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LIST OF ABBREVIATIONS

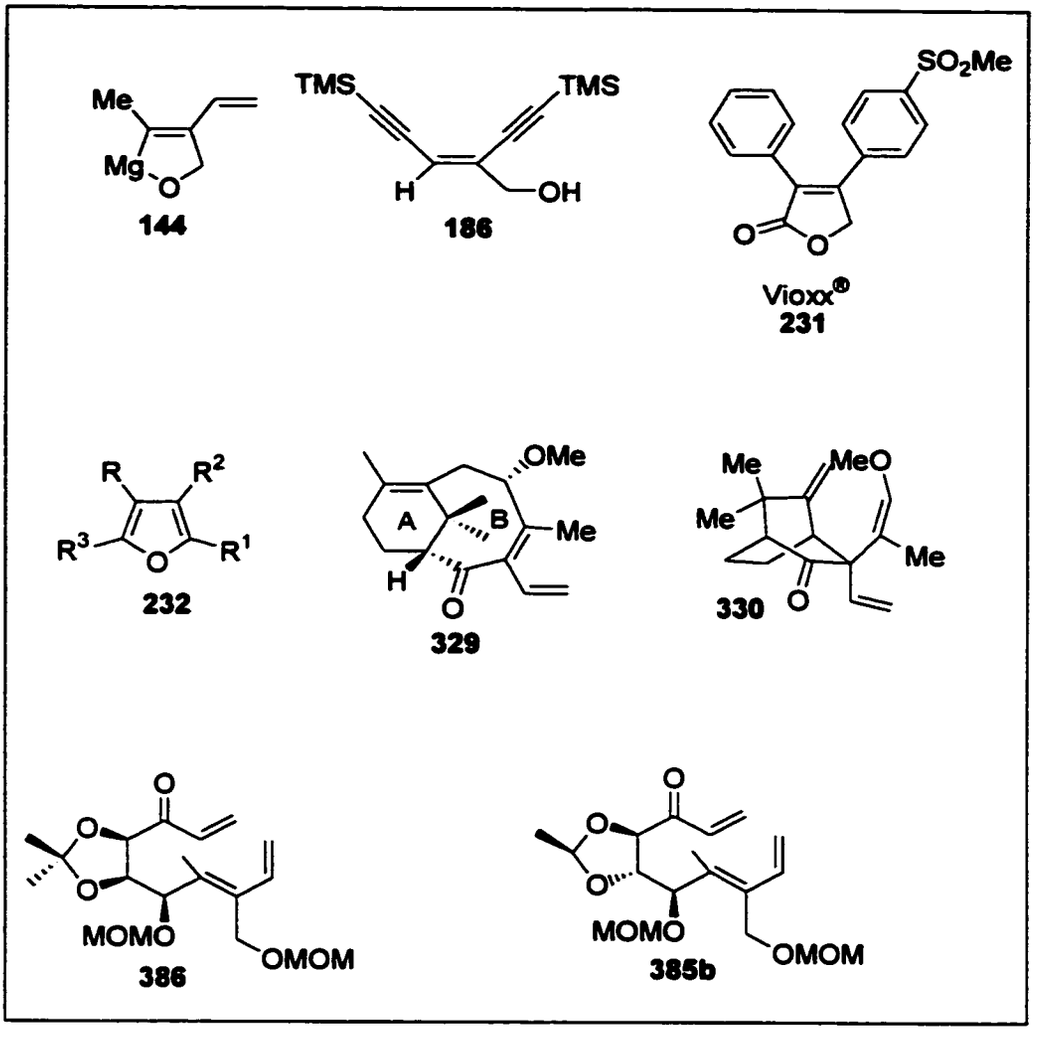
Ac	acetyl
AD	asymmetric dihydroxylation
AIBN	azobis(isobutyro)nitrile
Anal. Calc'd	elemental analysis calculated
Bn	benzyl
BOC	*t*-butoxycarbonyl
Bu	butyl
Bz	benzoyl
cat.	catalytic
CI	chemical ionization
CSA	camphorsulfonic acid
d	day
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCC	dicylohexylcoarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benozquinone
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DNA	deoxyribonucleic acid
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
E	electrophile
E_a	activation energy
EI	electron impact
eq.	equivalents
Et	ethyl
Ether	diethyl ether
GC	gas chromatography

h	hour
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrum
^{i}Pr	isopropyl
IR	infrared
LAH	lithium aluminum hyrdride
LDA	lithium diisopropylamide
m-CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
min	minutes
MOM	methoxymethyl
ms	molecular sieves
NMR	nuclear magnetic resonance
Nu	nucleophile
[O]	oxidation
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PG	protecting group
Piv	pivaloyl
PMB	*p*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
PTSA	*p*-toluenesulfonic acid
Py	pyridine
RT	room temperature
salen	*N,N'*-Bis(3,5-di-*t*-butylsalicylicylidene)-1,2-cyclohexane-diamino
s.m.	starting material
TBAF	tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl

THF	tetrahydrofuran
TIPS	triisopropylsilyl
TIPSOTf	triisopropylsilyl trifluoromethanesulfonate
TLC	thin layer chromatography
TMS	trimethylsilyl

ABSTRACT

Magnesium-mediated carbometallation has been employed as a route to a diverse range of organic synthons. The orginal carbometallation procedure has been optimized by a solvent study, which indicates that cyclohexane can be used in most cases, to improve the yields and consistency of the reaction. A wide-range of polysubstituted furans (**232**) were obtained when the reaction intermediate (**144**) was quenched with either dimethylformamide or benzonitrile. The use of carbon dioxide as an electrophile, provided a short (two-steps) synthesis of the Merck anti-inflammatory drug, Vioxx® (**231**). The reaction was also extended to a direct one-step synthesis of the ene-diyne chromophore (**186**). Additional research afforded a versatile route from **144** to dienophiles for intramolecular Diels-Alder reactions. An expedient route to the Taxol A/B-ring system (**329**) was developed. This ring system underwent a facile enone accelerated Cope rearrangement to generate a bicylco[2.2.2]octanone ring system (**330**). Finally, the dienophiles prepared from the carbomagnesiation reaction were employed as key steps in the preparation of tether controlled intramolecular Diels-Alder reactions. The reactions were shown to be more facile when *cis*-isopropylidene acetals (**386**) were employed in the tether. The *trans*-isopropylidene acetal tether (**385b**) was also prepared for a direct comparison. As anticipated the cycloaddition occurred at a much slower rate.


Me
Mg
O
144
TMS
TMS
H
OH
186
SO2Me
O
O
Vioxx®
231
R
R2
R3
O
R1
232
OMe
A
B
Me
H
O
329
Me
MeO
Me
Me
O
330
O
O
O
MOMO
OMOM
386
O
O
O
MOMO
OMOM
385b

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Alex Fallis. He has welcomed me into his "chemical" family and provided me with a great opportunity. I cannot imagine a better environment in which to have completed my doctoral work. Alex allowed me the freedom to investigate interesting new aspescts of projects and in the process I learned a great deal. He was not only my mentor, but also became a friend.

I also thank Tony Durst for many insightful conversations over the years, about both chemistry and life. His suggestions were always welcome and Tony also showed me what it means to be a great teacher.

I had the extreme great fortune of working with a number of excellent post-docs. However, three deserve special mention. Dr. Peter Wilson and Dr. Simon Woo both took me under their wing when I first arrived and each showed me what it means to be an experimental scientist. For this I am forever grateful. Dr. Stephanie Legoupy was also an outstanding chemist who taught me a great deal during her stay in Ottawa.

I would like to thank my lab colleagues throughout my years here, both past and present. The fruitful discussions on a whole range of subjects always kept things interesting. Shawn and Chris V., two chemists I greatly admired, had particularily outstanding suggestions on chemistry.

Nicole was an important part of my life while here in Ottawa, thank you for your support. I have been extremely lucky to have made a number of new friends with whom I have shared many great times. Helen, Chris C., Anne, Matt, Matthew, Arturo, Stephanie "para", Pete, Simon, Stephanie "ortho", Beth, Shawn, Jim, Chris V., Gonzalo, Stephen and everyone else. Thanks for making my time at Ottawa truly memorable.

Thank you to Tony and Dan, two great friends who if not for their help at UW, all that followed would not have been possible.

Special thanks to Stephen for help in proofreading the final draft.

Finally, thank you to my family for their ongoing support. I am indebted to you for all your help and fear I will never be able to do enough to repay you.

I. Carbometallation

I-i. Carbometallation Introduction

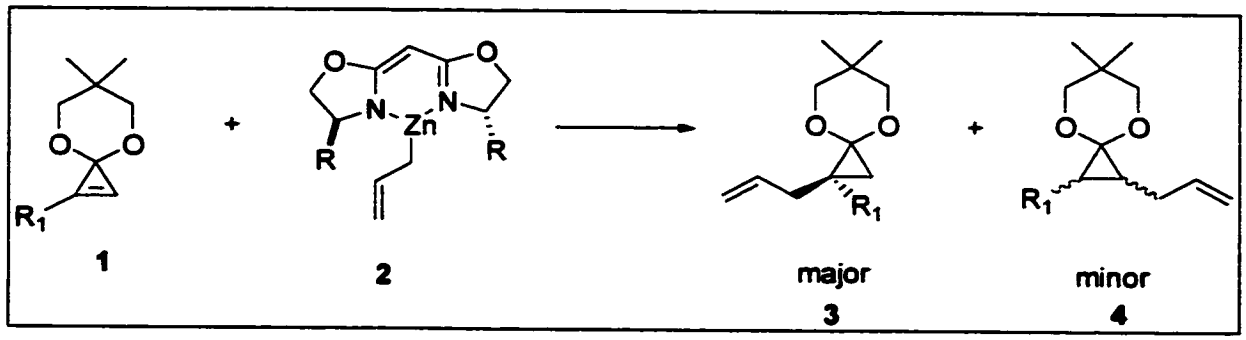
It appears that Bähr and Ziegler reported the first example of a carbometallation reaction in 1927.[1] Over the next 70 years, but particularly during the last decade, a broad cross-section of interrelated families of reactions involving the addition of diverse organometallics to a variety of alkenes and alkynes have been discovered. These accomplishments are summarized in several review articles.[2] The modern definition of the term carbometallation was suggested by Negishi and has been defined to encompass carbon-metal additions across unsaturated carbon bonds where the resulting carbon-metal bond can be employed in further transformations.[3]

Reactions that involve an alkyne or alkene acceptor containing an allylic or homoallylic heteroatom are the most widely reported. In general, oxygen is the most useful substituent, either as a free alcohol or ether. Related examples of conjugated systems have also been reported but are less common. Despite the similarity and interrelationships of several organometallic transformations the following has been divided by the element employed rather than the synthetic transformation described.

I-i-i. Zinc

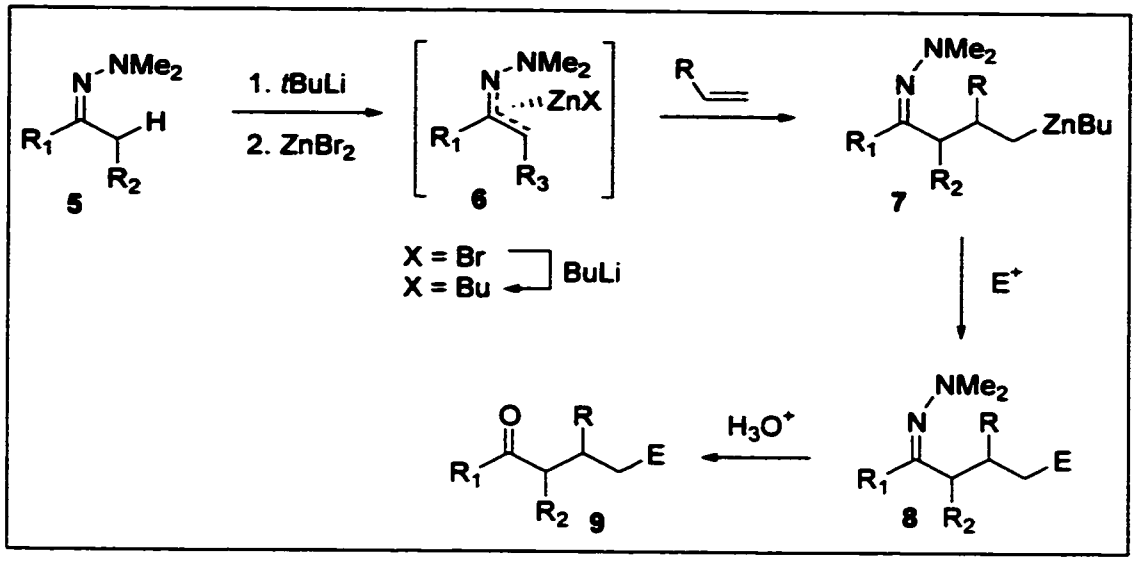
The construction of quaternary carbon centres in an enantioselective manner is a challenge and continues to receive a great deal of attention. Nakamura and co-workers have reported an efficient method for the addition of an allylic zinc reagent bearing a chiral bisoxazoline ligand, to tri-substituted olefins. The addition was regiospecific as

addition occurs exclusively at the more substituted terminus of the olefin.[4] High-pressure experiments did not enhance the enantioselectivity or regioselectivity, but accelerated the allylzincation reaction and improved the yield (Scheme 1).



Scheme 1: *Zinc-Mediated Route to Quaternary Carbon Centres*

The regioselectivity of the zinc addition to strained tri-substituted olefins of type **1** may be controlled by a combination of the choice of ligand for the zinc nucleophile, as well as incorporation of a metal substituent (R_1 = SiR_3, GeR_3 or SnR_3) (Scheme 1). The regioselectivity can be controlled by choice of the R_1 substituent. Thus with allyl zinc bromide as the nucleophile, addition predominated at the least substituted end of the olefin to yield **4** possessing a metal stabilized anion α to the R_1 metal component. Conversely, addition of the bisoxazoline (BOX) allylzinc reagent (**2**) reversed the selectively to give addition preferentially at the most substituted end of the olefin to generate **3**. This is likely a consequence of the steric effect of the large metal substituent and the BOX ligand. The reaction may also be catalyzed by iron (III) tri-chloride.[5] The enantioselective carbometallation of unactivated olefins is an expanding area of study that continues to receive increased attention.[6]

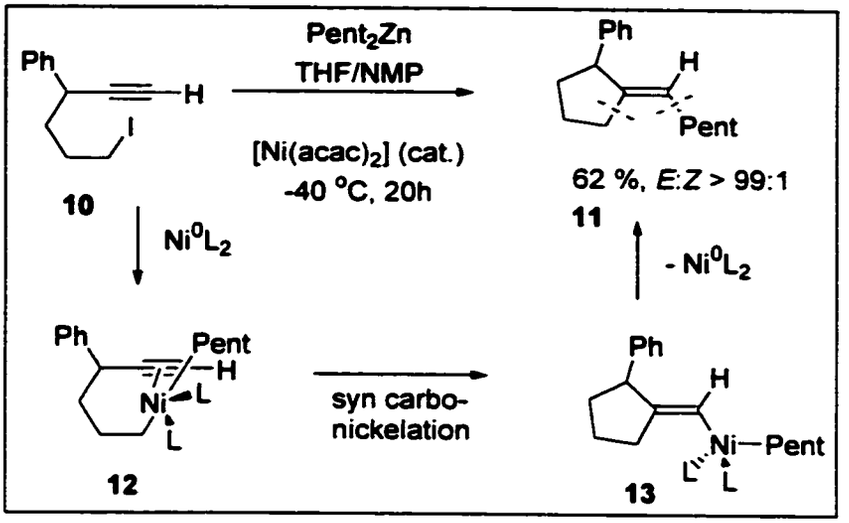


Scheme 2: *Zinc Mediated Three-Component Synthesis of Carbonyls*

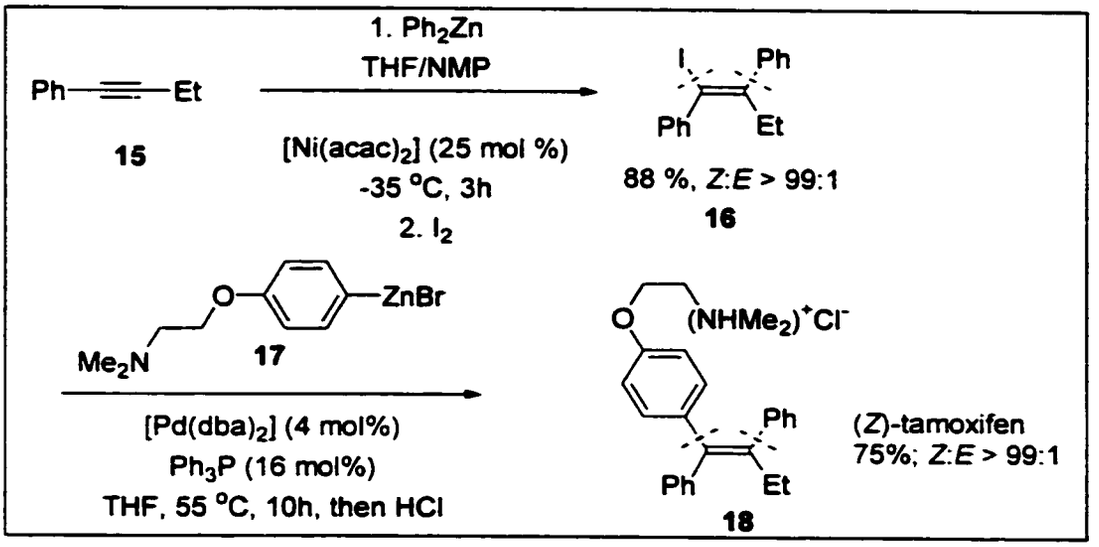
The carbometallation of unactivated olefins with Zn-azaenolates, developed by Kubota and Nakamura, provides an attractive route to effect the three-component synthesis of carbonyl derivatives.[7] A key feature contributing to the success of this reaction is the use of the *t*-$BuZn^{II}$ species rather than the $BrZn^{II}$ species, which otherwise results in an impractical, slow reaction (Scheme 2). Thus the intermediate hydrazone zinc salt **6** adds to the alkene to form the alkyl zinc species **7**, which may be reacted with various electrophiles to provide the substituted ketones **9** after hydrolysis.

Knochel and co-workers have reported an efficient nickel-catalyzed carbozincation of unactivated alkynes.[8] Initially, the intramolecular reaction of **10** revealed a significant *syn* stereoselectivity (Scheme 3). The mechanism for the *syn* addition is believed to involve the insertion of nickel(0) (generated *in-situ*), into the carbon-iodine bond followed by transmetallation with the pentenyl zinc reagent ($Pent_2Zn$) to afford the nickel(II) complex **12**, which controlled the *syn* carbonickelation of the

alkyne *via* formation of the alkenyl alkyl nickel(II) complex **13**. Reductive elimination then led to the (*E*)-*exo*-alkylidenecyclopentane **11**.



Scheme 3: *Nickel Catalyzed Stereoselective Olefin Synthesis*

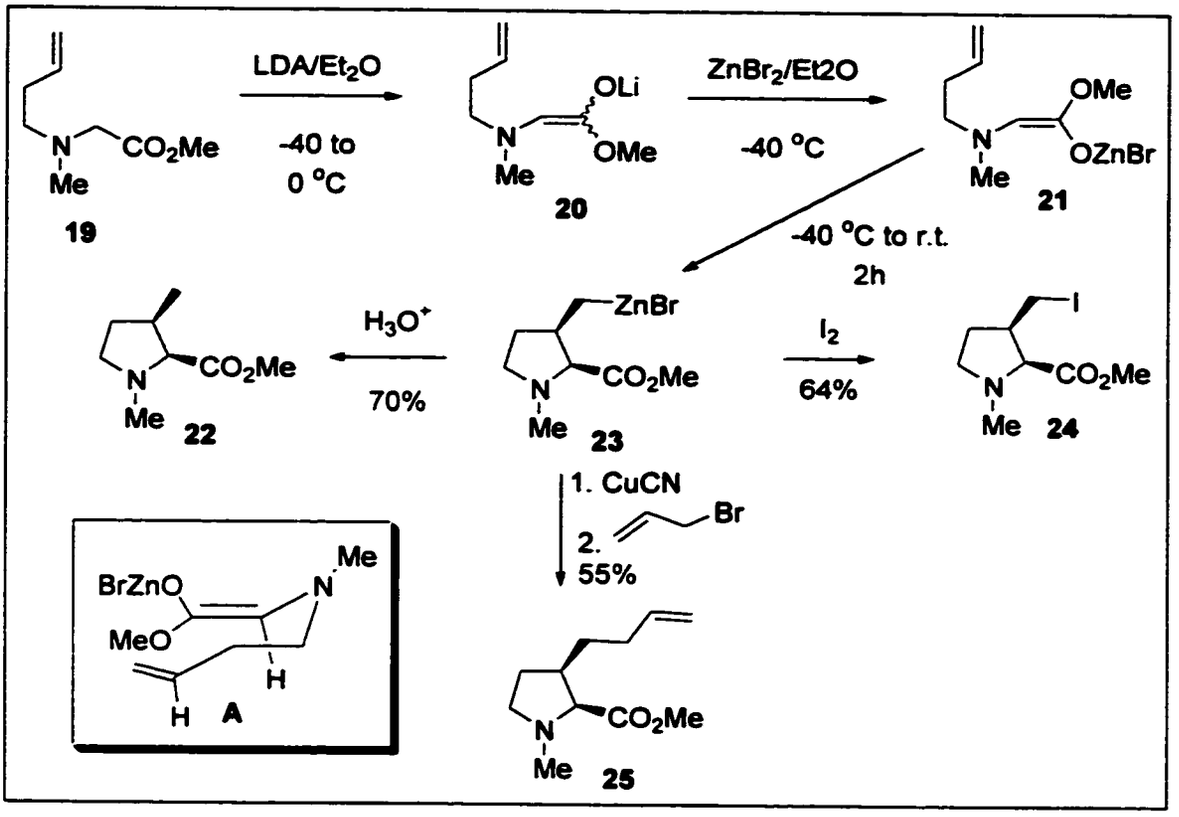


Scheme 4: *Tamoxifen Synthesis*

This *syn* selective procedure was extended to a direct two-step synthesis of (*Z*)-tamoxifen (**18**) (Scheme 4).[9] The addition of diphenylzinc to alkynes proceeded more readily than

the reaction with dialkyzinc reagents. Therefore, the addition of diphenylzinc to 1-phenyl-1-butyne (**15**) followed by an iodine quench gave the pure (*Z*)-alkene **16** in 88% yield. A subsequent zinc-palladium catalyzed coupling with the substituted phenyl zinc bromide **17** afforded the *anti*-estrogenic drug. This family of compounds is of current interest for the treatment of metastatic breast cancer.[10]

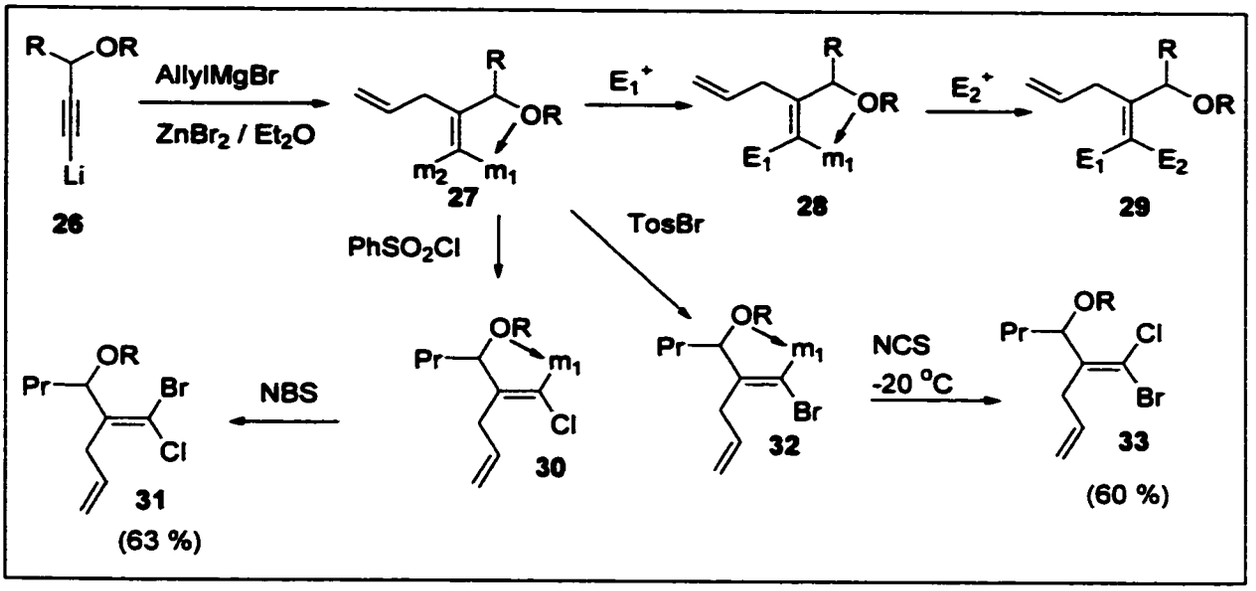
Normant and co-workers have developed a valuable method for the preparation of substituted pyrrolidines.[11] This sequence involved the diastereoselective generation of an amino-zinc-enolate **21,** formed from the initial lithium salt **20.** Intramolecular carbometallation onto the alkene afforded the heterocycle **23** that was reacted with a selection of electrophiles to generate the compounds **22**, **24,** and **25.** The observed stereochemistry may be rationalized by analyzing a chair-like amino-zinc-enolate transition state **A**.



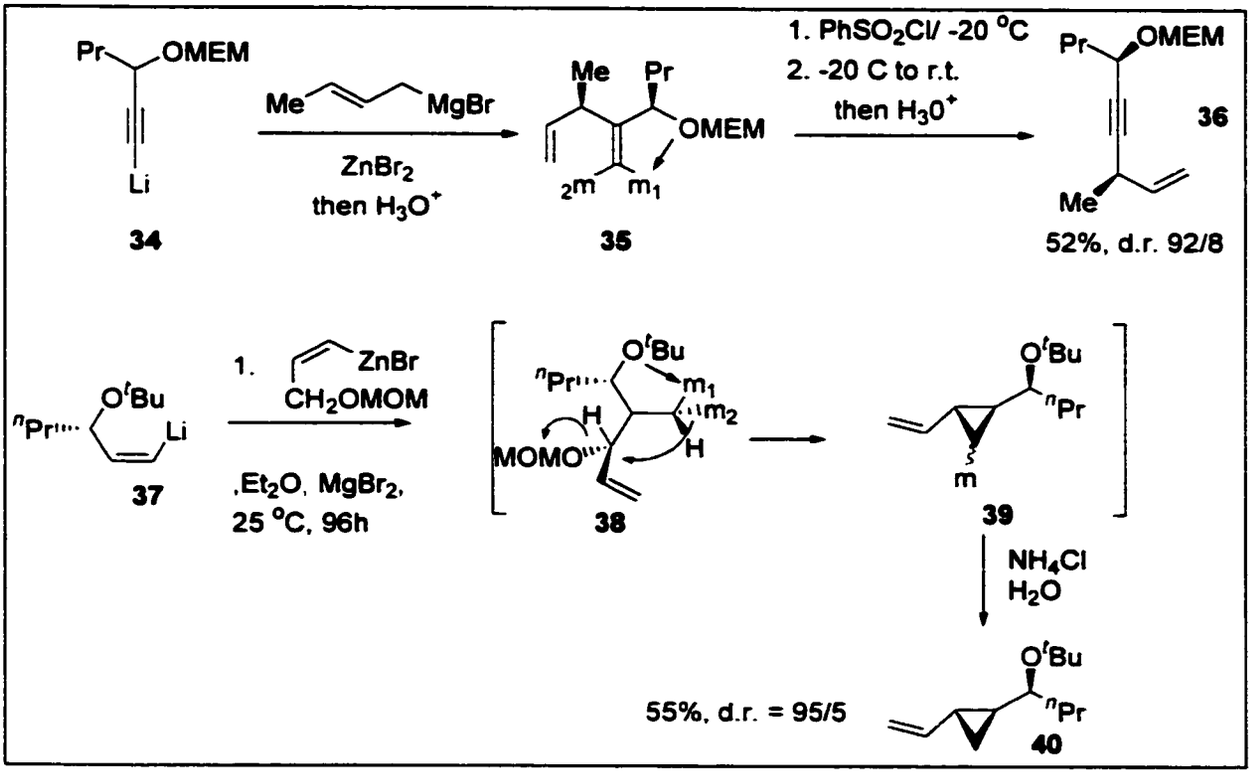
Scheme 5: *Pyrrolidine Synthesis via an Amino-Zinc Enolate*

I-i-ii. Bismetallic

Normant and co-workers have also devised has an excellent method to exploit the different reactivity of vinyl mixed metal 1,1-dianions such as **27**. These chelation-controlled reactions of propargyl ethers provided a direct route to stereodefined olefins. as illustrated in Scheme 6.[12] The versatility of this procedure is exemplified by the preparation of **31** and **33** from the common synthon **27** (R = ^{t}Pr).



Scheme 6: *Chelation Controlled Bis-Metallics*

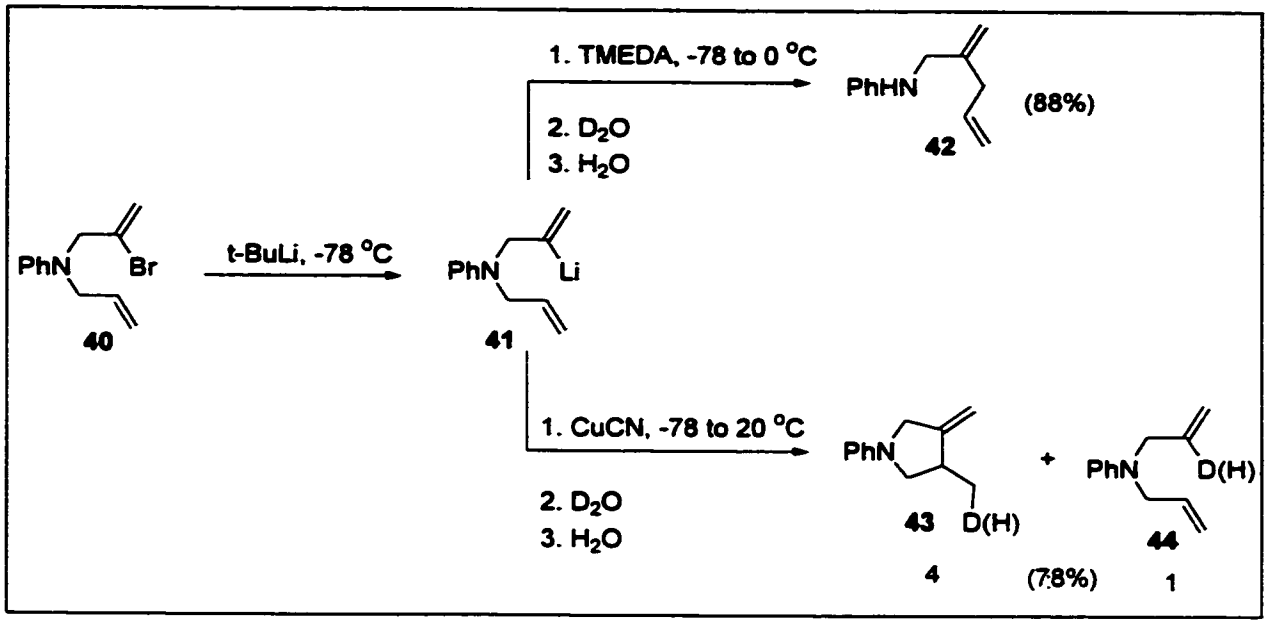


Scheme 7: *Bismetallics as a Route to Di-Substituted Alkynes and Cyclopropanes*

Additional investigations have resulted in modified sequences using these geminal-organobismetallics in the Fritsch-Buttenberg-Wiechell[13] (FBW)[14] rearrangement in order to yield di-substituted alkynes (Scheme 7).[15] This process provided the first example of the transfer of chirality in the FBW rearrangement *via* zinc carbenoids. The migration occurs with retention of configuration. A further extension employed these *gem*-bismetallics for the preparartion of 1,2-di-substituted cyclopropanes such as **40**, in a highly diastereoselective manner.[16] An excellent review has been published describing the preparation and application of these mixed metal sp^2 anions.[17]

I-i-iv. Copper

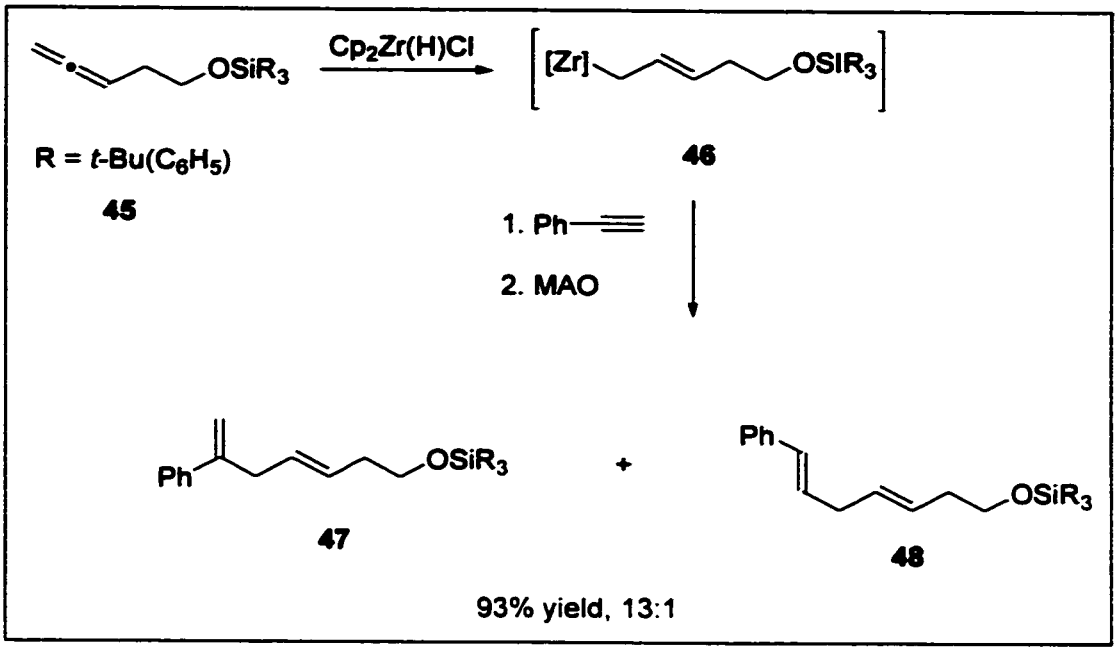
Barluenga and co-workers have developed an intramolecular carbometallation of olefins upon copper (I)[18] exchange with the lithium salt **41** to effect cyclization to **43**. The organometallic intermediate in the absence of copper, but with added TMEDA, followed a different pathway. Thus allyl transfer took precedence to afford **42** *via* a 6-*endo* addition.[19]



Scheme 8: *Intramolecular Carbometallation of Olefins*

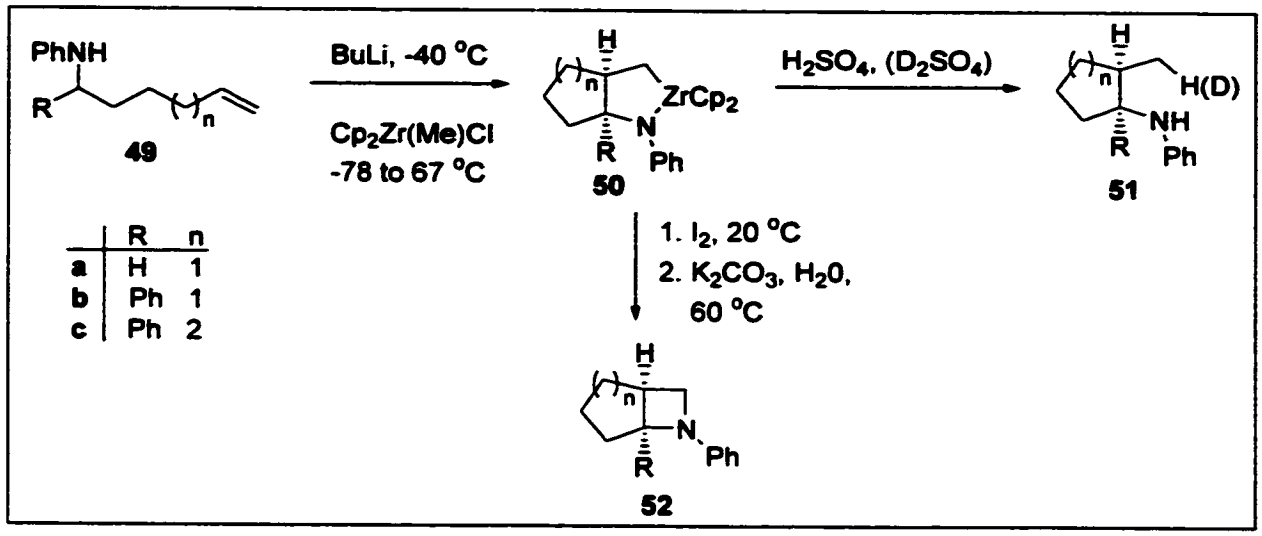
I-i-v Zirconium

Yamanoi and co-workers discovered that hydrozirconation of allenes in the presence of methylaluminoxane (MAO) effected the carbometallation of alkynes to provide a useful two-step method for the preparation of skipped dienes **47** and **48** in a regioselective manner.[20] The reaction failed in the absence of MAO and the regioselectivity was reduced to 9:1 from 13:1 when Et_3Al is employed rather than MAO (Scheme 9).



Scheme 9: *Hydrozirconation of Allenes*

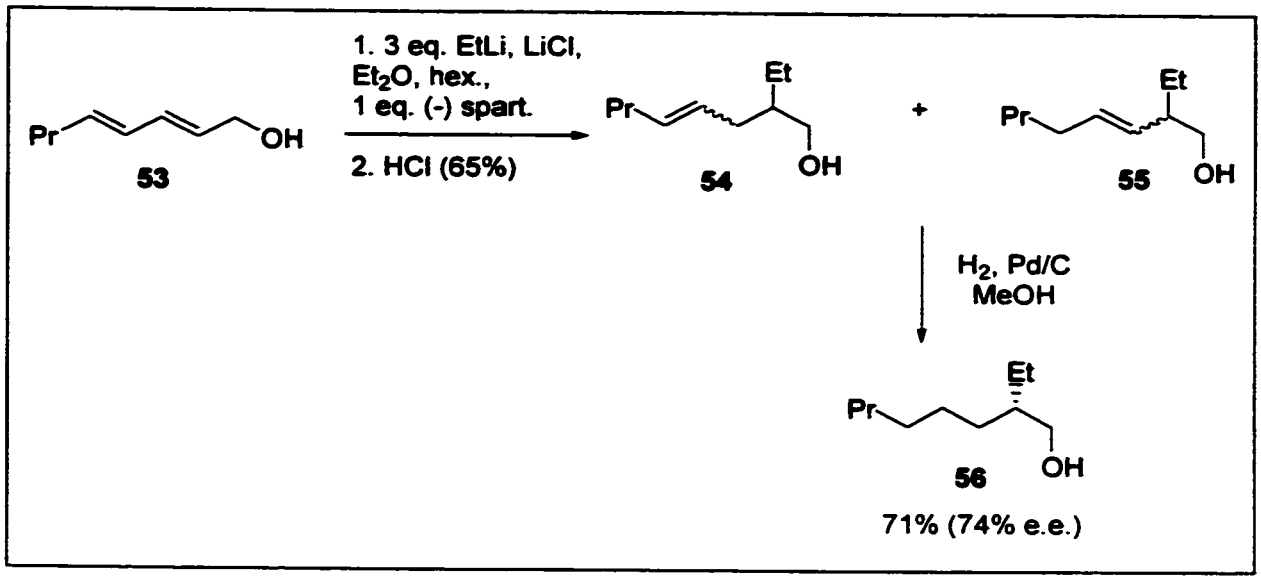
An interesting, related zirconium-mediated intramolecular coupling reaction, of unsaturated alkyl anilines reported by Barluenga *et al.*, afforded a versatile procedure for the synthesis of azetidines **52** from amino alkenes related to **49** (Scheme 10).[21] In a formal sense, this route to azetidines represents, a regio- and diastereoselective [2 + 2] cycloaddition between an imine and an alkene. Related transformations to these ring systems are usually difficult in the absence of activating groups.



Scheme 10: *Azetidine Synthesis from Amino Alkenes*

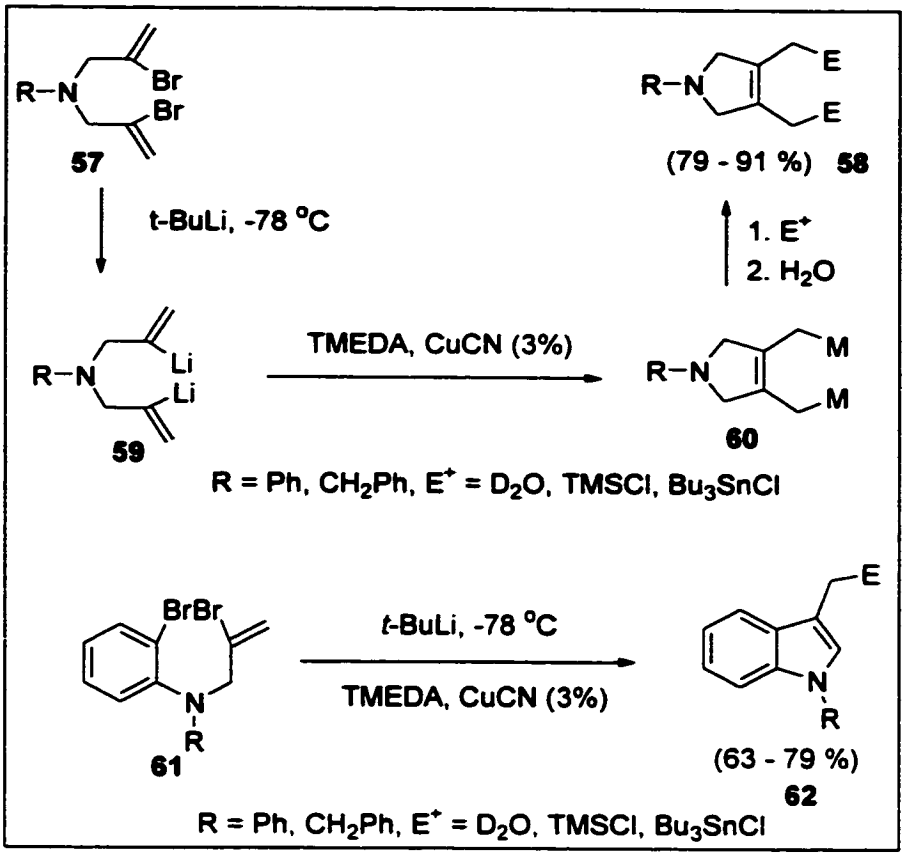
I-i-vi. Lithium

Normant and co-workers have examined the carbolithiation of allylic diene alcohols (**53**) in the presence of a molar equivalent of (-)-sparteine.[22] This enantio- and regioselective carbolithiation of diene-ols was accomplished in good yields with moderate enantioselectivity. Hexane is the preferred solvent due to diminished polymerization compared to ether (Scheme 11).



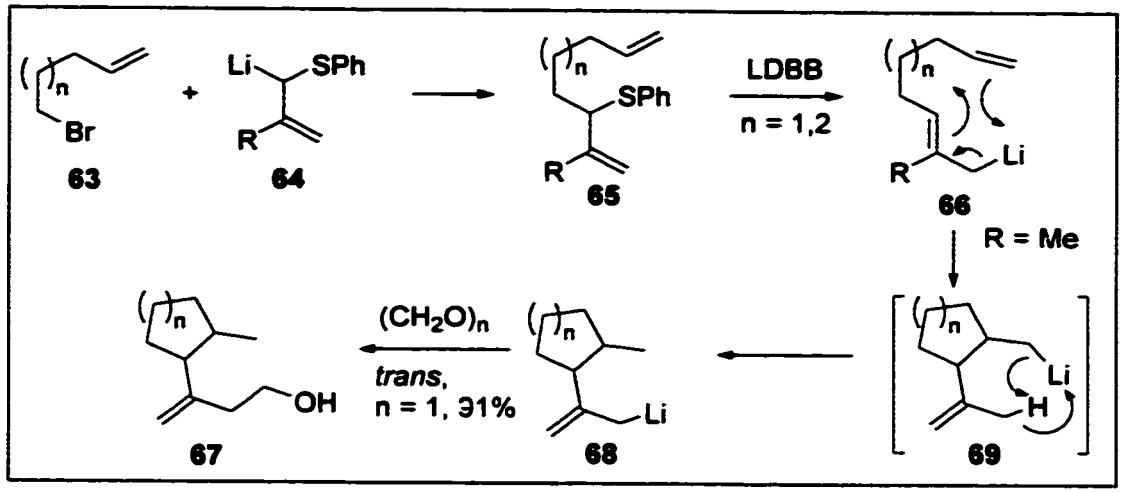
Scheme 11: *Enantio- and Regio-selective Carbolithiation of Diene-ols*

Barluenga and co-workers have developed a new synthesis of dihydropyrroles **58** and functionalized indoles **62** by copper cyanide intramolecular coupling of bis-vinyl lithium species derived from vinyl bromides **57** (Scheme 12).[23]



Scheme 12: *Intramolecular Coupling for the Preparation of Dihydropyrroles*

Cohen and co-workers have reported an interesting carbometallation sequence which involved intramolecular lithium-ene reactions derived from the addition the allyl-thio-lithium species **64** with bromoalkenes (Scheme 13).[24]

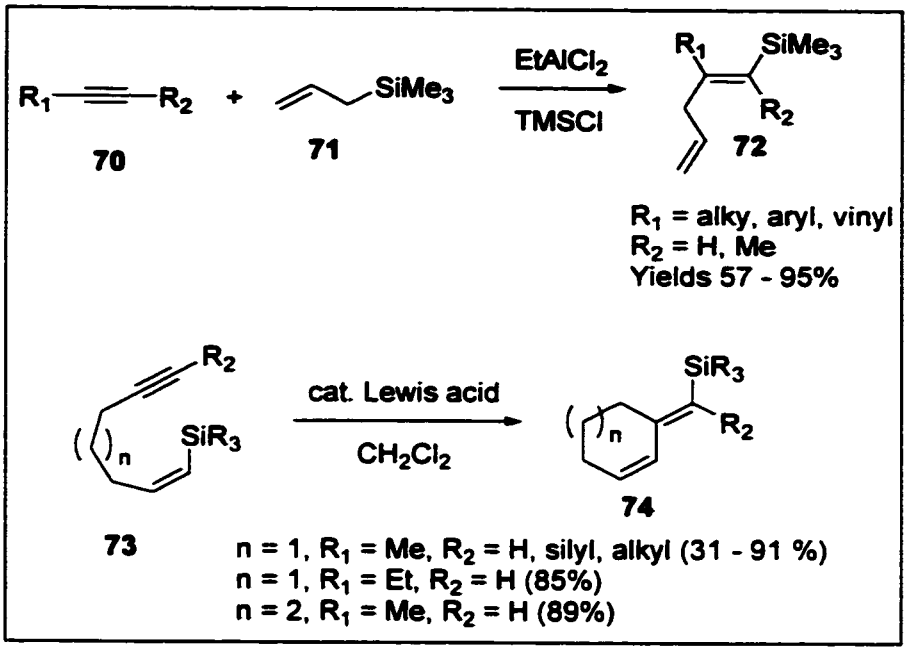


Scheme 13: *Intramolecular Lithium-Ene Reactions*

If no allylic protons are available, (R = H in **69**), the rearrangement depicted fails due to competitive proton abstraction from the solvent.

I-i-vii. Silicon

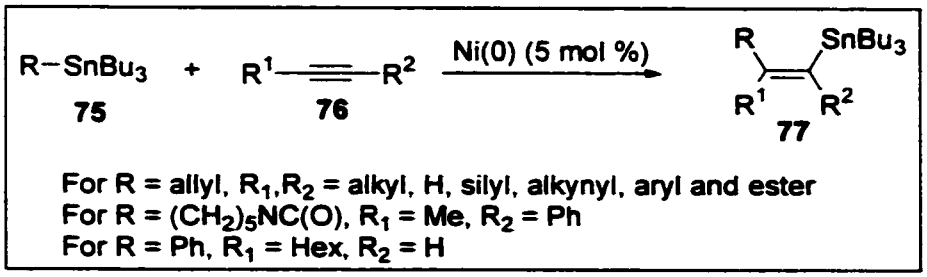
Yamamoto and colleagues have demonstrated that the *trans*-carbosilylation of a wide range of simple unactivated alkynes is accelerated in the presence of Lewis acid catalysts such as ethyl aluminum dichloride and hafnium tetrachloride (Scheme 14).[25] The relative ease of these reactions is surprising in view of the absence of activating or chelating groups. A mechanism for this reaction has been proposed.[26] This Lewis-acid catalyzed vinylsilylation of unactivated alkynes has been extended to intramolecular reactions for the preparation of cyclic olefins of type **74**.[27]



Scheme 14: *Allylsilylation of Unactivated Alkynes*

I-i-viii. Tin

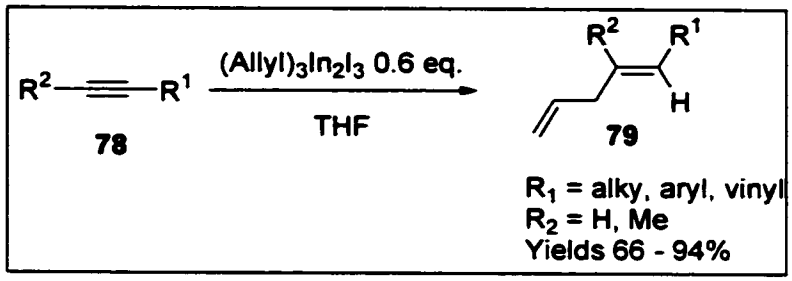
Carbostannlylation of alkynes is a useful method for the generation of stereo- and regio-defined vinylstannanes based on the wide variety of palladium(0) based synthetic transformations that afford more complex products. Hiyama and co-workers have recently developed a nickel-catalyzed carbostannylation of acetylene that provided *cis* vinyl stannanes substituted with various allyl, acyl and alkynyl groups.[28]



Scheme 15: *Carbostannylation of Alkynes*

I-i-ix. Indium

Additional research from Fujiwara and Yamamoto allowed allylation of unactivated and/or functionalized alkynes with allyl indium reagents to provide a versatile method for the preparation of a wide range of 1,4-dienes (Scheme 16).[29]



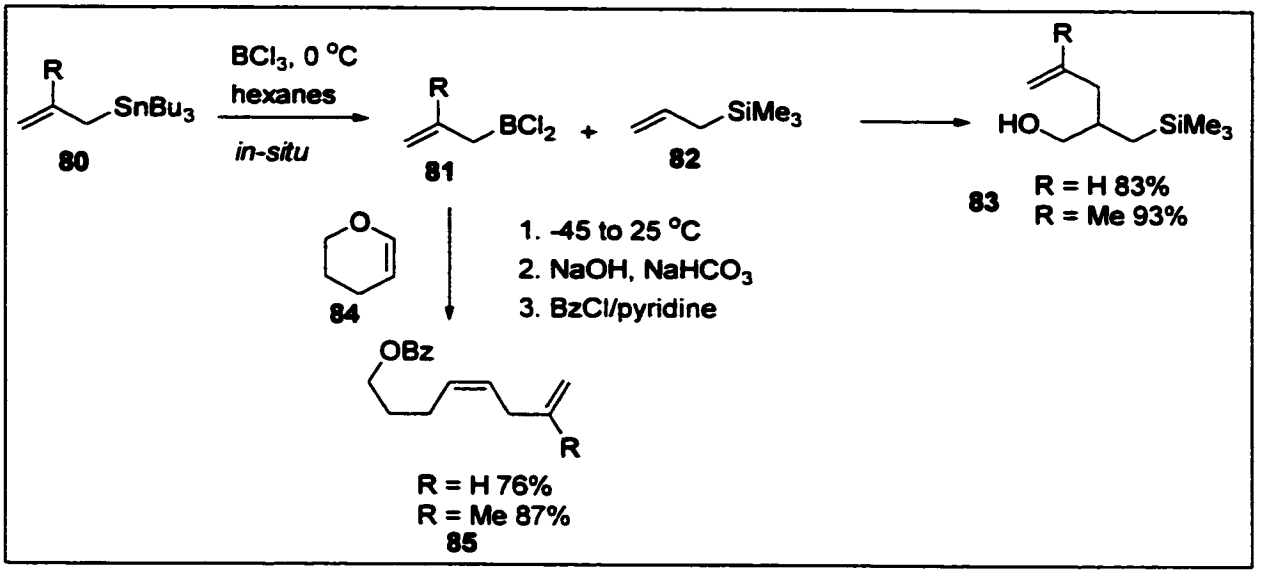
Scheme 16: *Allylation of Alkynes with Allyl Indium Reagents*

The use of silyl-substituted alkynes resulted in slower reaction rates and the reversal of the regioselectivity to afford the allylation product from the reaction on the terminal carbon. This allylindation has been extended to nitriles substituted with an electron-withdrawing group in the α-position to provide access to highly functionalized enamines.[30]

I-i-x. Boron

Singleton and co-workers have employed allylstannanes for the *in situ* generation of allylboranes in a reaction with allyl silanes as a method for the formation of alkenols such as **83** (Scheme 17).[31] Enol-ethers are also useful substrates for this protocol and the

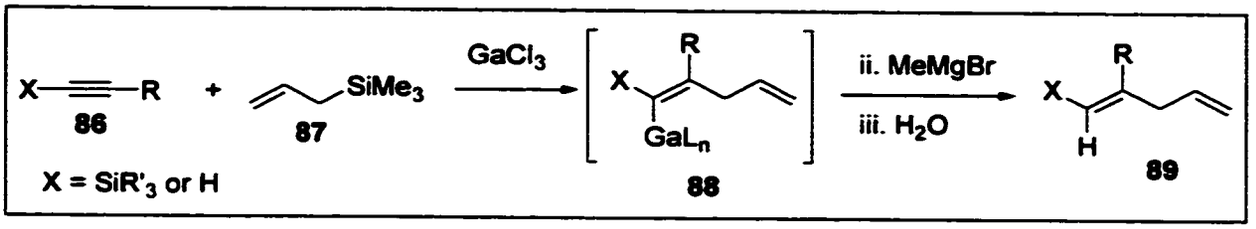
reaction with dihydropyran from the initial allylboration led to ring opened 1,4-diene ethers upon elimination of the β-alkoxy-borane substituent.



Scheme 17: *Preparation of Alkenols from Allylboranes*

I-i-xi. Gallium

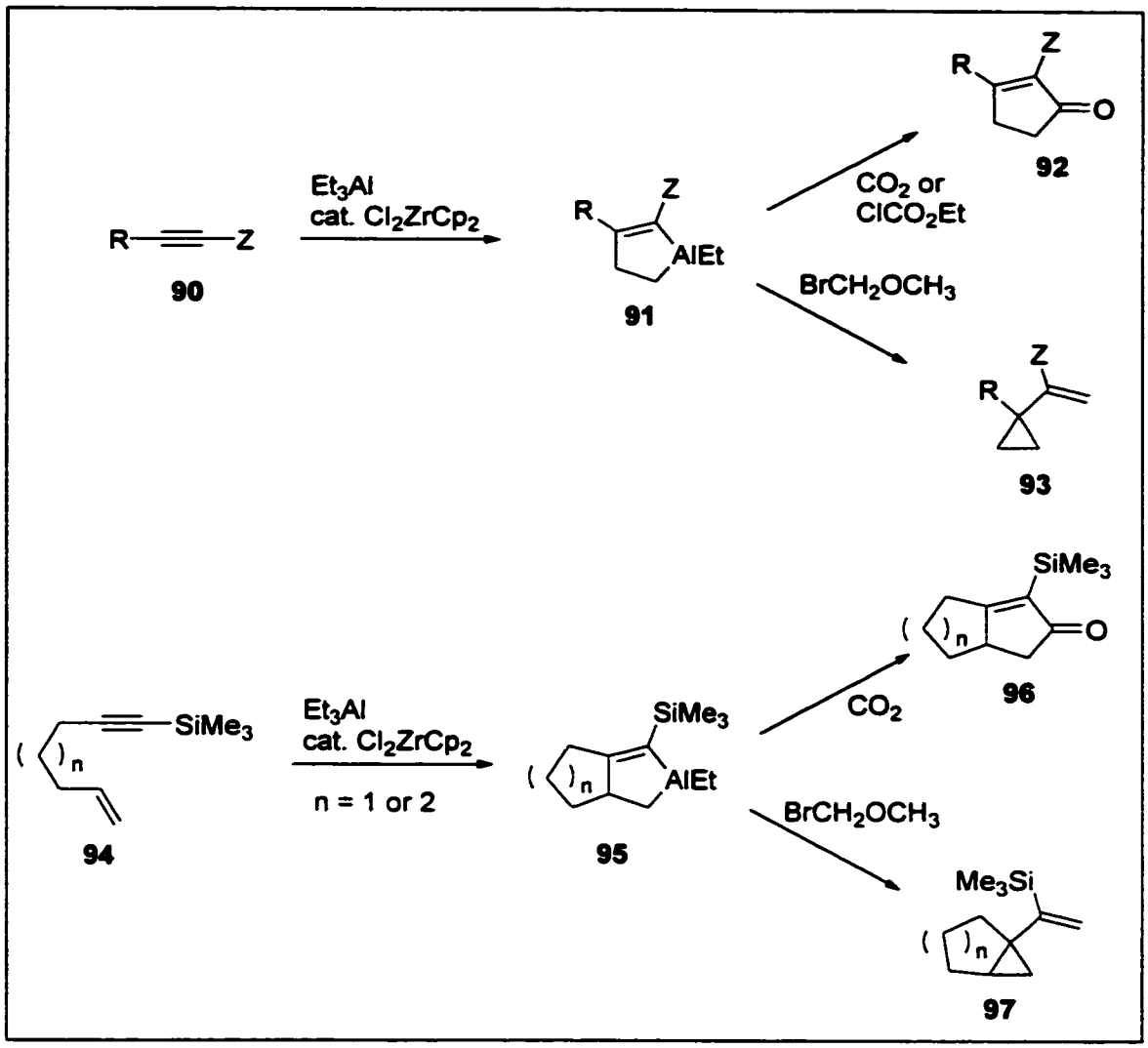
Hirama and co-workers have utilized gallium intermediates to introduce allyl units in a versatile preparation of various 1,4-dienes (Scheme 18).[32] A wide variety of alkynes partcipate in this reaction, including primary, secondary aliphatic, and aromatic systems. Tertiary aliphatic alkynes were inert. In the case of silylalkynes related to **86**, the reaction occurs regioselectively at the β-carbon atom to provide the (*E*)-isomer **89**. The relationship between the silyl and allyl groups was confirmed by NOE experiments. The terminal alkynes gave a mixture of *E*/*Z* isomers that was presumed to arise from the isomerization of the *E*- and *Z*-vinylgallium intermediates (**88**) based on their relative thermodynamic stability.



Scheme 18: *Gallium Mediated Allylation*

I-i-xii. Aluminum

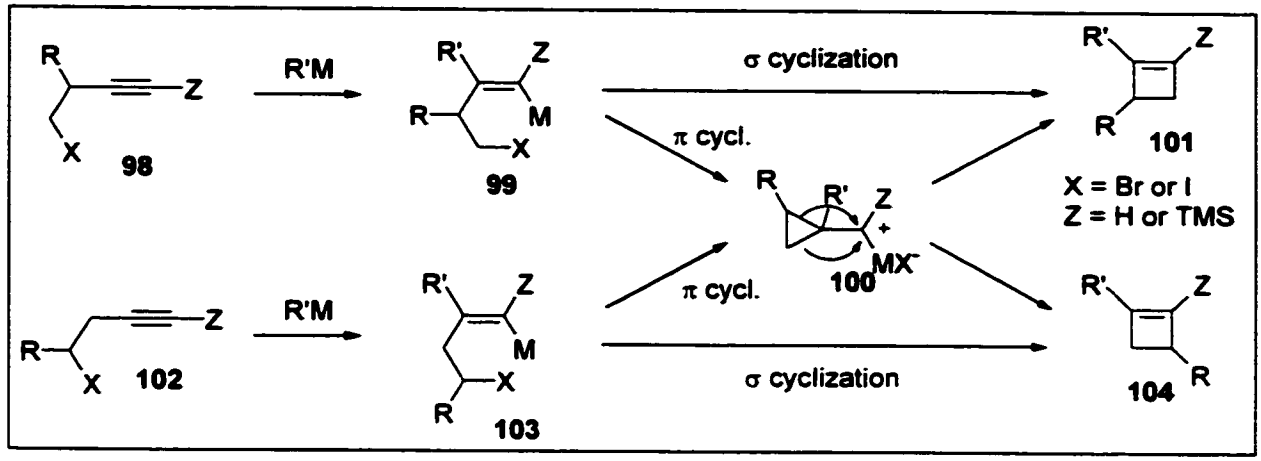
Negishi and co-workers have made significant contributions to the general area of zirconium-catalyzed carboalumination of alkynes and enynes. These protocols provide excellent routes to cyclic organic compounds in a concise fashion (Scheme 19).[33] Simple acetylenes **90** are converted the cyclic aluminum intermediate **91** to afford either cyclopentenones such as **92** or cyclopropanes related to **93** depending upon the synthetic objective. Related intramolecular combinations lead to bicyclic structures of different ring combinations as illustrated by **96** and **97**.



Scheme 19: *Zirconium Catalyzed Carboalumination of Alkynes and Enynes*

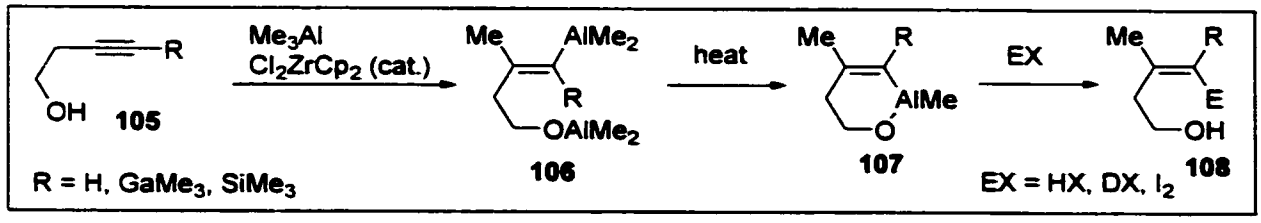
A related method has been developed for the synthesis of regio-defined cyclobutenes of type **101** and **104** (Scheme 20).[34] These molecules are often difficult to prepare and typically require photochemical conditions. The metal systems employed in these sequences are either a mixture or $AlMe_3/Cl_2ZrCp_2$ (X = Br, Z = TMS) or alternatively exposure to *n*-BuLi is followed by treatment with $ClAlMe_2$ or $AlMe_3$ and Cl_2ZrCp_2. The use of this metallation procedure commencing with propargyl alcohol was

the initial step in the total synthesis of freelingyne, a sesquiterpene from *Eremophila freelingii*.[35] The intermediate metallated olefins **99** and **103** can also be obtained directly from the metal-halogen exchange of the appropriate halo-alkene to provide a more versatile choice of starting materials *en route* to the desired cyclobutenes.



Scheme 20: *Regioselective Preparation of Cyclobutenes*

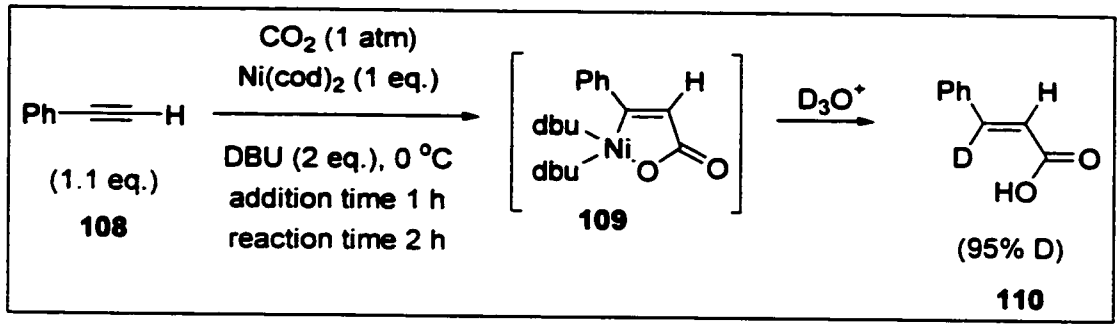
The preparation of substituted alkynes by *anti*-carbometallation is frequently difficult but the selective formation of *syn* versus *anti* olefins is extremely useful. This can be achieved from a common intermediate **106** through the chelation-controlled isomerization of the initial *syn*-carbometallation product from homopropargyl alcohols **105** to give **108** (Scheme 21).[36]



Scheme 21: *Zirconium Catalyzed Carboalumination of Alkynes*

I-i-xiii. Nickel

Yamamoto and co-workers have developed a nickel-mediated route *via* **109** for the regio- and chemo-selective carboxylation of alkynes in the presence of carbon dioxide (Scheme 22). This allows the direct synthesis of α,β-unsaturated carboxylic acids.[37] The reaction seems to be quite versatile since the umpulong addition of an electrophile at the β-position of the α,β-unsaturated carboxylic acid is possible.



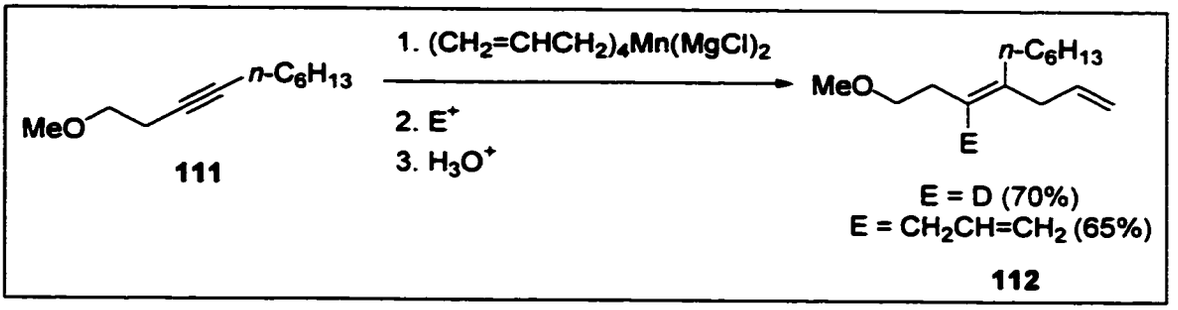
Scheme 22: *Nickel-Mediated Regio- and Chemo-Selective Carboxylation of Alkynes*

The reaction can be performed in the presence of two alkynes, with the regioselectivity favouring the least sterically hindered acetylene. Further the C-C bond formation occurs at the least hindered carbon of the acetylene.

I-i-xiv. Manganese

Oshima and coworkers have established that the treatment of both propargylic and homopropargylic alcohols or ethers with tetra-allylmanganate or tri-allylmanganate provided monoallylated 1,4-dienes with a high level of regio- and stereoselective control

(Scheme 23).[38] The intermediate alkenylmanganese compounds were trapped with a variety of electrophiles.

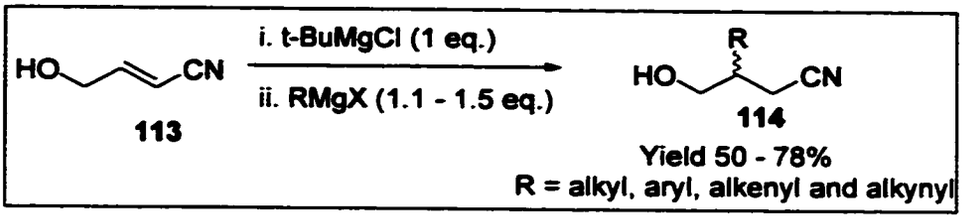


Scheme 23: *Preparation of Monoallylated 1,4-Dienes*

Diallylated products can be obtained directly when oxidative conditions (O_2 or PhI) are employed. The reaction can also be performed with allylmagnesium bromide and a catalytic amount of a manganese salt such as MnI_2, $Mn(acac)_3$ or $Mn(CO)_{10}$.

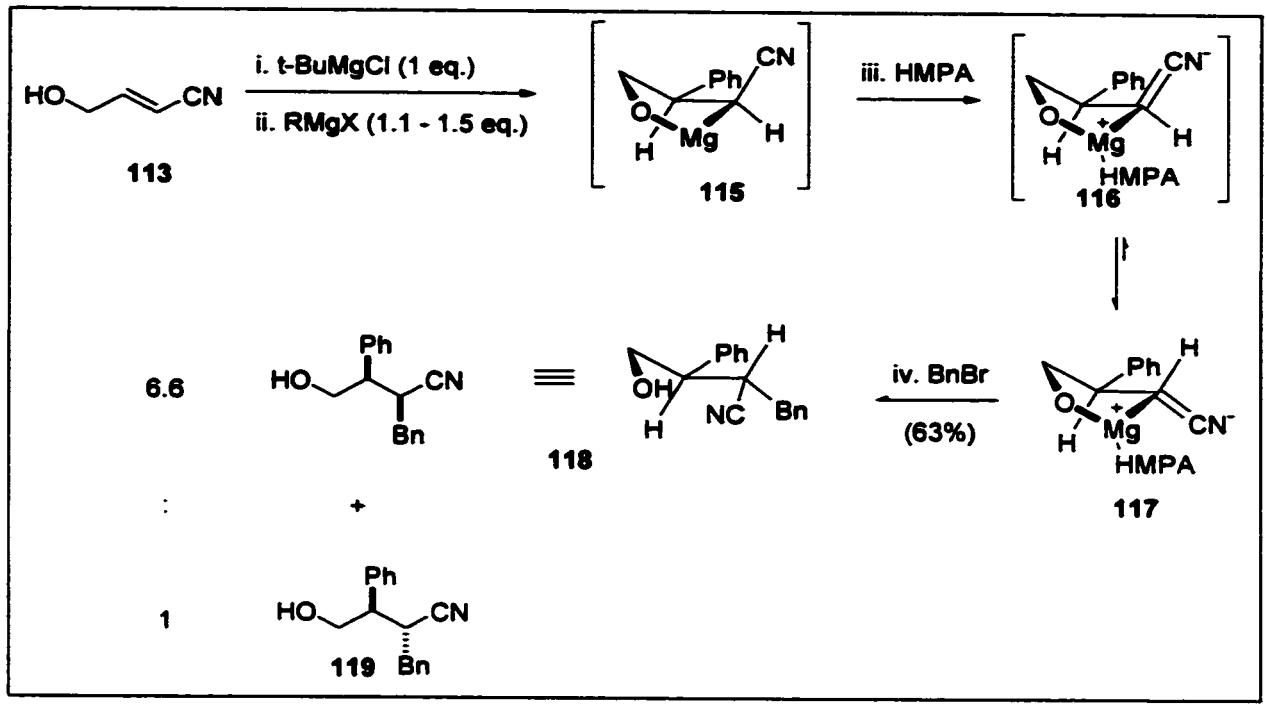
I-i-xv. Magnesium

It is widely recognized that conjugate addition of Grignard reagents to α,β-unsaturated nitriles are significantly more demanding, and troublesome, than the well-established additions to conjugated enones.[39] Fleming and coworkers have reported a chelation controlled conjugate addition, which facilitates the process with α,β-unsaturated nitriles due to the presence of an allylic alcohol as illustrated in the transformation **113** to **114** in Scheme 24.[40]



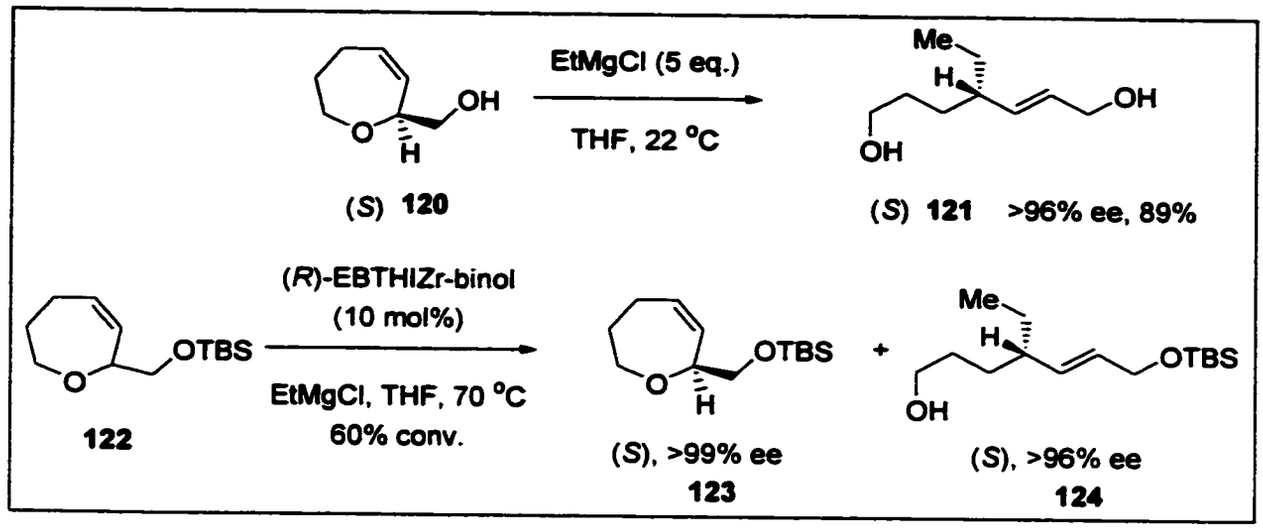
Scheme 24: *Chelation Controlled Conjugate Addition to α,β-Unsaturated Nitriles*

The scope of this reaction was extended to diastereoselective systems in which the intermediate anion, from addition to the conjugated nitrile, was quenched with a suitable electrophile in the presence of HMPA. Thus, the addition of a strong oxygen donor such as HMPA appeared to weaken the carbon-magnesium bond [41] and allowed alkylation to occur smoothly. In addition, the HMPA may improve the solvation of the complex, allowing more efficient equilibration between the two weakly coordinated[42] keteniminate anions **116** and **117** (Scheme 25). Consequently, alkylation occured preferentially on the less sterically hindered keteniminate **117** *via* a backside approach to afford the nitrile **118**, whose structure was established by X-ray analysis.



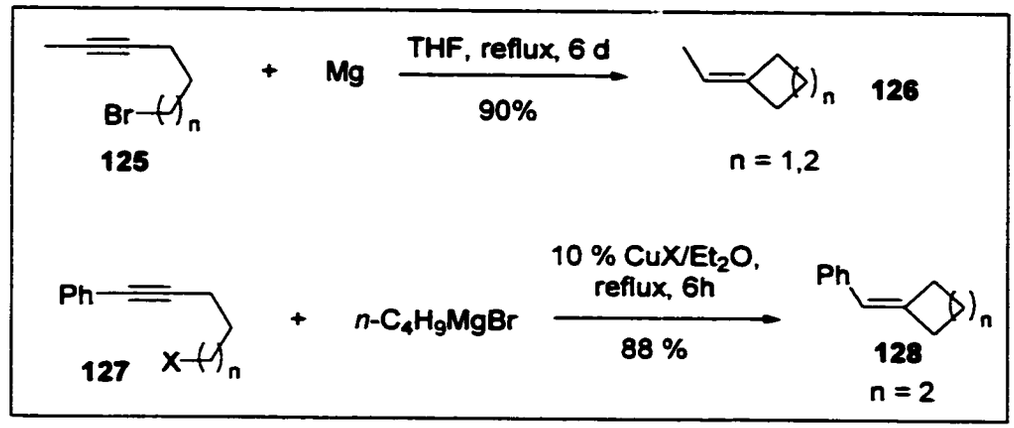
Scheme 25: *Diastereoselective Preparation of 1-Cyano-3-Hydroxy-Alkanes*

Hoveyda and coworkers have developed a related heteroatom assisted alkylation of cyclic allylic ethers such as **120** with Grignard reagents, to provide a convenient route to enantiomerically pure allylic diols of type **121** (Scheme 26).[43] A range of Grignard reagents were employed and benzyl and alkyl ethers may replace the free alcohol. Modification of the reaction protocol by addition of a chiral zirconium complex resulted in a catalytically controlled kinetic resolution[44] to yield the enantiomerically pure carbocycle **123** and the ring opened product **124**.

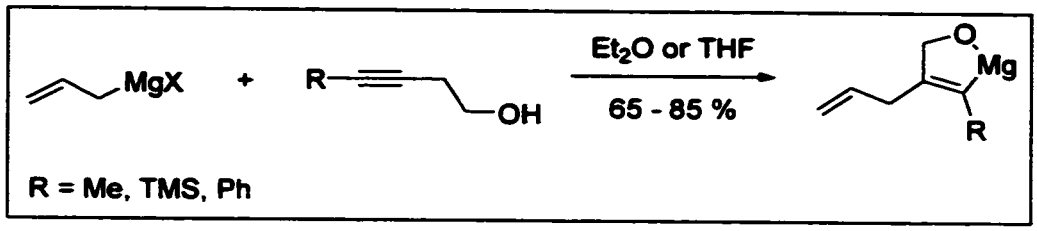


Scheme 26: *Heteroatom Assisted Alkylation Allylic Ethers with Grignard Reagents*

Organomagnesium compounds have long been a versatile building block for carbon-carbon bond forming reactions. Although Grignard reagents do not add easily to non-functionalized triple bonds (**125**), the reactions can become feasible with transition metal catalysis (Scheme 27) or with functionalized triple bonds[45] (Scheme 28).

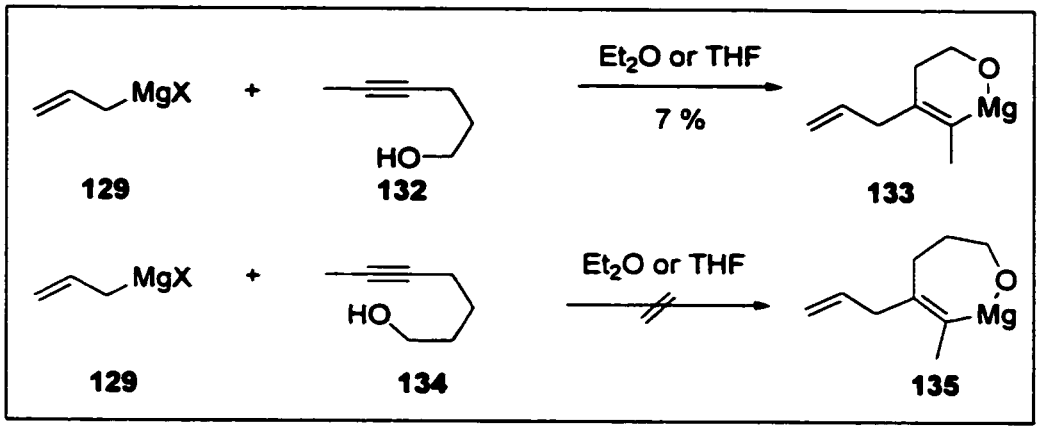


Scheme 27: *Carbomagnesiation of Non-Functionalized Alkynes*



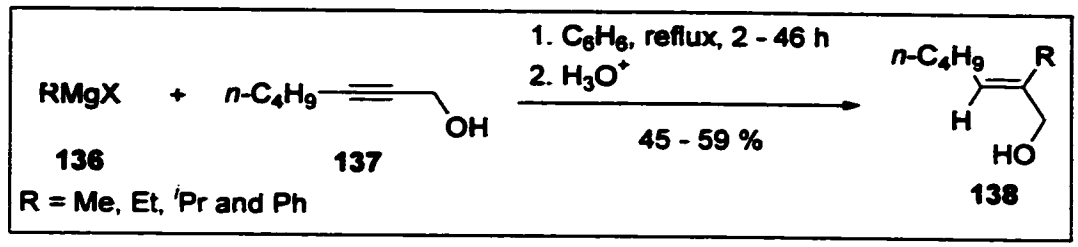
Scheme 28: *Carbomagnesiation of Functionalized Alkynes*

The enhanced reactivity of allylic (i.e. **129**) Grignard reagents (particularly with respect to vinyl Grignards) allows this reaction to occur in a relatively facile manner.[46] The reaction is oxygen-assisted since the yield drops to 7% in the case of 6-hydroxy-2-hexyne (**132**), and 0% in the case of 7-hydroxy-2-heptyne (**134**), where the heteroatom is too far removed for efficient chelation (Scheme 29).



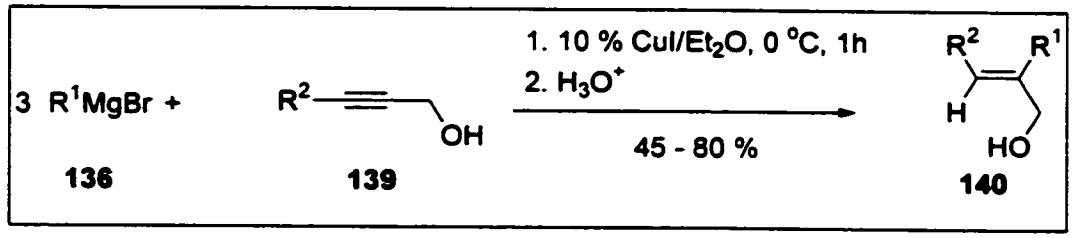
Scheme 29: *Heteroatom Proximity Effect of Carbomagnesiation Reactions*

Grignard reagents (**136**) other than those of the allylic type did not add well to alkynols (**137**). The reactions were generally sluggish and low yielding (Scheme 30).[47]



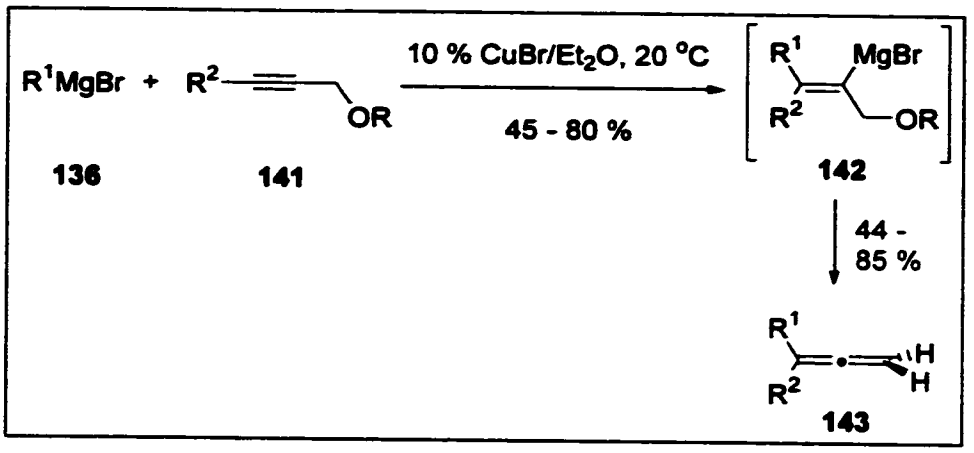
Scheme 30: *Carbomagnesiation of Propargyl Alcohols*

However, in the presence of 10% copper(I) iodide, most Grignard reagents (except vinyl) now are able to undergo addition under much milder conditions and still in an *anti*-fashion (Scheme 31).[48]



Scheme 31: *Copper Catalysis of Carbomagnesiation Reactions*

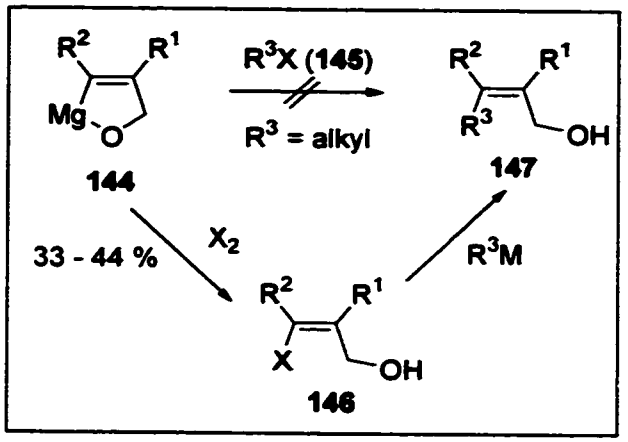
These heteroatom-assisted carbometallation reactions cannot be extended to other functionalities. Propargylic ethers (**141**), for example, afford allenes (**143**) on reaction at high temperatures.[49] In the presence of 10% copper(I) bromide, the same reaction occurs but at a lower temperature.[50] (Scheme 32)



Scheme 32: *Carbomagnesiation as a Route to Allenes*

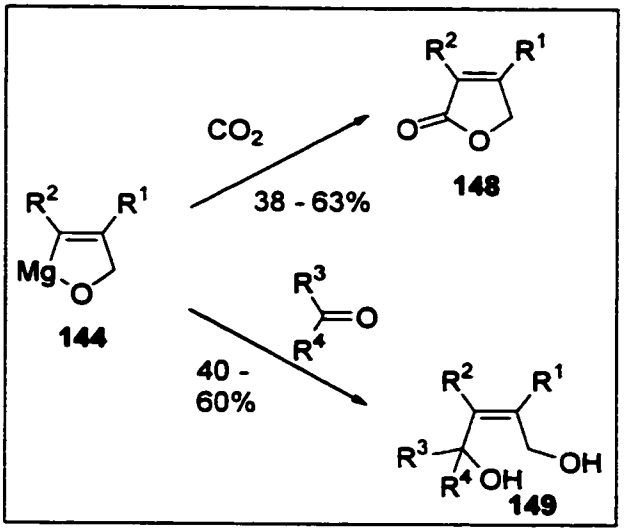
Propargylic tertiary amines can also react with Grignard reagents under stringent thermal conditions.[51]

The carbomagnesium reagents obtained from these reactions most likely exist in a cyclic form (**144**), which probably accounts for the low reactivity that is observed. For example, the alkylation reaction cannot be performed with alkyl iodides (**145**). Only allylic halides react satisfactorily (31 – 71 %). However, iodination is possible and the alkenyl iodides (**146**), thus obtained, react with other organometallic reagents to afford the alkylation products (**147**, Scheme 33).[52]



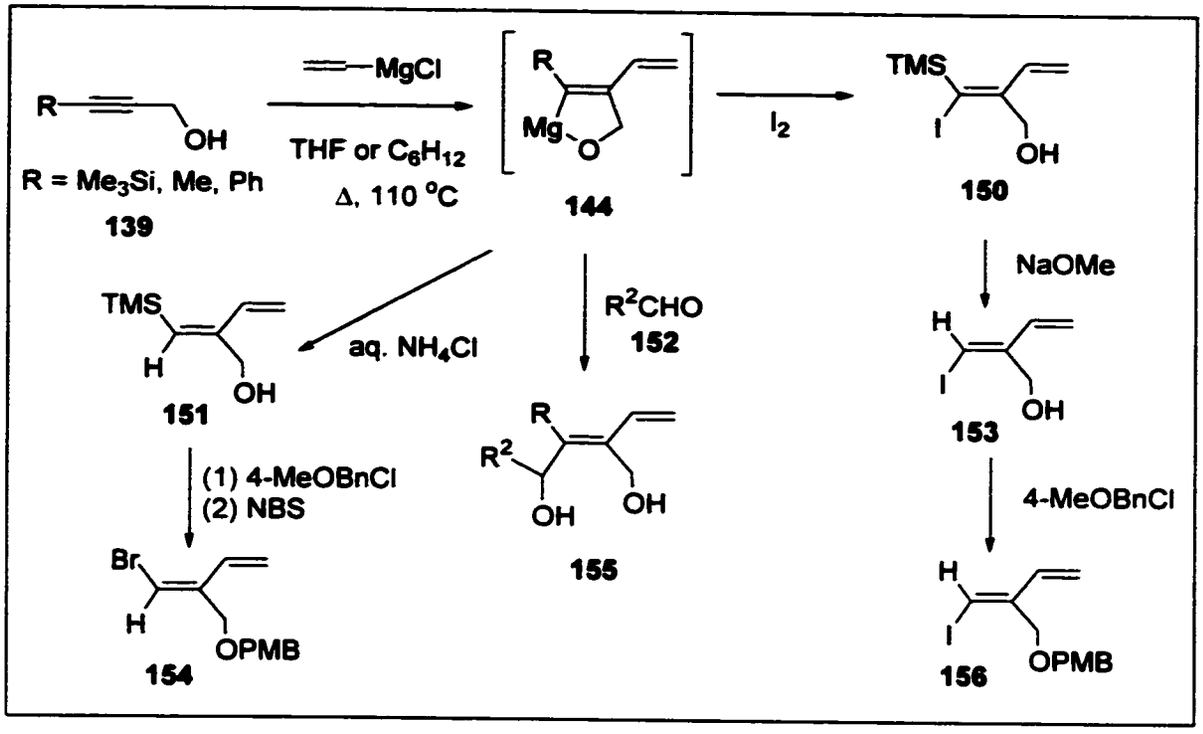
Scheme 33: *Indirect Route to Cross-Coupled Products from Carbomagnesiation*

Carbon dioxide reacts readily with the cyclic intermediates (**144**) to yield butenolides directly. Aldehydes and ketones also react to give the corresponding diols (**149**, Scheme 34).[53]



Scheme 34: *Electrophiles Employed in the Carbomagnesiation Reaction*

Fallis and co-workers have developed several related procedures for the magnesium-mediated carbometallation of propargyl alcohols. Depending upon the synthetic objective, vinyl and related Grignard reagents may be manipulated to afford a variety of different unsaturated systems from a common pathway. As illustrated in Scheme 35, different propargyl alcohols **139** were reacted with vinylmagnesium chloride to generate the intermediate magnesium chelate **144** (or a closely related species). Treatment with N-iodosuccinimide followed by desilylation and protection afforded the iodo-ether **156**. Alternatively, quenching **144** with a proton source provided **151**, which was converted to the bromide **154** upon reaction with *N*-bromosuccinimide (Scheme 35).[54] Thus, both of the *E* and *Z* halodienes may be prepared in a regiospecific manner from a common precursor. Condensation of **144** with an aldehyde did not generate the family of diene diols **155** directly and this became the starting point for these investigations. Thus a driving force for this research was to develop a protocol that would avoid the necessity of metal-halogen exchange with the diene halides.[55]

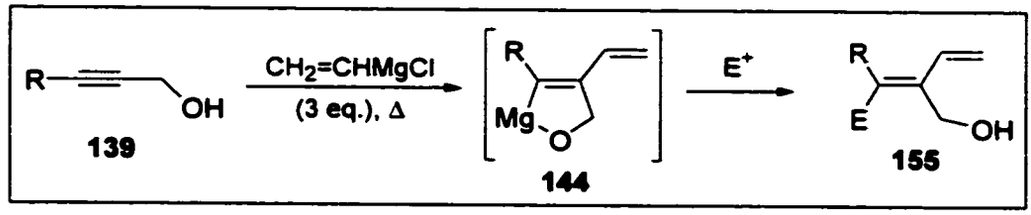


Scheme 35: *Preparation of E and Z Halodienes*

I-ii. Carbometallation Results

I-ii-i. Carbometallation Employing Vinyl Grignard Reagents[56]

Although carbometallation has been employed for a number of years, including recently in our laboratory (Scheme 36), it has remained a somewhat inconsistent reaction when vinyl Grignard reagents are employed.

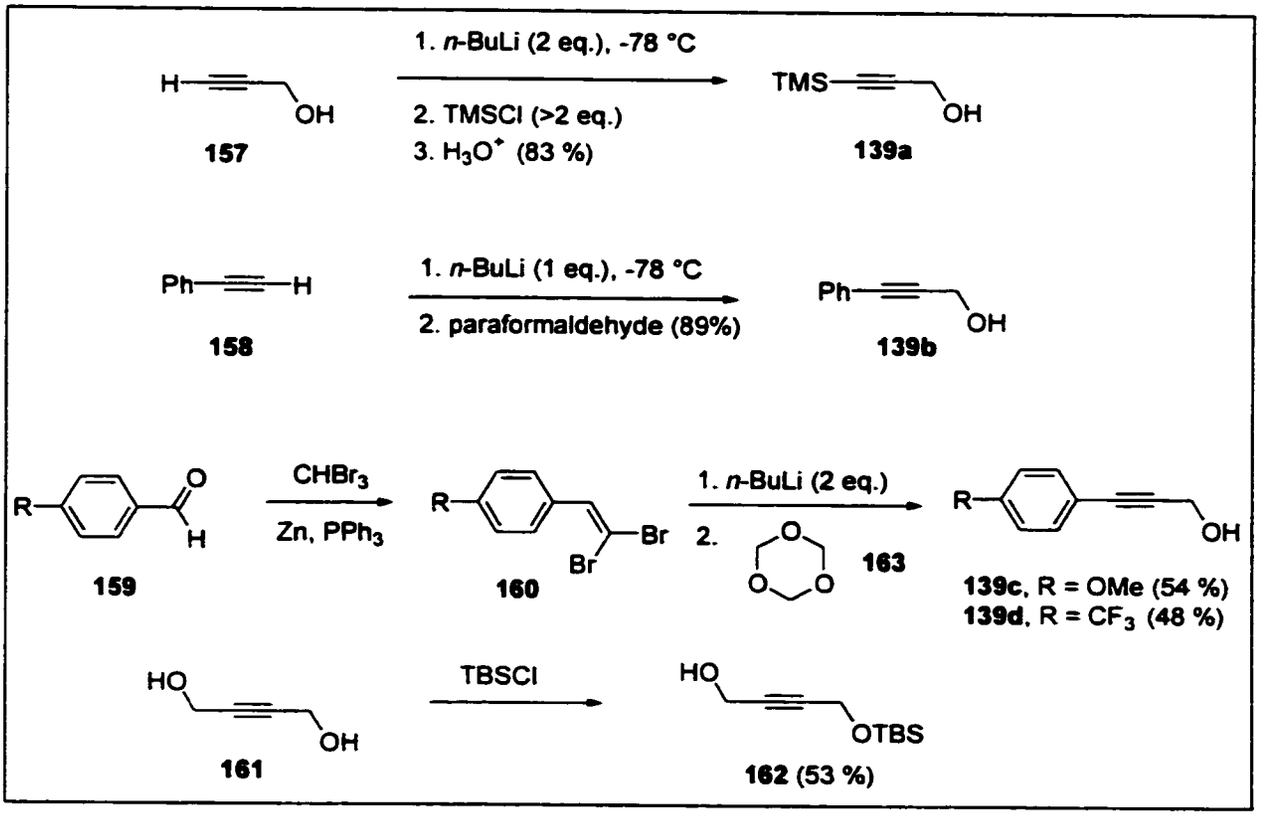


Scheme 36: *Fallis Carbometallation Protocol*

Initially, our studies were focused on determining conditions that would overcome these inconsistencies. These reactions were typically carried out in moderately polar solvents, such as THF. Our initial presumption was to use a solvent that had a similar or slightly higher boiling point, but was relatively less polar. The theory behind this assumption was that the less polar solvent would be able to stabilize the presumed five-membered magnesium chelate (**144**). It was felt that the instability of this chelate in the given reaction conditions was leading to inconsistent and lower yields. The solvent cage effect that may occur with a non-polar solvent would stabilize the intermediate (*i.e.* render it less reactive) and thus increase the yields and consistency of the reaction. Cyclohexane was chosen as the co-solvent with THF. It has the required properties of a

slightly higher boiling point (81 °C versus 65 - 67 °C) and is significantly less polar. A number of substrates were then prepared in order to test this theory.

The substrates were commercially available (**139**, R = Me), prepared from propargyl (**157**) alcohol *via* deprotontation of the terminal acetylene and quenching with an appropriate electrophile (Scheme 37). Phenylacetylene (**158**) was also employed as a starting material. Deprotonation followed by quenching with *p*-formaldehyde (**163**) gave to required propargylic alcohol (**139b**). The substituted aryl substrates were prepared *via* Corey-Fuchs[57] reaction of the appropriate aldehyde (**159**) followed by conversion of the resulting di-bromide (**160**) to the required propargylic alcohol (**139c**, **139d**).

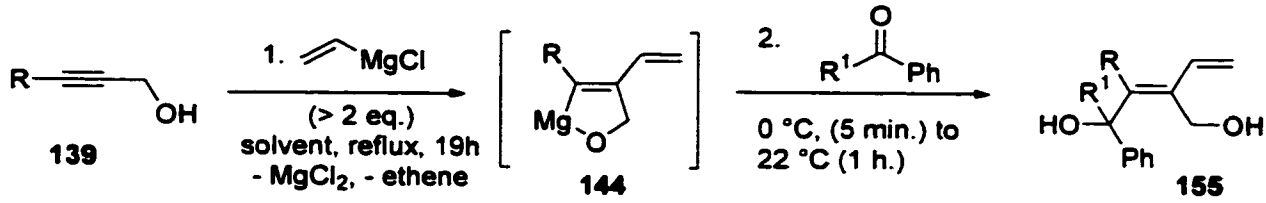


***Scheme 37:** Preparation of Propargyl Alcohol Substrates*

The protected propargyl-diol (**162**) was obtained from the mono-protection of the diol (**161**) with TBSCl.

The substrates were then subjected to the carbometallation protocol in order to determine if any benefit could be derived from altering the solvent for the reaction.

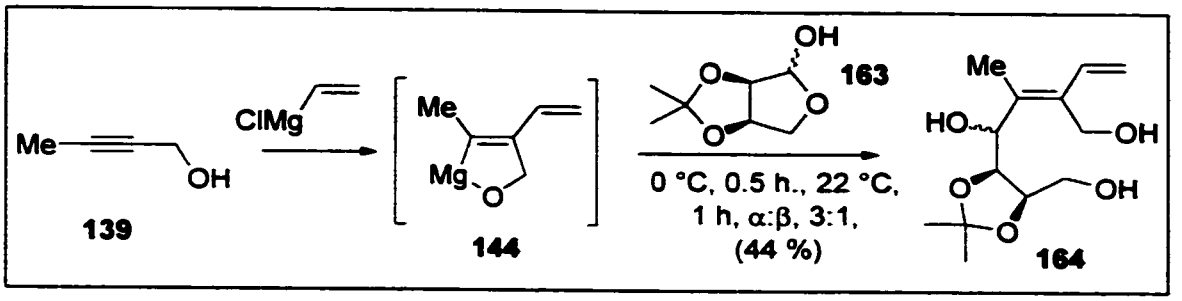
Table 1: *Carbometallation Solvent Study Results*



				Yield (%) of (**155**)	
Entry	**139** R	R^1	eq. of Grignard	THF	Cyclohexane
a	Me	H	3.2	50	80
b	Me	H	2.1	44	68
c	Ph	H	3.2	87	86
d	TMS	H	3.2	94	78
e	CH_2OTBS	H	3.2	0	0
f	4-$MeOC_6H_4$	H	3.2	59	77
g	4-$CF_3C_6H_4$	H	3.2	0	75
h	Me	Me	3.2	-	44

Table 1 summarizes the results of several addition-condensation reactions with various propargyl alcohols in cyclohexane and THF. In contrast with earlier reports, metal salts are not required with vinyl Grignards,[58] and in most cases the yields are improved by conducting the reaction in a refluxing mixture of cyclohexane and the THF derived from

the Grignard reagent (~60/40). If the quantity of the vinyl Grignard reagent is reduced from 3.2 to 2.1 equivalents, the yield is diminished (entry b), but this eliminates the competition of excess vinylmagnesium chloride for the electrophile. Thus, when quenching the reaction, only one nucleophile is present. However, the reduced yield also implies that some amount of the Grignard reagent is being destroyed during the course of the reaction and prior to carbometallation, thus the need for an excess of Grignard reagent. The presence of a silyl ether group attached to the alkyne appears to affect complex formation and is sufficient to inhibit this reaction (entry e). Entries f and g illustrate that variation in the electron density of the triple bond has a negligible effect on the reactions conducted in the cyclohexane-THF solvent mixture. However, the reaction with **139d** (entry g) failed in THF when an electron-withdrawing group was attached to the triple bond. This observation is consistent with the mechanistic rationale established earlier from investigations with allylmagnesium halides and α-alkenols, in which the initial reaction step involved an electrophilic attack of the magnesium reagent on the π-system assisted by the proximity of the C-O bond in the alkoxide.[2e,f] The reaction with a ketone afforded the expected product in modest yield (entry h), presumably due to the acidity of the α-protons and competing enolization.



Scheme 38: *Direct Condensation of Carbometallated Intermediate with a Lactol*

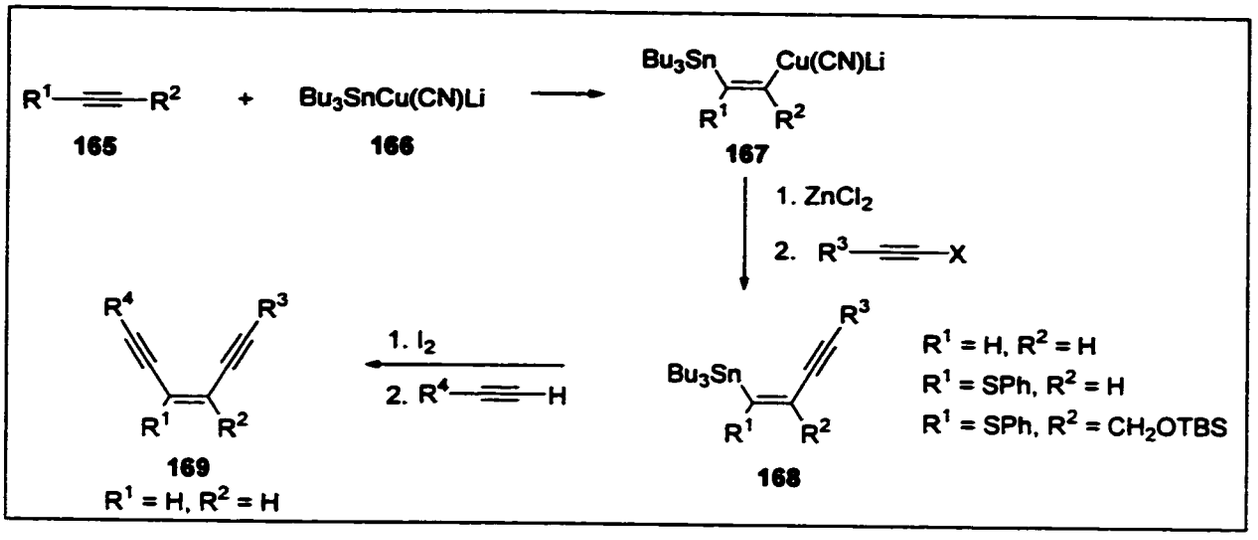
Direct condensation of the diene unit with carbonyl compounds is attractive, as the independent preparation of the vinyl halide (ie. **156**) is avoided. In addition, potential complications encountered with lithium-halogen exchange are circumvented.[59] Scheme 38 illustrates a typical example with a sensitive substrate, in which **144** is condensed with the hemi-acetal **163** to afford the triol **164** in 44% yield as a 3:1 mixture of diastereomers. Neither excess *n*-butyllithium nor excess of the lithium salt derived from diene **156** gave any product when reacted with **163**.

I-ii. Enediyne

I-ii-i. Introduction

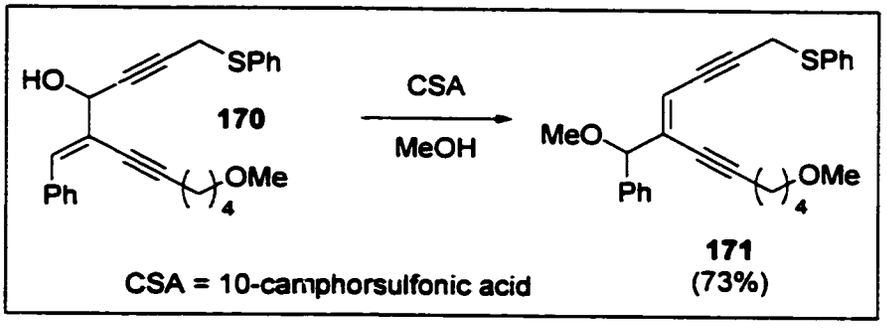
The unusual structure and biological activity of the enediyne antitumour antibiotics, such as neocarzinostatin chromophore,[60] calichemicin,[61] esperamicin[62] and dynemicin[63] have recently provided new incentives for studying the synthesis and chemistry of unsaturated diyne units.[64]

Although a number of synthesis of 3,4-unsubstituted enediynes have been demonstrated over the years,[65] preparation of 3,4-disubstituted- or 3-substituted enediynes remais relatively rare.[66] An interesting, recently reported example, involves the reaction of the Marino stannylvinyl cuprate (**166**) with 1-bromo- and 1-iodo-1-alkynes **165**, Scheme 39).[67]



Scheme 39: *Preparation of 3,4-Disubstituted Enediynes*

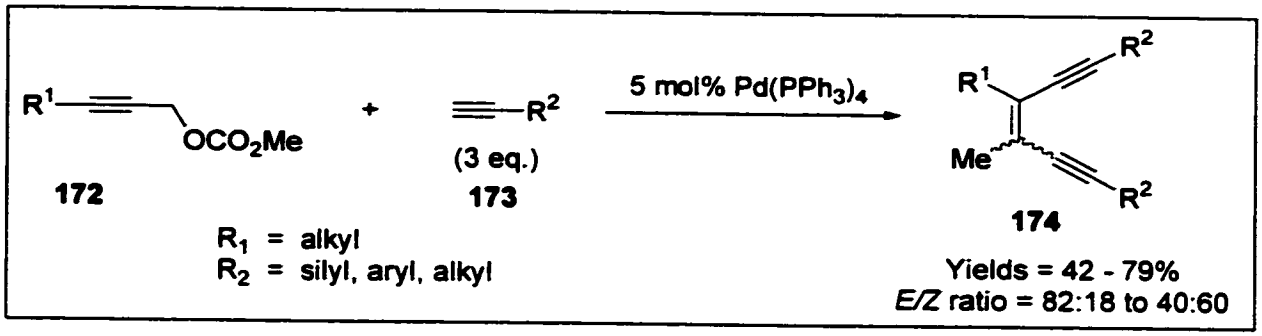
Others have continued in the quest to find new and more efficient routes to enediynes. Recently reported was an acid mediated allylic rearrangement from 1,5-diynes (**170**, Scheme 40).[68]



Scheme 40: *1,5-Allylic Rearrangement to Yield Enediynes*

A regioselective palladium-catalyzed bis-alkynylation of propargylic carbonates (**172**) in the synthesis of enediyne compounds has also been reported along with the postulated catalytic cycle (Scheme 41).[69] Although this method is quite versatile, the *E/Z*

ratio typically favoured the *E*-isomer. When the *Z*-isomer was favoured the ratio was modest (< 2:1).



Scheme 41: *A Regioselective Palladium-Catalyzed Bis-Alkynylation*

I-ii-ii. Selected Highlight in Enediyne Synthesis[70]

Myers and co-workers have highlighted the synthesis of the chromophore component of the antitumour agent neocarzinostatin (**175**), which exhibits potent cytotoxicity and DNA-cleaving activity.[71]

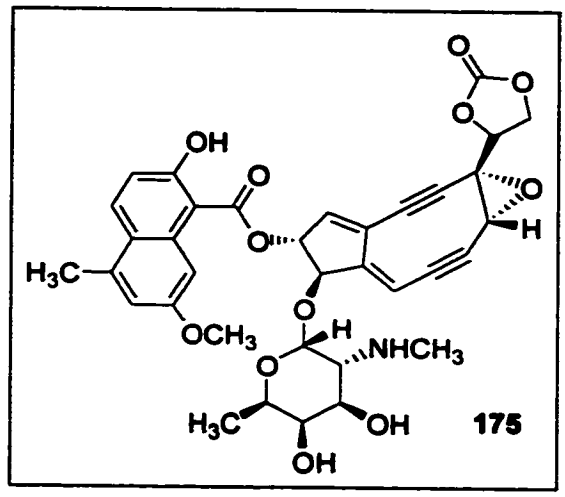
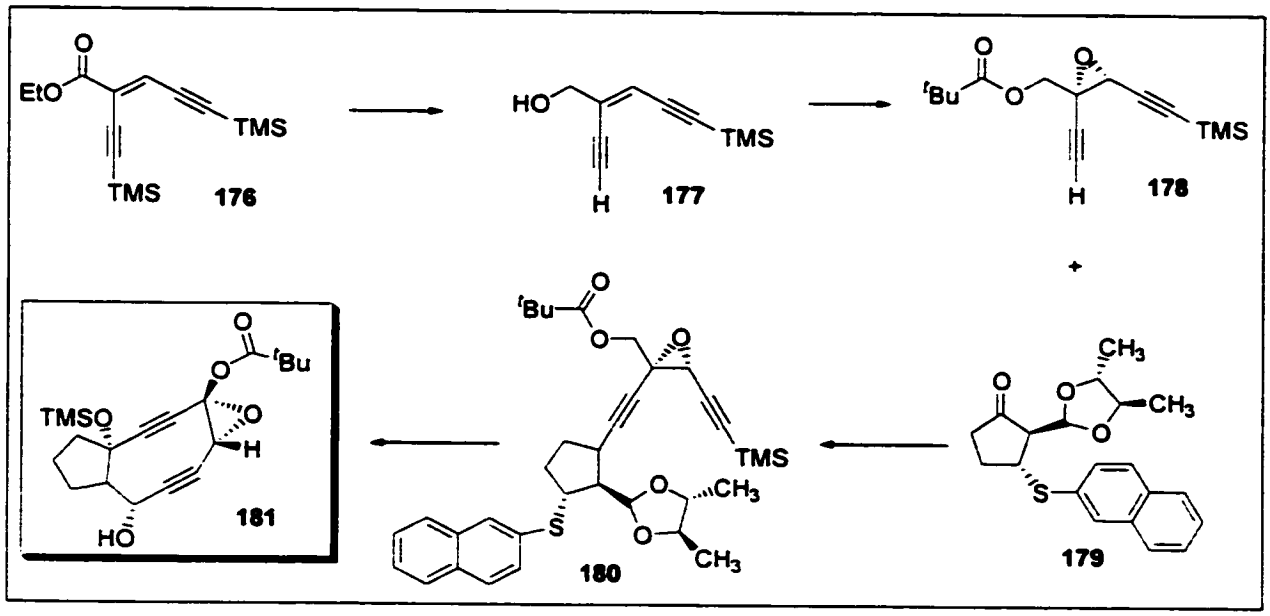


Figure 1: *Neocarzinostatin*

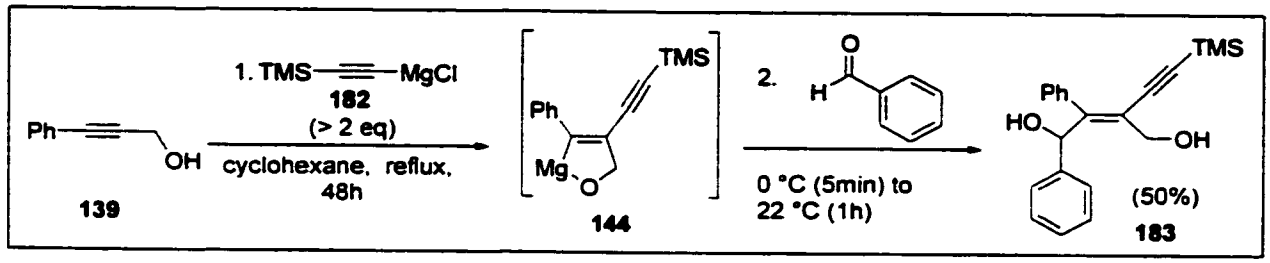
The synthesis of the core functionality (**181**) proceeds *via* the corresponding enediyne sub-unit (**176**) that may prove to be of value in the elucidation of the mechanism of DNA cleavage by **175** (Scheme 42).[72]



Scheme 42: *Synthesis of the Chromophore Component of Neocarzinostatin*

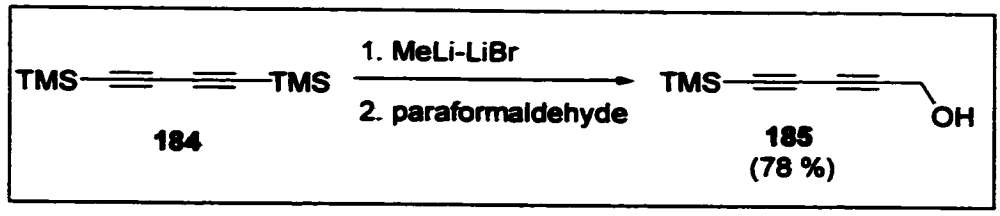
I-ii-iii. Carbometallation as a Route to Ene-Diynes

The study and synthesis of enyne and enediyne chromophores is a topic of current interest due to their challenging structures and biological activity as antibiotics and antitumor agents.[73] It was anticipated that an additional application, which illustrates the synthetic utility of this carbometallation method, would be the facile preparation of these enyne and enediyne synthons.[74] Initial experiments were undertaken to determine the feasibility of the additon of trimethylsilylethynylmagnesium chloride (**182**) to a propargylic alcohol (Scheme 43).



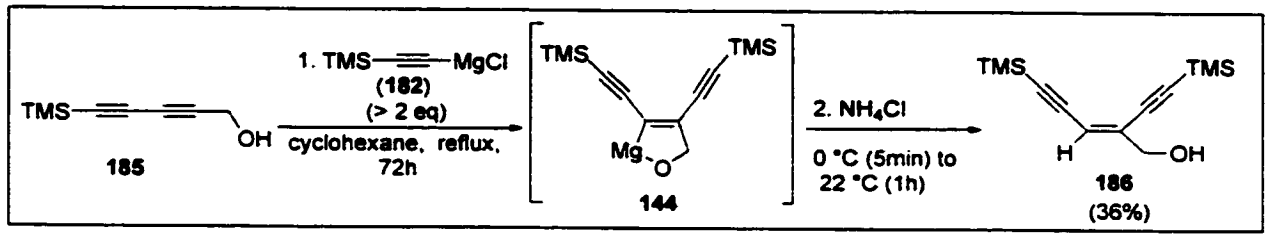
***Scheme 43:** Alknye Grignard Reagent in the Carbometallation Reaction*

Indeed, the acetylene-derived Grignard reagent could undergo the carbomagnesiation reaction. The resulting intermediate was quenched with an electrophile to yield the desired enyne. Having successfully employed the acetylene-derived Grignard, we wished to further extend this method for the preparation of enediynes. The required propargylic alcohol was prepared *via* a mono-deprotection of the bis-silyl-1,3-diyne (**184**) and concurrent electrophilic quenching to yield the corresponding diynol (**185**, Scheme 44).[75]



Scheme 44: *Preparation of Diyn-ol*

In a related fashion addition of **182** to the extended propargyl alcohol **185** provided the enediyne alcohol **186** (36% yield) in a very facile manner (Scheme 45). However, all attempts to quench the presumed intermediate in this case failed. The lower yields and longer reaction are presumably due to the lower nucleophilicity of the acetylide Grignard reagent compared to the vinyl cases.



Scheme 45: *One-Pot Preparation of a 3-Substituted Enediyne*

The majority of other routes require palladium mediated coupling.[73,74] This enediyne alcohol was employed in Myers' enantioselective synthesis of the epoxy diyne core of meocarzinostatin chromophore (**181**).[76]

Kinetic studies[77] were consistent with an intramolecular delivery of the allyl moiety in the case of alkenols and further research[78] established the intermediacy of **187**. As stated above, the net effect of this carbometallation method is a regiocontrolled *anti* addition of the vinyl group relative to the second carbon-carbon bond. A similar

mechanism appears to apply also to the vinyl Grignard reagents with the propargyl alcohols. Thus the stereochemical result suggests that the delivery of the vinyl group may involve an intramolecular process in which the bonding between a-b and c-d occurs in a synchronous manner as illustrated by **188**. A close analogy is provided by the *anti*-hydroalumination of propargyl alcohols with $LiAlH_4$ or Red-Al,[79] which are considered to involve intermediates of type **189**. Thus initial addition of the vinylmagnesium chloride to the complexed species related to **188** is followed by collapse to **144**. No evidence was detected in earlier investigations[78b] for the involvement of a unimolecular one-electron transfer mechanism.[80]

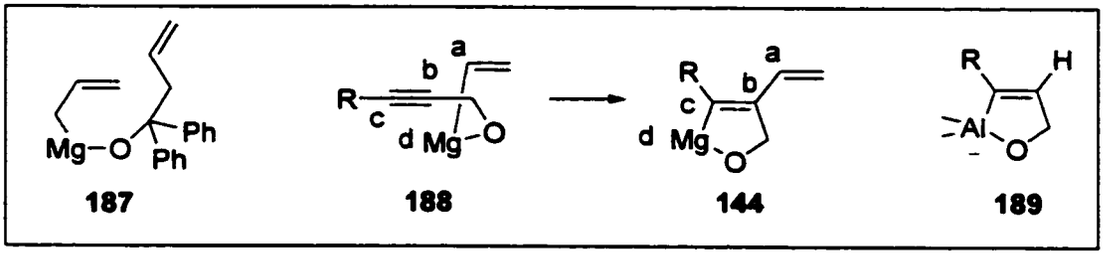


Figure 2: *Rational for trans Addition of Vinyl Grignard*

The magnesium mediated carbometallation protocols described above provide direct access to a number of useful unsaturated systems that may be employed for a variety of synthetic objectives. The potential of this procedure for the synthesis of stereodefined halo-dienes, dihydroxydienes and enyne and enediyne alcohols is of interest. In addition, the ease with which these compounds are prepared in one synthetic step renders this sequence attractive for additional applications.

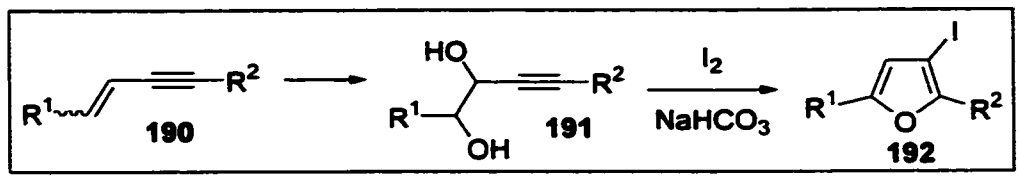
I-iii *Furans and Furanones*

I-iii-i. Furan Introduction

Furans constitute several important classes of compounds in organic chemistry[81] and serve as diverse intermediates in synthetic chemistry.[82] The widespread availability of many naturally occurring furans, such as furan fatty acids,[83] calicogorgins,[84] furanocembranolides,[85] and furanoterpenes[86] provide evidence of their importance. The synthesis of furans involves two divergent strategies. The furan substituents are either introduced prior to the formation of the furan ring system, or they can be added in subsequent steps *via* regioselective reactions.[87] A series of recent reviews by Gilchrist highlight many modern methods for the synthesis of aromatic heterocycles.[88]

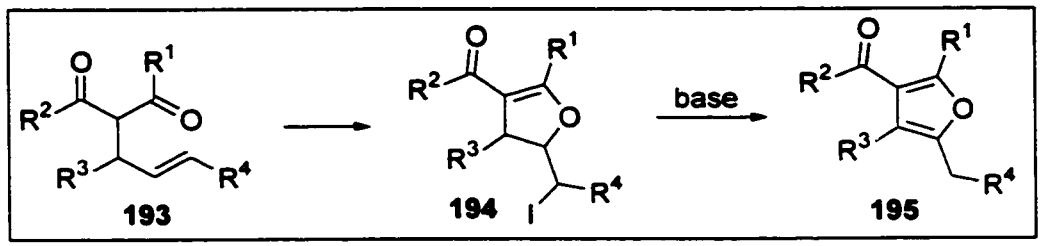
I-iii-ii. Selected Highlights in Furan Synthesis

Alkyne cyclization reactions provide an efficient method for the synthesis of furans. The preparation of 3-iodofurans (**192**) from conjugated enynes (**190**) in which the double bond is first hydroxylated, generating a diol (**191**), which is then cyclized with iodine has proven useful (Scheme 46).[89] A significant benefit of this route is the incorporation of a useful handle at the 3-position of the furan that can be exploited in subsequent reactions.



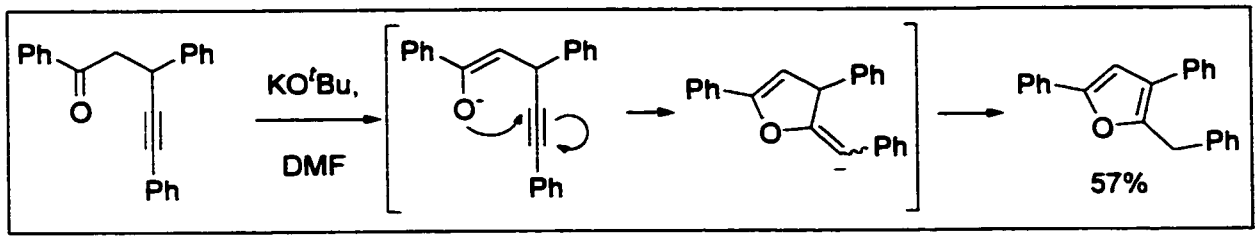
Scheme 46: *Preparation of 3-Iodofurans*

A closely related cyclization to the five-membered furan ring system (**196**), that also involves iodination as the key step, was recently developed for 4-alken-ones (**193**, Scheme 47).[90]



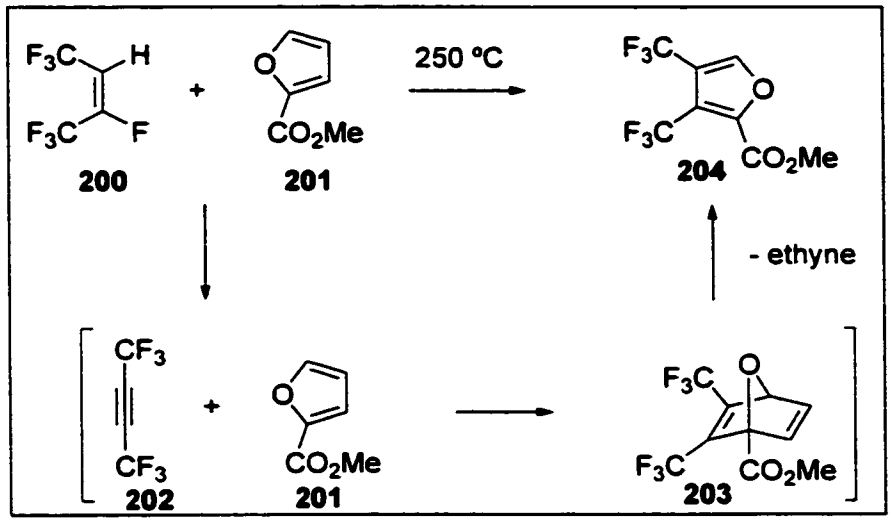
Scheme 47: *Iodine Catalyzed Route to Furans*

Treatment of 4-alkynyl-1-alkanones (**196**) with potassium *t*-butoxide leads to conversion to the corresponding furan (Scheme 48). The reaction proceeds *via* a 5-*exo* cyclization of the formed (**197**) enolate to yield the vinyl anion (**198**) that is then converted to the product.



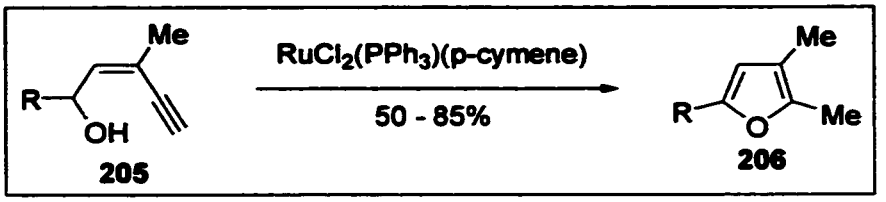
Scheme 48: *Intramolecular Cyclization onto Alkynes for the Formation of Furans*

Modification of previously prepared furans is often an efficient method for introduction of additional functionality. Typically, the 3 and 4 positions of furans are difficult to modify through classical chemistry. However, Diels-Alder reaction of a di-substituted acetylene (**202**), derived from the fluoro-alkene (**200**), and a mono-substituted furan (**201**) gives the required adduct (**203**) which then undergoes a retro-Diels-Alder to yield the corresponding tri-substituted furan (**204**, Scheme 49).[91]



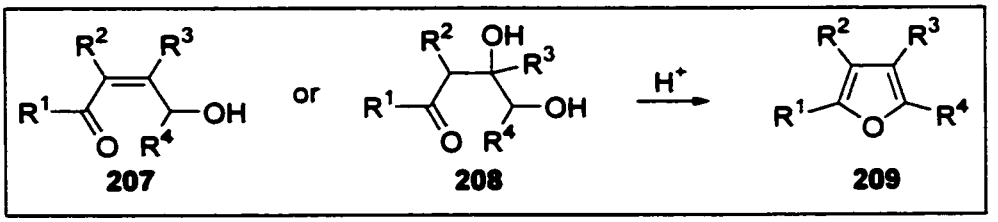
Scheme 49: *Diels-Alder Route to Furans*

Intramolecular transition metal catalyzed cyclizations of alcohols onto alkynes are another important method for the formation of furans (Scheme 50). The reaction is limited to terminal alkynes (**205**) and an intramolecular nucleophilic addition of the oxygen atom onto a coordinated triple bond was proposed.[92]



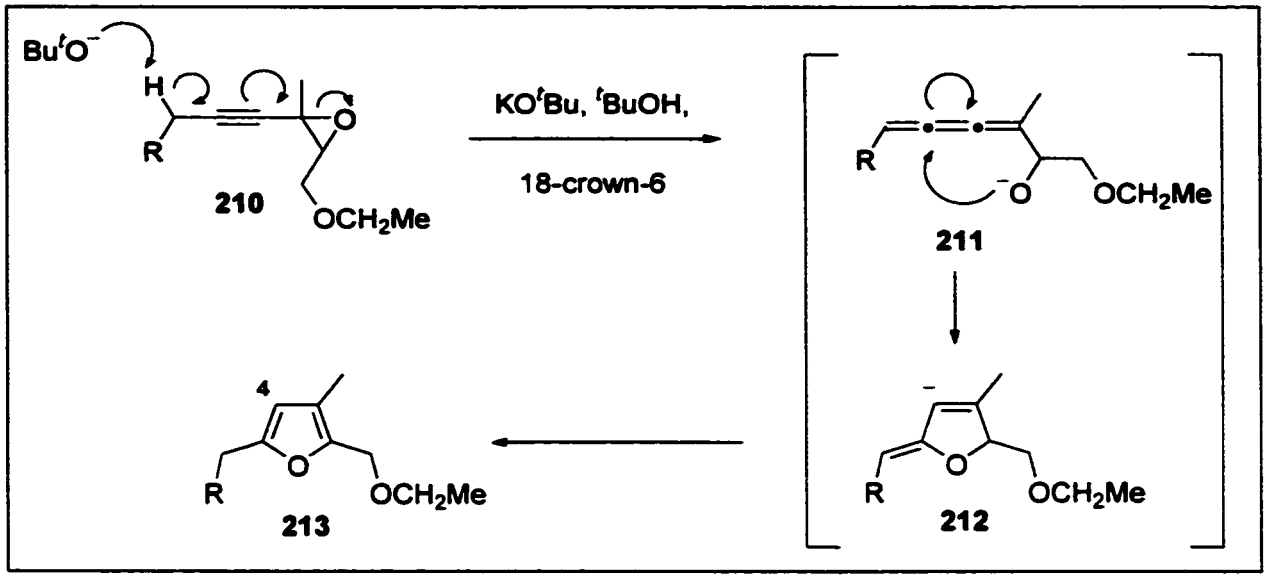
Scheme 50: *Transition Metal Catalyzed Cyclizations as a Route to Furans*

Another common method for the cyclization to furans involves acid catalysis of 4-hydroxy-1-ones (**207**, Scheme 51).[93] The initial cylization is followed by loss of H_2O (in the case of **208**) to yield the furan (**209**).



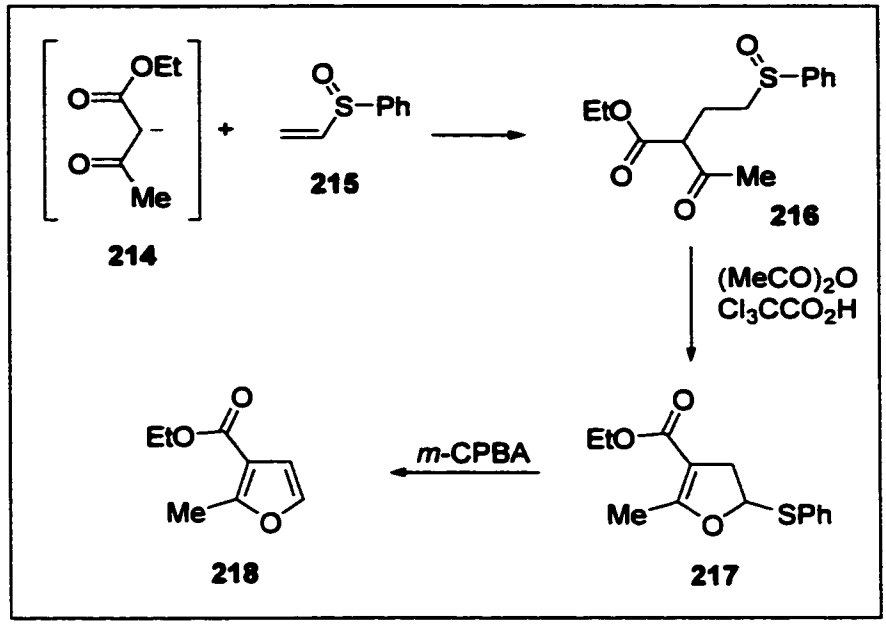
Scheme 51: *Acid Catalysis Cyclization of 4-Hydroxy-1-ones*

A particularly interesting route to tri-substituted furans involves the cyclization of a 2,3,4-trien-1-ol (**211**) that is generated *in situ* from a propargylic epoxide (**210**, Scheme 52).[94] A limitation of this reaction is that the 4-position of the furan cannot be substituted from the starting reagents, but it may be possible to quench the initial cyclized product (**212**) with a suitable electrophile prior to rearrangement to the furan product (**213**).



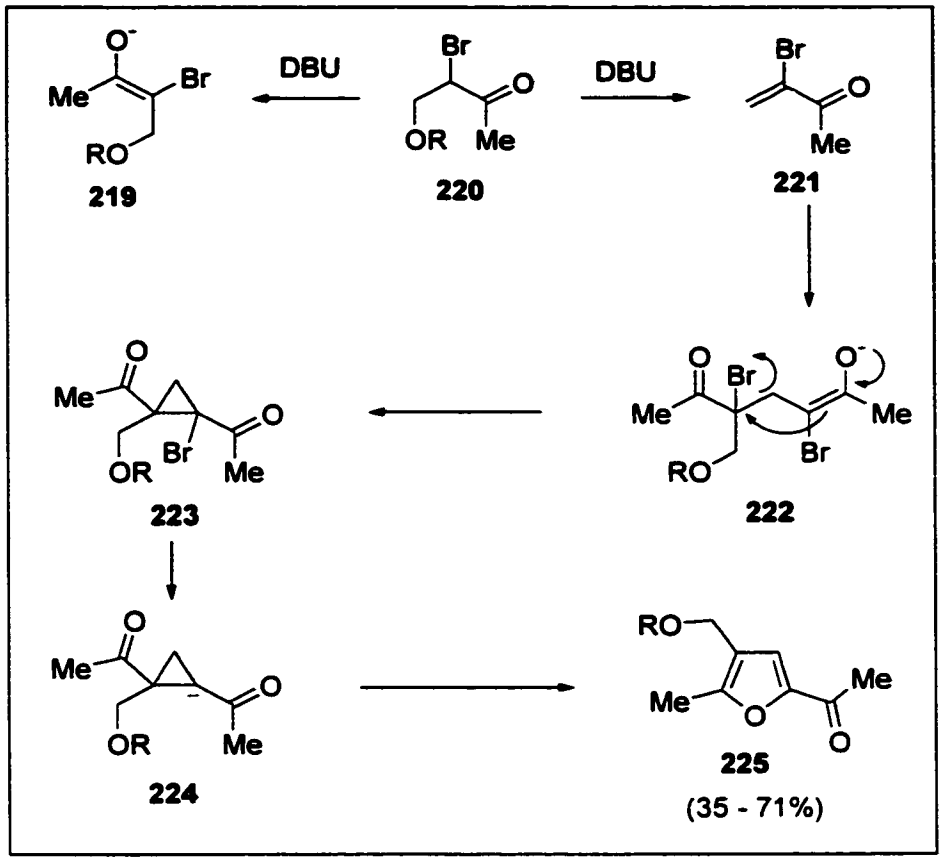
Scheme 52: *Base Catalyzed Cyclization of Propargyl Epoxides*

Conjugate addition of enolate anions (*ie* **214**) to vinyl sulfoxides (**215**) has been used as a route to di-substituted furans (**218**, Scheme 53). The cyclization to the furan framework is achieved via a Pummerer rearrangement of the intermediate sulfoxide (**216**).[95]



Scheme 53: *Conjugate Addition to Vinyl Sulfoxides as a Route to Furans*

DBU reacts with α-bromo-β-alkoxyketones (**220**) to give tri-substituted furans in moderate to good yields (Scheme 54).[96] One common reagent is involved as both the nucleophile (**219**) and electrophile (**221**) in a conjugate addition mechanism. Enolization of the ketone occurs simultaneously with elimination of the alkoxide to generate the α, β-unsaturated ketone (**221**). Subsequently, conjugate addition of the enolate (**219**) to the Michael acceptor (**221**) is followed by cycloproponation to form **223**, de-bromination and subsequent rearrangement to the desired furan (**225**).



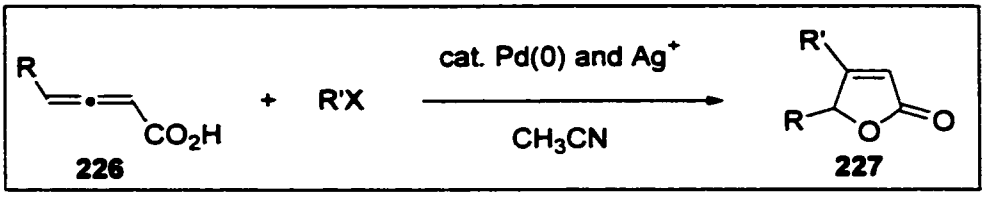
Scheme 54: *One-Pot Synthesis of Furans from α-Bromo-β-Alkoxyketones*

As is evident by these examples, as well as the numerous other examples in the literature, it is obvious that furans and their synthesis continue to generate a large amount of novel research.

I-iii-iii. Furanone Introduction

Furanones are an interesting class of compounds that continue to receive attention due to their potential biological activities. Numerous methods for their preparation have been reported.[97]

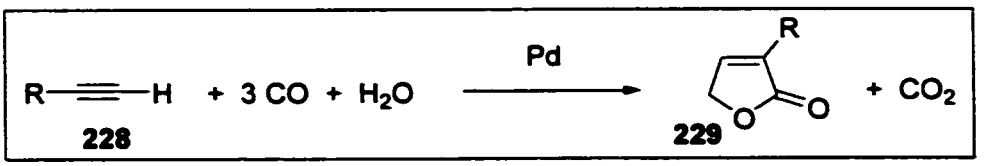
The following examples highlight the current interest in this class of compounds. Ma and co-workers revealed a $Pd(0)/Ag^+$ co-catalyzed one-step method for the synthesis of butenolides (**227**) starting from allene carboxylic acids (**226**) and alkyl halides (Scheme 55).[98]



Scheme 55: *Butenolide Synthesis from Allenes*

The limitation for the initial method was that 1-alkynyl halides could only be prepared in poor yields. The method was then modified so the alkyl halide that was employed was replaced by I_2.[99] This yields the corresponding halo-butenolide (**227**, R' = I) that can then be converted to the di-substituted alkynes *via* the Sonogashira coupling of terminal acetylenes.[100]

Gabriele and co-workers recently reported a new method for the synthesis of 3-alkyl- or 3-aryl-substituted furan-2-(5*H*)-ones (**229**) by palladium-catalysed reductive carbonylation of alk-1-ynes (**228**) in the presence of water (Scheme 56).[101]



Scheme 56: *Palladium-Catalysed Reductive Carbonylation of Alkynes*

I-iii-v. Vioxx

Painkillers are of great importance in the pharmaceutical industry. In 1999, Monsanto's Searle division, with the help of Pfizer, launched its new painkiller, Celebrex® (**230**). Merck quickly followed with its own product, Vioxx, ® (**231**) in order to try to capitalize on the $6 billion market for arthritis relief.[102]

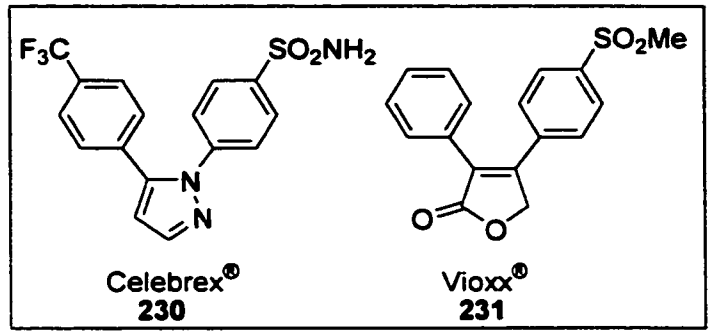
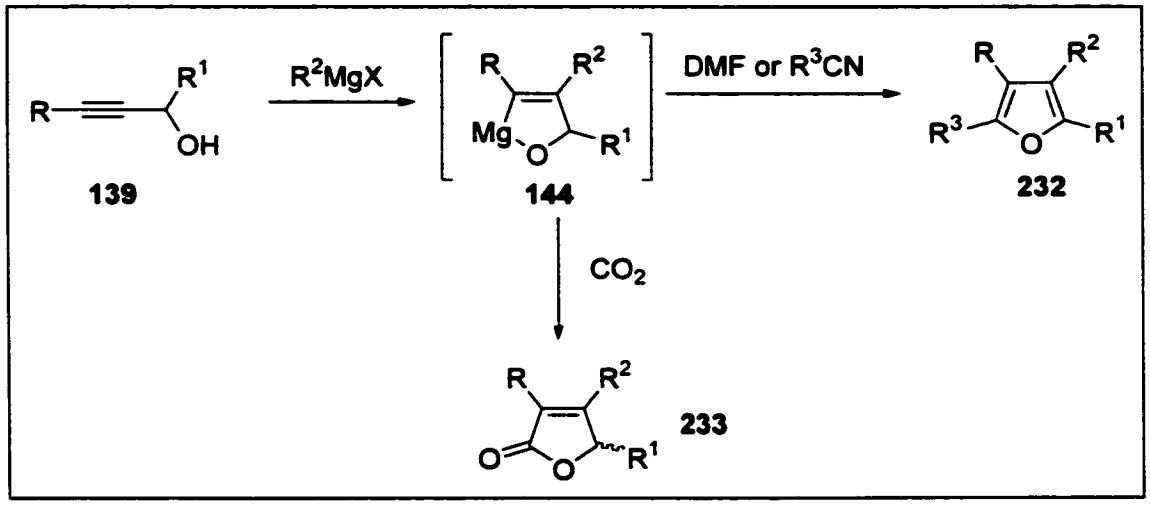


***Figure 3:** Celebrex® and Vioxx®*

Both drugs were highly anticipated due to their properties, which represented a new class of painkillers called COX-II inhibitors. They provide the same pain relief as non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and aspirin but without the often-serious stomach inflammation. Regular NSAIDs work by blocking the action of two enzymes, COX-II, which is believed to have a primary role in pain and inflammation, and COX-I, which is thought to help maintain the lining of the stomach. Thus, the COX-II selective drugs inhibit only the pain-causing enzyme, avoiding ulcers and other stomach complications that can develop when the stomach enzyme (COX-I) is blocked.

I-iii-vi. Carbometallation as a Route to Furans and Furanones.[103]

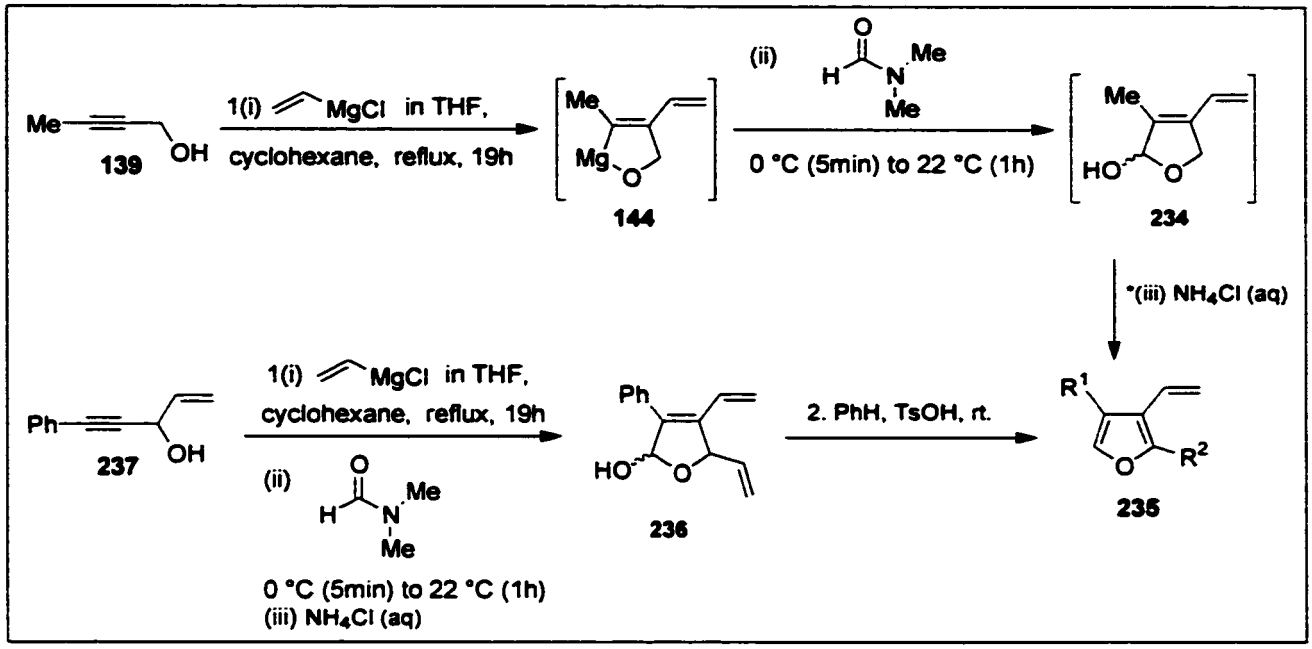
Due to the continuing interest in furans and furanones, we have extended the carbometallation investigations to versatile combinations, that permit the direct synthesis of substituted furans (**232**) by a novel method as well as 2-(5*H*)-furanones (butenolides) (**233**) depending upon the electrophiles selected (Scheme 57).



Scheme 57: *Furan and Furanone Synthesis*

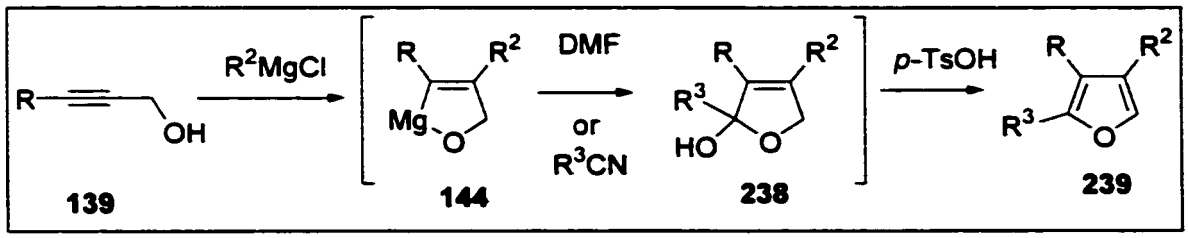
Furans comprise an important class of oxygen heterocycles. They have been isolated from a broad cross section of natural sources and have been employed both as key synthetic intermediates and as synthetic targets in their own right.[104] Consequently, new preparative routes continue to be developed.[105] However, few of these methods allow the synthesis of tetra-substituted furans.[106] Following the Grignard based carbometallation protocol described previously, substituted furans **232** may be synthesized directly upon reaction of **144**, derived from **139**, by reaction with

dimethylformamide (DMF) followed by acidification without isolation of the intermediate hemiacetal **234** (Scheme 58).



Scheme 58: *Preliminary Studies for the Preparation of Di- and Tri-Substituted Furans*

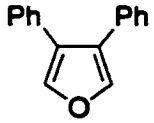
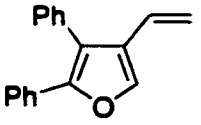
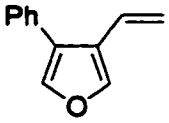
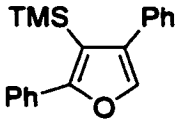
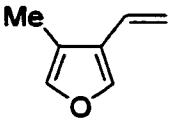
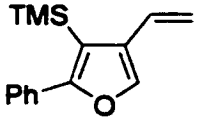
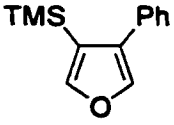
Alternatively condensation with aryl nitriles in place of DMF allow the direct synthesis of more highly substituted furans in which the substitution pattern at the 2-, 3-, and 4-positions may be controlled systematically (**239**, Scheme 59).



Scheme 59: *Nitrile Quenching to Yield Tri-Substituted Furans*

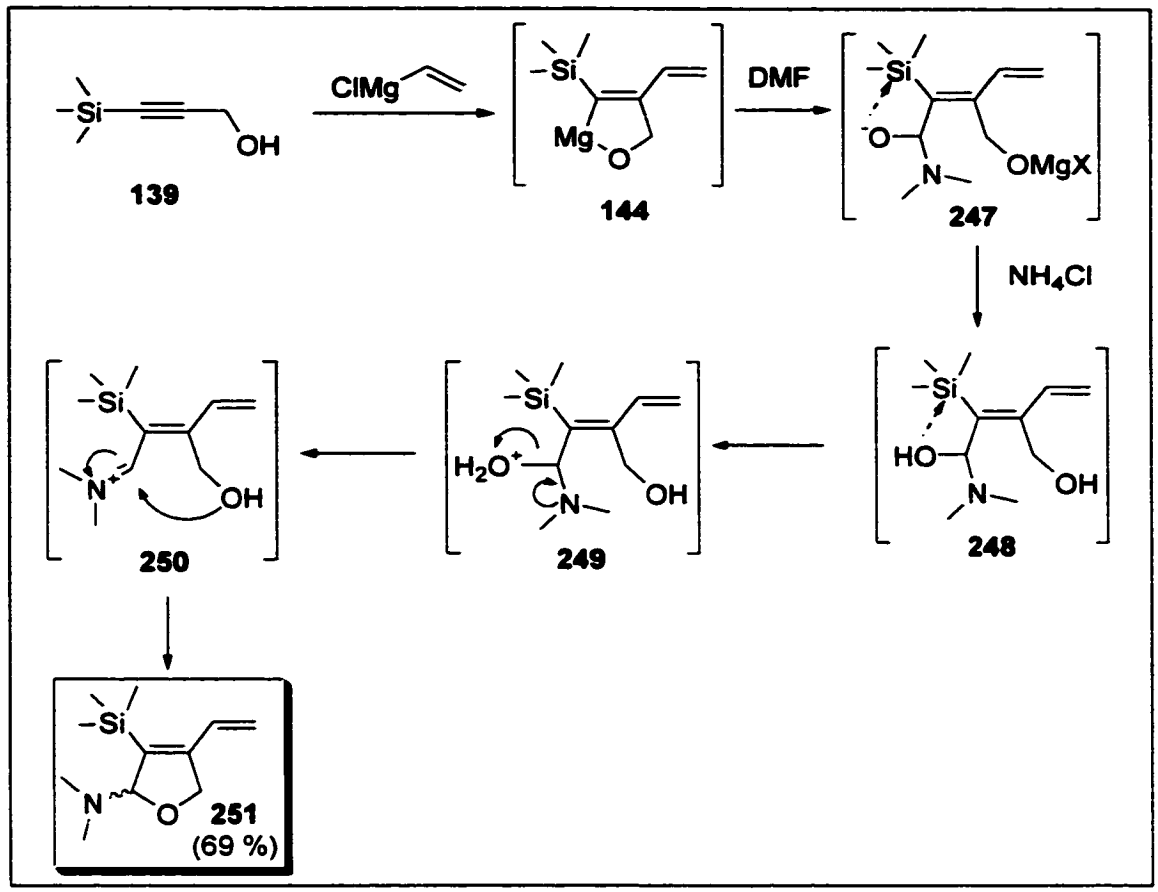
Table 2 illustrates various combinations with either DMF or benzonitrile as the electrophile for the carbometallation reaction.

Table 2: *Furan Synthesis from Propargyl Alcohols*

Entry	Reactants (DMF electrophile)	Furan (% Yield)	Entry	Reactants (PhCN electrophile)	Furan (% Yield)
a	Ph—≡—CH_2OH PhMgCl	 **240** (91 %)	**e**	Ph—≡—CH_2OH H_2C=CHMgCl	 **244** (25 %)
b	Ph—≡—CH_2OH H_2C=CHMgCl	 **241** (91 %)	**f**	TMS—≡—CH_2OH PhMgCl	 **245** (41 %)
c	Me—≡—CH_2OH H_2C=CHMgCl	 **242** (45 %)	**g**	TMS—≡—CH_2OH H_2C=CHMgCl	 **246** (88 %)
d	TMS—≡—CH_2OH PhMgCl	 **243** (33 %)			

Unfortunately, the acidic conditions required for the elimination of water also induced decomposition and reduced yields for the more labile compounds **243** and **244**. These vinyl furan systems contain useful functionality for the construction of more complex skeletons *via* a double Diels-Alder strategy and may also be used as monomers for the preparation of polymers with unique properties.

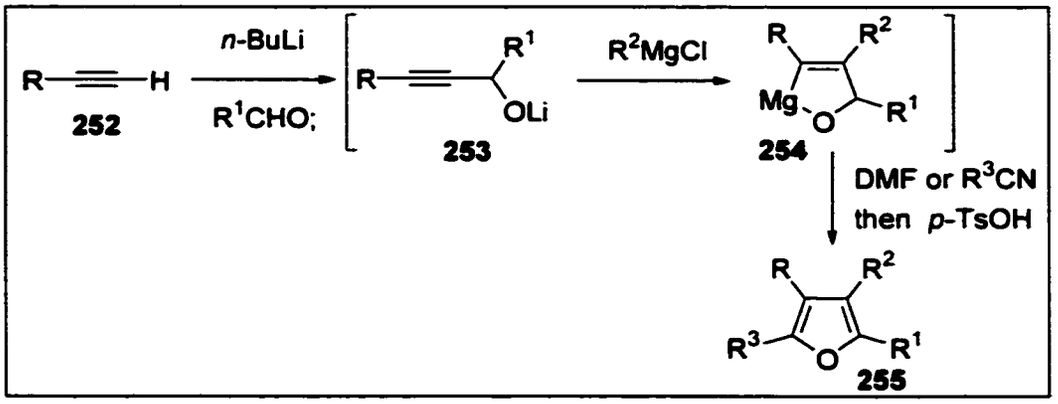
An interesting aberration of the furan synthesis *via* a DMF quench is the case where the vinyl Grignard is employed and a TMS-propargyl alcohol (**139**) is the substrate (Scheme 60). In this case, the final product which is obtained is the hemi-aminal (**251**), not the hemi-acetal which was exclusively obtained in all other cases. It is not entirely clear as to the reason for this single anomally. However, it is likely that the tetrahedral intermediate that is initially formed (**247**) can stabilize the oxygen anion through the d-orbitals of the silyl atom of the TMS group, somewhat analogous to the Peterson olefination.[107] This prevents the intermediate from collapsing and expelling dimethylamine that would lead to the hemi-acetal. Rather, upon work-up, the lone pair on nitrogen acts to expel water (**249**) and yield the iminium cation (**250**) which then undergoes the intramolecular cyclization to give the observed hemi-aminal (**251**).



Scheme 60: *Formation of Hemi-Aminal*

The versatility and scope of this furan synthesis was extended by the *in situ* generation of the intermediate chelate **144** *via* lithium-magnesium transmetallation. Thus, modification of the standard protocol permitted the introduction of substituents at the eventual C-5 position of the furan, to allow independent control of the substituent at the remaining position. Addition of the alkynyl lithium salt derived from **252** to an aldehyde afforded the lithium alkoxide **253** as illustrated in Scheme 61. This was followed by transmetallation with vinylmagnesium chloride and Grignard addition to form the chelate **144** that could then be reacted with either DMF or a nitrile derivative.

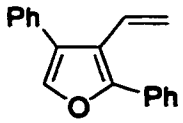
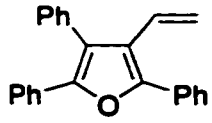
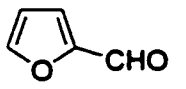
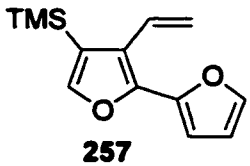
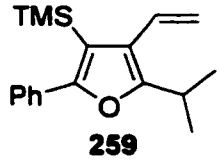
This protocol generated a family of furans **255** in which the substitution pattern at all four positions can be predetermined.



Scheme 61: *Synthesis of Poly-Substituted Furans*

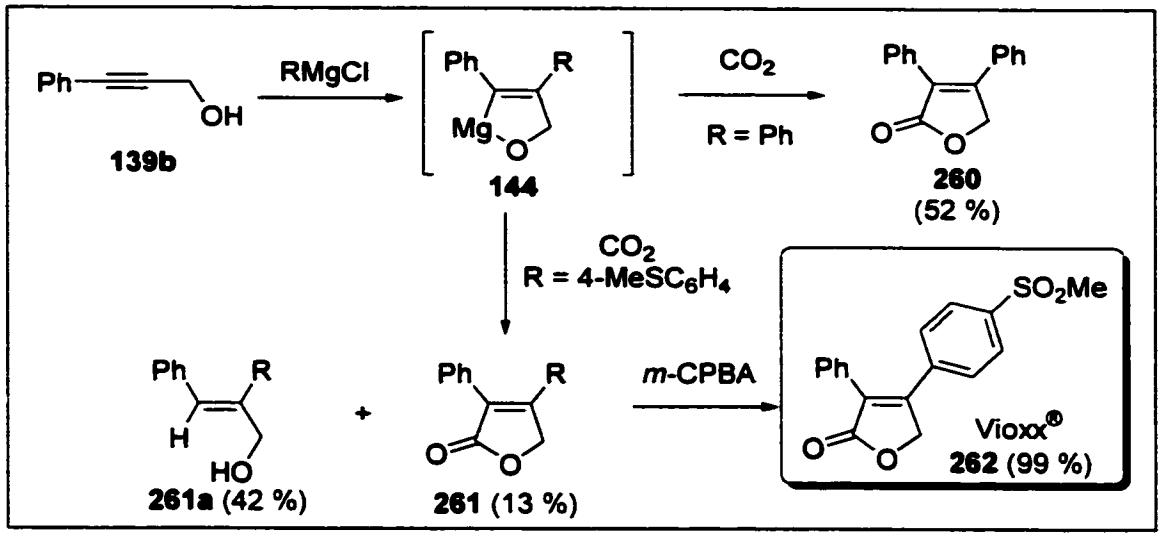
Table 3 lists various examples generated in this fashion. Thus, depending upon the substrate-reagent-reactant combination selected above, a large number of substituted furan systems may be prepared.

Table 3: *Furan Synthesis from Terminal Alkynes*

Entry	Reactants (DMF)	Furan (% Yield)	Entry	Reactants (PhCN)	Furan (% Yield)
a	Ph—≡—H PhCHO H_2C=CHMgCl	 **256** (25 %)	**c**	Ph—≡—H PhCHO H_2C=CHMgCl	 **258** (25 %)
b	TMS—≡—H  H_2C=CHMgCl	 **257** (29 %)	**d**	Ph—≡—H ^{i}Pr-CHO H_2C=CHMgCl	 **259** (28 %)

Early examples of dialkyl butenolides derived from the condensation of species related to **144** with carbon dioxide have been reported,[108] and other methods are available.[109] However, in view of the challenge and medicinal interest[110] in preparing 3,4-diaryl-2-(5H)-furanones such as 3,4-diphenylbutenolide (**260**), this aspect has also been examined. The lactone **260** was synthesized by the magnesium mediated carbometallation of phenylpropargyl alcohol (**139**) with phenylmagnesium chloride to form the chelate **144** followed by exposure to carbon dioxide (Scheme 62). Modification of this protocol in which **144** was reacted directly with 4-thiomethylphenylmagnesium chloride and the reaction quenched with carbon dioxide afforded **261**. Oxidation of **261** with *m*-chloroperoxybenzoic acid generated the sulfone **262** in quantitative yield. As

illustrated in Scheme 62, this butenolide, the new Merck anti-inflammatory drug Vioxx®, may be synthesized in a facile manner using this method.



Scheme 62: *Two Step Synthesis of Vioxx®*

The magnesium mediated carbometallation protocols described above provide direct access to various oxygen heterocycles that may be employed for a variety of synthetic objectives. Although in some cases the yields are modest, this short route to multi-substituted furans and 3,4-disubstituted butenolides in a controlled fashion is very useful. Thus, depending upon the substrate-reagent-reactant combination selected, a large number of compounds may be synthesized. In addition, the ease with which these compounds are prepared in one synthetic step renders this sequence attractive for the use of these building blocks for more complex targets.

II. Taxol®

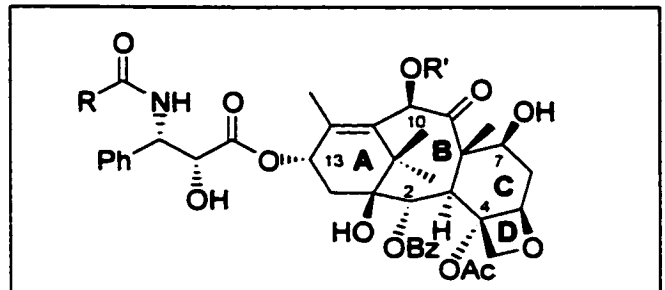
II-i. Introduction

Cancer is a family of deadly diseases that strikes thousands of Canadians each year. On April 24 1998, Cancer Care Ontario released a report stating that cancer had surpassed heart disease to become the leading cause of premature death in Ontario. In the 1960's, heart disease killed twice as many people as cancer. Today, the cancer mortality rate is 20% higher than that for heart disease.[111] Together, breast, lung, prostate and colon cancer account for more than half of all reported cancer cases.

Breast cancer is the leading cause of death in women, and it alone will affect approximately 10% of females in North America.[112] It is estimated that this year, 19,300 new cases of breast cancer will be reported in Canada, and another 180,300 in the United States. Each year 5,400 die of breast cancer in Canada, while in the U.S., a staggering 40,000 deaths are attributed to the disease annually.[113] The Ontario provincial government will spend in excess of 1.6 billion dollars this year on cancer treatment, prevention education, awareness and support services. The federal and provincial governments both commit billions of dollars to combat cancer; however, the cure continues to elude researchers.

In 1962 the National Cancer Institute (NCI), in a large scale screening process designed to target new anti-tumor compounds of natural origin, collected extracts from the Pacific Yew (*Taxus brevifolia*). Two years later, the extracts from the Yew tree were found to be active in a cytotoxicity assay. This was the beginning of the development of the drug now commonly referred to as Taxol®.

Paclitaxel (Taxol®, **263**, Figure 4) received worldwide interest due to its unique mode of action. At the time, many of the drugs on the market and under development (colchicine, podophyllotoxin, vinblastine) were spindle poisons, meaning they inhibited tubulin polymerization.[114] In contrast, Taxol® actually promotes tubulin polymerization and inhibits the disassembly of the stabilized microtubule, which is necessary for cell replication.[115] Epothilones and eleutherobin are known to have similar modes of action to Taxol.®[116] A smaller and simpler molecule, GS-164, has been recently suggested to also operate by a similar mechanism.[117]



263 Taxol R = Ph, R' = Ac
264 Taxotere R = ^{t}BuO, R' = H
265 10-Deacetyl baccatin III, OH at C13, R' = H

Figure 4: *Structure of Taxol® and Related Compounds.*

II-II Taxoid Development

II-II-i History

For centuries it has been known that the extracts from the Yew tree were fatal to humans. Julius Caesar reported that Catuvolcus committed suicide by taking extracts from the yew tree, and as far back as 50 AD, it was reported that the juice from the tree

was used to treat viper bites.[118] Yet, it was not until the twentieth century that Taxol's® full medicinal benefits would be revealed.

In 1963 paclitaxel (Taxol®) was discovered to have cytotoxicity activity, and in 1967 Taxol® was isolated for the first time. In 1971, the structure of Taxol® and its biological activity were published.[119] It was also found that Taxol® was active against B16 melanoma and MX-1 mammary tumors in 1974 and 1978, respectively.[120] Until this time, Taxol® had yet to receive much attention. The primary concerns were the difficulty in obtaining the compound. However, in 1979 it was discovered by Horowitz and Manfredi that Taxol® had a unique mode of action.[114] It was this discovery which spawned new interest in the compound, making Taxol® a valuable biochemical tool for studying mitosis, and in the following year Taxol® entered formulation studies and preclinical trials. Within four years, Taxol® entered Phase I Clinical Trials. It was at this time that a serious problem was discovered. Taxol® is very insoluble in water and was formulated as an emulsion with a polyethoxylated castor oil, Cremophor EL. Relatively large doses of Taxol® were required and thus patients also were administered large quantities of the Cremophor, which for some led to severe allergic reactions, including one death. Lengthening the infusion period and premedicating patients with glucocorticoids and antihistamines eventually solved the problem.[121] Taxol® then successfully completed both Phase II and III Clinical Trials, and in 1991 the first Canadian woman was treated with the drug.[122]

Taxol® was approved in Canada, the United States and Austria for treatment of ovarian cancer (January) and subsequently approved for breast cancer (December) in 1993.[123] An article in the Toronto Globe and Mail in 1990 read - "Scientists have tried to

synthesize the chemical, but ten years of effort have been futile - Taxol's highly complex chemical structure cannot be duplicated." However, in 1994 the first total syntheses were independently reported by both Holton and Nicolaou's groups.[124,125] More recently, other groups have published total syntheses of Taxol®.[126]

II-II-ii. Taxoid Dosage and Supply

One of the serious concerns over the use of Taxol® as an anti-cancer drug, and the primary reason that it was delayed for clinical use, was the limited supply of the drug. The Pacific yew is a slow-growing conifer that is usually found in moist soils, in the understory of old conifers and hardwoods.[127] A mature tree rarely exceeds 60 cm in diameter and 12 m in height. The concentration of taxol in the needles is 20-70 ppm while the concentration in the bark is 70-140 ppm. Taxol® was initially only isolated from the bark of the yew trees in yields of approximately 0.007%. The yield from the bark has now doubled to 0.014%.[128] This equates to 100 mg of the drug from 1 kg of dried bark.

A pilot plant contracted by the NCI could only handle about 5000 kg of bark per year to produce only 500 g of pure Taxol® annually.[129] This is far below useful quantities, since each patient could require 2 g of Taxol®. The trees are also important roosting habitats for endangered species, such as the spotted owl, and other birds. The collection of large amounts of bark for clinical trials (27000 kg in 1989) raised concerns about the impact of continued collection on the ecology of the U.S. Pacific Northwest and the survival of the *Taxus brevifolia*. It quickly became apparent that due to the slow growth of the trees and the killing of the trees by harvesting bark, Pacific yew bark was

not a sustainable resource for Taxol® production. Various solutions to this problem have been proposed and include total synthesis, partial synthesis, Taxol® analogues, plant tissue culture and fungal sources.

Total synthesis, although it has been successfully accomplished, relies on an extensive sequence of steps and results in a low overall yield. One recently published synthesis of Taxol® is 60 steps.[126e] The highly oxygenated, complex nature of the molecule has prevented any economically feasible commercial production. It is known that internal eight-membered rings are difficult to synthesize due to entropic and enthalpic factors,[130] and the synthesis is complicated further by the necessary incorporation of a geminal dimethyl group. In addition, the A ring contains a bridgehead double bond and the C ring is *trans*-fused with an angular methyl group. Finally, Taxol® contains many defined stereocentres, which further complicates the synthesis.

One of the more favourable routes is semisynthesis. The Taxol® precursor, 10-deacetyl baccatin III (**265**, Figure 4), can be isolated from the needles of *Taxus baccata* and other yews in 0.1% yield, and thus is a more renewable resource than the bark because the tree is not killed from the harvesting.[131] Docetaxel (Taxotere, **264**, Figure 4), is also prepared *via* a semisynthetic route from 10-deacetyl baccatin III and has been reported to be more active than Taxol® in murine and human tumor cell lines.[132] These options are still far from ideal because they rely on potentially limited natural resources.

Both plant tissue cultures and fungal production currently yield very low quantities of Taxol®.[133] They might however become feasible using both classical techniques and genetic engineering.

The disadvantages and difficulties in the above methods could be avoided using Taxol® analogues. These analogues ideally would be smaller compounds that are much easier to synthesize and possess cytotoxicities comparable to or better than that of Taxol®. There are four basic types of analogues that may be considered: close chemical analogues prepared from naturally occurring taxanes; close chemical analogues with substituents not accessible from natural taxanes; significantly simplified analogues prepared by total synthesis and retaining only critical shapes, groups and electronic properties; biological analogues binding at the same site on microtubules but with fundamentally different chemical structures. A number of analogues have been prepared under type 1 classification[134] as well as a few reports of type 2 analogues.[135] A number of structure-activity relationship studies are currently ongoing worldwide in an attempt to gather more data to allow for the design of type 3 analogues. Finally, type 4 analogues give rise to peptide sequences with Taxol®-like activity.

II-II-iii. Structure Activity Relationships

Research into structure-activity relationships of Taxol® is still incomplete, although a substantial amount of information has been obtained. The molecule can be divided into three basic areas: the side chain, the northern perimeter and the southern perimeter.

The presence of the C-13 side chain is an absolute requirement for activity. Cleavage of the side chain, to give Baccatin III, significantly reduces the activity in both cytotoxicity assays and tubulin-assembly assays.[136] The hydroxyl substituent at C-2' and the phenyl group at C-3' are also both needed for activity.[137] Several analogues have

been prepared with substituted 3'-phenyl groups, but all have been less active than Taxol®.[138] Variation of the substituents on the nitrogen at C-3' is tolerated, including aromatic or aliphatic groups such as amides or carbamates. One such analogue, Taxotere®, which has an N-*t*-butoxycarbonyl group in place of the N-benzoyl group (and lacks the C10-acetate), has been found to be about five times more active than Taxol®.[139]

The 'Northern perimeter' of Taxol® includes carbons 6-12, with oxygen functionalities at C-7, C-9 and C-10. In general, structural variations along the upper edge of the molecule do not affect activity, suggesting this region is not directly involved in binding to microtubules. The alcohol at C7 may be esterified, epimerized or even removed without any significant loss in activity.[140] Very little change in activity is observed with either reduction of the carbonyl[141] at C-9 or removal of the C-10 acetoxy group.[142]

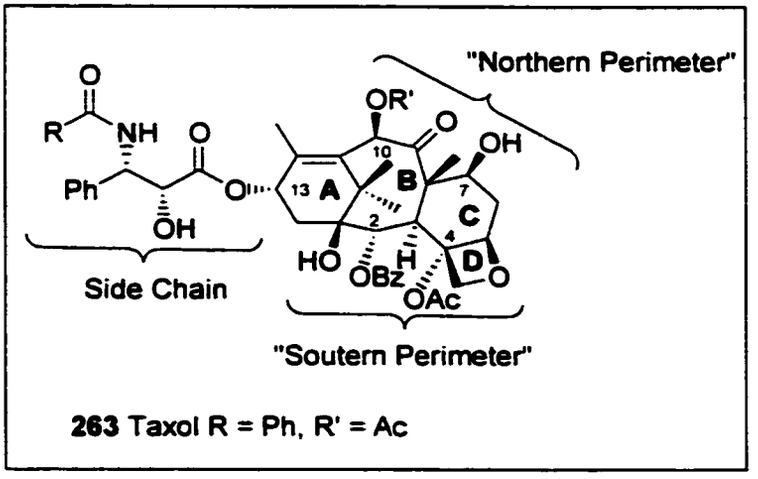


Figure 5: *Structure Activity Relationships of Taxol®*

The 'Southern perimeter' of Taxol® comprises C1-5 and C-14, with oxygen functionalities at C-1, C-2 and C-4, and the unusual oxetane ring at C-4 and C-5. In contrast to the flexibility of the functionalities of the upper perimeter, structural changes in the lower portion of the molecule have major effects on activity. The oxetane ring is crucial to activity and ring opening drastically reduces Taxol's® performance in both tubulin-assembly and cytotoxicity assays.[143] The oxetane is relatively chemically inert, suggesting its role may simply be to act as a lock to maintain the conformation of the diterpenoid ring system. The benzoyloxy group at C-2 is also important, since deoxygenation results in an inactive product.[144] Many analogues have been synthesized with substituted benzoyl groups; in general the *m*-substituted derivatives are more active than the corresponding *p*-substituted analogue.[145] π-Stacking interactions between the phenyl groups of the side chain and the C-2 benzoyl group have been proposed to rationalize the importance of the benzoyl group.[146] Yet, the difference in *m*- and *p*-substituted benzoyl analogues suggests steric factors must also come into play.

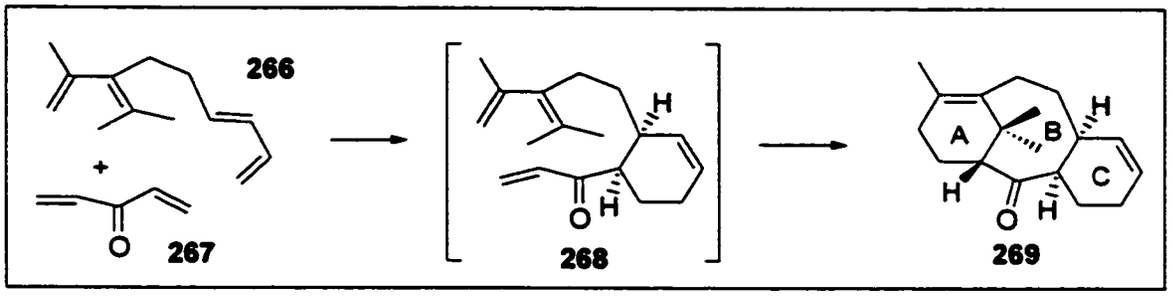
II-II-iv. Studies Towards Taxoid Ring Systems

Due to the importance of Taxol in the treatment of various forms of cancer and its continued preparation through semi-synthetic methods, it continues to receive a great amount of attention from organic chemists throughout the world. Although a number of total synthesis have been reported, a number of other groups continue to highlight novel and interesting chemistry towards the taxane ring system and structural analogues in hopes to find alternatives which may provide similar or increased activity.

II-II-v. Taxoid Chemstry

II-II-v-i. Routes to the Ring System

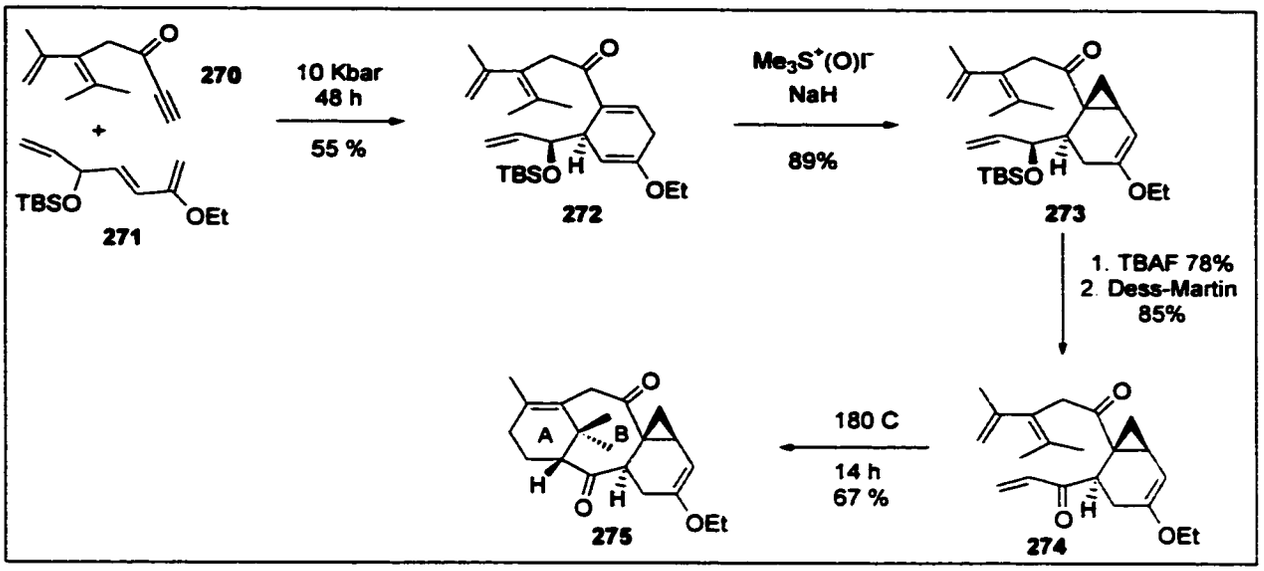
Winkler and co-workers have made valuable contributions in the area of synthesis of the Taxane ring system. A very concise tandem Diels-Alder strategy to the ABC-taxoid ring sytem was reported. The ring system is formed from the cycloaddition of bis-diene **266** and bis-dienophile **267** that leads to the formation of **269**, *via* **268** in good yields.[147]



Scheme 63: *Winkler Route to A/B Taxane Ring System*

Although this was an excellent method that underscored the utility of the tandem Diels-Alder reaction in organic synthesis, this construction does not address several critical issues in taxane synthesis, particularly the establishment of the *trans*-B/C ring fusion that is incorporated in the taxane ring system.

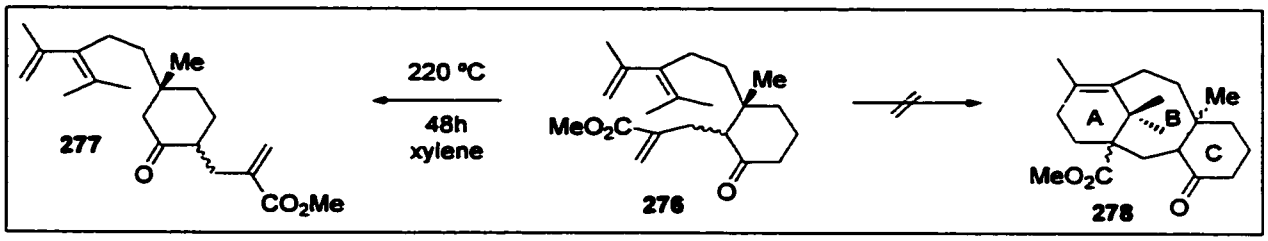
In order to overcome this problem in the original approach, a sequential Diels-Alder method was developed to incorporate the requisite *trans*-B/C ring fusion (Scheme 64).[148]



***Scheme 64:** Winkler Route to* trans-*fused A/B Ring System*

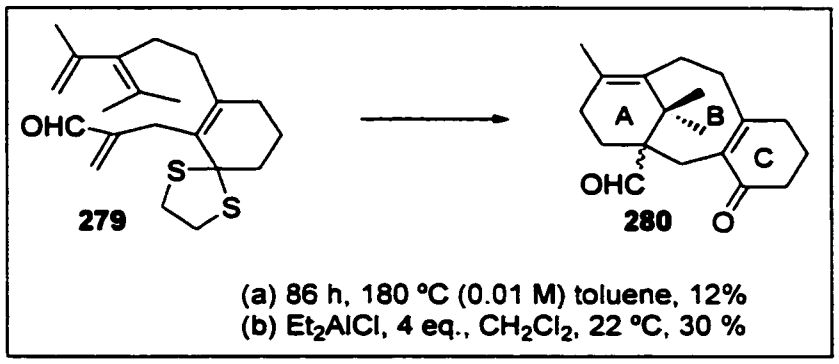
The formation of the dihydrobenzene **272** that results from the initial Diels-Alder reaction precludes the establishment of the undesired *cis*-B/C ring junction for the endo-selective intermolecular cycloaddition. Cyclopropanation of the olefin of the formed ene-one in a diastereoselective reaction thus yields the required *trans*-B/C ring junction (**273**).

Shea and co-workers also have made seminal contributions in the area of taxane research.[149] Shea demonstrated that when the C-ring cyclohexane was formed in advance of the A/B-ring formation, that no Diels-Alder product (**278**) was formed. Rather, only a [3.3] sigmatropic rearrangement occurs, presumably *via* an enol tautomer of **276**.



Scheme 65: *Rearrangement of Potential Diels-Alder Precursor*

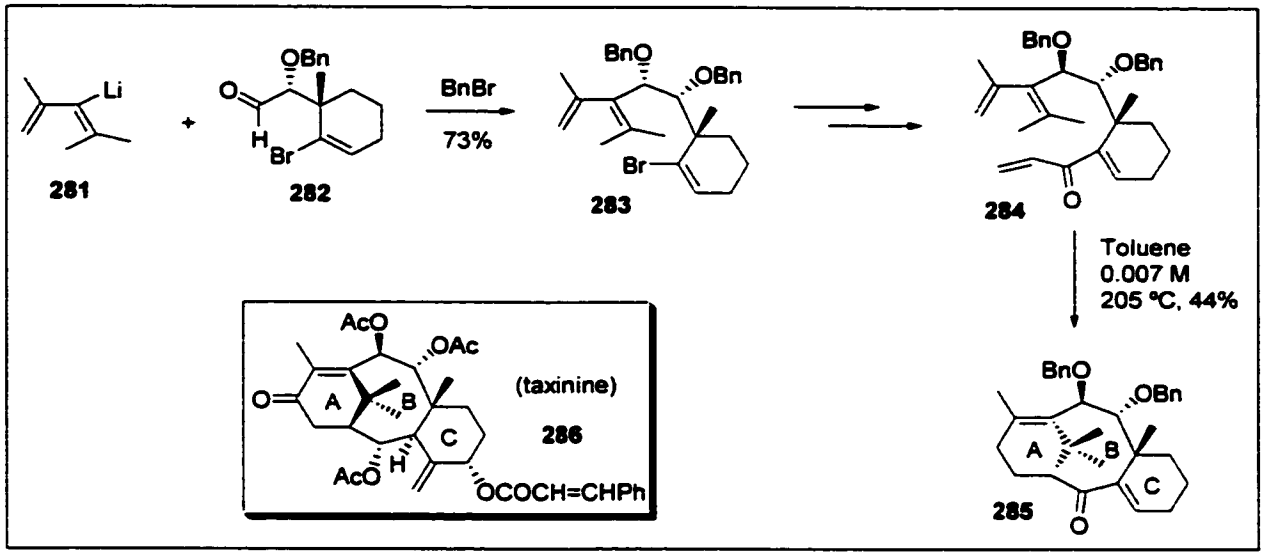
Shea altered his approach to ensure that the diene and dienophile were in close proximity in order to faciltate the Diels-Alder reaction. An alternative substrate (**279**) was prepared which contained an olefin that would limit the flexibility.[150] Although this approach was successful, modest yields were obtained of the desired ring system (**280**) under both Lewis acid catalysis and thermal conditions (Scheme 66).



Scheme 66: *Shea's Construction of the Taxane Ring System* via *an IMDA Reaction*

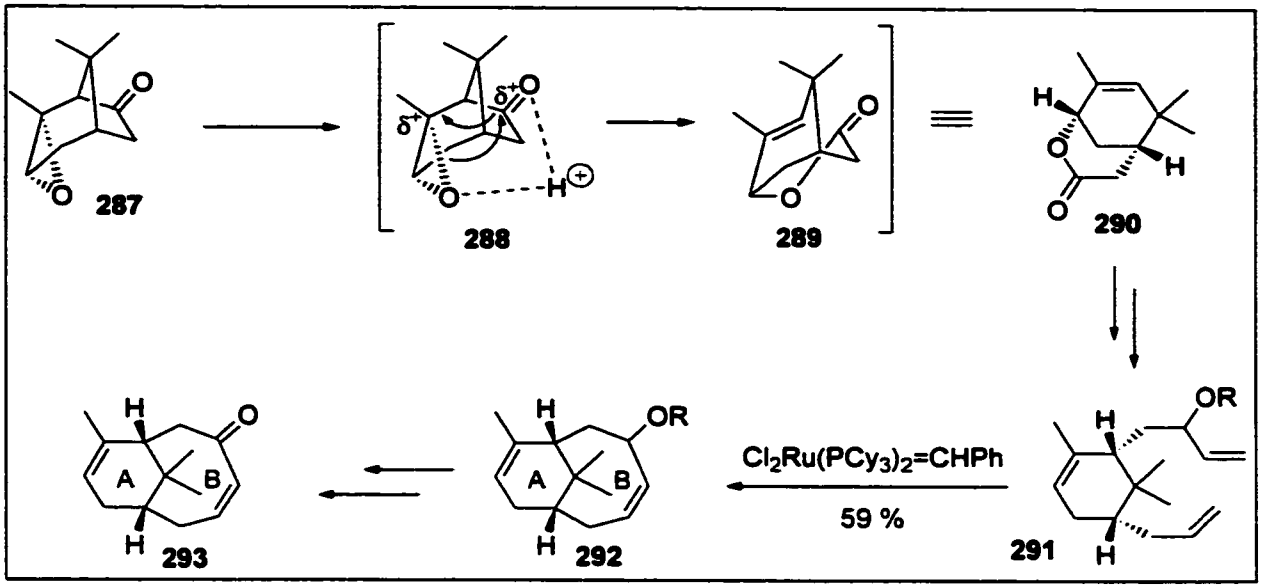
The atopisomerization of the formed adduct (**280**) was measured and the barrier separating the two conformational isomers was found to be between 18 and 25 kcal/mol.

More recently, Shea demonstrated a route that incorporated the C8 - C10 stereocentres found in the taxane natural products, e.g. taxinine, **286**, again employing an intramolecular Diels-Alder reaction of **284**.[151]



Scheme 67: *Shea's Route to a Highly Oxygenated Taxane Ring System*

An alternative method to the construction of enantiomerically pure A/B-ring system of the taxanes involving a ring-closing metathesis approach has recently been described (Scheme 68).[152] The key step is a novel rearrangment that was postulated occurs *via* simultaneous polarization of both oxygen functionalites (**288**) after which the oxirane is suitably located for nucleophilic attack on the carbonyl group. Due to the carbocationic character of the α-position, the adjacent σ-bond can open to form an alkene and regenerate the carbonyl group, thus furnishing the lactone (**290**). This approach lends itself to the formation of an A/B ring system (**293**) that is suited for a Diels Alder reaction for the formation of the required C-ring.



Scheme 68: *Ring Closing Metathesis Approach to Taxane Ring System*

II-II-v-ii. Taxol® Analogues

With the extreme difficulty involved in the total synthesis of Taxol®, it is not surprising that a number of research groups' worldwide have worked on or are currently working on analogues. Using the information gathered thus far regarding structure-activity relationships, a number of simpler molecules have been designed and synthesized with the hope of finding a drug more cytotoxic than Taxol® itself. A smaller and simpler molecule, with activity comparable to Taxol®, would allow for efficient large-scale industrial production. Most of the analogues are based on the same diterpenoid framework[153], with modifications at C-2[154], C-4[155], C-7[156], or at the N-terminal or C-3' of the side chain[157].

II-II-v-iii. Novel Taxol Analogues

The Fallis laboratory has had an ongoing interest in the synthesis of Taxol® analogues. A number of analogues have been proposed and synthesized from simple, inexpensive and readily available starting materials. The analogues are designed following the results of structure-activity relationships. The molecules are less complex than Taxol®, although it is still hoped that they will possess activities similar to, or better than, Taxol®. Computer assisted molecular modeling has allowed the design of compounds with similar spatial shape to that of Taxol®. It is hoped that maintaining the same basic shape might give the molecule the ability to function in a similar manner to Taxol® with respect to the binding sites.

Some of the initial analogues synthesized are shown in Figure 6. In the synthesis of each of these compounds the key step is an intramolecular tether controlled Diels-Alder reaction (IMDA). The tether serves to hold the diene and dienophile in close proximity. The advantages to these types of reactions are two-fold. First, the formation of two rings is observed in a single step. In addition, it has been reported that IMDA reactions can enhance regio- and stereoselectivity.[158] For these reasons, IMDA reactions incorporating removable tethers are commonly used in the synthesis of many natural products.[159] A planar aromatic tether control group was chosen to limit conformational flexibility, which can result in shorter reaction times, lower reaction temperatures and increased stereoselectivity.

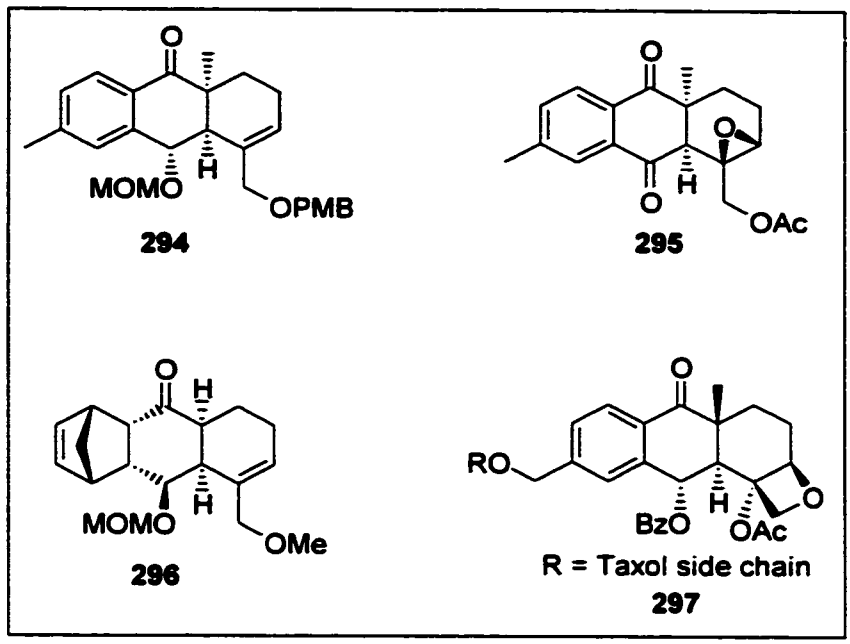


Figure 6: *Fallis group taxoid analogues*

Compounds **294** - **296** were successfully synthesized previously as part of a cycloaddition study.

II-II-vi. Diels-Alder Chemistry

The Diels-Alder reaction is one of the most powerful tools in modern synthetic chemistry. Discovered in 1928 by Diels and Alder, this thermally allowed [4+2] cycloaddition presents a convenient and highly stereospecific route to six-membered rings.[160] The reaction results in the formation of two new σ bonds and a π bond, with the creation of as many as four new stereogenic centres.

Ideally, the diene has an electron-donating group, and the dienophile an electron-withdrawing group. However, the reaction can occur in the unsubstituted case. These complementary electronic substituents decrease the HOMO-LUMO gap, and therefore

increase the reaction rate, by increasing the energy of the HOMO of the diene and decreasing the energy of the LUMO of the dienophile. Inverse electron demand may also occur when the diene has electron-withdrawing groups and the dienophile has electron-donating groups.

A requirement for the reaction to occur is the diene must be in the *s-cis* conformation in order to allow for correct orbital overlap. Therefore, in general, dienes with one exocyclic double bond cannot react, but endocyclic double bonds react readily. The reactivity of open chain dienes depends on the equilibrium constant for the conformational interconversion. A C1-substituent favours the *s-trans* form and slows the addition rate, while a C2-substituent favours the *s-cis* form and enhances the rate.[161]

One of the most important features of the Diels-Alder reaction is that it is stereospecific. The stereochemistry of the starting dieonophile is maintained during the reaction and a single product diastereomer results, as shown in Figure 7.

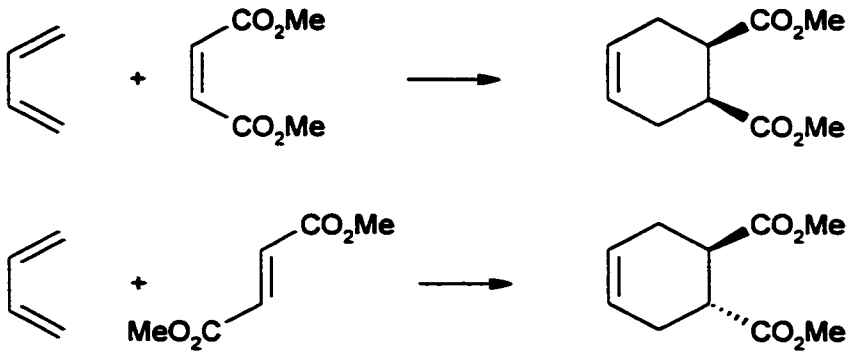


Figure 7: *Retention of stereochemistry in a Diels-Alder reaction*

A second important stereochemical feature is that the *endo* product is preferred over the *exo* product (Figure 8).

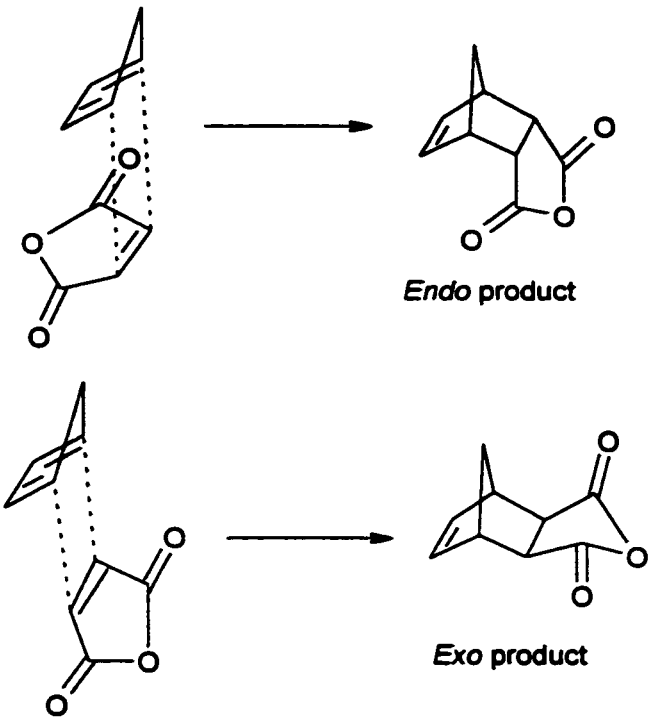


Figure 8: *Endo and Exo approaches in a Diels-Alder reaction*

If the dienophile is unsymmetrical it can approach the diene in two different orientations. In the *endo* approach, the dienophile substituents are under the π orbitals of the diene, whereas in the *exo* approach the dienophile substituents do not overlap with the diene (shown in Figure 9). When the dienophile has an unsaturated substituent, such as a carbonyl group, the secondary orbital overlap observed in the *endo* approach stabilizes the transition state and is favoured.

In the case where both the diene and dienophile are unsymmetrical, two regioisomers can result. When a dienophile containing a heteroatom reacts with a 1-substituted diene, the *ortho* product is normally preferred over the *meta* product. With 2-substituted dienes, the *para* product usually is generated instead of the *meta* isomer.

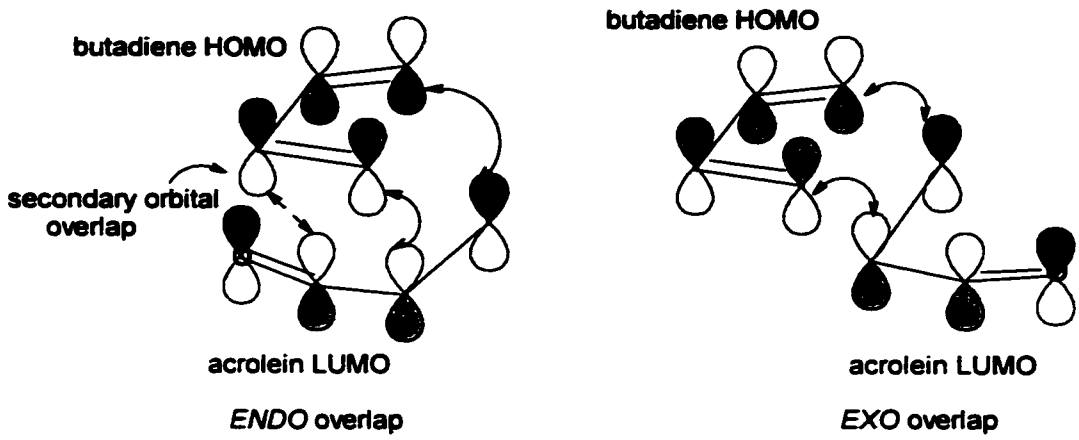
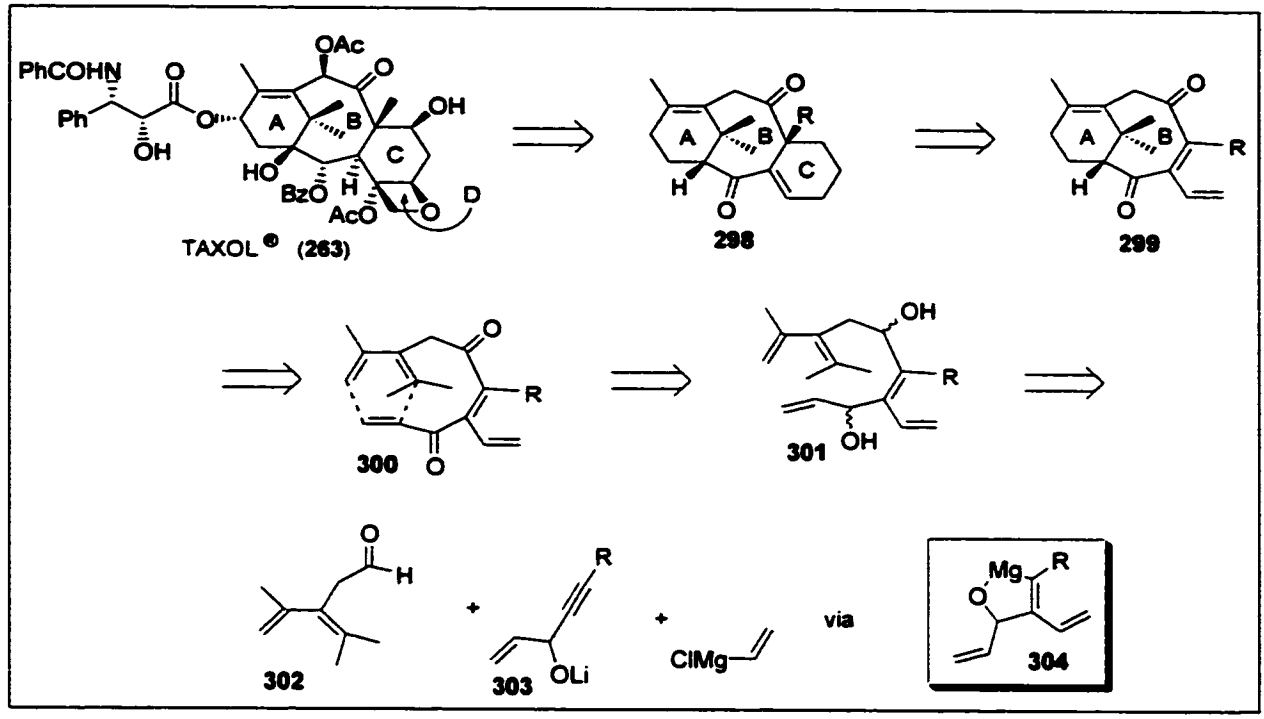


Figure 9: *Secondary orbital overlap in endo transition state*[162]

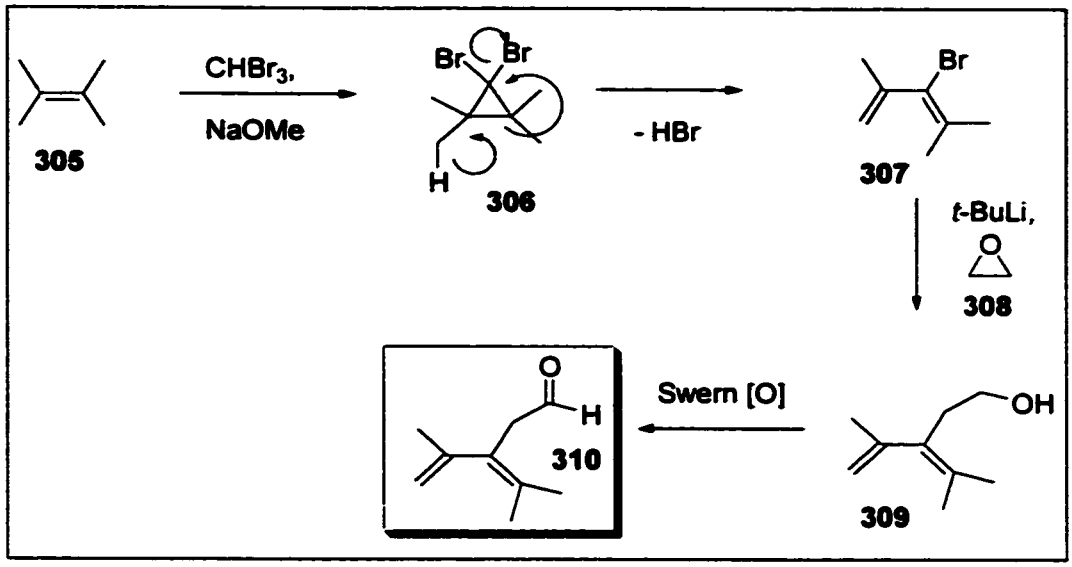
II-ii-vii. Route to AB-Ring System of Taxanes

We have described the direct addition of vinyl and related Grignard reagents to propargyl alcohols either directly or generated *in situ* to generate the putative magnesium chelate **5** followed by reaction with an appropriate electrophile. This procedure allows the direct synthesis of halodienes, diene-diols, substituted furans and 2-(5*H*)-furanones (butenolides) depending upon the synthetic objective.[163] Motivated in part, by our interests in the synthesis of taxoids[164] and the development of tether controlled intramolecular [4 + 2] cycloadditions, we have also established the beneficial influence of planar functionality in the side chain.[165] An attractive route for the synthesis of the A/B ring system of taxoids, that combines these protocols, is illustrated in Scheme 69. Initially this strategy envisaged the one pot synthesis of diols such as **301** from condensation of an acetylene with acrolein to generate the lithium alkoxide **303**. Subsequent transmetallation with excess vinylmagnesium chloride to afford the magnesium chelate **304**, followed by reaction with the diene aldehyde **302** will produce the corresponding diols (**301**) which can be elaborated to the Diels-Alder precursors such as **300** and allow examination of the intramolecular cyclization to afford the desired bicyclo[5.3.1]undecene skeleton **299**. This intermediate contains sufficient functionality for the eventual attachment of the C-ring by annulation, cycloaddition, or ring closing metathesis procedures.



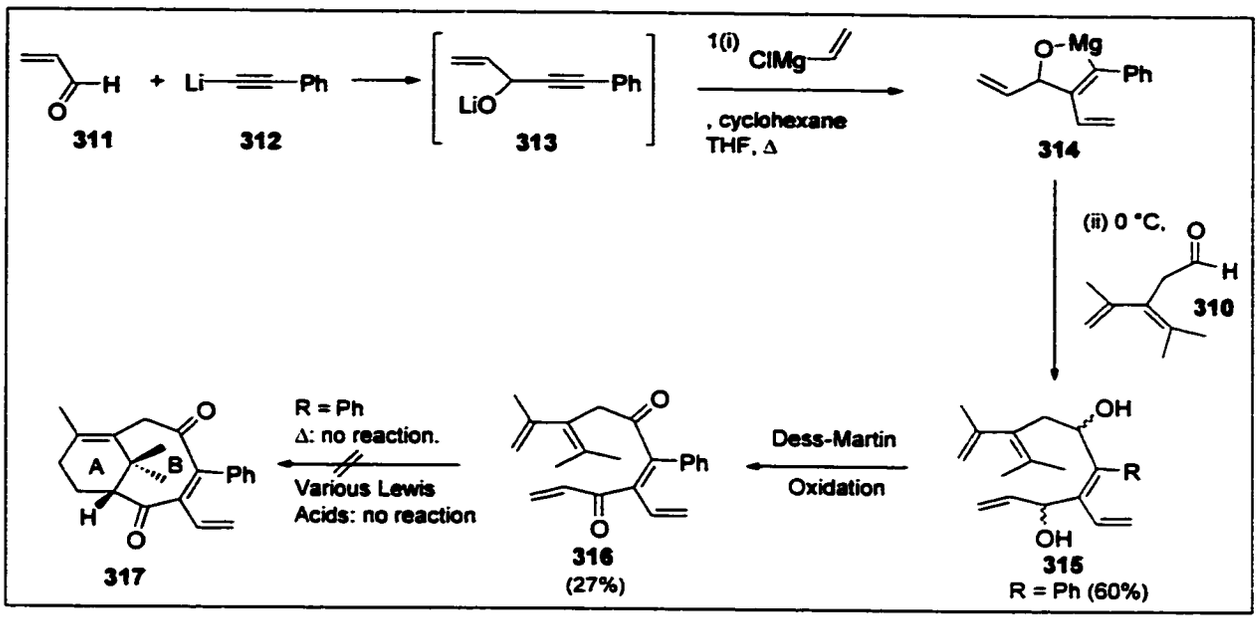
Scheme 69: *Retrosynthetic Analysis of Fallis Route to Taxane Ring System*

The A-ring diene was prepared in a 4-step sequence beginning from the commercially available olefin (**305**, Scheme 70). Cyclopropanation of the olefin (**306**)[166] followed by elimination of HBr yielded the required bromo-diene (**307**). Metal-halogen exchange and subsequent quenching with excess with ethylene oxide (**308**) gives the homoallylic alcohol (**309**) that is then oxidized to the desired, although unstable, aldehyde (**310**).



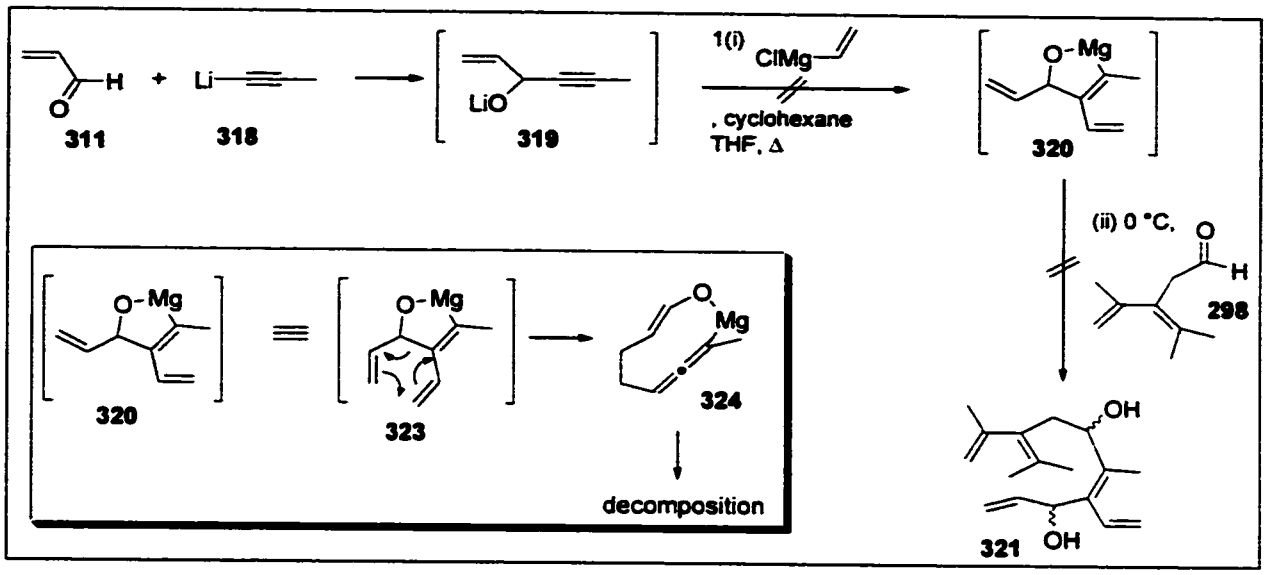
Scheme 70: *Route to A-Ring Diene*

In order to examine the feasibility of the sequence to the A/B-ring system of the taxanes, the lithium salt of phenyl acetylene **312** (R = Ph) was condensed with acrolein (**311**), treated with excess vinylmagnesium chloride and quenched with **310** to afford the pentadiene diol **315** (Scheme 71). Allylic oxidation of the secondary alcohols provided the diketone **316**. Attempted cycloadditions to **317** failed, presumably due to the presence of the bulky phenyl substituent and the excessively planar conformation of this monomethylene compound that impeded the achievement of the required transition state conformation for the Diels-Alder reaction.



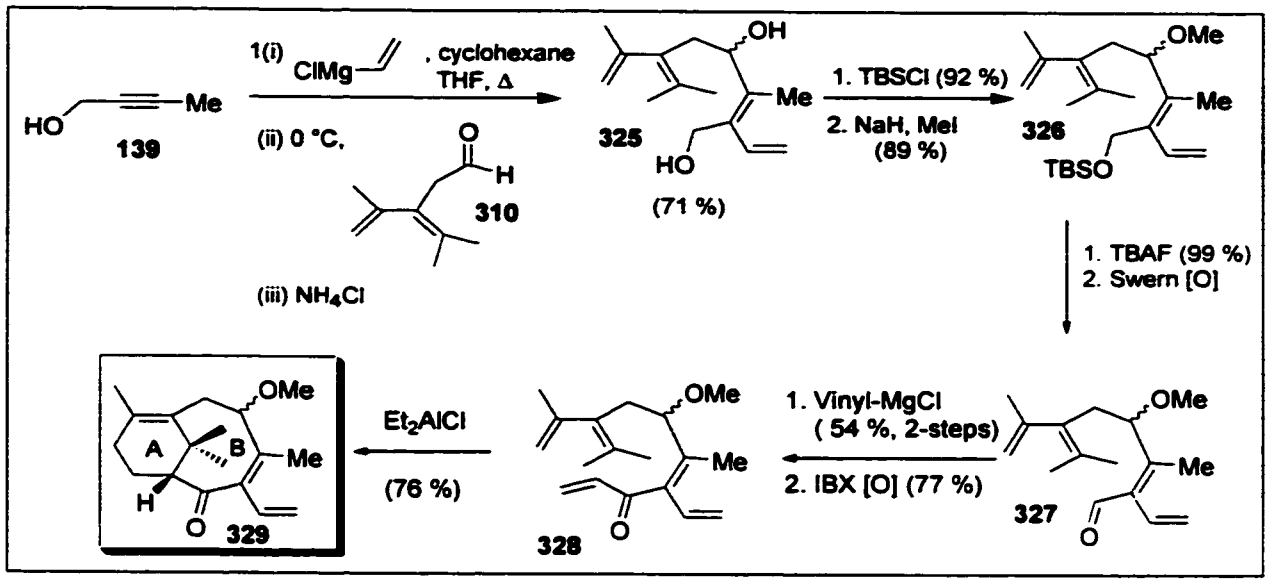
Scheme 71: *Preliminary Studies Towards Taxane Ring System*

Thus the sequence was repeated with propynyllithium with the objective of preparing **321** (Scheme 72) but the desired diol corresponding to **321** (R = Me) was not formed. Instead this combination appears to suffer from competing proton abstractions and an oxy-Cope rearrangement of the intermediate magnesium alkoxide to the allene aldehyde **324** (Box) that decomposed under the reaction conditions.



Scheme 72: *Initial Studies Towards Taxane Ring Systems*

Consequently, to circumvent these difficulties, the sequence was modified to commence with 2-butynol (**139**). The magnesium complex from addition of vinylmagnesium chloride was condensed with the aldehyde **310** to afford the tetraene diol **325** (Scheme 2). Selective protection of the secondary alcohol in **325** as its methyl ether was accomplished as follows. The primary alcohol was reacted with *t*-butyldimethylsilyl chloride followed by subsequent treatment of the secondary sodium alkoxide with iodomethane to yield **326**. Regeneration of the primary alcohol upon exposure to tetrabutylammonium fluoride gave followed by Dess-Martin oxidation to the aldehyde (**327**). vinyl Grignard addition and a second oxidation with 2-iodoxybenzoic acid provided the Diels-Alder precursor **328**.



Scheme 73: *Route to the A/B Ring System of the Taxanes*

Cycloaddition proceeded smoothly in the presence of Et_2AlCl (-78 to 0 °C) to afford the AB building block **329** in 76% yield as a single diastereomer. This selectivity is a consequence of chelation control provided by the complexation of the Lewis acid between the carbonyl and methyl ether substituents (Figure 10) *via* a seven membered ring complex. Similar chelation effects are known to control the selectivity for both intermolecular[167] and intramolecular cycloadditions.[168]

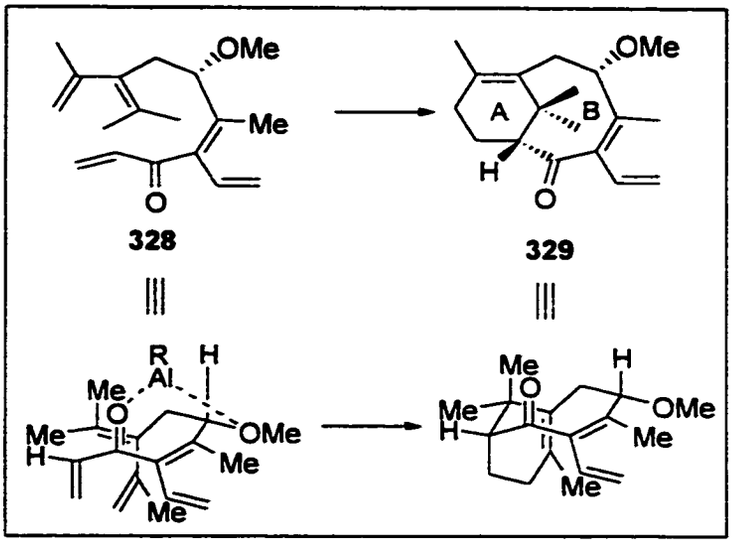


Figure 10: *Diastereoselectivity of the A/B Diels Alder Reaction*

The existance of atropisomerism in taxane ring systems is well established.[169] Thus, in order to determine the conformational bias in this bicyclo[5.3.1]undecene type synthon, variable temperature ^{1}H NMR was utilized. It was anticipated, that the details of the carbonyl-up and carbonyl-down conformers could be examined for their synthetic potential and stereochemical bias.

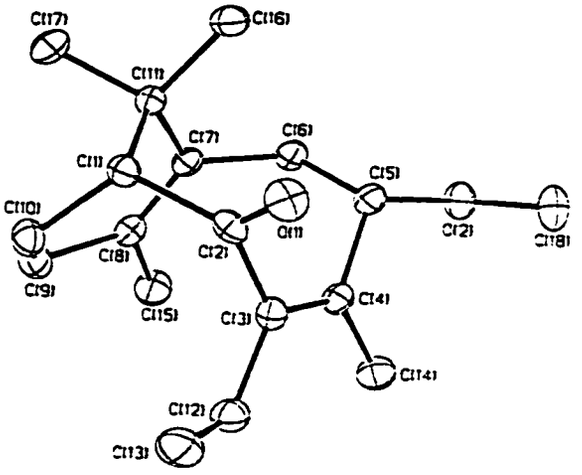


Figure 11: *Crystal Structure of Adduct* ***329***

However, rather than conformational isomerization, the enone **329** underwent facile Cope rearrangement, (commencing at ~60 °C), to give the bicyclo[2.2.2]octane system **330**. Experimentally this [3,3] sigmatropic rearrangement afforded the same bicyclic ketone **330** in 71% yield after 24 hours in refluxing toluene. It is noteworthy that the temperature of 110 °C is significantly less than is required for most carbocyclic rearrangements of this type.[170] Therefore, an attractive method for the preparation of densly substituted bicyclooctanes is provided. The reverse transformation from an oxy-Cope bicyclo[2.2.2]octene precursor was employed for previous approaches to the A/B taxane ring system.[171] The ease of the rearrangement in **329** is a consequence of the excellent alignment of the reactive diene units in a pre-organized chair-like conformation that mimics the required transition state (Figure 12). Single crytal X-ray analysis (Figure 11) confirmed the juxtaposition of the double bonds and revealed that the C_3-C_8 separation was 3.13 Å. This is less than the 3.2-3.3 Å separation required for the c-d distance of enediynes that undergo spontaneous cycloaromatization at room temperature.[172]

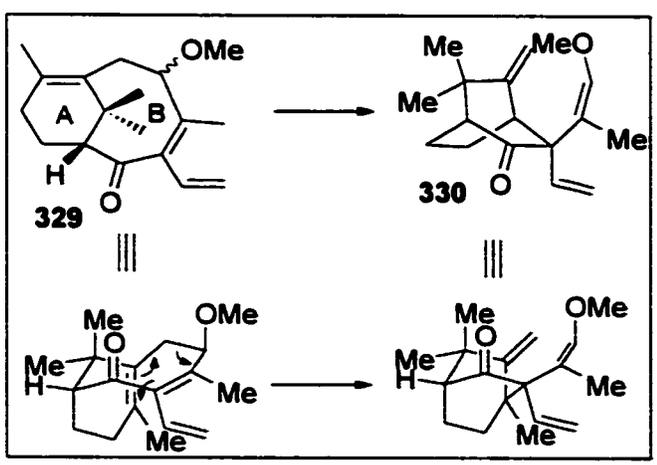
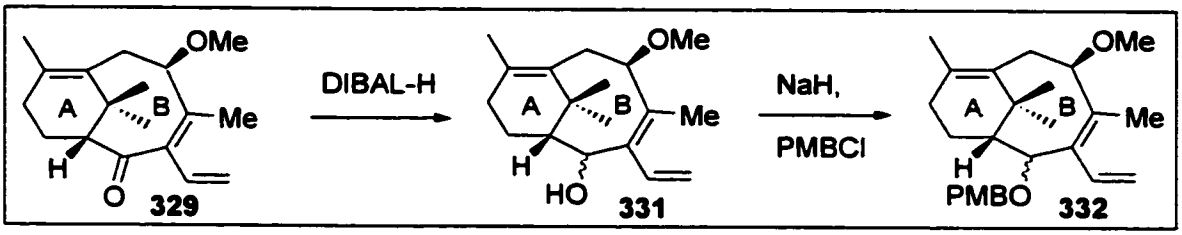


Figure 12: *Facile Cope Rearrangement*

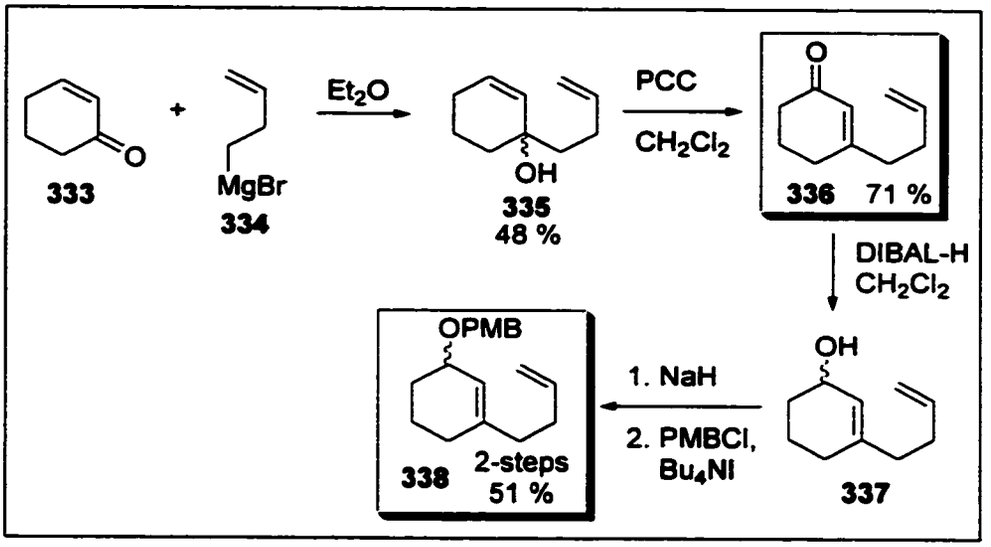
However, an additional beneficial influence from the carbonyl group is also implicated, as the isomerization was significantly retarded in the absence of the conjugated ketone. This was demonstrated by the behaviour of **332**, prepared by reduction of enone **329** to give the unstable alcohol **331** (~2:1 diastereomer ratio) which was subsequently protected as its *p*-methoxybenzyl ether **332**. This allylic ether was stable to prolonged reflux (20 h) in toluene, as well as 24 h in a sealed tube at an external temperature of 150 °C, and did not undergo rearrangement.



Scheme 74: *Derivatization of Cope Substrate*

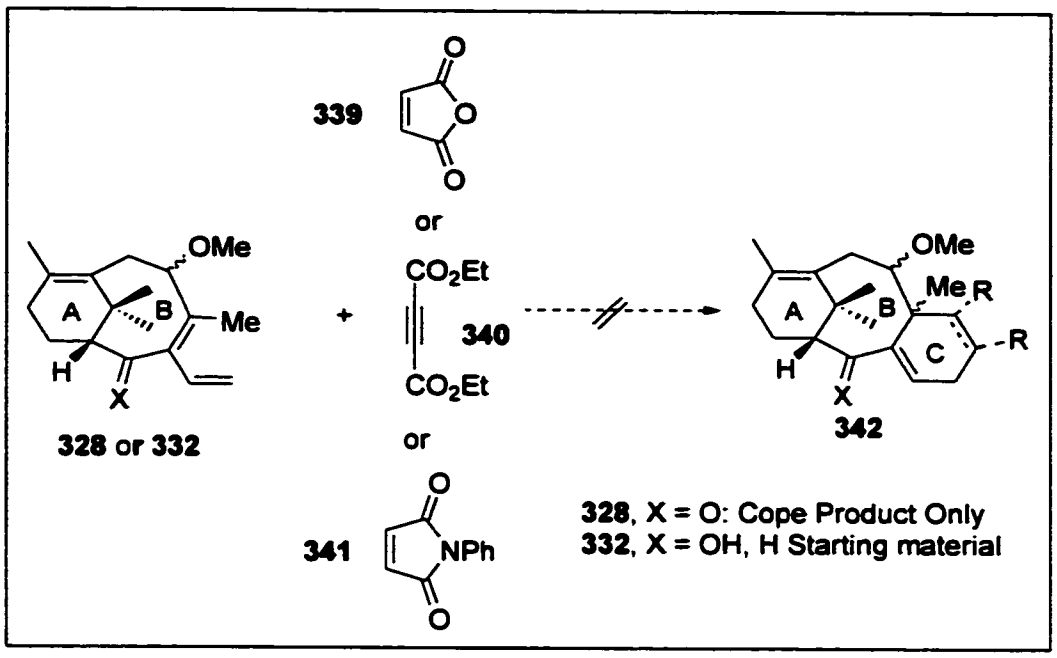
Additional evidence of the importance of the conjugated carbonyl and its electronic influence was provided by the ease with which the rearrangement occurred at 20 °C in the presence of a catalytic amount of Lewis acid (Et_2AlCl). Although the reaction give a complex mixture of products, there is clear evidence for the formation of the Cope product. The accelerating influence exerted by a conjugated carbonyl group in a carbocyclic [3,3] sigmatropic rearrangement does not appear to have been encountered previously. However, an early example of a conjugated cyclohexanone rearranging to a different cyclohexenone with trifluoroacetic acid at 25 °C is known.[173] In the case of **329** the related driving force to generate a new conjugated ketone is absent.

It is not yet clear the enone accelerated Cope rearrangement is a general phenomena. However, a simple cyclohexenone model did not rearrange at 110 °C (Scheme 75). Additional support for this contention is provided by the established influence of vinyl substituents on the rate of rearrangement. For example, both phenyl and cyano groups lower the enthalpy of activation for chair and boat transition states and vinyl substituents can also have an influence.[174] Recent evidence suggests an allylic methoxy also has an influence in anionic oxy-Cope rearrangements.[175] However, differentially substituted 1,5-dienes have not received systematic scrutiny and further studies are required to establish any magnitude of this potential conjugated carbonyl effect. Model studies were undertaken to determine the beneficial influence of the carbonyl group in simpler systems. However, extended heating of both **336** and **338** (toluene, sealed tube, 150 °C, 24 h.) showed no product observed which could be attributed from the Cope rearrangement. The cumulative effect in our system of a combination of steric and electronic effects may make this case relatively unique.



Scheme 75: *Model Studies for Cope Acceleration by Carbonyl Groups*

A number of attempts to cyclize the A/B-ring system that was prepared to form the C-ring *via* a Diels-Alder reaction were unsuccessful (Scheme 76). Spino and co-workers[176] reported cases where electron-withdrawing substituents at the 2- or 3-positions of dienes can accelerate the Diels-Alder reaction, even in cases when they are reacted with electron-deficient dienophiles. Thus, the first attempts all involved the 2-substituted carbonyl (**329**) with activated dienophiles (maleic anhydride (**339**), *N*-phenylmaleimide (**341**), diethyl acetylenedicarboxylate (**340**)). However, in all cases, the Cope reaction (to form **342**) occurred at a lower temperature than the desired Diels-Alder adduct. Reduction of the carbonyl and protection as its PMB-ether yielded the more traditional diene (**332**) for the Diels-Alder reaction. Again, no products were observed with the same three dienophiles. In these cases only starting material was recovered. In part this is a consequence of the "inside" methyl group that inhibits the formation of the required s-*cis*-diene conformer. For a successful solution to this dilemna in the decalin series, see Chapter III.



Scheme 76: *Diels-Alder Attempts at Obtaining the C-Ring*

In summary, our magnesium mediated carbometallation protocol has been extended to more complex systems. A direct route to AB ring building blocks for the taxanes has been established for future elaboration into the complete nucleus by different procedures. A new variant of the Cope rearrangement has been discovered in which enone functionality facilitates this [3.3] rearrangement in appropriate carbocyclic systems. In total, the procedures described above provide direct access to a number of useful unsaturated compounds and bicyclic ring systems that may be employed for a variety of synthetic objectives.

III. Tether-Controlled Cycloadditions

III-i. Introduction

A comparison of the influence of *cis*-isopropylidene acetal tether control groups versus *trans* tether control groups (i.e **343**) in the IMDA reaction has been examined (Figure 13). The beneficial influence of *cis*-isopropylidene acetal tether control groups, to facilitate the asymmetric synthesis of substituted decalins by intramolecular Diels-Alder reactions, is described. Compared to *trans*-acetonides these cases proceed under milder conditions to afford the *cis* fused adducts from an *endo* transition state. This strategy leads to the chiral non-racemic bicyclo[4.4.0]decane core of diverse natural products.

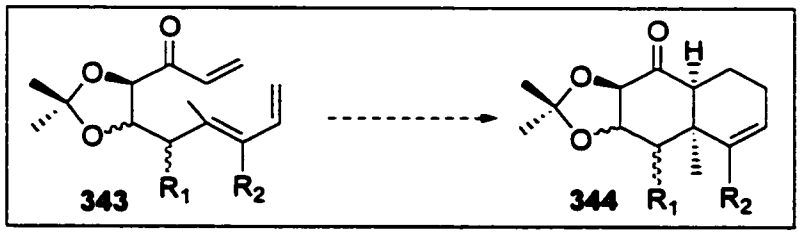


Figure 13: *Benefits of a* trans-*Acetal Tether*

A large number of natural products contain a decalin (bicyclo[4.4.0]decane) ring system as an important structural component.[177] These compounds, particularly the terpenoids, display a wide array of biological activities that have medicinal potential. Figure 14 illustrates two representative oxygenated examples. The fungal metabolite K-76 (**345**),[178] displays both anticomplement and antiinflammatory activity with potential for the treatment of arthritis, while phytocassane E (**346**)[179] is an antifungal agent.

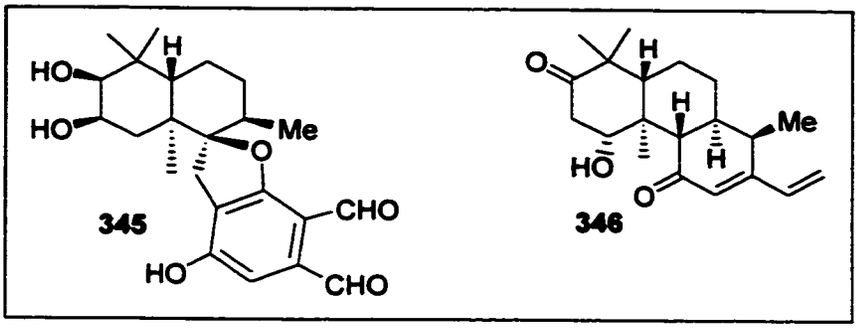


Figure 14: *Oxygenated Terpenoids*

Motivated in part, by our interest in the synthesis of taxoids.[180] the Fallis group have established that planar "tether control groups" (aromatic rings, *cis* double bonds) in the side chain have a dramatic influence on the ease of cyclization of substituted trienes in intramolecular Diels-Alder reactions (Figure 15).[181] Intramolecularity is often insufficient in and of itself to ensure the best level of facial selectivity in the Diels-Alder reaction. Trienes such as **347**, usually afford complex mixtures and require high temperatures to generate the corresponding adducts.[182] Incorporating a planar moiety, such as an olefin or an aromatic ring (e.g. **349** or **350**) should facilitate the transition state interaction between the reactive components (X,Y). Some representative reactions that have been reported which employ planar tether control groups include alkylations for formation of 10-membered rings,[183] radical cyclizations,[184] olefin metathesis[185] and cycloaddition of metal carbenes.[186]

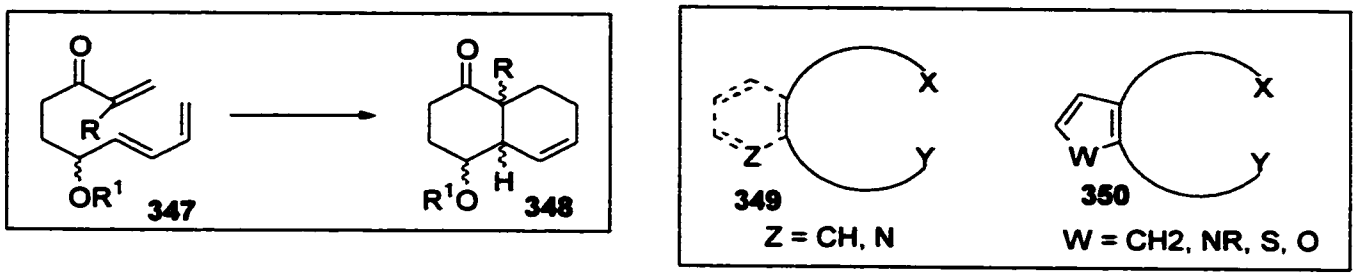
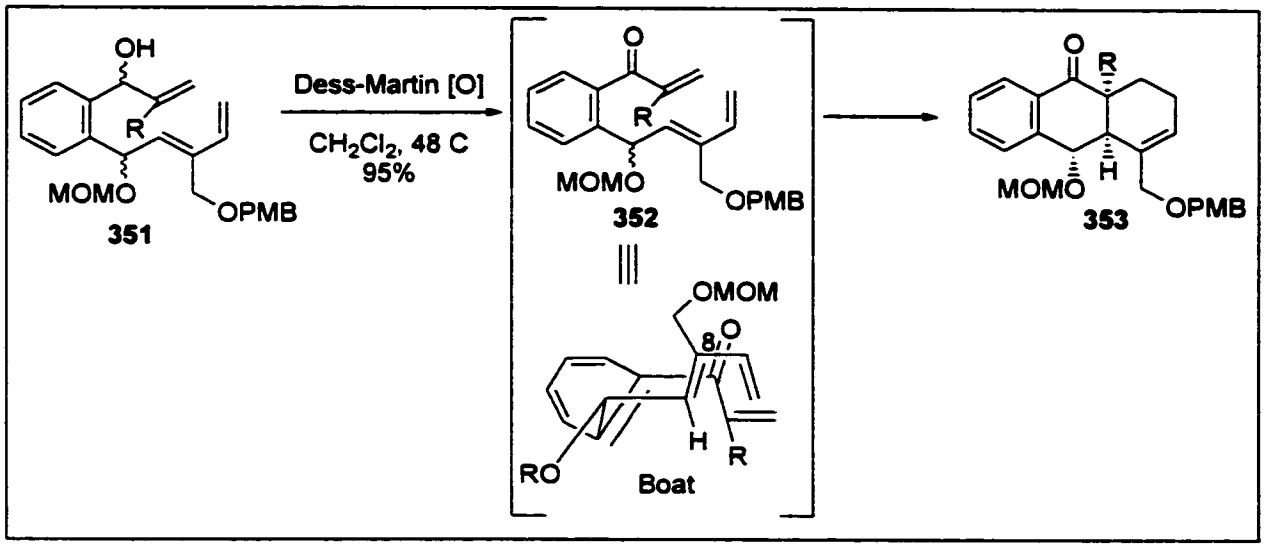


Figure 15: *Benefits of Employing a Tethering Group in the Diels Alder Reaction*

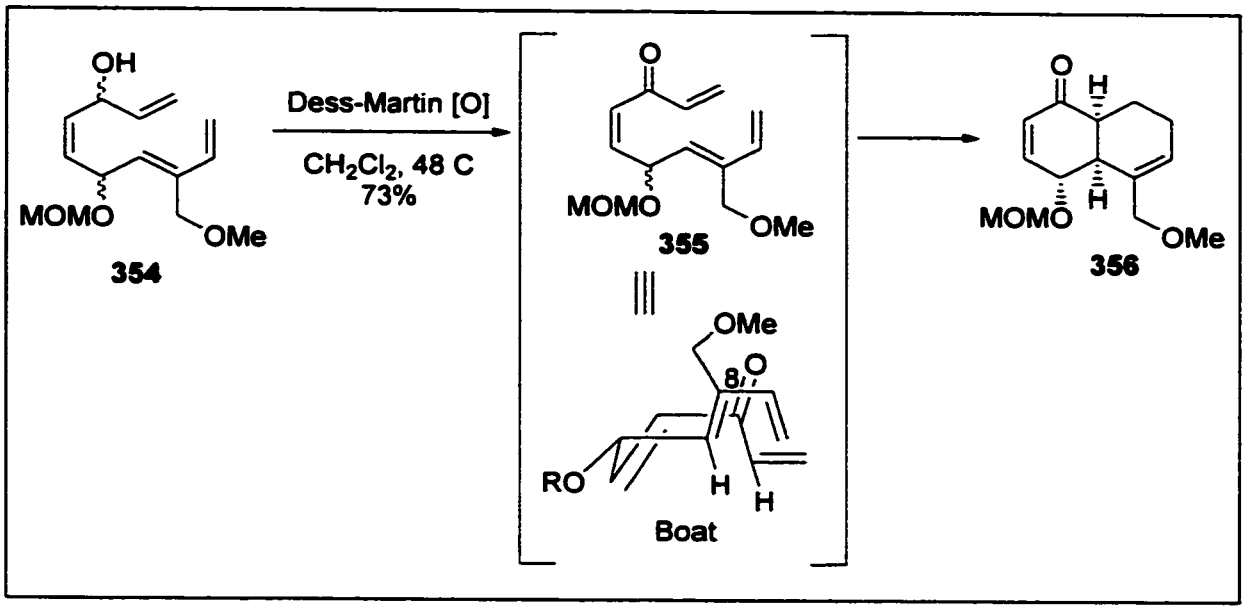
Introduction of functionality that limits the flexibility of the side chain should enhance the ease of a wide-variety of intramolecular reactions.

Fallis and co-workers demonstrated the incorporation of a phenyl ring as a planar tether control group (Scheme 77).[187] The reaction occurs spontaneously when gently warmed following oxidation to the eneone (**352**).



Scheme 77: *Aromatic Planar Tether-Control Group*

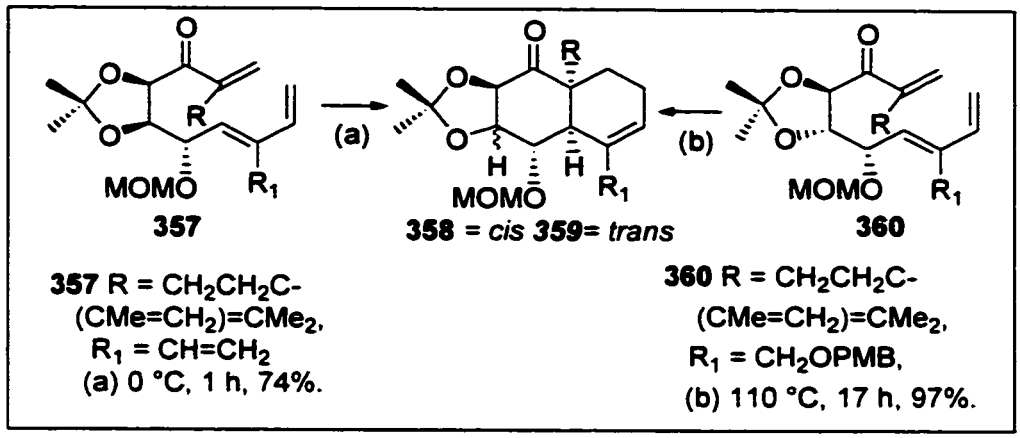
This planar tether control was extended to a *cis*-olefin (**354**) that also demonstrated similar benefits (Scheme 78).



Scheme 78: *Non-Aromatic Planar Tether-Control Group*

Subsequent research has demonstrated that tartrate and carbohydrate derived *trans*-isopropylidene acetals provide a significant improvement.[188] They limit the flexibility of the side chain to impose a restricted geometry on the reactive components and afford chiral non-racemic adducts. In addition, they are usually available in both optical series. We wish to report that *cis*-isopropylidene acetals are even better for inducing the overlap required for facile cyclization. There is a significant rate increase, permitting lower reaction temperatures, and it should also be possible to employ sterically encumbered dienes to generate the core nuclei of **345** and **346**. Preliminary results that demonstrate these advantageous features are illustrated in Scheme 79 with highly substituted, closely related, acetal isomers. Ketone **357** cyclized to the decalin **358**

at 0 °C without the aid of Lewis acid, while the *trans* isomer **360** required heating in refluxing toluene for 17 hours. Thus it appeared that in closely related systems, *cis* acetal improved the cycloaddition reaction, relative to the *trans* series, and leads to the same stereochemical result.



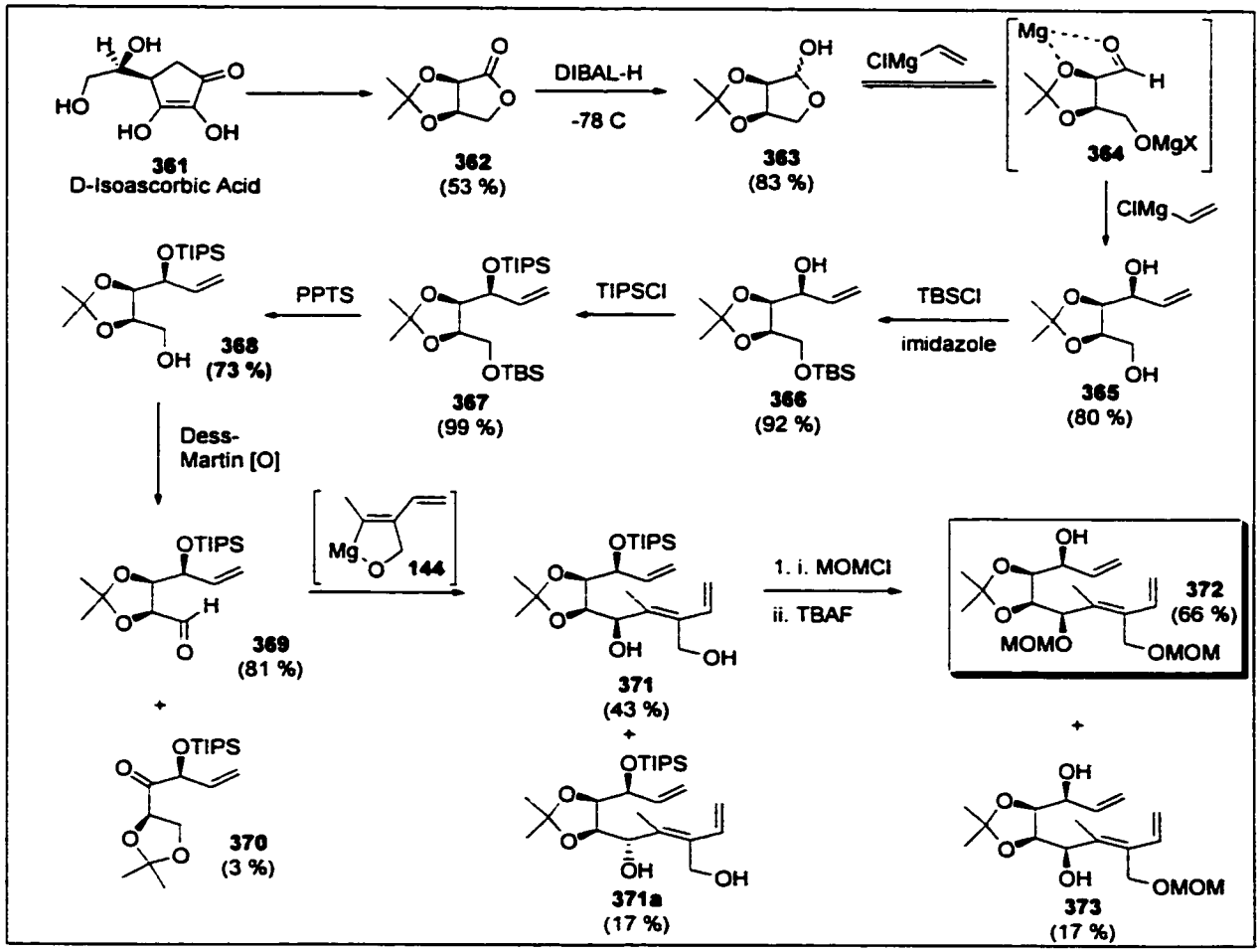
Scheme 79: *Comparison of* cis- *and* trans- *Acetal Cycloadditions*

It is usually difficult to conduct cycloadditions with an "inside" substituent that inhibits the formation of the required s-*cis*-diene conformer.[189] However, the application of this strategy to the synthesis of terpenoid skeletons requires this inside methyl feature on the diene.

III-II. Results

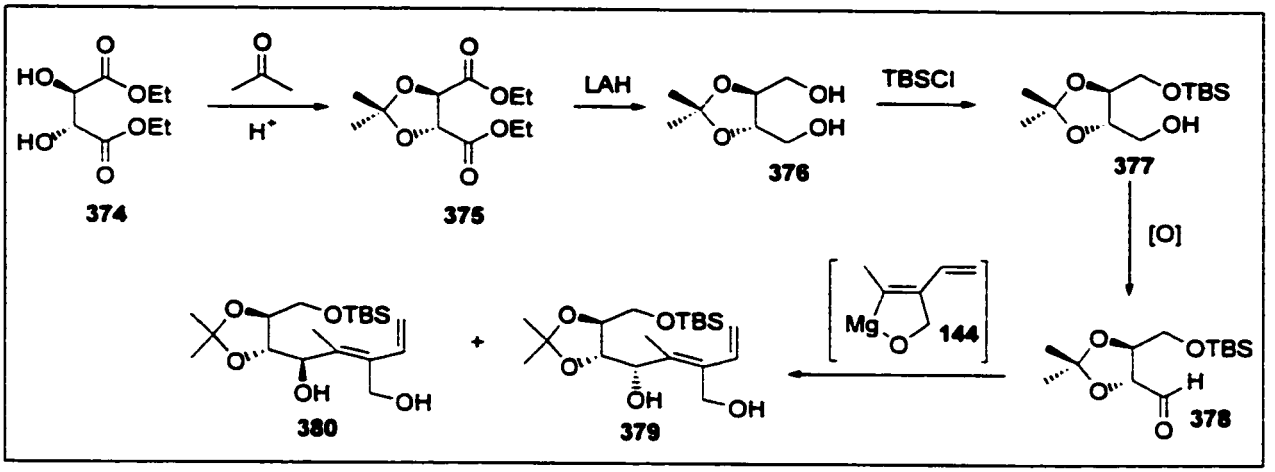
In order to investigate a direct comparison of the *trans*- versus *cis*-acetonide unit, two routes to the Diels Alder precursors were examined. The synthesis of the *cis*-system began with the known D-isoascorbic acid (**361**).[190] The lactone (**362**) that is obtained is selectively reduced to its hemi-acetal (**363**) and the Grignard addition yields the

corresponding diol (**365**). The protected secondary alcohol (**368**) is then prepared from selective protection of the primary alcohol (TBSCl), protection of the secondary alcohol and finally selective deprotection of the primary silyl-ether. Oxidation of the resulting primary alcohol (**368**) followed by Grignard–type addition of the previously described carbometallation species (**144**) yields the diol and the rearranged product (**370**). This diol is then protected as its bis-MOM ether and deprotection of the silyl ether reveals the requisite allylic alcohol (**372**). This is the reduced Diels-Alder precursor required, accompanied by some mono-protected diol (**373**).



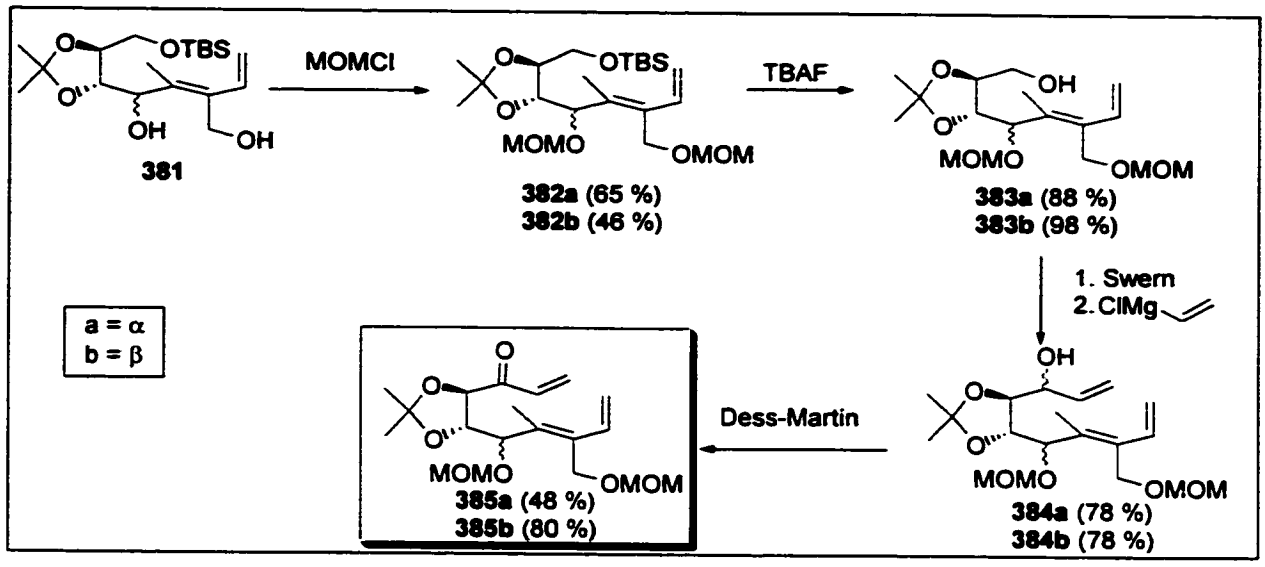
Scheme 80: *Preparation of a* cis*-Tether Control Group Substrate*

The route to the *trans* Diels Alder precursor began with the known preparation of the aldehyde (**378**) derived from diethyl tartrate (**374**).[191] Ketalization of the diol followed by exhaustive reduction of the ester yielded the diol (**376**) that wad selectively mono-protected to yield the silyl-ether alcohol (**377**). Oxidation led to the required aldehyde (**378**). The carbometallated species (**144**) was added to the aldehyde to yield an epimeric mixture of diols (**379** and **380**) that were successfully separated.



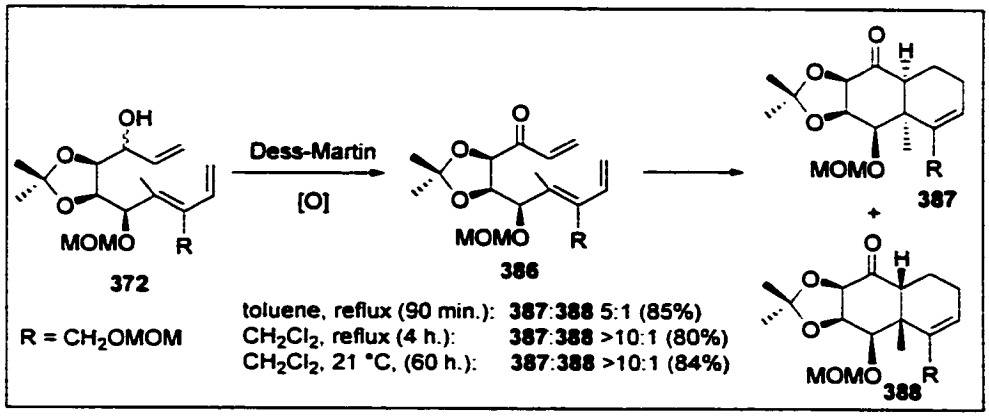
Scheme 81: *Preparation of a* trans-*Tether Control Group Substrate*

The diastereomers were brought forward separately, in a parallel sequence of reactions (Scheme 82). Bis-protection of the resulting diol followed by deprotection of the silyl-ether yielded the desired primary alcohol (**383**). Swern oxidation and *in-situ* Grignard addition allowed for the formation of the allylic alcohol as an inconsequential mixture of diastereoisomers (**384**). The alcohol was subsequently oxidized to the required Diels-Alder precursors (**385a**, **385b**).



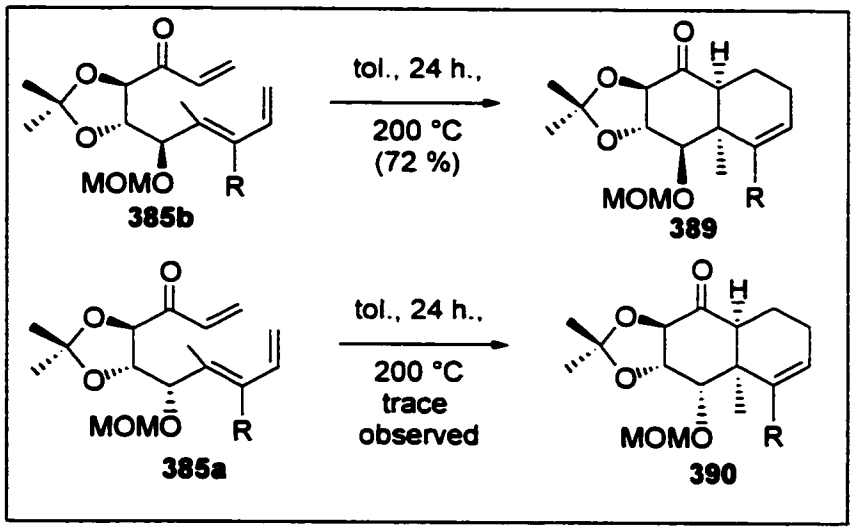
Scheme 82: *Preparation of a* trans-*Tether Control Group Substrate*

In order to obtain a preliminary indication of the cumulative effects of the *cis*-acetate and the methyl substituent diene, oxidation of the secondary alcohol **372** with Dess-Martin periodinane in dichloromethane generated the decatriene ketone **386** *in situ*, which cyclized spontaneously at room temperature (21 °C) over 60 hours or more efficiently in 4 hours at 40 °C during the oxidation reaction (87 %). The mild conditions for this cycloaddition of a sterically encumbered system are particularly expedient.



Scheme 83: cis-*Tether Control Diels Alder Reaction*

Additionally, conclusive evidence that demonstrated the distinct synthetic advantage of *cis* compared to *trans* acetonides as intramolecular Diels-Alder precursors, was provided by **385a** and **385b** (Scheme 84). Compound **386** cyclized at 21 °C and yet **385b**, its C5 acetal epimer, required 24 hours in a sealed tube at 200 °C to generate the corresponding adduct in 82 % yield. Further, the epimer (**385a**) of the MOM-ether centre also plays a role in reducing the rate of the reaction. Although some product was observed under the given conditions, the reaction is much more sluggish.



Scheme 84: trans-*Tether Control Diels Alder Reaction*

There are four possible transition state geometries for these *cis*-decatrienones of which Figure 16 illustrates the two most important *endo* conformations. Previous investigations have established that *cis*-fused boat-like transition states are usually favored in related systems.[192] As illustrated, the boat-like orientation is clearly preferred compared to the competing chair-like conformation, due to the minimization of non-bonded interactions in the boat-like arrangement. Although these interactions must play

a role due to the observed selectivity, performing the reaction at higher temperatures overrides this and decreases the selectivity (above).

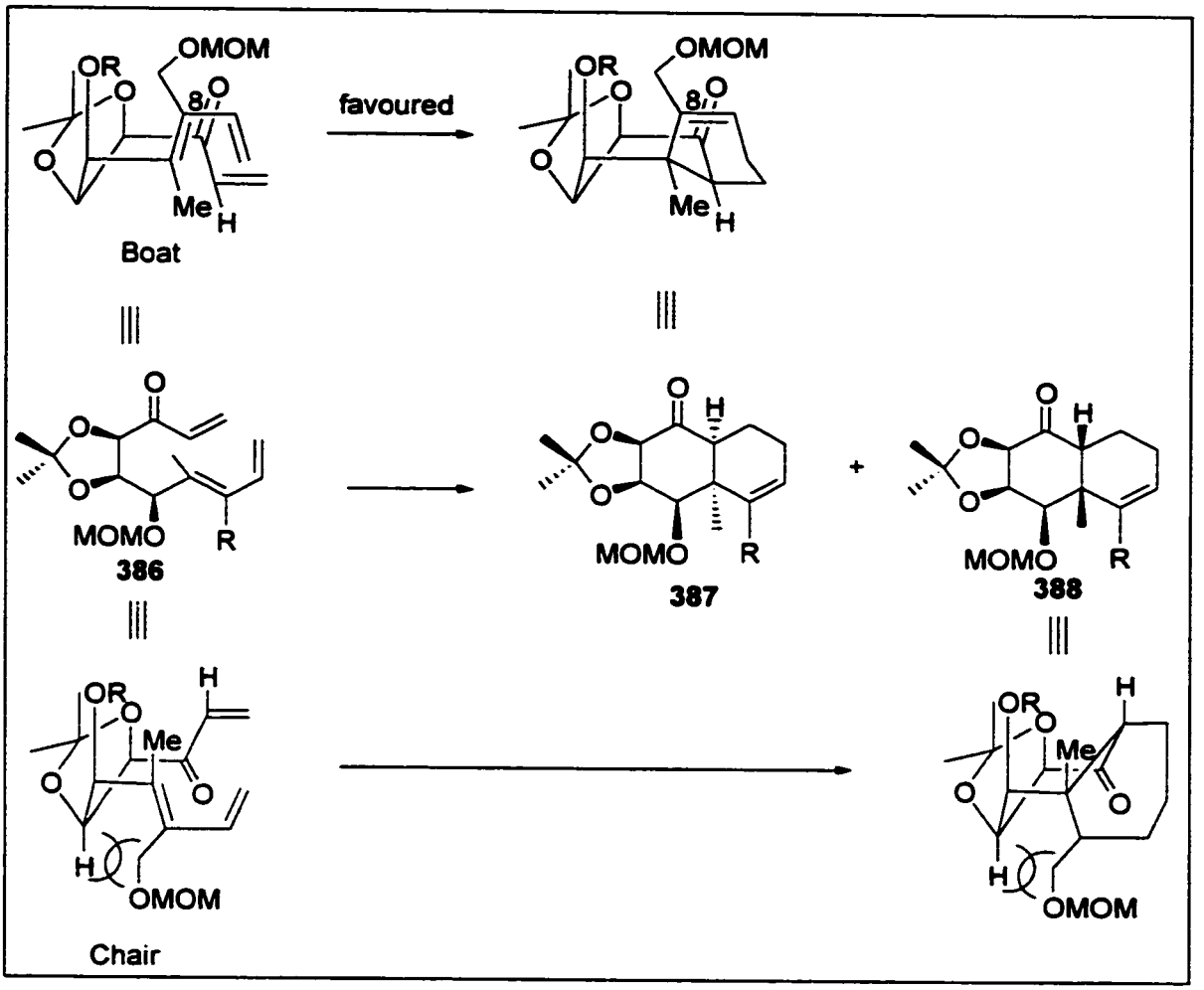


Figure 16: *Cycloaddition endo Transition State Conformations for* cis *acetals*

The *trans* series cycloaddition necessarily must go through an alternative transition state due to the fact that the stereochemical outcome of the Diels-Alder reaction is identical to that obtained in the *cis* series. As seen in Figure 17 and Figure 18, the Diels-Alder reaction occurs *via* a chair-like transition state. This minimizes the non-bonded interactions and is the clearly favoured route to the decalin ring illustrated.

Interestingly, despite the high temperatures required for the *trans* series cycloaddition, no product is observed from the alternative transition states, in contrast to the *cis* series.

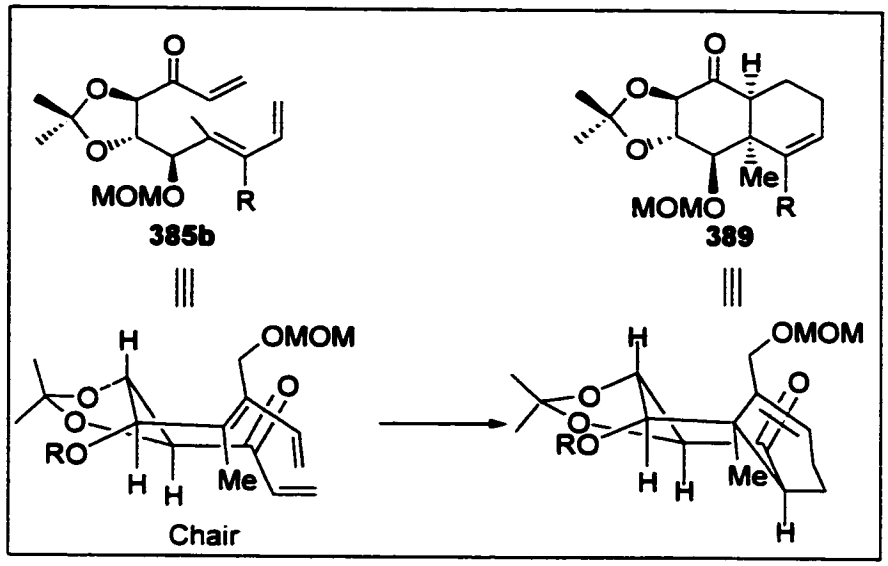


Figure 17: *Cycloaddition endo Chair Transition State Conformations for* trans *acetals*

Further, the epimer at the MOM-ether carbon was shown to produce only trace amounts of the Diels-Alder adduct. This is presumably due to the fact that this substituent must be axial in the chair transition state, thus further retarding the reaction.

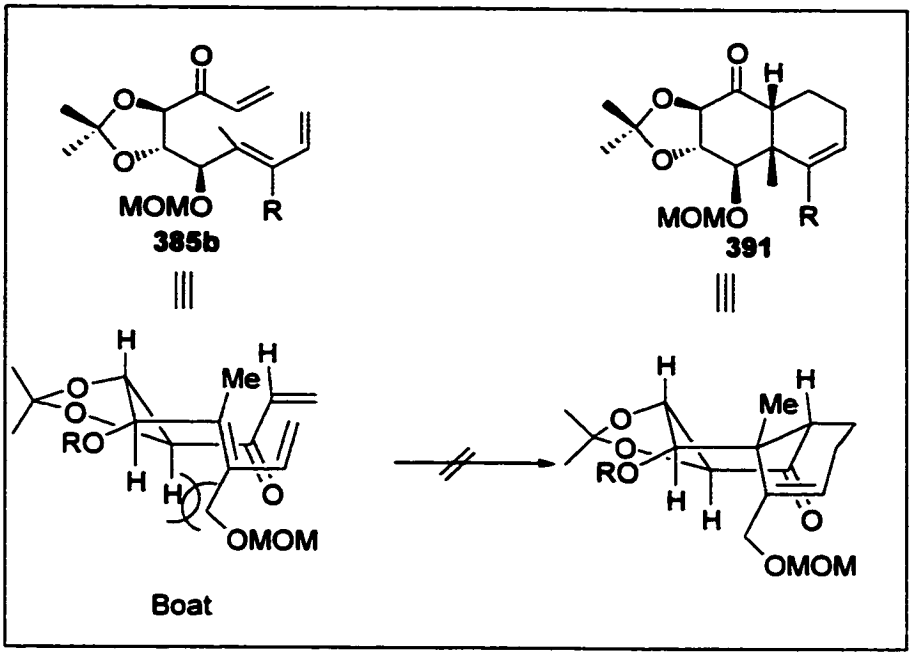


Figure 18: *Cycloaddition endo Chair Transition State Conformations for* trans *acetals*

In conclusion, we have established the advantage of *cis*-acetonides as tether control groups for the synthesis of decalins from highly substituted decadienones. This protocol is particularly useful for difficult substitution patterns. This strategy affords rapid entry to highly oxygenated multicyclic skeletons.

IV. Experimental

General. Melting points were determined in capillary tubes with a Thomas-Hoover Unit-Melt apparatus and are uncorrected. Infrared (IR) spectra were obtained either as neat films, or as a thin film of a dichloromethane solution of the compound on sodium chloride discs. All IR spectra were recorded on a Bonem Michelson 100 Fourier transform infrared spectrometer (FT-IR) and the data are reported in reciprocal centimeters (cm^{-1}). Proton magnetic resonance spectra (^1H NMR) were measured at 500 MHz with a Bruker AMX500 or at 200 MHz with a Varian Gemini spectrometer in hexadeuterobenzene unless otherwise stated. Carbon magnetic resonance were measured (^{13}C NMR) at 125 MHz (Bruker) or 50 MHz (Varian) in C_6D_6 unless otherwise noted. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (δ scale). The multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad), , number of protons and coupling constants (reported in Hz) are indicated in parentheses. Optical rotations were recorded on a Perkin-Elemer 241 polarimeter operating at 589 nm. Mass spectra (MS) were determined on a V.G. micromass 7070 HS instument using an ionization energy of 70 eV. Gas chromatograph – mass spectral (GC-MS) analyses were determined on a Hewlett-Packard 5890 Series II gas chromatograph – 5971 Mass Selective Detector equipped with a 12.5 m capillary column (0.2 mm i.d.) coated with cross-linked dimethylsilicone (0.33 μm). Elemental analyses were performed at M-H-W Laboratories, Phoenix, Arizona, USA. The purity of all title compounds was judged to be > 95 % as determined by a combination of GC-MS, ^1H NMR and ^{13}C NMR analyses.

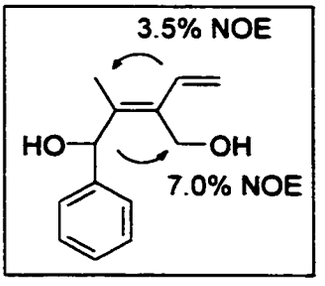
Unless otherwise stated, all non-aqueous reactions were performed under an atmosphere of dry nitrogen in flame or oven dried glassware equipped with a magnetic stir bar and a rubber septum. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents. Reactions were monitored by analytical thin layer chromatography (TLC) using commercial aluminum sheets pre-coated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck). The TLC spots were viewed under ultraviolet light and by heating the TLC plate after treatment, with either a 5% solution of ammonium molybdate in 10% aqueous sulfuric acid (w/v), or a *p*-anisaldehyde staining solution (80 mL 95% ethanol, 2.9 mL sulfuric acid, 0.86 mL acetic acid, 2.1 mL *p*-anisaldehyde). Product purification by conventional and flash column chromatography was performed using E. Merck Silica Gel (70-230 or 230-400 mesh). Solutions in organic solvents were dried over anhydrous magnesium sulfate and stripped of solvents with a rotary evaporator connected to an air or water aspirator. Trace solvents were removed on a vacuum pump. All compounds were stored at – 15 °C in vials flushed with nitrogen. Benzaldehyde was distilled and stored over activated 4 Å molecular sieves at 5 °C. Vinylmagnesium chloride was purchased from Fluka Chemika-BioChemika and titrated against diphenyl ditelluride.[193] The standard workup procedure involves addition of saturated NH_4Cl and stirring for 20 min. The organic layer was separated and the aqueous phase extracted with ether. The combined organic layers were dried, filtered and concentrated.

Petroleum ether refers to a mixture of hydrocarbons with a boiling range of 30 – 60 °C. Anhydrous diethyl ether (ether), anhydrous tetrahydrofuran (THF) were freshly distilled from benzophenone/sodium. Dry benzene, toluene, dimethylformamide (DMF),

dichlormethane (CH_2Cl_2), triethylamine, diisopropylamine, diisopropylethylamine and cyclohexane were distilled from NaH or CaH. All commercial starting materials were purchase from Aldrich Chemical Company unless otherwise stated.

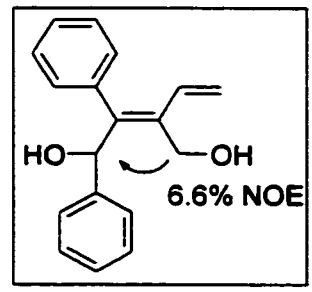
(2*Z*, 1*RS*)-3-Ethenyl-2-methyl-1-phenyl-2-butene-1,4-diol (155, R' = H).

Vinylmagnesium chloride (6.6 mL, 1.3 M in THF, 8.6 mmol) was added to a solution of 2-butyn-1-ol (**139**) (0.20 mL, 2.6 mmol) in cyclohexane (5 mL) at 22 °C. The solution was heated at reflux for 19 h. The solution was cooled to 0 °C and benzaldehyde (0.87 mL, 8.6 mmol) was added. The mixture was stirred 5 min at 0 °C followed by 1 h at 22 °C. Standard workup followed by chromatography (3:1 to 1:3 petroleum ether/ether) yielded the title compound as a yellow solid; mp 132-137 °C; ^{1}H NMR ∂ 1.59 (s, 3H), 3.23 (s, br, 2H), 4.25 (d, 1H, J = 11.9), 4.43 (d, 1H, J = 11.9), 5.07 (dd, 1H, J = 11.2, 0.7), 5.40 (dd, 1H, J = 17.5, 1.2), 5.89 (s, 1H), 6.54 (dd, 1H, J = 17.5, 11.1) 7.05-7.44 (m, 5H); ^{13}C NMR ppm 13.2, 57.6, 72.1, 114.7, 126.1, 127.1, 128.5, 133.0, 134.6, 141.2, 142.5; IR (NaCl) 3374, 2921, 1661, 1601, 1494, 1450, 1014, 910, 752, 701; HRMS (M^+ - H_2O) calc'd 186.1045, found 186.1050; Anal calc'd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. found: C, 76.55; H, 8.13.



(2*Z*, 1*RS*)-3-Ethenyl-1,2-diphenyl-2-butene-1,4-diol (155b).

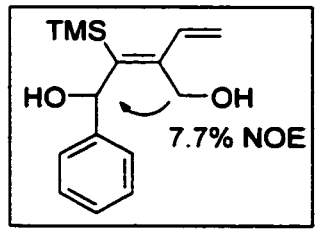
Vinylmagnesium chloride (4.0 mL, 1.3 M in THF, 5.2 mmol) was added to a solution of 3-phenyl-2-propyn-1-ol (**139a**) (0.22 g, 1.6 mmol) in cyclohexane (5 mL) at 22 °C. The solution was heated at reflux for 19 h. The solution was cooled to 0 °C and benzaldehyde (0.53 mL, 5.2 mmol) was added. The mixture was stirred 5 min at 0 °C followed by 1 h at 22 °C. Standard workup followed by flash column chromatography (3:1 to 1:3 petroleum ether/ether) yielded the title compound as a white solid; mp 75 - 79 °C; ^{1}H NMR ∂ 3.45 (s, br, 1H), 4.05 (s, br, 1H), 4.54 (dd, 2H, *J*-=11.8, 27.2), 4.90 (dd, 1H, *J* = 11.2, 0.9), 5.42 (d, 1H, *J* = 17.6), 6.12 (s, 1H), 6.33 (dd, 1H, *J* = 17.6, 11.1), 6.95-7.05 (m, 6H), 7.05-7.10 (m, 2H) 7.3 (d, 2H, *J* = 7.6); ^{13}C NMR ppm 57.5, 73.6, 115.0, 126.6, 127.2, 127.2, 127.9, 128.2, 130.5, 135.4, 136.2, 138.5, 142.4, 146.6; IR (NaCl) 3357, 3066, 1492, 1448, 1055, 1012, 912, 754, 704; HRMS (M^+) calc'd 266.1307, found 266.1320; Anal calc'd for $C_{13}H_{16}O_2$: C, 81.17; H, 6.81. found: C, 81.34; H, 6.92.



(2*E*, 1*RS*)-3-Ethenyl-2-(trimethylsilyl)-1-phenylbutene-1,4-diol (155a).

Vinylmagnesium chloride (5.3 mL, 1.4 M in THF, 7.4 mmol) was added to a solution of 3-(trimethylsilyl)-2-propyn-1-ol (**139a**) (0.30 g, 2.3 mmol) in cyclohexane (5 mL) at 22 °C. The solution was heated at reflux for 19 h. The solution was cooled to 0 °C and

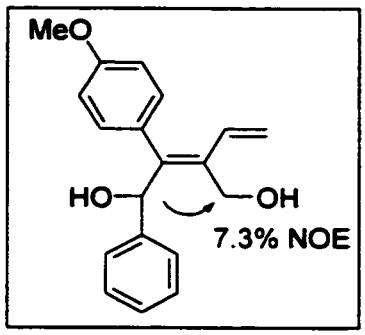
benzaldehyde (0.75 mL, 7.4 mmol) was added. The mixture was stirred 5 min at 0 °C followed by 1 h at 22 °C. Standard workup followed by chromatography (3:1 to 1:3 petroleum ether/ether) yielded the title compound as a yellow oil; ^{1}H NMR ∂ 0.16 (s, 9H), 2.42 (s, br, 1H), 3.54 (s, br, 2H), 4.17 (dd, 2H, J = 18.9, 11.7), 5.10 (dd, 1H, J = 11.1 , 0.8), 5.41 (dd, 1H, J = 17.3, 0.9) 5.85 (s, 1H), 6.85 (dd, 1H, J = 17.3,11.1), 7.06 (dt, 1H, J = 7.3, 0.7) 7.15-7.19 (m, 2H), 7.42-7.44 (m, 2H); ^{13}C NMR ppm 1.8, 58.1, 73.4, 115.3, 126.3, 127.0, 128.4, 137.9, 143.8, 147.1, 148.6; IR (NaCl) 3379, 2956, 2898, 1494, 1450, 1251, 1008, 911, 844, 755, 698; HRMS (M^+ - H_2O) calc'd 244.1284, found 244.1277.



(2*Z*, 1*RS*)-3-Ethenyl-2-(4-methoxyphenyl)-1-phenyl-2-butene-1,4-diol (155c)

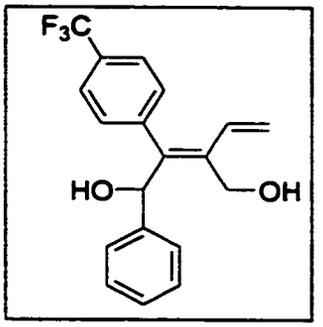
Vinylmagnesium chloride (5.2 mL, 1.4 M in THF, 7.3 mmol) was added to a solution of 3-(4-methoxyphenyl)-2-propyn-1-ol (**139c**) (0.38 g, 2.3 mmol) in THF (5 mL) at 22 °C. The solution was heated at reflux for 19 h. The solution was cooled to 0 °C and benzaldehyde (0.75 mL, 7.4 mmol) was added. The mixture was stirred 5 min at 0 °C followed by 1 h at 22 °C. Standard workup followed by chromatography (3:1 to 1:3 petroleum ether/ether) yielded the title compound as a yellow oil; ^{1}H NMR ∂ 3.22 (s, 4H), 3.91 (s, br, 1H), 4.56 (m, 2H), 4.96 (dd, 2H, J = 11.2, 1.0), 5.46 (dd, 1H, J = 17.7, 1.0), 6.14 (s, 1H) 6.43 (dd, 1H, J = 17.7, 11.1), 6.62 (dd, 2H, J = 8.9,1.2), 6.91 (d, 2H, J

= 8.1) 6.99-7.05 (m, 1H), 7.06 - 7.15 (m, 2H) 7.36 (m, 2H); ^{13}C NMR ppm 54.6, 57.6, 73.6, 113.5, 114.7, 126.6, 127.2, 128.3, 130.5, 131.8, 135.6, 136.5, 142.7, 146.4, 159.2; IR (NaCl) 3377, 2925, 1605, 1509, 1245, 1032; HRMS (M^+) calc'd 296.1413; found 296.1419.



(2*Z*, 1*RS*)-3-ethenyl-2-(4-trifluoromethylphenyl)-1-phenyl-2-butene-1,4-diol (155d). Vinylmagnesium chloride (4.8 mL, 1.5 M in THF, 7.2 mmol) was added to a solution of 3-(4-trifluoromethylphenyl)-2-propyn-1-ol (**139d**) (0.45 g, 2.2 mmol) in cyclohexane (5 mL) at 22 °C. The solution was heated at reflux for 19 h. The solution was cooled to 0 °C and benzaldehyde (0.73 mL, 7.2 mmol) was added. The mixture was stirred 5 min at 0 °C followed by 1 h at 22 °C. Standard workup followed by chromatography (3:1 to 1:3 petroleum ether/ether) yielded the title compound as an off-white solid; mp 108 - 109 °C; ^{1}H NMR ∂ 2.41 (s, br, 1H), 3.26 (s, br, 1H), 4.39 (dd, 2H, J = 27.5, 1.0), 4.88 (d, 1H, J = 11.2), 5.34 (d, 1H, J = 17.6), 5.94 (s, 1H) 6.04 (dd, 1H, J = 17.5, 11.1), 6.81 (d, 2H, J = 7.4), 6.97-7.06 (m, 3H) 7.12-7.20 (m, 4H); ^{13}C NMR ppm 57.4, 73.0, 115.8, 122.7 (q, $^1J_{C\text{-}F}$ =272.1), 124.7, 126.4, 127.5, 129.4 (q, $^2J_{C\text{-}F}$ = 32.4), 130.9, 135.5, 135.8, 141.7,

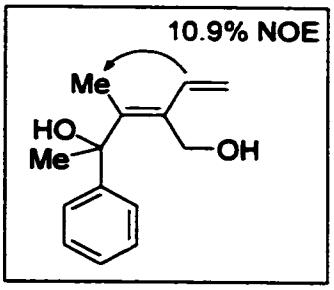
142.2, 145.2; IR (NaCl) 3353, 2979, 1615, 1326, 1108, 1019; HRMS (M^+ - H_2O) calc'd 316.1076; found 316.1050; Anal calc'd for $C_{19}H_{17}O_2F_3$: C, 68.26; H, 5.13. found: C, 68.40; H, 5.21.



(3*Z*, 2*RS*)-4-ethenyl-3-methyl-2-phenyl-3-penten-2,5-diol (155, R' = Me)

Vinylmagnesium chloride (5.7 mL, 1.5 M in THF, 8.6 mmol) was added to a solution of 2-butyn-1-ol (**139**) (0.45 g, 2.2 mmol) in cyclohexane (5 mL) at 22 °C. The solution was heated at reflux for 19 h. The solution was cooled to 0 °C and acetophenone (1.00 mL, 8.6 mmol) was added. The mixture was stirred 5 min at 0 °C followed by 1 h at 22 °C. Standard workup followed by chromatography (3:1 to 1:3 petroleum ether/ether) yielded the title compound as a yellow oil; ^{1}H NMR ∂ 1.50 (s, 3H), 1.62 (s, 3H), 2.98 (s, br, 1H), 4.09 (s, br. 1H), 4.26 (dd, 2H, J = 29.8, 11.8), 5.06 (dd, 1H, J = 11.2, 1.0) 5.39 (dd, 1H, J = 17.4, 1.1), 6.63 (dd, 1H, J = 17.7,11.1), 7.02 - 7.05 (m, 1H), 7.09 - 7.15 (m, 3H), 7.34 - 7.37 (m, 2H); ^{13}C NMR ppm 18.2, 30.5, 58.9, 78.6, 114.2, 125.6, 127.0, 128.3, 128.4, 134.4, 136.4, 144.0, 149.3; IR (NaCl) 3335, 2981, 2923, 1951, 1816, 1618, 1492, 1442,

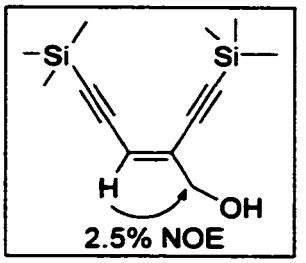
1212, 1158, 1070, 1030, 994, 908, 765; HRMS (M^+ - H_2O) calc'd 200.1202; found 200.1189.



(3*E*)-3-Methanol-1,6-di-(trimethylsilyl)-3-hexen-1,5-diyne (186)

Vinylmagnesium chloride (2.15 mL, 1.5 M in THF, 3.2 mmol) was added to a solution of TMS-acetylene (0.46 mL, 0.70 g/mL, 3.2 mmol) in cyclohexane (1 mL) at 22 °C. The solution was heated at reflux for 15 min followed by 30 min at 22 °C. This solution was then transferred *via* canula to a flask containing the di-yne-alkoxide (from **185**) (0.21 g, 1.4 mmol) in cyclohexane (1 mL). The resulting solution was heated at reflux for 72 h., cooled to 0 °C and quenched with NH_4Cl. Standard workup followed by chromatography (10:1 to 1:1 petroleum ether/ether) yielded the title compound as a yellow oil (0.13 g, 36 %); ^{1}H NMR ∂ 0.21 (s, 9H), 0.24 (s, 9H), 0.75 (s, br, 1H), 3.77 (m, br, 2H), 5.99 (t, 1H, J = 1.9); ^{13}C NMR ppm 0.0, 0.1, 64.4, 102.1, 102.2, 103.3,

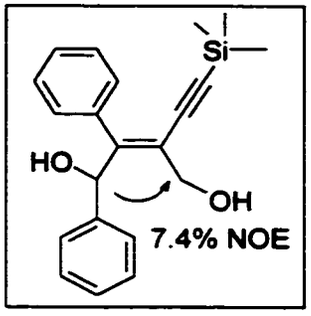
103.5,136.1; IR (NaCl) 3356, 2961, 2900, 2139, 1252, 887, 845, 760, 702; HRMS (M^+) calc'd 250.1210; found 250.1202.



***(2Z, 1RS)*-1,2-Diphenyl, 2-((trimetylsilyl)ethynyl)-2-buten-1,4-diol (183)**

Vinylmagnesium chloride (4.2 mL, 1.5 M in THF, 6.4 mmol) was added to a solution of TMS-acetylene (0.9 mL, 0.70 g/mL, 6.4 mmol) in cyclohexane (2.7 mL) at 22 °C. The solution was heated at reflux for 30 min followed by 30 min at 22 °C. This solution was then transferred *via* canula to a flask containing the yne-alkoxide (from **139**) (0.37 g, 2.8 mmol) in cyclohexane (1.8 mL). The resulting solution was heated at reflux for 65 h, cooled to 0 °C and quenched with freshly distilled benzaldehyde (0.9 mL, 1.04 g/mL, 9.1 mmol). Standard workup followed by chromatography (3:1 to 1:1 petroleum ether/ether) yielded the title compound as a yellow oil (0.46 g, 50 %); ^{1}H NMR ∂ 0.00 (s, 9H), 2.15 – 2.45 (m, 1H), 2.71 – 3.03 (m, 1H), 4.31 (s, broad, 2H), 5.80 (s, br, 1H), 6.97 – 7.07 (m, 5H), 7.23 – 7.29 (m, 5H); ^{13}C NMR ppm -0.3, 61.8, 73.5, 99.2, 105.9, 123.2, 126.6, 127.4, 127.6, 127.7, 128.4 129.9139.5, 142.0, 153.4; IR (NaCl) 3392, 2960, 2146, 1448,

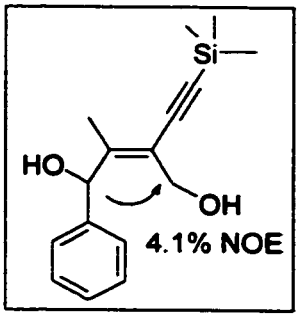
1251, 1017, 845, 760, 699; HRMS (M^+ - H_2O) calc'd 318.1441; found 318.1438. Anal calc'd for $C_{21}H_{24}O_2Si$: C, 74.96; H, 7.19. found: C, 75.12; H, 7.04.



***(2Z, 1RS)*-2-Methyl-1-phenyl, 2-((trimetylsilyl)ethynyl)-2-buten-1,4-diol (183a)**

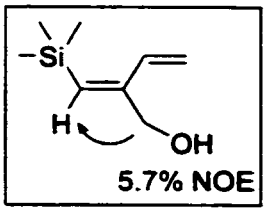
Vinylmagnesium chloride (5.7 mL, 1.5M in THF, 8.6 mmol) was added to a solution of TMS-acetylene (0.8 mL, 0.70 g/mL, 5.9 mmol) in cyclohexane (5 mL) at 22 °C. The solution was heated at reflux for 30 min followed by 30 min at 22 °C. To this solution was then added the yne-ol (**139**) (0.20 mL, 2.7 mmol) and the resulting solution was heated at reflux for 17 h., cooled to 0 °C and quenched with freshly distilled benzaldehyde (0.9 mL, 1.04 g/mL, 8.6 mmol). Standard workup followed by flash column chromatography (3:1 to 1:1 petroleum ether/ether) yielded the title compound as a yellow oil (0.04 g, 5%); ^{1}H NMR ∂ 0.19 (s, 9H), 1.97 (s, 3H), 4.13 (d, 1H, J = 11.8), 4.30 (d, 1H, J = 11.8), 5.62 (s, br, 1H), 7.05 – 7.08 (m, 1H), 7.13 – 7.16 (m, 2H), 7.36 – 7.38 (m, 5H); ^{13}C NMR ppm 0.1, 16.8, 61.2, 71.4, 99.2, 105.4, 120.5, 126.2, 127.3,

128.5, 141.9, 150.3; IR (NaCl) 3370, 2944, 2361, 2339, 2139, 1250, 1016, 847; HRMS (M^+ - H_2O) calc'd 256.1284; found 256.1282.



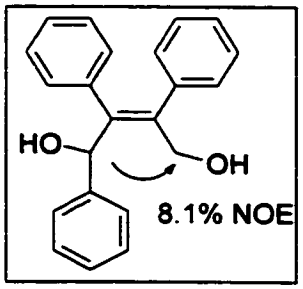
(*2E*)-2-Ethenyl-3-(trimethylsilyl)-2-ethen-1-ol (155x)

Vinylmagnesium chloride (5.3 mL, 1.4 M in THF, 7.4 mmol) was added to a solution of 3-(trimethylsilyl)-2-propyn-1-ol (**139a**) (0.30 g, 2.3 mmol) in cyclohexane (5 mL) at 22 °C. The solution was heated at reflux for 19 h. The solution was cooled to 0 °C and excess NH_4Cl was added. The mixture was stirred 5 min at 0 °C followed by 1 h at 22 °C. Standard workup followed by flash column chromatography (3:1 to 1:3 petroleum ether/ether) yielded the title compound as a yellow oil (0.21 g, 75 %); ^{1}H NMR ∂ 0.15 (s, 9H), 1.42 (s, br, 1H), 4.12 (s, 1H), 4.98 (dt, 1H, J = 11.2, 1.2), 5.11 (d, 1H, J = 18.1), 5.96 (s, br, 1H), 6.66 (dd, 1H, J = 18.1, 11.2); ^{13}C NMR ppm 0.3, 64.0, 114.5, 128.8, 135.9, 152.7; IR (NaCl) 3370, 2944, 2361, 2339, 2139, 1250, 1016, 847; MS, too volatile.



***(2Z, 1RS)*-1,2,3-Triphenyl-2-buten-1,4-diol (155w)**

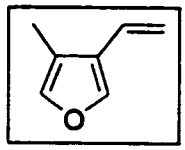
Phenylmagnesium chloride (4.5 mL, 1.9 M in THF, 8.3 mmol) was added to a solution of 3-phenyl-2-propyn-1-ol (**139b**) (0.3 g, 2.6 mmol) in cyclohexane (5 mL) at 22 °C. The solution was heated at reflux for 19 h. The solution was cooled to 0 °C and benzaldehyde (0.84 mL, 8.3 mmol) was added. The mixture was stirred 5 min at 0 °C followed by 1 h at 22 °C. Standard workup followed by chromatography (3:1 to 1:3 petroleum ether/ether) yielded the title compound as a yellow oil (0.72 g, 88 %); ^{1}H NMR ∂ 2.24 (s, br, 1H), 3.10 (s, br, 1H), 4.47 (s, broad, 2H), 6.06 (s, broad, 1H), 6.74 – 6.83 (m, 4H) 6.88 – 6.92 (m, 4H), 7.03 – 7.06 (m, 3H) 7.14 – 7.17 (m, 4H), 7.47 – 7.48 (m, 2H); ^{13}C NMR ppm 63.6, 73.9, 126.6, 126.7, 127.2, 127.6, 128.4, 129.7, 130.9, 139.5, 140.5, 142.0, 143.1, 144.4; IR (NaCl) 3341, 1491, 1444, 1032, 1012, 999, 699; HRMS (M^{+} - H_2O) calc'd 298.1359; found 298.1376.



3-Ethenyl-4-methylfuran (242)

Vinylmagnesium chloride (5.7 mL, 1.5 M in THF, 8.6 mmol) was added to a solution of 2-butyn-1-ol (**139**) (0.19 g, 2.7 mmol) in cyclohexane (5 mL) at 22 °C. The solution was heated at reflux for 19 h. The solution was cooled to 0 °C and dimethylformamide (1.24

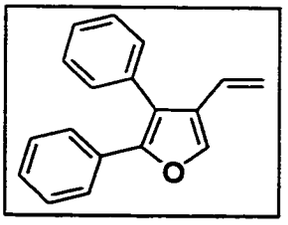
mL, 8.6 mmol) was added. The mixture was stirred 30 min at 0 °C followed by 2 h at 22 °C. Standard workup followed by chromatography (10:1 to 1:1 petroleum ether/ether) yielded the title compound as a volatile colouless oil (0.13 g, 45 %); ^{1}H NMR ∂ 2.07 (s, 3H), 3.10 (s, br, 1H), 5.13 (d, 1H, J = 11.3), 5.46 (d, 1H, J = 17.8), 6.49 (dd, 1H, J = 11.3, 17.8), 7.13 (s, 1H), 7.40 (s, 1H); ^{13}C NMR ppm 9.3, 113.9, 118.9, 124.4, 126.9, 140.4, 140.8; IR (NaCl) 3056, 1606, 1547, 1440, 1135, 803, 757, 696; MS, too volatile.



2,3-Diphenyl-4-ethenylfuran (244)

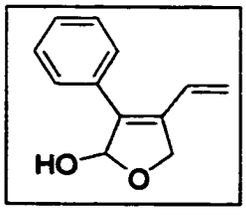
Vinylmagnesiumchloride (4.0 mL, 1.42 M in THF, 5.7 mmol) was added to a solution of 3-phenyl-2-propyn-1-ol (**139b**) (0.23 g, 1.8 mmol) in cyclohexane (5 mL) at 22 °C. The solution was heated at reflux for 19 h. The solution was cooled to 0 °C and benzonitrile (0.59 mL, 5.7 mmol) was added. The mixture was stirred 5 min at 0 °C after which it was heated at reflux for 2 h. Standard workup followed by flash column chromatography (5:1 to 2:1 petroleum ether/ether) yielded the title compound as a yellow oil (0.11 g, 25 %). ^{1}H NMR ∂ 4.99 (dd, 1H, J = 11.6, 1.5), 5.37 (dd, 1H, J = 17.3, 1.5), 6.49 (dd, 1H, J = 17.3, 11.1), 7.07 - 7.11 (m, 1H), 7.13 - 7.18 (m, 4H), 7.20 – 7.24 (m, 3H), 7.26 - 7.30 (m, 3H); ^{13}C NMR ppm 118.3, 118.5, 127.0, 128.5, , 128.6, 129.0, 135.8, 136.5, 138.2,

149.7; IR (NaCl) 3059, 1617, 1539, 1145, 888, 703; HRMS (M^+) calc'd 246.1045; found 246.1049.



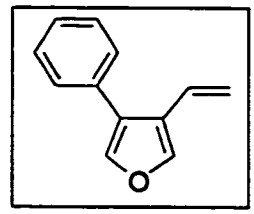
(2*RS*)-2,5-dihydro-4-ethenyl-2-hydroxy-3-phenylfuran (241a)

Vinylmagnesium chloride (4.0 mL, 1.42 M in THF, 5.7 mmol) was added to a solution of 3-phenyl-2-propyn-1-ol (**139b**) (0.23 g, 1.8 mmol) in cyclohexane (5 mL) at 22 °C. The solution was heated at reflux for 19 h. The solution was cooled to 0 °C and dimethylformamide (0.44 mL, 5.7 mmol) was added. The mixture was stirred 5 min at 0 °C after which it was heated at reflux for 2 h. Standard workup followed by chromatography (5:1 to 2:1 petroleum ether/ether) yielded the title compound as a yellow oil (0.26 g, 79 %); ^{1}H NMR ∂ 2.28 (d, 1H, J = 8.6), 4.62 - 5.06 (m, 4H), 6.18 (dd, 1H, J = 3.4, 8.6), 6.63 (dd, 1H, J = 11.3, 18.8), 7.15 - 7.30 (m, 2H), 7.40 - 7.52 (m, 3H); ^{13}C NMR ppm 73.4, 105.6, 118.1, 128.9, 133.3, 135.5, 136.5; IR (NaCl) 3382, 2865, 1097, 1057, 987, 765, 700; HRMS (M^+) calc'd 188.0838; found 188.0849.



3-Phenyl-4-ethenylfuran (241)

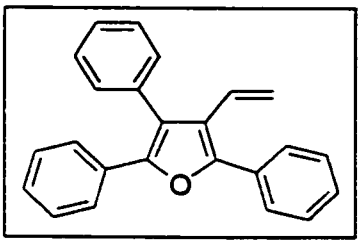
A catalytic amount of *p*-toluenesulfonic acid was added to a solution of (**241a**) in benzene at 0 °C. Stirred at 0 °C for 1 h. Standard workup followed by chromatography (10:1 to 5:1 petroleum ether/ether) yielded the title compound as a colourless oil (0.21 g, 91 %). ^{1}H NMR ∂ 4.97 (dd, 1H, J = 11.1,1.7), 5.32 (dd, 1H, J = 17.7,1.7), 6.45 (ddd, 1H, J = 17.7, 11.1, 0.8), 7.07 - 7.11 (m, 1H), 7.13 - 7.18 (m, 3H), 7.26 - 7.30 (m, 3H); ^{13}C NMR ppm 115.2, 124.0, 126.4, 126.9, 127.4, 128.3, 128.7, 128.9, 132.7, 140.6, 140.7; IR (NaCl) 3056, 1606, 1537, 1140, 1057, 876, 699; HRMS (M^{+}) calc'd 170.0732; found 170.0728.



2,3,5-Triphenyl-4-ethenylfuran (258)

n-Butyllithium (0.75 mL, 2.56 M in THF, 1.9 mmol) was added to phenylacetylene (0.20 mL, 1.8 mmol) in cyclohexane (5.2 mL) at 0 °C. The solution was allowed to stir at 23 °C for 30 min after which it was again cooled to 0 °C. Benzaldehyde (0.21 mL, 2.0 mmol) was added dropwise. The resulting solution was again warmed to 23 °C for 30 min followed by the addition of vinylmagnesium chloride (3.0 mL, 1.42 M in THF, 4.2 mmol). The solution was heated at reflux for 19 h. The solution was cooled to 0 °C and benzonitrile (0.62 mL, 6.0 mmol) was added. The mixture was stirred 5 min at 0 °C after which it was stirred at 23 °C for 18 h. Standard workup yielded the crude lactol that

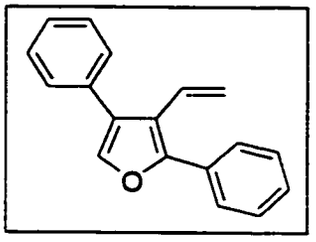
was immediately dissolved in benzene and treated with a catalytic amount of *p*-toluenesulfonic acid and stirred at room temperature for 2 h Standard workup followed by chromatography (20:1 to 12:1 petroleum ether/ether) yielded the title compound as a highly unstable yellow oil (0.15g, 25%). ^{1}H NMR ∂ 4.98 (dd, 1H, J = 11.6,1.7), 5.07 (dd, 1H, J = 17.9, 1.7), 6.68 (dd, 1H, J = 17.9, 11.6), 6.92 - 7.03 (m, 3H), 7.07 - 7.12 (m, 2H), 7.17 - 7.22 (m, 4H), 7.29-7.32 (m, 2H), 7.58-7.60 (m, 2H), 7.78-7.80 (m, 2H); ^{13}C NMR ppm 118.0, 122.0, 124.0, 126.1, 127.3, 127.5, 127.6, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 129.1, 129.4, 130.8, 131.3, 131.6, 132.4, 132.5, 134.6; IR (NaCl) 3502, 2932, 1491, 1444, 767, 693, 671; HRMS (H^+) calc'd 322.1358; found 322.1361.



2,4-Diphenyl-3-ethenylfuran (256)

n-Butyllithium (0.75 mL, 2.56 M in THF, 1.9 mmol) was added to phenylacetylene (0.20 mL, 1.8 mmol) in cyclohexane (5.2 mL) at 0 °C. The solution was allowed to stir at 23 °C for 30 min after which it was again cooled to 0 °C. Benzaldehyde (0.21 mL, 2.0 mmol) was added dropwise. The resulting solution was again warmed to 23 °C for 30 min followed by the addition of vinylmagnesium chloride (3.0 mL, 1.42 M in THF, 4.2 mmol). The solution was heated at reflux for 19 h. The solution was cooled to 0 °C and dimethylformamide (0.47 mL, 6.0 mmol) was added. The mixture was stirred 5 min at 0 °C after which it was stirred at 23 °C for 18 h. Standard workup yielded the crude lactol

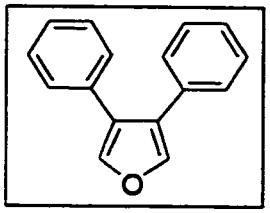
that was immediately dissolved in benzene and treated with a catalytic amount of *p*-toluenesulfonic acid and stirred at room temperature for 2 h. Standard workup followed by chromatography (20:1 to 12:1 petroleum ether/ether) yielded the title compound as a highly unstable yellow oil (0.11g, 26%). ^{1}H NMR ∂ 5.0 (dd, 1H, J = 11.3,1.7), 5.27 (dd, 1H, J = 17.8, 1.7), 6.71 (dd, 1H, J = 17.8, 11.3), 7.03 - 7.06 (m, 1H), 7.09 - 7.12 (m, 1H), 7.14 - 7.17 (m, 3H), 7.17 - 7.19 (m, 2H), 7.34 - 7.36 (m, 2H), 7.72 - 7.74 (m, 2H); ^{13}C NMR ppm 118.5, 119.1, 127.2, 127.4, 127.6, 128.0, 128.3, 128.6, 128.8, 129.4, 131.7, 133.1, 140.0, 151.4; IR (NaCl) 3055, 1606, 1492, 1445, 914, 765, 696; HRMS (M^+) calc'd 246.1045; found 246.1044.



3,4-Diphenylfuran (240)

Phenylmagnesium chloride (3.7 mL, 1.87 M in THF, 6.7 mmol) was added to a solution of 3-phenyl-2-propyn-1-ol (**139b**) (0.28g, 2.1 mmol) in cyclohexane (4.1 mL) at 22 °C. The solution was heated at reflux for 19 h. The solution was cooled to 0 °C and dimethylformamide (0.53 mL, 6.7 mmol) was added. The mixture was stirred 5 min at 0 °C followed by heating at reflux for 3 h. Standard workup yielded the crude lactol that was immediately dissolved in benzene and treated with a catalytic amount of *p*-toluenesulfonic acid and stirred at room temperature for 2 h. Standard workup followed by flash column chromatography (20:1 to 12:1 petroleum ether/ether) yielded the title

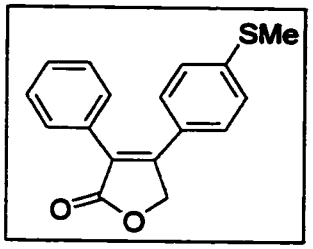
compound as a white solid (0.42 g, 91 %); mp 108 - 110 °C; ^{1}H NMR ∂ 7.00 - 7.06 (m, 6H), 7.17 - 7.20 (m, 4H), 7.26 (s, 2H); ^{13}C NMR ppm 126.4, 127.2, 128.3, 128.7, 128.9, 132.6, 141.1; IR (NaCl) 3055, 1606, 1548, 1488, 1440, 1135, 803,757, 696; HRMS (M^+) calc'd 220.0889; found 220.0894. Anal calc'd for $C_{16}H_{12}O$: C, 87.25; H, 5.49. found: C, 87.24; H, 5.37.



4-(4-Methylsulfanyl-phenyl)-3-phenyl-5-*H*-furan-2-one (261)

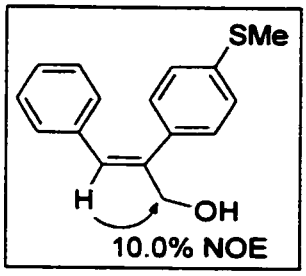
4-Bromothioanisole (1.5 g, 7.4 mmol) was added to a flask containing Mg shavings (0.19 g, 7.8 mmol) in THF (3 mL) and heated at reflux for 30 min 3-phenyl-2-propyn-1-ol (**139b**) (0.46 g, 3.4 mmol) was added to the above solution in cyclohexane (3 mL). The resulting solution was heated at reflux for 19 h. The solution was cooled to 0 °C and CO_2 (solid, excess) was added. The mixture was stirred 60 min at 0 °C. Standard workup followed by flash column chromatography (3:1 to 1:4 petroleum ether/ether) yielded the title compound as a white solid (0.12 g, 13 %, mp = 145 – 147 °C) and protonated by-product (0.39 g, 42 %, mp = 82 – 84 °C); ^{1}H NMR ∂ 2.45 (s, 3H), 5.14 (s, 2H), 7.13 – 7.14 (m, 2H), 7.20 – 7.24 (m, 2H), 7.35 – 7.42 (m, 5H); ^{13}C NMR ppm 14.9, 70.3, 125.4, 125.8, 126.9, 127.7, 128.7, 128.8, 129.3, 130.4, 142.8, 155.3, 173.5; IR (NaCl) 2923,

1743, 1642, 1592, 1059, 1032, 823, 701, 614; HRMS (M^+) calc'd 282.0715; found 282.0721.



2-((4-Thiomethyl)-phenyl)-3-phenyl-2-ethen-1-ol (261a)

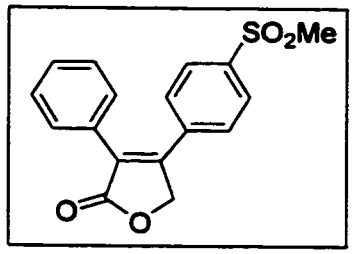
^{1}H NMR ∂ 2.47 (s, 3H), 4.43 (s, 3H), 6.67 (s, 1H), 7.01 – 7.03 (m, 2H), 7.08 – 7.15 (m, 5H), 7.18 – 7.19 (m, 2H); ^{13}C NMR ppm 15.5, 68.4, 126.6, 126.7, 126.8, 128.0, 129.1(8), 129.2(0), 135.0, 136.4, 137.8, 140.7; IR (NaCl) 3351, 2920, 1594, 1494, 1446, 750, 696; HRMS (M^+) calc'd 256.0923; found 256.0919.



4-(4-Methanesulfonyl-phenyl)-3-phenyl-5-*H*-furan-2-one (262)

m-CPBA (0.22 g, 50 wt. %, 0.6 mmol) was added to a solution of the sulfide (**261**) (0.04 g, 0.2 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The reaction was then warmed to 22 °C and stirred for 4 h Standard workup followed by chromatography (4:1 to 1:4 petroleum

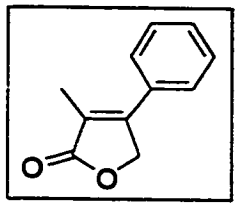
ether/ether) yielded the title compound as a colourless oil (0.05 g, 99 %); ^{1}H NMR (200 MHz) ∂ 3.04 (s, 3H), 5.18 (s, 2H), 7.35 (s, br, 5H), 7.47 – 7.51 (m, 2H), 7.86 – 7.92 (m, 2H); ^{13}C NMR (50 MHz) ppm 44.1, 70.3, 127.9, 128.0, 128.2, 128.3, 133.8, 136.3, 142.0, 153.5, 172.3; IR (NaCl) 2923, 1754, 1314, 1149, 1039, 959, 774; HRMS (M^+) calc'd 315.0736; found 315.0799.



3-Methyl-4-phenyl-5-*H*-furan-2-one (260)

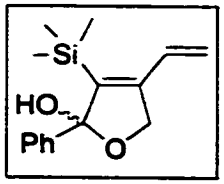
Phenylmagnesium chloride (4.3 mL, 2.0 M in THF, 8.0 mmol) was added to a solution of 2-butyn-1-ol (**139b**) (0.19 g, 2.7 mmol) in cyclohexane (4.4 mL) at 22 °C. The solution was heated at reflux for 19 h. The solution was cooled to 0 °C and CO_2 (solid, excess) was added. The mixture was stirred 60 min at 0 °C. Standard workup followed by chromatography (10:1 to 4:1 petroleum ether/ether) yielded the title compound as a white solid (0.23 g, 49 %, mp = 122 – 124 °C); ^{1}H NMR ∂ 2.13 (s, 3H), 5.04 (s, 2H), 7.33 – 7.36 (m, 4H), 7.42 – 7.50 (m, 13H), 7.58 – 7.61 (m, 8H); ^{13}C NMR ppm 10.3, 70.5,

127.1, 127.2, 128.7, 129.1, 130.2, 131.4, 141.2; IR (NaCl) 2959, 1743, 1455, 1429, 1091, 1047, 766, 729, 695; HRMS (M^+) calc'd 174.0681; found 174.0665.



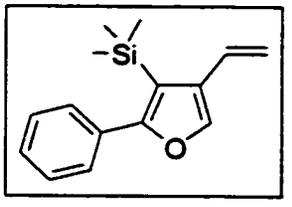
(2*RS*)-2,5-Dihydro-4-ethenyl-2-hydroxy-3-trimethylsilyl-2-phenylfuran (246a)

Vinylmagnesium chloride (10.1 mL, 0.9 M in THF, 8.6 mmol) was added to a solution of 3-(trimethylsilyl)-2-propyn-1-ol (**139a**) (0.34 g, 2.7 mmol) in cyclohexane (4 mL) at 22 °C. The solution was heated at reflux for 19 h. The solution was cooled to 0 °C and benzonitrile (0.88 mL, 8.6 mmol) was added. The mixture was stirred 5 min at 0 °C followed by 15 h at 22 °C. Standard workup followed by flash column chromatography (8:1 to 1:1 petroleum ether/ether) yielded the title compound as a yellow oil which was employed in the dehydration immediately following purification; ^{1}H NMR ∂ 0.17 (s, 9H), 5.04 (dd, 1H, J = 1.8, 10.8), 5.35 (dd, 1H, J = 1.8, 17.4), 6.62 (ddd, 1H, J = 0.9, 1.8, 17.4), 7.04 – 7.11 (m, 3H), 7.42 – 7.48 (m, 2H); ^{13}C NMR ppm 1.0, 114.2, 114.8, 128.1, 128.7, 129.7, 129.8, 131.5, 133.5, 139.0, 160.9; IR (NaCl) 3360, 2955, 1627, 1475, 1251, 839, 757, 690; HRMS (M^+ - H_2O) calc'd 242.1128; found 242.1134.



4-ethenyl-2-phenyl-3-trimethylsilylfuran (246)

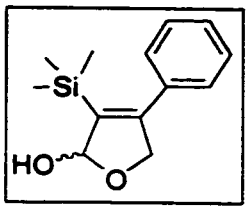
A catalytic amount of *p*-toluenesulfonic acid was added to a solution of (**246a**) (0.16 g, 0.6 mmol) in benzene (2 mL) at 0 °C. The solution was stirred at 0 °C for 1 h. Standard workup followed by chromatography (15:1 to 8:1 petroleum ether/ether) yielded the title compound as a colourless oil (0.13 g, 88 %, two-steps); ^{1}H NMR ∂ 0.17 (s, 9H), 5.03 (dd, J = 1.8,10.8, 1H), 5.35 (dd, J = 1.8,17.5 1H), 6.62 (ddd, J = 0.9,10.8,17.5, 1H), 7.07 - 7.08 (m, 3H), 7.42 (s, 1H), 7.46 - 7.48 (m, 2H); ^{13}C NMR ppm 1.5, 115.0, 115.6, 128.9, 128.5, 130.5, 130.6, 132.3, 134.3, 139.8, 161.7; IR (NaCl) 3078, 2956, 1477, 1251, 840, 697; HRMS (M^+) calc'd 242.1128; found 242.1138.



(2*RS*)-2,5-Dihydro-4-phenyl-2-hydroxy-3-trimethylsilylfuran (243a)

Phenylmagnesium chloride (5.9 mL, 1.9 M in THF, 11.0 mmol) was added to a solution of 3-(trimethylsilyl)-2-propyn-1-ol (**139a**) (0.43 g, 3.5 mmol) in cyclohexane (5 mL) at 22 °C. The solution was heated at reflux for 19 h. The solution was cooled to 0 °C and dimethylformamide (0.86 mL, 11.0 mmol) was added. The mixture was stirred 10 min at 0 °C followed by 18 h at 22 °C. Standard workup followed by flash column chromatography (8:1 to 1:1 petroleum ether/ether) yielded the title compound as a yellow oil (0.34 g, 46 %); ^{1}H NMR ∂ 0.08 (s, 9H), 2.56 (s, br, 1H), 4.73 – 4.82 (m, 2H), 6.26 (s,

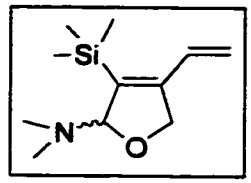
br, 1H), 7.02 – 7.07 (m, 5H); ^{13}C NMR ppm -0.4, 78.2, 109.8, 128.4, 135.4, 135.9, 153.5; IR (NaCl) 3384, 2954, 1597, 1249, 1032, 840, 757, 699; HRMS (M^+ - H_2O) calc'd 216.0971; found 216.0999.



(2*RS*)-2,5-Dihydro-2-dimethylamino-4-ethenyl-3-trimethylsilylfuran (251)

Vinylmagnesium chloride (8.1 mL, 1.4 M in THF, 11.0 mmol) was added to a solution of 3-(trimethylsilyl)-2-propyn-1-ol (0.43 g, 3.4 mmol) in cyclohexane (5 mL) at 22 °C. The solution was heated at reflux for 19 h. The solution was cooled to 0 °C and dimethylformamide (0.85 mL, 11.0 mmol) was added. The mixture was stirred 5 min at 0 °C followed by 14 h at 22 °C. Standard workup followed by chromatography (15:1 to 5:1 petroleum ether/ether) yielded the title compound as a yellow oil (0.50 g, 69 %); ^{1}H NMR ∂ 0.19 (s, 9H), 2.25 (s, 6H), 4.68 – 4.75 (m, 2H), 4.82 (d, 1H, J = 17.6), 4.99 (d, 1H, J = 10.9), 5.66 – 5.68 (m, 1H), 6.69 (dd, 1H, J = 10.9,17.6); ^{13}C NMR ppm –0.5, 39.2, 75.5, 108.1, 117.3, 130.4, 137.9, 149.2; IR (NaCl) 2942, 2869, 2835, 1574, 1247,

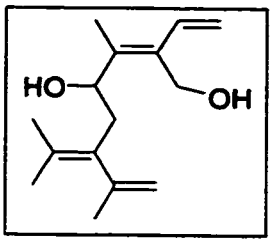
1057, 996, 837, 811; HRMS (M^+ - H_2O) calc'd 211.1393; found 211.1382. Anal calc'd for $C_{11}H_{21}ONSi$: C, 62.50; H, 10.01; N, 6.63. Found: C, 62.42; H, 10.18; N, 6.79.



4*RS*-6-Isopropenyl-3,7-dimethyl-2-vinyl-octa-2,6-diene-1,4-diol (325)

Vinylmagnesium chloride (3.2 mL, 4.54 mmol, 1.42 M in THF) was added to a solution of **139** (0.20 mL, 2.674 mmol) in dry cyclohexane (4 mL) at 21 °C. The solution was heated at reflux for 20 h, cooled to 21 °C and additional dry THF (5 mL) was added. The solution was cooled to -78 °C and the aldehyde **310** (120 mg, 0.89 mmol) was added dropwise as a solution in dry Et_2O (3 mL). The solution was stirred for 5 min at -78 °C, 30 min at 0 °C and 90 min at 21 °C. The reaction was cooled to 0 °C and saturated aqueous $NaHCO_3$ was added followed by standard workup and chromatograhy (1:1 to 5:1 ether/petroleum ether) provided the title compound as a colourless oil (146 mg, 71%); ^1H NMR δ = 1.65 (s, 3H), 1.66 (s, 3H), 1.73 (m, 3H), 1.82 (s, 3H), 2.19 (dd, 1H, J = 5.2, 14.0), 2.54 (br, 1H), 2.63 (dd, 1H, J = 8.5, 14.0), 4.24 (d, 1H, J = 11.9), 4.36 (d, 1H, J = 11.9), 4.67 (m, 1H), 4.85 (dd, 1H, J = 5.2, 8.5), 4.97 - 4.98 (m, 1H), 5.09 (dd, 1H, J = 1.2, 11.1), 5.42 (dd, 1H, J = 1.2, 17.9), 6.62 (dd, 1H, J = 11.1, 17.5). ^{13}C NMR ppm: 13.0, 20.2, 22.0, 22.6, 36.9, 57.5, 70.1, 114.1, 114.2, 129.0, 132.5, 133.4, 134.8, 141.0, 146.7.

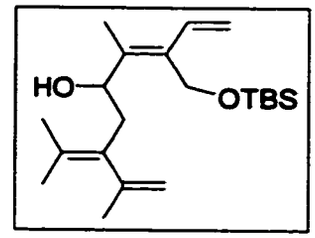
FT-IR (NaCl): 3355, 2964, 2917, 1630, 1442, 1374, 998, 900; HRMS (M^+): calcd for $C_{15}H_{24}O_2$ 236.1777; found 236.1791



5*RS*-3-(*t*-Butyl-dimethyl-silanyloxymethyl)-7-isopropenyl-4,8-dimethyl-nona-1,3,7-trien-5-ol (326a)

t-Butyl-dimethylsilyl chloride (0.37 g, 2.4 mmol) was added to a solution of diol (**325**) (0.53 g, 2.2 mmol) and DMAP (0.30 g, 2.4 mmol) in dichloromethane (17 mL) at 0 °C. The solution was then warmed to 22 °C and stirred for 19 h. Standard workup followed by chromatography (8:1 to 2:1 petroleum ether/ether) yielded the title compound as a colourless oil (0.72 g, 92 %); ^{1}H NMR ∂ 0.10 (d, 6H, J = 3.2), 0.96 (s, 9H), 1.66 (s, 6H), 1.77 (s, 3H), 1.86 (s, 3H), 2.12 (dd, 1H, J = 14.0, 3.1), 2.68 (dd, 1H, J = 14.0, 9.7), 4.35 (d, 1H, J = 11.4), 4.43 (d, 1H, J = 11.4), 4.71 (m, 1H), 4.95 – 4.98 (m, 1H), 5.02 – 5.03 (m, 1H), 5.16 (dd, 1H, J = 11.2, 1.4), 5.49 (dd, 1H, J = 17.5, 1.4), 6.69 (dd, 1H, J = 17.5, 11.2); ^{13}C NMR ppm: –5.1, 12.8, 18.4, 20.1, 22.0, 22.8, 26.1, 37.1, 58.4, 69.6, 114.0(9), 114.1(2), 129.3, 132.1, 133.3, 135.2, 140.8, 146.7; IR (NaCl) 3469, 2941, 2858, 1631,

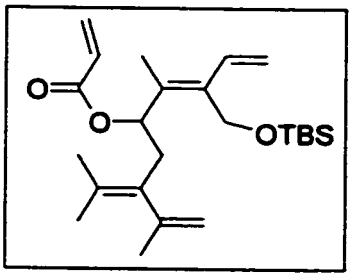
1472, 1377, 1254, 1053, 898, 776; HRMS (M^+ - H_2O) calc'd 332.2537; found 332.2552. Anal calc'd for $C_{21}H_{38}O_2Si$: C, 71.95; H, 10.65. found: C, 71.86; H, 10.65.



1*RS*-Acrylic acid 3-(*t*-butyl-dimethyl-silanyloxymethyl)-1-(2-isopropenyl-3-methyl-but-2-enyl)-2-methyl-penta-2,4-dienyl ester (326b)

Acryloyl chloride (0.06 mL, 1.114 g/mL, 0.6 mmol) was added to a solution of alcohol (**326a**) (0.10 g, 0.3 mmol), DMAP (0.004 g, 0.03 mmol) and pyridine (0.06 mL, 0.978 g/mL, 0.6 mmol) in dichloromethane (2 mL) at 0 °C. The solution was then warmed to 22 °C and stirred for 16 h. Standard workup followed by chromatography (20:1 to 12:1 petroleum ether/ether) yielded the title compound as a colourless oil (0.04 g, 32 %); ^{1}H NMR ∂ 0.16 (d, 6H, J = 4.9), 0.99 (s, 9H), 1.68 (s, 3H), 1.74 (s, 3H), 1.76 (s, 3H), 1.80 (s, 3H), 2.22 (dd, 1H, J = 14.1, 4.6), 2.88 (dd, 1H, J = 14.1, 9.7), 4.53 (d, 1H, J = 11.6), 4.74 (d, 1H, J = 11.6), 4.83 – 4.84 (m, 1H), 5.06 – 5.23 (m, 2H), 5.54 (dd, 1H, J = 17.5, 1.7), 5.92 (dd, 1H, J = 17.3, 10.4), 6.23 (dd, 1H, J = 17.3, 1.7), 6.32 – 6.35 (m, 1H), 6.59 (dd, 1H, J = 17.5, 11.2); ^{13}C NMR (ppm) –5.2, 13.3, 18.5, 20.3, 22.0, 22.9, 26.2, 34.9, 58.8, 72.7, 114.8, 115.7, 128.9, 129.1, 130.0, 132.3, 134.3, 134.6, 135.2, 146.0, 164.8; IR

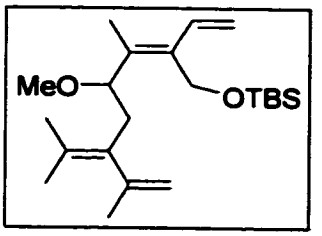
(NaCl) 2929, 2857, 1726, 1404, 1256, 1190, 1068, 840; HRMS (M^+ - (^{t}Bu + Me)) calc'd 332.2528; found 332.2510.



4*RS*-*t*-Butyl-(6-isopropenyl-4-methoxy-3,7-dimethyl-2-vinyl-octa-2,6-dienyloxy)-dimethyl-silane (326)

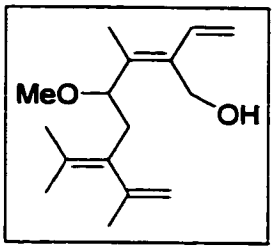
Pre-washed (2 x 2 mL pentane) sodium hydride (0.05 g, 2.0 mmol) was added to a solution of alcohol (**326a**) (0.29 g, 0.83 mmol) in THF (5 mL) at 0 °C and stirred for 15 min. Iodomethane (0.26 mL, 2.28 g/mL, 4.1 mmol) was then added and the solution was then warmed to 22 °C and stirred for 19 h. Standard workup followed by chromatography (20:1 to 6:1 petroleum ether/ether) yielded the title compound as a colourless oil (0.13 g, 89 %); ^{1}H NMR ∂ 0.11 (d, 6H, J = 2.7), 0.96 (s, 9H), 1.73 (s, 3H), 1.74 (s, 3H), 1.79 (s, 3H), 1.82 (s, 3H), 2.11 (dd, J = 14.2, 4.3, 1H), 2.79 (dd, J = 14.2, 8.9, 1H), 3.13 (s, 3H), 4.30 (d, 1H, J = 11.2), 4.46 – 4.50 (m, 2H), 4.74 (d, 1H, J = 11.6), 4.81 (m, 1H), 5.09 (s, 1H), 5.16 (dd, 1H, J = 11.2, 1.1), 5.50 (dd, 1H, J = 17.5, 1.4), 6.69 (dd, 1H, J = 17.5, 11.2); ^{13}C NMR (ppm) –5.2, 12.2, 20.2, 22.1, 22.9, 26.1, 36.2, 56.3, 57.9, 79.1, 114.0, 127.6, 133.5, 133.9, 135.0, 139.1, 147.0; IR (NaCl) 2929, 2858, 1633, 1463, 1146, 1383, 1255, 1100, 1068, 898, 851, 837, 774; HRMS (M^+) calc'd 364.2799;

found 364.2801. Anal calc'd for $C_{22}H_{40}O_2Si$: C, 72.97; H, 11.06. Found: C, 73.13; H, 11.06.



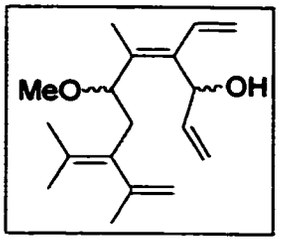
4*RS*-6-Isopropenyl-4-methoxy-3,7-dimethyl-2-vinyl-octa-2,6-dien-1-ol (327a)

Tetrabutylammonium fluoride (0.63 mL, 1.0 M, 0.6 mmol) was added to a solution of silane (**326**) (0.15 g, 0.42 mmol) in THF (4 mL) at 0 °C and stirred for 2 h. The solution was then warmed to 22 °C and stirred for 19 h. Standard workup followed by flash column chromatography (5:1 to 1:1 petroleum ether/ether) yielded the title compound as a colourless oil (0.10 g, 99 %); ^{1}H NMR 1.65 (s, 3H), 1.66 (s, 3H), 1.72 (s, 3H), 2.18 (dd, 1H, J = 14.1, 5.9), 2.67 (dd, 1H, J = 14.1, 7.6), 3.00 (s, 3H), 4.29 – 4.40 (m, 3H), 4.72 (d, 1H, J = 2.6), 4.99 (m, 1H), 5.10 (d, 1H, J = 11.1), 5.44 (dd, 1H, J = 17.7, 1.0), 6.59 (dd, 1H, J = 17.7, 11.1); ^{13}C NMR (ppm) 12.2, 20.1, 22.0, 22.7, 36.0, 56.0, 57.4, 79.1, 114.1, 114.2, 133.8, 134.5, 134.9, 139.3, 146.8; IR (NaCl) 3445, 2922, 1629, 1444, 1374, 1099, 996, 898, 691, 630; HRMS (M^+) calc'd 250.1934; found 250.1938.



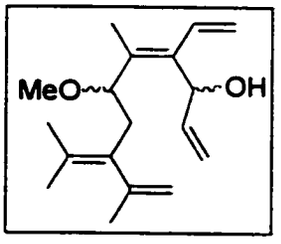
(6*RS*,3*RS*)-8-Isopropenyl-6-methoxy-5,9-dimethyl-4-vinyl-deca-1,4,8-trien-3-ol (328a)

Oxalyl chloride (0.07 mL, 1.46 g/mL, 0.7 mmol) was added to DMSO (0.11 mL, 1.101 g/mL, 1.5 mmol) in dichloromethane (1 mL) at –78 °C and stirred for 2 min. Alcohol (**327a**) (0.08g, 0.3 mmol) in dichloromethane was added at –78 °C and stirred for 1 h. Triethyl amine (0.46 mL, 0.73 g/mL, 3.3 mmol) was then added and stirred for 5 min followed by 1 h at 0 °C. The mixture then cooled to –78 °C followed by the addition of vinylmagnesium chloride (1.2 mL, 1.25 M, 1.4 mmol). The resulting solution was stirred for 4 h at 22 °C. Standard workup followed by chromatography (8:1 to 1:1 petroleum ether/ether) yielded the title compound as the major diastereomer (less polar diastereomer) as a colourless oil (0.05 g, 54%); ^{1}H NMR 1.60 (d, 1H, J = 5.1), 1.69 (s, 3H), 1.72 (s, 3H), 1.77 (m, 3H), 1.78 (s, 3H), 2.26 (dd, 1H, J = 14.1, 5.7), 2.67 (dd, 1H, J = 14.1, 7.7), 3.01 (s, 3H), 4.41 (dd, 1H, J = 7.7, 5.7), 4.83 – 4.84 (m, 1H), 5.02 – 5.06 (m, 2H), 5.17 (dd, 1H, J = 11.6, 1.9), 5.32 – 5.36 (m, 2H), 5.43 (dd, 1H, J = 17.9, 1.9), 6.04 (m, 1H), 6.36 (dd, 1H, J = 17.9, 11.6, 1H); ^{13}C NMR (ppm) 13.7, 20.2, 22.1, 22.7, 36.0, 56.2, 70.4, 79.0, 114.1, 114.2, 117.9, 133.4, 133.6, 136.5, 137.2, 140.4, 146.7; IR (NaCl) 3458, 2923, 1629, 1446, 1373, 1100, 990, 919, 625, 530; HRMS (M^{+}) calc'd 276.2090; found 276.2090.



6*RS*,3*RS*-8-Isopropenyl-6-methoxy-5,9-dimethyl-4-vinyl-deca-1,4,8-trien-3-ol (328b)

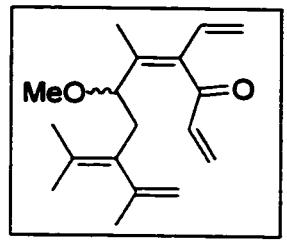
Colourless oil (more polar diastereomer, 0.02g, 17%); ^{1}H NMR 0.45 (s, br, 1H), 1.72 (s, 3H), 1.73 (s, 3H), 1.78 – 1.79 (m, 3H), 1.79 (s, 3H), 2.09 – 2.13 (m, 1H), 2.76 (dd, J = 14.1, 8.8, 1H), 3.03 (s, 3H), 4.47 (dd, J = 8.8, 4.5, 1H), 4.78 – 4.79 (m, 1H), 5.02 – 5.04 (m, 1H), 5.05 – 5.06 (m, 1H), 5.15 (dd, J = 11.6, 1.9, 1H), 5.32 – 5.39 (m, 3H), 5.93 – 6.00 (m, 1H), 6.40 (dd, J = 17.9, 11.6, 1H); ^{13}C NMR: 13.6, 20.1, 22.1, 22.8, 30.0, 35.9, 56.2, 70.0, 78.3, 113.8(8), 113.9(4), 117.4, 133.6, 136.3, 137.8, 140.5, 147.0; IR (NaCl) 3462, 2922, 1629, 1445, 1100, 991, 919, 896, 638; HRMS unstable.



6*RS*-8-Isopropenyl-6-methoxy-5,9-dimethyl-4-vinyl-deca-1,4,8-trien-3-one (328)

A solution of **328a** and **328b** (0.11 g, 0.4 mmol) in THF (1 mL) was added to a solution of IBX (0.27g, 1.0 mmol) in DMSO (2 mL) at 23 °C. The solution was stirred for 30 min and added 15 mL H_2O, filtered and extracted with Et_2O (3 x). Standard workup followed by purification by chromatography (10:1 to 6:1 petroleum ether/ether) provided the title compound as a colourless oil (0.08 g, 77 %); ^{1}H NMR 1.67 (s, 3H), 1.70 (s, 3H), 1.71 (s, 3H), 1.79 (s, 3H), 2.09 (dd, 1H, J = 14.2, 3.7), 2.69 (dd, 1H J = 14.2, 9.6), 3.01 (s, 3H), 3.91 (dd, 1H, J = 9.6, 3.7), 4.73 (d, 1H, J = 2.0), 4.98 – 5.03 (m, 3H), 5.39 (dd, 1H, J =

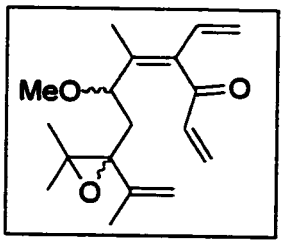
10.4, 1.4), 5.95 (dd, 1H, J = 17.6, 1.4), 6.28 (dd, 1H, J = 17.6, 10.4), 6.47 (dd, 1H, J = 17.7, 11.0); ^{13}C NMR: 20.2, 22.1, 22.7, 30.4, 35.5, 56.5, 80.6, 114.0, 117.2, 128.3, 129.7, 130.1, 131.6, 133.3, 137.8, 138.0, 139.1, 197.9; IR: 2970, 2925, 1738, 1444, 1366, 1228, 1217, 772, 686; HRMS (M^+): calc'd 274.1934, found 274.1935; Anal calc'd for $C_{18}H_{26}O_2$ C: 78.79 H: 9.55; found C 78.88, H 9.41.



6*RS*-7-(2*RS*-2-Isopropenyl-3,3-dimethyl-oxiranyl)-6-methoxy-5-methyl-4-vinyl-hepta-1,4-dien-3-one (328c)

Dess-Martin periodonane (0.17 g, 0.4 mmol) was added to a solution of alcohol (**328a** and **328b**) (0.06g, 0.2 mmol) and $NaHCO_3$ (0.1 g) in CH_2Cl_2 (1.5 mL) at 0 °C. The solution was stirred for 15 min followed by 19 h at 22 °C. Standard workup followed by column chromatography to yield the desired ketone (**328**) (14 mg, 26 %) and the title compound (**328c**) (18 mg, 31 %); ^{1}H NMR 1.17 (s, 3H), 1.29 (s, 3H), 1.59 (s, 3H), 1.71 (dd, 3H, J = 14.5, 2.3), 1.77 (s, 3H), 2.09 (dd, 1H, J = 14.5, 10.1), 3.01 (s, 3H), 3.99 (dd, 1H, J = 10.1, 2.3), 4.92 (m, 1H), 4.98 (m, 1H), 5.00 (s, 1H), 5.05 (d, 1H, J = 17.7), 5.40

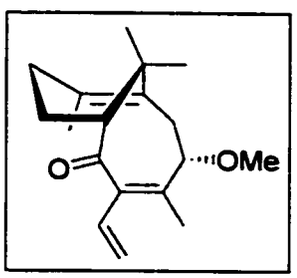
(dd, 1H, J = 10.4, 1.2), 5.90 (dd, 1H, J = 17.6, 1.2), 6.31 (dd, 1H, J = 17.6, 10.4), 6.43 (dd, 1H, J = 17.7, 11.0); ^{13}C NMR (ppm) 11.7, 19.9, 21.1, 22.0, 36.2, 56.3, 63.4, 68.6, 79.4, 112.5, 117.4130.0, 131.5, 137.6, 138.1, 138.1, 143.8, 198.0; IR (NaCl) 2926, 1666, 1609, 1448, 1399, 1376, 1096, 985, 907; HRMS (M^+) calc'd 290.1883, found 290.1852.



1*R,5*S**-Methoxy-4,8,11,11-tetramethyl-3-vinyl-bicyclo[5.3.1]undeca-3,7-dien-2-one (329)**

Diethylaluminum chloride (0.19 mL, 1.8 M in toluene, 0.33 mmol) was added to enone **328** (63 mg, 0.303 mmol) dissolved in anhydrous CH_2Cl_2 (50 mL) at -78 °C. The solution was slowly warmed to 0 °C and the reaction monitored by GC-MS. After approximately 5 min at 0 °C, the reaction appeared complete. The solution was cooled to -78 °C and saturated aqueous $NaHCO_3$ was added. The reaction was warmed 21 °C, the layers were separated and the aqueous phase was extracted with ether (3 x). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil. Purification by chromatography (4:1 to 1:1 petroleum ether/ether) provided the title compound as a white solid (48.1 mg, 76 %). mp. 76 - 81 °C (dec., rearranging); ^{1}H NMR 0.92 (s, 3H), 1.26 (s, 3H), 1.36 (s, 3H), 1.64 - 1.66 (m, 1H), 1.66 (s, 3H), 1.79 (ddd, 1H, J = 3.6, 10.2, 18.3), 1.90 - 1.96 (m, 1H), 2.10 - 2.16 (m, 1H), 2.51 - 2.56 (m, 1H), 2.62 (ddd, 1H, J = 2.5, 6.4, 12.5), 3.00 (s, 3H), 4.12 (dd, 1H, J = 6.4,

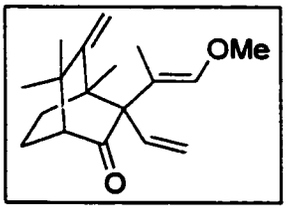
11.1), 4.92 (dd, 1H, J = 11.0, 0.5), 5.65 (dd, 1H, J = 17.5, 0.5), 6.42 (dd, 1H, J = 11.0, 17.5); ^{13}C NMR: 12.1, 19.8, 21.6, 25.1, 28.1, 29.0, 35.4, 37.8, 57.6, 63.4, 82.3, 115.5, 131.6, 131.8, 134.5, 135.1, 141.3, 212.3; FT-IR (cm^{-1}): 2927, 1673, 1378, 1463, 911, 750; HRMS (M^+): calc'd 274.1934, found 274.1951; Anal calc'd for $C_{18}H_{26}O_2$ C: 78.79 H: 9.55; found C 78.65, H 9.50; X-ray structural analyses: Crystal size 0.20 x 0.20 x 0.20 mm^3, orthorhombic, space group *Pbca*, scan range 4.88<2θ<41.62°, a=14.553(9), b=13.190(8), c=16.149(9) Å, V =3100(3) Å^3, Z=8, r_{calcd}=1.176 g cm-3, u=0.84 cm^{-1}, 1621 unique reflections at 173°K, [I_O>2.00δ(I)], R=0.0667, R_W=0.1415. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-139037. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).



3*S,4*S**-3-(2-Methoxy-1-methyl-vinyl)-4,6,6-trimethyl-5-methylene-3-vinyl-bicyclo[2.2.2]octan-2-one (330)**

A solution of trienone **329** (51.7 mg, 0.189 mmol) in toluene (3 mL) was heated in a sealed tube at an external temperature of 110 °C for 3 h to yield the title compound (36.9

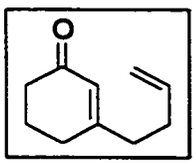
mg, 71 %). ^{1}H NMR 0.99 (s, 3H), 1.00 (s, 3H), 1.15 (s, 3H), 1.55 - 1.71 (m, 4H), 1.84 (d, 3H, J = 1.3), 2.03 (d, 1H, J = 2.2), 3.17 (s, 3H), 4.80 (s, 1H), 4.85 (s, 1H), 5.05 (dd, 1H, J = 1.3, 10.8), 5.35 (dd, 1H, J = 1.3, 17.5), 5.87 (dd, 1H, J = 10.8, 17.5), 5.94 (m, 1H). ^{13}C (ppm): 13.9, 18.2, 19.1, 29.8, 30.6, 31.0, 38.3, 45.4, 56.3, 58.9, 62.4, 106.9, 114.2, 116.7, 137.0, 148.9, 161.6, 212.1. IR: 2959, 2930, 1716, 1660, 1461, 1382, 1229, 1131, 764, 750, 621. HRMS (M^+) calc'd 274.1934; found 274.1945. Anal calc'd for $C_{18}H_{26}O_2$ C: 78.79 H: 9.55; found C 78.75, H 9.47.



3-But-3-enyl-cyclohex-2-enone (336)

Pyridium chlorochromate (6.1 g, 28.3 mmol) was added to alcohol (**335**) (0.86 g, 5.6 mmol) and silica gel (6.1 g) in dichloromethane (50 mL) at 22 °C and stirred for 4 h. The solvent was removed, Et_2O added (50 mL) and suspension was filtered. The solvent was then evaporated and the resulting residue was purified by chromatography (1:1 to 1:5 petroleum ether/ether) to yield the title compound as a colourless oil (0.60 g, 71 %); ^{1}H NMR 1.46 – 1.52 (m, 2H), 1.64 – 1.67 (m, 2H), 1.79 – 1.82 (m, 2H), 1.86 – 1.91 (m, 2H),

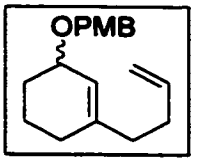
2.05 – 2.10 (m, 2H), 4.87 – 4.92 (m, 2H), 5.52 – 5.56 (m, 1H), 5.76 – 5.77 (m, 1H); ^{13}C NMR (ppm) 22.9, 29.5, 31.2, 37.1, 37.5, 115.3, 126.3, 137.5, 162.8, 196.9; IR (NaCl) 2929, 1670, 1625, 1426, 1325, 1254, 1192, 913, 887; HRMS (M^+) calc'd 150.1045; found 150.1042.



1-(1*RS*-3-But-3-enyl-cyclohex-2-enyloxymethyl)-4-methoxy-benzene (338)

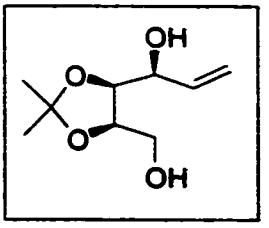
DIBAL-H (1.54 mL, 1.0 M, 1.5 mmol), was added to a solution of ketone (**336**) (0.20 g, 1.4 mmol) in dichloromethane at 0 °C and stirred for 2 h. Standard workup yielded the crude alcohol that was employed without purification. The alcohol was added in DMF (1 mL) to pre-washed (2 x 2 mL pentane) NaH (0.04 g, 1.7 mmol) in THF (2 mL) at 22 °C. The solution was stirred for 15 min followed by the addition of PMBCl (0.22 mL, 1.155 M, 1.6 mmol) and Bu_4NI (0.06 g, 0.2 mmol) and stirred for 18h. Standard workup followed by chromatography (15:1 to 8:1 petroleum ether/ether) yielded the title compound as a colourless oil (0.21 g, 51 %); ^1H NMR 1.39 – 1.45 (m, 1H), 1.63 – 1.82 (m, 5H), 1.93 – 1.97 (m, 2H), 2.05 – 2.09 (m, 2H), 3.34 (s, 3H), 3.87 (s, br, 1H), 4.38 – 4.45 (m, 2H), 4.93 – 5.01 (m, 2H), 5.63 (s, 1H), 5.70 – 5.78 (m, 1H), 6.75 (d, 2H, J =

8.2), 7.23 (d, 2H, J = 8.2); ^{13}C NMR (ppm) 20.0, 29.0, 32.2, 37.3, 54.6, 69.8, 72.7, 113.9, 114.6, 123.2, 129.1, 132.1, 137.4, 138.6, 140.8, 159.5; IR (NaCl) 2936, 1608, 1512, 1456, 1432, 1301, 1248, 1172, 1073, 1037, 910, 822; HRMS (M^+) calc'd 272.1777; found 272.1791.



1-(5*R*-Hydroxymethyl-2,2-dimethyl-[1,3]dioxolan-4*S*-yl)-propen-3*S*-ol (365)

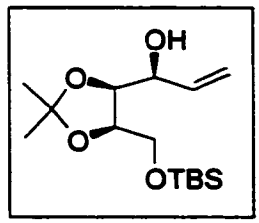
Vinylmagnesium chloride (41.9 mL, 41.9 mmol) was added to a solution of the hemiacetal (**363**) (1.34 g, 8.4 mmol) in THF (25 mL) at - 78 °C. The solution was stirred at -78 °C for 10 min then warmed to 22 °C and stirred an additional 90 min. Standard workup (EtOAc extraction) followed by column chromatography (1:1 to 10:1 ether/petroleum ether) yielded the title compound (1.26 g, 80 %). ^{1}H NMR 1.31 (s, 3H), 1.39 (s, 3H), 3.35 - 3.60 (s, br, 2H), 3.70 - 3.72 (m, 1H), 3.73 - 3.75 (m, 1H), 3.98 - 4.02 (m, 1H), 4.24 - 4.29 (m, 1H), 5.24 (d, 1H, J = 10.6), 5.35 (d, 1H, J = 17.3), 5.93 - 5.99 (m, 1H); ^{13}C 25.2, 27.7, 60.7, 70.6, 77.2, 79.5, 108.5, 116.7, 137.4; IR (neat) 3363, 2987, 1377, 1223, 1052, 994; HRMS (M^+ - CH_3) calc'd 173.0814; found 173.0808.



1*S*-[5*R*-(*t*-Butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4*S*-yl]-prop-2-en-1-ol (366)

Imidazole (0.56 g, 8.3 mmol) was added to a solution of diol (**365**) (0.65 g, 3.5 mmol) in THF (10 mL) and DMF (3.4 mL) at 0 °C. TBSCl (0.63 g, 4.1 mmol) was then added and the solution was stirred at 0 °C for 90 min. Standard workup followed by column chromatography (10:1 to 3:1 petroleum ether/ ether) yielded the title compound (0.96 g, 92 %).

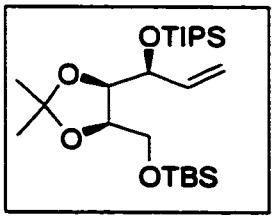
^{1}H NMR 0.07 (s, 6H), 0.88 (s, 9H), 1.34 (s, 3H), 1.47 (s, 3H), 3.72 - 3.76 (m, 2H), 3.91 - 4.11 (m, 1H), 4.16 - 4.20 (m, 1H), 4.34 - 4.35 (m, 1H), 4.37 (s, br, 1H), 5.20 (d, 1H, J = 10.6), 5.38 (d, 1H, J = 17.3), 5.95 - 6.02 (m, 1H); ^{13}C -5.4, 18.3, 24.9, 25.8, 27.0, 61.8, 70.0, 77.3, 79.7, 108.2, 115.8, 137.8; IR: 3350, 2941, 1468, 1377, 1254, 1090, 842; HRMS (M^+ - CH_3) calc'd 287.1679; found 287.1672.



4*R*-(*t*-Butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-5*S*-(1*S*-triisopropylsilanyloxy-allyl)-[1,3]dioxolane (367)

Collidene (0.92 g, 7.6 mmol) and TIPSOTf (1.17 g, 3.8 mmol) were added to a solution of alchohol (**366**) (0.96 g, 3.2 mmol) in CH_2Cl_2 (12 mL) at 0 °C. The solution was slowly warmed to 22 °C and stirred for 23 h. Standard workup followed by column

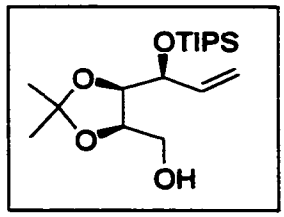
chromatography (20:1 to 8:1 petroleum ether/ ether) yielded the title compound (1.45 g, 99 %). ^{1}H NMR: δ 0.05 (s, 6H), 0.89 (s, 9H), 1.04 - 1.05 (s, br, 21H), 1.32 (s, 3H), 1.43 (s, 3H), 3.75 (dd, 1H, *J* = 10.0, 7.4), 3.93 (dd, 1H, *J* = 11.0, 3.8), 4.05 (dd, 1H, *J* = 6.4, 5.4, 1H), 4.16 - 4.20 (m, 1H), 4.50 (dd, 1H, *J* = 7.4, 5.4), 5.23 (dd, 1H, *J* = 17.2, 10.4), 5.82 - 5.89 (m, 1H); ^{13}C -5.3, -5.2, 12.7, 18.0, 25.3, 25.9, 27.6, 63.1, 78.7, 77.3, 80.0, 108.1, 117.3, 138.3; IR (neat) 2917, 1465, 1376, 1250, 1092, 924, 841, 778, 673; HRMS (M+ - CH3) calc'd 458.3015; found 443.3003.



[2,2-Dimethyl-5*S*-(1*S*-triisopropylsilanyloxy-allyl)-[1,3]dioxolan-4*R*-yl]-methanol (368)

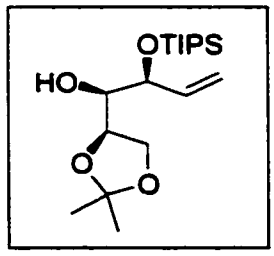
PPTS (0.32 g, 1.3 mmol) was added to solution of disilyl diether (**367**) (1.18 g, 2.6 mmol) was EtOH (15 mL) at 22 °C. The solution was stirred for 14 h. Standard workup followed by column chromatography (5:1 to 3:1 petroleum ether/ ether) yielded the title compound (0.64 g, 73 %) and the rearranged alcohol (**368a**) (0.03 g, 3 %). ^{1}H NMR 1.08 - 1.10 (s, br, 21H), 1.25 (s, 3H), 1.45 (s, 3H), 2.62 (dd, 1H, *J* = 8.2, 5.6), 3.83 - 3.98 (m, 3H), 4.19 (dd, 1H, *J* = 11.2, 5.8), 4.58 - 4.60 (m, 1H), 4.95 (d, 1H, *J* = 10.4), 5.08 (d, 1H, *J* = 17.2), 5.72 - 5.79 (m, 1H); ^{13}C 12.9, 18.3, 25.7, 27.9, 62.3, 73.8, 78.4, 80.2, 108.2,

117.5, 138.4; IR (neat) 3464, 2943, 2869, 1464, 1381, 1244, 1065, 926, 883, 672; HRMS (M^+ - CH_3) calc'd 329.2149; found 329.2172.



1-(2,2-Dimethyl-[1,3]dioxolan-4*R*-yl)-2*S*-triisopropylsilanyloxy-but-3-en-1*S*-ol (368a)

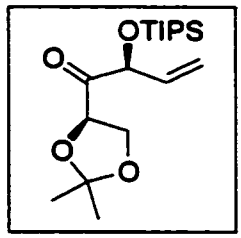
Rearranged alcohol (**368a**) (0.03 g, 3 %) ^{1}H NMR: δ 1.05 - 1.06 (s, br, 21H), 1.25 (s, 3H), 1.41 (s, 3H), 2.34 (s, br, 1H), 3.81 - 3.87 (m, 1H), 4.01 - 4.08 (m, 2H), 4.16 (dd, 1H, J = 8.2, 5.3), 4.60 (dd, 1H, J = 6.9, 3.0), 5.12 (d, 1H, J = 10.5), 5.32 (d, 1H, J = 17.3), 5.91 - 5.96 (m, 1H); ^{13}C 12.6, 18.2, 25.5, 27.1, 67.7, 75.4, 75.7, 76.6, 109.1, 117.3, 136.7; IR (neat) 3514, 2944, 2869, 1464, 1376, 1248, 1067, 926, 883, 672; HRMS (M^+ - CH_3) calc'd 329.2149; found 329.2142.



1-(2,2-Dimethyl-[1,3]dioxolan-4*R*-yl)-2*S*-triisopropylsilanyloxy-but-3-en-1-one (370)

Dess-Martin periodonane (0.21 g, 0.5 mmol) was added to solution of alcohol (**368a**) (0.13 g, 0.4 mmol) and $NaHCO_3$ (0.1 g) in CH_2Cl_2 (2.5 mL) at 22 °C. The solution was

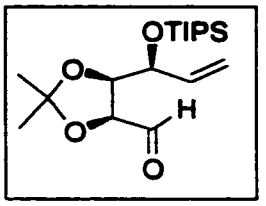
stirred for 4 h. Standard workup followed by column chromatography (8:1 to 2:1 petroleum ether/ ether) yielded the title compound (0.08 g, 52 %). ^{1}H NMR: δ 1.06 (s, br, 21H), 1.22 (s, 3H), 1.42 (s, 3H), 3.93 (dd, 1H, J = 8.6, 7.5), 4.16 (dd, 1H, J = 8.6, 5.6), 4.50 (dd, 1H, J = 7.5, 5.6), 5.08 (dd, 1H, J = 8.8, 1.7), 5.23 (dt, 1H, J = 5.3, 1.7), 5.53 (dt, 1H, J = 17.1, 1.7), 5.97 (ddd, 1H, J = 17.1, 8.8, 5.3); ^{13}C 12.6, 18.1, 25.3, 26.1, 66.8, 77.4, 79.0, 110.9, 117.5, 135.3, 205.1; IR (NaCl) 2845, 2868, 1738, 1469, 1377, 1217, 1112, 1071, 882, 676; HRMS (M^+ - CH_3) calc'd 327.1993; found 327.1995.



2,2-Dimethyl-5*S*-(1*S*-triisopropylsilanyloxy-allyl)-[1,3]dioxolane-4*R*-carbaldehyde (369)

Dess-Martin periodonane (0.66 g, 1.3 mmol) was added to solution of alcohol (**368**) (0.45 g, 1.3 mmol) and $NaHCO_3$ (0.2 g) in CH_2Cl_2 (10 mL) at 22 °C. The solution was stirred for 2 h. Standard workup followed by column chromatography (3:1 to 2:1 petroleum ether/ether) yielded the title compound (0.36 g, 81 %). ^{1}H NMR: δ 1.09 - 1.11 (s, br, 21H), 1.15 (s, 3H), 1.53 (s, 3H), 4.06 (dd, 1H, J = 7.3, 2.7), 4.13 (dd, 1H, J = 7.3, 3.3), 4.54 - 4.56 (m, 1H), 4.92 (d, 1H, J = 10.4), 4.97 (d, 1H, J = 17.3), 5.77 - 5.84 (m, 1H), 9.79 (d, 1H, J = 3.3); ^{13}C 12.7, 18.2, 25.0, 27.1, 73.9, 80.9, 84.3, 110.3, 138.0, 198.6; IR

(neat) 2943, 2869, 1734, 1464, 1381, 1216, 1145, 1079, 996, 934, 883, 862, 677; HRMS (M^+ - CH_3) calc'd 327.1993; found 327.2002.



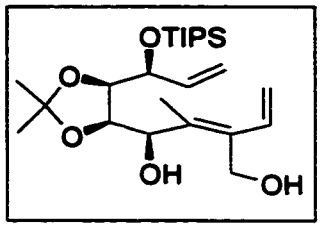
1-[2,2-Dimethyl-5*S*-(1*S*-triisopropylsilanyloxy-allyl)-[1,3]dioxolan-4*R*-yl]-2-methyl-3-vinyl-but-2-ene-1*R*,4-diol (371)

Vinylmagnesium chloride (4.6 mL, 1.42 M, 6.5 mmol) was added to a solution of 2-butyn-1-ol (**139**) (0.3 mL, 3.9 mmol) in cyclohexane (6 mL). The solution was heated at reflux for 22 h. The solution was cooled to - 78 °C and the aldehyde (**369**) (3.7g, 13.5 mmol) in THF (1 mL) was added dropwise. The mixture was stirred for 2 h at -78 °C followed by 19 h at 22 °C. Standard workup followed by flash column chromatography (3:1 to 1:10 petroleum ether/ether) yielded a mixture of the unstable title compound (0.19 g, 43 %) and its more polar (and more unstable) diastereomer (0.07 g, 16 %).

Less polar diastereomer: $[\alpha]_D^{23}$ = + 9.2° (c=1.3, MeOH)

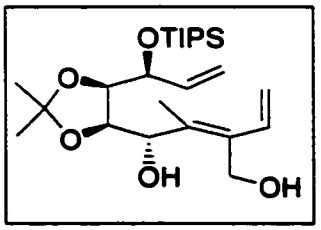
^{1}H NMR: δ 1.11 (s, br, 21H), 1.28 (s, 3H), 1.55 (s, br, 1H), 1.72 (s, 3H), 2.11 (s, 3H), 3.97 (dd, 1H, *J* = 6.6, 4.0), 4.00 (s, br, 1H), 4.16 (d, 1H, *J* = 6.6), 4.38 (m, 2H), 4.77 - 4.78 (m, 1H), 5.04 - 5.08 (m, 3H), 5.21 (d, 1H, *J* = 17.3), 5.39 (d, 1H, *J* = 17.5), 5.81 (ddd, 1H, *J* = 17.3, 10.7, 6.0), 6.72 (dd, 1H, *J* = 17.5, 11.1); ^{13}C 12.8, 15.4, 18.1, 25.8,

26.4, 58.1, 70.7, 73.0, 80.4, 81.2, 108.6, 113.4, 117.3, 132.5, 135.1, 137.4, 141.1; IR (neat) 3414, 2940, 2869, 1463, 1378, 1245, 1037, 885, 794, 682; HRMS unstable.



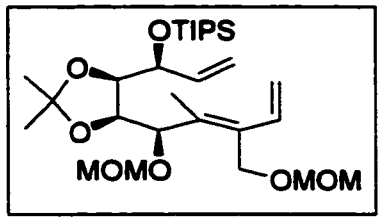
Other diastereomer (**371a**)

^{1}H NMR: δ 1.11 (s, br, 21H), 1.28 (s, 3H), 1.55 (s, br, 1H), 1.72 (s, 3H), 2.11 (s, 3H), 3.97 (dd, 1H, *J* = 6.6, 4.0), 4.00 (s, br, 1H), 4.16 (d, 1H, *J* = 6.6), 4.38 (m, 2H), 4.77 - 4.78 (m, 1H), 5.04 - 5.08 (m, 3H), 5.21 (d, 1H, *J* = 17.3), 5.39 (d, 1H, *J* = 17.5), 5.81 (ddd, 1H, *J* = 17.3, 10.7, 6.0), 6.72 (dd, 1H, *J* = 17.5, 11.1); ^{13}C 12.0, 13.3, 18.2, 18.3, 25.2, 27.3, 57.9, 68.3, 75.2, 77.8, 80.9, 108.8, 115.1, 119.2, 134.7, 136.1, 137.9, 138.2; IR (neat) 3414, 2940, 2869, 1463, 1378, 1245, 1037, 885, 794, 682; HRMS unstable.



Triisopropyl-{1*S*-[5*R*-(1*R*-methoxymethoxy-3-methoxymethoxymethyl-2-methyl-penta-2,4-dienyl)-2,2-dimethyl-[1,3]dioxolan-4*S*-yl]-allyloxy}-silane (371b)

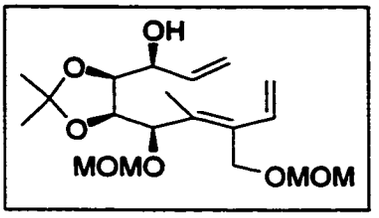
MOMCl (0.14 mL, 1.9 mmol) was added to a solution of diol (0.15 g, 0.3 mmol) and $^{i}PrN(Et)_2$ (0.3 mL, 1.9 mmol) in CH_2Cl_2 (2 mL) at 0 °C and stirred for 1 h. The solution was warmed to 22 °C and stirred for 14 h. Standard workup yielded the title compound that was used without further purification.



1-[5*R*-(1*R*-Methoxymethoxy-3-methoxymethoxymethyl-2-methyl-penta-2,4-dienyl)-2,2-dimethyl-[1,3]dioxolan-4*S*-yl]-prop-2-en-1*S*-ol (372)

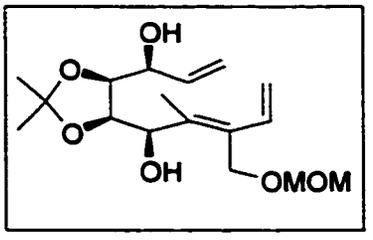
TBAF (0.41 mL, 0.41 mmol) was added to a solution of silyl ether (**371b**) (0.14 g, 0.27 mmol) in THF (7 mL) at 0 °C and stirred for 5 h. Standard workup followed by column chromatography (7:1 to 2:1 petroleum ether/ether) yielded the title compound (0.07 g, 66 %) and the mono-protected alcohol (**373**) (0.02 g, 17 %). ^{1}H NMR: δ 1.28 (s, 3H), 1.61 (s, 3H), 2.01 (s, 3H), 2.91 (m, br, 1H), 3.12 (s, 3H), 3.18 (s, 3H), 4.01 (dd, 1H, J = 9.0, 6.2), 4.30 - 4.32 (m, 2H), 4.36 - 4.41 (m, 3H), 4.45 - 4.48 (m, 2H), 4.81 - 4.84 (m, 1H), 5.13 (dd, 4H, J = 11.1, 0.9), 5.20 (dm, 1H, J = 10.7), 5.28 (d, 1H, J = 1.8), 5.51 (dm, 1H, J = 17.5), 5.57 (dm, 1H, J = 17.3) 6.29 - 6.35 (m, 1H), 6.72 (dd, 1H, J = 17.5, 11.1); ^{13}C 14.3, 25.9, 27.0, 55.3, 55.9, 62.0, 69.9, 73.1, 81.2, 94.8, 95.8, 109.2, 114.5, 114.6, 131.9,

134.7, 139.9, 140.5; IR (neat) 3449, 2985, 2927, 1628, 1376, 1223, 1151, 1053, 917; HRMS (M^+) calc'd 357.1814; found 357.1835.



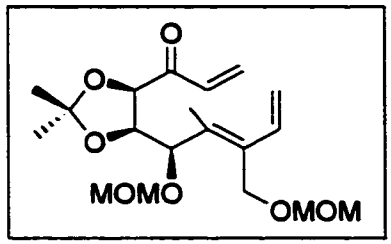
1-[5*S*-(1*S*-Hydroxy-allyl)-2,2-dimethyl-[1,3]dioxolan-4*R*-yl]-3-methoxymethoxymethyl-2-methyl-penta-2,4-dien-1*R*-ol (373)

^{1}H NMR: δ 1.14 (s, 3H), 1.42 (s, 3H), 1.99 (s, 3H), 2.78 (s, br, 1H), 3.00 (s, br, 1H), 3.15 (s, 3H), 3.94 - 3.97 (m, 1H), 4.19 (d, 1H, J = 6.6), 4.28 (d, 1H, J = 11.5), 4.36 (d, 1H, J = 11.5), 4.43 - 4.48 (m, 2H), 4.64 - 4.65 (m, 1H), 5.14 (d, 1H, J = 10.8), 5.29 (s, 1H), 5.45 (d, 1H, J = 17.3), 5.53 (d, 1H, J = 17.4), 6.20 (ddd, 1H, J = 17.3, 10.6, 4.6), 6.74 (dd, 1H, 17.4, 10.8); ^{13}C 13.9, 24.8, 26.9, 55.2, 62.2, 67.9, 70.7, 80.6, 81.0, 95.6, 108.6, 114.5, 115.1, 129.4, 135.0, 138.9, 142.7; IR (neat) 3402, 2985, 2932, 1378, 1216, 1131, 1051, 917; HRMS (M^+ - CH_3) calc'd 313.1652; found 313.1657.



1-[5*R*-(1*R*-Methoxymethoxy-3-methoxymethoxymethyl-2-methyl-penta-2,4-dienyl)-2,2-dimethyl-[1,3]dioxolan-4*S*-yl]-propenone (386)

Dess-Martin periodinane (0.15 g, 0.35 mmol) was added to a stirred solution of the corresponding alcohol (**372**) (0.07 g, 0.18 mmol) in dry CH_2Cl_2 (1.5 mL) at 0 °C. The reaction was stirred at 21 °C for 4 h. Et_2O (10 mL) was added, followed by standard workup and column chromatograpy (8:1 to 1:1 petroleum ether/Et_2O) to afford the title compound (0.06 g, 65 %) as a colourless oil. ^1H NMR: δ 1.11 (s, 3H), 1.57 (s, 3H), 2.03 (s, 3H), 3.13 (s, 3H), 3.31 (s, 3H), 4.30 - 4.45 (m, 5H), 4.57 - 4.65 (m, 3H), 4.90 (s, 1H), 5.12 (d, 1H, J = 11.9), 5.23 (d, 1H, J = 11.9), 5.50 (d, 1H, J = 18.4), 6.24 (d, 1H, J = 17.8), 6.73 (dd, 1H, J = 11.9, 18.4) 7.09 (dd, 1H, J = 11.9, 17.8). ^{13}C NMR: 24.8, 26.5, 55.2, 56.7, 62.1, 73.3, 81.2, 83.3, 95.8, 96.4, 110.3, 114.6, 126.7, 128.3, 131.9, 132.9, 134.8, 139.4, 197.8. IR: 2933, 1694, 1380, 1152, 1095, 1030. HRMS calc'd for $C_{18}H_{27}O_7$ (M^+ - CH_3OCH_2) 355.1757, found 355.1761.

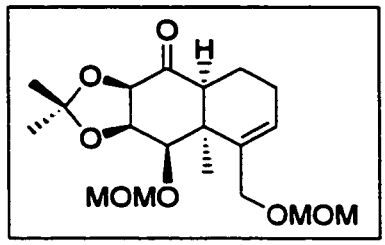


9*R*-Methoxymethoxy-8-methoxymethoxymethyl-2,2,8a*S*-trimethyl-4a*S*,5,6,8a,9,9a-hexahydro-3a*H*-naphtho[2,3-*d*][1*R*,3*S*]dioxol-4-one (387)

A stirred solution of enone **385** (28.3 mg, 0.076 mmol) in dry dichloromethane (1 mL) was heated at 40 °C for 4 h. The reaction was concentrated and chromatographed (3:1 to

1:5, petroleum ether/Et_2O) to afford the title compound (87 %, 24.6 mg) as a colourless oil: $[\alpha]_D^{25}$ = + 46.8° (c=1.1, MeOH)

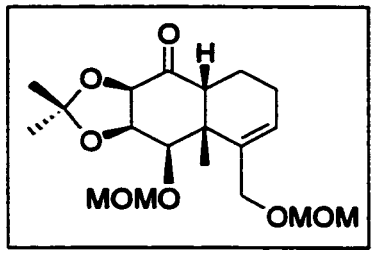
^{1}H NMR: δ 1.23 (s, 3H), 1.29 (s, 3H), 1.30 (s, 3H), 1.53 - 1.59 (m, 1H), 1.83-1.89 (m, 1H), 2.20 - 2.26 (m, 1H), 2.40 (t, 1H, *J* = 4.0), 2.42 - 2.46 (m, 1H), 3.07 (s, 3H), 3.20 (s, 3H), 4.11 (d, 1H, *J* = 12.3), 4.21 (d, 1H, *J* = 5.7), 4.31 (d, 1H, *J* = 3.6) 4.39 - 4.42 (m, 2H), 4.45 - 4.49 (m, 3H), 4.56 (d, 1H, *J* = 6.4), 5.56 (t, 1H, *J* = 3.5). ^{13}C NMR: 18.2, 22.4, 26.2, 27.0, 42.8, 49.5, 55.0, 55.9, 69.9, 77.6, 77.7, 78.2, 95.4, 97.8, 110.7, 126.2, 128.3, 137.8, 206.3; IR (neat) 2928, 1722, 1151, 1099, 1036; HRMS calc'd for $C_{19}H_{30}O_7$ (M^+) 370.1992, found 370.1993.



9*R*-Methoxymethoxy-8-methoxymethoxymethyl-2,2,8a*R*-trimethyl-4a*R*,5,6,8a,9,9a-hexahydro-3aH-naphtho[2,3-d][1*R*,3*S*]dioxol-4-one

Yield 3.2 mg (17%) ^{1}H NMR: δ 0.93 (s, 3H), 1.10 (s, 3H), 1.35 (s, 3H), 1.56 - 1.72 (m, 2H), 1.83 - 1.88 (m, 2H), 2.82 (d, 1H, *J* = 12.2), 3.20 (s, 3H), 3.27 (s, 3H), 3.88 (d, 1H, *J* = 5.0), 4.10 - 4.15 (m, 2H), 4.34 - 4.40 (m, 2H), 4.58 (s, 2H), 4.76 (d, 1H, *J* = 5.6), 4.87 (d, 1H, *J* = 5.6), 5.95 (d, 1H, *J* = 5.3); ^{13}C NMR: 16.3, 17.2, 24.5, 25.6, 27.5, 30.2, 32.2, 43.9, 49.7, 55.0, 56.7, 67.9, 77.7, 83.3, 83.6, 95.9, 96.7, 110.8, 125.3, 140.1, 204.9; IR

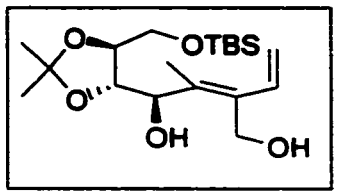
(neat) 2927, 1730, 1382, 1216, 1150, 1047; HRMS (M^+) calc'd 370.1992; found 370.1982.



1-[5*S*-(*t*-Butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4*R*-yl]-2-methyl-3-vinyl-but-2-ene-1*R*,4-diol (380)

Vinylmagnesium chloride (69 mL, 1.25 M, 86.4 mmol) was added to a solution of 2-butyn-1-ol (**139**) (2.1 mL, 27.0 mmol) in cyclohexane (60 mL). The solution was heated at reflux for 19 h. The solution was cooled to 0 °C and the aldehyde (3.7 g, 13.5 mmol) was added dropwise. The mixture was stirred for 30 min at 0 °C followed by 4 h at 22 °C. Standard workup followed by flash column chromatography (3:1 to 1:4 petroleum ether/ether) yielded a mixture of the title compound (1.91 g, 48 %) and its more polar diastereomer (1.40 g, 35 %). Less polar diastereomer: $[\alpha]_D^{23}$ = + 20° (c = 1.4, MeOH) ^{1}H NMR: δ 0.01 (s, 6H), 0.92 (s, 9H), 1.10 (s, 3H), 1.33 (s, 3H), 1.86 (s, 3H), 2,68 (d, 1H, *J* = 9.1), 3.03 (s, 1H), 3.70 (dd, 1H, *J* = 10.3, 6.2), 3.84 (dd, 1H, *J* = 10.3, 4.0), 3.90 (dd, 1H, *J* = 8.4, 8.0), 3.96 - 4.00 (m, 1H), 4.38 - 4.45 (m, 2H), 4.73 (dd, 1H, *J* = 8.4, 1.9), 5.15 (dd, 1H, *J* = 11.7, 1.3), 5.66 (dd, 1H, *J* = 17.4, 1.3), 6.69 (dd, 1H, *J* = 17.4, 11.7); ^{13}C -5.54, -5.51, 12.1, 18.4, 25.9, 26.7, 57.5, 64.4, 72.4, 79.1, 81.4, 109.5, 115.1, 134.7, 136.3, 137.3; IR (neat) 3417, 2927, 2856, 1472, 1254, 1072, 837, 778, 668; HRMS (M^+ -

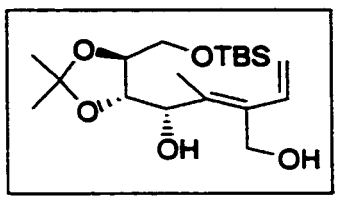
CH_3) calc'd 357.2098; found 357.2093; Anal calc'd for $C_{19}H_{36}O_5Si$ C, 61.25; H, 9.74. found: C, 61.20; H, 9.54.



1-[5*S*-(*t*-Butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4*R*-yl]-2-methyl-3-vinyl-but-2-ene-1*S*,4-diol (379)

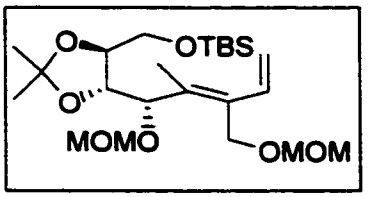
More polar diastereomer: $[\alpha]_D^{24}$ = + 17.4° (c = 4.5, MeOH)

^{1}H NMR: δ 0.03 (d, 6H, *J* = 6.9), 0.92 (s, 9H), 1.38 (s, 3H), 1.39 (s, 3H), 1.87 (s, 3H), 2.13 (s, br, 1H), 3.07 (s, br, 1H), 3.60 (dd, 1H, *J* = 11.2, 3.8), 3.70 (dd, 1H, *J* = 11.2, 4.1), 4.09 - 4.12 (m, 1H), 4.18 - 4.21 (m, 1H), 4.24 - 4.33 (m, 1H), 4.85 (d, 1H, *J* = 5.3), 5.09 (dd, 1H, *J* = 11.2, 0.8), 5.44 (dd, 1H, *J* = 17.4, 0.8), 6.59 (dd, 1H, *J* = 17.4, 11.2); ^{13}C - 5.4, -5.3, 13.9, 18.5, 26.1, 27.3, 27.5, 57.7, 63.5, 71.7, 78.7, 80.3, 109.3, 115.1, 134.5, 134.8, 137.5; IR (neat) 3389, 2930, 2858, 1472, 1375, 1254, 836, 778, 678; HRMS (M^+ - CH_3) calc'd 357.2098; found 357.2065; Anal calc'd for $C_{19}H_{36}O_5Si$ C, 61.25; H, 9.74. found: C, 60.98; H, 9.80.



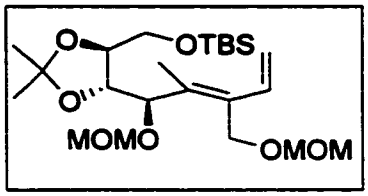
***t*-Butyl-[5*R*-(1*S*-methoxymethoxy-3-methoxymethoxymethyl-2-methyl-penta-2,4-dienyl)-2,2-dimethyl-[1,3]dioxolan-4*S*-ylmethoxy]-dimethyl-silane (382a)**

MOMCl (1.6 g, 20.0 mmol) was added to a solution of diol (**381a**) (1.37g, 3.7 mmol) and $^{i}PrN(Et)_2$ (3.6 mL, 20.7 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The solution was warmed to 22 °C and stirred for 14 h. Standard workup followed by column chromatography (7:1 to 2:1 petroleum ether/ether) yielded the title compound (1.12 g, 65 %). $[\alpha]_D^{26}$ = - 66.6° (c = 1.5, MeOH) ^{1}H NMR: δ 0.06 (d, 6H, *J* = 11.3), 0.55 (s, 1H), 0.94, (s, 9H), 1.09 (t, 1H, *J* = 7.0), 1.49 (s, 3H), 1.51 (s, 3H), 1.91 (s, 3H), 3.22 (s, 3H), 3.27 (s, 3H), 3.59 (dd, 1H, *J* = 16.4, 3.8), 3.80 (dd, 1H, *J* = 11.4, 3.1), 4.24 - 4.27 (m, 1H), 4.35 (d, 1H, *J* = 11.2), 4.43 (d, 1H, *J* = 11.2), 4.47 - 4.51 (m, 3H), 4.54 - 4.57 (m, 2H), 5.00 (d, 1H, *J* = 6.8), 5.12 (dd, 1H, *J* = 11.2, 1.1), 5.49 (dd, 1H, *J* = 17.4, 1.1), 6.69 (dd, 1H, *J* = 17.4, 11.2); ^{13}C -5.3, -5.1, 13.9, 18.6, 26.1, 27.5, 27.7, 55.2, 62.2, 63.2, 75.7, 78.7, 78.8, 94.0, 96.0, 109.0, 115.4, 133.6, 134.4, 137.1; IR (neat) 2987, 2858, 1631, 1596, 1471, 1380, 1256, 917, 836, 778; HRMS (M^+) calc'd 460.2858; found 460.2863.



***t*-Butyl-[5*R*-(1*R*-methoxymethoxy-3-methoxymethoxymethyl-2-methyl-penta-2,4-dienyl)-2,2-dimethyl-[1,3]dioxolan-4*S*-ylmethoxy]-dimethyl-silane (382b)**

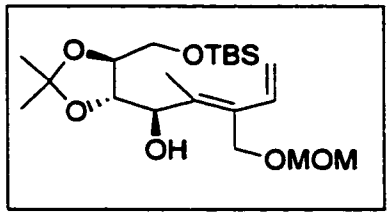
MOMCl (2.2 g, 27.6 mmol) was added to a solution of diol (**381b**) (1.90g, 5.1 mmol) and $^{i}PrN(Et)_2$ (5.0 mL, 28.6 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The solution was warmed to 22 °C and stirred for 14 h. Standard workup followed by column chromatography (7:1 to 2:1 petroleum ether/ether) yielded the title compound (1.09 g, 46 %) and the mono-protected alcohol (**382c**) (1.01 g, 48 %). $[\alpha]_D^{25}$ = + 66.6° (c = 1.0, MeOH). ^{1}H NMR: δ 0.14 (s, 6H), 1.01, (s, 9H), 1.40 (s, 3H), 1.41 (s, 3H), 1.83 (s, 3H), 3.12 (s, 3H), 3.24 (s, 3H), 3.85 (dd, 2H, *J* = 11.0, 4.8), 4.07 (dd, 1H, *J* = 11.0, 2.2), 4.20 - 4.29 (m, 3H), 4.44 (d, 1H, *J* = 11.7), 4.44 (d, 1H, *J* = 11.7), 4.55 - 4.64 (m, 4H), 4.99 (d, 1H, *J* = 8.2), 5.16 (dd, 1H, *J* = 11.2, 1.3), 5.61 (dd, 1H, *J* = 17.4, 1.3), 6.69 (dd, 1H, *J* = 17.4, 11.2); ^{13}C - 5.1(2), -5.1(0), 13.0, 18.6, 26.1, 27.2, 27.3, 55.1, 61.9, 64.7, 76.1, 77.0, 82.6, 93.9, 95.6, 109.5, 115.5, 134.5, 134.7, 136.2; IR (neat) 2986, 2858, 1633, 1597, 1472, 1379, 1257, 917, 859, 777; HRMS (M^+) calc'd 460.2858; found 460.2880.



1-[5*S*-(*t*-Butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4*R*-yl]-3-methoxymethoxymethy-l-2-methyl-penta-2,4-dien-1*R*-ol (382c)

Mono-protected alcohol: $[\alpha]_D^{26}$ = + 4.4° (c = 1.2, MeOH)

^{1}H NMR: δ 0.07 (s, 6H), 0.60, (s, 1H), 0.96 (s, 9H), 1.36 (s, 3H), 1.37 (s, 3H), 1.96 (s, 3H), 3.08 (s, 1H), 3.14 (s, 3H), 3.89 (d, 2H, *J* = 4.7), 4.12 (t, 1H, *J* = 7.8), 4.20 - 4.23 (m, 1H), 4.37 (d, 1H, *J* = 11.9), 4.47 - 4.51 (m, 2H), 4.60 (d, 1H, *J* = 11.9), 4.93 (dd, 1H, *J* = 8.3, 2.2), 5.13 (d, 1H, *J* = 11.2), 5.58 (dd, 1H, *J* = 17.4), 6.69 (dd, 1H, *J* = 17.4, 11.7); ^{13}C -5.4, 13.1, 18.5, 26.0, 27.1, 55.0, 61.9, 64.7, 72.6, 79.0, 82.0, 94.7, 109.3, 115.1, 134.9, 140.1; IR (neat) 3445, 2986, 2858, 1633, 1597, 1471, 1371, 1252, 1149, 917, 861, 780; HRMS (M^+ - CH_3) calc'd 401.2360; found 401.2359.

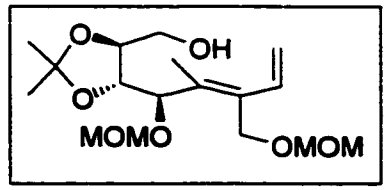


[5*R*-(1*R*-Methoxymethoxy-3-methoxymethoxymethyl-2-methyl-penta-2,4-dienyl)-2,2-dimethyl-[1,3]dioxolan-4*S*-yl]-methanol (383b)

TBAF (2.7 mL, 2.6 mmol) was added to a solution of the silyl ether (382b) (0.81 g, 1.8 mmol) in THF (15 mL) at 0 °C. The solution was warmed to 22 °C and stirred for 14 h. Standard workup followed by column chromatography (1:1 to 5:1 ether/petroleum ether) yielded the title compound (0.60 g, 98 %). $[\alpha]_D^{26}$ = + 88.2° (c = 2.9, MeOH)

^{1}H NMR: δ 0.64 (s, br, 1H), 1.29 (s, 3H), 1.35 (s, 3H), 1.49 (s, 3H), 2.22 (s, br, 1H), 3.06 (s, 3H), 3.22 (s, 3H), 3.83 - 3.91 (m, 2H), 4.10 - 4.22 (m, 3H), 4.42 (d, 1H, *J* = 11.7),

4.48 (d, 1H, J = 6.6), 4.54 - 4.61 (m, 3H), 4.95 (d, 1H, J = 8.3), 5.15 (d, 1H, J = 11.7), 5.59 (d, 1H, J = 17.4), 6.65 (dd, 1H, J = 17.4, 11.7); ^{13}C 26.9, 27.1, 55.1, 55.7, 61.8, 63.7, 76.6, 77.4, 82.1, 93.7, 95.5, 109.4, 115.6, 134.6, 134.7, 135.8; IR (neat) 3478, 2934, 2888, 1632, 1597, 1452, 1375, 1212, 1032, 917, 854; HRMS (M^+) calc'd 346.1992; found 346.1990. ; Anal calc'd for $C_{17}H_{30}O_7$ C, 59.29; H, 8.19. found: C, 59.22; H, 8.29.

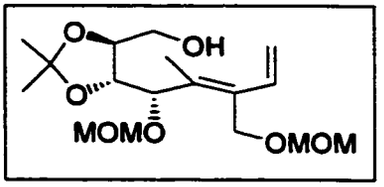


[5*R*-(1*S*-Methoxymethoxy-3-methoxymethoxymethyl-2-methyl-penta-2,4-dienyl)-2,2-dimethyl-[1,3]dioxolan-4*S*-yl]-methanol (383a)

TBAF (3.7 mL, 3.7 mmol) was added to a solution of the silyl ether (**382a**) (1.13 g, 2.5 mmol) in THF (20 mL) at 0 °C. The solution was warmed to 22 °C and stirred for 14 h. Standard workup followed by column chromatography (1:1 to 5:1 ether/petroleum ether) yielded the title compound (0.75 g, 88 %). $[\alpha]_D^{25}$ = - 82.0° (c = 1.7, MeOH).

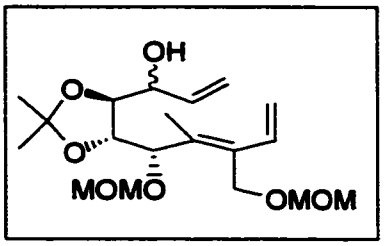
^{1}H NMR: δ 0.69 (s, br, 1H), 1.39 (s, 3H), 1.46 (s, 3H), 1.84 (s, 3H), 1.92 (s, br, 1H), 3.15 (s, 3H), 3.22 (s, 3H), 3.49 - 3.54 (m, 1H), 3.67 - 3.71 (m, 1H), 4.23 - 4.42 (m, 6H), 4.47 - 4.51 (m, 2H), 4.94 (d, 1H, J = 6.0), 5.09 (d, 1H, J = 11.2), 5.45 (d, 1H, J = 17.4), 6.60 (dd, 1H, J = 17.4, 11.2); ^{13}C 13.9, 27.2, 27.5, 55.2, 62.1, 62.3, 75.1, 78.5, 79.5, 94.0,

95.8, 109.0, 115.3, 133.6, 134.3, 137.3; IR (neat) 3474, 2987, 1631, 1596, 1596, 1452, 1375, 1255, 918, 853; HRMS (M^+) calc'd 346.1992; found 346.1988. ; Anal calc'd for $C_{17}H_{30}O_7$ C, 59.29; H, 8.19. found: C, 59.18; H, 8.32.



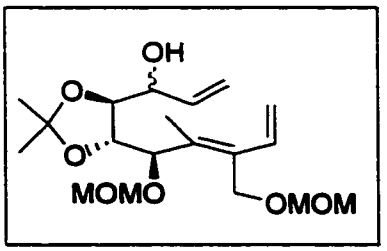
1-[5*R*-(1*S*-Methoxymethoxy-3-methoxymethoxymethyl-2-methyl-penta-2,4-dienyl)-2,2-dimethyl-[1,3]dioxolan-4*S*-yl]-prop-2-en-1*RS*-ol (384a)

Oxalyl chloride (0.57 mL, 1.46 g/mL, 6.5 mmol) was added to DMSO (0.92 mL, 1.101 g/mL, 13.0 mmol) in dichloromethane (9 mL) at –78 °C and stirred for 2 min. Alcohol (**383a**) (1.02 g, 2.94 mmol) in dichloromethane (5 mL) was added to the solution at –78 °C and stirred for 1 h. Triethyl amine (2.1 mL, 0.73 g/mL, 14.7 mmol) was added and the resulting solution stirred for 5 min followed by 1 h at 0 °C. The mixture was then cooled to –78 °C followed by the addition of vinylmagnesium chloride (23.0 mL, 0.91 M, 21.0 mmol). The resulting solution was stirred for 4 h at 22 °C. Standard workup followed by chromatography (8:1 to 1:1 petroleum ether/ether) yielded the title compound as a complex mixture of diastereoisomers that were employed without further purification (0.86 g, 78 %).



1-[5*R*-(1*R*-Methoxymethoxy-3-methoxymethoxymethyl-2-methyl-penta-2,4-dienyl)-2,2-dimethyl-[1,3]dioxolan-4*S*-yl]-prop-2-en-1*RS*-ol (384b)

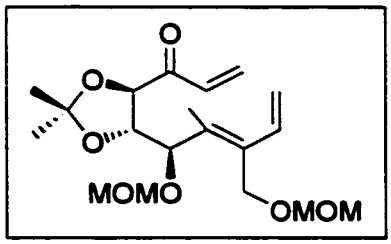
Added oxalyl chloride (0.50 mL, 1.46 g/mL, 5.7 mmol) to DMSO (0.81 mL, 1.101 g/mL, 11.4 mmol) in dichloromethane (8 mL) at –78 °C and stirred for 2 min. Added alcohol (**383b**) (0.90 g, 2.58 mmol) in dichloromethane (4 mL) at –78 °C and stirred for 1 h. Added triethyl amine (1.8 mL, 0.73 g/mL, 12.9 mmol) and stirred for 5 min followed by 1 h at 0 °C. The mixture was then cooled to –78 °C followed by the addition of vinylmagnesium chloride (18.0 mL, 0.91 M, 16.3 mmol). The resulting solution was stirred for 4 h at 22 °C. Standard workup followed by chromatography (8:1 to 1:1 petroleum ether/ether) yielded the title compound as a complex mixture of diastereoisomers that were employed without further purification (0.75 g, 78 %).



1-[5*R*-(1*R*-Methoxymethoxy-3-methoxymethoxymethyl-2-methyl-penta-2,4-dienyl)-2,2-dimethyl-[1,3]dioxolan-4*S*-yl]-propenone (385b)

Dess-Martin periodinane (0.49 g, 1.15 mmol) was added to a stirred solution of the corresponding alcohol (**384b**) (0.14 g, 0.38 mmol) in dry CH_2Cl_2 (3.3 mL) at 0 °C. The reaction was stirred at 21 °C for 4 h. Et_2O (10 mL) was added, followed by standard workup and column chromatograpy (6:1 to 3:1, petroleum ether/Et_2O) to afford the enone 22 (80%, 114 mg) as a colourless oil. $[\alpha]_D^{25} = +58.1°$ (c = 1.9, MeOH)

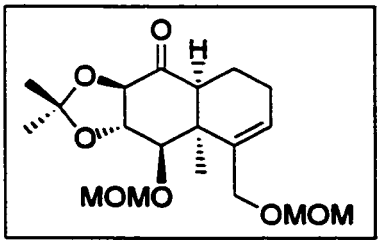
^{1}H NMR: δ 1.24 (s, 3H), 1.83 (s, 3H), 3.12 (s, 3H), 3.22(2) (s, 3H), 3.22(3) (s, 3H), 4.29 (d, 1H, *J* = 6.5), 4.40 (d, 1H, *J* = 11.6), 4.51 - 4.58 (m, 4H), 4.73 - 4.78 (m, 2H), 5.02 (d, 1H, *J* = 6.7), 5.14 (d, 1H, *J* = 11.2), 5.33 (d, 1H, *J* = 10.6), 5.56 (d, 1H, *J* = 17.4), 6.33 (d, 1H, *J* = 17.5), 6.67 (dd, 1H, *J* = 11.2, 17.4), 6.69 (dd, 1H, *J* = 10.6, 17.5). ^{13}C NMR: 10.3, 23.2, 24.0, 52.2, 52.6, 58.9, 73.3, 75.2, 79.7, 91.1, 92.6, 108.4, 112.5, 126.5, 131.6, 133.0, 138.8, 193.7; IR (neat) 2936, 1700, 1212, 1151, 1099, 1031 cm^{-1}. ; Anal. calc'd for $C_{19}H_{30}O_7$: % C 61.60, % H 8.16; found: % C 61.39, % H 7.93.



9*R*-Methoxymethoxy-8-methoxymethoxymethyl-2,2,8a*S*-trimethyl-4a*S*,5,6,8a*S*,9,9a-hexahydro-3aH-naphtho[2,3-d][1*S*,3*S*]dioxol-4-one (389)

A stirred solution of enone (**385b**) (35.0 mg, 0.094 mmol) in dry toluene (1 mL) was placed in a pressure tube equipped with an expansion side arm and sealed with a threaded Teflon cap. The reaction was heated at 220 °C for 24 h. The solution was allowed to cool to 21 °C, the reaction concentrated and chromatographed (3:2, petroleum ether/Et_2O)

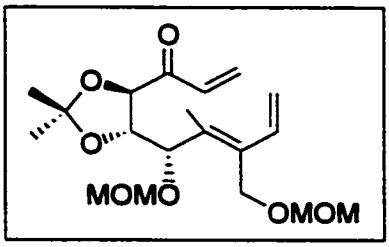
to afford the title compound (25.2 mg, 72%) as a colorless oil. $[\alpha]_D^{27}$ = - 22.0° (c = 0.3, MeOH). ^{1}H NMR: δ 1.28 (s, 3H), 1.31 (s, 3H), 1.32 (s, 3H), 1.35 - 1.44 (m, 1H), 1.66 - 1.73 (m, 1H), 2.15 - 2.23 (m, 2H), 2.49 - 2.56 (m, 1H), 3.18 (s, 3H), 3.26 (s, 3H), 3.82 - 3.86 (m, 2H), 4.01 (d, 1H, *J* = 11.0), 4.37 (s, 2H), 4.61 (d, 1H, *J* = 6.65) 4.67 (s, 1H), 4.74 (d, 1H, *J* = 11.0), 5.03 (d, 1H, *J* = 6.7 Hz), 5.42 - 5.44 (m, 1H). ^{13}C NMR: 17.1, 22.1, 26.7, 26.8, 27.0, 45.6, 49.2, 55.3, 56.1, 69.2, 75.2, 78.7, 80.0, 95.6, 97.8, 111.0, 131.1, 136.3, 201.1; IR (neat) 2933, 1737, 1152, 1031, 750. HRMS (M^+) calc'd 370.1992, found 370.1994.



1-[5*R*-(1*S*-Methoxymethoxy-3-methoxymethoxymethyl-2-methyl-penta-2,4-dienyl)-2,2-dimethyl-[1,3]dioxolan-4*S*-yl]-propenone (385a)

Dess-Martin periodinane (0.53 g, 1.24 mmol) was added to a stirred solution of the corresponding alcohol (**384a**) (0.15 g, 0.41 mmol) in dry CH_2Cl_2 (3.5 mL) at 0 °C. The reaction was stirred at 21 °C for 4 h. Et_2O (10 mL) was added, followed by standard workup and column chromatography (6:1 to 3:1, petroleum ether/Et_2O) to afford the enone (0.07 g, 48 %) as a colourless oil. $[\alpha]_D^{25}$ = - 95.1° (c = 3.3, $CHCl_3$). ^{1}H NMR: δ 1.30 (s, 3H), 1.48 (s, 3H), 1.94 (s, 3H), 3.22 (s, 3H), 3.24 (s, 3H), 4.33 (d, 1H, *J* = 11.1), 4.41 (d, 1H, *J* = 11.1), 4.48 - 4.59 (m, 4H), 4.76 (t, 1H, *J* = 6.1), 4.88 (d, 1H, *J* = 6.7), 5.06 – 5.08 (m, 2H), 5.25 (d, 1H, *J* = 10.6), 5.43 (d, 1H, *J* = 17.4), 6.28 (d, 1H, *J* = 17.5),

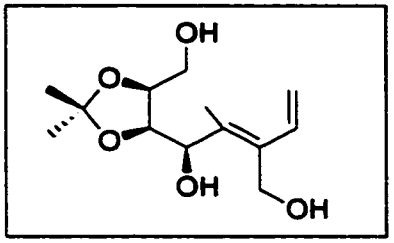
6.63 (dd, 1H, J = 17.4, 11.1), 6.69 (dd, 1H, J = 17.5, 10.6). ^{13}C NMR: 13.7, 26.6, 27.1, 55.2, 55.4, 62.2, 75.0, 80.8, 80.9, 94.1, 96.2, 111.4, 115.1, 129.5, 132.3, 133.8, 134.5, 137.5, 197.9; IR (neat) 2936, 1700, 1100, 1031, 917; HRMS calc'd for $C_{19}H_{30}O_7$ (M^+ - CH_3) 355.1751, found 355.1743. Anal. calc'd for $C_{19}H_{30}O_7$: % C 61.60, % H 8.16; found: % C 61.83, % H 7.98.



1-(5-Hydroxymethyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-2-methyl-3-vinyl-but-2-ene-1,4-diol (164)

Vinylmagnesium chloride (0.9 mL, 1.42 M, 1.3 mmol) was added to a solution of 2-butyn-1-ol (0.06 mL, 0.8 mmol) in cyclohexane (1.2 mL). The solution was heated at reflux for 22 h. The solution was cooled to - 78 °C and the aldehyde (**163**) (0.37g, 1.4 mmol) in THF (0.2 mL) was added. The mixture was stirred for 2 h at -78 °C followed by 19 h at 22 °C. Standard workup followed by flash column chromatography (3:1 to 1:20 petroleum ether/ether) yielded an inseperable mixture of the two diasteroisomers (0.14 g, 44 %). Major diastereomer (estimated by ^1H NMR, 0.12 g, 33 %): ^1H NMR: δ 1.43 (s,

6H), 1.71 (s, 3H), 3.56 (m, 2H), 3.97 (m, 1H), 4.03 (m, 1H), 4.19 – 4.23 (m, 3H), 5.05 (d, 1H, J = 10.9), 5.15 (d, 1H, J = 17.8), 6.28 (dd, 1H, J = 17.8, 10.9). ^{13}C NMR: 11.7, 28.6, 28.8, 62.2, 64.4, 70.7, 79.9, 81.8, 101.4, 119.5, 134.3, 134.8, 136.5; IR (neat) 2936, 1100, 1031, 917; HRMS calc'd for mixture of $C_{13}H_{22}O_5$ (M^+) 258.1467, found 258.1457. Anal. calc'd for mixture of $C_{19}H_{30}O_7$: % C 60.45, % H 8.58; found: % C 60.83, % H 8.79.



Claims to Original Research

1. Conditions to allow the direct condensation of chelate (**144**) with carbonyl compounds.

2. The facile synthesis of a range of poly-substituted furans (**232**) employing the magnesium-mediated carbometallation method.

3. A novel preparation of an ene-diyne chromophore (**186**) in one-step.

4. A short synthesis of the anti-inflammatory drug, Vioxx® (**231**).

5. An expedient route to the A/B-ring system of Taxol® (**329**) employing a diasteroselective intramolecular Diels-Alder reaction.

6. The development of a *cis*-acetal tether control group for the intramolecular Diels-Alder reaction.

7. The discovery of the *cis*-acetal effect whereby **386** undergoes room temperature cycloadditon even with sterically demanding dienes with an "internal" substituent.

8. Publications:

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   (b) Forgione, P.; Fallis, A.G. *Tetrahedron Lett.* **2000**, *41*, 11.

   (c) Fallis, A.G.; Forgione, P.; Woo, S.; Legoupy, S.; Py, S.; Harwig, C.; Rietveld, T. *Polyhedron* **2000**, *19*, 533.

   (d) Forgione, P.; Wilson, P.D.; Yap, G.P.A.; Fallis, A.G. *Synthesis* **2000**, 921.

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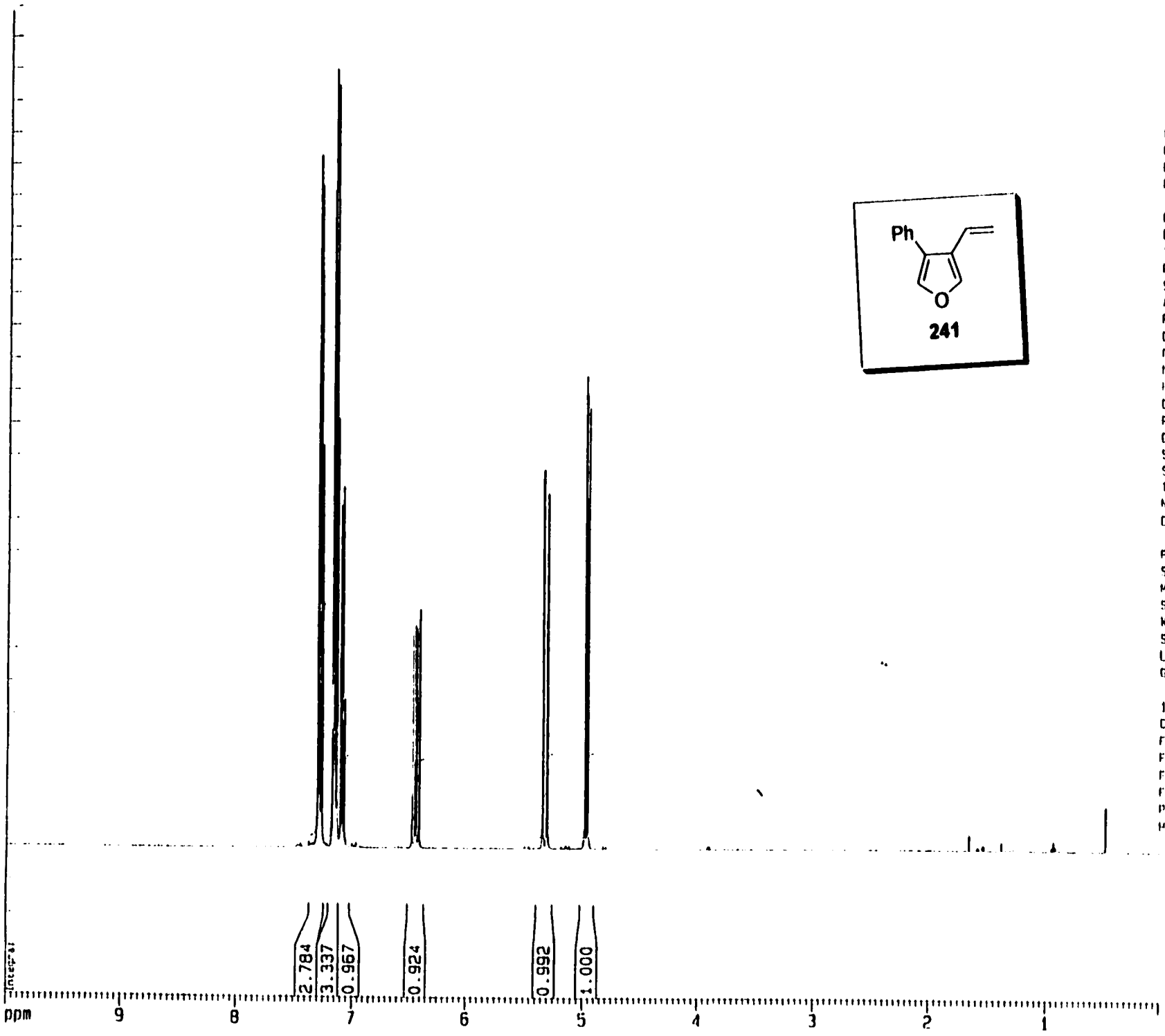
Appendix



Current Data Parameters
NAME dat_197
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date 980721
Time 14.09
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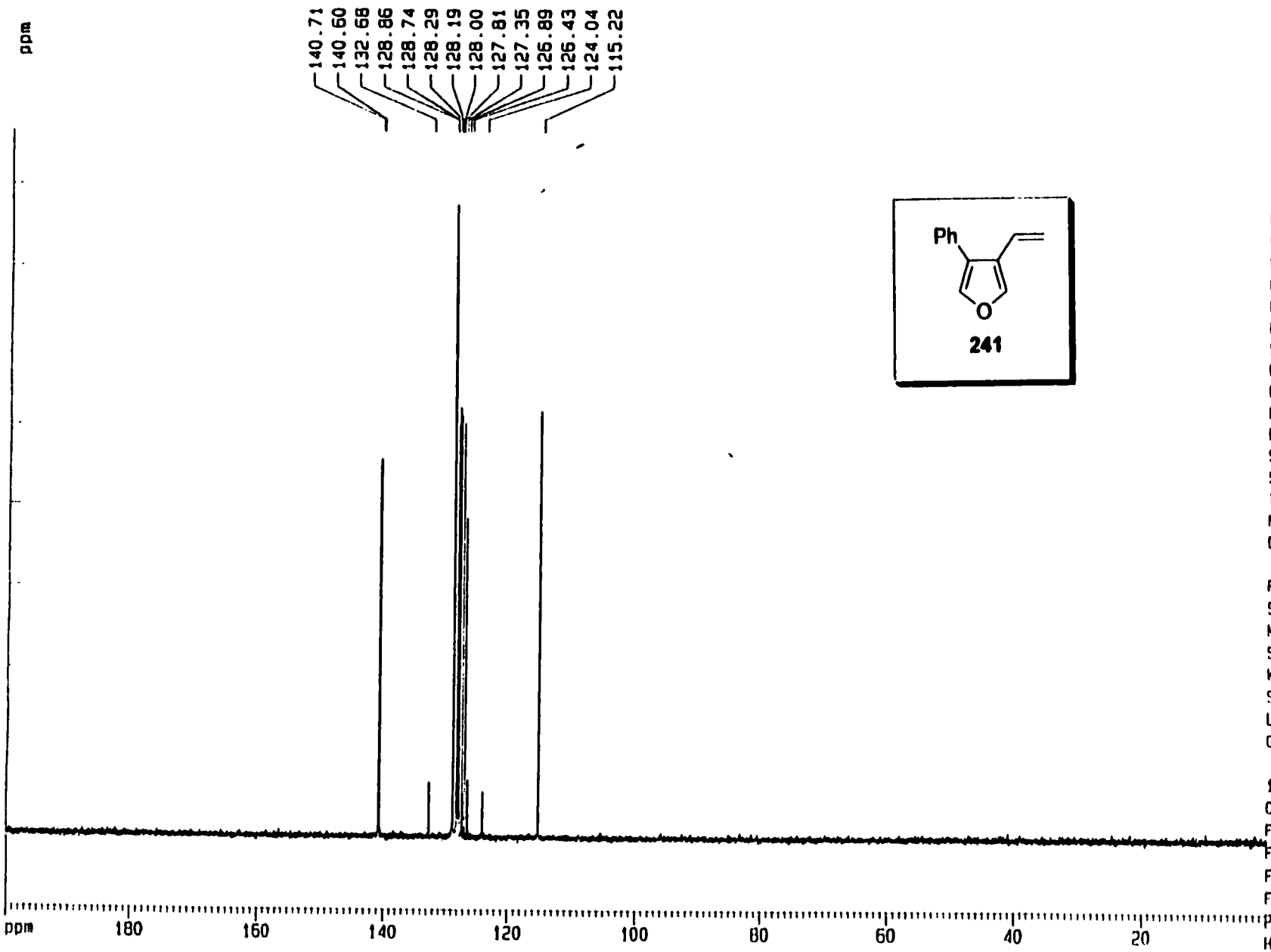
SOLVENT CDCl3
AQ 4.6530805 sec
FIDRES 0.107456 Hz
DW 71.0 usec
RG 64
NUCLEUS 1H
PL1 0 dB
D1 0.0100000 sec
P1 3.0 usec
DE 89.8 usec
SFO1 500.1381707 MHz
SWH 7042.25 Hz
TD 65536
NS 16
DS 0

F1 - Processing parameters
SI 32768
MC2 QF
SF 500.1354439 MHz
WDW EM
SSB 0
LB 0.00 Hz
GB 0

1D NMR plot parameters
CX 22.00 cm
F1P 10.000 ppm
F1 5001.35 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.45455 ppm/
HZCM 227.33429 Hz/



Current Data Parameters

NAME	pat_197
EXPNO	2
PROCNO	1

F2 - Acquisition Parame

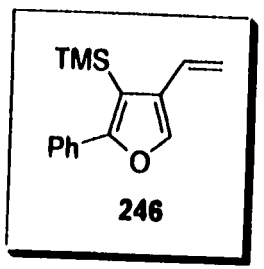
Date	980721
Time	14.26
PULPROG	zgdc
SOLVENT	CDCl3
AQ	1.0485960
FIDRES	0.476837
DW	16.0
RG	32768
NUCLEUS	13C
D11	0.0300000
P31	70.0
S2	22
HL1	22
D1	1.0000000
P1	5.0
DE	20.0
SFO1	125.7724464
SWH	31250.00
TD	65536
NS	128
DS	0

F1 - Processing paramet

SI	32768
MC2	QF
SF	125.7591197
WDW	EM
SSB	0
LB	1.00
GB	0

1D NMR plot parameters

CX	22.00
F1P	200.000
F1	25151.82
F2P	0.000
F2	0.00
PPMCM	9.09091
HZCM	1143.26465



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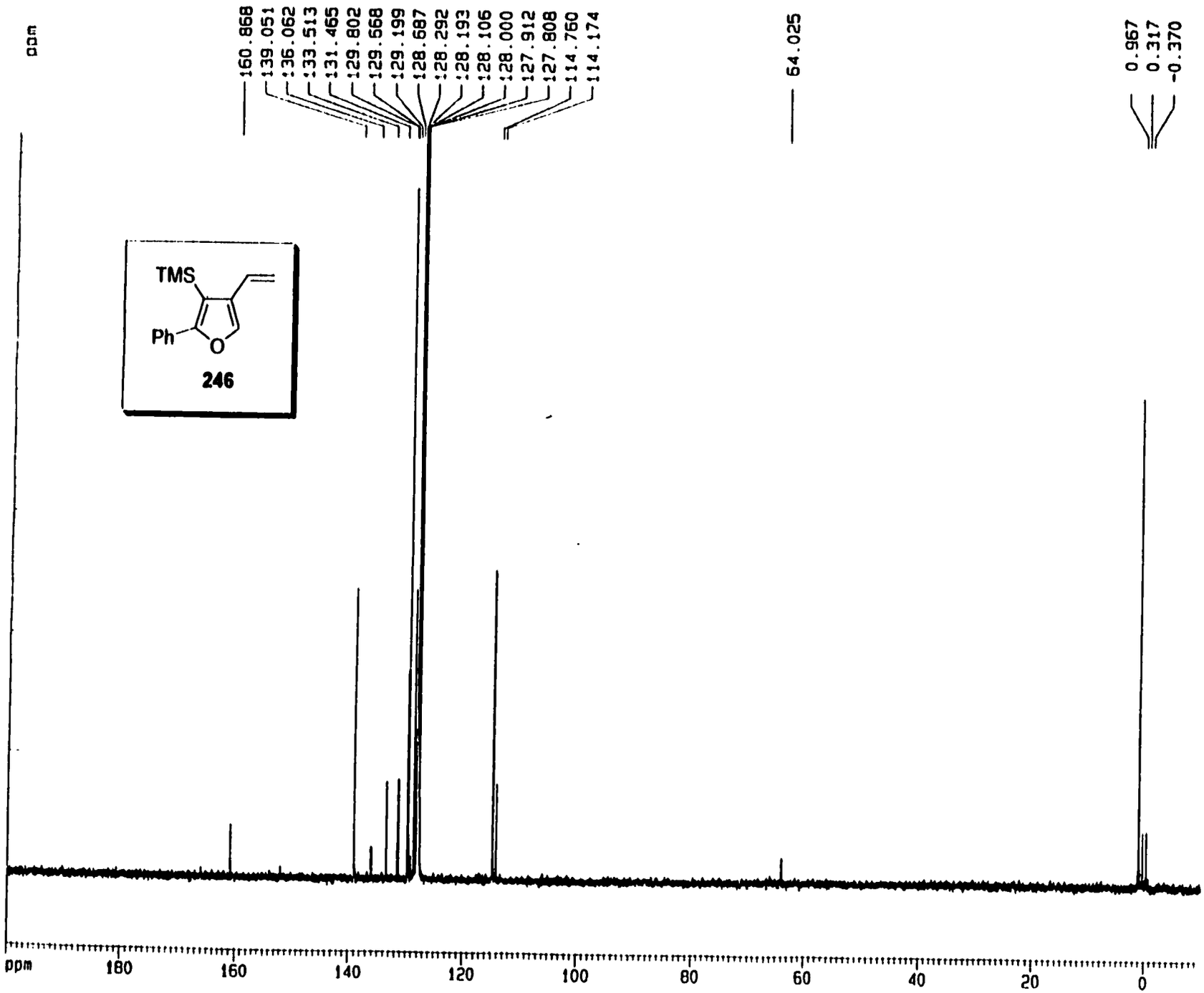
Current Data Parameters
NAME pat_414a
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date 20000312
Time 22.15
PULPROG zg
SOLVENT CDCl3
AQ 4.6530805 sec
FIDRES 0.107456 Hz
DW 71.0 usec
RG 1024
NUCLEUS 1H
ML1 0 dB
D1 0.0100000 sec
P1 3.0 usec
DE 88.8 usec
SFO1 500.1381707 MHz
SWH 7042.25 Hz
TD 65536
NS 16
DS 0

F1 - Processing parameters
SI 32768
WC2 DF
SF 500.1354495 MHz
WDW EM
SSB 0
LB 0.00 Hz
GB 0

1D NMR plot parameters
CX 22.00 cm
F1P 10.000 ppm
F1 5001.35 Hz
F2P -1.000 ppm
F2 -500.14 Hz
PPMCM 0.50000 ppm/
HZCM 250.06772 Hz/



Current Data Parameters

NAME	pat_414a
EXPNO	2
PROCNO	1

F2 - Acquisition Parame

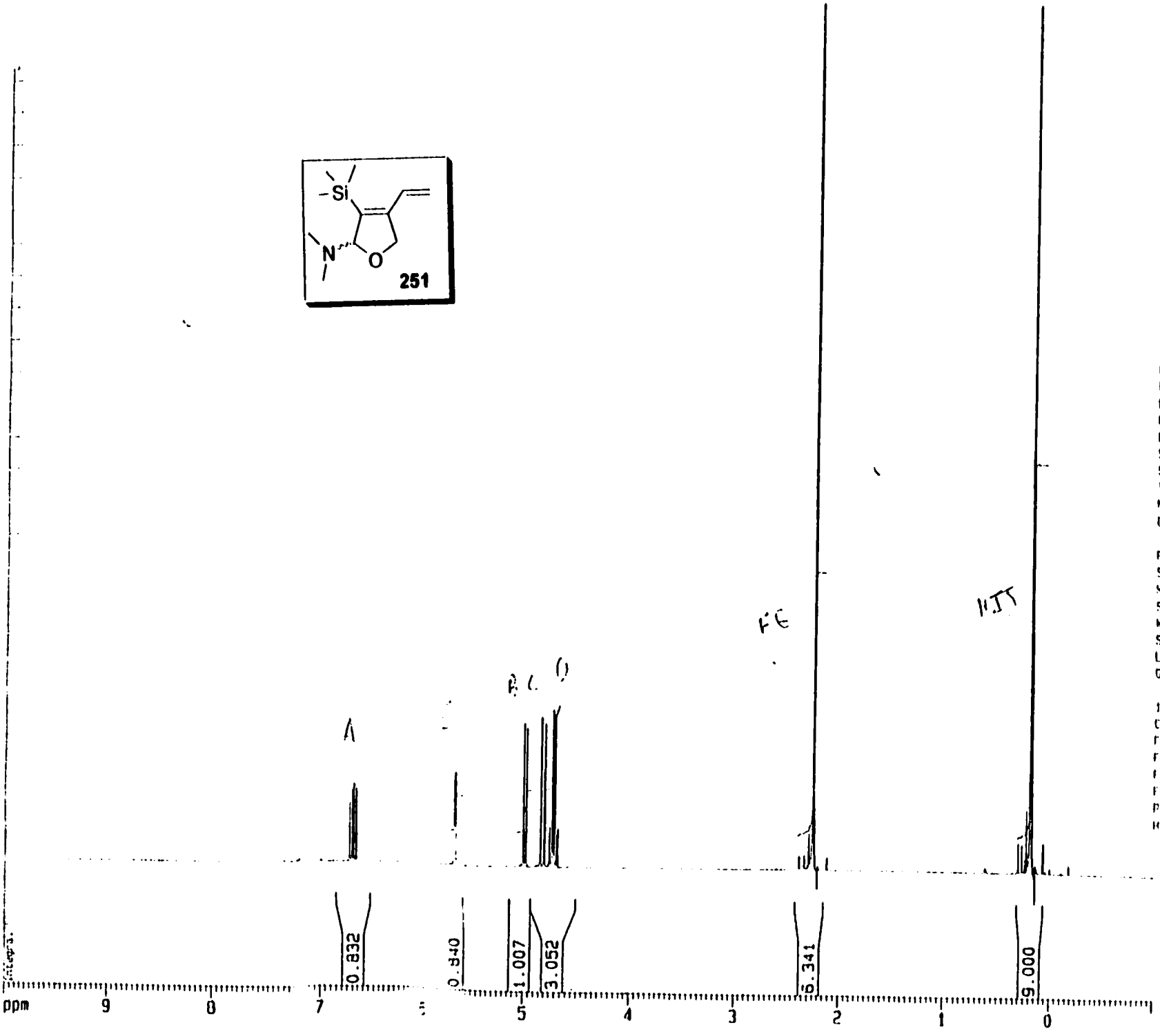
Date	20000312
Time	23.01
PULPROG	zgdc
SOLVENT	CDCl3
AQ	1.0485960
FIDRES	0.476837
DW	16.0
RG	32768
NUCLEUS	13C
D11	0.0300000
P31	70.0
S2	22
ML1	22
D1	1.0000000
P1	5.0
DE	20.0
SFO1	125.7724464
SWH	31250.00
TD	65536
NS	1578
DS	0

F1 - Processing paramet

SI	32768
WC2	QF
SF	125.7591177
WDW	EM
SSB	0
LB	1.00
GB	0

1D NMR plot parameters

CX	22.00
F1P	200.000
F1	25151.82
F2P	-10.000
F2	-1257.59
PPMCM	9.54545
HZCM	1200.42798



Current Data Parameters

NAME	pat_413
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

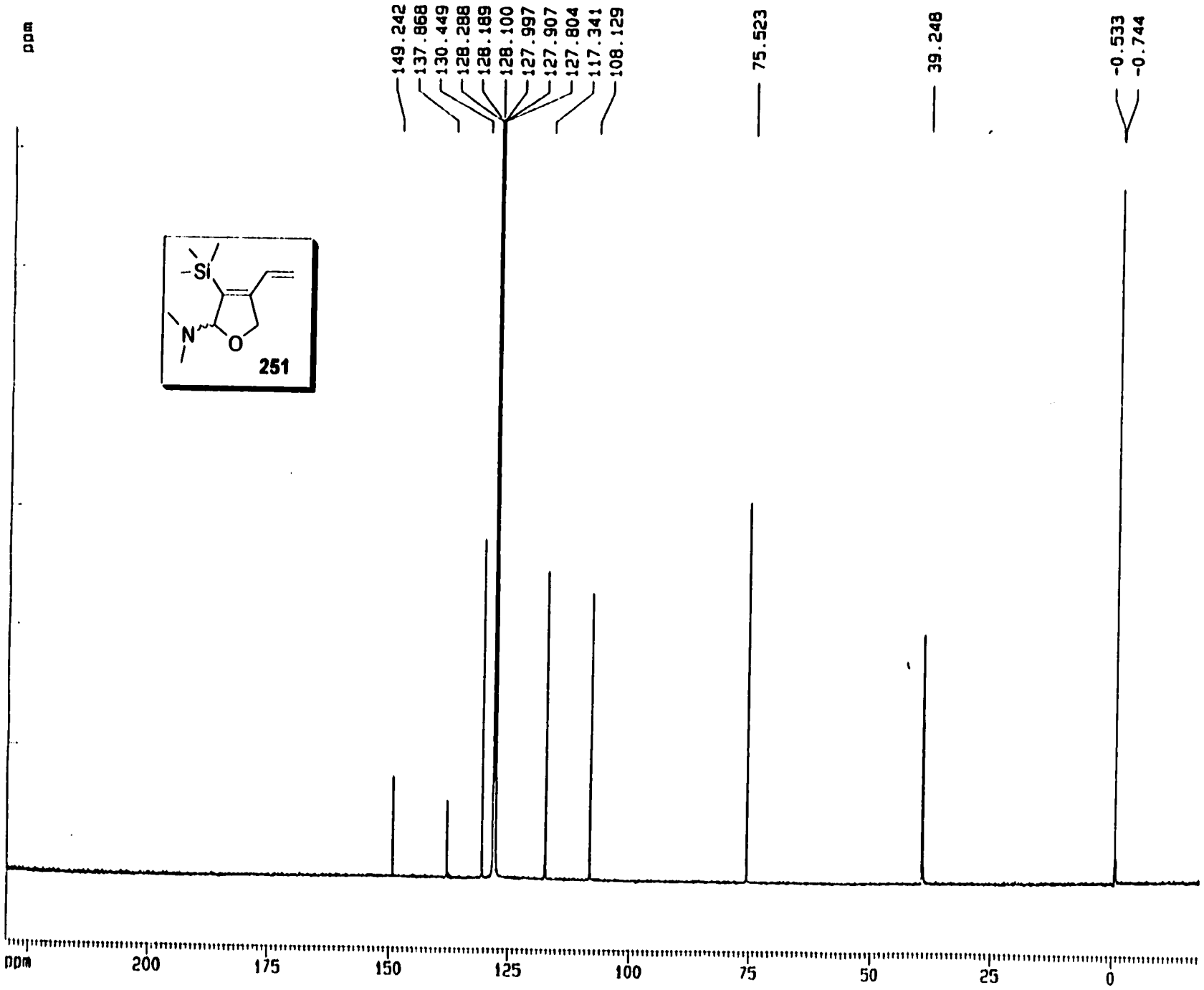
Date	20000316
Time	10.18
PULPROG	zg
SOLVENT	CDCl3
AQ	4.6530805 sec
FIDRES	0.107456 Hz
DW	71.0 usec
RG	1024
NUCLEUS	1H
HL1	0 dB
D1	0.0100000 sec
P1	3.0 usec
DE	88.8 usec
SFO1	500.1381707 MHz
SWH	7042.25 Hz
TD	65536
NS	16
DS	0

F1 - Processing parameters

SI	32768
WC2	QF
SF	500.1354501 MHz
WDW	EM
SSB	0
LB	0.00 Hz
GB	0

1D NMR plot parameters

CX	22.00 cm
F1P	10.000 ppm
F1	5001.35 Hz
F2P	-1.000 ppm
F2	-500.14 Hz
PPMCM	0.50000 ppm/
HZCM	250.06772 Hz/



Current Data Parameters

NAME	pat_413
EXPNO	4
PROCNO	1

F2 - Acquisition Parame

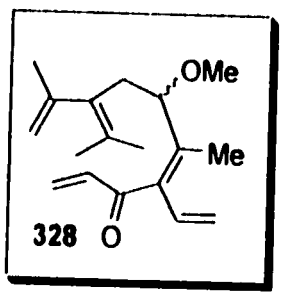
Date	20000316
Time	13.11
PULPROG	zgdc
SOLVENT	CDCl3
AQ	1.0485960
FIDRES	0.476837
DW	16.0
RG	32768
NUCLEUS	13C
D11	0.0300000
P31	70.0
S2	22
HL1	22
D1	1.0000000
P1	5.0
DE	20.0
SFO1	125.7724464
SWH	31250.00
TD	65536
NS	12288
DS	0

F1 - Processing paramet

SI	32768
WC2	QF
SF	125.7591177
WDW	EM
SSB	0
LB	1.00
GB	0

1D NMR plot parameters

CX	22.00
F1P	152.800
F1	19216.01
F2P	104.816
F2	13181.53
PPMCM	2.18111
HZCM	274.29456

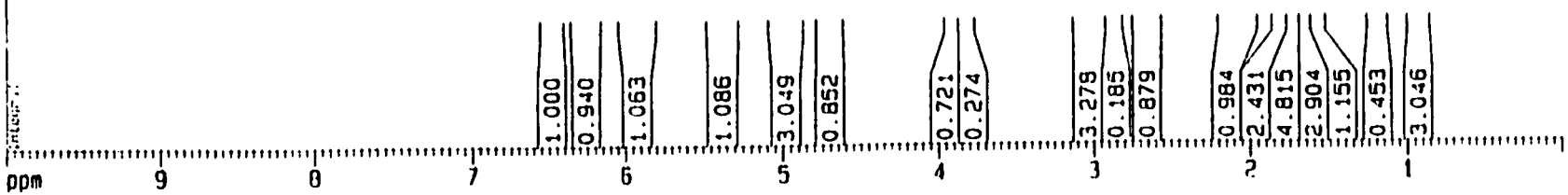


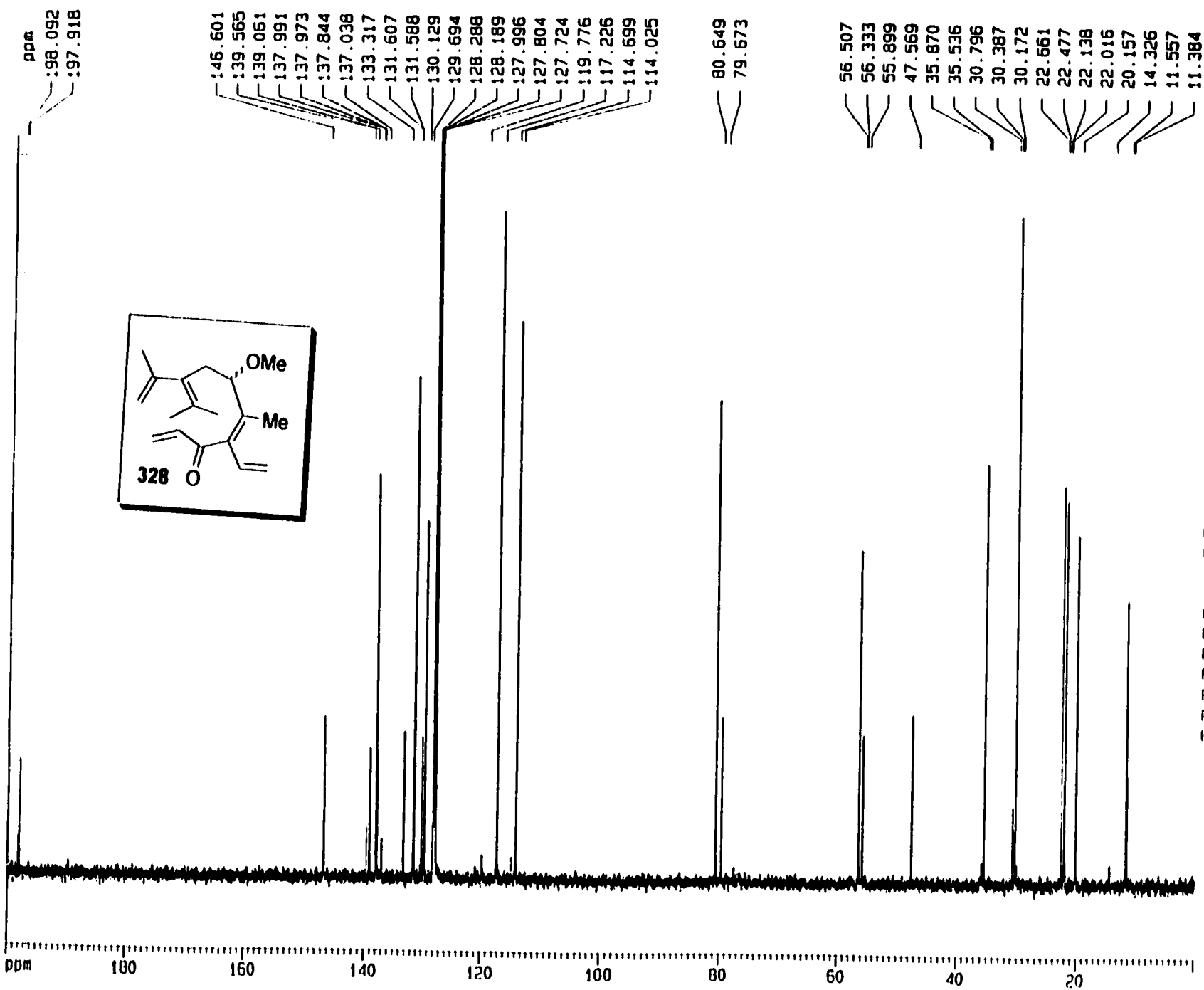
Current Data Parameters
NAME pat_352
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date 990902
Time 18 58
PULPROG zg
SOLVENT CDCl3
AQ 4 6530805 sec
FIDRES 0 107456 Hz
DW 71.0 usec
RG 64
NUCLEUS 1H
ML1 0 dB
D1 0 0100000 sec
P1 3.0 usec
DE 88.8 usec
SFO1 500.1381707 MHz
SWH 7042 25 Hz
TD 65536
NS 16
DS 0

F1 - Processing parameters
SI 32768
MC2 QF
SF 500.1354497 MHz
WDW EM
SSB 0
LB 0 00 Hz
GB 0

1D NMR plot parameters
CX 22 00 cm
F1P 10 000 ppm
F1 5001 35 Hz
F2P 0 000 ppm
F2 0 00 Hz
PPMCM 0.45455 ppm/
HZCM 227 33423 Hz/





Current Data Parameters

NAME	pat_352
EXPNO	4
PROCNO	1

F2 - Acquisition Parame

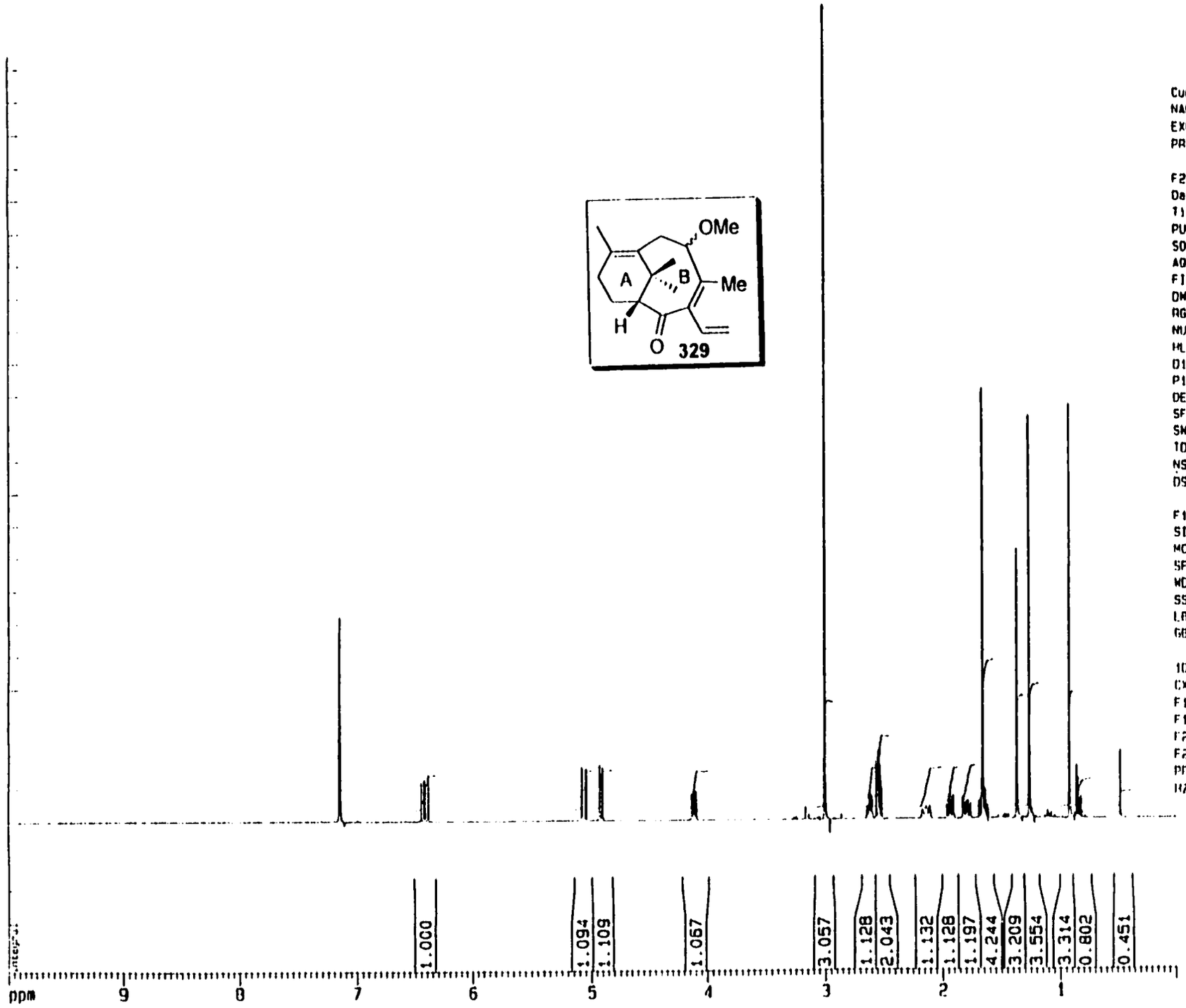
Date	990903
Time	13.02
PULPROG	zgdc
SOLVENT	CDCl3
AQ	1.0485960
FIDRES	0.476837
DW	16.0
RG	32768
NUCLEUS	13C
D11	0.0300000
P31	70.0
S2	22
ML1	22
D1	1.0000000
P1	5.0
DE	20.0
SFO1	125.7724464
SWH	31250.00
TD	65536
NS	289
DS	0

F1 - Processing paramet

SI	32768
MC2	QF
SF	125.7591168
WDW	EM
SSB	0
LB	1.00
GB	0

1D NMR plot parameters

CX	22.00
F1P	200.000
F1	25151.82
F2P	0.000
F2	0.00
PPMCM	9.09091
HZCM	1143.26465

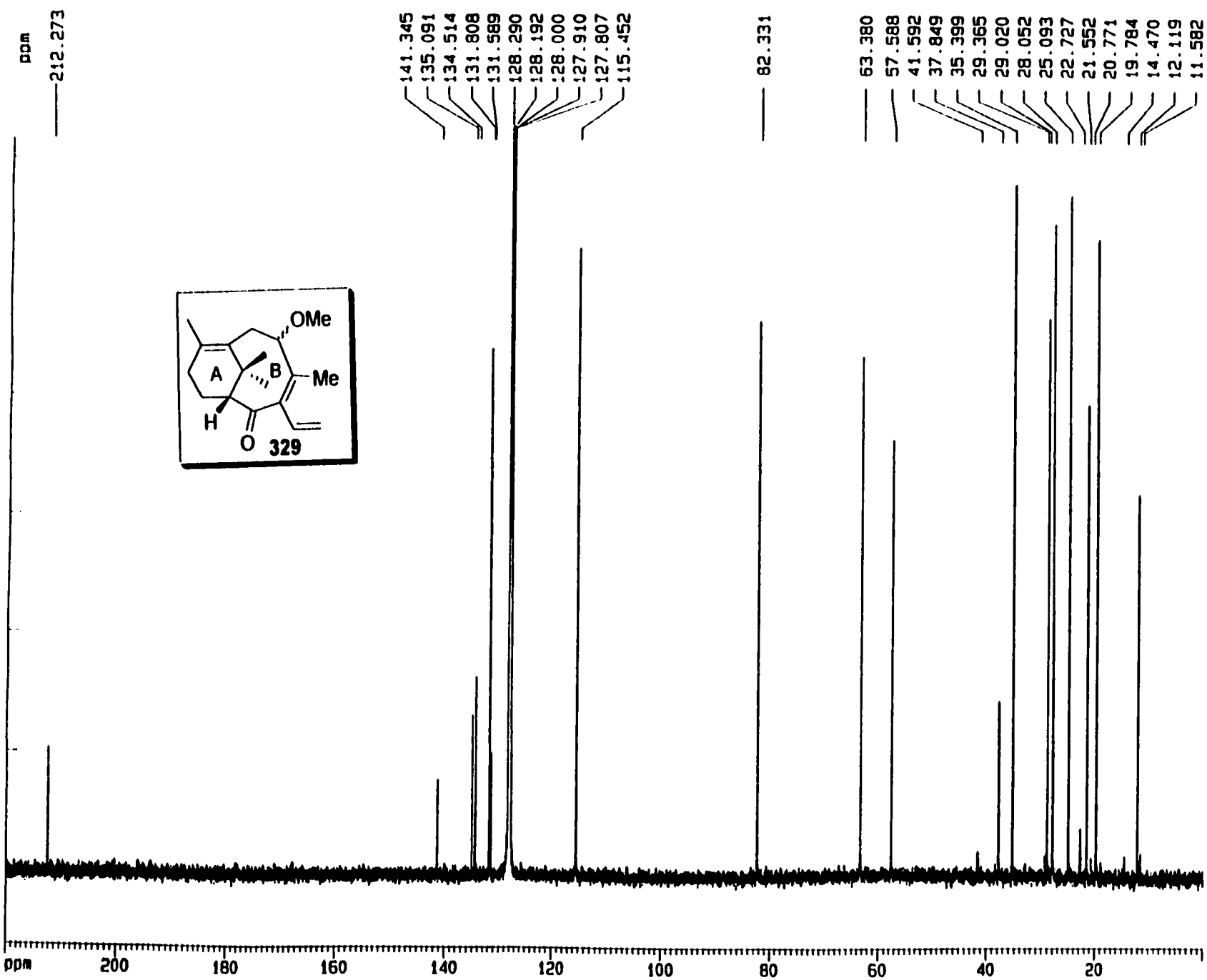


Current Data Parameters
NAME pat_318
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date 990723
Time 17.36
PULPROG zg
SOLVENT CDCl3
AQ 4.6530805 sec
FIDRES 0.107456 Hz
DW 71.0 usec
RG 1024
NUCLEUS 1H
ML1 0 dB
D1 0.0100000 sec
P1 3.0 usec
DE 88.8 usec
SFO1 500.1381707 MHz
SWH 7042.25 Hz
TD 65536
NS 16
DS 0

F1 - Processing parameters
SI 32768
MC2 QF
SF 500.1354501 MHz
WDW EM
SSB 0
LB 0.00 Hz
GB 0

1D NMR plot parameters
CX 22.00 cm
F1P 10.000 ppm
F1 5001.35 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.45455 ppm/
HZCM 227.33429 Hz/



Current Data Parameters

NAME	pat_318
EXPNO	4
PROCNO	1

F2 - Acquisition Parame

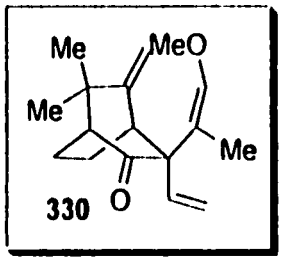
Date	990723
Time	21.42
PULPROG	zgdc
SOLVENT	CDCl3
AQ	1.0485960
FIDRES	0.476837
DW	16.0
RG	32768
NUCLEUS	13C
D11	0.0300000
P31	70.0
S2	22
NL1	22
D1	1.0000000
P1	5.0
DE	20.0
SFO1	125.7724464
SWH	31250.00
TD	65536
NS	12288
DS	0

F1 - Processing paramet

SI	32768
WC2	QF
SF	125.7591187
WDW	EM
SSB	0
LB	1.00
GB	0

1D NMR plot parameters

CX	22.00
F1P	220.000
F1	27667.01
F2P	0.000
F2	0.00
PPMCM	10.00000
HZCM	1257.59119

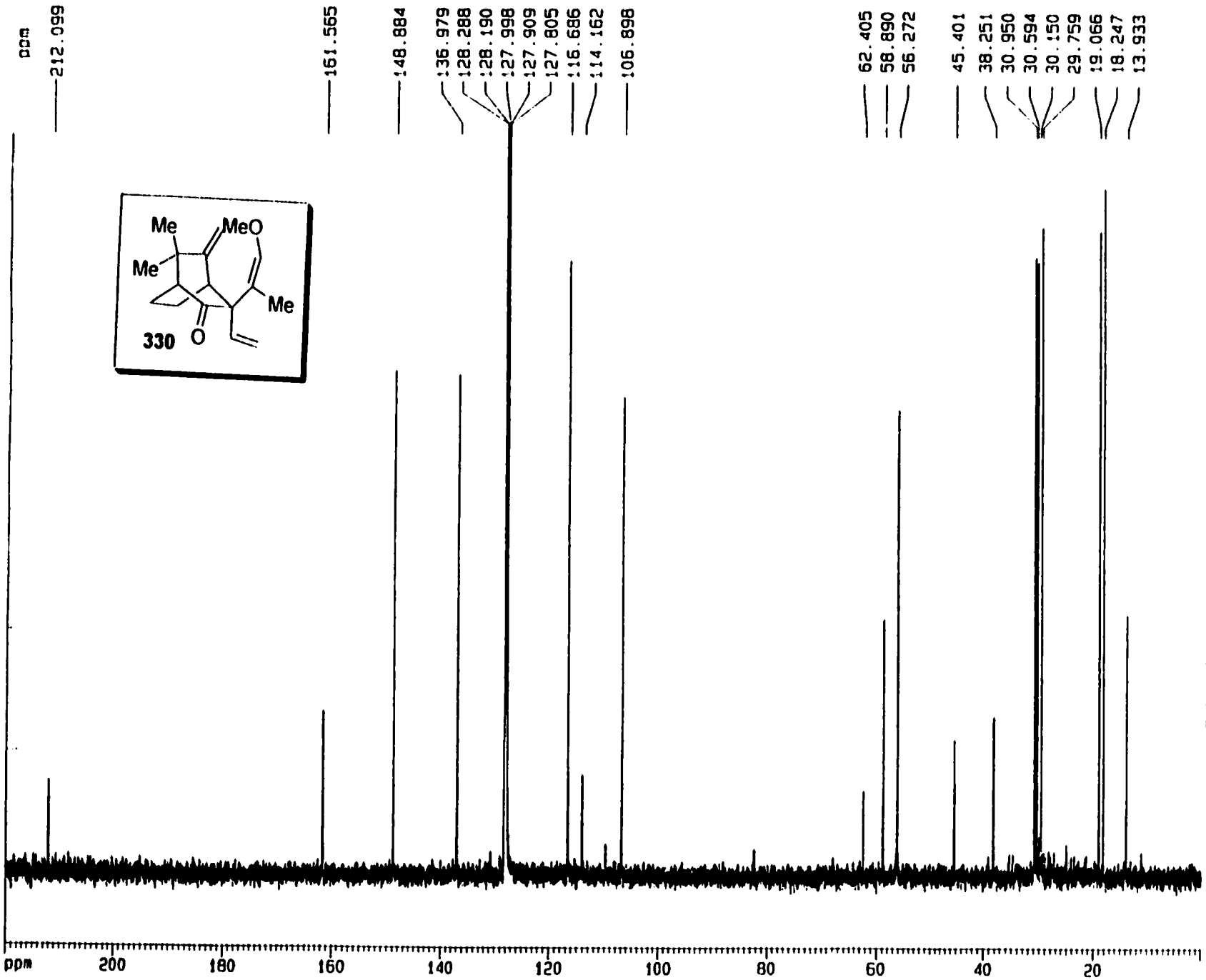


Current Data Parameters
NAME pat_357
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date 990924
Time 18.15
PULPROG zg
SOLVENT CDCl3
AQ 4.6530805 sec
FIDRES 0.107456 Hz
DW 71.0 usec
RG 256
NUCLEUS 1H
ML1 0 dB
D1 0.0100000 sec
P1 3.0 usec
DE 88.8 usec
SFO1 500.1381707 MHz
SWH 7042.25 Hz
TD 65536
NS 16
DS 0

F1 - Processing parameters
SI 32768
WC2 0
SF 500.1354501 MHz
WDW EM
SSB 0
LB 0.00 Hz
GB 0

1D NMR plot parameters
CX 22.00 cm
F1P 10.000 ppm
F1 5001.35 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.45455 ppm/
HZCM 227.33129 Hz/



Current Data Parameters

NAME	pat_357
EXPNO	4
PROCNO	1

F2 - Acquisition Parame

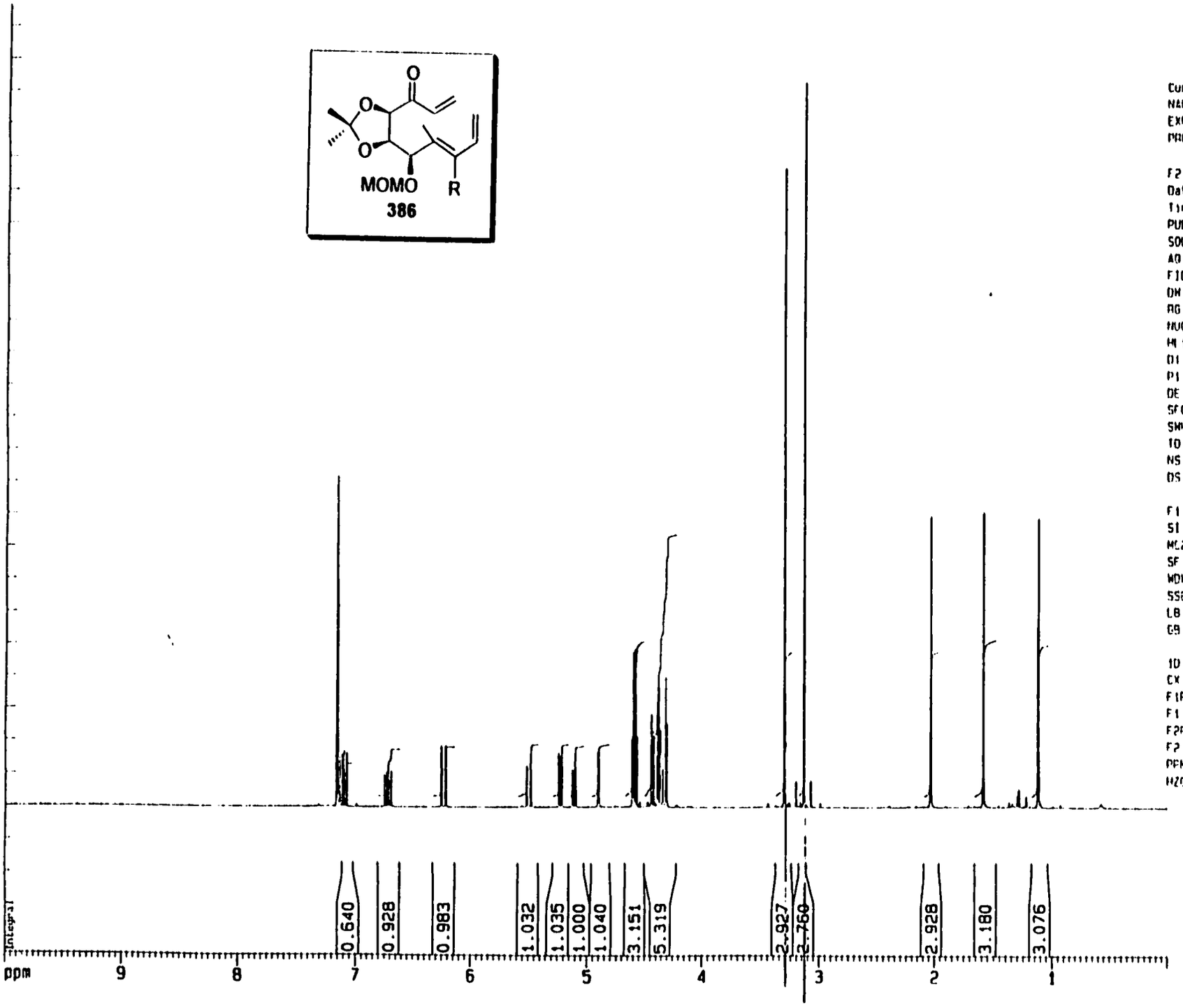
Date	990924
Time	22.09
PULPROG	zgdc
SOLVENT	CDCl3
AQ	1.0485960
FIDRES	0.476837
DW	16.0
RG	32768
NUCLEUS	13C
D11	0.0300000
P31	70.0
S2	22
HL1	22
D1	1.0000000
P1	5.0
DE	20.0
SFO1	125.7724464
SWH	31250.00
TD	65536
NS	1437
DS	0

F1 - Processing paramet

SI	32768
MC2	QF
SF	125.7591187
WDW	EM
SSB	0
LB	1.00
GB	0

1D NMR plot parameters

CX	22.00
F1P	220.000
F1	27667.01
F2P	0.000
F2	0.00
PPMCM	10.00000
HZCM	1257.59119

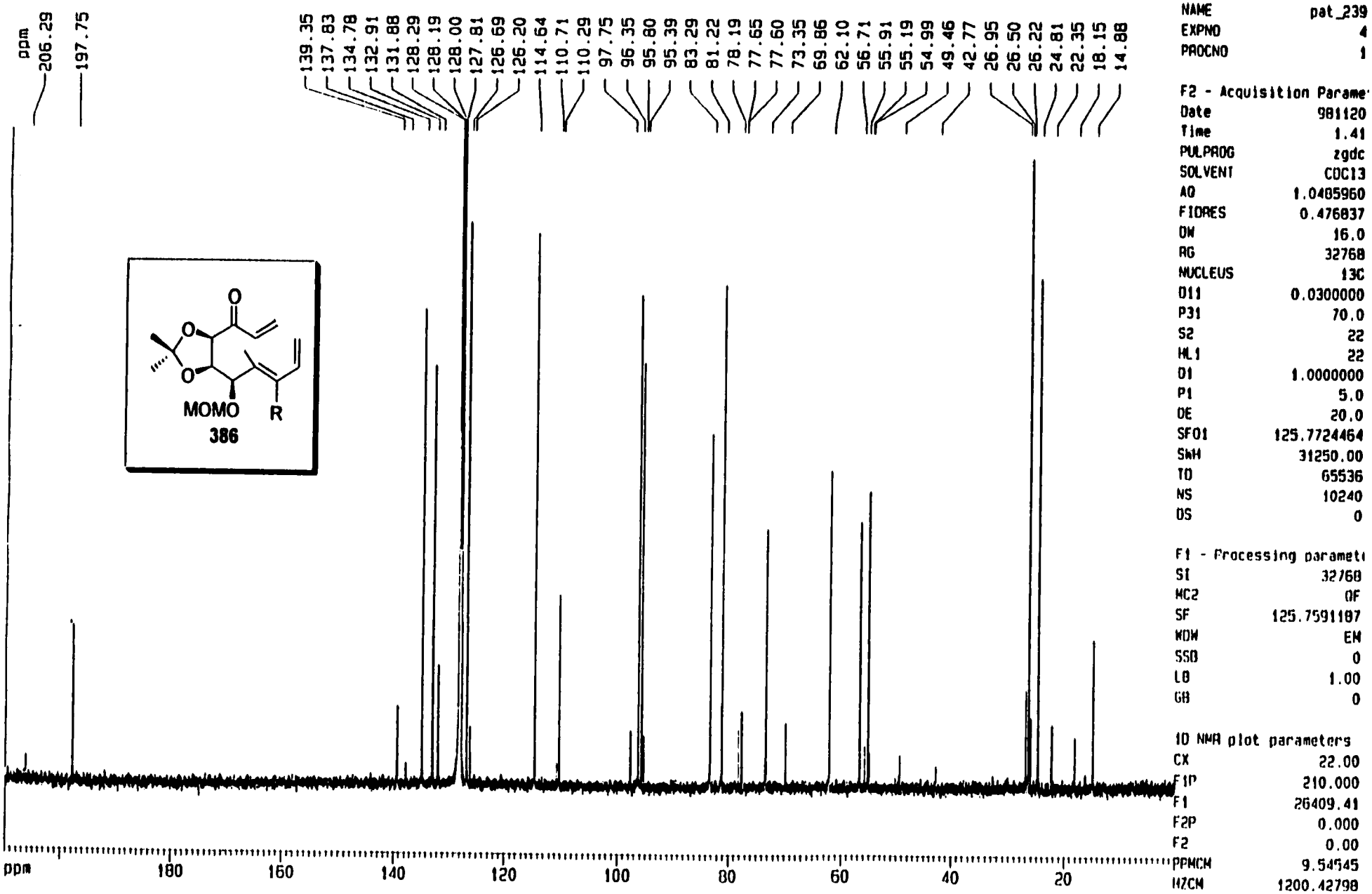


Current Data Parameters
NAME pat_239
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date 981119
Time 18 02
PULPROG zg
SOLVENT CDCl3
AQ 4.6530805 sec
FIDRES 0.107456 Hz
DW 71.0 usec
RG 512
NUCLEUS 1H
PL1 0 dB
D1 0.0100000 sec
P1 3.0 usec
DE 88.8 usec
SFO1 500.1381707 MHz
SWH 7042.25 Hz
TD 65536
NS 16
DS 0

F1 - Processing parameters
SI 32768
WDW EM
SSB 0
LB 0.00 Hz
GB 0

1D NMR plot parameters
CX 22.00 cm
F1P 10.000 ppm
F1 5001.35 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.45455 ppm/
HZCM 227.33423 Hz/



Current Data Parameters

NAME	pat_239
EXPNO	4
PROCNO	1

F2 - Acquisition Parame

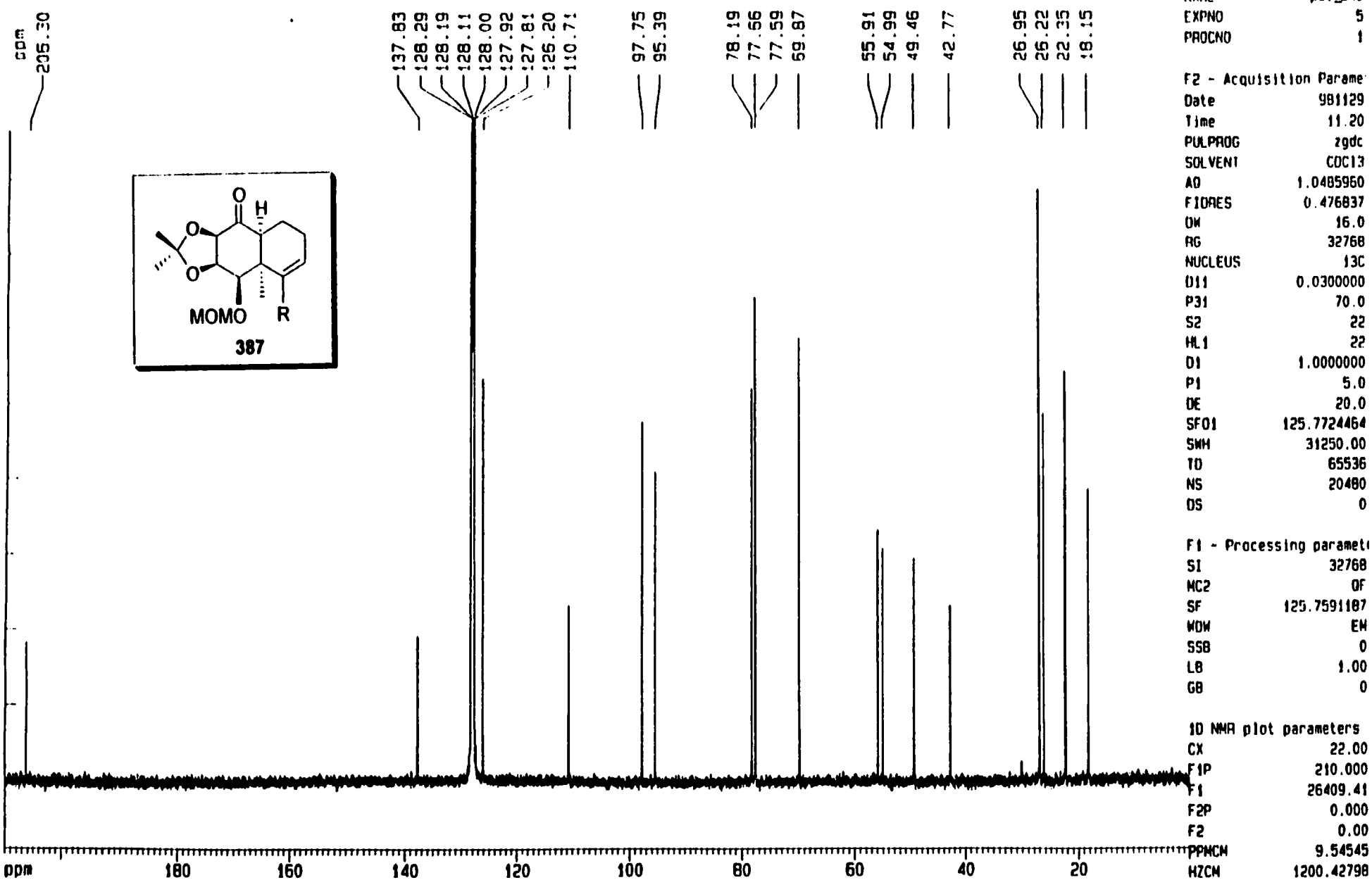
Date	981120
Time	1.41
PULPROG	zgdc
SOLVENT	CDCl3
AQ	1.0485960
FIDRES	0.476837
DW	16.0
RG	32768
NUCLEUS	13C
D11	0.0300000
P31	70.0
S2	22
HL1	22
D1	1.0000000
P1	5.0
DE	20.0
SFO1	125.7724464
SWH	31250.00
TD	65536
NS	10240
DS	0

F1 - Processing parameti

SI	32768
WC2	QF
SF	125.7591187
WDW	EM
SSB	0
LB	1.00
GB	0

1D NMR plot parameters

CX	22.00
F1P	210.000
F1	26409.41
F2P	0.000
F2	0.00
PPMCM	9.54545
HZCM	1200.42798



Current Data Parameters

NAME	pat_240
EXPNO	5
PROCNO	1

F2 - Acquisition Parame

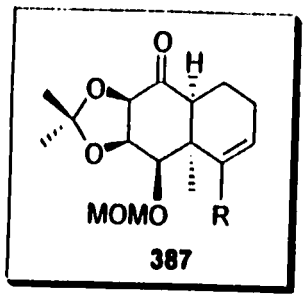
Date	981129
Time	11.20
PULPROG	zgdc
SOLVENT	CDCl3
AQ	1.0485960
FIDRES	0.476837
DW	16.0
RG	32768
NUCLEUS	13C
D11	0.0300000
P31	70.0
S2	22
HL1	22
D1	1.0000000
P1	5.0
DE	20.0
SFO1	125.7724464
SWH	31250.00
TD	65536
NS	20480
DS	0

F1 - Processing parameti

SI	32768
MC2	DF
SF	125.7591187
WDW	EM
SSB	0
LB	1.00
GB	0

1D NMR plot parameters

CX	22.00
F1P	210.000
F1	26409.41
F2P	0.000
F2	0.00
PPMCM	9.54545
HZCM	1200.42798



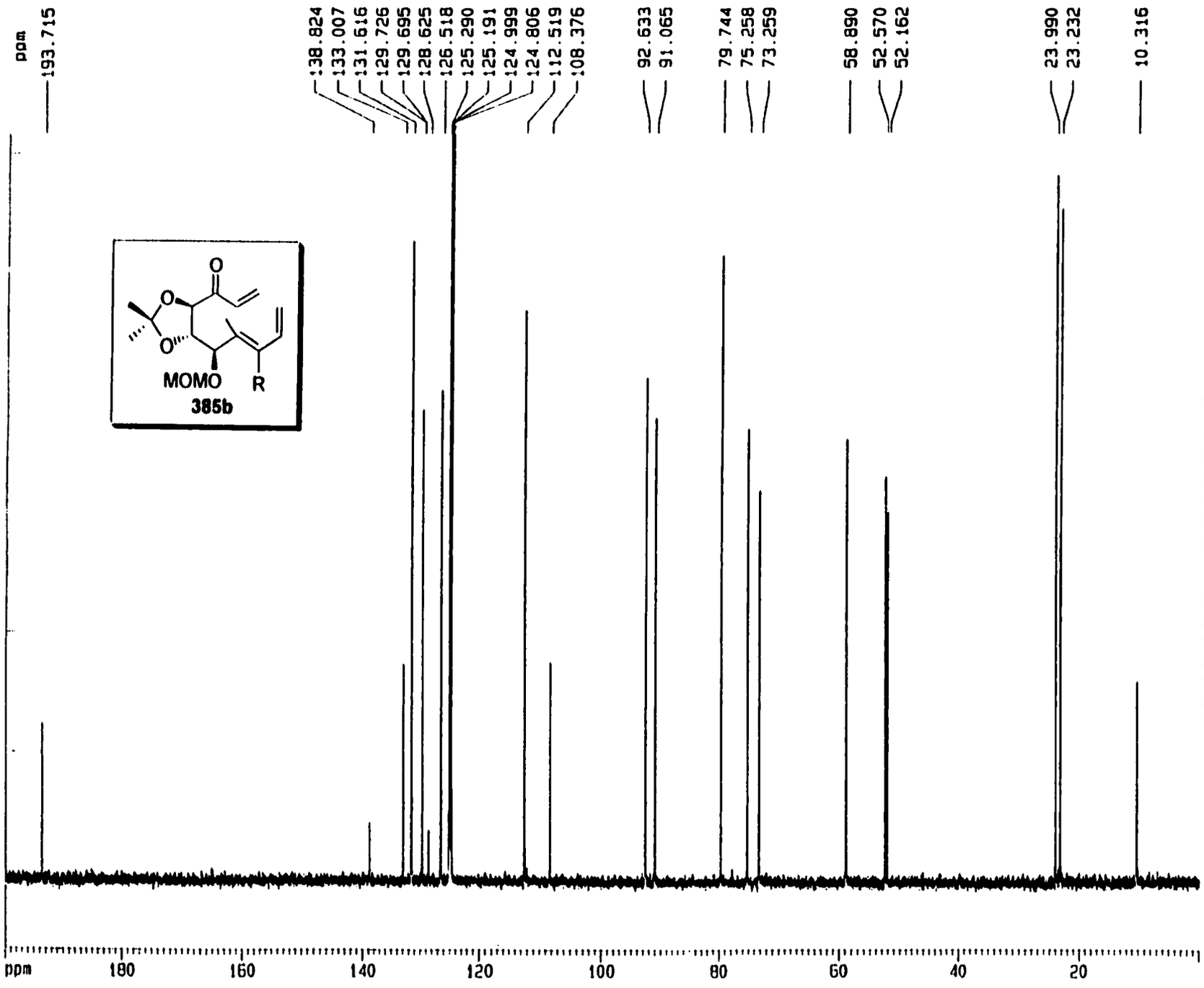
387

Current Data Parameters
NAME pat_240
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date 901127
Time 18 19
PULPROG zg
SOLVENT CDCl3
AQ 4 6530805 sec
FIDRES 0 107456 Hz
DW 71 0 use
NG 512
NUCLEUS 1H
PR 1 0 dB
D1 0 0100000 sec
P1 3 0 use
DE 88.8 use
SFO1 500 1381707 MHz
SWH 7042.25 Hz
TD 65536
NS 16
DS 0

F1 - Processing parameters
SI 32768
MC2 QF
SF 500.1354503 MHz
WDW EM
SSB 0
LB 0 00 Hz
GB 0

1D NMR plot parameters
CX 22.00 cm
F1P 10 000 ppm
F1 5001.35 Hz
F2P 0 000 ppm
F2 0.00 Hz
PPMCM 0.45455 ppm/
HZCM 227.33423 Hz/



Current Data Parameters

NAME	pat_355
EXPNO	4
PROCNO	1

F2 - Acquisition Parame

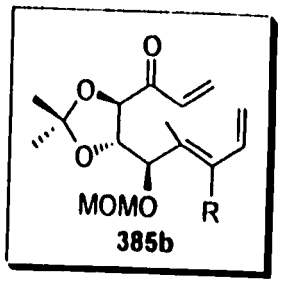
Date	990909
Time	18.24
PULPROG	zgdc
SOLVENT	CDCl3
AQ	1.0485960
FIDRES	0.476837
DW	16.0
RG	32768
NUCLEUS	13C
D11	0.0300000
P31	70.0
S2	22
HL1	22
D1	1.0000000
P1	5.0
DE	20.0
SFO1	125.7724464
SWH	31250.00
TD	65536
NS	256
DS	0

F1 - Processing paramet

SI	32768
MC2	QF
SF	125.7594950
WDW	EM
SSB	0
LB	1.00
GB	0

1D NMR plot parameters

CX	22.00
F1P	200.000
F1	25151.90
F2P	0.000
F2	0.00
PPMCM	9.09091
HZCM	1143.26819



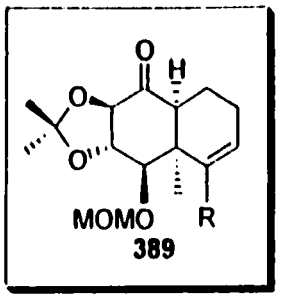
385b

Current Data Parameters
NAME dat_355
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date 990909
Time 17.39
PULPROG zg
SOLVENT CDCl3
AQ 4.6530805 sec
FIDRES 0.107456 Hz
DW 71.0 use
DG 64
NUCLEUS 1H
PL1 0 dB
D1 0.0100000 sec
P1 3.0 use
DE 88.8 use
SFO1 500.1381707 MHz
SWH 7042.25 Hz
TD 65536
NS 16
DS 0

F1 - Processing parameters
SI 32768
WC2 QF
SF 500.1354495 MHz
WDW EM
SSB 0
LB 0.00 Hz
GB 0

1D NMR plot parameters
CX 22.00 cm
F1P 10.000 ppm
F1 5001.35 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.45455 ppm/
HZCM 227.33429 Hz/

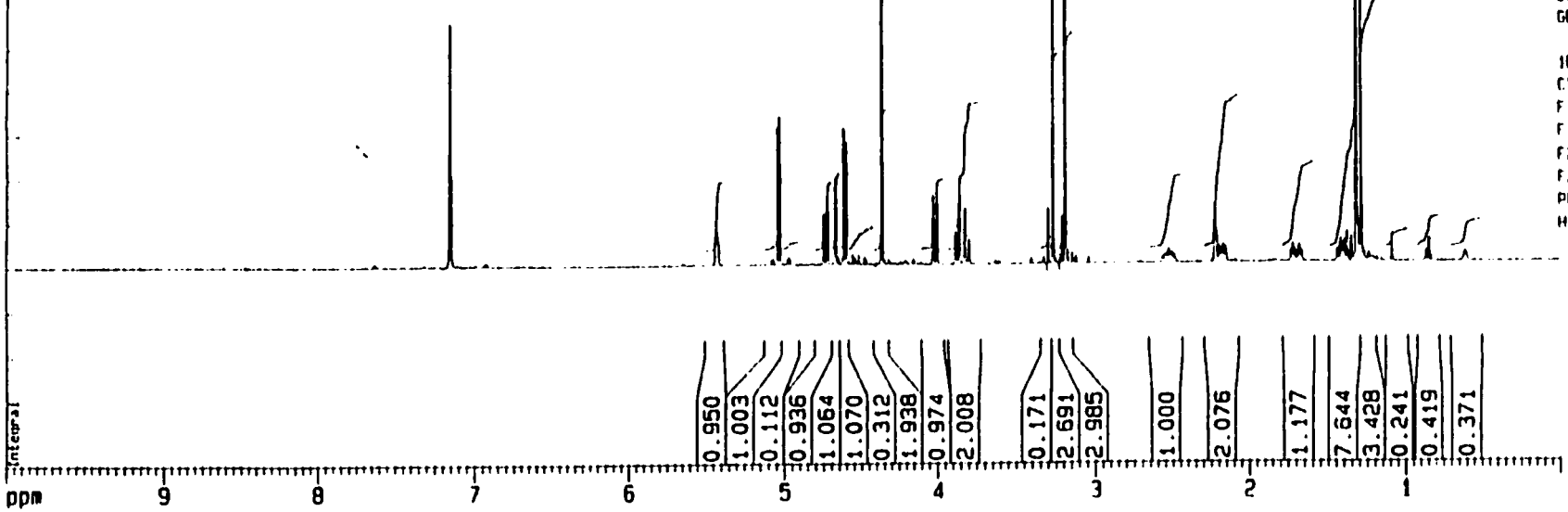


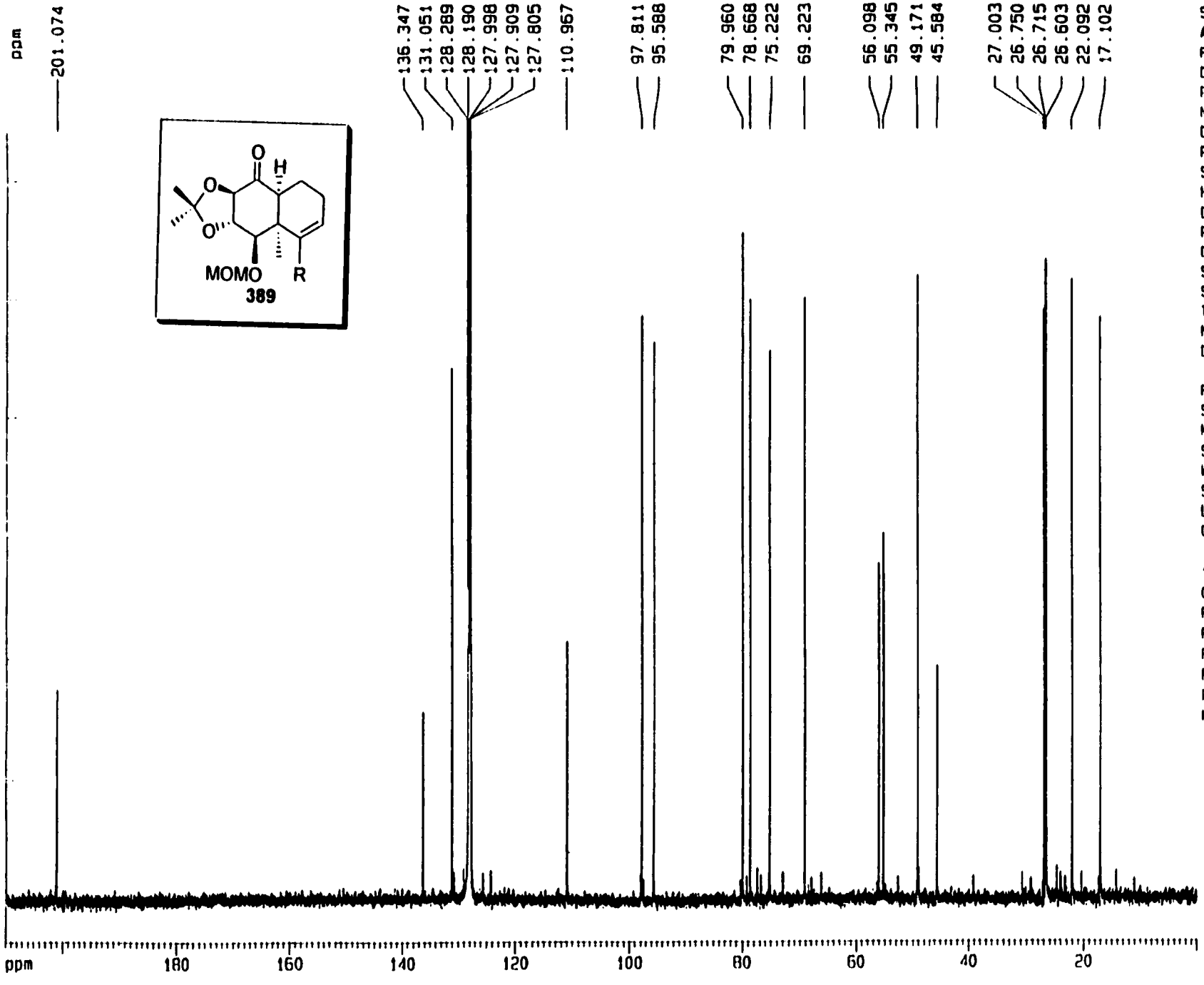
Current Data Parameters
NAME pat_350
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date 990910
Time 23.38
PULPROG zg
SOLVENT CDCl3
AQ 4.6530805 sec
FIDRES 0.107456 Hz
DW 71.0 usec
RG 512
NUCLEUS 1H
PL1 0 dB
D1 0.0100000 sec
P1 3.0 usec
DE 88.8 usec
SFO1 500.1381707 MHz
SWH 7042.25 Hz
TD 65536
NS 16
DS 0

F1 - Processing parameters
SI 32768
WDW EM
SSB 0
LB 0.00 Hz
GB 0

1D NMR plot parameters
CX 22.00 cm
F1P 10.000 ppm
F1 5001.35 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.45455 ppm/
HZCM 227.33429 Hz/





Current Data Parameters

NAME	pat_350
EXPNO	4
PROCNO	1

F2 - Acquisition Parame

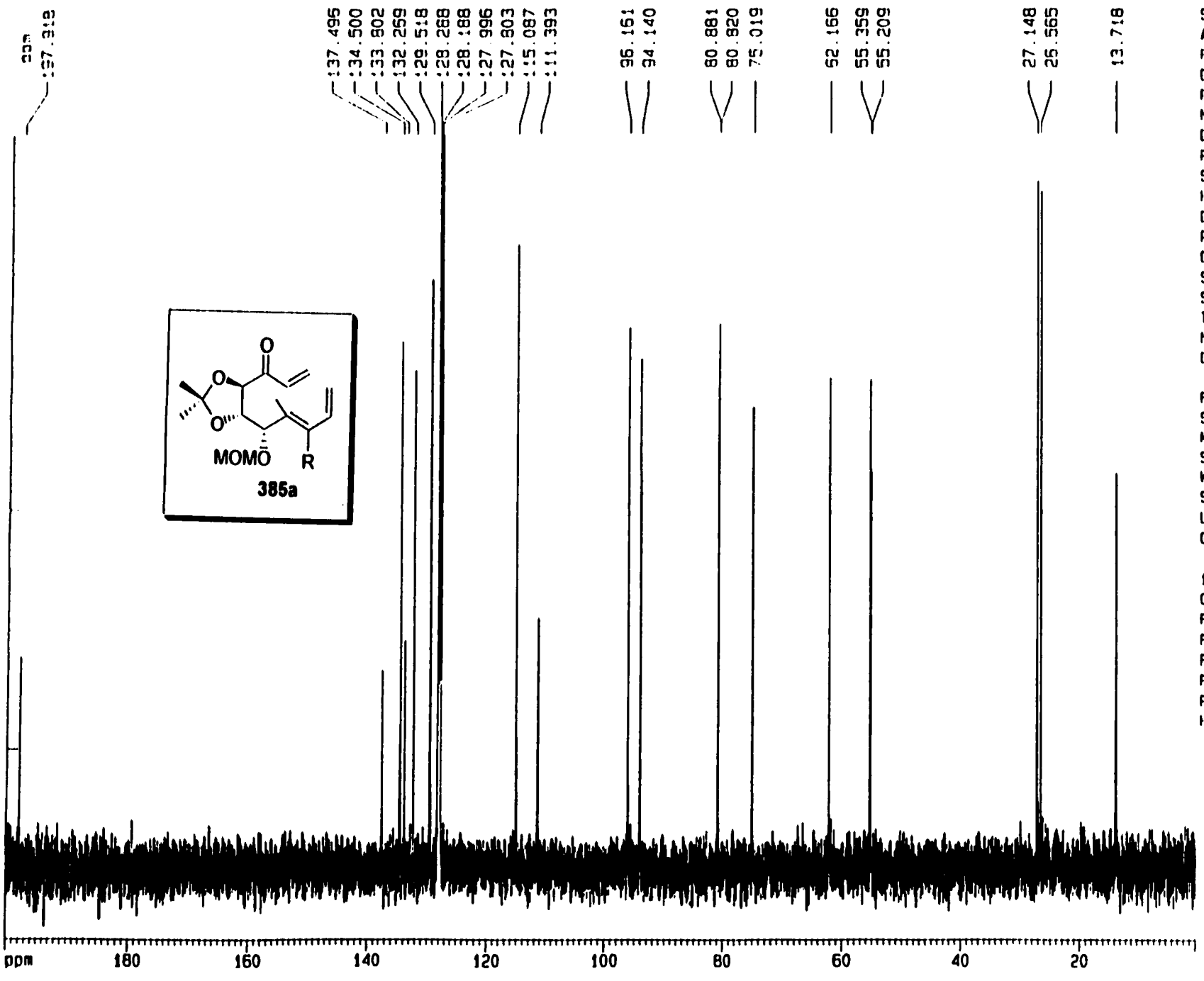
Date	990911
Time	3.48
PULPROG	zgdc
SOLVENT	CDCl3
AQ	1.0485960
FIDRES	0.476837
DW	16.0
RG	32768
NUCLEUS	13C
D11	0.0300000
P31	70.0
S2	22
ML1	22
D1	1.0000000
P1	5.0
DE	20.0
SFO1	125.7724464
SWH	31250.00
TD	65536
NS	10240
DS	0

F1 - Processing paramet

SI	32768
WC2	QF
SF	125.7591187
WDW	EM
SSB	0
LB	1.00
GB	0

1D NMR plot parameters

CX	22.00
F1P	210.000
F1	26409.41
F2P	0.000
F2	0.00
PPMCM	9.54545
HZCM	1200.42798



Current Data Parameters

NAME	pat_356
EXPNO	5
PROCNO	1

F2 - Acquisition Parame

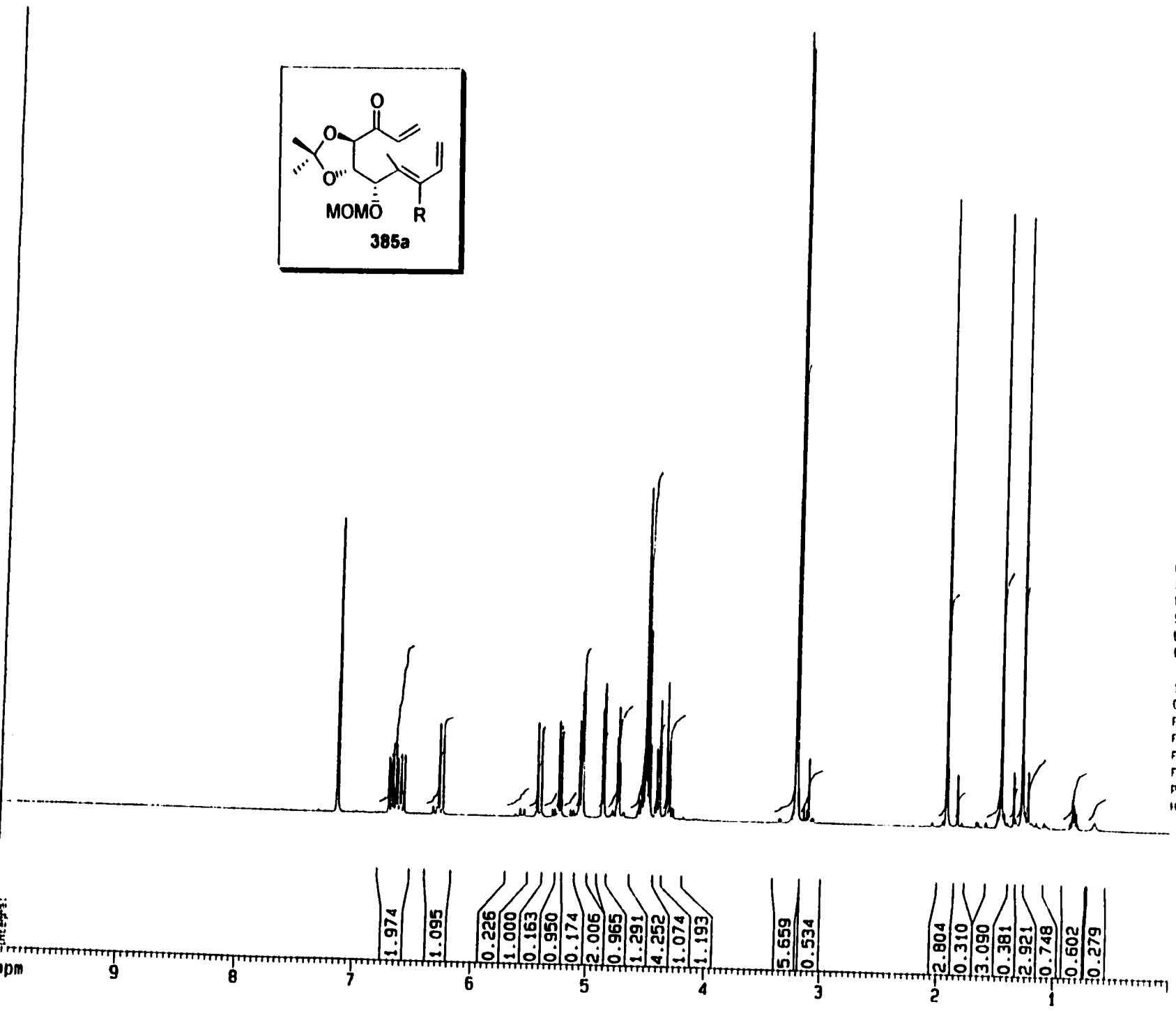
Date	990913
Time	16.08
PULPROG	zgdc
SOLVENT	CDCl3
AQ	1.0485960
FIDRES	0.476837
DW	16.0
RG	32768
NUCLEUS	13C
D11	0.0300000
P31	70.0
S2	22
HL1	22
D1	1.0000000
P1	5.0
DE	20.0
SFO1	125.7724464
SWH	31250.00
TD	65536
NS	256
DS	0

F1 - Processing paramet

SI	32768
WC2	QF
SF	125.7591187
WDW	EM
SSB	0
LB	1.00
GB	0

1D NMR plot parameters

CX	22.00
F1P	200.000
F1	25151.82
F2P	0.000
F2	0.00
PPMCM	9.09091
HZCM	1143.26465


O
O
O
MOMO
R
385a
Current Data Parameters
NAME dat_356
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date 990913
Time 15 21
INSTRUM zg
SOLVENT CDCl3
AQ 4 6530880 sec
DW 71 0 use
DE 88 8 use
SFO1 500 1381707 MHz
SWH 7042 25 Hz
TD 65536
NS 16
DS 0
F1 - Processing parameters
SI 32768
WDW EM
SSB 0
LB 0 00 Hz
GB 0
1D NMR plot parameters
CX 22 00 cm
F1P 10.000 ppm
F1 5001 35 Hz
F2P 0.000 ppm
F2 0 00 Hz
PPMCM 0.45455 ppm/
HZCM 227 33423 Hz/
1.974
1.095
0.226
1.000
0.163
0.950
0.174
2.006
0.965
1.291
4.252
1.074
1.193
5.659
0.534
2.804
0.310
3.090
0.381
2.921
0.748
0.602
0.279
ppm
9
8
7
6
5
4
3
2
1