The Allenic Carbocyclization Reaction of Allene-ynes: Progress towards the Syntheses of Fumagillol and Ovalicin

by

Jolie Elaine DeForrest

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DEPARTMENT OF CHEMISTRY

This dissertation was presented

by

Jolie Elaine DeForrest

It was defended on

April 14, 2009

and approved by

Professor Dennis P. Curran, Department of Chemistry

Professor Paul E. Floreancig, Department of Chemistry

Professor Billy W. Day, Department of Pharmaceutical Sciences

Thesis Director:

Professor Kay M. Brummond, Department of Chemistry

The Allenic Carbocyclization Reaction of Allene-ynes: Progress towards the Syntheses of Fumagillol and Ovalicin

Jolie E. DeForrest, Ph.D.

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The Rh(I)-catalyzed allenic carbocyclization reaction is a powerful strategy for the assembly of densely functionalized cyclic cross-conjugated trienes. This methodology exhibits excellent functional group compatibility, and allows for the construction of five-, six-, and seven-membered rings in high yields from allene-yne precursors. In this thesis, progress towards the total synthesis of (–)-fumagillol and (–)-ovalicin is reported. The entire carbocyclic skeleton of both structurally related natural products has been synthesized in a single synthetic transformation via an allenic carbocyclization reaction. It is anticipated that the allylic hydroxyl group of the functionalized cross-conjugated can be used for the chemo- and stereoselective installation of epoxides and hydroxyl groups incorporated in both sesquiterpenes.

The constitutional group selectivity of the β-hydride elimination step in the allenic carbocyclization reaction has been investigated. We found that TMS-alkynyl allenes with an appending isobutylene group can be reacted under Rh(I)-catalyzed allenic carbocyclization reaction conditions to afford regioisomerically pure cross-conjugated trienes in good yields. The examples within, indicate that a coordinating alkene can be incorporated into the allene-yne substrate to control the β-hydride elimination step of the cyclization reaction to yield trienes with a 1,1-disubstituted alkene side chain.

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LIST OF ABBREVIATIONS

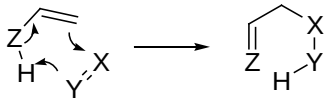
Ac	acetyl
aq	aqueous
BINAP	2,2’-bis(diphenylphosphanyl)-1,1’-binaphthyl
Brsm	based on recovered starting material
COD	1,5-cyloocatadiene
CO	carbon monoxide
dba	dibenzylidene acetone
DCC	dicyclohexylcarbodiimide
DCE	1, 2-dichloroethane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIAD	diisopropylazodicarboxylate
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DOS	diversity-oriented synthesis
dr	diastereomeric ratio
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·HCl
ee	enantiomeric excess
EI	electro impact (ionization)
ESI	electrospray ionization
EtOAc	ethyl acetate
GC	gas chromatography
h	hour(s)
HMPA	hexamethylphosphoric triamide
HPLC	high pressure liquid chromatography
IR	infrared
KHMDS	potassium hexamethyldisilazide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamine
LHMDS	lithium hexamethyldisilazide
m-CPBA	*m*-chloroperoxybenzoic acid
MetAP	methionine aminopeptidase
min	minute(s)
NaHMDS	sodium hexamethyldisilazide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect

NMO	*N*-methylmorpholine-*N*-oxide
Ph	phenyl
R_f	retention factor
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
TESCl	chlorotriethylsilane
TFE	trifluoroethanol
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin-layer chromatography
TMEDA	*N*,*N*,*N*,'*N*'-tetramethylethylenediamine
TMS	trimethylsilyl
Tosyl	4-toluenesulfonyl (also Ts)
UPCMLD	University of Pittsburgh Center for Chemical Methodologies and Library Development
wt	weight

1.0 THE ALLENIC CARBOCYCLIZATION REACTION OF ALLENE-YNES: PROGRESS TOWARDS THE SYNTHESES OF FUMAGILLOL AND OVALICIN

1.1 INTRODUCTION: THE ALDER-ENE REACTION

The Alder-ene[1, 2] reaction is a powerful and atom-economical process[3] that is used for carbon-carbon bond formation. This reaction occurs between two carbon-carbon π bonds with one carbon-carbon double bond bearing an allylic hydrogen. During the course of the reaction, the allylic hydrogen is transferred to the alkene. As shown in Scheme 1, one σ bond migrates and one σ bond is formed at the expense of one π bond. The thermal Alder-ene reaction requires elevated temperatures (typically 250 - 600°C) and can be accomplished either intra- or intermolecularly.

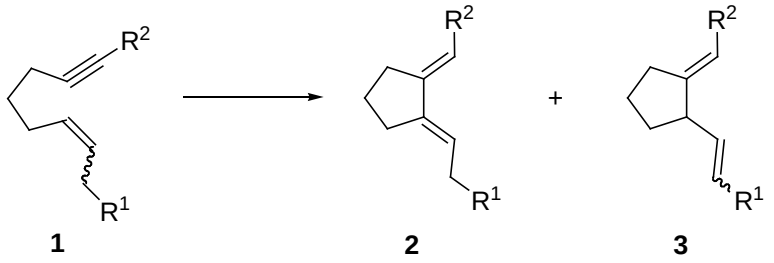


Scheme 1: Intermolecular Alder-ene Reaction

1.2 THE TRANSITION METAL-CATALYZED ENYNE CARBOCYCLIZATION REACTION

The use of transition metals in carbocyclization processes, like the Alder-ene reaction, allows for mild reaction conditions, increased efficiency of synthetic transformations, and often higher functional group tolerance than their respective thermal processes. Transition metals are also advantageous as they can be designed to meet the requirements of specific carbocyclization precursors.[4]

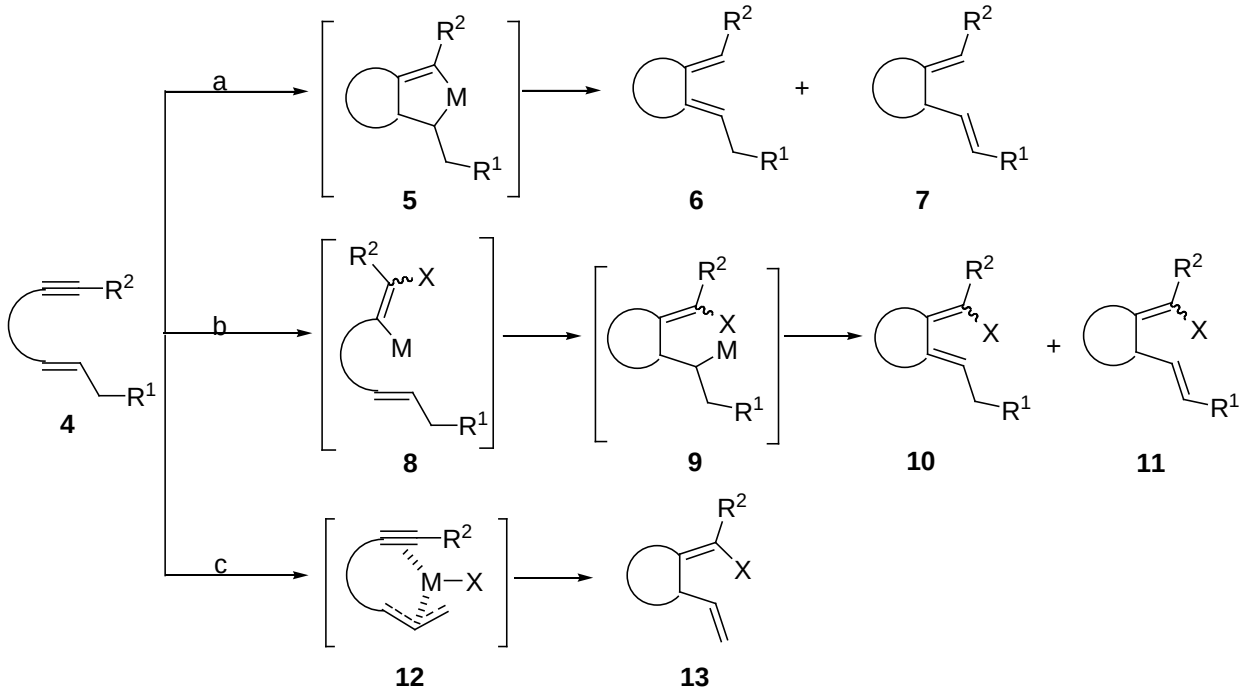
One example of a transition metal-catalyzed carbocyclization reaction is the cycloisomerization of 1,6-enynes. As seen in Scheme 2, enyne **1** can be reacted with a variety of palladium,[4, 5] ruthenium,[6-8] titanium,[9] iron,[10] and rhodium[11] transition-metal complexes to yield cyclic 1,3- and 1,4-dienes.



Scheme 2: Cycloisomerization of Enyne 1

Three different mechanistic pathways have been proposed for this reaction. The first process (path a, Scheme 3) involves oxidative coupling of the alkene and alkyne moieties of enyne **4** to form metallocycle **5**, which upon β-hydride elimination and then reductive elimination produces 1,3- and 1,4-dienes **6** and **7**. Ruthenium,[7] titanium,[9] and rhodium[11] catalysts are a few of the transitional-metal complexes that can react with enynes via this mechanism. A different pathway (path b), where X = H, halogen, or OAc is favored for palladium catalyst systems and has been extenstively studied by Trost and coworkers.[12] In this

case, the catalyst undergoes addition to the alkyne of enyne **4** to form alkenylmetal species **8**. The alkene in intermediate **8** can then insert into the carbon-metal bond of the alkenylmetal moiety to produce **9**, which after β-hydride elimination gives cyclized compounds **10** and **11**. The less commonly observed mechanistic pathway c can occur when palladium[13] and rhodium[14] catalysts are reacted enynes possessing an allylic activated group. This reaction results in the formation of metal π-allyl complex **12**, which cyclizes to 1,4-diene **13**.[14, 15]

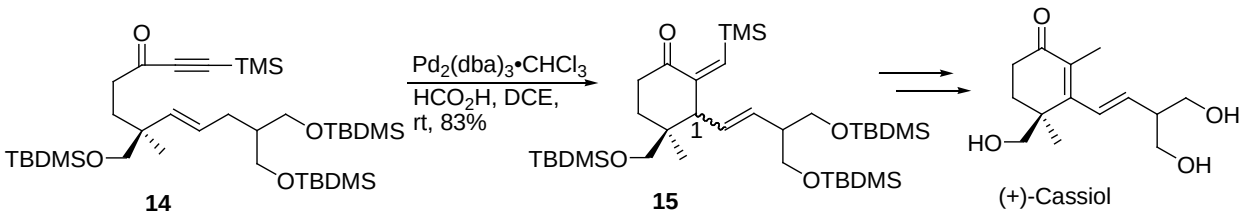


M = transition metal; R^1 = H or leaving group; X = H or nucleophile

Scheme 3: Proposed Mechanisms for the Carbocyclization of 1,6-Enynes[14, 15]

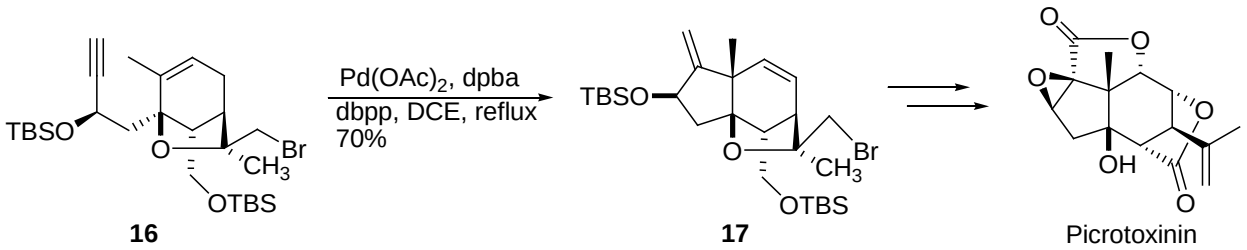
The transition metal-catalyzed carbocyclization reaction of 1,6-enynes has been successfully applied to natural product synthesis. For example, Trost and coworkers used a palladium-catalyzed carbocyclization reaction as a key transformation for the construction of the cyclohexyl framework of (+)-cassiol (Scheme 4).[16] Alkynone **14**, when reacted with $Pd_2(dba)_3{\cdot}CHCl_3$ and formic acid in 1,2-dichloroethane (DCE) at room temperature, produced cyclohexenone **15** in 83% yield as a 3 : 1 mixture of diastereomers at C1. The "ligandless"

palladium catalyst allows for bidentate coordination of the enyne **14**, which is required for the cycloisomerization process. This synthesis also illustrates the benefit of a transition metal-catalyzed process over a thermal one; for example, heating **14** to 500 °C only produces a trace amount of product.



Scheme 4: Palladium-Catalyzed Enyne Carbocyclization of Enyne 14, A Synthesis of (+)-Cassiol[16]

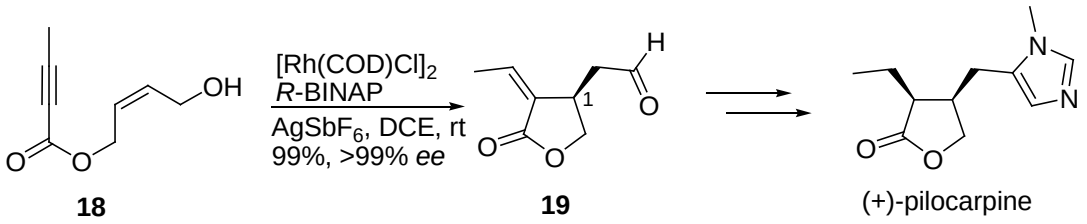
Additionally, Trost and Krische employed a palladium-catalyzed enyne carbocyclization reaction in the synthesis of picrotoxinin and the structurally related compounds picrotin, corianin, and methyl picrotoxate (Scheme 5).[4] Trost obtained bicyclic carbocycle **17** in 70% yield from enyne **16** using palladium(II)acetate, 2-(diphenylphosphino)benzoic acid (dpba) and 1,3-bis(dibenzophospholyl)propane (dbpp) in refluxing DCE. An extensive survey of reaction conditions showed that combining dbpp, a ligand capable of internal proton delivery, with the small Lewis acidic ligand dpba would produce an optimal ligand system for this particular carbocyclization reaction. Trost's design and development of the unique palladium catalyst employed for the cycloisomerization of enyne **16** exemplifies the advantage of using tunable transition metals catalysts for carbobocyclization processes.



Scheme 5: Palladium-Catalyzed Carbocyclization Reaction of Enyne 16, A Synthesis of Picrotoxinin[4]

Zhang and coworkers have effectively applied a rhodium-catalyzed carbocyclization reaction to a formal synthesis of (+)-pilocarpine (Scheme 6).[17] Reacting enyne **18** with $[Rh(COD)_2Cl]_2$, (*R*)-BINAP, and $AgSbF_6$ resulted in the formation of α-alkylidene-γ-butyrolactone (*R*)-**19** in 99% yield and 99% *ee*, a structure that allowed Zhang to intersect Büchi's synthesis of (+)-pilocarpine. Butyrolactone (*R*)-**19** was assembled in 91% overall yield and 99% *ee* in two steps from commercially available 2-butynoic acid and (*Z*)-2-buten-1,4-diol, demonstrating the utility of the transition-metal catalyzed carbocyclization reaction in natural product synthesis.

Alternatively, Büchi constructed (*R*)-**19** with the desired stereochemistry at C1 through a five step synthesis featuring an asymmetric reduction reaction and subsequent Claisen rearrangement of the resulting chiral allylic alcohol.[18] This approach, however, produced α-alkylidene-γ-butyrolactone (*R*)-**19** in only 20% overall yield and 92% *ee*.

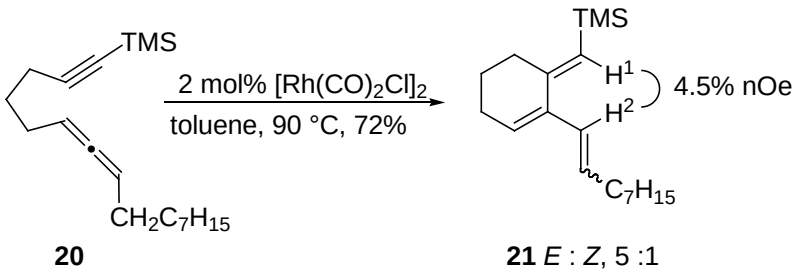


Scheme 6: Rhodium-Catalyzed Carbocyclization of Enyne 18, A Synthesis of (+)-Pilocarpine

1.3 THE RHODIUM-CATALYZED ALLENIC CARBOCYCLIZATION REACTION: THE CONSTRUCTION OF CYCLIC CROSS-CONJUGATED TRIENES

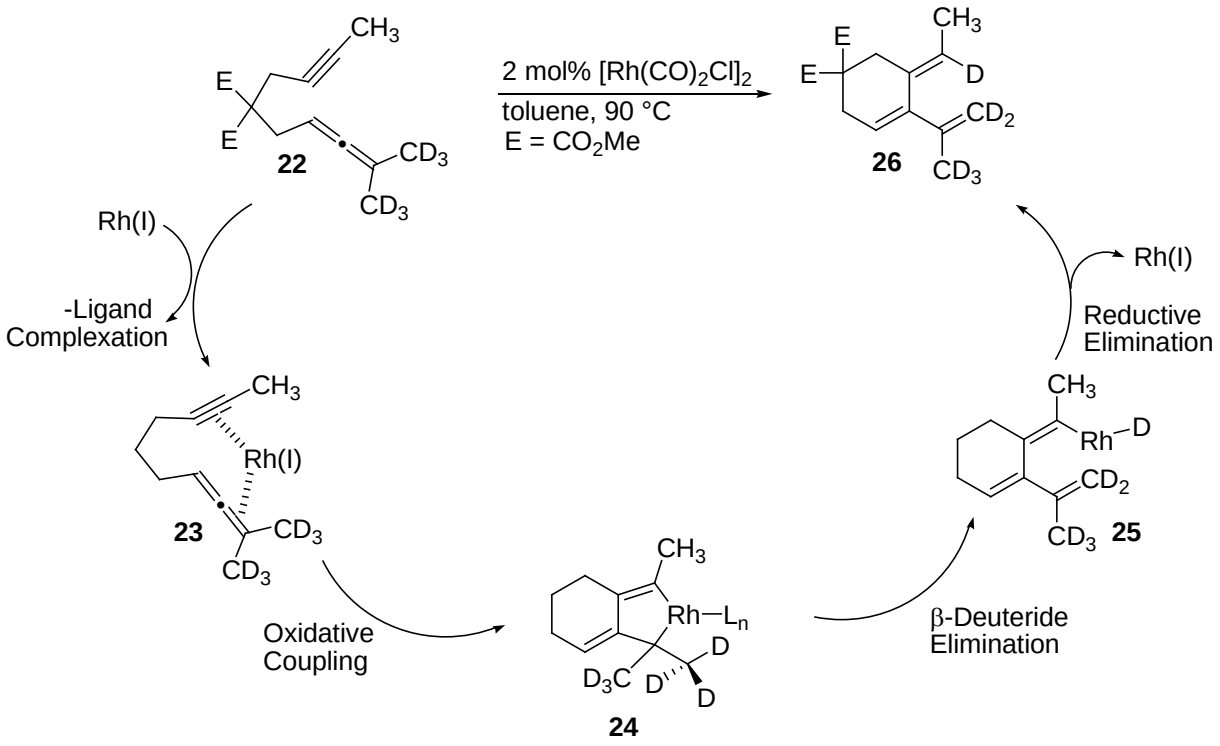
The Brummond group has been interested in the design and development of the Rh(I)-catalyzed allenic carbocyclization reaction, which effectively uses an allene in place of the alkene

component to access cyclic cross-conjugated trienes.[19] An example of the allenic carbocyclization is depicted in Scheme 7. Allene-yne **20** is reacted with 2 mol% of $[Rh(CO)_2Cl]_2$[20] to afford carbocyclic triene **21** in 72% yield; producing the *E* isomer of the alkenyl silane exclusively as evidenced by the 4.5% nOe between H^1 and H^2. The appending alkene, however, is produced as a mixture of *E*:*Z* isomers in a 5:1 ratio.



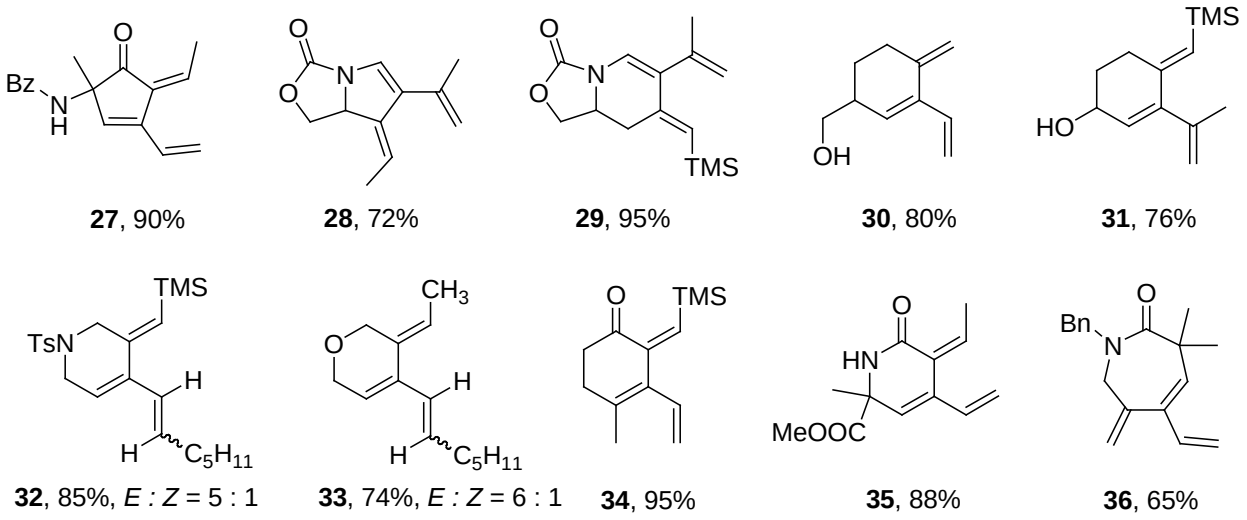
Scheme 7: The Allenic Carbocyclization of Allene-yne 20[19]

Brummond and coworkers[19] have proposed that the mechanism for the Rh(I)-catalyzed allenic carbocyclization reaction involves oxidative coupling of the rhodium catalyst to the alkyne and external double bond of the allene in allene-yne **22** to produce metallocycle **24** (Scheme 8). Metallocycle **24** then undergoes β-deuteride elimination giving intermediate **25** followed by reductive elimination of the metallo-deuteride to produce cross-conjugated triene **26**. A deuterium-labeling study showed that the reaction occurs with complete and stereoselective transfer of a deuterium to the exocyclic alkene, supporting the postulated mechanism.



Scheme 8: Proposed Mechanism for the Rh(I)-Catalyzed Allenic Carbocyclization Reaction[19]

The Rh(I)-catalyzed allenic carbocyclization reaction developed in the Brummond group has proven to be a powerful strategy for the assembly of structurally interesting cross-conjugated trienes. As seen in Scheme 9, this methodology is well-suited for the formation of five-, six-, and seven-membered rings in yields of 65-95%.[21-24] This rhodium(I)-catalyzed transformation also exhibits excellent functional group compatibility. For example, free hydroxyl groups are tolerated during the course of the reaction as evidenced by the formation of trienes **30** and **31** in good yield.[21] Other functional groups such as benzamide,[22] oxazolidinone,[23] and amide[24] groups are also tolerated as illustrated by formation of trienes **27-29**, and **35-36** in excellent yields. Additionally, piperdine and pyran derived cross-conjugated trienes such as **32** and **33** can be accessed from allene-yne precursors in high yields of 85% and 74% respectively.[19]



27, 90% **28**, 72% **29**, 95% **30**, 80% **31**, 76%

32, 85%, *E : Z* = 5 : 1 **33**, 74%, *E : Z* = 6 : 1 **34**, 95% **35**, 88% **36**, 65%

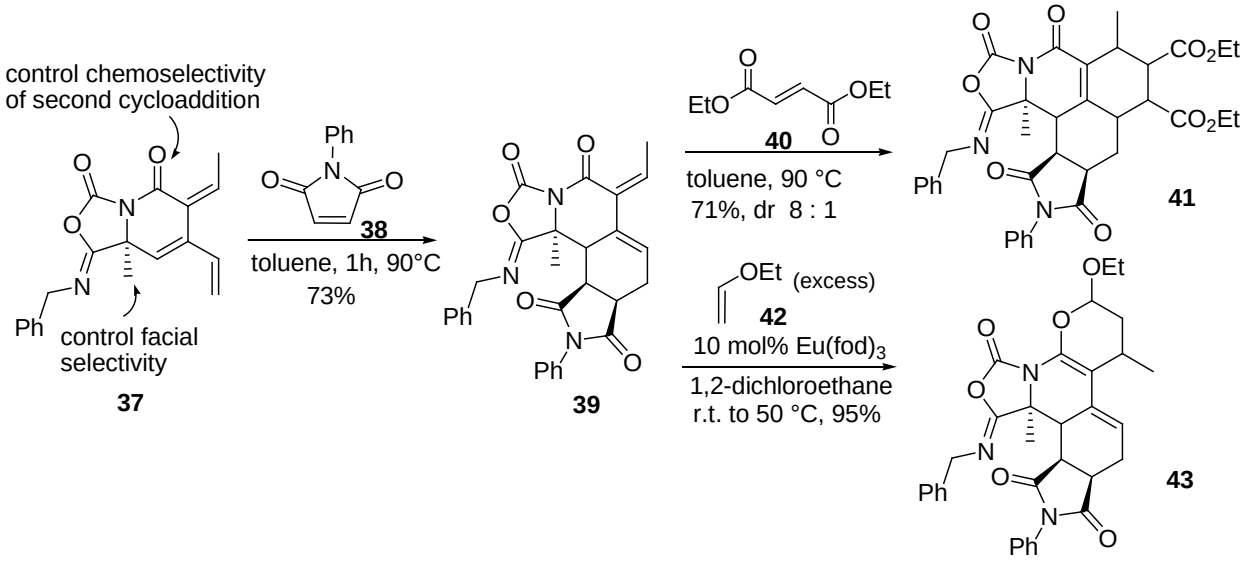
Scheme 9: Cross-Conjugated Trienes Constructed via an Allenic Carbocyclization Reaction

1.4 CROSS-CONJUGATED TRIENES IN LIBRARY DEVELOPMENT AND NATURAL PRODUCT SYNTHESIS

Cross-conjugated trienes are an exciting class of compounds because of their potential for rapid increases in molecular complexity. For example, cross-conjugated trienes have been extensively employed as Diels-Alder substrates to access fused polycyclic ring systems.[21, 25-28] In 2006, Brummond and coworkers designed imino-oxazolidinone fused trienes of type **37** for the construction of novel heterocyclic scaffolds.[29] As seen in Scheme 10, cross-conjugated triene **37** undergoes a stereoselective intermolecular Diels-Alder reaction with *N*-phenylmaleimide (**38**) to give monocycloadduct **39** in 73% yield as a single diastereomer. This cycloaddition reaction occurs from the less sterically hindered face of triene **37**, opposite of the angular methyl group, and with *endo* selectivity. The triene was designed so that the presence of the electron

withdrawing carbonyl functionality prevents a second Diels-Alder reaction with *N*-phenylmaleimide from occurring, thus maximizing the diversity potential of this scaffold.

Diene **39** was subsequently transformed into polycyclic compound **41** in 71% yield as an 8 : 1 mixture of diastereomers when reacted with diethyl fumarate (**40**) at 90 °C. Alternatively, the enone moiety of **39** can undergo a hetero-Diels-Alder reaction with ethyl vinyl ether (**42**) in the presence of $Eu(fod)_3$ to afford pyran **43** in 95% yield as a single diastereomer. This methodology cleverly demonstrates the utility of the cross-conjugated triene moiety for the formation of unique heterocyclic structures via diastereo- and chemoselective cycloaddition reactions, and was used in the synthesis of a library of compounds by the UPCMLD.[30]

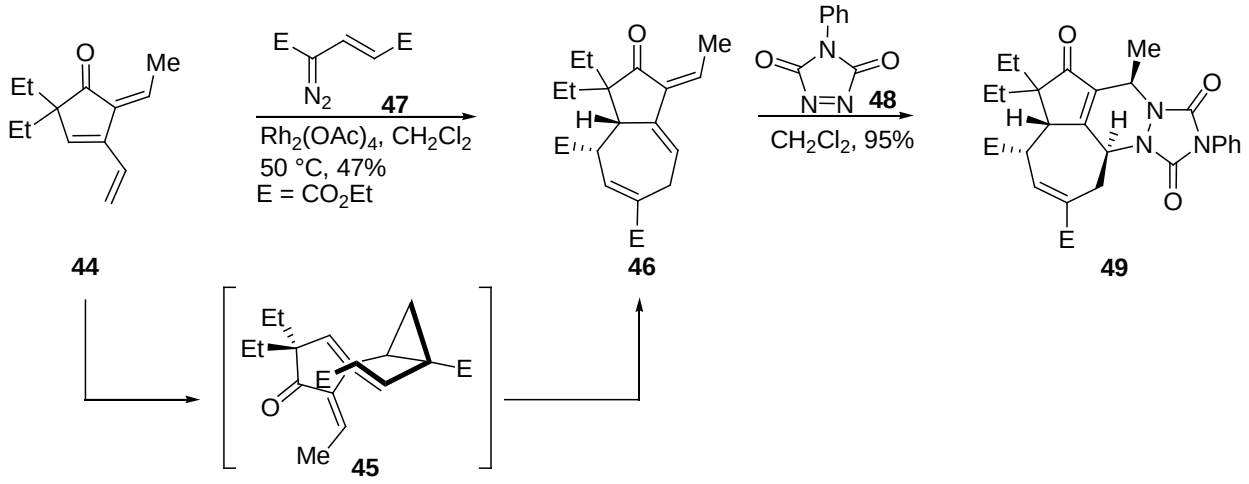


Scheme 10: Cycloaddition Reactions of Amino-Acid Derived Cross-Conjugated Triene 37[29]

More recently, Brummond and coworkers have shown that hydroazulenones such as **46** can be synthesized from five-membered cross-conjugated trienones (Scheme 11).[31] Using reaction conditions developed by Davies,[32] triene **44** was reacted with *E*-diethyl-4-diazo-2-pentenedioate (**47**) and rhodium(II) acetate to yield hydroazulenone **46** as a single diastereomer in 47% yield. This formal [3 + 4] cycloaddition proceeds through the selective cyclopropanation

of the vinyl group in **44** by the rhodium-stabilized vinylcarbenoid to produce *cis*-divinylcyclopropane **45**. This strained intermediate then undergoes a Cope rearrangement to afford the seven-membered ring of bicyclo[5.3.0]decadienone **46**. The small amount of *trans*-divinylcyclopropane formed during the reaction is recovered (not shown).

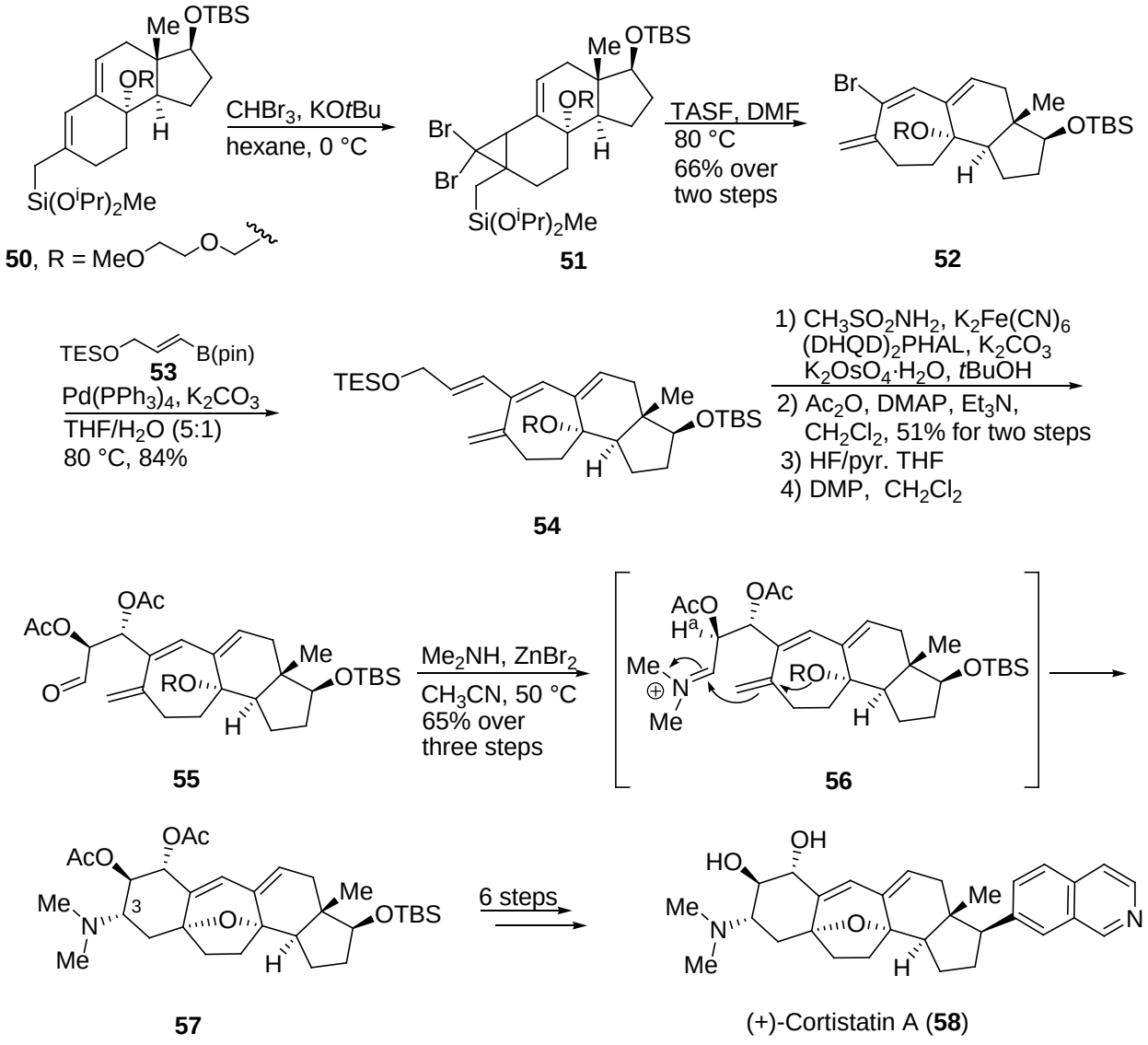
The skeletal diversity of these small molecules was further expanded by reacting *cis*-diene **46** with 4-methyl-1,2,4-triazoline-3,5-dione (**48**) to produce the Diels-Alder adduct **49** in high yield. This methodology has allowed the synthesis of 44 hydroazulenoisoindoles resembling **49**, two of these compounds were found to inhibit nuclear accumulation of GFP-GR at low micromolar concentrations as tested by Day and Johnston.[31] The selective chemical transformations of the double bonds in trieneones similar to **44** has provided access to natural-product like hydroazulenoisoindoles and illustrates the synthetic potential of the cross-conjugated triene scaffold.



Scheme 11: A Tandem Cyclopropanation/Cope Rearrangement of Trieneone 44[31]

Shair and coworkers have synthesized the potent angiogenesis inhibitor (+)-cortistatin A (**58**) from a cyclic cross-conjugated triene precursor (Scheme 12).[33] This enantioselective synthesis of **58** began by converting enantiomerically pure Hajos-Parrish ketone[34] into tricyclic

intermediate **50** via a twelve-step reaction sequence (not shown). With diene **50** in hand, a regio- and diastereoselective cyclopropantion reaction with dibromocarbene was performed to access cyclopropane **51**. A subsequent silicate-directed ring expansion reaction with tris(dimethylamino)sulfonium difluorotrimethylsilicate was then used to access vinyl bromide **52** (66% yield for two steps).



Scheme 12: Synthesis of (+)-Cortistatin A from Cross-Conjugated Triene 54[33]

The key intermediate **54** was obtained in 84% yield through a palladium-catalyzed coupling reaction between vinyl bromide **52** and the vinyl boronic ester **53**. Chemoselective dihydroxylation of the disubstituted alkene in cross-conjugated triene **54** was used to construct the allylic diol moiety of cortistatin A, via Sharpless' asymmetric dihydroxylation protocol. The resulting diol was then subjected to a three-step reaction sequence involving aceylation of the diol and deprotection/oxidation of the primary alcohol to give aldehyde **55**.

Reacting **55** with dimethyl amine and zinc dibromide ($ZnBr_2$) resulted in a tandem aza-Prins cyclization and transannular etherification reaction (Scheme 12). The MEM protecting group was removed *in situ* to yield the polycyclic compound **57** in 65% yield over three steps. The C-3 stereocenter was produced in >95% diastereoselectivity during the aza-Prins cyclization and is attributed to the coplanar geometry of H_a and the internal *N*-methyl group of iminum ion **56**. This preferred geometry minimizes A(1,3) strain and prevents nucleophilic addition from the *Re* face. Shair and coworkers were able to transform amine **57** into (+)-cortistatin A in six steps.

The synthetic utility of the cross-conjugated triene moiety is clearly demonstrated by Shair's elegant synthesis of (+)-cortistatin A. For example, selective functionalization of the unsaturated system in cross-conjugated triene **54** provided access to the diol moiety of **58**, and set the stage for the key tandem aza-Prins/transannular cyclization reaction.

1.5 BIOLOGICAL ACTIVTY OF FUMAGILLOL, OVALICIN, AND RELATED SESQUITERPENES

As evidenced by the examples in the previous section, the functionally compact nature of the cross-conjugated triene makes it an attractive building block for the construction of biologically

active compounds and natural products. We envision that fumagillol (**60**), ovalicin (**61**), and structurally related cyclic sesquiterpenes can be synthesized from a cross-conjugated triene precursor (Figure 1).

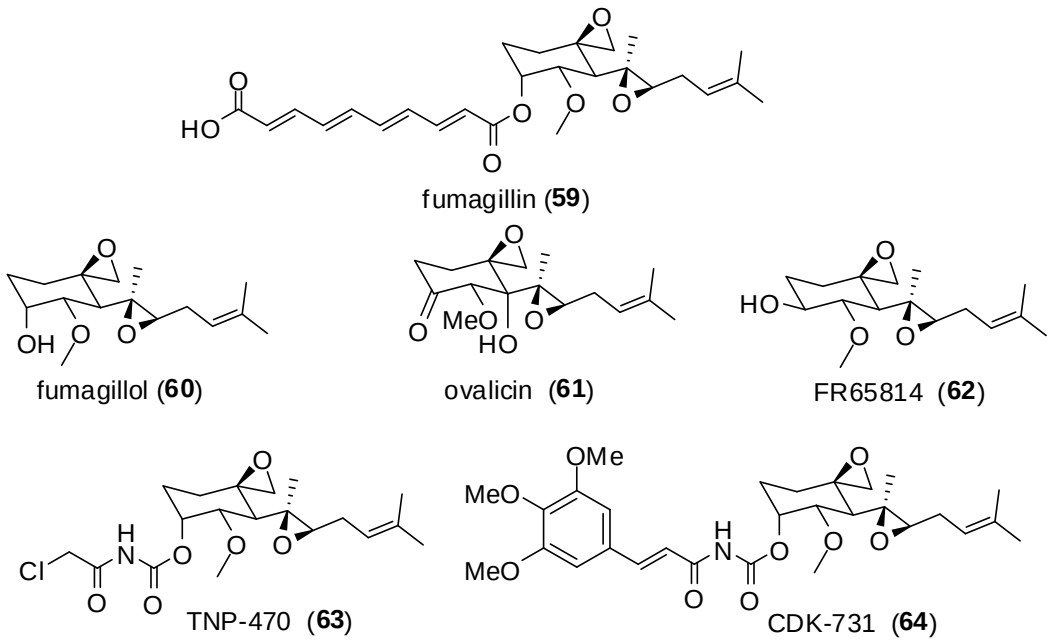


Figure 1: Fumagillin and Related Spiroepoxides

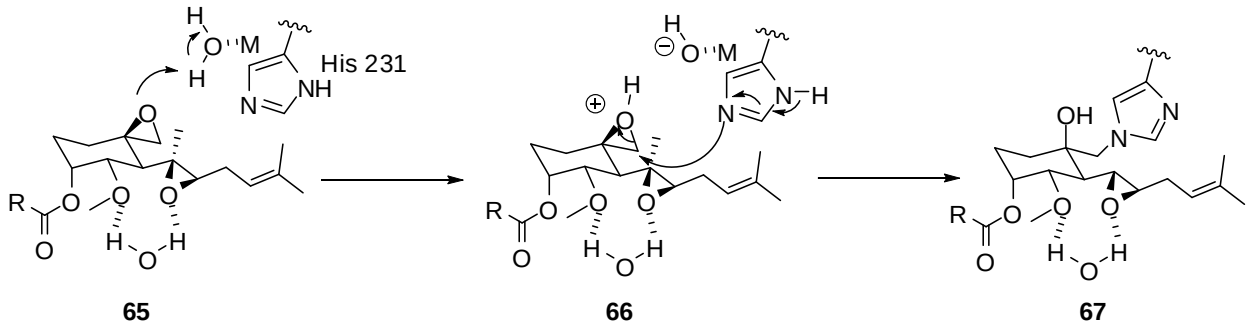
In 1949, fumagillin (**59**) was isolated from the microbial organism *Aspergillus fumigatus* (Figure 1).[35, 36] Through chemical degradation and X-ray crystallographic analysis, the structure and stereochemical configuration of fumagillin and fumagillol were established.[37-39] Originally, fumagillin was classified solely as an anti-microbial agent since it possessed antibiotic activity against *Staphylococcus aureus*.[35] In 1990, Folkman and coworkers discovered that fumagillin also showed *in vivo* inhibition of angiogenesis, the generation of new blood vessels.[40] Angiogenesis is believed to be important for tumor growth, and synthetic inhibitors of angiogenesis such as TNP-470[41, 42] (**63**) and CDK-731[43] (**64**) have been developed as potential anti-cancer drugs. Currently, fumagillin and TNP-470 are some of the only drug treatments for

micosporidiosis, a disease caused by microscopic parasitic infection that is often seen in HIV-positive patients.[44-46]

In 1968, Sigg and Weber isolated ovalicin (**61**, Figure 1) from culture filtrates of the fungus *Pseudeurotium ovalis* Stolk.[47] This sesquiterpene alkaloid was found to be more potent than fumagillin (**59**), exhibiting the same activity as TNP-470 (**63**). However, unlike fumagillin and TNP-470, ovalicin has been found to be stable at room temperature for at least two years.[48]

Fumagillin, ovalicin, and other structurally related spiroepoxides selectively target methinone aminopeptidase 2 (MetAP-2) but are not inhibitors of the closely related enzyme methinone aminopeptidase 1 (MetAP-1).[49, 50] These metalloproteases have been shown to co-translationally remove the N-terminal methionine residue in specific protein targets;[49, 51] however, the complex relationship between inhibition of MetAP-2 and the medical utility of fumagillin remains unclear.[52-54]

The mechanism of inhibition by this class of sesquiterpenes has been shown to be related to its spiroepoxide functionality;[49, 55] removal of this functionality results in a 1000-fold decrease in MetAP-2 inhibition[50] (Scheme 13). Removal of the side chain epoxide, however, has been shown to have little effect on activity.[50] One proposed mechanism of action suggests that His231 in the MetAP-2 binding site acts as a nucleophile to open the protonated spiroepoxide (**66**), which produces a covalent bond between the histidine residue and the methylene of the spiroepoxide (**67**).[56] It has been found that fumagillin-binding affinity increases at low pH,[57] further supporting the presence of the protonated spiroepoxide in the mechanism of action.



Scheme 13: One Model for MetAP-Inhibition[57]

1.6 SYNTHETIC STRATEGIES TO FUMAGILLOL AND OVALICIN

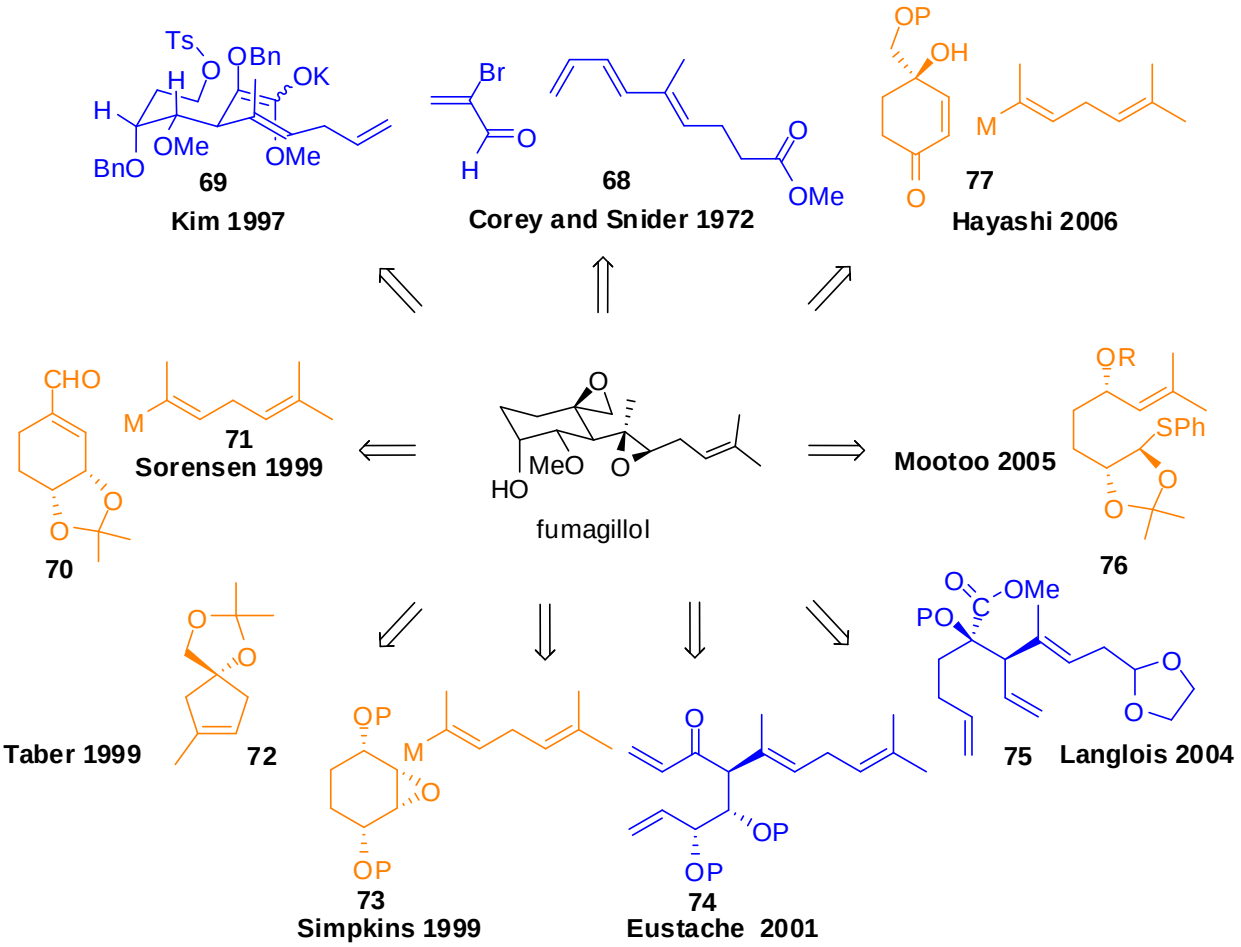
1.6.1 Previous Syntheses of Fumagillol

Fumagillol's selective inhibition of angiogenesis in tumor cells has made it an attractive target for total synthesis. There are two main synthetic strategies employed for the construction of fumagillol. One strategy involves the formation of the cyclohexyl framework with the side chain already intact (colored in blue, Scheme 14). Corey and Snider took advantage of this approach with their elegant synthesis of (±)-fumagillol by employing a regioselective Diels-Alder cycloaddition between α-bromoacrolein and the functionalized triene **68**.[58] This transformation allowed for the construction of the complete carbocyclic framework of fumagillol in a single step (Scheme 14).

Kim and coworkers[59] also assembled the carbocyclic skeleton of (–)-fumagillol in a single synthetic transformation. As seen in Scheme 14, intermediate **69** is synthesized via a glycolate Claisen rearrangement and then subjected to an intramolecular ester enolate alkylation reaction. It is worth noting that the alkylation reaction afforded the desired

cyclohexancarboxylate in an 11 : 1 diastereoselectivity, which was attributed to the "H-eclipsed" transition state geometry of **69**.

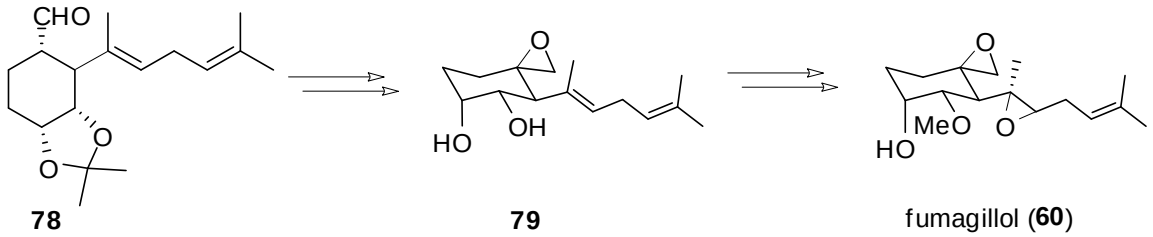
More recently in 2001 and 2004, Eustache[60] and Langlois[61] both employed a ring closing metathesis reaction to construct the principal framework of (–)-fumagillol. Interestingly, Grubbs' first generation catalyst was found to be effective for this key cyclization reaction for both syntheses.



Scheme 14: Previous Syntheses of Fumagillol

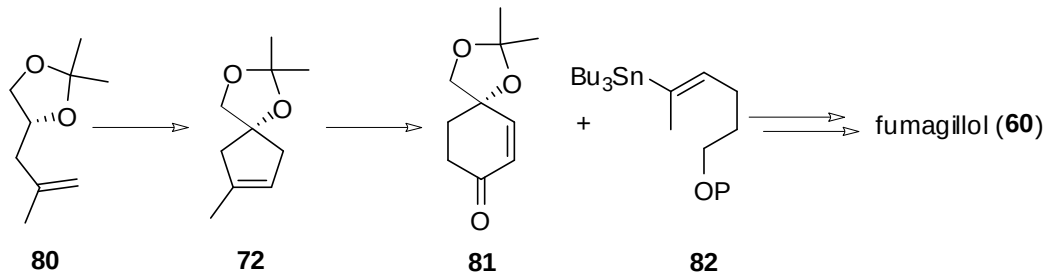
Another synthetic strategy involves the formation of a functionalized cyclohexane followed by addition of the side chain in a separate step (shown in orange). This approach was first employed by Sorensen and coworkers, who synthesized (±)-fumagillol by performing a 1,4-

addition of organocuprate reagent **71** onto the electron-deficient olefin in (±)-enal **70** in the presence of $BF_3{\cdot}OEt_3$ (Scheme 14).[62] This addition occurred with high regio- and diastereoselectivity, giving a 3 : 1 mixture of the desired : undesired aldehyde **78** (Scheme 15). Four years later, in 2003, Sorensen published the enantioselective synthesis of fumagillol by using (–)-enal **79**.[63] Sorensen's enantioselective synthesis has subsequently been intersected by Simpkins,[64] Langlois,[61] Mootoo,[65] and Hayashi.[66]



Scheme 15: Sorensen's Route to Fumagillol

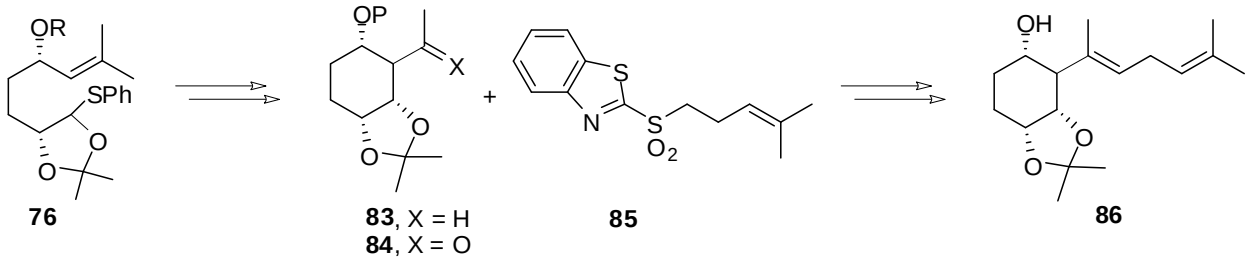
Taber's synthesis of (–)-fumagillol used a unique C-H insertion process to construct cyclopentene **72** with retention of configuration from alkene **80** (Scheme 16).[67] Cyclopentene **72** was then converted to cyclohexenone **81** through a ring expansion process using ozonolysis followed by an aldol condensation. Vinyl stannane **82** was reacted with *n*-BuLi and copper(I)cyanide to produce a cuprate that was added to enone **81** via 1,4-addition. This copper-mediated reaction produced the anti addition product in a 96 : 4 diastereomeric ratio.



Scheme 16: Taber's Synthetic Strategy to (–)-Fumagillol

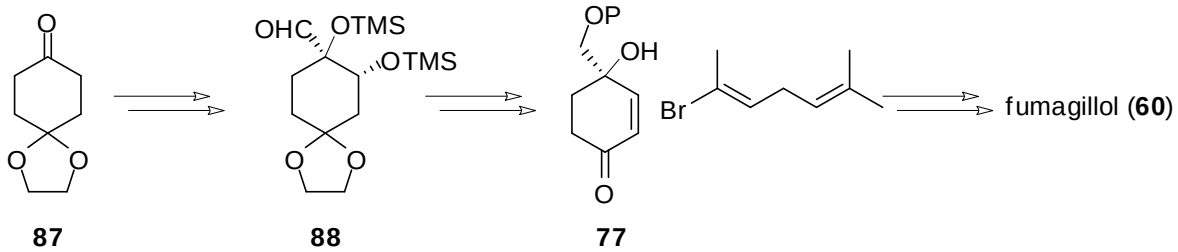
In 2005, Mootoo and coworkers used a highly stereoselective oxocarbenium ion-alkene cyclization as the key transformation for their formal synthesis of fumagillin.[65] As seen in

Scheme 17, alkene **76** was transformed into cyclohexane **83** upon reaction with methyl triflate (MeOTf) and 4-methyl-2,6-di-*tert*-butylpyridine (DTBMP). Ozonolysis of **83** produced methyl ketone **84**, which was then reacted with benzothiazole sulfone **85** and LiHMDS to give the corresponding trisubstituted alkene as a 1:6 mixture of *E*/*Z* isomers. The desired *E*-isomer was obtained via Vedejs' two-step isomerization procedure[68] and was subsequently converted into intermediate **86**, constituting a formal synthesis.



Scheme 17: Mootoo's Oxocarbenium Ion Cyclization of 76, A Formal Synthesis of Fumagillin

Most recently, Hayashi and coworkers have completed enantioselective total syntheses of (–)-fumagillol and other members of the fumagillin family from the common intermediate **88** (Scheme 18).[66] Their route begins by transforming ketal **87** into bis(trimethylsilyl ether) cyclohexane **88** via a four-step reaction sequence featuring a proline-mediated asymmetric α-aminoxylation and cyanation of the resulting hydroxy ketone with TMSCN and Et_3N. Aldehyde **88** ws converted into enone **77**, which was subjected to a diastereoselective Michael addition with a vinyl zincate reagent prepared from (*E*)-2-bromo-6-methylhepta-2,5-diene, *t*-BuLi, and Me_2Zn. The conjugate addition product was converted into (–)-fumagillol in six steps.



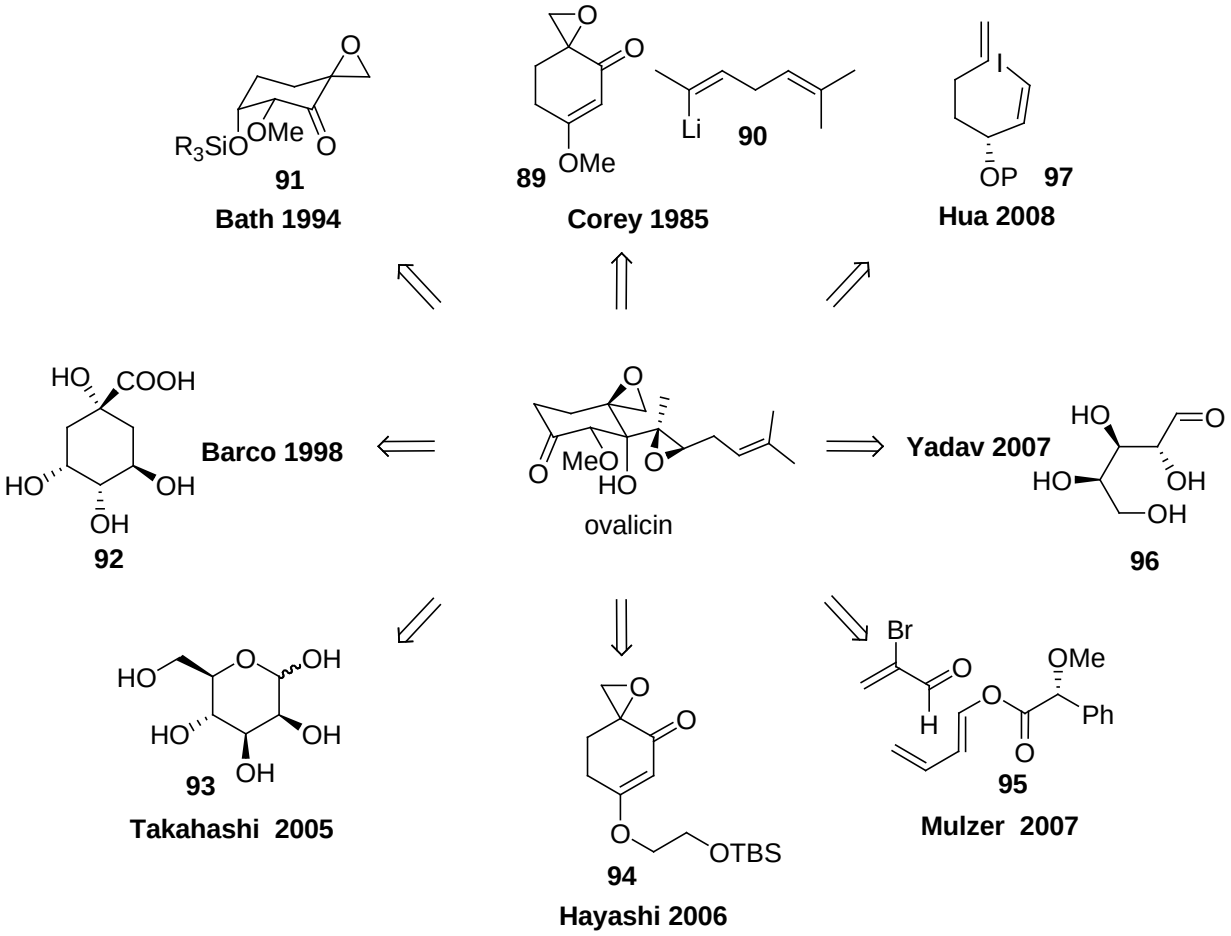
Scheme 18: Hayashi's Route to (–)-Fumagillol

1.6.2 Previous Syntheses of Ovalicin

Like fumagillol, ovalicin's potent biological activity has made it a popular target for natural product synthesis (Scheme 19). E. J. Corey and coworkers published both racemic and enantioselective synthetic routes to ovalicin in 1985[69] and 1994[48] respectively. Corey's racemic synthesis involved the stereoselective addition of vinyllithium reagent **90** to epoxy enone **89** to produce the desired tertiary alcohol in 83% yield. The enantioselective synthesis involved an OsO_4-biscinchona alkaloid catalyzed dihydroxylation to produce enantiopure epoxy enone **89**, which was then converted to ovalicin using the previously developed protocol.

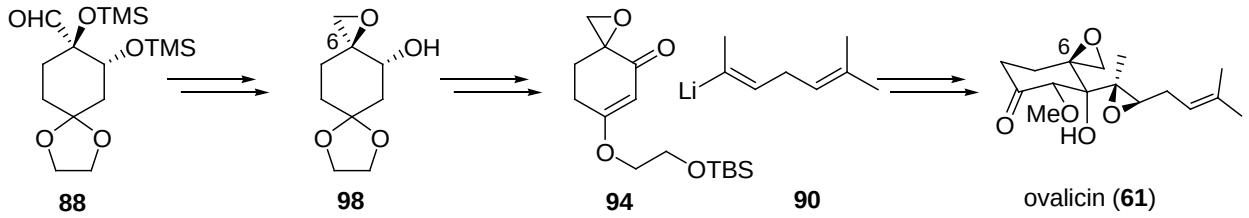
In 1994, Bath and coworkers synthesized (–)-ovalicin in three steps from functionalized epoxy ketone **91** (Scheme 19). Intermediate **91**, in turn, was obtained from commercially available L-quebrachitol, which already contains the C-2 methoxy group present in ovalicin. The side chain of ovalicin was then installed by reacting vinyllithium **90** with the ketone moiety of **91**.[70]

To date, Bath's synthesis of ovalicin has been intersected at epoxy ketone **91** by Barco,[71] Takahashi,[72] Mulzer,[73] Yadav,[74] and Hua.[75] Ketone **91**, however, has been accessed from a variety of naturally occurring chiral materials such as (–)-quinic acid (**92**), D-mannose (**93**), and D-ribose (**96**) by Barco, Takahashi, and Yadav, respectively.



Scheme 19: Previous Syntheses of Ovalicin

Similar to his fumagillol synthesis, Hayashi has also synthesized ovalicin from bis(trimethylsilyl ether) cyclohexane **88**.[66] As seen in Scheme 20, **88** is transformed into epoxy alcohol **98** via reduction of the aldehyde, mesylation of the resulting alcohol, and elimination to give the desired epoxide moiety at C6. Oxidation of **98** with Dess-Martin periodinane gives the analogous ketone, which is then treated with acid and TBSCl to yield cyclohexenone **94**. Reacting enone **94** with vinyllithium reagent **90** allows for installation of the side chain in 91% yield. The addition product was transformed into ovalicin in five steps.



Scheme 20: Hayashi's Route to Ovalicin

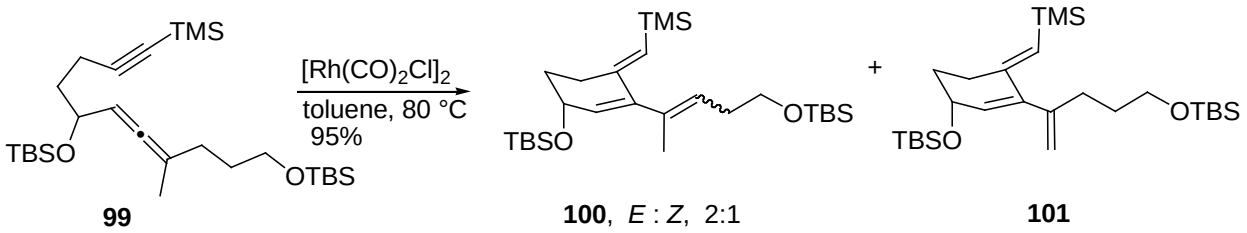
Mulzer and coworkers[73] employed an enantioselective Diels-Alder reaction between Trost diene **95**[76] and α-bromoacrolein in the presence of $BF_3{\cdot}OEt_3$ for their synthesis of (–)-ovalicin (Scheme 19). This cycloaddition reaction occurred with *endo* selectivity and produced the Diels-Alder adduct in 75% yield as an 8:1 mixture of diastereomers.

Most recently in 2008, Hua and coworkers utilized an intramolecular Heck reaction of alkenyl iodide **97** for the construction of the cylohexyl framework of ovalicin (Scheme 19).[75] The 4-methylenecyclohexene product was then converted into epoxy ketone **91**, which can be transformed into ovalicin via known protocol.

1.6.3 Brummond and Coworkers' Previous Approach to Ovalicin

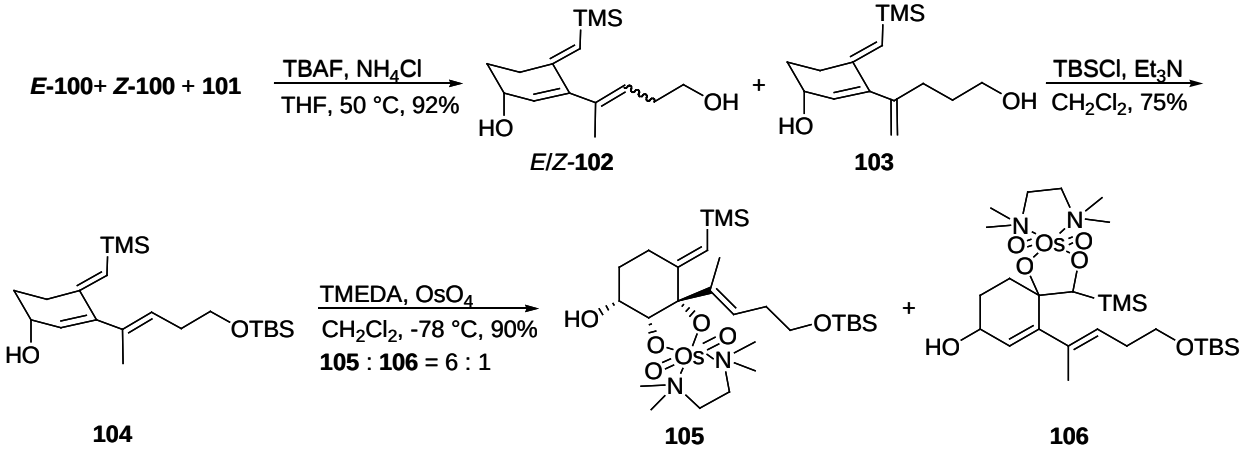
Brummond and coworkers' novel approach towards ovalicin employed an allenic carbocyclization reaction for the construction of the carbocyclic skeleton with the side chain already intact. This strategy is advantageous as selective oxidation reactions of the cross-conjugated triene system will produce the oxygenated framework of ovalicin.

Work done in our group by Jamie McCabe showed that cross-conjugated trienes **100** and **101** could be obtained in a 90:10 isomeric ratio from allene-yne **99** in 95% yield (Scheme 21). The appending trisubstituted double bond of triene **100** was formed as a 2:1 mixture of *E*:*Z* isomers.[77]



Scheme 21: Rh(I)-catalyzed Carbocyclization of Allene-yne 99[77]

With cross-conjugated trienes *E*-**100**/*Z*-**100**/**101** in hand, the silyl protecting groups were removed with TBAF to give diols *E*/*Z*-**102** and **103**, which were separable via column chromatography (Scheme 22). The primary alcohol of *E*-**102** was then selectively protected with TBSCl and Et_3N to give silyl ether **104** in 75% yield. Subsequent alcohol-directed dihydroxylation of triene **104** with TMEDA and OsO_4 (1 equiv) resulted in the formation of osmate esters **105** and **106** in 90% yield as a 6:1 isomeric mixture. A small discrepancy found in the ^1H NMR of **105**, however, prevents conclusive evidence as to whether the desired osmate ester was obtained.[77]



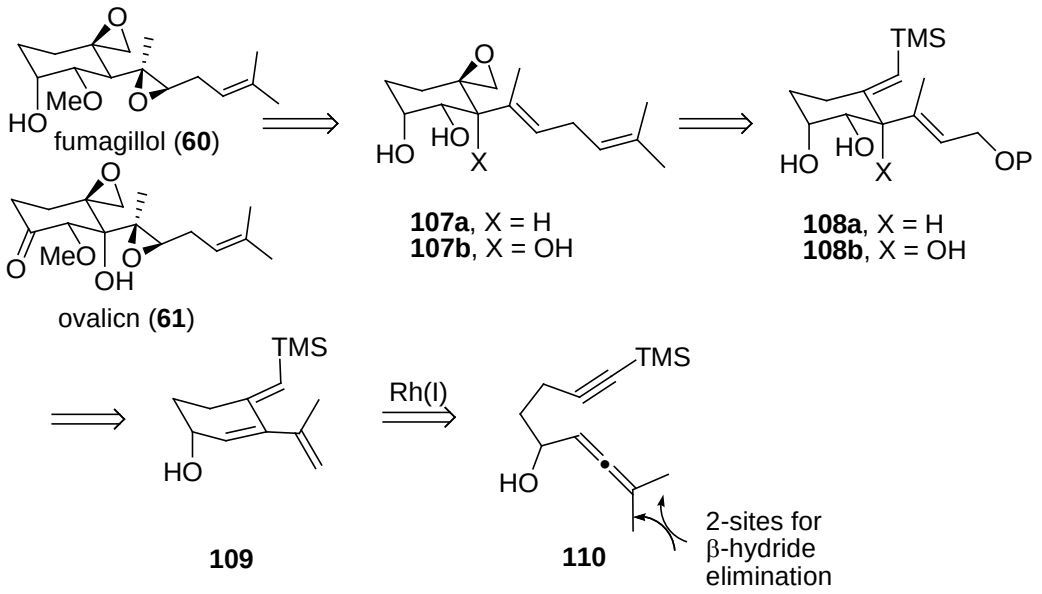
Scheme 22: Synthesis and Oxidation of Triene 104[77]

The high yield and functional group compatibility of the Rh(I)-catalyzed allenic carbocyclization reaction is illustrated by the cyclization of allene-yne **99**. Moreover, the

densely functionalized carbocyclic skeleton of *E*-**104** demonstrates the utility of the cross-conjugated scaffold in natural product synthesis.

1.6.4 Retrosynthetic Analysis: Brummond / DeForrest Approach to Fumagillol / Ovalicin via an Allenic Carbocyclization Reaction

Retrosynthetically, we envision that fumagillol can be obtained from diol **107a** and ovalicin from triol **107b** (Scheme 23). We plan to construct the skipped diene side chain of intermediates **107a** and **107b** from the primary allylic alcohol of **108a** and **108b** via an oxidation and homologation reaction sequence.[67] In turn, **108a** and **108b** will be prepared via diverging transformations involving selective oxidations of cross-conjugated triene **109**. More specifically, we plan to use the hydroxyl group of triene **109** as a chemoselective control element for the sequential introduction of epoxides and hydroxyl groups embedded in these natural products. A cross-metathesis reaction will be used to convert the 1,1-disubstituted alkene of triene **109** into the trisubstituted alkene of **108a**/**b**. Cross-conjugated triene **109** can be accessed from allene-yne **110** via the Rh(I)-catalyzed allenic carbocyclization reaction previously developed in our laboratory.[19] Considering the isomeric mixtures of trienes previously reported by McCabe,[77] allene-yne **110** was chosen for our syntheses as the two sites available for β-hydride elimination are identical and will only produce cross-conjugated triene **109**.



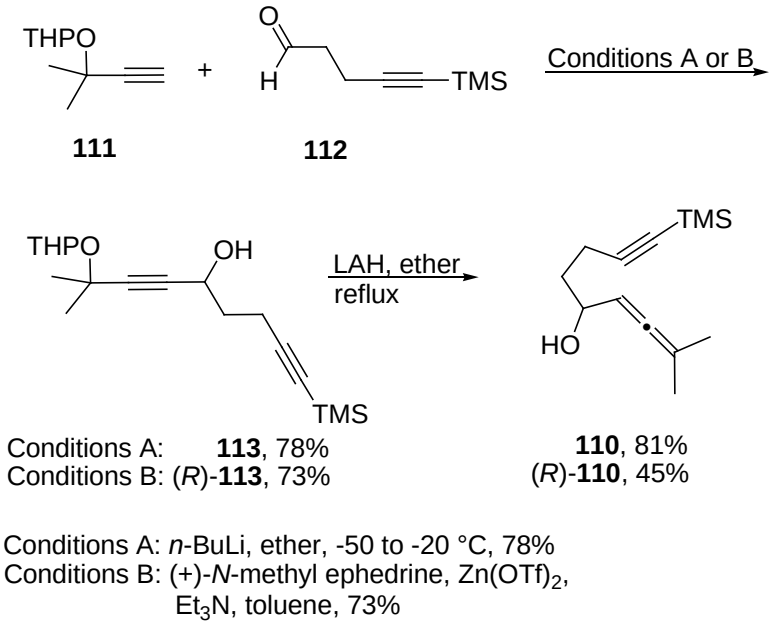
Scheme 23: Retrosynthetic Analysis of Fumagillol and Ovalicin from Allenyne 110

1.7 RESULTS AND DISCUSSION: SYNTHESIS AND FUNCTIONALIZATION OF A CROSS-CONJUGATED TRIENE PRECURSOR FOR THE SYNTHESES OF FUMAGILLOL AND OVALICIN

1.7.1 Synthesis of Cross-conjugated Triene 109

Allene-yne **110** can be prepared in two steps from known propargyl tetrahydropyranyl ether **111**[78] and aldehyde **112**[79] (Scheme 24). Employing Brandsma's[80] procedure for the construction of propargyl alcohols, the alkyne terminus of **111** was first deprotonated with *n*-BuLi at –50 °C, and then reacted with aldehyde **112** (Conditions A). Warming the reaction to –20 °C gave propargyl alcohol **113** in 78% yield. The formation of propargyl alcohol **113** is supported by the IR spectrum, which has the characteristic alcohol and alkyne absorbances at 3396 cm^{-1} and 2167 cm^{-1}, respectively.[81]

With propargyl alcohol **113** in hand, we investigated the aluminum-mediated reduction protocol developed by Landor and coworkers for the formation of allene-yne **110** (Scheme 24).[82] Reacting propargyl alcohol **113** with LAH in refluxing diethyl ether produced allene-yne **110** in 81% yield. Interestingly, decreasing the reaction temperature (–20 to 0 °C) gave a separable mixture of the corresponding allylic tetrahydropyranyl ether (22%) and the desired allene-yne **110** (21%).



Scheme 24: Synthesis of Racemic and Enantioselective Allene-yne 110 and (*R*)-110

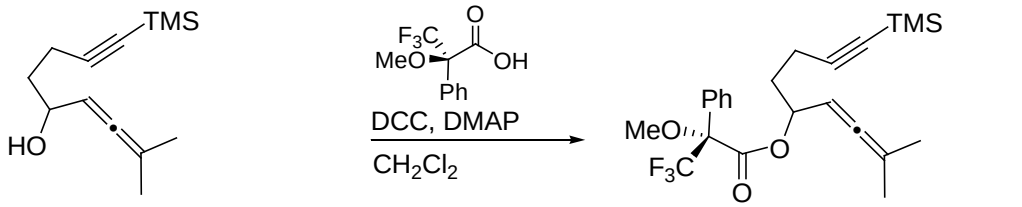
The formation of allene-yne **110** is evidenced by a resonance at 5.12-5.06 ppm (m) in the ^{1}H NMR, corresponding to the allene proton, and a resonance at 199.8 ppm in the ^{13}C NMR, corresponding to the *sp* hybridized carbon of the allene.[81]

Allene-yne (*R*)-**110** has also been prepared in high enantioselectivity from terminal alkyne **111** and aldehyde **112** utilizing enantioselective alkynylation protocol developed by Carreira and coworkers (Scheme 24).[83] The formation of propargyl alcohol (*R*)-**113** was accomplished in 73% yield by adding aldehyde **112** (1 equiv) to an excess of alkyne **111** (3.1 equiv), triethylamine (3.1 eq), (+)-*N*-methylephedrine (3.1 equiv), and zinc triflate (3 equiv) over

4 h via syringe pump addition (Conditions B). The ^{1}H NMR and ^{13}C NMR of propargyl alcohol (*R*)-**113** are in agreement with the spectral data obtained for **113**.

Reacting propargyl alcohol (*R*)-**113** with LAH in refluxing ether gave chiral non-racemic allene-yne (*R*)-**110** in 45% yield (Scheme 24). The low yield obtained for (*R*)-**110** is likely due to the small scale on which the reduction reaction was performed. For example, reacting 1.1 mmol of propargyl alcohol (*R*)-**113** with LAH gave allene-yne (*R*)-**110** in 45% yield, whereas subjecting 9.0 mmol of propargyl alcohol **113** to the same reaction conditions gave allene-yne **110** in an increased 81% yield. The spectral data obtained for (*R*)-**110** matches that obtained for **110**.

Mosher esters **114** and (*R*)-**114** were synthesized from the analogous allenic alcohol precursors to determine the enantiomeric excess of (*R*)-**110**. As seen in Scheme 25, subjecting allene-ynes **110** and (*R*)-**110** to esterification reaction conditions with (*R*)-(+)-alpha-methoxy-alpha-(trifluromethyl)-phenylacetic acid, *N*,*N*'-dicyclohexylcarbodiimide (DCC), and 4-dimethylaminopyridine (DMAP) resulted in the desired esters **114** and (*R*)-**114** in crude yields of 82% and 85%, respectively.



110
(*R*)-**110**

114, 82 % crude yield
(*R*)-**114**, 84 % crude yield

Scheme 25: Formation of Mosher Esters 114 and (*R*)-114

The ^{19}F NMR of racemic allene-yne **114** shows two resonances with equal integrations at -72.1 ppm and -72.2 ppm, indicating that **114** is a 1:1 mixture of two diastereomers (Figure 2). The ^{19}F NMR of (*R*)-**114** shows the same two resonances at -72.1 ppm and -72.2 ppm, however,

with integrations of 1F and 28F, respectively. The integrations in the ^{19}F NMR of (*R*)-**114** show that allene-yne (*R*)-**110** was produced in 93% *ee*. The absolute configuration of (*R*)-**110** was assigned by analogy to Carreira's substrates, which showed that employing (+)-*N*-methylephedrine as the chiral additive for the alkynylation reaction produces the *R*-enantiomer of the propargyl alcohol product.[84]

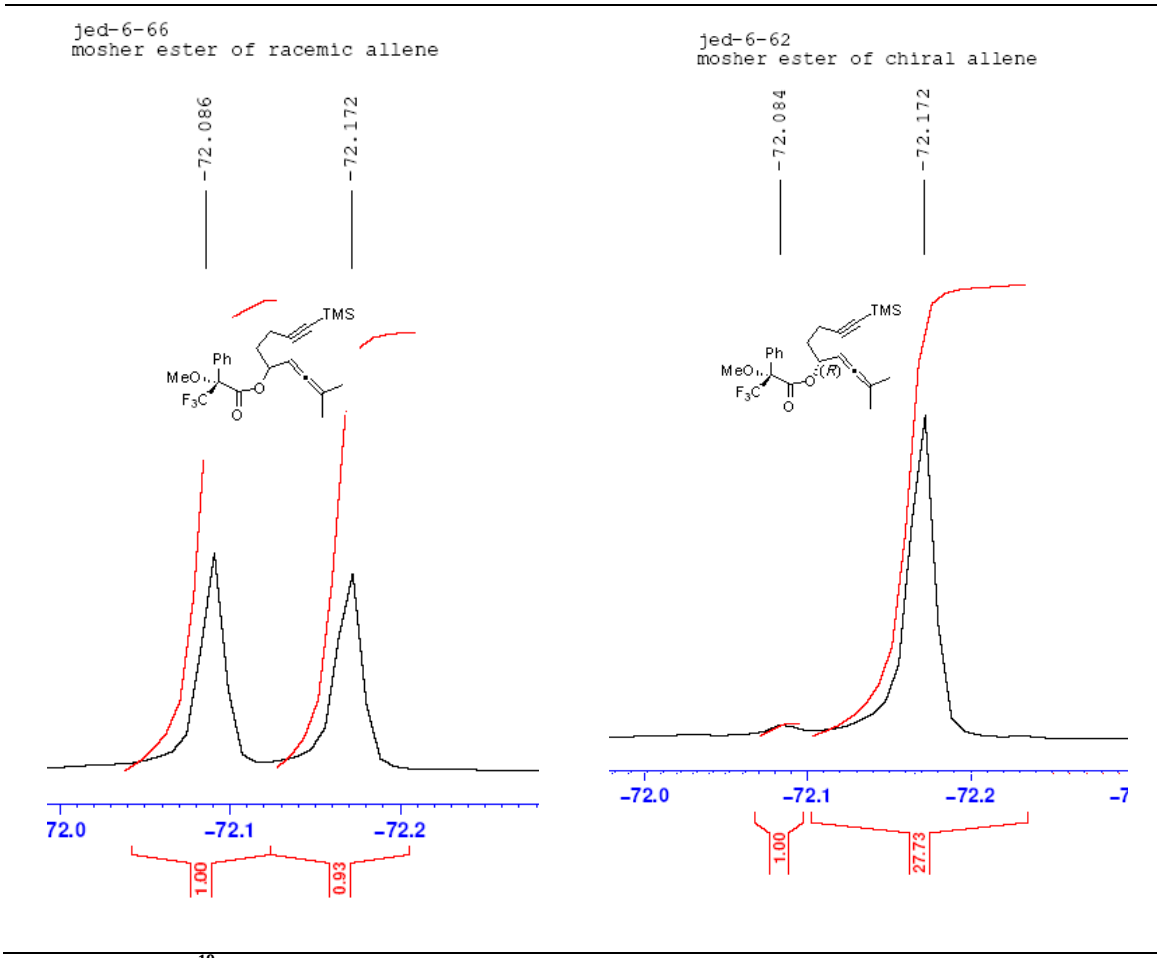
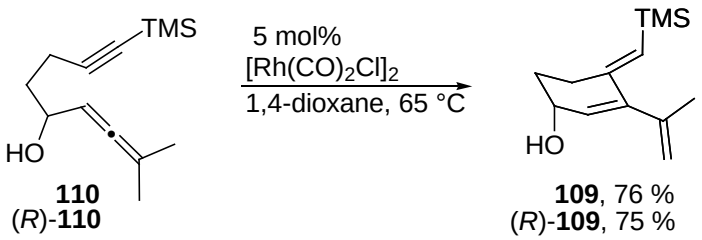


Figure 2: ^{19}F NMR of Racemic Allene-yne 114 and Enantioenriched Allene-yne (*R*)-114

With allene-ynes **110** and (*R*)-**110** in hand, the rhodium-catalyzed allenic carbocyclization reaction was employed for the construction of cross-conjugated trienes **109** and (*R*)-**109**. Reacting allene-yne **110** with 5 mol% of $[Rh(CO)_2Cl]_2$ in 1,4-dioxane at 65 °C resulted in cross-conjugated triene **109** in 76% yield (Scheme 26). Similarly, subjecting chiral allene-

yne (*R*)-**110** to the cyclization reaction conditions resulted in cross-conjugated triene (*R*)-**109** in 75% yield. The high yield obtained for cross-conjugated trienes **109** and (*R*)-**109** demonstrates the synthetic utility of the Rh(I)-catalyzed carbocyclization for natural product synthesis, as (*R*)-**109** possesses the cyclohexenol scaffold found in ovalicin and fumagillol.



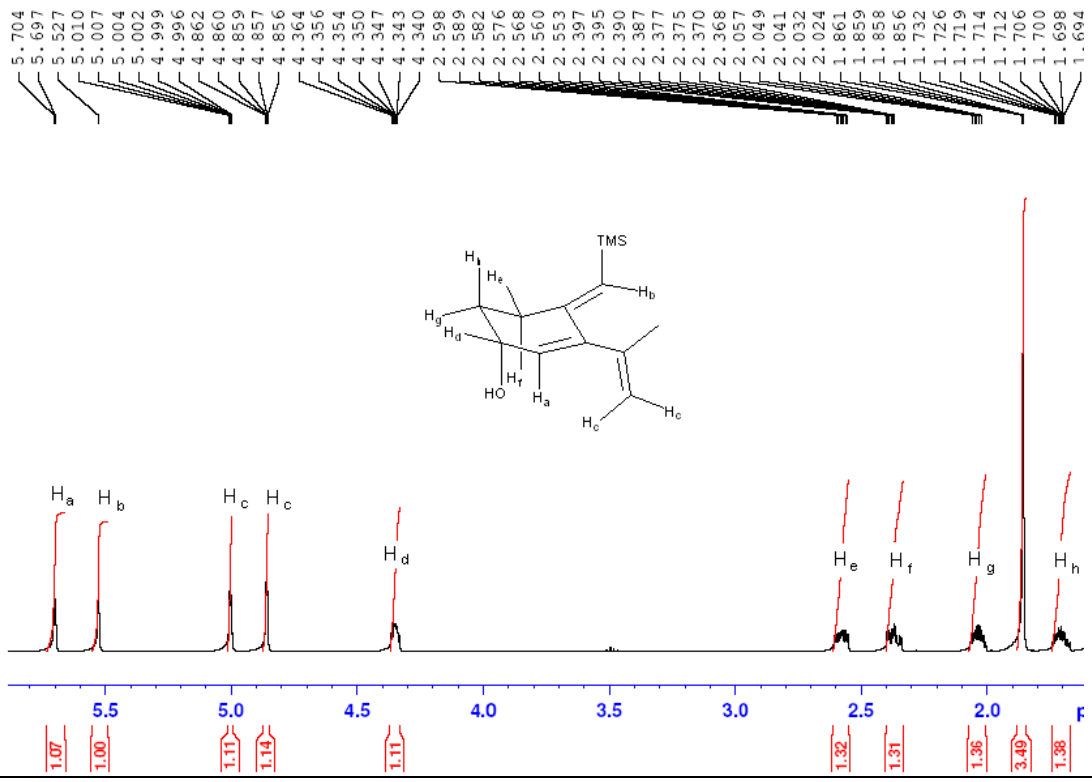
110
(*R*)-**110**

109, 76 %
(*R*)-**109**, 75 %

Scheme 26: Formation of Racemic and Chiral Cross-conjugated Trienes 109 and (*R*)-109

The formation of cross-conjugated trienes **109** and (*R*)-**109** is clearly evidenced by the ^{1}H NMR data (Table 1). For example, the ^{1}H NMR of (*R*)-**109** shows resonances at 5.70 ppm and 5.53 ppm that correspond to H_a (d, J = 3.5 Hz) and the vinyl silane proton H_b (singlet), respectively. The other resonances in the alkene region at 5.00 ppm (dq, J = 3.0, 1.5 Hz) and 4.88-4.85 ppm (multiplet) correspond to the appending 1,1-disubstituted alkene protons H_c. The resonance at 4.35 ppm corresponds to H_d (ddd, J = 7.0, 5.0, 3.5 Hz). The allylic protons H_e and H_f correspond to the resonances at 2.58 ppm and 2.37 ppm, while the neighboring methylene protons H_g and H_h correlate to the resonances at 2.04 ppm and 1.71 ppm, respectively.

Table 1: ^{1}H NMR of Cross-conjugated Triene (*R*)-109 ($CDCl_3$, rt, 500 MHz)

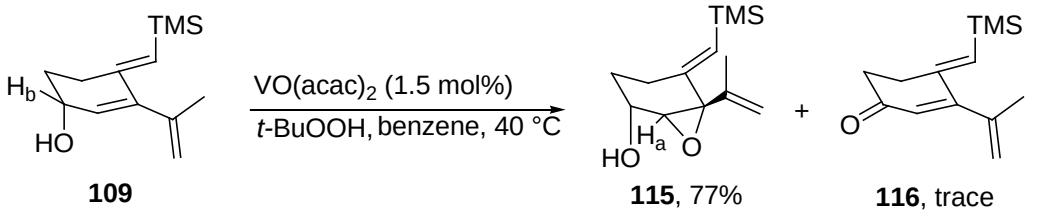


	Chemical Shift	Spin multiplicity	*J* Values (Hz)
H_a	5.70 ppm	d	3.5
H_b	5.53 ppm	s	-----
H_c	5.00 ppm	dq	3.0, 1.5
H_c	4.88-4.85 ppm	m	-----
H_d	4.35 ppm	ddd	7.0, 5.0, 3.5
H_e	2.58 ppm	ddd	14.5, 8.0, 3.5
H_f	2.37 ppm	dddd	14.5, 10.0, 3.5, 1.0
H_g	2.04 ppm	ddt	12.5, 8.0, 4.5
H_h	1.71 ppm	dddd	12.5, 10.5, 7.0, 4.0

Cross-conjugated triene **109** can be synthesized in three steps from alkyne **111** and aldehyde **112** in 47% overall yield and can be conducted on multigram scale. This synthetic strategy also offers the possibility for the asymmetric syntheses of (–)-ovalicin and (–)-fumagillol, becuase Carreira's enantioselective alkynylation protocol can be utilized for the assembly of propargyl alcohol (*R*)-**113**.

1.7.2 Alcohol-Directed Epoxidation of Triene 109: Formation of a Pivotal Intermediate for the Syntheses of Ovalicin and Fumagillol

With the racemic and enantioselective syntheses of cross-conjugated triene **109** in hand, we explored an alcohol-directed epoxidation protocol to selectively functionalize the endocyclic alkene of triene **109**. To our delight, we found that reacting triene **109** with 1.5 mol% of vanadyl acetyl acetonate[85] and *tert*-butyl hydroperoxide in benzene at 40 °C produced bis-allylic epoxide **115** in 77% yield as a single diastereomer (Scheme 27). The formation of **115** is supported by the ^{1}H NMR, which shows a resonance at 3.22 ppm (d, J = 2.0 Hz) corresponding to H_a, and the absence of the resonance at 5.70 ppm (d, J = 3.5 Hz) corresponding to the endocyclic alkene proton of **109**.



109 **115**, 77% **116**, trace

Scheme 27: Formation of Epoxide 115 from Triene 109

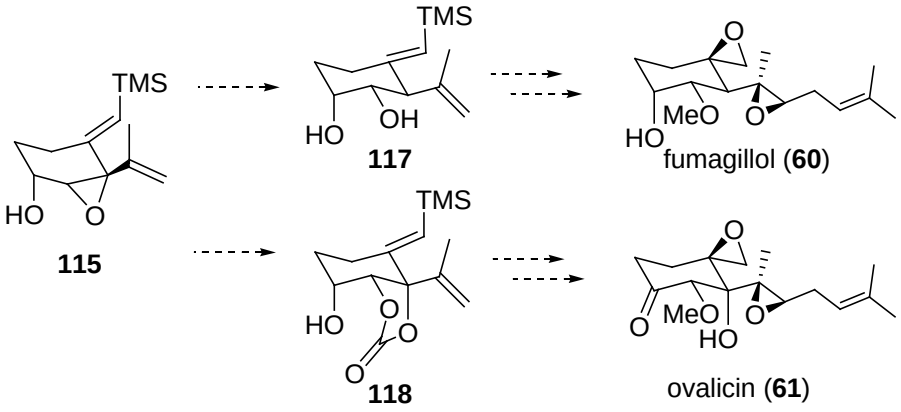
Interestingly, applying the $VO(acac)_2$/TBHP epoxidation protocol to triene **109** at –15 to 25 °C only resulted in the corresponding enone in 8% yield. The low yield obtained could be due to the volatility of **116**. The formation of **116** is evidenced by the ^{1}H NMR, which no longer shows the resonance at 4.35 ppm corresponding to H_b. Vanadium-catalyzed enone formation has also been observed by Teranishi and coworkers during their vanadium-catalyzed epoxidation studies of cyclic allylic alcohols.[86]

The vanadium-catalyzed epoxidation conditions used for the construction of epoxide **115** from triene **109** were found to be superior to the other methods explored.[85] For example,

treatment of triene **109** with Ti(O*i*Pr)$_4$, DIPT, and *tert*-butyl hydrogen peroxide in the presence of 4 Å molecular sieves[87] only resulted in the recovery of starting material. Additionally, subjecting **109** to buffered peracid epoxidation reaction conditions with *m*-CPBA and Na_2HPO_4 gave a mixture of compounds that were inseparable via column chromatography.

1.7.2.1 Diverging Palladium-Catalyzed Transformations of Epoxide 115

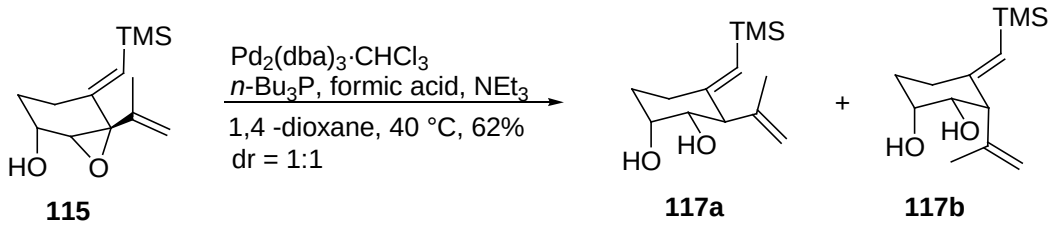
Next, diverging palladium-catalyzed transformations of epoxide **115** were investigated to access the oxygenated cyclohexyl core of ovalicin and fumagillol (Scheme 28). It is envisioned that allylic epoxide **115** can be transformed into diol **117** via a palladium-catalyzed hydrogenolysis reaction and into carbonate **118** through a palladium-catalyzed CO_2 insertion reaction. These diverging transformations will allow for the assembly of both structurally related natural products from a single intermediate.



Scheme 28: Projected Diverging Transformations of Epoxide 115 to the Oxygenated Rings of 60 and 61

1.7.2.2 Palladium-Catalyzed Hydrogenolysis of Epoxide 115: Synthesis of Diol 117a/b

Construction of the *cis*-diol moiety of fumagillol began with palladium-catalyzed hydrogenolysis protocol developed by Tsuji and coworkers.[88] Reacting epoxide **115** with $Pd_2(dba)_3 \cdot CHCl_3$, tri-*n*-butylphosphine, formic acid, and triethylamine in 1,4-dioxane at 40 °C gave a separable (1:1) mixture of diols **117a** and **117b** in a 62% combined yield (Scheme 29). The diastereomeric ratio was established by integrating the resonances corresponding to the vinyl silane proton of **117a**/**b** at 5.33 ppm and 5.18 ppm in the crude ^{1}H NMR.

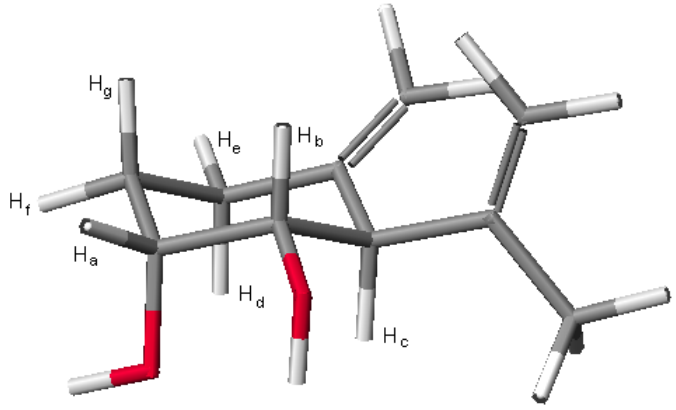


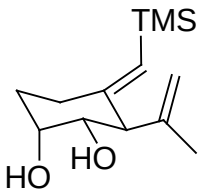
Scheme 29: Formation of Diols 117a/b from Epoxide 115

Molecular modeling* predicts that the desired diol **117a** exists in a conformation where one of the hydroxyl groups and the appending alkene are in an equatorial orientation, and the other hydroxyl group is in an axial position (Table 2, the silyl methyl groups have been removed for clarity). Calculations predict an axial-axial coupling between H_b and H_c (typically between 8-10 Hz) and an axial-equatorial coupling (usually 2-3 Hz) between H_b and H_a. The predicted *J* values are indeed observed; the axial-axial coupling between H_b and H_c is observed to be 9.7 Hz, and the axial-equatorial coupling between H_b and H_a is 2.9 Hz.

*modeling study conducted using Cache worksystem Pro Version 6.1.12.33, AM1 energy minimization

Table 2: ^{1}H NMR Assignment of Diol 117a (500 MHz, $CDCl_3$)



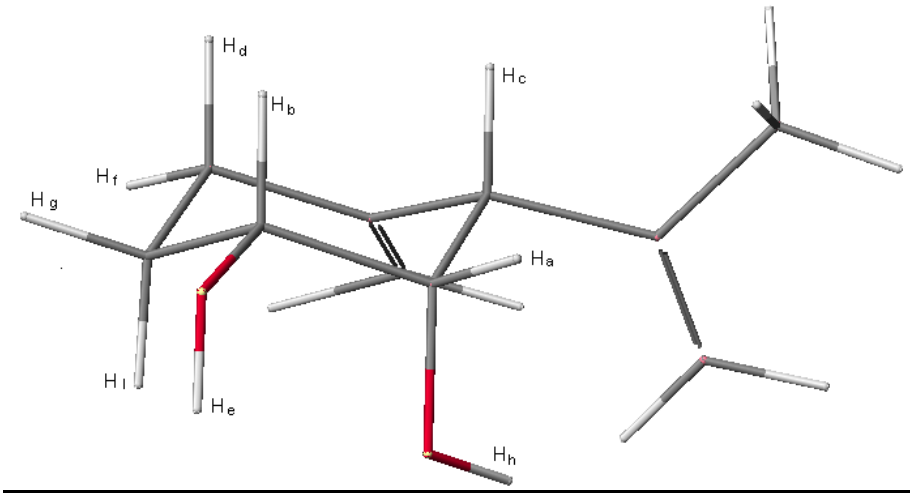


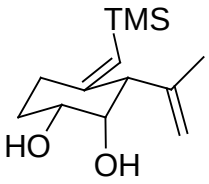
117a

	Chemical Shift (ppm)	Spin multiplicity	*J* values (Hz)
H_a	4.14-4.12	m	-------
H_b	3.73	dd	9.7, 2.9
H_c	3.12	d	9.7
H_d	2.38	td	13.1, 4.4
H_e	2.31	dt	13.5, 4.4
H_f	1.99	dq	13.4, 4.4
H_g	1.59-1.49	m	-------

Diastereomer **117b** also adopts a chair-like conformation (Table 3, the silyl methyl groups have been removed for clarity). A resonance in the ^{1}H NMR corresponding to H_b appears as a dddd, resulting from axial-axial coupling with H_I (11.5 Hz), equatorial-equatorial coupling with H_a and H_g (2.5 and 4.5 Hz), and coupling with the hydroxyl proton H_e (9.0 Hz). A resonance at 4.13 ppm corresponding to H_a is a doublet due to coupling with H_h. Additionally, the resonance corresponding to H_c at 2.79 ppm is a broad singlet. These observed coupling constants give some evidence that **117b** was obtained.

Table 3: ^{1}HNMR Assignment of Diol 117b (500 MHz, $CDCl_3$)

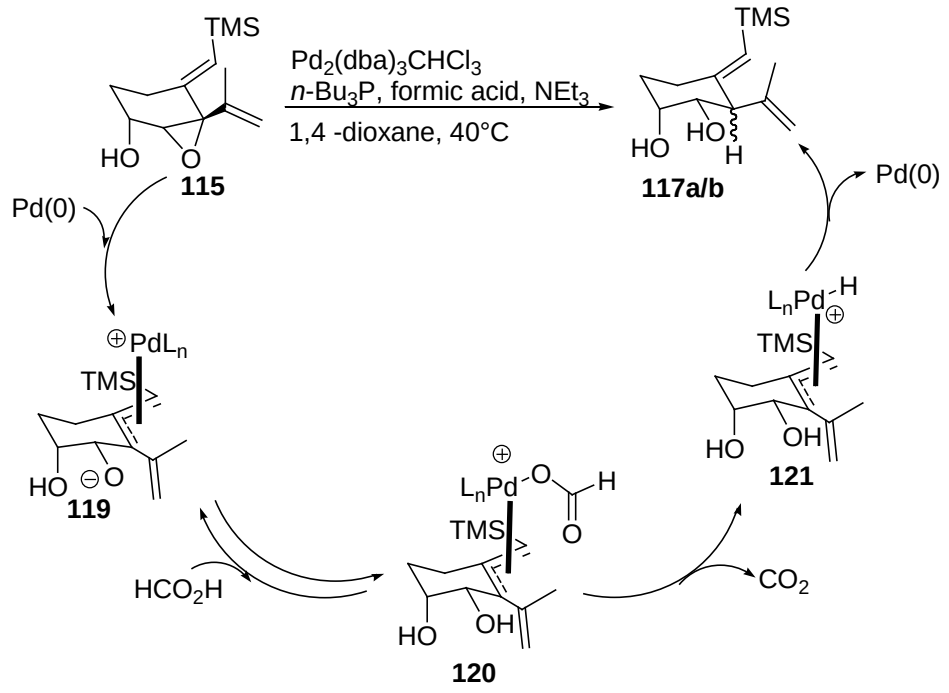




117b

	Chemical Shift (ppm)	Spin multiplicity	*J* values (Hz)
H_a	4.13	d	8.5
H_b	3.69	dddd	11.5, 9.0, 4.5, 2.5
H_c	2.79	bs	--------
H_d	2.59-2.54	m	--------
H_e	2.11	d	9.5
H_f	2.05-1.96	m	--------
H_g	2.05-1.96	m	--------
H_h	1.53	d	8.0
H_I	1.50-1.43	m	--------

The mechanism for the palladium-catalyzed hydrogenolysis reaction begins with stereoselective opening of the epoxide ring to produce π-allylpalladium species **119** (Scheme 30). Formic acid insertion produces π-allylpalladium formate **120**, which decarboxylates to the palladium hydride complex **121**. Reductive elimination yields diol **117** with the hydride delivered to the more substituted side of the π-allyl complex.[88] The mixture of diastereomeric diols **117a** and **117b** produced from bis-allylic epoxide **115** is likely due to inversion of the palladium catalyst during the reaction.[89]



Scheme 30: Proposed Mechanism for the Conversion of Epoxide 115 into Diol 117a/b

A molecular modeling study* suggests that the 1,1-disubstituted alkene present in bis-allylic epoxide **115** prefers to reside perpendicular to the alkylidenecyclohexane ring, which minimizes unfavorable van der Waals and allylic A(1,3) steric interactions (Figure 3, the silyl methyl groups have been removed for clarity). The energy minimization calculation infers optimal orbital overlap between the epoxide and the vinyl silane, suggesting that the π-allylpalladium species forms at the vinyl silane moiety rather than the 1,1-disubstituted alkene.

*modeling study conducted using Cache worksystem Pro Version 6.1.12.33, AM1 energy minimization

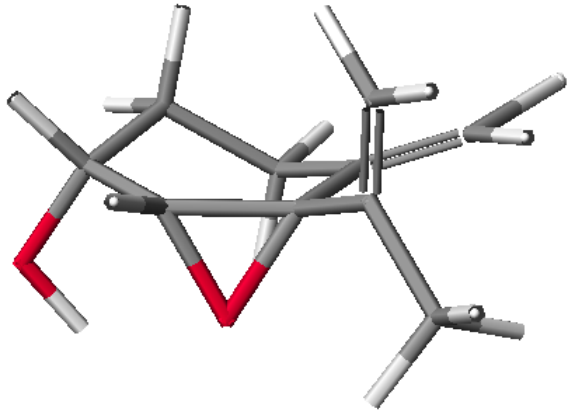
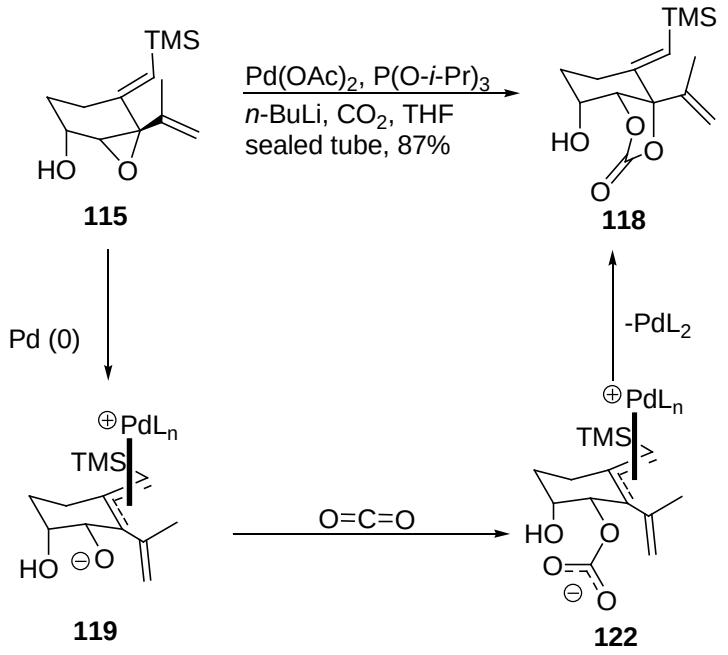


Figure 3: Minimum Energy Conformation of Epoxide 115

1.7.2.3 Palladium-Catalyzed CO_2-Insertion of Epoxide 115: Formation of Carbonate 118

With a synthetic strategy to access the oxygenated framework of fumagillol from epoxide **115**, oxidation protocol to access the masked triol moiety of ovalicin was explored. Subjecting epoxide **115** to Trost's palladium-catalyzed CO_2 insertion reaction conditions gave carbonate **118** in 87% yield as a single diastereomer (Scheme 31).[90] The proposed mechanism for the formation of carbonate **118** involves an S_N2 type metal-mediated epoxide opening to produce π-allylpalladium complex **119**. The newly generated alkoxide then undergoes nucleophilic addition to carbon dioxide, producing intermediate **122**, which then cyclizes to yield desired carbonate **118** as a single diastereomer.



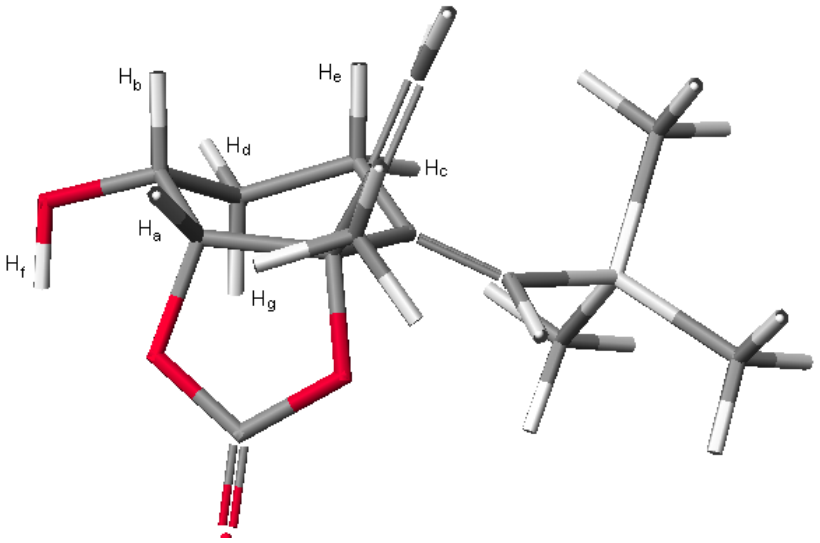
Scheme 31: Formation of Carbonate 118 from Epoxide 115

The IR spectrum of carbonate **118** has an absorbance at 1814 cm^{-1}, which is characteristic for the carbonyl stretch of cyclic carbonates. Furthermore, the ^{13}C NMR spectrum has the resonance at 153.1 ppm that is typically observed for the carbonate carbonyl carbon.[81]

The formation of **118** as the *cis* carbonate is evidenced by the ^{1}H NMR coupling constants (shown in Table 4). Molecular modeling* has shown that carbonate **118** adopts a conformation where the hydroxyl group resides in the equatorial position. In this conformation, the resonance corresponding to H_b is an apparent triplet of triplet resulting from coupling with the hydroxyl proton H_f (10.9 Hz), axial-axial coupling with H_g (10.9 Hz), and axial-equatorial coupling with both H_a (4.2 Hz) and H_d (4.2 Hz).

* modeling study conducted using Cache worksystem Pro Version 6.1.12.33, AM1 energy minimization

Table 4: ^{1}HNMR Assignment of Carbonate 118 (600 MHz, $CDCl_3$)



	Chemical Shift (ppm)	Spin multiplicity	*J* values (Hz)
H_a	4.84	d	3.5
H_b	4.04	tt	10.9, 4.2
H_c	2.62	dt	14.7, 4.1
H_d	2.08	dq	12.6, 3
H_e	2.04-1.99	m	-------
H_f	1.96	d	9.9
H_g	1.68	qd	11.5, 4.2

The *trans* carbonate, like the *cis* carbonate, also adopts a conformation where the hydroxyl group is in the equatorial position (as shown by molecular modeling* in Figure 5). In this configuration, the calculated dihedral angle between H_a and H_e is 36°, which would result in a coupling constant in the range of 5-6 Hz rather than the observed 10.9 Hz coupling constant (Table 4).

* modeling study conducted using Cache worksystem Pro Version 6.1.12.33, AM1 energy minimization

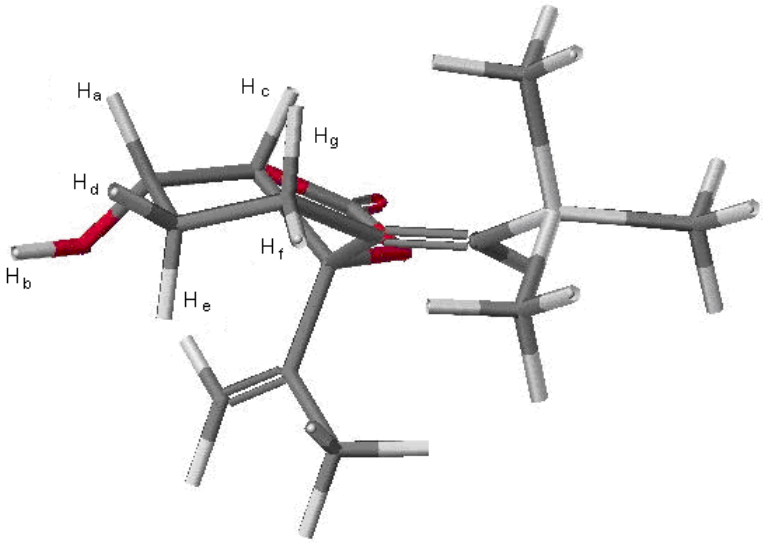
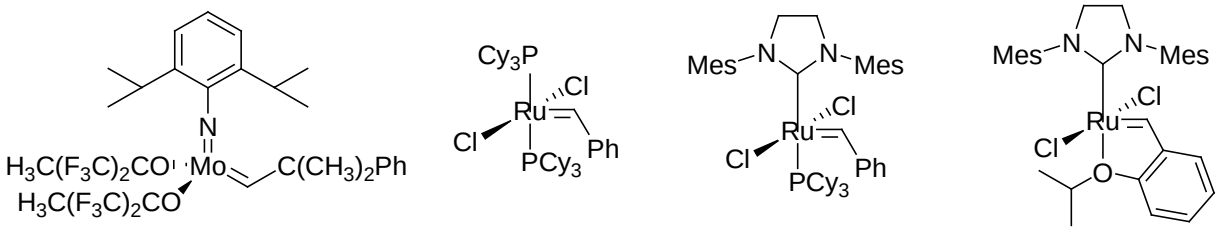


Figure 4: Minimum Energy Conformation of *trans*-Carbonate 118

1.8 INVESTIGATING THE REACTIVITY OF THE CROSS-CONJUGATED TRIENE MOIETY AND DERIVATIVES TOWARDS CROSS-METATHESIS: APPENDING THE ISOBUTYLENE SIDE CHAIN OF OVALICIN AND FUMAGILLOL TO THE TRIENE

With the development of well-defined catalysts such as Schrock's molybdenum alkylidene **123**, Grubbs' ruthenium carbene complexes **124** and **125**, and the Hoveyda-Grubbs catalyst **126**, olefin metathesis has become one of the most powerful and popular transition-metal catalyzed methods for carbon-carbon bond formation (Scheme 32).[91-94] Ring-closing metathesis (RCM), for example, is routinely used to construct small, medium, and large ring systems from acyclic dienes. The intermolecular variant cross-metathesis (CM), has been shown to have more limitations, exhibiting poor stereo- and product selectivity.[91-95] However, despite these limitations, cross-metathesis is extensively employed by the organic community to construct

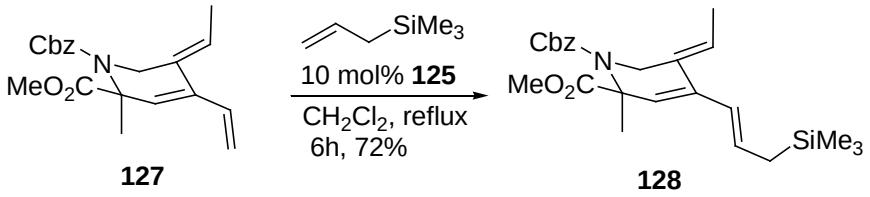
functionalized olefins from simple alkene precursors.[91-95] It is our goal to use cross-metathesis to convert the 1,1-disubstituted alkene in triene **109** into a trisubstituted alkene that can be converted into the side chain of fumagillol and ovalicin (Scheme 28).



123 **124** **125** **126**

Scheme 32: Catalysts Commonly used for Olefin Metathesis

While conjugated systems have been shown to be poor cross-metathesis substrates due to the electron deficient nature of the conjugated system and poor regioselectivity of the catalyst,[95, 96] previous work done in our group done by Branko Mitasev[97] showed that reacting cross-conjugated triene **127** with 10 mol% of Grubbs 2nd generation ruthenium carbene **125** produced functionalized triene **128** in 72% yield. The thermodynamically favored *E* isomer was produced exclusively (Scheme 33). Considering this result, we pursued cross-metathesis for the functionalization of the 1,1-disubstituted alkene in triene **109**.



127 **128**

Scheme 33: Conversion of Cross-Conjugated Triene 127 to Allyl Silane 128 via Cross-metathesis[97]

Generally, 1,1-disubstituted olefins are considered to be troublesome cross-metathesis substrates. However, active catalysts such as **124**,[91-94] **125**,[98, 99] and **126**[100, 101] have been

successfully used to construct tri- and tetrasubstituted alkenes. Molecular modeling* of triene **109** has shown that allylic A(1,3) strain forces the appending 1,1-disubstituted alkene away from the cyclohexene ring, making it more accessible for coordination and subsequent reaction with the CM catalyst (Figure 5, the silyl methyl groups have been removed for clarity).

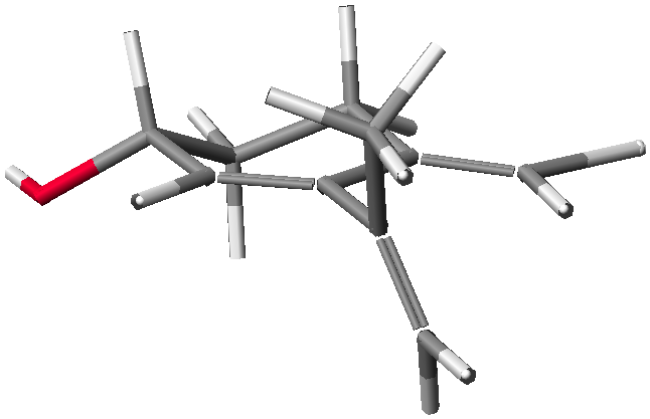
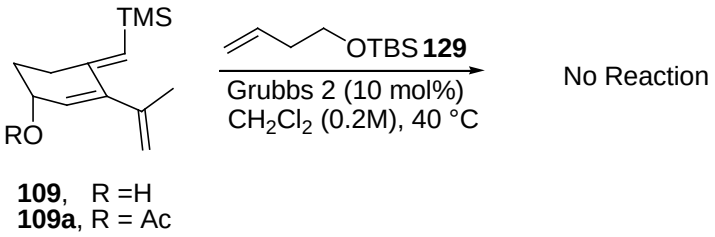


Figure 5: Minimum Energy Conformation of Triene 109

As seen in Scheme 34, reacting triene **109** with an excess of terminal alkene **129** and 10 mol% of Grubbs 2nd generation catalyst **125** in refluxing CH_2Cl_2 for 24 h only resulted in the dimerization of **129**. Similarly, reacting acetate **109a** with **129** under CM conditions resulted in the recovery of **109a** and the dimerization of **129**. The recovery of trienes **109** and **109a** suggested that the electronically deficient nature of the cross-conjugated triene system, and sterically congested environment of the 1,1-disubstituted alkene prevented the desired cross-metathesis reaction from occurring.

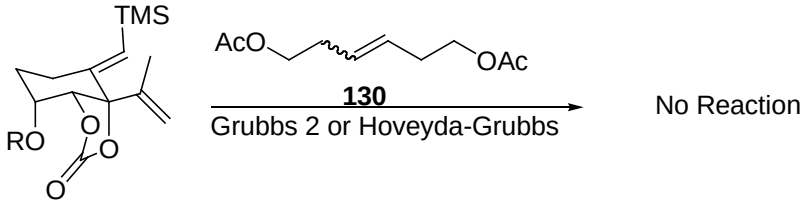
* modeling study conducted using Cache worksystem Pro Version 6.1.12.33, AM1 energy minimization



109, R =H
109a, R = Ac

Scheme 34: Attempted Cross-Metathesis Between Triene 109 and Alkene 129

The reactivity of carbonate **118** towards cross-metathesis was next investigated (Scheme 35). Based on a report[102] that the dimer is a better cross-metathesis substrate than the respective monomer, we employed homodimer **130** as the cross-metathesis partner in the CM reactions. When carbonate **118** was reacted with excess dimer **130** and 5 mol% of ruthenium carbene **125** in refluxing CH_2Cl_2, no reaction was observed and **118** was recovered in 38% yield. Reacting the analogous acetate with excess **130** and 10 mol% of **125** in refluxing CH_2Cl_2, benzene, and toluene led to the recovery of **118a** in 51%, 45%, and 39% yields, respectively. Employing the more active Hoveyda-Grubbs catalyst for the metathesis reaction between **118a** and **130** in refluxing CH_2Cl_2 and benzene again resulted in a 49% and 12% recovery of starting material, respectively.

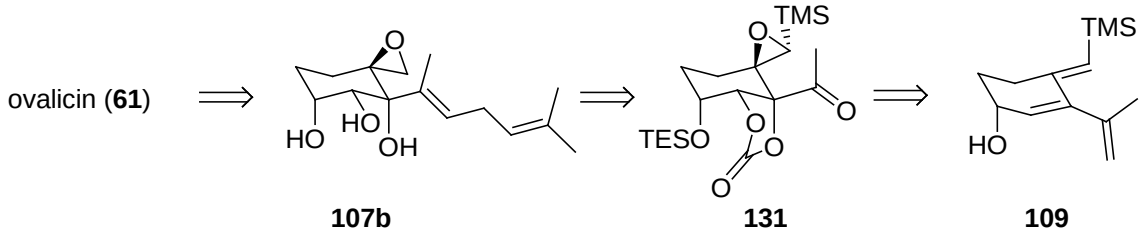


118, R = H
118a, R = Ac

Scheme 35: Attempted Metathesis Reaction Between Carbonate Derivatives and Alkene 130

1.9 REVISED RETROSYNTHETIC ANALYSIS: INSTALLATION OF THE SIDE CHAIN OF OVALICIN THOUGH AN OLEFINATION REACTION

The recalcitrance of the 1,1-disubstituted alkene of **109**, **109a**, **118**, and **118a** to participate in cross-metathesis reactions forced a re-evaluation of the synthetic plan to include methyl ketone **131** in the retrosynthetic analysis of ovalicin (Scheme 36). For example, the skipped diene side chain of advanced intermediate **107b** will be constructed from the ketone moiety of **131** through an olefination reaction. In turn, the ketone group in **131** will be constructed from the 1,1-disubstituted alkene of cross-conjugated triene **109** via a dihydroxylation and oxidative cleavage reaction sequence. Triene **109** can be easily assembled from allene-yne **110** via an allenic carbocyclization reaction.



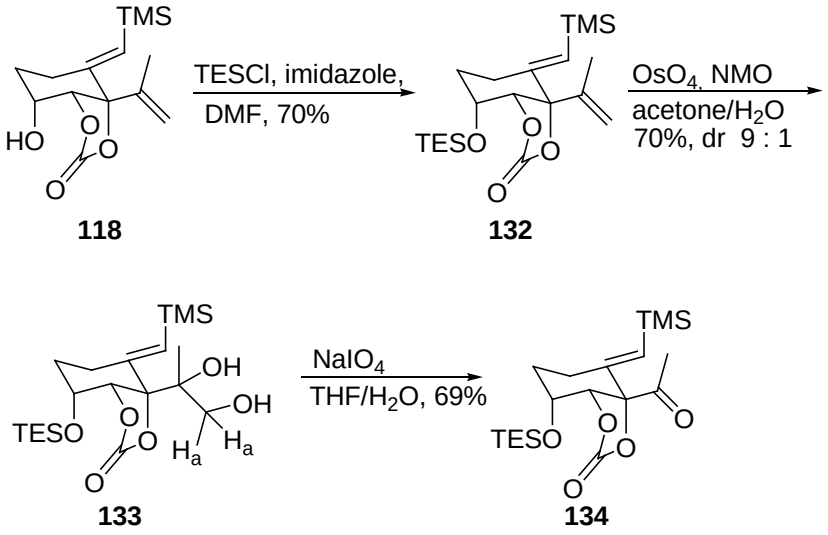
Scheme 36: Revised Retrosynthetic Analysis of Ovalicin from Ketone 131

1.9.1 Synthesis of Epoxy Ketone 131: Construction of the Oxygenated Carbocyclic Framework of Ovalicin

As seen in Scheme 37, carbonate **118** was first converted into silyl ether **132** in 70% yield with TESCl and imidazole. The TES protecting group was chosen as it will allow us to intersect Bath's synthesis[70] of ovalicin. The formation of silyl ether **132** is evidenced by the molecular ion peak $[M+Na]^+$ *m*/*z* 419 in the high resolution mass spectrum.

Reacting diene **132** with OsO_4 and NMO resulted in the selective dihydroxylation of the appending alkene to give diol **133** in 70% yield (Scheme 37). The ^1H NMR shows an AB quartet corresponding to H_a at resonances 3.75 ppm and 3.41 ppm (J = 11.9 Hz) for the major diastereomer and at resonances 3.97 ppm and 3.46 ppm (J = 11.4 Hz) for the minor diastereomer. Based upon integration of the resonances at 3.75 ppm and 3.97 ppm, diol **133** was produced as a 9:1 diastereomeric mixture.

Oxidative cleavage of the diol moiety in **133** with $NaIO_4$ in a 1:1 mixture of THF:H_2O produced the corresponding methyl ketone **134** in 69% yield (Scheme 37). The IR spectrum of **134** has the absorbance at 1720 cm^{-1} that is typically observed for the carbonyl stretch of ketones.[81]

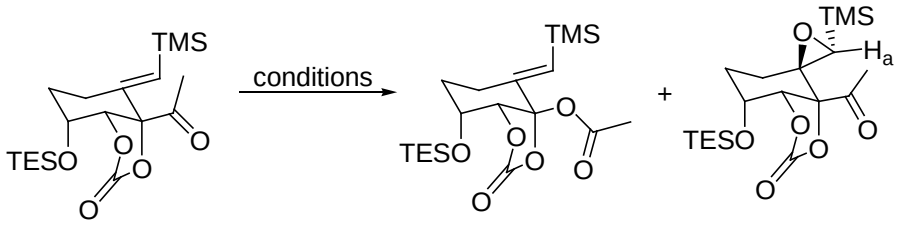


Scheme 37: Formation of Ketone 134 from Carbonate 118

Epoxidation protocols for the installation of the spiroepoxide in ovalicin was investigated. Reacting methyl ketone **134** with *m*-CPBA in the presence of Na_2HPO_4 resulted in the exclusive formation of Baeyer-Villiger product **135** in 62% yield as a single diastereomer (entry 1, Table 5). Similarly, the reaction of **134** with magnesium bis(monoperoxyphthalate) hexahydrate (MMPP) gave ketal **135** in 69% yield (entry 2). Performing the reaction with

DMDO gave no reaction and **134** was recovered in 35% yield (entry 3). Reacting **134** with only *m*-CPBA produced the desired spiroepoxide **131** in 54% yield as a single diastereomer (entry 4). Warming the reaction temperature from 25 °C to 40 °C increased the yield of spiroepoxide **131** to 73% (entry 5). The epoxidation reaction likely occurred from less sterically hindered top face of vinyl silane **145**, opposite of silyl ether and carbonate groups, to yield **131** with the stereochemistry shown.

Table 5: Formation of Ketal 135 and Epoxide 131 from Ketone 134



134 **135** **131**

Entry	Reagent	Temperature (° C)	Yield
1	*m*-CPBA, Na_2HPO_4	25	62% of **135**
2	MMPP	25	69% of **135**
3	DMDO	0 to 25	no reaction
4	*m*-CPBA	25	53% of **131**
5	*m*-CPBA	40	73% of **131**

The formation of ketal **135** is supported by the absorbance at 1749 cm^{-1} in the IR spectrum and the ester carbonyl resonance at 169.3 ppm in the ^{13}C NMR.[81] Alternatively, the ketone moiety of spiroepoxide **131** is evidenced by the absorbance at 1723 cm^{-1} in the IR and by a resonance at 204.5 ppm in the ^{13}C NMR. The epoxide group of **131** is confirmed by the resonance at 2.76 ppm (s, 1H) in ^{1}H NMR corresponding to H_a.[81]

The selective formation of ketal **135** from ketone **134** is attributed to the nucleophilic peracid anion of *m*-CPBA/Na_2HPO_4 and MMPP, which preferentially reacts with the electrophilic ketone moiety of **134**. Reacting **134** with only *m*-CPBA, however, promotes

nucleophilic addition of the vinyl silane to the electrophilic epoxidizing agent to afford spiroepoxide **131**.

1.9.2 Olefination of Methyl Ketone 131: Installation of the Masked Skipped Diene Side of Ovalicin

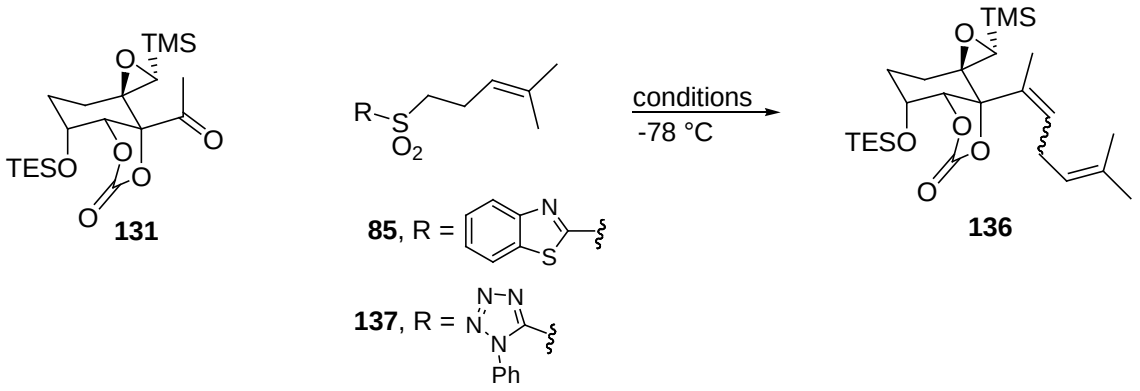
With functionalized epoxy methyl ketone **131** in hand, a modified Julia olefination[103] reaction with benzothiazolyl (BT) sulfone **85**[65] was examined for the installation of the skipped diene side chain (Table 6). Sulfone **85** has been successfully employed by Mootoo for the installation of the side chain in fumagillol.[65]

Reacting ketone **131** and BT-sulfone **85** with LiHMDS in THF gave trisubstituted alkene **136** in 43% yield as a 2:98 mixture of *E*:*Z* isomers (entry 1, Table 6). Employing KHMDS as the base produced only the *Z*-isomer of **136** in 27% yield and was contaminated with impurities that were inseparable by column chromatography (entry 2).

Changing the solvent from THF to DME still mostly produced the *Z*-isomer of **136** in 44% yield (entry 3, Table 6).[104] Employing KHMDS as the base resulted in *Z*-**136** in 17% yield; using NaHMDS gave *E*/*Z*-**136** in 48% yield (*E*:*Z* = 4:96) (entries 4 and 5).

Because 1-phenyl-1*H*-tetrazol-5-yl (PT) sulfones typically yield functionalized alkenes in higher *E*:*Z* ratios than their BT-sulfone counterparts, BT-sulfone **85** was replaced with the analogous PT-sulfone **137**.[104] However, reacting PT-sulfone **137** and ketone **131** with LiHMDS in THF produced **136** in an *E*:*Z* ratio of 32:68 in only 5% yield (enrty 6, Table 6).

Table 6: Formation of Functionalized Alkene 136



Entry	Solvent	Base	Sulfone	*E* : *Z* ratio[a]	Yield
1	THF	LiHMDS	**85**	2 : 98	43%
2[b]	THF	KHMDS	**85**	0 : 100	27%, 41% brsm
3	DME	LiHMDS	**85**	5 : 95	44%
4[b]	DME	KHMDS	**85**	0 : 100	17%, 24% brsm
5	DME	NaHMDS	**85**	4 : 96	48%
6	THF	LiHMDS	**137**	32 : 68	5%

[a]Product ratios were determined by integration of alkene protons in the ^{1}H NMR. [b] Product obtained contained inseparable byproducts

The formation of functionalized alkene *Z*-**136** is supported by the ^{1}H NMR (Figure 6). For example, the resonance at 5.44 ppm (tq, J = 7.5, 1.5 Hz) corresponds to the alkenyl proton H_a, and the resonance at 5.05 ppm (tt, J = 7.0, 1.5 Hz) corresponds to alkenyl proton H_b. The proton H_c (d, J = 3.5 Hz) correlates to the resonance at 4.72 ppm.

The *Z*-geometry of the trisubstituted alkene in *Z*-**136** was determined by nOe analysis. Irradiation of the resonance corresponding to appending vinyl methyl group at 1.76 ppm resulted in a 9% enhancement of the resonance corresponding to H_a.

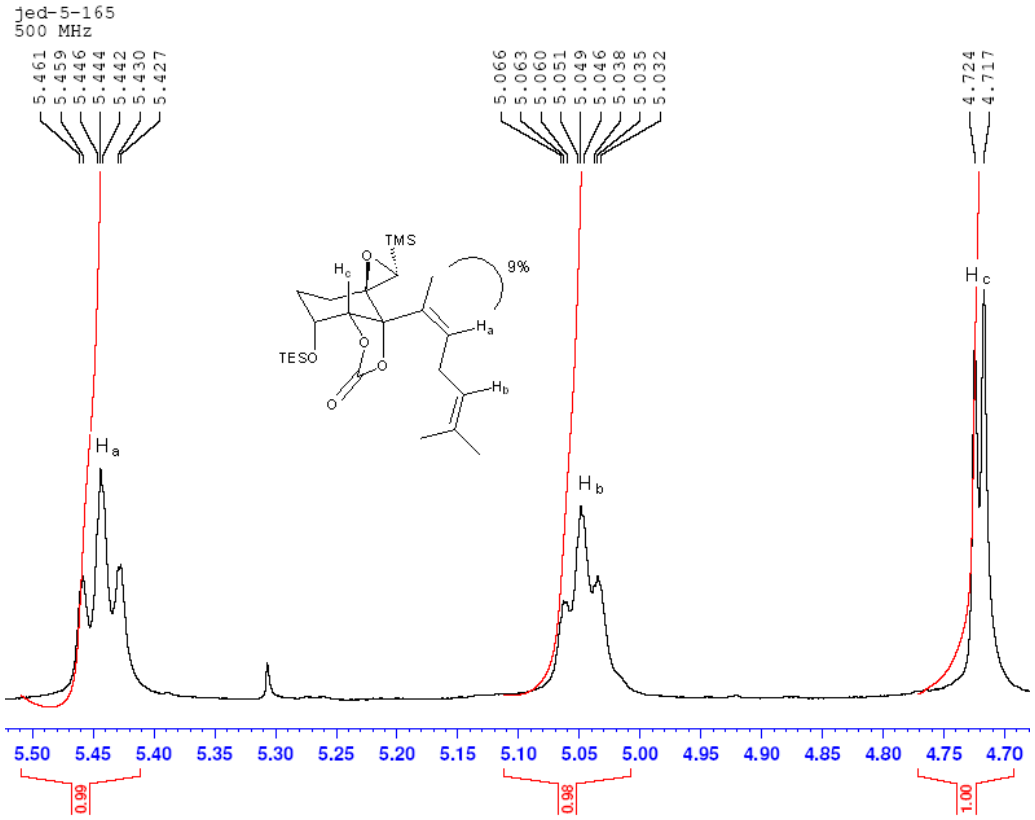
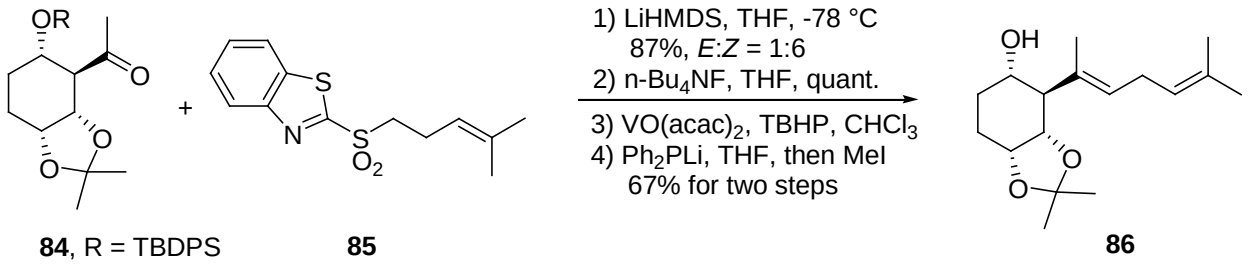


Figure 6: ^{1}H NMR of Skipped Diene 136 ($CDCl_3$, rt, 500 MHz)

Benzothiazolyl sulfones have been used to construct trisubstituted alkenes in high *E*:*Z* selectivites.[105, 106] However, Mootoo and coworkers[65] also largely obtained the *Z*-alkene from the olefination reaction between BT-sulfone **85** and the structurally similar methyl ketone **84** (Scheme 38).

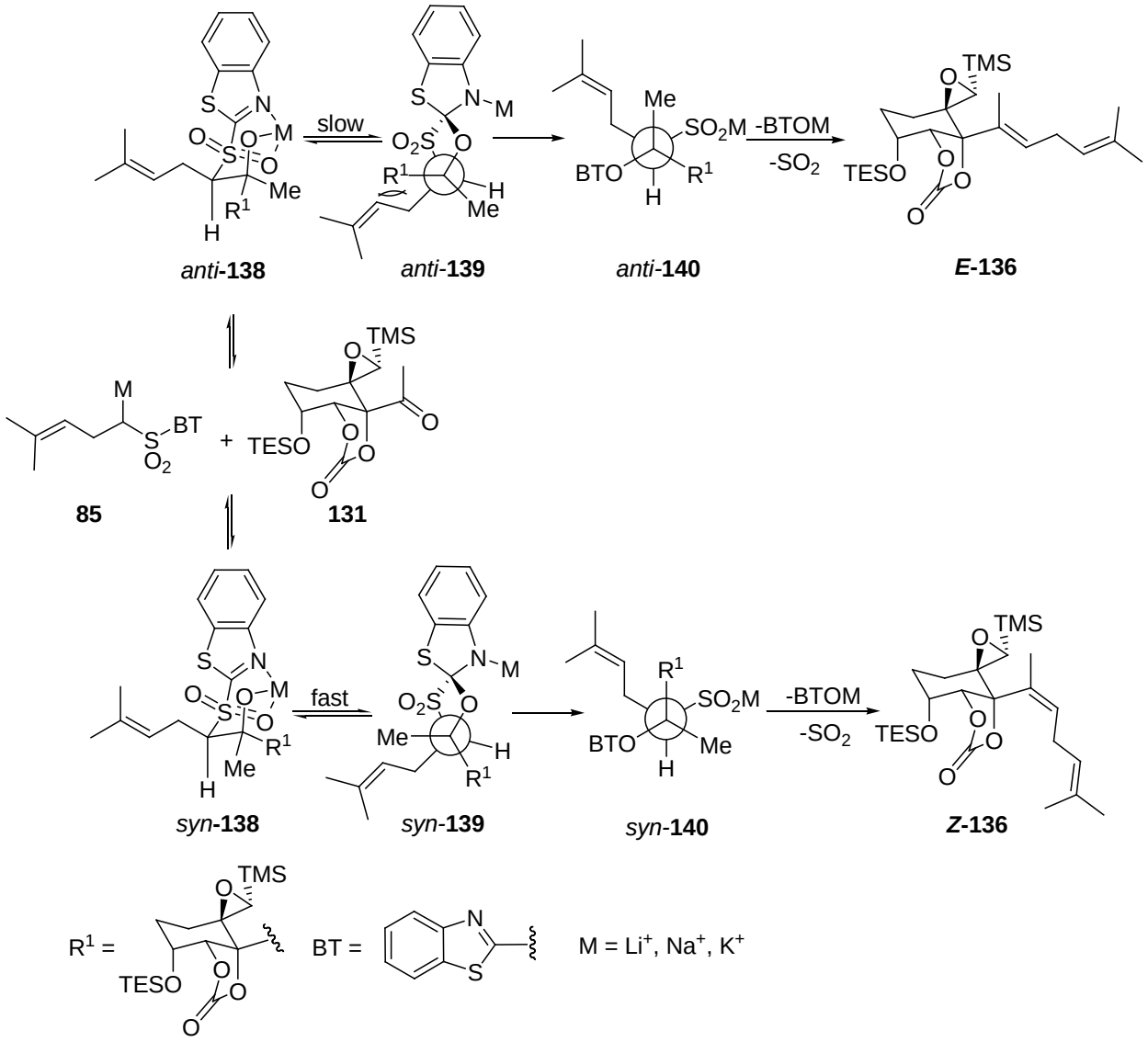


84, R = TBDPS **85** **86**

Scheme 38: Mootoo's Formal Synthesis of Fumagillol from Ketone 84 and BT-Sulfone 85

A reaction mechanism proposed by Julia and coworkers accounts for the predominate formation of ***Z*-136** from ketone **131** and BT-sulfone **85** (Scheme 39).[107, 108] First, the metallated

sulfone **85** undergoes a reversible nucleophilc addition to ketone **131** giving *syn*- and *anti*-β-alkoxysulfone diastereomers *syn*-**138** and *anti*-**138**. In the preferred chair conformation shown, the cation (Li^+, K^+, or Na^+) is chelated by the neighboring heterocyclic nitrogen atom and by one of the sulfone oxygen atoms. Subsequent nucleophilic addition of the alkoxide moiety onto the imine-like functionality of the benzothiazole leads to spirocyclic amides *syn*-**139** and *anti*-**139**, which suffer from steric strain. However, intermediate *anti*-**139** suffers from a more severe eclipsed interaction than *syn*-**139** due to the *gauche* arrangement of the large cyclohexyl moiety (R^1) and neighboring alkyl chain. This unfavorable interaction increases the energy barrier of the succeeding Smiles rearrangement and suppresses the formation of ***E*-136**. Spirocycle *syn*-**139**, on the other hand, is able to undergo a facile Smiles rearrangement/elimination reaction that results in the preferential formation of ***Z*-136**.

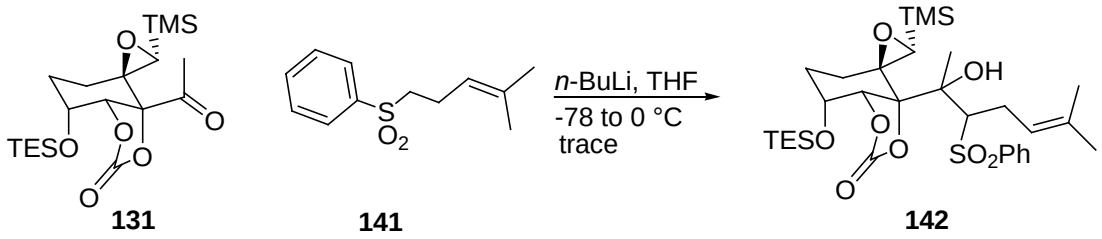


Scheme 39: Explanation for the Predominate Formation of *Z*-136 from Ketone 131 and Sulfone 85[107, 108]

1.9.3 Investigation of the Julia and Wittig Olefination Reactions for the Installation of the Side Chain in Ovalicin

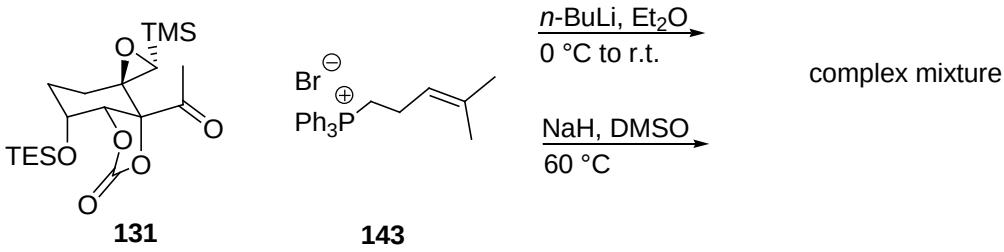
The Julia olefination reaction was explored for the construction of the side chain in ovalicin because of the high *E*-selectivity observed for the reductive elimination of the β-hydroxy sulfone products (Scheme 40).[109] However, reacting methyl ketone **131** with the

lithium anion of 1-(4-methylpent-3-enylsulfonyl)benzene **141** in THF resulted in a trace amount of the desired β-hydroxy sulfone **142**, and the recovery of **131** (29%).



Scheme 40: Reaction of Ketone 131 with Phenyl Sulfone 141

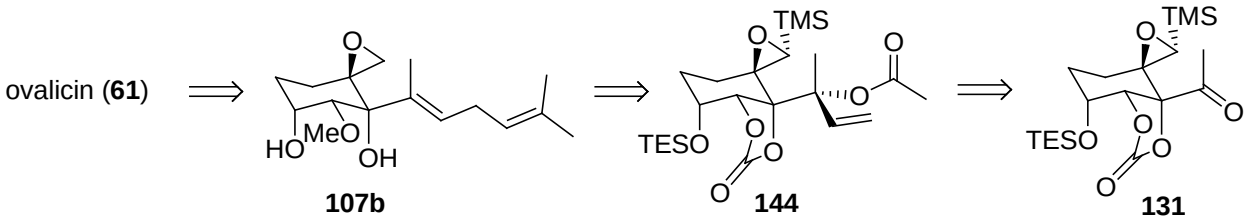
The Wittig olefination was also investigated for the installation of the side chain, because typically the reaction of sterically hindered ketones with 4-methyl-3-pentyltriphenylphosphonium bromide (**143**) produces alkene products with *E*-geometry.[110-112] However, reacting ketone **131** with the lithium anion of **143** at 0 to 25 °C resulted in a complex mixture of compounds that did not contain *E*-**136** by ^{1}H NMR (Scheme 41).[111] Similarly, performing the reaction at 60 °C in DMSO resulted in a mixture of compounds that did not contain the desired alkene.[112] The complex mixture obtained from the reaction of ketone **131** with ylide **143** could be due to the presence of the electrophilic epoxy silane and carbonate moieties that are adjacent to the appending methyl ketone.



Scheme 41: Reaction of Ketone 131 with 4-Methyl-3-pentyltriphenylphosphonium Bromide

1.10 THIRD GENERATION APPROACH TO OVALICIN: INSTALLATION OF THE SIDE CHAIN OF OVALICIN VIA A [3,3]-SIGMATROPIC REARRANGEMENT

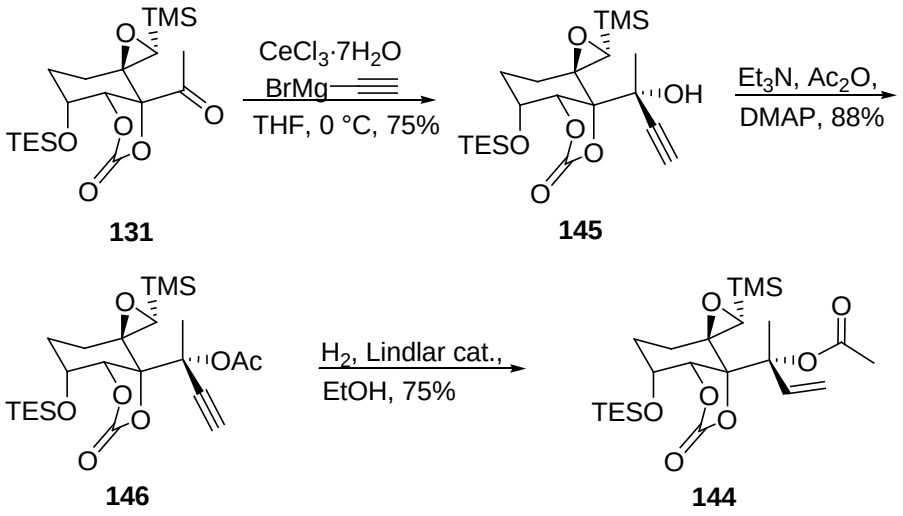
It is envisioned that the construction of the appending *E*-alkene of skipped diene **107b** can be accomplished through via a Claisen rearrangement reaction of allylic acetate **144** (Scheme 42). Allylic acetate **144** will be formed from ketone **131** through a Grignard addition and esterification reaction.



Scheme 42: Retrosynthetic Analysis of Ovalicin from Allylic Acetate 144

1.10.1 Synthesis of and Claisen Rearrangement of Allylic Acetate 144

Nucleophilic addition of ethynylmagnesium bromide to the ketone moiety of **131** in the presence of cerium (III) chloride gave propargyl alcohol **145** in 75% yield as a single diastereomer (Scheme 43).[113] It is presumed that the nucleophilic addition occurred from the less sterically hindered *Re* face of ketone **131** to avoid unfavorable steric interactions with the neighboring epoxy silane. The formation of propargyl alcohol **145** is confirmed by the IR spectrum, which shows absorbances at 3402 cm^{-1} and 2114 cm^{-1}, supporting the presence of the alcohol and alkyne functionalities, respectively. Interestingly, performing the analogous reaction with vinylmagnesium bromide and cerium (III) chloride resulted in decomposition of **131**.



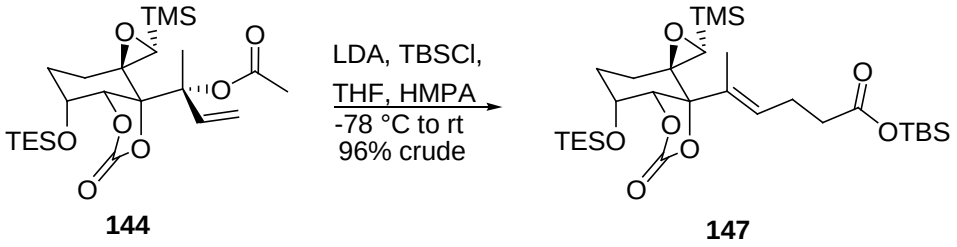
Scheme 43: Formation of Allylic Acetate 144 from Ketone 131

Acetylation of the newly generated tertiary alcohol in **145** with acetic anhydride and DMAP in Et_3N produced propargyl acetate **146** in 88% yield (Scheme 43).[114] The IR spectrum of propargyl acetate **146** has the characteristic absorbances at 1814 cm^{-1} and 1761 cm^{-1} for the carbonyl stretch of the carbonate and ester, respectively.[81]

Hydrogenation of propargyl acetate **146** with Lindlar's catalyst in ethanol produced allylic acetate **144** in 75% yield (Scheme 43). The formation of **144** is evidenced by the ^1H NMR, which shows resonances at 5.95 ppm (dd, J = 17.6, 11.1 Hz), 5.32 ppm (d, J = 11.1 Hz), and 5.21 ppm (d, J = 17.6 Hz) corresponding to the vinyl group.

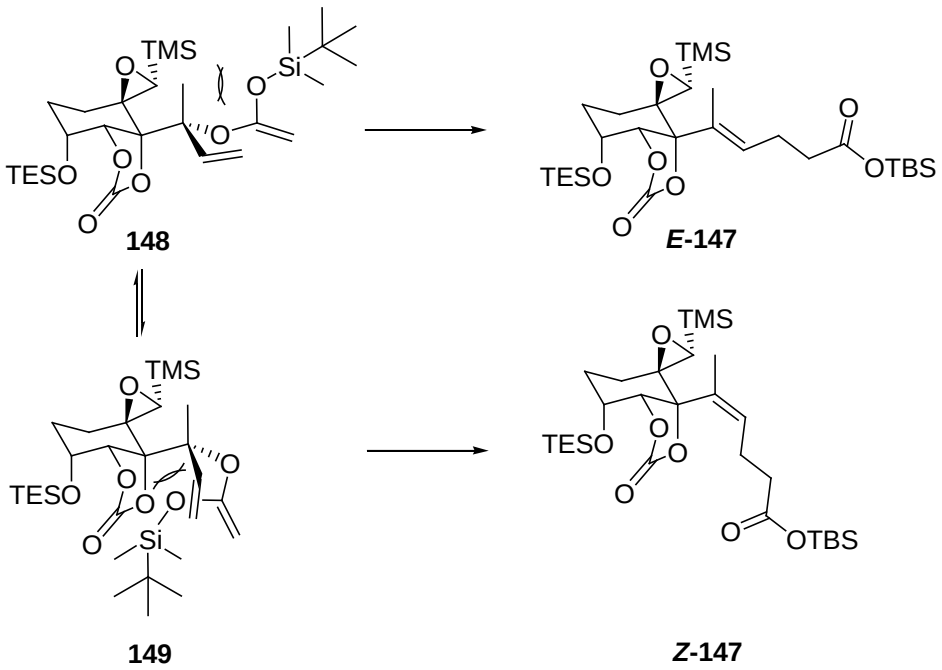
With allylic acetate **144** in hand, an Ireland-Claisen rearrangement reaction was employed for the construction of the side chain of ovalicin.[115] Reacting **144** with LDA and TBSCl in the presence of HMPA resulted in the formation silyl ester **147** as a single isomer in 96% crude yield (Scheme 44). A resonance at 5.76-5.68 ppm (m) in the ^1H NMR corresponds to the trisubstituted alkene proton, and resonances at 0.95 ppm (s, 9H), 0.32 ppm (s, 3H) and 0.31 ppm (s, 3H) correspond to the *tert*-butyl and dimethyl groups of the TBS ester. Furthermore, the

^{13}C NMR has resonances at 172.7 ppm, 131.1 ppm, and 125.8 ppm that support the presence of the ester and alkene functionalities.



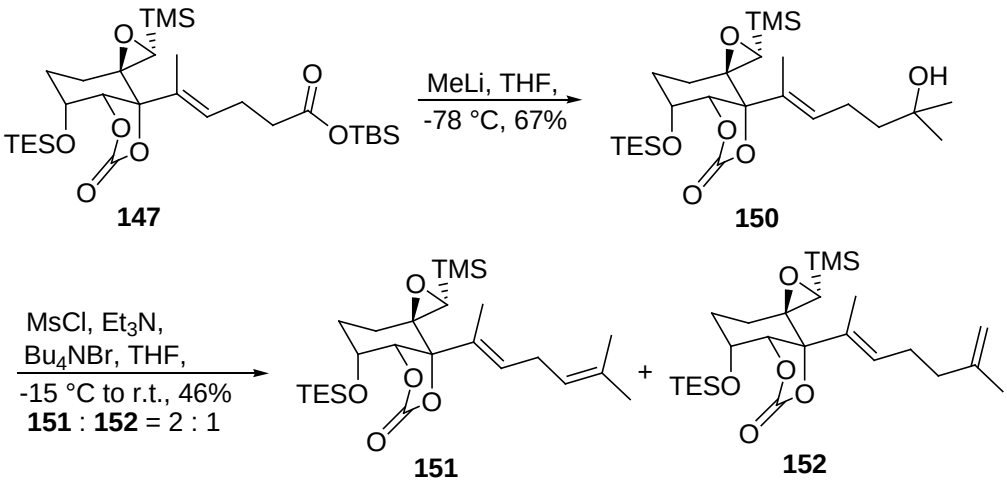
Scheme 44: Formation of Silyl Ester 147 from Allylic Acetate 144

It is presumed that *E* isomer of **147** was selectively produced from allylic acetate **144**, as it is well established that the Claisen rearrangement of acyclic substrates proceeds through chair-like transition-states **148** or **149** (Scheme 45).[116] The transition state leading to the Z-isomer (**149**), however, suffers from a severe 1,3-diaxial strain induced by the large cyclohexyl ring and the silyl ketene acetal. On the other hand, transition state **148** is able to undergo a facile rearrangement reaction that results in the selective formation of *E*-**147**.



Scheme 45: Explanation for the Selective Formation of *E*-147

In continuing with the synthesis of ovalicin, the crude silyl ester **147** was reacted with methyllithium at low temperature to give tertiary alcohol **150** in 67% yield (Scheme 46). Interestingly, adding MeMgBr to silyl ester **147** resulted in no reaction and a 73% yield of **147** was recovered. The IR spectrum of **150** shows the typical alcohol absorbance at 3397 cm^{-1}.



Scheme 46: Formation of Skipped Dienes 151/ 152 from Silyl Ester 147

The newly generated tertiary alcohol is then converted into the corresponding mesylate with triethylamine and methanesulfonyl chloride (MsCl) at –15 °C (Scheme 46).[117] Addition of Bu_4NBr resulted in the formation of elimination products **151** and **152** in a 46% combined yield.[118, 119] The formation of dienes **151** and **152** is evidenced by the alkene region in the ^1H NMR. A resonance at 5.07 ppm (tt, J = 7.2, 1.5 Hz) corresponds to the alkenyl proton H_b of **151**, and resonances at 4.74-4.71 ppm and 4.67-4.64 ppm correspond to the 1,1-disubstituted alkene protons H_c of **152** (Figure 7). Based upon the integrations of the resonances at 5.07 ppm and 4.74-4.71 ppm, **151** and **152** were produced in a 2:1 isomeric ratio. The isomeric ratio obtained for **151** and **152** is similar to the 3:1 isomeric ratio obtained by Corey and Snider for the dehydration of a late-stage intermediate employed in their synthesis of fumagillol.[58]

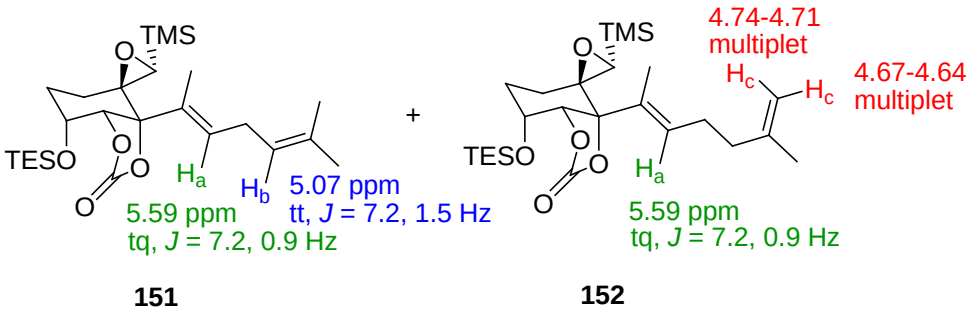
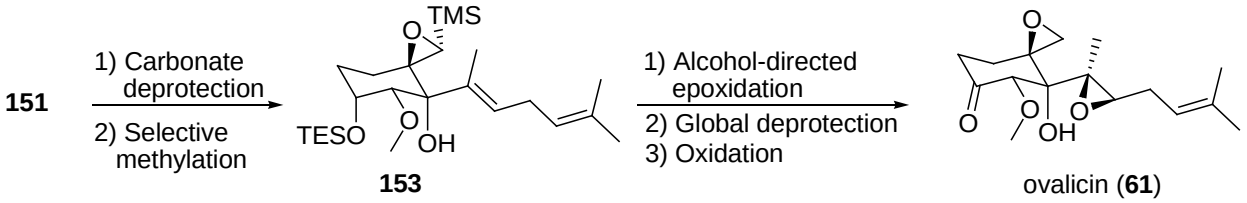


Figure 7: Assignment of H_a, H_b, and H_c in the ^{1}H NMR Spectrum of 151 and 152 (300 MHz, C_6D_6)

1.10.2 Projected End-game of Ovalicin from Diene 151

It is anticipated that functionalized diene **151** can be converted into ovalicin through the five-step reaction sequence shown in Scheme 47. First, deprotection of the carbonate group and selective methylation of the secondary hydroxyl group with *t*BuONa, MeI, and 15-crown-5[62] in THF should produce alcohol **153**. The side chain epoxide of **61** will be installed though a vanadium-catalyzed alcohol-directed epoxidation reaction. Next, global deprotection of the silyl protecting groups and oxidation of the secondary alcohol to the corresponding ketone will afford ovalicin. However, the synthesis of ovalicin from diene **151** was not pursued due to the lengthy nine step-reaction sequence required for the installation of the *E*-alkene side chain.



Scheme 47: Projected Synthesis of Ovalicin from Diene 151

1.10.3 Summary and Conclusions for the Synthesis and Functionalization of Cross-conjugated Triene 109

In summary, we have developed a facile route to cross-conjugated triene **109** in three steps from known alkyne **111** and aldehyde **112** that features a high yielding Rh(I)-catalyzed allenic carbocyclization reaction. An enantioselective synthetic strategy to (*R*)-**109** from **111** and **112** has also been developed utilizing an enantioselective alkynylation reaction, which could prove useful for the asymmetric syntheses of (–)-fumagillol and (–)-ovalicin.

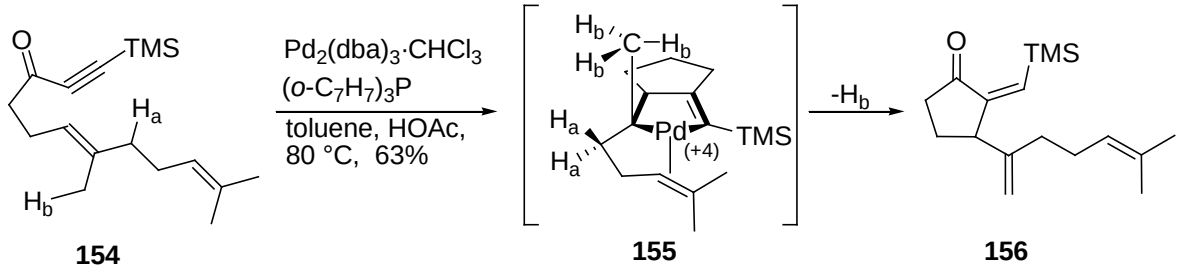
We have demonstrated that the double bonds of cross-conjugated triene **109** can be selectively functionalized via epoxidation and dihydroxylation protocol. More specifically, a bis-allylic epoxide (**115**) was synthesized from a cross-conjugated triene precursor (**109**) in high yield using an alcohol-directed epoxidation reaction. This pivotal intermediate was then used to construct the oxygenated framework of fumagillol and ovalicin through diverging palladium-catalyzed transformations.

A modified Julia olefination reaction has been employed to transform ketone **131** into the Z-isomer of the masked skipped diene side chain in ovalicin. It is envisioned that application of Vedejs'[68] two-step isomerization procedure to *Z*-**136** will yield *E*-**136**, which could serve as a useful intermediate in the synthesis of ovalicin. Alternately, an Ireland-Claisen rearrangement can be used to install the skipped diene side chain of ovalicin with the required *E*-geometry.

1.11 THE CARBOCYCLIZATION REACTION OF ALLENE-YNES: INVESTIGATING THE CONSTITUTIONAL SITE SELECTIVITY OF DIFFERENTIALLY FUNCTIONALIZED 1,1-DISUBSTITUTED ALLENES AND ITS APPLICATION TO OVALICIN AND FUMAGILLOL

1.11.1 Trost's Constitutional Site Selectivity Study of 1,6-Enynes Appended to an Isobutylene Group

Trost has shown that the palladium-catalyzed carbocyclization reaction of 1,6-enynes possessing an isobutylene group selectively yields cyclic 1,4-dienes with an appending 1,1-disubstituted alkene side chain.[12, 120-125] For example, reacting alkynone **154** with $Pd_2(dba)_3{\cdot}CHCl_3$, tri-*o*-tolylphosphine, and acetic acid in toluene at 80 °C produces only carbocycle **156** in 63% yield (Scheme 48).[124] The selective formation of **155** is attributed to coordination of the remote alkene in enyne **154** to the palladium catalyst. This pseudo-cycle prevents *syn* periplanar alignment of the Pd-C-C-H_a system during the β-hydride elimination step of the carbocyclization, resulting in the exclusive formation of **156**. Similar observations have been reported by Trost and coworkers during their ruthenium-catalyzed carbocyclization studies of 1,6-enynes tethered to an isobutylene moiety.[7, 8]



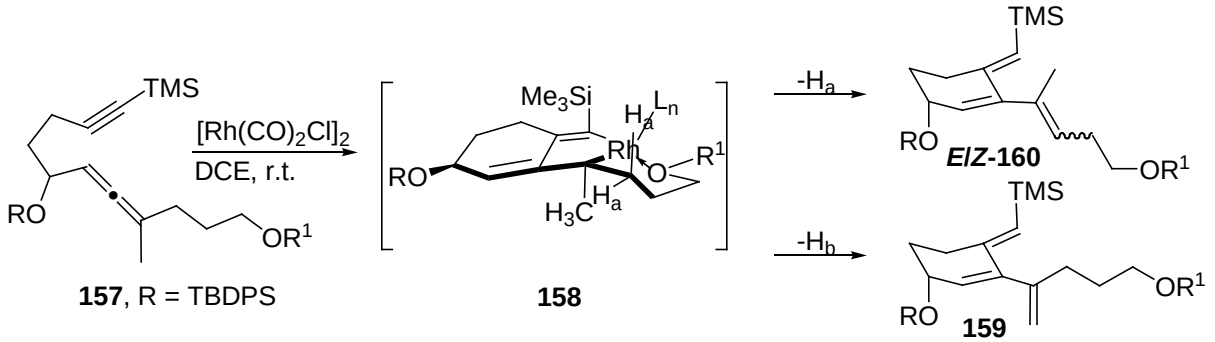
154 **155** **156**

Scheme 48: Palladium-Catalyzed Carbocyclization Reaction of 1,6-Enyne 154[124]

1.11.2 Previous Studies Regarding the Constitutional Site Selectivity in the Allenic Carbocyclization Reaction

With an eye towards the synthesis of ovalicin, the constitutional site selectivity of the β-hydride elimination step in the allenic carbocyclization reaction was investigated, i.e. the formation of isomeric products differing in line formulae.[126] More specifically, the selective participation of the methylene position over the methyl position in the elimination process was examined. Previous studies conducted by Jamie McCabe showed that appending a coordinating functionality such as a hydroxyl propyl group to the distal double bond of the allene resulted in a mixture of trienes **159** and *E*/*Z*-**160** in a 40:60 isomeric ratio (Table 7, entry 1).[77] Reacting the analogous primary silyl ether (R^1 = TBS) with a catalytic amount of $[Rh(CO)_2Cl]_2$ produced cross-conjugated trienes **159** and *E*/*Z*-**160** in a 15:85 isomeric ratio. The increased formation of triene **159** when R^1 = H can be explained by coordination of the free hydroxyl group to the rhodium center of metallocycle **158**, producing a rhodacycle that geometrically prohibits β-hydride elimination of the β-methylene hydrogen atoms H_a.

Table 7: Carbocyclization Reaction of Allene-yne 157[77]



157, R = TBDPS **158**

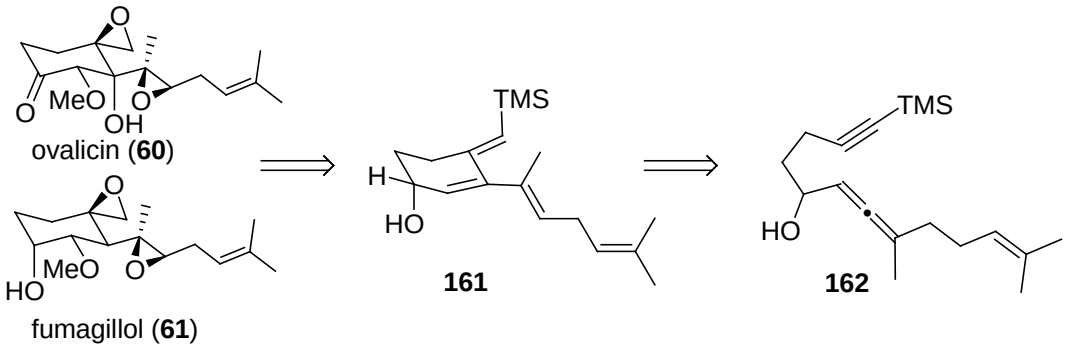
Entry	R^1	Ratio of 159 : *E*/*Z*160[a]	E : Z ratio[a]	Yield (%)[b]
1	H	40 : 60	1.5 : 1	50
2	TBS	15 : 85	1 : 1	55

[a]Product ratios were determined by integration of olefin peaks in the ^{1}H NMR. [b]Combined yield of **159** and *E*/*Z*-**160**

1.11.3 Retrosynthetic Analysis of Ovalicin and Fumagillol from α-Hydroxy Allene-yne 162

The constitutional site selectivity of the allenic carbocyclization reaction was further investigated by tethering an isobutylene group to the allene moiety to determine its effect on the β-hydride elimination step. In addition, the hydroxyl containing tether was deemed to be an important control element in the pre-cyclization and post-cyclization reactions, thus it too was incorporated. Allene-yne **162** was chosen for our studies as it will allow entry into the carbocyclic framework of fumagillol (**60**) and ovalicin (**61**) in a single synthetic transformation (Scheme 49).

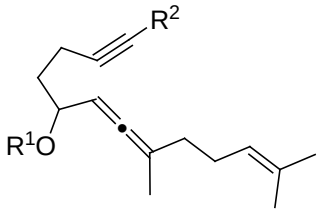
It is envisioned that reacting a catalytic amount of $[Rh(CO)_2Cl]_2$ with allene-yne **162** will produce cross-conjugated triene **161**, which possesses the entire carbocyclic skeleton of structurally related natural products fumagillol (**60**) and ovalicin (**61**). Moreover, it is anticipated that the allylic hydroxyl group of triene **161** can be used for the chemo- and stereoselective installation of epoxides and hydroxyl groups incorporated in both sesquiterpenes (Scheme 49).



Scheme 49: Retrosynthetic Analysis of Ovalicin and Fumagillol from Allene-yne 162

1.11.4 Synthesis of Allene-ynes Tethered to an Isobutylene Group

1.11.4.1 Substrate Design of α-Hydroxy Allene-ynes



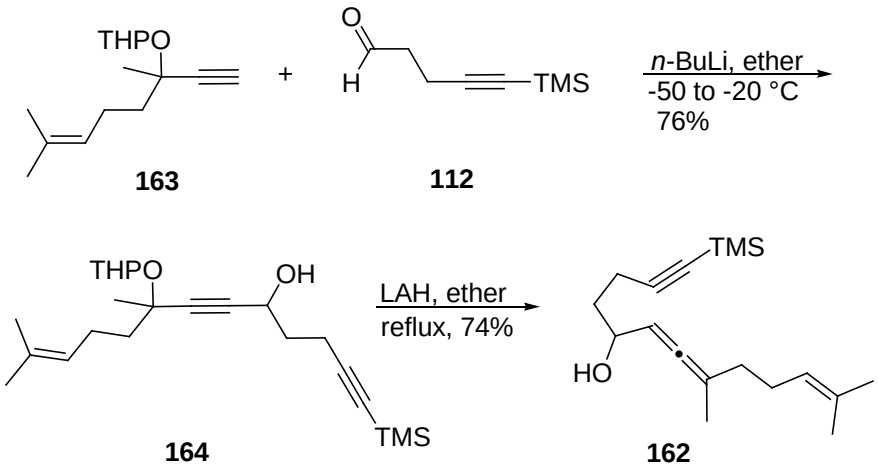
R^1 = H, TBS, Ac, Piv
R^2 = H, TMS, Ph

Figure 8: Desired Allene-yne Substrates

Design of 1,1-disubstituted allene-ynes required a tunable scaffold that would allow for substrate-controlled selectivity of the carbocyclization reaction (Figure 8). We plan to alter the allene-yne hydroxyl (R^1) and alkyne groups (R^2) to determine the effect of the substitution at these sites on the regioselectivity of the carbocyclization reaction.

Allene-yne **162** can be prepared in two steps from known propargyl tetrahydropyranyl ether **163**[127] and aldehyde **112**[79] (Scheme 50). Following Brandsma's procedure for the addition of alkynes to aldehydes, *n*-BuLi was reacted with an excess of alkyne **163** at –50 °C.[80] Addition of aldehyde **112** to the resulting lithium anion and warming the reaction to –20 °C gave propargyl alcohol **164** in 76% yield as an inseparable mixture of diastereomers by column chromatography. Integration of the two resonances at 1.49 ppm and 1.42 ppm in the ^{1}H NMR, which correspond to the diastereomeric methyl groups, indicate that **164** was produced as a 1.4:1 diastereomeric mixture.

Subjecting propargyl alcohol **164** to $LiAlH_4$ in refluxing Et_2O gave allene-yne **162** in 74% yield (Scheme 50).[82] The formation of allene-yne **162** is supported by a resonance at 5.20-5.13 ppm (m) in the ^{1}H NMR corresponding to the allene proton.

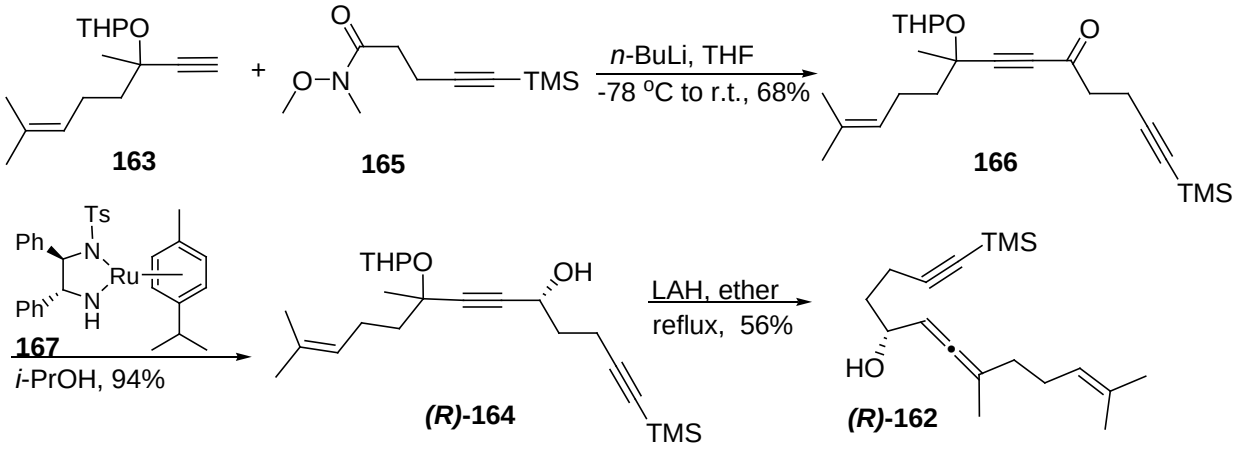


Scheme 50: Synthesis of Allene-yne 162

Allene-yne **162** has been prepared in high diastereoselectivity in three steps from terminal alkyne **163** and Weinreb amide **165** (Scheme 51). Alkynone **166** is formed in 68% yield by reacting the acetylide anion of **163** with amide **165**.[128] The formation of alkynone **166** is evidenced by IR spectrum with the absorbance at 1681 cm^{-1}.

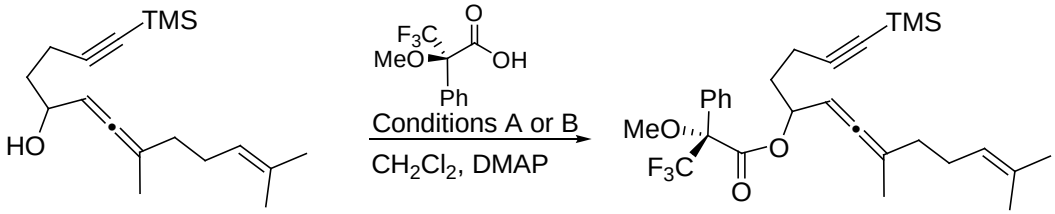
Selective reduction of the ketone moiety of **163** with Noyori's chiral ruthenium catalyst **167** gave (*R*)-**164** in 94% yield.[129, 130] The ^{1}H NMR and ^{13}C NMR of (*R*)-**164** are in agreement with the spectral data obtained for the **164**.

Reduction of propargyl alcohol (*R*)-**164** with LAH afforded allene-yne (*R*)-**162** in 56% yield (Scheme 51). The low yield obtained for (*R*)-**162** is attributed to performing the reduction reaction on small scale. For example, reacting 1.13 mmol of propargyl alcohol (*R*)-**164** with LAH gave allene-yne (*R*)-**162** in 56% yield, whereas subjecting 7.58 mmol of propargyl alcohol **164** to the same reaction conditions gave allene-yne **162** in an increased 74% yield. The ^{1}H NMR and ^{13}C NMR of the enantioenriched allene-yne (*R*)-**162** match the spectral data obtained for the racemic allene-yne **162**. The formation of the allene-yne (*R*)-**162** is exciting as it could serve as a useful intermediate for the asymmetric syntheses of (–)-fumagillol and (–)-ovalicin.



Scheme 51: Synthesis of (*R*)-162

Racemic and enantioenriched allene-ynes **162** and (*R*)-**162** were converted into the analogous Mosher esters **168** and (*R*)-**168** to determine the diastereomeric ratio of (*R*)-**162** (Scheme 52). Racemic Mosher ester **168** was produced by reacting allene-yne **162** with (*R*)-(+)-alpha-methoxy-alpha-(trifluromethyl)-phenylacetic acid, *N*,*N*'-dicyclohexylcarbodiimide (DCC), and 4-dimethylaminopyridine (DMAP) (Conditions A). Similarly, Mosher ester (*R*)-**168** was formed by reacting allene-yne (*R*)-**162** with (*R*)-(+)-alpha- methoxy-alpha-(trifluromethyl)-



162, Conditions A: DCC
(*R*)-**162**, Conditions B: EDC

168, quant. crude yield
(*R*)-**168**, quant. crude yield

Scheme 52: Formation of Mosher Esters 168 and (*R*)-168

phenylacetic acid, 1-(3-dimethylaminopropyl)-3- ethylcarbodiimide hydrochloride (EDC), and 4-dimethylaminopyridine (DMAP) (Conditions B). Employing EDC for the coupling reaction of (*R*)-**162** avoids the urea byproduct produced by DCC, which is not water soluble and is difficult to remove without employing column chromatography. The ^{19}F NMR of racemic allene-yne **168**

shows three resonances at -72.0 ppm, -72.1 ppm, and -72.2 ppm with integrations of 2F, 1F, and 1F, respectively (Figure 9). This spectral data indicates that four diastereomers of **168** are present in equal quantities. The ^{19}F NMR of (*R*)-**168** still shows three resonances at -72.0 ppm, -72.1 ppm, and -72.2 ppm, however, with integrations of 0.16F, 1F, and 1F, respectively. Based upon the integrations in the ^{19}F NMR of (*R*)-**168**, allene-yne (*R*)-**162** was produced in a 93:7 diastereomeric ratio (Scheme 51).

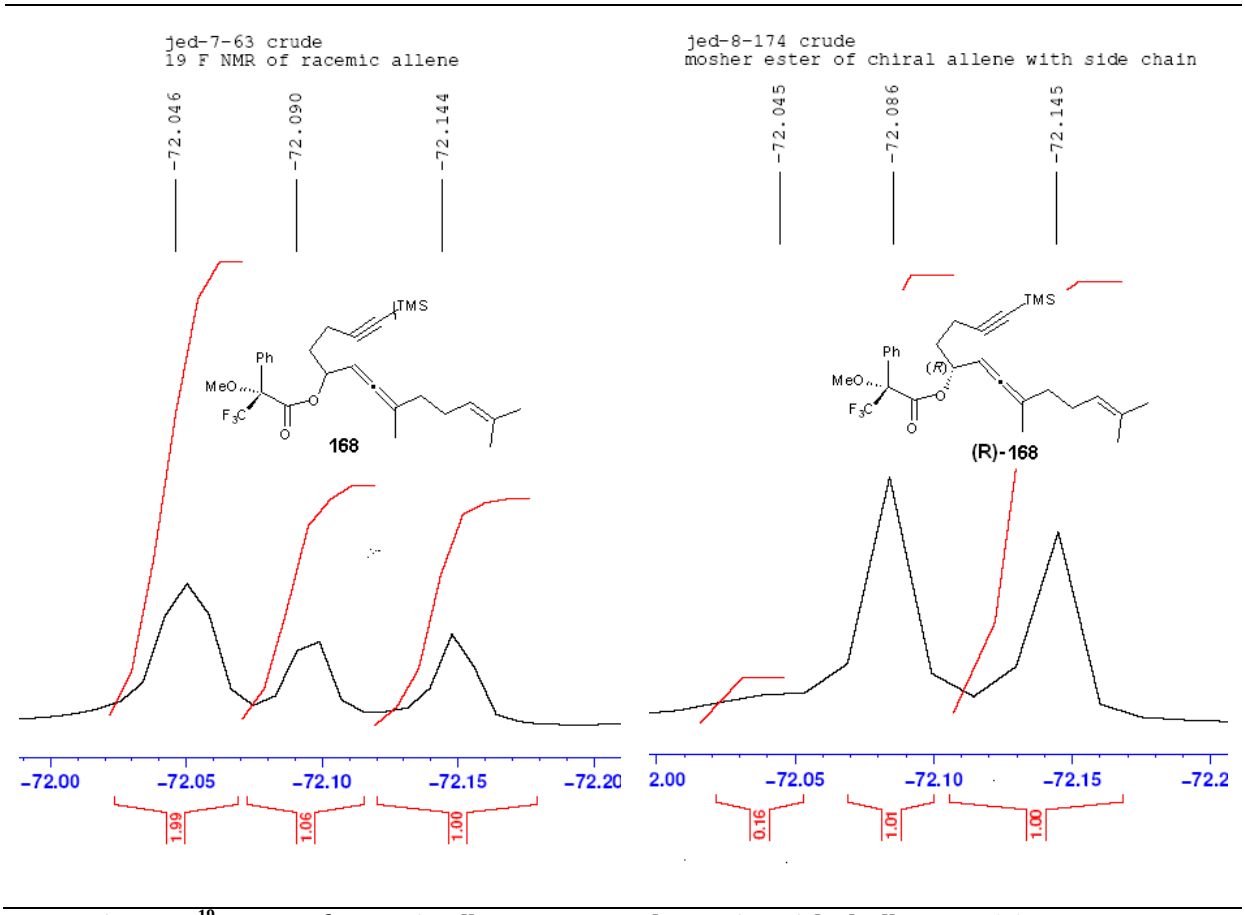
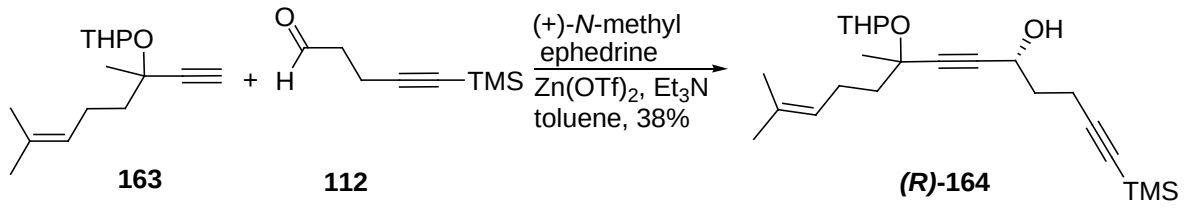


Figure 9: ^{19}F NMR of Racemic Allene-yne 168 and Enantioenriched Allene-yne (*R*)-168

Interestingly, Carreira's asymmetric alkynylation protocol produced (*R*)-**164** in only 38% yield, even when excess (+)-*N*-methylephedrine (3.1 equiv), alkyne **163** (3.1 equiv), and zinc triflate (3 equiv) were used (Scheme 53).[83] The low yield obtained from this reaction could be due to a self-condensation reaction of aldehyde **112**, which is supported by the presence of a

slightly more polar product by TLC. Aldol condensations are facile processes for aldehydes that do not possess any α- or β-substituents.[84, 130, 131] The absolute stereochemistry of (*R*)-**161** was assigned by analogy to Carreira's substrates prepared using (+)-*N*-methylephedrine.[83]

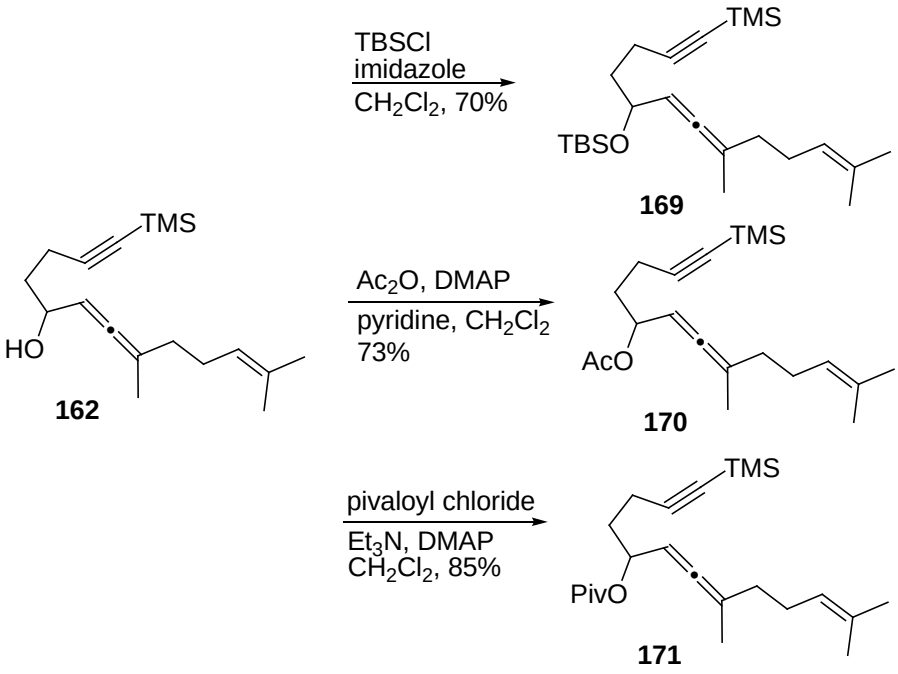


Scheme 53: Formation of (*R*)-164 via Carreira's Asymmetric Alkynylation Protocol

With the synthesis of allene-yne **162** in hand, allene-yne derivatives containing different R^1 substituents were constructed to examine the role of the hydroxyl group on the β-hydride elimination step of the carbocyclization reaction (Scheme 54). More specifically, silyl ether **169**, acetate **170**, and pivaloate ester **171** were synthesized to determine the effect of an electron donating, withdrawing, and sterically demanding functionality on the selectivity of the reaction.

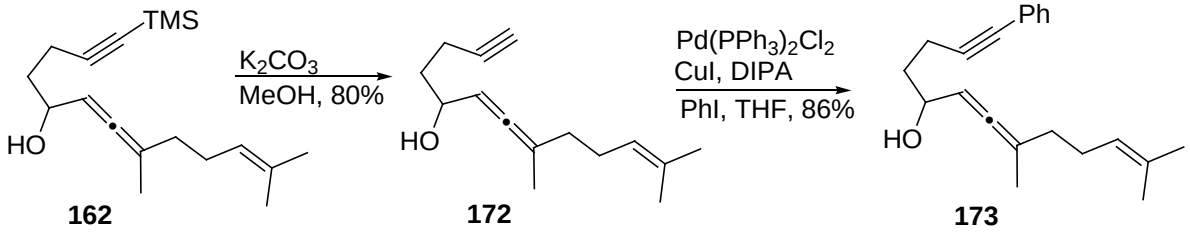
Silyl ether **169** was obtained in 70% yield by reacting **162** with TBSCl and imidazole (Scheme 54). The formation of *tert*-butyldimethyl silyl ether **169** is evidenced by the molecular ion ($M^{+\cdot}$ *m*/*z* 404) peak in the high resolution mass spectrum.

Reaction of **162** with acetic anhydride, DMAP, and pyridine gave the analogous acetate **170** in 70% yield. Similarly, pivaloate ester **171** was produced in 85% yield when alcohol **162** was reacted with pivaloyl chloride, DMAP, and triethylamine (Scheme 54). The IR spectrum of acetate **170** and pivaloate ester **171** have the corresponding absorbances at 1743 cm^{-1} and 1731 cm^{-1}, indicative of the carbonyl stretch.[81]



Scheme 54: Formation of Silyl ether 169, Acetate 170, and Pivaloate ester 171

The substitution on the alkyne terminus (R^2) was adjusted by synthesizing terminal alkyne **172** and phenyl alkyne **173** from TMS-alkyne **162** (Scheme 55). The TMS group of **162** was removed with K_2CO_3 in MeOH to give terminal alkyne **172** in 80% yield. The formation of alkyne **172** is evidenced by a resonance at 1.97 ppm (t, J = 2.7 Hz) in the ^{1}H NMR that corresponds to the terminal alkyne proton.

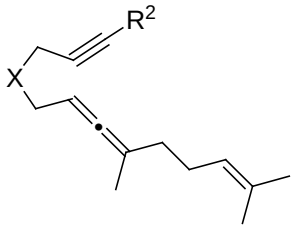


Scheme 55: Formation of Allene-ynes 172 and 173

A Sonogashira coupling reaction was then performed with $Pd(PPh_3)_2Cl_2$, CuI, diisopropylamine (DIPA), and iodobenzene to afford the analogous phenyl-alkyne **173** in 86%

yield (Scheme 55). The molecular ion peak at $M^{+\cdot}$ *m*/*z* 294 in the high resolution mass spectrum supports that **173** was obtained.

1.11.4.2 Synthesis of Malonate and Heteroatom Tethered Allene-ynes



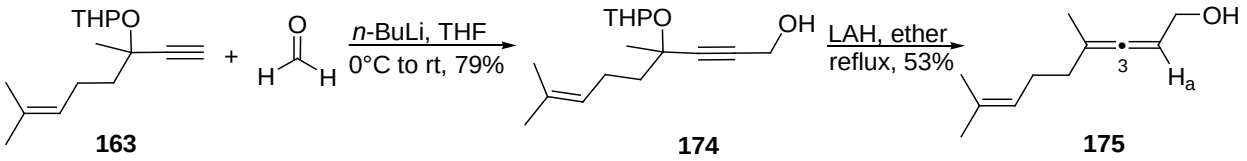
X = C(CO_2Et), NTs, O
R^2 = H, TMS, Ph, Me

Figure 10: Malonate and Heteroatom Tethered Allene-yne Derivatives

The selectivity study of the allenic carbocyclization reaction of allenes attached to an isobutylene group was expanded to include allene-ynes with different tether substituents X (Figure 10). Our goal is to use malonate, sulfonamide, and ether tethered allene-ynes to determine if modification of the allene-yne backbone will affect the β-hydride elimination step in the carbocyclization reaction

Allene-yne **175**, the synthetic precursor to malonate and heteroatom tethered allene-ynes, was constructed from propargyl tetrahydropyranyl ether **163**[127] and paraformaldehyde (Scheme 56). The alkyne terminus of **163** was first deprotonated with *n*-butyllithium at 0 °C and then reacted with paraformaldehyde. Warming the reaction to room temperature produced the desired propargyl alcohol **174** in 79% yield. Alcohol **174** was afforded as a 1.2:1 mixture of diastereomers based upon integration of the two resonances at 1.49 ppm and 1.41 ppm in the ^{1}H NMR that correspond to the diastereomeric tertiary methyl groups.

Reacting propargyl alcohol **174** with LAH in refluxing ether resulted in allene-yne **175** in 53% yield (Scheme 56).[82] A resonance at 5.29-5.21 ppm (m) in the ^{1}H NMR of **175** corresponds to H_a, and a resonance at 200.0 ppm in the ^{13}C NMR corresponds to C3.

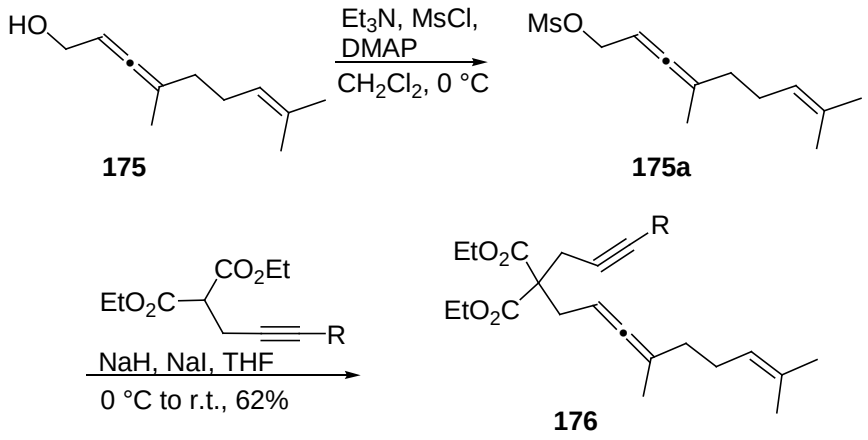


Scheme 56: Formation of Allene-yne 175

With allene-yne **175** in hand, malonate tethered allene-ynes **176**-**179** were synthesized to examine the effect of the tether on the selectivity of the carbocyclization reaction (Table 8). Malonate tethered allene-yne derivatives **176**-**179** were constructed through an alkylation reaction between α-allenyl mesylate **175a** and a variety of malonate carbanions.[132]

For example, the formation of malonate-tethered allene-yne **176** was accomplished by converting alcohol **175** into mesylate **175a** with triethylamine, DMAP, and methanesulfonyl chloride (MsCl) at 0 °C (Table 8). In a separate reaction flask, diethyl 2-(3-(trimethylsilyl)prop-2-ynyl)malonate was deprotonated with sodium hydride and the crude mesylate was then added to the resulting carbanion at 0 °C. Warming the reaction to room temperature followed by the addition of sodium iodide resulted in the formation of allene-yne **176** in 62% yield (entry 1, Table 8). The alkylation reactions illustrated in entries 2 through 4 of Table 8 were performed similarly and gave allene-ynes **177**-**179** in yields of 73-76%. The formation of malonate-tethered allene-yne **176** is evidenced by the molecular ion ($M^{+\cdot}$ *m*/*z* 418) peak in the high resolution mass spectrum and by absorbances in the IR at 2180 cm^{-1} and 1737 cm^{-1}. The spectral data obtained for allene-ynes **177** though **179** are similar to that obtained for **176**.

Table 8: Synthesis of Malonate tethered Allene-ynes 176 through 179

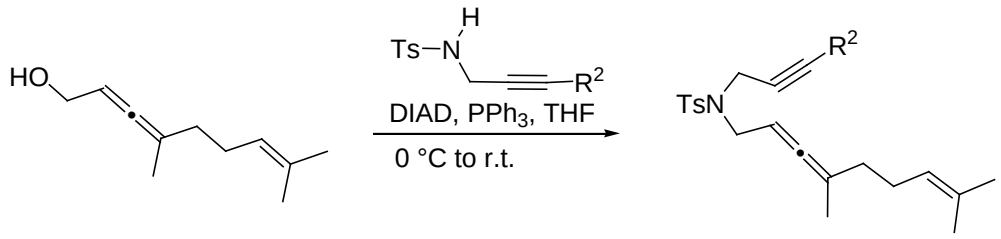


Entry	R^2	Allene-yne	Yield (%)
1	TMS	**176**	62
2	Ph	**177**	73
3	Me	**178**	76
4	H	**179**	76

Next, a nitrogen heteroatom was incorporated into the allene-yne tether by synthesizing *N*-tosylallene-ynes **181**-**183** to investigate if a coordinating functionality in the allene-yne backbone will affect the selectivity of the carbocyclization reaction (Table 9). For example, *N*-tosylallene-yne **181** was prepared using a Mitsunobu reaction by adding diisopropyl azodicarboxylate (DIAD) to a mixture of 3-phenyl-*N*-tosylprop-2-yn-1-amine, triphenylphosphine, and allenic alcohol **175** in THF at 0 °C. Warming the reaction to room temperature produced the desired allene-yne **181** in 78% yield.

The construction of *N*-tosylallene-yne **181** from allenyl alcohol **175** is supported by resonances at 5.04-4.96 ppm (m, 1H) and 2.34 ppm (s, 3H) in the ^{1}H NMR that correspond to the allene proton and the tosylate methyl group, respectively. Allene-ynes **182** and **183** were prepared according to the procedure described for **180** and have comparable spectral data.

Table 9: Formation of *N*-Tosylallene-ynes 181-183



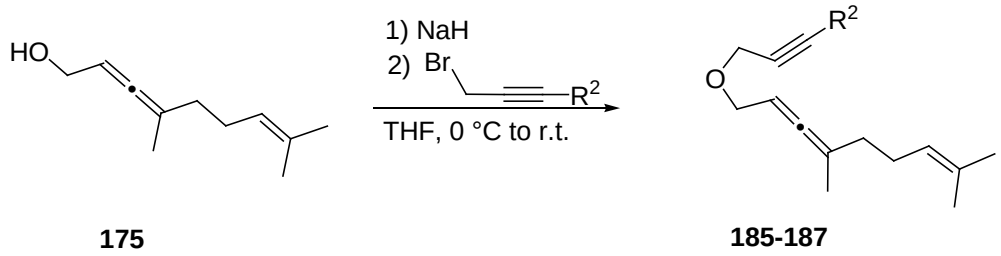
175 **181-183**

Entry	R^2	*N*-Tosylallene-yne	Yield (%)
1	Ph	**181**	78
2	Me	**182**	80
3	H	**183**	87

Ether-tethered allene-ynes **185-187** were synthesized to investigate the effect of an oxygen heteroatom in the allene-yne tether on the constitutional site selectivity of the allenic Alder-ene reaction (Table 10). The construction of allene-yne **185** was accomplished by first deprotonating alcohol **175** with sodium hydride. Subsequent *O*-alkylation of the resulting oxyanion with 1-(3-bromoprop-1-ynyl)benzene gave ether-tethered allene-yne **185** in 81% yield. Structurally similar allene-ynes **186** and **187** were prepared in yields of 76% and 80% according to the described procedure.

The ^{13}C NMR of allene-yne **185**, with resonances at 203.1 ppm, 86.01 ppm, and 85.2 ppm, supports the presence of the allene and alkyne functionalities.[81] The spectral data obtained for **186** and **187** is similar to that obtained for **185**.

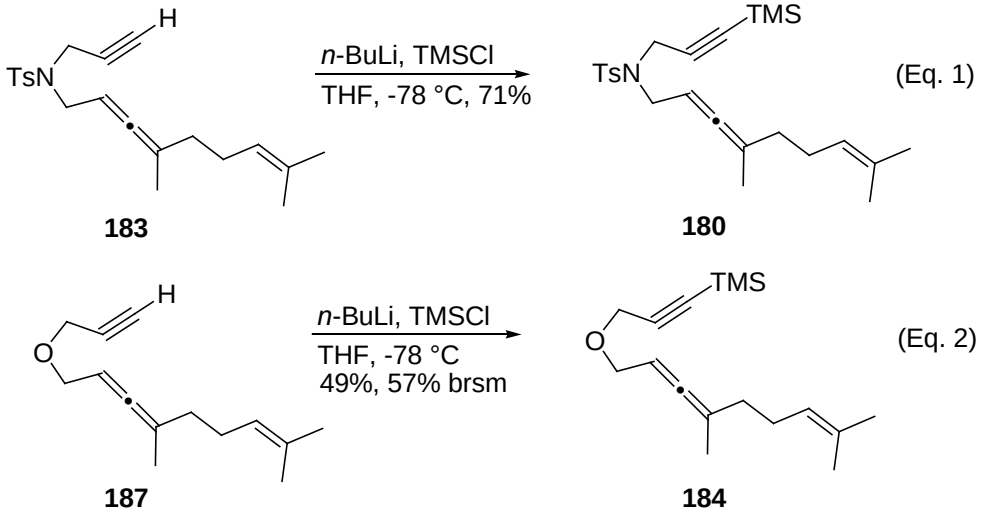
Table 10: Formation of Ether-tethered Allene-ynes 185-187



175 **185-187**

Entry	R^2	Allene-yne	Yield (%)
1	Ph	**185**	81
2	Me	**186**	76
3	H	**187**	80

Additionally, sulfonamide- and ether-tethered allene-yne derivatives possessing a TMS-substituted alkyne were obtained from terminal alkyne precursors to examine the effect of a TMS-alkyne on the selectivity of the cycloisomerization reaction. Reacting terminal alkynes **183** and **187** with *n*-BuLi and TMSCl at low temperature produced the corresponding allene-ynes **180** and **184** in yields of 71% and 49% (Scheme 57). The formation of TMS-alkynes **180** and **184** is evidenced by the ^{1}H NMR, which has resonances corresponding to the TMS group at -0.02 ppm (s, 9H) and 0.18 ppm (s, 9H), respectively.

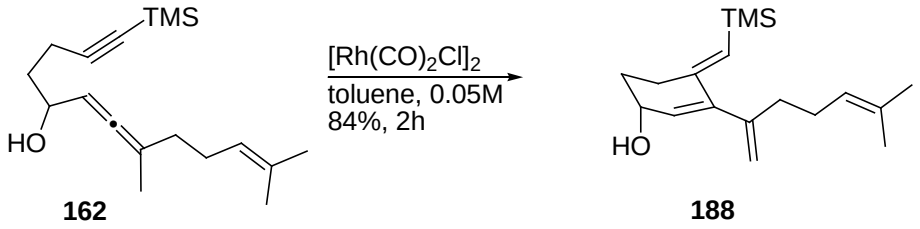


Scheme 57: Formation of TMS-Substituted Alkynes 180 and 184

1.11.5 The Constitutional Site Selectivity of Allene-ynes Tethered to an Isobutylene Group

1.11.5.1 Investigating the Role of the Allene-yne Functional Groups on the Selectivity of the Allenic Carbocyclization Reaction

Reacting allene-yne **162** with 10 mol% of $[Rh(CO)_2Cl]_2$ in toluene at room temperature produced only cross-conjugated triene **188** in 84% yield (Scheme 58). The selective formation of cross-conjugated triene **188** in yields of 83%, 77%, and 75% is also observed when *t*-butyl methyl ether, fluorobenzene, and α,α,α-trifluoromethyltoluene are employed as solvents, respectively. To the best of our knowledge,[133] this is the only example of a trisubstituted allene-yne being transformed into a regioisomerically pure cross-conjugated triene.

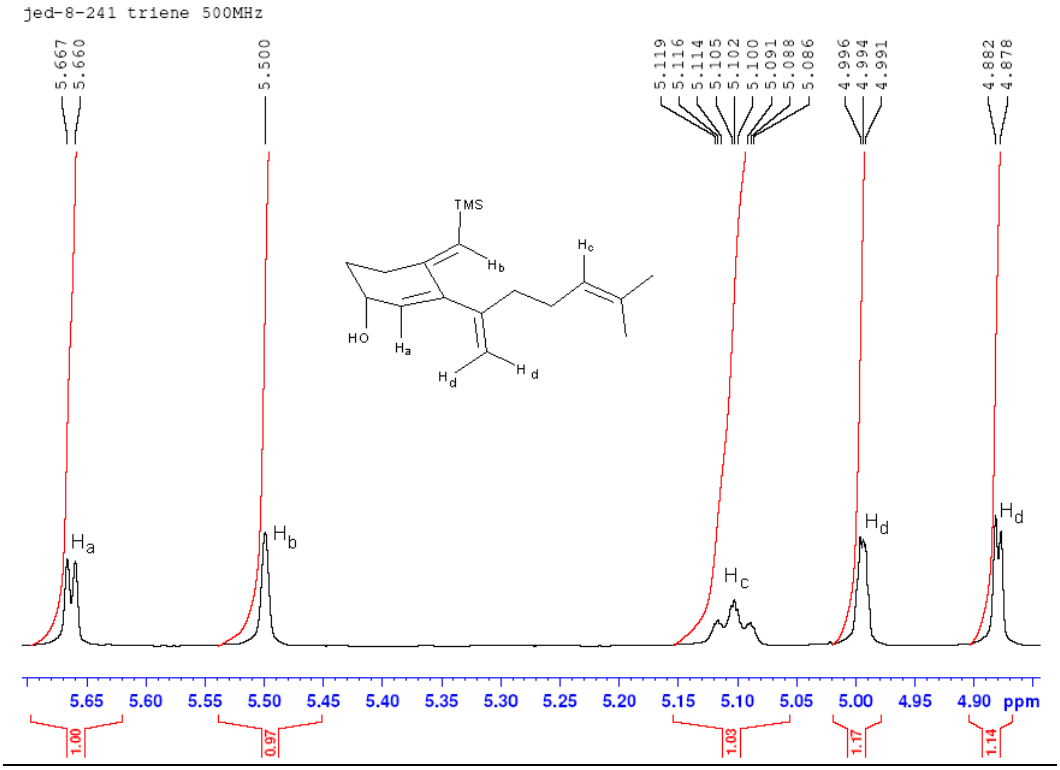


162 **188**

Scheme 58: Selective Formation of Cross-conjugated Triene 188 from Allene-yne 162

The selective formation of cross-conjugated triene **188** is illustrated by the alkene region in the ^{1}H NMR (Table 11). Resonances at 5.66 ppm (d, J = 3.5 Hz), 5.50 ppm (s), and 5.10 ppm (tt, J = 7.0, 1.5 Hz) correspond to H_a, H_b, and H_c, respectively. The appending 1,1-disubstituted alkene protons H_d correspond to the resonances at 5.01-4.98 ppm and 4.88 ppm (d, J =2.0 Hz).

Table 11: ^{1}H NMR of Cross-conjugated Triene 188 (alkene region, $CDCl_3$, rt, 500 MHz)

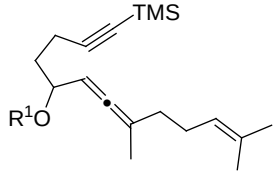
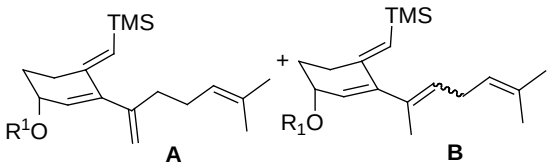


	Chemical Shift	Spin multiplicity	*J* Values (Hz)
H_a	5.66 ppm	d	3.5
H_b	5.50 ppm	s	-----
H_c	5.10 ppm	tt	7.0, 1.5
H_d	5.01-4.98 ppm	m	-----
H_d	4.88 ppm	d	2.0

Intrigued by the selective formation of triene **188**, we next sought to investigate the role of the hydroxyl group on the allenic carbocyclization reaction. The corresponding silyl ether **169**, acetate **170**, and pivaloate ester **171** were examined to determine the effect of an electron donating, withdrawing, and sterically demanding functionality on the selectivity of the reaction. As seen in Table 12, allene-ynes **169**, **170**, and **171** were selectively transformed into cross-conjugated trienes **189**, **191**, and **193** in yields of 92%, 84%, and 75%, respectively. These results indicate that the substitution on the α-allenic hydroxyl group has no effect on the

constitutional site selectivity of the carbocyclization reaction. However, the presence of the bulky pivaloate ester did produce cross-conjugated triene **193** in a lower 75% yield.

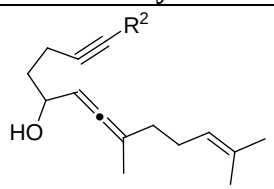
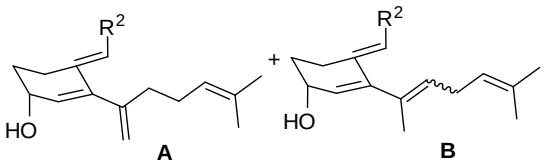
Table 12: Allenic Carbocyclization Reaction of Allene-ynes 169 through 171

Entry	Allene-yne	Trienes A : B[a]	Time	Yield
				
1	**169**, R^1=TBS	**189** : **190**, 100 : 0	1 h	92%
2	**170**, R^1=Ac	**191** : **192**, 100 : 0	1.5 h	84%
3	**171**, R^1=Piv	**193** : **194**, 100 : 0	2 h	75%

[a]Single isomer detected by ^{1}H NMR

The effect of the substitution on the alkyne terminus was next investigated. Interestingly, replacing the alkynyl TMS group with a phenyl substituent resulted in trienes **195** and *E*/*Z*-**196** as an 85:15 isomeric mixture in 88% yield (entry 1, Table 13). Cross-conjugated trienes **195** and *E*/*Z*-**196** were characterized as a mixture, because the isomeric ratio could be determined by ^{1}H NMR. For example, resonances at 5.09-5.06 ppm (m) and 4.98 ppm (d, J = 2.1 Hz) correspond to the appending 1,1-disubstituted alkene protons of **195**, and resonances at 5.39 ppm (t, J = 6.9 Hz) and 5.18 ppm (tt, J = 6.9, 1.2 Hz) correspond to the alkenyl protons in the diene side of *E*/*Z*-**196**. The isomeric ratio of **195** and *E*/*Z*-**196** was determined by integration of the resonances at 4.98 ppm (d, J = 2.1) and 5.39 ppm (t, J = 6.9 Hz) in the ^{1}H NMR.

Table 13: Allenic Carbocyclization Reaction of Allene-ynes 172 and 173

Entry	Allene-yne	Trienes A : B	*E*:*Z*	Time	Yield[a]
					
1	**172**, R^2 = Ph	**195** : **196**, 85 : 15	1 : 1	20 min	88%
2	**173**, R^2 = H	**197** : **198**, 56 : 44	1 : 1	7 h	32%

[a]Combined yield of cross-conjugated trienes A and B

Subjecting allene-yne **173**, which possesses a terminal alkyne, to the Rh(I)-catalyzed Alder-ene reaction conditions gave cross-conjugated trienes **197** and *E*/*Z*-**198** in a 56:44 isomeric ratio, but in a lower 32% combined yield (entry 2, Table 13). The low yield and extended reaction time for the formation of trienes **197**/*E*/*Z*-**198** is attributed to the reactive acetylenic proton that can react with the rhodium catalyst.[124] The isomeric ratio of cross-conjugated trienes **197**/*E*/*Z*-**198** was determined by integration of the three peaks in the GC chromatogram at retention times 5.6 min, 5.8 min, and 6.1 min. Based upon integration of the two smaller peaks at 5.6 min and 6.1 min, cross-conjugated triene **197** was produced as a 1:1 mixture of *E*:*Z* isomers. The isomeric ratios were assigned based on the retention times of the constitutional site and *E*:*Z* isomer of trienes **188** and *E/Z*-**161**, which were determined via nOe analysis and will be discussed later in section 1.11.5.5.

The isomeric mixture of trienes produced from allene-ynes **172** and **173** suggests that substitution at the alkynyl position does influence the β-hydride elimination step of the Rh(I)-catalyzed carbocyclization reaction. Moreover, the substitution on the alkyne terminus could serve as a control element for the selective formation of isomerically pure cross-conjugated trienes from 1,1-disubstituted allene-yne precursors.

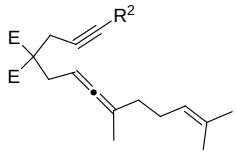
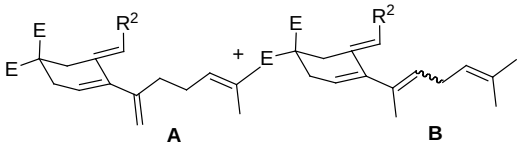
The effect of the tether substituents was studied next to further probe the selectivity of the carbocyclization reaction, and malonate tethered allene-yne derivatives were examined (Table 14). Allene-yne **176**, which has an alkynyl TMS group, was selectively cyclized to cross-conjugated triene **199** in 74% yield in 20 min (entry 1).

Replacement of the TMS-alkyne with a phenyl-substituted alkyne produced a 72% yield of trienes **201** and *E*/*Z*-**202** in an 88:12 isomeric ratio (entry 2, Table 14). The isomeric ratio of cross-conjugated trienes **201** and *E*/*Z*-**202** was determined by integration of the three peaks in the

GC chromatogram at retention times 14.7 min (*E*/*Z*-**202**), 16.5 min (**201**), and 17.6 min (*E*/*Z*-**202**).

Subjecting methyl derived allene-yne **178** to the carbocyclization reaction conditions gave a 72% yield of **203** and *E*/*Z*-**204** (entry 3, Table 14). Based upon integration of the three peaks in the GC chromatogram at retention times 8.6 min (*E*/*Z*-**204**), 8.9 min (**203**), and 9.2 min (*E*/*Z*-**204**), cross-conjugated trienes **203** and *E*/*Z*-**204** were produced in an 86:14 isomeric ratio.

Table 14: The Carbocyclization Reaction of Malonate-Tethered Allene-ynes Containing an Appending Isobutylene Group

Entry	Allene-yne	Trienes A : B[a]	*E*:*Z*[a]	Time	Yield[c]
		 A B			
1[b]	**176**, R^2 = TMS	**199** : **200**, 100 : 0	-----	20 min	74%
2	**177**, R^2 = Ph	**201** : **202**, 88 : 12	1 : 1	2.5 h	72%
3	**178**, R^2 = Me	**203** : **204**, 86 : 14	3 : 1	1.8 h	72%
4	**179**, R^2 = H	**205** : **206**, 56 : 44	2 : 1	24h	29%

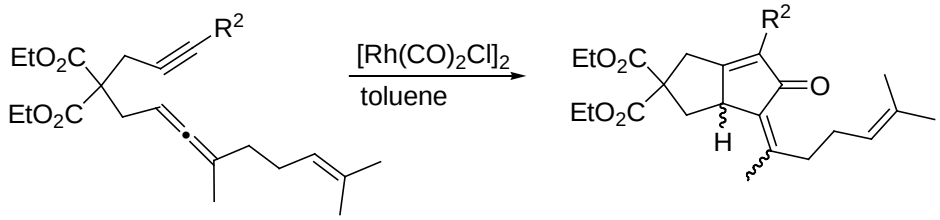
[a] Product ratios determined by GC analysis. [b]Single isomer detected by ^{1}H NMR [c]Combined yield of trienes A and B

When the cyclization reaction was performed with allene-yne **179**, cross-conjugated trienes **205** and *E*/*Z*-**206** were produced in a low 29% yield as a 56:44 isomeric mixture (entry 4, Table 14). The low yield and long reaction time observed for this reaction is attributed to the reactive terminal alkyne in allene-yne **179**.[124] The formation of cross-conjugated trienes **205** and *E*/*Z*-**206** is supported by the three peaks in the GC chromatogram at retention times 8.2 min (*E*/*Z*-**206**), 8.4 min (**205**), and 8.8 min (*E*/*Z*-**206**).

The Rh(I)-catalyzed carbocyclization reaction conducted with malonate tethered allene-ynes **176** through **179** produced a small amount of the corresponding α-alkylidene cyclopentenone products in addition to cross-conjugated trienes **199**-**206** (Table 15). Cyclocarbonylation products **207**-**210** were isolated in yields ranging from 8% to 14% and could

account for the lower yields obtained for cross-conjugated trienes **199**-**206** (compare Tables 12 and 13 with Table 14).

Table 15: Formation of Cyclopentenones 207-210



176-**179** **207**-**210**

Entry	Allene-yne	Cyclopentenone	Yield (%)
1	**176**, R^2 = TMS	**207**	14
2	**177**, R^2 = Ph	**208**	10
3	**178**, R^2 = Me	**209**	8
4	**179**, R^2 = H	**210**	8

The formation of cyclopentenones **207**-**210** is evidenced by resonances in the ^{1}H NMR. For example, the ^{1}H NMR of **207** shows resonances at 3.58-3.46 ppm (m, 1H) and 2.84-2.75 ppm (m, 1H), corresponding to the methylene protons H_a; an AB quartet (J = 18.3 Hz) at resonances 3.32 ppm and 3.22 ppm, corresponding to H_b; and resonances at 2.96 ppm (triplet, J = 8.1 Hz) and 2.92* ppm (triplet, J = 8.1 Hz), corresponding to the diastereomeric ring fusion hydrogen H_c. Integration of the resonances at 1.67 ppm and 1.60 ppm that correlate to the isomeric α-alkylidene methyl group indicate that **207** was produced as a 1:1 mixture of diastereomers.

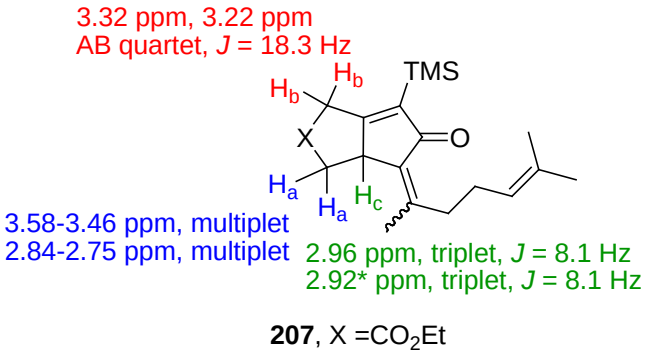


Figure 11: Assignment of H_a H_b, and H_c in the ^{1}H NMR Spectrum of 207 (300 MHz, $CDCl_3$)

Next, the effect of heteroatoms on the regioselectively of the β-hydride elimination step was explored. *N*-Tosylallene-yne **180** and ether-tethered allene-yne **184**, which possess a TMS substituted alkyne, were exclusively converted into trienes **211** and **223** in yields of 63% and 61%, respectively (entries 1 and 5, Table 16).

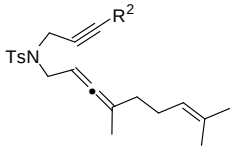
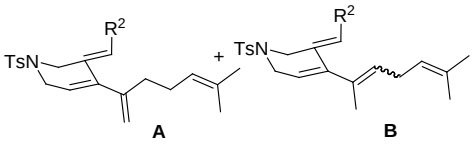
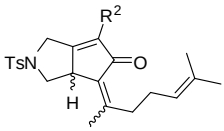
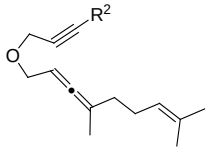
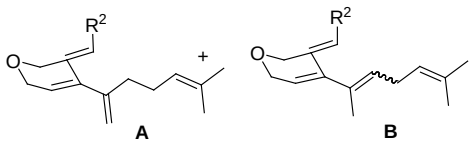
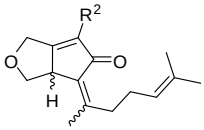
As seen in entries 2 and 6 of Table 16, exchanging the TMS-alkyne with a phenyl alkyne produced an isomeric mixture of trienes. Sulfonamide **181** is cyclized to trienes **214**/*E*/*Z*-**215** in an 85:15 isomeric ratio in 56% yield, and allenyl ether **185** is converted to trienes **226**/*E*/*Z*-**227** in an isomeric ratio of 74:26 in 60% yield.

Similarly, mixtures of cross-conjugated trienes are again observed when the allene-yne substrates have a methyl-substituted alkyne (compare entries 2 and 6 with entries 3 and 7). As seen in entries 3 and 7, allene-ynes **182** and **186** are transformed to the corresponding cross-conjugated trienes **217**/*E*/*Z*-**218** and **229**/*E*/*Z*-**230** in isomeric ratios of 79:21 and 75:25, respectively.

Additionally, reacting terminal alkynes **183** and **187** with $[Rh(CO)_2Cl]_2$ produced cross-conjugated trienes **220**/*E*/*Z*-**221** and **232**/*E*/*Z*-**233** in increased isomeric ratios of 43:57 and 45:55, respectively (entries 4 and 8, Table 16). Cross-conjugated trienes **220**/*E*/*Z*-**221** and **232**/*E*/*Z*-**233**,

however, were isolated with impurities that were inseparable via column chromatography in low yields of 36% and 21%, respectively.

Table 16: The Carbocyclization of Heteroatom-Tethered Allene-ynes with an Appending Isobutylene Group

Entry	Allene-yne	Trienes A : B[a], Yield[d]	*E*:*Z*[a]	Cyclopentenone, Yield	Time
					
1	**180**, R^2 = TMS	**211** : **212**, 100 : 0, 63%	-----	**213**, 20%	15 min
2	**181**, R^2 = Ph	**214** : **215**, 85 : 15, 56%	1 : 1	**216**, 24%	8.5 h
3	**182**, R^2 = Me	**217** : **218**, 79 : 21, 64%	1 : 1	**219**, 25%	20 min
4[c]	**183**, R^2 = H	**220** : **221**, 43 : 57, 36%	2 : 1	**222**, 25%	24 h
					
5	**184**, R^2 = TMS	**223** : **224** 100 : 0, 61%	-----	**225**, 39%	40 min
6[b]	**185**, R^2 = Ph	**226** : **227** 74 : 26, 60%	1 : 1	**228**, 30%	35 min
7[b]	**186**, R^2 = Me	**229** : **230** 75 : 25, 41%	1 : 1	**231**, 36%	20 min
8[c]	**187**, R^2 = H	**232** : **233** 45 : 55, 21%	3 : 1	**234**, 28%	24 h

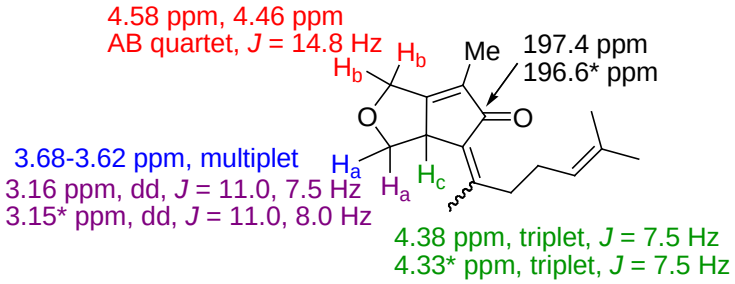
[b]Product ratios were determined by integration of distinct protons in ^{1}H NMR. [b]Product ratios determined by GC analysis. [c]Triene products contained inseparable impurities. [d]Combined yield of cross-conjugated trienes A and B

Unfortunately, the heteroatom-tethered allene-ynes examined produced increased amounts of α-alkylidene cyclopentenones. *N*-Tosylallenynes **180**-**183** led to the corresponding cyclocarbonylation products in yields of 20-25%, and ether-tethered allene-ynes **184**-**187** gave cyclopentenones in yields of 28-39% (Table 16).

The formation of α-alkylidene cyclopentenones **213**-**234** is evidenced by the ^{1}H NMR. The ^{1}H NMR of **231**, for example, shows an AB quartet (J = 14.8 Hz) at resonances 4.58 ppm and 4.46 ppm corresponding to H_b and resonances at 4.38 ppm (triplet, J = 7.5 Hz) and 4.33* ppm (triplet, J = 7.5 Hz) that correspond to the diastereomeric ring fusion hydrogen H_c. A resonance at 3.68-3.62 ppm corresponds to one H_a proton (m), while the overlapping resonances

at 3.16 ppm (dd, J = 11.0, 7.5 Hz) and 3.15* ppm (dd, J = 11.0, 8.0 Hz) correspond to the other diastereomeric H_a proton (Figure 12).

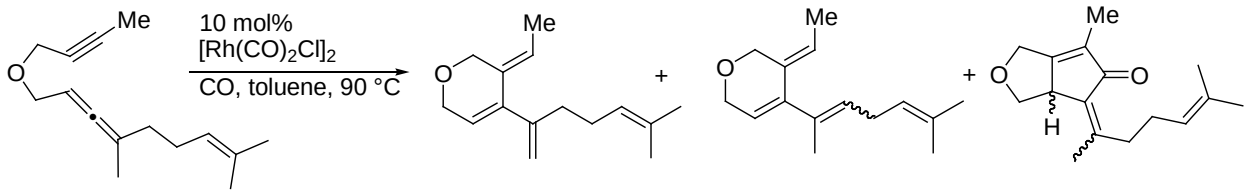
Furthermore, the ^{13}C NMR of **231** has resonances for the carbonyl carbon and sp^3 ring fusion carbon of α-alkylidene cyclopentenones at 197.4/196.9* ppm and 47.7/47.5* ppm, respectively.[134, 135] Integration of the two peaks in the GC chromatogram at retention times 7.5 min and 7.7 min indicate that **231** was produced as a 1:1 mixture of diastereomers.



231

Figure 12: Assignment of H_a H_b, and H_c in the ^1H NMR Spectrum of 231 (500 MHz, $CDCl_3$)

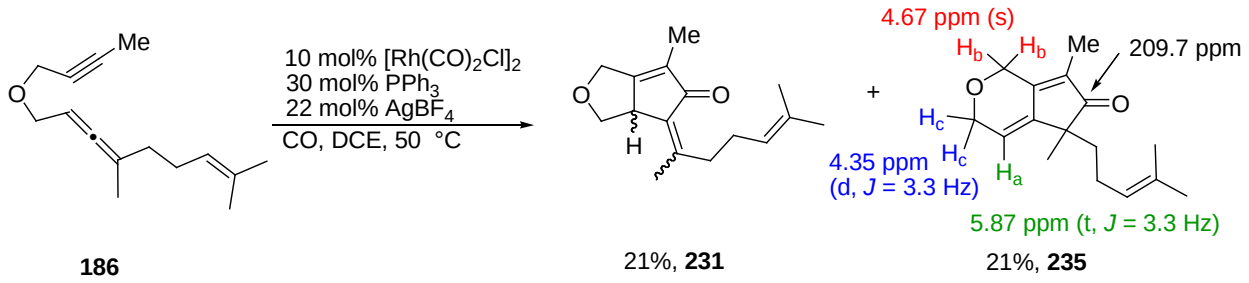
To confirm the structure of **231**, allene-yne **186** was reacted with 10 mol% of $[Rh(CO)_2Cl]_2$ at 90 °C under a carbon monoxide atmosphere, which formed α-alkylidene cyclopentenone **231** in 65% yield. A small amount of the corresponding cross-conjugated trienes **229** and *E*/*Z*-**230** were obtained in 31% yield as an 88:12 isomeric mixture. The isomeric ratio of **229** : *E*/*Z*-**230** was determined by integration of the three peaks in the GC chromatogram at retention times 5.3 min (*E*/*Z*-**230**), 5.6 min (**229**), and 5.9 min (*E*/*Z*-**230**). It should be noted that these reaction conditions are typically used to form 4-alkylidene cyclopentenones.[136, 137]



186 31% **229**/***E*/*Z*-230** 65%, **231**

Scheme 59: Formation of Cyclopentenone 231 from Allene-yne 186

Interestingly, subjecting allene-yne **186** to a catalyst system prepared *in situ* from 10 mol% $[Rh(CO)_2Cl]_2$, 30 mol% PPh_3, and 22 mol% $AgBF_4$ under 1 atm of CO produced a chromatographically separable mixture of α-alkylidene cyclopentenone **231** (21%) and 4-alkylidene cyclopentenone **235** (21%) in a 42% combined yield (Scheme 60).[135] The formation of 4-alkylidene cyclopentenone **235** is evidenced by resonances in the ^1H NMR at 5.87 ppm (t, J = 3.3 Hz), corresponding to H_a; 4.67 ppm, corresponding to H_b (s, 2H); and at 4.35 ppm (d, J = 3.3 Hz), corresponding to H_c. Further evidence that **235** was obtained is provided by the ^{13}C NMR, which shows the characteristic resonance at 209.7 ppm that is typically observed for the carbonyl carbon of 4-alkylidene cyclopentenones.[135, 136]

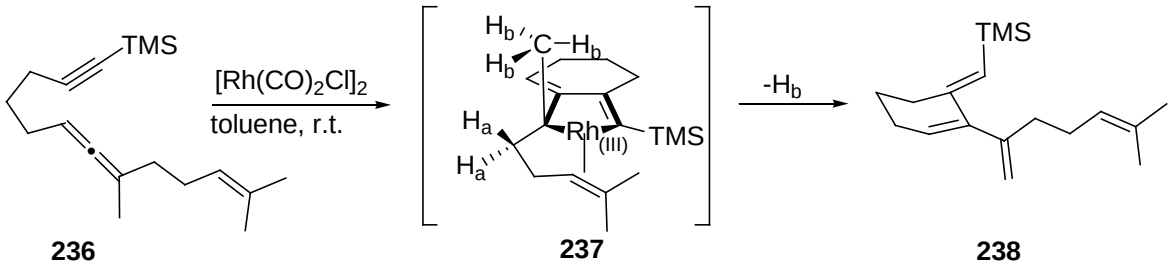


Scheme 60: Formation of Isomeric Cyclopentenones 231 and 235 from Allene-yne 186

The selective coordination and subsequent reaction of $[Rh(CO)_2Cl]_2$ with the proximal double bond of the allene might be explained by the coordination of the heteroatom in the allene-yne tether to the rhodium metal. This hypothesis is further supported by the increased yields of 20-39% obtained for cyclopentenones produced from nitrogen- and oxygen-tethered allene-ynes.

1.11.5.2 Explanation for the Constitutional Site Selectivity of the Allenic Carbocyclization Reaction of Allene-ynes containing an Isobutylene group

The selective transformation of allene-ynes of type **236** to cross-conjugated trienes **238** can be explained by coordination of the appending double bond to the rhodium metal center giving intermediate **237** (Scheme 61). In this conformation, *syn* periplanar alignment of the Rh-C-C-H_a system during the β-hydride elimination step is geometrically unattainable, leading to β-hydride elimination of H_b and the formation of cross-conjugated triene **238**.



Scheme 61: Explanation for the Selectivity of the Alder-ene Reaction of Allene-ynes Tethered to an Alkene

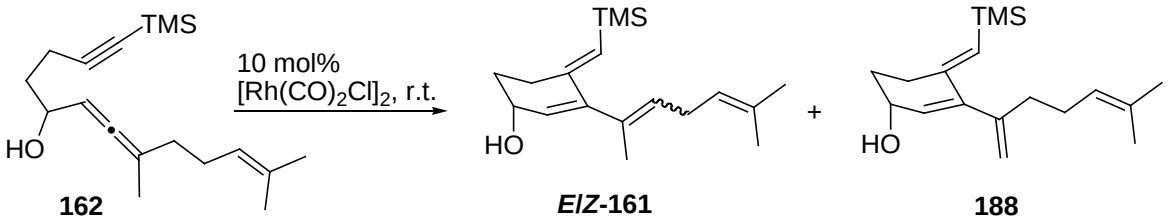
1.11.5.3 Examining the Effect of Coordinating Solvents on the Regioselectivity of the Rh(I)-Catalyzed Allenic Carbocyclization Reaction

In continuing with the investigation of the constitutional site selectivity of the allenic Alder-ene reaction, a variety of solvents were examined for the carbocyclization reaction. Allene-yne **162** was chosen for our solvent studies as it can produce the cyclic framework of fumagillol (**60**) and ovalicin (**61**).

To test our hypothesis that the appended alkene of the allene-yne substrate is coordinating to the rhodium catalyst, toluene was replaced with a more coordinating solvent. As seen in Table 17, performing the carbocyclization reaction in solvents such as acetone (entry 4)

and 1,4-dioxane (entry 5) lead to slightly increased ratios of *E*/*Z*-**161** : **188** (21:79 and 22:78), while THF (entry 6) gave trienes *E*/*Z*-**161** : **188** in a 34:66 isomeric ratio. Interestingly, using acetonitrile as the solvent resulted in a dramatic increase in the formation of *E*/*Z*-**161**, and trienes *E*/*Z*-**161** and **188** were produced in a 99:1 isomeric ratio in 29% yield (entry 7). The appending trisubstituted alkene of *E*/*Z*-**161** was produced in a *E*:*Z* ratio of 1:5. The preferential formation of *Z*-**161** in entries 2 though 7 is unique, because typically the metal-catalyzed carbocyclization reaction predominately produces the thermodynamically favored *E*-isomer.[6, 138] The isomeric ratio of *E*/*Z*-**161** and **188** was determined by integration of the three peaks in the GC chromatogram at retention times of 6.9 min, 7.1 min, and 7.4 min, which correspond to *Z*-**161**, **188**, and *E*-**161**, respectively.

Table 17: Solvent Study for the Allenic Carbocyclization Reaction of Allene-yne 162



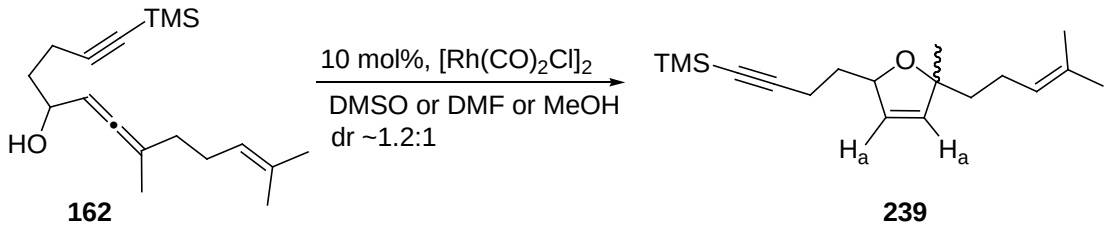
162 ***E*/*Z*-161** **188**

Entry	Solvent	*E*/*Z*-161:188[a]	*E*:*Z*[a]	Yield (%)[b]
1	toluene	0 : 100	------	84
2	1,2-DCE	7 : 93	1 : 4	80
3	DME	18 : 82	1 : 4	50
4	acetone	21 : 79	1 : 9	25
5	1,4-dioxane	22 : 78	1 : 4	77
6	THF	34 : 66	1 : 6	46
7	CH_3CN	99 : 1	1 : 5	29
8	TFE	------	------	complex mixture

[a]Product ratios determined by GC analysis. [b]Combined yield of *E*/*Z*-**161** and **188**

Interestingly, reacting allene-yne **162** with $[Rh(CO)_2Cl]_2$ in solvents such as DMSO, DMF, and MeOH gave 2,5-dihydropyran **239** in yields of 51%, 59%, and 78%, respectively (Scheme 62). The ^{1}H NMR shows that the major diastereomer of **239** has resonances at 5.74 ppm (dd, J = 6.3, 0.9 Hz) and 5.68 ppm (dd, J = 6.0, 2.1 Hz) that correspond to the *cis*-alkene

protons H_a. Similarly, the resonance at 5.72 ppm (s) corresponds to the *cis*-alkene protons of the minor diastereomer.[139, 140] Based upon the integration of the resonances at 1.29 ppm and 1.27 ppm in the ^{1}H NMR corresponding to the diastereomeric methyl groups, **239** was produced as a 1.2:1 diastereomeric mixture.

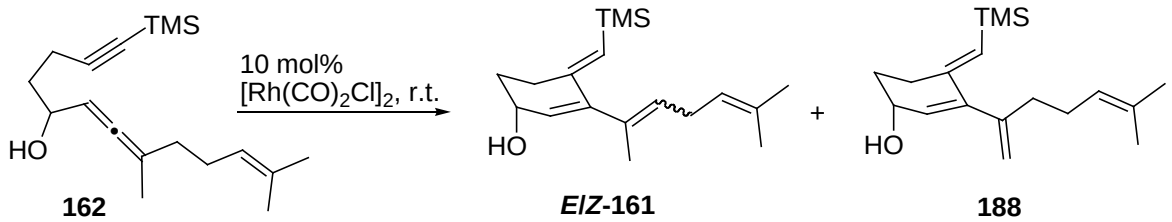


162 **239**

Scheme 62: Formation of 2,5-Dihydropyran 239 from Allene-yne 162

Encouraged by the results depicted in Table 17, coordinating alkenes were incorporated into our solvent system. As seen in Table 18, performing the carbocyclization reaction in acyclic and cyclic alkenes produced an increased amount of *E*/*Z*-**161** (entries 2-9 and 11-14). Most notably, reacting allene-yne **162** with a catalytic amount of $[Rh(CO)_2Cl]_2$ in styrene produced cross-conjugated trienes *E*/*Z*-**161** and **188** in 78% yield as a 61:39 isomeric mixture (entry 13). Triene *E*/*Z*-**161** was produced in a high *E*:*Z* ratio of 8:1 during this reaction. Alternatively, adding 1,5-cyclooctadiene to the reaction prohibited the cycloisomerization reaction from occurring and is attributed to the increased binding ability of 1,5-cyclooctadiene (COD) to the rhodium catalyst (entries 15-17).[89]

Table 18: Allenic Carbocyclization Reaction of Allene-yne 162 in Alkene Solvents Systems



162 ***E*/*Z*-161** **188**

Entry	Solvent	*E*/*Z*-161:188[a]	*E*:*Z*[a]	Yield (%)[b]
1	toluene	0 : 100	------	84
2	toluene (ethylene atmosphere)	53 : 47	4 : 1	80
3	toluene/1-decene (500 : 1)	11 : 89	4 : 1	69
4	toluene/1-decene (1 : 1)	54 : 46	7 : 1	53
5	1-decene	61: 39	6 : 1	58
6[c]	*trans*-4-octene	20 : 80	1 : 1	29 (40 brsm)
7	*cis*-cyclooctene	56 : 44	3 : 1	20 (67 brsm)
8	cycloheptene	49 : 51	3 : 1	55
9	cyclohexene	21 : 79	3 : 1	67
10	cyclopentene	------	------	complex mixture
11	1,4-cyclohexadiene	44 : 56	5 : 1	78
12	isoprene	55 : 45	4 : 1	68
13	**styrene**	**61 : 39**	**8 : 1**	**78**
14	allyl benzene	14 : 86	2 : 1	21
15	1,5-cyclooctadiene	------	------	no reaction
16	toluene/1,5-cyclooctadiene (1:1)	------	------	no reaction
17	toluene/1,5-cyclooctadiene (500:1)	------	------	no reaction

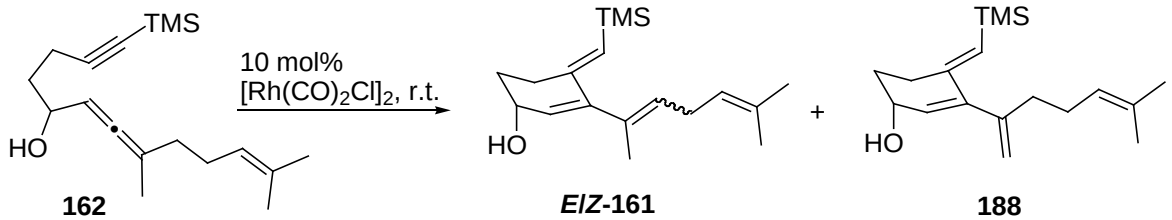
[a]Product ratios determined by GC analysis. [b]Combined yield of *E*/*Z*-**161** and **188**. [c]Triene product contaminated with impurities.

The high yield and isomeric ratio of *E*/*Z*-**161** : **188** produced when styrene is used as the solvent for the cycloisomerization reaction warranted further investigation. To determine if the styrene is affecting the β-hydride elimination step of the carbocyclization reaction, the reaction was carried out in a mixture of toluene and styrene. As shown in Table 20, employing this mixed solvent system decreased the formation of *E*/*Z*-**161** (entries 3-4).

The role of temperature on the regioselectivity of the allenic Alder-ene reaction in styrene was also investigated. Performing the carbocyclization reaction in styrene at 50 °C and 90 °C gave *E*/*Z*-**161** and **188** in decreased isomeric ratios of 39:61 and 17:83, respectively (compare entry 2 with entries 5 and 6). Performing the cycloisomerization reaction at -20 to 0 °C required

the addition of $AgSbF_6$, and **188** was still produced as the major isomer. The results summarized in Table 19 indicate that the styrene solvent is affecting the selectivity of the Rh(I)-catalyzed carbocyclization reaction, and that elevated reaction temperatures favor the formation of *Z*-**161** and **188**.

Table 19: Examining the Rh(I)-Catalyzed Carbocyclization of Allene-yne 162 in Styrene



162 ***E/Z*-161** **188**

Entry	Solvent/Conditions	Temp (°C)	*E*/*Z*-161:188[a]	*E*:*Z*[a]	Yield(%)[b]
1	toluene	25	0 : 100	------	84
2	styrene	25	61 : 39	8 : 1	78
3	toluene/styrene (1 : 1)	25	54 : 46	7 : 1	76
4	toluene/ styrene (500 : 1)	25	12 : 88	3 : 1	81
5	styrene	50	39 : 61	3 : 1	73
6[c]	styrene	90	17 : 83	1 : 16	36
7	styrene/$AgSbF_6$	-20 to 0	39 : 61	1 : 3	18

[a]Product ratios determined by GC analysis. [b]Combined yield of *E*/*Z*-**161** and **188**. [c]Triene product contaminated with impurities.

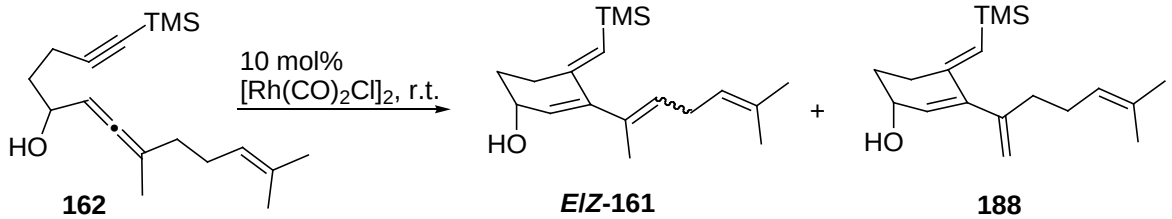
1.11.5.4 Exploring Rhodium and Ruthenium Catalysts for the Carbocyclization of Allene-yne 162

Next, it was postulated that formation of pseudo-cycle **237** and β-hydride elimination of H_b could be suppressed by the catalyst (Scheme 61). Thus, we examined rhodium catalysts yielding a coordinatively saturated Rh(III)-metallocycle intermediate upon oxidative coupling of the allene-yne substrate.

Reacting 10 mol% of *trans*-$RhCl(CO)(PPh_3)_2$[141] with **162** at 25 to 50 °C in THF[142] gave trienes *E*/*Z*-**161** and **188** in a 43:57 isomeric ratio in 8% yield (entry 3, Table 20). Allene-yne **162** was recovered in 75% yield from this reaction. Increasing the reaction temperature to 80

°C[143] resulted in cross-conjugated trienes *E*/*Z*-**161** and **188** in a isomeric ratio of 27:73 in 38% yield (compare entries 3 and 4). As seen in entry 5, employing a more sterically encumbered catalyst like $(PPh)_3RhCl$ (Wilkinson's catalyst)[144] for the cyclization resulted in a 51:49 isomeric ratio of *E*/*Z*-**161** : **188** in 44% yield. The appending trisubstituted alkene of *E*/*Z*-**161** was produced in a high 6:1 *E*:*Z* ratio. The increased formation of *E*/*Z*-**161** when *trans*-$RhCl(CO)(PPh_3)_2$ and $Rh(PPh)_3Cl$ are employed for the carbocyclization reaction suggests that the phosphine ligands on the rhodium catalyst are capable of suppressing coordination of the appending alkene to the rhodium metallocycle. However, the low yields obtained are not synthetically useful.

Table 20: Investigation of Catalysts for the Formation of Cross-Conjugated Triene 161



162 ***E/Z*-161** **188**

Entry	Conditions	Solvent	T(°C)	*E*/*Z*-161:188[a]	*E*:*Z*[a]	Yield (%)[c]
1	$[Rh(CO)_2Cl]_2$,	toluene	25	0 : 100	-----	84
2	$[Rh(CO)_2Cl]_2$	DCE	25	7 : 93	1 : 4	80
3[b]	$RhCl(CO)(PPh_3)_2$	THF	25-50	43 : 57	2 : 1	8 (33 brsm)
4	$RhCl(CO)(PPh_3)_2$	DCE	80	27 : 73	3 : 1	38
5	$(PPh)_3RhCl$	toluene	110	51 : 49	6 : 1	44
6[b]	$[Rh(COD)_2Cl]_2$,$AgBF_4$,PPh_3	DCE	25	14 : 86	1 : 0	36
7	$[Rh(CO)_2Cl]_2$,$AgBF_4$, PPh_3	DCE	25	-----	-----	complex mixture
8	$[Rh(CO)_2Cl]_2$,$AgBF_4$, BINAP	THF	25-60	22 : 78	1 : 1	8 (10 brsm)
9	$CpRu(CH_3CN)_3PF_6$	DMF	25	-----	-----	unknown cmpd
10[d]	$CpRu(CH_3CN)_3PF_6$	acetone	25	0 : 100	-----	trace

[a]Product ratios determined by GC analysis. [b]Product ratios determined by integration of peaks in the ^1H NMR. [c]Combined yield of *E*/*Z*-**161** and **188** [d]Product contained impurities

The Brummond group has shown that employing cationic rhodium catalysts for the allenic carbocyclization reaction produces the alkene side chain of the triene products with enhanced *E*:*Z* selectivities.[19] Considering these results, we reacted **162** with 10 mol%

$[Rh(COD)Cl]_2$, 22 mol% $AgBF_4$, and 30 mol% PPh_3, which lead to cross-conjugated trienes *E*/*Z*-**161** and **188** in a 14:86 isomeric ratio in 36% yield (entry 6). Reacting **162** with 10 mol% $[Rh(CO)_2Cl]_2$, 20 mol% $AgBF_4$ and 20 mol% *rac*-BINAP in THF lead to trienes *E*/*Z*-**161** and **188** in 8% yield as a 22:78 isomeric mixture (entry 8). Thin-layer chromatography (TLC) showed that using cationic rhodium catalysts for the carbocyclization reaction produced many byproducts in addition to the desired cross-conjugated trienes.

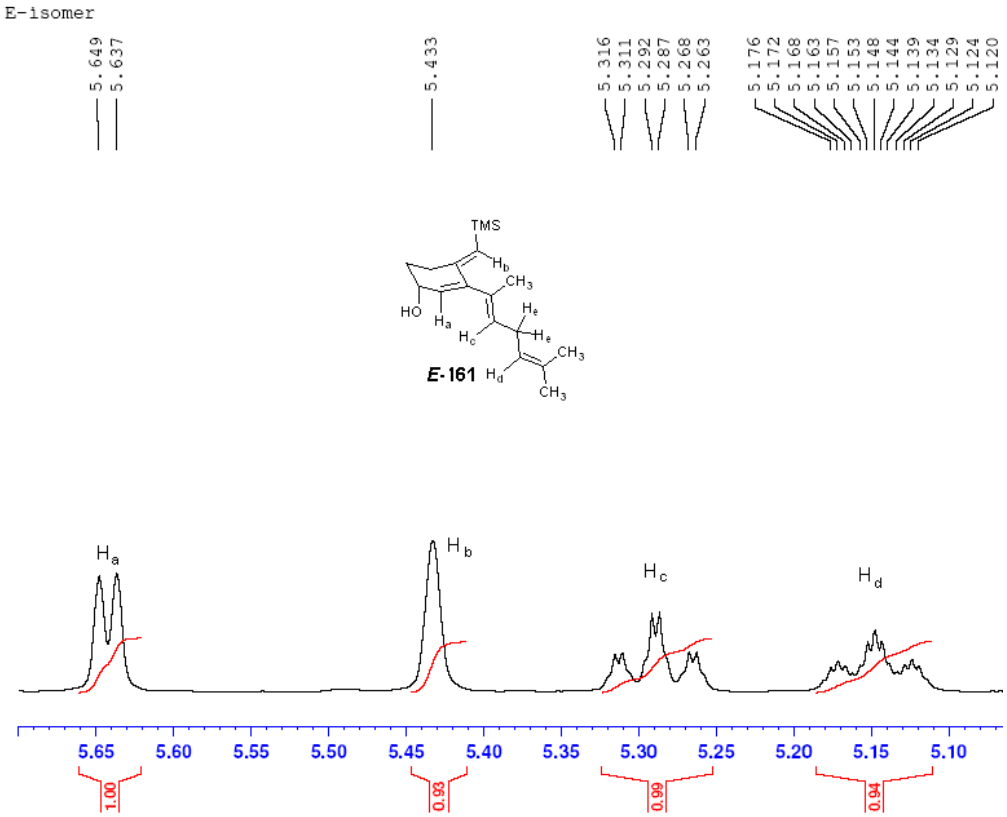
We next examined a ruthenium-derived catalyst for the cyclization of allene-yne **162**. Based on a report by Trost and Toste that showed $CpRu(CH_3CN)_3PF_6$ in DMF could transform geranyl derived enynes into their carbocyclic counterparts with high *E* selectivity, we reacted **162** with 10 mol% of $CpRu(CH_3CN)_3PF_6$.[8] Interestingly, these reaction conditions resulted in the formation of an unknown compound (6 mg on 28 mg scale) with olefinic resonances at 5.66 ppm (d, *J* = 3.3 Hz, 1H), 5.61 ppm (d, *J* = 2.1 Hz, 1H), 5.60 ppm (d, *J* = 2.1 Hz, 1H), 5.50 ppm (s, 1H), 5.15-5.01 ppm (m, 3H), 4.99 ppm (dt *J* = 2.1, 1.2 Hz, 1H), and 4.88 ppm (d, *J* = 2.1 Hz, 1H) in the ^{1}H NMR (entry 9, Table 20). Performing the Ru-catalyzed carbocyclization reaction in acetone lead to a trace amount of cross-conjugated triene **188**, which was contaminated with impurities that were inseparable via column chromatography.

1.11.5.5 Assignment of the Stereochemistry of Cross-Conjugated Trienes *E*-161 and *Z*-161 through nOe Analysis

Cross-conjugated triene *E*-**161** was separated from the constitutional and Z-isomers **188** and *Z*-**161** using normal phase HPLC. The alkene region in the ^{1}H NMR of *E*-**161** is shown in Table 21. The resonances corresponding to H_a (d, *J* = 3.6 Hz) and H_b (s) are at 5.64 ppm and

5.43 ppm, respectively. Additionally, resonances at 5.29 ppm (tq, J = 7.0, 1.5 Hz) and 5.15 ppm (tt, J = 7.0, 1.5 Hz) correlate to alkenyl protons H_c and H_d in the skipped diene side chain.

Table 21: ^{1}H NMR of Cross-conjugated Triene *E*-161 (alkene region, $CDCl_3$, rt, 300 MHz)



	Chemical Shift	Spin multiplicity	*J* Values (Hz)
H_a	5.64 ppm	d	3.6
H_b	5.43 ppm	s	-----
H_c	5.29 ppm	tq	7.2, 1.5
H_d	5.15 ppm	tt	7.2, 1.2

The *E*- and *Z*-isomers of cross-conjugated triene **161** were assigned based upon nOe data (Figure 13). For example, irradiating the resonance corresponding to H_e of ***E*-161** resulted in 3.0% and 1.9% enhancements for the resonances corresponding to the proximal alkenyl methyl groups. Additional 3.2% and 1.9% enhancements were observed for the resonances corresponding to the adjacent alkenyl protons H_c and H_d. Irradiating the alkenyl proton H_c resulted in 6.0% and 3.0% enhancements for the resonances corresponding to H_a and H_e,

respectively. No enhancement, however, was observed for the resonance corresponding to the appending vinyl methyl group. The 3.0% nOe between H_e and the proximal vinyl methyl group supports the *E*-geometry of *E*-**161**.

Alternatively, irradiating H_c of *Z*-**161** resulted in 2.8% and 2.1% enhancements of the resonances corresponding to the neighboring methyl and methylene groups. The 2.8% enhancement of the resonance corresponding to the appending vinyl methyl group supports that the trisubstituted alkene of *Z*-**161** has the assigned *Z*-geometry.

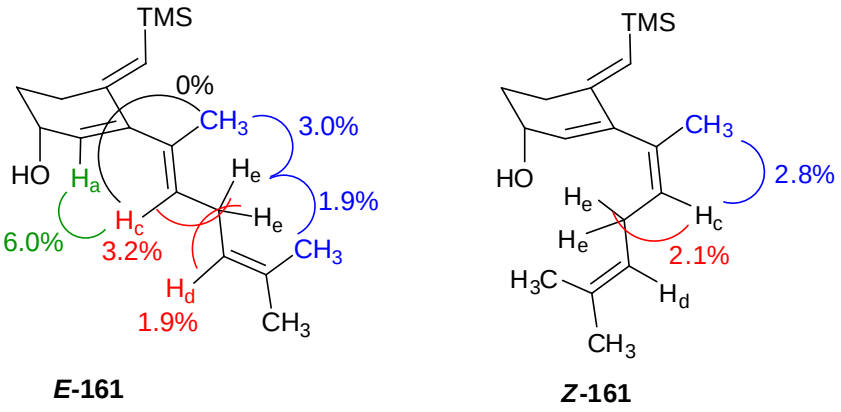


Figure 13: nOe Analysis of *E*-161 and Z-161 after HPLC separation

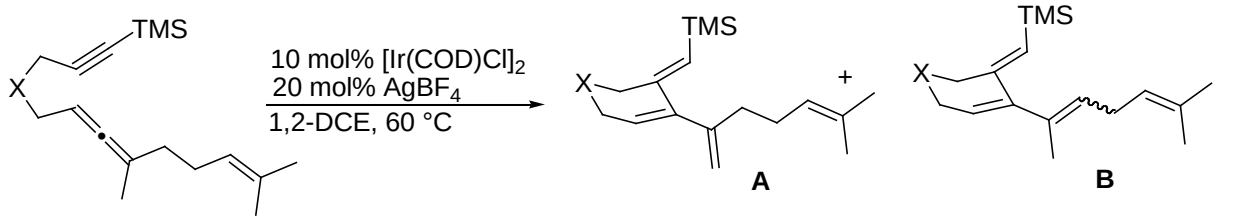
1.11.5.6 The Iridium-Catalyzed Allenic Carbocyclization of Allene-ynes Containing Tethered Alkenes

Brummond and coworkers have shown that employing $[Ir(COD)Cl]_2$ and $AgBF_4$ for the allenic carbocyclization reaction yields cross-conjugated trienes in high *E*:*Z* selectivities.[19] Considering this, allene-yne **176** was reacted with $[Ir(COD)Cl]_2/AgBF_4$ to produce cross-conjugated trienes **199** and *E*/*Z*-**200** in 66% yield as a 27:73 isomeric mixture. A high *E*:*Z* ratio of 21:1 was obtained for triene *E*/*Z*-**200** (entry 2, Table 22). Desilylation of **199** and *E*/*Z*-**200** was also observed during this reaction (23%). The ability of the $[Ir(COD)Cl]_2$ and $AgBF_4$ to convert

allene-yne **176** into *E*/*Z*-**200** in a high *E*:*Z* ratio contrasts sharply to $[Rh(CO)_2Cl]_2$, which only produces cross-conjugated triene **199** (compare entries 1 and 2).

Similarly, subjecting sulfonamide **180** to the iridium-catalyzed carbocyclization conditions gave **211** and *E*/*Z*-**212** in 78% yield in a 32:68 isomeric ratio. Cross-conjugated triene *E*/*Z*-**212** was obtained with an *E*:*Z* selectivity of 6:1 (entry 4). The increased 78% yield of **211**/*E*/*Z*-**212** obtained from the iridium-catalyzed Alder-ene reaction is likely due to the formation of Pauson-Khand cyclopentenone products when $[Rh(CO)_2Cl]_2$ is employed for the cycloisomerization (compare entries 3 and 4).

Table 22: Ir(I)- and Rh(I)-Catalyzed Carbocyclization Reaction of Allene-ynes Containing Tethered Alkenes

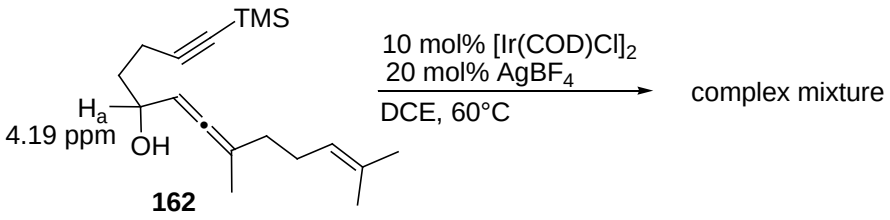


Entry	Allene-yne	Ratio of A:B[b]	Conditions[a]	*E*:*Z*[b]	Yield(%)[e]
1	**176**, X= CO_2Et	**199**:**200**, 100:0	A	------	74
2	**176**, X= CO_2Et	**199**:**200**, 27:73	B	21 : 1	66
3	**180**, X= NTs	**211**:**212**, 100: 0	A	------	63
4[c]	**180**, X= NTs	**211**:**212**, 32:68	B	6 : 1	78
5	**184**, X= O	**223**:**224**, 100:0	A	------	61
6[d]	**184**, X= O	**223**:**224**, 32:68	B	10 : 1	28

[a]Conditions: (A) 10 mol% $[Rh(CO)_2Cl]_2$, toluene. (B) 10 mol% $[Ir(COD)Cl]_2$, 20 mol% $AgBF_4$, DCE, 60 °C. [b] *E*:*Z* ratio determined by GC analysis. [c] Product Ratios determined by integration of peaks in the ^1H NMR. [d] Substrate was added to a pre-mixed solution of $[Ir(COD)Cl]_2$ and $AgBF_4$ in DCE. [e]Combined yield of trienes A and B

Ether-tethered allene-yne **184** proved to be sensitive to the cationic iridium reaction conditions. For example, addition of **184** to a solution of $[Ir(COD)Cl]_2$ followed by immediate addition of a solution of $AgBF_4$ gave a complex mixture of compounds. Alternatively, addition of **184** to a pre-mixed solution of $[Ir(COD)Cl]_2$ and $AgBF_4$ gave trienes **223** and *E*/*Z*-**224** in a 32:68 isomeric ratio, albeit in 28% yield. Triene *E*/*Z*-**224** was produced in a *E*:*Z* ratio of 10:1 (entry 6).

Unfortunately, as seen in Scheme 63, addition of **162** to pre-mixed solution of $[Ir(COD)Cl]_2$ and $AgBF_4$ resulted in a complex mixture of more non-polar products. The absence of the resonance at 4.19 ppm corresponding to H_a in the ^1H NMR indicates that the secondary alcohol was either eliminated or oxidized during the reaction. However, the complex nature of the mixture obtained prevents conclusive identification of its many products.

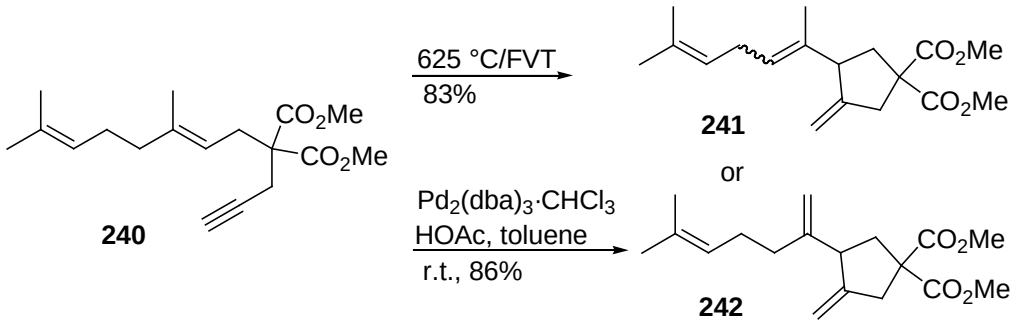


Scheme 63: Reaction of 162 with $[Ir(COD)Cl]_2$ and $AgBF_4$

The results summarized in Table 22 demonstrate that the allenic carbocyclization of allene-ynes containing an isobutylene group can be performed with $[Ir(COD)Cl]_2$ and $AgBF_4$ to access trienes with an appending trisubstituted alkene side chain in high *E*:*Z* selectivies. However, the low yield obtained for ether-tethered trienes **223**/*E*/*Z*-**224** and the complex mixture obtained from allene-yne **162** (Scheme 63) indicate that the iridium catalyst system derived from $[Ir(COD)Cl]_2/AgBF_4$ is not as functional group tolerant as $[Rh(CO)_2Cl]_2$.

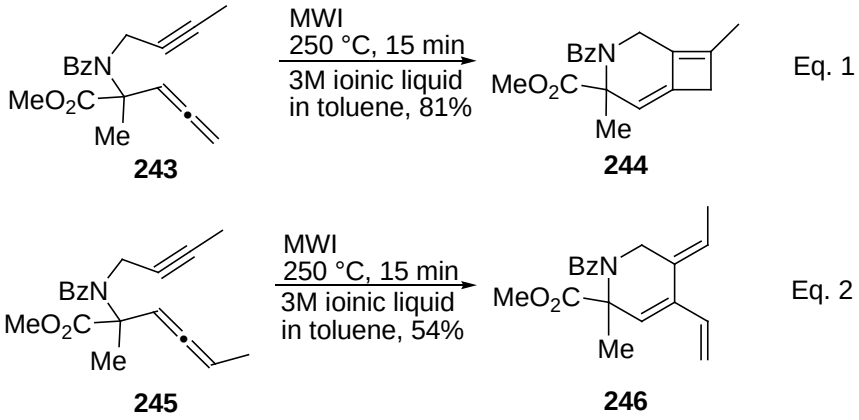
1.11.5.7 The Thermally Induced Ene Cyclization of Allene-yne 162

In 1985 Trost and Lautens found that heating enyne **240** to 625 °C produced only skipped diene **241** in 83% yield.[120] The selective formation **241** results from exclusive abstraction of a methylene hydrogen during the thermally-induced cyclization (Scheme 64). Alternatively, the palladium-catalyzed carbocyclization[121] reaction of **240** with $Pd_2(dba)_3{\cdot}CHCl_3$ and HOAc gave only **242**, resulting from selective β-hydride elimination of a methyl group hydrogen.



Scheme 64: Carbocyclization of Enyne 240[120, 121]

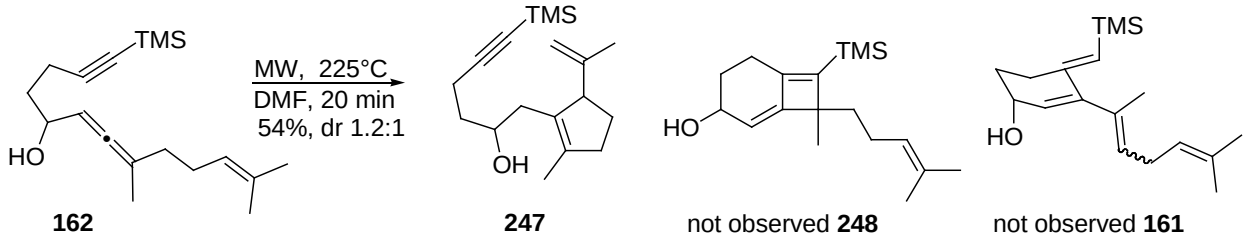
More recently in 2005, the Brummond group has shown that microwave irradiation (MWI) can be employed for the construction of bicycle[4.2.0]octa-1,6-dienes and cross-conjugated trienes from allene-yne precursors.[145] As seen in Eq. 1 of Scheme 65, microwave irradiation of allene-yne **243**, which possesses a terminal allene, yields cyclobutene **244** in 81% yield. Alternatively, subjecting disubstituted allene-yne **245** to MWI results in the selective formation of cross-conjugated triene **246** in 54% yield (Scheme 65, Eq. 2).



Scheme 65: Microwave Irradiation of Allene-ynes[145]

In view of these results, we investigated microwave irradiation reaction conditions for the carbocyclization of allene-yne **162**. Heating **162** to 225 °C for 20 min produced cyclopentene **247** in 54% yield as a ~1:1 separable mixture of diastereomers (Scheme 66). Interestingly, the formation of cyclobutene **248** and cross-conjugated triene **161** was not observed during this reaction. The selective formation of **247** indicates that the ene reaction between the allene and

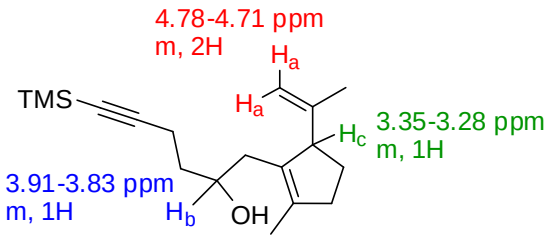
alkene functionalities of **162** is faster than both the [2 + 2] cycloaddition and the allenic carbocyclization between the allene and alkyne moieties.



162 **247** not observed **248** not observed **161**

Scheme 66: Selective Formation of Cyclopentene 247 from Allene-yne 162

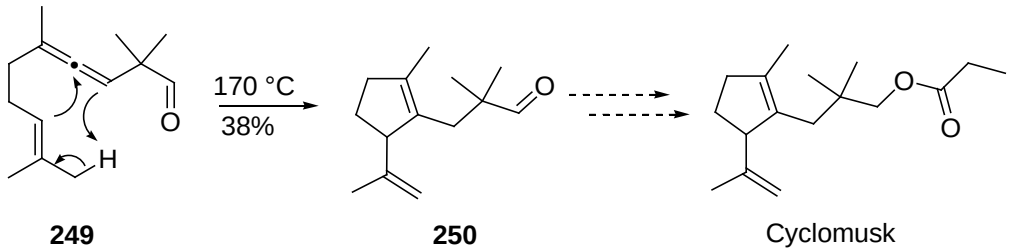
The ^{1}H NMR of the more polar diastereomer of **247** has a resonance at 4.78-4.71 ppm corresponding to the 1,1-disubstituted alkene protons H_a (Figure 14). The resonances at 3.91-3.83 ppm and 3.35-3.28 ppm correspond to H_b and the bis-allylic proton H_c, respectively. Additionally, the IR spectrum has absorbances at 3345 cm^{-1} and 2174 cm^{-1} that support the presence of the alcohol and alkyne functionalities.[81]



247

Figure 14: Assignment of H_a H_b, and H_c in the ^{1}H NMR Spectrum of 247 (500 MHz, $CDCl_3$)

The formation of **247** is exciting as it possesses the 1-methyl-3-(prop-1-ene-2yl)cyclopentene scaffold found in a variety of biologically interesting compounds like Cyclomusk®,[146] a cyclopentenyl ethyl ester that has a strawberry-like musky odor (Scheme 67). Interestingly, cyclopentenyl aldehyde **250**, a precursor to Cylcomusk®, has been previously synthesized via a thermally-induced ene reaction of allene-ene **249** in 38% yield by Érman and coworkers.[147]



Scheme 67: Thermal Cyclization of Allene-ene 249[147]

1.11.5.8 Summary and Conclusions for the Allenic Carbocyclization Reaction of Allene-ynes with an Appending Isobutylene Group

We have achieved the first instance of a Rh(I)-catalyzed allenic carbocyclization reaction wherein an isobutylene group is appended to the allene-yne substrate to selectively produce cross-conjugated trienes containing a 1,1-disubstituted alkene side chain. The scope and limitation studies conducted indicate that a coordinating isobutylene functionalitity can be used to control the β-hydride elimination step of the cyclization reaction. Incorporation of malonate, sulfonamide, and ether substituents into the allene-yne backbone minimally affects the reaction and regioisomerically pure cross-conjugated trienes are obtained in good yields. Substitution at the alkynyl position is also tolerated. However, the isomeric cross-conjugated trienes produced from allene-yne substrates containing a phenyl, methyl, or terminal alkyne indicates that the alkynyl-substituent can influence the selectivity of the carbocyclization reaction. The bis-diene moiety of the cross-conjugated trienes produced from TMS-alkynyl allenes could function as a powerful building block for the rapid construction of polycyclic compounds via transmissive Diels-Alder reactions.

Complementary regioselectivity of the appending alkenyl side chain is obtained by performing the Rh(I)-catalyzed carbocyclization reaction in a coordinating solvent. For

example, employing styrene as the reaction solvent produces a cross-conjugated triene that possesses the entire carbocyclic framework of fumagillol and ovalicin in high *E*:*Z* selectivity. This high yielding transformation demonstrates the utility of the Rh(I)-catalyzed carbocyclization reaction for natural product synthesis. Furthermore, it is envisioned that applying these carbocyclization reaction conditions to allene-yne (*R*)-**162** will allow for the asymmetric syntheses of (–)-fumagillol and (–)-ovalicin from a chiral cross-conjugated triene precursor.

Our investigations showed that reacting malonate- and heteroatom-tethered allene-ynes containing an isobutylene group with $[Rh(CO)_2Cl]_2$ produced α-alkylidene cyclopentenones in yields of 8-14% and 20-39%, respectively. The formation of these cyclocarbonylation by-products is unique, because typically $[Rh(CO)_2Cl]_2$ reacts with the distal double bond of the allene to give 4-alkylidene cyclopentenones.[148]

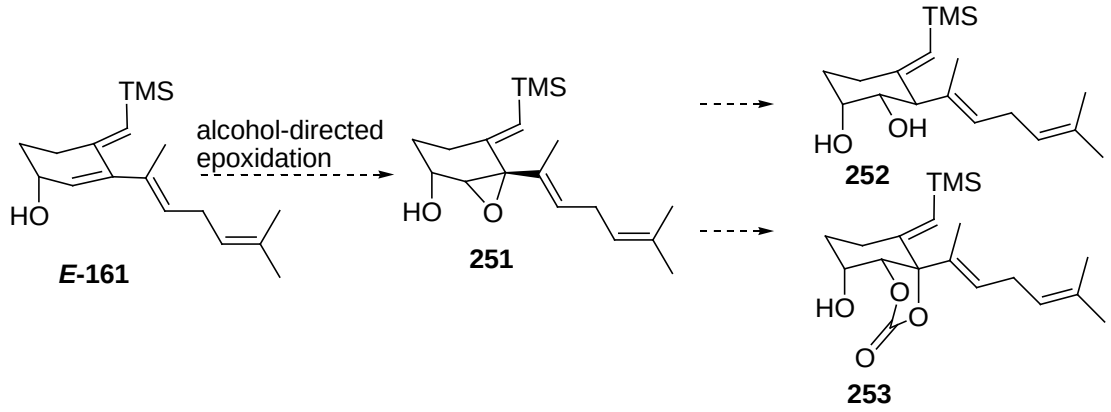
We demonstrated that $[Ir(COD)Cl]_2$ and $AgBF_4$ can be employed to transform allene-ynes containing an isobutylene group into cross-conjugated triene products in high yields and *E*:*Z* selectivities. This cationic catalyst system is advantageous as it circumvents the formation cyclopentenone by-products observed with $[Rh(CO)_2Cl]_2$.

Additionally, we have reported the construction of a cyclopentene carbocycle via a microwave irradiation-induced ene reaction of an allene-yne substrate possessing a remote alkene. This thermally induced cyclization suggests the ene reaction between the allene and alkene functionalities of allene-yne **162** is faster than the alternative [2 + 2] cycloaddition or carbocyclization reaction pathways between the allene and alkyne moieties.

1.12 INVESTIGATING THE REACTIVITY OF CROSS-CONJUGATED TRIENE *E*-161 TOWARDS SELECTIVE OXIDATION REACTIONS

1.12.1 Application of Alcohol-Directed Oxidation Reactions to Cross-Conjugated Triene *E*-161

It is envisioned that the endocyclic alkene of *E*-**161** can be selectively oxidized through an alcohol-directed epoxidation reaction to yield **251**. The bis-allylic epoxide will be converted into diol **252** through a palladium-catalyzed hydrogenolysis reaction and into carbonate **253** via a palladium-catalyzed CO_2 insertion reaction (Scheme 68). Diol **252** and carbonate **253** then will be used to access the structurally related natural products fumagillol and ovalicin, respectively.

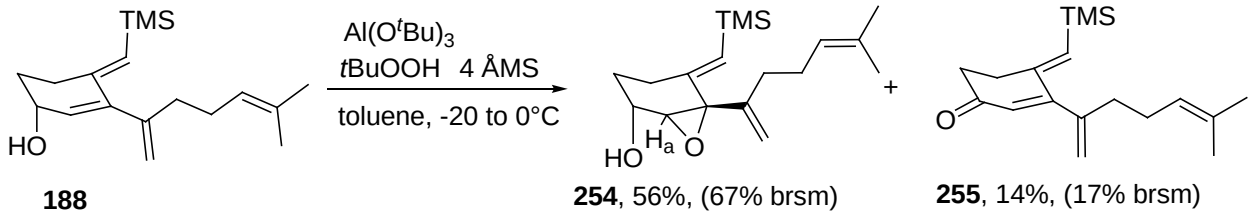


Scheme 68: Anticipated Transformations of Bis-Allylic Epoxide 251

1.12.1.1 Application of Alcohol-Directed Epoxidation Reaction Conditions to Cross-Conjugated Triene *E*-161

Reacting cross-conjugated triene **188** with $Al(O^tBu)_3$ and *t*BuOOH in the presence of 4Å MS produced bis-allylic epoxide **254** in 56% yield as a single diastereomer and enone **255** in 14%

yield (Scheme 69).[149-151] The formation of **254** is supported by the ^{1}H NMR, which has a resonance at 3.19 ppm (d, J = 1.5 Hz) corresponding to H_a.

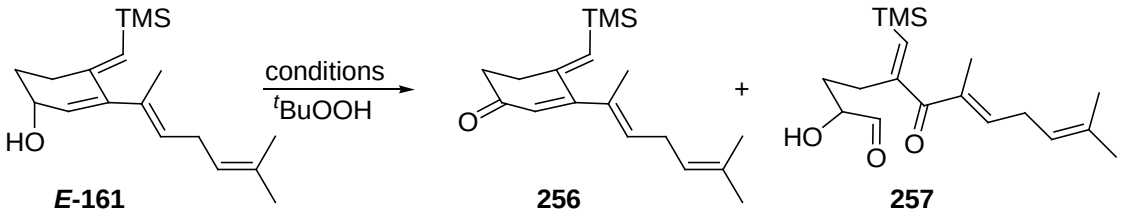


Scheme 69: Alcohol-directed Epoxidation of Cross-conjugated Triene 188

Unfortunately, reacting the isomeric cross-conjugated triene *E*-**161** with Al(O^{t}Bu)$_3$ and ^{t}BuOOH only resulted in enone **256** in 13% yield and the recovery of starting material (entry 1, Table 23). A small amount of an unknown more polar compound was also isolated from this reaction. However, based upon the single resonance in the alkene region at 5.23 ppm (tt, J = 7.0, 1.5 Hz) in the ^{1}H NMR, over-oxidation of the cross-conjugated triene system occurred. Subjecting *E*-**161** to Ti(O*i*Pr)$_4$, DIPT, and ^{t}BuOOH also resulted in a small amount of the over-oxidized compound and unreacted starting material (entry 2).[87]

Reacting *E*-**161** with VO(acac)$_2$/*t*BuOOH at reaction temperatures ranging from 70-25°C resulted in the isolation of enone **256** and aldehyde **257** (entries 3-5, Table 23).[85] Switching from VO(acac)$_2$ to VO(OEt)$_3$ again produced enone **256** and ketone **257** (entries 6-7).[152, 153] The formation of aldehyde **257** is likely due to a vanadium-catalyzed epoxide opening by *t*BuOOH. This process has been shown to be a favorable reaction pathway for 1,1-disubstituted alkenes and conjugated dienes.[154, 155] A resonance at 9.23 ppm (d, J = 2 Hz) in the ^{1}H NMR corresponds to the aldehyde proton and supports that **257** was obtained.

Table 23: Reaction of *E*-161 with Vanadium-catalyzed Epoxidation Reaction Conditions

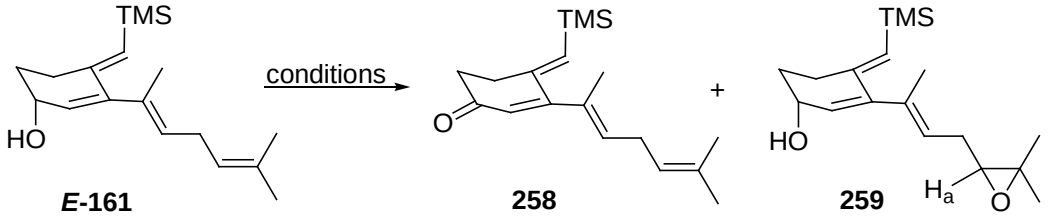


***E*-161** **256** **257**

Entry	Reagents	Temp (°C)	Yield of 256 (%)	Yield of 257 (%)
1	$Al(O^tBu)_3$,4 ÅMS	–20 to 0	13 (17 brsm)	-----
2	$Ti(O^iPr)_4$, 4 ÅMS	–20 to 0	0	0
3	$VO(acac)_2$	70	24 (27 brsm)	26 (30 brsm)
4	$VO(acac)_2$	40	8 (10 brsm)	28 (34 brsm)
5	$VO(acac)_2$	25	29 (48 brsm)	5 (9 brsm)
6	$VO(OEt)_3$	0	11 (16 brsm)	-----
7	$VO(OEt)_3$	0 to 25	trace	14
8	$Mo(CO)_6$	25 to 80	43 (50 brsm)	-----

Peracid epoxidation conditions were next investigated and *E*-**161** was reacted with *m*-CPBA and $NaHCO_3$. This reaction resulted in a 32% yield of epoxide **259** (entry 1, Table 24). A resonance at 2.81 ppm (t, J = 6.5 Hz) in the ^{1}H NMR corresponds to H_a and supports the regioselectivity of the epoxidation. Based upon integration of the resonances at 66.4 ppm and 63.3 ppm in the ^{13}C NMR, **259** was produced as a 1.2:1 mixture of diastereomers. Reacting *E*-**161** with *m*-CPBA in an emulsion[156] or with magnesium bis(monoperoxyphthalate) hexahydrate (MMPP)[157, 158] also resulted in epoxidation of the remote alkene in the side chain.

Table 24: Formation of Epoxide 259 from Cross-Conjugated Triene *E*-161



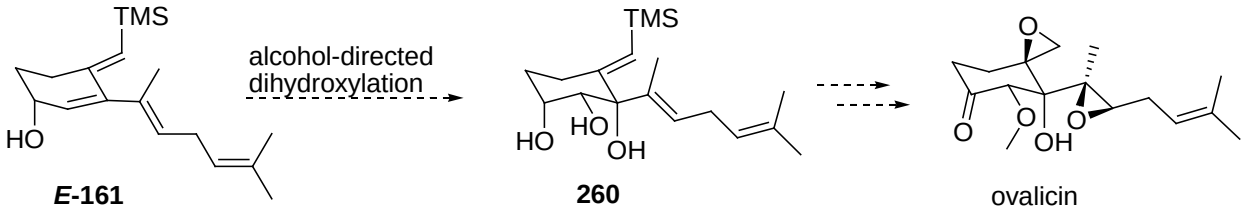
***E*-161** **258** **259**

Entry	Reagents	Temp (°C)	Yield of 259 (%)	Yield of 259 (%)
1	*m*CPBA, $NaHCO_3$	0	-----	32 (36 brsm)
2	*m*CPBA, in emulsion	25	10 (12 brsm)	9 (11 brsm)
3	MMPP, $NaHCO_3$	0 to 40	-----	29
4	TFAA, H_2O_2, Na_2HPO_4	0	complex mixture	complex mixture

The results summarized in Tables 23 and 24 indicate that the desired alcohol-directed epoxidation of *E*-**161** is a challenging process. The inability of the oxidizing reagents screened to convert *E*-**161** into bis-allylic epoxide **251** caused the examination of alcohol-directed dihydroxylation protocol.

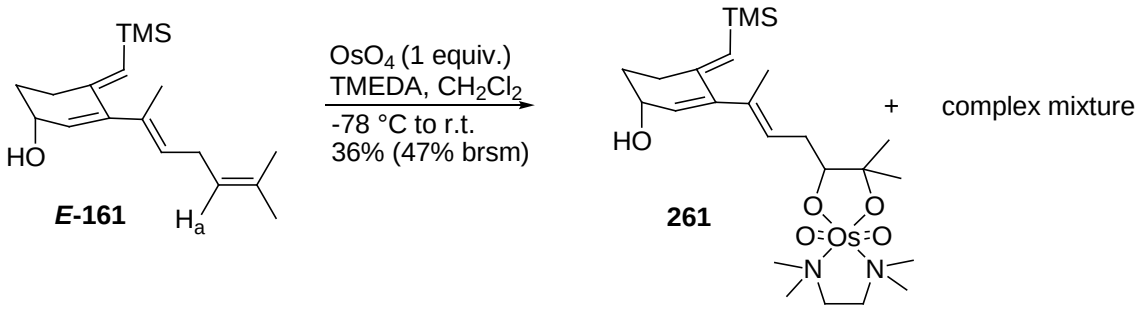
1.12.1.2 Application of Alcohol-Directed Dihydroxylation Reaction Conditions to *E*-161

An alcohol–directed dihydroxylation reaction was examined to selectively oxidize the endocyclic alkene of *E*-**161**. As seen in Scheme 70, reacting *E*-**161** with OsO_4 (1 equiv) and TMEDA is predicted to produce *syn*-triol **260**, which could be employed for the synthesis of ovalicin.



Scheme 70: Predicted Formation of Triol 261 via Dihydroxylation of Tetraene *E*-161

Subjecting *E*-**161** to the stereo- and chemoselective dihydroxylation protocol developed by Donohoe and coworkers produced osmate ester **261** in 36% yield and a complex mixture of compounds (Scheme 71).[159, 160] The presence of the osmate ester in **261** is supported by resonances at 2.85 ppm (s, 3H), 2.83 ppm (s, 3H), 2.82 ppm (s, 3H), and 2.81 ppm (s, 3H) in the ^{1}H NMR that correspond to the TMEDA methyl groups. The regioselectivity of the osmate ester is confirmed by the absence of the resonance corresponding to H_a at 5.15 ppm (tt, J = 7.0, 1.5 Hz).

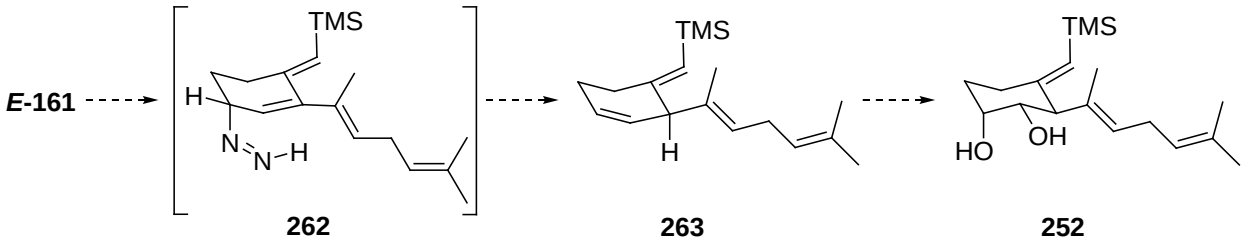


Scheme 71: Reaction of *E*-161 with Stoichiometric OsO_4 and TMEDA

The sterically congested environment of the endocyclic alkene in *E*-**161** could explain the preferential oxidation of the accessible side chain alkene. Additionally, the electron rich nature of the unconjugated alkene in *E*-**161** accounts for the increased reactivity of the remote alkene towards the electrophilic oxidizing reagents examined.

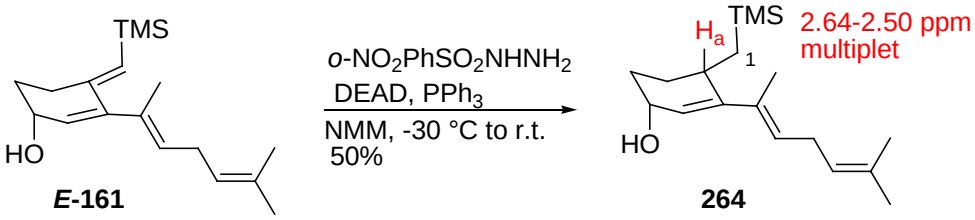
1.12.1.3 Allylic 1,3-Transposition: Exploration of Myers' Protocol for the Reductive Rearrangement of *E*-161

Myers and coworkers have developed a regio- and stereoselective method for the reductive 1,3-transposition of allylic alcohols.[161] It is anticipated that subjecting *E*-**161** to these rearrangement conditions will produce the allylic diazene intermediate **262**, which upon sigmatropic elimination will yield tetraene **263**. Subsequent dihydroxylation of the strained endocyclic alkene in **263** using Sharpless' asymmetric dihydroxylation protocol will result in diol **252**. *syn*-Diol **252** will be used in the synthesis of fumagillol (Scheme 72).



Scheme 72: Projected Synthesis of diol 252 from *E*-161

Interestingly, reacting ***E*-161** with *o*-nitrobenzenesulfonylhydrazide (NBSH), diethyl azodicarboxylate (DEAD), and triphenylphosphine (PPh_3) in *N*-methyl morpholine produced **264** in 50% yield (Scheme 73). The formation of **264** is evidenced by a resonance at 2.64-2.50 ppm (m) in the ^1H NMR that corresponds to the allylic proton H_a. Additional resonances at 0.79 ppm (dd, J = 15, 1.2 Hz), 0.73* ppm (dd, J = 15.3, 2.1 Hz), 0.61* ppm (dd, J = 15.3, 11.7 Hz), and 0.50 ppm (dd, J = 15.0, 11.7 Hz) correspond to the diastereomeric methylene protons at C1. Based upon integration of the resonances at 0.61 ppm and 0.50 ppm, **264** was produced as a 1.3:1 mixture of diastereomers, which are inseparable via column chromatography.



Scheme 73: Selective Vinyl Silane Reduction: Synthesis of 264

The selective formation of **264** from ***E*-161** using Myers' reductive rearrangement protocol is intriguing as it provides an avenue for the selective functionalization of vinyl silanes. O'Doherty and coworkers[162] have also observed that the application of Myers'[161] protocol to unsaturated systems can result in alkene reduction.

1.12.1.4 Summary and Conclusions for the Functionalization of *E*-161

In summary we have shown that the unconjugated alkene in the side chain of *E*-**161** can be selectivity oxidized under buffered peracid epoxidation conditions and Donohoe's dihydroxylation protocol. The epoxide moiety of **259** and the osmate ester in **261** could serve as an alkene protecting group that will allow for the selective oxidation of the cross-conjugated system in *E*-**161** and the syntheses of fumagillol and ovalicin.

Alternatively, subjecting *E*-**161** to Myers' reductive rearrangement reaction conditions with *o*-nitrobenzenesulfonylhydrazide (NBSH) resulted in the selective reduction of the vinyl silane moiety. In the future, the observed reduction reaction will be prevented by performing the Mitsunobu reaction with the more stable acetone hydrazone of NBSH. This transformation should allow for the formation of tetraene **263**, a potentially useful intermediate in the synthesis of fumagillol.

1.13 EXPERIMENTAL SECTION

1.13.1 General Methods

Unless otherwise noted, all reactions were performed under an atmosphere of N_2 or Ar in flame dried glassware using standard syringe, cannula, and septum techniques. All commercially available compounds were purchased from Aldrich Chemical Co., GFS Chemicals, Strem Chemicals, and Acros Organics and were used as received unless otherwise stated. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were further dried and deoxygenated using the

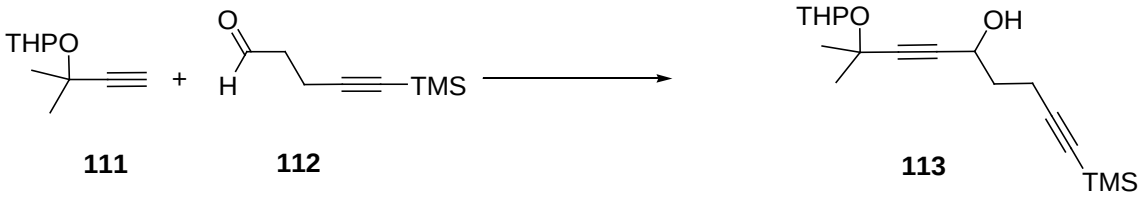
Sol-Tek ST-002 solvent purification system via activated alumina and Q5 columns under a nitrogen atmosphere. Dichloromethane (CH_2Cl_2) was further purified using the Sol-Tek ST-002 solvent purification system with an activated alumina column. Toluene, 1,2-dichloroethane (DCE), triethylamine (Et_3N), diisopropylamine (DIPA), and *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA) were freshly distilled from CaH_2 prior to use. Pyridine, *N*,*N*'-dimethylformamide (DMF), and hexamethylphosphoric amide (HMPA) were freshly distilled from CaH_2 and were stored over activated 4 Å molecular sieves.

The progress of reactions was monitored by silica gel thin-layer chromatography (TLC) plates (60 F_{254} plates of 250 μm thickness), and visualized using UV and charred using potassium permanganate, *p*-anisaldehyde, 2,4-dinitrophenylhydrazine, or cerium molybdate stain. Flash chromatography used for the purification of compounds was carried out using silica gel (32-63 μm particle size, 60 Å pore size) or a Biotage Horizon Flash Collector (40-63 μm particle size, 60 Å pore size). HPLC purification was performed on a Varian-Prostar 210 instrument using a Varian Microsorb Dynamax 100-5 Si column (5μ packing, 250 mm x 10 mm).

All ^{1}H, ^{13}C, and ^{19}F nuclear magnetic resonance spectra were taken on a Bruker 300, 500, or 600 MHz instrument, with chemical shifts (δ) reported relative to the respective solvent peak $CDCl_3$ (7.27 ppm). All NMR spectra were acquired at room temperature unless otherwise stated. The abbreviations used to describe spin multiplicity for all ^{1}H NMR spectra are as follows: s = singlet, d = doublet, t = triplet, q = quartet, b = broad, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublet, etc, etc. All infrared spectra were obtained from a Nicolet Avatar E.S.P 360 FT-IR. EI mass spectrometry was performed on a Fisons VG Autospec high resolution mass spectrometer. ESI low resolution mass spectrometry

was performed on a Hewlett Packard Series 1100 MSD LCMS and high resolution was performed on a Waters Q-Tof API-US mass spectrometer. Gas chromatography was carried out using Shimadzu GC-17A gas chromatograph equipped with an FID detector using a Shimadzu RTX-5 capillary column (Crossbond®-5% diphenyl-95% dimethylpolysiloxane, 0.25 mmID, 0.25 μm df, flow rate = 1.94 mL·min^{-1}). The GC ratios reported for the various isomeric cross-conjugated trienes were obtained using the following method: Injection temperature = 250 °C, column temperature = 80 °C to 220 °C, ramp rate = 20 °C·min^{-1}.

1.13.2 Experimental Procedures

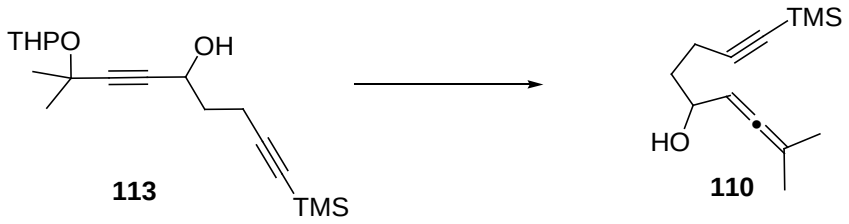


111 **112** **113**

8-Methyl-1-(trimethylsilyl)-8-(tetrahydro-2*H*-pyran-2-yloxy)nona-1,6-diyn-5-ol (113).

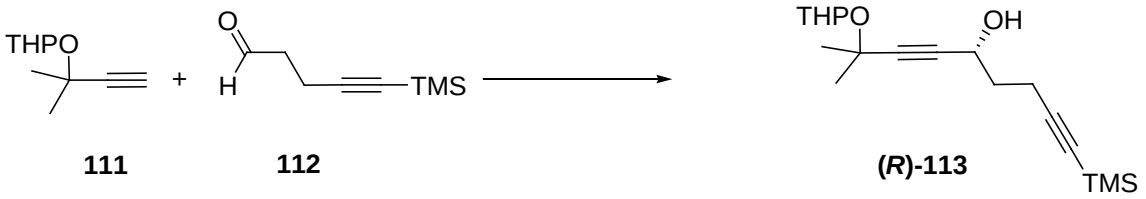
A two-necked, 25-mL round-bottomed flask is equipped with a stir bar, rubber septum, a low-temperature thermometer, and a nitrogen inlet. The flask is charged with alkyne **111**[78] (0.92 g, 5.5 mmol) and Et_2O (4 mL). The mixture is cooled between –50 and –60 ˚C with a dry ice-acetone bath and *n*-butyllithium (3.1 mL of a 1.6 M hexane soln, 5.0 mmol) is added dropwise via syringe. The reaction is stirred between –50 and –60 ˚C for 10 min before aldehyde **112**[79] (0.92 mg, 6.0 mmol) is added to the reaction via cannula. The reaction is warmed to –20 ˚C over 1 h before ice cold sat'd aq NH_4Cl is added. The aq layer was separated and extracted with EtOAc. The combined organic layers are dried over $MgSO_4$, filtered using gravity filtration, and concentrated under reduced pressure by rotary evaporation. The residue is purified by silica gel eluting with 5-20% EtOAc/hexanes to afford 1.25 g of the title compound as viscous yellow oil

in 78% yield. R_f 0.2 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.07-5.00 (m, 1H), 4.54 (q, *J* = 5.5 Hz, 1H), 3.99-3.92 (m, 1H), 3.54-3.47 (m, 1H), 2.52-2.34 (m, 2H), 2.32 (bs, 1H), 1.91 (q, *J* = 6.5 Hz, 2H), 1.88-1.78 (m, 1H), 1.76-1.65 (m, 1H), 1.62-1.50 (m, 4H), 1.53 (s, 3H), 1.48 (s, 3H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 106.1, 95.9, 87.8, 85.4, 84.1, 70.8, 63.2, 61.4, 36.4, 32.0, 30.4, 29.9, 25.4, 20.3, 15.9, 0.1 (3C); IR (thin film): 3396, 2938, 2167, 1244 cm^{-1}; EI-MS *m/z* (%) 237 (5), 221 (16), 131 (55), 85 (97), 73 (100); EI-HRMS calcd for $C_{13}H_{21}O_2Si$: *m/z* (M-C_5H_9O) 237.1311; found: 237.1315.



8-Methyl-1-(trimethylsilyl)nona-6,7-dien-1-yn-5-ol (110). A 50-mL, single-necked round-bottomed flask equipped with a reflux condenser, nitrogen inlet, and stir bar is charged with LAH (0.38 g, 9.9 mmol) and Et_2O (18 mL). The mixture is heated and stirred at reflux (oil bath temperature 40-45 °C) for 15 min before a solution of propargylic alcohol **113** (2.9 g, 9.0 mmol) in Et_2O (3.6 mL) is added dropwise over 5-10 min to the refluxing reaction via cannula. Immediately after the addition is complete, the reaction mixture is cooled to rt and diluted with Et_2O. To the flask is slowly added H_2O (0.4 mL), 10% NaOH (0.8 mL), followed by sat'd aq KF solution (1.5 mL). After stirring for 5 min at rt, the resulting solids are filtered off via gravity filtration. The solids are washed with Et_2O and the filtrate is concentrated under reduced pressure by rotary evaporation. The residue is purified by silica gel chromatography eluting with 5-10% Et_2O/pentanes to afford allenyl alcohol **110** (1.61 g in 81% yield) as a light yellow oil. R_f 0.4 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.12-5.04 (m, 1H), 4.22 (q, *J* = 6.7 Hz, 1H), 2.39-2.33 (m, 2H), 1.84 (bs, 1H), 1.82-1.70 (m, 2H), 1.73 (s, 3H), 1.72 (d, *J* = 0.6 Hz,

3H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.8, 106.9, 99.1, 93.1, 84.9, 69.1, 36.0, 20.6 (2C), 16.1, 0.1 (3C); IR (thin film): 3356, 2958, 2175, 1968, 1249 cm^{-1}; EI-MS *m/z* (%) 222 (3, $M^{+\cdot}$), 207 (4), 179 (23), 70 (51), 61 (100); EI-HRMS calcd for $C_{13}H_{22}OSi$: *m/z* ($M^{+\cdot}$) 222.1440; found: 222.1435.

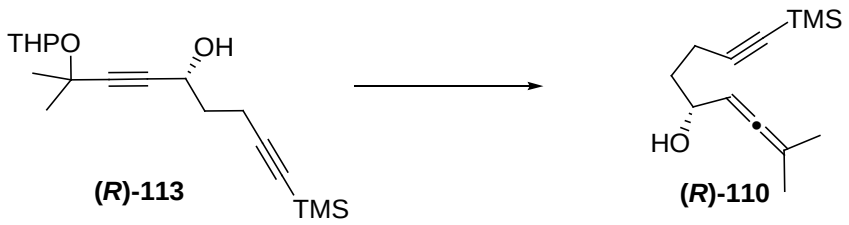


111 **112** **(*R*)-113**

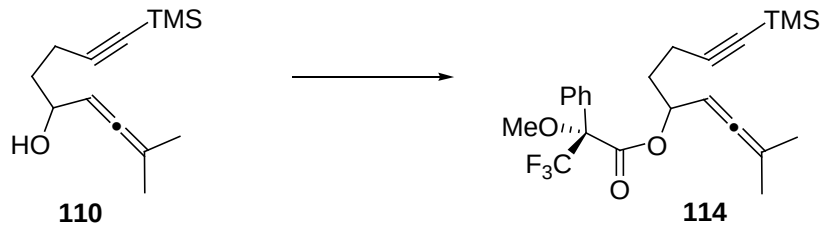
(*R*)-8-Methyl-1-(trimethylsilyl)-8-(tetrahydro-2*H*-pyran-2-yloxy)nona-1,6-diyn-5-ol (*R*-113)

A 100-mL, single-necked, round-bottomed flask equipped with a stir bar, nitrogen inlet, rubber septum, $Zn(OTf)_2$ (2.83 g, 7.79 mmol) and (+)-*N*-methylephedrine (1.44 g, 8.05 mmol) is purged with nitrogen for 15 min. To the flask is then added anhydrous toluene (22 mL), and Et_3N (1.12 mL, 8.05 mmol) via syringe. The resulting mixture is vigorously stirred at rt for 2 h before alkyne **111** (1.35 g, 8.05 mmol) is added to the reaction flask by syringe. After 15 min, a solution of aldehyde **112** (400 mg, 2.60 mmol) in toluene (6.5 mL) is added to the flask over 4 h via syringe pump addition. When the addition of aldehyde **112** is complete, the reaction is observed to be complete by TLC and sat'd aq NH_4Cl is added. The reaction mixture is transferred to a separatory funnel and the layers are separated. The aq layer is extracted with Et_2O and the combined organic layers are washed with brine, dried over $MgSO_4$, and filtered using gravity filtration. The filtrate is concentrated under reduced pressure by rotary evaporation and the resulting residue is purified on silica gel eluting with 5-20% EtOAc/hexanes to afford 611 mg of the title compound as viscous yellow oil in 73% yield. R_f 0.2 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.05-5.00 (m, 1H), 4.51 (q, *J* = 5.7 Hz, 1H), 3.99-3.90 (m, 1H), 3.55-3.46 (m, 1H), 2.84-2.65 (m, 1H), 2.51-2.30 (m, 2H), 1.89 (q, *J* = 6.9 Hz, 2H), 1.85-1.75 (m,

1H), 1.75-1.64 (m, 1H), 1.61-1.50 (m, 4H), 1.51 (s, 3H), 1.47 (s, 3H), 0.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 106.1, 95.9, 87.6, 85.3, 84.2, 70.8, 63.1, 61.2, 36.4, 31.9, 30.4, 29.9, 25.3, 20.3, 15.9, 0.0 (3C).



(*R*)-8-Methyl-1-(trimethylsilyl)nona-6,7-dien-1-yn-5-ol (*R*-110). A 5-mL, single-necked round-bottomed flask equipped with a reflux condenser, nitrogen inlet, and stir bar is charged with LAH (48 mg, 1.3 mmol) and Et_2O (2.3 mL). The mixture is heated and stirred at reflux (oil bath temperature 40-45 °C) for 15 min before a solution of propargylic alcohol (*R*)-**113** (370 mg, 1.14 mmol) in Et_2O (0.5 mL) is added dropwise over 2-5 min to the refluxing reaction via cannula. Immediately after the addition is complete, the reaction mixture is cooled to rt and diluted with Et_2O. To the flask is slowly added H_2O (48 μL), 10% NaOH (96 μL), followed by sat'd aq KF solution (192 μL). After stirring for 5 min at rt, the resulting solids are filtered off via gravity filtration. The solids are washed with Et_2O and the filtrate is concentrated under reduced pressure by rotary evaporation. The residue is purified by silica gel chromatography eluting with 5-10% Et_2O/pentanes to afford allenyl alcohol (*R*)-**110** (114 mg in 45% yield) as a light yellow oil. R_f 0.4 (20% EtOAc/hexanes); $[\alpha]_D^{23}$ = -29.6 (c = 1.14 in CH_2Cl_2).



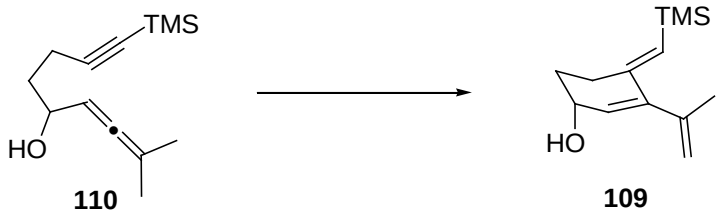
110 **114**

8-Methyl-1-(trimethylsilyl)nona-6,7-dien-1-yn-5-yl 3,3,3-trifluro-2-methoxy-2-phenyl-propanoate (114). A 5-mL, single-necked round-bottomed flask equipped with a rubber septum, nitrogen inlet, and stir bar is charged with (*R*)-(+)-alpha-methoxy-alpha-(trifluromethyl)-phenylacetic acid (41 mg, 0.18 mmol), *N*,*N*'-dicyclohexylcarbodiimide (36 mg, 0.18 mmol), and CH_2Cl_2 (0.3 mL). To the flask is then sequentially added allene-yne **110** (13 mg, 0.06 mmol) in CH_2Cl_2 (0.3 mL) via cannula, and DMAP (4 mg, 0.03 mmol) in one portion. The reaction is stirred at rt until consumption of **110** is observed by TLC. The reaction mixture is transferred into a separatory funnel containing Et_2O and sat'd aq $NaHCO_3$. The aq layer is separated and extracted with Et_2O (3X). The combined organic layers are washed with H_2O, brine, are dried over $MgSO_4$, and filtered via gravity filtration. The filtrate is concentrated under reduced pressure by rotary evaporation to give 21 mg of ester **114** in 82% crude yield. R_f 0.7 (20% EtOAc/hexanes); ^{19}F NMR (300 MHz, $CDCl_3$): δ -72.1 (s, 1F), -72.2 (s, 1F). Enantiomeric excess: 0%.

(*R*)-110 **(*R*)-114**

(2*S*)-(*R*)-8-Methyl-1-(trimethylsilyl)nona-6,7-dien-1-yn-5-yl 3,3,3-trifluro-2-methoxy-2-phenylpropanoate (*R*-114). A 5-mL, single-necked round-bottomed flask equipped with a rubber septum, nitrogen inlet, and stir bar is charged with (*R*)-(+)-alpha-methoxy-alpha-

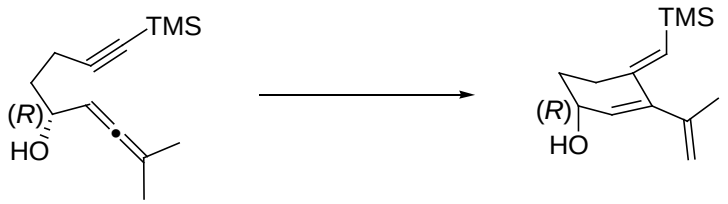
(trifluromethyl)-phenylacetic acid (66 mg, 0.28 mmol), *N*,*N*'-dicyclohexylcarbodiimide (58 mg, 0.28 mmol), and CH_2Cl_2 (0.4 mL). To the flask is then sequentially added allene-yne (*R*)-**110** (21 mg, 0.09 mmol) in CH_2Cl_2 (0.4 mL) via cannula, and DMAP (6 mg, 0.05 mmol) in one portion. The reaction is stirred at rt until consumption of (*R*)-**110** is observed by TLC. The reaction mixture is transferred into a separatory funnel containing Et_2O and sat'd aq $NaHCO_3$. The aq layer is separated and extracted with Et_2O (3X). The combined organic layers are washed with H_2O, brine, are dried over $MgSO_4$, and filtered via gravity filtration. The filtrate is concentrated under reduced pressure by rotary evaporation to give 35 mg of ester (*R*)-**114** in 85% crude yield. R_f 0.7 (20% EtOAc/hexanes); ^{19}F NMR (300 MHz, $CDCl_3$): δ -72.1 (s, 1F), -72.2 (s, 28F). Enantiomeric excess: 93%.



110 **109**

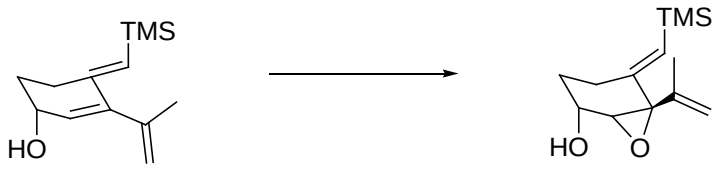
(4*E*)-3-(6-Methylhepta-1,5-dien-2-yl)-4-((trimethylsilyl)methylene)cyclohexen-2-ol (109) A flame-dried 500-mL, single-necked round-bottomed flask equipped with a stir bar, rubber septum, and argon balloon is charged with allene-yne **110** (2.19 g, 9.85 mmol) and 1,4-dioxane (197 mL). Argon is bubbled through the solution using a balloon filled with argon attached to a syringe, then $[Rh(CO)_2Cl]_2$ (191 mg, 0.495 mmol) is added in one portion. The mixture is heated and stirred at 65 °C for 20 min before consumption of **110** is observed by TLC. The solution is cooled to rt and is concentrated under reduced pressure by rotary evaporation. The residue is purified by silica gel chromatography eluting with 5-20% Et_2O/pentanes to afford 1.67 g of cross-conjugated triene **109** in 76% yield. R_f 0.4 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 5.60 (d, J = 3.2 Hz, 1H), 5.43 (s, 1H), 4.94-

4.88 (m, 1H), 4.80-4.74 (m, 1H), 4.28-4.21 (m, 1H), 2.48 (ddd, *J* = 14.6, 7.9, 3.7 Hz, 1H), 2.26 (dddd, *J* = 14.8, 9.9, 3.7, 1.3 Hz, 1H), 1.93 (ddt, *J* = 12.5, 7.9, 4.3 Hz, 1H), 1.76 (d, *J* = 0.9 Hz, 3H), 1.66-1.55 (m, 1H), 0.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.9, 146.0, 145.0, 128.2, 126.9, 114.7, 107.2, 66.1, 31.4, 28.0, 23.1, 0.0 (3C); IR (thin film): 3319, 2953, 1578, 1248 cm^{-1}; EI-MS *m/z* (%) 222 (6, $M^{+\cdot}$), 205 (11), 132 (71), 117 (56), 73 (100); EI-HRMS calcd for $C_{13}H_{22}OSi$: *m/z* ($M^{+\cdot}$) 222.1440; found: 222.1439.



(*R*)-110 **(*R*)-109**

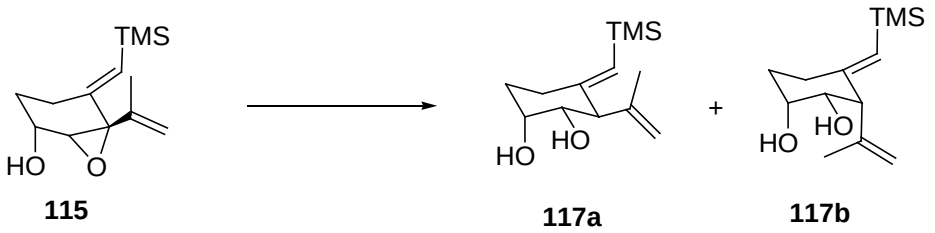
(*R*,4*E*)-3-(6-Methylhepta-1,5-dien-2-yl)-4-((trimethylsilyl)methylene)cyclohexen-2-ol (*R*-109). A flame-dried 50-mL, single-necked round-bottomed flask equipped with a stir bar, rubber septum, and argon balloon is charged with allene-yne (*R*)-**110** (393 mg, 1.77 mmol) and 1,4-dioxane (35 mL). Argon is bubbled through the solution using a balloon filled with argon attached to a syringe, then $[Rh(CO)_2Cl]_2$ (34 mg, 0.09 mmol) is added in one portion. The mixture is heated and stirred at 65 °C for 20 min before consumption of (*R*)-**110** is observed by TLC. The solution is cooled to rt and is concentrated under reduced pressure by rotary evaporation. The residue is purified by silica gel chromatography eluting with 5-20% Et_2O/pentanes to afford 296 mg of cross-conjugated triene (*R*)-**109** in 75% yield. R_f 0.4 (20% EtOAc/hexanes); $[\alpha]_D^{24}$ = 61.2 (c = 0.83 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.70 (d, *J* = 3.5 Hz, 1H), 5.53 (s, 1H), 5.00 (dq, *J* = 3.0, 1.5 Hz, 1H), 4.88-4.85 (m, 1H), 4.35 (ddd, *J* = 7.0, 5.0, 3.5 Hz, 1H), 2.58 (ddd, *J* = 14.5, 8.0, 3.5 Hz, 1H), 2.37 (ddd, *J* = 14.5, 10.0, 3.5, 1.0 Hz, 1H), 2.04 (ddt, *J* = 12.5, 8.5, 4.5 Hz, 1H), 1.86 (dd, *J* = 1.5, 1.0 Hz, 3H), 1.71 (ddd, *J* = 12.5, 10.5, 7.0, 4.0, 1H), 1.51 (bs, 1H), 0.14 (s, 9H).



109 **115**

5-((Trimethylsilyl)methylene)-6-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-ol (115).

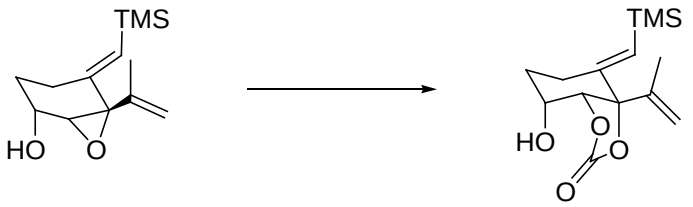
A 10-mL, single-necked, round-bottomed flask equipped with a stir bar, rubber septum, and nitrogen line is charged with $VO(acac)_2$ (3 mg, 12 μmol) and benzene (2.4 mL). A solution of allylic alcohol **109** (178 mg, 0.800 mmol) in benzene (0.4 mL) is added to the flask via cannula. The green solution is heated to 40 °C in an oil bath for 5 min before *t*-butyl hydrogen peroxide (0.24 mL of a 5.0–6.0 M decane solution, ~0.96 mmol) is added dropwise with a gas tight syringe. Upon addition of the peroxide, the reaction mixture flashes deep red and becomes orange. After 1.5 h of stirring at 40 °C (oil bath temperature), the reaction does not proceed any further as observed by TLC, and is cooled to rt. The reaction mixture is directly applied to silica gel treated with Et_3N eluting with 5-30% Et_2O/pentane to afford allylic epoxide **115** (147 mg, 77%, 86% brsm) as a light yellow oil. R_f 0.5 (35% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 5.84 (d, *J* = 1.9 Hz, 1H), 5.20-5.13 (m, 1H), 4.99 (t, *J* = 1.5 Hz, 1H), 4.15-4.03 (m, 1H), 3.22 (d, *J* = 2.0 Hz, 1H), 2.52 (ddd, *J* = 15.0, 5.4, 3.1 Hz, 1H), 2.01 (ddd, *J* = 15.0, 12.5, 3.7, 1.9 Hz, 1H), 1.90-1.78 (m, 2H), 1.76-1.71 (m, 3H), 1.53 (tdd, *J* = 12.5, 9.4, 3.2 Hz, 1H), 0.12 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.1, 142.1, 132.4, 113.0, 67.8, 67.6, 64.3, 28.8, 28.4, 20.2, -0.2 (3C); IR (thin film): 3319, 2953, 1578, 1249, 1072; EI-MS *m/z* (%) 194 (17), 179 (27), 165 (20), 84 (66), 73 (100); EI-HRMS calcd for $C_{13}H_{22}O_2Si$: *m/z* ($M^{+\cdot}$); 238.1389 found: 238.1395



115 **117a** **117b**

(*E*,1*S*,2*R*,3*S*)-4-(Trimethylsilyl)methylene)-3-(prop-1en-2-yl)cyclohexane-1,2-diol (117a), (*E*,1*S*,2*R*,3*R*)-4-(Trimethylsilyl)methylene)-3-(prop-1en-2-yl)cyclohexane-1,2-diol (117b). A 5-mL, single-necked, round-bottomed flask equipped with a stir bar, rubber septum, and argon balloon is charged with $Pd_2(dba)_3 \cdot CHCl_3$ (16 mg, 0.02 mmol) and 1,4–dioxane (0.3 mL). To the flask is added *n*-Bu_3P (8 μL, 0.03 mmol) with a gas tight syringe. A premixed solution of formic acid (118 μL, 3.08 mmol), and Et_3N (171 μL, 1.23 mmol) in 1,4–dioxane (0.3 mL) is then added to the reaction flask via cannula. After stirring at rt for 5 min, a solution of allylic epoxide **115** (147 mg, 0.62 mmol) in 1,4–dioxane (1.8 mL) is added via cannula to the dark red catalyst mixture. The reaction is heated and stirred at 40 °C in an oil bath for 40 min when the reaction is observed to be complete by TLC analysis. The reaction is quenched with H_2O which causes the reaction to turn from red to brown. The aq layer is separated and extracted with Et_2O. The combined organic layers are washed with H_2O, brine, are dried over $MgSO_4$, and filtered via gravity filtration. The filtrate is concentrated under reduced pressure by rotary evaporation. The resulting residue is purified via silica gel chromatography using a Biotage Horizon Flash Collector (Biotage Si 25 + M, 25 x 150 mm, Et_2O/pentanes = 2-50%, flow rate = 10 mL/Min) to yield 92 mg of diastereomeric diols **117a** and **117b** in 62% yield as a 1:1 isomeric mixture. R_f 0.2, 0.3 (35% EtOAc/hexanes); **desired diol 117a** ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.19 (s, 1H), 5.17 (t, *J* = 1.4 Hz, 1H), 4.89 (s, 1H), 4.14-4.12 (m, 1H), 3.73 (dd, *J* = 9.7, 2.9 Hz, 1H), 3.12 (d, *J* = 9.7 Hz, 1H), 2.47 (bs, 1H), 2.38 (td, *J* = 13.1, 4.4 Hz, 1H), 2.31 (dt, *J* = 13.5, 4.4 Hz, 1H), 2.16 (bs, 1H), 1.99 (dq, *J* = 13.4, 4.4 Hz, 1H), 1.77 (s, 3H), 1.59-1.49 (m, 1H), 0.10 (s, 9H); ^{13}C

NMR (75 MHz, $CDCl_3$): δ 155.0, 143.1, 123.4, 114.7, 73.3, 68.1, 56.5, 30.4, 28.1, 21.9, 0.2 (3C); IR (thin film): 3400, 2953, 1610, 1248, 1077 cm^{-1}; EI-MS *m/z* (%) 240 (2, $M^{+\cdot}$), 222 (8), 117 (32), 106 (39), 73 (100); EI-HRMS calcd for $C_{13}H_{24}O_2Si$: *m/z* ($M^{+\cdot}$) 240.1546; found: 240.1530. **undesired diol 117b** ^1H NMR (500 MHz, $CDCl_3$): δ 5.33 (s, 1H), 5.26 (s, 1H), 5.09-5.06 (m, 1H), 4.13 (d, *J* = 8.5 Hz, 1H), 3.69 (dddd, *J* = 11.5, 9.0, 4.5, 2.5 Hz, 1H), 2.79 (s, 1H), 2.60-2.54 (m, 1H), 2.11 (d, *J* = 9.5, 1H), 2.05-1.96 (m, 2H), 1.72 (s, 3H), 1.53 (d, *J* = 8.0, 1H), 1.50-1.43 (m, 1H), 0.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.9, 143.0, 126.6, 114.1, 73.5, 71.9, 56.3, 32.4, 31.9, 23.8, 0.2 (3C); IR (thin film): 3400, 2953, 1618, 1248, 1077 cm^{-1}; EI-MS *m/z* (%) 240 (18, $M^{+\cdot}$), 222 (54), 166 (81), 106 (100); EI-HRMS calcd for $C_{13}H_{24}O_2Si$: *m/z* ($M^{+\cdot}$) 240.1546; found: 240.1538.

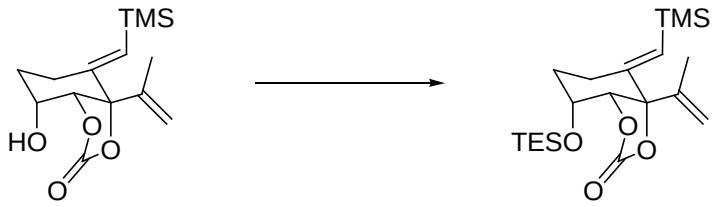


115 **118**

Hexahydro-1-hydroxy-4-((trimethylsilyl)methylene)-3-(prop-1-en-2-yl)benzo[1,3]dioxol-2-one (118). A 5-mL, single-necked, pear-shaped flask equipped with a stir bar, rubber septum, and argon balloon is charged with palladium acetate (1 mg, 4 μmol) and THF (0.2 mL). Triisopropyl phosphite (7 μL, 30 μmol) is rapidly added to the stirring orange solution with a gas tight syringe. The reaction mixture immediately turns colorless upon addition of triisopropyl phosphite and is stirred at rt for 5 min. A solution of *n*-butyllithium (6.0 μL of a 1.6 M hexane soln, 8.8 μmol) is then added to the colorless solution via syringe. After stirring for 30 min at rt, the catalyst solution is added via cannula into a 15 mL thick-walled tube containing a stirring solution of allylic epoxide **115** (35 mg, 0.15 mmol) in THF (0.2 mL) under an argon atmosphere. Dry ice (72 mg, 1.6 mmol)* is added in one portion and the tube is quickly capped. The reaction

is stirred for 5 h in the pressurized sealed tube at rt, after which time the reaction mixture is directly subjected to silica gel chromatography eluting with 5-30% EtOAc/hexanes to afford 36 mg cyclic carbonate **118** as a single diastereomer in 87% yield. R_f 0.2 (30% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.03 (s, 1H), 5.17 (d, *J* = 1.4 Hz, 1H), 5.06 (s, 1H), 4.84 (d, *J* = 3.5 Hz, 1H), 4.04 (tt, *J* = 10.9, 4.2 Hz, 1H), 2.62 (dt, *J* = 14.7, 4.1 Hz, 1H), 2.08 (dq, *J* = 12.6, 4.3 Hz, 1H), 2.04-1.98 (m, 1H), 1.96 (d, *J* = 9.9 Hz, 1H), 1.82 (s, 3H), 1.68 (qd, *J* = 11.5, 4.2 Hz, 1H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.1, 149.0, 140.3, 130.2, 115.8, 88.8, 82.4, 68.0, 29.6, 27.2, 18.3, -0.2 (3C); IR (thin film): 3434, 2955, 1814, 1249 cm^{-1}; EI-MS *m/z* (%) 267 (26), 224 (72), 179 (83), 69 (100); EI-HRMS calcd for $C_{14}H_{22}O_4Si$: *m/z* ($M^{+\cdot}$) 282.1287; found: 282.1295.

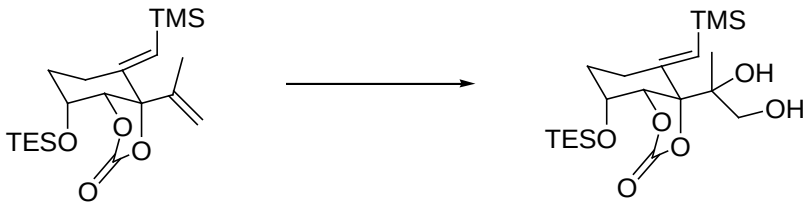
- The quantity of dry ice used was based upon the calculated amount leading to a pressure of 2.72 atm in a 15 mL tube



118 **132**

Hexahydro-1-(triethylsilyloxy)-4-((trimethylsilyl)methylene)-2-oxo-3-(prop-1-en-yl)benzo-[1,3]dioxol-7-one (132). A 10-mL, single-necked, round-bottomed flask equipped with a stir bar, rubber septum, and nitrogen line is charged with allylic carbonate **118** (118 mg, 0.418 mmol), DMF (3 mL), and imidazole (43 mg, 0.63 mmol). The reaction mixture is then cooled to 0 °C in an ice bath and TESCl (84 μL, 0.50 mmol) is added dropwise via syringe. The reaction is slowly warmed to rt and is stirred until consumption of starting material is observed by TLC. The reaction mixture is transferred into a separatory funnel containing H_2O and Et_2O. The aq layer is separated and extracted with Et_2O. The combined organic layers are washed with H_2O,

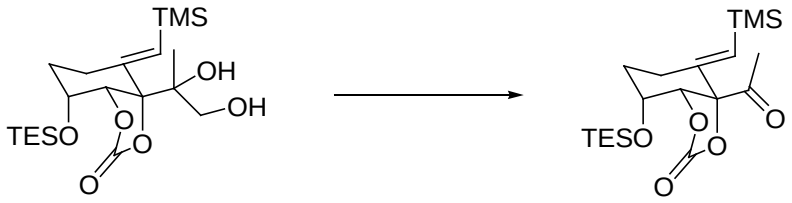
brine, are dried over $MgSO_4$, and filtered via gravity filtration. The filtrate is concentrated under reduced pressure by rotary evaporation. The residue is purified by silica gel chromatography eluting with 5% Et_2O/pentane to give the desired silyl ether **132** (116 mg) in 70% yield as a colorless oil. R_f 0.7 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 5.94 (s, 1H), 5.13 (s, 1H), 5.06 (s, 1H), 4.61 (d, *J* = 3.3 Hz, 1H), 4.09 (dt, *J* = 8.1, 3.9 Hz, 1H), 2.63 (dt, *J* = 15.0, 5.1 Hz, 1H), 2.14-1.98 (m, 1H), 1.91-1.77 (m, 2H), 1.79 (s, 3H), 0.97 (t, *J* = 8.1 Hz, 9H), 0.63 (q, *J* = 8.1 Hz, 6H), 0.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.7, 148.9, 141.1, 129.6, 115.1, 88.2, 82.2, 67.6, 28.8, 26.4, 18.3, 6.7 (3C), 4.7 (3C), -0.3 (3C); IR (thin film): 2955, 1812, 1249, 1098 cm^{-1}; ESI-MS *m/z* (%) 419 (100, $[M+Na]^+$), 375 (9), 335 (21), 131 (32); ESI-HRMS calcd for $C_{20}H_{36}O_4NaSi_2$: *m/z* $[M+Na]^+$ 419.2050; found: 419.2035.



132 **133**

Hexahydro-7-(triethylsilyloxy)-3-(1,2-dihydroxypropan-2-yl)-4-((trimethylsilyl)methylene)-benzo[1,3]dioxol-2-one (133). A 25-mL, single-necked, round-bottomed flask equipped with a stir bar, rubber septum, and nitrogen line is charged with silyl ether **132** (479 mg, 1.21 mmol), acetone (6 mL), and H_2O (0.7 mL). Osmium tetroxide (0.76 mL of a 2.5 wt% *tert*-butanol soln, 0.06 mmol) and NMO (142 mg, 1.21 mmol) are sequentially added. The resulting brown reaction mixture is stirred at rt until consumption of starting material is observed via TLC. The reaction mixture is then diluted with ether and solid $NaHCO_3$, Na_2SO_3, Na_2SO_4 are added. After 10 min of stirring, the solids are filtered off using gravity filtration, and the filtrate is concentrated under reduced pressure by rotary evaporation. The residue is purified on silica gel eluting with 5-50% EtOAc/hexanes to afford 362 mg of the title compound as a brown oil in

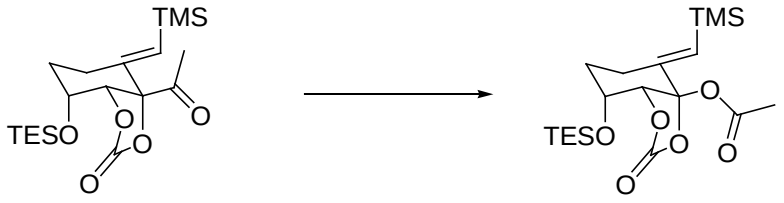
70% yield as a 9:1 mixture of diastereomers (determined by integration of the resonances at 3.97 ppm and 3.75 ppm in the ^{1}H NMR). R_f 0.3 (35% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) *designates minor diastereomer where resolved: δ 5.93 (d, *J* = 1.8 Hz, 1H), 5.82* (d, *J* = 1.5 Hz, 1H), 4.91 (d, *J* = 3.3 Hz, 1H), 4.33-4.25 (m, 1H), 4.21* (dt, *J* = 6.0, 3.3 Hz, 1H), 3.97* (A of an ABq, *J* = 11.4, 1H), 3.75 (A of an ABq, *J* = 11.9, 1H), 3.46* (B of an ABq, *J* = 11.4, 1H), 3.41 (B of an ABq, *J* = 11.9, 1H), 2.95 (bs, 1H), 2.69 (dt, *J* = 15.3, 6.6 Hz, 1H), 2.28 (dtd, *J* = 15.3, 7.2, 1.8 Hz, 1H), 2.10 (bs, 1H), 1.89-1.78 (m, 2H), 1.27 (s, 3H), 0.95 (t, *J* = 7.8 Hz, 9H), 0.61 (q, *J* = 7.8 Hz, 6H), 0.14 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.1, 150.2, 128.3, 88.5, 80.3, 75.4, 66.8, 66.3, 27.2, 26.9, 20.0, 6.7 (3C), 4.6 (3C), -0.4 (3C); IR (thin film): 3419, 2953, 1774, 1247 cm^{-1}; ESI-MS *m/z* (%) 453 (100, $[M+Na]^+$), 430 (8); ESI-HRMS calcd for $C_{20}H_{38}O_6NaSi_2$: *m/z* $[M+Na]^+$ 453.2105; found: 453.2090.



133 **134**

3-Acetylhexahydro-7-(triethylsilyloxy)-4-((trimethylsilyl)methylene)benzo[1,3]dioxol-2-one (134). A 10-mL, single-necked, round-bottomed flask equipped with a stir bar, rubber septum, and nitrogen line is charged with diol **133** (281 mg, 0.652 mmol), THF (1.8 mL) and H_2O (1.8 mL). To the light brown solution is added $NaIO_4$ (140 mg, 0.657 mmol) in one portion and the reaction is stirred until consumption of diol **133** is observed by TLC. The reaction mixture is transferred into a separatory funnel containing H_2O and Et_2O. The aq layer is separated and extracted with Et_2O until no product remains in the aq layer as observed by TLC. The combined organic layers are washed with H_2O, brine, are dried over $MgSO_4$, and filtered via gravity filtration. The filtrate is concentrated under reduced pressure by rotary evaporation. The residue

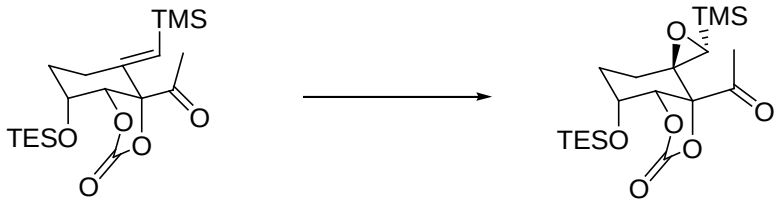
is purified by silica gel chromatography eluting with 5-10% Et_2O/pentane to give 180 mg of methyl ketone **134** as a light yellow oil in 69% yield. R_f 0.8 (35% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.03 (s, 1H), 4.75 (d, *J* = 3.3 Hz, 1H), 4.24 (dt, *J* = 6.0, 3.3 Hz, 1H), 2.56 (dt, *J* = 15.6, 5.8, 1H), 2.28 (s, 3H), 2.07 (dtd, *J* = 15.4, 7.8, 1.9 Hz, 1H), 1.90-1.73 (m, 2H), 0.93 (t, *J* = 8.0 Hz, 9H), 0.59 (q, *J* = 8.0 Hz, 6H), 0.11 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.0, 152.6, 145.6, 128.6, 89.9, 80.0, 66.6, 27.0, 23.9, 23.6, 6.6 (3C), 4.6 (3C), -0.5 (3C); IR (thin film): 2955, 1819, 1720, 1248 cm^{-1}; EI-MS *m/z* (%) 398 (14, $M^{+\cdot}$), 355 (16), 325 (100), 267 (5), 73 (16); EI-HRMS calcd for $C_{19}H_{34}O_5Si_2$: *m/z* ($M^{+\cdot}$) 398.1945; found: 398.1942.



134 **135**

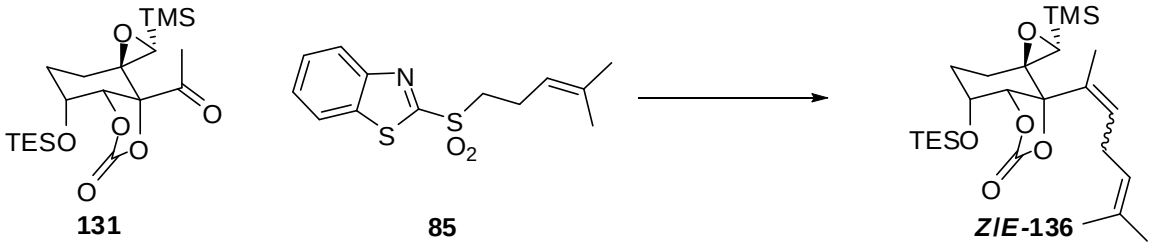
(*E*)-Hexahydro-4-(triethylsilyloxy)-7-((trimethylsilyl)methylene)-2-oxobenzo[1,3]dioxol-7-yl acetate (135). A 5-mL, single-necked, round-bottomed flask equipped with a stir bar, rubber septum, and nitrogen line is charged with vinyl silane **134** (17 mg, 0.04 mmol), CH_2Cl_2 (0.2 mL), and Na_2HPO_4 (11 mg, 0.08 mmol). The flask is cooled to 0 °C in an ice bath and a solution of *m*-CPBA (77%, 15 mg, 0.06 mmol) in 0.2 mL of CH_2Cl_2 is added via cannula. The reaction is slowly warmed to rt and is complete after 3 h as observed by TLC. The reaction mixture is transferred into a separatory funnel containing sat'd aq Na_2SO_3 and Et_2O. The aq layer is separated and extracted with Et_2O. The combined organic layers are washed with sat'd aq $NaHCO_3$, H_2O, brine, and are dried over $MgSO_4$. The solids are filtered off via gravity filtration and the filtrate is concentrated under reduced pressure by rotary evaporation. The residue is purified by silica gel eluting with 5-20% Et_2O/pentane to afford 11 mg of ketal **135** and as a light yellow oil in 62% yield. R_f 0.7 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.01 (s,

1H), 4.81 (d, *J* = 4.0 Hz, 1H), 4.26 (q, *J* = 3.5 Hz, 1H), 2.78-2.63 (m, 1H), 2.51 (dt, *J* = 16.3, 4.8 Hz, 1H), 2.10 (s, 3H), 1.93-1.83 (m, 2H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.64 (q, *J* = 7.9 Hz, 6H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3, 145.5, 130.2, 103.7, 81.1, 65.9, 25.7, 23.6, 21.6, 6.6 (3C), 4.6 (3C), -0.7 (3C); IR (thin film): 2955, 1828, 1749, 1016 cm^{-1}; EI-MS *m/z* (%) 414 (43, $M^{+\cdot}$), 341 (19), 299 (100), 283 (9), 131 (34); EI-HRMS calcd for $C_{19}H_{34}O_6Si_2$: *m/z* ($M^{+\cdot}$) 414.1894; found: 414.1885.



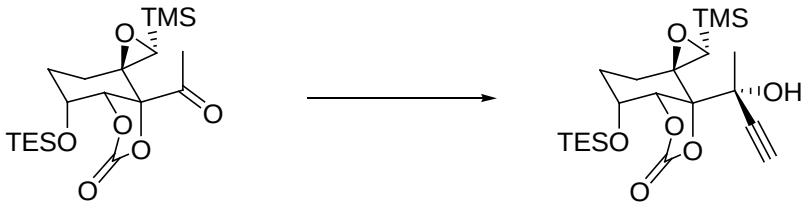
3-Acetyl-hexahydro-7-(triethylsilyloxy)-4-((trimethylsilyl)oxirane)-benzo[1,3]dioxol-2-one (136). A 15-mL, single-necked, round-bottomed flask equipped with a stir bar, reflux condenser, and nitrogen line is charged with vinyl silane **134** (228 mg, 0.573 mmol), CH_2Cl_2 (5.7 mL), and *m*-CPBA (77%, 167 mg, 0.743 mmol). The reaction is then heated and stirred at 40 °C in an oil bath until consumption of starting material is observed by TLC. The reaction mixture is cooled to rt and is transferred into a separatory funnel containing sat'd aq Na_2SO_3 and Et_2O. The aq layer is separated and extracted with Et_2O. The combined organic layers are washed with sat'd aq $NaHCO_3$, H_2O, brine, and are dried over $MgSO_4$. The solids are filtered off via gravity filtration and the filtrate is concentrated under reduced pressure by rotary evaporation. The resulting residue is purified on silica gel eluting with 50% CH_2Cl_2/hexanes to afford 172 mg of epoxide **131** in 73% yield. R_f 0.6 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.79 (d, *J* = 3.3 Hz, 1H), 4.29 (q, *J* = 3.6 Hz, 1H), 2.76 (s, 1H), 2.31 (s, 3H), 1.98-1.82 (m, 3H), 1.74-1.61 (m, 1H), 0.98 (t, *J* = 8.1 Hz, 9H), 0.68 (q, *J* = 8.1 Hz, 6H), 0.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.5, 152.8, 87.5, 80.0, 66.3, 62.2, 55.9, 27.8, 26.3, 23.1, 6.8 (3C), 4.7 (3C), -

1.9 (3C); IR (thin film): 2957, 1821, 1723, 1107 cm^{-1}; EI-MS *m/z* (%) 414 (10, $M^{+\cdot}$), 371 (39), 341 (34), 115 (49), 73 (100); EI-HRMS calcd for $C_{19}H_{34}O_6Si_2$: *m/z* ($M^{+\cdot}$) 414.1894; found: 414.1886.



Hexahydro-7-triethylsiloxy-((*Z*)-6-methylhepta-2,5-dien-2-yl)-4-((trimethylsilyl)oxirane)-benzo[α][1,3]dioxol-2-one (*Z*-136), **Hexahydro-((*E*)-6-hydroxy-6-methylhept-2-en-2-yl)-7-triethylsiloxy-4-((trimethylsilyl)oxirane)benzo[α][1,3]dioxol-2-one (*E*-136)**. A 10-mL, single-necked, round-bottomed flask equipped with a stir bar, rubber septum, and nitrogen line is charged with methyl ketone **131** (44 mg, 0.11 mmol), sulfone **85**[65] (150 mg, 0.533 mmol), and 5 mL of THF. The flask is cooled to –78 °C in a dry ice-acetone bath and LiHMDS (0.53 mL, 1.0 M soln in THF, 0.53 mmol) is added dropwise via syringe. Upon addition of LiHMDS, the reaction turns from light yellow to bright orange. After 10 min, consumption of ketone **131** is observed by TLC and cold sat'd aq NH_4Cl is added. The reaction mixture is transferred into a separatory funnel and the aq layer is separated and extracted with Et_2O. The combined organic layers are washed with H_2O, brine, and are dried on $MgSO_4$. The solids are filtered off via gravity filtration and the filtrate is concentrated under reduced pressure by rotary evaporation. The resulting residue is purified on silica gel eluting with 5% Et_2O/pentane to afford 22 mg of diene *Z*/*E*-**136** in 43% yield as a 2:98 mixture of *E*:*Z* isomers (based upon integration of the resonances at 5.59 ppm and 5.44 ppm). R_f 0.7 (20% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) *designates *E*-isomer where resolved: δ 5.59* (t, *J* = 7.5 Hz, 1H), 5.44 (tq, *J* = 7.5, 1.5 Hz, 1H), 5.05 (tt, *J* = 7.0, 1.5 Hz, 1H), 4.72 (d, *J* = 3.5 Hz, 1H), 4.54* (d, *J* = 4.0 Hz, 1H), 4.33

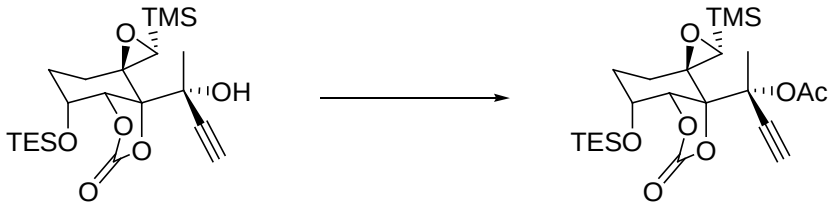
(dt, *J* = 8.0, 4.0 Hz, 1H), 4.07* (dt, *J* = 9.0, 4.0 Hz, 1H), 2.92-2.76 (m, 2H), 2.51 (ddd, *J* = 16.0, 9.0, 7.5 Hz, 1H), 2.39* (dt, *J* = 15.5, 6.0 Hz, 1H), 2.27 (s, 1H), 1.97-1.81 (m, 2H), 1.76 (s, 3H), 1.70 (s, 3H), 1.63 (s, 3H), 1.34 (ddd, *J* = 15.0, 6.5, 4.5 Hz, 1H), 0.98 (t, *J* = 7.8 Hz, 9H), 0.65 (q, *J* = 7.8 Hz, 6H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.1, 132.9, 132.6, 128.2, 122.0, 89.6, 81.8, 65.7, 59.5, 53.2, 28.4, 25.7, 25.1, 23.0, 22.6, 17.9, 6.7 (3C), 4.6 (3C), -1.8 (3C); IR (thin film): 2921, 1816, 1463, 1250 cm^{-1}; EI-MS *m/z* (%) 480 (7, $M^{+\cdot}$), 407 (18), 279 (37), 157 (49), 149 (100); EI-HRMS calcd for $C_{25}H_{44}O_5Si_2$: *m/z* ($M^{+\cdot}$) 480.2727; found: 480.2743.



131 **145**

Hexahydro-3a-(2-hydroxybut-3-yn-2-yl)-7-triethylsiloxy-4-((trimethylsilyl)oxirane)-benzo[1,3]dioxol-2-one (145). A 5-mL, single-necked, round-bottomed flask equipped with a stir bar and vacuum adaptor is charged with $CeCl_3 \cdot 7H_2O$ (135 mg, 0.362 mmol). The white solid is stirred under vacuum (4 mm Hg) and is immersed into a sand bath, which is then heated to 140 °C for 12 h. The flask is removed from the sand bath and allowed to cool to rt. The vacuum adaptor is replaced with a rubber septum and nitrogen line, and the flask is evacuated and charged with N_2 (1X). To the flask is then added 2.4 mL of THF via syringe and the resulting white suspension is vigorously stirred for 1 h before being cooled to 0 °C in an ice bath. Ethynylmagnesium bromide (0.70 mL of a 0.5 M THF soln, 0.35 mmol) is added to the white suspension dropwise via syringe. The resulting brown solution is stirred at 0 °C for 1.5 h before a solution of methyl ketone **131** (25 mg, 0.06 mmol) in 0.4 mL of THF is added to the reaction flask via cannula. Immediately upon completion of addition of **131**, the reaction is complete as observed via TLC and H_2O is added dropwise. The reaction mixture is transferred into a

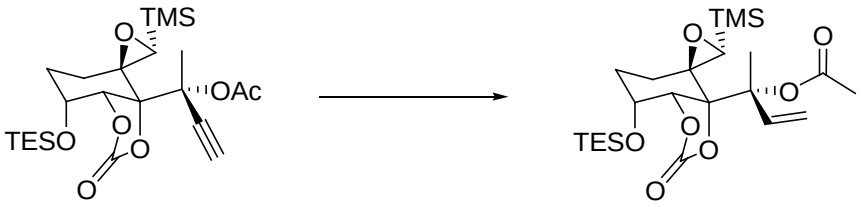
separatory funnel, and the aq layer is separated and extracted with Et_2O until no product remains as observed by TLC. The combined organic layers are washed with H_2O, brine, and are dried on $MgSO_4$. The solids are filtered off via gravity filtration and the filtrate is concentrated under reduced pressure by rotary evaporation. The residue is purified on silica gel eluting with 5-20% Et_2O/pentane to give 20 mg of propargyl alcohol **145** as a single diastereomer in 75% yield. R_f 0.3 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 5.06 (bs, 1H), 4.64 (d, *J* = 3.3 Hz, 1H), 4.27 (dt, *J* = 6.3, 3.3 Hz, 1H), 2.90 (s, 1H), 2.67 (s, 1H), 2.37-2.26 (m, 1H), 1.99-1.78 (m, 3H), 1.54 (s, 3H), 0.98 (t, *J* = 7.8, 9H), 0.67 (q, *J* = 7.8, 6H), 0.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.3, 84.3, 84.2, 80.3, 75.1, 72.8, 66.4, 65.7, 58.8, 26.4, 25.3, 24.6, 6.8 (3C), 4.6 (3C), -1.9 (3C); IR (thin film): 3402, 3308, 2956, 2114, 1815, 1251 cm^{-1}; ESI-MS *m/z* (%) 463 (100, $[M+Na]^+$), 437 (19), 405 (6), 358 (5); ESI-HRMS calcd for $C_{21}H_{36}O_6NaSi_2$: *m/z* $[M+Na]^+$ 463.1948; found: 463.1959.



145 **146**

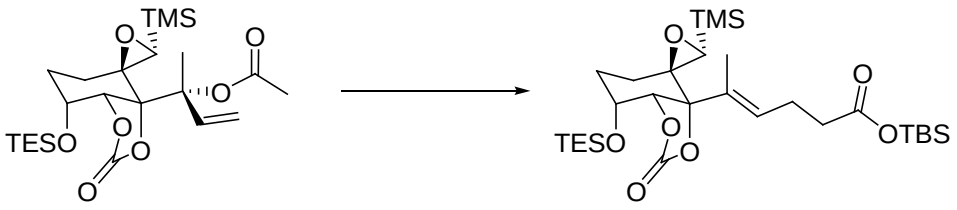
2-Hexahydro-4-triethylsiloxy-7-((trimethylsilyl)oxirane)-2-oxobenzo[1,3]dioxol-7a-yl-but-3-yn-2-yl acetate (146). A 1-mL conical vial equipped with a stir bar, rubber septum, and nitrogen line is charged with propargyl alcohol **145** (25 mg, 0.06 mmol), Et_3N (0.08 mL, 0.57 mmol), DMAP (7 mg, 57 μmol), and Ac_2O (27 μL, 0.28 mmol). The reaction is stirred at rt until consumption of **145** is observed by TLC. The reaction mixture is diluted with Et_2O and H_2O and is transferred into a separatory funnel. The aq layer is separated and extracted with Et_2O and the combined organic layers are washed with H_2O, brine, and are dried on $MgSO_4$. The solids are filtered off via gravity filtration and the filtrate is concentrated under reduced pressure by rotary

evaporation. The residue is purified on silica gel eluting with 5–20% Et_2O/pentane to give 24 mg of propargyl acetate **146** in 88% yield. R_f 0.8 (5% EtOAc/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.06 (d, *J* = 3.0 Hz, 1H), 4.24 (dt, *J* = 7.8, 3.6 Hz, 1H), 2.73 (s, 1H), 2.72, (s, 1H), 2.16-1.80 (m, 3H), 2.10 (s, 3H), 1.99 (s, 3H), 1.67 (dt, *J* = 12.3, 6.3 Hz, 1H), 0.99 (t, *J* = 8.1 Hz, 9H), 0.67 (q, *J* = 8.1 Hz, 6H), 0.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 153.0, 83.9, 81.9, 79.9, 79.3, 73.6, 67.0, 63.2, 56.1, 27.0, 25.8, 22.4, 21.7, 6.8 (3C), 4.7 (3C), -1.7 (3C); IR (thin film): 3253, 2957, 2878, 1814, 1761, 1223 cm^{-1}; ESI-MS *m/z* (%) 505 (100, $[M+Na]^+$), 443 (21), 365 (13); ESI-HRMS calcd for $C_{23}H_{38}O_7NaSi_2$: *m/z* $[M+Na]^+$ 505.2054; found: 505.2032.



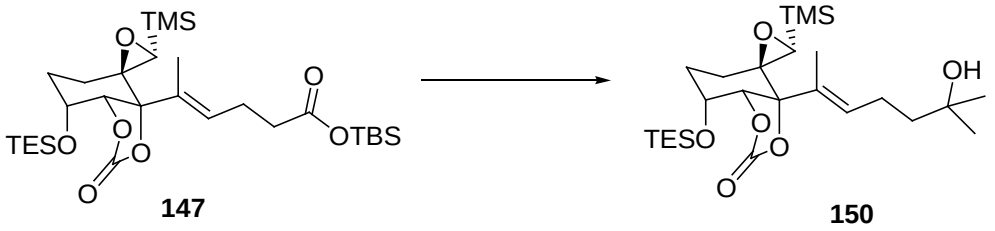
2-(Hexahydro-4-triethylsiloxy-7-((trimethylsilyl)oxirane)-2-oxobenzo[1,3]dioxol-7a-yl)-but-3-en-2-yl acetate (144). A 10-mL, single-necked, round-bottomed flask equipped with a stir bar and rubber septum is charged with propargyl acetate **146** (61 mg, 0.13 mmol), EtOH (6.3 mL), and Lindlar's catalyst (39 mg). The flask is evacuated and charged with H_2 (3X) and is vigorously stirred until consumption of **146** is observed by TLC. The reaction mixture is filtered through a sintered glass funnel of medium porosity packed with celite. The filtrate is concentrated under reduced pressure by rotary evaporation and the residue is purified by silica gel chromatography eluting with 5–20% EtOAc/hexanes to afford 46 mg of **144** in 75% yield as a light yellow oil. R_f 0.9 (5% EtOAc/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.96 (dd, *J* = 17.6, 11.1, Hz, 1H), 5.33 (d, *J* = 11.1 Hz, 1H), 5.22 (d, *J* = 17.6 Hz, 1H), 4.75 (d, *J* = 3.6 Hz, 1H), 4.23 (dt, *J* = 6.6, 3.0 Hz, 1H), 2.65 (s, 1H), 2.07 (s, 3H), 2.05-1.90 (m, 2H), 1.88 (s, 3H), 1.90-1.73 (m, 2H), 0.98 (t, *J* = 7.8 Hz, 9H), 0.66 (q, *J* = 7.8 Hz, 6H), 0.17 (s, 9H); ^{13}C NMR (75

MHz, $CDCl_3$): δ 167.9, 153.5, 136.2, 117.7, 85.8, 85.7, 80.4, 66.6, 62.6, 56.6, 26.7, 25.7, 22.2, 19.7, 6.8 (3C), 4.7 (3C), -1.8 (3C); IR (thin film): 2956, 2878, 1812, 1752, 1235 cm^{-1}; ESI-MS *m/z* (%) 507 (100, $[M+Na]^+$), 487 (64), 425 (86); ESI-HRMS calcd for $C_{23}H_{40}O_7NaSi_2$: *m/z* $[M+Na]^+$ 507.2210; found: 507.2231.



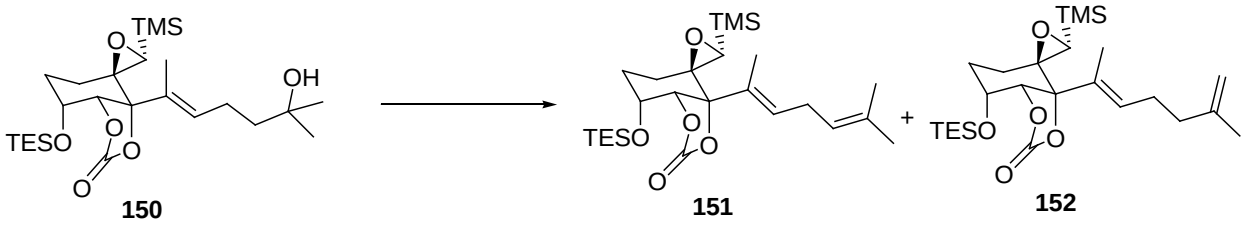
***tert*-Butyldimethylsilyl-5-((*E*)hexahydro-4-triethylsiloxy-7-((trimethylsilyl)oxirane)-2-oxobenzo[1,3]dioxol-7a-yl)hex-4-enoate (147)**. A 5-mL, single-necked, round-bottomed flask equipped with a stir bar, rubber septum, and nitrogen line is charged with THF (0.18 mL) and is cooled to –78 °C with a dry ice-acetone bath. A solution of freshly prepared LDA (64 μL of a 1.0 M THF soln, 0.06 mmol) and HMPA (18 μL) are then added to the flask via gas tight syringe. The pale yellow solution is stirred at –78 °C for 5 min before a solution of allylic acetate **144** (15.5 mg, 0.032 mmol) in 0.1 mL of THF is added via cannula. The reaction is stirred for 2 min before a solution of TBSCl (10 mg, 0.06 mmol) in 0.6 mL of THF is added to the stirring reaction via cannula. At this time, consumption of **144** is observed by TLC and the reaction is slowly warmed to rt over 2 h. After an additional 30 min, the reaction mixture is diluted with Et_2O and H_2O and is transferred into a separatory funnel. The aq layer is separated and extracted with Et_2O and the combined organic layers are washed with H_2O, brine, and are dried on $MgSO_4$. The solids are filtered off via gravity filtration and the filtrate is concentrated under reduced pressure by rotary evaporation to give 18.5 mg of **147** in 96% crude yield. R_f 0.5 (20% EtOAc/hexanes); ^1H NMR (300 MHz, C_6D_6): δ 5.76-5.68 (m, 1H), 4.13 (d, *J* = 4.5 Hz, 1H), 3.94-3.87 (m, 1H), 2.63 (ddd, *J* = 14.1, 12.0, 4.5 Hz, 1H), 2.50 (s, 1H), 2.48-2.28 (m, 2H),

2.19-2.00 (m, 5H), 1.59 (s, 3H), 1.04 (t, *J* = 7.8 Hz, 9H), 0.95 (s, 9H), 0.72-0.60 (m, 6H), 0.32 (s, 3H), 0.31 (s, 3H), 0.06 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 172.7, 153.6, 131.1, 125.8, 88.5, 78.5, 65.8, 59.6, 51.7, 35.1, 26.2, 25.8 (3C), 23.1, 23.0, 17.7, 14.9, 7.0 (3C), 5.0 (3C), -1.9 (3C), -4.7 (2C); IR (thin film): 2955, 2933, 1813, 1717, 1252 cm^{-1}; ESI-MS *m/z* (%) 621 (100, $[M+Na]^+$), 604 (28), 587 (8); ESI-HRMS calcd for $C_{29}H_{54}O_7NaSi_3$: *m/z* $[M+Na]^+$ 621.3075; found: 621.3055.



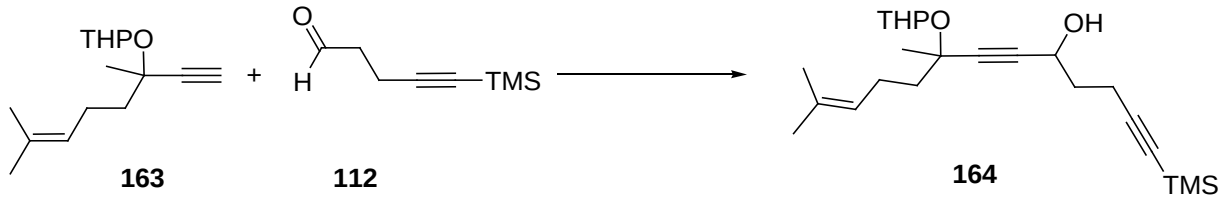
Hexahydro-((*E*)-6-hydroxy-6-methylhept-2-en-2-yl)-7-triethylsiloxy-4-((trimethylsilyl)-oxirane)benzo[α][1,3]dioxol-2-one (150). A 5-mL, single-necked, round-bottomed flask equipped with a stir bar, rubber septum, and nitrogen line is charged with crude silyl ester **147** (9.0 mg, 15 μmol) and THF (0.1 mL). The flask is cooled to –78 °C with a dry ice-acetone bath and methyllithium (21 μL of a 1.6 M diethyl ether solution, 33 μmol) is added dropwise with a gas tight syringe. After 30 min, another 2.2 equivalents of methyllithium (21 μL of a 1.6 M diethyl ether soln, 33 μmol) is added to the reaction flask via syringe and the reaction is stirred until consumption of **147** is observed by TLC. The reaction mixture is transferred into a separatory funnel Et_2O and H_2O and the aq layer is separated and extracted with Et_2O. The combined organic layers are washed with H_2O, brine, and are dried on $MgSO_4$. The solids are filtered off via gravity filtration and the filtrate is concentrated under reduced pressure by rotary evaporation. The residue is purified on silica gel eluting with 5–20% EtOAc/hexanes to give 5 mg of alcohol **150** in 67% yield. R_f 0.1 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, C_6D_6): δ 5.84 (td, *J* = 7.2, 0.9 Hz, 1H), 4.14 (d, *J* = 4.5 Hz, 1H), 3.94-3.88 (m, 1H), 2.68 (ddd, *J* = 14.1,

12.0, 4.5 Hz, 1H), 2.50 (s, 1H), 2.07-1.89 (m, 3H), 1.64 (s, 3H), 1.41-1.18 (m, 4H), 1.04 (t, *J* = 7.8, 9H), 0.96 (s, 3H), 0.95 (s, 3H), 0.72-0.60 (m, 6H), 0.03 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 153.8, 129.5, 129.4, 88.7, 78.4, 69.8, 65.8, 59.6, 51.7, 42.8, 29.4, 29.2, 26.3, 23.1, 22.9, 15.0, 7.0 (3C), 5.0 (3C), -1.9 (3C); IR (thin film): 3397, 2924, 1808, 1250 cm^{-1}; ESI-MS *m/z* (%) 521 (100, $[M+Na]^+$), 479 (76), 437 (70), 347 (27); ESI-HRMS calcd for $C_{25}H_{46}O_6NaSi_2$: *m/z* $[M+Na]^+$ 521.2731; found: 521.2715.



Hexahydro-7-triethylsiloxy-((*E*)-6-methylhepta-2,5-dien-2-yl)-4-((trimethylsilyl)oxirane)-benzo[α][1,3]dioxol-2-one (151), **Hexahydro-7-triethylsiloxy-((*E*)-6-methylhepta-2,6-dien-2-yl)-4-((trimethylsilyl)oxirane)benzo[α][1,3]dioxol-2-one (152)**. A 5-mL, single-necked, round-bottomed flask equipped with a stir bar, rubber septum, and nitrogen line is charged with tertiary alcohol **150** (9 mg, 18 μmol) and THF (0.6 mL). The flask is cooled to –78 °C with a dry ice-acetone bath and Et_3N (6 μL, 45 μmol) and MsCl (2 μL, 27 μmol) are added sequentially to the reaction flask with a gas tight syringe. The reaction is stirred for 1 h before a solution of *n*-Bu_4NBr (6 mg, 18 μmol) in 0.6 mL of THF is added via cannula. The reaction is slowly warmed to rt and is stirred for 2 h before H_2O is added. The aq layer is separated from the organic layer and is extracted with Et_2O. The combined organic layers are washed with H_2O, brine, and are dried on $MgSO_4$. The solids are filtered off via gravity filtration and the filtrate is concentrated under reduced pressure by rotary evaporation. The resulting residue is purified on silica gel eluting with 5% Et_2O/pentane to afford 4 mg of dienes **151** and **152** in 46% combined yield. Based upon integrations of the resonances at 5.07 ppm and 4.74-4.71 ppm, **151** and **152** were

produced in a 2:1 isomeric ratio, respectively. R_f 0.9 (35% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) *designates **152** where resolved: δ 5.59 (td, *J* = 7.2, 0.9 Hz, 1H), 5.07 (td, *J* = 7.2, 1.5 Hz, 1H), 4.74-4.71* (m, 1H), 4.67-4.64* (m, 1H), 4.55 (d, *J* = 3.9 Hz, 1H), 4.53* (d, *J* = 3.3 Hz, 1H), 4.31 (dt, *J* = 6.6, 3.0 Hz, 1H), 2.71 (t, *J* = 7.2 Hz, 2H), 2.60-2.46* (m, 4H), 2.27* (s, 1H), 2.26 (s, 1H), 2.15-2.00 (m, 2H), 2.00-1.85 (m, 2H), 1.71* (s, 3H), 1.69 (s, 3H), 1.67 (s, 3H), 1.61 (s, 3H), 0.99 (t, *J* = 7.7 Hz, 9H), 0.71-0.60 (m, 6H), 0.14 (s, 9H); IR (thin film): 2922, 1813, 1458, 1251 cm^{-1}; EI-MS *m/z* (%) 407 (83), 131 (26), 103 (100); EI-HRMS calcd for $C_{22}H_{35}O_5Si$: *m/z* (M-TMS) 407.2254; found: 407.2243.



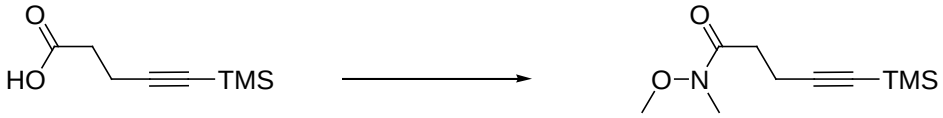
8, 12-Dimethyl-1-(trimethylsilyl)-8-(tetrahydro-2*H*-pyran-2-yloxy)trideca-11-en-1,6-diyn-5-ol (164). A two-necked, 25-mL round-bottomed flask is equipped with a stir bar, rubber septum, low-temperature thermometer, and a nitrogen inlet. The flask is charged with alkyne **163**[127] (2.4 g, 10 mmol) and Et_2O (7.2 mL). The mixture is cooled between –50 and –60 ˚C with a dry ice-acetone bath and *n*-butyllithium (5.7 mL of a 1.6 M hexane soln, 9.1 mmol) is added dropwise via syringe. The reaction is stirred between –50 and –60 ˚C for 10 min before aldehyde **112**[79] (1.7 g, 11 mmol) is added to the reaction via cannula. The reaction is warmed to –20 ˚C over 1 h. At this time, TLC analysis shows that the desired propargyl alcohol has been formed and ice cold sat'd aq NH_4Cl is added. The aq layer is separated and extracted with EtOAc (3X). The combined organic layers are washed with H_2O, brine, are dried over $MgSO_4$, and filtered via gravity filtration. The filtrate is concentrated under reduced pressure by rotary evaporation. The residue is purified on silica gel eluting with 5-30% EtOAc/hexanes to afford 2.7 g of the title

compound as viscous yellow oil in 76% yield in a 1.4:1 diastereomeric ratio (as determined by integration of the resonances at 1.49 ppm and 1.42 ppm in the ^{1}H NMR). R_f 0.3 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) *designates minor diastereomer where resolved: δ 5.18-5.00 (m, 2H), 4.57-4.45 (m, 1H), 4.01-3.88 (m, 1H), 3.56-3.45 (m, 1H), 3.06-2.83 (m, 1H), 2.51-2.29 (m, 2H), 2.21-2.06 (m, 2H), 1.93-1.63 (m, 6H), 1.67 (s, 3H), 1.61 (s, 3H), 1.58-1.50 (m, 4H), 1.49 (s, 3H), 1.42* (s, 3H), 0.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) *designates minor diastereomers where resolved: δ 131.6, 123.9, 106.2, 106.0*, 95.8, 95.1*, 95.0*, 86.8*, 86.2, 85.9, 85.2, 74.0, 73.5*, 73.4*, 63.0*, 62.9*, 62.8, 61.2*, 61.1, 43.0, 42.3*, 36.4, 32.1, 31.7*, 28.3, 27.3*, 25.6, 25.4, 25.3*, 23.4*, 23.2, 20.1, 20.0*, 17.6, 15.9, 15.8*, 0.0 (3C); IR (thin film): 3411, 2957, 2175, 1687 cm^{-1}; EI-MS *m/z* (%) 288 (22), 273 (57), 245 (43), 85 (100), 73 (39); EI-HRMS calcd for $C_{18}H_{28}OSi$: *m/z* (M-$C_5H_9O_2$) 288.1909; found: 288.1920.

164 **162**

8, 12-Dimethyl-1-(trimethylsilyl)trideca-6,7,11-trien-1-yn-5-ol (162). A 50-mL, two-necked round-bottomed flask equipped with a cold finger, nitrogen inlet, and stir bar is charged with LAH (0.32 g, 8.3 mmol) and Et_2O (15.4 mL). The mixture is heated and stirred at reflux (oil bath temperature 40-45 °C) for 10 min before a solution of propargylic alcohol **164** (2.9 g, 7.6 mmol) in Et_2O (3 mL) is added dropwise over 5-10 min to the refluxing reaction via cannula. Immediately after the addition of **164** is complete, the reaction mixture is cooled to rt and diluted with Et_2O. To the flask is slowly added H_2O (0.3 mL), then 10% NaOH (0.6 mL), followed by sat'd aq KF solution (1.2 mL). After stirring for 5 min at rt, the resulting solids are filtered off via gravity filtration. The solids are washed with Et_2O and the filtrate is concentrated under

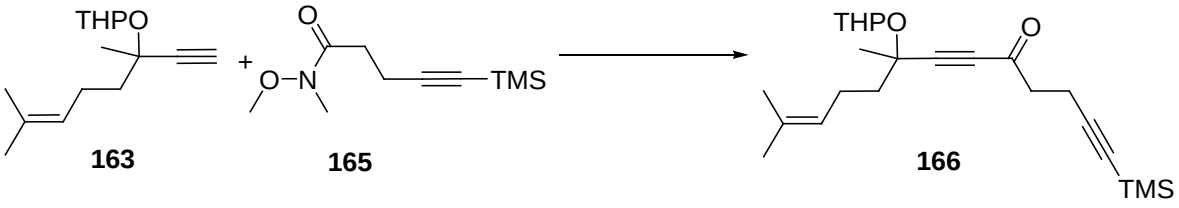
reduced pressure by rotary evaporation. The residue is purified by silica gel chromatography eluting with 5-10% Et_2O/pentanes to afford 1.6 g of allenyl alcohol **162** in 74% yield as a light yellow oil. Allene-yne **162** was produced as a 1:1 mixture of diastereomers based upon integration of the resonances at 107.0 ppm and 106.9 ppm in the ^{13}C NMR. R_f 0.4 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 5.20-5.13 (m, 1H), 5.10 (tq, *J* = 6.9, 1.5 Hz, 1H), 4.19 (q, *J* = 5.7 Hz, 1H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.16-2.05 (m, 2H), 2.03-1.95 (m, 2H), 1.95-1.84 (m, 1H), 1.84-1.70 (m, 2H), 1.71 (d, *J* = 2.7 Hz, 3H), 1.68 (d, *J* = 0.6 Hz, 3H), 1.60 (s, 3H), 0.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) *designates minor diastereomer where resolved: δ 199.2, 132.1, 124.0*, 123.9, 107.0, 106.9*, 103.4, 94.7, 84.8, 68.9, 68.8*,36.2, 36.0*, 34.0, 26.0, 25.7, 19.2*, 19.1, 17.7, 16.1, 16.0*, 0.1 (3C); IR (thin film): 3350, 2961, 2175, 1965, 1249 cm^{-1}; EI-MS *m/z* (%) 290 (73, $M^{+\cdot}$), 275 (83), 273 (89), 217 (83), 137 (100); EI-HRMS calcd for $C_{18}H_{30}OSi$: *m/z* ($M^{+\cdot}$) 290.2066; found: 290.2060.



165a **165**

***N*-Methoxy-*N*-methyl-5-(trimethylsilyl)pent-4-ynamide (165).** A 5-mL, single-necked round-bottomed flask equipped with a rubber septum, nitrogen inlet and stir bar is charged with 5-(trimethylsilyl)pent-4-ynoic acid[163] (75 mg, 0.44 mmol) and CH_2Cl_2 (1 mL). The solution is cooled to –15 ˚C with a dry ice-acetone bath before *N*-methylpiperdine (160 μL, 1.3 mmol) and isobutyl chloroformate (86 μL, 0.6 mmol) are sequentially added via syringe. After 1 h, consumption of acid **165a** is observed by TLC (R_f of acid **165a** = 0.1 in 20% EtOAc/hexanes). The reaction is warmed to 0 ˚C in an ice bath before MeNHOMe·HCl (215 mg, 2.20 mmol) and *i*PrMgCl (2.2 mL of a 2.0 M THF soln, 4.4 mmol) are added. After 30

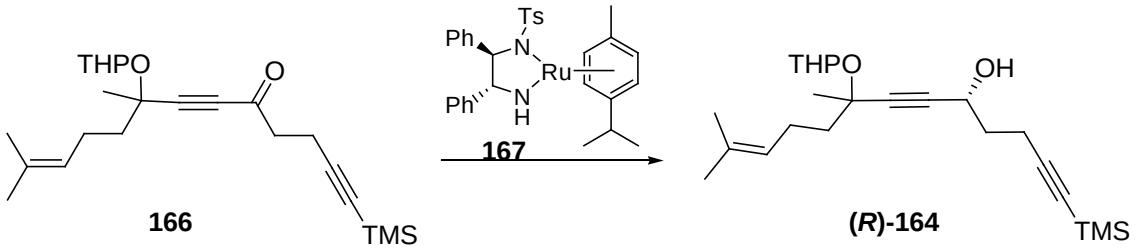
min, the reaction does not progress any longer as observed by TLC and additional MeNHOMe·HCl (86 mg, 0.88 mmol) and *i*PrMgCl (0.9 mL of a 2.0 M THF soln, 1.8 mmol) are added. The reaction is warmed to rt and is stirred until consumption of the mixed anhydride intermediate is observed via TLC (R_f of mixed anhydride = 0.7 in 20% EtOAc/hexanes). The reaction mixture is transferred into a separatory funnel containing sat'd aq NH_4Cl and EtOAc. The aq layer is separated and extracted with EtOAc (3X). The combined organic layers are washed with H_2O, brine, are dried over $MgSO_4$, and filtered via gravity filtration. The filtrate is concentrated under reduced pressure by rotary evaporation. The residue is purified by silica gel chromatography eluting with 5-30% EtOAc/hexanes to afford Weinreb amide **165** (81 mg in 87% yield). R_f 0.2 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.71 (s, 3H), 3.19 (s, 3H), 2.74-2.61 (m, 2H), 2.61-2.50 (m, 2H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 106.0, 84.9, 61.3, 36.1, 31.3, 15.3, 0.1 (3C); IR (thin film): 2960, 2176, 1669, 844 cm^{-1}; EI-MS *m/z* (%) 213 (68, $M^{+\cdot}$), 182 (41), 168 (100), 153 (42); EI-HRMS calcd for $C_{10}H_{19}NO_2Si$: *m/z* ($M^{+\cdot}$) 213.1185; found: 213.1184.



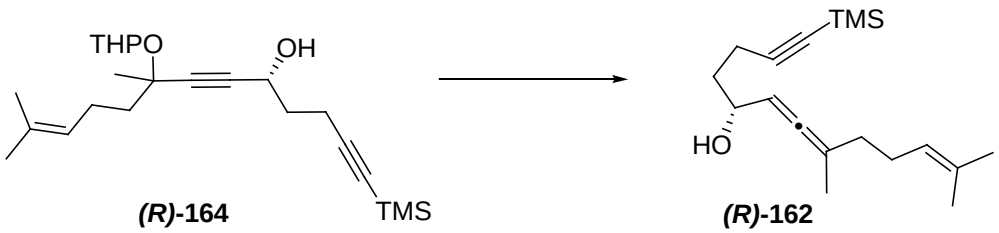
163 **165** **166**

8,12-Dimethyl-1-(trimethylsilyl)-8-(tetrahydro-2*H*-pyran-2-yloxy)trideca-11-en-1,6-diyn-5-one (166). A 5-mL, single-necked round-bottomed flask equipped with a rubber septum, nitrogen inlet and stir bar is charged with alkyne **163** (104 mg, 0.440 mmol) and THF (1.2 mL). The solution is cooled to –78 ˚C with a dry ice -acetone bath and *n*-butyllithium (0.27 mL of a 1.6 M hexane soln, 0.44 mmol) is added dropwise via syringe. The reaction is kept at –78 ˚C for 10 min before being placed in a –20 ˚C bath for 30 min.

The flask is then cooled to –78 ˚C and a solution of amide **165** (17 mg, 0.08 mmol) in 0.2 mL of THF is added via cannula. The reaction is allowed to slowly warm to 0 ˚C over 2 h and is kept at 0 ˚C for 30 min before being warmed to rt. The reaction was monitored by TLC, and after an additional 30 min of stirring at rt, consumption of amide **165** is observed. The reaction mixture is transferred into a separatory funnel containing sat'd aq NH_4Cl and EtOAc. The aq layer is separated and extracted with EtOAc (3X). The combined organic layers are washed with H_2O, brine, are dried over $MgSO_4$, and filtered via gravity filtration. The filtrate is concentrated under reduced pressure by rotary evaporation. The residue is purified by silica gel chromatography eluting with 5-20% Et_2O/pentanes to afford alkynone **166** (21 mg in 68% yield, d.r. = 1:1 based upon integration of the resonances at 185.1 ppm and 184.9 ppm in the ^{13}C NMR) as a light yellow oil. R_f 0.6 (20% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) *designates minor diastereomer where resolved: δ 5.15-5.09 (m, 1H), 5.05-5.02 (m, 1H), 5.02-4.99* (m, 1H), 4.01-3.91 (m, 1H), 3.56-3.50 (m, 1H), 2.83-2.79 (m, 2H), 2.57 (t, *J* = 7.0 Hz, 2H), 2.25-2.09 (m, 2H), 1.89-1.70 (m, 4H), 1.69 (s, 3H), 1.62 (s, 3H), 1.59-1.53 (m, 4H), 1.51 (s, 3H), 0.14 (9H); ^{13}C NMR (125 MHz, $CDCl_3$) *designates minor diastereomer where resolved: δ 185.1*, 184.9, 132.2, 123.4*, 123.3, 104.7, 104.5*, 96.3, 95.6*, 95.0*, 94.1, 85.6, 85.5*, 83.8, 83.0*, 73.8, 73.0*, 63.2, 63.1*, 44.4, 44.3*, 42.5, 41.8*, 31.9*, 31.6, 27.6*, 26.4, 25.7*, 25.3*, 23.1, 23.0*, 20.1, 20.0*, 17.6, 14.5, 0.0 (3C); IR (thin film): 2942, 2210, 2178, 1682, 844 cm^{-1}; ESI-MS *m/z* (%) 411 (100, $[M+Na]^+$), 365 (21), 217 (21); ESI-HRMS calcd for $C_{23}H_{36}O_3NaSi$: *m/z* $[M+Na]^+$ 411.2331; found: 411.2351.

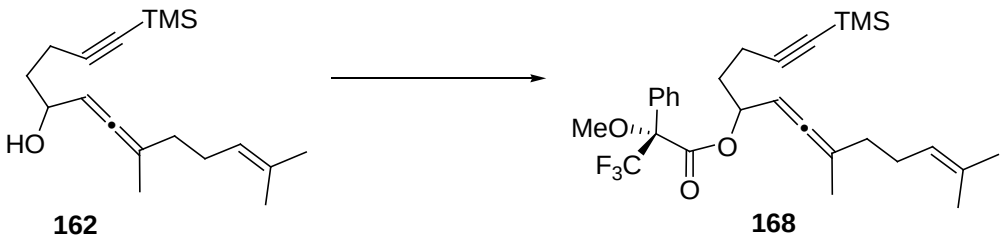


(5*R*)-8,12-Dimethyl-1-(trimethylsilyl)-8-(tetrahydro-2*H*-pyran-2-yloxy)trideca-11-en-1,6-diyn-5-ol (*R*-164). A single-necked, 10-mL round-bottomed flask equipped with a stir bar, rubber septum, and argon balloon is charged with alkynone **166** (472 mg, 1.21 mmol) and *i*PrOH (3.6 mL). Argon is bubbled through the solution using a balloon filled with argon attached to a syringe before Noyori's catalyst **167**[129, 130] (109 mg, 0.18 mmol, 0.15 equiv.) is added in one portion. Upon addition of **167**, the reaction turns dark orange/red from colorless. After 5 min of stirring at rt, consumption of alkynone **166** is observed by TLC. The reaction mixture is concentrated under reduced pressure. The residue is purified on silica gel eluting with 5-30% EtOAc/hexanes to afford 444 mg of the propargyl alcohol (*R*)-**164** as viscous yellow oil in 94% yield, d.r. = 1.6:1 (as determined by integration of the resonances at 1.51 ppm and 1.45 ppm in the ^{1}H NMR). R_f 0.3 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) *designates minor diastereomer where resolved: δ 5.14 (tt, *J* = 7.2, 1.5 Hz, 1H), 5.09-5.00 (m, 1H), 4.61-4.51 (m, 1H), 4.02-3.90 (m, 1H), 3.56-3.47 (m, 1H), 2.54-2.33 (m, 2H), 2.25-2.08 (m, 2H), 1.92 (qd, *J* = 6.9, 2.7 Hz, 2H), 1.86-1.65 (m, 4H), 1.69 (s, 3H), 1.63 (s, 3H), 1.58-1.51 (m, 4H), 1.51 (s, 3H), 1.45* (s, 3H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) *designates minor diastereomer where resolved: δ 131.6, 123.9, 106.2, 106.0*, 95.7, 95.1*, 95.0*, 86.9*, 86.2, 85.9, 85.3*, 85.2*, 85.1, 74.0, 73.5*, 73.4*, 63.0*, 62.9*, 62.8, 61.2, 61.1*, 43.0, 42.3*, 42.2*, 36.4, 32.1, 31.7*, 28.3, 27.3*, 25.6, 25.4, 25.3*, 23.4*, 23.2, 20.1, 20.0*, 17.6, 15.9, 15.8*, 0.0 (3C).



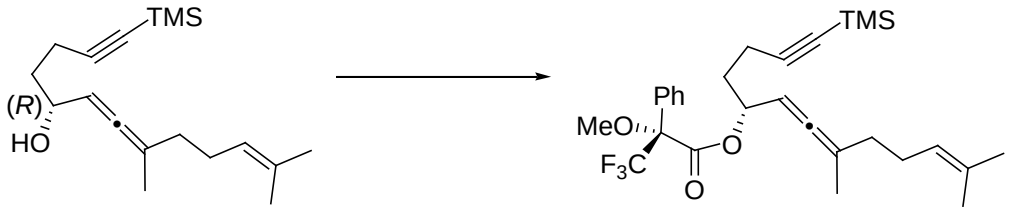
***(R)*-164** ***(R)*-162**

(*5R*)-8,12-Dimethyl-1-(trimethylsilyl)trideca-6,7,11-trien-1-yn-5-ol (*R*-162). A 10-mL, two-necked round-bottomed flask equipped with a cold finger, nitrogen inlet, and stir bar is charged with LAH (47 mg, 1.2 mmol) and Et_2O (2.3 mL). The mixture is heated and stirred at reflux (oil bath temperature 40-45 °C) for 5 min before a solution of propargylic alcohol (*R*)-**164** (440 mg, 1.13 mmol) in Et_2O (0.5 mL) is added dropwise over 3-5 min to the refluxing solution via cannula. Immediately after the addition is complete, the reaction mixture is cooled to rt and is diluted with Et_2O. To the flask is slowly added H_2O (47 μL), then 10% NaOH (94 μL), followed by sat'd aq KF solution (188 μL). After stirring for 5 min at rt, the resulting solids are filtered off via gravity filtration. The solids are washed with Et_2O and the filtrate is concentrated under reduced pressure by rotary evaporation. The residue is purified by silica gel chromatography eluting with 5-10% Et_2O/pentanes to afford allenyl alcohol (*R*)-**162** as a light yellow oil (183 mg in 56% yield, d.r. = 1.3:1 based upon integration of the resonances at 107.0 ppm and 106.9 ppm in the ^{13}C NMR). R_f 0.4 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 5.20-5.14 (m, 1H), 5.14-5.06 (m, 1H), 4.24-4.15 (m, 1H), 2.36 (t, *J* = 7.5 Hz, 2H), 2.16-2.06 (m, 2H), 2.04-1.96 (m, 2H), 1.91-1.81 (m, 1H), 1.80-1.71 (m, 1H), 1.72 (d, *J* = 2.7 Hz, 3H), 1.69 (s, 3H), 1.61 (s, 3H), 0.14 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) *designates minor diastereomer where resolved: δ 199.2, 132.2, 124.0, 107.0, 106.9*, 103.5, 94.7, 84.9, 68.9*, 68.8, 36.2*, 36.1, 34.0, 26.0, 25.7, 19.2*, 19.1, 17.8, 16.1*, 16.0, 0.1 (3C).

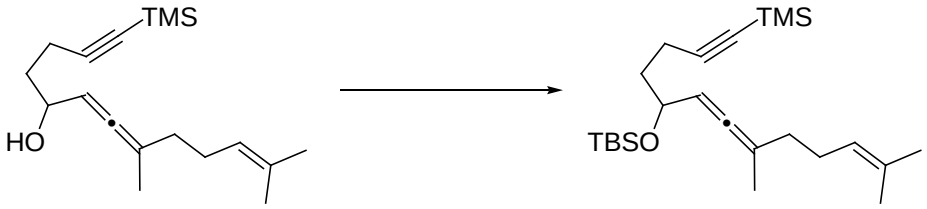


162 **168**

(2*R*)-8,12-Dimethyl-1-(trimethylsilyl)trideca-6,7,11-trien-1-yn-5-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (168). A 5-mL, single-necked round-bottomed flask equipped with a rubber septum, nitrogen inlet, and stir bar is charged with (*R*)-(+)-alpha-methoxy-alpha-(trifluromethyl)-phenylacetic acid (36 mg, 0.15 mmol), *N*,*N*'-dicyclohexylcarbodiimide (32 mg, 0.15 mmol), and CH_2Cl_2 (0.3 mL). To the flask is then sequentially added allene-yne **162** (15 mg, 0.05 mmol) in CH_2Cl_2 (0.3 mL) via cannula, and DMAP (3 mg, 0.03 mmol) in one portion. The reaction is stirred at rt until consumption of **162** is observed by TLC. The reaction mixture is transferred into a separatory funnel containing Et_2O and sat'd aq $NaHCO_3$. The aq layer is separated and extracted with Et_2O (3X). The combined organic layers are washed with H_2O, brine, are dried over $MgSO_4$, and filtered via gravity filtration. The filtrate is concentrated under reduced pressure by rotary evaporation to give ester **168** in quantitative crude yield. R_f 0.6 (20% EtOAc/hexanes); ^{19}F NMR (300 MHz, $CDCl_3$): δ -72.0 (s, 2F), -72.1 (s, 1F), -72.2 (s, 1F). Diastereomeric excess: 0%.



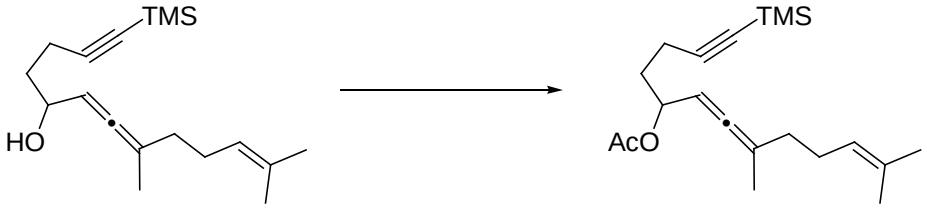
(2*R*,5*R*)-8,12-Dimethyl-1-(trimethylsilyl)trideca-6,7,11-trien-1-yn-5-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (*R*-168). A 5-mL, single-necked round-bottomed flask equipped with a rubber septum, nitrogen inlet, and stir bar is charged with (*R*)-(+)-alpha-methoxy-alpha-(triflurомethyl)-phenylacetic acid (39 mg, 0.17 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (32 mg, 0.17 mmol), and CH_2Cl_2 (0.3 mL). To the flask is then sequentially added allene-yne (*R*)-**162** (16 mg, 0.06 mmol) in CH_2Cl_2 (0.3 mL) via cannula, and DMAP (3 mg, 0.03 mmol) in one portion. The reaction is stirred at rt until consumption of (*R*)-**162** is observed by TLC. The reaction mixture is transferred into a separatory funnel containing Et_2O and sat'd aq $NaHCO_3$. The aq layer is separated and extracted with Et_2O (3X). The combined organic layers are washed with H_2O, brine, are dried over $MgSO_4$, and filtered via gravity filtration. The filtrate is concentrated under reduced pressure by rotary evaporation to give ester (*R*)-**168** in quantitative crude yield. R_f 0.6 (20% EtOAc/hexanes); ^{19}F NMR (300 MHz, $CDCl_3$): δ -72.0 (s, 0.16F), -72.1 (s, 1F), -72.2 (s, 1F). Diastereomeric ratio: 97:3.



162 **169**

5-(*tert*-Butyldimethylsilyloxy)-8,12-dimethyl-1-(trimethylsilyl)trideca-6,7,11-trien-1-yn (169). A 5-mL, single-necked round-bottomed flask equipped with a rubber septum, nitrogen inlet, and stir bar is charged with allene-yne **162** (69 mg, 0.24 mmol) and CH_2Cl_2 (1.7 mL). To the flask is sequentially added imidazole (29 mg, 0.42 mmol) and TBSCl (54 mg, 0.36 mmol). When consumption of starting material is observed by TLC, the reaction mixture is transferred into a separatory funnel containing Et_2O and H_2O. The aq layer is separated and extracted with Et_2O (3X). The combined organic layers are washed with H_2O, brine, are dried over $MgSO_4$, and filtered via gravity filtration. The filtrate is concentrated under reduced pressure by rotary evaporation. The residue is purified by silica gel chromatography eluting with 5% Et_2O/pentanes to afford silyl ether **169** as a light yellow oil (67 mg in 70% yield, d.r. = 1:1 based upon integration of the resonances at 107.4 ppm and 107.3 ppm in the ^{13}C NMR). R_f 0.8 (5% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) *designates minor diastereomer where resolved: δ 5.17-5.09 (m, 1H), 5.03-4.96 (m, 1H), 4.26-4.15 (m, 1H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.15-2.04 (m, 2H), 2.01-1.91 (m, 2H), 1.83-1.67 (m, 2H), 1.70 (s, 6H), 1.62 (s, 3H), 0.90 (s, 9H), 0.15* (s, 9H), 0.14 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) *designates minor diastereomer where resolved: δ 200.1, 199.9*, 131.8, 131.7*, 124.0, 107.4*, 107.3, 100.9*, 100.6, 94.6, 84.5, 84.4*, 71.3, 70.5*, 37.4, 34.2, 34.1*, 26.4*, 26.3, 25.9 (3C), 25.8* (3C), 25.7, 19.1, 18.7*, 18.2, 18.1*, 17.8, 17.7*, 16.3, 16.1*, 0.1 (3C), -4.2, -4.3*, -4.9; IR (thin film): 2929, 2175, 1079, 840 cm^{-1};

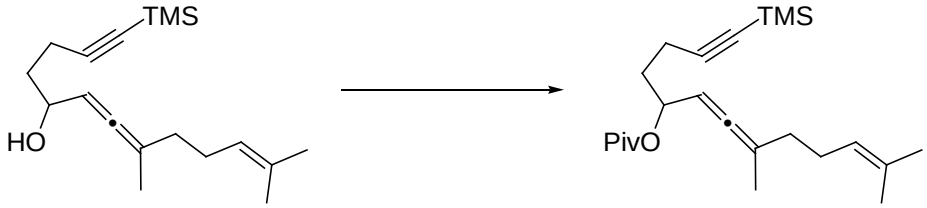
EI-MS *m/z* (%) 404 (27, $M^{+\cdot}$), 347 (53), 73 (100). EI-HRMS calcd for $C_{24}H_{44}OSi_2$: *m/z* ($M^{+\cdot}$) 404.2931; found: 404.2927.



162 **170**

8,12-Dimethyl-1-(trimethylsilyl)trideca-6,7,11-trien-1-yn-5-yl acetate (170). A 5-mL, single-necked round-bottomed flask equipped with a rubber septum, nitrogen inlet, and stir bar is charged with allene-yne **162** (102 mg, 0.351 mmol) and CH_2Cl_2 (1.2 mL). To the flask is sequentially added DMAP (4 mg, 0.04 mmol), pyridine (57 μL, 0.70 mmol), and acetic anhydride (40 μL, 0.42 mmol). When consumption of starting material is observed by TLC, the reaction mixture is transferred into a separatory funnel containing Et_2O and H_2O. The aq layer is separated and extracted with Et_2O. The combined organic layers are washed with H_2O, brine, are dried over $MgSO_4$, and filtered via gravity filtration. The filtrate is concentrated under reduced pressure by rotary evaporation. The residue is purified by silica gel chromatography eluting with 5% Et_2O/pentanes to afford allenyl acetate **170** as a light yellow oil (85 mg in 73% yield, d.r. = 1.2:1 based upon integration of the resonances at 102.6 ppm and 102.5 ppm in the ^{13}C NMR). R_f 0.5 (10% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) *designates minor diastereomer where resolved: δ 5.30-5.20 (m, 1H), 5.16-5.06 (m, 2H), 2.31 (dd, *J* = 6.9, 2.7 Hz, 1H), 2.29 (dd, *J* = 7.8, 3.0 Hz, 1H), 2.14-2.03 (m, 2H), 2.05 (s, 3H), 2.04* (s, 3H), 2.01-1.93 (m, 2H), 1.92-1.83 (m, 2H), 1.71 (d, *J* = 3.0 Hz, 3H), 1.69 (d, *J* = 1.5 Hz, 3H), 1.62 (s, 3H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) *designates minor diastereomer where resolved: δ 201.7, 201.3*, 170.2, 170.1*, 131.9, 131.8*, 124.0*, 123.9, 106.1, 102.6*, 102.5, 90.3*, 90.2, 85.0*, 84.9, 71.8, 71.6*, 33.9, 33.1, 33.0*, 26.2, 26.1*, 25.7, 21.2, 21.1*, 18.9*, 18.8, 17.7, 16.2, 16.1*,

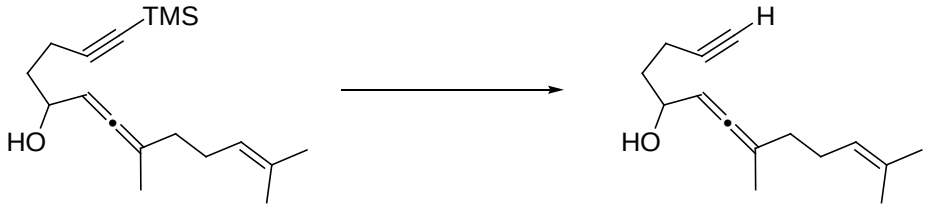
0.1 (3C); IR (thin film): 2961, 2176, 1968, 1743, 1243 cm^{-1}; EI-MS *m/z* (%) 272 (49), 221 (47), 73 (100). EI-HRMS calcd for $C_{18}H_{28}Si$: *m/z* (M-OAc) 272.1960; found: 272.1954.



162 **171**

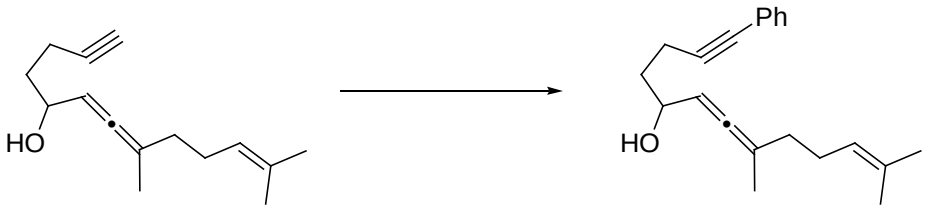
8,12-Dimethyl-1-(trimethylsilyl)trideca-6,7,11-trien-1-yn-5-yl pivalate (171). A 5-mL, single-necked round-bottomed flask equipped with a rubber septum, nitrogen inlet, and stir bar is charged with allene-yne **162** (54 mg, 0.19 mmol) and CH_2Cl_2 (0.3 mL). To the flask is sequentially added DMAP (1 mg, 9 μmol), Et_3N (65 μL, 0.47 mmol), and pivaloyl chloride (39 μL, 0.32 mmol). When consumption of starting material is observed by TLC, the reaction mixture is transferred into a separatory funnel containing sat'd aq NH_4Cl and Et_2O. The aq layer is separated and extracted with Et_2O (3X). The combined organic layers are washed with H_2O, brine, are dried over $MgSO_4$, and filtered via gravity filtration. The filtrate is concentrated under reduced pressure by rotary evaporation. The residue is purified by silica gel chromatography eluting with 5% Et_2O/pentanes to afford **171** as a light yellow oil (59 mg in 85% yield, d.r. = 1.1:1 based upon integration of the resonances at 102.6 ppm and 102.5 ppm in the ^{13}C NMR). R_f 0.6 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 5.22 (q, *J* = 6.6 Hz, 1H), 5.16-5.07 (m, 2H), 2.36-2.25 (m, 2H), 2.13-2.03 (m, 2H), 1.99-1.84 (m, 4H), 1.71-1.66 (m, 6H), 1.61 (s, 3H), 1.19 (s, 9H), 0.14 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) *designates minor diastereomer where resolved: δ 201.4, 201.0*, 177.4, 177.3*, 131.8, 131.7*, 124.0*, 123.9, 106.2, 102.6*, 102.5, 90.7*, 90.4, 84.9, 70.9, 70.7*, 38.8, 33.9, 33.3*, 33.2, 27.1 (3C), 26.5, 26.1, 26.0*, 25.7*, 19.0*, 18.9, 17.7, 16.1, 16.0*, 0.1 (3C); IR (thin

film): 2963, 2177, 1968, 1731, 1153 cm^{-1}; ESI-MS *m/z* (%) 397 (100, $[M+Na]^+$), 365 (47), 305 (9); ESI-HRMS calcd for $C_{23}H_{38}O_2NaSi$: *m/z* $[M+Na]^+$ 397.2539; found: 397.2553.



162 **172**

8,12-Dimethyltrideca-6,7,11-trien-1-yn-5-ol (172). A 10-mL, single-necked round-bottomed flask equipped with a rubber septum, nitrogen inlet, and stir bar is charged with allene-yne **162** (171 mg, 0.589 mmol) and MeOH (4.9 mL). To the flask is added K_2CO_3 (122 mg, 0.883 mmol) in one portion. When consumption of starting material is observed by TLC, the reaction mixture is transferred into a separatory funnel containing sat'd aq NH_4Cl and Et_2O. The aq layer is separated and extracted with Et_2O (3X). The combined organic layers are washed with H_2O, brine, are dried over $MgSO_4$, and filtered via gravity filtration. The filtrate is concentrated under reduced pressure by rotary evaporation. The residue is purified by silica gel chromatography eluting with 5-10% Et_2O/pentanes to afford terminal alkyne **172** as a light yellow oil (103 mg in 80% yield, d.r. = 1.2:1 based upon integration of the resonances at 68.7 ppm and 68.6 ppm in the ^{13}C NMR). R_f 0.4 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 5.21-5.15 (m, 1H), 5.14-5.07 (m, 1H), 4.25-4.18 (m, 1H), 2.34 (td, *J* = 7.2, 2.7 Hz, 2H), 2.16-2.06 (m, 2H), 2.05-1.98 (m, 2H), 1.97 (t, *J* = 2.7 Hz, 1H), 1.86-1.71 (m, 2H), 1.73 (d, *J* = 2.4 Hz, 3H), 1.70 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *designates minor diastereomer where resolved: δ 199.3, 132.3, 132.2*, 124.0, 123.9*, 103.6, 94.7, 84.1, 84.1*, 68.7*, 68.6, 68.5, 36.1*, 35.9, 34.0, 26.0, 25.7, 19.2, 19.1*,17.8, 14.7*, 14.6; IR (thin film): 3400, 3306, 2919, 2118, 1964 cm^{-1}; EI-MS *m/z* (%) 203 (36), 160 (100), 135 (49), 83 (53); EI-HRMS calcd for $C_{15}H_{22}O$: *m/z* ($M^{+\cdot}$) 218.1671; found: 218.1675.



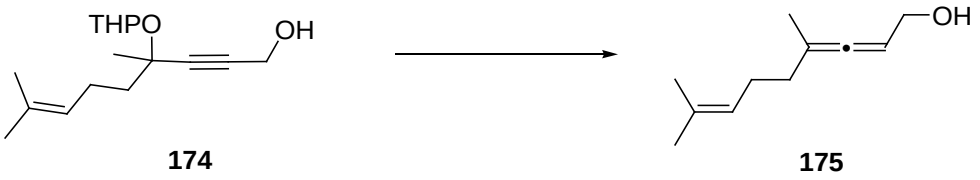
172 **173**

8,12-Dimethyl-1-phenyltrideca-6,7,11-trien-1-yn-5-ol (173). A 5-mL, single-necked round-bottomed flask equipped with a rubber septum, argon balloon, and stir bar is charged with CuI (~1 mg, 2 μmol) and $Pd(PPh_3)_2Cl_2$ (~1 mg, 1 μmol). The flask is evacuated and purged with argon before 0.3 mL of THF is added. To the flask is then sequentially added a solution of allene-yne **172** (25 mg, 0.11 mmol) in THF (0.3 mL), PhI (38 μL, 0.34 mmol), and diisopropylamine (0.16 mL, 1.2 mmol). When consumption of starting material is observed by TLC, the reaction is concentrated under reduced pressure. The residue is purified by silica gel chromatography eluting with 5-30% Et_2O/pentanes to afford **173** as a light yellow oil (29 mg in 86% yield, d.r. = 1.2:1 based upon integration of the resonances at 68.9 ppm and 68.8 ppm in the ^{13}C NMR). R_f 0.6 (15% EtOAc/toluene); ^1H NMR (300 MHz, $CDCl_3$): δ 7.44-7.20 (m, 5H), 5.28-5.18 (m, 1H), 5.13 (t, *J* = 6.9 Hz, 1H), 4.35-4.24 (m, 1H), 2.57 (t, *J* = 7.2 Hz, 2H), 2.19-2.08 (m, 2H), 2.07-1.98 (m, 2H), 1.91-1.78 (m, 2H), 1.75 (d, *J* = 2.7 Hz, 3H), 1.71 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *designates minor diastereomer where resolved: δ 199.3, 132.2, 131.5 (2C), 128.1 (2C), 127.5, 124.0, 123.9, 103.6, 94.8, 89.7, 89.6*, 80.9, 68.9*, 68.8, 36.4*, 36.3, 34.1, 26.1, 25.6, 19.2, 19.1*,17.8, 15.7; IR (thin film): 3355, 2922, 2235, 1964, 1442 cm^{-1}; EI-MS *m/z* (%) 294 (30, $M^{+\cdot}$), 223 (72), 179 (100); EI-HRMS calcd for $C_{21}H_{26}O$: *m/z* ($M^{+\cdot}$) 294.1984; found: 294.1978.

163 **174**

4,8-Dimethyl-4-(tetrahydro-2*H*-pyran-2-yloxy)non-7-en-2-yn-ol (174). A single-necked, 15-mL round-bottomed flask is equipped with a stir bar, rubber septum, and nitrogen inlet is charged with alkyne **163**[127] (540 mg, 2.28 mmol) and THF (4.8 mL). The mixture is cooled to 0 °C in an ice bath and *n*-butyllithium (2.3 mL of a 1.6 M hexane soln, 3.6 mmol) is added dropwise via syringe. Upon addition of *n*-BuLi, the reaction turns from colorless to yellow/brown. After 1 h at 0 °C, paraformaldehyde (218 mg, 7.28 mmol) is added in one portion and the reaction is slowly warmed to rt. When consumption of **163** is observed by TLC, the reaction mixture is transferred into a separatory funnel containing H_2O and Et_2O. The aq layer is separated and extracted with Et_2O (3X). The combined organic layers are washed with H_2O, brine, are dried over $MgSO_4$, and filtered via gravity filtration. The filtrate is concentrated under reduced pressure by rotary evaporation. The residue is purified on silica gel eluting with 5-30% Et_2O/pentanes to afford 468 mg of the title compound as pale yellow oil in 77% yield, d.r. = 1.2:1 (based upon integration of the resonances at 1.49 ppm and 1.41 ppm in the ^{1}H NMR). R_f 0.2 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) *designates minor diastereomer where resolved: δ 5.20-5.00 (m, 2H), 4.26 (t, *J* = 6.0, 2H), 4.03-3.87 (m, 1H), 3.56-3.46 (m, 1H), 3.30-2.92 (m, 1H), 2.22-2.07 (m, 2H), 1.89-1.63 (m, 4H), 1.66 (s, 3H), 1.60 (s, 3H), 1.58-1.50 (m, 4H), 1.49 (s, 3H), 1.41* (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *designates minor diastereomers where resolved: δ 131.6, 123.9, 95.6, 94.9*, 86.9, 86.3*, 84.1*, 83.4, 74.0*, 73.6, 62.8, 62.7*, 50.7, 43.0, 42.2*, 32.0*, 31.6, 28.3*, 27.3, 25.6, 25.4, 25.3*, 23.3, 23.1*, 19.9, 19.8*, 17.5; IR

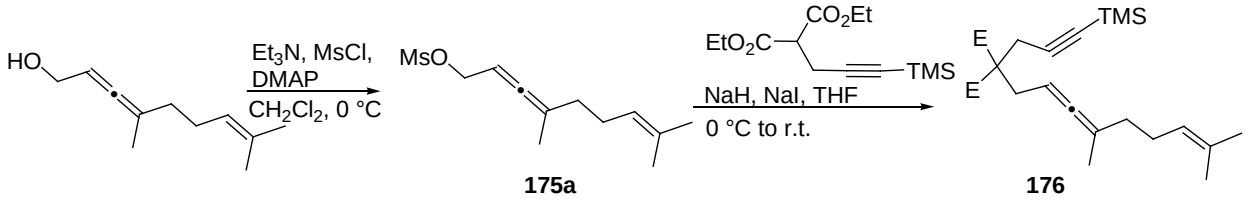
(thin film): 3423, 2935, 1441, 1024 cm^{-1}; EI-MS *m/z* (%) 251 (28), 235 (50), 165 (23), 85 (100); EI-HRMS calcd for $C_{15}H_{23}O_3$: *m/z* (M-CH_3) 251.1647; found: 251.1643.



174 **175**

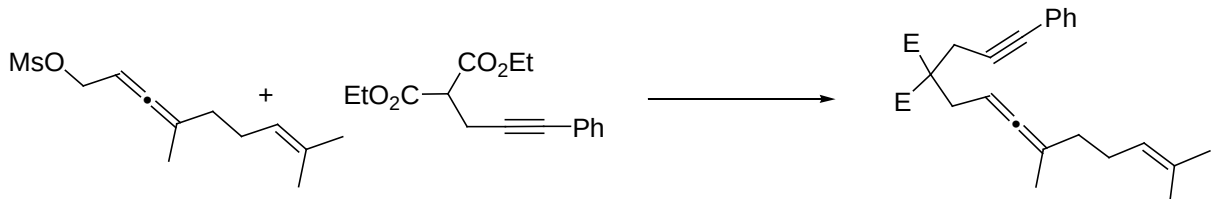
4,8-Dimethylnona-2,3,7-trien-1-ol (175). A 10-mL, two-necked round-bottomed flask equipped with a cold finger, nitrogen inlet, and stir bar is charged with LAH (70 mg, 1.8 mmol) and Et_2O (3.4 mL). The mixture is heated and stirred at reflux (oil bath temperature 40-45 °C) for 5 min before a solution of propargylic alcohol **174** (443 mg, 1.68 mmol) in Et_2O (0.7 mL) is added dropwise over 3-5 min to the refluxing reaction via cannula. Immediately after the addition of **174** is complete, the reaction mixture is cooled to rt and diluted with Et_2O. To the flask is slowly added H_2O (70 μL), then 10% NaOH (140 μL), followed by sat'd aq KF solution (240 μL). After stirring for 5 min at rt, the resulting solids are filtered off via gravity filtration. The solids are washed with Et_2O and the filtrate is concentrated under reduced pressure by rotary evaporation. The residue is purified by silica gel chromatography eluting with 5-15% Et_2O/pentanes to afford allenyl alcohol **175** (149 mg in 53% yield) as a light yellow oil. R_f 0.4 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 5.30-5.20 (m, 1H), 5.09 (tq, *J* = 6.9, 1.2 Hz, 1H), 4.04 (d, *J* = 5.4 Hz, 2H), 2.15-2.05 (m, 2H), 2.03-1.94 (m, 2H), 1.78 (bs, 1H), 1.71 (d, *J* = 3.0 Hz, 3H), 1.68 (d, *J* = 0.6 Hz, 3H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.0, 132.0, 124.0, 102.7, 91.4, 60.8, 33.9, 26.0, 25.6, 19.1, 17.7; IR (thin film): 3332, 2922, 1965, 1443 cm^{-1}; EI-MS *m/z* (%) 148 (34), 83 (78), 69 (84), 55 (100); EI-HRMS calcd for $C_{11}H_{16}$: *m/z* (M-H_2O) 148.1252; found: 148.1255.

General Procedure A: Preparation of malonate-tethered allene-ynes 176-179



Diethyl 2-(4,8-dimethylnona-2,3,7-trienyl)-2-(3-(trimethylsilyl)prop-2-ynyl)malonate (176). A 5-mL, single-necked round-bottomed flask equipped with a stir bar, rubber septum, and nitrogen inlet is charged with allene-yne **175** (40 mg, 0.24 mmol), CH_2Cl_2 (1 mL), and DMAP (6 mg, 0.05 mmol). The reaction flask is cooled to 0 °C in an ice bath before Et_3N (0.1 mL, 0.72 mmol) and methanesulfonyl chloride (44 μL, 0.57 mmol) are sequentially added via syringe. The reaction turns from colorless to yellow upon addition of MsCl. After 1 h the reaction is complete as observed by TLC and is transferred into a separatory funnel containing H_2O and CH_2Cl_2. The aq layer is separated and extracted with CH_2Cl_2 (3X). The combined organic layers containing crushed ice are washed with 1M aq HCl, sat'd aq $NaHCO_3$, brine, and are dried over $MgSO_4$. The solids are filtered off via gravity filtration and the filtrate is concentrated under reduced pressure by rotary evaporation. Mesylate **175a** is produced as an orange oil and is used in the next step without further purification. A 5-mL, single-necked round-bottomed flask equipped with a stir bar, rubber septum, and nitrogen inlet is charged with NaH (7 mg of 60% dispersion in mineral oil, 0.17 mmol) and 0.4 mL of THF. The suspension is cooled to 0 °C in an ice bath and a solution of diethyl 2-(3-(trimethylsilyl)prop-2-ynyl)malonate (28 mg, 0.11 mmol) in 0.4 mL of THF is added via cannula. The reaction is warmed to rt and is stirred for 1 h before a solution of the freshly prepared crude mesylate **175a** in THF (1 mL) is added via cannula. To the reaction is then added NaI (16 mg, 0.11 mmol) in one portion. When consumption of the propargyl

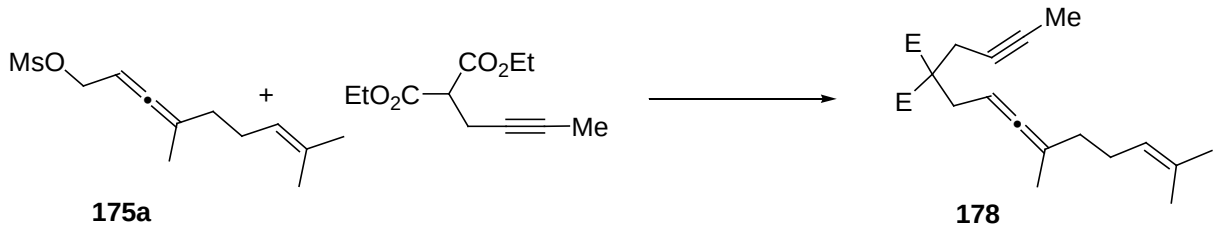
malonate is observed by TLC, the reaction mixture is transferred into a separatory funnel containing H_2O and Et_2O. The aq layer is separated and extracted with Et_2O (3X). The combined organic layers are washed with H_2O, brine, dried over $MgSO_4$, and filtered via gravity filtration. The filtrate is concentrated under reduced pressure by rotary evaporation. The residue is purified by silica gel chromatography eluting with 2-5% Et_2O/pentanes to afford malonate **176** (27 mg in 62% yield) as a light yellow oil. R_f 0.8 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.12 (tt, *J* = 6.9, 1.5 Hz, 1H), 4.86-4.77 (m, 1H), 4.26-4.13 (m, 4H), 2.89 (s, 2H), 2.72 (d, *J* = 7.8 Hz, 1H), 2.14-2.04 (m, 2H), 1.97-1.88 (m, 2H), 1.70 (s, 3H), 1.66 (d, *J* = 2.7 Hz, 3H), 1.62 (s, 3H), 1.26 (t, *J* = 6.9 Hz, 6H), 0.12 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.6, 169.8, 169.7, 131.7, 124.1, 101.5, 99.3, 87.8, 83.8, 61.5 (2C), 57.2, 34.0, 32.7, 26.2, 25.7, 23.8, 19.1, 17.7, 14.1 (2C), -0.1 (3C); IR (thin film): 2963, 2180, 1737, 844 cm^{-1}; EI-MS *m/z* (%) 418 (21, $M^{+\cdot}$), 345 (24), 271 (78), 187 (100); EI-HRMS calcd for $C_{24}H_{38}O_4Si$: *m/z* ($M^{+\cdot}$) 418.2539; found: 418.2556.



175a **177**

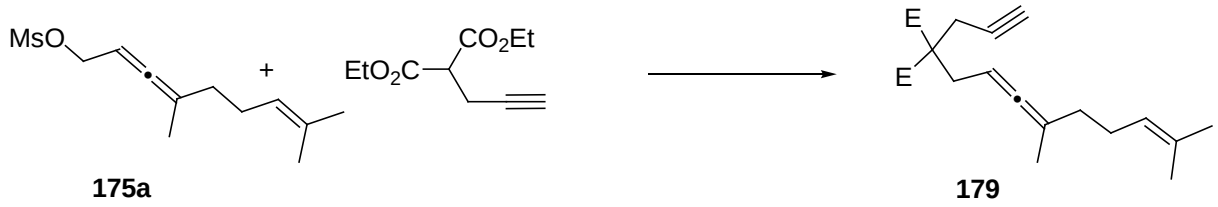
Diethyl 2-(4,8-dimethylnona-2,3,7-trienyl)-2-(3-phenylprop-2-ynyl)malonate (177). Prepared according to General Procedure A using: allene-yne **175** (33 mg, 0.20 mmol), DMAP (5 mg, 0.04 mmol), Et_3N (83 μL, 0.60 mmol) and methanesulfonyl chloride (37 μL, 0.47 mmol) in CH_2Cl_2 (0.8 mL). The subsequent alkylation reaction used NaH (6.0 mg of 60% dispersion in mineral oil, 0.14 mmol), diethyl-2-(3-phenylprop-2-ynyl)malonate (24 mg, 0.09 mmol), and NaI (15 mg, 0.10 mmol) in 0.6 mL of THF. Yield **177** (27 mg, 73%). R_f 0.6 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.34 (m, 2H), 2.30-7.24 (m, 3H), 5.12 (tt, *J* = 7.2, 1.5 Hz,

1H), 4.93-4.84 (m, 1H), 4.29-4.17 (m, 4H), 3.10 (s, 2H), 2.81 (d, *J* = 7.5 Hz, 1H), 2.15-2.05 (m, 2H), 1.97-1.90 (m, 2H), 1.68 (d, *J* = 1.2 Hz, 3H), 1.67 (d, *J* = 2.7 Hz, 3H), 1.60 (s, 3H) 1.27 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.6, 169.9 (2C), 131.7, 131.6 (2C), 128.1 (2C), 127.8, 124.1, 123.4, 99.5, 84.6, 83.8, 83.3, 61.5 (2C), 57.4, 34.0, 32.8, 26.2, 25.7, 23.4, 19.1, 17.7, 14.1 (2C); IR (thin film): 2923, 1735, 1443, 1202 cm^{-1}; EI-MS *m/z* (%) 422 (51, $M^{+\cdot}$), 353 (17), 308 (100); EI-HRMS calcd for $C_{27}H_{34}O_4$: *m/z* ($M^{+\cdot}$) 422.2457; found: 422.2460.



175a **178**

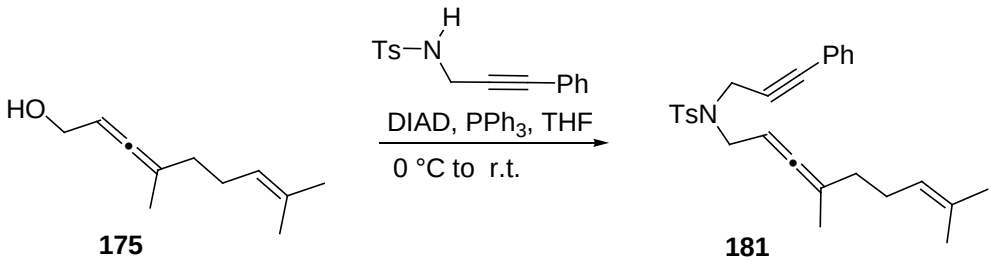
Diethyl 2-(but-2-ynyl)-2-(4,8-dimethylnona-2,3,7-trienyl)malonate (178). Prepared according to General Procedure A using: allene-yne **175** (36 mg, 0.22 mmol), DMAP (5 mg, 0.04 mmol), Et_3N (92 μL, 0.66 mmol) and methanesulfonyl chloride (41 μL, 0.52 mmol) in CH_2Cl_2 (0.9 mL). The subsequent alkylation reaction used NaH (6 mg of 60% dispersion in mineral oil, 0.15 mmol), diethyl 2-(but-2-ynyl)malonate (20 mg, 0.09 mmol), and NaI (17 mg, 0.11 mmol) in 0.7 mL of THF. Yield **178** (26 mg, 76%). R_f 0.7 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.11 (tt, *J* = 6.9, 1.5 Hz, 1H), 4.87-4.78 (m, 1H), 4.25-4.13 (m, 4H), 2.80 (q, *J* = 2.4 Hz, 2H), 2.73-2.68 (m, 2H), 2.13-2.04 (m, 2H), 1.96-1.88 (m, 2H), 1.74 (t, *J* = 2.4 Hz, 3H), 1.69 (d, *J* = 0.9 Hz, 3H), 1.65 (d, *J* = 2.7 Hz, 3H), 1.61 (s, 3H) 1.25 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.5, 170.1 (2C), 131.6, 124.1, 99.3, 83.9, 78.5, 73.5, 61.4 (2C), 57.3, 34.0, 32.6, 26.2, 25.7, 22.8, 19.0, 17.7, 14.0 (2C), 3.5; IR (thin film): 2979, 1736, 1443, 1203 cm^{-1}; EI-MS *m/z* (%) 360 (36, $M^{+\cdot}$), 345 (15), 268 (100); EI-HRMS calcd for $C_{22}H_{32}O_4$: *m/z* ($M^{+\cdot}$) 360.2301; found: 360.2311.



175a **179**

Diethyl 2-(4,8-dimethylnona-2,3,7-trienyl)-2-prop-2-ynyl)malonate (179). Prepared according to General Procedure A using: allene-yne **175** (58 mg, 0.35 mmol), DMAP (9 mg, 0.07 mmol), Et_3N (0.15 mL, 1.1 mmol) and methanesulfonyl chloride (65 μL, 0.83 mmol) in CH_2Cl_2 (1.4 mL). The subsequent alkylation reaction used NaH (10 mg of 60% dispersion in mineral oil, 0.24 mmol), diethyl 2-(prop-2-ynyl)malonate (30 mg, 0.15 mmol), and NaI (27 mg, 0.18 mmol) in 1.1 mL of THF. Yield **179** (40 mg, 76%). R_f 0.6 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.11 (tt, *J* = 6.9, 1.5 Hz, 1H), 4.87-4.76 (m, 1H), 4.26-4.14 (m, 4H), 2.87 (d, *J* = 2.4 Hz, 2H), 2.73 (d, *J* = 7.8 Hz, 2H), 2.13-2.03 (m, 2H), 1.99 (t, *J* = 2.4 Hz, 1H), 1.96-1.88 (m, 2H), 1.69 (s, 3H), 1.65 (d, *J* = 2.7 Hz, 3H), 1.61 (s, 3H) 1.26 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.6, 169.7 (2C), 131.7, 124.1, 99.5, 83.6, 79.0, 71.1, 61.6 (2C), 57.0, 34.0, 32.6, 26.2, 25.7, 22.4, 19.0, 17.7, 14.0 (2C); IR (thin film): 3289, 2979, 1966, 1736, 1204 cm^{-1}; EI-MS *m/z* (%) 346 (31, $M^{+\cdot}$), 331 (15), 303 (48), 84 (100); EI-HRMS calcd for $C_{21}H_{30}O_4$: *m/z* ($M^{+\cdot}$) 346.2144; found: 346.2141.

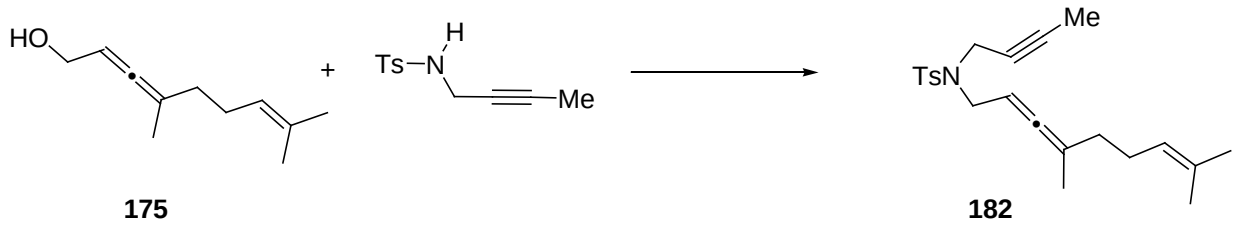
General Procedure B: Formation of *N*-tosylallene-ynes via a Mitsunobu reaction



175 **181**

4,8-Dimethyl-*N*-(3-phenylprop-2-ynyl)-*N*-tosylnona-2,3,7-trien-1-amine (181). A 5-mL, single-necked round-bottomed flask equipped with a nitrogen inlet and stir bar is charged with 3-

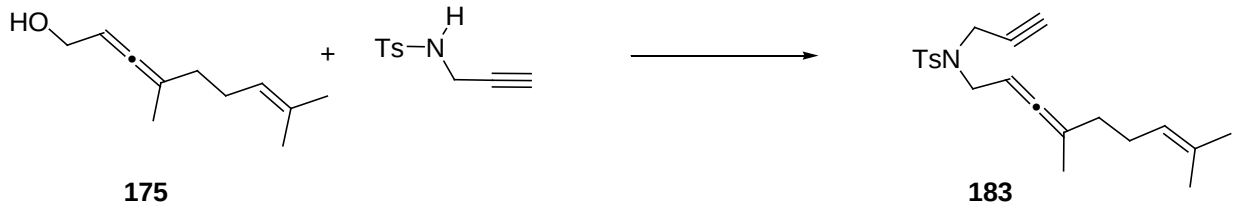
phenyl-*N*-tosylprop-2-yn-1-amine (65 mg, 0.23 mmol), allene-yne **175** (49 mg, 0.29 mmol), triphenylphosphine (78 mg, 0.29 mmol), and THF (1.5 mL). The flask is cooled to 0 °C in an ice bath and diisopropyl azodicarboxylate (DIAD, 58 μL, 0.29 mmol) is added via syringe. The reaction is slowly warmed to rt and stirred until consumption of starting material is observed by TLC. The reaction is then concentrated under reduced pressure, diluted with cold Et_2O, and filtered though a pad of celite. The filtrate is concentrated under reduced pressure by rotary evaporation. The residue is purified by silica gel chromatography eluting with 5% Et_2O/pentane to afford **181** (77 mg in 78% yield) as a light yellow oil. R_f 0.5 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.34-7.20 (m, 5H), 7.05 (dd, *J* = 8.4, 1.8 Hz, 2H), 5.08 (tt, *J* = 6.9, 1.5 Hz, 1H), 5.04-4.96 (m, 1H), 4.39 (s, 2H), 3.86 (dd, *J* = 6.9, 1.2 Hz, 2H), 2.34 (s, 3H), 2.13-2.03 (m, 2H), 1.98-1.90 (m, 2H), 1.68 (d, *J* = 2.7 Hz, 3H), 1.65 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.5, 143.4, 136.1, 131.9, 131.5 (2C), 129.5 (2C), 128.3, 128.1 (2C), 127.8 (2C), 123.8, 122.4, 101.4, 85.5, 81.8, 77.2, 47.0, 36.5, 33.8, 26.1, 25.6, 21.4, 19.0, 17.7; IR (thin film): 2919, 1965, 1598, 1349 cm^{-1}; ESI-MS *m/z* (%) 456 (7), 312 (20), 122 (100).



175 **182**

***N*-(But-2-ynyl)-4,8-dimethyl-*N*-tosylnona-2,3,7-trien-1-amine (182)**. Prepared according to General Procedure B using: *N*-tosylbut-2-yn-1-amine (34 mg, 0.15 mmol), allene-yne **175** (33 mg, 0.20 mmol), triphenylphosphine (52 mg, 0.20 mmol), and DIAD (39 μL, 0.20 mmol) in THF (1 mL). Yield **182** (45 mg, 80%). R_f 0.6 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 5.13-1.04 (m, 1H), 4.97-4.87 (m, 1H), 4.10 (q,

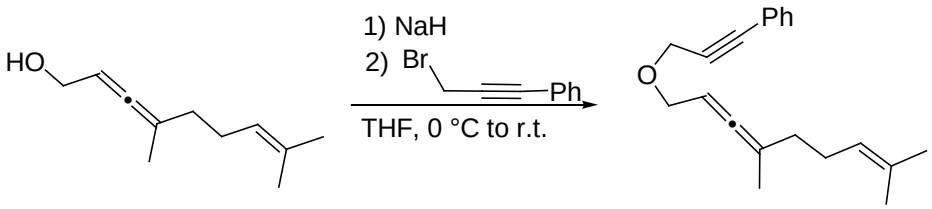
J = 2.1 Hz, 2H), 3.77 (d, *J* = 6.9 Hz, 2H), 2.42 (s, 3H), 2.13-2.02 (m, 2H), 1.98-1.89 (m, 2H), 1.67 (s, 3H), 1.66 (s, 3H), 1.59 (s, 3H), 1.54 (t, *J* = 2.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.3, 143.1, 136.4, 131.8, 129.2 (2C), 127.8 (2C), 123.9, 101.2, 85.5, 81.2, 71.7, 46.7, 36.1, 33.9, 26.1, 25.6, 21.5, 18.9, 17.7, 3.2; IR (thin film): 2919, 1965, 1598, 1349 cm^{-1}; EI-MS *m/z* (%) 373 (100), 372 (52); EI-HRMS calcd for $C_{22}H_{29}NO_2S$: *m/z* ($M^{+\cdot}$) 371.1919; found: 371.1922.



175 **183**

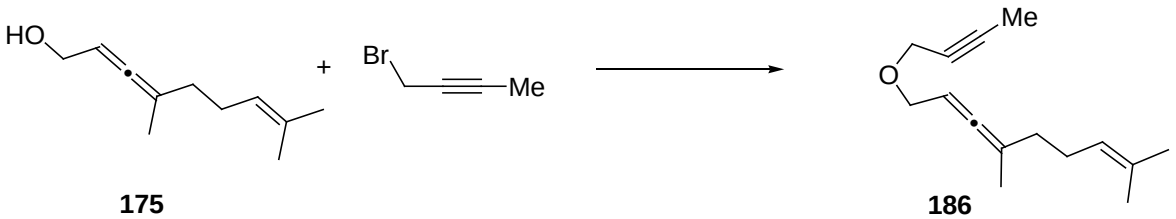
4,8-Dimethyl-*N*-(prop-2-ynyl)-*N*-tosylnona-2,3,7-trien-1-amine (183). Prepared according to General Procedure B using: *N*-tosylprop-2-yn-1-amine (33 mg, 0.16 mmol), allene-yne **175** (34 mg, 0.20 mmol), triphenylphosphine (54 mg, 0.21 mmol), and DIAD (41 μL, 0.21 mmol) in THF (1 mL). Yield **183** (49 mg, 87%). R_f 0.5 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 5.09 (tt, *J* = 6.9, 1.2 Hz, 1H), 4.97-4.88 (m, 1H), 4.18 (d, *J* = 2.4 Hz, 2H), 3.80 (d, *J* = 6.9 Hz, 2H), 2.43 (s, 3H), 2.12-2.02 (m, 2H), 1.99 (t, *J* = 2.4 Hz, 1H), 1.98-1.90 (m, 2H), 1.68 (d, *J* = 2.4 Hz, 3H), 1.67 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.5, 143.4, 136.2, 131.9, 129.4 (2C), 127.7 (2C), 123.8, 101.4, 85.2, 73.4, 46.7, 35.6, 33.8, 26.1, 25.7, 21.5, 18.9, 17.7; IR (thin film): 3282, 2920, 1964, 1349 cm^{-1}; EI-MS *m/z* (%) 357 (20, $M^{+\cdot}$), 342 (22), 202 (32), 162 (100); EI-HRMS calcd for $C_{21}H_{27}NO_2S$: *m/z* ($M^{+\cdot}$) 357.1763; found: 357.1768.

General Procedure C: *O*-alkylation of allenic alcohol 175 with propargyl bromides



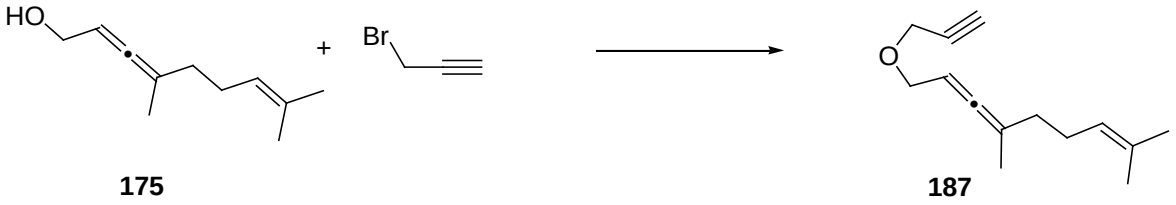
175 **185**

1-(3-(4,8-Dimethylnona-2,3,7-trienyloxy)prop-1-ynyl)benzene (185). A 5-mL, single-necked round-bottomed flask equipped with a nitrogen inlet and stir bar is charged with NaH (16 mg of 60% dispersion in mineral oil, 0.40 mmol) and 1 mL of THF. The suspension is cooled to 0 °C in an ice bath and a solution of allene-yne **175** (22 mg, 0.13 mmol) in THF (1 mL) is added via cannula. The reaction is warmed to rt and is stirred for 1 h before a solution of 1-(3-bromoprop-1-ynyl)benzene (28 mg, 0.15 mmol) in THF (0.2 mL) is added via cannula. To the reaction is then added HMPA (5 μL, 26 μmol) via syringe and the reaction is stirred until consumption of **175** is observed by TLC. The reaction mixture is then transferred into a separatory funnel containing sat'd aq NH_4Cl and Et_2O. The aq layer is separated and extracted with Et_2O (3X). The combined organic layers are washed with H_2O, brine, dried over $MgSO_4$, and filtered via gravity filtration. The filtrate is concentrated under reduced pressure by rotary evaporation. The residue is purified by silica gel chromatography eluting with 2-5% Et_2O/pentanes to afford **185** (30 mg in 81% yield) as a light yellow oil. R_f 0.7 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51-7.42 (m, 2H), 7.40-7.29 (m, 3H), 5.24- 5.08 (m, 2H), 4.41 (s, 2H), 4.13 (d, *J* = 6.9 Hz, 2H), 2.18-2.07 (m, 2H), 2.04-1.95 (m, 2H), 1.73 (d, *J* = 3.0 Hz, 3H), 1.69 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.1, 131.8, 131.7 (2C), 128.3, 128.2 (2C), 124.0, 122.7, 100.4, 87.1, 86.1, 85.2, 68.7, 57.2, 33.9, 26.2, 25.7, 19.0, 17.7; IR (thin film): 2922, 1965, 1442, 1081 cm^{-1}; EI-MS *m/z* (%) 265 (28), 135 (15), 115 (100); EI-HRMS calcd for $C_{19}H_{21}O$: *m/z* (M-CH_3) 265.1592; found: 265.1596.



175 **186**

1-(But-2-ynyloxy)-4,8-dimethylnona-2,3,7-triene (186). Prepared according to General Procedure C using: allene-yne **175** (23 mg, 0.14 mmol), NaH (11 mg of 60% dispersion in mineral oil, 0.28 mmol), 1-bromobut-2-yne (13 μL, 0.15 mmol) and HMPA (5 μL, 26 μmol) in 2.1 mL of THF. Yield **186** (23 mg, 76%). R_f 0.8 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.20-5.05 (m, 2H), 4.12 (q, *J* = 2.4 Hz, 2H), 4.03 (d, *J* = 6.9 Hz, 2H), 2.17-2.05 (m, 2H), 2.03-1.93 (m, 2H), 1.86 (t, *J* = 2.4 Hz, 3H), 1.71 (d, *J* = 3.0 Hz, 3H), 1.70 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.9, 131.7, 124.0, 100.2, 87.2, 82.2, 75.2, 68.5, 57.0, 33.9, 26.1, 25.7, 18.9, 17.7, 3.6; IR (thin film): 2923, 1965, 1445, 1079 cm^{-1}; EI-MS *m/z* (%) 218 (10, $M^{+\cdot}$), 203 (21), 173 (75), 53 (100); EI-HRMS calcd for $C_{15}H_{22}O$: *m/z* ($M^{+\cdot}$) 218.1671; found: 218.1670.

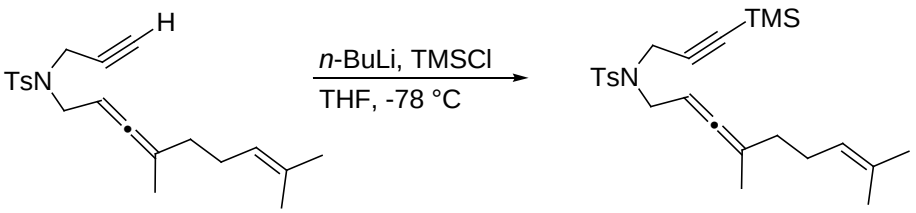


175 **187**

4,8-Dimethyl-1-(prop-2-ynyloxy)nona-2,3,7-triene (187). Prepared according to General Procedure C using: allene-yne **175** (62 mg, 0.37 mmol), NaH (45 mg of 60% dispersion in mineral oil, 1.1 mmol), propargyl bromide (80% wt. in toluene, 0.12 mL, 1.1 mmol), and HMPA (13 μL, 75 μmol) in 5.8 mL of THF. Yield **187** (61 mg, 80%). R_f 0.8 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.18-5.06 (m, 2H), 4.17 (d, *J* = 2.4 Hz, 2H), 4.05 (d, *J* = 6.9 Hz, 2H), 2.42 (t, *J* = 2.4 Hz, 1H), 2.16-2.05 (m, 2H), 2.03-1.93 (m, 2H), 1.71 (d, *J* = 3.0 Hz, 3H), 1.69 (d, *J* = 0.9 Hz, 3H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.1, 131.7, 123.9,

100.4, 86.9, 79.8, 74.1, 68.6, 56.3, 33.9, 26.1, 25.7, 18.9, 17.7; IR (thin film): 3304, 2923, 2116, 1965, 1085 cm^{-1}; EI-MS *m/z* (%) 204 (41, $M^{+\cdot}$), 148 (53), 133 (100), 55 (87); EI-HRMS calcd for $C_{14}H_{20}O$: *m/z* ($M^{+\cdot}$) 204.1514; found: 204.1510.

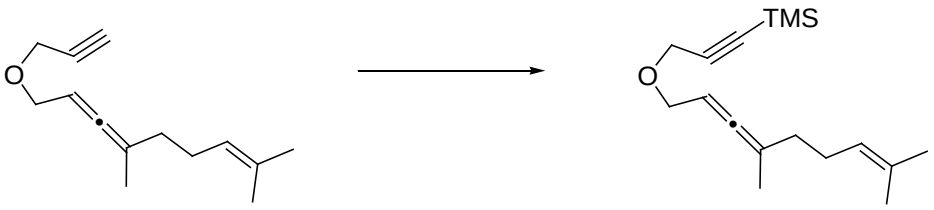
General Procedure D: Formation of TMS-alkyne heteroatom-tethered allene-ynes



183 **180**

4,8-Dimethyl-*N*-(3-(trimethylsilyl)prop-2-ynyl)-*N*-tosylnona-2,3,7-trien-1-amine (180). A 5-mL, single-necked round-bottomed flask equipped with a rubber septum, nitrogen inlet, and stir bar is charged with *N*-tosylallene-yne **183** (27 mg, 0.08 mmol) and THF (0.6 mL). The reaction flask is cooled to –78 ˚C with a dry ice-acetone bath and *n*-butyllithium (61 μL of a 1.6 M hexane soln, 0.1 mmol) is added dropwise via syringe. After 30 min, chlorotrimethylsilane (TMSCl, 19 μL, 0.15 mmol) is added via syringe. The reaction is allowed to slowly warm to rt at which time consumption of starting material is observed by TLC analysis. The reaction mixture is transferred into a separatory funnel containing sat'd aq NH_4Cl and Et_2O. The aq layer is separated and extracted with Et_2O (3X). The combined organic layers are washed with H_2O, brine, are dried over $MgSO_4$, and filtered via gravity filtration. The filtrate is concentrated under reduced pressure by rotary evaporation. The residue is purified by silica gel chromatography eluting with 5-10% Et_2O/pentane to afford **180** (23 mg in 71% yield) as a light yellow oil. R_f 0.8 (5% EtOAc/toluene); ^1H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 5.09 (tt, *J* = 7.2, 1.5 Hz, 1H), 4.99-4.89 (m, 1H), 4.22 (A of an ABq, *J* = 19.9 Hz, 1H), 4.15 (B of an ABq, *J* = 19.9 Hz, 1H), 3.86-3.71 (m, 2H), 2.42 (s, 3H), 2.13-2.03 (m, 2H), 1.97-1.90 (m, 2H), 1.68 (d, *J* = 2.4 Hz, 3H), 1.67 (s, 3H), 1.60 (s, 3H), -0.02 (s, 9H); ^{13}C NMR (75

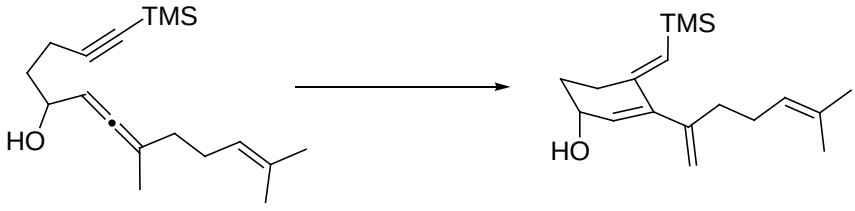
MHz, $CDCl_3$): δ 203.5, 143.3, 136.1, 131.9, 129.5 (2C), 127.7 (2C), 123.9, 101.2, 97.8, 90.7, 85.3, 46.6, 36.5, 33.8, 26.0, 25.7, 21.5, 19.0, 17.8, -0.5 (3C); IR (thin film): 2961, 2178, 1965, 845 cm^{-1}; EI-MS *m/z* (%) 429 (54, $M^{+\cdot}$), 294 (100), 274 (99), 91 (99); EI-HRMS calcd for $C_{24}H_{35}NO_2SiS$: *m/z* ($M^{+\cdot}$) 429.2158; found: 429.2141.



187 **184**

(3-(4,8-Dimethylnona-2,3,7-trienyloxy)prop-1-ynyl)trimethylsilane (184). Prepared according to General Procedure D using: allene-yne **187** (32 mg, 0.16 mmol), *n*-butyllithium (0.13 mL of a 1.6 M hexane soln, 0.20 mmol), TMSCl (40 μL, 0.31 mmol) in THF (1.3 mL). Yield **184** (21 mg, 49%). R_f 0.9 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.19-5.07 (m, 2H), 4.17 (s, 2H), 4.05 (d, *J* = 6.9 Hz, 2H), 2.18-2.05 (m, 2H), 2.04-1.94 (m, 2H), 1.71 (d, *J* = 3.0 Hz, 3H), 1.70 (s, 3H), 1.61 (s, 3H), 0.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.1, 131.8, 124.0, 101.6, 100.3, 91.1, 87.0, 68.7, 57.2, 33.9, 26.1, 25.7, 19.0, 17.7, -0.2 (3C); IR (thin film): 2924, 2174, 1965, 844 cm^{-1}; EI-MS *m/z* (%) 276 (10, $M^{+\cdot}$), 261 (46), 203 (89), 111 (100); EI-HRMS calcd for $C_{16}H_{25}OSi$: *m/z* (M-CH_3) 261.1675; found: 261.1670.

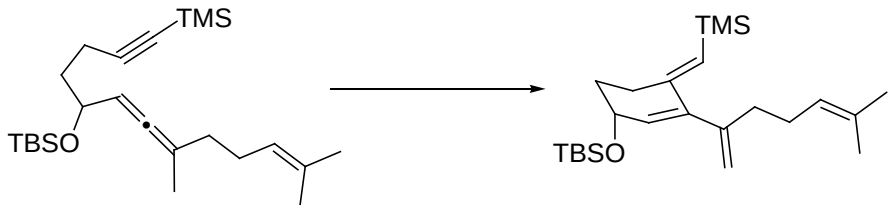
General Procedure E: Rh(I)-catalyzed allenic carbocyclization reaction.



162 **188**

(4*E*)-3-(6-Methylhepta-1,5-dien-2-yl)-4-((trimethylsilyl)methylene)cyclohexen-2-ol (188). A flame-dried 13 x 100 mm test tube equipped with a stir bar, rubber septum, and argon balloon is

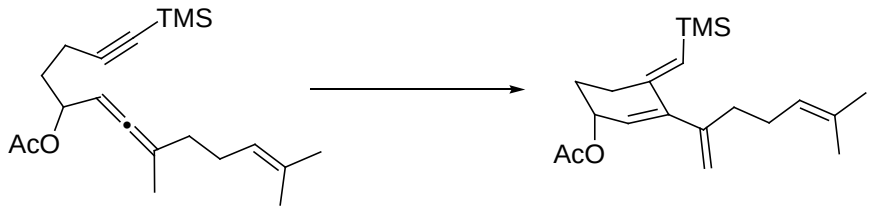
charged with allene-yne **162** (16 mg, 0.06 mmol) and toluene (1 mL). Argon is bubbled through the solution using a balloon filled with argon attached to a syringe before $[Rh(CO)_2Cl]_2$ (2 mg, 6 μmol) is added in one portion. Upon completion of the reaction based upon TLC analysis, the solution is directly subjected to silica gel chromatography eluting with 5-20% Et_2O/pentane to give 13.5 mg of cross-conjugated triene **188** in 84% yield. R_f 0.3 (20% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$): δ 5.66 (d, *J* = 3.5 Hz, 1H), 5.50 (s, 1H), 5.10 (tt, *J* = 7.0, 1.5 Hz, 1H), 5.01-4.98 (m, 1H), 4.88 (d, *J* = 2.0 Hz, 1H), 4.35 (tdd, *J* = 7.0, 5.0, 3.5 Hz, 1H), 2.58 (ddd, *J* = 14.5, 8.0, 4.0 Hz, 1H), 2.36 (dddd, *J* = 14.5, 10.0, 3.5, 1.0 Hz, 1H), 2.20-2.14 (m, 2H), 2.08-2.00 (m, 3H), 1.70 (tdd, *J* = 13.0, 13.0, 7.0, 4.0 Hz, 1H), 1.69 (s, 3H), 1.59 (s, 3H), 1.46 (d, *J* = 6.5 Hz, 1H), 0.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.3, 149.2, 145.2, 131.6, 128.9, 127.3, 124.0, 113.8, 66.3, 36.2, 32.9, 28.0, 26.8, 25.7, 17.7, 0.0 (3C); IR (thin film): 3338, 2954, 1576, 1248 cm^{-1}; EI-MS *m/z* (%) 290 (34, $M^{+\cdot}$), 272 (11), 131 (91), 73 (100); EI-HRMS calcd for $C_{18}H_{30}OSi$: *m/z* ($M^{+\cdot}$) 290.2066; found: 290.2058.



169 **189**

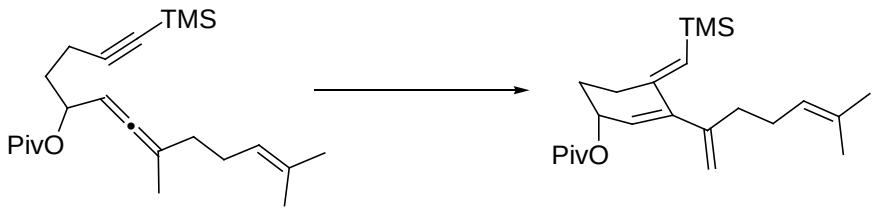
((4*E*)-3-(6-Methylhepta-1,5-dien-2-yl)-4-(trimethylsilyl)methylene))cyclohex-2-enyl oxy-*tert*-butyldimethylsilane (189). Prepared according to General Procedure E using: **169** (26 mg, 0.06 mmol), $[Rh(CO)_2Cl]_2$ (2 mg, 6 μmol). Yield **189** (24 mg, 92%). R_f 0.9 (5% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 5.55 (d, *J* = 2.7 Hz, 1H), 5.42 (s, 1H), 5.11 (tt, *J* = 6.6, 1.2 Hz, 1H), 4.99-4.95 (m, 1H), 4.87 (d, *J* = 2.1 Hz, 1H), 4.35 (ddd, *J* = 7.8, 4.5, 3.0 Hz, 1H), 2.60 (ddd, *J* = 14.6, 6.6, 3.6 Hz, 1H), 2.29 (dddd, *J* = 14.6, 11.1, 3.3, 1.2 Hz, 1H), 2.20-2.12 (m, 2H), 2.09-2.00 (m, 2H), 2.00-1.89 (m, 1H), 1.74-1.64 (m, 1H), 1.69 (s, 3H), 1.59 (s, 3H),

0.91 (s, 9H), 0.12 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.7, 149.6, 143.8, 131.6, 130.9, 126.0, 124.2, 113.5, 67.4, 36.2, 33.4, 28.6, 26.8, 25.9 (3C), 25.7, 18.2, 17.7, 0.1 (3C), -4.5 (2C); IR (thin film): 2954, 1577, 1250, 1091 cm^{-1}; EI-MS *m/z* (%) 404 (48, $M^{+\cdot}$), 331 (7), 131 (18), 73 (100); EI-HRMS calcd for $C_{24}H_{44}OSi_2$: *m/z* ($M^{+\cdot}$) 404.2931; found: 404.2936.



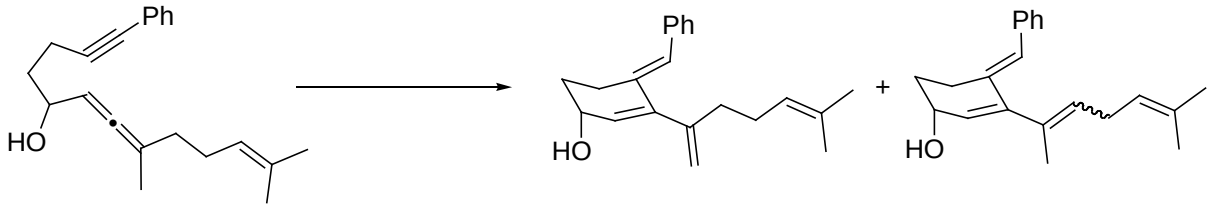
170 **191**

((4*E*)-3-(6-Methylhepta-1,5-dien-2-yl)-4-(trimethylsilyl)methylene))cyclohex-2-enyl acetate (191). Prepared according to General Procedure E using: **170** (19 mg, 0.06 mmol), $[Rh(CO)_2Cl]_2$ (2 mg, 6 μmol). Yield **191** (16 mg, 84%). R_f 0.5 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.60 (d, *J* = 3.9 Hz, 1H), 5.54 (s, 1H), 5.39 (td, *J* = 5.4, 3.9 Hz, 1H), 5.10 (tt, *J* = 6.9, 1.5 Hz, 1H), 5.00 (dt, *J* = 2.1, 1.2, Hz, 1H), 4.88 (d, *J* = 2.4 Hz, 1H), 2.57 (ddd, *J* = 13.7, 8.7, 3.6 Hz, 1H), 2.41 (dddd, *J* = 13.7, 8.4, 3.6, 0.9 Hz, 1H), 2.21-2.13 (m, 2H), 2.07 (s, 3H), 2.08-1.96 (m, 3H), 1.81 (dddd, *J* = 15.3, 9.0, 6.3, 4.2 Hz, 1H), 1.68 (d, *J* = 0.6 Hz, 3H), 1.59 (s, 3H), 0.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 149.0, 148.7, 146.9, 131.7, 128.2, 124.3, 124.0, 114.1, 68.7, 36.1, 29.2, 27.9, 26.8, 25.7, 21.4, 17.7, 0.0 (3C); IR (thin film): 2955, 1738, 1579, 1237, 863 cm^{-1}; EI-MS *m/z* (%) 332 (22, $M^{+\cdot}$), 273 (9), 203 (22), 73 (100); EI-HRMS calcd for $C_{20}H_{32}O_2Si$: *m/z* ($M^{+\cdot}$) 332.2172; found: 332.2171.



171 **193**

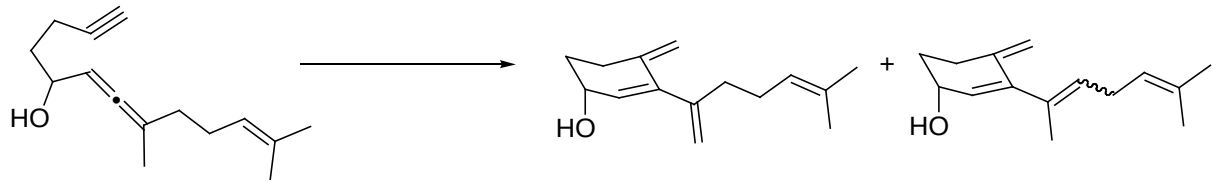
((4*E*)-3-(6-Methylhepta-1,5-dien-2-yl)-4-(trimethylsilyl)methylene))cyclohex-2-enyl pivalate (193). Prepared according to General Procedure E using: **171** (20 mg, 0.05 mmol), $[Rh(CO)_2Cl]_2$ (2 mg, 5 μmol). Yield **193** (15 mg, 75%). R_f 0.8 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.59 (d, *J* = 3.6 Hz, 1H), 5.53 (s, 1H), 5.35 (app q, *J* = 4.2 Hz, 1H), 5.10 (tt, *J* = 6.9, 1.2 Hz, 1H), 4.99 (dt, *J* = 2.4, 1.2, Hz, 1H), 4.88 (d, *J* = 2.4 Hz, 1H), 2.56 (ddd, *J* = 13.7, 8.7, 3.6 Hz, 1H), 2.42 (dddd, *J* = 13.7, 9.6, 3.9, 0.9 Hz, 1H), 2.21-2.13 (m, 2H), 2.10-1.95 (m, 3H), 1.80 (dddd, *J* = 14.4, 9.0, 5.7, 3.9 Hz, 1H), 1.68 (s, 3H), 1.59 (s, 3H), 1.20 (s, 9H), 0.14 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.1, 149.2, 148.9, 146.7, 131.7, 128.0, 124.5, 124.0, 114.0, 68.2, 38.8, 36.2, 29.2, 27.9, 27.1 (3C), 26.8, 25.7, 17.7, 0.0 (3C); IR (thin film): 2958, 1727, 1579, 1153, 863 cm^{-1}; ESI-MS *m/z* (%) 381 (6), 397 (100, $[M+Na]^+$); ESI-HRMS calcd for $C_{23}H_{38}O_2NaSi$: *m/z* $[M+Na]^+$ 397.2539; found: 397.2541.



172 **195** ***E*/*Z*-196**

(4*E*)-4-Benzylidene-3-(6-methylhepta-1,5-dien-2-yl)cyclohex-2-enol (195), (4*E*)-4-benzylidene-3-(6-methylhepta-2,5-dien-2-yl)cyclohex-2-enol (*E*/*Z*-196). Prepared according to General Procedure E using: **172** (16 mg, 0.05 mmol), $[Rh(CO)_2Cl]_2$ (2 mg, 5 μmol). Combined yield **195** and *E*/*Z*-**196** (14 mg, 88%). The isomeric ratio of **195**:*E*/*Z*-**196** was determined by integration of the resonances at 4.98 ppm and 5.39 ppm in the ^{1}H NMR. R_f 0.4 (15% EtOAc/toluene); ^{1}H

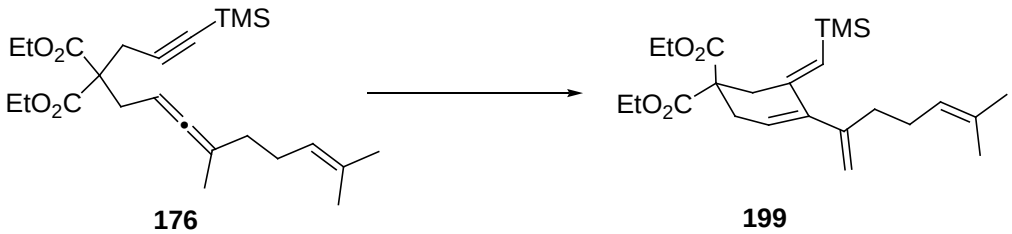
NMR (300 MHz, $CDCl_3$) *designates isomers *E*/*Z*-**196** where resolved: δ 7.41-7.18 (m, 5H), 6.49 (s, 1H), 6.43* (s, 1H), 5.73 (d, *J* = 3.6 Hz, 1H), 5.69-5.65* (m, 1H), 5.39* (t, *J* = 6.9 Hz, 1H), 5.18* (t, *J* = 6.9 Hz, 1H), 5.12 (tt, *J* = 6.9, 1.5 Hz, 1H), 5.09-5.06 (m, 1H), 4.98 (d, *J* = 2.1 Hz, 1H), 4.40 (ddd, *J* = 10.8, 6.9, 3.9 Hz, 1H), 2.81 (ddd, *J* = 14.6, 6.9, 4.2 Hz, 1H), 2.58 (dddd, *J* = 14.6, 9.6, 3.9, 1.5 Hz, 1H), 2.31-2.23 (m, 2H), 2.16-2.05 (m, 2H), 1.98 (dtd, *J* = 12.6, 8.4, 4.2 Hz, 1H), 1.85 (d, *J* = 11.7 Hz, 1H), 1.74-1.62 (m, 1H), 1.69 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.1, 144.4, 137.7, 135.1, 131.7, 129.3, 129.1 (2C), 128.1 (2C), 127.8, 126.6, 124.0, 114.2, 66.2, 36.4, 32.4, 26.8, 25.7, 24.0, 17.7; IR (thin film): 3332, 2923, 1606, 1071 cm^{-1}; EI-MS *m/z* (%) 294 (19, $M^{+\cdot}$), 225 (39), 91 (100), 77 (30); EI-HRMS calcd for $C_{21}H_{26}O$: *m/z* ($M^{+\cdot}$) 294.1984; found: 294.1983.



173 **197** ***E*/*Z*-198**

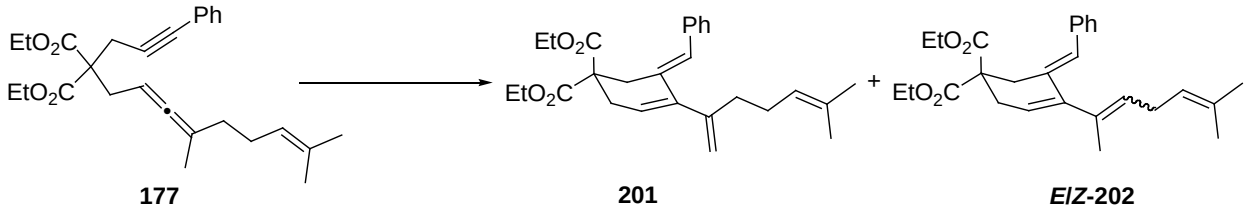
4-Methylene-3-(6-methylhepta-1,5-dien-2-yl)cyclohex-2-enol (197), **4-Methylene-3-(6-methylhepta-2,5-dien-2-yl)cyclohex-2-enol (*E*/*Z*-198)**. Prepared according to General Procedure E using: **173** (19 mg, 0.09 mmol), $[Rh(CO)_2Cl]_2$ (3 mg, 9 μmol). Combined yield of **197** and *E*/*Z*-**198** (6 mg, 32%). The isomeric ratio of **197**:*E*/*Z*-**198** was determined by integration of the three peaks in the GC chromatogram at retention times 5.6 min, 5.8 min, and 6.1 min (*E*/*Z*-**198** : **197** : *E*/*Z*-**198**). R_f 0.3 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) *designates isomers *E*/*Z*-**198** where resolved: δ 5.65 (d, *J* = 3.0 Hz, 1H), 5.63* (d, *J* = 2.7 Hz, 1H), 5.58* (s, 1H), 5.36-5.26* (m, 1H), 5.18-5.03 (m, 1H), 5.03-4.98 (m, 1H), 4.96 (s, 2H), 4.89 (d, *J* = 1.5 Hz, 1H), 4.42-4.30 (m, 1H), 2.77* (t, *J* = 7.2 Hz, 2H), 2.60-2.44 (m, 1H), 2.42-2.26 (m, 1H), 2.25-2.18 (m, 2H), 2.10-1.94 (m, 3H), 1.80* (d, *J* = 0.9 Hz, 3H), 1.78* (s, 3H), 1.76-1.66 (m, 1H), 1.71* (s,

3H), 1.68 (s, 3H), 1.65* (s, 3H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *designates isomers *E*/*Z*-**198** where resolved: δ 148.6, 143.1, 141.5, 128.9, 128.1*, 127.9*, 126.4, 124.0, 123.0*, 122.5*, 113.7, 112.5, 112.3*, 66.6*, 66.5, 36.2, 32.9*, 32.8, 28.9, 28.4*, 27.2*, 26.8, 25.7, 24.5*, 17.7, 16.9*; IR (thin film): 3332, 2923, 1598, 1052 cm^{-1}; EI-MS *m/z* (%) 218 (18, $M^{+\cdot}$), 200 (19), 149 (57), 131 (100); EI-HRMS calcd for $C_{15}H_{22}O$: *m/z* ($M^{+\cdot}$) 218.1671; found: 218.1665.

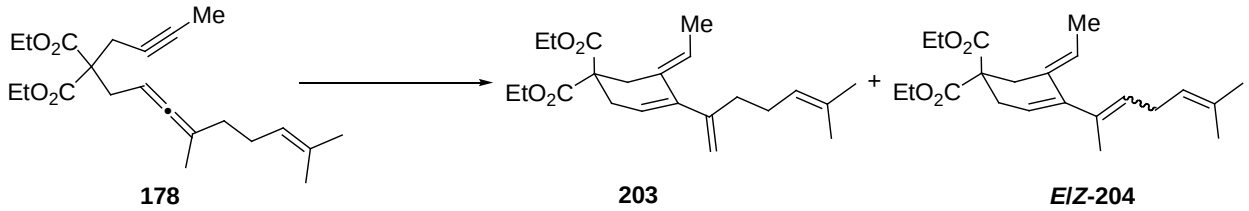


176 **199**

(5*E*)-Diethyl 4-(6-methylhepta-1,5-dien-2-yl)-5-((trimethylsilyl)methylene))cyclohex-3-ene-1,1-dicarboxylate (199). Prepared according to General Procedure E using: **176** (13.5 mg, 0.03 mmol), $[Rh(CO)_2Cl]_2$ (1 mg, 3 μmol). Yield **199** (10 mg, 74%). R_f 0.5 (5% EtOAc/toluene); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.61 (t, *J* = 4.2 Hz, 1H), 5.52 (s, 1H), 5.08 (tt, *J* = 6.9, 1.2 Hz, 1H), 4.96 (dt, *J* = 2.4, 0.9, Hz, 1H), 4.79 (d, *J* = 2.4 Hz, 1H), 4.24-4.12 (m, 4H), 2.97 (d, *J* = 1.5 Hz, 2H), 2.70 (d, *J* = 3.9 Hz, 2H), 2.15-2.09 (m, 2H), 2.03-1.93 (m, 2H), 1.68 (d, *J* = 1.2 Hz, 3H), 1.59 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 6H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9 (2C), 149.6, 145.5, 142.9, 131.5, 128.0, 124.1 (2C), 113.7, 61.4 (2C), 54.3, 36.5, 35.8, 31.4, 25.7, 17.7, 14.0 (2C), 0.0 (3C); IR (thin film): 2959, 1736, 1246, 860 cm^{-1}; EI-MS *m/z* (%) 418 (18, $M^{+\cdot}$), 345 (26), 73 (100); EI-HRMS calcd for $C_{24}H_{38}O_4Si$: *m/z* ($M^{+\cdot}$) 418.2539; found: 418.2534.

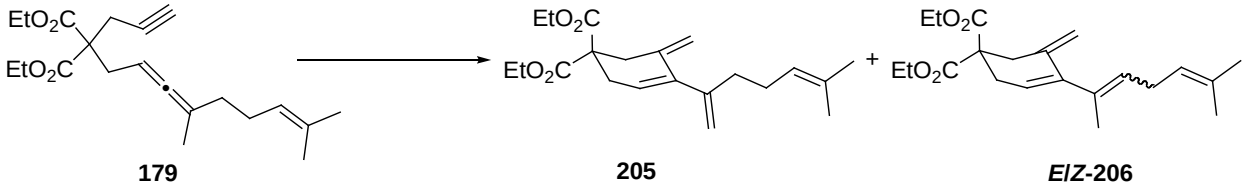


(5*E*)-Diethyl 5-benzylidene-4-(6-methylhepta-1,5-dien-2-yl)cyclohex-3-ene-1,1-dicarboxylate (201), **(5*E*)-diethyl 5-benzylidene-4-(6-methylhepta-2,5-dien-2-yl)cyclohex-3-ene-1,1-dicarboxylate (*E*/*Z*-202)**. Prepared according to General Procedure E using: **177** (18 mg, 0.04 mmol), $[Rh(CO)_2Cl]_2$ (2 mg, 4 μmol). Combined yield of **201** and *E*/*Z*-**202** (13 mg, 72%). The isomeric ratio of **201**:*E*/*Z*-**202** was determined by integration of the three peaks in the GC chromatogram at retention times 14.7 min, 16.6 min, and 17.6 min (*E*/*Z*-**202** : **201** : *E*/*Z*-**202**). R_f 0.4 (5% EtOAc/toluene); ^{1}H NMR (300 MHz, $CDCl_3$) *designates isomers *E*/*Z*-**202** where resolved: δ 7.38-7.18 (m, 5H), 6.51 (s, 1H), 6.49* (s, 1H), 6.44* (s, 1H), 5.67 (t, *J* = 3.9 Hz, 1H), 5.60* (t, *J* = 4.2 Hz, 1H), 5.40-5.29* (m, 1H), 5.16* (tt, *J* = 7.2, 1.2 Hz, 1H), 5.11 (tt, *J* = 6.9, 1.2 Hz, 1H), 5.03 (dt, *J* = 2.4, 1.2 Hz, 1H), 4.92 (d, *J* = 2.4 Hz, 1H), 4.10 (q, *J* = 7.2 Hz, 4H), 3.16 (d, *J* = 1.5 Hz, 2H), 3.14* (d, *J* = 1.8 Hz, 2H), 2.76 (d, *J* = 4.2 Hz, 2H), 2.73* (d, *J* = 4.5 Hz, 2H), 2.57* (t, *J* = 7.5 Hz, 2H), 2.27-2.19 (m, 2H), 2.05 (app q, *J* = 6.9 Hz, 2H), 1.82* (d, *J* = 1.2 Hz, 3H), 1.79* (s, 3H), 1.71* (d, *J* = 0.9 Hz, 3H), 1.68 (d, *J* = 0.9 Hz, 3H), 1.67* (s, 3H), 1.60 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9 (2C), 149.3, 142.0, 137.5, 132.0, 131.6, 129.0 (2C), 128.6, 128.1 (2C), 126.5, 124.1, 124.0, 114.2, 61.4 (2C), 54.2, 36.4, 31.6, 31.5, 26.8, 25.7, 17.7, 13.9 (2C); IR (thin film): 2921, 1734, 1246, 1060 cm^{-1}; EI-MS *m/z* (%) 422 (23, $M^{+\cdot}$), 353 (100), 349 (21), 69 (70); EI-HRMS calcd for $C_{27}H_{34}O_4$: *m/z* ($M^{+\cdot}$) 422.2457; found: 422.2451.

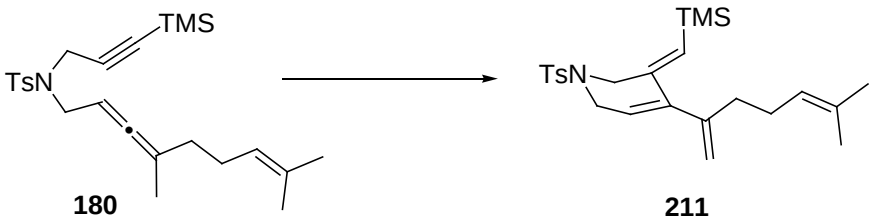


178 **203** ***E*/*Z*-204**

(5*E*)-Diethyl 5-ethylidene-4-(6-methylhepta-1,5-dien-2-yl)cyclohex-3-ene-1,1-dicarboxylate (203), **(5*E*)-diethyl 5-ethylidene-4-(6-methylhepta-2,5-dien-2-yl)cyclohex-3-ene-1,1-dicarboxylate (*E*/*Z*-204)**. Prepared according to General Procedure E using: **178** (25 mg, 0.07 mmol), $[Rh(CO)_2Cl]_2$ (3 mg, 7 μmol). Combined yield of **203** and *E*/*Z*-**204** (18 mg, 72%). The isomeric ratio of **203**:*E*/*Z*-**204** was determined by integration of the three peaks in the GC chromatogram at retention times 8.6 min, 8.9 min, and 9.2 min (*E*/*Z*-**204** : **203** : *E*/*Z*-**204**). R_f 0.4 (5% EtOAc/toluene); ^{1}H NMR (300 MHz, $CDCl_3$) *designates isomers *E*/*Z*-**204** where resolved: δ 5.54 (q, *J* = 6.9 Hz, 1H), 5.44 (t, *J* = 4.2 Hz, 1H), 5.37* (t, *J* = 3.6 Hz, 1H), 5.26-5.18* (m, 1H), 5.12* (tt, *J* = 6.9, 1.2 Hz, 1H), 5.07 (tt, *J* = 6.9, 1.2 Hz, 1H), 4.93 (dt, *J* = 2.1, 1.2 Hz, 1H), 4.79 (d, *J* = 2.1 Hz, 1H), 4.21-4.12 (m, 4H), 2.86 (s, 2H), 2.84* (s, 2H), 2.70 (d, *J* = 4.2 Hz, 2H), 2.67* (d, *J* = 3.9 Hz, 2H), 2.48* (t, *J* = 7.5 Hz, 2H), 2.17-2.09 (m, 2H), 2.02-1.92 (m, 2H), 1.73 (d, *J* = 7.2 Hz, 3H), 1.67 (s, 3H), 1.64* (s, 3H), 1.62* (s, 3H), 1.58 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2 (2C), 149.5, 141.9, 131.5, 131.0, 124.2, 123.4, 121.0, 113.4, 61.3 (2C), 54.1, 36.3, 31.3, 30.7, 26.8, 25.7, 17.7, 14.0 (2C), 13.3; IR (thin film): 2978, 1735, 1444, 1245 cm^{-1}; EI-MS *m/z* (%) 360 (18, $M^{+\cdot}$), 291 (78), 287 (32), 217 (100), 145 (47); EI-HRMS calcd for $C_{22}H_{32}O_4$: *m/z* ($M^{+\cdot}$) 360.2301; found: 360.2307.

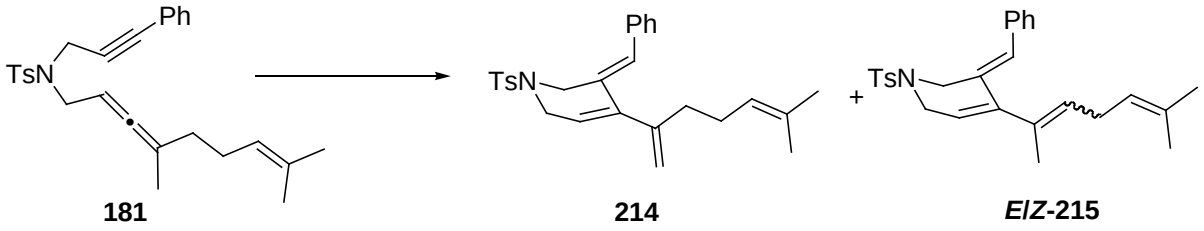


Diethyl 5-methylene-4-(6-methylhepta-1,5-dien-2-yl)cyclohex-3-ene-1,1-dicarboxylate (205), **diethyl 5-methylene-4-(6-methylhepta-2,5-dien-2-yl)cyclohex-3-ene-1,1-dicarboxylate (*E*/*Z*-206)**. Prepared according to General Procedure E using: **179** (31 mg, 0.09 mmol), $[Rh(CO)_2Cl]_2$ (4 mg, 9 μmol). Combined yield of **205** and *E*/*Z*-**206** (9 mg, 29%). The isomeric ratio of **205**: *E*/*Z*-**206** was determined by integration of the three peaks in the GC chromatogram at retention times 8.2 min, 8.4 min, and 8.8 min (*E*/*Z*-**206** : **205** : *E*/*Z*-**206**). R_f 0.5 (5% EtOAc/toluene); ^{1}H NMR (300 MHz, $CDCl_3$) *designates isomers *E*/*Z*-**206** where resolved: δ 5.59 (t, *J* = 3.3 Hz, 1H), 5.56* (t, *J* = 3.9 Hz, 1H), 5.52* (t, *J* = 3.6 Hz, 1H), 5.31-5.33* (m, 1H), 5.12* (tt, *J* = 6.9, 1.5 Hz, 1H), 5.08 (tt, *J* = 7.2, 1.5 Hz, 1H), 4.99 (s, 1H), 4.98-4.95 (m, 2H), 4.95-4.93* (m, 2H), 4.93-4.90* (m, 2H), 4.84 (d, *J* = 2.4 Hz, 1H), 4.22-4.13 (m, 4H), 2.89 (s, 2H), 2.87* (s, 2H), 2.72 (d, *J* = 4.2 Hz, 2H), 2.69* (d, *J* = 4.2 Hz, 2H), 2.21-2.14 (m, 2H), 2.05-1.95 (m, 2H), 1.80* (s, 3H), 1.75* (d, *J* = 0.9 Hz, 3H), 1.73* (s, 3H), 1.70* (s, 3H), 1.68 (s, 3H), 1.64* (s, 3H), 1.59 (s, 3H) 1.23 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) *designates isomers *E*/*Z*-**206** where resolved: δ 170.9* (2C), 170.8 (2C), 148.7, 143.3*, 140.6, 138.4*, 135.0*, 131.5, 127.8, 126.9*, 124.1, 123.9*, 123.0, 122.7*, 113.7, 113.6, 113.5*, 61.4 (2C), 61.3* (2C), 54.2, 37.3*, 37.2, 36.3, 31.6, 27.2*, 26.8, 25.7, 17.7, 16.8*, 14.0 (2C); IR (thin film): 2978, 1735, 1444, 1244 cm^{-1}; EI-MS *m/z* (%) 346 (39, $M^{+\cdot}$), 277 (42), 273 (100), 203 (81); EI-HRMS calcd for $C_{21}H_{30}O_4$: *m/z* ($M^{+\cdot}$) 346.2144; found: 346.2142.



180 **211**

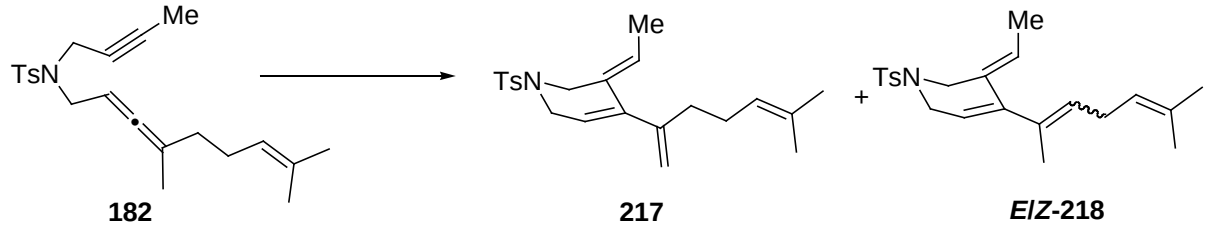
(3*Z*)-1,2,3,6-Tetrahydro-4-(6-methylhepta-1,5-dien-2-yl)-3-((trimethylsilyl)methylene)-1-tosylpyridine (211). Prepared according to General Procedure E using: **180** (19 mg, 0.04 mmol), $[Rh(CO)_2Cl]_2$ (2 mg, 4 μmol). Yield of **211** (12 mg, 63%). R_f 0.5 (5% EtOAc/toluene); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 5.54 (s, 1H), 5.49 (t, *J* = 3.6 Hz, 1H), 5.02 (t, *J* = 6.6 Hz, 1H), 4.98-4.92 (m, 1H), 4.68 (d, *J* = 1.8 Hz, 1H), 3.92 (s, 2H), 3.80 (d, *J* = 3.6 Hz, 2H), 2.43 (s, 3H), 2.07-1.99 (m, 2H), 1.97-1.88 (m, 2H), 1.66 (s, 3H), 1.55 (s, 3H), 0.20 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.9, 143.5, 143.1, 142.0, 133.8, 131.7, 129.6 (2C), 128.6, 127.7 (2C), 123.8, 121.4, 114.6, 48.1, 45.2, 35.9, 26.6, 25.6, 21.5, 17.7, 0.0 (3C); IR (thin film): 2921, 1595, 1165, 866 cm^{-1}; ESI-MS *m/z* (%) 453 (3), 452 (100, $[M+Na]^+$); ESI-HRMS calcd for $C_{24}H_{35}NO_2NaSiS$: *m/z* $[M+Na]^+$ 452.2055; found: 452.2068.



181 **214** ***E*/*Z*-215**

(3*Z*)-3-Benzylidene-1,2,3,6-tetrahydro-4-(6-methylhepta-1,5-dien-2-yl)-1-tosylpyridine (214), **(3*Z*)-3-benzylidene-1,2,3,6-tetrahydro-4-(6-methylhepta-2,5-dien-2-yl)-1-tosylpyridine (*E*/*Z*-215)**. Prepared according to General Procedure E using: **181** (16 mg, 0.04 mmol), $[Rh(CO)_2Cl]_2$ (2 mg, 4 μmol). Combined yield of **214** and *E*/*Z*-**215** (9 mg, 56%). The isomeric ratio of **214**:*E*/*Z*-**215** was determined by integration of the resonances at 6.40 ppm and 6.32 ppm in the ^{1}H NMR. R_f 0.4 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$)

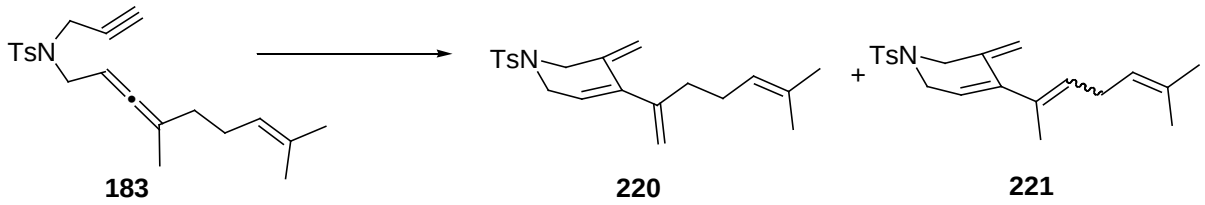
*designates isomers *E*/*Z*-**215** where resolved: δ 7.58* (d, *J* = 8.1 Hz, 2H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.43-7.36 (m, 2H), 7.32-7.21 (m, 3H), 7.18 (d, *J* = 8.4 Hz, 2H), 6.40 (s, 1H), 6.32* (s, 1H), 5.51 (t, *J* = 3.6 Hz, 1H), 5.48* (t, *J* = 3.6 Hz, 1H), 5.32* (tq, *J* = 7.2, 0.9 Hz, 1H), 5.10* (tt, *J* = 7.2, 1.2 Hz, 1H), 5.08-5.00 (m, 1H), 4.98 (dt, *J* = 2.1, 0.9, Hz, 1H), 4.68 (d, *J* = 2.1 Hz, 1H), 4.23 (d, *J* = 0.9 Hz, 2H), 3.95 (d, *J* = 4.2 Hz, 2H), 3.94* (d, *J* = 4.8 Hz, 2H), 2.73* (t, *J* = 7.2 Hz, 2H), 2.42 (s, 3H), 2.40* (s, 3H), 2.36* (t, *J* = 6.9 Hz, 2H), 2.14-2.06 (m, 2H), 2.03-1.93 (m, 2H), 1.72* (d, *J* = 0.9, Hz, 3H), 1.69* (d, *J* = 1.2, Hz, 3H), 1.66 (d, *J* = 0.9, Hz, 3H), 1.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.8, 143.4, 141.1, 136.2, 134.5, 131.8, 129.4 (2C), 129.3, 128.9 (2C), 128.7, 128.5 (2C), 127.4 (2C), 127.3, 123.7, 121.4, 114.8, 45.3, 44.6, 36.0, 26.7, 25.7, 21.5, 17.7; IR (thin film): 2920, 1633, 1349, 1163 cm^{-1}; EI-MS *m/z* (%) 433 (30, $M^{+\cdot}$), 278 (68), 91 (97), 69 (100); EI-HRMS calcd for $C_{27}H_{31}NO_2S$: *m/z* ($M^{+\cdot}$) 433.2076; found: 433.2069.



182 **217** ***E*/*Z*-218**

(3*Z*)-3-Ethylidene-1,2,3,6-tetrahydro-4-(6-methylhepta-1,5-dien-2-yl)-1-tosylpyridine (217), **(3*Z*)-3-ethylidene-1,2,3,6-tetrahydro-4-(6-methylhepta-2,5-dien-2-yl)-1-tosylpyridine (*E*/*Z*-218)**. Prepared according to General Procedure E using: **182** (22 mg, 0.06 mmol), $[Rh(CO)_2Cl]_2$ (2 mg, 6 μmol). Combined yield of **217** and *E*/*Z*-**218** (14 mg, 64%). The isomeric ratio of **217**:*E*/*Z*-**218** was determined by integration of the resonances at 5.32 ppm, 5.29 ppm, and 5.28 ppm in the ^{1}H NMR. R_f 0.7 (15% EtOAc/toluene); ^{1}H NMR (500 MHz, $CDCl_3$) *designates isomers *E*/*Z*-**218** where resolved: 7.68 (d, *J* = 8.0 Hz, 2H), 7.67* (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.47 (q, *J* = 7.5 Hz, 1H), 5.39* (q, *J* = 7.0 Hz, 1H), 5.32 (t, *J* = 3.5 Hz, 1H), 5.29* (t, *J* = 3.5 Hz, 1H), 5.28* (t, *J* = 3.5 Hz, 1H), 5.22* (tq, *J* = 7.5, 1.5 Hz, 1H), 5.09* (tt,

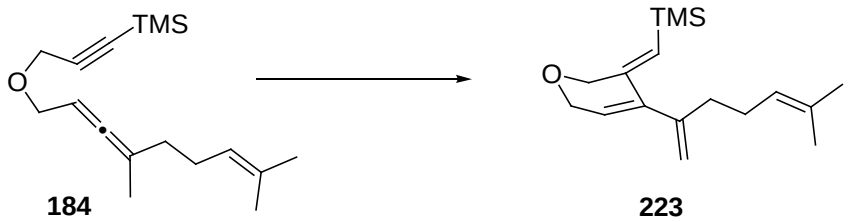
J = 7.0, 1.5 Hz, 1H), 5.07* (tt, *J* = 7.0, 1.5 Hz, 1H), 5.01 (tt, *J* = 7.0, 1.5 Hz, 1H), 4.90 (dt, *J* = 2.5, 1.0, Hz, 1H), 4.63 (d, *J* = 2.5 Hz, 1H), 3.93 (s, 2H), 3.82 (d, *J* = 3.5 Hz, 2H), 3.80* (d, *J* = 3.5 Hz, 2H), 2.68* (t, *J* = 7.0 Hz, 2H), 2.43* (s, 3H), 2.42 (s, 3H), 2.41* (s, 3H), 2.32* (t, *J* = 7.5 Hz, 2H), 2.04-1.98 (m, 2H), 1.96-1.89 (m, 2H), 1.74 (d, *J* = 7.5 Hz, 3H), 1.70* (d, *J* = 1.0 Hz, 3H), 1.68* (s, 3H), 1.67* (s, 3H), 1.65 (d, *J* = 0.5 Hz, 3H), 1.63* (s, 3H), 1.61* (d, *J* = 1.5 Hz, 3H), 1.60* (s, 3H), 1.55 (s 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.0, 143.4, 140.8, 134.2, 131.7, 129.4 (2C), 128.8, 127.7 (2C), 123.8, 123.6, 118.7, 114.1, 45.1, 43.7, 36.0, 26.6, 25.7, 21.5, 17.7, 13.3; IR (thin film): 2919, 1597, 1348, 1161 cm^{-1}; ESI-MS m/z (%) 394 (100, $[M+Na]^+$), 386 (57); ESI-HRMS calcd for $C_{22}H_{29}NO_2NaS$: *m/z* $[M+Na]^+$ 394.1817; found: 394.1844.



183 **220** **221**

1,2,3,6-Tetrahydro-3-methlyene-4-(6-methylhepta-1,5-dien-2-yl)-1-tosylpyridine (220), **1,2,3,6-Tetrahydro-3-methlyene-4-(6-methylhepta-2,5-dien-2-yl)-1-tosylpyridine (*E*/*Z*-221)**. Prepared according to General Procedure E using: **183** (22 mg, 0.06 mmol), $[Rh(CO)_2Cl]_2$ (2 mg, 6 μmol). Combined yield of **220** and *E*/*Z*-**221** (8 mg in 36% yield, product contains inseparable impurities). The isomeric ratio of **220**:*E*/*Z*-**221** was determined by integration of the resonances at 2.70 ppm, 2.35 ppm, and 2.11-2.03 in the ^{1}H NMR. R_f 0.5 (5% EtOAc/toluene); ^{1}H NMR (300 MHz, $CDCl_3$) *designates isomers *E*/*Z*-**221** where resolved: δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.68* (d, *J* = 8.4 Hz, 2H), 7.67* (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 7.8 Hz, 2H), 7.29* (d, *J* = 8.1 Hz, 2H), 7.28* (d, *J* = 7.8 Hz, 2H), 5.49-5.46* (m, 1H), 5.46-5.41 (m, 1H), 5.12-5.02 (m, 1H), 5.03-4.98 (m, 2H), 4.95 (dt, *J* = 2.4, 0.9 Hz, 1H), 4.93-4.90* (m, 2H), 4.70 (d, *J* = 2.1 Hz, 1H), 3.87-3.84 (m, 2H), 3.83* (d, *J* = 3.6 Hz, 2H), 3.81 (d, *J* = 3.6 Hz, 2H), 2.70* (t, *J* = 7.2 Hz, 2H),

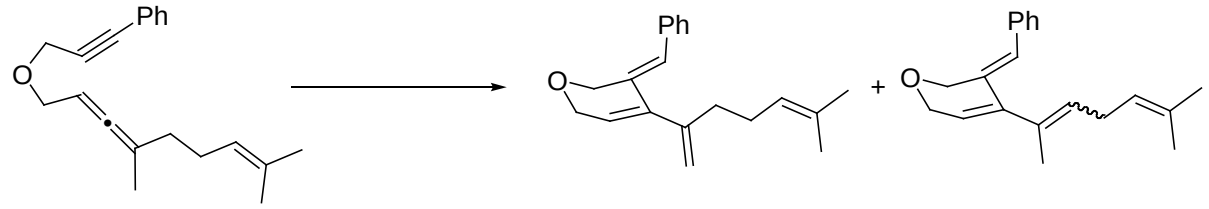
2.45* (s, 3H), 2.42 (s, 3H), 2.35* (t, *J* = 6.6 Hz, 2H), 2.11-2.03 (m, 2H), 1.99-1.88 (m, 2H), 1.70* (d, *J* = 1.2 Hz, 3H), 1.65* (d, *J* = 0.9 Hz, 3H), 1.63 (s, 3H), 1.55 (s, 3H), minor inseparable impurities (by column chromatography): 5.31-5.28 (m, 0.4H), 4.72 (q, *J* = 2.7 Hz, 1.1H), 4.16 (dq, *J* = 14.1, 1.8 Hz, 1.4H), 3.92 (t, *J* = 2.1 Hz, 1.3H), 3.66 (app t, *J* = 9.6 Hz, 1.6H), 3.15 (app t, *J* = 9.6 Hz, 1.3H), 2.20-2.30 (m, 2.5H); ^{13}C NMR (75 MHz, $CDCl_3$) *designates isomers *E*/*Z*-**221** where resolved: δ 146.6, 143.6, 143.5*, 143.4*, 139.8, 136.1, 133.9*, 133.2, 133.0*, 132.5*, 132.0*, 131.8, 129.6 (2C), 129.5* (2C), 129.5* (2C), 127.9* (2C), 127.8* (2C), 127.7 (2C), 123.7, 122.3*, 121.6*, 120.8*, 114.4, 113.4*, 113.2, 49.5, 49.4*, 45.5, 45.4*, 35.9, 35.7*, 30.5, 27.2*, 26.0*, 25.6, 21.5, 21.4*, 17.7; IR (thin film): 2959, 1597, 1348, 1163 cm^{-1}; EI-MS m/z (%) 357 (62, $M^{+\cdot}$), 288 (34), 202 (61), 91 (100); EI-HRMS calcd for $C_{21}H_{27}NO_2S$: *m/z* ($M^{+\cdot}$) 357.1763; found: 357.1777.



184 **223**

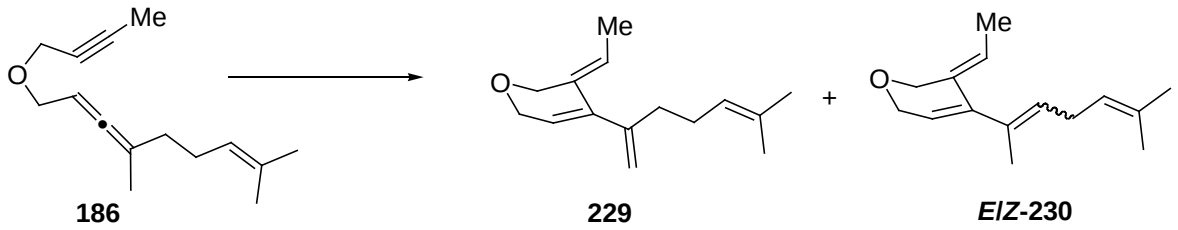
Trimethyl((1*Z*)-(4-(6-methylhepta-1,5-dien-2-yl)-2*H*-pyran-3(6*H*)-ylidene)methyl)silane (223). Prepared according to General Procedure E using: **184** (14 mg, 0.05 mmol), $[Rh(CO)_2Cl]_2$ (2 mg, 5 μmol). Yield of **223** (8.5 mg, 61%). R_f 0.5 (5% EtOAc/toluene); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.68 (td, *J* = 3.0, 0.6 Hz, 1H), 5.53 (d, *J* = 0.6 Hz, 1H), 5.11 (tt, *J* = 6.9, 1.5 Hz, 1H), 5.03 (dt, *J* = 2.4, 1.5, Hz, 1H), 4.90 (d, *J* = 2.4 Hz, 1H), 4.35 (d, *J* = 0.6 Hz, 2H), 4.27 (dd, *J* = 3.0, 0.9 Hz, 2H), 2.23-2.14 (m, 2H), 2.11-2.00 (m, 2H), 1.69 (d, *J* = 1.2 Hz, 3H), 1.60 (s, 3H), 0.14 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.0, 145.8, 140.7, 131.7, 125.4, 125.0, 124.0, 114.3, 68.5, 65.8, 36.1, 26.8, 25.7, 17.7, 0.2 (3C); IR (thin film): 2926, 1583, 1249, 864 cm^{-1}; EI-

MS *m/z* (%) 276 (22, $M^{+\cdot}$), 261 (14), 207 (78), 75 (100); EI-HRMS calcd for $C_{17}H_{28}OSi$: *m/z* ($M^{+\cdot}$) 276.1909; found: 276.1901.



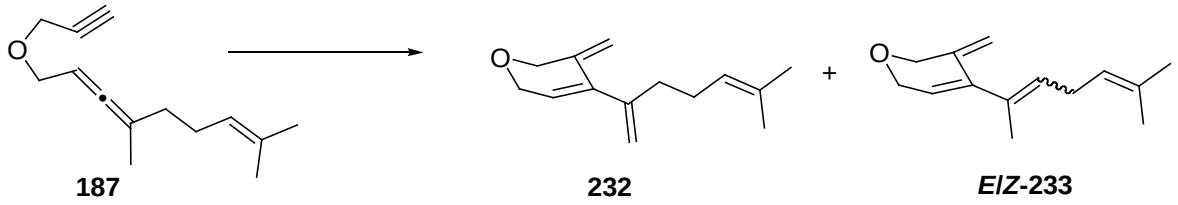
185 **226** ***E*/*Z*-227**

(3*Z*)-3-Benzylidene-3,6-dihydro-4-(6-methylhepta-1,5-dien-2-yl)-2*H*-pyran (226), **(3*Z*)-3-Benzylidene-3,6-dihydro-4-(6-methylhepta-2,5-dien-2-yl)-2*H*-pyran (*E*/*Z*-227)**. Prepared according to General Procedure E using: **185** (15 mg, 0.05 mol), $[Rh(CO)_2Cl]_2$ (2 mg, 5 μmol). Combined yield of **226** and *E*/*Z*-**227** (9 mg, 60%). The isomeric ratio of **226**:*E*/*Z*-**227** was determined by integration of the three peaks in the GC chromatogram at retention times 8.5 min, 8.9 min, and 9.3 min (*E*/*Z*-**227** : **226** : *E*/*Z*-**227**). R_f 0.5 (5% EtOAc/toluene); ^{1}H NMR (300 MHz, $CDCl_3$) *designates isomers *E*/*Z*-**227** where resolved: δ 7.40-7.31 (m, 2H), 7.28-7.21 (m, 1H), 7.14 (d, *J* = 7.8 Hz, 2H), 6.51 (s, 1H), 6.45* (s, 1H), 6.43* (s, 1H), 5.73 (t, *J* = 3.0 Hz, 1H), 5.68* (t, *J* = 2.7 Hz, 1H), 5.44* (t, *J* = 7.2 Hz, 1H), 5.13 (tt, *J* = 6.9, 0.9 Hz, 1H), 5.12-5.09 (m, 1H), 5.02 (d, *J* = 2.4 Hz, 1H), 4.59 (d, *J* = 1.5 Hz, 2H), 4.58* (d, *J* = 1.5 Hz, 2H), 4.33 (d, *J* = 3.0 Hz, 2H), 4.30* (d, *J* = 2.7 Hz, 2H), 2.83* (t, *J* = 7.2 Hz, 2H), 2.68* (t, *J* = 7.2 Hz, 2H), 2.34-2.25 (m, 2H), 2.18-2.07 (m, 2H), 1.89* (s, 3H), 1.86* (s, 3H), 1.73* (s, 3H), 1.70 (s, 3H), 1.61 (s, 3H) 1.60* (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.0, 139.6, 136.7, 132.4, 131.8, 129.1 (2C), 128.2 (2C), 126.9, 126.2, 124.9, 123.9, 114.6, 65.8, 65.2, 36.2, 26.8, 25.7, 17.8; IR (thin film): 2923, 1444, 1121 cm^{-1}; EI-MS *m/z* (%) 280 (25, $M^{+\cdot}$), 211 (18), 91 (100), 69 (59); EI-HRMS calcd for $C_{20}H_{24}O$: *m/z* ($M^{+\cdot}$) 280.1827; found: 280.1835.



186 **229** ***E*/*Z*-230**

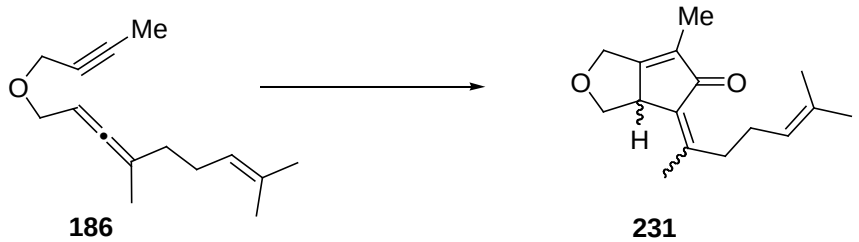
(3*Z*)-3-Ethylidene-3,6-dihydro-4-(6-methylhepta-1,5-dien-2-yl)-2*H*-pyran (229), **(3*Z*)-3-Ethylidene-3,6-dihydro-4-(6-methylhepta-2,5-dien-2-yl)-2*H*-pyran (*E*/*Z*-230)**. Prepared according to General Procedure E using: **186** (22 mg, 0.10 mmol), $[Rh(CO)_2Cl]_2$ (4 mg, 10 μmol). Combined yield of **229** and *E*/*Z*-**230** (9 mg, 41%). The isomeric ratio of **229**:*E*/*Z*-**230** was determined by integration of the three peaks in the GC chromatogram at retention times 5.3 min, 5.6 min, and 5.9 min (*E*/*Z*-**230** : **229** : *E*/*Z*-**230**). R_f 0.7 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) *designates isomers *E*/*Z*-**230** where resolved: δ 5.53 (t, *J* = 3.0 Hz, 1H), 5.50 (q, *J* = 7.0 Hz, 1H), 5.46* (t, *J* = 3.0 Hz, 1H), 5.43* (q, *J* = 7.0 Hz, 1H), 5.42* (q, *J* = 7.0 Hz, 1H), 5.34-5.29* (m, 1H), 5.14* (tt, *J* = 7.0, 1.5 Hz, 1H), 5.10 (tt, *J* = 7.0, 1.5 Hz, 1H), 5.05* (tt, *J* = 7.0, 1.5 Hz, 1H), 5.00 (dt, *J* = 2.5, 1.5 Hz, 1H), 4.89 (d, *J* = 2.5 Hz, 1H), 4.36 (s, 2H), 4.35* (s, 2H), 4.25 (d, *J* = 3.0 Hz, 2H), 4.23* (d, *J* = 3.0 Hz, 2H), 2.77* (t, *J* = 7.5 Hz, 2H), 2.58* (t, *J* = 7.0 Hz, 2H), 2.21-2.17 (m, 2H), 2.09-2.03 (m, 2H), 1.79* (q, *J* = 1.5 Hz, 3H), 1.77-1.75* (m, 3H), 1.71* (d, *J* = 1.5 Hz, 3H), 1.69 (d, *J* = 6.5 Hz, 3H), 1.69 (d, *J* = 1.0 Hz, 3H), 1.61* (s, 3H), 1.60 (s, 3H), 1.58* (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.2, 139.4, 131.6, 131.2, 124.0, 122.2, 120.8, 113.8, 65.8, 64.4, 36.2, 26.8, 25.7, 17.7, 12.8; IR (thin film): 2918, 1448, 1129 cm^{-1}; EI-MS m/z (%) 218 (20, $M^{+\cdot}$),189 (24), 69 (100); EI-HRMS calcd for $C_{15}H_{22}O_2$: *m/z* ($M^{+\cdot}$) 218.1671; found: 218.1670.



187 **232** ***E*/*Z*-233**

3,6-Dihydro-3-methylene-4-(6-methylhepta-1,5-dien-2-yl)-2*H*-pyran (232), 3,6-dihydro-3-methylene-4-(6-methylhepta-2,5-dien-2-yl)-2*H*-pyran (*E*/*Z*-233). Prepared according to General Procedure E using: **187** (34 mg, 0.16 mmol), $[Rh(CO)_2Cl]_2$ (6 mg, 16 μmol). Combined yield of **232** and *E*/*Z*-**233** (7 mg in 21% yield, product contains inseparable impurities). The isomeric ratio of **232** : *E*/*Z*-**233** was determined by integration of the resonances at 5.68-5.64 ppm, 5.64-5.62 ppm, and 5.61-5.58 ppm in the ^{1}H NMR. R_f 0.5 (5% EtOAc/toluene); ^{1}H NMR (500 MHz, $CDCl_3$) *designates isomers *E*/*Z*-**233** where resolved: δ 5.68-5.64 (m, 1H), 5.64-5.62* (m, 1H), 5.61-5.58* (m, 1H), 5.37* (tq, *J* = 7.5, 1.5 Hz, 1H), 5.35* (tq, *J* = 7.5, 1.5 Hz, 1H), 5.14* (tt, *J* = 7.0, 1.5 Hz, 1H), 5.10 (tt, *J* = 7.0, 1.5 Hz, 1H), 5.05* (tt, *J* = 7.0, 1.5 Hz, 1H), 5.03 (dt, *J* = 2.5, 1.5 Hz, 1H), 5.01 (s, 1H), 4.95 (s, 1H), 4.94 (d, *J* = 2.5 Hz, 1H), 4.92-4.89* (m, 2H), 4.30 (d, *J* = 3.0 Hz, 2H), 4.28* (d, *J* = 3.5 Hz, 2H), 4.25 (s, 2H), 4.23* (s, 2H), 2.78* (t, *J* = 7.0 Hz, 2H), 2.59* (t, *J* = 7.0 Hz, 2H), 2.26-2.21 (m, 2H), 2.10-2.04 (m, 2H), 1.83* (s, 3H), 1.72* (s, 3H), 1.69 (s, 3H), 1.66* (s, 3H), 1.60 (s, 3H), 1.59* (s, 3H), minor inseparable impurities (by column chromatography): 4.54 (A of an ABq , q, *J* = 13.5, 1.5 Hz, 2H), 4.48 (B of an ABq , q, *J* = 13.5, 2.0 Hz, 2H), 4.17-4.13 (m, 2H), 4.13-4.07 (m, 2H), 3.80 (dd, *J* = 9.0, 7.5 Hz, 2H), 2.50-2.44 (m, 4.5H), 2.31 (q, *J* = 6.5 Hz, 4.4H); ^{13}C NMR (125 MHz, $CDCl_3$) *designates isomers *E*/*Z*-**233** where resolved: δ 150.5, 147.3, 140.9*, 138.6, 138.5*, 138.4*, 133.2, 132.0*, 131.7*, 128.4*, 125.1*, 125.0, 124.1*, 123.9, 122.5*, 114.1, 110.3, 110.1*, 69.9*, 69.8, 66.2, 66.1*, 36.0, 27.3*, 26.8, 25.7, 25.6*, 24.2, 17.8*, 17.7; IR (thin film): 2917, 1453,

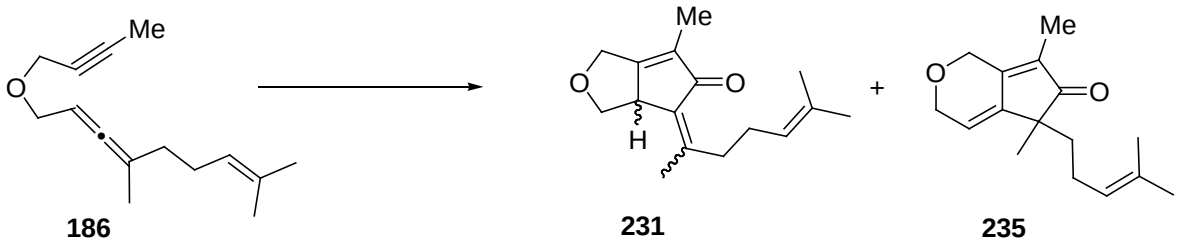
1129 cm^{-1}; EI-MS m/z (%) 204 (65, $M^{+\cdot}$), 189 (23), 135 (48), 107 (100); EI-HRMS calcd for $C_{14}H_{20}O$: *m/z* ($M^{+\cdot}$) 204.1514; found: 204.1511.



186 **231**

3a,4-Dihydro-6-methyl-4-(6-methylhepta-5-en-2-ylidene)-1H-cyclopenta[c]furan-5-(3*H*)-one (231). A flame-dried 13 x 100 mm test tube equipped with a stir bar and rubber septum is charged with allene-yne **186** (26 mg, 0.12 mmol) and toluene (1.2 mL). The test tube is then evacuated under vacuum by insertion of an 18 gauge needle into the septum and charged three times with CO(g) from a balloon. To the allene-yne solution is then added $[Rh(CO)_2Cl]_2$ (5 mg, 12 μmol) in one portion and the test tube is evacuated and refilled with CO again (3X). The test tube is placed in a preheated 90 °C oil bath and is stirred under a balloon of CO. After 30 min, consumption of **186** is observed by TLC. The reaction is cooled to rt and is directly subjected to silica gel chromatography eluting with 5-30% Et_2O/pentane to give 19 mg of α-alkylidene cyclopentenone **231** in 65% yield, d.r. = 1:1 based upon integration of the resonances at 5.17 ppm and 5.06 ppm in the ^1H NMR. R_f 0.2 (5% EtOAc/toluene); ^1H NMR (300 MHz, $CDCl_3$) *designates where minor diastereomer is resolved: δ 5.17 (t, *J* = 7.5 Hz, 1H), 5.06* (t, *J* = 6.9 Hz, 1H), 4.58 (A of an ABq, *J* = 14.7, 1H), 4.45 (B of an ABq, *J* = 14.7, 1H), 4.38 (t, *J* = 7.5 Hz, 1H), 4.33* (t, *J* = 7.8 Hz, 1H), 3.71-3.60 (m, 1H), 3.15 (dd, *J* = 11.1, 7.8 Hz, 1H), 3.14* (dd, *J* = 10.8, 7.8 Hz, 1H), 2.91-2.71 (m, 1H), 2.30* (s, 3H), 2.26-2.05 (m, 3H), 1.88 (s, 3H), 1.80 (s, 3H), 1.68 (s, 3H), 1.62 (s, 3H), 1.61* (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *designates where minor diastereomer is resolved: δ 197.4, 196.6*, 166.7, 166.3*, 151.3*, 150.8, 135.7, 132.8, 132.1*, 130.6*, 130.3, 123.7*, 122.9, 70.6, 70.4*, 64.2*, 64.1, 47.7*, 47.5, 39.1, 32.7, 25.7, 22.9,

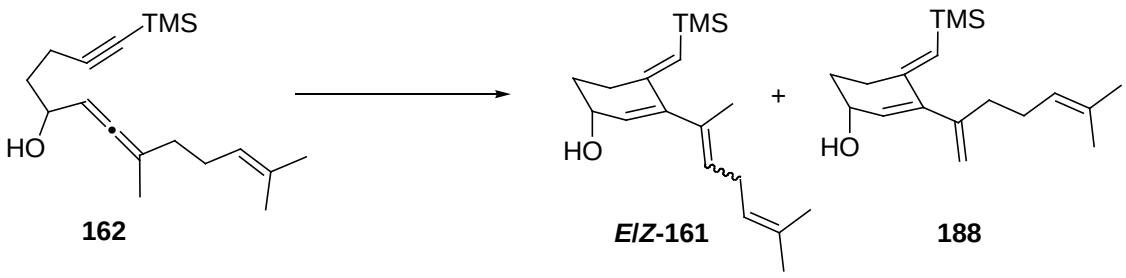
17.7*, 17.3, 9.5; IR (thin film): 2918, 1683, 1632, 1444 cm^{-1}; EI-MS m/z (%) 246 (27, $M^{+\cdot}$), 173 (20), 148 (68), 69 (100); EI-HRMS calcd for $C_{16}H_{22}O_2$: *m/z* ($M^{+\cdot}$) 246.1620; found: 246.1611.



186 **231** **235**

3a,4-Dihydro-6-methyl-4-(6-methylhepta-5-en-2-ylidene)-1H-cyclopenta[c]furan-5-(3*H*)-one (231), 5,7-diemthyl-5-(4-methylpent-3-enyl)cyclopenta[c]pyran-6(1*H*,3*H*,5*H*)-one (235). A flame-dried 13 x 100 mm test tube equipped with a stir bar and rubber septum is charged with $[Rh(CO)_2Cl]_2$ (4 mg, 11 μmol) and DCE (0.3 mL). To the solution is then added PPh_3 (9 mg, 34 μmol) in DCE (0.3 mL) dropwise via syringe. The test tube is then evacuated under vacuum by insertion of an 18 gauge needle into the septum and charged three times with CO(g) from a balloon. After 5 min of stirring, a solution of $AgBF_4$ (0.5 mL of a 0.05 M soln in DCE, 25 μmol) is added dropwise via syringe. The reaction is stirred for an additional 5 min at rt before a solution of allene-yne **186** (25 mg, 0.11 mmol) in DCE (0.3 mL) is added via syringe. The test tube is placed in a preheated 50 °C oil bath and is stirred under a balloon of CO. After 1 h of stirring, consumption of **186** is observed by TLC. The reaction is cooled to rt and is directly subjected to silica gel chromatography eluting with 5-20% Et_2O/pentane to give 6 mg of α-alkylidene cyclopentenone **231** in 21% yield, and 6 mg of 4-alkylidene cyclopentenone **235** in 21% yield. Spectral data for α-alkylidene cyclopentenone **231** matched that from above. **4-alkylidene cyclopentenone 235:** R_f 0.3 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) 4-alkylidene cyclopentenone **235** (contaminated with trace amount of **231**): δ 5.87 (t, *J* = 3.3 Hz, 1H), 5.02-4.94 (m, 1H), 4.67 (s, 2H), 4.35 (d, *J* = 3.3 Hz, 2H), 1.86-1.60 (m, 4H), 1.76 (s, 3H), 1.75 (s, 3H), 1.63 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.7, 156.7, 142.7,

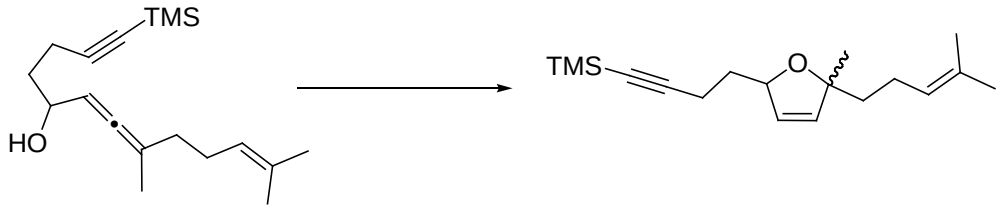
131.7, 130.9, 124.1, 118.6, 64.9, 63.6, 47.7, 37.3, 25.6, 23.4, 22.8, 17.6, 7.8; IR (thin film): 2920, 1701, 1631, 1126 cm^{-1}; EI-MS m/z (%) 246 (50, $M^{+\cdot}$), 164 (51), 117 (100), 69 (70); EI-HRMS calcd for $C_{16}H_{22}O_2$: *m/z* ($M^{+\cdot}$) 246.1620; found: 246.1612.



162 ***E*/*Z*-161** **188**

(4*E*)-3-(6-Methylhepta-2,5-dien-2-yl)-4-((trimethylsilyl)methylene)cyclohexen-2-ol (*E*/*Z*-161), (4*E*)-3-(6-Methylhepta-1,5-dien-2-yl)-4-((trimethylsilyl)methylene)cyclohexen-2-ol (188). A flame-dried 13 x 100 mm test tube equipped with a stir bar, rubber septum, and argon balloon is charged with allene-yne **162** (18 mg, 0.06 mmol) and styrene (1.2 mL). Argon is bubbled through the solution using a balloon filled with argon attached to a syringe before $[Rh(CO)_2Cl]_2$ (2 mg, 6 μmol) is added in one portion. Upon completion of the reaction as observed by TLC analysis, the solution is directly subjected to silica gel chromatography eluting with 5-20% Et_2O/pentane to give 14 mg of cross-conjugated trienes *E*/*Z*-**161** and **188** in 78% yield. The isomeric ratio of *E*/*Z*-**161** and **188** was determined by integration of the three peaks in the GC chromatogram at retention times at 6.9 min, 7.1 min, and 7.4 min, which correspond to *Z*-**161**, **188**, and *E*-**161**, respectively. The *E* isomer of **161** was separated from the *Z* (*Z*-**161**) and constitutional site isomers (**188**) using HPLC (Varian Microsorb Dynamax 100-5 Si column, 23 °C, isopropanol / hexanes = 1%, flow rate = 3 $mL \cdot min^{-1}$). Isomers *Z*-**161** and **188** were inseparable and co-eluted using this method. R_f 0.3 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) *E*-**161**: δ 5.64 (d, *J* = 3.6 Hz, 1H), 5.43 (s, 1H), 5.29 (tq, *J* = 7.2, 1.5 Hz, 1H), 5.15 (tt, *J* = 7.2, 1.5 Hz, 1H), 4.32 (s, 1H), 2.77 (t, *J* = 7.2 Hz, 2H), 2.56 (ddd, *J* = 14.7, 8.1, 3.6 Hz, 1H),

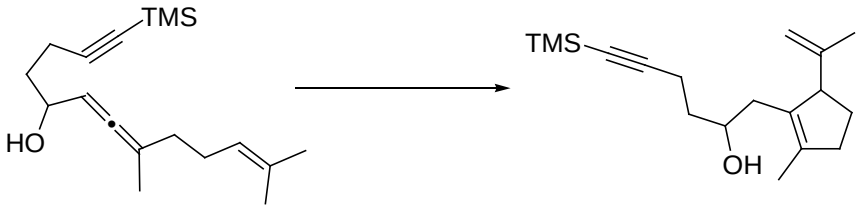
2.34 (dddd, *J* = 14.7, 10.8, 3.9, 1.2 Hz, 1H), 2.01 (ddt, *J* = 12.6, 8.4, 4.5 Hz, 1H), 1.73 (d, *J* = 0.6 Hz, 3H), 1.72-1.62 (m, 1H), 1.71 (d, *J* = 0.6 Hz, 3H), 1.65 (s, 3H), 0.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.5, 147.8, 135.0, 131.9, 128.2, 127.9, 127.1, 122.6, 66.4, 33.0, 28.0, 27.2, 25.6, 17.7, 17.0, 0.1 (3C); IR (thin film): 3306, 2920, 1577, 1247 cm^{-1}; EI-MS *m/z* (%) 290 (39, $M^{+\cdot}$), 221 (16), 131 (100), 73 (93); EI-HRMS calcd for $C_{18}H_{30}OSi$: *m/z* ($M^{+\cdot}$) 290.2066; found: 290.2064. ^{1}H NMR (500 MHz, $CDCl_3$) *designates where minor isomer *Z*-**161** is resolved from **188**: δ 5.66 (d, *J* = 3.5 Hz, 1H), 5.60* (d, *J* = 3.0 Hz, 1H), 5.50 (s, 1H), 5.31* (tq, *J* = 7.0, 1.5 Hz, 1H), 5.10 (tt, *J* = 7.0, 1.5 Hz, 1H), 5.05* (tt, *J* = 7.5, 1.5 Hz, 1H), 5.00 (d, *J* = 1.5 Hz, 1H), 4.88 (d, *J* = 2.0 Hz, 1H), 4.40-2.31 (m, 1H), 2.58 (ddd, *J* = 14.5, 7.5, 3.5 Hz, 1H), 2.52* (t, *J* = 7.0 Hz, 2H), 2.37 (dddd, *J* = 14.5, 10.0, 4.0, 1.5 Hz, 1H), 2.20-2.14 (m, 2H), 2.08-2.00 (m, 3H), 1.78* (s, 3H), 1.71 (ddd, *J* = 13.5, 7.0, 3.5 Hz, 1H), 1.69 (s, 3H), 1.68* (s, 3H), 1.59 (s, 3H), 1.57* (s, 3H), 0.13 (s, 9H).



162 **239**

(4-(2,5-Dihydro-5-methyl-5-(4-methylpent-3-enyl)furan-2-yl)but-1-ynyl)trimethylsilane (239). A flame-dried 13 x 100 mm test tube equipped with a stir bar, rubber septum, and argon balloon is charged with allene-yne **162** (9 mg, 0.03 mmol) and MeOH (0.6 mL). Argon is bubbled through the solution using a balloon filled with argon attached to a syringe before $[Rh(CO)_2Cl]_2$ (1 mg, 3 μmol) is added in one portion. Upon completion of the reaction as observed by TLC analysis, the solution is directly subjected to silica gel chromatography eluting with 5% Et_2O/pentane to give 7 mg of furan **239** in 78% yield as a 1.2:1 mixture of diastereomers. R_f 0.8 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) *designates minor

diastereomer where resolved: δ 5.74 (dd, *J* = 6.3, 0.9 Hz, 1H), 5.72* (s, 2H), 5.68 (dd, *J* = 6.0, 2.1 Hz, 1H), 5.16-5.05 (m, 1H), 4.87 (t, *J* = 6.3 Hz, 1H), 2.39-2.26 (m, 2H), 2.07-1.87 (m, 2H), 1.83-1.72 (m, 2H), 1.71-1.60 (m, 2H), 1.68* (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H), 1.29 (s, 3H), 1.27* (s, 3H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) *designates minor diastereomer where resolved: δ 134.6*, 134.1, 131.4, 131.2*, 128.5, 128.3*, 124.6, 124.5*, 107.3, 107.2*, 90.0, 89.8*, 84.7, 84.6, 83.6*, 41.3*, 41.2, 35.8, 35.5*, 28.1, 26.2*, 25.7, 23.5*, 23.0, 17.6, 16.3*, 16.0, 0.1 (3C); IR (thin film): 2924, 2175, 1456, 842 cm^{-1}; EI-MS m/z (%) 290 (53, $M^{+\cdot}$), 221 (32), 207 (88), 73 (100); EI-HRMS calcd for $C_{18}H_{30}OSi$: *m/z* ($M^{+\cdot}$) 290.2066; found: 290.2059.

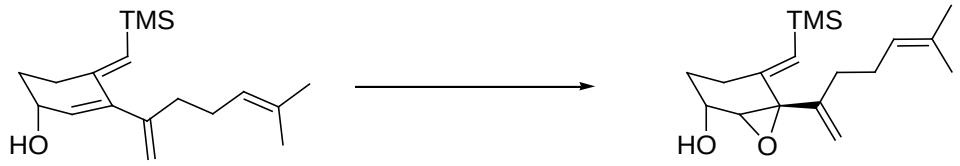


162 **247**

1-(2-Methyl-5-(prop-1-en-2-yl)cyclopent-1-enyl)-6-(trimethylsilyl)hex-5-yn-2-ol (247).

A Biotage microwave 2-5 mL vial is equipped with a stir bar and a solution of allene-yne **162** (40 mg, 0.14 mmol) in 2.8 mL of DMF. The vial is heated under microwave irradiation in a Biotage Initiator microwave reactor at 225 °C for 20 min (Absorption level: very high; pre-stirring: 0; initial power: 0; dynamic deflector optimization: on; stir rate: 600; approximate ramp time 3 min). Consumption of starting material was observed via TLC analysis after the described time. The mixture was partitioned between Et_2O and H_2O. The aq layer is separated and extracted with Et_2O (3X). The combined organic layers are washed with H_2O, brine, dried over $MgSO_4$, and filtered via gravity filtration. The filtrate is concentrated under reduced pressure by rotary evaporation. The residue is purified by silica gel chromatography eluting with 2.5-10% Et_2O/pentanes to afford 21.5 mg of **247** in 54% yield as approximately a 1:1 mixture of separable diastereomers. R_f 0.6 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) :δ 4.76-

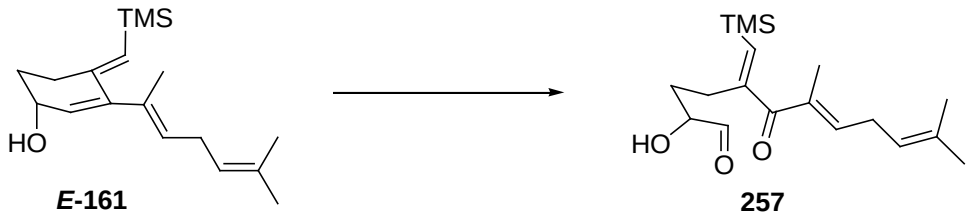
4.69 (m, 2H), 3.83-3.76 (m, 1H), 3.37 (d, *J* = 8.5 Hz, 1H), 2.42 (ddd, *J* = 14.5, 8.5, 5.5 Hz, 1H), 2.38 (t, *J* = 7.0 Hz, 2H), 2.32 (dd, *J* = 9.5, 5.0 Hz, 1H), 2.24 (dd, *J* = 13.5, 9.5 Hz, 1H), 2.10-1.98 (m, 1H), 1.97 (d, *J* = 13.0 Hz, 1H), 1.72 (s, 3H), 1.74-1.63 (3 H), 1.58 (d, *J* = 1.0 Hz, 3H), 0.15 (s, 9H), minor inseparable impurities (by column chromatography): 4.24-4.18 (m, 0.1H), 3.90-3.80 (m , 0.3H), 3.70-3.63 (m, 0.1H), 3.33-3.28 (bs, 0.1H), 2.72-2.54 (m, 1.2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.1, 138.0, 132.6, 111.0, 107.1, 84.7, 68.2, 55.7, 37.7, 35.9, 34.7, 27.7, 18.5, 16.5, 14.3, 0.1 (3C). R_f 0.5 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.78-4.71 (m, 2H), 3.91-3.83 (m, 1H), 3.35-3.28 (m, 1H), 2.37 (dd, *J* = 7.0, 3.5, 1H), 2.36 (dd, *J* = 6.5, 2.0, 1H), 2.34-2.30 (m, 2H), 2.27 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.07 (dd, *J* = 13.5, 6.5 Hz, 1H), 2.00 (dtd, *J* = 13.0, 9.5, 6.0 Hz, 1H), 1.70 (s, 3H), 1.69-1.61 (m, 2H), 1.59 (d, *J* = 0.5 Hz, 3H), 1.59-1.46 (m, 1H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.3, 136.7, 132.7, 111.0, 107.2, 85.1, 69.9, 56.9, 37.5, 35.3, 35.1, 27.9, 18.6, 16.6, 14.4, 0.1 (3C); IR (thin film): 3382, 2954, 2174, 843 cm^{-1}; EI-MS m/z (%) 290 (82, $M^{+\cdot}$), 247 (64), 217 (17), 84 (100); EI-HRMS calcd for $C_{18}H_{30}OSi$: *m/z* ($M^{+\cdot}$) 290.2066; found: 290.2062.



188 **254**

(*E*)-6-(6-Methylhepta-1,5-dien-2-yl)-5-((trimethylsilyl)methylene)-7-oxa-bicyclo[4.1.0]heptan-2-ol (254). A 5-mL, single-necked, round-bottomed flask equipped with a stir bar, rubber septum, and nitrogen line is charged with allylic alcohol **188** (29 mg, 0.10 mmol), toluene (1 mL), and 4 Å powdered molecular sieves (60 mg). To the flask is added aluminum (III) *tert*-butoxide (37 mg, 0.15 mmol) in one portion and the reaction is cooled to –20 °C. *t*-Butyl hydrogen peroxide (48 μL of a 5.5 M decane soln, 0.26 mmol) is then added dropwise with a gas

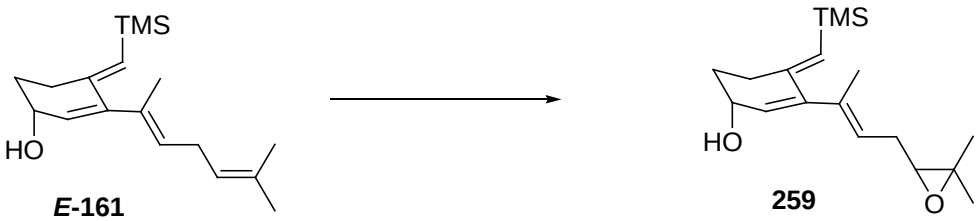
tight syringe. The reaction is stirred at –20 °C for 4 h before being warmed to 0 °C. The reaction is stirred for an additional 3 h at 0 °C when TLC analysis shows trace amount of cross-conjugated triene **188**. The reaction is quenched with sat'd aq Rochelle's salt (1.3 mL), is warmed to rt, and is vigorously stirred for 1 h. The reaction mixture is then transferred to a separatory funnel and the aq layer is separated and extracted with EtOAc. The combined organic layers are washed with H_2O, brine, and are dried on $MgSO_4$. The solids are filtered off via gravity filtration and the filtrate is concentrated under reduced pressure by rotary evaporation. The resulting residue is purified on silica gel eluting with 5-20% Et_2O/pentane to afford 17 mg of epoxide **254** in 56% yield, 67% brsm. R_f 0.2 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.83 (d, *J* = 2.0 Hz, 1H), 5.22 (d, *J* = 1.5 Hz, 1H), 5.09 (tt, *J* = 6.0, 1.5 Hz), 5.02 (s, 1H), 4.06 (dt, *J* = 6.0, 4.0 Hz, 1H), 3.19 (d, *J* = 1.5 Hz, 1H), 2.53 (ddd, *J* = 15.0, 5.0, 3.0 Hz, 1H), 2.14-2.04 (m, 4H), 2.02 (dddd, *J* = 15.0, 13.0, 3.5, 2.0 Hz, 1H), 1.85 (dq, *J* = 12.5, 4.0 Hz, 1H), 1.69 (s, 3H), 1.61 (s, 3H), 1.52 (tdd, *J* = 13.0, 9.5, 3.0 Hz, 1H), 0.12 (9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.3, 146.2, 132.8, 132.1, 123.7, 112.0, 68.0, 67.1, 64.6, 34.0, 29.0, 28.4, 26.3, 25.7, 17.7, -0.2 (3C); IR (thin film): 3384, 2925, 1609, 1248 cm^{-1}; EI-MS *m/z* (%) 306 (60, $M^{+\cdot}$), 237 (46), 179 (55), 129 (100); EI-HRMS calcd for $C_{18}H_{30}O_2Si$: *m/z* ($M^{+\cdot}$) 306.2015; found: 306.2009.



***E*-161** **257**

(5*E*,7*E*)-2-Hydroxy-7,11-dimethyl-5-((trimethylsilyl)methylene)-6-oxododeca-7,10-dienal (257). A 5-mL, single-necked, round-bottomed flask equipped with a stir bar, rubber septum, and nitrogen line is charged with $VO(acac)_2$ (1 mg, 1 μmol) and benzene (0.2 mL). A solution of

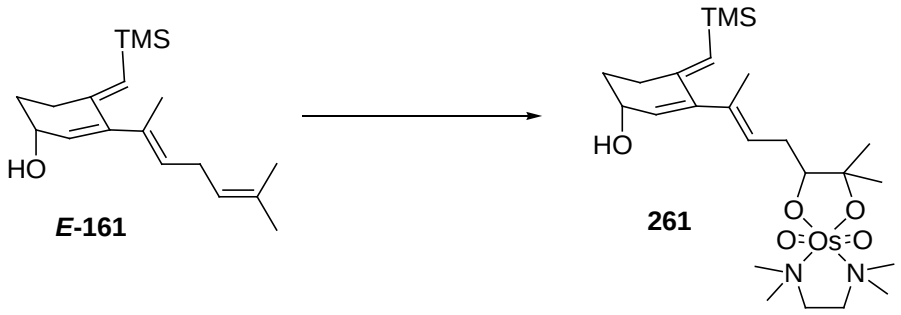
allylic alcohol *E*-**161** (26 mg, 0.09 mmol) in benzene (0.2 mL) is added to the flask via cannula. The green solution is heated to 40 °C in an oil bath for 5 min before *t*-butyl hydrogen peroxide (21 μL of a 5.0–6.0 M decane soln, ~0.11 mmol) is added dropwise with a gas tight syringe. Upon addition of the peroxide, the reaction mixture flashes deep red and becomes orange. After 1 h of stirring at 40 °C (oil bath temperature), the reaction does not proceed any longer as observed by TLC, and is cooled to rt. The reaction mixture is directly applied to silica gel eluting with 5-30% Et_2O/pentane to afford allylic ketone **257** (8 mg, 28%, 34% brsm) as a light yellow oil. R_f 0.4 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.23 (d, *J* = 2.0 Hz, 1H), 5.42 (t, *J* = 2.5 Hz, 1H), 5.17 (tq, *J* = 7.0, 1.0 Hz, 1H), 5.11 (tt, *J* = 7.0, 1.0 Hz, 1H), 4.19 (tdd, *J* = 9.0, 6.0, 2.0 Hz, 1H), 3.68 (d, *J* = 9.5 Hz, 1H), 2.81 (t, *J* = 7.0 Hz, 2H), 2.62 (ddt, *J* = 17.5, 9.0, 2.5 Hz, 1H), 2.31 (dddd, *J* = 17.5, 11.0, 8.5, 2.5 Hz, 1H), 2.09 (dddd, *J* = 12.0, 9.0, 6.0, 3.0 Hz, 1H), 1.84-1.76 (m, 1H), 1.71 (s, 3H), 1.64 (s, 3H), 1.57 (s, 3H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.4, 202.3, 154.1, 149.3, 131.8, 131.3, 130.3, 122.1, 72.2, 31.8, 30.0, 27.6, 25.7, 17.8, 13.2, -0.5 (3C); IR (thin film): 3444, 2956, 1705, 1611.



***E*-161** **259**

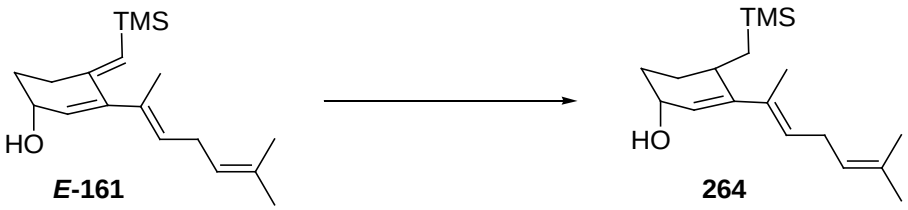
(4*E*)-3-((*E*)-4-(3,3-Dimethyloxiran-2-yl)but-2-en-2-yl)-((trimethylsilyl)methylene)cyclohex-2-enol (259). A 5-mL, single-necked, round-bottomed flask equipped with a stir bar, rubber septum, and nitrogen line is charged with allylic alcohol *E*-**161** (15 mg, 0.05 mmol), CH_2Cl_2 (0.6 mL) and $NaHCO_3$ (11 mg, 0.13 mmol). The mixture is cooled to 0 °C in an ice bath and *m*-CPBA (77%, 15 mg, 0.07 mmol) is added in one portion. The reaction is slowly warmed to rt. After 2.5 h the reaction does not proceed further by TLC and additional amounts of $NaHCO_3$ (4

mg, 0.1 mmol) and *m*-CPBA (77%, 6 mg, 0.03 mmol) are sequentially added. The reaction mixture is transferred to a separatory funnel containing sat'd aq Na_2SO_3 and Et_2O. The aq layer is separated and extracted with Et_2O. The combined organic layers are washed with sat'd aq $NaHCO_3$ (3X), H_2O (3X), and brine (3X), and are dried on $MgSO_4$. The solids are filtered off via gravity filtration and the filtrate is concentrated under reduced pressure by rotary evaporation. The resulting residue is purified on silica gel eluting with 5-50% Et_2O/pentane to afford 5 mg of epoxide **259** in 32% yield, 36% brsm as a 1.2:1 mixture of diastereomers (based upon integration of the resonances at 66.4 ppm and 63.3 ppm in the ^{13}C NMR). R_f 0.2 (20% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$): δ 5.66 (d, *J* = 3.0 Hz, 1H), 5.41 (s, 1H), 5.37 (tq, *J* = 7.5, 1.5 Hz, 1H), 4.35 (s, 1H), 2.80 (t, *J* = 6.5 Hz, 1H), 2.57 (ddd, *J* = 14.5, 8.0, 4.0 Hz, 1H), 2.48 (dt, *J* = 14.5, 6.5 Hz, 1H), 2.36 (ddd, *J* = 13.5, 11.0, 3.5 Hz, 1H), 2.23 (dt, *J* = 14.5, 7.5 Hz, 1H), 2.03 (ddt, *J* = 16.5, 8.0, 4.0 Hz, 1H), 1.75 (s, 3H), 1.70 (dddd, *J* = 16.5, 12.5, 6.5, 3.5 Hz, 1H), 1.34 (s, 3H), 1.32 (s, 3H), 0.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): *designates minor diastereomer where resolved: δ 149.3, 147.6, 138.0*, 137.9, 128.3*, 128.2, 127.3*, 127.2, 123.6, 66.4, 66.3*, 63.5, 58.3, 33.0*, 32.9, 28.3, 28.0*, 27.9, 24.9, 18.7, 17.4, 0.1 (3C); IR (thin film): 3423, 2923, 1579, 1248 cm^{-1}; EI-MS *m/z* (%) 306 (17, $M^{+\cdot}$), 263 (36), 233 (29), 73 (100); EI-HRMS calcd for $C_{18}H_{30}O_2Si$: *m/z* ($M^{+\cdot}$) 306.2015; found: 306.2029.



***E*-161** **261**

(4*E*)-((Trimethylsilyl)methylene)-2-cyclohexenol-3-((*E*)-5,6-*N',N',N'',N''*-tetramethyl-ethylene-diamine)osmate ester (261). A 15-mL, single-necked, round-bottomed flask equipped with a stir bar, rubber septum, and nitrogen line is charged with allylic alcohol *E*-**161** (22 mg, 0.08 mmol), CH_2Cl_2 (7.6 mL) and freshly distilled TMEDA (12 μL, 0.08 mmol). The mixture is cooled to –78 °C in a dry ice-acetone bath and OsO_4 (203 μL of a 0.39 M CH_2Cl_2 soln, 0.08 mmol) is added dropwise. Upon addition of OsO_4, the reaction turns orange and then brown in color. After 1 h at –78 °C, the reaction is warmed to rt and is stirred overnight. After 24 h, the reaction is concentrated under reduced pressure. The residue is purified by silica gel chromatography eluting with 20-100% acetone/EtOAc to yield 18 mg of osmate ester **261** in 36% yield, 47% brsm. R_f 0.2 (50% acetone/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.65 (d, *J* = 3.0 Hz, 1H), 5.56-5.51 (m, 1H), 5.46 (s, 1H), 4.35-4.29 (m, 1H), 4.01 (td, *J* = 7.5, 1.0 Hz, 1H), 3.06 (s, 4H), 2.85 (s, 3H), 2.83 (s, 3H), 2.82 (s, 3H), 2.81 (s, 3H), 2.62-2.50 (m, 3H), 2.35 (dddt, *J* = 14.5, 9.5, 3.0, 1.0 Hz, 1H), 2.01 (ddt, *J* = 13.0, 8.0, 4.0 Hz, 1H), 1.93 (bs, 1H), 1.76 (s, 3H), 1.69 (dddd, *J* = 13.0, 9.5, 6.5, 3.5 Hz, 1H), 1.5 (s, 3H), 1.23 (d, *J* = 0.5 Hz, 3H), 0.12 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.5, 148.2, 135.5, 127.9, 127.3, 127.0, 96.2, 87.0, 66.4, 64.3, 63.9, 51.6, 51.3, 51.2, 51.1, 32.9, 31.7, 28.0, 26.6, 21.4, 17.5, 0.1 (3C); IR (thin film): 3384, 2926, 1577, 1459 cm^{-1}; ESI-MS *m/z* (%) 685 (100, $[M+Na]^+$), 663 (30), 569 (76), 427 (3); ESI-HRMS calcd for $C_{24}H_{46}N_2O_5NaOsSi$: *m/z* $[M+Na]^+$ 685.2689; found: 685.2665.



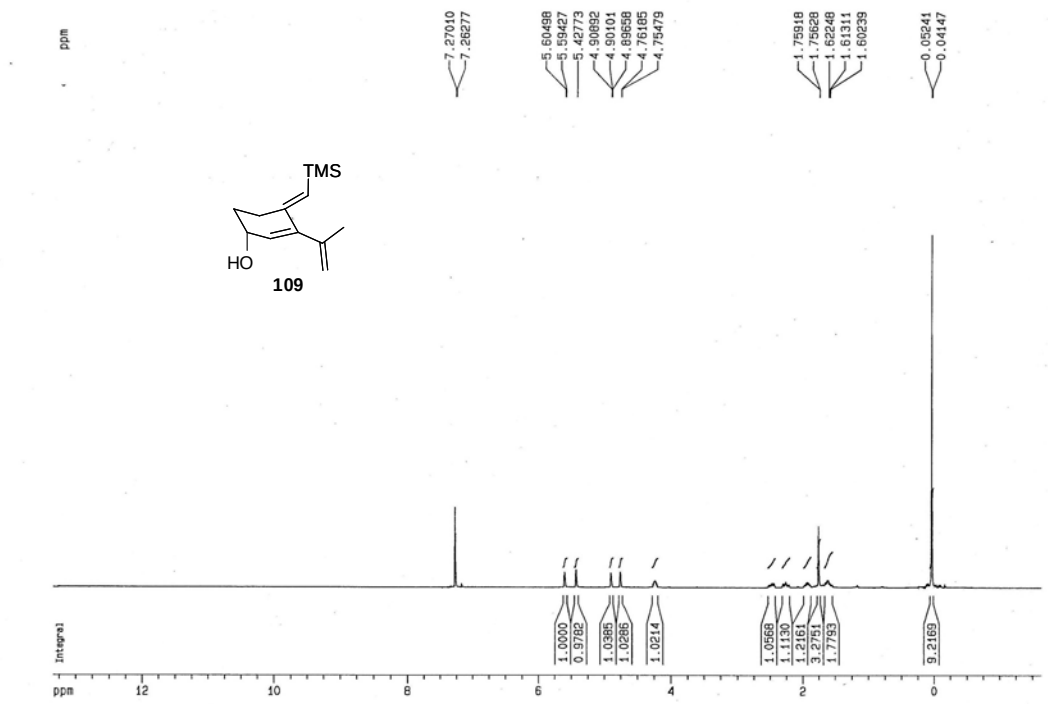
***E*-161** **264**

(*E*)-3-(6-Methylhepta-2,5-dien-2-yl)-4-((trimethylsilyl)methyl)cyclcohex-2-enol (264). A 5-mL, single-necked, round-bottomed flask equipped with a stir bar, rubber septum, and nitrogen line is charged with triphenylphosphine (41 mg, 0.15 mmol) and *N*-methyl morpholine (0.1 mL). The flask is cooled to –30 °C for before diethyl azodicarboxylate (24 μL, 0.15 mmol) is added via gas tight syringe. After 5 min of stirring a solution of allylic alcohol *E*-**161** (15 mg, 0.05 mmol) in *N*-methyl morpholine (0.1 mL) is added via cannula. The reaction is stirred for 10 min before *o*-nitrobenzenesulfonylhydrazide (NBSH) is added. After 2 h at –30 °C, TLC analysis shows no change. The reaction is warmed to rt and is stirred overnight. The reaction is then diluted with Et_2O and is transferred to a separatory funnel containing sat'd aq $NaHCO_3$ and Et_2O. The aq layer is separated and extracted with Et_2O (3X). The combined organic layers are washed with H_2O (3X) and brine (3X), and are dried on Na_2SO_4. The solids are filtered off via gravity filtration and the filtrate is concentrated under reduced pressure by rotary evaporation. The residue is purified by silica gel chromatography eluting with 5-20% Et_2O/pentane to yield 7.5 mg of **264** in 50% yield. Based upon the integration of the resonances at 0.61 ppm and 0.50 ppm in the ^1H NMR, **264** was produced as a 1.3:1.0 mixture of diastereomers. R_f 0.3 (20% EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) *designates minor diastereomer where resolved: δ 5.65 (d, *J* = 4.2 Hz, 1H), 5.58* (d, *J* = 3.0 Hz, 1H), 5.43 (tq, *J* = 7.2, 1.2 Hz, 1H), 5.14 (tt, *J* = 7.2, 1.2 Hz, 1H), 4.28* (s, 1H), 4.21 (s, 1H), 2.08 (t, *J* = 7.2 Hz, 2H), 2.64-2.50 (m, 1H), 1.97-1.81 (m, 3H), 1.75 (s, 3H), 1.71 (s, 3H), 1.65 (s, 3H), 1.63-1.55 (m, 1H), 0.79 (dd, *J* = 15.0, 1.2 Hz, 1H), 0.73* (dd, *J* = 15.3, 2.1 Hz, 1H), 0.61* (dd, *J* = 15.3, 11.7 Hz, 1H), 0.50 (dd, *J* = 15.0,

11.7 Hz, 1H), 0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) *designates minor diastereomer where resolved: δ 149.9, 149.1*, 134.1, 133.6*, 132.0, 126.6, 126.3*, 124.1, 122.7*, 122.6, 67.9*, 65.4, 30.2, 29.8*, 28.0*, 27.9, 27.5, 27.0*, 25.6, 25.1, 21.5*, 20.6, 17.7, 14.9, 14.8*, -0.6 (3C), -0.7* (3C); IR (thin film): 3320, 2949, 1448, 1247 cm^{-1}; EI-MS *m/z* (%) 292 (49, $M^{+\cdot}$), 223 (37), 109 (67), 73 (100); EI-HRMS calcd for $C_{18}H_{32}OSi$: *m/z* ($M^{+\cdot}$) 292.2222; found: 292.2219.

APPENDIX A

SPECTRAL DATA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4.90692
4.90101
4.89658
4.76185
4.75479
1.75918
1.75628
1.62248
1.61311
1.60239
0.05241
0.04147
TMS
HO
109
Integral
1.0000
0.9782
1.0385
1.0286
1.0214
1.0568
1.1130
1.2161
3.2751
1.7793
9.2169
ppm
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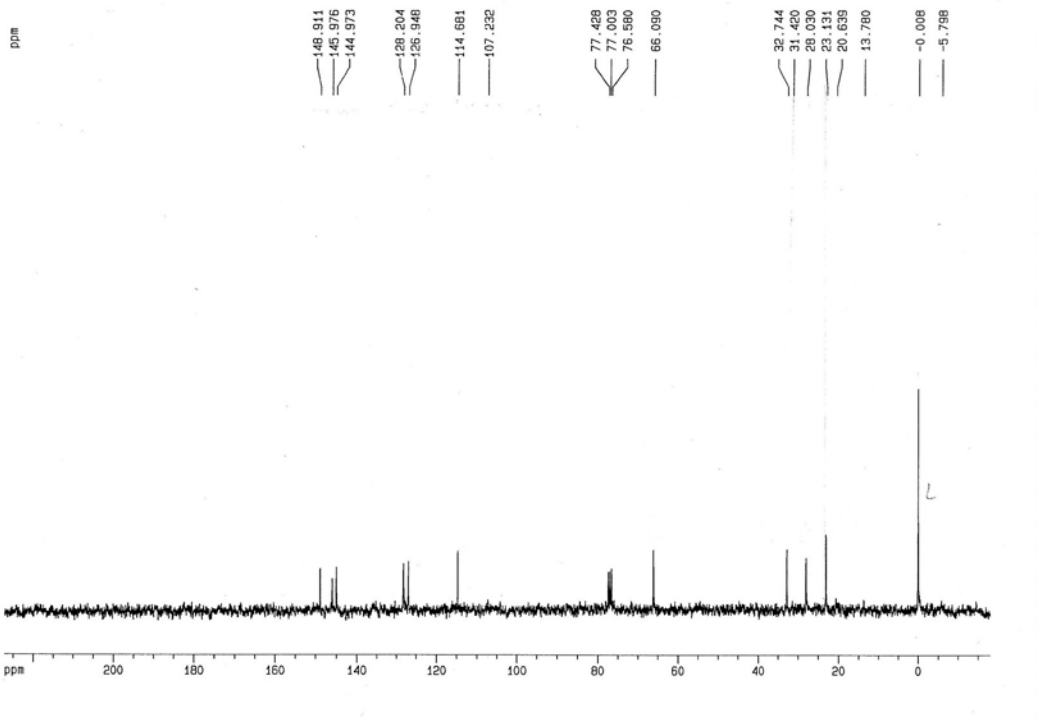
10
8
6
4
2
0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77.003
76.580
66.090
32.744
31.420
28.030
23.131
20.639
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-5.798
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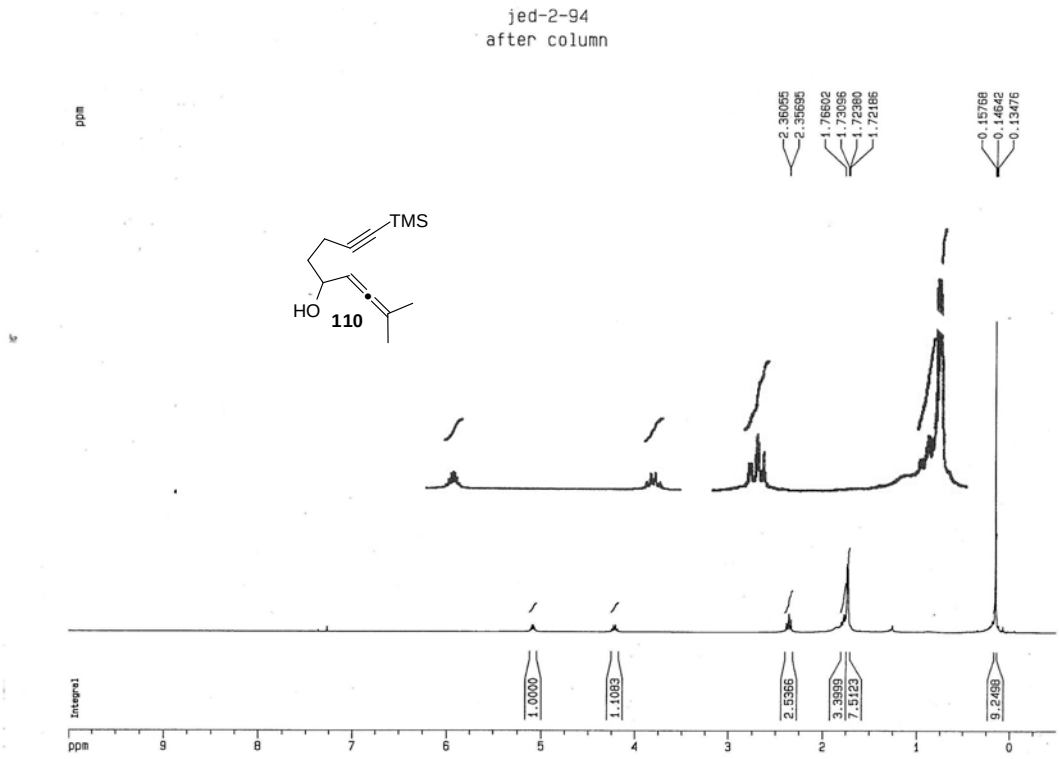
140
120
100
80
60
40
20
0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0.15768
0.14642
0.13476
TMS
HO
110
Integral
1.0000
1.1083
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7.5123
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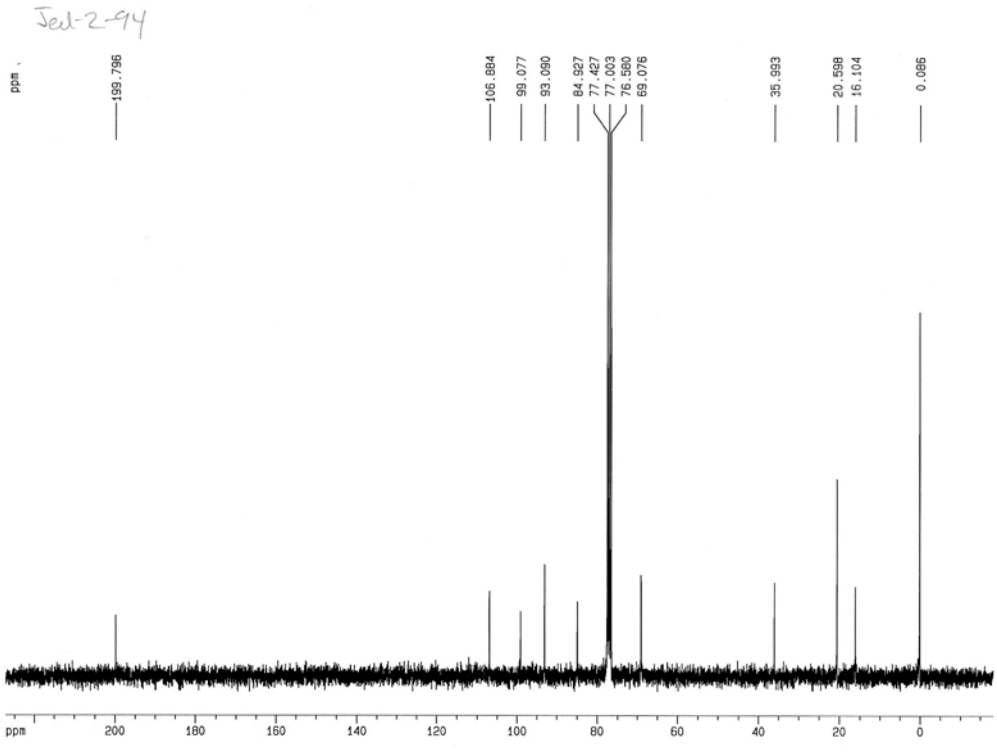
ppm
9
8
7
6
5
4
3
2
1
0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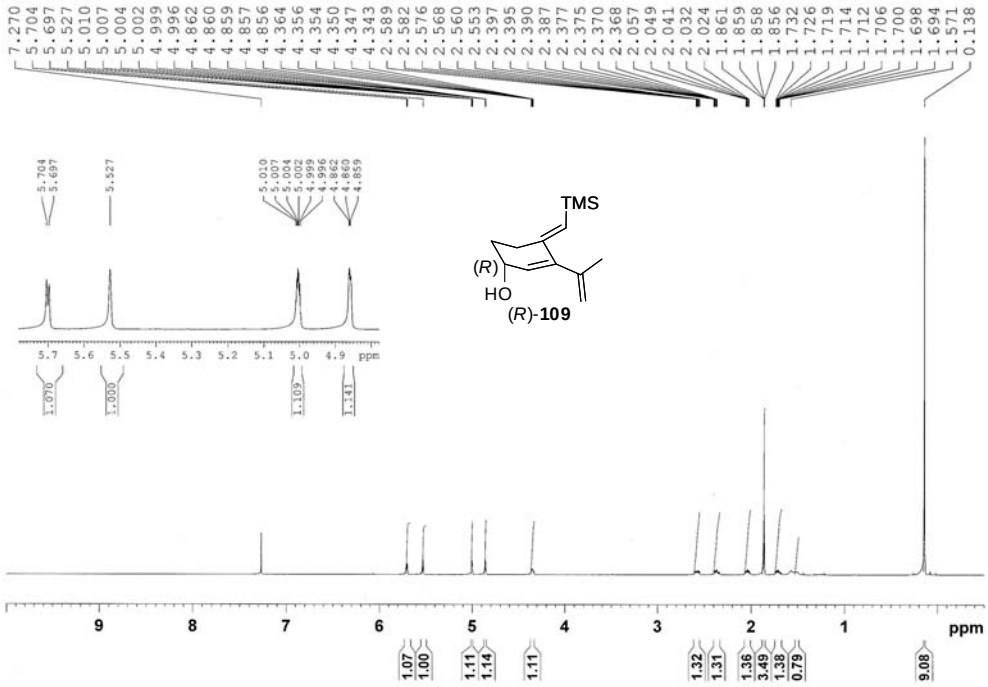
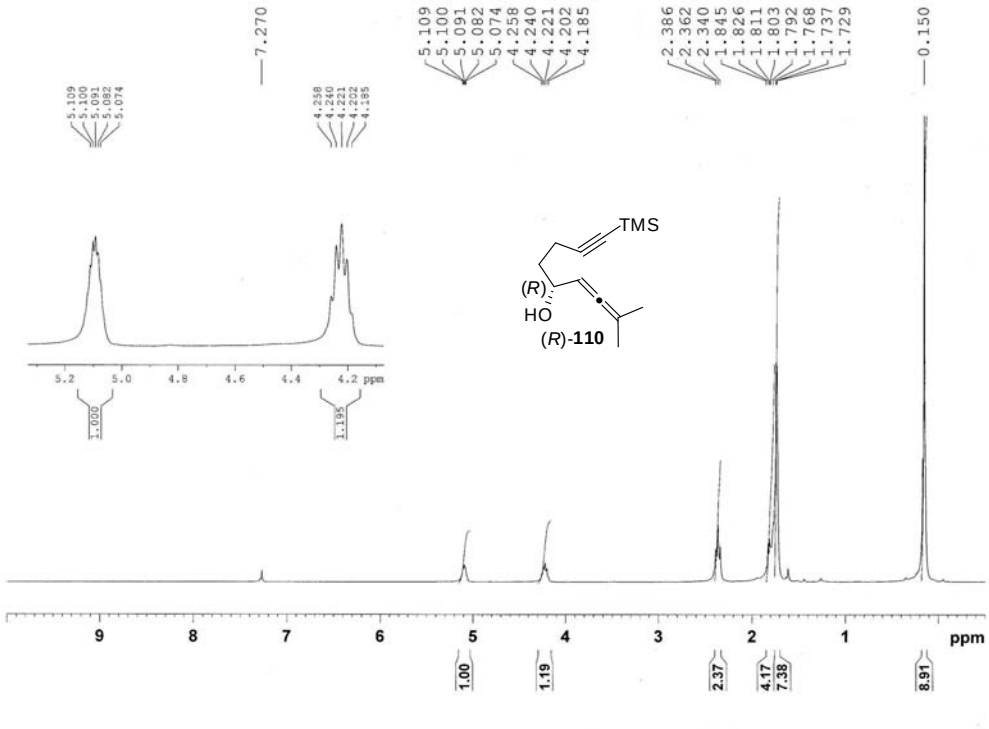
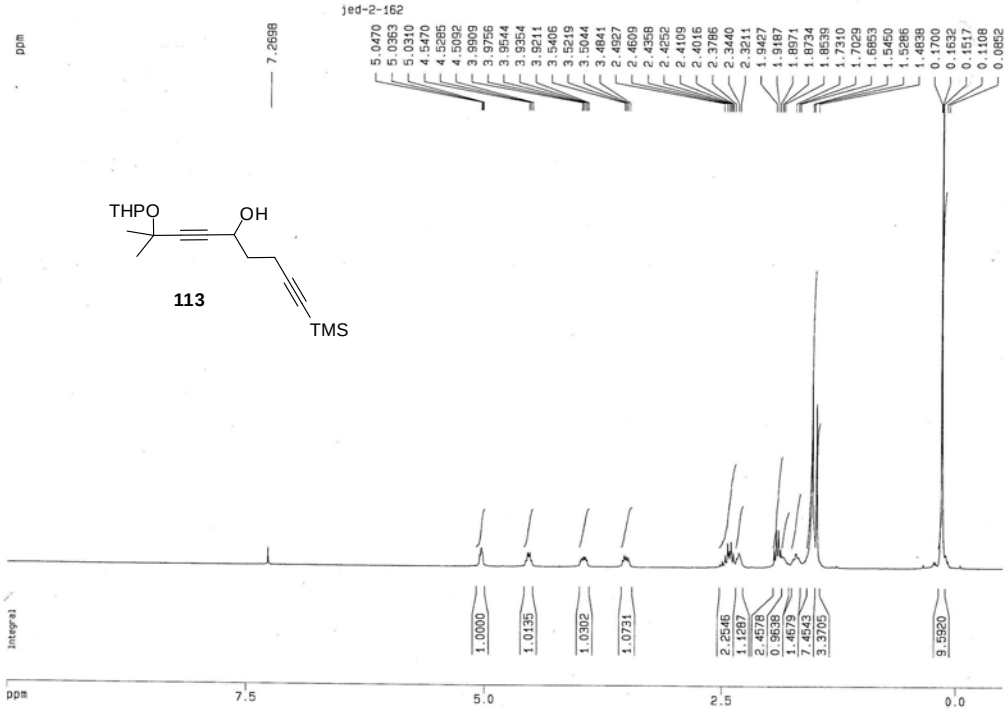
99.077
93.090
84.927
77.427
77.003
76.580
69.076
35.993
20.598
16.104
0.086
ppm
200
180
160
140
120
100
80
60
40
20
0

jed-6-208
chiral triene 500 MHz



jed-6-56 R allene

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4.5092
3.9909
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3.9544
3.9354
3.8211
3.5406
3.5219
3.5044
3.4841
2.4927
2.4609
2.4358
2.4252
2.4109
2.4016
2.3786
2.3440
2.3211
1.9427
1.9187
1.8971
1.8734
1.8539
1.7310
1.7029
1.6853
1.5450
1.5286
1.4838
0.1700
0.1632
0.1517
0.1108
0.0852
THPO
OH
TMS
113
Integral
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1.0135
1.0302
1.0731
2.2546
1.1287
2.4578
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9.5920
ppm
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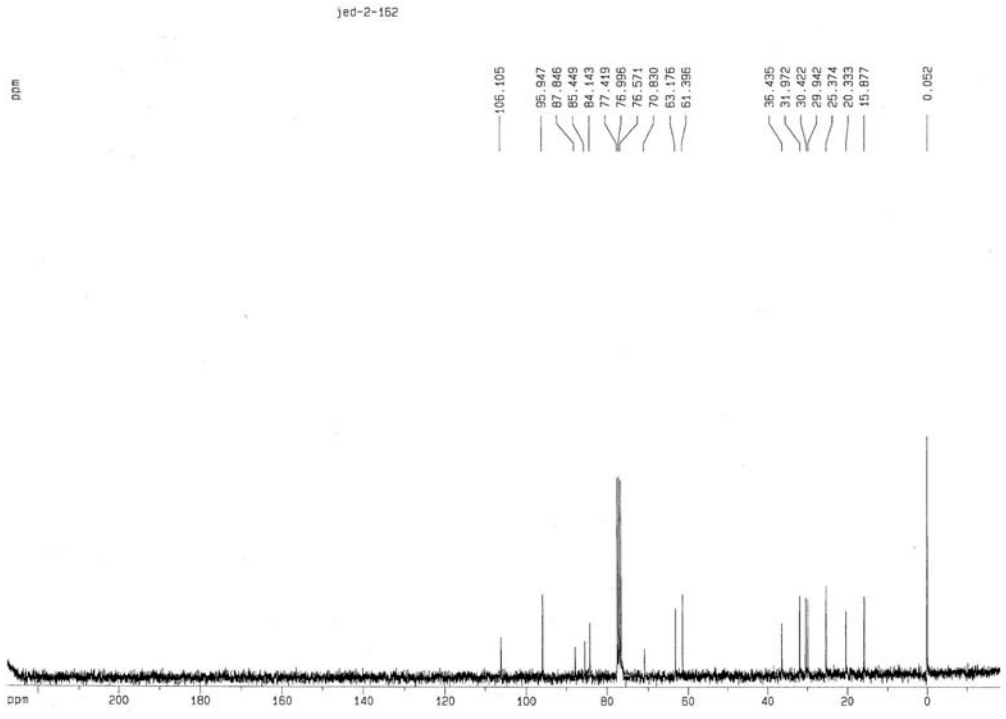
5.0
2.5
0.0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77.419
76.996
76.571
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63.176
61.396
36.435
31.972
30.422
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15.877
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ppm
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180
160
140
120
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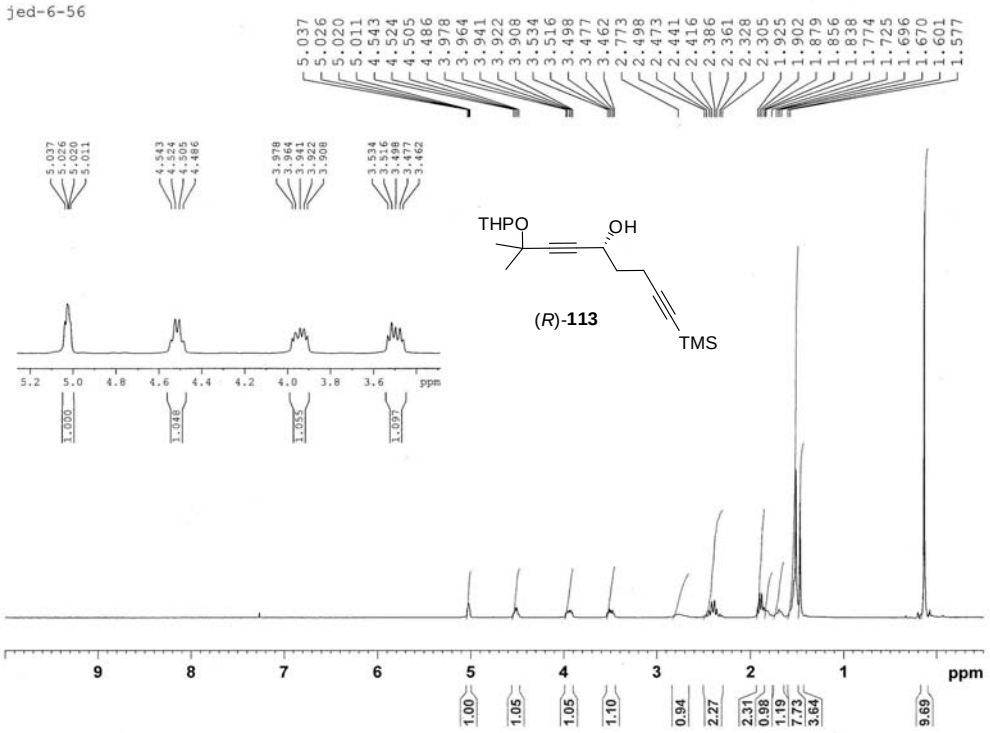
80
60
40
20
0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5.020
5.011
4.543
4.524
4.505
4.486
3.978
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3.941
3.922
3.908
3.534
3.516
3.498
3.477
3.462
2.773
2.498
2.473
2.441
2.416
2.386
2.361
2.328
2.305
1.925
1.902
1.879
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1.696
1.670
1.601
1.577
THPO
OH
TMS
(R)-113
ppm
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1.05
1.10
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0.98
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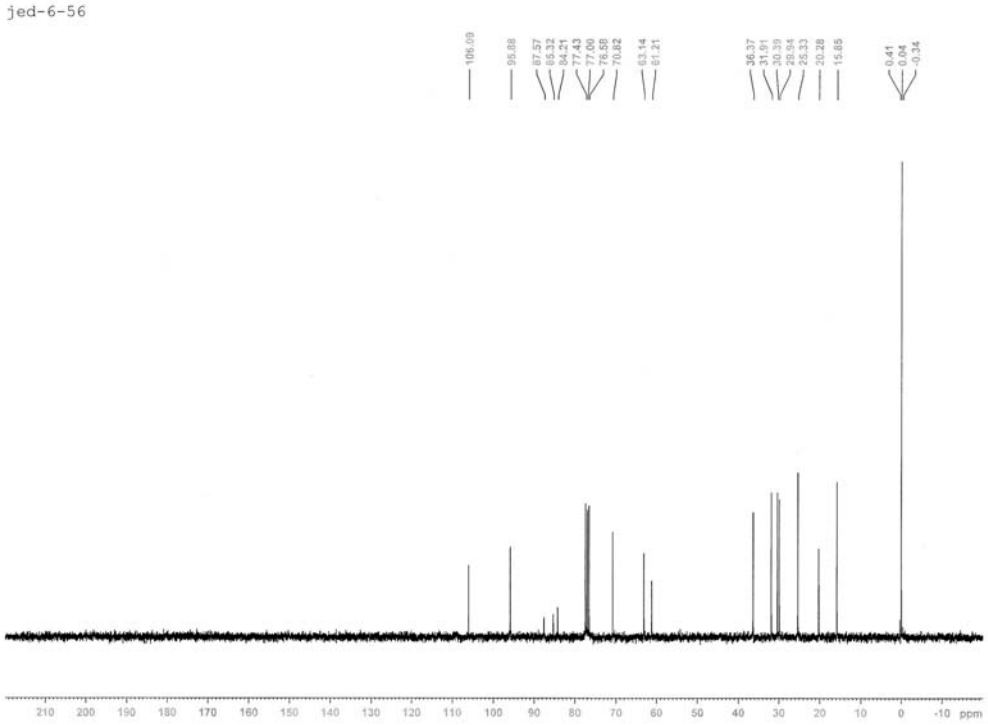
7.73
3.64
9.69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85.32
84.21
77.43
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76.58
70.82
63.14
61.21
36.37
31.91
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20.28
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jed-6-66
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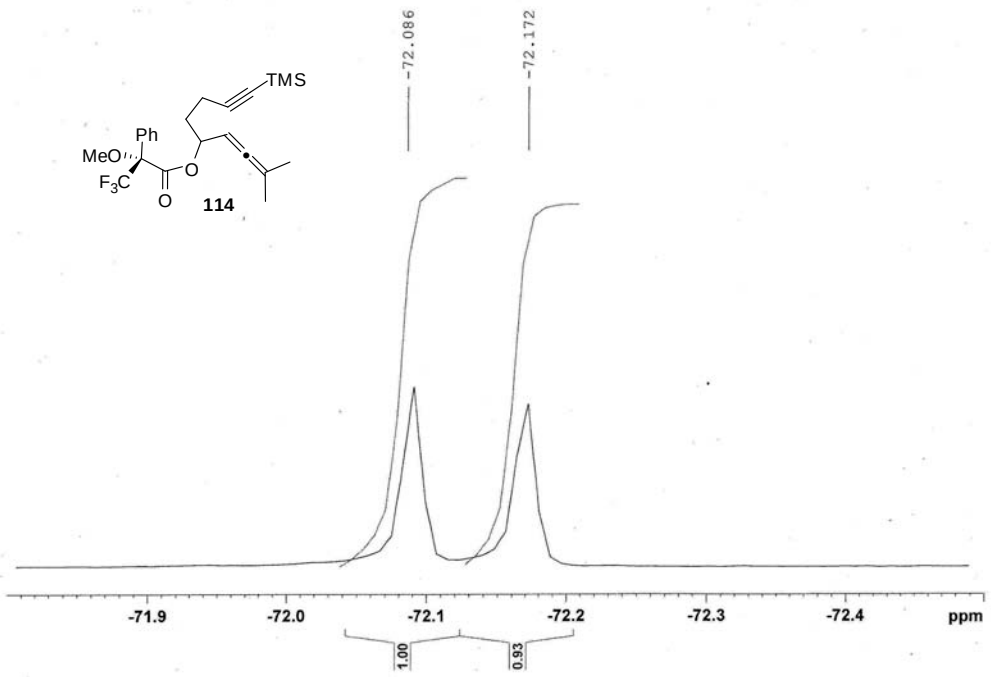
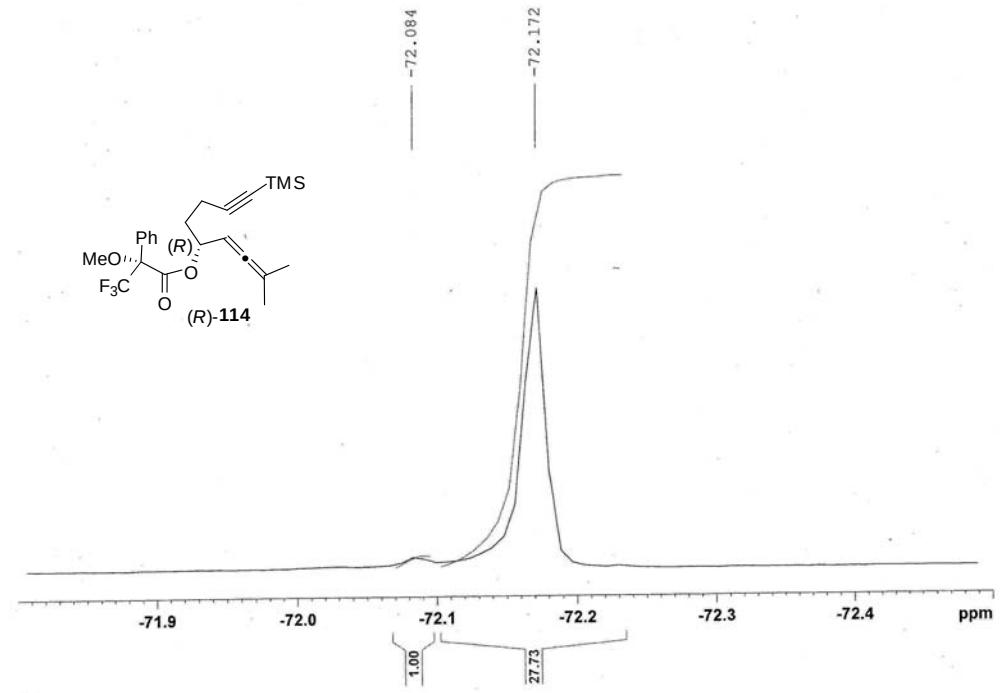
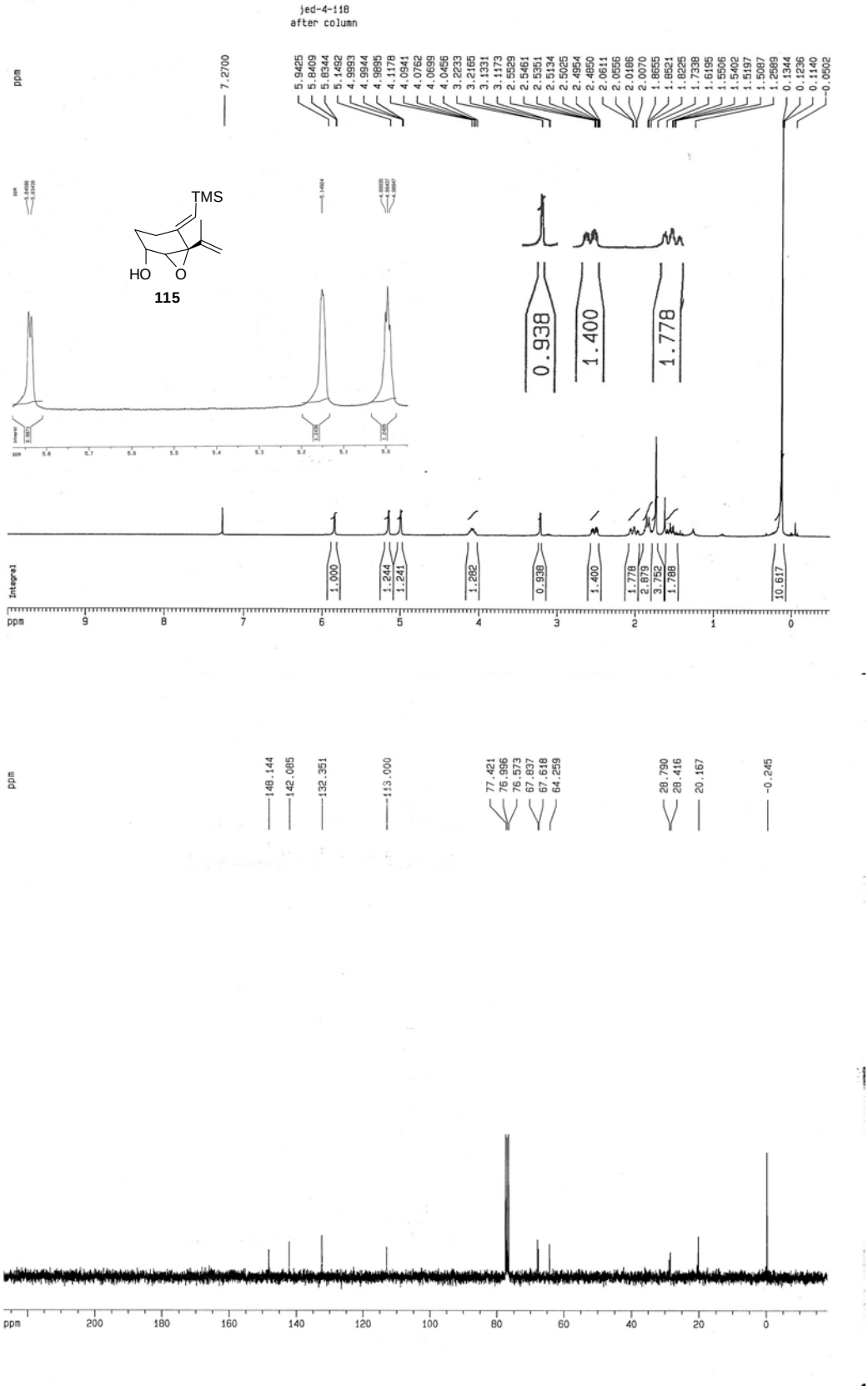


jed-6-62
mosher ester of chiral allene

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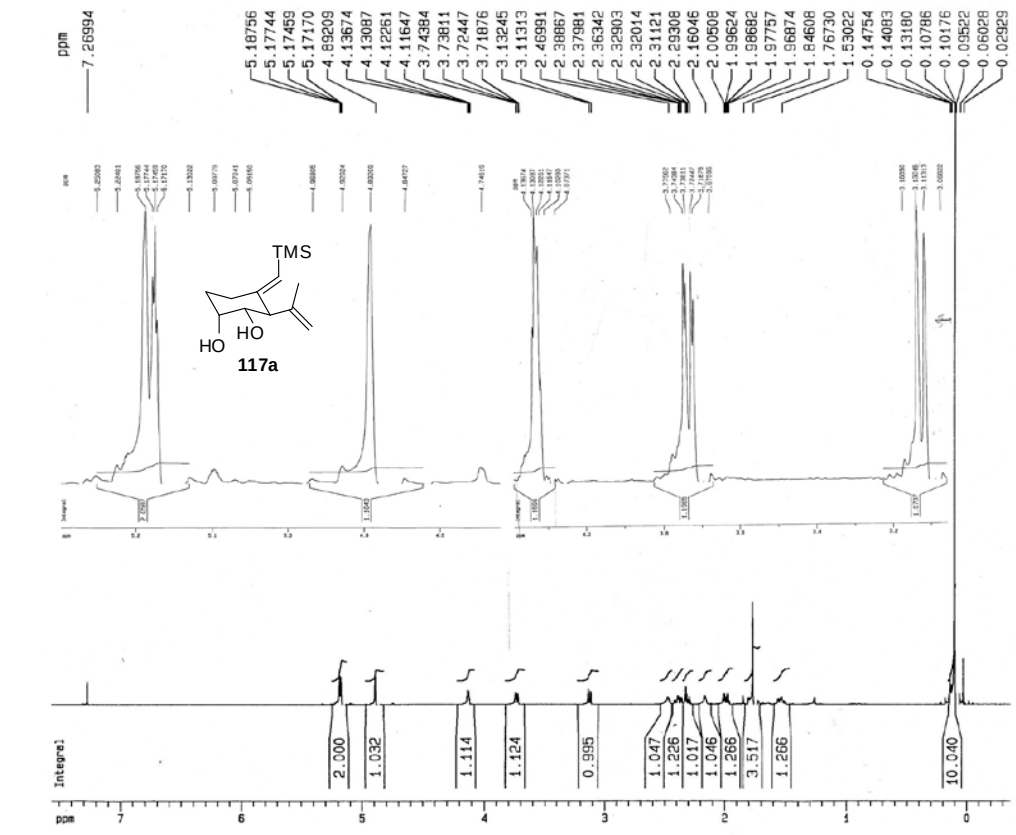
integral
ppm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HO
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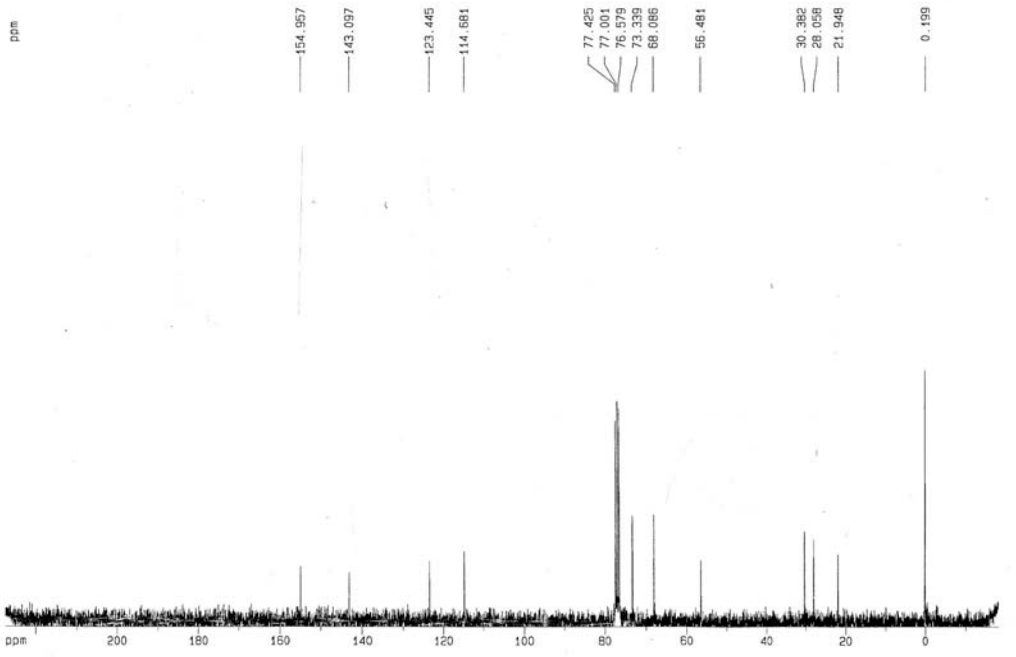
1.226
1.017
1.046
1.266
3.517
1.266
10.040
ppm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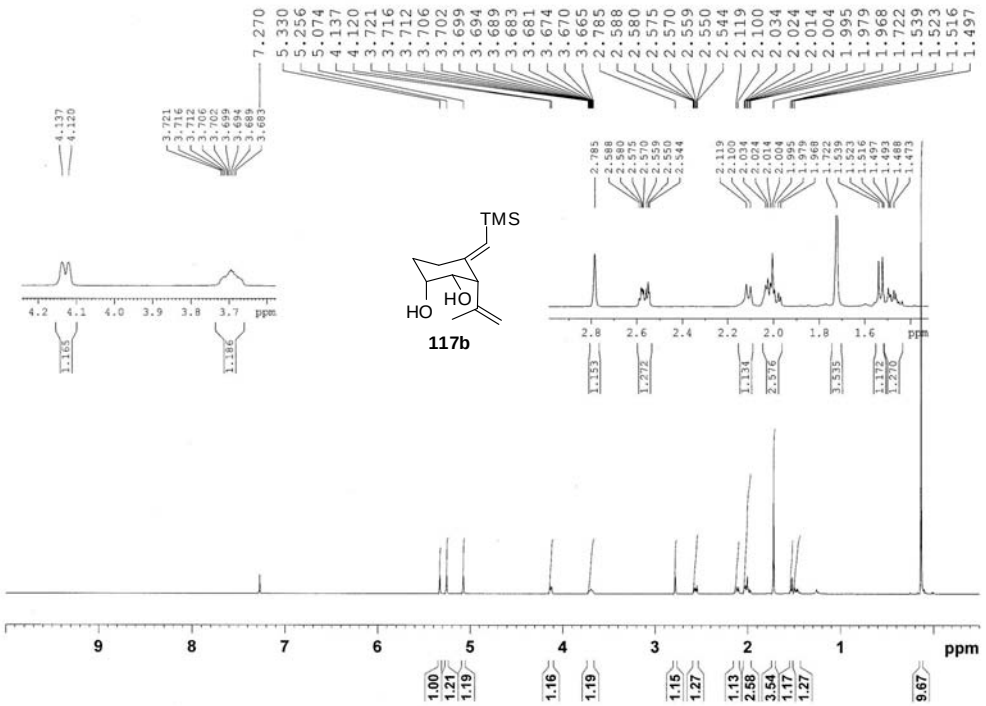
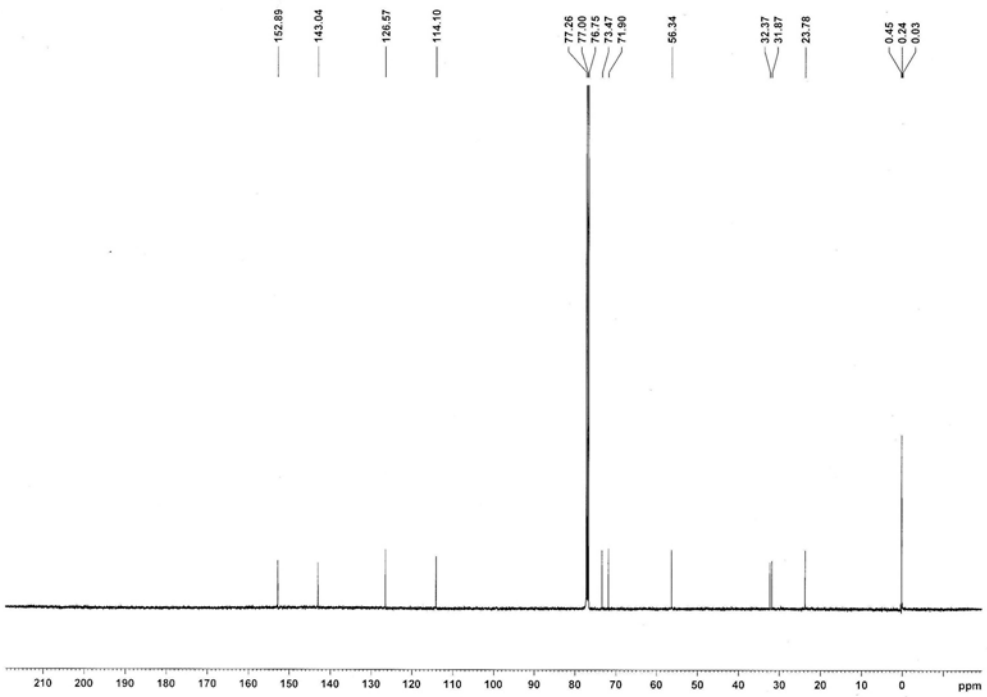
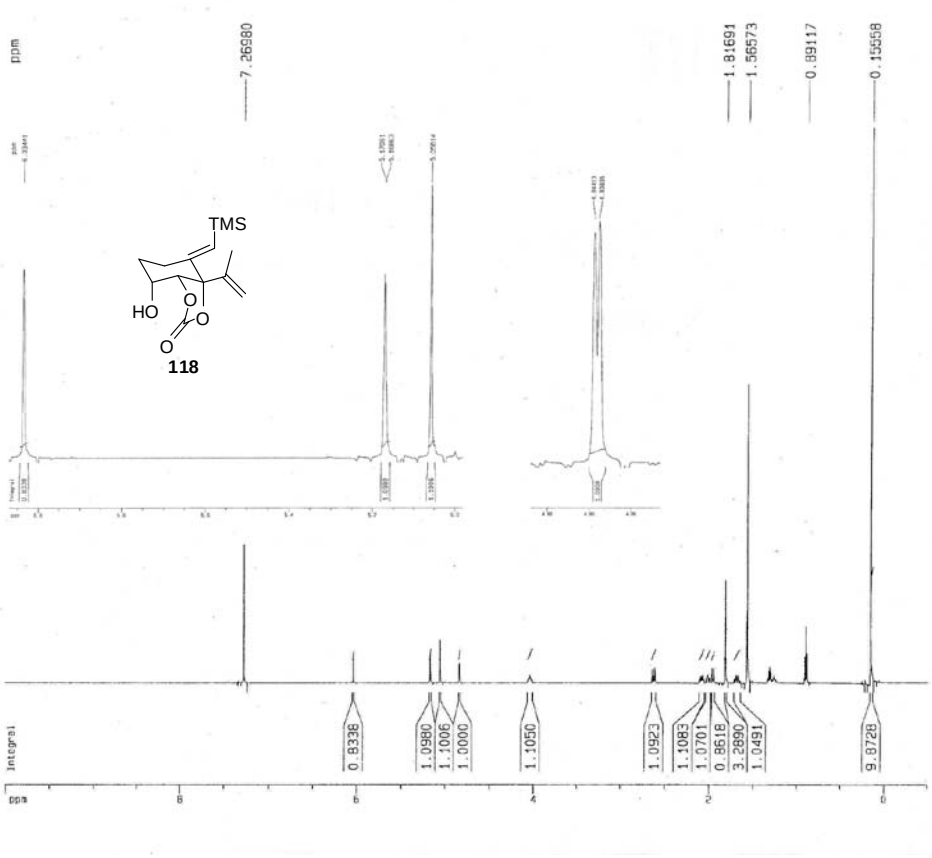
0.199

undesired diol 500 MHz



undesired diol

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TMS
HO
O
O
O
118
Integral
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1.1006
1.0000
1.1050
1.0923
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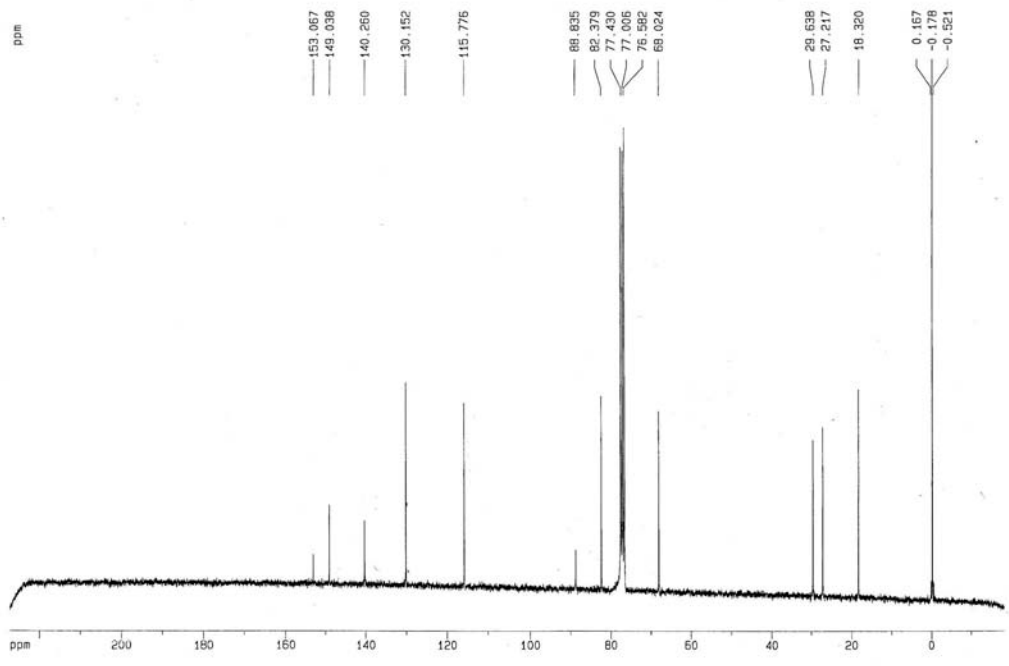
1.0701
0.8618
3.2890
1.0491
9.8728
ppm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76.582
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140
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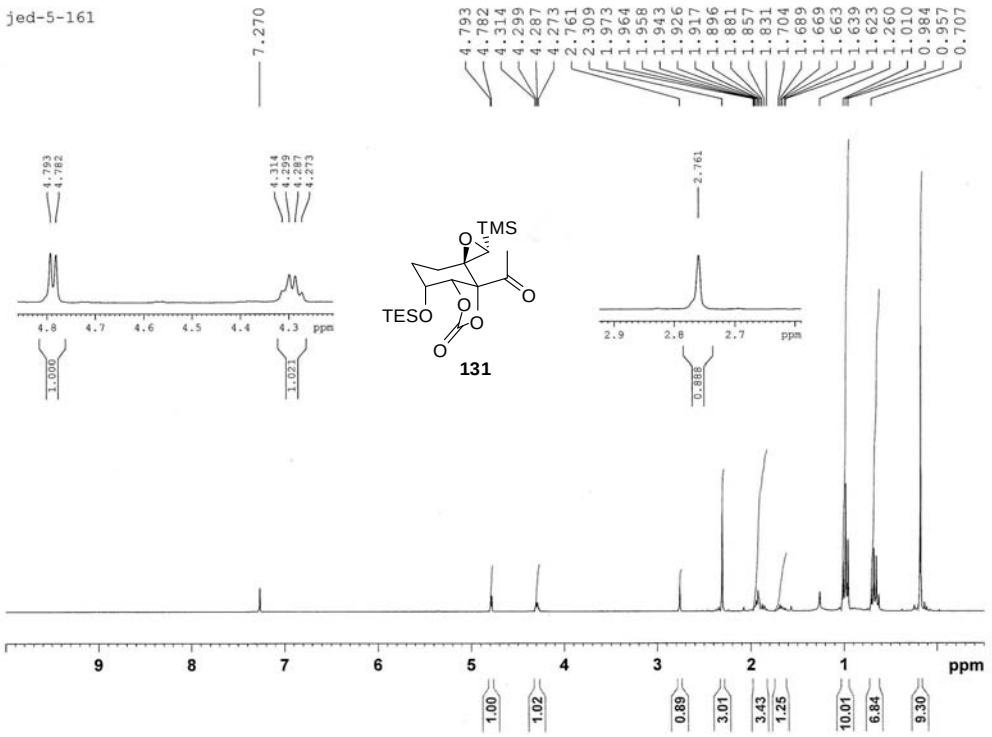
80
60
40
20
0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4.782
4.314
4.299
4.287
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2.309
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1.917
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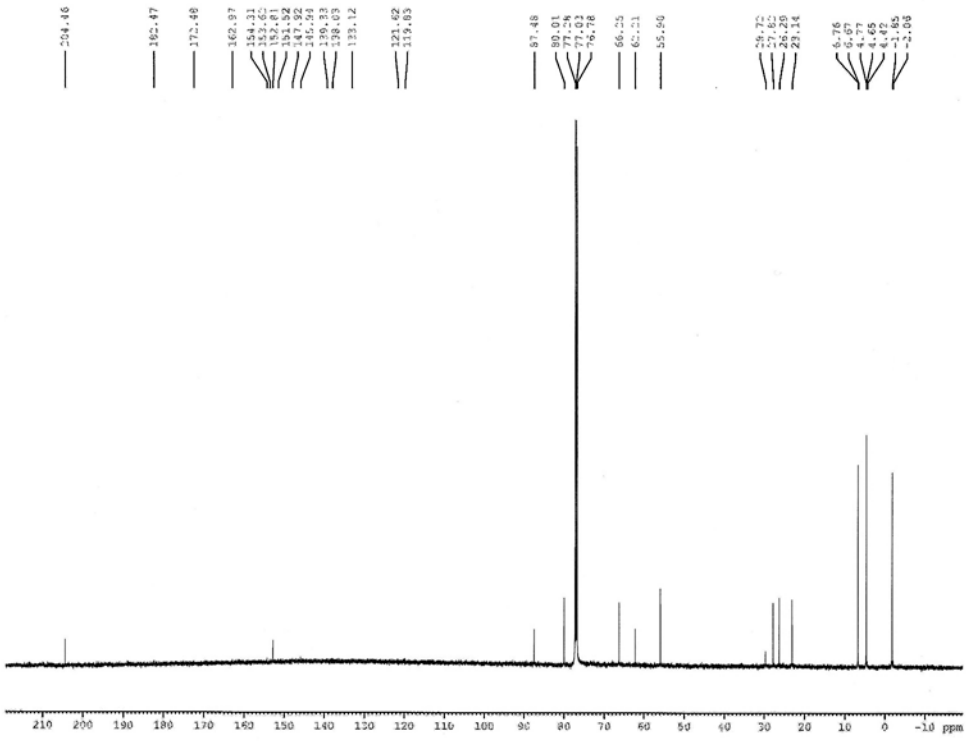
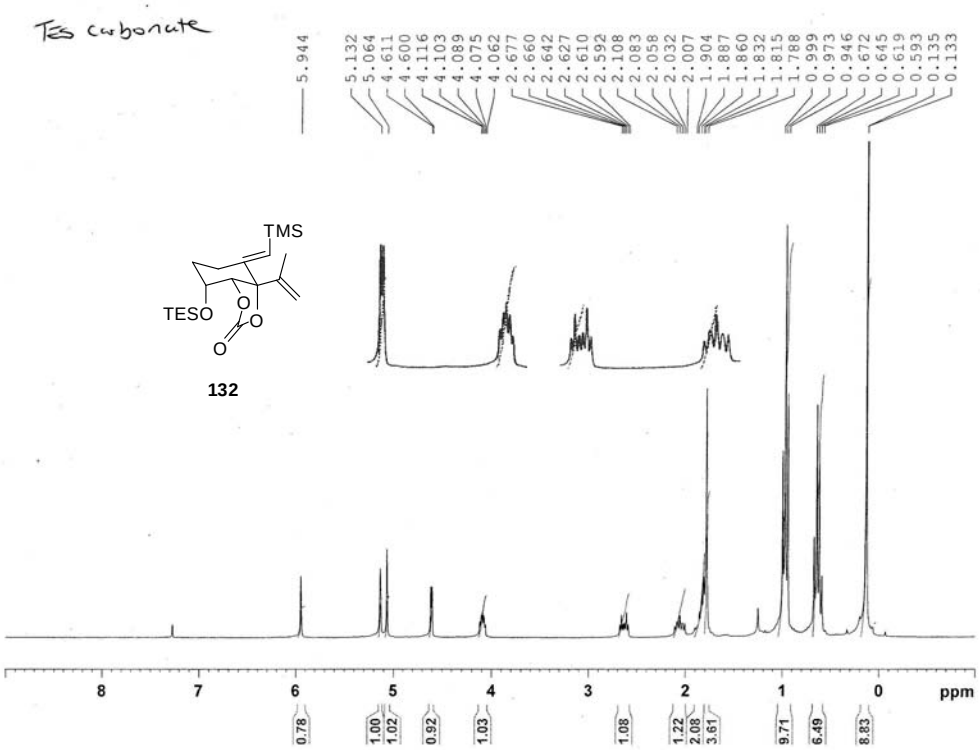
1.881
1.857
1.831
1.704
1.689
1.669
1.663
1.639
1.623
1.260
1.010
0.984
0.957
0.707
TMS
TESO
131
ppm
1.00
1.02
0.89
3.01
3.43
1.25
10.01
6.84
9.30

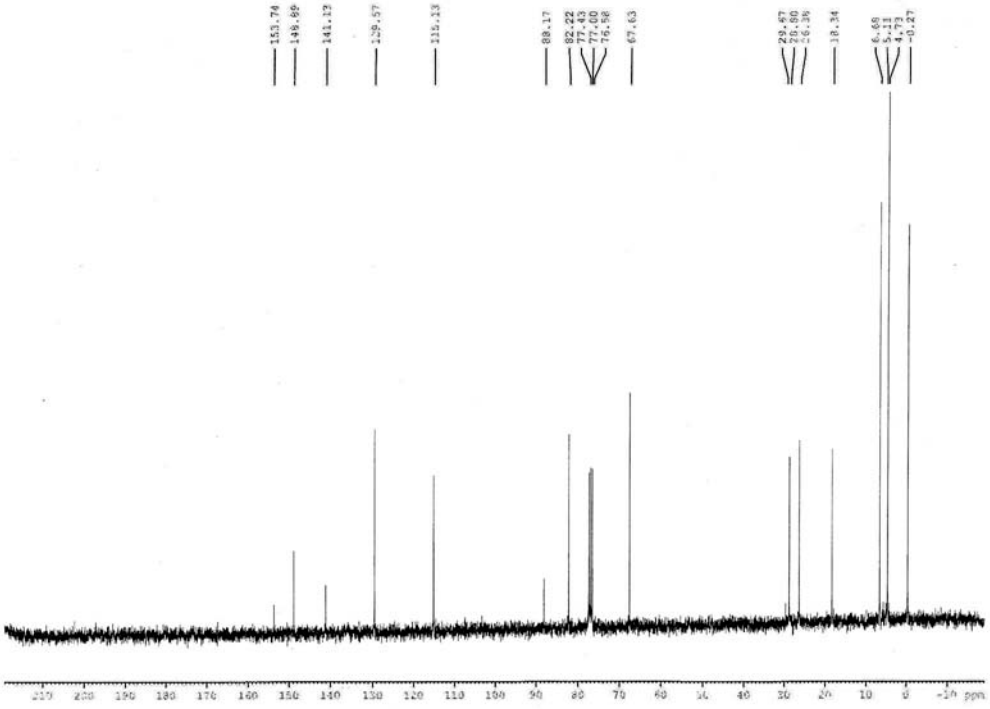

204.46
162.47
172.40
162.97
154.31
152.81
147.92
145.94
139.33
138.03
133.12
121.62
119.83
87.48
80.01
77.24
77.03
76.78
55.50
29.72
27.82
26.28
23.14
6.76
6.67
4.77
4.65
4.42
-1.86
-2.08
ppm

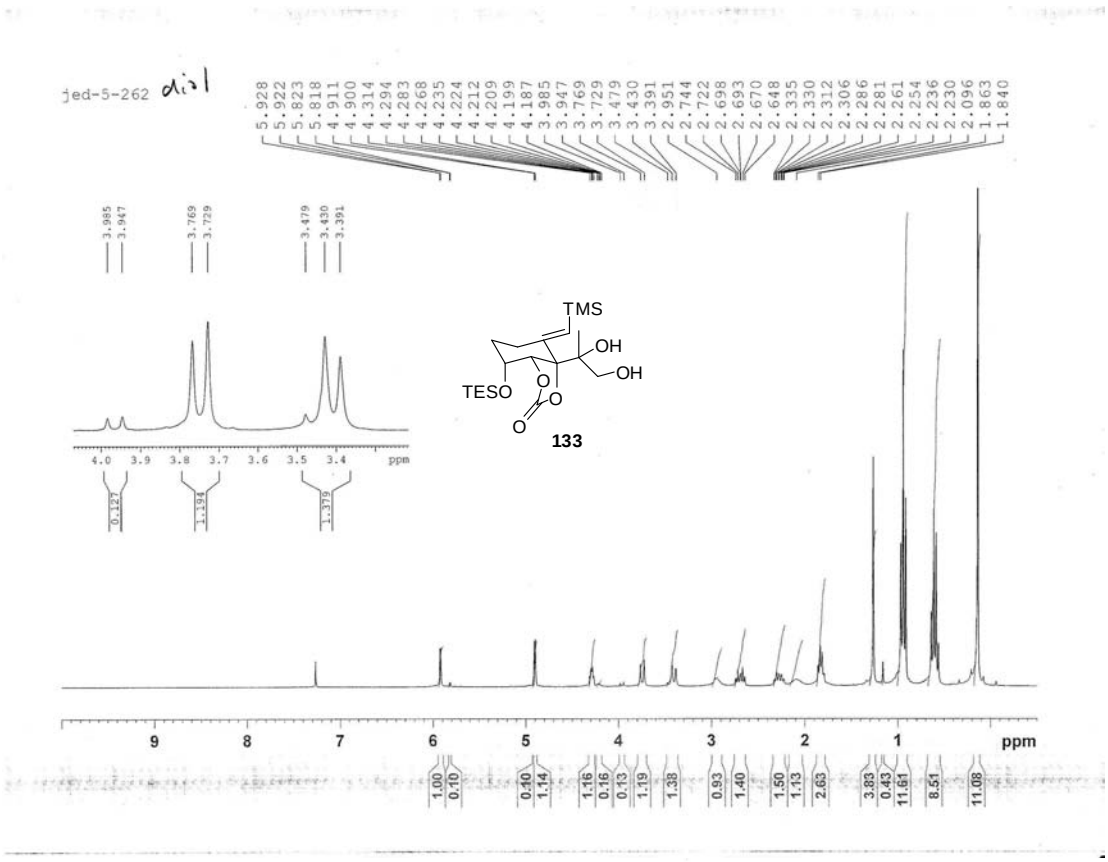
TES carbonate

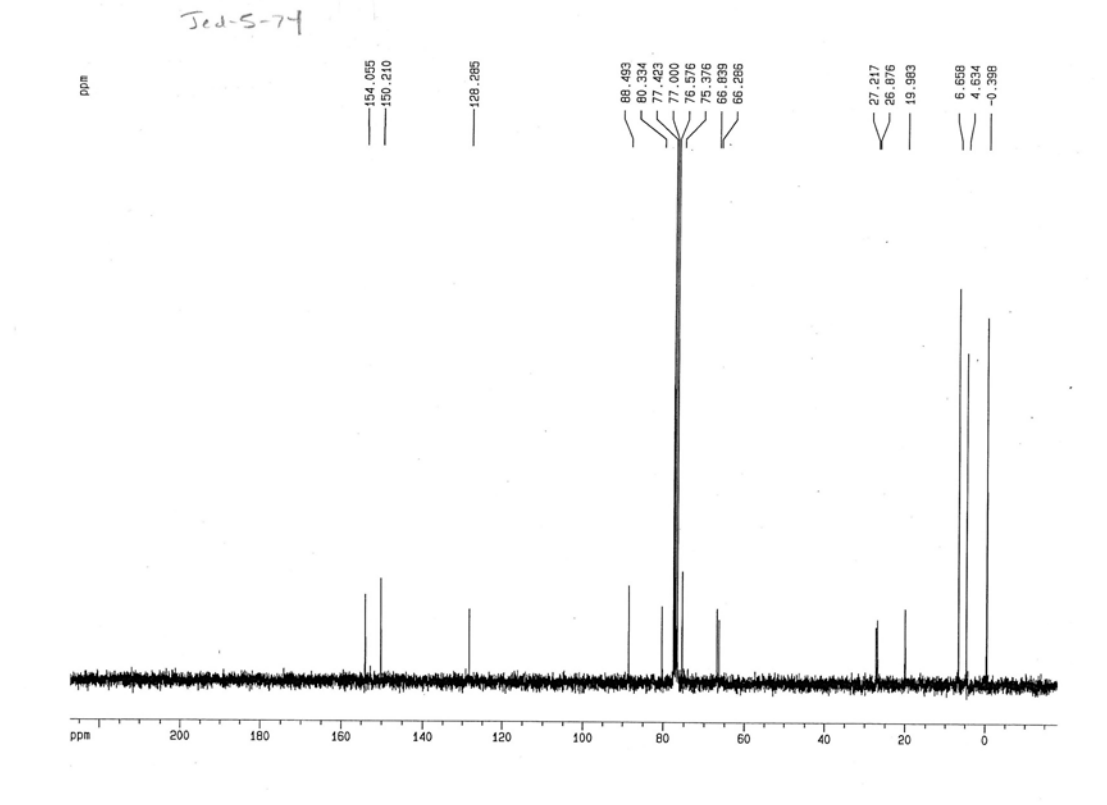


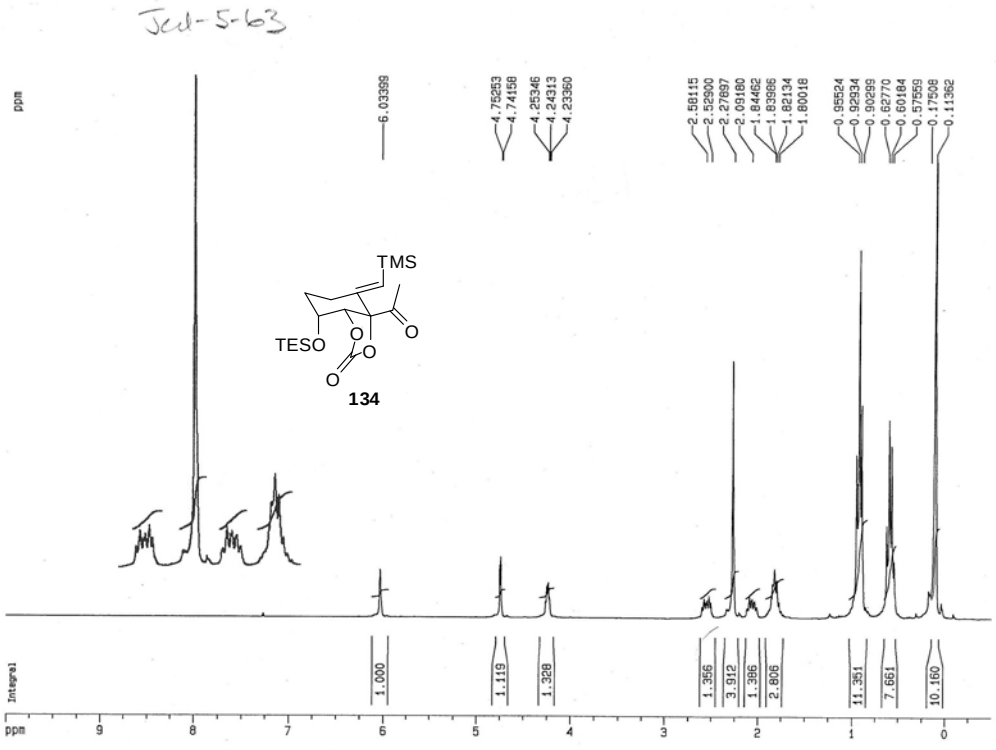
132

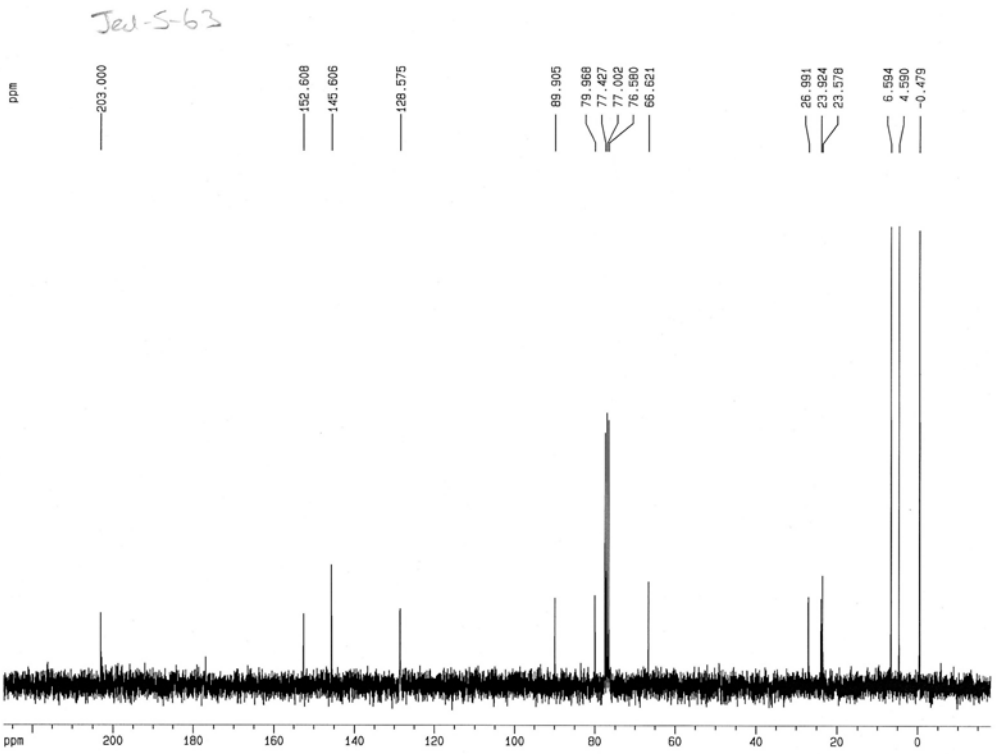
TES carbonate

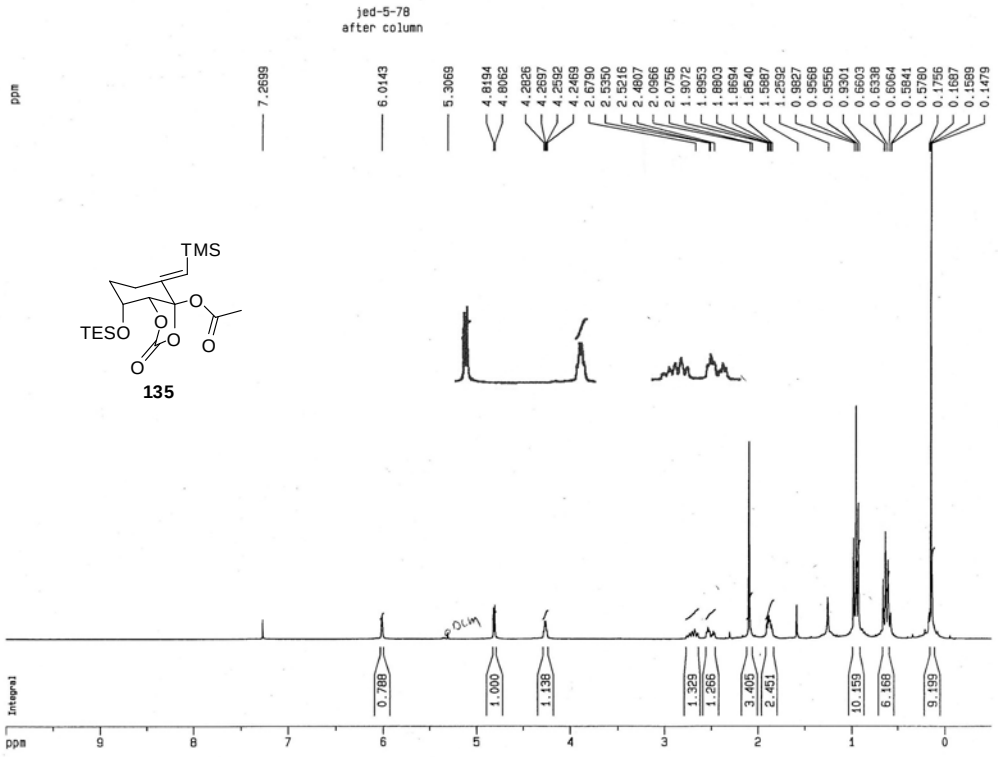


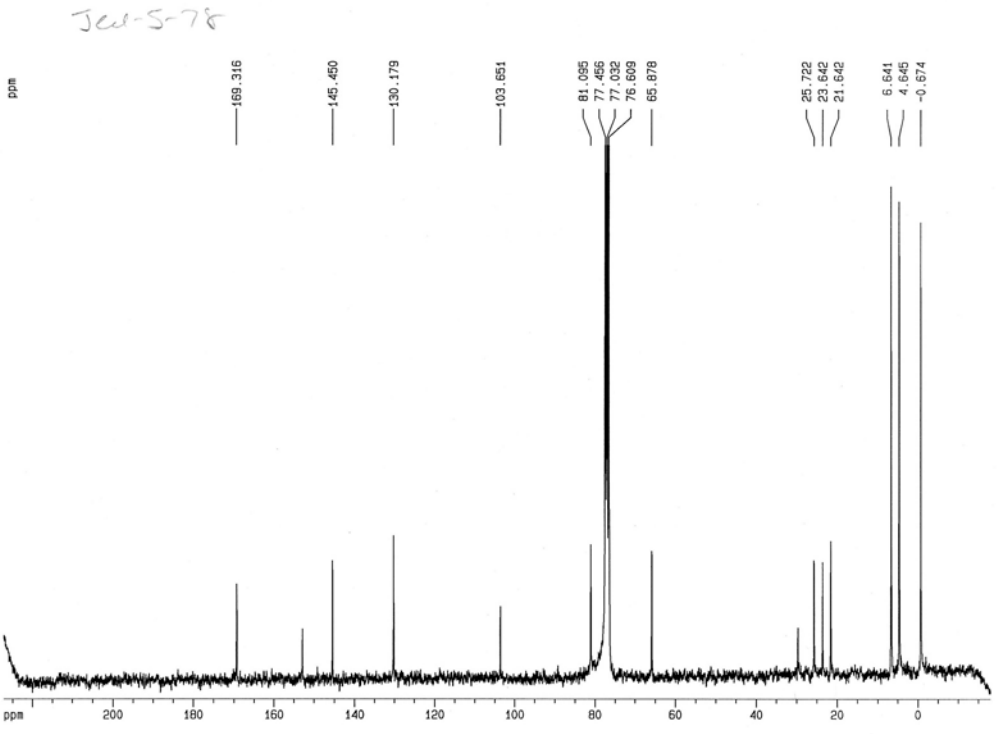

jed-5-262 diol
TMS
OH
OH
TESO
O
O
O
133
ppm


Jed-5-74
ppm

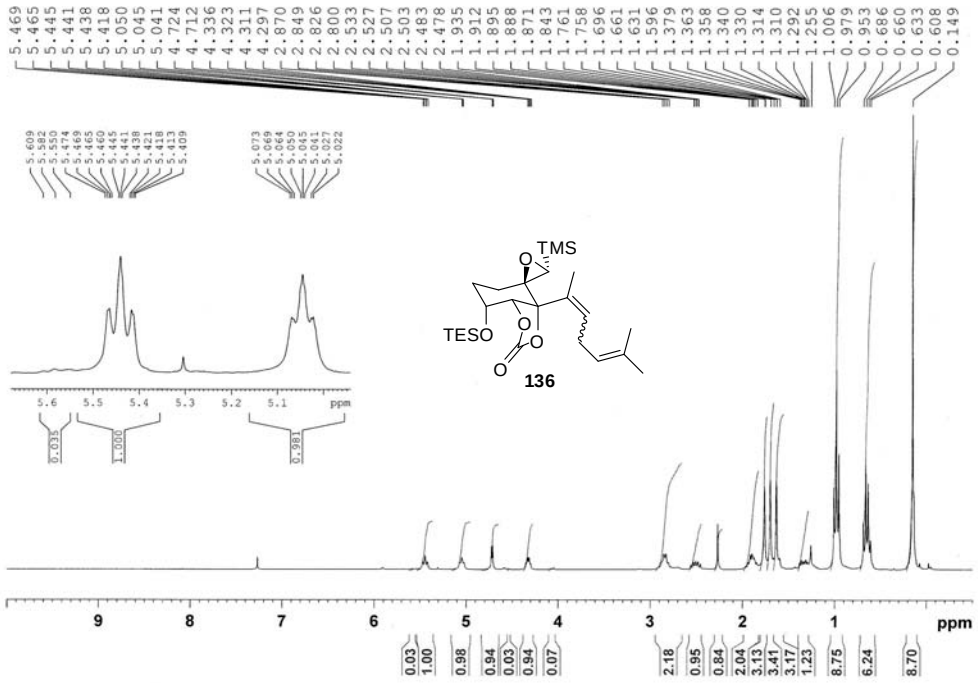

Jed-5-63
ppm
6.03399
4.76263
4.74156
4.25346
4.24313
4.23360
2.58115
2.52900
2.27697
2.09180
1.84462
1.83986
1.82134
1.80018
0.95524
0.92934
0.90299
0.62770
0.60184
0.57559
0.17508
0.11362
TMS
TESO
O
O
O
O
134
Integral
1.000
1.119
1.328
1.356
3.912
1.386
2.806
11.351
7.661
10.160
ppm
9
8
7
6
5
4
3
2
1
0


Jed-5-63
ppm
203.000
152.608
145.606
128.575
89.905
79.968
77.427
77.002
76.580
66.621
26.991
23.924
23.578
6.594
4.590
-0.479
ppm
200
180
160
140
120
100
80
60
40
20
0

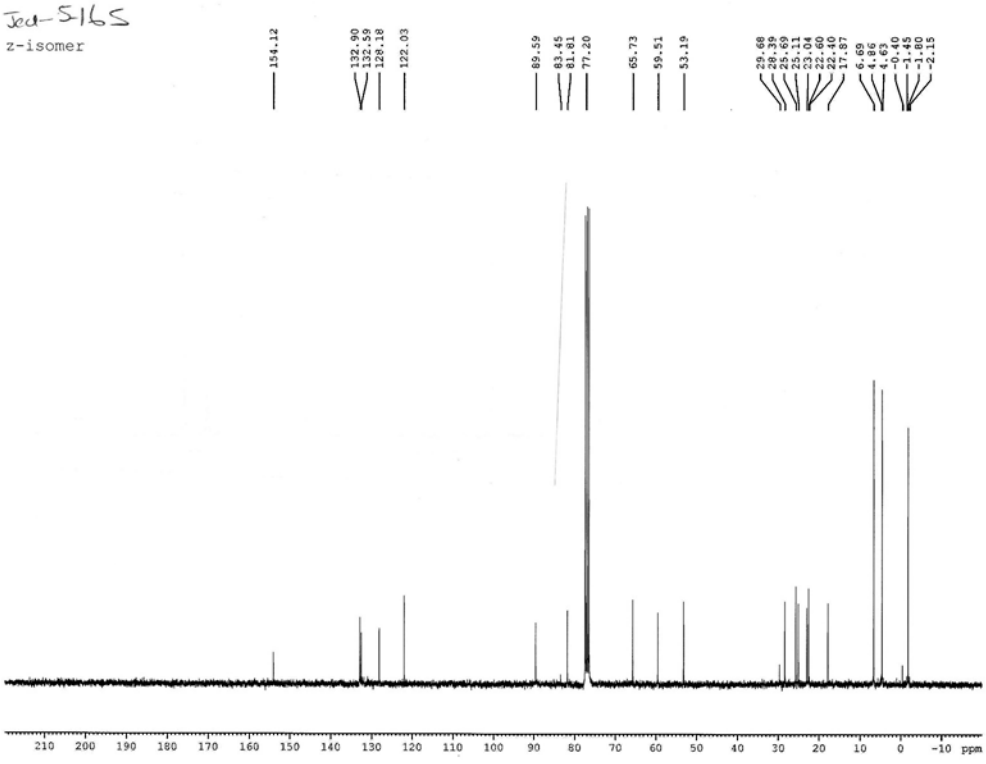

jed-5-78
after column
ppm
7.2699
6.0143
5.3069
4.8194
4.8062
4.2826
4.2697
4.2592
4.2469
2.6790
2.5350
2.5216
2.4807
2.0966
2.0756
1.9072
1.8953
1.8803
1.8694
1.8540
1.5887
1.2592
0.9827
0.9568
0.9556
0.9301
0.6603
0.6338
0.6064
0.5841
0.5780
0.1756
0.1687
0.1598
0.1479
TMS
TESO
O
O
O
O
O
135
Integral
0.788
1.000
1.138
1.329
1.266
3.406
2.451
10.159
6.168
9.199
ppm
9
8
7
6
5
4
3
2
1
0

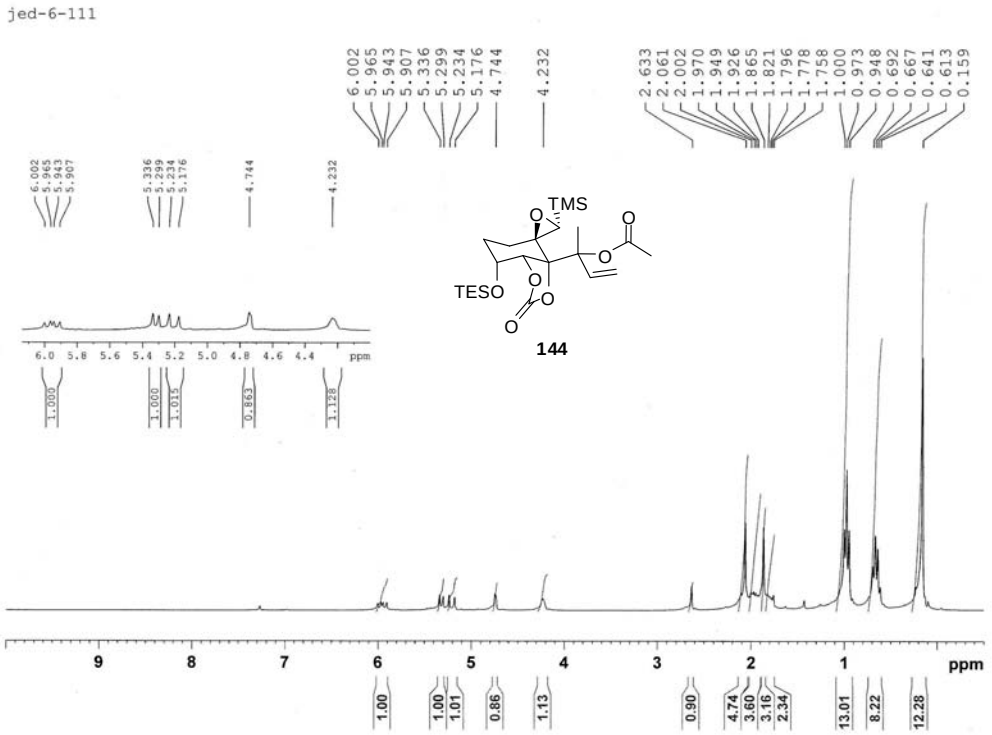

Jed-5-78
ppm
169.316
145.450
130.179
103.651
81.095
77.456
77.032
76.609
65.878
25.722
23.642
21.642
6.641
4.645
-0.674
ppm
200
180
160
140
120
100
80
60
40
20
0

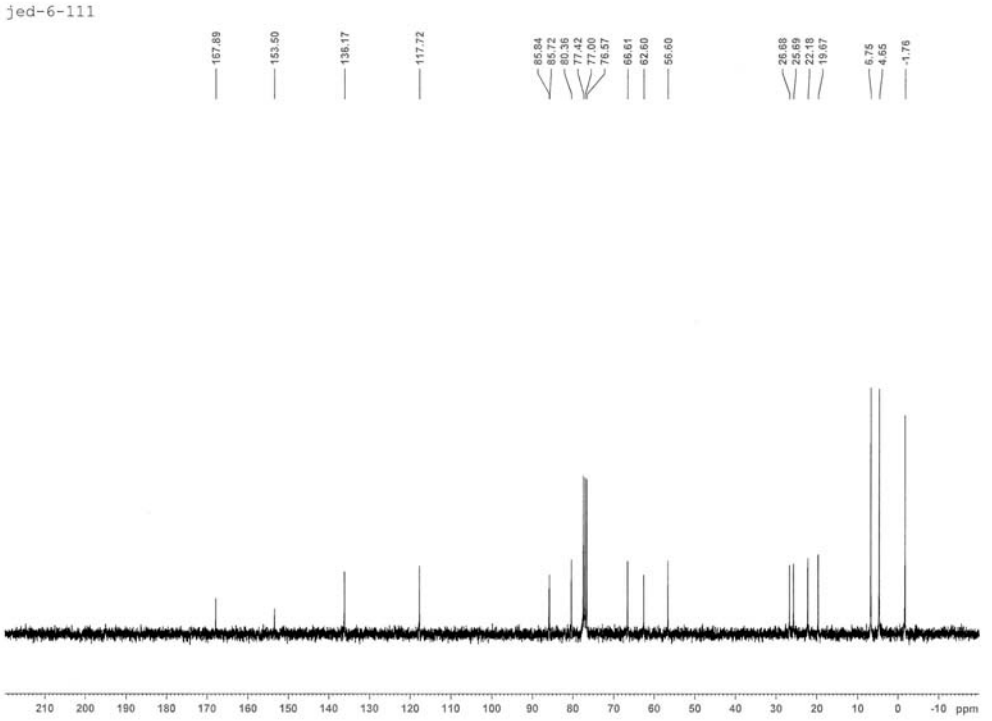
jed-5-165



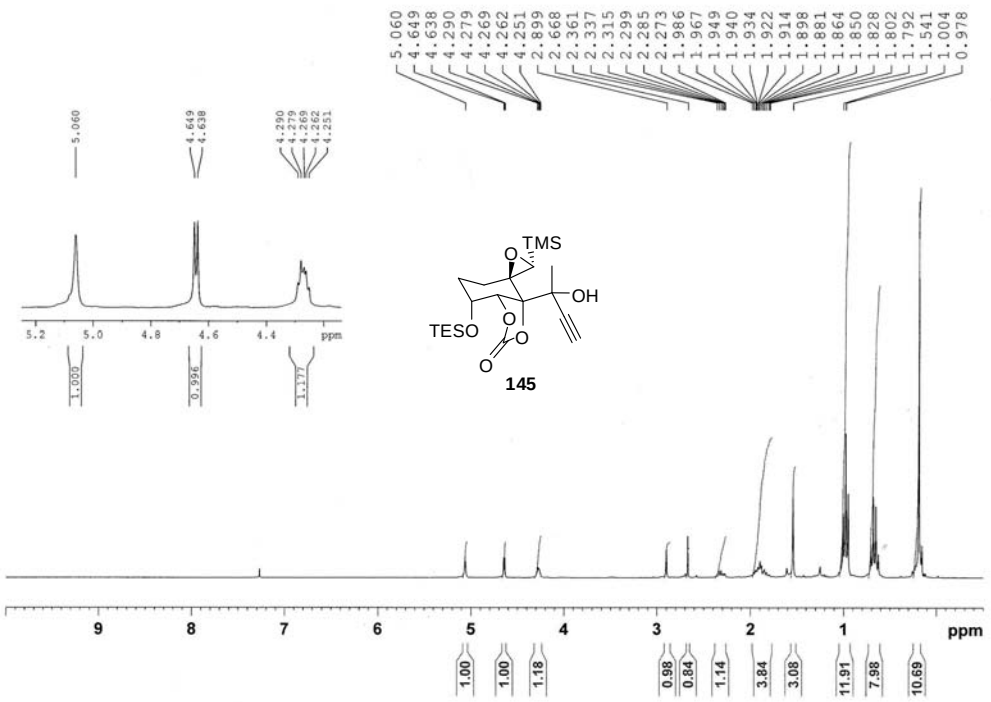
Jed-5165
z-isomer



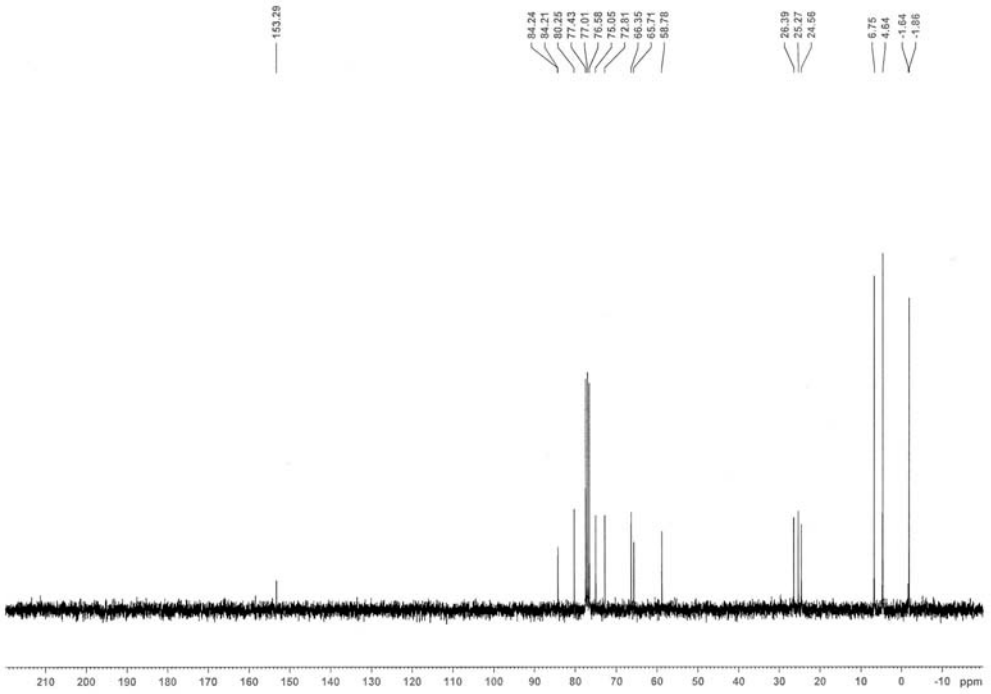

jed-6-111
6.002
5.965
5.943
5.907
5.336
5.299
5.234
5.176
4.744
4.232
2.633
2.061
2.002
1.970
1.949
1.926
1.865
1.821
1.796
1.778
1.758
1.000
0.973
0.948
0.692
0.667
0.641
0.613
0.159
TMS
TESO
144
ppm
1.00
1.00
1.01
0.86
1.13
0.90
4.74
3.60
3.16
2.34
13.01
8.22
12.28

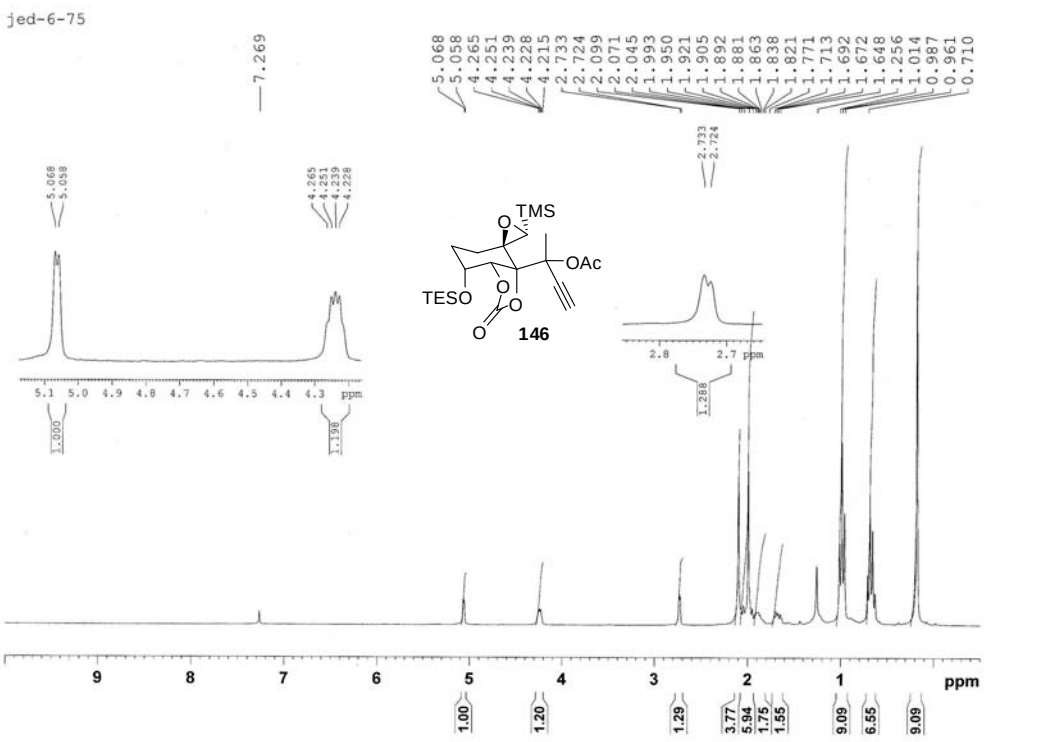

jed-6-111
167.89
153.50
136.17
117.72
85.84
85.72
80.35
77.42
77.00
76.57
66.61
62.60
56.60
26.68
25.69
22.18
19.67
6.75
4.65
-1.76
ppm

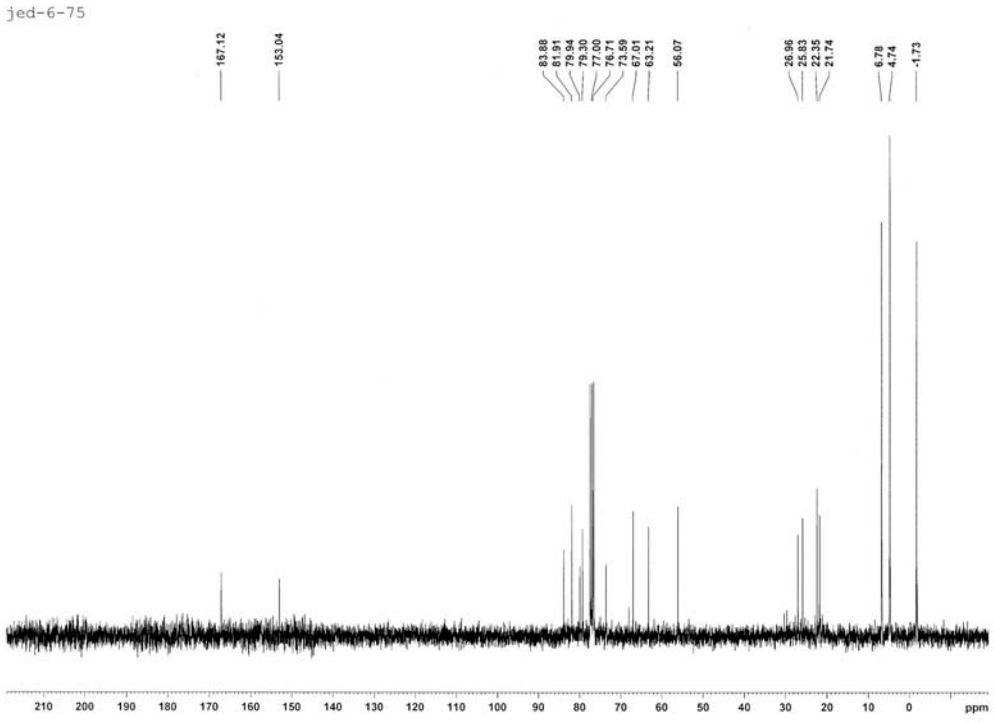
jed-6-48 after column

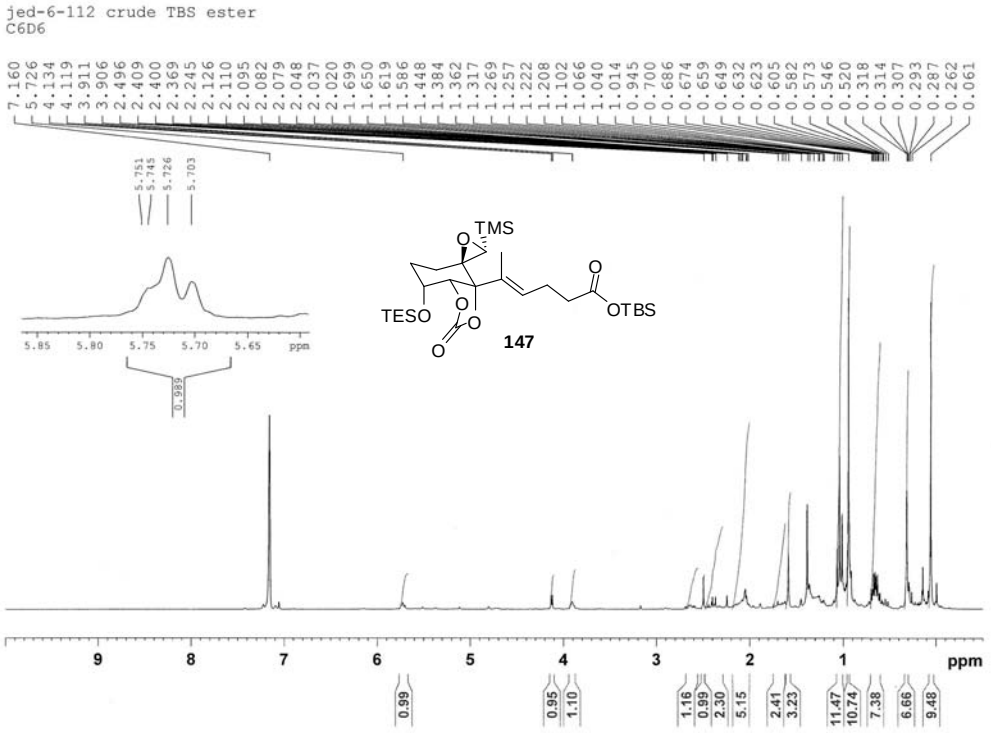


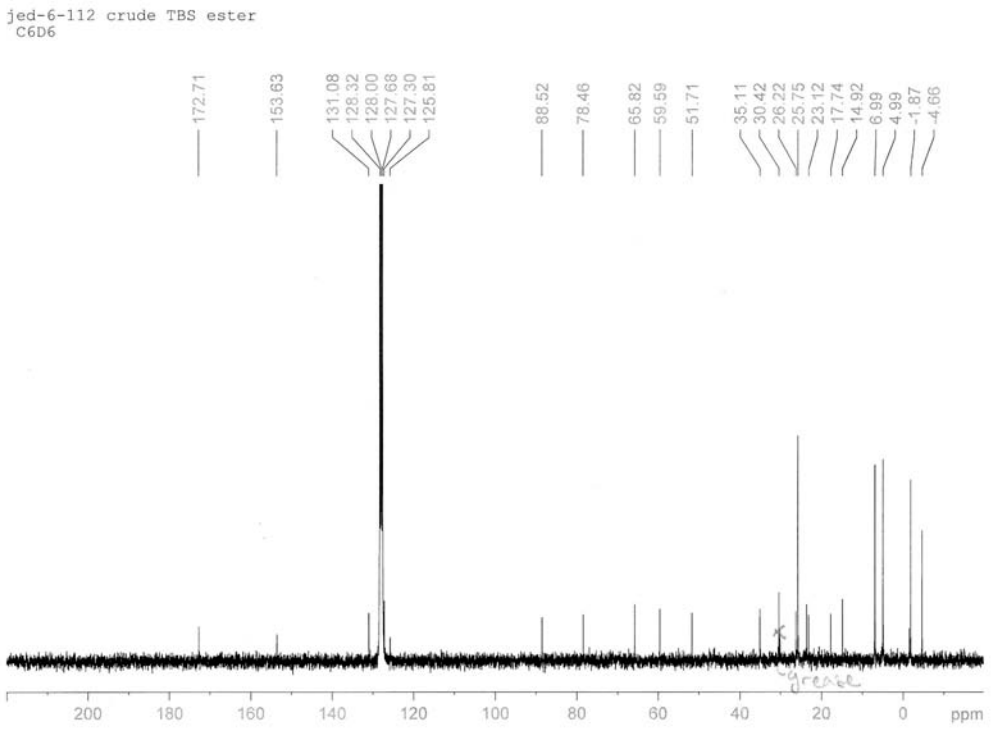
jed-6-48 after column

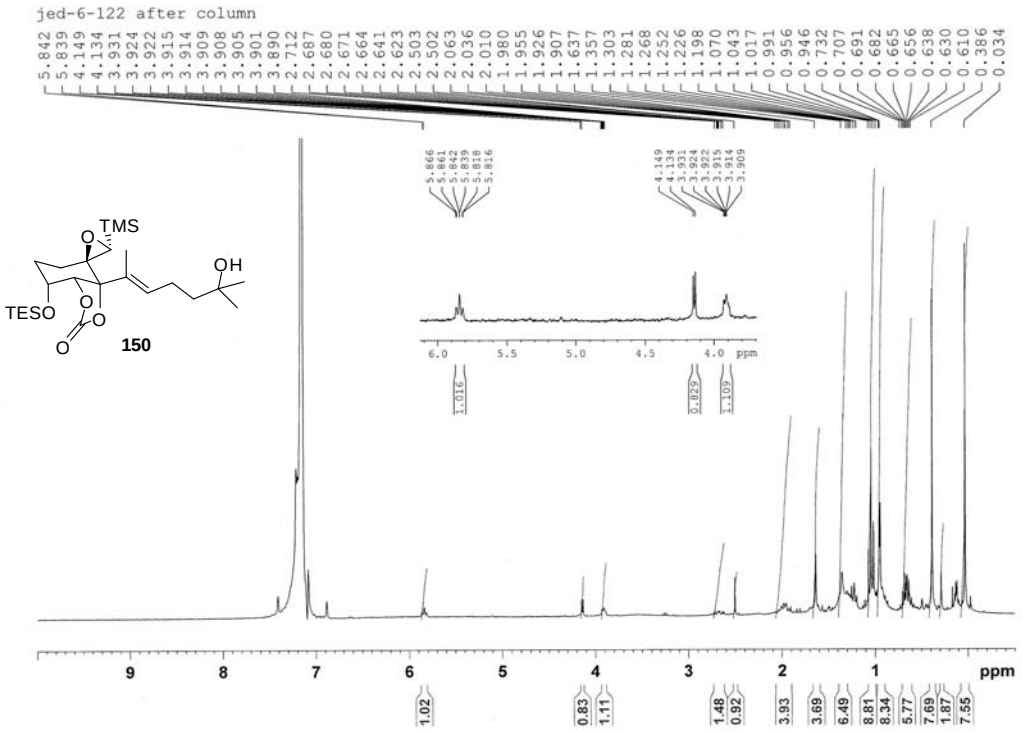


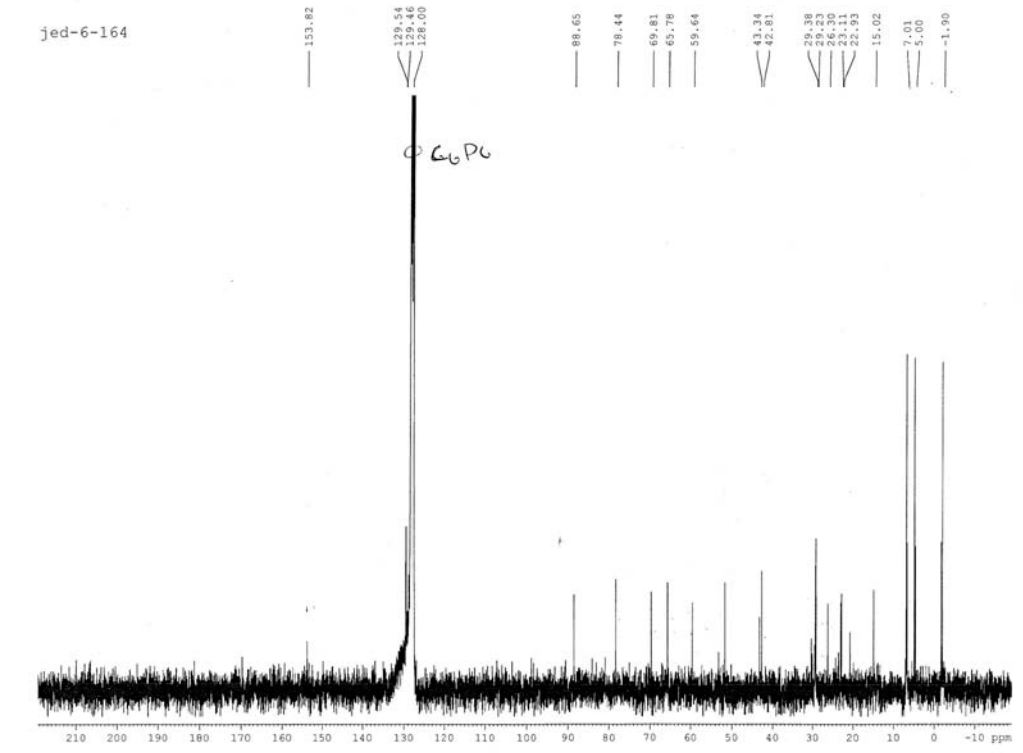

jed-6-75
7.269
5.068
5.058
4.265
4.251
4.239
4.228
4.215
2.733
2.724
2.099
2.071
2.045
1.993
1.950
1.921
1.905
1.892
1.881
1.863
1.838
1.821
1.771
1.713
1.692
1.672
1.648
1.256
1.014
0.987
0.961
0.710
TMS
OAc
TESO
O
O
O
O
146
ppm
1.00
1.20
1.29
3.77
5.94
1.75
1.55
9.09
6.55
9.09

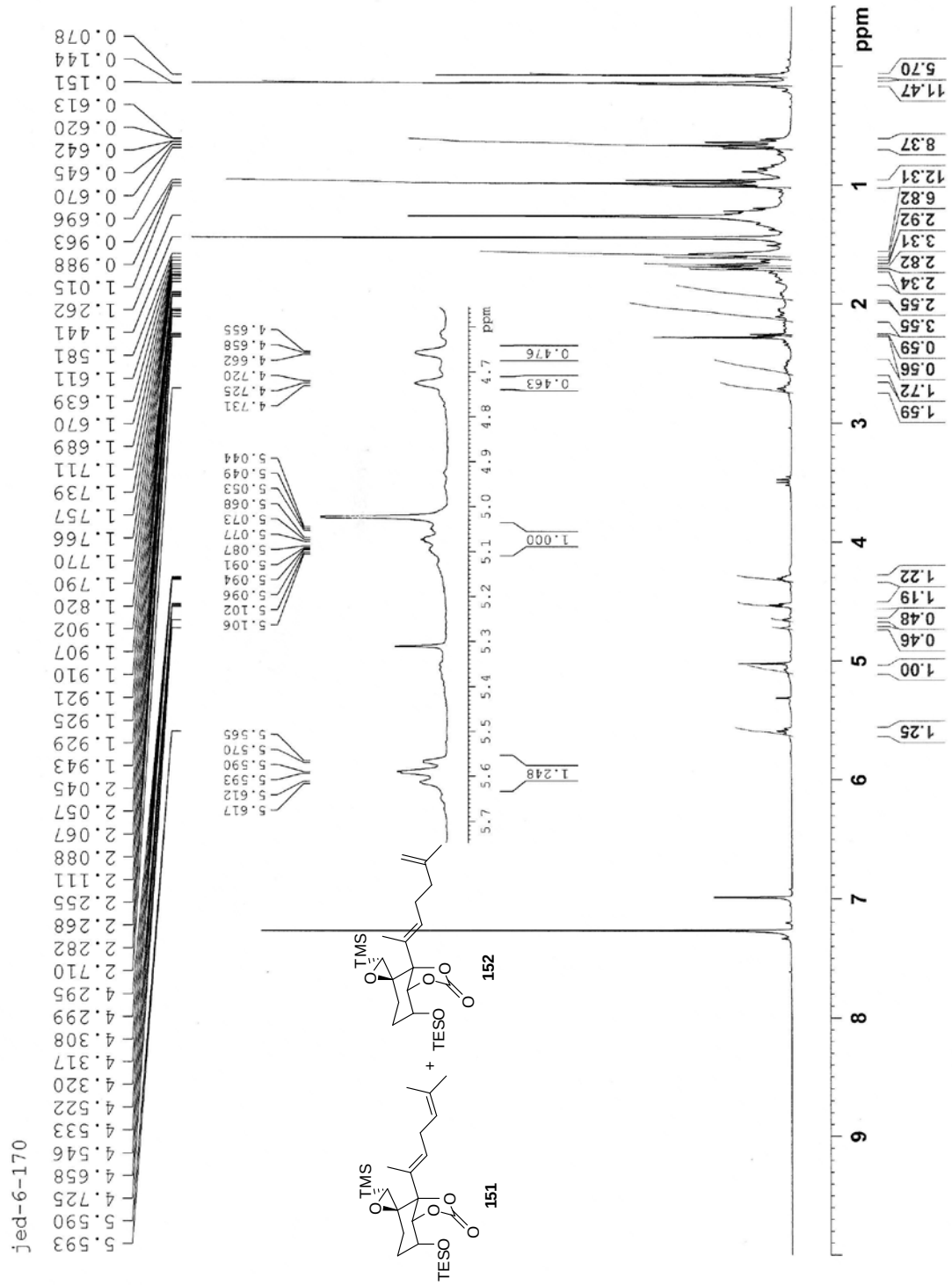

jed-6-75
167.12
153.04
83.88
81.91
79.94
79.30
77.00
76.71
73.59
67.01
63.21
56.07
26.96
25.83
22.35
21.74
6.78
4.74
-1.73
ppm

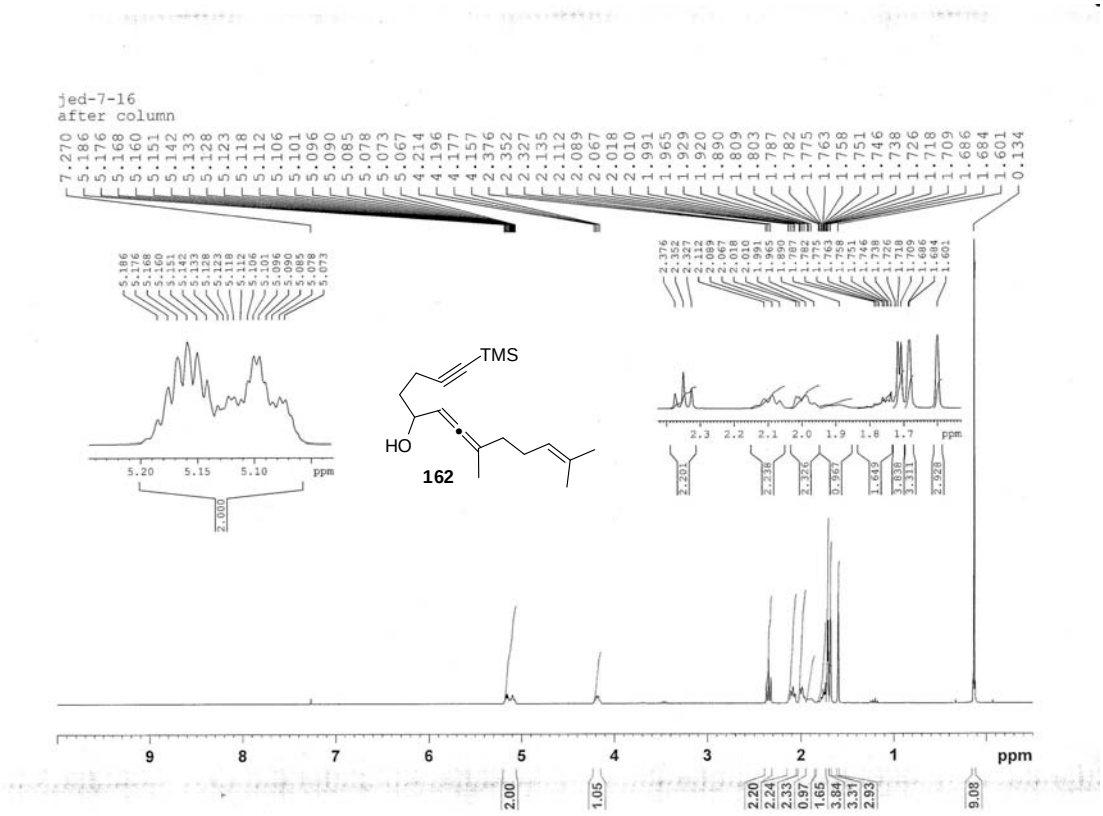

jed-6-112 crude TBS ester
C6D6
TMS
TESO
OTBS
147
ppm

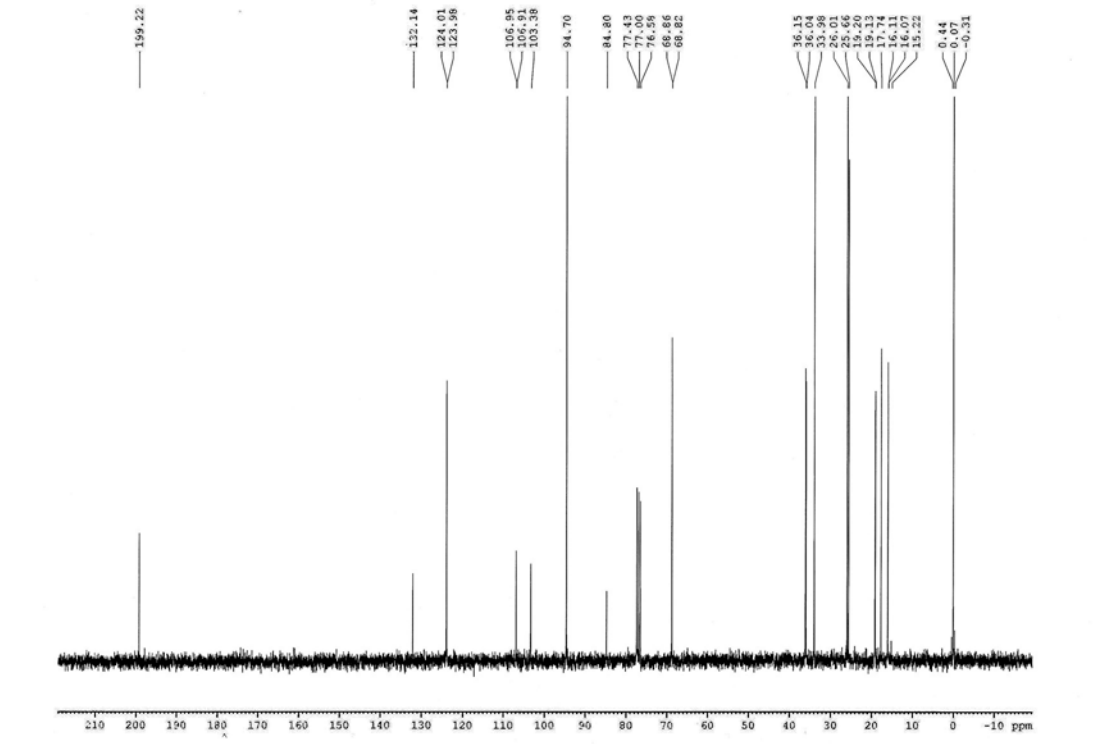

jed-6-112 crude TBS ester
C6D6
ppm


jed-6-122 after column
TMS
OH
TESO
150
ppm

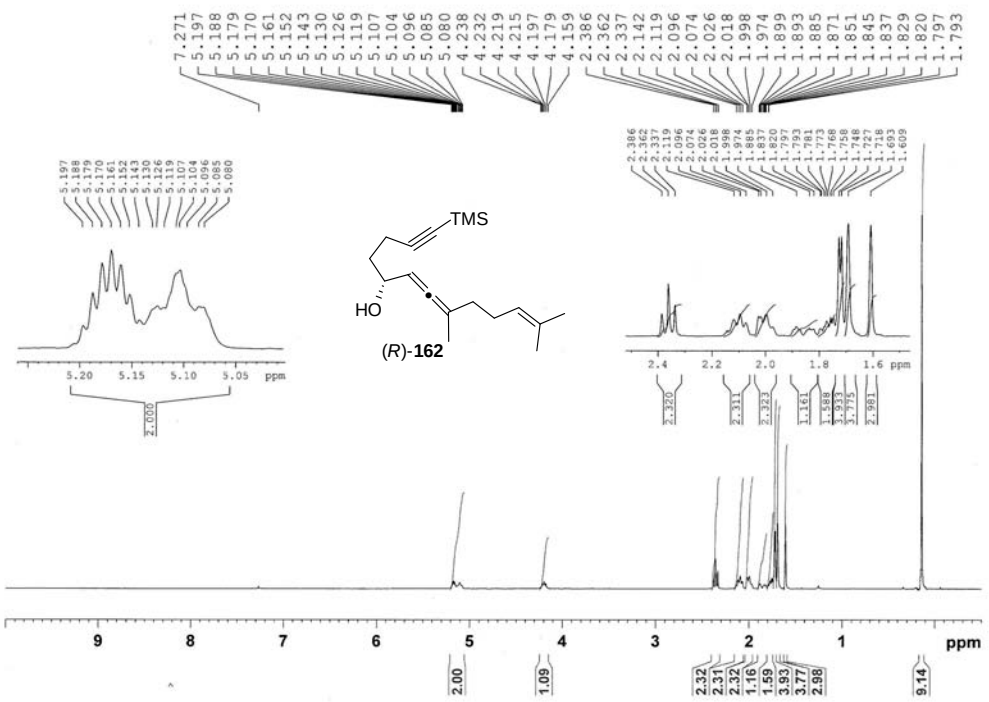

jed-6-164
ppm


jed-6-170
ppm
TMS
TESO
151
152

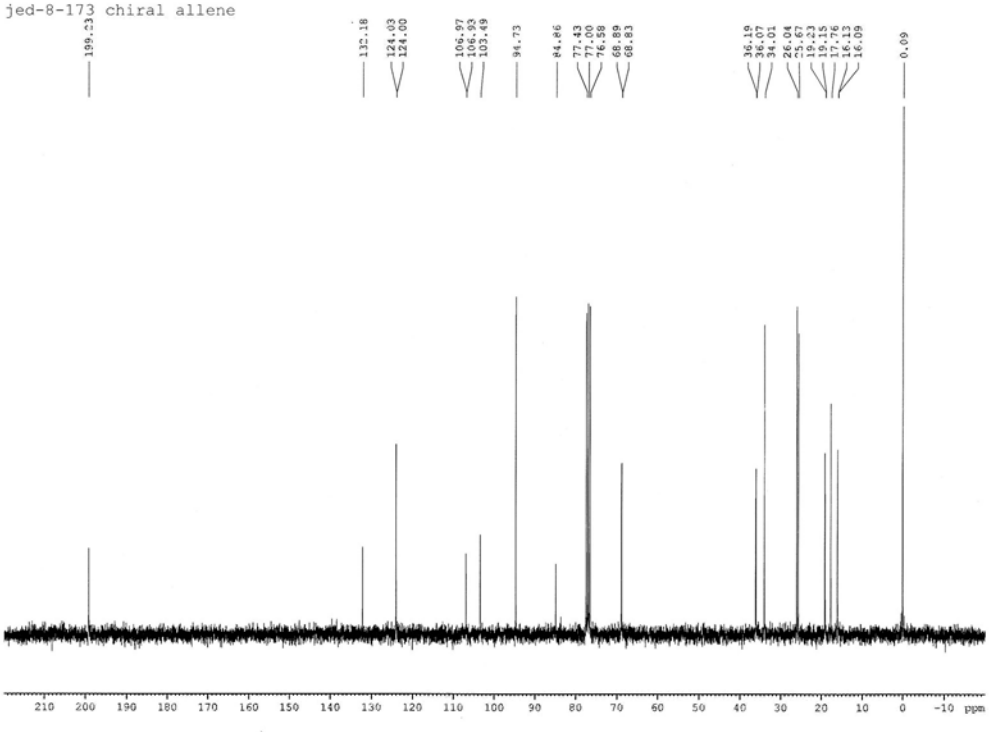

jed-7-16
after column
TMS
HO
162
ppm

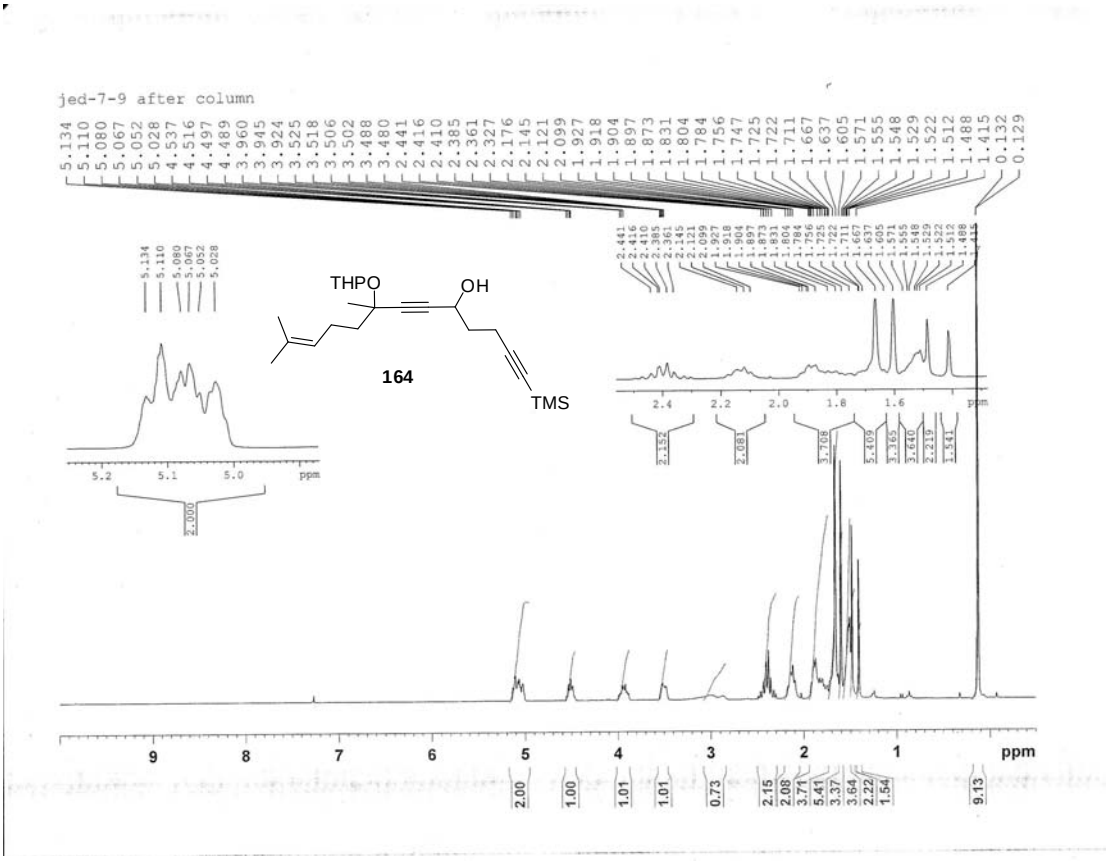

ppm

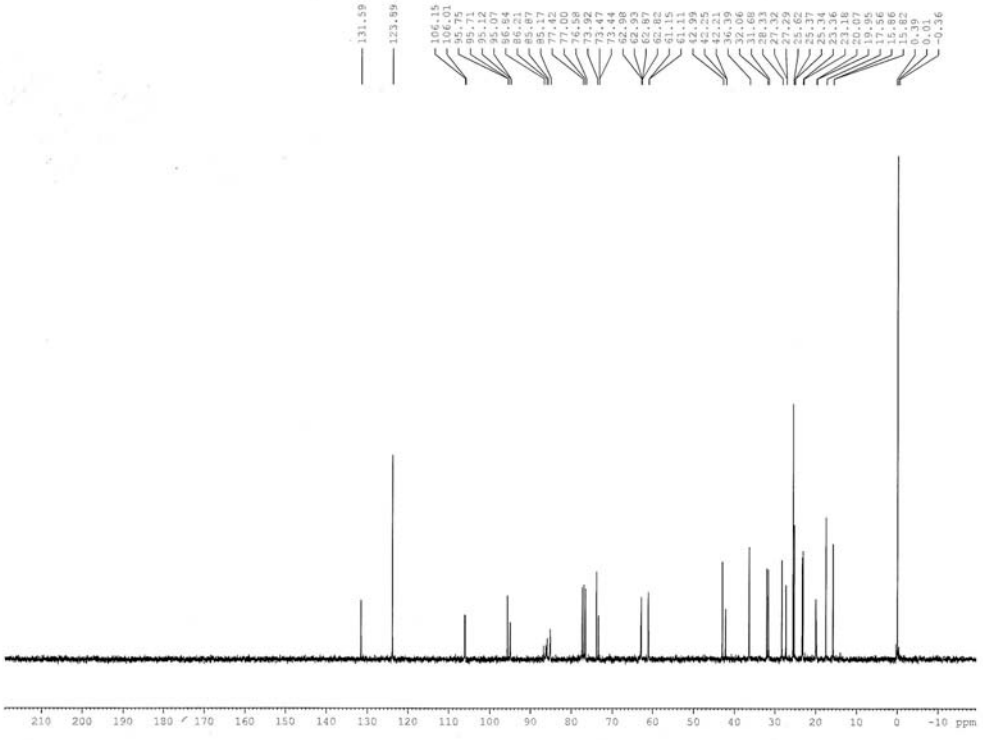
jed-8-173 chiral allene

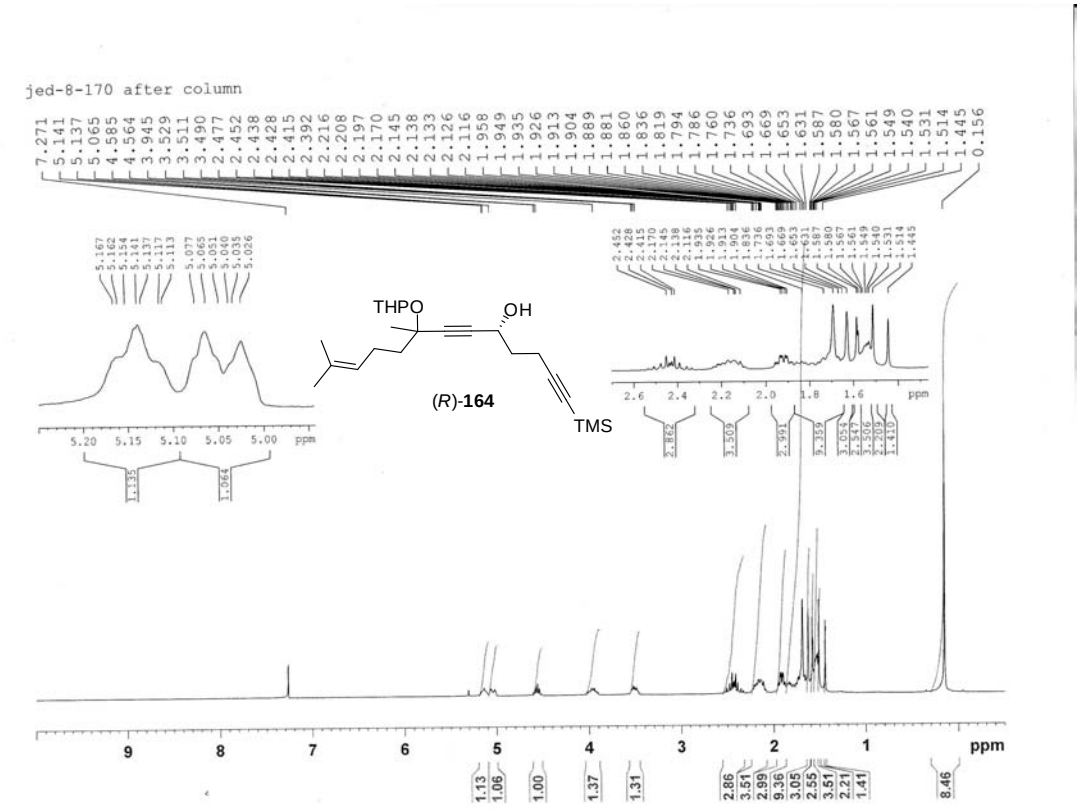


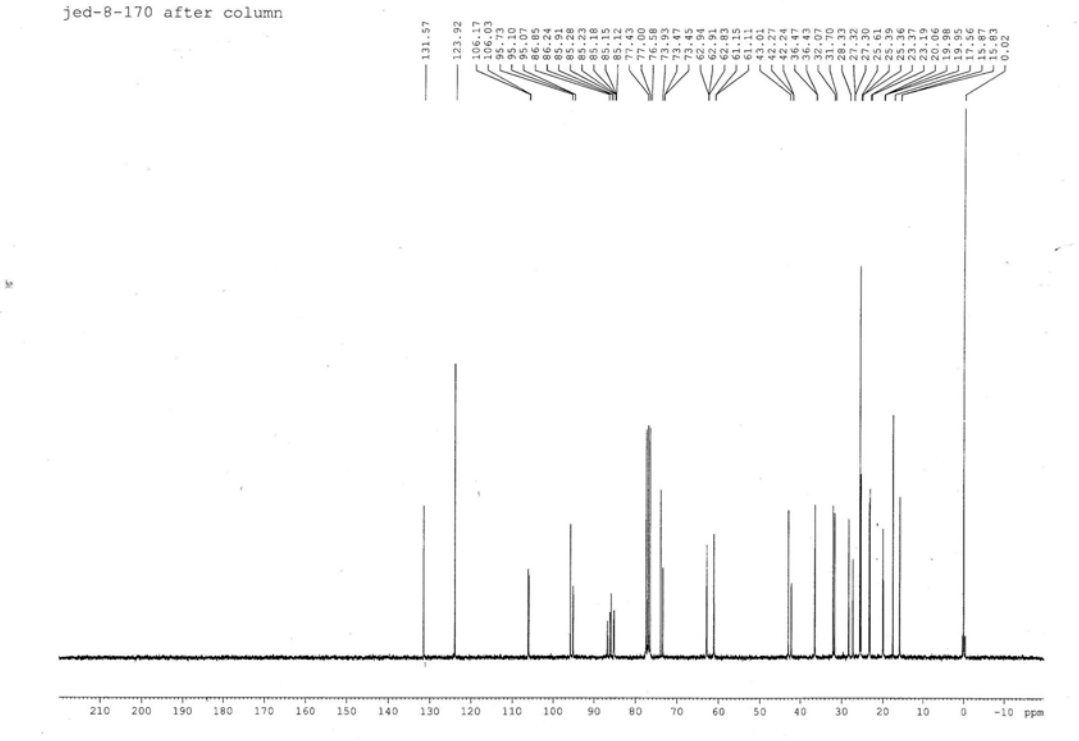
jed-8-173 chiral allene



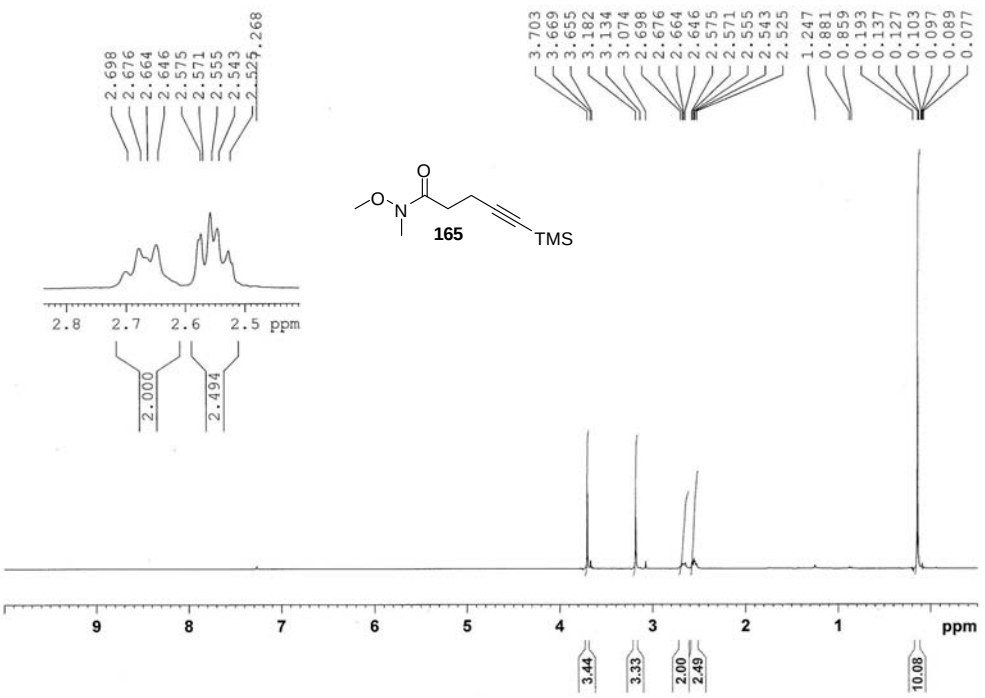

jed-7-9 after column
THPO
OH
164
TMS
ppm


ppm

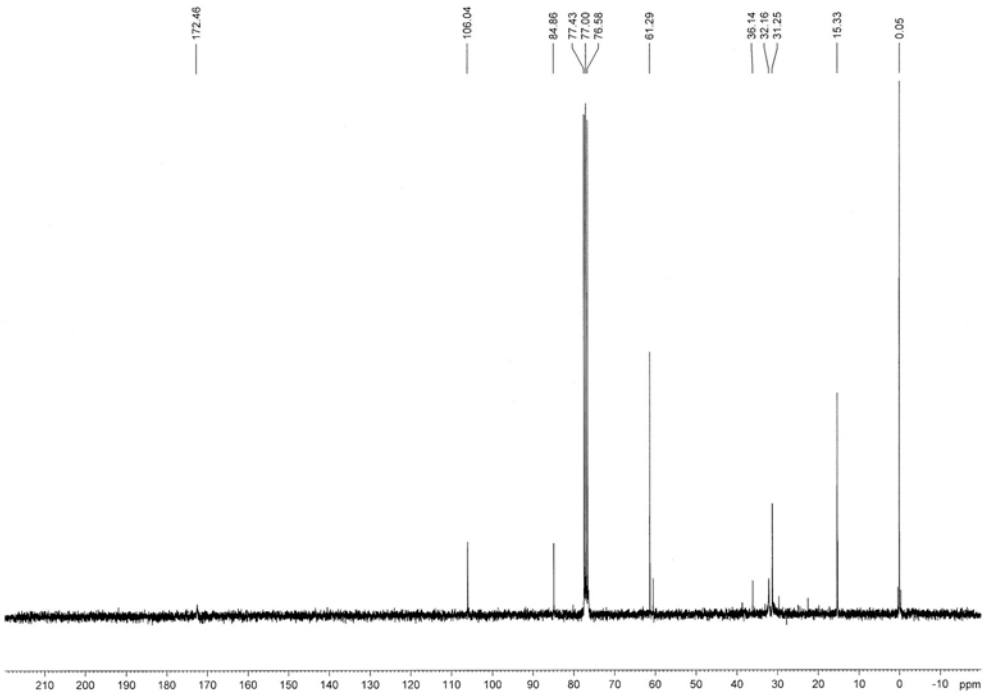

jed-8-170 after column
THPO
OH
TMS
(R)-164
ppm

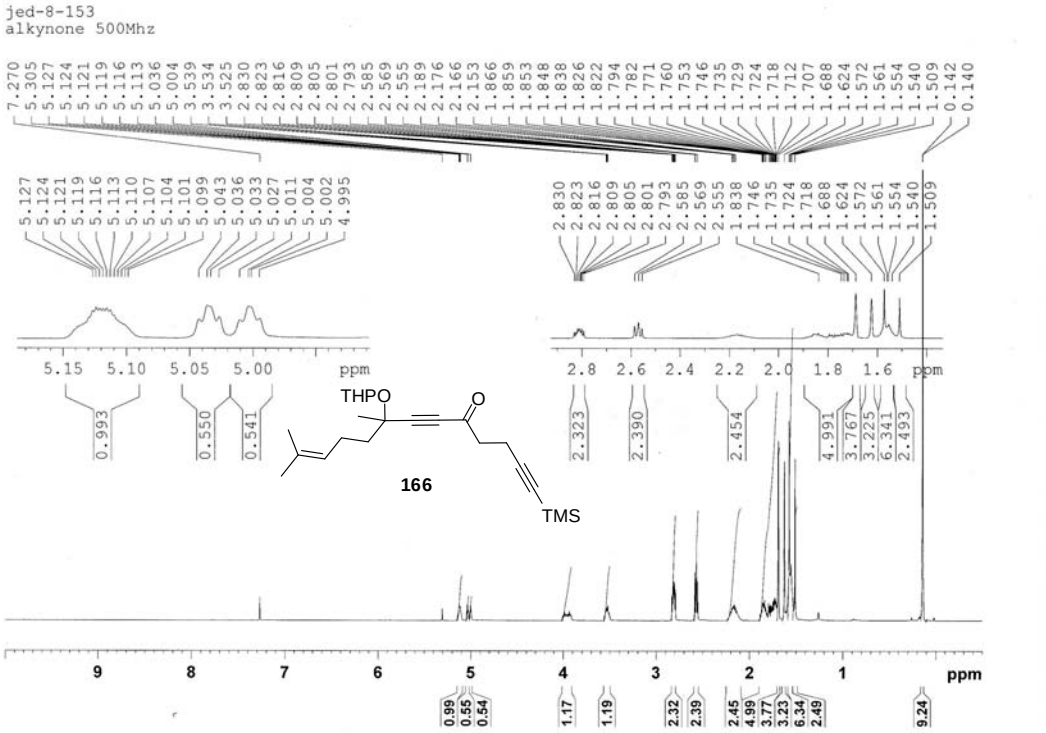

jed-8-170 after column
ppm

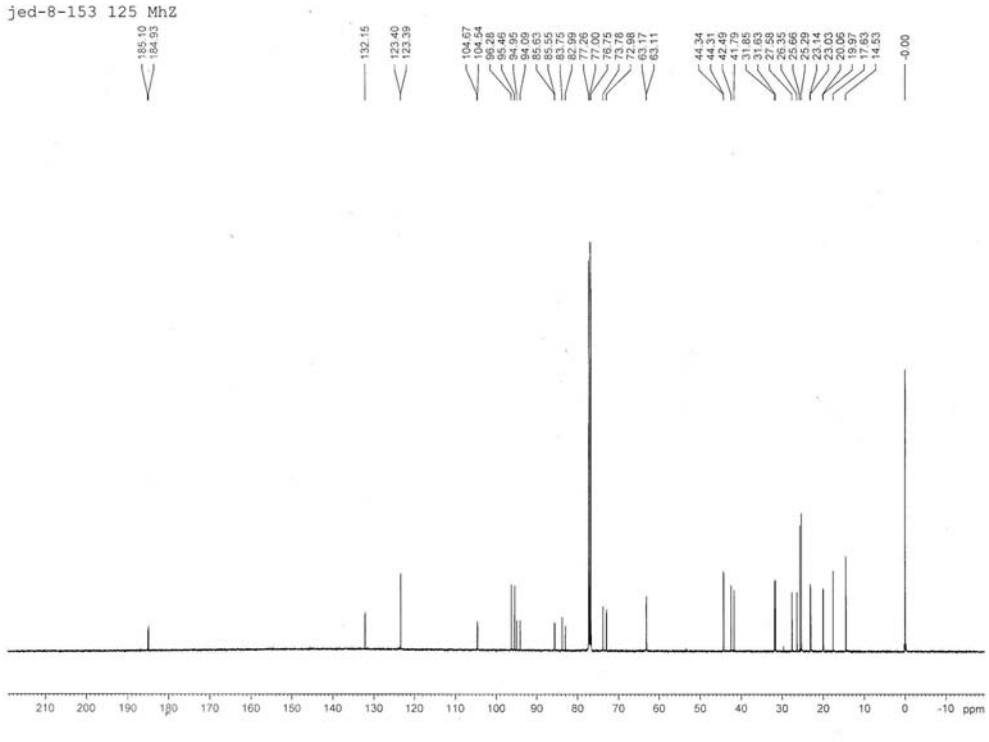
jed-8-265 weinreb amide



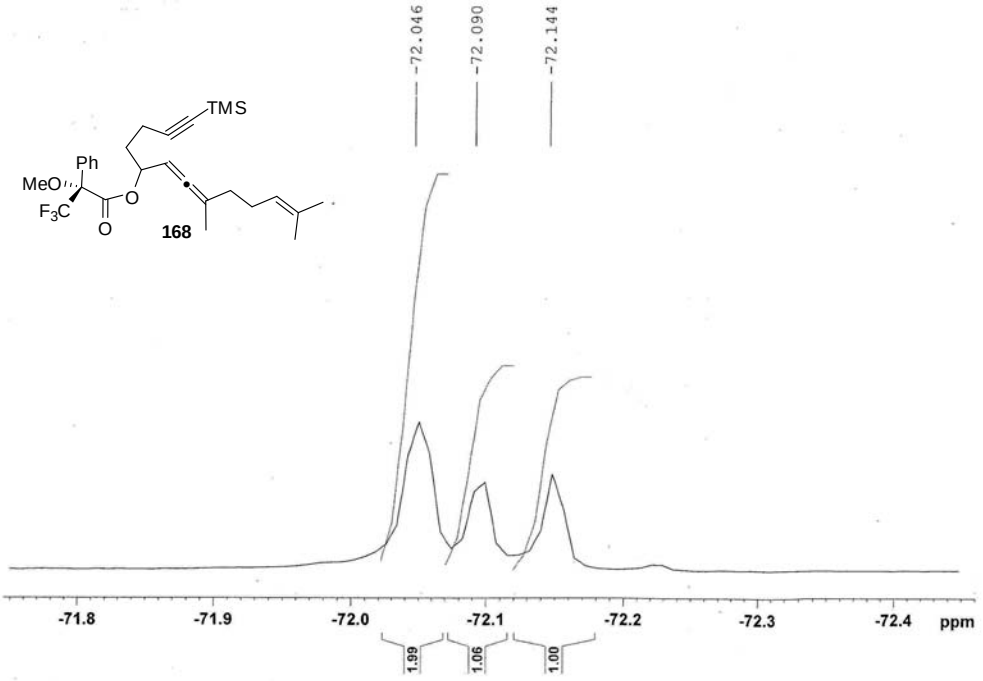
jed-8-265 weinreb amide



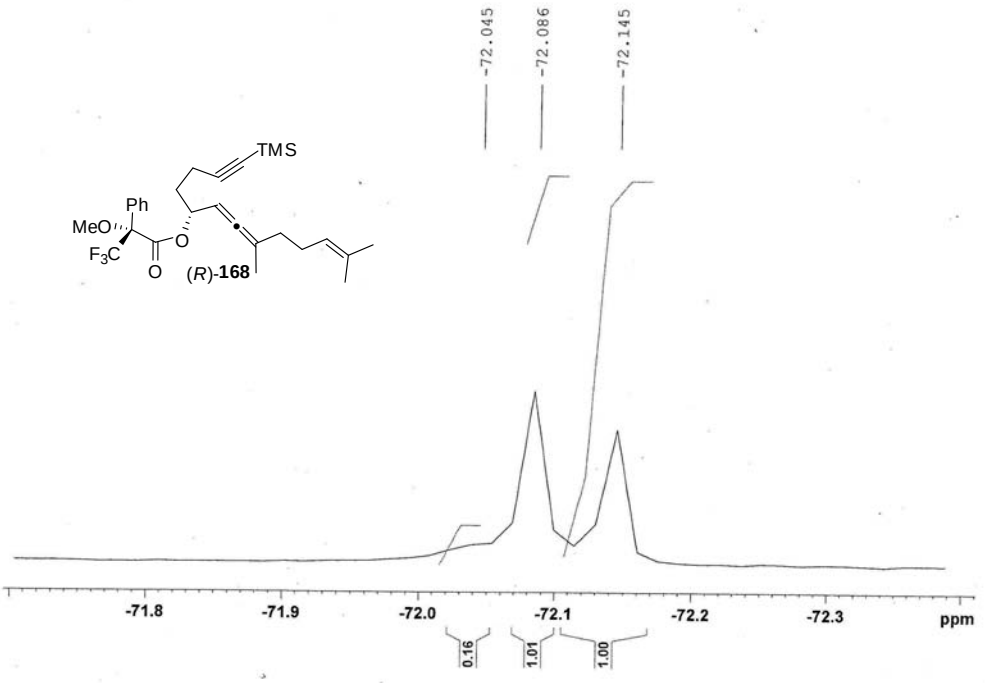

jed-8-153
alkynone 500Mhz
THPO
O
TMS
166
ppm

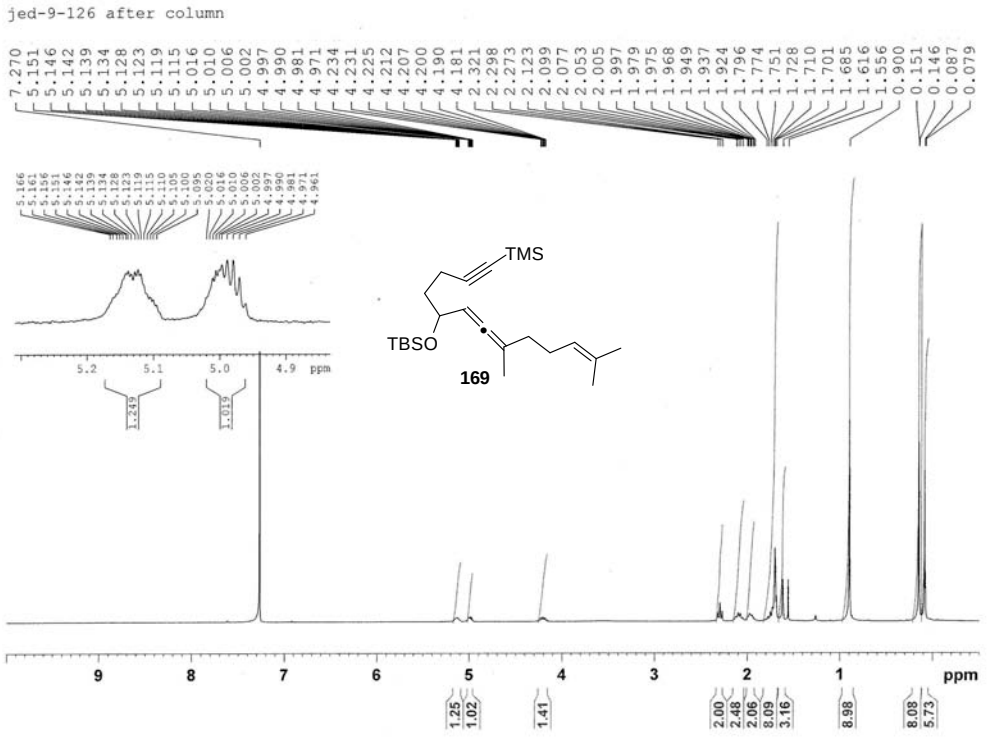

jed-8-153 125 MhZ
ppm

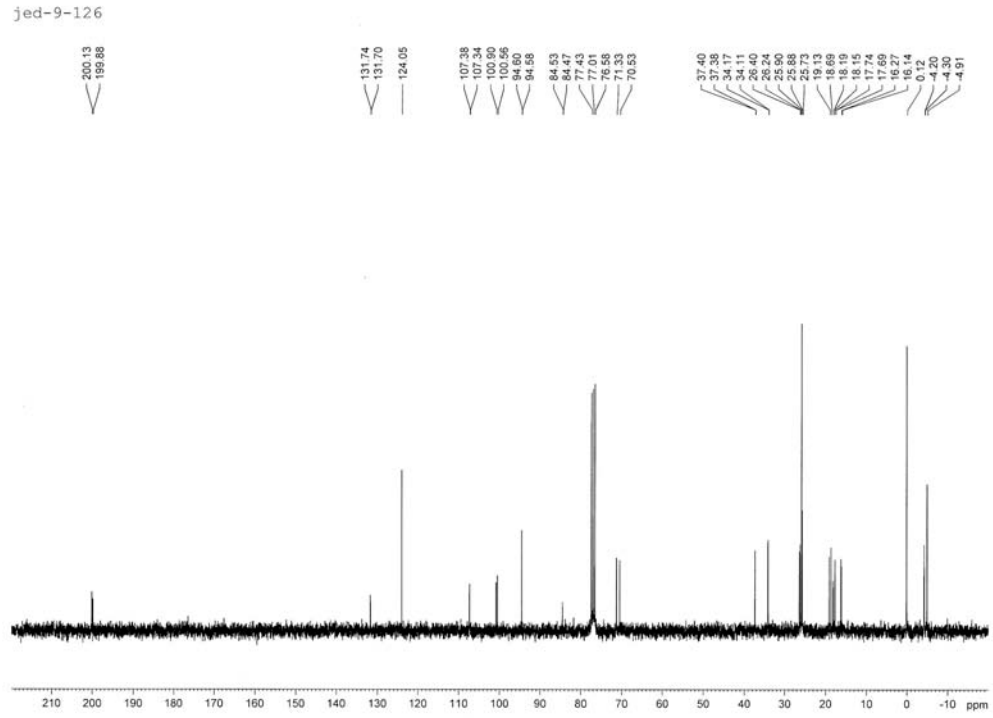
jed-7-63 crude
19 F NMR of racemic allene

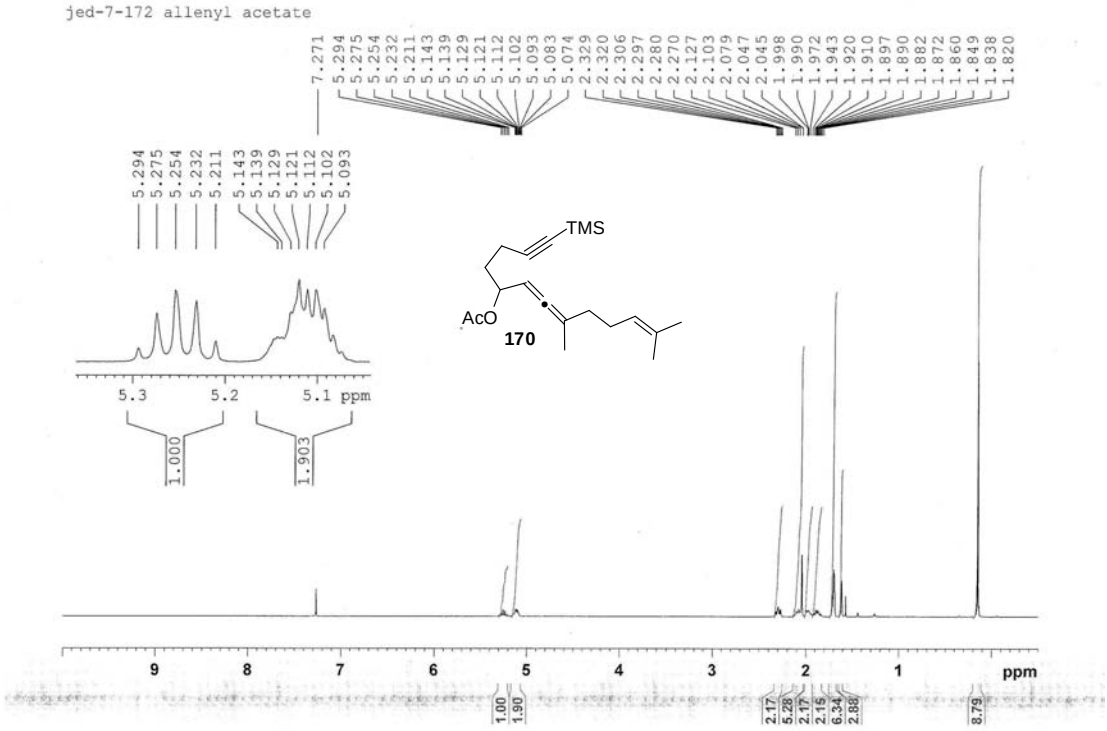


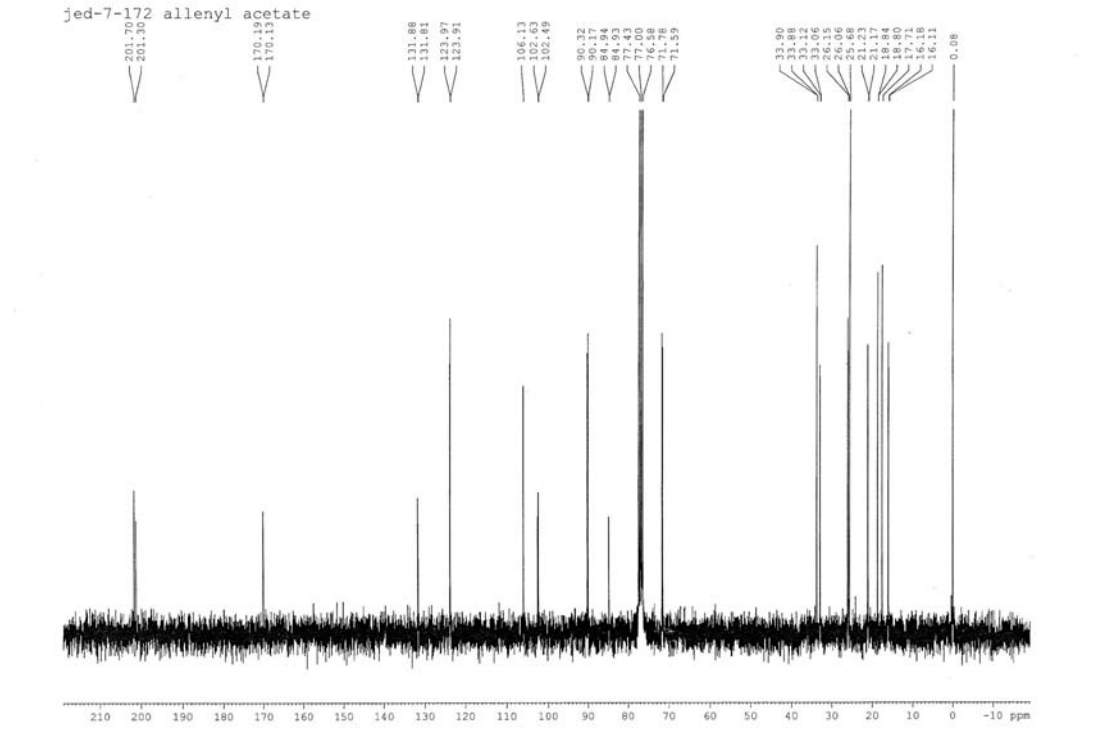
jed-8-174 crude
mosher ester of chiral allene with side chain

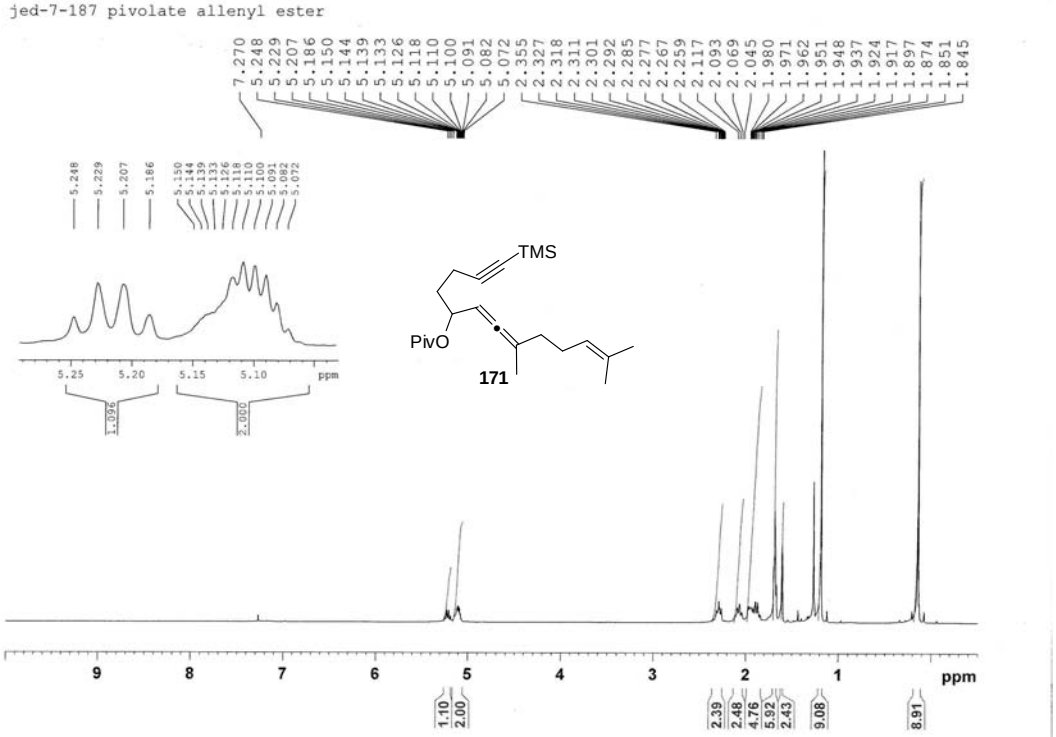


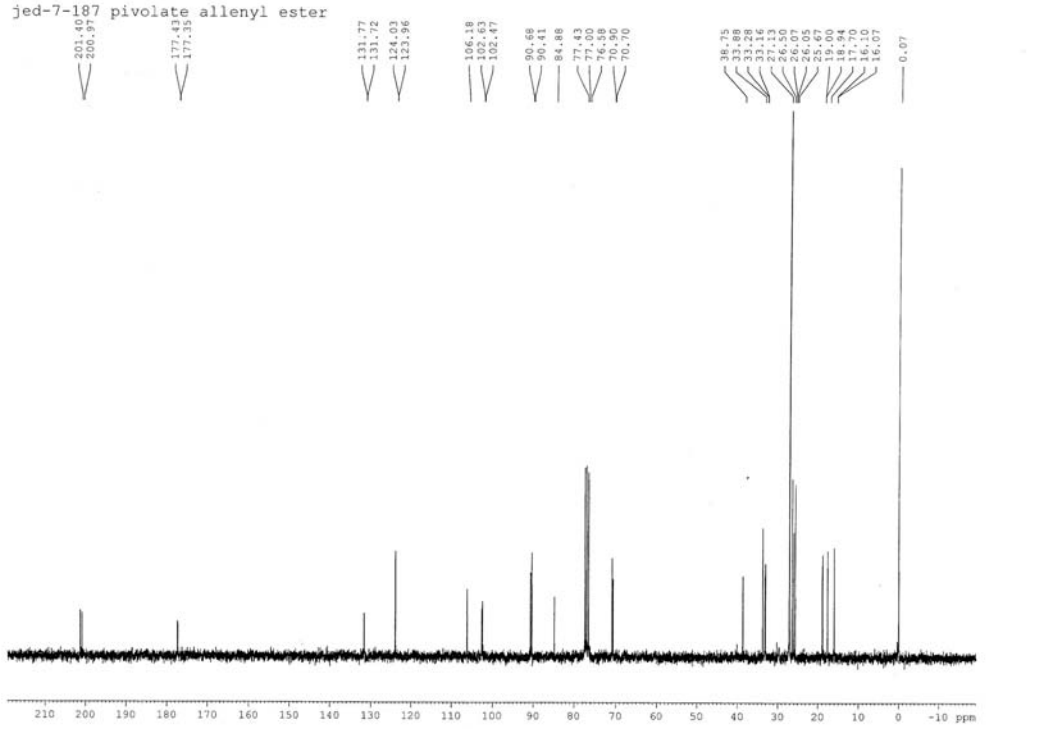

jed-9-126 after column
TMS
TBSO
169
ppm

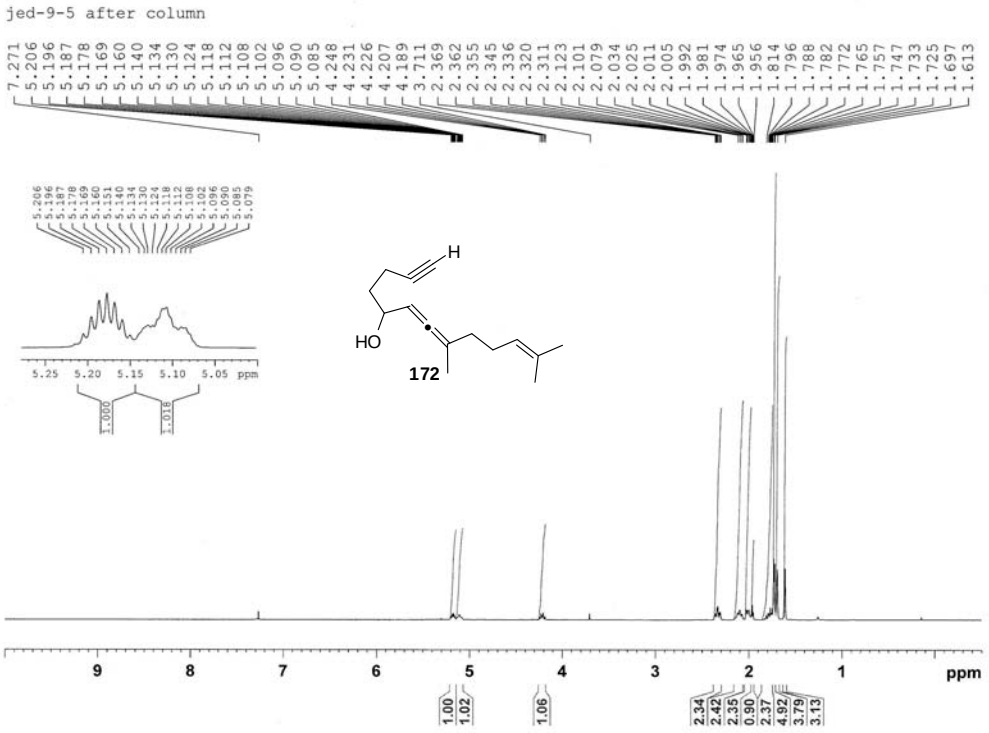

jed-9-126
ppm

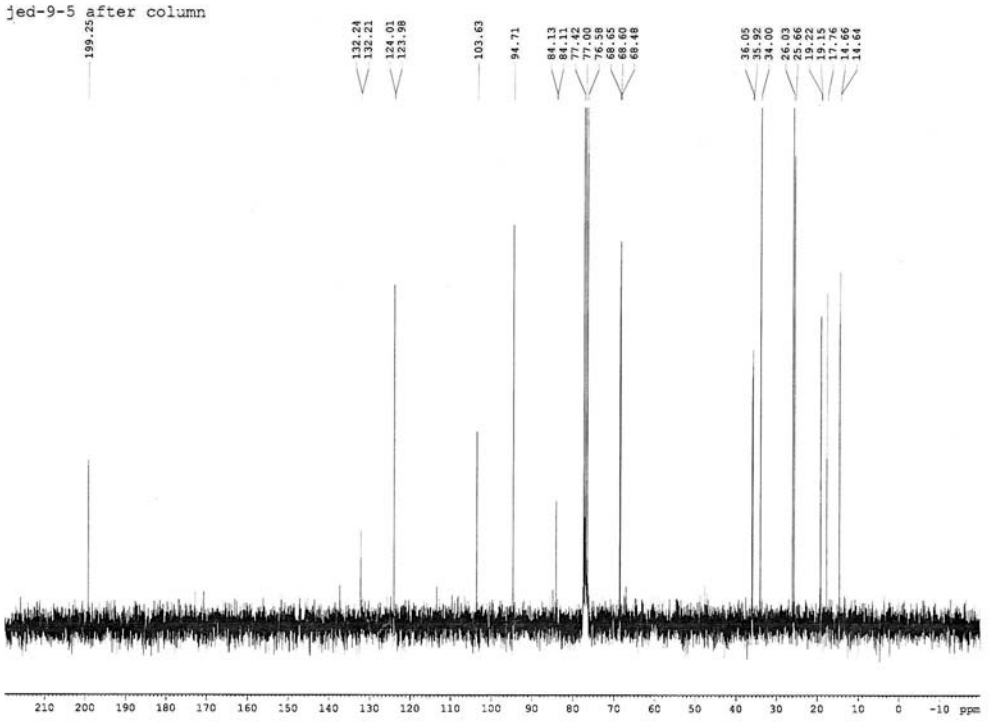

jed-7-172 allenyl acetate
TMS
AcO
170
5.3
5.2
5.1 ppm
1.000
1.903
9
8
7
6
5
4
3
2
1
ppm

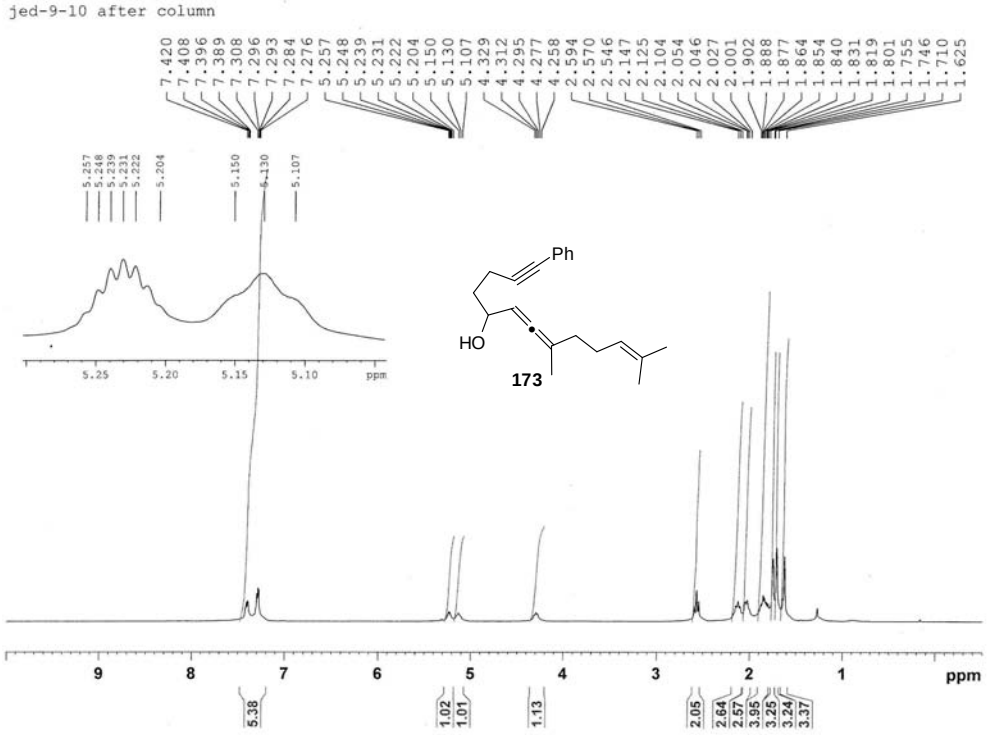

jed-7-172 allenyl acetate
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10 ppm

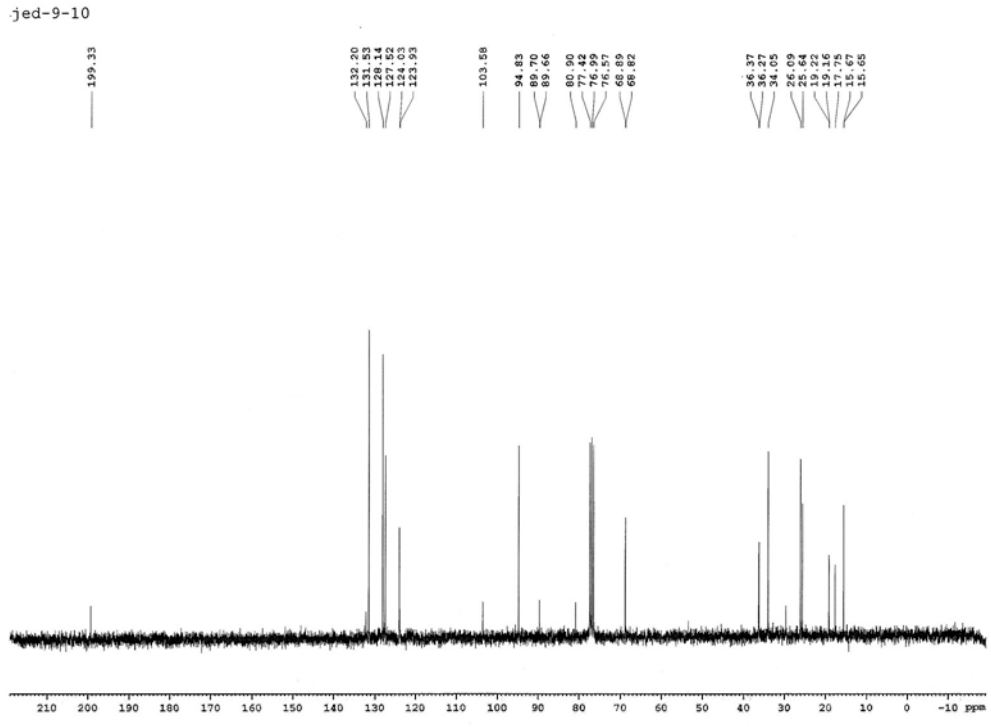

jed-7-187 pivolate allenyl ester
TMS
PivO
171
ppm


jed-7-187 pivolate allenyl ester
ppm

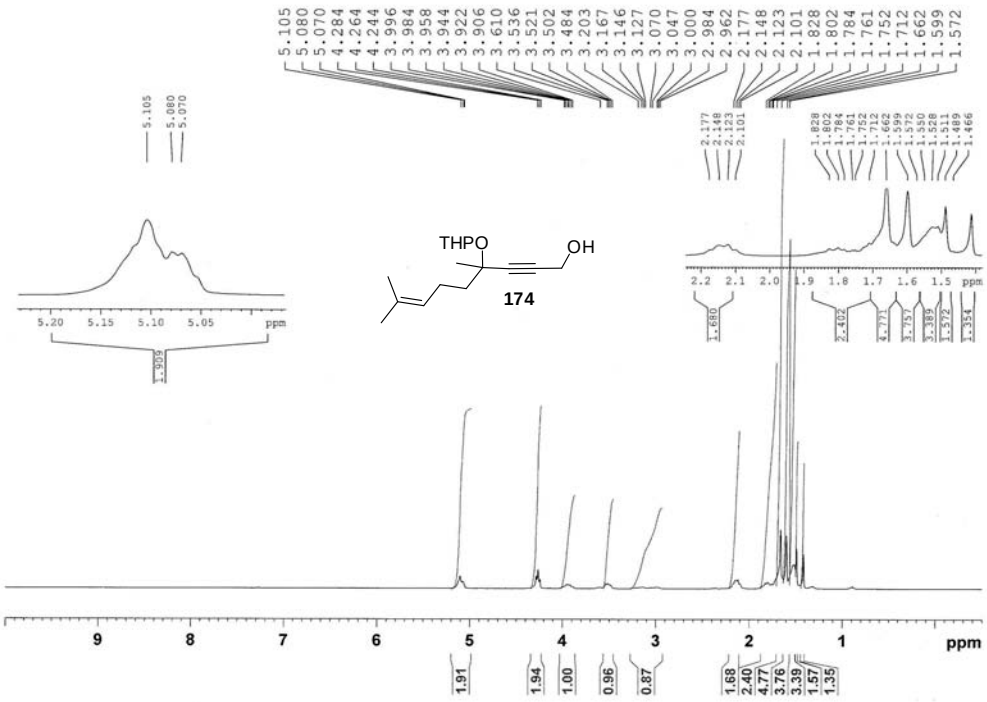

jed-9-5 after column
HO
172
ppm


jed-9-5 after column
ppm

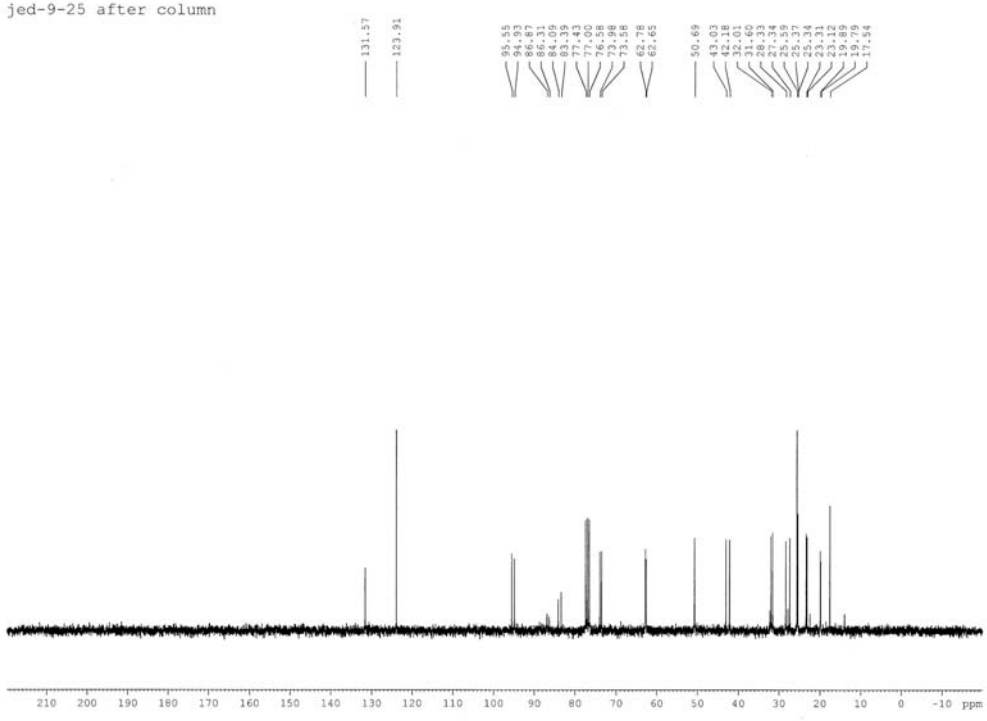

jed-9-10 after column
7.420
7.408
7.396
7.389
7.308
7.296
7.293
7.284
7.276
5.257
5.248
5.239
5.231
5.222
5.204
5.150
5.130
5.107
4.329
4.312
4.295
4.277
4.258
2.594
2.570
2.546
2.147
2.125
2.104
2.054
2.046
2.027
2.001
1.902
1.888
1.877
1.864
1.854
1.840
1.831
1.819
1.801
1.755
1.746
1.710
1.625
Ph
HO
173
ppm
5.38
1.02
1.01
1.13
2.05
2.64
2.57
3.95
3.25
3.24
3.37

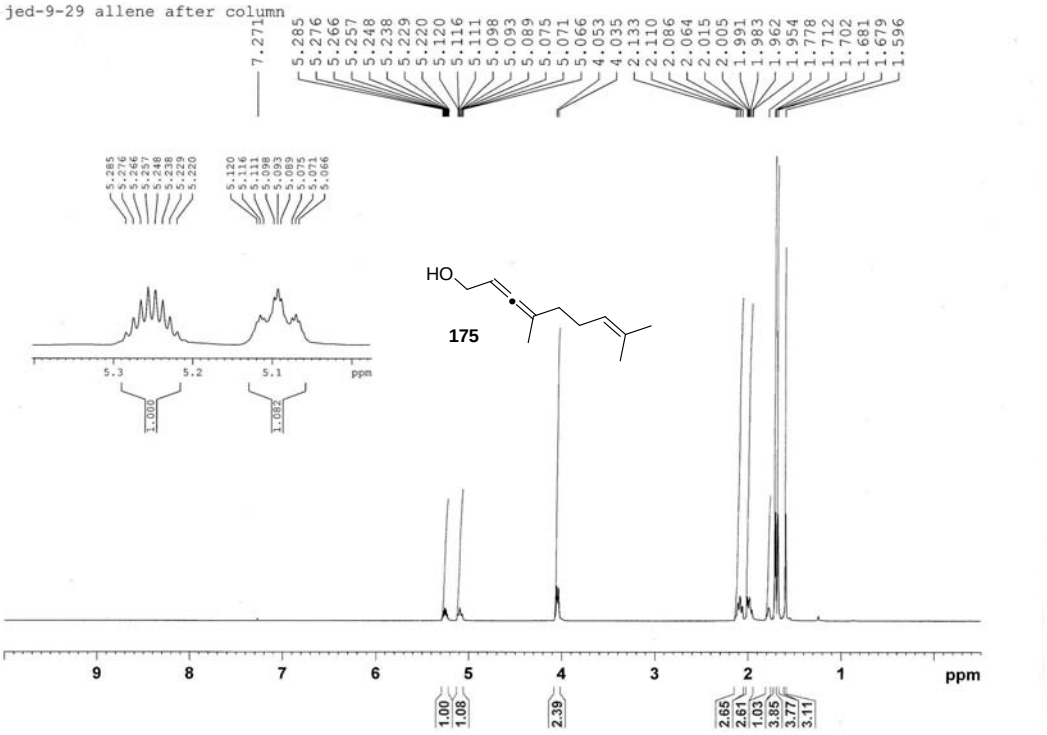

jed-9-10
199.33
132.20
131.53
128.14
127.52
124.03
123.93
103.58
94.83
89.70
89.66
80.90
77.42
76.99
76.57
68.89
68.82
36.37
36.27
34.05
26.09
25.64
19.22
19.16
17.75
15.67
15.65
ppm

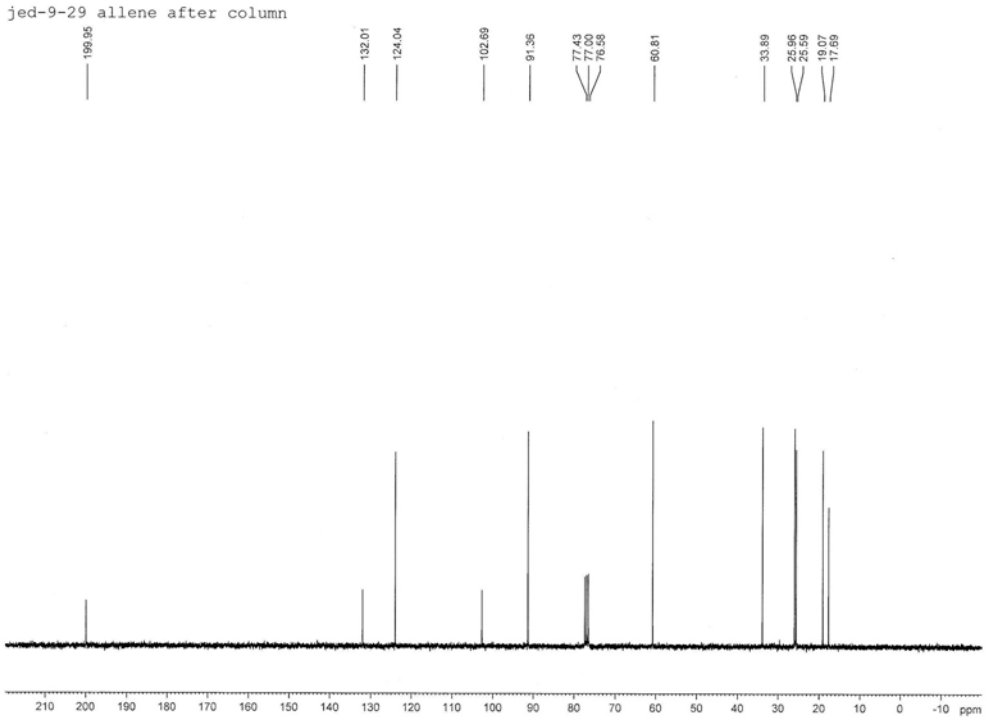
jed-9-25 after column

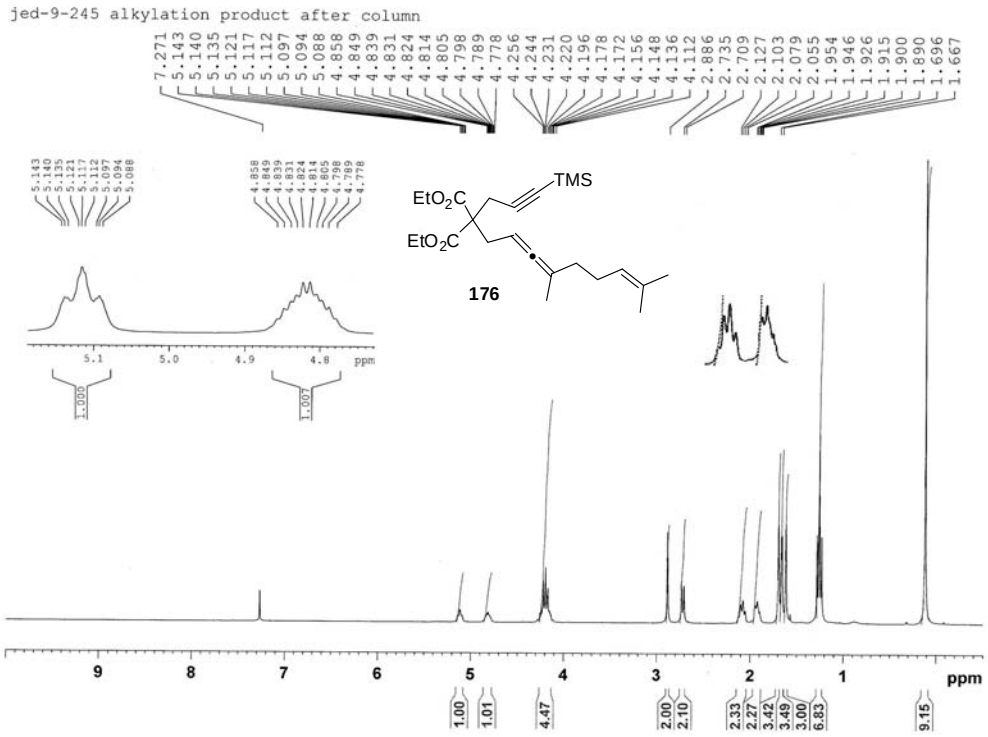


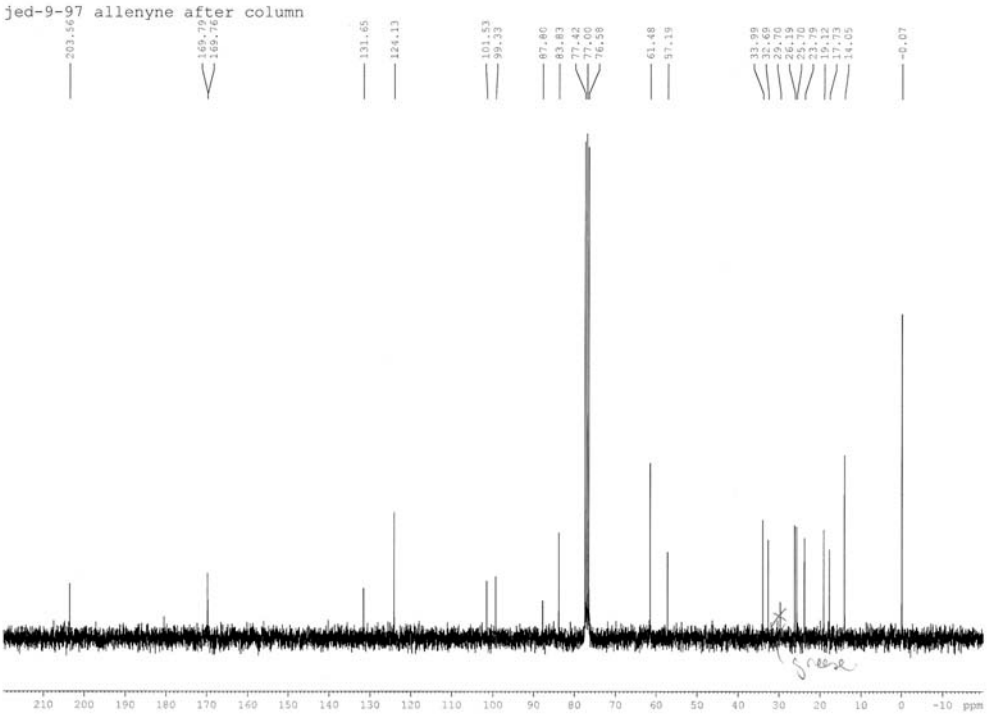
jed-9-25 after column

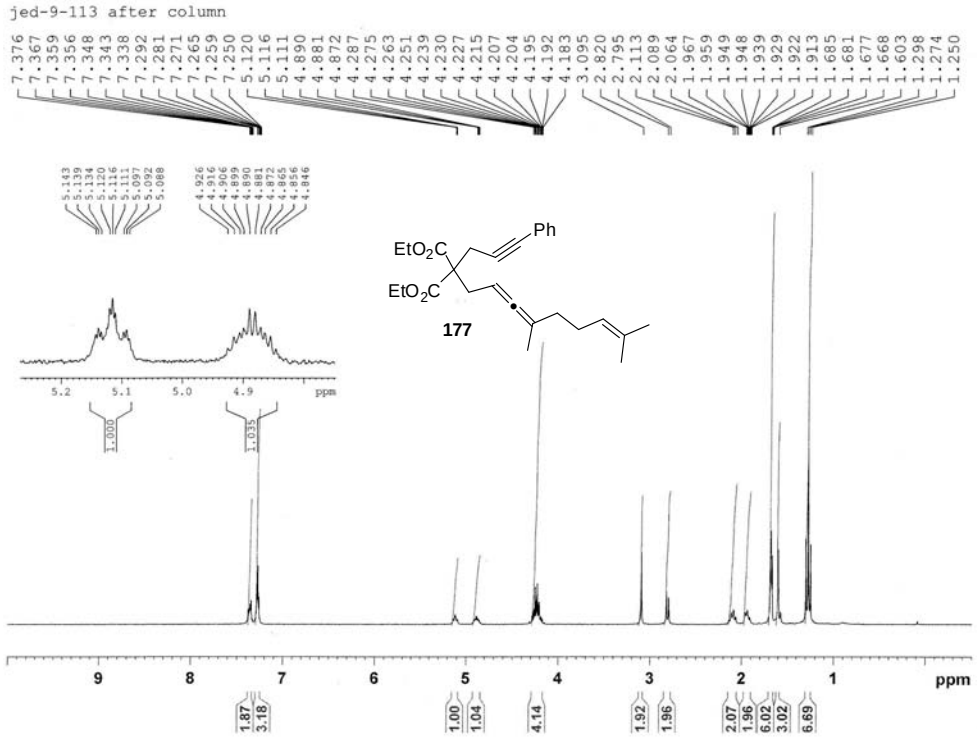


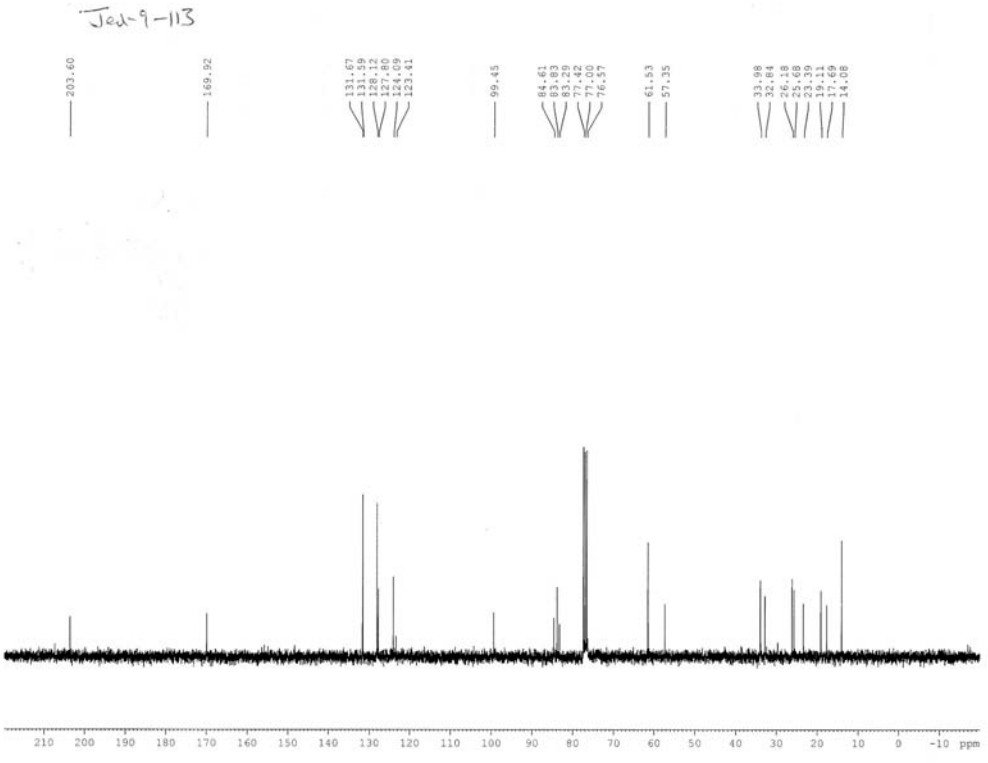

jed-9-29 allene after column
7.271
5.285
5.276
5.266
5.257
5.248
5.238
5.229
5.220
5.120
5.116
5.111
5.098
5.093
5.089
5.075
5.071
5.066
4.053
4.035
2.133
2.110
2.086
2.064
2.015
2.005
1.991
1.983
1.962
1.954
1.778
1.712
1.702
1.681
1.679
1.596
HO
175
5.3
5.2
5.1
ppm
1.000
1.082
9
8
7
6
5
4
3
2
1
ppm
1.00
1.08
2.39
2.65
2.61
1.03
3.85
3.77
3.11

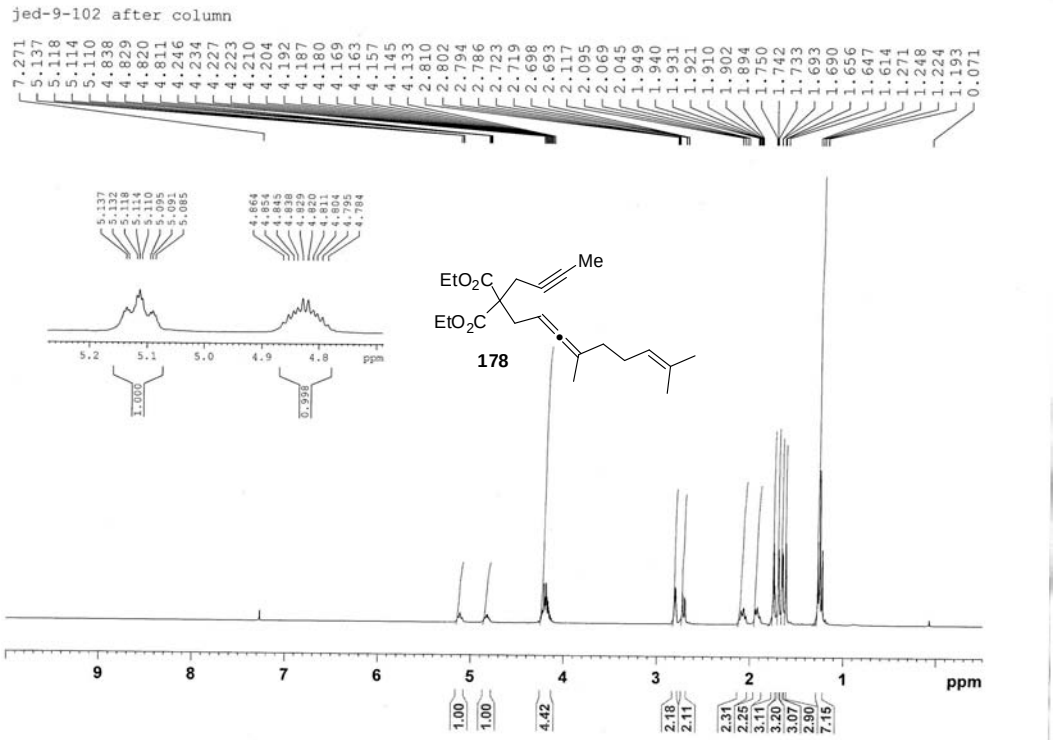

jed-9-29 allene after column
199.95
132.01
124.04
102.69
91.36
77.43
77.00
76.58
60.81
33.89
25.96
25.59
19.07
17.69
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

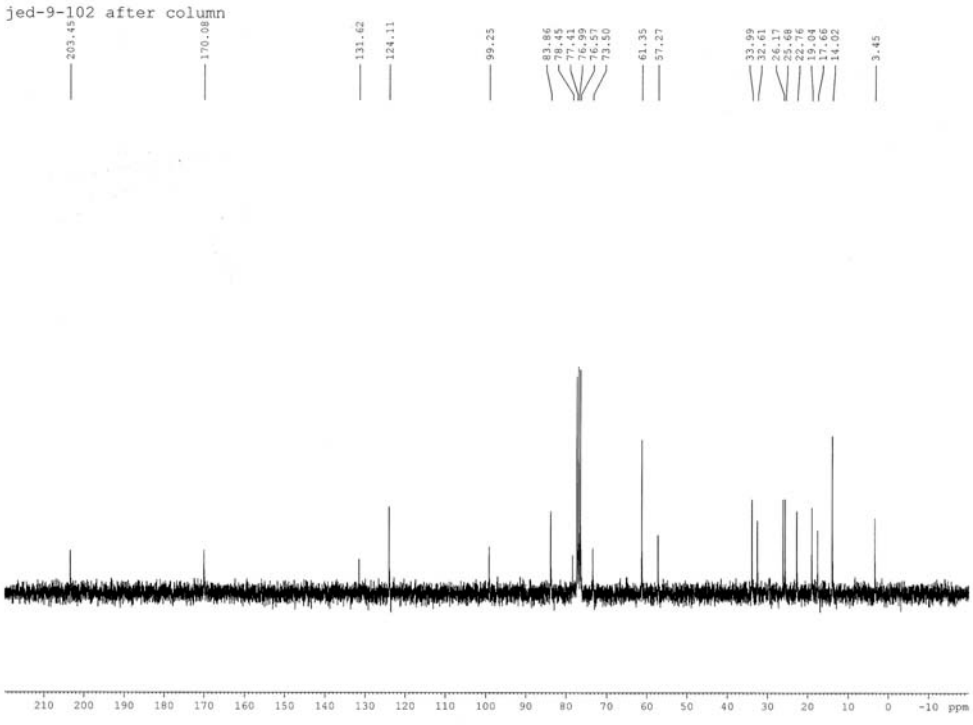

jed-9-245 alkylation product after column
7.271
5.143
5.140
5.135
5.121
5.117
5.112
5.097
5.094
5.088
4.858
4.849
4.839
4.831
4.824
4.814
4.805
4.798
4.789
4.778
4.256
4.244
4.231
4.220
4.196
4.178
4.172
4.156
4.148
4.136
4.112
2.886
2.735
2.709
2.127
2.103
2.079
2.055
1.954
1.946
1.926
1.915
1.900
1.890
1.696
1.667
TMS
EtO2C
EtO2C
176
5.1
5.0
4.9
4.8
ppm
1.000
1.007
9
8
7
6
5
4
3
2
1
ppm
1.00
1.01
4.47
2.00
2.10
2.33
2.27
3.42
3.49
3.00
6.83
9.15

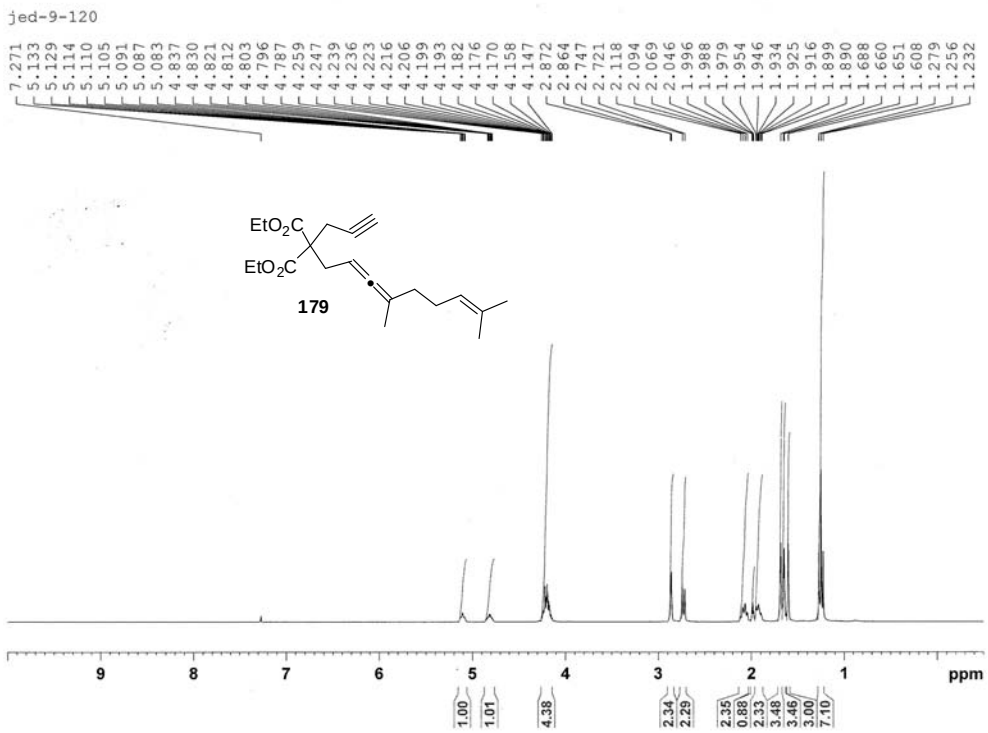

jed-9-97 allenyne after column
203.66
169.79
169.76
131.65
124.13
101.53
99.33
87.80
83.83
77.42
77.00
76.58
61.48
57.19
33.99
32.69
29.70
26.19
25.70
23.19
19.12
17.73
14.05
-0.07
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

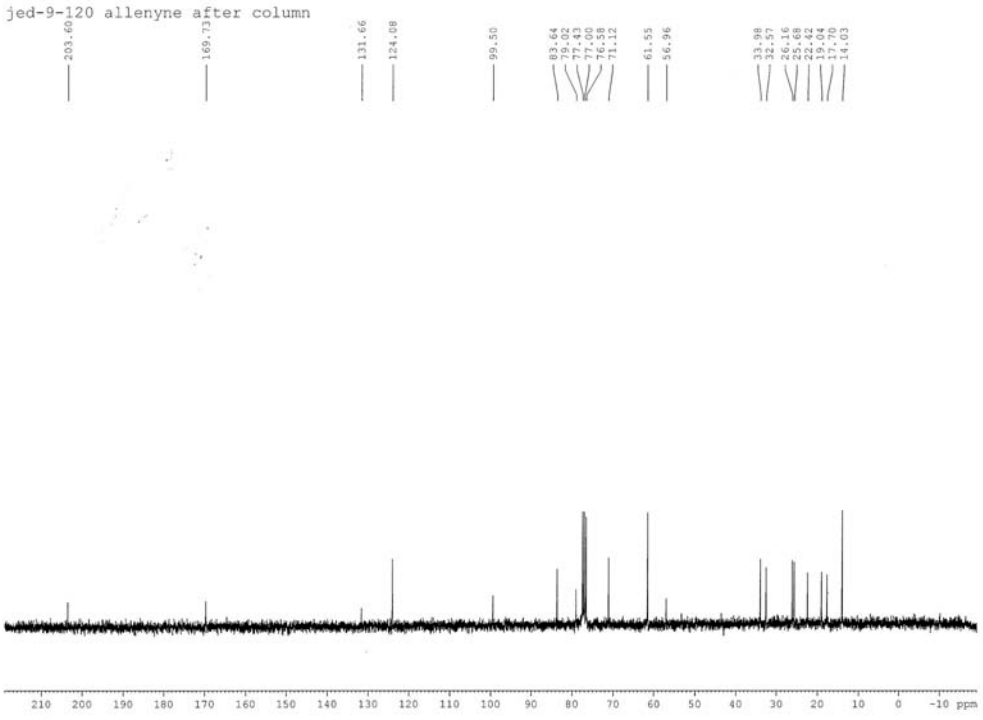

jed-9-113 after column
7.376
7.367
7.359
7.356
7.348
7.343
7.338
7.292
7.281
7.271
7.265
7.259
7.250
5.120
5.116
5.111
4.890
4.881
4.872
4.287
4.275
4.263
4.251
4.239
4.230
4.227
4.215
4.207
4.204
4.195
4.192
4.183
3.095
2.820
2.795
2.113
2.089
2.064
1.967
1.959
1.949
1.948
1.939
1.929
1.922
1.913
1.685
1.681
1.677
1.668
1.603
1.298
1.274
1.250
5.143
5.139
5.134
5.120
5.116
5.111
5.097
5.092
5.088
4.926
4.916
4.906
4.899
4.890
4.881
4.872
4.865
4.856
4.846
EtO2C
EtO2C
Ph
177
5.2
5.1
5.0
4.9
ppm
1.000
1.035
9
8
7
6
5
4
3
2
1
ppm
1.87
3.18
1.00
1.04
4.14
1.92
1.96
2.07
1.96
6.02
3.02
6.69

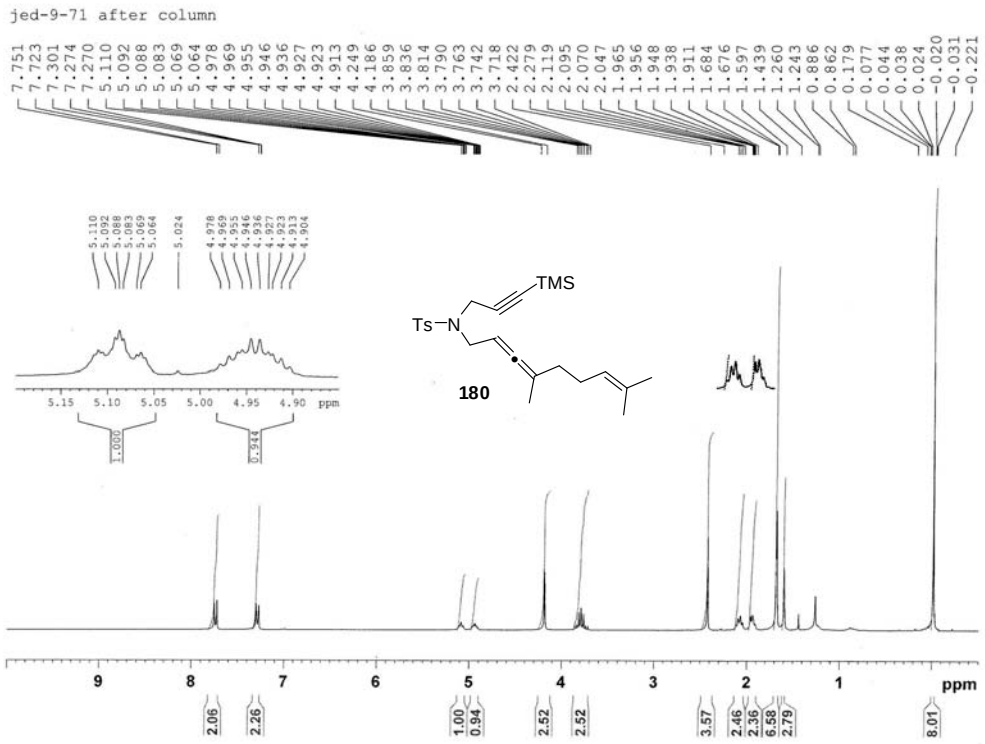

Jed-9-113
203.60
169.92
131.67
131.59
128.12
127.80
124.09
123.41
99.45
84.61
83.83
83.29
77.42
77.00
76.57
61.53
57.35
33.98
32.64
26.68
25.68
23.39
19.11
17.69
14.08
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10 ppm

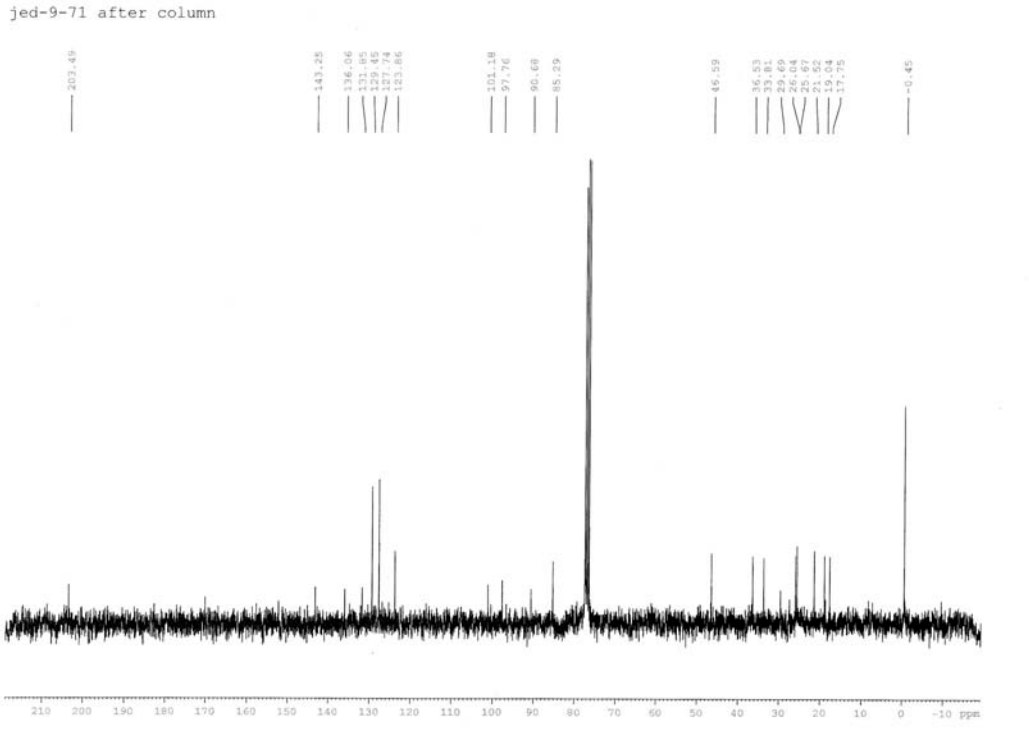

jed-9-102 after column
7.271
5.137
5.118
5.114
5.110
4.838
4.829
4.820
4.811
4.246
4.234
4.227
4.223
4.210
4.204
4.192
4.187
4.180
4.169
4.163
4.157
4.145
4.133
2.810
2.802
2.794
2.786
2.723
2.719
2.698
2.693
2.117
2.095
2.069
2.045
1.949
1.940
1.931
1.921
1.910
1.902
1.894
1.750
1.742
1.733
1.693
1.690
1.656
1.647
1.614
1.271
1.248
1.224
1.193
0.071
Me
EtO2C
EtO2C
178
ppm
1.00
1.00
4.42
2.18
2.11
2.31
2.25
3.11
3.20
3.07
2.90
7.15

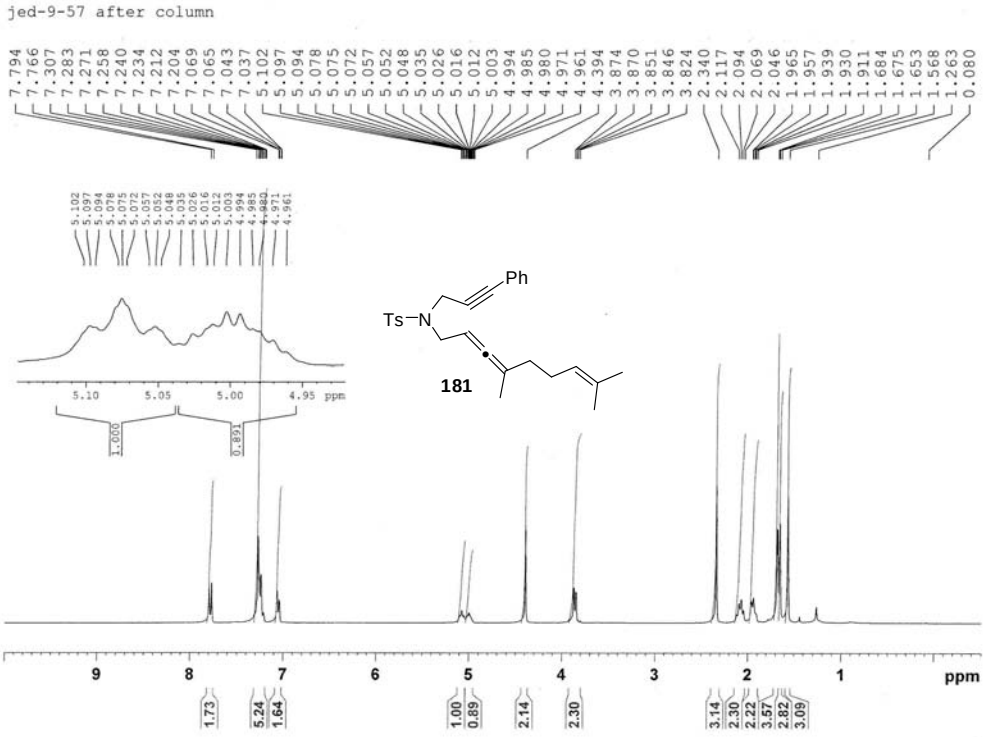

jed-9-102 after column
203.45
170.08
131.62
124.11
99.25
83.86
78.45
77.41
76.99
76.57
73.50
61.35
57.27
33.99
32.61
26.17
25.68
22.76
21.04
17.66
14.02
-5.45
ppm

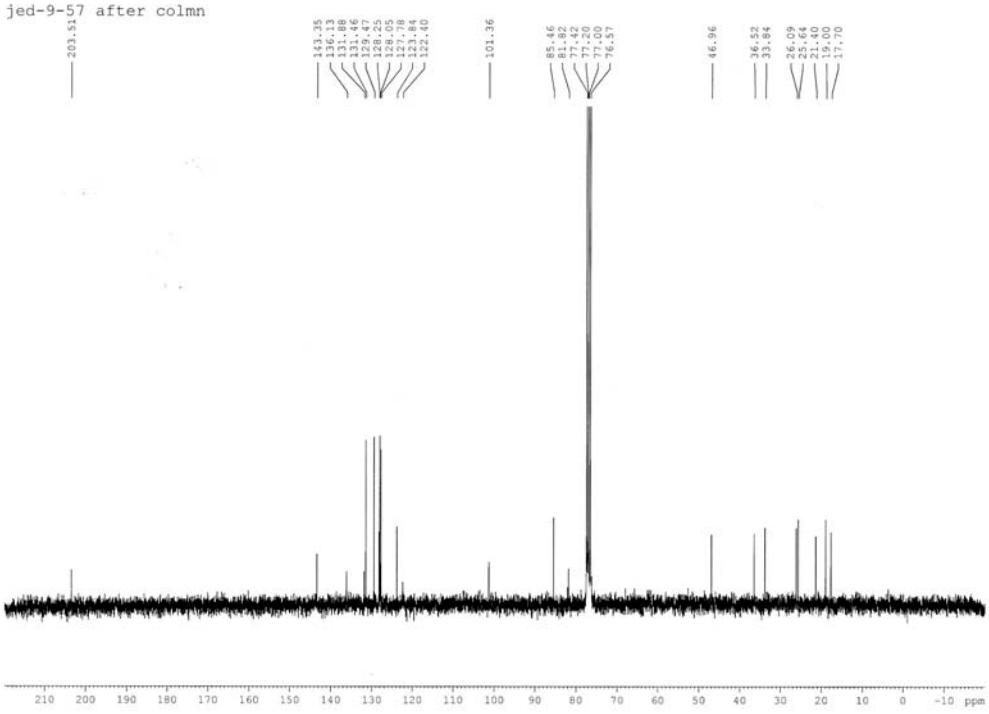

jed-9-120
7.271
5.133
5.129
5.114
5.110
5.105
5.091
5.087
5.083
4.837
4.830
4.821
4.812
4.803
4.796
4.787
4.259
4.247
4.239
4.236
4.223
4.216
4.206
4.199
4.193
4.182
4.176
4.170
4.158
4.147
2.872
2.864
2.747
2.721
2.118
2.094
2.069
2.046
1.996
1.988
1.979
1.954
1.946
1.934
1.925
1.916
1.899
1.890
1.688
1.660
1.651
1.608
1.279
1.256
1.232
EtO2C
EtO2C
179
9
8
7
6
5
4
3
2
1
ppm
1.00
1.01
4.38
2.34
2.29
2.35
0.88
2.33
3.48
3.46
3.00
7.10


jed-9-120 allenyne after column
203.60
169.73
131.66
124.08
99.50
83.64
79.02
77.43
77.00
76.58
71.12
61.55
56.96
33.98
32.57
26.16
25.68
22.49
19.04
17.70
14.03
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10 ppm

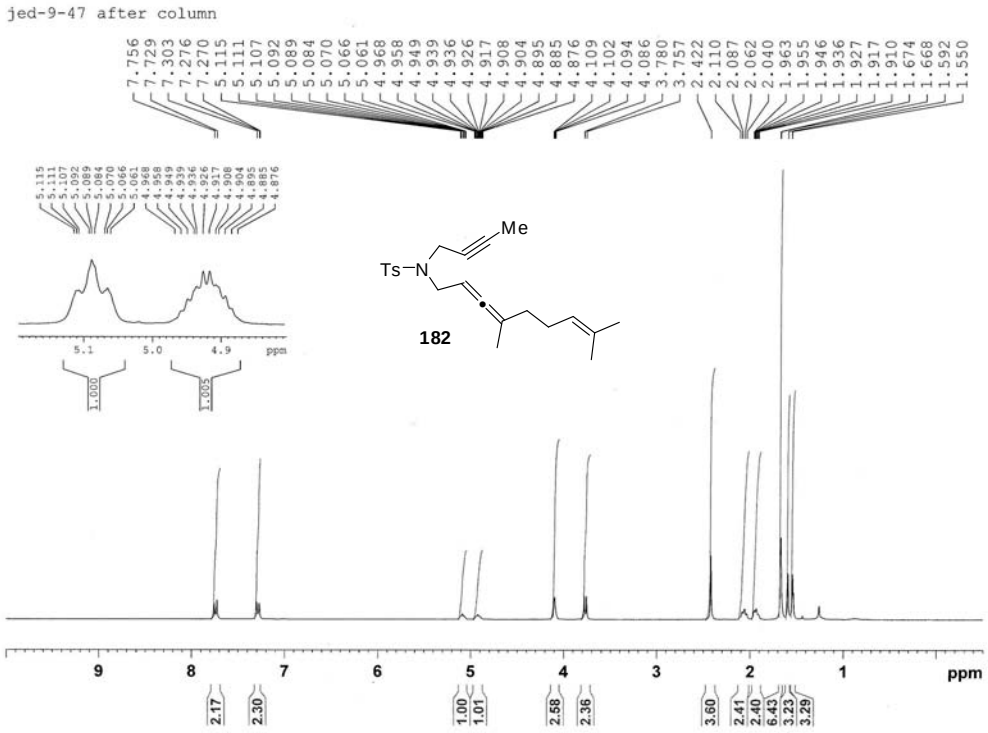

jed-9-71 after column
TMS
Ts–N
180
ppm


jed-9-71 after column
ppm

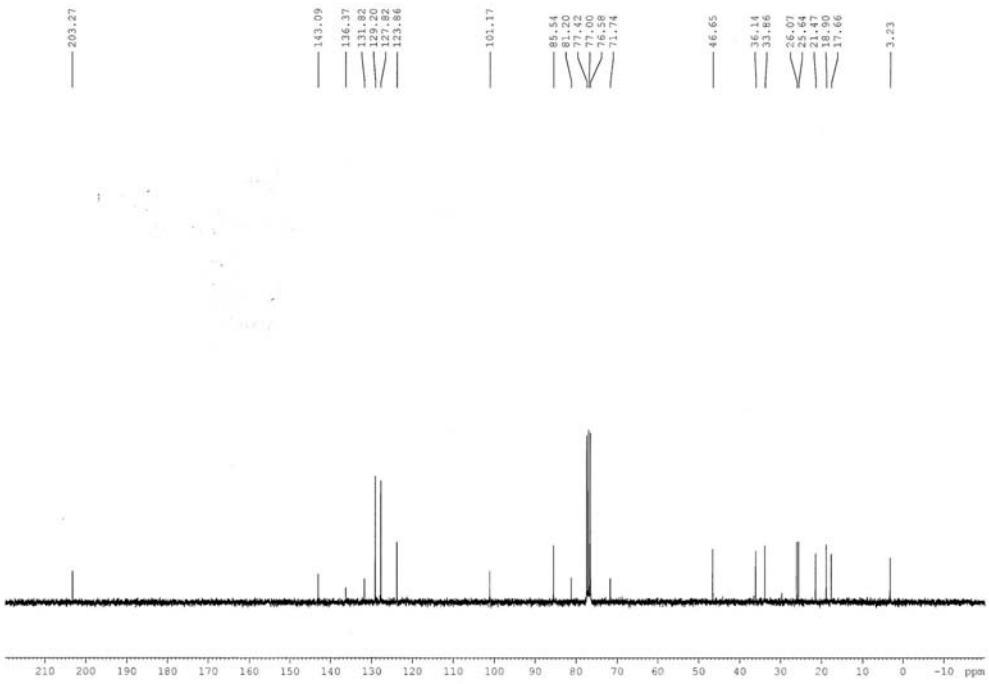

jed-9-57 after column
Ph
Ts–N
181
ppm

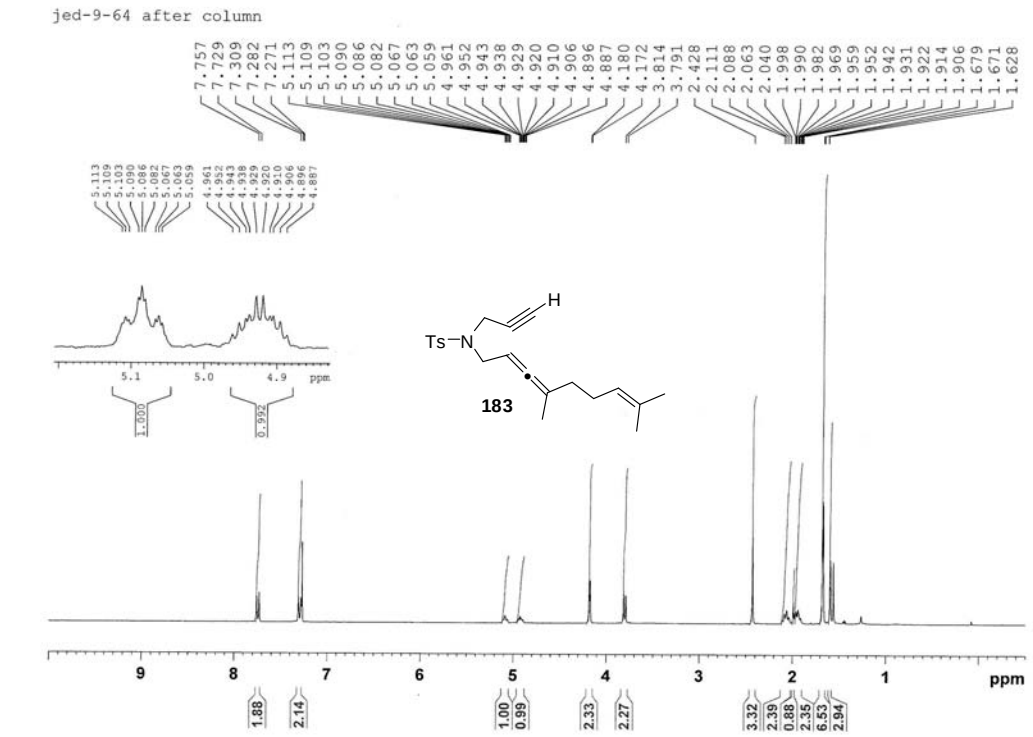

jed-9-57 after colmn
ppm

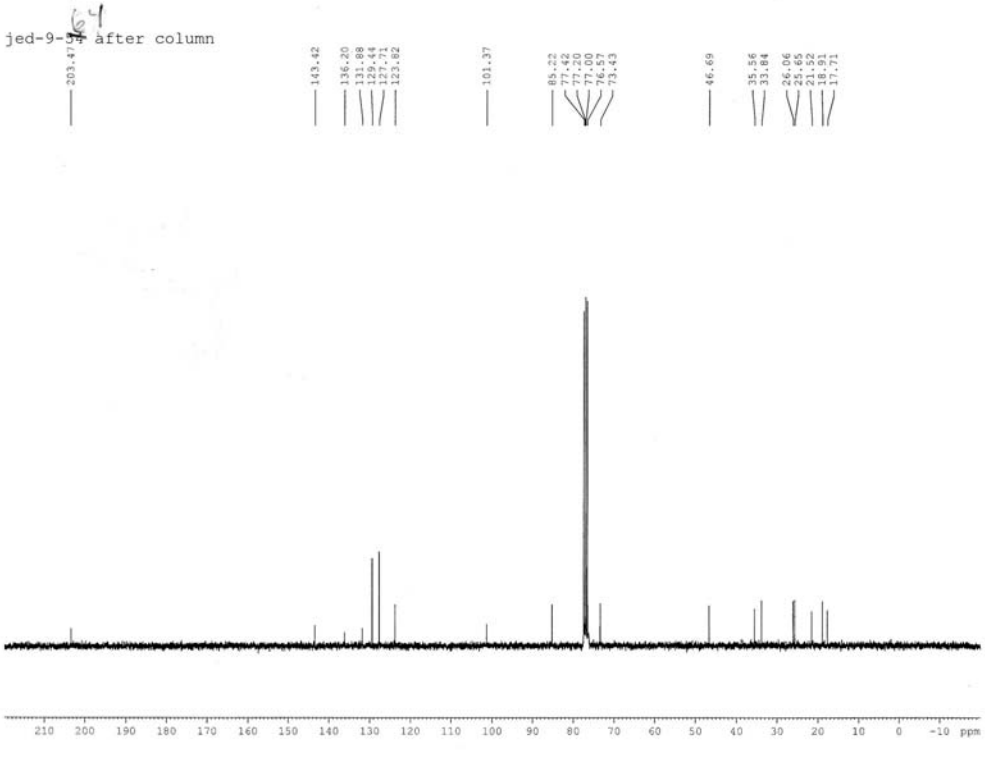
jed-9-47 after column

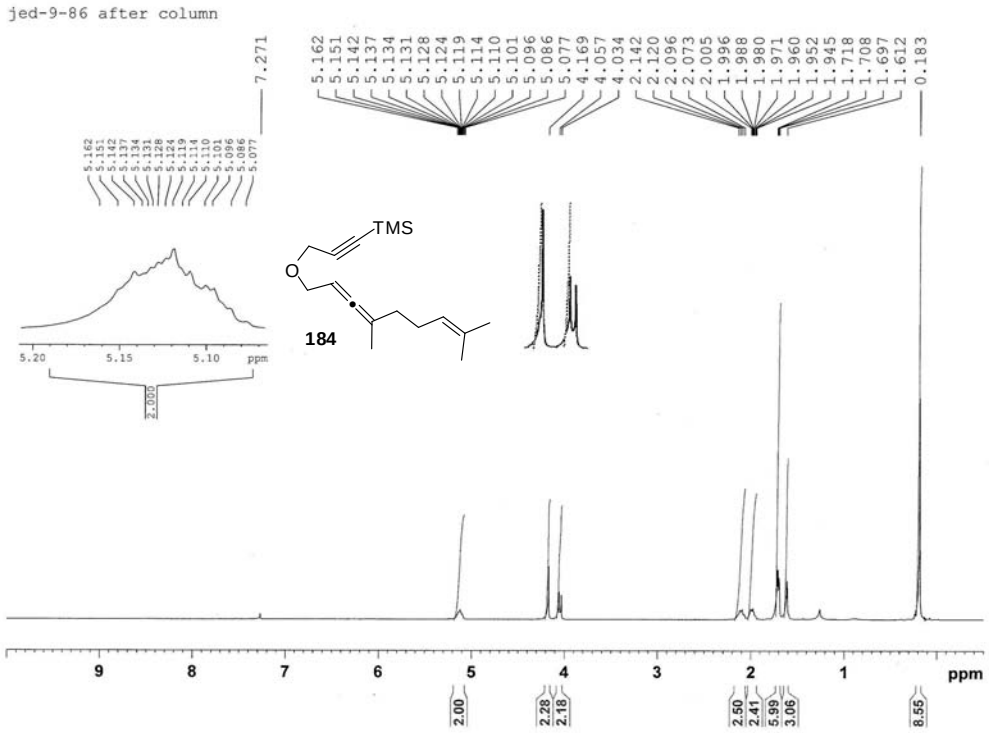


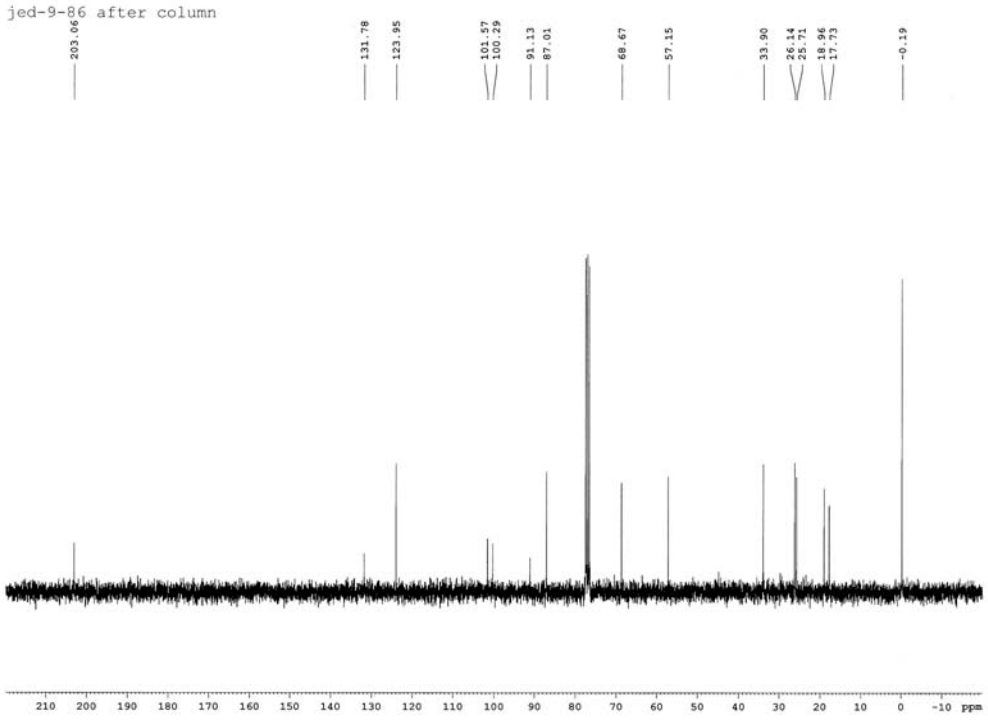
jed-9-~~57~~ 47 after column

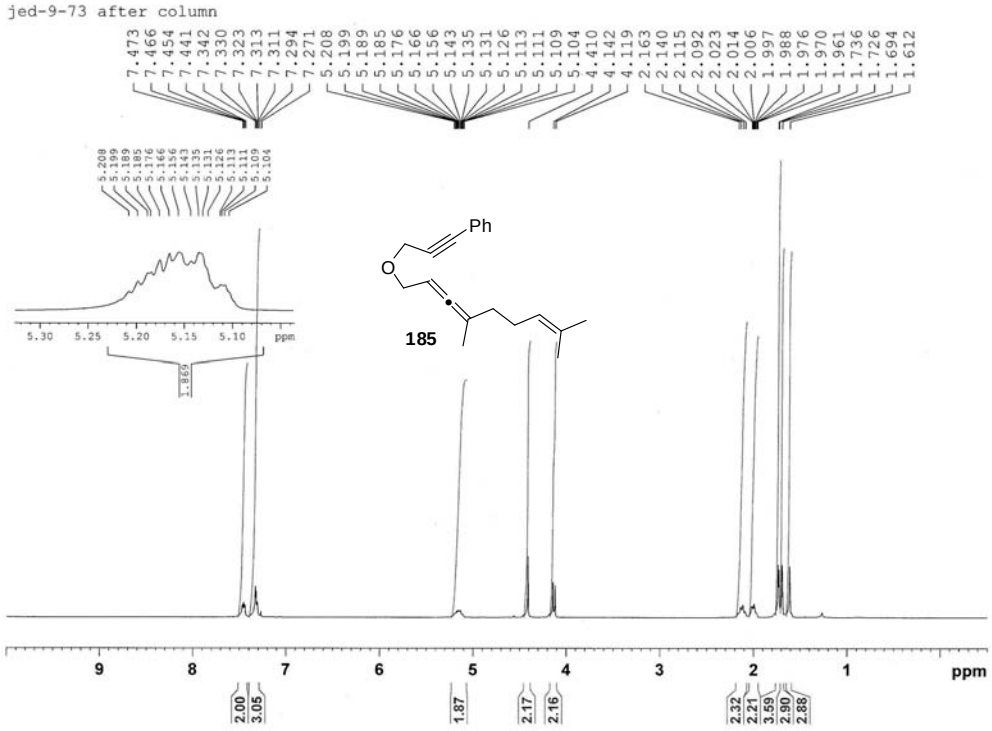


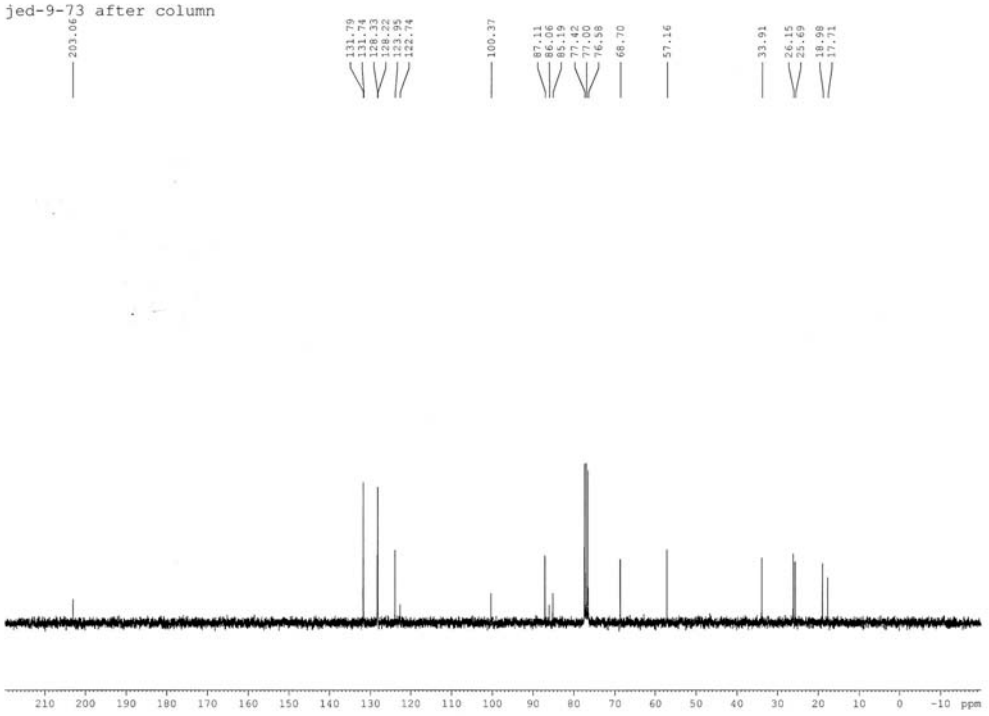

jed-9-64 after column
7.757
7.729
7.309
7.282
7.271
5.113
5.109
5.103
5.090
5.086
5.082
5.067
5.063
5.059
4.961
4.952
4.943
4.938
4.929
4.920
4.910
4.906
4.896
4.887
4.180
4.172
3.814
3.791
2.428
2.111
2.088
2.063
2.040
1.998
1.990
1.982
1.969
1.959
1.952
1.942
1.931
1.922
1.914
1.906
1.679
1.671
1.628
5.1
5.0
4.9
ppm
1.000
0.992
Ts
N
H
183
9
8
7
6
5
4
3
2
1
ppm
1.88
2.14
1.00
0.99
2.33
2.27
3.32
2.39
0.88
2.35
6.53
2.94

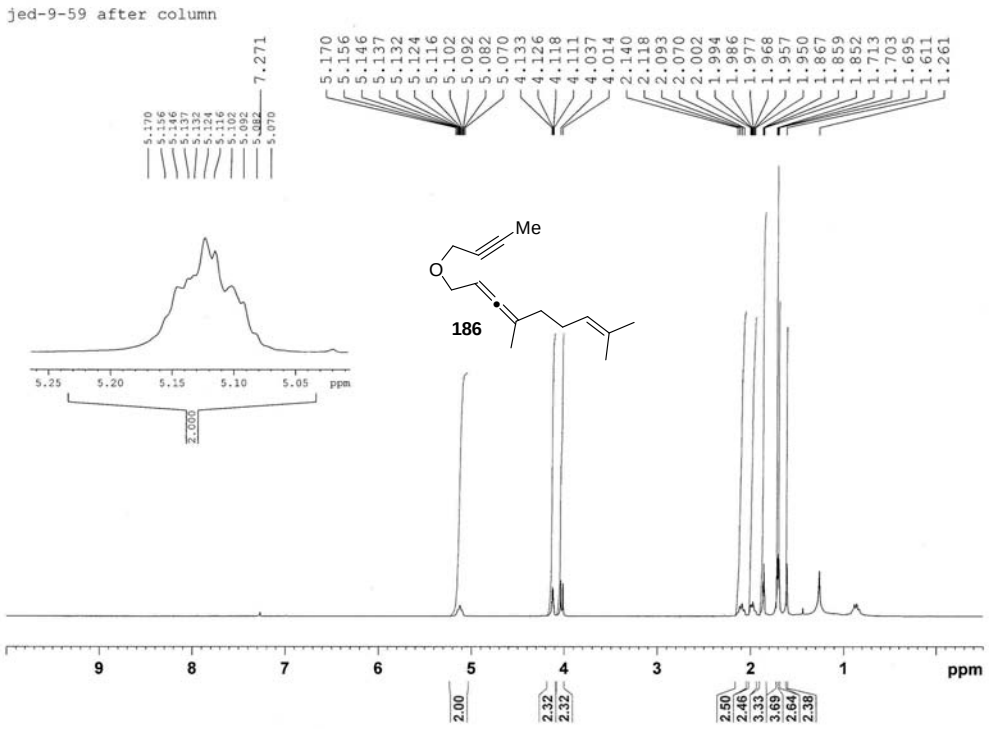

jed-9-64 after column
203.47
143.42
136.20
131.88
129.44
127.71
123.62
101.37
85.22
77.42
77.20
77.00
76.57
73.43
46.69
35.56
33.84
26.06
25.65
21.52
18.91
17.71
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

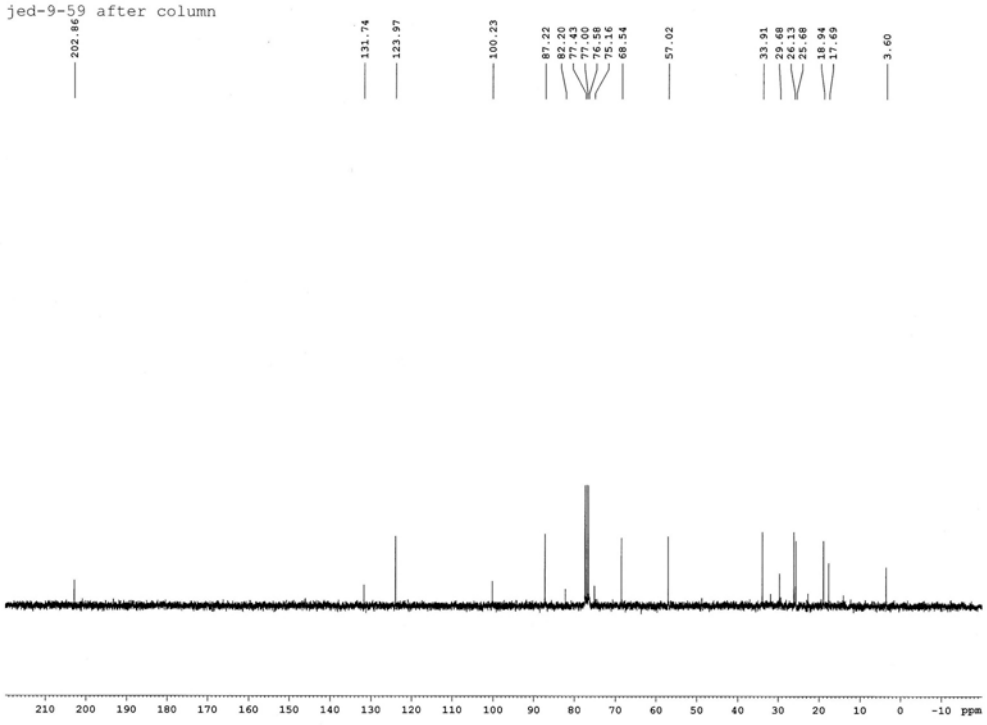

jed-9-86 after column
TMS
O
184
ppm

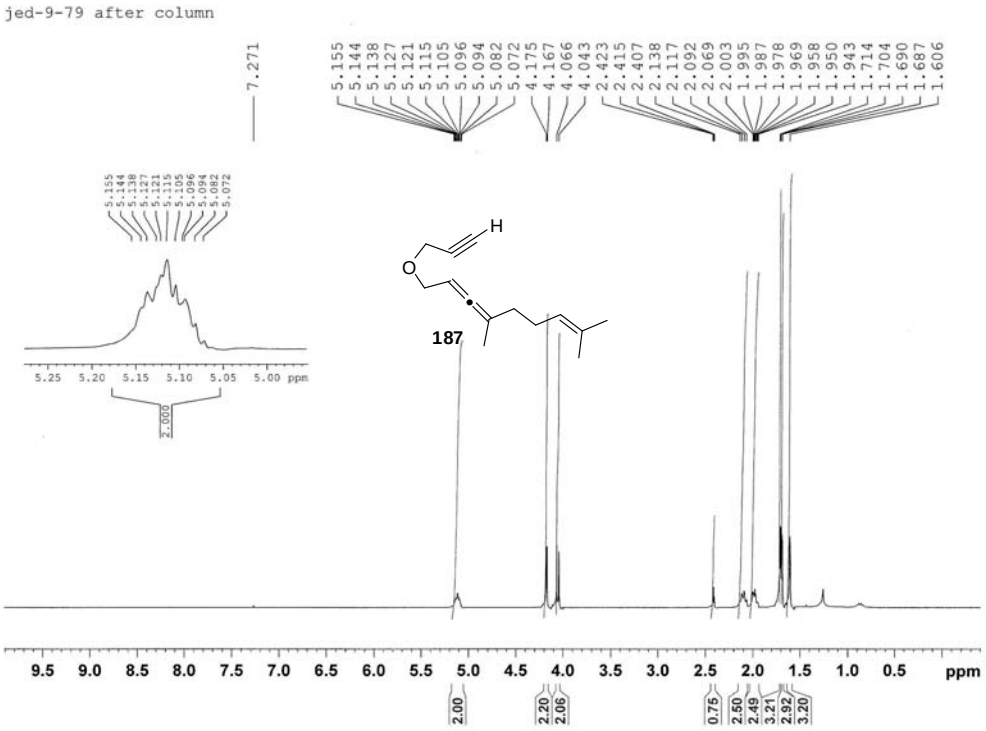

jed-9-86 after column
ppm

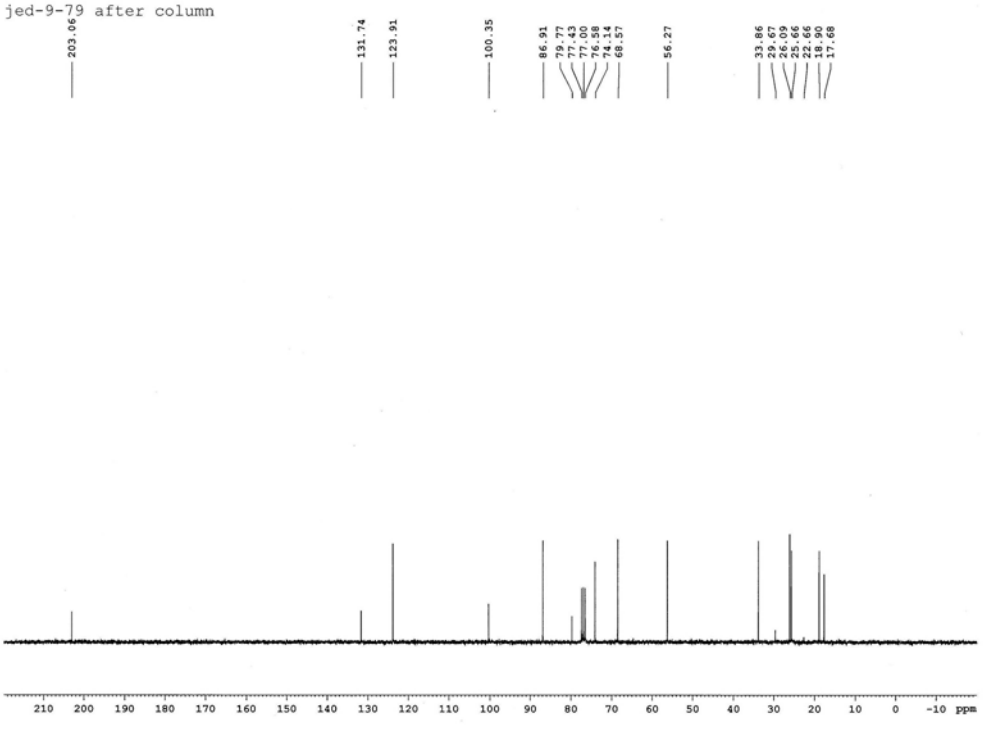

jed-9-73 after column
Ph
O
185
ppm
2.00
3.05
1.87
2.17
2.16
2.32
2.21
3.59
2.90
2.88

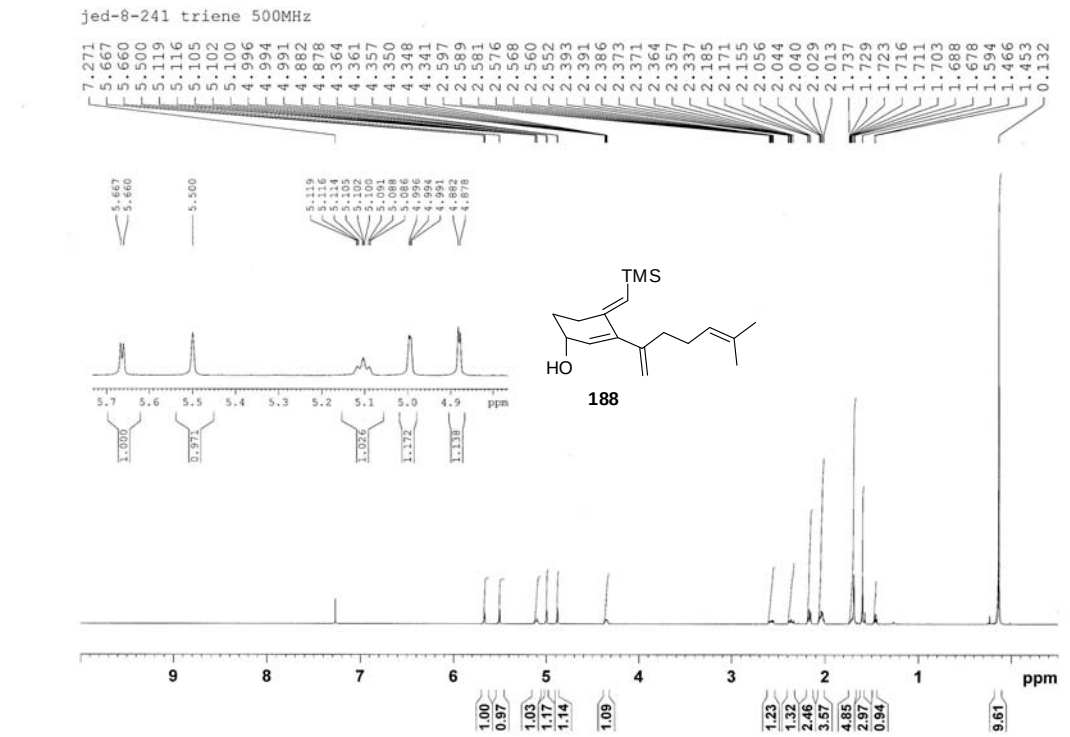

jed-9-73 after column
ppm

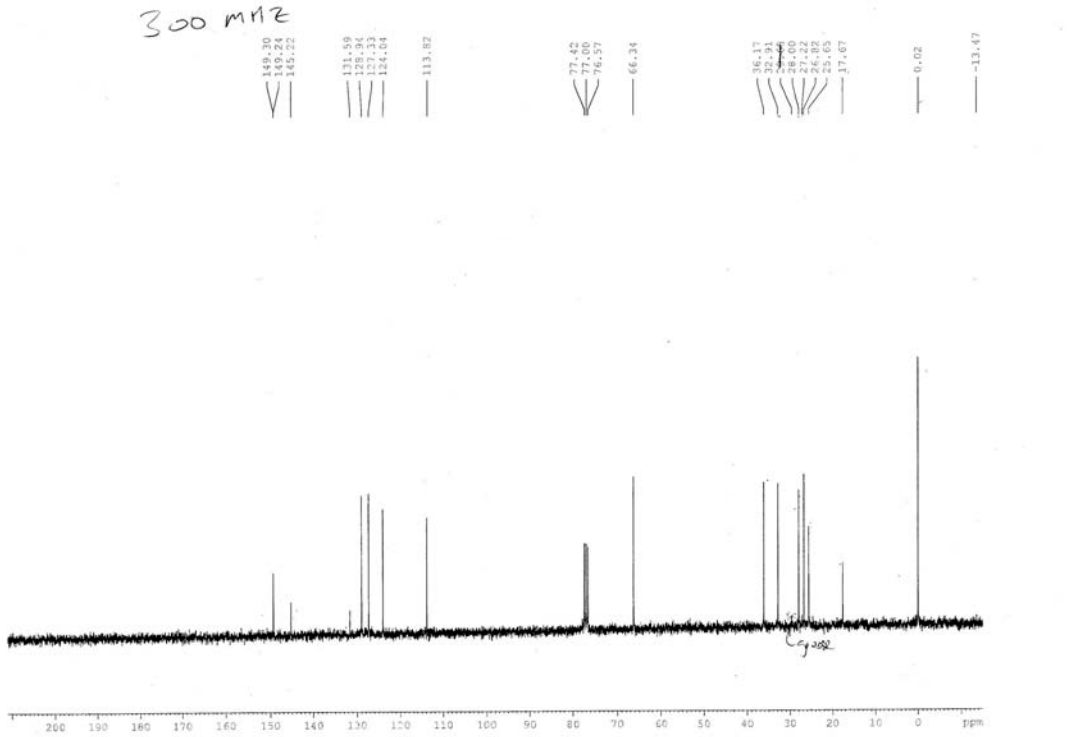

jed-9-59 after column
Me
O
186
ppm
2.00
2.32
2.32
2.50
2.46
3.33
3.69
2.64
2.38

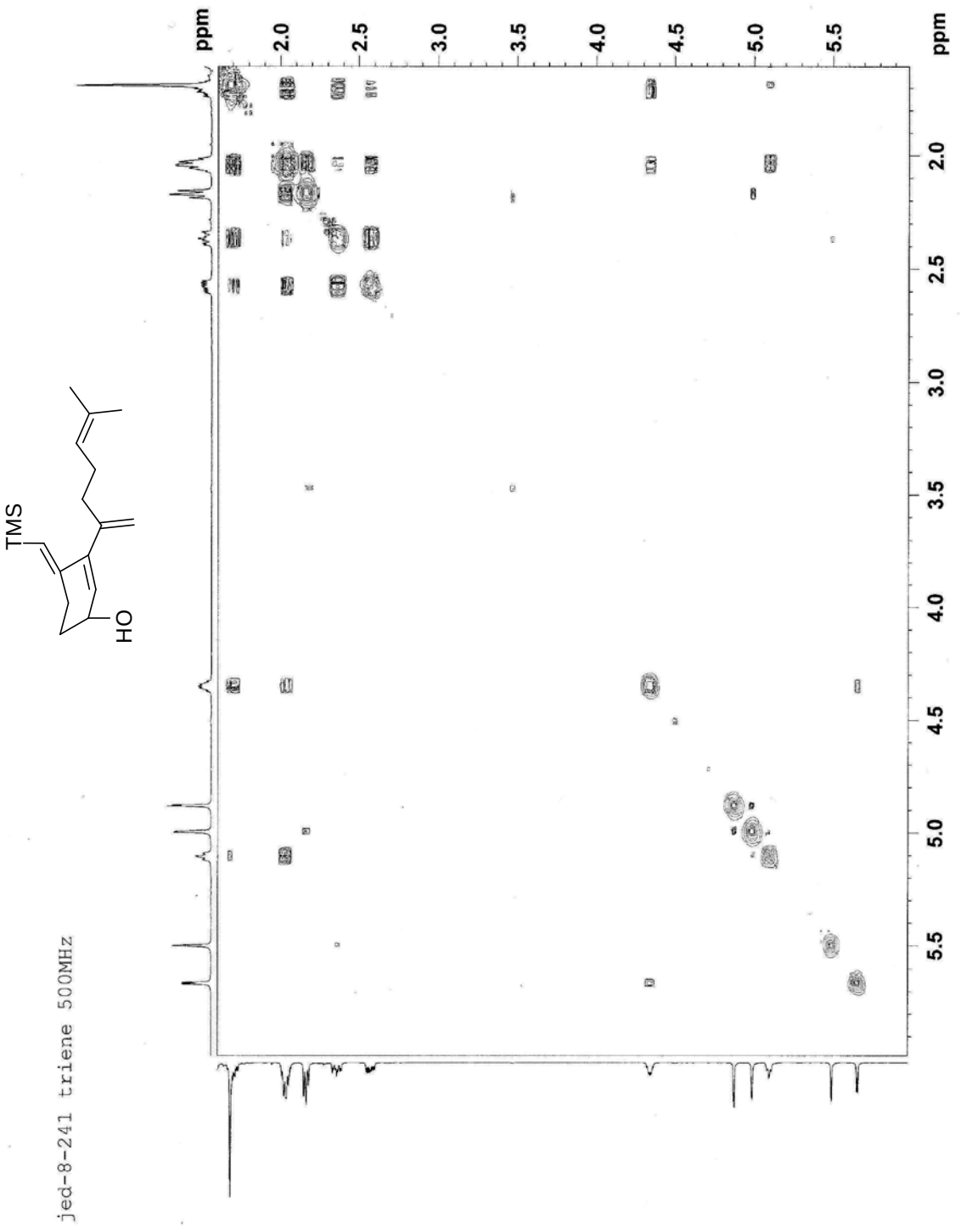

jed-9-59 after column
ppm

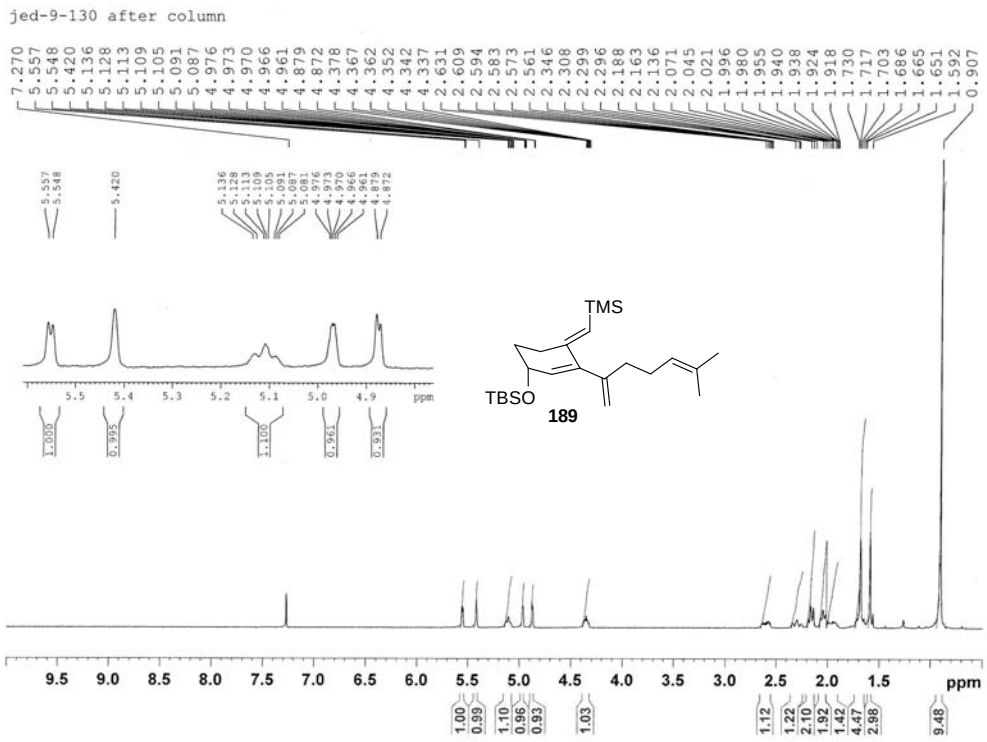

jed-9-79 after column
7.271
5.155
5.144
5.138
5.127
5.121
5.115
5.105
5.096
5.094
5.082
5.072
4.175
4.167
4.066
4.043
2.423
2.415
2.407
2.138
2.117
2.092
2.069
2.003
1.995
1.987
1.978
1.969
1.958
1.950
1.943
1.714
1.704
1.690
1.687
1.606
H
O
187
5.25 5.20 5.15 5.10 5.05 5.00 ppm
2.000
9.5 9.0 8.5 8.0 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 ppm
2.00
2.20
2.06
0.75
2.50
2.49
3.21
2.92
3.20

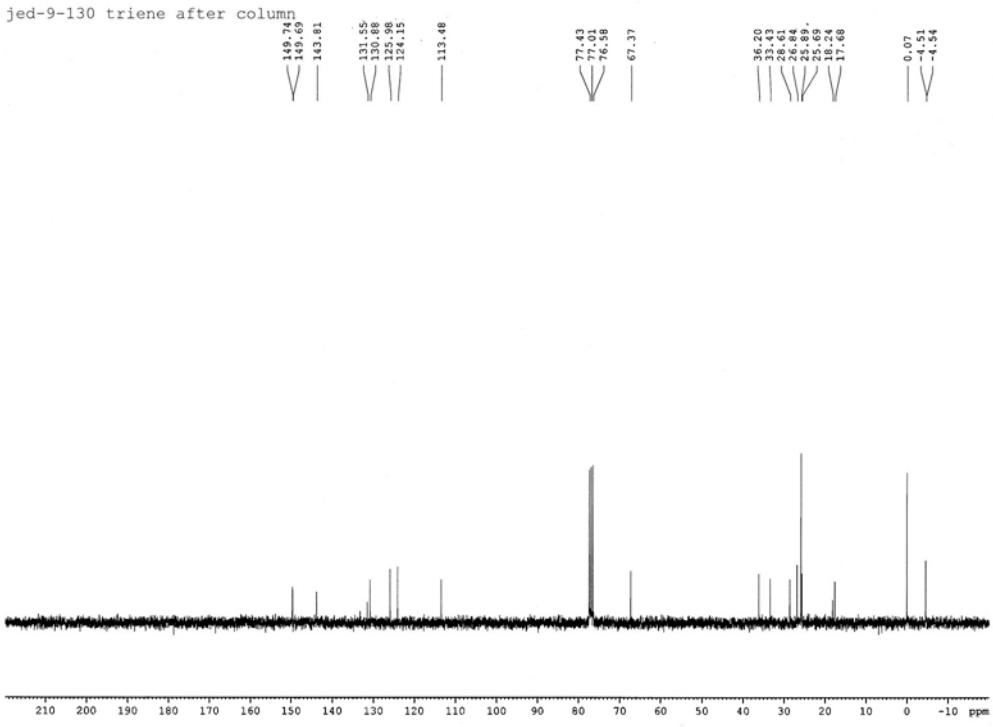

jed-9-79 after column
203.06
131.74
123.91
100.35
86.91
79.77
77.43
77.00
76.58
74.14
68.57
56.27
33.86
29.67
26.09
25.66
22.66
18.90
17.68
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

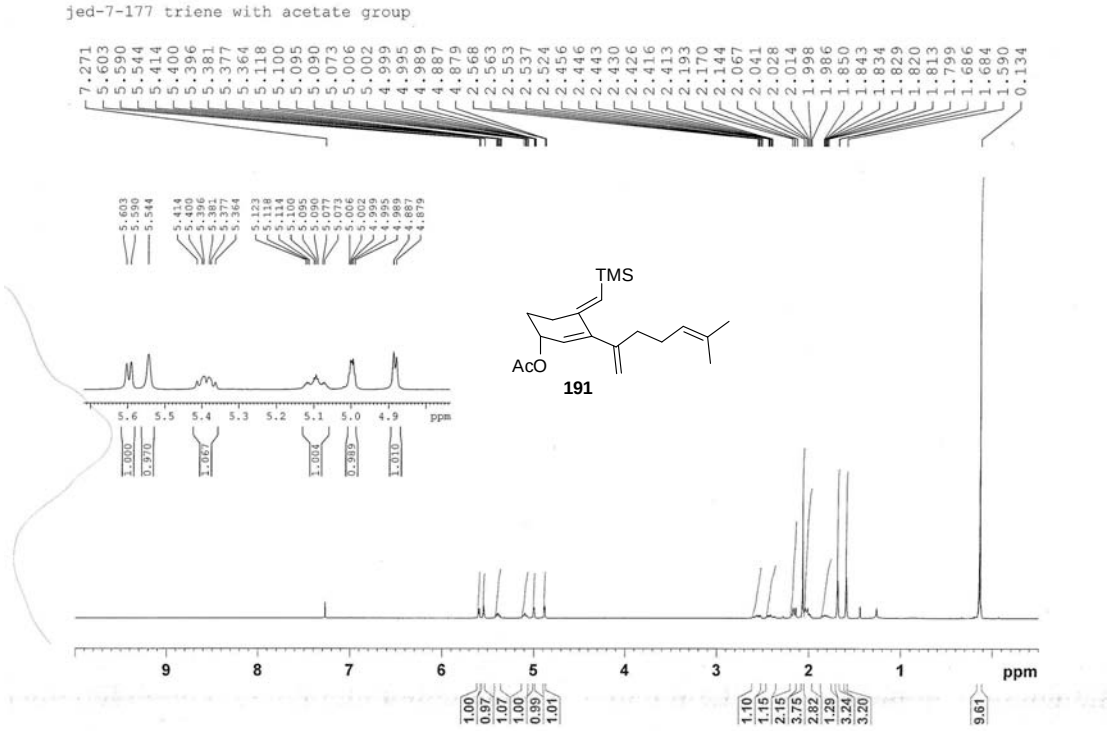

jed-8-241 triene 500MHz
TMS
HO
188
ppm

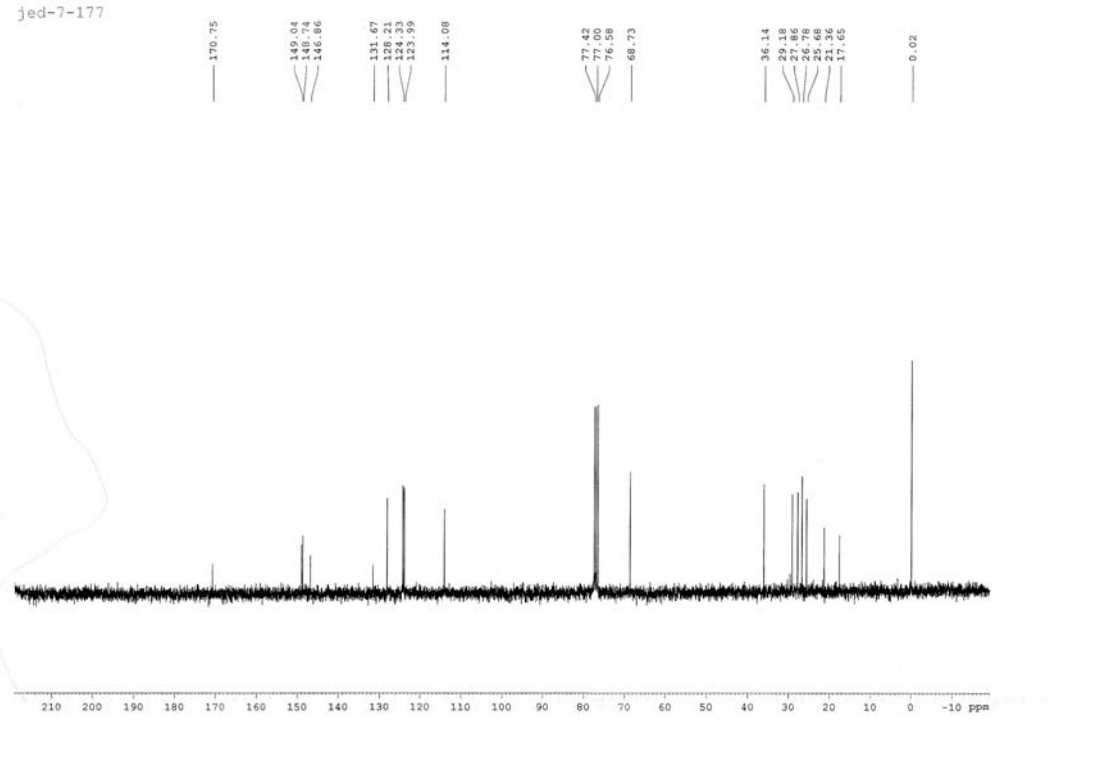

300 MHz
ppm


TMS
HO
ppm
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
jed-8-241 triene 500MHz

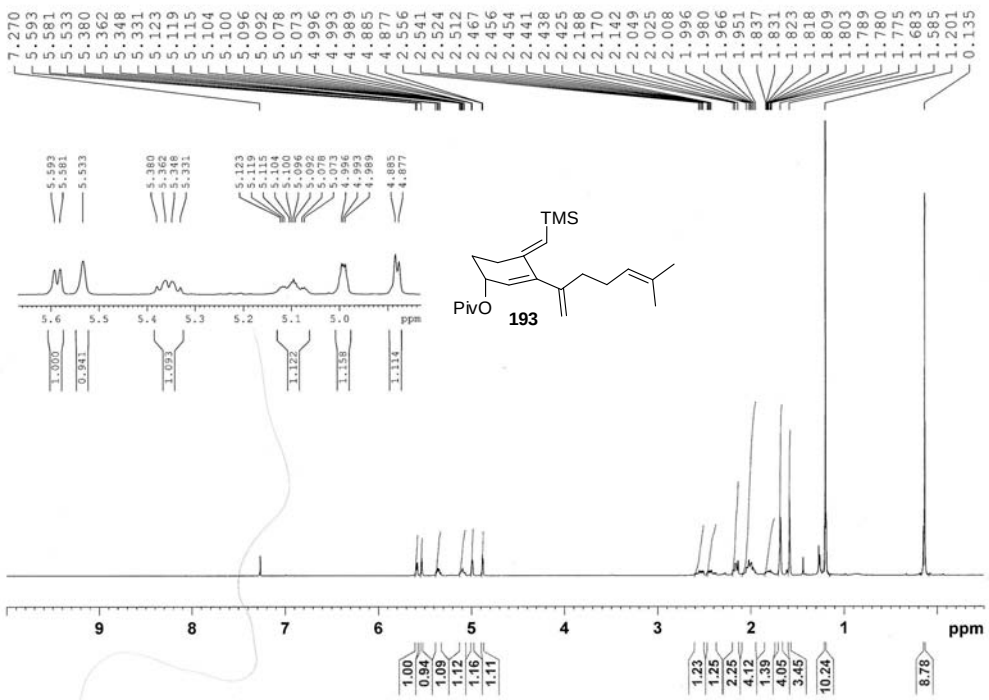

jed-9-130 after column
TMS
TBSO
189
ppm


jed-9-130 triene after column
ppm

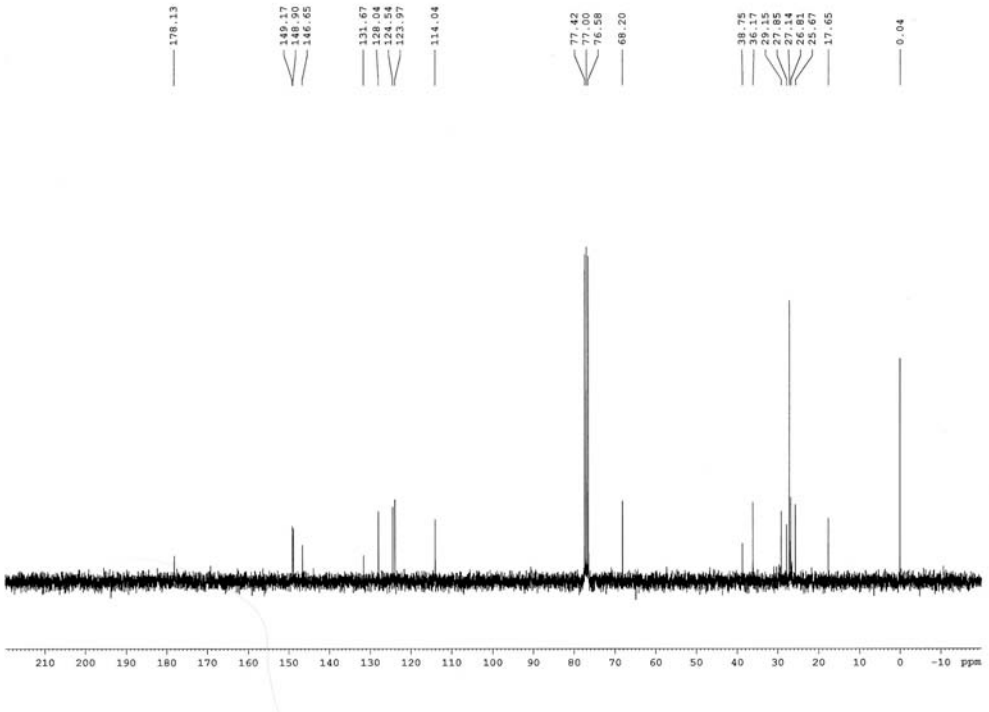

jed-7-177 triene with acetate group
TMS
AcO
191
ppm

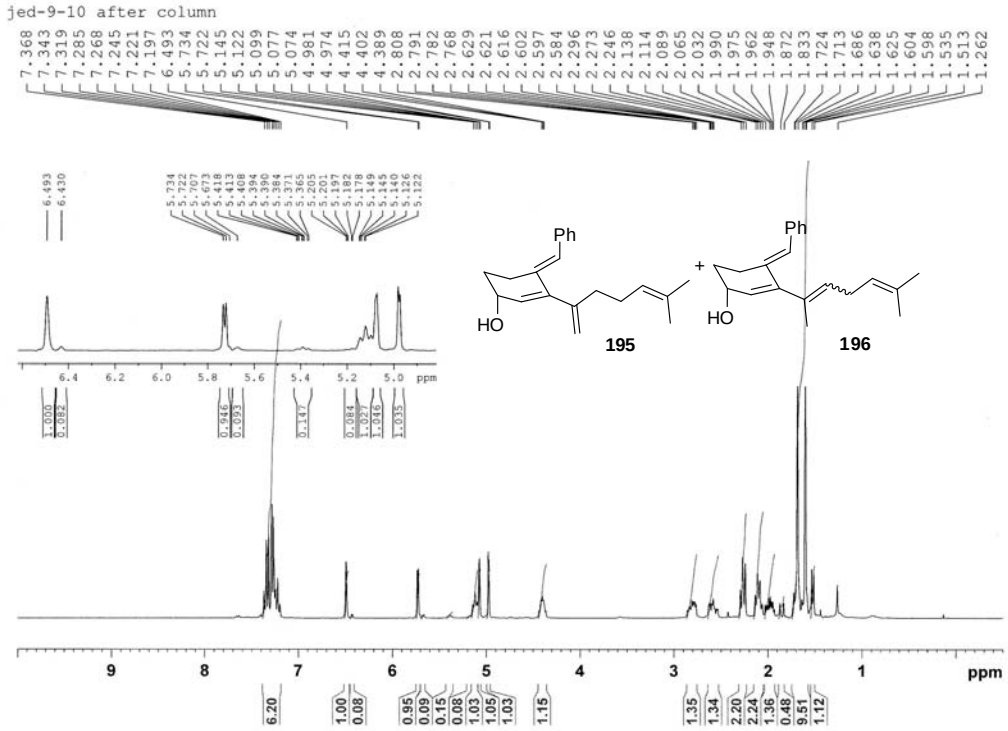

jed-7-177
ppm

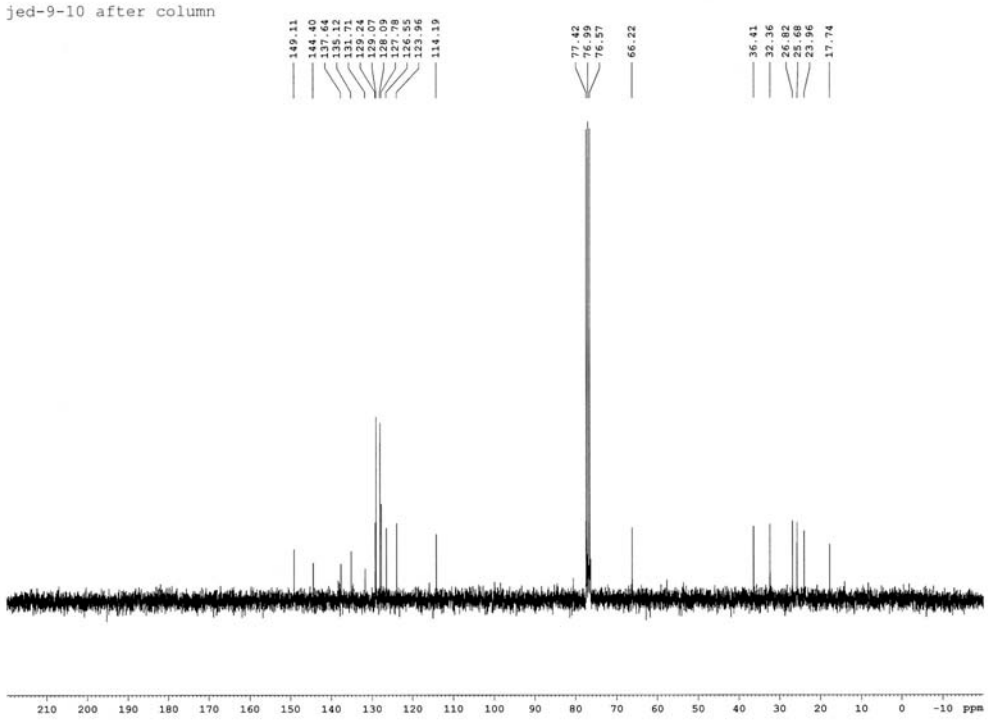
jed-7-188 pivolate ester triene

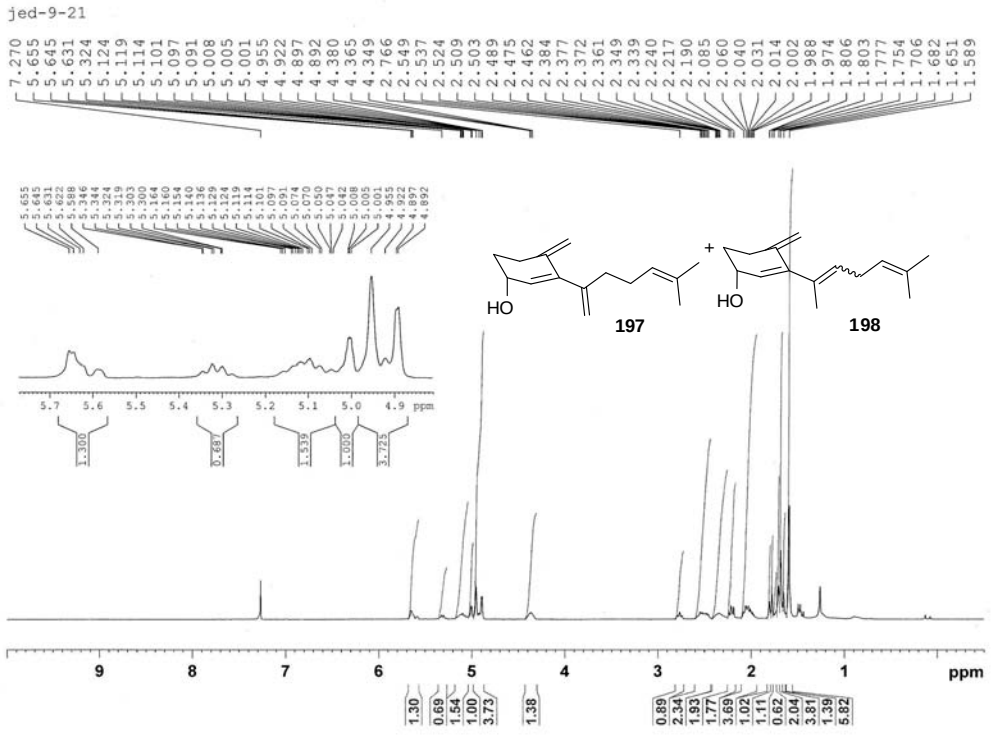


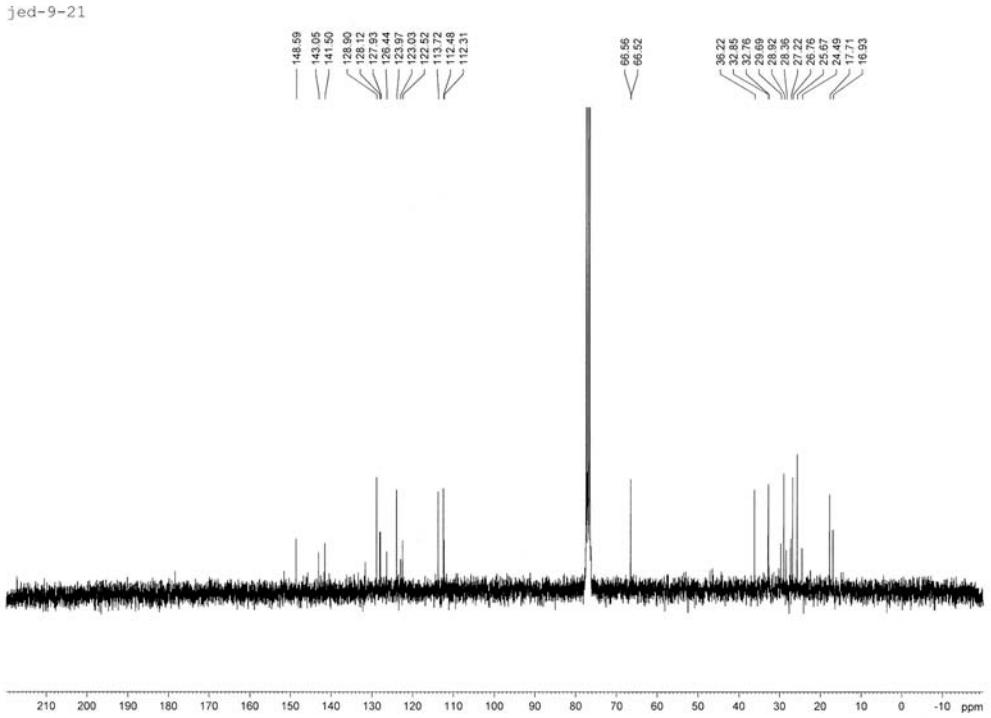
jed-7-188 pivolate ester triene



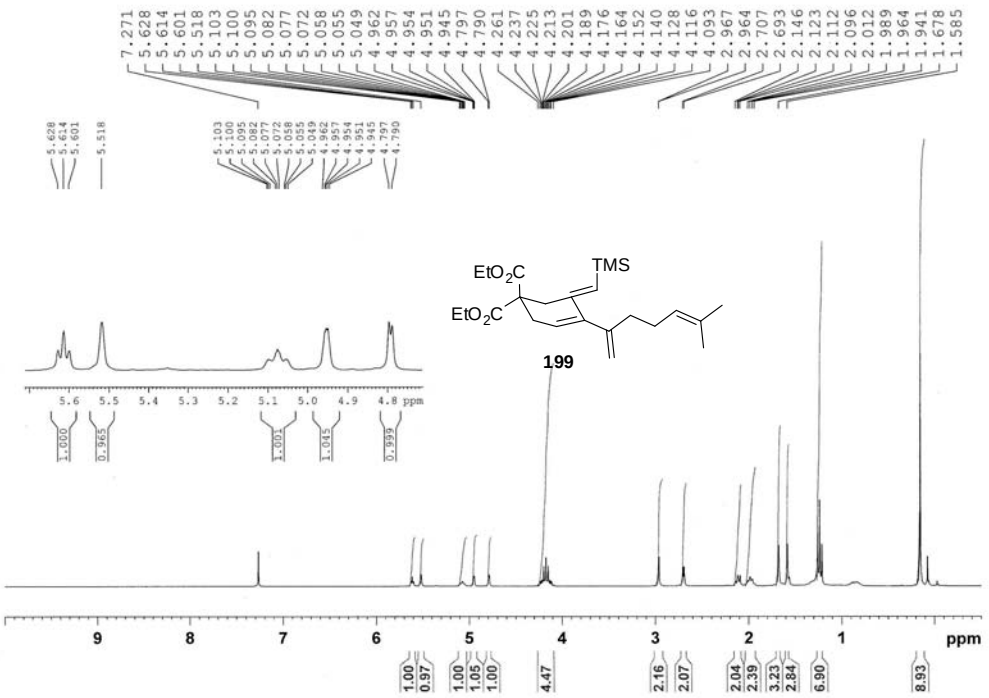

jed-9-10 after column
Ph
HO
195
Ph
HO
196
ppm


jed-9-10 after column
ppm

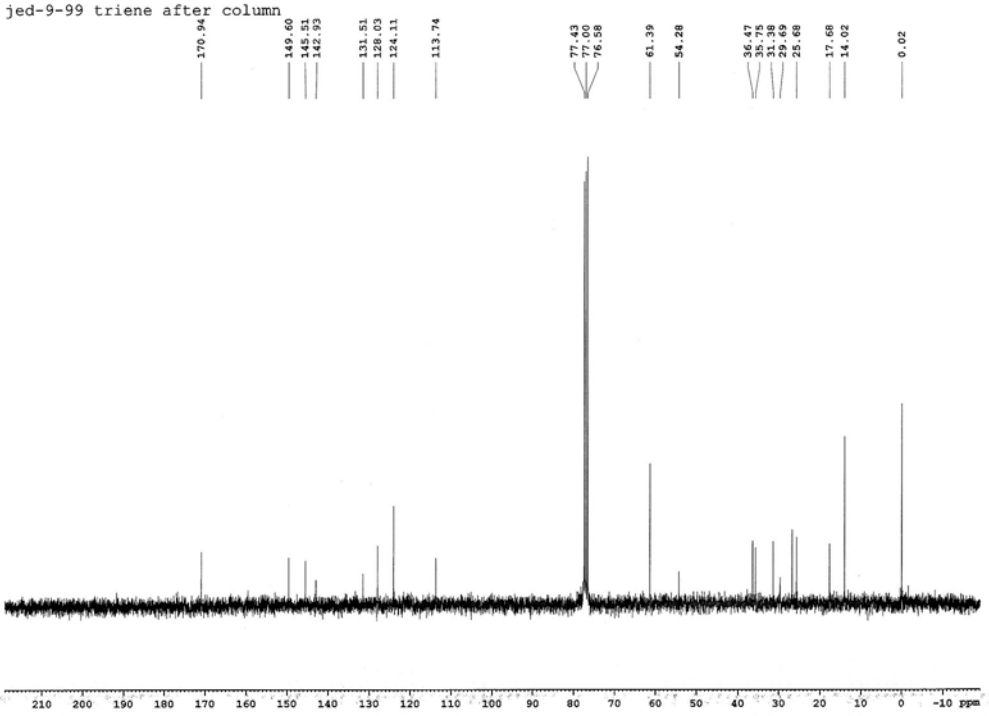

jed-9-21
HO
197
HO
198
ppm


jed-9-21
ppm

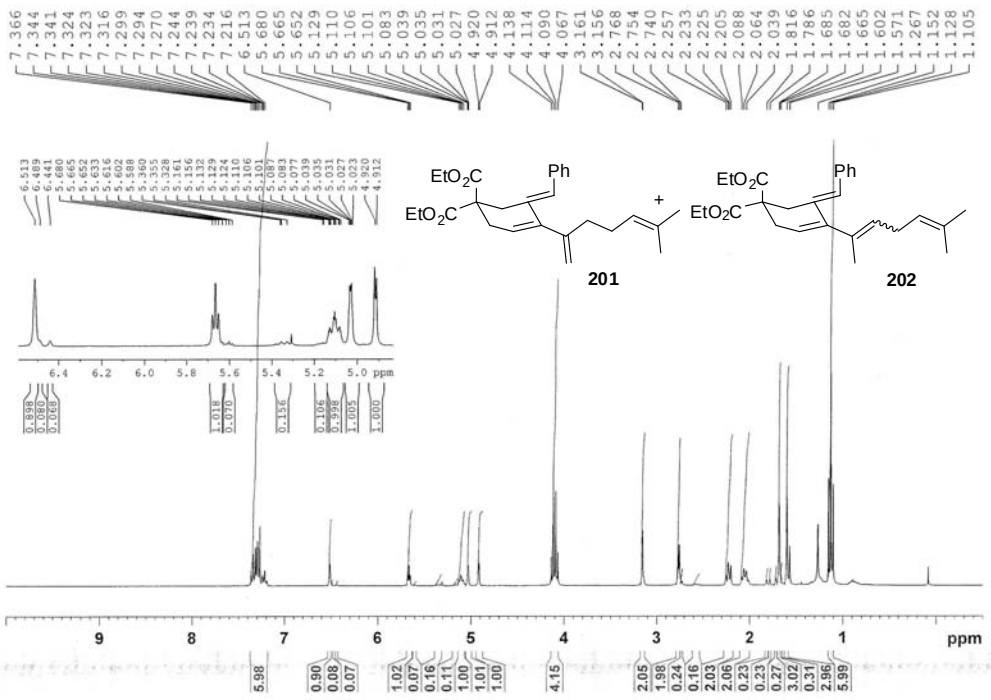
jed-9-99 triene



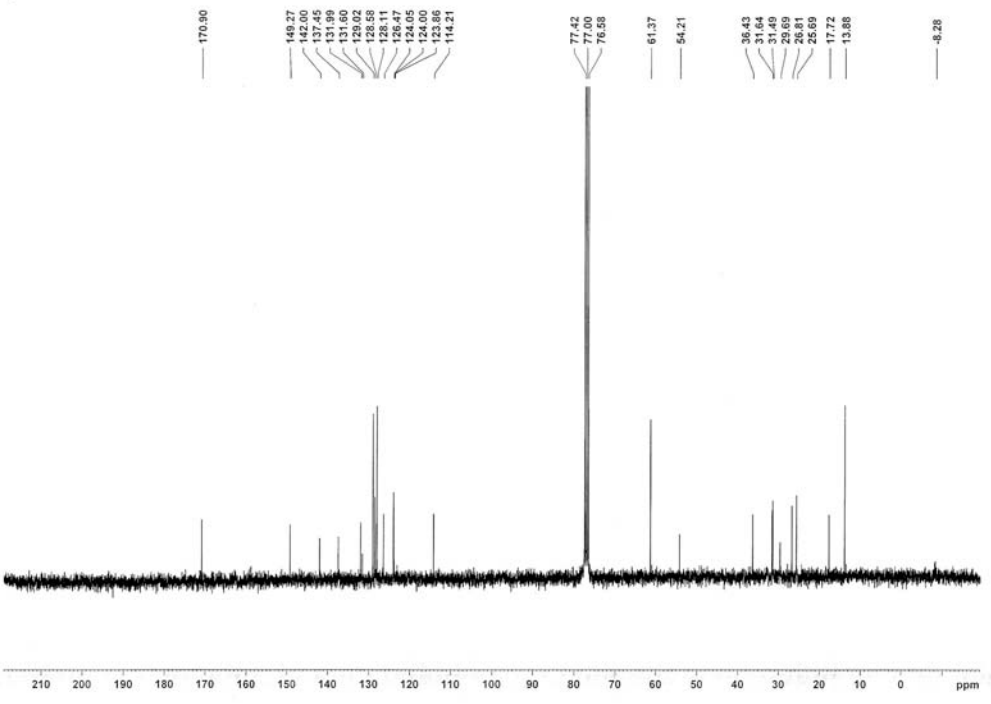
jed-9-99 triene after column

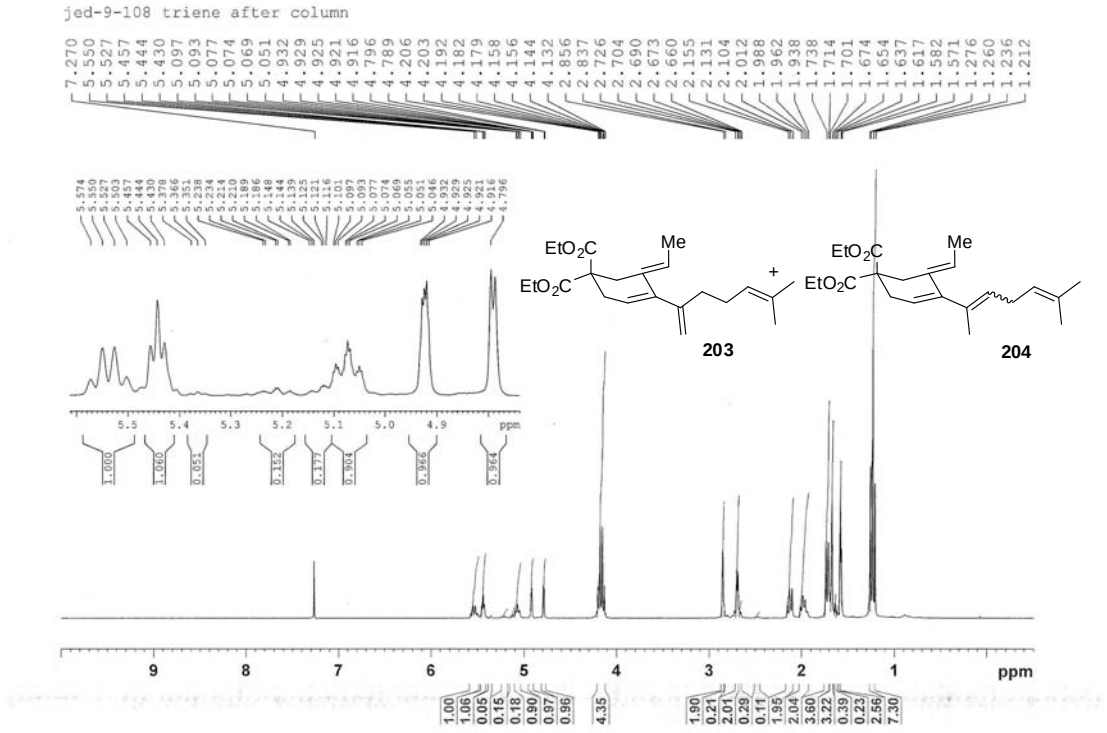


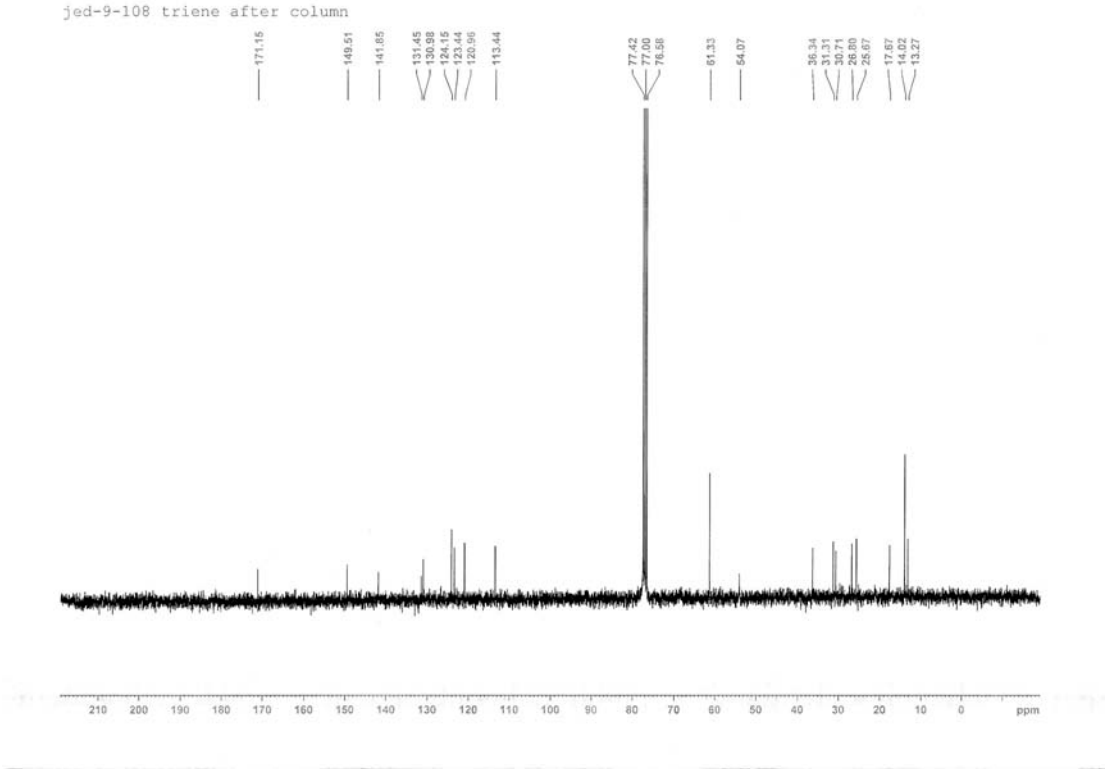
jed-9-115 triene after column

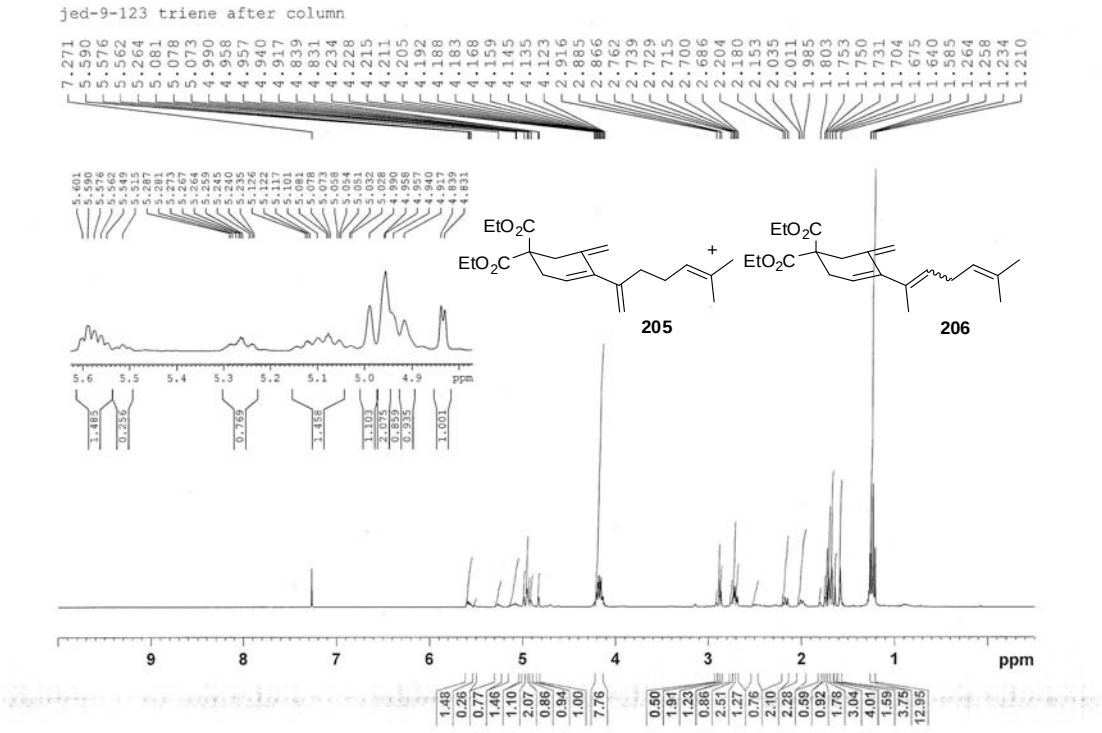


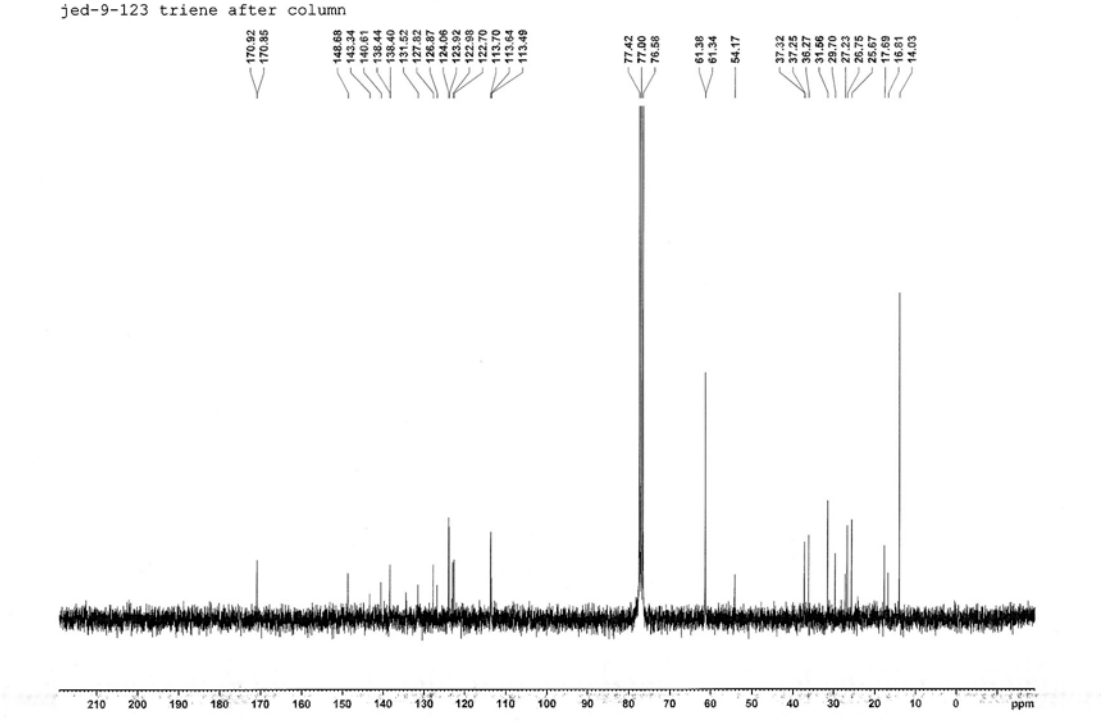
jed-9-115 triene after column

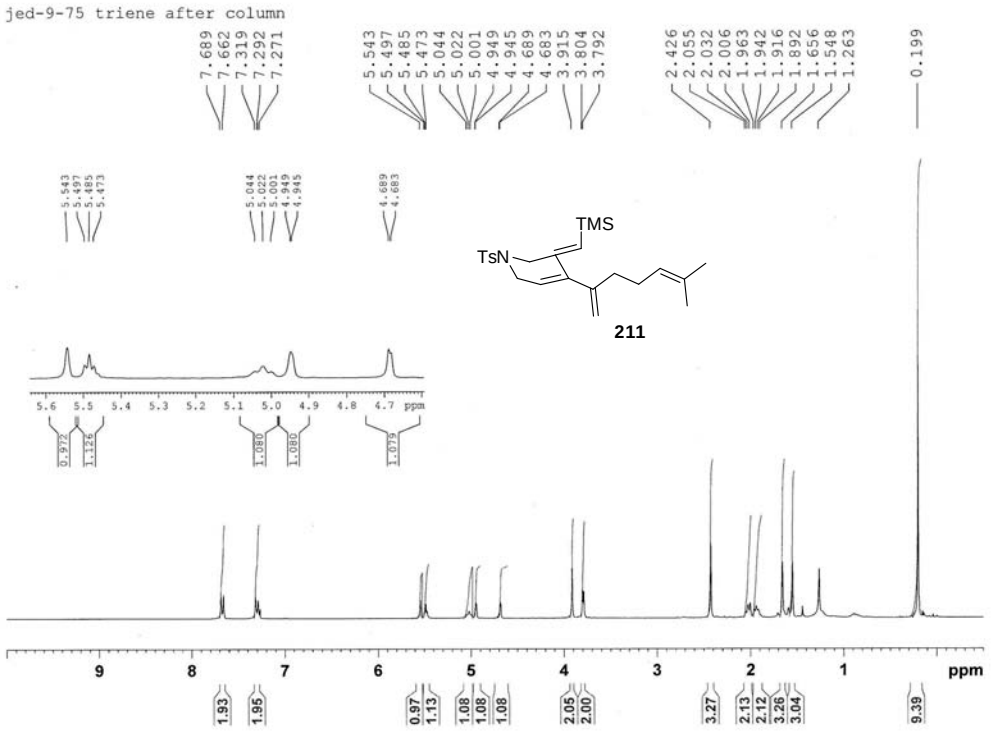


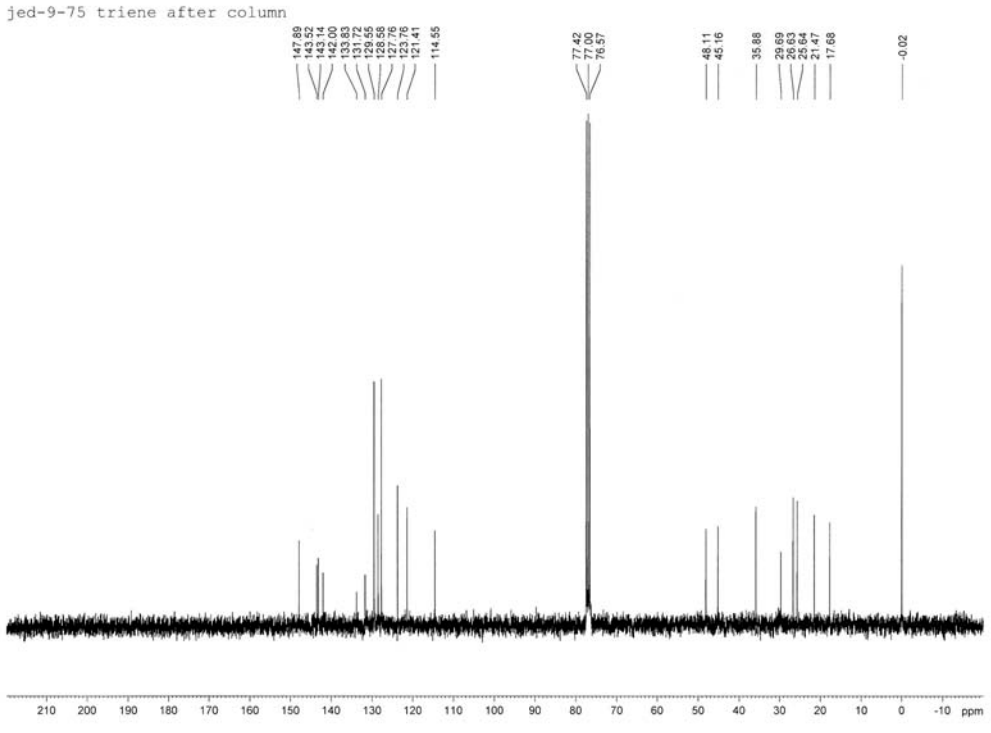

jed-9-108 triene after column
EtO2C
EtO2C
Me
203
204
ppm

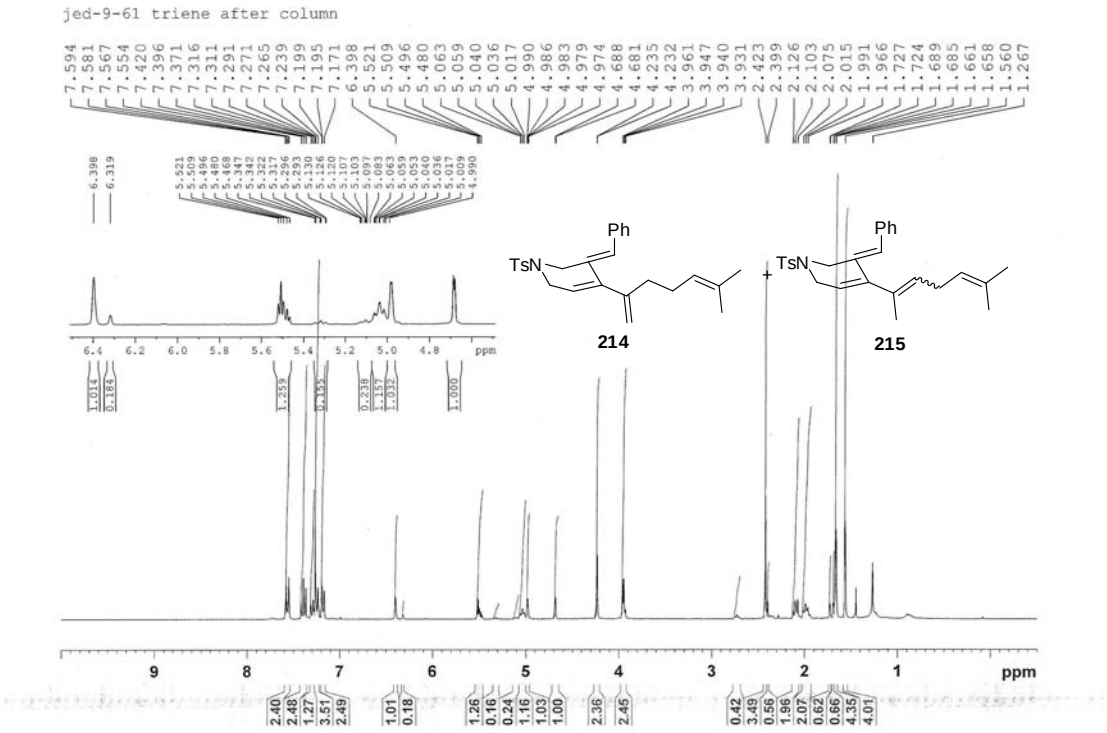

jed-9-108 triene after column
ppm

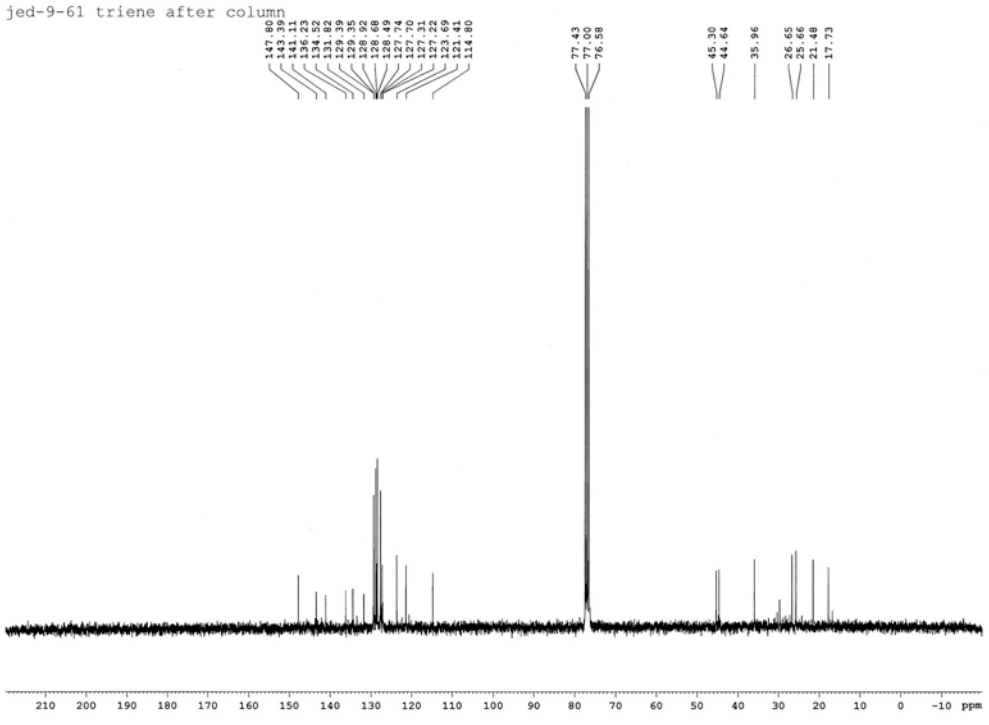

jed-9-123 triene after column
EtO2C
EtO2C
205
206
ppm

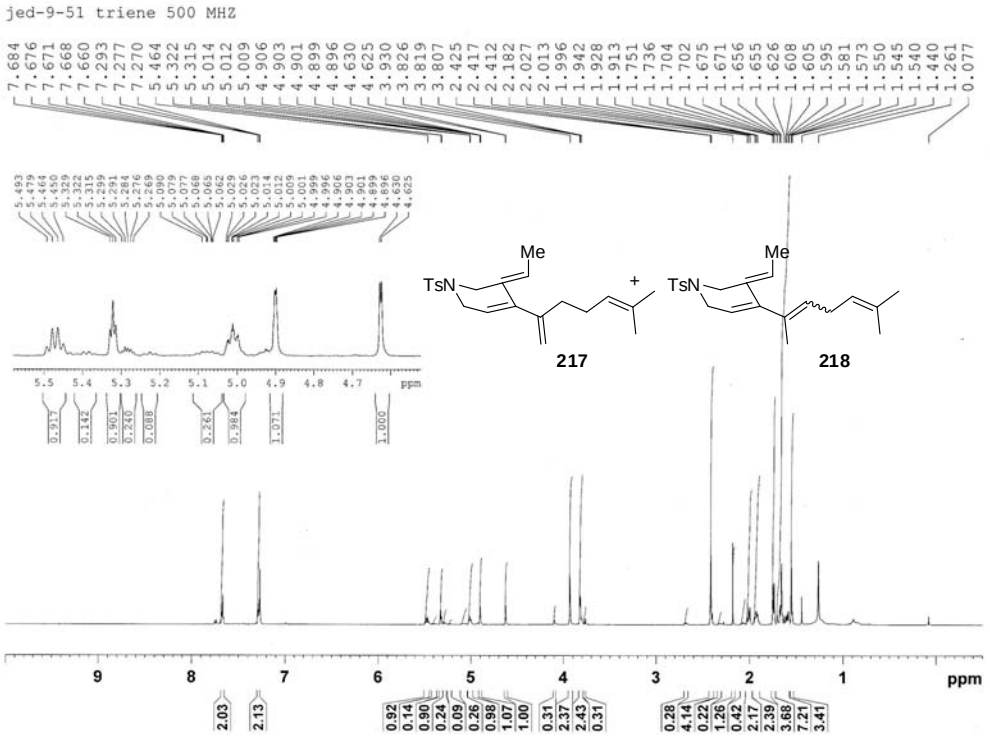

jed-9-123 triene after column
ppm

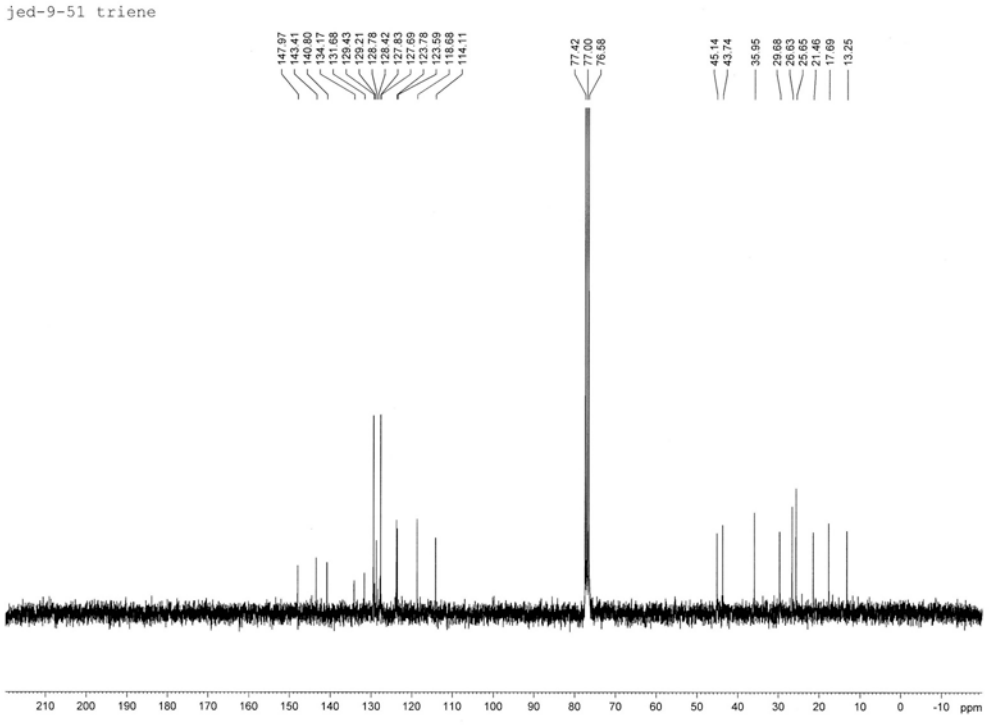

jed-9-75 triene after column
7.689
7.662
7.319
7.292
7.271
5.543
5.497
5.485
5.473
5.044
5.022
5.001
4.949
4.945
4.689
4.683
3.915
3.804
3.792
2.426
2.055
2.032
2.006
1.963
1.942
1.916
1.892
1.656
1.548
1.263
0.199
TMS
TsN
211
ppm
1.93
1.95
0.97
1.13
1.08
1.08
1.08
2.05
2.00
3.27
2.13
2.12
3.26
3.04
9.39


jed-9-75 triene after column
147.89
143.52
143.14
142.00
133.83
131.72
129.55
128.66
127.76
123.76
121.41
114.55
77.42
77.00
76.57
48.11
45.16
35.88
29.69
26.63
25.64
21.47
17.68
-0.02
ppm

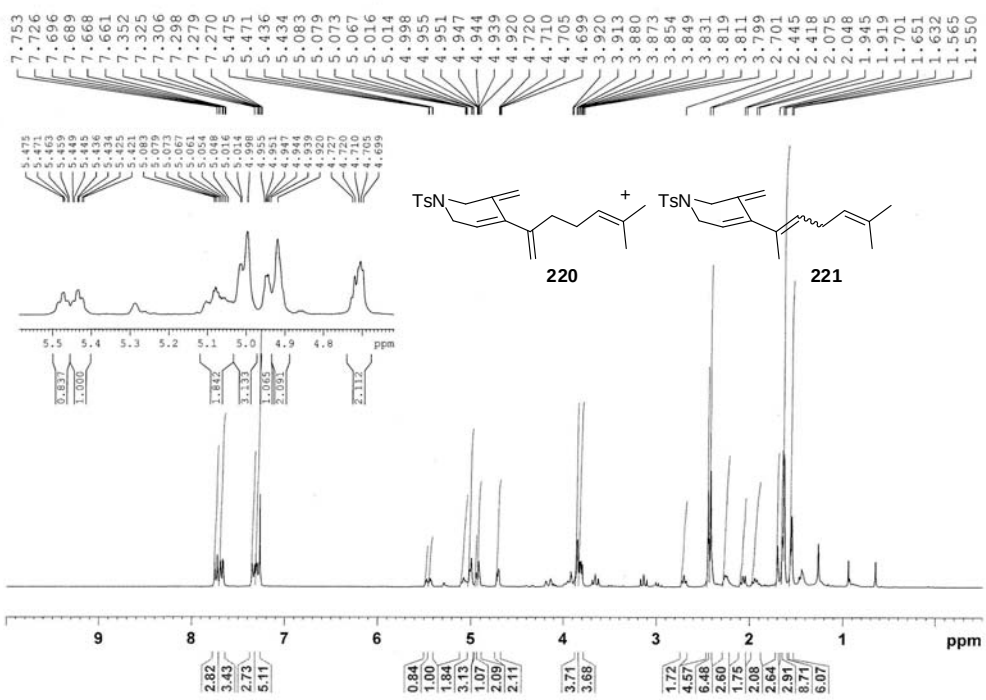

jed-9-61 triene after column
Ph
TsN
214
Ph
TsN
215
ppm


jed-9-61 triene after column
ppm

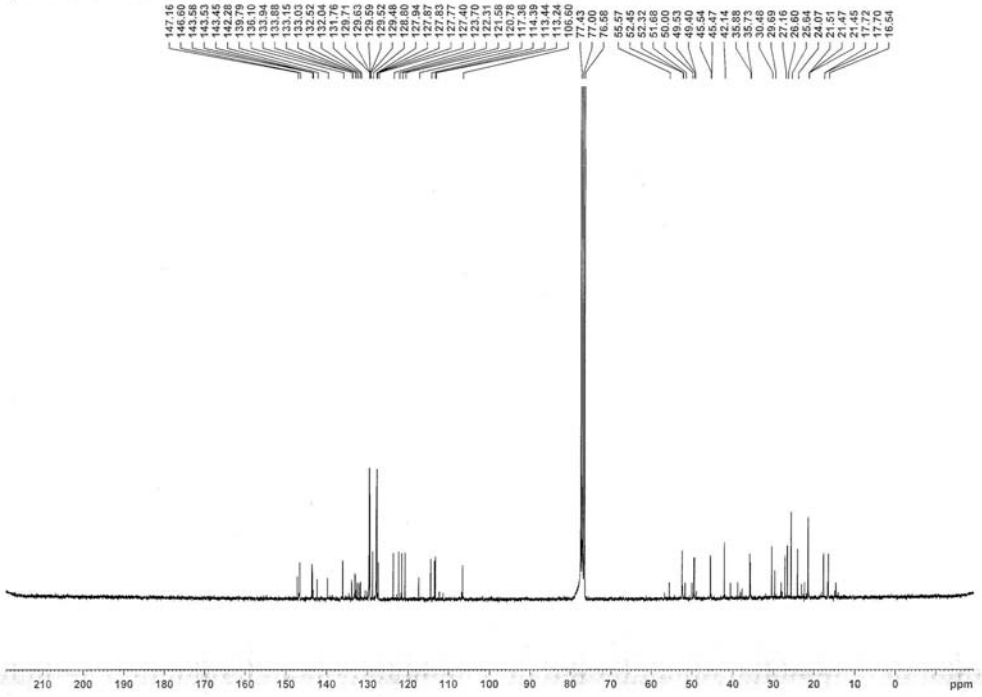

jed-9-51 triene 500 MHZ
Me
TsN
+
217
Me
TsN
218
ppm


jed-9-51 triene
ppm

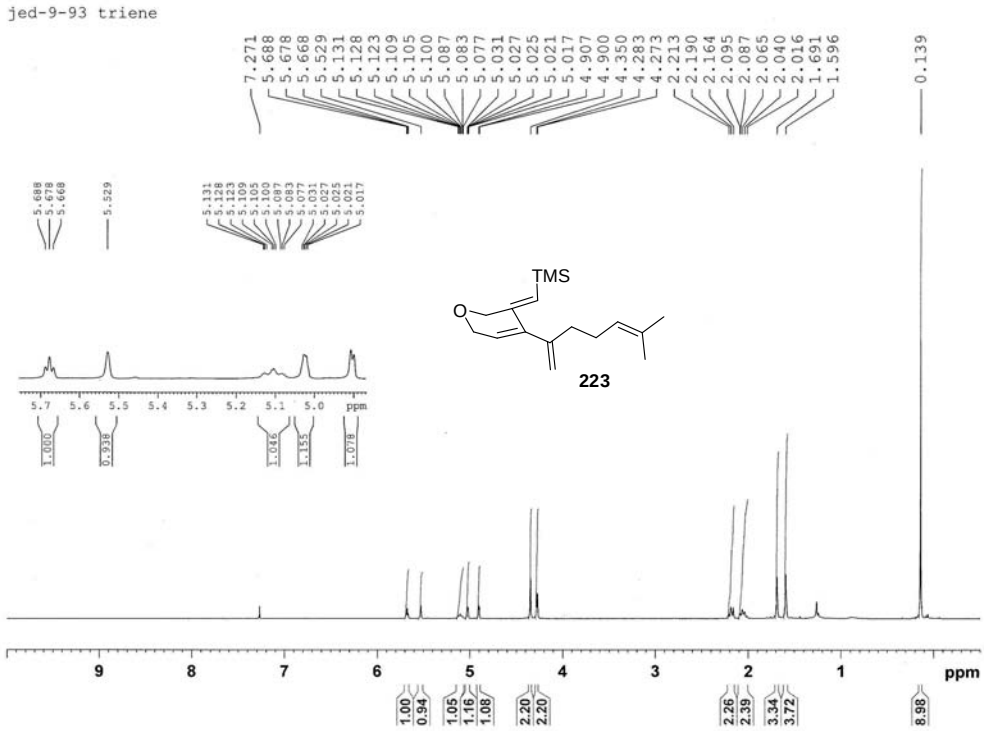
jed-9-141 triene after column



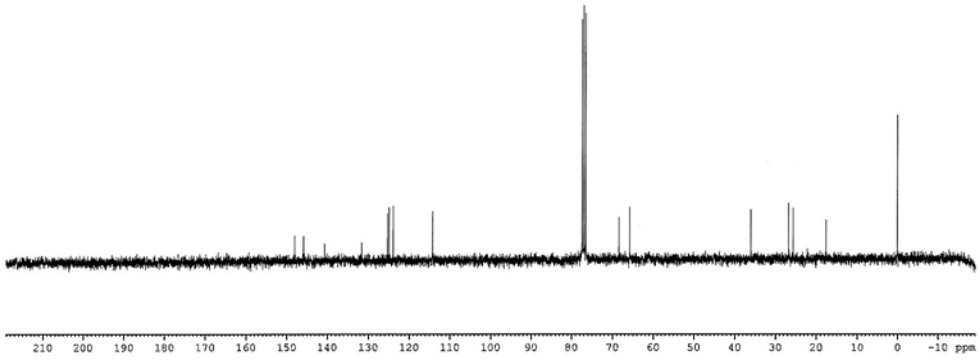
jed-9-141 triene

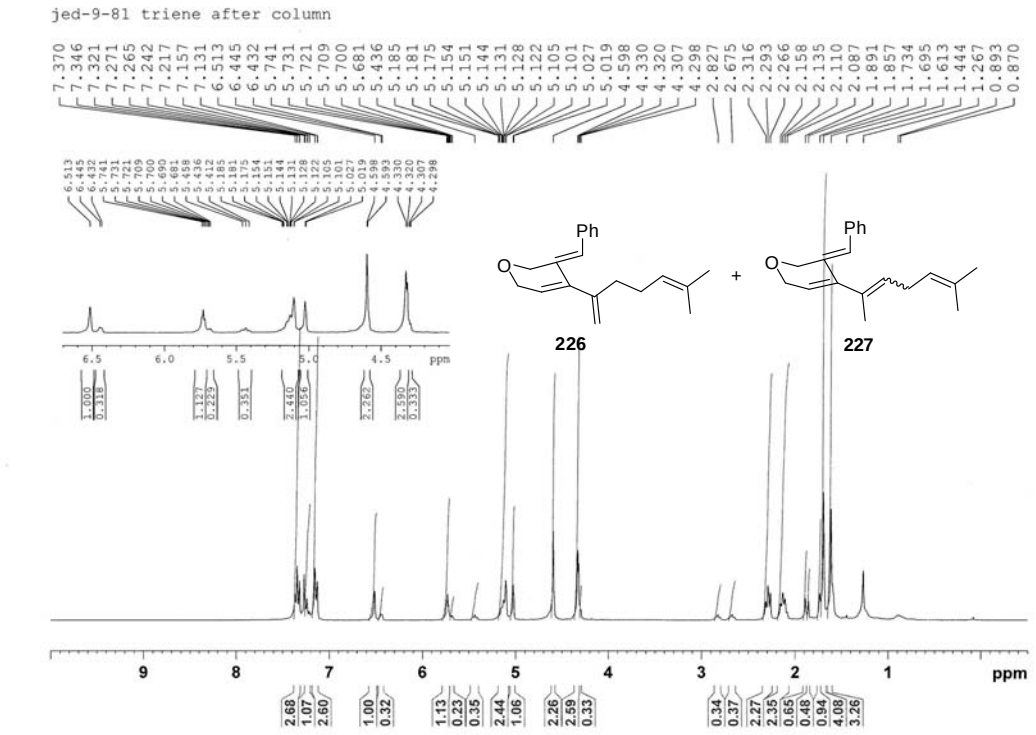


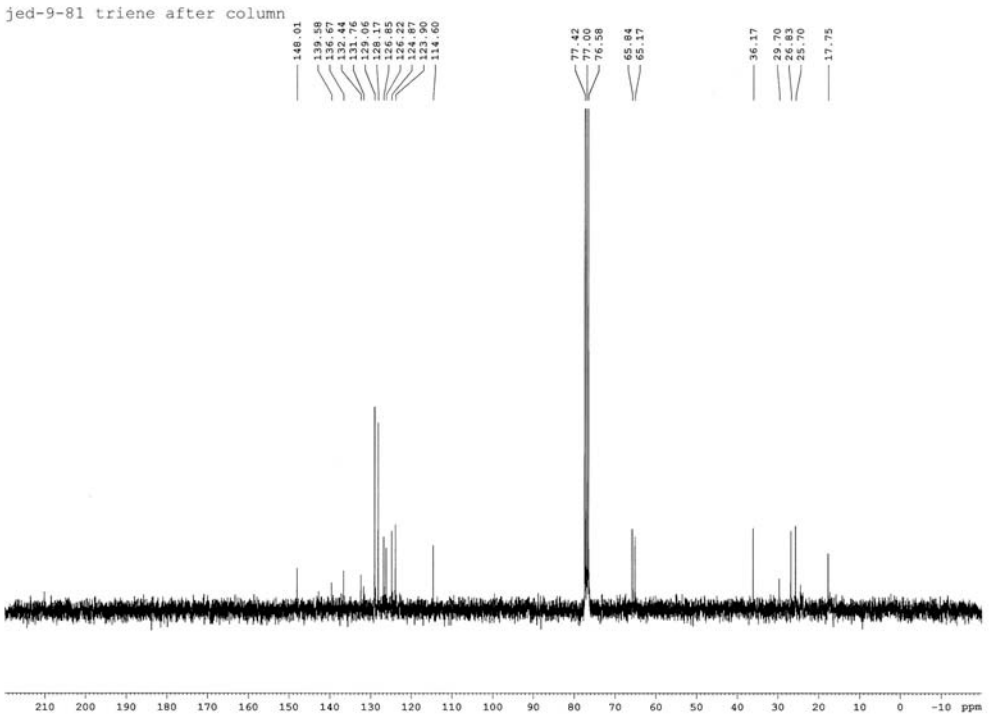
jed-9-93 triene

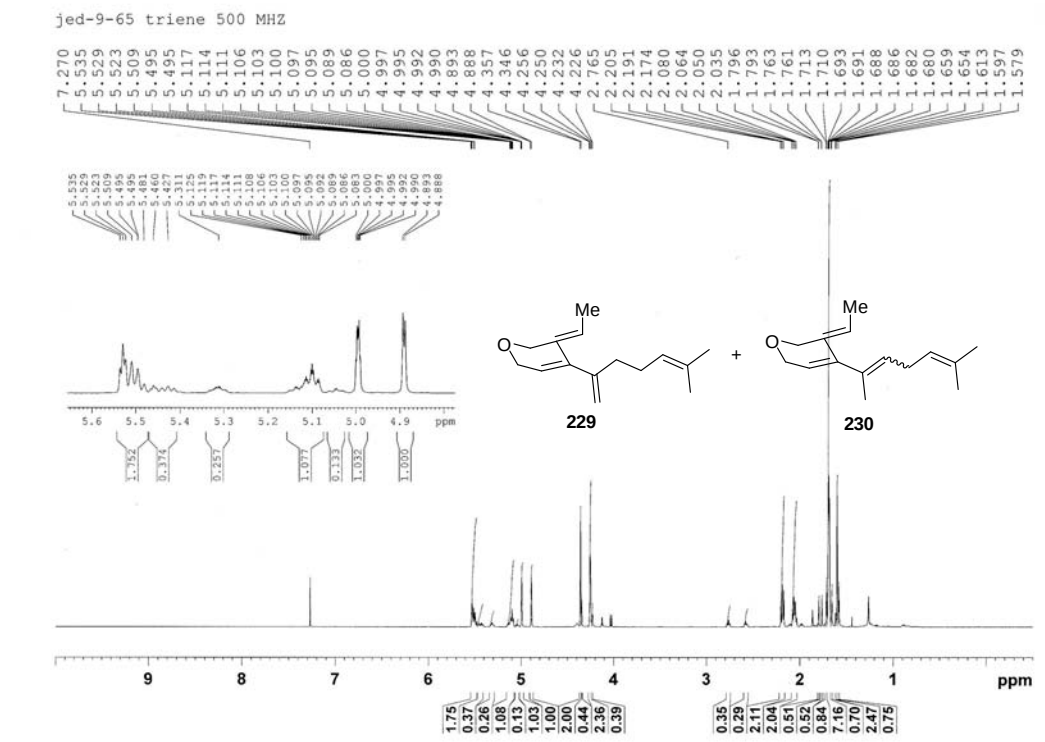


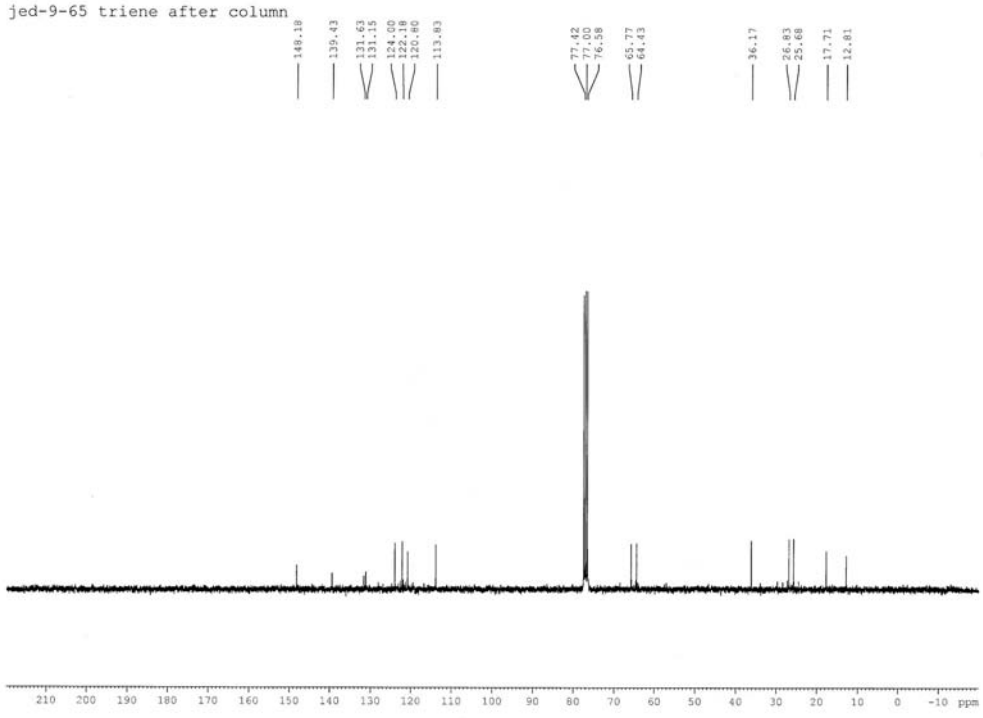
jed-9-93 triene

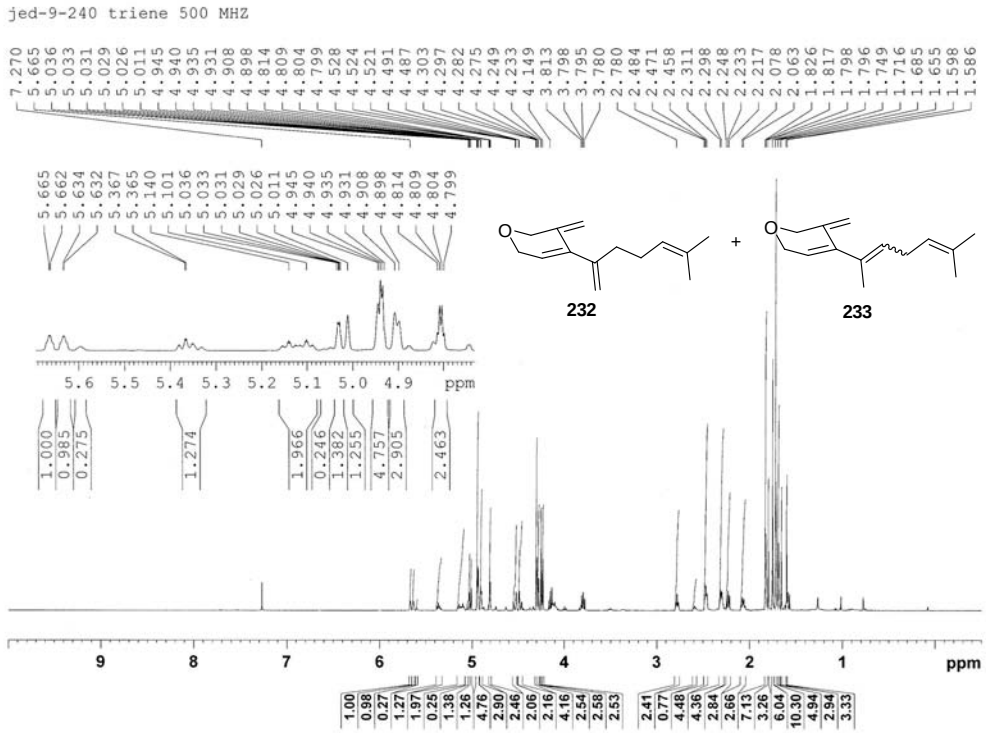


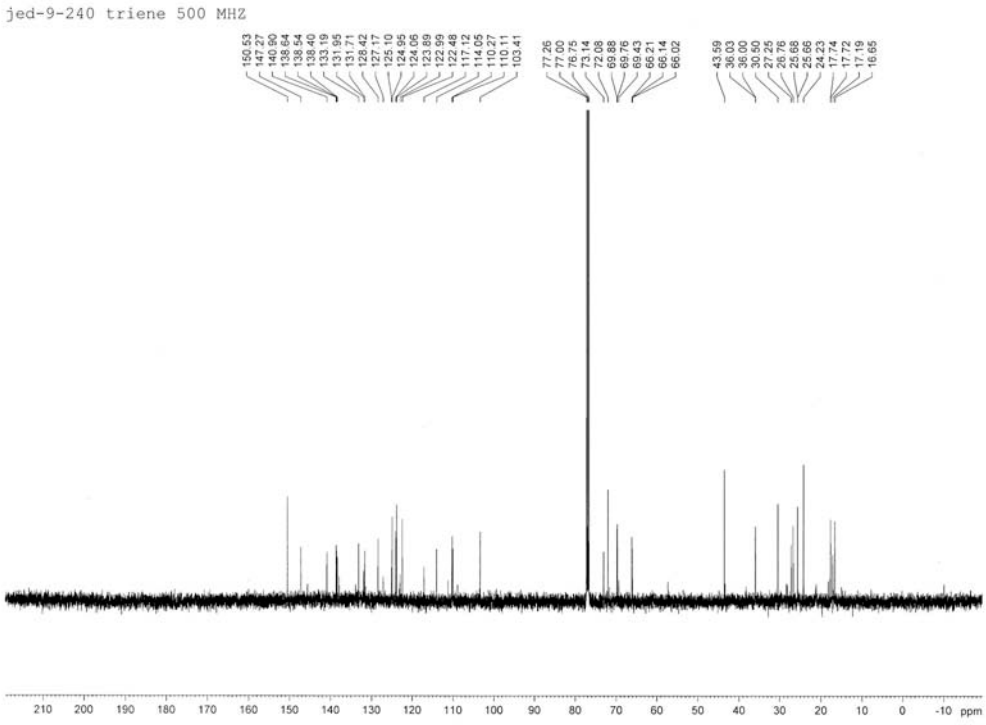

jed-9-81 triene after column
Ph
O
226
+
Ph
O
227
ppm

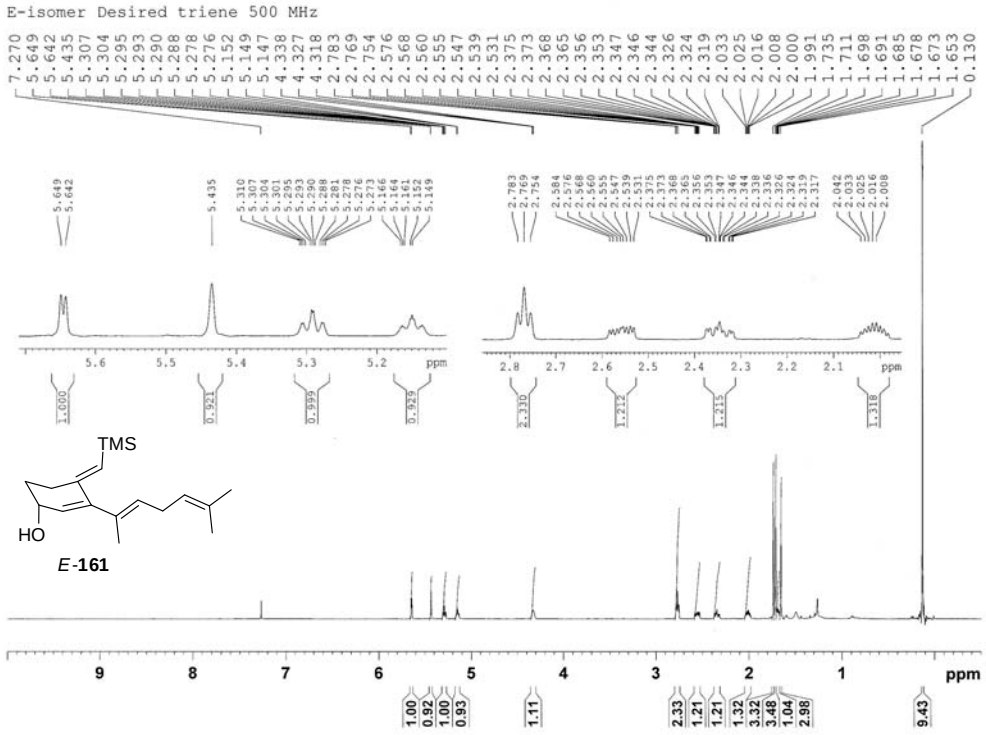

jed-9-81 triene after column
ppm

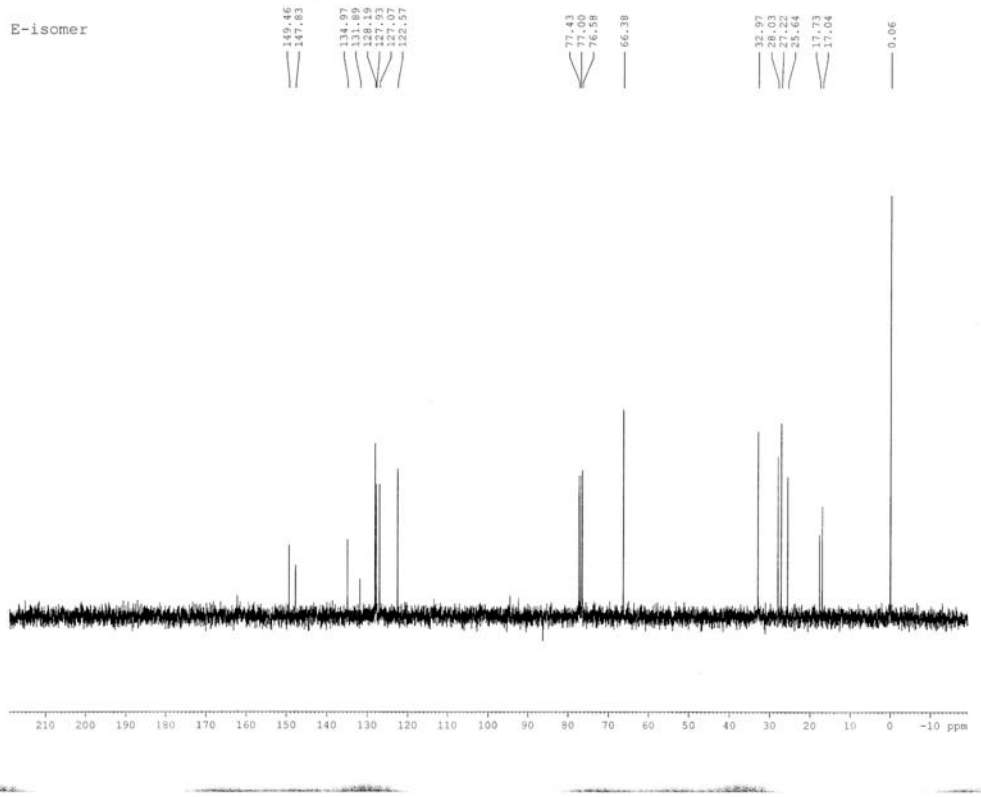

jed-9-65 triene 500 MHZ
Me
O
229
+
Me
O
230
ppm

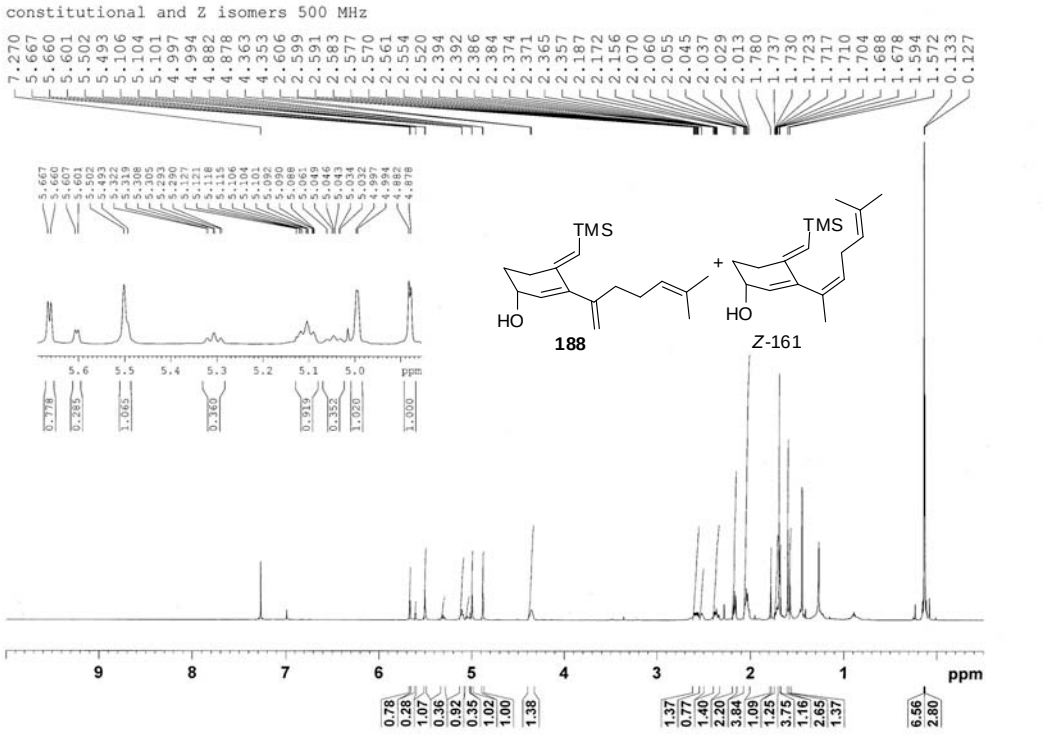

jed-9-65 triene after column
ppm

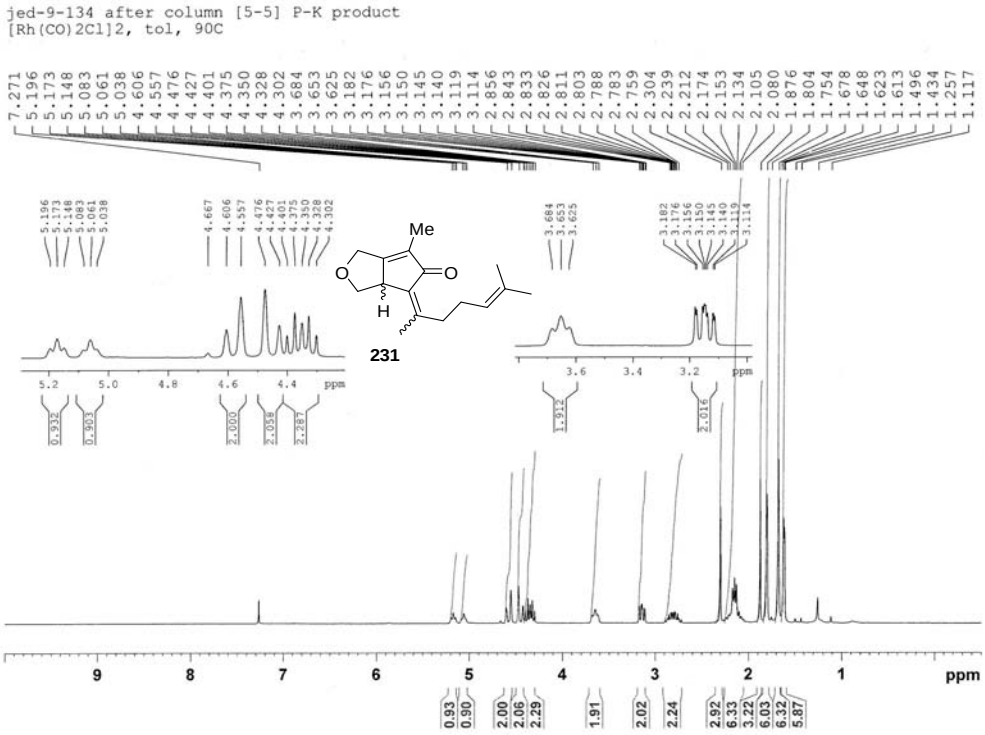

jed-9-240 triene 500 MHZ
232
233
ppm

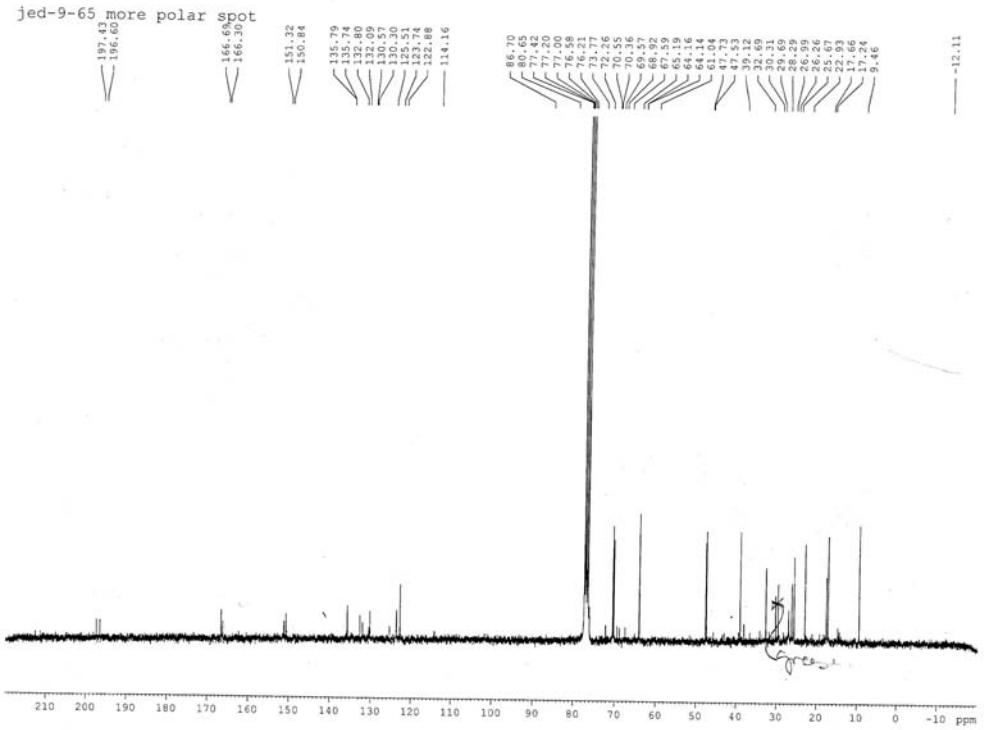

jed-9-240 triene 500 MHZ
ppm

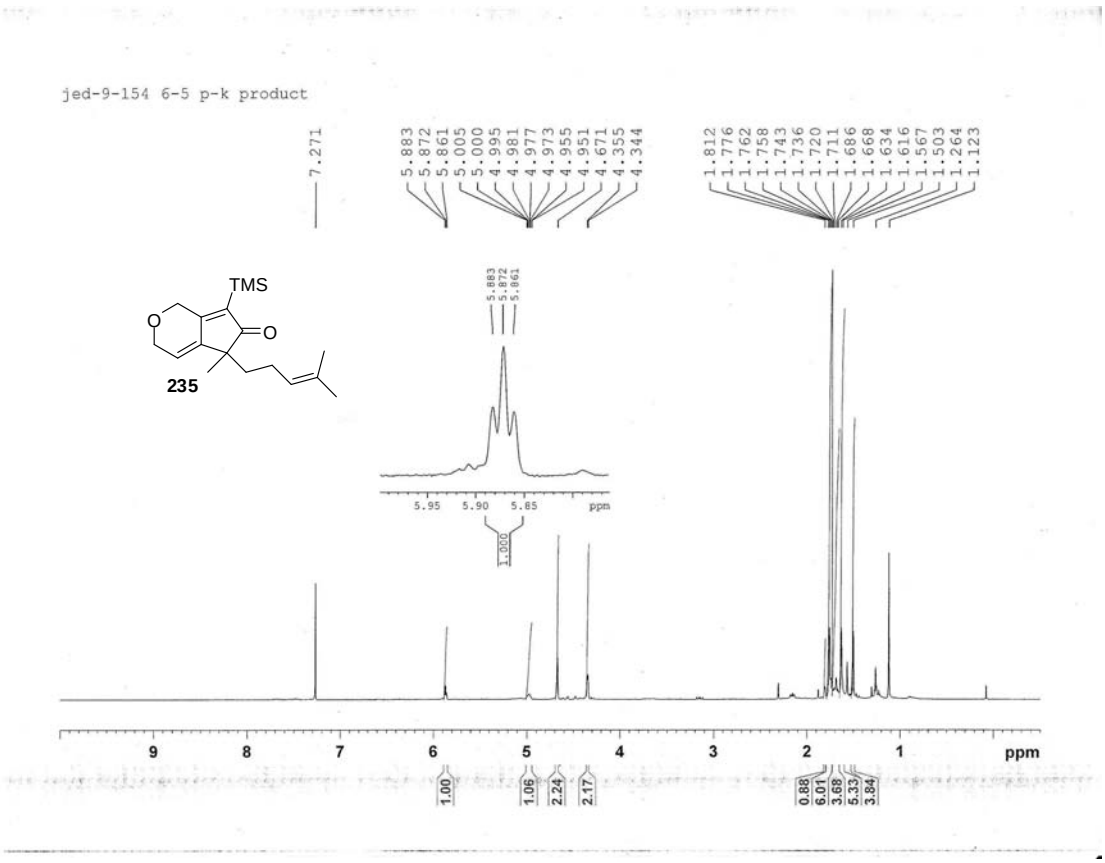

E-isomer Desired triene 500 MHz
TMS
HO
E-161
ppm

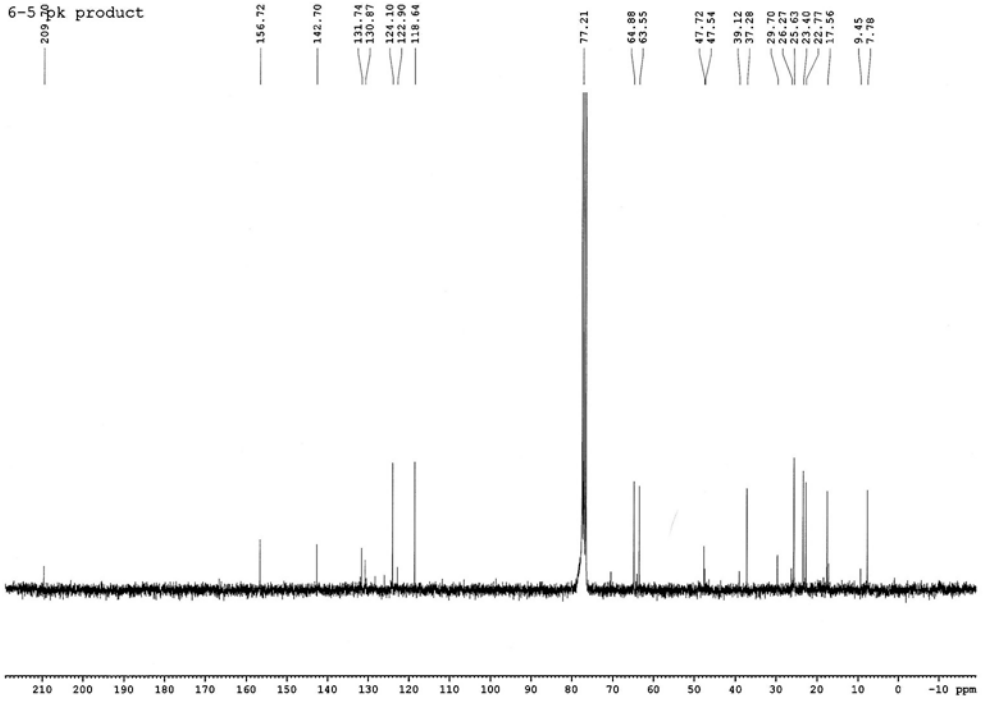

E-isomer
ppm

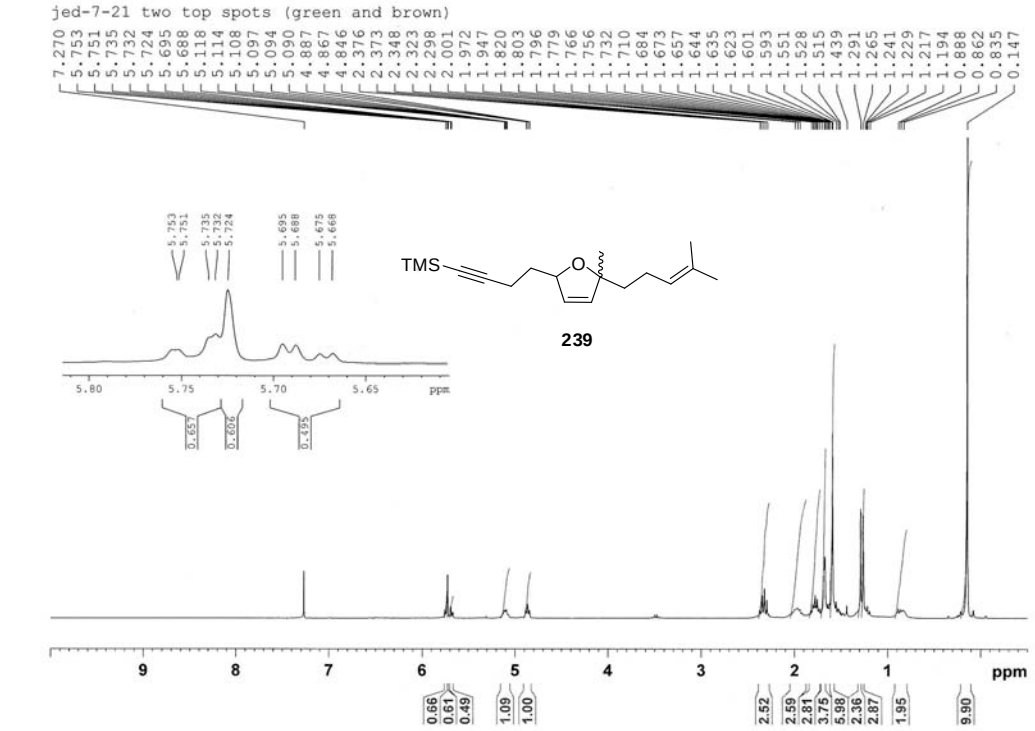

constitutional and Z isomers 500 MHz
TMS
HO
188
+
TMS
HO
Z-161
ppm

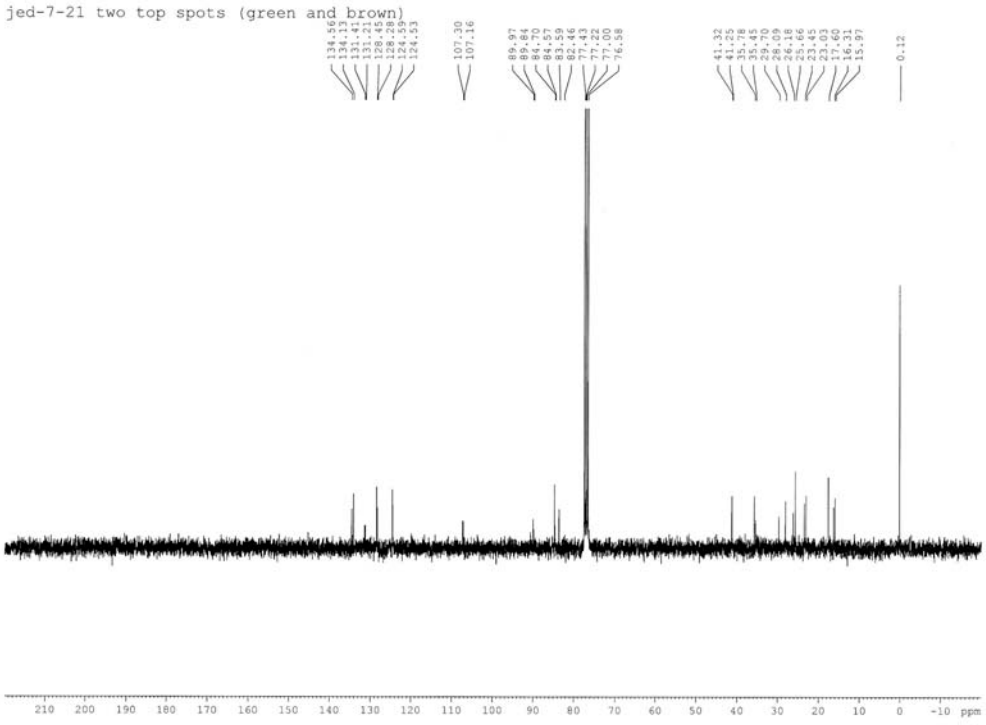

jed-9-134 after column [5-5] P-K product
[Rh(CO)2Cl]2, tol, 90C
Me
O
O
H
231
ppm

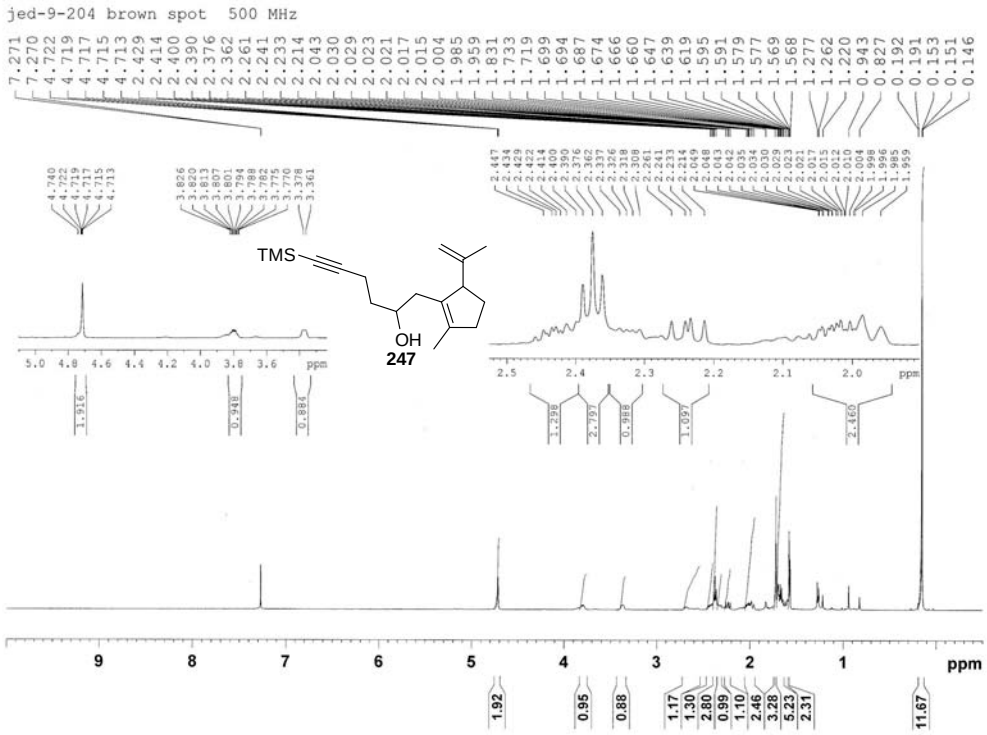

jed-9-65 more polar spot
ppm

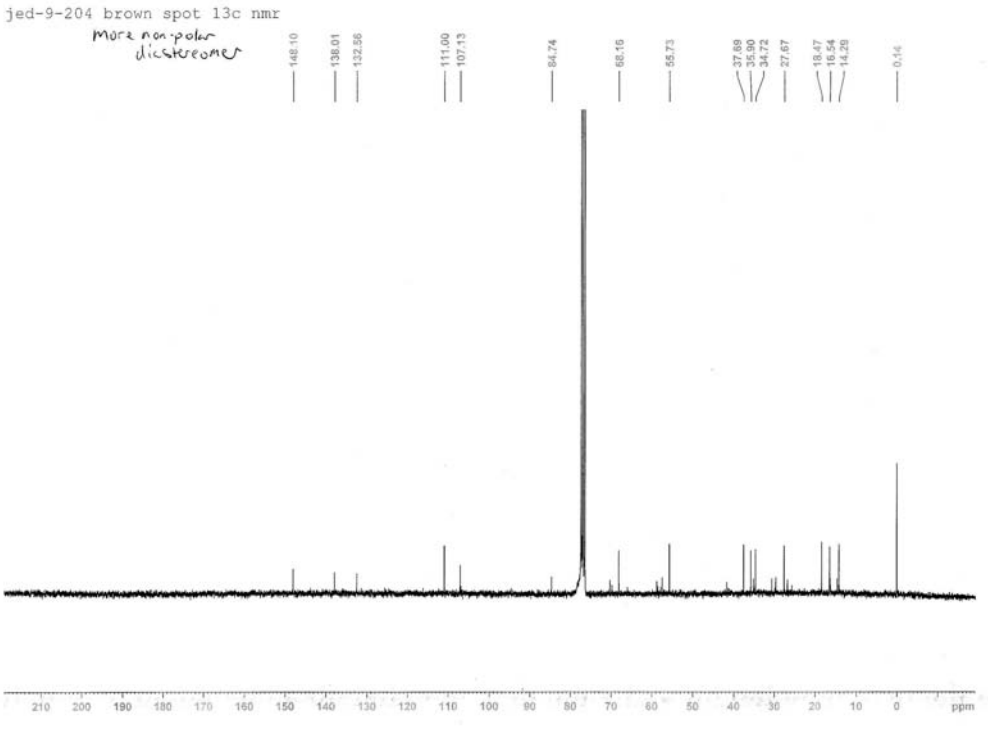

jed-9-154 6-5 p-k product
TMS
O
O
235
ppm

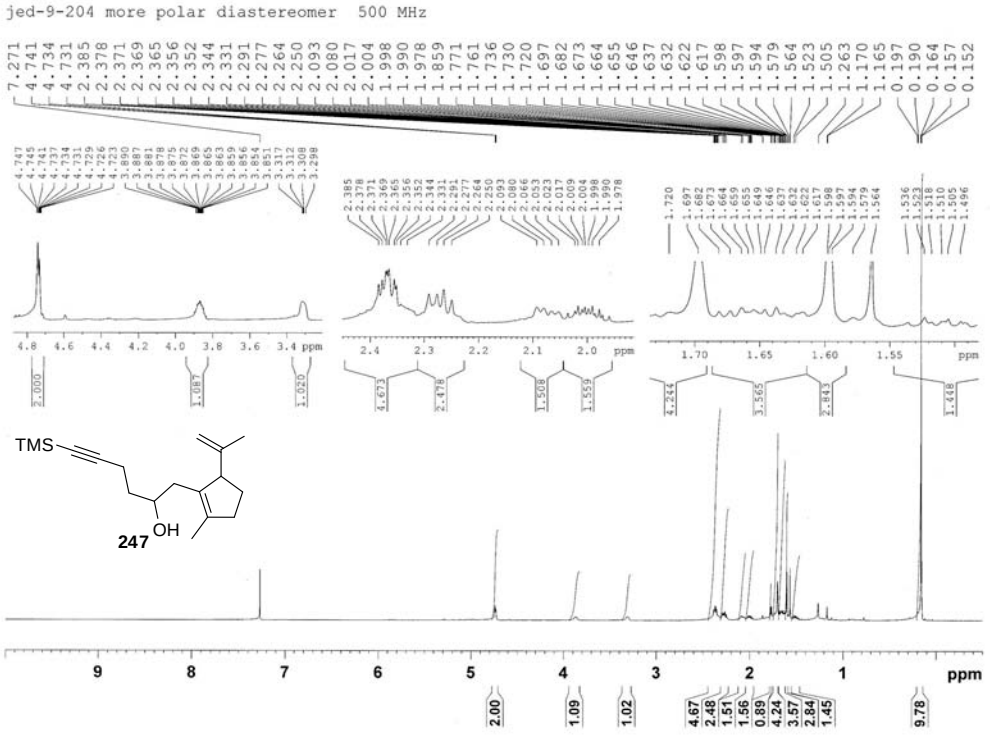

6-5 pk product
ppm

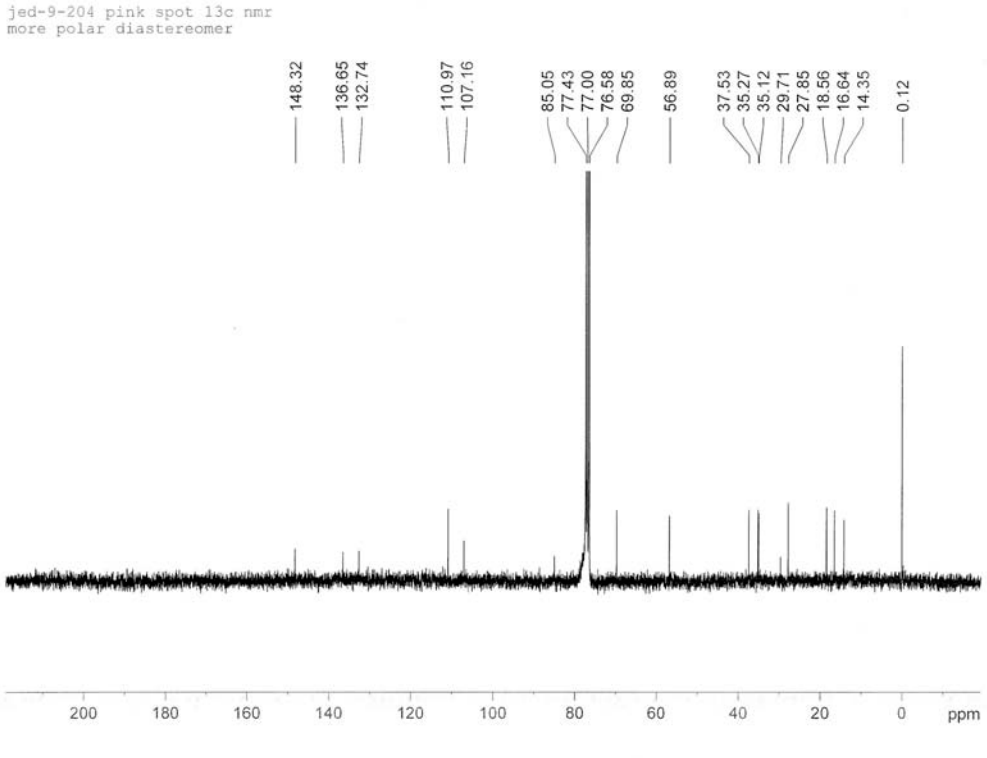

jed-7-21 two top spots (green and brown)
TMS
O
239
ppm

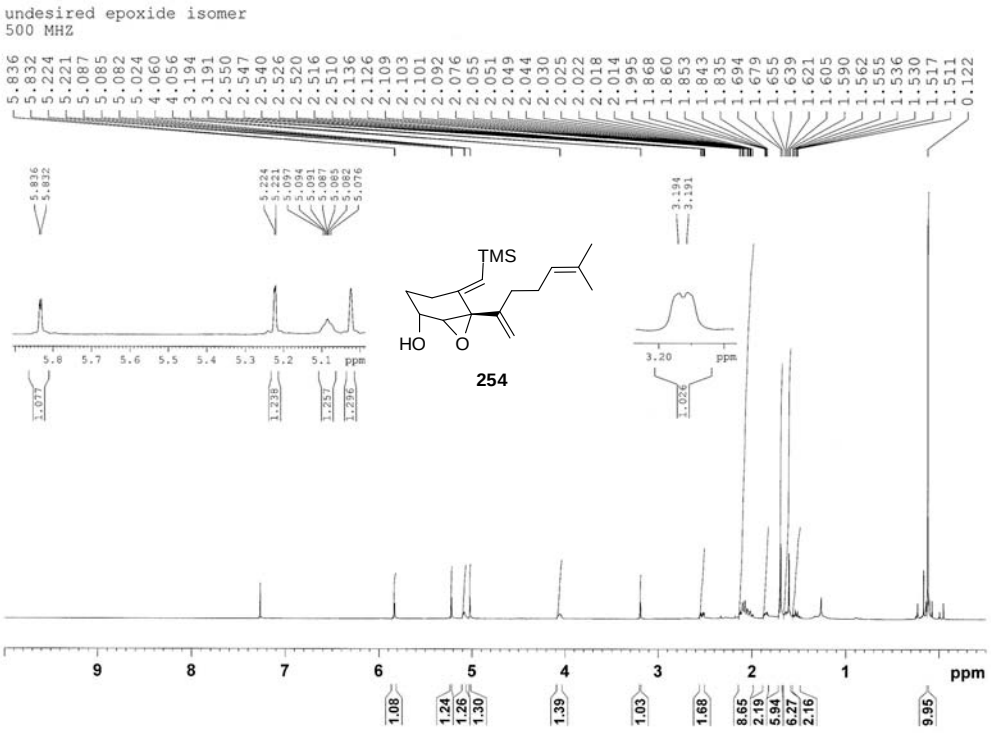

jed-7-21 two top spots (green and brown)
ppm

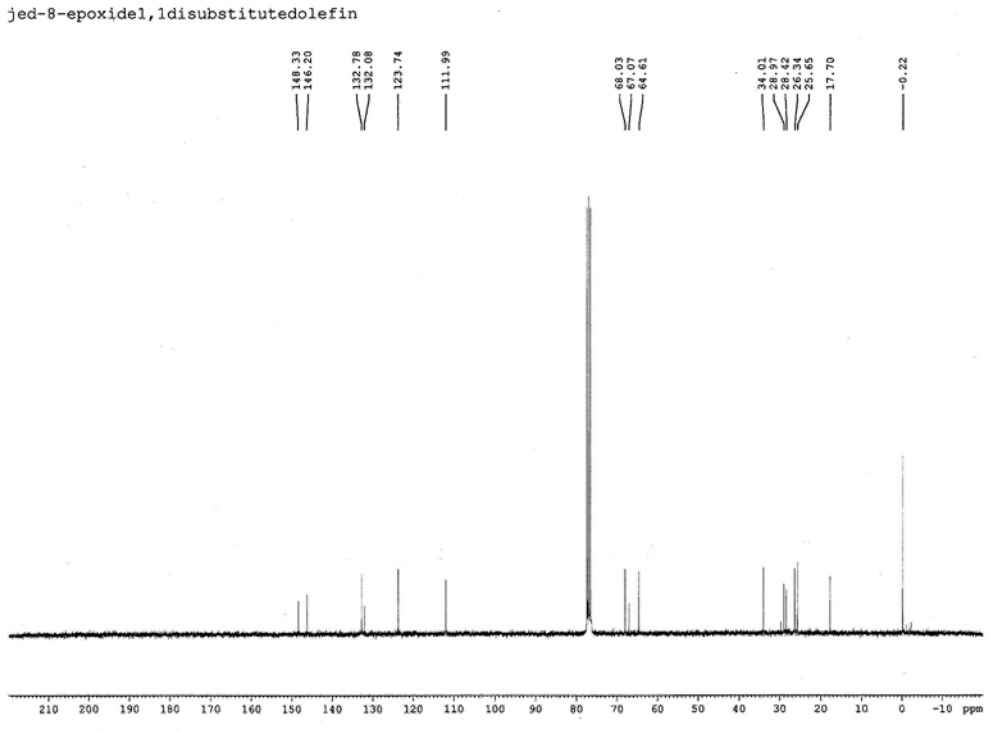

jed-9-204 brown spot 500 MHz
TMS
OH
247
ppm


jed-9-204 brown spot 13c nmr
more non-polar diastereomer
ppm

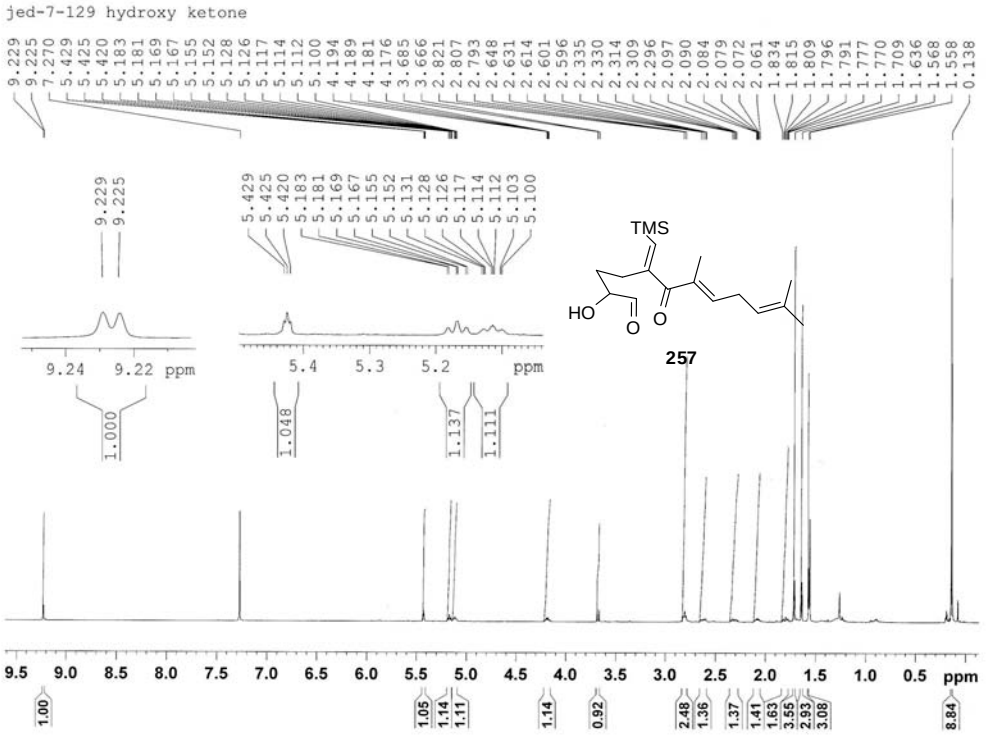

jed-9-204 more polar diastereomer 500 MHz
TMS
OH
247


jed-9-204 pink spot 13c nmr
more polar diastereomer

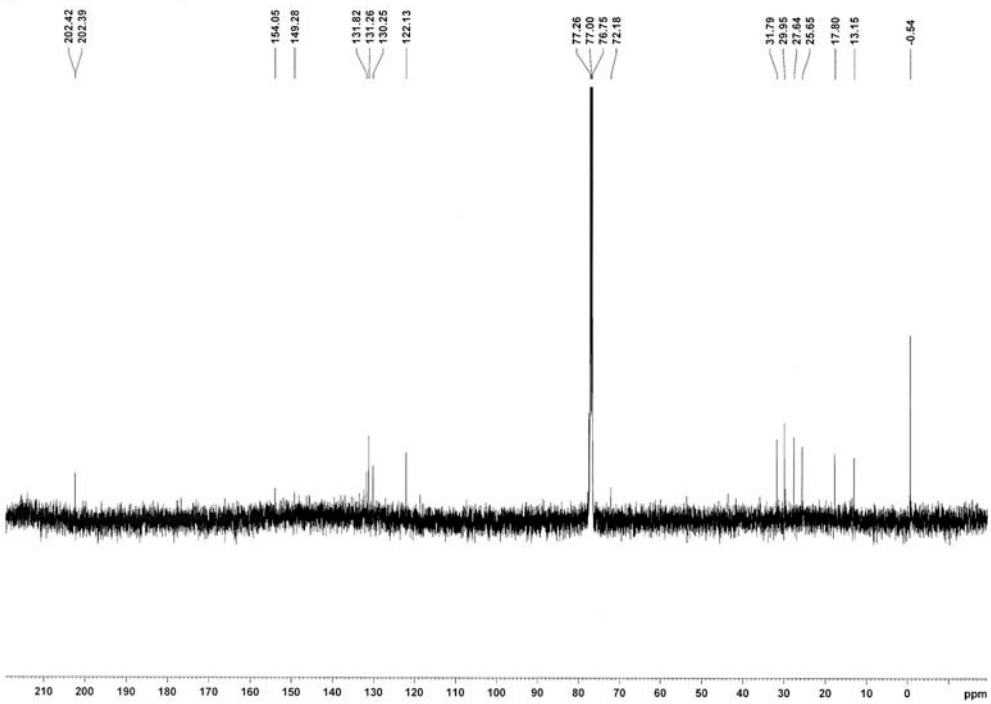

undesired epoxide isomer
500 MHZ
TMS
HO
O
254
ppm


jed-8-epoxide1,1disubstitutedolefin
ppm

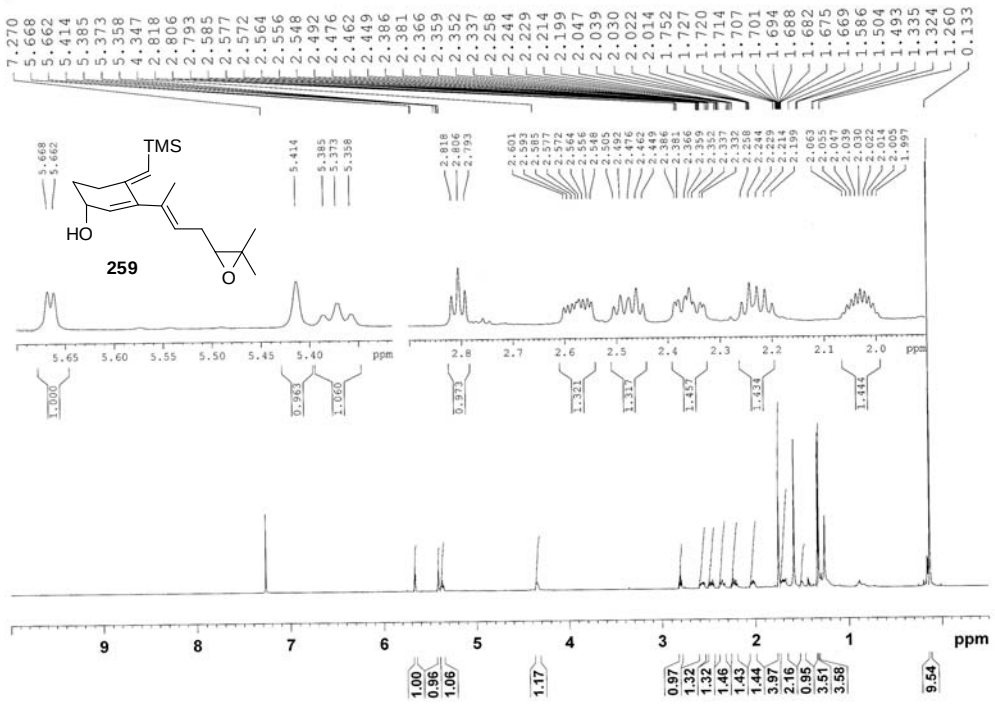
jed-7-129 hydroxy ketone



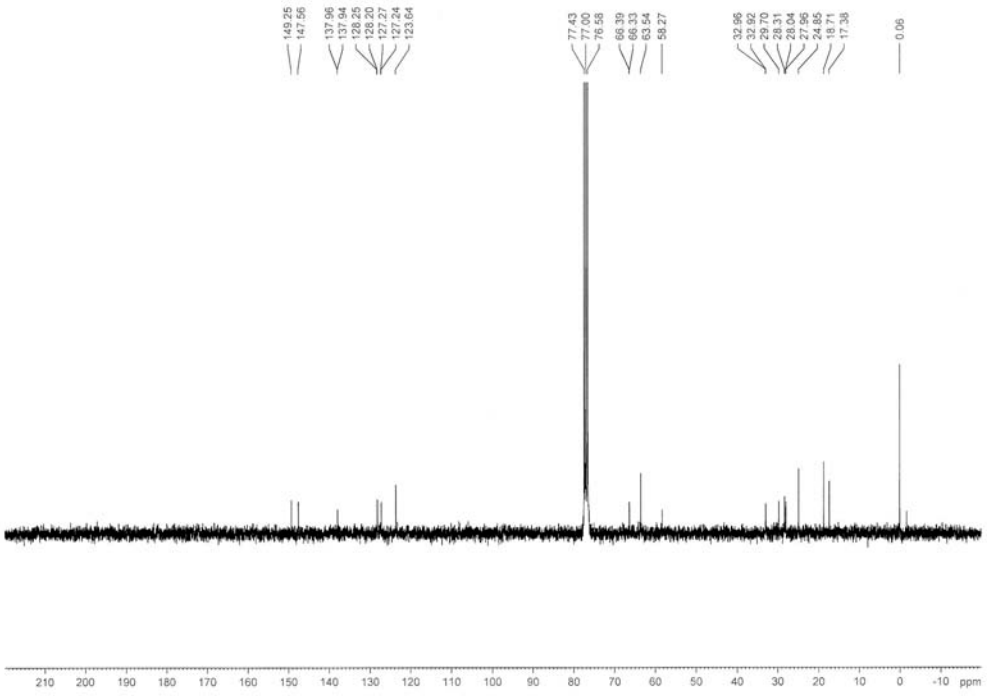
jed-7-129 brown spot

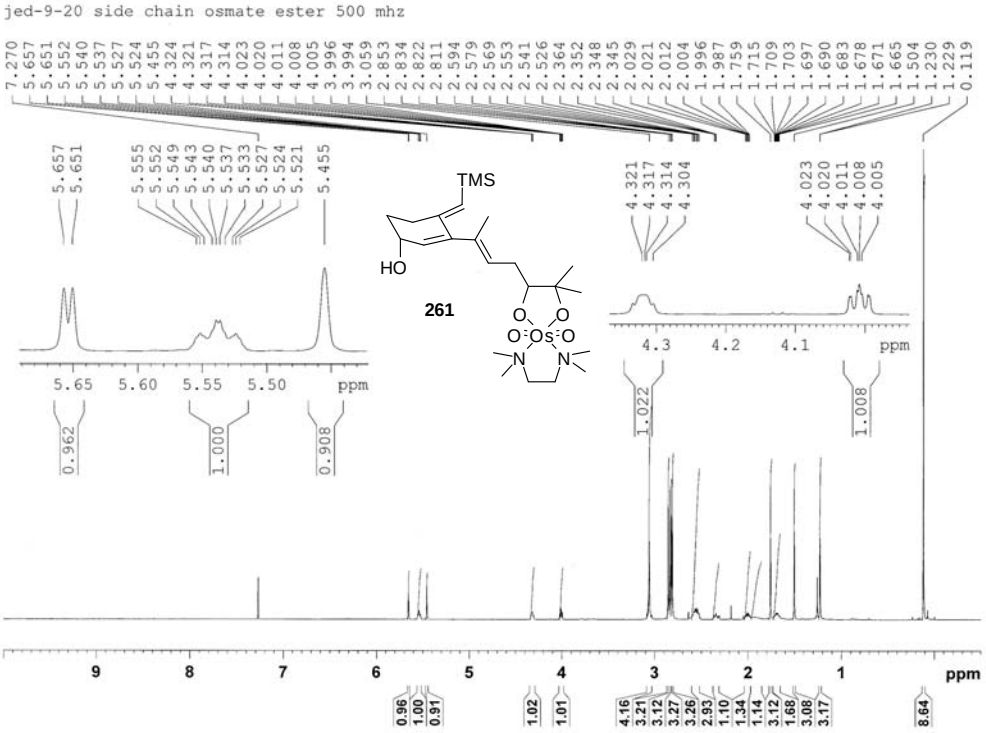


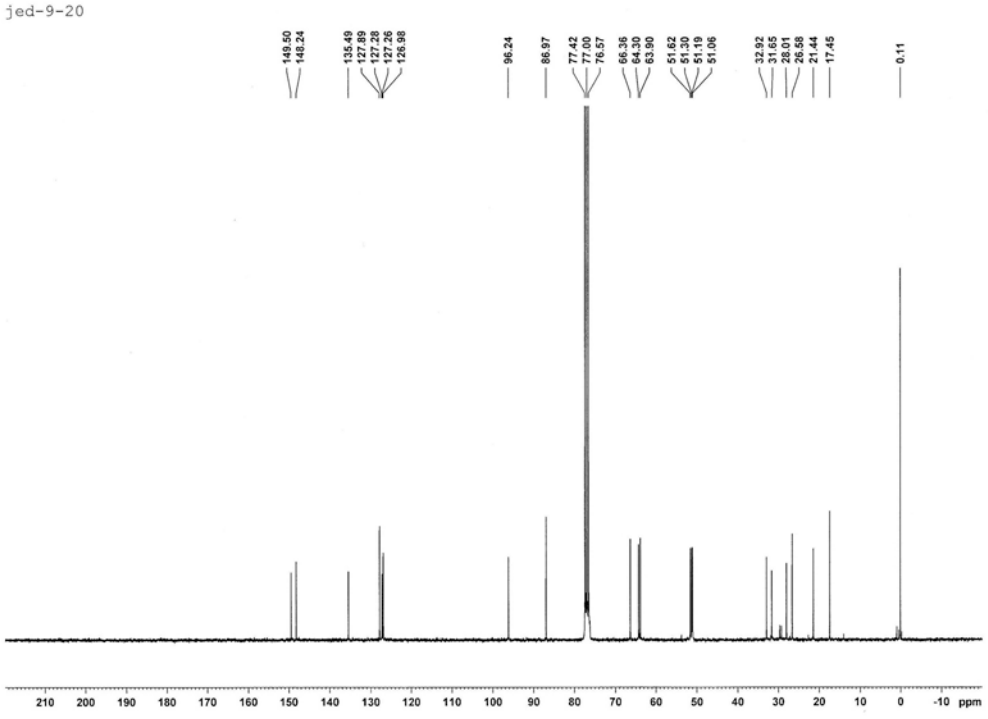
jed-9-28 E-isomer side chain epoxide 500 MHHZ

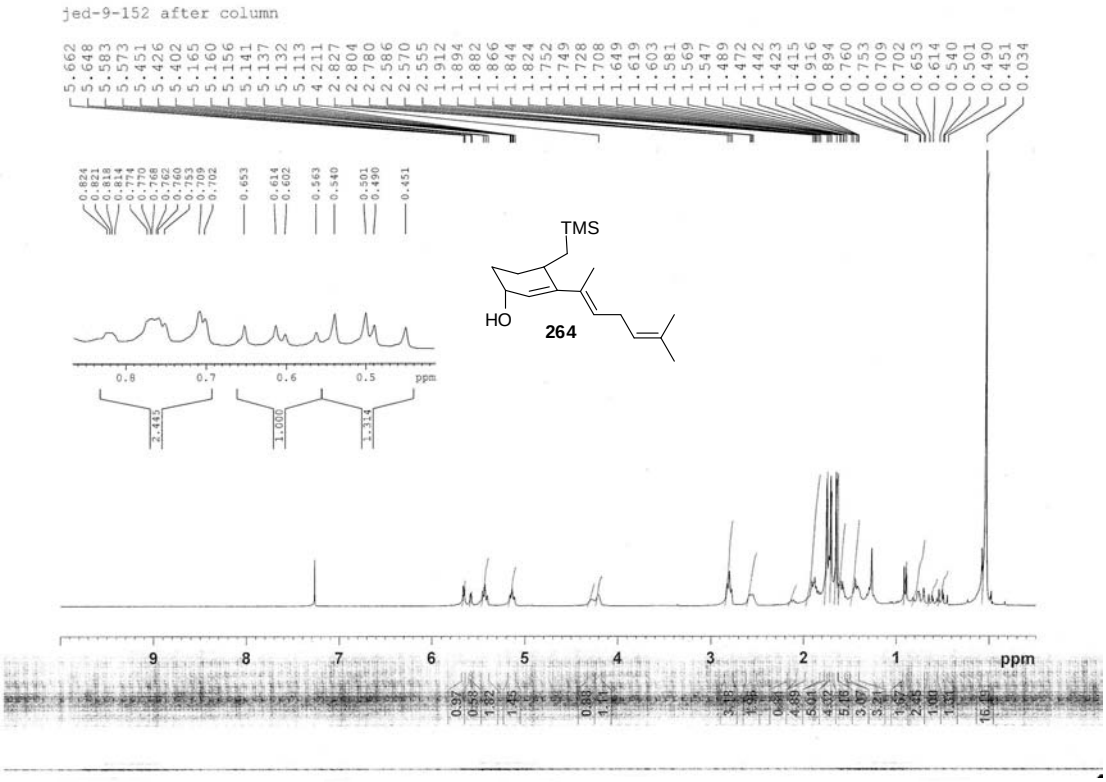


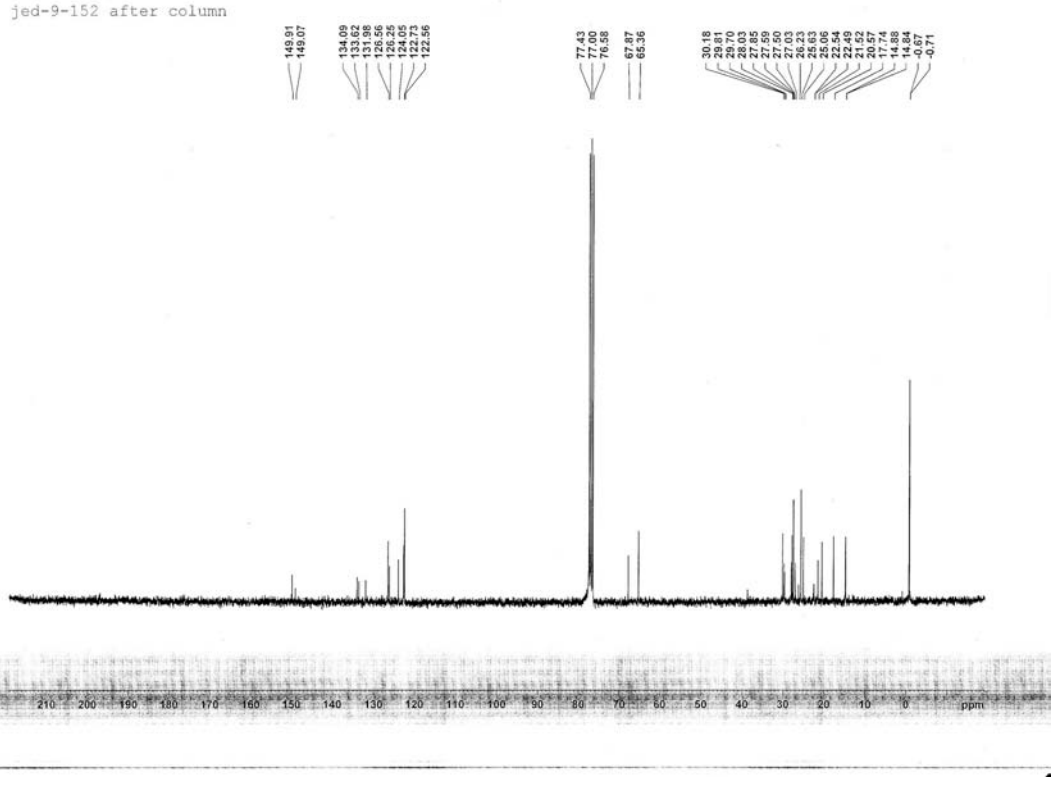
jed-9-27 side chain epoxide




jed-9-20 side chain osmate ester 500 mhz
TMS
HO
261
O
O
O
Os
O
N
N
ppm


jed-9-20
ppm


jed-9-152 after column
TMS
HO
264
ppm


jed-9-152 after column
ppm

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