A 1,3-DIPOLAR CYCLOADDITION APPROACH TO THE SYNTHESIS OF RESINIFERATOXIN

by

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The Rh(I)-catalyzed allenic cyclocarbonylation reaction is a formal [2 + 2 + 1] cycloaddition process that has been used to gain access to 4-alkylidenecyclopentenones. Incorporation of a six-membered ring on the tether between the allene and the alkyne components allows access to a variety of [6-7-5] ring structures featured in the skeletons of various natural products, including resiniferatoxin. This thesis describes the development of two systems, each with a future synthesis of resiniferatoxin in mind. First, a model system was designed to demonstrate the compatibility of the isoxazoline moiety with the Rh(I)-catalyzed cyclocarbonylation reaction. The second investigation involved the synthesis of an asymmetrically functionalized 2-cyclohexenone in order to attempt a stereoselective 1,3-dipolar cycloaddition. The first model system successfully led to the synthesis of the unfunctionalized [6-7-5] core of resiniferatoxin via cyclocarbonylation of an isoxazoline-containing allene-yne. Unfortunately, under numerous conditions, the functionalized cyclohexenone synthesized for the second study failed to undergo 1,3-dipolar cycloaddition with a nitrile oxide.

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Thank you, Erech. Go Team Venture!

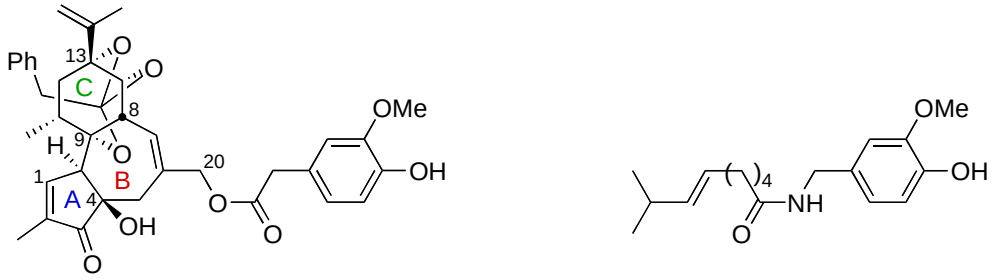
ABBREVIATIONS

Ac_2O	Acetic anhydride
9-BBN	9-Borabicyclo[3.3.1]nonane
BINOL	1,1'-Bi(2-naphthol)
DCM	Dichloromethane
DIPA	Diisopropylamine
DMAP	4-*N*,*N*-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
EtOAc	Ethyl acetate
NMR	Nuclear magnetic resonance
PAA	*para*-Anisaldehyde
PhH	Benzene
TBS	*tert*-Butyldimethylsilyl
TEA	Triethylamine
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl

1.0 INTRODUCTION

1.1 RESINIFERATOXIN

The therapeutic benefits of euphorbium—the dried latex of plants of the genus *Euphorbia*—have been appreciated for several centuries; in his posthumously published *Tractatus de Materia Medica,* 18th century French chemist and physician Etiénne-François Geoffroy cites euphorbium as an effective remedy for bone cavities and nerve pains.[1] Although euphorbium disappeared from the documented pharmacopoeia in the 1800s, interest in its active constituent, resiniferatoxin (**1**, Figure 1), has been renewed, as resiniferatoxin shows potential in treating, among other ailments, chronic pain and bladder incontinence.



1 **2**

Figure 1. Structures of resiniferatoxin and capsaicin

Resiniferatoxin was isolated in 1975 from the latex of *Euphorbia resinifera* and related plants by Hecker and colleagues.[2] The high irritant activity of the compound was immediately recognized as novel and, seven years later, Hecker published a revised structure of the natural product along with the results of preliminary structure-activity studies.[3] Although the

pharmacophore has not been determined, the phenol and orthoester moieties have been deemed essential for potency.

Resiniferatoxin is a known agonist of the transient receptor potential vanilloid (TRPV1). Analogous physiological effects and structural similarities to capsaicin (**2**)—also an irritant that binds to a TRPV1—suggest a common mode of action for the two compounds. Both natural products induce pain, neurogenic edema and hypothermia in rats.[4]

Vanilloid receptors are ligand-gated cation channels located in the membranes of nociceptive sensory nerves. Activation of the proteins by chemical agonists or heat causes the channel to open, leading to an influx of intracellular calcium cations; this depolarization generates an action potential that is perceived by the central nervous system and leads to a burning sensation. In 1997, Julius and coworkers[5] cloned TRPV1 and characterized the protein as containing six transmembrane domains. The vanilloid binding pocket was later located through the use of radiolabeled resiniferatoxin, and was shown to exist between domains three and four.[6]

Although capsaicin and resiniferatoxin cause initial irritation at the site of application, tachyphylaxis is demonstrated upon subsequent exposure. This phenomenon is much more prominant with the use of resiniferatoxin than with capsaicin, although the initial irritation caused by resiniferatoxin is only marginally more severe. The exact mechanism of desensitization remains elusive, but summaries of thoughtful speculation can be found in several reviews.[7-9]

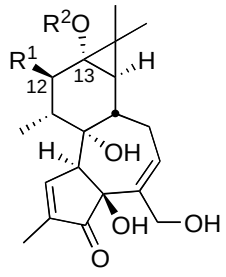
Not only are nociceptors exposed to resiniferatoxin densensitized to further treatment with resiniferatoxin, but they often show diminished responses to other stimuli as well, including capsaicin, heat and other exogenous inflammatory agents. Thus, resiniferatoxin is viewed as a

potentially valuable analgesic for those suffering from chronic neurogenic pain and other phenomena that result from hyperactive nociceptors.

In particular, some subjects exhibiting symptoms of overactive bladder and incontinence have been reported to have an abnormally high density of nociceptive neurons present in their bladder tissues. Introduced intravesically, low concentration solutions of resiniferatoxin have been shown to lead to a decreased frequency in incontinent episodes in some of these patients; the effects of a single treatment can last up to three months and the initial discomfort is minimal.[10, 11]

Current investigation of clinical applications of resiniferatoxin seems to be taking place predominantly in the academic arena. This may be due, in part, to a 2004 press release issued by ICOS stating their findings that resiniferatoxin did not pass Phase II trials for treatment of interstitial cystitis[12] and that ICOS's interest in resiniferatoxin had ceased.[13] Since this statement by ICOS, however, additional contradictory reports[14] demonstrating the efficacy of resiniferatoxin in treating bladder pain syndrome and interstitial cystitis have appeared in the literature.

Some scientists have expressed reservations with respect to treating humans with resiniferatoxin based on the similarities between its structure and those of the tumor-promoting phorbol esters (12,13-diesters of **3**, R^1 = OH, R^2 = H, Figure 2);[15] however, these concerns are not corroborated by experimental evidence. Notably, prostratin (**3**, R^1 = H, R^2 = Ac, Figure 2), a 12-deoxytigliane recently synthesized by Wender and coworkers[16] from phorbol, was shown to be a non-tumor-promoting potential anti-HIV therapeutic. Prostratin is currently in preclinical development.



3
phorbol R^1 = OH, R^2 = H
prostratin R^1 = H, R^2 = Ac

Figure 2. Phorbol and prostratin

The FDA designated resiniferatoxin as an orphan drug in 2003 for the treatment of "intractable pain at end-stage disease."[17] This classification seems especially befitting in light of a 2005 publication from the School of Veterinary Medicine at the University of Pennsylvania. Administered intrathecally, resiniferatoxin appeared to largely diminish the pain associated with bone cancer as experienced by a group of canine companion animals.[18] When the dogs entered the study, many were not deemed to be achieving adequate pain relief through the use of conventional analgesics. After treatment with resiniferatoxin, the comfort level of most of the dogs seemed to improve so drastically that analgesic use was tapered or in some cases discontinued completely. No lasting ill effects of resiniferatoxin were observed, pre- or postmortem.

TRPV1 has become a popular target for development of analgesics; a number of TRPV1 antagonists are in clinical development to address painful phenomena ranging from migraine headaches to HIV neuropathy-associated pain.[19, 20] Capsaicin is available over-the-counter as a topical ointment for the treatment of arthritis pain. Recent publications regarding the therapeutic possibilities of resiniferatoxin include a study of its use as a long-lasting local anasthetic[21] and a patent application alleging the efficacy of injections of resiniferatoxin in treating joint pain.[22]

The isolation of resiniferatoxin from euphorbium continues to be a materials-intensive and fairly noxious process. Fattorusso[23] has published an improved procedure for the isolation of resiniferatoxin, but only managed a 0.0020% yield from the fresh latex of the *E. resinifera* plant. One of the altruistic goals of the synthesis of resiniferatoxin is to provide a vehicle for synthesis and testing of analogs that are more accessible or that perhaps possess more optimal biological activity than the natural product itself.

1.2 STRUCTURALLY-RELATED NATURAL PRODUCTS

While it is our objective to carry out a synthesis of resiniferatoxin, our expectation is that the methods that we utilize will find application in the synthesis of structurally-similar molecules. Many daphnane diterpenoids have been isolated from natural sources; they collectively exhibit a wide variety of fascinating and potentially useful biological activities.[24] Several of these natural products are depicted in Figure 3 with their corresponding biological activities.[25-31] Phorbol (**3**, R^1 = OH, R^2 = H, Figure 2), a tigliane diterpene, is also notable not only for the biological activity of its 12,13-diesters, but also for the inspirational amount of creative chemistry that has been developed in pursuit of its synthesis.

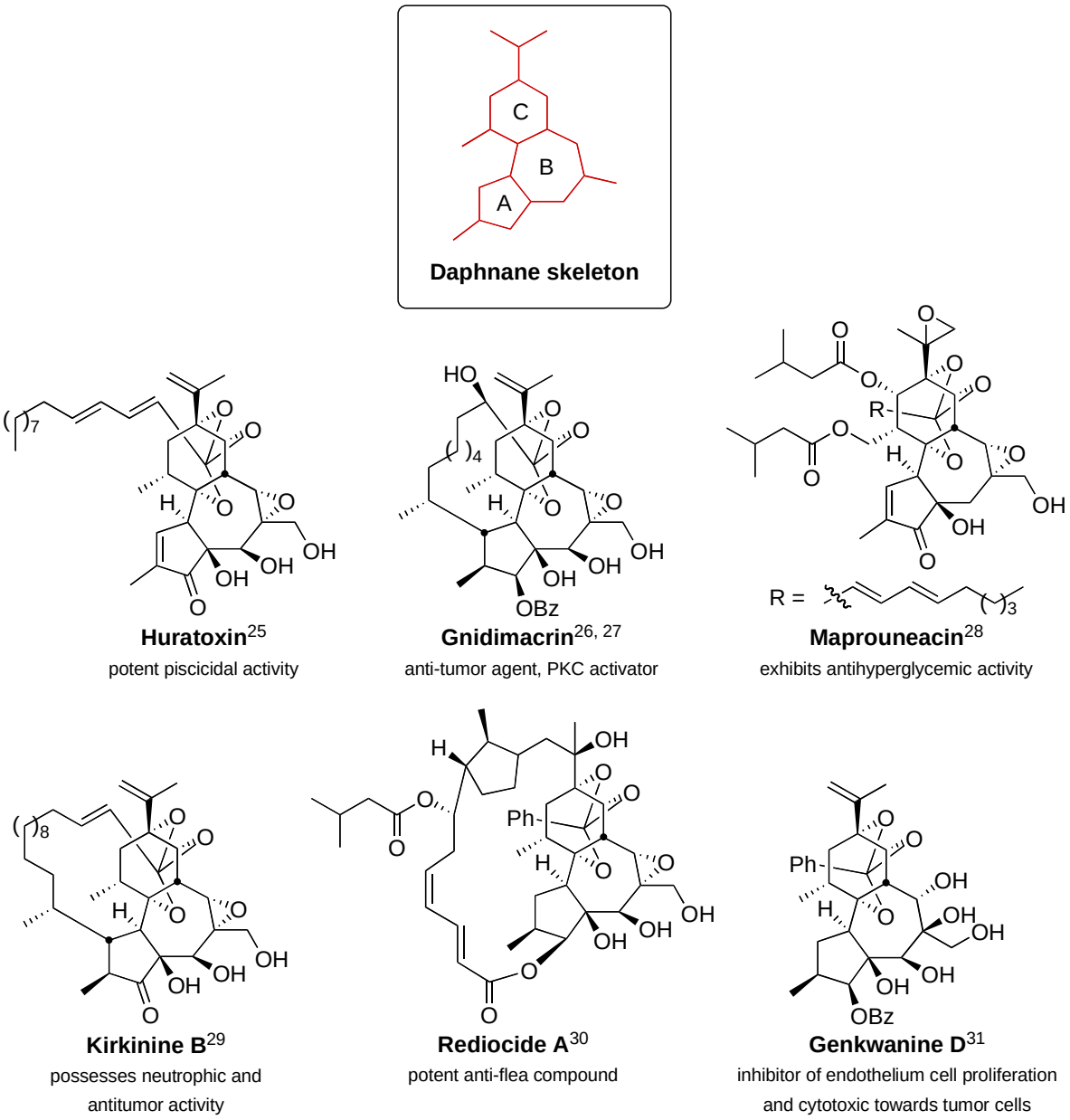
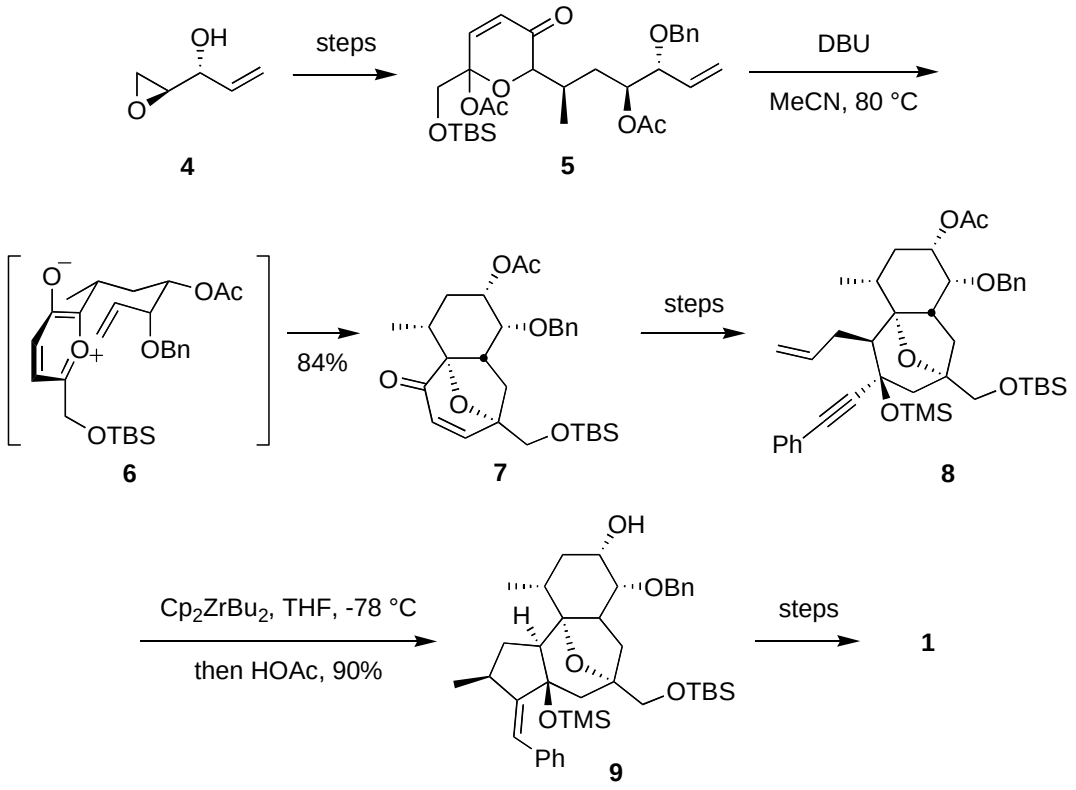


Figure 3. Daphnane natural products

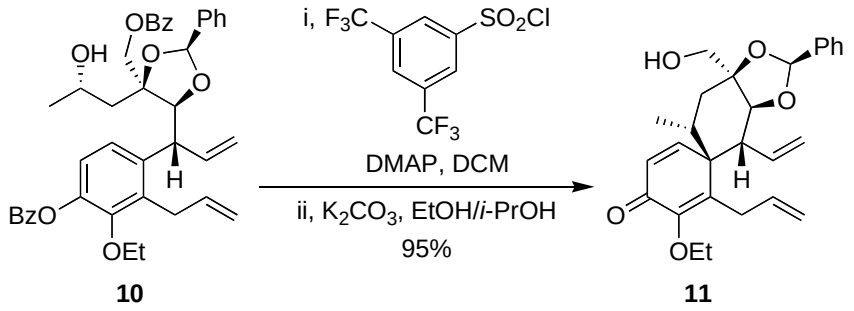
2.0 PREVIOUS APPROACHES TO THE SYNTHESIS OF RESINIFERATOXIN AND RELATED COMPOUNDS

To date, there has been only one total synthesis of resiniferatoxin, published by Wender in 1997.[32] The absolute stereochemistry was set in the first step: known epoxide **4** (Scheme 1) was synthesized from 1,4-pentadien-3-ol using Sharpless' asymmetric epoxidation conditions. Subsequent steps proceeded stereoselectively, affording intermediate **5**. The key step in Wender's synthesis was a [5 + 2] intramolecular cycloaddition of oxidopyrylium **6**, forming the B and C rings simultaneously. An advantage of this tactic was the resulting rigidity of the tricyclic ring system. The presence of the bridging ether in **7** lent bias to the formation of subsequent stereocenters. A zirconium-mediated cyclization of enyne **8** closed the A ring of resiniferatoxin and further elaboration of **9** led to completion of the natural product. Esterification at C20 and construction of the orthoester were performed towards the end of the synthesis, since these moieties have been shown to be essential for potent irritant activity.

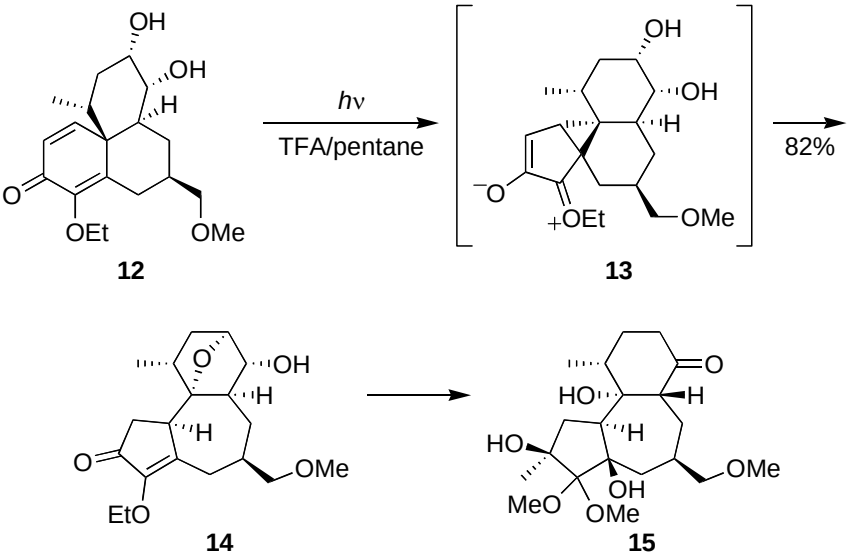


Scheme 1. Wender's synthesis of resiniferatoxin

Carreira's group[33, 34] has published two papers disseminating complementary approaches to the construction of angular [6-7-5] ring structures. Substrates and conditions for diastereoselective phenol *para*-alkylation were developed in order to gain access to spiro-fused cyclohexadienones (Scheme 2).[34] Conversion of optically pure alcohol **10** to the 3,5-bistrifluoromethylbenzenesulfonate ester and subsequent Winstein alkylation provided cyclohexadienone **11** as a single stereoisomer in 95% yield. Previously, Carreira and colleagues[33] had shown that tricyclic compound **12** could undergo photorearrangement via intermediate **13** to directly provide the [6-7-5] core **14** of resiniferatoxin and similar natural products (Scheme 3). Enone **14** was elaborated further to give the highly oxygenated ketal **14** in order to demonstrate the synthetic potential of the photorearrangement approach.



Scheme 2. Phenol *p*-alkylation to yield spirocycle **11**



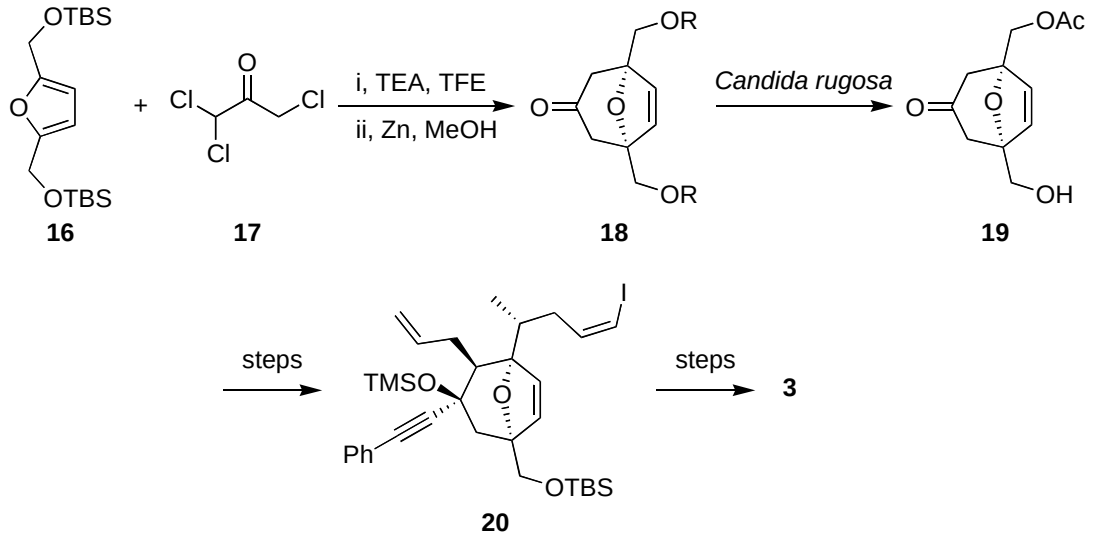
Scheme 3. Carreira's approach to resiniferatoxin

The Wender group has applied their [5 + 2] cycloaddition chemistry several times to the synthesis of phorbol; their most recent synthesis was asymmetric.[35-38] Wender[39] recently published preliminary results on the application of this methodology towards the synthesis of gnidimacrin.

The only other complete synthesis of phorbol to date was published by Lee and Cha[40] in 2001. Like Wender, Lee and Cha employed a cycloaddition as a key step. [4 + 3] Cycloaddition of furan **16** (Scheme 4) and the oxyallyl generated from 1,1,3-trichloroacetone (**17**), followed by dechlorination with zinc, afforded *meso* compound **18** (R = TBS). Desymmeterization of the corresponding acetate (**18**, R = Ac) was performed enzymatically to give alcohol **19** in 90% yield

and 80% *ee*. Subsequent steps proceeded diastereoselectively to give substrate **20** which underwent an intramolecular Heck reaction to close the C ring. Lee and Cha later intersected with Wender's synthesis of phorbol.

There have been numerous innovative approaches to the construction of a suitably functionalized angular [6-7-5] tricyclic core of phorbol; these strategies include: Diels–Alder cyclization,[41-43] an intramolecular 1,3-dipolar cycloaddition,[44, 45] a diyl-trapping cycloaddition,[46] and an anionic oxy-Cope rearrangement.[47] The obvious challenges of constructing the polycyclic core of resiniferatoxin and related natural products that possess opportunely located functionality have inspired many chemists in the synthetic community, including the Brummond group.

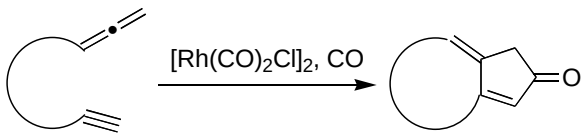


Scheme 4. Cha's synthesis of phorbol

3.0 RETROSYNTHETIC ANALYSIS OF RESINIFERATOXIN

3.1 ACCESSING THE A AND B RINGS VIA A Rh(I)-CATALYZED ALLENIC CYCLOCARBONYLATION REACTION

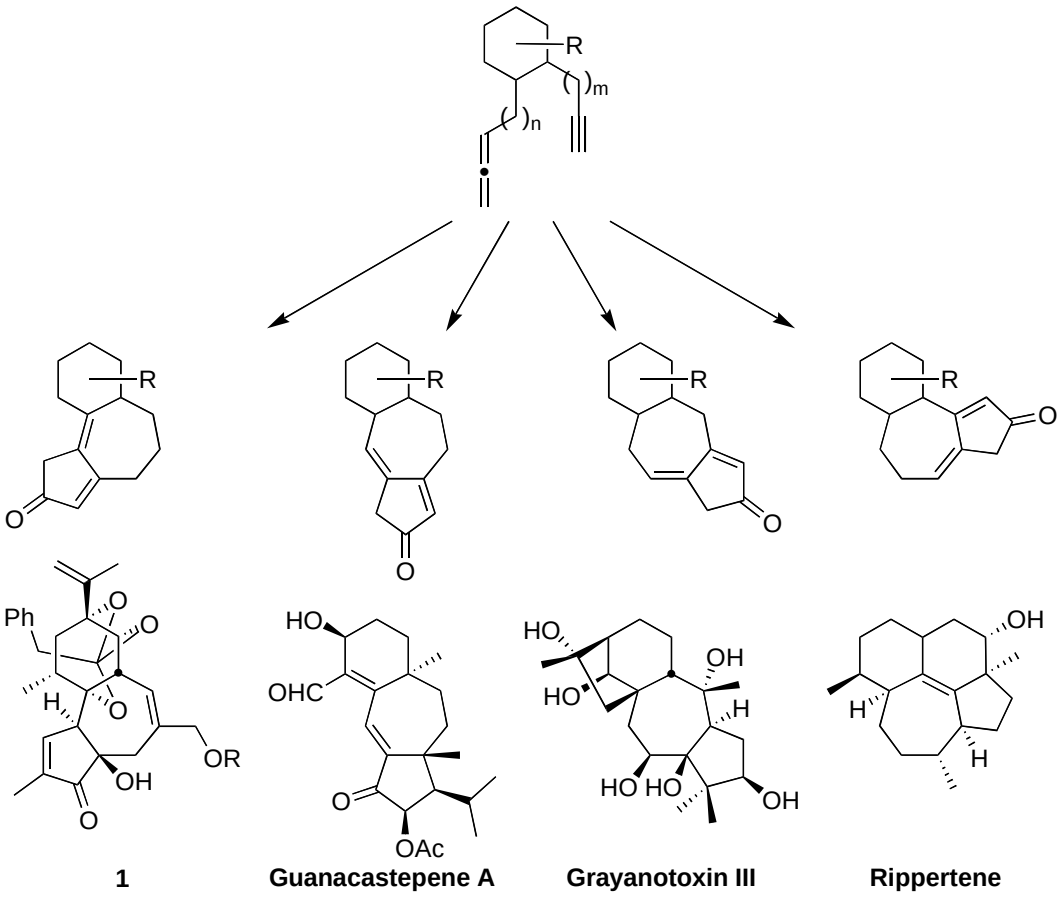
The Brummond group has been preeminent in applying transition metal catalysis to the creation of a diverse array of polycyclic scaffolds via the Pauson–Khand-type cyclocarbonylation of allenes.[48-55] Former group members have demonstrated the utility of the molybdenum-mediated and rhodium-catalyzed methodologies in their application to natural product synthesis.[48, 50-52] A unique feature of the rhodium-catalyzed system is its selectivity for reaction with the distal double bond of the allene;[49] in this way, our group has been able to selectively access a variety of 4-alkylidene cyclopentenones by varying the length of the tether between the allene and alkyne moieties (Scheme 5).



Scheme 5. Cyclocarbonylation of a tethered allene-yne

Incorporation of a six-membered ring on the tether between the allene and alkyne has allowed access to a variety of angular and linear [6-7-5] tricyclic skeletons present in several natural products (Scheme 6).[48, 50] The angular [6-7-5] substructure present in resiniferatoxin seems specially suited to showcase our group's cyclocarbonylation methodology.[48] The

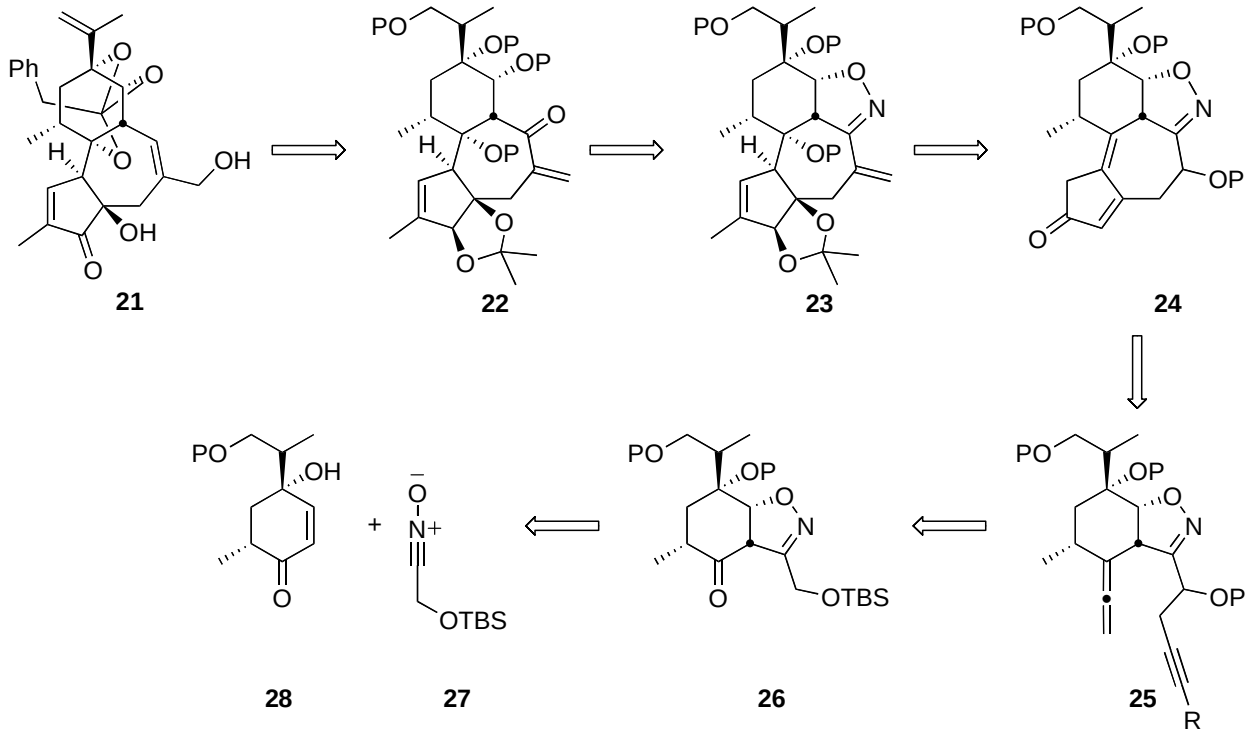
unsaturation present in the cyclocarbonylation product is conveniently situated at sites requiring oxidation. Further, the rhodium-catalyzed reaction has demonstrated excellent functional group compatibility. In the case of resiniferatoxin, this tolerance would permit us to submit an allene-yne tethered by a functionalized C ring to the cyclocarbonylation reaction, yielding an advanced synthetic intermediate.



Scheme 6. Access of [6-7-5] skeletons via allenic cyclocarbonylation reaction

We envision a formal synthesis of resiniferatoxin, intersecting Wender's total synthesis at intermediate alcohol **21** (Scheme 7). We intend to gain access to this intermediate via functional group manipulation of **22**. A key premise of our proposal is the use of the isoxazoline moiety as a masked aldol equivalent (see section 3.2); thus, opening of the isoxazoline ring in **23** will yield β-hydroxy ketone **22**. Isoxazoline **23** may be obtained by performing selective oxidations and

olefination of **24**, the cyclocarbonylation product of allenyne **25**. Conversion of the ketone present in **26** to the allene, followed by deprotection of the TBS ether, oxidation to the aldehyde, and propargylation will yield allene-yne **25**. We propose that a regio- and stereospecific 1,3-dipolar cycloaddition of enone **28** and nitrile oxide **27** will provide access to isoxazoline **26**.



Scheme 7. Retrosynthetic analysis of resiniferatoxin

3.2 THE MASKED ALDOL STRATEGY: 1,3-DIPOLAR CYCLOADDITION TO FORM AN ISOXAZOLINE

1,3-Dipolar cycloaddition of nitrile oxides to provide isoxazolines followed by reduction of the N-O bond and hydrolysis of the resulting imine is a strategy for accessing β-hydroxy ketones.[56] While numerous synthetic innovations allow for control of aldol product stereochemistry and preferential formation of a singular cross-aldol product, the cycloaddition of nitrile oxides and

olefins continues to offer an elegant alternative to the aldol reaction.[57-61] The characteristics that attracted us to the nitrile oxide cycloaddition approach were:

(1) The potential for selectively establishing two stereocenters and latent functionality in a single step;

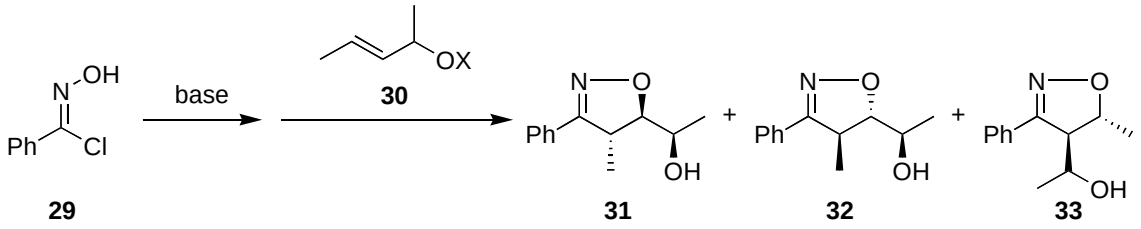
(2) The ability of the isoxazoline to act as a protecting group for functionality to be unmasked late in the synthesis; and

(3) Rigidification of the cyclocarbonylation product to provide a clear facial preference for subsequent oxidations.

We anticipate that the regioselectivity of the cycloaddition will be influenced by the presence of the enone. High regioselectivity has been reported for the reaction of nitrile oxides with cycloalkenones, largely due to steric effects.[62] We anticipate that the hydroxyl group may aid in guiding the nitrile oxide to a *syn* approach, as well as in reinforcing the regioselectivity; although, this type of assistance is not well supported in the literature. While hydrogen-bonding has not been observed to be a strong enough force to consistently direct the 1,3-dipolar cycloaddition of nitrile oxides,[63-65] supplanting the proton of the alcohol with a stronger Lewis acid has been demonstrated to lead to high regio- and stereoselectivity.[66-70]

Kanemasa and colleagues[70] found that conversion of allylic alcohols to the corresponding magnesium alkoxide (e.g., **30**, X = MgBr, Table 1) and subsequent exposure to benzonitrile oxide (generated through dehydrohalogenation of hydroximoyl chloride **29**) gave the corresponding isoxazolines in a highly regio- and stereoselective fashion (Table 1, entry 2). It was noted, however, that the reaction of the magnesium alkoxide generated from 2-cyclohexenol "led to the formation of a complex mixture of many products."

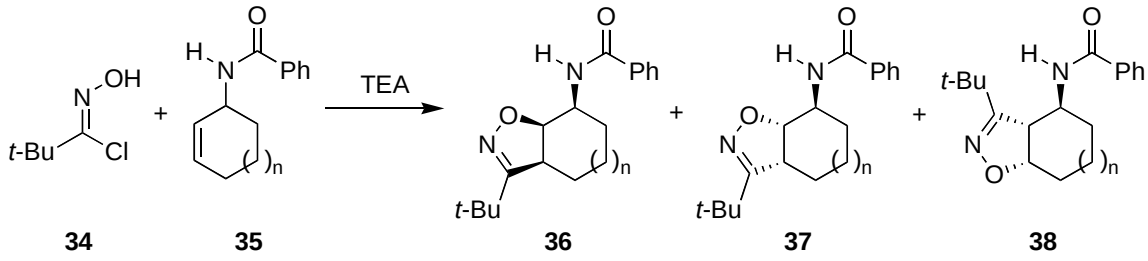
Table 1. Magnesium alkoxide direction in 1,3-dipolar cycloaddition (Kanemasa)



Base	X	Yield (%)	**31** : **32** : **33**
TEA	H	28	55 : 27 : 18
EtMgBr	MgBr	53	94 : 6 : 0

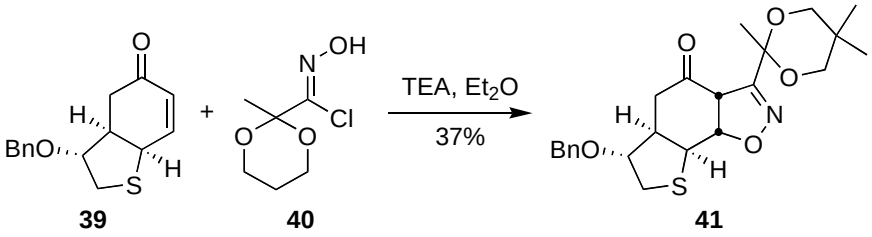
A related result was realized in a study of the directing abilities of 2° amides conducted by a member of the Curran group. After exposure to conditions that led to satisfactory formation of the *syn*-cycloadduct **36** of the corresponding cyclopentenyl amide (**35**, n = 0, Table 2, entry 1), unreacted cyclohexenyl amide (**35**, n = 1) was recovered, even when the reaction was heated to 80 °C for nearly 10 days (Table 2, entries 2 and 3).[68] Choi suggested this result was due to the relatively low reactivity of cyclohexene-derived substrates towards cycloaddition and to the inability of such substrates to adopt the necessary hydrogen-bonded transition state.

Table 2. Hydrogen bond direction in 1,3-dipolar cycloaddition (Choi)



Entry	n	Time (days)	T (°C)	Yield (%)	**36** : **37** : **38**
1	0	4.5	25	92	85 : 1 : 14
2	1	4.5	25	NR	NA
3	1	9.5	80	NR	NA

It is possible that the facial selectivity of the 1,3-dipolar cycloaddition will be controlled by sterics alone. In studies directed toward the synthesis of breynolide, the Martin group[71, 72] observed a single cycloadduct **41** resulting from addition of the nitrile oxide generated from hydroximoyl chloride **40** *anti* to a large substituent on a cyclohexenone substrate **39** (Scheme 8).



39 **40** **41**

Scheme 8. Steric direction of nitrile oxide cycloaddition (Martin)

The presence of the isoxazoline ring will impose considerable conformational constraints on our synthetic intermediates. Molecular modeling of the two possible diastereomers (resulting from the propargylation step) of the cyclocarbonylation product using Spartan shows that each molecule possesses a convex and a concave face (Figure 4). In both cases, the more sterically accessible convex face is the face on which we hope to perform selective oxidations of the enone.

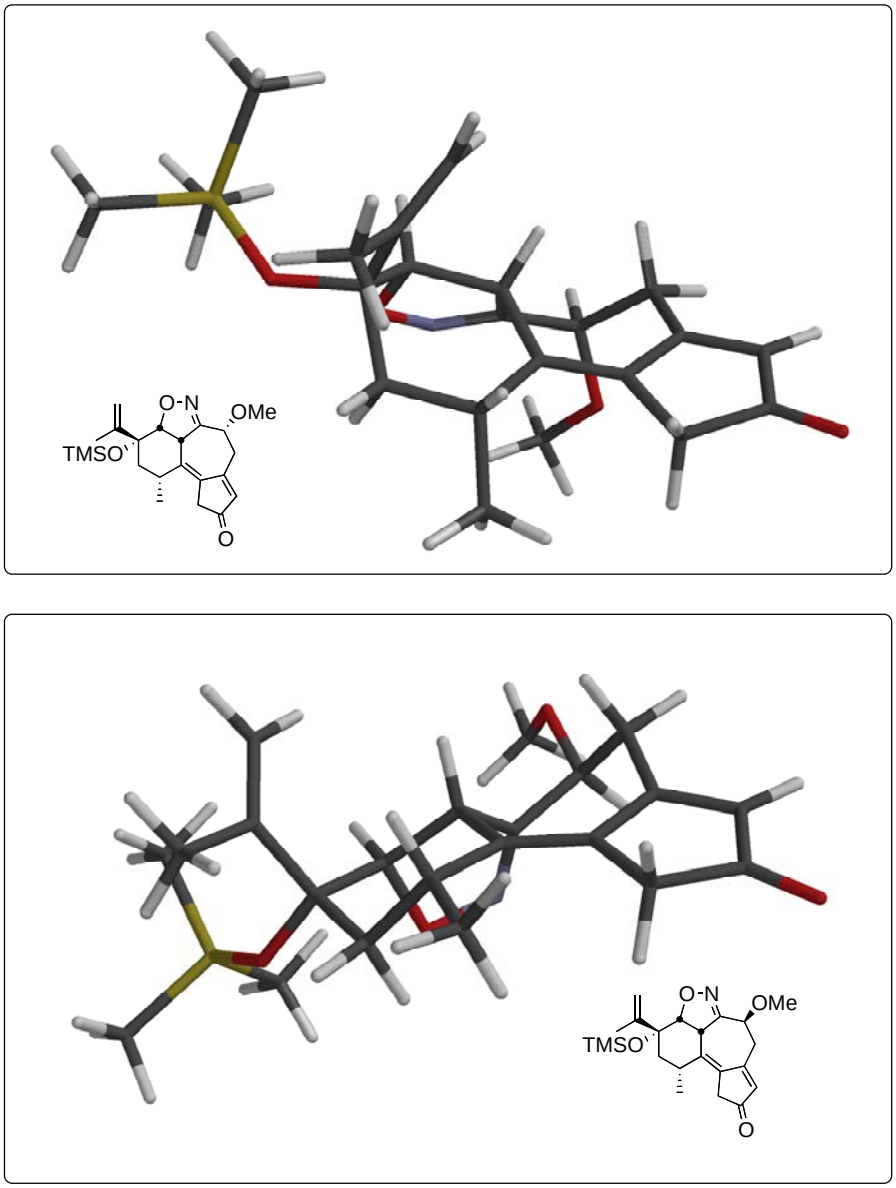


Figure 4. Molecular modeling of cyclocarbonylation products

4.0 RESULTS AND DISCUSSION

4.1 INTRODUCTION

Prior to committing to the synthesis of resiniferatoxin, our retrosynthetic plan required that we address three questions:

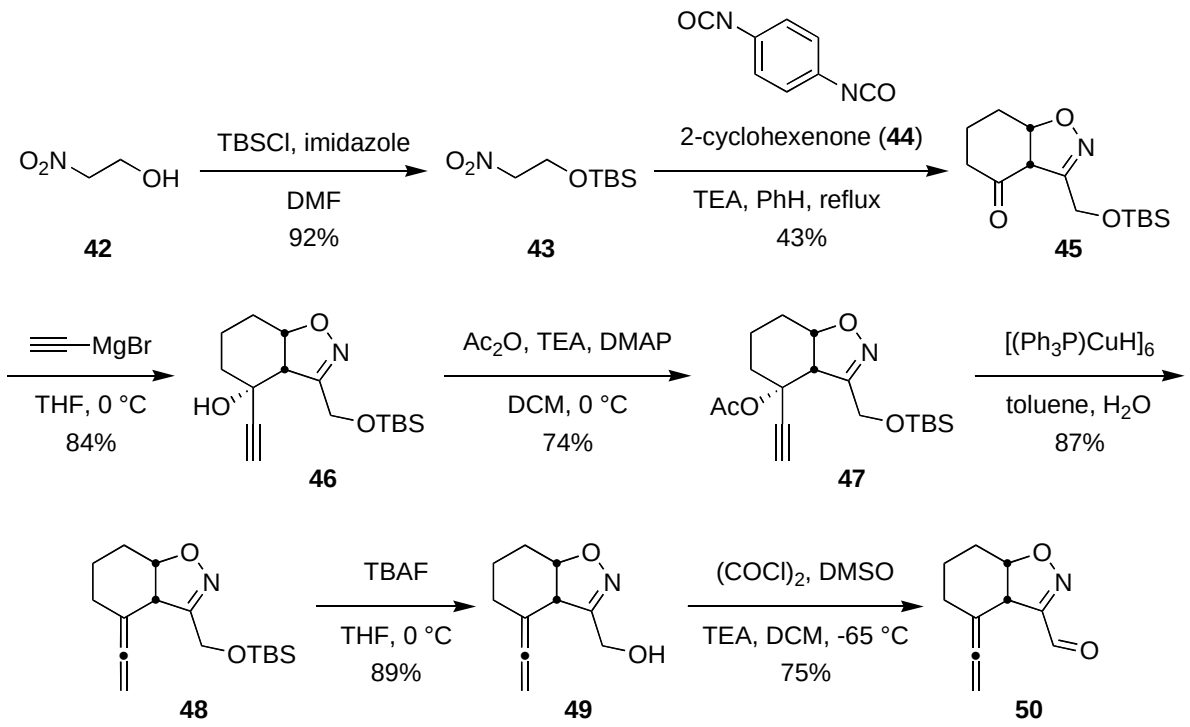
(1) Is the isoxazoline moiety tolerated by the reaction conditions we wish to employ, namely the Rh(I)-catalyzed cyclocarbonylation protocol?

(2) Is selective oxidation of the resulting alkylidene cyclopentenone feasible?

(3) Are we able to carry out a stereoselective [3 + 2] cycloaddition?

In order to satisfy these queries, we embarked on two separate investigations. We utilized a model system to demonstrate the compatibility of the isoxazoline moiety with the rhodium-catalyzed cyclocarbonylation reaction (section 4.2). Also, this model system will allow us to ascertain the utility of the cyclocarbonylation product in subsequent selective oxidation. Concurrently, an asymmetrically functionalized C ring was prepared to probe the possibility of obtaining selectivity in the 1,3-dipolar cycloaddition (section 4.3).

4.2 MODEL SYSTEM CONTAINING AN UNFUNCTIONALIZED C RING

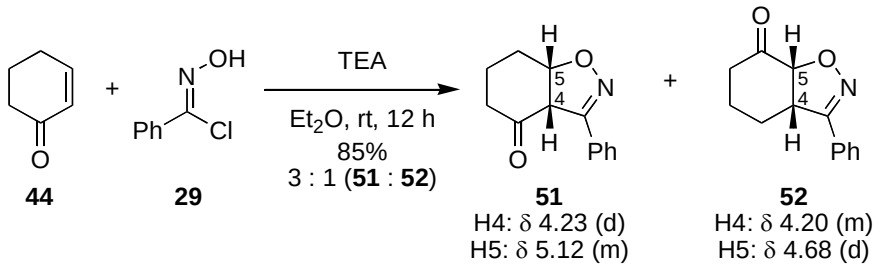


Scheme 9. Synthesis of model system

Under my direction, undergraduate researcher Darla Seifried explored the steps shown in Scheme 9.[73] I have since repeated the reactions several times to investigate the propargylation and subsequent cyclocarbonylation steps. All yields reported are from my syntheses. Nitroethanol (**42**) was protected as the TBS ether **43**, which then underwent *in situ* dehydration and 1,3-dipolar cycloaddition with 2-cyclohexenone (**44**) to give bicycle **45** as a single regioisomer. Initially, phenylisocyanate was used as the dehydrating agent;[74] however, the diphenyl urea byproduct generated during the reaction was extremely difficult to remove from the desired product via either multiple precipitations (using ethyl acetate, hexanes, ether, or water) of the urea or column chromatography.[73] Kurth and colleagues[75] have reported a clever solution to this frequently observed problem: the use of 1,4-phenylene diisocyanate generates a

polyurea that is insoluble in organic solvents (THF, methylene chloride and benzene) and can therefore be removed by filtration. We found Kurth's method to be satisfactory, although a single filtration is rarely sufficient to remove the significant quantities of polymeric urea present in the reaction mixture.

The regioselectivity of the cycloaddition was confirmed by ^{1}H NMR. In isoxazoline **45**, H5 gives a doublet of triplets resonance at δ 4.95 ppm and H4 appears as a doublet at δ 3.86 ppm (Figure 5). This is consistent with the findings of Grünanger and colleagues[62] in their studies of the relationship between regioisomers and chemical shift in similar systems. In the addition of benzonitrile oxide to 2-cyclohexenone (**44**), the multiplet resonance for H5 appears significantly downfield from the H4 doublet in the major product **51** (Scheme 10). The $\Delta\delta_{H4,H5}$ is much smaller for the regioisomer **52**, and the more deshielded proton—H5—is *alpha* to the ketone and therefore only split by H4 (i.e., appears as a doublet). Grünanger observed only *cis*-addition to cycloalkenones, the products exhibiting a characteristically large $^{3}J_{H4,H5}$ (8.8 to 12.0 Hz). The ^{3}J coupling (9.7 Hz) exhibited by H4 and H5 in isoxazoline **45** falls neatly within this range.[76, 77]



Scheme 10. Dependence of chemical shift on regioselectivity in nitrile oxide cycloaddition (Grünanger)

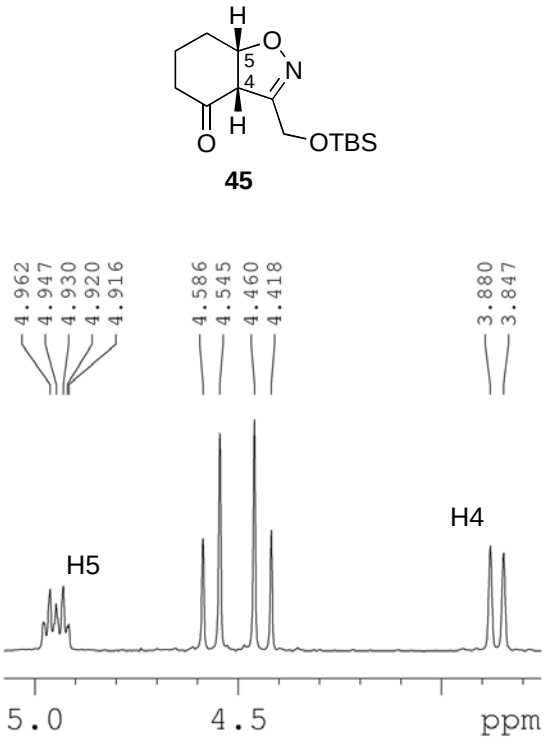
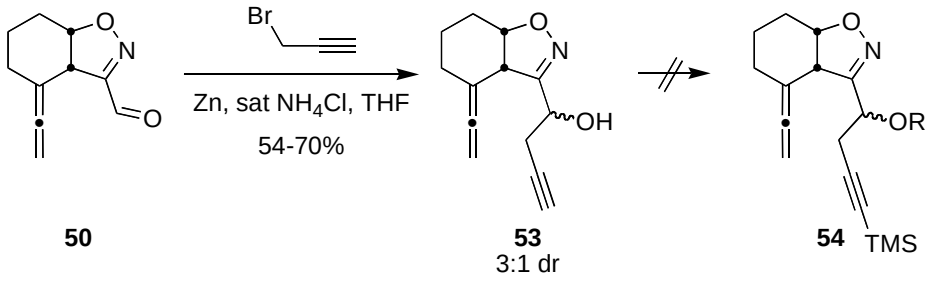


Figure 5. ^{1}H NMR verification of regioselectivity

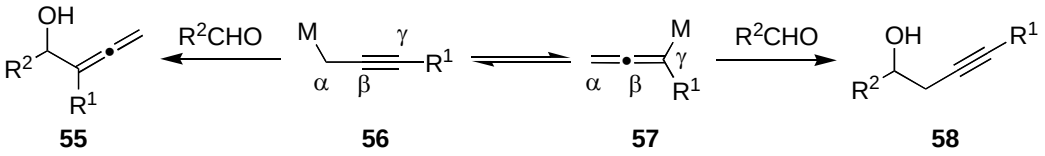
Addition of ethynylmagnesium bromide to the ketone **45**, followed by acylation of the tertiary alcohol **46**, gave propargyl acetate **47** as a single diastereomer. As has been experienced by other group members,[48, 51] Stryker's reagent ($[(Ph_3P)CuH]_6$) was suitable for the reduction of the propargyl acetate **47** to the corresponding 1,1-disubstituted allene **48**. Initial yields obtained for the reduction of the propargyl acetate **47** using commercial samples of Stryker's reagent were around 45%. Others[78-80] have remarked on the variable (and generally inferior) quality of commercial $[(Ph_3P)CuH]_6$[81] as compared to Stryker's reagent that has been prepared in the laboratory. Consequently, the copper hydride species was prepared according to the literature[82] and, using the fresh reagent, the yield of allene **48** nearly doubled to 87%. Deprotection of the TBS ether **48** followed by Swern oxidation[83] of the primary alcohol **49** gave aldehyde **50**.

The addition of nucleophiles to 3-formyl-Δ^2-isoxazolines is precedented,[84] although propargylation has not been reported. A zinc Barbier reaction of the aldehyde **50** and propargyl bromide in aqueous ammonium chloride produced the desired homopropargyl alcohol **53** in variable yield as a 3:1 mixture of diastereomers (Scheme 11). However, subjecting this substrate to the $[Rh(CO)_2Cl]_2$ cyclocarbonylation conditions led mostly to decomposition. Other group members have observed similar behavior in the case of terminal alkynes.[48] Attempts at protecting the terminal alkyne **53** with a trimethylsilyl group proved unsuccessful and efforts to force the formation of **54** by exposure of the protected alcohol to excess base led primarily to decomposition.



Scheme 11. Propargylation of aldehyde **50**

In reexamining the propargylation step, it seemed necessary to install the propargyl group and to protect the terminal alkyne in a single step. There are relatively few methods of accomplishing this. Most propargylation conditions rely upon the favorable equilibrium of the propargylic and allenic organometallic species, **56** and **57**, respectively (Scheme 12), the latter leading to the α-addition product **58** via an S_E2' mechanism.[85] Sterically demanding groups on the terminus of the alkyne (e.g., R^1 = TMS) may shift this equilibrium to favor the propargyl organometallic species **56**, giving the allenic alcohol **55** preferentially. The product distribution has, however, been found to be highly dependent on the metal used, the nature of the substituent on the alkyne (R^1), the electrophile, and reaction solvent.

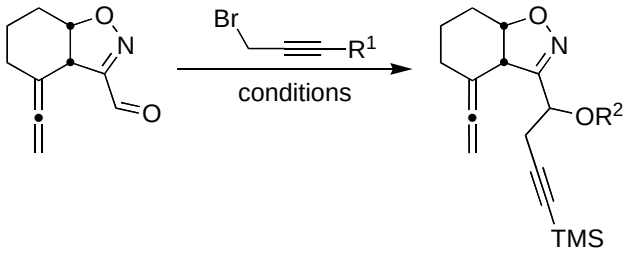


Scheme 12. Regioselectivity in propargylation reactions

Paquette and Daniels[86] have published an often-cited study that exemplifies the capricious behavior of propargylation reactions. Treatment of aldehydes and ketones with trimethylsilylpropargylzinc bromide in THF led to selective formation of the homopropargylic alcohol, while treatment of the same substrates with the analogous aluminum reagent yielded allenyl alcohols preferentially. Additionally, increasing the coordinating ability of the solvent was highly influential in the product distribution of protonolysis of the aluminum reagent; in diethyl ether, 1-trimethylsilylpropyne was obtained after quenching the organometallic species, while in THF or diglyme the regioselectivity was reversed.

Unfortunately, Paquette and Daniels'[87] zinc amalgam protocol failed to produce the desired homopropargyl alcohol **54** (Table 3, entry 1). The majority of the starting material **50** was recovered. Propargylation of aldehyde **50** was attempted using conditions developed by Loh and Lin,[88] who have shown that simple aldehydes undergo regioselective propargylation with trialkylsilyl propargyl bromides in the presence of indium and catalytic indium trifluoride. Lin and Loh attribute the high selectivity for the α-alkylation product to the probable coordination of the halogen and the silicon in the allenic organometallic species **57**. This protocol proved ineffective in the propargylation of our aldehyde **50**, however (entry 2). The majority of the starting material was recovered.

Table 3. Propargylation of aldehyde **50**

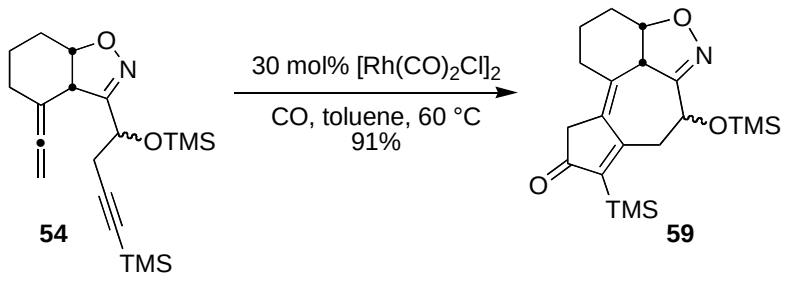


50 **54**

Entry	R^1	Conditions	R^2	Yield of **54** (%)
1	TMS	Zn, $HgCl_2$, cat I_2	NA	NR
2	TMS	In, InF_3, THF, reflux	NA	NR
3	H	2 equiv *n*-BuLi, TMEDA, then TMSCl	TMS	21 (2:1 dr)

Cabezas[89, 90] has also presented an approach to the problem of regioselective addition, in which 1,3-dilithiopropyne is prepared from propargyl bromide and added to the aldehyde. Quenching of the reaction with TMSCl protects both the newly formed alcohol and the alkyne terminus. Employment of this method gave the desired bis-protected homopropargyl alcohol **54** (R^2 = TMS), albeit in 21% yield as a 2:1 mixture of diastereomers by ^{1}H NMR (Table 3, entry 3).

Gratifyingly, when subjected to $[Rh(CO)_2Cl]_2$ in the presence of CO, allene-yne **54** smoothly underwent cyclocarbonylation to give the desired product **59** in 91% yield after 3 hours (Scheme 13). Following cyclocarbonylation, the two diastereomers (originating in the propargylation step) were easily separated by column chromatography, yielding 10 mg (73%) of the major diastereomer, and 3 mg (18%) of the minor isomer.

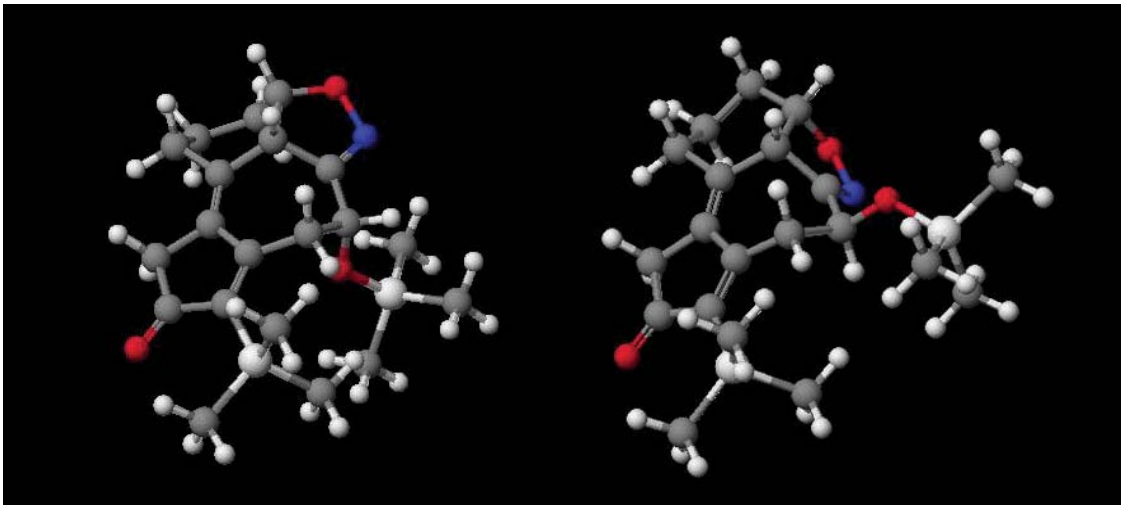


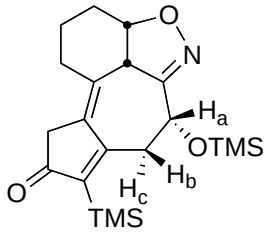
Scheme 13. Cyclocarbonylation of the model system

There is a minor discrepancy between the isolated yields of the diastereomers of **59** and the previously observed 2:1 dr observed in the ^{1}H NMR of the homopropargyl silyl ether **54**. Were the remaining 9% of the material not isolated as product comprised solely of the minor diastereomer of **54**, the diastereomeric ratio observed in the cyclocarbonylation reaction (potentially 73:27) still would not be equivalent to 2:1. This lack of agreement may be attributed to two things. First, the 2:1 dr is based on the integration of methine protons that are not fully resolved in the ^{1}H NMR spectrum (see Appendix A). Second, the margin of error in weighing milligram quantities is presumably large enough to account for the observed discrepancy.

In an effort to gain insight into the relative stereochemistry of the cyclocarbonylation products, the two epimers of **59** were modeled using CAChe. The global minimum conformation for each isomer was found using CONFLEX/MM3 parameters (Figure 6).[91] The minimum energy conformer for the epimer with the α-TMS ether (**59α**) exhibited dihedral angles of 70.2 and 44.3° between H_a and H_b, and H_a and H_c, respectively. The measured dihedral angles for **59β** are 176.2 and 60.9°. Based on these calculations, one would expect to observe a doublet of doublets with two medium-to-small ^3J couplings for the resonance of H_a in **59α**. In contrast, the calculated dihedral angles for **59β** predict a doublet of doublets with one large and one small vicinal coupling. Indeed, the resonance for H_a in the ^{1}H NMR spectrum of the major diastereomer of **59** is a triplet at δ 5.01 ppm with J = 3.6 Hz (see Appendix A). The

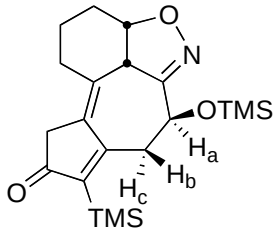
corresponding signal in the ^{1}H NMR spectrum of the minor diastereomer is a doublet of doublets at δ 4.76 ppm with J = 10.8 and 5.4 Hz. Therefore, the major and minor diastereomers can tentatively be assigned as **59α** and **59β**, respectively.





59α

H_a-C-C-H_b ∠ 70.2°
H_a-C-C-H_c ∠ 44.3°
observed for H_a: δ 5.01 (t, J = 3.6 Hz)



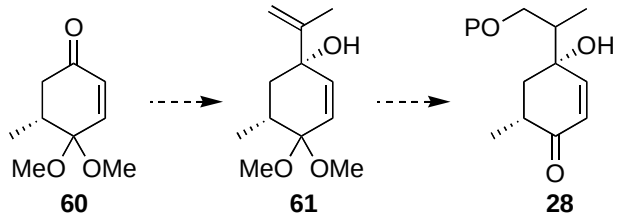
59β

H_a-C-C-H_b ∠ 176.2°
H_a-C-C-H_c ∠ 60.9°
observed for H_a: δ 4.75 (dd, J = 10.8, 5.4 Hz)

Figure 6. Minimum energy conformations and dihedral angles for **59α** (left) and **59β** (right)

4.3 SYNTHESIS OF AN ASYMMETRICALLY-FUNCTIONALIZED C RING

Our strategy for the synthesis of a functionalized C ring was to add isopropenyl Grignard to known enone **60** (Scheme 14), hydrate the exocyclic olefin of **62** and cleave the ketal to access functionalized enone **28**.

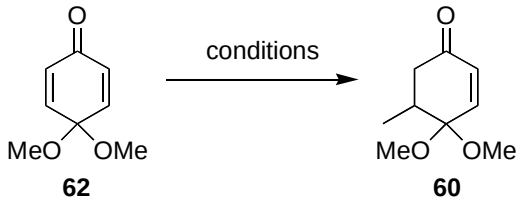


Scheme 14. Proposed synthesis of functionalized C ring

4.3.1 Conjugate addition to cyclohexadienone 62 to form enone 60

There are only a few literature examples of conjugate addition of a methyl group to quinone monoketal **62**. Addition of lithium dimethylcopper to quinone monoketal **62**[92] is known to lead to reductive aromatization rather than conjugate addition (Table 4, entry 1).[93] Complexation of quinone monoketals with an organoaluminum reagent followed by addition of either an alkyllithium or Grignard reagent has been shown to yield the corresponding 1,4-addition products in many cases; however, in the case of the addition of methyllithium, only a 24% yield of the desired product **60** was achieved (entry 2).[94] Fortunately, Feringa and colleagues[95] have developed an enantioselective copper-catalyzed conjugate addition protocol that was reported to give the desired enone **60** in 76% yield and 99% *ee* from quinone monoketal **62** (entry 3).

Table 4. Literature examples of conjugate addition to quinone monoketal **62**

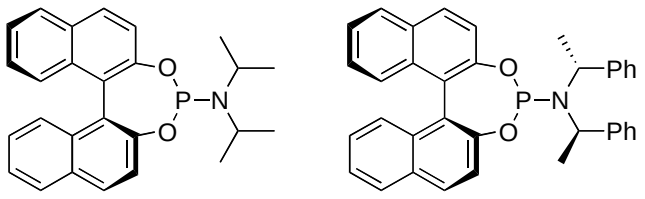


62 **60**

Entry	Conditions	Yield (%)	Ref.
1	$LiMe_2Cu$	—[a]	93
2	MAD,[b] MeLi	24	94
3	$Cu(OTf)_2$, (*S,R,R*)-**64**, Me_2Zn	76 (99% *ee*)	95

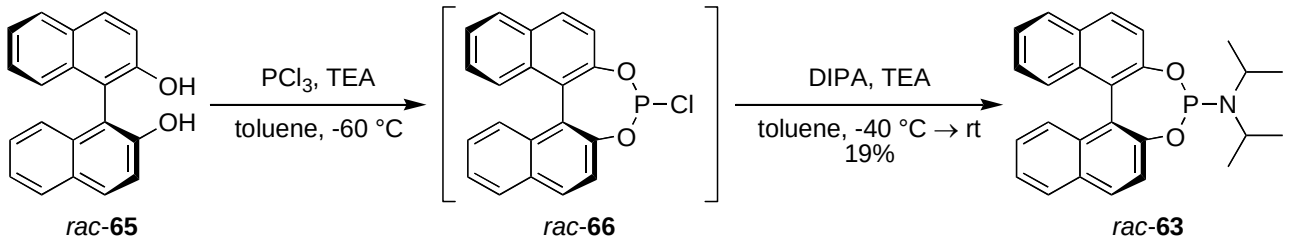
[a]*p*-Methoxyphenol obtained exclusively; [b]MAD = methylaluminum bis(2,6)-di-tert-butyl-4-methylphenoxide)

The enantioselectivity of Feringa's protocol arises from the use of chiral phosphoramidite ligand **64** (Figure 7). The Feringa group has published the use of a variety of phosphoramidite ligands synthesized from BINOL, PCl_3, and 2° amines.[96] Because the price of the amines varies widely, we sought to synthesize an effective phosphoramidite ligand while minimizing cost. We were encouraged to see that both ligand (*S*)-**63** and (*S,R,R*)-**64** were effective in the copper-catalyzed addition of diethylzinc to 2-cyclohexenone, each giving 3-ethylcyclohexanone in >75% yield and 83% *ee* and >98% *ee*, respectively.[96] Initially less concerned with the enantiopurity of the enone than with obtaining the desired material, we opted to synthesize racemic phosphoramidite **63** from racemic BINOL (*rac*-**65**), PCl_3, and diisopropylamine (Scheme 15).



(*S*)-**63** (*S,R,R*)-**64**

Figure 7. Chiral phosphoramidite ligands



rac-**65** *rac*-**66** *rac*-**63**

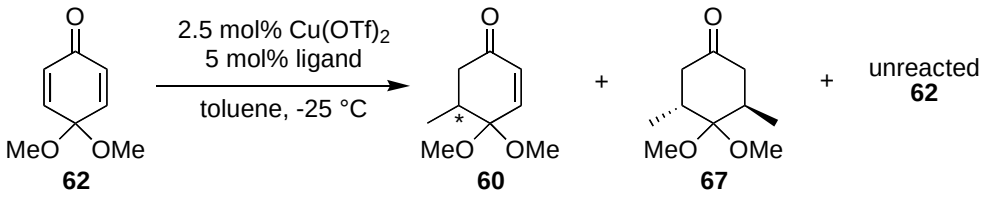
Scheme 15. Synthesis of racemic phosphoramidite ligand **63**

Unfortunately, exposure of quinone monoketal **62** to $Cu(OTf)_2$, ligand *rac*-**63**, and Me_2Zn in toluene at –25 °C failed to produce the desired product **60** in a reasonable yield (Table 5, entries 1 and 2). The reaction did not go to completion, even when the mixture was allowed to stir at -25 °C for several days. The lack of desired reactivity may have been due, at least in part, to the poor solubility of the catalyst complex in toluene at the reaction temperature. Upon cooling the premixed solution of $Cu(OTf)_2$ and ligand from room temperature to -25 °C, significant precipitation was observed.

Enantiomerically pure phosphoramidite (*S,R,R*)-**64** was synthesized in 26% yield in a fashion analogous to the previous phosphoramidite synthesis.[96] $Cu(OTf)_2$ was premixed with the phosphoramidite ligand and was then cooled to -25 °C; the quinone monoketal was added followed by a solution of Me_2Zn. Within approximately six hours, all cyclohexadienone **62** starting material was consumed (this is in contrast to the 16 hours the reaction is reputed[95] to require). Surprisingly, a significant amount of the diaddition product **67** was observed in the product mixture (Table 5, entry 3). Protonation of the Zn-enolate intermediate prior to quenching of the catalyst is requisite in order for a second 1,4-addition to occur. TLC indicated a dramatic difference in the relative amounts of mono- and diaddition products (**60** and **67**, respectively) before and after quenching. The final ratio of mono- to diaddition products has been found to be somewhat contingent on the method of quenching. This trend is summarized in Table 5 (entries 3-5), although it is important to note that exact ratios were not reproducible.

Following the published procedure,[95] the addition of saturated aqueous NH_4Cl to the reaction mixture led to greater relative amounts of the diaddition product **67** in the crude ^1H NMR than did a basic quench (entries 3 and 4), which was prescribed by Rosalinde Imbos in her Ph.D. thesis.[97] The ratio of mono- to diaddition product (**60** : **67**) was further improved by performing a reverse basic quench (entry 5).

Table 5. Product distribution in copper-catalyzed conjugate addition to cyclohexadienone **62**



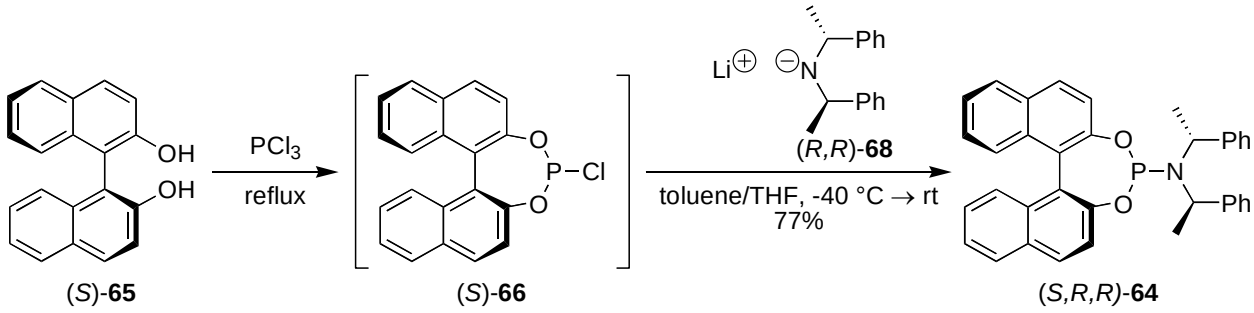
Entry	Ligand	Equiv Me_2Zn	Time (h)	Quench	**60** : **67** : **62**[a]	Yield of **60** (%)
1	*rac*-**63**	1.6	16	direct, sat NH_4Cl	—	17
2	*rac*-**63**	1.6 + 1[b]	48	direct, sat NH_4Cl	—	20
3	(*S*,*R*,*R*)-**64**	1.6	6	direct, sat NH_4Cl	18 : 82 : 0	—[c]
4	(*S*,*R*,*R*)-**64**	1.6	16	direct, 1 M NaOH	60 : 40 : 0	33
5	(*S*,*R*,*R*)-**64**	1.6	6	reverse, 1 M NaOH	71 : 29 : 0	—[c]
6	(*S*,*R*,*R*)-**64**	1.6	4[d]	reverse, 1.5 M NaOH	75 : 0 : 25	50
7	(*S*,*R*,*R*)-**64**[e]	1.6	16	direct, 1 M NaOH	100 : 0 : 0	21[f]

[a]determined by integration of crude ^1H NMR; [b]additional equivalent Me_2Zn added after 45 h; [c]yield not determined; [d]reaction followed closely by TLC and quenched at first faint sign of diaddition product; [e]ligand of high purity; [f]low yield due to volatility of product

The presence of the diaddition product proved to be problematic since separation of the mono- and diaddition products by column chromatography was not possible. Two methods of minimizing the formation of the diaddition product were discovered. The first was to monitor the reaction closely and quench the reaction as soon as there was TLC evidence of diaddition product forming (Table 5, entry 6). An early quench of the reaction allowed for the isolation of an easily separable 3:1 mixture (by ^1H NMR) of desired product **60** to unreacted starting

material. (Fortuitously, ketone **67** stains very darkly with PAA and although the diaddition product was evident by TLC, it often was only faintly—if at all—visible in the crude ^{1}H NMR.)

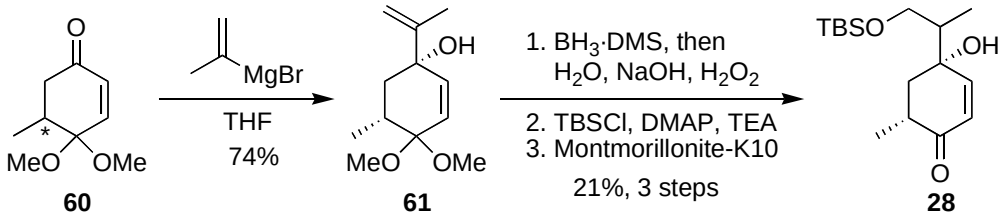
The use of phosphoramidite ligand of a higher purity also suppressed the formation of the unwanted diaddition product.[98] Unsatisfied with the previously low-yielding synthesis of phosphoramidite **64**, we developed a revised synthesis based on methods reported in Ate Duursma's Ph.D. thesis.[99] (*S*)-BINOL (**65**) was refluxed in PCl_3 (Scheme 16). Removal of the excess PCl_3 under vacuum furnished phosphochloridite **66**, which was dissolved in toluene and added to a solution of deprotonated amine (*R,R*)-**68**. Not only did this method drastically improve the isolated yield of the ligand **64** (77% versus 26%), but also the ligand was significantly more pure by ^{1}H NMR.[100] Use of this ligand in the copper-catalyzed conjugate addition led only to the desired monoaddition product (Table 5, entry 7). Unfortunately, repetition of the improved ligand synthesis procedure led to ligand of inferior purity that, in turn, led to significant quantities of diaddition product **67** produced in the copper-catalyzed 1,4-addition reaction.



Scheme 16. Improved synthesis of phosphoramidite (*S,R,R*)-**64**

4.3.2 Elaboration of enone 60

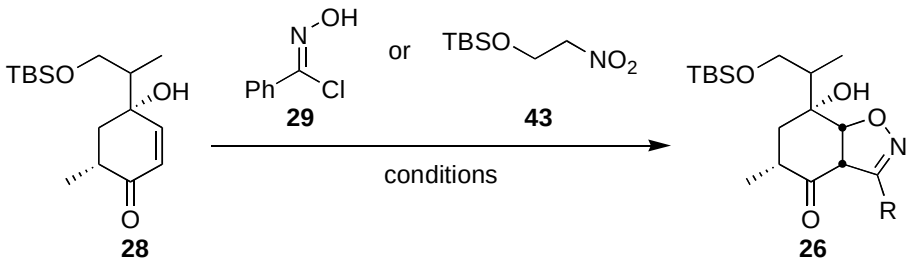
Isopropenylmagnesium bromide was added to the ketone **60**, affording the tertiary alcohol **61** in 74% yield (Scheme 17). Hydroboration of the 1,1-disubstituted olefin with BH_3·DMS followed by oxidation[101] gave the corresponding primary alcohol as a mixture of diastereomers. Attempts to improve the diastereoselectivity by using bulky 9-BBN led to no appreciable hydroboration, as observed by the ^{1}H NMR spectra of aliquots of the reaction mixture. The mixture of diastereomers was taken on crude due to the lability of the ketal on silica gel, even when the column was pretreated with TEA. The primary alcohol was protected as the TBS ether[102] prior to cleavage of the ketal by Montmorillonite K10 clay,[103] giving the enone **28** in 21% yield from **61** as a 2:1 mixture of diastereomers by ^{1}H NMR.



Scheme 17. Synthesis of enone **28**

A variety of 1,3-dipolar cycloaddition conditions were surveyed, all of which were designed to generate the nitrile oxide very gradually to minimize homodimerization of the nitrile oxide.[56] Unfortunately, enone **28** failed to undergo 1,3-dipolar cycloaddition and, in all cases, most of the starting material was recovered (Table 6). A very small amount of a mixture of unknown products was isolated from the reaction of enone **28** with nitroalkane **43** when Kurth's diisocyanate methodology[75] was used (entry 6). Since selectivity was not exhibited, investigation was discontinued.

Table 6. Attempted stereoselective cycloaddition of enone **26**



Entry	**29** or **43**	Conditions	Scale (mg of **28**)	Yield of **26** (%)
1	**29**	EtMgBr, DCM[70]	10	—
2	**29**	TEA, Et_2O[71]	10	—
3	**29**	$KHCO_3$, DME[104]	10	—
4	**29**	$KHCO_3$, DME, Δ	10	—
5	**29**	4 Å mol sieves, DCM[105]	21	—
6	**43**	1,4-phenylene diisocyanate, TEA, PhH, reflux[75]	21	—[a]

[a]Most of starting material was unreacted; however, a small amount of a mixture of unknown products was obtained.

5.0 CONCLUSION

Our proposed plan for the synthesis of resiniferatoxin required that we addressed several uncertainties, namely whether an isoxazoline moiety would be tolerated by the Rh(I)-catalyzed cyclocarbonylation reaction, whether selective oxidations of the resulting alkylidene cyclopentenone could be carried out, and whether a stereoselective 1,3-dipolar cycloaddition was feasible. We synthesized a simple isoxazoline-containing model system, which underwent Rh(I)-catalyzed allenic cyclocarbonylation to give the unfunctionalized angular [6-7-5] core of resiniferatoxin in 91% yield. The cyclopentenone scaffold produced by the cyclocarbonylation reaction was an appropriate substrate for probing conditions for selective olefin oxidation, although selective oxidation was not pursued due to the disappointing results obtained in the area of stereoselective 1,3-dipolar cycloaddition. An asymmetrically functionalized enone, corresponding to the C ring of resiniferatoxin, was synthesized utilizing Feringa's Cu-catalyzed asymmetric conjugate addition protocol. Unfortunately, the functionalized 2-cyclohexenone failed to undergo stereoselective 1,3-dipolar cycloaddition under numerous conditions tested.

6.0 EXPERIMENTAL

6.1 GENERAL

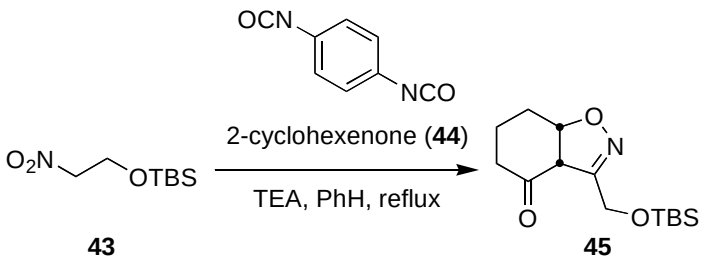
Unless otherwise specified, all nonaqueous reactions were performed in flame- or oven-dried glassware under N_2 atmosphere using the appropriate syringe, cannula, and septum techniques. All solvents and reagents were purchased commercially and used as received unless otherwise noted. Toluene, acetonitrile (MeCN), triethylamine (TEA), *N,N,N',N'*-tetramethylethylendiamine (TMEDA), and chlorotrimethylsilane (TMSCl) were distilled from CaH_2 prior to use. Dimethyl sulfoxide (DMSO) was distilled from CaH_2 and stored over activated 4 Å mol sieves. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried and deoxygenated by sequential passage through activated alumina and Q5 columns in a Sol-Tek ST-002 solvent purification system; dichloromethane (DCM) was passed through an activated alumina column in the same system. 2-Cyclohexenone was distilled (47 °C at 9 mm Hg) and stored at -20 °C. Acetic anhydride (Ac_2O) was distilled (30 °C at 20 mm Hg) from P_2O_5 and stored in a desiccator. $Cu(OTf)_2$ and $[(Ph_3P)CuH]_6$ were stored in a glove box and dispensed using standard glove box techniques. All solvents used in the preparation and reactions of air-sensitive reagents were degassed by bubbling N_2 for 20-30 min before use.

Column chromatography was performed using silica gel (32-63 μm particle size, 60 Å pore size) purchased from Scientific Adsorbents, Inc. following the guidelines described in the

seminal publication on flash chromatography by Still and colleagues.[106] Ethyl acetate (EtOAc) and hexanes used for chromatography were distilled prior to use. TLC was performed using silica gel plates (60 F_{254}, 250 μm thickness).

^{1}H and ^{13}C NMR spectra were obtained on Varian 300 MHz instruments. All chemical shifts (δ) are reported in ppm. ^{1}H NMR spectra were calibrated to the residual $CHCl_3$ peak at δ 7.27; ^{13}C NMR spectra were referenced to the $CDCl_3$ resonance at δ 77.0. The following abbreviations are used to denote the indicated splitting pattern ^{1}H NMR spectra: s = singlet, d = doublet, t = triplet, q = quartet; abbreviations are used in combination to indicate more complex splitting (e.g., dtd = doublet of triplets of doublets). Infrared spectra were obtained on a Nicolet Avatar E. S. P. 360 FT-IR.

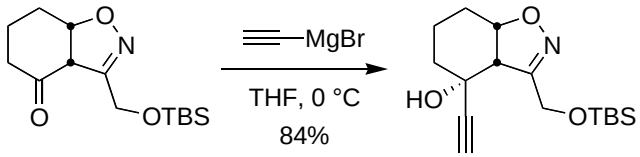
6.2 SYNTHESIS AND CHARACTERIZATION



43 45

3-((*tert*-Butyldimethylsilyloxy)methyl)-5,6,7,7a-tetrahydrobenzo[*d*]isoxazol-4(3a*H*)-one (45). A mixture of cyclohexenone (**44**) (1.80 mL, 18.59 mmol, 1.0 equiv), nitroalkane **43** (3.75 g, 18.28 mmol, 1.0 equiv), 1,4-phenylenediisocyanate (9.08 g, 56.69 mmol, 3.1 equiv) and TEA (0.50 mL, 3.59 mmol, 0.2 equiv) in benzene (180 mL) was refluxed. After approximately 16 h, the turbid yellow mixture was cooled to rt; water (9 mL) was added and the mixture stirred 1 h. The polymeric urea was removed via vacuum filtration through a pad of celite; the filtrate was

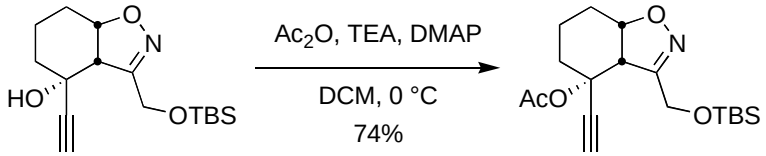
dried ($MgSO_4$) and concentrated under reduced pressure. Benzene was added and the filtration step was repeated. The filtrate was concentrated onto silica gel, which was dry-loaded onto a silica gel column for purification. Gradient elution with EtOAc/hexanes (1:9 to 1:6) yielded isoxazoline **45** (2.212 g, 43%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.95 (dt, *J* = 9.7, 4.5 Hz, 1H), 4.56 (A of ABq, *J* = 12.5 Hz, 1H), 4.44 (B of ABq, *J* = 12.5 Hz, 1H), 3.86 (d, *J* = 9.7 Hz, 1H), 2.54-2.45 (m, 1H), 2.37-2.26 (m, 1H), 2.16-1.79 (m, 4H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.3, 157.4, 81.5, 58.7, 58.5, 39.9, 26.4, 25.8, 18.4, 18.3, -5.5, -5.6; IR (neat, NaCl): 2930, 2857, 1713, 1088, 837 cm^{-1}; MS *m/z* (%): 283 (9), 268 (73), 226 (90), 74 (100); EI-HRMS calcd for $C_{14}H_{25}NO_3Si$ $[M]^+$ *m/z*: 283.1604, found: 283.1610.



45 **46**

3-((*tert*-Butyldimethylsilyloxy)methyl)-4-ethynyl-3a,4,5,6,7,7a-hexahydrobenzo[*d*]isoxazol-4-ol (46). To a solution of the ketone **45** (0.511 g, 1.802 mmol, 1 equiv) in THF (18 mL) at 0 °C was added ethynylmagnesium bromide (14 mL of a 0.5 M soln in THF, 7 mmol, 4 equiv) over 25 min via syringe pump. The mixture stirred at 0 °C and reaction progress was monitored by TLC. Complete consumption of the starting material was observed ~30 min after the addition was finished; the reaction was quenched by pouring the mixture into a flask containing sat NH_4Cl solution. The aqueous layer was extracted with Et_2O (4×) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified via column chromatography, using EtOAc/hexanes (1:6) as the eluent, to give pure propargyl alcohol **46** (0.470 g, 84%) as a colorless oil. ^{1}H NMR (300

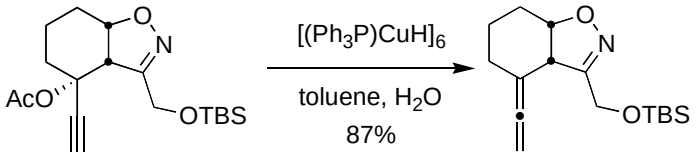
MHz, $CDCl_3$): δ 4.67-4.61 (m, 1H), 4.62 (A of ABq, *J* = 11.7 Hz, 1H), 4.45 (B of ABq, *J* = 11.7 Hz, 1H), 3.53 (d, *J* = 9.0 Hz, 1H), 2.48 (s, 1H), 1.97-1.71 (m, 4H), 1.61-1.50 (m, 1H), 0.93 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.6, 87.2, 80.2, 71.6, 65.4, 58.6, 57.9, 36.6, 25.8, 25.0, 18.2, 16.1, -5.5; IR (neat, NaCl): 3416, 3310, 2930, 2090, 1257, 1081, 838 cm^{-1}; MS *m/z* (%): 309 (9), 294 (69), 252 (82), 105 (74), 74 (100); EI-HRMS calcd for $C_{16}H_{27}NO_3Si$ $[M]^+$ *m/z*: 309.1760, found: 309.1762.



46 **47**

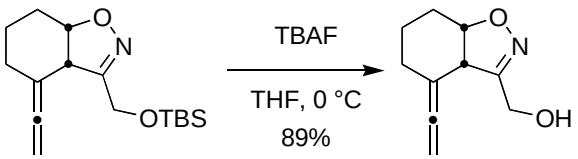
3-((*tert*-Butyldimethylsilyloxy)methyl)-4-ethynyl-3a,4,5,6,7,7a-hexahydrobenzo[*d*]-isoxazol-4-yl acetate (47). To a soln of the propargyl alcohol **46** (0.560 g, 1.81 mmol, 1 equiv) and DMAP (0.230 g, 1.88 mmol, 1 equiv) in DCM (18 mL) at 0 °C were added Ac_2O (1.7 mL, 18.00 mmol, 10 equiv) and TEA (2.5 mL, 17.94 mmol, 10 equiv). The mixture stirred at 0 °C and reaction progress was monitored by TLC. After approximately 12 h, the reaction was quenched by addition of saturated $NaHCO_3$ soln and the aqueous layer was extracted with DCM (3×). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography, eluting with EtOAc/hexanes (1:6), to give pure propargyl acetate **47** (0.504 g, 74%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.58 (A of ABq, *J* = 12.7 Hz, 1H), 4.52 (B of ABq, *J* = 12.7 Hz, 1H), 4.54-4.50 (m, 1H), 3.58 (d, *J* = 8.4 Hz, 1H), 2.72-2.66 (m, 1H), 2.68 (s, 1H), 2.12-2.04 (m, 1H), 2.03 (s, 3H), 1.87-1.57 (m, 5H), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7, 159.8, 82.8, 79.0, 74.9, 70.8, 58.7, 54.3, 32.4, 25.8, 24.2, 21.8, 18.2, 15.3, -5.2, -5.4; IR (neat, NaCl): 3250, 2931, 2100, 1748, 1221, 1076, 838 cm^{-1}; MS *m/z* (%) 294 (85), 234

(100), 156 (20), 117 (41), 105 (24); EI-HRMS calcd for $C_{17}H_{26}NO_4Si$ $[M]^+$ *m/z*: 336.1631, found: 336.1631.



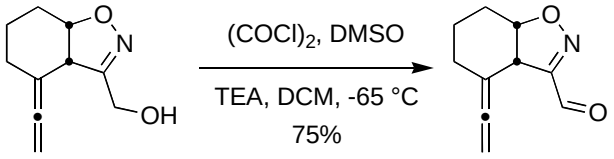
47 **48**

3-((*tert*-Butyldimethylsilyloxy)methyl)-4-vinylidene-3a,4,5,6,7,7a-hexahydrobenzo[*d*]isoxazole (48). To a dark red suspension of $[(Ph_3P)CuH]_6$[82] (1.68 g, 0.86 mmol, 0.50 equiv) in toluene (8.5 mL) was added a mixture of the propargyl acetate **47** (0.607 g, 1.727 mmol, 1 equiv), toluene (17 mL) and water (0.08 mL, 4.44 mmol, 2.57 equiv) via cannula over 20 min. The mixture gradually turned brown (i.e., appeared quenched) approximately 1 h after the addition. The septum was removed from the flask and the contents stirred open to the air for 20 min before being diluted with Et_2O and filtered through a plug of silica gel. After concentration under reduced pressure, the filtrate was purified by column chromatography using gradient elution with hexanes/EtOAc (19:1, 9:1). A second purification using 19:1 hexanes/EtOAc was required to remove remaining PPh_3. Allene **48** (0.305 g, 87%) was obtained as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.72-4.60 (m, 3H), 4.46 (A of ABq, *J* = 13.2 Hz, 1H), 4.42 (B of ABq, *J* = 13.2 Hz, 1H), 3.86 (br d, *J* = 9.3 Hz, 1H), 2.17-2.12 (m, 2H), 1.79-1.62 (m, 4H), 1.53-1.45 (m, 1H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.6, 160.2, 95.3, 79.7, 75.2, 58.0, 49.0, 27.2, 26.1, 25.7, 19.3, 18.1, -5.5, -5.6; IR (neat, NaCl): 2953, 2830, 1960, 1255, 1088, 839 cm^{-1}; MS *m/z* (%): 278 (41), 239 (33), 238 (96), 237 (73), 236 (100), 156 (13); EI-HRMS calcd for $C_{15}H_{24}NO_2Si$ $[M]^+$ *m/z*: 278.1576, found: 278.1576.



48 **49**

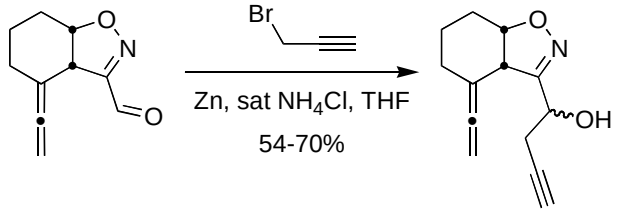
(4-Vinylidene-3a,4,5,6,7,7a-hexahydrobenzo[*d*]isoxazol-3-yl)methanol (49). To a soln of the TBS ether **48** (0.166 g, 0.565 mmol, 1 equiv) in THF (5.7 mL) at 0 °C was added TBAF (0.85 mL of a 1.0 M soln in THF, 0.85 mmol, 1.5 equiv) dropwise. Mixture stirred at 0 °C and the reaction progress was monitored by TLC. Approximately 20 min after the addition was complete, the reaction was quenched by the addition of sat. NH_4Cl soln. The aqueous layer was extracted with Et_2O (4×). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified via column chromatography, using EtOAc/hexanes (3:7), to give alcohol **49** (0.075 g, 75%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.72-4.71 (m, 2H), 4.64 (dt, *J* = 9.1, 5.1 Hz, 1H), 4.42 (A of ABq, *J* = 14.7 Hz, 1H), 4.34 (B of ABq, *J* = 14.7 Hz, 1H), 3.84 (br d, *J* = 9.1 Hz, 1H), 3.25 (br s, 1H), 2.20-2.10 (m, 2H), 1.78-1.58 (m, 3H), 1.53-1.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.4, 161.0, 95.0, 79.7, 75.6, 57.6, 49.1, 27.1, 26.1, 19.4; IR (neat, NaCl): 3392, 2941, 1959, 1610, 1442, 1037 cm^{-1}.



49 **50**

4-Vinylidene-3a,4,5,6,7,7a-hexahydrobenzo[*d*]isoxazole-3-carbaldehyde (50). To a soln of oxalyl chloride (0.08 mL, 0.932 mmol, 2.1 equiv) in DCM (3 mL) at –65 °C was added a soln of DMSO (0.14 mL, 1.971 mmol, 4.4 equiv) in DCM (1.5 mL) dropwise over 10 min. The mixture stirred 10 min before a soln of the alcohol **49** (0.080 g, 0.446 mmol, 1 equiv) in DCM (1.5 mL)

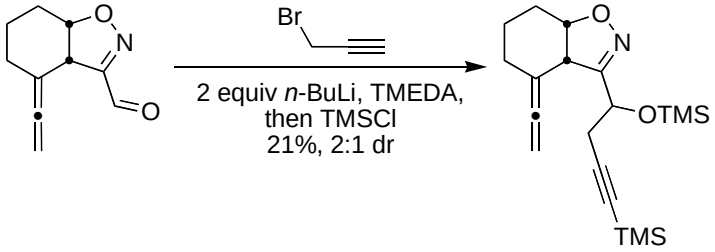
was added dropwise over 10 min. The mixture became cloudy while stirring for approximately 20 min at –65 °C. TEA was added dropwise over 5 min and the mixture was allowed to warm to room temperature over 30 min. The reaction mixture was washed with sat NH_4Cl soln and water. The combined aqueous washings were back-extracted with DCM (3×). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified via column chromatography, eluting with hexanes/EtOAc (6:1), to give aldehyde **50** (0.059 g, 75%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.90 (s, 1H), 4.75-4.64 (m, 2H), 3.94 (dt, *J* = 8.7, 3.6 Hz, 1H), 2.30-2.01 (m, 3H), 1.88-1.77 (m, 1H), 1.71-1.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.9, 185.4, 162.2, 95.4, 84.5, 76.9, 44.4, 26.9, 24.7, 19.4; IR (neat, NaCl): 2946, 2843, 1960, 1696, 1160 cm^{-1}; MS *m/z* (%): 177 (65), 160 (82), 106 (87), 105 (100), 104 (70); EI-HRMS calcd for $C_{10}H_{11}NO_2$ $[M]^+$ *m/z*: 177.0790, found: 177.0781.



50 **53**

1-(4-Vinylidene-3a,4,5,6,7,7a-hexahydrobenzo[*d*]isoxazol-3-yl)but-3-yn-1-ol (53). To a slurry of Zn dust (0.046 g, 0.701 mmol, 5 equiv) in THF (0.2 mL) at 0 °C, a soln of the aldehyde **50** (0.025 g, 0.140 mmol, 1 equiv) in THF (0.2 mL) and propargyl bromide (0.04 mL of an 80 wt% soln in toluene, 0.359 mmol, 2.5 equiv) were added, followed by the addition of sat NH_4Cl soln (0.16 mL) dropwise over 45 min. The reaction mixture was allowed to slowly warm to room temperature and stirred overnight. After approximately 20 hours, TLC indicated complete consumption of starting material and the reaction mixture was filtered through a pad of Celite.

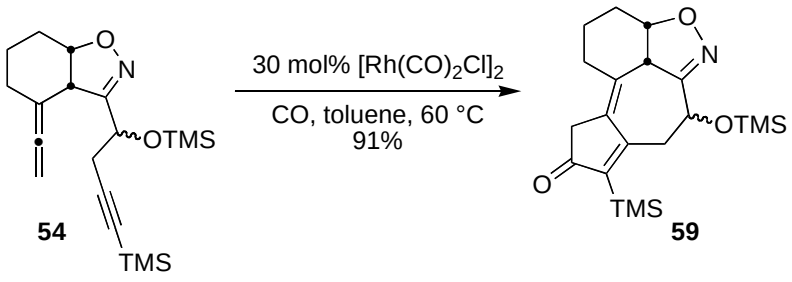
The filtrate was washed with sat NH_4Cl soln and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified via column chromatography using hexanes/EtOAc (3:1) as the eluent. The homopropargyl alcohol **53** (0.021 g, 70%) was achieved as a pale yellow crystalline solid and an approximate 3:1 mixture of diastereomers (^{1}H NMR). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.78-4.75 (m, 3H), 4.68-4.66 (m, 1H), 4.00 (br d, *J* = 9.3, 0.2 H),* 3.89 (br d, *J* = 9.0, 0.8 H),** 2.96 (br d, *J* = 5.7, 1H), 2.75 (A of ABqdd, *J* = 17.1, 5.4, 2.7, 1H), 2.65 (B of ABqdd, *J* = 17.1, 5.7, 2.7, 1H), 2.26-2.13 (m, 2H), 2.08 (t, *J* = 2.7, 1H), 1.86-1.48 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.8, 161.1, 95.3, 80.6, 78.9, 75.8, 71.6, 66.8, 49.8, 27.2, 26.3, 25.6, 19.5; IR (neat, NaCl): 3390, 3292, 2946, 2120, 1958, 1059. (*Minor diastereomer; **major diastereomer.)



50 **54**

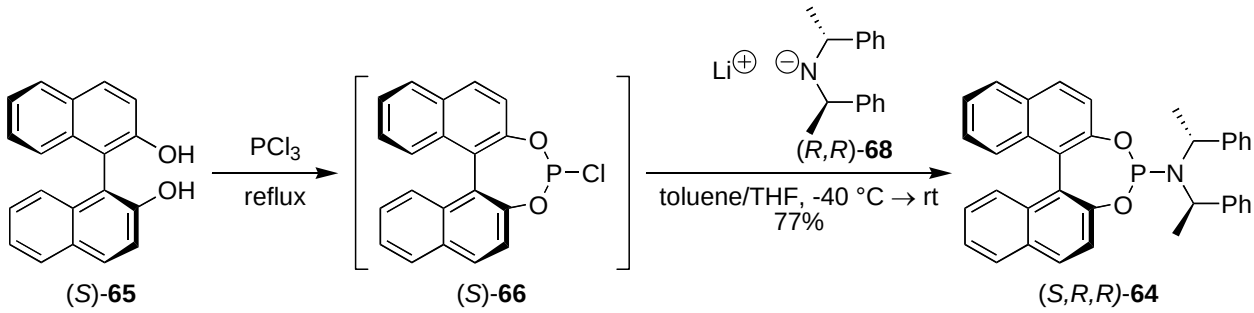
3-(4-(Trimethylsilyl)-1-(trimethylsilyloxy)but-3-ynyl)-4-vinylidene-3a,4,5,6,7,7a-hexahydrobenzo[*d*]isoxazole (54). *n*-BuLi (0.5 mL of a 1.6 M soln in hexanes, 0.8 mmol, 4.2 equiv) was added to a mixture of Et_2O (0.7 mL) and hexanes (0.3 mL) at -78 °C. TMEDA (30 μL, 0.2 mmol, 1.05 equiv) was added dropwise followed by slow dropwise addition of propargyl bromide (45 μL of an 80 wt% soln in toluene, 0.5 mmol, 2.1 equiv). A white precipitate developed upon stirring at –78 °C 20 min. A soln of the aldehyde **50** (0.034 g, 0.192 mmol, 1 equiv) in Et_2O (0.25 mL) was added dropwise and the mixture continued to stir at –78 °C until complete consumption of starting material was observed by TLC. The reaction was then quenched by rapid addition of TMSCl (0.10 mL, 0.79 mmol, 4 equiv). The mixture was allowed

to slowly approach room temperature until no additional progress was observed by TLC, at which point the mixture was poured into an Erlenmeyer flask containing ~10 mL H_2O. The aqueous layer was extracted with Et_2O (4×). The combined organic portions were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography, using hexanes/EtOAc (9:1) as the eluent, to give allene-yne **54** (0.014 g, 21%) as a 2:1 mixture of diastereomers (^{1}H NMR). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.74-4.67 (m, 4H), 3.98 (d, 9.9 Hz, 0.3H),* 3.92 (d, *J* = 9.6 Hz, 0.7H),** 2.78 (A of ABqd, *J* = 16.8, 5.7 Hz, 1H), 2.65 (B of ABqd, *J* = 16.8, 7.8 Hz, 1H), 2.28-2.20 (m, 2H), 1.80-1.35 (m, 4H), 0.20 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.1, 160.2, 103.2, 95.8, 86.8, 80.2, 75.3, 67.4, 49.6, 27.0, 26.5, 26.4, 19.3, 0.3, 0.0; IR (neat, NaCl): cm^{-1}; TOF-HRMS calcd for $C_{19}H_{31}NO_2Si_2$ $[M+H]^+$ *m/z*: 362.1972, found: 362.1955. (*Minor diastereomer; **major diastereomer.)



Cyclopentenone 59. To a test tube containing the allene-yne **54** (0.013 g, 0.036 mmol) and a stir bar was added toluene (0.4 mL). The test tube was evacuated and flushed with CO (3×). $[Rh(CO)_2Cl]_2$ (0.005 g, 0.012 mmol, 0.33 equiv) was added in one portion and the test tube was evacuated and flushed with CO (3×) before being placed under CO (1 atm) and immersed in a 60 °C bath. TLC analysis indicated near complete consumption of starting material after 3.5 h, at which point the reaction mixture was flushed through a plug of silica gel with hexanes/EtOAc (1:1) to remove the Rh catalyst. The collected eluent was concentrated under reduced pressure

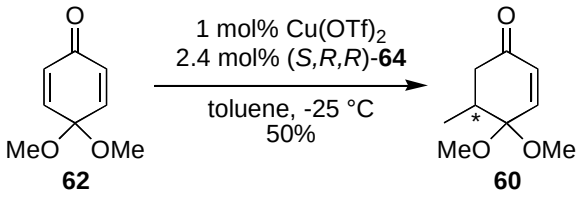
and the residue was purified via column chromatography using hexanes/EtOAc (3:1) as the eluent, giving the major diastereomer of cyclopentenone **59** (0.010 g, 73%) followed by the minor diastereomer (0.003 g, 21%). Both were white crystalline solids. Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.01 (t, *J* = 3.6 Hz, 1H), 4.55 (dt, *J* = 8.2, 3.0 Hz, 1H), 3.81 (br d, *J* = 8.2 Hz, 1H), 3.39 (dd, *J* = 14.4, 3.6 Hz, 1H), 2.95 (A of ABq, *J* = 20.4 Hz, 1H), 2.88 (B of ABq, *J* = 20.4, 1H), 2.85 (dd, *J* = 14.4, 3.6 Hz, 1H), 2.58-2.53 (m, 1H), 2.28-2.24 (m, 1H), 1.87-1.67 (m, 4H), 0.28 (s, 9H), 0.20 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.2, 173.4, 162.7, 135.8, 132.8, 80.4, 66.3, 49.3, 41.6, 37.3, 31.0, 25.1, 19.2, 0.2, 0.1; IR (neat, NaCl): 2950, 2880, 1676, 1549, 1246, 839 cm^{-1}; MS *m/z* (%): 389 (11), 374 (61), 147 (29), 75 (74), 73 (100); HR-EIMS calcd for $C_{20}H_{31}NO_3Si$ $[M]^+$ *m/z*: 389.1843, found: 389.1839. Minor diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.76 (dd, *J* = 10.8, 5.4 Hz, 1H), 4.55-4.53 (m, 1H), 3.92 (d, *J* = 6.9 Hz, 1H), 3.35 (dd, *J* = 13.5, 5.4 Hz, 1H), 2.99-2.78 (m, 3H), 2.56-2.51 (m, 1H), 2.35-2.31 (m, 1H), 2.04-1.69 (m, 4H), 0.29 (s, 9H), 0.21 (s, 9H).



(*S*)-**65** (*S*)-**66** (*S,R,R*)-**64**

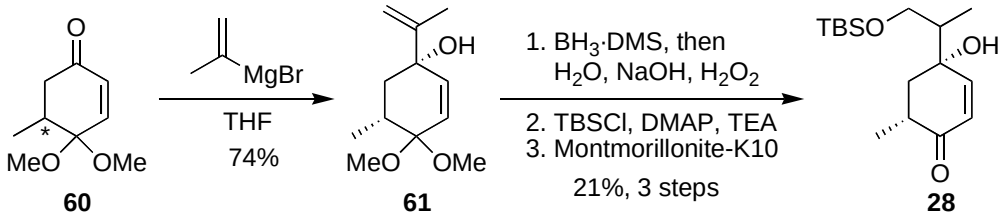
***O,O'*-(*S*)-(1,1'-Dinaphthyl-2,2'-diyl)-*N,N'*-di-(*R,R*)-1-phenylethylphosphoramidite (64).** In the glove box, a 25 mL schlenk flask was charged with (*S*)-BINOL (**65**, 1.063 g, 3.714 mmol, 1 equiv) and PCl_3 (4 mL, 46 mmol, 12 equiv). The flask was removed from the glove box and the suspension was heated to reflux under Ar atmosphere. After refluxing 16 h, the mixture had become a homogeneous solution. After an additional 8 h, the excess PCl_3 was removed under vacuum at 40 °C. The foamy residue was dissolved in toluene (3 mL) and the solvent was

removed under vacuum. This step was repeated two more times (2 × 3 mL toluene). The residue remained under vacuum for 16 h after the final rinse. In a separate flask, *n*-BuLi (2.6 mL of a 1.6 M soln in hexanes, 4.2 mmol, 1.1 equiv) was added dropwise via syringe to a soln of bis((*R*)-phenylethyl)amine (0.85 mL, 3.72 mmol, 1 equiv) in THF (13 mL) at -78 °C. The fuschia-colored soln was allowed to warm to -40 °C. The phosphochloridite **66** was dissolved in toluene (20 mL) and the soln was added to the deprotonated amine **68** via cannula. The amber-colored soln was allowed to warm from -40 °C to rt and stirred 16 h. The resulting cloudy mixture was filtered through a pad of celite and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography using hexanes/EtOAc (14:1) as the eluent to give pure phosphoramidite (*S,R,R*)-**64** (1.770 g, 77%) as a white foamy solid. The ^{1}H NMR spectrum is in agreement with published values.[96]



4,4-Dimethoxy-5-methyl-2-cyclohexenone (60). To a two-neck roundbottom flask fitted with a thermometer adapter and containing a suspension of $Cu(OTf)_2$ (0.059 g, 0.162 mmol, 0.010 equiv) in toluene (25 mL) was added a soln of the phosphoramidite ligand (*S,R,R*)-**64** (0.201 g, 0.373 mmol, 0.024 equiv) in toluene (6 mL). The pale orange mixture stirred 1 h before being cooled to -25 °C in a cryocool bath. The cyclohexadienone **62**[92] (2.390 g, 15.51 mmol, 1 equiv) was added. Me_2Zn (21 mL of a 1.2 M soln in toluene, 25 mmol, 1.6 equiv) was added so that the internal temperature ≤-20 °C. The bright yellow reaction mixture stirred at -25 °C and the reaction progress was monitored every 30 min by TLC. After 4 h, the slightly less polar diaddition product was visible above the monoaddition product spot on the TLC plate. The

reaction was quenched by pouring the mixture into an Erlenmeyer flask containing rapidly stirring 1.5 M NaOH. The aqueous layer was extracted with Et_2O (3×). The combined organic layers were washed with 1.5 N NaOH and brine, dried (Na_2SO_4), filtered and carefully concentrated under reduced pressure to remove most of the Et_2O. The remaining 3:1 mixture (by ^1H NMR) of enone **60** and unreacted sm in toluene was applied to a silica gel column and eluted with pentane/Et_2O (3:1 to 0:1) to separate the toluene from the product mixture. Fractions containing the product were combined and carefully concentrated under reduced pressure. The residue was purified by column chromatography, eluting with pentane/Et_2O (3:1) to give pure cyclohexenone **60** (1.321 g, 50%) as a colorless oil. The ^1H NMR spectrum is in agreement with literature values.[95]



4-(1-(*tert*-Butyldimethylsilyloxy)propan-2-yl)-4-hydroxy-6-methyl-2-cyclohexenone (28). To the enone **60** (0.557 g, 3.28 mmol, 1 equiv) in THF (16 mL) at 0 °C was added isopropenylmagnesium bromide (20 mL of a 0.5 M soln in THF, 10 mmol, 3 equiv) via syringe pump over 20 min. The reaction was monitored by TLC and quenched by pouring the reaction mixture into a flask containing saturated aqueous NH_4Cl. The aqueous layer was extracted with Et_2O (4×). The combined organic portions were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was flushed through a plug of pretreated (TEA) silica gel with hexanes/EtOAc (4:1) to remove major impurities. Tertiary alcohol **61** (0.514 g, 74%) was obtained as an amber oil. ^1H NMR (300 MHz, $CDCl_3$): δ 5.80 (A of ABq, J = 10.2 Hz, 1H), 5.74 (B of ABq, J = 10.2 Hz, 1H), 5.02 (s, 1H), 4.88 (quintet, J = 1.5 Hz, 1H),

3.28 (s, 3H), 3.22 (s, 3H), 2.18-2.12 (m, 2H), 1.77 (s, 3H), 1.68 (dd, *J* = 15.6, 6.6 Hz, 1H), 1.05 (d, *J* = 6.9 Hz, 3H).

To a soln of the olefin **61** (0.271 g, 1.276 mmol, 1 equiv) in THF (2 mL) was added BH_3·DMS (0.64 mL of a 2 M soln in THF, 1.28 mmol, 1 equiv) dropwise via syringe. The reaction was monitored by ^{1}H NMR analysis of aliquots. The reaction stirred 16 h, at which point the flask was placed in an ambient temperature water bath and H_2O (0.11 mL, 6.1 mmol, 5 equiv) was added followed by dropwise addition of NaOH (5 mL of a 3 M aqueous soln, 15 mmol, 12 equiv) and H_2O_2 (2.2 mL of a 33 wt% aqueous soln, 23.5 mmol, 18 equiv). The mixture stirred 3 h and was diluted with Et_2O. The aqueous layer was extracted with Et_2O (4×). The combined organic portions were washed with brine, dried (Na_2SO_4), decanted, and concentrated under reduced pressure to give the crude primary alcohol (0.207 g, 71%).

To a soln of DMAP (11 mg, 0.09 mmol, 0.1 equiv) and the primary alcohol (0.207 g, 0.900 mmol, 1 equiv) in DCM (1 mL) was added TEA (0.31 mL, 2.22 mmol, 2.5 equiv) followed by dropwise addition of a soln of TBSCl (0.163 g, 1.08 mmol, 1.2 equiv) in DCM (0.5 mL). Reaction progress was monitored by TLC. After 2 h, the mixture was diluted in H_2O and the aqueous layer was extracted with DCM (3×). The combined organic layers were washed with brine, dried (Na_2SO_4), decanted, and concentrated under reduced pressure, giving the crude silyl ether (0.310 g, 84%).

To a soln of the ketal (0.259 g, 0.752 mmol) in DCM (15 mL) was added Montmorillonite K10 clay (0.378 g). Reaction progress was monitored by TLC. After 10 min, additional clay was added (0.376 g). When no starting material was observable by TLC, the reaction mixture was filtered through a pad of celite and the filtrate was concentrated under reduced pressure. The crude residue, containing a 2:1 mix of diastereomers of **28** by ^{1}H NMR,

was purified by column chromatography using 4:1 hexanes/EtOAc as the eluent to give the desired enone **28** (0.082 g, 36% from **57**). Partial separation of the diastereomers was achieved during column chromatography. Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.87 (dd, *J* = 10.3, 2.1 Hz, 1H), 5.92 (d, *J* = 10.3 Hz, 1H), 4.43 (s, 1H), 4.07 (dd, *J* = 10.5, 3.3 Hz, 1H), 3.68 (dd, *J* = 10.5, 4.5 Hz, 1H), 2.48-2.36 (m, 2H), 2.08-1.94 (m, 2H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.14 (d, *J* = 6.9 Hz, 3H), 0.93 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.2, 154.7, 127.9, 73.6, 66.9, 43.7, 40.2, 38.8, 18.0, 15.8, 12.7, -5.7, -5.8; IR (neat, NaCl): 3463, 2931, 2858, 1684, 1462, 1377, 1073, 836 cm^{-1}; MS *m/z* (%): 321 (12), 281 (16), 251 (80), 191 (13), 121 (29); TOF-HRMS calcd for $C_{16}H_{30}O_3NaSi$ $[M + Na]^+$ *m/z*: 321.1862, found: 321.1858; Minor diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 (dd, *J* = 10.2, 2.1 Hz, 1H), 5.92 (d, *J* = 10.2 Hz, 1H), 4.39 (s, 1H), 4.05 (dd, *J* = 10.2, 3.0 Hz, 1H), 3.69 (dd, *J* = 10.2, 2.7 Hz, 1H), 2.39 (dqd, *J* = 13.5, 6.6, 4.7 Hz, 1H), 2.27 (ddd, *J* = 13.5, 4.7, 2.1 Hz, 1H), 1.99 (qt, *J* = 7.2, 3.0 Hz, 1H), 1.76 (t, *J* = 13.5 Hz, 1H), 1.19 (d, *J* = 7.2 Hz, 3H), 1.18 (d, *J* = 6.6 Hz, 3H), 0.94 (s, 9 H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.3, 156.3, 127.3, 73.8, 67.1, 41.2, 39.1, 38.4, 25.8, 18.0, 15.7, 12.6, -5.7, -5.8.

APPENDIX A

^{1}H AND ^{13}C NMR SPECTRA FOR NEW COMPOUNDS

OTBS
45

205.27
157.41
81.50
58.65
58.45
39.93
26.40
25.76
18.35
18.29
-5.52
-5.56
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140
120
100
80
60
40
20
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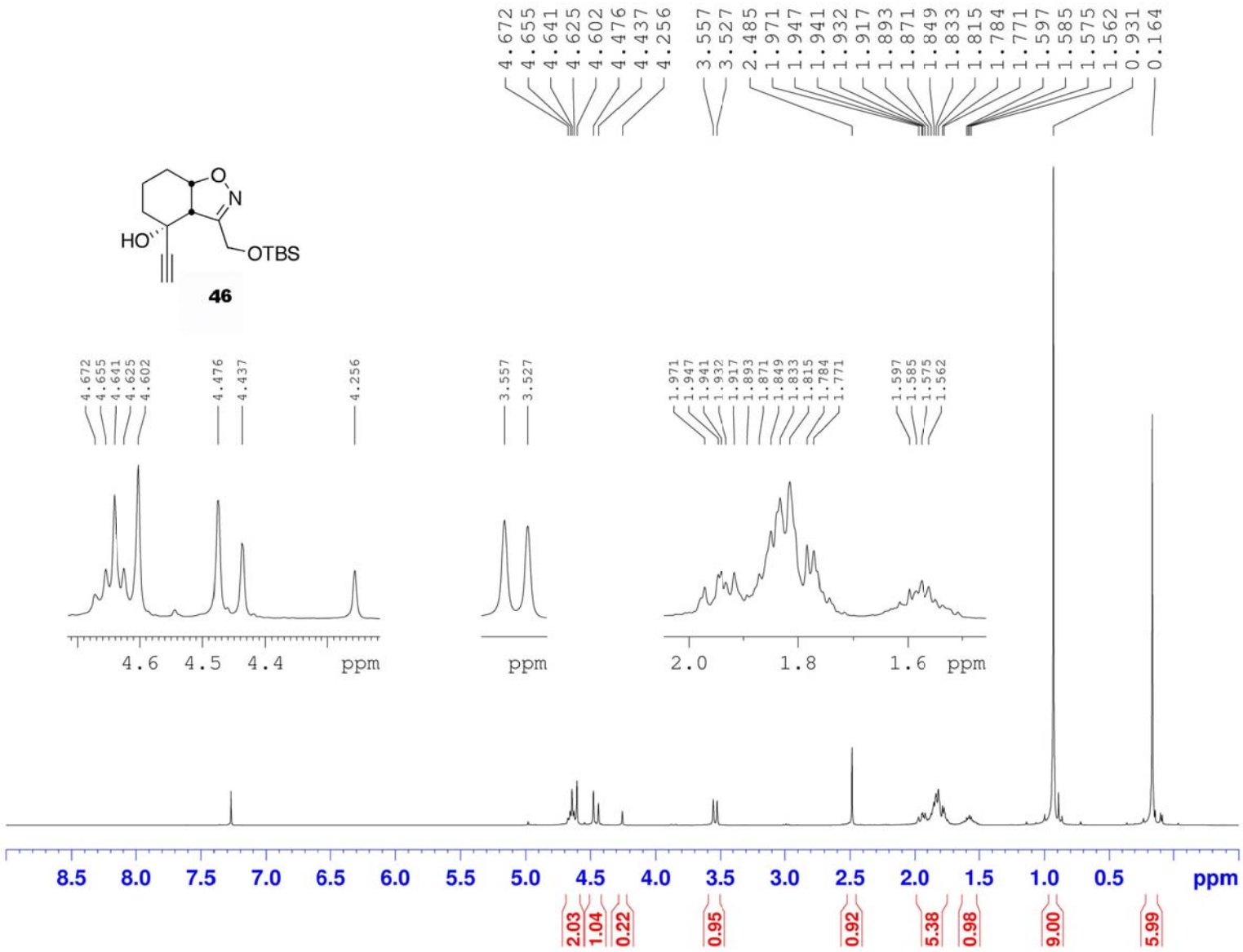
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1.947
1.941
1.932
1.917
1.893
1.871
1.849
1.833
1.815
1.784
1.771
1.597
1.585
1.575
1.562
0.931
0.164
HO
N
O
OTBS
46
4.6
4.5
4.4
ppm
2.0
1.8
1.6
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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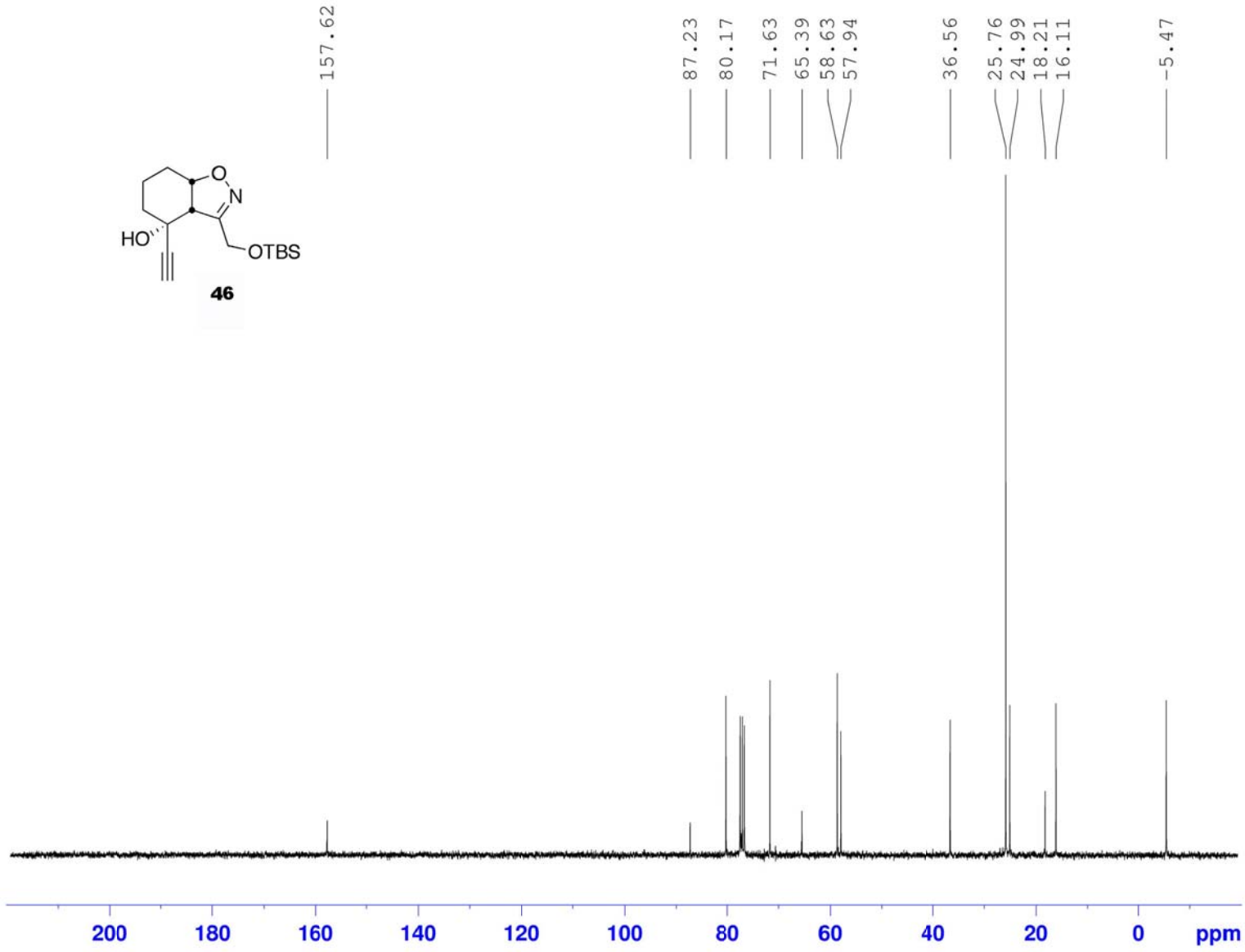
5.99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58.63
57.94
36.56
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16.11
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HO
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140
120
100
80
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40
20
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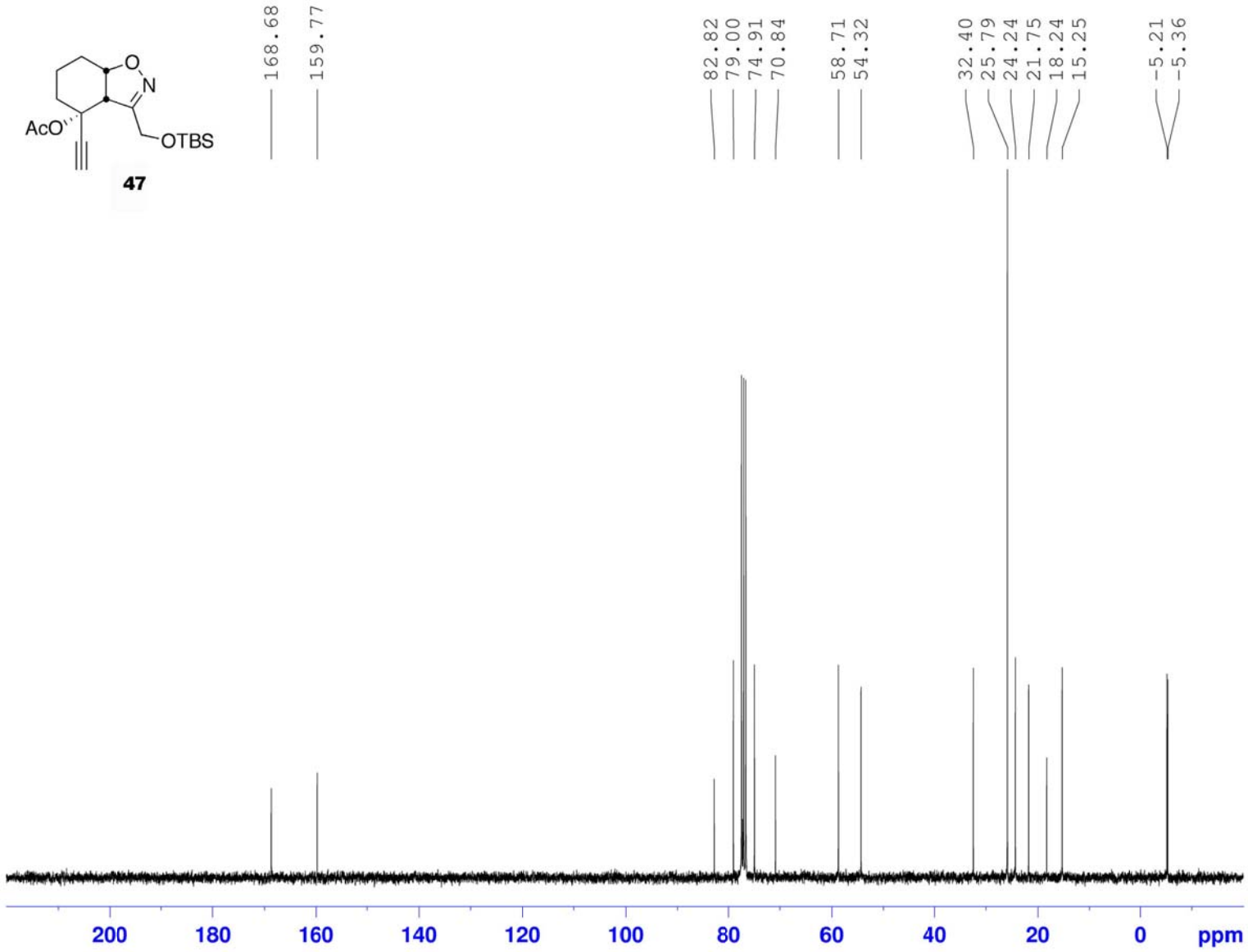
ppm

47
OTBS
AcO
ppm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24.24
21.75
18.24
15.25
-5.21
-5.36
200
180
160
140
120
100
80
60
40
20
0
ppm

48
OTBS
ppm

-5.59
-5.51
18.12
19.31
25.66
26.07
27.21
49.01
58.04
75.22
79.65
95.32
160.24
205.63
OTBS
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ppm
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20
40
60
80
100
120
140
160
180
200

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4.668
4.651
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4.620
4.603
4.443
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1.751
1.736
1.722
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1.525
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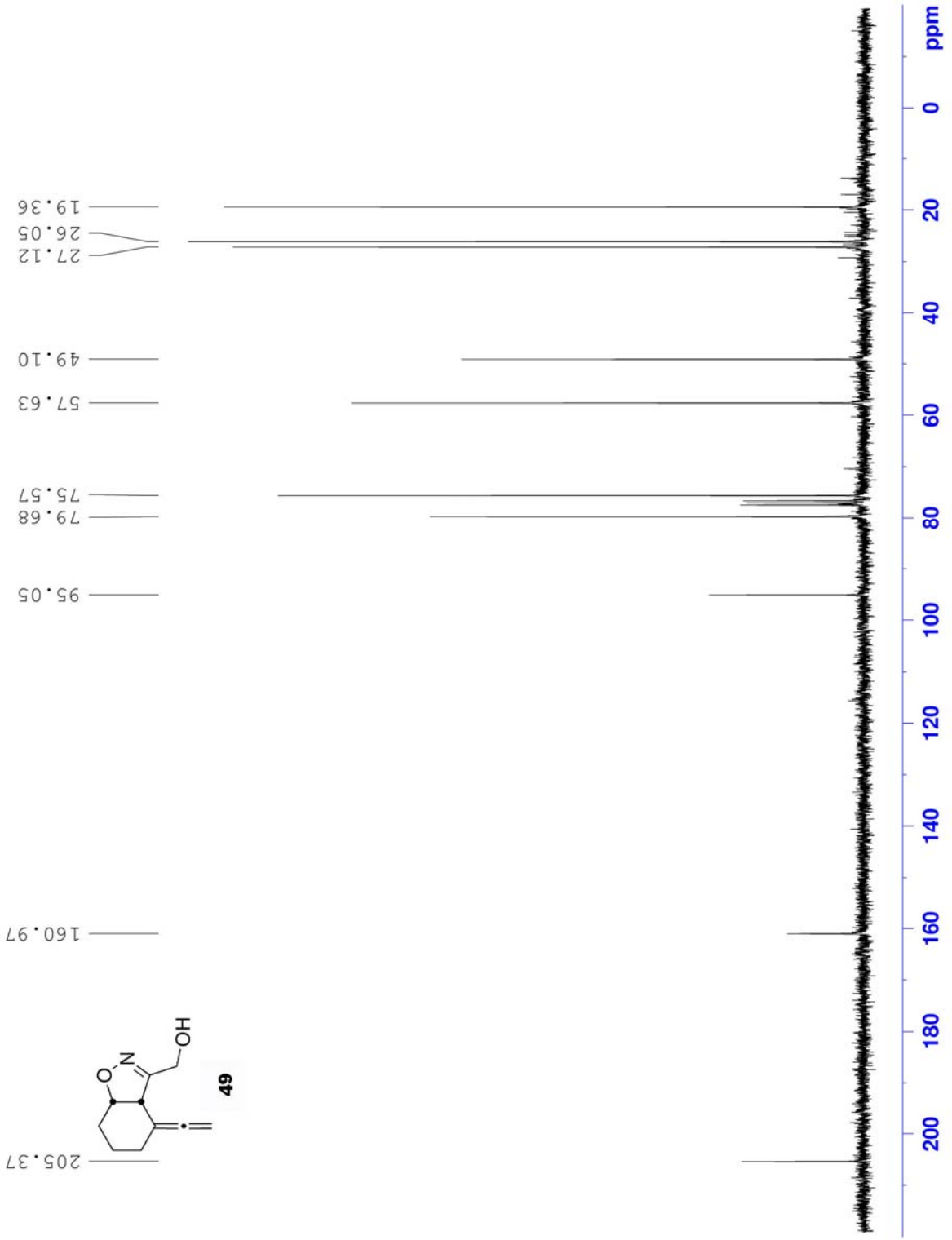
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120
140
160
180
200
49

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4.733
4.718
4.710
4.704
4.699
4.693
4.687
4.681
4.675
4.669
3.964
3.952
3.937
3.923
3.911
2.271
2.224
2.209
2.196
2.182
2.172
2.158
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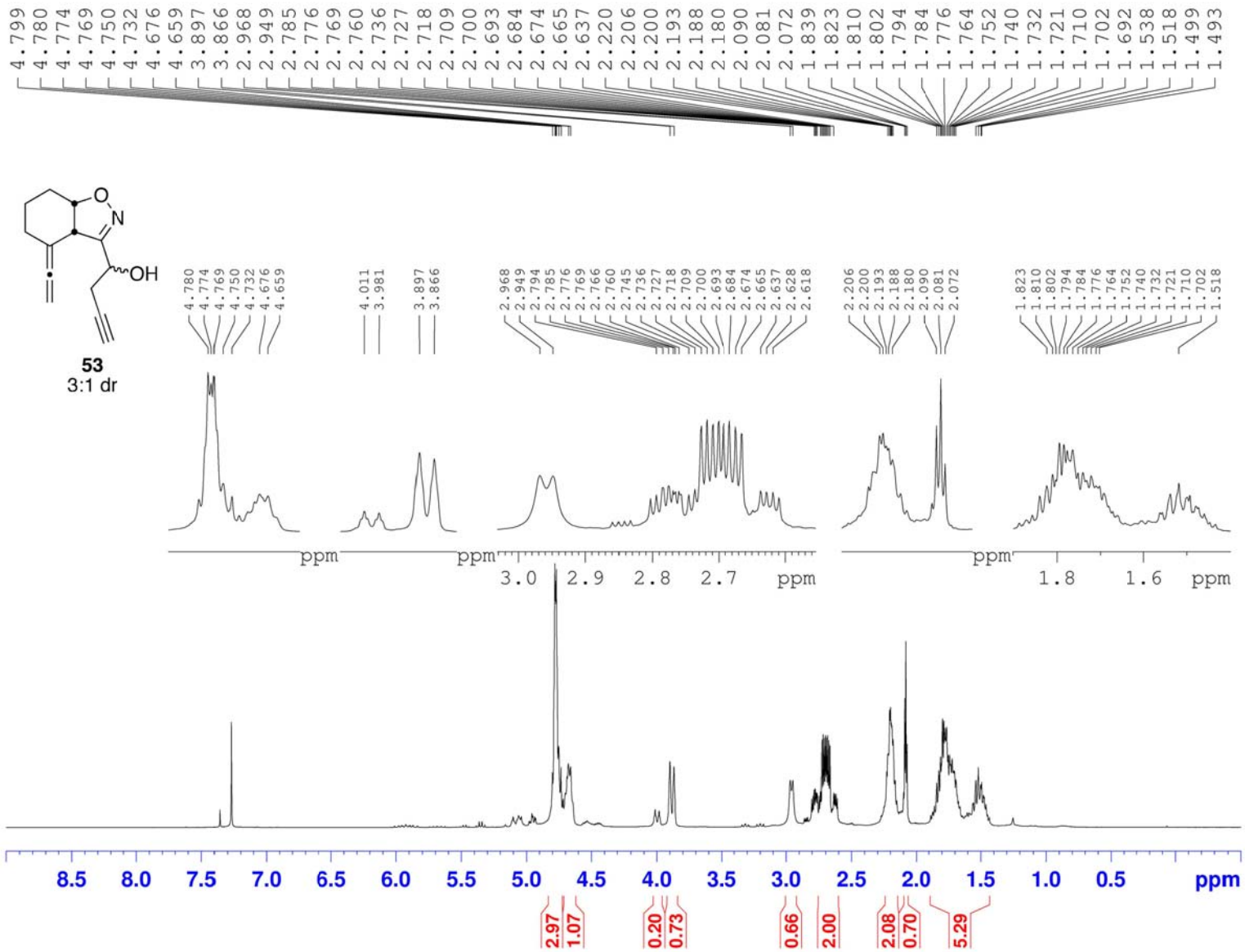
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OH
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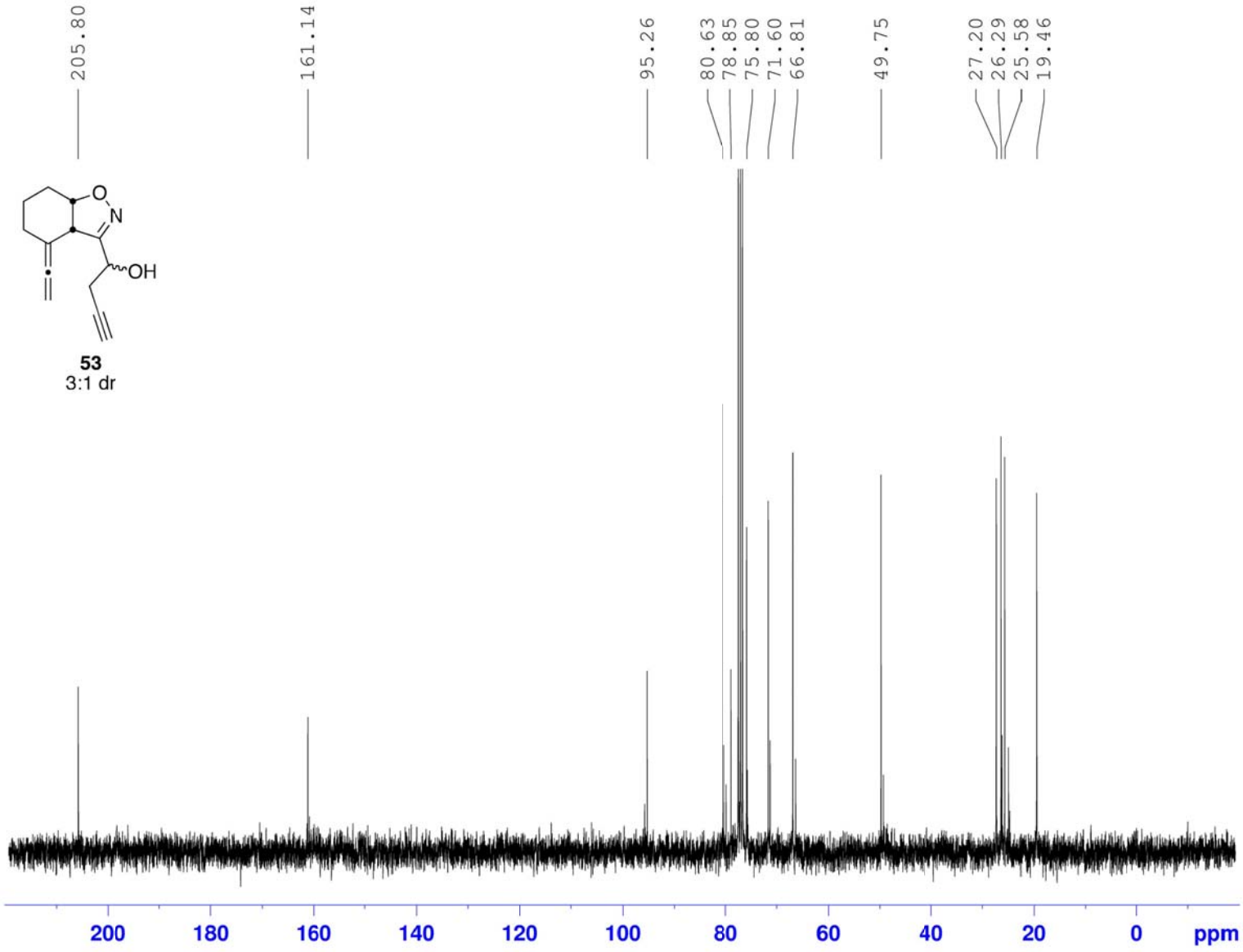
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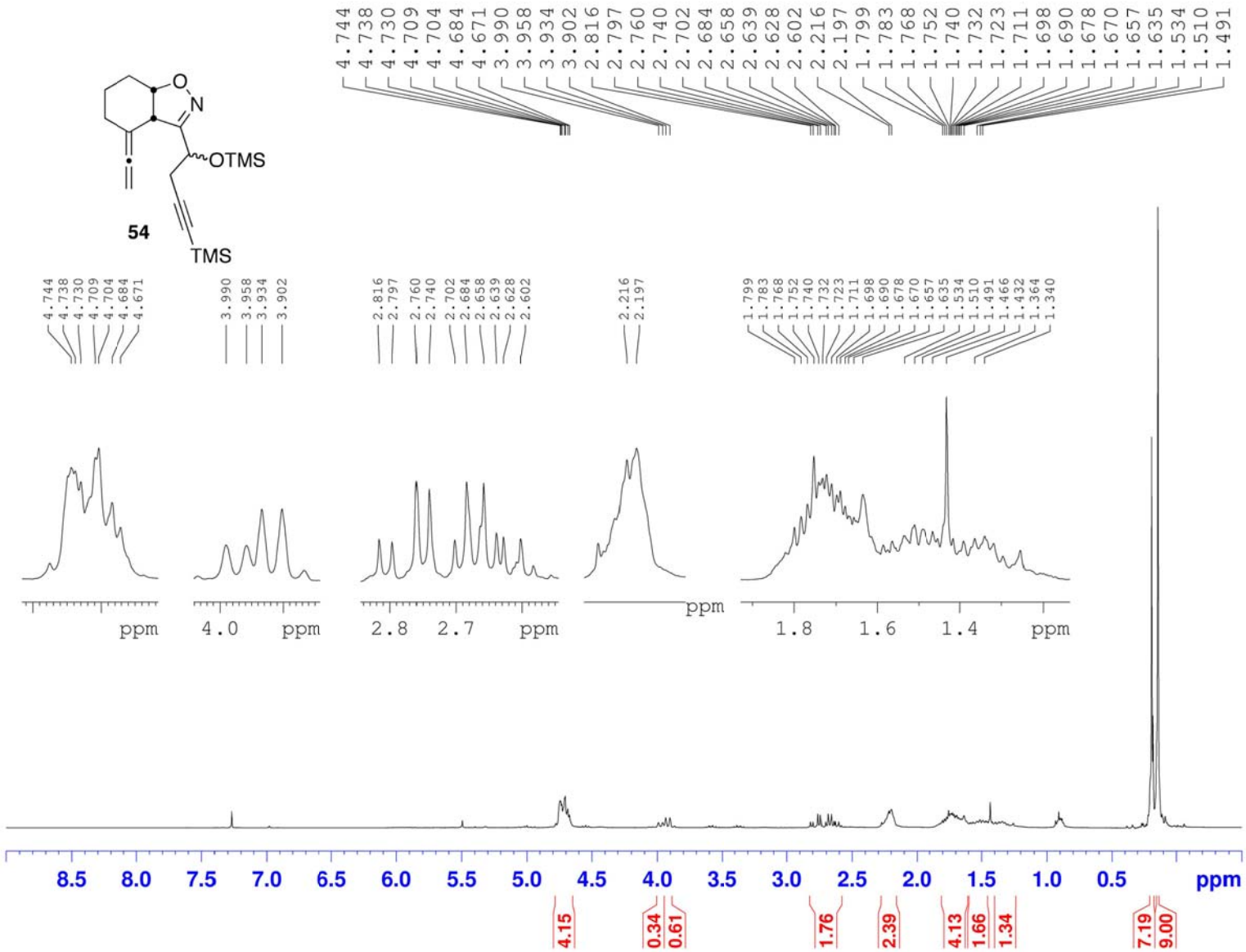
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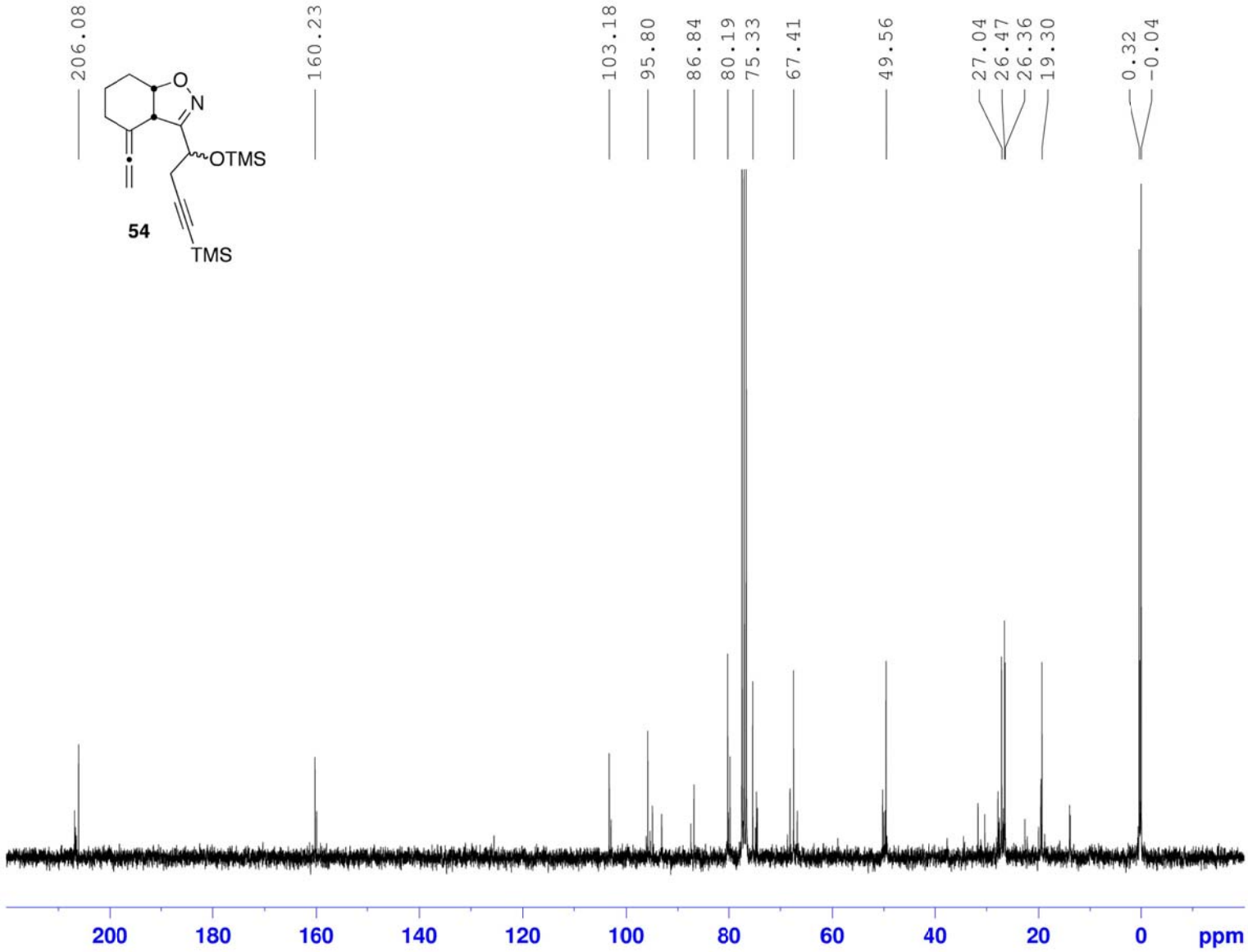
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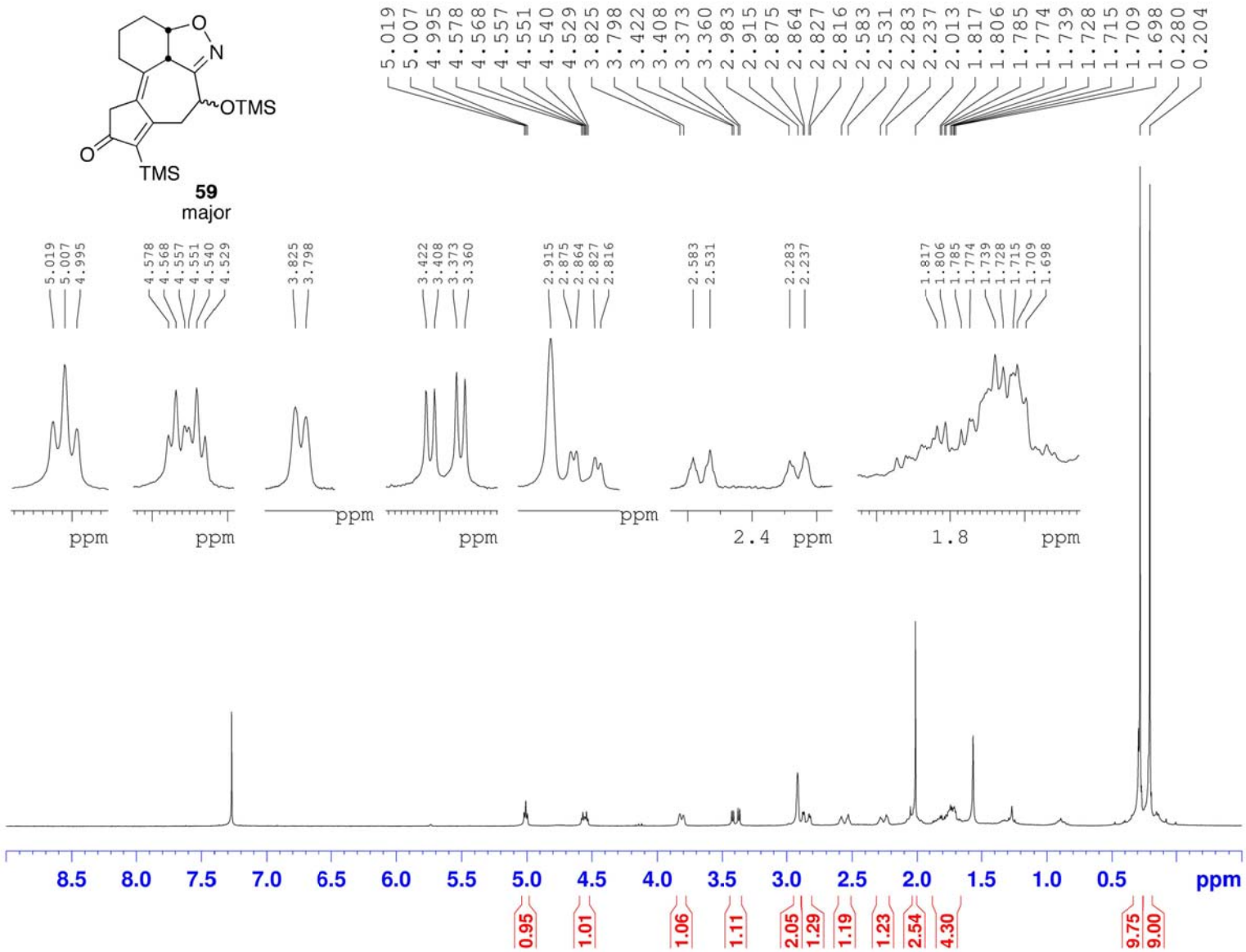
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3.360
2.983
2.915
2.875
2.864
2.827
2.816
2.583
2.531
2.283
2.237
2.013
1.817
1.806
1.785
1.774
1.739
1.728
1.715
1.709
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O
N
OTMS
O
TMS
59
major
ppm
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7.5
7.0
6.5
6.0
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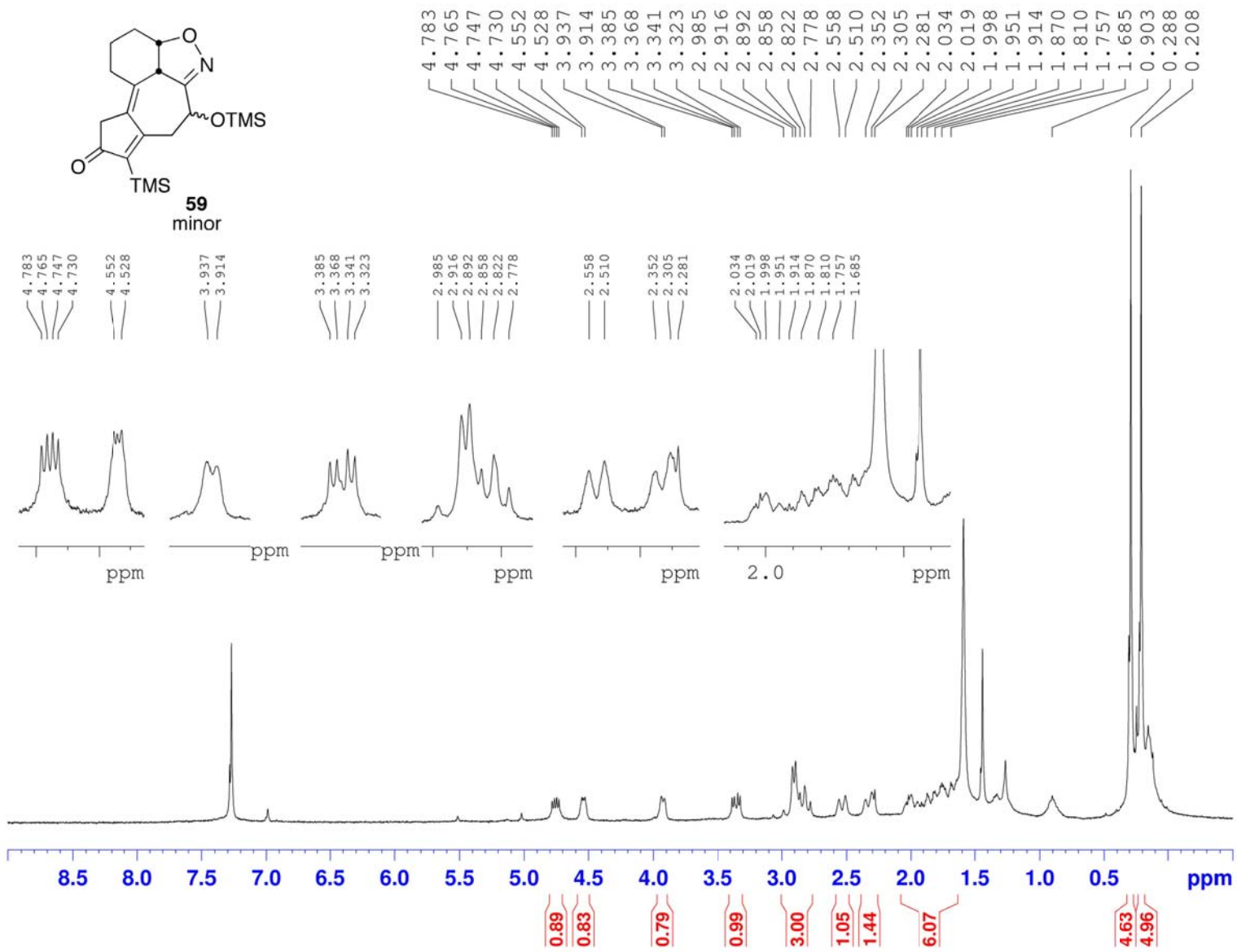
59
major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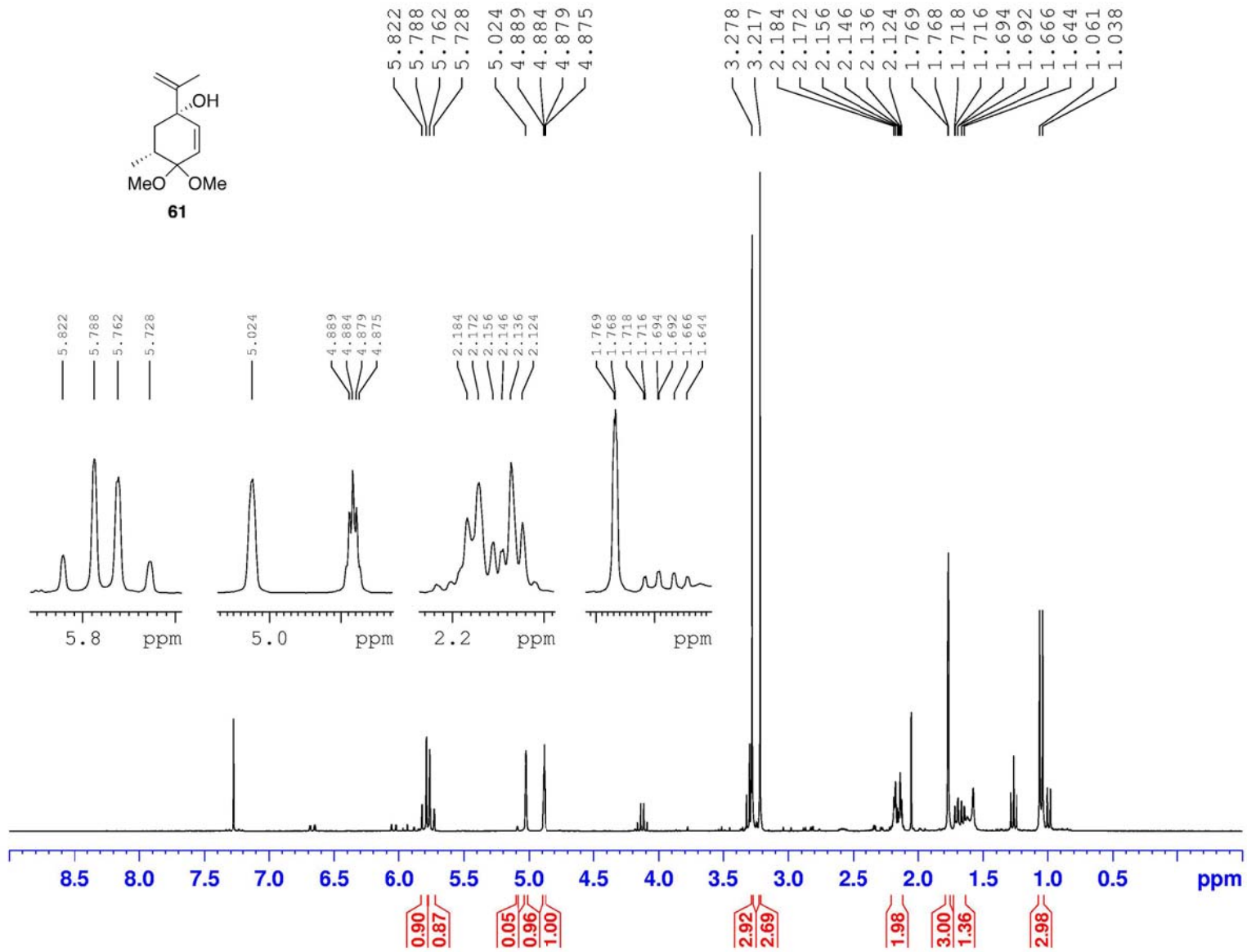
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5.0 ppm
2.2 ppm
ppm
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TBSO
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O
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major
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127.87
127.30
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73.56
67.07
66.90
43.74
41.16
40.21
39.06
38.83
38.41
25.74
18.03
15.83
15.69
12.72
12.58
-5.72
-5.76
TBSO
OH
O
28
mixture of
diastereomers
ppm
200
180
160
140
120
100
80
60
40
20
0

TBSO
OH
O
28
minor

-5.75
-5.68
12.60
15.71
18.04
25.76
38.43
39.06
41.17
67.11
73.78
127.34
156.33
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TBSO
OH
O
28
minor
ppm
0
20
40
60
80
100
120
140
160
180
200

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