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THE APPLICATIONS OF THE ANNULATIONS OF FISCHER CARBENE COMPLEXES

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Major Professor's Signature

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Date

THE APPLICATIONS OF THE ANNULATIONS OF FISCHER CARBENE COMPLEXES

VOLUME I

By

Chunrui Wu

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Submitted to
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ABSTRACT

THE APPLICATION OF THE ANNULATIONS OF FISCHER CARBENE COMPLEXES

By

Chunrui Wu

This dissertation covers the chromium Fischer carbene complexes in the annulation reactions in the following area: the chemoselectivity of different alkynes in the benzannulation reaction, the mechanism of the benzannulation reaction, and the applications of the benzannulation reaction toward the synthesis of natural products.

A competition study in the benzannulation reaction of Fischer carbene complexes between different alkynes was examined. The temperature, solvent and the scope of alkynes were investigated. The chemoselectivity between the different alkynes was controlled by the steric interaction between the carbene complex and the alkyne. The solvent has small effect on the selectivity.

A pseudo-symmetric intermediate was designed to generate in the reaction to probe the vinyl intermediate in the benzannulation reaction. The alkyne insertion step was proved to be irreversible. Electronic perturbation in the benzannulation was pursued by designing another pseudo-symmetric intermediate with two electronically differentiated arms. Between the two mechanisms demonstrated in this thesis, mechanism I with the initial formation of the η^1,η^3-carbene complexed intermediate is considered the more likely but the results of the present study could not rule out mechanism II which proposed the initial formation of the metallacyclobutene intermediate.

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The tautomer-arrested annulation was strategically applied in the attempts to the synthesis of Richardianidin-1 to construct the BC ring moiety. Both intramolecular and intermolecular methods were attempted. The intramolecular annulation involves the tethering of the alkyne to the oxygen stabilizing substituent of the carbene carbon, and the outcome of the annulation was dependent on the nature of substituent on the alkyne. The study of the intermolecular approach was focus on the regioselectivity of the alkyne incorporation, and this annulation provided higher regioselectivity than the regular benzannulation.

The cyclohexadienone annulation was successfully applied to the total synthesis of Phomactin B2. The bicyclic frame of Phomactin B2 could be generated in a single step by intramolecular cyclohexadienone annulation. Both diastereomers from the annulation could be converted to the natural product concisely by similar synthetic routes. An alternative pathway utilizing intermolecular cyclohexadienone annulation reaction and RCM as the key steps was also demonstrated. This intermolecular pathway provided the mutual bicyclic intermediates in high diastereoselectivity, and potentially could lead to the asymmetric synthesis of (+)-Phomactin B2 in the near future.

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ABBREVIATIONS

Ac	acetyl
Acac	acetyl acetonyl
Ar	argon
Bn	benzyl
Bz	benzoyl
Calcd	calculated
CAN	cerium ammonium nitrate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DIEPA	diisoproylethyl amine
DMAP	4-(dimethylamino) pyridine
DMF	N, N-dimethylformaide
DMP	Dess-martin periodinate
DMPU	1, 3-dimethyl 3, 4, 5, 6-tetrahydro-2 (*1H*)- pyrimidinone
EI	electron ionization
FAB	fast atom bombardment
FCC	Fischer carbene complex
GC	gas chromatography
HMPA	Hexamethylphosphoramide
HRMS	high resolution mass spectrometry
IR	infrared spectroscopy
KHDMS	potassium hexamethyldisilazide
LAH	lithium aluminum hydride
LHDMS	lithium hexamethyldisilazide
MEM	2-methoxyethoxymethyl
Mes	2,4,6-trimethylphenyl

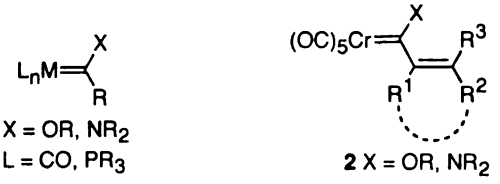
MOM	methoxymethyl
MS	mass Spectrometry
NMR	nuclear magnetic resonance
PAF	platelet activating factor
PMB	4-methoxybenzyl
PNB	*para*-nitrobenzoic
Py	pyridine
RCM	ring-closure metathesis
rt	room temperature
SEM	2-(Trimethylsilyl)ethoxymethyl
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyl dimethyl silyl
TBP	*tert*-butyl hydroperoxide
Temp	temperature
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
tol	toluene
Tr	triphenyl methyl (trityl)

CHAPTER 1

Introduction and Background of Chromium Fischer Carbene Complexes

The Fischer carbene complex (Figure 1.1) was first discovered by Fischer and Maasböl in 1964.[1] Structurally, a Fischer carbene complex (**1**) contains a metal center in a low oxidation state equipped with π-acceptor ligands. The metal also binds itself to an electron-deficient carbene through a metal–carbon double bond, and the carbene carbon, in turn, bears a heteroatom, usually oxygen or nitrogen. Electronically the carbene carbon is considered electron-deficient, due to the electron-withdrawing nature of the metal center.[2] The presence of the heteroatom is essential to balance the electron-deficient nature by delocalizing its lone pair electrons to the metal–carbon double bond. Among all Fischer carbene complexes, the α,β-unsaturated chromium Fischer carbene complex (**2**) is arguably one of the most investigated and have been known to serve as versatile reagents for a variety of transformations.[3]

Figure 1.1 General Structure of Fischer Carbene Complexes



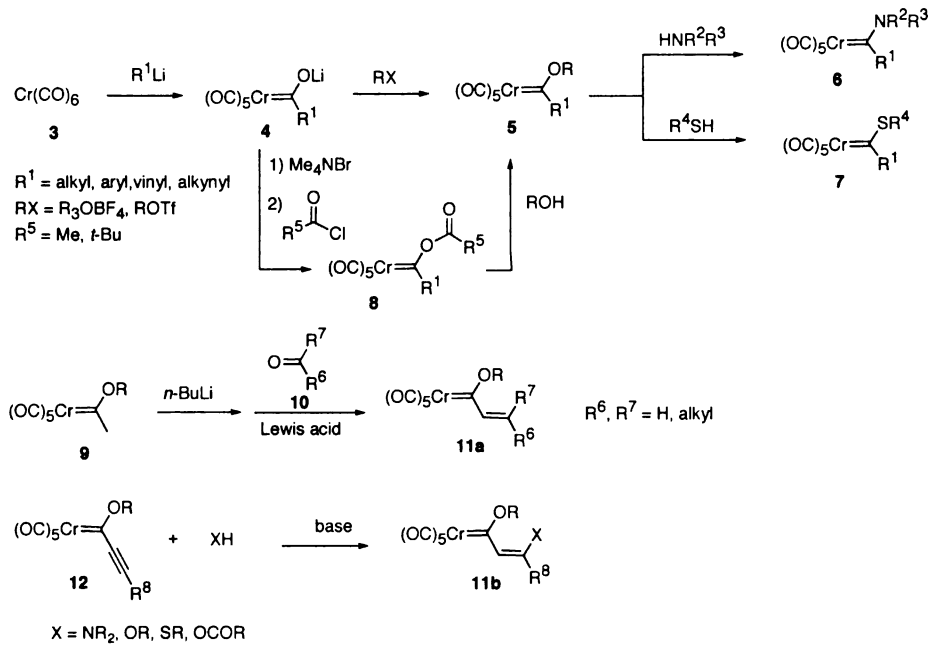
1 X = OR, NR_2
L = CO, PR_3

2 X = OR, NR_2

Fischer carbene complexes can generally be prepared from $Cr(CO)_6$ (Scheme 1.1). Addition of an organolithium species to one of the carbonyls of $Cr(CO)_6$ generates the lithium acylate **4**, which can be trapped by a strong electrophile such as an alkyl triflate or a trialkyloxonium tetrafluoroborate to afford

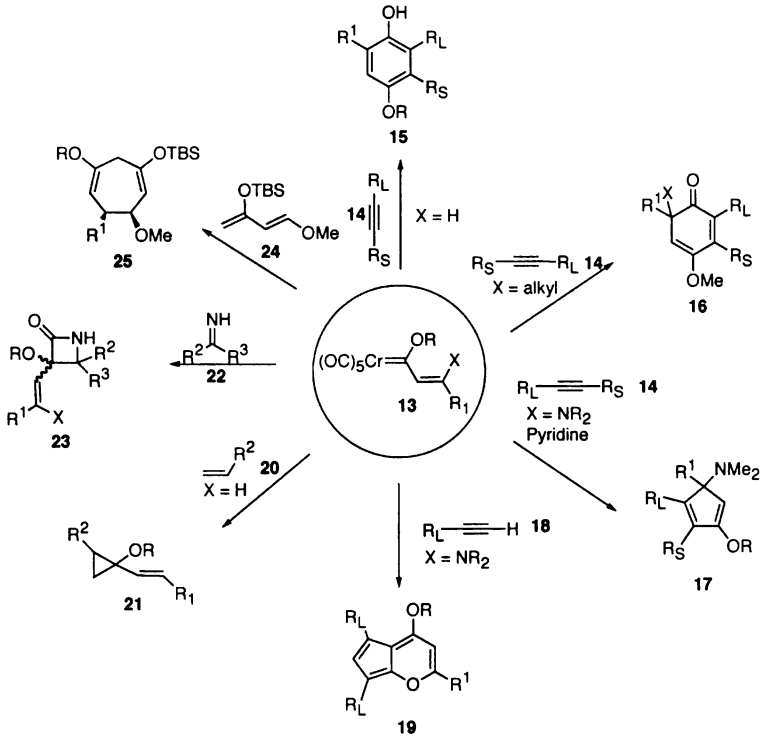
the carbene complex **5**.[4] Further substitution of the alkoxy group with amines or thiols lead to carbene complexes with nitrogen or sulfur on the carbene carbon (**6** and **7**, respectively).[5] This substitution can also be carried out with alcohols, via the acyloxy complex **8** to generate more complicated alkoxy carbene complexes including those derived from chiral alcohols.[6] Alternatively, alkenyl carbene complexes **11** can be prepared from the alkyl carbene complexes **9** by condensation with aldehydes and ketones[7] in an aldol-like reaction or from the alkynyl carbene complexes **12** in a Michael-like addition with amines,[8a] alcohols,[8b] thiols[8c] and carboxylic acids[8b].

Scheme 1.1 Preparation of Fischer Carbene Complexes



Synthetically, Fischer carbene complexes, especially α,β-unsaturated chromium Fischer carbene complexes, have proven to be important reagents in organic syntheses (Scheme 1.2).[3] The carbene moiety can participate in cyclopropanation reactions with olefins or allenes. These carbene complexes can react with a variety of alkynes to afford a wide range of cyclized products, in which, the alkyne, carbene carbon and an α,β-unsaturated substituent of the carbene carbon are incorporated. These cyclizations can be selective depending on the reaction conditions and substituents on carbene complexes and on the alkynes. Photolysis of Fischer carbene complexes with aldehydes or imines generates lactones or lactams. Representative examples are discussed in detail in this chapter.

Scheme 1.2 Brief Summary of Reactions of Fischer Carbene Complex



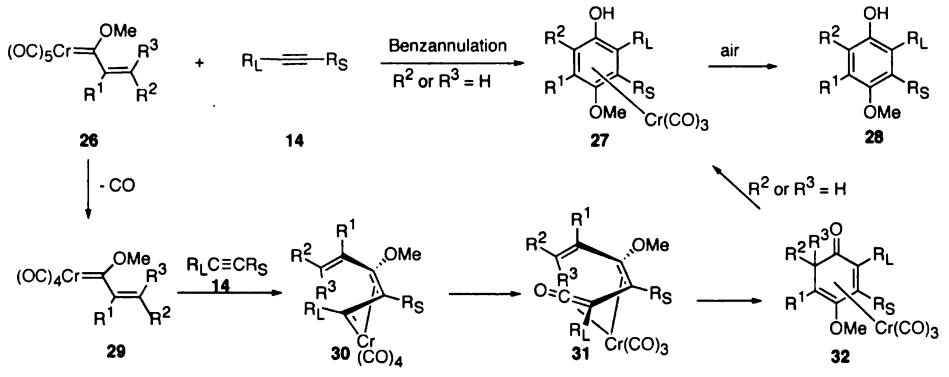
1.1 Annulation reactions of Fischer carbene complexes with acetylenes

1.1.1 Benzannulation

Discovered by Dötz in 1975,[2] the benzannulation reaction of α,β-unsaturated chromium carbene complexes with alkynes is one of the most widely used reactions of group VI Fischer carbene complexes.[9] This formal [3 + 2 + 1] annulation reaction unites the α,β-unsaturated moiety as well as the carbene carbon of the chromium carbene complex **26** with an alkyne molecule **14** and a CO ligand, ultimately affording a 4-alkoxy phenol **28** after aromatization and demetallation (Scheme 1.3). Mechanistically,[10] the reaction starts with the

carbene complex **26**. After releasing a CO ligand to give the unsaturated 16e⁻ complex **29**, alkyne insertion follows to generate the η^1,η^3-vinyl intermediate **30**. This intermediate undergoes carbonyl insertion followed by electrocyclization to afford the cyclohexadienone complex **32**. When the carbene complex is mono-substituted at the β-position, **32** aromatizes to give **27**. The phenol chromium tricarbonyl complex **27** is the primary product of the reaction. Exposure to air usually results in loss of the metal and the formation of the phenol **28**. However, protection of the phenol function in **27** can lead to air stable chromium tricarbonyl complex to give the thermodynamically more stable phenol complex.[11]

Scheme 1.3 Benzannulation Reaction



The formation of the phenolic products through this benzannulation reaction can be regioselective with the preferred orientation of the large group of the alkyne adjacent to the hydroxy group (Scheme 1.3). For terminal alkynes, the selectivity is excellent; whereas for internal alkynes, the selectivity is not high unless a significant difference in the size of the two substituents exists (Scheme 1.4).[12]

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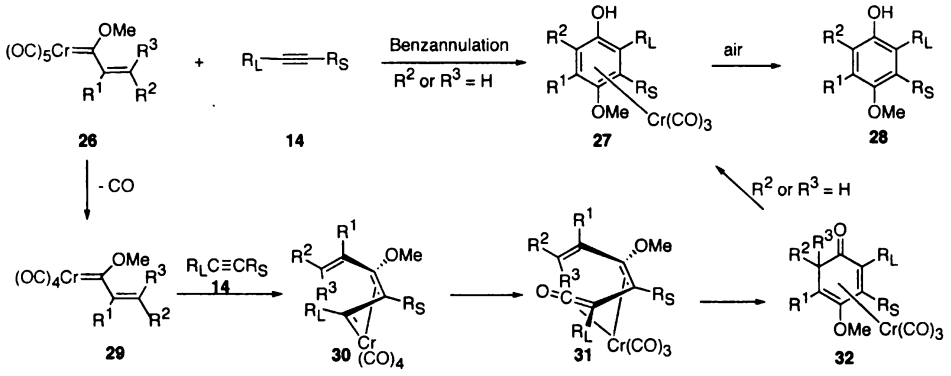

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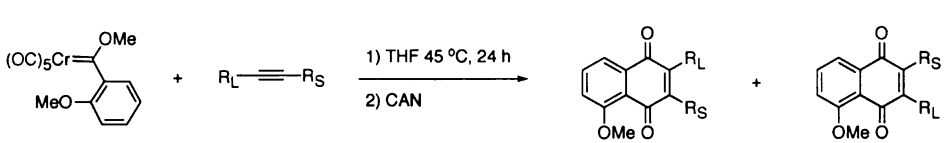
Scheme 1.4 Regioselectivity of the Benzannulation Reaction



R_L	R_S	**34 / 35**
Et	Me	1.5 : 1
i-Pr	Me	4.8 : 1
n-Pr	H	>111 : 1
Ph	Me	45 : 1

Application of this benzannulation reaction as the key step in natural product total synthesis has also been reported. Recent examples include aflatoxin B2,[13] arylglycines,[14] landomycin A,[15] and calphostins A.[16]

Recent years have witnessed the application of new techniques to this benzannulation reaction, such as microwave-assisted conditions and solid-supported conditions.[17-18] Kerr and coworkers reported that microwave-assisted benzannulations can be completed in as short as 5 minutes in equal or better yield than the traditional thermolysis.[17] The solid-supported annulation uses carbene complexes that are resin-bound via attachment to the heteroatom stabilizing substituent to afford resin-bound phenols, which can be cleaved off the resin by CAN workup to give free quinones.[18] By virtue of phase separation, the solid-supported benzannulation reaction is much less sensitive to reaction conditions, including the solvent, and is much cleaner than traditional solution-phase reactions. These new applications obviously provide more efficient and rapid access to broad range of aromatic compounds, which in turn can be used in the synthesis of bioactive targets.

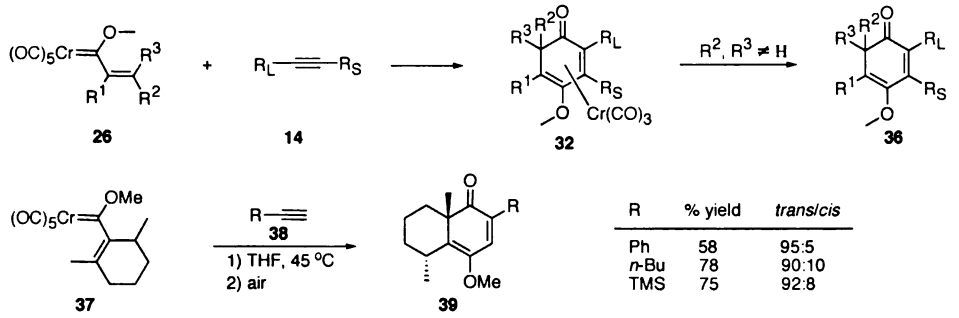
1.1.2 Cyclohexadienone annulation

As mentioned previously, the mechanism of the benzannulation reaction involves the aromatization of intermediate **32** to afford a phenol (Scheme 1.3). Such an aromatization can only be achieved if at least one of the two substituents R^2 or R^3 in structure **32** is hydrogen. Consequently, in cases where neither R^2 or R^3 is hydrogen, this aromatization will not occur and the reaction will stop at the cyclohexadienone intermediate **32**. This feature can be exploited when a β,β-dialkyl substituted alkenyl chromium carbene complex is used as the substrate (Scheme 1.5). In this case, the presence of the two substituents at the β-position does not allow aromatization and therefore, cyclohexadienone **36** can be selectively generated after loss of the metal from complex **32**.[19] This specific annulation provides a unique approach to cyclohexadienones, which are common structural motifs and synthetic intermediates.[20] Like the benzannulation reaction, the cyclohexadienone annulation can be highly regioselective with the preferred orientation of the larger group of the alkyne adjacent to the carbonyl.

However, unlike the benzannulation reaction, the cyclohexadienone annulation creates a new chiral center. This unique feature of the cyclohexadienone annulation thus offers the promise of stereo control in these reactions, which in turn has prompted several different studies on how that can be affected.[21] It has been found that intermolecular stereochemical control can be achieved by using an existing chiral center in the carbene complex to control the stereochemical outcome of this newly formed stereogenic center.[19] Thus,

annulation of Fischer carbene complex **37** bearing a chiral center provided annulated product **39** with good diastereoselectivity (Scheme 1.5).

Scheme 1.5 Cyclohexadienone Annulation



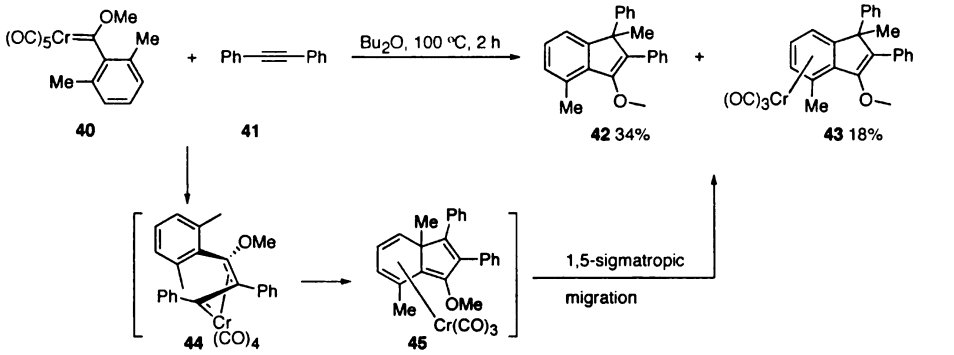
1.1.3 Tautomer-arrested annulation

The benzannulation reaction can give rise to phenol products when the α,β-unsaturated substituent is part of a double bond (Scheme 1.3) and part of an aromatic ring (Scheme 1.4). However, when the aromatic ring is 2,6-disubstituted, such as carbene complex **40**, annulation will selectively give indenes as the major product (Scheme 1.6).[22] Mechanistically, this type of annulation is similar to the benzannulation reaction in the early steps, leading to intermediate **44**, where CO insertion does not occur. Cyclization of **44** followed by a 1,5-sigmatropic migration of the angular methyl group to restore the aromaticity generates indene **42** and the corresponding chromium tricarbonyl complex **43**.

As a special case of this indene forming reaction, tautomer-arrested annulation is observed for complexes where the 2,6-disubstituted aromatic ring is further equipped with a 4-hydroxy group. This hydroxy group can tautomerize to

the corresponding ketone in the intermediate **48** (Scheme 1.6) and therefore interrupt the 1,5-migration of the methyl group.[23] Thus, this tautomer-arrested annulation can afford hydrindenone products of the type-**49**. However, depending on the relative rate of tautomerization and 1,5-sigmatropic migration, annulation of 2,6-disubstituted 4-hydroxyphenyl chromium carbene complexes can give both hydrindenones and indenes depending on the nature of the alkyne. Thus, as shown in Scheme 1.6, 1-pentyne and 3-hexyne can react with carbene complex **46** to give exclusively tautomer-arrested hydrindenone product **49**, whereas the TMS substituted acetylene give exclusively the indene product **50**.

Scheme 1.6 Tautomer-arrested Annulation



R^1	R^2	Yield (**49** + **50**) (%)	**49** / **50**
Et	Et	75	100 : 0
H	Pr	9	100 : 0
TMS	*i*-Pr	51	0 : 100

1.1.4 Annulation reaction with β-amino substituted carbene complexes

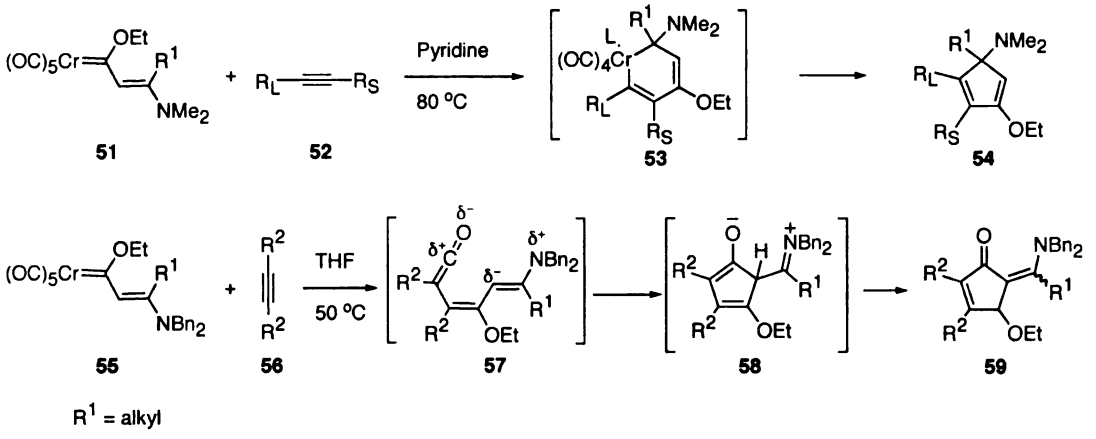
β-Amino alkenyl carbene complexes are another class of substrates that behave differently in the annulation reaction with alkynes due to the electron-donating feature of the *N*-substituent.[3a] These substrates do not afford the regular benzannulation products. Instead, they undergo a variety of different annulations, including formal [3 + 2], [2 + 2 + 1], [4 + 2] annulations, to afford cyclopentadienes, cyclopentanones, cyclopentapyrans among others. The course of the reaction depends upon the nature of the carbene complex and the alkyne as well upon the reaction conditions. In these cases, insertion of CO may not occur, and insertion of two molecules of alkyne may take place (Schemes 1.7 and 1.8). The reactivity of these β-amino alkenyl carbene complex can vary greatly and only small changes in the substrate structure and reaction conditions can cause a complete change in product formation. The exact reason for this sensitivity to substrate structure and reaction conditions remains elusive, but the electron-donating feature of the nitrogen is clearly an important factor. This electron-donating effect results in a more electron-rich chromium center which presumably leads to the different reactivity.

For example, reaction of carbene complex **51** with internal alkyne **52** in pyridine follows a formal [3 + 2] annulation to generate amino cyclopentadiene **54** without the insertion of CO (Scheme 1.7).[24] The absence of the CO insertion has been primarily attributed to the electron-donating effect of the nitrogen, resulting in a more electron-rich chromium center and a stronger Cr–CO bond. The use of coordinating solvents also suppresses the insertion of CO. The regioselectivity of

this annulation is the same as other annulations, and results in the incorporation of the large group on the alkyne adjacent to the amino group.

However, the same reaction run in THF did not give cyclopentadiene **54**.[25] Instead, a formal [2 + 2 + 1] annulation affords cyclopentenone **59**. In this case, only the carbene carbon and the α carbon are incorporated into the 5-membered ring. Mechanistically, the annulation begins with insertion of the alkyne and then CO insertion occurs to afford the ketene intermediate **57**. Due to the presence of the nitrogen, intermediate **57** has a strong dipole. Therefore, instead of the normal electrocyclic ring closure to give a phenol product, intermediate **57** undergoes enamine addition to the ketene to generate zwiterion **58**. A 1,5-sigmatropic migration of hydrogen then generats **59** as a mixture of isomers.

Scheme 1.7 Annulation Reaction of β-Amino Fischer Carbene Complex with Internal Alkynes

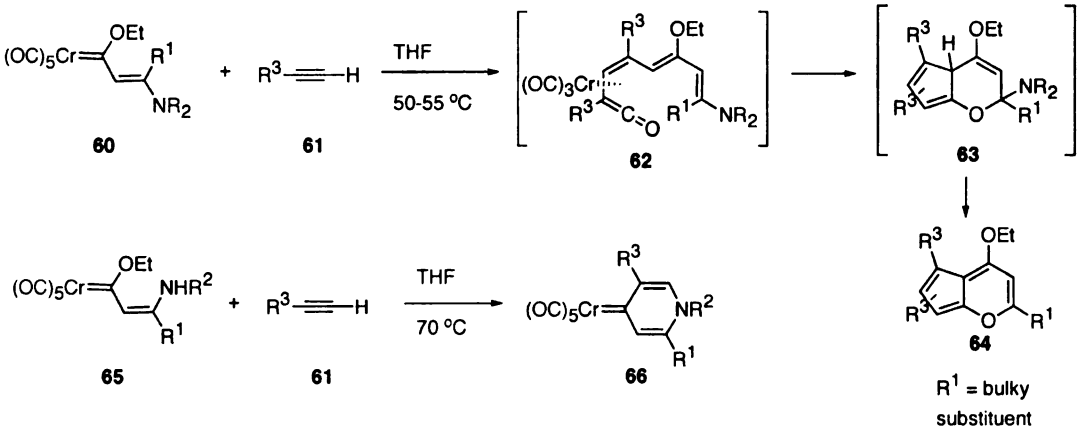


The reaction of terminal alkynes with amino-substituted carbene complexes is again different (Scheme 1.8). This reaction is dependent on the steric bulk of the R^1 of carbene complex. With small R^1 groups, the annulation

takes place with the insertion of a single alkyne and without CO insertion to give cyclopentadiene products of the type-**54** products in very low yield. But with bulky R^1 groups, the annulation occurres with double alkyne insertion and a CO insertion to form cyclopentapyran **64** (Scheme 1.7).[26] The proposed mechanism for the cyclopentapyran involves an intramolecular [4 + 2] hetero-Diels-Alder-type cycloaddition and an elimination of the amino group. The regioselectivity of the second alkyne insertion is not high and a mixture of regioisomers was obtained.

Carbene complexes with a secondary amino substituent react in a totally different way.[27] Thermolysis of carbene complex **65** with a terminal alkyne undergoes a [4 + 2] cycloaddition to give carbene complex **66**. This complex has moderate stability due to the partial aromaticity of the ring, and the reaction stops at this point.

Scheme 1.8 Annulation Reaction of β-Amino Fischer Carbene Complex with Terminal Alkynes

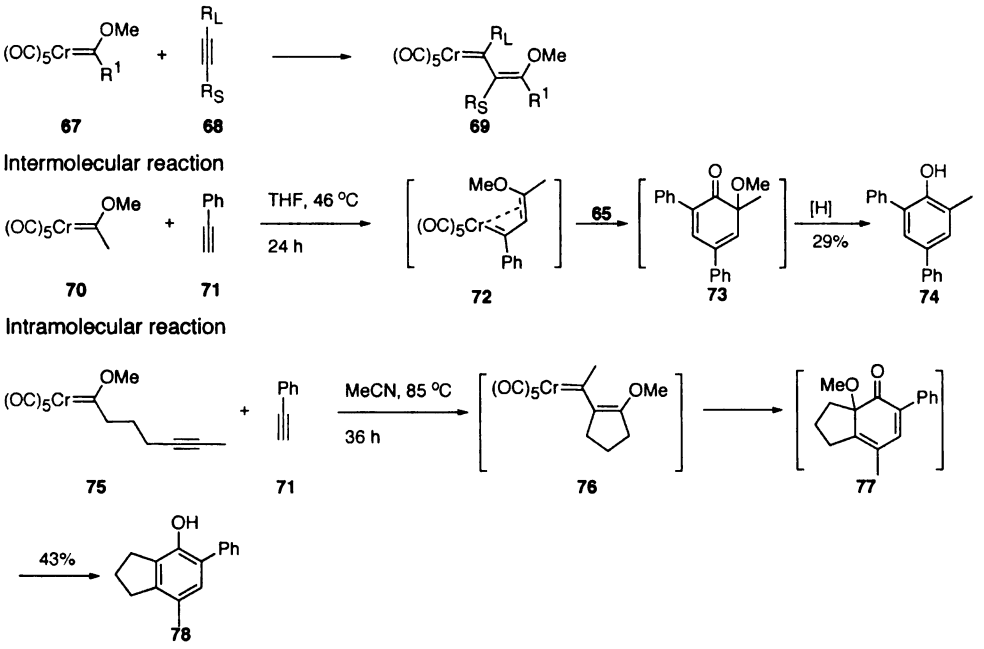


1.1.5 Reaction of α,β-unsaturated Fischer carbene complex prepared *in situ*

Since α,β-unsaturated Fischer carbene complexes can be prepared from the reaction of acetylenes with simple alkyl Fischer carbene complexes, it is possible to initiate the annulation reactions using simple alkyl carbene complexes as starting materials. In this process, the alkyl carbene complex will first react with one molecule of acetylene to generate the α,β-unsaturated Fischer carbene complex, which in turn reacts with a second molecule of the acetylene to furnish the annulation product.

Two examples of this type of process are shown in Scheme 1.9. The intermolecular reaction of complex **70** with two molecules of phenylacetylene gives rise to the phenol **74**. This reaction involves the intermediate of Fischer carbene complex **72** which is not strictly a Fischer carbene complex because the carbene carbon does not bear a heteroatom. Reaction of intermediated **72** and the second alkyne furnishes the intermediate **73**, which is further converted to the phenolic product **74**.[28] The formation of **74** can be attributed to an *in situ* reduction of **73** via a chromium(0) species. The intramolecular example of complex **75** and alkyne **71** has the first alkyne moiety incorporated in the starting carbene complex, which gives the vinylogous Fischer carbene complex **76** which further reacts with alkyne **71** in an intermolecular fashion to furnish the intermediate **77**. Final reduction leads to the phenol product **78**.[29]

Scheme 1.9 Reaction of α,β-Unsaturated Fischer Carbene Complex Generated *in situ*



1.2 Reaction of Fischer carbene complexes with alkenes

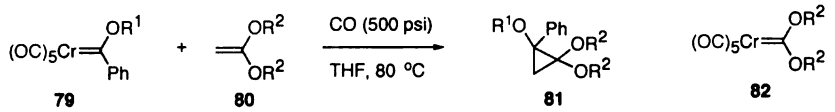
1.2.1 Cyclopropanation with simple alkenes

Cyclopropanation of chromium Fischer carbene complexes with alkenes has been extensively investigated.[30] The best alkene substrates are those substituted with either electron-releasing groups or electron-withdrawing groups.[31] Electron-neutral alkenes are known to best react intramolecularly, although in rare cases intermolecular examples are known.[32] For alkenes equipped with electron-releasing groups, such as ketene acetal **80**, the reaction must be carried out under CO pressure. In the absence of CO, the alkene

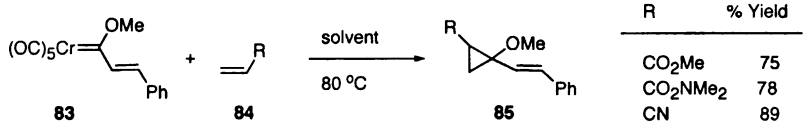
metathesis product **82** is the major product (Scheme 1.10).[33] The cyclopropanation reaction has good functional group tolerance, including esters, ethers and cyano groups. The reaction does not tolerate good leaving groups at the allylic positions.

The diastereoselectivity of this cyclopropanation is generally not high. However, it can be improved if either the carbene carbon or the alkene is conjugate to a π-system. Barluenga and coworkers reported that the β-aryl alkenyl carbene complex **86** will react with simple alkenes, such as 1-hexene, to afford cyclopropane **88** in moderate to good yields and diastereoselectivities.[32] The large substituent on the alkene preferentially incorporated into the cyclopropane trans to the alkenyl group from the carbene complex.

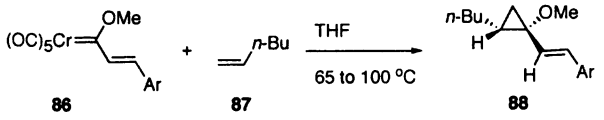
Scheme 1.10 Cyclopropanation of Fischer Carbene Complex



R^1	R^2	% Yield
i-Pr	Et	69
L-menthol	Me	98



R	% Yield
CO_2Me	75
CO_2NMe_2	78
CN	89



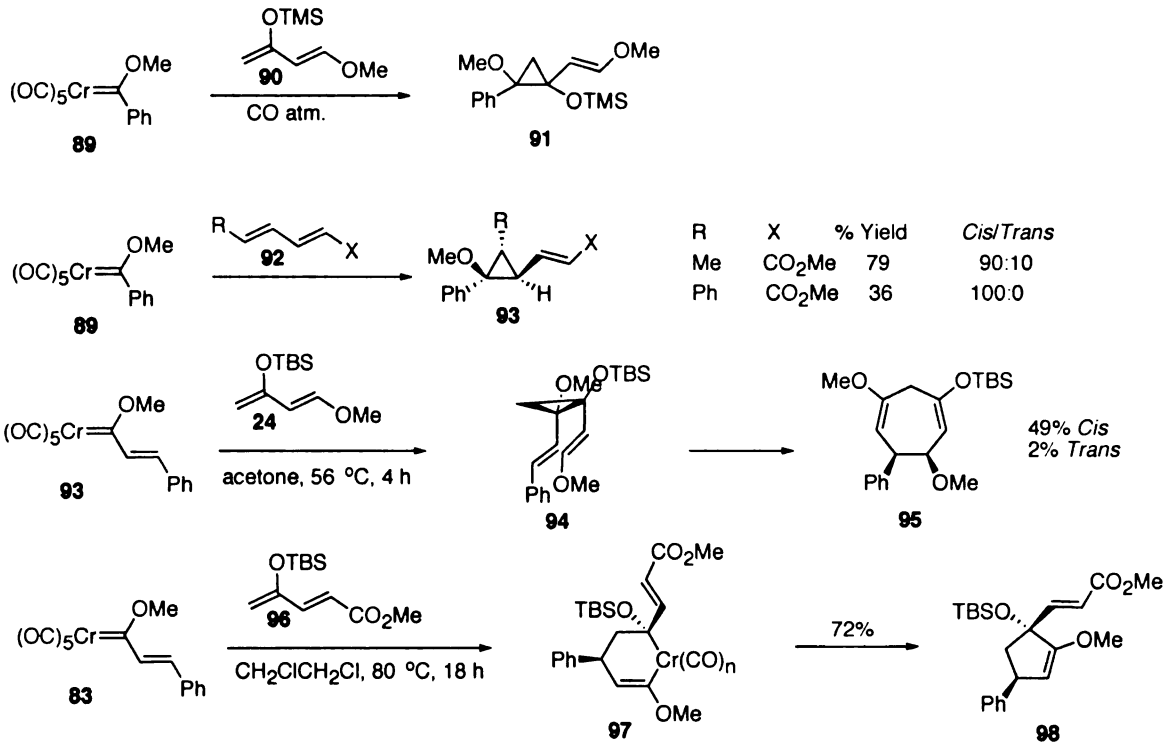
moderate to good yields and *de*

1.2.2 Cyclopropanation with dienes

Dienes can also react with chromium Fischer carbene complexes to give cyclopropanes. The reaction tends to occur at the less hindered or the more electron-rich double bond. Thus, the terminal alkene in diene **90** selectively reacts due to steric and electronics reasons, and the γ,δ-double bond in diene **92** selectively reacts due to electronic reasons.[34] In certain cases, the cyclopropanation can be followed by other reactions in a domino process. For example, vinyl carbene complex **83** reacts with diene **24** to afford cyclopropane **94**, which is set up for a subsequent [3,3]-sigmatropic rearrangement, eventually affording cycloheptadiene **95** with high diastereoselectivity.[35]

The reaction of diene **96** which has both an electron withdrawing and electron releasing substituent with carbene complex **83** goes through a different pathway.[36] It has been suggested that this reaction takes place via a hetero [4 + 2] cycloaddition between the electron-deficient chromadiene and the electron-rich terminal double bond of the siloxydiene. This cycloaddition is apparently *endo*-selective to give **97** and subsequent reductive elimination of the chromium fragment affords cyclopentene **98**.

Scheme 1.11 Annulation of Fischer Carbene Complex with Dienes

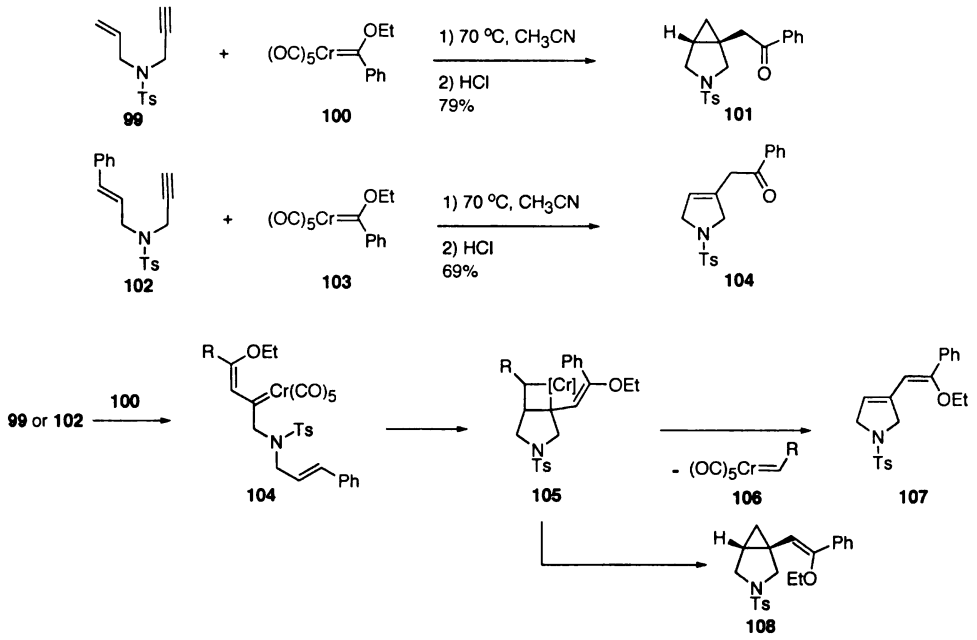


1.2.3 Metathesis

Metathesis reactions of chromium-carbene double bonds are rare. Mori reported that ring-closing enyne metathesis of enyne **102** with carbene complex **100** could afford metathesis product **103** in moderate yield.[37] However, with the simplified enyne **99**, reaction with same complex only provided the cyclopropane product **101**. The difference in these two reactions is obviously the presence of the phenyl group. Insertion of the alkyne into the carbene complex gives the intermediates **104**, which then undergoes [2 + 2] cycloaddition to give the chromacyclobutane intermediate **105**. Metathesis would be expected to be more facile when R is phenyl than when R is hydrogen because this would involve an

extrusion of a more stabilized carbene complex **106**. At the current stage, metathesis using chromium carbene complex is limited to a few examples and not yet general enough to be useful in synthesis.

Scheme 1.12 Enyne Metathesis of Fischer Carbene Complex



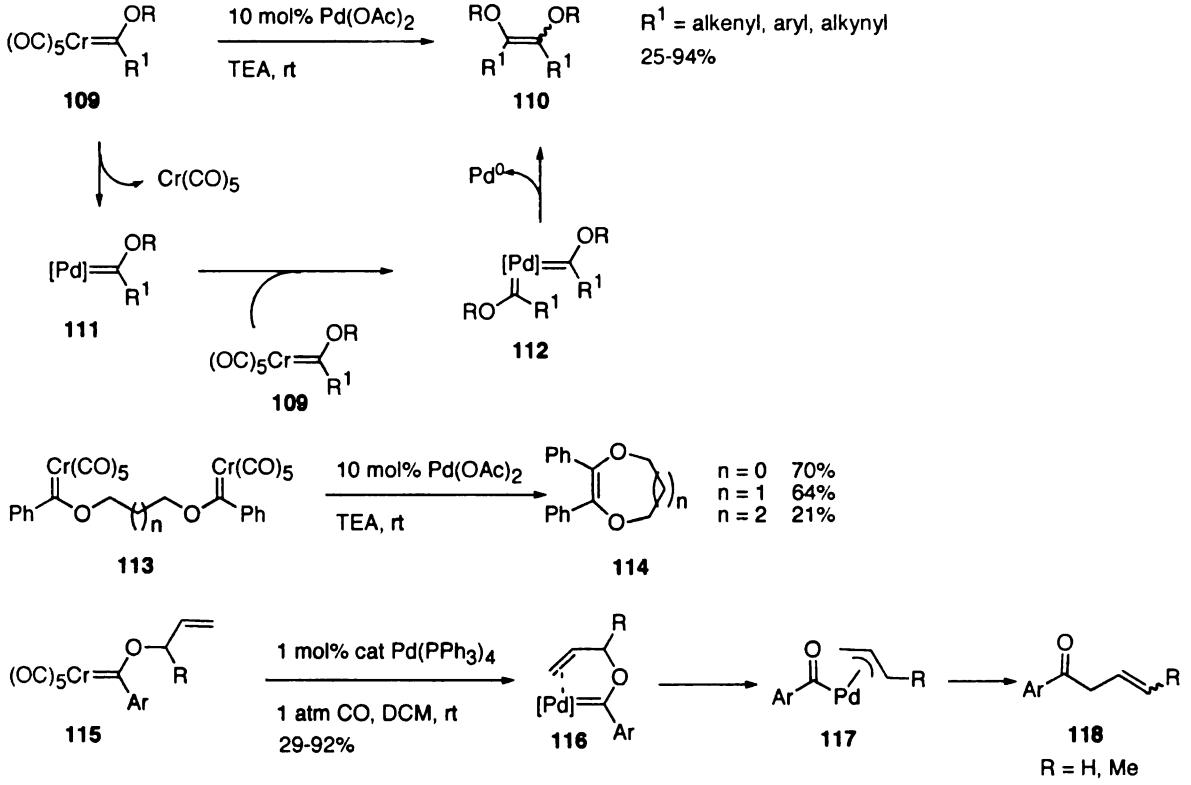
1.3 Reactions of Fischer carbene complexes involving metal-mediated transformation

1.3.1 Pd-catalyzed dimerizations

In the last few years, catalytic transmetalations involving group VI Fischer carbene complexes have experienced enormous attention.[38] The dimerization of such Fischer carbene complexes catalyzed by palladium species (Scheme 1.14) is among the newly discovered reactions in this class. Active palladium catalysts

include $Pd(OAc)_2$, $Pd_2(dba)_3 \cdot CHCl_3$, $PdCl_2 \cdot (MeCN)_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$.[39] As a general example, chromium carbene complexes of the type **109** could undergo dimerization to afford endiol ether **110** in the presence of $Pd(OAc)_2$. The scope includes complexes **109** where R^1 is an akenyl, aryl or alkynyl group and the yield varies significantly with different substrates. The mechanism of this reaction starts with a Pd–Cr exchange to give Pd-carbene complex **111**. In the case where R^1 is alkyl group containing an α-hydrogen, a β-hydride elimination occurs followed by a reductive elimination to give the vinyl ethers. Subsequent transmetallation with another molecular of chromium carbene complex generates Pd–*bis*carbene complex **112**, which reductive eliminates Pd^0 and gives dimer **110**. Similarly, intramolecular dimerization of *bis*-chromium carbene complex **113** afforded a cyclic enol-ether **114**, with the best yields for six- or seven-membered rings. A special case is the allyloxy aryl chromium carbene complex **115**, which underwent 2,3-sigmatropic rearrangement to furnish allyl aryl ketone **118** (Scheme 1.13).[40] The mechanism of this reaction probably involves the Pd-alkene-carbene complex **116**.

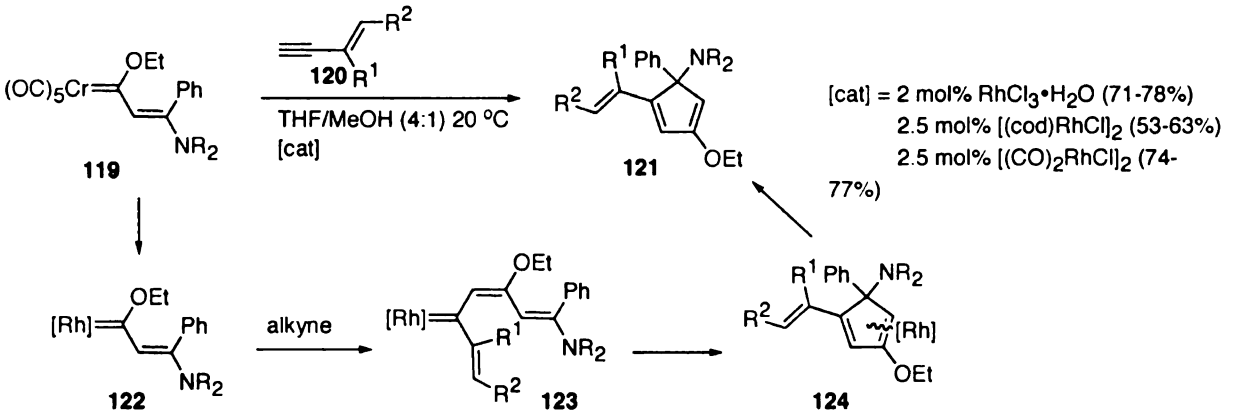
Scheme 1.13 Pd Catalyzed Transmetallation



1.3.2 Rh-catalyzed annulations

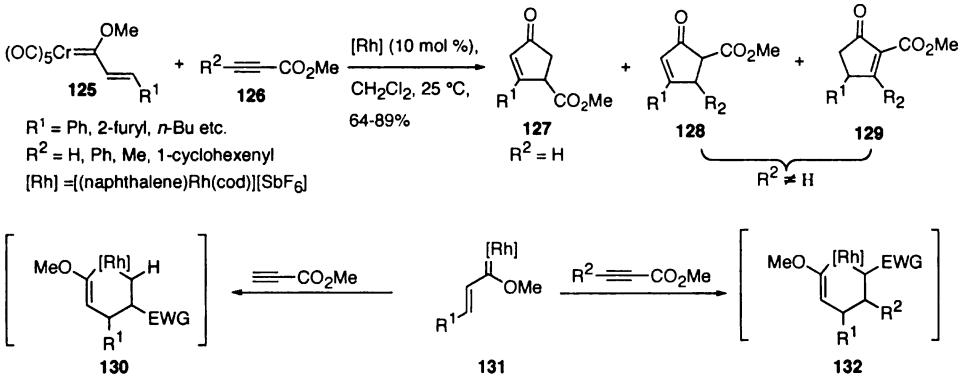
The first example of a rhodium-catalyzed annulation of a chromium Fischer carbene complex and an alkyne was reported by Aumann and coworkers in 1999.[41] The annulation of carbene complex **119** with alkyne **120** generated cyclopentadiene **121** in the presence of a rhodium catalyst (Scheme 1.14).[42] Mechanistically, this reaction starts with the transmetallation to give the rhodium-carbene complex **122**. Alkyne insertion into **122** gives intermediate **123**, which undergoes electrocyclization to give the rhodium bound cyclopentadiene **124**. Demetallation of **124** gives the cyclopentadiene product **121** and regenerates the Rh catalyst.

Scheme 1.14 Rh Catalyzed Annulation of Fischer Carbene Complex with Alkynes



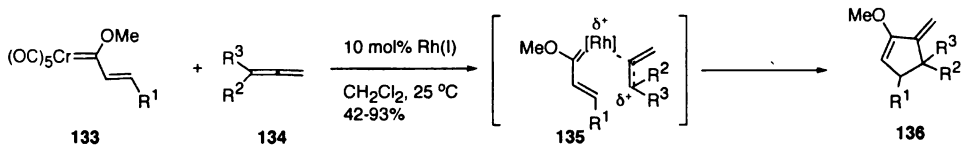
It's well known that electron-withdrawing alkynes gave poor yield in the benzannulation reaction.[43] However, in the presence of a rhodium catalyst, electron withdrawing alkynes will react with vinyl Fischer carbene complexes smoothly to give cyclopentenones.[44a] As shown in Scheme 1.15, Fischer carbene complex **125** reacts with alkyne **126** to generate regioisomers **127-129**, the ratio of which depends on the nature of alkyne. Presumably this reaction involves a metalla-Diels-Alder cyclization to give intermediate **130** or **132**. For terminal alkynes, the cyclization is sterically controlled to give intermediate **130** with the smaller H aligning near the metal. For internal alkynes, the steric factor is diminished and the cyclization is controlled by the interaction between the electrophilic metal and the more nucleophilic alkyne carbon.

Scheme 1.15 Rh Catalyzed Annulation of Fischer Carbene Complex with Alkynes II



The other example of a catalyzed annulation involves the reaction of a transmetallated rhodium carbene complex with allenes.[44b] As demonstrated by the example in Scheme 1.16, Fischer carbene complex **133** can undergo transmetalation with a rhodium catalyst, followed by reaction with allene **134** to give a cyclopentene product **135**. Presumably this transformation involves a non-concerted metalla-[4 + 2] cycloaddition to generate intermediate **136** followed by reductive elimination to give **135**.

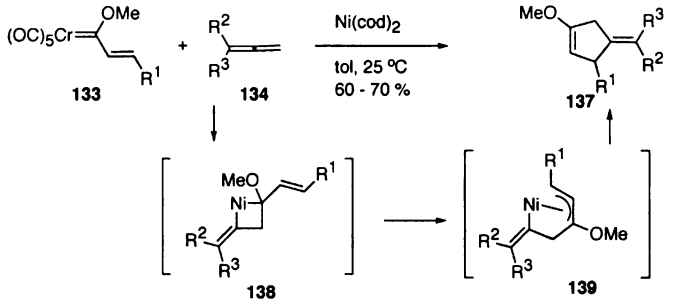
Scheme 1.16 Rh Catalyzed Annulation of Fischer Carbene Complex with Allenes



1.3.3 Ni-mediated annulations

Under nickel(0)-mediated conditions, alkenyl chromium carbene complexes can react with allenes, alkynes, and alkenes to provide a wide range of products. As reported by Barluenga's group, alkenyl chromium carbene complexes can react with allenes and a stoichiometric amount of a nickel species to furnish cyclopentenol ethers (Scheme 1.17).[44b] This reaction starts with a Ni/Cr exchange, followed by a [2 + 2] cycloaddition of the less substituted C=C bond of the allene to give intermediates **138**. This intermediate rearranges to structure **139**, which is presumably driven by release of the ring strain, and then subsequent reductive elimination affords the final product. It should be noted that the selectivity for the two double bonds in the allene in this reaction is different from that of the Rh-catalyzed reaction, where the more substituted double bond reacted (Scheme 1.16).

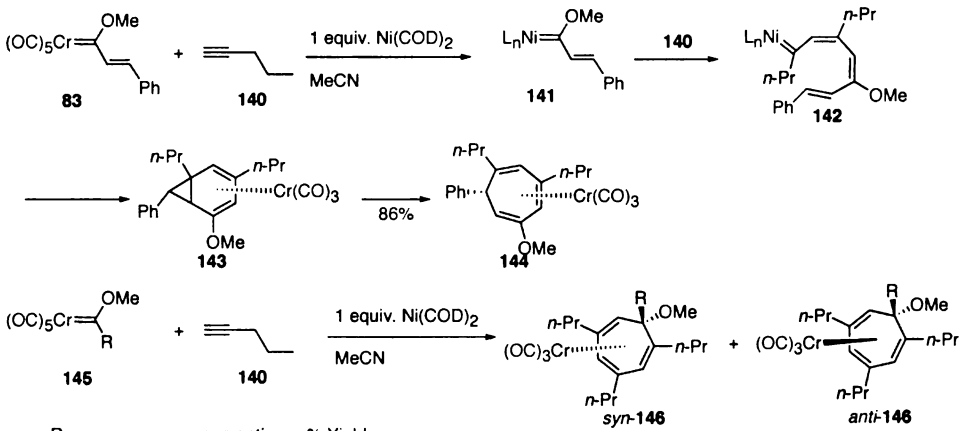
Scheme 1.17 Ni Catalyzed Reaction of Fischer Carbene Complex with Allenes



The annulation reaction of alkenyl chromium Fischer carbene complex with alkynes also requires a stoichiometric amount of nickel.[45] The overall

reaction is a formal [3 + 2 + 2] annulation involving double insertion of the alkyne to form cycloheptatriene **144** (Scheme 1.18). The aryl chromium carbene complex **145** also provides cycloheptatriene products **146** by reacting with 3 equivalents of the alkyne.

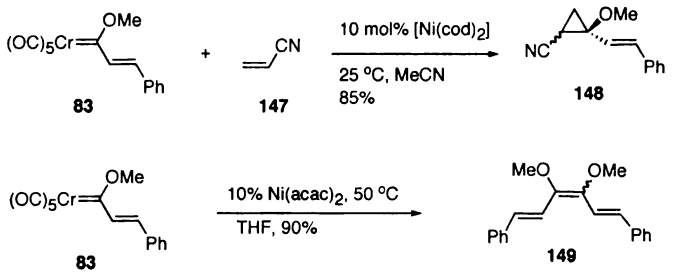
Scheme 1.18 Annulation of Fischer Carbene Complex Involving Ni^0



R	*syn*:*anti*	% Yield
Ph	60:40	68
p-MeO-C_6H_4	>98:2	83
2-Furyl	90:10	86

Alkenes are also known to react with Fischer carbene complexes under Ni-catalyzed reaction conditions to provide cyclopropanation products (Scheme 1.19).[46] The reaction conditions are milder than without the Ni-catalyst (Scheme 1.10). The dimerization of Fischer carbene complexes could also be catalyzed by Ni species (Scheme 1.19).[47] In both cases, the active intermediates were believed to be that of the corresponding nickel carbene complex via Ni/Cr exchange.

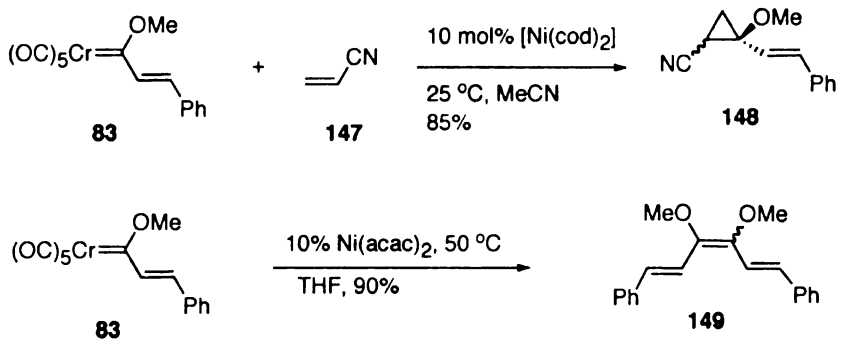
Scheme 1.19 Ni Catalyzed Cyclopropanation and Dimerization



1.4 Photolysis of Fischer carbene complexes

It's known that chromium carbene complexes will rearrange into a ketene complex **151** upon photolysis. Ketene complexes generated in this way are very reactive and able to readily react with aldehydes or imines to form β-lactones or β-lactams (Scheme 1.20). [48] For example, the reaction between carbene complex **89** and aldehyde **152** under photolytic conditions in the presence of DMAP and under a CO atmosphere provided β-lactones **153** as a pair of diastereomers.[49] It was found that certain substrates (electron-rich or unsaturated aldehydes) under these reaction conditions generated the decarboxylated product **154**.

Scheme 1.19 Ni Catalyzed Cyclopropanation and Dimerization



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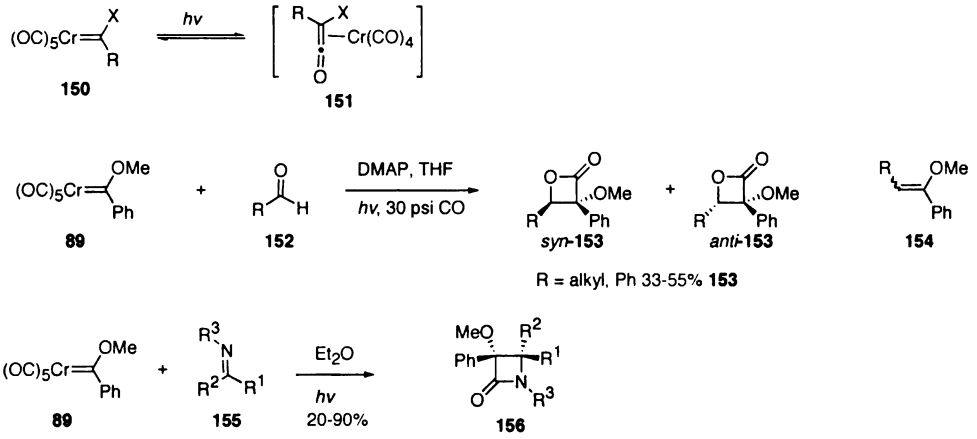
Scheme 1.20 Photolysis of Fischer Carbene Complexes



150 151 89 152 syn-153 anti-153 154 89 155 156

1.5 Summary

During the past few decades, Fischer carbene complexes, especially those of chromium, have been shown to have broad and powerful utility in synthetic organic chemistry. Such metal complexes offer versatile reactivities under a variety of reaction conditions to provide a broad scope of different products. Although many reactions are undoubtedly yet to be discovered and others have yet to be developed, many reactions of Fischer carbene complexes have been developed into mature, reliable, and useful synthetic protocols. The applications of such reactions have also been realized in total synthesis of natural products and in the preparation of chiral ligand for asymmetric catalyst.[43]

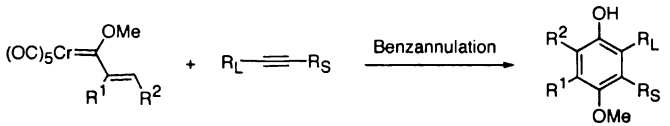
CHAPTER 2

A Competition Study in the Benzannulation Reaction of Fischer Chromium Carbene Complexes: Terminal vs. Internal Alkynes

2.1 Background

As discussed in Chapter 1, the benzannulation reaction of chromium carbene complexes with alkynes has been widely used in organic syntheses to construct highly functionalized aromatic rings (Scheme 2.1).[5,51]

Scheme 2.1 Benzannulation Reaction



157 **14** **28**

The product distributions from this reaction are generally dependent upon the concentration of alkynes, temperature and solvent. The phenolic product is favored under high concentrations, lower temperatures, and in non-coordinating solvents.[52-54] Other side-reactions can also take place to generate a variety of side-products including indenes,[52a] vinylcyclopentadienones,[52a] furans,[52b] cyclobutenones,[53] and two-alkyne phenols.[54] In nearly all cases, there is a preference for the larger alkyne substituent to be incorporated adjacent to the hydroxy group (Structure **28**, Scheme 2.1).[12] The reaction generates a single regioisomer for terminal alkynes, and two regioisomers for internal alkynes, and the ratio of the latter is dependent upon the steric bulk of the two substituents on

the alkyne. Electronic perturbations have rarely been reported to disturb the normal steric control of the regioselectivity.[55]

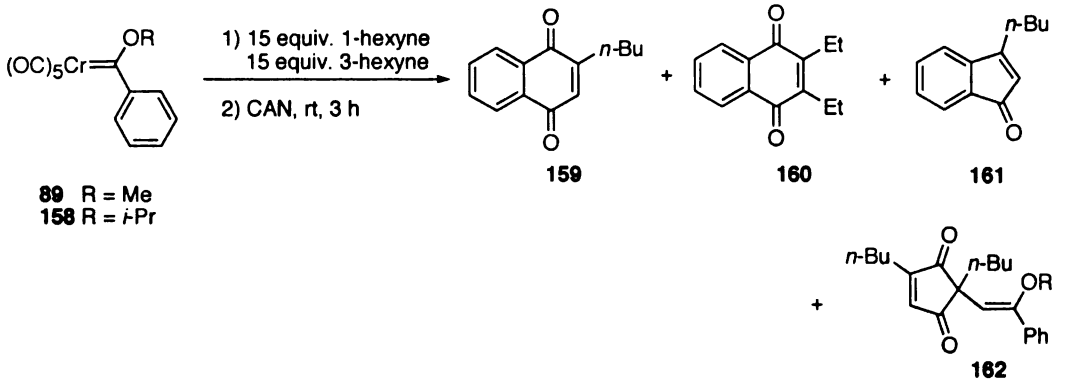
2.2 Competition reaction between terminal and internal alkynes

Despite the numerous studies on the chemoselectivity[53-54] and regioselectivity[12,55] of the benzannulation reaction, to the best of our knowledge, no previous studies investigated the competition between different alkynes in the benzannulation reaction. We expected that this competition study could potentially provide valuable information for employing substrates bearing multiple alkynes in the benzannulation reactions.

The competition study was first carried out between terminal and internal alkynes. The benzannulation reaction with methoxy phenyl chromium carbene complex **89** was initially carried out using 15 equivalents of both 1-hexyne and 3-hexyne in benzene at 80 °C (Scheme 2.2).[52a] With large excesses of alkynes, the concentration of the two alkynes could be considered as a constant even if one of the two alkynes was consumed more rapidly. Thus, the difference in the concentration of the two alkynes could be considered negligible. Since the resulting phenolic products were unstable to air, these reactions were subjected to an oxidative workup with CAN (0.5 M cerium (IV) ammonium nitrate in 0.1 M HNO_3 solution) to convert the phenol products into the corresponding quinones and the major indene side-product into indenone. Such an oxidative workup should not be expected to introduce significant error in the product ratios, since previous studies in Wulff's laboratory demonstrated that an oxidative workup

afforded quinines in the same isolated yields as phenols with an oxidative workup using air.[54] We thus chose the more practical CAN oxidative workup protocol. It was quickly realized that the benzannulation reaction was very selective, as the ratio of annulated products **159** and **160** was determined to be 93:7 by GC analysis for the reaction in benzene at 80 °C (Table 2.1, Entry 1).

Scheme 2.2 Benzannulation of Carbene Complexes with 1-Hexyne and 3-Hexyne



Having obtained such an encouraging initial result, more detailed studies were undertaken to investigate how other perturbations affect the selectivity of this reaction. Since temperature and the nature of the solvent are known to affect the yields and product distributions of the benzannulation reaction,[53] the same reaction between methoxy phenyl carbene complex **89** and the 1-hexyne/3-hexyne mixture as shown in Scheme 2.2 was carried out in various solvents at 40 °C and 80 °C. In addition, the reaction of the *iso*-propoxy phenyl carbene complex **158** was also explored to determine the effect of the size of the group on oxygen stabilizing substituent (Table 2.1, Entries 8-14).

Table 2.1 Temperature and Solvent Effects in the Reaction of Fischer Carbene Complexes with 1-Hexyne/3-Hexyne[a, b]

Entry	Carbene complex	Temp. (°C)	Solvent	% Yield **159**[b]	Ratio[d] of **159/160**
1	**89** (R = Me)	80	Benzene	84	93:7
2		80	THF	42	94:6
3		80	CH_3CN	41	98:2
4		40	Benzene	69	95:5
5		40	THF	35	98:2
6		40	CH_3CN	33	98:2
7		40	Hexane	64	96:4
8	**158** (R = *i*-Pr)	80	Benzene	84	94:6
9		80	THF	56	99:1
10		80	CH_3CN	41	99:1
11		40	Benzene	74	>99:1
12		40	THF	55	99:1
13		40	CH_3CN	40	98:2
14		40	Hexane	79	>99:1

a) All of the above reactions were run in 0.3 mmol scale with 5 mL solvent. The reaction time was 16 hours for 80 °C and 22 hours for 40 °C. b) Trace amount of **161** and **162** could be detected by GC-MS. c) Isolated yield; d) Determined by GC and GC-MS.

As can be seen by the data in Table 2.1, the benzannulation reaction exhibits excellent selectivity for the reaction of 1-hexyne over 3-hexyne. The level of selectivity for the reaction of the methoxy complex **89** was between 93:7 to 98:2 for all temperatures and solvents that were examined. In all cases, 1-hexyne was far more reactive than 3-hexyne in this benzannulation reaction. This

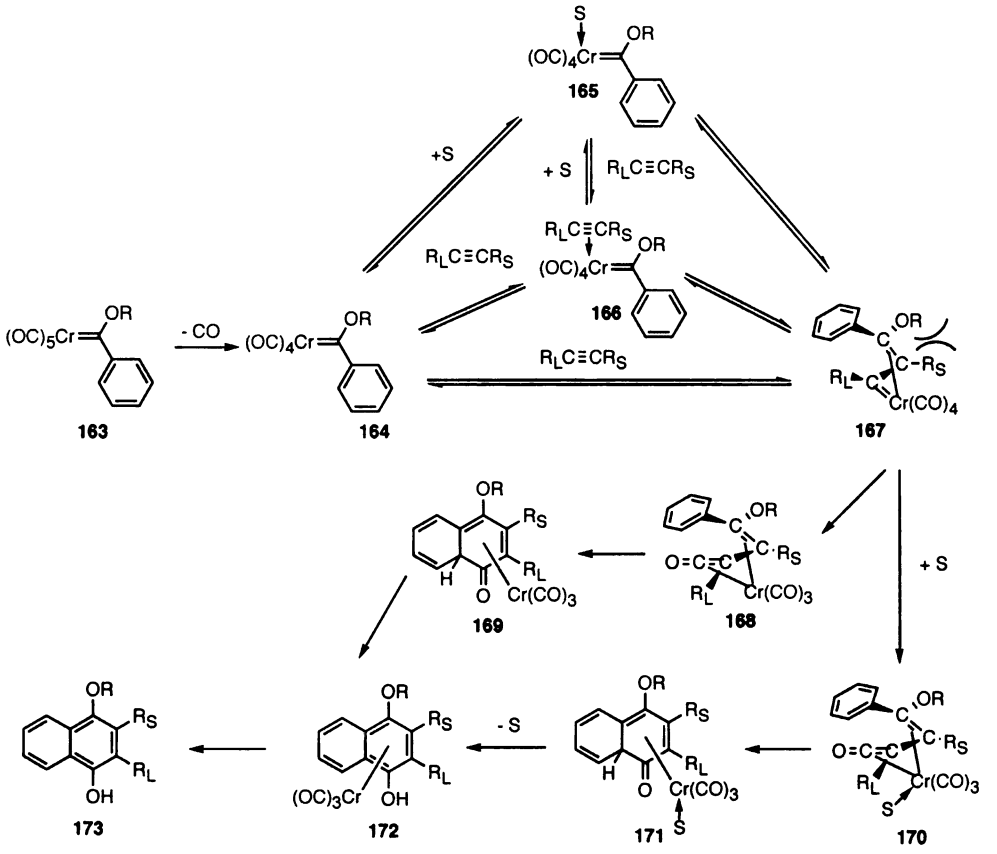
selectivity can be attributed to steric differences between the two alkynes and the origins of this will be discussed in more detail below.

A mechanistic account of the selectivity seen between 1-hexyne and 3-hexyne is shown in Scheme 2.3.[10] The first step is a rate-limiting loss of CO to give the 16e$^-$ unsaturated carbene complex **164**.[10h] Although not rate limiting, the next step involves a bimolecular reaction of **164** with an alkyne to give whether the alkyne complex **166**, or with carbon–carbon bond formation to give the η^1,η^3-vinyl carbene complex **167**. It is not known whether the formation of **166** or **167** from **164** involves reversible steps or not.[10d] The next involves insertion of CO into the Cr–C bond of **167** to give **168** or **170**. There is evidence suggests that CO insertion is not reversible.[10d] The origins of the selectivity between 1-hexyne and 3-hexyne must lie in the kinetic formation of either **166** or **167**, or if these steps are reversible, in the relative stability of **167** derived from 1-hexyne and from 3-hexyne. Thermodynamically, the former would be expected to give **167** with lower energy, given the close contacts expected between R_S (H vs. Et) and the alkoxy substituent. The same expectation would pertain to the transition state for the formation of **167** under kinetic conditions. Therefore, the reaction with 1-hexyne would be expected to be greatly faster and more favored.

When the methoxy carbene complex **89** was substituted with the more sterically demanding *iso*-propoxy carbene complex **158**, the chemoselectivity between 1-hexyne and 3-hexyne was even more pronounced. Greater than 99:1 selectivity (Entries 11 and 14, Table 2.1) could be observed in both benzene and hexanes. The more bulky *iso*-propoxy group in complex **158** would be expected

to induce a stronger interaction with R_S in the η^1,η^3-vinyl carbene complex **167** (Scheme 2.3), which should lead to a more selective process.

Scheme 2.3 Proposed Mechanistic Accounting of the Selectivity



Other than the structure of the carbene complex, temperature and solvent both had an influence on the reaction. It was observed that the selectivity at a lower temperature (40 °C) was better than that at a higher temperature (80 °C) (Table 2.1). This is understandable from a basic kinetic point of view. Solvents also played a role in effecting the selectivity. Competition reactions carried out in non-coordinating solvents such as benzene and hexane were more sensitive to

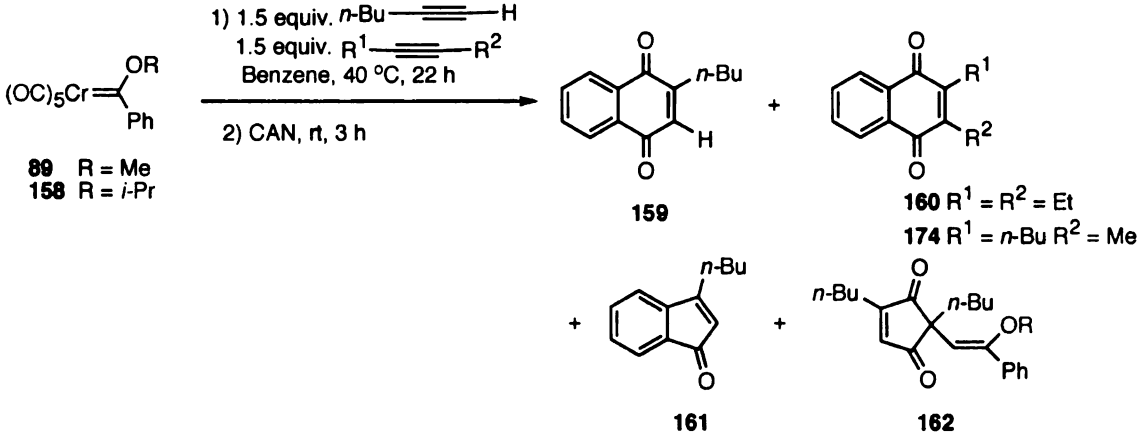
temperature, while reactions in polar coordinating solvents such as THF and CH_3CN were less sensitive, and the selectivity remained the same at both temperature. This may suggest that the $16e^-$ chromium center in the unsaturated complex **164** can be intercepted by a coordinating solvent to give the saturated complex **165**. This in turn could lead to a difference in the associative reaction of **164** versus **165** with an alkyne. The latter could have the largest difference in rate with the two alkynes. It was also found that compared to non-coordinating solvents, coordinating solvents tented to lead to poorer yields but better selectivity.

The aforementioned results revealed a significant chemoselectivity difference between terminal and internal alkynes when they are allowed to compete in large excess. Although the results are quite dramatic, they may not be practical in syntheses because of the large excess of alkynes employed. Thus, further investigations using only 2 equivalents of each alkyne were performed (Table 2.2). In this case, when the more reactive 1-hexyne is consumed, the relative ratio of 1-hexyne and 3-hexyne would decrease, and it would thus not be certain whether the same high selectivity would be observed. As the investigation was conducted, the results (Table 2.2, Entries 1 and 2) demonstrated that the same high selectivity is observed with 1.5 equivalents as it is with 10 equivalents of each alkyne. This suggests that 1-hexyne is still reactive enough in the presence of excess 3-hexyne to give the same high chemo-selectivity. This implies that it should be feasible to use substrates with multiple

alkynes in the benzannulation reaction with the expectation that a terminal alkyne should react selectively with an internal alkyne in the same substrate.

In addition to 1-hexyne and 3-hexyne, the competition reaction between 1-hexyne and 2-heptyne was also examined (Table 2.2, Entries 3 and 4). The selectivity between them was similar to the selectivity between 1-hexyne and 3-hexyne. This result presumably can also be attributed to the steric difference of the two alkynes.

Table 2.2 Competition Reactions with 1.5 Equivalents of Alkynes[a, b]



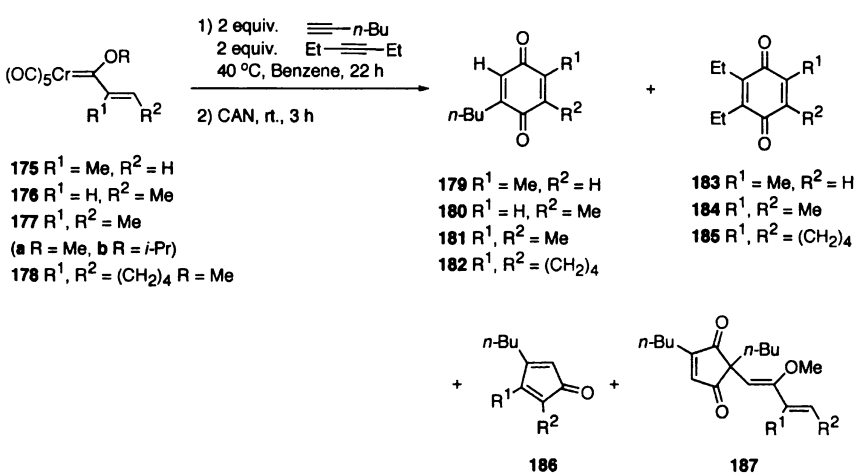
Entry	Carbene complex	R^1	R^2	% Yield **159**[b]	Ratio of **159/160**[d] or **159/174**
1	**89**	Et	Et	78	96:4
2	**158**	Et	Et	75	>99:1
3	**89**	*n*-Bu	Me	70	97:3
4	**158**	*n*-Bu	Me	85	>99:1

a) All of the above reactions were run in 0.3 mmol scale in 5 mL solvent; b) Trace amount of **161** and **162** could be detected by GC-MS. c) Isolated yield; d) Determined by GC and GC-MS.

The data above demonstrates that 1-hexyne will preferentially react with the phenyl carbene complex over either 3-hexyne or 2-heptyne with very high

selectivity. Next attention was turned to further expand this study to alkenyl carbene complexes **175-178** which includes complexes with an α-substituent, a β-substituent and α,β-disubstituents (Table 2.3).[11] The competition involved 1-hexyne and 3-hexyne (2 equivalents each) for this study as well. It was observed that these carbene complexes all gave good to excellent selectivities in this competition and greater than 95:5 selectivity could be realized in each case. It was observed that α-substituted and α,β-disubstituted carbene complexes gave slightly better selectivity than β-substituted carbene complexes. Perhaps this is the case because the α-substituent is closer to the chromium atom lead to a stronger interaction with the alkyne as it becomes incorporated (Scheme 2.3). Although the effect was small, the overall finding from the experiments summarized in Table 2.3 is that there is a higher selectivity in the competition experiments for α-substituted alkenyl complexes.

Table 2.3 Competition Reaction of Carbene Complex 175-178 with 1-Hexyne and 3-Hexyne[a, b]



175 R^1 = Me, R^2 = H
176 R^1 = H, R^2 = Me
177 R^1, R^2 = Me
(**a** R = Me, **b** R = *i*-Pr)
178 R^1, R^2 = $(CH_2)_4$ R = Me

179 R^1 = Me, R^2 = H
180 R^1 = H, R^2 = Me
181 R^1, R^2 = Me
182 R^1, R^2 = $(CH_2)_4$

183 R^1 = Me, R^2 = H
184 R^1, R^2 = Me
185 R^1, R^2 = $(CH_2)_4$

186

187

Entry	Carbene complex	R^1	R^2	Major product	% Yield [c]	Ratio[d]
1	**175a**	Me	H	**179**[e]	62	99:1
2	**175b**	Me	H	**179**[e]	73	>99:1
3	**176a**	H	Me	**180**[e]	41	96:4
4	**176b**	H	Me	**180**[e]	32	98:2
5[f]	**177a**	Me	Me	**181**	57	99:1
6[f]	**177b**	Me	Me	**181**	83	>99:1
7	**178**	$-(CH_2)_4-$		**182**	72	99:1

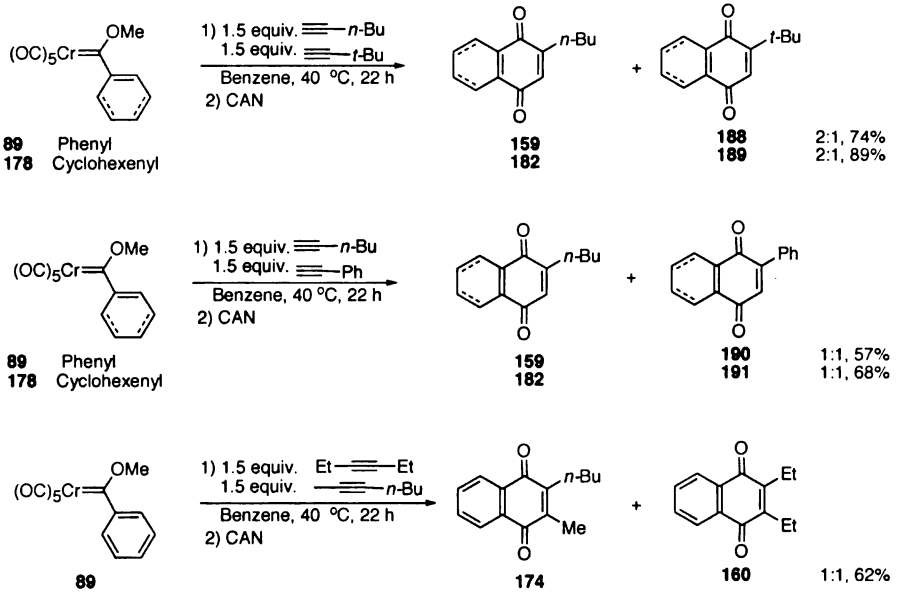
a) All of the above reactions were run in 0.3 mmol scale with 5 mL solvent; b) Trace amount of **186** and **187** could be detected by GC-MS; c) Isolated yield; d) Determined by GC and GC-MS. e) Regioisomer was not detected by GC-MS. f) The reaction was performed with 1.5 equivalents of alkynes.

2.3 Competition reaction between different terminal alkynes and competition between different internal alkynes

Having obtained good results from the competition reaction between terminal and internal alkynes, attention was then turn to a more challenging but also informative competition between different terminal alkynes or between different internal alkynes (Scheme 2.4). Thus, the benzannulation reaction of methoxy phenyl carbene complex **89** and the cyclohexenyl carbene complex **178** with 1.5 equivalents of *n*-butyl acetylene and *t*-butyl acetylene both afforded 2:1 ratio of corresponding products in 74% and 89% combined yields, respectively. The alkyne with smaller primary substituent was slightly preferred in the benzannulation reaction over the alkyne with the larger tertiary substituent, but there wasn't a large difference in the relative rates. The competition between an aliphatic terminal alkyne and an aromatic terminal alkyne was also examined

(Scheme 2.4). However, no selectivity was observed between *n*-butyl acetylene and phenyl acetylene since equal amounts of the two quinones were obtained in the reactions with both carbene complex **89** and **178**. Finally, the benzannulation reaction of complex **89** was carried out with two equivalents of 3-hexyne and 2-heptyne. The experiment gave approximately a 1:1 ratio.

Scheme 2.4 Competition Reactions with Different Terminal Alkynes or Internal Alkynes

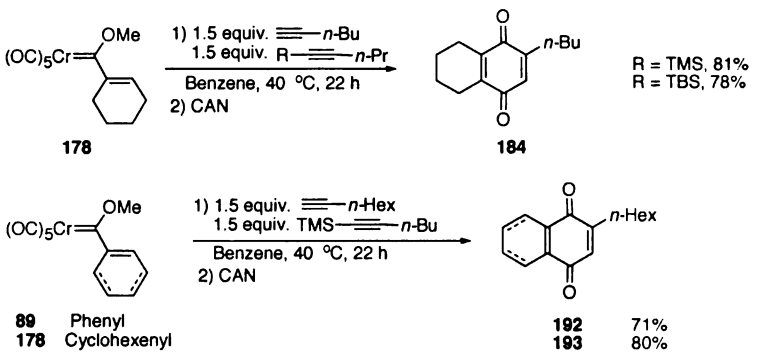


2.4 Competition studies between terminal alkyne and 1-silyl protected terminal alkyne

To address the problem of the unsatisfactory selectivity between two terminal alkynes in the benzannulation reaction (Scheme 2.4), a competition

study was conducted between terminal alkynes and 1-silyl alkynes, the latter of which could serve as a protected version of a terminal alkyne. Thus, the reaction of 1-hexyne and 1-trimethylsilyl-1-pentyne with methoxy cyclohexenyl chromium carbene complex **178** provided an 81% yield of compound **182** as the exclusive product.[57] This suggests that the benzannulation reaction was completely selective against the 1-silyl alkynes. The same result was observed when 1-*tert*-butyldimethylsilyl-1-pentyne was used in place of 1-trimethylsilyl-1-pentyne. In addition, when the phenyl carbene complex **89** or cyclohexenyl carbene complex **178** was used as the substrate in the competition between 1-octyne and 1-trimethylsilyl-1-hexyne, and the 1-silyl alkyne was completely unreactive and only the quinone **192** or **193** was formed (Scheme 2.5).

Scheme 2.5 Competition Reaction between Terminal Alkyne and 1-Silyl Alkyne



2.5 Summary

In summary, the competition between two different alkynes in the benzannulation reaction with Fischer chromium carbene complexes has been systematically studied. Terminal alkynes react in preference to internal alkynes with excellent chemoselectivity in a variety of solvents and different temperatures. This selectivity was observed to be slightly higher for α-substituted and α,β-disubstituted carbene complexes than for β-substituted carbene complexes. The selectivity between two terminal alkynes is not synthetically significant and when there is a slight preference it is for the least bulky alkyne. This problem could be addressed by protecting one of the terminal alkynes with a silyl group at which point the reaction becomes completely selective for the unprotected alkyne. On the basis of the above results and other control experiments, it is clearly possible that the selectivity of the reaction of different alkynes in the benzannulation reaction can be controlled by the steric interaction of the carbene complex and the alkyne.

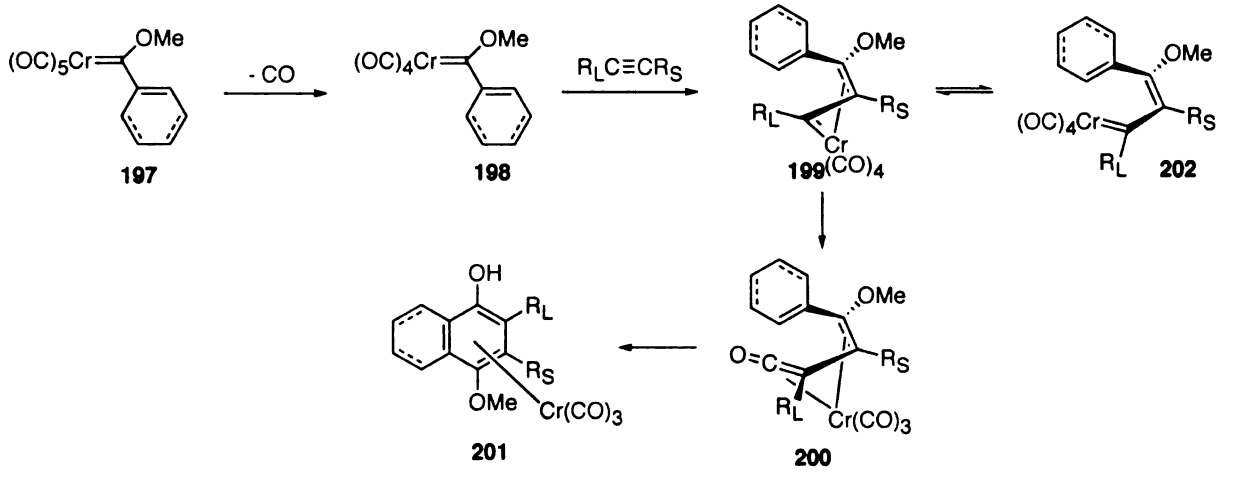
CHAPTER 3

Mechanistic Study on the Benzannulation Reaction: A Probe for Symmetrical Vinyl Carbene Complexed Intermediates

3.1 Introduction

As mentioned in Chapter 1, the application of benzannulation reaction has been well established. However the mechanism of this reaction has not yet been fully elucidated.[10,59] The currently accepted mechanism (Mechanism I) for the formation of the phenolic product involves the generation of an η^1,η^3-vinyl carbene complexed intermediate **199** (Scheme 3.1).[10] The initial rate-determining dissociation of a carbonyl ligand from the chromium Fischer carbene complex[58] gives the unsaturated species **198** followed by an alkyne insertion generates **199**. Migratory CO insertion into the chromium–carbene carbon bond leads to an η^4-vinyl ketene intermediate **200**, which undergoes subsequent electrocyclization and tautomerization to give phenolic product **201** as the major product. Although this is the most widely accepted mechanism, experimental support for the existence of intermediate **199** is lacking.

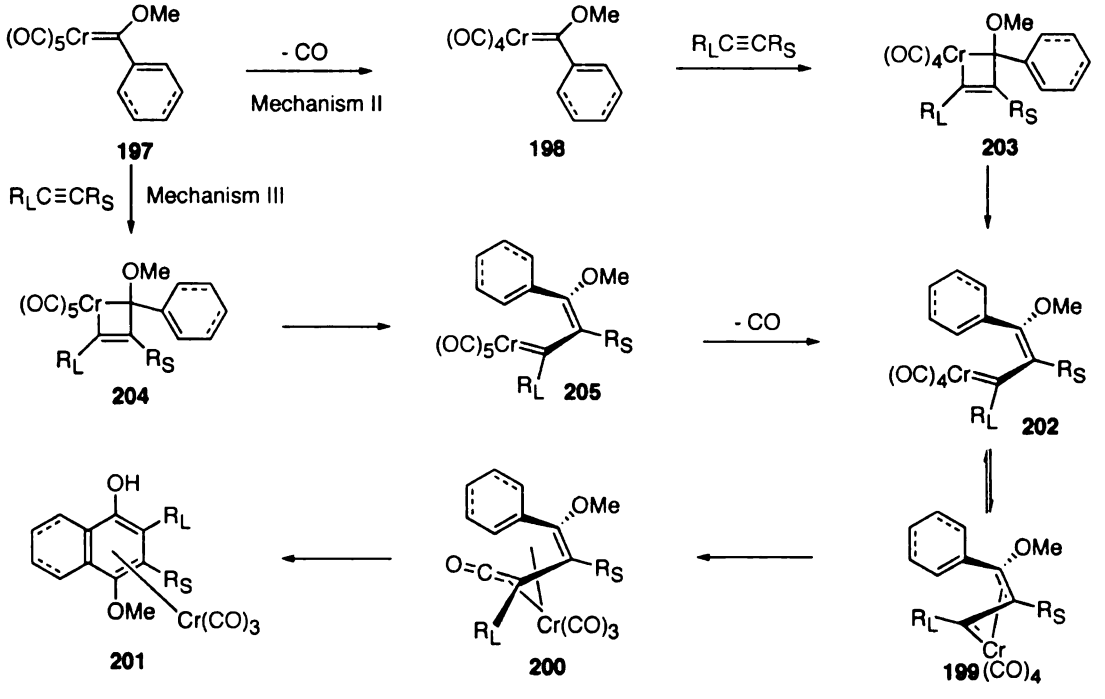
Scheme 3.1 Currently Accepted Mechanism for the Benzannulation Reaction (Mechanism I)



Nonetheless, in addition to this mechanism, other versions of mechanism differing in details have also been proposed for this benzannulation reaction (Mechanism II and III, Scheme 3.2) .[59,60] One mechanism proposed by Dötz (Mechanism II) early on involves a [2 + 2] cycloaddition of the Cr–carbene carbon bond in structure **198** with an alkyne to give a metallacyclobutene intermediate **203**, followed by a retro-[2 + 2] ring-opening to afford the η^1-intermediate **202** (Scheme 3.2). Although this intermediate was then proposed to be converted to, or to be in equilibrium with, the intermediate **199**,[60] mechanism II has a key difference: the initial formation of **202** prior to the formation of **199**. The origin of this proposal is based on the fact that the metallacyclobutenes have been isolated from the reactions of alkylidine complexes and alkynes.[61] However, Hofmann's extended Hückel calculations suggested that intermediate **203** should have higher energy than **199** and is not likely a real intermediate.[60a] Other DFT-level calculations also indicated that **199** is more stable than **202**.[10d] However,

there is no existing experimental data that can directly support or disfavor mechanism II.

Scheme 3.2 Mechanisms Involving η^1-Intermediate (Mechanisms II and III)



Both of the above mechanisms are dissociative mechanisms involving a CO dissociation as the first step. An alternative mechanism has been proposed by Solà which is an associative mechanism involving the insertion of an alkyne into the saturated 18e⁻ carbene complex **197**. On the basis of DFT calculations using the Gaussian 94 program (Scheme 3.2),[59] he claimed that alkyne insertion and cyclization to give the metallacyclobutene intermediate **204** is a highly exothermic and nearly barrierless process, and that the loss of CO from **205** is less endothermic and easier to occur than the loss of CO from **197**. He argued that several structures of seven-coordinated derivatives of group VI metal carbonyls were known.[62] However, this mechanism does not agree with the

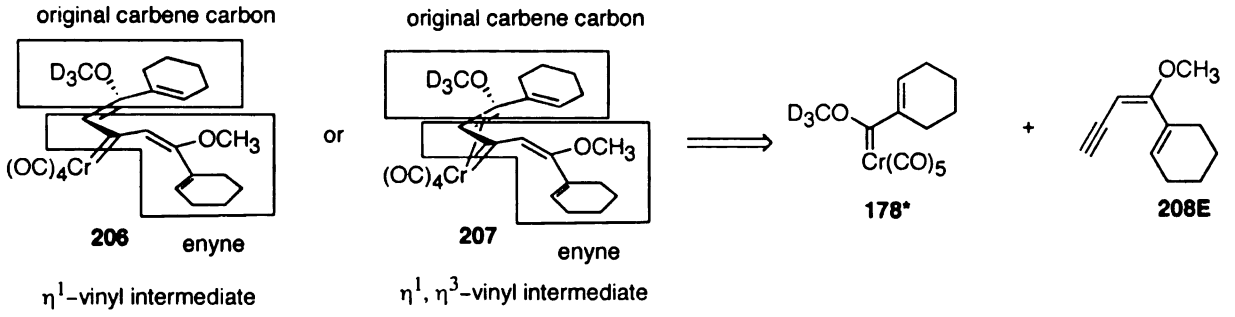
experimental facts. Kinetic studies have shown that the benzannulation reaction is first order in carbene complex and zero order in alkyne.[58] Therefore, this mechanism is probably the easiest one to be ruled out.[59]

3.2 Mechanistic studies with deuterium labeled pseudo-symmetric vinyl intermediate

3.2.1 Introduction

As indicated in Schemes 3.1 and 3.2, mechanisms I and II only differ in the formation of intermediates **199** and **202**. Mechanism I calls for the formation of **199** first, which gives rise to the ketene intermediate **200** directly. In this mechanism, the olefin-dissociated η^1-intermediate **202** is either not formed, or formed as a dead-end compound along the reaction path. Mechanism II, on the other hand, calls for the formation of **202** first, which then is transformed to **199**. It was envisioned that if intermediates **199** and **202** could give different products, it might be able to distinguish these two mechanisms. Toward this end, a pseudo-symmetric intermediate **206** or **207** was designed and both of which have the "same" substituents on either side of the carbene carbon (Scheme 3.3). However, one of the side arms is isotopically labeled by deuterium. The deuteriums are designed to be far away enough from the reaction center such that they would not be expected to contribute to an observable isotope effect. Intermediate **206** or **207** could be generated from carbene complex **178** and alkyne **208E*** or from carbene complex **178*** and alkyne **208E**.

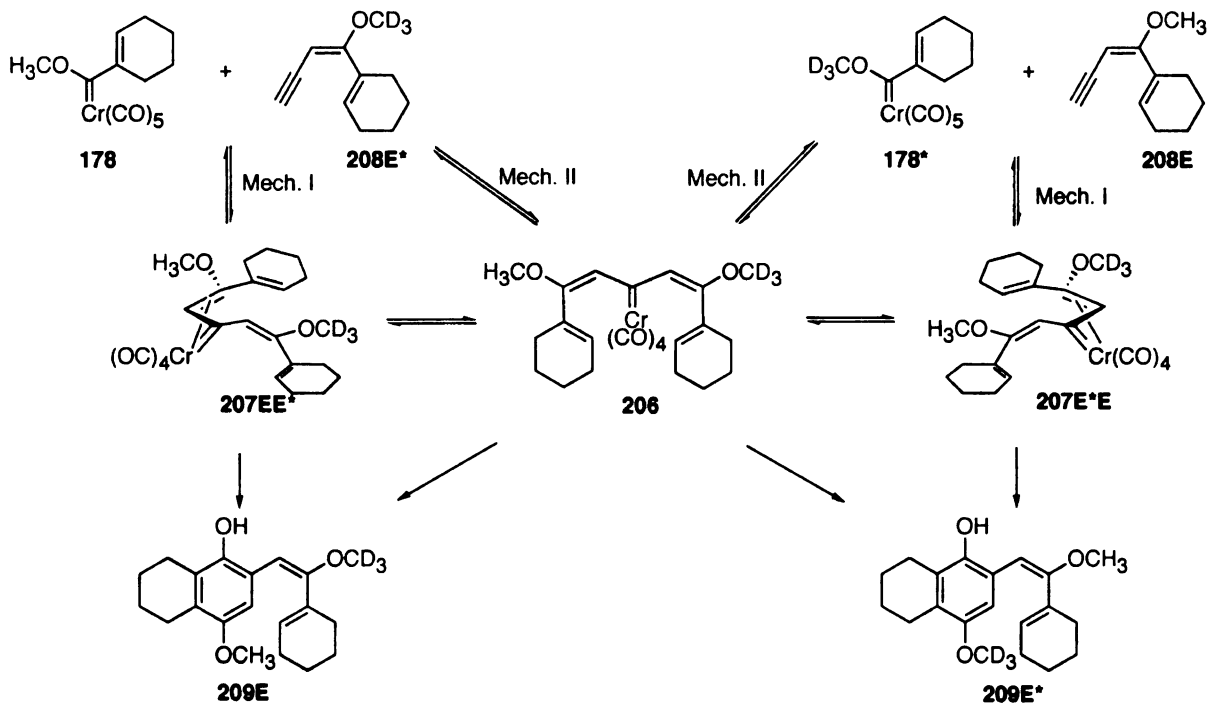
Scheme 3.3 Designed Intermediates 206 and 207



The idea for using intermediate **206** or **207** as the probe for the mechanistic investigation lies in the following: if mechanism I is operating, the benzannulation reaction of carbene complex **178*** with enyne **208E** should initially generate the η^1,η^3-intermediate **207E*E** (corresponding to **199**) and bypass the intermediate **206** (corresponding to **202**, Scheme 3.4). Unless the olefin dissociation to give **206** is substantially faster than CO insertion, **207E*E** should undergo CO insertion followed by cyclization with the labeled arm to give product **209*** exclusively. However, if mechanism II is operating, the benzannulation reaction of carbene complex **178*** and enyne **208E** should initially generate the η^1-intermediate **206**. Since the two arms now are the "same", the cyclization would not have any preference for either side and therefore should give equal amounts of products **209** and **209***. Hence, the ratio of **209/209*** should reflect the mechanism of the reaction: a less than unity ratio suggests mechanism I, where as a unity ratio suggests mechanism II. The same will apply to the reaction starting from carbene **178** and alkyne **208***: a greater than unity ratio of **209/209*** suggests mechanism I, whereas a unity ratio suggests mechanism II.

However, it should be noted that such an analysis might be complicated by the relative rate of CO insertion and olefin dissociation. If the CO insertion is not substantially faster than the olefin dissociation, then the initially formed intermediate **207E*E** can isomerize to η^1-intermediate **206** and to η^1,η^3-intermediate **207EE***. This will result in scrambling of the deuterium and the formation of **209*** and **209** in a ratio close to unity. Nonetheless, performing such an intramolecular competition would provide information on the nature and symmetry of reaction intermediates in these reactions.

Scheme 3.4 Possible Product Distributions

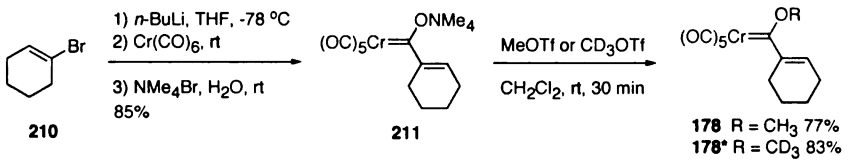


3.2.2 Preparation of carbene complexes and alkynes

The ammonium acylate **211** was prepared from cyclohexenyl bromide **210** using the standard procedure (Scheme 3.5) as described in Chapter 1.[4]

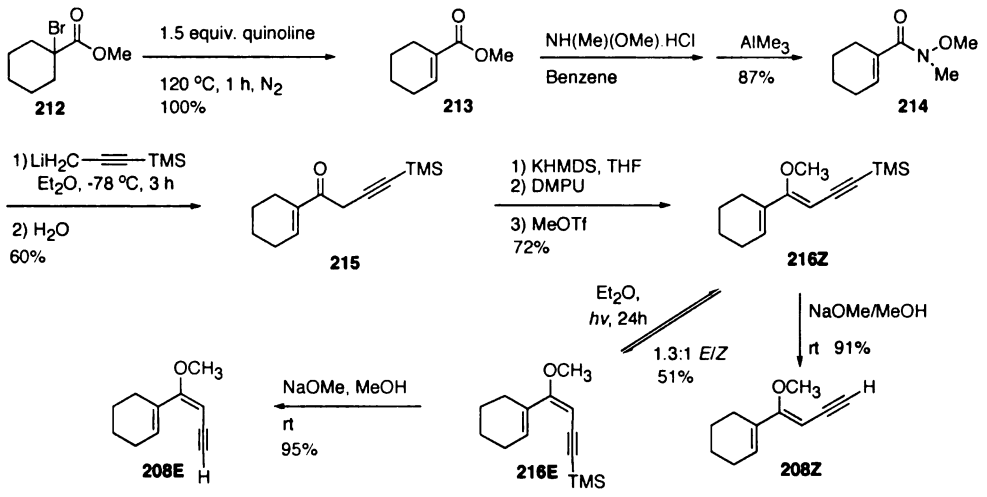
Treatment of this acylate with methyl triflate or methyl-d_3 triflate provided carbene complex **178** or the corresponding deuterium labeled complex **178***.

Scheme 3.5 Syntheses of Carbene Complexes 178 and 178*



The methoxy enyne **208** was prepared from the bromo ester **212** (Scheme 3.6). Elimination of HBr followed by functional group manipulation afforded the key intermediate, Weinreb's amide **214**.[63] Addition of TMS-protected propargyl lithium to this Weinreb's amide followed by quenching with H_2O gave propargyl ketone **215**. Treatment of **215** with KHMDS in the presence of DMPU followed by the addition of MeOTf furnished *Z*-silyl enyne **216Z**. The *E*-enyne **216E** could be obtained by the photolysis of **216Z**. This photolysis of **216Z** led to an equilibrium between the *Z*- and *E*-isomers in a 1:1.3 ratio, but the stereoisomers could be separated by column chromatograph using Et_3N-treated silica gel. The silyl group was then removed with a catalytic amount of sodium methoxide in methanol to afford enynes **208Z** and **208E**. The geometry of the double bonds is maintained during the desilylation process.

Scheme 3.6 Syntheses of *Z*- and *E*-Alkynes



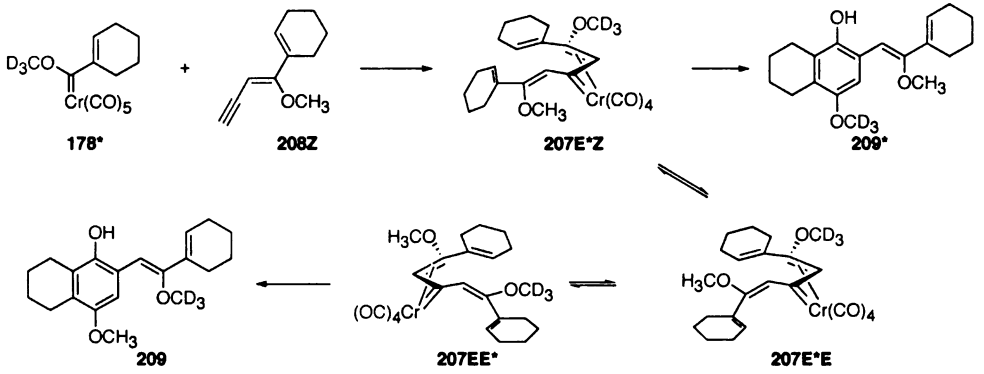
3.2.3 Benzannulation reaction with deuterium labeled substrates

With carbene complex **178*** and enynes **208** in hand, the benzannulation reaction was carried out to probe the mechanism of this reaction (Table 3.1). Previously, Marcey Waters in our group had demonstrated that the benzannulation of **178** and **208Z*** (Scheme 3.3) gave 1:1 ratio of scrambled products **209** and **209*** in benzene as solvent and a 2:1 ratio in hexanes.[64] She also found that carbene complex **178*** with enyne **208*Z*** gave 1:1 ratio of **209*:209** in CH_2Cl_2, THF and benzene. But the same reaction in hexanes provided a 2:1 ratio of **209*** over **209** (Table 3.1, Entries 1 and 2).

This observation could be explained by the operation of mechanism I as outlined in Scheme 3.1 in which the scrambling of the deuterium via the intermediate **202** is completed in benzene but not in hexanes. Alternatively, this observation could be explained by mechanism II as shown in Scheme 3.2, which involves the initial formation of intermediate **202**. As shown in more detail in

Scheme 3.7, the reaction of **178*** and **208Z** gives the intermediate **207E*Z** which has the correct geometry about the deuterated enol ether to give **209***, but not on the unlabeled enol ether for cyclization to **209**. Thus, the slightly higher ratio of **209***:**209** in hexanes may be just the consequence of the fact that isomerization of the *Z*-enol ether in **207E*Z** to give the *E*-enol ether in **207E*E** may be slower in hexanes than in benzene relative to cyclization to **209***.

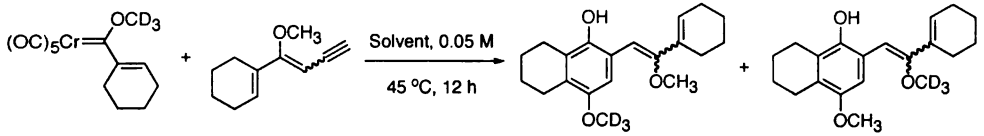
Scheme 3.7 Detailed Mechanism for the Formation of 209 and 209*



As shown in Scheme 3.4, the electrocyclization step must occur through the *E*-geometry. Therefore, initiating the reaction with pure *E*-stereoisomer of the enyne **208** would eliminate the complication that is caused by the *E/Z* isomerization step that must occur before cyclization. Unfortunately, Marcey Waters did not run the reaction of complexes **178*** with enyne **208E** in hexanes. One of the goals of the present work was thus to carry out this reaction with the *E*-enyne to see if the hexanes result means that mechanism II can be eliminated or if the situation of mechanism I shown in Scheme 3.7 pertains. The reaction of complex **178*** with **208E** was found to give a 1:1 mixture of **209*** and **209** in both

hexanes and benzene. The products **209** and **209*** were each isolated as mixtures of *E* and *Z* isomers which varied depending on workup. This is the result of the fact that isomerization can occur rapidly in either $CDCl_3$ or on silica gel to give the more stable *Z*-isomer. For this reason, the ratio of the products was determined on the crude reaction mixture with d_6-benzene as solvent.

Table 3.1 Benzannulation of Deuterated Carbene Complex with Enyne



178* 208 209* 209

Entry	Solvent	Enyne	Ratio of 209*:209[a]	% Yield of 209* + 209[b]	Configuration of 209* and 209[a]
1[c]	Benzene	**208Z**	1:1	74	*Z*
2[c]	Hexanes	**208Z**	2:1	73	*Z*
3[c]	Benzene	**208E**	1:1	77	1:3 *E/Z*
4	Benzene	**208Z**	1:1	67	*Z*
5	Hexanes	**208Z**	2:1	81	*Z*
6	Benzene	**208E**	1:1	36	1:10 *E/Z*
7	Hexanes	**208E**	1:1	50	1:10 *E/Z*

a) Determined by crude ^{1}H NMR in C_6D_6 and ^{1}HNMR in $CDCl_3$ after purification. b) Isolated yield as a mixture. c) Performed by Marcey Waters.

3.2.4 Discussion

As mentioned in the previous section, the 2:1 ratio of **209***:**209** obtained from reaction of **178*** with **208Z** in hexanes supports the operation of mechanism I (Scheme 3.1) for the benzannulation reaction. The 1:1 product ratio in benzene

and other polar solvents could be consistent with mechanism I if there is a fast equilibrium between the eight isomers of intermediate **207** shown in Scheme 3.8. However, it is also consistent with mechanism II shown in Scheme 3.2 and thus the experiments summarized in Table 3.1 do not allow for a determination of which mechanism is operating. If the more widely accepted mechanism I is operating, then the results in Table 3.1 could be explained by the mechanism in Scheme 3.8. The 1:1 ratio of products **209** and **209*** from the reaction of **178*** and **208E** in hexanes could also be attributed to a faster equilibrium among the isomers of intermediate **207** than for those from the reaction of **178*** and **208Z**. Such interconversion between **207E*E** and **207EE*** or **207E*Z** and **207ZE*** could occur directly by an associative displacement of OMe double bond by another or via a η^1-intermediate **206** (Scheme 3.4) in which neither of the double bonds is chelated to the metal. As mentioned before, this non-unity ratio from the reaction of **178*** and **208Z** might just be due to the fact that the isomerization of the *Z*-enol ether in hexanes is slower than in other solvents (Scheme 3.7).

Before a discussion of the possible equilibrium between **207E*E** and **207EE*** and the mechanism as a whole is undertaken, a few points need to be mentioned. The reactions of carbene complex **178*** and **208** can serve to probe whether the alkyne insertion is reversible. According to the mechanism outlined in Scheme 3.8, the reaction of **178*** and **208E** would lead to the initial formation of the η^1,η^3-vinyl carbene complexed intermediate **207E*E** or **207Z*E**. Isomerization of **207E*E** via the $16e^-$ intermediated **206** as shown in Scheme 3.4

would led to the formation of **207EE***. If the alkyne insertion step is reversible, then the intermediate **207EE*** should reverse to complex **178** and alkyne **208E*** (Scheme 3.4). Thus, a probe for the reversibility of the alkyne insertion step could be performed by isolating unreacted enyne **208E** from its reaction with carbene complex **178*** and analyzing for deuterium incorporation. Based on Marcey Water's observation, no detectable amount of deuterium substituted alkyne **208*** was observed for the remaining alkyne in the ^{1}H NMR of the crude mixture from the reaction of **178*** and excess **208E**. The same outcome was also observed when this reaction was repeated for the present work. This experimental outcome was consistent with the results obtained from a theoretical DFT study by Hess[10d] and Solà[59] which predicts that alkyne insertion will be irreversible.

Furthermore, the *E/Z* isomerization of the olefin moiety of the starting enyne must occur between alkyne insertion and CO insertion. As mentioned previously, the electrocyclization step in the mechanism must occur through the *E*-geometry of the intermediate **207E*E** or **207EE*** (Scheme 3.7). Therefore, the double bond in **208Z** must isomerize to *E* in order to produce phenol products. The isomerization does not occur before alkyne insertion, as Marcey Waters has demonstrated that the *E*-enyne **208*E*** did not convert to *Z*-enyne **208Z** under the reaction conditions.[64] It is also unlikely to occur after the CO insertion, since Wulff has suggested that the cyclization of vinyl ketene intermediate **200** (Scheme 3.1) is extremely rapid since the vinyl ketene could not be trapped even by intramolecular reaction with an alcohol.[65] Calculations by Hess also indicated that the vinyl ketene **200** (Scheme 3.1) does not have an energy minimium, and that

the CO insertion and electrocyclization occurred in a single exothermic step with a very low energy barrier.[10d] Thus existing evidence suggests that the vinyl ketene intermediate **200** (Scheme 3.1) undergoes immediate electrocyclization without leaving enough time for any other event to happen including isomerization of the olefin in the alkyne. The isomerization after the formation of phenol **209** is also unlikely to occur, since the products **209Z** and **209E** can both be isolated from the reaction. The isomerization of **209E** to **209Z** does however occur in the present of silica gel and $CDCl_3$. If **209E** was isomerizing to **209Z** under the reaction condition, then the reactions from *E*- and *Z*-enyne should both give the same *E/Z* ratio in the products.

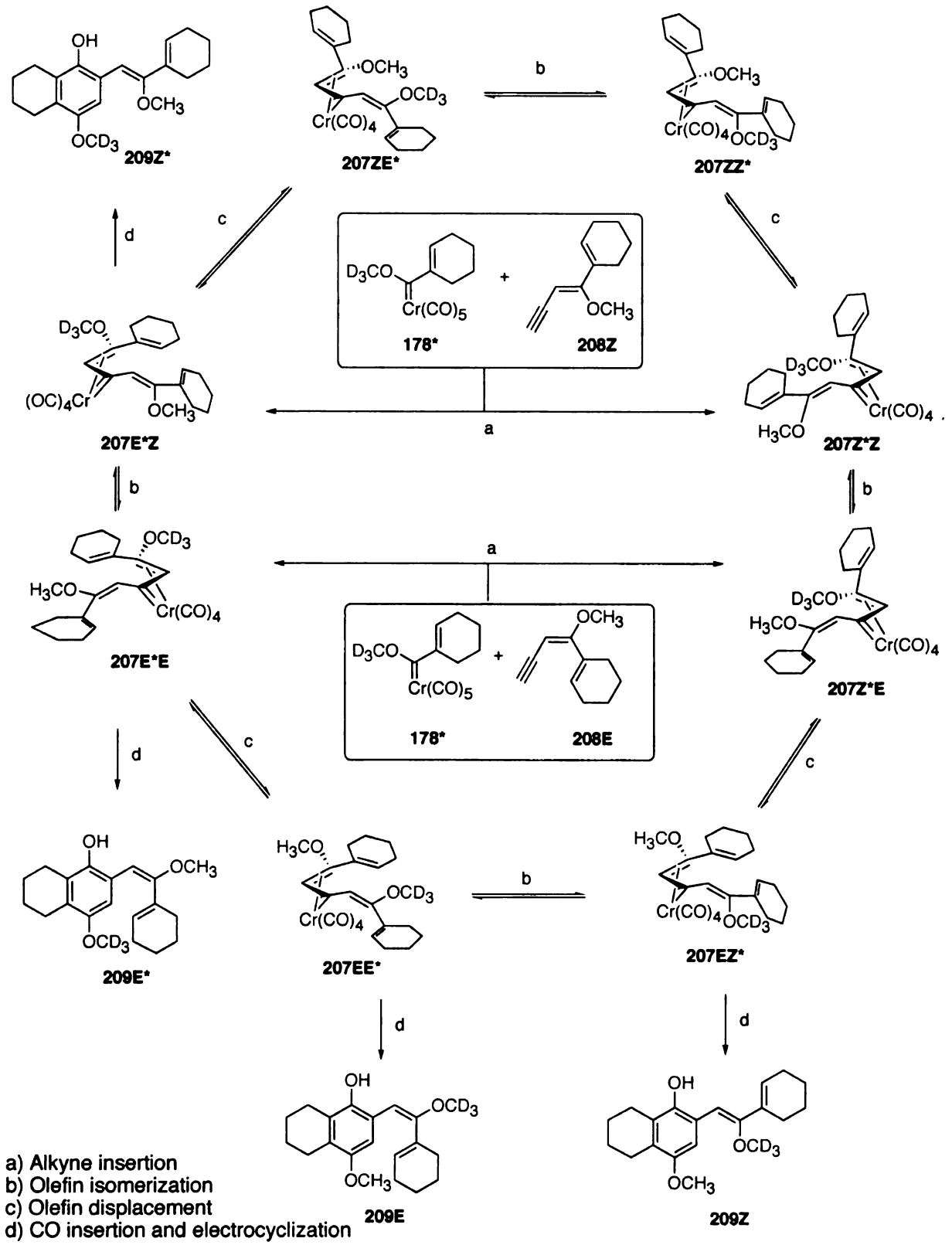
With the above information and considerations in mind, a detailed mechanism explaining the results obtained in the previous section is presented in Scheme 3.8 and is based on mechanism I (Scheme 3.1). This scheme is far more detailed than Scheme 3.4 which is primarily due to the complication of the *E/Z* isomerization issue. The initial reaction between **178*** and **208E** affords directly two possible intermediates **207E*E** and **207Z*E**, which differ only at the geometry of the newly formed olefin. Intermediate **207E*E** can directly undergo a CO insertion and cyclization to provide product **209E*** or interconvert to **207EE***, while intermediate **207Z*E** cannot directly undergo CO insertion and cyclization due to the geometry constraint. However, intermediate **207Z*E** can undergo olefin displacement to exchange the olefin ligand at the chromium to afford **207EZ***, which can then undergo a CO insertion and cyclization to provide product **209Z**. Intermediate **207E*E** can undergo the same process, namely an

olefin displacement to exchange the olefin ligand at the chromium, a CO insertion, and cyclization to provide **209E** product. This olefin isomerization could also occur on **207EE*** to afford **207EZ***, which could undergo CO insertion and cyclization to provide product **209Z**. When the reaction was initiated from **178*** and **208Z**, the initial intermediates would be **207E*Z** and **207Z*Z**, and the formation of products **209Z*** and **209Z** can be explained from the interconversion between all eight of the isomers of intermediate **207**.

When the reaction of **178*** and **208Z** was carried out in benzene and other polar solvents, the interconversion between the eight isomers of intermediate **207** is faster than the subsequent CO insertion since the ratio of **209*** to **209** is 1:1 whether the reaction is carried out with the enyne **208Z** or **208E** (Table 3.1). Equilibration of all eight isomers of **207** is apparently not quite complete in benzene since a 1:10 ratio of *E*:*Z* isomers of **209*** and **209** were observed when starting with **208E**, whereas, only the *Z*-isomers of **209*** and **209** were observed when starting with **208Z** (Table 3.1). The result also suggests that the CO insertion from **207EZ*** and **207E*Z** is faster than from **207EE*** and **207E*E**. When the reaction was carried out in hexanes, the interconversion between the eight isomers of intermediate **207** was further slowed down and became somewhat comparable with the subsequent CO insertion.[66] When staring with **208Z**, the CO insertion in hexanes is slightly faster than isomerization of **207E*Z** to **207EZ***, and leads to preference of **209Z*** over **209Z**. Where as starting with **209E**, intermediate **207E*E** and **207EE*** apparently reach equilibrium very fast and lead to **209E*** and **209E** without any preference. It was though that the following

possibilities may contribute to some of the phenomena in the reactions, although the detailed reasons may be elusive. First, isomers of intermediate **207** do interconvert, but some interconversions are faster than others. This may result in the accumulation of certain intermediates rather than others, and lead to a formation of certain products in preference. Second, different intermediates may have different rates for the CO insertion step. Some intermediates may be faster in the subsequent CO insertion and lead to a predominate product. However, at this point, there is no sufficient data to provide a detailed explanation with regard to the product distribution. We hope that future work in this area may provide a more detailed picture of this mechanism.

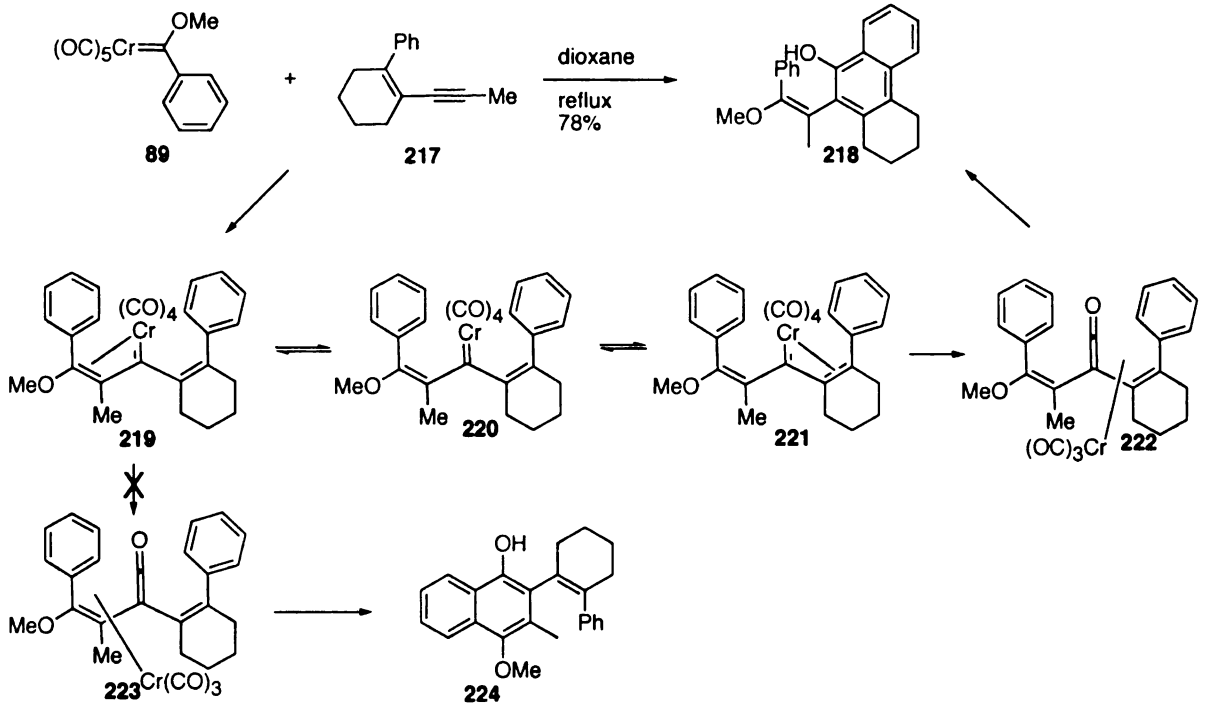
Scheme 3.8 Proposed Mechanism for Product Distributions



3.3 Electronic perturbation of the benzannulation reaction

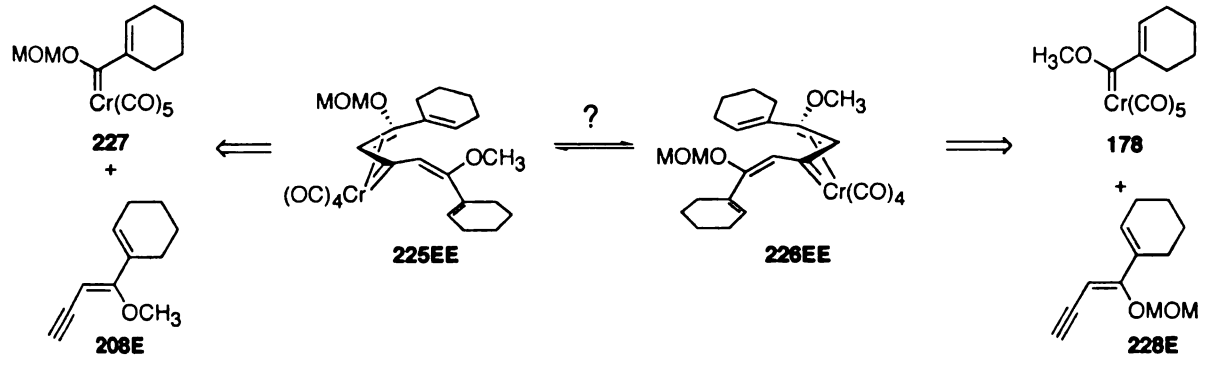
To further investigate the equilibrium between the vinyl carbene intermediates, an electronic perturbation of the vinyl carbene intermediate **207** was considered (Scheme 3.3) such that the two arms are differentiated by electronics. In fact, a similar example has been reported by Herdon.[67] He demonstrated that the reaction of phenyl methoxy carbene complex **89** with aryl enyne **217** did not give the normal benzannulation product **224**. Instead, the reaction generated exclusively phenol **218** with the incorporation of the aryl group on the enyne. Herndon proposed that this reaction involved a fast olefin disassociation/coordination between intermediates **219** and **221**, and further more that the CO insertion was faster for intermediate **221** than **219**. The chromium is coordinated to a more electron-deficient double bond in **221** than in **219** which leads to enhanced back-bonding from chromium to the olefin in **221** and therefore less back-bonding to the CO ligand and a more rapid CO insertion to give **222**. The electrocyclization of the resulting ketene **222** led to the observed product **218**.

Scheme 3.9 Herndon's Studies



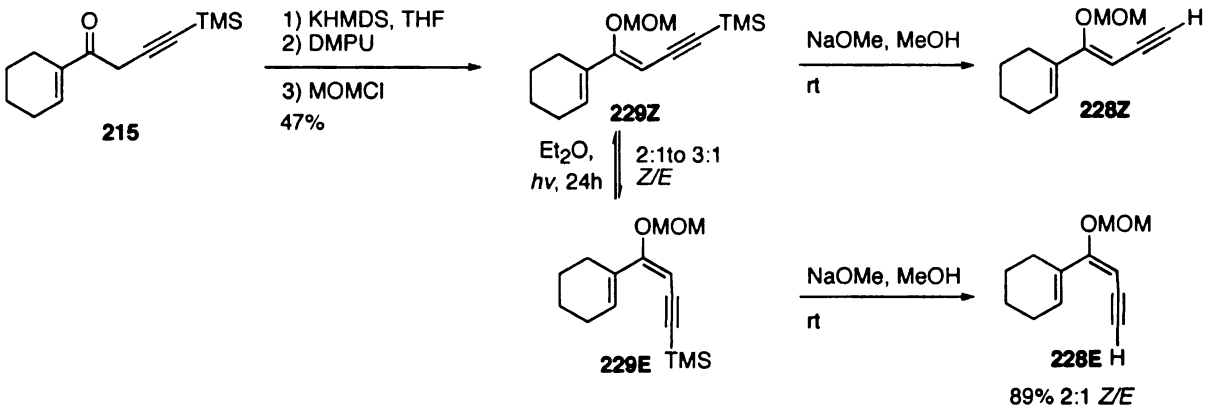
Based on Herndon's result, it was envisioned that a double bond bearing a MOM group should have lower electron density than one bearing a methoxy group, and thus CO insertion and the cyclization should occur more rapidly on the MOMO-substituted olefin (Scheme 3.10). Intermediates **225EE** and **226EE** could be generated from the MOM carbene complex **227** and methoxy enyne **208E** or from the methoxy carbene complex **178** and MOM enyne **228E**.

Scheme 3.10 Electronic Perturbation by MOMO-Substituent



The MOM-enyne **228** was also prepared from ketone **215** (Scheme 3.11). A standard MOM protection led to the enol acetal **229Z**. Photolysis of **229Z** provided 2:1 ratio of **229Z** and **229E**, which were inseparable by chromatography. Fortunately, these compounds could be separated after removal of the trimethylsilyl-protecting group. The geometry of the double bonds was retained in this removal of the TMS group.

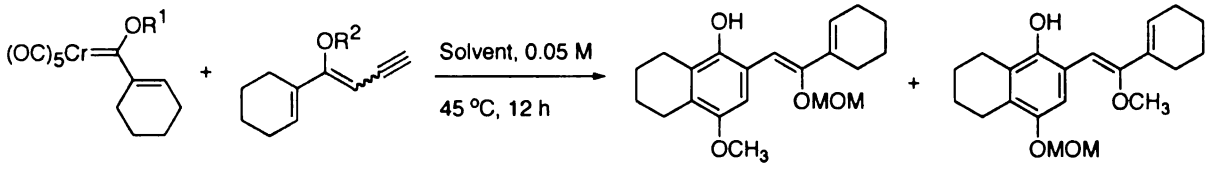
Scheme 3.11 Preparation of MOM-Enyne 228



Having both isomers of the enyne **228** in hand, the benzannulation reactions were carried out at 45 °C in different solvents (Table 3.2). The reaction of MeO-carbene **178** with *Z*-MOM-enyne **228Z** gave a 1:1 ratio of **230/231** in benzene based on the crude ^{1}H NMR analysis (Entry 1). The same reaction in hexanes provided 3:1 ratio of **230/231** (Entry 2). However, the reaction was carried out with MOM-carbene **227** and *Z*-MeO-enyne **208Z**, the ratio of products was reversed. Reaction in benzene provided a 1:4 ratio of **230/231** and the reaction in hexanes provided 1:5 ratio (Entried 3-4). The reaction of complex **178** and enyne **208Z** had been previously reported by Marcey Waters who obtained a 1:4.7 ratio of **230** and **231**.[64] She also was able to assigned the structures of **230**

and **231** by acid catalyzed cyclization of each to benzofurans. The reaction with *E*-enynes, regardless of the solvents and starting materials (**178** + **228** or **227** + **208**), gave a ratio of **230/231** that was consistently in favor of **231** in a ratio that varied from 1:3 to 1:5. The reactions with the *E*-enynes gave more complex crude mixtures than those with the *Z*-enynes, and the ratio of the products was simplified by measuring the ratio of the major *Z*-isomers.

Table 3.2 Benzannulation of 178 with 228 and 227 with 208



178 $R^1 = CH_3$
227 R^1 = MOM
228 R^2 = MOM
208 $R^2 = CH_3$
230
231

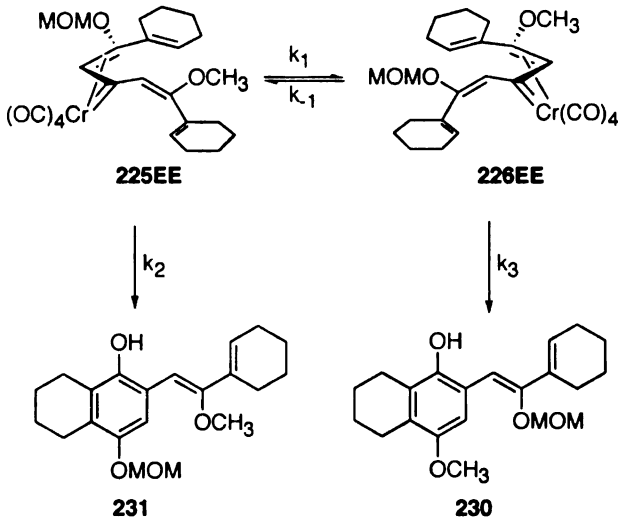
Entry	R_1	R_2		Solvent	Ratio of **230**:**231**	Yield of **230**[c]	Yield of **231**[c]
1	Me	MOM	*Z*	Benzene	1:1[a]	25	30
2			*Z*	Hexanes	3:1[a]	32	15
3	MOM	Me	*Z*	Benzene	1:4[a]	-[d]	32
4			*Z*	Hexanes	1:5[a]	12	74
5	Me	MOM	*E*	Benzene	1:5[b]	-[d]	37
6			*E*	Hexanes	1:4[b]	-[d]	39
7	MOM	Me	*E*	Benzene	1:3[a]	-	35[e]
8			*E*	Hexanes	1:3[a]	-	34[e]

a) Determined by crude ^{1}H NMR in $CDCl_3$. b) Determined by crude ^{1}HNMR in C_6D_6 based on the major isomers. c) Isolated yield. d) The product was not pure. e) Combined yield of **230** and **231**.

The results obtained from the annulations with *E*-enynes are expected, because as mentioned before, it was expected that since the MOMO-substituted

olefin has less electron density it should therefore be able to coordinate to the chromium more tightly, resulting in the cyclization to occur more preferentially on the MOM-substituted arm (Scheme 3.12). In other words, the equilibrium between **225EE** and **226EE** should lie towards **225EE**. Thus, the formation of **231** as the major product would follow.

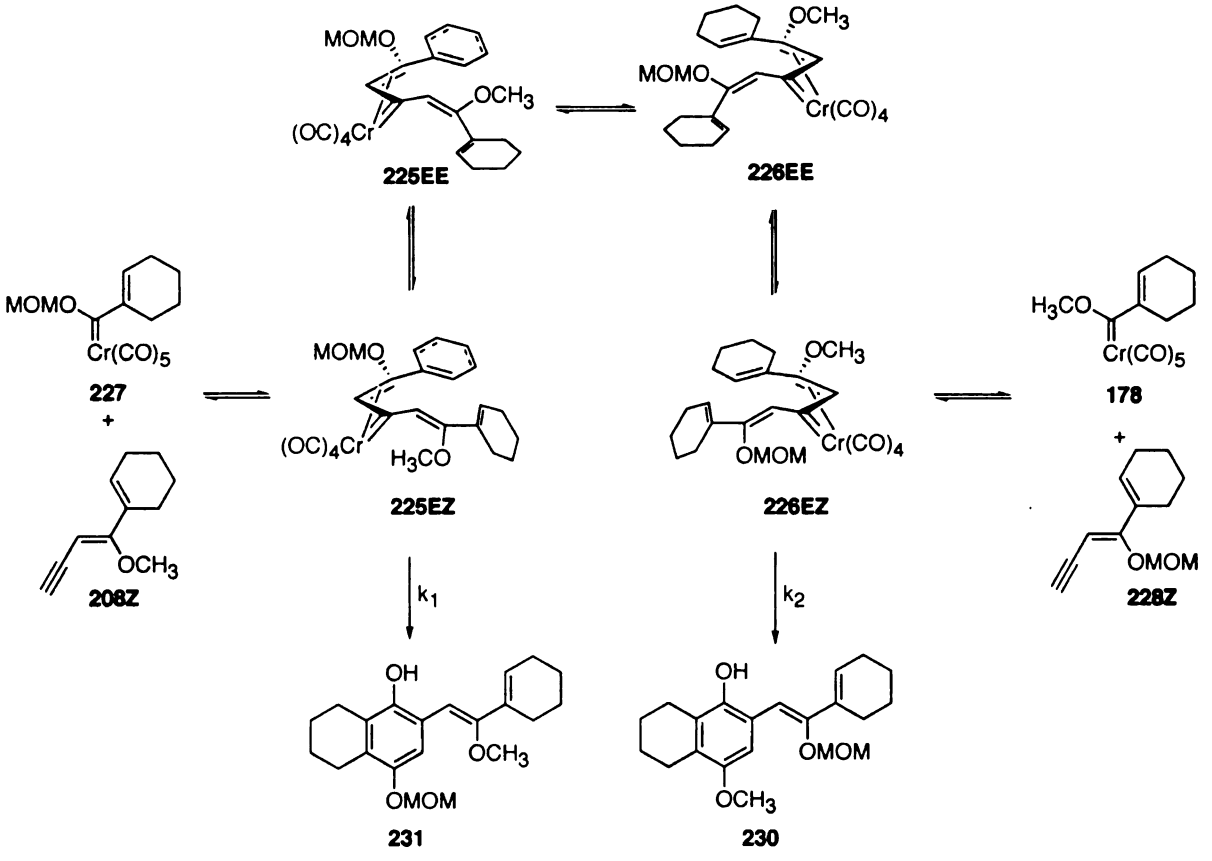
Scheme 3.12 Proposed Product Distribution



However, things are more complicated in the reactions with the *Z*-enynes. The ratio of products is dependent upon the starting materials and the reaction conditions. The product **230** resulting from cyclization to the methoxy bearing double-bond can be obtained in similar or even larger amounts than **231**. Note that this is the situation where olefin isomerization must occur before cyclization (see discussion in section 3.2). Specially, the interconversion between intermediate **225EZ** and intermediate **226EZ** (Scheme 3.13) contains an olefin isomerization in addition to a double bond swap, and therefore is expected to be slower than the interconversion between **225EE** and **226EE** (Scheme 3.13). When the reaction starts from **227** and **208Z**, it is intermediate **225EZ** that is

formed first. Similarly, when the reaction starts from **178** and **228Z**, it is intermediate **226EZ** that is formed first. If it is assumed that CO insertion is faster in **225EZ** than it is in **226EZ** ($k_1 > k_2$) for the reasons discussed above. Then, the results can be explained by the situation where the CO insertion and cyclization of **225EZ** is faster than isomerization to **226EZ**. Whereas, the CO insertion and cyclization of **226EZ** is slower than isomerization to **225EZ**. The solvent effect can also be explained (Entries 2 and 4, Table 3.2). Using hexanes as solvent further reduces the rate of the interconversion of **226EZ** to **225EZ**, and therefore, the product distribution will be more reflective of the starting materials.

Scheme 3.13 Proposed Mechanism for Product Distribution from *Z*-Enynes



Based on the above studies, the electronic effect plays an important role in the inverconversion between the vinyl carbene complexed intermediates. The CO insertion and cyclization in these intermediates is preferred to occur at the intermediate with the chromium coordinated to the more electron-deficient double bond.

3.4 Summary

The mechanism of the benzannulation reaction was probed by a pseudo-symmetric intermediate assumed to generate along the reaction path. The product distributions suggest that the η^1,η^3-vinyl carbene complexed intermediates do interconvert via an olefin dissociation/re-association and can be accompanied with *E/Z* isomerization of the pendent olefins. A solvent effect is observed in these investigations, resulting in a finding that hexanes can suppress the interconversion between η^1,η^3-vinyl carbene complexed intermediates. Between the two mechanisms that have been put forward, mechanism I is considered the more likely but the results of the present study could not rule out mechanism II.

Electronic perturbation in the benzannulation was pursued by designing another pseudo-symmetric intermediate with two electronically differentiated arms. The benzannulation prefers to occur with the chromium coordinated to more electron-poor double bond in the η^1,η^3--vinyl carbene complexed intermediates, but the rate of interconversion between the two possible η^1,η^3-vinyl carbene complexed intermediates is solvent dependent.

CHAPTER 4

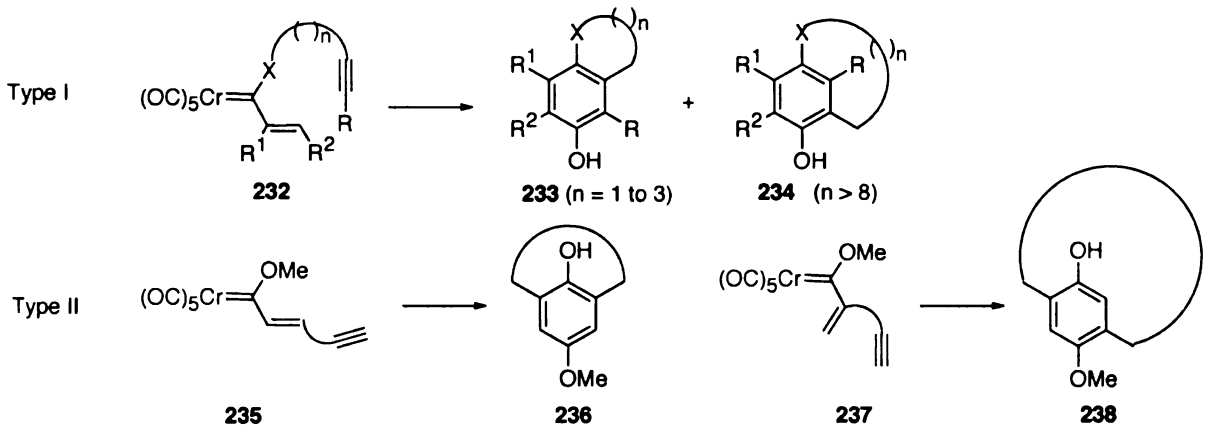
Studies Toward Total Synthesis of Richardianidin-1

4.1 Background

4.1.1 Intramolecular Annulation of Fischer Carbene Complex

In the previous chapters, we have discussed the intermolecular annulations of Fischer carbene complexes. Intramolecular reactions of carbene complexes with alkynes are also known and have been investigated. There are two types of intramolecular benzannulation reactions and these are shown in Scheme 4.1. The first type of reaction involves a carbene complex bearing an alkyne tethered to the heteroatom, and the second type involves the carbene complex bearing an alkyne tethered to either the α- or the β- carbon of the alkenyl carbene complex.

Scheme 4.1 Intramolecular Benzannulation Reactions

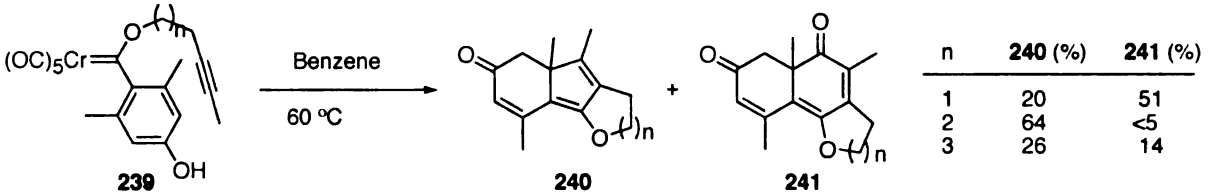


The type I of intramolecular reaction has been thoroughly studied and has been utilized in the syntheses of natural products.[68,69] Semmelhack and

coworkers reported the first example of this type of intramolecular annulation and applied this methodology to the total synthesis of deoxyfrenolicin.[68] The annulation gave good yields when the tether length was 2 to 4 carbons. It should be noted that in these intramolecular reactions, the regioselectivity of the alkyne insertion is reversed as a consequence of ring strain leading to the formation of **233**. When the tether is long enough (n > 8), the *meta*-bridged phenol **234** is obtained with the same regioselectivity as the intermolecular annulation.[69]

The tautomer-arrested version of the type I intramolecular annulation is also known. However, it is limited to a single example published by Wulff *et al* (Scheme 4.2).[70] In this example, thermolysis of carbene complex **239** gave hydrindenone **240** and the CO insertion product **241**. The hydrindenone product **240** was favored with the formation of 6-membered oxacycle (n = 2), while the shorter tether (n = 1) preferentially gave the diketone **241**, and longer tether (n = 3) gave decreased overall yield.

Scheme 4.2 Tautomer-arrested Type I Intramolecular Annulation



n	**240** (%)	**241** (%)
1	20	51
2	64	<5
3	26	14

On the other hand, only a few examples of the type II intramolecular annulation have been published.[71] This type of annulation requires the tether to be longer than 6 carbons, due to the ring strain (see Scheme 5.8). As can be seen in Scheme 4.1, the carbene complex with an alkyne tethered to the β-

carbon will afford the *meta*-bridged product, whereas the carbene complex with an alkyne tethered to the α-carbon will give the *para*-bridged product. The regioselectivity of these annulations results in the alkyne and the tether being attached to the arene ring in the product adjacent to the phenol which is the same as that for the intermolecular annulation.

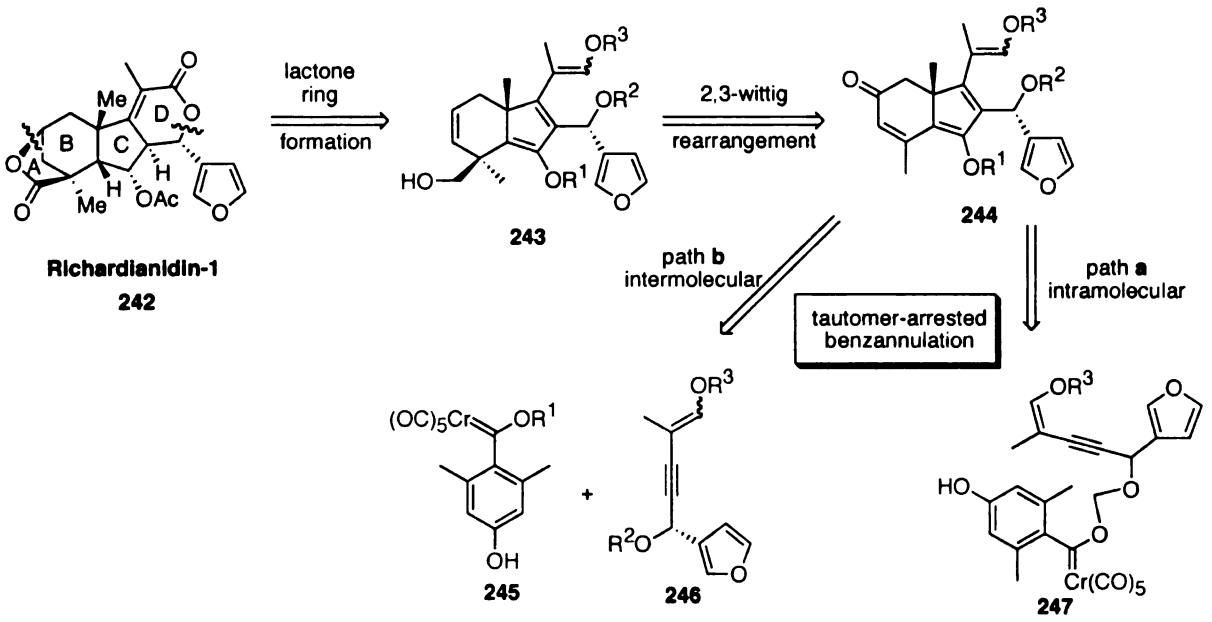
4.1.2 Retrosynthetic analysis of Richardianidin-1

Richardianidin-1 (**242**) was isolated in 1988 from the leaves of *Cluytia Richardiania* (L.), which grows in the mountain regions of western and southern Saudi Arabia.[72] The *Cluytia* species are used in folk medication and have significant hypoglycemic activities *in vitro* and *in vivo*.[73] The structural challenge to the synthesis of Richardianidin-1 is highlighted by the tetracyclic system rich in stereogenic centers. Although having interesting bioactivity and possessing structural uniqueness, there has been no total synthesis of Richardianidin-1 reported. Only one approach to the framework of this natural product has been published.[74] The key step in a synthesis to be examined in the present work is the construction of the BC rings of Richardianidin-1 (**242**) by the tautomer-arrested annulation.

The retrosynthetic analysis for Richardianidin-1 (**242**) shown in Scheme 4.3 was previously studied by Mary Bos in this research group and her studies can be found in her thesis.[75] The retrosynthesis starts with the ring opening of the lactone to give intermediate **243** (Scheme 4.3). This intermediate is envisioned to

result from a 2,3-Wittig rearrangement that ultimately leads back to hydrindenone **244**,[76] which in turn can be synthesized via either an inter- or intramolecular tautomer-arrested annulation of 4-hydroxy-2,6-dimethylphenyl carbene complexes **245** or **247** respectively. Between the two approaches, the intramolecular was initially favored, because it presumably offers better control of the regioselectivity. The applications of tautomer-arrested annulation in total synthesis never have been used, and thus would make this approach more favorable.

Scheme 4.3 Retrosynthetic Analysis of Richardianidin-1



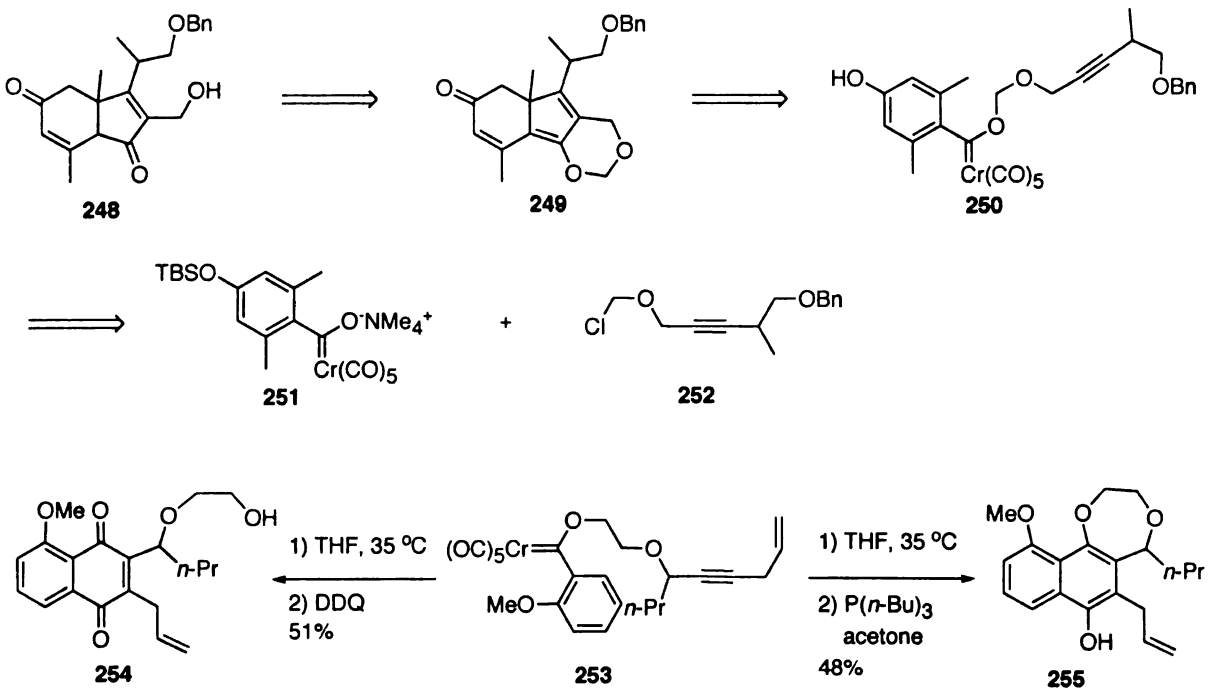
4.2 Intramolecular approach

4.2.1 Intramolecular annulation of Fischer carbene complexes containing an acetal tether

The intramolecular approach was first examined with the target simplified model hydrindenone **248** (Scheme 4.4). It was envisioned that compound **248**

could be easily obtained by hydrolysis of enol acetal **249**, which could in turn be obtained from carbene complex **250** via an intramolecular tautomer-arrested annulation. The acetal in the tether is critical in this approach for two reasons. The first is that hydrolysis of the acetal in **249** liberates the properly oxygenated intermediate **248**. The second is that, as mentioned before (Scheme 4.2), the hydrindenone product is only favored over the CO inserted product when the tether length is four atoms from the alkyne to the carbene carbon.[70]

Scheme 4.4 Intramolecular Annulation Analysis



Semmelhack has previously developed a cleavable tether and employed it in the total synthesis of deoxyfrenolicin.[68a,b] This tether involved an ethylenoxy linkage which involves a total of 5 atoms in the liner (Scheme 4.4). In addition, cleavage of the linker involved an oxidation elimination sequence and thus would not be as convenient as a simple acetal linkage. Acetal linkers such as that

presented in carbene complex **250** have not been previously employed in intramolecular benzannulation reactions. It is anticipated that these complexes could be accessed from alkylation of the ammonium acylate **251** with the chloromethyl propargyl ether **257**. A series of carbene complexes **259** were prepared such that the generally of these complexes in the annulation could be examined (Scheme 4.5). Thus, propargyl alcohol **256** was allowed to react with paraformadehyde and TMSCl to give the corresponding chloromethyl ether **257**,[77] which was then reacted with ammonium salt **251** to afford the TBS-protected carbene complex **258**. This preparation was sensitive to the propargylic substituent. Unfortunately, compounds **264** and **266**, with a phenyl or 2-furyl group at the propargylic carbon could not be prepared with this route. Removal of the TBS group in **258** could only be accomplished by treatment with sodium methoxide in methanol; using TBAF led to the decomposition of the carbene complex.

It was pleasing to find that, the thermolysis of **259a**, the simplest model compound, in benzene at 60 °C afforded hydrindenone **260a** as the major product in 51% yield. A trace amount of the indene product **262** resulting from methyl migration was also detected by ^{1}H NMR. Thermolysis of **259a** in toluene gave the same product **260a** in 49% yield accompanied with a trace amount of indene **262**. However, when the substituent on the triple bond (R^1) was changed from methyl to ethyl and *iso*-propyl, the yields of hydrindenone **260** dropped dramatically and the CO insertion product **261** was observed, all with a significant decrease in overall yield. In the *iso*propyl case, hydrindenone **260c** was not

observed. This result greatly reduces the prospects for this intramolecular approach to Richardianidin-1. However, in the actual retrosynthesis, R^2 would not be hydrogen in carbene complexes. Therefore, complex **259d** was synthesized to study the effect of α-substituents ($R_2 \neq H$). The reaction of the α-substituted propargyl ether tethered carbene complex **259d** afforded near a 1:1 ratio of the desired product **260d** and the CO insertion product **261d**. This result indicated that the α-substituent had a small impact at most on this annulation reaction.

Scheme 4.5 Syntheses and Thermolysis of Carbene Complexes 259

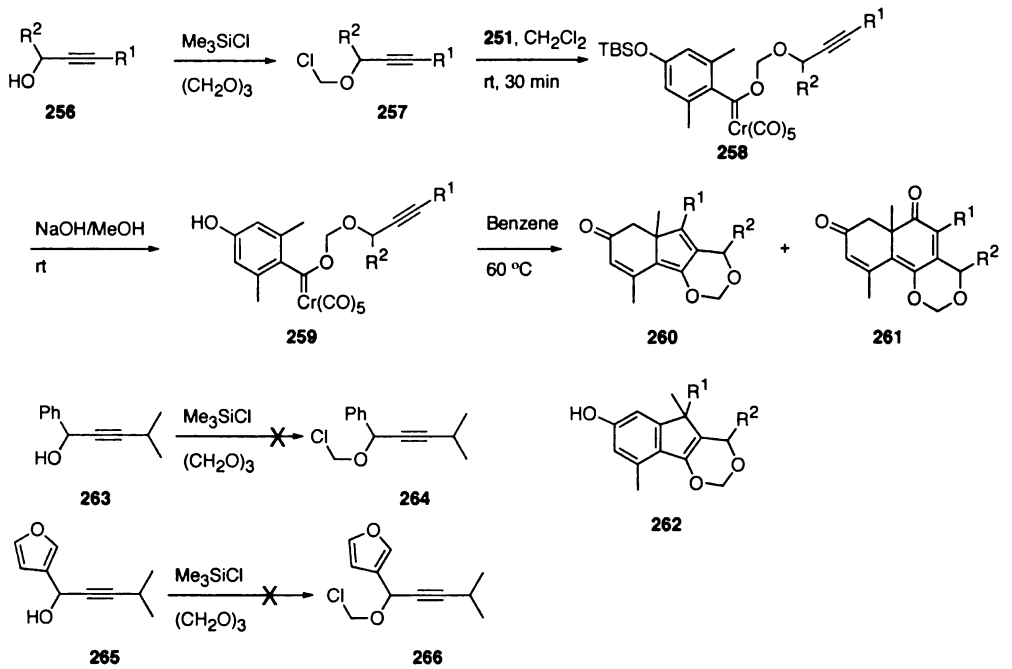


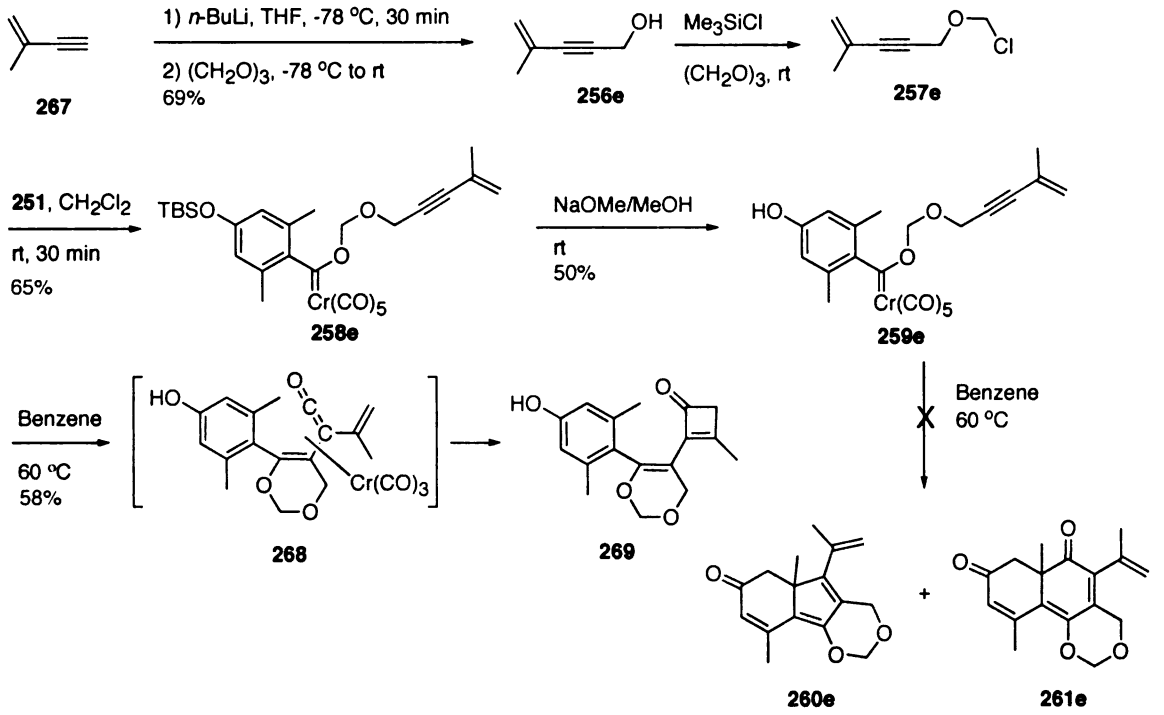
Table 4.1 Syntheses and Thermolysis of Carbene Complexes 259

Series	R^1	R^2	% Yield **258**	% Yield **259**	% Yield **260**	% Yield **261**
a	Me	H	91	59	51[a]	-
b	Et	H	97	46	9	25
c	*i*-Pr	H	68	55	-	16
d	Pr	Et	100	40	18	21

a) Thermolysis of carbene complex **259a** in toluene provided 49% of **260a**.

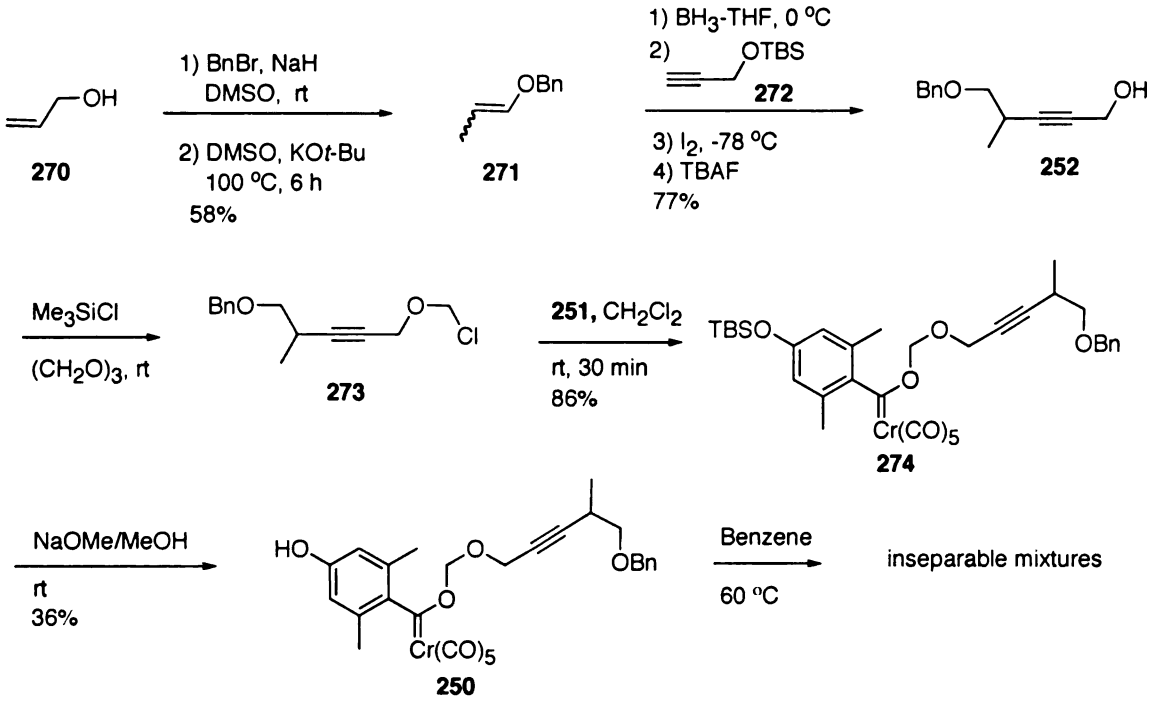
As indicated in retrosynthetic analysis (Scheme 4.3) the most desirable substituent on the alkyne of carbene complex **247** is an alkenyl group. Therefore, carbene complex **259e** with R^1 as an *iso*-propenyl group was prepared. This complex was prepared as shown in Scheme 4.6. Perhaps the steric and electronic differences between an *iso*-propenyl and *iso*-propyl group would lead to a greater preference for the hydrindenone product. However, when carbene complex **259e** was subjected to the thermolysis conditions in benzene, the desired product **260e** was not detected at all. Nor was the CO insertion product **261e**. The only product obtained in this reaction was the phenol **269** whose structure was determined after extensive NMR studies. This product is thought to form via vinyl ketene **268** and subsequent electrocyclic ring-closure.

Scheme 4.6 Thermolysis of Carbene Complex 259e



Given the failure of tautomer-arrested annulation of the *iso*-propenyl substituted complex **259e**, the complex **250** was next prepared which had a benzyloxy propyl group as a surrogate for the *iso*-propenyl group. The synthesis of **250** is shown in Scheme 4.7 and begins with the propargylic alcohol **252** which in turn was prepared from allylic alcohol **270**. After Benzyl-protection and olefin migration to obtain **271**, a hydroboration was performed, followed by I_2-induced coupling of the alkyl group in the borane and alkyne **272**.[78] Desilylation afforded **252** in good overall yield. Then, following a route similar to that outlined in Schemes 4.5 and 4.6, alcohol **252** was then taken onto carbene complex **250**, albeit in lowered yield. To our disappointment, thermolysis of **250** gave a complicated mixture of many compounds, which was not further characterized.

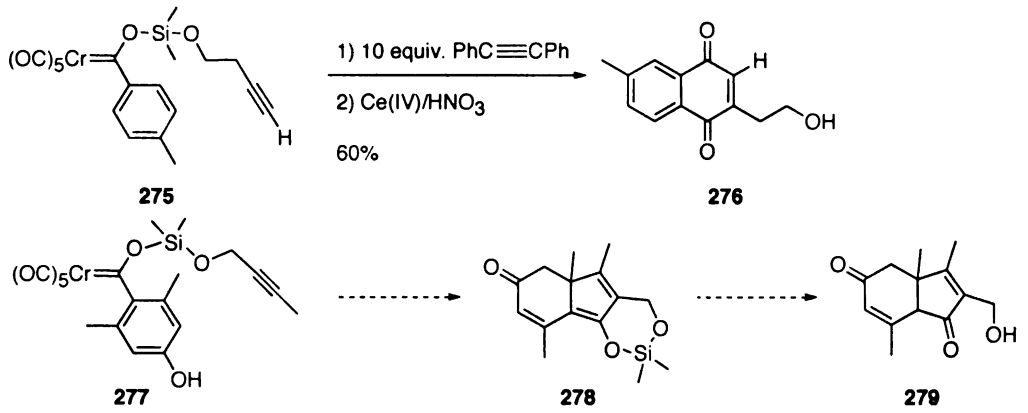
Scheme 4.7 Preparation and Thermolysis of Carbene Complex 250



4.2.2 Intramolecular annulation of Fischer carbene complexes containing a silicon tether

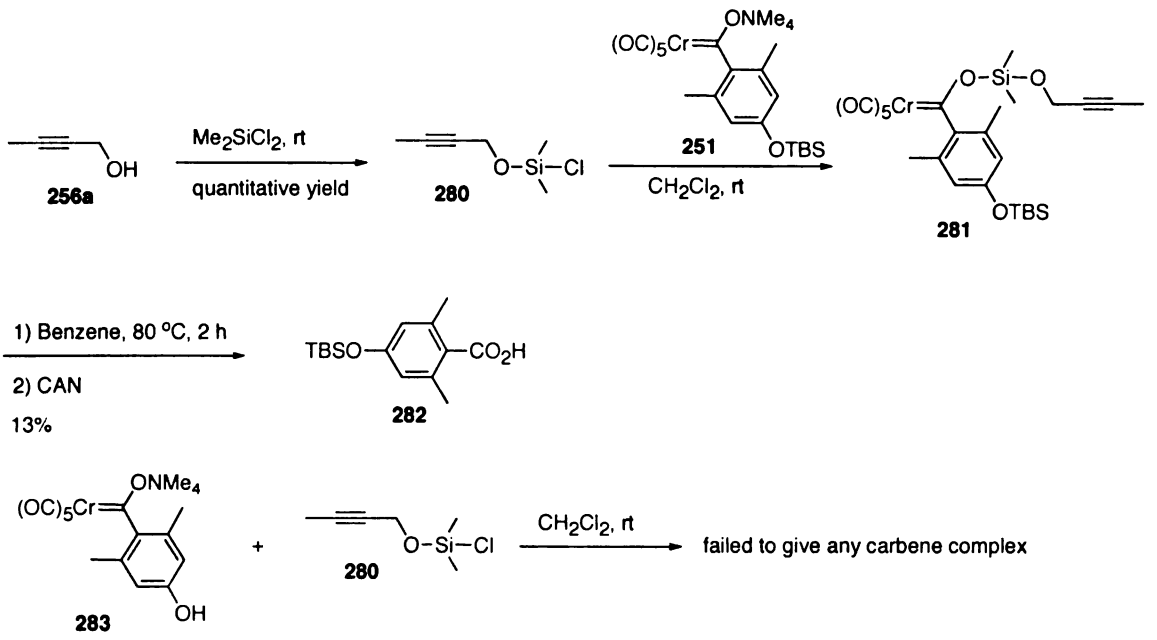
Finn and coworkers reported that thermolysis of silicon tethered carbene complex **275** in the presence of a large excess of diphenyl acetylene followed by CAN oxidation could afford the hydrolyzed benzannulation product **276** in good yield (Scheme 4.8).[79] Thus, it was of interest to see if the silicon-tethered carbene complex **277** (Scheme 4.8) could be used in the intramolecular tautomer-arrested annulation. It was hoped that this approach might provide desired hydrindenone product **279** upon thermolysis and hydrolysis of **277**.

Scheme 4.8 Proposed Synthesis of 279



Preparation of the TBS-protected carbene complex **281** could be achieved by treatment of alcohol **256a** sequentially with Me_2SiCl_2 and ammonium salt **251**. However, the silicon-tethered carbene complex **281** was unstable and readily decomposed upon quenching the reaction with $NaHCO_3$ or upon loading the reaction mixture directly onto a triethylamine-treated silica column. Thermolysis of the unpurified and unstable red compound in benzene followed by CAN workup did not furnish any cyclized product. The only detectable product was the carboxylic acid **282** which was isolated in 13% yield. The ammonium acylate **283** with a free hydroxy group failed to react with **280** to give any carbene complex. Thus, the plan to synthesize carbene complex **277** was abandonee.

Scheme 4.9 Synthesis of Carbene Complex Tethered with Silylether



With these results in hand, the intramolecular approach has met a major obstacle. With the understanding gained in the present work on the reactivity of carbene complexes in the intramolecular tautomer-arrested annulation, it becomes clear that this reaction will not likely be able to provide an efficient access to the desired intermediate **244** in the synthesis of Richardianidin-1 (**242**) (Scheme 4.3). Thus, an alternative approach needs to be considered.

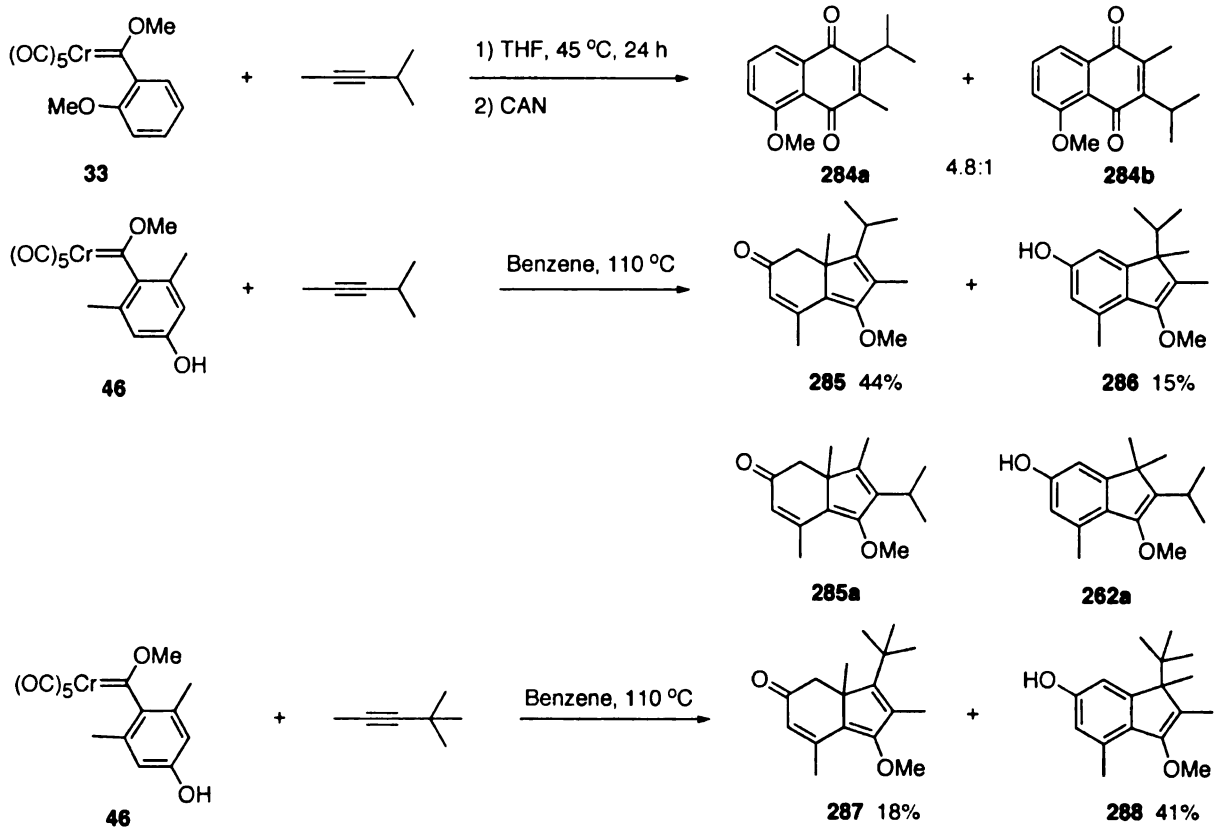
4.3 Intermolecular Approach

Due to the difficulties encountered during the studies on the intramolecular approach, attention was turned to utilize the intermolecular tautomer-arrested annulation to construct the BC ring of Richardianidin-1 (Scheme 4.3). The biggest problem to be addressed in this approach is the regioselectivity. The regioselectivity is generally not high for internal alkynes in the benzannulation

reaction (Scheme 4.10).[12] For example the reaction of carbene complex **33** and *iso*-propyl methyl acetylene gave a 4.8:1 ratio of **284a** and **284b**.[12] In addition, it is known that the regioselectivity decreases with increasing temperature.[66] This is particularly troublesome for the prospects for regioselectivity for the tautomer-arrested annulation since this reaction requires higher temperatures (110 °C) than the normal benzannulation (45 °C).

As expected on the basis of the discussion above, the reaction of complex **46** with *iso*-propyl methyl acetylene provided two products in a 3:1 ratio. However, after careful analysis, the two products were found not to be regioisomers. Instead, they were hydrindenone **285** (tautomer-arrested product) and indene **286** (methyl-migration product), respectively. Surprisingly enough, neither **285** nor **286** was contaminated by its regioisomers **285a** or **286a**. Thus, this annulation is completely regioselective. The reason for this excellent regioselectivity is still elusive, but the result made the intermolecular approach to Richardianidin-1 much more promising. The reaction between carbene complex **46** and methyl *tert*-butyl acetylene was also examined. This annulation also provided excellent regioselectivity, but the desired hydrindenone **287** now became the minor product in this case.

Scheme 4.10 Studies of the Regioselectivity in the Intermolecular Annulation

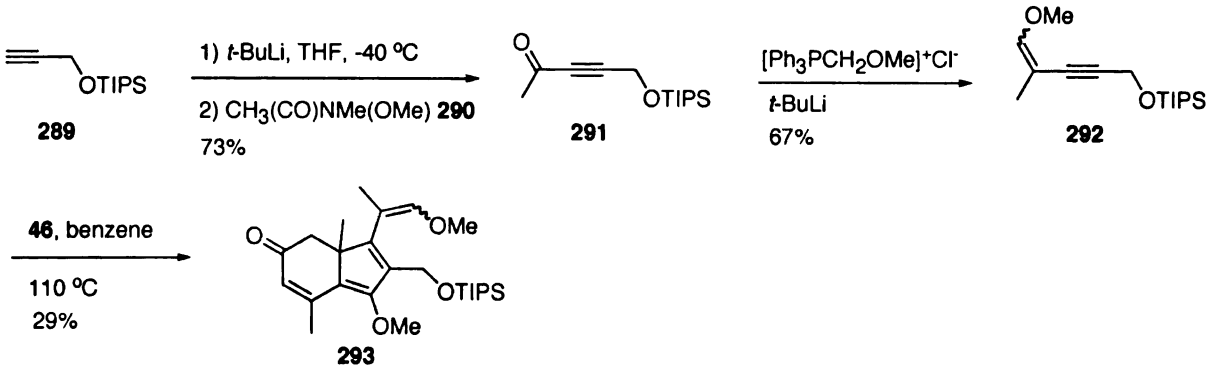


The excellent regioselectivity for an alkyne bearing a methyl and *iso*-propyl groups prompted the design of alkyne **292** (Scheme 4.11). The annulation with carbene complex **46** should produce hydrindenone **293** as the product. Compound **293** contains all but one of the carbons on the BC ring in Richardianidin-1. Furthermore, compound **293** should be able to be converted to the key intermediate **244** (Scheme 4.3) by functional group manipulation.

Alkyne **292** was prepared in 2 steps from **289**. Deprotonation of the terminal alkyne followed by trapping with Weinreb amide **290**[63] led to compound **291**. Subsequent Wittig reaction with methoxymethylene phosphorane gave enyne **292** as a 1:1 mixture of *E*/*Z* isomers. This stereochemistry is not important,

since this enol ether will be converted to a ketone at a later stage in the synthesis. Thus, the annulation was performed with this *E*/*Z*-mixture. Thermolysis of alkyne **292** with carbene complex **46** did provide the desired product **293** as a single regioisomer, but the yield of this reaction is only 29%.

Scheme 4.11 Annulation of Carbene Complex 46 and Alkyne 292



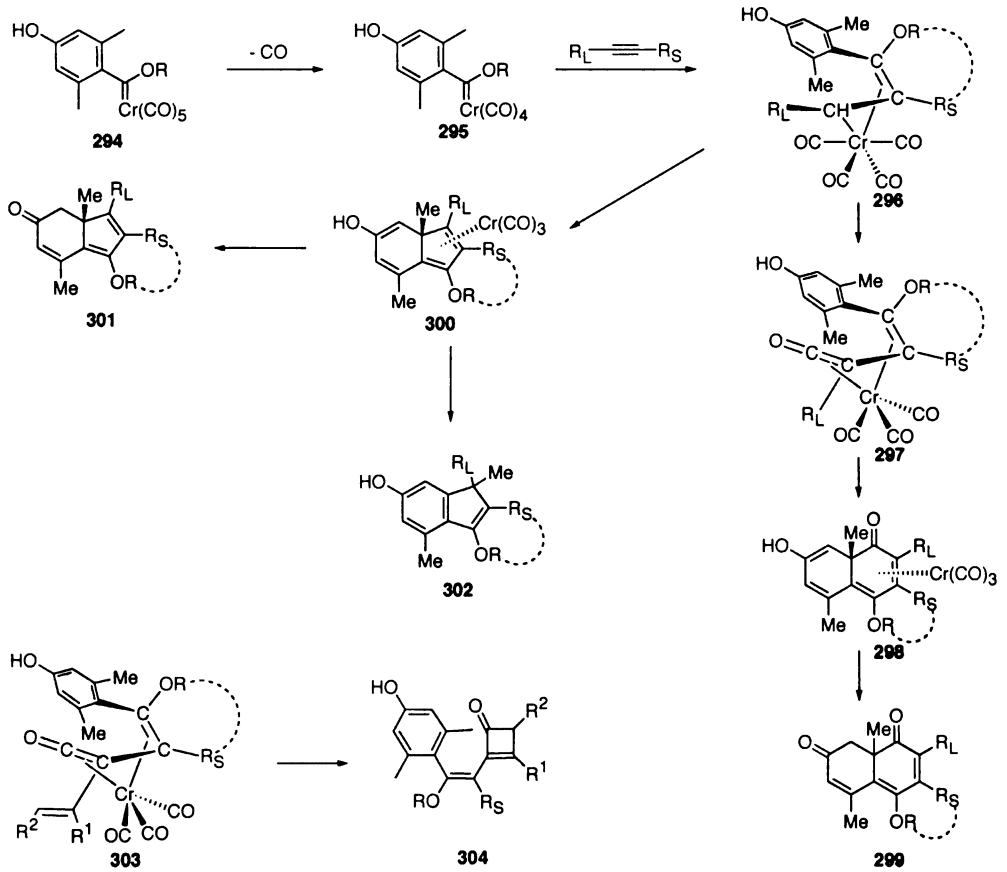
4.4 Mechanistic considerations

During the investigations described in this chapter, it was noticed that the product distributions were quite different for the intra- and inter-molecular tautomer-arrested annulations. The intramolecular reaction generates hydrindenone **301** and CO insertion product **299** (Scheme 4.12), while the intermolecular reaction gives hydrindenone **301** and indene **302**. A mechanism for the diverse array of outcomes is proposed and is presented in Scheme 4.12. It is believed that the initial steps, namely the dissociation of a CO ligand and alkyne insertion to generate a η^1,η^3-vinyl intermediate **296**, are the same in both inter- and intra-molecular reactions. In the normal benzannulation reaction, this intermediate prefers to undergo CO insertion to give intermediate **297**. However

in the intermolecular tautomer-arrested annulation, such insertion of CO is not favored. The presence of the two *ortho* methyl groups on the phenyl must either depress the insertion of CO in **296** or if **296** and **297** are in equilibrium, it must slow down the cyclization of the vinyl ketene intermediate **297**. Either would enhance the formation of the 5-membered cyclized intermediate **300**, which then ultimately leads to **301** or **302**. Possible reasons for the appearance of CO inserted products in the intra-molecular tautomer-arrested annulation have been discussed by Mary Bos who examined a series of complexes with different tether links between the alkyne and carbene carbon.[75] Her work suggests that the strain in the ring bridging R_S and OR in structure **296** is the major contributing factor.

When R_L is a vinyl group in the intramolecular tautomer-arrested annulation, the vinyl ketene intermediate **303** is trapped by the vinyl group and gives cyclobutenone **304**. In contrast, Wulff *et al* reported that in the regular benzannulation reaction, similar vinyl-substituted ketene intermediates are very reactive and could not be trapped in this manner but rather cyclize to the normal phenol product.[65] Thus, the presence of the *ortho* methyl groups for presumably steric reasons must decrease the rate of the cyclization of the ketene onto the phenyl ring, so that the electrocyclic ring closure to **304** is favored.

Scheme 4.12 Mechanism of Tautomer-arrested Annulation



4.5 Summary

The studies toward the total synthesis approach to Richardianidin-1 are still underway. Currently, the intramolecular approach has encountered a major obstacle. An advanced intermediate with the carbene carbon and alkyne tethered though an acetal did not provide the desired cyclization product in acceptable selectivity and yield. An intermediate with the carbene carbon and alkyne tethered through a silicon linkage failed to give any desired cyclization product.

The intermolecular approach provides excellent regioselectivity for the desired application, but suffers from low yield in the key step of the annulation.

CHAPTER 5

Total Synthesis of Phomactin B2: the Application of an Intramolecular Cyclohexadienone Annulation of Fischer Carbene Complexes

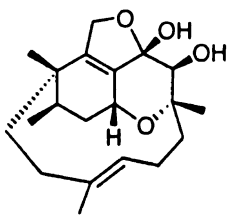
5.1 Background on Phomactins

5.1.1 Isolation and bioactivity of Phomactins

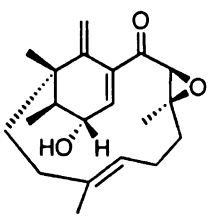
Phomactins (Figure 5.1) were isolated from the culture of marine fungus *Phoma sp.*, a parasite on the shell of a crab *Chinoecetes opilio* harvested from the coast of Japan.[80] Phomactins have shown remarkable bioactivity as platelet activating factor (PAF) antagonists. PAF is an ether-phospholipid that induces the release of histamine from platelet, and it is involved in platelet aggregation, cardiovascular, inflammatory, and respiratory diseases.[81] Thus, Phomactins could offer potential treatment for these diseases.

The Phomactin family shares a rare [9.3.1] pentadecane bicyclic ring system, which contains a highly substituted cyclohexane core and a bridged decane ring with multiple oxygen substituents. Among them, Phomactins A, B2 and D have the highest biological activity.[80b] Their unique structures, as well as their bioactivity, have made them attractive targets for synthesis.[82]

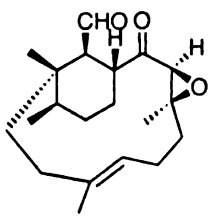
Figure 5.1 Structures of Some Natural Occurring Phomactins



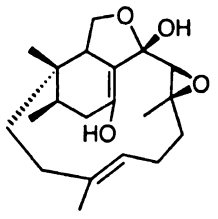
Phomactin A
305



Phomactin B2
306



Phomactin D
307



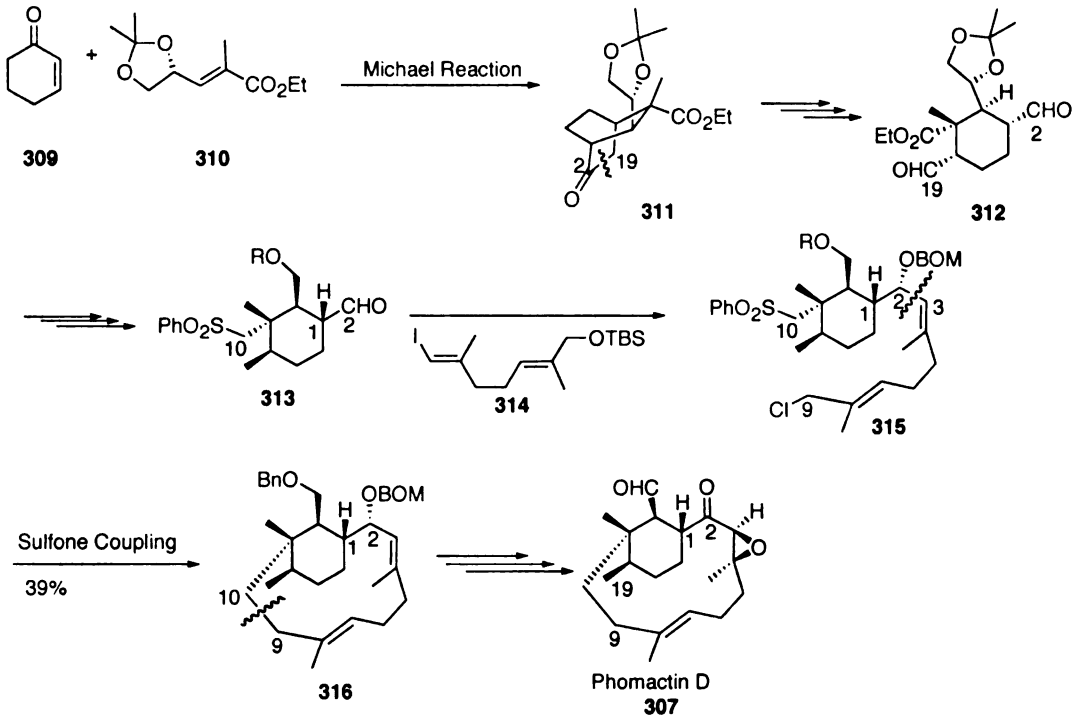
Phomactin G
308

5.1.2 Previous total syntheses of Phomactins

The two major challenges in the syntheses of Phomactins are the construction of the highly substituted cyclohexane core, and the formation of the macrocycle. Despite many efforts aimed at the construction of the structural framework of this natural product family, to date, only two total syntheses of Phomactin A (**305**),[83] two total syntheses of Phomactin D (**307**),[84] and one total synthesis of Phomactin G (**308**)[85] have been completed. All of the reported strategies have in common the initial assembly of the cyclohexane core and then the construction of the 12-membered macrocycle. Different methods have been utilized for the latter task, including sulfone coupling,[84a] Suzuki coupling,[83c] and NHK coupling.[83a,b, 85]

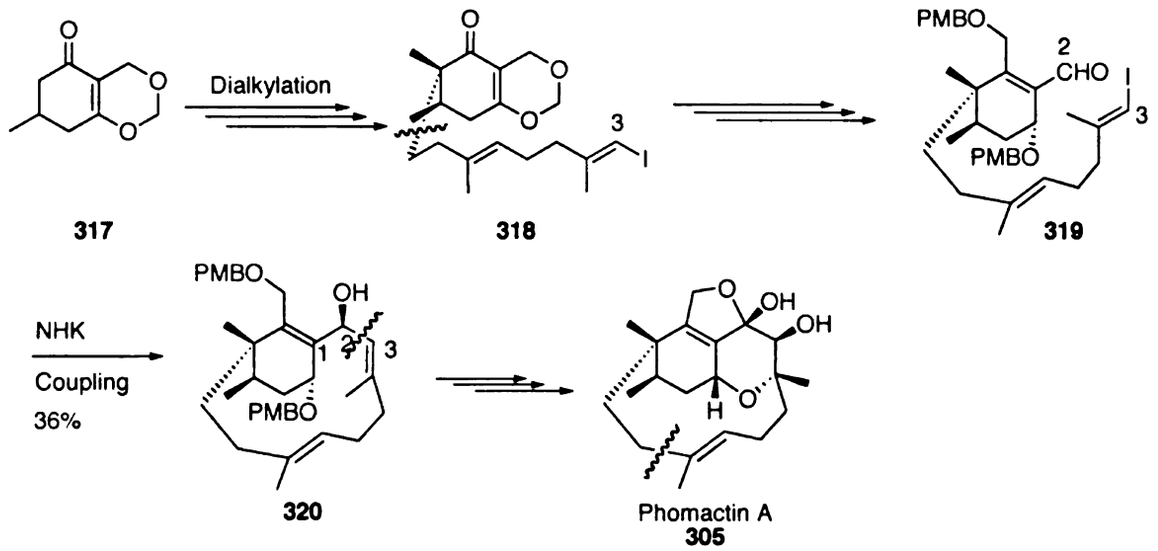
The pioneering work of Yamada and coworkers lead to the first synthesis of a member of the phomactin family in 1996.[84a] Their strategy for the synthesis of Phomactin D (**307**) involved the later-stage sulfone coupling of an allylic chloride to construct the macrocycle (formation of C9–C10 bond). The construction of precursor **312** was accomplished by sequential Michael addition reactions and an oxidative cleavage of the C2–C19 bond in compound **311**. A similar sulfone coupling strategy was also used by the Thomas group to make the macrocycle in their approach to the skeleton of Phomactins.[86m] The Halcomb group has also completed a total synthesis of Phomactin D but this is only published at this point in a thesis.[84b]

Scheme 5.1 Yamada's Total Synthesis of Phomactin D



The first total synthesis of racemic Phomactin A (**305**) was published by Pattenden's group in 2002.[583a,b] Their approach involved the intramolecular Nozaki-Hiyama-Kishi (NHK) coupling reaction to construct the C2–C3 bond in the macrocycle. The precursor **319** was in turn obtained by straightforward manipulations from **317**. The same group also published the first total synthesis of Phomactin G using a similar strategy.[85]

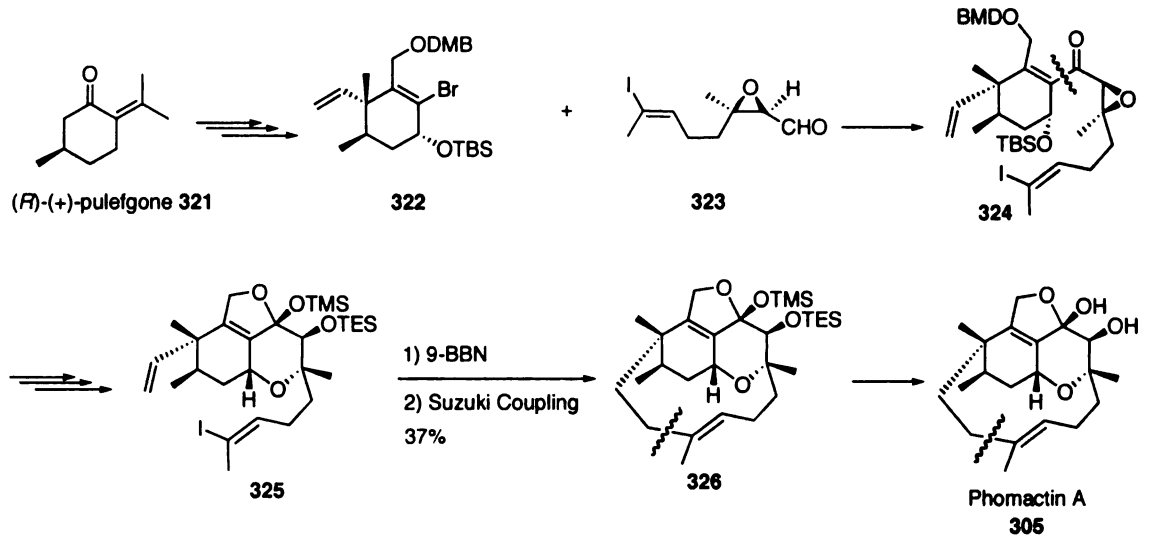
Scheme 5.2 Pattenden's Total Synthesis of Phomactin A



317 318 319 320 Phomactin A 305

Almost at the same time, Halcomb and coworkers accomplished the first enantioselective synthesis of (+)-Phomactin A (**305**).[83c] They used (*R*)-(+)-pulefgone (**321**) from the chiral pool to build the enantiomerically pure multiple substituted cyclohexene **322**, which was coupled with epoxy aldehyde **323** to synthesize **324**. After functional group manipulations, a key Suzuki coupling closed the macrocycle which ultimately led to the desired target molecule.

Scheme 5.3 Halcomb's Total Synthesis of (+)-Phomactin A



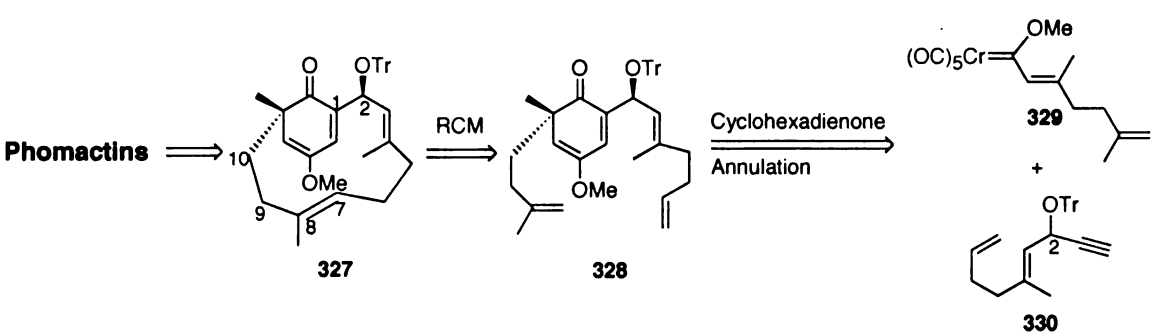
The total syntheses of phomactin employ a variety of methods to construct the macrocycle. However, all of the above strategies discussed above suffered from the low yield (~ 40%) in the key macrocyclization step. In addition to the above total syntheses, a number of synthetic approaches to Phomactins have also been published involving other methods to construct the macrocycle,[86] including sulfone coupling,[86m] oxa-[3+3] cycloaddition,[86l] Stille coupling,[86j] and ring-closing metathesis[83b].

5.1.3 Retrosynthetic analysis of Phomactins and previous work in our group

Our synthetic strategy towards the total synthesis of Phomactins involves the cyclohexadienone annulation of the Fischer carbene complex. An introduction to the cyclohexadienone annulation was presented in Chapter 1 (Scheme 1.5).[19] Retrosynthetic approaches to the phomactins have been designed for both inter- and intramolecular variations of the cyclohexadienone

annulation. The intermolecular cyclohexadienone annulation will utilize carbene complex **329** and alkyne **330** to construct cyclohexadienone **328**, followed by a ring-closing metathesis (RCM) to form the macrocycle (Scheme 5.4). The resultant cyclohexadienone **327** could serve with proper manipulation to provide a convergent approach to several members of the Phomactins. The annulation of carbene complex **329** and alkyne **330** has been attempted by Ms. Ying Liu in the group and resulted in an 88% yield of **328** with a 98:2 diastereoselectivity.[87] However, the RCM reaction of **328** with Grubb's generation I catalyst failed to give any desired bicyclic product. Only dimer was observed in this reaction. Now, with newer RCM catalysts available,[88] it might be expected this problem can be overcome and this will be discussed in Chapter 6.

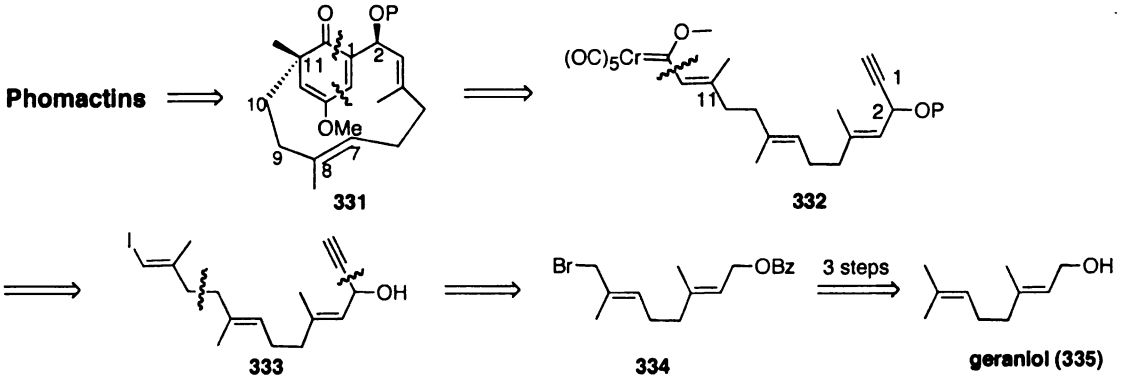
Scheme 5.4 Retrosynthesis of Phomactins (Intermolecular Version)



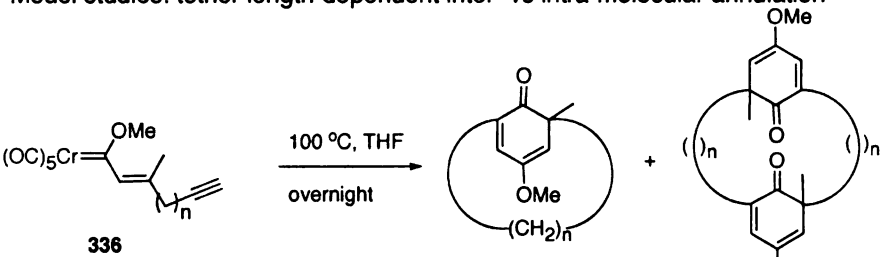
An intramolecular strategy was also proposed based on results from a model study performed by Dr. Jie Huang (Scheme 5.5).[89] Dr. Huang demonstrated that thermolysis of carbene complexes **336** with a 6-carbon tether between the β-carbon of the carbene complex and the alkyne give dimer and trimer products, whereas carbene complexes with 8- and 10-carbon tethers will cyclize to afford the desired bicyclic products **337** in moderate yields (Scheme

5.5). Accordingly, the bicyclic intermediate **331** could be expected from the thermolysis of carbene complex **332**, which contains a 9-carbon tether between the β-carbon of the carbene complex and the alkyne. The diastereoselectivity of this annulation and the stereochemistry at C2 are not important in a racemic synthesis, since C2 will be converted to a ketone at a later stage in the synthesis. Carbene complex **332** is envisioned to be obtained from vinyl iodine **333**, which in turn was designed to be derived from the known allylic bromide **334**.[90]

Scheme 5.5 Retrosynthesis of Phomactins (Intramolecular Version)



Model studies: tether length-dependent inter- vs intra-molecular annulation



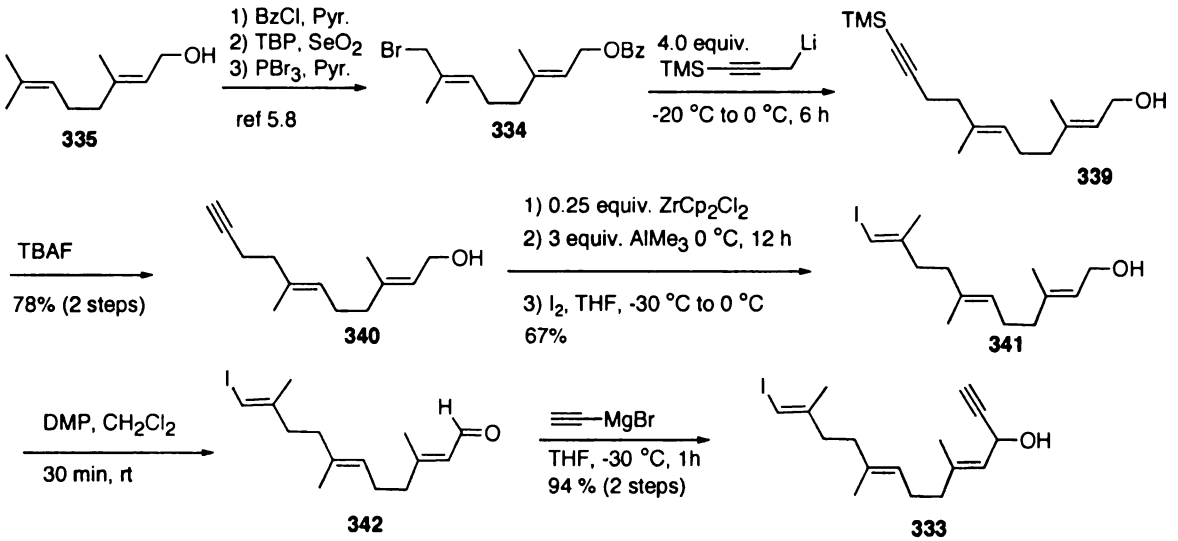
	337 (%)	338 (%)
n = 6	-	18
n = 8	45	-
n = 10	43	-
n = 13	64	-

5.2 Synthesis of key intermediates 331

5.2.1 Synthesis of vinyl iodine 333

With the strategy set, the synthesis of vinyl iodine **333** became the target of the first stage. The synthesis of **333** follows that developed by Dr. Huang with some modifications.[91] Thus, starting from the commercially available geraniol (**335**), which contains the desired double bond geometry in intermediate **331**, a 3-step operation following literature procedures afforded allylic bromide **334**.[90] The coupling reaction of allylic bromide **334** with 4 equivalents of TMS-protected propargyl lithium elongates the carbon chain and simultaneously deprotectes the benzoyl-protecting group to give silyl acethylene **339**. The stoichiometry of the lithium reagent was critical, as lower equivalents led to a complex mixture. Desilylation of **339** with TBAF afforded terminal alkyne **340** in 78% yield for the two steps from allylic bromide **334**. This terminal alkyne was then subjected to Negishi's carbometallation with 3 equivalents of $AlMe_3$ and a catalytic amount of $ZrCp_2Cl_2$ to afford vinyl iodine **341** in 67% yield.[92] Using a stoichiometric amount of $ZrCp_2Cl_2$ actually gave a slightly lower yield. Dess-Martin oxidation,[93] followed by alkylation with ethynyl magnesium bromide provided vinyl iodine **333** in 94% yield from compound **341**.

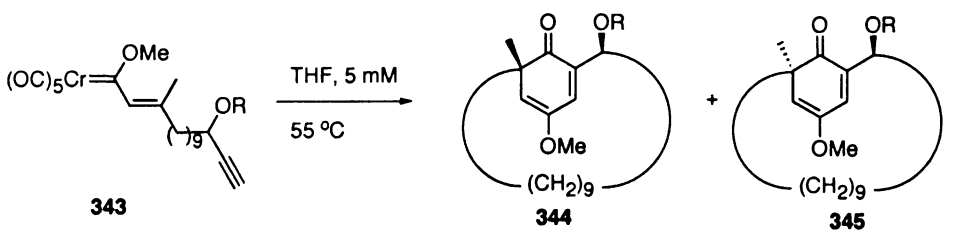
Scheme 5.6 Synthesis of Vinyl Iodine 333 from Geraniol (335)



5.2.2 Synthesis of carbene complexes

On the basis of Dr. Huang's model study, the best diastereoselectivity for the intramolecular cyclohexadienone annulation was achieved when the propargyl alcohol was protected as tri-*iso*-propylsilyl (TIPS) ether (Scheme 5.7).[91] Thus, we chose to protect the propargyl alcohol **333** as a TIPS ether (**346**) (Scheme 5.8).

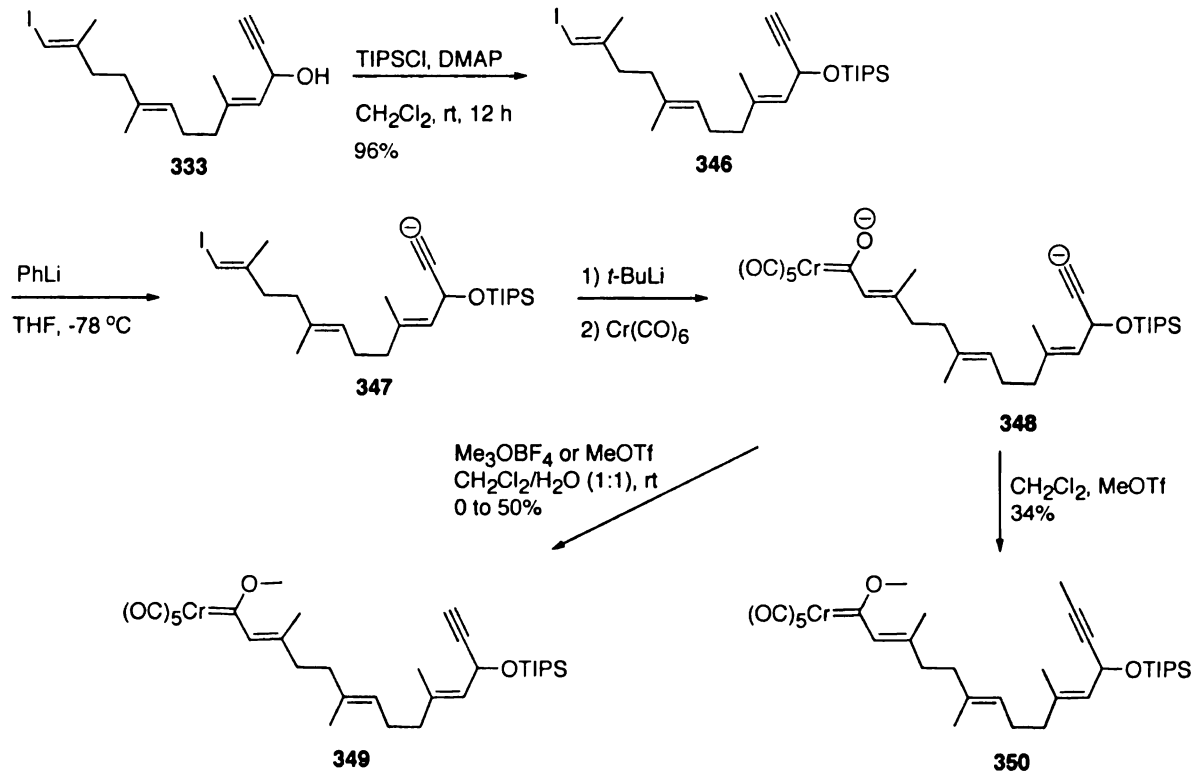
Scheme 5.7 1,4–Asymmetric Induction in Intramolecular Cyclohexadienone Annulation



R	over all yield	344:345
Tr	65	1.0:1.1
TIPS	45	3.0:1.0
Me	66	2.1:1.0
MOM	44	1.0:1.1

With compound **346** in hand, the preparation of carbene complex **349** was carried out according to the procedure developed by Jie Huang,[91] which employed the dianion procedure developed by Huan Wang.[94] Wang noted that the presence of the terminal acetylene proton caused problems in the lithium/halogen exchange step. His solution was to deprotonate the alkyne using PhLi before the lithium/halogen exchange. This process begins with the addition of PhLi to the vinyl iodine **346** to deprotonate the acetylene proton, followed by addition of *t*-BuLi and $Cr(CO)_6$ subsequentially to give dianion **348**. Methylation of dianion **348** with Meerwein's salt (Me_3OBF_4) or MeOTf in 1:1 mixture of CH_2Cl_2/H_2O yielded the desired carbene complex **349**. The addition of water to protonate the acetylene anion in **348** but not the oxygen anion of the carbene complex was crucial for success. Without water, the acetylene anion was also methylated and afforded carbene complex **350** as the only product.

Scheme 5.8 Synthesis of Carbene Complex 349



5.2.3 Modification of the carbene complex preparation

Although the synthetic route to carbene complex **349** outlined in Scheme 5.7 worked well on small scales, upon scale up, the conversion of vinyl iodine **346** to carbene complex **349** became quite capricious. For unknown reasons, the yields of this reaction were not reproducible and varied from 0-50% for different runs. It was thought that the presence of the acetylene proton was the main reason for the low and irreproducible yield. Thus, to optimize the yield for the preparation of carbene complex **349**, the synthetic route need to be modified.

It was considered that the quality of the PhLi might affect the subsequent reactions. Thus, the use of an alternative aryl lithium source was considered for the deprotonation step. The organolithium should be basic enough to

deprotonate the acetylene proton but not reactive enough to cause the lithium/halogen exchange with the vinyl iodine to occur. Alkyl lithium were not considered on the basis of the studies by Huan Wang who found that they effected lithium/halogen exchange.[94] The search for an optimal aryl lithium was carried out on the model vinyl iodine **353**, which contains a 10-carbon tether between the β-carbon and the tethered alkyne (Scheme 5.9).[91] The synthesis of compound **353** starts from the commercially available trimethylsilyl acetylene. Deprotonation followed by coupling with 1,10-diiododecane provided **351** in 97% yield. Desilylation with TBAF affords diyne **352** in 66% yield. Compound **352** was then subjected to Negishi's carbometallation-iodination reaction with 1 equivalent of $AlMe_3$ and a catalytic amount of $ZrCp_2Cl_2$ to provide vinyl iodine **353** in moderate yield (34%).[92]

With model compound **353** in hand, the efficiency of different aryl lithium species to serve as bases for the deprotonation of **353** was evaluated in the preparation of the carbene complex **354** as outlined in Table 5.1. Unfortunately, aryl lithiums with either electron withdrawing groups or electron donating groups on the aryl ring provided no general trend and in no cases high yield of the carbene complex **354** was obtained (Entries 1 to 4). The best results were obtained using either phenyl or 4-fluorophenyl lithium as base, and the carbene complex **354** was obtained in 40-50% yield (Entries 11 and 3). The use of heteroaromatic lithiums did not provided even moderate yields of **354** (Entries 8 to 10).

Scheme 5.9 Preparation of Vinyl Iodide 353

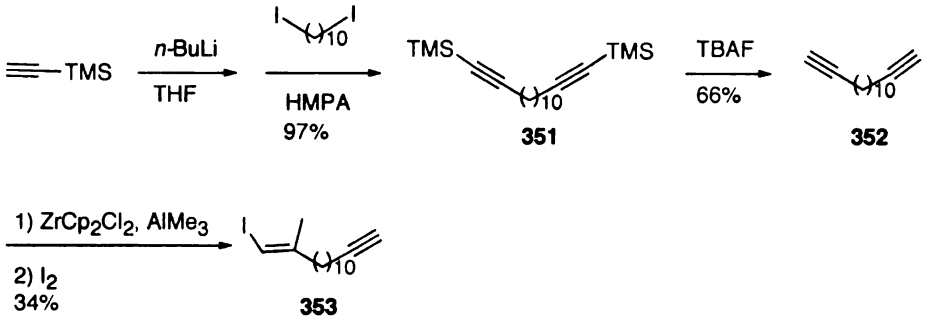
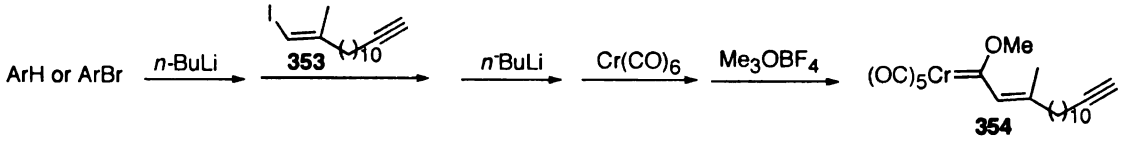


Table 5.1 Model Study of Carbene Complex Synthesis



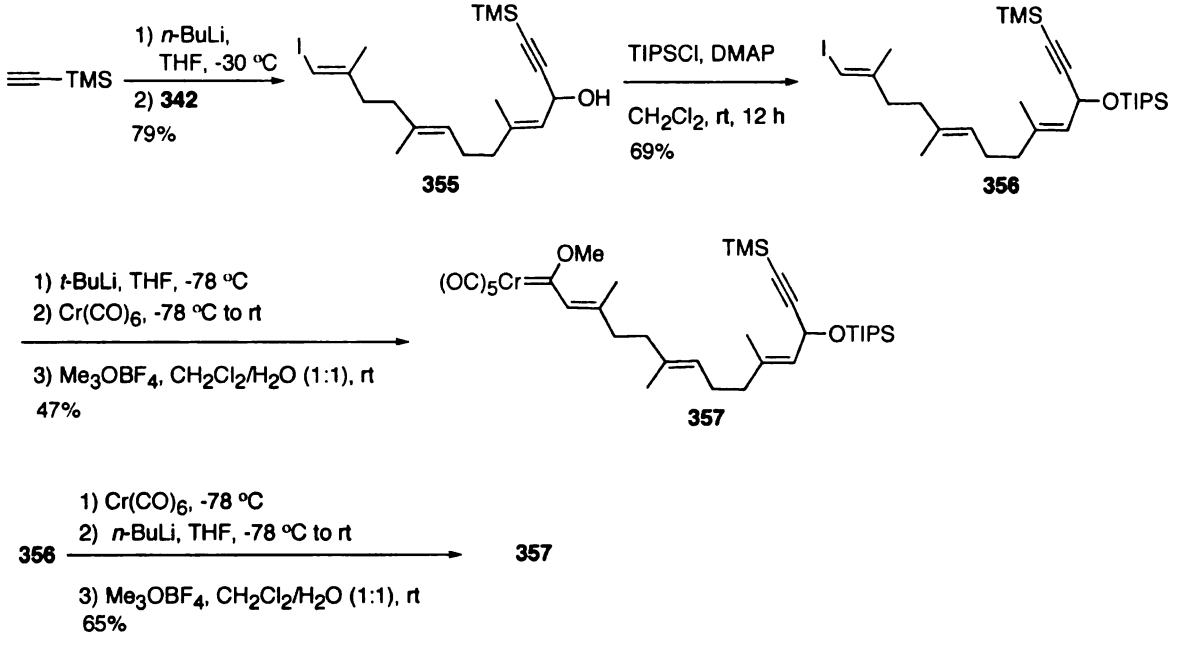
Entry	ArBr or ArH	Yield of **354**[a] (%)
1	1-bromo-4-methoxybenzene	Trace[b]
2	1-bromo-4-(trifluoromethyl)benzene	29
3	1-bromo-4-fluorobenzene	42
4	4-bromobenzonitrile	Trace
5	2-bromo-1,3-dimethylbenzene	Trace
6	1-bromonaphthalene	13
7	2-bromonaphthalene	0
8	2-bromothiophene	18
9	1-benzyl-1H-imidazole	0
10	1-methyl-1H-imidazole	0
11	Phenyllithium	49[c]

a). The yields listed are isolated yield. b) Less than 5% yield. c) The reaction was performed by Dr. Huang in a 49% yield.

With the lack of success in identifying an optimal organolithium, improvement in the preparation of the carbene complex **349** was sought by protection of the terminal acetylene (Scheme 5.10). Thus the vinyl iodine **355**

with a TMS-protected acetylene moiety was prepared from aldehyde **342** via alkynylation and TIPS protection. Conversion of **356** to carbene complex **357** could be achieved without the deprotonation and a 47% yield was obtained according to the aforementioned procedure. The overall yield could be improved to 65% by altering the order of addition. In this new procedure, the chromium carbonyl is mixed together with the vinyl iodine **356** and then the lithium reagent was added to effect metal/halogen exchange.

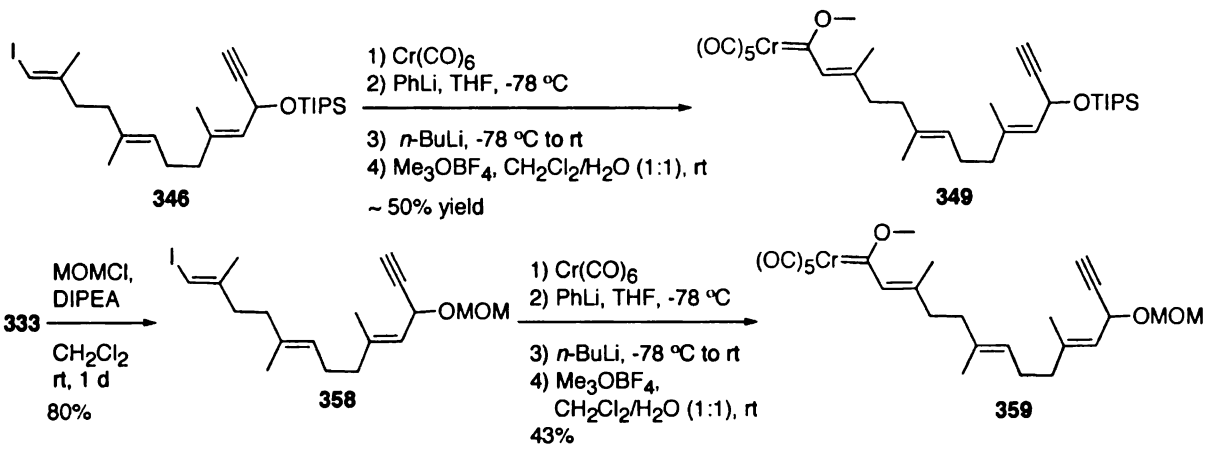
Scheme 5.10 Preparation of Carbene Complex with Protected Acetylene



Although it may be possible to convert carbene complex **357** to our desired carbene complex **349** by a simple deprotection, a perhaps even better solution would be if the new order of addition could improve the reliability of the original procedure. Delightfully, it was found that when this new procedure was applied to substrate **346**, a reproducible 50% yield was obtained even with scaled up reactions with different scales. A MOM-protected version of vinyl iodine

358 was also prepared from propargyl alcohol **333**. The corresponding carbene complex **359** could be obtained in 43% yield using the optimized procedure.

Scheme 5.11 Optimized Synthesis of Carbene Complexes

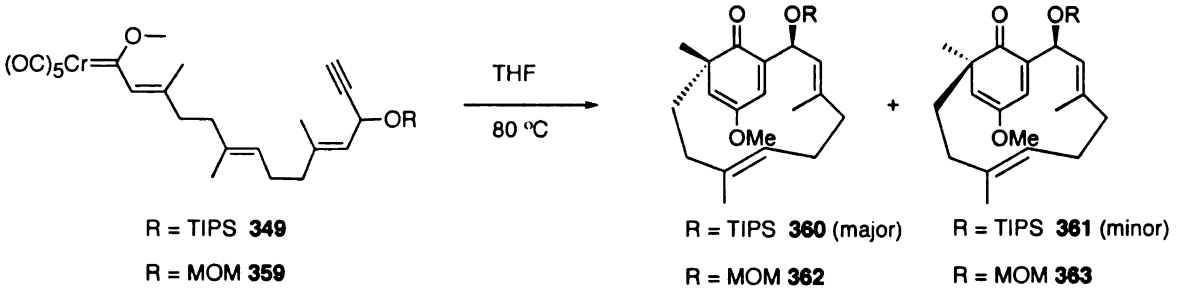


5.2.4 Thermolysis of carbene complexes 349 and 359

The thermolysis of carbene complex **349** was performed in THF at 80 °C until the color of the carbene complex was pale (around 12 hours). As had been previously reported by Jie Huang and as indicated in Table 5.2, bicyclic product **360** was formed as the major isomer at a concentration of 0.005 M (Entry 1).[91] The yield and diastereoselectivity of the annulation dropped slightly when the concentration was increased to 0.02 M. The relative stereochemistry of the two diastereomers had been determined by Jie Huang by an X-ray diffraction of the more crystalline minor isomer **361**.[91] It's noteworthy that no dimer was formed under these conditions even at a concentration of 0.02 M. Thermolysis of MOM-carbene complex **359** at 0.005 M provided **362** and **363** in 29% yield, but the reaction did not show any observable diastereoselectivity, as isomers **362** and

363 were obtained in a 1:1 ratio. Evidence suggests that the diastereoselectivity of the cyclohexadienone annulation is controlled by stereoelectronic effects.[21d]

Table 5.2 Cyclization of Carbene Complex



R = TIPS **349**
R = MOM **359**

R = TIPS **360** (major)
R = MOM **362**

R = TIPS **361** (minor)
R = MOM **363**

Entry	Carbene complex	Concentration (M)	Overall yield (%)[a]	Diastereomeric ratio[b]
1	**349**	0.005	60	3:1
2	**349**	0.02	56	2:1
3	**359**	0.005	26	1:1

a). Isolated yield. b). Diastereomeric ratio was determined by crude ^{1}H NMR based on vinyl proton on C12. c). Configuration of **361** was determined by X-ray analysis.

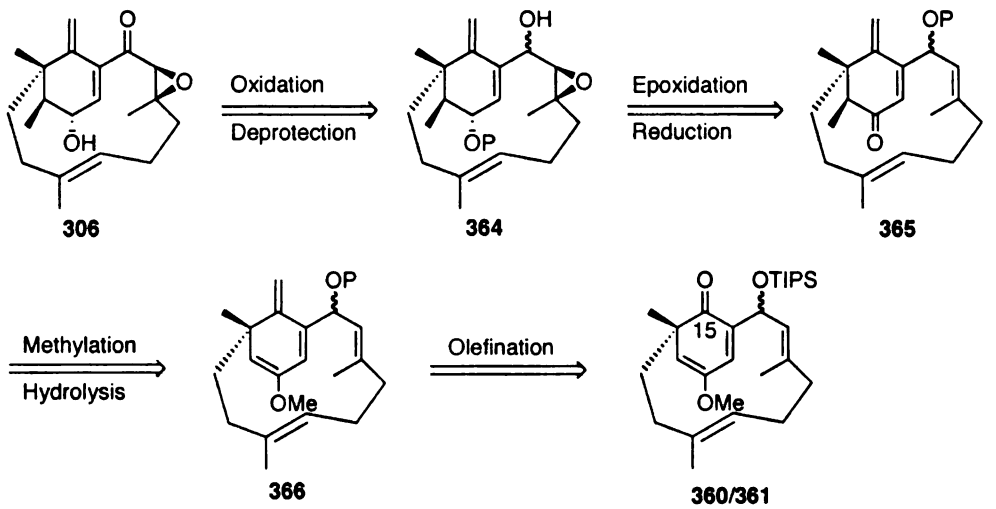
With the success of the intra-molecular cyclohexadienone annulation of complexes **349** and **359**, the syntheses of the Phomactins were taken forward with the TIPS-protected isomers **360** and **361** given the higher yields of the former rather than with the MOM-protected compounds **362** and **363**.

5.3 Total synthesis of Phomactin B2 from the minor isomer 361

With the bicyclic intermediates **360** and **361** in hand, a straightforward synthetic strategy toward Phomactin B2 was proposed (Scheme 5.12). Olefination of **360/361** should be able to install the exo double-bond at C15 to give compound **366**. After hydrolysis of the enol ether in **366**, it should be

possible to methylate at the α-position of the resulting dienone stereoselectively to give compound **365**, which has the complete carbon skeleton of Phomactin B2. A hydroxy-directed epoxidation followed by subsequent oxidation of the epoxy alcohol and deprotection would finish the total synthesis of Phomactin B2.

Scheme 5.12 Retrosynthesis of Phomactin B2 from 360 and 361



5.3.1 Synthesis of key intermediate 370

The synthesis of phomactin B2 was first carried out with the more crystalline minor isomer **361** (Scheme 5.13). The structure of **361** is drawn as the enantiomer that is shown in Table 5.2 to be consistent with the absolute configuration of the natural occurring Phomactin B2. The first step in the plan is an olefination of the highly congested carbonyl of **361**. Considering the steric challenge, the Peterson olefination[95] reaction was chosen instead of the Wittig olefination reaction to install the exo double-bond given its higher reactivity and known effectiveness for hindered ketones.[96] Compound **361** was allowed to react with trimethylsilylmethyllithium to give intermediate **367**. Although this reaction is

very fast, for unknown reasons, 3 equivalents of the lithium reagent were required. The use of less than 3 equivalents resulted in no reaction. Elimination could be accomplished by various potassium bases, including KH, KO*t*Bu and KHMDS.[91] In all cases, the elimination reactions provided enol ether **368** as the single product in the crude reaction mixture. This enol ether **368** was very sensitive to acid and thus was not isolated but rather converted to the more stable ketone **369** by hydrolysis with HCl. The transformation from **361** to **369** could be carried out in ~85% overall yield for either a one-pot process where KO*t*Bu is added directly to the reaction mixture in which **367** is generated, or in a process that involves the quenching of the reaction and treatment of crude **367** with KO*t*Bu.

The methylation at the α-position of ketone **369** was performed with LHMDS and MeI, since the methylation of model compound **371** demonstrated that LHMDS was more efficient than LDA in this reaction.[91] The methylation reaction gave a single diastereomer **370** in 98% yield. This newly installed methyl group was expected to be on the top face opposite to the macrocycle. This hypothesis was conformed by the X-ray diffraction of ketone **370** (Figure 5.2) which revealed the relative stereochemistry.

Scheme 5.13 Peterson Olefination and Methylation

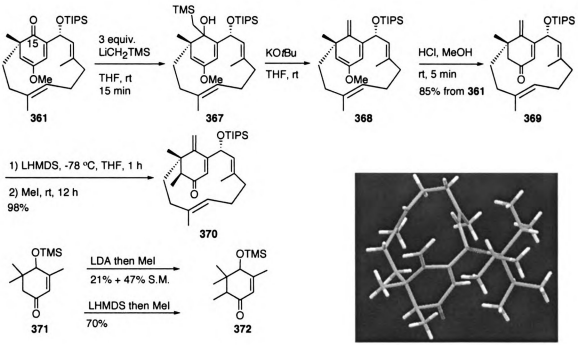


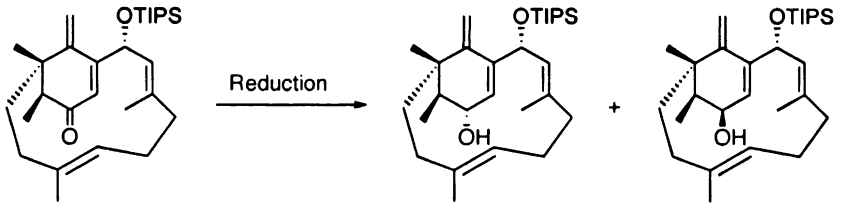
Figure 5.2 X-ray structure of **370**

5.3.2 Synthesis of allylic alcohol

Upon the successful installation of the methyl group, all of the carbon atoms present in Phomactin B2 have been introduced. The next plan was to synthesize the allylic alcohol **375a** as a precursor to the epoxide **376a** (Scheme 5.14). Before the desilylation of the TIPS-protecting group, it was necessary to reduce the ketone to obtain the desired α-alcohol **373a**. According to the X-ray structure of **370** (Figure 5.2), the methyl group at the α-position to the ketone **370** is axial-oriented. Accordingly, since the macrocycle obviously blocks the other face of the ketone, it's very difficult to predict the stereoselectivity of the reduction. A variety of reductants were examined, in an effort to optimize the

yield and selectivity of this reduction, and the results are summarized in Table 5.3. Due to the steric hindrance of this ketone, sterically small reduction reagents were first considered and examined (Entries 1 though 5). As can be seen from Table 5.3, $NaBH_4$ provided the best yield, while $LiBEt_3$ provided the best selectivity. The more sterically demanding KS-selectride and L-selectride did not react with ketone **370**. All of the reducing reagents provided the same major isomer **373b**. The structure of the major isomer as **373b** ultimately was determined upon the completion of the total synthesis of Phomactin B2.

Table 5.3 Reduction of Ketone 370



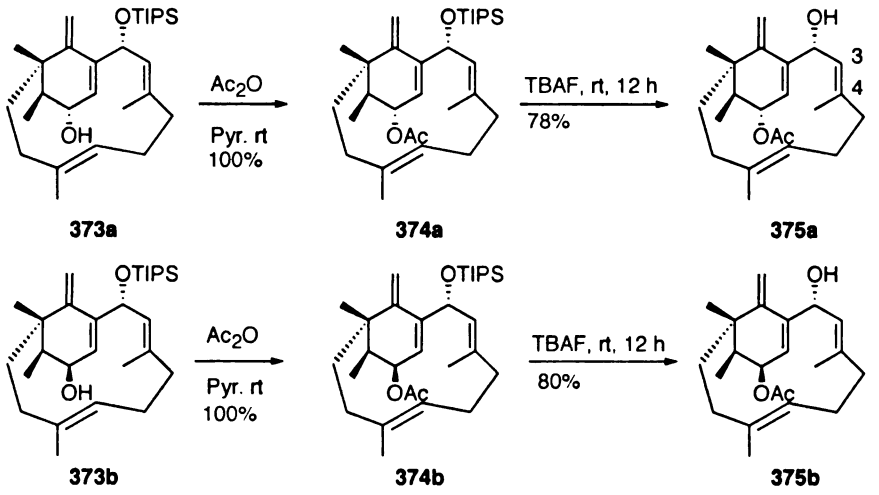
370 373a 373b

Entry	Reagent	Solvent	Temp. (°C)	Time	Yield (%)[a]	Ratio[b,c] **373a**: **373b**
1	$NaBH_4$	MeOH/Et_2O	rt	2 d	94	1: 3
2	$NaBH_4/CeCl_3$	MeOH	-20 to rt	1 d	44	1: 3
3	$LiBHEt_3$	THF	-78 to rt	1 d	37	1: 7
4	$LiBH_4$	THF	0 to rt	1 d	71	1: 6
5	$LiAlH_4$	THF	0	5 min	58	1: 4
6	Red-Al	THF	0 to rt	1 d	80	2: 3
7	KS-selectride	THF	0 to rt	15 h	0	-
8	L-selectride	THF	rt	2 d	0	-

a) Isolated yield. b) Determined by crude ^1H NMR. c) See text for the assignment (page X)

The diastereomers **373a** and **373b** could be separated by chromatography, but the relative stereochemistry of these two alcohols was not determined at this stage. Instead, both of them were carried on independently in the following functional group manipulations. Acetylation and desilylation of **373a** and **373b** gave allylic alcohol **375a** and **375b** in good yields. The choice of acetyl as a protecting group was to electronically aid in the differentiation of the two olefins of the *bis*-allylic alcohol. Such that epoxidation is chemoselectively directed to the more electron-rich allylic double bond (C3–C4) in the macrocycle.

Scheme 5.14 Synthesis of Allylic Alcohol



5.3.3 Epoxidation and end-game of the synthesis of Phomactin B2

According to the X-ray structures of **361** (Figure 5.3) and **370** (Figure 5.2), the two sides of C3–C4 olefin are sterically differentiated. The undesired *si*-face is sterically blocked by the bicyclic core of the molecule, and therefore is not available for epoxidation. Hence, the epoxidation of **375a** or **375b** would be expected to occur on the desired *re*-face if molecules **375a** and **375b** adopt the same conformation as **361** and **370**. This expectation proved correct (Scheme 5.15). The epoxidation of **375a** was both stereoselective and chemoselective with $VO(acac)_2$ and *t*BuOOH.[97] Only one stereoisomer was observed from the epoxidation. However, the exocyclic olefin was expoxidized to a small extent, giving the undesired, over epoxidized side-product **377a** (**376a/377a** 10:1). The other olefin (C1–C14) was completely intact. For reasons are not completely clear, this epoxidation has to be carried out using a fresh bottle of *t*BuOOH. Serious overepoxidation was observed with an old bottle giving nearly equal amounts of **376a** and **377a**.

Since **376a** and **377a** were inseparable, this epoxidation mixture was converted to epoxy ketones **378a** and **379a** by treatment with $NaHCO_3$ buffered Dess-Martin periodinane (DMP). The buffer was important to prevent the decomposition of the epoxide. Fortunately, the acetate derivative **378a** had been previously prepared from Phomactin B2 and its spectroscopic data has been published (Table 5.4).[80b] Therefore, the stereochemistry of **378a** was unambiguously assigned, which led to the assignment of stereochemistry for both the ketone reduction (Table 5.3) to **373a/373b** and the epoxidation of **375a**. Deacetylation of **378a** with NaOH afforded the desired natural product Phomactin B2 (**306**) in 94% yield. A comparison of the ^{13}C NMR data of synthetic phomactin B2 (**306**) and literature data for the natural product is summarized in Table 5.4 as well as those of natural and synthetic samples of acetate **378a**.[83b]

The epoxidation of the isomer **375b** gave a 6.5:1 mixture of mono-epoxy alcohol **376b** and *bis*-epoxy alcohol **377b**, which were subjected to Dess-Martin oxidation to give mono-epoxy ketone **378b** and *bis*-epoxy ketone **379b**. Based on NMR studies, the second epoxide of the *bis*-epoxy ketone **379b** was assigned to be at position C15–C21. The stereo outcome of the second epoxidation was proposed to be β-oriented, since the macrocycle blocks the α-face of the exo double-bond. Two possible reasons could account for the formation of the second epoxide: first, the exo double-bond was homoallylic to the hydroxy group; second, the inductive effect of the acetyl group might predominately fall on the allylic double bond in the 6-membered ring and reduce the electron density dramatically to prevent the occurrence of epoxidation at that position.

Deacetylation of **378b** by treatment with NaOH provided alcohol **380**, which was not identical to Phomactin B2. But a simple Mitsunobu inversion followed by a hydrolysis converted **380** to Phomactin B2.[98] This confirmed that, despite the different stereochemistry at C13, **375a** and **375b** were epoxidized to give epoxides with the same stereochemistry.

Scheme 5.15 Total Synthesis of Phomactin B2

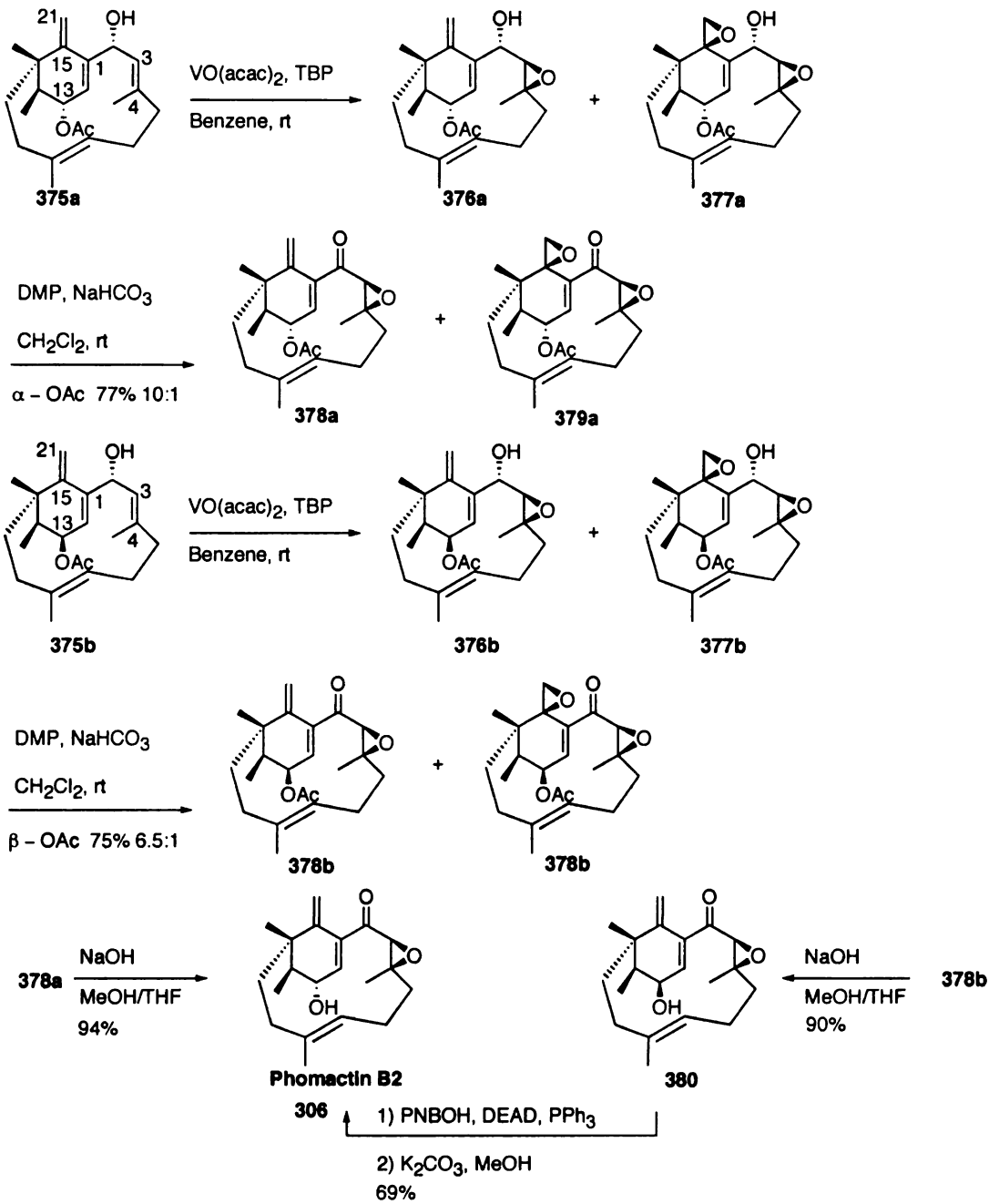


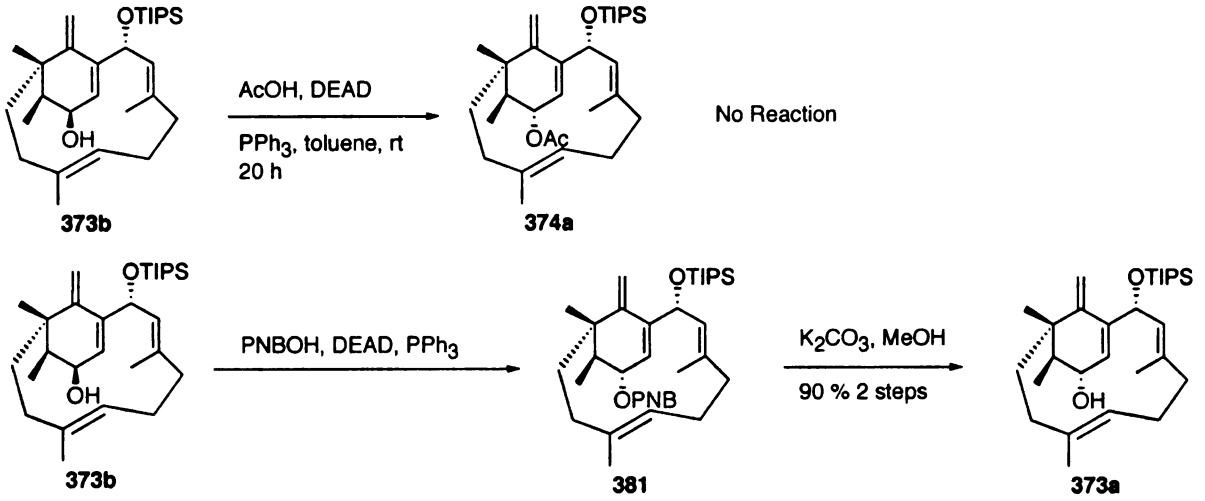
Table 5.4 ^{13}C NMR Chemical Shifts of Phomactin B2 and Compound 378a (CD_3OD)

Phomactin B2 (**306**)			Compound **378a**		
Natural (ppm)	Synthetic (ppm)	Difference (ppm)	Natural (ppm)	Synthetic (ppm)	Difference (ppm)
14.7	14.62	0.08	14.8	14.74	0.06
15.4	15.35	0.05	14.8	14.77	0.03
16.6	16.53	0.07	16.4	16.38	0.02
23.8	23.70	0.10	21.1	21.06	0.04
24.5	24.51	-0.01	22.7	22.63	0.07
34.7	34.66	0.04	24.7	24.69	0.01
35.3	35.34	-0.04	34.5	34.54	-0.04
38.4	38.34	0.06	35.1	35.06	0.04
42.4	42.45	-0.05	38.9	38.93	-0.03
45.9	45.90	0.00	42.7	42.93	-0.23
64.7	64.75	-0.05	44.5	44.56	-0.06
66.1	66.14	-0.04	64.9	64.93	-0.03
72.0	71.98	0.02	66.3	66.33	-0.03
117.0	117.04	-0.04	74.4	74.43	-0.03
123.7	123.66	0.04	119.0	118.99	0.01
134.3	134.28	0.02	123.4	123.39	0.01
137.9	137.93	-0.03	129.2	129.22	-0.02
142.4	142.42	-0.02	137.9	137.91	-0.01
146.6	146.62	-0.02	144.6	144.63	-0.03
201.8	201.82	-0.02	145.0	145.06	-0.06
			171.8	171.83	-0.03
			200.7	200.84	-0.14

Both of the epimeric alcohols **373a** and **373b** could be taken on to Phomactin B2 since the intermediates **375a** and **375b** both gave the same stereoselectivity in the epoxidation. Final convergent to Phomactin B2 occurs in

the last step, the Mitsunobu inversion in alcohol **380**. A more efficient utilization of the alcohols **373a** and **373b** would be a direct interconversion of **373b** to **373a**. The first attempt was directly convert **373b** to **374a** via a Mitsunobu reaction with acetic acid, which would not only effect the necessary inversion but also install the oxygen on the proper protected form for the epoxidation. However, this reaction met with failure. It was pleasing to find that alcohol **373b** could be converted to *p*-nitrobenzoate **381**, which gave α-alcohol **373a** in good yield after treatment with K_2CO_3. With this conversion, the synthesis of Phomactin B2 is now more convergent.

Scheme 5.16 Mitsunobu Reaction of Compound 373b



5.4 Total synthesis of Phomactin B2 from major isomer 360

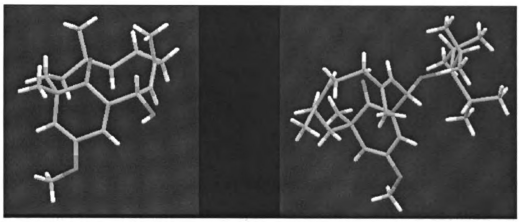
Upon finishing the total synthesis of Phomactin B2 from the minor isomer **361**, the next undertaking was to convert the major isomer **360** to Phomactin B2 utilizing a similar pathway.

5.4.1 Peterson olefination

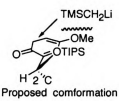
Right from the beginning there was doubt that a synthesis of Phomactin B2 could be achieved from the major isomer **360**. Jie Huang had shown that while the Peterson olefination was facile for the minor isomer **361**,[91] this reaction was completely shut down for the major isomer. Compound **361** reacted in 10 minutes at room temperature, but compound **360** failed to react with trimethylsilylmethyl lithium after 2 days at room temperature. At 40 °C, the reaction was rapid and gave a complex mixture. An alternative Peterson olefination reagent trimethylsilylmethyl magnesium chloride also failed to react with **360** (Scheme 5.17).

An explanation for the different reactivity between the major isomer **360** and the minor isomer **361** was proposed on the basis of the X-ray structure of **383** and **361** (Figure 5.3). As can be seen from Figure 5.3, the hydrogen of the carbinol carbon (C2) in **361** is *anti* to the carbonyl, which should allow $TMSCH_2Li$ to attack the carbonyl at the Burgi-Dunitz angle. However, the same hydrogen in **383** is *syn* to the carbonyl. Assuming that the conformation of **360** is similar to that of **383**, this would result in the situation that the *O*-substituent in **360** blocks the approaching of $TMSCH_2Li$. It was thus rationalized that if the protecting group on oxygen was capable of chelating to the organolithium, it may assist in delivering the nucleophile rather than sterically blocking it.

Figure 5.3 X-ray Structures of 383 and 361

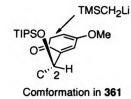


X-ray structure of **383**



Proposed comformation in **360**

X-ray structure of **361**

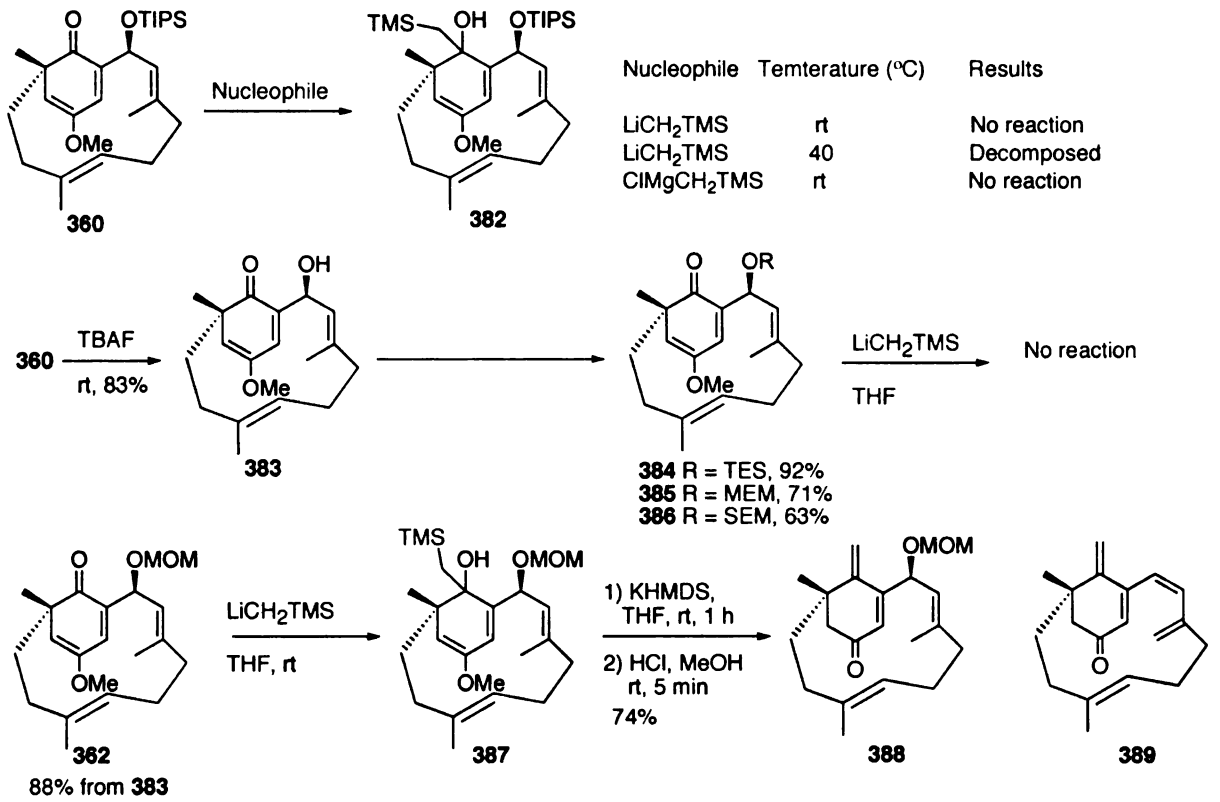


Comformation in **361**

Thus, a series of analogues of **360** were prepared from alcohol **383**, which was prepared from **360** by treatment with TBAF (Scheme 5.17). A variety of different protecting groups were investigated. As a test of the steric effects of the OTIPS group, compound **384** with the less hindered TES group was first subjected to the Peterson olefination condition, but as with the OTIPS group no reaction occurred. Compounds **362**, **385** and **386** with MOM-, MEM- and SEM-protecting group were next synthesized from alcohol **383**. It was found more convenient to prepare the MOM-compound **362** from alcohol **383** rather then directly from the thermolysis of carbene complex **359** due to the poor yield and diastereoselectivity (Table 5.2). Among these analogues, only the MOM-protected derivative **362** reacted with $TMSCH_2Li$. The reaction of **362** with $TMSCH_2Li$ was very fast and finished within 15 minutes. However, the elimination

step in **387** was sensitive to the nature of base. The MOM-protected hydroxy group was eliminated if KO*t*Bu was used as the base which resulted in a substantial amount of an unexpected polyene, which upon hydrolysis with HCl gave rise to compound **389**. The use of KO*t*Bu was further disfavored by the low conversion and low yield, even when freshly sublimed KO*t*Bu was used. At this point it was imperative to find another base for the elimination of silyl alcohol **387**. A search of the literature revealed a Peterson olefination reaction in which KHMDS gave better results than KO*t*Bu,[99] and proved to be the right choice. After acidic workup, ketone **388** could be obtained in 74% yield from **383**. The overall transformation of **362** to **388** was best performed in two steps since it gives better yield and less elimination product **389** than for the one-pot reaction. The Peterson olefination using unprotected alcohol **383** as substrate gave a complex mixture.[100]

Scheme 5.17 Peterson Olefination

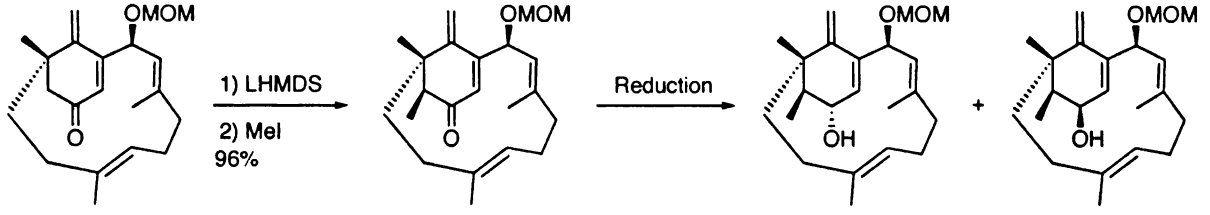


5.4.2 Synthesis of allylic alcohols

The methylation of **388** was accomplished by treating with LHMDS and MeI which gave **390** as a single stereoisomer in 96% yield. The orientation of the newly installed methyl group was assumed to be on the β-face, since this same stereochemistry was shown by X-ray to occur for the related structure **370** (Scheme 5.13). The reduction of **390** with $NaBH_4$ at room temperature was extremely slow, and the reaction was not complete after 2 days. However, the reduction was finished in 2 hours when the temperature was increased to 45 °C. Two inseparable over-reduction products were also observed by ^1H NMR in this reaction. The stronger reducing reagent LAH led to a complex mixture within 15 minutes. The reduction with super hydride provided the unreacted ketone **390**

and an unknown compound, and none desired alcohols **391a** or **391b** were detected by ^{1}H NMR. The diastereomeric alcohols **391a** and **391b** could be separated by chromatography, but each were isolatied with inseparable over-reduced products.

Table 5.5 Synthesis of Intermediate 391a and 391b



388 390 391a 391b

Entry	Reagent	Temperature (°C)	Time	Yield (%)	Ratio[a] **391a: 391b**
1	$NaBH_4$	rt	2 d	37[b]	1: 2
2	$LiAlH_4$	rt	15 min	-[c]	-
3	$LiBHEt_3$	rt	2 d	-[c]	-
4	$NaBH_4$	45	2 h	69[d]	1: 2

a) Determined by crude ^{1}H NMR. b) Isolated yield. c) Complex mixture. d) The products could not be isolated in pure form, which accompanied with the 1,6-over reduction product. See experimental for details.

Alcohols **391a** and **391b** were then separately acetylated to afford acetates **392a** and **392b** (Scheme 5.18). In preparation for the key epoxidation, the next step required was the removal of the MOM group to give alcohol **393a** and its C13-epimer **393b**. However, it was disappointing to find that, all attempts to cleave the MOM group were unsuccessful.[104] In most cases, compound **392b** decomposed very rapidly. Although occasionally it was possible to observe the

desired product (Entries 1, 6 and 7), the low yield of this reaction made this approach impractical.

Scheme 5.18 Acetylation of Compounds 391a and 391b

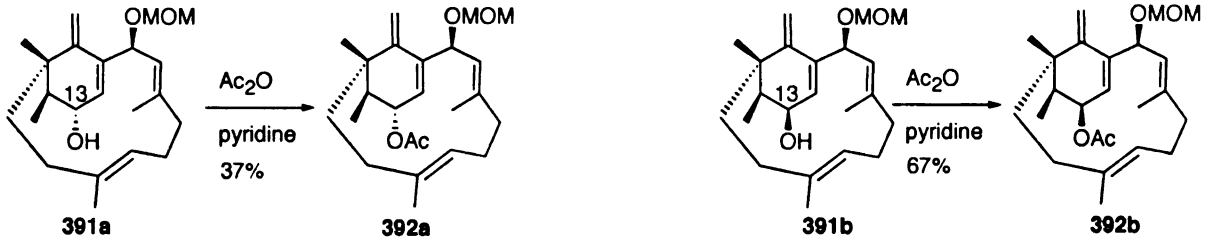
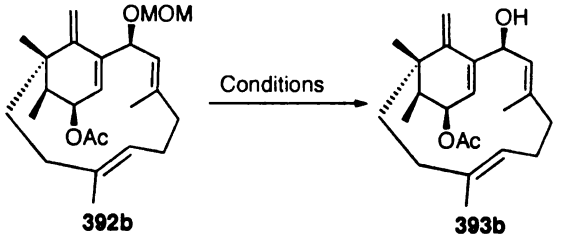


Table 5.6 Cleavage of MOM-protected Group in 392b



Entry	Reagent	Temp. (°C)	Time (h)	Results
1	1N HCl/EtOH (5 equiv.)	45	16	Complex mixture[a]
2	1N HCl/THF (5 equiv.)	45 to 75	2	Decomposition
3	$BF_3.OEt_2$, PhSH (2 equiv.)	-78 to -20	0.67	Decomposition
4	TMSBr (5 equiv.)	-30	0.25	Decomposition
5	TMSCl+Bu_4NBr (5 equiv.)	-30	0.67	No reaction
6	TMSCl+ Bu_4NBr (3 equiv.)	rt	24	~ 20% yield
7	Crotylbromoborane (1 equiv.)	-78	0.25	Complex mixture[a]
8	Crotylbromoborane (1 equiv.)	rt	0.33	Decomposition

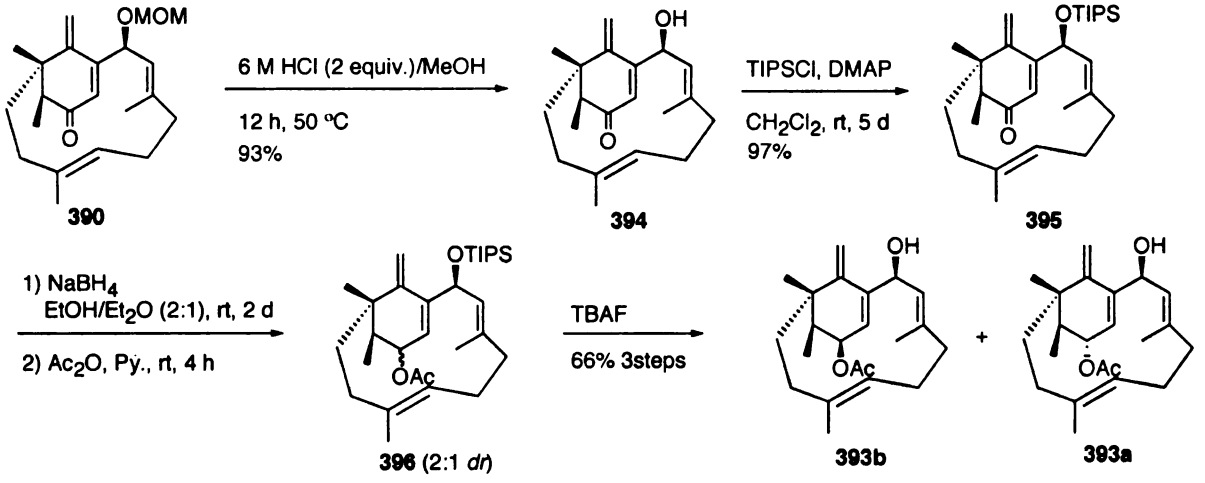
a) Alcohol **393b** could be detected by ^1H NMR as part of a mixture of products.

5.4.3 Synthesis of Phomactin B2 from 390

The failure of the removal of MOM group removal in **392a** and **392b** promoted the design of an alternative strategy. It was decided to deprotect the

MOM group at an earlier stage and then protect the resulting alcohol with another protecting group or to invert the stereocenter at C2. Based on the fact that only the MOM-protected compound **362** could undergo Peterson olefination, compound **390** represented an ideal intermediate for removal of the MOM group (Scheme 5.19). It was pleasing to find that the MOM group in compound **390** could be smoothly removed with 6 M HCl at 55 °C to give the alcohol **394** in 93% yield. Alcohol **394** was then protected as a TIPS ether to give compound **395**, which was then reduced with $NaBH_4$ to afford inseparable mixture alcohols with 2:1 diastereoselectivity. Acetylation followed by desilylation of these 2 alcohols afforded the isomeric and separable allylic alcohols **393b** and **393a** in a 2:1 ratio.

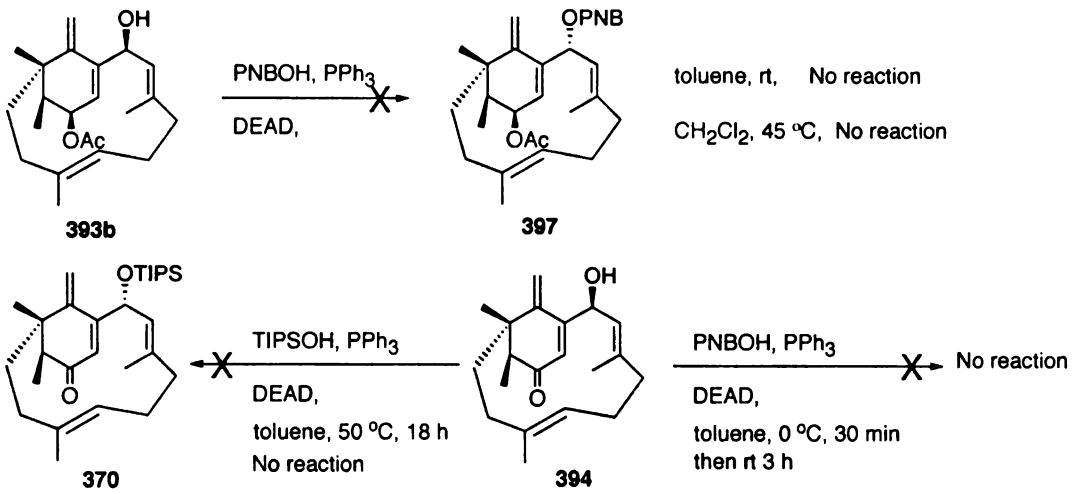
Scheme 5.19 Preparation of Allylic Alcohol 393b and 393a



At this stage, an attempt was made to invert the stereocenter at C2 in either the intermediate **394** or the intermediate **393b** such that the synthesis from the major isomer **360** was convergent with the synthesis from the minor isomer **361** via either the intermediate **370** (Scheme 5.13) or intermediate **373a** (Scheme 5.14). However, both attempts were unsuccessful. The Mitsunobu reaction of

393b using *p*-nitrobenzoic acid as the nucleophile did not proceed at all. The Mitsunobu reaction of **394** using *p*-nitrobenzoic acid or triisopropylsilanol as nucleophile also failed to proceed (Scheme 5.20).

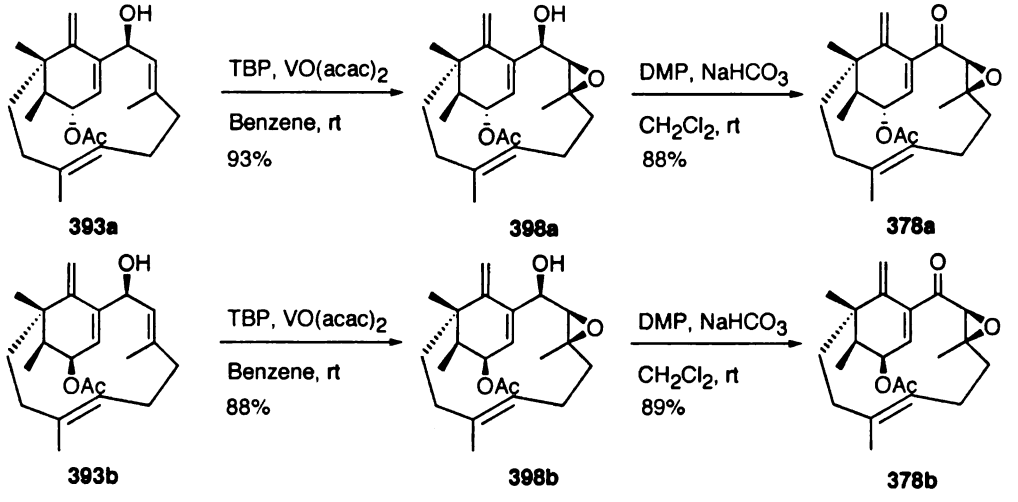
Scheme 5.20 Mitsunobu Reaction of 393b and 394



Since it was not possible to invert the C2 stereochemistry of either **394** or **393b** and converge the total synthesis, it was decided to push forward with the epoxidation of **393b** and **393a** (Scheme 5.21). The epoxidation of allylic alcohol **393a** produced a single mono-epoxy alcohol **398a** together with only a trace amount of a *bis*-epoxy alcohol. Oxidation of **398a** by Dess-Martin periodinate gave an epoxy ketone, whose NMR data matched the NMR data of the epoxy ketone **378a** synthesized from the minor cyclized product **361** (Scheme 5.15). When the same two chemical steps were applied to **393b**, it also produced a single epoxy ketone, which was identical to compound **378b** synthesized from the minor cyclized product **361**. These results suggests that the epoxidation of both **393a** and **393b** occur from the desired β-face. Therefore, the

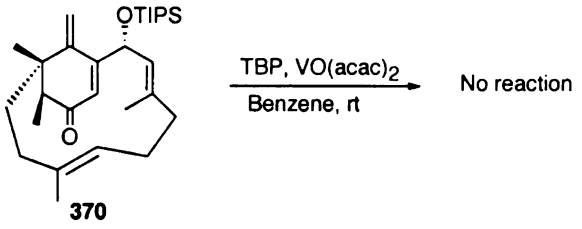
stereochemical outcome of the epoxidation is independent of the C2 stereochemistry. The structures of epoxy ketones generated from **393a** and **393b** were further confirmed by deacetylation to afford Phomactin B2 and its C-13 epimer **380**, as outlined in Scheme 5.15.

Scheme 5.21 Synthesis of Phomactin B2 from 393b and 393a



As discussed above, it was found that the epoxidation step provided the same stereochemical outcome regardless of the orientation of C2 hydroxy group, it was curious to see what the outcome of the epoxidation would be if the C2 hydroxy group was protected. Thus, compound **370** was subjected to the epoxidation conditions (Scheme 5.22). However, it was found that the epoxidation reaction did not occur with compound **370**. Clearly, the directing effect of the free hydroxyl is crucial in the epoxidation of **393a**, **393b** (Scheme 5.21) and **373a**, **373b** (Scheme 5.15).

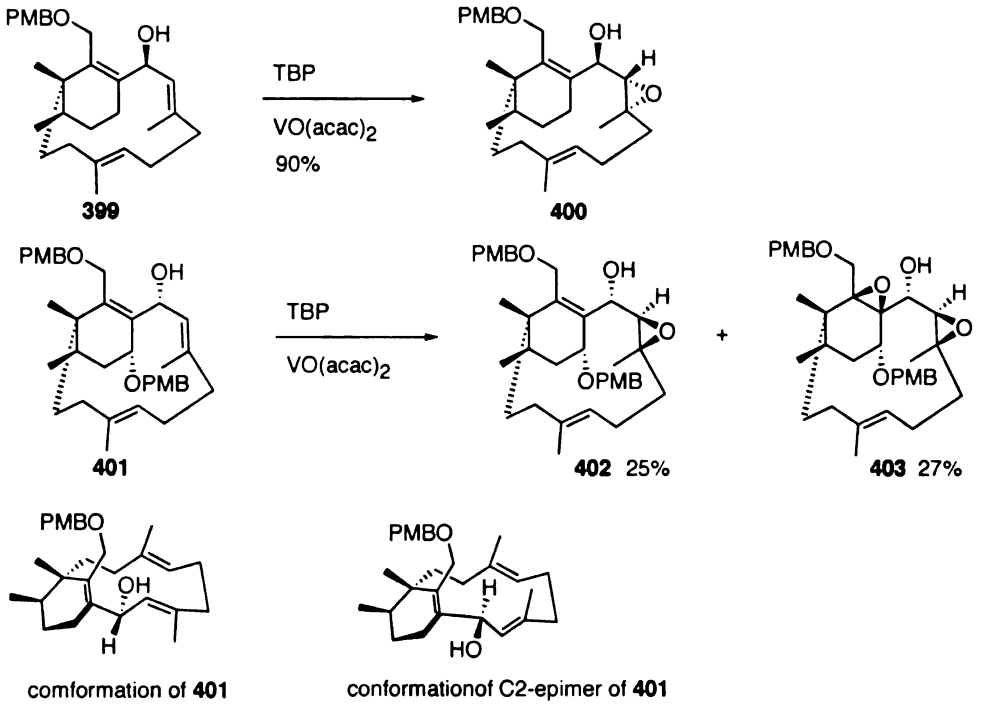
Scheme 5.22 Epoxidation of Compound 370



370

While the stereochemical outcome of the epoxidations described in this work are independent of the configuration at C-2, a very different observation was made by Pattenden in his total synthesis of Phomactin A. Pattenden and coworkers reported that the epoxidation of α-alcohol **401** gave the correct β-orientated epoxide **402** accompanied with *bis*-epoxide **403**.[83b] In contrast, the epoxidation of β-alcohol **399** under a similar reaction conditions produced an isomeric α-epoxide **400** in excellent yield. They determined the conformation of alcohol **401** and it's β-epimer at C-2 by molecular mechanics calculations (Scheme 5.23). The results reveal **401** was conformationally predisposed to form the correct β-epoxide. This was reversed in the C-2 epimer of **401** where the low energy conformation exposes the α-face of the trisubstituted double-bond of the allylic alcohol

Scheme 5.23 Epoxidation in Pattenden's Total Synthesis of Phomactin A



5.5 Attempts to invert the stereocenter at C2

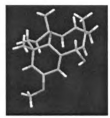
5.5.1 Conversion of stereocenter at C2 from β to α

As described in previous sections, the total synthesis of Phomactin B2 could be achieved from either of the diastereomers **360** and **361**, obtained from the cyclohexadienone annulation reaction. However, overall efficiency suffers from the need for the lengthy repetitive manipulation of these two isomers in separate and parallel processing. It would thus be very beneficial to convert **360** to **361** at an early stage, to reduce the total number of steps required for the total synthesis. The conversion from **361** to **360** was not considered at this stage, since the total synthesis of Phomactin B2 from the major isomer **360** requires additional four steps for the protecting group manipulations. However, a

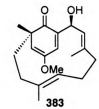
conversion from β-alcohol **404** into α-alcohol **383** will be described in Scheme 5.29 after discussing the conversion of **360** to **361**.

To effect conversion of **360** to **361**, an attempt was made to invert the configuration of the hydroxyl group in **383**, which was obtained from **360** via a single deprotection step (Scheme 5.17). When *p*-nitrobenzoic acid was used as the nucleophile in a Mitsunobu reaction on **383**, a mixture of at least two compounds were obtained that were inseparable. The use of benzoic acid also provided mixtures of products that were not characterized. The mixture of compounds obtained from the Mitsunobu reaction of **383** with nitrobenzoic acid was hydrolyzed with K_2CO_3 in methanol. However, neither of the resulting alcohols was identical with **404**, which was prepared independently from **361** in 98% yield. A trace amount of alcohol **383** with retention of configuration at C2 was detected from the crude reaction mixtures by ^1H NMR. The mixture of products obtained from the Mitsunobu reaction of **383** by mass spectrum were found to have the proper molecular weight for the desired benzoates of alcohol **404**. However, since hydrolysis of this mixture did not give **404**, it is possible an S_N2' reaction of **383** and a reaction with configuration retention occurred instead of an S_N2 reaction. However, this could not be confirmed since these compounds could not be obtained in pure form.

Scheme 5.24 Mitsunobu Reaction of β-Alcohol 383

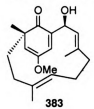


X- ray structure of **383**



383

PNBOH, DEAD, PPh_3
Toluene or THF
-78 °C → No reaction
-20 °C → Complex Mixture



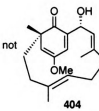
383

PhCOOH, DEAD, PPh_3
Toluene, 0 °C

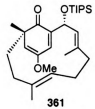
Mixture of compounds

K_2CO_3
MeOH

not

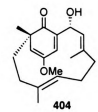


404



361

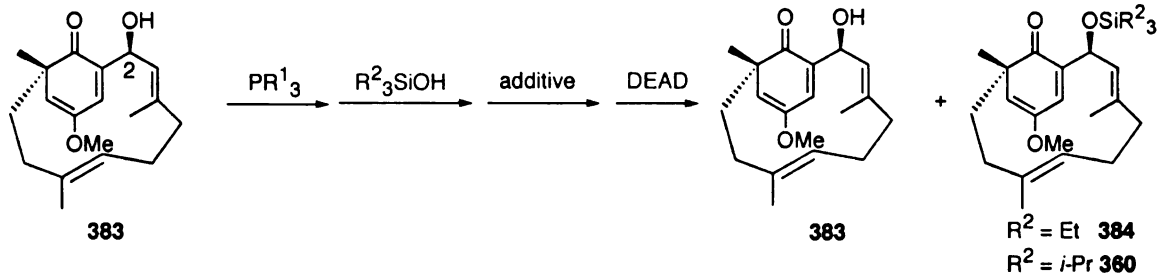
TBAF, THF
98%



404

The next oxygen nucleophile examined for the Mitsunobu reaction was the silanols (Table 5.7).[101] This reaction would allow for conversion of **383** directly to **361** in a single step. However, it was found that this reaction did not proceed with triethylsilanol in either the presence or absence of Et_3N (Entries 1 and 2). When imidazole was added as additive,[102] the reaction with triethylsilanol gave mixtures of the starting material **383** and a silyl ether (Entry 3). Surprisingly, the silyl ether has β-configuration at C2 instead of the inverted α-configuration, since the ^1H NMR of this silyl ether matches the NMR of compound **384** prepared from alcohol **383**. The reaction with a less hindered phosphine (Entry 4) did not give significantly different results. The Mitsunobu reaction with the more sterically demanding triisoproylsilanol did not give any silyl ether (Entries 5 and 6).

Table 5.7 Mitsunobu Reaction with Silanols



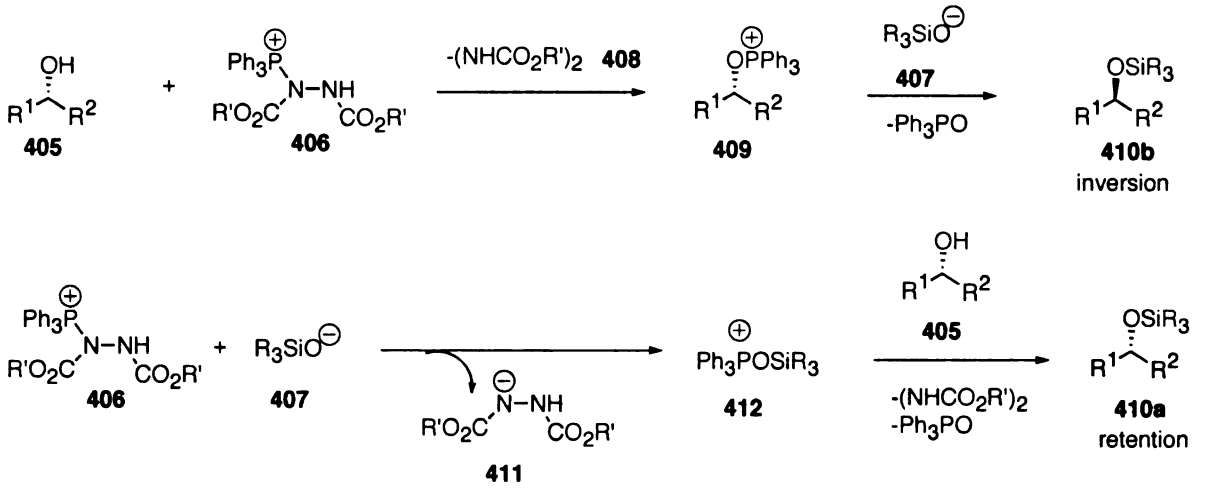
383 383 R^2 = Et **384** R^2 = *i*-Pr **360**

Entry	R^1	R^2	Solvent	Additive	Temperature (°C)	Time	Results[a]
1	Ph	Et	Toluene	None	0 to rt	40 min	**383** only
2	Ph	Et	Toluene	Et_3N	rt	18 h	**383** only
3	Ph	Et	THF	Imidazole	rt	50 min	2:1 **383/384**
4	*n*-Bu	Et	THF	Imidazole	rt 1 h then 50 °C	20 h	4:1 **383/384**
5	Ph	*i*-Pr	THF	Imidazole	rt	16 h	**383** only
6	Ph	*i*-Pr	THF	Imidazole	50 °C	7 h	Decomposed

a) The ratios were determined by crude ^{1}H NMR and the products were not isolated.

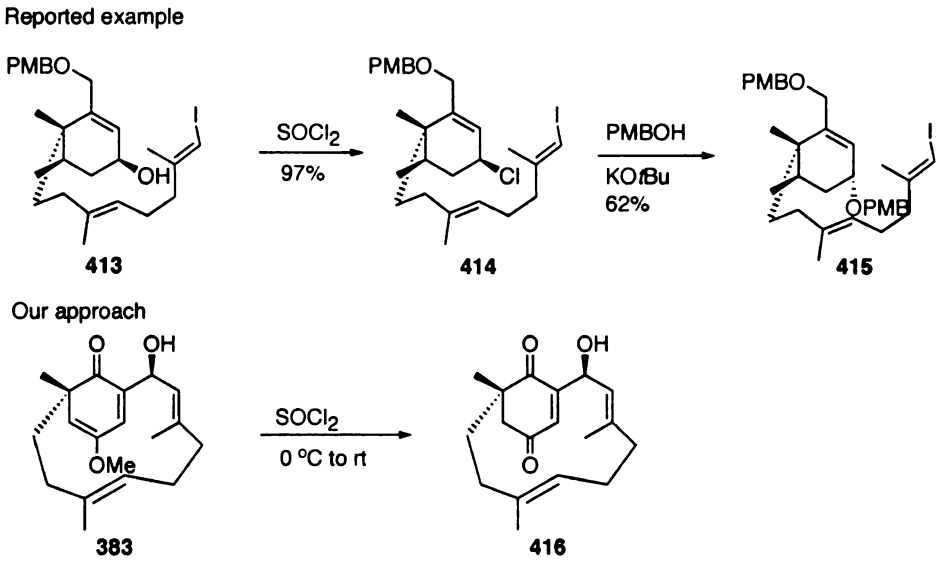
It's known in the literature that Mitsunobu reactions could sometimes give products with retention of configuration if the alcohol is sterically hindered (Scheme 5.25).[103] The most probable reason for this is that the steric hindrance of the alcohol prohibits the attack of the alcohol on the Ph_3P-DEAD complex **406**. In such cases, the deprotonated silyloxy anion **407** then displaces the hydrazide ion to give the acyloxyphosphonium ion **412**. Nucleophilic attack by the hydroxyl group of the substrate on the activated silyl group leads to the silyl ether **410a** with retention of configuration.[103] Given the situation that alcohol **383** is sterically encumbered, the failure in the Mitsunobu inversion can be understood.

Scheme 5.25 Mechanistic Pathways for the Mitsunobu Reaction



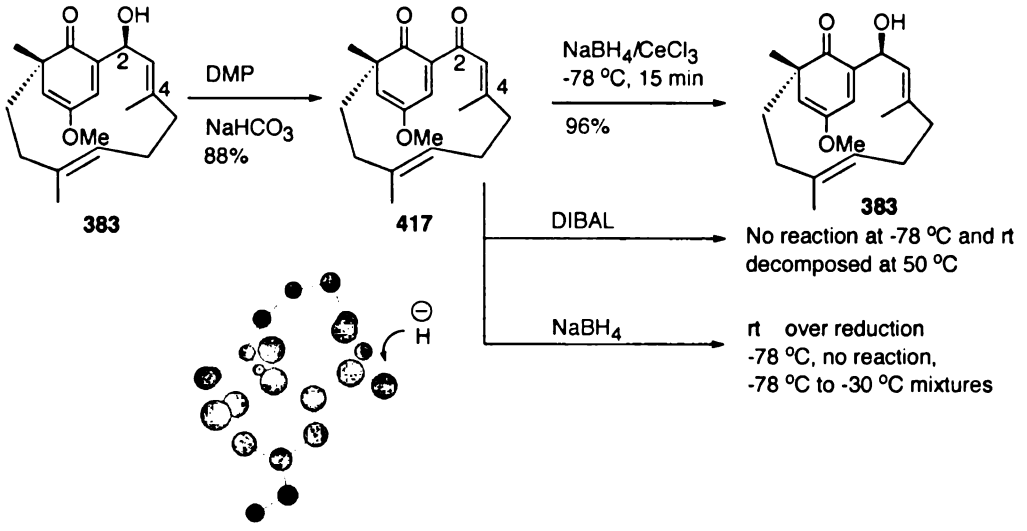
The next effort to invert the alcohol was an attempt to convert the hydroxy group in **383** into a better leaving group. Pattenden and coworker reported an alternative to the Mitsunobu reaction via an allylic chloride in their synthesis of Phomactin A (Scheme 5.26).[83a] An attempt was made to applied the similar transformation to substrate **383**. However, treatment of alcohol **383** with thionyl chloride only resulted in the hydrolyzed dione **416**.

Scheme 5.26 Mitsunobu Reaction via Allylic Chloride



Another pathway for the inversion of an alcohol is an oxidation/reduction sequence (Scheme 5.27). Treatment of alcohol **383** with DMP in the presence of $NaHCO_3$ provided dione **417** in 88% yield. The carbonyl at the C2 position should be less hindered than the carbonyl in the 6-membered ring, and therefore should be much easier to reduce. Reaction of **417** with $NaBH_4$ at room temperature for one minute gave a mixture of over reduced products. When the reduction was carried out at -78 °C, no reaction occurred, and increasing the temperature slowly afforded complex mixtures. An alternative reducing reagent DIBAL also suffered from failure. It did not react with **417** at room temperature and gave mixtures at a higher temperature. Fortunately, the reduction with $NaBH_4/CeCl_3$ at –78 °C for 15 minutes gave exclusively a single alcohol. However the result was not what was desired: the reduction gave back the β-alcohol **383**. According to a Chem-3D structure of dione **417**, the β-face of the ketone in the macrocycle is blocked by the methyl group on C4. Thus, the reducing reagent could only approach from the α-face to give the β-alcohol.

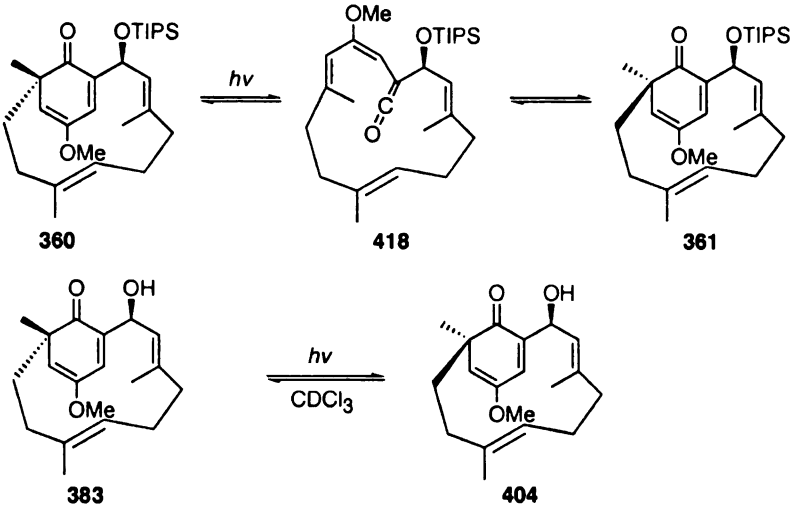
Scheme 5.27 Reduction of Dione 417



Chem 3D predicted comformation of **417**

A final attempt to convert **360** into **361** was by made photolysis. Since **360** and **361** are formed by electrocyclization of ketene **418**, photolysis of **360** might prompt the re-opening and closure of the cyclohexadienone and the generation of **361** (Scheme 5.28). Thus, compound **360** was dissolved in a deuterated solvent in the NMR tube and irradiated with UV light by a Rayonet reactor. When **360** was irradiated in $CDCl_3$ for 1 hour, 10% of **361** was detected. Longer irradiation resulted in the formation of an unknown product but the ratio of **361**:**360** did not substantially change. Photolysis in CD_3OD resulted in the very rapid decomposition of **360**. Photolysis of the unprotected alcohol **383** in $CDCl_3$ led to the decomposition of the starting material in a very short period. Therefore, while photo isomerization of **360** did occur, it was not sufficiently favorable for the formation of **361** to be synthetically useful.

Scheme 5.28 Photolysis of 360 and 383

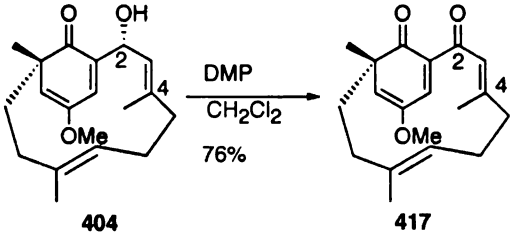


Solvent	Time	360/361/unknown
$CDCl_3$	1 h	1: 0.11
	2 h	1: 0.15: 0.10
	4 h	1: 0.17: 0.42
	16 h	decomposed
CD_3OD	3 h	decomposed

5.5.2 Conversion of stereocenter at C2 from α to β

Several different methods to invert the stereocenter of C2 in compound **383** failed including the Mitsunobu reaction, oxidation/reduction sequence and photolysis. However, as described in Scheme 5.27, the reduction of dione **417** with $NaBH_4/CeCl_3$ gave alcohol **383** as the only product. Thus, it is possible to invert the β-configuration in alcohol **404** into α-configuration via an oxidation/reduction sequence reaction. It was delightful to find that the oxidation of alcohol **404** with DMP smoothly gave dione **417**.

Scheme 5.29 Conversion of Alcohol 404 into Dione 417



With this conversion, the total synthesis of Phomactin B2 is more convergent. Attention next was turned to the asymmetric synthesis of Phomactin B2, which will be the subject of the next chapter.

5.6 Summary

In summary, a total synthesis of Phomactin B2 was accomplished via the intramolecular cyclohexadienone annulation of Fischer carbene complex as the key step. This annulation provided two diastereomers and both isomers could be converted to the natural product. This is the first application of the cyclohexadienone annulation reaction in natural product synthesis and the route developed here is more efficient than other published total synthesis of Phomactins.

CHAPTER 6

Intermolecular Cyclohexadienone Annulation Approach to the Formal Total Synthesis of Phomactin B2

The successful synthesis of Phomactin B2 using the intramolecular cyclohexadienone annulation as the key step encouraged the design of an alternative synthetic strategy that would potentially allow for an enantioselective synthesis. Obviously, the aforementioned intramolecular approach (Chapter 5) gave a pair of diastereomers in less than ideal selectivity (See Table 5.2) and is therefore not well qualified for such requirement. The new strategy would utilize the intermolecular cyclohexadienone annulation to construct the cyclohexane core, it was expected that if a single stereoisomer at the alkyne partner was used, the stereochemistry of this partner would be successfully transferred to the stereochemistry at the bridgehead carbon C11 (See Scheme 6.2 for details).

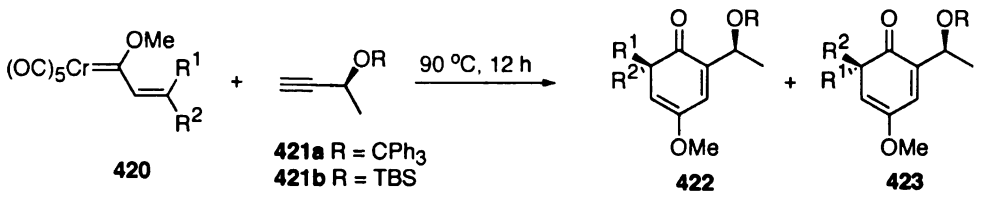
6.1 Background

6.1.1 Diastereoselective cyclohexadienone annulation

Hsung and co-workers reported the first example of 1,4-asymmetric induction in the cyclohexadienone annulation.[21d] As indicated in Table 6.1, this annulation reaction was both stereoselective and stereospecific with alkyne **421a** and **421b**. The annulation gave compound **422** as the major product, which contained the OR group *syn* to R^1. The selectivity dropped from around 90:10 to 82:18 when the substituent in the alkyne changed from trityl (Tr, CPh_3) group to

tert-butyl dimethyl silyl (TBS) group. This outcome was believed to be due to the electronic effect.[105]

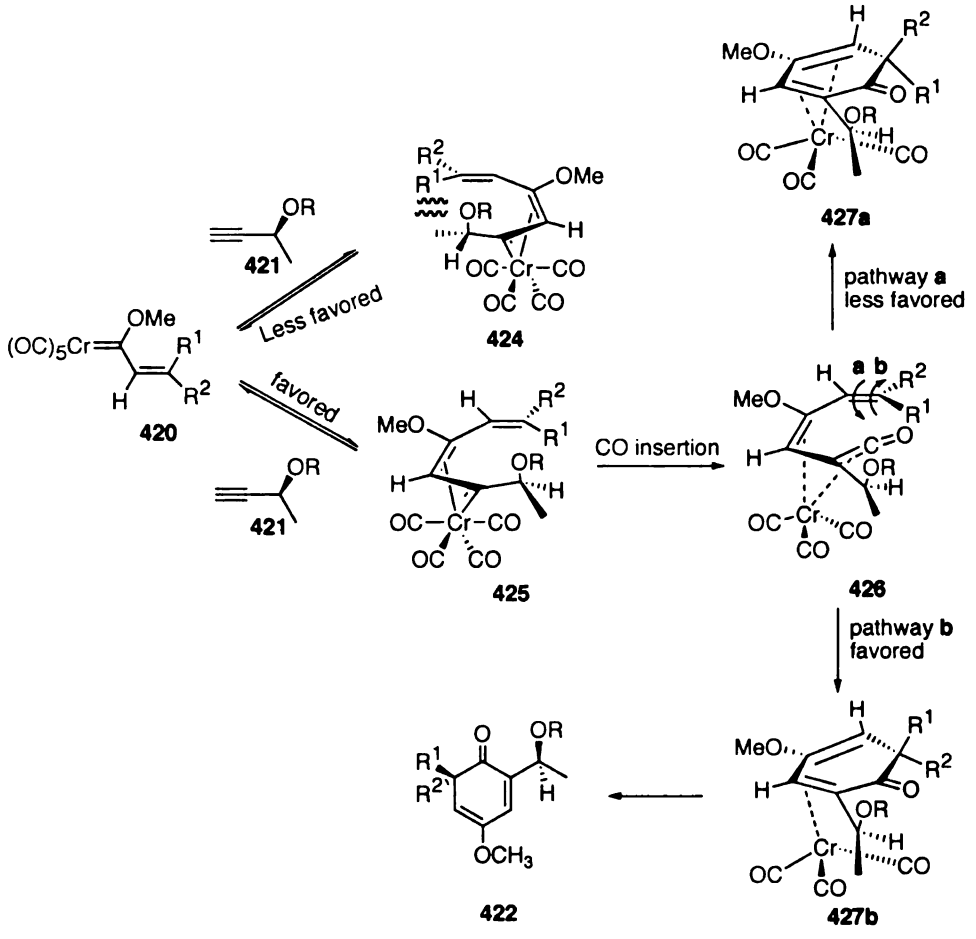
Table 6.1 Asymmetric Cyclohexandienone Annulation



Entry	R^1	R^2	R	Yield (%)	**422/423**
1	Me	Et	CPh_3	73	92:8
2	Et	Me	CPh_3	66	91:9
3	Me	Ph	CPh_3	72	90:10
4	Me	Ph	TBS	73	82:18

A mechanism was proposed to explain the diastereoselectivity.[21d] For electronic reasons, the oxygen substituent on the propargyl position is preferred to align on the *anti* position of the chromium, and the alkyne insertion intermediate **425** is more favored than **424** due to the induced steric repulsion.[105] The ketene **426** resulted from CO insertion has two possible directions for the electrocyclic ring closure. The favored direction of bond rotation is **b**, since R^1 can be rotated up and away from the chromium center in the vinyl ketene complex to give cyclohexadienone **422**. Downward rotation of R^1 substituent is disfavored due to the closer interaction of R^1 with the chromium.

Scheme 6.1 Possible Mechanism for the Diastereoselectivity

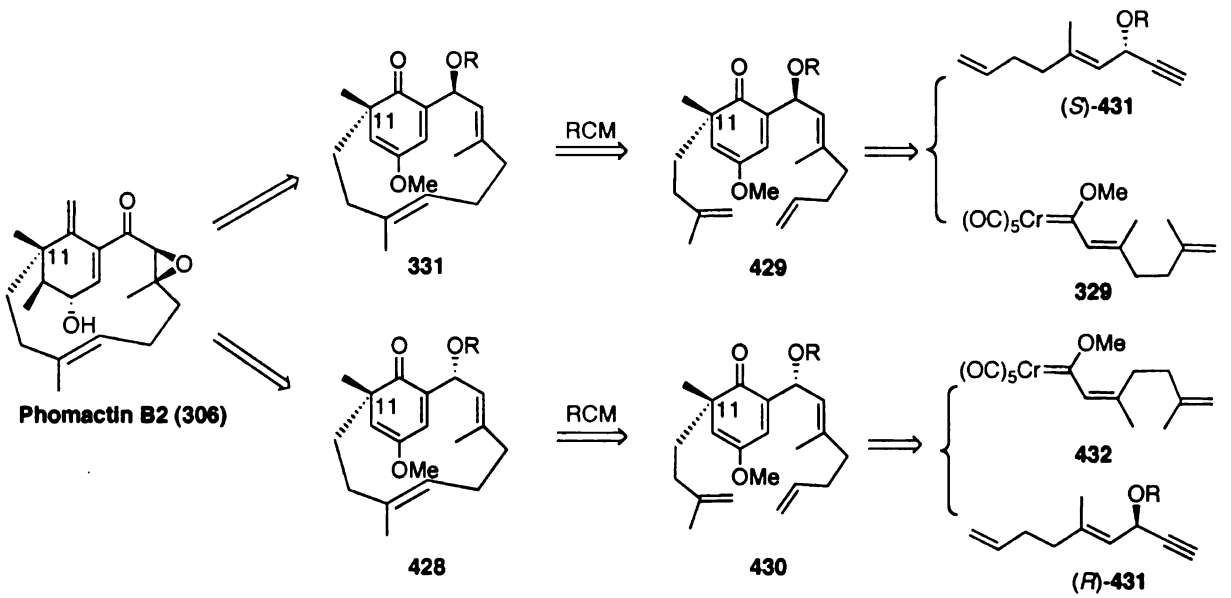


6.1.2 Retrosynthetic analysis of Phomactin B2 involving intermolecular cyclohexadienone annulation

This intermolecular cyclohexadienone annulation using a chiral alkyne was very promising to be used as a strategic step in the total synthesis of Phomactins. As mentioned before in Chapter 5, both cyclohexadienones **360** and **361** could be used to synthesize Phomactin B2. It was envisioned that the olefin moiety of the macrocycle could be potentially constructed via an RCM step, allowing the total synthesis of Phomactin B2 to begin with either **429** or **430**.[88] These two compounds could be directly obtained via the intermolecular

cyclohexadienone annulation of alkyne **431** with either carbene complex **329** or carbene complex **432**, although some uncertainties along our route was expected, such as the diastereoselectivity of the annulation in this elaborated system, and the olefin geometry in the RCM reaction.

Scheme 6.2 Retrosynthesis of Phomactin B2



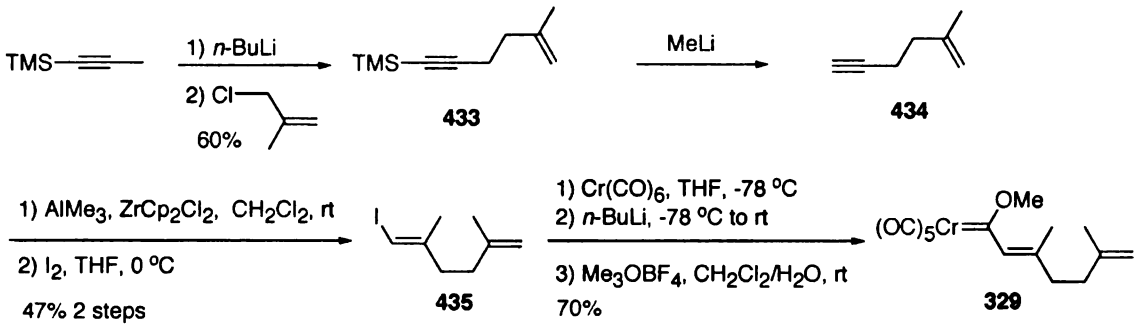
6.2 Intermolecular cyclohexadienone annulation

6.2.1 Preparation of carbene complex 329 and alkyne 431

The initial effort targeted on the preparation of carbene complex **329**, since previous work in the group showed that the *E*-carbene complex gave better results than the *Z*-carbene complex in the cyclohexadienone annulation reaction.[91] Thus, following Ms. Ying Liu's procedure (Scheme 6.3),[87] TMS propyne was deprotonated with *n*-BuLi, and the resulting anion was allowed to

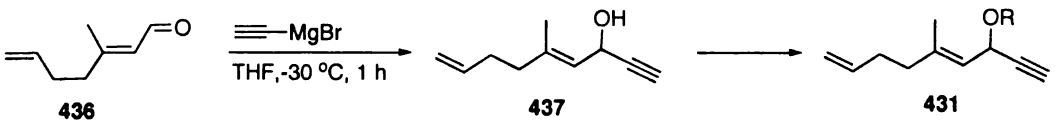
react with methallyl chloride to give TMS-protected enyne **433** in 60% yield. Desilylation followed by Negishi carbometallation gave vinyl iodine **435** in 47% yield. Carbene complex **329** was then prepared in 70% yield by the modified procedure described in Chapter 5, in which chromium carbonyl was added to the vinyl iodine **435** before the lithium/halogen exchange.

Scheme 6.3 Synthesis of Carbene Complex 329



The synthesis of alkyne **431** was more straightforward (Table 6.2). Aldehyde **436** was prepared from geraniol acetate according to the literature.[83b] Treatment of **436** with ethynyl magnesium bromide afforded propargyl alcohol **437**. A series of propargyl ether **431** were synthesized in order to study the diastereoselectivity of the intermolecular cyclohexadienone annulation.

Table 6.2 Preparation of Alkyne 431



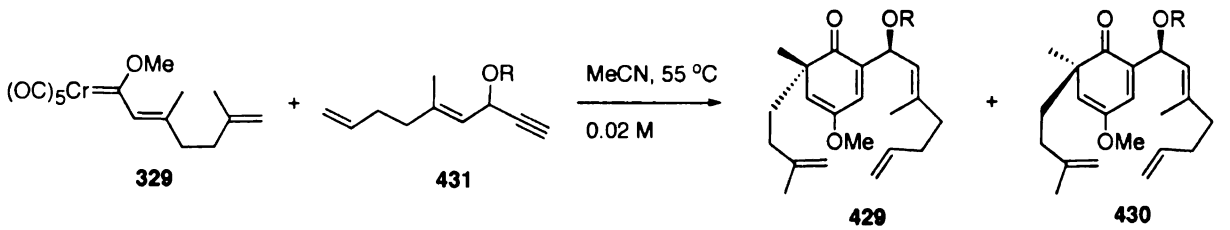
436 437 431

Series	Product	R	Reagent	Yield (%)
a	**330**	Tr	TrCl, DBU	98
b	**431b**	TIPS	TIPSCl, DMAP	84
c	**431c**	$SiPh_3$	$SiPh_3Cl$, DMAP	94
d	**431d**	TES	TESOTf, Et_3N	73
e	**431e**	MOM	MOMCl, DIEPA	86

6.2.2 Annulation of carbene complex 329 and alkyne 431

Having the required precursors **329** and **431** in hand, the cyclohexadienone annulation was performed at 55 °C in CH_3CN at a concentration of 0.02 M. As shown in Table 6.3, trityl and TIPS protected compounds (Series **a** and **b**) provided the best diastereoselectivity (98:2). However, other protecting group proved far less satisfactory. Triphenyl silyl and triethyl silyl-protected propargyl alcohols gave a 2:1 diastereomeric ratio, and MOM-protected one gave a 3:1 ratio. Obviously, both electronics and sterics had to come to play in order to explain this dramatically different behavior, but the exact reason for such variation remains elusive. The structures of the major isomers in the annulations were assigned to **429** on the basis of the previous studies in the group.

Table 6.3 Cyclohexadienone Annulation of 329 with 431



329 431 429 430

Series	R	Yield (%)[a] **429** + **430**	Ratio[b] **429/430**
a	CPh_3	83	96:4
b	TIPS	78	98:2
c	$SiPh_3$	63	67:33
d	$SiEt_3$	64	67:33
e	MOM	63	75:25

a) Isolated yield. b) Determined by crude ^1H NMR.

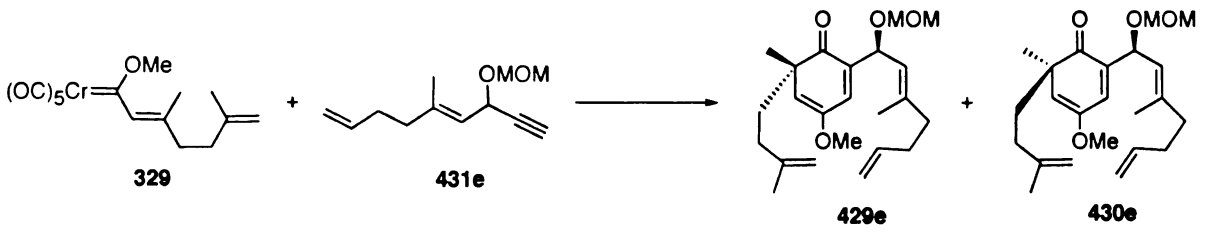
6.2.3 Optimization of annulation reaction between 329 and 431e

Although the Tr and TIPS protected **328** and **429b** could be prepared with excellent stereoselectivity, the precious experience mentioned in Chapter 5 somewhat discounted their value as the synthetic intermediate toward Phomactin B2. This is because after RCM, series of compound **429** would be converted to bicycle **331**, and only MOM-protected compound **362** could be further manipulated to Phomactin B2. Compound **360** already experienced a failure in the critical Peterson olefination step, and compound **327** was expected to give a failure in this Peterson olefination either. Therefore, an optimization of the reaction condition for the thermolysis with MOM-alkyne **431e** was attempted for an improved diastereoselectivity (Table 6.4).

It was disappointing to find that this optimization did not lead to a satisfactory point. The reaction carried out at a lower temperature (40 °C) suffered from poorer diastereoselectivity and a much slower reaction rate (Entry 2). Increasing the concentration to 0.1 M or decreasing the concentration to 0.005 M also resulted in poorer selectivity (Entries 3 and 4). Usage of other solvents in place of CH_3CN also proved no success. The annulation reaction performed in non-polar solvent benzene, polar solvent THF and coordinating solvent CH_3CN gave essentially the same results.

This failure led to the discard the use of the MOM group in the preparation of **429e**. Either Trityl or TIPS was used as the protecting group and hoped that the Peterson olefination problem could be avoided by running the Peterson olefination before the RCM step, or a protecting group swap after RCM could satisfy the need for MOM protecting group.

Table 6.4 Optimization of Annulation Reaction of 329 with 431e



329 431e 429e 430e

Entry	Solvent	Temp. (°C)	Conc. (M)	Time (h)	**429e + 430e** (%)[a]	**429e/430e**[b]
1	CH_3CN	55	0.02	12	63	3:1
2	CH_3CN	40	0.02	60	45	1.5:1
3	CH_3CN	55	0.005	12	41	1.4:1
4	CH_3CN	55	0.1	12	59	2:1
5	THF	55	0.02	12	42	3:1
6	Benzene	55	0.02	12	50	3:1

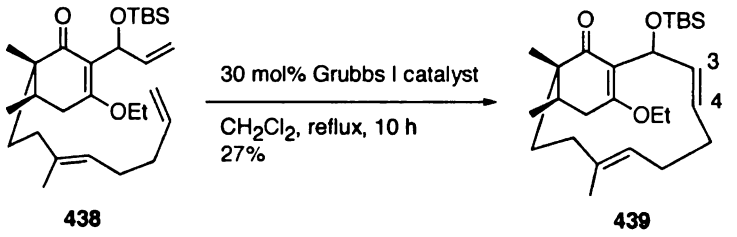
a) Isolated yield. b) Determined by crude ^1H NMR.

6.3 Ring-closing metathesis

6.3.1 Ring-closing metathesis of 328

Although RCM has been widely used in the syntheses of natural products.[88a] To the best of our knowledge, such reaction has not been successfully applied to the synthesis of phomactin families. The only published example was in Pattenden's total synthesis of Phomactin A, where RCM was used to construct the C3–C4 olefin in a low 27% yield.[83b]

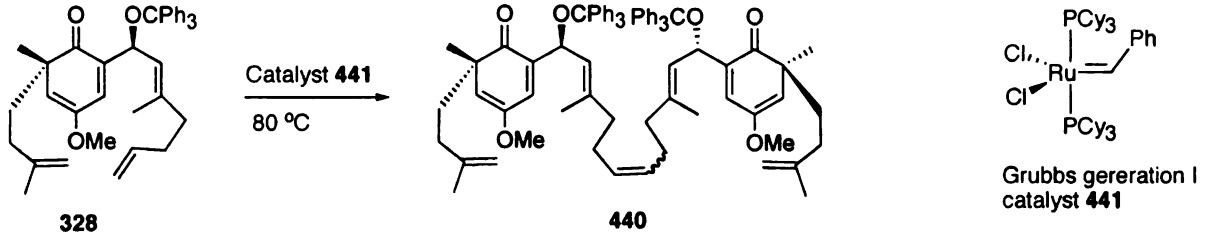
Scheme 6.4 RCM in Pattenden's Synthesis of Phomactin A



438 439

Another attempt of using RCM in the synthesis of Phomactins was performed by Ms. Ying Liu in the group. Her studies of RCM using Grubbs generation I catalyst **441** showed only dimer formation and no detectable desired macrocycle in different solvents and concentrations.[87]

Scheme 6.5 RCM of 328 with Grubbs Generation I Catalyst

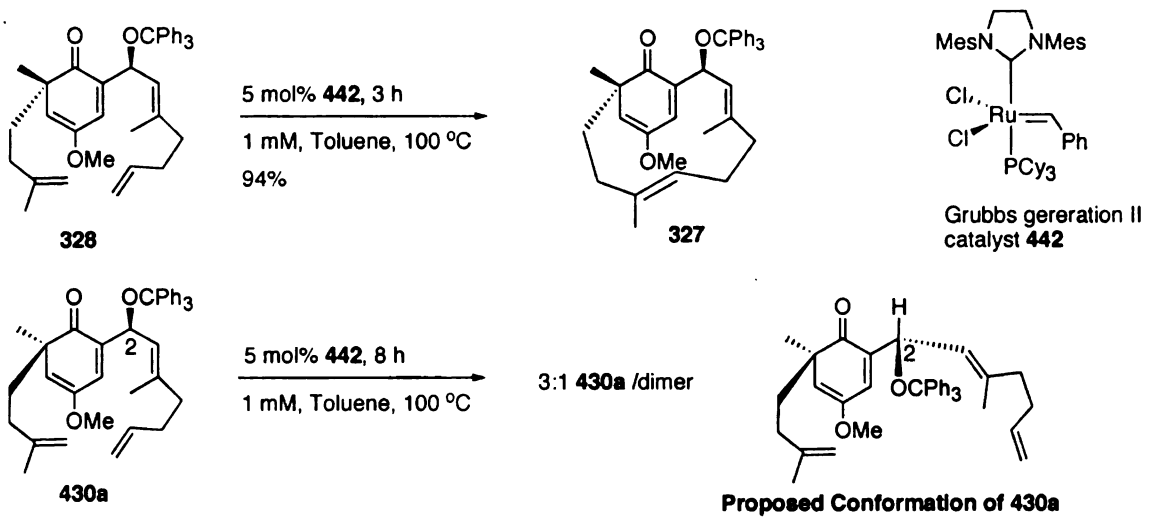


328 440

To date, more catalysts for ring-closing metathesis have been invented and become commercially available. The next catalyst being examined was Grubbs's generation II catalyst **442**. This reaction was initially performed by Barabanov and the desired cyclized product **327** was obtained in excellent yield and the resultant olefin has exclusively *E*-geometry.[134] In a parallel reaction, **328**'s diastereomer **430a** failed to give any cyclized product under the same reaction conditions. The difference in the reactivity between **328** and **430a** might due to their different conformations. It was envisioned that in order to minimize

the strain induced by the C2 substituent, compound **430a** has to adopt a conformation, where the two olefin unites were simply too far away to react.

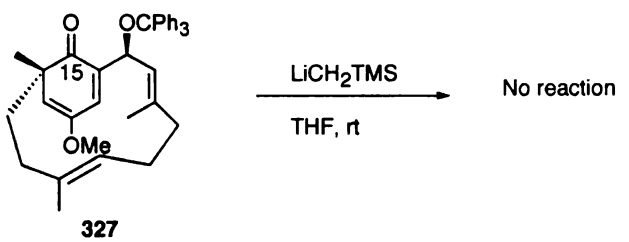
Scheme 6.6 RCM of 328 and 430a with Grubbs II Generation Catalyst



6.3.2 Cleavage of the trityl group in 327

With compound **327** in hand, the next plan was to install the exo double-bond at C15. Unfortunately, the Peterson olefination reaction did not work with compound **327** due to the reason proposed in Chapter 5 for compound **360** (Figure 5.3).

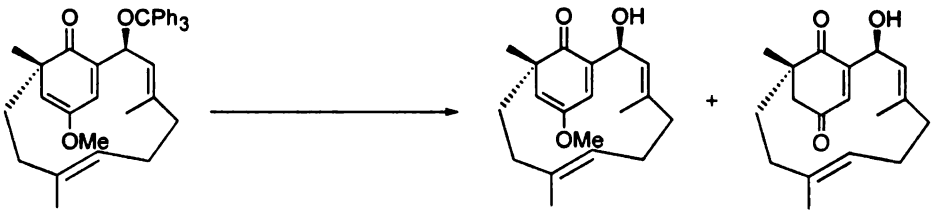
Scheme 6.7 Peterson Olefination of Compound 327



Therefore, the trityl group in **327** needs to be cleaved before running the Peterson olefination. However, with the presence of the enol ether functional

group in **327**, the trityl group cleavage was challenging. As indicated in the Table 6.5, cleavage of the trityl group selectively while keeping the enol ether intact reached complete failure under a variety of conditions. Using TFA with Et_3SiH[106] (Entry 1) provided compound **416** with both enol ether hydrolysis and trityl group cleavage. The reaction with Lewis acids $ZnBr_2$[107] and BCl_3[108] (Entries 2 and 4) did not give compound **383** nor **416**. Other methods using I_2[109], CAN on silicagel[110] and CBr_4[111] (Entries 5, 6, 7) also failed to react with compound **327**. Even a mild acid PPTS (Entry 3) failed to react with **327**. Thus, the synthesis needs to reroute either by using different protecting groups or different order of reactions.

Table 6.5 Cleavage of Trityl Group in Compound 327



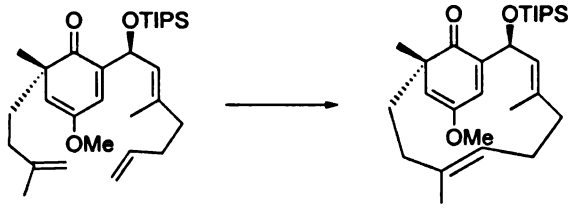
Entry	Reagent	Solvent	Temp. (°C)	Time	Results[a]
1	1% TFA/5% Et_3SiH	CH_2Cl_2	rt	2 h	**416** only
2	$ZnBr_2$	MeOH	0	20 min	**327** only
3	PPTS	MeOH	rt	10 h	**327** only
4	BCl_3	CH_2Cl_2	-30	30 min	**327** only
5	I_2	MeOH	rt	1 h	**327** only
			55	5 h	Decomposition
6	CAN/SiO_2	CH_3CN	rt	1 h	**327** only
7	CBr_4	MeOH	rt	1 h	**327** only
			60	3.5 h	**416** only

a) Monitored by TLC and checked by crude ^1H NMR.

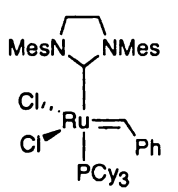
6.3.3 Ring-closing metathesis of 429b

The failure of removing trityl group in **327** prompted an investigation of the RCM of compound **429b**. The reaction was first carried out under similar conditions applied to compound **328**. But the reaction only gave 1:1 ratio of the starting material **429b** and dimer. After several attempts (Table 6.6), it was found that the desired product **360** could be obtained in 83% yield when the concentration of **429b** was reduced to 0.2 mM (Entry 3). However, this concentration was too dilute and impractical for the scaling up of the synthesis. The slow addition of substrate was also attempted by adding **429b** slowly to the solution of catalyst **442** in toluene using syringe pump (Entry 4) to reach the transient low concentration, but this led to a complete failure. Increasing the loading of the catalyst or changing to a more polar solvent did not provide better results (Entries 5-8). Hoveyda catalyst **443** was another generally used catalyst in the ring-closing metathesis reaction to form multi-substituted double-bond.[112] Thus, RCM with catalyst **443** was also performed (Entries 9-11), but again no satisfied results were obtained under these conditions.

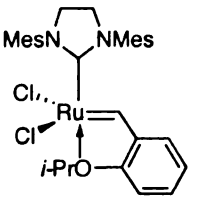
Table 6.6 RCM of 429b with Catalysts 442 and 443



429b **360**



Grubbs gereration II catalyst **442**



Hoveyda Catalyst **443**

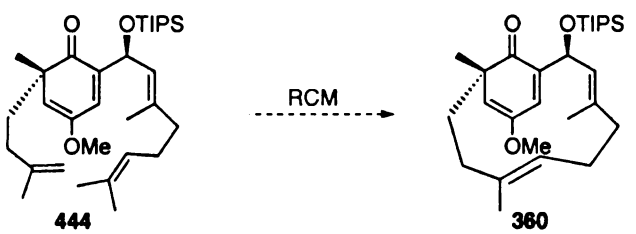
Entry	Catalyst	Conc. (mM)	Solv.	Temp. (°C)	Time (h)	Result[a] **360/429b/** dimer	Yield of **360** (%)
1	5 mol% **442**	2	Tol.	90	21	N[d]:1:1	-
2	5 mol% **442**	1	Tol.	100	3	3:N:1	39[b]
3	5 mol% **442**	0.2	Tol.	100	8	**360** only	83
4[c]	5 mol% **442**	2	Tol.	100	5.5	N:3:1	-
5	20 mol% **442**	1	Tol.	100	0.33	1:1:0.3	24
6	5 mol% **442**	1	CH_2Cl_2	40	48	1:2:N	29
7	5 mol% **442**	1	DCE	75	3	Mixture	-
8	5 mol% **442**	1	CH_2Cl_2	40	24	2:1:N	55
9	10 mol% **443**	1	CH_2Cl_2	rt	20	**429b**/trace dimer	-
10	10 mol% **443**	1	CH_2Cl_2	40	48	1:3:N.25	21
11	10 mol% **443**	1	Tol.	100	32	1:2:2	-

a) Determined by crude ^{1}H NMR. b) The product **360** was inseparable with **429b** and dimer, and the yield was obtained by calculation. c) Slow addition of **429b** over 3.5 hours. d) Not detectable by ^{1}H NMR.

6.3.4 Ring-closing metathesis of 444

Inspired by Nicolaous's results that a prenyl group could participate in RCM to form macrocycle,[113] compound **444** bearing a prenyl group on the right-side arm was synthesized for the RCM reaction (Scheme 6.8).

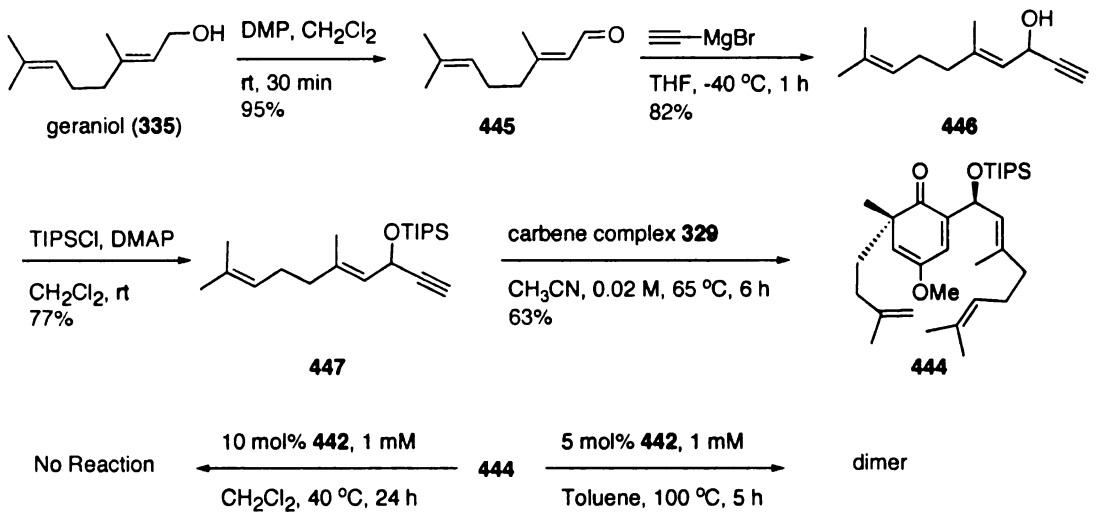
Scheme 6.8 RCM with Substrate 444



444 360

Compound **444** was prepared straightforward from the commercial available geraniol. Dess-martin periodinate oxidation of geraniol (**335**) gave rise to aldehyde **445** in 95% yield. Alkylation of **445** with ethynyl magnesium bromide provided propargyl alcohol **446**, which was then protected as TIPS ether (**447**). Annulation of alkyne **447** with carbene complex **329** in CH_3CN at the concentration of 0.02 M gave **444** as the only diastereomer in 63% yield. However, RCM of **444** with 5 mol% **442** at 100 °C or with 10 mol% **442** at 40 °C did not afford any desired macrocycle **360**.

Scheme 6.9 RCM of Compound 444

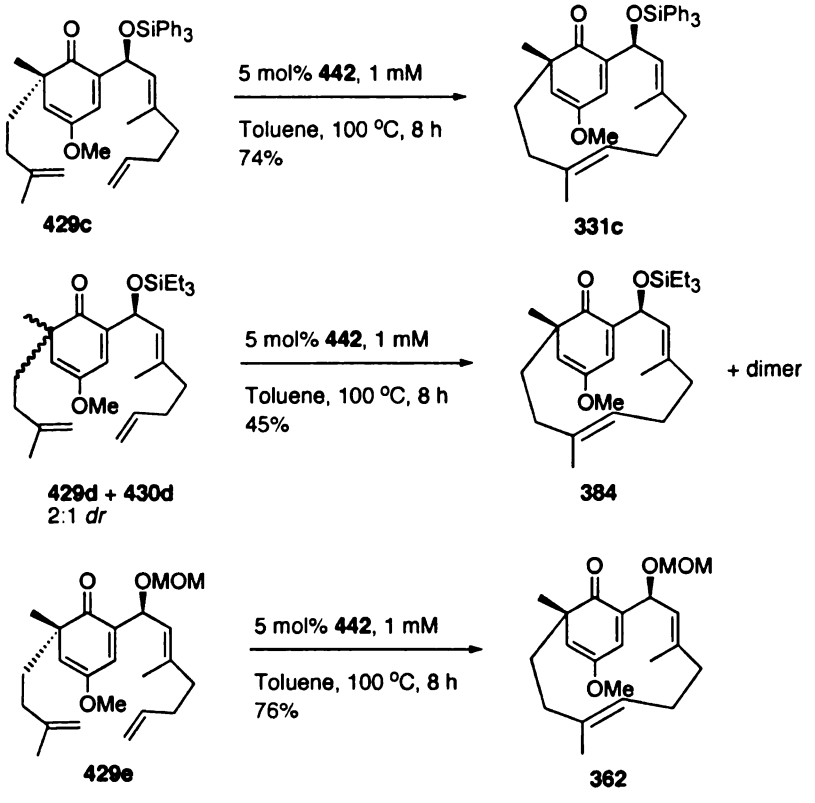


6.3.5 Ring-closing metathesis of 429c-e

The RCM reaction of Ph_3Si-substituted **429c**, TES-substituted **429d** and MOM-substituted **429e** were next examined for more information (Scheme 6.10). Hopefully, the ring-closing metathesis of these dienes could provide some information for the intricate cyclization of **429b**. Treatment of **429c** with 5 mol% of **442** in toluene at 100 °C provided the expected cyclized product **331c** in 74%

yield. TES-protected compound **429d** and **430d** were inseparable and were subjected to RCM reaction together under similar condition. It was not surprising to find that only cyclized product from **429d** was found and no corresponding cyclized product from **430d** was detected. RCM of MOM-substituted compound **429e** under similar condition provided **362** in 76% yield as the single product. Successful as they are, these results throw more questions as why specifically TIPS-substituted **429b** failed in the RCM reaction, while very similar Ph_3Si or TES-substituted analogues went on RCM successfully.

Scheme 6.10 RCM of 429c-e



6.3.6 Mini-conclusion

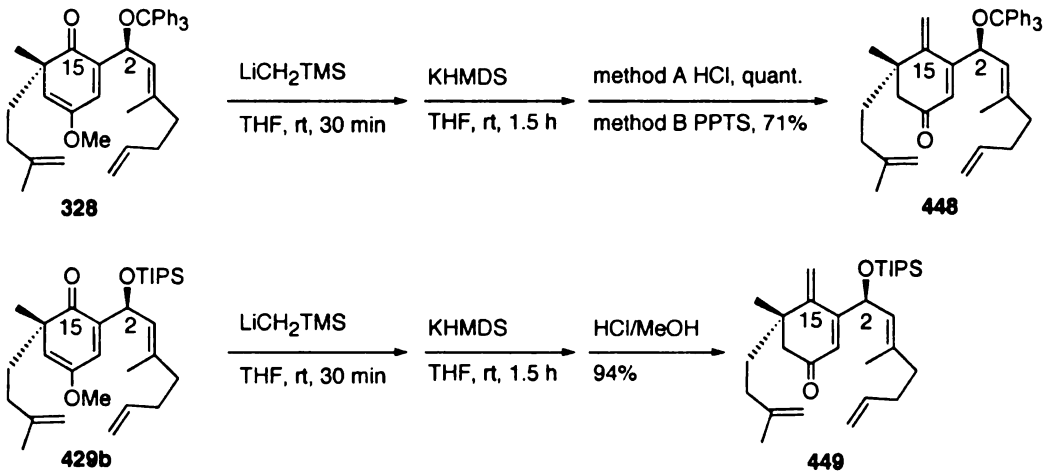
As to this point, the original proposed synthesis plan (Scheme 6.2) has to be considerably revised. The RCM reaction on epimer **430** was not successful

and the RCM on epimer **429** experienced incompatible protecting group with reactivity. The Tr-protected **328** was able to undergo RCM, but removal of Tr failed. The TIPS-protected **429b** suffered from an impractical RCM condition. Other protecting groups were compatible with RCM but came with low diastereoselectivity in the annulation. Therefore, there is no perfect strategic compound that could satisfy all the desirable criteria. For these reasons, the preparation of **430** and **429** from annulation between **432** and **431** was suspended due to the failed RCM, and an alternative pathway was considered involving running Peterson olefination prior to the RCM reaction.

6.4 Peterson olefination of 328 and 429b

The next strategy considered was installing the exo double-bond at C15 before RCM (Scheme 6.11). This revision of order of reactions has two purposes: first, it was hoped that RCM would be more smooth after this olefination, and second, as mentioned in Scheme 5.16, such Peterson olefination does not work with C2-(*S*) stereochemistry once the macrocycle is constructed. Therefore, switching these two steps was potentially the key to both of the problems above. Delightfully, compound **328** and **429b** could undergo Peterson olefination smoothly. The reaction took only 30 minutes at room temperature. The following elimination and hydrolysis afforded dienone **448** and **449** in excellent yields. It was reasoned that the success of this olefination is due to the absence of the macrocycle. The more free conformation the molecule could adopt that allowed for the nucleophile to approach.

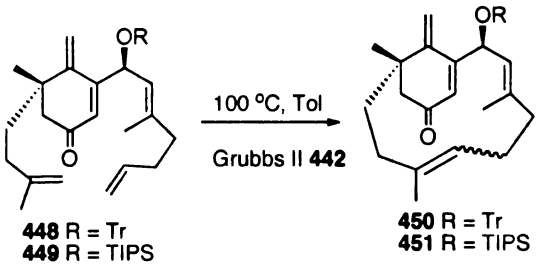
Scheme 6.11 Peterson Olefination of 328 and 429b



The next step was the methylation to install the methyl group or ring-closing metathesis to form the macrocycle ring. The RCM reaction was examined first, since the methylation of **448** and **449** might lead to a mixture of diastereomers without the constructed macrocycle.

The ring-closing metathesis of compound **448** was first carried out under the conditions described in Scheme 6.10. This reaction provided 2:1 ratio of the inseparable *E/Z* isomers of cyclized products **450**. The dimer was not observed since the terminal alkene protons were not detected in ^{1}H NMR. Ring-closing metathesis of TIPS protected substrate **449** under the same conditions resulted in a low conversion and 62% of the starting material **449** was recovered. Although higher loading of the catalyst and longer reaction time was able to push the reaction to complete with satisfied yield, the 1:0.8 of *E/Z* isomer was far from being satisfactory.

Table 6.7 RCM of Compound 448 and 449



448 R = Tr
449 R = TIPS

450 R = Tr
451 R = TIPS

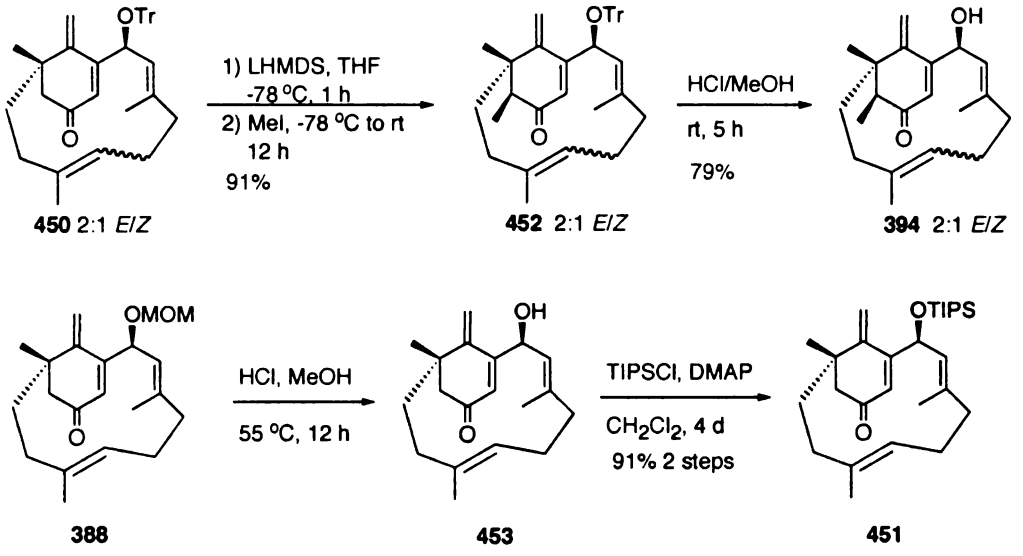
Reactant	mol% of cat.	Time (h)	% Yield	*E*/*Z*[a]
448	5	8	70	2:1
449	5	8	27[b]	3:1
449	10	24	82	1:0.8

a) The *E*/*Z* isomers were inseparable by chromatography and the ratio was determined by ^{1}HNMR. b) The starting material **449** was recovered in 62% yield.

Since both compounds **450** and **451** were obtained as inseparable *E*/*Z* isomers, the structures of the desired *E*-isomers were verified by converting the mixture to known compound. Thus, compound **450**, as a mixture of isomers, was subjected to methylation condition to give inseparable *E*/*Z* mixture **452**. The newly installed methyl groups in both isomers of **452** were incorporated exclusively from one face and were assumed to be β-oriented. Treatment of **452** with 6 M HCl at room temperature for 5 hours successfully cleaved the trityl group and gave 2:1 ratio of isomers **394**, which were still inseparable by chromatography. However, *E*-**394** has been prepared in Chapter 5, and the major stereoisomer in **450** was assigned to *E*-configuration by comparing the NMR spectra. To verify the structure of compound **451**, compound **388** obtained from Chapter 5 was carried on to standard protecting-group manipulation. Again,

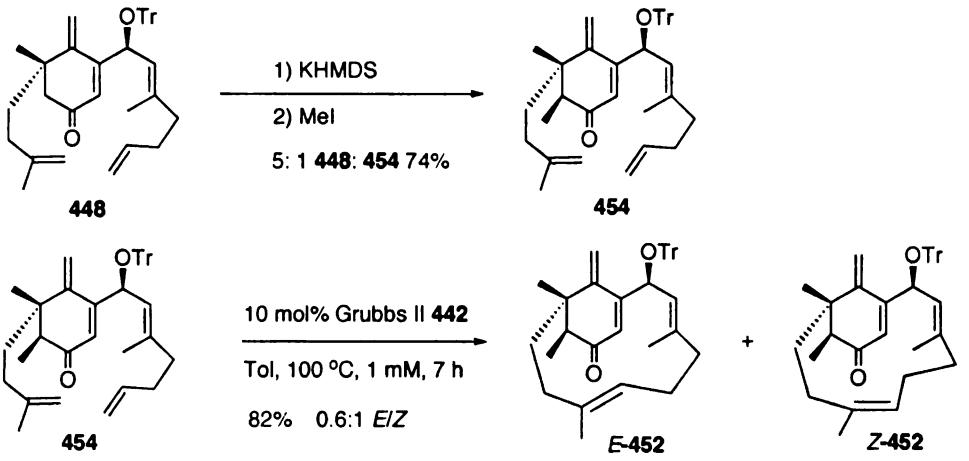
the major stereoisomer in **451** was also assigned to *E*-configuration by comparing the NMR spectra.

Scheme 6.12 Verification of Structure *E*-452 and *E*-451



Due to the low *E/Z* selectivity in the RCM reaction of **448** and **449**, an alternative pathway that installing the methyl group before ring-closing metathesis was next considered and performed (Scheme 6.13). The methylation reaction of **448** with LHDMS and MeI resulted in less than 40% conversion. Luckily, the methylation proceeded smoothly with KHDMS and MeI to afford **454** in 74% yield as a single stereoisomer. The newly incorporated methyl group was assumed to install from the less hindered β-face. However, the ring-closing metathesis of **454** came with even lower *E/Z* selectivity. This time, the undesired *Z*-isomer was obtained as the major isomer. As these isomers were again inseparable, and all of the attempts have reached less than ideal results, the synthesis of Phomactin B2 via this intermolecular annulation route was halted and give way to the asymmetric synthesis.

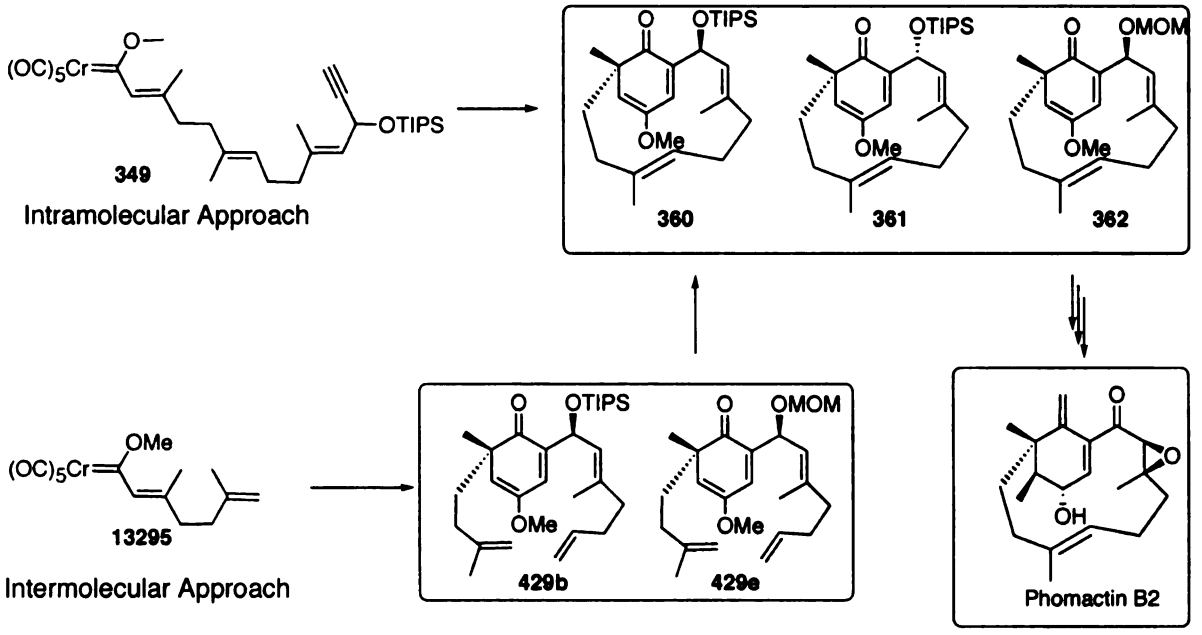
Scheme 6.13 Methylation and RCM of Compound 448



6.5 Summary

In summary, the intermolecular cyclohexadienone annulation approach has been attempted to the total synthesis of Phomactin B2. In this route, carbene complex **329** could be successfully coupled with alkynes **330** and **431b** with excellent diastereoselectivity. The resultant annulated product with a TIPS-protecting group could be converted to **360** via RCM at a dilute concentration. The MOM-protected analogue **429e** was obtained from the annulation reaction with lower diastereoselectivity. This diene could undergo smooth RCM to afford **362** in acceptable yield. Both **360** and **362** were mutual intermediates in the intramolecular version of synthesis. Thus, the formal total synthesis of Phomactin B2 could be realized via the intermolecular pathway. This was the first time that RCM was used successfully in the total synthesis of Phomactin families.

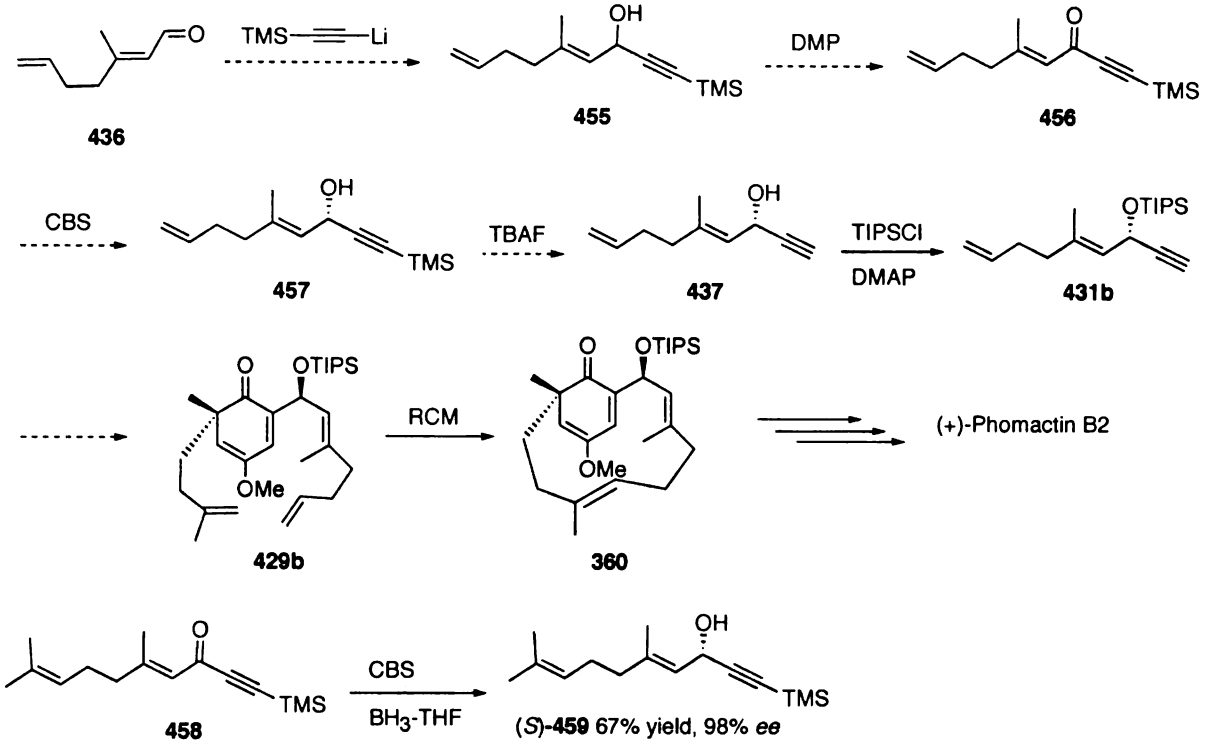
Scheme 6.14 Summary of Total Synthesis of Phomactin B2



6.6 Future Work

The asymmetric synthesis of Phomactin B2 will be accessible via the pathway described in Scheme 6.15. Alkylation of aldehyde **436** with lithium TMS acetylene will provide propargyl alcohol **455**. Dess-Martin oxidation will convert this alcohol to ketone **456**. Asymmetric reduction of **456** with CBS is anticipated to provide alcohol **457** with high enantioselectivity. A similar reduction has been attempted by Keith in our group on compound **458** with 98% *ee* induction. Desilylation of **457** followed by protection will produce enantiomerically pure alkyne **437**. With **437** in hand, the asymmetric synthesis of Phomactin B2 will follow the procedure described before in the racemic synthesis to give the natural product in a pure enantiomeric form.

Scheme 6.15 Asymmetric Approach to Phomactin B2



CHAPTER 7

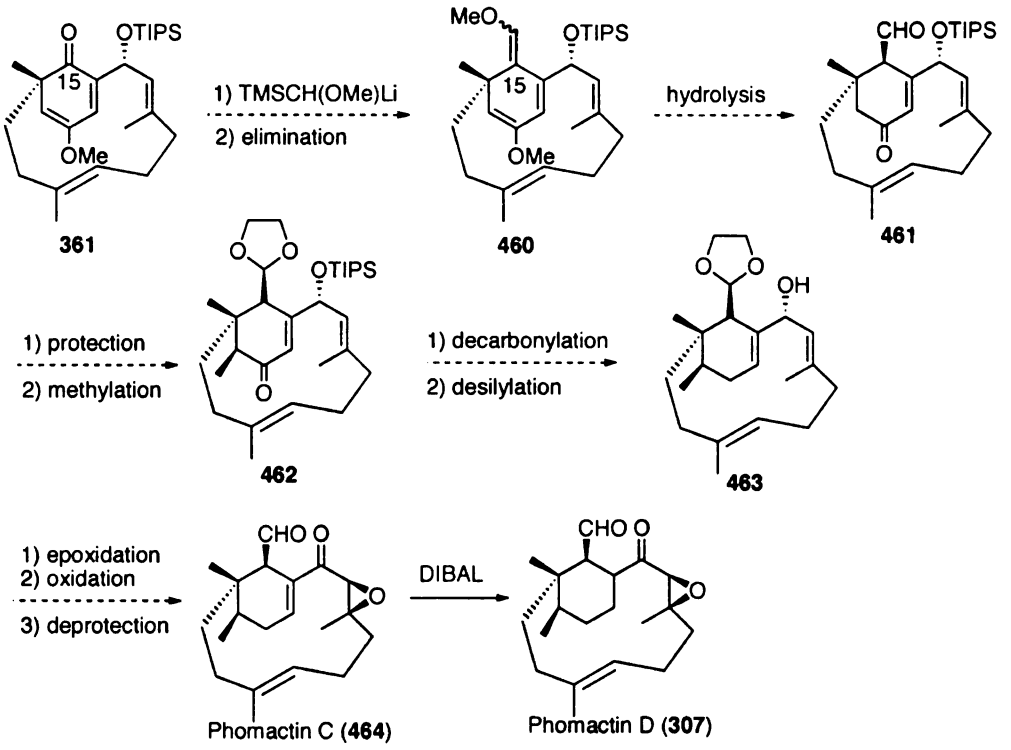
Preliminary Studies toward the Synthesis of Phomactins C and D

Upon the completion of the total synthesis of Phomactin B2, the attention was moved on to synthesize other Phomactins. Due to the limit of time and effort, only preliminary studies were performed in this area.

7.1 Peterson olefination for the total synthesis of Phomactins C and D

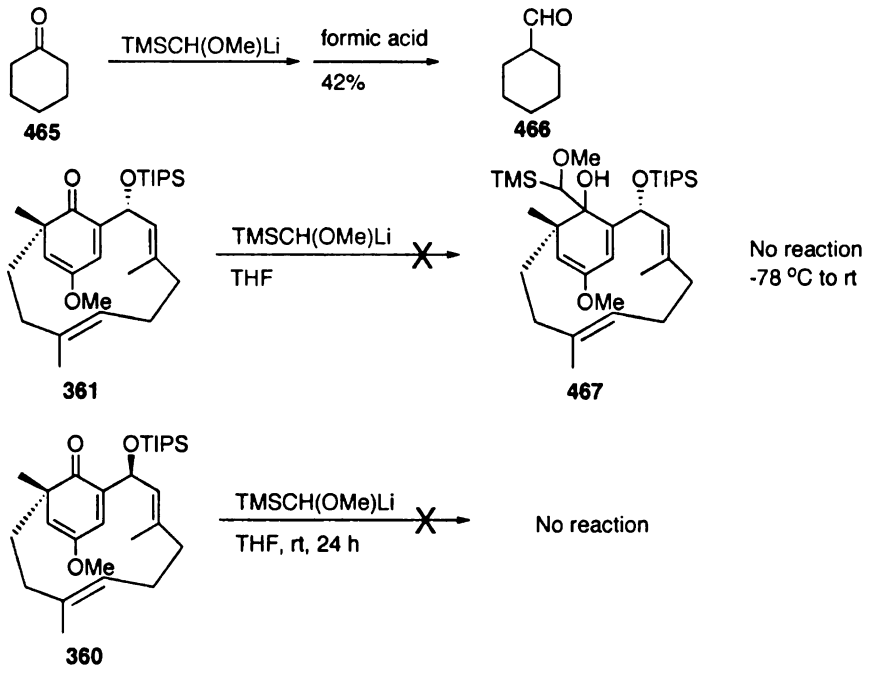
Phomactin D has the strongest PAF antagonist activity among Phomactins. A synthetic pathway parallel to the synthesis of Phomactin B2 was designed for the synthesis of Phomactin D (Scheme 7.1). In fact, the proposed total synthesis of Phomactin D starts from compound **361**, a known intermediate along the synthesis of Phomactin B2. The first step will also be Peterson olefination to introduce another enol ether at C15. Hydrolysis of both two enol ethers should provide keto-aldehyde **461**. The formal group was expected to epimerize to the β-face away from the macrocycle for thermodynamic reasons. Selective protection of the aldehyde followed by methylation should give ketone **462**. Removal of the carbonyl in **462** might be the most challenging step. If this step could be accomplished, the synthesis of Phomactin C and D would be very straightforward from compound **463**

Scheme 7.1 Proposed Total Synthesis Route for Phomactins C and D



The Peterson olefination in this case used a different silylmethyllithium species. This trimethylsilylmethoxymethyl lithium was generated *in situ* from trimethylsilylmethoxymethane and *sec*-butyl lithium.[114] It is known to react with cyclohexanone to give cyclohexanecarbaldehyde after treatment with formic acid.[115] However, this lithium reagent did not react with **361** at different temperatures. The less reactive diastereomer **360**, another known intermediate along the synthesis of Phomactin B2, also failed to react with TMSCH(OMe)Li. Thus, this proposed olefination encountered a failure.

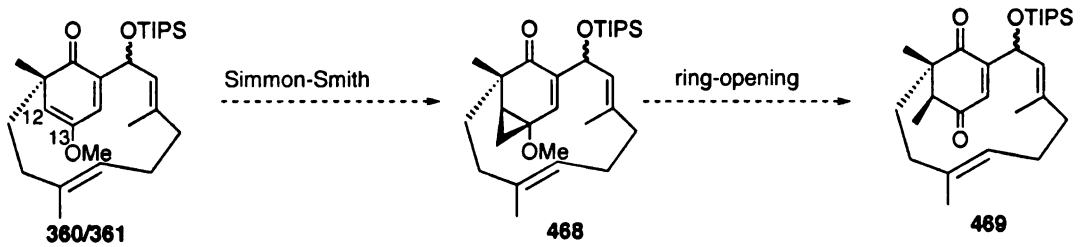
Scheme 7.2 Peterson Olefination of 360 and 361



7.2 Simmon-Smith cyclopropanation

Meanwhile, an alternative pathway was considered which introduces the methyl group at C12 via Simmon-Smith cyclopropanation (Scheme 7.3).[116] The electron rich C12–C13 olefin should be more active to the organozinc reagent and the cyclopropane was expected to be chemoselectively formed at this position from the face opposite to the macrocycle. Acid catalyzed ring opening of the cyclopropane would lead to α-methyl ketone **469**.

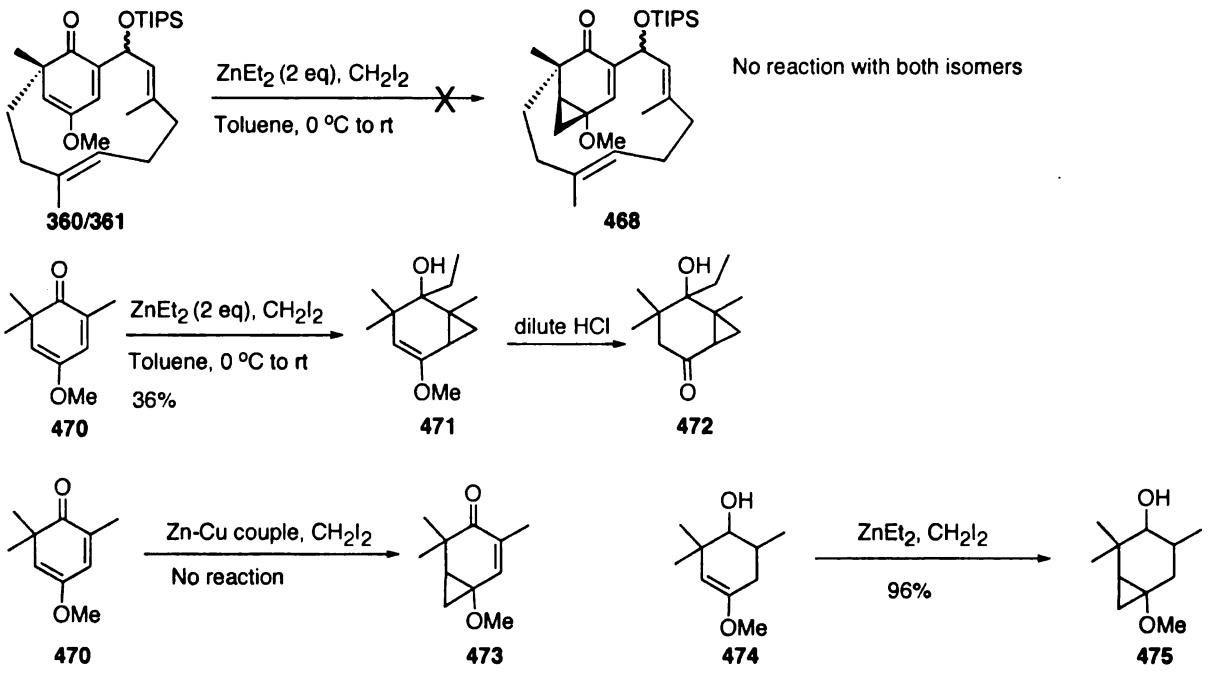
Scheme 7.3 Proposed Simmon-Smith Reaction of 360 and 361



However, treatment of **360** with $ZnEt_2$ and CH_2I_2 resulted in no reaction. The reaction of its diastereomer **361** under similar condition gave similar results. Since C12–C13 olefin was conjugated with the carbonyl, the electron density might be reduced by the carbonyl through conjugation and led to the lowered reactivity.

Due to the limited quantity of the substrates **360** and **361**, a model study was performed for Simmon-Smith reaction using **470** as the simplified substrate. When **470** was treated with diethyl zinc and methylene iodine, no desired cyclopropane **473** was observed.[116b] Instead, the undesired cyclopropane **471** was isolated in 36% yield with the 3-member ring formation at the wrong place and ethyl group addition to the ketone. It was envisioned that this result may come from an initial diethyl zinc addition to the carbonyl, followed by the subsequent O^--directed cyclopropanation at the allylic double bond. Other procedures were attempted to perform the cyclopropanation, including adding enol ether **470** to the mixture of diethyl zinc and methylene iodine, and the procedure involving use of zinc-copper couple.[117] However, neither of these attempts gave desired product **473**, and the starting material was simply recovered in those reactions. Dr. Jie Huang has demonstrated that the Simmon-Smith reaction can be performed on a reduced model **474** to obtain cyclopropane **475** in 96% yield.[91] Based on the results of the model study, the carbonyl in **360/361** needs to be reduced before the cyclopropanation.[91]

Scheme 7.4 Simmon-Smith Reaction and Model Study

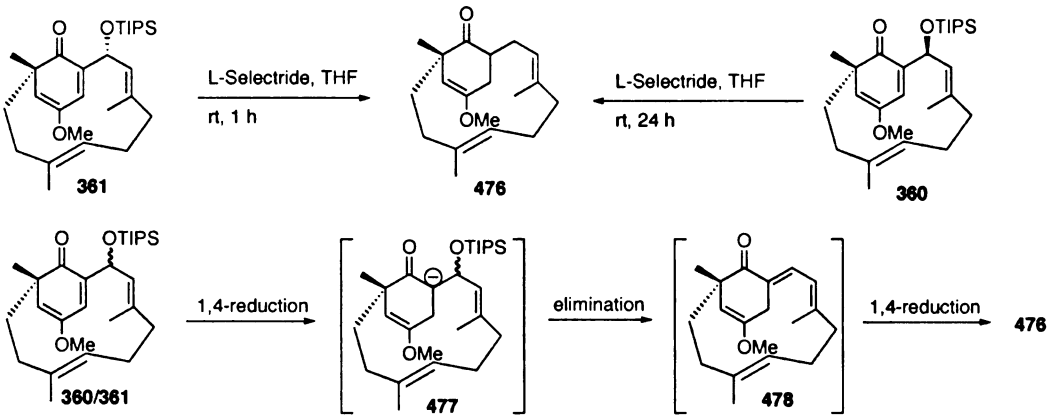


7.3 Reduction of Compounds 360 and 361

Understanding the necessity to reduce the carbonyl, compound **360/361** was then planned to subject to a 1,4-reduction, followed by a subsequent reduction of the resulting ketone to generated **474**-type alcohol (Scheme 7.4). But the attempts for such 1,4-reduction of **360** and **361** were not successful at 0°C and resulted in no reaction. When the temperature increased to room temperature, the minor isomer **361** was converted to a new compound within 1 hour. The reduction of the major isomer **360** took longer time, but essentially gave the same product. The structure of this new compound was determined to be compound **476** by NMR and MS analysis. It was envisioned that when **360** or **361** was treated with L-selectride, a 1,4-reduction occurred to give anion **477**, which underwent a β-elimination of the OTIPS group to afford another α,β-unsaturated ketone **478**. A subsequent 1,4-reduction of **478** gave compound **476**

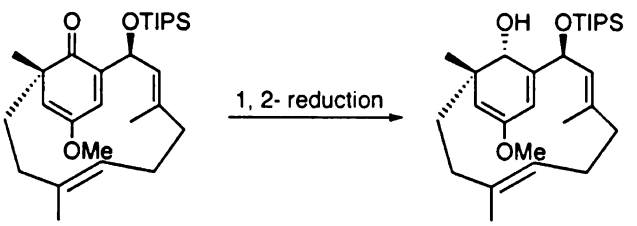
as the final product. With all that being said, the 1,4-reduction announced a failure, and it was considered to run a 1,2-reduction of the carbonyl in compound **360** and **361**. The resulting alcohol from 1,2-reduction might be able to facilitate the Simmon-Smith cyclopropanation.

Scheme 7.5 Reduction by L-Selectride



The 1,2-reduction of compound **360** was performed with $NaBH_4$, DIBAL, superhydride, and LAH (Table 7.1). Among all these reducing agent, only LAH was be able to reduce compound **360** at room temperature to afford **479**. This reduction gave **479** as a single diastereomer, but it was inseparable with 10% of starting martial. The resultant mixture was then subjected to the Simmon-Smith reaction, but complex mixtures were obtained. Obviously, simply removing the carbonyl seemed not enough to restore the reactivity of the enol ether olefin toward the Simmon-Smith cyclopropanation.

Table 7.1 1,2-Reduction of 360



360 479

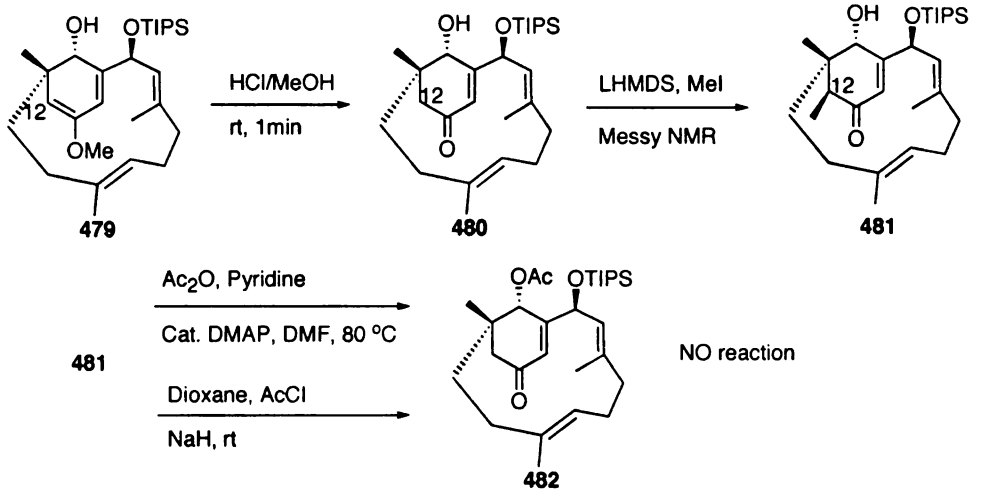
Reagent	Equivalents	Temperature (°C)	Time	Results[a]
$NaBH_4$	2	rt	3 d	No conversion
$NaBH_4/CeCl_3$	10	rt	3 d	No conversion
DIBAL	2	rt	24 h	No conversion
Superhydride	2	-78 - rt	20 h	No conversion
Superhydride	4	rt	30 min	Decomposition
LAH	4	rt	16 h	85[b]

a) Monitored by crude H ^{1}NMR. b) Isolated yield.

Having announced a failed Simmon-Smith cyclopropanation, a more traditional method was considered for the installation of the C12 methyl group. Along these lines, compound **479** was first hydrolyzed to the ketone **480** in quantitative yield. The directed methylation of enone **480** with the free hydroxy group gave complicated mixtures. Thus, the hydroxy group in **480** needs to protect before the methylation. An acetate was initially considered, since it could have some electronic perturbation to help differentiate the double bonds in the macrocycle and the one in 6-membered ring, and hence should be able to drive the later-stage epoxidation at the desired position. However, no reaction happened when **480** was treated with Ac_2O in the presence of pyridine and DMAP at room temperature. Increasing the temperature to 80 °C did not improve the condition, and in both cases compound **480** could be recovered. Compound

480 also did not react with the more reactive acetic chloride. At this time, the plan to synthesize Phomactin D was suspended.

Scheme 7.6 Methylation of Compound 480



THE APPLICATIONS OF THE ANNULATIONS OF FISCHER CARBENE COMPLEXES

VOLUME II

By

Chunrui Wu

A DISSERTATION

Submitted to
Michigan State University
In partial fulfillment of the requirements
For the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

2007

EXPERIMENTAL SECTION

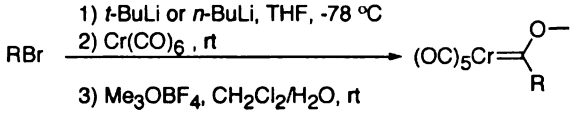
GC spectra were recorded on a Varian Star 3600 instrument with capillary Alltech ECONO-CAP SE 54 column (30m * 0.53 mm ID * 1.2μm). GC-MS spectra were recorded on either a Varian Saturn 2000R GC-MS instrument, or a HP 5890 Series II GC in tandem with a Trio-1 MS instrument. The latter instrument was also used to record MS spectra with direct-probe inlet. Infrared spectra were obtained on a Nicolet IR/42 spectrometer. Melting Points were measured on a Thomas Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Gemimi-300, Varian Inova-300, Varian VXR-500 and Varian Unity-plus 500 spectrometers (300, 500 MHz for ^{1}H, respectively, and 75, 125 MHz for ^{13}C, respectively). Chemical shifts for ^{1}H and ^{13}C were reported in part-per-million (ppm) values relative to the residue peaks of solvent $CDCl_3$ (δ 7.24 for ^{1}H and 77.0 for ^{13}C). High-resolution mass spectra were obtained at Michigan State University Mass Spectrometry Service Center with a JOEL-AX505 mass spectrometer (resolution 7000).

General procedure for the preparation of methoxy/*iso*propoxy Fischer chromium carbene complex (Procedure I)

To a flame dried round bottom flask under argon, was added 1 equivalent of halide in THF (0.1 M). The solution was cooled to –78 °C, and 2 equivalents of

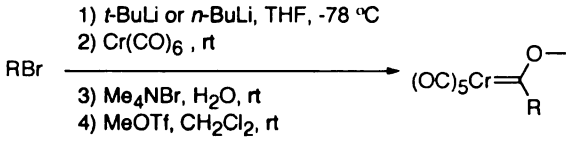
t-BuLi or 1 equivalent of *n*-BuLi was added dropwise. The resulting solution was stirred at –78 °C for 30 minutes, and then cannulated to a flask with 1.1 equivalents of $Cr(CO)_6$ in THF (0.05 M) at room temperature. The solution was allowed to stir at room temperature for 2 hours. The resulting carbene lithium acylate solution was concentrated *in vacuo*, and allowed to stand under high vacuum for 10 minutes. At this point the methoxy and *iso*propoxy carbene complexes were prepared using different methods.

Method A (for methoxy carbene complex)



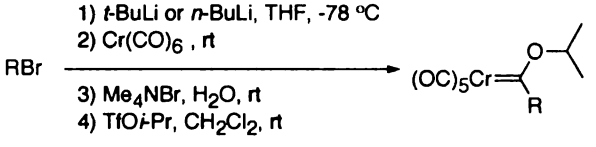
The acylate was dissolved in 1:1 CH_2Cl_2/H_2O, and then 1.5 equivalents of Me_3OBF_4 was added to the solution and kept stirring for 30 minutes at room temperature under argon. The reaction was quenched by pouring into a separatory funnel with saturated $NaHCO_3$ and pentane. The aqueous layer was separated and extracted with pentane until no red color was seen in the aqueous layer. The combined organic layer was washed with brine twice, and then dried over $MgSO_4$. The dried solution was filtered through a fritted funnel dry packed with Celite 503. The product was purified by silica gel chromatography using pure pentane as eluent.

Method B (for methoxy carbene complex)



The acylate was dissolved in 20 mL water, and then 1.5 equivalents of Me_4NBr was added with vigorously shaking. The solution was stirred at room temperature for 30 minutes. At this time, the crude carbene ammonium salt was extracted with CH_2Cl_2 three times. The organic layer was dried over $MgSO_4$, and then the solvent was removed *in vacuo*. The crude ammonium salt was dissolved in dried CH_2Cl_2, and 1.5 equiv. of methyltriflate was added. The reaction was stirred at room temperature for 30 minutes and worked up with the same method mentioned in method A.

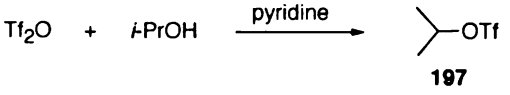
Method C (for *iso*propoxy carbene complex)



The acylate was dissolved in 20 mL water, and then 1.5 equivalents of Me_4NBr was added with vigorously shaking. The solution was stirred at room temperature for 30 minutes. At this time, the crude carbene ammonium salt was extracted with CH_2Cl_2 three times. The organic layer was dried over $MgSO_4$, and then the solvent was removed *in vacuo*. The crude ammonium salt was dissolved in dried CH_2Cl_2, and 1.5 equiv. of freshly prepared *iso*propyltriflate was added as

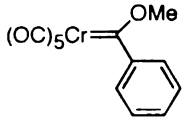
a concentrated solution in CH_2Cl_2. The reaction was stirred at room temperature for 30 minutes and worked up with the same method mentioned in method A.

Preparation of *iso*propyltriflate 197[118]

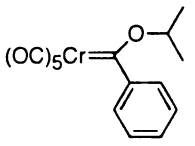


197

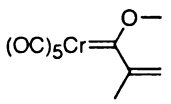
To a 25 mL flame dried round bottom flask was added 4 mL CH_2Cl_2 and 1.1 mL triflate anhydride (6.6 mmol) at 0 °C. A solution made with 0.51 mL (6.6 mmol) *iso*propanol, 0.52 mL (6.6 mmol) pyridine and 3 mL CH_2Cl_2 was added dropwise to the triflate anhydride solution in 10 minutes. The solution was kept Stirring at ice bath for extra 30 minutes, and then worked up with H_2O (8 mL). The organic layer was dried over $MgSO_4$, filtered and then used without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ1.7 (d, 6H), 5.7 (m, 1H), 7.2-7.5 (m, 5H).



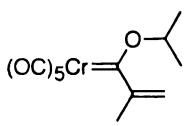
Phenyl methoxy chromium carbene complex **89**[119] Carbene complex **89** (0.88 g, 2.82 mmol) was prepared from bromobenzene (0.40 mL, 4 mmol) according to Procedure I in 70% yield. ^1H NMR ($CDCl_3$, 500 MHz) δ 4.69 (s, 3H), 7.24-7.27 (m, 2H), 7.38-7.40 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 67.09, 122.98, 128.17, 130.32, 153.71, 216.14, 224.10, 351.09.



Phenyl *iso*propoxy chromium carbene complex **158**[119] Carbene complex **158** (1.28 g, 3.76 mmol)was prepared from bromobenzene (1.05 mL, 10 mmol) according to Procedure I in 38% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.56 (d, 6H, *J* = 6.1 Hz), 5.64 (br s, 1H), 7.19-7.19 (m, 2H), 7.28-7.40 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.63, 85.73, 122.40, 128.14, 129.76, 153.78, 216.26, 224.39, 345.82.

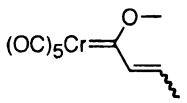


I s o-propenyl methoxy chromium carbene complex **175a**[120] Carbene complex **175a** (0.767 g, 2.78 mmol) was prepared from the corresponding ammonium salt (1.42 g, 4 mmol) according to Procedure I in 69% yield.

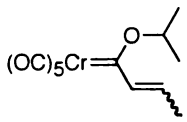


Iso-propenyl *iso*propoxy chromium carbene complex **175b** Carbene complex **175b** (0.302 g, 0.99 mmol) was prepared from the corresponding ammonium salt (0.50 g, 1.4 mmol) according to Procedure I in 71% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.49(d, 6H, *J* = 5.4 Hz), 1.85 (s, 3H), 4.83 (br, 1H), 4.98 (br, 1H), 5.50 (br, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.54, 22.68, 85.16, 157.26, 216.39, 224.07, 349.75 (1 sp^2 Carbon was not located); IR (neat) 1980s, 1920brs, 1611w cm^{-1}; mass spectrum *m/z* (% rel intensity) 304 M^+

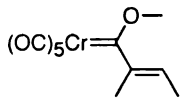
(3), 276 (14), 248 (10), 164 (100), 122 (42). Red solid, mp 63-64 °C; R_f = 0.30 (hexanes).



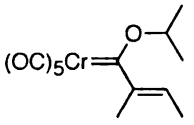
Propenyl methoxy chromium carbene complex **176a**[120] Carbene complex **176a** (0.63 g, 2.28 mmol) was prepared from 1-bromoprop-1-ene (0.43 mL, 5 mmol) according to Procedure I in 46% yield from the corresponding vinyl bromide.



Propenyl *iso*propoxy chromium carbene complex **176b**[121] Carbene complex **176b** (0.91 g, 3.0 mmol) was prepared from 1-bromoprop-1-ene (0.86 mL, 10 mmol) according to Procedure I in 30% yield.

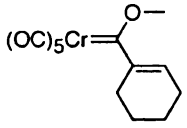


Sec-butenyl methoxy chromium carbene complex **177a**[122] Carbene complex **177a** (0.71 g, 2.45 mmol) was prepared from the corresponding ammonium salt (1.0 g, 2.87 mmol) according to Procedure I in 85% yield. The ammonium salt (5.88 g, 16.8 mmol) was prepared from (*E*)-2-bromobut-2-ene (1.85 mL, 20 mmol) in 84% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.47 (d, 3H, *J* = 7.1 Hz), 1.85 (s, 3H), 4.24 (br, 3H), 4.97 (q, 1H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.49, 19.52, 63.91, 114.00, 146.11, 216.26, 224.29, 361.48.



Sec-butenyl *iso*propoxy chromium carbene complex **177b**

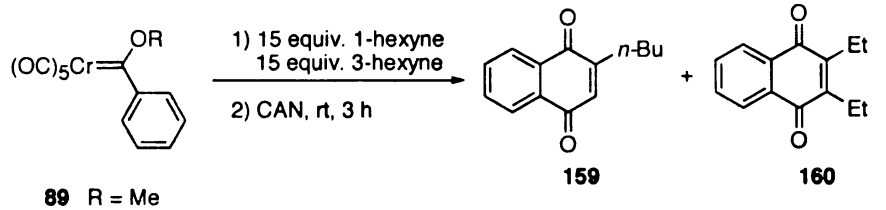
Carbene complex **177b** (0.896 g, 2.81 mmol) was prepared from the corresponding ammonium salt (1.02 g, 3 mmol) according to Procedure I in 94% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.46 (s, 3H), 1.50 (d, 6H, *J* = 6.1 Hz), 1.85 (s, 3H), 4.93 (br, 1H), 5.09 (br, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.04, 20.09, 22.62, 23.03, 83.23, 113.69, 146.07, 216.55, 224.47, 356.31; IR (neat) 2986, 2084, 1991, 1379, 1254, 1178, 1082, 988, 878, 711, 661, 621 cm^{-1}; mass spectrum *m/z* (% rel intensity) 318 M^+ (1), 178 (31), 136 (28), 135 (41), 126 (42), 107 (28), 105 (20), 84 (100), 83 (83), 80 (18), 67 (26), 55 (93). Anal Calcd for $C_{13}H_{14}CrO_6$: C, 49.06; H, 4.43. Found: C, 49.01; H, 4.60. Red oil; R_f = 0.29 (pentane).



Cyclohexenyl methoxy chromium carbene complex **178**[120]

Carbene complex **178** (1.62 g, 5.13 mmol) was prepared from the corresponding ammonium salt (2.50 g, 6.67 mmol) according to Procedure I in 77% yield. The ammonium salt (9.55 g, 25.5 mmol) was prepared from 1-bromocyclohex-1-ene (4.85 g, 30 mmol) in 85% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.50-1.60 (m, 2H), 1.63-1.68 (m, 2H), 2.13-2.14 (m, 2H), 2.28-2.30 (m, 2H), 4.61 (s, 3H), 6.31 (br, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.42, 21.84, 25.29, 25.71, 66.11, 135.39, 154.21, 216.80, 223.88, 350.72.

General procedure for the benzannulation of carbene complexes with 15 equivalent of 1-hexyne and 15 equivalents of 3-hexyne (Procedure II)



89 R = Me
158 R = *i*-Pr

159 **160**

To a 50 mL flame dried Shlenk flask equipped with a Teflon screw top was added carbene complex **89** or **158** in a certain solvent (~0.06 M). 15 equivalents of 1-hexyne and 15 equivalents of 3-hexyne were added to this solution. The system was degassed by running 3 cycles of freeze-pump-thaw. After the third cycle, the flask was back-filled with Ar, and sealed. The reaction was heated to 80 °C for 16 hours or 40 °C for 22 hours. The crude reaction mixture was diluted with Et_2O and treated with 10 equivalents of 0.5 M CAN solution. The biphasal reaction was stirred for 3 hours at room temperature. At this point, the reaction was poured into a 125 mL separatory funnel and diluted with Et_2O. A saturated $NaHCO_3$ solution was added to the funnel to quench the CAN solution, and separated without shaking to avoid emulsion. The organic layer was washed with saturated $NaHCO_3$ (2 * 10 mL). The aqueous layer was then back extracted with ether (2 * 10 mL). The combined organics were then washed with brine (15 mL) and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in 20 mL Et_2O, kept 1 mL solution for GC and GC-MS analysis, the rest crude product was subjected on silica gel chromatography (usually 2 * 25 cm, 5%

EtOAc in hexanes) to gain yields. The yield was calculated based on 95% of the starting material.

Reaction with carbene complex 89 in benzene at 80 °C: Carbene complex **89** (0.125 g, 0.40 mmol), 1-hexyne (0.75 mL, 6.5 mmol) and 3-hexyne (0.70 mL, 6.2 mmol) was dissolved in 5 mL benzene and thermolyzed according to Procedure II to give **159** (0.0682 g, 0.32 mmol, 84%) and **160** in 93:7 ratio.

Reaction with carbene complex 89 in THF at 80 °C: Carbene complex **89** (0.0995 g, 0.319 mmol), 1-hexyne (0.60 mL, 5.2 mmol) and 3-hexyne (0.60 mL, 5.2 mmol) was dissolved in 5 mL THF and thermolyzed according to Procedure II to give **159** (0.0274 g, 0.128 mmol, 42%) and **160** in 94:6 ratio.

Reaction with carbene complex 89 in CH_3CN at 80 °C: Carbene complex **89** (0.104 g, 0.33 mmol), 1-hexyne (0.60 mL, 5.2 mmol) and 3-hexyne (0.60 mL, 5.2 mmol) was dissolved in 5 mL CH_3CN and thermolyzed according to Procedure II to give **159** (0.0276 g, 0.128 mmol, 41%) and **160** in 98:2 ratio.

Reaction with carbene complex 89 in benzene at 40 °C: Carbene complex **89** (0.157 g, 0.50 mmol), 1-hexyne (0.75 mL, 6.5 mmol) and 3-hexyne (0.70 mL, 6.2 mmol) was dissolved in 5 mL benzene and thermolyzed according to Procedure II to give **159** (0.0703 g, 0.33 mmol, 69%) and **160** in 95:5 ratio.

Reaction with carbene complex 89 in THF at 40 °C: Carbene complex **89** (0.105 g, 0.31 mmol), 1-hexyne (0.60 mL, 5.2 mmol) and 3-hexyne (0.60 mL, 5.2 mmol) was dissolved in 5 mL THF and thermolyzed according to Procedure II to give **159** (0.0222 g, 0.104 mmol, 35%) and **160** in 98:2 ratio.

Reaction with carbene complex 89 in CH_3CN at 40 °C: Carbene complex **89** (0.104 g, 0.33 mmol), 1-hexyne (0.60 mL, 5.2 mmol) and 3-hexyne (0.60 mL, 5.2 mmol) was dissolved in 5 mL CH_3CN and thermolyzed according to Procedure II to give **159** (0.0222 g, 0.104 mmol, 33%) and **160** in 98:2 ratio.

Reaction with carbene complex 89 in hexane at 40 °C: Carbene complex **89** (0.150 g, 0.48 mmol), 1-hexyne (0.60 mL, 5.2 mmol) and 3-hexyne (0.60 mL, 5.2 mmol) was dissolved in 5 mL hexane and thermolyzed according to Procedure II to give **159** (0.0630 g, 0.294 mmol, 64%) and **160** in 96:4 ratio.

Reaction with carbene complex 158 in benzene at 80 °C: Carbene complex **158** (0.12 g, 0.35 mmol), 1-hexyne (0.60 mL, 5.2 mmol) and 3-hexyne (0.60 mL, 5.2 mmol) was dissolved in 5 mL benzene and thermolyzed according to Procedure II to give **159** (0.0602 g, 0.28 mmol, 84%) and **160** in 94:6 ratio.

Reaction with carbene complex 158 in THF at 80 °C: Carbene complex **158** (0.105 g, 0.309 mmol), 1-hexyne (0.60 mL, 5.2 mmol) and 3-hexyne (0.60

mL, 5.2 mmol) was dissolved in 5 mL THF and thermolyzed according to Procedure II to give **159** (0.0355 g, 0.166 mmol, 56%) and **160** in 99:1 ratio.

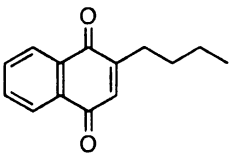
Reaction with carbene complex 158 in CH_3CN at 80 °C: Carbene complex **158** (0.104 g, 0.31 mmol), 1-hexyne (0.60 mL, 5.2 mmol) and 3-hexyne (0.60 mL, 5.2 mmol) was dissolved in 5 mL *CH_3CN* and thermolyzed according to Procedure II to give **159** (0.0259 g, 0.121 mmol, 41%) and **160** in 99:1 ratio.

Reaction with carbene complex 158 in benzene at 40 °C: Carbene complex **158** (0.108 g, 0.32 mmol), 1-hexyne (0.60 mL, 5.2 mmol) and 3-hexyne (0.60 mL, 5.2 mmol) was dissolved in 5 mL benzene and thermolyzed according to Procedure II to give **159** 0.0482 g, 0.225 mmol, 74%) and **160** in >99:1 ratio.

Reaction with carbene complex 158 in THF at 40 °C: Carbene complex **158** (0.108 g, 0.32 mmol), 1-hexyne (0.60 mL, 5.2 mmol) and 3-hexyne (0.60 mL, 5.2 mmol) was dissolved in 5 mL THF and thermolyzed according to Procedure II to give **159** (0.0362 g, 0.168 mmol, 55%) and **160** in 99:1 ratio.

Reaction with carbene complex 158 in CH_3CN at 80 °C: Carbene complex **158** (0.105 g, 0.31 mmol), 1-hexyne (0.60 mL, 5.2 mmol) and 3-hexyne (0.60 mL, 5.2 mmol) was dissolved in 5 mL CH_3CN and thermolyzed according to Procedure II to give **159** (0.0250 g, 0.117 mmol, 40%) and **160** 98:2 ratio.

Reaction with carbene complex 158 in hexane at 40 °C: Carbene complex **158** (0.146 g, 0.43 mmol), 1-hexyne (0.60 mL, 5.2 mmol) and 3-hexyne (0.60 mL, 5.2 mmol) was dissolved in 5 mL hexane and thermolyzed according to Procedure II to give **159** (0.0688 g, 0.321 mmol, 79%) and **160** in >99:1 ratio.

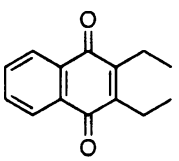


2-butylnaphthalene-1,4-dione **159**[123] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.93 (t, 3H, *J* = 7.3 Hz), 1.38-1.42 (m, 2H), 1.52-1.56 (m, 2H), 2.55 (td, 2H, *J* = 7.9, 1.3 Hz), 6.77 (t, 1H, *J* = 1.3 Hz), 7.69-7.71 (m, 2H), 8.03-8.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.81, 22.47, 29.27, 30.12, 126.00, 126.57, 132.12, 132.34, 133.57, 133.59, 134.72, 151.98, 185.23, 185.27.

General procedure for the benzannulation of carbene complex with a alkyne (Procedure III for the preparation of minor product in the competition reaction)

To a 50 mL flame dried Shlenk flask equipped with a Teflon screw top was added carbene complex in benzene (~0.06 M) and 2 equivalents of alkyne. The system was degassed by running 3 cycles of freeze-pump-thaw. After the third cycle, the flask was back-filled with Ar, and sealed. The reaction was heated to 80 °C for 16 hours. The crude reaction mixture was diluted with Et_2O and treated with 10 equivalents of 0.5 M CAN solution. The biphasal reaction was stirred for 3 hours at room temperature. At this point, the reaction was poured into a 125 mL separatory funnel and diluted with Et_2O. A saturated $NaHCO_3$ solution was

added to the funnel to quench the CAN solution, and separated without shaking to avoid emulsion. The organic layer was washed with saturated $NaHCO_3$ (2 * 10 mL). The aqueous layer was then back extracted with ether (2 * 10 mL). The combined organics were then washed with brine (15 mL) and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified on silica gel chromatography (usually 2 * 25 cm, 5% EtOAc in hexanes).

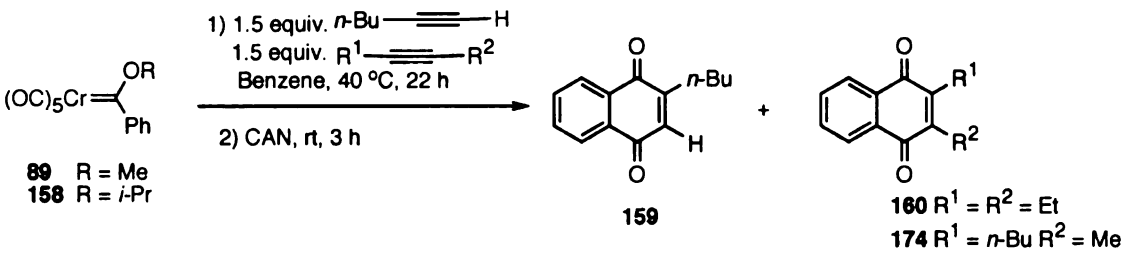


2,3-diethylnaphthalene-1,4-dione **160**[119] Quinone **160** (0.869 g, 0.406 mmol, 90%) was prepared from carbene complex **158** (0.153 mg, 0.45 mmol) and 3-hexyne according to procedure III. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.13 (t, 6H, *J* = 7.5 Hz), 2.62 (q, 4H, *J* = 7.5 Hz), 7.66 (dd, 2H, *J* = 5.8, 3.3 Hz), 8.04 (dd, 2H, *J* = 5.7, 3.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.94, 20.12, 126.13, 132.24, 133.24, 148.05, 185.00.

General procedure for the benzannulation of carbene complexes with 1.5 or 2 equivalents of two different alkynes (Procedure IV)

To a 50 mL flame dried Shlenk flask equipped with a Teflon screw top was added carbene complex in benzene (~0.06 M). 1.5 or 2 equivalents of two different alkynes were added to this solution. The system was degassed by running 3 cycles of freeze-pump-thaw. After the third cycle, the flask was back-filled with Ar, and sealed. The reaction was heated to 40 °C for 22 hours. The crude reaction mixture was diluted with Et_2O and treated with 10 equivalents of

0.5 M CAN solution. The biphasal reaction was stirred for 3 hours at room temperature. At this point, the reaction was poured into a 125 mL separatory funnel and diluted with Et_2O. A saturated $NaHCO_3$ solution was added to the funnel to quench the CAN solution, and separated without shaking to avoid emulsion. The organic layer was washed with saturated $NaHCO_3$ (2 * 10 mL). The aqueous layer was then back extracted with ether (2 * 10 mL). The combined organics were then washed with brine (15 mL) and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in 20 mL Et_2O, kept 1 mL solution for GC and GC-MS analysis, the rest crude product was subjected on silica gel chromatography (usually 2 * 25 cm, 5% EtOAc in hexanes) to gain yields. The yield was calculated based on 95% of the starting material.

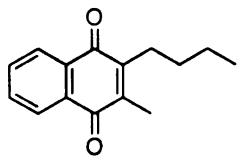


Reaction of carbene complex 89 with 1-hexyne and 3-hexyne: Carbene complex **89** (0.107 g, 0.34 mmol), 1-hexyne (0.060 mL, 0.52 mmol) and 3-hexyne (0.058 mL, 0.51 mmol) was dissolved in 5 mL benzene and thermolyzed according to Procedure IV to give **159** (0.0540 g, 0.252 mmol, 78%) and **160** in 96:4 ratio.

Reaction of carbene complex 158 with 1-hexyne and 3-hexyne: Carbene complex **158** (0.128 g, 0.38 mmol), 1-hexyne (0.065 mL, 0.57 mmol) and 3-hexyne (0.065 mL, 0.57 mmol) was dissolved in 5 mL benzene and thermolyzed according to Procedure IV to give **159** (0.0580 g, 0.271 mmol, 78%) and **160** in >99:1 ratio.

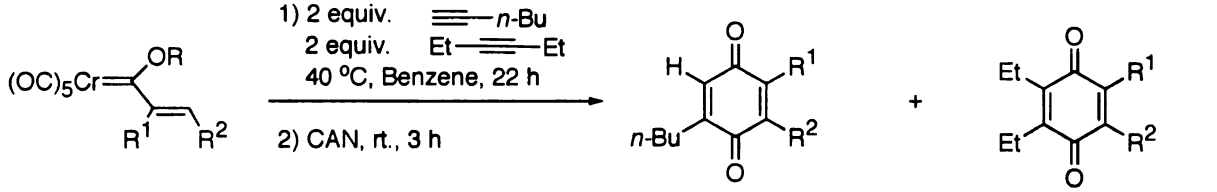
Reaction of carbene complex 89 with 1-hexyne and 2-heptyne: Carbene complex **89** (0.101 g, 0.32 mmol), 1-hexyne (0.055 mL, 0.48 mmol) and 2-heptyne (0.062 mL, 0.48 mmol) was dissolved in 5 mL benzene and thermolyzed according to Procedure IV to give **159** (0.0525 g, 0.245 mmol, 81%) and **174** in 97:3 ratio.

Reaction of carbene complex 158 with 1-hexyne and 2-heptyne: Carbene complex **158** (0.101 g, 0.30 mmol), 1-hexyne (0.052 mL, 0.45 mmol) and 2-heptyne (0.058 mL, 0.45 mmol) was dissolved in 5 mL benzene and thermolyzed according to Procedure IV to give **159** (0.0521 g, 0.243 mmol, 85%) and **174** in > 99:1 ratio.



2-butyl-3-methylnaphthalene-1,4-dione **174**[124] Quinone **174** (0.0500 g, 0.22 mmol, 73%) was prepared from carbene complex **158** (0.102 mg, 0.30 mmol) and 2-heptyne according to procedure III. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.93 (t, 3H, *J* = 7.1 Hz), 1.41-1.46 (m, 4H), 2.17 (s, 3H), 2.61-2.64 (m,

2H), 7.66-7.68 (m, 2H), 8.05-8.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.60, 13.88, 23.08, 26.82, 30.86, 126.16, 126.25, 132.17, 132.21, 133.25, 133.29, 143.09, 147.56, 184.72, 185.38.



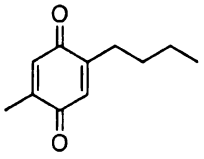
175 R^1 = Me, R^2 = H
176 R^1 = H, R^2 = Me
177 R^1, R^2 = Me
178 R^1, R^2 = $(CH_2)_4$
(**a** R = Me, **b** R = *i*-Pr)

179 R^1 = Me, R^2 = H
180 R^1 = H, R^2 = Me
181 R^1, R^2 = Me
182 R^1, R^2 = $(CH_2)_4$

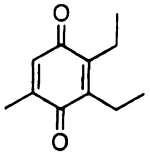
183 R^1 = Me, R^2 = H
184 R^1, R^2 = Me
185 R^1, R^2 = $(CH_2)_4$

Reaction of carbene complex 175a with 1-hexyne and 3-hexyne: Carbene complex **175a** (0.170 g, 0.616 mmol), 1-hexyne (0.141 mL, 1.23 mmol) and 3-hexyne (0.1.40 mL, 1.23 mmol) was dissolved in 6.2 mL benzene and thermolyzed according to Procedure IV to give **179** (0.0642 g, 0.360 mmol, 62%) and **183** in 99:1 ratio.

Reaction of carbene complex 175b with 1-hexyne and 3-hexyne: Carbene complex **175b** (0.157 g, 0.50 mmol), 1-hexyne (0.115 mL, 1.0 mmol) and 3-hexyne (0.114 mL, 1.0 mmol) was dissolved in 5 mL benzene and thermolyzed according to Procedure IV to give **179** (0.0620 g, 0.348 mmol, 73%) and **183** in >99:1 ratio.



2-butyl-5-methylcyclohexa-2,5-diene-1,4-dione **179**[125] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.91 (t, 3H, *J* = 7.2 Hz), 1.33-1.37 (m, 2H), 1.43-1.48 (m, 2H), 2.01 (d, 3H, *J* = 1.6 Hz), 2.36-2.40 (m, 2H), 6.52 (t, 1H, *J* = 1.5 Hz), 6.56 (q, 1H, *J* = 1.6 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.76, 15.42, 22.37, 28.40, 29.91, 132.38, 133.56, 145.48, 149.62, 187.82, 188.28.

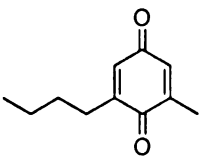


2,3-Diethyl-5-methyl-[1,4]benzoquinone **183** Quinone **183** (0.032 g, 0.18 mmol, 36%) was prepared from carbene complex **176b** (0.152 mg, 0.50 mmol) and 3-hexyne according to procedure III. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.04 (t, 3H, *J* = 7.4 Hz), 1.05 (t, 3H, *J* = 7.4 Hz), 2.00 (d, 3H, *J* = 1.5 Hz), 2.44 (q, 2H, *J* = 7.4 Hz), 2.46 (q, 2H, *J* = 7.4 Hz), 6.52 (q, 1H, *J* = 1.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.94 (br, 2C), 15.81, 19.43, 19.70, 133.21, 145.31, 145.38, 145.54, 187.67, 188.02; IR cm^{-1}; mass spectrum *m/z* (% rel intensity) 178 M^+ (100), 164 (11), 163 (85), 149 (32), 135 (38), 121 (40), 107 (23), 91 (22), 79 (17), 77 (14), 67 (18), 53 (12). Yellow oil, R_f = 0.35 (5% EtOAc in hexanes).

Reaction of carbene complex 176a with 1-hexyne and 3-hexyne: Carbene complex **176a** (0.138 g, 0.50 mmol), 1-hexyne (0.115 mL, 1.0 mmol) and 3-hexyne (0.114 mL, 1.0 mmol) was dissolved in 5 mL benzene and

thermolyzed according to Procedure IV to give **180** (0.0350 g, 0.197 mmol, 41%) and **183** in 96:4 ratio.

Reaction of carbene complex 176b with 1-hexyne and 3-hexyne: Carbene complex **176b** (0.152 g, 0.50 mmol), 1-hexyne (0.115 mL, 1.0 mmol) and 3-hexyne (0.114 mL, 1.0 mmol) was dissolved in 5 mL benzene and thermolyzed according to Procedure IV to give **180** (0.0270 g, 0.152 mmol, 32%) and **183** in 98:2 ratio.

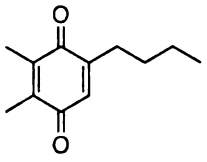


2-Butyl-6-methyl-[1,4]benzoquinone **180** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.91 (t, 3H, *J* = 7.2 Hz), 1.34-1.38 (m, 2H), 1.43-1.48 (m, 2H), 2.03 (d, 3H, *J* = 1.5 Hz), 2.40 (t, 2H, *J* = 7.7 Hz), 6.47-6.48 (m, 1H), 6.52-6.53 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.65, 15.89, 22.27, 28.73, 29.82, 132.17, 132.94, 145.78, 149.45, 187.70, 187.79; IR (neat) 2959, 2932, 2874, 1653, 1614, 1294, 914 cm^{-1}; mass spectrum *m/z* (% rel intensity) 178 M^+ (79), 163 (63), 135 (100), 121 (11), 107 (26), 91 (22), 79 (12), 77 (11). Anal Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.54, H, 8.29. Yellow oil; R_f = 0.30 (5% EtOAc in hexanes).

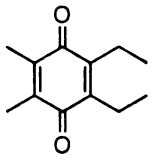
Reaction of carbene complex 177a with 1-hexyne and 3-hexyne: Carbene complex **177a** (0.38 g, 1.31 mmol), 1-hexyne (0.226 mL, 1.97 mmol) and 3-hexyne (0.223 mL, 1.0 mmol) was dissolved in 13 mL benzene and

thermolyzed according to Procedure IV to give **181** (0.0136 g, 0.708 mmol, 57%) and **184** in greater than 99:1 ratio.

Reaction of carbene complex 177b with 1-hexyne and 3-hexyne: Carbene complex **177b** (0.268 g, 0.842 mmol), 1-hexyne (0.145 mL, 1.26 mmol) and 3-hexyne (0.143 mL, 1.26 mmol) was dissolved in 8.4 mL benzene and thermolyzed according to Procedure IV to give **181** (0.1270 g, 0.66 mmol, 83%) and **184** in greater than 99:1 ratio.

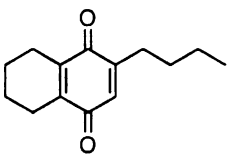


5-butyl-2,3-dimethylcyclohexa-2,5-diene-1,4-dione **181**[126] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, 3H, *J* = 7.1 Hz), 1.28-1.43 (m, 4H), 1.93 (s, 3H), 1.95 (s, 3H), 2.33 (t, 2H, *J* = 7.4 Hz), 6.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.95, 12.33, 13.75, 22.34, 28.68, 29.86, 131.91, 140.31, 140.85, 148.95, 187.41, 187.53.

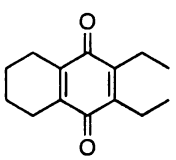


2,3-diethyl-5,6-dimethylcyclohexa-2,5-diene-1,4-dione **184**[127] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.04 (t, 6H, *J* = 7.6 Hz), 1.98 (s, 6H), 2.46 (q, 4H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.28, 14.01, 19.69, 140.41, 145.04, 187.49.

Reaction of carbene complex 178 with 1-hexyne and 3-hexyne: Carbene complex **178** (0.16 g, 0.5 mmol), 1-hexyne (0.115 mL, 1.0 mmol) and 3-hexyne (0.114 mL, 1.0 mmol) was dissolved in 5 mL benzene and thermolyzed according to Procedure IV to give **182** (0.075 g, 0.344 mmol, 72%) and **185** in 99:1 ratio.



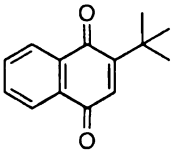
2-butyl-5,6,7,8-tetrahydronaphthalene-1,4-dione **182**[127] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (td, 3H, *J* = 7.3, 1.8 Hz), 1.33-1.37 (m, 2H), 1.44-1.47 (m, 2H), 1.65-1.67 (m, 4H), 2.36-2.40 (m, 6H), 6.44-6.45 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.68, 20.89, 21.08, 22.23, 22.30, 22.58, 28.53, 29.86, 131.91, 141.88, 142.31, 148.99, 187.49, 187.68.



2,3-diethyl-5,6,7,8-tetrahydronaphthalene-1,4-dione **185**[128] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.04 (t, 6H, *J* = 7.5 Hz), 1.63-1.65 (m, 4H), 2.37-2.37 (m, 4H), 2.44 (q, 4H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.01, 19.52, 21.20, 22.53, 141.90, 144.97, 187.53.

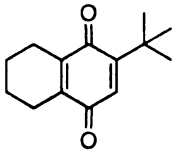
Reaction of carbene complex 89 with n-butyl acetylene (1-hexyne) and t-butyl acetylene: Carbene complex **89** (0.247 g, 0.79 mmol), 1-hexyne (0.136 mL, 1.19 mmol) and *t*-butyl acetylene (0.142 mL, 1.19 mmol) was

dissolved in 8 mL benzene and thermolyzed according to Procedure IV to give **159** (0.079 g, 0.369 mmol, 49%) and **188** (0.040 g, 0.187 mmol, 25%) in 2:1 ratio. The ratio determined by crude ^{1}H NMR of **159/188** was 2:1.



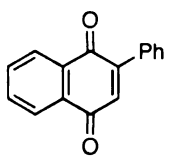
2-tert-butylnaphthalene-1,4-dione **188**[129] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.34 (s, 9H), 6.81 (s, 1H), 7.66-.769 (m, 2H), 7.99-8.01 (m, 1H), 8.04-8.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.36, 35.71, 125.57, 126.84, 131.52, 133.24, 133.54, 133.69, 133.82, 158.32, 184.91, 185.88.

Reaction of carbene complex 178 with n-butyl acetylene (1-hexyne) and t-butyl acetylene: Carbene complex **178** (0.236 g, 0.75 mmol), 1-hexyne (0.129 mL, 1.12 mmol) and *t*-butyl acetylene (0.138 mL, 1.12 mmol) was dissolved in 7.5 mL benzene and thermolyzed according to Procedure IV to give **182** (0.089 g, 0.408 mmol, 57%) and **189** (0.050 g, 0.229 mmol, 32%) in 2:1 ratio. The ratio determined by crude ^{1}H NMR of **182/189** was 2:1.



2-tert-butyl-5,6,7,8-tetrahydronaphthalene-1,4-dione **189**[130] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23 (s, 9H), 1.63-1.65 (m, 4H), 2.35-2.38 (m, 4H), 6.48 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.92, 21.29, 22.07, 22.84, 29.27, 35.07, 131.13, 140.91, 143.91, 155.60, 187.42, 188.37.

Reaction of carbene complex 89 with n-butyl acetylene (1-hexyne) and phenyl acetylene: Carbene complex **89** (0.156 g, 0.50 mmol), 1-hexyne (0.086 mL, 0.75 mmol) and phenyl acetylene (0.082 mL, 0.75 mmol) was dissolved in 5 mL benzene and thermolyzed according to Procedure IV to give **159** (0.0397 g, 0.186 mmol, 39%) and **190** (0.0204 g, 0.087 mmol, 18%) in 55:45 ratio. The ratio determined by crude ^{1}H NMR of **159/190** was 1:1.

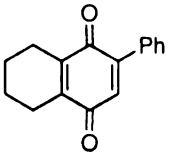


2-phenylnaphthalene-1,4-dione **190**[131] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.04 (s, 1H), 7.43-7.46 (m, 3H), 7.54-7.56 (m, 2H), 7.73-7.75 (m, 2H), 8.07-8.09 (m, 1H), 8.14-8.15 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 125.87, 126.95, 128.38, 129.36, 129.94, 131.99, 132.36, 133.31, 133.73, 133.79, 135.12, 148.00, 184.26, 185.01.

Reaction of carbene complex 89 with n-butyl acetylene (1-hexyne) and phenyl acetylene: Carbene complex **89** (0.102 g, 0.33 mmol), 1-hexyne (0.076 mL, 0.66 mmol) and phenyl acetylene (0.075 mL, 0.66 mmol) was dissolved in 5 mL benzene and thermolyzed according to Procedure IV to give **160** and **174** (0.0460 g in total, 62% by calculation) in 1:1 ratio.

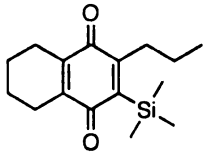
Reaction of carbene complex 178 with n-butyl acetylene (1-hexyne) and phenyl acetylene: Carbene complex **178** (0.158 g, 0.50 mmol), 1-hexyne

(0.086 mL, 0.75 mmol) and phenyl acetylene (0.082 mL, 0.75 mmol) was dissolved in 5 mL benzene and thermolyzed according to Procedure IV to give **159** (0.0386 g, 0.180 mmol, 38%) and **191** (0.0333 g, 0.142 mmol, 30%) in 1:1 ratio. The ratio determined by crude ^{1}H NMR of **159/191** was 1:1.



5,6,7,8-tetrahydro-2-phenylnaphthalene-1,4-dione **191**[132] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.68-1.70 (m, 4H), 2.43-2.47 (m, 4H), 6.74 (s, 1H), 7.37-7.40 (m, 3H), 7.42-7.44 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.83, 21.10, 22.30, 22.82, 128.22, 129.10, 129.56, 132.28, 133.14, 142.12, 142.50, 145.47, 186.54, 187.47.

Reaction of carbene complex 178 with 1-hexyne and 1-TMS-1-pentyne: Carbene complex **178** (0.158 g, 0.50 mmol), 1-hexyne (0.086 mL, 0.75 mmol) and 1-TMS-1-pentyne (0.138 mL, 0.75 mmol) was dissolved in 5 mL benzene and thermolyzed according to Procedure IV to give **159** (0.0884 g, 0.406 mmol, 81%) as the only product. TMS-substituted quinone **194** was not detected by GC-MS and crude ^{1}H NMR.

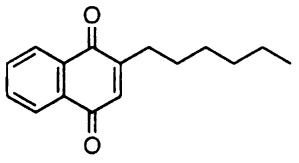


5,6,7,8-tetrahydro-2-(trimethylsilyl)-3-propylnaphthalene-1,4-dione **194** Quinone **194** (45 mg, 0.145 mmol, 44%) was prepared from carbene complex **178** (103 mg, 0.33 mmol) with 1-TMS-1-pentyne. ^{1}H NMR ($CDCl_3$, 500

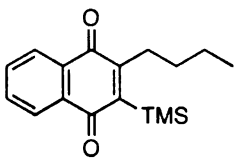
MHz) δ 0.26 (s, 9H), 0.93 (t, 3H, J = 7.3 Hz), 1.35-1.40 (m, 2H), 1.62-1.64 (m, 4H), 2.33-2.37 (m, 4H), 2.45-2.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 1.60, 14.25, 21.11, 21.17, 22.46, 22.56, 24.67, 30.67, 141.93, 143.47, 145.50, 156.53, 186.76, 192.03; IR 2942, 2874, 1644, 1273, 868, 844 cm^{-1}; mass spectrum *m/z* (% rel intensity) 276 M^+ (34), 262 (22), 261 (100), 233 (26). HRMS (CI) calcd for $C_{16}H_{25}O_2Si$ *m/z* 277.1624, meas 277.1619. Yellow oil; R_f = 0.51 (20:1:1 hexanes/Et_2O/CH_2Cl_2).

Reaction of carbene complex 178 with 1-hexyne and 1-TBS-1-pentyne: Carbene complex **178** (0.158 g, 0.50 mmol), 1-hexyne (0.086 mL, 0.75 mmol) and 1-TBS-1-pentyne (0.138 g, 0.75 mmol) was dissolved in 5 mL benzene and thermolyzed according to Procedure IV to give **159** (0.0848 g, 0.389 mmol, 78%) as the only product. TBS-substituted quinone was not detected by GC-MS and crude ^1H NMR.

Reaction of carbene complex 89 with 1-octyne and 1-TMS-1-hexyne: Carbene complex **89** (0.109 g, 0.35 mmol), 1-octyne (0.0774 mL, 0.52 mmol) and 1-TMS-1-hexyne (0.105 mL, 0.52 mmol) was dissolved in 6.9 mL benzene and thermolyzed according to Procedure IV to give **192** (0.0596 g, 0.246 mmol, 70%) and trace amount of the TMS-substituted quinone **195** (>100:1) based on crude ^1H NMR.



2-hexylnaphthalene-1,4-dione **192**[131] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.83-0.86 (m, 3H), 1.25-1.29 (m, 4H), 1.34-1.37 (m, 2H), 1.50-1.55 (m, 2H), 2.50-2.53 (m, 2H), 6,74 (t, 1H, *J* = 1.4 Hz), 7.66-7.68 (m, 2H), 7.99-8.01 (m, 1H), 8.03-8.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.98, 22.46, 27.91, 28.98, 29.50, 31.48, 125.92, 126.49, 132.04, 132.26, 133.48, 133.51, 134.62, 151.91, 185.11, 185.15.

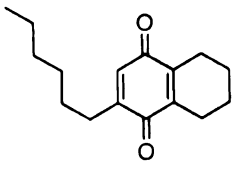


2-butyl-3-(trimethylsilyl)naphthalene-1,4-dione **195**[127]

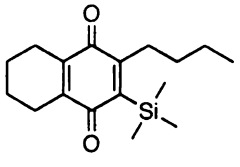
Quinone **195** (27.8 mg, 0.087 mmol, 25%) was prepared from carbene complex **89** (107 mg, 0.343 mmol) with 1-TMS-1-hexyne. A side-product 3-butyl-2,3-dihydroinden-1-one (35.3 mg, 0.188) was also isolated in 55% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.36 (s, 9H), 0.93-0.95 (m, 3H), 1.41-1.45 (m, 4H), 2.67-2.70 (m, 2H), 7.64-7.67 (m, 2H), 7.96-7.98 (m, 1H), 8.01-8.03 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 1.76, 13.94, 23.17, 29.23, 33.48, 125.97, 126.15, 132.21, 133.06, 133.29, 133.34, 148.80, 159.37, 184.64, 189.64.

Reaction of carbene complex 178 with 1-octyne and 1-TMS-1-hexyne: Carbene complex **178** (0.0778 g, 0.25 mmol), 1-octyne (0.0404 mL, 0.38 mmol) and 1-TMS-1-hexyne (0.075 mL, 0.38 mmol) was dissolved in 5 mL benzene and thermolyzed according to Procedure IV to give **193** (0.0492 g, 0.20 mmol, 80%)

and trace amount of the TMS-substituted quinone **196** (>100:1) based on crude ^{1}H NMR.



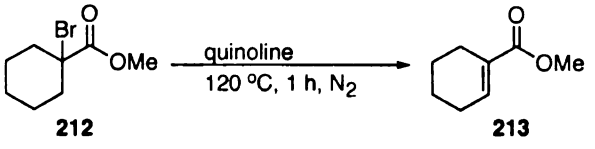
2-Hexyl-5,6,7,8-tetrahydro-[1,4]naphthoquinone **193** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, 3H, *J* = 6.6 Hz), 1.25-1.34 (m, 6H), 1.45-1.48 (m, 2H), 1.66 (m, 4H), 2.35-2.40 (m, 6H), 6.44 (t, 1H, *J* = 1.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.93, 20.90, 21.09, 22.24, 22.42, 22.60, 27.73, 28.84, 28.88, 31.43, 131.91, 141.89, 142.32, 149.03, 187.51, 187.71; IR (neat) 2932, 2861, 1651, 1616, 1294 cm^{-1}; mass spectrum *m/z* (% rel intensity) 246 M^+ (50), 203 (38), 178 (24), 177 (100), 176 (33), 175 (21), 161 (26), 149 (15), 148 (23), 147 (15), 91 (16), 79 (16), 77 (16). Anal Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.84; H, 9.14. Yellow oil; R_f = 0.30 (20: 1: 1 hexanes: Et_2O: CH_2Cl_2).



2-Butyl-3-trimethylsilanyl-5,6,7,8-tetrahydro-[1,4] naphthoquinone **196** Quinone **196** (50.1 mg, 0.155 mmol, 47%) was prepared from carbene complex **178** (103 mg, 0.33 mmol) with 1-TMS-1-hexyne. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.26 (s, 9H), 0.89 (t, 3H, *J* = 7.1 Hz), 1.32-1.35 (m, 4H), 1.62-1.64 (m, 4H), 2.34-2.36 (m, 4H), 2.47-2.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 1.62, 13.89, 21.11, 21.17, 22.45, 22.56, 23.10, 28.66, 33.50, 141.93, 143.48, 145.36, 156.75, 186.77, 192.03; IR (neat) 2938, 1645, 1273, 868, 847

cm^{-1}; mass spectrum *m/z* (% rel intensity) 290 M^+ (10), 276 (35), 275 (36), 247 (18), 234 (31), 233 (84), 73 (18). HRMS (CI) calcd for $C_{17}H_{27}O_2Si$ $(M+H)^+$ *m/z* 291.1780, measd 291.1782. Yellow oil; R_f = 0.41 (20:1:1 hexanes/Et_2O/CH_2Cl_2).

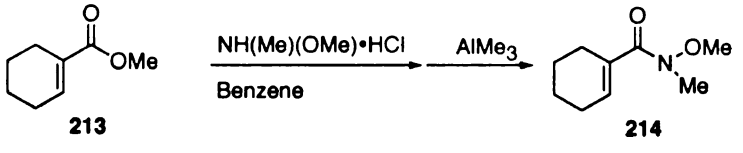
Preparation of methyl cyclohex-1-enecarboxylate 213[16] (Commercially available)



212 213

A solution of **212** (20.0 g, 90.5 mmol) and freshly distilled quinoline (17.1 mL, 145 mmol) was heated at 120 °C with stirring under N_2 for 1 hour. After 15 minutes of heating, a slight exothermic reaction was noted. The mixture was cooled, washed with brine, and dried over $MgSO_4$. Removal of the solvent and distillation of the residue gave **213** (12.69 g, 90.5 mmol) as colorless oil in quantitative yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.56-1.63 (m, 4H), 2.15-2.18 (m, 2H), 2.20-2.24 (m, 2H), 3.69 (s, 3H), 6.94-6.96 (m, 1H). b.p. (76-78 °C at 9 torr).

Preparation of N-methoxy-N-methylcyclohex-1-enecarboxamide 214[133]

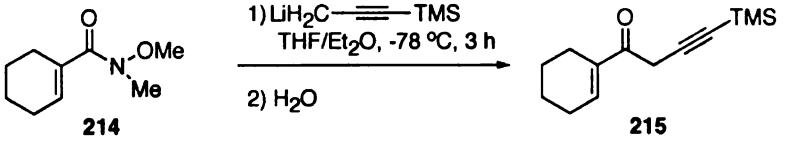


213 214

To a solution of *N*-methoxymethanamine hydrochloride (0.90 g, 0.92 mmol) in 5 mL benzene at 0 °C was added $AlMe_3$ (4.6 mL, 2.0 M in hexanes, 9.2

mmol) dropwise. After the addition was completed, the reaction was warmed to room temperature and stirred one hour. The solution was then transferred via cannula to a solution of methyl 1-carboxy-1-cyclohexene **213** (0.60 mL, 4.40 mmol) in 10 mL benzene at room temperature, and then heated to reflux for 2 hours. The reaction mixture was quenched carefully with ice chips and extracted with CH_2Cl_2 (3 * 10 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by chromatography on silica gel (2:1:1 hexanes/Et_2O/CH_2Cl_2) to afford 87 % of **214** (0.648 g, 3.80 mmol). Some of the following data was taken from the thesis of Marcey Waters. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.61-1.63 (m, 4H), 2.11-2.13 (m, 2H), 2.20-2.24 (m, 2H), 3.20 (s, 3H), 3.63 (s, 3H), 6.12 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.35, 21.88, 24.70, 25.26, 33.42, 60.68, 130.68, 133.51, 171.57; IR (neat) 2934s, 2859m, 1657s, 1642s, 1477m, 1410m, 1376s, 1357m, 1187m, 989m cm^{-1}; mass spectrum *m/z* (% rel intensity) 169 M^+ (3), 110 (8), 109 (100), 81 (77), 79 (25), 55 (7). Anal Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.27. Found: C, 63.85; H, 9.04; N, 8.40. Colorless oil; R_f = 0.10 (4:1:1 hexanes/Et_2O/CH_2Cl_2).

Preparation of 1-cyclohexenyl-4-(trimethylsilyl)but-3-yn-1-one 215

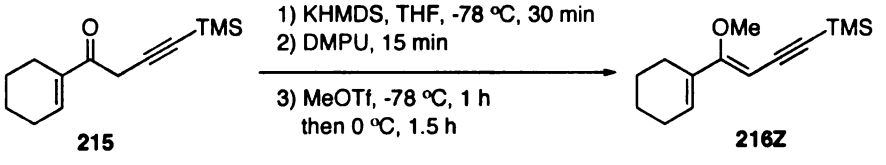


214 215

To a solution of 1-trimethyl-1-propyne (3.98 mL, 24.67 mmol) in 44 mL THF at 0 °C was added *t*-BuLi (1.7 M, 14.5 mL, 24.67 mmol) dropwise. The

reaction was stirred at that temperature for 1 hour, and then transferred via cannula to a solution of amide **214** in 88 mL Et_2O at –78 °C. The solution was stirred at –78 °C for 3 hours and quenched with H_2O. The solution was transferred to a separatory funnel and washed with 30 mL portions of H_2O until the aqueous layer was no longer basic. The aqueous layer was neutralized with 3 N HCl and extracted once with Et_2O. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (10:1:1 hexanes/Et_2O/CH_2Cl_2) to afford 60% of **215** (3.26 g, 14.8 mmol). Some of the following data was taken from the thesis of Marcey Waters. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.16 (s, 9H), 1.60-1.70 (m, 4H), 2.05-2.23 (m, 4H), 3.54 (s, 2H), 6.94 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.19, 21.29, 21.67, 23.03, 26.00, 30.41, 88.88, 99.33, 137.71, 141.84, 193.62; IR (neat) 2937, 2178, 1675, 1638, 1250, 843, 760 cm^{-1}; mass spectrum *m/z* (% rel intensity) 220 M^+ (51), 205 (75), 109 (100), 96 (25), 81 (100), 74 (65), 53 (95). Colorless oil; R_f = 0.41 (10:1:1 hexanes/Et_2O/CH_2Cl_2).

Preparation of ((3Z)-4-cyclohexenyl-4-methoxybut-3-en-1-ynyl) trimethylsilane 216Z

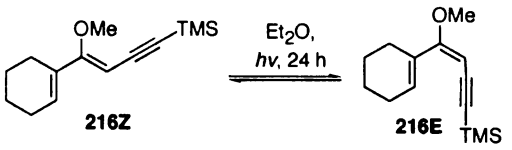


215 **216Z**

To a solution of KHMDS (22.35 mmol, 44.7 mL, 0.5 M solution in toluene) in THF (25 mL) at –78 °C was added ketone **215** (4.47 g, 20.32 mmol), which

was dissolved in 10 mL THF. After stirring for 30 minutes, 25 mL DMPU was added and the solution was stirred for an additional 15 minutes. Upon addition of the MeOTf (2.41 mL, 21.33 mmol), the solution turned yellow-orange. The reaction was stirred at –78 °C for 1 hour and 0 °C for 1.5 hours, and then quenched with 50 mL saturated $NaHCO_3$. The solution was diluted with Et_2O, washed with H_2O (3 * 30 mL) and brine (30 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography using Et_3N-treated silica gel with hexanes as eluent to give 72 % of *Z*-silyl enyne **216Z** (3.43 g, 14.63 mmol). Some of the following data was taken from the thesis of Marcey Waters. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.16 (s, 9H), 1.52-1.56 (m, 2H), 1.60-1.65 (m, 2H), 2.00-2.03 (m, 2H), 2.10-2.14 (m, 2H), 3.97 (s, 3H), 4.95 (s, 1H), 6.29 (t, 1H, J = 4.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -0.08, 21.83, 22.53, 24.89, 25.65, 59.70, 85.71, 99.35, 102.48, 128.26, 131.72, 166.22; IR (neat) 2956, 2937, 2929, 2126, 1630, 1592, 1248, 1224, 1070, 1043, 865, 759 cm^{-1}; mass spectrum *m/z* (% rel intensity) 234 M^+ (25), 219 (25), 89 (50), 73 (35), 59 (40). Anal calcd for $C_{14}H_{22}OSi$: C. 71.73; H, 9.46. Found: C, 71.82; H, 9.69. Yellow oil; R_f = 0.60 (20:1:1 hexanes/Et_2O/CH_2Cl_2). 72% yield.

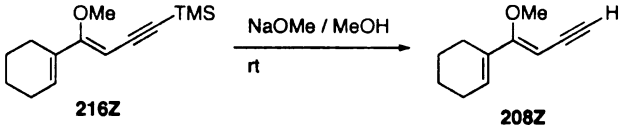
Preparation of *E*-silyl methoxyl enyne 216*E*



Preparative photochemistry was carried out in a Rayonet reactor equipped a Pyrex, water-cooled immersion well with a 450 W Hanovia medium pressure mercury arc light source. Submerging the immersion well in deionized water in a mirrored dewar maintained the temperature between 17~23°C, which fluctuated with the temperature of the cooling water. The immersion well was fitted with a Pyrex (>290 nm) sleeve. The *Z*-silyl enyne **216Z** (2.51 g, 10.7 mmol) was photolyzed in deoxygenated ether (100 mL) for 24 hours using a quartz filter, resulting in a 1:1.3 ratio of *Z*- to *E*- isomers. These isomers could be separated by running column chromatography (4 cm * 40 cm) 3 times using Et_3N-treated silica gel with hexanes as eluent to give combined *E*-isomer in 51% yield (1.28 g, 5.47 mmol) and Z-isomer in 43% yield (1.07 g, 4.57 mmol). Some of the following data was taken from the thesis of Marcey Waters. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.14 (s, 9H), 1.57-1.60 (m, 2H), 1.61-1.66 (m, 2H), 2.12-2.14 (m, 2H), 2.28-2.29 (m, 2H), 3.55 (s, 3H), 4.68 (s, 1H), 6.39-6.40 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 0.05, 21.86, 22.50, 25.29, 25.99, 55.30, 78.90, 96.07, 103.75, 131.09, 132.61, 168.88; IR (neat) 2957, 2936, 2131, 1591, 1248, 1221s, 1124, 941, 758 cm^{-1}; mass spectrum *m/z* (% rel intensity) 234 M^+ (14), 220 (26), 219 (100), 204 (12), 203 (15), 189 (11), 161 (13), 160 (12), 159 (16), 145 (13), 129 (10), 75 (14), 73 (18), 59 (31). Anal calcd for $C_{14}H_{22}OSi$: C. 71.73; H, 9.46.

Found: C, 71.68; H, 9.46. Yellow oil; R_f = 0.65 (20:1:1 hexanes/Et_2O/CH_2Cl_2), 51% yield.

Preparation of 1-(*Z*-1-methoxybut-1-en-3-ynyl)cyclohex-1-ene 208Z

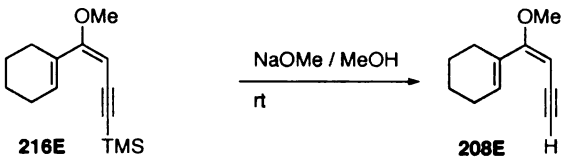


216Z **208Z**

The silyl enyne **216Z** (1.07 g, 4.57 mmol) was dissolved in 8 mL methanol. Approximately 20 mg of freshly prepared NaOMe was added and the solution was stirred at room temperature until all of the starting material was comsumed (monitored by TLC). The reaction was diluted with 20 mL Et_2O and washed three times with 15 mL H_2O. The aqueous layer was back extracted with 20 mL Et_2O. The combined organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography using Et_3N-treated silica gel with hexanes as eluent to give 91% of **208Z** (0.67 g, 4.14 mmol). Some of the following data was taken from the thesis of Marcey Waters. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.53-1.58 (m, 2H), 1.62-1.67 (m, 2H), 2.03-2.06 (m, 2H), 2.11-2.16 (m, 2H), 3.12 (d, 1H, *J* = 2.7 Hz), 3.93 (s, 3H), 4.92 (t, 1H, *J* = 1.4 Hz), 6.27-6.30 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.85, 22.51, 24.99, 25.63, 59.83, 80.71, 81.91, 85.35, 128.53, 131.53, 166.96; IR (neat) 3297, 2931, 2091w, 1631, cm^{-1}; mass spectrum *m/z* (% rel intensity) 162 M^+ (75), 163 (10), 161 (30), 147 (37), 134 (55), 119 (30), 105 (38), 104 (38), 91 (100), 79 (71), 77 (58), 65 (56), 63 (29), 55 (25), 53 (69), 52 (30), 51 (70), 50 (30), 45 (23). Anal

calcd for $C_{11}H_{14}O$: C. 81.44; H, 8.70. Found: C, 81.26; H, 8.66. Yellow oil; R_f = 0.62 (10:1:1 hexanes/Et_2O/CH_2Cl_2).

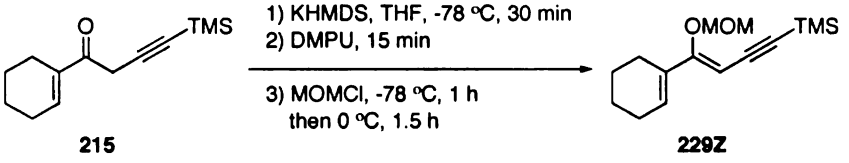
Preparation of 1-(*E*-1-methoxybut-1-en-3-ynyl)cyclohex-1-ene 208E



The silyl enyne **216E** (2.50 g, 10.7 mmol) was dissolved in 8 mL methanol. Approximately 30 mg of freshly prepared NaOMe was added and the solution was stirred at room temperature until all of the starting material was comsumed (monitored by TLC). The reaction was diluted with 20 mL Et_2O and washed three times with 15 mL H_2O. The aqueous layer was back extracted with 20 mL Et_2O. The combined organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography using Et_3N-treated silica gel with hexanes as eluent to give 95% of **208E** (1.64 g, 10.1mmol). Some of the following data was taken from the thesis of Marcey Waters. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.57-1.60 (m, 2H), 1.63-1.65 (m, 2H), 2.11-2.13 (m, 2H), 2.26-2.27 (m, 2H), 2.90 (d, 1H, *J* = 1.7 Hz), 3.56 (s, 3H), 4.61 (d, 1H, *J* = 1.7 Hz), 6.35 (t, 1H, *J* = 1.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.81, 22.46, 25.25, 25.99, 55.28, 77.66, 79.00, 81.65, 130.95, 132.59, 169.08; IR (neat) 3299, 2934, 2099, 1601, 1221, 1186, 1107 cm^{-1}; mass spectrum *m/z* (% rel intensity) 162 M^+ (65), 163 (18), 161 (49), 147 (42), 135 (15), 134 (99), 131 (54), 129 (18), 121 (22), 119 (68), 115 (26), 105 (23), 104 (40), 103 (25), 91 (100), 79 (24), 78 (37),

77 (41), 65 (26) 63 (15), 51 (23), 50 (23). Anal calcd for $C_{11}H_{14}O$: C. 81.44; H, 8.70. Found: C, 81.35; H, 8.83. Yellow oil; R_f = 0.50 (20:1:1 hexanes/Et_2O/CH_2Cl_2).

Preparation of ((3Z)-4-cyclohexenyl-4-(methoxymethoxy)but-3-en-1-ynyl) trimethylsilane 229Z

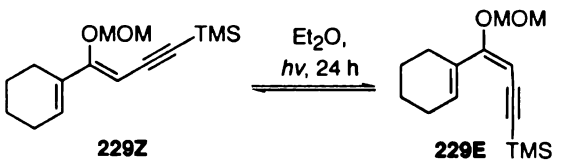


215 229Z

To a solution of KHMDS (33 mmol, 66 mL, 0.5 M solution in toluene) in 40 mL THF at –78 °C was added ketone **215** (6.61 g, 30 mmol), which was dissolved in 15 mL THF. After stirring for 30 minutes, 40 mL DMPU was added and the solution was stirred for an additional 15 minutes. Upon addition of the MOMCl (2.51 mL, 33 mmol), the solution turned yellow-orange. The reaction was stirred at –78 °C for 1 hour and 0 °C for 1.5 hours, and then quenched with saturated $NaHCO_3$ (30 mL). The solution was diluted with Et_2O, washed three times with H_2O, and once with brine. The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography using Et_3N-treated silica gel with hexanes as eluent to furnish 47% of **229Z** (3.73 g, 14.1 mmol) as yellow oil. Some of the following data was taken from the thesis of Marcey Waters. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.16 (s, 9H), 1.53-1.56 (m, 2H), 1.62-1.65 (m, 2H), 2.02-2.04 (m, 2H), 2.14-2.15 (m, 2H), 3.53 (s, 3H), 5.07 (s, 1H), 5.18 (s, 2H), 6.33 (br s, 1H); ^{13}C NMR ($CDCl_3$,

125 MHz) δ -0.10, 21.78, 22.42, 24.93, 25.67, 57.46, 89.35, 97.57, 99.46, 102.07, 128.92, 131.66, 164.30; IR (neat) 2934, 2134, 1590, 1248, 1159, 1011, 841 cm^{-1}; mass spectrum *m/z* (% rel intensity) 264 M^+ (21), 249 (17), 234 (55), 233 (53), 110 (73), 109 (63), 89 (19), 82 (59), 80 (31), 75 (19), 74 (80), 72 (33), 60 (23), 54 (19), 43 (100). HRMS calcd for $C_{15}H_{25}O_2Si$ $(M+H)^+$ *m/z* 265.1624, meas 265.1624. Yellow oil; R_f = 0.42 (10:1:1 hexanes/Et_2O/CH_2Cl_2).

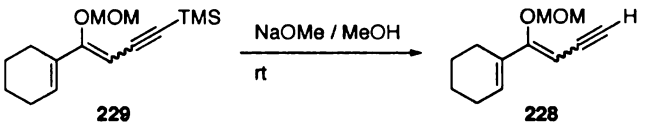
Preparation of *E*-silyl MOM enyne 229E



Preparative photochemistry was carried out in a Rayonet reactor equipped a Pyrex, water-cooled immersion well with a 450 W Hanovia medium pressure mercury arc light source. Submerging the immersion well in deionized water in a mirrored dewar maintained the temperature between 17~23°C, which fluctuated with the temperature of the cooling water. The immersion well was fitted with a Pyrex (>290 nm) sleeve. The *Z*-silyl enyne **229Z** (3.03 g, 15.8 mmol) was photolyzed in deoxygenated ether (100 mL) for 24 hours using a quartz filter, resulting in a 3:1 ratio of *Z*- to *E*- isomers. These isomers could not be separated by column chromatography. After passing though a short flash column with Et_3N-treated silica gel, the mixture went directly to the desilylation step. The following data for **229E** was extracted from the spectra on a mixture of *E*- and *Z*-isomers. Partial spectrum for **229E** ^1H NMR ($CDCl_3$, 300 MHz) δ 0.14 (s, 9H),

1.57-1.65 (m, 4H), 2.11-2.14 (m, 2H), 2.28-2.32 (m, 2H), 3.55 (s, 3H), 4.68 (s, 2H), 6.40-6.42 (m, 1H); mass spectrum *m/z* (% rel intensity) 264 M^+ (25), 249 (17), 235 (14), 234 (31), 233 (100), 221 (13), 219 (12), 205 (23), 204 (14), 182 (31), 181 (10), 131 (14), 109 (60), 106 (52), 81 (35), 79 (22), 77 (44), 75 (16), 73 (29), 51 (13), 50 (14); Yellow oil; R_f = 0.42 (10:1:1 hexanes/Et_2O/CH_2Cl_2).

Preparation of 1-((*Z/E*)-1-(methoxymethoxy)but-1-en-3-ynyl)cyclohex-1-ene 228



229 228

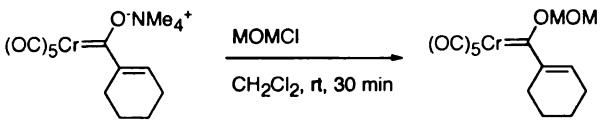
The silyl enyne **229** (3.0 g, 113 mmol, 3:1 *Z/E*) was dissolved in 30 mL methanol. Approximately 40 mg of NaOMe was added and the solution was stirred at room temperature until all of the starting material had disappeared (monitored by TLC). The reaction was diluted with 30 mL Et_2O and washed three times with 20 mL H_2O. The aqueous layer was back extracted with 30 mL Et_2O. The combined organic layer was dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The isomers were purified by column chromatography (4 cm * 40 cm) three times using Et_3N-treated silica gel with hexanes as eluent to give 1.90 g of **228** (3:1 *Z/E*, 100 mmol, 89%).

Z*-MOM enyne 228*Z Some of the following data was taken from the thesis of Marcey Waters. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.53-1.55 (m, 2H), 1.62-1.64 (m, 2H), 2.03-2.06 (m, 2H), 2.13-2.14 (m, 2H), 3.10 (d, 1H, *J* = 2.6 Hz), 3.51

(s, 3H), 5.01 (s, 1H), 5.15 (s, 2H), 6.31 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.72, 22.34, 24.95, 25.57, 57.39, 80.42, 81.89, 88.29, 97.48, 129.03, 131.50, 164.77; IR (neat) 3292m, 2929s, 2829m, 2090w, 1590m, 1158s, 1048m, 997s, 973m cm^{-1}; mass spectrum *m/z* (% rel intensity) 192 M^+ (12), 109 (78), 81 (27), 45 (100). HRMS (CI) calcd for $C_{12}H_{17}O_2$ $(M+H)^+$ *m/z* 193.1229, meas 193.1236. Colorless oil; R_f = 0.35 (10:1:1 hexanes/Et_2O/CH_2Cl_2).

E*-MOM enyne 228*E ^1H NMR ($CDCl_3$, 500 MHz) δ 1.58-1.62 (m, 2H), 1.63-1.66 (m, 2H), 2.14-2.16 (m, 2H), 2.28-2.31 (m, 2H), 2.93 (d, 1H, *J* = 2.7 Hz), 3.41 (s, 3H), 4.94 (s, 2H), 4.98 (d, 1H, *J* = 2.7 Hz), 6.37 (t, 1H, *J* = 1.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.80, 22.45, 25.33, 26.11, 56.25, 79.69, 81.33, 82.51, 94.35, 131.44, 132.19, 166.45; IR (neat) 3297, 2934, 2097, 1597, 1156, 1061, 1049, 976 cm^{-1}; mass spectrum *m/z* (% rel intensity) 192 M^+ (4), 109 (88), 81 (29), 45 (100). HRMS calcd for $C_{12}H_{17}O_2$ $(M+H)^+$ *m/z* 193.1229, meas 193.1236. Colorless oil; R_f = 0.45 (10:1:1 hexanes/Et_2O/CH_2Cl_2).

Preparation of MOM-carbene complex 227

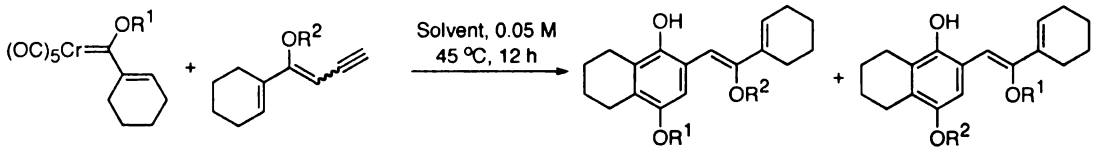


211 227

Carbene complex **227** (1.07 g, 3.09 mmol) was prepared from the corresponding ammonium salt **211** (1.50 g, 4.0 mmol) and MOMCl (0.334 mL, 4.4 mmol) according to Procedure I in 77% yield. ^1H NMR ($CDCl_3$, 500 MHz) δ1.59-1.68 (m, 4H), 2.17-2.30 (m, 4H), 3.64 (s, 3H), 5.76 (s, 2H), 6.26 (br, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.37, 21.78, 25.52, 25.59, 58.24, 102.81, 134.40, 154.06, 216.54, 223.98, 349.53; IR (neat) 2837, 2862, 2060, 1906, 1617, 1451, 1192, 1161, 1065, 656 cm^{-1}; mass spectrum *m/z* (% rel intensity) 346 M^+ (0.1), 318 (1), 290 (2), 263 (48), 232 (20), 231 (18), 109 (100), 91 (22), 81 (77), 79 (79). Red oil, R_f = 0.19 (hexanes).

General procedure for the thermolysis of the following carbene complexes and enynes (Procedure V)



178 R^1 = Me
178* R^1 = CD_3
227 R^1 = MOM

208 R^2 = Me
228 R^2 = MOM

209* R^1 = CD_3, R^2 = CH_3
230 R1 = Me, R^2 = MOM

209 R^1 = CH_3, R^2 = CD_3
231 R1 = MOM, R^2 = Me

The carbene complex, alkyne (2 equiv.) and solvent (0.05 M) were combined in a Schlenk flask equipped with a threaded high-vacuum Teflon stopcock. The mixture was deoxygenated with three freeze-pump-thaw cycles, and then warmed to room temperature and filled with Ar. The stopcock was then sealed and the reaction was placed in a 45 °C oil bath for 12 hours. The reaction was cooled to room temperature, and completion of the reaction was verified by TLC against starting carbene complex. The solution was transferred to a round bottom flask and concentrated *in vacuo*. The remaining brown film was dissolved in 10 mL Et_2O and stirred in air at room temperature for 2 hours to demetallate the products. The solution was then filtered through Celite, concentrated, and a

crude ^{1}H NMR spectrum was taken to determine the product ratio. The product was then purified by column chromatography with Et_3N-treated silica gel using 20:1:1 hexanes/CH_2Cl_2/Et_2O as eluent.

The ratio of **209/209*** was determined by the integral of crude ^{1}H NMR in C_6D_6 for the following peaks: δ 3.22 (vinyl OMe) and δ 3.49 (aryl OMe). This ratio was further conformed by ^{1}H NMR in $CDCl_3$ of isolated phenol mixtures: δ 3.53 (vinyl OMe) and δ 3.74 (aryl OMe). .

The ratio of **230** to **231** was determined by the integral of the major isomer (Z-isomer) in crude ^{1}H NMR in C_6D_6 (for *E*-enyne) or $CDCl_3$ (for *Z*-enyne) for the following peaks: δ 4.63, 4.99 (in C_6D_6) or 4.76, 5.10 (in $CDCl_3$). Since the crude ^{1}H NMR for reactions with *E*-enyne was quite complex and could contain some *E*-isomers of **230** and **231**, the product ratio in entry 5 in Table 3.2 was determined by the following ways: first, the crude products were taken in $CDCl_3$ and completely isomerized to *Z*-isomers; second, the products were pass through a short silica gel column; third, the products were combined after isolating on silica gel chromatography. In all there cases, the ratio of the products was 1:3, which was consistent with the ratio taken in the aforementioned method.

Annulation of carbene complex 178* with alkyne 208Z in benzene ($R^1 = CD_3$, $R^2 = CH_3$)

The reaction of carbene complex **178*** (112 mg, 0.35 mmol) with alkyne **208Z** (113 mg, 0.70 mmol) in 7 mL benzene was performed according to the general procedure to give 75 mg of **209/209*** (0.235 mmol, 67%) in 1:1 ratio.

Annulation of carbene complex 178* with alkyne 208Z in hexanes ($R^1 = CD_3$, $R^2 = CH_3$)

The reaction of carbene complex **178*** (112 mg, 0.35 mmol) with alkyne **208Z** (113 mg, 0.70 mmol) in 7 mL hexanes was performed according to the general procedure to give 90 mg of **209/209*** (0.283 mmol, 81%) in 1:2 ratio.

Annulation of carbene complex 178* with alkyne 208E in benzene ($R^1 = CD_3$, $R^2 = CH_3$)

The reaction of carbene complex **178*** (112 mg, 0.35 mmol) with alkyne **208E** (113 mg, 0.70 mmol) in 7 mL benzene was performed according to the general procedure to give 40 mg of **209/209*** (0.126 mmol, 36%) in 1:1 ratio.

Annulation of carbene complex 178* with alkyne 208E in hexanes ($R^1 = CD_3$, $R^2 = CH_3$)

The reaction of carbene complex **178*** (112 mg, 0.35 mmol) with alkyne **208E** (113 mg, 0.70 mmol) in 7 mL hexane was performed according to the general procedure to give 55 mg of **209/209*** (0.174 mmol, 50%) in 1:1 ratio.

Annulation of carbene complex 227 with alkyne 208Z in benzene (R^1 = MOM, $R^2 = CH_3$)

The reaction of carbene complex **227** (112 mg, 0.35 mmol) with alkyne **208Z** (113 mg, 0.70 mmol) in 7 mL benzene was performed according to the

general procedure to give 38 mg of **231** (0.11 mmol, 32%). The ratio of **231/230** was 4:1 based on the crude ^{1}H NMR.

Annulation of carbene complex 227 with alkyne 208Z in hexanes (R^1 = MOM, R^2 = CH_3)

The reaction of carbene complex **227** (121 mg, 0.35 mmol) with alkyne **208Z** (113 mg, 0.70 mmol) in 7 mL hexanes was performed according to the general procedure to give 89 mg of **231** (0.26 mmol, 74%). The ratio of **231/230** was 5:1 based on the crude ^{1}H NMR.

Annulation of carbene complex 178 with alkyne 228Z in benzene (R^1 = CH_3, R^2 = MOM)

The reaction of carbene complex **178** (94.8 mg, 0.30 mmol) with alkyne **228Z** (115 mg, 0.60 mmol) in 6 mL benzene was performed according to the general procedure to give 26 mg of **231** (0.076 mmol, 25%) and 32 mg of **230** (0.093 mmol, 31%). The ratio of **231/230** was 1:1 based on the crude ^{1}H NMR.

Annulation of carbene complex 178 with alkyne 228Z in hexanes (R^1 = CH_3, R^2 = MOM)

The reaction of carbene complex **178** (94.8 mg, 0.30 mmol) with alkyne **228Z** (115 mg, 0.60 mmol) in 6 mL hexanes was performed according to the general procedure to give 15 mg of **231** (0.044 mmol, 15%) and 33 mg of **230** (0.096 mmol, 32%). The ratio of **231/230** was 1:3 based on the crude ^{1}H NMR.

Annulation of carbene complex 227 with alkyne 208E in benzene (R^1 = MOM, $R^2 = CH_3$)

The reaction of carbene complex **227** (173 mg, 0.50 mmol) with alkyne **208E** (162 mg, 1.0 mmol) in 10 mL benzene was performed according to the general procedure to give 60.2 mg of **231** and **230** (0.175 mmol, 35%). The ratio of **231/230** was 3:1 based on the crude ^1H NMR, and the ^1H NMR of the combined isolated products.

Annulation of carbene complex 227 with alkyne 208E in hexanes (R^1 = MOM, $R^2 = CH_3$)

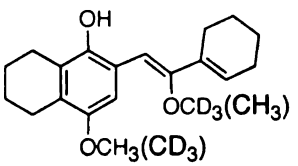
The reaction of carbene complex **227** (173 mg, 0.50 mmol) with alkyne **208E** (162 mg, 1.0 mmol) in 10 mL hexanes was performed according to the general procedure to give 58.6 mg of **231** (0.170 mmol, 34%). The ratio of **231/230** was 3:1 based on the crude ^1H NMR, and the ^1H NMR of the combined isolated products.

Annulation of carbene complex 178 with alkyne 228E in benzene ($R^1 = CH_3$, R^2 = MOM)

The reaction of carbene complex **178** (47.4 mg, 0.15 mmol) with alkyne **228E** (57.6 mg, 0.30 mmol) in 3 mL benzene was performed according to the general procedure to give 19 mg of **231** (0.055 mmol, 37%). The ratio of **231/230** was 5:1 based on the crude ^1H NMR.

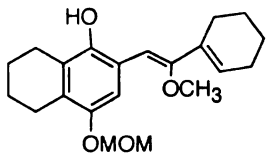
Annulation of carbene complex 178 with alkyne 228E in hexanes ($R^1 = CH_3$, R^2 = MOM)

The reaction of carbene complex **178** (47.4 mg, 0.15 mmol) with alkyne **228E** (57.6 mg, 0.30 mmol) in 6 mL hexanes was performed according to the general procedure to give 20 mg of **231** (0.058 mmol, 39%). The ratio of **231/230** was 4:1 based on the crude ^{1}H NMR. Some of the following data was taken from the thesis of Marcey Waters.

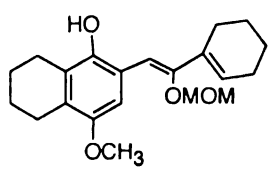


Phenol **209** and **209*** (R^1, R^2 = Me, CD_3) ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.60-1.64 (m, 2H), 1.70-1.76 (m, 6H), 2.19-2.24 (m, 4H), 2.62 (t, 2H, *J* = 5.8 Hz), 2.72 (t, 2H, *J* = 5.8 Hz), 3.53 (s, 3H), 3.74 (s, 3H), 5.93 (s, 1H), 6.21 (t, 1H, *J* = 3.9 Hz), 6.38 (s, 1H), 8.24 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.04, 22.25, 22.52, 22.64, 23.54, 24.05, 25.39, 25.63, 55.56, 60.35, 108.64, 110.59, 117.35, 125.90, 127.42, 127.47, 130.67, 146.04, 150.35, 153.56; ^{1}H NMR(C_6D_6, 500 MHz,) δ 1.40-1.43 (m, 2H), 1.47-1.51 (m, 2H), 1.63-1.68 (m, 4H), 1.97-2.02 (m, 4H), 2.88 (t, 2H, J = 6.0 Hz), 3.07 (t, 2H, J = 6.1 Hz), 3.22 (s, 3H), 3.49(s, 3H), 6.03 (s, 3H), 6.13 (t, 1H, J = 4.0 Hz), 6.48 (s, 1H), 8.51 (s, 1H); IR (neat) 3245m, 2938s, 2857s, 2836s, 2247w, 1943w, 1727w, 1713w, 1632m, 1612m, 1477s, 1464s, 1436s, 1320s, 1310s, 1246s, 1114s, 1098s, 1065s, 1038s cm^{-1}; mass spectrum *m/z* (% rel intensity) 317 M^+ (27), 287 (21), 285 (100), 283 (24), 282 (91), 274 (33), 257 (38), 254 (37), 251 (20), 141 (18), 128 (19), 77 (35).

HRMS (FAB) calcd for $(C_{20}H_{23}D_3O_3+H)^+$ *m/z* 317.2070, meas 317.2072. Yellow oil; R_f = 0.32 (20:1:1 hexanes/CH_2Cl_2/Et_2O).



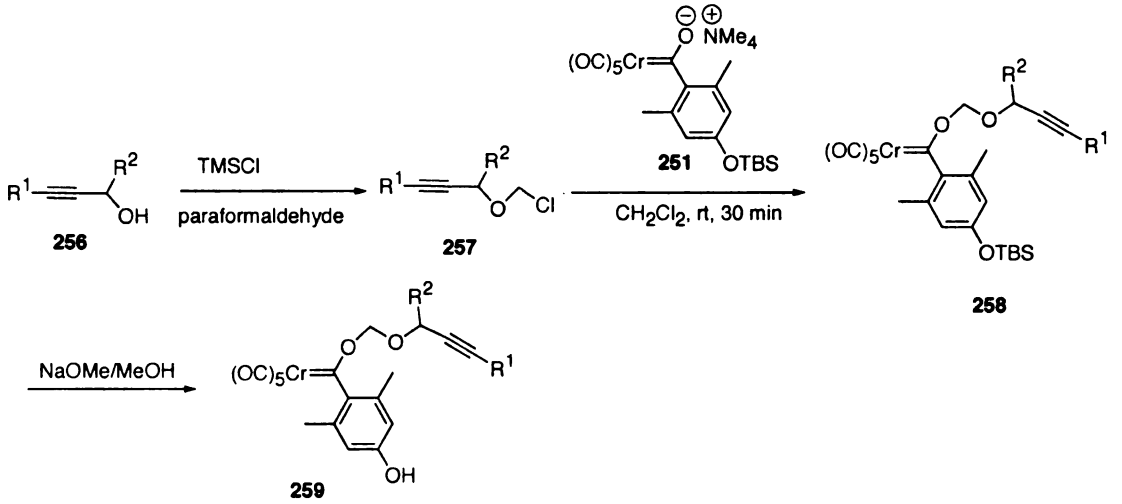
Phenol **231** (R^1 = MOM, R^2 = Me) ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.59-1.63 (m, 2H), 1.72-1.75 (m, 6H), 2.19-2.20 (m, 4H), 2.65 (t, 2H, *J* = 6.0 Hz), 2.71-2.72 (t, 2H, *J* = 5.8 Hz), 3.47 (s, 3H), 3.52 (s, 3H), 5.10 (s, 2H), 5.90 (s, 1H), 6.20 (s, 1H), 6.63 (s, 1H), 8.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.03, 22.26, 22.51, 22.63, 23.78, 24.05, 25.39, 25.63, 55.89, 60.41, 95.18, 110.65, 113.12, 117.77, 125.93, 127.27, 128.37, 130.67, 147.02, 148.02, 153.49; IR (neat) 3230m (br), 2930s, 2857m, 2096w, 1475m, 1314m, 1151m, 1090m, 1048s, 1036s, 982m cm^{-1}; mass spectrum *m/z* (% rel intensity) 344 M^+ (29), 299 (36), 267(22), 128 (27), 115 (22), 109 (21), 91 (21), 81 (23), 79 (25), 77 (17), 45 (100). HRMS calcd for $C_{21}H_{29}O_4$ $(M+H)^+$ *m/z* 345.2066, meas 345.2058. Yellow oil; R_f = 0.45 (10:1:1 hexanes/CH_2Cl_2/Et_2O).



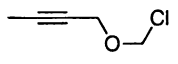
Phenol **230** (R^1 = Me, R^2 = MOM) ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.60-1.63 (m, 2H), 1.69-1.75 (m, 6H), 2.18-2.21 (m, 2H), 2.22-2.25 (m, 2H), 2.60-2.62 (m, 2H), 2.68-2.69 (m, 2H), 3.32 (s, 3H), 3.74 (s, 3H), 4.76 (s, 2H), 6.02 (s, 1H), 6.25 (t, 1H, *J* = 4.1 Hz), 6.41 (s, 1H), 7.55 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.98, 22.23, 22.48, 22.59, 23.49, 24.02, 25.59, 25.62,

55.47, 57.95, 98.23, 108.38, 111.23, 117.81, 126.64, 127.25, 127.30, 131.37, 145.33, 150.52, 151.05; IR (neat) 3300m (br), 2928s, 2066w, 1473m, 1448m, 1436m, 1318m, 1264w, 1246w, 1162m, 1123m, 1111m, 1093m, 1083m, 1064m, 1006m, 960w cm^{-1}; Mass spectrum *m/z* (% rel intensity) 344 M^+ (17), 219 (19), 217 (72), 204 (27), 203 (36), 175 (19), 128 (26), 115 (23), 109 (69), 105 (17), 91 (26), 81 (92), 79 (38), 67 (15), 53 (21), 45 (100). HRMS calcd for $C_{21}H_{29}O_4$ $(M+H)^+$ *m/z* 345.2066, meas 345.2080. Yellow oil; R_f = 0.37 (10:1:1 hexanes/CH_2Cl_2/Et_2O).

General procedure for the preparation of carbene complexes 259 illustrated for complex 259a. (Procedure VI)

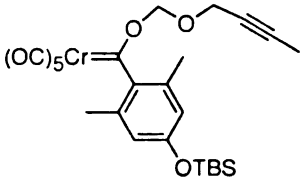


Series a (R^1 = Me, R^2 = H)



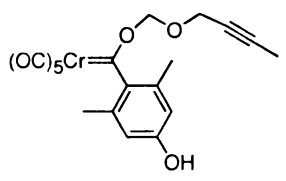
2-Butyn-1-ol (175 mg, 2.50 mmol) was added dropwise to a suspension of paraformaldehyde (75.0 mg, 2.50 mmol) in trimethylchlorosilane

(10.0 mmol, 1.25 mL) at RT. The mixture was stirred at RT until the paraformaldehyde was consumed. The clear solution was evaporated under reduced pressure to remove the excess trimethylchlorosilane to afford 1-(2-butynyl)chloromethoxy ether **257a**. The purity of the chloromethyl ether was checked by ^{1}H NMR, and then used without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.82 (t, 3H, *J* = 2.2 Hz), 4.29 (q, 2H, *J* = 2.2 Hz), 5.54 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 54.98, 56.60, 72.48, 80.05, 84.30.



The freshly prepared chloromethyl ether **257a** (2.50 mmol) in 5 mL CH_2Cl_2 was added dropwise to a solution of ammonium salt **251** (recrystallized from CH_2Cl_2) (1.08 g, 2.00 mmol) in 20 mL CH_2Cl_2 at RT. The resulting red solution was stirred at RT for 15 minutes under argon, and then passed through a short silica gel column (3 * 10 cm) to give 91% of the TBS-protected carbene complex **258a** (980 mg, 1.82 mmol) as red oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.18 (s, 6H), 0.95 (s, 9H), 1.84 (s, 3H), 2.09 (s, 6H), 4.52 (s, 2H), 5.25 (s, 2H), 6.47 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ –4.46, 12.36, 13.50, 19.52, 25.58, 57.69, 72.70, 90.73, 97.14, 119.54, 128.15, 144.85, 155.24, 216.26, 224.65, 365.35; IR (neat) 2957m, 2932m, 2860m, 2230vw, 2064s, 1991s, 1941vs, 1601m, 1471w, 1315m, 1157s, 1060m, 841s, 656s cm^{-1}; mass spectrum *m/z* (% rel intensity) 510 (M^+–CO) (0.09), 398 (M^+–5CO) (18), 369 (23),

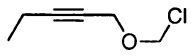
368 (63), 275 (57), 263(24), 163 (16), 125 (25), 105 (16), 75 (35), 73 (73), 53 (55), 52 (100). Red oil; R_f = 0.60 (9:1 hexanes/Et_2O).



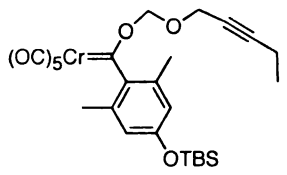
The TBS-protected carbene complex **258a** (2.14 g, 3.97 mmol) was dissolved in 20 mL dry Et_2O, and then treated with two equivalents of NaOMe in methanol. The reaction was stirred under argon at RT until TLC showed complete desilylation. The reaction mixture was then quenched with water, and extracted with Et_2O (2 * 10 mL). The combined organic layer was washed with brine (10 mL), dried over $MgSO_4$, concentrated and chromatograghed (2:1 hexanes/EtOAc as eluent) to afford 59% of the carbene complex with free hydroxy group **259a** (995 mg, 2.35 mmol) as red oil. In most cases the carbene complex was characterized as the TBS derivative **258**. The *para*-phenol complex **258** was typically generated and utilized in the next step directly although it could be stored for periods of a day or so without decomposition. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.84 (s, 3H), 2.11 (s, 6H), 4.52 (s, 2H), 4.84 (s, 1H), 5.26 (s, 2H), 6.48 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.56, 19.47, 57.80, 72.60, 85.07, 97.08, 114.96, 128.74, 144.32, 155.17, 216.24, 224.56, 365.39; IR (neat) 3397brw, 2965w, 2933w, 2231w, 2068s, 1917vs, 1609s, 1456m, 1309m, 1236m, 1152m, 897m, 791m cm^{-1}; mass spectrum *m/z* (% rel intensity) 424 M^+ (0.07), 159 (31), 149 (63), 122 (35), 119 (33), 115 (22), 108 (15), 107 (47), 104 (17), 91 (47), 82 (16), 80 (34), 79 (25), 77 (47), 69 (24),

65 (17), 54 (18), 53 (55), 52 (100), 50 (16). Anal calcd for $C_{19}H_{16}CrO_8$: C. 53.78; H, 3.80. Found: C, 53.60; H, 4.22. Red oil; R_f = 0.20 (2:1 hexanes/EtOAc).

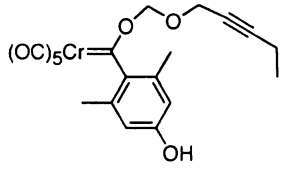
Series b (R^1 = Et, R^2 = H)



The chloromethyl ether **257b** was prepared from 2-pentyn-1-ol (210 mg, 2.50 mmol) according to the general procedure. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.09-1.16 (m, 3H), 2.19-2.24 (m, 2H), 4.35 (t, 2H, *J* = 2.2 Hz), 5.58 (s, 2H).

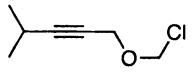


The carbene complex **258b** (1.07 g, 1.94 mmol) was prepared from the salt **251** (1.08 g, 2.00 mmol) and chloromethyl ether **257b** (2.50 mmol) in 97% yield as red oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.18 (s, 6H), 0.96 (s, 9H), 1.12 (t, 3H, *J* = 7.7 Hz), 2.10 (s, 6H), 2.17 (qt, 2H, *J* = 7.7, 2.2 Hz), 4.55 (t, 2H, *J* = 2.2 Hz), 5.26 (br s, 2H), 6.48 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ –4.44, 12.39, 13.52, 18.16, 19.53, 25.60, 57.71, 72.74, 90.76, 97.19, 119.56, 128.17, 144.91, 155.26, 216.28, 224.66, 365.40; IR (neat) 2959m, 2934m, 2861w, 2064s, 1991s, 1937s, 1601m, 1473w, 1315m, 1157s, 1069m, 841s, 655s cm^{-1}; mass spectrum *m/z* (% rel intensity) 552 M^+ (0.02), 412 (25), 410(16), 383 (26), 382 (79), 380 (23), 301 (20), 263 (22), 179 (30), 126 (17), 107 (16), 80 (31), 75 (33), 73 (68), 67 (16), 52 (100); Anal calcd for $C_{26}H_{32}CrO_8Si$: C. 56.51; H, 5.84. Found: C, 56.66; H, 5.99. Red Oil; R_f = 0.25 (9:1 hexanes/CH_2Cl_2).

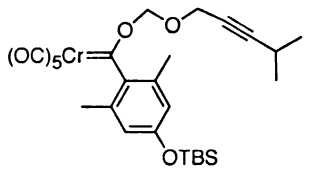


The carbene complex **258b** (1.05 g, 1.90 mmol) was desilylated according to the above procedure to give a 46% yield of phenol carbene complex **259b** (384 mg, 0.877 mmol) as red oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.12 (t, 3H, *J* = 7.4 Hz), 2.11 (s, 6H), 2.20 (qt, 2H, *J* = 7.4, 2.2 Hz), 4.55 (t, 2H, *J* = 2.2 Hz), 5.28 (br s, 2H), 6.48 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.37, 13.49, 19.50, 57.73, 72.67, 90.81, 97.01, 114.96, 128.69, 144.22, 155.22, 216.24, 224.56, 365.31; IR (neat) 3407brw, 2982w, 2938w, 2232vw, 2064s, 1937vs, 1607m, 1308m, 1238m, 1152m, 1069m, 891m, 654m cm^{-1}; mass spectrum *m/z* (% rel intensity) 438 M^+ (0.03), 410 (0.05), 216 (15), 188 (16), 187 (55), 149 (100), 137 (17), 121 (27), 115 (16), 108 (33), 91 (37), 80 (42), 79 (18), 77 (35), 74 920), 67 (22), 65 (17), 59 (24), 55 (19), 54 (22), 52 (69), 51 (23). Anal calcd for $C_{20}H_{18}CrO_8$: C. 54.80; H, 4.14. Found: C, 55.04; H, 4.37. Red oil; R_f = 0.24 (4:1 hexanes/Et_2O).

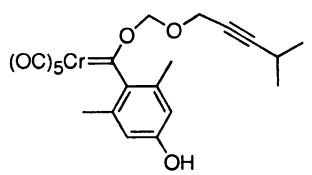
Series c (R^1 = *i*-Pr, R^2 = H)



The chloromethyl ether **257c** was prepared from 4-methyl-2-pentyn-1-ol (392 mg, 4.00 mmol) according to the general procedure. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17 (d, 6H, *J* = 7.1 Hz), 2.56-2.59 (m, 1H), 4.35 (d, 2H, *J* = 2.2 Hz), 5.57 (s, 2H).



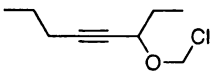
The carbene complex **258c** (1.16 g, 2.04 mmol) was prepared from the salt **251** (1.61 g, 3.00 mmol) and chloromethyl ether **257c** in 68% yield as red oil. ^{1}H NMR ($CDCl_3$) δ 0.18 (s, 6H), 0.96 (s, 9H), 1.14 (d, 6H, *J* = 6.9 Hz), 2.10 (s, 6H), 2.55 (m, 1H), 4.55 (d, 2H, *J* = 2.2 Hz), 5.25 (br s, 2H), 6.48 (s, 2H); ^{13}C NMR ($CDCl_3$) δ –4.47, 18.14, 19.51, 19.56, 20.39, 22.39, 22.73, 25.57, 65.56, 93.45, 97.36, 119.43, 119.63, 127.87, 128.30, 144.88, 155.20, 216.32, 224.63, 364.69; IR (neat) 2936m, 2250w, 2086s, 1935vs, 1601m, 1474w, 1315m, 1156s, 910s, 841s, 656s cm^{-1}; mass spectrum *m/z* (% rel intensity) 538 (M^+ – CO) (0.03), 426 (M^+ – 5CO, 32), 397 (31), 396 (100), 358 (19), 357 (79), 351 (21), 329 (25), 303 (36), 301 (39), 263 (57), 229 (18), 219 (18), 215 (17), 191 (15), 179 (40), 163 (22), 126 (21), 125 (20), 108 (19), 103 (18), 102 (21), 91 (19), 82 (34), 81 (38), 79 (52), 75 (40), 74 (30), 73 (91), 72 (77), 57 (19), 52 (68). Red oil; R_f = 0.40 (4:1 hexanes/Et_2O).



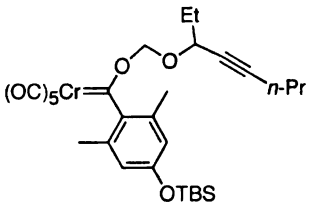
The carbene complex **258c** (467 mg, 0.825 mmol) was desilylated according to the above procedure to give a 55% yield of phenol carbene complex **259c** (206 mg, 0.456 mmol) as red oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.13 (d, 6H, *J* = 6.9 Hz), 2.11 (s, 6H), 2.56 (sept, 1H, *J* = 6.9 Hz), 3.76 (br s, 1H), 4.55 (d, 2H, *J* = 1.9 Hz), 5.25 (s, 2H), 6.48 (s, 2H); ^{13}C NMR ($CDCl_3$, 75

MHz) δ 19.52, 20.48, 22.62, 57.64, 72.49, 94.85, 96.95, 114.93, 128.69, 144.30, 155.18, 216.24, 224.56, 365.33; IR (neat) 3402brm, 2976m 2936w, 2257vw, 2068s, 1927vs, 1608m, 1590m, 1454m, 1308m, 1237m, 1150s, 1070s, 898s, 709s cm^{-1}; mass spectrum *m/z* (% rel intensity) 452 M^+ (0.03), 312 $(M - 5CO)^+$ (2), 187 (30), 180 (15), 149 (100), 121 (30), 91 (15), 90 (18), 80 (27), 79 (19), 77 (31), 53 (16), 52 (42). Red oil; R_f = 0.15 (1:1 hexanes/CH_2Cl_2).

Series d (R^1 = *n*-Pr, R^2 = Et)

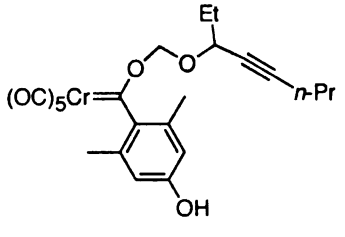


The chloromethyl ether **257d** was prepared from 4-octyn-3-ol (315 mg, 2.50 mmol) according to the general procedure. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.97 (t, 3H, *J* = 7.4 Hz), 0.98 (t, 3H, *J* = 7.1 Hz), 1.52 (m, 2H), 1.72 (m, 2H), 2.19 (td, 2H, *J* = 7.2 Hz, 1.9 Hz), 4.46 (t, 1H, *J* = 6.3 Hz), 5.56 (d, 1H, *J* = 5.4 Hz), 5.72 (d, 1H, *J* = 5.4 Hz).



The carbene complex **258d** (1.16 g, 1.95 mmol) was prepared from the salt **251** (1.05 g, 1.95 mmol) and chloromethyl ether **257d** in 100% yield as red oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.18 (s, 6H), 0.94 (t, 3H, *J* = 7.4 Hz), 0.96 (s, 9H), 1.03 (t, 3H, *J* = 7.5 Hz), 1.49 (q, 2H, *J* = 7.5 Hz), 1.80 (m, 2H), 2.10 (s, 6H), 2.16 (td, 2H, *J* = 6.8, 1.9 Hz), 4.67 (t, 1H, *J* = 6.4 Hz), 5.20 (br

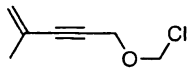
s, 1H), 5.43 (br s, 1H), 6.47 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ –4.48, 9.43, 13.36, 18.14, 19.44, 19.54, 20.58, 21.92, 25.58, 29.08, 71.06, 88.59, 97.67, 119.46, 119.62, 127.90, 128.24, 145.00, 155.21, 216.33, 224.63, 364.34; IR (neat) 2963m, 2936m, 2886w, 2237vw, 2084s, 1940vs, 1601m, 1471m, 1315m, 1253m, 1155s, 1064m, 912m, 841s, 655s cm^{-1}; mass spectrum *m/z* (% rel intensity) 594 M^+ (0.03), 454 $(M - 5CO)^+$ (19), 425 (18), 424 (47), 423 (37), 422 (91), 420 (25), 385 (15), 373 (15), 372 (24), 371 (22), 358 (20), 357 (33), 356 (39), 343 (16), 330 (20), 329 (53), 327 (25), 315 (23), 271 (17), 263 (63), 257 (33), 243 (17), 191 (23), 165 (16), 163 (18), 128 (19), 125 (18), 115 (19), 75 (36), 74 (24), 73 (100), 72 (64), 59 (18), 57 (36), 56 (28), 55 (24), 52 (47), 51 (25). Anal calcd for $C_{29}H_{38}CrO_8Si$: C, 58.57; H, 6.44. Found: C, 57.88; H, 6.58. Red oil; R_f = 0.13 (hexanes).



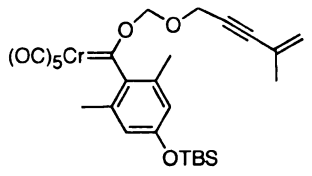
The carbene complex **258d** (951 mg, 1.60 mmol) was desilylated according to the above procedure to give a 40% yield of phenol carbene complex **259d** (309 mg, 0.643 mmol) as red oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, 3H, *J* = 7.4 Hz), 1.03 (t, 3H, *J* = 7.4 Hz), 1.49 (q, 2H, *J* = 7.1 Hz), 1.80 (m, 2H), 2.12 (s, 6H), 2.17 (t, 2H, *J* = 7.1 Hz), 4.67 (br s, 1H), 5.28 (br s, 1H), 5.44 (br, 1H), 6.48 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.43, 13.37, 19.44, 19.55, 20.58, 21.90, 29.07, 71.15, 88.72, 97.54, 114.88, 115.02, 128.46, 128.82, 144.40, 155.12, 216.31, 224.56, 364.30; IR (neat) 3400brw, 2970w, 2933w,

2881w, 2237vw, 2064s, 1943vs, 1149m, 904m, 654m cm^{-1}; mass spectrum *m/z* (% rel intensity) 480 M^+ (0.03), 318 (32), 290 (15), 289 (77), 275 (16), 261 (22), 25), 247 (43), 245 (47), 231 (25), 220 (17), 219 (17), 218 (19), 217 (100), 203 (40), 189 (39) 187 (20), 175 (42), 161 (27), 159 (15), 149 (65), 147 (22), 145 (16), 13 (20), 128 (18), 122 (31), 121 (31), 119 (19), 115 (24), 109 (18), 108 (49), 107 939), 105 (30), 97 (24), 95 (15), 94 (18), 93 (26), 91 (58), 81 (37), 80 (76), 79 (69), 78 (19), 77 (69), 69 (23), 67 (54), 65 (25), 57 (35), 55 (46), 53 (38), 52 (98). Red oil; R_f = 0.25 (4:1 hexanes/Et_2O).

Series e (R^1 = *i*-Propenyl, R^2 = H)

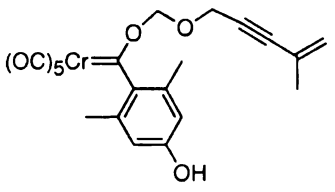


The chloromethyl ether **257e** was prepared from 4-methylpent-4-ene-2-yn-1-ol (384 mg, 4.00 mmol) according to the general procedure. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.87 (s, 3H), 4.48 (s, 2H), 5.26 (s, 1H), 5.32 (s, 1H), 5.57 (s, 2H).



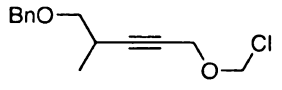
The carbene complex **258e** (919 mg, 1.63 mmol) was prepared from the salt **251** (1.34 g, 2.50 mmol) and chloromethyl ether **257e** in 65% yield and obtained as red oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.18 (s, 6H), 0.96 (s, 9H), 1.86 (s, 3H), 2.10 (s, 6H), 4.69 (s, 2H), 5.27-5.30 (m, 4H), 6.48 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ –4.44, 18.15, 19.54, 23.07, 25.59, 57.63,

81.24, 89.47, 97.03, 119.58, 123.29, 125.72, 128.19, 144.86, 155.30, 216.25, 224.64, 365.59; IR (neat) 2957w, 2932w, 2220vw, 2064s, 1940s, 1601w, 1315w, 1155w, 841m, 653m cm^{-1}; mass spectrum *m/z* (% rel intensity) 564 M^+ (0.08), 263 (17), 262 (25), 221 (23), 220 (40), 207 (46), 191 (16), 179 (94), 177 (12), 163 (16), 149 (14), 107 (62), 105 (27), 86 (64), 84 (98), 80 (100), 77 (16), 75 (100), 73 (47), 59 (55), 57 (16), 51 (100), 49 (94), 45 (27). Red oil; R_f = 0.24 (9:1 hexanes/CH_2Cl_2).

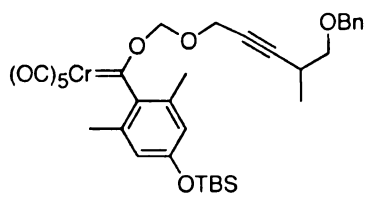


The carbene complex **257e** (722 mg, 1.28 mmol) was desilylated according to the above procedure to give a 50% yield of phenol carbene complex **548e** (287 mg, 0.637 mmol) as red oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.86 (s, 3H), 2.12 (s, 6H), 4.69 (s, 2H), 5.05 (br s, 4H), 6.47 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ19.53, 23.09, 57.66, 81.19, 89.48, 96.84, 114.97, 123.37, 125.69, 128.75, 144.27, 155.18, 216.23, 224.56, 365.52; IR (neat) 3384brw, 2959w, 2928w, 2228vw, 2064sm 1940vs, 1609m, 1456m, 1307m, 1236m, 1150m, 1064m, 897m, 653s cm^{-1}; mass spectrum *m/z* (% rel intensity) 394 (M^+ - 2CO) (0.2), 228 (12), 213 (15), 187 (10), 185 (16), 149 (100), 121 (16), 115 (12), 108 (11), 91 (29), 80 916), 79 (30), 78 (14), 77 (52), 53 (15), 52 (23), 51 915). Red oil; R_f = 0.21 (2:1 hexanes/Et_2O).

Series f



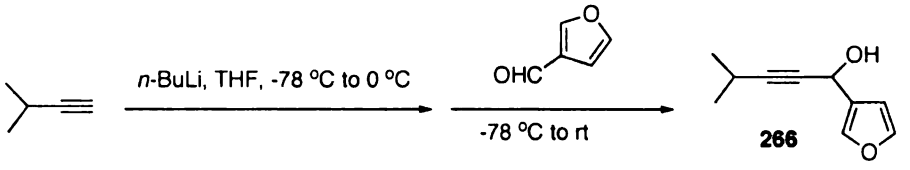
The chloromethyl ether **273** was prepared from 4 -((benzyloxy)methyl)pent-2-yn-1-ol (334 mg, 1.64 mmol) according to the general procedure. ^{1}H NMR ($CDCl_3$) δ 1.19 (d, 3H, *J* = 6.9 Hz), 2.77 (m, 1H), 3.37 (m, 1H), 3.49 (m, 1H), 4.36 (d, 2H, *J* = 2.2 Hz), 4.54 (s, 2H), 5.56 (s, 2H), 7.32 (m, 5H).



The carbene complex **274** (748 mg, 1.11 mmol) was prepared from the salt **251** (700 mg, 1.30 mmol) and chloromethyl ether **273** in 86% yield and obtained as red oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.18 (s, 6H), 0.96 (s, 9H), 1.18 (d, 3H, *J* = 7.1 Hz), 2.08 (s, 6H), 2.77 (m, 1H), 3.36 (m, 1H), 3.47 (m, 1H), 4.51 (s, 2H), 4.56 (d, 2H, *J* = 2.2 Hz), 5.24 (br s, 2H), 6.47 (s, 2H), 7.27-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ –4.44, 17.45, 18.15, 19.54, 25.59, 26.83, 57.56, 73.02, 73.60, 74.30, 91.03, 97.00, 119.55, 127.57, 127.65, 128.17, 128.35, 138.05, 144.91, 155.27, 216.26, 224.64, 365.58; IR (neat) 2959w, 2933w, 2862w, 2243w, 2064s, 1943vs, 1601m, 1471w, 1316m, 1156m, 841m, 655s cm^{-1}. Red oil; R_f = 0.45 (9:1 hexanes/EtOAc).

The carbene complex **274** (560 mg, 0.832 mmol) was desilylated according to the above procedure to give a 36% yield of phenol carbene complex **250** (175 mg, 0.313 mmol) as red oil.

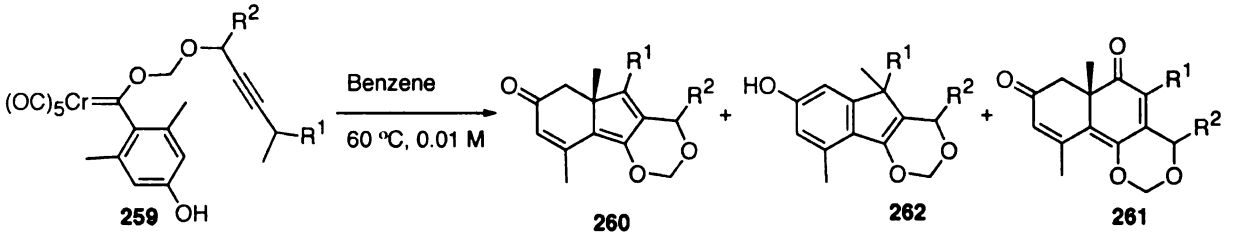
Preparation of 1-(furan-3-yl)-4-methylpent-2-yn-1-ol



266

To a solution of *iso*propyl acetylene (1.0 mL, 9.8 mmol) in 20 mL THF at –78 °C was added *n*-BuLi (2.5 M, 4.0 mL, 10 mmol) dropwise. The mixture was stirred at –78 °C fro 10 minutes then warmed up to 0 °C for 1 hour. After cooling down again to –78 °C, the aldehyde (1.15 mL, 13.3 mmol) was added dropwise. The reaction was allowed to warm to room temperature and then quenched with saturated NH_4Cl solution (20 mL). The aqueous layer was isolated and extracted with Et_2O (2 * 20 mL). The combined organic layer was dried over $MgSO_4$, concentrated. The crude product was isolated by chromatography using 9:1 hexanes/Et_2O as eluent to give 1.63 g of alcohol **266** (9.8 mmol, 99%). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.17(d, 6H, *J* = 6.9 Hz), 1.99 (d, 1H, *J* = 6.9 Hz), 2.59-2.62 (septet, 1H, *J* = 6.9 Hz), 5.35 (d, 1H, *J* = 6.3 Hz), 6.48 (d, 1H, *J* = 1.4 Hz), 7.36 (t, 1H, *J* = 1.4 Hz), 7.48 (t, 1H, *J* = 1.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.48, 22.83, 57.42, 78.62, 91.44, 109.21, 127.08, 140.11, 143.51; IR (neat) 3350 br, 2971m, 2933w, 2871w, 2253w, 1503w, 1320w, 1159w, 1022s, 875m cm^{-1}; mass spectrum *m/z* (% rel intensity) 164 M^+ (55), 149 (49), 148 (17), 147 (100), 135 (28), 121 (97), 117 (17), 107 (25), 105 (18), 103 (22), 95 (31), 93 (37), 91 (72), 79 (29), 77 (55), 67 (25), 65 (40), 55 (18), 53 (32), 51 (28), 50 (22). Colorless oil; R_f = 0.23 (10% Et_2O in hexanes).

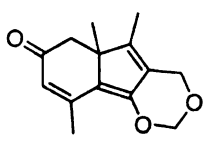
General procedure for the intramolecular tautomer-arrested annulation of carbene complex 259 illustrated for complex 259a. (Procedure V)



259 260 262 261

Thermolysis of 259a. (R^1 = Me, R^2 = H)

The carbene complex **259a** (155 mg, 0.365 mmol) was dissolved in 36.5 mL benzene (0.01 M) and transferred to a schlenk flask equipped with a threaded Teflon high vacuum stopcock. The reaction was deoxygenated by the freeze-thaw procedure for 3 cycles. The flask was filled with argon at room temperature, sealed and heated at 60 °C. After the reaction was completed (indicated by the color of the carbene complex), the reaction mixture was cooled to room temperature, and the solvent was removed *in vacuo*. The residue was dissolved in 1:1 mixture of CH_2Cl_2 and Et_2O and stirred in air at room temperature. After stirring 2 hours, the solution was passed through Celite 503, concentrated, and then purified by chromatography to afford 51% of the cyclized product **260a** (44.5 mg, 0.193 mmol).

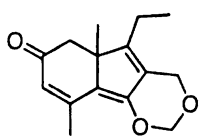


Compound **260a** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.06 (s, 3H), 1.79 (s, 3H), 1.88 (d, 1H, *J* = 14.8 Hz), 2.17 (s, 3H), 2.43 (d, 1H, *J* = 14.8 Hz), 4.69 (s, 2H), 5.16 (s, 2H), 5.61 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.16, 20.50,

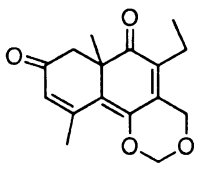
22.55, 46.28, 51.47, 65.28, 92.16, 120.14, 120.80, 125.38, 150.03, 150.30, 152.07, 198.81; IR (neat) 2958w, 2920w, 1642s, 1575s, 1443w, 1424w, 1180m, 1072m cm^{-1}; mass spectrum *m/z* (% rel intensity) 233 (48), 232 M^+ (94), 203 (17), 202 (96), 187 (75), 174 (85), 159 (100), 131 (51), 115 (21), 91 (27), 51 (15). Yellow solid, mp 88-90 °C; R_f = 0.23 (9:1 hexanes/Et_2O).

Thermolysis of 259b. (R^1 = Et, R^2 = H)

A solution of carbene complex **259b** (134 mg, 0.307 mmol) in 30.7 mL benzene was heated according to the general procedure to give 9% of compound **260b** (7.0 mg, 0.0284 mmol) and 25% of compound **261b** (21.0 mg, 0.0768 mmol) after purification.



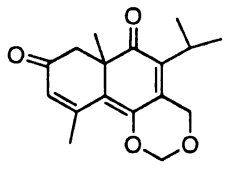
Compound **260b** ^1H NMR ($CDCl_3$, 300 MHz) δ 1.07 (t, 3H, *J* = 7.7 Hz), 1.10 (s, 3H), 1.95 (d, 1H, *J* = 14.8 Hz), 2.19 (s, 3H), 2.22-2.32 (m, 2H), 2.42 (d, 1H, *J* = 14.8 Hz), 4.76 (s, 2H), 5.18 (s, 2H), 5.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.09, 19.30, 20.65, 22.57, 46.54, 51.76, 65.50, 91.98, 119.72, 120.84, 125.53, 150.15, 150.36, 157.90. 198.86; IR (neat) 2924m, 1635s, 1578s, 1456m, 1180m, 1074m, 918m cm^{-1}; mass spectrum *m/z* (% rel intensity) 246 M^+ (55), 216 (30), 188(100), 187 (73), 160 (28), 159 (38), 131 (27), 91 (15). HRMS (CI) calcd for $(C_{15}H_{18}O_3+H)^+$ *m/z* 247.1334, meas 247.1323. Yellow oil; R_f = 0.25 (2:1 Hexanes/EtOAc).



Compound **261b** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98 (t, 3H, *J* = 7.4 Hz), 1.19 (s, 3H), 2.10-2.20 (m, 1H), 2.26 (d, 1H, *J* = 16.8 Hz), 2.30 (s, 3H), 2.35-2.44 (m, 1H), 2.85 (d, 1H, *J* = 16.8 Hz), 4.81 (q, 2H, *J* = 16.5 Hz), 5.09 (d, 1H, *J* = 5.7 Hz), 5.24 (d, 1H, *J* = 5.7 Hz), 5.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.12, 17.83, 24.79, 26.96, 44.07, 48.57, 65.18, 90.63, 122.56, 127.60, 135.37, 136.66, 145.81, 151.81, 196.97, 200.84; IR (neat) 2971, 1659, 1626, 1363, 1251, 1184, 1076 cm^{-1}; mass spectrum *m/z* (% rel intensity) 274 M^+ (38), 259 (15), 231 (26), 230 (21), 229 (100), 216 (38), 215 (27), 202 (17), 201 (56), 188 (27), 159 (23), 93 (19), 91 (17), 77 (20), 65 (15). Yellow solid, mp 126-128 °C; R_f = 0.11 (2:1 hexanes/EtOAc).

Thermolysis of **259c**. (R^1 = *i*-Pr, R^2 = H)

A solution of carbene complex **259c** (206 mg, 0.456 mmol) in 45.6 mL benzene was heated according to the general procedure to give 16% of compound **261c** (20.3 mg, 0.705 mmol) after purification.

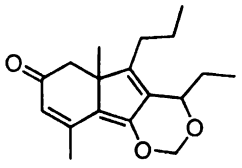


Compound **261c** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15 (s, 3H), 1.16 (d, 3H, *J* = 6.8 Hz), 1.27 (d, 3H, *J* = 6.8 Hz), 2.27 (d, 1H, *J* = 17.0 Hz), 2.31 (s, 3H), 2.58 (m, 1H), 2.81 (d, 1H, *J* = 17.0 Hz), 4.72 (d, 1H, *J* = 16.8 Hz), 4.95 (d, 1H, *J* = 16.8 Hz), 5.07 (d, 1H, *J* = 5.5 Hz), 5.23 (d, 1H, *J* = 5.5 Hz), 5.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.68, 21.22, 24.91, 25.90, 27.36, 29.70,

43.46, 65.47, 90.41, 121.93, 127.72, 135.65, 138.60, 146.16, 151.40, 197.20, 201.32; IR (neat) 2926m, 1661s, 1615m, 1383m, 1251m, 1186m, 1074s cm^{-1}; mass spectrum *m/z* (% rel intensity) 289 (16), 288 M^+ (57), 273 (18), 259 (20), 258 (86), 245 (52), 244 (100), 243 (26), 231 (26), 216 (33), 215 (40); 203 (17), 201 (24), 189 (18), 188 (24), 187 (43), 176 (19), 173 (24), 159 (26), 145 (20), 131 (15), 115 (20), 91 (23), 77 (30), 51 (16). Yellow solid; R_f = 0.22 (1:1 hexanes/Et_2O).

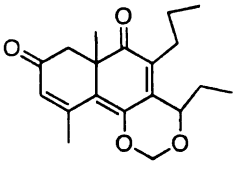
Thermolysis of 259d. (R^1 = *n*-Pr, R^2 = Et)

A solution of carbene complex **259d** (120 mg, 0.250 mmol) in 25.0 mL benzene was heated according to the general procedure to give 18% of compound **260d** (13.1 mg, 0.0455 mmol) and 21% of compound **261d** (16.8 mg, 0.0532 mmol) after purification.



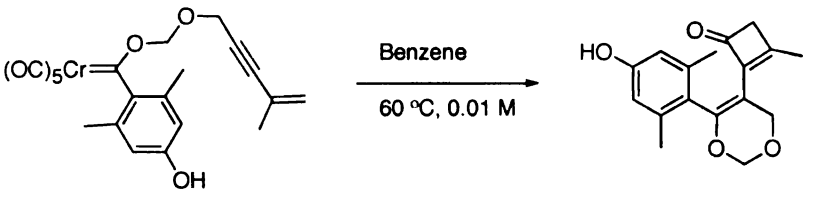
Compound **260d** ^1H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, 3H, *J* = 7.4 Hz), 1.01 (t, 3H, *J* = 7.4 Hz), 1.09 (s, 3H), 1.12-1.40 (m, 2H), 1.50-1.62 (m, 1H), 1.81-1.88 (m, 2H), 1.93 (d, 1H, *J* = 14.7 Hz), 2.10-2.26 (m, 1H), 2.19 (s, 3H), 2.53 (d, 1H, *J* = 14.7 Hz), 4.70 (t, 1H, *J* = 6.1 Hz), 5.09 (d, 1H, *J* = 5.8 Hz), 5.25 (d, 1H, *J* = 5.8 Hz), 5.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.33, 14.69, 20.68, 22.51, 22.76, 25.69, 28.83, 46.77, 51.77, 76.13, 88.87, 119.58, 120.72, 129.67, 150.42, 150.90, 157.34, 198.89; IR (neat) 2963m, 1657m, 1632s, 1568s, 1557m, 1425w, 1182w, 1065m, 922m cm^{-1}; mass spectrum *m/z* (% rel intensity) 288 M^+ (34), 258 (46), 243 (21), 229 (25), 217 (16), 216 (96), 215 (100), 201 (39), 188

(39), 187 (67), 173 (23), 171 (15), 159 (31), 145 (20), 143 (17), 141 (20), 129 (26), 128 (51), 115 (32), 105 (21), 93 (18), 91 (39), 77 (26), 65 (19), 57 (15), 55 (18), 53 (17). HRMS (CI) calcd for $(C_{18}H_{24}O_3+H)^+$ *m/z* 289.1804, meas 289.1818. Yellow gel; R_f = 0.30 (1:1 Hexanes/Et_2O).



Compound **261d** ^{1}HNMR ($CDCl_3$, 300 MHz) δ 0.97 (t, 3H, *J* = 7.5 Hz), 1.04 (t, 3H, *J* = 7.4 Hz), 1.16 (s, 3H), 1.33-1.40 (m, 1H), 1.45-1.49 (m, 1H), 1.82-1.88 (m, 2H), 2.10-2.16 (m, 1H), 2.28 (dd, 1H, *J* = 16.7, 1.1 Hz), 2.31 (s, 3H), 2.37-2.39 (m, 1H), 2.82 (dd, 1H, *J* = 16.7, 1.1 Hz), 4.94 (dd, 1H, *J* = 7.1, 4.0 Hz), 4.97(d, 1H, *J* = 5.8 Hz), 5.21 (d, 1H, *J* = 5.8 Hz), 5.86 (t, 1H, *J* = 1.1 Hz); ^{13}CNMR ($CDCl_3$, 75 MHz) δ 9.12, 14.54, 21.90, 24.81, 26.49, 28.14, 28.61, 43.79, 48.42, 74.79, 88.10, 121.12, 127.34, 135.42, 141.05, 148.85, 151.33, 197.06, 202.44; IR (neat) 2967m, 2930w, 2874w, 1771w, 1663s, 1620w, 1361w, 1076, 1012w cm^{-1}; mass spectrum *m/z* (% rel intensity) 316 M^+ (17), 286 (39), 271 (100), 257 (22), 243 (63), 173 (43), 215 (55), 201 (25), 187 (39), 159 (24), 149 (29), 129 (16), 128 (37), 115 (24), 107 (23), 93 (20), 92 (38), 91 (45), 79 (27), 77 (19), 76 (35), 67 (27), 64 (15), 57 (19), 55 (26), 53 (20). HRMS (FAB) calcd for $C_{19}H_{24}O_4$ *m/z* 317.1755, meas 317.1753. Yellow gel; R_f = 0.27 (2:1 hexanes/Et_2O).

Thermolysis of 259e.



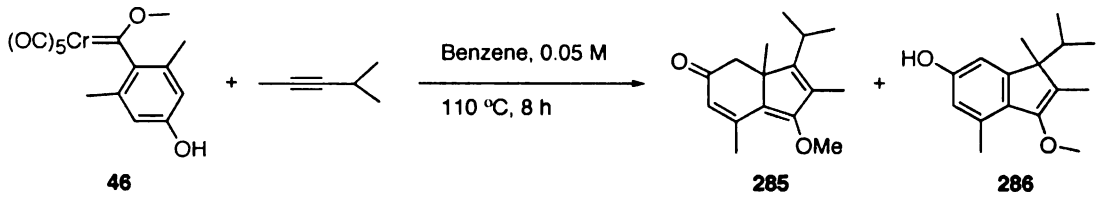
259e **269**

A solution of carbene complex **259e** (184 mg, 0.408 mmol) in 40.8 mL benzene was heated according to the general procedure to give 58% of compound **269** (59.1mg, 0.207 mmol) after purification. Compound **269** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.56 (s, 3H), 2.20 (s, 6H), 2.96 (s, 2H), 4.61 (s, 2H), 5.15 (s, 2H), 5.40 (s, 1H), 6.50 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.49, 19.75, 51.67, 64.53, 90.38, 105.44, 114.53, 126.31, 139.23, 140.96, 150.59, 156.03, 168.65, 188.81; IR (neat) 3400br, 2924m, 2857w, 1754s, 1611m, 1318m, 1194s, 1157m, 1017m, 904w, 736w cm^{-1}; mass spectrum *m/z* (% rel intensity) 286 M^+ (20), 241 (59), 213 (58), 185 (23), 149 (100), 121 (28), 91 (33), 77 (27). HRMS (FAB) calcd for $C_{17}H_{18}O_4$ *m/z* 286.1204, meas 286.1205. Light yellow solid, m.p. 152-154 °C; R_f = 0.31 (1:1 hexanes/Et_2O).

Thermolysis of 250

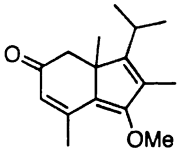
A solution of carbene complex **250** (87.0 mg, 0.156 mmol) in 15.6 mL benzene was heated according to the general procedure to give unstable cyclized product, which was decomposed during isolation.

Reaction of complex 46 with *iso*-propylmethylacetylene



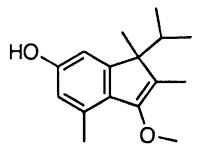
46 **285** **286**

A solution containing 0.486 mmol carbene complex **46** (173 mg) and 0.97 mmol alkyne (79.5 mg) in 9.72 mL benzene was deoxygenated by the freeze-thaw method and heated at 110 °C for 8 hours. The reaction mixture was cooled to RT, and then diluted with Et_2O. After stirring 2 hours at RT in air, the solution was passed through Celite 503, concentrated, and then purified by chromatography (2:1 hexanes/EtOAc as eluent) to give 44% of compound **285** (52.1 mg, 0.212 mmol) and 15% of compound **286** (17.9 mg, 0.0728 mmol).



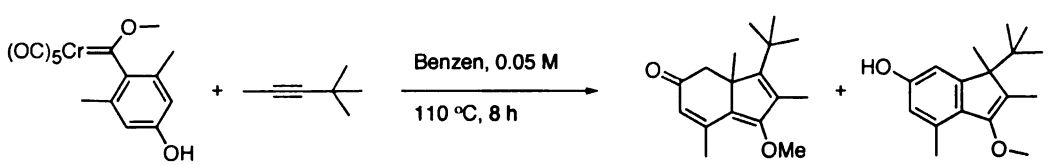
Compound **285** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.06 (s, 3H), 1.12 (d, 3H, *J* = 7.1 Hz), 1.20 (d, 3H, *J* = 7.2 Hz), 1.88 (d, 1H, *J* = 15.1 Hz), 1.93 (s, 3H), 2.21 (s, 3H), 2.55 (d, 1H, *J* = 15.0 Hz), 2.62 (sept, 1H, *J* = 7.1 Hz), 3.72 (s, 3H), 5.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.76, 20.29, 21.31, 21.70, 21.79, 27.04, 46.34, 52.35, 60.73, 122.69, 128.07, 131.82, 149.44, 159.89, 163.19, 199.55; IR (neat) 2963m, 2932w, 1655s, 1626m, 1570s, 1445w, 1318m, 1119w cm^{-1}; mass spectrum *m/z* (% rel intensity) 247 (54), 246 M$^+$ (100), 245 (22), 244 (44), 231 (57), 204 (37), 203 (89), 201 (35), 189 (38), 188 (15), 187 (17), 176 (15), 175 (63), 173 (22), 171 (17), 161 (26), 160 (18), 159 (17), 145

(22), 115 (15), 91 (21), 77 (16). Anal calcd for $C_{16}H_{22}O_2$: C. 78.01; H, 9.00. Found: C, 77.67; H, 8.95. Yellow solid, 30-32 °C; R_f = 0.24 (2:1 hexanes/Et_2O).



Compound **286** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.54 (d, 3H, *J* = 6.6 Hz), 0.94 (d, 3H, *J* = 6.6 Hz), 1.16 (s, 3H), 1.79 (s, 3H), 1.89 (m, 1H), 2.44 (s, 3H), 3.72 (s, 3H), 4.81 (s, 1H), 6.43 (s, 1H), 6.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.72, 17.32, 17.91, 21.86, 33.83, 51.92, 60.14, 60.20, 108.46, 115.24, 129.86, 130.04, 130.66, 151.65, 152.96, 153.37; IR (neat) 3386 br, 2983s, 2932m, 2874w, 1644w, 1609 m, 1468m, 1360m, 1306m, 1145m cm^{-1}; mass spectrum *m/z* (% rel intensity) 247 (31), 246 M$^+$ (95), 231 (61), 204 (29), 203 (100), 189 (26), 175 (38), 171 (17), 161 (25), 149 (32), 91 (18). HRMS (FAB) calcd for $C_{16}H_{22}O_2$ *m/z* 246.1619, meas 246.1620. Yellow oil; R_f = 0.37 (2:1 hexanes/Et_2O).

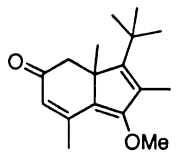
Reaction of complex 46 with *tert*-butylmethylacetylene



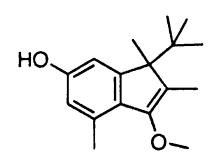
46 **287** **288**

A solution containing 0.40 mmol carbene complex **46** (142 mg) and 0.60 mmol alkyne (77.0 mg) in 8 mL benzene was deoxygenated by the freeze-thaw method and heated at 110 °C for 8 hours. The reaction mixture was cooled to RT, and then diluted with Et_2O. After stirring 2 hours at RT in air, the solution was

passed through Celite, concentrated. The crude product was purified by chromatography (2:1 hexanes/EtOAc as eluent) to give 18% of compound **287** (18.6 mg, 0.0715 mmol) and 41% of compound **288** (42.8 mg, 0.165 mmol).

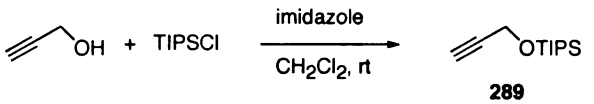


Compound **287** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24 (s, 3H), 1.28 (s, 9H), 1.99 (s, 3H), 2.07 (d, 1H, *J* = 15.3 Hz), 2.22 (s, 3H), 2.98 (d, 1H, *J* = 15.3 Hz), 3.69 (s, 3H), 5.72 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.40, 20.48, 22.70, 30.83, 35.96, 47.26, 53.88, 60.83, 122.84, 129.05, 133.40, 149.13, 159.45, 164.43, 199.83; IR (neat) 2961m, 1655s, 1622s, 1570m, 1547m, 1447m, 1395m, 1329m, 1124m cm^{-1}; mass spectrum *m/z* (% rel intensity) 261 (47), 260 M$^+$ (100), 245 (18), 204 (53), 203 (20), 189 (69), 175 (17), 161 (22); yellow solid, mp 50-55 °C; R_f = 0.21 (2:1 hexanes/Et_2O).



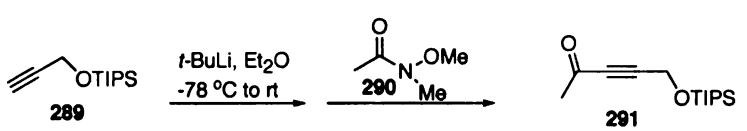
Compound **288** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (s, 9H), 1.18 (s, 3H), 1.90 (s, 3H), 2.44 (s, 3H), 3.72 (s, 3H), 4.69 (brs, 1H), 6.42 (s, 1H), 6.71 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.72, 17.72, 17.86, 27.22, 35.81, 54.76, 59.87, 110.13, 115.13, 129.43, 130.54, 130.79, 152.37, 152.78, 154.85; IR (neat) 3387brm, 2961s, 1635m, 1597m, 1359s, 1302m, 1251m, 1155m, 1136m, 1708m, 1007m, 860w cm^{-1}; mass spectrum *m/z* (% rel intensity) 260 M$^+$ (5), 204 (17), 203 (100), 188 (9), 145 (5). HRMS (FAB) calcd for $C_{17}H_{24}O_2$ *m/z* 260.1777; meas 260.1776. White solid; decomposed at >140 °C; R_f = 0.38 (2:1 hexanes/Et_2O).

Preparation of tri*iso*propyl(prop-2-ynyloxy)silane 289[70]



To the solution of propargyl alcohol (1.28 mL, 22 mmol) and TIPSCl (4.28 mL, 20 mmol) was added imidazole (1.77 g, 26 mmol). The mixture was stirred at room temperature for 12 hours, and then quenched with saturated $NaHCO_3$ (20 mL). The solution was diluted with Et_2O (20 mL), washed three times with H_2O (20 mL), and once with brine (20 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product **289** (4.14 g, 19.5 mmol, 97%) was purified by distillation. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.09 (m, 21H), 2.39 (t, 1H, *J* = 2.4 Hz), 5.06 (d, 2H, *J* = 2.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.89, 17.81, 51.69, 72.57, 82.34.

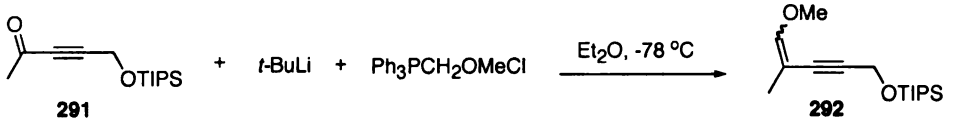
Preparation of ketone 291[70]



To a round bottom flask containing alkyne **289** (10.62 g, 50 mmol) and 100 mL Et_2O at –78 °C, *tert*-butyl lithium (32.3 mL, 55 mmol) was added dropwise. The reaction mixture was stirred for 1 hour at –78 °C, and then the amide **290** was added dropwise. The reaction was stirred for 1 more hour at –78 °C, and then warmed up to –20 °C for 2 hours and 1 hour at room temperature.

After addition of 50 mL water, the separated aqueous layer was extracted with Et_2O (3 * 25 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (9:1 hexanes/Et_2O as eluent) to give 73% of ketone **291** (9.65 g, 36.5 mmol). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.08 (m, 21H), 2.36 (s, 3H), 4.55 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.85, 17.80, 32.50, 51.73, 84.04, 90.25, 184.19; IR (neat) 2945s, 2893m, 2888s, 2209w, 1684s, 1464m, 1360m, 1221s, 1105s, 1071m, 997w, 883m, 685m cm^{-1}; mass spectrum *m/z* (% rel intensity) 212 $(M-42)^+$ (22), 211 (100), 169 (54), 153 (10), 142 (12), 141 (74), 139 (16), 125 (33), 113 (12), 111 (13), 75 (13), 61 (10), 45 (10).). Anal calcd for $C_{14}H_{26}O_2Si$: C, 66.09; H, 10.30. Found: C, 65.78; H, 10.56. Yellow oil; R_f = 0.55 (9:1 hexanes/Et_2O).

Preparation of enol ether 292[70]



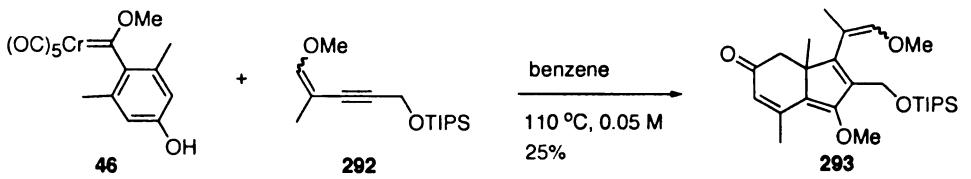
In a round bottom flask containing 10 mL Et_2O was introduced Ph_3PCH_2OMeCl (0.754 g, 2.2 mmol). The solution was cooled to –78 °C, and *t*-BuLi (1.29 mL, 1.7 M, 2.2 mmol) was added dropwise. The red reaction mixture was stirred for 0.5 hour. Then the ketone **291** (0.300 g, 1.2 mmol) was added and the mixture was stirred at –78 °C for 2 more hours. Before warming up to room temperature, 5 mL H_2O was added. The separated aqueous layer was extracted

with Et_2O (3 * 15 mL). The combined organic layer was dried over $MgSO_4$, filtrate and the amount of Et_2O was reduced to about 10 mL. Hexanes (10 mL) was added to the solution to remove maximum amount of phosphine oxide. After filtration and evaporation, the mixture was purified on a column chromatography using 2% EtOAc in hexanes as eluent to give *cis*-isomer (69 mg, 0.244 mmol) in 20% yield and *trans*-isomer (48 mg, 0.170 mmol) in 14% yield.

***Cis*-292**[70]: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.07 (m, 21H), 1.66 (d, 3H, J = 1.5 Hz), 3.64 (s, 3H), 4.53 (s, 2H), 6.14 (q, 1H, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.05, 17.26, 17.95, 52.64, 60.11, 81.82, 92.19, 94.67, 151.87; IR (neat) 2942, 2867, 2218, 1684, 1647, 1464, 1258, 1211, 1145, 883, 683 cm^{-1}; mass spectrum *m/z* (% rel intensity) 282 M^+ (1), 267 (16), 247 (19), 239 (100), 233 (22), 209 (79), 198 (22), 197 (99), 184 (48), 167 (37), 152 (45), 145 (38), 139 (29), 109 (78), 89 (23), 79 (19), 77 (24), 75 (30), 59 (17). Light yellow oil; R_f = 0.50 (95:5 hexanes/EtOAc).

***Trans*-292**[70]: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.07 (m, 21H), 1.67 (d, 3H, J = 1.6 Hz), 3.64 (s, 3H), 4.45 (s, 2H), 6.33 (q, 1H, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.06, 13.73, 17.95, 52.49, 60.08, 85.10, 85.24, 96.71, 152.91; IR (neat) 2946, 2868, 2220, 1645, 1464, 1233, 1138, 1091, 886, 683 cm^{-1}; mass spectrum *m/z* (% rel intensity) 282 M^+ (1), 281 (5), 267 (15), 247 (17), 239 (42), 216 (28), 152 (26), 145 (33), 137 (25), 120 (15), 117 (21), 109 (100). Light yellow oil; R_f = 0.60 (95:5 hexanes/EtOAc).

Annulation of carbene complex 46 with alkyne 292

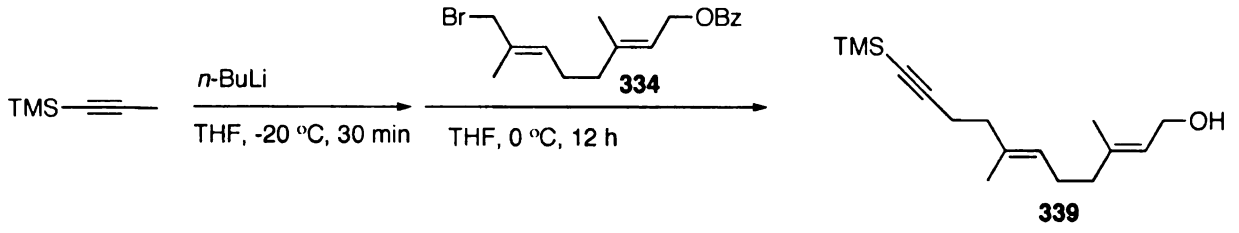


A solution containing carbene complex **46** (150 mg, 0.42 mmol) and alkyne **292** (1:1 *E/Z*, 0.63 mmol 178.0 mg) in 8.4 mL benzene was deoxygenated by the freeze-thaw method and heated at 110 °C for 8 hours. The reaction mixture was cooled to RT, and then diluted with Et_2O. After stirring 2 hours at RT in air, the solution was passed through Celite, concentrated, and then purified by chromatography to give 25% of compound **293** (47 mg, 0.105 mmol) as mixture.

***E*-293**[70] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.06 (m, 24H), 1.75 (s, 3H), 2.09 (d, 1H, *J* = 15.1 Hz), 2.25 (s, 3H), 2.68 (d, 1H, *J* = 15.1 Hz), 3.64 (s, 3H), 3.87 (s, 3H), 4.37 (d, 1H, *J* = 11.2 Hz), 4.52 (d, 1H, *J* = 11.2 Hz), 5.70 (s, 1H), 6.04 (s, 1H); ^{13}CNMR ($CDCl_3$, 75 MHz) δ 12.11, 13.86, 18.08, 20.57, 23.20, 47.22, 52.71, 59.64, 59.81, 61.12, 108.45, 122.79, 128.98, 135.76, 147.67, 150.36, 159.31, 160.10, 199.33.

***Z*-293**[70] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.03 (m, 21H), 1.07 (s, 3H), 1.70 (s, 3H), 2.13 (d, 1H, *J* = 15.0 Hz), 2.24 (s, 3H), 2.58 (d, 1H, *J* = 15.0 Hz), 3.47 (s, 3H), 3.94 (s, 3H), 4.36 (d, 2H, *J* = 3.2 Hz), 5.69 (s, 1H), 5.97 (s, 1H); ^{13}CNMR ($CDCl_3$, 75 MHz) δ 11.99, 18.00, 18.56, 20.68, 22.68, 47.78, 52.23, 57.74, 59.40, 60.14, 107.01, 122.46, 128.61, 136.90, 145.37, 150.90, 156.28, 159.16, 199.96.

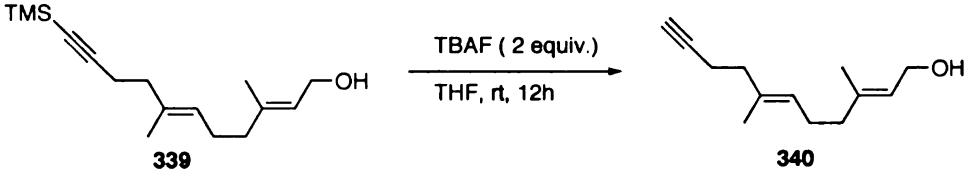
Preparation of (2*E*,6*E*)-3, 7-dimethyl-11-(trimethylsilyl)undeca-2,6-dien-10-yn-1-ol 339



This procedure for the preparation of **339** was adopted from that reported by Jie Huang.[91] To a solution of TMS propyne (26 mL, 175 mmol) in THF (100 mL) at –20 °C was added *n*-BuLi (2.5 M, 70.0 mL, 175 mmol) dropwise. After 30 minutes, the bromide **334** (14.73 g, 43.7 mmol) in THF (50 mL) was transferred by cannulated to the above solution and the temperature was raised to 0 °C slowly. The reaction mixture was stirred for 12 hours at 0 °C and then quenched with H_2O. The aqueous layer was separated and extracted with Et_2O (2 * 50 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (3 * 30 mL), brine (30 mL) and dried over $MgSO_4$. Concentration followed by flash chromatography on silica gel with a 4:1 mixture of hexanes/EtOAc as eluent provided the title compound **339** which was not further purified but taken on directly in the next step. A sample can be further purified for characterization. ^{1}HNMR ($CDCl_3$, 300 MHz) δ 0.07 (s, 9H), 1.58 (s, 3H), 1.66 (s, 3H), 2.02-2.28 (m, 8H), 4.12-4.14 (d, 2H, *J* = 6.6 Hz), 5.14 (t, 1H, *J* = 6.6 Hz), 5.39 (t, 1H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.09, 15.80, 16.22, 19.17, 26.18, 38.52, 39.37, 59.36, 84.55, 107.18, 123.33, 125.04, 133.75, 139.61; IR (neat) 3360br, 2925, 2176, 1250, 1003, 814s, 760 cm^{-1}; MS (EI) *m/z* (% rel intensity): 264 M^+ (0.03),

249 (1.30), 159 (31), 149 (30), 135 (21), 119 (21), 105 (21), 96 (47), 83 (32), 81 (32), 75 (49), 73 (100), 59 (68). Anal calcd for $C_{16}H_{28}OSi$: C. 72.66; H, 10.67. Found: C, 72.83; H, 10.39. Colorless oil; R_f = 0.35 (3:1 hexanes/EtOAc).

Preparation of (2*E*,6*E*)-3,7-dimethylundeca-2,6-dien-10-yn-1-ol 340

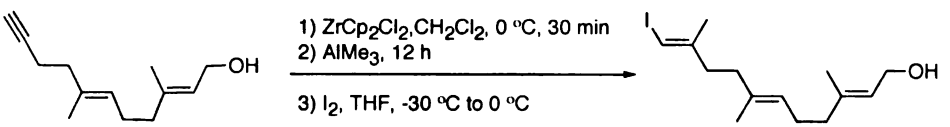


339 **340**

This procedure for the preparation of **340** was adopted from that reported by Jie Huang.[91] The trimethylsilyl protected acetylene **339** prepared by the previous procedure was treated with TBAF (1.0 M in THF, 100 mL) at room temperature for 12 hours followed by quenching with saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted with Et_2O (2 * 50 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (3 * 30 mL), brine (30 mL) and dried over $MgSO_4$. Concentration followed by Flash chromatography on silica gel with a 4:1 mixture of hexanes/EtOAC as eluent provided the desired product **340** as a colorless oil (6.09 g, 0.0317 mmol, 71% 2 steps). ^{1}HNMR ($CDCl_3$, 300 MHz) δ 1.59 (s, 3H), 1.65 (s, 3H), 1.93 (t, 1H, *J* = 2.4 Hz), 2.00-2.29 (m, 8H), 4.12-4.14 (d, 2H, *J* = 6.9 Hz), 5.16 (t, 1H, *J* = 6.3 Hz), 5.40 (t, 1H, *J* = 6.6 Hz); ^{13}CNMR ($CDCl_3$, 75 MHz) δ 15.79, 16.25, 17.56, 26.19, 38.21, 39.34, 59.39, 68.36, 84.37, 123.50, 125.13, 133.55, 139.53; IR (neat) 3350br, 3304, 2922, 2857, 2118, 1725, 1668, 1445, 1383 cm^{-1}; MS (EI) *m/z* (% rel intensity): 191 $(M-1)^+$ (0.02), 177 (1), 173 (0.23), 161 (3), 159 (6), 105 (43), 91

(100), 79 (76). Anal calcd for $C_{13}H_{20}O$: C. 81.20; H, 10.48. Found: C, 81.36; H, 10.38. Colorless oil; R_f = 0.29 (3:1 hexanes/EtOAc).

Preparation of (2*E*,6*E*,10*E*)-11-iodo-3,7,10-trimethylundeca-2,6,10-trien-1-ol 341

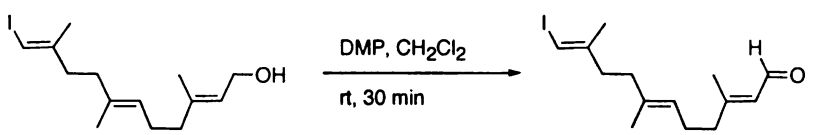


340 341

To a solution of zirconocene dichloride (1.25 g, 4.28 mmol) in CH_2Cl_2 (34 mL) at room temperature under an argon atmosphere, was added dropwise a solution of trimethylaluminum in pentane (2 M in pentane, 25.7 mL, 51.4 mmol). After 15 minutes, the solution was cooled to 0 °C, and a solution of alkyne **340** (3.25 g, 17.1 mmol) dissolved in CH_2Cl_2 (34 mL) was added to the above lemon yellow solution. The reaction mixture was stirred at 0 °C for 12 hours and then cooled to –30 °C. Iodine (8.69 g, 34.2 mmol) was added as a solution in 20 mL of THF. The resulting brown slurry was raised to 0 °C and poured slowly with stirring into an iced saturated aqueous $NaHCO_3$. The aqueous layer was extracted with Et_2O (3 * 50 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. Concentration followed by flash chromatography on silica gel with 4:1 hexanes/EtOAC as eluent provided the desired product **341** as a colorless oil (3.69 g, 11 mmol, 65%). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.57 (s, 3 H), 1.66 (s, 3 H), 1.80 (s, 3 H), 1.97-2.10 (m, 6 H), 2.27 (t, 2H, *J* = 6.6 Hz), 4.13 (d, 2H, *J* = 6.9 Hz), 5.08 (t, 1H, *J* =6.9 Hz), 5.39 (t,

1H, J = 6.9 Hz), 5.83 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.82, 26.26, 23.85, 26.17, 37.84, 38.21, 39.41, 59.39, 74.66, 123.41, 124.70, 134.21, 139.60, 147.82; IR (neat) 3312br, 2919, 2858, 1441 cm^{-1}; MS (EI) *m/z* (% rel intensity): 239 (3), 207 $(M-127)^+$ (2), 189 (11), 181 (44), 121 (80), 107 (98), 93 (100), 53 (73). Anal calcd for $C_{14}H_{23}OI$: C. 50.31; H, 6.94. Found: C, 50.64; H, 6.90. Colorless oil; R_f = 0.30 (3:1 hexanes/EtOAc).

Preparation of (2*E*,6*E*,10*E*)-11-iodo-3,7,10-trimethylundeca-2,6,10-trienal 342

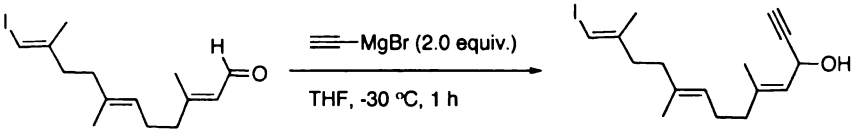


341 **342**

This procedure for the preparation of **342** was adopted from that reported by Jie Huang.[91] To a solution of allylic alcohol **341** (0.80 g, 2.4 mmol) in CH_2Cl_2 (10 mL) was added freshly prepared DMP[93] (1.10 g, 2.6 mmol) as powder. The reaction mixture was stirred at room temperature for 30 minutes before quenching with 10% aqueous NaOH (10 mL). The stirring was continued for another 5 minutes, and then Et_2O (3 * 10 mL) was added to extract the product from the reaction mixture. The combined organic layer was dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by flash chromatography on a silica gel column (9:1 hexanes/EtOAc as eluent) provided the desired aldehyde **342** as a colorless oil (0.784 g, 2.36 mmol, 98%). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.58 (s, 3H), 1.80 (s, 3H), 2.15 (s, 3H), 2.05-2.29 (m, 8H), 5.02-5.08 (m, 1H), 5.83-5.86 (m, 1H), 5.83 (s, 1H), 9.97 (d, 1H, J = 7.8 Hz); ^{13}C

NMR ($CDCl_3$, 75 MHz) δ 15.89, 17.61, 23.83, 25.57, 37.77, 38.13, 40.50, 74.79, 123.45, 127.46, 135.43, 147.63, 163.47, 191.22. IR (neat) 2939m, 2853m, 2772w, 1684s, 1437m, 1194m, 1122m, 827w, 667w cm^{-1}; MS (EI) *m/z* (% rel intensity): 332 M^+ (3), 205 (22), 187 (34), 181 (77), 177 (33), 161 (17), 159 (16), 149 (16), 145 (24), 135 (16), 133 (24), 125 (20), 121 (100), 107 (76), 105 (28), 95 (67), 93 (73), 84 (30), 81 (100), 67 (63), 55 (85), 53 (86). Anal calcd for $C_{14}H_{21}OI$: C. 50.61; H, 6.37. Found: C, 50.28; H, 6.64. Colorless oil; R_f = 0.6 (3:1 hexanes/EtOAc).

Preparation of (4*E*,8*E*,12*E*)-13-iodo-5,9,12-trimethyltrideca-4,8,12-trien-1-yn-3-ol 333

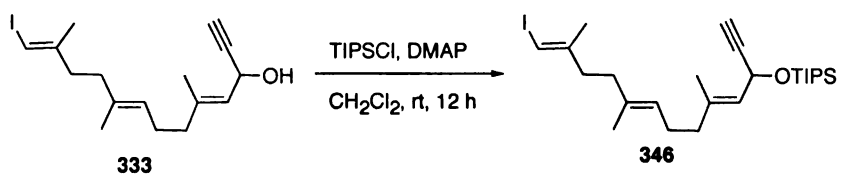


342 333

To a solution of aldehyde **342** (0.16 g, 0.48 mmol) in THF (2 mL) at –30 °C under an argon atmosphere was added ethynyl magnesium bromide (0.5 M solution in THF, 1.92 mL, 0.96 mmol) dropwise. The reaction mixture was stirred at –30 °C for 1 hour and quenched with saturated aqueous NH_4Cl (8 mL). The aqueous layer was extracted with Et_2O (3 * 5 mL). The combined organic layer was washed with brine (15 mL) and dried over $MgSO_4$. Flash chromatography on a silica gel column using 15% EtOAC in hexanes as eluent provided the desired propargylic alcohol **333** as a colorless oil (0.16 g, 0.45 mmol, 93%). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.57 (s, 3H), 1.70 (s, 3H), 1.80 (s, 3H), 2.01-2.10 (m, 6H),

2.27 (t, 2H, J = 7.2 Hz), 2.47 (d, 1H, J = 2.1 Hz), 5.07-5.12 (m, 2H), 5.37 (d, 1H, J = 8.4 Hz), 5.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.87, 16.59, 23.86, 25.94, 37.82, 38.22, 39.13, 58.89, 72.49, 74.69, 84.44, 124.09, 124.36, 134.46, 140.77, 147.81; IR (neat) 3400 (broad), 3299, 2919, 2853, 2120 (weak), 1956, 1667 cm^{-1}. HRMS (CI) calcd for $C_{16}H_{22}I$ $(M-H_2O+H)^+$ *m/z* 341.0766, meas 341.0771. Colorless oil; R_f = 0.43 (3:1 hexanes/EtOAc).

Preparation of ((4*E*,8*E*,2*E*)-13-iodo-5,9,12-trimethyltrideca-4,8,12-trien-1-yn-3-yloxy) tri*iso*propylsilane 346

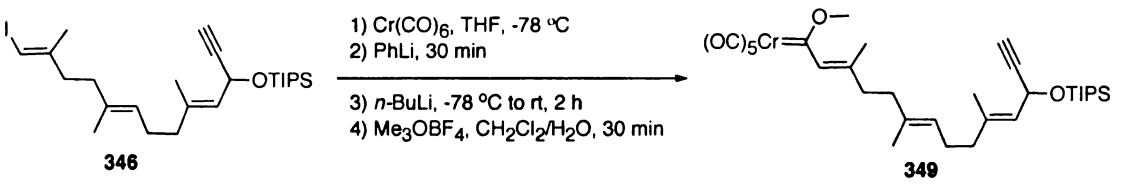


333 346

This procedure for the preparation of **346** was adopted from that reported by Jie Huang.[91] To a solution of propargyl alcohol **333** (1.0 g, 2.8 mmol) in CH_2Cl_2 (10 mL) was added DMAP (0.68 g, 5.6 mmol) and TIPSCl (1.2 mL, 5.6 mmol). The reaction mixture was stirred at room temperature for 12 hours and quenched with H_2O (10 mL). Diethyl ether (3 * 20 mL) was added to extract the product from the aqueous layer. The combined organic layer was washed with saturated aqueous NH_4Cl (50 mL), brine (50 mL), and then dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by flash chromatography on silica gel (19:1 hexanes/EtOAc as eluent) provided the desired product **346** as a colorless oil (1.43 g, 2.8 mmol, 100%). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.03-1.13 (m, 21H), 1.57 (s, 3H), 1.65 (s, 3H), 1.80 (s, 3H),

1.98-2.08 (m, 6H), 2.58 (t, 2H, J = 2.7Hz), 2.41 (d, 1H, J = 2.1Hz), 5.07-5.12 (m, 2H), 5.32-5.34 (d, 1H, J = 7.8 Hz), 5.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.19, 15.89, 16.68, 17.90, 23.88, 25.98, 37.90, 38.29, 39.08, 59.94, 71.43, 74.61, 85.08, 124.54, 126.19, 134.25, 136.56, 147.91; IR (neat) 3308, 2942, 2889, 1462 cm^{-1}; MS (EI) *m/z* (% rel intensity) 514 M^+ (0.04), 471 (1.4), 131 (81), 103 (100), 75 (83). Anal calcd for $C_{25}H_{43}OISi$: C. 58.35; H, 8.42. Found: C, 58.60; H, 8.77. Colorless oil; R_f = 0.20 (hexanes).

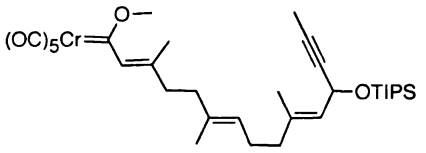
Preparation of carbene complex 349



346 **349**

This is a modification of a procedure Jie Huang reported for the preparation of **349**.[91] To a solution of vinyl iodine **346** (375 mg, 0.73 mmol) in THF (15 mL) at room temperature was added $Cr(CO)_6$ (177 mg, 0.80 mmol) as a powder. The reaction mixture was cooled to –78 °C, and PhLi (0.456 mL, 0.73 mmol, 1.6 M solution) was added dropwise. The mixture was stirred for 30 minutes at –78 °C, and then *n*-BuLi (0.34 mL, 0.73 mmol, 2.27 M) was added dropwise. The solution was stirred for another 30 minutes, and then warmed up to room temperature and stirred for 1.5 hours. The solvent of the reaction was then removed *in vacuo*, and the residue was dissolved in 1:1 H_2O/CH_2Cl_2 (15 mL). Upon addition of Me_3OBF_4 (210 mg, 1.47 mmol), the solution turned red immediately. After stirring 30 minutes at room temperature, saturated aqueous

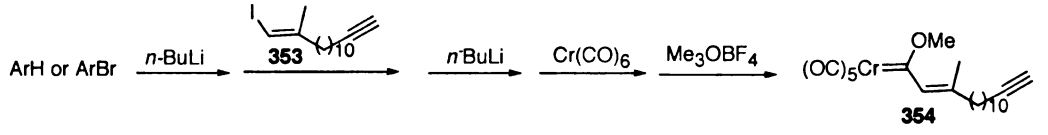
$NaHCO_3$ and Et_2O was added to quench the alkylation. The aqueous layer was extracted with Et_2O until the color of the aqueous layer was pale. The combined organic layer was washed with brine, and then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using 2% EtOAC in hexanes as eluent to give carbene complex **349** (233 mg, 0.37 mmol, 51%) as a red oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.03-1.10 (m, 21), 1.60 (s, 3 H), 1.65 (s, 3H), 1.82 (s, 3H), 2.00-2.15 (m, 8H), 2.40 (d, 1 H, *J* = 2.1Hz), 4.69 (s, 3H), 5.01-5.12 (m, 2H), 5.32 (d, 1 H, *J* = 7.8Hz), 7.20 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.10, 15.87, 16.57, 17.85, 17.91, 20.61, 25.86, 37.80, 38.96, 39.74, 59.86, 66.13, 71.43, 84.97, 124.66, 126.15, 133.94, 136.40, 140.95, 142.79, 216.75, 223.94, 339.37; IR (neat) 2946w, 2868w, 2058s, 1935vs, 1250w, 1061w, 667s, 650m cm^{-1}. Anal calcd for $C_{32}H_{46}CrO_7Si$: C. 61.71; H, 7.44. Found: C, 62.05; H, 7.76. Red oil; R_f = 0.63 (3:1 hexanes/EtOAc).



Carbene complex **350** Methylated carbene complex **350** was obtained in a 34% yield when CH_2Cl_2 was the only solvent in the methylation step of the above reaction. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.03-1.09 (m, 21H), 1.60 (s, 3H), 1.63 (s, 3H), 1.80 (d, 3H, *J* = 2.1 Hz), 1.82 (s, 3H), 1.97-2.15 (m, 6H), 2.17-2.20 (m, 2H), 4.69 (s, 3H), 5.05 (dd, 1H, *J* = 8.1, 2.0 Hz), 5.12 (t, 1H, *J* = 6.8 Hz), 5.30 (dd, 1H, *J* = 8.1, 1.0 Hz), 7.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.67, 12.28, 15.91, 16.56, 17.94, 20.56, 26.02, 37.88, 39.04, 39.75, 60.75, 66.14, 79.59, 80.60, 124.92, 127.02, 133.89, 135.37, 140.98,

142.77, 216.80, 223.97, 339.94; IR (neat) 2946, 2869, 2058, 1939, 1585, 1455, 1250, 667 cm^{-1}. Red oil.

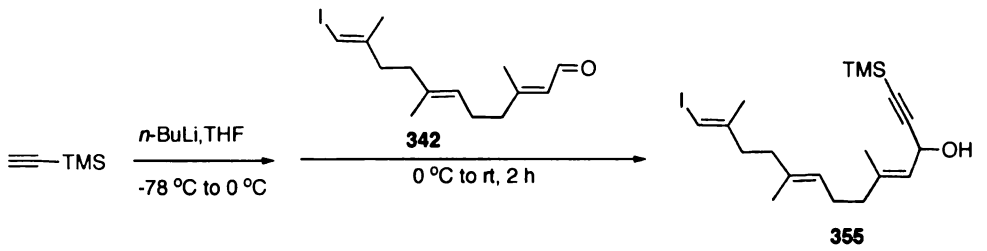
General procedure for preparation of model carbene complex 354[91]



To a flame dried round bottom flask filled with an argon atmosphere was added the appropriate aryl lithium precursor (Table 5.1) and THF (0.02 M) and cooled to –78 °C. *n*-BuLi (1 equiv.) or *t*-BuLi (2 equiv.) was added dropwise to the above solution. After 30 minutes, a solution of vinyl iodine **353** (1 equiv.) in THF (0.02 M) was added dropwise. The mixture was stirred for 30 minutes at –78 °C, then *n*-BuLi (1 equiv.) or *t*-BuLi (2 equiv.) was added. After 30 minutes, $Cr(CO)_6$ (1.1 equiv.) was added to the solution as a powder and the cooling bath was removed. The solution was warmed to room temperature and stirred for 1.5 hours before the solvent was removed on rotary evaporator. The residue was taken up in a two-phase solvent system of CH_2Cl_2 and H_2O (1:1), and Me_3OBF_4 (2 equiv.) was added to the above mixture as a solid at room temperature. The reaction mixture was stirred for 30 minutes before quenching with saturated aqueous $NaHCO_3$. The aqueous layer was extracted three times with Et_2O. The combined organic layer was washed with brine, and dried over $MgSO_4$. Concentration followed by chromatography on a silica gel column with 2% EtOAC in hexanes as eluent provided the carbene complex **354** in yields that are

listed in Table 5.1. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.26-1.30 (m, 10 H), 1.37-1.38 (m, 2H), 1.45-1.52 (m, 4H), 1.82 (d, 3H, *J* = 1.0 Hz), 1.92 (t, 1H, *J* = 2.7 Hz), 2.10 (t, 2H, *J* = 7.7 Hz), 2.19 (td, 2H, *J* = 7.2, 2.7 Hz), 4.70 (s, 3H), 7.23 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.37, 20.56, 27.77, 28.45, 28.71, 29.04, 29.23, 29.40, 41.19, 66.15, 68.01, 84.74, 141.02, 143.48, 216.83, 223.98, 339.50 (2 sp^3 carbons were not located). Red oil; R_f = 0.11 (hexanes).

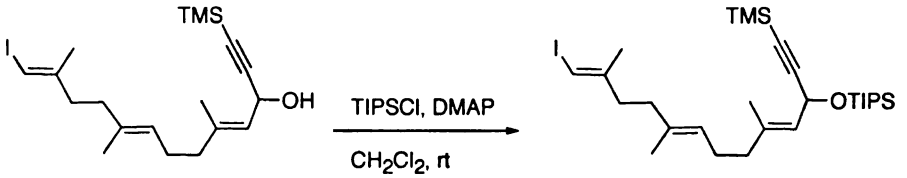
Preparation of alcohol 355



To a solution of trimethylsilyl acetylene (0.22 mL, 1.5 mmol) in 2.0 mL of THF at –78 °C was added *n*-BuLi (0.60 mL, 1.5 mmol, 2.5 M in hexanes) dropwise. The solution was stirred at –78 °C for 30 minutes then at 0 °C for 50 minutes, and then the aldehyde **342** (166 mg, 0.50 mmol) in 1 mL of THF was added to the above solution. The solution was stirred at 0 °C for 1 hour then warmed up to room temperature for another 1 hour. The reaction mixture was quenched with 5 mL of saturated aqueous NH_4Cl, and the aqueous phase was separated and extracted with Et_2O (2 * 10 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using 9:1 hexanes/EtOAC as eluent to give **355** (169 mg, 0.392 mmol, 79%) as a colorless

oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.13 (s, 9H), 1.56 (s, 3H), 1.68 (d, 3H, *J* = 1.2 Hz), 1.78 (d, 3H, *J* = 1.0 Hz), 1.96-2.01 (m, 3H), 2.04-2.10 (m, 4H), 2.24-2.27 (m, 2H), 5.03 (dd, 1H, *J* = 8.6, 3.9 Hz), 5.06 (td, 1H, *J* = 6.6, 1.2 Hz), 5.32 (dd, 1H, *J* = 8.5, 1.2 Hz), 5.82 (q, 1H, *J* = 1.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -0.18, 15.82, 16.55, 23.80, 25.87, 37.75, 38.14, 39.10, 59.32, 74.74, 88.85, 106.07,124.27, 124.39, 134.25, 140.29, 147.66; IR (neat) 3322 br, 2918, 1853, 2172, 1668, 1250, 1028, 843 cm^{-1}. Anal calcd for $C_{19}H_{31}IOSi$: C, 53.02; H, 7.26. Found: C, 53.20; H, 7.45. Colorless oil; R_f = 0.25 (9:1 hexanes/Et_2O).

Preparation of alkyne 356

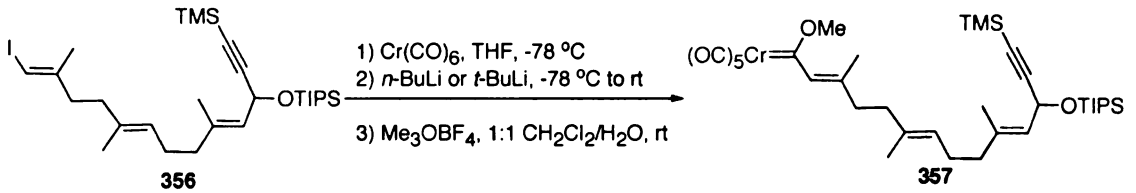


355 **356**

To a solution of alcohol **355** (86 mg, 0.20 mmol) in 2 mL of CH_2Cl_2 at room temperature was added DMAP (48.4 mg, 0.40 mmol) and TIPSCl (0.086 mL, 0.40 mmol) respectively. The solution was stirred overnight and then quenched with H_2O. The aqueous phase was separated and extracted with Et_2O (2 * 10 mL). The combined organic layer was washed with brine (15 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using 2% EtOAC in hexanes as eluent to give **356** (80.4 mg, 0.137 mmol, 69%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.12 (s, 9H), 1.04-1.10 (m, 21H), 1.57 (s, 3H), 1.64 (d, 3H, *J* =2.2 Hz), 1.81 (d,

3H, J = 1.1 Hz), 1.98-2.05 (m, 2H), 2.06-2.09 (m, 4H), 2.25-2.28 (m, 2H), 5.07 (s, 1H), 5.09 (t, 1H, J = 3.3 Hz), 5.29 (dq, 1H, J = 9.3, 2.2 Hz), 5.84 (q, 1H, J = 1.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -0.15, 12.24, 15.89, 16.71, 17.95, 23.89, 25.98, 37.91, 38.31, 39.14, 60.46, 74.66, 87.88, 106.98, 124.64, 126.16, 134.15, 136.47, 147.88; IR (neat) 2944s, 2867s, 2172w, 1464m, 1250m, 1059s, 843s cm^{-1}. Anal calcd for $C_{28}H_{51}IOSi_2$: C, 57.31; H, 8.76. Found: C, 57.33, H, 9.04. Colorless oil; R_f = 0.22 (hexanes).

Preparation of carbene complex 357

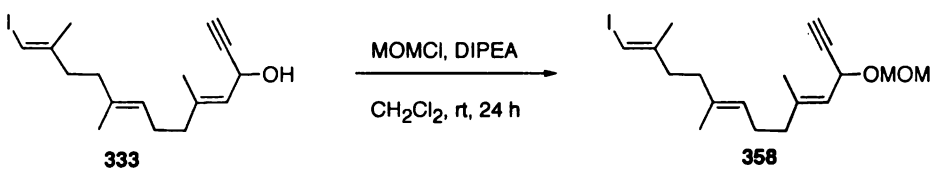


356 357

To a solution of vinyl iodine **356** (50 mg, 0.085 mmol) in 2 mL of THF at room temperature was added $Cr(CO)_6$ (20.6 mg, 0.094 mmol) as a powder. The solution was cooled to –78 °C, and *t*-BuLi (1.0 mL, 0.17 mmol) was added dropwise. The solution was stirred for 30 minutes at –78 °C, and then warmed up to room temperature slowly and stirred for 1.5 hours. The solvent of the reaction was removed *in vacuo*, and the residue was dissolved in 2 mL of 1:1 mixture of H_2O/CH_2Cl_2. Upon addition of Me_3OBF_4, the solution turned red immediately. After stirring 30 minutes at room temperature, 10 mL of saturated aqueous $NaHCO_3$ and 10 mL of Et_2O was added to the above solution. The aqueous layer was extracted with Et_2O until the color of the aqueous layer was pale. The

combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using 2% EtOAC in hexanes as eluent to give carbene complex **357** (38.6 mg, 0.056 mmol, 65%) as a red oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.12 (s, 9H), 1.04-1.08 (m, 21H), 1.60 (s, 3H), 1.64 (s, 3H), 1.82 (s, 3H), 1.98-2.20 (m, 8H), 4.69 (s, 3H), 5.08 (d, 1H, *J* = 8.0 Hz), 5.13 (t, 1H, *J* = 6.4 Hz), 5.29 (t, 1H, *J* = 7.6 Hz), 7.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -0.16, 12.24, 15.90, 16.68, 17.89, 17.94, 20.59, 26.01, 37.88, 39.09, 39.76, 60.48, 66.15, 87.91, 106.98, 124.89, 126.19, 133.90, 136.44, 141.01, 216.80, 223.99, 339.86; IR (neat) 2946m, 2869m, 2170w, 2058s, 1941vs, 1250m, 843m, 667m cm^{-1}. Red oil; R_f = 0.45 (hexanes).

Preparation of MOM protected vinyl iodine 358

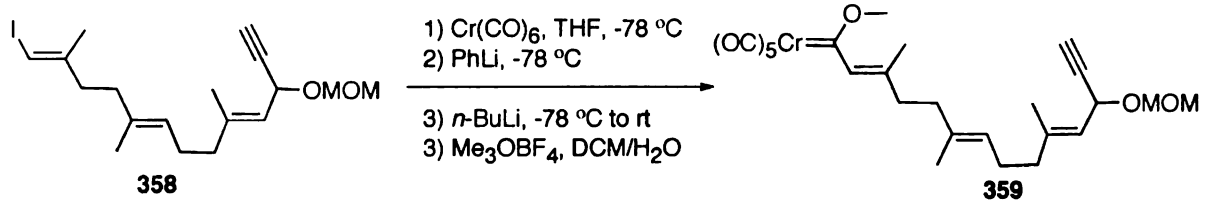


333 **358**

To a solution of **333** (562 mg, 1.57 mmol) in 10 mL of CH_2Cl_2 at room temperature was added DIPEA (0.820 mL, 4.71 mmol) and MOMCl (0.238 mL, 3.14 mmol). The resulting solution was stirred for 1 day, and then quenched with saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with Et_2O (2 * 10 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was purified by chromatography on silica gel using 9:1 hexanes/EtOAC as eluent to give an 80%

yield of MOM ether **358** (504 mg, 1.25 mmol). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.57 (s, 3H), 1.71 (d, 3H, *J* = 1.3 Hz), 1.80 (d, 3H, *J* = 1.1 Hz), 2.02-2.14 (m, 6H), 2.25-2.27 (m, 2H), 2.43 (d, 1H, *J* = 2.1 Hz), 3.38 (s, 3H), 4.60 (d, 1H, *J* = 6.9 Hz), 4.82 (d, 1H, *J* = 6.9 Hz), 5.02-5.09 (m, 2H), 5.29 (dq, 1H, *J* = 8.9, 1.2 Hz), 5.83-5.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.88, 16.57, 23.85, 25.94, 37.84, 38.24, 39.20, 55.61, 61.46, 73.13, 74.66, 82.18, 93.13, 121.63, 124.36, 134.44, 141.56, 147.82; IR (neat) 3295, 2926, 1449, 1150, 1094, 1028, 924, 629 cm^{-1}; HRMS (CI) calcd for $(C_{18}H_{27}O_2I+H)^+$ *m/z* 403.1134, meas 403.1124. Colorless oil; R_f = 0.34 (9:1 hexanes/EtOAc).

Preparation of carbene complex 359

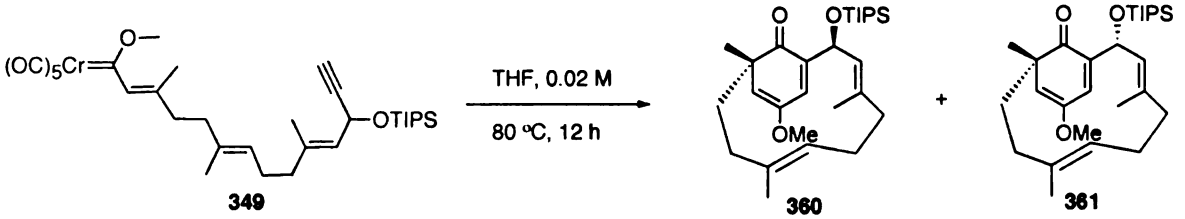


358 **359**

To a solution of vinyl iodine **358** (49.1 mg, 0.122 mmol) in THF (5 mL) at room temperature was added $Cr(CO)_6$ (30 mg, 0.136 mmol) as a powder. The solution was cooled to –78 °C, and PhLi (0.076 mL, 0.122 mmol, 1.6 M in THF) was added dropwise. After stirring for 30 minutes at –78 °C, *n*-BuLi (0.047 mL, 0.122 mmol, 2.6 M in hexanes) was added dropwise. The solution was stirred for another 30 minutes, and then warmed up to room temperature and stirred for 1.5 hours. The solvent of the reaction was removed *in vacuo*, and the residue was dissolved in 1:1 mixture of H_2O/CH_2Cl_2. Upon addition of Me_3OBF_4 (36 mg, 0.249

mmol), the solution turned red immediately. After stirring 30 minutes at room temperature, saturated aqueous $NaHCO_3$ (10 mL) and Et_2O (10 mL) was added to quench the alkylation reaction. The aqueous layer was extracted with Et_2O until the color of the aqueous layer was pale. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using 9:1 hexanes/EtOAC as eluent to give carbene complex **359** as a red oil (26.6 mg, 0.052 mmol, 43%). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.60 (s, 3H), 1.71 (d, 3H, *J* = 1.1 Hz), 1.82 (s, 3H), 2.03-2.21 (m, 8H), 2.44 (d, 1H, *J* = 2.2 Hz), 3.38 (s, 3H), 4.60 (d, 1H, *J* = 6.9 Hz), 4.70 (s, 3H), 4.83 (d, 1H, *J* = 6.9 Hz), 5.05 (dd, 1H, *J* = 8.9, 2.2 Hz), 5.10-5.13 (m, 1H), 5.28-5.30 (m, 1H), 7.21 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.60, 16.55, 20.60, 25.98, 37.88, 39.18, 39.75, 55.64, 61.54, 66.18, 73.14, 82.22, 93.20, 115.23, 121.77, 124.57, 134.27, 141.02, 141.47, 216.82, 223.97 (The carbene carbon was not located); IR (neat) 3308, 2919, 2058, 1931, 665 cm^{-1}. Red oil; R_f = 0.19 (9:1 hexanes/EtOAc).

Thermolysis of carbene complex 349



349 360 361

This procedure for the themolysis of **349** was adopted from that reported by Jie Huang.[91] The carbene complex **349** (212 mg, 0.341 mmol) was dissolved

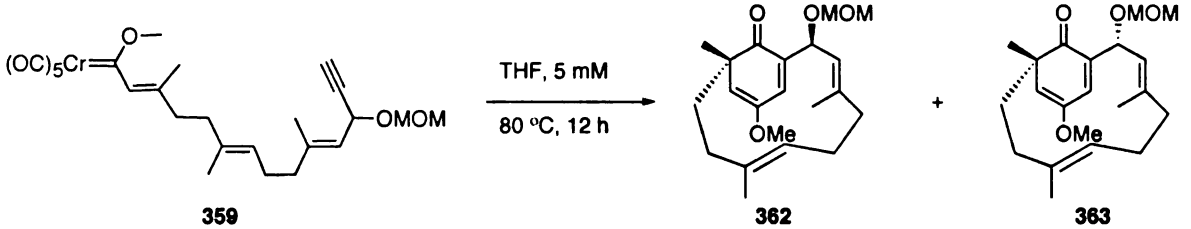
in THF (17 mL) and transferred to a Schlenk flask equipped with a threaded Teflon high vacuum stopcock. The reaction mixture was deoxygenated by the freeze-pump-thaw procedure with 3 cycles. Then the flask was back filled with an argon atmosphere at room temperature, sealed and heated to 80 °C. After the reaction was completed (indicated by the fading of the red color of **349**), the solvent was removed *in vacuo*. The residue was taken up in 1:1 mixed solvent of Et_2O and CH_2Cl_2, and stirred in air for 12 hours. Then the solvent was removed again and the residue was taken up in pure Et_2O. The insoluble material was removed by filtration through silica gel in a pipette-sized column using Et_2O as the eluent. Concentration of the filtrate provided the crude product mixture, which was further purified by flash column chromatography on silica gel (45:1:1 hexanes/Et_2O/CH_2Cl_2 as the eluent) to give a 37% yield of major isomer (57.7 mg, 0.126 mmol) and a 19% yield of minor isomer (29.7 mg, 0.065 mmol). The 2:1 ratio of diastereomers **360** and **361** was also verified on the crude reaction mixture by ^1H NMR based on the integral of the following vinyl peaks: δ 6.99 for **360** and 6.42 for **361**.

Major isomer 360 ^1H NMR ($CDCl_3$, 500 MHz) δ 0.98-1.06 (m, 21H), 1.10 (s, 3H), 1.34-1.42 (m, 2H), 1.52 (s, 3H), 1.64 (s, 3H), 1.67-2.09 (m, 4H), 2.26-2.39 (m, 2H), 3.63 (s, 3H), 4.48 (d, 1H, J = 11.4 Hz), 4.67 (d, 1H, J = 8.1 Hz), 4.90 (d, 1H, J = 3.3 Hz), 5.42 (dd, 1H, J = 9.0, 0.9 Hz), 6.99 (dd, 1H, J = 3.3, 0.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.13, 15.28, 15.67, 17.91, 17.96, 25.53, 29.85, 36.24, 37.96, 46.70, 54.71, 64.93, 65.83, 110.40, 124.70, 129.97, 134.18, 134.38, 134.86, 141.82, 151.12, 202.25; IR (neat) 2944, 2867, 1647 cm^{-1}; MS(EI)

m/z (% rel intensity) 458 M^+ (10), 430 (7), 415 (18), 347 (19), 324 (52), 279 (66), 241 (80), 189 (41), 131 (30), 115 (34), 103 (48), 81 (100), 75 (100). HRMS calcd for $C_{28}H_{46}O_3Si$ *m/z* 458.3216, meas 458.3218. Light yellow oil; R_f = 0.65 (10:1:1 hexanes/Et_2O/CH_2Cl_2).

Minor isomer 361 ^1H NMR ($CDCl_3$, 500 MHz) δ 0.99-1.03 (m, 21H), 1.12 (s, 3H), 1.35-1.56 (m, 2H), 1.43 (s, 3H), 1.45 (s, 3H), 1.85-2.13 (m, 5H), 2.30 (t, 1H, *J* = 11.4 Hz), 3.60 (s, 3H), 4.59 (t, 1H, *J* = 8 Hz), 4.86 (d, 1H, *J* = 8.1 Hz), 4.93 (d, 1H, *J* = 2.7 Hz), 5.72 (d, 1H, *J* = 8.1 Hz), 6.42 (d, 1H, *J* = 3.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.19, 15.45, 15.50, 17.99, 25.29, 28.30, 36.01, 38.11, 39.43, 50.14, 54.80, 72.73, 111.05, 123.03, 130.67, 132.29, 134.92, 137.11, 138.35, 149.65, 201.08; IR (neat) 2940, 2864, 1651 cm^{-1}; MS (EI) *m/z* (% rel intensity) 458 M^+ (2), 415 (33), 347 (15), 279 (100), 241(11), 189 (13), 131 (30), 103 (38), 81 (67), 75 (68); HRMS calcd for $C_{28}H_{46}O_3Si$ *m/z* 458.3216, meas 458.3216. Light yellow solid, m.p. 84-86 °C; R_f = 0.60 (10:1:1 hexanes/Et_2O/CH_2Cl_2).

Thermolysis of carbene complex 359



359 **362** **363**

The carbene complex **359** (26.6 mg, 0.052 mmol) was dissolved in THF (10.4 mL) and transferred to a Schlenk flask equipped with a threaded Teflon

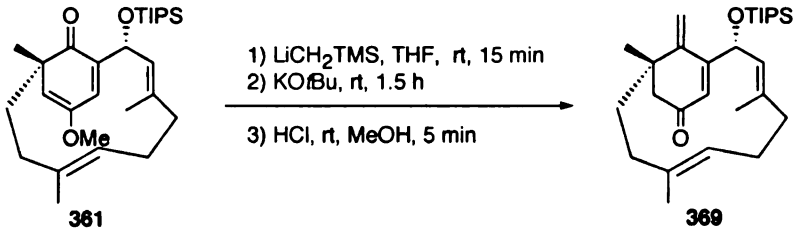
high vacuum stopcock. The reaction mixture was deoxygenated by the freeze-pump-thaw procedure with 3 cycles. Then the flask was back filled with an argon atmosphere at room temperature, sealed and heated to 80 °C. After the reaction was completed (indicated by the fading of the red color of **359**), the solvent was removed *in vacuo*. The residue was taken up in a 1:1 mixture of Et_2O and CH_2Cl_2, and stirred in air for 12 hours. Then the solvent was removed again and the residue was taken up in pure Et_2O. The insoluble material was removed by filtration through silica gel in a pipette-sized column using Et_2O as the eluent. Concentration of the filtrate provided the crude product mixture, which was further purified by flash column chromatography on silica gel (15:1:1 hexanes/Et_2O/CH_2Cl_2 as the eluent) to give a 1:1 ratio of **362** (2.2 mg, 0.0064 mmol, 12%) and **363** (2.5 mg, 0.0072 mmol, 14%). The ratio of diastereomers **362** and **363** was determined on the crude reaction mixture by ^1H NMR based on the integral of the following vinyl peaks: δ 6.92 for **362** and 6.58 for **363**.

Isomer 362 ^1H NMR ($CDCl_3$, 500 MHz) δ 1.14 (s, 3H), 1.39-1.42 (m, 1H), 1.52 (s, 3H), 1.69 (s, 3H), 1.71-1.76 (m, 1H), 1.87-1.89 (m, 1H), 1.93-2.02 (m, 2H), 2.08-2.12 (m, 1H), 2.24-2.36 (m, 2H), 3.34 (s, 3H), 3.63 (s, 3H), 4.50 (d, 1H, *J* = 11.3 Hz), 4.55 (d, 1H, *J* = 6.4 Hz), 4.57 (d, 1H, *J* = 7.8 Hz), 4.71 (d, 1H, *J* = 6.4 Hz), 4.90 (d, 1H, *J* = 3.2 Hz), 5.37 (4.57 (d, 1H, *J* = 9.8 Hz), 6.92 (dd, 1H, *J* = 3.1 Hz, 1.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.37, 15.71, 25.41, 29.59, 35.93, 38.16, 39.33, 49.56, 54.77, 55.49, 67.56, 93.66, 110.64, 124.55, 126.48, 134.60, 135.07, 138.80, 138.90, 150.80, 202.12; IR (neat) 2919, 1647, 1383, 1036 cm-1; mass spectrum *m/z* (% rel intensity) 346 M^+ (1), 318 (5), 284 (14),

253 (12), 241 (10), 212 (17), 203 (22), 189 (81), 175 (16), 164 (14), 151 (19), 91 (24), 81 (23), 67 (16), 45 (100). HRMS (FAB) calcd for $(C_{21}H_{30}O_4+H)^+$ *m/z* 347.2221; meas 347.2222. Light yellow solid, m.p. 77-79 °C; R_f = 0.28 (9:1 hexanes/Et_2O).

Isomer 363 ^1H NMR ($CDCl_3$, 500 MHz) δ 1.17 (s, 3H), 1.30-1.37 (m, 1H), 1.45 (s, 3H), 1.48 (s, 3H), 1.84-1.89 (m, 1H), 1.92-2.06 (m, 3H), 2.10-2.15 (m, 2H), 2.25 (ddd, 1H, *J* = 13.9, 11.9, 2.1 Hz), 3.30 (s, 3H), 3.60 (s, 3H), 4.58 (d, 1H, *J* = 6.8 Hz), 4.59-4.62 (m, 1H), 4.65 (d, 1H, *J* = 6.8 Hz), 4.77 (d, 1H, *J* = 8.6 Hz), 4.98 (d, 1H, *J* = 3.0 Hz), 5.64 (d, 1H, *J* = 8.3 Hz), 6.58 (d, 1H, *J* = 3.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.58, 15.65, 25.07, 27.32, 35.16, 38.18, 39.44, 50.29, 54.79, 55.33, 75.07, 93.81, 111.96, 123.52, 126.42, 135.55, 136.01, 136.48, 137.65, 149.53, 201.88; IR (neat) 2917, 2849, 1649, 1390, 1042 cm^{-1}; mass spectrum *m/z* (% rel intensity) 346 M^+ (0.5), 318 (12), 241 (12), 189 (38), 91 (22), 81 (30), 45 (100). HRMS (CI) calcd for $(C_{21}H_{30}O_4+H)^+$ *m/z* 347.2222, meas 347.2213. Yellow oil; R_f = 0.20 (9:1 hexanes/Et_2O).

Preparation of dienone ketone 369



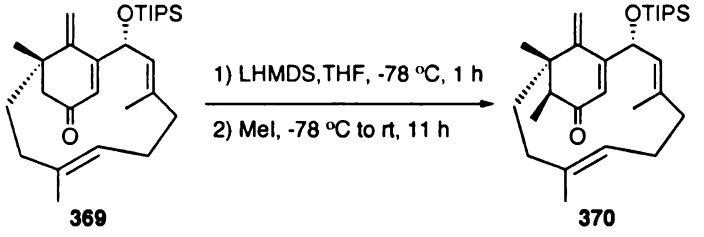
361 **369**

This procedure for the preparation of **369** was adopted from that reported by Jie Huang.[91] Trimethylsilylmethyllithium (0.13 mmol, 0.13 mL, 1.0 M in THF)

was added dropwise to a solution of compound **361** (20 mg, 0.0437 mmol) in 4.3 mL of THF at room temperature. The solution was stirred for 10 minutes, and then potassium *tert*-butoxide (10 mg, 0.89 mmol) was added and stirred for 1.5 hours. The light brown solution was quenched with H_2O. The aqueous phase was separated and extracted with Et_2O (3 * 10 mL). The combined organic layer was washed with brine (15 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give an unstable enol ether. The residue was dissolved in 1 mL of methanol, then treated with 1 mL of 1% aqueous HCl and stirred at room temperature for 5 minutes. The mixture was diluted with Et_2O (5 mL) and neutralized with saturated aqueous $NaHCO_3$ (5 mL). The aqueous phase was separated and then extracted with Et_2O (3 * 10 mL). The combined organic layer was washed with brine (15 mL), and then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using 9:1 hexanes/Et_2O as eluent to give ketone **369** (16.4 mg, 0.037 mmol, 85%). ^1H NMR ($CDCl_3$, 500 MHz) δ 0.98-1.06 (m, 24H), 1.34 (s, 3H), 1.38 (s, 3H), 1.52-1.68 (m, 2H), 1.95-2.11 (m, 6H), 2.17 (d, 1H, *J* = 15.6 Hz), 2.42 (d, 1H, *J* = 15.6 Hz), 4.62 (d, 1H, *J* = 10.4 Hz), 4.98 (d, 1H, *J* = 7.4 Hz), 5.42 (d, 1H, *J* = 7.4 Hz), 5.46 (s, 1H), 5.78 (s, 1H), 6.44 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.07, 14.89, 15.22, 17.92, 24.12, 24.63, 34.32, 35.51, 39.28, 42.84, 53.24, 76.25, 120.81, 124.86, 125.85, 129.64, 134.73, 134.81, 143.72, 156.09, 200.74; IR (neat) 2944, 2867, 1676, 1464, 1080, 1051, 881 cm^{-1}; mass spectrum *m/z* (% rel intensity) 442 M^+ (3), 399 (41), 130 (30), 103 (54), 91 (20), 81 (40), 75 (100), 62 (63), 58 (45). HRMS calcd

for $(C_{28}H_{46}O_2Si+H)^+$ *m/z* 443.3341, meas 443.3345. White solid, m.p. 72-74 °C; R_f = 0.42 (9:1 hexanes/Et_2O).

Methylation of dienone 369

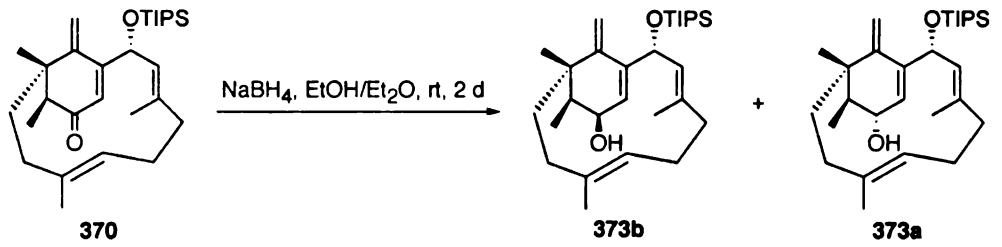


369 370

This procedure for the preparation of **370** was adopted from that reported by Jie Huang.[91] To a solution of ketone **369** (37 mg, 0.0837 mmol) in THF (4.0 mL) at –78 °C was added LHMDS (0.167 mL, 0.167 mmol, 1.0 M solution in THF) dropwise. After stirring for 1 hour at –78 °C, iodomethane (15.6 μL, 0.167 mmol) was added. The cooling bath was removed immediately and the reaction mixture was allowed to warm to room temperature. After stirring for 11 hours, 5 mL of saturated aqueous NH_4Cl was added to the flask. The aqueous layer was extracted with Et_2O (2 * 10 mL). The combined organic layer was washed with brine (10 mL), and then dried over $MgSO_4$. The residue was purified by flash column chromatography on silica gel using 9:1 hexanes/Et_2O as eluent to give ketone **370** (37.4 mg, 0.082 mmol, 98%). ^1H NMR ($CDCl_3$, 500 MHz) δ 0.95-1.06 (m, 27H), 1.23-1.29 (m, 2H), 1.34 (s, 3H), 1.37 (s, 3H), 1.64-1.71 (m, 1H), 1.90-2.15 (m, 6H), 4.62 (d, 1H, *J* = 10.4 Hz), 4.98 (d, 1H, *J* = 7.5 Hz), 5.42 (d, 1H, *J* = 8.0 Hz), 5.45 (s, 1H), 5.66 (s, 1H), 6.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.06, 13.69, 14.93, 15.14, 17.90, 17.93, 21.22, 24.22, 34.66, 36.46,

39.33, 45.85, 55.03, 76.28, 122.88, 123.75, 124.99, 129.79, 134.77, 134.83, 142.13, 155.05, 205.70; IR (neat) 2941s, 2887s, 1678s, 1462w, 1267w, 1057m, 885w cm^{-1}; mass spectrum *m/z* (% rel intensity) 456 M^+ (2), 413 (33), 265 (10), 157 (13), 135 (31), 115 (33), 105 (25), 104 (40), 103 (79), 95 (19), 93 (20), 91 (23), 82 (27), 81 (36), 79 (21), 75 (52), 75 (100), 73 (28), 61 (80), 59 (43), 55 (41). HRMS calcd for $(C_{29}H_{48}O_2Si+H)^+$ *m/z* 457.3500, meas 457.3502. White solid, m.p. 78-80 °C; R_f = 0.44 (9:1 hexanes/Et_2O).

Reduction of dienone 370



370 373b 373a

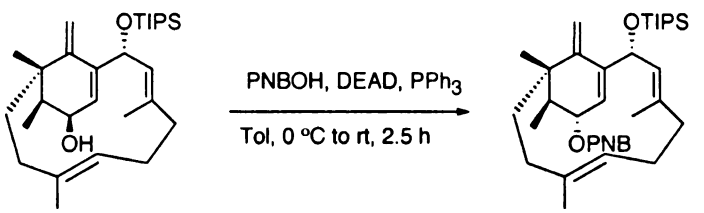
To a solution of enone **370** (74 mg, 0.162 mmol) in 3.0 mL of 2:1 mixture of EtOH/Et_2O at room temperature was added $NaBH_4$ (28 mg, 0.823 mmol). The reaction mixture was stirred until **370** was totally consumed (monitored by TLC). Then the reaction was quenched with H_2O (20 mL). The aqueous layer was extracted with Et_2O (3 * 10 mL). The combined organic layer was washed with brine (15 mL) and dried over Na_2SO_4. Filtration and concentration followed by flash chromatography on silica gel using 19:1 hexanes/EtOAc as eluent provided a 3:1 mixture of alcohol **373b** and alcohol **373a** as a colorless oil (70 mg in total, 0.153 mmol, 94%). These compounds can be completed separate with these chromatographic conditions but are most easily isolated together.

Major isomer 373b ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.73 (d, 3H, *J* = 6.8 Hz), 1.00 (s, 3H), 1.01-1.03 (m, 21H), 1.23-1.27 (m, 1H), 1.32 (s, 3H), 1.32-1.40 (m, 1H), 1.43 (s, 3H), 1.69-1.72 (m, 1H), 1.76-1.91 (m, 3H), 1.97-2.13 (m, 3H), 4.58 (t, 1H, *J* = 6.2 Hz), 4.65 (d, 1H, *J* = 10.8 Hz), 4.84 (d, 1H, *J* = 7.2 Hz), 5.02 (s, 1H), 5.35 (s, 1H), 5.46 (d, 1H, *J* = 7.2 Hz), 6.03 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 7.96, 12.06, 14.56, 15.28, 17.95, 18.02, 21.94, 23.85, 33.59, 35.27, 39.25, 45.41, 45.50, 68.32, 115.67, 124.77, 127.77, 131.36, 132.36, 135.49, 140.19, 142.51. IR (neat) 3397br, 2942, 2868, 1464, 1385, 1082, 1053, 883 cm^{-1}; mass spectrum *m/z* (% rel intensity) 458 M^+ (0.3), 440 (4), 397 (3), 359 (6), 266 (7), 173 (14), 171 (14), 131 (84), 119 (22), 115 (21), 105 (21), 103 (84), 91 (25), 81 (24), 75 (100), 61 (35), 59 (23). HRMS (FAB) calcd for $(C_{29}H_{50}O_2Si\text{-}H)^+$ *m/z* 457.3500, meas 457.3502. Colorless oil, R_f = 0.31 (9:1 hexanes/Et_2O).

Minor isomer 373a ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.77 (d, 3H, *J* = 7.3 Hz), 0.94 (s, 3H), 0.98-1.03 (m, 21H), 1.37 (s, 3H), 1.44 (s, 3H), 1.46-1.61 (m, 3H), 1.69-1.73 (m, 1H), 1.90-2.13 (m, 5H), 3.91 (t, 1H, *J* = 4.4 Hz), 4.66 (d, 1H, *J* = 9.3 Hz), 4.88 (d, 1H, *J* = 7.4 Hz), 5.11 (t, 1H, *J* = 1.6 Hz), 5.45 (d, 1H, *J* = 7.4 Hz), 5.53 (d, 1H, *J* = 4.5 Hz), 6.08 (d, 1H, *J* = 1.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.08, 12.15, 14.95, 15.28, 17.95, 17.97, 22.11, 23.88, 35.27, 37.19, 39.06, 42.08, 46.15, 72.58, 116.25, 124.72, 125.40, 130.95, 132.61, 135.60, 139.44, 143.11; IR (neat) 3368, 2941, 2868, 1462, 1385, 1082, 1055, 884 cm^{-1}; mass spectrum *m/z* (% rel intensity) 458 M^+ (1), 440 (11), 359 (20), 167 (18), 185 (15), 173 (25), 171 (24), 157 (27), 145 (18), 143 (17), 133 (19), 131 (94), 129 (16), 119 (24), 115 (25), 105 (24), 103 (81), 95 (16), 91 (23), 87 (16), 81 (33), 79

(16), 79(16), 75 (100), 73 (40), 61 (44), 59 (32); HRMS (FAB) calcd for $(C_{29}H_{50}O_2Si)^+$ *m/z* 458.3578, meas 458.3580. Colorless oil; R_f = 0.28 (9:1 hexanes/Et_2O).

Preparation of PNB ester of alcohol 381

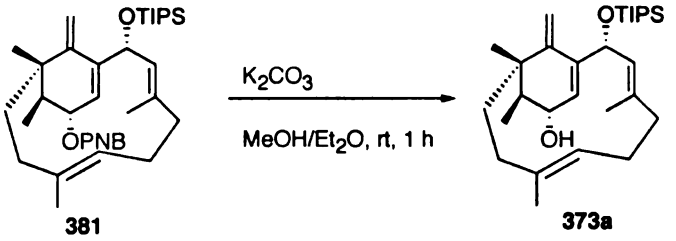


373b **381**

To a solution of *para*-nitrobenzoic acid (27.7 mg, 0.166 mmol), alcohol **373b** (38 mg, 0.083 mmol) and PPh_3 (43 mg, 0.166 mmol) in 1.0 mL of toluene at 0 °C was added DEAD (27.7 μL, 0.166 mmol) dropwise. The reaction mixture was stirred at 0 °C for 1 hour, and then allowed to warm up to room temperature for 1.5 hours. The reaction was quenched with 5 mL of a saturated aqueous $NaHCO_3$. The aqueous layer was extracted with Et_2O (3 * 5 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. Filtration and concentration followed by flash chromatography on silica gel using 19:1 hexanes/EtOAc as eluent provided ester **381** (46.3 mg, 0.076 mmol, 91%) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.92 (d, 3H, *J* = 7.3 Hz), 0.98 (s, 3H), 1.00-1.04 (m, 21H), 1.32 (s, 3H), 1.41-1.47 (m, 2H), 1.49 (s, 3H), 1.73-1.84 (m, 3H), 1.92-2.25 (m, 4H), 4.70 (d, 1H, *J* = 10.4 Hz), 4.92 (d, 1H, *J* =7.3 Hz), 5.28 (s, 1H), 5.29 (d, 1H, *J* = 0.8 Hz), 5.47 (d, 1H, *J* = 4.0 Hz), 5.58 (d, 1H, *J* = 4.8 Hz), 6.20 (s, 1H), 8.16 (d, 2H, *J* = 9.0 Hz), 8.27 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR

($CDCl_3$, 125 MHz) δ 12.11, 14.70, 14.90, 15.21, 17.95, 17.99, 21.62, 23.84, 35.00, 37.17, 39.25, 42.05, 43.78, 75.83, 117.99, 120.11, 123.57, 125.09, 130.52, 130.94, 133.11, 135.19, 136.13, 142.15, 142.72, 150.55, 164.01; IR (neat) 2944, 2866, 1723, 1532, 1348, 1271, 1115, 1101, 1082, 918, 735, 720, 682 cm^{-1}; mass spectrum *m/z* (% rel intensity) 607 M^+ (0.2), 280 (60), 266 (18), 185 (21), 173 (47), 171 (42), 159 (25), 157 (36), 150 (85), 143 (26), 133 (28), 131 (100), 119 (40), 115 (27), 105 (30), 104 (39), 103 (98), 95 (31), 81 (95), 75 (100), 61 (58), 59 (52). HRMS (CI) calcd for $(C_{29}H_{49}OSi)^+$ *m/z* 441.3553 meas 441.3562. Colorless oil; R_f = 0.40 (19:1 hexanes/EtOAc).

Cleavage of PNB ester 381

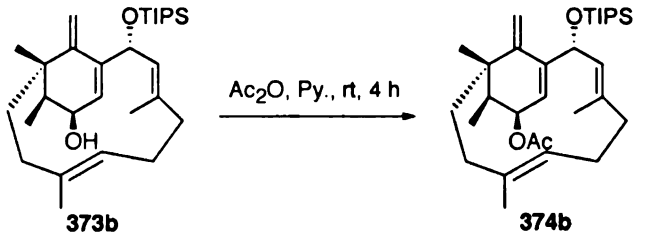


381 **373a**

To a solution of PNB-ester **381** (30.8 mg, 0.051 mmol) in 4.5 mL of a mixture of $MeOH/Et_2O$ (2:1) at room temperature was added K_2CO_3 (35 mg, 0.25 mmol) as a powder. The reaction mixture was stirred at room temperature until the starting material was totally consumed, and then quenched with saturated aqueous NH_4Cl (5 mL). The aqueous layer was extracted with Et_2O (3 * 5 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. Filtration and concentration followed by flash chromatography on silica

gel using hexanes/EtOAC (9:1) as eluent provided alcohol **373a** (23.1 mg, 0.050 mmol, 99%) as a colorless oil.

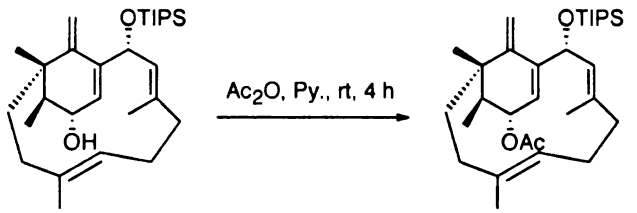
Preparation of acetate 374b



To a solution of alcohol **373b** (12.9 mg, 0.0282 mmol) in 1.0 mL of pyridine was added 0.2 mL of acetic anhydride. The mixture was stirred at room temperature for 4 hours and then was evaporated to dryness. The residue was purified by silica gel column chromatography using 9:1 hexanes/EtOAc as eluent to give acetate **374b** (14.3 mg, 0.0282 mmol, 100%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.72 (d, 3H, *J* = 6.8 Hz), 0.95 (s, 3H), 1.00-1.04 (m, 21H), 1.31 (s, 3H), 1.44 (s, 3H), 1.46-1.60 (m, 2H), 1.76-1.93 (m, 4H), 2.00-2.13 (m, 3H), 2.05 (s, 3H), 4.65 (d, 1H, *J* = 10.9 Hz), 4.84 (d, 1H, *J* =7.3 Hz), 5.04 (s, 1H), 5.25 (s, 1H), 5.46 (d, 1H, *J* = 7.1 Hz), 5.64 (dd, 1H, *J* = 6.0, 2.2 Hz), 6.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 9.03, 12.04, 14.61, 15.38, 17.96, 21.28, 21.70, 23.87, 33.72, 35.37, 39.25, 42.65, 45.60, 71.87, 76.64, 116.09, 123.62, 124.77, 131.13, 132.60, 135.53, 141.14, 142.21, 170.83; IR (neat) 2944, 2867, 1742, 1242, 1082, 883 cm^{-1}; mass spectrum *m/z* (% rel intensity) 500 M^+ (0.2), 398 (2), 359 (2), 268 (8), 173 (100), 131 (24), 103 (18), 81 (35), 75 (28), 61 (17), 59 (15),

43 (35). HRMS (FAB) calcd for $(C_{31}H_{52}O_3Si)^+$ m/z 500.3682, meas 500.3686. Colorless oil; R_f = 0.33 (19:1 hexanes/EtOAc).

Preparation of acetate 374a

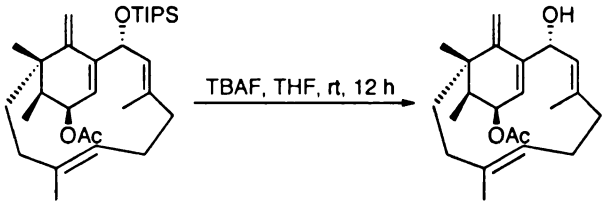


373a 374a

To a solution of alcohol **373a** (28 mg, 0.061 mmol) in 1.0 mL of pyridine was added 0.5 mL of acetic anhydride. The mixture was stirred at room temperature for 4 hours and then was evaporated to dryness. The residue was purified by silica gel column chromatography using 9:1 hexanes/EtOAc as eluent to give acetate **374a** (30.5 mg, 0.061 mmol, 100%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.82 (d, 3H, *J* = 7.4 Hz), 0.93 (s, 3H), 0.98-1.01 (m, 21H), 1.34 (s, 3H), 1.45 (s, 3H), 1.58-1.71 (m, 3H), 1.93-2.14 (m, 6H), 2.00 (s, 3H), 4.65 (d, 1H, *J* = 10.8 Hz), 4.87 (d, 1H, *J* = 7.3 Hz), 4.96 (d, 1H, *J* = 4.8 Hz), 5.13 (t, 1H, *J* = 1.5 Hz), 5.44-5.46 (m, 2H), 6.13 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.09, 14.69, 14.79, 14.97, 17.98, 21.40, 21.80, 23.88, 34.91, 36.56, 39.27, 41.96, 43.49, 74.19, 77.18, 117.15, 121.12, 124.58, 130.94, 132.86, 135.67, 141.69, 142.51, 170.56; IR (neat) 2941, 2867, 1734, 1240, 1082, 882 cm^{-1}; mass spectrum *m/z* (% rel intensity) 500 M^+ (0.1), 457 (2), 397 (7), 267 (11), 174 (15), 173 (100), 171 (25), 157 (26), 145 (25), 142 (16), 133 (21), 129 (70), 115 (16), 105 (27), 103 (44), 95 (22), 81 (56), 75 (60), 61 (38), 59 (40). HRMS (FAB) calcd

for $(C_{31}H_{52}O_3Si\text{-}H)^+$ *m/z* 499.3605, meas 499.3608. Colorless oil; R_f = 0.30 (19:1 hexanes/EtOAc).

Preparation of allylic alcohol 375b

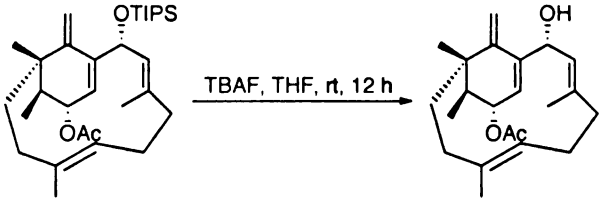


374b **375b**

To a solution of compound **374b** (39.5 mg, 0.079 mmol) in 2.0 mL of dry THF at room temperature was added TBAF (0.16 mL, 0.16 mmol, 1.0 M in THF) dropwise. The mixture was stirred overnight and then quenched with H_2O. The aqueous layer was extracted with Et_2O (3 * 10 mL). The combined organic layer was washed with brine (15 mL) and dried over Na_2SO_4. Filtration and concentration followed by flash chromatography using 4:1 hexanes/EtOAc as eluent provided alcohol **375b** (21.8 mg, 0.063 mmol, 80%) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.74 (d, 3H, *J* = 6.8 Hz), 0.98 (s, 3H), 1.29-1.34 (m, 1H), 1.36 (s, 3H), 1.44 (s, 3H), 1.48-1.57 (m, 2H), 1.77-1.81 (m, 2H), 1.87-1.96 (m, 3H), 2.10-2.16 (m, 2H), 2.07 (s, 3H), 4.65 (d, 1H, *J* = 10.8 Hz), 4.93 (d, 1H, *J* = 7.6 Hz), 5.09 (s, 1H), 5.41 (d, 1H, *J* = 1.2 Hz), 5.49 (d, 1H, *J* = 8.3 Hz), 5.66 (dd, 1H, *J* = 6.0 Hz, 2.3 Hz), 5.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.15, 14.79, 15.30, 21.22, 21.71, 23.94, 33.73, 35.02, 39.24, 42.42, 45.57, 71.61, 76.36, 115.95, 124.91, 125.08, 128.09, 135.44, 135.56, 140.90, 141.95, 170.58; IR (neat) 3416br, 2977, 2917, 2851, 1740, 1242, 1020 cm^{-1}; mass spectrum *m/z*

(% rel intensity) 344 M^+ (0.5), 302 (1), 284 (5), 269 (6), 203 (23), 201 (18), 187 (28), 185 (21), 175 (18), 171 (34), 161 (31), 160 (18), 159 (49), 157 (31), 149 (30), 147 (53), 145 (50), 143 (25), 137 (44), 135 (58), 131 (34), 129 (21), 121 (75), 115 (25), 107 (36), 106 (36), 95 (28), 91 (46), 81 (72), 56 (49), 43 (100). HRMS (FAB) calcd for $(C_{22}H_{32}O_3)^+$ *m/z* 344.2352, meas 344.2352. White solid, m.p. 134-135 °C; R_f = 0.32 (3:1 hexanes/EtOAc).

Preparation of allylic alcohol 375a

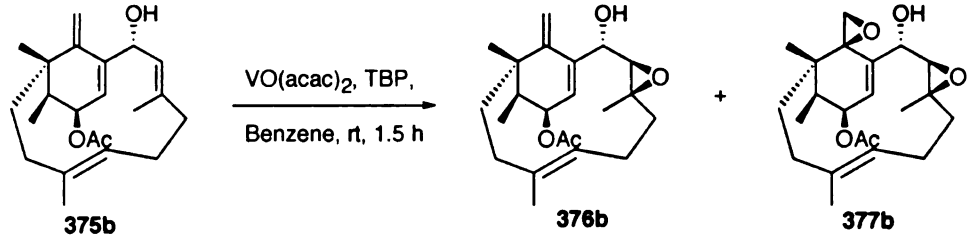


374a **375a**

To a solution of compound **374a** (30.5 mg, 0.061 mmol) in 1.2 mL of dry THF at room temperature was added TBAF (0.12 mL, 1.0 M in THF) dropwise. The mixture was stirred overnight and then quenched with H_2O. The aqueous layer was extracted with Et_2O (3 * 10 mL). The combined organic layer was washed with brine (15 mL) and dried over Na_2SO_4. Filtration and concentration followed by flash chromatography using 4:1 hexanes/EtOAc as eluent provided alcohol **375a** (16.4 mg, 0.048 mmol, 78%) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.84 (d, 3H, *J* = 7.3 Hz), 0.95 (s, 3H), 1.40 (s, 3H), 1.45 (s, 3H), 1.59-1.63 (m, 1H), 1.69-1.73 (m, 3H), 1.92-1.95 (m, 2H), 2.01 (s, 3H), 2.04-2.19 (m, 4H), 4.65 (d, 1H, *J* = 10.7 Hz), 4.95 (d, 1H, *J* = 8.3 Hz), 4.96 (d, 1H, *J* = 5.6 Hz), 5.17 (s, 1H), 5.47 (d, 1H, *J* = 7.8 Hz), 5.60 (d, 1H, *J* = 4.6 Hz), 6.02 (s, 1H); ^{13}C

NMR ($CDCl_3$, 125 MHz) δ 14.89. 14.93, 14.95, 21.36, 21.83, 23.99, 34.94, 36.15, 39.28, 42.03, 43.30, 73.82, 76.86, 116.79, 122.87, 124.68, 127.98, 135.66, 135.89, 141.12, 142.37, 170.48; IR (neat) 3441br, 2917, 1732, 1240, 1017 cm^{-1}; mass spectrum *m/z* (% rel intensity) 344 M^+ (2), 187 (16), 173 (28), 171 (18), 159 (28), 149 (34), 147 (30), 145 (29), 135 (20), 133 (39), 131 (21), 121 (36), 119 (49), 107 (18), 105 (35), 95 (20), 91 (36), 81 (45), 79 (27), 67 (23), 54 (39), 53 (18), 43 (100). HRMS (FAB) calcd for $(C_{22}H_{32}O_3)^+$ *m/z* 344.2352, meas 344.2352. Colorless oil; R_f = 0.29 (3:1 hexanes/EtOAc).

Epoxidation of allylic alcohol 375b



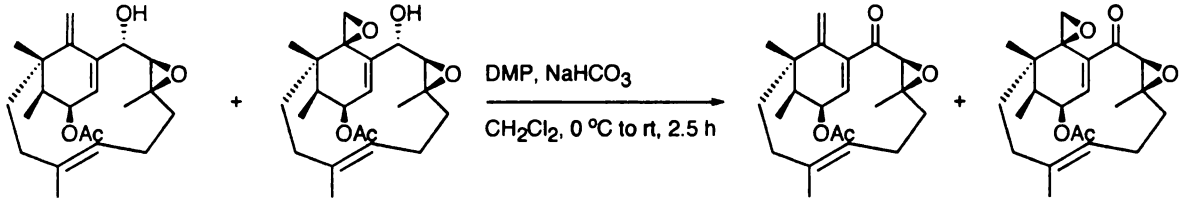
375b **376b** **377b**

A solution of newly opened *tert*-butyl hydroperoxide (75% W/W) in H_2O (0.016 mL) was added dropwise to a stirred solution of vanadyl acetylacetonate (25 mol%, 0.011 mmol) and the allylic alcohol **375b** (15.0 mg, 0.0436 mmol) in 1.0 mL of benzene at room temperature. The light green solution was turned to yellow brown and was stirred at room temperature for 90 minutes. The mixture was quenched with saturated aqueous $Na_2S_2O_3$ (5 mL) and stirred for another 15 minutes. The aqueous layer was extracted with Et_2O (3 * 5 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. Filtration and concentration followed by flash chromatography on silica gel using 2:1

hexanes/EtOAc as eluent provided mono-expoxide **376b** and *bis*-epoxide **377b** as an inseparable mixture (1:0.3, 11.7 mg total). This mixture was taken on to the next step without further purification.

The following spectral data for **376b** was collected on a sample of 6.5:1 mixture of **376b**:**377b**. **Mono-epoxide 376b** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.76 (d, 3H, *J* = 6.8 Hz), 1.03 (s, 3H), 1.09-1.15 (m, 1H), 1.16 (s, 3H), 1.52 (s, 3H), 1.58-1.65 (m, 1H), 1.81-1.85 (m, 1H), 1.93-1.98 (m, 2H), 2.00-2.25 (m, 4H), 2.07 (s, 3H), 3.28 (d, 1H, *J* = 8.5 Hz), 3.96 (dd, 1H, *J* = 8.4, 2.2 Hz), 4.83 (t, 1H, *J* = 6.1 Hz), 5.15 (s, 1H), 5.41 (s, 1H), 5.74 (dd, 1H, *J* = 6.1, 2.1 Hz), 6.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.05, 15.69, 16.46, 21.18, 22.60, 23.52, 32.81, 33.71, 38.79, 42.18, 45.50, 61.20, 65.54, 71.33, 79.52, 116.48, 121.84, 127.51, 136.71, 137.87, 142.44, 170.56; IR (neat) 3441, 2924, 1728, 1385, 1242, 1022 cm^{-1}. White solid (not pure); R_f = 0.20 (2:1 hexanes/EtOAc).

Oxidation of epoxy alcohol 376b and 377b



376b **377b** **378b** **378b**

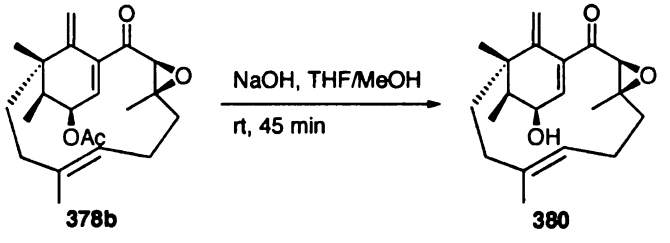
Freshly prepared DMP[93] (0.064 mmol, 27 mg) was added to a mixture of $NaHCO_3$ (22 mg, 0.26 mmol) and a mixture of the epoxy alcohols **376b** ∫and **377b** (11.7 mg) in 1 mL of dry CH_2Cl_2 at 0 °C. The mixture was stirred at 0 °C for 30 minutes and then allowed to warm to room temperature over a period of 2.5

hours. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with Et_2O (3 * 10 mL). The combined organic layer was washed with brine (15 mL) and dried over Na_2SO_4. Filtration and concentration followed by flash chromatography on silica gel using 3:1 hexanes/EtOAc containing 1% Et_3N as eluent provided epoxy ketone **378b** (10.2 mg, 65% 2 steps) and diepoxyketone **379b** (1.6 mg, 10% 2 steps).

Mono-epoxy ketone 378b ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.72 (d, 3H, *J* = 7.0 Hz), 1.079 (s, 3H), 1.082 (s, 3H), 1.15-1.23 (m, 2H), 1.47-1.53 (m, 1H), 1.55 (s, 3H), 1.86-1.94 (m, 2H), 1.96-2.02 (m, 1H), 2.07 (s, 3H), 2.07-2.21 (m, 3H), 4.04 (s, 1H), 4.98 (t, 1H, *J* = 6.8 Hz), 5.20 (s, 1H), 5.31 (s, 1H), 5.83 (dd, 1H, *J* = 5.9, 2.3 Hz), 5.86-5.87 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.16, 14.25, 16.82, 21.04, 22.22, 23.71, 32.30, 32.71, 38.23, 42.40, 45.85, 63.48, 65.18, 70.30, 116.76, 121.43, 129.92, 136.75, 142.80, 143.26, 170.50, 198.01. ^{1}H NMR (CD_3OD, 500 MHz) δ 0.70 (d, 3H, *J* = 7.0 Hz), 1.03 (d, 3H), 1.09 (s, 3H), 1.12-1.23 (m, 2H), 1.55 (s, 3H), 1.48-1.63 (m, 1H), 1.89-2.18 (m, 6H), 2.04 (s, 3H), 4.10 (s, 1H), 5.02 (t, 1H, *J* = 6.3 Hz), 5.26 (s, 1H), 5.34 (s, 1H), 5.77-5.78 (m, 2H); ^{13}C NMR (CD_3OD, 125 MHz) δ 9.46, 14.57, 16.74, 20.91, 22.58, 24.61, 33.52, 33.80, 39.01, 43.47, 46.98, 64.69, 66.66, 71.76, 117.86, 122.91, 131.23, 137.91, 144.14, 144.42, 172.04, 199.92. IR (neat) 2926, 1740, 1696, 1385, 1238, 1215, 1024 cm^{-1}; mass spectrum *m/z* (% rel intensity) 358 M^+ (0.05), 316 (2), 288 (1), 283 (2), 255 (2), 149 (17), 147 (26), 121 (24), 109 (22), 105 (21), 93 (17), 91 (29), 81 (24), 79 (20), 55 (23), 43 (100); HRMS (FAB) calcd for $(C_{22}H_{31}O_4)^+$ *m/z* 359.2223, meas 359.2222. Colorless oil; R_f = 0.21 (3:1 hexanes/EtOAc).

***Bis*-epoxy ketone 379b** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (s, 3H), 1.02 (d, 3H, *J* = 7.2 Hz), 1.15 (s, 3H), 1.22-1.31 (m, 2H), 1.55-1.61 (m, 1H), 1.62 (s, 3H), 1.97-2.06 (m, 2H), 2.09 (s, 3H), 2.10-2.35 (m, 4H), 3.07 (d, 1H, *J* = 3.2 Hz), 3.12 (d, 1H, *J* = 3.2 Hz), 3.67 (s, 1H), 5.20 (t, 1H, *J* = 6.4 Hz), 5.84 (dd, 1H, *J* = 6.4, 2.3 Hz), 6.01 (dd, 1H, *J* = 2.3, 1.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.71, 14.75, 17.66, 18.03, 20.99, 23.46, 31.39, 31.44, 37.65, 41.89, 42.97, 47.56, 55.63, 63.33, 65.94, 70.41, 119.98, 135.38, 136.52, 142.95, 170.50, 196.09; IR (neat) 2924, 1738, 1730, 1691, 1381, 1235, 1024 cm^{-1}; mass spectrum *m/z* (% rel intensity) 374 M^+ (0.01), 163 (19), 131 (18), 119 (23), 91 (25), 81 (26), 79 (20), 67 (22), 54 (17), 43 (100). HRMS (FAB) calcd for $(C_{22}H_{31}O_5)^+$ *m/z* 375.2172, meas 375.2171. Colorless oil; R_f = 0.13 (3:1 hexanes/EtOAc).

Cleavage of Acetate 378b

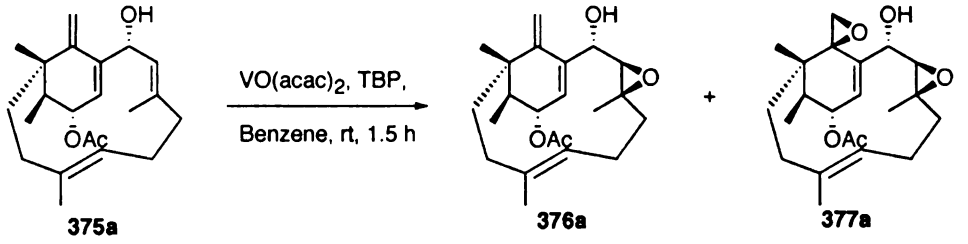


378b **380**

A solution of acetate **378b** (7.5 mg, 0.0208 mmol) in 1.0 mL of 1:4 mixture of THF/MeOH containing 8.3 mg of NaOH (0.21 mmol) was stirred at room temperature for 45 minutes. The reaction was then quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with Et_2O (3 * 10 mL). The combined organic layer was washed with brine (15 mL) and dried over Na_2SO_4. Filtration and concentration followed by flash chromatography on silica gel with

1:1 hexanes/EtOAc containing 1% Et_3N as eluent provided the C13-epimer of phomactin B2 **380** (5.9 mg, 0.0186 mmol, 90%) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.74 (d, 3H, *J* = 6.9 Hz), 1.09 (s, 3H), 1.10 (s, 1H), 1.13-1.23 (m, 2H), 1.39-1.45 (m, 2H), 1.54 (s, 3H), 1.57 (br, 1H), 1.85-1.95 (m, 3H), 2.08-2.18 (m, 4H), 4.03 (s, 1H), 4.77 (s, 1H), 4.97-5.00 (m, 1H), 5.17 (s, 1H), 5.28 (s, 1H), 5.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 8.15, 14.25, 16.77, 22.50, 23.74, 32.11, 32.64, 38.25, 44.98, 45.79, 63.34, 65.25, 67.72, 116.31, 121.34, 133.54, 136.79, 142.16, 143.67, 198.35. ^1H NMR (CD_3OD, 500 MHz) δ 0.70 (d, 3H, *J* = 6.8 Hz), 1.02 (s, 3H), 1.08 (s, 3H), 1.14-1.20 (m, 1H), 1.35 (s, 1H), 1.39-1.45 (m, 1H), 1.54 (s, 3H), 1.77-1.79 (m, 1H), 1.98-1.98 (m, 1H), 2.06-2.17 (m, 4H), 4.12 (s, 1H), 4.70 (dd, 1H, *J* = 5.8, 2.2 Hz), 5.01 (t, 1H, *J* = 6.8 Hz), 5.20 (s, 1H), 5.27 (s, 1H), 5.87 (t, 1H, *J* = 0.7 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 8.84, 14.54, 16.70, 22.83, 24.66, 33.62, 33.84, 39.15, 46.55, 46.97, 64.59, 66.80, 67.87, 116.79, 122.88, 136.14, 138.08, 142.87, 145.32, 200.40; IR (neat) 3483, 2973, 2924, 1689, 1251, 1039, 887 cm^{-1}; mass spectrum *m/z* (% rel intensity) 316 M^+ (1), 301 (2), 189 (18), 175 (19), 165 (56), 164 (33), 163 (26), 161 (22), 149 (84), 147 (27), 145 (15), 137 (20), 135 (66), 121 (60), 109 (40), 107 (44), 105 (40), 93 (46), 91 (73), 81 (60), 69 (33), 67 (37), 55 (30), 43 (100). HRMS (FAB) calcd for $(C_{20}H_{28}O_3+H)^+$ *m/z* 317.2116, meas 317.2117. Colorless oil; R_f = 0.31 (1:1 hexanes/EtOAc).

Epoxidation of allylic alcohol 375a

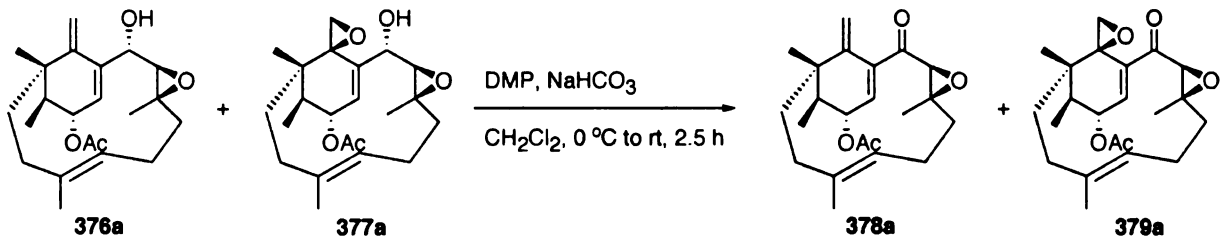


375a 376a 377a

A solution of newly opened *tert*-butyl hydroperoxide (75% W/W) in H_2O (0.008 mL) was added dropwise to a stirred solution of vanadyl acetylacetonate (3.2 mg, 0.012 mmol) and the allylic alcohol **375a** (16.5 mg, 0.048 mmol) in 1.0 mL of benzene at room temperature. The light green solution was turned to yellow brown and was stirred at room temperature for 90 minutes. The mixture was quenched with saturated aqueous $Na_2S_2O_3$ (5 mL) and stirred for another 15 minutes. The aqueous layer was extracted with Et_2O (3 * 10 mL). The combined organic layer was washed with brine (15 mL) and dried over Na_2SO_4. Filtration and concentration followed by flash chromatography on silica gel using 2:1 hexanes/EtOAc as eluent provided mono-epoxy alcohol **376a** and *bis*-epoxy alcohol **377a** as a 10:1 inseparable mixture (10:1, 11.7 mg in total), 78% based on recovered starting material. A small amount of starting material was also isolated (3.5 mg). The following spectral data for **376a** was collected on a sample of 10:1 mixture of **376a**:**377a**. Spectrum of mono-epoxy alcohol **376a** ^1H NMR ($CDCl_3$, 500 MHz) δ 0.86 (d, 3H, *J* = 7.3 Hz), 1.00 (s, 3H), 1.11-1.18 (m, 2H), 1.19 (s, 3H), 1.28-1.34 (m, 1H), 1.52 (s, 3H), 1.64-1.78 (m, 1H), 1.73-1.78 (m, 1H), 1.94-2.10 (m, 5H), 2.03 (s, 3H), 3.26 (d, 1H, *J* = 8.8 Hz), 3.97 (d, 1H, *J* = 8.5 Hz), 4.84-4.86 (m, 1H), 4.99 (dd, 1H, *J* = 4.8, 3.4 Hz), 5.23 (s, 1H), 5.59 (d,

1H, J = 4.6 Hz), 6.13 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.73, 15.94, 16.05, 21.34, 22.86, 23.53, 34.19, 34.52, 38.73, 42.00, 42.86, 61.59, 65.28, 73.56, 79.71, 117.26, 121.90, 125.28, 136.76, 138.28, 142.93, 170.38; IR (neat) 3443, 2924, 1732, 1385, 1240, 1020 cm^{-1}; R_f = 0.21 (2:1 hexanes/EtOAc).

Oxidation of epoxy alcohols 376a and 377a



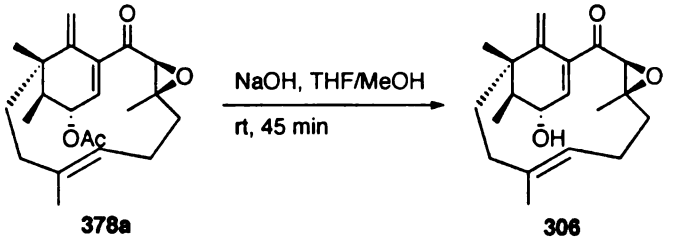
376a **377a** **378a** **379a**

Freshly prepared DMP[93] (24.7 mg, 0.058 mmol) was added to a mixture of $NaHCO_3$ (20 mg, 0.24 mmol) and a mixture of the epoxy alcohols **376a** and **377a** (10.5 mg mixture, 0.0264 mmol of **376a**) in 0.5 mL of dry CH_2Cl_2 at 0 °C. The mixture was stirred at 0 °C for 30 minutes and then allowed to warm to room temperature over a period of 2.5 hours. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with Et_2O (3 * 10 mL). The combined organic layer was washed with brine (15 mL) and dried over Na_2SO_4. Filtration and concentration followed by flash chromatography on silica gel using 3:1 hexanes/EtOAc containing 1% Et_3N as eluent provided epoxy ketone **378a** (6.5 mg, 0.018 mmol, 69%) as a colorless oil. Trace amount of **379a** was isolated, but not characterized.

Mono-epoxy ketone 378a ^1H NMR ($CDCl_3$, 500 MHz) δ 0.83 (d, 3H, J = 7.3 Hz), 1.06 (s, 3H), 1.13 (s, 3H), 1.20-1.26 (m, 1H), 1.29-1.35 (m, 1H), 1.55 (s,

3H), 1.71-1.76 (m, 1H), 1.83-1.88 (m, 1H), 2.06 (s, 3H), 2.10-2.19 (m, 4H), 2.27-2.29 (m, 1H), 4.03 (s, 1H), 5.01-5.02 (m, 1H), 5.05 (dd, 1H, J = 4.6, 1.5 Hz), 5.30 (d, 1H, J = 1.7 Hz), 5.33 (s, 1H), 5.97-5.98 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.43, 14.51, 16.38, 21.24, 22.26, 23.79, 33.00, 33.88, 38.12, 41.47, 43.48, 63.66, 64.76, 73.02, 117.86, 121.80, 127.93, 136.71, 143.28, 143.75, 170.06, 198.91. ^{1}H NMR (CD_3OD, 500 MHz) δ 0.79 (d, 3H, J = 7.3 Hz), 1.02 (d, 3H, J = 0.5 Hz), 1.05 (s, 3H), 1.17-1.22 (m, 1H), 1.32-1.37 (m, 1H), 1.53 (s, 3H), 1.70-1.72 (m, 1H), 1.85-1.89 (m, 1H), 2.00 (s, 3H), 2.02-2.23 (m, 5H), 4.08 (s, 1H), 4.98-5.00 (m, 2H), 5.34 (s, 1H), 5.35 (s, 1H), 5.90-5.91 (m, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 14.74, 14.77, 16.38, 21.06, 22.63, 24.69, 34.54, 35.06, 38.93, 42.93, 44.56, 64.93, 66.33, 74.43, 118.99, 123.39, 129.22, 137.91, 144.63, 145.06, 171.83, 200.84. IR (neat) 2923, 1734, 1690, 1237 cm^{-1}; mass spectrum *m/z* (% rel intensity) 316 $(M-42)^+$ (5), 255 (6), 201 (15), 147 (100), 133 (18), 119 (21), 91 (24), 79 (20). HRMS (FAB) calcd for $(C_{22}H_{30}O_4+Na)^+$ *m/z* 381.2042, meas 381.2051. Colorless oil; R_f = 0.43 (2:1 hexanes/EtOAc).

Cleavage of Acetate 378a



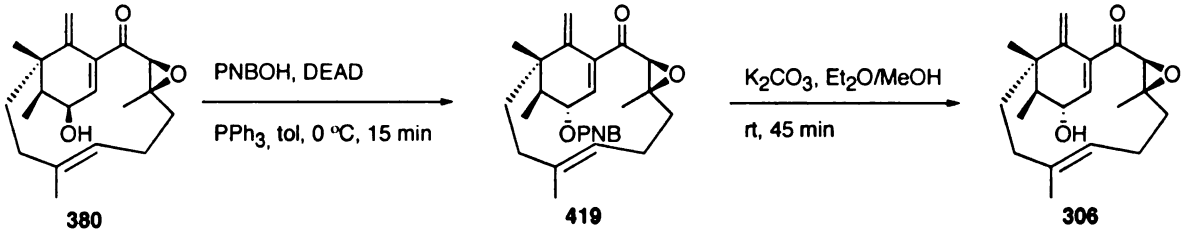
378a **306**

A solution of acetate **378a** (6.5 mg, 0.018 mmol) in 1.0 mL of 1:4 mixture of THF/MeOH containing NaOH (8.4 mg, 0.21 mmol) was stirred at room

temperature for 45 minutes. The reaction was quenched with saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with Et_2O (3 * 5 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. Filtration and concentration followed by flash chromatography using 1:1 hexanes/EtOAc containing 1% Et_3N as eluent provided 5.4 mg of phomactin B2 **306** (0.017 mmol, 94%) as a colorless oil. The following spectral match those reported for the natural product.[80b] ^1H NMR ($CDCl_3$, 500 MHz) δ 0.81 (d, 3H, *J* = 7.3 Hz), 1.05 (s, 3H), 1.14 (s, 3H), 1.30-1.35 (m, 1H), 1.48-1.52 (m, 1H), 1.55 (s, 3H), 1.69-1.72 (m, 1H), 1.80 (br, 1H), 1.85-1.89 (m, 1H), 2.06-2.19 (m, 4H), 2.27-2.31 (m, 1H), 4.04 (s, 1H), 4.06 (s, 1H), 5.00 (t, 1H, *J* = 6.4 Hz), 5.26 (s, 1H), 5.27 (d, 1H, *J* = 1.5 Hz), 6.06 (d, 1H, *J* =3.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.45, 14.95, 16.48, 23.00, 23.65, 33.55, 34.15, 37.61, 41.35, 45.44, 63.54, 64.68, 71.57, 116.74, 122.23, 131.92, 136.67, 141.47, 144.73, 199.61. ^1H NMR (CD_3OD, 500 MHz) δ 0.76 (d, 3H, *J* = 7.3 Hz), 1.02 (s, 3H), 1.05 (s, 3H), 1.26-1.32 (m, 1H), 1.46-1.50 (m, 1H), 1.52 (s, 3H), 1.64-1.67 (m, 1H), 1.85-1.89 (m, 1H), 1.98-2.15 (m, 4H), 2.10-2.30 (m, 1H), 3.92 (t, 1H, *J* = 3.0 Hz), 4.06 (s, 1H), 5.01 (tq, 1H, *J* = 6.8 1.2 Hz), 5.19 (s, 1H), 5.27 (d, 1H, *J* = 1.6 Hz), 5.93 (d, 1H, *J* = 4.0 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 14.62, 15.35, 16.53, 23.70, 24.51, 34.66, 35.34, 38.34, 42.45, 45.90, 64.75, 66.14, 71.98, 117.04, 123.66, 134.28, 137.93, 142.42, 146.62, 201.82. IR (neat) 3477, 2919, 1688, 1381, 1217, 1009 cm^{-1}; mass spectrum *m/z* (% rel intensity) 316 M^+ (0.4), 301 (2), 273 (3), 189 (16), 175 (17), 165 (71), 164 (28), 163 (24), 161 (20), 159 (17), 149 (55), 147 (34), 145 (20), 137 (20), 135 (45), 133 (35), 121 (56), 119 (38), 109 (43), 107

(41), 105 (49), 93 (53), 91 (81), 81 (56), 77 (48), 69 (26), 67 (48), 55 (74), 53 (48), 43 (100). HRMS (CI) calcd for $(C_{20}H_{28}O_3+Na)^+$ *m/z* 339.1936, meas 339.1945. Colorless oil; R_f = 0.31 (1:1 hexanes/EtOAc).

Mitsunobu reaction of C13-epimer 380



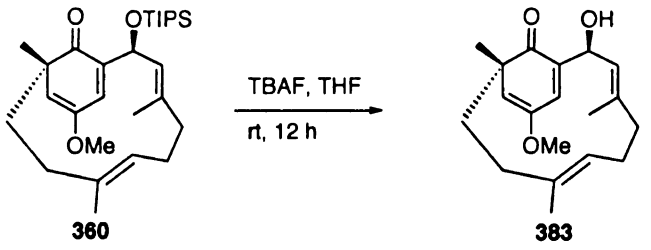
To a solution of *para*-nitrobenzoic acid (6.2 mg, 0.037 mmol), C13-epimer **380** (5.9 mg, 0.0187 mmol) and PPh_3 (9.8 mg, 0.037 mmol) in 0.9 mL of toluene at 0 °C was added DEAD (5.9 μL, 0.037mmol) dropwise. The reaction mixture was stirred at 0 °C for 15 minutes, and then quenched with saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with Et_2O (3 * 5 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. Filtration and concentration followed by flash chromatography using 3:1 hexanes/EtOAc as eluent provided ester **419** (7.0 mg, 0.015 mmol, 81%) as a yellow oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.92 (d, 3H, *J* = 7.3 Hz), 1.11 (s, 3H), 1.12 (s, 3H), 1.21-1.25 (m, 1H), 1.37-1.44 (m, 1H), 1.59 (s, 3H), 1.86-1.92 (m, 2H), 2.15-2.22 (m, 4H), 2.38-2.41 (m, 1H), 4.07 (s, 1H), 5.04-5.05 (m, 1H), 5.36 (d, 1H, *J* = 4.7 Hz), 5.38 (s, 1H), 5.43 (s, 1H), 6.11(d, 1H, *J* = 4.6 Hz), 8.16 (d, 2H, *J* = 9.0 Hz), 8.29 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.41, 14.61, 16.41, 22.01, 23.88, 33.31, 33.94, 38.19, 41.58, 43.83, 63.83, 64.80,

74.49, 118.73, 122.14, 123.72, 126.83, 130.62, 135.45, 136.50, 143.26, 143.86, 150.65, 163.66, 198.61; IR (neat) 2926, 1722, 1690, 15530, 1271, 1101, 720 cm^{-1}; mass spectrum *m/z* (% rel intensity) 300 $(M\text{-}OPNB)^+$ (3), 299 (4), 151 (73), 150 (63), 148 (91), 146 (100), 133 (26), 120 (80), 119 (100), 115 (25), 105 (91), 103 (36), 94 (16), 93 (33), 91 (91), 81 (49), 79 (21), 77 (25), 69 (21), 67 (22), 55 (73), 53 (25). HRMS (CI) calcd for $(C_{27}H_{31}NO_6+H)^+$ *m/z* 466.2243, meas 466.2237. Colorless oil; R_f = 0.41 (33% EtOAc in hexanes).

Cleavage of PNB ester 419

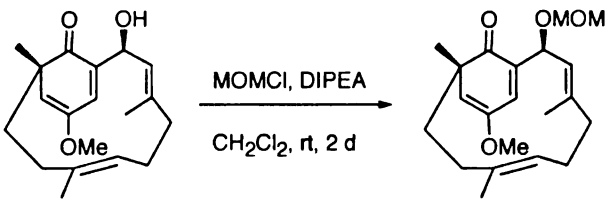
To a solution of PNB-ester **419** (5.0 mg, 0.0108 mmol) in 0.5 mL of MeOH/Et_2O (2:1) at room temperature was added K_2CO_3 (7.4 mg, 0.054 mmol) as a powder. The reaction mixture was stirred at room temperature until all of the starting material was consumed, and then quenched with saturated aqueous NH_4Cl (5 mL). The aqueous layer was extracted with Et_2O (3 * 5 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. Filtration and concentration followed by flash chromatography using 1:1 hexanes/EtOAc as eluent provided phomactin B2 **306** (2.9 mg, 0.0092 mmol, 85%) as a colorless oil.

Preparation of alcohol 383



To a solution of **360** (72 mg, 0.157 mmol) in 2.0 mL of THF at room temperature was added TBAF (0.31 mL, 1.0 M in THF). The reaction mixture was stirred overnight and then quenched with 5 mL of water. The aqueous layer was extracted with Et_2O (3 * 5 mL). The combined organic layer was washed with brine (5 mL), and then dried over $MgSO_4$, concentrated and chromatographed on silica gel using 9:1 hexanes/EtOAc as eluent to afford a 83% yield of the alcohol **383** (39.5 mg, 0.131 mmol). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.13 (s, 3H), 1.38-1.42 (m, 2H), 1.52 (s, 3H), 1.57 (br s, 1H), 1.69 (s, 3H), 1.70-1.75 (m, 1H), 1.86-1.89 (m, 1H), 1.92-1.98 (m, 2H), 2.25-2.36 (m, 2H), 3.63 (s, 3H), 4.49 (d, 1H, *J* = 11.3 Hz), 4.67 (d, 1H, *J* = 9.3 Hz), 4.90 (d, 1H, *J* = 3.2 Hz), 5.46 (d, 1H, *J* = 9.3 Hz), 6.99 (d, 1H, *J* = 3.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.32, 15.79, 25.42, 29.62, 35.95, 38.10, 39.21, 49.64, 54.77, 64.44, 110.65, 124.51, 128.33, 134.51, 134.58, 137.36, 140.51, 150.86, 202.29; IR (neat) 3443br m, 2917m, 1645s, 1597m, 1383s, 1129m, 1043m, 733m cm^{-1}; mass spectrum *m/z* (% rel intensity) 302 M^+ (4), 274 (16), 205 (18), 203 (21), 191 (17), 189 (73), 175 (26), 168 (42), 165 (17), 150 (18), 121 (16), 105 (15), 91 (26), 86 (62), 84 (100), 77 (24), 67 (18), 55 (25). HRMS (FAB) calcd for $(C_{19}H_{26}O_3+H)^+$ *m/z* 303.1959, meas 303.1960. Light yellow needle, m.p. 130-132 °C; R_f = 0.45 (3:1 hexanes/EtOAc).

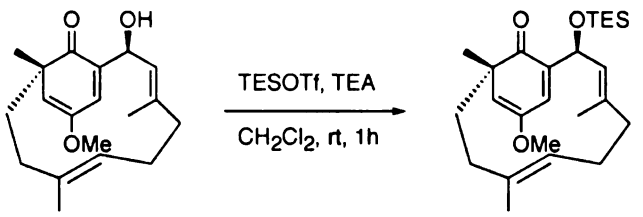
Preparation of MOM ether 362 from alcohol 383



383 **362**

To a solution of **383** (166 mg, 0.55 mmol) in 10 mL of CH_2Cl_2 at room temperature was added DIPEA (0.287 mL, 1.65 mmol) and MOMCl (0.083 mL, 1.10 mmol). The resulting solution was stirred for 2 days, and then quenched with saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with Et_2O (2 * 10 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel with 9:1 hexanes/EtOAc as eluent to give an 88% yield of MOM ether **362** (167 mg, 0.0484 mmol). The spectral data for this compound matched that for a product obtained from the thermolysis of compound **359** (vide supra).

Preparation of TES-ether 384

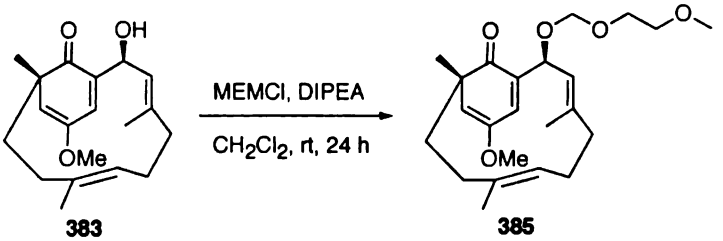


383 384

To a solution of **383** (2.2 mg, 0.0073 mmol) in 0.2 mL of CH_2Cl_2 at room temperature was added TEA (10 μL, 0.036 mmol) and TESOTf (3.3 μL, 0.014 mmol). The resulting solution was stirred for 1 hours, and then quenched with saturated aqueous $NaHCO_3$ (2 mL). The aqueous layer was extracted with Et_2O (2 * 5 mL). The combined organic layer was washed with brine (10 mL), and then dried over Na_2SO_4, filtered and concentrated. The crude product was purified by chromatography on silica gel with 9:1 hexanes/EtOAc as eluent to give a 92% yield of **384** (2.8 mg, 0.0067 mmol). ^1H NMR ($CDCl_3$, 500 MHz) δ 0.56 (qd, 6H, *J* = 7.8, 1.4 Hz), 0.91 (t, 9H, *J* = 7.8 Hz), 1.12 (s, 3H), 1.38-1.41 (m, 1H), 1.52 (d, 3H, *J* = 1.0 Hz), 1.66 (d, 3H, *J* = 1.1 Hz), 1.69-1.75 (m, 1H), 1.84-1.87 (m, 1H), 1.90-1.96 (m, 2H), 2.04-2.08 (m, 1H), 2.23-2.36 (m, 2H), 3.63 (s, 3H), 4.48 (d, 1H, *J* = 10.0 Hz), 4.63 (dd, 1H, *J* = 9.3, 1.2 Hz), 4.89 (d, 1H, *J* = 3.2 Hz), 5.37 (dd, 1H, *J* = 9.3, 1.0 Hz), 6.96 (dd, 1H, *J* = 3.2, 1.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.90, 6.78, 15.34, 15.59, 25.45, 29.75, 36.06, 37.95, 39.20, 49.66, 54.72, 64.70, 110.40, 124.62, 129.59, 134.42, 134.70, 134.78, 141.45, 151.04, 202.29; IR (neat) 2953, 2915, 2876, 1647, 1383, 1086, 843, 747 cm^{-1}; mass spectrum *m/z* (% rel intensity) 416 M^+ (7), 319 (23), 227 (24), 282 (57), 269 (17), 200 (21), 251 (41), 241 (71), 203 (28), 189 (94), 187 (22), 175 (21), 173 (20), 115 (46), 103

(26), 91 (30), 87 (100), 81 (40), 79 (24), 77 (24), 75 (58), 67 (21), 59 (73). HRMS (FAB) calcd for $(C_{25}H_{40}O_3Si+H)^+$ *m/z* 417.2825, meas 417.2828. colorless oil.

Preparation of MEM ether 385

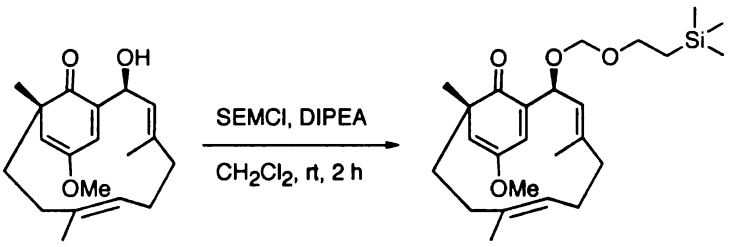


383 **385**

To a solution of **383** (10.9 mg, 0.036 mmol) in 0.5 mL of CH_2Cl_2 at room temperature was added DIPEA (12 μL, 0.072 mmol) and MEMCl (6.2 μL, 0.054 mmol). The resulting solution was stirred for 24 hours, and then quenched with 2 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with Et_2O (2 * 5 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was purified by chromatography on silica gel with 9:1 hexanes/EtOAc as eluent to give a 71% yield of **385** (10.0 mg, 0.0256 mmol). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.13 (s, 3H), 1.37-1.42 (m, 1H), 1.51 (s, 3H), 1.69 (s, 3H), 1.70-1.75 (m, 1H), 1.86-1.89 (m, 1H), 1.93-2.00 (m, 2H), 2.07-2.11 (m, 1H), 2.24-2.36 (m, 2H), 3.46 (s, 3H), 3.50 (td, 2H, *J* = 4.1, 1.2 Hz), 3.62 (s, 3H), 3.63-3.70 (m, 2H), 4.49 (d, 1H, *J* = 11.2 Hz), 4.56 (d, 1H, *J* = 9.5 Hz), 4.65 (d, 1H, *J* = 6.6 Hz), 4.77(dd, 1H, *J* = 6.6, 1.1 Hz), 4.90 (d, 1H, *J* = 2.9 Hz), 5.39 (dd, 1H, *J* = 9.5, 1.0 Hz), 6.90 (dd, 1H, *J* = 3.2, 1.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.36, 15.74, 25.41, 29.60, 35.94, 38.15, 39.33, 49.55, 54.76, 58.97, 66.98, 67.62, 71.82, 92.64, 110.63, 124.56, 126.42,

134.58, 135.05, 138.77, 138.88, 150.80, 202.06; IR (neat) 2919, 1647, 1599, 1451, 1382, 1129. 1038 cm^{-1}; mass spectrum *m/z* (% rel intensity) 390 M^+ (1), 362 (4), 284 (13), 203 (27), 189 (79), 175 (20), 167 (16) 151 (29), 144 (15), 135 (22), 115 (15), 105 (21), 89 (100), 81 (58), 79 (270, 77 (22), 67 (21), 59 (100), 55 (20), 53 (21). HRMS (FAB) calcd for $(C_{23}H_{34}O_5+H)^+$ *m/z* 391.2484, meas 391.2471. Light yellow oil; R_f = 0.30 (3:1 hexanes/EtOAc).

Preparation of SEM ether 386

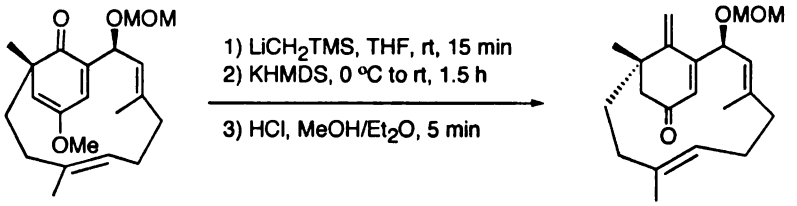


383 386

To a solution of **383** (11.1 mg, 0.0368 mmol) in 0.5 mL of CH_2Cl_2 at room temperature was added DIPEA (12.8 μL, 0.0736 mmol), SEMCl (10 μL, 0.0552 mmol) and Bu_4NI (16.3 mg, 0.044 mmol). The resulting solution was stirred for 2 hours, and then quenched with 2 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with Et_2O (2 * 5 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel with 9:1 hexanes/EtOAc as eluent to give a 63% yield of **386** (10.0 mg, 0.0231 mmol). ^1H NMR ($CDCl_3$, 500 MHz) δ -0.03 (s, 9H), 0.89 (t, 2H, *J* = 8.5 Hz), 1.13 (s, 3H), 1.37-1.42 (m, 1H), 1.52 (s, 3H), 1.69 (s, 3H), 1.71-1.76 (m, 1H), 1.86-1.89 (m,

1H), 1.93-2.00 (m, 2H), 2.08-2.12 (m, 1H), 2.24-2.37 (m, 2H), 3.53-3.61 (m, 2H), 3.62 (s, 3H), 4.50 (d, 1H, J = 11.3 Hz), 4.57 (d, 1H, J = 9.8 Hz), 4.61 (d, 1H, J = 6.6 Hz), 4.73 (d, 1H, J = 6.6 Hz), 4.90 (d, 1H, J = 3.2 Hz), 5.38 (d, 1H, J = 9.5 Hz), 6.91 (dd, 1H, J = 3.2 Hz, 1.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -1.43, 15.35, 15.74, 18.17, 25.43, 29.61, 35.96, 38.15, 39.33, 49.54, 54.74, 65.25, 67.60, 92.14, 110.57, 124.58, 126.64, 134.58, 135.06, 138.59, 138.93, 150.83, 202.09; IR (neat) 2951, 2918, 1649, 1383, 1055, 1028, 835 cm^{-1}; mass spectrum *m/z* (% rel intensity) 432 M^+ (0.4), 284 (10), 189 (44), 82 (22), 73 (100). HRMS (FAB) calcd for $(C_{25}H_{40}O_4Si)^+$ *m/z* 432.2696, meas 432.2699. Colorless oil; R_f = 0.32 (9:1 hexanes/EtOAc).

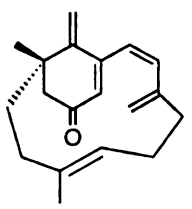
Preparation of dienone 388



362 **388**

Trimethylsilylmethyllithium (1.0 M in THF, 0.12 mL) was added dropwise to a solution of compound **362** (20.7 mg, 0.0598 mmol) in 0.3 mL of THF at 0 °C. The solution was stirred for 15 minutes at 0 °C, and then KHMDS (0.24 mL, 0.12 mmol, 0.5 M in toluene) was added. The reaction mixture was stirred for 1.5 hours at room temperature before quenching with H_2O (5 mL). The aqueous phase was separated and extracted with Et_2O (3 * 10 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in*

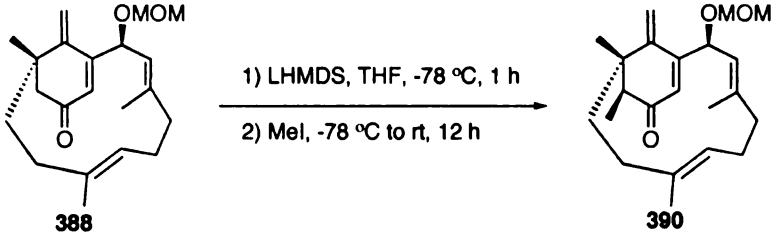
vacuo to give an unstable enol ether intermediate. The crude enol ether was dissolved in 1 mL of MeOH, and then treated with 1 mL of 1% aqueous HCl and stirred at room temperature for 5 minutes. The mixture was diluted with Et_2O (5 mL) and neutralized with saturated aqueous $NaHCO_3$ (10 mL). The aqueous phase was separated and then extracted with Et_2O (2 * 10 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel with a 9:1 hexanes/Et_2O as eluent to give ketone **388** (14.6 mg, 0.0442 mmol, 74%). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.18 (s, 3H), 1.35-1.41 (m, 1H), 1.44 (s, 3H), 1.67 (d, 3H, *J* = 1.2 Hz), 1.69-1.80 (m, 2H), 2.02-2.13 (m, 5H), 2.23 (d, 1H, *J* = 16.0 Hz), 2.46 (d, 1H, *J* = 16.0 Hz), 3.35 (s, 3H), 4.53 (d, 1H, *J* = 6.8 Hz), 4.63-4.67 (m, 2H), 4.69 (d, 1H, *J* = 6.8 Hz), 5.27 (dd, 1H, *J* = 9.8, 1.1 Hz), 5.30 (d, 1H, *J* = 1.5 Hz), 5.42 (s, 1H), 6.28 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.33, 16.74, 24.34, 24.84, 34.23, 35.59, 38.43, 42.81, 54.21, 55.46, 68.86, 93.23, 114.90, 122.99, 124.46, 124.63, 135.80, 140.37, 146.42, 157.38, 199.45; IR (neat) 2923, 1671, 1583, 1150, 1036, 916 cm^{-1}; mass spectrum *m/z* (% rel intensity) 330 M^+ (0.8), 285 (2), 269 (3), 247 (3), 105 (15), 91 (24), 81 (15), 66 (18), 45 (100). HRMS (FAB) calcd for $(C_{21}H_{30}O_3+H)^+$ *m/z* 331.2271, meas 331.2273. Light yellow oil; R_f = 0.40 (3:1 hexanes/EtOAc).



Compound **389** was isolated when KO*t*Bu was used in Peterson elimination (0 to 46% in different runs). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.21 (s,

3H), 1.25 (s, 3H), 1.79-2.11 (m, 6H), 2.30-2.33 (m, 2H), 2.34-2.35 (m, 2H), 4.93 (s, 1H), 5.01 (d, 1H, J = 8.3 Hz), 5.17 (s, 1H), 5.37 (s, 1H), 5.41 (s, 1H), 5.86 (s, 1H), 6.23 (d, 1H, J = 16.1 Hz), 6.83 (d, 1H, J = 16.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.17, 24.40, 29.47, 34.52, 34.84, 36.20, 43.91, 54.26, 111.57, 115.33, 123.56, 125.25, 126.97, 136.91, 141.93, 147.10, 147.60, 155.79, 199.28; IR (neat) 2938, 1655, 1553, 1260, 901, 733 cm^{-1}; mass spectrum *m/z* (% rel intensity) 268 M^+ (25), 253 (16), 240 (18), 226 (20), 224 (21), 209 (19), 198 (16), 196 (20), 185 (16), 183 (34), 171 (19), 169 (41), 159 (25), 155 (39), 145 (33), 141 (47), 133 (29), 128 (67), 121 (75), 115 (69), 105 (66), 91 (100), 77 (28), 65 (24), HRMS (FAB) calcd for $(C_{19}H_{24}O_3+H)^+$ *m/z* 269.1906, meas 269.1906. Light yellow oil; R_f = 0.48 (4:1 hexanes/EtOAc).

Methylation of dienone 388

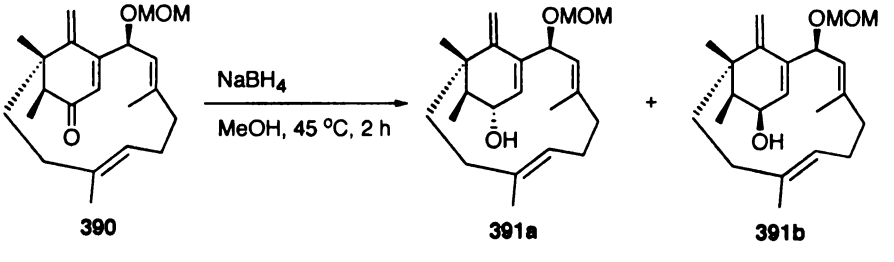


388 390

A solution of ketone **388** (9.7 mg, 0.0292 mmol) in 0.50 mL of THF was added to a solution of LHMDS (1.0 M in THF, 0.050 mL, 0.050 mmol) in THF at –78 °C. After stirring for 1 hour, iodomethane (4 μL, 0.07 mmol) was added. The cooling bath was removed immediately and the reaction mixture was allowed to warm to room temperature. After stirring for 11 hours, 2 mL of saturated aqueous NH_4Cl was added to the flask. The aqueous layer was extracted with Et_2O (2 * 10

mL). The combined organic layer was washed with brine (10 mL), and then dried over $MgSO_4$. The residue was purified by flash column chromatography on silica gel with 9:1 hexanes/Et_2O as eluent to give ketone **390** (9.0 mg, 0.0261 mmol, 96%). ^1H NMR ($CDCl_3$, 500 MHz) δ 0.96 (d, 3H, *J* = 7.3 Hz), 1.09 (s, 3H), 1.35-1.41 (m, 1H), 1.53 (s, 3H), 1.67 (d, 3H, *J* = 1.2 Hz), 1.69-1.74 (m, 1H), 1.78-1.83 (m, 1H), 2.01-2.16 (m, 6H), 3.35 (s, 3H), 4.53 (d, 1H, *J* = 6.5 Hz), 4.64-4.66 (m, 2H), 4.68 (d, 1H, *J* = 6.5 Hz), 5.26-5.28 (m, 2H), 5.51 (s, 1H), 6.17 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.95, 16.48, 16.58, 21.07, 24.33, 34.50, 36.41, 38.21, 45.65, 55.48, 55.51, 68.82, 93.34, 116.94, 120.98, 124.56, 124.80, 135.84, 140.14, 144.69, 156.08, 204.60; IR (neat) 2934, 1671s, 1587, 1150, 1036, 916 cm^{-1}; mass spectrum *m/z* (% rel intensity) 344 M^+ (1), 329 (0.4), 135 (13), 119 (15), 107 (16), 95 (12), 91 (15), 81 (22), 79 (17), 55 (24), 45 (100); HRMS (FAB) calcd for $(C_{22}H_{32}O_3+H)^+$ *m/z* 345.2430, meas 345.2430. Colorless oil; R_f = 0.38 (3:1 hexanes/EtOAc).

Reduction of ketone 390



390 **391a** **391b**

To a solution of ketone **390** (32.5 mg, 0.094 mmol) in 0.2 mL of MeOH at room temperature was added sodium borohydride (63.9 mg, 1.88 mmol) as a powder. The reaction mixture was heated at 45 °C until **390** was all consumed

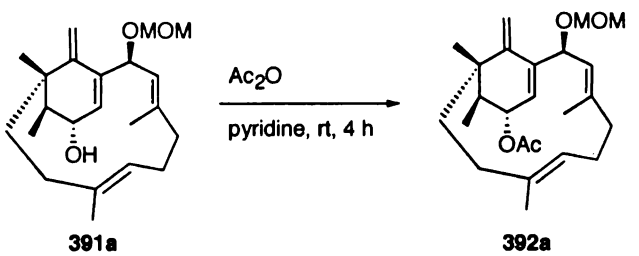
(monitored by TLC). The reaction was cooled to room temperature and diluted with Et_2O (5 mL), and then quenched with water (5 mL). The aqueous layer was extracted with Et_2O (3 * 5 mL). The combined organic layer was washed with brine (5 mL), dried over $MgSO_4$, concentrated and carefully chromatographed on silica gel (15% EtOAc in hexanes as eluent) to afford alcohol **391a** (10.0 mg, contaminated by ~ 3:1 over-reduction product, 0.0216 mmol, 23%) and **391b** (15.2 mg, 0.0437 mmol, 46%, contaminated by over-reduction product, the ratio was not determined). The two isomers of **391** (2:1 *dr*) could be separated by careful chromatography. However, each isomer was contaminated by an impurity (~30% of impurity), which was tentatively identified as a 1,6-over-reduction product.

Major isomer 391b ^1H NMR ($CDCl_3$, 500 MHz) δ 0.91 (d, 3H, *J* = 6.9 Hz), 0.92 (s, 3H), 1.48 (s, 3H), 1.64 (d, 3H, *J* = 1.2 Hz), 1.74 (d, 1H, *J* = 1.4 Hz), 1.81-1.86 (m, 2H), 1.98-2.15 (m, 6H), 3.36 (s, 3H), 3.99-4.01 (m, 1H), 4.57 (d, 1H, *J* = 6.5 Hz), 4.68-4.70 (m, 3H), 4.97 (d, 1H, *J* = 1.4 Hz), 4.99 (s, 1H), 5.12-5.15 (m, 1H), 6.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.91, 15.75, 16.18, 25.28, 25.40, 34.47, 34.71, 39.17, 40.32, 42.48, 55.35, 68.77, 70.87, 93.27, 109.09, 125.01, 125.34, 127.45, 134.93, 137.86, 138.20, 147.10; IR (neat) 3409, 2922, 1452, 1148. 1200, 1038 cm^{-1}; mass spectrum *m/z* (% rel intensity) 346 M^+ (0.08), 284 (5), 269 (4), 203 (10), 175 (15), 161 (18), 159 (18), 149 (18), 147 (20), 145 (20), 135 (25), 133 (23), 121 (34), 119 (21), 107 (30), 105 (30), 95 (27), 93 (21), 91 (33), 81 (37), 79 (24), 67 (29), 55 (36), 45 (100); HRMS (FAB) calcd

for $(C_{22}H_{34}O_3\text{-}H)^+$ *m/z* 345.2430, meas 345.2431. Colorless oil; R_f = 0.20 (4:1 hexanes/EtOAc).

Minor isomer 391a ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.73 (d, 3H, *J* = 6.8 Hz), 1.06 (s, 3H), 1.36-1.41 (m, 2H), 1.47 (s, 3H), 1.64 (d, 3H, *J* = 2.3 Hz), 1.67-1.74 (m, 2H), 1.84-1.89 (m, 1H), 1.99-2.09 (m, 4H), 3.36 (s, 3H), 4.56 (d, 1H, *J* = 6.6 Hz), 4.64-4.65 (m, 3H), 4.67 (d, 1H, *J* =6.5 Hz), 4.86 (s, 1H), 5.13 (s, 1H), 5.13 (d, 1H, *J* = 9.6 Hz), 5.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 8.36, 16.19, 17.00, 21.96, 24.44, 33.66, 35.44, 38.51, 44.78, 46.22, 55.32, 68.62, 68.79, 93.32, 110.26, 123.45, 124.75, 127.11, 136.08, 137.81, 138.79, 145.05; IR (neat) 3428, 2936, 1439, 1148, 1098, 1037 cm^{-1}; mass spectrum *m/z* (% rel intensity) 346 M^+ (0.3), 301 (3), 284 (9), 203 (18), 187 (17), 175 (20), 173 (24), 161 (25), 159 (33), 15), 131 (23), 127 (25), 147 (27), 145 (38), 143 (20), 135 (32), 133 (36), 131 (23), 121 (39), 119 (51), 115 (17), 107 (36), 105 (46), 91 (47), 81 (55), 79 (32), 67 (35), 55 (44), 45 (100).); HRMS (FAB) calcd for $(C_{22}H_{34}O_3)^+$ *m/z* 346.2508, meas 346.2509. Colorless oil; R_f = 0.16 (4:1 hexanes/EtOAc).

Acetylation of alcohol 391a

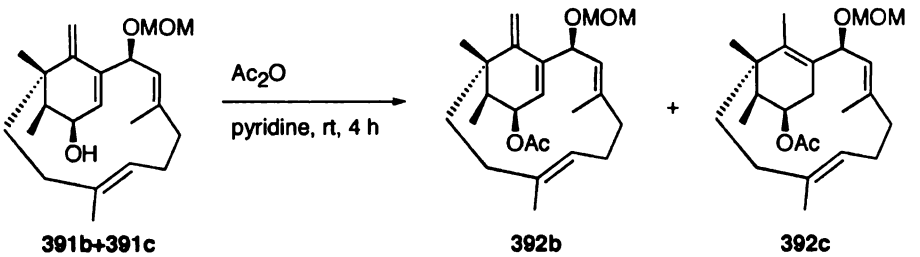


391a **392a**

To a solution of alcohol **391a** (10.7 mg, 0.0307 mmol) in pyridine (1.0 mL) was added acetic anhydride (0.2 mL). The mixture was stirred at room

temperature for 4 hours and then the solvent was evaporated to dryness. The residue was subjected to silica gel column chromatography (9:1 hexanes/EtOAc as eluent) to give **392a** (4.4 mg, 0.011 mmol, 37%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.71 (d, 3H, *J* = 6.8 Hz), 0.82-0.87 (m, 1H), 1.04 (s, 3H), 1.48 (s, 3H), 1.64 (d, 3H, *J* = 1.2 Hz), 1.73-1.78 (m, 1H), 1.83-1.90 (m, 2H), 2.01-2.10 (m, 5H), 2.06 (s, 3H), 3.36 (s, 3H), 4.56 (d, 1H, *J* = 6.5 Hz), 4.64 (d, 1H, *J* = 1.1 Hz), 4.67 (d, 1H, *J* = 6.5 Hz), 4.68 (br, 1H), 4.89 (s, 1H), 5.10 (s, 1H), 5.14 (d, 1H, *J* = 9.8 Hz), 5.70 (s, 1H), 5.73 (d, 1H, *J* = 5.6 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.32, 16.16, 17.05, 21.35, 21.68, 24.44, 33.67, 35.58, 38.56, 43.44, 44.86, 55.33, 68.83, 72.28, 93.31, 110.74, 119.74, 124.70, 126.99, 136.11, 138.02, 139.97, 144.72, 170.80; IR (neat) 2924, 2851, 1837, 1240, 1038 cm-1; mass spectrum *m/z* (% rel intensity) 326 $(M-62)^+$ (1), 284 (5), 203 (18), 201 (19), 187 (26), 185 (19), 173 (44), 171 (40), 159 (28), 157 (21), 147 (30), 106 (34), 133 (28), 107 (29), 91 (21), 82 (37), 57 (26), 46 (100). Colorless oil; R_f = 0.43 (15% EtOAc in hexanes).

Acetylation of alcohol 391b



391b+391c **392b** **392c**

To a solution of alcohol **391b** (18.2 mg, 0.0523 mmol) in pyridine (1.0 mL) was added acetic anhydride (0.2 mL). The mixture was stirred at room temperature for 4 hours and then the solvent was evaporated to dryness. The

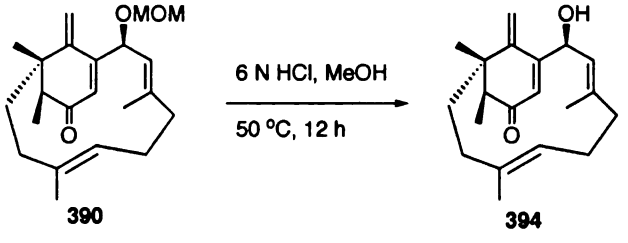
residue was subjected to silica gel column chromatography (9:1 hexanes/EtOAc as eluent) to give **392b** (13.7 mg, 0.035 mmol, 67%) and 1,6-over-reduction product **392c** in (3.4 mg, 0.0087 mmol, 18%).

Compound 392b ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.83 (d, 3H, *J* = 7.1 Hz), 0.97 (s, 3H), 1.48 (s, 3H), 1.59-1.64 (m, 1H), 1.65 (d, 3H, *J* = 1.2 Hz), 1.72-1.76 (m, 1H), 1.79-1.85 (m, 2H), 2.07 (s, 3H), 2.00-2.25 (m, 5H), 3.35 (s, 3H), 4.54 (d, 1H, *J* = 6.5 Hz), 4.67 (d, 1H, *J* = 6.5 Hz), 4.68-4.71 (m, 2H), 4.99 (d, 1H, *J* = 1.7 Hz), 5.05 (s, 1H), 5.13-5.15 (m, 2H), 5.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.83, 15.87, 16.25, 21.42, 24.18, 24.97, 29.69, 34.72, 38.78, 40.58, 40.84, 55.35, 68.83, 73.41, 93.30, 110.33, 120.25, 124.85, 127.04, 135.38, 138.04, 139.80, 146.08, 170.77; mass spectrum *m/z* (% rel intensity) 388 M^+ (0.14), 284 (12), 266 (30), 252 (22), 213 (19), 211 (19), 209 (28), 203 (35), 201 (34), 197 (22), 195 (30), 187 (40), 185 (40), 183 (31), 175 (17), 173 (70), 171 (100), 169 (35), 165 (19), 159 (44), 157 (48), 147 (44), 145 (46), 133 (45), 119 (54), 105 (38), 91 (43), 81 (60), 79 (33), 55 (40). Colorless oil; R_f = 0.43 (15% EtOAc in hexanes).

Compound **392c** was tentatively assigned to the above structure based on the NMR analysis. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (d, 3H, *J* = 7.1 Hz), 0.94 (s, 3H), 1.33-1.38 (m, 1H), 1.39-1.41 (m, 3H), 1.53 (s, 3H), 1.58-1.66 (m, 1H), 1.73 (m, 3H), 1.86-1.89 (m, 1H), 1.91-2.03 (m, 2H), 2.00 (s, 3H), 2.06-2.12 (m, 3H), 2.25-2.45 (m, 3H), 3.32 (s, 3H), 4.42 (d, 1H, *J* = 6.4 Hz), 4.54 (d, 1H, *J* = 6.4 Hz), 4.77 (d, 1H, *J* = 11.0 Hz), 5.03 (d, 1H, *J* = 1.2 Hz), 5.13 (d, 1H, *J* = 10.6 Hz), 5.24-5.26 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.95, 14.80, 15.59, 16.57,

21.39, 23.03, 26.59, 28.07, 32.91, 35.36, 36.03, 38.74, 40.99, 55.15, 70.71, 73.27, 93.01, 123.67, 126.22, 128.12, 132.93, 133.83, 137.02, 171.12; IR (neat) 2924, 2851, 1736, 1250, 1036 cm^{-1}; mass spectrum *m/z* (% rel intensity) 330 $(M-60)^+$ (2), 268 (20), 253 (16), 239 (15), 197 (15), 187 (19), 186 (20), 185 (26), 175 (24), 173 (33), 171 (100), 159 (27), 157 (26), 147 (32), 145 (31), 133 (43), 128 (31), 121 (31), 119 (54), 109 (26), 107 (29), 105 (49), 98 (58), 95 (28), 91 (53), 83 (23), 81 (41), 79 (39), 67 (31), 55 (38). HRMS (FAB) calcd for $(C_{22}H_{33}O_2$ $(M-OMOM))^+$ *m/z* 329.2481, meas 329.2480. Light yellow oil; R_f = 0.41 (15% EtOAc in Hexanes).

Cleavage of MOM group in 390

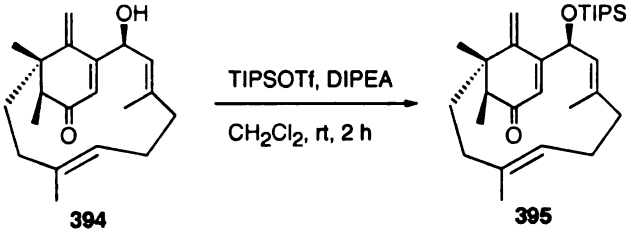


390 394

To a solution of MOM ether **390** (25 mg, 0.0727 mmol) in 3.7 mL of MeOH at room temperature was added 6 N HCl (0.024 mL). The reaction mixture was heated at 50 °C for 12 hours, and then cooled to room temperature. The mixture was diluted with Et_2O (5 mL) and neutralized with saturated aqueous $NaHCO_3$ (10 mL). The aqueous phase was separated and then extracted with Et_2O (2 * 10 mL). The combined organic layer was washed with brine (10 mL), and then dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel with 7:3 hexanes/Et_2O as eluent to give

alcohol **394** (20.2 mg, 0.0672 mmol, 93%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.95 (d, 3H, *J* = 7.2 Hz), 1.08 (s, 3H), 1.35-1.41 (m, 1H), 1.43 (s, 3H), 1.67 (d, 3H, *J* = 1.4 Hz), 1.71-1.72 (m, 1H), 1.78-1.83 (m, 1H), 2.02-2.14 (m, 6H), 4.64 (t, 1H, *J* = 6.5 Hz), 4.76 (dd, 1H, *J* = 9.5, 1.0 Hz), 5.24 (d, 1H, *J* = 1.6 Hz), 5.35 (d, 1H, *J* = 9.6 Hz), 5.47 (s, 1H), 6.24 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.89, 16.59, 16.37, 21.00, 24.29, 34.48, 36.43, 38.07, 45.72, 55.60, 66.50, 116.75, 120.28, 124.87, 126.74, 135.86, 128.98, 144.45, 157.73, 204.63; IR (neat) 3405 brs, 2932, 1653, 1385 cm^{-1}; mass spectrum *m/z* (% rel intensity) 300 M^+ (11), 189 (22), 187 (18), 176 (20), 173 (23), 169 (15), 161 (25), 159 (26), 148 (20), 145 (21), 141 (23), 135 (61), 128 (26), 121 (29) 105 (35), 91 (63), 81 (98), 77 (71), 67 (52), 55 (80), 53 (42), 41 (100); HRMS (FAB) calcd for $(C_{20}H_{28}O_2+H)^+$ *m/z* 301.2168, meas 301.2166. Colorless oil; R_f = 0.11 (3:1 hexanes/EtOAc).

Preparation of compound 395

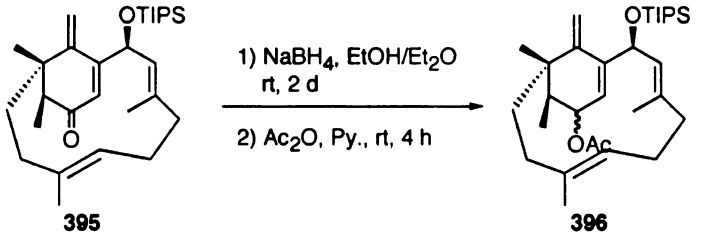


394 395

To a solution of allylic alcohol **394** (10.4 mg, 0.0347 mmol) in CH_2Cl_2 (1.7 mL) was added DIEPA (0.024 mL, 0.139 mmol) followed by the addition of tri*iso*propylsilyl triflate (0.019 mL, 0.069 mmol). The reaction mixture was stirred at room temperature for 2 hours and quenched with H_2O (10 mL). Diethyl ether (3 * 10 mL) was added to extract the product from the aqueous layer. The combined

organic layer was washed with brine (15 mL), and then dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by flash chromatography on silica gel (9:1 hexanes/EtOAc as eluent) provided the desired product **395** (15.4 mg, 0.0337 mmol, 97%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.93 (d, 3H, *J* = 7.2 Hz), 1.00-1.07 (m, 21H), 1.08 (s, 3H), 1.35-1.40 (m, 1H), 1.44 (s, 3H), 1.59 (d, 3H, *J* = 2.4 Hz), 1.67-1.71 (m, 1H), 1.76-1.81 (m, 1H), 2.03-2.10 (m, 6H), 4.67-4.69 (m, 1H), 4.81 (d, 1H, *J* = 8.8 Hz), 5.24 (d, 1H, *J* = 1.5 Hz), 5.30 (dd, 1H, *J* = 9.0, 1.1 Hz), 5.45 (s, 1H), 6.30 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.15, 13.74, 16.40, 16.76, 17.87, 17.98, 20.99, 24.39, 34.34, 36.85, 38.60, 45.70, 55.87, 67.00, 116.42, 121.10, 124.50, 127.67, 135.75, 136.75, 144.67, 158.72, 205.07; IR (neat) 2944, 2857, 1671, 1462, 1109, 1096, 884 cm^{-1}; mass spectrum *m/z* (% rel intensity) 456 M^+ (7), 413 (42), 171 (17), 157 (16), 143 (18), 141 (18), 131 (51), 128 (42), 119 (30), 103 (86), 95 (36), 91 (28), 81 (45), 79 (38), 76 (58), 75 (100), 73 (29), 61 (81), 59 (58), 55 (40), 43 (37); HRMS (FAB) calcd for $(C_{29}H_{48}O_2Si+H)^+$ *m/z* 457.3489, meas 457.3484. White solid; R_f = 0.29 (9:1 hexanes/EtOAc).

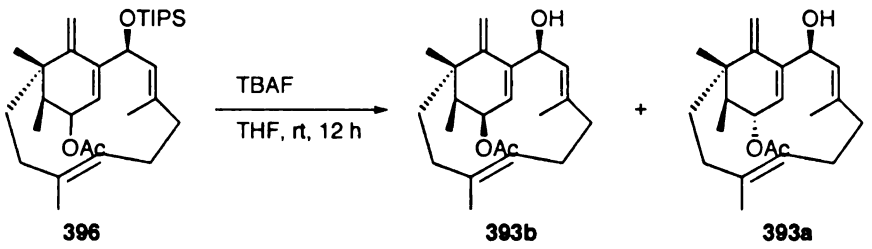
Reduction and acetylation of dienone 396



395 396

To a solution of dienone **395** (71.2 mg, 0.156 mmol) in 3.0 mL of 1:1 mixture of EtOH/Et_2O was added $NaBH_4$ (53 mg, 1.56 mmol) at room temperature. The reaction mixture was stirred at room temperature until all of the ketone was consumed (monitored by TLC, ~ 2 days). The reaction was quenched with H_2O, and the aqueous layer was extracted with Et_2O (3 * 20 mL). The combined organic layer was washed with brine (20 mL) and dried over Na_2SO_4. After filtration and concentration, the residue was dissolved in 4 mL of pyridine, and then 1.0 mL of acetic anhydride was added. The mixture was stirred at room temperature for 4 hours and then was evaporated to dryness. The residue was purified by column chromatography on silica gel using 9:1 hexanes/EtOAc as eluent to give inseparable acetate **396** as a 2:1 Inseparable mixture of isomers (65.5 mg, 0.131 mmol, 84%) as a colorless oil.

Desilylation of TIPS-ether 396



396 **393b** **393a**

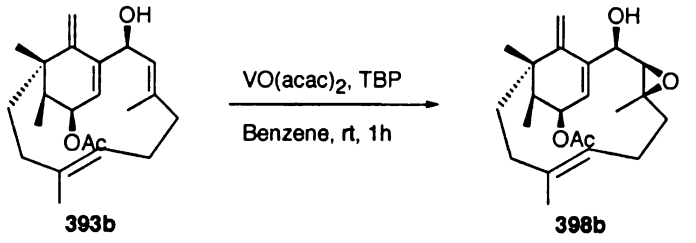
To a solution of the above mixture of acetated **396** (65.5 mg, 0.131 mmol) in 6.5 mL of dry THF at room temperature was added TBAF (0.26 mL, 0.26 mmol, 1.0 M in THF) dropwise. The mixture was stirred overnight and then quenched with H_2O (15 mL). The aqueous layer was extracted with Et_2O (3 * 20 mL). The combined organic layer was washed with brine (20 mL) and dried over Na_2SO_4. Filtration and concentration followed by flash chromatography on silica gel using 4:1 hexanes/EtOAc as eluent provided a ratio of 1:2 allylic alcohols **393a** (10.1 mg) and **393b** (20.0 mg) and 5.4 mg of mixture of the two products (0.103 mmol, 79% overall yield) as a colorless oil.

Major isomer 393b ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.71 (d, 3H, *J* = 6.8 Hz), 1.04 (s, 3H), 1.48 (s, 3H), 1.49-1.51 (m, 1H), 1.64 (s, 3H, *J* = 1.2 Hz), 1.71-1.76 (m, 1H), 1.84-1.89 (m, 2H), 2.06 (s, 3H), 2.01-2.10 (m, 5H), 4.65-4.68 (m, 1H), 4.75 (d, 1H, *J* = 9.5 Hz), 4.89 (s, 1H), 5.07 (s, 1H), 5.21-5.23 (m, 1H), 5.73 (d, 1H, *J* = 5.6 Hz), 5.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.31, 16.35, 17.03, 21.31, 21.62, 24.43, 33.71, 35.57, 38.40, 43.49, 44.92, 66.37, 72.19, 110.72, 118.91, 124.86, 128.96, 136.04, 136.84, 141.96, 144.49, 170.79; IR (neat) 3445, 2936, 1734, 1719, 1242, 1022 cm^{-1}; mass spectrum *m/z* (% rel intensity) 344 M^+ (1), 302 (1), 203 (16), 187 (19), 185 (17), 173 (34), 171 (25),

161 (16), 159 (30), 157 (19), 147 (34), 145 (31), 137 (25), 135 (36), 133 (36), 121 (45), 119 (67), 115 (23), 107 (44), 105 (61), 95 (36), 93 (49), 91 (69), 84 (43), 81 (100), 79 (43), 77 (33), 67 (32), 556 (32), 55 (27); HRMS (CI) calcd for $(C_{22}H_{31}O_2)^+$ (M-H_2O+H) *m/z* 327.2324, meas 327.2313. Colorless oil; R_f = 0.31 (3:1 hexanes/EtOAc).

Minor isomer 393a ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.83 (d, 3H, *J* = 6.8 Hz), 0.97 (s, 3H), 1.48 (s, 3H), 1.49 (d, 1H, *J* = 2.4 Hz), 1.65 (d, 3H, *J* = 1.5 Hz), 1.73-1.75 (m, 1H), 1.81-1.85 (m, 2H), 2.01-2.06 (m, 4H), 2.08 (s, 3H), 2.11-2.15 (m, 1H), 4.68-4.70 (m, 1H), 4.78 (d, 1H, *J* = 9.6 Hz), 4.99 (d, 1H, *J* = 1.5 Hz), 5.04 (s, 1H), 5.11-5.14 (m, 1H), 5.23 (d, 1H, *J* = 9.3 Hz), 5.92-5.93 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.92, 15.91, 16.42, 21.42, 24.04, 24.91, 34.68, 34.81, 38.64, 40.61, 41.03, 66.41, 73.35, 110.39, 119.46, 124.89, 128.94, 135.40, 136.79, 141.93, 145.82, 170.78; IR (neat) 3438br, 2922, 1732, 1242,1022 cm^{-1}; mass spectrum *m/z* (% rel intensity) 344 M^+ (1), 266 (17), 251 (16), 209 (17), 195 (20), 185 (32), 183 (22), 173 (52), 171 (64), 159 (39), 157 (64), 147 (29), 143 (38), 134 (32), 128 (67), 119 (49), 105 (43), 95 (32), 93 (32), 91 (50), 81 (91), 77 (55), 69 (29), 67 (37), 60 (22), 55 (51), 53 (28), 45 (34), 43 (100); HRMS (CI) calcd for $(C_{22}H_{31}O_2)^+$ (M-H_2O+H) *m/z* 327.2324, meas 327.2325. Colorless oil; R_f = 0.29 (3:1 hexanes/EtOAc).

Epoxidation of allylic alcohol 393b

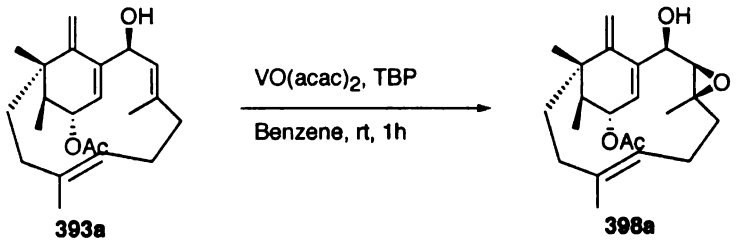


393b 398b

A solution of new *tert*-butyl hydroperoxide (75% W/W) in H_2O (1.8 μL) was added to a stirred solution of vanadyl acetylacetonate (1.0 mg, 0.0038 mmol) and the allylic alcohol **393b** (5.0 mg, 0.0145 mmol) in 0.72 mL of benzene at room temperature. After 15 minutes, another 0.9 μL of *tert*-butyl hydroperoxide was added to the solution. The light green solution turned yellow brown, and was stirred at room temperature for 60 minutes before quenching with 2 mL of saturated aqueous $Na_2S_2O_3$. The aqueous layer was extracted with Et_2O (3 * 10 mL). The combined organic layer was washed with brine (15 mL) and dried over Na_2SO_4. Filtration and concentration followed by flash chromatography on silica gel using 2:1 hexanes/EtOAc as eluent provided epoxy alcohol **398b** (4.6 mg, 0.0128 mmol, 88%) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.72 (d, 3H, *J* = 7.0 Hz), 1.03 (d, 3H, *J* = 0.5 Hz), 1.04-1.12 (m, 1H), 1.26 (s, 3H), 1.52 (s, 3H), 1,55-1.59 (m, 1H), 1.65-1.69 (m, 1H), 1.78-1.82 (m, 1H), 1.95-2.04 (m, 3H), 2.05 (s, 3H), 2.06-2.09 (m, 2H), 2.64 (s, 1H), 3.11 (d, 1H, *J* = 1.5 Hz), 4.79 (t, 1H, *J* = 6.8 Hz), 4.99 (s, 1H), 5.13-5.14 (m, 1H), 5.26 (s, 1H), 5.78-5.79 (m, 1H), 5.82-5.83 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.05, 14.82, 16.51, 21.25, 22.52, 23.43, 32.65, 34.25, 39.04, 43.04, 45.32, 62.59, 64.37, 65.02, 71.69, 111.29, 121.26, 121.57, 135.56, 137.14, 144.18,170.74; IR (neat) 3497br, 2924,

1738, 1373, 1242, 1024 cm^{-1}; mass spectrum *m/z* (% rel intensity) 318 $(M-42)^+$ (3), 167 (39), 162 (23), 150 (89), 149 (94), 135 (43), 124 (47), 121 (100), 119 (48), 105 (87), 91 (72), 81 (95); HRMS (CI) calcd for $(C_{22}H_{31}O_3)^+$ $(M-H_2O+H)$ *m/z* 343.2273, meas 343.2281. Colorless oil; R_f = 0.30 (3:1 hexanes/EtOAc).

Epoxidation of allylic alcohol 393a

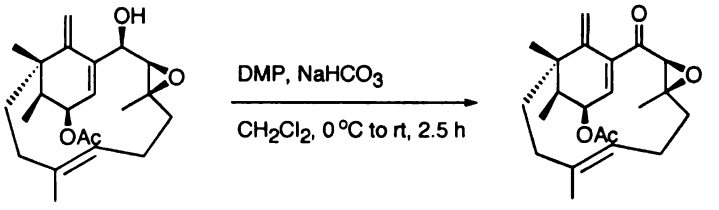


393a **398a**

A solution of new *tert*-butyl hydroperoxide (75% W/W) in H_2O (2.2 μL) was added to a stirred solution of vanadyl acetylacetonate (1.1 mg, 0.0041 mmol) and the allylic alcohol **393a** (6.0 mg, 0.0174 mmol) in 0.87 mL of benzene at room temperature. After 15 minutes, another 1.1 μL of *tert*-butyl hydroperoxide was added to the solution. The light green solution turned yellow brown, and was stirred at room temperature for 60 minutes before quenching with 2 mL of saturated aqueous $Na_2S_2O_3$. The aqueous layer was extracted with Et_2O (3 * 10 mL). The combined organic layer was washed with brine (15 mL) and dried over Na_2SO_4. Filtration and concentration followed by flash chromatography on silica gel using 2:1 hexanes/ EtOAc as eluent provided epoxy alcohol **398a** (7.6 mg, 0.0211 mmol, 93%) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.84 (d, 3H, *J* = 7.3 Hz), 0.99 (s, 3H), 1.31 (s, 3H), 1.33-1.42 (m, 2H), 1.52 (s, 3H), 1.68-1.73 (m, 2H), 1.98-2.02 (m, 1H), 2.03 (s, 3H), 2.05-2.13 (m, 3H), 2.63 (s, 1H), 3.08 (d,

1H, J = 4.4 Hz), 4.83-4.85 (m, 1H), 5.06-5.08 (m, 2H), 5.16-5.17 (m, 1H), 5.33 (s, 1H), 5.96-5.97 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.63, 15.14, 16.21, 21.42, 23.02, 23.42, 33.98, 35.13, 39.09,41.95, 42.92, 62.68, 64.23, 65.31, 73.25, 112.02, 118.92, 121.18, 136.37, 137.06, 144.61, 170.45; IR (neat) 3495br, 2924, 1730, 1385, 1240 cm^{-1}; colorless oil; R_f = 0.25 (3:1 hexanes/EtOAc).

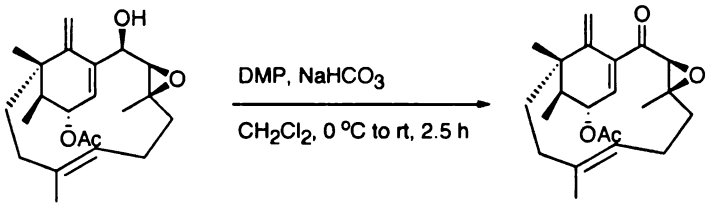
Oxidation of epoxy alcohol 398b



398b **378b**

Freshly prepared DMP[93] (0.047 mmol, 20 mg) was added to a mixture of $NaHCO_3$ (0.189 mmol, 16 mg) and the epoxy alcohol **398b** (8.5 mg, 0.0236 mmol) in 1 mL of dry CH_2Cl_2 at 0 °C. The mixture was stirred at 0 °C for 30 minutes, and then allowed to warm to room temperature over 2.5 hours. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with Et_2O (3 * 10 mL). The combined organic layer was washed with brine (15 mL) and dried over Na_2SO_4. Filtration and concentration followed by flash chromatography on silica gel using 3:1 hexanes/EtOAc containing 1% Et_3N as eluent provided epoxy ketone **378b** (7.5 mg, 0.021 mmol, 89%). The data for this product matched that obtained from the oxidation of **376b** (vide infra).

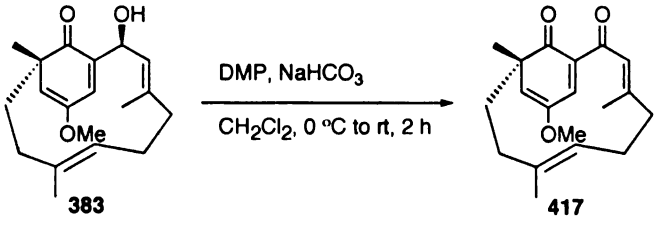
Oxidation of epoxy alcohol 398a



398a **378a**

Freshly prepared DMP[93] (0.032 mmol, 13.4 mg) was added to a mixture of $NaHCO_3$ (10.6vmg, 0.126 mmol) and the epoxy alcohol **398a** (5.7 mg, 0.0158 mmol) in 1 mL of dry CH_2Cl_2 at 0 °C. The mixture was stirred at 0 °C for 30 minutes and then allowed to warm to room temperature over 2.5 hours. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with Et_2O (3 * 10 mL). The combined organic layer was washed with brine (15 mL) and dried over Na_2SO_4. Filtration and concentration followed by flash chromatography on silica gel using 3:1 hexanes/EtOAc containing 1% Et_3N as eluent provided epoxy ketone **378a** (5.0 mg, 0.014 mmol, 88%). The data for this product matched that obtained from the oxidation of **376a** (vide supra).

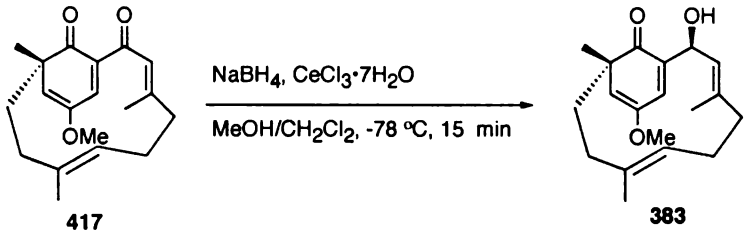
Oxidation of alcohol 383



Freshly prepared DMP[93] (138 mg, 0.325 mmol) was added to a mixture of $NaHCO_3$ (137 mg, 1.63 mmol) and alcohol **383** (49.3 mg, 0.163 mmol) in 5 mL of dry CH_2Cl_2 at 0 °C. The mixture was stirred at 0 °C for 30 minutes and then allowed to warm to room temperature over a period of 1.5 hours. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with Et_2O (3 * 5 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. Filtration and concentration followed by flash chromatography using 3:1 hexanes/EtOAc as eluent provided dione **417** (43.1 mg, 0.144 mmol, 88%) as a yellow solid. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.27 (s, 3H), 1.28 (s, 3H), 1.52-1.57 (m, 1H), 1.76 (d, 3H, *J* = 1.1 Hz), 1.75-1.80 (m, 1H), 1.97-2.03 (m, 1H), 2.09-2.22 (m, 5H), 3.56 (s, 3H), 4.79-4.82 (m, 1H), 5.22 (d, 1H, *J* = 3.4 Hz), 6.72 (s, 1H), 7.44 (d, 1H, *J* = 3.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.11, 17.79, 20.29, 26.31, 33.16, 37.36, 38.94, 51.62, 55.03, 117.02, 126.62, 128.22, 134.82, 134.97, 141.64, 148.73, 149.89, 188.90, 203.52; IR (neat) 2919, 2851, 1678, 1662, 1632, 1563, 1383, 1370, 1250, 1212, 1020 cm^{-1}; mass spectrum *m/z* (% rel intensity) 300 M^+ (2), 285 (4), 205 (26), 175 (21), 165 (19), 135 (19), 124 (27), 123 (55), 12 (29), 109 (100), 107 (34), 105 (19), 91 (52), 82 (43), 81 (38), 79 (39), 77 (38), 67 (21), 55 (28), 54 (30). HRMS (CI) calcd

for $(C_{19}H_{24}O_3+H)^+$ *m/z* 301.1799, meas 301.1804. Yellow solid, m.p. 130-132 °C; R_f = 0.39 (3:1 hexanes/EtOAc).

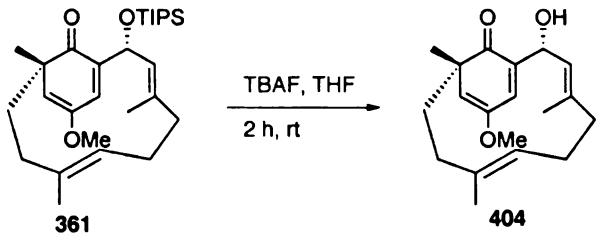
Reduction of ketone 417 with $NaBH_4/CeCl_3$



417 **383**

To a solution of dione **417** (17.2 mg, 0.057 mmol) in 4 mL of 1:1 mixture of $MeOH/CH_2Cl_2$ at –78 °C was added $NaBH_4$ (3.9 mg, 0.114 mmol) and $CeCl_3 \cdot 7H_2O$ (32 mg, 0.086 mmol). The reaction mixture was stirred at –78 °C for 15 minutes, and then diluted with Et_2O (5 mL) and quenched with water (5 mL). The aqueous layer was extracted with Et_2O (2 * 5 mL). The combined organic layer was washed with brine (10 mL), and then dried over Na_2SO_4, filtered and concentrated. The crude product was purified by chromatography on silica gel using 3:1 hexanes/EtOAc as eluent to give a 96% yield of β-alcohol **383** (16.5 mg, 0.0547 mmol). The spectral data for this compound matched that for a product obtained from the deprotection of compound **360** (vide supra).

Preparation of α-alcohol 404

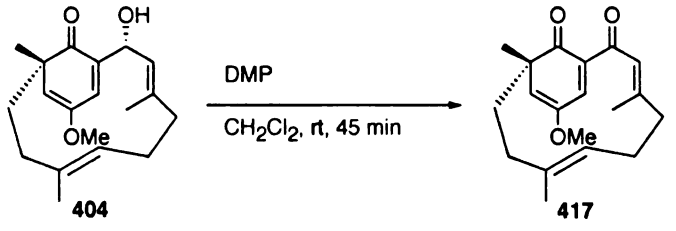


361 404

To a solution of **361** (19.1 mg, 0.042 mmol) in THF (1.0 mL) at room temperature was added TBAF (1.0 M solution in THF, 0.084 mL, 0.084 mmol). The reaction mixture was stirred for 2 hours and then quenched with water (5 mL). The aqueous layer was extracted with Et_2O (3 * 5 mL). The combined organic layer was washed with brine (5 mL), and then dried over $MgSO_4$, concentrated and chromatographed on silica gel (9:1 hexanes/EtOAc) to afford a 98% yield of alcohol **404** (12.4 mg, 0.041 mmol). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.17 (s, 3H), 1.45 (s, 3H), 1.41-1.49 (m, 1H), 1.52 (s, 3H), 1.84-1.99 (m, 4H), 2.16-2.21 (m, 2H), 2.32-2.37 (m, 1H), 3.61 (s, 3H), 3.77 (d, 1H, *J* = 11.0 Hz), 4.55 (t, 1H, *J* = 6.9 Hz), 4.76 (dd, 1H, *J* = 11.0, 8.5 Hz), 4.95 (d, 1H, *J* = 3.2 Hz), 5.36 (d, 1H, *J* = 8.5 Hz), 6.50 (d, 1H, *J* = 2.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.55, 16.66, 25.19, 28.85, 36.20, 37.16, 39.62, 50.20, 54.87, 72.30, 110.96, 124.47, 129.31, 134.11, 134.90, 136.22, 137.14, 149.93, 206.07; IR (neat) 3514 br, 2917, 2851, 1636, 1391, 1251, 1017 cm^{-1}; mass spectrum *m/z* (% rel intensity) 302 M^+ (3), 287 (13), 274 (79), 205 (33), 203 (22), 191 (35), 189 (91), 176 (26), 175 (100), 165 (44), 163 (26), 159 (20), 151 (47), 138 (29), 123 (34), 121 (31), 114 (24), 109 (31), 107 (331), 105 (37), 93 (31), 91 (87), 81 (42), 79 (52), 77 (67), 67 (43).

HRMS (FAB) calcd for $(C_{19}H_{26}O_3)^+$ *m/z* 302.1882, meas 302.1880. Colorless oil; R_f = 0.40 (3:1 hexanes/EtOAc).

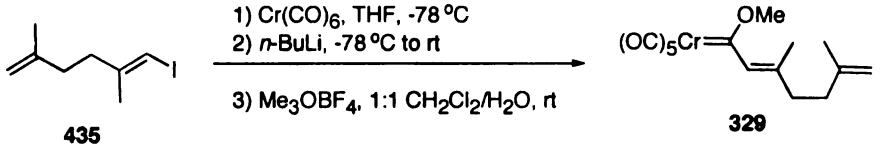
Oxidation of alcohol 404



404 **417**

Freshly prepared DMP[93] (17 mg, 0.040 mmol) was added to a solution of alcohol **404** (6.1 mg, 0.0202 mmol) in 0.5 mL of dry CH_2Cl_2 at room temperature. The mixture was stirred at room temperature for 45 minutes, and then quenched with 5% NaOH solution (2 mL). The aqueous layer was extracted with Et_2O (3 * 5 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. Filtration and concentration followed by flash chromatography using 3:1 hexanes/EtOAc as eluent provided dione **417** (4.6 mg, 0.0153 mmol, 76%) as yellow solid.

Preparation of carbene complex 329

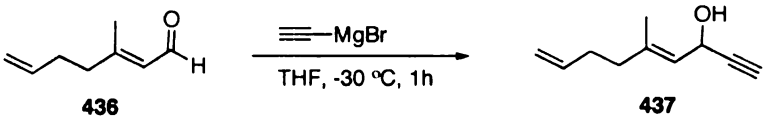


435 **329**

To a flame dried round bottom flask under Ar was added vinyl iodine **435** (755 mg, 3.20 mmol), $Cr(CO)_6$ (739 mg, 3.36 mmol) and THF (32 mL). The

solution was cooled to –78 °C, and *n*-butyl lithium (1.6 mL, 3.2 mmol, 2.0 M in hexanes) was added dropwise. The solution was stirred at –78 °C for 30 minutes, and then allowed to warm up to room temperature during 2 hours. The resulting carbene lithium acylate solution was concentrated *in vacuo*, and allowed to stand under high vacuum for 10 minutes. The acylate was dissolved in 20 mL of 1:1 CH_2Cl_2/H_2O, and then Me_3OBF_4 (947 mg, 6.40 mmol) was added to the solution and keep stirring for 30 minutes at room temperature under Ar. The reaction was quenched by pouring into a separatory funnel with saturated aqueous $NaHCO_3$ and hexanes. The aqueous layer was extracted with pentane until no red color was seen in the aqueous layer. The combined organic layer was washed with brine twice, and then dried over $MgSO_4$. The dried solution was filtered through a fritted funnel dry packed with Celite 503. The crude product was purified by silica gel chromatography on silica gel using pure pentane as eluent to provide carbene complex **329** (825 mg, 2.40 mmol, 75%) as a red oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.73 (s, 3H), 1.83 (s, 3H), 2.20-2.26 (m, 4H), 4.70 (s, 4H), 4.74 (s, 1H), 7.21 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.48, 22.30, 35.86, 39.09, 66.18, 110.82, 140.97, 142.02, 144.36, 216.76, 224.00, 340.25; IR (neat) 3079, 2957, 2058, 1917, 1651, 1586, 1455, 1377, 1250, 1094, 1042, 982, 891 cm^{-1}; mass spectrum *m/z* (% rel intensity) 344 M^+ (2), 288 (8), 260 (6), 232 (22), 204 (42), 172 (95), 148 (95), 107 (60), 91 (81). Anal calcd for $C_{15}H_{16}CrO_6$: C. 52.33; H, 4.68. Found: C, 52.68; H, 4.76. Red oil; R_f = 0.19 (hexanes).

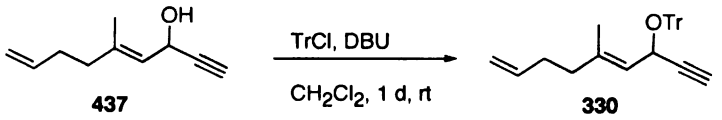
Preparation of propargyl alcohol 437



436 437

To a solution of aldehyde **436** (0.167 g, 1.33 mmol) in THF (4 mL) at –30 °C under an argon atmosphere was added ethynyl magnesium bromide (0.5 M solution in THF, 4.0 mL, 2.0 mmol) dropwise. The reaction mixture was stirred at –30 °C for 1 hour and quenched with saturated aqueous NH_4Cl (8 mL). The aqueous layer was extracted with Et_2O (3 * 10 mL). The combined organic layer was washed with brine (15 mL) and dried over $MgSO_4$. Flash chromatography on a silica gel column (eluent: 10% EtOAc in hexanes) provided the desired propargyl alcohol **437** as a colorless oil (0.141 g, 0.94 mmol, 71%). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.72 (d, 3H, *J* = 1.2 Hz), 1.73 (d, 1H, *J* = 5.1 Hz), 2.09-2.12 (m, 2H), 2.16-2.19 (m, 2H), 2.47 (d, 1H, *J* = 2.2 Hz), 4.94-4.96 (m, 1H), 5.01 (dq, 1H, *J* = 17.1, 2.0 Hz), 5.06 (ddd, 1H, *J* = 8.3, 6.1, 2.2 Hz), 5.38 (dq, 1H, *J* = 8.3, 1.2 Hz), 5.78 (ddt, 1H, *J* = 16.6, 10.0, 6.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 16.56, 31.70, 38.51, 58.89, 72.52, 84.40, 114.83, 124.37, 137.91, 140.46; IR (neat) 3300br, 1079, 2934, 2116, 1641, 1449, 1005, 914, 639 cm^{-1}; mass spectrum *m/z* (% rel intensity) 150 M^+ (9), 149 (100), 104 (5), 71 (9), 70(9), 57 (11). Anal calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.98; H, 9.46. Coclorless oil; R_f = 0.29 (CH_2Cl_2).

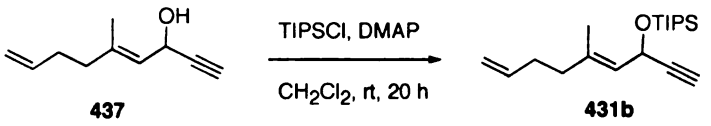
Preparation of trityl ether 330



437 330

To a solution of alcohol **437** (46.1 mg, 0.307 mmol) and TrCl (171 mg, 0.614 mmol) in 1 mL of CH_2Cl_2 was added DBU (0.10 mL, 0.614 mmol) dropwise. The solution was stirred at room temperature for 1 day, and then poured slowly into ice-cold water. The aqueous layer was extracted with CH_2Cl_2 (2 * 10 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), and dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel using 9:1 hexanes/EtOAc as eluent provided trityl ether **330** (118 mg, 0.301 mmol, 98%) as a colorless oil, which was crystallized in freezer after 1 week. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.28 (d, 3H, *J* = 1.2 Hz), 1.84-1.90 (m, 2H), 1.96-2.02 (m, 2H), 2.04 (d, 1H, *J* = 2.1 Hz), 4.67 (dd, 1H, *J* = 8.1, 2.1 Hz), 4.86-4.97 (m, 2H), 5.17-5.21 (m, 1H), 5.63-5.77 (m, 1H), 7.11-7.24 (m, 9H), 7.42-7.48 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.70, 31.74, 38.35, 61.95, 72.10, 83.27, 88.25, 114.56, 124.34, 127.02, 127.71, 128.98, 136.34, 138.24, 144.34. IR (neat) 3291, 3059, 2930, 1637m 1491, 1449, 1026, 708, 631 cm^{-1}; mass spectrum *m/z* (% rel intensity) 244 (35), 243 $(CPh_3)^+$ (100). Anal calcd for $C_{29}H_{28}O$: C. 88.73; H, 7.19. Found: C, 88.60; H, 7.08. Colorless needle, mp 47-48 °C; R_f = 0.60 (9:1 hexanes/Et_2O).

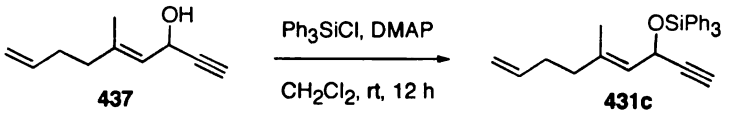
Preparation of TIPS-ether 431b



437 **431b**

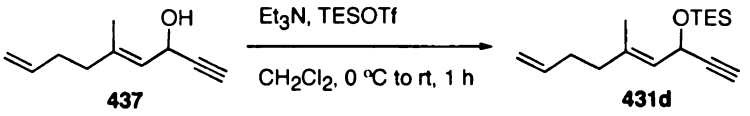
To a solution of propargyl alcohol **437** (149 mg, 0.99 mmol) in CH_2Cl_2 (10 mL) was added DMAP (366 mg, 3.00 mmol) followed by the addition of tri*iso*propylsilyl chloride (0.428 mL, 2.00 mmol). The reaction mixture was stirred at room temperature for 20 hours and then quenched with saturated aqueous $NaHCO_3$ (10 mL). Diethyl ether (3 * 20 mL) was added to extract the product from the aqueous layer. The combined organic layer was washed with brine (25 mL), and then dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by flash chromatography on silica gel (19:1 hexanes/EtOAC as eluent) provided the desired product **431b** (258 mg, 0.84 mmol, 84%) as colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.03-1.09 (m, 21H), 1.66 (d, 3H, *J* = 1.3 Hz), 2.06-2.09 (m, 2H), 2.14-2.19 (m, 2H), 2.40 (d, 1H, *J* = 2.2 Hz), 4.91-4.94 (m, 1H), 4.98-5.02 (m, 1H), 5.10 (dd, 1H, *J* = 8.0, 2.2 Hz), 5.34 (dq, 1H, *J* = 7.9, 1.3 Hz), 5.74-5.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.17, 16.66, 17.85, 17.90, 31.78. 38.46, 59.91, 71.47, 85.00, 114.66, 126.39, 136.21, 138.11; IR (neat) 3312, 3081, 2946, 2866, 1641, 1464, 1063, 883, 684, 654 cm^{-1}; mass spectrum *m/z* (% rel intensity) 263 $(M-43)^+$ (46), 131 (62), 130 (43), 103 (73), 91 (18), 77 (17), 75 (89), 61 (100). Anal calcd for $C_{19}H_{34}OSi$: C. 74.44; H, 11.18. Found: C, 74.33; H, 11.47. Colorless oil; R_f = 0.15 (hexanes).

Preparation of triphenylsilyl-ether 431c



To a solution of propargyl alcohol **437** (0.737 g, 4.91 mmol) in CH_2Cl_2 (10 mL) was added DMAP (1.20 g, 9.82 mmol) and triphenylsilyl chloride (2.17 g, 7.36 mmol) respectively. The reaction mixture was stirred at room temperature for 12 hours and quenched with saturated aqueous $NaHCO_3$ (10 mL). Diethyl ether (3 * 10 mL) was added to extract the product from the aqueous layer. The combined organic layer was washed with saturated aqueous NH_4Cl (25 mL), brine (25 mL), and then dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by flash chromatography on silica gel (19:1 hexanes/EtOAc as eluent) provided the desired product **431c** (1.88 g, 4.60 mmol, 94%) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.28 (d, 3H, *J* = 1.4 Hz), 1.97-2.00 (m, 2H), 2.03-2.09 (m, 2H), 2.38 (d, 1H, *J* = 2.2 Hz), 4.90-4.92 (m, 1H), 4.95-5.00 (m, 1H), 5.14 (dd, 1H, *J* = 8.6, 2.2 Hz), 5.42 (dq, 1H, *J* = 8.6, 1.4 Hz), 5.72 (ddt, 1H, *J* = 16.6, 10.3, 6.4 Hz), 7.34-7.37 (m, 6H), 7.39-7.41 (m, 3H), 7.64-7.66 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.27, 31.63, 38.44, 60.78, 72.38, 84.33, 114.65, 125.07, 127.75, 130.02, 134.03, 135.55, 137.88, 138.07; IR (neat) 3291, 3071, 2934, 2116 w, 1590, 1429, 1117, 1053, 712 cm^{-1}; mass spectrum *m/z* (% rel intensity) 408 M^+ (2), 289 (13), 259 (96), 210 (17), 199 (79), 197 (100), 181 (38), 180 (58), 105 (47), 91 (40), 79 (17), 77 (69). HRMS (CI) calcd for $(C_{28}H_{28}O+H)^+$ *m/z* 409.1988, meas 409.1998. Colorless oil; R_f = 0.41 (9:1 hexanes/EtOAc).

Preparation of TES-ether 431d

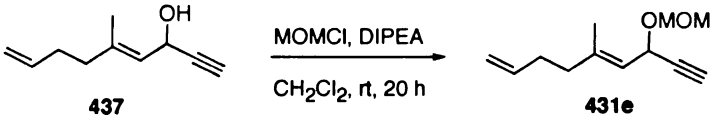


437 **431d**

To a solution of propargyl alcohol **437** (0.217 g, 1.45 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added TEA (1.0 mL, 7.17 mmol) followed by the addition of triethylsilyl triflate (0.654 mL, 2.89 mmol). The reaction mixture was allowed to warm to room temperature and stirred until all of the propargyl alcohol was consumed. The reaction was then quenched with saturated aqueous $NaHCO_3$ (10 mL). Diethyl ether (3 * 10 mL) was added to extract the product from the aqueous layer. The combined organic layer was washed with saturated aqueous NH_4Cl (15 mL), brine (15 mL), and then dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by flash chromatography on silica gel (49:1 hexanes/EtOAc as eluent) provided the desired product **431d** (278 mg, 1.05 mmol, 73%) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.63 (qd, 6H, *J* = 7.8, 2.0 Hz), 0.95 (t, 9H, *J* = 7.8 Hz), 1.67 (d, 3H, *J* = 1.2 Hz), 2.06-2.09 (m, 2H), 2.15-2.19 (m, 2H), 2.41 (d, 1H, *J* = 2.2 Hz), 4.92-4.95 (m, 1H), 4.98-5.02 (m, 1H), 5.04 (dd, 1H, *J* = 8.1, 2.2 Hz), 5.34 (dq, 1H, *J* = 8.3, 1.2 Hz), 5.79 (ddt, 1H, *J* = 16.6, 10.0, 6.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.79, 6.67, 16.48, 31.71, 38.51, 59.41, 71.64, 84.87, 114.66, 125.76, 137.16, 138.06; IR (neat) 3312, 2955, 2876, 1641, 1458, 1063, 1005, 749, 628 cm^{-1}; mass spectrum *m/z* (% rel intensity) 235 $(M-29)^+$ (4), 115 (14), 103 (100), 91 (18), 87 (27), 75 (70), 57 (23).

HRMS (CI) calcd for $(C_{16}H_{28}O+H)^+$ *m/z* 265.1988, meas 265.1991. Colorless oil; R_f = 0.35 (49:1 hexanes/EtOAc).

Preparation of MOM-ether 431e



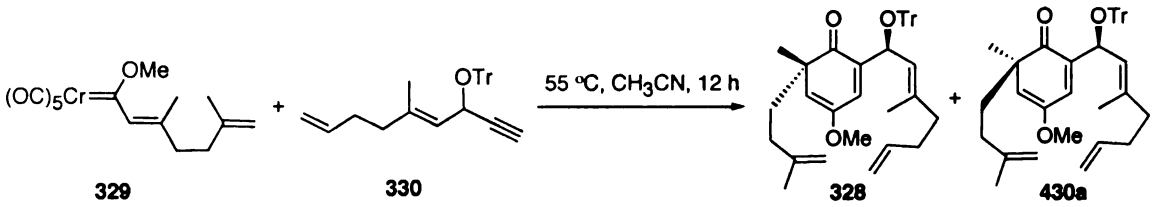
437 **431e**

To a solution of **437** (119 mg, 0.793 mmol) in CH_2Cl_2 (5 mL) at room temperature was added DIPEA (0.415 mL, 2.38 mmol) and MOMCl (0.12 mL, 1.59 mmol). The above solution was stirred for 20 hours, and then quenched with saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with Et_2O (2 * 10 mL). The combined organic layer was washed with brine (15 mL), and then dried over Na_2SO_4, filtered and concentrated. The crude product was purified by chromatography on silica gel using 9:1 hexanes/EtOAc as eluent to give a 86% yield of **431e** (133 mg, 0.696 mmol). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.70 (d, 3H, *J* = 1.2 Hz), 2.09-2.12 (m, 2H), 2.15-2.20 (m, 2H), 2.42 (d, 1H, *J* = 2.0 Hz), 3.36 (s, 3H), 4.59 (d, 1H, *J* = 6.8 Hz), 4.81 (d, 1H, *J* = 6.8 Hz), 4.93 (d, 1H, *J* = 10.3 Hz), 4.99 (d, 1H, *J* = 17.0 Hz), 5.03 (dd, 1H, *J* = 8.8, 2.2 Hz), 5.30 (dd, 1H, *J* = 8.8, 1.0 Hz), 5.73-5.80 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.51, 31.69, 38.57, 55.57, 61.45, 73,13, 82.12, 93.14, 114.77, 121.88, 137.90, 141.11; IR (neat) 3297, 3079, 2936, 1641, 1152, 1094, 1030, 942 cm^{-1}. Anal calcd for $C_{12}H_{18}O_2$: C. 74.19; H, 9.34. Found: C, 74.22; H, 9.72. Colorless oil; R_f = 0.36 (9:1 hexanes/EtOAc).

General procedure for the thermolysis of carbene complex 329 and alkynes

The carbene complex **329** and alkyne (1.2 equiv.) was dissolved in acetonitrile (0.02 M) and transferred to a schlenk flask equipped with a threaded Teflon high vacuum stopcock. The reaction was deoxygenated by the freeze-thaw procedure with 3 cycles. The flask was filled with an argon atmosphere at room temperature, sealed and heated at 55 °C. After the reaction was completed (indicated by the color of the carbene complex), the reaction mixture was cooled to room temperature, and the solvent was removed *in vacuo*. The residue was dissolved in 1:1 mixture of CH_2Cl_2/Et_2O and stirred in air at room temperature. After stirring 12 hours, the solution was passed through Celite 503, concentrated, and then purified by chromatography on silica gel (30:1:1 hexanes/ CH_2Cl_2/Et_2O) to afford the cyclized products.

Thermolysis of carbene complex 329 with alkyne 330



329 330 328 430a

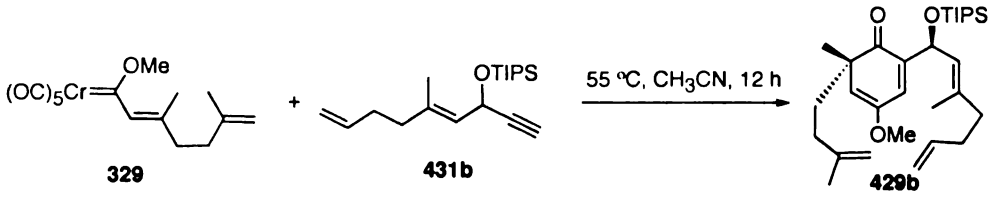
The thermolysis was performed with carbene complex **329** (68.8 mg, 0.20 mmol) and alkyne **330** (94 mg, 0.24 mmol) in 10 mL of CH_3CN according to the general procedure to afford **328** (97.4 mg, 0.167 mmol, 83%) and **430a** (98:2 *dr*) as yellow oil.

Major isomer 328 ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.93 (s, 3H), 1.26-1.35 (m, 3H), 1.52 (s, 3H), 1.56 (d, 3H, *J* = 1.4 Hz), 1.76-1.81 (m, 1H), 1.98-2.02 (m, 2H), 2.08-2.12 (m, 2H), 3.50 (s, 3H), 4.45 (s, 1H), 4.54 (s, 1H), 4.69 (d, 1H, *J* = 3.2 Hz), 4.92 (dq, 1H, *J* = 10.1, 2.0 Hz), 5.00 (dq, 1H, *J* = 17.0, 2.1 Hz), 5.04-5.06 (m, 1H), 5.30 (dd, 1H, *J* = 9.0, 0.7 Hz), 5.73-5.80 (m, 1H), 6.65 (dd, 1H, *J* = 3.1, 1.0 Hz), 7.11-7.14 (m, 3H), 7.18-7.21 (m, 6H), 7.43-7.43 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.98, 22.38, 27.02, 32.23, 32.37, 38.98, 41.25, 48.57, 54.54, 66.98, 87.79, 109.38, 109.47, 114.42, 125.38, 126.76, 127.60, 128.84, 136.02, 136.24, 138.29, 138.58, 144.63, 145.43, 150.44, 202.80; IR (neat) mass spectrum *m/z* (% rel intensity) 312 (4), 244 (Ph_3C+1) (33), 243 (95), 189 (24), 166 (19), 165 (100), 123 (79), 105 (32), 95 (14), 91 (17). Anal calcd for $C_{40}H_{44}O_3$: C. 83.88; H, 7.74. Found: C, 84.04; H, 8.09. Light yellow solid, m.p. 109-111 °C; R_f = 0.24 (30:1:1 hexanes/ CH_2Cl_2/ Et_2O).

Minor isomer 430a ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.94 (s, 3H), 1.22-1.32 (m, 2H), 1.48 (d, 3H, *J* = 1.2 Hz), 1.51-1.58 (m, 2H), 1.70 (s, 3H), 1.87-1.96 (m, 2H), 2.00-2.08 (m, 2H), 3.53 (s, 3H), 4.62-4.63 (m, 1H), 4.66-4.67 (m, 1H), 4.79 (d, 1H, *J* = 3.2 Hz), 4.87 (dq, 1H, *J* = 10.3, 2.0 Hz), 4.96 (dq, 1H, *J* = 17.2, 2.0 Hz), 4.98-5.01 (m, 1H), 5.29 (dd, 1H, *J* = 8.8, 0.9 Hz), 5.68-5.75 (m, 1H), 6.74 (dd, 1H, *J* = 3.1, 0.9 Hz), 7.12-7.15 (m, 3H), 7.18-7.22 (m, 6H), 7.44-7.48 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.97, 22.67, 27.41, 32.17, 33.71, 38.64, 39.05, 49.37, 54.63, 67.59, 87.97, 109.47, 109.52, 114.34, 125.52, 126.80, 127.62, 128.90, 135.62, 135.99, 138.38, 138.43, 144.78, 145.94, 150.31, 202.57; IR (neat) 3063, 2921, 1647, 1449, 1046, 704 cm^{-1}; mass spectrum *m/z* (% rel

intensity) 244 $(Ph_3C+H)^+$ (84), 243 (100), 189 (13), 166 934), 165 (51), 123 (24), 105 (16). HRMS (CI) calcd for $(C_{40}H_{44}O_3+H)^+$ *m/z* 573.3369, meas 573.3361. Yellow oil.

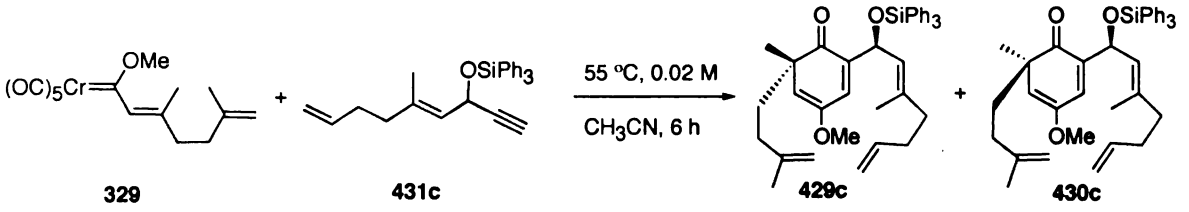
Thermolysis of carbene complex 329 with alkyne 431b



The thermolysis was performed with carbene complex **329** (68.8 mg, 0.20 mmol) and alkyne **431b** (74 mg, 0.24 mmol) in 10 mL of CH_3CN according to the general procedure to afford 83% of **429b** (81.2 mg, 0.167 mmol, >98:2 *dr*) as a yellow oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.99-1.01 (m, 21H), 1.16 (s, 3H), 1.45 (td, 1H, *J* = 12.3, 3.9 Hz), 1.51-1.54 (m, 1H), 1.58 (s, 3H), 1.73-1.77 (m, 1H), 1.78 (d, 3H, *J* = 1.3 Hz), 1.95-2.01 (m, 3H), 2.04-2.10 (m, 2H), 3.61 (s, 3H), 4.52 (s, 1H), 4.58 (s, 1H), 4.86(dq, 1H, *J* = 10.3, 2.0 Hz), 4.91- 4.96 (m, 3H), 5.47 (dd, 1H, *J* = 8.8, 1.1 Hz), 5.68-5.74 (m, 1H), 7.00 (dd, 1H, *J* = 3.2, 1.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.17, 16.95, 17.93, 18.01, 22.50, 26.88, 32.16, 32.73, 38.97, 40.87, 49.34, 54.73, 65.11, 109.67, 109.96, 114.35, 127.44, 135.76, 136.20, 138.40, 141.24, 145.53, 150.73, 203.63; IR (neat) 3077, 2946, 2869, 1649, 1601, 1385, 1047, 884, 689 cm^{-1}; mass spectrum *m/z* (% rel intensity) 443 $(M - 43)^+$ (14), 387 (15), 321 (20), 319 (16), 312 (43), 279 (22), 277 (19), 263 (15), 257 (23), 244 (48), 235 (26), 221 (27), 189 (66), 188 (51), 157 (16), 115

(29), 109 (20), 103 (28), 102 (20), 91 (16), 87 (24), 81 (17), 75 (45), 73 (37), 69 (50), 67 (24), 61 (27), 59 (81), 41 (100). HRMS (CI) calcd for $(C_{30}H_{50}O_3+H)^+$ *m/z* 487.3607, meas 487.3606. Yellow oil; R_f = 0.30 (30:1:1 hexanes /CH_2Cl_2/Et_2O).

Thermolysis of carbene complex 329 with alkyne 431c



329 431c 429c 430c

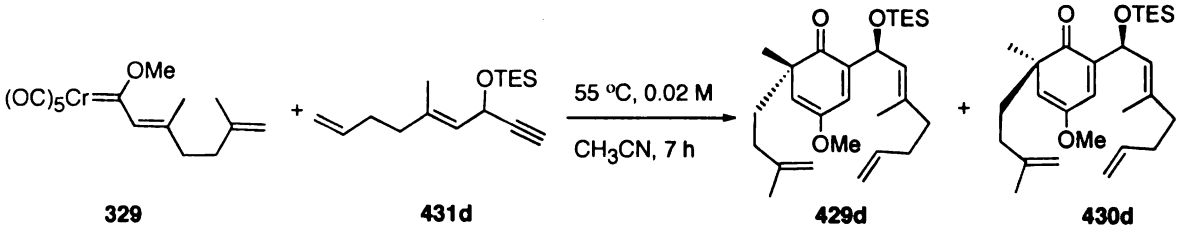
The thermolysis was performed with carbene complex **329** (62.5 mg, 0.182 mmol) and alkyne **431c** (89.2 mg, 0.218 mmol) in 9.1 mL of CH_3CN according to general procedure to afford major isomer **429c** (45.9 mg, 0.078 mmol) in 43% yield and minor isomer **430c** (21.5 mg, 0.036) in 20% yield. The ratio of diastereomers determined by crude ^1H NMR was 2:1.

Major 429c ^1H NMR ($CDCl_3$, 500 MHz) δ 1.08 (s, 3H), 1.37 (d, 3H, *J* = 1.1 Hz), 1.43 (td, 1H, *J* = 12.2, 4.0 Hz), 1.50-1.55 (m, 1H), 1.57 (s, 3H), 1.70-1.76 (m, 1H), 1.87-1.90 (m, 2H), 1.92-2.00 (m, 3H), 3.61 (s, 3H), 4.52 (s, 1H), 4.58 (s, 1H), 4.84-4.86 (m, 1H), 4.90-4.97 (m, 2H), 5.01-5.03 (m, 1H), 5.61 (d, 1H, *J* = 9.0 Hz), 5.67 (ddt, 1H, *J* = 16.4, 10.1, 6.2 Hz), 7.14 (dd, 1H, *J* = 3.1, 0.9 Hz), 7.32-7.35 (m, 6H), 7.37-7.40 (m, 3H), 7.58-7.62 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.47, 22.46, 26.89, 31.96, 32.75, 38.88, 40.73, 49.25, 54.73, 66.42, 109.68, 110.12, 114.31, 125.91, 127.70, 129.85, 134.44, 135.48, 136.41, 137.49, 138.34, 140.09, 145.48, 150.57, 203.21; IR (neat) 3071, 2832, 1647, 1429, 1110, 1046,

711 cm^{-1}; mass spectrum *m/z* (% rel intensity) 560 $(M-28)^+$ 312 (20), 260 (21), 259 (89), 258 (64), 257 (15), 244 (23), 199 (28), 198 (34), 189 (100), 181 (22), 180 (20), 121 (19). HRMS (CI) calcd for $(C_{39}H_{44}O_3+H)^+$ *m/z* 589.3138, meas 589.3149. Yellow oil; R_f = 0.15 (30:1:1 hexanes/CH_2Cl_2/Et_2O).

Minor 430c ^1H NMR ($CDCl_3$, 500 MHz) δ 1.07 (s, 3H), 1.32 (d, 3H, *J* = 1.3 Hz), 1.40 (td, 1H, *J* = 12.5, 4.0 Hz), 1.54-1.60 (m, 1H), 1.64 (s, 3H), 1.67-1.73 (m, 1H), 1.85-1.89 (m, 2H), 1.94-1.99 (m, 2H), 2.03 (td, 1H, *J* = 12.3, 5.1 Hz), 3.61 (s, 3H), 4.57-4.58 (m, 1H), 4.63 (s, 1H), 4.80-4.85 (m, 1H), 4.89-4.93 (m, 1H), 4.95 (d, 1H, *J* = 3.2 Hz), 4.99-5.02 (m, 1H), 5.59 (dd, 1H, *J* = 9.0, 1.2 Hz), 5.64 (ddt, 1H, *J* = 16.9, 10.3, 6.7 Hz), 7.14 (dd, 1H, *J* = 3.2, 1.1 Hz), 7.30-7.33 (m, 6H), 7.36-7.40 (m, 3H), 7.57-7.61 (m, 6H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.42, 22.59, 27.16, 31.86, 33.19, 38.89, 39.87, 49.57, 54.75, 66.52, 109.77, 110.12, 114.31, 125.87, 127.70, 129.86, 134.45, 135.48, 136.22, 137.46, 138.35, 140.01, 145.72, 150.49, 203.01; IR (neat) 3071m 2930, 1647, 1429, 1117, 711 cm^{-1}; mass spectrum *m/z* (% rel intensity) 560 $(M-28)^+$ (4), 312 (20), 261 (28), 259 (97), 258 (78), 243 (22), 206 (76), 199 (33), 198 (38), 189 (100), 181 (27), 180 (24), 177 (29), 11 (20), 105 (17), 55 (18). HRMS (CI) calcd for $(C_{39}H_{44}O_3+H)^+$ *m/z* 589.3138, meas 589.3135. Yellow oil; R_f = 0.19 (30:1:1 hexanes/CH_2Cl_2/Et_2O).

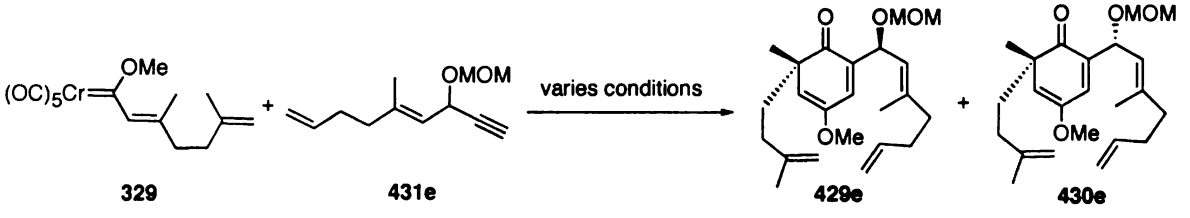
Thermolysis of carbene complex 329 with alkyne 431d



329 431d 429d 430d

The thermolysis was performed with carbene complex **329** (42.2 mg, 0.123 mmol) and alkyne **431d** (38.9 mg, 0.147 mmol) in 6.2 mL of CH_3CN according to general procedure to afford 2:1 ratio of inseparable diastereomers **429d** and **430d** (34.9 mg in total, 0.0786 mmol, 64%) as yellow oil. IR (neat) 2955, 2878, 1647, 1383, 1047, 747 cm^{-1}; mass spectrum *m/z* (% rel intensity) 416 $(M-28)^+$ (3), 312 (7), 244 (18), 189 (49), 188 (82), 115 (55), 103 (24), 87 (100), 75 (20), 60 (22), 59 (22). Yellow oil; R_f = 0.21 (30:1:1 hexanes/CH_2Cl_2/Et_2O).

General procedure for the thermolysis of carbene complex 329 with alkyne 431e



329 431e 429e 430e

The carbene complex **329** and alkyne **431e** (1.2 equiv.) was dissolved in the certain amount of solvent and transferred to a schlenk flask equipped with a threaded Teflon high vacuum stopcock. The reaction was deoxygenated by the

freeze-thaw procedure with 3 cycles. The flask was filled with an argon atmosphere at room temperature, sealed and heated at the specific temperatures. After the reaction was completed (indicated by the color of the carbene complex), the reaction mixture was cooled to room temperature, and the solvent was removed *in vacuo*. The residue was dissolved in 1:1 mixture of CH_2Cl_2/Et_2O and stirred in air at room temperature. After stirring 12 hours, the solution was passed through Celite 503, concentrated, and then purified by chromatography on silica gel (30:1:1 hexanes/ CH_2Cl_2/Et_2O) to afford the cyclized products **429e** and **430e** as yellow oil. The ratio of **429e** to **430e** was determined on the crude reaction mixture by ^1H NMR based on the integral of the following peaks: δ 6.94 for **429e** and 6.92 for **430e**.

Annulation reaction in CH_3CN at 55 °C at a concentration of 0.02 M

The thermolysis was performed with carbene complex **329** (90 mg, 0.26 mmol) and alkyne **431e** (60.9 mg, 0.314 mmol) in 13 mL of CH_3CN at 55 °C for 12 hours according to general procedure to afford 48% of **429e** (46.3 mg, 0.124 mmol) and 15% of **430e** (14.6 mg, 0.039 mmol). ^1H NMR determined ratio **429e/430e** = 3:1.

Annulation reaction in benzene at 55 °C at a concentration of 0.02 M

The thermolysis was performed with carbene complex **329** (66 mg, 0.192 mmol) and alkyne **431e** (44.7 mg, 0.230 mmol) in 9.6 mL of benzene at 55 °C for

28 hours according to general procedure to afford 50% of **429e** and **429e** (36.0 mg in total, 0.096 mmol). ^{1}H NMR determined ratio **429e/430e** = 3:1.

Annulation reaction in THF at 55 °C at a concentration of 0.02 M

The thermolysis was performed with carbene complex **329** (66.2 mg, 0.192 mmol) and alkyne **431e** (44.7 mg, 0.230 mmol) in 9.6 mL of THF at 55 °C for 28 hours according to general procedure to afford 33% of **429e** (23.4 mg, 0.0626 mmol) and 10% of **430e** (7.0 mg, 0.0187 mmol). ^{1}H NMR determined ratio **429e/430e** = 3:1.

Annulation reaction in CH_3CN at 40 °C at a concentration of 0.02 M

The thermolysis was performed with carbene complex **329** (53.9 mg, 0.157 mmol) and alkyne **431e** (36.5 mg, 0.188 mmol) in 6.9 mL of CH_3CN at 40 °C for 60 hours according to general procedure to afford 27% of **429e** (16.0 mg, 0.043 mmol) and 18% of **430e** (10.5 mg, 0.028 mmol). ^{1}H NMR determined ratio **429e/430e** = 3:2.

Annulation reaction in CH_3CN at 55 °C at a concentration of 0.005 M

The thermolysis was performed with carbene complex **329** (40.2 mg, 0.117 mmol) and alkyne **431e** (27.2 mg, 0.140 mmol) in 23.4 mL of CH_3CN at 55 °C for 12 hours according to general procedure to afford 24% of **429e** (10.4 mg, 0.028 mmol) and 17% of **430e** (7.5 mg, 0.020 mmol). ^{1}H NMR determined ratio **429e/430e** = 4:3.

Annulation reaction in CH_3CN at 55 °C at a concentration of 0.1 M

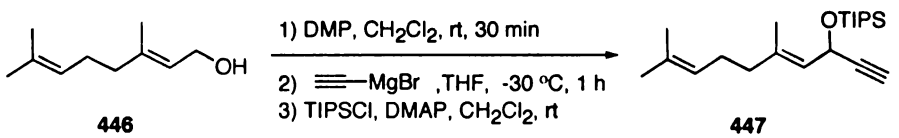
The thermolysis was performed with carbene complex **329** (41 mg, 0.119 mmol) and alkyne **431e** (27.7 mg, 0.142 mmol) in 1.2 mL of CH_3CN at 55 °C for 24 hours according to general procedure to afford 43% of **429e** (19.0 mg, 0.051 mmol) and 16% of **430e** (7.3 mg, 0.020 mmol). ^1H NMR determined ratio **429e/430e** = 2:1.

Major isomer 429e ^1H NMR ($CDCl_3$, 500 MHz) δ 1.19 (s, 3H), 1.47 (td, 1H, *J* = 12.4, 3.0 Hz), 1.60 (q, 3H, *J* = 0.8 Hz), 1.73-1.79 (m, 1H), 1.79 (d, 3H, *J* = 1.4 Hz), 1.98-2.14 (m, 6H), 3.32 (s, 3H), 3.61 (s, 3H), 4.52 (d, 1H, *J* = 6.5 Hz), 4.53-4.54 (m, 1H), 4.59-4.60 (m, 1H), 4.67 (d, 1H, *J* = 6.5 Hz), 4.87-4.97 (m, 3H), 5.00 (d, 1H, *J* = 3.2 Hz), 5.37 (dd, 1H, *J* = 9.2, 1.0 Hz), 5.68-5.75 (tdd, 1H, *J* = 16.9, 9.9, 6.5 Hz), 6.94 (dd, 1H, *J* = 3.2, 1.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.68, 22.51, 26.85, 32.06, 32.79, 38.99, 40.84, 49.35, 54.80, 55.40, 67.36, 93.47, 109.76, 110.42, 114.61, 123.11, 136.91, 138.15, 138.20, 140.89, 145.48, 150.37, 203.55; IR (neat) 2932, 1649, 1385, 1034 cm^{-1}; mass spectrum *m/z* (% rel intensity) 374 M^+ (1), 346 (2), 312 (5), 244 (17), 189 (100), 95 (33), 69 (16), 67 (16), 55 (21). Anal calcd for $C_{23}H_{34}O_4$: C. 73.76; H, 9.15. Found: C, 73.40; H, 8.90. Yellow oil; R_f = 0.36 (9:1 hexanes/EtOAc).

Minor isomer 430e ^1H NMR ($CDCl_3$, 500 MHz) δ 1.14 (s, 3H), 1.49 (td, 1H, *J* = 11.6, 4.2 Hz), 1.64 (s, 3H), 1.69-1.73 (m, 1H), 1.78 (d, 3H, *J* = 1.2 Hz), 2.05-2.14 (m, 6H), 3.31 (s, 3H), 3.61 (s, 3H), 4.52 (d, 1H, *J* = 6.6 Hz), 4.58-4.59

(m, 1H), 4.61-4.62 (m, 1H), 4.66 (d, 1H, J = 6.6 Hz), 4.88 (dq, 1H, J = 10.3, 1.1 Hz), 4.94 (dq, 1H, J = 6.0, 1.5 Hz), 4.96-4.97 (m, 1H), 5.00 (d, 1H, J = 3.2 Hz), 5.36 (dd, 1H, J = 9.2 Hz, 1.0 Hz), 5.67-5.74 (m, 1H), 6.92 (dd, 1H, J = 3.1, 1.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.64, 22.58, 27.13, 31.95, 33.12, 39.00, 40.05, 49.56, 54.80, 55.38, 67.42, 93.54, 109.75, 110.45, 114.60, 123.13, 136.89, 138.08, 138.16, 140.74, 145. 65, 150.29, 203.38; IR (neat) 2930, 1649, 1385, 1034 cm^{-1}; mass spectrum *m/z* (% rel intensity) 312 $(M-62)^+$ (4), 189 (78), 91 (20), 55 (20), 45 (100). HRMS (CI) calcd for $(C_{23}H_{34}O_4+H)^+$ *m/z* 375.2535, meas 375.2539. Yellow oil; R_f = 0.31 (9:1 hexanes/EtOAc).

Preparation of propargyl TIPS-ether 447



446 **447**

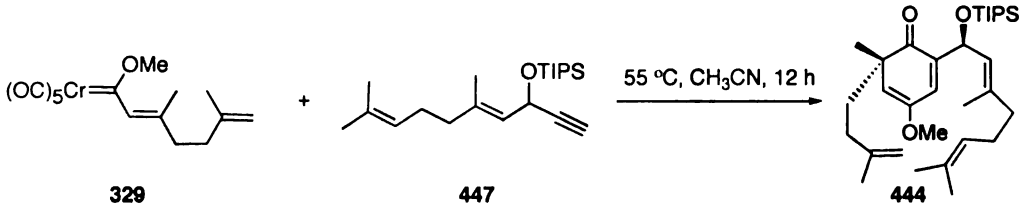
To a solution of geraniol **446** (0.879 g, 5.7 mmol) in CH_2Cl_2 (10 mL) under an argon atmosphere was added freshly prepared DMP[93] (3.60 g, 8.5 mmol) as powder. The reaction mixture was stirred at room temperature for 30 minutes before it was quenched with 10% aqueous NaOH (10 mL). The stirring was continued for another 5 minutes and then Et_2O (3 * 10 mL) was added to extract the product from the reaction mixture. The combined organic layer was dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by flash chromatography on a silica gel column (9:1 hexanes/EtOAC as eluent) provided the desired aldehyde as a colorless oil, which was used immediately.

To the above aldehyde in THF (20 mL) at to –30 °C under an argon atmosphere was added ethynyl magnesium bromide (0.5 M solution in THF, 20 mL, 10 mmol) dropwise. The reaction mixture was stirred at –30 °C for 1 hour and quenched with saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with Et_2O (3 * 15 mL). The combined organic layer was washed with brine (25 mL) and dried with $MgSO_4$. Flash chromatography on a silica gel column (4:1 hexanes/EtOAc as eluent) provided the desired propargylic alcohol as a colorless oil (790 mg, 4.44 mmol, 78%). The alcohol was used immediately to prepare the corresponding TIPS-ether.

To a solution of the above propargyl alcohol (537 mg, 3.02 mmol) in CH_2Cl_2 (10 mL) was added DMAP (737 mg, 6.4 mmol) followed by the addition of tri*iso*propylsilyl chloride (0.65 mL, 3.04 mmol). The reaction mixture was stirred at room temperature for 12 hours and quenched with water (10 mL). Diethyl ether (3 * 20 mL) was added to extract the product from the aqueous layer. The combined organic layer was washed with saturated aqueous NH_4Cl (25 mL), brine (25 mL), and then dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by flash chromatography on silica gel (19:1 hexanes/EtOAc as eluent) provided the desired product **447** as a colorless oil (773 mg, 2.32 mmol, 77%). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.04-1.11 (m, 21H), 1.58 (s, 3H), 1.650 (s, 3H), 1.652 (s, 3H), 1.99-2.01 (m, 2H), 2.06-2.09 (m, 2H), 2.40 (d, 1H, *J* = 2.1 Hz), 5.07 (tt, 1H, *J* = 7.0, 1.3 Hz), 5.11 (dd, 1H, *J* = 7.9, 2.2 Hz), 5.33 (dq, 1H, *J* = 7.9, 1.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.18, 16.64, 17.67, 17.85, 17.91, 25.67, 26.10, 39.18, 59.97, 71.39, 85.09, 123.81, 126.13,

131.70, 136.66; IR (neat) 3312, 2944, 2888, 1671, 1464, 1060, 883, 685, 650 cm^{-1}; mass spectrum *m/z* (% rel intensity) 334 M^+ (0.2), 291 (16), 131 (66), 103 (100), 91 (25), 89 (18), 76 (37), 75 (74), 70 (52), 69 (46), 61 (37). Colorless oil; R_f = 0.52 (19:1 hexanes/EtOAc)

Thermolysis of carbene complex 329 and alkyne 447



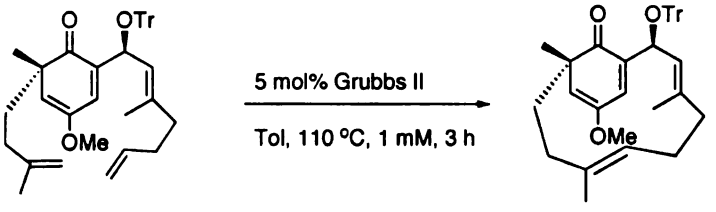
329 **447** **444**

The thermolysis was performed with carbene complex **329** (45.8 mg, 0.133 mmol) and alkyne **447** (53.0 mg, 0.159 mmol) in 6.2 mL of CH_3CN according to general procedure to afford 63% of **444** (43.2 mg, 0.084 mmol) as a single isomer. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.99-1.00 (m, 21H), 1.17 (s, 3H), 1.43-1.51 (m, 1H), 1.54 (s, 3H), 1.57 (s, 3H), 1.61-1.63 (m, 3H), 1.70-1.75 (m, 2H), 1.77 (d, 3H, *J* = 1.2 Hz), 1.87-1.92 (m, 2H), 1.95-2.02 (m, 3H), 3.61 (s, 3H), 4.51 -4.52 (m, 1H), 4.56-4.58 (m, 1H), 4.91-4.93 (m, 1H), 4.96 (d, 1H, *J* = 3.2 Hz), 5.01-5.04 (m, 1H), 5.47 (d, 1H, *J* = 8.7 Hz), 7.00 (dd, 1H, *J* = 3.2, 1.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.16, 16.94, 17.60, 17.93, 18.01, 22.47, 25.64, 26.49, 26.91, 32.75, 39.67, 40.94, 49.32, 54.73, 65.10, 109.73, 109.89, 124.12, 127.11, 131.42, 136.15, 136.21, 141.31, 145.53, 150.73, 203.66. IR (neat) 2944, 2888, 1647, 1383, 883 cm^{-1}; Mass spectrum *m/z* (% rel intensity) 471 $(M - 43)^+$ (2), 340 (15), 272 (26), 271 (38), 189 (41), 135 (28), 115 (19), 107 (15), 93 (18),

87 (18), 75 (32), 70 (96), 69 (100), 59 (66). HRMS (CI) calcd for $(C_{32}H_{54}O_3+H)^+$ *m/z* 515.3920, meas 515.3923. Yellow oil; R_f = 0.31 (30:1:1 Hexanes/CH_2Cl_2/Et_2O).

General procedure for ring-closing metathesis Diene was dissolved in a certain amount of solvent (toluene or CH_2Cl_2), and transferred to a schlenk flask equipped with a threaded Teflon high-vacuum stopcock under an argon atmosphere. To this solution was added Grubbs 2nd gerneration catalyst or Hoveda catalyst (5 mol% to 25 mol%) and the stopcock was closed. The solution was heated in an oil bath at a specific temperature and time. Then the reaction was cooled to room temperature and the solvent was removed *in vacuo*. Crude ^{1}H NMR was taken to determine the ratio of products.

RCM of diene 328

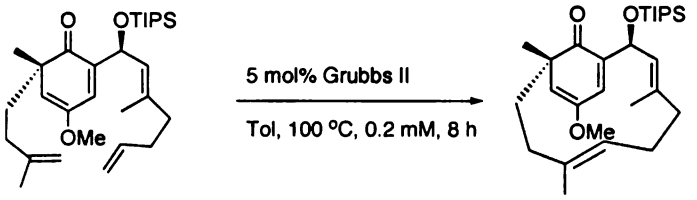


328 **327**

RCM of diene **328** (20.0 mg, 0.035 mmol) was carried out in 35 mL of toluene at 110 °C for 3 hours with 5 mol% loading of Grubbs II catalyst according to the general procedure. The crude product was purified by chromatography on silica gel (30:1:1 hexanes/CH_2Cl_2/Et_2O) to give bicyclic compound **327** (18.0 mg, 0.033 mmol) in 94% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.79 (s, 3H), 1.43 (s,

3H), 1.45 (s, 3H), 1.55-1.67 (m, 2H), 1.81-1.86 (m, 2H), 2.00 (td, 1H, *J* = 12.5, 4.8 Hz), 2.12-2.28 (m, 3H), 3.51 (s, 3H), 4.41 (d, 1H, *J* = 11.5 Hz), 4.62 (d, 1H, *J* = 3.2 Hz), 4.84 (d, 1H, *J* = 9.4 Hz), 5.23 (d, 1H, *J* = 8.6 Hz), 6.64 (dd, 1H, *J* = 3.2, 0.6 Hz), 7.10-7.14 (m, 3H), 7.17-7.22 (m, 6H), 7.42-7.47 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.03, 15.63, 25.54, 30.43, 36.17, 37.93, 39.37, 49.12, 54.62, 66.92, 87.72, 109.89, 124.62, 126.78, 127.29, 127.65, 128.86, 134.39, 134.83, 135.32, 139.23, 144.76, 150.73, 201.67. IR (neat) 2918, 1645, 1448, 1385, 1046, 704 cm^{-1}; mass spectrum *m/z* (% rel intensity) 301 $(M\text{-}Ph_3C)^+$ (3), 244 (23), 243 (100), 165 (58). HRMS (CI) calcd for $(C_{38}H_{40}O_3+H)^+$ *m/z* 545.3056, meas 545.3071. Light yellow solid, mp 209-212 °C; R_f = 0.27 (30:1:1 hexanes/CH_2Cl_2/Et_2O).

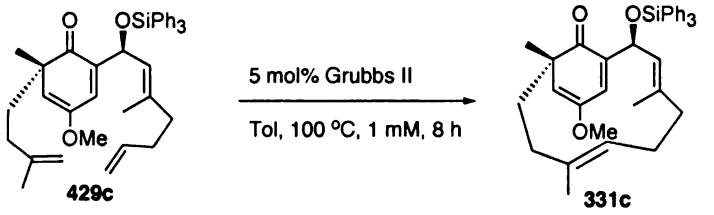
RCM of diene 429b



429b **360**

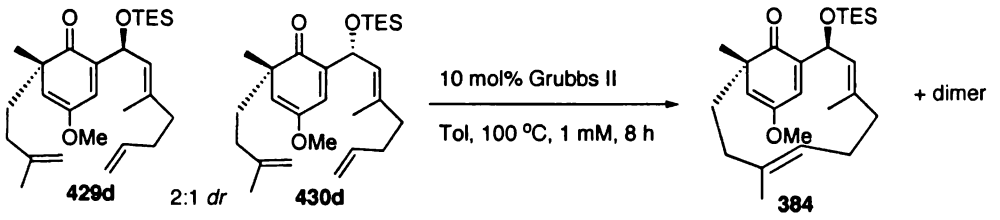
RCM of diene **429b** (9.2 mg, 0.019 mmol) was carried out in 95 mL of toluene at 100 °C for 8 hours with 5 mol% loading of Grubbs II catalyst according to the general procedure. The crude product was purified by chromatography on silica gel (30:1:1 hexanes/CH_2Cl_2/Et_2O) to give bicyclic compound **360** (8.0 mg, 0.0175 mmol) in 93% yield. The spectral data for this compound matched that for a product obtained from the thermolysis of compound **349** (vide supra).

RCM of diene 429c



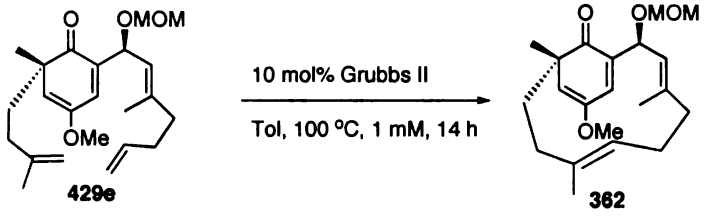
RCM of diene **429c** (5.4 mg, 0.0092 mmol) was carried out in 9.2 mL of toluene at 100 °C for 8 hours with 5 mol% loading of Grubbs II catalyst according to the general procedure. The crude product was purified by chromatography on silica gel (30:1:1 hexanes/CH_2Cl_2/Et_2O) to give bicyclic compound **331c** (3.8 mg, 0.0068 mmol) in 74% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.97 (s, 3H), 1.31 (d, 3H, *J* = 1.0 Hz), 1.32-1.38 (m, 1H), 1.52 (s, 3H), 1.65-1.70 (m, 1H), 1.80-1.92 (m, 3H), 1.96-2.00 (m, 1H), 2.17-2.29 (m, 2H), 3.61 (s, 3H), 4.44 (d, 1H, *J* = 1.2 Hz), 4.75 (m, 1H), 4.83 (d, 1H, *J* = 3.2 Hz), 5.57 (dd, 1H, *J* = 9.2, 1.0 Hz), 7.08 (dd, 1H, *J* = 3.2, 1.1 Hz), 7.29-7.32 (m, 6H), 7.35-7.38 (m, 3H), 7.57-7.62 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.21, 15.32, 25.45, 29.80, 36.12, 37.90, 39.17, 49.51, 54.70, 66.10, 110.44, 124.61, 127.71, 128.79, 129.84, 134.38, 134.40, 134.96, 135.45, 135.61, 140.70, 150.92, 201.82; IR (neat) 3071, 2919, 2851, 1647, 1599, 1429, 1383, 1117, 1044, 712, 700 cm^{-1}; mass spectrum *m/z* (% rel intensity) 560 M^+ (5), 426 (15), 347 (16), 259 (100), 241 (26), 199 (40), 189 (42), 181 (32), 105 (21), 91 (18), 77 (22). HRMS (FAB) calcd for $(C_{37}H_{40}O_3Si+H)^+$ *m/z* 561.2825, meas 561.2821. Colorless oil; R_f = 0.20 (30:1:1 hexanes/CH_2Cl_2/Et_2O).

RCM of mixtures of 429d/430d



RCM of mixtures of diene **429d** and **430d** (5.2 mg, 0.0117 mmol, 2:1 *dr*) was carried out in 11.7 mL of toluene at 100 °C for 8 hours with 10 mol% loading of Grubbs II catalyst according to the general procedure. The crude product was purified by chromatography on silica gel (30:1:1 hexanes/CH_2Cl_2/Et_2O) to give 3.7 mg of bicyclic compound **384** together with inseperable dimer (3:1 ratio based on crude ^1H NMR). No RCM product from diene **430d** was detected. The spectral data for this compound matched that for a product obtained from compound **383** (vide supra).

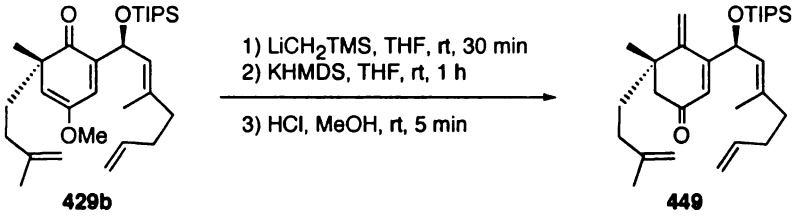
RCM of diene 429e



RCM of diene **429e** (24.7 mg, 0.066 mmol) was carried out in 66 mL of toluene at 100 °C for 14 hours with 10 mol% loading of Grubbs II catalyst according to the general procedure. The crude product was purified by chromatography on silica gel (30:1:1 hexanes/CH_2Cl_2/Et_2O) to give a 76% yield

of bicyclic compound **362** (17.3 mg, 0.050 mmol) and 2.9 mg of unreacted **429e**. The spectral data for this compound matched that for a product obtained from the thermolysis of compound **359** (vide supra).

Peterson olefination of compound 429b



429b **449**

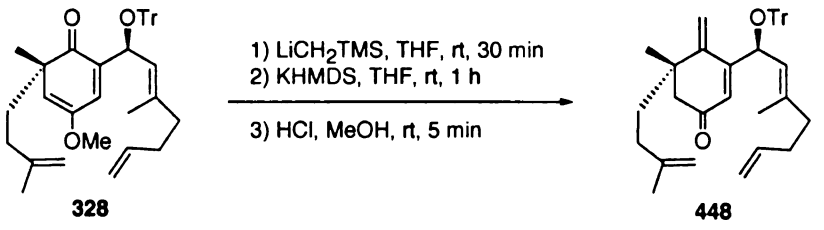
Trimethylsilylmethyllithium (0.142 mmol, 0.237 mL, 0.6 M in THF) was added dropwise to a solution of compound **429b** (23.1 mg, 0.0475 mmol) in 5.0 mL of THF at room temperature. The solution was stirred for 30 minutes, and then quenched with H_2O. The aqueous phase was separated and extracted with Et_2O (3 * 10 mL). The combined organic layer was washed with brine (15 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give an silyl alcohol.

The residue was dissolved in 5 mL of THF, and then KHMDS (0.12 mL, 0.060 mmol, 0.5 M in toluene) was added dropwise. The reaction mixture was stirred for 1.5 hours at room temperature, and then quenched with H_2O (5 mL). The aqueous phase was separated and extracted with Et_2O (3 * 10 mL). The combined organic layer was washed with brine (15 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give an unstable enol ether.

The residue was dissolved in 1 mL of methanol, and then treated with 1 mL of 1% HCl and stirred at room temperature for 5 minutes. The mixture was

diluted with Et_2O (5 mL) and neutralized with saturated aqueous $NaHCO_3$ (5 mL), and the aqueous phase was separated and then extracted with Et_2O (3 * 10 mL). The combined organic layer was washed with brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using 9:1 hexanes/Et_2O as eluent to give (20.9 mg, 0.0444 mmol, 94%) ketone **449**. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.01-1.09 (m, 21H), 1.17 (s, 3H), 1.33-1.41 (m, 1H), 1.55-1.64 (m, 2H), 1.61 (s, 3H), 1.68 (d, 3H, *J* = 1.0 Hz), 1.78-1.84 (m, 1H), 1.96-2.02 (m, 2H), 2.06-2.10 (m, 2H), 2.34-2.42 (m, 2H), 4.54 (s, 1H), 4.61 (s, 1H), 4.89-4.91 (m, 1H), 4.94-4.98 (m, 1H), 5.04-5.06 (m, 1H), 5.26 (d, 1H, *J* = 1.5 Hz), 5.37 (d, 1H, *J* = 9.0 Hz), 5.52 (s, 1H), 5.72 (ddt, 1H, *J* = 16.6, 10.0, 6.3 Hz), 6.33 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.27, 17.33, 17.92, 18.02, 22.73, 25.06, 31.81, 32.51, 36.51, 38.88, 42.24, 51.73, 68.43, 109.51, 114.48, 114.66, 123.72, 127.27, 136.42, 138.04, 145.46, 147.04, 159.72, 199.63; IR (neat) 2944, 2867, 1671, 1093, 883 cm^{-1}; mass spectrum *m/z* (% rel intensity) 470 M^+ (0.1), 427 (24), 131 (28), 105 (35), 103 (100), 95 (25), 91 (21), 81 (24), 75 (65), 73 (20), 62 (27), 61 (39), 58 (25). HRMS (CI) calcd for $(C_{30}H_{50}O_3+H)^+$ *m/z* 471.3658, meas 471.3676. Light yellow oil; R_f = 0.59 (9:1 hexanes/EtOAc).

Peterson olefination of compound 328



328 448

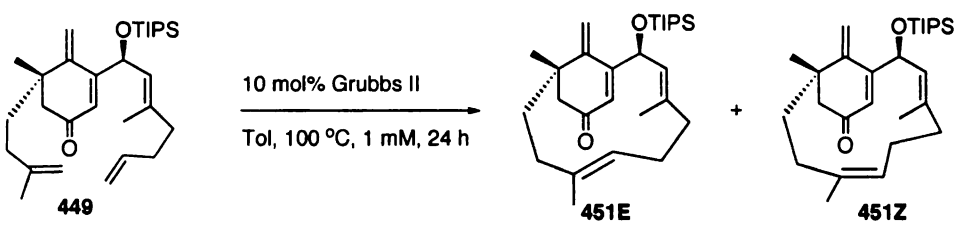
Trimethylsilylmethyllithium (0.210 mmol, 0.35 mL, 0.6 M in THF) was added dropwise to a solution of compound **328** (40.9 mg, 0.070 mmol) in 5.0 mL of THF at room temperature. The solution was stirred for 30 minutes, and then quenched with H_2O (5 mL). The aqueous phase was separated and extracted with Et_2O (3 * 10 mL). The combined organic layer was washed with brine (15 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give a silyl alcohol.

The residue was dissolved in 5 mL of THF, and then KHMDS (0.21 mL, 0.105 mmol, 0.5 M in toluene) was added dropwise. The reaction mixture was stirred for 1.5 hours at room temperature before quenching with H_2O (5 mL). The aqueous phase was separated and extracted with Et_2O (3 * 10 mL). The combined organic layer was washed with brine (15 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give an enol ether.

The residue was dissolved in 1 mL of MeOH, and then treated with 1 mL of 1% HCl and stirred at room temperature for 5 minutes. The mixture was diluted with Et_2O (5 mL) and neutralized with a saturated aqueous $NaHCO_3$ (5 mL), and the aqueous phase was separated and then extracted with Et_2O (3 * 10 mL). The combined organic layer was washed with brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column

chromatography on silica gel using 9:1 hexanes/Et_2O as eluent to give ketone **448** (35.0 mg, 0.0626 mmol) in 89% yield. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.00 (s, 3H), 1.19-1.25 (m, 2H), 1.42 (s, 3H), 1.43-1.49 (m, 2H), 1.55 (s, 3H), 1.665-1.72 (m, 1H), 1.94-2.00 (m, 3H), 2.07-2.13 (m, 2H), 4.48 (s, 1H), 4.57 (s, 1H), 4.93-4.96 (m, 1H), 4.99-5.03 (m, 2H), 5.14 (s, 2H), 5.19 (s, 1H), 5.76 (ddt, 1H, *J* = 16.5, 10.2, 6.5 Hz), 6.02 (s, 1H), 7.15-7.31 (m, 9H), 7.43-7.48 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.62, 22.68, 25.08, 31.89, 32.45, 36.36, 38.83, 41.72, 51.17, 70.18, 88.47, 109.42, 114.73, 114.98, 124.90, 125.09, 127.00, 127.77, 127.91, 136.94, 138.03, 144.39, 145.44, 145.91, 157.38,199.34; IR (neat) 3061, 2922, 1669, 1449, 1026, 706 cm^{-1}; mass spectrum *m/z* (% rel intensity) 243 $(CPh_3)^+$ (100), 227 (22), 166 (99), 164 (94), 105 (83), 95 (18), 91 (33), 77 (19), 55 (24). HRMS (CI) calcd for $(C_{40}H_{44}O_2+H)^+$ *m/z* 557.3420, meas 557.3434. Light yellow solid, m.p. 50-52 °C; R_f = 0.19 (9:1 hexanes/EtOAc).

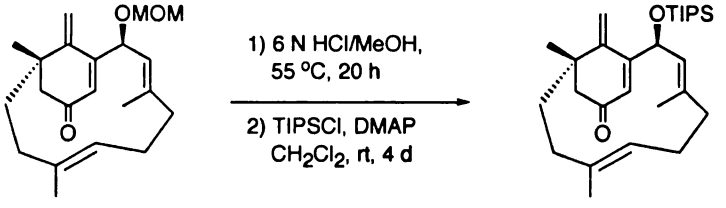
RCM of diene 449



RCM of diene **449** (4.5 mg, 0.0093 mmol) was carried out in 9.3 mL of toluene at 100 °C for 24 hours with 10 mol% loading of Grubbs II catalyst according to the general procedure. The crude product was purified by chromatography on silica gel (9:1 hexanes/EtOAc) to give 1:0.8 mixture of *E*- and

Z- bicyclic compound **451** (3.5 mg in total, 0.0076 mmol) in 82% yield. The spectra of **451Z** was extracted from the mixture of *E*- and *Z*-**451**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.01-1.03 (m, 21H), 1.13 (s, 3H), 1.38-1.44 (m, 1H), 1.53 (s, 3H), 1.69 (d, 3H, *J* = 1.0 Hz), 1.80-1.97 (m, 2H), 2.00-2.08 (m, 5H), 2.32 (d, 1H, *J* = 16.4 Hz), 2.42 (d, 1H, *J* = 16.4 Hz), 4.96 (d, 1H, *J* = 8.2 Hz), 5.04-5.07 (m, 1H), 5.24 (d, 1H, *J* = 1.4 Hz), 5.32 (dd, 1H, *J* = 15.3, 1.1 Hz), 5.41 (s, 1H), 6.29 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.15, 17.87, 18.00, 18.78, 22.57, 23.33, 25.65, 26.01, 35.52, 39.07, 43.05, 54.25, 68.60, 113.97, 121.83, 123.81, 126.00, 138.01, 147.43, 160.71, 199.54 (1 sp^2 carbon was not located). Colorless oil, R_f = 0.45 (9:1 hexanes/EtOAc).

Preparation of TIPS-ether 451 from MOM-ether 388



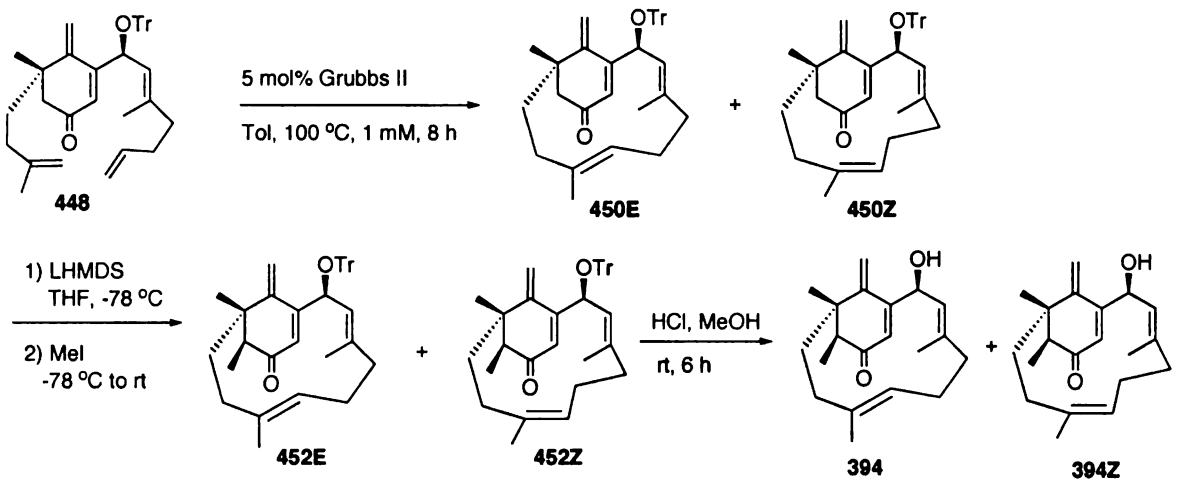
388 451

To a solution of MOM ether **388** (11 mg, 0.033 mmol) in 1.0 mL of MeOH was added 6 N HCl (0.011 mL) at room temperature. The reaction mixture was heated at 55 °C for 20 hours, and then cooled to room temperature. The mixture was diluted with Et_2O (5 mL) and neutralized with saturated aqueous $NaHCO_3$ (10 mL). The aqueous phase was separated and then extracted with Et_2O (2 * 10 mL). The combined organic layer was washed with brine (10 mL), dried over

Na_2SO_4 and concentrated *in vacuo*. The crude product was passed through a short silica gel column in pipette, concentrated and went directly to the next step.

To the solution of the above alcohol in CH_2Cl_2 (1 mL) was added DMAP (12.2 mg, 0.10 mmol) followed by the addition of TIPSCl (0.014 mL, 0.066 mmol). The reaction mixture was stirred at room temperature for 4 days and quenched with water (5 mL). Diethyl ether (3 * 10 mL) was added to extract the product from the aqueous layer. The combined organic layer was washed with saturated aqueous $NaHCO_3$ (15 mL), brine (15 mL), and then dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by flash chromatography on silica gel (9:1 hexanes/EtOAc as eluent) provided the desired product **451** as a colorless oil (13.3 mg, 0.030 mmol, 91%). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.00-1.03 (m, 21H), 1.18 (s, 3H), 1.36-1.41 (m, 1H), 1.45 (s, 3H), 1.58 (d, 3H, *J* = 1.4 Hz), 1.71-1.80 (m, 2H), 2.01-2.07 (m, 5H), 2.22 (d, 1H, *J* = 15.6 Hz), 2.44 (d, 1H, *J* = 15.6 Hz), 4.68-4.70 (m, 1H), 4.79 (d, 1H, *J* = 9.3 Hz), 5.26 (d, 1H, *J* = 1.6 Hz), 5.32 (dd, 1H, *J* = 9.3, 1.2 Hz), 5.35 (s, 1H), 6.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.24, 16.39, 17.02, 17.92, 18.04, 24.42, 24.85, 34.10, 36.02, 38.71, 42.96, 54.77, 67.22, 114.23, 123.11, 124.43, 127.88, 135.68, 136.01, 146.54, 160.05, 199.88; IR (neat) 2942, 2867, 1671, 1464, 1094, 1044, 884 cm^{-1}; mass spectrum *m/z* (% rel intensity) 442 M^+ (7), 399 (43), 135 (21), 131 (28), 105 (22), 103 (27), 102 (27), 95 (28), 91 (23), 81 (38), 77 (22), 75 (100), 61 (46), 59 (19). HRMS (CI) calcd for $(C_{28}H_{46}O_2+H)^+$ *m/z* 443.3345, meas 443.3331. Colorless oil; R_f = 0.45 (9:1 hexanes/EtOAc).

RCM of diene 450



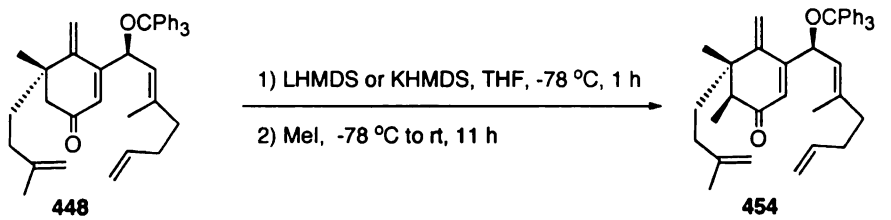
RCM of diene **448** (21.3 mg, 0.0372 mmol) was carried out in 34.2 mL of toluene at 100 °C for 8 hours with 5 mol% loading of Grubbs II catalyst according to the general procedure. The crude product was purified by chromatography on silica gel (10% EtOAc in hexanes) to give a 2:1 mixture of inseparable *E*- and *Z*-bicyclic compounds **450E** and **450Z** (14.2 mg, 0.0260 mmol) in 70% yield.

To a solution of the above mixture in THF (1.0 mL) at –78 °C was added LHMDS (0.052 mL, 0.052 mmol, 1.0 M solution in THF) dropwise. After stirring for 1 hour at –78 °C, iodomethane (6.5 μL, 0.104 mmol) was added. The cooling bath was removed immediately and the reaction mixture was allowed to warm to room temperature. After stirring 11 hours, 5 mL of saturated aqueous NH_4Cl was added to the flask. The aqueous layer was extracted with Et_2O (2 * 10 mL). The combined organic layer was washed with brine (10 mL), and then dried over $MgSO_4$. The residue was purified by flash column chromatography on silica gel using 9:1 hexanes/Et_2O as eluent to give a 2:1 mixture of ketones **452E** and **452Z** (13.2 mg in total, 0.0236 mmol, 91%).

The resulting ketones were treated with 2 equivalent of 6 N HCl in 1 mL of MeOH at room temperature until the trityl group was totally cleaved (monitored by TLC). Then 5 mL of saturated aqueous NH_4Cl was added to the flask to quench the reaction. The aqueous layer was extracted with Et_2O (2 * 10 mL). The combined organic layer was washed with brine (10 mL), and then dried over $MgSO_4$. The residue was purified by flash column chromatography on silica gel using 9:1 hexanes/Et_2O as eluent to give inseparable mixture of *E*- and *Z*-alcohols **394** and **394Z** (5.6 mg in total, 0.0187 mmol, 2:1 *dr*, 79%).

The spectra for *Z*-isomer **394Z** was extracted from the mixture of *E*- and *Z*-**394**. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.97 (d, 3H, *J* = 7.2 Hz), 1.04 (s, 3H), 1.35-1.41 (m, 1H), 1.53 (s, 3H), 1.76 (d, 3H, *J* = 1.2 Hz), 1.92-1.95 (m, 2H), 2.06-2.18 (m, 6H), 4.98 (d, 1H, *J* = 8.5 Hz), 5.03 (t, 1H, *J* = 8.2 Hz), 5.22 (d, 1H, *J* = 1.5 Hz), 5.39 (d, 1H, *J* = 9.0 Hz), 5.58 (s, 1H), 6.15 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.28, 18.76, 19.67, 22.57, 25.97, 36.30, 38.91, 46.02, 54.89, 67.88, 116.40, 119.49, 123.74, 124.52, 136.04, 141.10, 145.22, 158.11, 204.03 (1 sp^3 carbon was not located).

Methylation of dienone 448

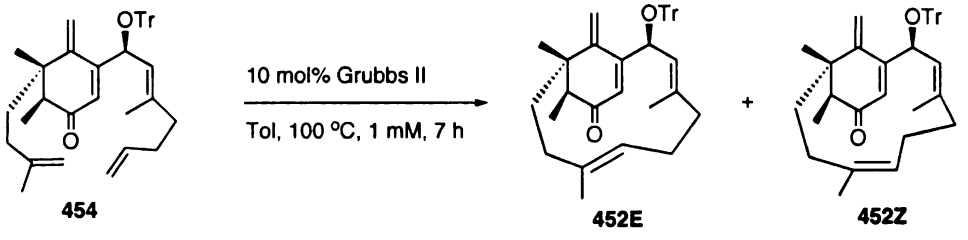


448 454

To a solution of ketone **448** (4.1 mg, 0.00716 mmol) in THF (0.2 mL) at –78 °C was added KHMDS (0.029 mL, 0.0145 mmol, 0.5 M solution in toluene) dropwise. After stirring for 1 hour at –78 °C, iodomethane (4.5 μL, 0.0716 mmol) was added. The cooling bath was removed immediately, and the reaction mixture was allowed to warm to room temperature. After stirring 5 hours, 5 mL of aqueous saturated NH_4Cl was added to the flask. The aqueous layer was extracted with Et_2O (2 * 10 mL). The combined organic layer was washed with brine (10 mL), and then dried over $MgSO_4$. The residue was purified by flash column chromatography on silica gel using 9:1 hexanes/Et_2O as eluent to give 5: 1 of ketone **454** and starting material **448** (3.7 mg in total, 0.0053 mmol of **454**, 74%). ^1H NMR ($CDCl_3$, 500 MHz) δ 0.63 (d, 3H, *J* = 7.3 Hz), 0.92 (s, 3H), 1.37 (s, 3H), 1.46-1.58 (m, 3H), 1.56 (s, 3H), 1.68-1.71 (m, 1H), 1.92-2.05 (m, 3H), 2.09-2.11 (m, 2H), 4.48 (s, 1H), 4.57 (s, 1H), 4.95 (m, 2H), 5.02 (dq, 1H, *J* = 16.1, 1.8 Hz), 5.15 (br, 3H), 5.77 (ddt, 1H, *J* = 16.9,10.2, 6.5 Hz), 6.09 (s, 1H), 7.15-7.30 (m, 9H), 7.45-7.47 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.45, 17.58, 21.14, 22.71, 31.85, 32.31, 37.13, 38.90, 44.88, 53.09, 70.17, 88.66, 109.39, 114.74, 116.60, 123.07, 125.66, 127.05, 127.73, 127.93, 128.99, 136.99, 138.08, 144.57, 145.53, 157.11, 204.04; IR (neat) 3059, 2924, 1667, 1449, 1026, 706

cm^{-1}; mass spectrum *m/z* (% rel intensity) 243 $(CPh_3)^+$ (100), 165 (25), HRMS (CI) calcd for $(C_{41}H_{46}O_2+H)^+$ *m/z* 571.3576, meas 571.3551. Light yellow oil; R_f = 0.35 (9:1 hexanes/EtOAc).

RCM of diene 454

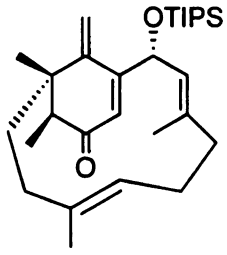


454 452E 452Z

RCM of diene **454** (3.6 mg, 0.0061 mmol) was carried out in 6.1 mL of toluene at 100 °C for 7 hours with 10 mol% loading of Grubbs II catalyst according to the general procedure. The crude product was purified by chromatography on silica gel (9:1 hexanes/EtOAc) to give 0.6:1 mixture of *E*- and *Z*- bicyclic compounds **452** (2.8 mg in total, 0.0050 mmol) in 82% yield. Colorless oil; R_f = 0.35 (9:1 hexanes/EtOAc).

APPENDICES

Figure A-1 ORTEP Drawing of the Structure of Compound **370**



370

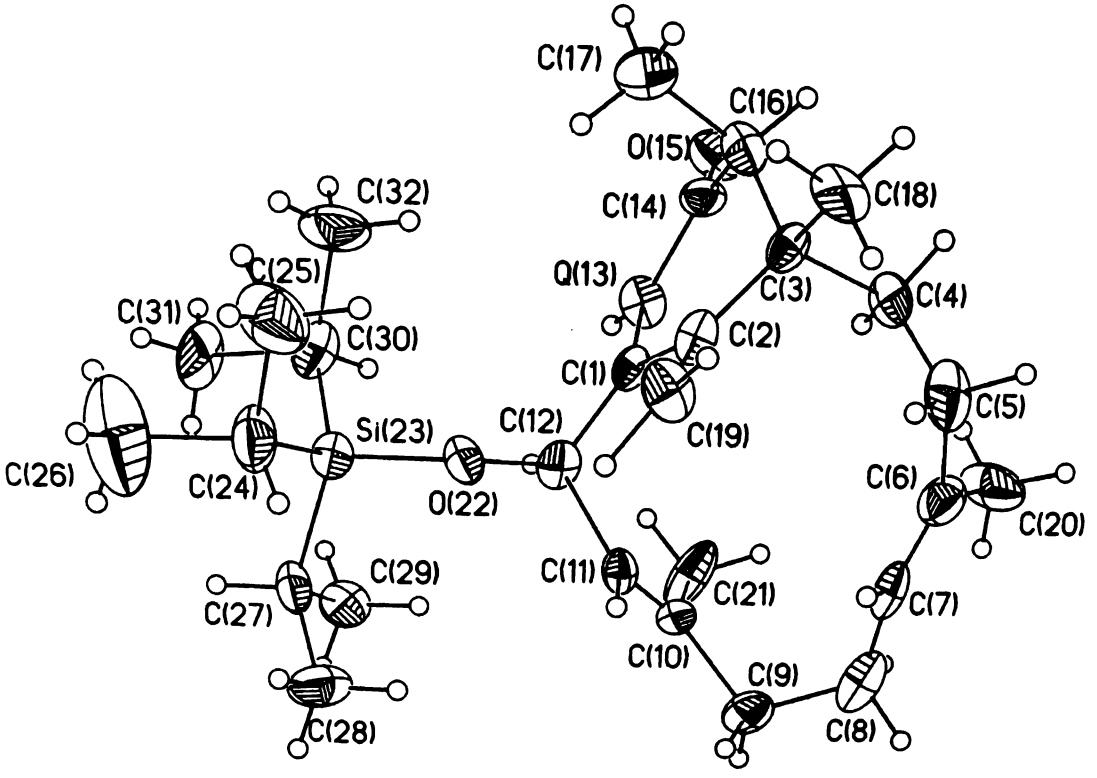


Table 1. Crystal data and structure refinement for wf021005

Identification code	p21
Empirical formula	C58 H93 O4 Si2
Formula weight	910.50
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 10.600(2) A b = 22.885(5) A c = 12.657(3) A alpha = 90 deg. beta = 108.01(3) deg. gamma = 90 deg.
Volume	2919.9(10) A^3
Z	2
Density (calculated)	1.036 Mg/m^3
Absorption coefficient	0.101 mm^-1
F(000)	1002
Crystal size	0.6 x 0.4 x 0.2 mm
Theta range for data collection	1.69 to 28.23 deg.
Index ranges	-14<=h<=14, -29<=k<=30, -16<=l<=16
Reflections collected / unique	35046 / 13757 [R(int) = 0.0940]
Completeness to theta = 28.23	97.8%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	13757 / 1 / 593
Goodness-of-fit on F^2	0.245
Final R indices [I>2sigma(I)]	R1 = 0.0449, wR2 = 0.1101
R indices (all data)	R1 = 0.1004, wR2 = 0.1236
Absolute structure parameter	0.5(3)
Largest diff. peak and hole	0.259 and -0.217 e.A^-3

Table 2. Atomic coordinates (x 10^4), equivalent isotropic displacement parameters (A^2 x 10^3), and occupancies for wf021005

	x	y	z	U(eq)	Occ.
C(1)	-656(6)	3708(3)	2393(5)	24(2)	1
C(2)	-562(7)	4046(3)	3455(5)	26(2)	1
C(3)	-1606(6)	4496(3)	3374(5)	28(2)	1
C(4)	-1379(7)	5061(3)	2697(6)	37(2)	1
C(5)	-105(7)	5368(3)	3197(6)	49(2)	1
C(6)	799(8)	5403(3)	2435(7)	42(2)	1
C(7)	1934(8)	5135(3)	2665(6)	37(2)	1
C(8)	2807(8)	5031(3)	1972(7)	51(2)	1
C(9)	3186(7)	4413(3)	1874(6)	37(2)	1
C(10)	1956(7)	3997(3)	1589(6)	35(2)	1
C(11)	1699(7)	3686(3)	2397(6)	26(2)	1
C(12)	430(6)	3340(3)	2260(5)	28(2)	1
Q(13)	-1802(6)	3752(3)	1520(5)	27(2)	1
C(14)	-3021(7)	4059(3)	1560(6)	32(2)	1
O(15)	-3935(5)	4133(2)	742(4)	44(1)	1
C(16)	-2999(7)	4259(3)	2729(6)	37(2)	1
C(17)	-3465(7)	3746(3)	3327(6)	40(2)	1
C(18)	-1631(7)	4718(3)	4555(5)	40(2)	1
C(19)	408(8)	3915(3)	4367(6)	40(2)	1
C(20)	223(7)	5742(4)	1378(6)	62(2)	1
C(21)	1056(7)	4073(3)	440(6)	57(2)	1
O(22)	706(4)	2864(2)	3051(4)	30(1)	1
Si(23)	588(2)	2159(1)	2770(2)	29(1)	1
C(24)	966(8)	1863(3)	4175(6)	52(2)	1
C(25)	-78(9)	2004(4)	4780(7)	66(2)	1
C(26)	1001(10)	1187(4)	4265(6)	109(4)	1
C(27)	1945(7)	1916(3)	2189(6)	37(2)	1
C(28)	3348(7)	2115(4)	2975(7)	50(2)	1
C(29)	1745(7)	2122(3)	1022(6)	44(2)	1
C(30)	-1060(7)	1996(3)	1733(6)	41(2)	1
C(31)	-1142(8)	1335(3)	1312(7)	58(2)	1
C(32)	-2307(7)	2120(4)	2085(7)	61(3)	1
C(33)	5710(6)	3297(3)	7578(6)	26(2)	1
C(34)	5569(6)	2998(3)	6553(6)	27(2)	1
C(35)	6615(6)	2502(3)	6608(6)	32(2)	1
C(36)	6357(7)	1980(3)	7231(6)	36(2)	1
C(37)	4980(6)	1643(3)	6761(6)	32(2)	1
C(38)	4228(8)	1622(3)	7564(6)	34(2)	1
C(39)	3055(7)	1919(3)	7323(6)	39(2)	1
C(40)	2171(7)	1978(3)	8070(6)	37(2)	1
C(41)	1798(7)	2658(3)	8049(6)	41(2)	1

Table 2 (cont'd)

C(42)	3003(7)	3018(3)	8376(5)	32(2)	1
C(43)	3309(7)	3330(3)	7607(6)	36(2)	1
C(44)	4537(6)	3678(3)	7746(6)	28(2)	1
C(45)	6787(7)	3288(3)	8430(6)	36(2)	1
C(46)	7954(7)	2958(3)	8405(6)	33(2)	1
O(47)	8934(5)	2884(2)	9263(5)	48(2)	1
C(48)	7989(6)	2763(3)	7294(6)	30(2)	1
C(49)	8438(7)	3306(3)	6732(6)	44(2)	1
C(50)	6664(7)	2328(3)	5492(6)	47(2)	1
C(51)	4608(7)	3111(3)	5596(6)	36(2)	1
C(52)	4849(8)	1258(3)	8608(6)	66(2)	1
C(53)	3925(6)	3003(3)	9579(5)	49(2)	1
O(54)	4295(4)	4152(2)	6957(4)	32(1)	1
Si(55)	4412(2)	4864(1)	7233(2)	29(1)	1
C(56)	6051(7)	5040(3)	8306(6)	41(2)	1
C(57)	6167(8)	5651(4)	8720(8)	73(3)	1
C(58)	7277(8)	4866(4)	7956(8)	64(3)	1
C(59)	3056(7)	5098(3)	7808(5)	31(2)	1
C(60)	3235(7)	4873(3)	9009(5)	49(2)	1
C(61)	1720(7)	4925(3)	7092(6)	52(2)	1
C(62)	4103(7)	5172(3)	5764(4)	30(2)	1
C(63)	3700(8)	5826(3)	5645(6)	61(2)	1
C(64)	5097(8)	4943(4)	5209(6)	62(2)	1

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Table 3. Bond lengths [A] and angles [deg] for wf021005

C(1)-Q(13)	1.370(9)	C(38)-C(52)	1.527(10)
C(1)-C(12)	1.477(8)	C(39)-C(40)	1.529(9)
C(1)-C(2)	1.528(8)	C(40)-C(41)	1.603(9)
C(2)-C(19)	1.321(9)	C(41)-C(42)	1.468(9)
C(2)-C(3)	1.492(9)	C(42)-C(43)	1.325(9)
C(3)-C(16)	1.548(9)	C(42)-C(53)	1.535(9)
C(3)-C(18)	1.586(8)	C(43)-C(44)	1.489(9)
C(3)-C(4)	1.610(9)	C(44)-O(54)	1.443(7)
C(4)-C(5)	1.480(9)	C(45)-C(46)	1.458(9)
C(5)-C(6)	1.557(9)	C(46)-O(47)	1.261(8)
C(6)-C(7)	1.302(10)	C(46)-C(48)	1.487(9)
C(6)-C(20)	1.502(10)	C(48)-C(49)	1.577(10)
C(7)-C(8)	1.478(10)	O(54)-Si(55)	1.662(5)
C(8)-C(9)	1.485(10)	Si(55)-C(59)	1.878(7)
C(9)-C(10)	1.564(9)	Si(55)-C(56)	1.889(7)
C(10)-C(11)	1.342(9)	Si(55)-C(62)	1.920(6)
C(10)-C(21)	1.482(10)	C(56)-C(57)	1.485(10)
C(11)-C(12)	1.524(8)	C(56)-C(58)	1.549(10)
C(12)-O(22)	1.445(8)	C(59)-C(61)	1.480(10)
Q(13)-C(14)	1.486(9)	C(59)-C(60)	1.560(9)
C(14)-O(15)	1.191(8)	C(62)-C(64)	1.529(9)
C(14)-C(16)	1.541(10)	C(62)-C(63)	1.551(9)
C(16)-C(17)	1.558(10)	Q(13)-C(1)-C(12)	118.6(6)
O(22)-Si(23)	1.649(5)	Q(13)-C(1)-C(2)	118.2(6)
Si(23)-C(24)	1.829(7)	C(12)-C(1)-C(2)	123.2(6)
Si(23)-C(30)	1.869(7)	C(19)-C(2)-C(3)	125.3(6)
Si(23)-C(27)	1.890(7)	C(19)-C(2)-C(1)	118.3(6)
C(24)-C(26)	1.551(10)	C(3)-C(2)-C(1)	116.4(5)
C(24)-C(25)	1.562(10)	C(2)-C(3)-C(16)	111.1(5)
C(27)-C(29)	1.502(9)	C(2)-C(3)-C(18)	112.6(5)
C(27)-C(28)	1.579(10)	C(16)-C(3)-C(18)	108.6(5)
C(30)-C(32)	1.546(9)	C(2)-C(3)-C(4)	111.2(5)
C(30)-C(31)	1.597(9)	C(16)-C(3)-C(4)	106.1(5)
C(33)-C(45)	1.307(9)	C(18)-C(3)-C(4)	107.1(5)
C(33)-C(34)	1.432(9)	C(5)-C(4)-C(3)	114.9(6)
C(33)-C(44)	1.586(8)	C(4)-C(5)-C(6)	114.5(6)
C(34)-C(51)	1.345(9)	C(7)-C(6)-C(20)	122.3(7)
C(34)-C(35)	1.574(8)	C(7)-C(6)-C(5)	122.7(7)
C(35)-C(50)	1.484(9)	C(20)-C(6)-C(5)	114.8(7)
C(35)-C(36)	1.503(9)	C(6)-C(7)-C(8)	130.5(8)
C(35)-C(48)	1.565(9)	C(7)-C(8)-C(9)	116.0(6)
C(36)-C(37)	1.594(8)	C(8)-C(9)-C(10)	111.7(6)
C(37)-C(38)	1.474(9)	C(11)-C(10)-C(21)	126.1(6)
C(38)-C(39)	1.366(9)	C(11)-C(10)-C(9)	119.9(7)

Table 3 (cont'd)

C(21)-C(10)-C(9)	113.2(6)	C(48)-C(35)-C(34)	105.7(5)
C(10)-C(11)-C(12)	124.7(6)	C(35)-C(36)-C(37)	118.9(6)
O(22)-C(12)-C(1)	110.4(5)	C(38)-C(37)-C(36)	112.8(6)
O(22)-C(12)-C(11)	109.3(5)	C(39)-C(38)-C(37)	118.6(6)
C(1)-C(12)-C(11)	112.5(5)	C(39)-C(38)-C(52)	125.7(7)
C(1)-Q(13)-C(14)	124.8(6)	C(37)-C(38)-C(52)	115.7(6)
O(15)-C(14)-Q(13)	121.3(7)	C(38)-C(39)-C(40)	126.5(7)
O(15)-C(14)-C(16)	124.0(7)	C(39)-C(40)-C(41)	105.7(6)
Q(13)-C(14)-C(16)	114.7(6)	C(42)-C(41)-C(40)	110.5(6)
C(14)-C(16)-C(3)	109.8(6)	C(43)-C(42)-C(41)	119.0(7)
C(14)-C(16)-C(17)	109.3(6)	C(43)-C(42)-C(53)	121.0(7)
C(3)-C(16)-C(17)	113.7(6)	C(41)-C(42)-C(53)	119.9(6)
C(12)-O(22)-Si(23)	127.0(4)	C(42)-C(43)-C(44)	127.2(7)
O(22)-Si(23)-C(24)	100.0(3)	O(54)-C(44)-C(43)	111.0(6)
O(22)-Si(23)-C(30)	109.8(3)	O(54)-C(44)-C(33)	107.4(5)
C(24)-Si(23)-C(30)	119.0(4)	C(43)-C(44)-C(33)	112.6(5)
O(22)-Si(23)-C(27)	110.8(3)	C(33)-C(45)-C(46)	121.4(7)
C(24)-Si(23)-C(27)	107.7(3)	O(47)-C(46)-C(45)	121.9(7)
C(30)-Si(23)-C(27)	109.1(3)	O(47)-C(46)-C(48)	121.3(7)
C(26)-C(24)-C(25)	100.0(6)	C(45)-C(46)-C(48)	116.5(6)
C(26)-C(24)-Si(23)	115.8(5)	C(46)-C(48)-C(35)	110.4(5)
C(25)-C(24)-Si(23)	115.1(5)	C(46)-C(48)-C(49)	106.8(6)
C(29)-C(27)-C(28)	110.4(6)	C(35)-C(48)-C(49)	114.2(6)
C(29)-C(27)-Si(23)	113.4(5)	C(44)-O(54)-Si(55)	127.3(4)
C(28)-C(27)-Si(23)	110.6(5)	O(54)-Si(55)-C(59)	110.2(3)
C(32)-C(30)-C(31)	107.8(6)	O(54)-Si(55)-C(56)	110.7(3)
C(32)-C(30)-Si(23)	117.3(5)	C(59)-Si(55)-C(56)	107.7(3)
C(31)-C(30)-Si(23)	111.5(5)	O(54)-Si(55)-C(62)	100.2(3)
C(45)-C(33)-C(34)	124.1(6)	C(59)-Si(55)-C(62)	110.4(3)
C(45)-C(33)-C(44)	114.8(6)	C(56)-Si(55)-C(62)	117.5(3)
C(34)-C(33)-C(44)	121.2(6)	C(57)-C(56)-C(58)	111.0(6)
C(51)-C(34)-C(33)	124.1(6)	C(57)-C(56)-Si(55)	114.4(5)
C(51)-C(34)-C(35)	120.4(6)	C(58)-C(56)-Si(55)	114.0(6)
C(33)-C(34)-C(35)	115.5(6)	C(61)-C(59)-C(60)	108.3(6)
C(50)-C(35)-C(36)	110.6(6)	C(61)-C(59)-Si(55)	112.9(5)
C(50)-C(35)-C(48)	109.2(5)	C(60)-C(59)-Si(55)	114.0(5)
C(36)-C(35)-C(48)	107.6(5)	C(64)-C(62)-C(63)	119.6(6)
C(50)-C(35)-C(34)	112.5(5)	C(64)-C(62)-Si(55)	112.6(5)
C(36)-C(35)-C(34)	110.9(5)	C(63)-C(62)-Si(55)	114.1(4)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for wf021005

	U11	U22	U33	U23	U13	U12
C(1)	30(4)	20(3)	20(3)	-8(3)	6(3)	-9(3)
C(2)	40(4)	25(3)	9(3)	2(2)	4(3)	-7(3)
C(3)	36(4)	27(3)	21(3)	-6(3)	9(3)	11(3)
C(4)	38(4)	26(4)	43(4)	17(3)	5(3)	12(3)
C(5)	88(6)	34(4)	36(4)	-11(3)	33(4)	-1(4)
C(6)	48(5)	38(4)	49(5)	-3(4)	26(4)	-11(4)
C(7)	50(5)	21(3)	38(4)	5(3)	10(4)	-12(3)
C(8)	62(6)	39(5)	47(5)	0(4)	11(4)	-22(4)
C(9)	27(4)	43(4)	33(3)	-2(3)	0(3)	-7(3)
C(10)	21(4)	26(4)	57(5)	-6(3)	13(3)	-3(3)
C(11)	30(4)	20(4)	24(4)	3(3)	4(3)	3(3)
C(12)	27(4)	29(4)	18(3)	-7(3)	-8(3)	-7(3)
Q(13)	34(4)	34(4)	4(2)	2(2)	-5(3)	5(3)
C(14)	21(4)	34(4)	41(4)	8(3)	9(3)	2(3)
O(15)	28(3)	56(4)	39(3)	-1(3)	-3(3)	8(3)
C(16)	41(5)	31(4)	39(4)	2(3)	13(4)	8(3)
C(17)	26(4)	54(5)	34(4)	-1(3)	0(3)	-4(3)
C(18)	59(5)	48(4)	26(3)	-8(3)	30(3)	9(4)
C(19)	48(5)	38(5)	28(4)	-12(3)	5(4)	4(4)
C(20)	45(4)	67(5)	81(6)	48(4)	30(4)	30(4)
C(21)	74(5)	48(4)	36(4)	-7(3)	-1(4)	-39(4)
O(22)	37(3)	24(3)	31(3)	2(2)	14(2)	7(2)
Si(23)	35(1)	27(1)	26(1)	-1(1)	11(1)	-2(1)
C(24)	79(5)	25(4)	67(5)	1(3)	44(4)	4(3)
C(25)	71(5)	75(5)	59(5)	28(4)	28(4)	30(4)
C(26)	231(11)	68(6)	49(4)	25(4)	74(6)	41(6)
C(27)	46(5)	20(4)	45(5)	1(3)	15(4)	6(3)
C(28)	29(4)	62(5)	58(5)	-16(4)	13(3)	-11(3)
C(29)	50(5)	42(4)	52(5)	-16(3)	33(4)	-1(3)
C(30)	55(5)	35(4)	36(4)	1(3)	16(4)	-9(4)
C(31)	72(6)	26(3)	70(6)	-25(4)	13(5)	-21(3)
C(32)	23(4)	77(6)	79(6)	-2(5)	8(4)	3(4)
C(33)	23(4)	20(3)	35(4)	10(3)	9(3)	7(3)
C(34)	16(3)	21(3)	43(4)	-4(3)	7(3)	2(3)
C(35)	26(4)	29(4)	38(4)	5(3)	9(3)	18(3)
C(36)	34(4)	33(4)	37(4)	-4(3)	5(3)	-9(3)
C(37)	18(3)	22(3)	52(4)	-4(3)	5(3)	-7(2)
C(38)	49(5)	15(3)	34(4)	-2(3)	5(4)	4(3)
C(39)	39(4)	43(4)	36(4)	-17(3)	14(4)	-12(3)
C(40)	31(4)	37(4)	47(5)	-4(3)	20(4)	-4(3)
C(41)	39(4)	35(4)	63(5)	1(3)	34(3)	1(3)
C(42)	37(4)	37(4)	23(3)	-4(3)	13(3)	2(3)

Table 4 (cont'd)

C(43)	21(4)	38(4)	43(5)	-7(4)	2(3)	6(3)
C(44)	36(4)	17(3)	35(4)	6(3)	20(3)	11(3)
C(45)	28(4)	27(4)	53(4)	-5(3)	16(3)	-1(3)
C(46)	32(4)	27(4)	31(4)	0(3)	-4(3)	-6(3)
O(47)	36(3)	51(4)	47(4)	7(3)	-3(3)	5(3)
C(48)	16(4)	35(4)	38(4)	0(3)	5(3)	6(3)
C(49)	43(4)	43(4)	55(5)	-4(3)	29(4)	9(3)
C(50)	36(4)	31(4)	71(5)	-7(3)	14(4)	-1(3)
C(51)	36(4)	33(4)	31(4)	-2(3)	-1(3)	8(3)
C(52)	99(7)	46(4)	63(5)	-3(4)	40(5)	3(4)
C(53)	52(4)	61(4)	43(4)	12(3)	29(4)	0(3)
O(54)	37(3)	18(2)	32(3)	3(2)	0(2)	0(2)
Si(55)	34(1)	19(1)	34(1)	2(1)	10(1)	2(1)
C(56)	26(4)	32(4)	60(5)	-10(4)	6(3)	-8(3)
C(57)	50(6)	95(6)	73(7)	-14(5)	19(5)	-21(5)
C(58)	56(6)	53(5)	84(7)	-13(5)	23(5)	-22(4)
C(59)	40(5)	29(4)	25(4)	-7(3)	12(3)	-1(3)
C(60)	57(5)	60(5)	35(4)	23(3)	19(4)	5(4)
C(61)	51(5)	48(5)	54(5)	-5(4)	11(4)	22(4)
C(62)	47(4)	30(4)	13(3)	11(2)	10(3)	1(3)
C(63)	83(4)	23(3)	67(4)	13(3)	9(3)	-1(3)
C(64)	76(5)	91(5)	36(4)	-11(3)	40(4)	-28(4)

The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

Table 5. Hydrogen coordinates (x 10^4), isotropic displacement parameters (A^2 x 10^3), and occupancies for wf021005

	x	y	z	U(eq)	Occ.
H(4A)	-1428	4940	1950	45	1
H(4B)	-2097	5334	2635	45	1
H(5A)	378	5169	3879	59	1
H(5B)	-291	5762	3390	59	1
H(7A)	2247	4984	3381	44	1
H(8A)	3611	5257	2275	61	1
H(8B)	2365	5178	1231	61	1
H(9A)	3823	4291	2569	44	1
H(9B)	3610	4383	1298	44	1
H(11A)	2341	3681	3091	31	1
H(12A)	142	3173	1511	34	1
H(13A)	-1817	3578	852	32	1
H(16A)	-3636	4579	2641	44	1
H(17A)	-4326	3616	2881	60	1
H(17B)	-3509	3876	4036	60	1
H(17C)	-2846	3428	3434	60	1
H(18A)	-775	4872	4960	61	1
H(18B)	-1844	4398	4959	61	1
H(18C)	-2288	5019	4459	61	1
H(19A)	370(30)	4099(14)	5110(30)	9(9)	1
H(19B)	1230(50)	3620(30)	4380(50)	70(20)	1
H(20A)	817	5723	940	93	1
H(20B)	102	6142	1553	93	1
H(20C)	-617	5576	967	93	1
H(21A)	320	3809	314	85	1
H(21B)	1530	3991	-78	85	1
H(21C)	735	4468	341	85	1
H(24A)	1829	2016	4624	63	1
H(25A)	229	1855	5526	99	1
H(25B)	-908	1823	4388	99	1
H(25C)	-195	2419	4799	99	1
H(26A)	1279	1075	5034	164	1
H(26B)	1613	1034	3913	164	1
H(26C)	131	1033	3905	164	1
H(27A)	1939	1488	2176	44	1
H(28A)	4025	1982	2676	75	1
H(28B)	3495	1951	3701	75	1
H(28C)	3375	2534	3027	75	1
H(29A)	2460	1983	773	66	1
H(29B)	1728	2542	1003	66	1
H(29C)	920	1973	543	66	1

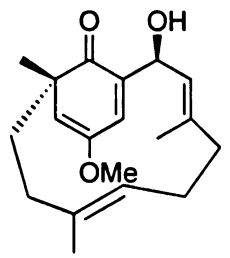
Table 5 (cont'd)

H(30A)	-1130	2243	1085	50	1
H(31A)	-1968	1274	737	87	1
H(31B)	-1088	1076	1921	87	1
H(31C)	-420	1257	1025	87	1
H(32A)	-3088	2041	1472	92	1
H(32B)	-2307	2522	2301	92	1
H(32C)	-2301	1873	2700	92	1
H(36A)	6989	1855	7879	43	1
H(37A)	4446	1835	6089	38	1
H(37B)	5150	1247	6568	38	1
H(39A)	2765	2103	6636	47	1
H(40A)	2642	1854	8821	44	1
H(40B)	1377	1743	7789	44	1
H(41A)	1253	2766	7307	50	1
H(41B)	1289	2728	8555	50	1
H(43A)	2688	3332	6903	43	1
H(44A)	4826	3842	8498	33	1
H(45A)	6810	3496	9067	43	1
H(48A)	8663	2457	7399	36	1
H(49A)	8465	3200	6006	66	1
H(49B)	9303	3430	7179	66	1
H(49C)	7818	3620	6669	66	1
H(50A)	6817	2668	5102	70	1
H(50B)	5837	2152	5081	70	1
H(50C)	7371	2053	5570	70	1
H(51A)	4260(50)	2860(20)	4960(50)	80(20)	1
H(51B)	4060(30)	3455(15)	5530(30)	5(8)	1
H(52A)	4288	1270	9075	99	1
H(52B)	5705	1414	9003	99	1
H(52C)	4944	861	8400	99	1
H(53A)	4683	3247	9645	73	1
H(53B)	4212	2609	9777	73	1
H(53C)	3457	3145	10067	73	1
H(57A)	7036	5712	9234	110	1
H(57B)	5513	5720	9087	110	1
H(57C)	6026	5916	8106	110	1
H(58A)	8071	4980	8526	96	1
H(58B)	7241	5060	7274	96	1
H(58C)	7280	4451	7850	96	1
H(59A)	3074	5526	7840	38	1
H(60A)	2523	5017	9256	74	1
H(60B)	4065	5010	9500	74	1
H(60C)	3227	4453	9011	74	1

Table 5 (cont'd)

H(61A)	1066	5057	7421	78	1
H(61B)	1675	4508	7020	78	1
H(61C)	1550	5100	6372	78	1
H(63A)	3624	5957	4907	91	1
H(63B)	4364	6053	6174	91	1
H(63C)	2863	5874	5779	91	1
H(64A)	4935	5126	4497	94	1
H(64B)	4999	4528	5114	94	1
H(64C)	5982	5032	5667	94	1

Figure A-2 ORTEP Drawing of the Structure of Compound **383**



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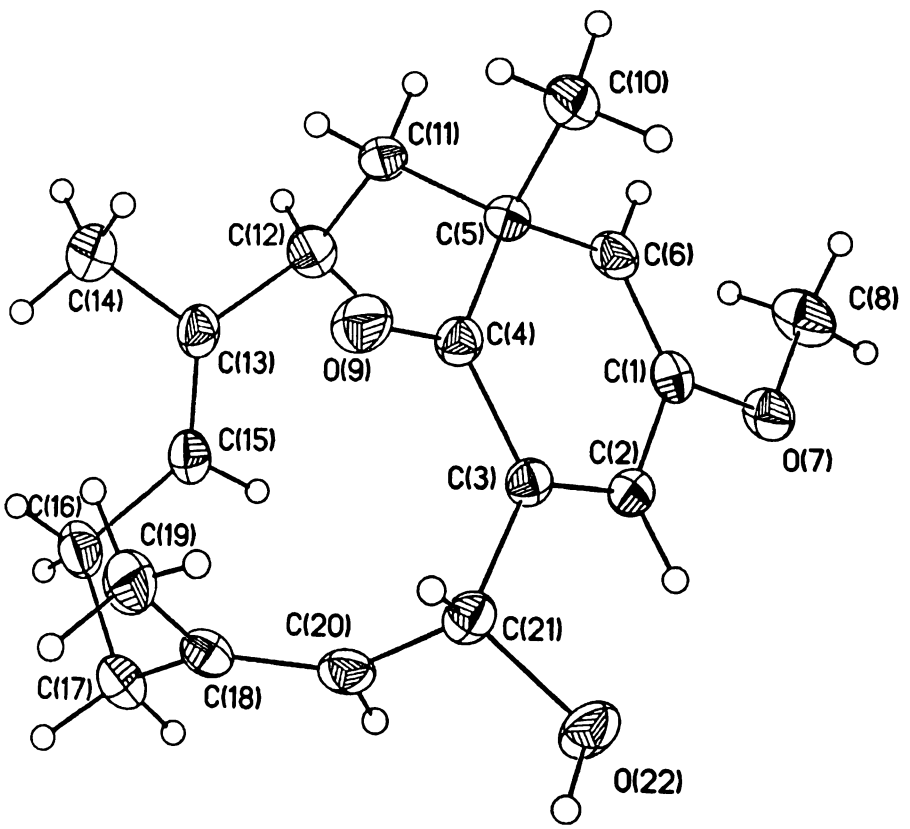

Table 1. Crystal data and structure refinement for wf072805

Identification code	p-1
Empirical formula	C19 H26 O3
Formula weight	302.40
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 6.4091(13) A b = 14.590(3) A c = 18.406(4) A alpha = 90.37(3) deg. beta = 94.69(3) deg. gamma = 100.75(3) deg.
Volume	1684.9(6) A^3
Z	4
Density (calculated)	1.192 Mg/m^3
Absorption coefficient	0.079 mm^-1
F(000)	656
Crystal size	1.4 x 1.2 x 0.5 mm
Theta range for data collection	1.78 to 28.31 deg.
Index ranges	-8<=h<=8, -19<=k<=19, -24<=l<=23
Reflections collected / unique	20386 / 7977 [R(int) = 0.0315]
Completeness to theta = 28.31	94.9%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7977 / 0 / 405
Goodness-of-fit on F^2	1.093
Final R indices [I>2sigma(I)]	R1 = 0.0514, wR2 = 0.1508
R indices (all data)	R1 = 0.0620, wR2 = 0.1559
Largest diff. peak and hole	0.556 and -0.311 e.A^-3

Table 2. Atomic coordinates (x 10^4), equivalent isotropic displacement parameters (A^2 x 10^3), and occupancies for wf072805

	x	y	z	U(eq)	Occ.
C(1)	2902(2)	4041(1)	294(1)	22(1)	1
C(2)	2480(2)	4148(1)	-485(1)	22(1)	1
C(3)	3210(2)	3642(1)	-983(1)	20(1)	1
C(4)	4546(2)	2961(1)	-746(1)	21(1)	1
C(5)	5065(2)	2839(1)	69(1)	22(1)	1
C(6)	4041(2)	3420(1)	557(1)	24(1)	1
O(7)	1991(2)	4634(1)	691(1)	28(1)	1
C(8)	2241(3)	4553(1)	1462(1)	37(1)	1
O(9)	5300(2)	2517(1)	-1191(1)	32(1)	1
C(10)	7507(2)	3150(1)	206(1)	30(1)	1
C(11)	4479(2)	1793(1)	255(1)	26(1)	1
C(12)	2113(2)	1329(1)	124(1)	29(1)	1
C(13)	1398(2)	889(1)	-625(1)	26(1)	1
C(14)	2684(3)	194(1)	-862(1)	42(1)	1
C(15)	-329(2)	1069(1)	-1006(1)	26(1)	1
C(16)	-1290(2)	666(1)	-1740(1)	32(1)	1
C(17)	-1575(2)	1439(1)	-2286(1)	32(1)	1
C(18)	484(2)	2139(1)	-2301(1)	27(1)	1
C(19)	2306(2)	1781(1)	-2597(1)	33(1)	1
C(20)	641(2)	2977(1)	-1981(1)	25(1)	1
C(21)	2620(2)	3700(1)	-1793(1)	23(1)	1
O(22)	2234(2)	4620(1)	-1936(1)	31(1)	1
C(1A)	2206(2)	6079(1)	-5577(1)	22(1)	1
C(2A)	2426(2)	5816(1)	-4817(1)	22(1)	1
C(3A)	1598(2)	6227(1)	-4287(1)	20(1)	1
C(4A)	396(2)	6980(1)	-4461(1)	22(1)	1
C(5A)	100(2)	7267(1)	-5256(1)	24(1)	1
C(6A)	1199(2)	6770(1)	-5784(1)	25(1)	1
O(7A)	3147(2)	5539(1)	-6014(1)	28(1)	1
C(8A)	3201(2)	5785(1)	-6763(1)	36(1)	1
O(9A)	-420(2)	7349(1)	-3989(1)	33(1)	1
C(10A)	-2329(2)	7017(1)	-5471(1)	33(1)	1
C(11A)	787(2)	8338(1)	-5312(1)	30(1)	1
C(12A)	3135(2)	8752(1)	-5082(1)	32(1)	1
C(13A)	3691(2)	9002(1)	-4280(1)	31(1)	1
C(14A)	2366(3)	9635(1)	-3967(1)	51(1)	1
C(15A)	5329(2)	8724(1)	-3909(1)	30(1)	1
C(16A)	6145(3)	8942(1)	-3123(1)	37(1)	1
C(17A)	6284(2)	8051(1)	-2686(1)	37(1)	1
C(18A)	4179(2)	7376(1)	-2768(1)	30(1)	1
C(19A)	2357(3)	7676(1)	-2420(1)	41(1)	1

Table 2 (cont'd)

C(20A)	3987(2)	6623(1)	-3198(1)	26(1)	1
C(21A)	1969(2)	5994(1)	-3491(1)	24(1)	1
O(22A)	2262(2)	5041(1)	-3418(1)	29(1)	1

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Table 3. Bond lengths [A] and angles [deg] for wf072805

C(1)-C(6)	1.3345(19)
C(1)-O(7)	1.3687(15)
C(1)-C(2)	1.4529(17)
C(2)-C(3)	1.3392(17)
C(3)-C(4)	1.4734(17)
C(3)-C(21)	1.5159(17)
C(4)-O(9)	1.2238(16)
C(4)-C(5)	1.5282(17)
C(5)-C(6)	1.5006(18)
C(5)-C(10)	1.5455(19)
C(5)-C(11)	1.5495(18)
O(7)-C(8)	1.4232(17)
C(11)-C(12)	1.540(2)
C(12)-C(13)	1.516(2)
C(13)-C(15)	1.331(2)
C(13)-C(14)	1.503(2)
C(15)-C(16)	1.506(2)
C(16)-C(17)	1.541(2)
C(17)-C(18)	1.513(2)
C(18)-C(20)	1.3361(19)
C(18)-C(19)	1.505(2)
C(20)-C(21)	1.5047(19)
C(21)-O(22)	1.4330(15)
C(1A)-C(6A)	1.3346(19)
C(1A)-O(7A)	1.3708(15)
C(1A)-C(2A)	1.4566(17)
C(2A)-C(3A)	1.3376(18)
C(3A)-C(4A)	1.4788(18)
C(3A)-C(21A)	1.5154(17)
C(4A)-O(9A)	1.2214(16)
C(4A)-C(5A)	1.5310(18)
C(5A)-C(6A)	1.5025(18)
C(5A)-C(11A)	1.5489(19)
C(5A)-C(10A)	1.5490(19)
O(7A)-C(8A)	1.4290(17)
C(11A)-C(12A)	1.537(2)
C(12A)-C(13A)	1.515(2)
C(13A)-C(15A)	1.334(2)
C(13A)-C(14A)	1.507(2)
C(15A)-C(16A)	1.508(2)
C(16A)-C(17A)	1.546(2)
C(17A)-C(18A)	1.510(2)
C(18A)-C(20A)	1.331(2)
C(18A)-C(19A)	1.508(2)

Table 3 (cont'd)

C(20A)-C(21A)	1.497(2)
C(21A)-O(22A)	1.4433(16)
C(6)-C(1)-O(7)	126.72(12)
C(6)-C(1)-C(2)	121.43(12)
O(7)-C(1)-C(2)	111.86(11)
C(3)-C(2)-C(1)	122.67(12)
C(2)-C(3)-C(4)	119.88(12)
C(2)-C(3)-C(21)	122.48(11)
C(4)-C(3)-C(21)	117.56(11)
O(9)-C(4)-C(3)	121.04(12)
O(9)-C(4)-C(5)	119.71(11)
C(3)-C(4)-C(5)	119.21(11)
C(6)-C(5)-C(4)	114.53(10)
C(6)-C(5)-C(10)	105.75(11)
C(6)-C(5)-C(11)	110.48(11)
C(4)-C(5)-C(11)	109.62(11)
C(10)-C(5)-C(11)	108.30(11)
C(1)-C(6)-C(5)	122.13(12)
C(1)-O(7)-C(8)	116.01(11)
C(12)-C(11)-C(5)	116.78(11)
C(13)-C(12)-C(11)	116.34(12)
C(15)-C(13)-C(14)	123.96(13)
C(15)-C(13)-C(12)	121.13(13)
C(14)-C(13)-C(12)	114.75(13)
C(13)-C(15)-C(16)	127.74(13)
C(15)-C(16)-C(17)	111.56(12)
C(18)-C(17)-C(16)	110.33(12)
C(20)-C(18)-C(19)	124.69(14)
C(20)-C(18)-C(17)	119.02(13)
C(19)-C(18)-C(17)	115.82(12)
C(18)-C(20)-C(21)	128.09(13)
O(22)-C(21)-C(20)	111.08(11)
O(22)-C(21)-C(3)	108.04(10)
C(20)-C(21)-C(3)	107.27(10)
C(6A)-C(1A)-O(7A)	127.23(12)
C(6A)-C(1A)-C(2A)	121.45(12)
O(7A)-C(1A)-C(2A)	111.32(11)
C(3A)-C(2A)-C(1A)	122.70(12)
C(2A)-C(3A)-C(4A)	120.12(12)
C(2A)-C(3A)-C(21A)	122.23(11)
C(4A)-C(3A)-C(21A)	117.52(11)
O(9A)-C(4A)-C(3A)	121.22(12)
O(9A)-C(4A)-C(5A)	120.03(11)

Table 3 (cont'd)

C(3A)-C(4A)-C(5A)	118.70(11)
C(6A)-C(5A)-C(4A)	114.91(11)
C(6A)-C(5A)-C(11A)	110.60(11)
C(4A)-C(5A)-C(11A)	109.88(11)
C(6A)-C(5A)-C(10A)	107.96(11)
C(4A)-C(5A)-C(10A)	105.52(11)
C(11A)-C(5A)-C(10A)	107.59(11)
C(1A)-C(6A)-C(5A)	121.93(12)
C(1A)-O(7A)-C(8A)	116.56(11)
C(12A)-C(11A)-C(5A)	116.67(12)
C(13A)-C(12A)-C(11A)	116.52(13)
C(15A)-C(13A)-C(14A)	123.93(14)
C(15A)-C(13A)-C(12A)	121.15(13)
C(14A)-C(13A)-C(12A)	114.77(14)
C(13A)-C(15A)-C(16A)	127.86(14)
C(15A)-C(16A)-C(17A)	112.29(12)
C(18A)-C(17A)-C(16A)	110.57(13)
C(20A)-C(18A)-C(19A)	124.46(14)
C(20A)-C(18A)-C(17A)	119.01(13)
C(19A)-C(18A)-C(17A)	116.12(13)
C(18A)-C(20A)-C(21A)	127.40(13)
O(22A)-C(21A)-C(20A)	108.20(11)
O(22A)-C(21A)-C(3A)	110.72(10)
C(20A)-C(21A)-C(3A)	106.78(11)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for wf072805

	U11	U22	U33	U23	U13	U12
C(1)	22(1)	21(1)	20(1)	-4(1)	3(1)	1(1)
C(2)	24(1)	19(1)	21(1)	1(1)	1(1)	4(1)
C(3)	22(1)	17(1)	18(1)	3(1)	3(1)	2(1)
C(4)	22(1)	19(1)	22(1)	1(1)	2(1)	3(1)
C(5)	25(1)	21(1)	21(1)	0(1)	-2(1)	5(1)
C(6)	28(1)	26(1)	17(1)	-1(1)	-1(1)	3(1)
O(7)	31(1)	33(1)	21(1)	-8(1)	2(1)	11(1)
C(8)	41(1)	54(1)	19(1)	-9(1)	2(1)	13(1)
O(9)	38(1)	36(1)	26(1)	-2(1)	4(1)	18(1)
C(10)	25(1)	30(1)	34(1)	-4(1)	-3(1)	4(1)
C(11)	34(1)	21(1)	24(1)	4(1)	-6(1)	6(1)
C(12)	36(1)	24(1)	23(1)	6(1)	1(1)	0(1)
C(13)	32(1)	18(1)	28(1)	1(1)	3(1)	0(1)
C(14)	45(1)	34(1)	48(1)	-10(1)	-8(1)	16(1)
C(15)	31(1)	21(1)	25(1)	-2(1)	3(1)	1(1)
C(16)	35(1)	28(1)	31(1)	-6(1)	-2(1)	1(1)
C(17)	34(1)	34(1)	27(1)	-7(1)	-7(1)	6(1)
C(18)	35(1)	31(1)	15(1)	1(1)	-2(1)	9(1)
C(19)	43(1)	33(1)	23(1)	-5(1)	4(1)	11(1)
C(20)	30(1)	29(1)	16(1)	4(1)	0(1)	10(1)
C(21)	33(1)	22(1)	17(1)	4(1)	6(1)	8(1)
O(22)	50(1)	23(1)	21(1)	7(1)	6(1)	12(1)
C(1A)	21(1)	23(1)	18(1)	-4(1)	2(1)	1(1)
C(2A)	24(1)	20(1)	21(1)	2(1)	1(1)	3(1)
C(3A)	21(1)	20(1)	18(1)	3(1)	1(1)	1(1)
C(4A)	22(1)	22(1)	22(1)	0(1)	1(1)	3(1)
C(5A)	27(1)	23(1)	22(1)	0(1)	-2(1)	6(1)
C(6A)	28(1)	27(1)	17(1)	2(1)	0(1)	2(1)
O(7A)	32(1)	35(1)	20(1)	-4(1)	6(1)	9(1)
C(8A)	33(1)	56(1)	18(1)	-3(1)	5(1)	10(1)
O(9A)	38(1)	38(1)	27(1)	-3(1)	5(1)	17(1)
C(10A)	28(1)	36(1)	35(1)	-3(1)	-5(1)	8(1)
C(11A)	38(1)	23(1)	30(1)	4(1)	-5(1)	8(1)
C(12A)	38(1)	23(1)	32(1)	5(1)	2(1)	2(1)
C(13A)	35(1)	19(1)	36(1)	-4(1)	3(1)	1(1)
C(14A)	56(1)	42(1)	60(1)	-19(1)	-6(1)	23(1)
C(15A)	33(1)	24(1)	31(1)	-6(1)	3(1)	0(1)
C(16A)	38(1)	34(1)	36(1)	-12(1)	-2(1)	-1(1)
C(17A)	37(1)	44(1)	25(1)	-10(1)	-6(1)	3(1)
C(18A)	34(1)	38(1)	17(1)	0(1)	-2(1)	5(1)
C(19A)	42(1)	53(1)	26(1)	-14(1)	4(1)	6(1)
C(20A)	29(1)	32(1)	18(1)	4(1)	1(1)	7(1)

Table 4 (cont'd)

C(21A)	31(1)	24(1)	16(1)	4(1)	4(1)	6(1)
O(22A)	39(1)	24(1)	22(1)	7(1)	1(1)	5(1)

The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

Table 5. Hydrogen coordinates (x 10^4), isotropic displacement parameters (A^2 x 10^3), and occupancies for wf072805

	x	y	z	U(eq)	Occ.
H(2A)	1669	4585	-645	26	1
H(6A)	4205	3345	1058	29	1
H(8A)	1554	4998	1689	56	1
H(8B)	3731	4673	1625	56	1
H(8C)	1607	3934	1594	56	1
H(10A)	7901	3798	93	45	1
H(10B)	8201	2784	-98	45	1
H(10C)	7937	3062	709	45	1
H(11A)	5299	1450	-29	32	1
H(11B)	4930	1727	765	32	1
H(12A)	1807	851	484	34	1
H(12B)	1257	1796	209	34	1
H(14A)	2129	-52	-1339	63	1
H(14B)	2600	-305	-523	63	1
H(14C)	4144	497	-877	63	1
H(15A)	-1025	1494	-794	32	1
H(16A)	-2666	275	-1686	38	1
H(16B)	-376	278	-1930	38	1
H(17A)	-1995	1163	-2770	39	1
H(17B)	-2694	1753	-2147	39	1
H(19A)	3531	2275	-2584	49	1
H(19B)	1909	1562	-3091	49	1
H(19C)	2642	1277	-2305	49	1
H(20A)	-631	3133	-1860	30	1
H(21A)	3782	3573	-2070	28	1
H(22A)	2290(30)	4731(14)	-2432(11)	47(5)	1
H(2AA)	3173	5342	-4695	26	1
H(6AA)	1177	6948	-6268	30	1
H(8AA)	3887	5362	-7016	53	1
H(8AB)	3982	6410	-6797	53	1
H(8AC)	1773	5748	-6979	53	1
H(10D)	-2804	6356	-5439	49	1
H(10E)	-2625	7206	-5961	49	1
H(10F)	-3065	7335	-5145	49	1
H(11C)	480	8505	-5813	36	1
H(11D)	-92	8633	-5015	36	1
H(12C)	3994	8307	-5218	38	1
H(12D)	3543	9310	-5359	38	1
H(14D)	2820	9760	-3461	77	1
H(14E)	893	9337	-4017	77	1
H(14F)	2543	10211	-4225	77	1

Table 5 (cont'd)

H(15B)	6056	8350	-4166	36	1
H(16C)	5205	9287	-2898	44	1
H(16D)	7548	9335	-3105	44	1
H(17C)	7390	7755	-2859	44	1
H(17D)	6661	8218	-2175	44	1
H(19D)	1101	7201	-2504	61	1
H(19E)	2093	8249	-2628	61	1
H(19F)	2719	7768	-1904	61	1
H(20B)	5250	6469	-3331	31	1
H(21B)	774	6100	-3222	28	1
H(22B)	1120(40)	4629(17)	-3697(14)	77(7)	1

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