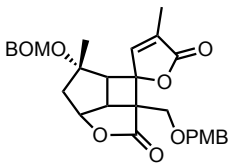
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.73/7.49 (m, 1H), 7.33-7.27 (m, 7H), 6.89-6.86 (m, 2H), 6.02 (m, 1H), 5.37-5.22 (m, 1H), 5.17-5.15 (m, 1H), 4.98-4.95 (m, 1H), 4.72-4.50 (m, 4H), 4.25-4.21 (m, 2H), 3.80 (s, 3H), 2.38-2.10 (m, 2H), 2.02-2.01 (m, 3H), 1.65 (s, 3H).




**5-((*S*,*Z*)-2-((Benzyloxy)methoxy)-2-methyl-3-(4-methyl-5-oxofuran-2(5*H*)-ylidene)propyl)-3-(((4-methoxybenzyl)oxy)methyl)furan-2(5*H*)-one (616):** To a solution of crude acid **615** (0.161 mmol, 1.0 eq.) in MeOH (6 mL) containing $H_2O$ (1 drop) was added $AgNO_3$ (3 mg, 0.0161 mmol, 0.1 eq.). The resulting solution was stirred at room

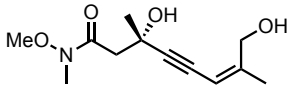
temperature for 1 h before the solvents were removed *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to yield alkylidene butenolide **616** (52 mg, 62% over 2 steps) as a colorless oil.

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.36-7.26 (m, 7H), 6.98/6.93 (m, 1H), 6.90-6.88 (m, 2H), 5.42/5.25 (s, 1H), 5.23-5.17 (m, 1H), 4.93-4.86 (m, 2H), 4.66-4.65 (m, 2H), 4.53/4.52 (s, 2H), 4.22 (s, 2H), 3.81 (s, 3H), 2.41-2.20 (m, 1H), 2.12-2.02 (m, 1H), 1.99 (s, 3H), 1.70/1.67 (s, 3H).




**(2*S*)-2-((Benzyloxy)methoxy)-5a-(((4-methoxybenzyl)oxy)methyl)-2,4'-dimethyl-1a,1a$^1$,2,3,3a,5a-hexahydro-5*H*,5'*H*-4-oxaspiro[cyclobuta[*cd*]pentalene-1,2'-furan]-5,5'-dione (617):** A solution of butenolide **616** (52 mg, 0.0999 mmol, 1.0 eq.) was dissolved in $(CD_3)_2CO$ (10 mL) and added to a quartz test tube. The solution was irradiated with a 450 W medium-pressure Hg lamp through a pyrex filter and monitored by $^1$H NMR. After 6 h, starting material was consumed and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to yield cyclobutane **617** (36 mg, 69%) as a complex mixture of isomers.

**Experimental Procedures: Section 4.6**




**(*S*,*Z*)-3,8-Dihydroxy-*N*-methoxy-*N*,3,7-trimethyloct-6-en-4-ynamide (618):** A solution of Weinreb amide **606** (6.96 g, 40.7 mmol, 1.0 eq.) and vinyl iodide **300** (9.66 g, 48.8 mmol, 1.2 eq.) in $CH_3CN$ (135 mL) was deoxygenated with a stream of Ar for 10 min, at which time $NEt_3$ (11.3 mL, 81.3 mmol, 2.0 eq.) was added and the stream was continued for an addition al 5 min. CuI (774 mg, 4.07 mmol, 0.1 eq.) followed by $Pd(PPh_3)_4$ (470 mg, 0.407 mmol, 0.01 eq.) was added and the resulting orange solution was stirred at room temperature for 1.5 h. The solvent was removed *in vacuo* and the residue was taken up in with $Et_2O$ 250 mL) and filtered through a plug of celite. The filtrate was concentrated *in vacuo* and the orange residue was purified by flash column chromatography (hexanes/EtOAc, 1:1 to EtOAc) to yield diol **618** (9.08 g, 93%, >90% purity) as an orange oil.

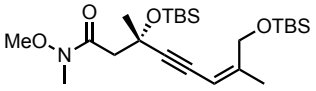
$R_f$ 0.16 (1:1 hexanes/ethyl acetate, UV/PAA (pink))

$[\alpha]^{20}_D$ 110.9 (c = 1.0, $CHCl_3$)

IR (NaCl) v 3407, 2935, 2348, 1634, 1397, 1266, 1178, 1014.

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.37 (s, 2H, 1H exchanges w/ $D_2O$), 4.31-4.22 (m, 2H), 3.71 (s, 3H), 3.23 (s, 3H), 3.06 (d, *J* = 15.7 Hz, 1H), 2.57 (d, *J* = 15.7 Hz, 1H), 2.07 (bs, 1H, exchanges w/ $D_2O$), 1.86 (s, 3H), 1.55 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 172.6, 150.9, 105.7, 95.7, 79.1, 66.0, 63.4, 61.4, 42.8, 31.6, 29.7, 20.3.




**(*S*,*Z*)-3,8-Bis((*tert*-butyldimethylsilyl)oxy)-*N*-methoxy-*N*,3,7-trimethyloct-6-en-4-ynamide (619):** A solution of diol **618** (9.18 g, 38.0 mmol, 1.0 eq.) in $CH_2Cl_2$ (38 mL) was cooled to -78 ºC. 2,6-lutidine (11.1 mL, 95.1 mmol, 2.5 eq.) was added followed by a dropwise addition of TBSOTf (18.4 mL, 79.9 mmol, 2.1 eq.). The resulting mixture was stirred at -78 ºC for 15 min before the cooling bath was removed and the resulting thick slurry was allowed to warm to room temperature. After 30 min, the reaction mixture was quenched by addition of saturated $NH_4Cl$ (50 mL). The phases were separated and the organic layer was extracted with $CH_2Cl_2$ (3 x 125 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 19:1 to 9:1) to yield TBS ether **619** (13.3 g, 74%) as a pale yellow oil.

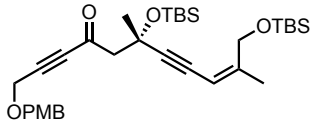
$R_f$ 0.23 (9:1 hexanes/ethyl acetate, UV/PAA (pink))

$[\alpha]^{20}_D$ -29.5 (c = 1.0, $CHCl_3$)

IR (NaCl) v 2944, 2873, 1674, 1453, 1384, 1259, 1089, 1013.

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.31 (s, 1H), 4.37 (s, 2H), 3.68 (s, 3H), 3.16 (s, 3H), 2.82 (s, 2H), 1.83 (s, 3H), 1.68 (s, 3H), 0.90 (s, 9H), 0.85 (s, 9H), 0.16(4) (s, 3H), 0.15(6) (s, 3H), 0.07 (s, 6H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 170.4, 151.0, 104.6, 96.5, 80.7, 68.1, 63.8, 61.0, 45.2, 31.1, 25.8, 25.6, 19.7, 18.2, 17.9, -3.0, -3.2, -5.4.




**(*S*,*Z*)-6,11-Bis((*tert*-butyldimethylsilyl)oxy)-1-((4-methoxybenzyl)oxy)-6,10-dimethylundeca-9-en-2,7-diyn-4-one (620):** A solution of alkyne **121** (8.33 g, 47.3. mmol, 1.8 eq.) in THF (266 mL) was cooled to -78 ºC and $^n$BuLi (19.3 mL, 42.6 mmol, 1.6 eq., 2.2 M solution in hexanes) was added dropwise over 10 min. After 20 min of additional stirring, the resulting dark purple solution was transferred via cannula to a pre-cooled solution of Weinreb amide **619** (12.5 g, 26.6 mmol, 1.0 eq.) in THF (53 mL) at -10 ºC. The reaction mixture was stirred for 1.5 h until TLC had indicated consumption of starting material. The reaction mixture was then quenched by addition of 1N HCl (100 mL) then extracted with EtOAc (3 x 150 mL). The combined organic extracts were dried over $MgSO_4$,

filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 19:1) to yield alkynone **620** (12.9 g, 83%) and excess alkyne **121** (3.80 g) as an inseparable mixture.

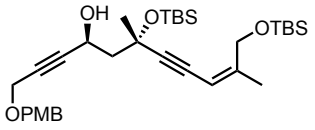
A sample of alcohol **621** was re-oxidized with $MnO_2$ (10.0 eq. in $CH_2Cl_2$) to obtain **620** as a colorless oil, which was analytically pure for characterization.

$R_f$ 0.34 (9:1 hexanes/ethyl acetate, UV/PAA (purple))

$[\alpha]^{20}_D$ -27.5 (c = 2.0, $CHCl_3$)

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.26-7.24 (m, 2H), 6.88-6.85 (m, 2H), 5.29 (m, 1H), 4.51 (s, 2H), 4.36 (s, 2H), 4.25 (s, 2H), 3.79 (s, 3H), 2.94 (s, 2H), 1.81 (d, *J* = 1.3 Hz, 3H), 1.60 (s, 3H), 0.89 (s, 9H), 0.85 (s, 9H), 0.16(2) (s, 3H), 0.15(5) (s, 3H), 0.07 (s, 6H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 183.3, 159.5, 151.7, 129.7, 128.8, 113.8, 104.2, 95.3, 87.9, 86.8, 81.9, 71.6, 67.6, 63.8, 58.9, 56.6, 55.2, 31.4, 25.8, 25.6, 19.7, 18.2, 17.9, -3.0, -3.3, -5.4.



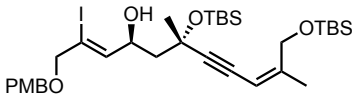

**(4*S*,6*S*,*Z*)-6,11-Bis((*tert*-butyldimethylsilyl)oxy)-1-((4-methoxybenzyl)oxy)-6,10-dimethylundeca-9-en-2,7-diyn-4-ol (621):** A solution of alkynone **620** (7.68 g, 13.1 mmol, 1.0 eq.) and **(*S*)–525** (7.28 g, 26.3 mmol, 2.0 eq.) in THF (130 mL) was cooled to -10 ºC (ice/acetone bath) before the addition of $BH_3$•$Me_2S$ (6.2 mL, 65.6 mmol, 5.0 eq.). The resulting solution was stirred at that temperature for 30 min. The reaction mixture was then quenched by the careful addition of MeOH (7 mL). Once the bubbling had ceased, the reaction mixture was diluted with $Et_2O$ (300 mL) and washed with saturated $NH_4Cl$ (2 x 50 mL), saturated $NaHCO_3$ (2 x 50 mL), and brine (2 x 50 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 19:1 to 9:1) to yield alcohol **621** (5.66 g, 73%, d.r. = 7.4:1). Note: diastereoselectivity was diminished with larger scales, although the yield was unaffected.

$R_f$ 0.22 (9:1 hexanes/ethyl acetate, UV/PAA (pink))

$[\alpha]^{20}_D$ 16.6 (c = 2.0, $CHCl_3$)

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.28-7.26 (m, 2H), 6.88-6.86 (m, 2H), 5.34 (s, 1H), 5.02 (d, *J* = 9.6 Hz, 1H), 4.52 (s, 2H), 4.37 (s, 2H), 4.18 (d, *J* = 1.3 Hz, 2H), 3.97 (s, 1H, exchanges w/ $D_2O$), 3.79 (s, 3H), 2.20 (dd, *J* = 14.4, 9.9 Hz, 1H), 2.01 (dd, *J* = 14.4, 1.5 Hz, 1H), 1.86 (s, 3H), 1.56 (s, 3H), 0.91 (s, 9H), 0.88 (s, 9H), 0.23 (s, 3H), 0.22 (s, 3H), 0.09 (s, 6H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 159.3, 152.0, 129.6, 113.7, 104.0, 94.4, 86.9, 82.3, 80.1, 71.3, 71.0, 63.8, 61.0, 57.0, 55.2, 51.2, 31.8, 25.8, 25.6, 25.5, 19.7, 18.2, 17.8, -2.8, -3.3, -5.4.



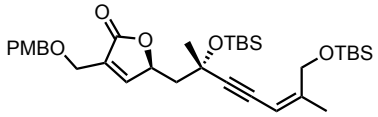

**(2*Z*,4*S*,6*S*,9*Z*)-6,11-Bis((*tert*-butyldimethylsilyl)oxy)-2-iodo-1-((4-methoxybenzyl)oxy)-6,10-dimethylundeca-2,9-dien-7-yn-4-ol (622):** A solution of RedAl (10.0 mL, 35.1 mmol, 2.0 eq., 3.5 M solution in PhMe) in THF (88 mL) was cooled to -10 ºC and a solution of alcohol **621** (10.3 g, 17.5 mmol, 1.0 eq.) in THF (44 mL) was added dropwise via addition funnel over 1 h. After the addition was complete, the addition funnel was rinsed with 5 mL THF. The reaction mixture was stirred for 1 h before the excess RedAl was quenched by addition of EtOAc (3.41 mL, 34.9 mmol, 1.99 eq.) and the resulting solution was cooled to -78 ºC. A solution of $I_2$ (8.91 g, 35.1 mmol, 2.0 eq.) in THF (35 mL) was then added via addition funnel. The resulting dark red solution was stirred at -78 ºC for 30 min before the cooling bath was removed. After an additional 30 min, the reaction mixture was quenched by pouring onto saturated $Na_2S_2O_3$ (75 mL) and 10% Rochelle's salt (75 mL) and stirred vigorously for 1 h, until the color dissipated. The aqueous layer was then extracted with EtOAc (3 x 200 mL) and the combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1) to yield vinyl iodide **622** (9.36 g, 75%) as a colorless oil.

$R_f$ 0.25 (9:1 hexanes/ethyl acetate, UV/PAA (pink))

$[\alpha]^{20}_D$ 36.8 (c = 1.0, $CHCl_3$)

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.29-7.27 (m, 2H), 6.89-6.87 (m, 2H), 6.12 (d, *J* = 7.1 Hz, 1H), 4.98-4.94 (m, 1H), 4.43-4.36 (m, 4H), 4.17-4.09 (m, 2H), 4.05 (s, 1H, exchanges w/ $D_2O$), 3.80 (s, 3H), 1.93-1.80 (m, 5H), 1.57 (s, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.26 (s, 3H), 0.25 (s, 3H), 0.09 (s, 6H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 159.2, 151.6, 139.5, 129.7, 129.5, 113.7, 104.3, 103.0, 94.8, 82.5, 74.7, 71.7, 71.0, 64.1, 55.2, 49.2, 32.1, 25.8, 25.7, 25.6, 19.8, 18.2, 17.8, -2.7, -3.2, -5.3.




**(*S*)-5-((*S*,*Z*)-2,7-Bis((*tert*-butyldimethylsilyl)oxy)-2,6-dimethylhept-5-en-3-yn-1-yl)-3-(((4-methoxybenzyl)oxy)methyl)furan-2(5*H*)-one (623):** A solution of vinyl iodide **622** (9.36 g, 13.1 mmol, 1.0 eq.), $NEt_3$ (1.82 mL, 13.1 mmol, 1.0 eq.), and $Pd(PPh_3)_4$ (757 mg, 0.655 mmol, 0.05 eq.) in PhMe (30 mL) was added to a Parr High Pressure Reactor. The reactor was pressurized with CO gas to ~8.0 atm and heated to 80 ºC. The reaction mixture was stirred under those conditions for 4 h, before cooling back to room temperature. Once the reaction had cooled, the vessel was depressurized and the solvent was removed *in vacuo* to yield crude butenolide **623** which was used immediately without further purification.

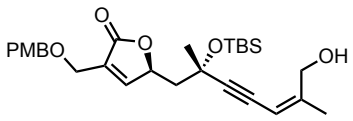
An aliquot was purified by flash column chromatography (hexanes/EtOAc, 9:1) to yield pure butenolide **623** as a brown oil for characterization.

$R_f$ 0.16 (9:1 hexanes/ethyl acetate, UV/PAA (pink))

$[\alpha]^{20}_D$ 25.5 (c = 1.0, $CHCl_3$)

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.51 (d, *J* = 1.6 Hz, 1H), 7.28-7.26 (m, 2H), 6.89-6.87 (m, 2H), 5.34-5.27 (m, 2H), 4.53 (s, 2H), 4.34 (s, 2H), 4.24-4.22 (m, 2H), 3.80 (s, 3H), 2.11 (dd, *J* = 14.3, 6.6 Hz, 1H), 2.01 (dd, *J* = 14.3, 6.3 Hz, 1H), 1.84 (d, *J* = 1.1 Hz, 3H), 1.58 (s, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H), 0.07 (s, 6H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 172.1, 159.3, 151.8, 150.8, 131.1, 129.6, 129.4, 113.8, 104.1, 96.1, 81.6, 78.9, 72.9, 67.5, 63.8, 63.6, 55.2, 48.2, 31.2, 25.8, 25.7, 19.7, 18.2, 18.0, -2.9, -3.2, -5.4.



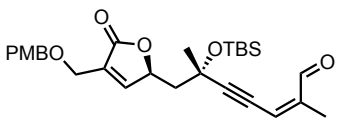

**(*S*)-5-((*S*,*Z*)-2-((*tert*-Butyldimethylsilyl)oxy)-7-hydroxy-2,6-dimethylhept-5-en-3-yn-1-yl)-3-(((4-methoxybenzyl)oxy)methyl)furan-2(5*H*)-one (624):** A solution of crude butenolide **623** (13.1 mmol, 1.0 eq.) in THF (130 mL) was cooled to 0 ºC and 1N HCl (130 mL) was added dropwise via addition funnel. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was then quenched by addition to a separatory funnel containing saturated $NaHCO_3$ (150 mL). The aqueous layer was extracted with EtOAc (3 x 250 mL) and the combined aqueous layers were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1 to 2:1) to yield alcohol **624** (5.49 g, 84% over 2 steps) as a yellow oil.

$R_f$ 0.36 (2:1 hexanes/ethyl acetate, UV/PAA (pink))

$[\alpha]^{20}_D$ 17.7 (c = 1.0, $CHCl_3$)

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.61-7.60 (m, 1H), 7.28-7.26 (m, 2H), 6.89-6.87 (m, 2H), 5.35 (m, 1H), 5.27-5.23 (m, 1H), 4.53 (s, 2H), 4.33-4.28 (m, 1H), 4.25-4.18 (m, 3H), 3.80 (s, 3H), 2.31 (bs, 1H, exchanges w/ $D_2O$), 2.19 (dd, *J* = 14.3, 6.1 Hz, 1H), 1.99 (dd, *J* = 14.3, 6.6 Hz, 1H), 1.86 (d, *J* = 1.4 Hz, 3H), 1.56 (s, 3H), 0.87 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 172.2, 159.4, 151.2, 150.6, 130.9, 129.6, 129.3, 113.8, 105.4, 95.6, 81.8, 79.3, 73.1, 67.3, 63.7, 63.4, 55.2, 48.2, 31.6, 25.6, 20.1, 17.9, -2.9, -3.3.




**(*S*,*Z*)-6-((*tert*-Butyldimethylsilyl)oxy)-7-((*S*)-4-(((4-methoxybenzyl)oxy)methyl)-5-oxo-2,5-dihydrofuran-2-yl)-2,6-dimethylhept-2-en-4-ynal**

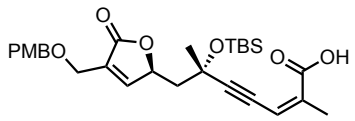
**(625):** To a solution of alcohol **624** (5.49 g, 11.0 mmol, 1.0 eq.) in $CH_2Cl_2$ (110 mL) was added $PhI(OAc)_2$ (4.59 g, 14.3 mmol, 1.3 eq.) followed by TEMPO (171 mg, 1.10 mmol, 0.1 eq.). The resulting orange solution was stirred at room temperature for 20 h, at which time it was judged complete by TLC. The solvent was removed *in vacuo* and the crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1 to 2:1) to yield aldehyde **625** (4.88, 89%) as a brown oil.

$R_f$ 0.21 (4:1 hexanes/ethyl acetate, UV/PAA (pink))

$[\alpha]^{20}_D$ 31.6 (c = 1.0, $CHCl_3$)

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 10.15 (s, 1H), 7.45 (d, *J* = 1.6 Hz, 1H), 7.27-7.25 (m, 2H), 6.89-6.87 (m, 2H), 6.52 (d, *J* = 1.9 Hz, 1H), 5.29-5.25 (m, 1H), 4.53 (s, 2H), 4.23 (t, *J* = 2.0 Hz, 1H), 3.80 (s, 3H), 2.11-2.05 (m, 2H), 1.85 (d, *J* = 1.6 Hz, 3H), 1.63 (s, 3H), 0.87 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 191.4, 171.9, 159.4, 150.7, 150.1, 146.8, 131.6, 129.4, 124.3, 113.8, 102.6, 79.3, 78.5, 73.0, 67.7, 63.6, 55.2, 47.9, 30.7, 25.6, 18.0, 15.1, -2.9, -3.2.




**(*S*,*Z*)-6-((*tert*-Butyldimethylsilyl)oxy)-7-((*S*)-4-(((4-methoxybenzyl)oxy)methyl)-5-oxo-2,5-dihydrofuran-2-yl)-2,6-dimethylhept-2-en-4-ynoic acid (626):** To a solution of aldehyde **625** (2.69 g, 5.39 mmol, 1.0 eq.) in $^t$BuOH (108 mL) and $H_2O$ (108 mL) was added 2-methyl-2-butene (57 mL, 539 mmol, 100.0 eq.) followed by $KH_2PO_4$ (7.34 g, 53.9 mmol, 10.0 eq.) and $NaClO_2$ (6.10 g, 53.9 mmol, 10.0 eq., 80%). The resulting biphasic mixture was vigorously stirred for 3 h before it was diluted with EtOAc (500 mL). The layers were separated and the organic phase was washed with 1N HCl (50 mL), saturated $Na_2S_2O_3$ (50 mL), and brine (50 mL). The organic layer was dried over $Na_2SO_4$, filtered, and concentrated *in vacuo* to yield crude acid **626**, which was used without further purification. Note: care should be taken to remove most of the $^t$BuOH prior to the following step.

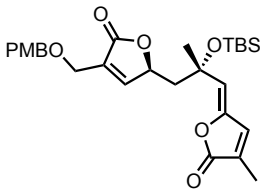
An aliquot was purified by flash column chromatography (hexanes/EtOAc, 2:1 to 1:1) to yield pure acid **626** as a pale yellow oil for characterization.

$R_f$ 0.10 (1:1 hexanes/ethyl acetate, UV/PAA (purple))

$[\alpha]^{20}_D$ 25.3 (c = 0.5, $CHCl_3$)

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.95 (d, *J* = 1.6 Hz, 1H), 7.34-7.32 (m, 2H), 6.90-6.88 (m, 2H), 6.04 (d, *J* = 1.6 Hz, 1H), 5.29-5.25 (m, 1H), 4.69 (d, *J* = 1.5 Hz, 2H), 4.28-4.26 (m, 2H), 3.81 (s, 3H), 2.40 (dd, *J* = 13.3, 4.9 Hz, 1H), 2.03 (d, *J* = 1.5 Hz, 3H), 1.84 (dd, *J* = 13.2, 9.0 Hz, 1H), 1.59 (s, 3H), 0.88 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 171.9, 167.7, 159.7, 151.3, 138.9, 130.2, 129.6, 129.5, 128.2, 116.3, 113.9, 81.8, 79.4, 73.1, 67.3, 63.4, 55.2, 47.9, 32.6, 25.6, 19.8, 18.0, -2.9, -3.3.



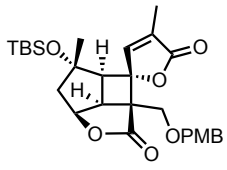

**(*S*)-5-((*S*,*Z*)-2-((*tert*-Butyldimethylsilyl)oxy)-2-methyl-3-(4-methyl-5-oxofuran-2(5*H*)-ylidene)propyl)-3-(((4-methoxybenzyl)oxy)methyl)furan-2(5*H*)-one (627):** To a solution of crude acid **626** (5.39 mmol, 1.0 eq.) in MeOH (180 mL) was added a solution of $AgNO_3$ (0.92 mL, 0.539 mmol, 0.1 eq., 10% w/w in $H_2O$). The resulting solution was stirred at room temperature for 1 h before the solvents were removed *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to yield alkylidene butenolide **627** (2.35, 85% over 2 steps) as a colorless oil.

$R_f$ 0.42 (2:1 hexanes/ethyl acetate, UV/PAA (purple))

$[\alpha]^{20}_D$ -32.7 (c = 2.0, $CHCl_3$)

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.31 (d, *J* = 1.6 Hz, 1H), 7.27-7.25 (m, 2H), 6.97 (d, *J* = 1.4 Hz, 1H), 6.89-6.87 (m, 2H), 5.25-5.22 (m, 1H), 5.20 (s, 1H), 4.52 (s, 2H), 4.22-4.21 (m, 2H), 3.80 (s, 3H), 2.24 (dd, *J* = 14.4, 3.9 Hz, 1H), 2.05-1.99 (m, 4H), 1.69 (s, 3H), 0.89 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 172.0, 170.3, 159.3, 150.8, 145.8, 138.7, 131.3, 129.6, 129.5, 129.3, 120.1, 113.8, 78.8, 73.7, 72.9, 63.6, 55.2, 46.5, 28.5, 25.7, 18.0, 10.4, -2.2, -2.6.




**(1*S*,1a*R*,1a$^1$*S*,2*S*,3a*S*,5a*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-5a-(((4-methoxybenzyl)oxy)methyl)-2,4'-dimethyl-1a,1a$^1$,2,3,3a,5a-hexahydro-5*H*,5'*H*-4-oxaspiro[cyclobuta[*cd*]pentalene-1,2'-furan]-5,5'-dione (628):** A solution of alkylidene butenolide **627** (4.10 g, 7.97 mmol, 1.0 eq.) and $Ph_2CO$ (145 mg, 0.797 mmol, 0.1 eq.) in cy (76 mL) and $CH_2Cl_2$ (4 mL) was degassed with three freeze-pump-thaw cycles. The solution was then injected by syringe pump into a flow photochemical reactor as described by Danheiser.[166] The solution was irradiated with a 450 W medium-pressure Hg lamp at a flow rate of 6 mL/h. Once the injection was complete, the reactor was flushed with $CH_2Cl_2$ while irradiation was continued at 6 mL/h. The solvents were then removed *in vacuo* to yield crude cyclobutane **628**, which was used without further purification.

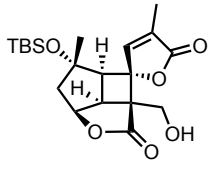
An aliquot was purified by flash column chromatography (hexanes/EtOAc, 6:1) to yield pure cyclobutane **628** as a white foam for characterization.

$R_f$ 0.54 (2:1 hexanes/ethyl acetate, UV (weak)/PAA (purple))

$[\alpha]^{20}_D$ 1.6 (c = 1.0, $CHCl_3$)

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.23-7.21 (m, 2H), 6.97 (d, *J* = 1.3 Hz, 1H), 6.87-6.85 (m, 2H), 5.29-5.24 (m, 1H), 4.50-4.42 (m, 2H), 3.91 (d, *J* = 9.7 Hz, 1H), 3.79 (s, 3H), 3.64 (d, *J* = 9.7 Hz, 1H), 3.51 (t, *J* = 8.0 Hz, 1H), 3.17 (dd, *J* = 7.6, 1.5 Hz, 1H), 2.64 (ddd, *J* = 15.7, 8.0 1.8 Hz, 1H), 1.96-1.91 (m, 4H), 1.25 (s, 3H), 0.81 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

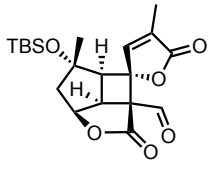
$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 175.8, 171.1, 159.3, 144.2, 131.7, 129.5, 129.3, 113.8, 85.5, 83.5(2), 83.4(8), 73.4, 65.8, 59.8, 55.2, 54.5, 50.9, 42.1, 25.4, 23.0, 17.7, 10.8, -2.5(5), -2.5(9).




**(1*S*,1a*R*,1a$^1$*S*,2*S*,3a*S*,5a*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-5a-(hydroxymethyl)-2,4'-dimethyl-1a,1a$^1$,2,3,3a,5a-hexahydro-5*H*,5'*H*-4-oxaspiro[cyclobuta[*cd*]pentalene-1,2'-furan]-5,5'-dione (276):** A solution of crude cyclobutane **628** (7.97 mmol, 1.0 eq.) in $CH_2Cl_2$ (76 mL) and pH7 buffer (4 mL) was cooled to 0 ºC before the addition of DDQ (2.71 g, 12.0 mmol, 1.5 eq.). The resulting dark green suspension was allowed to warm slowly to room temperature and stirred for 4 h. The reaction mixture was then quenched with saturated $NaHCO_3$ (20 mL) and extracted with $CH_2Cl_2$ (3 x 100 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1 to 2:1) to yield alcohol **276** as an off-white solid. Spectral data matched reported values.[64]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 6.99-6.98 (m, 1H), 5.34-5.29 (m, 1H), 4.03-4.00 (m, 1H), 3.89 (dd, *J* = 11.8, 6.7 Hz, 1H), 3.57 (t, *J* = 7.9 Hz, 1H), 3.19 (dd, *J* = 7.5, 1.7 Hz, 1H), 2.67 (ddd, *J* = 15.7, 8.2, 2.0 Hz, 1H), 2.32 (bs, 1H), 1.98-1.93 (m, 4H), 1.27 (s, 3H), 0.81 (s, 9H), 0.08(1) (s, 3H), 0.07(5) (s, 3H).

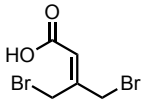
**Experimental Procedures: Section 5.1**




**(1S,1aR,1a$^1$S,2S,3aS,5aS)-2-((tert-Butyldimethylsilyl)oxy)-2,4'-dimethyl-5,5'-dioxo-1a,1a$^1$,3,3a-tetrahydro-2H,5'H-4-oxaspiro[cyclobuta[cd]pentalene-1,2'-furan]-5a(5H)-carbaldehyde (277):** A solution of freshly distilled $(COCl)_2$ (0.80 mL, 7.91

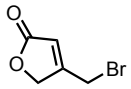
mmol, 2.0 eq.) in $CH_2Cl_2$ (80 mL) was cooled to -78 ºC before the dropwise addition of DMSO (1.12 mL, 15.8 mmol, 4.0 eq.). The resulting solution was stirred for 15 min and alcohol **276** (1.56 g, 3.95 mmol, 1.0 eq.) was then added as a solution in $CH_2Cl_2$ (20 mL). After stirring at -78 ºC for 1 h, $NEt_3$ (3.31 mL, 23.7 mmol, 6.0 eq.) was added. The resulting solution was kept at -78 ºC for 2 h then allowed to warm slowly to room temperature over 1 h. The reaction mixture was then quenched with saturated $NaHCO_3$ (25 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (25 mL) and brine (25 mL), dried over $MgSO_4$, and filtered through a plug of $SiO_2$. The solvent was removed *in vacuo* to yield crude aldehyde **277**, which was used without further purification. Spectral data matched reported values.[64]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 9.59 (s, 1H), 7.09 (d, *J* = 1.3 Hz, 1H), 5.37-5.32 (m, 1H), 3.95 (t, *J* = 7.8 Hz, 1H), 3.18 (dd, *J* = 7.6, 1.8 Hz, 1H), 2.72 (ddd, *J* = 15.6, 8.0, 1.9 Hz, 1H), 2.01 (d, *J* = 1.7 Hz, 1H), 1.98-1.93 (m, 2H), 1.28 (s, 3H), 0.83 (s, 9H), 0.09(4) (s, 3H), 0.08(7) (s, 3H).



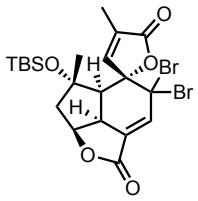
**4-Bromo-3-(bromomethyl)but-2-enoic acid (630):** A solution of acid **629** (2.00 g, 20.0 mmol, 1.0 eq.) and NBS (7.47 g, 41.9 mmol, 2.1 eq.) in $CCl_4$ (40 mL) was heated to reflux before the addition of $(BzO)_2$ (48 mg, 0.200 mmol, 0.01 eq.). The reaction mixture was stirred at reflux for 2 h before the addition of a second portion of $(BzO)_2$ (48 mg, 0.200 mmol, 0.01 eq.). After 2.5 h, the reaction mixture was cooled to room temperature, filtered, and the solvent was removed *in vacuo* to yield crude dibromide **630** which was used without further purification. Spectral data matched reported values.[170]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 6.08 (s, 1H), 4.72 (s, 2H), 4.19 (s, 2H).



**4-(Bromomethyl)furan-2(5H)-one (631):** To a flask containing crude dibromide **630** (20.0 mmol, 1.0 eq.) was added an aqueous solution of NaOH (16 mL, 5%). The resulting mixture was stirred at room temperature for 15 h. The reaction mixture was then extracted with $CH_2Cl_2$ (2 x 100 mL) and the combined organic extracts were washed with saturated $NaHCO_3$ (2 x 15 mL) and $H_2O$ (2 x 15 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to yield butenolide **631** (1.52 g, 43%). Spectral data matched reported values.[170]

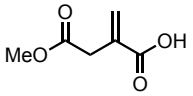
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 6.13 (s, 1H), 4.94-4.93 (m, 2H), 4.23 (s, 2H).



**(2S,2a¹'S,5a'R,6'S,7a'S)-4',4'-Dibromo-6'-((tert-butyldimethylsilyl) oxy)-4,6'-dimethyl-2a¹',4',5a',6',7',7a'-hexahydro-2'H,5H-spiro[furan-2,5'-indeno[1,7-bc] furan]-2',5-dione (637):** To a solution of $PPh_3$ (364 mg, 1.39 mmol, 4.0 eq.) in $CH_2Cl_2$ (3.5 mL) at 0 ºC was added $CBr_4$ (230 mg, 0.694 mmol, 2.0 eq.). After 5 min, a solution of crude aldehyde **277** (0.347 mmol, 1.0 eq.) in $CH_2Cl_2$ (3.5 mL) was added dropwise. The resulting yellow reaction mixture was stirred for 30 min, then it was quenched with $H_2O$ (2 mL). The layers were partitioned and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 6:1) to yield dibromide **637** (90 mg, 47% over 2 steps).

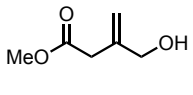
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.27 (s, 1H), 6.48 (d, *J* = 1.7 Hz, 1H), 5.27-5.21 (m, 1H), 3.99 (td, *J* = 9.5, 4.0 Hz, 1H), 3.31 (dd, *J* = 10.2, 2.0 Hz, 1H), 2.39 (ddd, *J* = 12.7, 6.7, 1.8 Hz, 1H), 2.09-1.95 (m, 4H), 1.27 (s, 3H), 0.87 (s, 9H), 0.20 (s, 3H), 0.13 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 170.7, 166.9, 143.8, 140.7, 137.1, 133.9, 91.7, 85.1, 81.1, 61.8, 51.0, 48.2, 43.7, 25.5, 22.3, 17.9, 10.7, -2.4, -2.8.



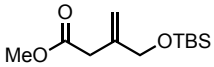
**4-Methoxy-2-methylene-4-oxobutanoic acid (646):** To a refluxing solution of itaconic acid (**645**, 10.0 g, 76.9 mmol, 1.0 eq.) in MeOH (20 mL) was added AcCl (0.16 mL, 2.30 mmol, 0.03 eq.) and the solution was refluxed for 1.5 h. After cooling to room temperature, the solvent was removed *in vacuo* and the crude residue was dissolved in hot PhMe (20 mL). Heptane (30 mL) was then added and the solution was set at 4 ºC for 30 min. The resulting crystals were collected by filtration and dried *in vacuo* to yield acid **646** (7.78 g, 70%). Spectral data matched reported values.[248]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 6.47 (s, 1H), 5.84 (d, *J* = 0.9 Hz, 1H), 3.71 (s, 3H), 3.35 (s, 2H).



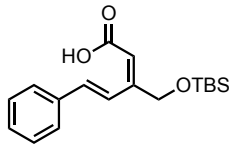
**Methyl 3-(hydroxymethyl)but-3-enoate (647):** To a solution of acid **646** (1.00 g, 6.94 mmol, 1.0 eq.) and $NEt_3$ (1.06 mL, 7.63 mmol, 1.1 eq.) in THF (4.5 mL) at 0 ºC was added ClCOOEt (0.73 mL, 7.63 mmol, 1.1 eq.) as a solution in THF (5 mL) dropwise via addition funnel. The resulting mixture was stirred at that temperature for 1.5 h then filtered through a frit, washing with THF (2 x 3 mL). The collected filtrate was cooled to 0 ºC and $NaBH_4$ (787 mg, 20.8 mmol, 3.0 eq.) and MeOH (18 mL) were added sequentially. The reaction

mixture was stirred at 0 ºC for 2 h and quenched by the careful addition of 1N HCl (10 mL). The reaction mixture was extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo* to yield crude alcohol **647**, which was used immediately in the next step.




**Methyl 3-(((tert-butyldimethylsilyl)oxy)methyl)but-3-enoate (648):** To a solution of crude alcohol **647** (6.94 mmol, 1.0 eq.) in $CH_2Cl_2$ (30 mL) were added sequentially ImH (520 mg, 7.63 mmol, 1.0 eq.), DMAP (spatula tip), and TBSCl (1.05 g, 6.94 mmol, 1.0 eq.). The reaction mixture was stirred at room temperature for 19 h and then quenched with $H_2O$ (15 mL). The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 19:1) to yield silyl ether **648** (525 mg, 31% over 2 steps).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 5.20 (d, *J* = 1.1 Hz, 1H), 4.99 (d, *J* = 1.1 Hz, 1H), 4.16 (s, 2H), 3.68 (s, 3H), 3.08 (s, 2H), 0.91 (s, 9H), 0.07 (s, 6H).

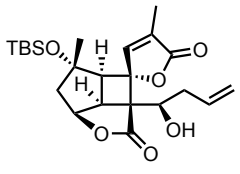



**(2E,4E)-3-(((tert-Butyldimethylsilyl)oxy)methyl)-5-phenylpenta-2,4-dienoic acid (650):** A solution of silyl ether **648** (54 mg, 0.221 mmol, 1.5 eq.) in THF (1.5 mL) was cooled to -78 ºC before the dropwise addition of KHMDS (0.22 mL, 0.221 mmol, 1.5 eq., 1.0 M solution in THF). The reaction mixture was stirred for 1 h before warming to -10 ºC. Benzaldehyde (**649**, 0.02 mL, 0.147 mmol, 1.0 eq.) was then added neat and the reaction mixture was stirred at -10 ºC for 1.5 h. The reaction mixture was then quenched with saturated $NH_4Cl$ (2 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to yield diene **650** (31 mg, 66%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 8.21 (d, *J* = 17.1 Hz, 1H), 7.53-7.51 (m, 2H), 7.38-7.28 (m, 3H), 6.85 (d, *J* = 17.1 Hz, 1H), 6.19 (s, 1H), 4.63 (s, 2H), 0.97 (s, 9H), 0.15 (s, 6H).

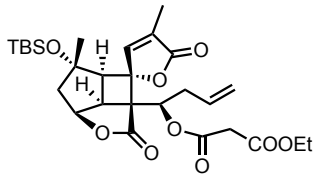
$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 171.9, 154.4, 136.4, 133.7, 128.8, 128.7, 127.2, 123.1, 114.2, 62.6, 25.8, 18.3, -5.4.

**Experimental Procedures: Section 5.2**



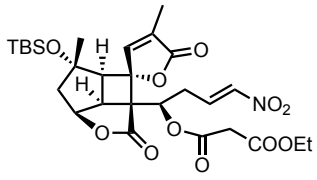

**(1*S*,1a*R*,1a$^1$*S*,2*S*,3a*S*,5a*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-5a-((*R*)-1-hydroxybut-3-en-1-yl)-2,4'-dimethyl-1a,1a$^1$,2,3,3a,5a-hexahydro-5*H*,5'*H*-4-oxaspiro [cyclobuta[*cd*]pentalene-1,2'-furan]-5,5'-dione (652):** A suspension of **278** (1.56 g, 7.40 mmol, 2.0 eq.) and In$^o$ powder (850 mg, 7.40 mmol, 2.0 eq.) in THF (37 mL) was cooled to -10 $^o$C before the addition of pyr (0.60 mL, 7.40 mmol, 2.0 eq.) and allyl bromide (1.28 mL, 14.8 mmol, 4.0 eq.). The reaction mixture was stirred for 30 min then crude aldehyde **277** (3.70 mmol, 1.0 eq.) was added as a solution in THF (12.3 mL). The reaction mixture was allowed to warm slowly to room temperature and stirred for 19 h. Upon completion, the reaction mixture was diluted with EtOAc (150 mL), filtered through a plug of celite, and concentrated *in vacuo*. The crude residue was purified by ISCO (80 g, gradient: 15% to 25% EtOAc in hexanes over 35 min) to yield alcohol **652** (842 mg, 52% over 2 steps) as a white solid. Spectral data matched reported values.[64]

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.01-7.00 (m, 1H), 5.94-5.93 (m, 1H), 5.30-5.25 (m, 1H), 5.16-5.11 (m, 2H), 4.14-4.11 (m, 1H), 3.65 (t, *J* = 8.1 Hz, 1H), 3.17 (dd, *J* = 7.8, 1.8 Hz, 1H), 2.72-2.64 (m, 2H), 2.42-2.34 (m, 1H), 2.20-2.15 (m, 1H), 1.98-1.93 (m, 4H), 1.27 (s, 3H), 0.83 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H).




**(*R*)-1-((1*S*,1a*R*,1a$^1$*S*,2*S*,3a*S*,5a*R*)-2-((*tert*-Butyldimethylsilyl) oxy)-2,4'-dimethyl-5,5'-dioxo-1a,1a$^1$,3,3a-tetrahydro-2*H*,5'*H*-4-oxaspiro[cyclobuta[*cd*] pentalene-1,2'-furan]-5a(5*H*)-yl)but-3-en-1-yl ethyl malonate (660):** To a solution of alcohol **652** (262 mg, 0.603 mmol, 1.0 eq.) and ethyl hydrogen malonate (0.21 mL, 1.81 mmol, 3.0 eq.) in $CH_2Cl_2$ (6 mL) at 0 $^o$C was added DMAP (22 mg, 0.181 mmol, 0.3 eq.) and DCC (410 mg, 1.99 mmol, 3.3 eq.). The resulting suspension was stirred at that temperature for 2.5 h then diluted with $CH_2Cl_2$ (50 mL). The organic phase was washed with saturated $NH_4Cl$ (6 mL) and brine (6 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to yield malonate ester **660** (293 mg, 88%).

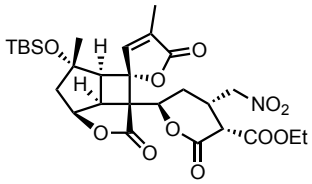
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 6.98 (d, *J* = 1.9 Hz, 1H), 5.77-5.66 (m, 1H), 5.63 (dd, *J* = 9.3, 2.8 Hz, 1H), 5.28-5.23 (m, 1H), 5.10-5.04 (m, 2H), 4.23-4.15 (m, 2H), 3.53 (t, *J* = 8.6 Hz, 1H), 3.39 (d, *J* = 3.2 Hz, 2H), 3.22 (dd, *J* = 7.9, 1.7 Hz, 1H), 2.76-2.60 (m, 2H), 2.15-2.10 (m, 1H), 1.97-1.92 (m, 4H), 1.30-1.24 (m, 6H), 0.83 (s, 9H), 0.09 (s, 6H).




**(*R*,*E*)-1-((1*S*,1a*R*,1a$^1$*S*,2*S*,3a*S*,5a*R*)-2-((*tert*-Butyldimethylsilyl) oxy)-2,4'-dimethyl-5,5'-dioxo-1a,1a$^1$,3,3a-tetrahydro-2*H*,5'*H*-4-oxaspiro[cyclobuta[*cd*] pentalene-1,2'-furan]-5a(5*H*)-yl)-4-nitrobut-3-en-1-yl ethyl malonate (661):** To a suspension of malonate ester **660** (288 mg, 0.525 mmol, 1.0 eq.) and powdered 4Å MS (spatula tip) in 1,4-dioxane (5.3 mL) was added $^t$BuONO (0.28 mL, 2.10 mmol, 4.0 eq., 90%) and TEMPO (123 mg, 0.787 mmol, 1.5 eq.). The resulting orange reaction mixture was heated to 90 ºC under a balloon atmosphere of air and stirred for 2 h. After cooling to room temperature, the solvent was removed *in vacuo* and the crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to yield nitroalkene **661** (243 mg, 78%).

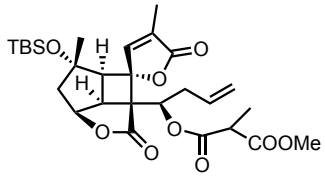
$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.13-7.06 (m, 1H), 7.03-6.96 (m, 2H), 5.72 (dd, *J* = 9.2, 2.8 Hz, 1H), 5.32-5.27 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.51 (t, *J* = 8.1 Hz, 1H), 3.41 (s, 2H), 3.24-3.21 (m, 1H), 2.70-2.62 (m, 2H), 2.29-2.22 (m, 1H), 1.96-1.92 (m, 4H), 1.29-1.25 (m, 6H), 0.82 (s, 9H), 0.08 (s, 6H).

$^{13}$C NMR (100 MHz, $CDCl_3$) ∂ 170.4, 166.0, 165.6, 144.4, 141.6, 136.1, 132.5, 85.3, 83.8, 83.3, 70.0, 61.8, 59.5, 55.4, 50.8, 42.7, 41.3, 29.0, 25.4, 23.2, 17.7, 14.0, 10.8, -2.5, -2.6.



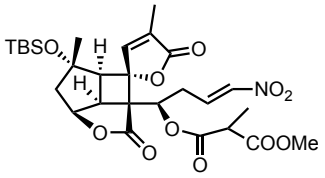

**ethyl (3*R*,4*S*,6*R*)-6-((1*S*,1a*R*,1a$^1$*S*,2*S*,3a*S*,5a*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-2,4'-dimethyl-5,5'-dioxo-1a,1a$^1$,3,3a-tetrahydro-2*H*,5'*H*-4-oxaspiro [cyclobuta[*cd*]pentalene-1,2'-furan]-5a(5*H*)-yl)-4-(nitromethyl)-2-oxotetrahydro-2*H*-pyran-3-carboxylate (662):** To a solution of nitroalkene **661** (217 mg, 0.366 mmol, 1.0 eq.) in $CH_3CN$ (7.3 mL) was added $Cs_2CO_3$ (262 mg, 0.804 mmol, 2.2 eq.). The reaction immediately turned orange, and the resulting suspension was stirred at room temperature for 21 h. The reaction mixture was then quenched with AcOH (0.23 mL, 3.71 mmol, 10.0 eq.) and the solvents were removed *in vacuo*. The crude residue was purified by flash column chromatography ($CH_2Cl_2$/MeOH, 100:1) to yield lactone **662** (100 mg, 46%, dr = 1.6:1).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 7.02 (m, 1H), 5.37-5.32 (m, 1H), 5.06/4.93 (dd, *J* = 10.7, 3.1 Hz, 1H), 4.48/4.39 (m, 2H), 4.34-4.27 (m, 2H), 3.70-3.60 (m, 2H), 3.25-3.05 (m, 2H), 2.89-2.64 (m, 2H), 2.04-1.92 (m, 4H), 1.35-1.26 (m, 6H), 0.82 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H).




**1-((*R*)-1-((1*S*,1a*R*,1a$^1$*S*,2*S*,3a*S*,5a*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-2,4'-dimethyl-5,5'-dioxo-1a,1a$^1$,3,3a-tetrahydro-2*H*,5'*H*-4-oxaspiro[cyclobuta[*cd*]pentalene-1,2'-furan]-5a(5*H*)-yl)but-3-en-1-yl) 3-methyl 2-methylmalonate (668):** To a solution of alcohol **652** (56 mg, 0.128 mmol, 1.0 eq.) and acid **667** (51 mg, 0.385 mmol, 3.0 eq.) in $CH_2Cl_2$ (1.3 mL) at 0 ºC was added DMAP (5 mg, 0.0385 mmol, 0.3 eq.) and DCC (87 mg, 0.423 mmol, 3.3 eq.). The resulting suspension was stirred at that temperature for 1.5 h then diluted with $CH_2Cl_2$ (15 mL). The organic phase was washed with saturated $NH_4Cl$ (2 mL) and brine (2 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to yield malonate ester **668** (54 mg, 77%).

$^1$H NMR (400 MHz, $CDCl_3$) ∂ 6.98-6.96 (m, 1H), 5.75-5.65 (m, 1H), 5.62/5.54 (dd, *J* = 9.0, 2.7 Hz, 1H), 5.25-5.20 (m, 1H), 5.09-5.03 (m, 2H), 3.73/3.72 (s, 3H), 3.53-3.43 (m, 2H), 3.23-3.19 (m, 1H), 2.75-2.60 (m, 2H), 2.23-2.10 (m, 1H), 1.98-1.92 (m, 4H), 1.45/1.43 (d, *J* = 3.3 Hz, 3H), 1.28/1.27 (s, 3H), 0.83 (s, 9H), 0.09 (s, 6H).



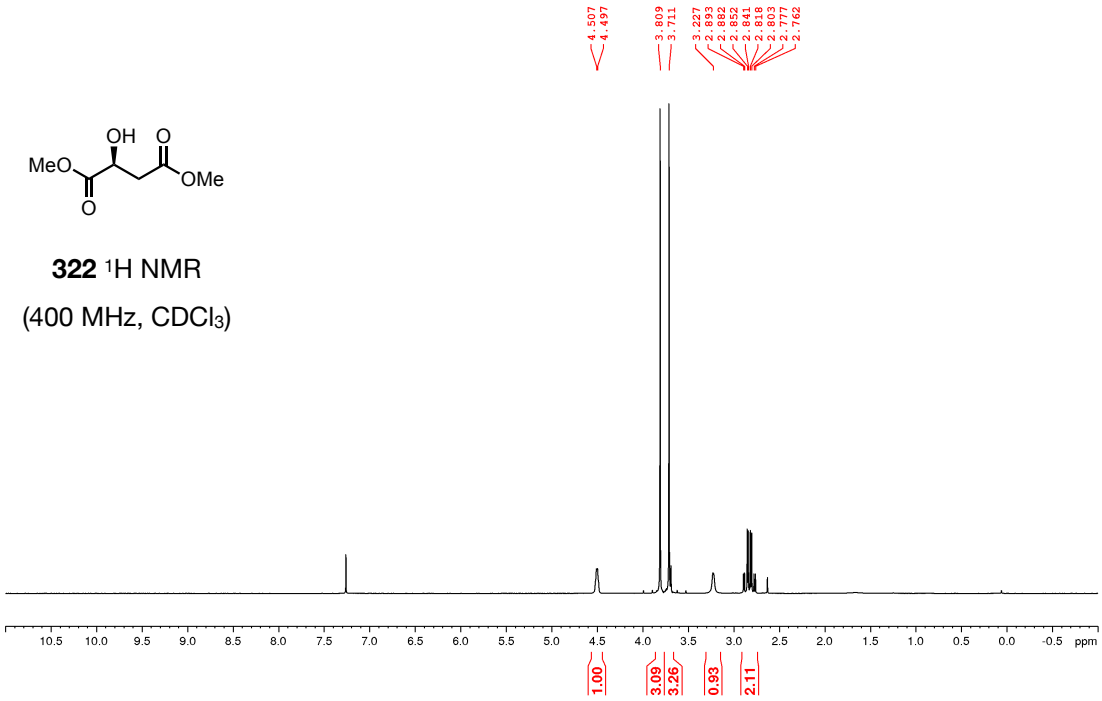

**1-((*R*,*E*)-1-((1*S*,1a*R*,1a$^1$*S*,2*S*,3a*S*,5a*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-2,4'-dimethyl-5,5'-dioxo-1a,1a$^1$,3,3a-tetrahydro-2*H*,5'*H*-4-oxaspiro[cyclobuta[*cd*]pentalene-1,2'-furan]-5a(5*H*)-yl)-4-nitrobut-3-en-1-yl) 3-methyl 2-methylmalonate (669):** To a suspension of malonate ester **668** (54 mg, 0.0984 mmol, 1.0 eq.) and powdered 4Å MS (spatula tip) in 1,4-dioxane (1.0 mL) was added $^t$BuONO (0.05 mL, 0.394 mmol, 4.0 eq., 90%) and TEMPO (23 mg, 0.148 mmol, 1.5 eq.). The resulting orange reaction mixture was heated to 90 ºC under a balloon atmosphere of air and stirred for 2.5 h. After cooling to room temperature, the solvent was removed *in vacuo* and the crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to yield nitroalkene **669** (43 mg, 74%).

$^{1}$H NMR (400 MHz, $CDCl_3$) ∂ 7.14-7.04 (m, 1H), 7.00-6.95 (m, 2H), 5.72/5.66 (dd, *J* = 9.5, 2.8 Hz, 1H), 5.29-5.22 (m, 1H), 3.71 (s, 3H), 3.51 (t, *J* = 8.1 Hz, 1H), 3.52-3.40 (m, 2H), 3.22-3.21 (m, 1H), 3.07-2.93 (m, 1H), 2.68-2.63 (m, 1H), 2.32-2.23 (m, 1H), 1.96-1.90 (m, 4H), 1.44-1.41 (m, 3H), 1.27 (s, 3H), 0.82 (s, 9H), 0.08 (s, 6H).

# Appendix

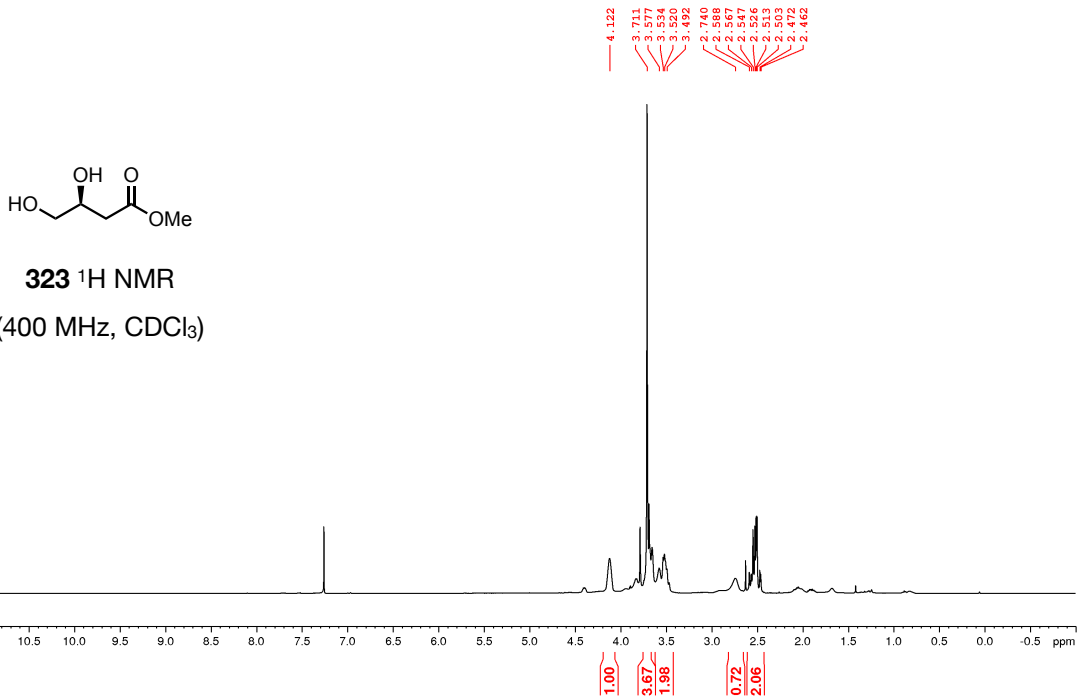
## Spectra

### NMR Spectra: Section 3.1:



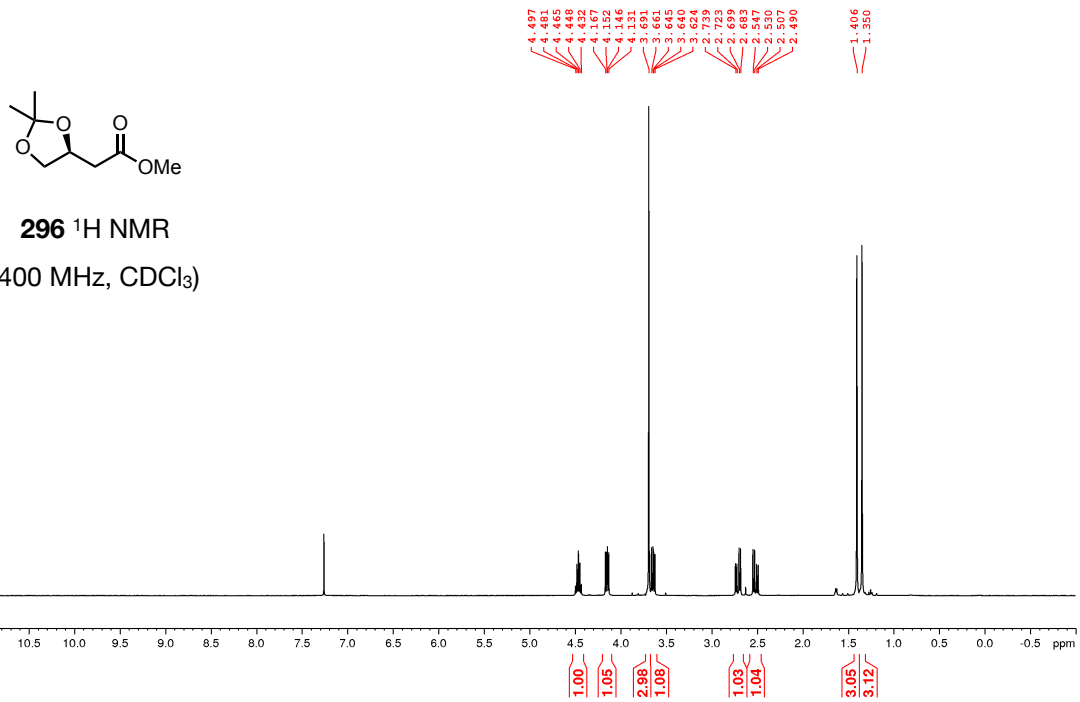

**322** $^{1}$H NMR

(400 MHz, $CDCl_3$)



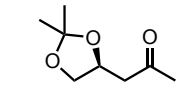

**323** $^1$H NMR

(400 MHz, $CDCl_3$)




**296** $^1$H NMR

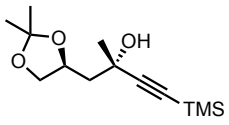
(400 MHz, $CDCl_3$)



**204** $^{1}$H NMR

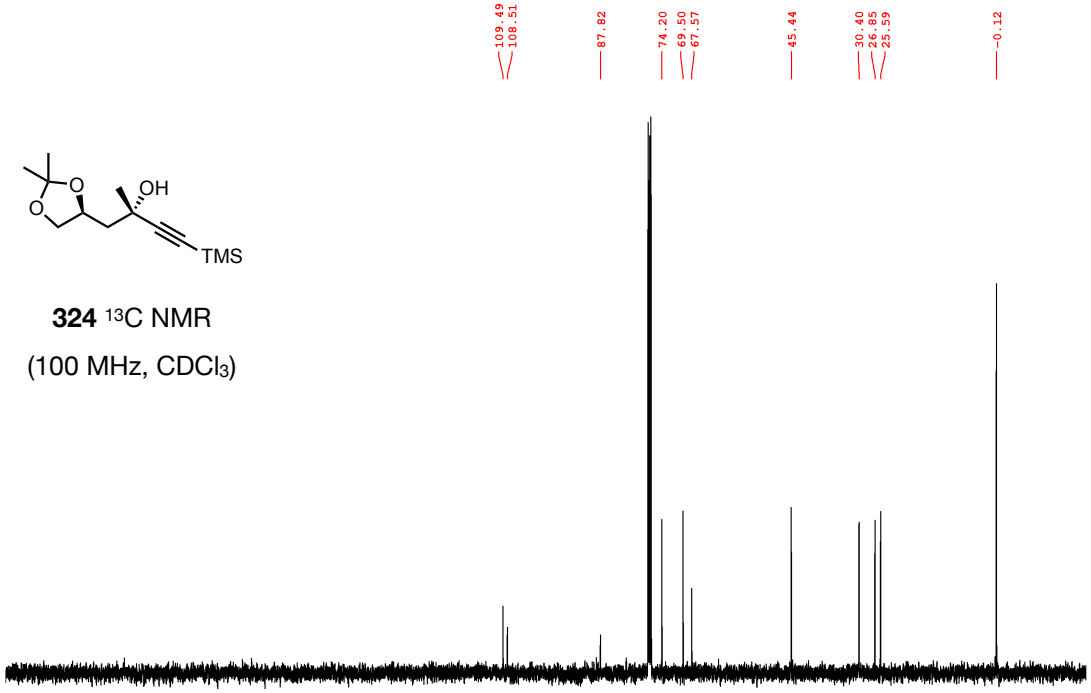
(400 MHz, $CDCl_3$)



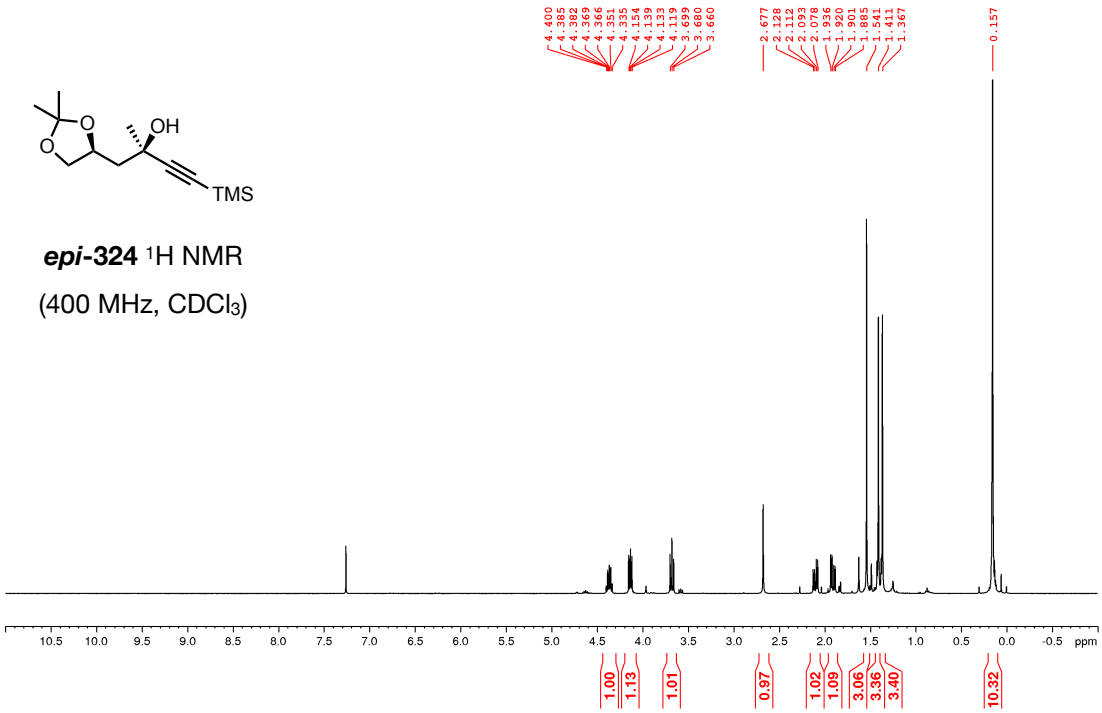

**324** $^{1}$H NMR

(400 MHz, $CDCl_3$)



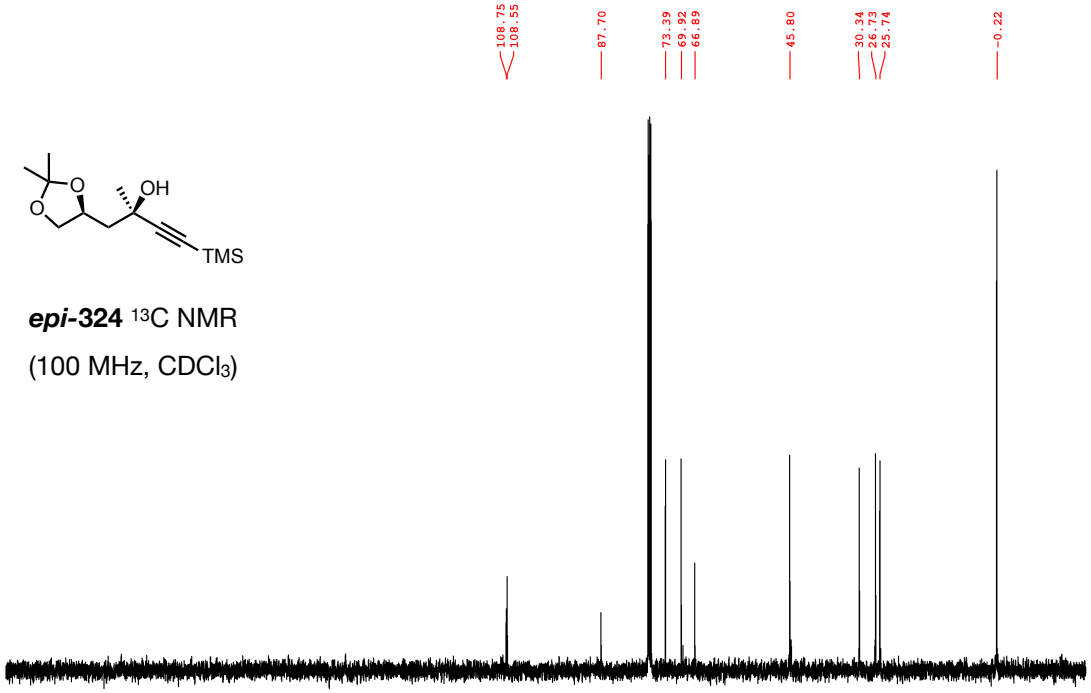

**324** $^{13}$C NMR

(100 MHz, $CDCl_3$)



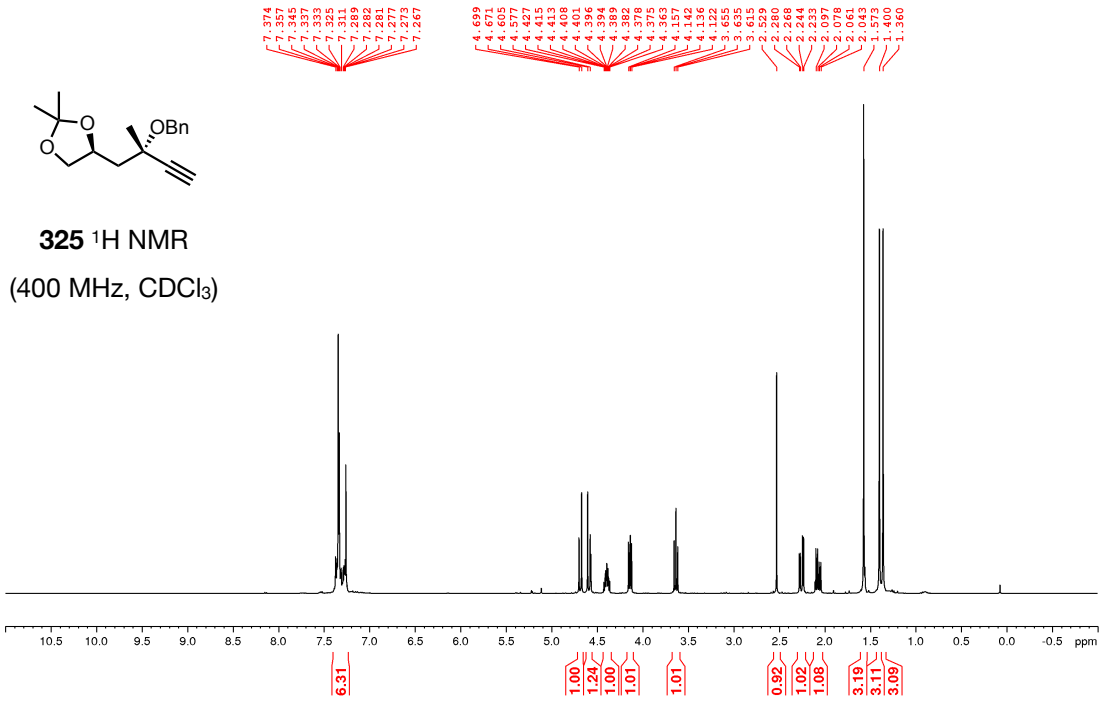

***epi*-324** $^{1}$H NMR

(400 MHz, $CDCl_3$)



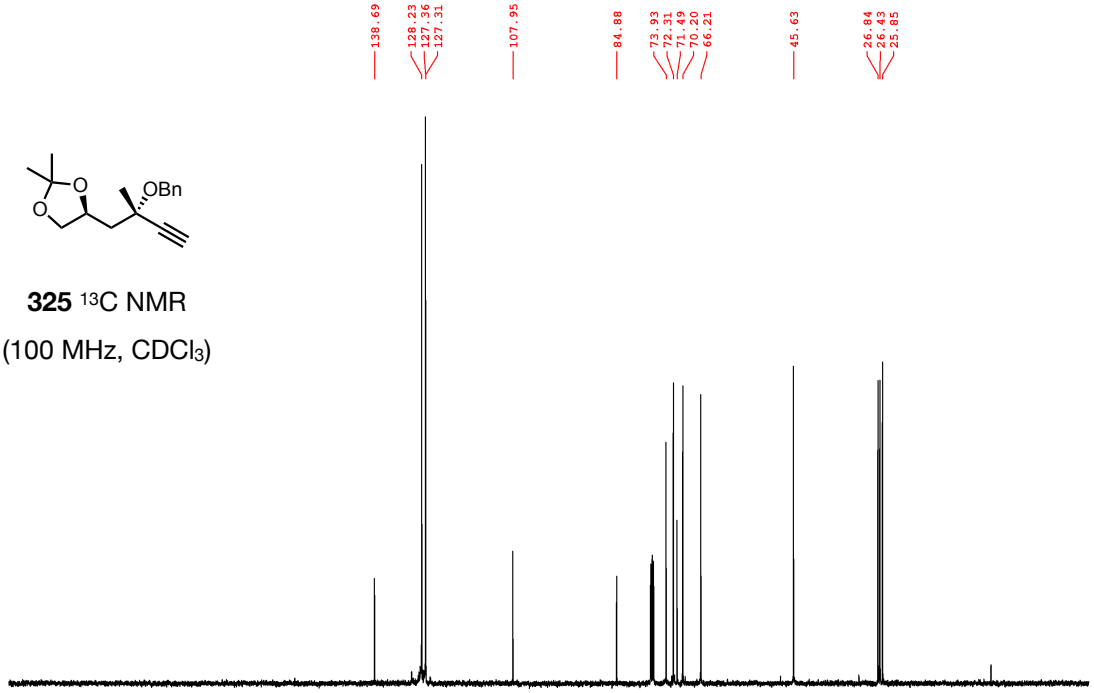

***epi*-324** $^{13}$C NMR

(100 MHz, $CDCl_3$)



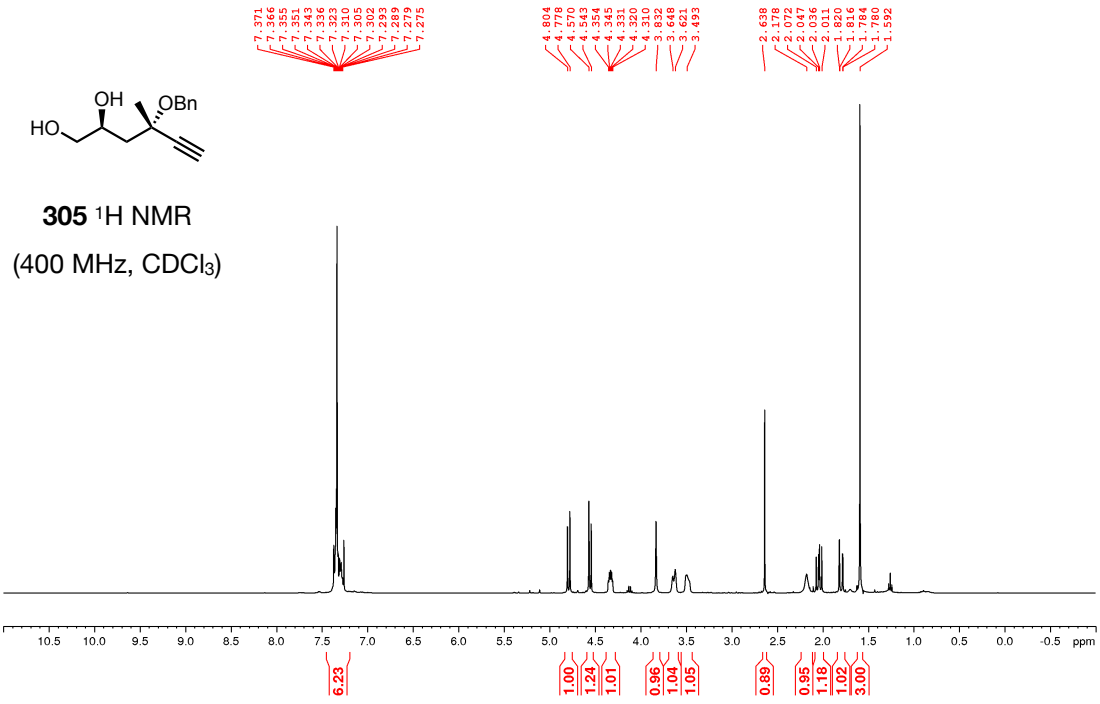

**325** $^{1}$H NMR

(400 MHz, $CDCl_3$)



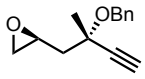

**325** $^{13}C$ NMR

(100 MHz, $CDCl_3$)




**305** $^{1}H$ NMR

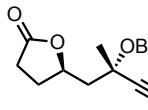
(400 MHz, $CDCl_3$)




**326** $^{1}$H NMR

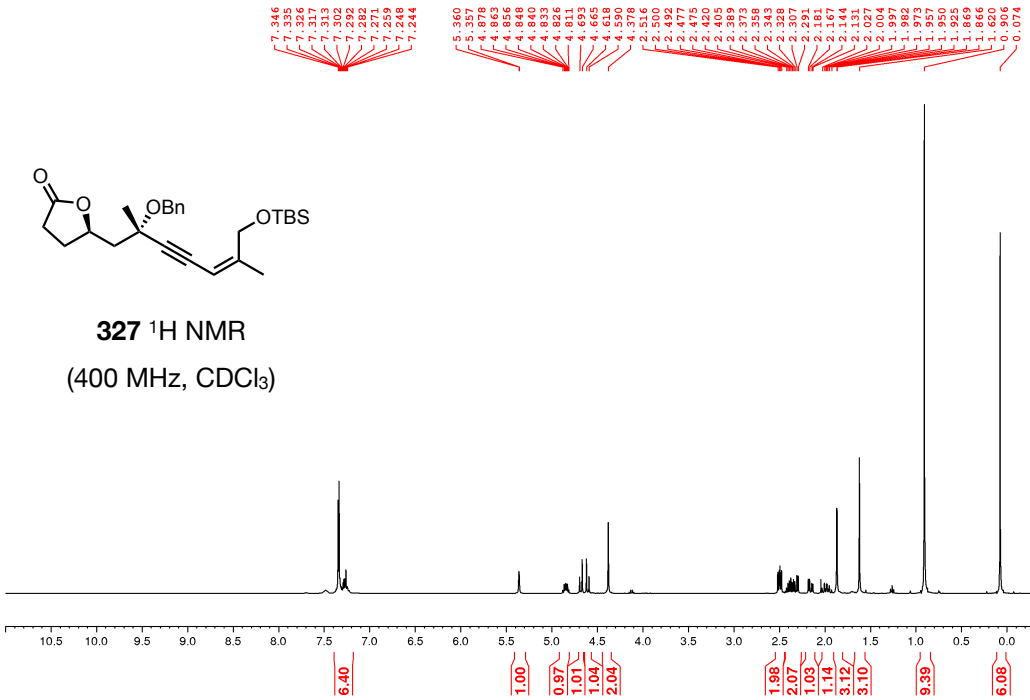
(400 MHz, $CDCl_3$)



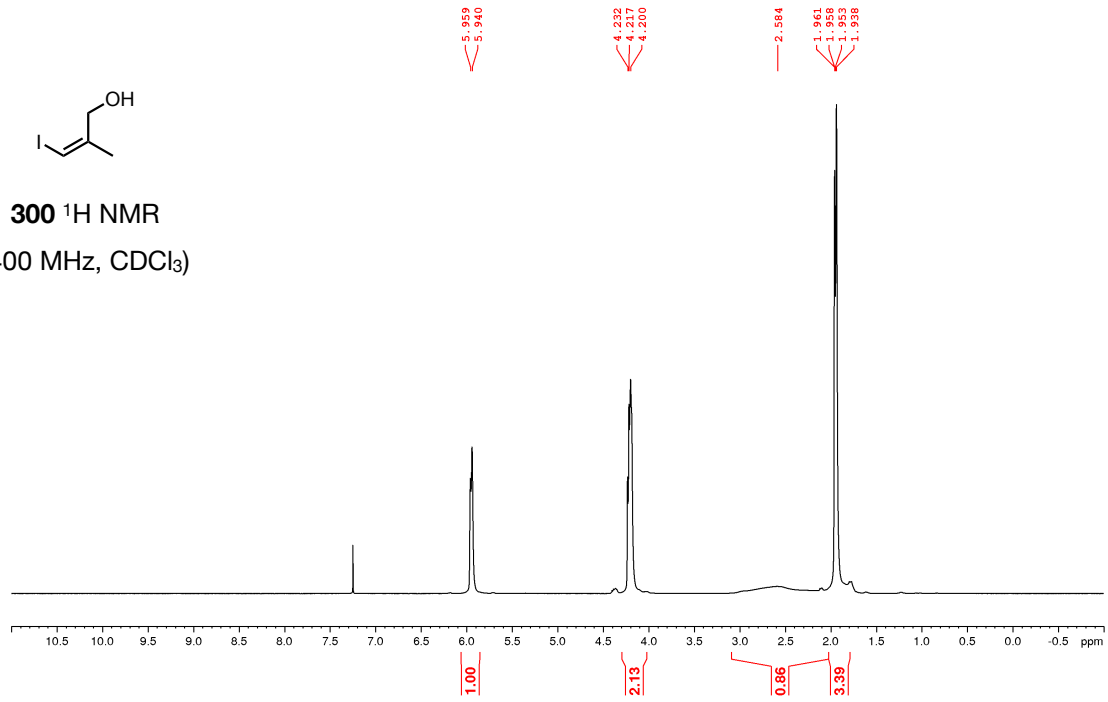

**307** $^{1}$H NMR

(400 MHz, $CDCl_3$)



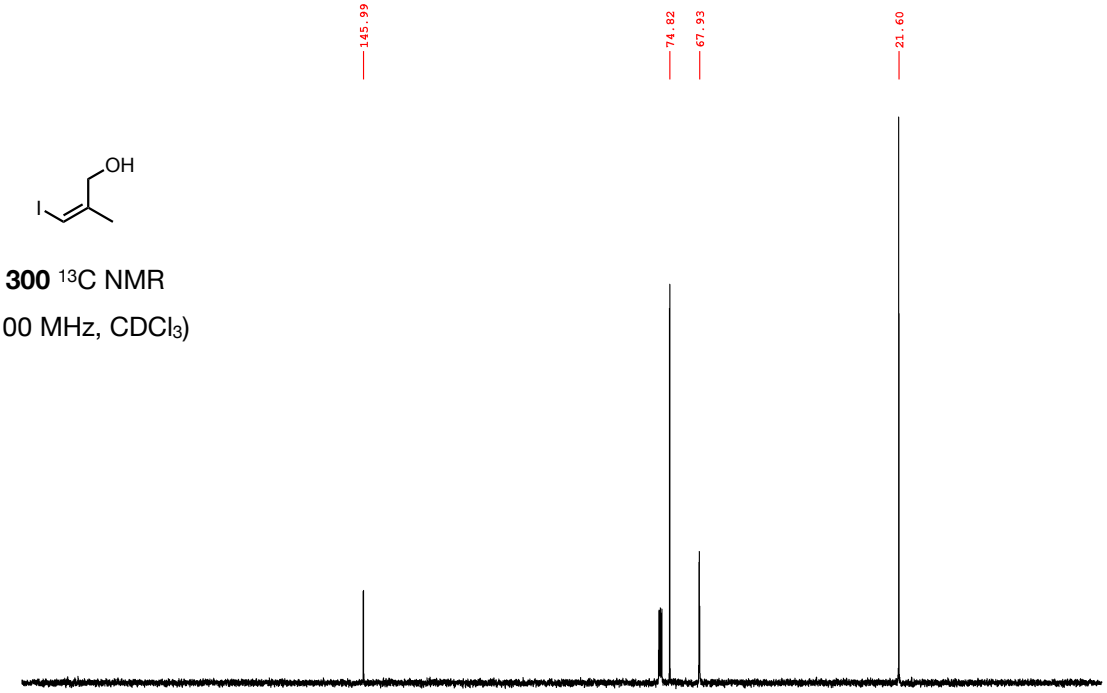

**327** $^{1}$H NMR

(400 MHz, $CDCl_3$)



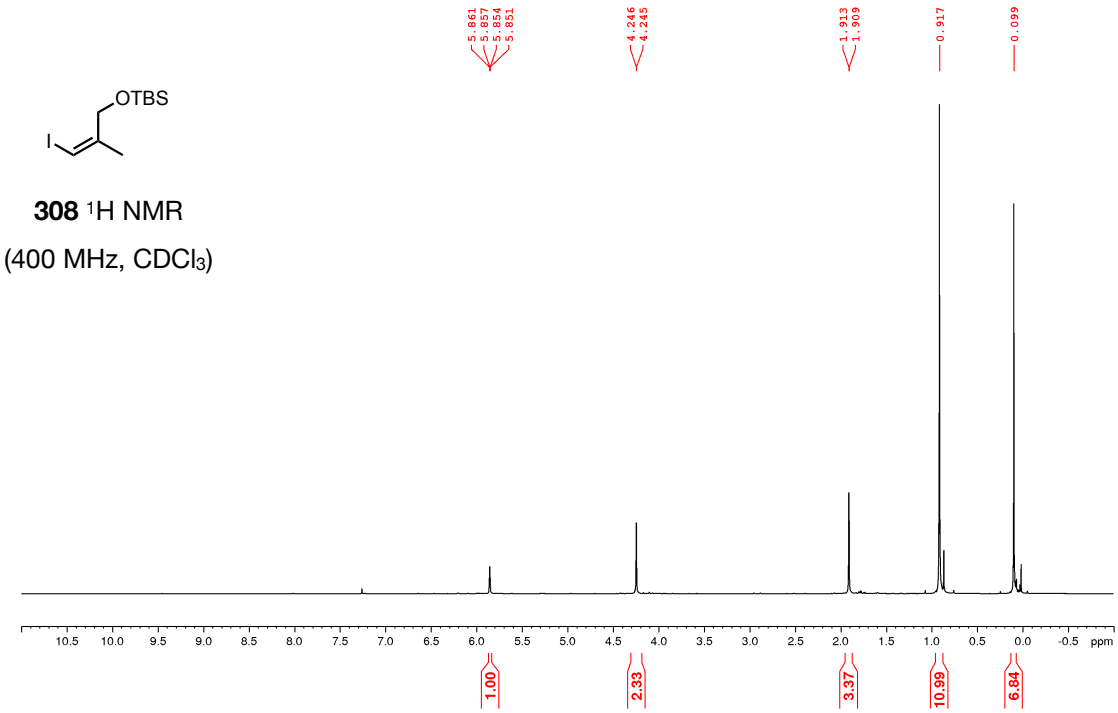

**300** $^{1}$H NMR

(400 MHz, $CDCl_3$)




**300** $^{13}C$ NMR

(100 MHz, $CDCl_3$)




**308** $^{1}H$ NMR

(400 MHz, $CDCl_3$)


**328** $^{1}$H NMR

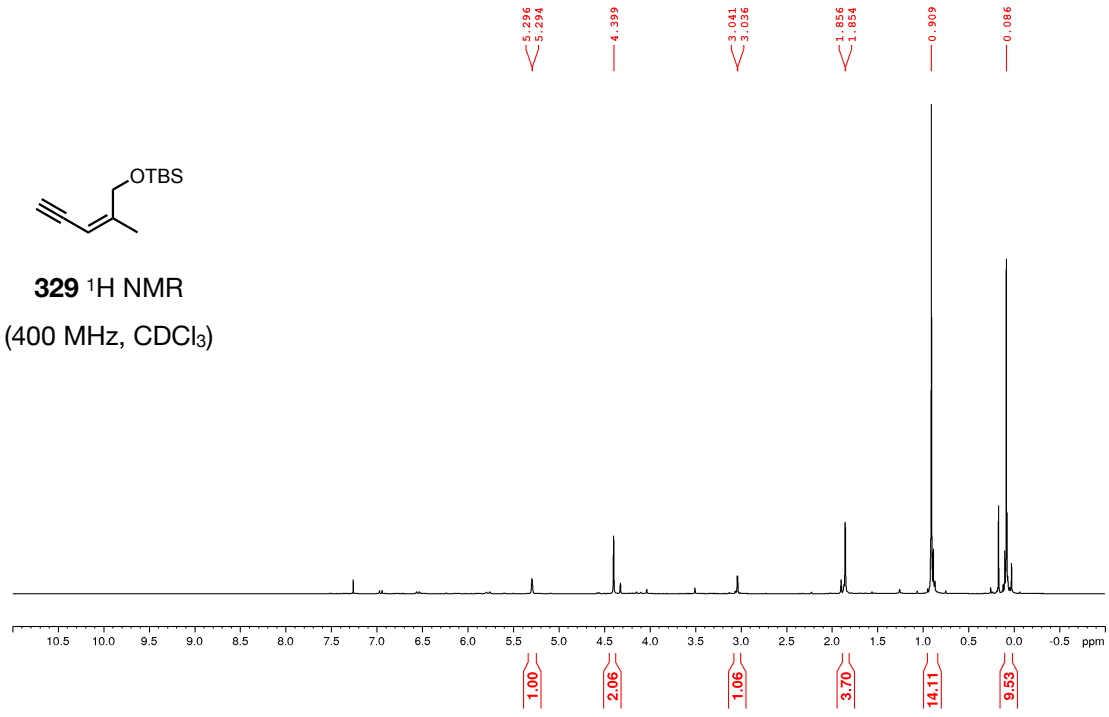
(400 MHz, $CDCl_3$)





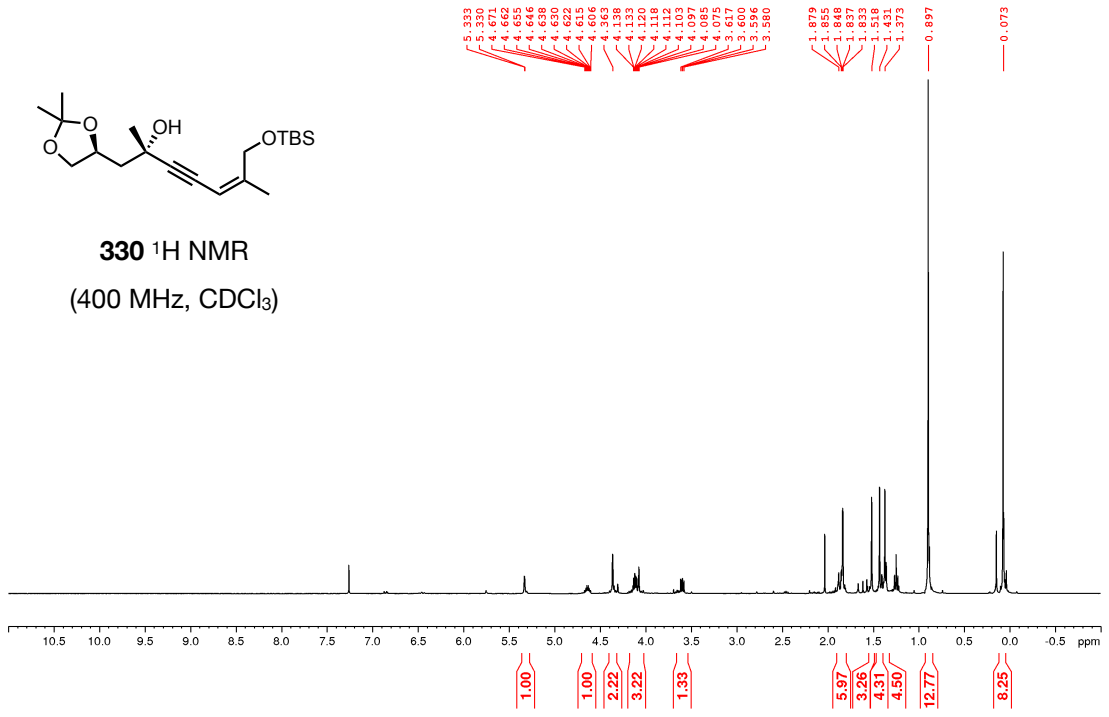
**328** $^{13}$C NMR

(100 MHz, $CDCl_3$)



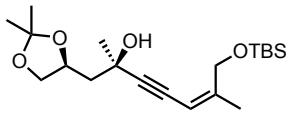

**329** $^1$H NMR

(400 MHz, $CDCl_3$)




**330** $^1$H NMR

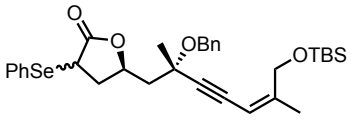
(400 MHz, $CDCl_3$)




***epi*-330** $^1$H NMR

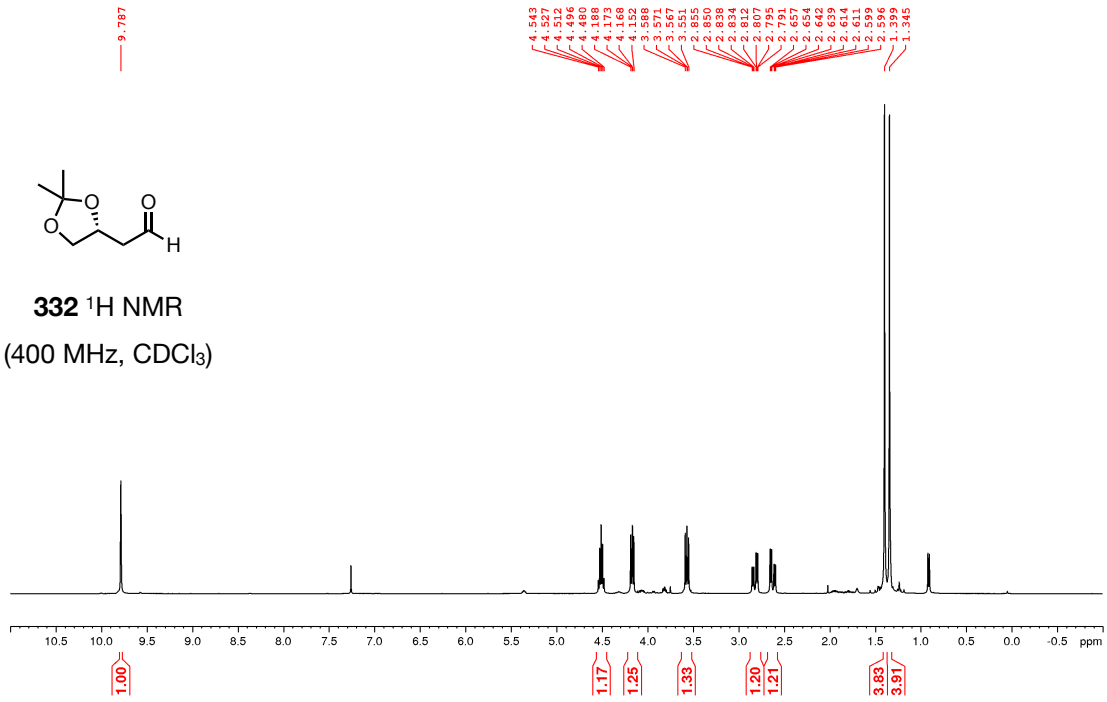
(400 MHz, $CDCl_3$)



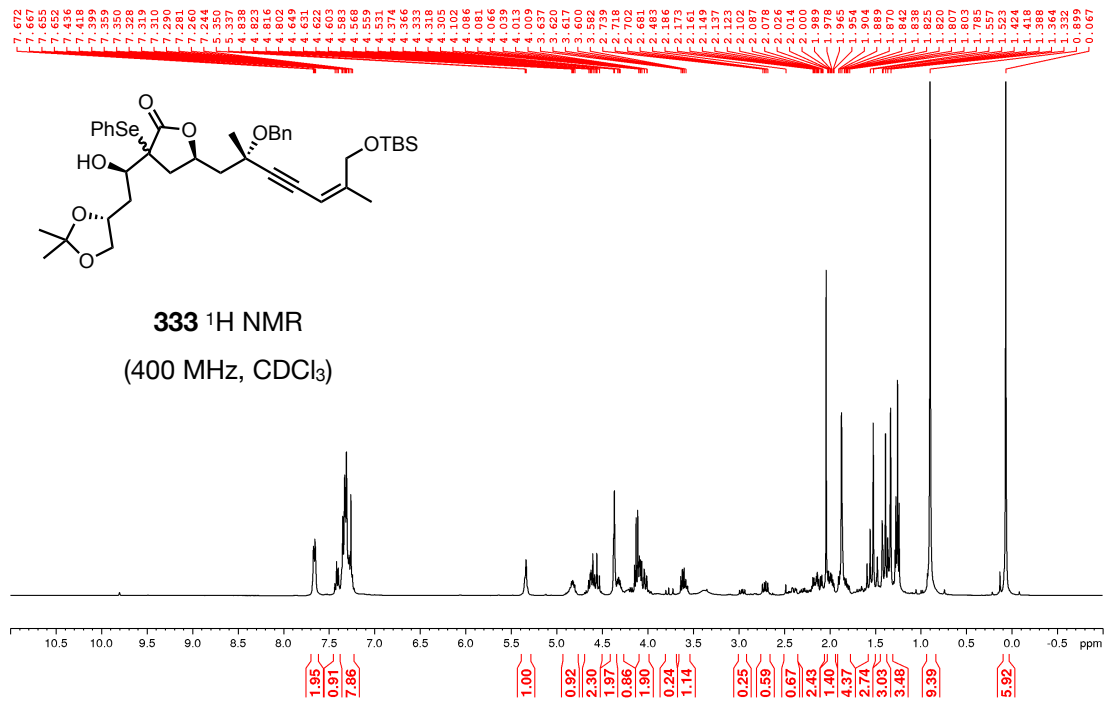

**309** $^1$H NMR

(400 MHz, $CDCl_3$)



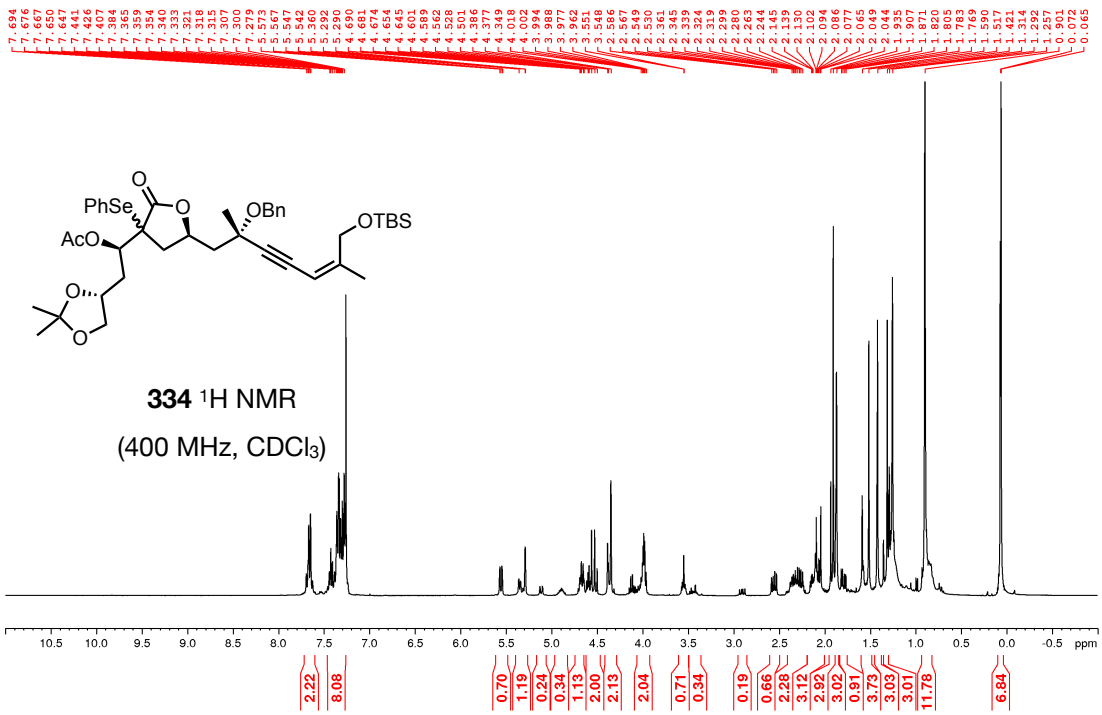
**332** $^{1}$H NMR

(400 MHz, $CDCl_3$)



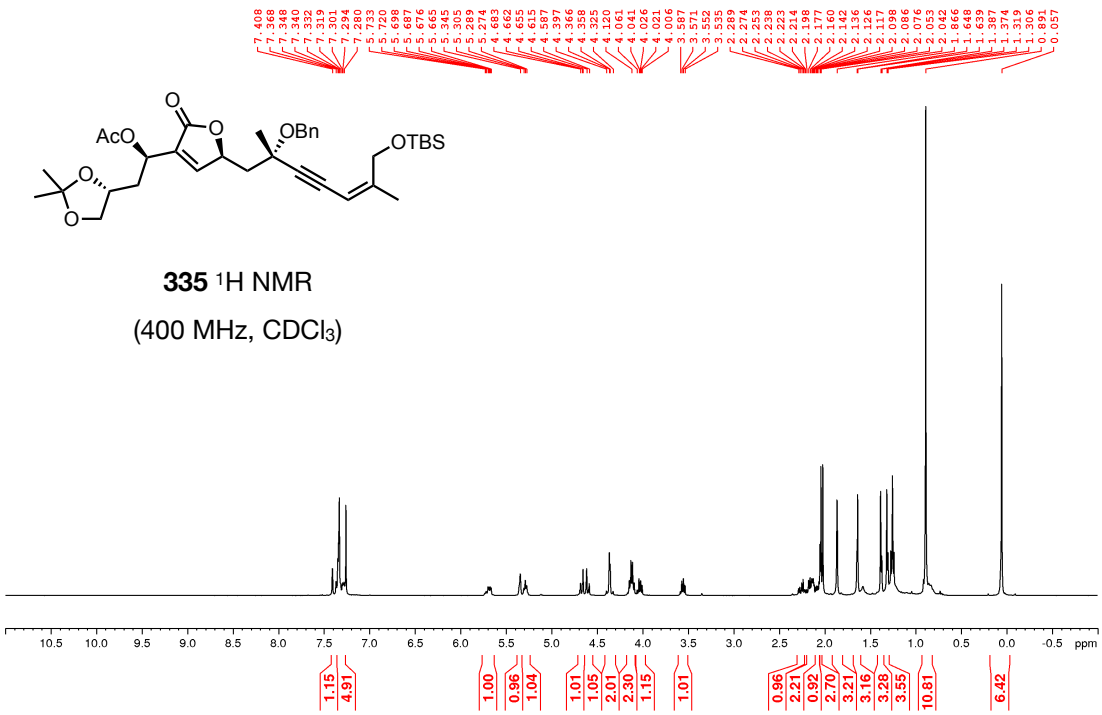
**333** $^{1}$H NMR

(400 MHz, $CDCl_3$)



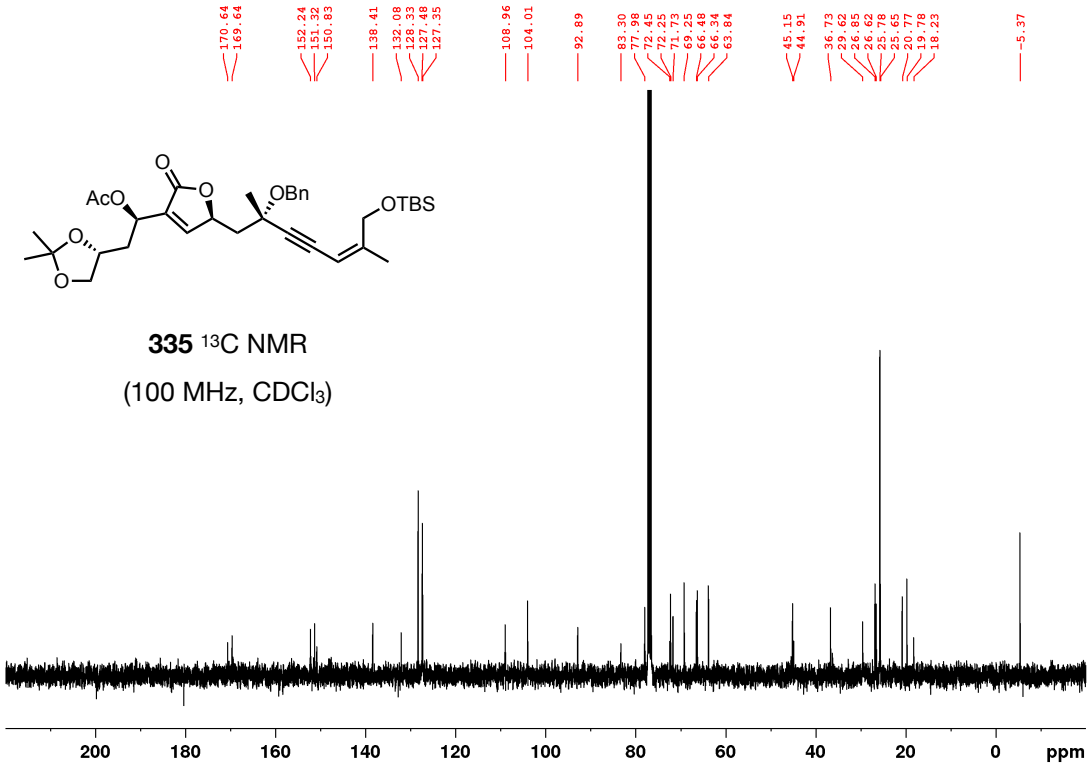

**334** $^1$H NMR

(400 MHz, $CDCl_3$)




**335** $^1$H NMR

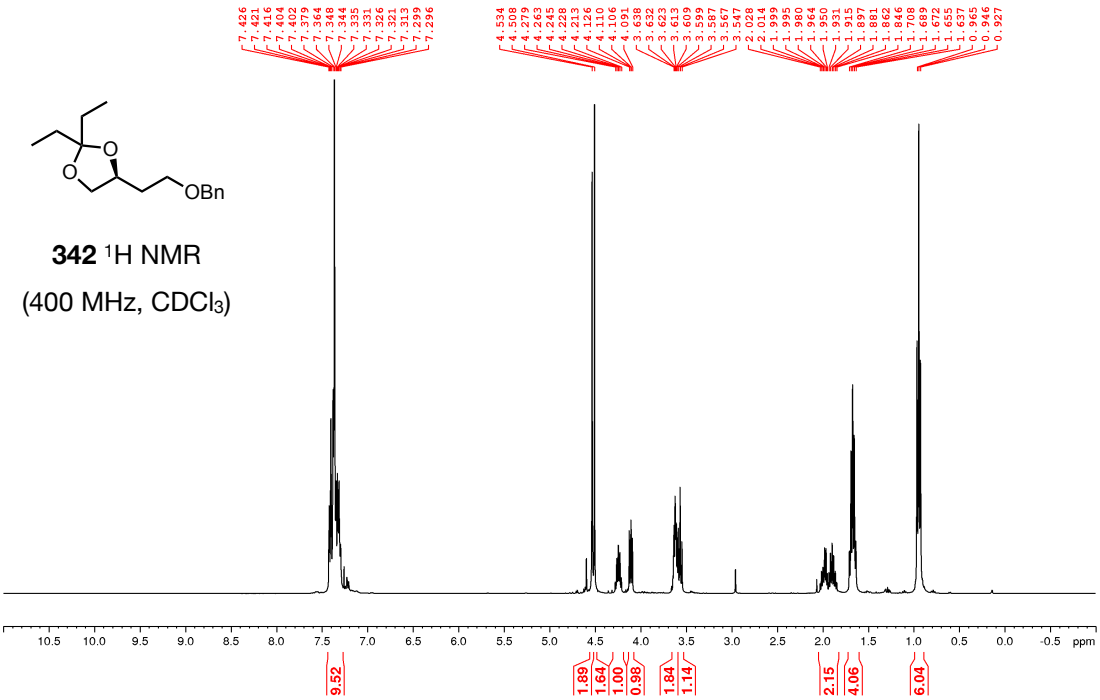
(400 MHz, $CDCl_3$)




**335** $^{13}$C NMR

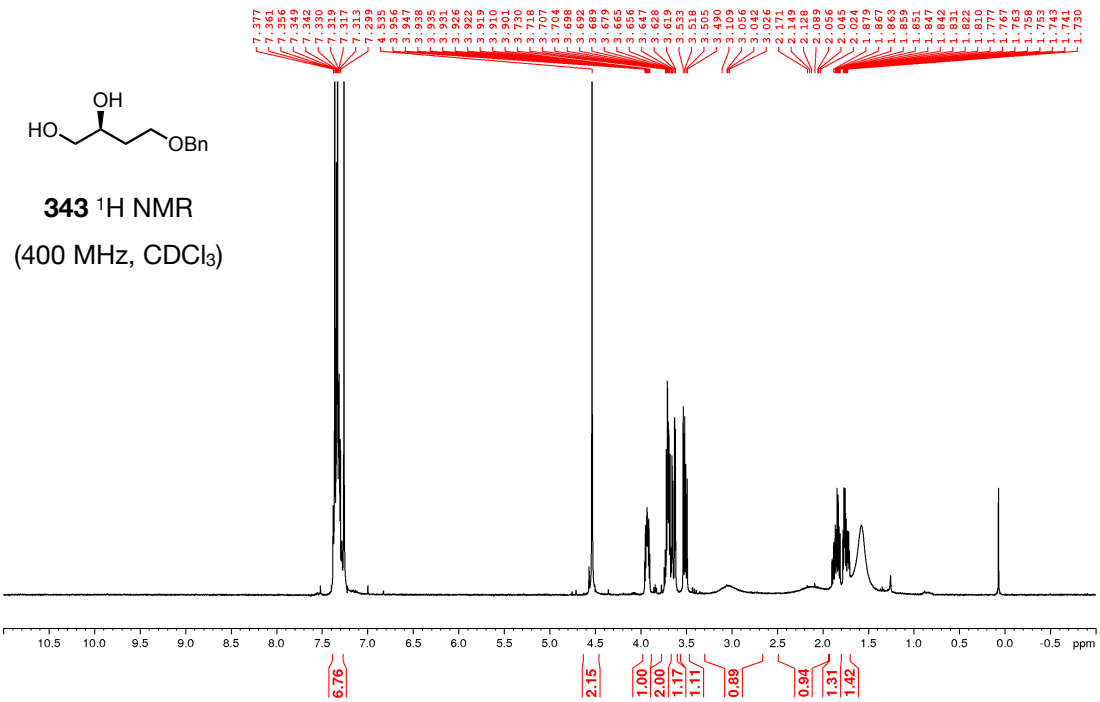
(100 MHz, $CDCl_3$)

**NMR Spectra: Section 3.2:**



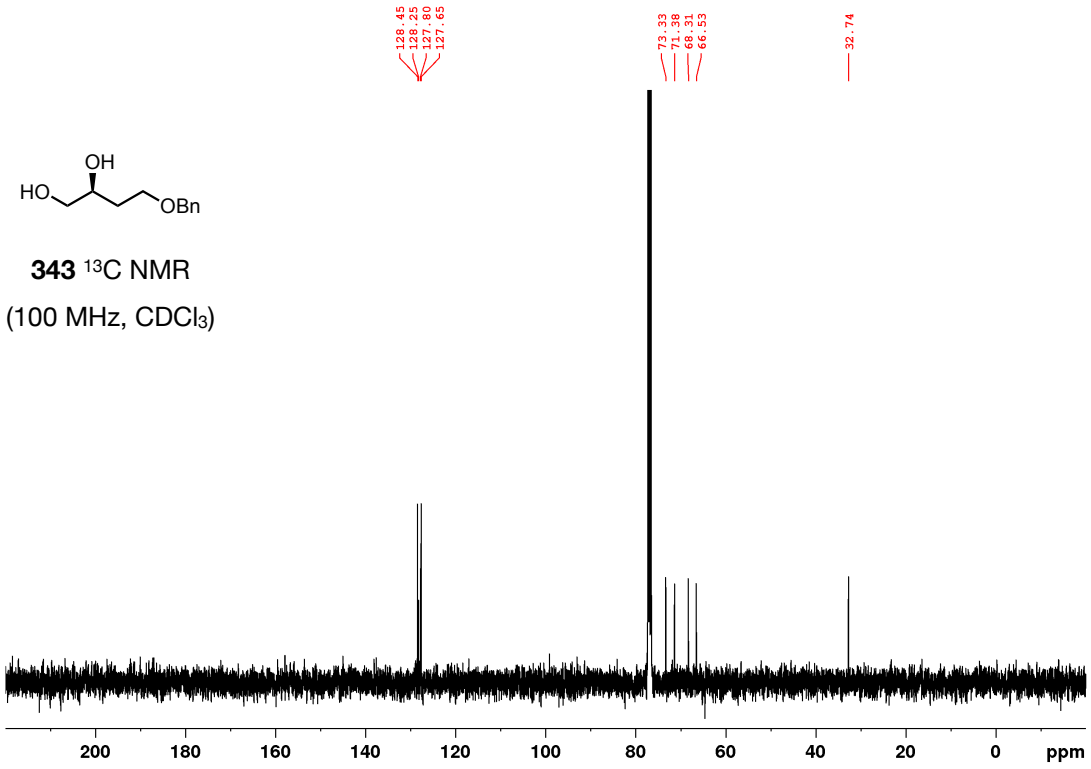
**342** $^{1}$H NMR

(400 MHz, $CDCl_3$)



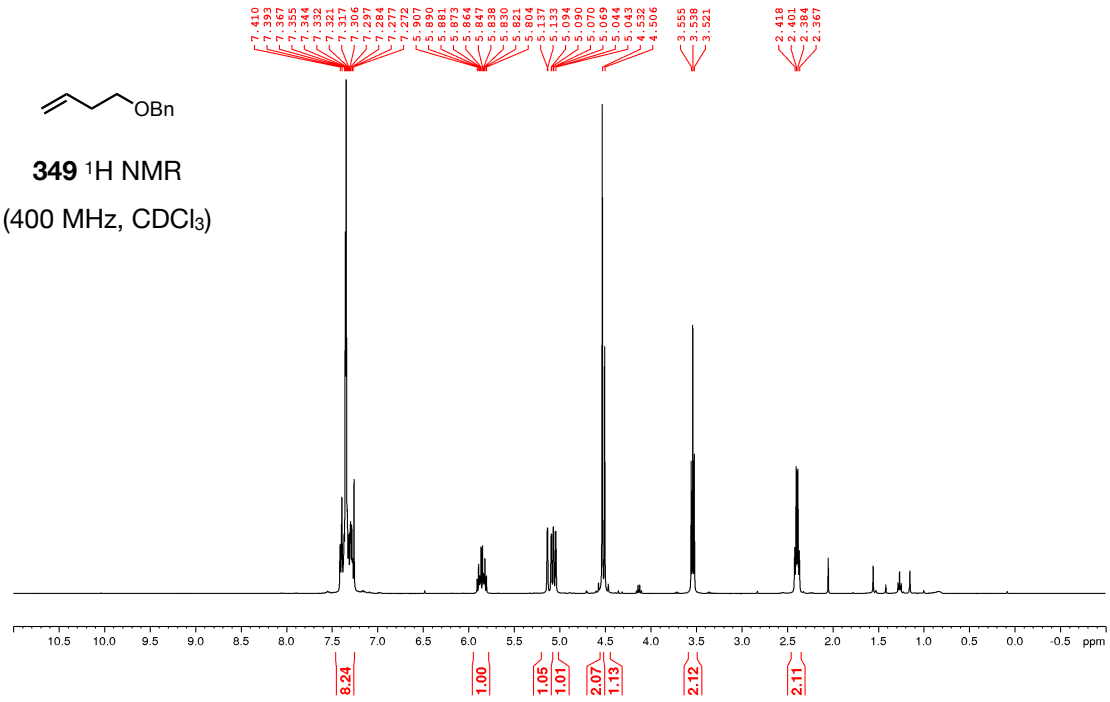
**343** $^{1}$H NMR

(400 MHz, $CDCl_3$)



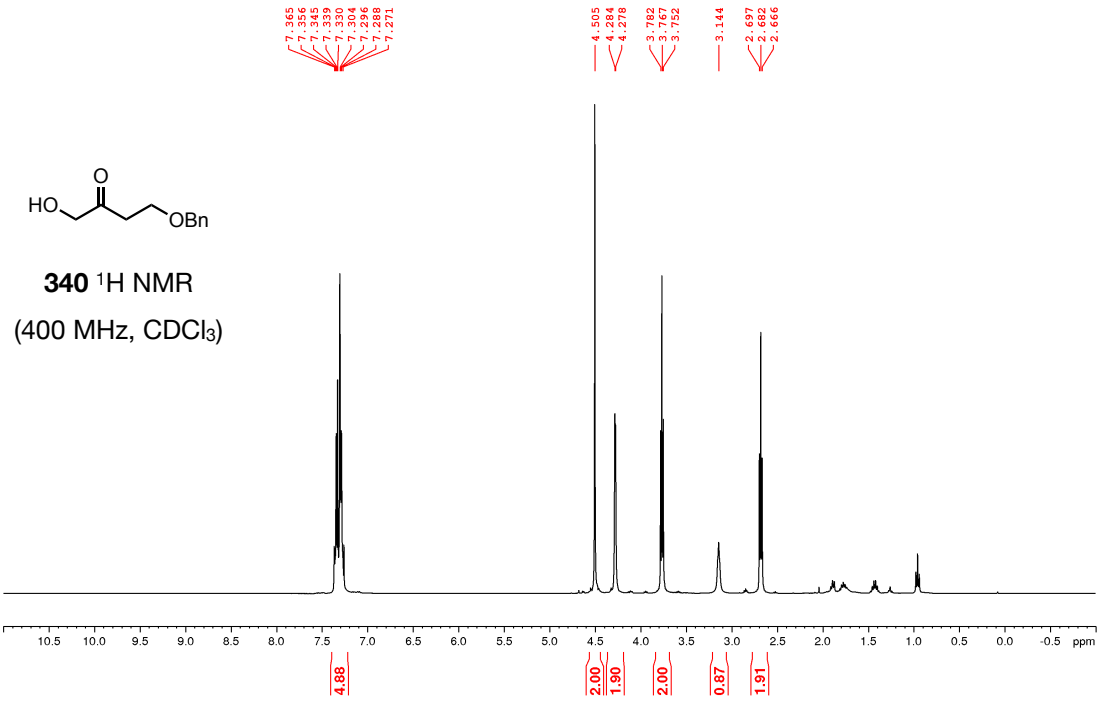

**343** $^{13}$C NMR

(100 MHz, $CDCl_3$)



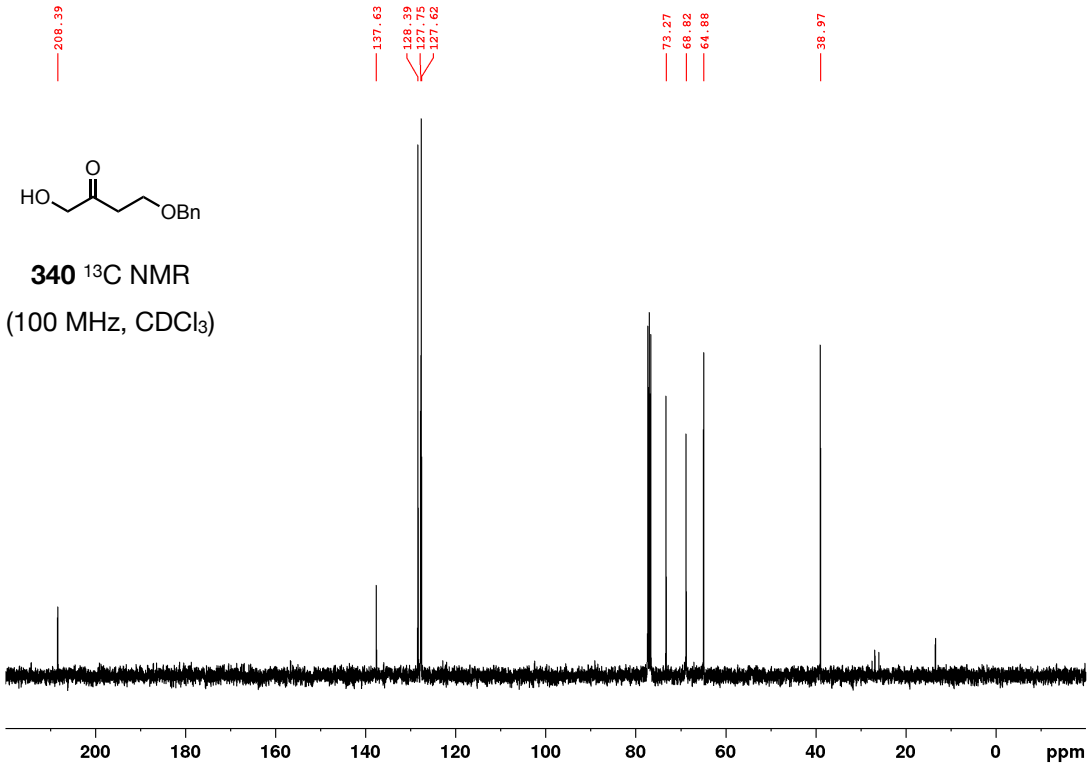

**349** $^{1}$H NMR

(400 MHz, $CDCl_3$)



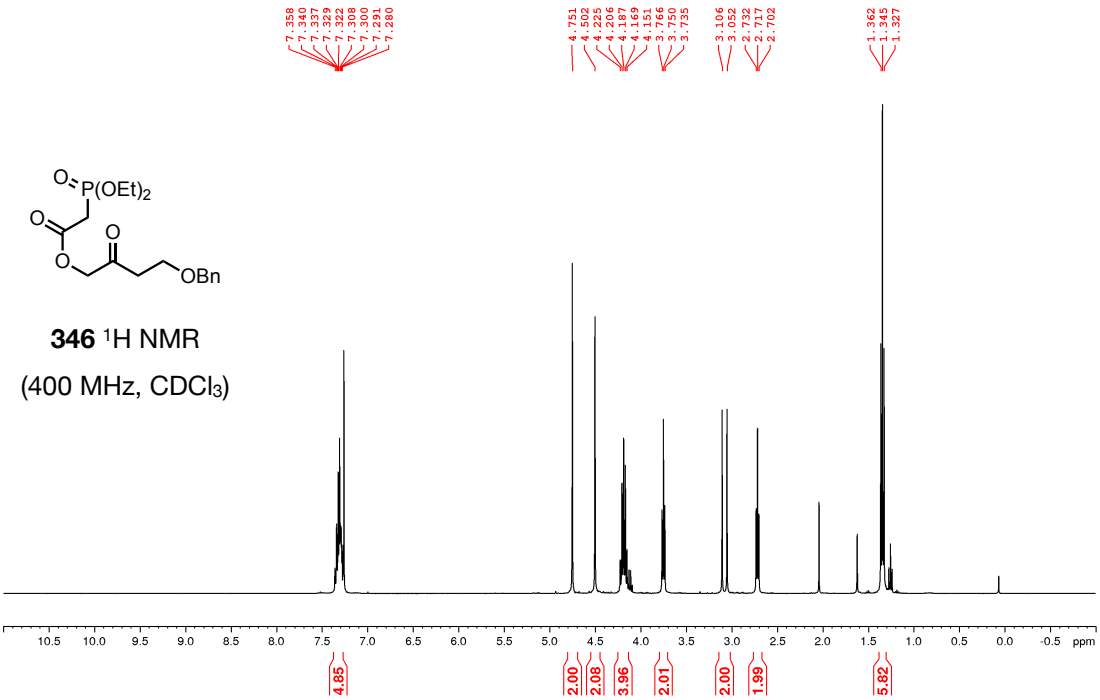

**340** $^{1}$H NMR

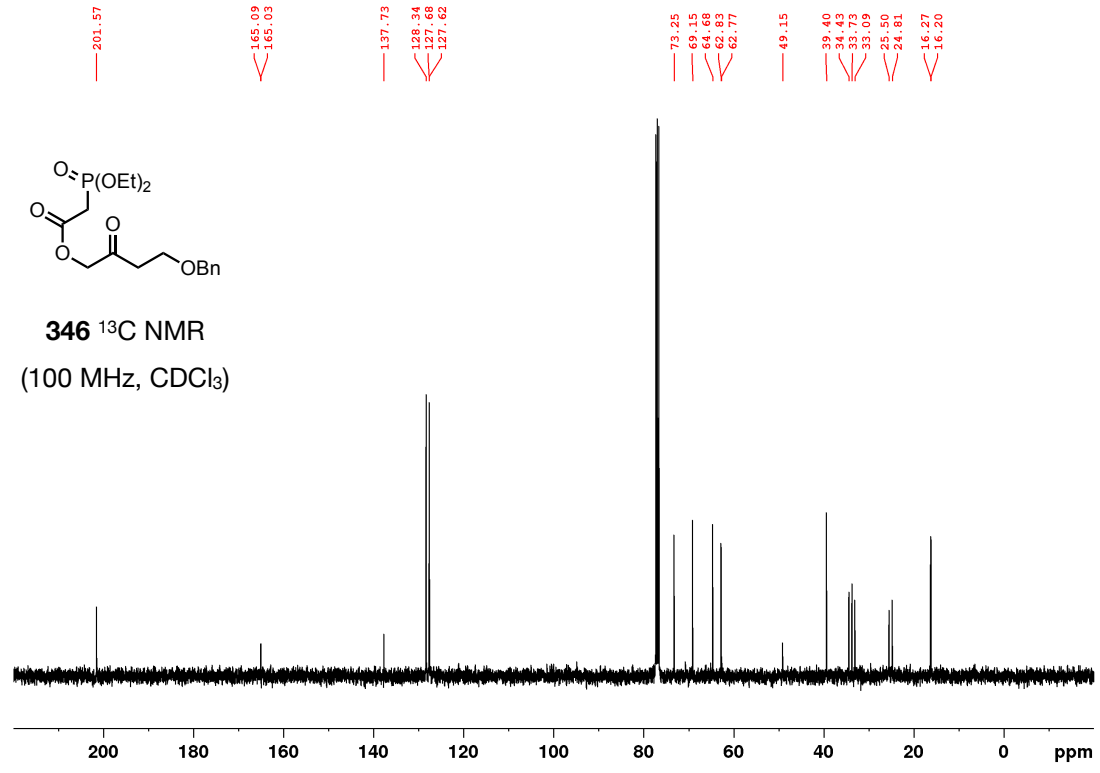
(400 MHz, $CDCl_3$)

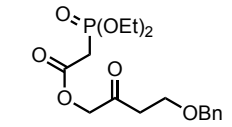



**340** $^{13}$C NMR

(100 MHz, $CDCl_3$)


7.358
7.340
7.337
7.329
7.322
7.308
7.300
7.291
7.280
4.751
4.502
4.225
4.206
4.187
4.169
4.151
3.766
3.750
3.735
3.106
3.052
2.732
2.717
2.702
1.362
1.345
1.327
O
P(OEt)2
O
O
O
OBn
346 1H NMR
(400 MHz, CDCl3)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm
4.85
2.00
2.08
3.96
2.01
2.00
1.99
5.82

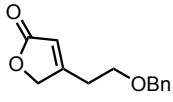

201.57
165.09
165.03
137.73
128.34
127.68
127.62
73.25
69.15
64.68
62.83
62.77
49.15
39.40
34.43
33.73
33.09
25.50
24.81
16.27
16.20
O
P(OEt)2
O
O
O
OBn
346 13C NMR
(100 MHz, CDCl3)
200 180 160 140 120 100 80 60 40 20 0 ppm




**346** $^{31}$P NMR

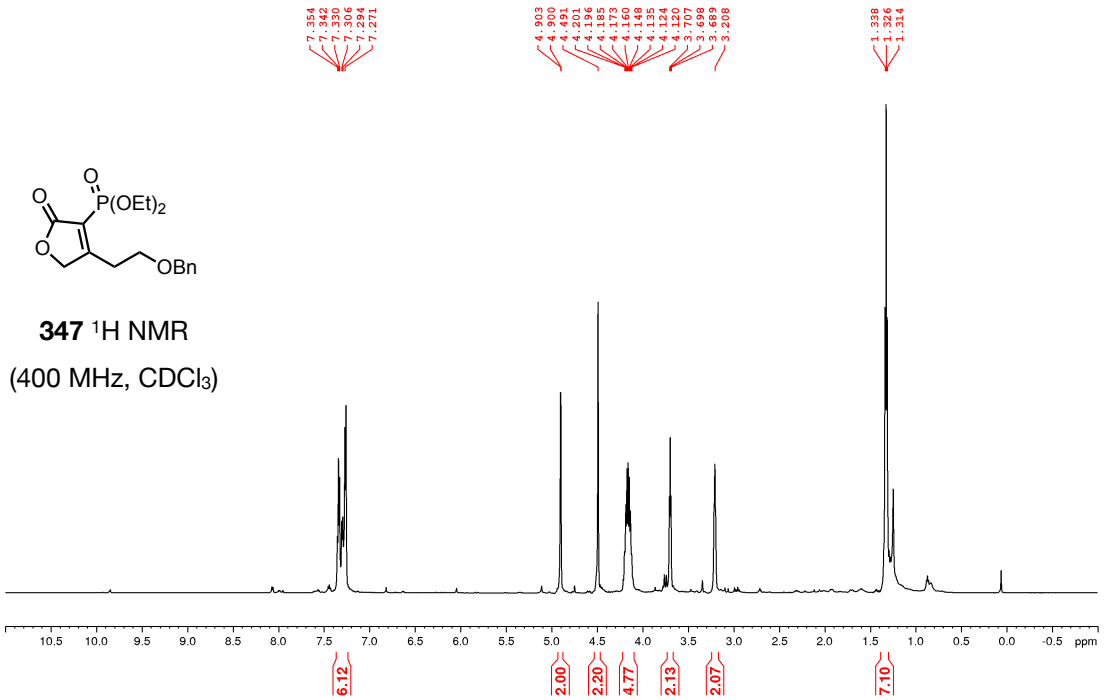
(160 MHz, $CDCl_3$)

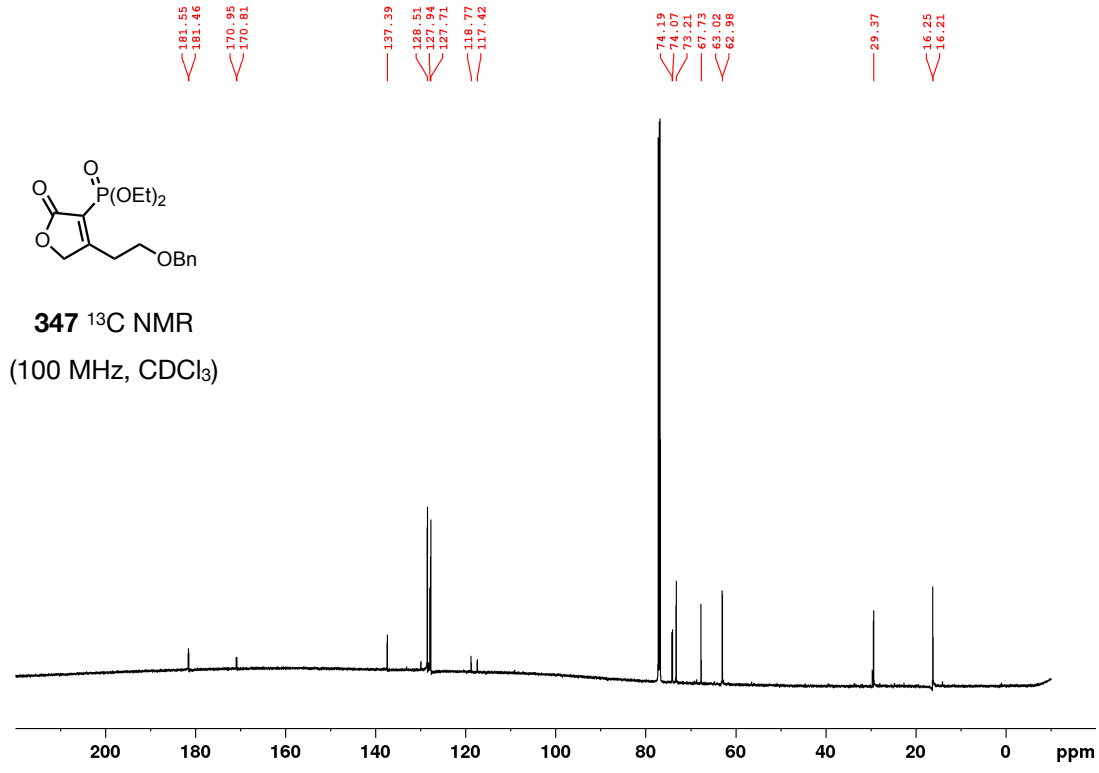


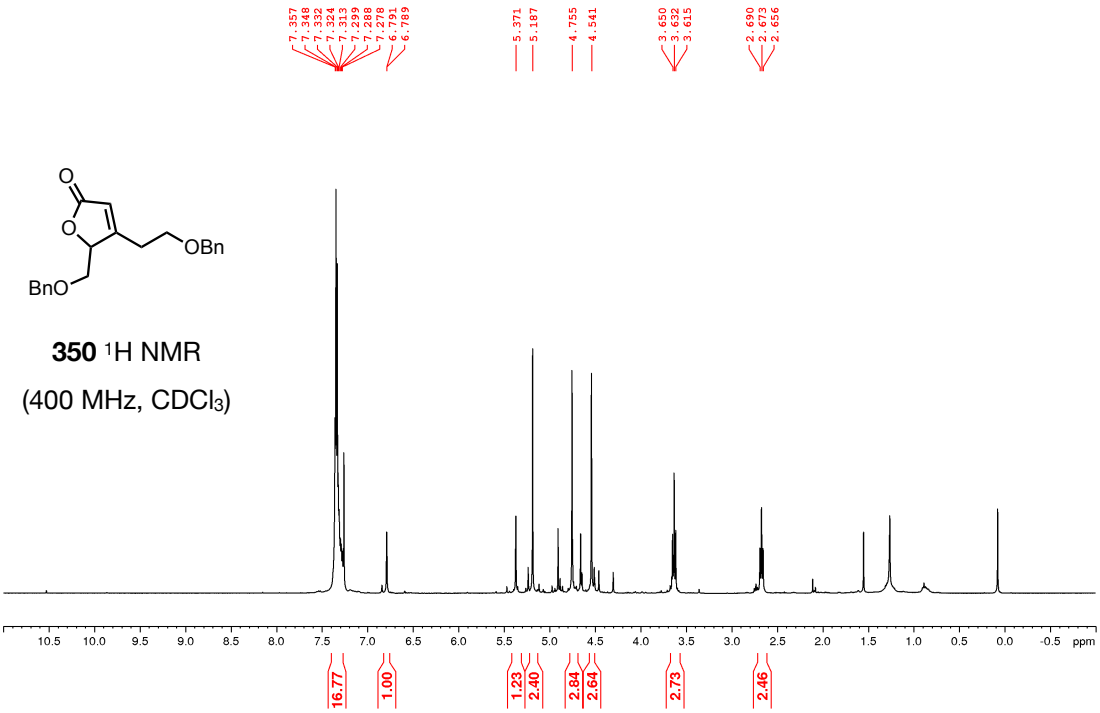




**339** $^{1}$H NMR

(400 MHz, $CDCl_3$)

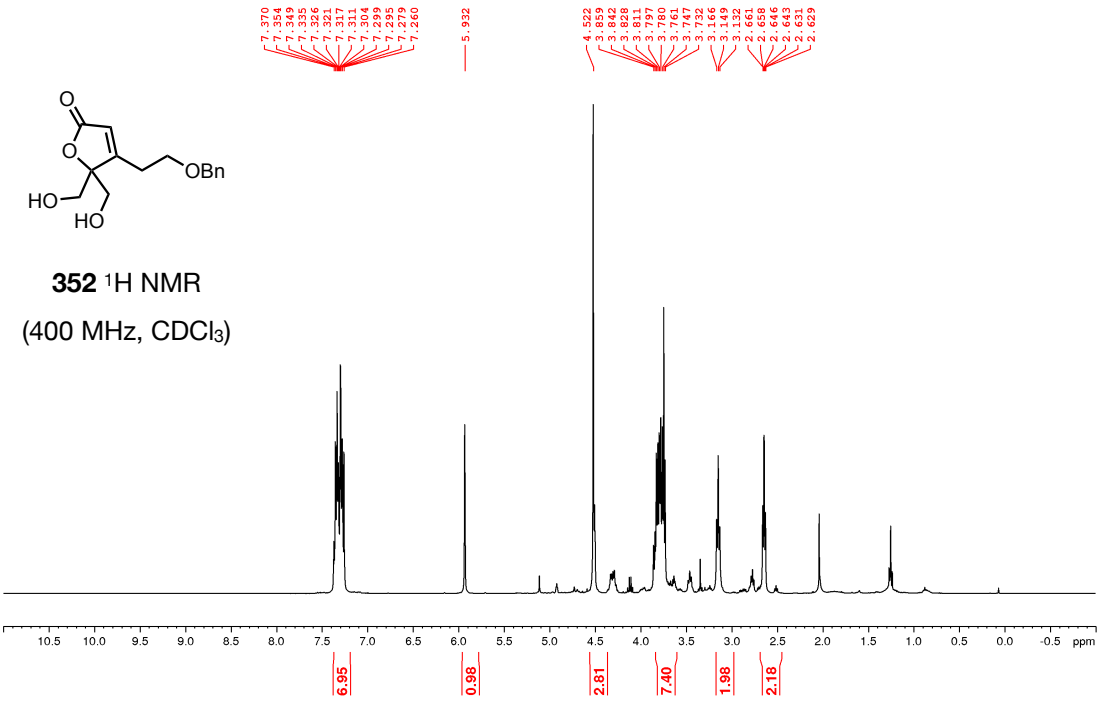

7.354
7.342
7.330
7.306
7.294
7.271
4.903
4.900
4.491
4.201
4.196
4.185
4.173
4.160
4.148
4.135
4.124
4.120
3.707
3.698
3.689
3.208
1.338
1.326
1.314
O
O
P(OEt)2
O
OBn
347 1H NMR
(400 MHz, CDCl3)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm
6.12
2.00
2.20
4.77
2.13
2.07
7.10


181.55
181.46
170.95
170.81
137.39
128.51
127.94
127.71
118.77
117.42
74.19
74.07
73.21
67.73
63.02
62.98
29.37
16.25
16.21
O
O
P(OEt)2
O
OBn
347 13C NMR
(100 MHz, CDCl3)
200 180 160 140 120 100 80 60 40 20 0 ppm



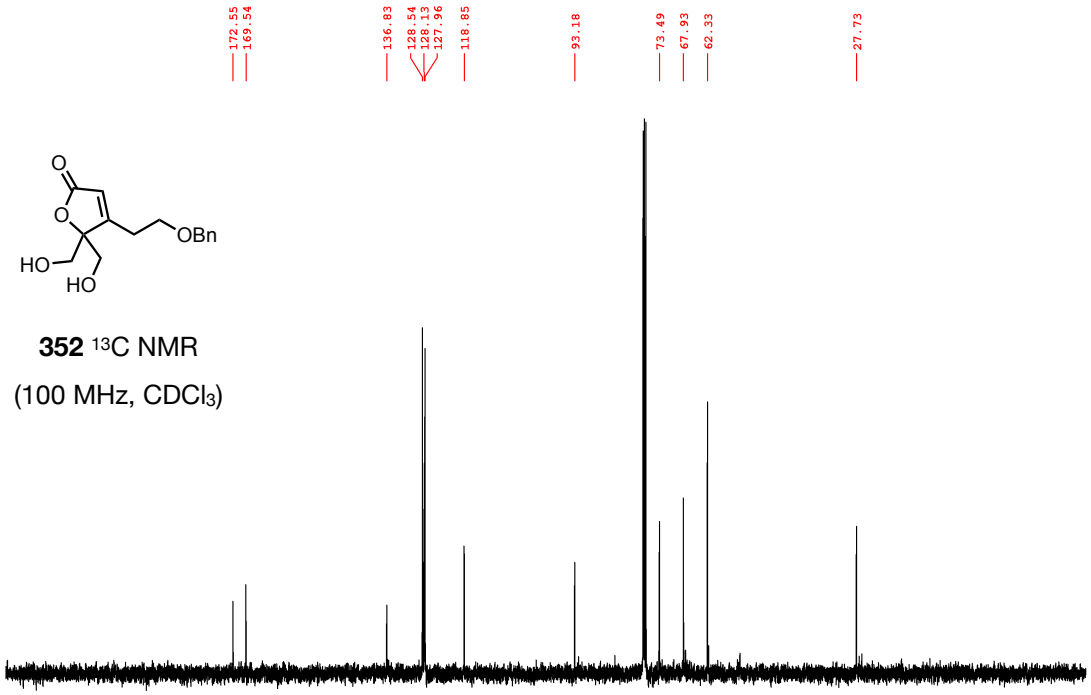

**350** $^1$H NMR

(400 MHz, $CDCl_3$)



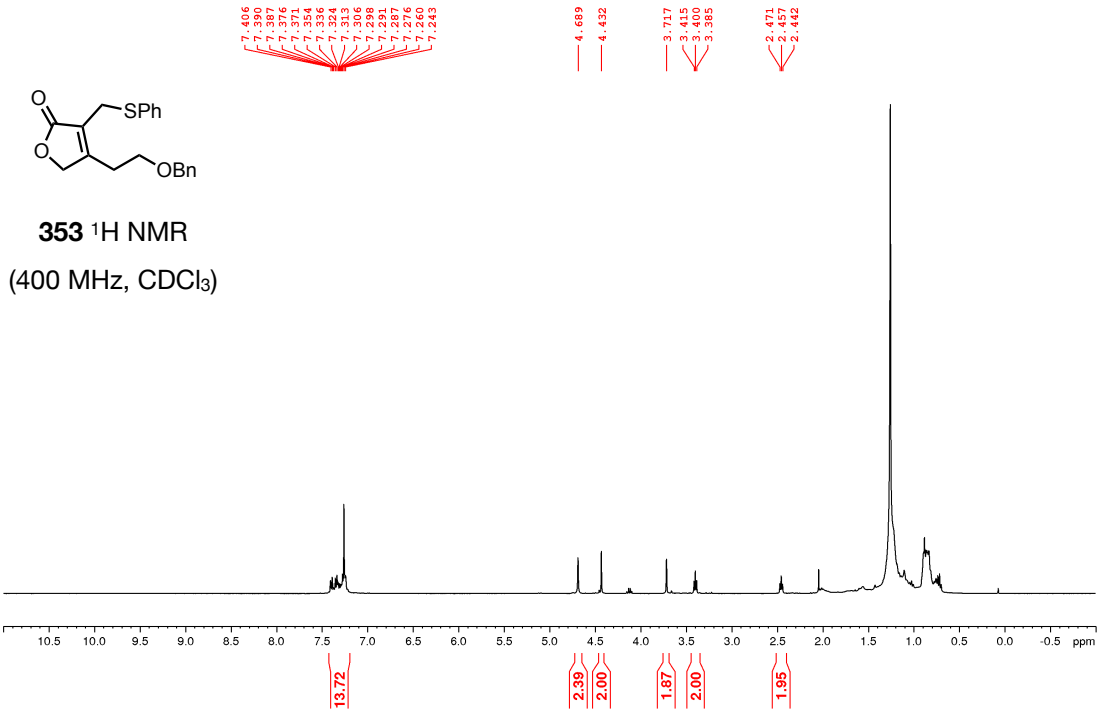

**352** $^1$H NMR

(400 MHz, $CDCl_3$)




**352** $^{13}$C NMR

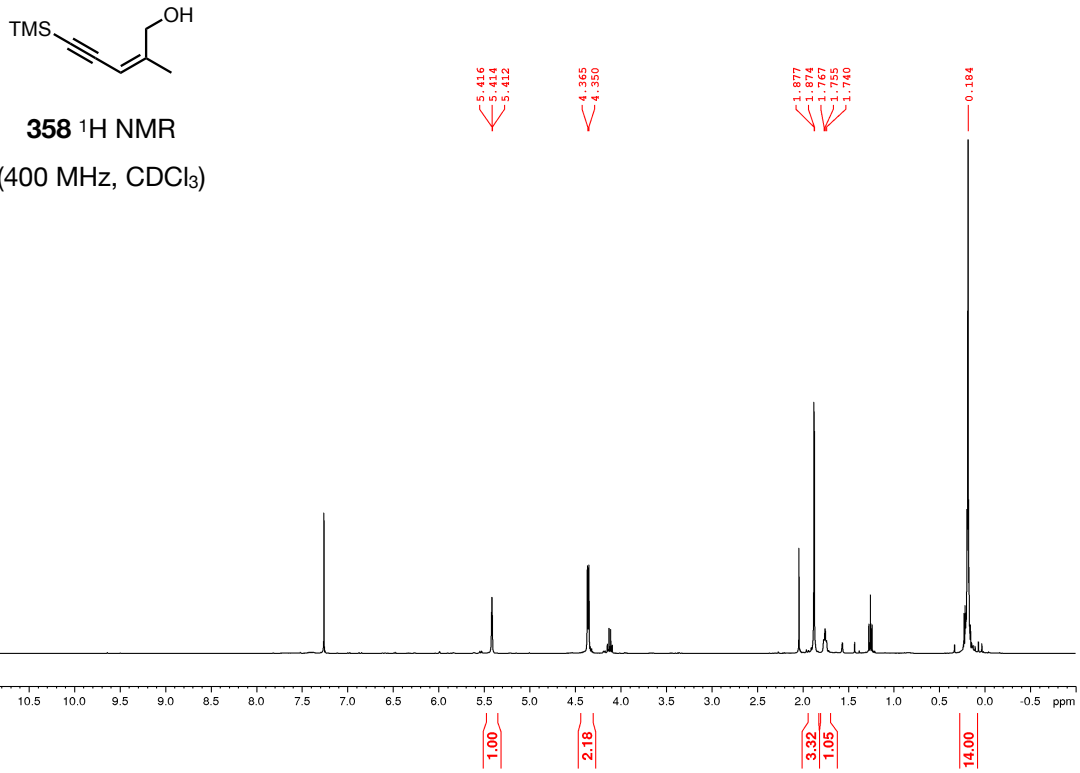
(100 MHz, $CDCl_3$)




**353** $^{1}$H NMR

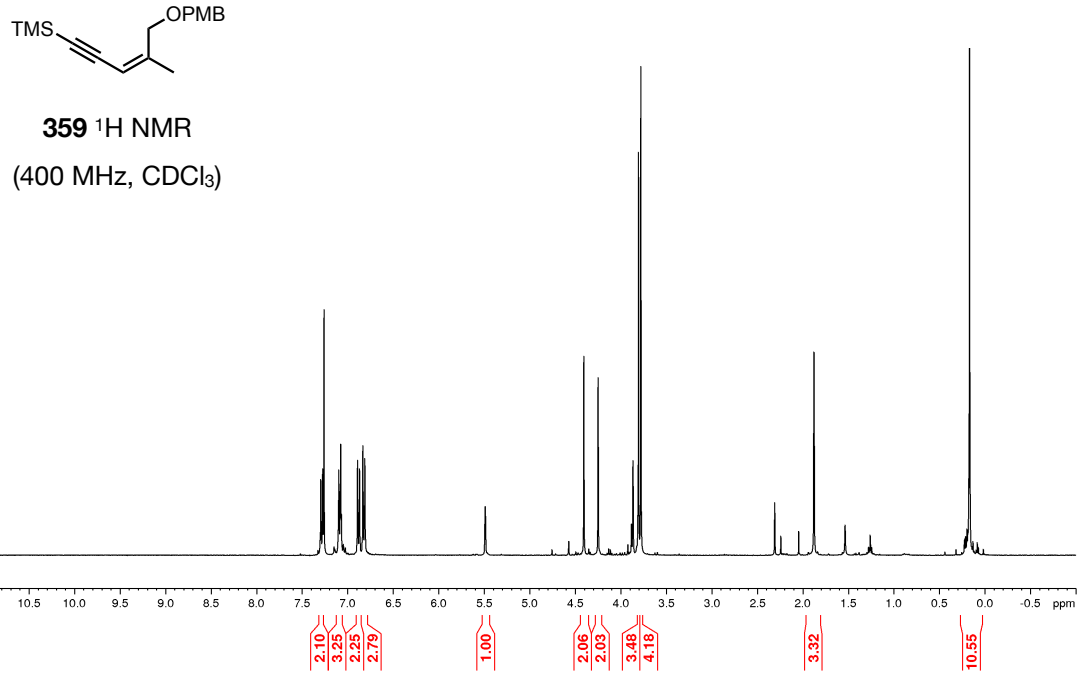
(400 MHz, $CDCl_3$)

**NMR Spectra: Section 3.3:**



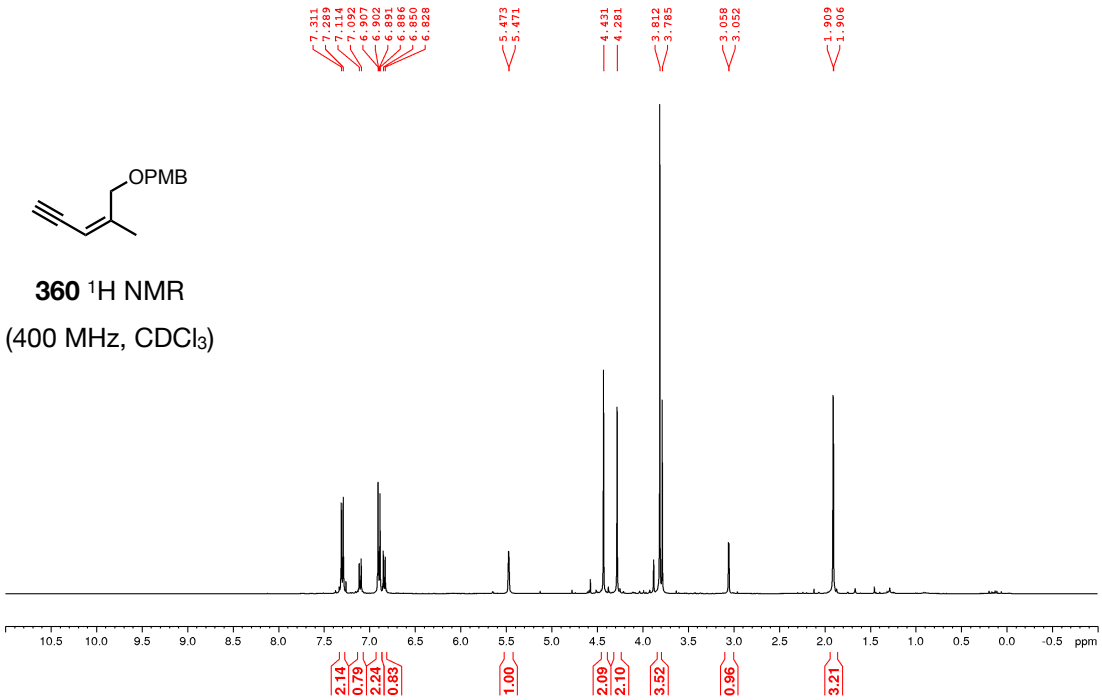

**358** $^{1}$H NMR

(400 MHz, $CDCl_3$)



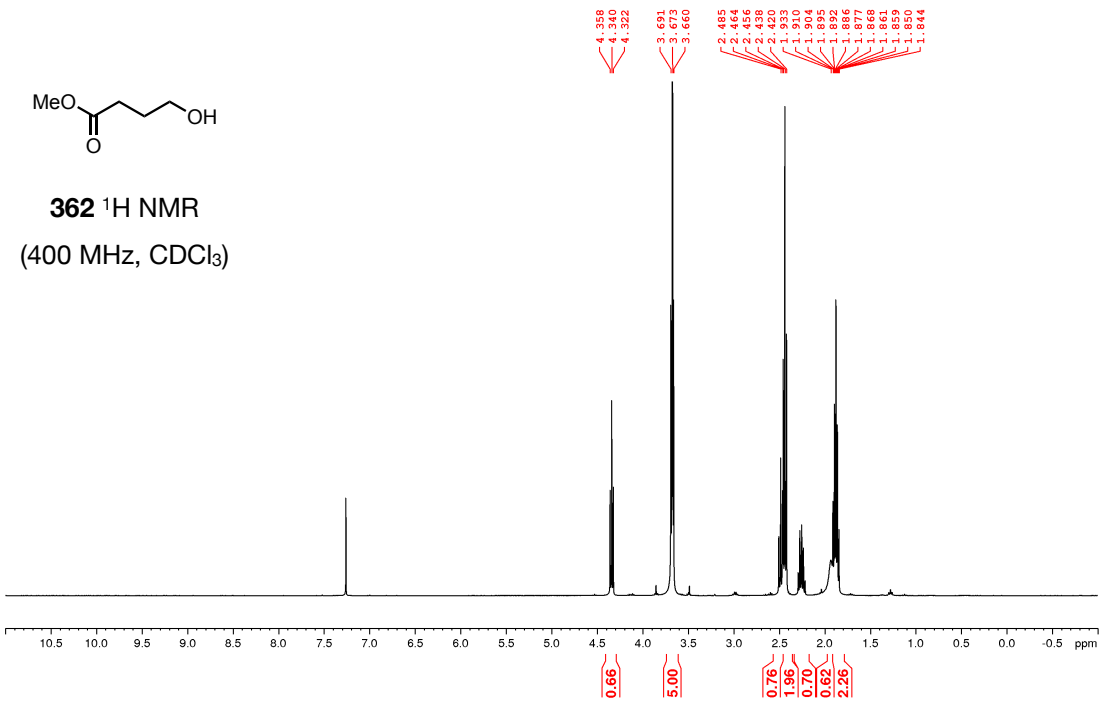

**359** $^{1}$H NMR

(400 MHz, $CDCl_3$)



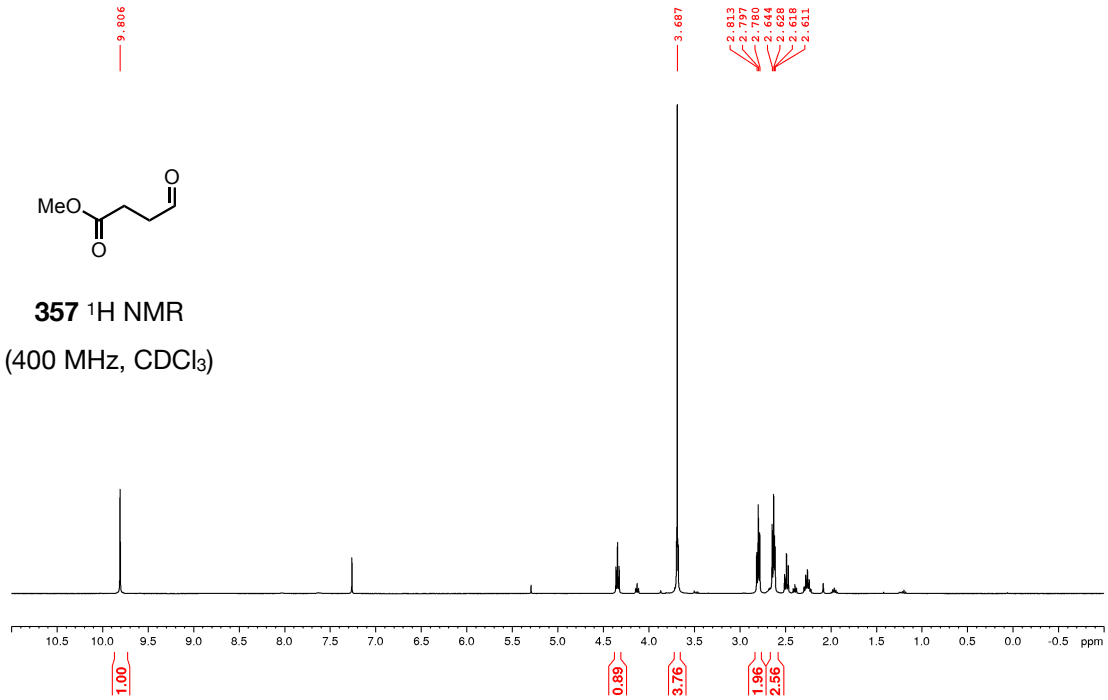

**360** $^{1}$H NMR

(400 MHz, $CDCl_3$)



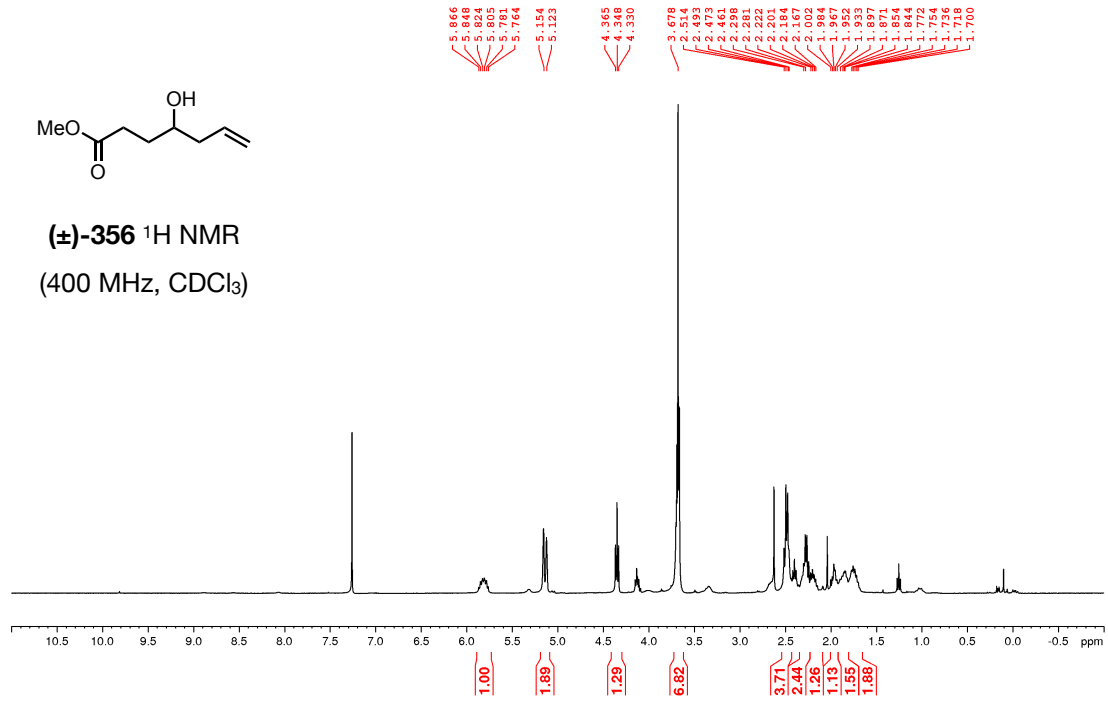

**362** $^{1}$H NMR

(400 MHz, $CDCl_3$)



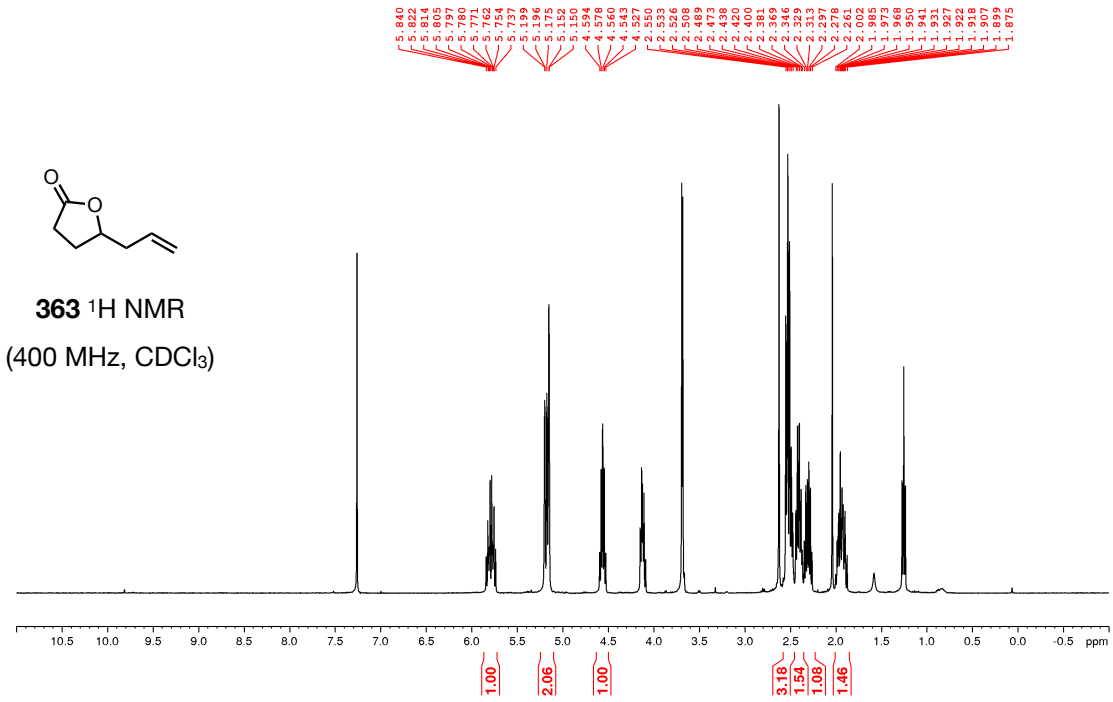

**357** $^1$H NMR

(400 MHz, $CDCl_3$)



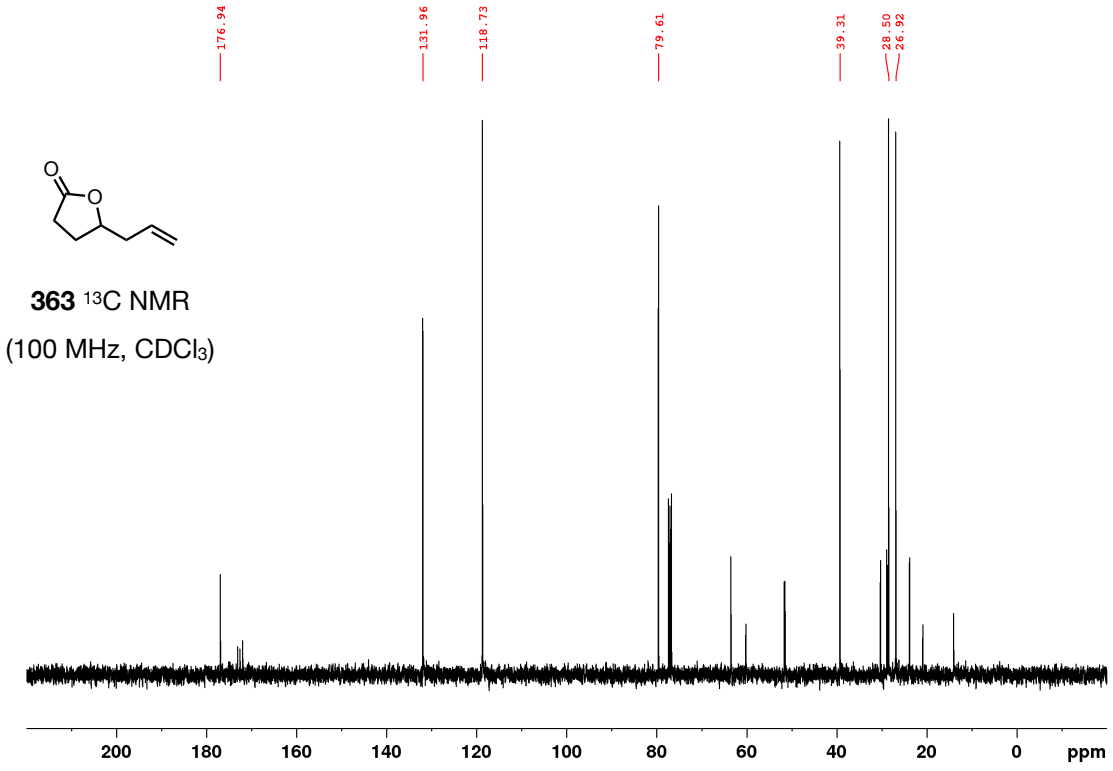

**(±)-356** $^1$H NMR

(400 MHz, $CDCl_3$)



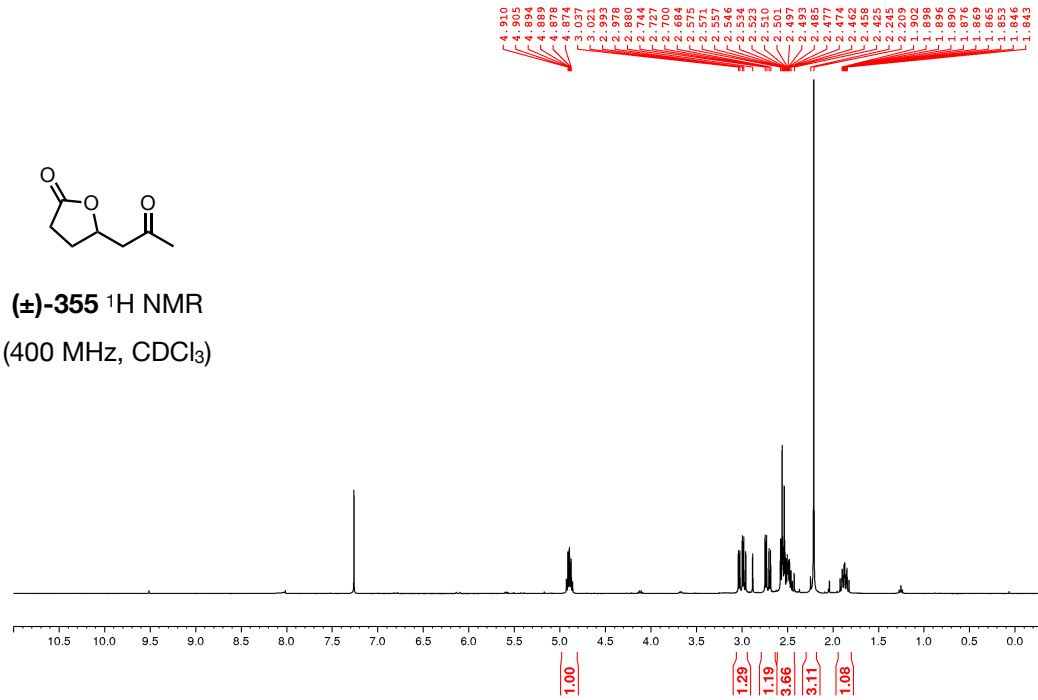

**363** $^{1}$H NMR

(400 MHz, $CDCl_3$)



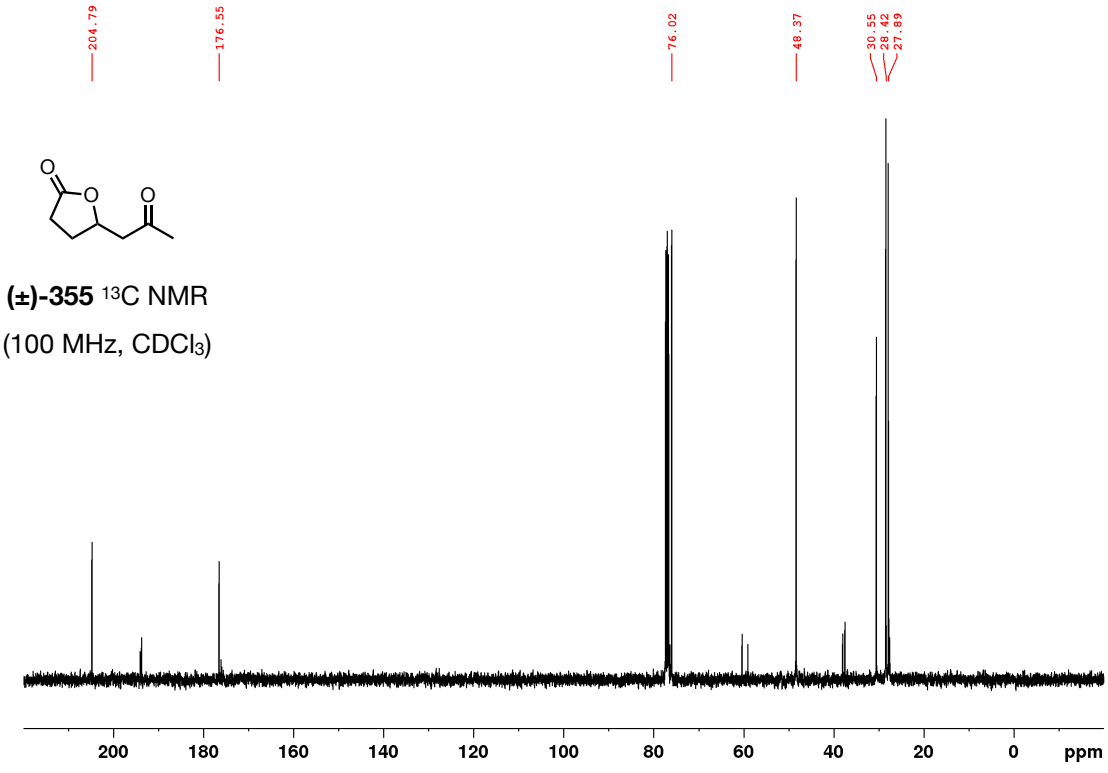

**363** $^{13}$C NMR

(100 MHz, $CDCl_3$)



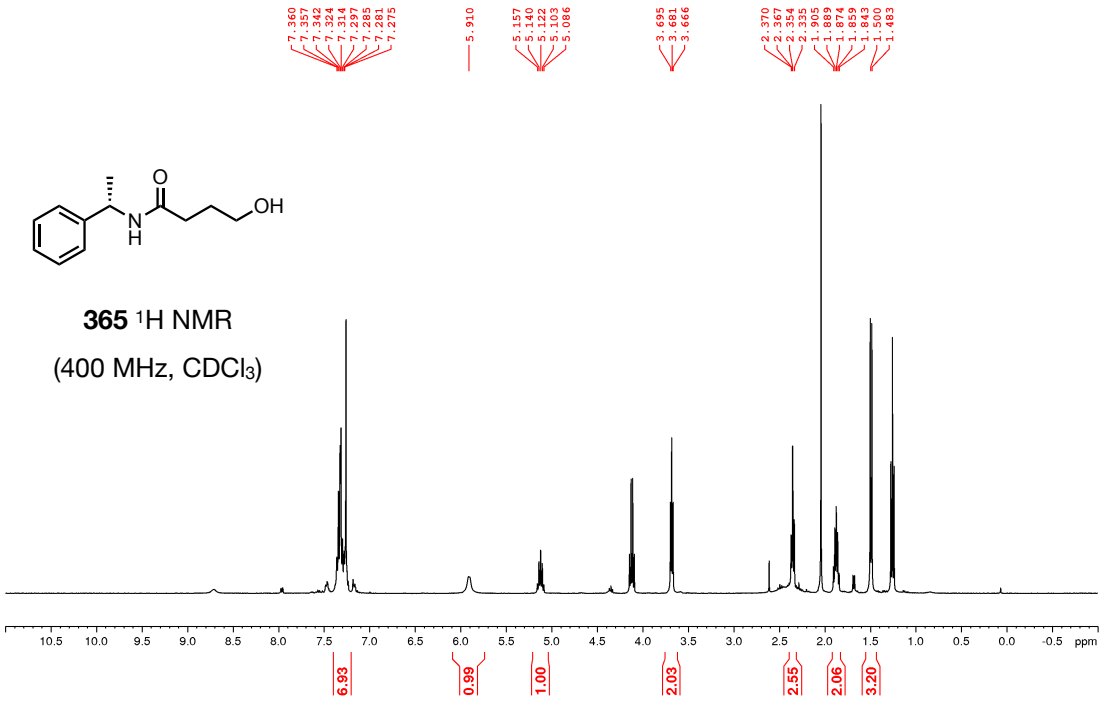
**(±)-355** $^{1}$H NMR

(400 MHz, $CDCl_3$)



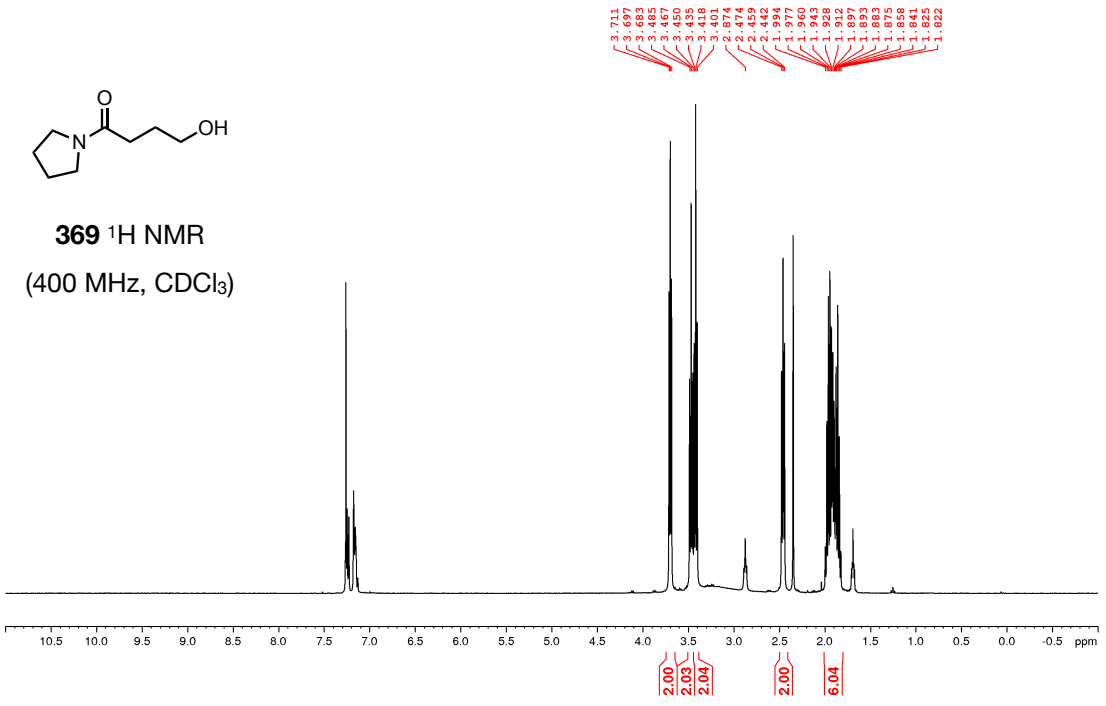
**(±)-355** $^{13}$C NMR

(100 MHz, $CDCl_3$)



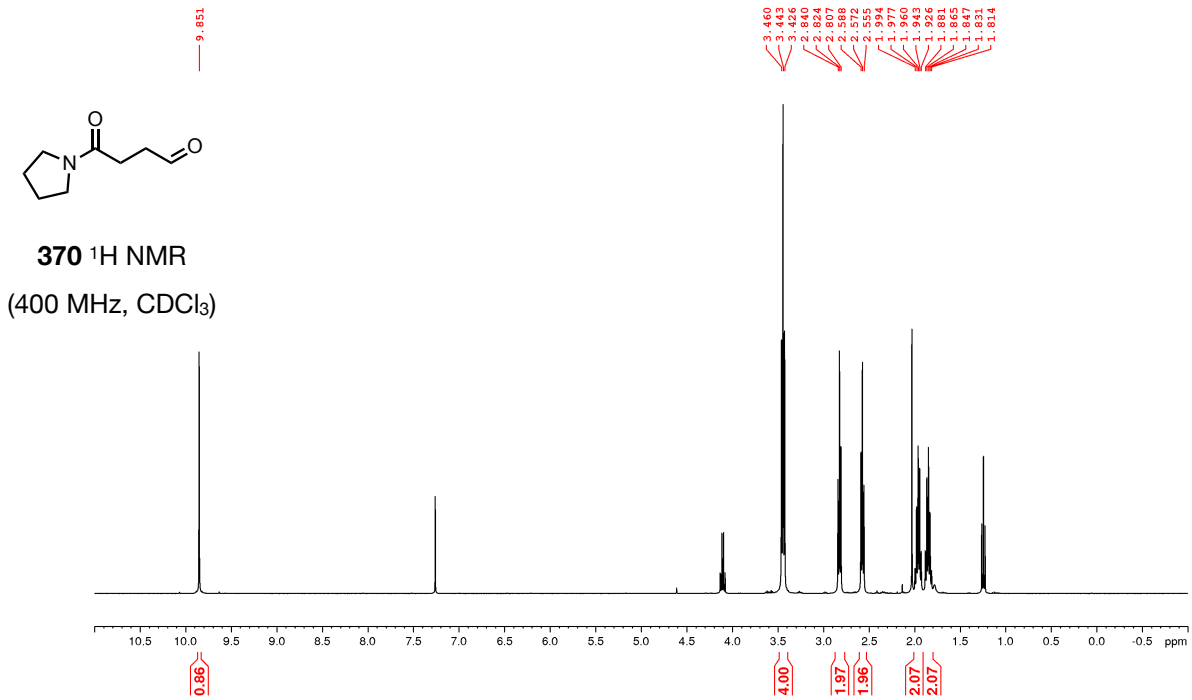

**365** $^{1}$H NMR

(400 MHz, $CDCl_3$)



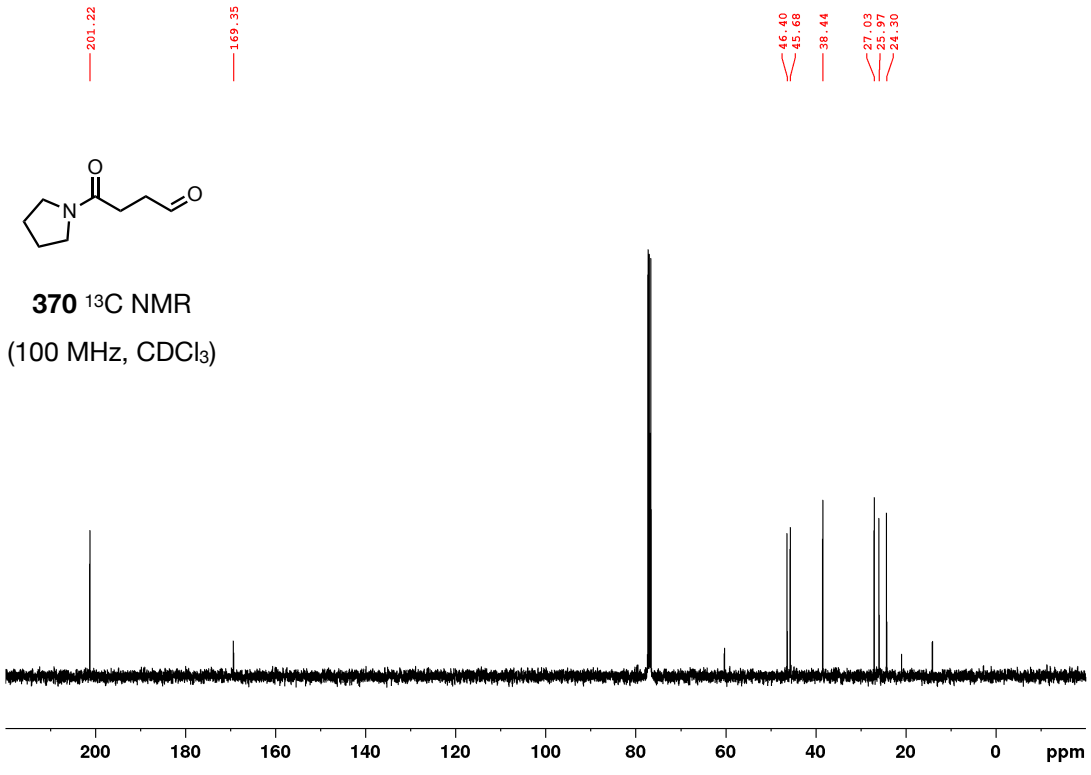

**369** $^{1}$H NMR

(400 MHz, $CDCl_3$)



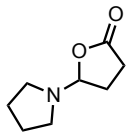

**370** $^{1}$H NMR

(400 MHz, $CDCl_3$)



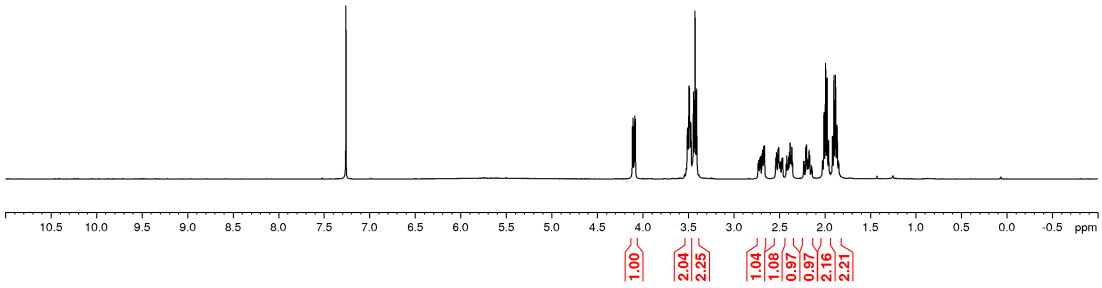

**370** $^{13}$C NMR

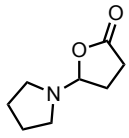
(100 MHz, $CDCl_3$)



**371** $^{1}$H NMR

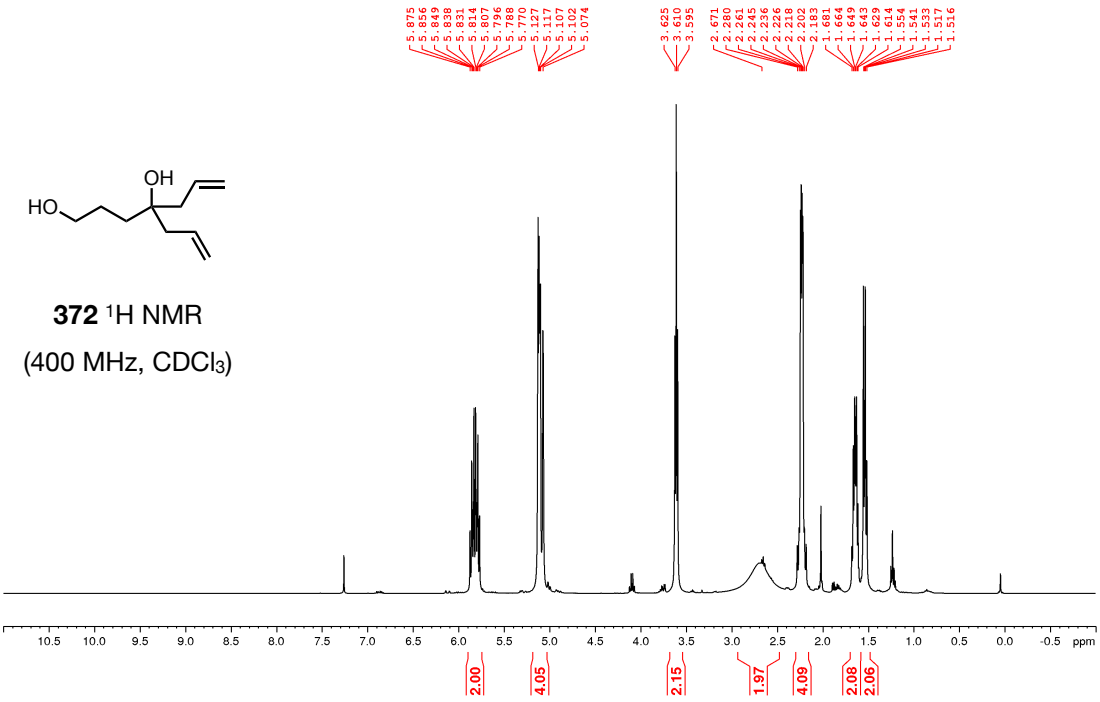
(400 MHz, $CDCl_3$)





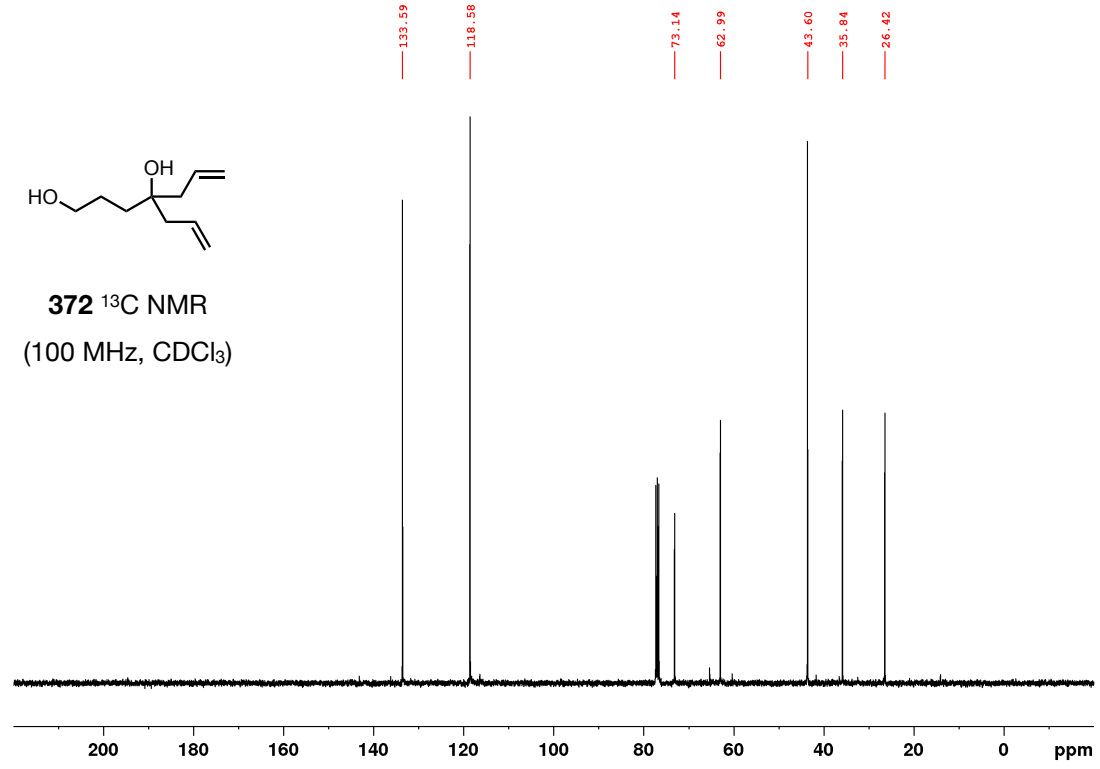
**371** $^{13}$C NMR

(100 MHz, $CDCl_3$)




**372** $^{1}$H NMR

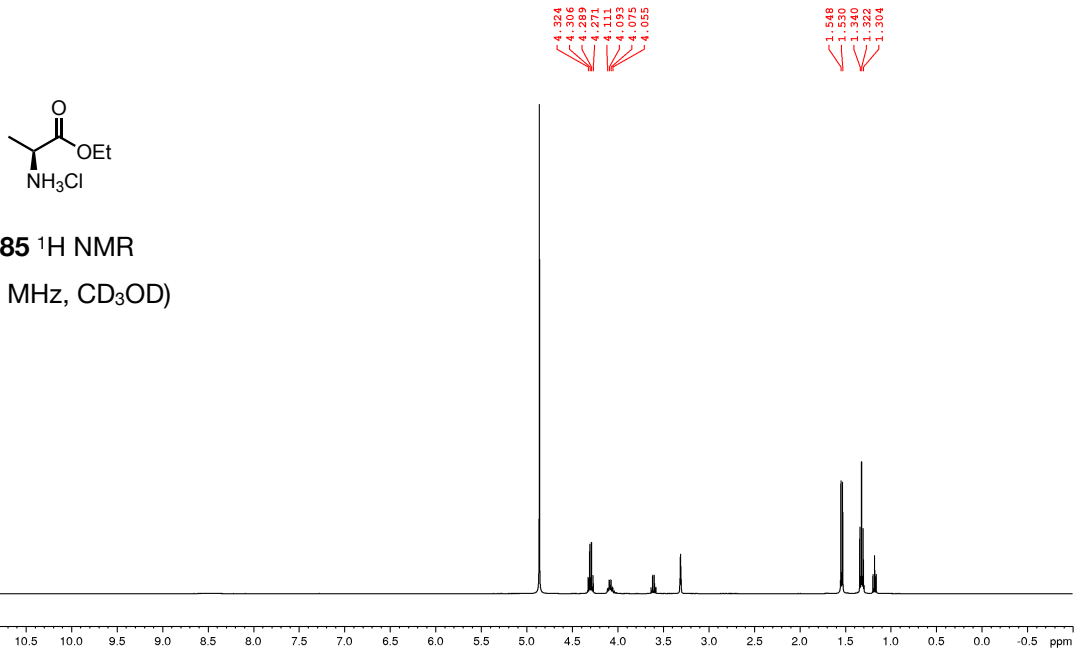
(400 MHz, $CDCl_3$)




**372** $^{13}$C NMR

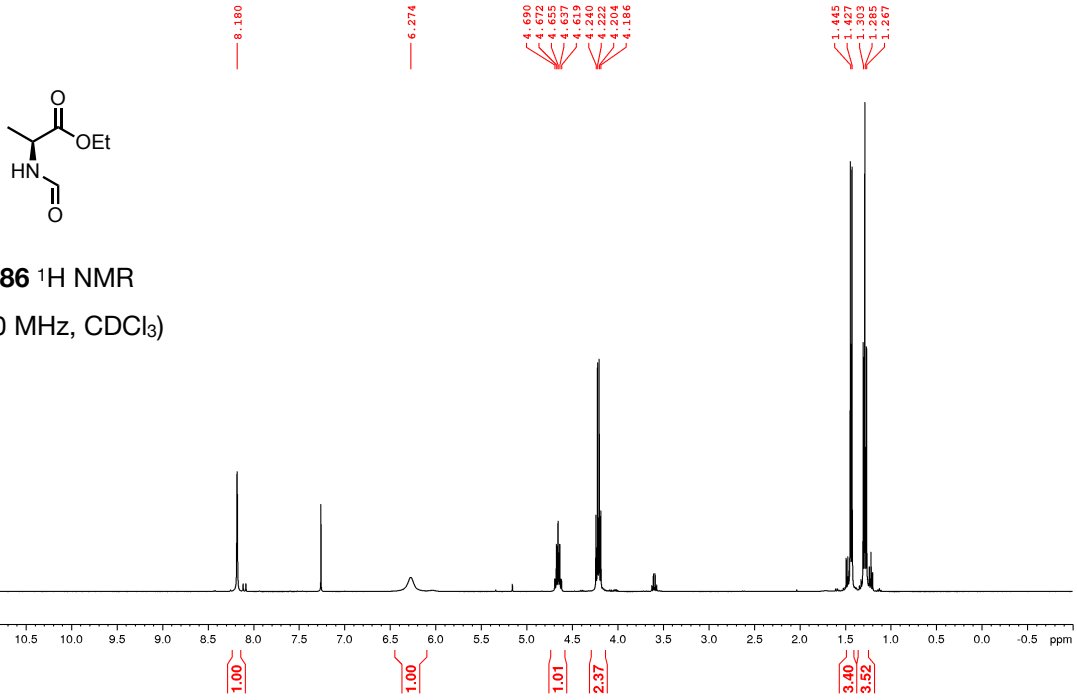
(100 MHz, $CDCl_3$)

**NMR Spectra: Section 3.4:**



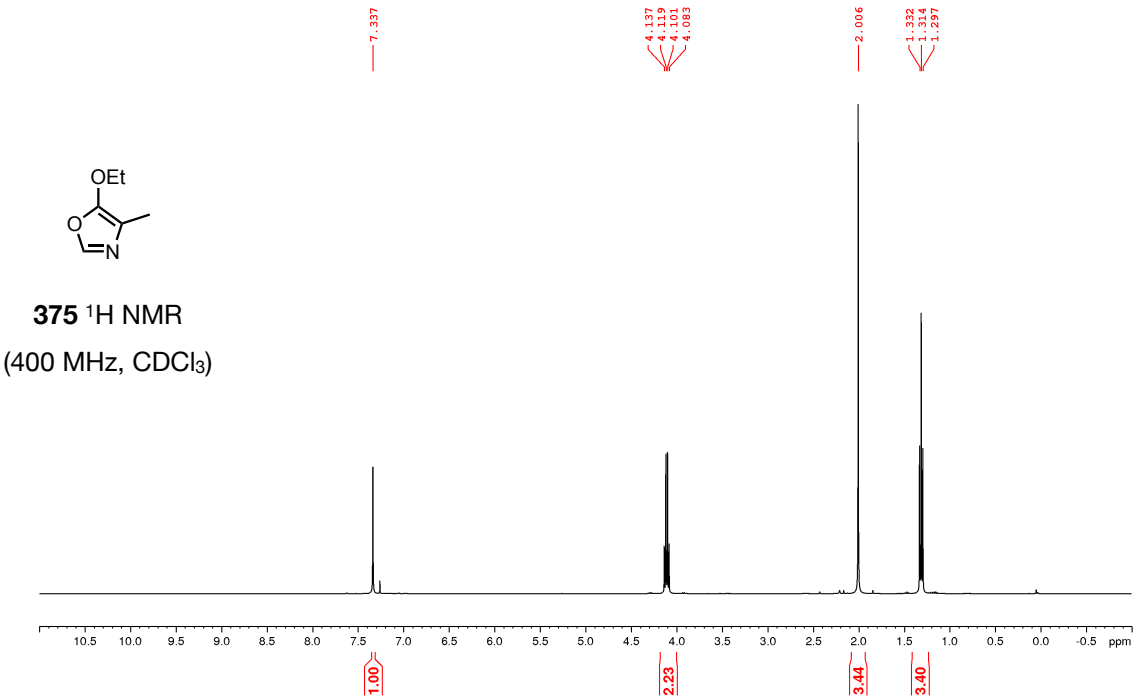

**385** $^{1}$H NMR

(400 MHz, $CD_3OD$)



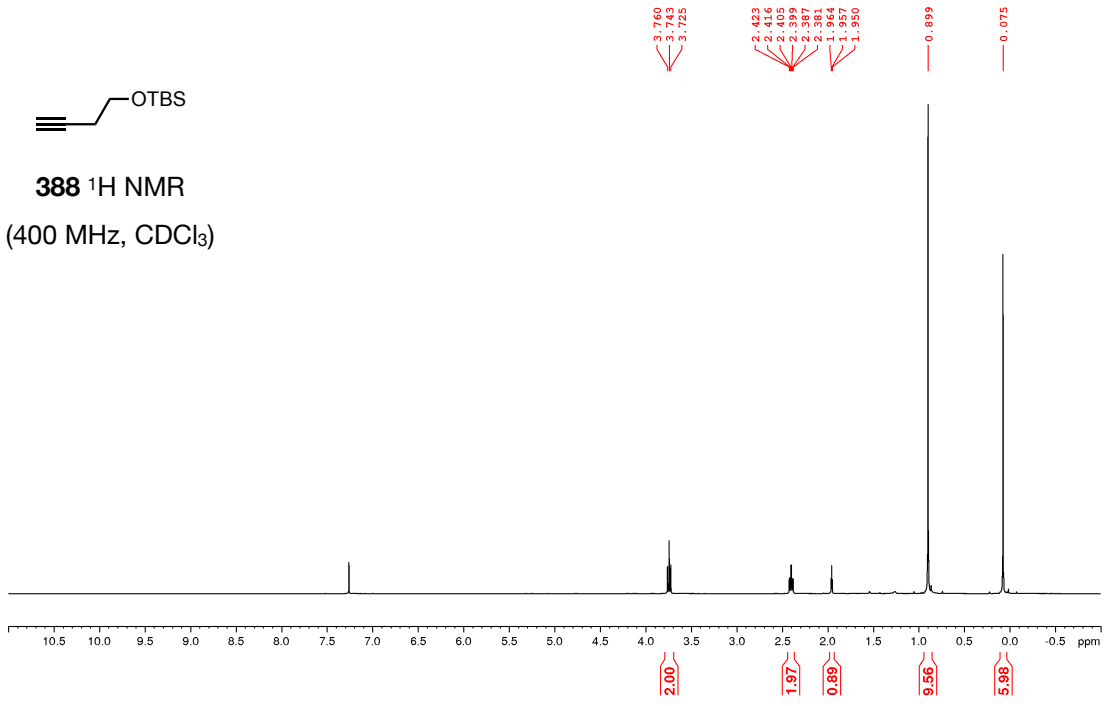

**386** $^{1}$H NMR

(400 MHz, $CDCl_3$)



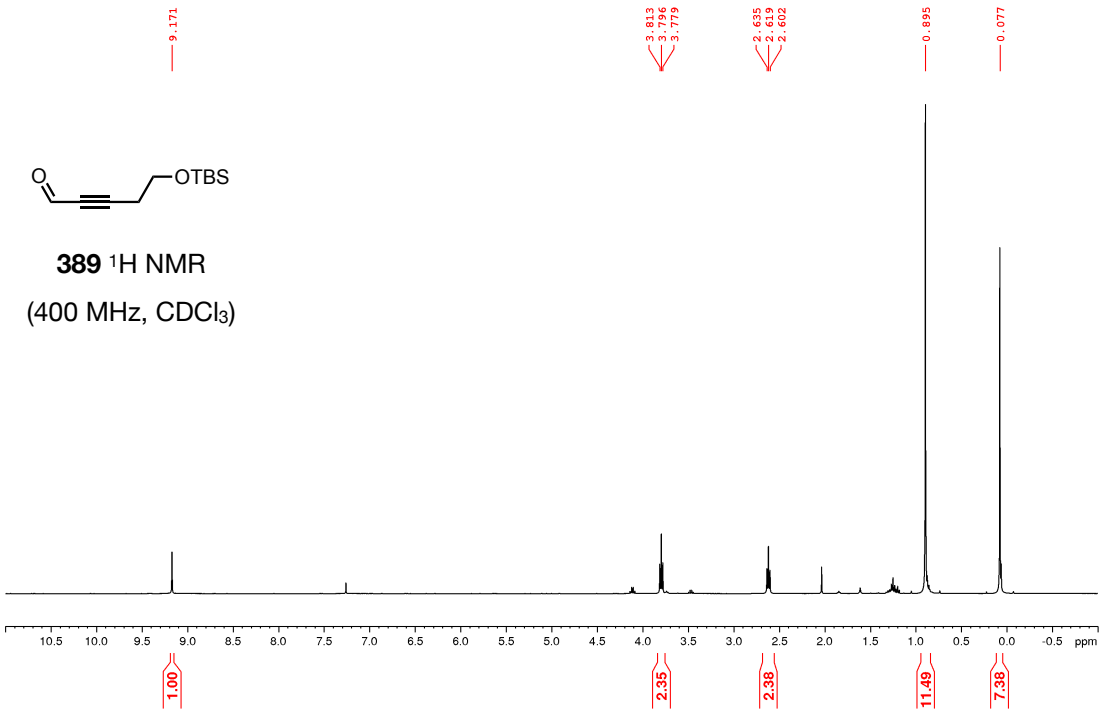

**375** $^1$H NMR

(400 MHz, $CDCl_3$)



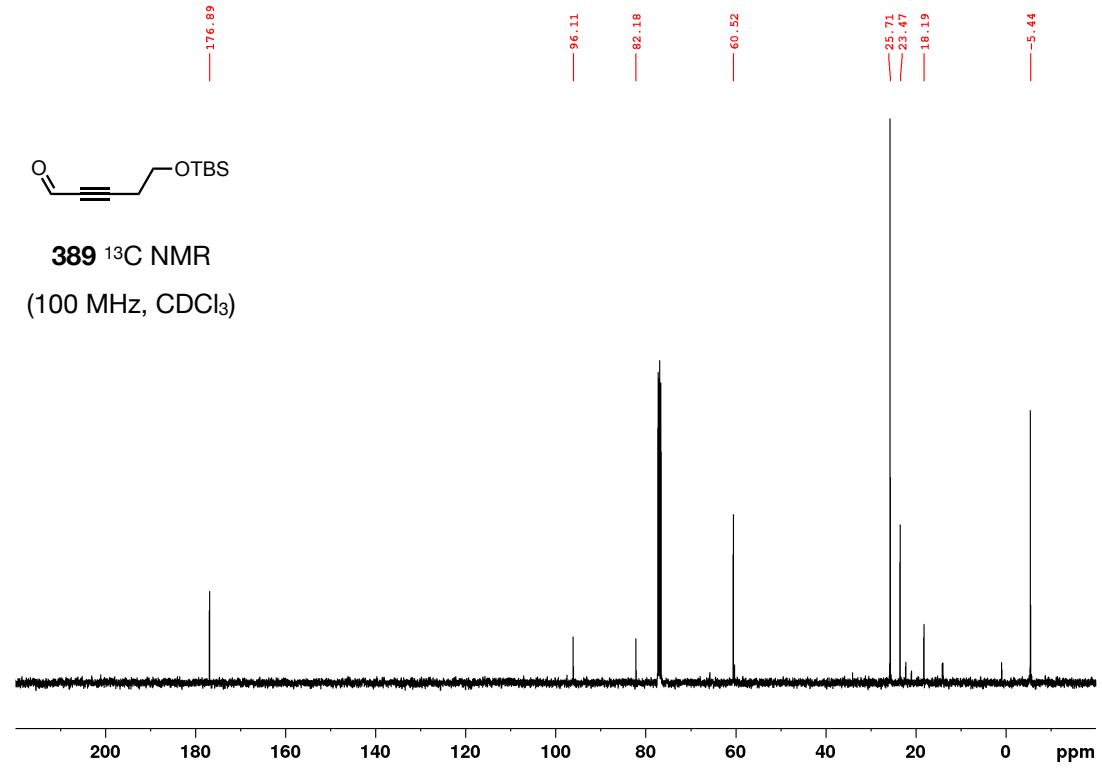

**388** $^1$H NMR

(400 MHz, $CDCl_3$)



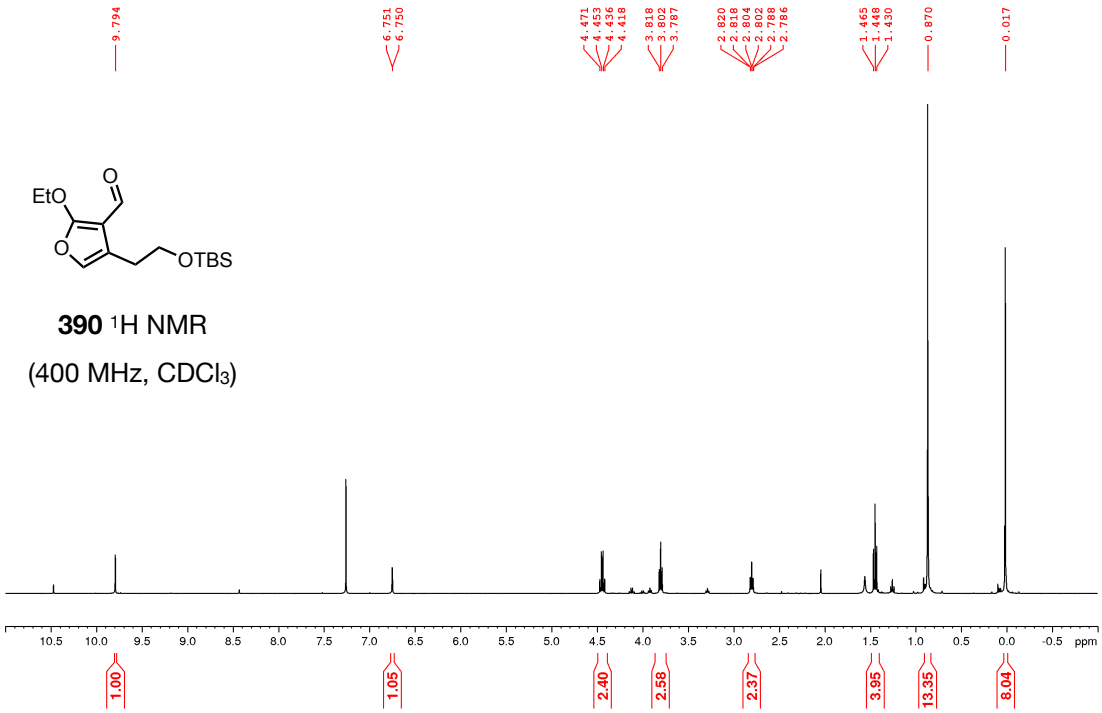

**389** $^{1}$H NMR

(400 MHz, $CDCl_3$)



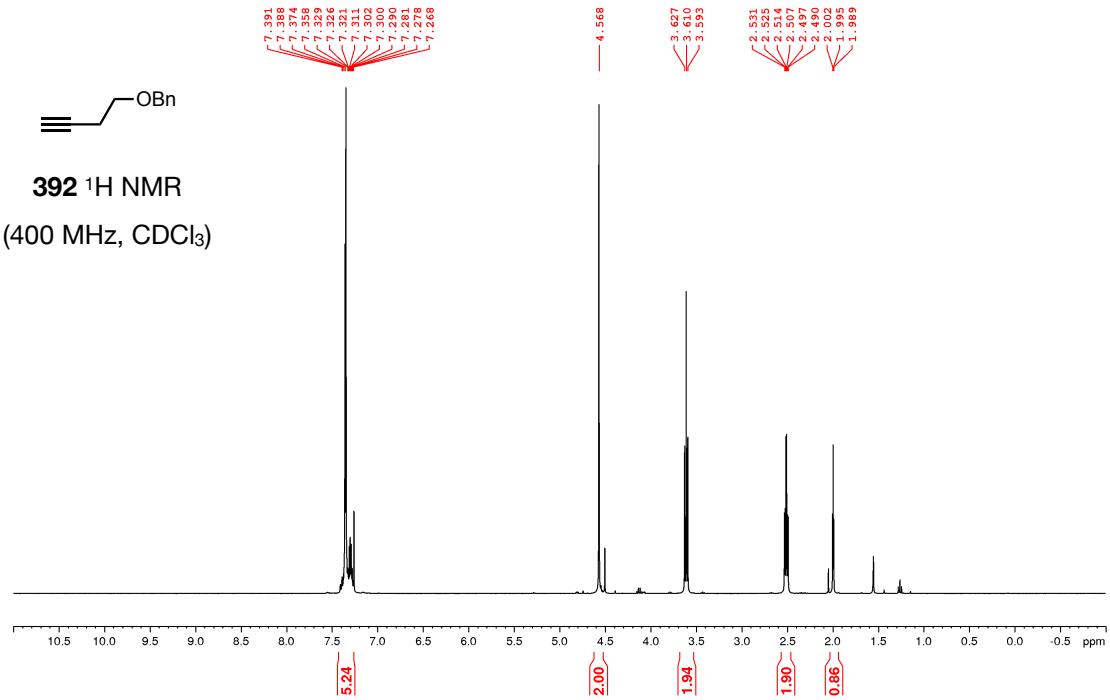

**389** $^{13}$C NMR

(100 MHz, $CDCl_3$)



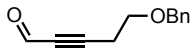

**390** $^1$H NMR

(400 MHz, $CDCl_3$)



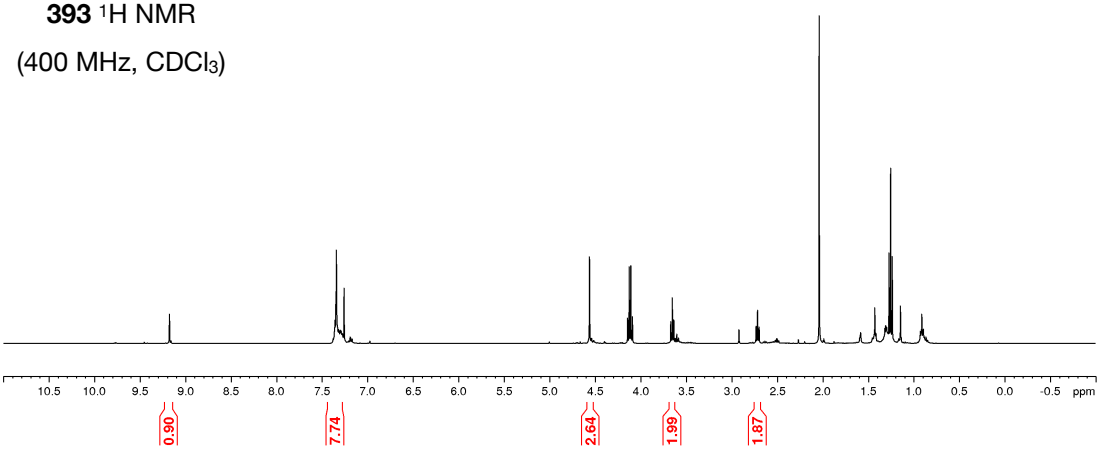

**392** $^1$H NMR

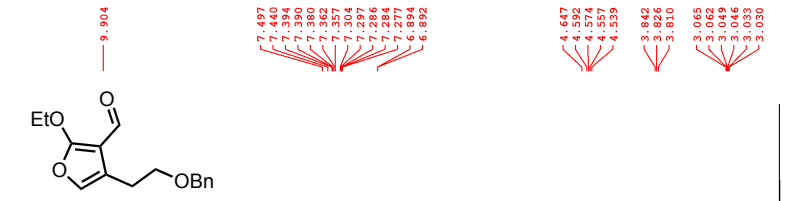
(400 MHz, $CDCl_3$)


**393** $^1$H NMR

(400 MHz, $CDCl_3$)



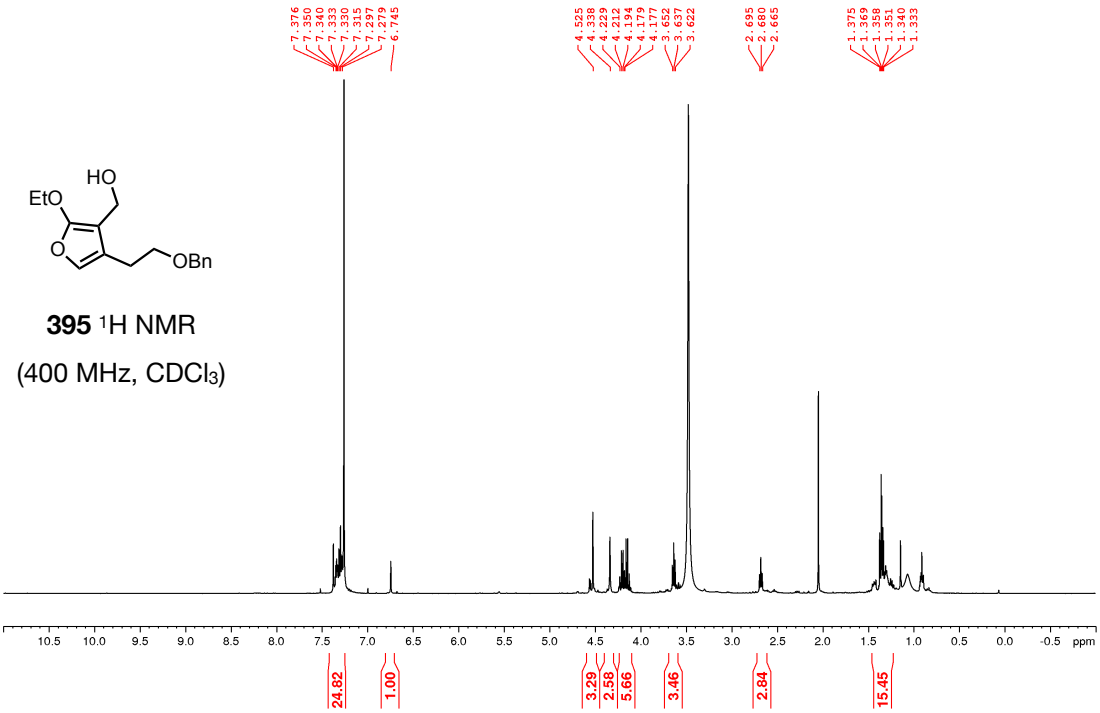







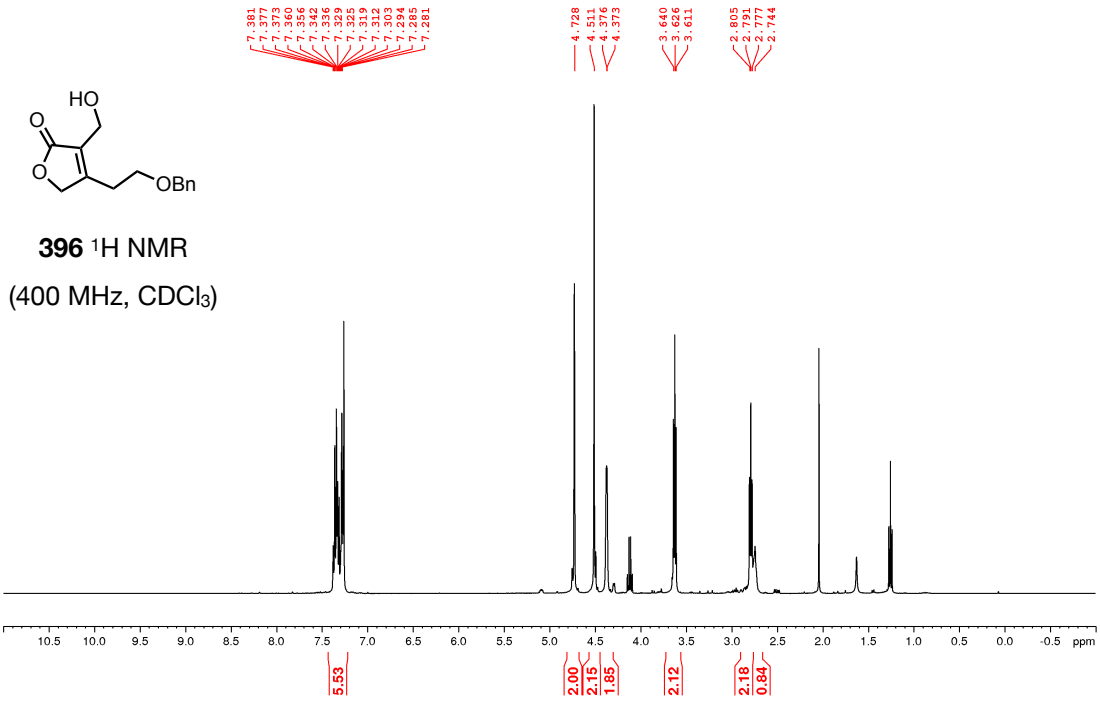
**394** $^1$H NMR

(400 MHz, $CDCl_3$)



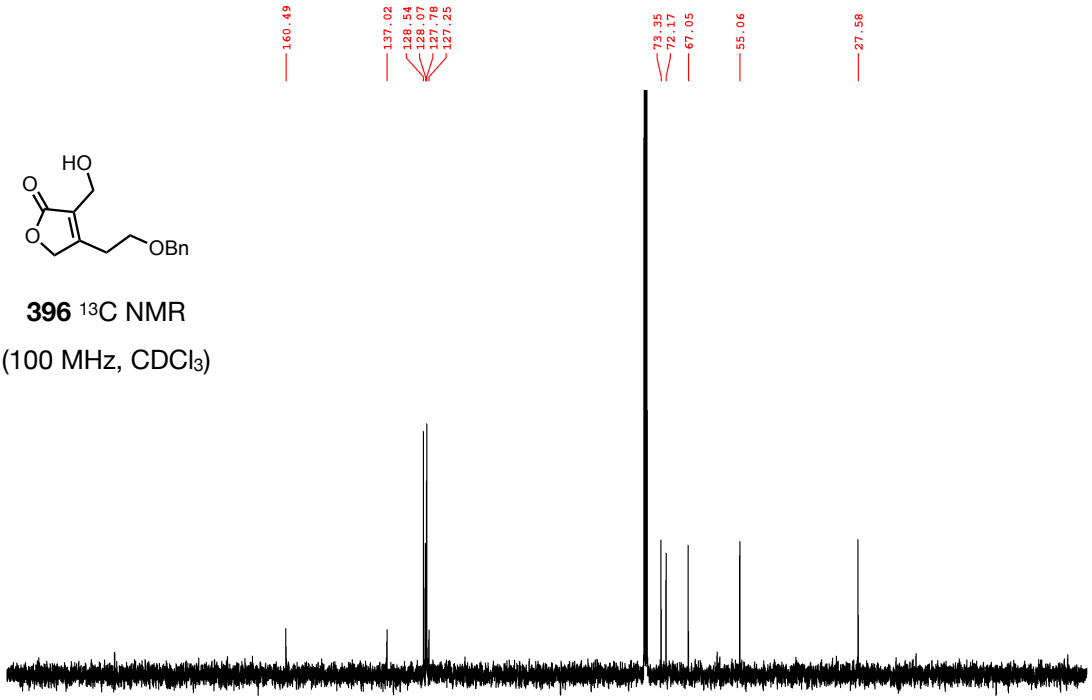

**395** $^{1}$H NMR

(400 MHz, $CDCl_3$)



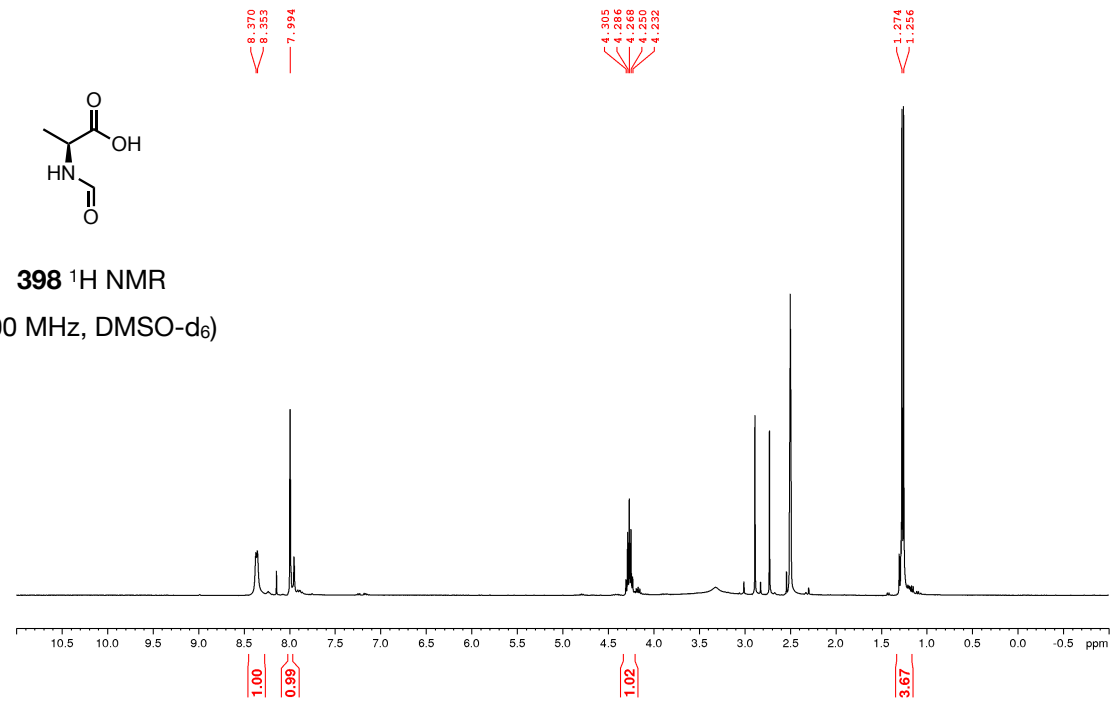

**396** $^{1}$H NMR

(400 MHz, $CDCl_3$)



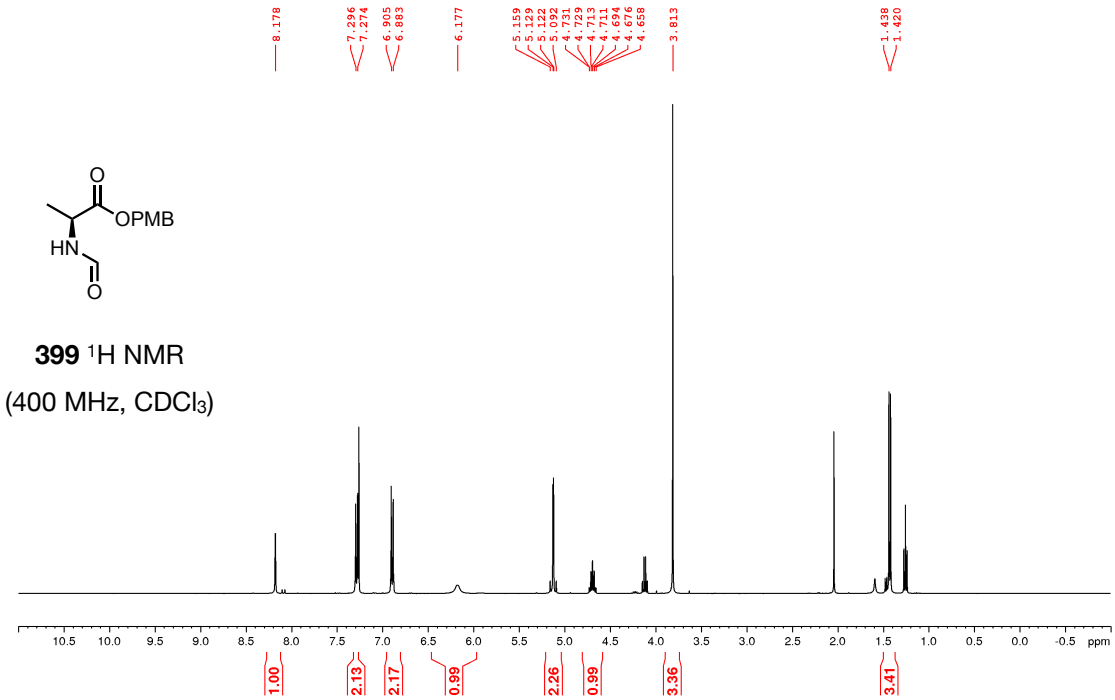

**396** $^{13}$C NMR

(100 MHz, $CDCl_3$)



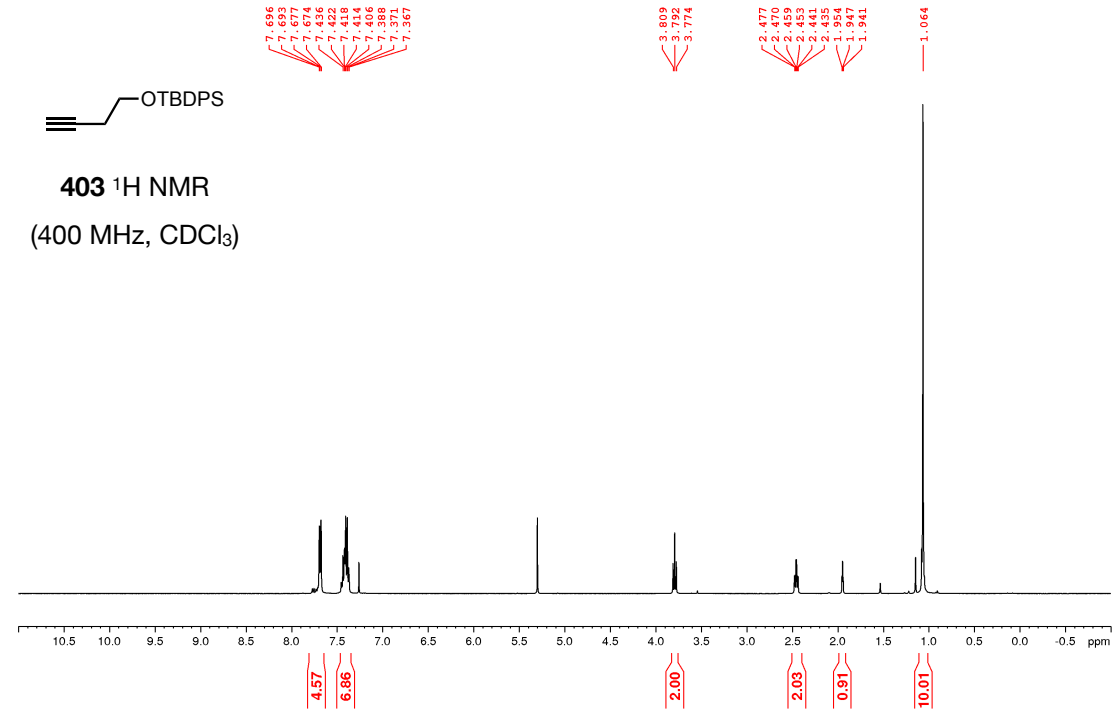

**398** $^{1}$H NMR

(400 MHz, DMSO-$d_6$)



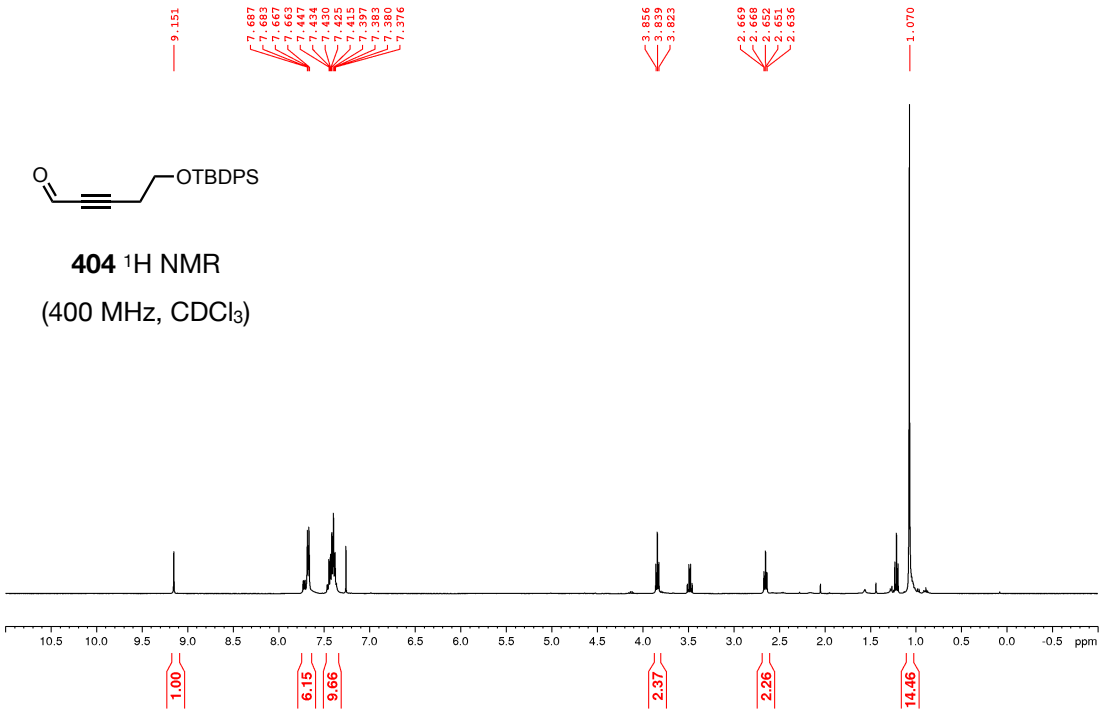

**399** $^{1}$H NMR

(400 MHz, $CDCl_3$)



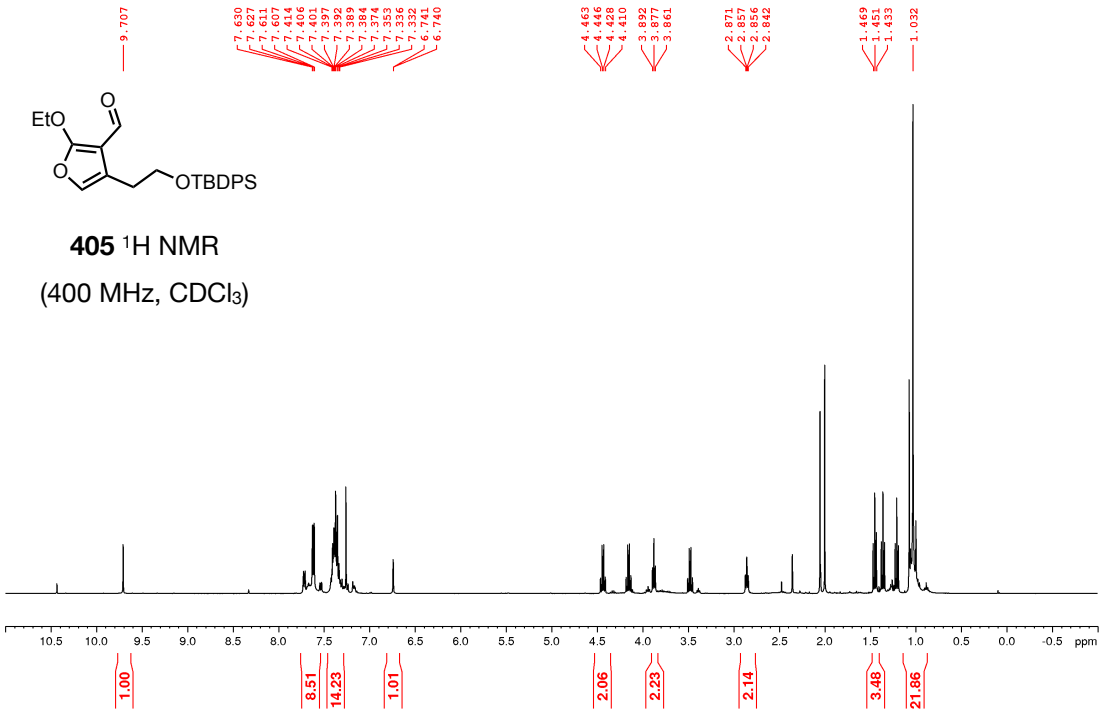

**403** $^{1}$H NMR

(400 MHz, $CDCl_3$)



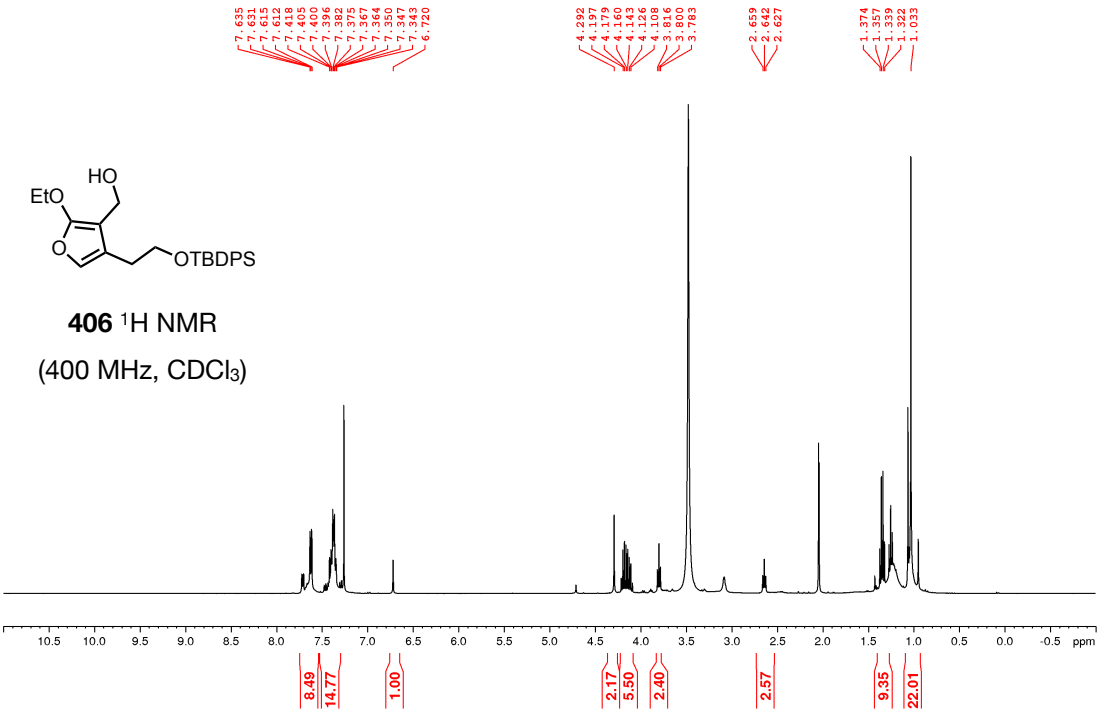

**404** $^{1}$H NMR

(400 MHz, $CDCl_3$)



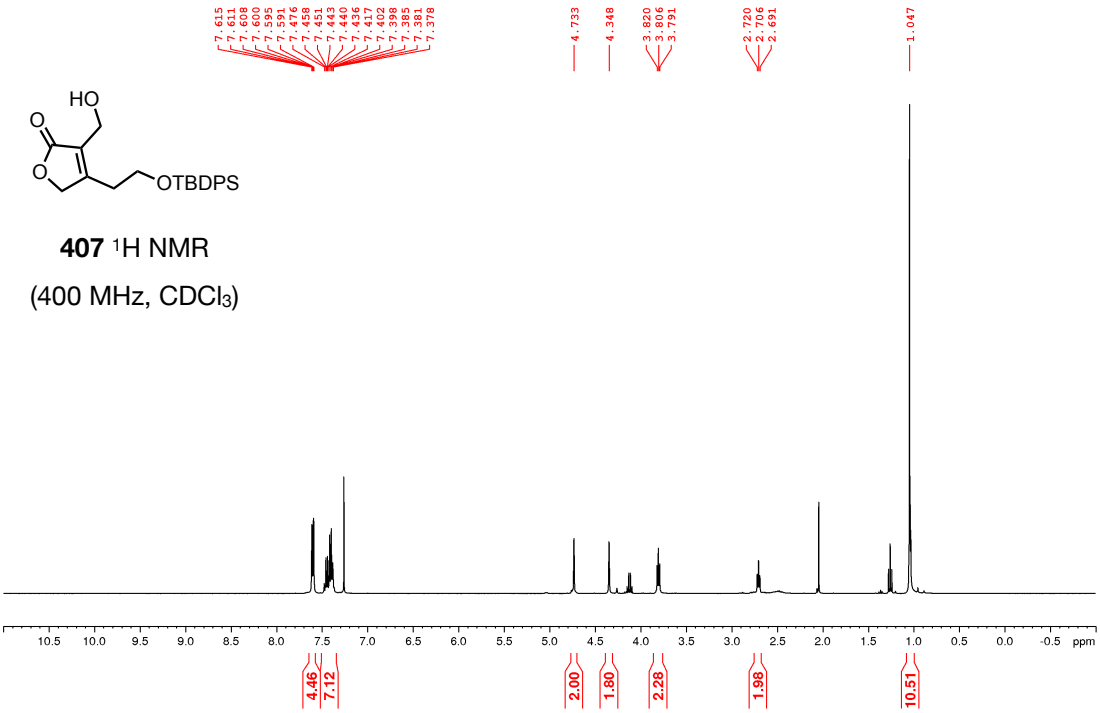

**405** $^{1}$H NMR

(400 MHz, $CDCl_3$)



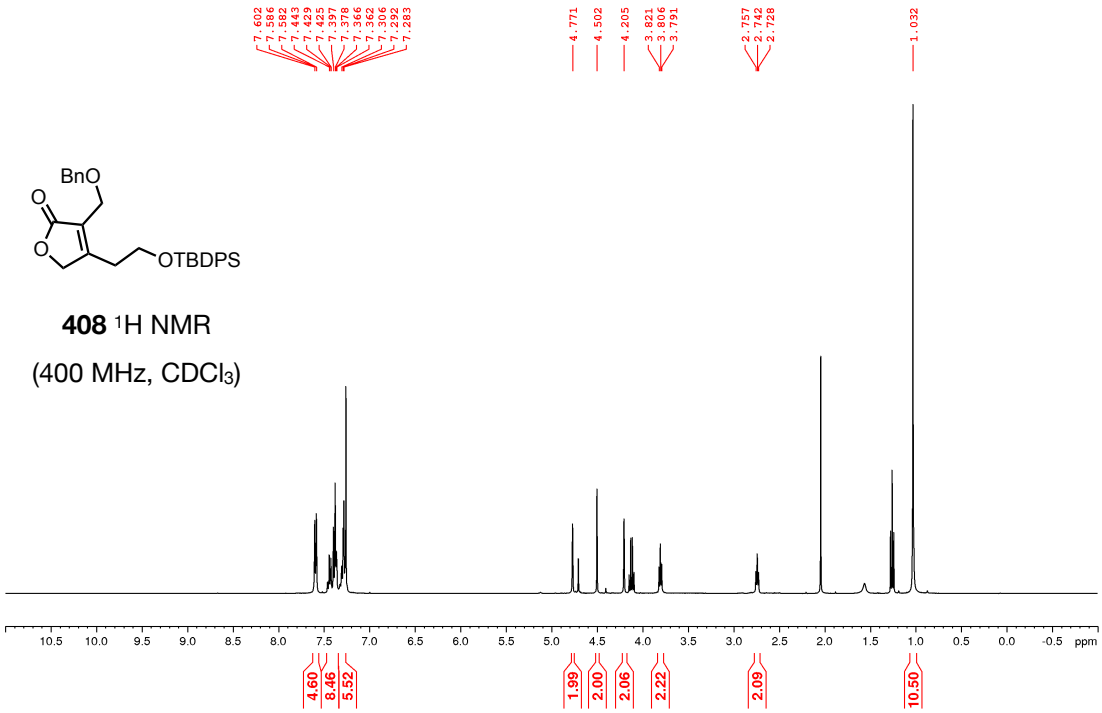

**406** $^{1}$H NMR

(400 MHz, $CDCl_3$)

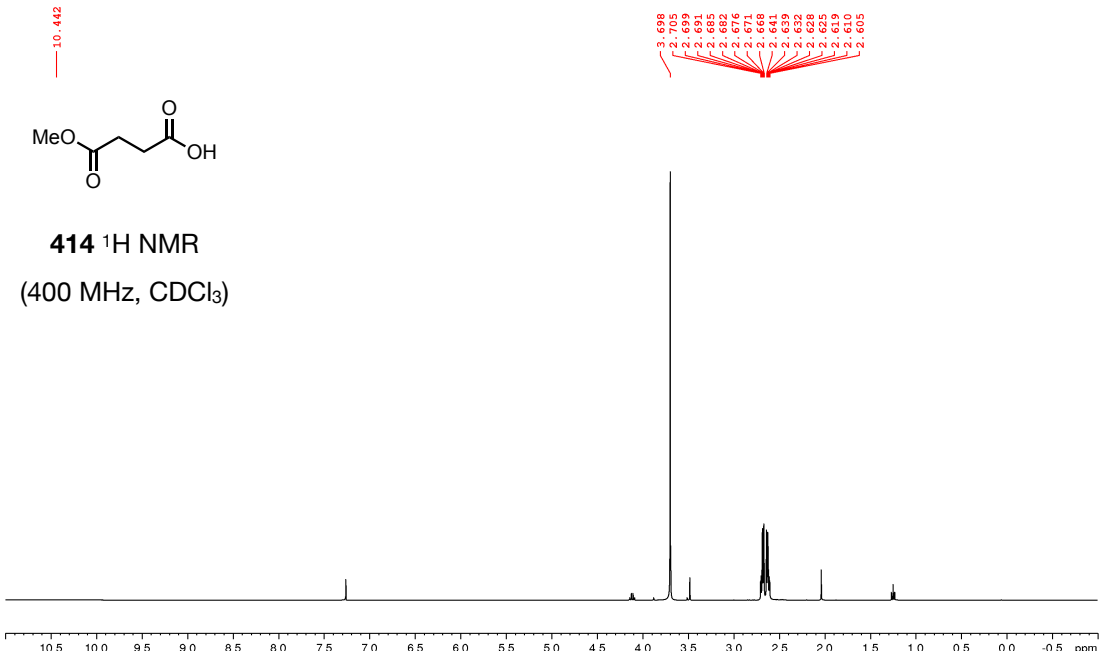



**407** $^{1}$H NMR

(400 MHz, $CDCl_3$)

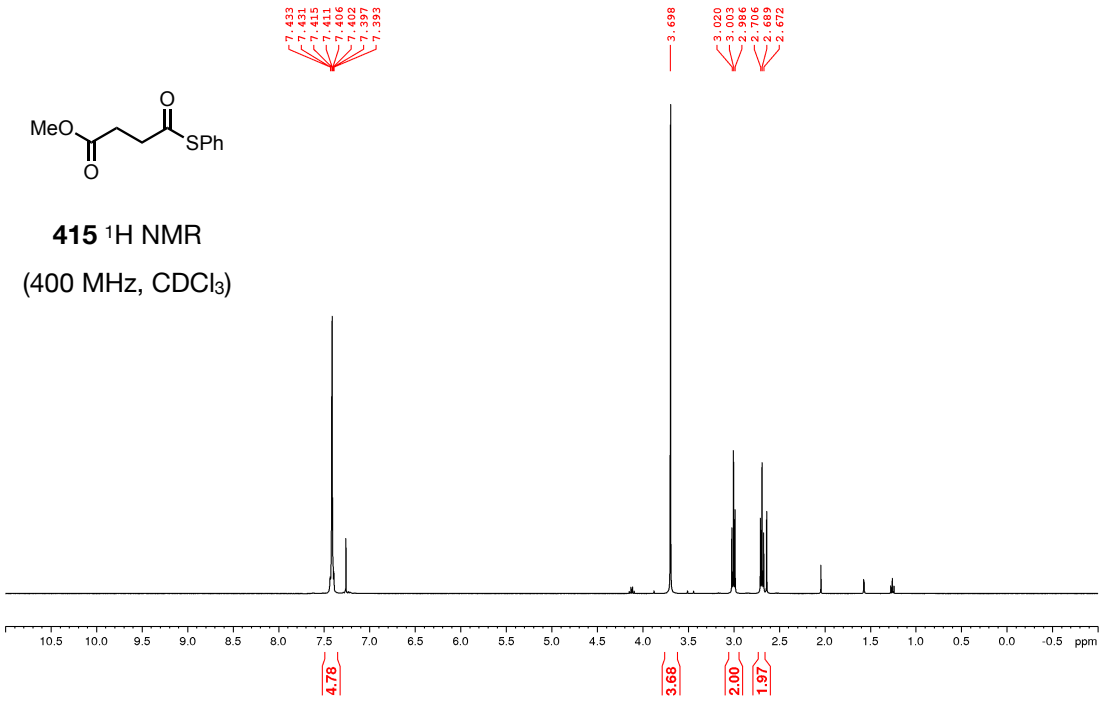

7.602
7.586
7.582
7.443
7.429
7.425
7.397
7.378
7.366
7.362
7.296
7.292
7.283
4.771
4.502
4.205
3.821
3.806
3.791
2.757
2.742
2.728
1.032
BnO
O
O
OTBDPS
408 1H NMR
(400 MHz, CDCl3)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm
4.60
8.46
5.52
1.99
2.00
2.06
2.22
2.09
10.50

**NMR Spectra: Section 3.5:**



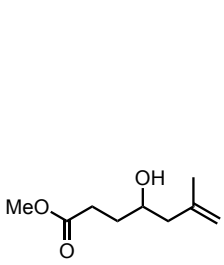

**414** $^{1}$H NMR

(400 MHz, $CDCl_3$)




**415** $^{1}$H NMR

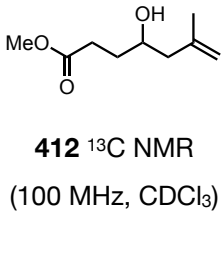
(400 MHz, $CDCl_3$)




**412** $^{1}$H NMR

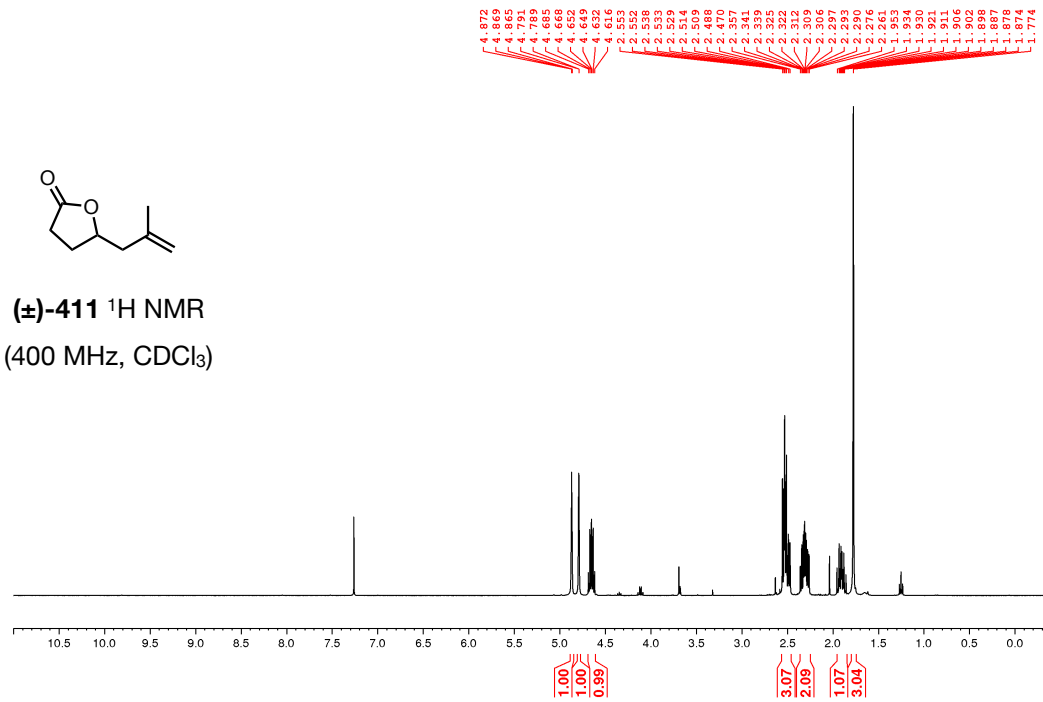
(400 MHz, $CDCl_3$)



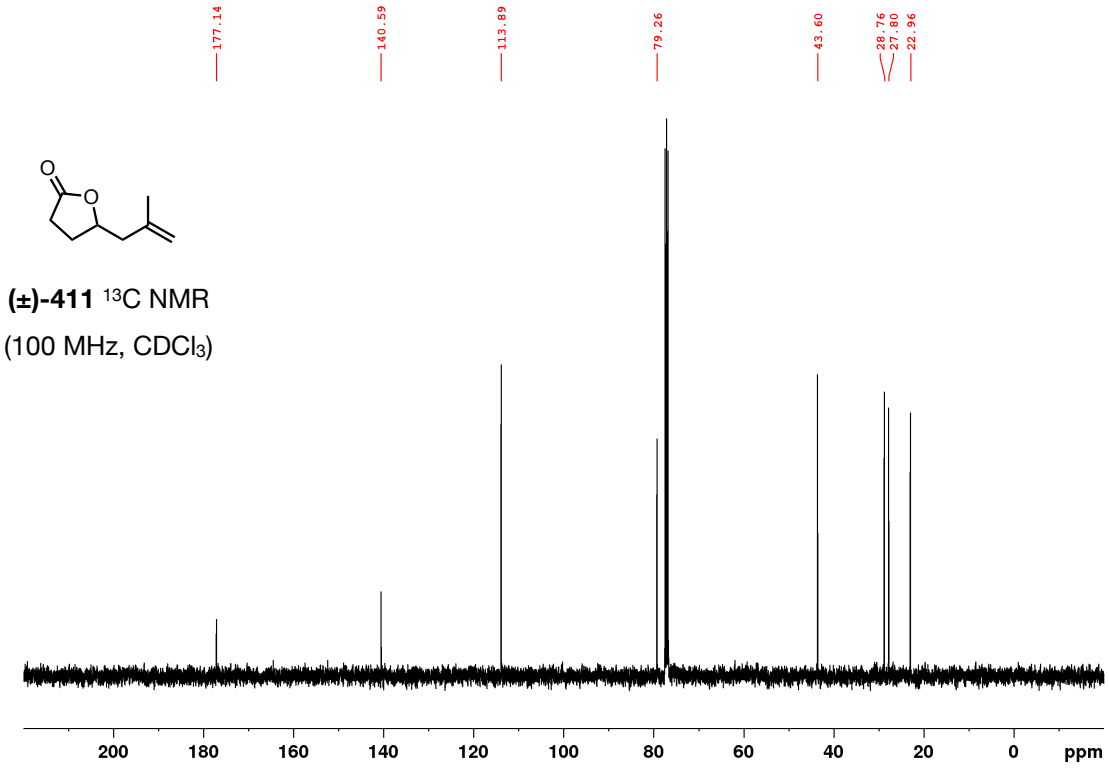

**412** $^{13}$C NMR

(100 MHz, $CDCl_3$)



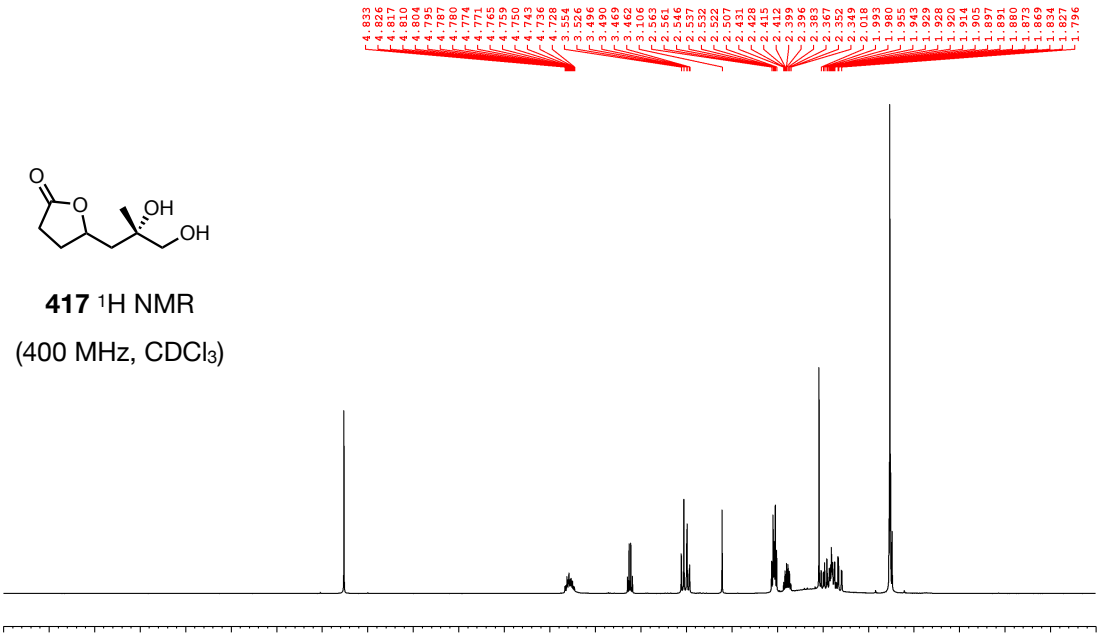
**(±)-411** $^{1}$H NMR

(400 MHz, $CDCl_3$)



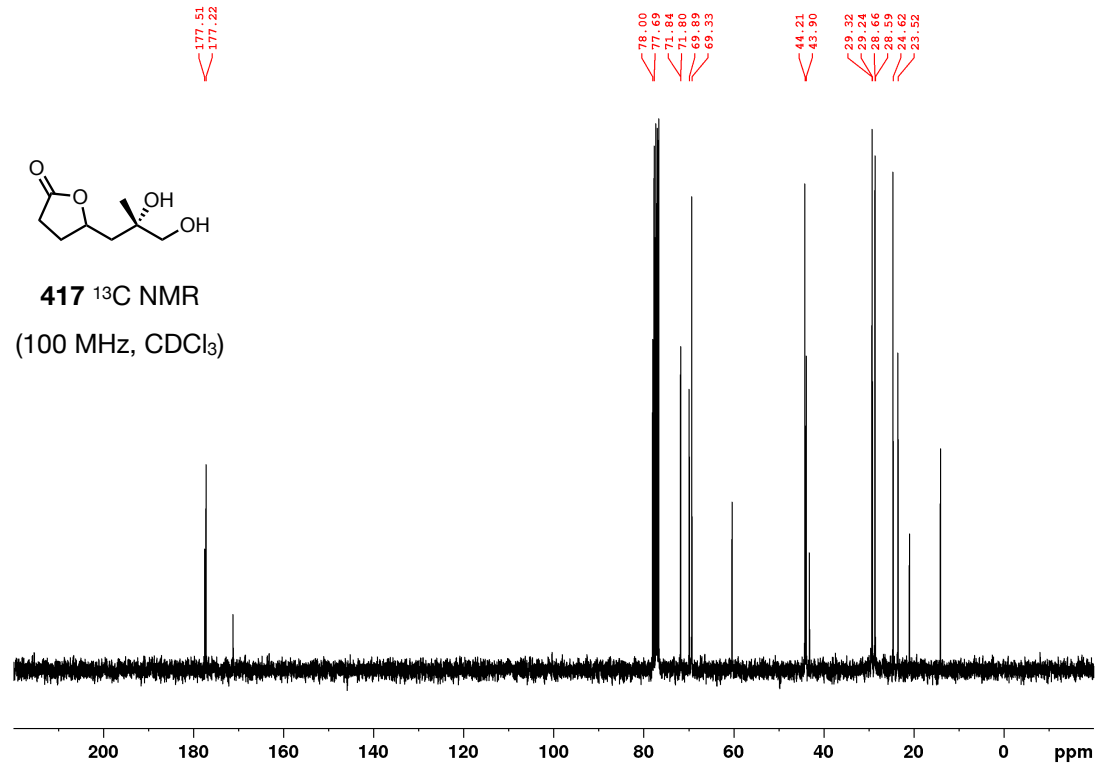
**(±)-411** $^{13}$C NMR

(100 MHz, $CDCl_3$)



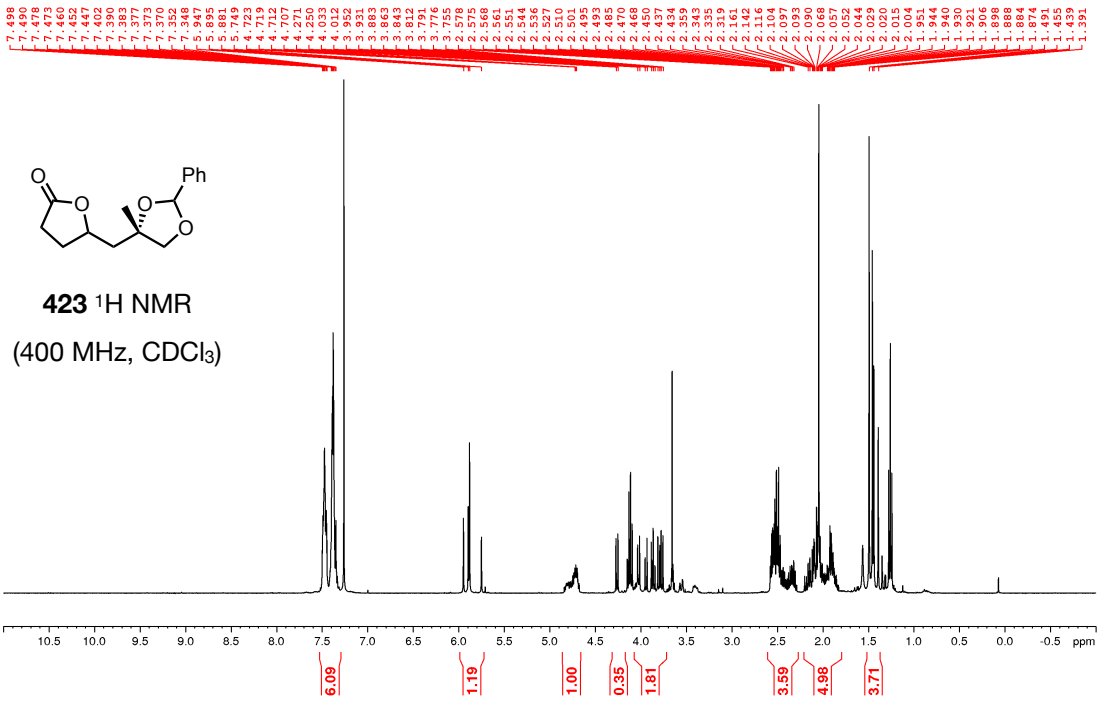

**417** $^{1}$H NMR

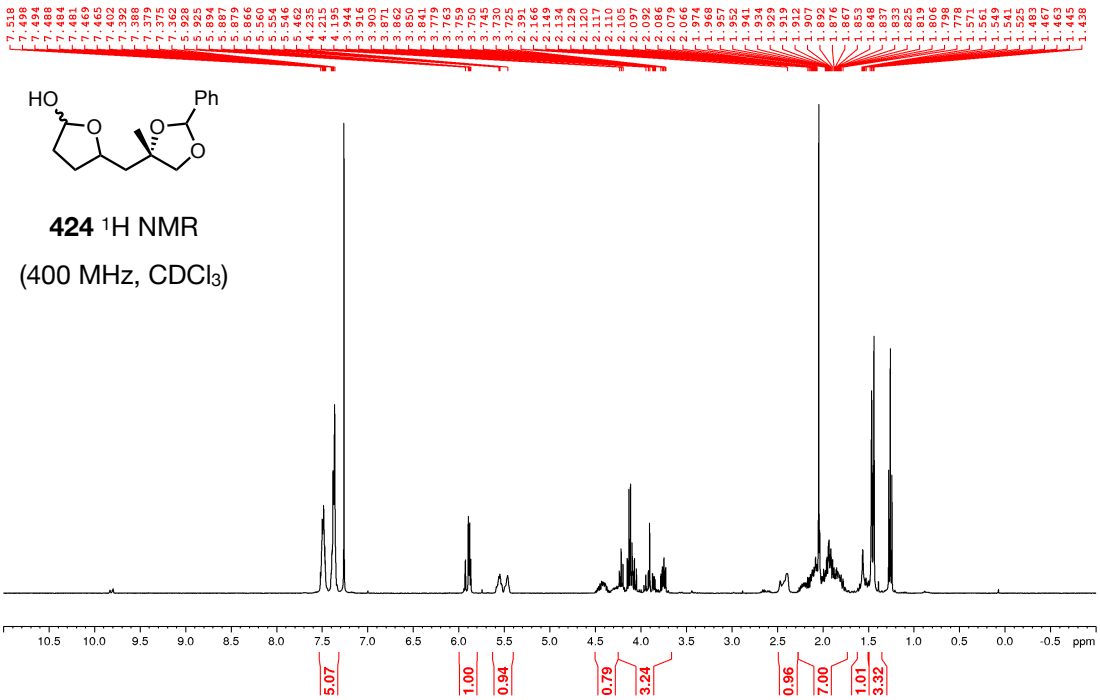
(400 MHz, $CDCl_3$)

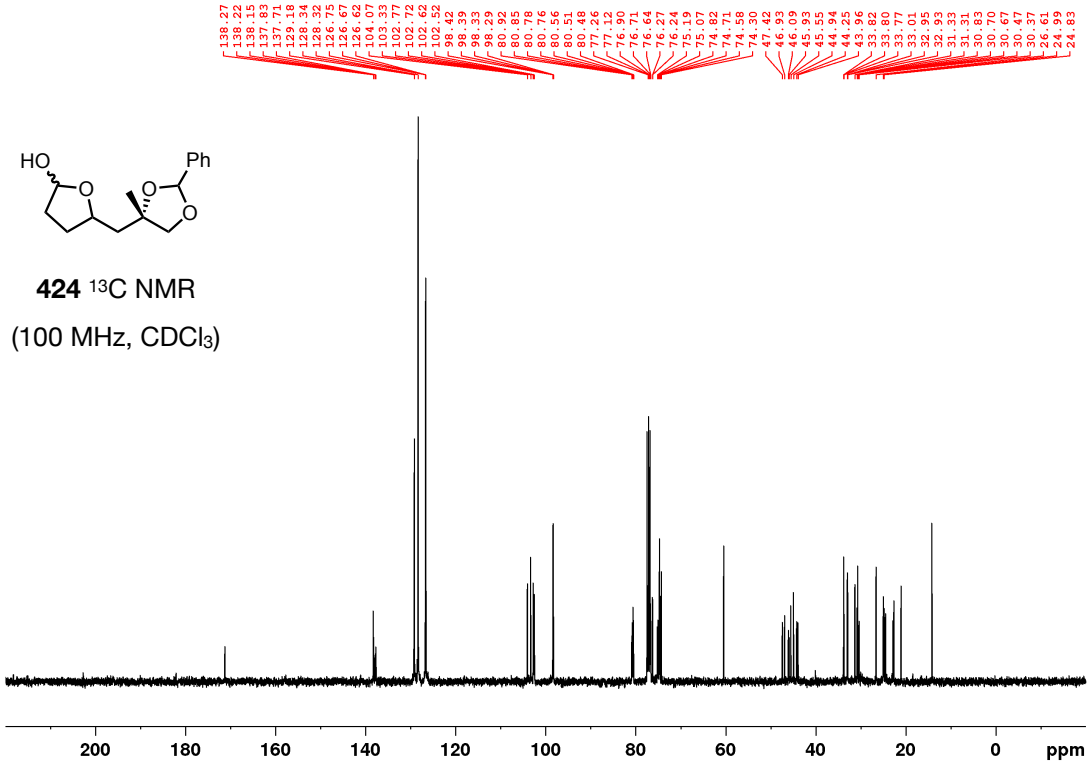



**417** $^{13}$C NMR

(100 MHz, $CDCl_3$)

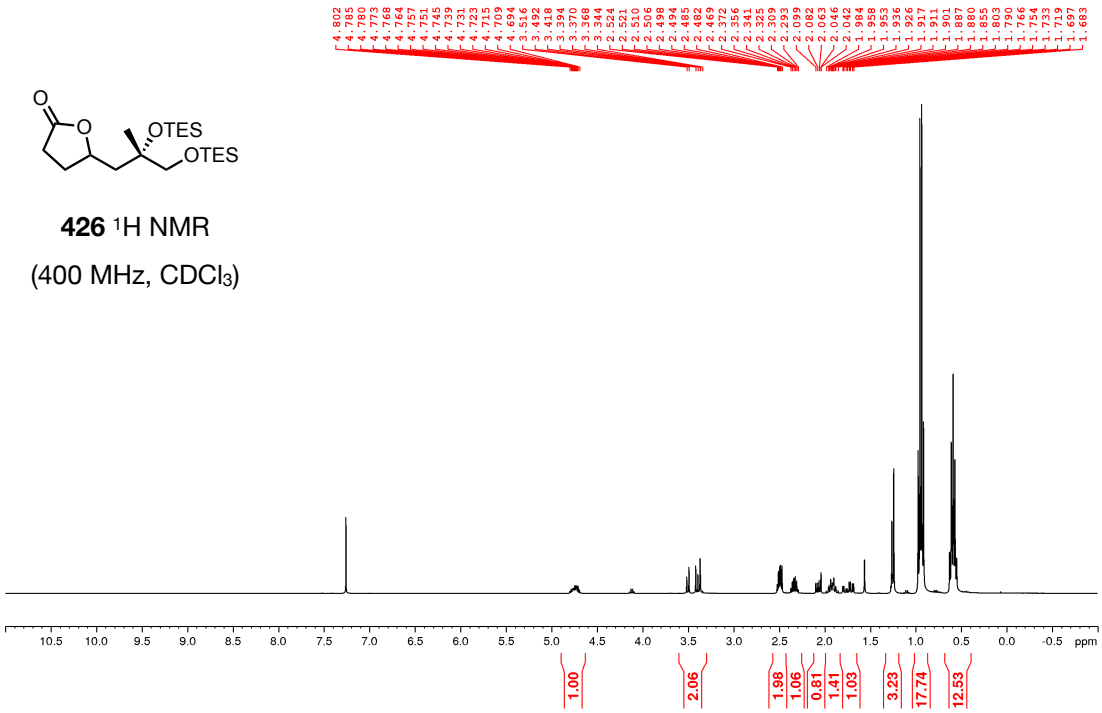

Ph
O
O
O
O
423 1H NMR
(400 MHz, CDCl3)
ppm
6.09
1.19
1.00
0.35
1.81
3.59
4.98
3.71


HO
Ph
O
O
O
424 1H NMR
(400 MHz, CDCl3)
ppm
5.07
1.00
0.94
0.79
3.24
0.96
7.00
1.01
3.32



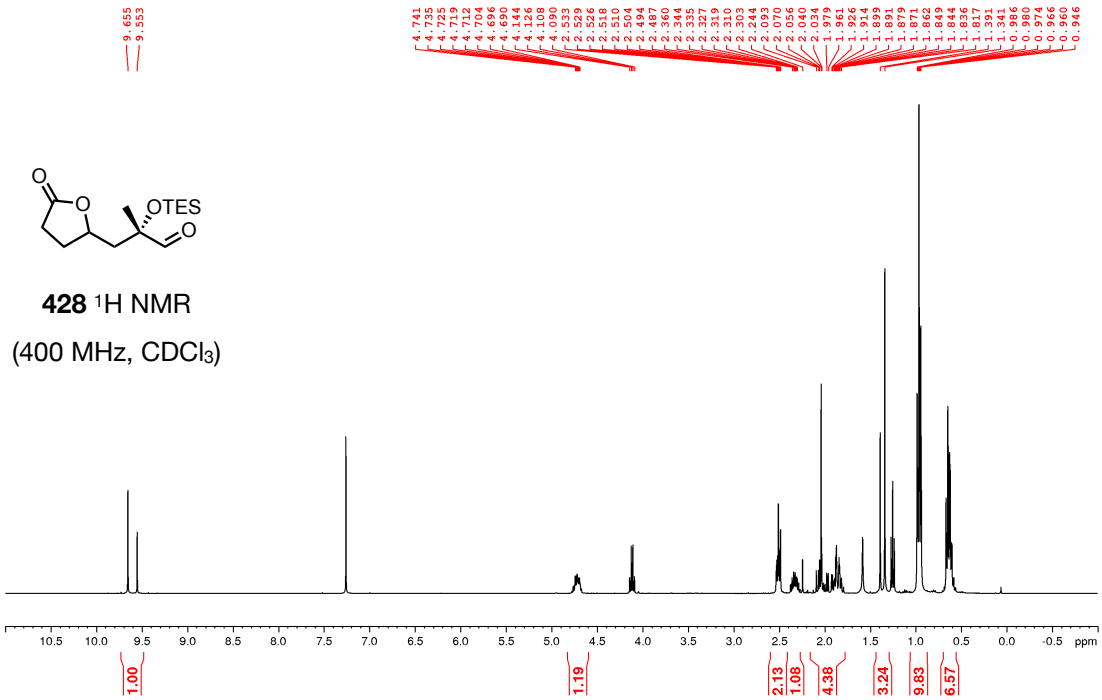

**424** $^{13}C$ NMR

(100 MHz, $CDCl_3$)



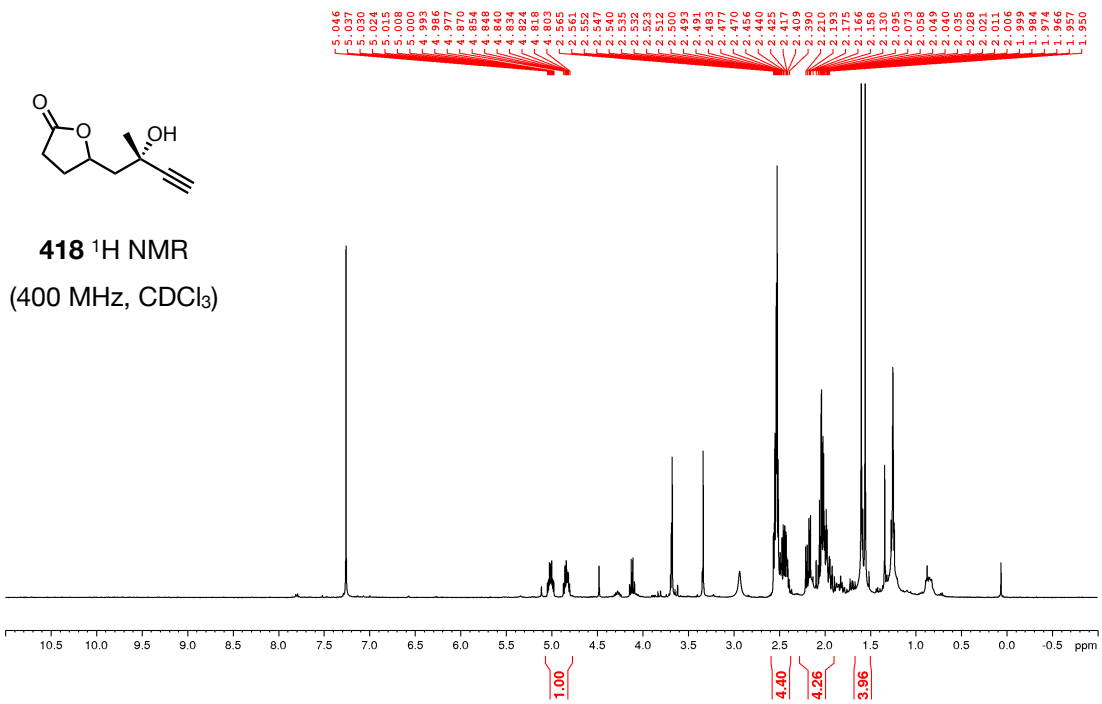

**426** $^{1}H$ NMR

(400 MHz, $CDCl_3$)



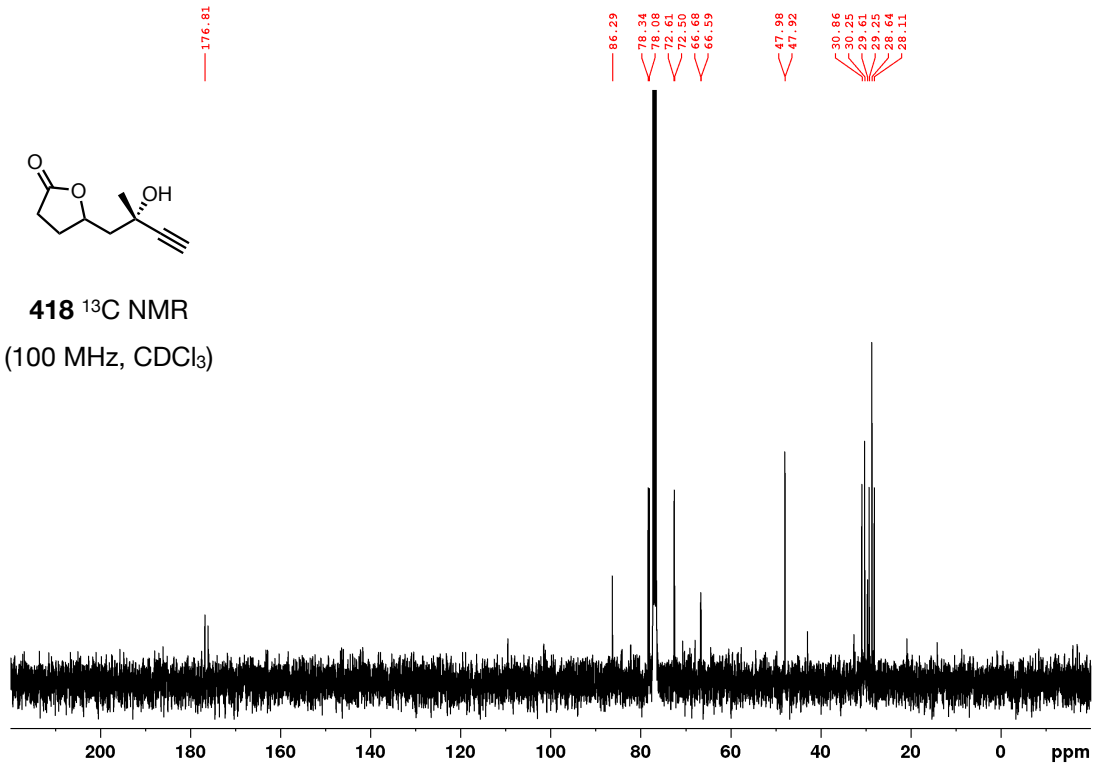

**428** $^{1}$H NMR

(400 MHz, $CDCl_3$)




**418** $^{1}$H NMR

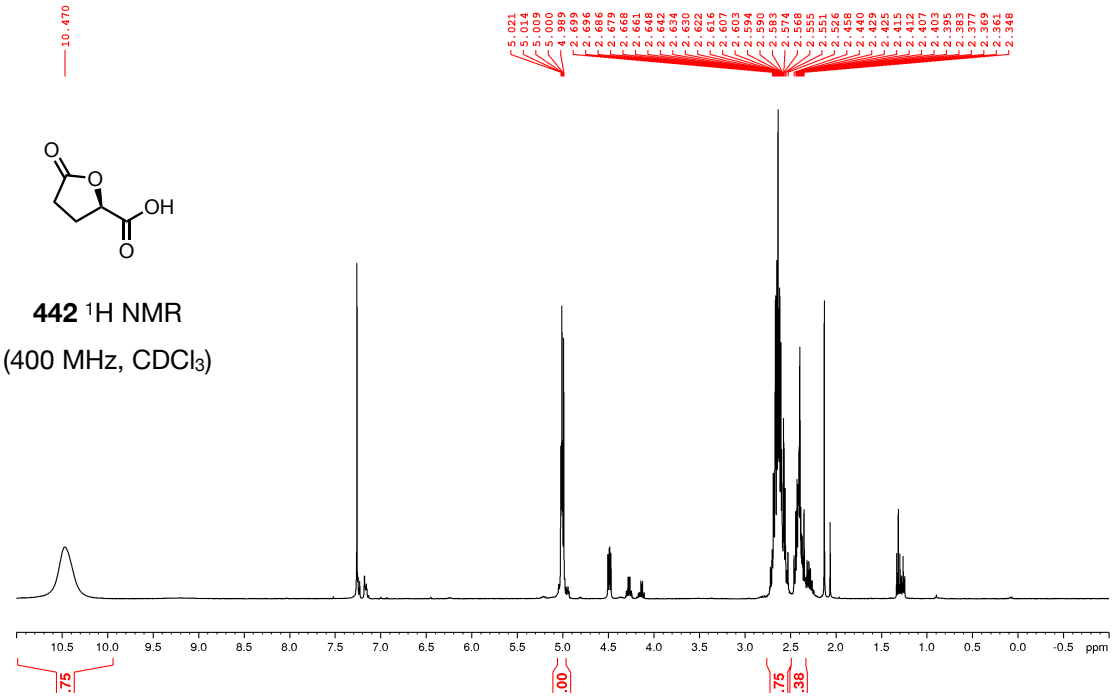
(400 MHz, $CDCl_3$)




**418** $^{13}C$ NMR

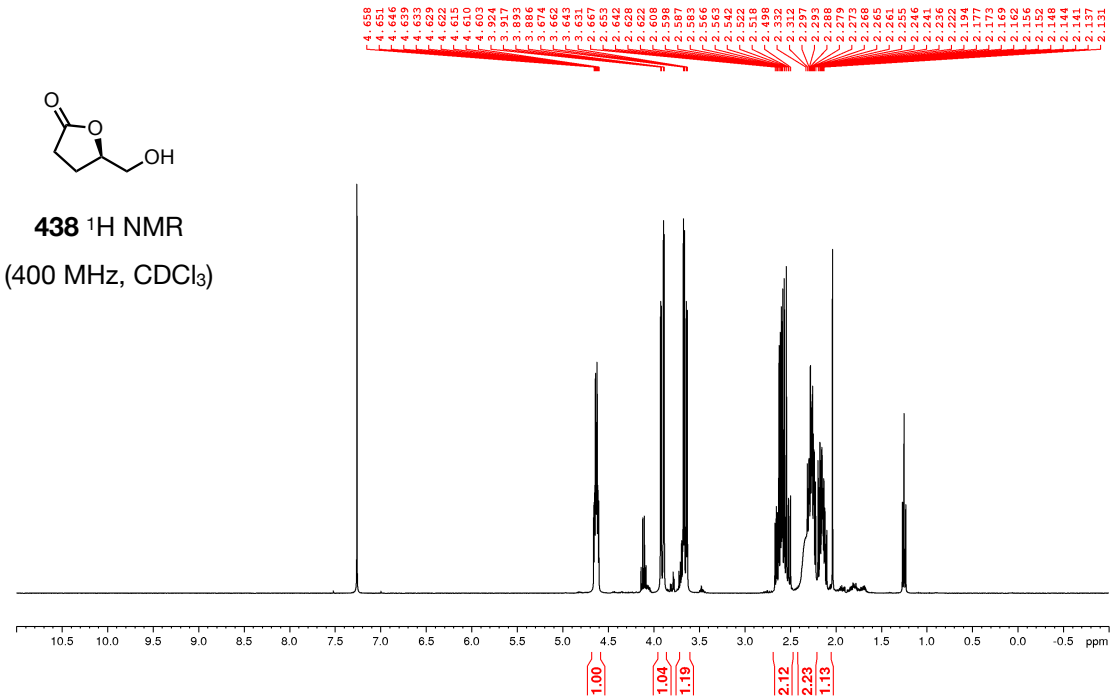
(100 MHz, $CDCl_3$)

**NMR Spectra: Section 3.6:**



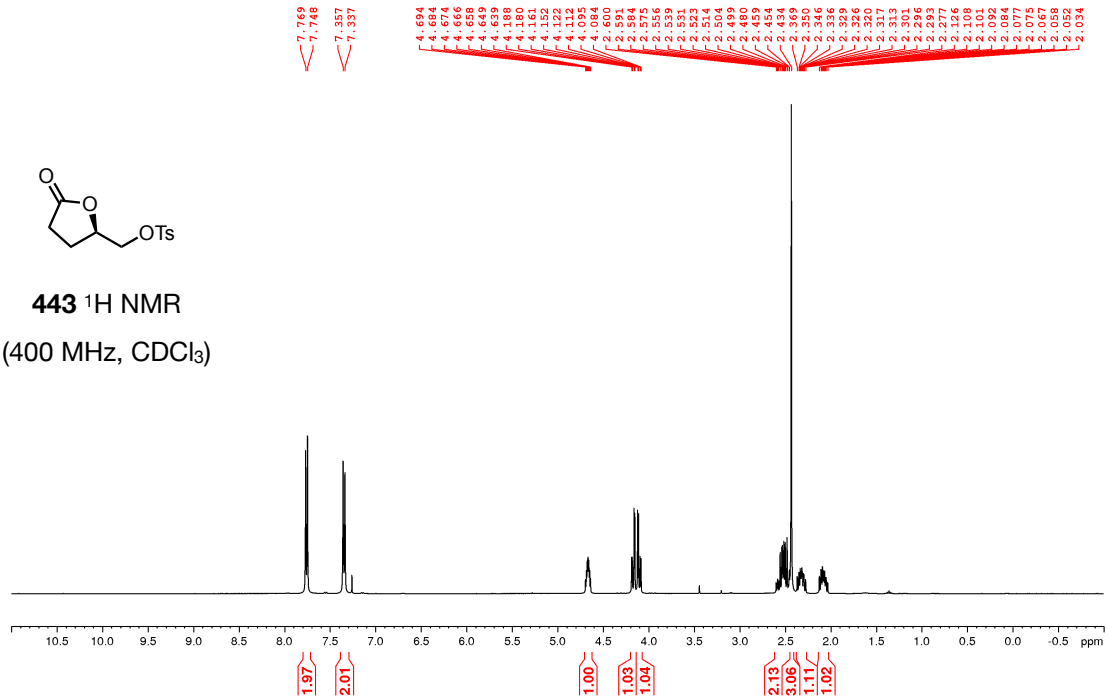
**442** $^{1}$H NMR

(400 MHz, $CDCl_3$)



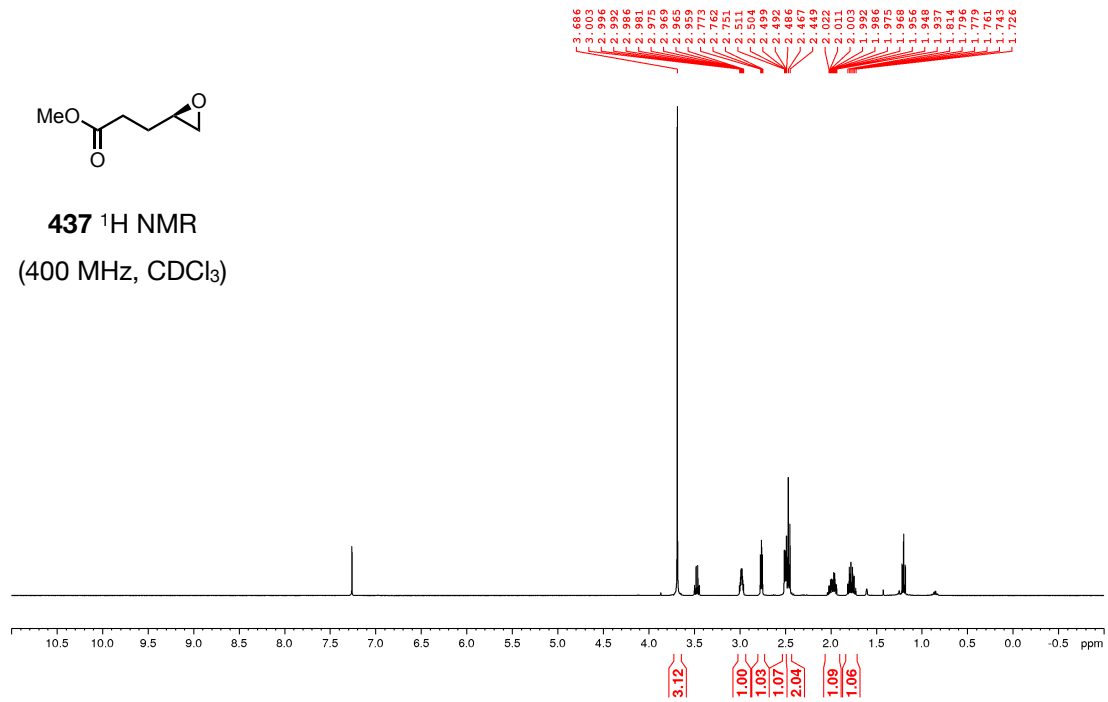
**438** $^{1}$H NMR

(400 MHz, $CDCl_3$)



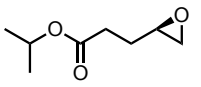

**443** $^{1}$H NMR

(400 MHz, $CDCl_3$)




**437** $^{1}$H NMR

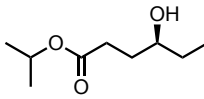
(400 MHz, $CDCl_3$)



**445** $^{1}$H NMR

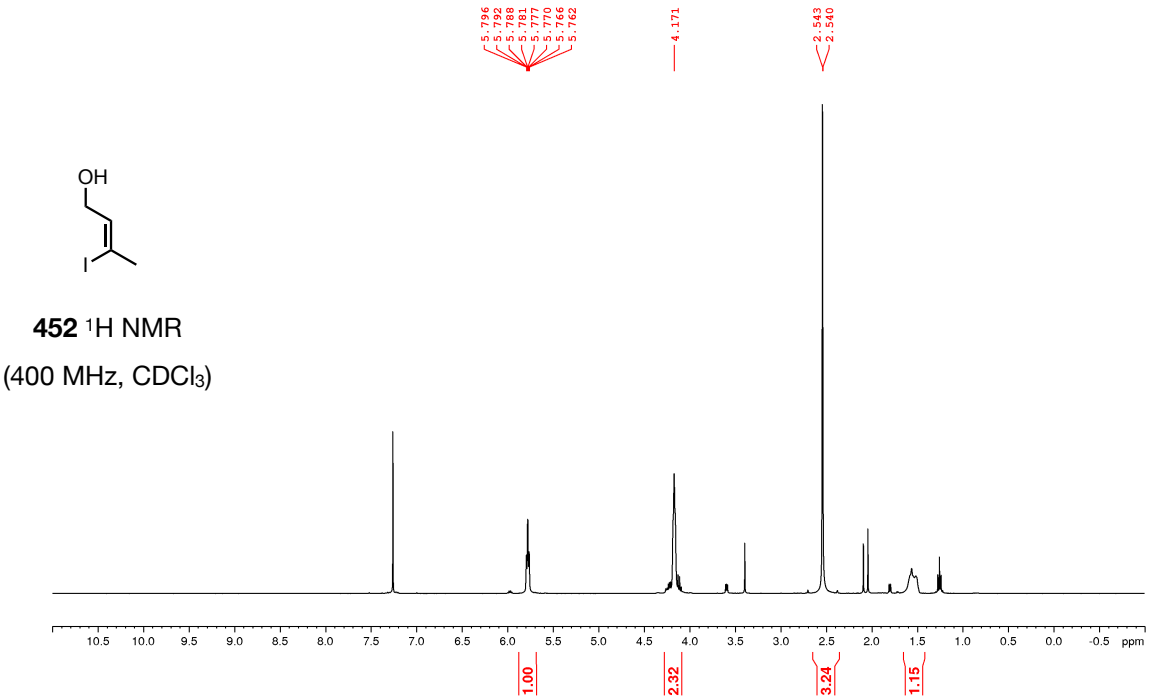
(400 MHz, $CDCl_3$)



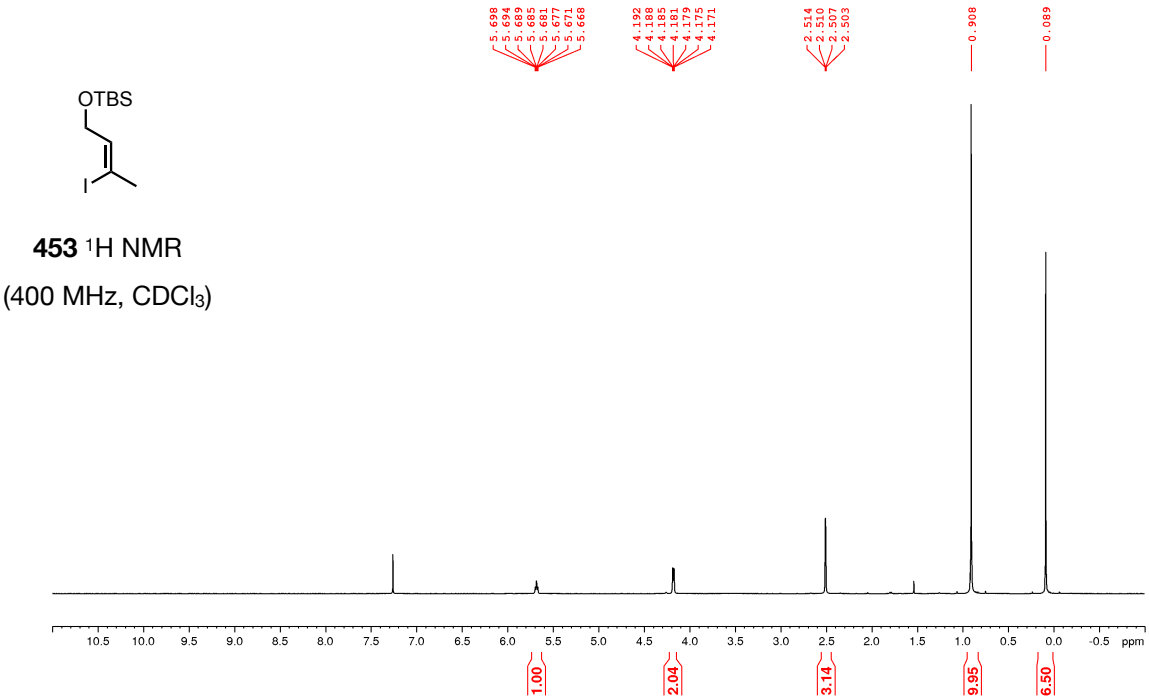
**446** $^{1}$H NMR

(400 MHz, $CDCl_3$)



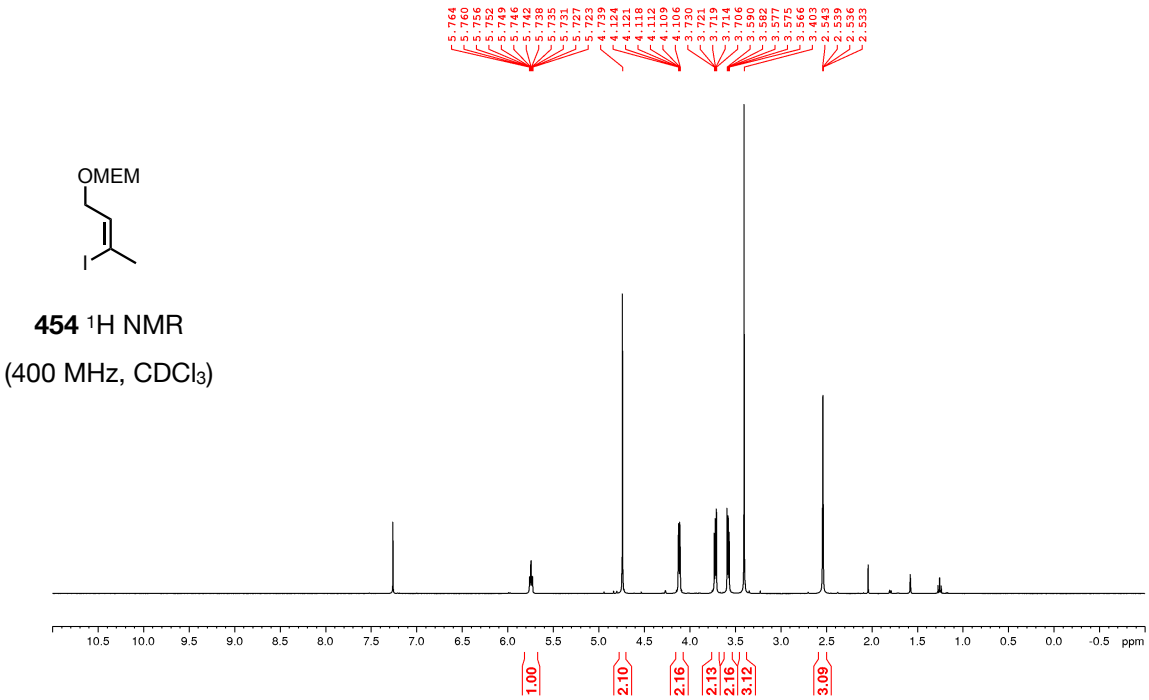

**452** $^{1}$H NMR

(400 MHz, $CDCl_3$)



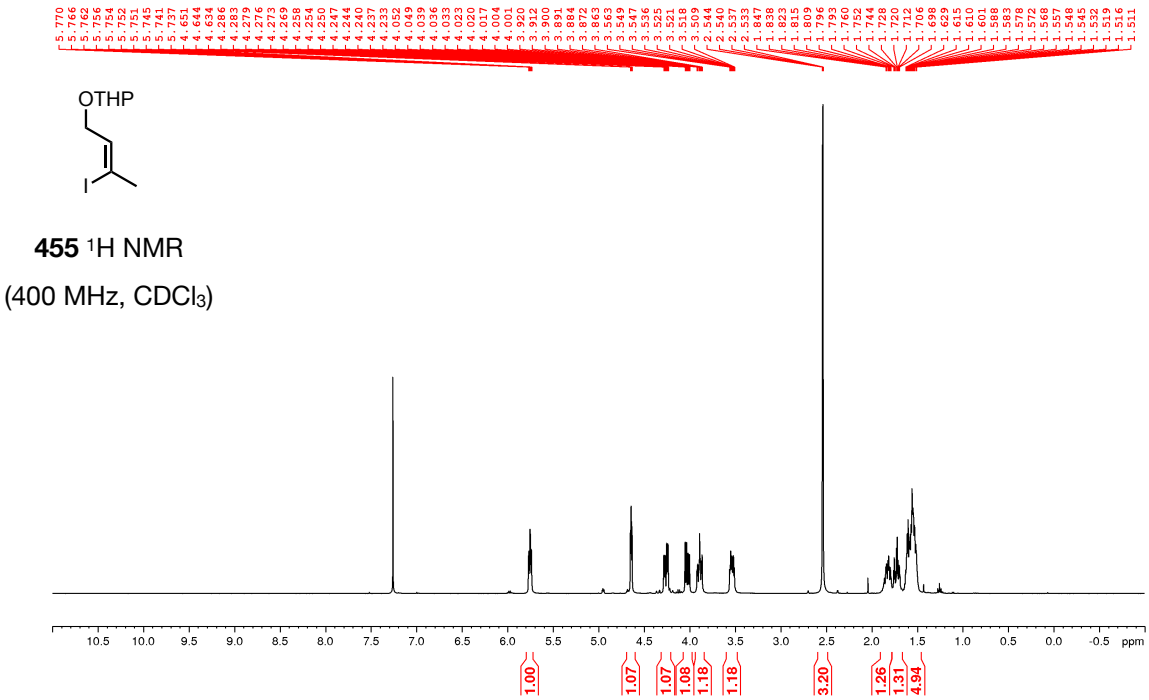

**453** $^{1}$H NMR

(400 MHz, $CDCl_3$)



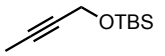

**454** $^{1}$H NMR

(400 MHz, $CDCl_3$)




**455** $^{1}$H NMR

(400 MHz, $CDCl_3$)




**456** $^{1}$H NMR

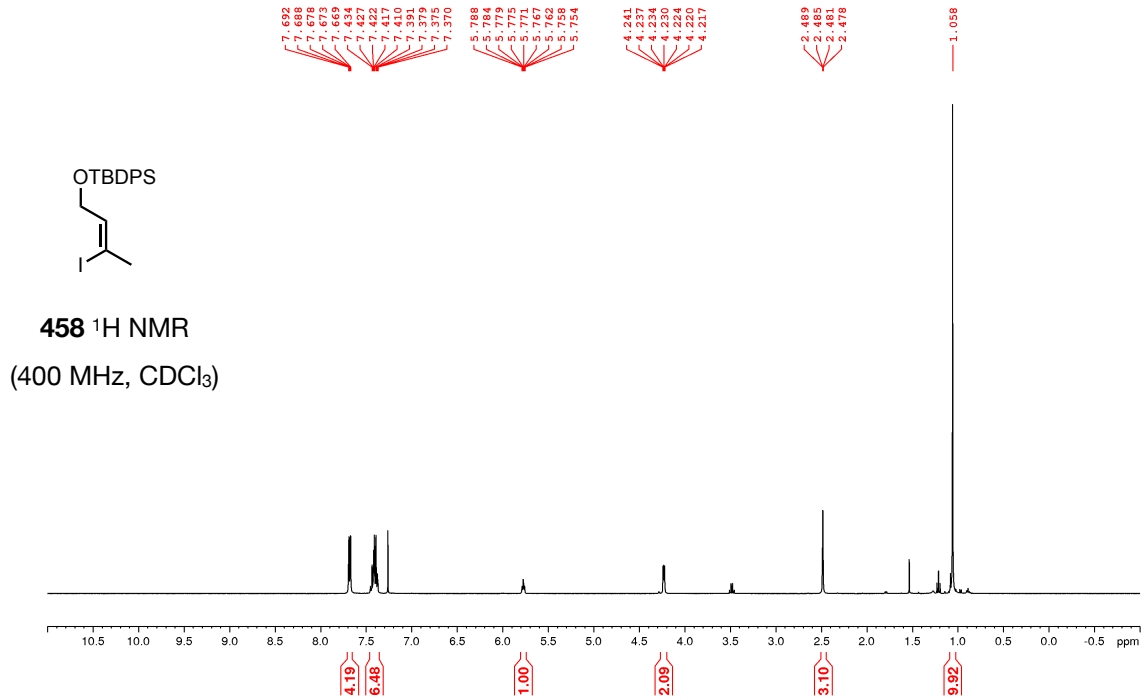
(400 MHz, $CDCl_3$)





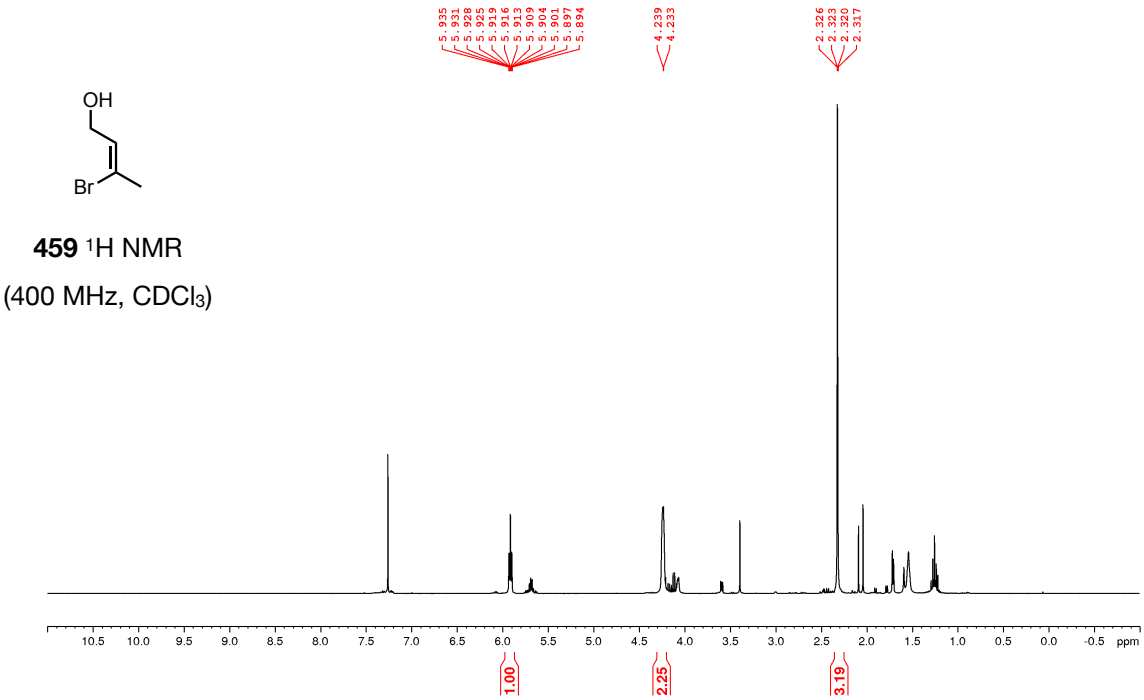
**457** $^{1}$H NMR

(400 MHz, $CDCl_3$)



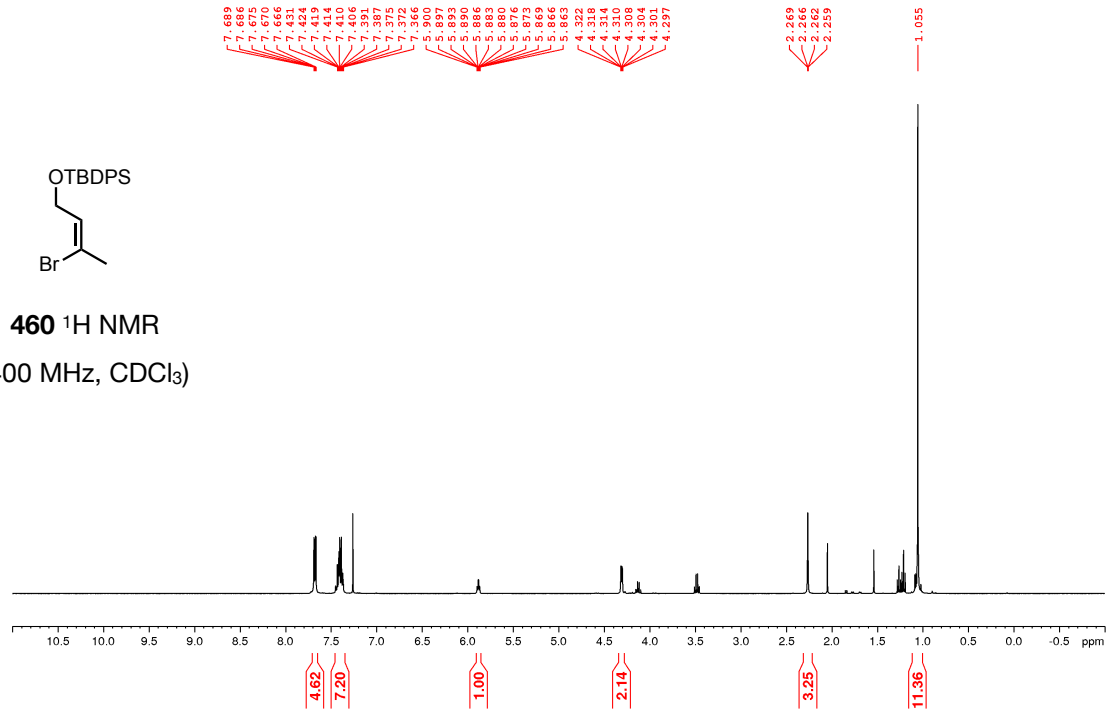

**458** $^{1}$H NMR

(400 MHz, $CDCl_3$)



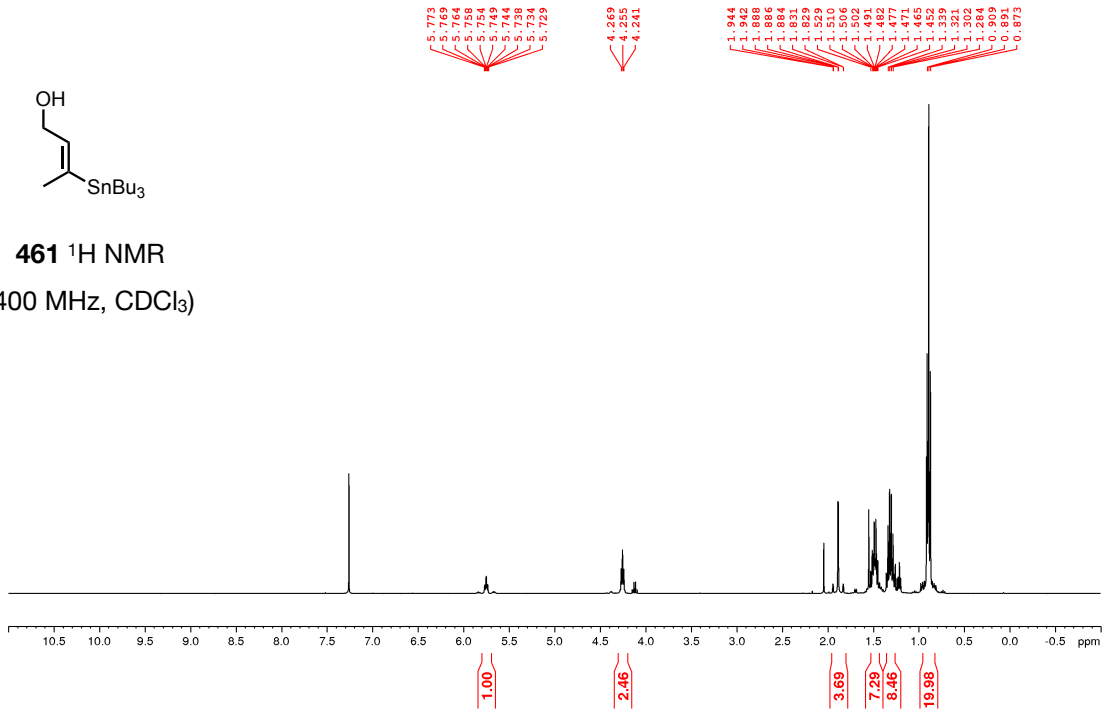

**459** $^{1}$H NMR

(400 MHz, $CDCl_3$)



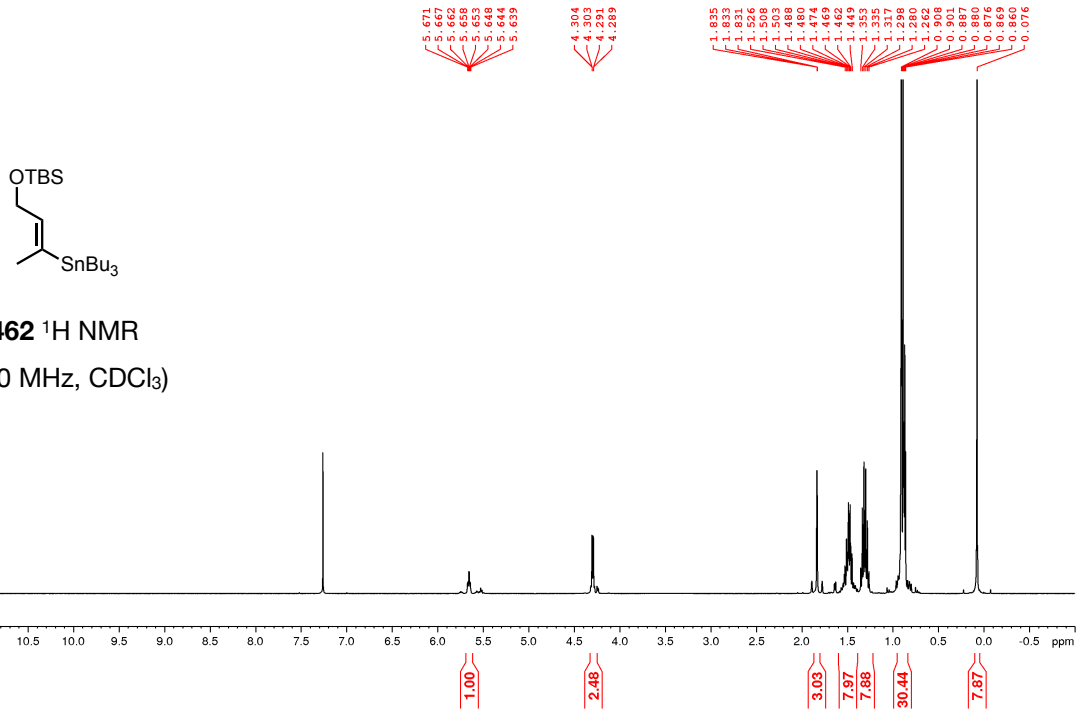

**460** $^1$H NMR

(400 MHz, $CDCl_3$)



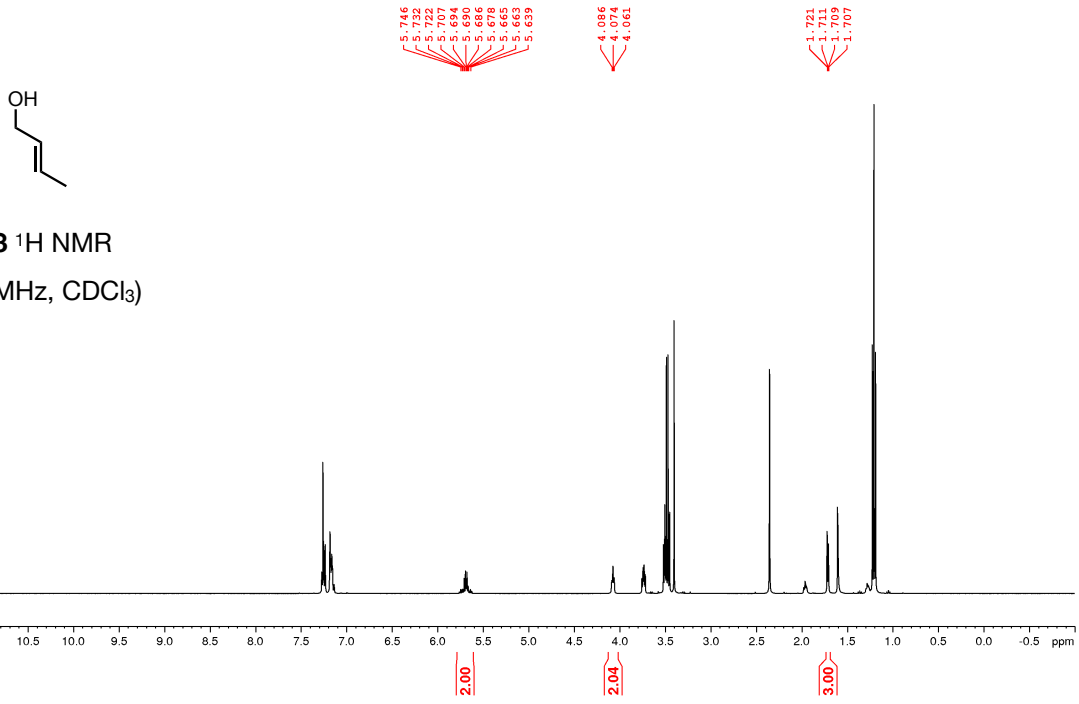

**461** $^1$H NMR

(400 MHz, $CDCl_3$)



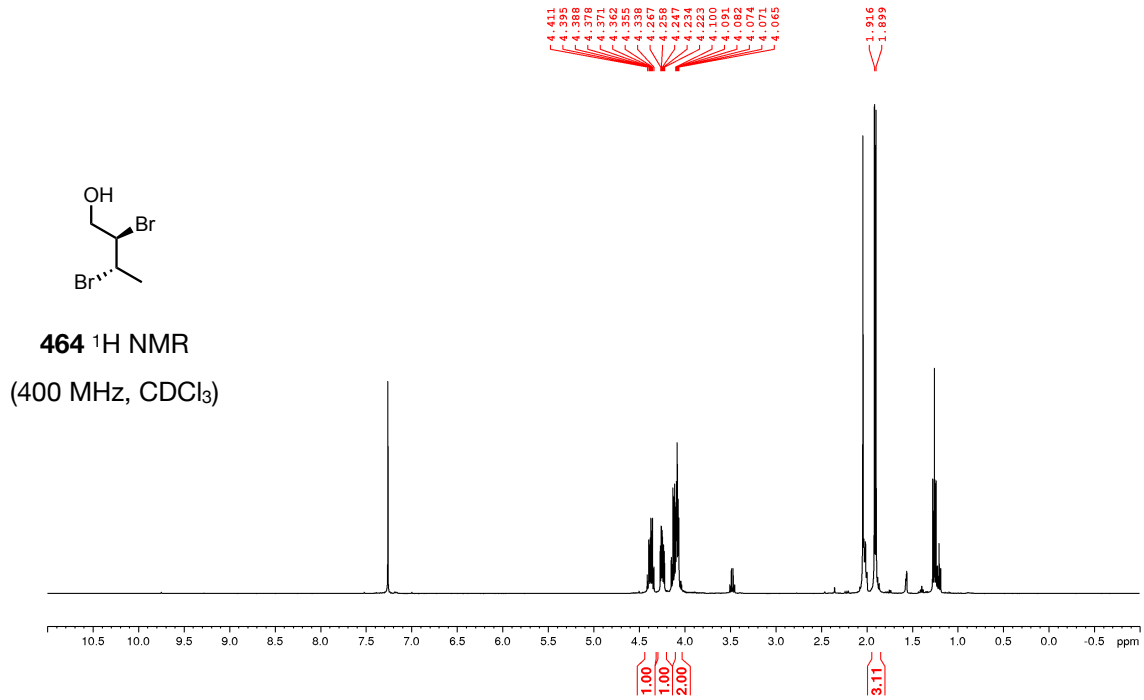

**462** $^{1}$H NMR

(400 MHz, $CDCl_3$)



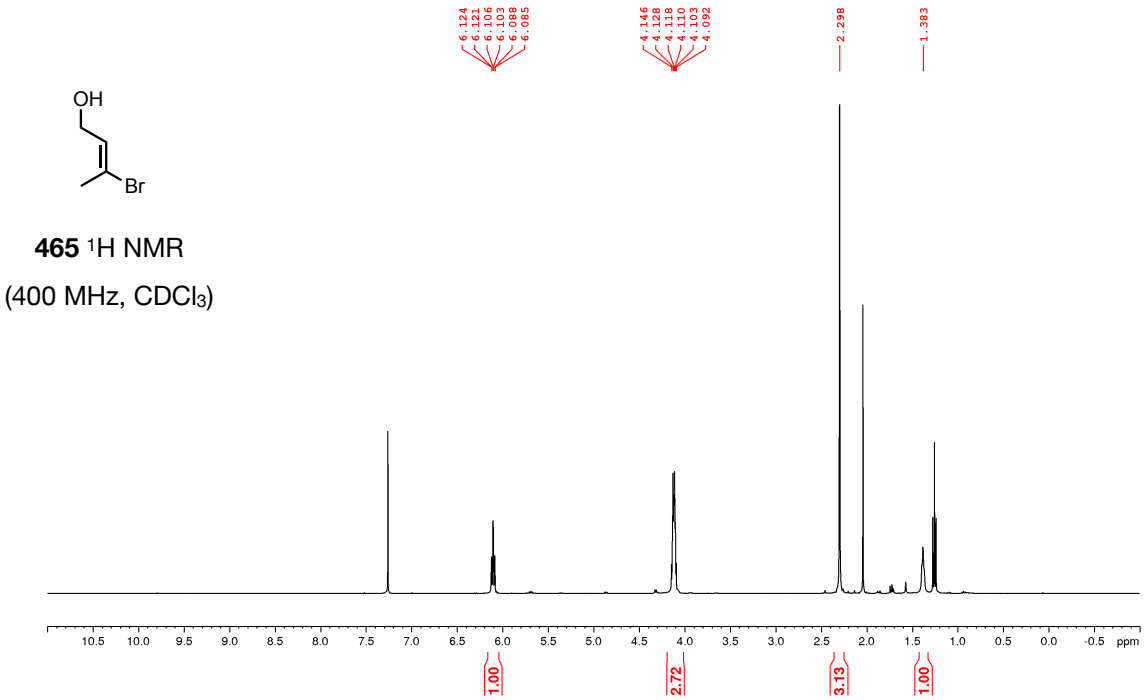

**463** $^{1}$H NMR

(400 MHz, $CDCl_3$)



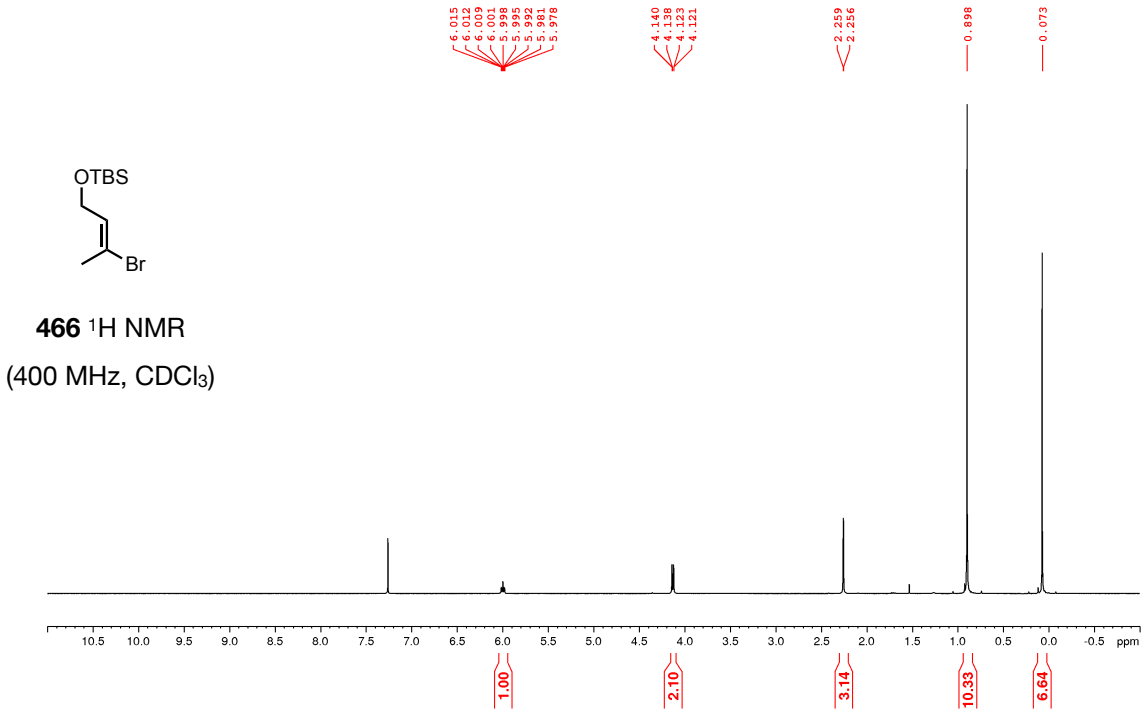

**464** $^{1}$H NMR

(400 MHz, $CDCl_3$)




**465** $^{1}$H NMR

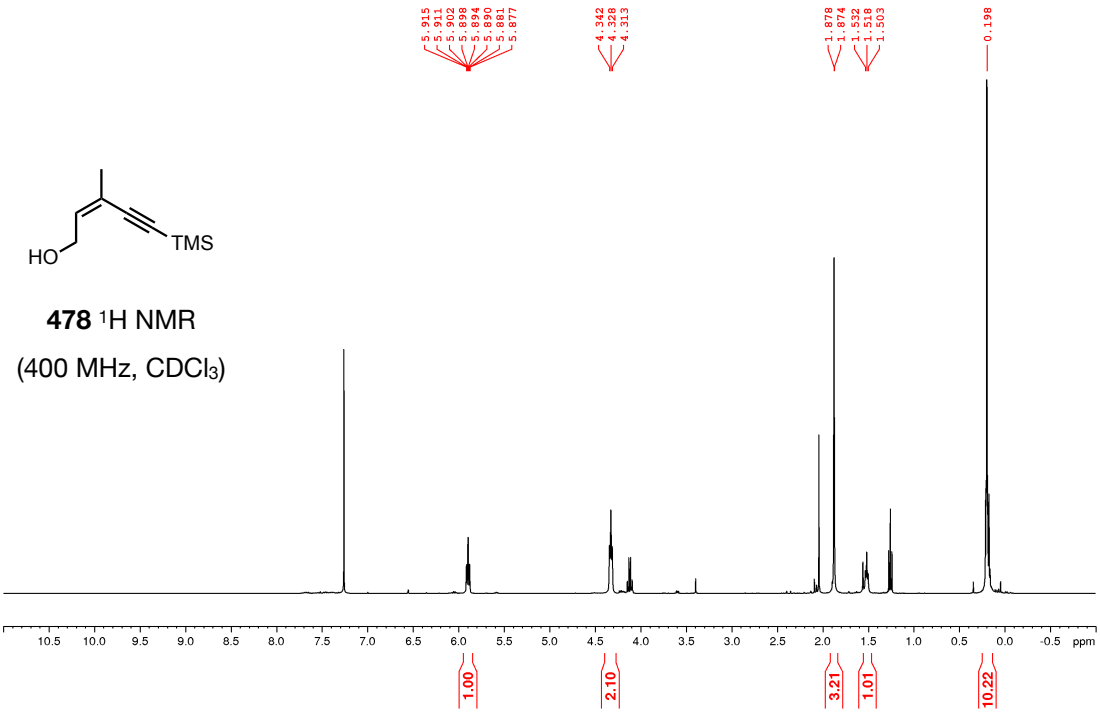
(400 MHz, $CDCl_3$)




**466** $^{1}$H NMR

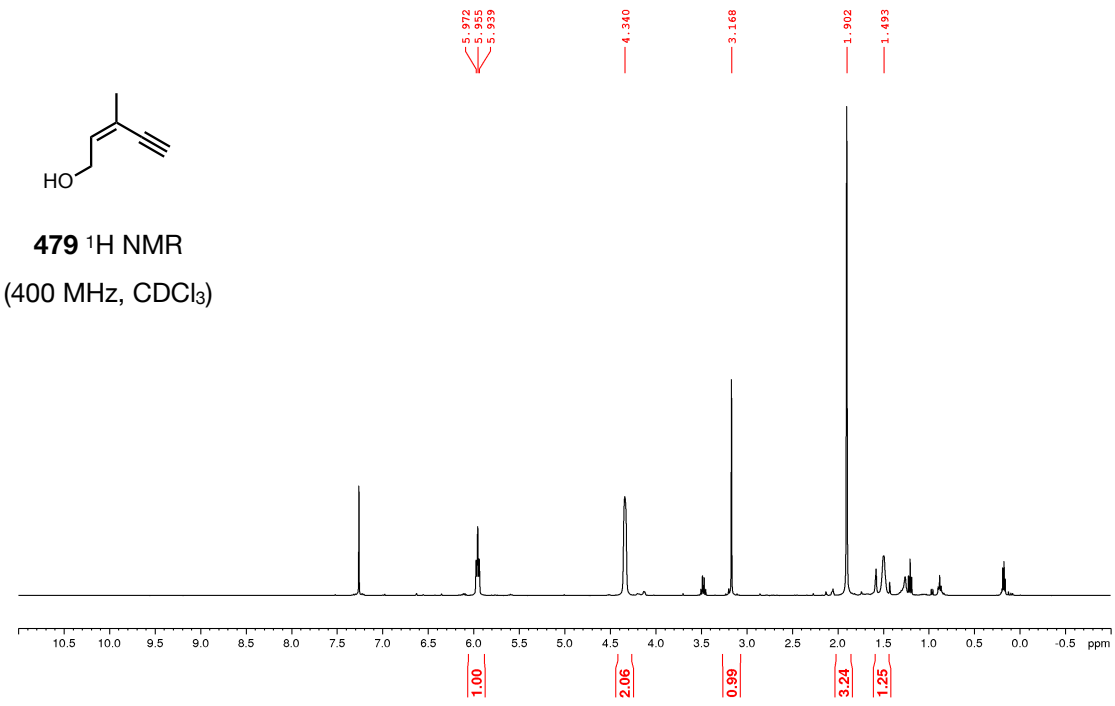
(400 MHz, $CDCl_3$)

**NMR Spectra: Section 4.1:**



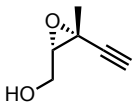

**478** $^{1}$H NMR

(400 MHz, $CDCl_3$)




**479** $^{1}$H NMR

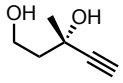
(400 MHz, $CDCl_3$)




**480** $^{1}$H NMR

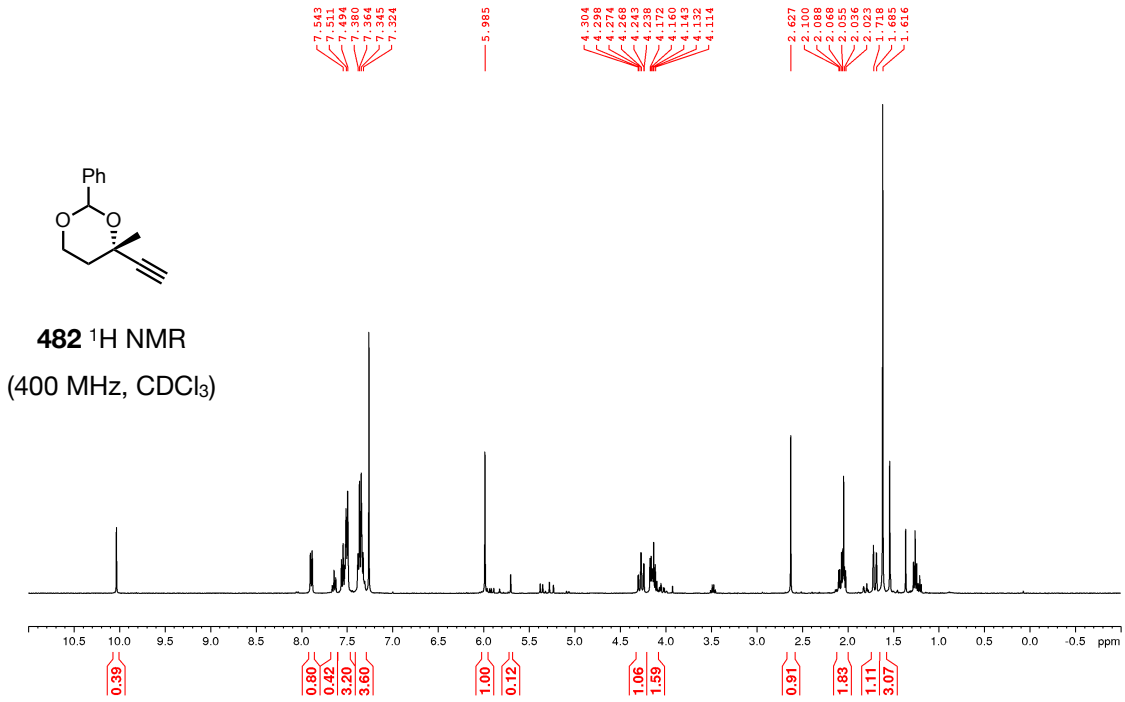
(400 MHz, $CDCl_3$)



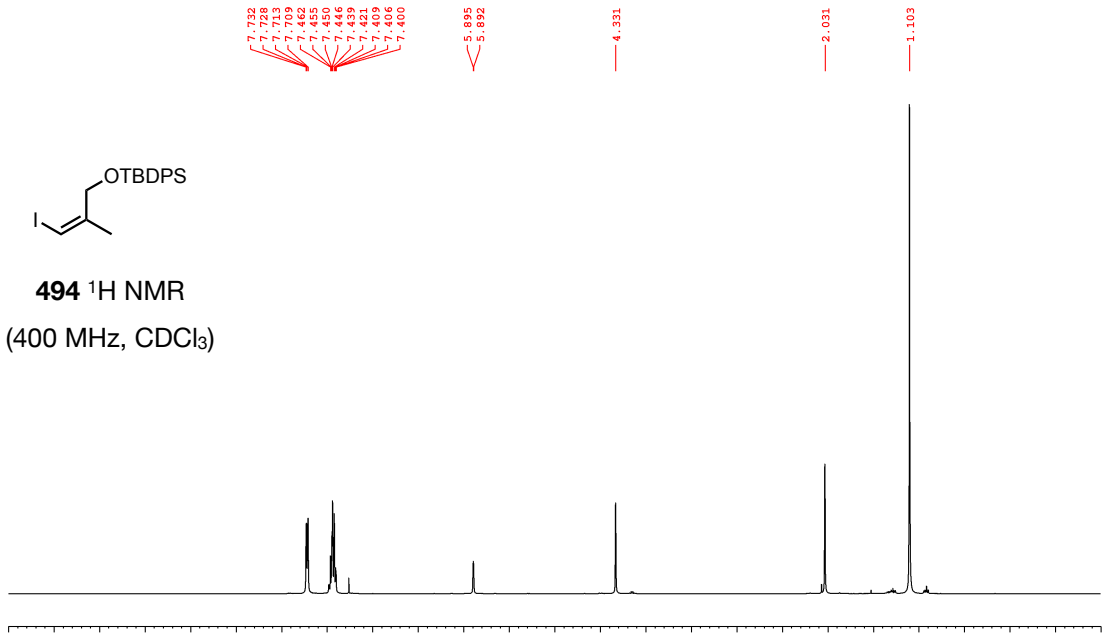




**481** $^{1}$H NMR

(400 MHz, $CDCl_3$)

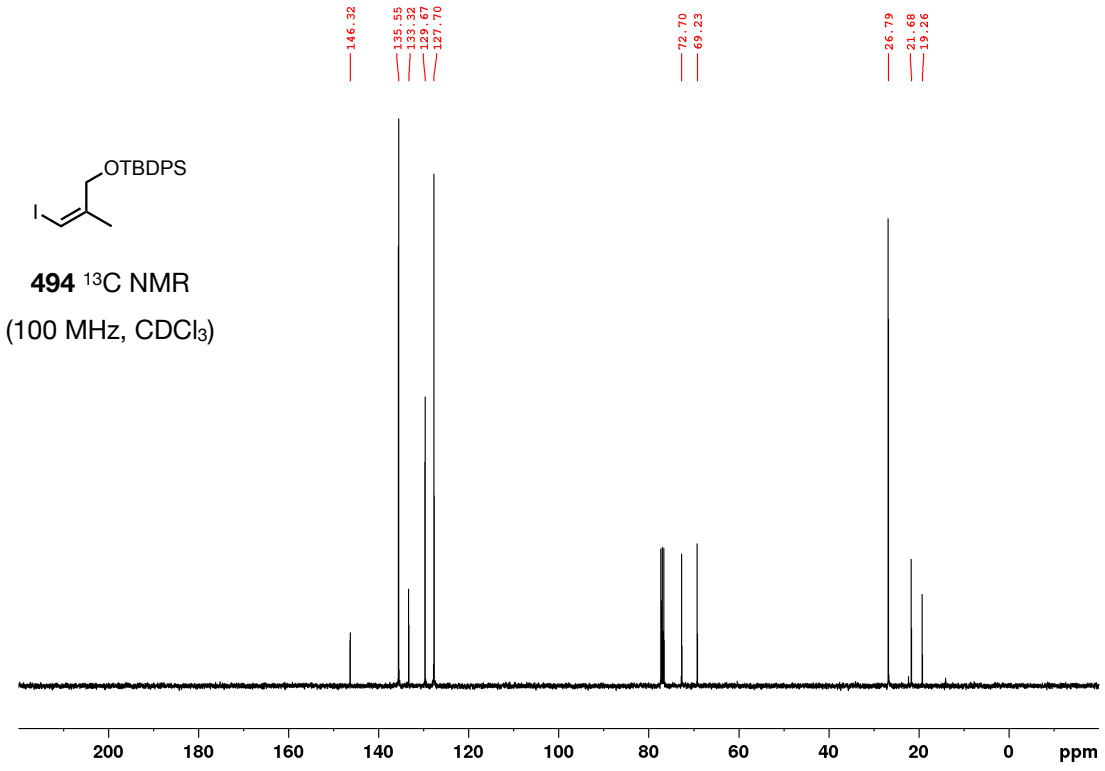

7.543
7.511
7.494
7.380
7.364
7.345
7.324
5.985
4.304
4.298
4.274
4.268
4.243
4.238
4.172
4.160
4.143
4.132
4.114
2.627
2.100
2.088
2.068
2.055
2.036
2.023
1.718
1.685
1.616
Ph
O
O
482 1H NMR
(400 MHz, CDCl3)
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
0.39
0.80
0.42
3.20
3.60
1.00
0.12
1.06
1.59
0.91
1.83
1.11
3.07

**NMR Spectra: Section 4.2:**



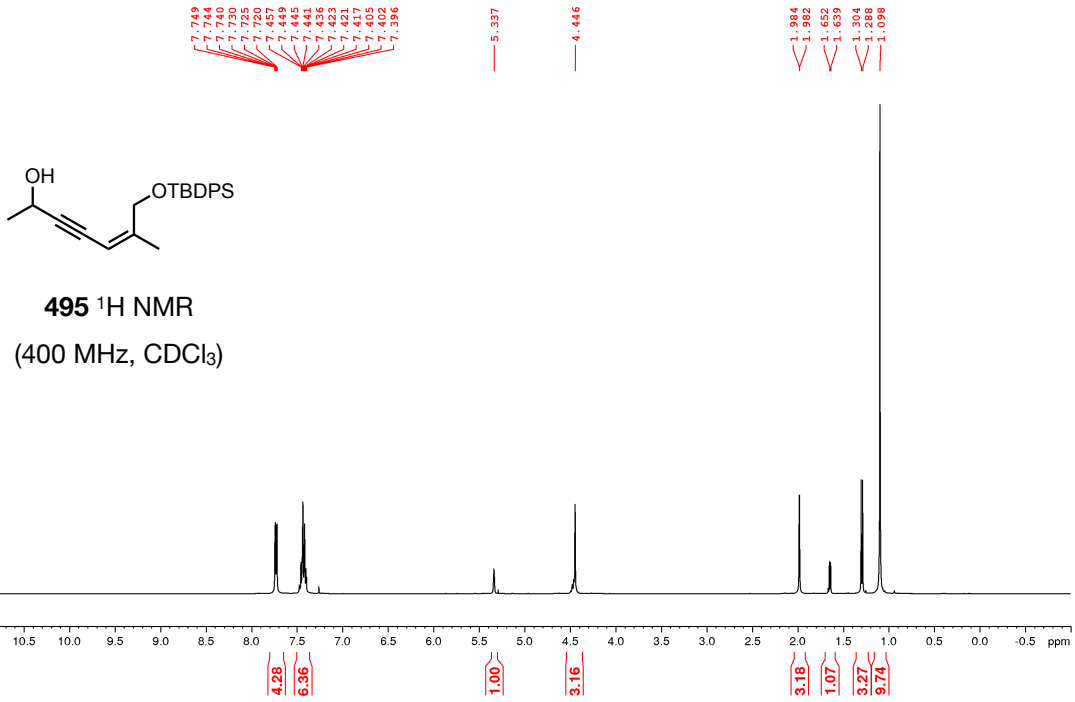

**494** $^{1}$H NMR

(400 MHz, $CDCl_3$)



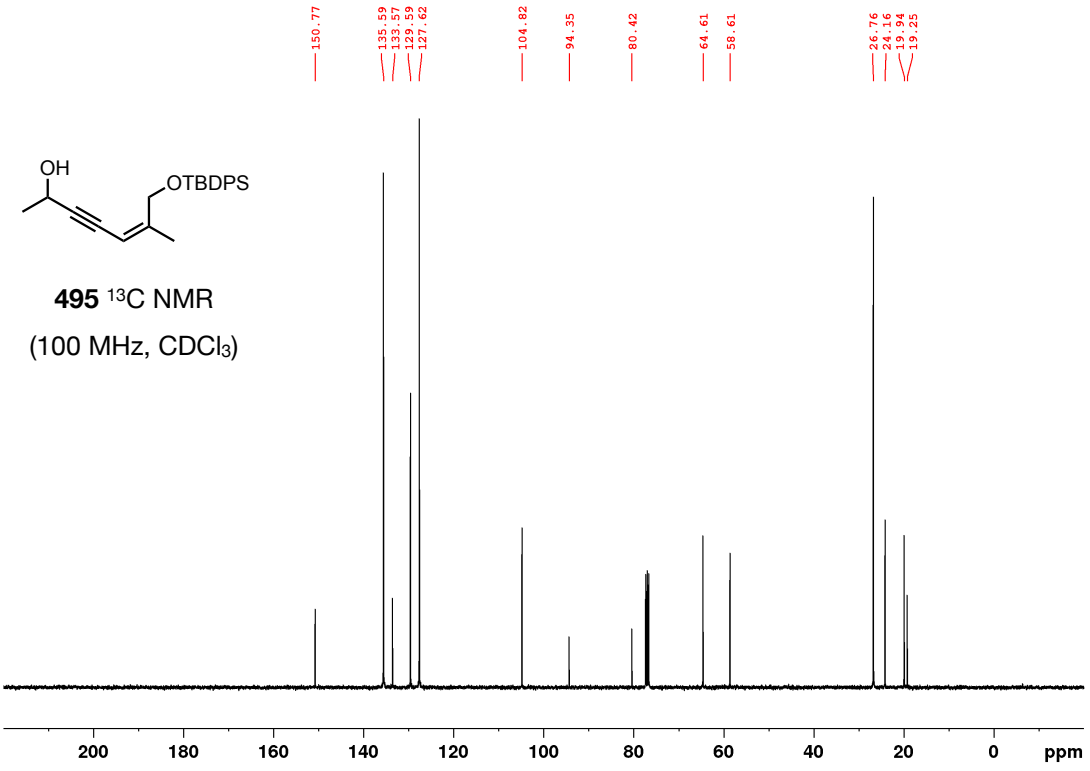

**494** $^{13}$C NMR

(100 MHz, $CDCl_3$)



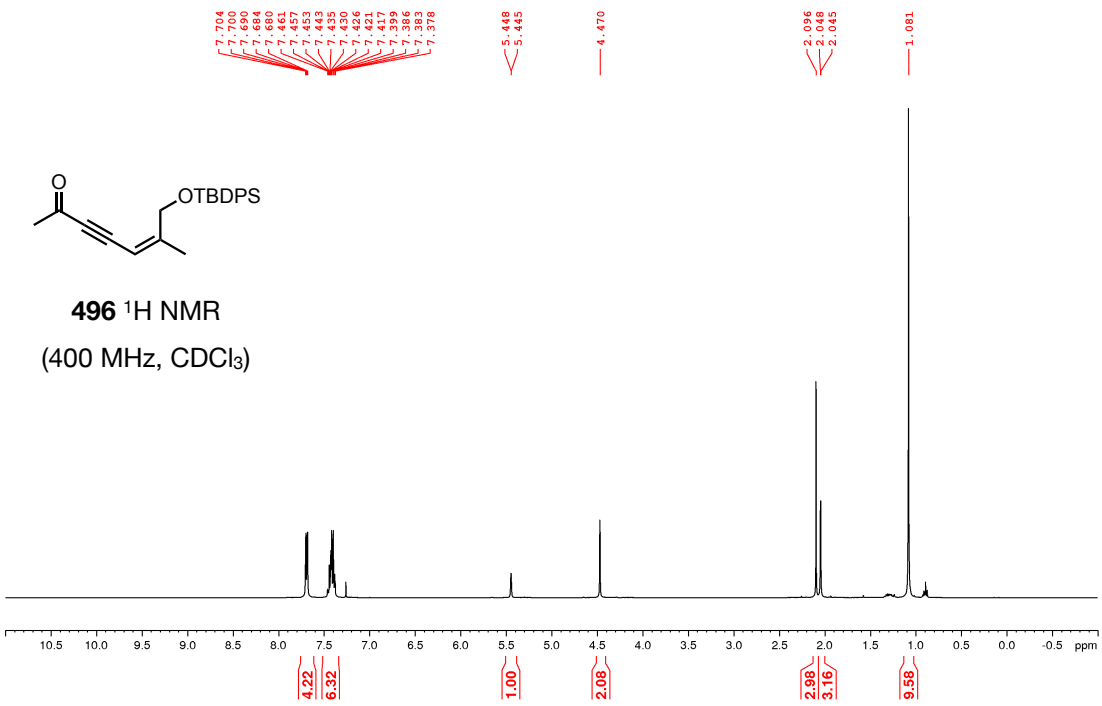

**495** $^{1}$H NMR

(400 MHz, $CDCl_3$)



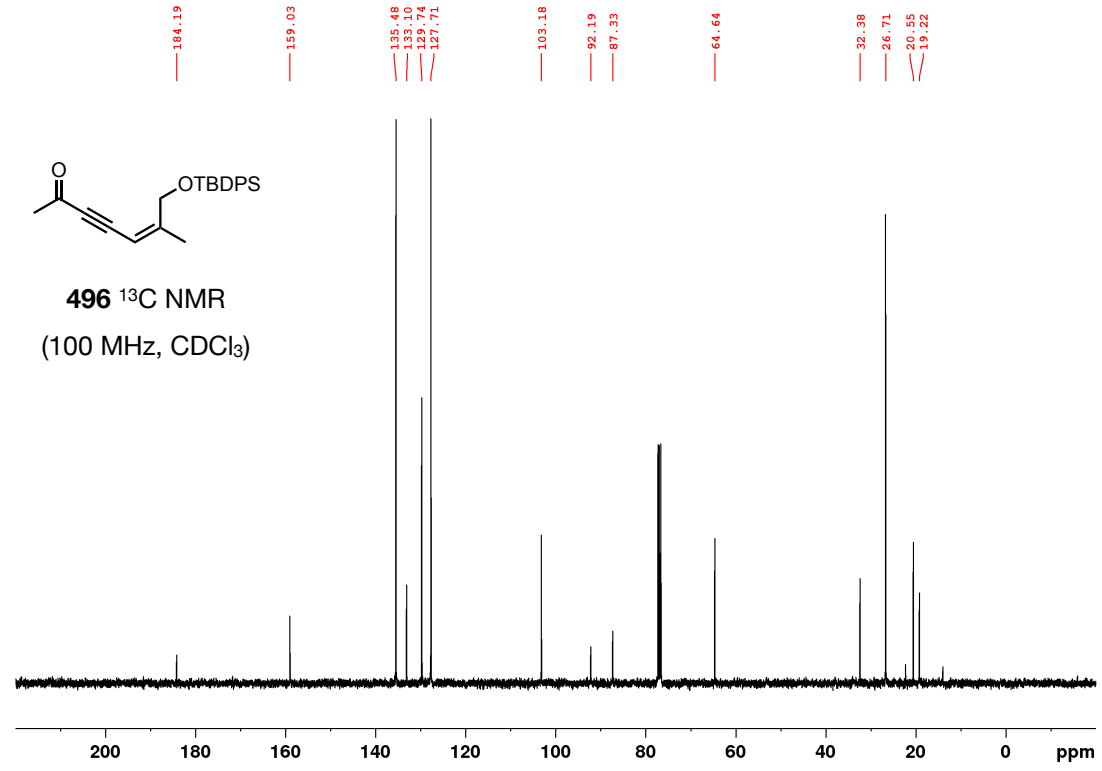

**495** $^{13}$C NMR

(100 MHz, $CDCl_3$)



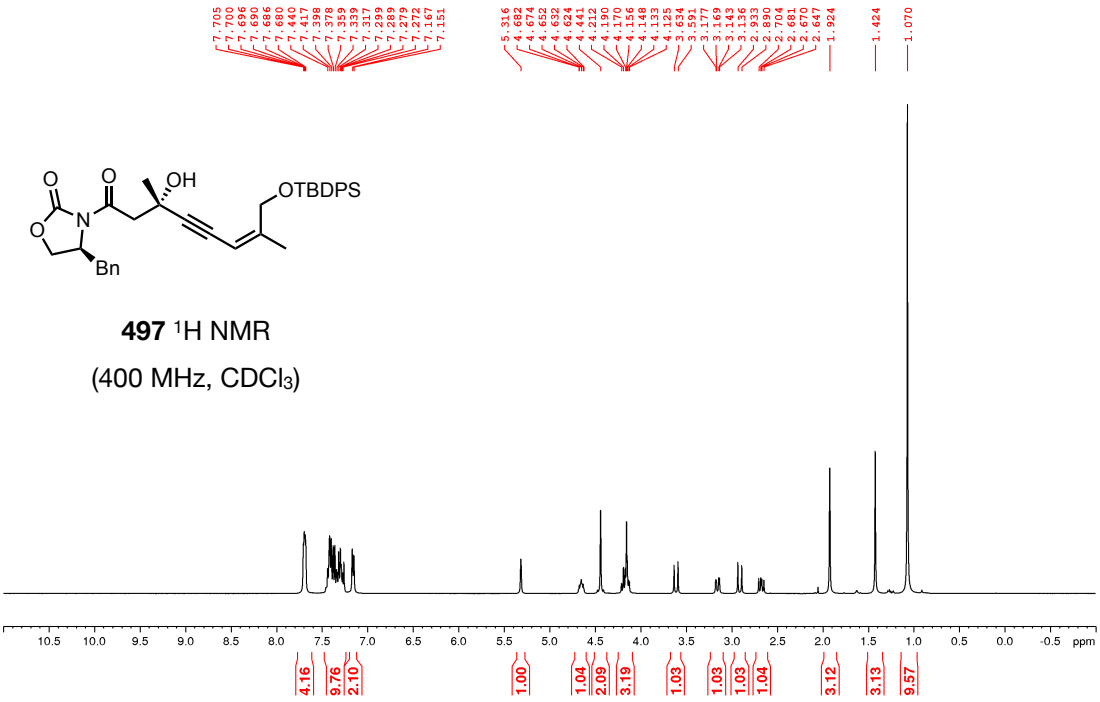

**496** $^{1}$H NMR

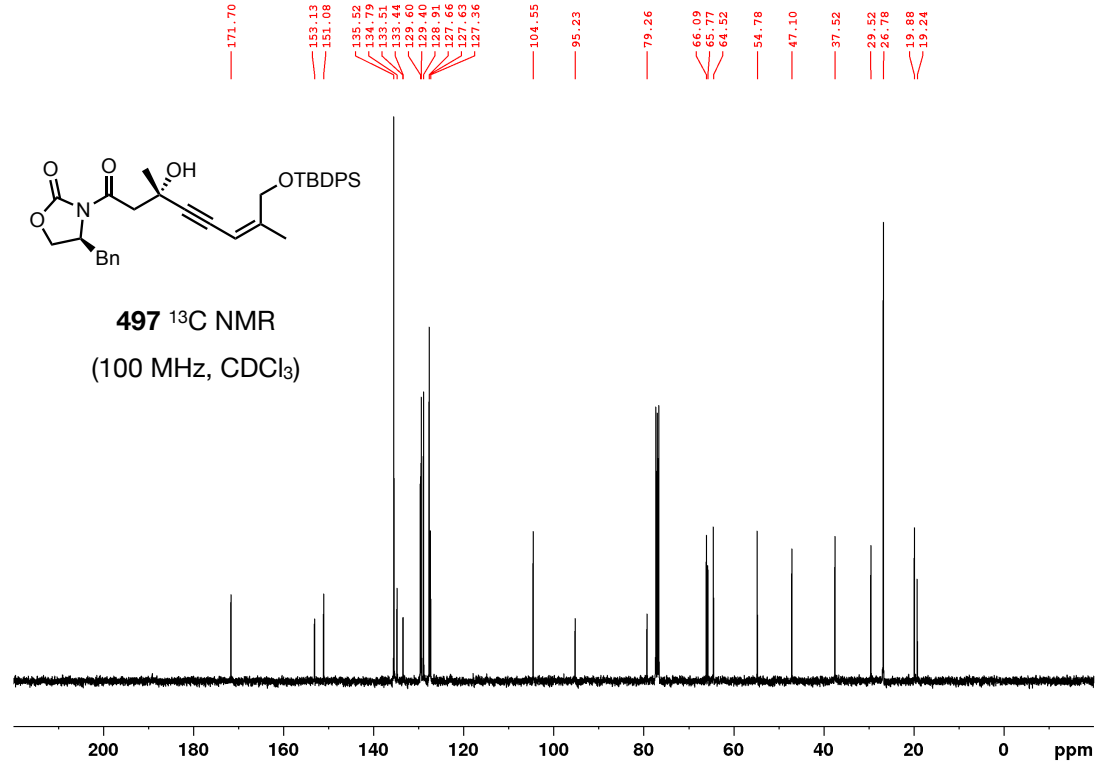
(400 MHz, $CDCl_3$)

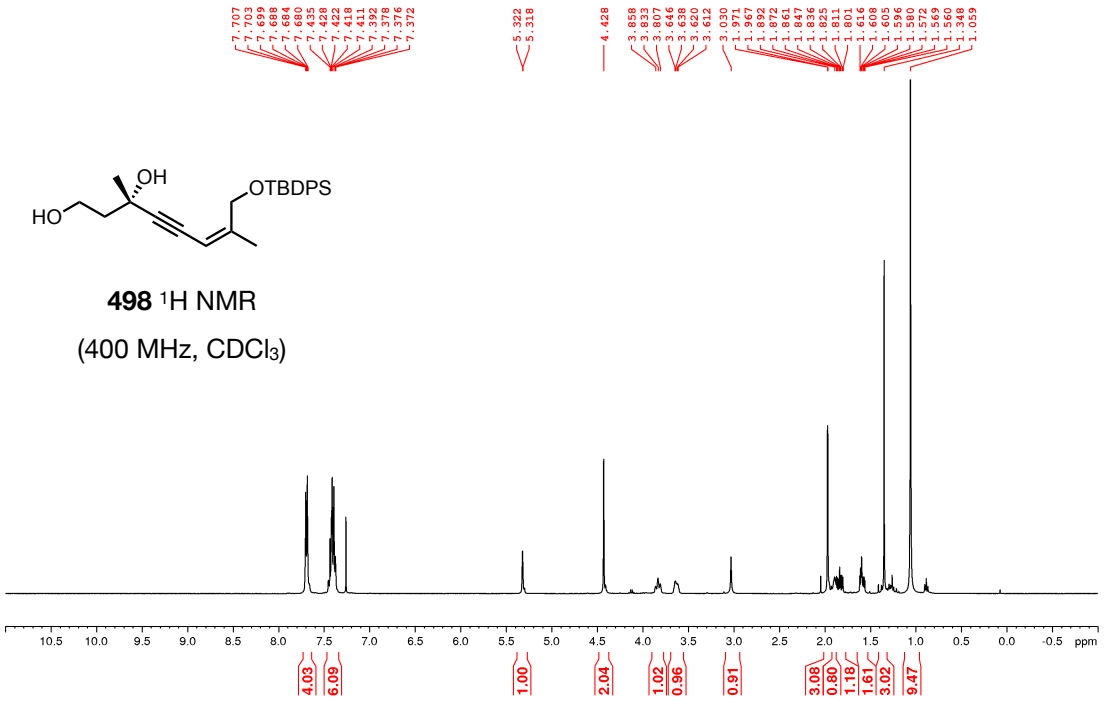



**496** $^{13}$C NMR

(100 MHz, $CDCl_3$)

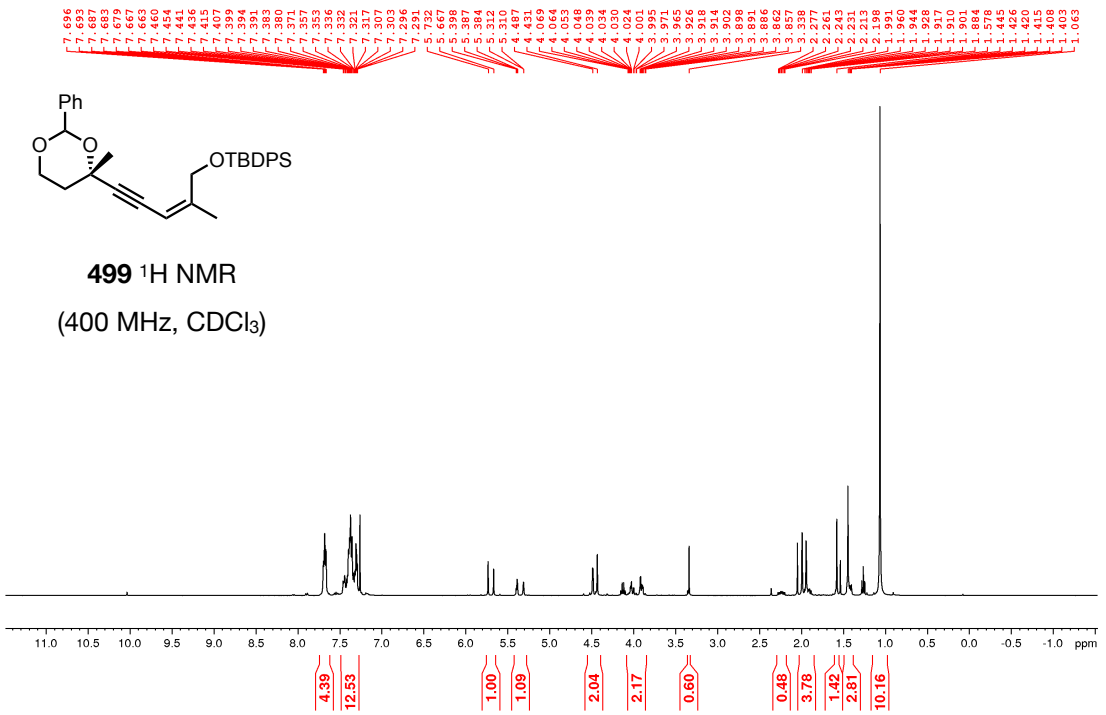

OTBDPS
OH
Bn
497 1H NMR
(400 MHz, CDCl3)
ppm


OTBDPS
OH
Bn
497 13C NMR
(100 MHz, CDCl3)
ppm



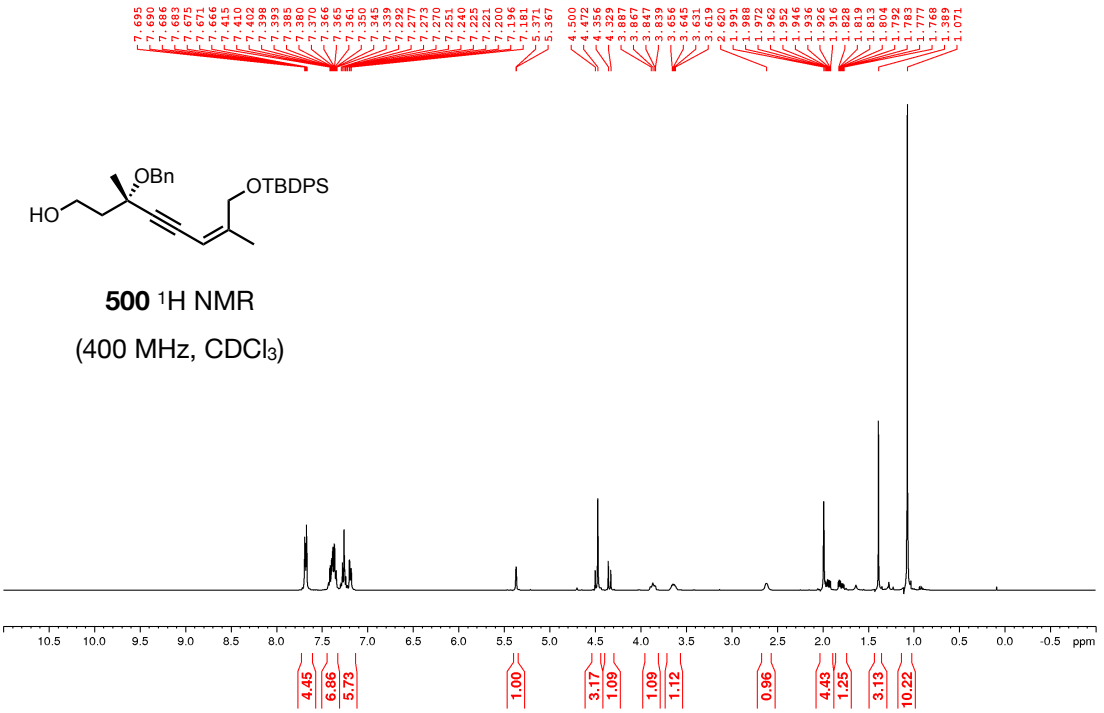

**498** $^{1}$H NMR

(400 MHz, $CDCl_3$)



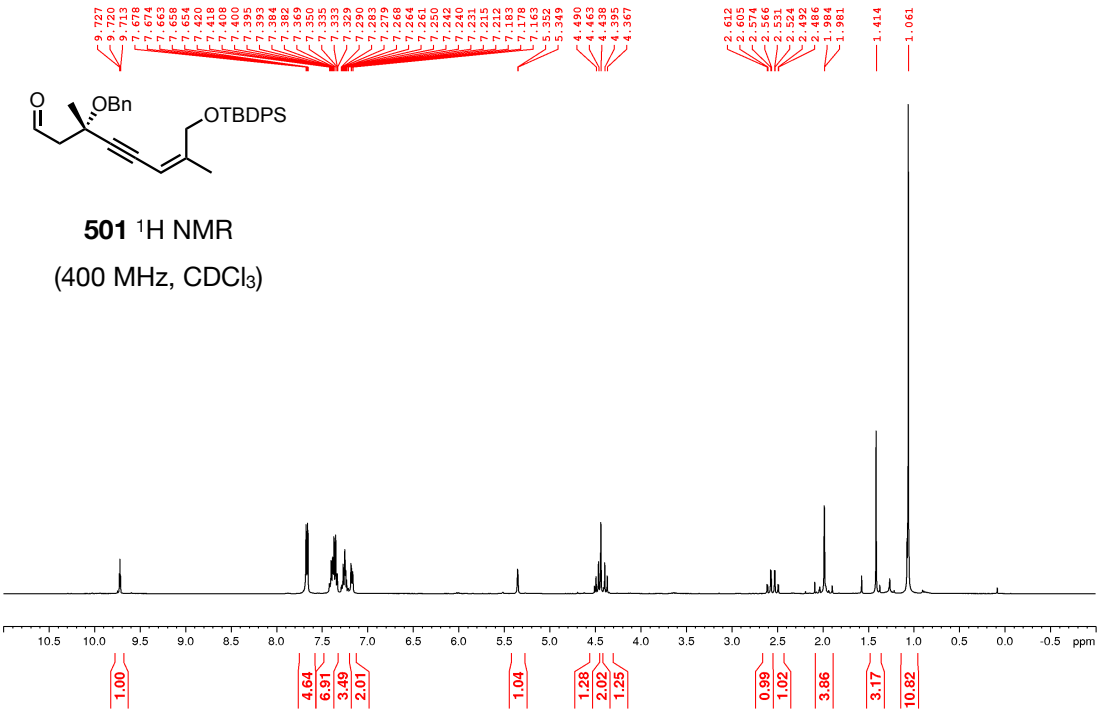

**499** $^{1}$H NMR

(400 MHz, $CDCl_3$)



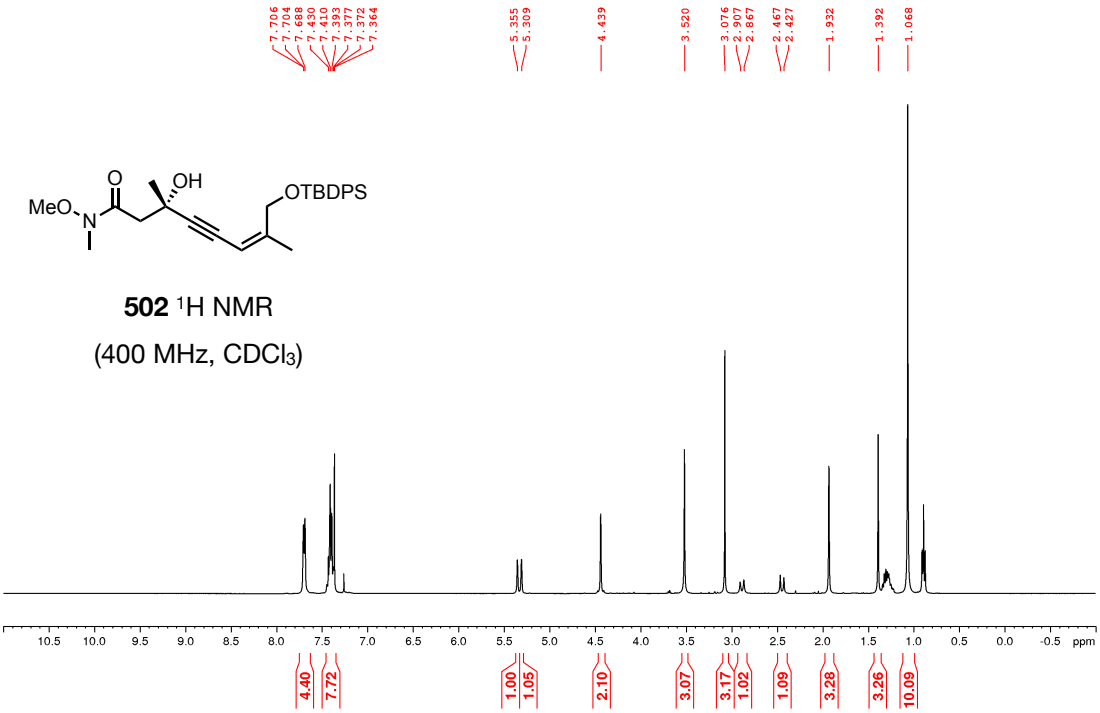

**500** $^1$H NMR

(400 MHz, $CDCl_3$)



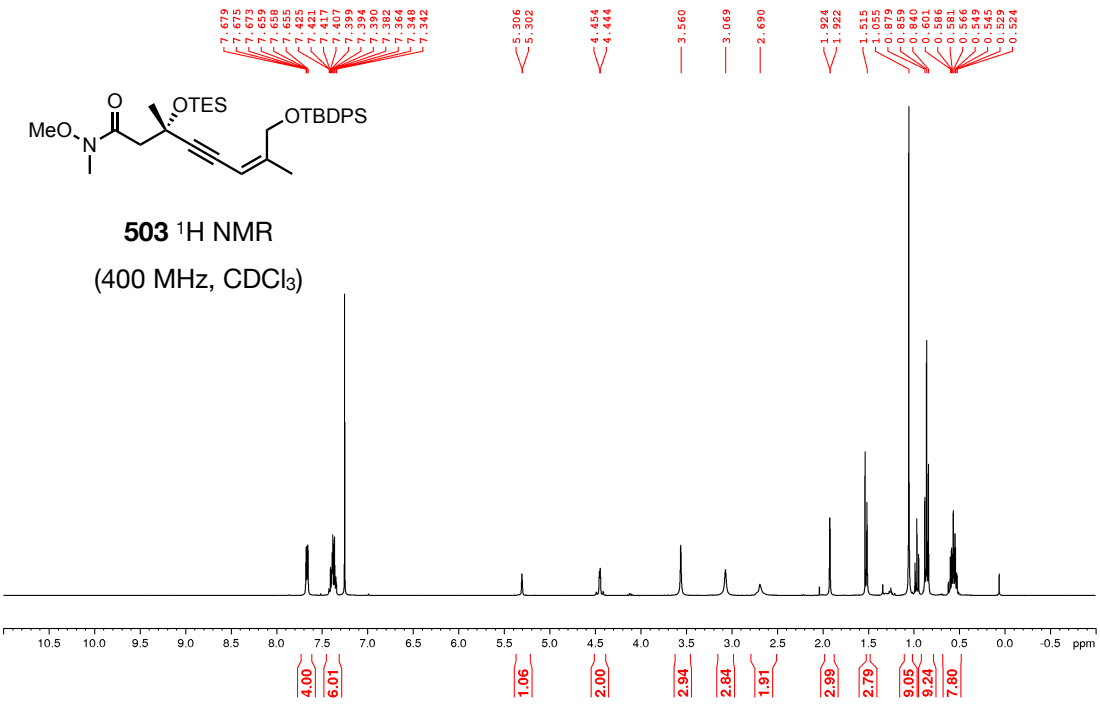

**501** $^1$H NMR

(400 MHz, $CDCl_3$)



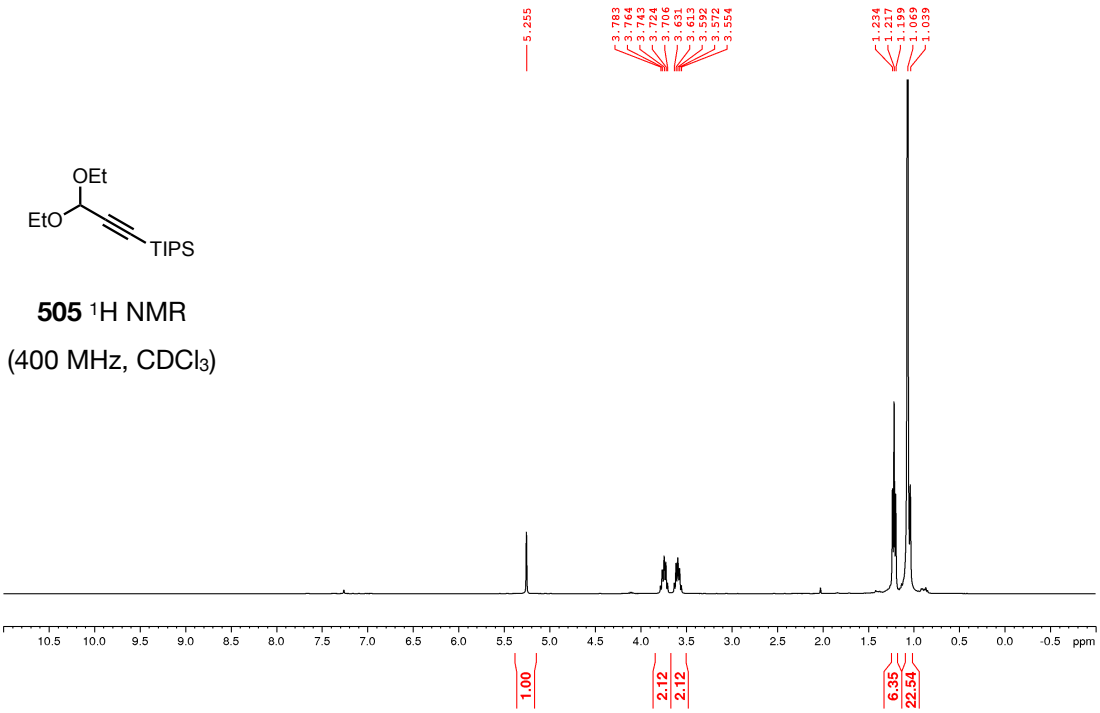

**502** $^{1}$H NMR

(400 MHz, $CDCl_3$)



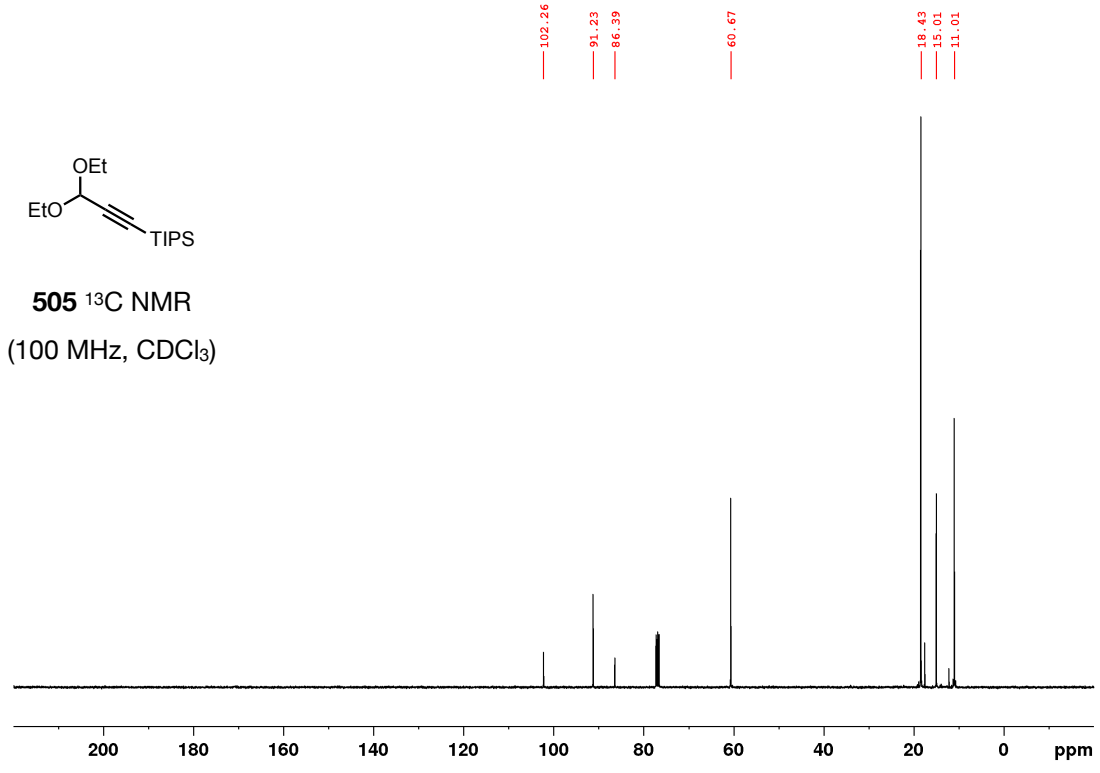

**503** $^{1}$H NMR

(400 MHz, $CDCl_3$)



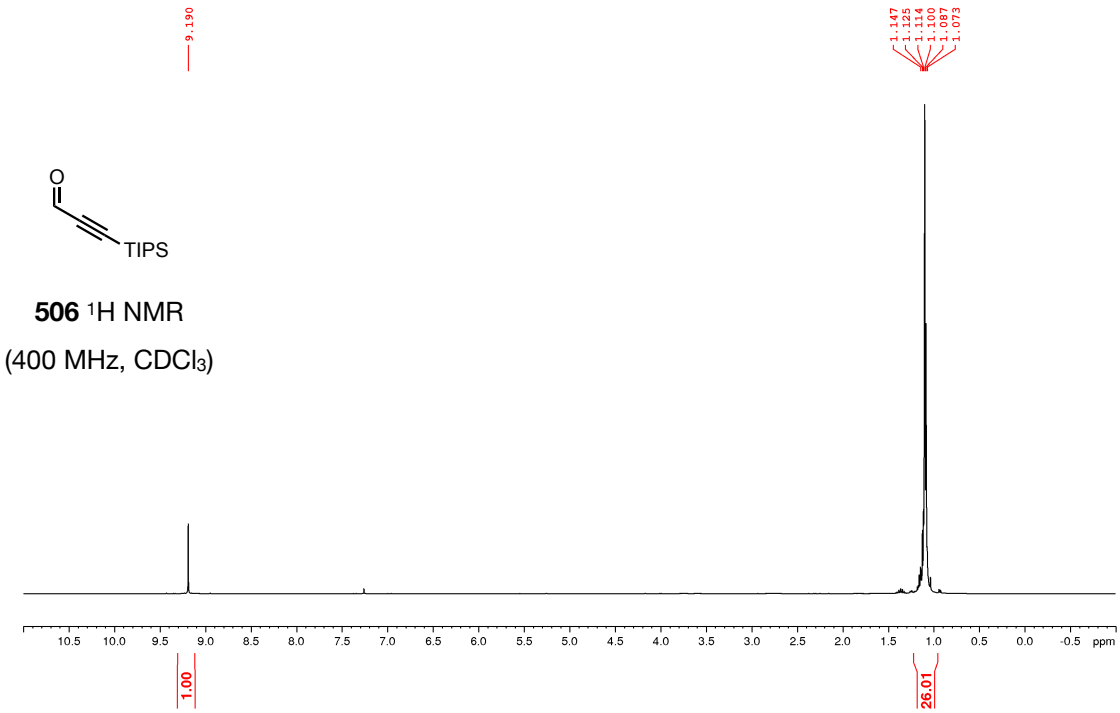

**505** $^{1}$H NMR

(400 MHz, $CDCl_3$)



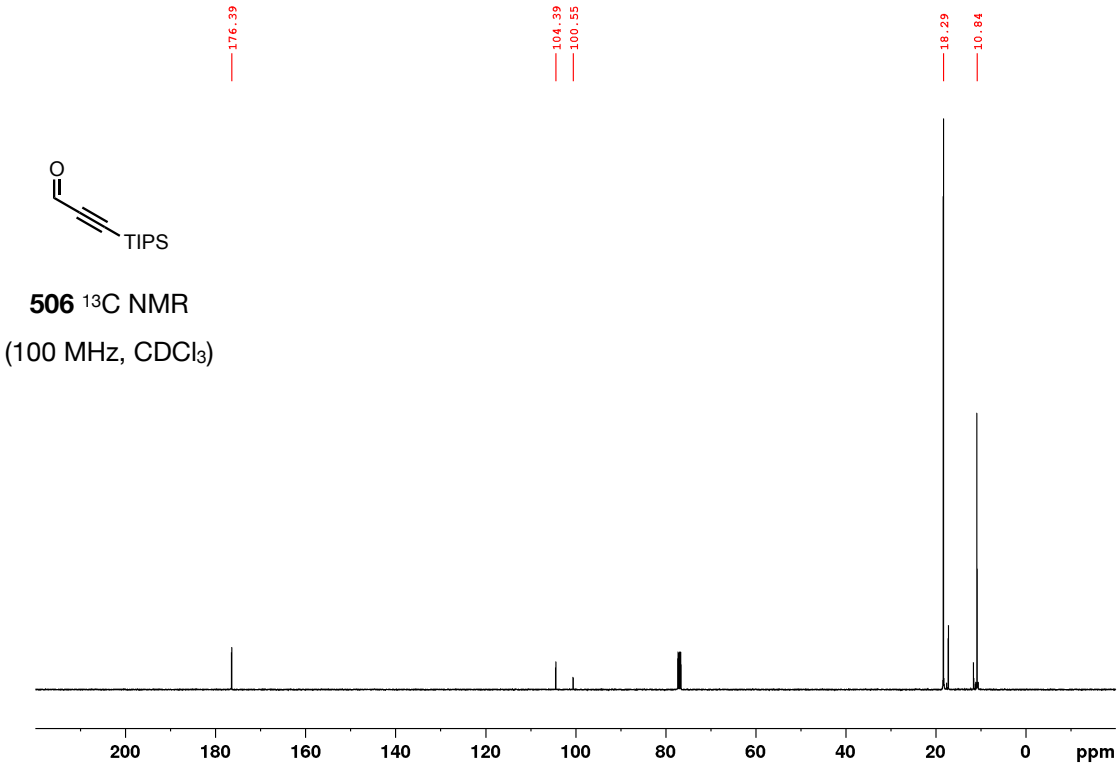

**505** $^{13}$C NMR

(100 MHz, $CDCl_3$)



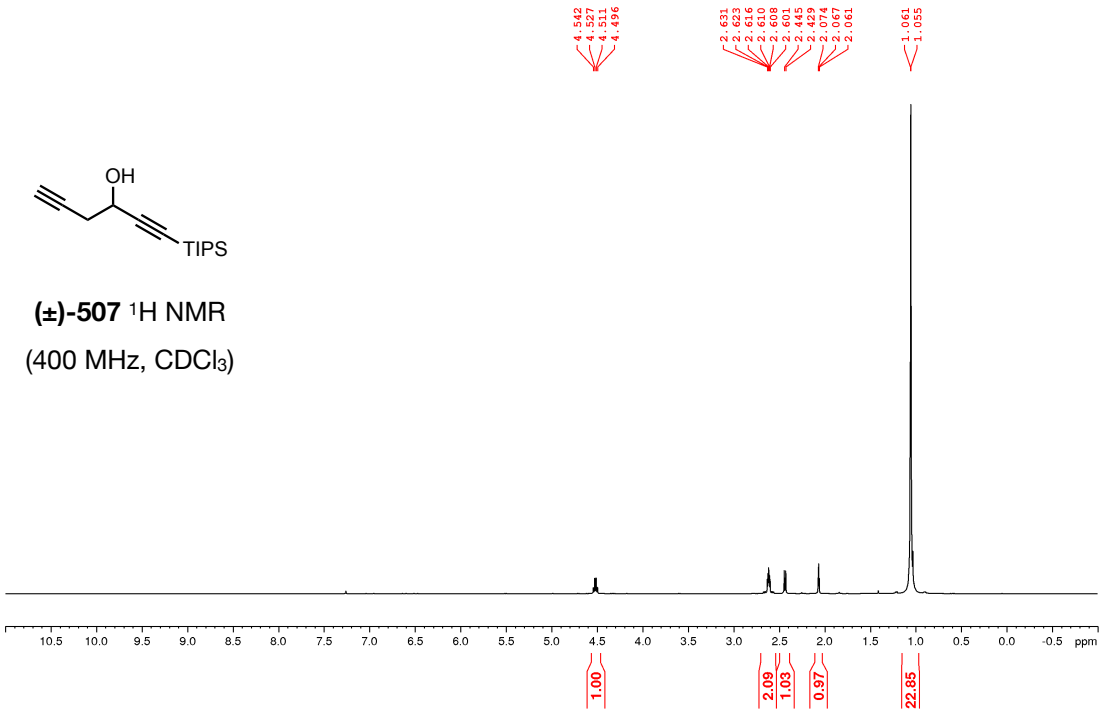

**506** $^{1}$H NMR

(400 MHz, $CDCl_3$)



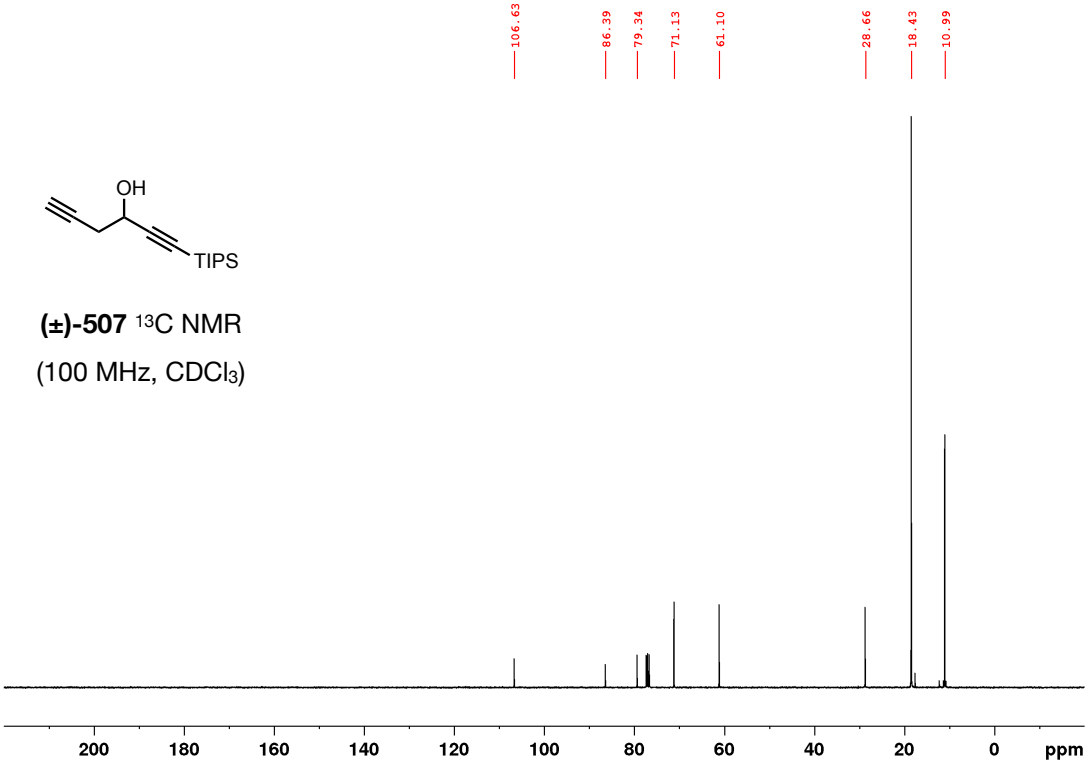

**506** $^{13}$C NMR

(100 MHz, $CDCl_3$)



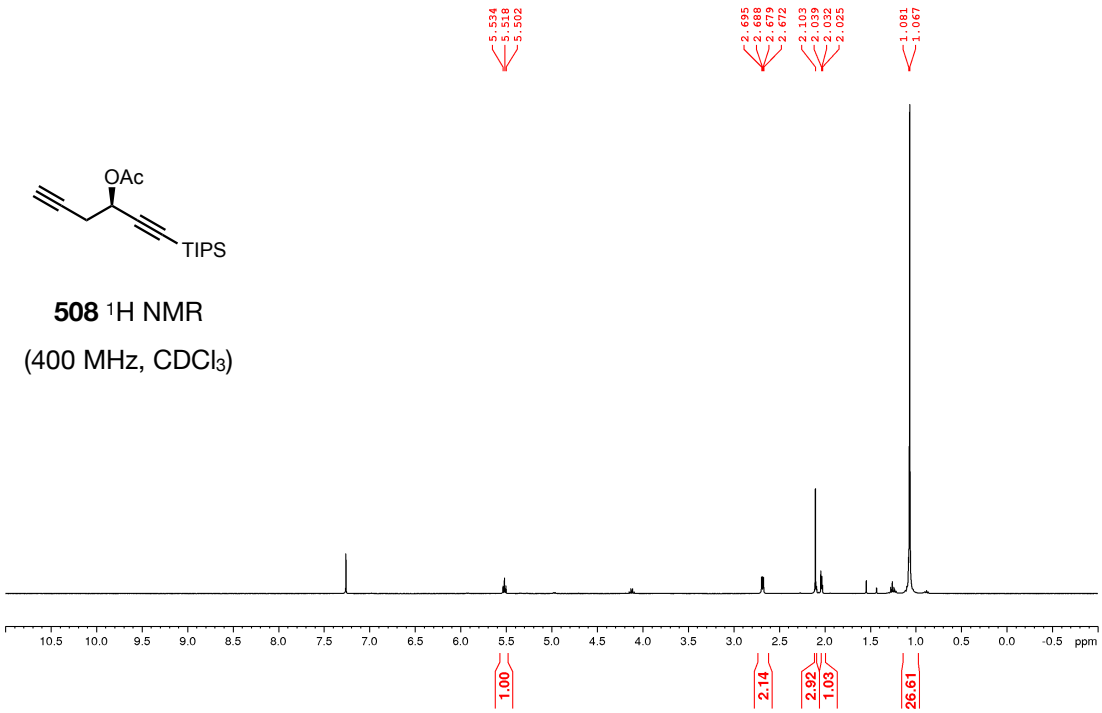

**(±)-507** $^{1}$H NMR

(400 MHz, $CDCl_3$)



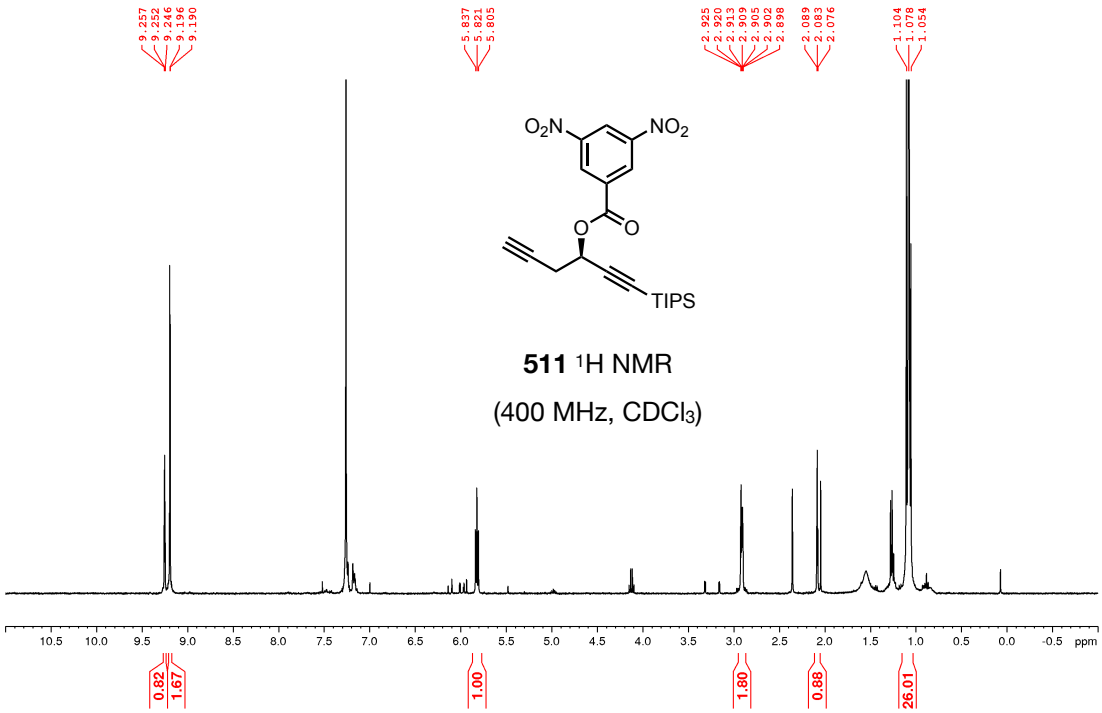

**(±)-507** $^{13}$C NMR

(100 MHz, $CDCl_3$)



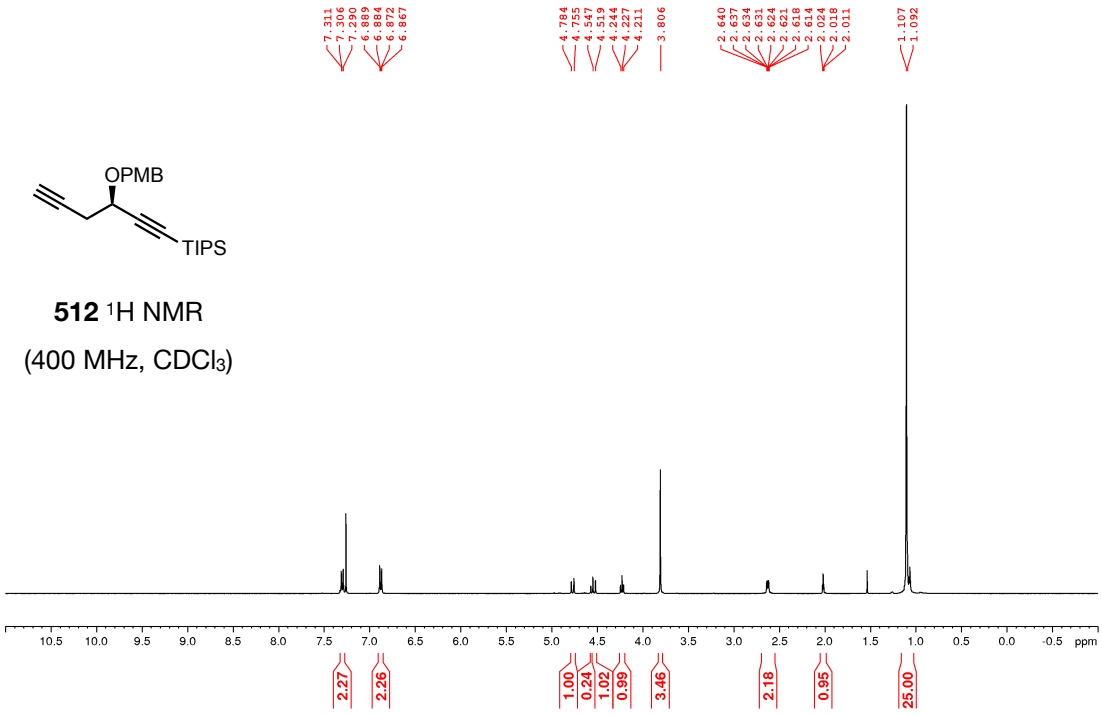

**508** $^{1}$H NMR

(400 MHz, $CDCl_3$)



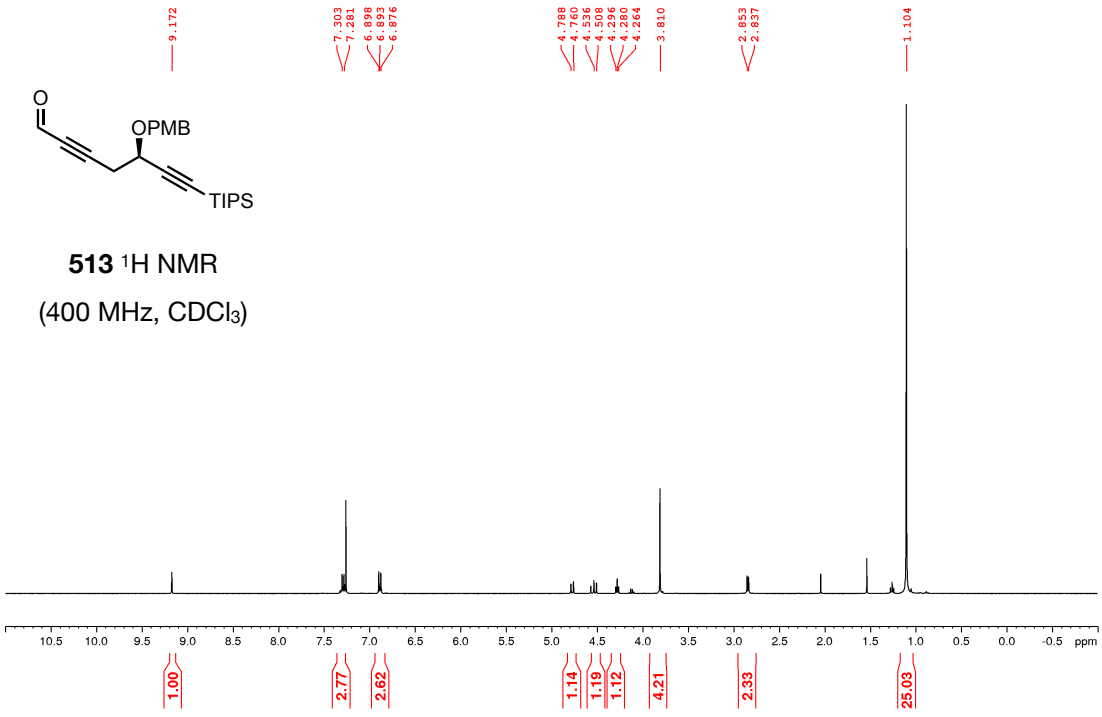

**511** $^{1}$H NMR

(400 MHz, $CDCl_3$)



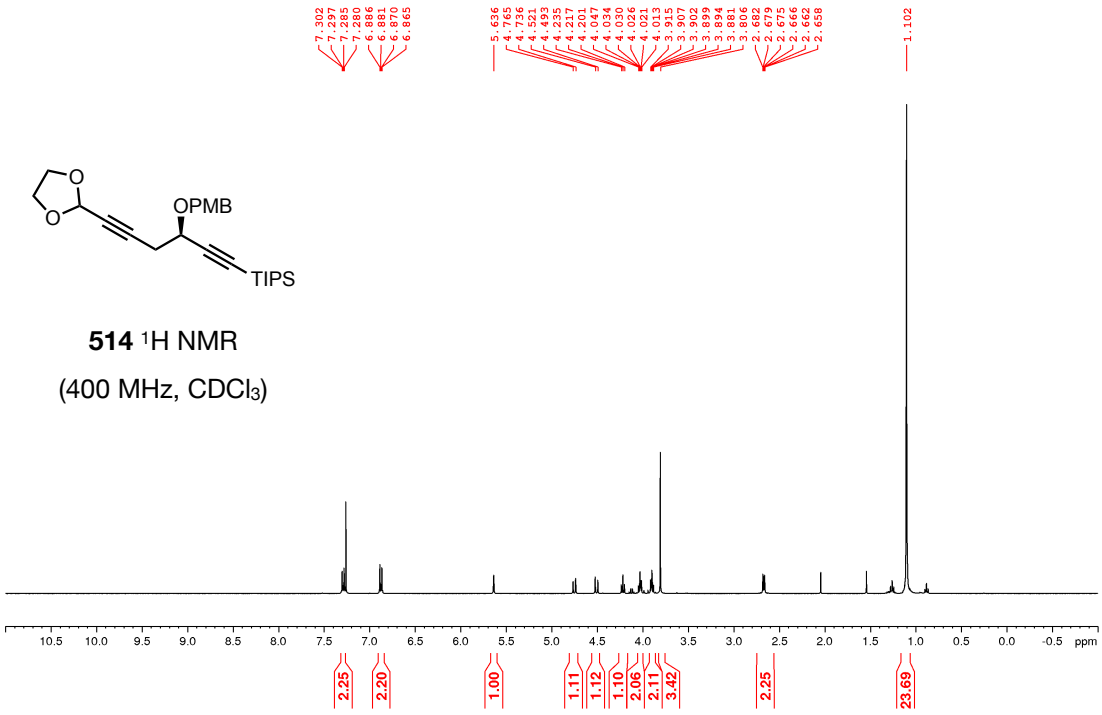

**512** $^{1}$H NMR

(400 MHz, $CDCl_3$)



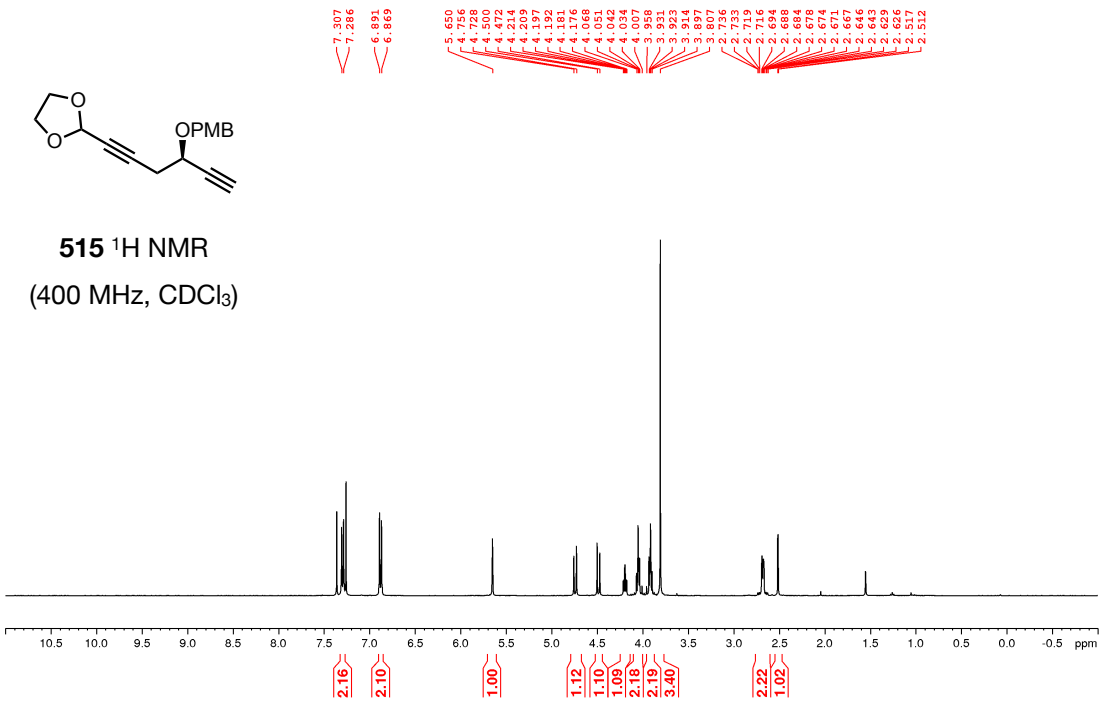

**513** $^{1}$H NMR

(400 MHz, $CDCl_3$)



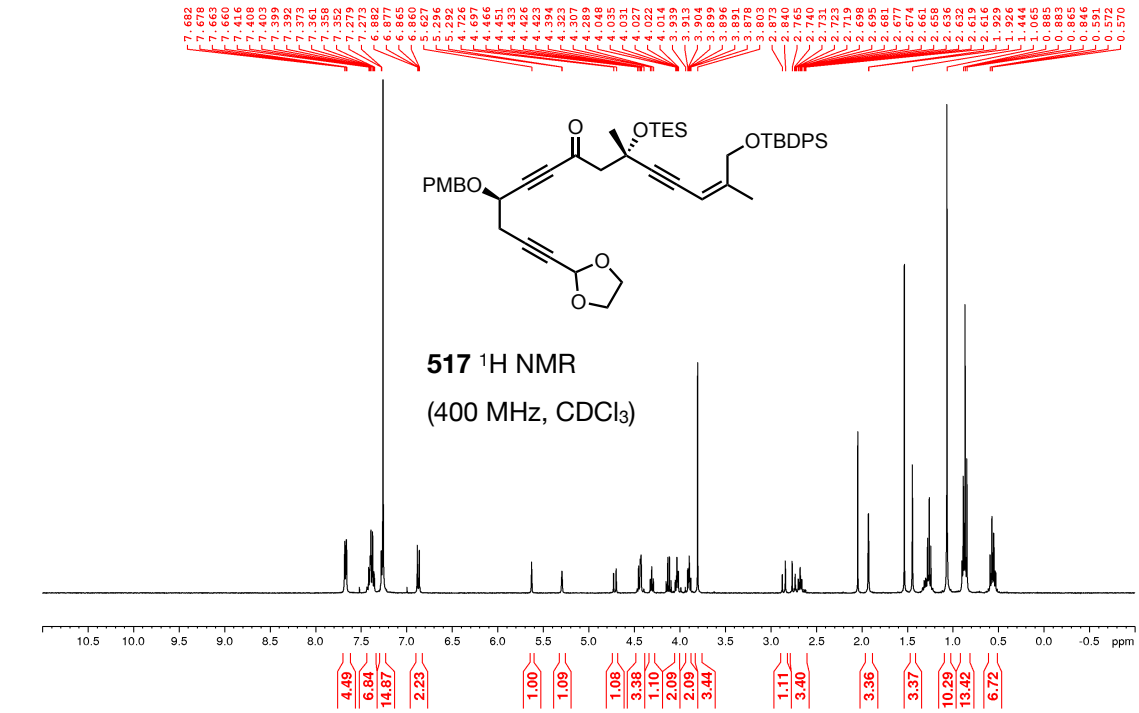

**514** $^{1}$H NMR

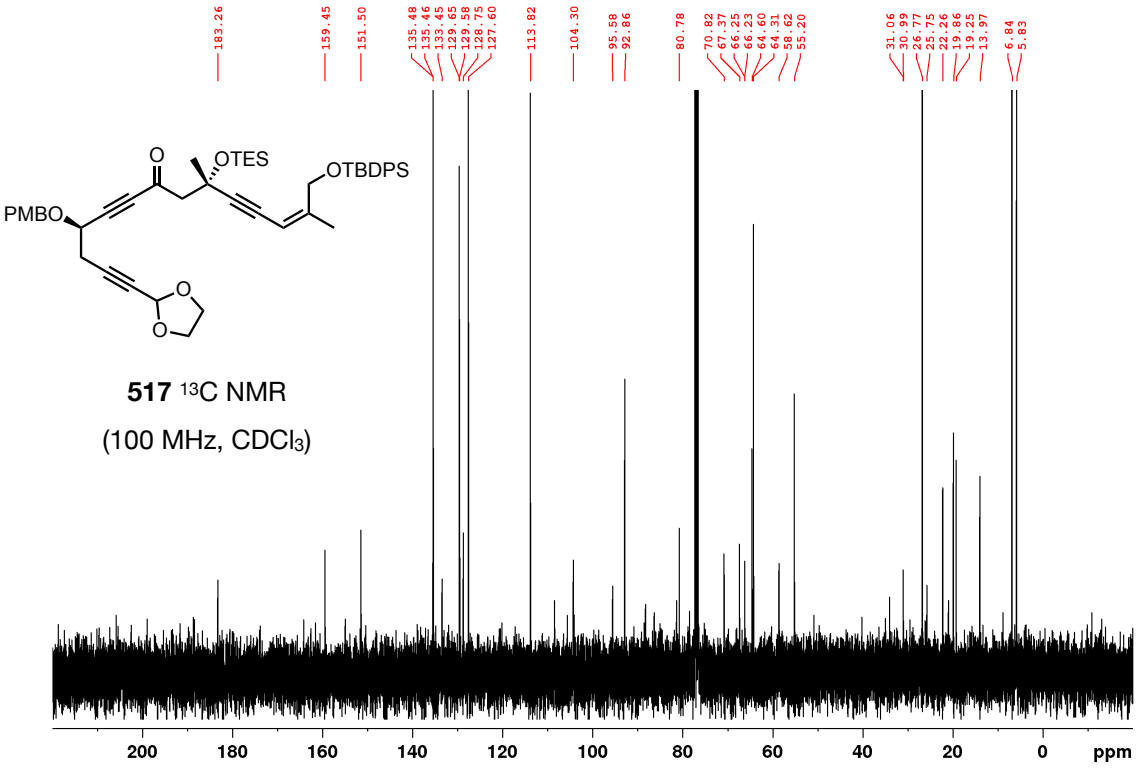
(400 MHz, $CDCl_3$)

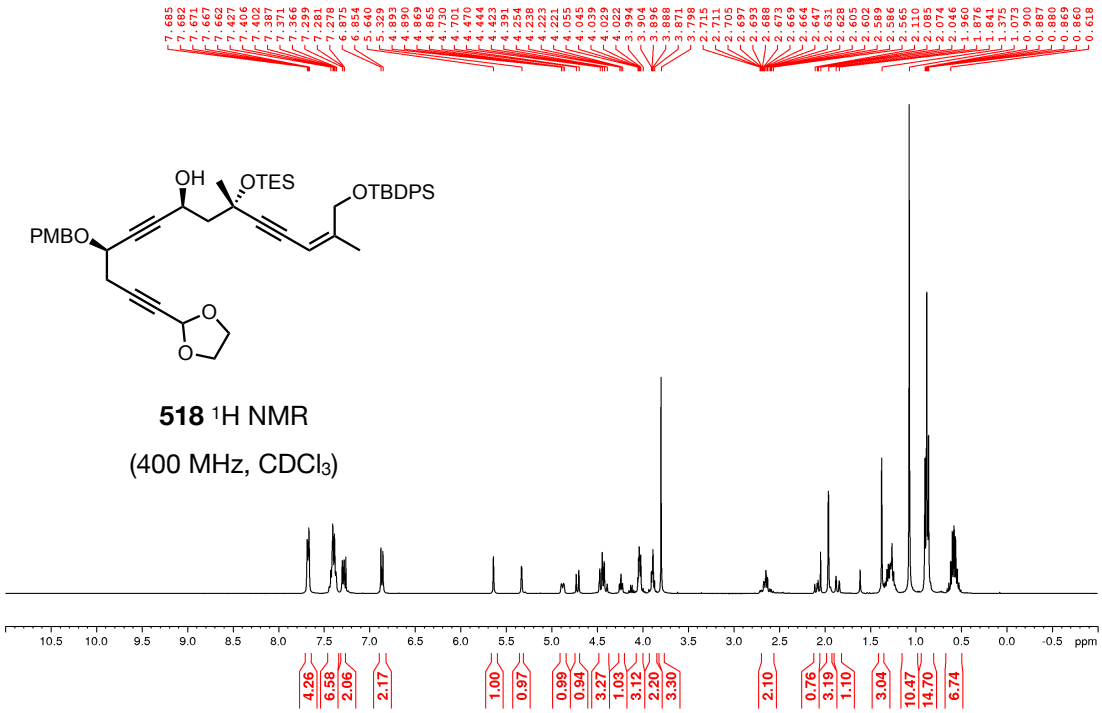


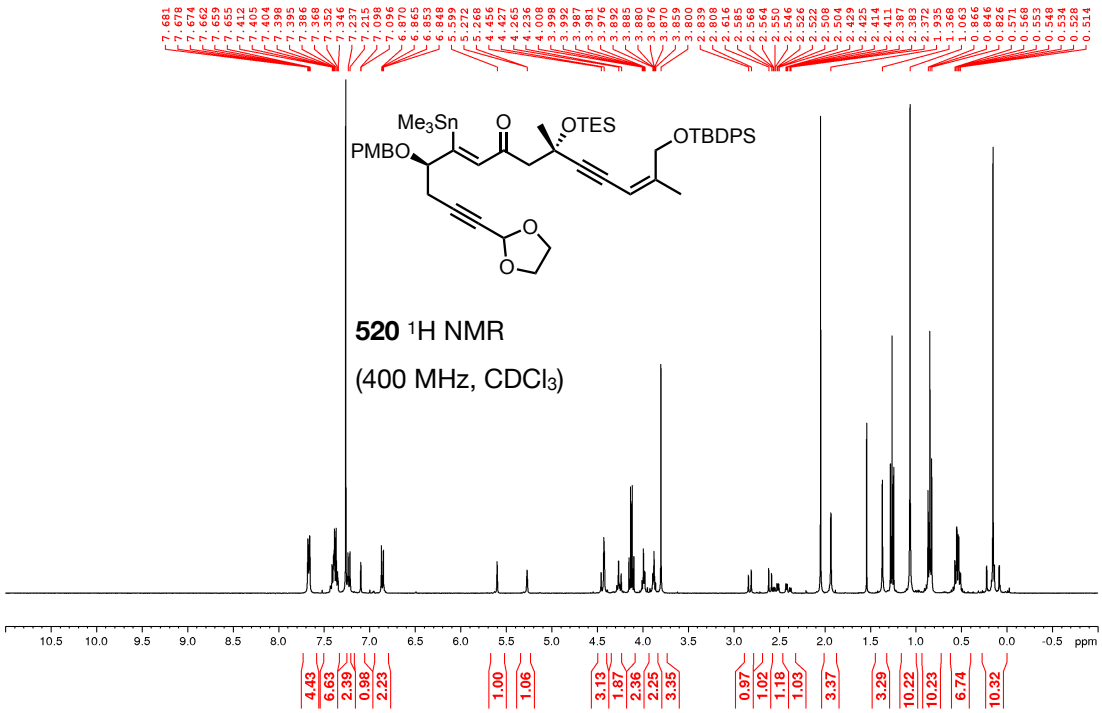

**515** $^{1}$H NMR

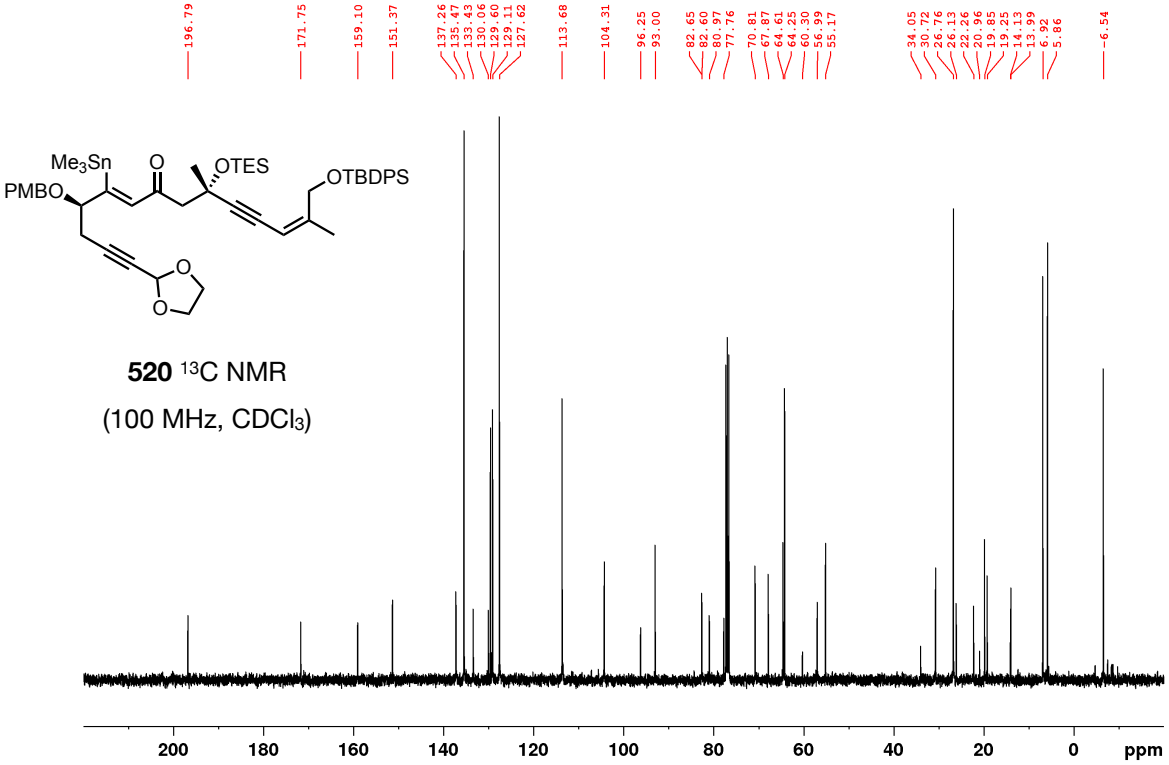
(400 MHz, $CDCl_3$)


O
OTES
OTBDPS
PMBO
O
O
517 1H NMR
(400 MHz, CDCl3)
ppm


O
OTES
OTBDPS
PMBO
O
O
517 13C NMR
(100 MHz, CDCl3)
ppm

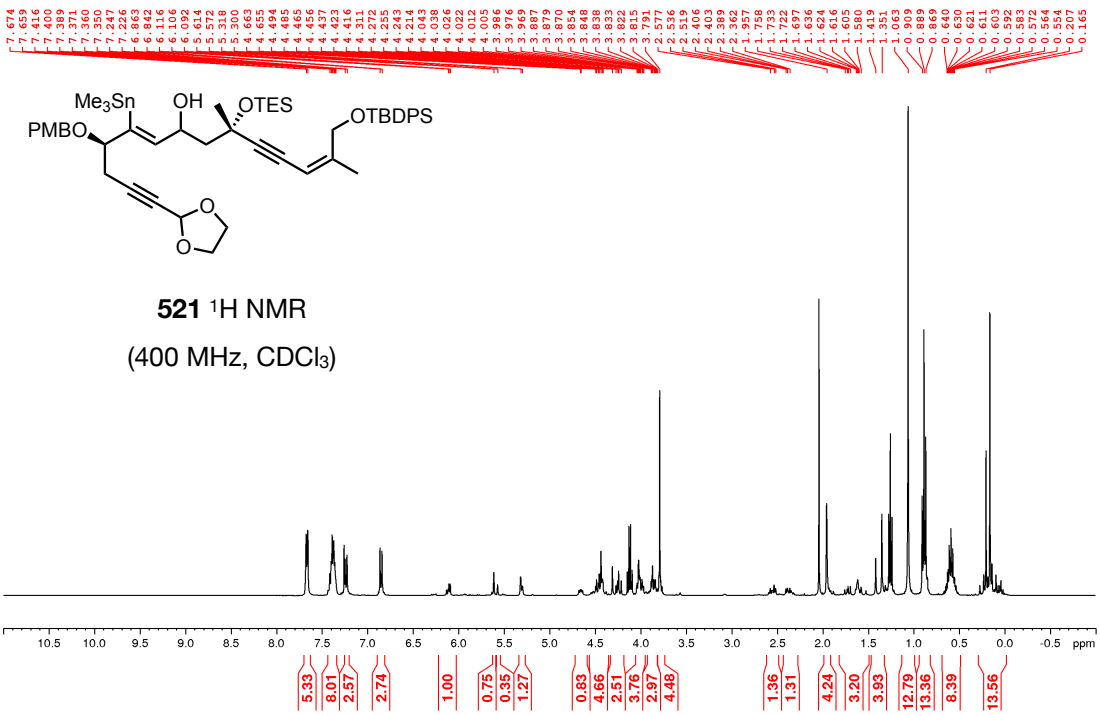

OH
OTES
OTBDPS
PMBO
O
O
518 1H NMR
(400 MHz, CDCl3)
ppm


Me3Sn
O
OTES
OTBDPS
PMBO
O
O
520 1H NMR
(400 MHz, CDCl3)
ppm



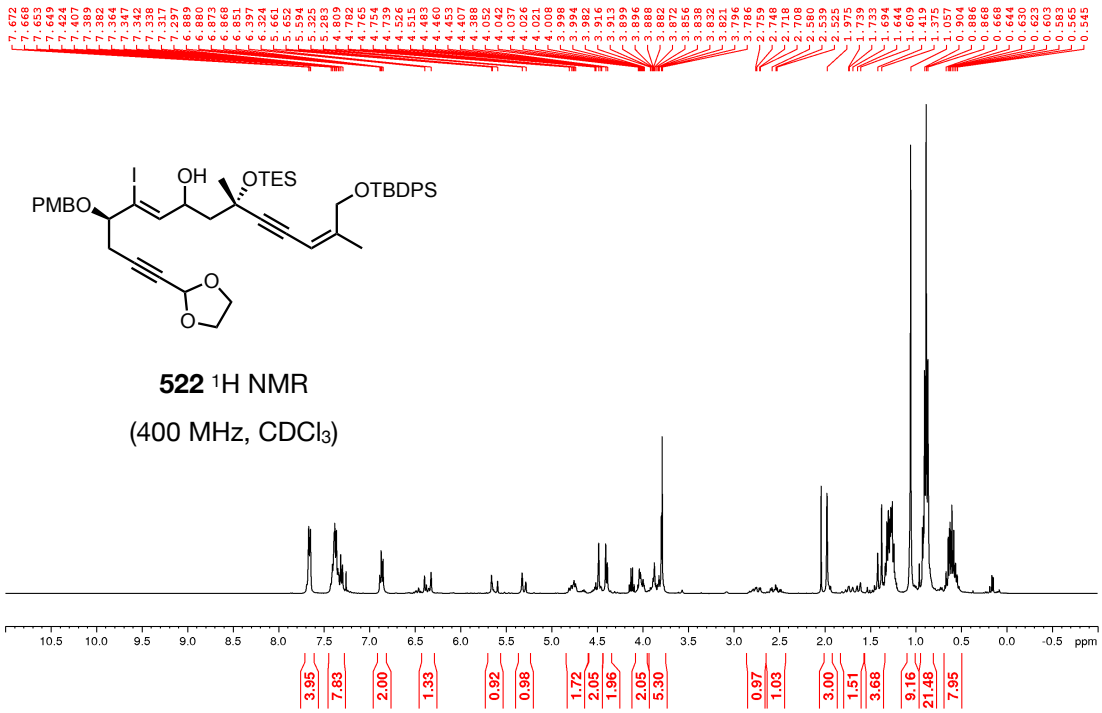

**520** $^{13}$C NMR

(100 MHz, $CDCl_3$)

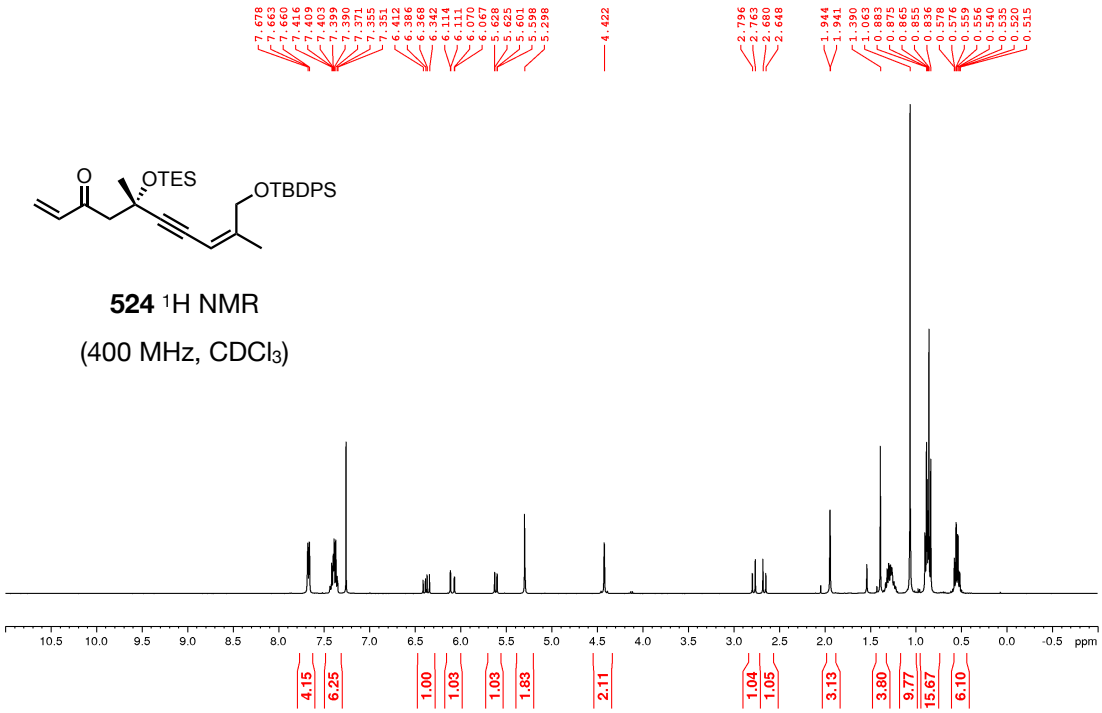



**521** $^{1}$H NMR

(400 MHz, $CDCl_3$)

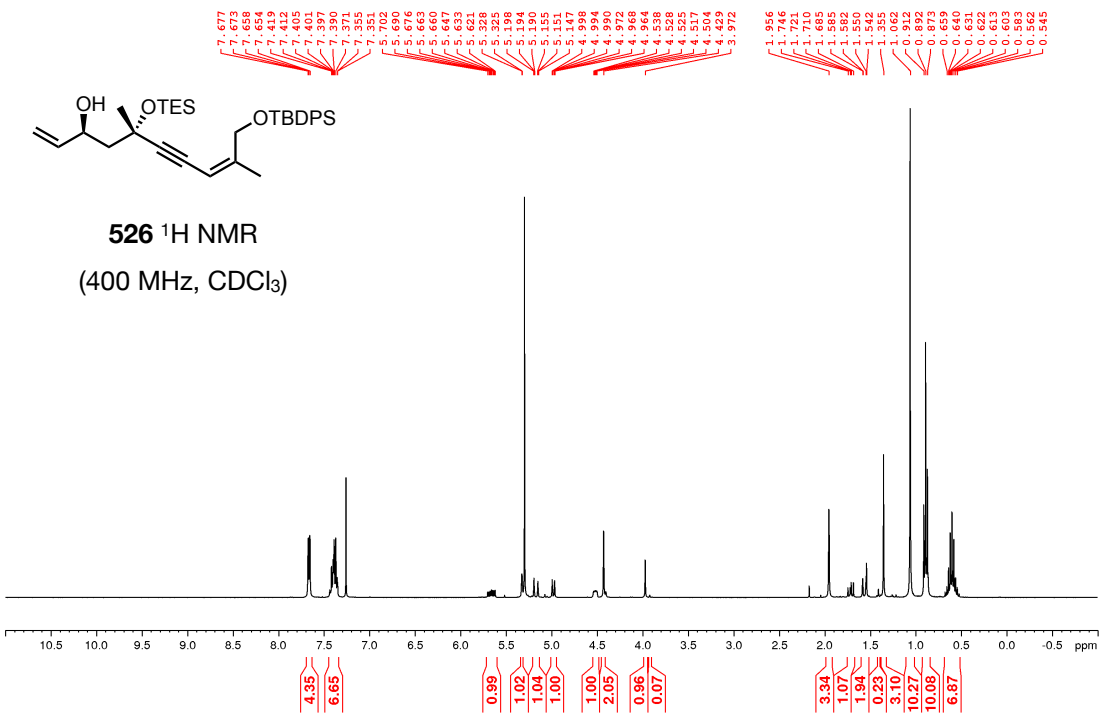

PMBO
I
OH
OTES
OTBDPS
O
O
522 1H NMR
(400 MHz, CDCl3)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm
3.95 7.83 2.00 1.33 0.92 0.98 1.72 2.05 1.96 2.05 5.30 0.97 1.03 3.00 1.51 3.68 9.16 21.48 7.95

**NMR Spectra: Section 4.3:**



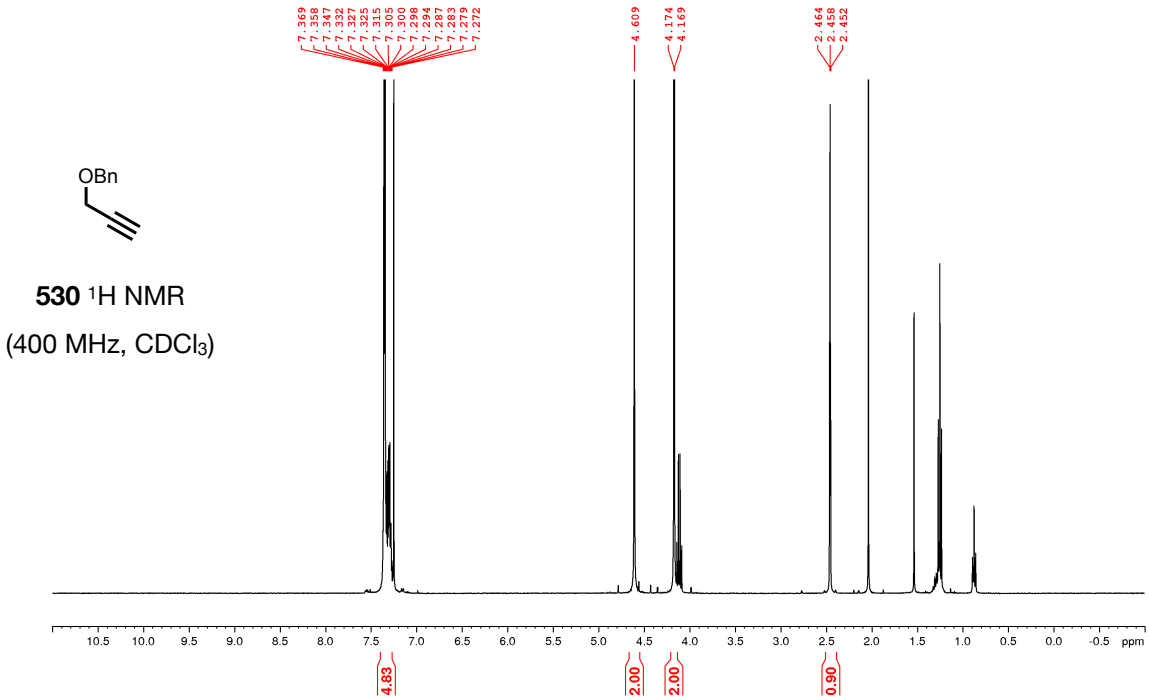

**524** $^1$H NMR

(400 MHz, $CDCl_3$)



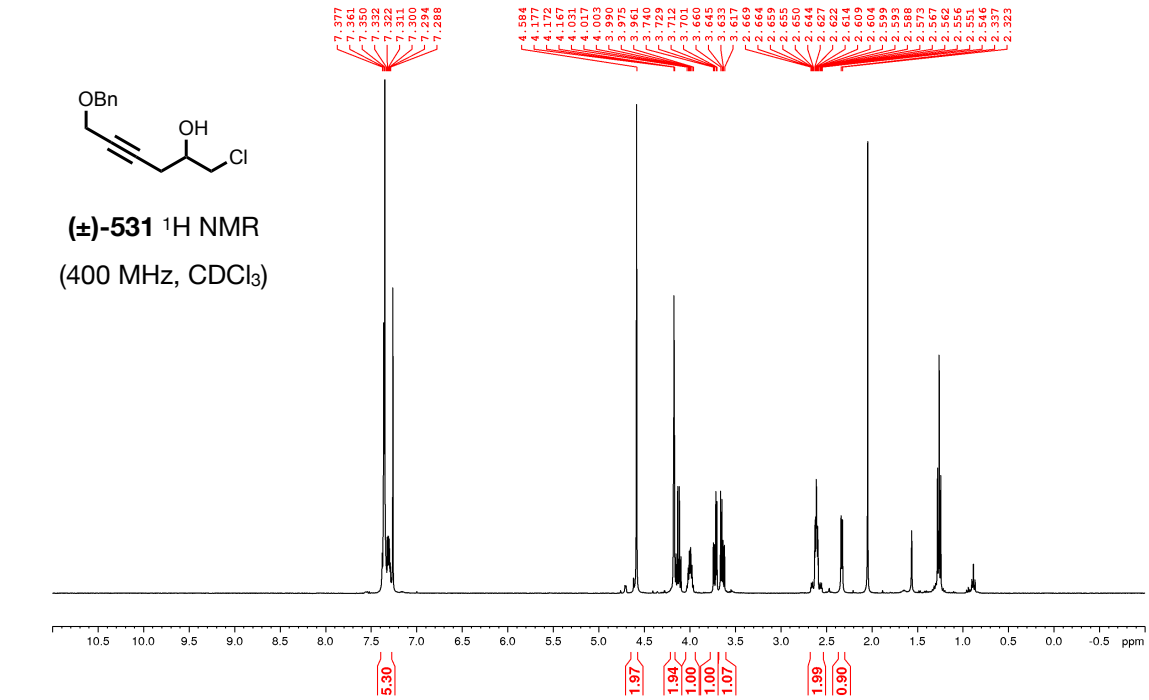

**526** $^1$H NMR

(400 MHz, $CDCl_3$)



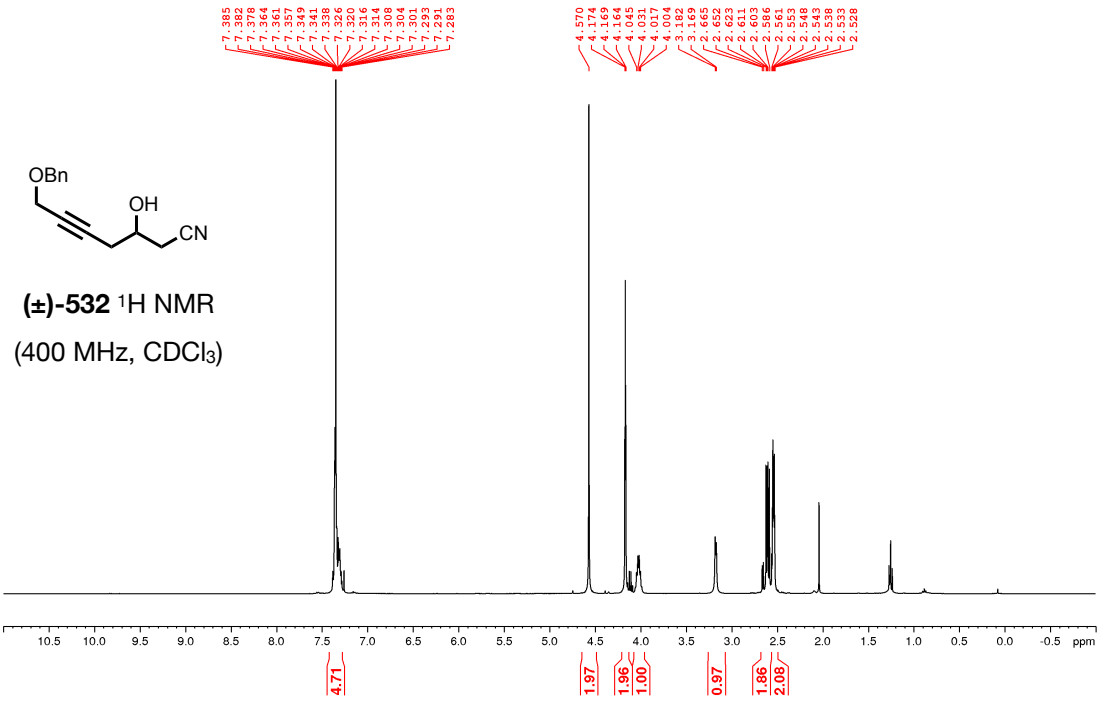

**530** $^{1}$H NMR

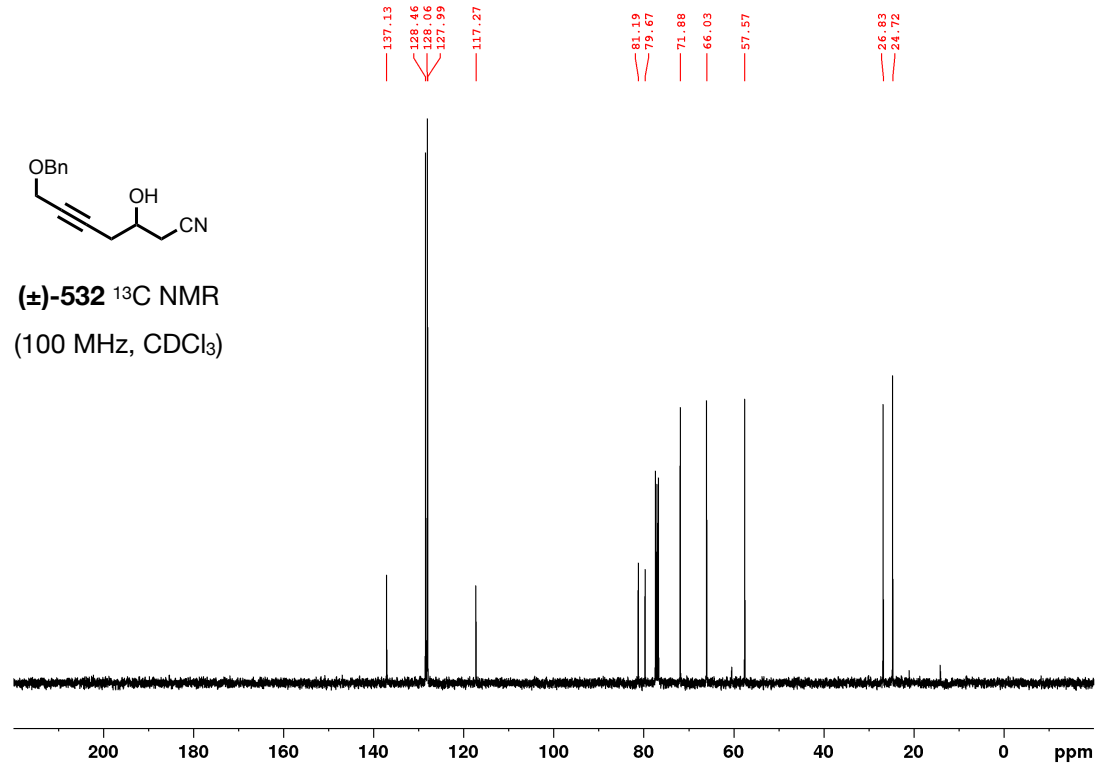
(400 MHz, $CDCl_3$)

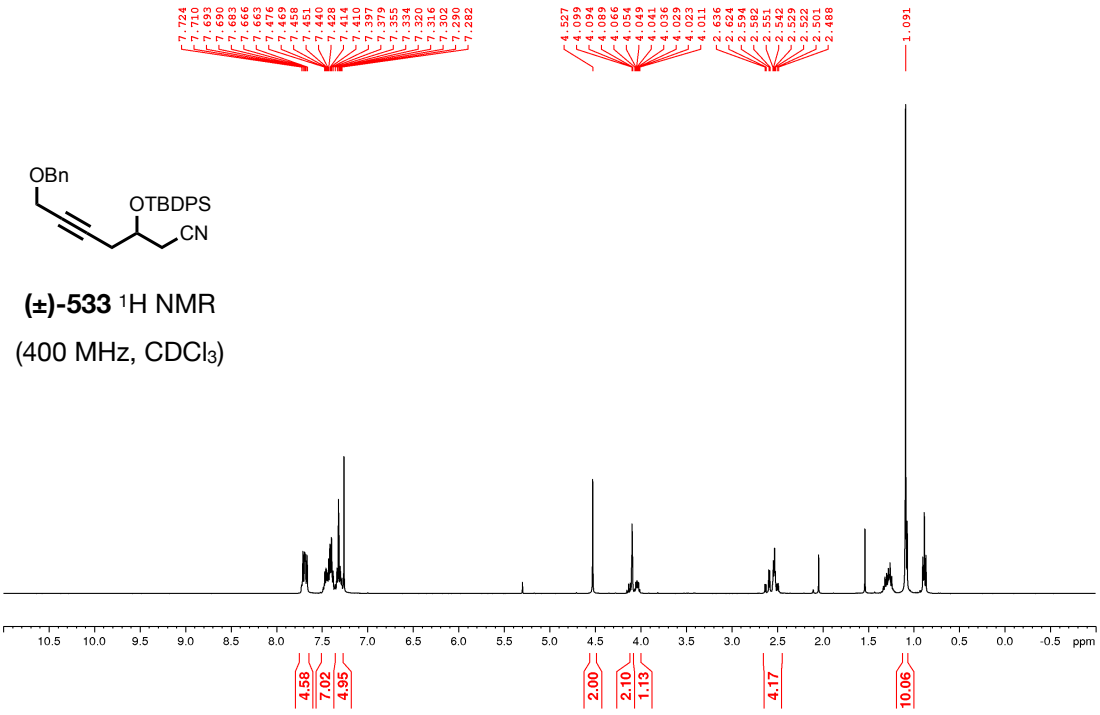



**(±)-531** $^{1}$H NMR

(400 MHz, $CDCl_3$)

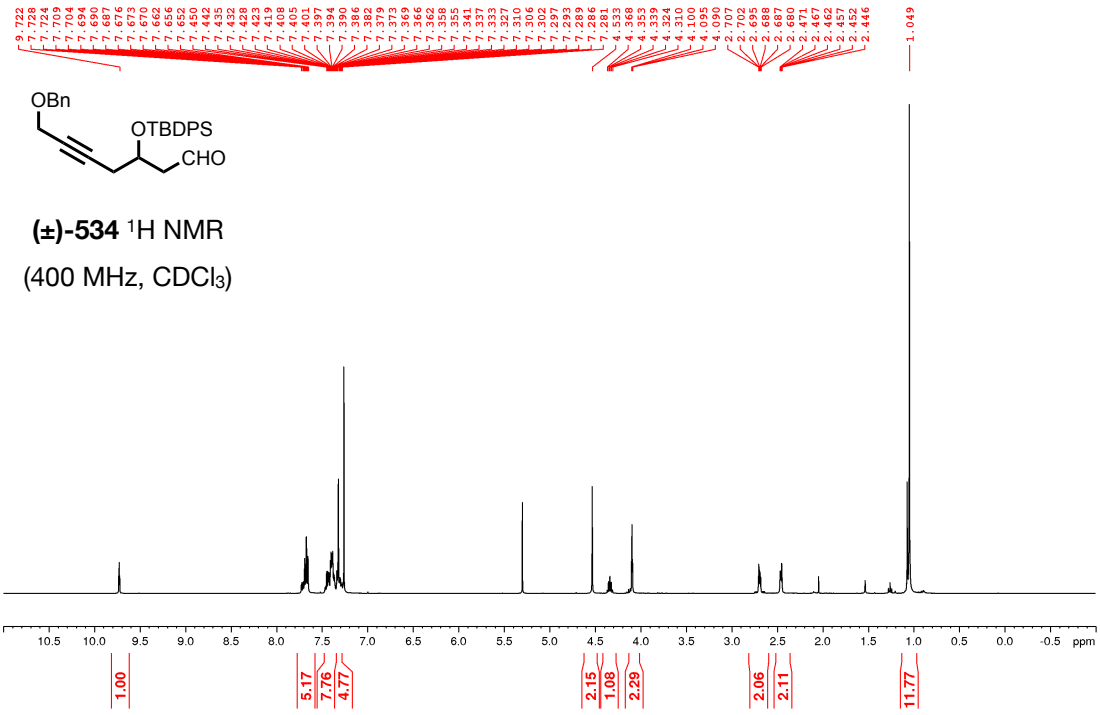

OBn
OH
CN
(±)-532 1H NMR
(400 MHz, CDCl3)
7.385
7.382
7.378
7.364
7.361
7.357
7.349
7.341
7.338
7.326
7.320
7.316
7.314
7.308
7.304
7.301
7.293
7.291
7.283
4.570
4.174
4.169
4.164
4.045
4.031
4.017
4.004
3.182
3.169
2.665
2.652
2.623
2.611
2.603
2.586
2.561
2.553
2.548
2.543
2.538
2.533
2.528
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm
4.71
1.97
1.96
1.00
0.97
1.86
2.08


OBn
OH
CN
(±)-532 13C NMR
(100 MHz, CDCl3)
137.13
128.46
128.06
127.99
117.27
81.19
79.67
71.88
66.03
57.57
26.83
24.72
200 180 160 140 120 100 80 60 40 20 0 ppm



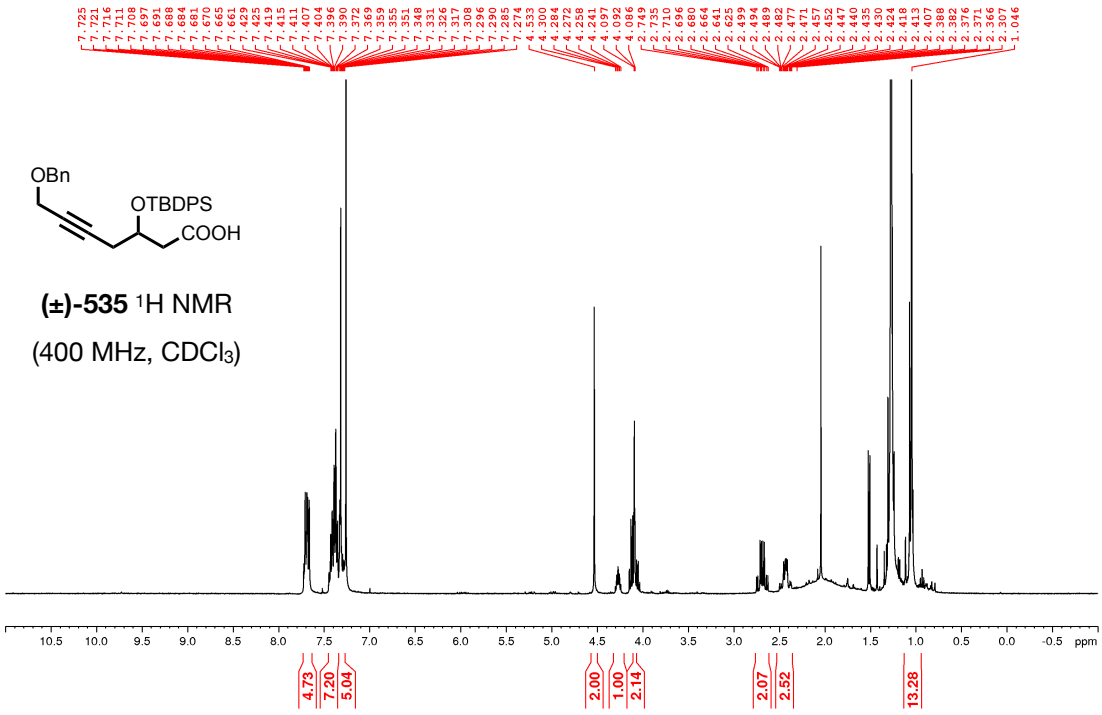

**(±)-533** $^{1}$H NMR

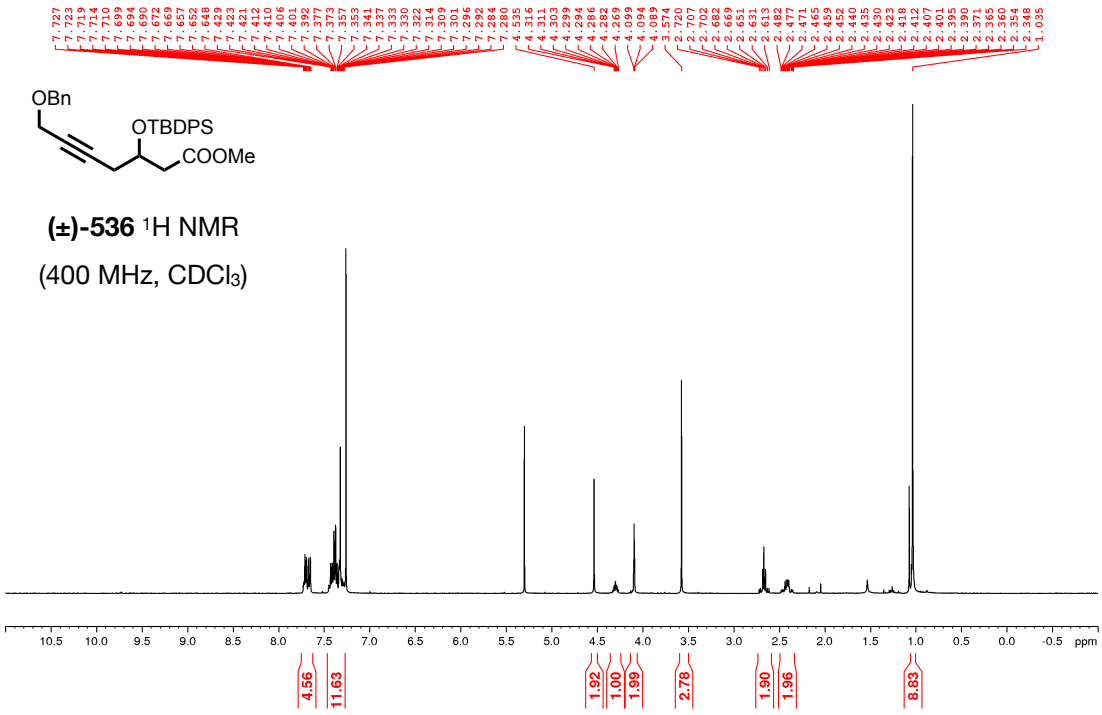
(400 MHz, $CDCl_3$)

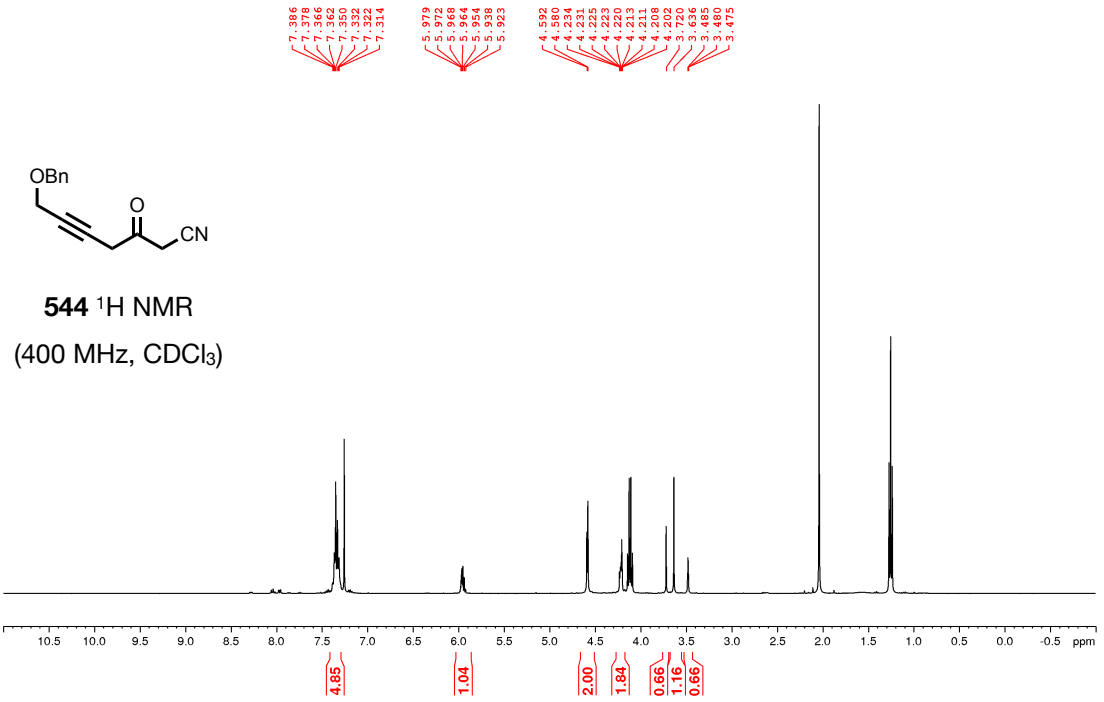



**(±)-534** $^{1}$H NMR

(400 MHz, $CDCl_3$)

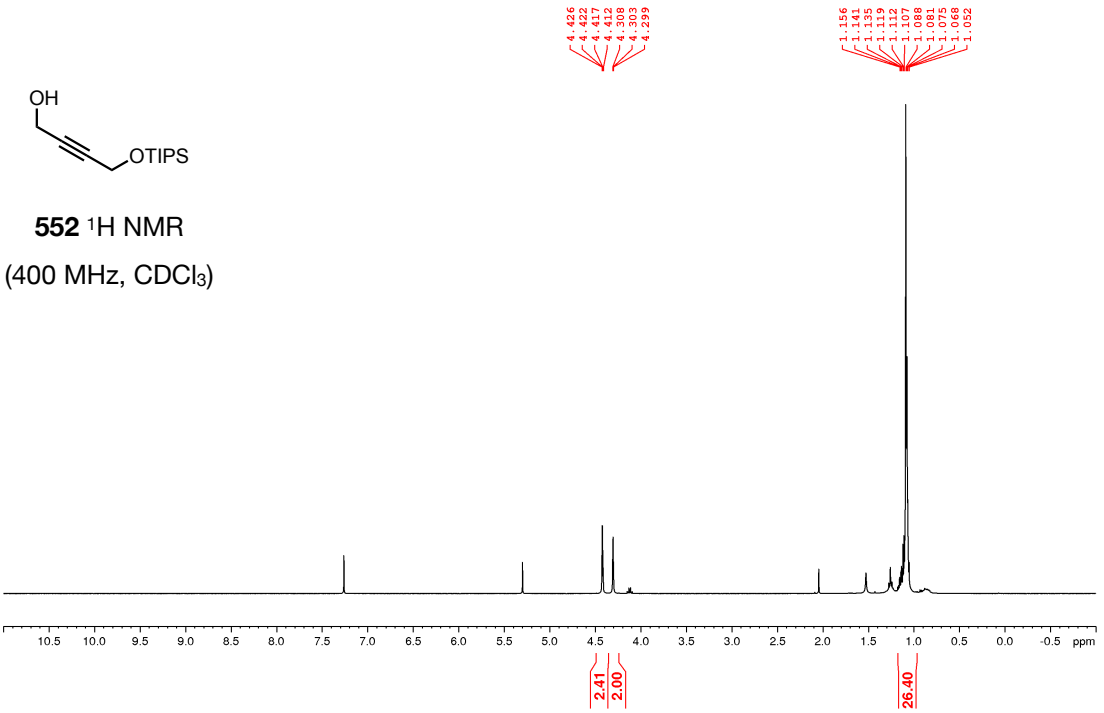

OBn
OTBDPS
COOH
(±)-535 1H NMR
(400 MHz, CDCl3)
ppm


OBn
OTBDPS
COOMe
(±)-536 1H NMR
(400 MHz, CDCl3)
ppm



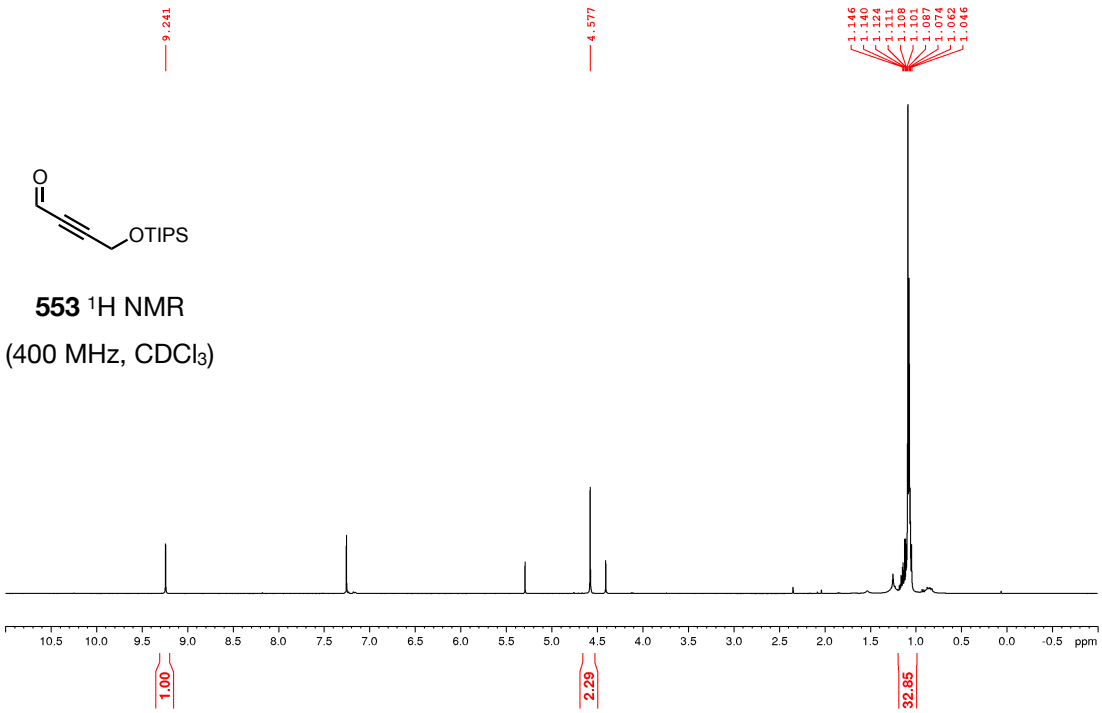

**544** $^{1}$H NMR

(400 MHz, $CDCl_3$)



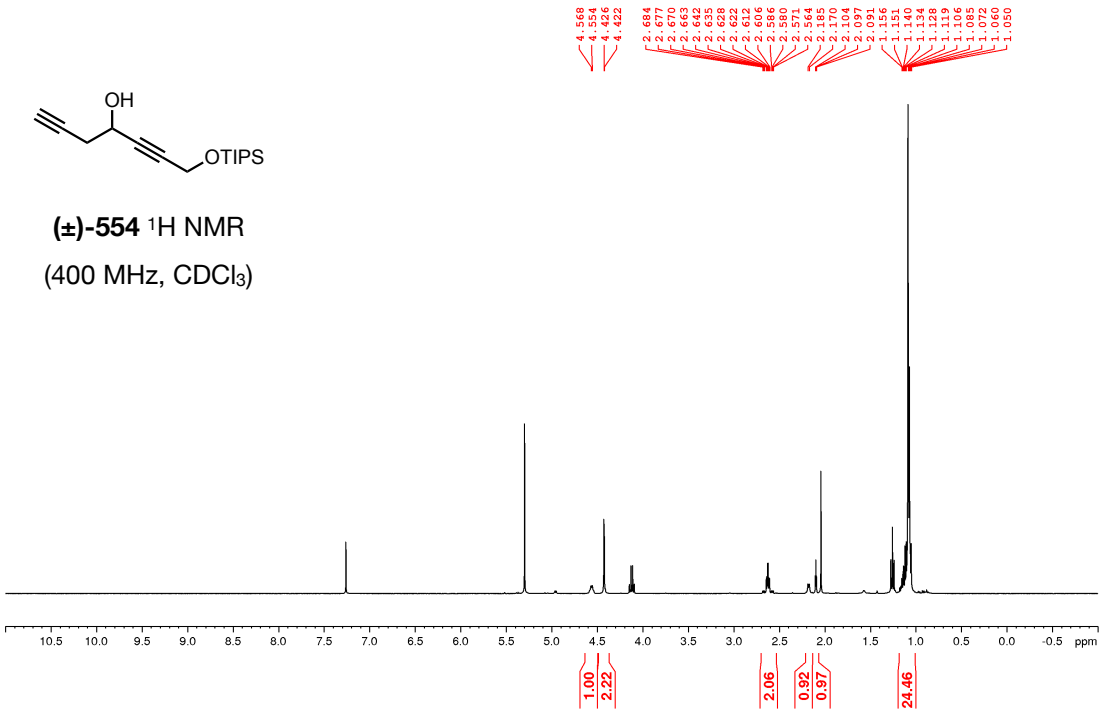

**552** $^{1}$H NMR

(400 MHz, $CDCl_3$)



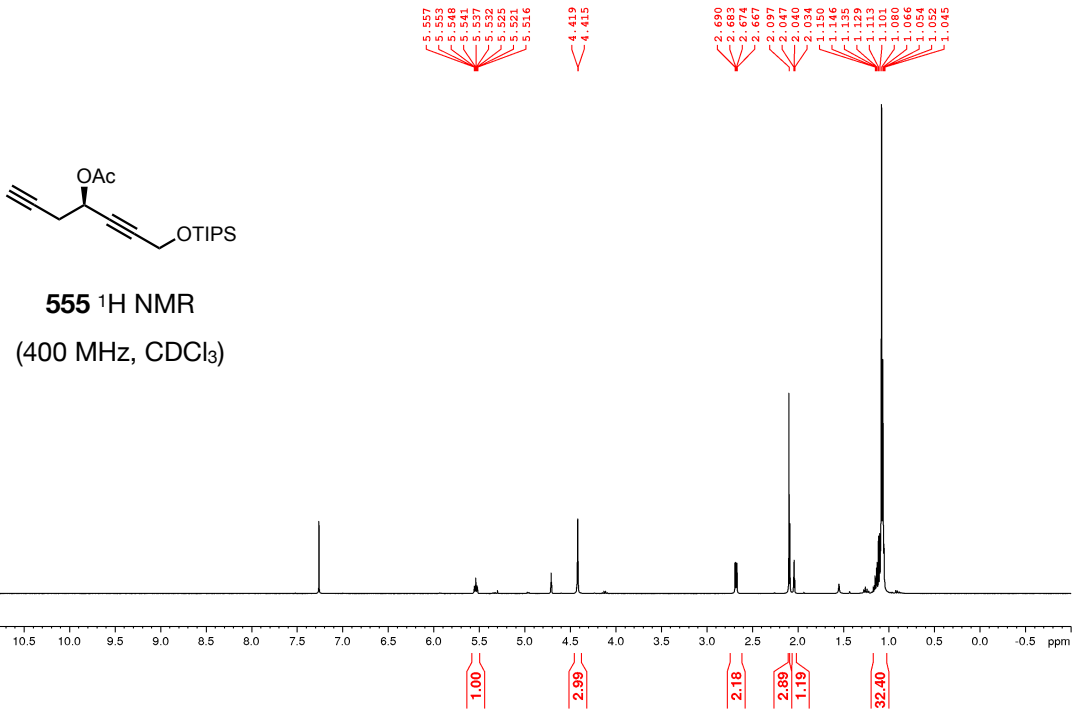

**553** $^{1}$H NMR

(400 MHz, $CDCl_3$)



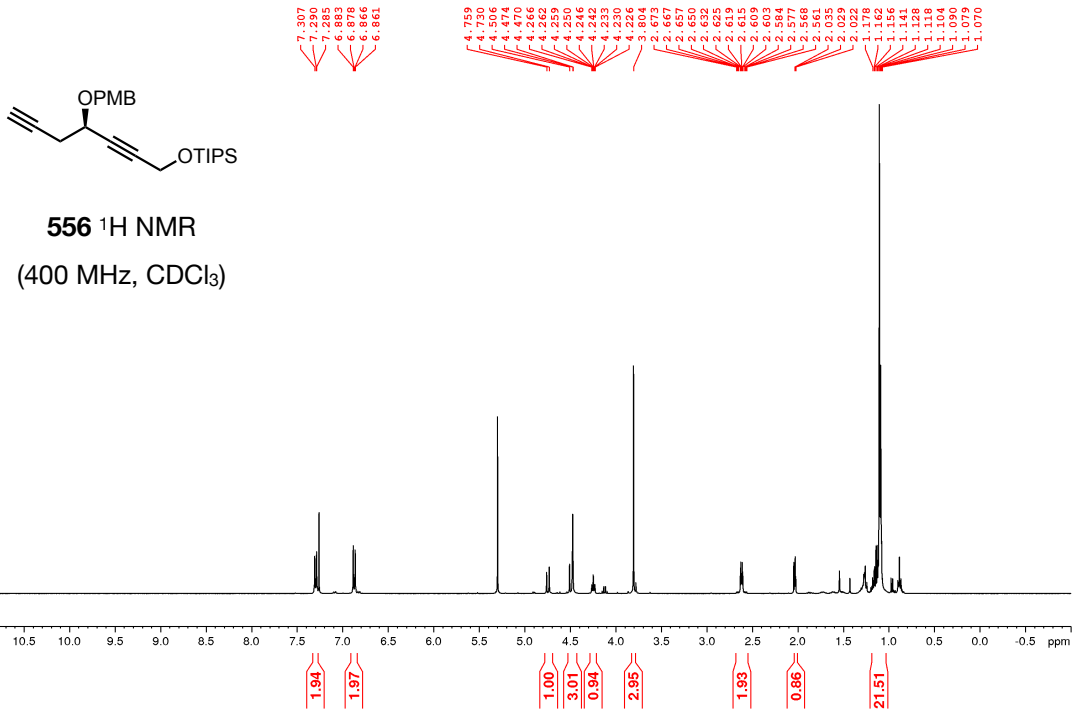

**(±)-554** $^{1}$H NMR

(400 MHz, $CDCl_3$)



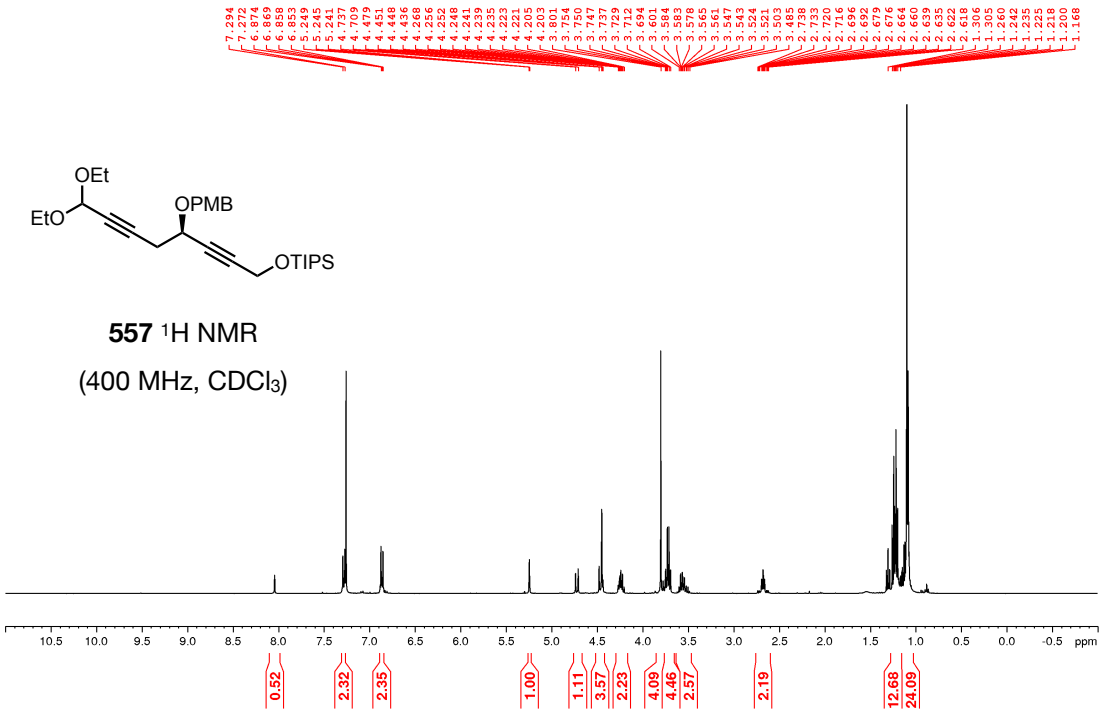

**555** $^{1}$H NMR

(400 MHz, $CDCl_3$)



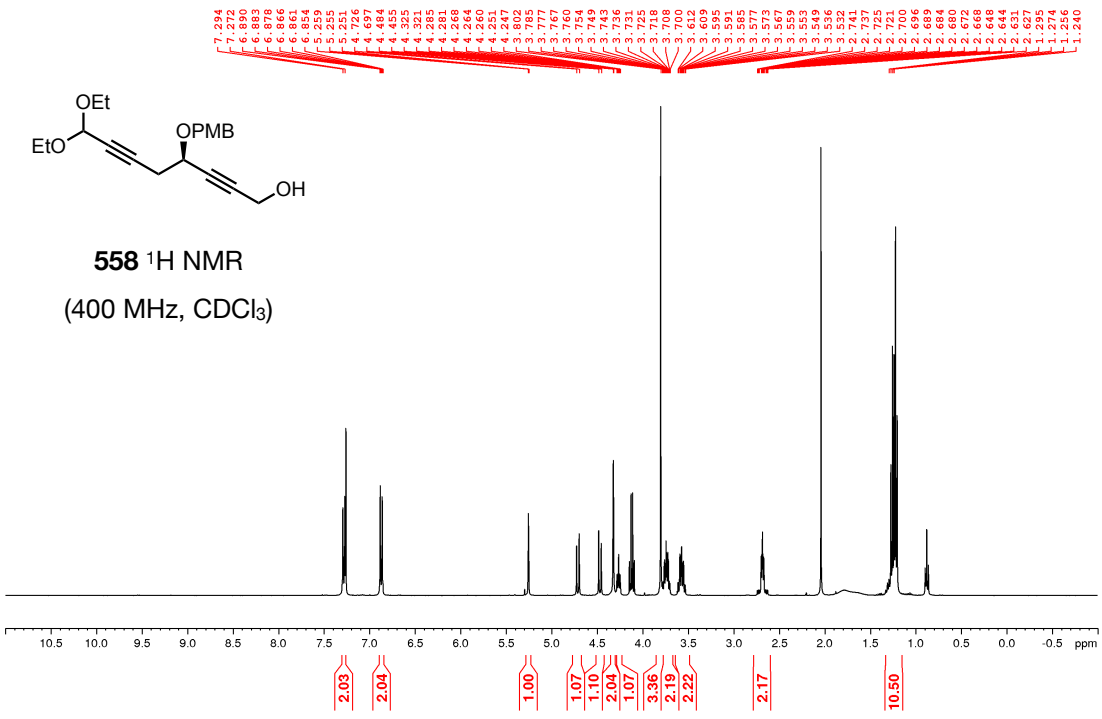

**556** $^{1}$H NMR

(400 MHz, $CDCl_3$)



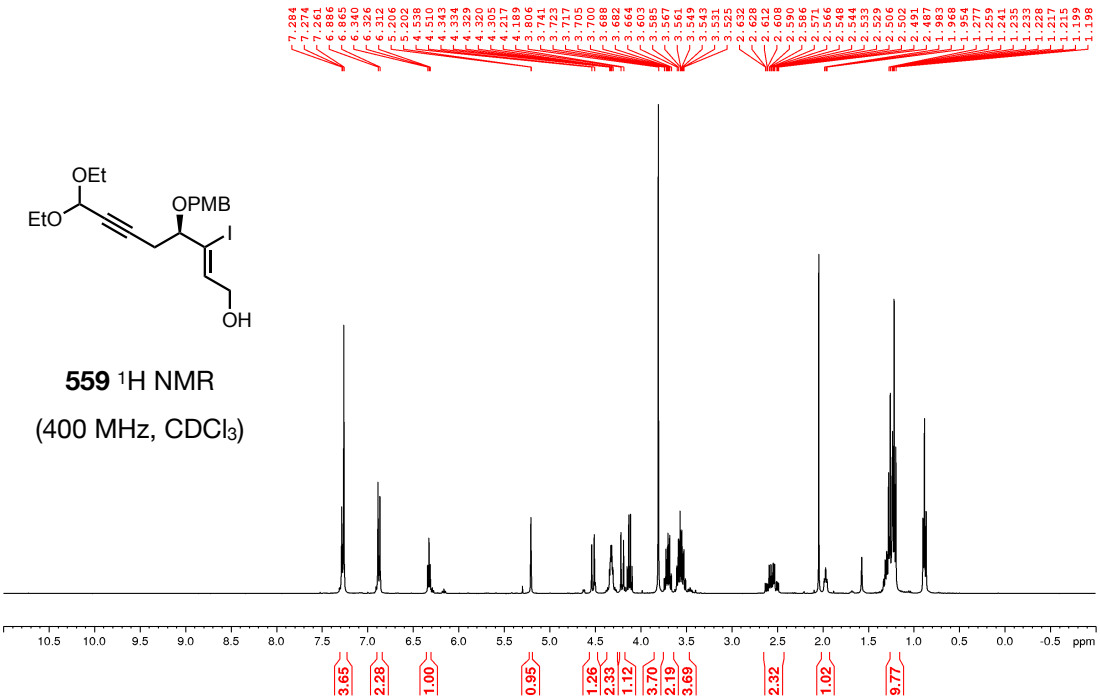

**557** $^{1}$H NMR

(400 MHz, $CDCl_3$)



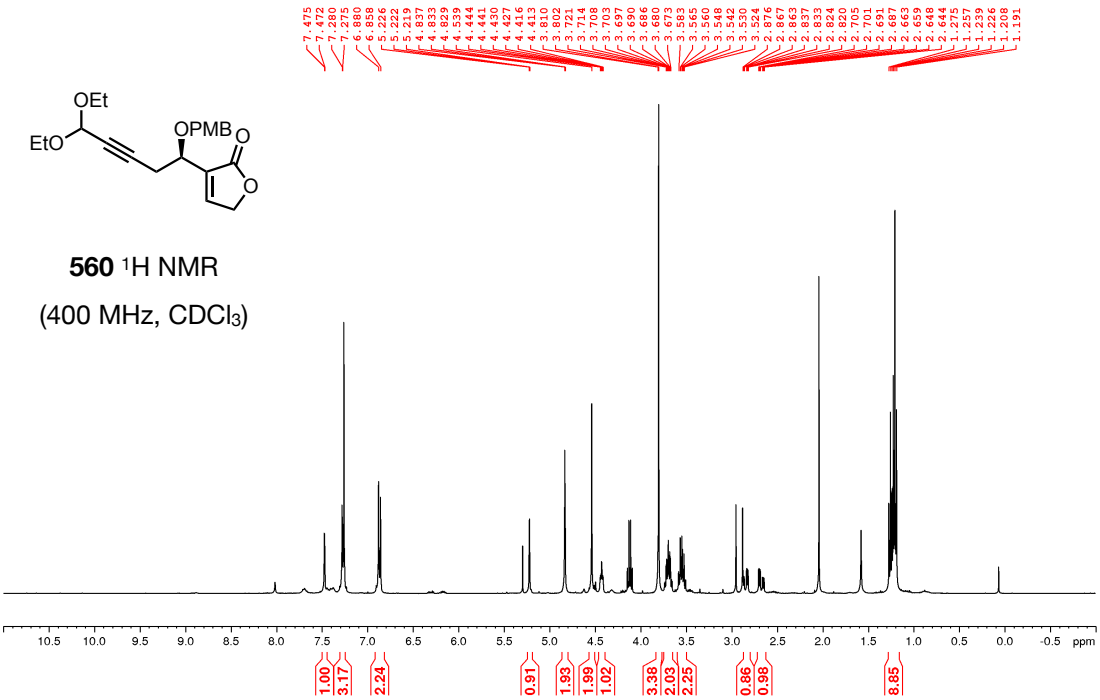

**558** $^{1}$H NMR

(400 MHz, $CDCl_3$)



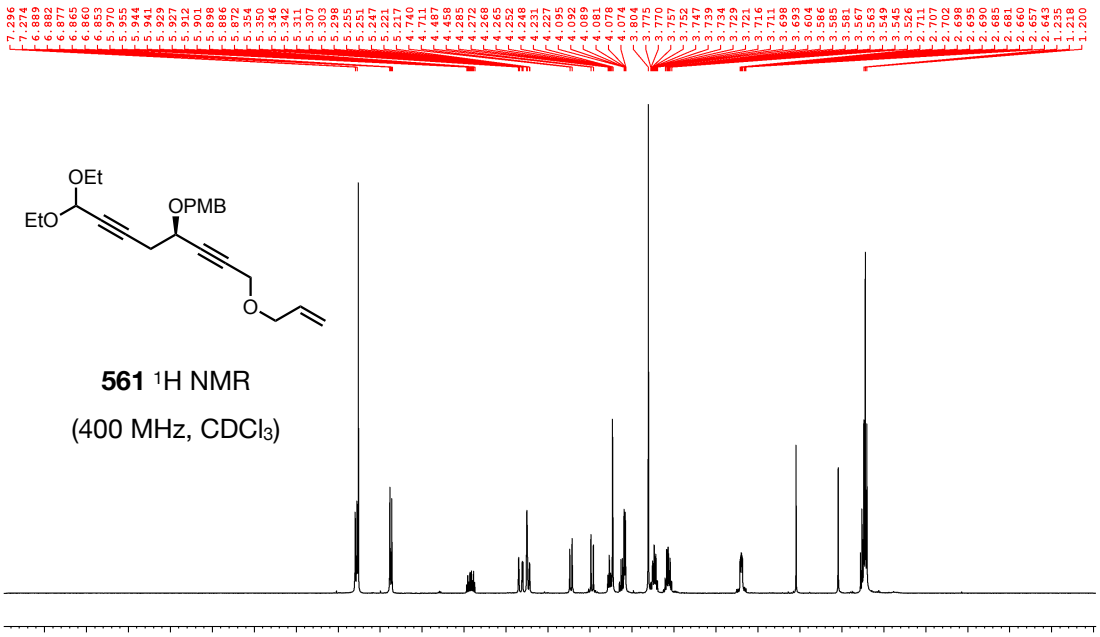

**559** $^1$H NMR

(400 MHz, $CDCl_3$)



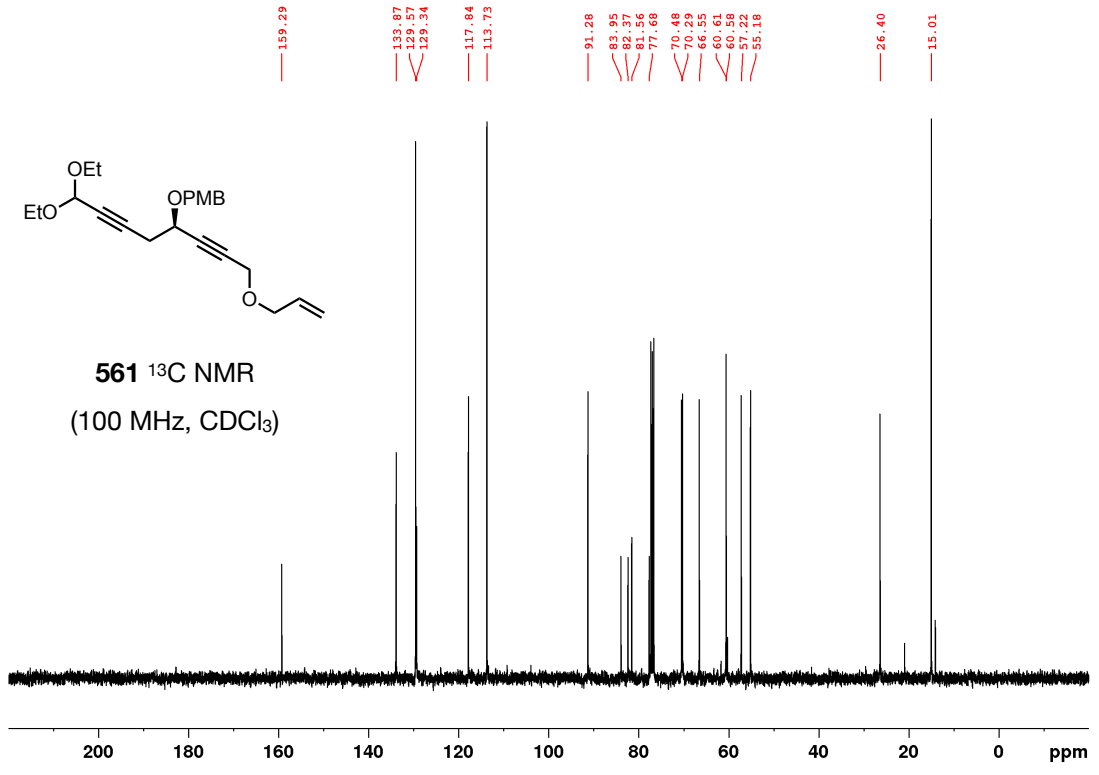

**560** $^1$H NMR

(400 MHz, $CDCl_3$)



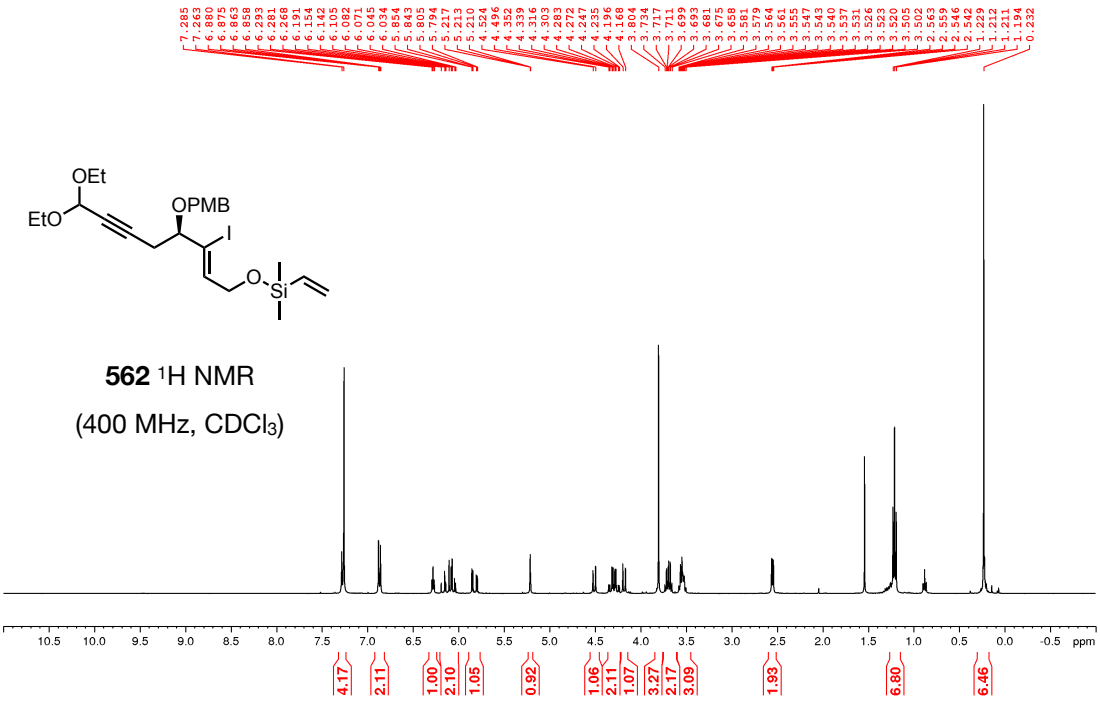

**561** $^{1}$H NMR

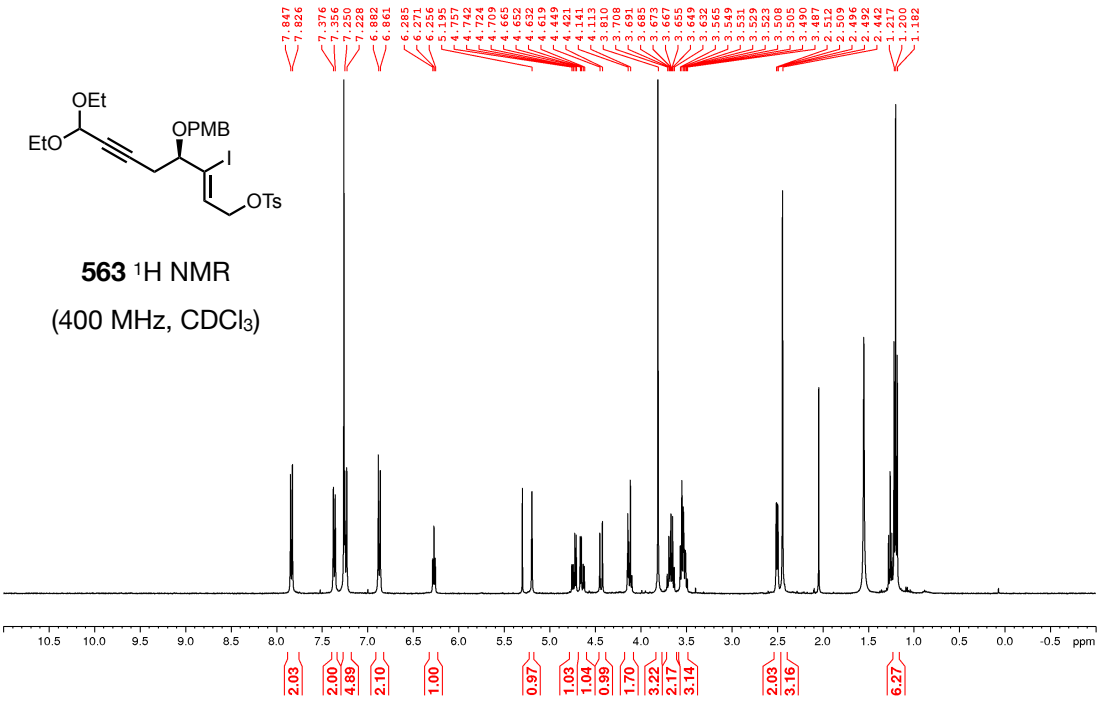
(400 MHz, $CDCl_3$)

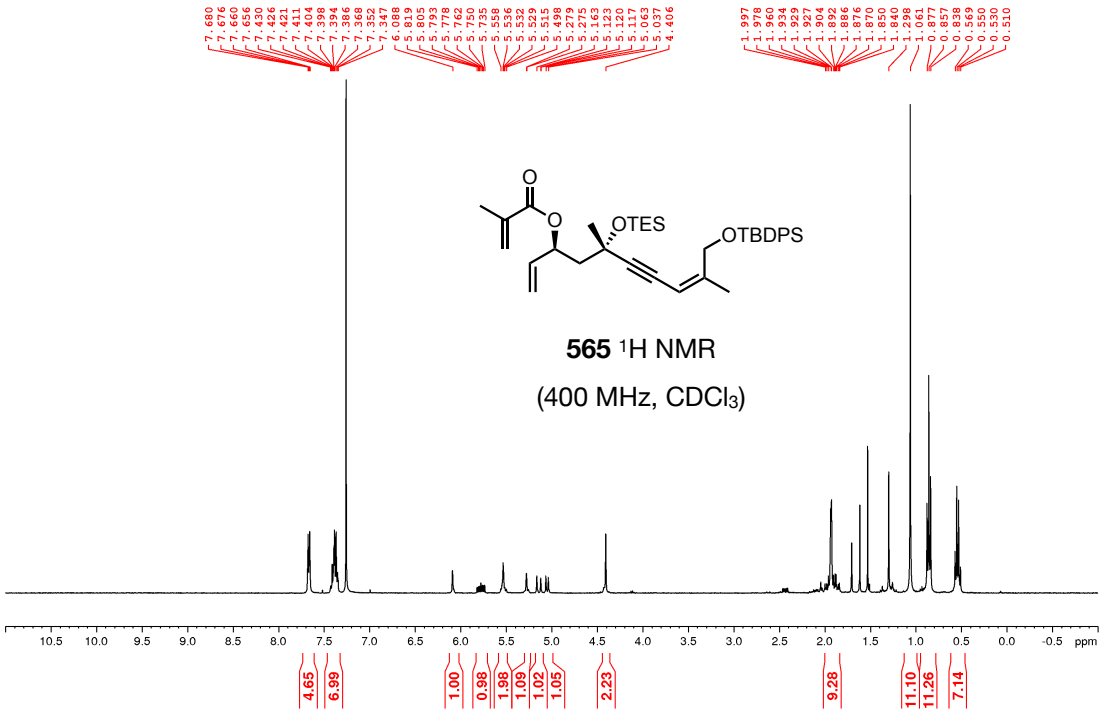



**561** $^{13}$C NMR

(100 MHz, $CDCl_3$)

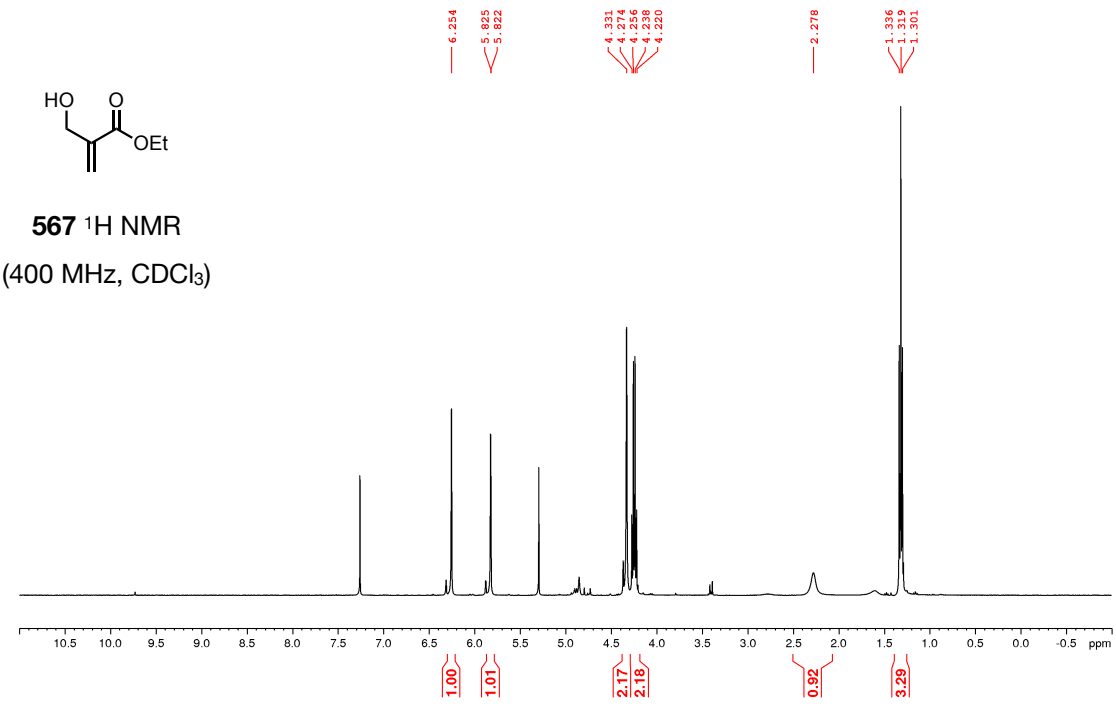

OEt
EtO
OPMB
I
O
Si
562 1H NMR
(400 MHz, CDCl3)
ppm


OEt
EtO
OPMB
I
OTs
563 1H NMR
(400 MHz, CDCl3)
ppm



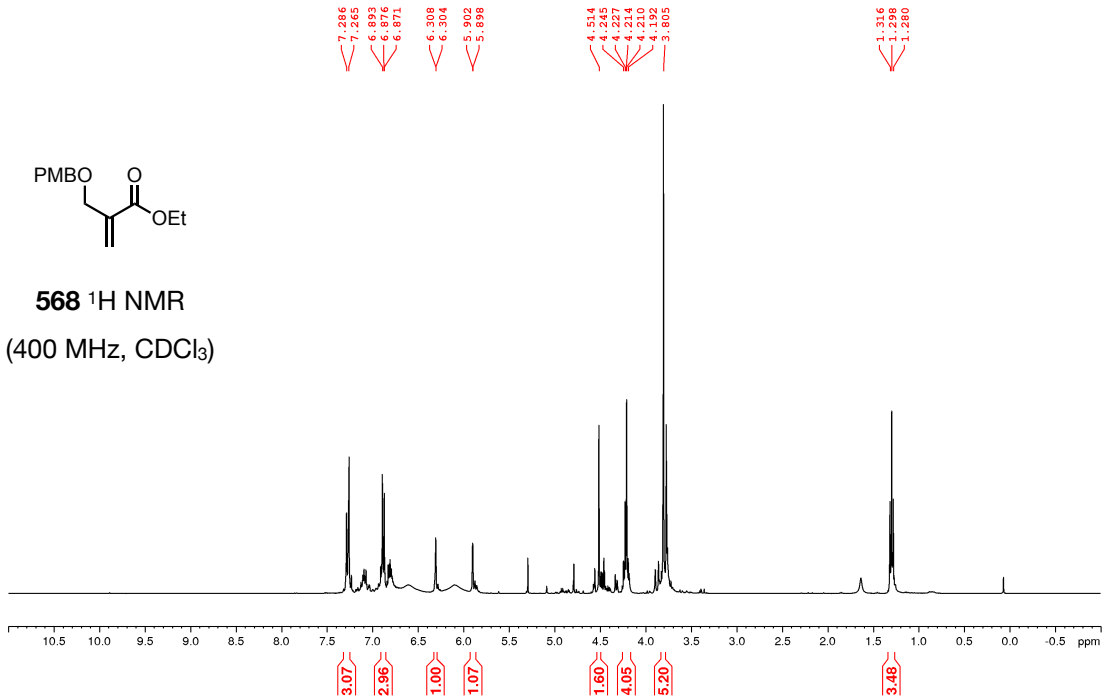

**565** $^1$H NMR

(400 MHz, $CDCl_3$)



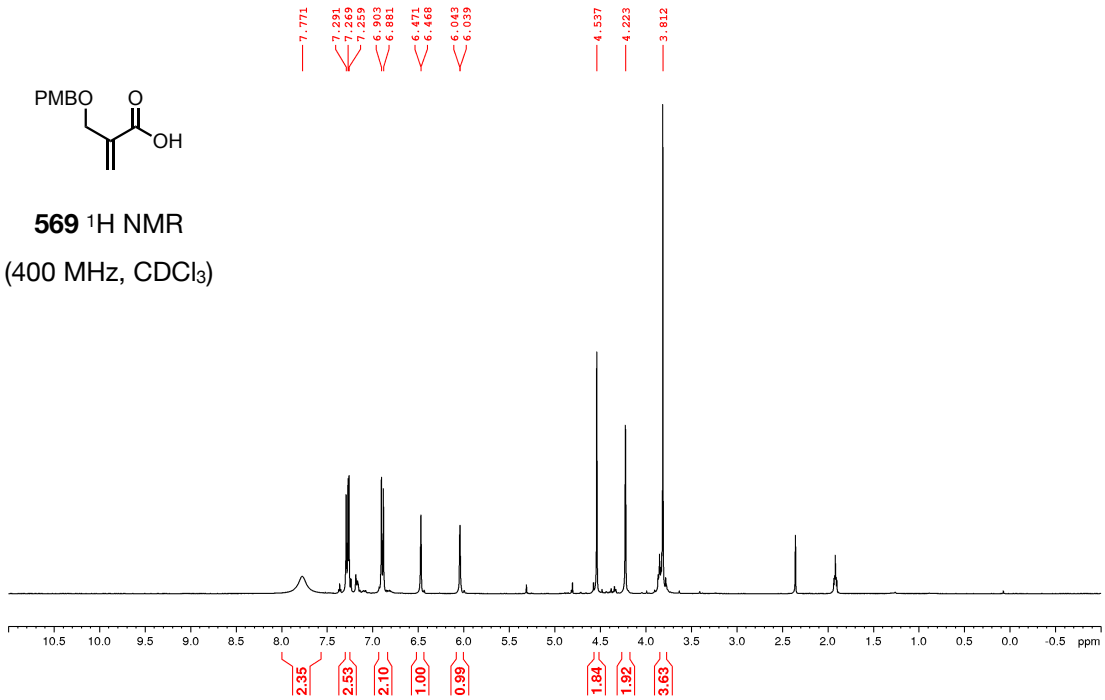

**567** $^1$H NMR

(400 MHz, $CDCl_3$)



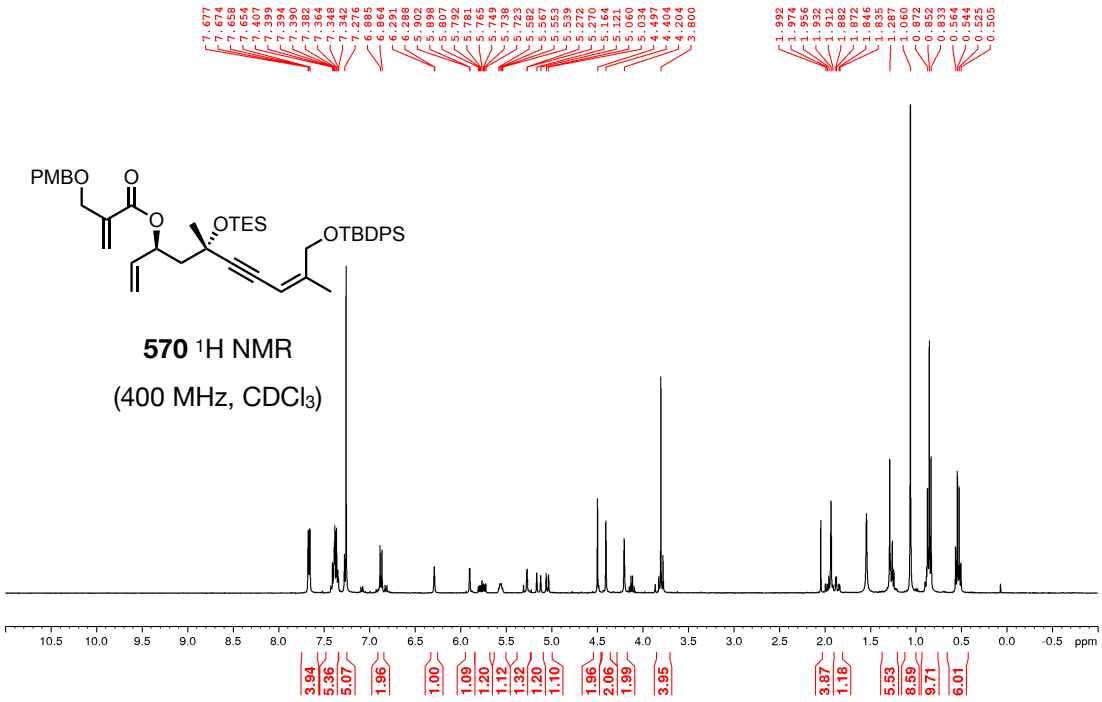

**568** $^{1}$H NMR

(400 MHz, $CDCl_3$)



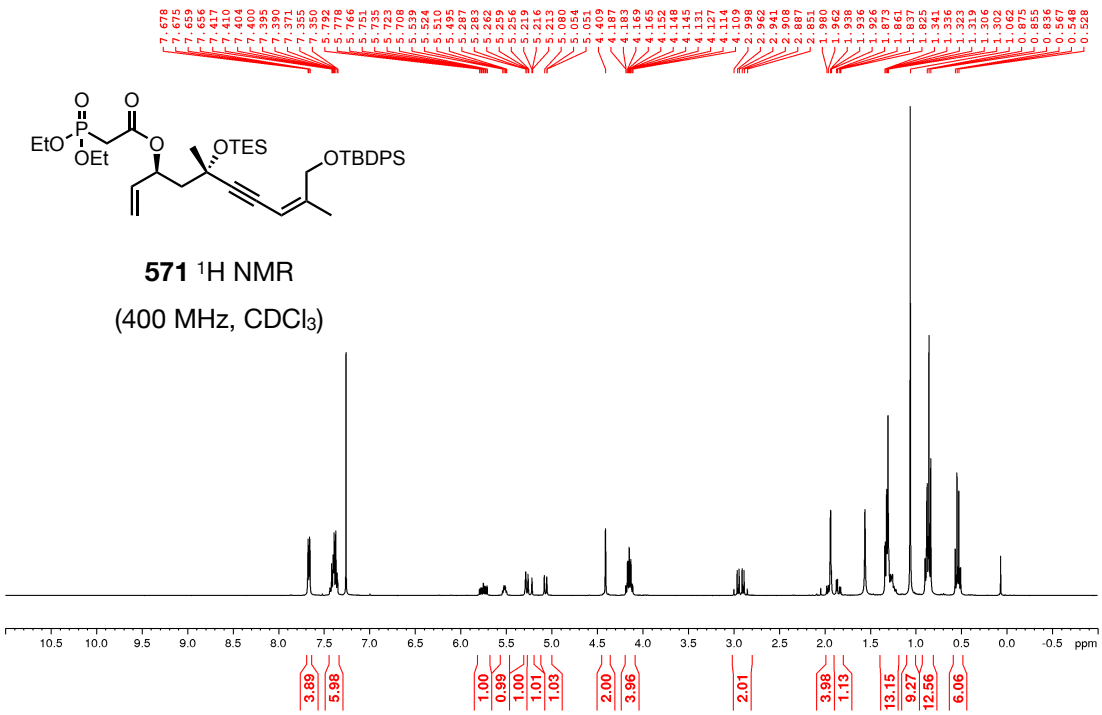

**569** $^{1}$H NMR

(400 MHz, $CDCl_3$)



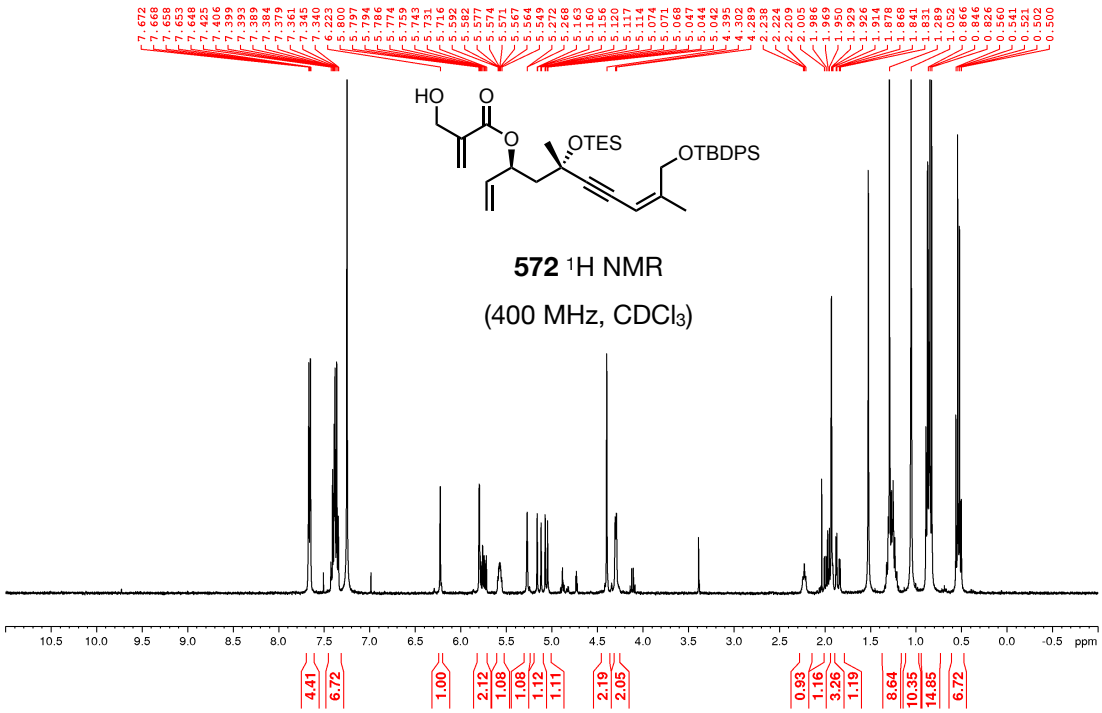

**570** $^{1}$H NMR

(400 MHz, $CDCl_3$)



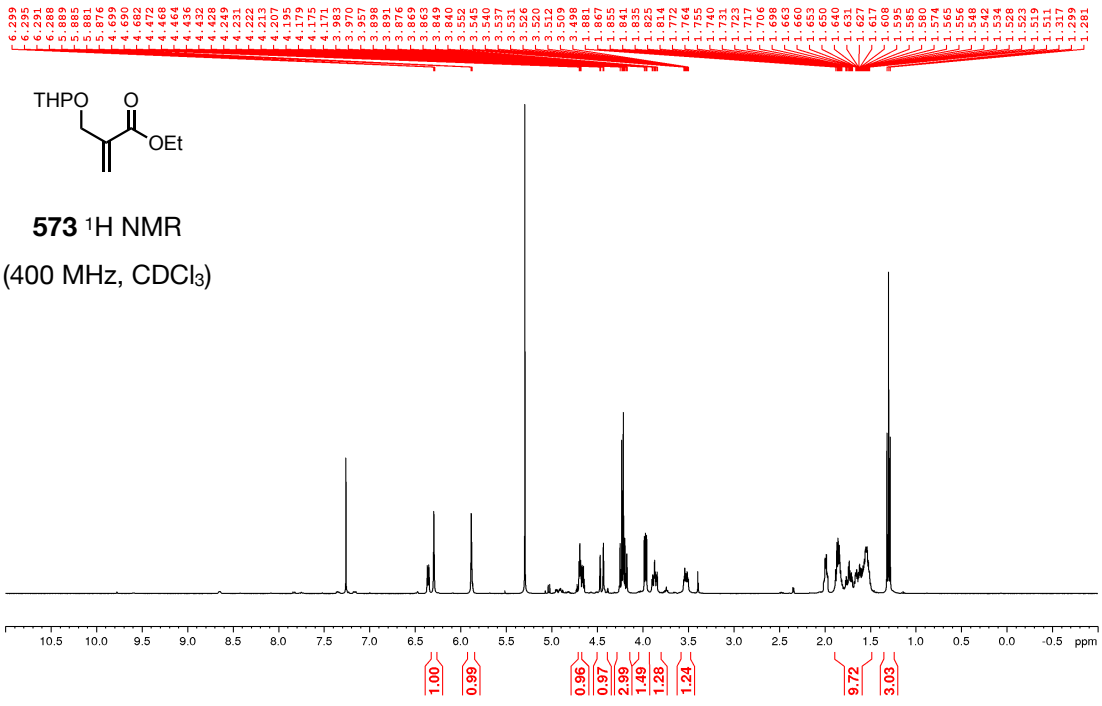

**571** $^{1}$H NMR

(400 MHz, $CDCl_3$)



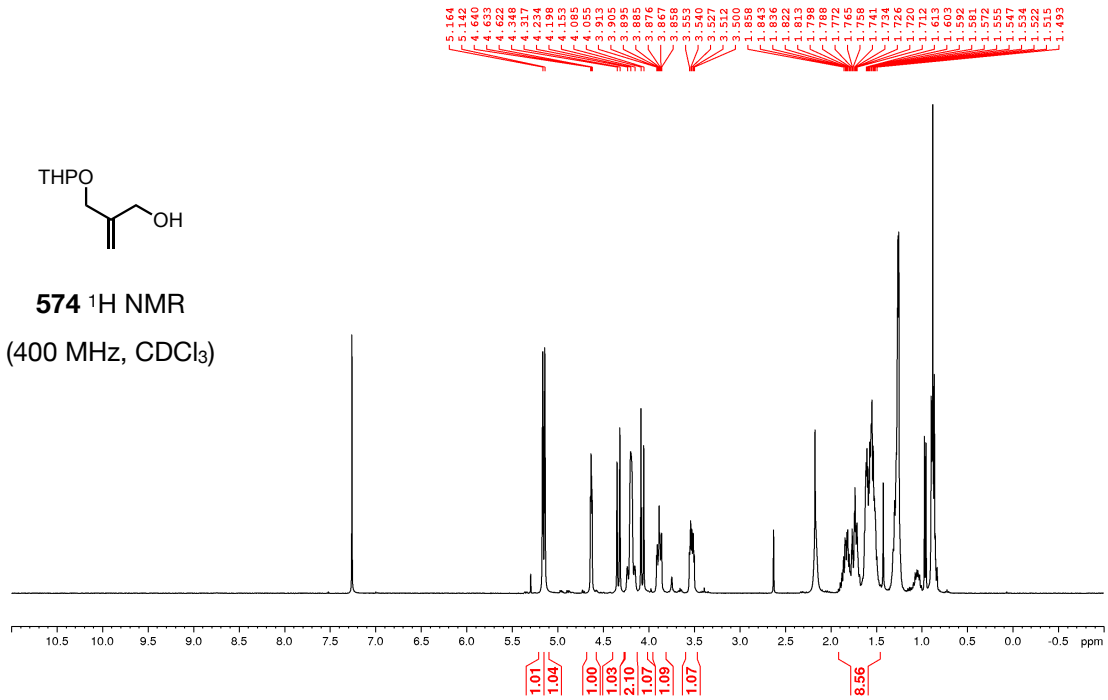

**572** $^{1}$H NMR

(400 MHz, $CDCl_3$)



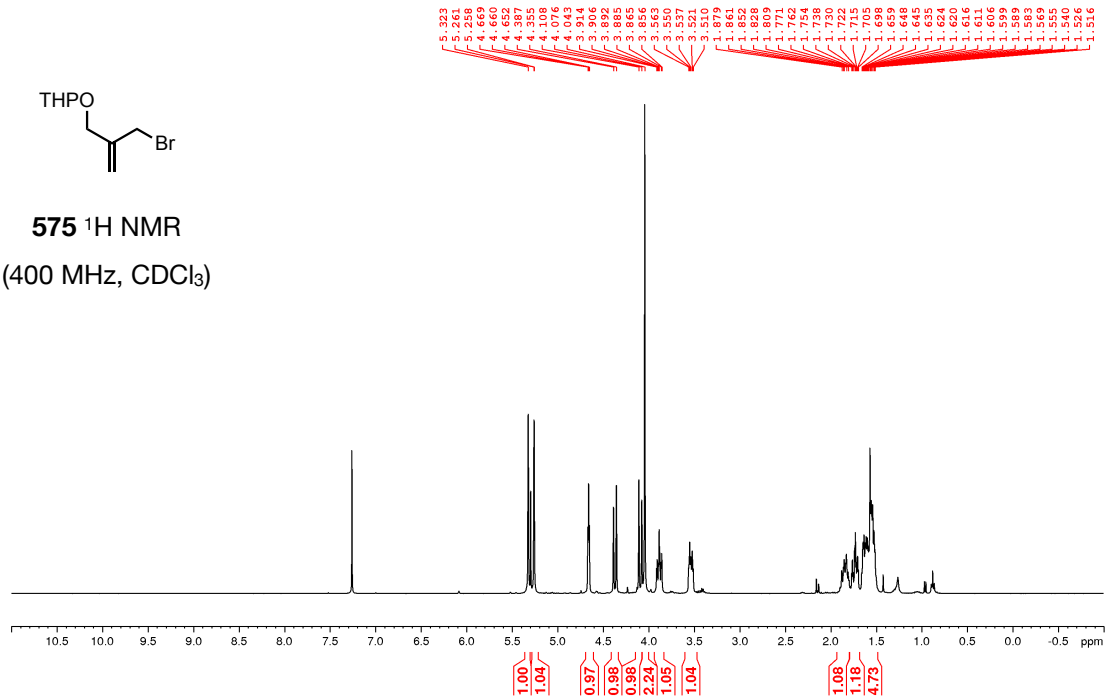

**573** $^{1}$H NMR

(400 MHz, $CDCl_3$)



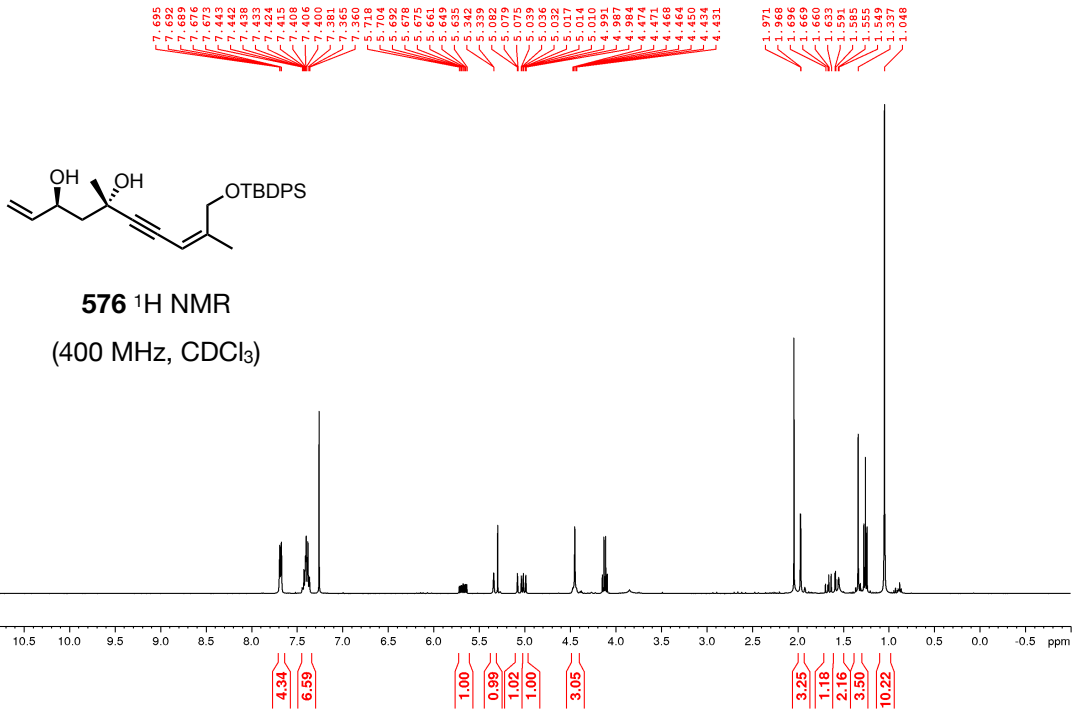

**574** $^{1}$H NMR

(400 MHz, $CDCl_3$)




**575** $^{1}$H NMR

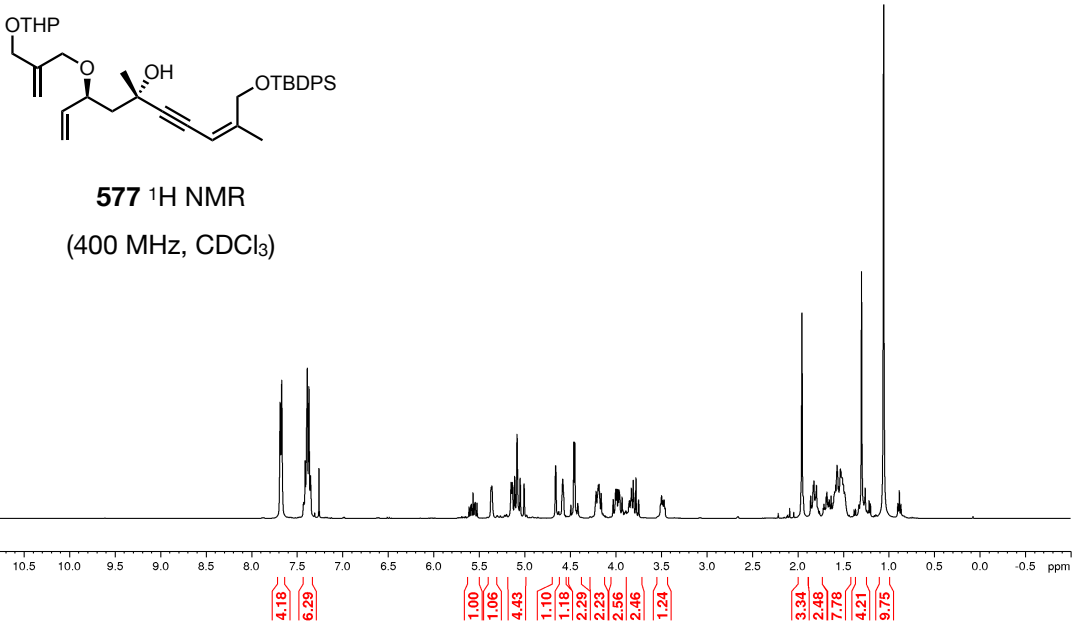
(400 MHz, $CDCl_3$)




**576** $^{1}$H NMR

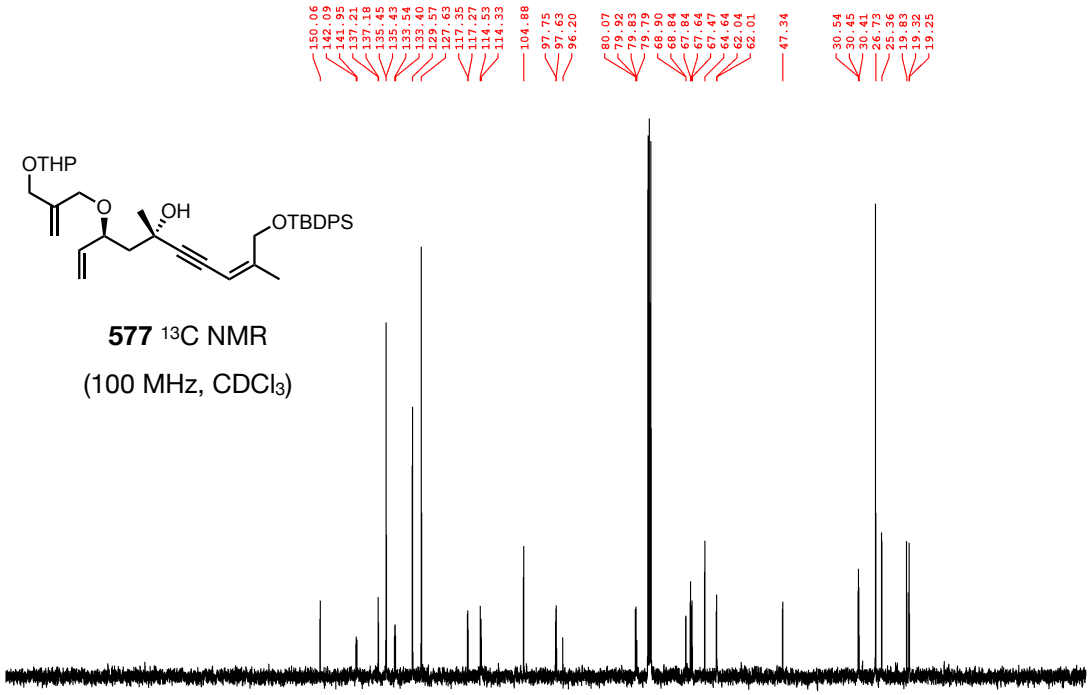
(400 MHz, $CDCl_3$)





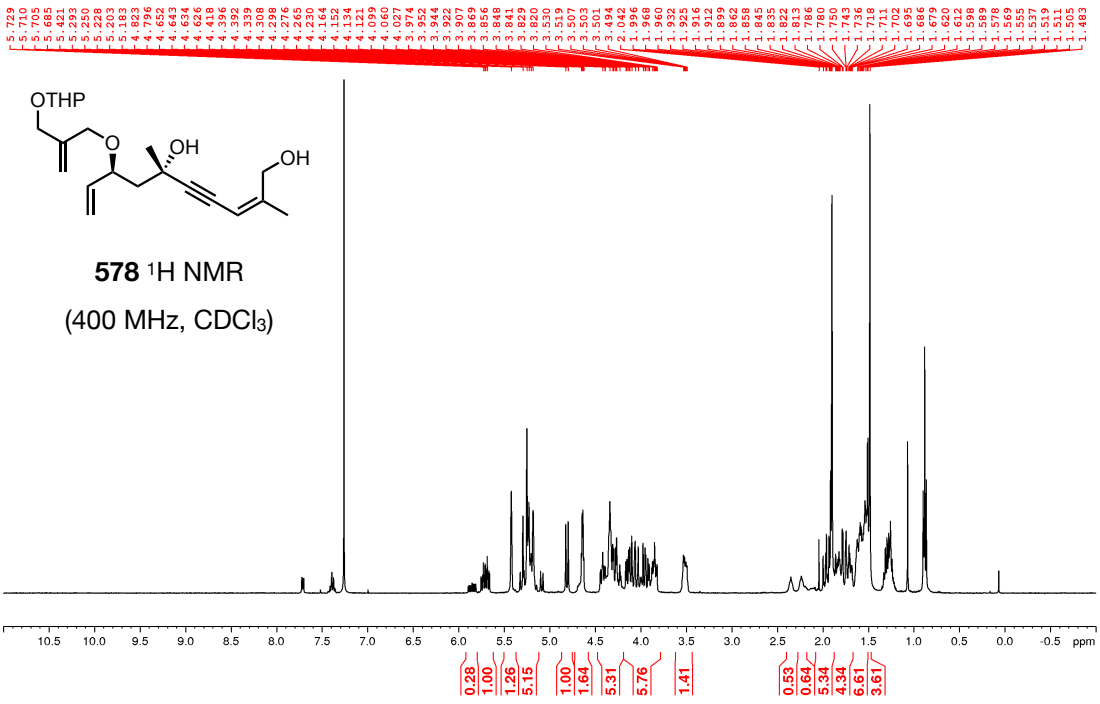

**577** $^{1}$H NMR

(400 MHz, $CDCl_3$)



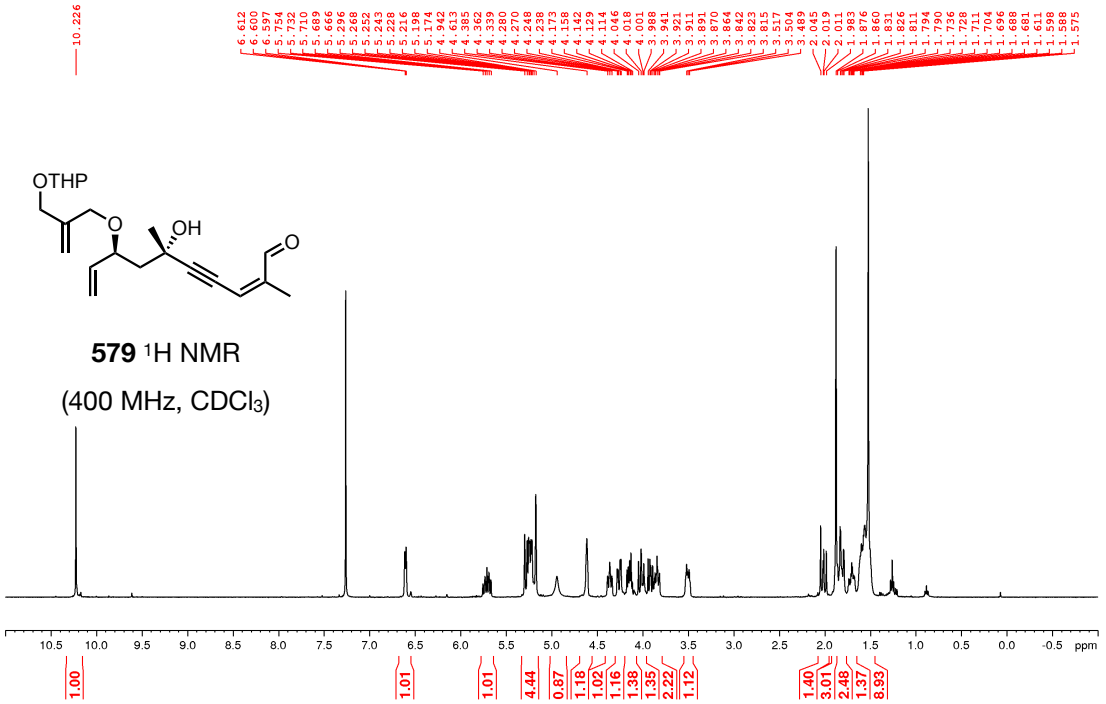

**577** $^{13}$C NMR

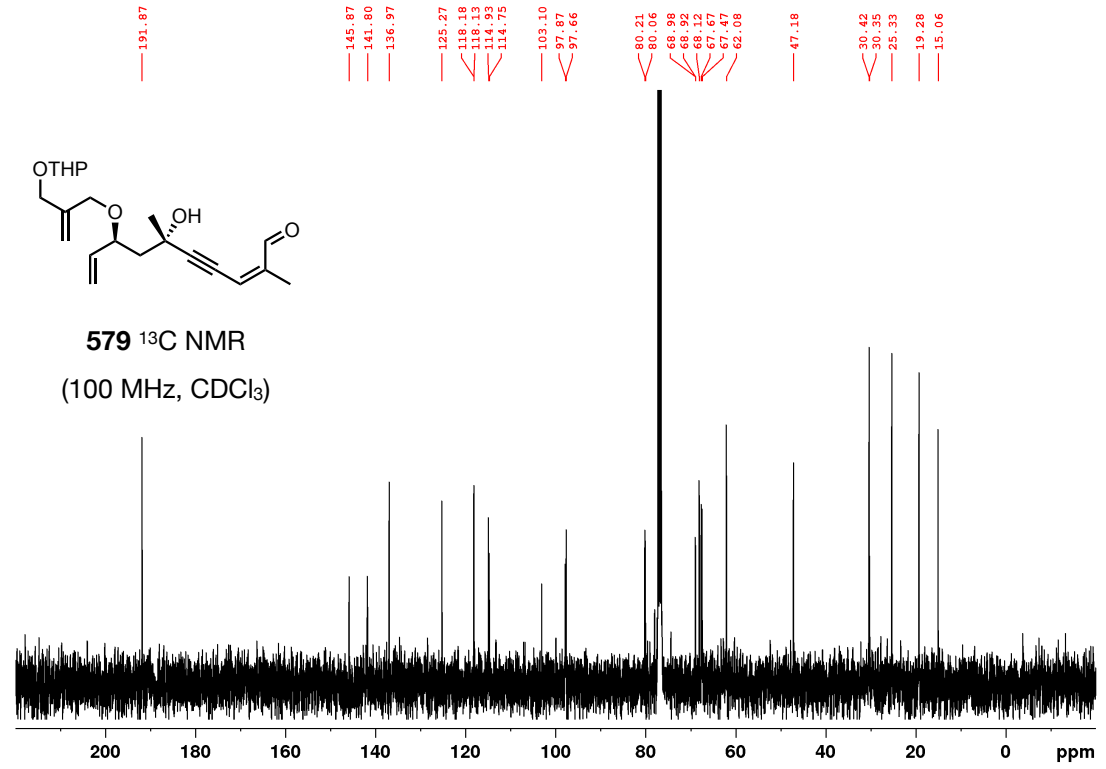
(100 MHz, $CDCl_3$)



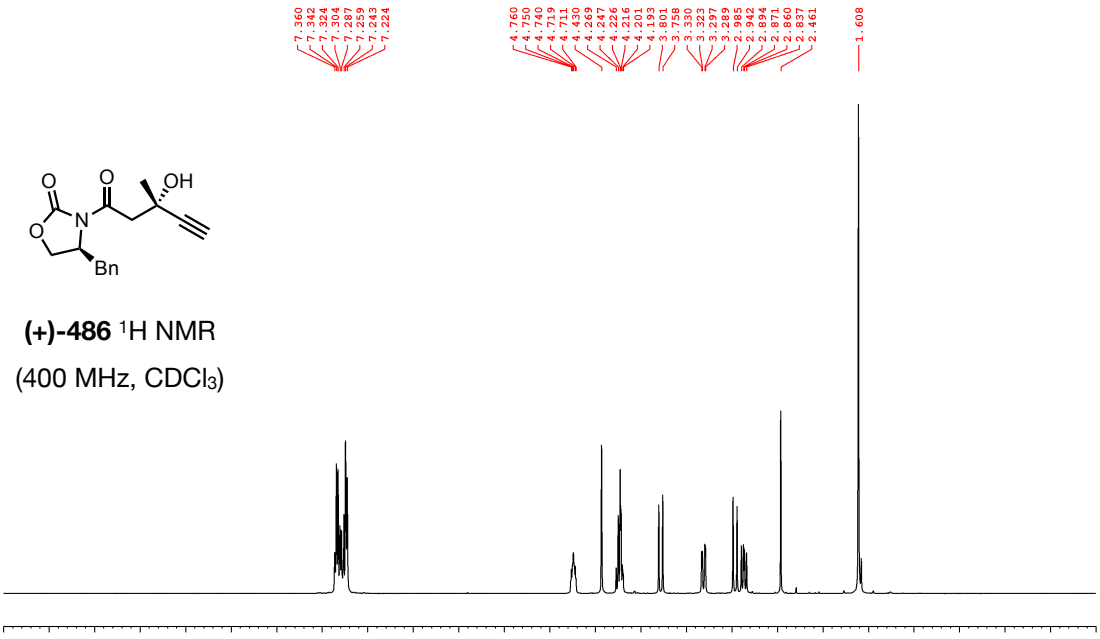

**578** $^{1}$H NMR

(400 MHz, $CDCl_3$)


OTHP
O
OH
O
579 1H NMR
(400 MHz, CDCl3)
ppm

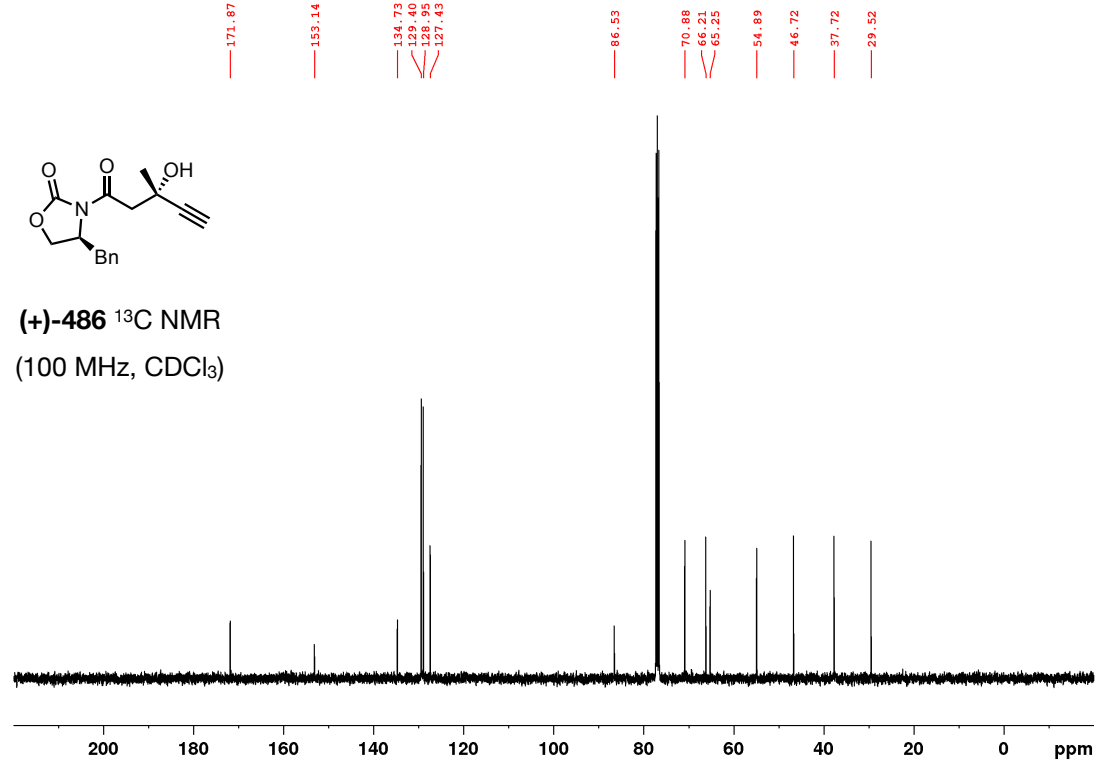

OTHP
O
OH
O
579 13C NMR
(100 MHz, CDCl3)
ppm

**NMR Spectra: Section 4.4:**



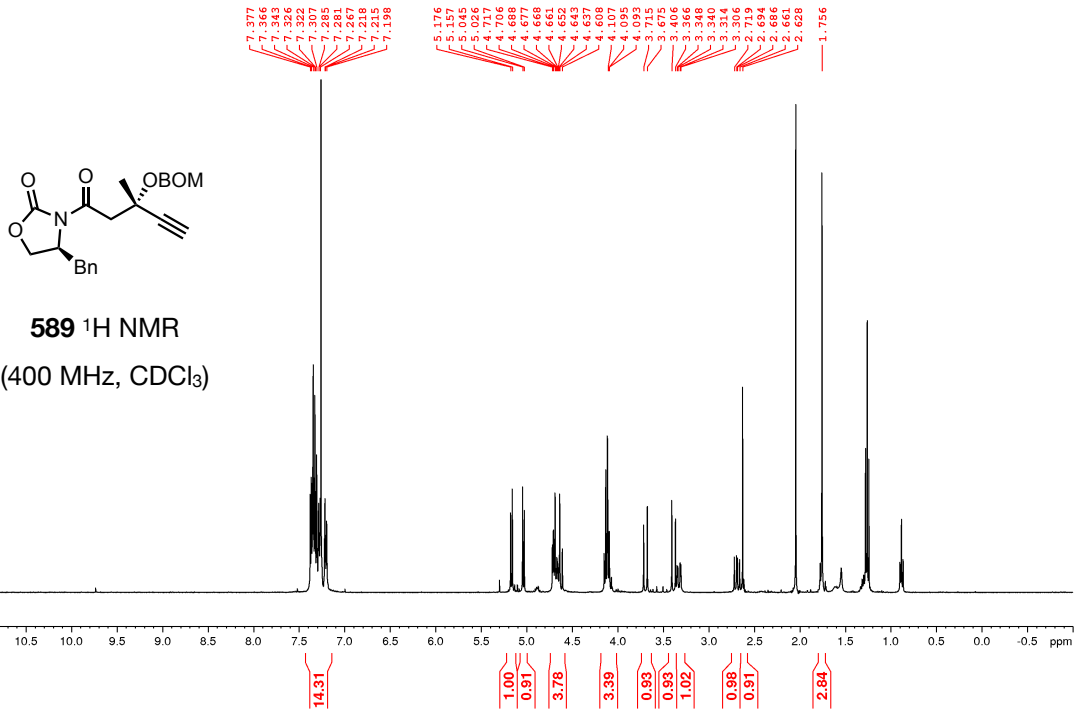

**(+)-486** $^{1}$H NMR

(400 MHz, $CDCl_3$)



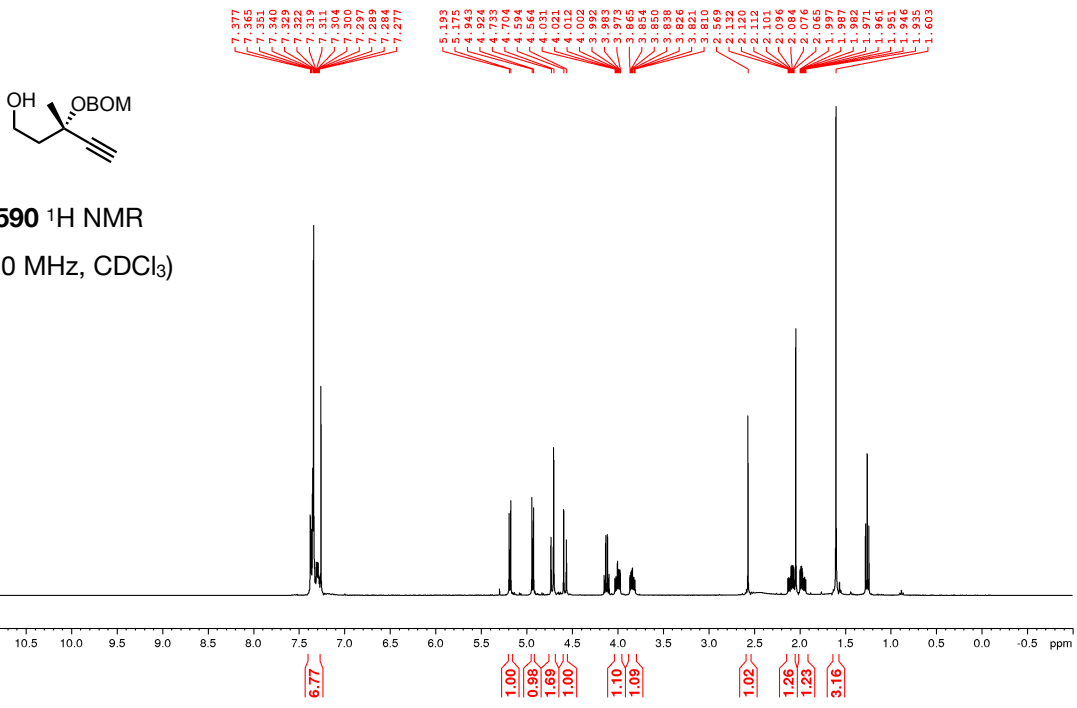

**(+)-486** $^{13}$C NMR

(100 MHz, $CDCl_3$)



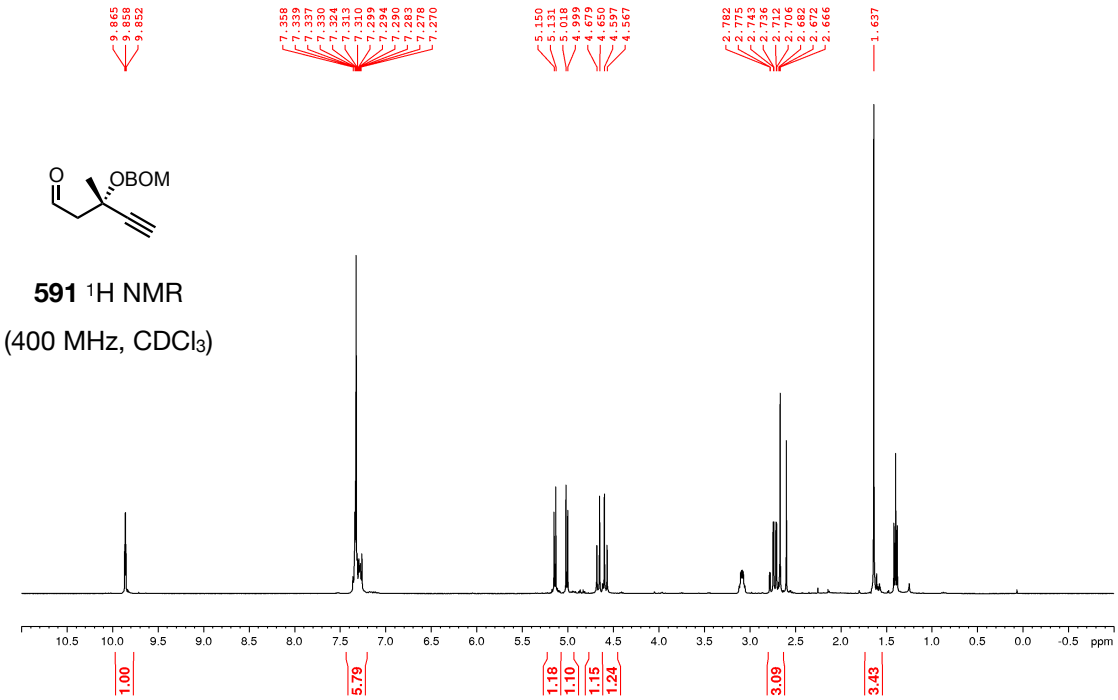

**589** $^1$H NMR

(400 MHz, $CDCl_3$)



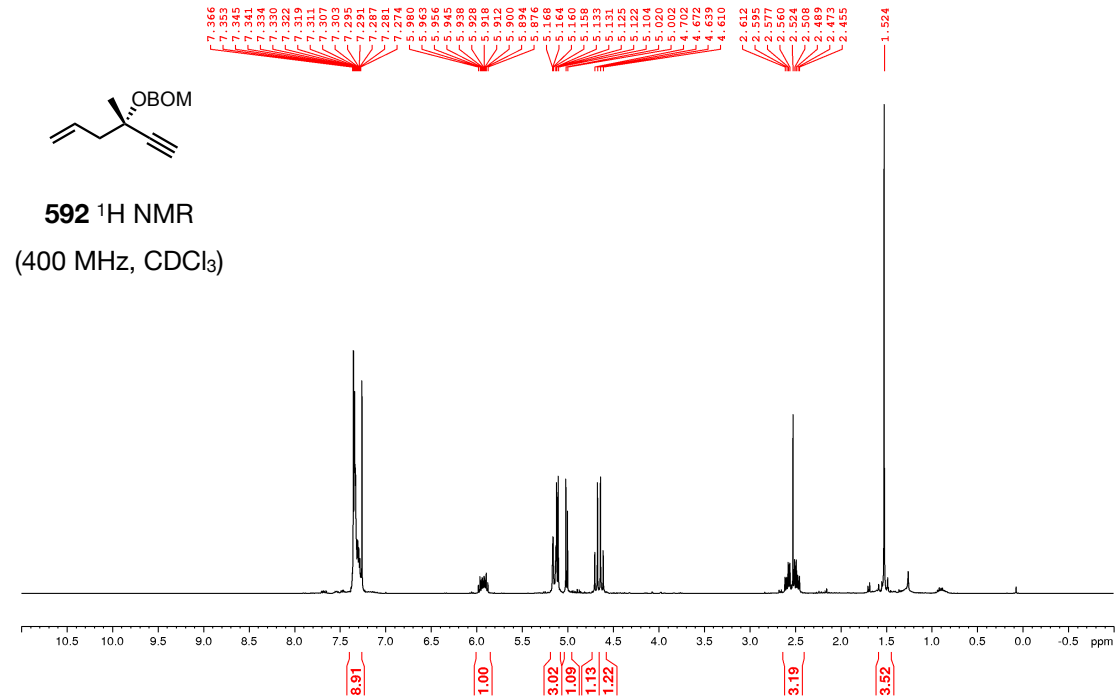

**590** $^1$H NMR

(400 MHz, $CDCl_3$)



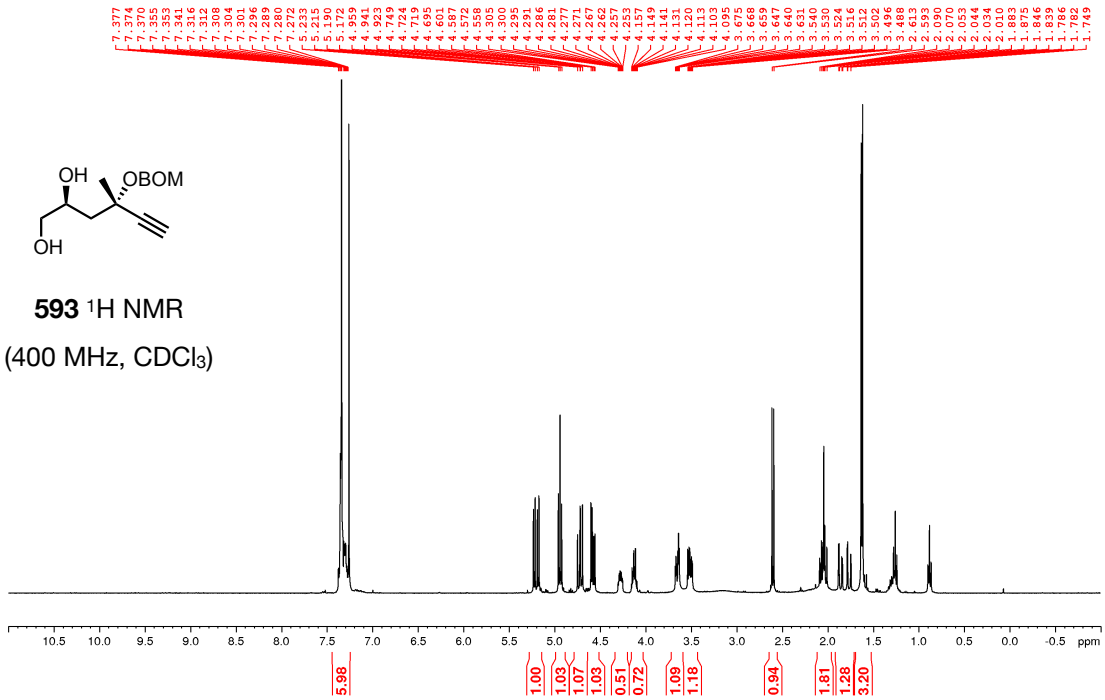

**591** $^{1}$H NMR

(400 MHz, $CDCl_3$)



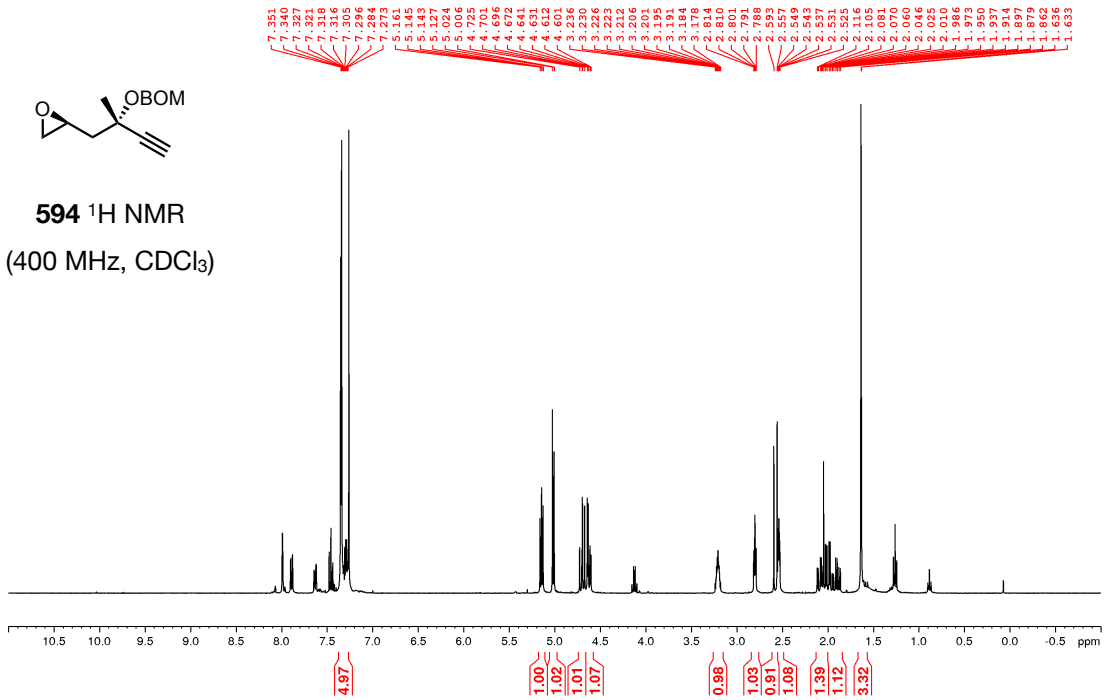

**592** $^{1}$H NMR

(400 MHz, $CDCl_3$)




**593** $^{1}$H NMR

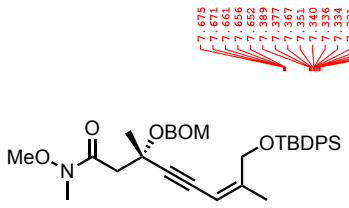
(400 MHz, $CDCl_3$)




**594** $^{1}$H NMR

(400 MHz, $CDCl_3$)

**NMR Spectra: Section 4.5:**




**587** $^1$H NMR

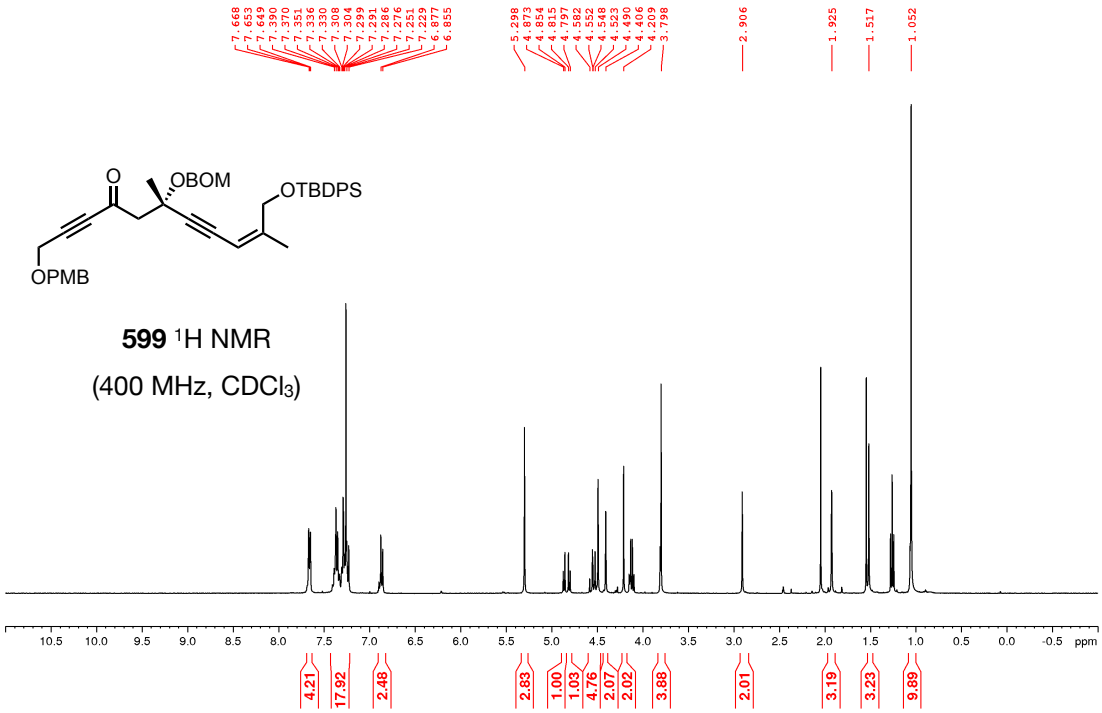
(400 MHz, $CDCl_3$)

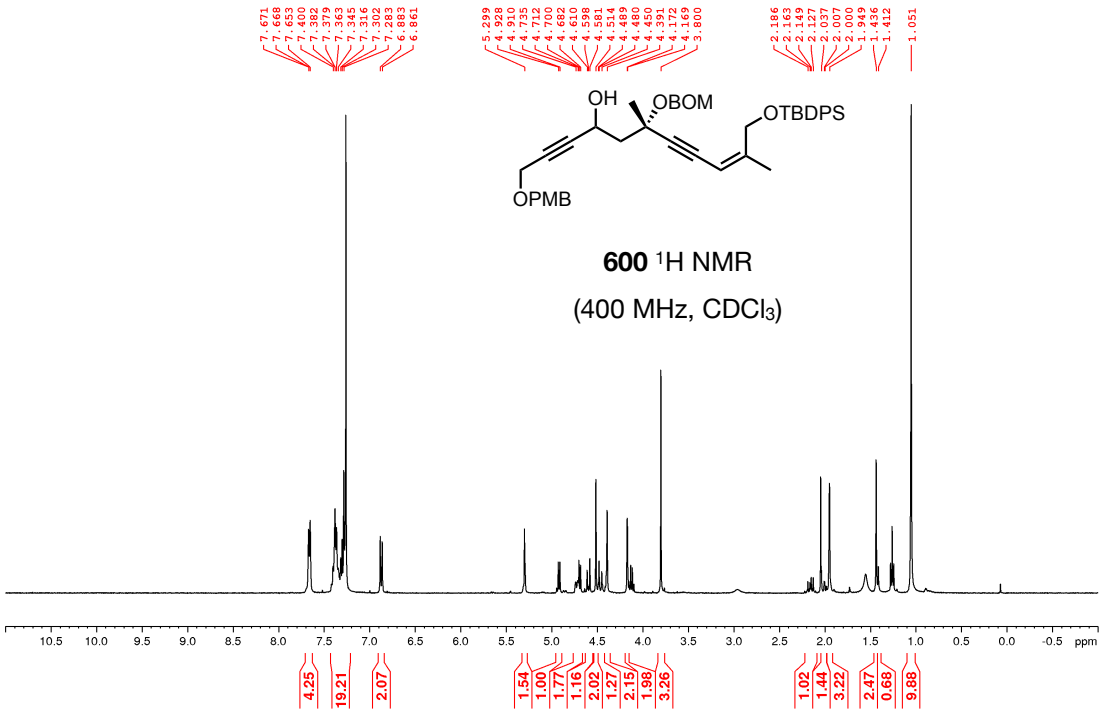


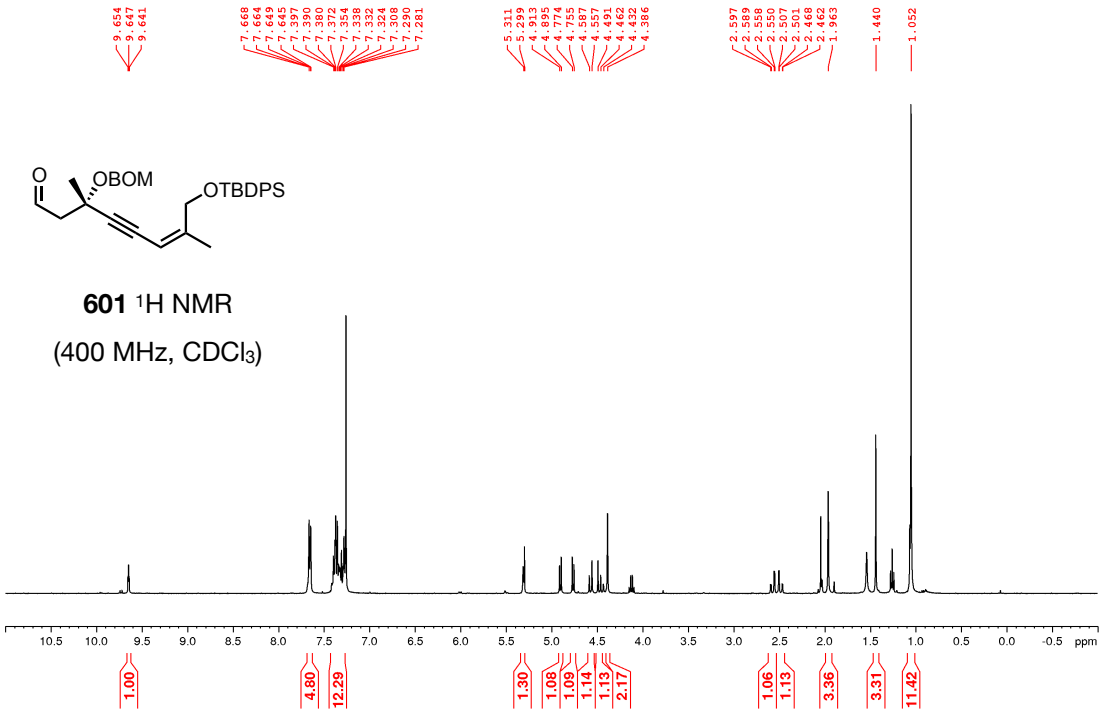


**121** $^1$H NMR

(400 MHz, $CDCl_3$)

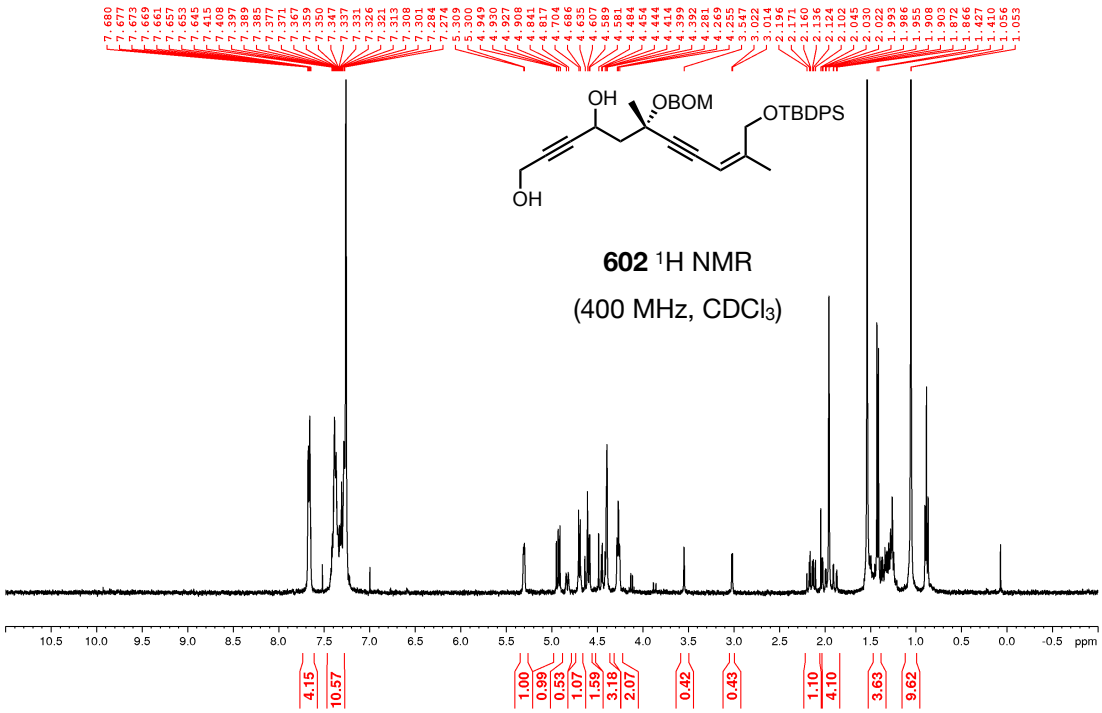

O
OBOM
OTBDPS
OPMB
599 1H NMR
(400 MHz, CDCl3)
ppm


OH
OBOM
OTBDPS
OPMB
600 1H NMR
(400 MHz, CDCl3)
ppm



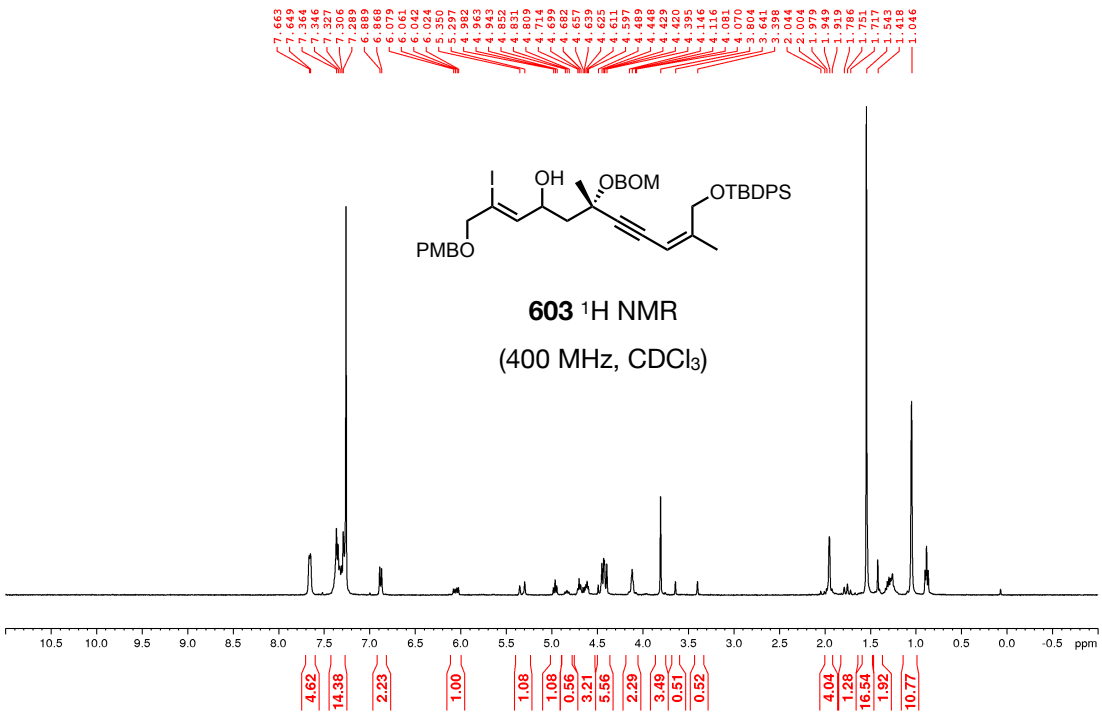

**601** $^{1}$H NMR

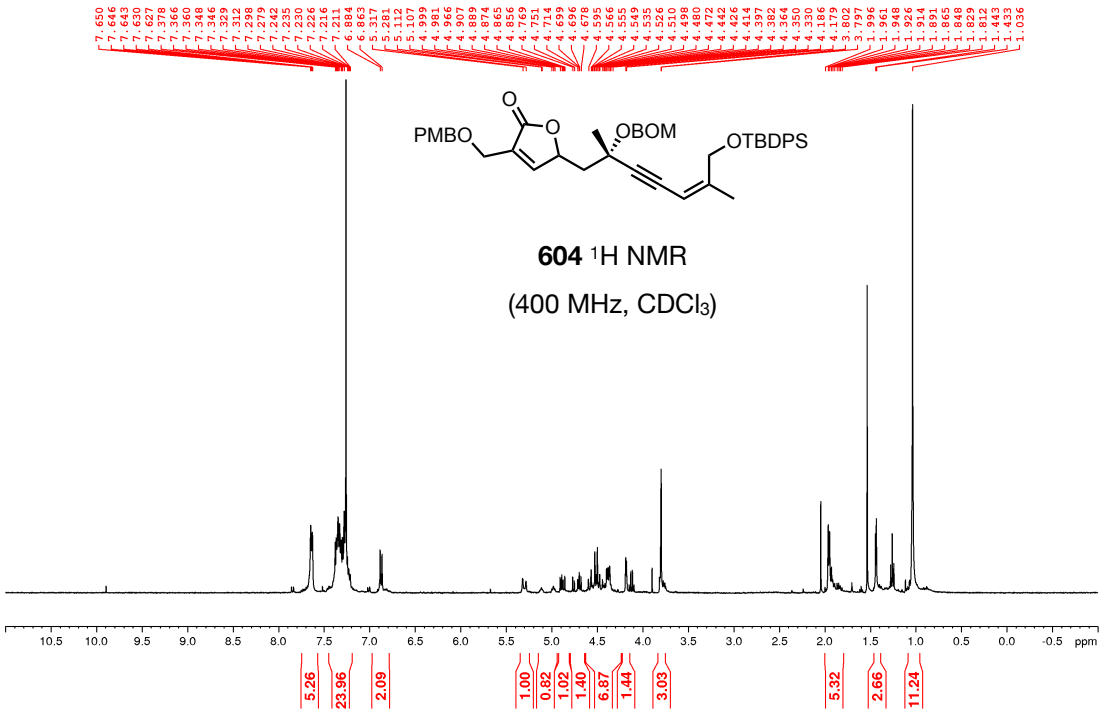
(400 MHz, $CDCl_3$)

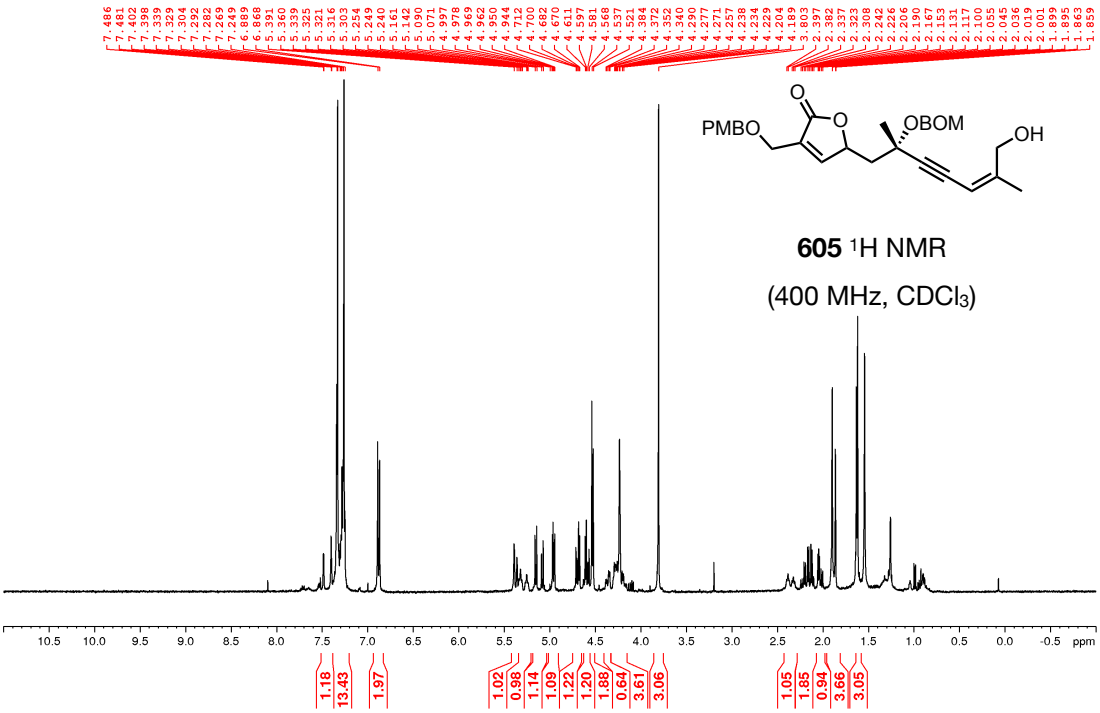


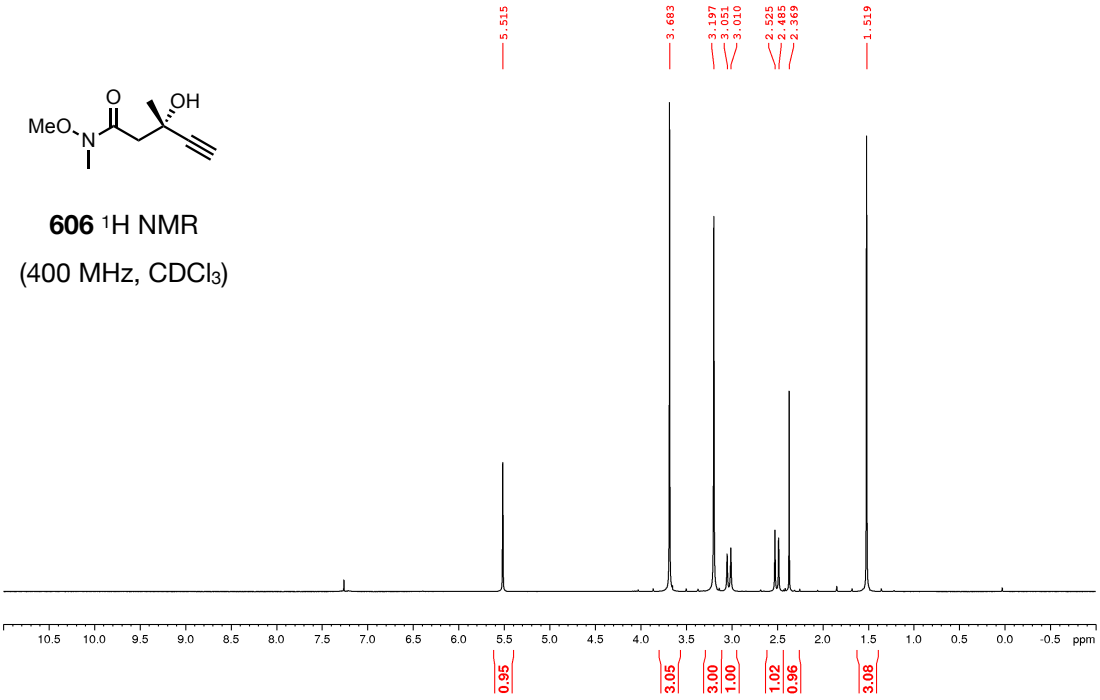

**602** $^{1}$H NMR

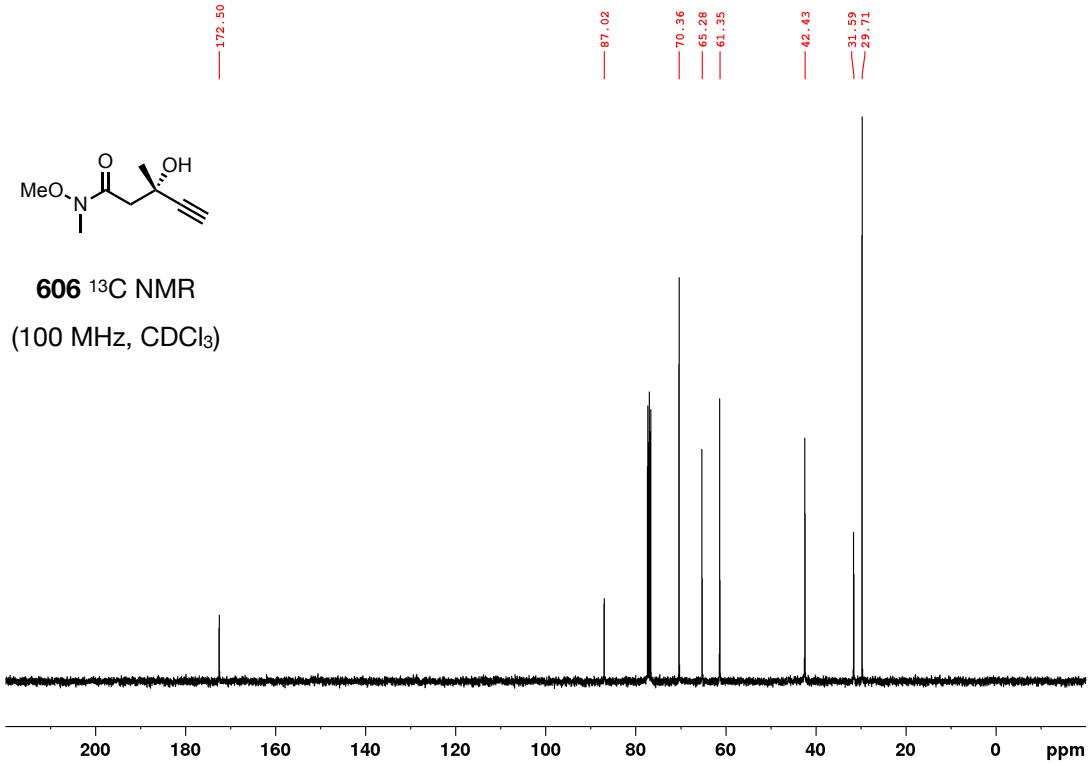
(400 MHz, $CDCl_3$)


I
OH
OBOM
OTBDPS
PMBO
603 1H NMR
(400 MHz, CDCl3)


O
O
PMBO
OBOM
OTBDPS
604 1H NMR
(400 MHz, CDCl3)

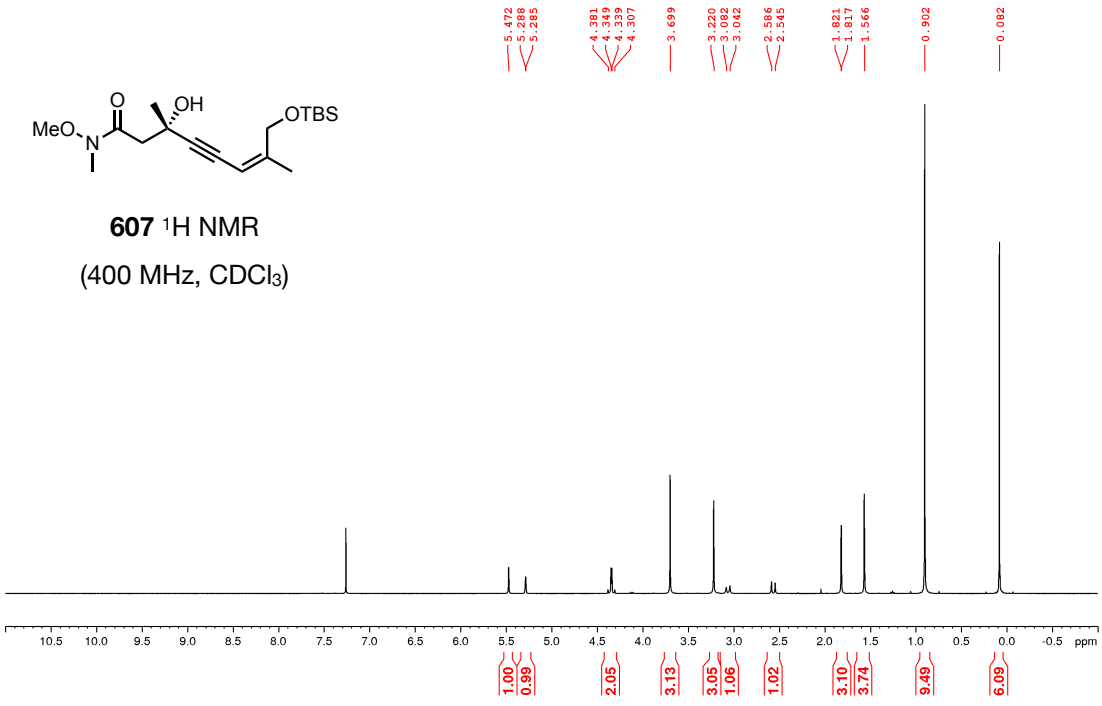

PMBO
O
O
OBOM
OH
605 1H NMR
(400 MHz, CDCl3)
ppm


MeO
N
O
OH
606 1H NMR
(400 MHz, CDCl3)
ppm



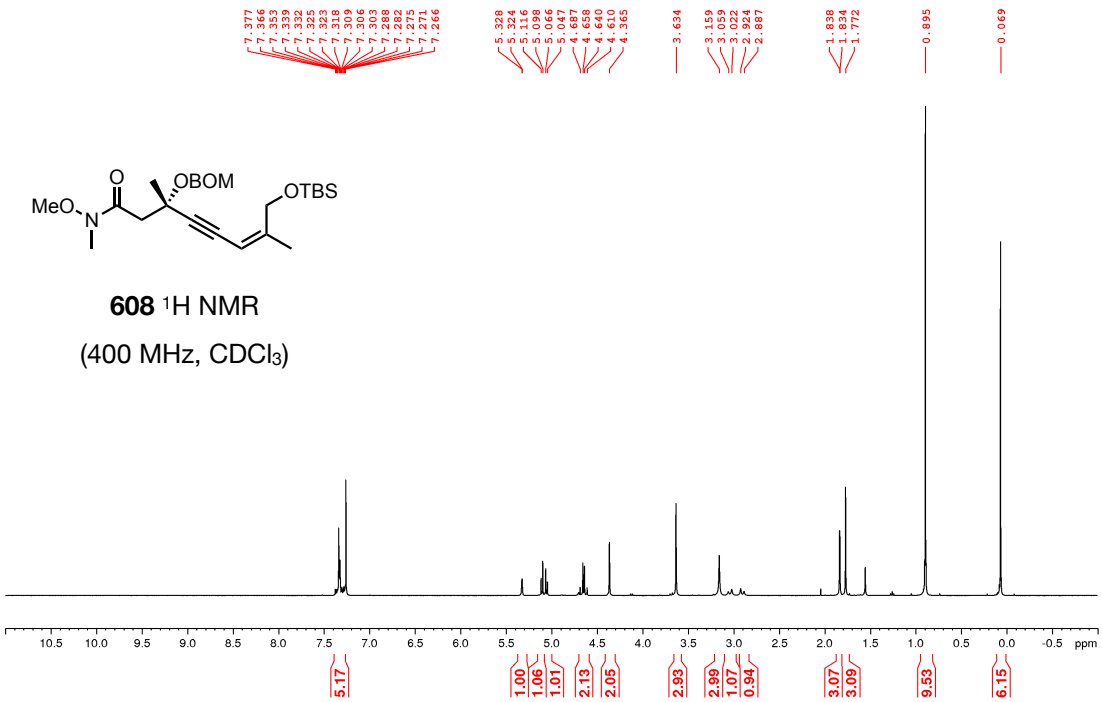

**606** $^{13}$C NMR

(100 MHz, $CDCl_3$)



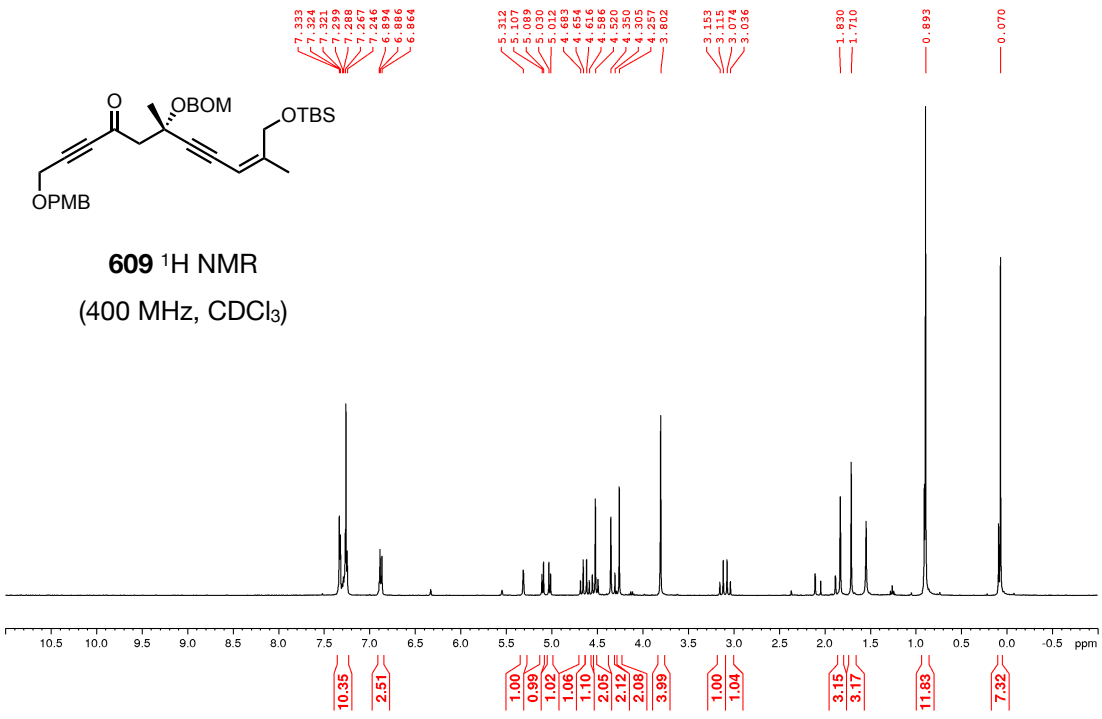

**607** $^{1}$H NMR

(400 MHz, $CDCl_3$)



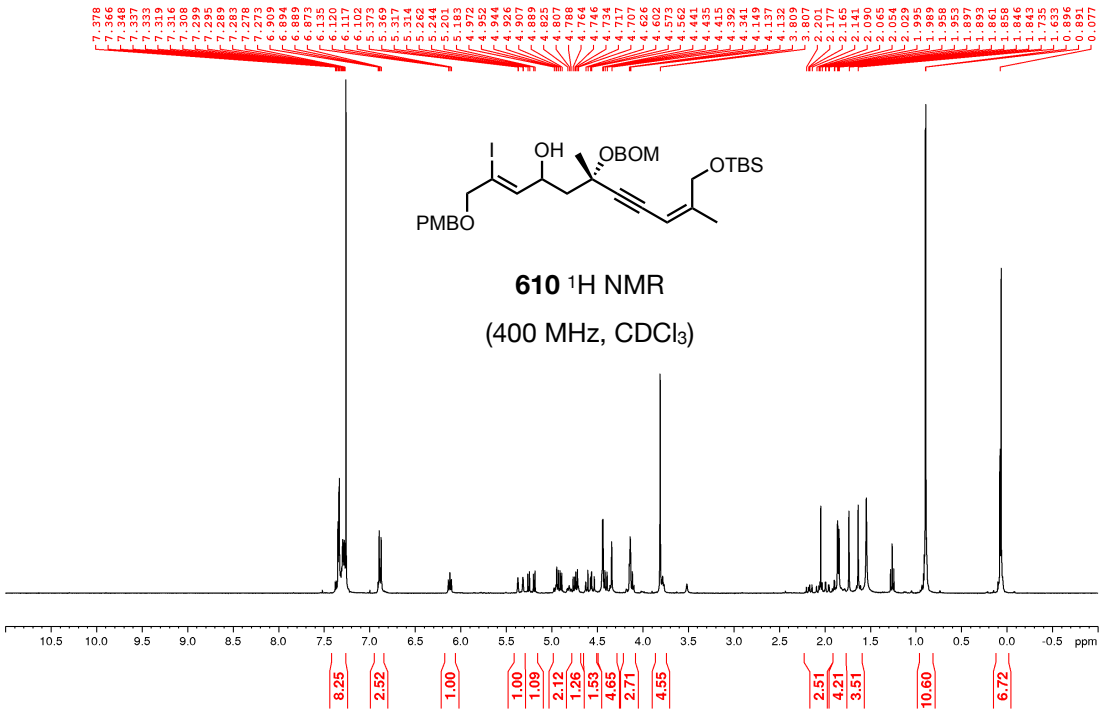

**608** $^{1}$H NMR

(400 MHz, $CDCl_3$)



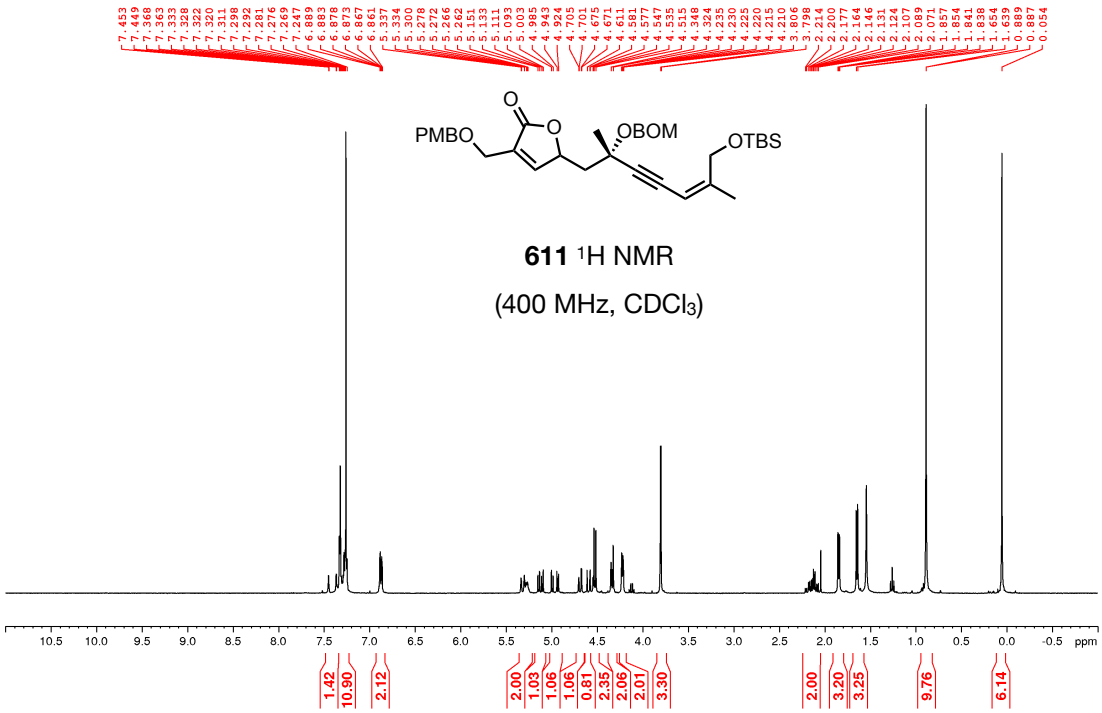

**609** $^{1}$H NMR

(400 MHz, $CDCl_3$)



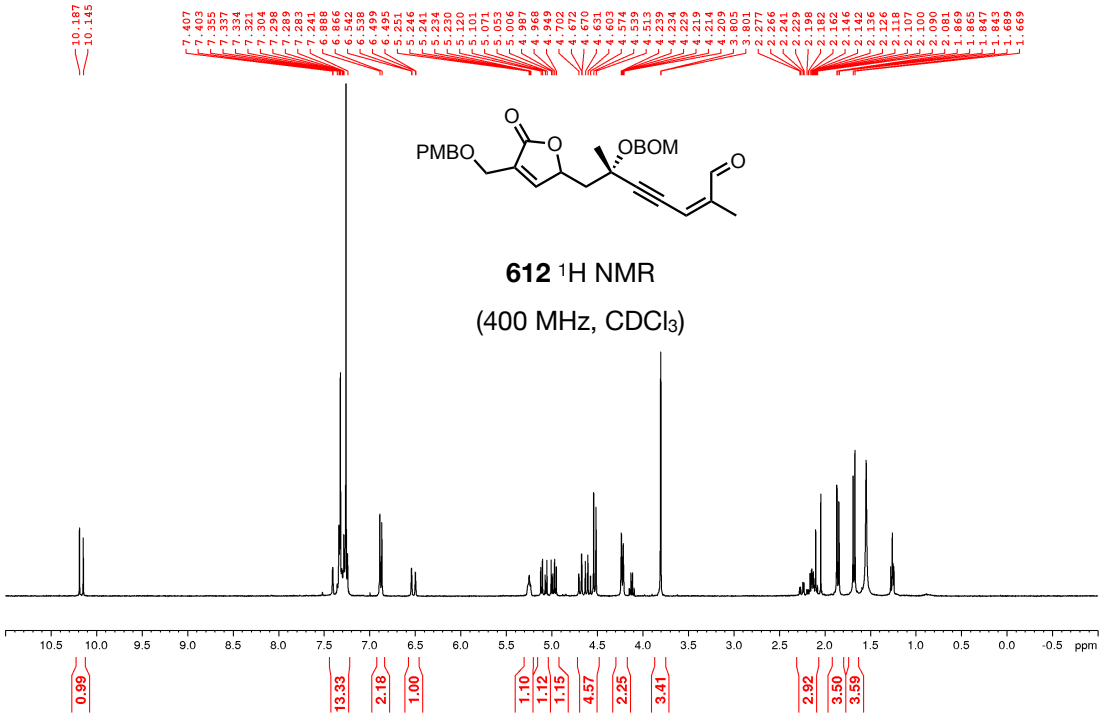

**610** $^{1}$H NMR

(400 MHz, $CDCl_3$)



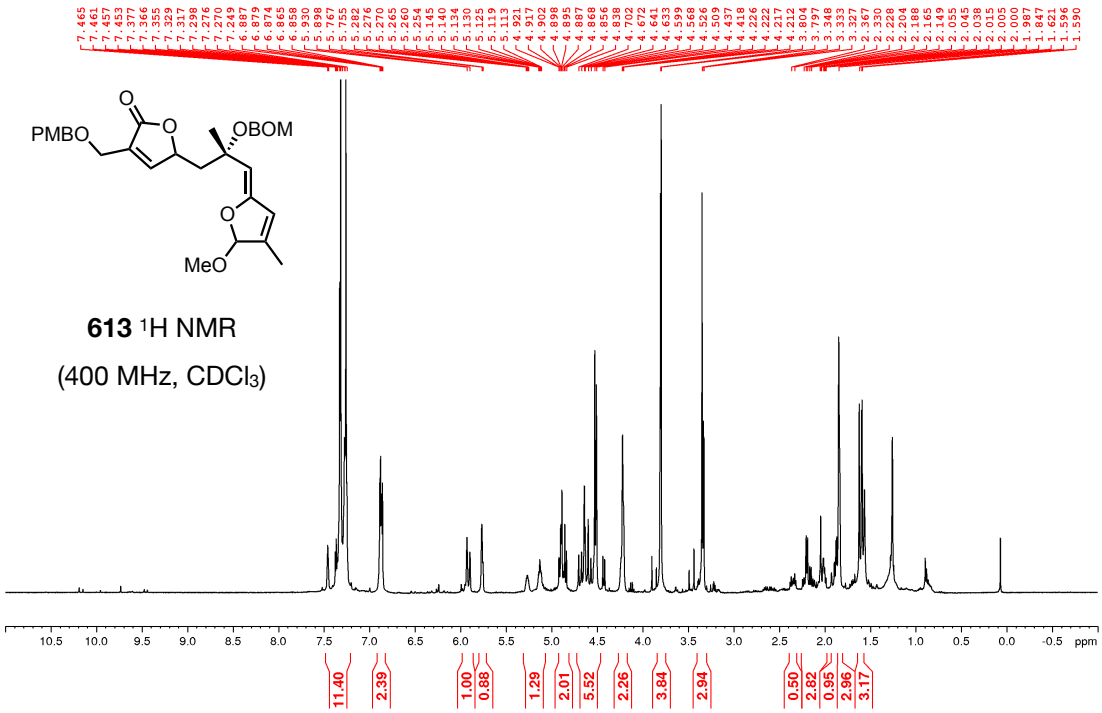

**611** $^{1}$H NMR

(400 MHz, $CDCl_3$)



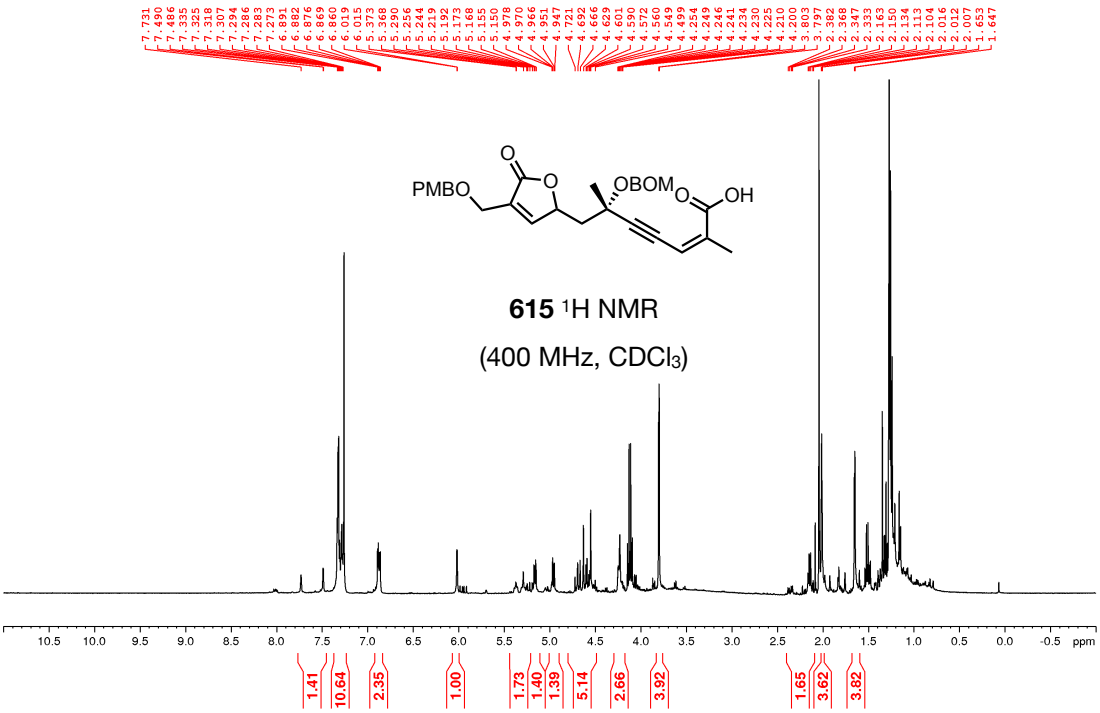

**612** $^1$H NMR

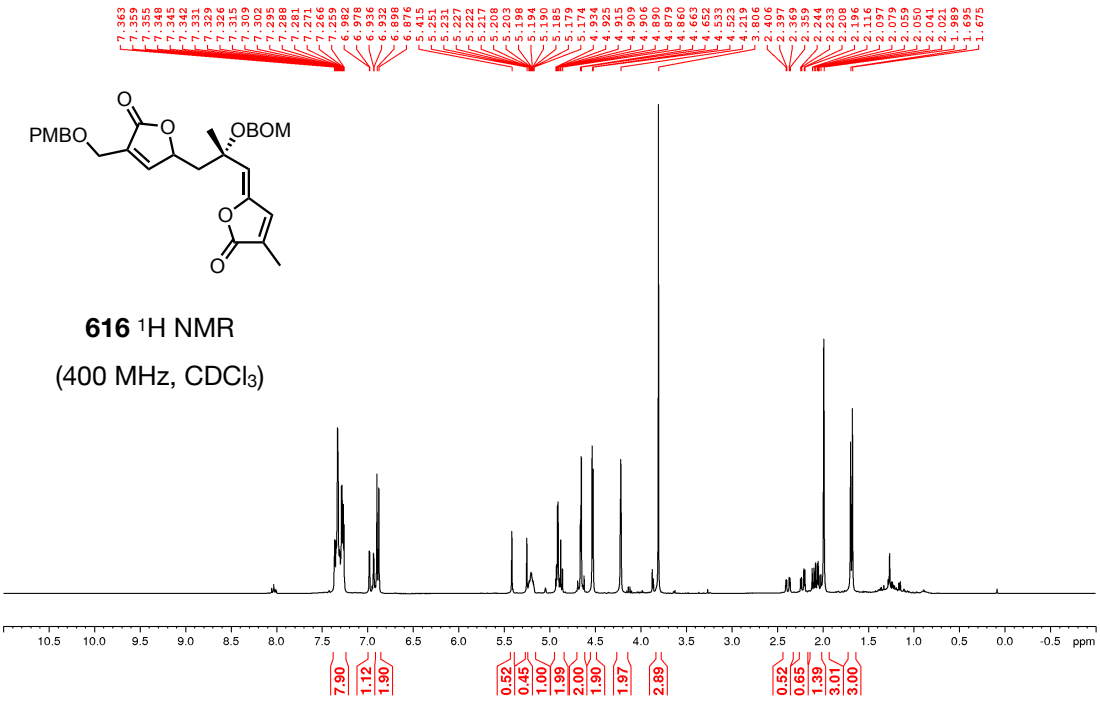
(400 MHz, $CDCl_3$)

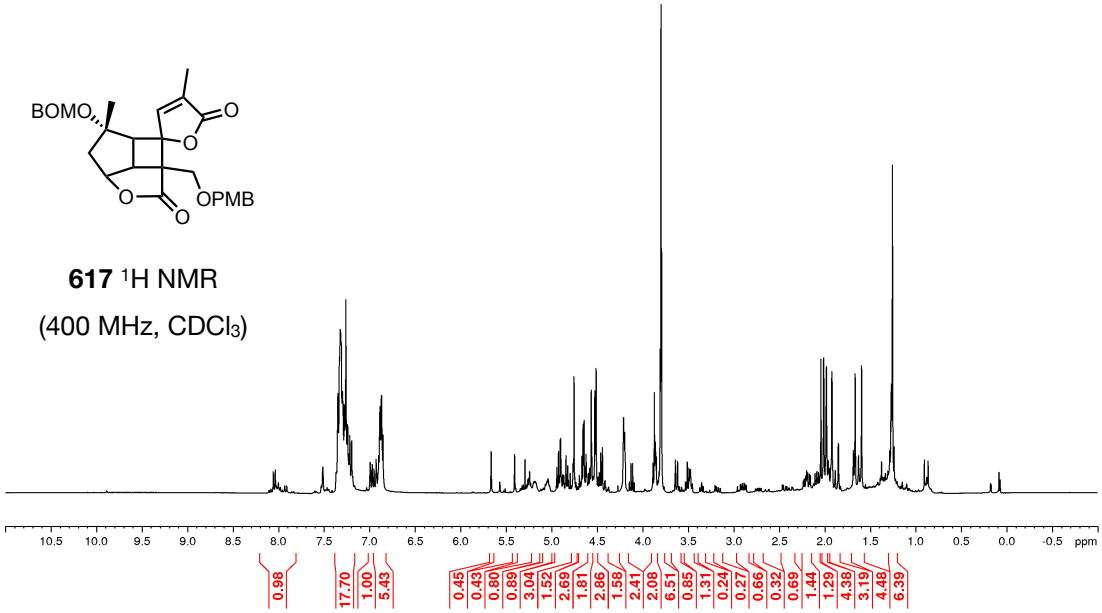



**613** $^1$H NMR

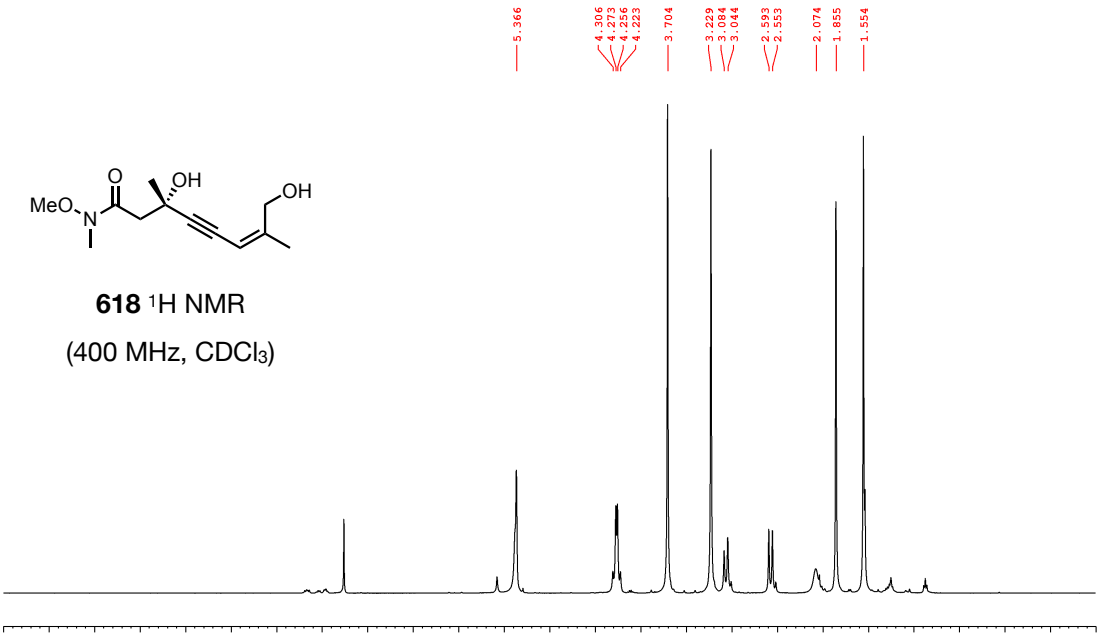
(400 MHz, $CDCl_3$)


PMBO
O
O
OBOM
O
OH
615 1H NMR
(400 MHz, CDCl3)
ppm


PMBO
O
O
OBOM
O
O
616 1H NMR
(400 MHz, CDCl3)
ppm

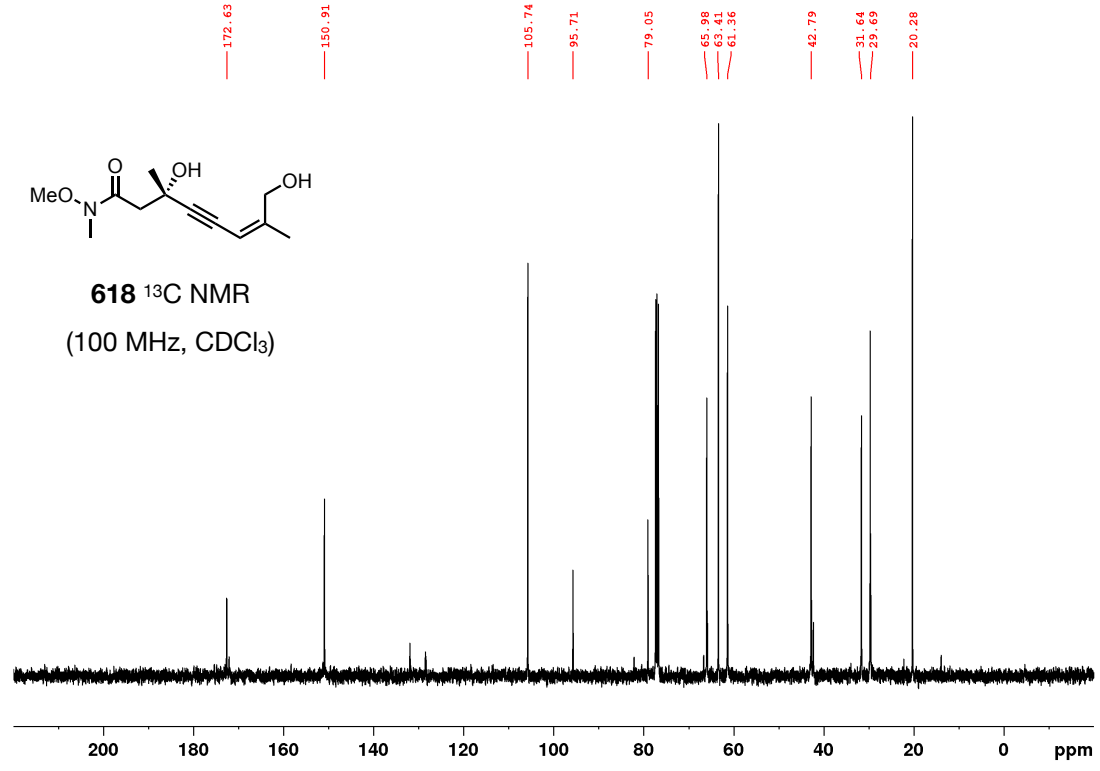

BOMO
O
O
O
O
OPMB
617 1H NMR
(400 MHz, CDCl3)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm
0.98 17.70 1.00 5.43 0.45 0.43 0.80 0.89 3.04 1.52 2.69 1.81 2.86 1.58 2.41 2.08 6.51 0.85 1.31 0.24 0.27 0.66 0.32 0.69 1.44 1.29 4.38 3.19 4.48 6.39

**NMR Spectra: Section 4.6:**



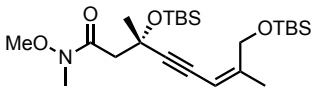

**618** $^{1}$H NMR

(400 MHz, $CDCl_3$)




**618** $^{13}$C NMR

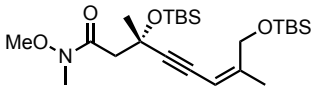
(100 MHz, $CDCl_3$)




**619** $^{1}$H NMR

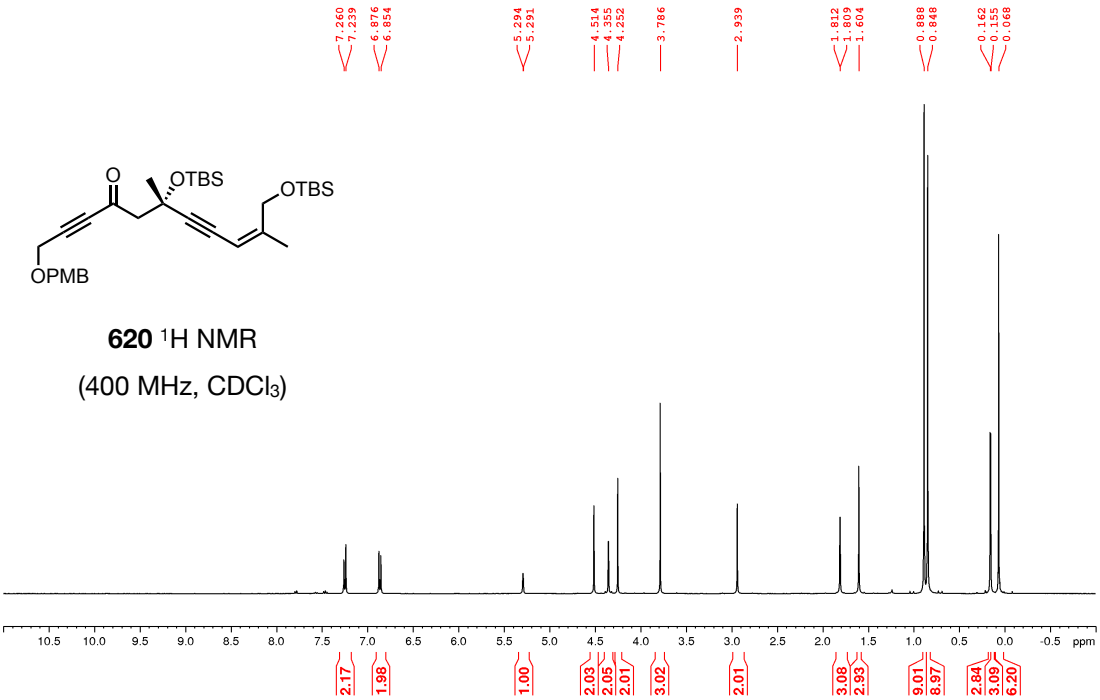
(400 MHz, $CDCl_3$)

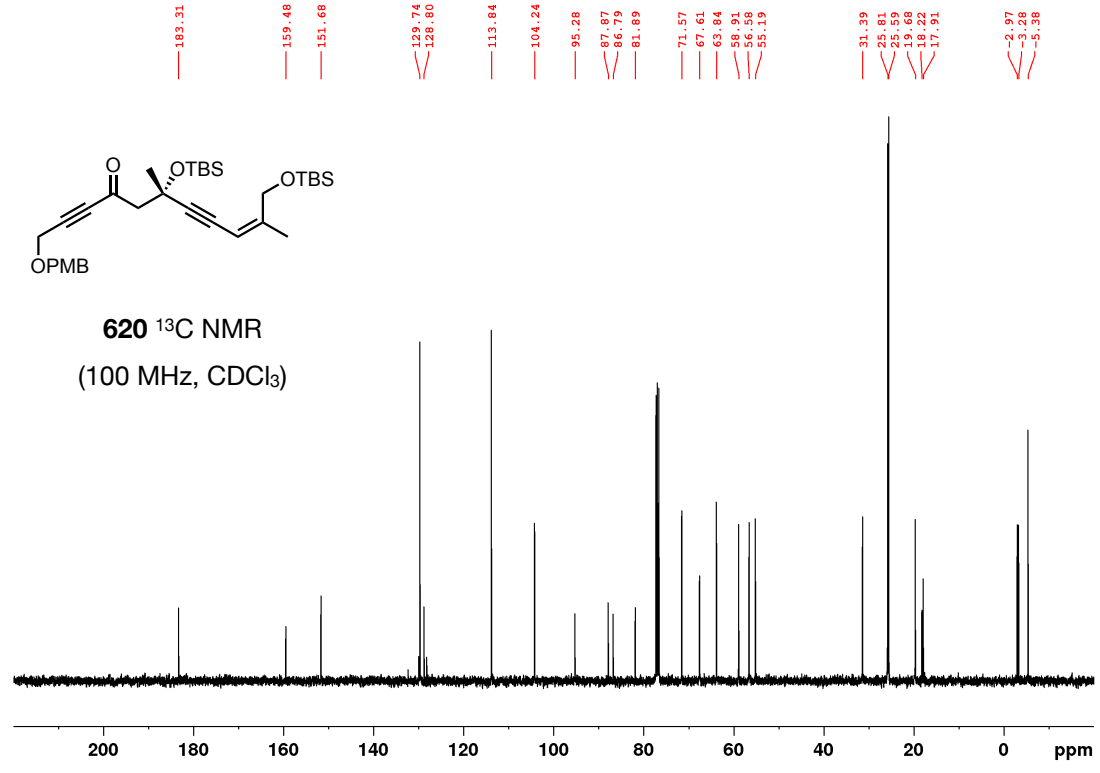


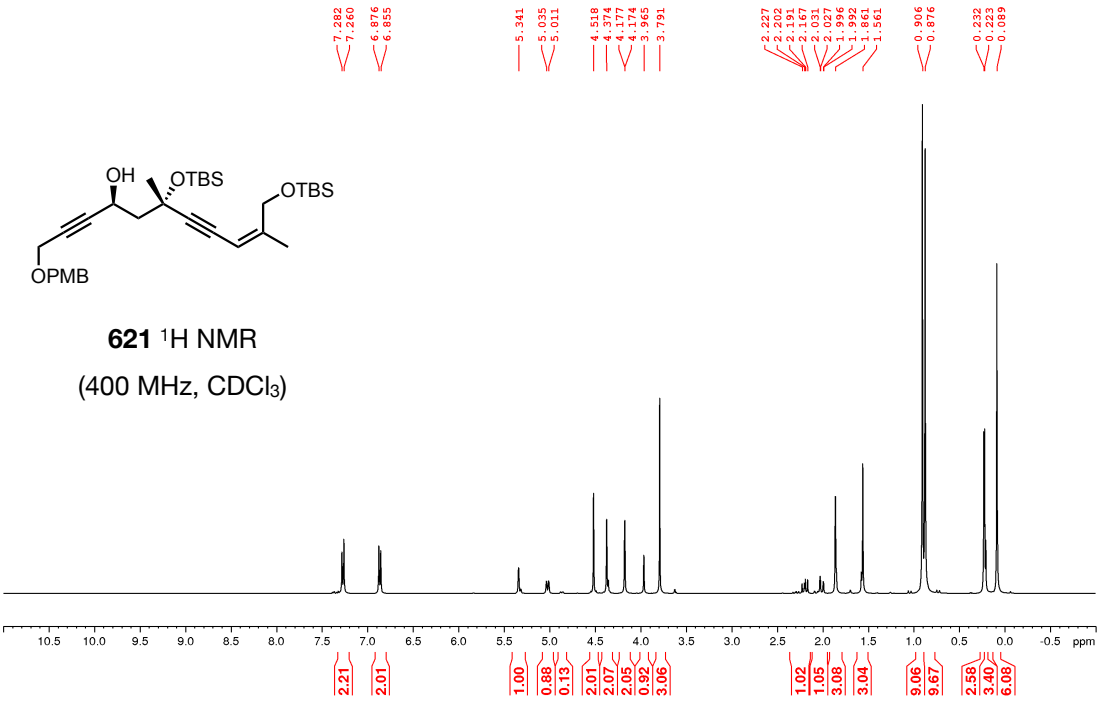




**619** $^{13}$C NMR

(100 MHz, $CDCl_3$)


OTBS
OTBS
OPMB
620 1H NMR
(400 MHz, CDCl3)
ppm


OTBS
OTBS
OPMB
620 13C NMR
(100 MHz, CDCl3)
ppm




**621** $^{1}$H NMR

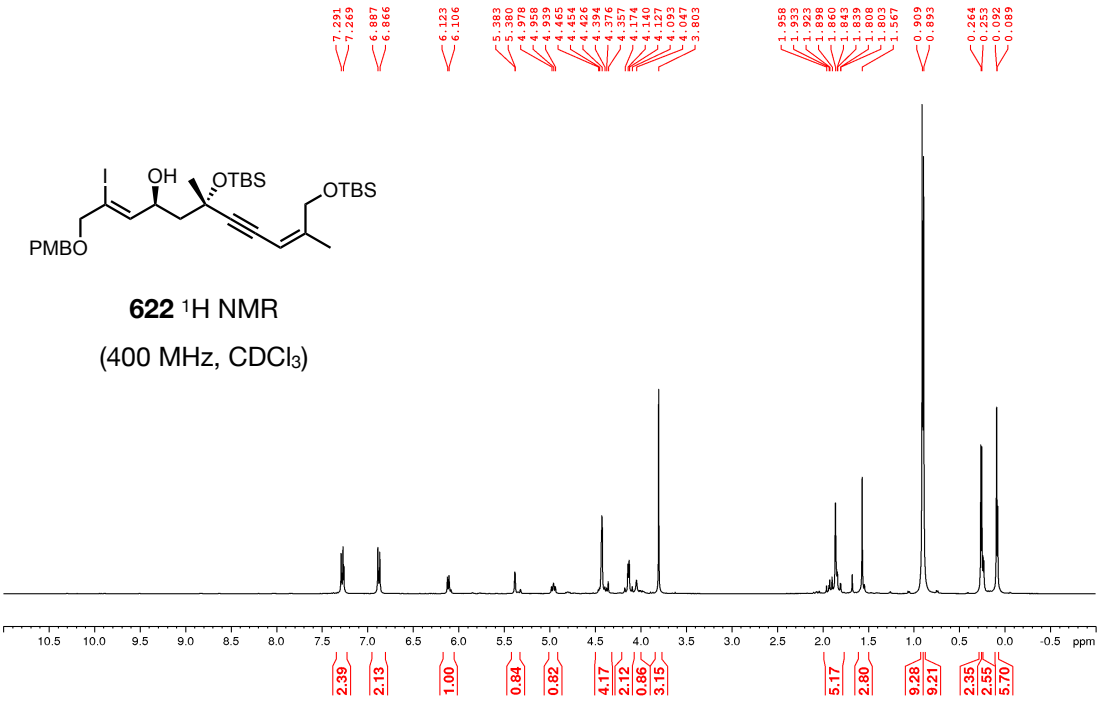
(400 MHz, $CDCl_3$)





**621** $^{13}$C NMR

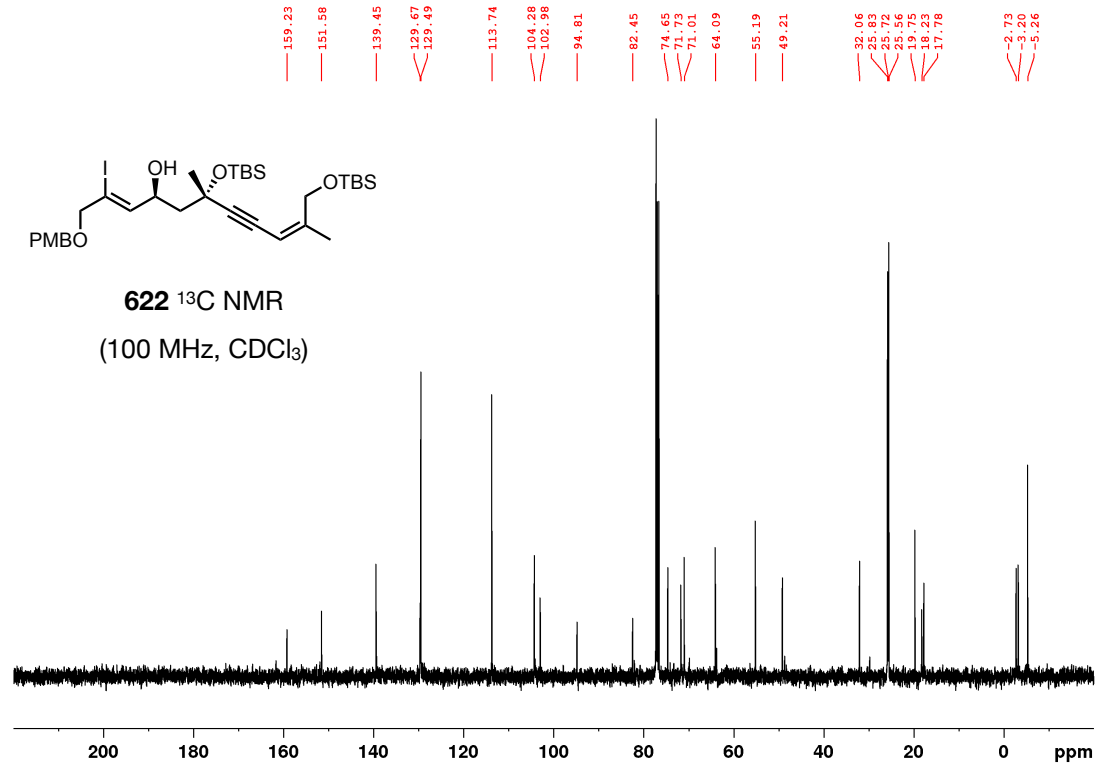
(100 MHz, $CDCl_3$)




**622** $^{1}$H NMR

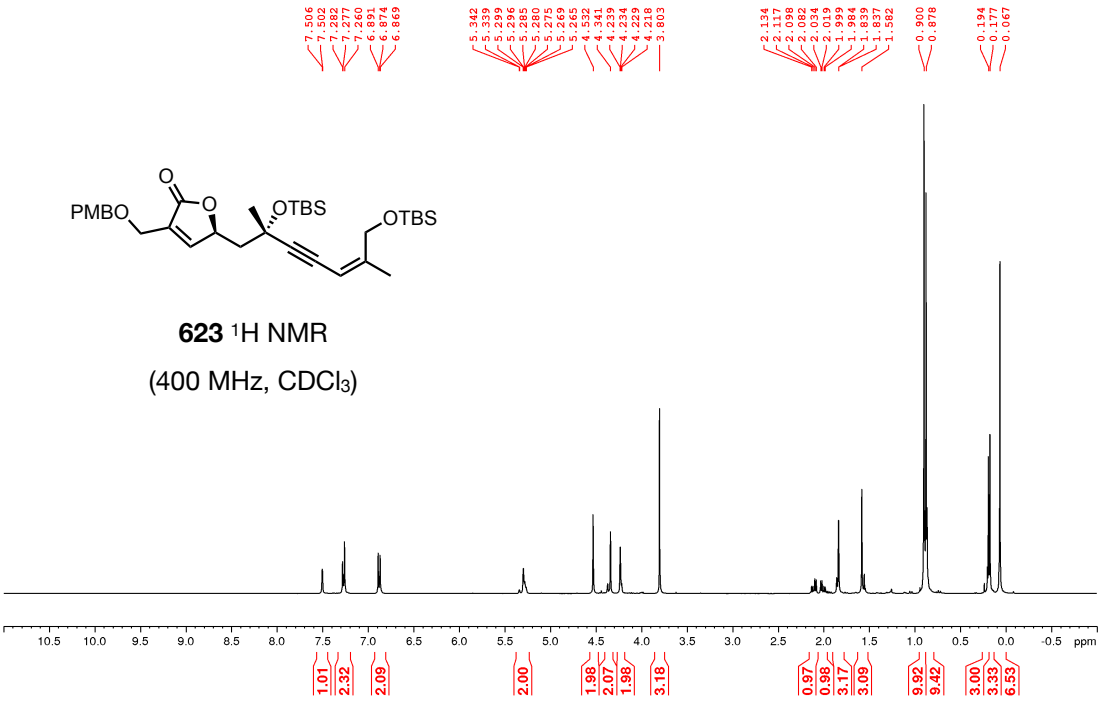
(400 MHz, $CDCl_3$)




**622** $^{13}$C NMR

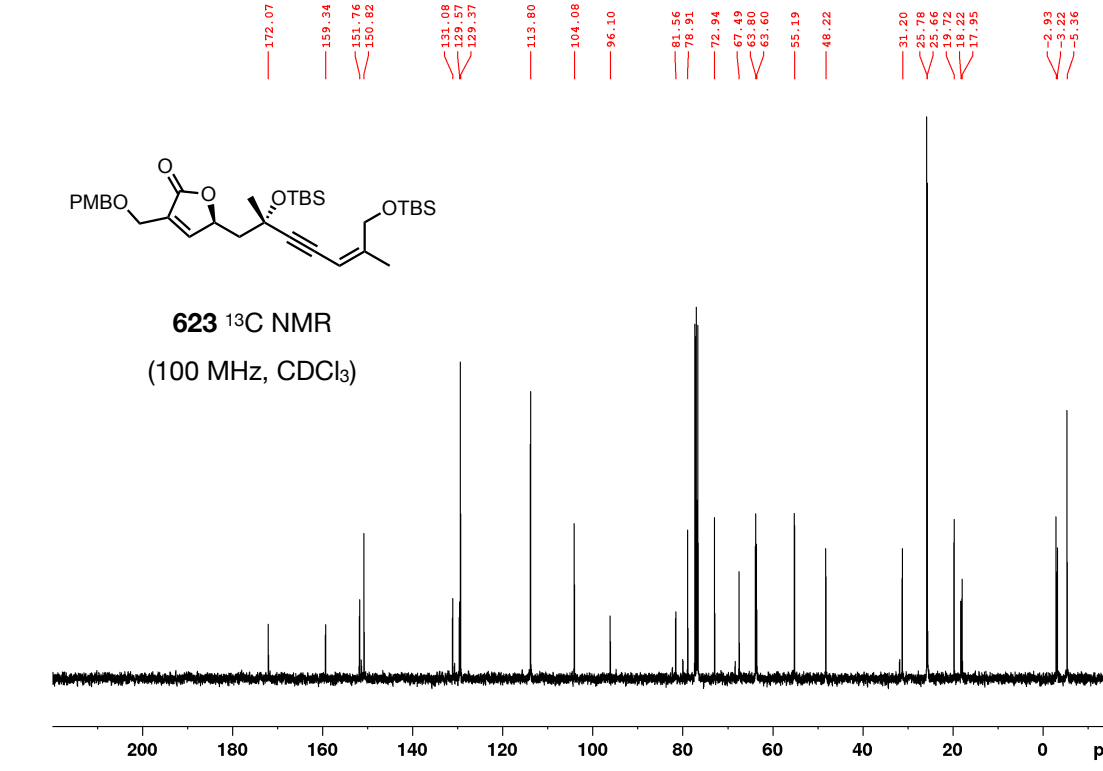
(100 MHz, $CDCl_3$)




**623** $^{1}$H NMR

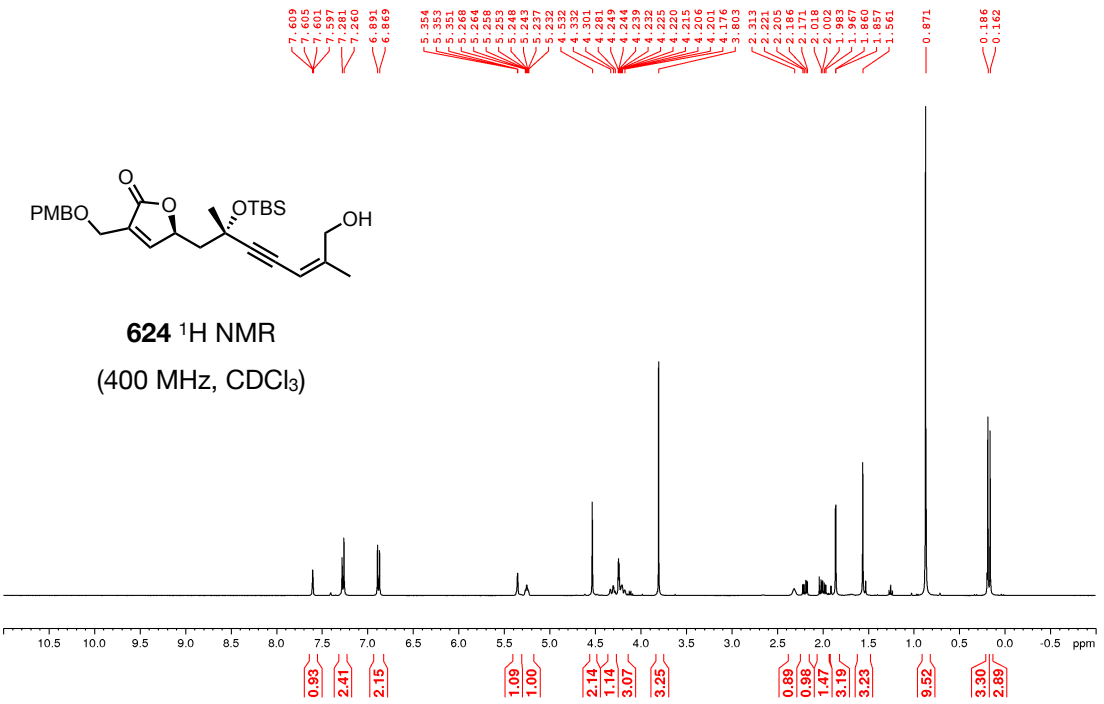
(400 MHz, $CDCl_3$)




**623** $^{13}$C NMR

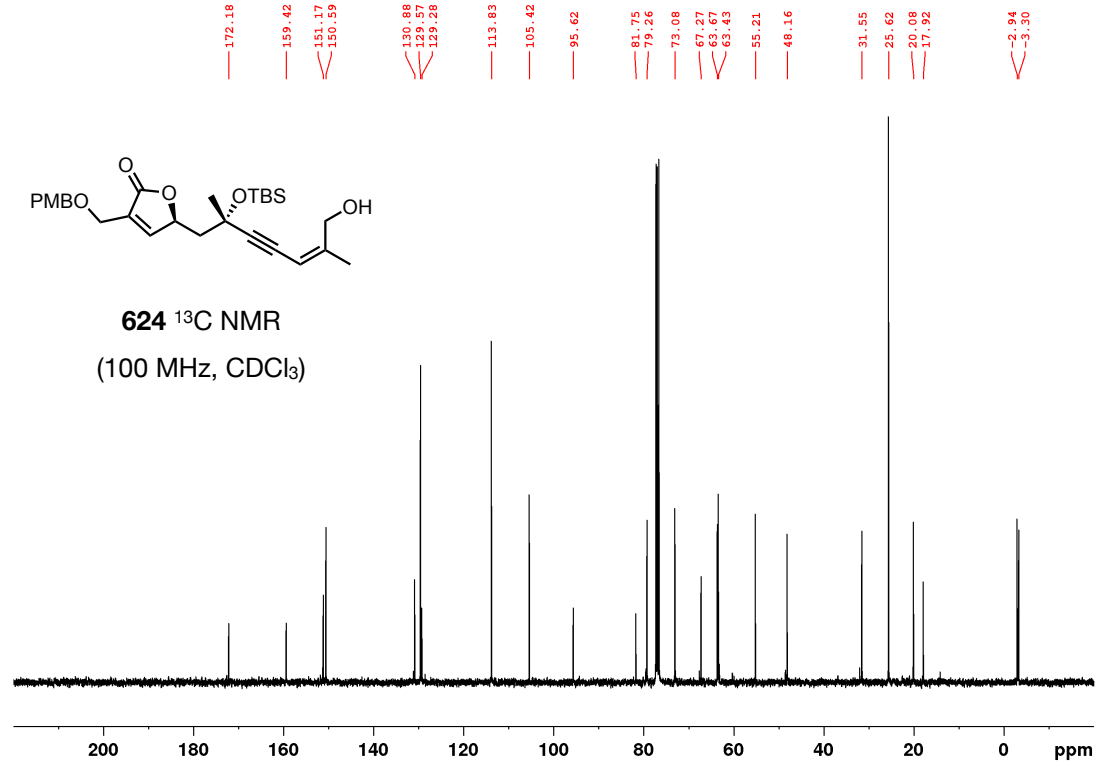
(100 MHz, $CDCl_3$)




**624** $^{1}$H NMR

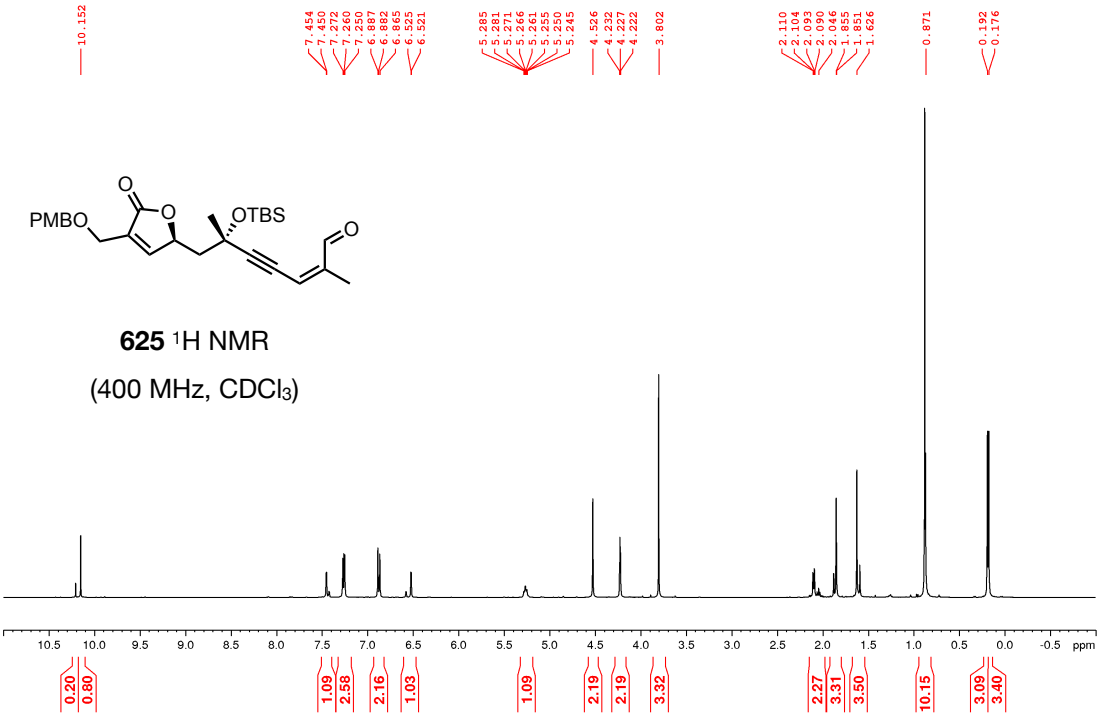
(400 MHz, $CDCl_3$)



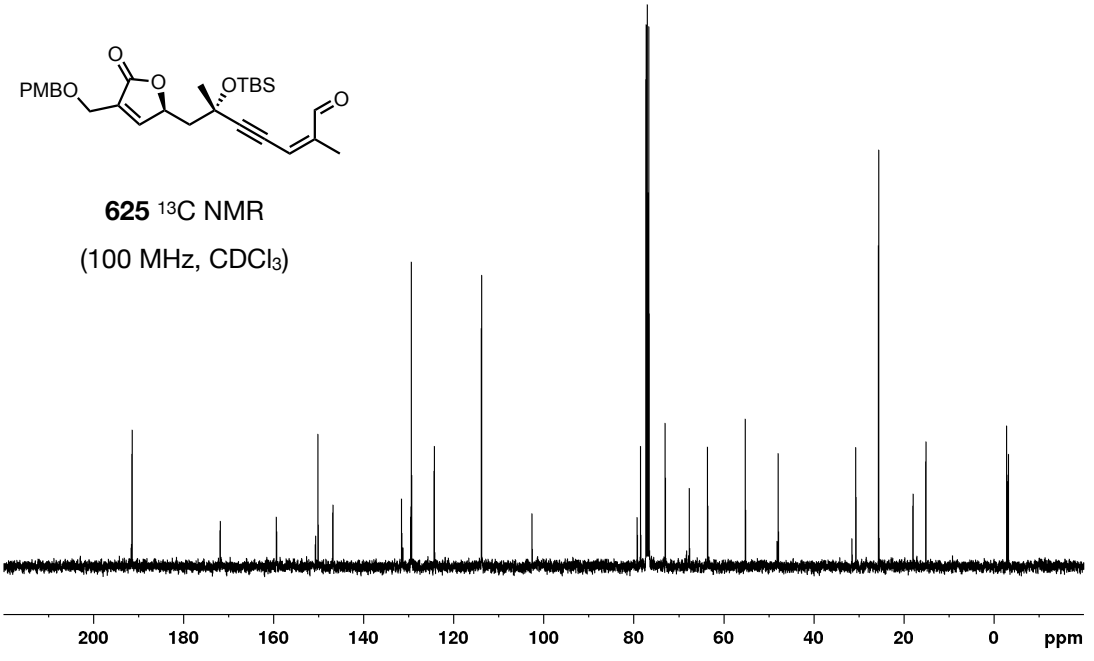

**624** $^{13}$C NMR

(100 MHz, $CDCl_3$)



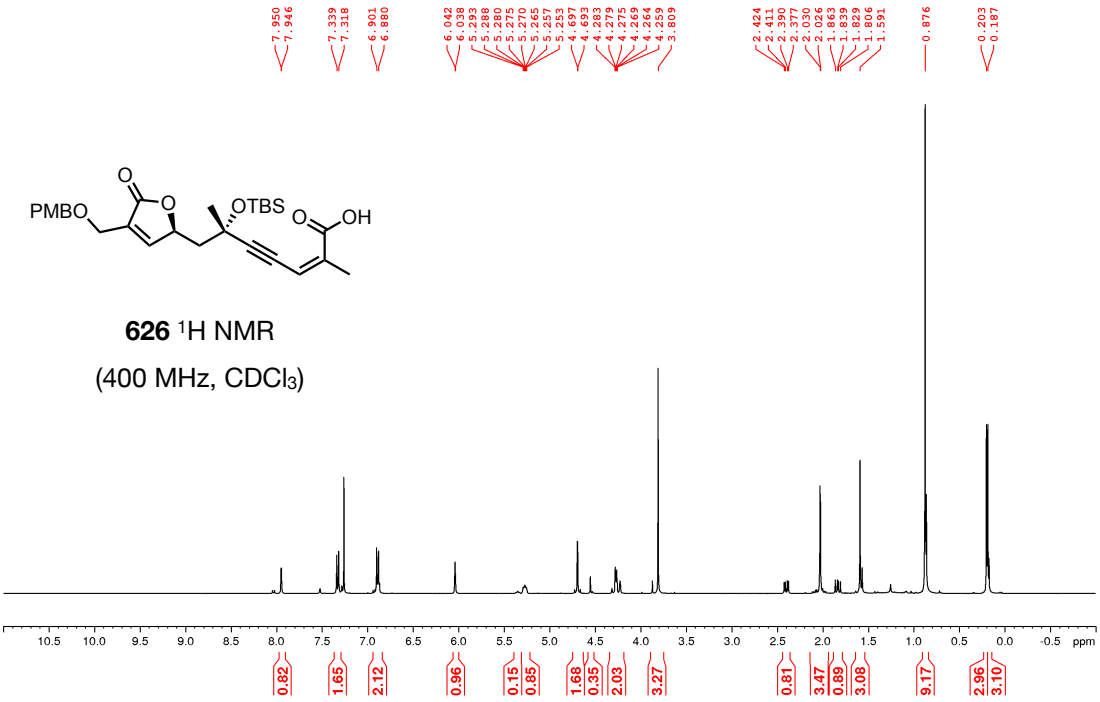

**625** $^{1}$H NMR

(400 MHz, $CDCl_3$)




**625** $^{13}$C NMR

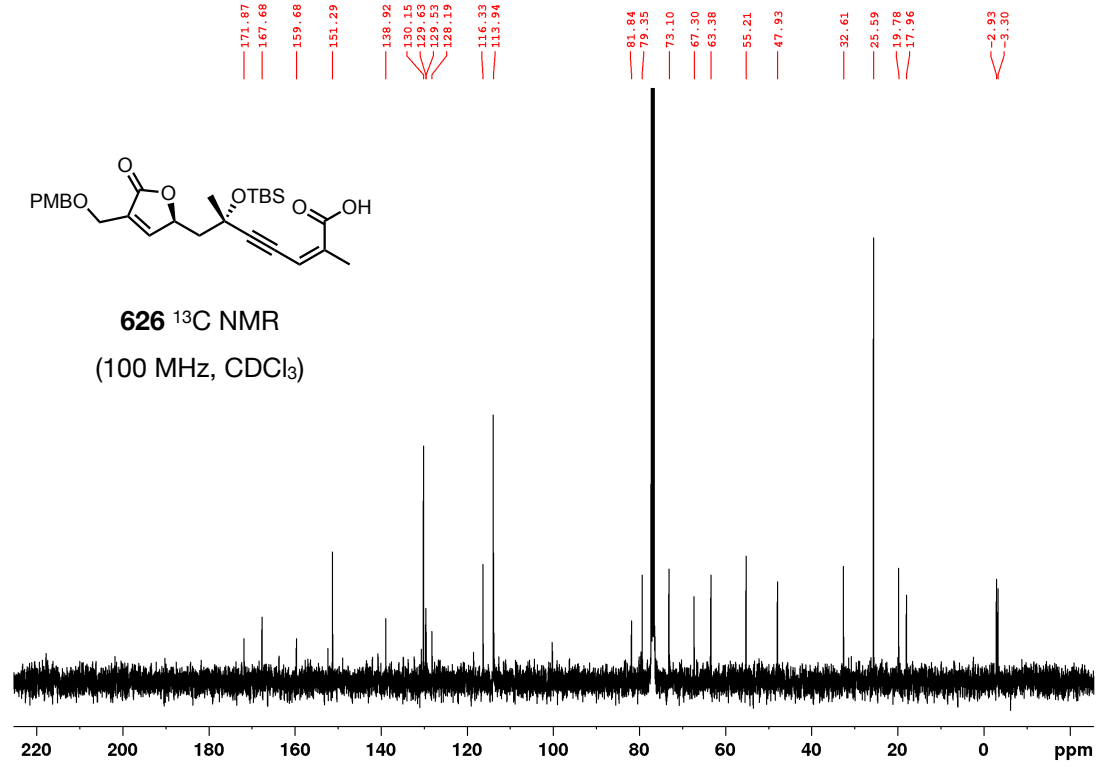
(100 MHz, $CDCl_3$)




**626** $^{1}$H NMR

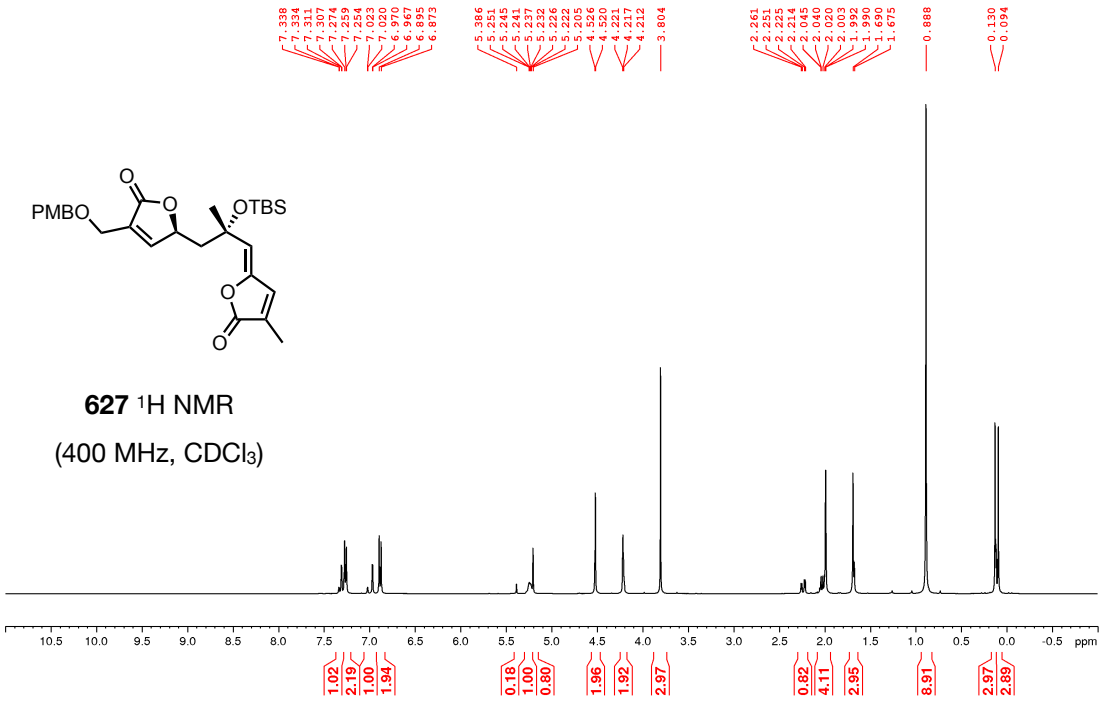
(400 MHz, $CDCl_3$)

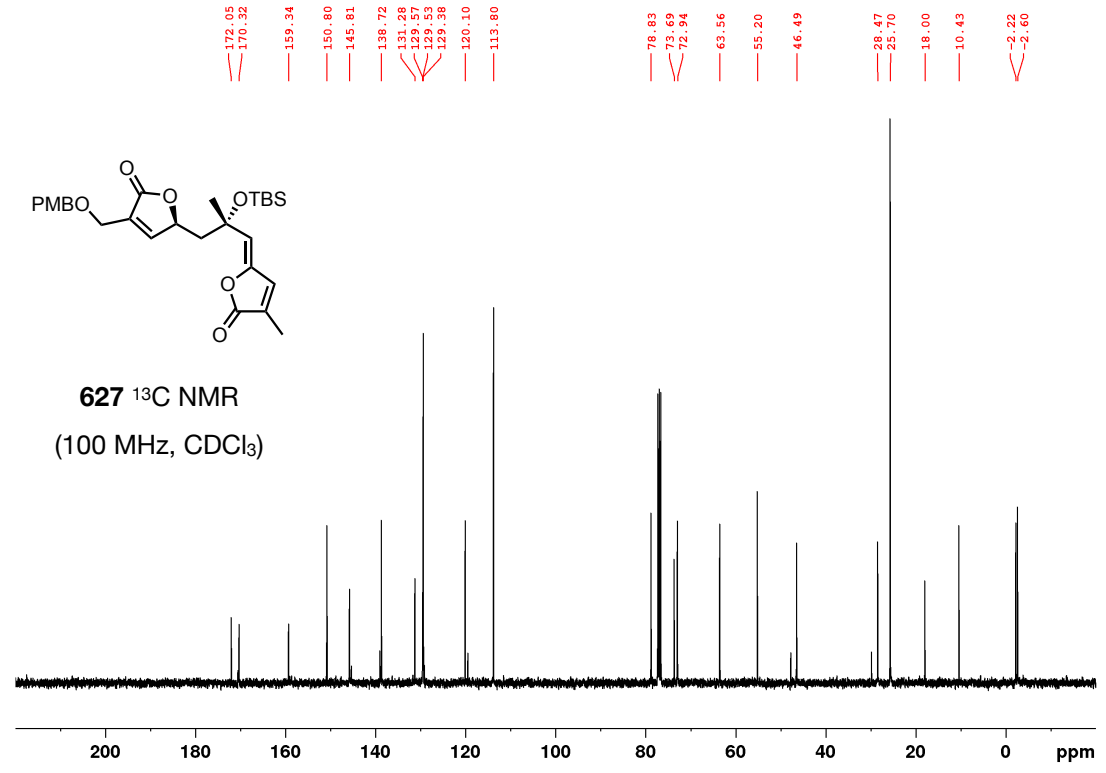


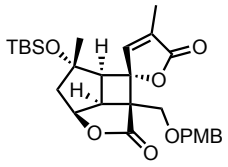




**626** $^{13}$C NMR

(100 MHz, $CDCl_3$)


PMBO
OTBS
O
O
O
O
O
627 1H NMR
(400 MHz, CDCl3)
7.338
7.334
7.311
7.307
7.274
7.259
7.254
7.023
7.020
6.970
6.967
6.895
6.873
5.386
5.251
5.245
5.241
5.237
5.232
5.226
5.222
5.205
4.526
4.520
4.221
4.217
4.212
3.804
2.261
2.251
2.225
2.214
2.045
2.040
2.030
2.003
1.992
1.990
1.690
1.675
0.888
0.130
0.094
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm
1.02
2.19
1.00
1.94
0.18
1.00
0.80
1.96
1.92
2.97
0.82
4.11
2.95
8.91
2.97
2.89

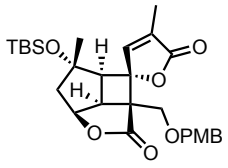

PMBO
OTBS
O
O
O
O
O
627 13C NMR
(100 MHz, CDCl3)
172.05
170.32
159.34
150.80
145.81
138.72
131.28
129.57
129.53
129.38
120.10
113.80
78.83
73.69
72.94
63.56
55.20
46.49
28.47
25.70
18.00
10.43
-2.22
-2.60
200 180 160 140 120 100 80 60 40 20 0 ppm




**628** $^{1}$H NMR

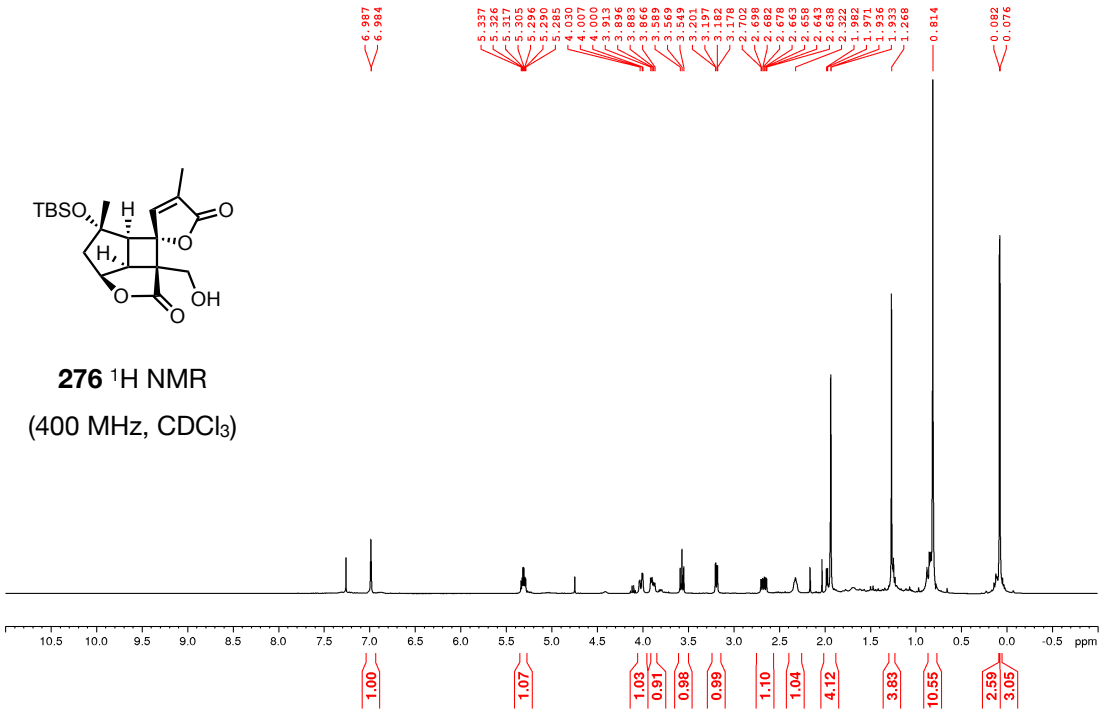
(400 MHz, $CDCl_3$)




**628** $^{13}$C NMR

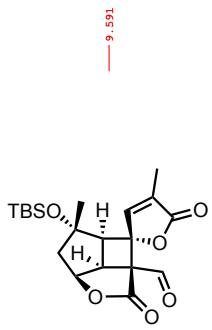
(100 MHz, $CDCl_3$)




**276** $^{1}$H NMR

(400 MHz, $CDCl_3$)

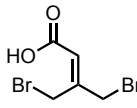
**NMR Spectra: Section 5.1:**




**277** $^1$H NMR

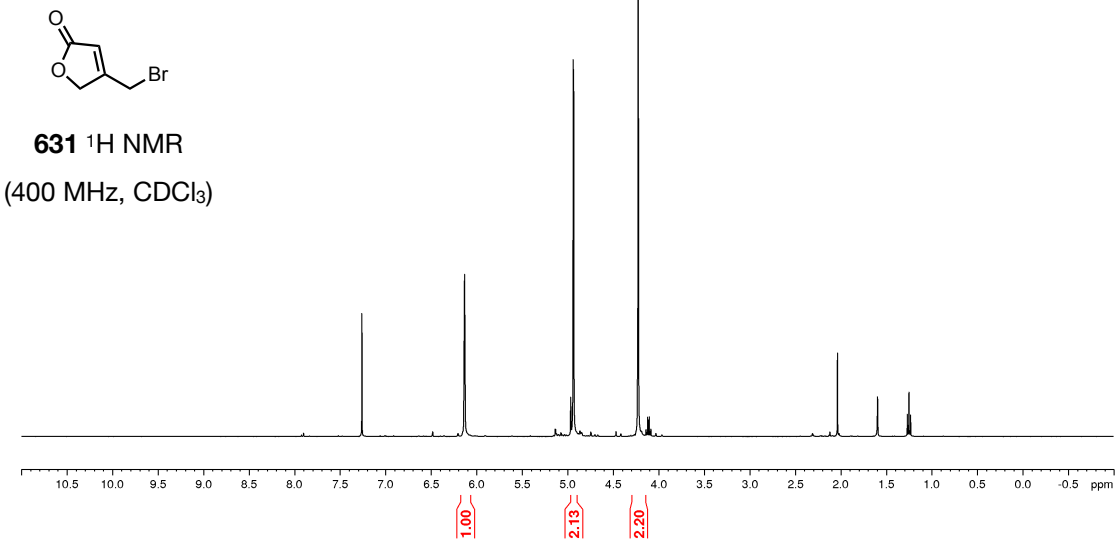
(400 MHz, $CDCl_3$)



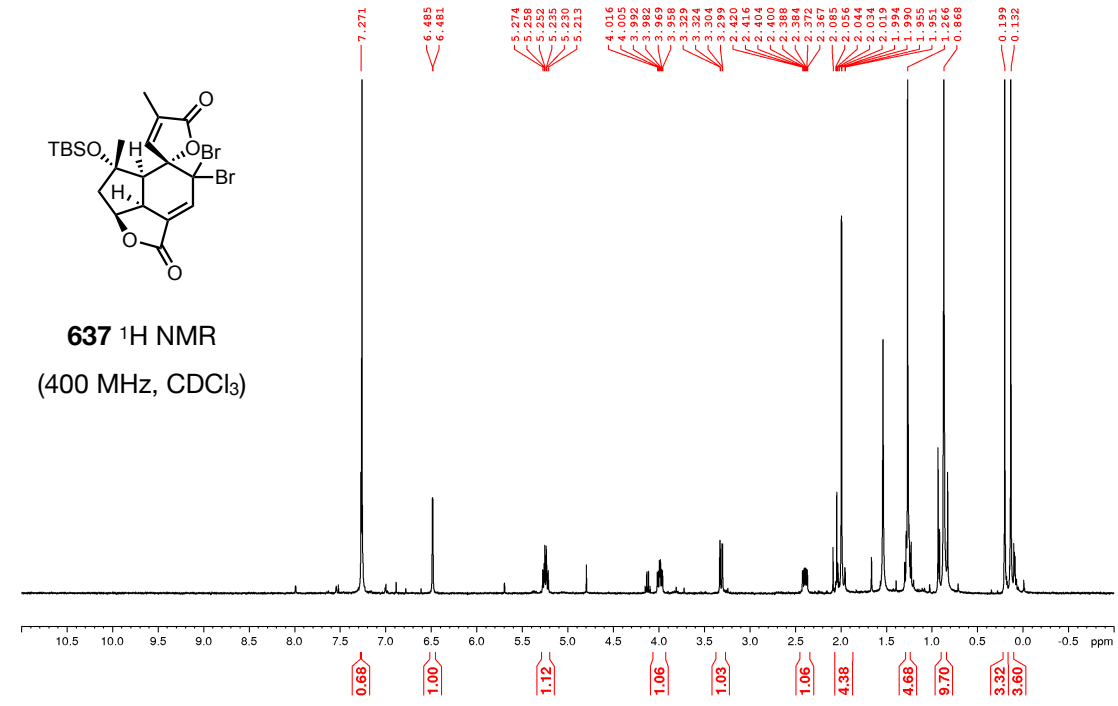

**630** $^1$H NMR

(400 MHz, $CDCl_3$)



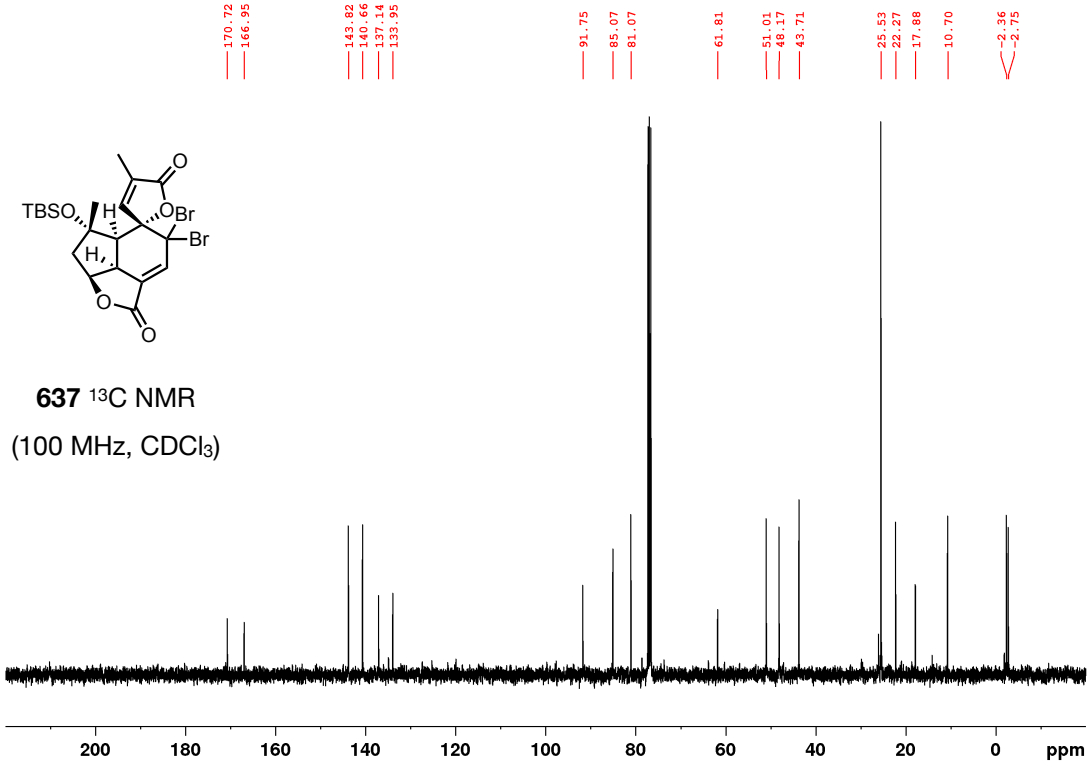

**631** $^{1}$H NMR

(400 MHz, $CDCl_3$)



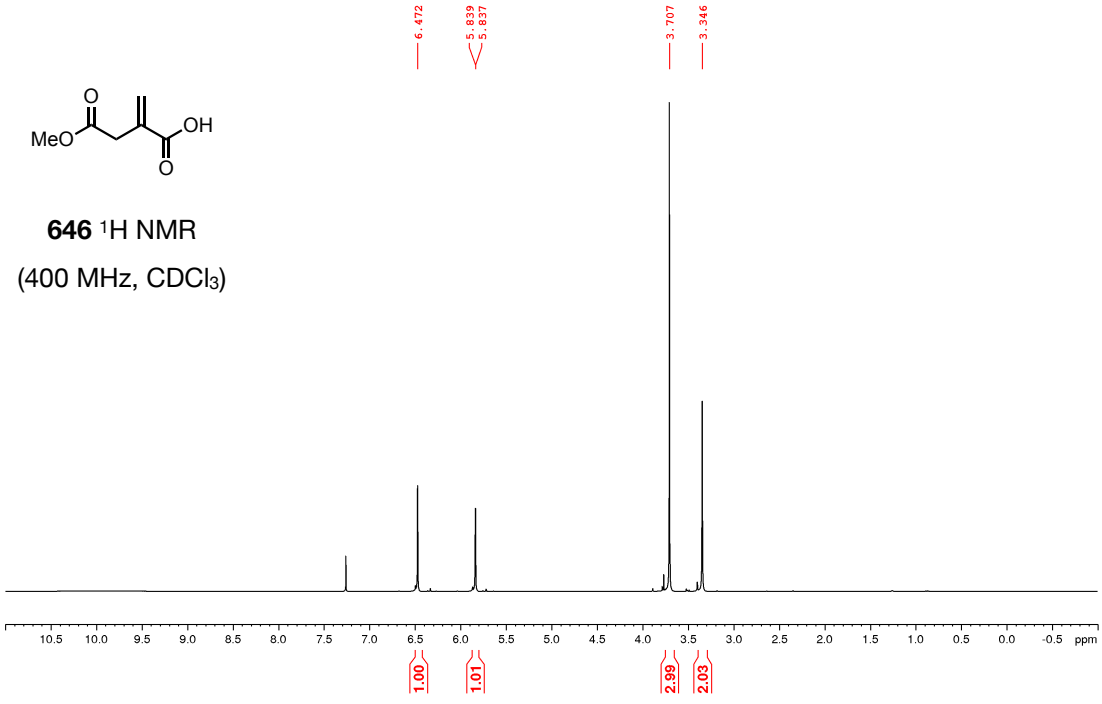

**637** $^{1}$H NMR

(400 MHz, $CDCl_3$)



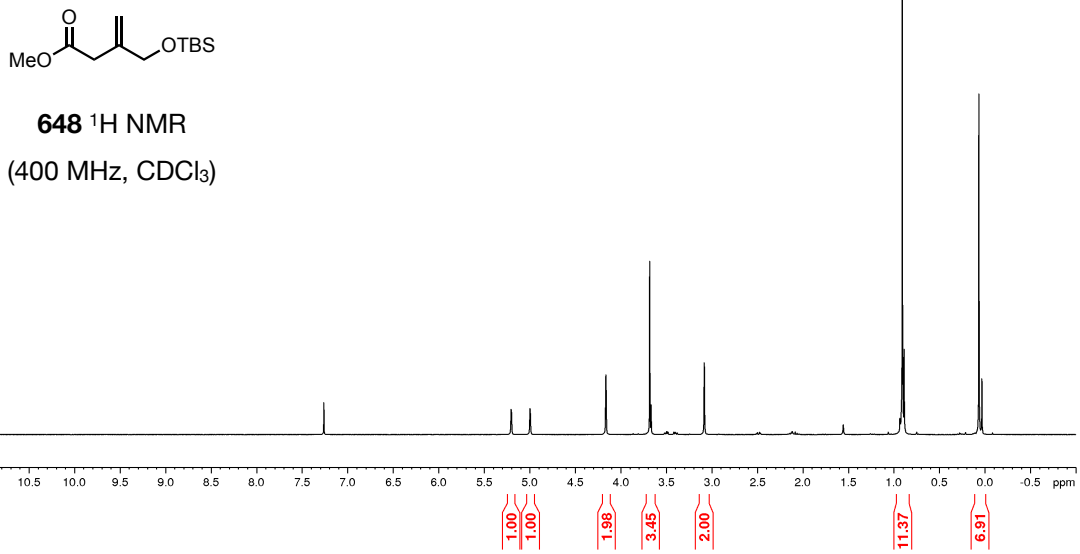

**637** $^{13}C$ NMR

(100 MHz, $CDCl_3$)



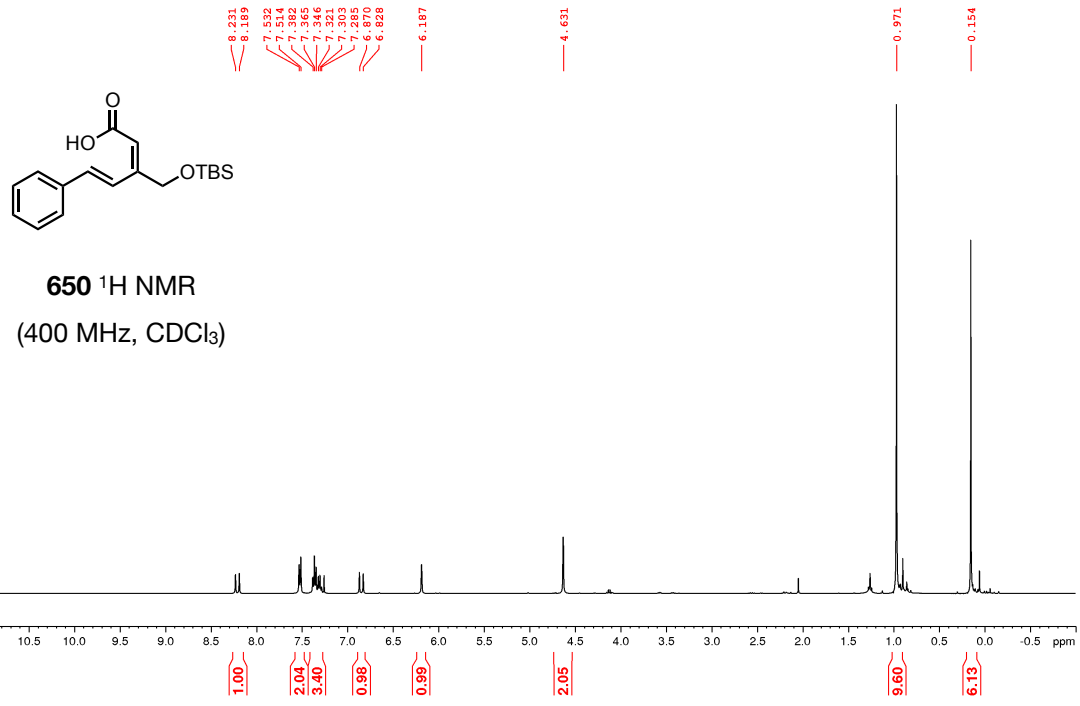

**646** $^{1}H$ NMR

(400 MHz, $CDCl_3$)



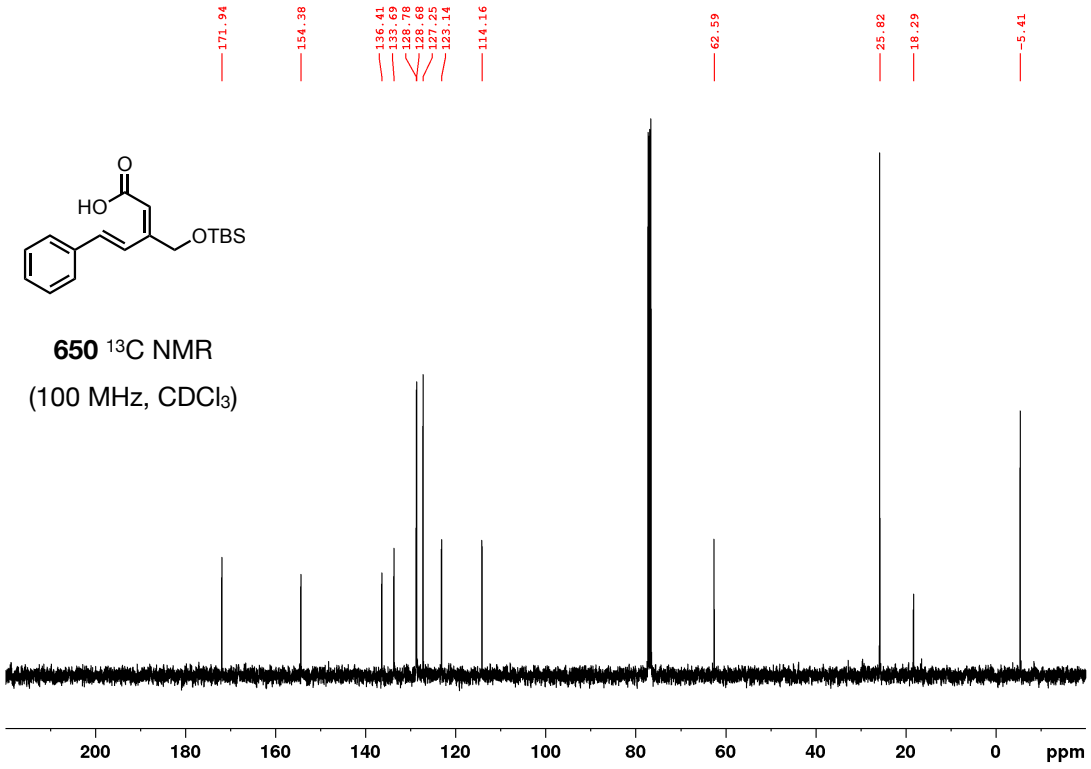

**648** $^{1}$H NMR

(400 MHz, $CDCl_3$)




**650** $^{1}$H NMR

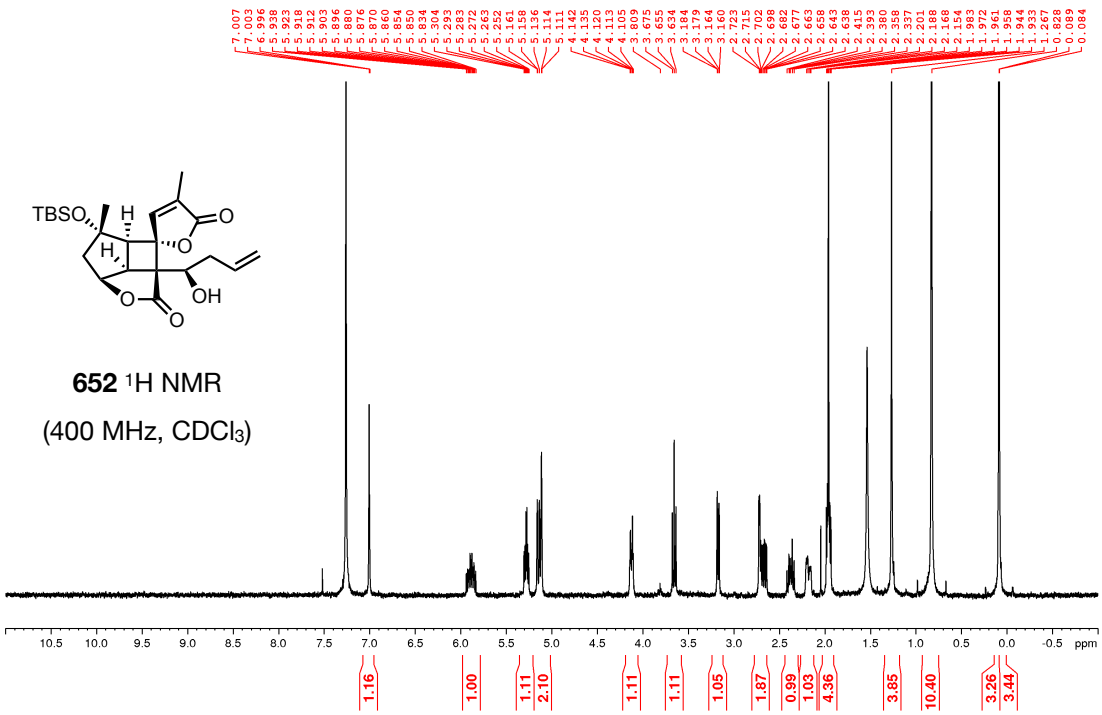
(400 MHz, $CDCl_3$)




**650** $^{13}C$ NMR

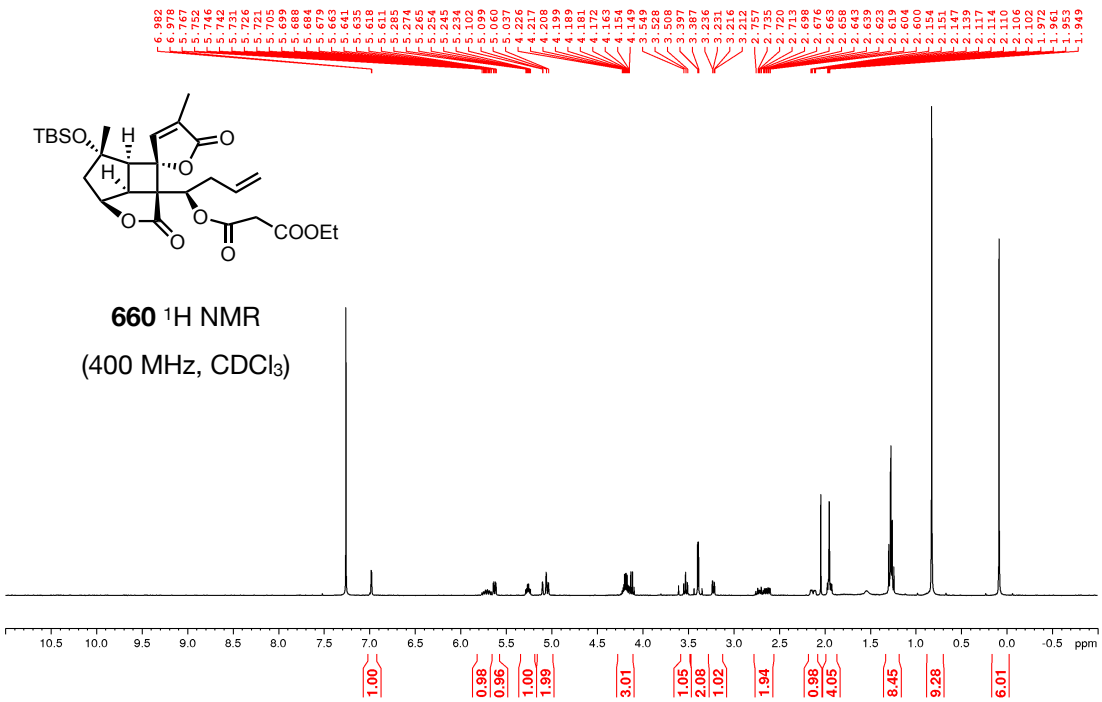
(100 MHz, $CDCl_3$)

**NMR Spectra: Section 5.2:**



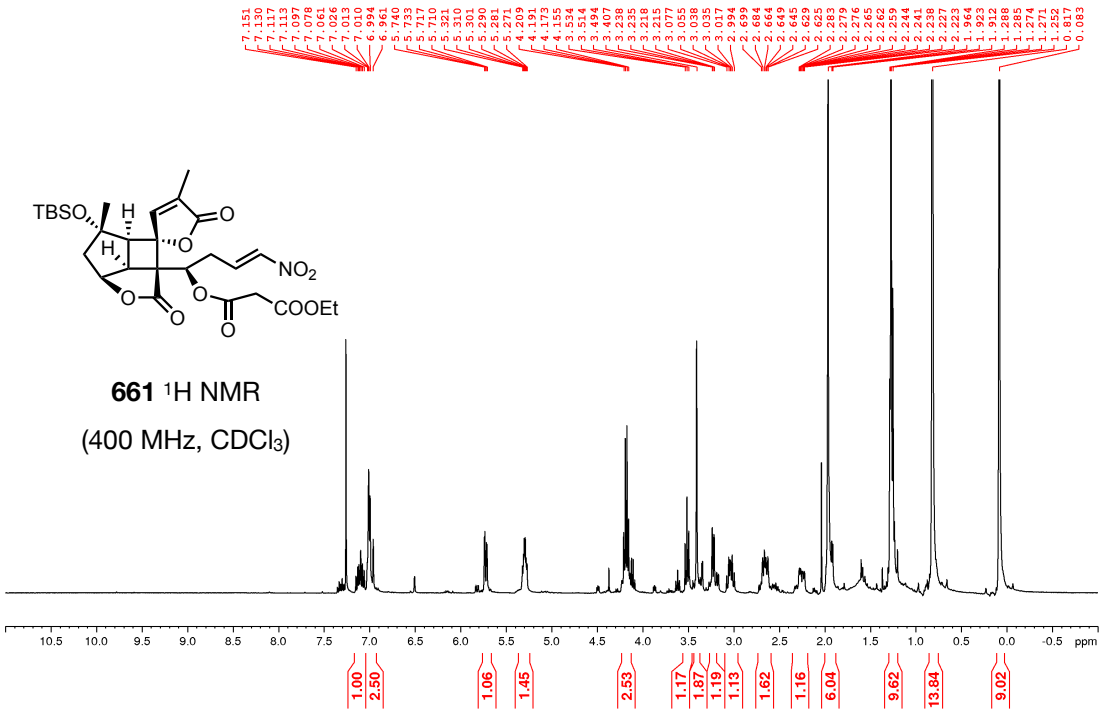

**652** $^{1}$H NMR

(400 MHz, $CDCl_3$)




**660** $^{1}$H NMR

(400 MHz, $CDCl_3$)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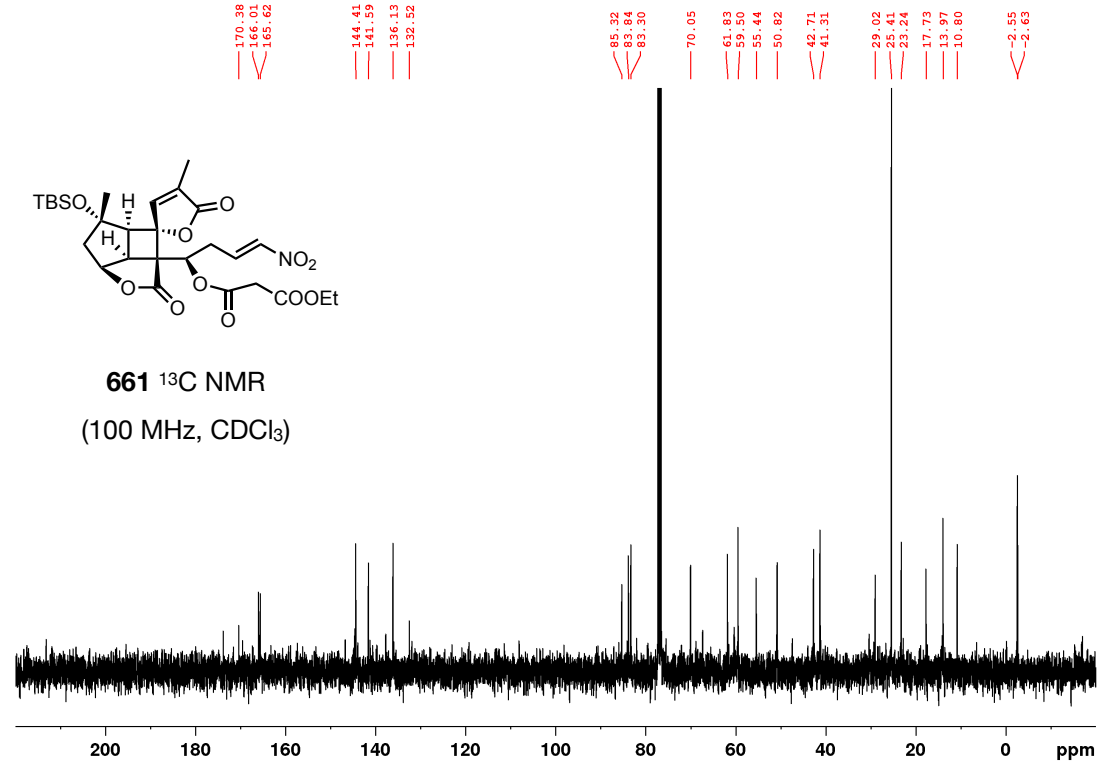
O
NO2
COOEt
661 1H NMR
(400 MHz, CDCl3)
ppm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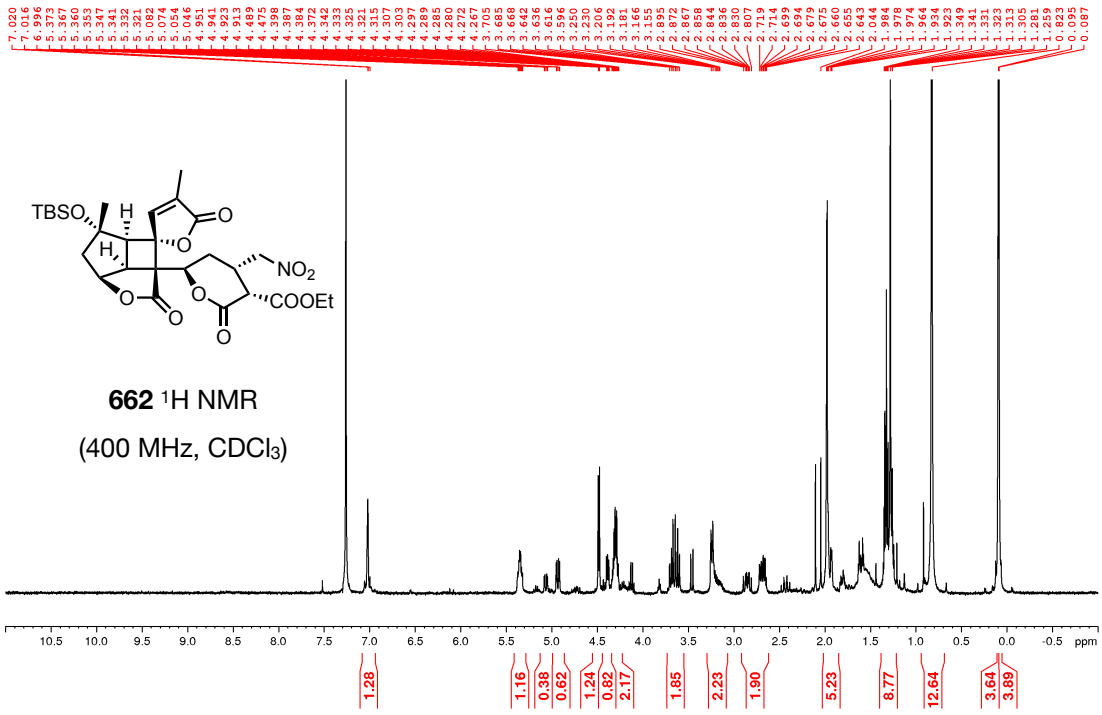
(100 MHz, CDCl3)
ppm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(400 MHz, CDCl3)
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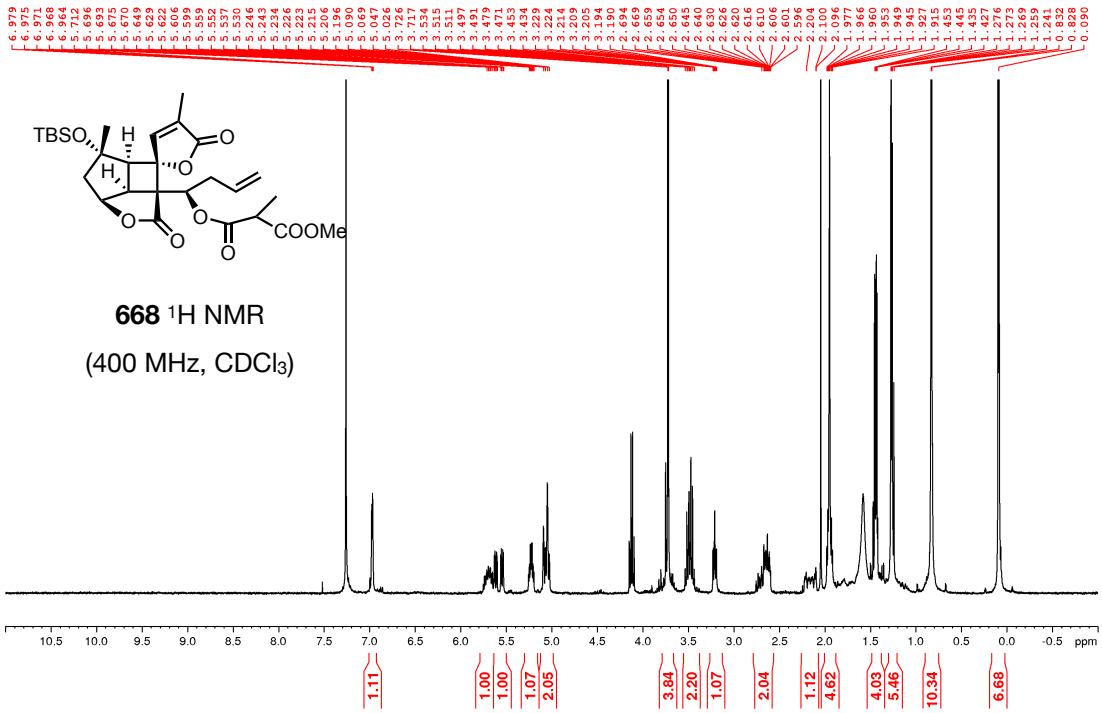
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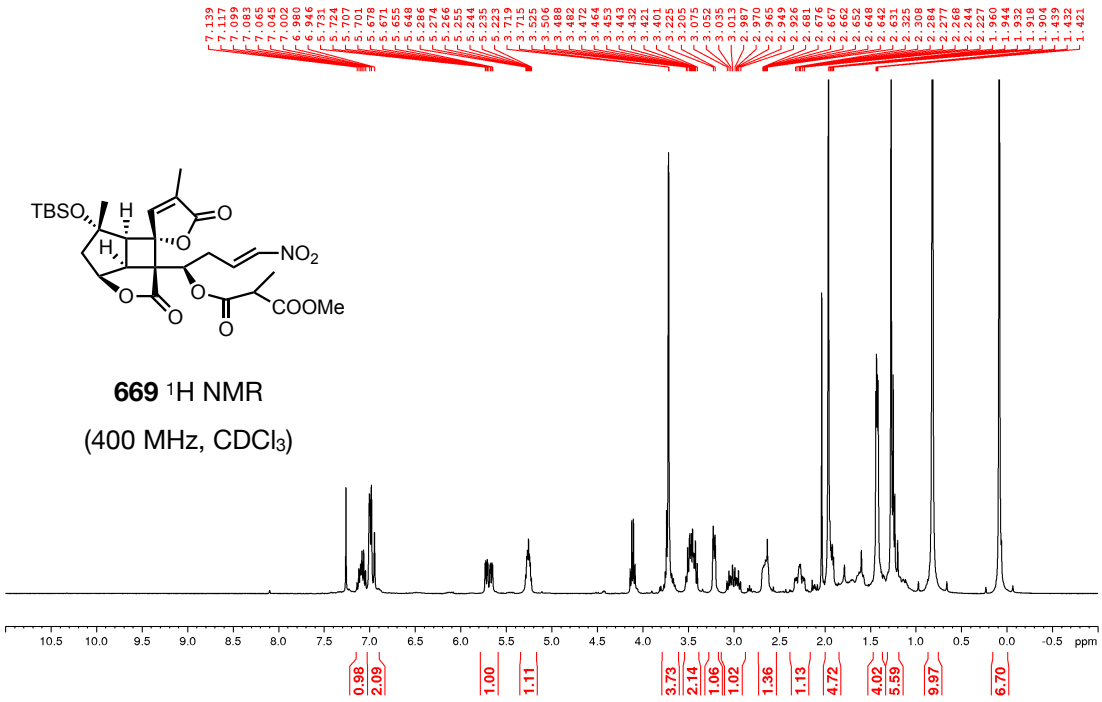
(400 MHz, CDCl3)
ppm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669 1H NMR
(400 MHz, CDCl3)
ppm

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## Vita

Jason Reed Hudlicky was born on November 6, 1989 in Roanoke, Virginia, to Josie Reed and Tomas Hudlicky. He spent his early years in Blacksburg, Virginia, before moving with the family to Gainesville, Florida, where Jason attended kindergarten through the seventh grade. In 2003, the family moved to St. Catharines, Ontario, and Jason enrolled in Ridley College and graduated in 2008. In the fall of that he started undergraduate study at the University of British Columbia in Vancouver. He did his undergraduate research in chemistry with Professor Glenn Sammis working on the total synthesis of amphidinolide K. He graduated with both a Bachelor of Science in Chemistry and a Bachelor of Arts in Art History in May 2013.

Jason took off a year from school after graduation, and during that time he spent seven months working as a research assistant in the Department of Organic Chemistry at Charles University in Prague, Czech Republic. In the fall of 2014, he joined the research group of Professor Gary Sulikowski at Vanderbilt University in Nashville, Tennessee. That same fall, Jason married Inge Klaps, of Bree, Belgium, whom he met in a Mayan Art class while she was an exchange student at UBC.

After defending his thesis, in April 2021, Jason and Inge will move (along with their cat, Sir Oliver Twiskers, affectionally known as Ollie) to California, where he will be starting a Research Scientist position at Gilead Sciences in Foster City.