STUDIES ON VINYL-ALKYL BASED TRANSITION METAL CATALYZED COUPLING REACTIONS AND SYNTHETIC APPROACH TO THE FUSICOCCANE DITERPENOIDS

by

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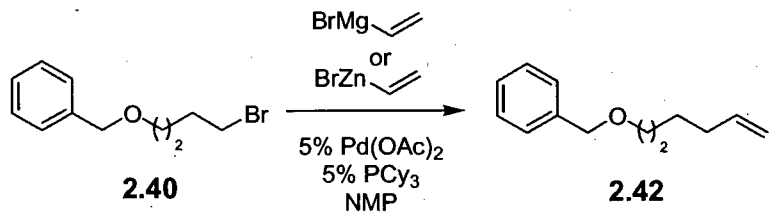
ABSTRACT

Work relating to the transition metal catalyzed cross coupling of sp^3 hybridized carbons to sp^2 hybridized carbons is reported along with an asymmetric synthetic approach to the fusicoccane diterpenoids.

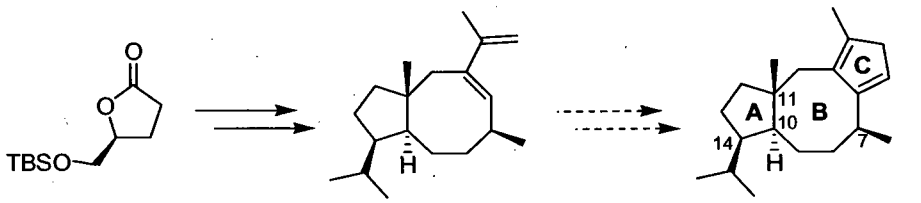
A novel cross-coupling reaction between alkyl bromides (such as **2.40**) with vinylzinc and vinylmagnesium reagents was developed. A catalytic system (5 mol % $Pd(OAc)_2$, 5 mol % PCy_3) and reaction conditions (NMP, 66 °C) were found which provided slightly over 50 % yield with a minimum amount of side product formation. The use of this reaction was explored in a tandem carboalumination/macrocyclization protocol.

The formation of unsaturated macrocycles by way of intramolecular Negishi cross-coupling reaction was investigated. Neopentyl iodides were found to cross-couple with vinyl iodides in the intermolecular stereospecific formation of trisubstituted alkenes, although extending this to the complementary intramolecular reaction was challenging. Reaction conditions were found which allowed for the selective zinc activation of an alkyl iodide in the presence of a vinyl iodide contained within the substrate.

The synthesis of the advanced intermediate towards fusicoccadiene, **4.2** was achieved in twenty-one steps (longest linear sequence) from the known (*S*)-(+)-4-(*tert*-butyldimethylsilyl)oxymethyl-γ-butyrolactone (**4.15**). Model studies revealed that fusicoccadiene may be obtained from **4.2** in additional four steps through the use of an acid catalyzed cyclodehydration reaction to form the C-ring. The formation of the 8-membered B-ring was achieved through the use of ring closing enyne metathesis. Other key features of the synthesis include the preparation of the functionalized cyclopentane A-ring through the use of a stereoselective Pauson-Khand [2+2+1] cycloaddition to establish the C-10 and C-14 stereocentres followed by the Norrish Type I reaction and an asymmetric cyclopropanation reaction to establish the remote C-7 stereocentre. Significantly, all stereocentres but one are established by stereochemical relay of the stereochemistry present in **4.15**.



2.40 **2.42**



4.15 **4.2** **fusicoccadiene**

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Å	-	angstrom
Ac	-	acetyl
acac	-	acetyl acetonate
AIBN	-	2,2'-azobisisobutyronitrile
amu	-	atomic mass unit
anal.	-	analysis
Ar	-	aryl
BBN	-	borobicyclo[3.3.1]nonane
BHT	-	2,6-bis(1,1-dimethylethyl)-4-methylphenol
BINAP	-	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	-	benzyl
b.p.	-	boiling point
br	-	broad
BRSM	-	based on recovered starting material
Bu	-	butyl
°C	-	degrees Celsius
CAD	-	Canadian
calcd	-	calculated
CI	-	chemical ionization
COD	-	1,5-cyclooctadiene
C-X	-	carbon number X
Cy	-	cyclohexyl
Cyp	-	cyclopentyl
d	-	doublet
dd	-	doublet of doublets
δ	-	chemical shift in parts per million from tetramethylsilane
dba	-	dibenzylideneacetone
DBU	-	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	-	*N,N'*-dicyclohexyl-carbodiimide
DCI	-	desorption chemical ionization
DDQ	-	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	-	diethyl azodicarboxylate
DMDO	-	dimethyldioxirane
dppf	-	1,1'-bis(diphenylphosphino)ferrocene
dppp	-	1,3-bis(diphenylphosphino)propane
DibalH	-	diisobutylaluminum hydride
DMAc	-	*N,N*-dimethylacetamide
DMAP	-	4-dimethylaminopyridine
DMF	-	*N,N*-dimethylformamide
dr	-	diastereomeric ratio
DMSO	-	dimethyl sulfoxide
E	-	entgegen (configuration)
ed.	-	edition
Ed., Eds.	-	editor, editors
EI	-	electron ionization
endo	-	endocyclic
Eq.	-	equation

equiv	-	equivalent
ESI	-	electrospray ionization
Et	-	ethyl
Et_2O	-	diethyl ether
exo	-	exocyclic
g	-	gram(s)
GC	-	gas chromatography
GC/MS	-	gas chromatography/mass spectrometry
GFPP	-	geranylfarnasyl pyrophosphate
h	-	hour(s)
HMBC	-	heteronuclear multiple bond coherence
HMPA	-	hexamethylphosphoramide
HMQC	-	heteronuclear multiple quantum coherence
hυ	-	light
HRMS	-	high resolution mass spectrometry
H-X	-	hydrogen number X
Hz	-	hertz (s^{-1})
i	-	iso
i.e.	-	Id Est (that is)
Im	-	imidazole
IMes	-	*N,N*-bis(mesityl)imidazol-2-ylidene
IR	-	infrared
ISC	-	intersystem crossing
J	-	coupling constant
kg	-	kilogram(s)
KDA	-	potassium diisopropylamide
KHMDS	-	potassium bis(trimethylsilyl)amide
LA	-	Lewis acid
LAH	-	lithium aluminum hydride
LDA	-	lithium diisopropylamide
LHMDS	-	lithium bis(trimethylsilyl)amide
m	-	multiplet
M	-	molar
M^+	-	molecular ion
MABR	-	methylaluminum(III)bis(4-bromo-2,6-di-*tert*-butylphenoxide)
MCPBA	-	*meta*-chloroperbenzoic acid
Me	-	methyl
Mes	-	mesityl
min	-	minute(s)
mg	-	miligram(s)
MHz	-	megahertz
µL	-	microlitre(s)
mmol	-	milimole(s)
m.p.	-	melting point
Ms	-	methanesulfonyl (mesyl)
MS	-	molecular sieves
n	-	normal
ND	-	not determined
NI	-	not isolated

NMI	-	*N*-methylimidazole
NMO	-	*N*-methylmorpholine-*N*-oxide
NMP	-	1-methyl-2-pyrrolidinone
NMR	-	nuclear magnetic resonance
NOE	-	nuclear Overhauser effect
NR	-	no reaction
[O]	-	oxidizing conditions
p	-	*para*
PG	-	protecting group
Ph	-	phenyl
PMB	-	*para*-methoxybenzyl
ppm	-	parts per million
PPTS	-	pyridinium *para*-toluenesulfonate
Pr	-	propyl
Pybox	-	pyridinebis(oxazoline)
pyr	-	pyridine
Q	-	quartenary
q	-	quartet
quin	-	quintet
rt	-	room temperature
R	-	alkyl group, aryl group or hydrogen atom
R	-	rectus (configuration)
RCM	-	ring closing metathesis
rec'd	-	recovered
S	-	sinister (configuration)
s	-	singlet
SM	-	starting material
T	-	temperature
t	-	time
TBAB	-	tetrabutylammonium bromide
TBAF	-	tetrabutylammonium fluoride
TBAI	-	tetrabutylammonium iodide
TBDPS	-	*tert*-butyldiphenylsilyl
TBS	-	*tert*-butyldimethylsilyl
tert	-	tertiary
TES	-	triethylsilyl
TESH	-	triethylsilane
Tf	-	trifluoromethanesulfonyl (triflate)
TFA	-	trifluoroacetic acid
TfMS	-	*p*-Trifluoromethylstyrene
TFP	-	2,2,3,3-tetrafluoropropan-1-ol
THF	-	tetrahydrofuran
TIPS	-	triisopropylsilyl
TLC	-	thin layer chromatography
TM	-	transition metal
TMEDA	-	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	-	trimethylsilyl
TPAP	-	tetra-*n*-propylammonium perruthenate
Ts	-	*para*-toluenesulfonyl (tosyl)

TS	-	transition state
TsCl	-	*para*-toluenesulfonyl chloride
TsOH	-	*para*-toluenesulfonic acid
TSA	-	*para*-toluenesulfonic acid
X	-	halogen atom
Z	-	zusammen (configuration)
·	-	coordination complex
±	-	racemic
®	-	registered trademark
©	-	copyright

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DEDICATION

To my parents

For stressing the importance of an education

Chapter One

Vinyl-Alkyl Based Transition Metal Catalyzed Coupling Reactions

I. Introduction

The constant search for novel reactions and methodologies for achieving the synthesis of evermore complex practical molecules has been a primary focus in organic chemistry.[1] Hence, the development of efficient reactions is justifiably an important branch of synthetic organic chemistry. The efficiency of a reaction is generally dependent on two factors which characterize methodological studies: selectivity and atom economy.[2] Selectivity involves the minimization of unwanted compounds relative to the desired materials from a reaction. This may be a result of chemoselectivity and regioselectivity, which involve the location of the reactive centre in a molecule, and diastereoselectivity and enantioselectivity, which revolve around stereochemistry issues at a specific reaction centre. The efficiency of a reaction also involves minimizing the amount of reagent material required in a reaction or sequence of reactions, hence the importance of atom economy.

A primary objective of methodological studies is the creation of new types of bond forming reactions that also address the twin issues of selectivity and atom economy. A principal bond forming reaction, if not the most important in organic chemistry, is that which fuses two carbon atoms. Reactions of this type catalyzed by transition metals have been extensively studied and developed in the last 30 years. In fact, the use of transition metals as catalysts in C-C bond forming reactions addresses the importance of selectivity and atom economy, hence the vast amount of work developed for this reaction. Since the initial discovery of the nickel catalyzed coupling of alkylmagnesium halides with vinyl or aryl bromides in 1972 (Kumada-Corriu),[3] a number of variants for the coupling of organometallic reagents to carbon electrophiles have been developed using predominantly Group 10 metal catalysts. Among others, these involve Zn (Negishi),[4] Sn (Stille),[5] B (Suzuki-Miyaura)[6] and Si (Hiyama)[7] as the organometallic partner (Eq. 1.1).

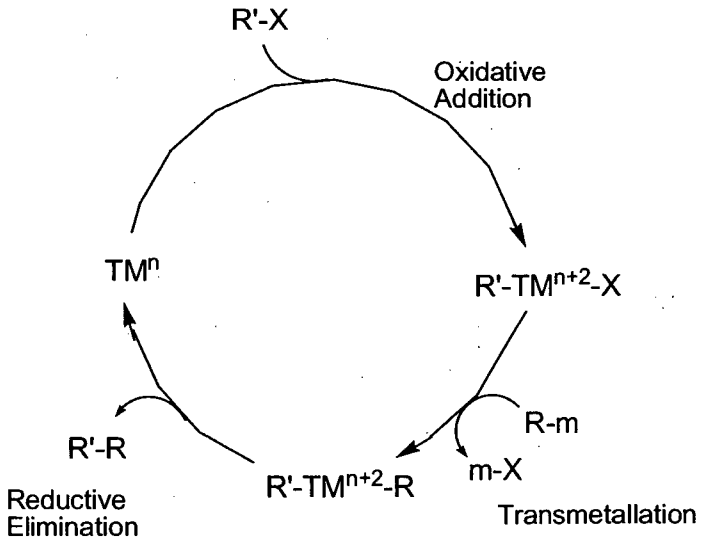
$$\text{R-m} + \text{R'-X} \xrightarrow{\text{catalyst TM}} \text{R-R'} \qquad (1.1)$$

m = Mg (Kumada, Corriu)
Zn (Negishi)
Sn (Stille)
B (Suzuki-Miyaura)
Si (Hiyama) .....

TM = Ni, Pd.....

X = I, Br, Cl, OTf.....

The mechanisms for all of these C-C bond forming reactions proceed in a similar manner. Generally, the reaction begins with the oxidative addition of the electrophile (R'-X) to the transition metal catalyst (TM^n). This is followed by the slow transmetallation with the organometallic reagent (R-m) and a reductive elimination to furnish the coupled compound containing a new fused C-C bond and regenerate the catalyst (TM^n).



Scheme 1.1 Generalized Mechanism for the Transition Metal Catalyzed C-C Cross-Coupling Reaction

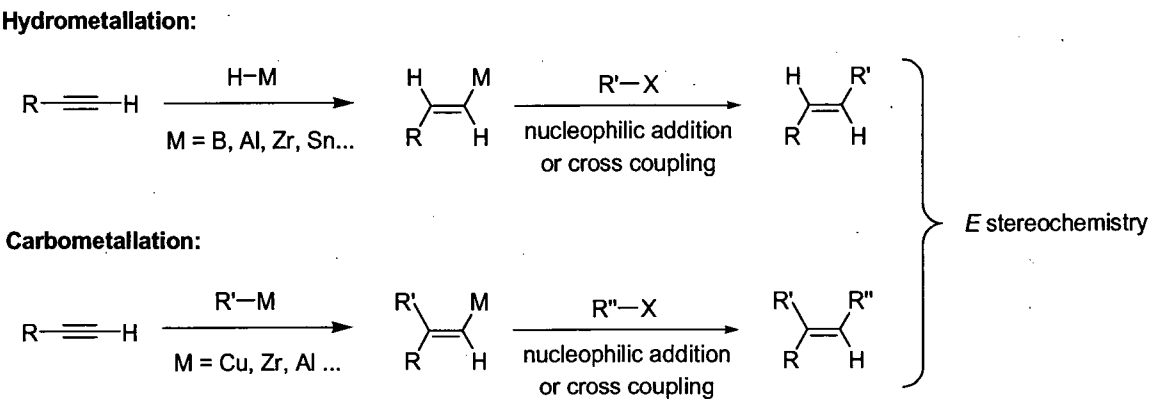
A variety of combinations of transition metal catalyzed cross-coupling reactions have been developed for the coupling of organometallics with organic electrophiles to form bonds between differing types of hybridized carbons.[8] These include coupling partners containing alkyl, allyl, aryl and vinyl carbons at the reactive centres. However, there are still limitations in the possible combination of organometallic and electrophilic coupling partner. Specifically, the use of an alkyl electrophile remains challenging. The

coupling between two alkyl carbons, an alkyl organometallic and an alkyl electrophile, has only recently been developed by the research groups of Fu, Kambe and Knochel.[9] Various methods for the coupling of aryl organometallics and alkyl electrophiles have also only recently been developed by Kambe, Beller, Hayashi, Nakamura, Fu and Knochel.[9c] However, the coupling between vinyl organometallics and alkyl electrophiles remains yet to be fully developed, although a few recent examples have been reported in the last two years.[9c] Hence, this last case remains as the only combination of transition metal catalyzed C-C cross-coupling reaction to be fully explored. Complementary transition metal catalyzed intramolecular reactions have also been developed, although examples remain sparse or non-existent for certain combinations. No example exists for the macrocyclic coupling of either a vinyl organometallic and an alkyl electrophile or an alkyl organometallic and a vinyl electrophile. The discussion which follows will thus focus on the transition metal mediated formation of C-C bonds between vinyl and alkyl carbons as well as their applications to macrocyclization reactions.

In a first section, the preparation of vinylorganometallics will be presented, most notably in the form of hydrometallation and carbometallation reactions of alkynes, as well as their applications to synthesis. A second section will cover recent work on the transition metal catalyzed cross-coupling reactions of alkyl electrophiles, detailing the relevant systems for such processes.

II. Vinylorganometallics in Organic Synthesis

A common method for the formation of vinyl organometallics, which in turn provides useful fragments for transition metal cross-coupling reactions, is the hydrometallation or carbometallation of alkynes (Scheme1.2). The following section serves as a brief description for such processes. In addition, the chemistry of the resulting vinylorganometallics is also described.



Scheme 1.2 Hydrometallation and Carbometallation of Terminal Alkynes

A. Hydrometallation and Carbometallation

A large number of metal hydrides have been found to perform hydrometallations in the last 45 years. The most common examples involve hydrides of boron,[10] aluminum,[11] zirconium[12] and tin.[13]

The addition of alkyltin hydrides (R_3SnH) to alkynes may be performed at elevated temperature in the presence of azoisobutyronitrile (AIBN).[14] Although this results in the formation of terminal vinylstannanes in the case of terminal alkynes, *E*/*Z* mixtures often result. The *E* isomer may be prepared stereoselectively through the use of catalytic Pd^0.[15] Vinylboranes can also be synthesized by the direct hydroboration of terminal alkynes using a boron hydride reagent. The process is usually regioselective and provides the *E* isomer. However, possibilities of dihydroboration or polymerization limit the scope of the process.[16] Similarly, vinylalanes may be prepared regio- and stereoselectively through the use of aluminum hydrides (usually diisobutylaluminum hydride).[17]

Hydrometallation of alkynes, in particular hydrozirconation using Schwartz's reagent ($HZrCp_2Cl$), was found to be well suited for the synthesis of stereodefined alkenes. As hydrometallation involves the concerted addition of the metalhydride to a terminal alkyne in a stereoselective *syn* addition, vinylzirconates of *E* stereochemistry may be obtained exclusively, which may result ultimately in *E* disubstituted alkenes (Scheme 1.2). Formally, the concerted *syn* process involves complexation of the alkene to the metal such that the latter requires the presence of an empty low-lying

orbital. In terms of frontier orbital interactions, the addition reaction closely parallels the Dewar-Chatt-Duncanson model for π-complexation, although the difference between σ and the nonbonding orbitals is clearly present (Figure 1.1).

The resulting vinylstannanes, boranes, alanes and zirconates however were found to be poor nucleophiles so their initial use as substrates in C-C bond forming reactions was limited. This issue was circumvented by the discovery of transmetallation methods which allowed for the vinyl organometallic to display properties and reactivities of the newly incorporated metal. Subsequently, transition metal catalyzed cross-coupling reactions were also developed (*vide infra*).

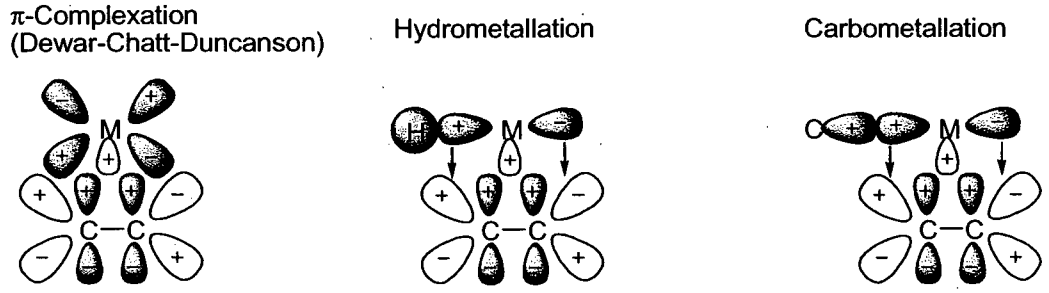
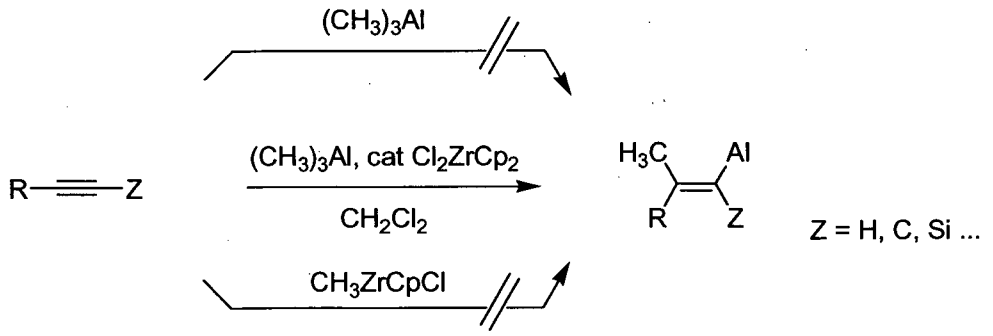


Figure 1.1 Frontier Orbital Interactions for π-complexation, Hydrometallation and Carbometallation

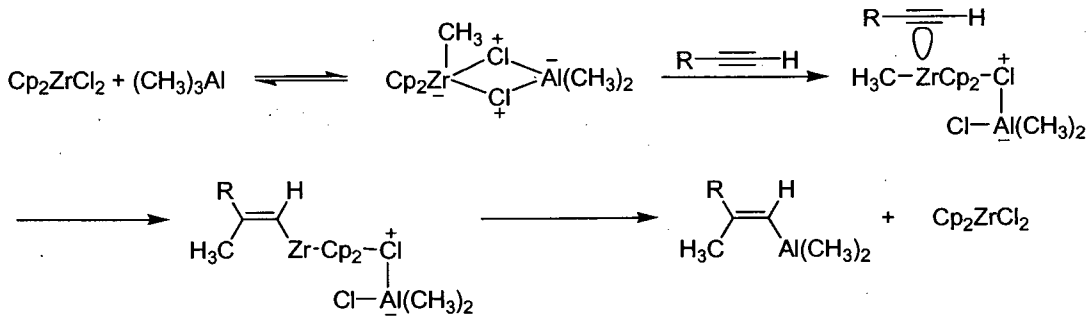
In the case of the formation of *E* trisubstituted alkenes, selectivity issues surrounding the hydrometallation of an internal alkyne become problematic. Alternatively, carbometallation of a terminal alkyne would simplify this issue.

Carbometallation processes were first introduced by Normant and co-workers in 1971 in the form of carbocupration of alkynes.[18] However, difficulties with the simple case of methylcupration have limited its use in natural product chemistry. The discovery of zirconium catalyzed carboaluminations of alkynes in 1978 by Negishi and co-workers generalized and expanded the scope of the process.[19] The simplest case, methylalumination, involves the premixing of trimethylaluminum and a catalytic amount of bis(cyclopentadienyl)zirconium dichloride and the subsequent addition of this mixture to a terminal alkyne (Eq. 1.2).



(1.2)

The stereoselectivity of the reaction is found to result from a concerted *syn* addition of the reagent in a similar manner as for hydrometallation (Figure 1.1). Mechanistically, the process proved to be rather complex as neither trimethylaluminum alone nor preformed bis(cyclopentadienyl)methylzirconium chloride without aluminum provided the desired methylmetallation (Eq. 1.2). This strongly suggests a bimetallic mechanism for the crucial stage. Various experiments have suggested the reactive species to be $MeZrCp_2^{\delta+}$-Cl-$^{\delta-}AlMe_2Cl$ in which the Zr is not only coordinatively unsaturated but also more positively polarized. The mechanistic details are beyond the scope of this review but simplistically this entails an acyclic and bimetallic Zr-centered process (Scheme 1.3).[20,21]



Scheme 1.3 Mechanism of the Reaction of Terminal Alkynes with $Al(CH_3)_3$-Cl_2ZrCp_2

The Zr catalyzed ethyl and higher alkylaluminations have also been investigated. However, the lack of regioselectivity as well as the observation that the carbometallations proceed more readily and cleanly in non-polar solvents suggest that the mechanism may be different than for the methylalumination process. In fact numerous studies have shown this to be rather complex but the mechanism appears to

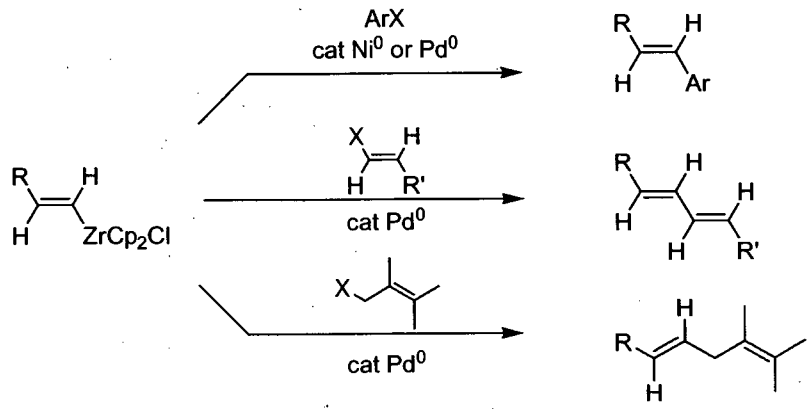
involve a cyclic bimetallic process as opposed to the acyclic process encountered for methylalumination.[22]

B. Chemistry and Reactivity of Vinyl Organometallics

The hydrometallation and carbometallation products obtained from alkynes proved to be useful and versatile products for further reactions. Their potential as nucleophiles, as organometallics for cross-coupling, or as species which can undergo transmetallation and further functionalization was well recognized. The following presents a brief overview of the chemistry of vinyl organometallics and focuses on those obtained from hydrometallation and carbometallation reactions.[23]

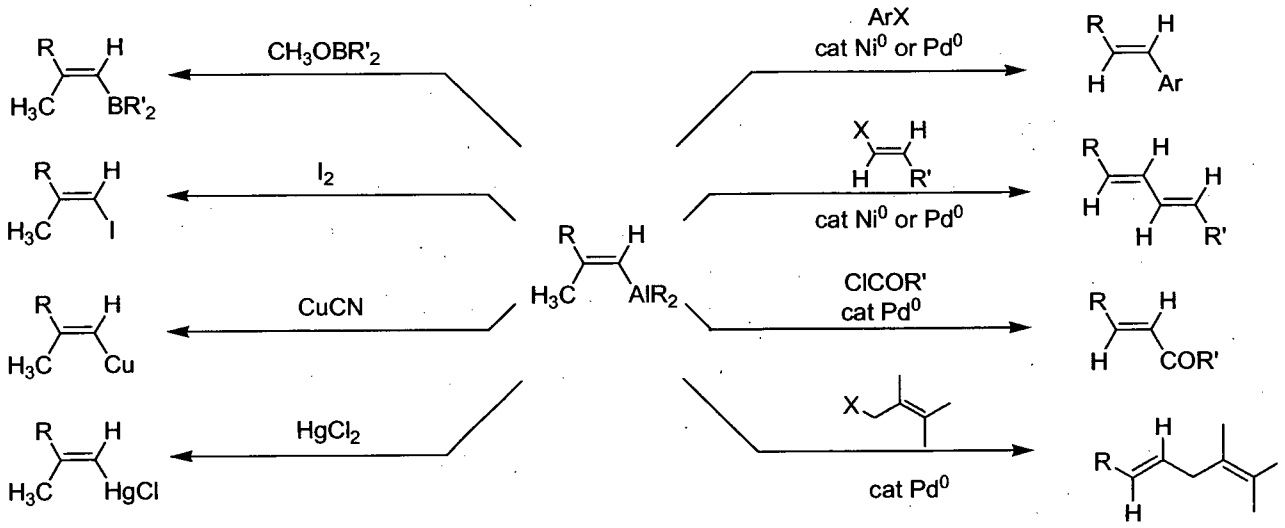
In the case of vinylstannanes, these may readily be converted to vinyllithium intermediates with retention of configuration. This process is often used to prepare vinylcuprates by way of further transmetallation, which can then be used to perform cuprate-type chemistry.[24] Vinylcuprates can also be prepared directly from vinylstannanes through metal exchange with higher order cyanocuprates.[25] An attractive feature of vinylstannes obtained from hydrostannylation is their use as organometallic reagents in Stille type cross-coupling reactions with allyl, vinyl and aryl electrophiles.[26] Vinylboranes also undergo cross-coupling reactions (Suzuki-Miyaura coupling) with similar electrophiles.[27]

Vinyl organometallic derivatives of zirconium are usually regarded as poor nucleophiles.[28] However, these transmetallate readily to other organometals upon treatment with metal halides containing Al,[29] B,[30] and Sn.[31] Halodezirconation may also be performed to yield vinyl halides.[32] Although vinylzirconocenes may be transformed into other reactive species, these vinyl organometallics have also been found to be useful directly in Ni or Pd catalyzed cross-coupling reactions (Scheme 1.4).[33] Additionally, the discovery of Pd-Zn and Ni-Zn double metal catalysis (with the use of zinc chloride as co-catalyst) has substantially expanded the scope of the cross-coupling reaction.[4a]



Scheme 1.4 Ni and Pd Catalyzed Cross-Coupling Reactions of Vinylzirconocenes

The chemical behavior of vinylalanes is found to be quite similar to that of vinylzirconocenes. The importance of vinylalanes stems from the fact that these are easily obtained from the carboalumination reaction (*vide supra*), and in as such, their chemistry has been studied extensively, specifically with regards to the stereoselective formation of trisubstituted alkenes (Scheme 1.5).



Scheme 1.5 Reactions of Vinylalanes

Among the many possible transformations that vinylalanes undergo, transmetallation with B,[34] Hg,[35] and Cu[36] appear to be the most important. The use of copper further allows for conjugate addition to enones which results in functionalized trisubstituted alkenes when used in conjunction with carbometallation.[37] The addition of

iodine to vinylalanes provides for vinyl iodides which can be further used in cross-coupling reactions to also yield trisubstituted alkenes, notably in the Negishi cross-coupling reaction (*vide infra*).[4a] Additionally, vinylalanes resulting from carbometallations have been found to be useful vinyl organometallics in Ni or Pd catalyzed cross-coupling reactions similar to those presented for vinylzirconocenes to form trisubstituted alkenes. Pd catalyzed acylations are also possible.

C. Negishi Cross-coupling Reaction

The following section presents a brief overview of the cross-coupling reaction between vinyl iodides and zinc organometallics, often referred to as the Negishi cross-coupling reaction (Eq. 1.1). Emphasis will be placed on the formation of Csp^2-Csp^3 bonds. Since it is often used in conjunction with carboalumination, discussion of the Negishi cross-coupling reaction will focus on the formation of trisubstituted alkenes.

The use of organozinc compounds in synthesis was limited until the development of transition metal catalyzed C-C bond forming reactions, mainly because of their low nucleophilicity towards various electrophiles. In fact, this characteristic distinguishes organozincs as highly chemoselective reagents in transition metal catalyzed reactions. Along with B and Sn, Zn organometallics appear among the most used reagents in cross-coupling reactions.

Cross-coupling reactions with organozincs were first introduced by Negishi and co-workers in 1977 in the form of aryl and benzyl zinc coupling to aryl halides under the influence of Pd^0 to form unsymmetrical biaryl compounds.[38] Subsequently, a number of organozinc halides were found to undergo such reactions and the scope has been expanded to include all the possible combinations between two unsaturated carbon groups (Figure 1.2).

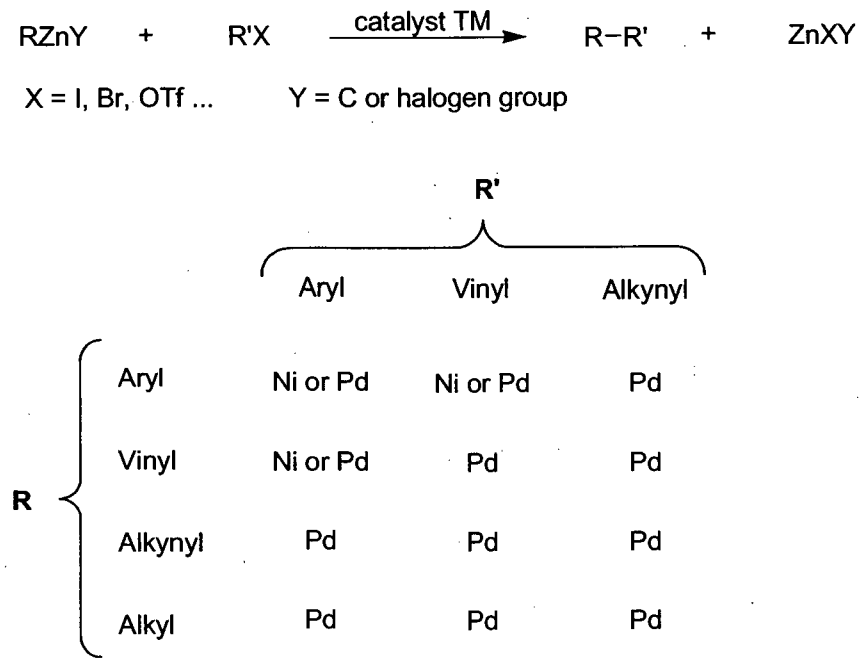
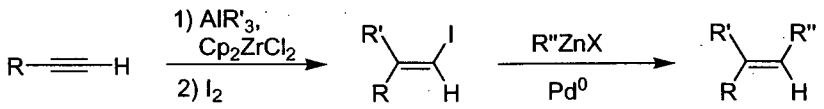
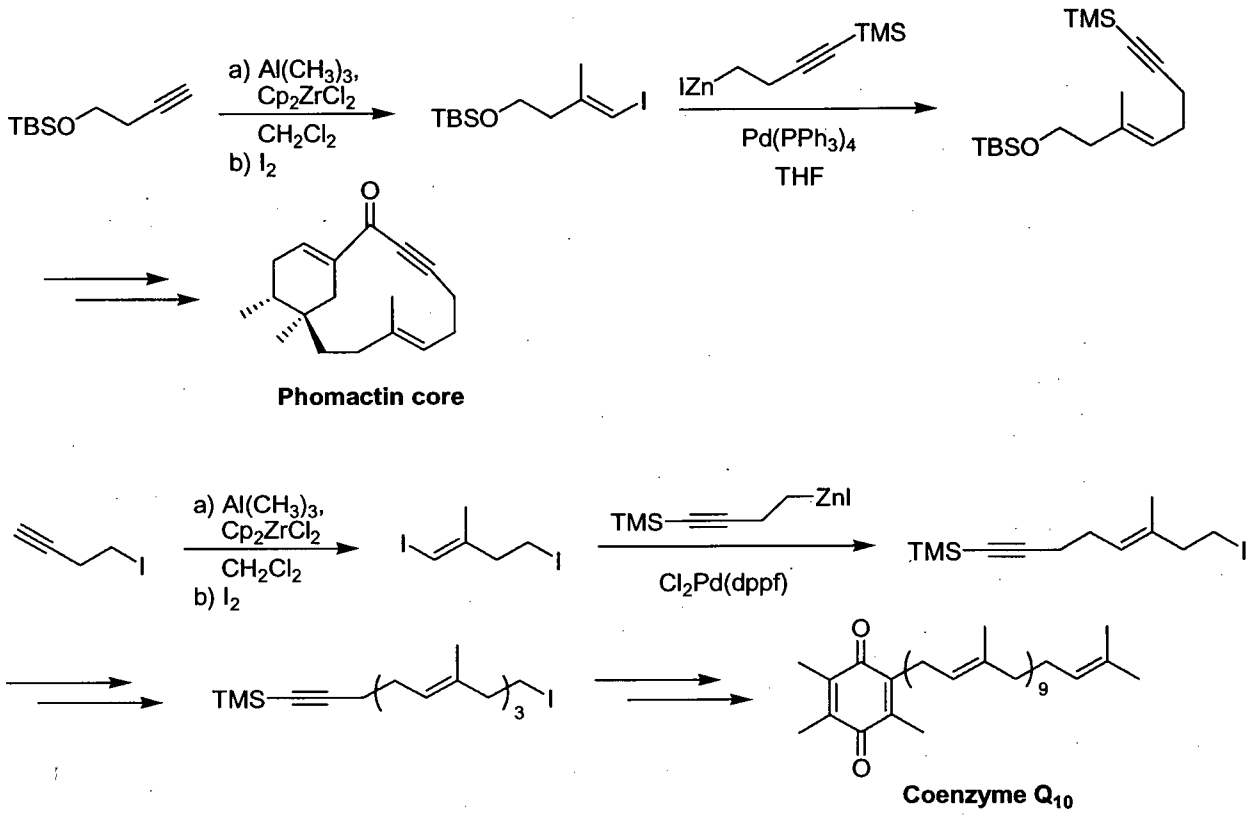


Figure 1.2 Possible Combination of Organozinc Cross-Coupling Reactions

Of further interest, alkyl zinc reagents were found to be suitable organometallics for cross-coupling with vinyl iodides under the influence of Pd^0.[39] An interesting feature is its use in conjunction with carboalumination of terminal alkynes to form trisubstituted alkenes (Eq. 1.3). The ease of preparation of alkyl zinc reagents and the mildness and stereoselectivity of the combination makes this an attractive protocol in the synthesis of natural products as exemplified in Scheme 1.6. Although there exist other examples of the coupling between vinyl electrophiles and alkyl organometallics, the Negishi coupling is the most general and broad in scope for this type of process.



(1.3)

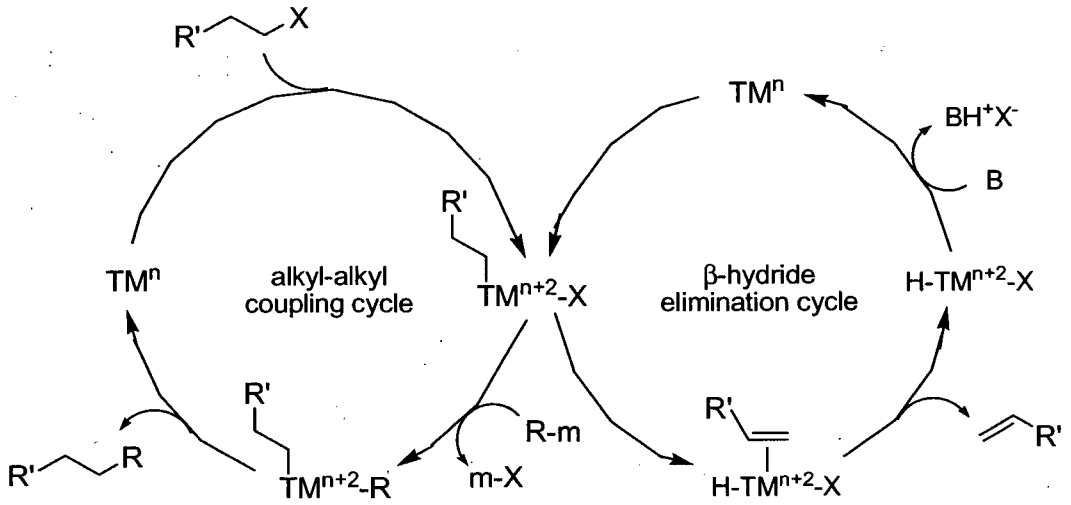


Scheme 1.6 Use of Carboalumination-Negishi Coupling Process in the Synthesis of Natural Products[40,41]

III. Transition Metal Catalyzed Cross-Coupling Reactions of Alkyl Electrophiles

The previous section alluded to the use of vinyl organometallics, specifically vinylzirconocenes, vinylalanes and vinylzincs as cross-coupling reagents in the formation of C-C bonds. Most often, these vinyl organometallics are coupled to aryl or vinyl electrophiles such that Csp^2-Csp^2 bonds are formed. The previous section also introduced the use of the Negishi cross-coupling reaction, specifically its use in the formation of Csp^2-Csp^3 bonds. This entails the coupling of an alkyl organometallic and a vinyl electrophile. The formation of Csp^2-Csp^3 bonds can also be conceived to be created by the cross-coupling of a vinyl organometallic and an alkyl electrophile. However the use of alkyl electrophiles as coupling partners has been found to be problematic since these represent a more difficult class of electrophiles for cross-coupling reactions than the corresponding vinyl or aryl electrophile.

Until recently no efficient and general metal catalyzed cross-coupling methodologies existed for non-activated alkyl electrophiles.[42] The general feasibility of the reaction with such electrophiles was demonstrated by a few prior isolated examples. Kochi and Tamura reported in 1971 the silver or copper catalyzed cross-coupling reaction of alkyl magnesium bromides and alkyl bromides.[43] In 1992 Suzuki and co-workers demonstrated the palladium catalyzed cross-coupling reaction between alkyl boranes and alkyl halides.[44] In either examples however, yields were modest and no general applications were established.



Scheme 1.7 Generalized Mechanism for the Alkyl-Alkyl Cross-Coupling Reaction and for the Competitive β-Hydride Elimination Reaction

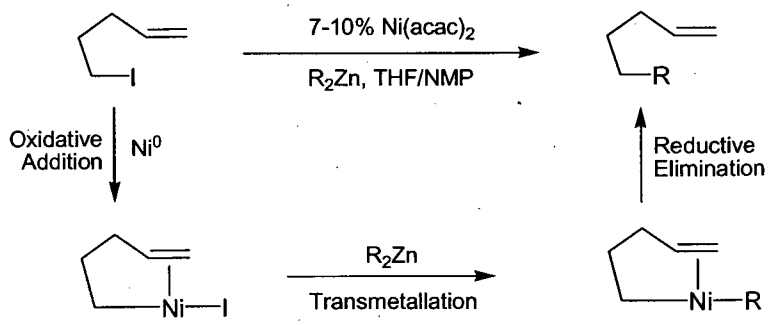
The difficulty which arises from the cross-coupling of alkyl electrophiles relies on three factors which are related to the three general steps in transition metal catalyzed cross-coupling reactions (Scheme 1.7). In the first step, the propensity of alkyl halides to undergo oxidative addition to a low-valent transition metal complex is much lower than for aryl or vinyl halides since the Csp^3 bond is more electron rich than the Csp^2 bond. In the second step, the resulting alkyl-metal complex is highly reactive towards β-hydride elimination relative to the slow transmetallation. This results from the presence of β-hydrogens and the absence of stabilizing electronic interactions with the metal d-orbitals. In the third step, the relatively slow reductive elimination of the cross-coupling product from the catalyst (aryl-aryl > aryl-alkyl > alkyl-alkyl) allows for side-reactions to become competitive. Hence, the design of more reactive catalyst

systems and the development of suitable reaction conditions for cross-coupling reactions of alkyl electrophiles have generally been aimed at facilitating the oxidative addition and the reductive elimination steps and preventing the competing β-hydride elimination. In the last five years, a variety of highly selective transition metal catalyzed cross-coupling reactions with alkyl electrophiles has been reported. An overview of the recent advances in transition metal catalyzed cross-coupling reactions of alkyl electrophiles is presented in the following section. Since the development of these reactions relies on the catalyst system and reaction conditions, the following description for alkyl electrophile cross-coupling reactions has been organized in this manner.

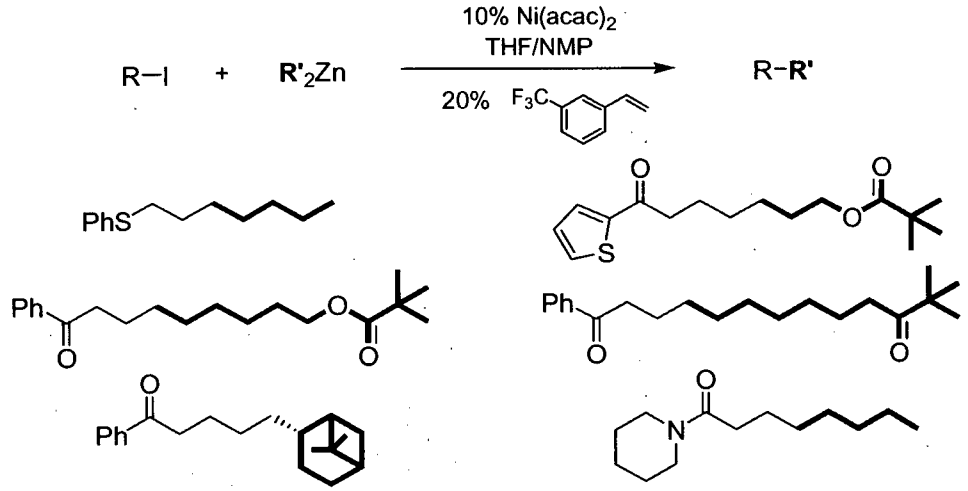
A. Knochel Coupling System

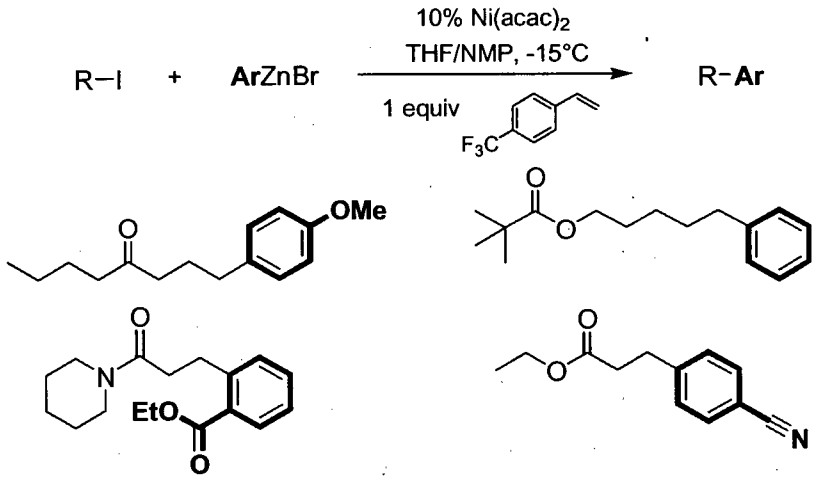
The first generalized system which allowed for the coupling of organometallics with alkyl electrophiles was reported by Knochel and co-workers in 1995.[45] This involved a Negishi-type reaction using $Ni(acac)_2$ catalyzed cross-coupling between dialkylzincs and alkyl iodides in a tetrahydrofuran/1-methyl-2-pyrrolidinone (THF/NMP) solvent system (Scheme 1.8). However, successful reactions only resulted from alkyl iodide substrates which contained an alkene at the 4- or 5-position, specifically with electron-withdrawing substituents on the double bond. This suggested the intermolecular nickel coordination with the alkene in the intermediate following oxidative addition, which allows for a faster reductive elimination due to the delocalization of the nickel d-orbital electrons.

The scope of the methodology was subsequently extended to alkyl halide substrates which did not contain a pendant alkene ligand. Exploiting the observation of the intramolecular alkene coordination at the nickel, the cross-coupling was achieved with the addition of a π-acceptor ligand.[46] A ligand screening found *p*-trifluoromethylstyrene to be the most effective co-catalyst (Scheme 1.9). The relative mildness of the reaction conditions allowed for the use of substrates containing esters and amides. Interestingly, alkyl halides containing thioethers and thioacetals lead to an increase in reaction rate, presumably through additional coordination of the sulfur to the metal complex. Only primary dialkylzinc reagents were found to undergo the coupling reaction.



Scheme 1.8 Nickel Catalyzed Cross-Coupling of DialkylZinc with Alkyl Iodides Containing an Alkene at the 4-Positon (Knochel)[45]

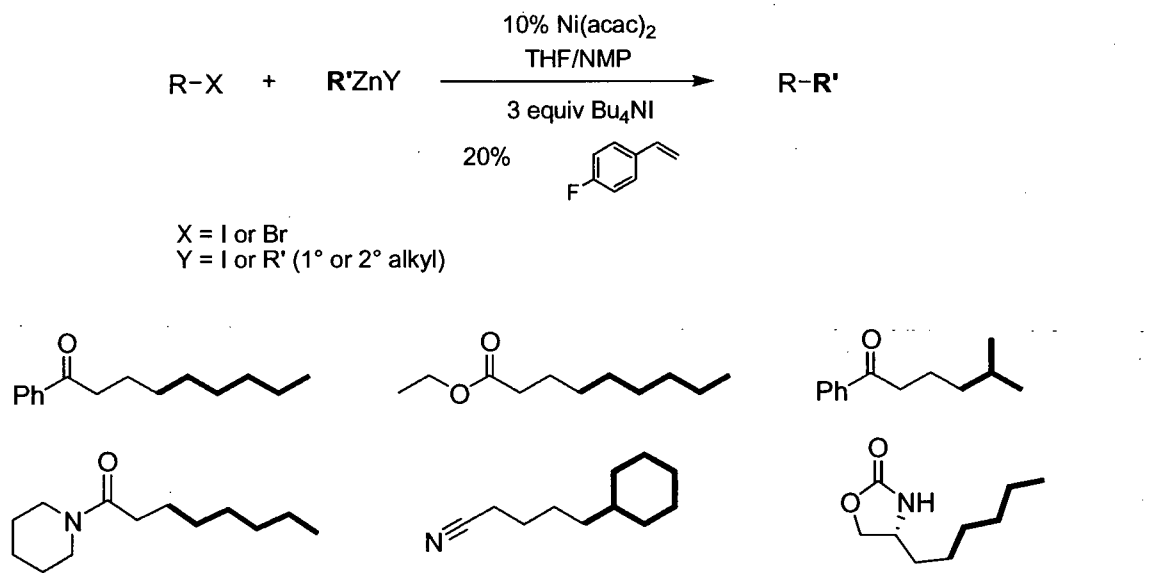




Scheme 1.9 Nickel Catalyzed Cross-Coupling of DialkylZincs and Arylzinc Halides with Alkyl Iodides Along with Selected Examples (Knochel)[46,47]

Similar conditions were used to couple arylzinc bromides with alkyl iodides (Scheme 1.9).[47] In the absence of stoichiometric 4-trifluoromethylstyrene, homocoupling and iodine-zinc exchange products were observed instead.

Knochel and co-workers also found that the reaction rate was significantly increased upon addition of stoichiometric amounts of tetrabutylammonium iodide in the presence of 4-fluorostyrene as the co-catalyst (Scheme 1.10). This allowed for the cross-coupling reaction to be performed with less reactive systems.[48] Alkylzinc iodides and secondary dialkylzincs were found to react with alkyl iodides and alkyl bromides. The reaction conditions were tolerant to a variety of functional groups such as ethers, ketones, esters, amides and nitriles. However, the role of the tetrabutylammonium iodide was not clear.

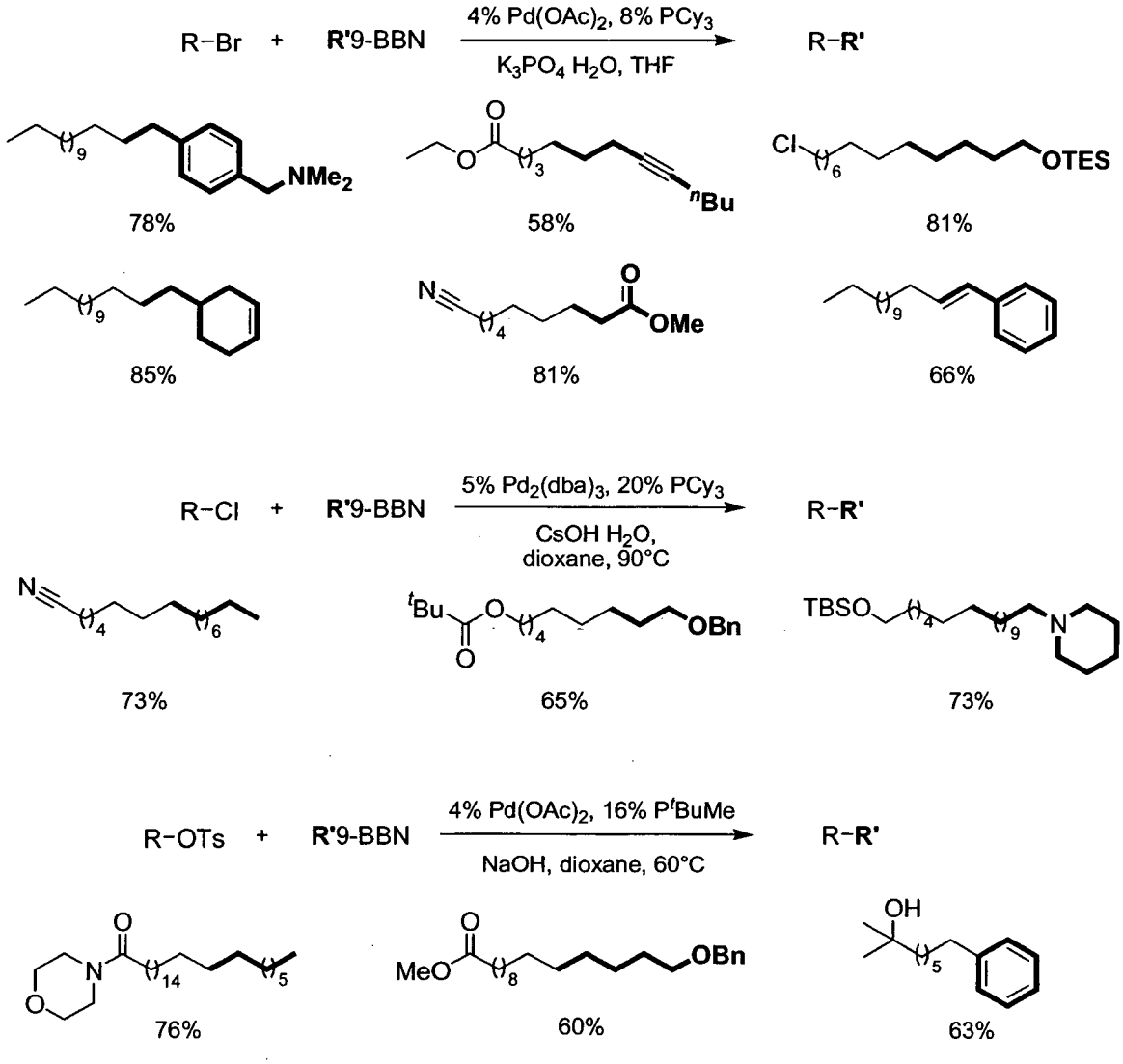


Scheme 1.10 Nickel Catalyzed Cross-Coupling of Alkylzinc Halides and Secondary DialkylZincs and Alkyl Halides Along with Selected Examples (Knochel)[48]

B. Fu Coupling System

The most significant general method for cross-coupling reactions of alkyl electrophiles in the last couple of years was developed by Fu and co-workers and is based on the Suzuki reaction. Although the palladium catalyzed cross-coupling of

alkylboranes with alkyl iodides was previously demonstrated by Suzuki and co-workers (*vide supra*),[44] the scope and generality of the reaction was expanded by Fu and co-workers to include other alkyl electrophiles. Hence, primary alkyl bromides,[49] chlorides[50] and tosylates[51] were coupled to alkyl and arylboranes under the influence of a palladium catalyst with bulky and electron-rich phosphine ligands (Scheme 1.11).



Scheme 1.11 Palladium Catalyzed Cross-Coupling of Organoboranes and Alkyl Halides and Tosylates Along with Selected Examples (Fu)[49,50,51]

Generally, individual fine-tuning of the palladium pre-catalyst, ligand and base employed was required to ensure high selectivity for coupling products. After extensive screening, PCy_3 (Cy = cyclohexyl) as the ligand was found to provide the highest yield for alkyl bromides and chlorides whereas in the case of alkyl tosylates P*t*Bu_2Me was

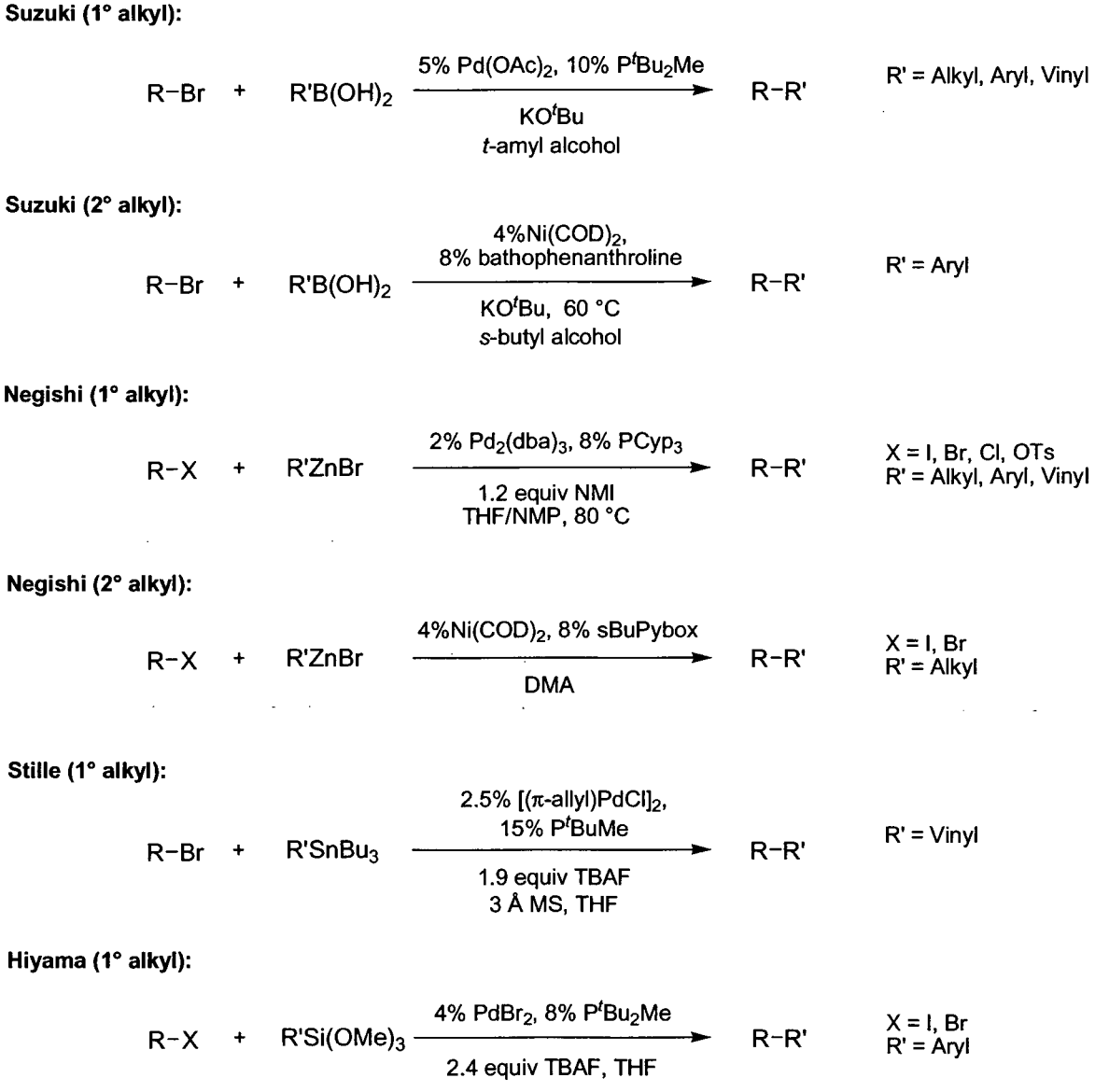
found to be optimal. For the precatalyst, $Pd(OAc)_2$ was preferred except for chlorides in which $Pd_2(dba)_3$ was favoured. The mildness of the reaction conditions and of the alkylborane reagents allowed for the compatibility of numerous functionalities. Consequently, substrates which contained esters, nitriles, amides, ethers, amines, alkenes and alkynes were successfully coupled. It is also important to note that 1-bromododecane was found to couple with (*E*)-9-styryl-9-BBN (see Scheme 1.11), which appears to be the first example of the coupling of a vinylmetal to an alkyl electrophile under the influence of a transition metal catalyst.

As mentioned above, the success of the reaction requires the use of sterically hindered electron-rich phosphine ligands. The increased electron donating ability of trialkylphosphines allows for easier oxidative insertion into the Csp^3-halide bond and the steric demand facilitates the reductive elimination step.[52] The electron donating ability is a reflection of the nature of the substituents but also depends on the Tolman cone angle.[53] Additionally, the cone angle is also related to the steric hindrance imposed by the ligand. The experimentations suggest that a delicate balance of steric and electronic features has to be attained for the ligand to be adequate. If a donor ligand is too large, then the intermediate palladium complex after oxidative insertion may only coordinate a single phosphine ligand, and the coordinatively unsaturated metal complex would more likely undergo β-hydride elimination.

The organoborane reagents can be prepared easily from the hydroboration of alkenes. However, commercial available and air-stable alkyl boronic acids were also shown to cross couple with alkyl bromides using $Pd(OAc)_2$ and P*t*Bu_2Me.[54] The air-sensitive phosphine can be substituted with the air-stable and commercially available phosphonium salt, which provides similar yields.

A number of alkyl electrophile cross-coupling reaction types with various organometals was subsequently developed using sterically hindered electron-rich phosphine ligands. Fu and Zhou have developed a Negishi variant in which alkyl iodides, bromides, chlorides and tosylates cross couple to alkylzinc bromides with $Pd_2(dba)_3$ and $PCyp_3$ (Cyp = cyclopentyl) as ligand (Scheme 1.12).[55] The use of a stoichiometric amount of *N*-methylimidazole was key for the success of the reaction, presumably by activating the organozinc towards transmetallation.[56] As in the case of Knochel's coupling protocol (*vide supra*), the use of 1-methyl-2-pyrrolidinone as

co-solvent was also required. The scope was expanded to include arylzinc bromides and more interestingly, vinylzinc bromides. Additionally, a one-pot hydrozincation of alkynes followed by cross-coupling procedure was developed.



Scheme 1.12 Transition Metal Catalyzed Cross-Coupling of Organometallics and Alkyl Electrophiles Along with Selected Examples (Fu)[54,55,57,58,59,61]

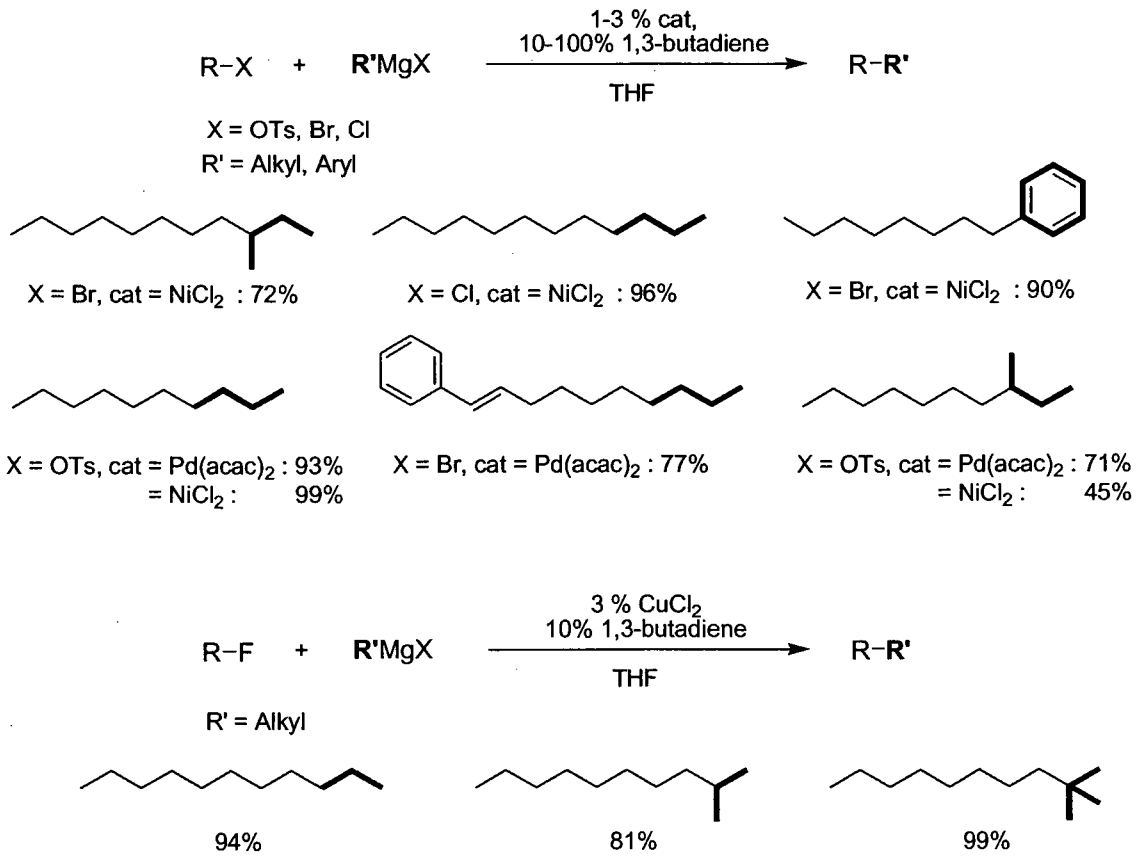
Only primary alkyl electrophiles have been described so far. Using a nickel variant of the Negishi coupling, Fu and Zhou have however developed conditions in which secondary alkyl iodides and bromides reacted with alkylzinc bromides (Scheme 1.12).[57] Fine tuning of the required ligand revealed that bis(oxazolinyl)pyridines were

optimal for this reaction. Secondary alkyl bromides were subsequently found to couple to aryl boronic acids under Suzuki conditions (Scheme 1.12). In this case, a nickel catalyst was also used but phenanthroline ligands were found to work best in the cross-coupling reaction.[58]

The palladium catalyzed Stille cross-coupling has recently been developed for the coupling of primary alkyl bromides with vinylstannanes (Scheme 1.12).[59] In the presence of catalytic $[(\pi\text{-allyl})PdCl]_2$, P*t*$Bu_2Me$ as phosphine ligand was found to provide the highest yield. The use of stoichiometric tetrabutylammonium fluoride was essential, presumably by forming a more reactive hypervalent stannane. Under a similar procedure, arylstannanes have been coupled to alkyl halides.[60] Additionally, a Hiyama cross-coupling procedure for alkyl iodides and bromides with aryl silanes has also been developed using $PdBr_2$ (Scheme 1.12).[61] Similarly to the previously reported conditions for the Stille reaction, P*t*Bu_2Me as the phosphine ligand was found to provide the highest yield and stoichiometric tetrabutylammonium fluoride was found to be essential for the success of the reaction. A zirconium-Negishi procedure has been developed for the cross-coupling of vinylzirconocenes and alkyl halides using $Pd(acac)_2$.[62] The reaction was found to proceed without the use of phosphine ligands and appears to be the first example of "ligandless" cross-coupling reaction of alkyl electrophiles.

C. Alkyl Halide Cross-Coupling Systems with Organomagnesium Halides

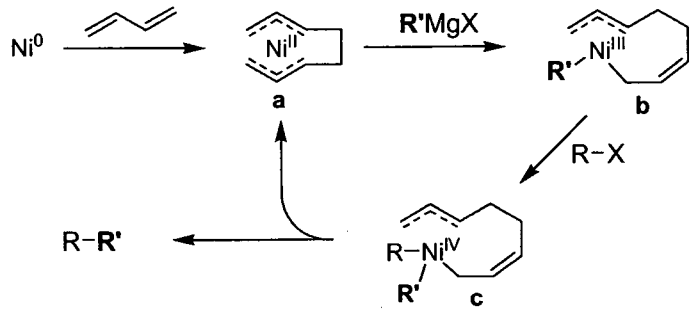
As an extension of the copper catalyzed Kumada type coupling of alkyl magnesium bromides and alkyl bromides initially investigated by Kochi and Tamura (*vide supra*),[43a] Cahiez and co-workers found that the stoichiometric use of 1-methyl-2-pyrrolidinone along with catalytic copper dramatically increased the yields and chemoselectivity for the coupling between alkyl halides and alkylmagnesium bromides.[63] However, secondary and tertiary bromides as well as other alkyl electrophiles were found to be unreactive.



Scheme 1.13 Nickel and Palladium Catalyzed Cross-Coupling of Organomagnesium Halides and Alkyl Electrophiles Along with Selected Examples (Kambe)[64,65,66]

In 2002, Kambe and co-workers expanded the scope of this reaction by coupling organomagnesium reagents to a variety of alkyl electrophiles.[64] In the presence of Ni(II) catalysts, alkyl bromides, chlorides and tosylates were found to cross-couple to alkylmagnesium halides and arylmagnesium halides (Scheme 1.13). The key for the success of the reaction was the addition of 1,3-butadienes as catalytic ligands for nickel. This catalyst stabilizes the active catalyst and accelerates the reductive elimination step. In the absence of the diene, hydrodehalogenation or elimination products were obtained. The mechanism has been postulated to involve a diallyl-Ni (II) catalyst **a** formed from the complexation of Ni(0) and two equivalents of the 1,3-butadiene (Scheme 1.14). The active catalyst **a**, unreactive towards the alkyl halide, is proposed to undergo a transmetallation with the Grignard reagent to form an anionic alkyl Ni(III) complex **b**. This more nucleophilic species then undergoes alkylation with the electrophile forming the Ni (IV) intermediate **c** followed by a reductive

elimination to produce the coupled product and regenerate the active catalyst complex **a**.



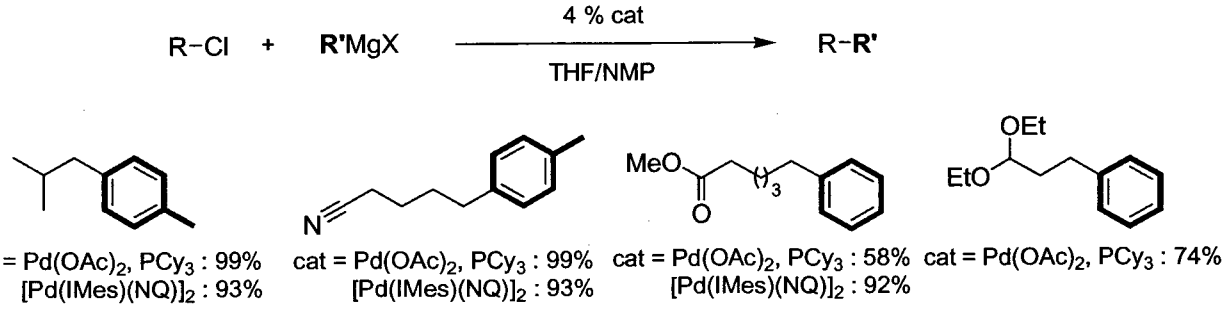
Scheme 1.14 Mechanism for the Nickel Catalyzed Cross-Coupling of Organomagnesium Halides and Alkyl Electrophiles (Kambe)[64]

The complementary palladium reaction was subsequently explored by Kambe and co-workers.[65] Alkyl bromides and tosylates were found to couple with alkylmagnesium halides in the presence of $Pd(acac)_2$ and 1,3-butadienes. The mechanism for the reaction is proposed to proceed via Pd(II)-Pd(IV) catalytic cycle analogous to the nickel catalyzed pathway. The system was found to be highly chemoselective for alkyl tosylates and worked well for secondary alkylmagnesium halides.

The procedure was expanded to the cross-coupling of alkyl fluoride using Ni(II) and 1,3-butadiene although the yields were modest at best, owing to the strength of the carbon-fluoride bond.[66] However, the use of Cu(II) was found to provide near quantitative yields (Scheme 1.13). Primary alkyl fluorides were found to cross-couple efficiently with secondary or tertiary alkylmagnesium halides under these reaction conditions, although arylmagnesium halides were found to react best without the use of 1,3-butadiene. Surprisingly, the reactivities of the alkyl halides increased in the order Cl < F < Br, a trend which could not be explained from bond energies alone.

Beller and co-workers have recently found that alkyl chlorides can be cross-coupled with arylmagnesium halides using catalytic palladium along with sterically hindered electron-rich phosphine ligands (Scheme 1.15).[67] PCy_3 was found to be the optimal choice as ligand and the use of 1-methyl-2-pyrrolidinone as solvent was crucial as it appears to suppress β-hydride elimination, presumably by weakly coordinating to

the catalyst. The reaction has also been performed using an *N*-heterocyclic carbene ligand. Hence, the use of the monocarbene palladium dimer $[Pd(IMes)(NQ)]_2$ (IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene, NQ = naphthoquinone) provided high yields of coupled products.[68] The reaction was found to be compatible for a variety of functional groups on either the electrophile or the arylmagnesium halide such as ethers, ester, acetyl, nitriles and carbamates.

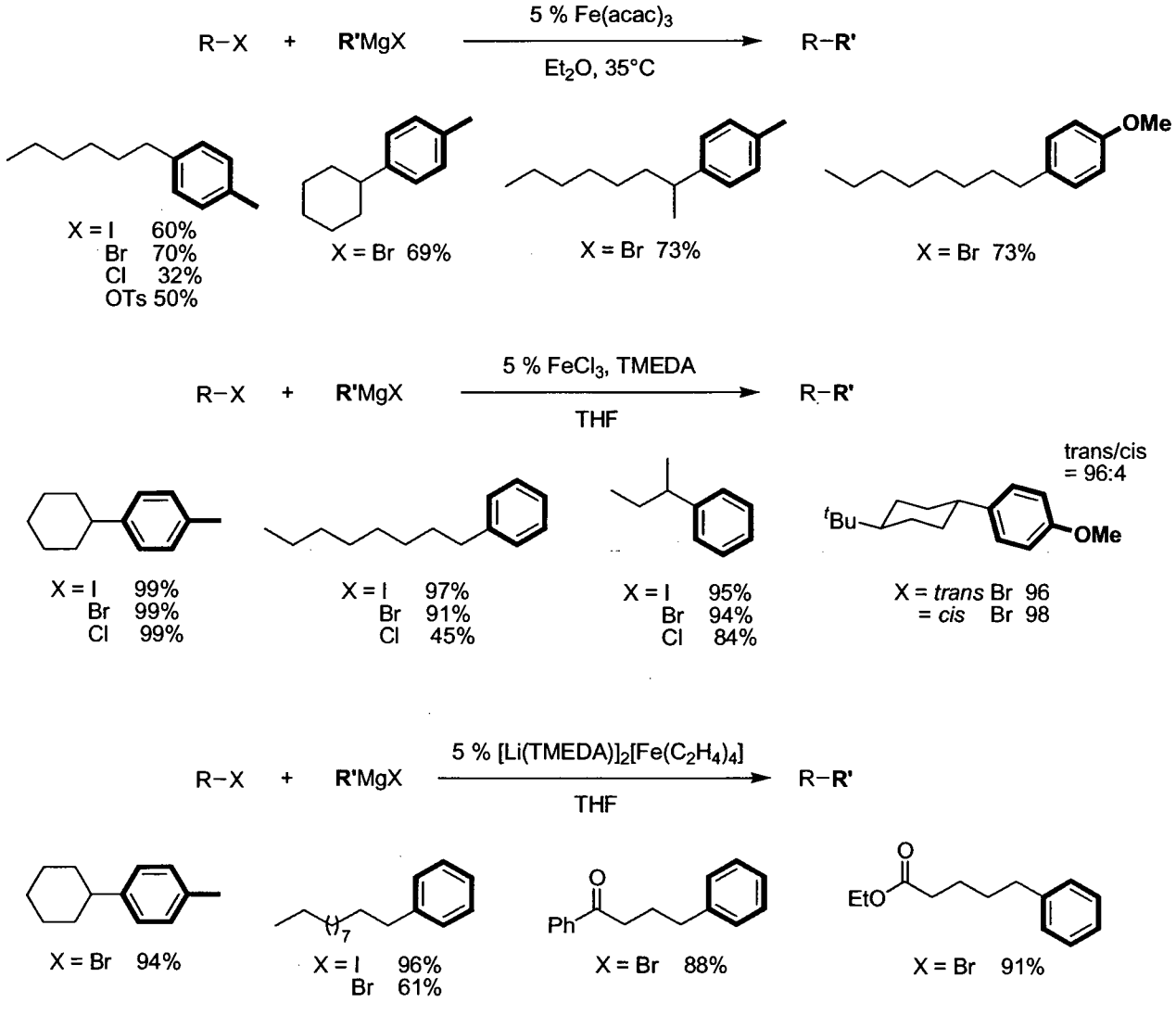


Scheme 1.15 Palladium Catalyzed Cross-Coupling of Organomagnesium Halides and Alkyl Electrophiles Along with Selected Examples (Beller) [67,68]

Recently, the iron catalyzed cross-coupling of secondary alkyl electrophiles with arylmagnesium halides has been independently described by two research groups (Scheme 1.16). Hayashi and Nagano found that $Fe(acac)_3$ in refluxing diethyl ether was effective for the cross-coupling of alkyl iodides, bromides, chlorides and tosylates, although secondary bromides provided the best results.[69] Nakamura and co-workers also found similar results with $FeCl_3$.[70] In the presence of stoichiometric TMEDA (*N,N,N',N'*-tetramethylethylenediamine), the reaction was found to be highly selective for cross-coupling products over β-hydride elimination and hydrodehalogenation products. Secondary alkyl halides were more reactive than primary halides while tertiary halides were most reactive, although large amounts of byproducts were obtained in this case.

Fürtsner and Martin further postulated that the active catalyst in the iron catalyzed cross-coupling of alkyl halides involved Fe/Mg clusters of the formal composition $[Fe(MgX)_2]_n$ formed *in situ*.[71] Kumada type cross-coupling of alkyl halides and arylmagnesium bromides were carried out with the tetrakis(ethylene)ferrate(II) complex $[Li(TMEDA)]_2[Fe(C_2H_4)_4]$ (Scheme 1.16). The reaction was successful for primary and secondary alkyl iodides and bromides, as well as for propargyl and allyl

bromides, although tertiary halides and alkyl chlorides were not compatible. The reaction conditions appear to be mild such that a variety of functional groups which are usually sensitive to a variety of Grignard reagents may be present. This indicates that the activation of the alkyl halide occurs faster than the attack of the Grignard reagent to the sensitive functional group. A variety of results have suggested that iron catalyzed cross-coupling of alkyl electrophiles may proceed by way of a radical mechanism.



Scheme 1.16 Iron Catalyzed Cross-Coupling of Arylmagnesium Halides and Alkyl Halides Along with Selected Examples.[69,70,71]

IV. Concluding Remarks

Carbometallation reactions provide a direct entry for the formation of vinyl organometallics. The stereoselectivity of the reactions is an attractive feature which allows for its use in the formation of stereodefined alkenes. The resulting vinyl organometallic is a useful nucleophile, specifically for the purpose of transition metal catalyzed cross-coupling reactions. This can be quenched with iodine to form a vinyl electrophile which can undergo oxidative insertion with the catalyst metal and cross-coupling with a nucleophile. Alternatively, the vinyl organometallic can be cross-coupled directly with electrophiles. The recent progress in the transition metal catalyzed cross-coupling reactions of alkyl electrophiles presented in this chapter has demonstrated that these substrates can be used effectively in such processes. However, until recently, only a single example existed in the literature for the cross-coupling of a vinyl organometallic and an alkyl electrophile.[49] It is only two years ago that such a reaction has been further explored. Fu and co-workers have cross coupled vinylstannanes[59,60] and vinylzincs[55] with alkyl electrophiles. However, the combination of a tandem carbometallation of alkynes and cross-coupling reaction with alkyl electrophiles, which remains to be explored, would provide for stereodefined functionalized alkenes directly from terminal alkynes.

V. References

1. The relationship between *methodological studies* and *total synthesis* in organic chemistry is described further in the introduction section of Chapter Three.

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Chapter Two

Studies on Vinyl-Alkyl Based Transition Metal Catalyzed Coupling Reactions

I. Proposal

The previous chapter introduced common methods of transition metal catalyzed coupling reactions. Aside from the Negishi protocol, cross-coupling between vinyl (sp^2 hybridized) and alkyl (sp^3 hybridized) carbon centers yielding isolated double bonds have received little attention, especially in intramolecular cases. However, a number of natural products contain a trisubstituted alkene incorporated into macrocycle. Nitiol[1] (**2.1**) and xenovulene A[2] (**2.2**) (Firure 2.1) are two such natural products which are of interest in our laboratory. These two terpenoids also contain a neopentyl carbon at the homoallyl centre which may complicate further the formation of the alkene. Although there exists a number of macrocyclization methods yielding alkene products, most are hindered by the steric constraints and result in little or no stereoselectivity in the formation of tri- or tetra-substituted alkenes.

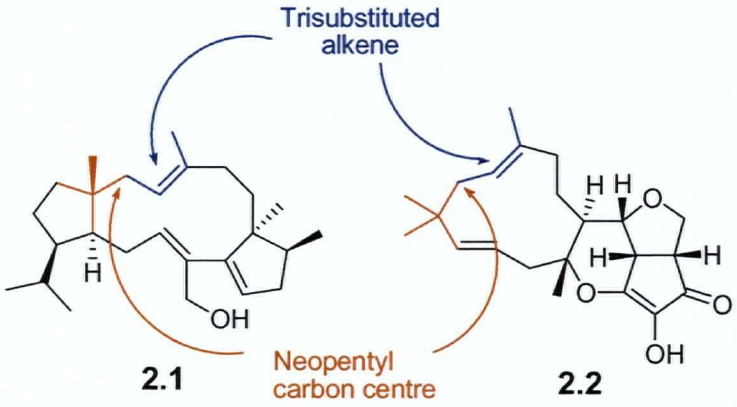
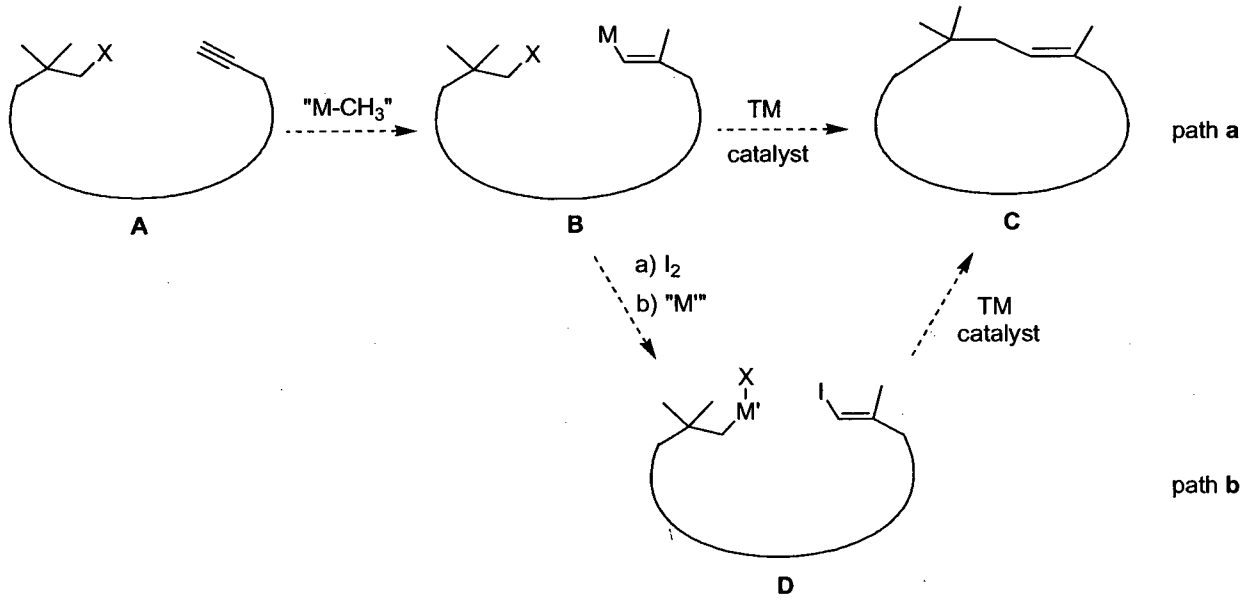


Figure 2.1 Structures of Nitiol (2.1) and Xenovulene A (2.2)

Our strategy for macrocyclization in the synthesis of nitiol (**2.1**) and xenovulene A (**2.2**) involves a two step sequence making use of carbometallation of the terminal alkyne of a substrate of type **A** followed by a subsequent intramolecular coupling to a neopentyl carbon centre (Scheme 2.1). Two pathways may be envisioned in such a process, differing in the macrocyclization step. The first (path **a**) makes use of the vinyl metal **B** from the carbometallation as the organometallic reagent in a transition metal catalyzed cross-coupling reaction with the electrophilic neopentyl centre either directly or by way of an *in situ* transformation to another vinyl metal species, forming the

macrocycle **C**. The second (path **b**) involves quenching the intermediate vinyl metal species **B** with iodine and activating the neopentyl carbon as the organometallic segment to provide an alkyl organometallic species **D**. This can then undergo an intramolecular cross-coupling reaction with the vinyl iodide segment to yield the macrocycle **C**.



Scheme 2.1 Strategy for the Macrocyclic Formation of Trisubstituted Alkenes

Carbometallations[3,4] of alkynes have been extensively studied. Addition of the alkylmetal proceeds via stereoselective *syn* addition. Regioselectivity is also observed in the addition to terminal alkynes, yielding a terminal vinylmetal species. The zirconocene-catalyzed carboalumination of alkynes with trimethylaluminum has served as an effective route in the synthesis of stereo- and regio-defined trisubstituted alkenes.[5] The vinylalanes obtained in the carboalumination reactions are attractive intermediates in the preparation of a wide variety of trisubstituted alkenes since they undergo addition reactions or may be transmetallated to more reactive vinylmetal intermediates. A variety of vinylmetals undergo cross-coupling reactions with retention of stereochemistry. Otherwise, the vinylalanes obtained from the carboalumination can be quenched with an electrophile to produce a vinyl carbon which can be further functionalized and cross-coupled. Hence, carboalumination of a terminal alkyne

followed by intramolecular cross-coupling solves certain stereochemical problems in the formation of trisubstituted alkenyl macrocycles.

Exploration of two generalized types of cross-coupling macrocyclizations was therefore envisioned. The first formally involves the coupling of a vinyl organometallic sp^2 hybridized carbon to an electrophilic sp^3 hybridized carbon (path **a**), whereas the second entails the coupling between an alkyl sp^3 hybridized organometallic carbon and an electrophilic vinyl sp^2 hybridized carbon (path **b**).

The intermolecular version for the coupling represented in path **a**, at the outset of this project, was unknown with the exception of a single example in the literature,[6] although Fu and co-workers have now recently developed conditions for this reaction in the Stille[7] and Negishi[8] cases. The similar coupling with aryl organometallics (arylzincs and arylmagnesium in particular) under the influence of nickel(II) and palladium(II) had recently been reported by Knochel and co-workers[9] as well as by Beller and co-workers,[10] and were known at the onset of this project. The intermolecular version for the coupling represented in path **b** is well known in the case of alkyl zinc organometallics under the influence of Group 10 transition metals (palladium or nickel) and is commonly referred to as the Negishi cross-coupling of an alkyl organometallic. However, to the best of our knowledge, the macrocyclic version for this reaction has yet to be developed. In either case, the development of a carbometallation/macrocyclic cross-coupling protocol would require the additional development of novel cross-coupling reactions.

Hence, the work presented in this chapter is divided into two major sections along the lines of the proposed two routes for the macrocyclic formation of trisubstituted alkenes that is envisioned in Scheme 2.1. In a first part, the work on the tandem carboalumination/cross-coupling reaction is presented, along with the effort regarding the development of a generalized method for the cross-coupling of a vinylorganometallic sp^2 hybridized carbon to an electrophilic sp^3 hybridized carbon. In a second section, the attempt to formulate a protocol for the macrocyclic Negishi cross-coupling reaction between neopentyl and alkene carbons is presented.

II. Tandem Carboalumination/Cross-coupling Reactions

Structural analysis of nitiol (**2.1**) and xenovulene A (**2.2**) (Figure 2.1) show that both natural products contain a trisubstituted alkene of *E* stereochemistry in a 12 or 11-membered macrocycle respectively. In order to study the macrocyclic cross-coupling reactions, model substrates containing a neopentyl electrophile and a terminal alkyne tethered together such that the macrocyclization results in 12-membered lactones and cyclic ethers of type **C** (Scheme2.1) were envisioned.

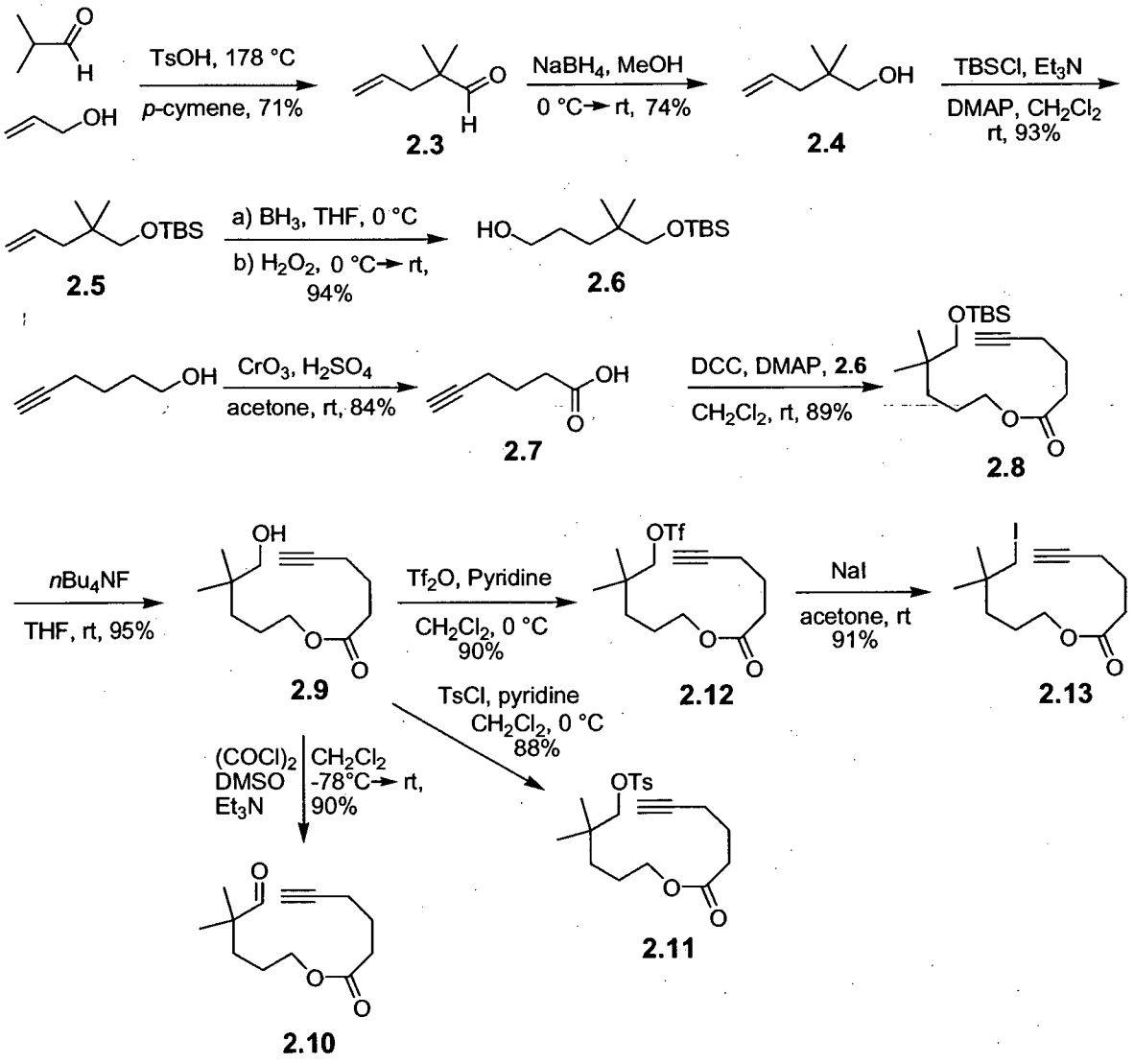
A. Substrate Preparation

The preparation of the ester and ether substrates required the synthesis of the common alcohol **2.6** (Scheme 2.2). Condensation of isobutyraldehyde with allylic alcohol in the presence of a catalytic amount of acid followed by a Claisen rearrangement[11] resulted in alkenal **2.3**, which was then reduced to the alkenol **2.4** using sodium borohydride.[12] Protection of the neopentyl alcohol[13] as its silyl ether and hydroboration yielded the alcohol **2.6**. This is a known compound and the spectral analysis agreed with that previously reported.[13]

5-Hexynoic acid (**2.7**) was obtained via the Jones oxidation of the commercially available 5-hexyn-1-ol,[14] and this was coupled to alcohol **2.6** using carbodiimide chemistry, forming the ester **2.8**. Evidence for the coupling reaction was observed from the presence of an ester C=O stretching frequency of 1737 cm^{-1} in the IR spectrum and the ^{13}C NMR spectrum showed a signal resulting from the presence of an ester carbonyl carbon at δ 173.1. Subsequent fluoride deprotection of the silyl group provided the alkynol **2.9**, which was evidenced by the presence of an O-H stretching frequency of 3424 cm^{-1} in the IR spectrum.

Using the alkynol **2.9**, a number of ester substrates were prepared with a variety of electrophilic neopentyl substituents (Scheme 2.2). The aldehyde **2.10** was obtained by way of a Moffatt-Swern oxidation and evidenced by the presence of an aldehyde C=O stretching frequency of 1728 cm^{-1} in the IR spectrum, an aldehyde proton signal in the ^1H NMR spectrum at δ 9.41 and an aldehyde carbonyl carbon signal in the ^{13}C NMR spectrum at δ 205.7. The tosylate **2.11** was obtained and the structure confirmed from

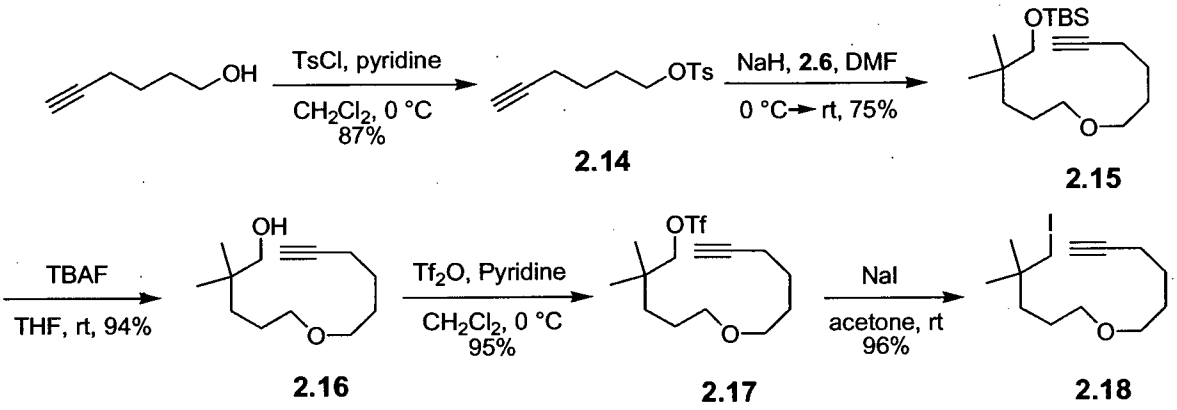
the ^{1}H NMR spectrum which showed the presence of the tosyl phenyl proton doublet signals at δ 7.75 and 7.33. The triflate **2.12** was obtained similarly and observed from the ^{13}C NMR spectrum as a quartet at δ 118.6 for the triflate carbon. Finally, it was found that the iodide **2.13** could be best prepared directly from the triflate **2.12** using a Finkelstein type reaction on the hindered neopentyl carbon centre with sodium iodide. This was structurally confirmed by the presence of the iodomethyl proton singlet signal at δ 3.11 in the ^{1}H NMR spectrum.



Scheme 2.2 Synthesis of Macrocyclic Ester Substrates

The ether substrates were obtained from the nucleophilic displacement of tosylate **2.14** with the anion of **2.6** to give the coupled ether **2.15** (Scheme 2.3). The

coupling reaction was evidenced by the existence of two triplet signals in the ^{1}H NMR at δ 3.40 and 3.34 representative of the methylene protons on the carbons on either side of the ether oxygen. Deprotection of the siloxy group and triflation yielded **2.17** which displayed a characteristic quartet signal at δ 120.8 for the triflate carbon in the ^{13}C NMR spectrum. Substitution with sodium iodide yielded the iodide **2.18** which was structurally confirmed by the presence of the iodomethyl proton singlet signal at δ 3.14 in the ^{1}H NMR spectrum.



Scheme 2.3 Synthesis of Macrocyclic Ether Substrates

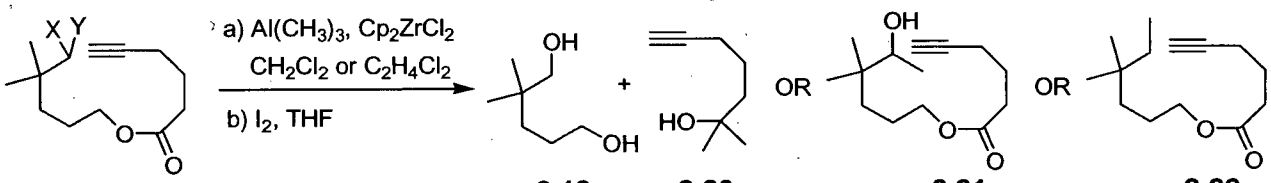
B. Methylalumination

The ester substrates **2.9**, **2.10**, **2.11**, **2.12** and **2.13** were each subjected to the Negishi carboalumination protocol. It was believed that the bifunctional macrocyclization substrate containing a vinyl organometallic could be obtained in this manner. However, to verify the carboalumination for each of the above mentioned substrates, the reaction was quenched with iodine (Table 2.1).

Treatment of the neopentyl alcohol substrate **2.9** with trimethylaluminum produced no reaction after 24 hours at room temperature (entry 1). Heating the reaction mixture in refluxing methylene chloride (40 °C) also produced no reaction (entry 2) and further heating in refluxing dichloroethane (83 °C) resulted in nucleophilic addition of a methyl group to the ester moiety, resulting in diol **2.19** and alkynol **2.20** (entry 3). When the neopentyl aldehyde substrate **2.10** was subjected to

trimethylaluminum at room temperature, nucleophilic addition of a methyl group to the aldehyde was observed within 1 hour, resulting in **2.21** (entry 4). In the cases of the tosylate **2.11** (entry 5) and triflate **2.12** (entry 6) substrates, nucleophilic substitution of the sulfonate group was observed. No reaction was observed for the carboalumination of the neopentyl iodide **2.13** at room temperature (entry 7). In all cases no addition of trimethylaluminum to the alkyne was observed. A literature search alluded to the possibility that the carboalumination reaction conditions are not tolerant of substrates containing esters since no successful examples exist for ester substrates.

Table 2.1 Attempted Methylalumination of Ester Substrates



X = OH, Y = H **2.9**
X, Y, = O **2.10**
X = OTs, Y = H **2.11**
X = OTf, Y = H **2.12**
X = I, Y = H **2.13**

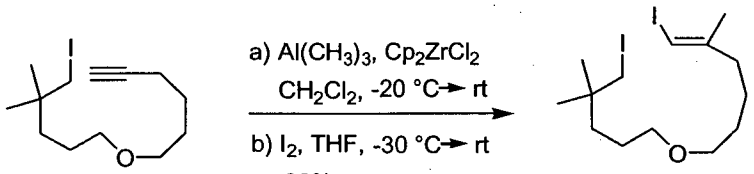
entry	substrate	$Al(CH_3)_3$ (equiv)	T (°C)	product	yield	Ref.[c]
1	**2.9**	3	rt	NR[a]	——	E-14
2	**2.9**	3	rt→40	NR[a]	——	E-18
3	**2.9**	3	rt→83	**2.19 + 2.20**	ND[b]	E-22
4	**2.10**	2	rt	**2.21**	74%	E-01
5	**2.11**	2	rt	**2.22**	32%	E-31
6	**2.12**	2	rt	**2.22**	61%	E-10
7	**2.13**	2	rt	NR[a]	——	E-16
8	**2.13**	3	rt→40	NR[a]	——	E-17

[a] No Reaction. [b] Not Determined. [c] Refers to laboratory notebook page.

However, the observation that trimethylaluminum did not react with the neopentyl iodide of substrate **2.13** (entry 7) in the same manner as was observed with the electrophilic functional groups of substrates **2.10**, **2.11**, and **2.12** was encouraging. Even when **2.13** was treated with a third equivalent of trimethylaluminum and heated in refluxing methylene chloride (40 °C), no reaction was observed (entry 8). These results indicate that a neopentyl iodide is tolerated by the carboalumination reaction conditions.

In view of the fact that there was the possibility of the ester functionality interfering with the carboalumination process, focus was switched on attempting the reaction using the ether tethered substrates. Since the neopentyl iodide appeared as the only electrophilic functional group in which the above reaction process tolerated, the investigation began with the iodide **2.18.**

Addition of two equivalents of trimethylaluminum to **2.18** at room temperature or in refluxing methylene chloride (40 °C) followed by an iodine quench of the vinylalane yielded initially only trace amounts of the vinyl iodide **2.23** along with mostly starting material. However, when three equivalents of trimethylaluminum were used, carbometallation of the alkyne proceeded in 83% yield (Eq. 1.1). Evidence for the formation of the iodine quenched carboalumination product **2.23** was obtained from the ^{1}H NMR spectrum which revealed a vinyl proton signal at δ 5.85 and a signal for the vinyl methyl protons at δ 1.77.



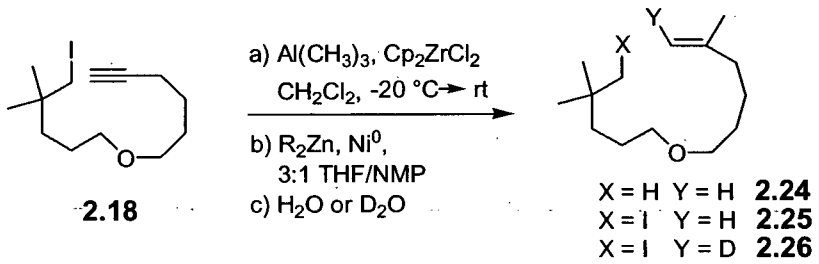
2.18 **2.23** 2.1

It was proposed that the lack of reactivity in the ester substrates may result from the strong oxophilic character of aluminum. Organoaluminum compounds are known to form long lived complexes with oxygenated substrates.[15] In the case of carboalumination of **2.18**, the first equivalent of trimethylaluminum is presumably rendered unreactive by complexation with the ether oxygen, and therefore a minimum of three equivalents are required. In the case of the ester substrates, a number of unreactive complexes exist, and additional trimethylaluminum would be required.

C. Macrocyclizations

As noted in the previous chapter, the nickel catalyzed cross-coupling between benzyl[16] or aryl[17] zinc derivatives and alkyl iodides has recently been demonstrated by Knochel and co-workers. Also, it is well known that vinylaluminum can be transmetalated to vinylzinc species.[18] It was believed that the tandem carboalumination of the alkyne **2.18** followed by transmetallation using diethylzinc and intramolecular coupling with the neopentyl iodide under the influence of catalytic Ni^0 may provide a viable route for a macrocyclization (Table 2.2).

Table 2.2 Attempted Tandem Carboalumination-Negishi Cross-Coupling Reactions



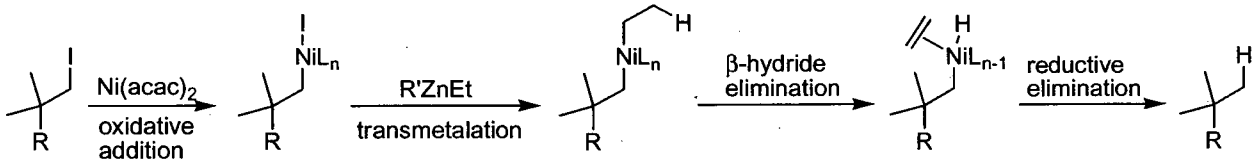
2.18

X = H Y = H **2.24**
X = I Y = H **2.25**
X = I Y = D **2.26**

entry	R_2Zn (equiv)	Ni^0 (5 mol%)	H_2O or D_2O quench	product	yield	Ref.[a]
1	Et_2Zn (1.5)	$Ni(acac)_2$	H_2O	**2.24**	70%	F-04
2	Et_2Zn (1.5)	——	H_2O	**2.25**	79%	F-06
3	Et_2Zn (0.5)	$Ni(acac)_2$	H_2O	**2.24 + 2.25** (1.6:1)	61%	F-07
4	——	$Ni(acac)_2$	H_2O	**2.25**	82%	F-12
5	Et_2Zn (1.5)	Nidppf[b]	H_2O	**2.24**	64%	F-13
6	Et_2Zn (1.5)	$Ni(acac)_2$	D_2O	**2.24**	77%	F-10
7	Me_2Zn (1.5)	$Ni(acac)_2$	D_2O	**2.26**	82%	F-39
8	Me_2Zn (1.5)	——	D_2O	**2.26**	80%	F-37

[a] Refers to laboratory notebook page. [b] Ni^0 Prepared *in situ* from the addition of 0.1 equiv *n*-butyllithium to 0.05 equiv $Ni(dppf)Cl_2$.

The investigation began with the use of the optimized conditions for the cross-coupling between alkyl iodides and aryl zincs developed by Knochel and co-workers (5 mol% $Ni(acac)_2$, 3:1 THF/NMP).[17] In a first case, the vinylalane resulting from the carboalumination was transmetalated using 1.5 equivalents of diethylzinc and this mixture was added under high dilution conditions to a solution of $Ni(acac)_2$, yielding **2.24** as the only product (entry 1). Evidence for the formation of **2.24** was provided by ^1H NMR, which showed the appearance of vinyl proton signals at δ 4.64-4.69 and the disappearance of the signal for the methylene protons bearing the iodide in **2.18** at δ 3.14. Although no macrocyclization was obtained, the presence of the dehalogenated product **2.24** demonstrates that the neopentyl iodide was activated by the nickel catalyst by oxidative addition. It was believed that the alkyl nickel complex could then undergo transmetalation with excess diethylzinc or an ethyl vinylzinc species, placing an ethyl ligand on the nickel (Scheme 2.4). The nickel complex bearing the ethyl ligand may undergo a β-hydride elimination, followed by a reductive elimination, placing a hydrogen at the neopentyl carbon. Hence, Ni^0 would be regenerated after the β-hydride elimination and the catalytic cycle repeated without intramolecular cross-coupling.



Scheme 2.4 Mechanism for the β-Hydride Elimination in the Activation of 2.18

In fact, when the same procedure was repeated in the absence of $Ni(acac)_2$, the neopentyl iodide **2.25** was obtained (entry 2), as was observed from the presence of the iodomethylene proton signal at δ 3.14 in the ^1H NMR spectrum along with signals for vinyl protons at δ 4.64-4.69. Reducing the amount of diethylzinc used to 0.5 equivalents in order to minimize the amount of transferable ethyl ligand resulted in a mixture of **2.24** and **2.25** (entry 3), and the analogous reaction with no ethylzinc yielded **2.25** as the only major product[i] (entry 4), demonstrating the requirement of zinc in the activation of the neopentyl iodide. When diphenylphosphinoferrocene nickel (0) (Nidppf) was used as the source of Ni^0 a slightly lower yield was obtained (entry 5).

[i] Trace amounts of **2.24** were observed in the crude ^1H NMR spectrum.

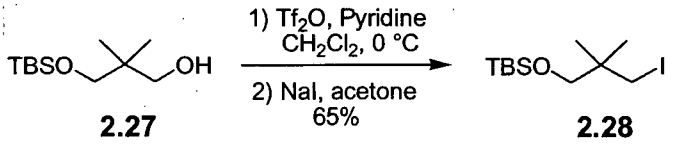
In order to investigate the competitive β-hydride elimination in the attempted cross-coupling reaction, the initial reaction condition was repeated and the mixture quenched with deuterium oxide instead of water (entry 6). No deuterium incorporation was observed. This was expected for the neopentyl carbon centre if the nickel complex resulting from the oxidative addition with the neopentyl iodide undergoes a β-hydride elimination mechanism. More surprising was that no deuterium incorporation was observed on the vinyl carbon resultant of the carboalumination. This could also be explained from a possible β-hydride elimination mechanism, although no further examination was pursued.

The use of dimethylzinc as a substitute for the diethylzinc was examined since in this case no β-hydrogens are present. The reaction was performed with dimethylzinc using the initial reaction conditions and quenched with deuterium oxide to yield **2.26** as the single major product (entry 7). The presence of a vinyl deuterium was confirmed from the ^{1}H NMR spectrum which showed a singlet signal integrating for a single vinyl proton at δ 4.63, and from the ^{13}C NMR spectrum which revealed a triplet signal at δ 109.6 corresponding to the terminal vinyl carbon bearing the deuterium. However, no macrocyclization product was obtained and the ^{1}H NMR showed the presence of the methylene protons bearing the iodide at δ 3.13. Although it is assumed that a catalytic amount of the product resulting from oxidative addition of nickel is formed, the presence of the neopentyl iodide demonstrates that no β-hydride elimination processes occured as was observed when diethylzinc was used (entry 1). This is likewise the case for the observed presence of a vinyl deuterium in **2.26**. Therefore, other factors than the competitive β-hydride elimination must also contribute to the lack of macrocyclization. The procedure was repeated in the absence of $Ni(acac)_2$ to yield the same product **2.26** (entry 8).

D. Intermolecular Coupling

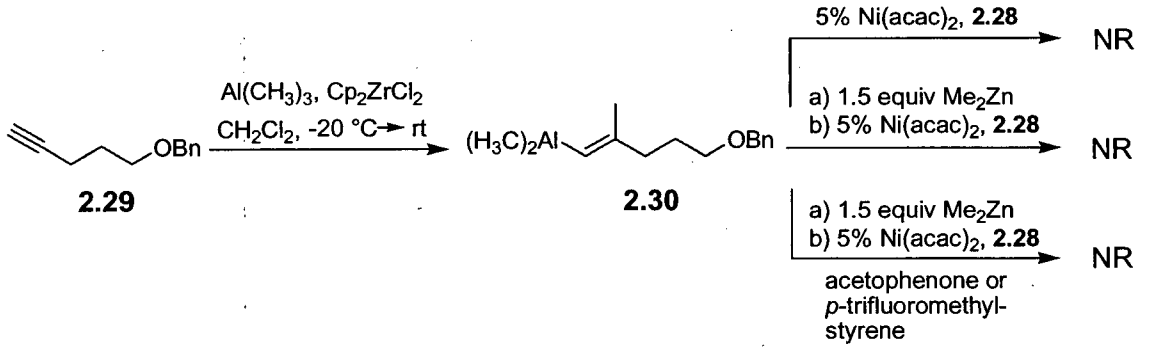
Uncertainties arose about the source of failure for the macrocyclizations. In light of this failure, attention was focused on developing and optimizing suitable reaction conditions for the tandem carboalumination/macrocyclization in intermolecular

processes. Hence, the neopentyl iodide substrate **2.28** was constructed from the known neopentyl alcohol **2.27**[19] using the standard conditions (Eq. 1.2).



2.27 **2.28** 2.2

The known benzyloxy alkyne **2.29**,[20] prepared from the benzylation of 4-pentyn-1-ol, was subjected to the carboalumination conditions and the resulting vinylalane was added to a solution of catalytic $Ni(acac)_2$ and **2.28** (Eq. 1.2). No cross-coupling product was obtained directly from the vinylalane. A similar result was observed with the addition of dimethylzinc prior to transferring to the solution of $Ni(acac)_2$ and **2.28**. Although Knochel reported that the addition of π-acceptor ligands promoted the cross-coupling between alkyl halides and alkyl[21] or arylzincs[22] under these reaction conditions, the use of acetophenone or *p*-trifluoromethylstyrene did not aid the reaction.

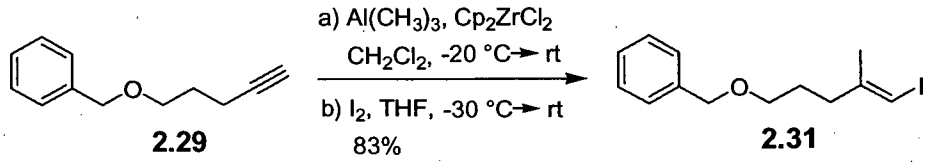


2.29 **2.30** 2.3

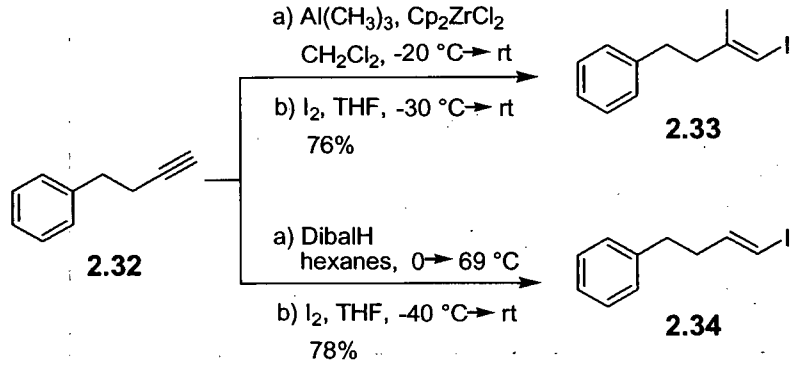
In light of these results, it was decided that the process should be simplified and a study of the direct cross-coupling of alkyl iodides with vinylzincs was pursued. Knochel and co-workers found that vinylzincs can be prepared from vinyl halides via a lithium-halide exchange with *n*-butyllithium in a Trapp solvent mixture[23] followed by addition of zinc iodide.[24] Hence, the cross-coupling of alkyl iodides with vinylzincs was attempted from the corresponding vinyl iodide.

The vinyl iodide **2.31** was prepared from the alkyne **2.29** using the carboalumination procedure and followed by quenching the reaction mixture with iodine

(Eq. 2.4). The same procedure was performed to prepare vinyl iodide **2.33** from 4-phenyl-1-butyne (**2.32**), whereas vinyl iodide **2.34** was prepared from the hydroalumination of **2.32** with diisobutylaluminum hydride and quenching the reaction with iodine in a similar manner (Eq. 2.5).

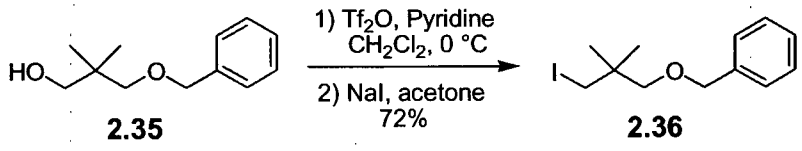


2.4

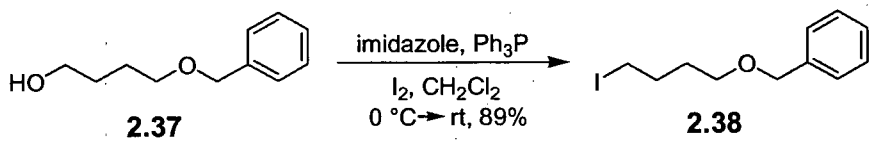


2.5

The alkyl iodides were prepared from the corresponding alcohols by way of the trifluoromethanesulfonate intermediate in the case of **2.36** (Eq. 2.6), or using triphenylphosphine and iodine (imidazole, Ph_3P, I_2, CH_2Cl_2) in the case of **2.38** (Eq. 2.7).

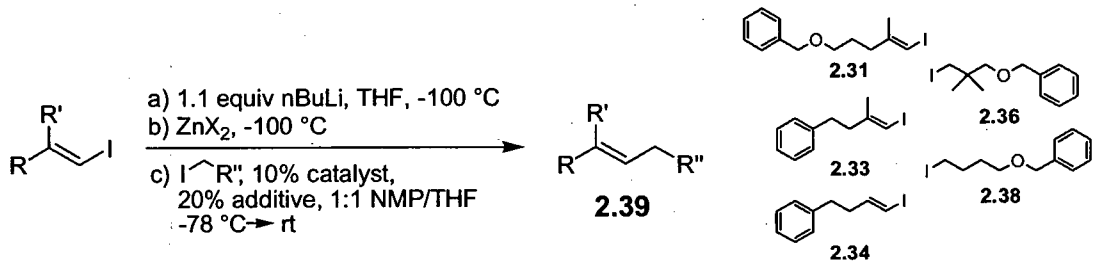


2.6



2.7

Table 2.3 Cross-Coupling Between Alkyl Iodides and Vinylzincs Obtained from Vinyl Iodides



entry	vinyl iodide	alkyl iodide	ZnX_2	catalyst	additive	yield	Ref.[a]
1	**2.33**	**2.36**	ZnI_2	$Ni(acac)_2$	TfMS[b]	——	H-06
2	**2.31**	**2.38**	ZnI_2	$Ni(acac)_2$	TfMS[b]	——	G-18
3	**2.34**	**2.36**	ZnI_2	$Ni(acac)_2$	TfMS[b]	——	H-07
4	**2.34**	**2.38**	ZnI_2	$Ni(acac)_2$	TfMS[b]	——	H-20
5	**2.34**	**2.38**	ZnI_2	$Ni(COD)_2$	TfMS[b]	——	H-17
6	**2.34**	**2.38**	ZnI_2	$NiCl_2$	TfMS[b]	——	H-18
7	**2.34**	**2.38**	$ZnCl_2$	$Ni(acac)_2$	TfMS[b]	trace	I-27
8	**2.34**	**2.38**	$ZnCl_2$	$Ni(acac)_2$	——	6%	I-43
9	**2.34**	**2.38**	$ZnCl_2$	Nidppf	——	——	I-36
10	**2.34**	**2.38**	$ZnCl_2$	$Pd(OAc)_2$	PCy_3	9%	I-29
11[c]	**2.34**	**2.38**	$ZnCl_2$	$Pd(OAc)_2$	PCy_3	7%	I-38
12[d]	**2.34**	**2.38**	$ZnCl_2$	$Pd(OAc)_2$	PCy_3	7%	I-39
13	**2.34**	**2.38**	ZnI_2	$Pd(OAc)_2$	PCy_3	——	H-22
14	**2.34**	**2.38**	$ZnCl_2$	$Pd(PPh_3)_4$	——	——	I-41

[a] Refers to laboratory notebook page. [b] *p*-Trifluoromethylstyrene. [c] The reaction was performed using 2.2 equiv *n*-butyllithium. [d] The reaction was performed using 30% $Pd(OAc)_2$ and 60% PCy_3.

The vinylzincs were thus prepared from the corresponding vinyl iodides by treatment with 1.1 equivalents of *n*-butyllithium at -100 °C followed by the addition of 1.1 equivalents of zinc iodide (Table 2.3). In a first case, the vinylzinc solution obtained from the vinyl iodide **2.33** was added to a solution of 10% $Ni(acac)_2$, 20% of the

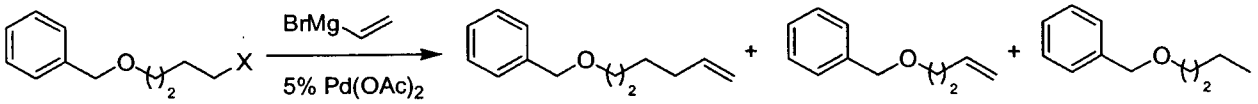
promoter *p*-trifluoromethylstyrene and the alkyl iodide **2.36** in 1:1 THF/NMP under the similar reaction conditions reported by Knochel and co-workers for the cross-coupling between alkyl halides and alkyl[21] or arylzincs[22] (entry 1). No cross-coupling was however observed and only starting materials were recovered in near quantitative yields.

The steric hindrance which may encumber the possible coupling was reduced by performing the reaction between the trisubstituted vinyl iodide **2.31** and the primary alkyl iodide **2.38** (entry 2), and that between the disubstituted vinyl iodide **2.34** and the neopentyl iodide **2.36** (entry 3). The simplest case, the coupling between disubstituted vinyl iodide **2.34** and the primary alkyl iodide **2.38** (entry 4) was also attempted. In all cases, no cross-coupling was observed using the above mentioned reaction conditions. The cross-coupling between **2.34** and **2.38** was also unsuccessful when $Ni(COD)_2$ (entry 5) or $NiCl_2$ (entry 6) was used. When zinc iodide was substituted for zinc chloride, a trace amount of the cross-coupling product **2.39** was observed by GC/MS (entry 7). This suggests that the vinylzinc chloride formed *in situ* is more effective then the corresponding iodide for the process, and consequently, zinc chloride was used in subsequent reactions. When the reaction was repeated without the use of the *p*-trifluoromethylstyrene as promoter, a slightly improved yield of 6% of isolated **2.39** was obtained along with starting materials (entry 8). This is interesting since Knochel and co-workers have reported this promoter to be essential for the cross-coupling between alkyl halides and alkyl[21] or arylzincs.[22] Evidence for the presence of the cross-coupling product was obtained from the ^1H NMR spectrum which revealed the appearance of a multiplet at δ 5.44-5.39 corresponding to two vinyl protons. The use of Nidppf as catalyst did not provide any observable cross-coupling product (entry 9).

The coupling product was also obtained in 9% using the reaction conditions developed by Fu and co-workers for the cross-coupling of alkyl bromides with alkylboranes[6] (10% $Pd(OAc)_2$, 20% PCy_3) (entry 10). The remaining mass balance for the reaction mixture was starting materials. Although the alkyl iodide contains β-hydrogens, similarly to the cases in which nickel was used, no β-hydride elimination product was observed. Increasing the amount of *n*-butyllithium (2.2 equiv, entry 11) or of the catalyst system (30% $Pd(OAc)_2$, 60% PCy_3, entry 12) had no effect on the yield of the reaction. If zinc iodide was used rather then the chloride, no reaction was observed,

suggesting that the vinylzinc chloride is more effective then the corresponding iodide for the process (entry 13). The effectiveness of the bulky, electron rich PCy_3 ligand was validated from the lack of reaction observed when triphenylphosphine was used as ligand (entry 14). It appeared that the progression of the reaction was inhibited by a low or no catalytic turnover although no further experimentations were performed.

Table 2.4 Cross-Coupling Between Alkyl Halides and Vinylmagnesium Bromide



X = I **2.38**
= Br **2.40**
= Cl **2.41**

2.42 **2.43** **2.44**

entry	X	yield[a] 2.42	2.43	2.44	SM[b]	Ref.[c]
1	I	39%	28%	16%	1%	K-24
2	Br	33%	3%	2%	54%	K-31
3	Cl	15%	1%	0%	79%	K-32

[a] Determined by GC versus an internal calibrated standard of dodecane. [b] Starting Material: Refers to unreacted **2.38**, **2.40** or **2.41**. [c] Refers to laboratory notebook page.

Interest in the coupling reaction was extended to investigating other vinylorganometallic sources using the similar $Pd(OAc)_2/PCy_3$ conditions. Beller and co-workers have used comparable reaction conditions to investigate the coupling between alkyl chlorides and arylmagnesium bromides.[10] Hence, the cross-coupling of the alkyl iodide **2.38** with commercially available vinylmagnesium bromide was attempted (Table 2.4). Upon addition of a solution of vinylmagnesium bromide in THF to a solution of **2.38** and the catalytic system in NMP, the starting material was completely consumed in less than 10 minutes at room temperature. The cross-coupling product **2.42** was observed as the major constituent, along with a significant amount of β-hydride elimination product **2.43** and dehalogenated product **2.44** (entry 1). Evidence for the formation of the cross-coupling product was obtained from the ^1H NMR and ^{13}C NMR spectra which revealed the presence of vinyl proton signals at δ 5.04-4.90 and

alkene carbon signals at δ 138.7 and at δ 114.5. An alkene C=C stretching frequency of 1640 cm^{-1} was also observed in the IR spectrum.

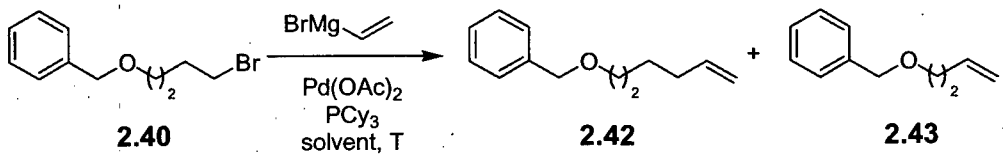
An investigation of other alkyl halide electrophiles followed. When the alkyl bromide **2.40** was used, mostly coupling product **2.42** was obtained with only trace amounts of β-hydride elimination product **2.43** and **2.44** (entry 2), although the reaction did not go to completion as a significant amount of **2.38** was recovered. In the case were the alkyl chloride **2.41** was used, coupling product **2.42** was obtained almost exclusively (entry 3). In this case however, the reaction appeared sluggish and a significant amount of starting materiel **2.41** was recovered. The addition of another 5 mol % of $Pd(OAc)_2$ and PCy_3 to the reaction mixture did not appear to increase the conversion. The reaction was repeated without the use of $Pd(OAc)_2$ and PCy_3 in the case of alkyl bromide **2.40** to verify the catalytic nature of the process. In this case no conversion was observed as **2.40** was recovered unreacted.

A reactivity trend appears to predominate in the reaction for the varying types of alkyl halides: I > Br > Cl. Alkyl iodides appear to provide the best conversion although significant amounts of by-products are obtained. When alkyl bromides or alkyl chlorides are used instead, the formation of the by-products is suppressed, at a cost of reactivity however.

Other variables were investigated for the reaction of alkyl bromide **2.40** with vinylmagnesium bromide (Table 2.5). NMP appeared to be the only effective solvent (entry 1) as dimethylacetamide (entry 2), THF (entry 3), DMSO (entry 5) and dimethylformamide (entry 6) produce no or minimal conversions. Even the use of 10 equivalents of NMP as a co-solvent in THF failed to produce substantial conversion (entry 4).

The reason for the low conversion of the reaction was not apparent since the use of a substantially larger amount of catalyst provided for only a small increase in the conversion of the reaction (entry 7). This did not appear to be a result of product inhibition since the addition of **2.42** prior to the addition of vinylmagnesium bromide provided no significant loss in conversion (entry 8). The use of larger amounts of vinylmagnesium bromide also failed to provide an increase in conversion (entry 9).

Table 2.5 Cross-Coupling Between Alkyl Bromide 2.40 and Vinylmagnesium Bromide: Dependence on Solvent and Temperature



2.40 **2.42** **2.43**

entry	solvent	T (°C)	mol % catalyst[a]	yield[b] 2.42	yield[b] 2.43	yield[b] 2.40	Ref.[c]
1	NMP	rt	5	33%	3%	54%	L-01
2	DMAc	rt	5	0%	0%	100%	L-13
3	THF	rt	5	6%	0%	90%	L-14
4	THF[d]	rt	5	5%	0%	91%	L-21
5	DMSO	rt	5	0%	0%	100%	L-15
6	DMF	rt	5	1%	0%	96%	L-16
7	NMP	rt	30	42%	5%	44%	L-10
8	NMP[e]	rt	5	28%	2%	67%	L-11
9	NMP[f]	rt	5	32%	10%	46%	L-12
10	NMP	-23→rt	5	16%	5%	65%	L-17
11	NMP	66	5	52%	9%	31%	L-20
12	NMP	115	5	25%	39%	19%	L-31
13	NMP	66	20	48%	12%	33%	L-45
14	NMP[g]	rt	5	2%	0%	96%	L-32

[a] Refers to mol % of $Pd(OAc)_2$ and PCy_3 used. [b] Determined by GC versus an internal calibrated standard of dodecane. [c] Refers to laboratory notebook page. [d] The reaction was performed with 10 equiv of NMP in the THF solvent. [e] The reaction was performed with 1 equiv of **2.42**. [f] The reaction was performed using 3 equiv of vinylmagnesium bromide instead of 1.5 equiv. [g] The solution of **2.42** and catalyst in NMP was added inversely to a solution of vinylmagnesium bromide.

The dependence of the reaction on temperature was also investigated. The pathway for the inhibition of the reaction relative to cross-coupling did not appear to be slowed by lowering the reaction temperature to -23 °C and slowly warming to room

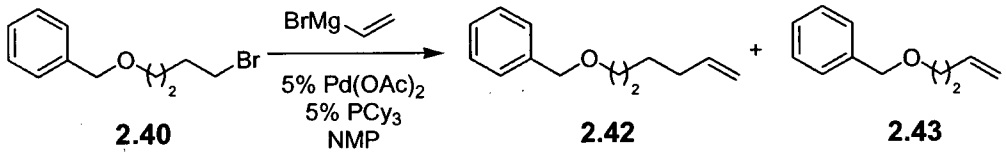
temperature (entry 10). In fact, the reaction only appeared to proceed at temperatures superior to 0 °C. Larger conversions were obtained at higher temperature (entry 11-12), although a substantial amount of β-hydride elimination product was obtained at a temperature of 115 °C. An optimal temperature of 66 °C was found that provided **2.42** with a minimal amount of β-hydride elimination. The use of larger amounts of catalyst at this temperature again did not provide for a larger conversion (entry 13). Interestingly, inversing the addition of the solution containing the substrate **2.40** and the catalyst system to a solution of vinylmagnesium bromide in THF yielded very little conversion (entry 14).

This last result of the inversed addition of reagents led us to consider the possibility that the vinylmagnesium bromide solution itself may render the reaction inactive. A possibility for the lack of reactivity which was considered was the presence of the Schlenck equilibrium with vinylmagnesium bromide (Eq. 2.8).[25] This results in the existence of magnesium bromide and divinylmagnesium in solution, of which the extent is dependent on various factors such as temperature, solvent, halide and organo (R) groups, and is complex.[26]

$$2\ R\text{-}Mg\text{-}Br \rightleftharpoons R\text{-}Mg\text{-}R + Br\text{-}Mg\text{-}Br \qquad 2.8$$

Magnesium bromide is considered a moderate Lewis acid and diorganomagesium (R_2Mg) reagents are known to have different reactivities than organomagnesium halides.[27] Diorganomagnesiums tend to be more nucleophilic and harder bases. Regardless, various factors which may affect the Schlenk equilibrium were considered (Table 2.6). A slight decrease in conversion was observed when 1 equivalent of magnesium bromide itself or if bromide in the form of tetrabutylammonium bromide was added to the reaction mixture (entry 2-3). However, a marked decrease was noticed when the vinylmagnesium bromide was freshly prepared from vinyl bromide and added directly to the reaction mixture (entry 4-5). The addition of tetrabutylammonium bromide appeared to improve the conversion, although a variation of the amount added did not appear to significantly influence the yield (entry 6-8).

Table 2.6 Cross-Coupling Between Alkyl Bromide 2.40 and Vinylmagnesium Bromide: Investigating the Schlenk Equilibrium



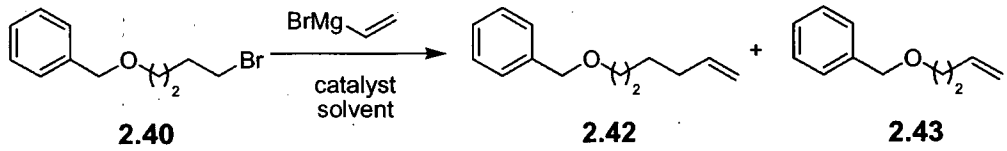
2.40 2.42 2.43

entry	vinylmagnesium bromide[a]	additive (equiv)	yield[b] 2.42	2.43	2.40	Ref.[c]
1	Aldrich	——	33%	3%	54%	L-01
2	Aldrich	$MgBr_2$ (1)	19%	0%	67%	L-08
3	Aldrich	TBAB[d] (1)	23%	0%	67%	L-07
4	from vinyl bromide (1.4 equiv) and magnesium (1 equiv)	——	0%	0%	100%	L-03
5	from vinyl bromide (1 equiv) and magnesium (1 equiv)	——	7%	0%	72%	L-04
6	from vinyl bromide (1 equiv) and magnesium (1 equiv)	TBAB[d] (1)	16%	0%	74%	L-05
7	from vinyl bromide (1 equiv) and magnesium (1 equiv)	TBAB[d] (2)	10%	3%	76%	L-18
8	from vinyl bromide (1 equiv) and magnesium (1 equiv)	TBAB[d] (3)	17%	6%	65%	L-19

[a] Vinyl magnesium bromide was either purchased from the Aldrich Chemical Co. or was freshly prepared from vinyl bromide. [b] Determined by GC versus an internal calibrated standard of dodecane. [c] Refers to laboratory notebook page. [d] Tetrabutylammonium bromide.

Interest in varying the catalyst system was also investigated (Table 2.7). Copper(I) had previously been known to catalyze the cross-coupling of alkyl halides with alkylmagnesium bromides from the early work of Kochi and Tamura.[28] The addition of CuCl to the system was investigated, although this proved detrimental as a lowered conversions were observed when used as a co-catalyst with $Pd(OAc)_2/PCy_3$ (entry 2) or on its own (entry 3). This was not an unreasonable choice as a catalyst source since, subsequently to the period in which this work was performed, Kambe and co-workers had found that the use of copper improved the reactivity in the cross-coupling of alkyl fluorides with alkylmagnesium bromides.[29] Whereas the reaction occurred readily for alkyl bromides and chlorides using palladium and nickel catalysts (no copper used), poor reaction conversions were observed for alkyl fluorides under these conditions.

Table 2.7 Cross-Coupling Between Alkyl Bromide 2.40 and Vinylmagnesium Bromide: Variation of the Catalyst System



2.40 **2.42** **2.43**

entry	catalyst[a]	solvent	yield[b] 2.42	yield[b] 2.43	yield[b] 2.40	Ref.[c]
1	$Pd(OAc)_2$, PCy_3	NMP	33%	3%	54%	L-01
2	$Pd(OAc)_2$, PCy_3, CuCl	NMP	13%	8%	55%	L-27
3	CuCl	NMP	6%	3%	72%	L-28
4	$PdCl_2$, PCy_3	NMP	0%	0%	95%	L-34
5	$PdCl_2(CH_3CN)_2$, PCy_3	NMP	1%	0%	91%	L-35
6	$PdCl_2(PPh_3)_2$, PCy_3	NMP	6%	2%	71%	L-37
7	$Pd(PPh_3)_4$, PCy_3	NMP	18%	3%	60%	L-38
8	$Pd_2(dba)_3$, PCy_3	NMP	12%	2%	61%	L-39
9	$Pd(OAc)_2$, (*S*)-BINAP, PCy_3	NMP	12%	0%	78%	L-46
10	$NiCl_2$, PCy_3	THF	0%	9%	69%	L-25
11	$NiCl_2$, PCy_3	THF	2%	1%	75%	L-26
12	$FeCl_3$	THF	2%	22%	61%	L-23
13	$FeCl_3$	NMP	18%	5%	59%	L-24

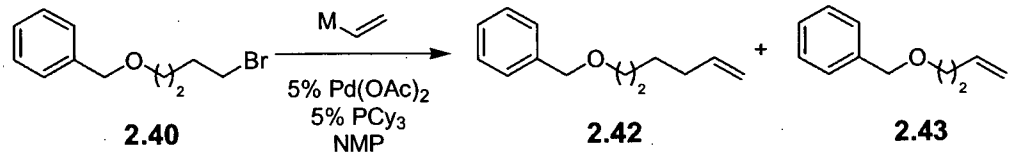
[a] 5 mol % of each of the catalyst components were used in each case. [b] Determined by GC versus an internal calibrated standard of dodecane. [c] Refers to laboratory notebook page.

A variety of other sources of palladium were probed. Lowered conversions were observed in all cases however, and the best source for the palladium catalyst remained $Pd(OAc)_2$ in conjunction with PCy_3 (entry 1, 4-9). $NiCl_2$ also proved to be a poor choice for the catalyst (entry 10, 11). Fürstner and co-workers had previously demonstrated the applicability of iron(III) catalyzed cross-coupling of organomagnesium reagents with aryl electrophiles.[30] The use of $FeCl_3$ did provide some cross-coupling product, albeit

again in lowered conversion. In the case where the reaction was performed in THF solvent, a large amount of the β-hydride elimination product **2.43** was obtained (entry 12). When this same reaction was performed in NMP however, the cross-coupling product **2.42** was predominant (entry 13). For the cross-coupling with alkyl electrophiles using $FeCl_3$, it appears that NMP is a superior solvent in that the β-hydride elimination pathway is substantially suppressed. This result is interesting in light of subsequent observations reported in the literature. Recently, Fürstner and co-workers have demonstrated the cross-coupling of alkyl bromides with arylmagnesium halides using $Fe(acac)_3$ in THF solvent with no observable β-hydride elimination products.[31] Interestingly, Nakamura and co-workers found that the similar cross-coupling reaction performed with $FeCl_3$ in THF provided largely the β-hydride elimination products unless a stoichiometric amount of *N,N,N',N'*-tetramethylethylenediamine was added.[32]

In a final effort, the choice of the vinylorganometallic metal was varied (Table 2.8). Vinylzinc bromide, prepared from zinc bromide and vinylmagnesium bromide,[33] was found to provide cross-coupling product **2.42** in only slightly lower yield than when vinylmagnesium bromide is used, with no formation of the β-hydride elimination product **2.43** (entry 2). The use of divinylzinc, also prepared from zinc bromide and vinylmagnesium bromide,[34] provided a markedly lowered conversion (entry 3). Vinylalane proved to be a poor choice as a vinylorganometallic for the reaction as little conversion was observed for this case (entry 4). No improvement was observed even when a substoichiometric amount of zinc chloride was added (entry 5), although the vinylalanate complex proved to be slightly more reactive (entry 6). In terms of choice of the vinylorganometallic, vinylzinc bromide may appear to be a viable substitute for vinylmagnesium bromide, although no further experimentation was performed with regards to this.

Table 2.8 Cross-Coupling Between Alkyl Bromide 2.40 and Vinylorganometallics



2.40 **2.42** **2.43**

entry	M	additive	Yield[a] 2.42	2.43	2.40	Ref.[b]
1	BrMg	—	33%	3%	54%	L-01
2	BrZn	—	24%	0%	61%	L-29
3	Zn	—	10%	2%	68%	L-30
4	$(Bu^i)_2Al$	—	2%	0%	93%	L-42
5	$(Bu^i)_2Al$	$ZnCl_2$	5%	0%	89%	L-40
6	$Me(Bu^i)_2Al^-$	—	10%	2%	58%	L-43

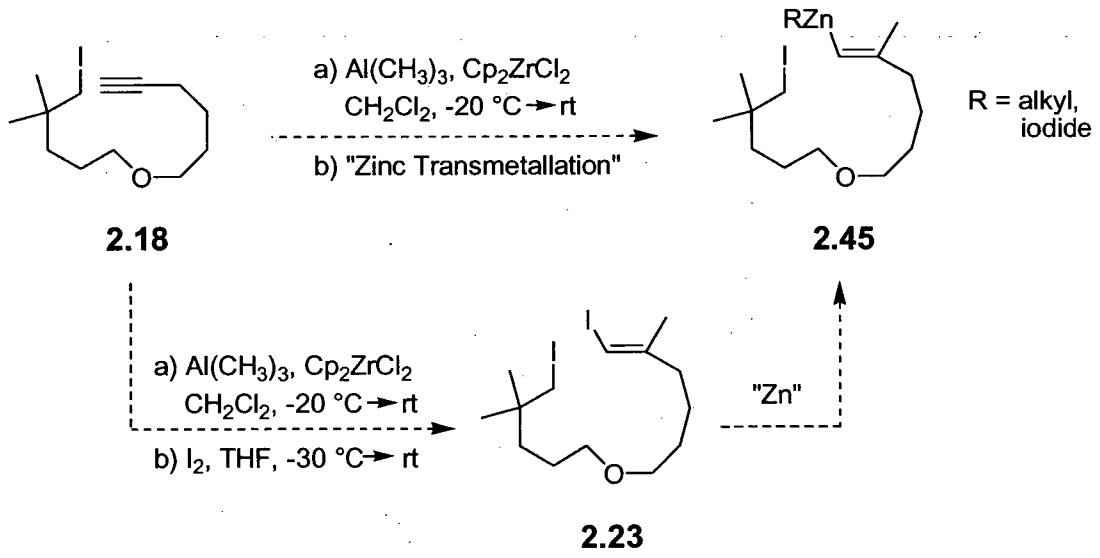
[a] Determined by GC versus an internal calibrated standard of dodecane. [b] Refers to laboratory notebook page.

Subsequent to this work, Fu and co-workers have managed to develop a number of procedures for the cross-coupling of vinylorganometallics with alkyl electrophiles. This includes the use of vinylzirconates (Negishi coupling),[35] vinylstannanes (Stille coupling),[36] vinylboranes (Suzuki coupling)[37] and vinylzincs (Negishi coupling)[38] as coupling partners. It is worth mentioning that for each organometallic reagent employed, very specific reaction conditions and catalyst systems were developed and individual fine tuning from one system to the other was required. The use of vinylzincs is of obvious interest relating to the work presented above. Fu and Zhou found that the *use of a stoichiometric amount of N-methylimidazole was essential for the success of the cross-coupling reaction* under similar reaction conditions to those presented in entry 2, Table 2.8 ($Pd_2(dba)_3$ instead of $Pd(OAc)_2$, $PCyp_3$ (Cyp = cyclopentyl) instead of PCy_3), although the reason for the reaction enhancement is not well understood.[39]

However, the complimentary coupling reaction in which a vinylmagnesium reagent is used has yet to be reported in the literature.

III. Negishi Cross-Coupling Macrocyclization Reactions

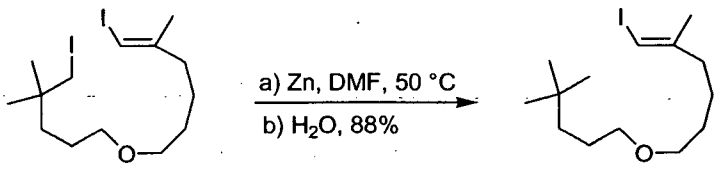
Since the one pot tandem carboalumination followed by activation with Ni^0 methods were attempted thus far for the macrocyclization reactions (*vide supra*) contained excess aluminum and zirconium species which may complicate the coupling reaction, a two-step procedure was desired. This would allow for the carboalumination product to be isolated and purified before being subjected to macrocyclization. It was hoped that quenching the carboalumination product with iodine to yield a vinyl iodide (such as **2.23**) and then obtaining a vinylzinc **2.45** via a selective zinc halogen exchange would be a viable and "cleaner" route in the macrocyclization process (Scheme 2.5).



Scheme 2.5 Possible Direct and Two-Step Routes to Vinylzincs

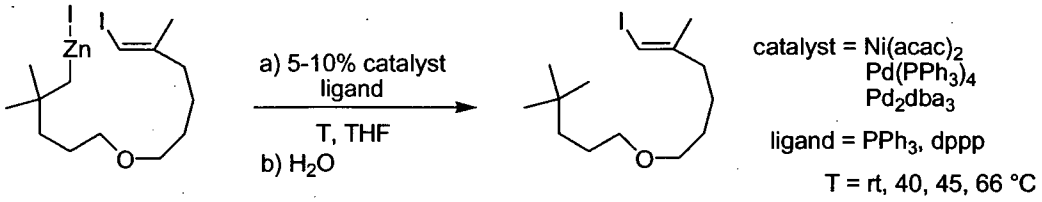
When **2.23** was treated with diethylzinc in hexane at 0 °C, no reaction was observed. The same result was obtained when the reaction was performed in THF at room temperature and when heated to reflux (69 °C). When elemental zinc was used in refluxing THF (66 °C) no reaction occurred, but when the same reaction was performed

in DMF at 50 °C a new product was obtained after quenching with water (Eq. 2.9). Structural analysis showed this to be **2.46**, resulting from selective oxidative insertion of zinc at the neopentyl iodide site over vinyl iodide-zinc exchange. The ^{1}H NMR spectrum showed the disappearance of the signal for the methylene bearing the iodide in **2.23** at δ 3.14, but the vinyl proton signal remained unchanged at δ 5.85. A Literature survey did not reveal a chemoselective method for the formation of an alkylzinc iodide in the presence of a vinyl iodide. Although this was not the intended product, selective formation of an alkylzinc iodide allowed for possible intramolecular cross-coupling with the vinyl iodide under the influence of Ni^0 or Pd^0. Negishi and co-workers have developed this type of reaction in an intermolecular manner via a similar procedure.[40] However, the macrocyclization version for this reaction is unknown and interest was pursued in investigating this possibility as an alternative two step sequence for the tandem carboalumination/cyclization sequence.



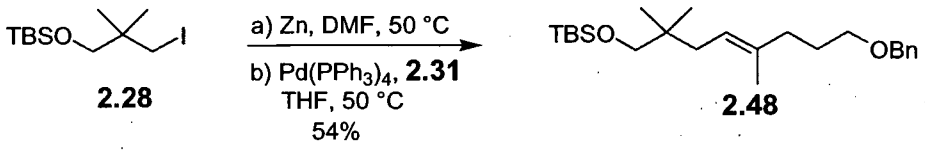
2.23 **2.46** 2.9

The neopentylzinc derivative **2.47** obtained from subjecting **2.23** to zinc in DMF, was treated under a number of Negishi reaction conditions in order to induce macrocyclization. However, treatment with a number of catalysts ($Ni(acac)_2$, $Pd(PPh_3)_4$, Pd_2dba_3) on their own or in the presence of additional phosphine ligand additives, as an attempt to prolong the catalyst lifetime, provided only the uncyclized product **2.46** (Eq 2.10).

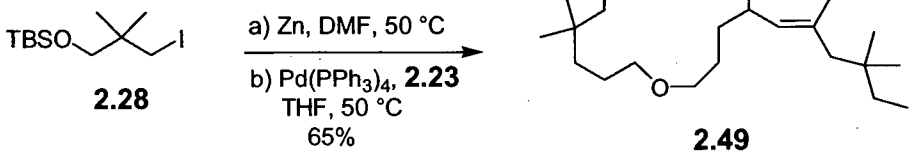


2.47 **2.46** 2.10

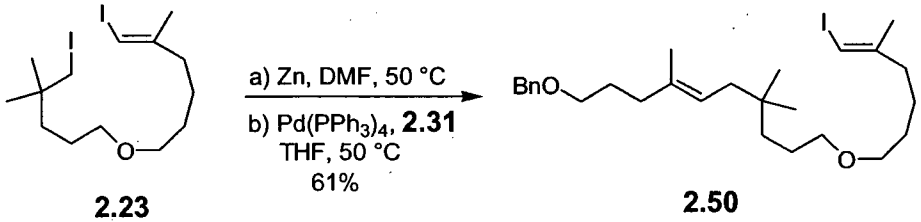
Suspicion for the lack of cyclization was directed on whether this was a result of coupling to a sterically hindered neopentyl reactive centre or due to unfavourable entropic factors involved in the joining of the reactive centres. Interestingly, **2.47** did not cross-couple intermolecularly to iodobenzene, even under reaction conditions in which alkylzinc iodides are known to perform such coupling reactions (10% $Ni(acac)_2$, THF).[41] Reaction conditions which resulted in intermolecularly joining a trisubstituted vinyl iodide such as **2.31** with a neopentylzinc iodide obtained from a neopentyl iodide such as **2.28** were found ($Pd(PPh_3)_4$, THF, 50 °C), yielding the coupled product **2.48**. (Eq 2.11). This was evidenced from the ^1H NMR spectrum which revealed the diagnostic triplet signal corresponding to the vinyl proton for the trisubstituted double bond. Additionally, neopentyl iodide **2.28** could be coupled to the vinyl iodide centre in the macrocyclic substrate **2.23** (yielding **2.49**), and the vinyl iodide **2.31** could be coupled to the neopentyl iodide centre of **2.23** (yielding **2.50**). The preceding results demonstrate that a vinyl iodide or a neopentyl iodide can be coupled to either reactive centres of the macrocyclic substrate **2.23** in an intermolecular manner. However the same reaction conditions resulted in no intramolecular reaction for **2.23**. These experiments support the notion that entropic factors are likely responsible for the lack of macrocyclization in using a substrate such as **2.23**.



2.28 **2.48** 2.11

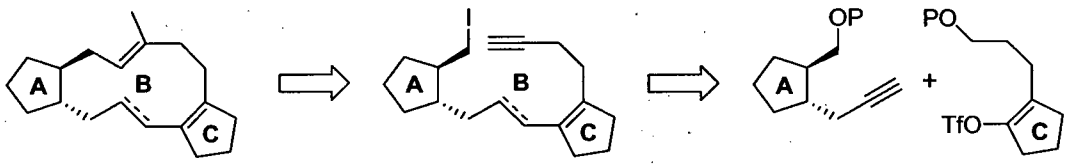


2.28 **2.49** 2.12



2.23 **2.50** 2.13

In view of the failures of the attempted Negishi macrocyclizations using the ether substrate **2.23**, the synthesis of a substrate which minimizes unfavourable entropy factors and more closely resembles the natural product Nitiol, which was of interest in our laboratory at the time, was desired. The iodide **2.51** which contained two cyclopentyl rings tethered by either a saturated or an unsaturated 3-membered carbon chain would be a suitable substrate which would provide the tricycle **2.52** following a carboalumination and Negishi macrocyclization (Scheme 2.6).[ii] The reactive centres of **2.51** are disposed in such a way that they are spatially in closer proximity to one another and the entropic degrees of freedom are limited relative to the ether substrate **2.23**. Further disconnection at the tethering carbon chain leads to the two cyclopentyl fragments **2.53** and **2.54**.



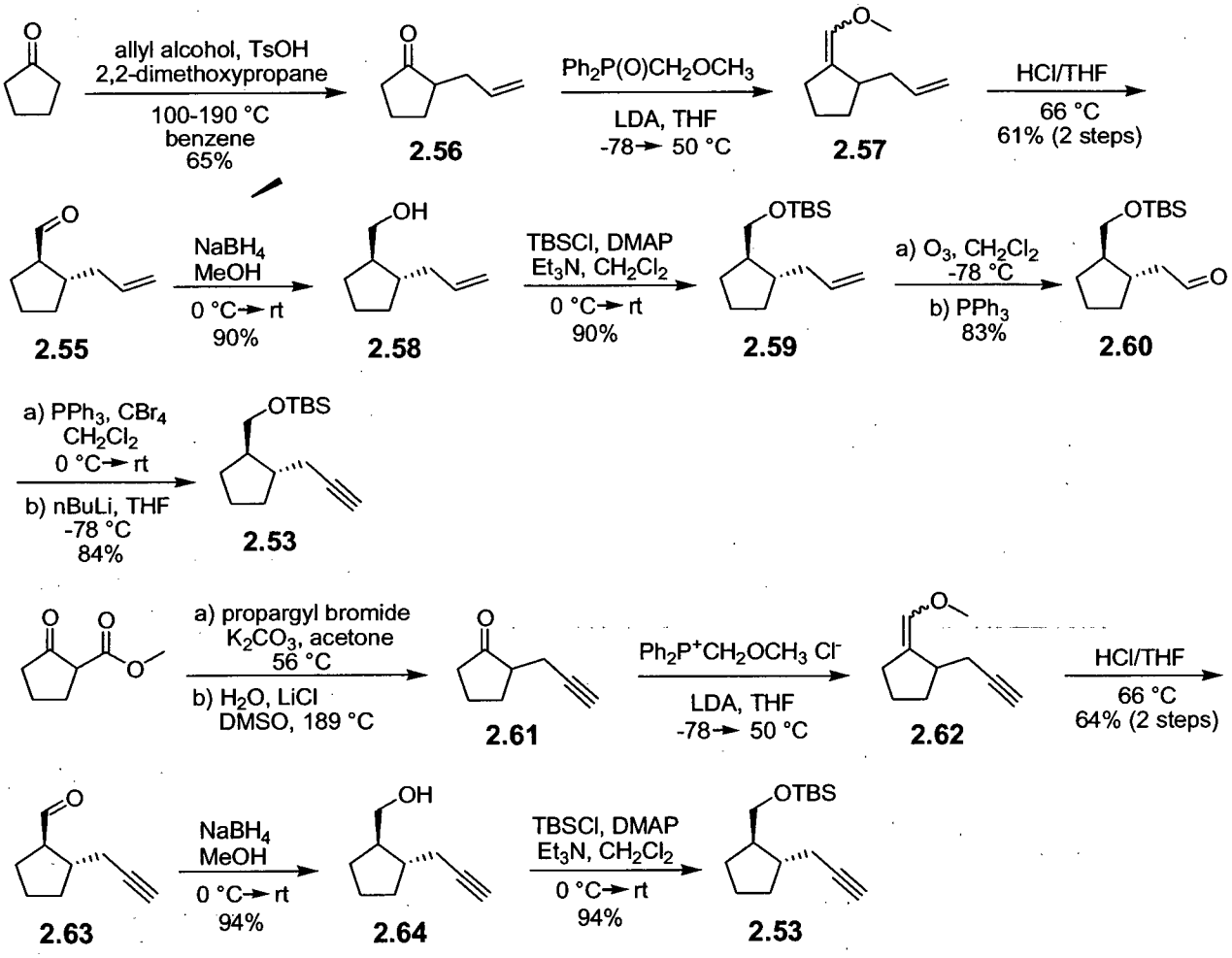
2.52 **2.51** **2.53** **2.54**

Scheme 2.6 Retrosynthetic Analysis for the Synthesis of the Negishi Macrocyclization Substrate

The cyclopentyl A-ring fragment **2.53** was prepared from the known aldehyde **2.55**, which was obtained by way of olefination of 2-allylcyclopentanone (**2.56**) followed by acid hydrolysis (Scheme 2.7).[42] Borohydride reduction of **2.56** provided alcohol **2.58**, which was evidenced by the disappearance of the aldehyde C=O stretching frequency of 1734 cm^{-1} and the appearance of a O-H stretching frequency of 3333 cm^{-1}in the IR spectrum. This was followed by protection of the hydroxyl substituent as a *tert*-butyldimethylsilyl ether and ozonolysis of the allyl substituent. Formation of the aldehyde **2.60** was observed from the IR spectrum which revealed the presence of an aldehyde C=O stretching frequency of 1734 cm^{-1} and from the ^{1}H and ^{13}C NMR spectra which showed an aldehyde proton signal at δ 9.71 and an aldehyde carbon signal at δ 202.2. Finally, the alkyne was prepared via the Corey-Fuchs reaction.[43] Evidence for

[ii] The three rings of the tricyclic macrocyle **2.52** were arbitrarily labeled as A, B and C in relation to the labeling for Nitiol.[1]

the formation of the alkyne was obtained from the IR spectrum which revealed a C≡C stretching frequency of 3314 cm^{-1}, and the ^{13}C NMR spectrum which showed the presence of alkyne carbon signals at δ 83.9 and 68.3.

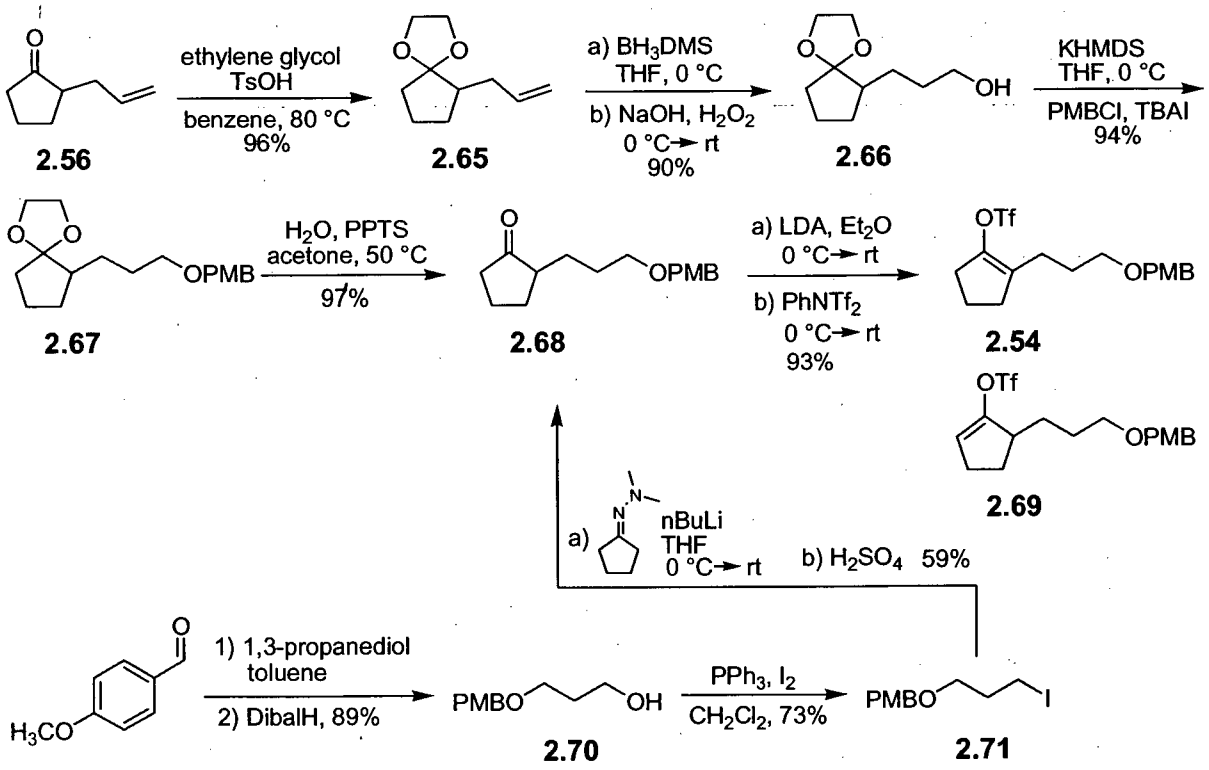


Scheme 2.7 Synthesis of Cyclopentyl Fragment 2.53

Alternatively, the alkyne **2.53** was also prepared using a slightly shorter sequence (Scheme 2.7). This involved the preparation of ynone **2.61** via a propargylation and decarboxylation of methyl-2-oxocyclopentane carboxylate. Olefination and acid hydrolysis followed to yield **2.63**. The formation of the ynal **2.63** was confirmed by the presence of an aldehyde proton signal at δ 9.62 in the ^1H NMR spectrum. Borohydride reduction of **2.63** provided alcohol **2.64**, which was evidenced by the disappearance of the aldehyde C=O stretching frequency of 1734 cm^{-1} and the appearance of a O-H stretching frequency of 3333 cm^{-1}in the IR spectrum. This was

followed by protection of the hydroxyl substituent as its *tert*-butyldimethylsilyl ether, yielding the product **2.53**.

The second B-ring cyclopentyl fragment was synthesized also from cyclopentenone **2.56**. Ketalization with ethylene glycol provided **2.65** as observed from the disappearance of the C=O stretching frequency of 1741 cm^{-1} in the IR spectrum. Hydroboration followed with oxidative workup yielded the alcohol **2.66**. This was evidenced by the appearance of a broad O-H stretching frequency of 3423 cm^{-1} in the IR spectrum. The hydroxyl was then protected as its 4-methoxybenzyl ether to yield **2.67**, the formation of which was confirmed by the appearance of aromatic proton signals in the ^1H NMR spectrum at δ 7.24 and δ 6.85, and of a proton signal corresponding to the methoxy at δ 3.78. Acid hydrolysis of the ketal then provided the cyclopentanone **2.68**. The structure was substantiated by the appearance of a C=O stretching frequency of 1734 cm^{-1} in the IR spectrum.



Scheme 2.8 Synthesis of Cyclopentyl Fragment 2.54

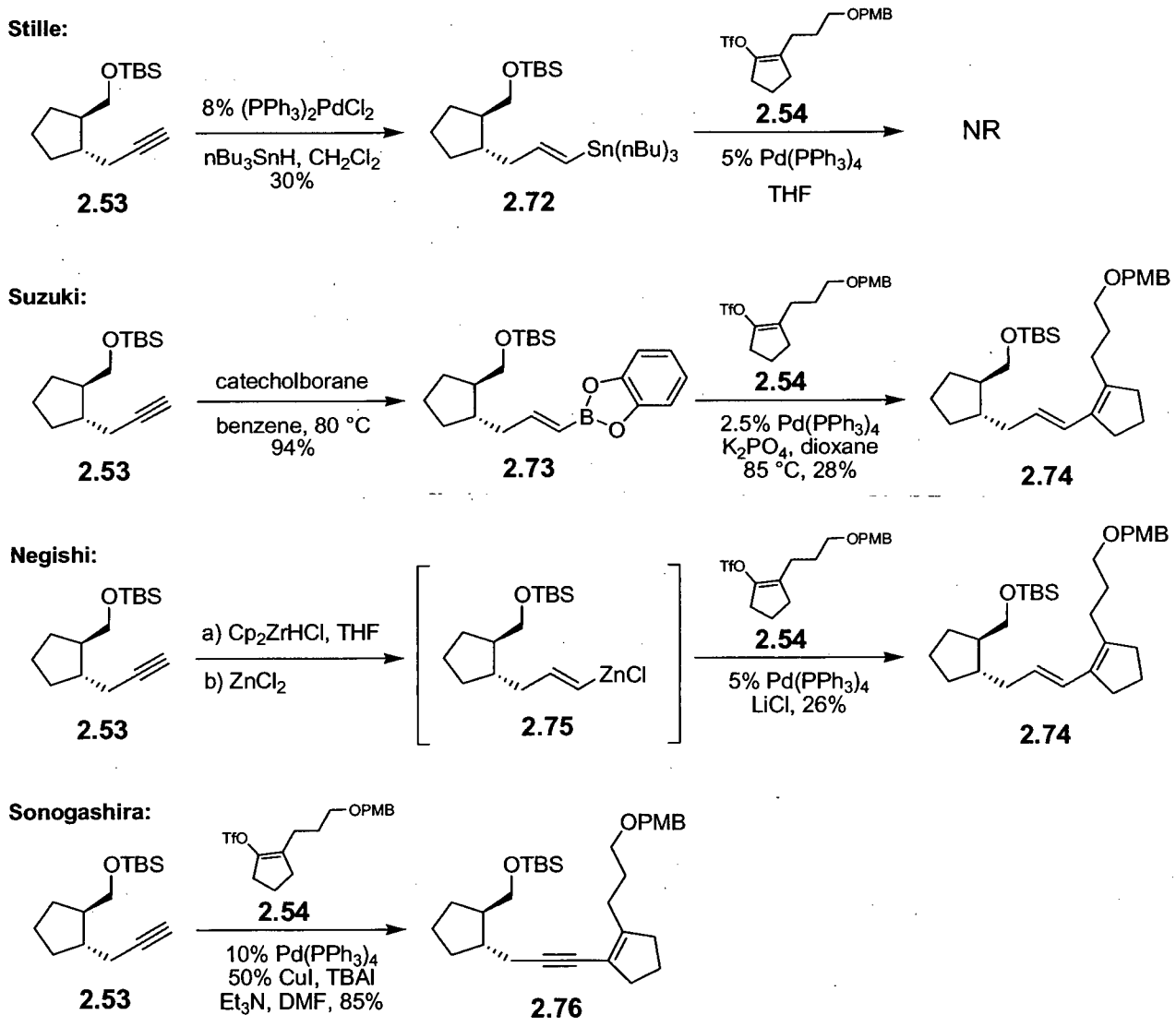
Alternatively, the cyclopentanone **2.68** could also be obtained from the alkylation of 2-cyclopentylidene-1,1-dimethylhydrazine[44] with the known iodide **2.71**.[45] The iodide

2.71 was prepared from the ketalization of *p*-anisaldehyde with 1,3-propanediol[46] followed by reduction to yield **2.70**, and treatment with iodine and triphenylphosphine.

The vinyltrifluorosulfonimide **2.54** was then obtained from the treatment of an excess of cyclopentanone **2.68** with lithium diisopropylamide followed with *N*-phenyltrifluoromethanesulfonimide. The structure was confirmed from the ^{13}C NMR spectrum which displayed a characteristic quartet signal at δ 120.8 for the triflate carbon and the appearance of alkene carbon signals at δ 142.5 and 132.2, in addition to the disappearance of the carbonyl carbon at δ 221.1. Formation of the thermodynamic vinyltrifluorosulfonimide **2.54** as opposed to the formation of the kinetic product **2.69**, was substantiated by the absence of a vinyl proton signal in the ^{1}H NMR spectrum. Additionally, the kinetic vinyltrifluorosulfonimide **2.69** was prepared from the cyclopentanone **2.68** by treatment with an excess of lithium diisopropylamide followed with *N*-phenyltrifluoromethanesulfonimide, of which the ^{1}H NMR spectrum revealed the presence of a vinyl proton signal at δ 5.61.

With the two cyclopentyl fragments **2.53** and **2.54** in hand, attention was focused on the coupling of these two fragments. A variety of transition metal catalyzed processes were attempted (Scheme 2.9). The vinylstannane **2.72** was prepared by way of a palladium catalyzed hydrostannation of the alkyne **2.53**.[47] However, a large amount of dehydrostannation occurred during the course of the reaction and in the subsequent workup, as a yield of 30% at best was achieved. The cross-coupling was nevertheless attempted with the vinyltrifluorosulfonimide **2.54** under Stille reaction conditions (5% $Pd(PPh_3)_4$, LiCl, THF, 66 °C).[48] However, no cross-coupling was observed as only starting materials were obtained. Hydroboration of **2.53** with catecholborane provided the vinylborane **2.73** which was then subjected to Suzuki cross-coupling reaction conditions with **2.54** (2.5% $Pd(PPh_3)_4$, K_2PO_4, dioxane, 85 °C).[49] The cross-coupling diene product **2.74** was thus obtained, albeit in only 28% yield along with a number of unidentified byproducts. Hydrozirconation of **2.53** with the Schwartz reagent followed by transmetallation to the vinylzinc **2.75** intermediate using $ZnCl_2$ and cross-coupling with **2.54** under Negishi reaction conditions (5% $Pd(PPh_3)_4$, THF)[50] initially provided no diene product **2.74** and consisted mostly of starting materials. However the addition of a stoichiometric amount of lithium chloride[51] to the same reaction conditions provided the cross-coupling product **2.74** in 26% along with starting

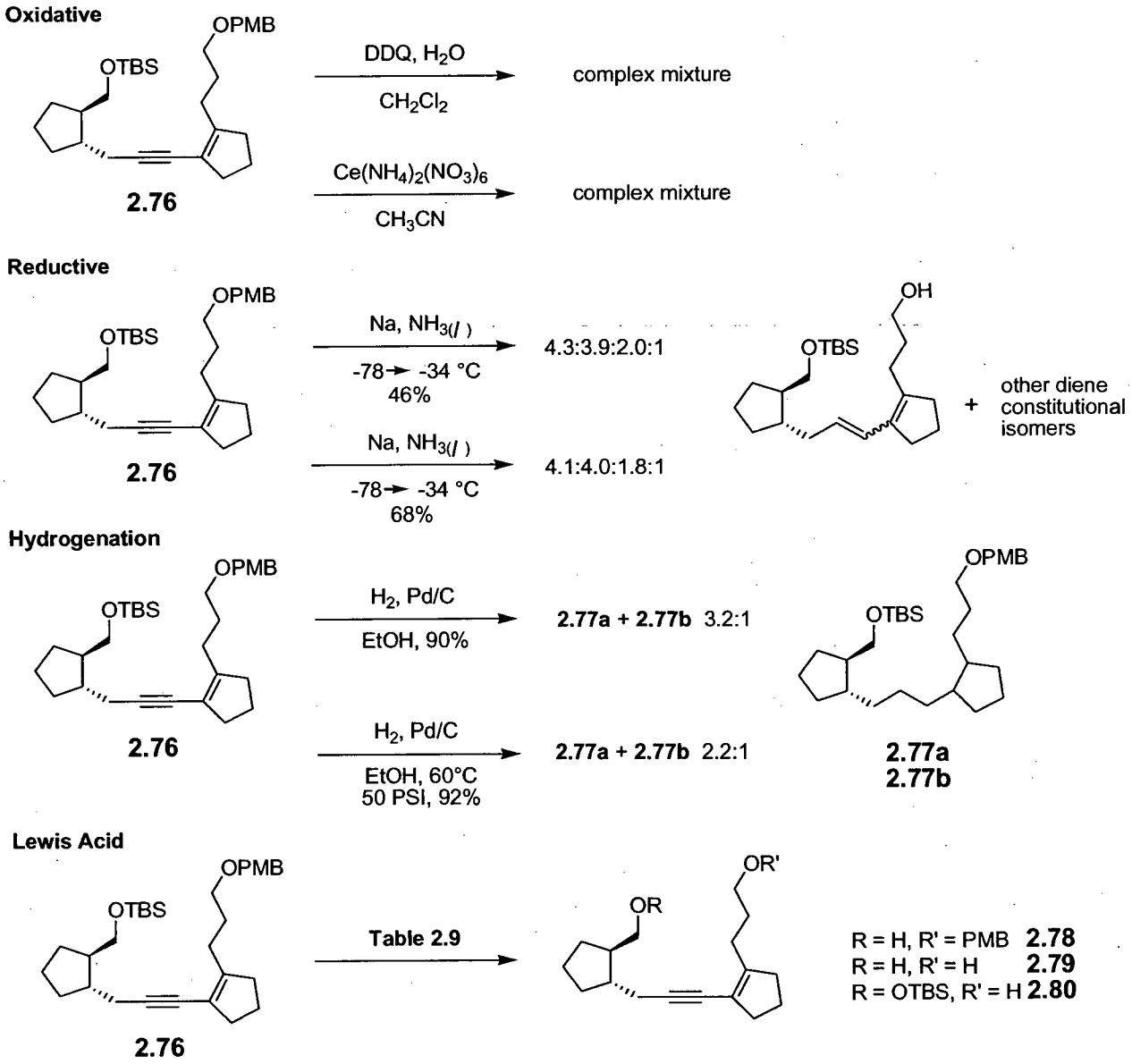
materials and unidentified by-products. This appears to be the first example of Negishi cross-coupling with vinyltrifluorosulfonimides. However, this was not investigated further as we found that the best cross-coupling conditions were achievable under Sonogashira reaction conditions (10% $Pd(PPh_3)_4$, 50% CuI, TBAI, Et_3N, DMF)[52] which provided the enyne **2.76** in 85% yield.



Scheme 2.9 Attempts at Coupling Cyclopentyl Fragments Using Various Transition Metal Catalyzed Systems

With the A-ring and the C-ring tethered, attention was focused on the functionalization of the ring side chains with the removal of the 4-methoxybenzyl protecting group as the immediate interest. The removal of this group had previously

been attempted on the diene product **2.74** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone oxidative conditions (DDQ, CH_2Cl_2, H_2O), although this was found to produce a large number of unidentified products. When these same oxidative conditions were applied to enyne **2.76** (Scheme 2.10), a complex mixture was also observed. A similar result was obtained with cerric ammonium nitrate ($Ce(NH_4)_2(NO_3)_6$, CH_3CN, H_2O). It was assumed that the enyne could interfere with the single electron transfers in the reaction, and hence other methods for the removal of the 4-methoxybenzyl protecting group were considered.



Scheme 2.10 Attempts at the Removal of the 4-Methoxybenzyl Group of 2.76

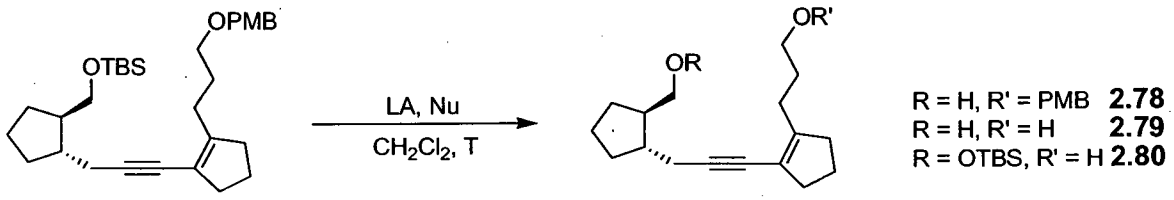
Birch reduction conditions (Na or Li, $NH_{3(\ell)}$, -78 °C→-34 °C) provided a single spot by TLC which was purified by column chromatography (Scheme 2.10). However, GC/MS analysis revealed this to be an inseparable mixture of four products composed of the same molecular weight. ^{1}H NMR analysis showed the disappearance of the aromatic proton signals at δ 7.25 and 6.85 corresponding to the removal of the 4-methoxybenzyl group. However a number of vinyl proton signals were observed between δ 5.3 and 6.1. This indicated that the enyne was reduced to a mixture of four dienes, although no further work was performed to determine the structure of these products and additional optimizations were not performed. It was additionally noted through ^{1}H NMR analysis that if the reaction temperature was kept at -78 °C, the appearance of vinyl proton signals was observed without the disappearance of the aromatic proton signals. This indicated that the enyne was reduced at a faster rate than the removal of the 4-methoxybenzyl group.

An attempt to remove the 4-methoxybenzyl group using hydrogenation under standard conditions (H_2, Pd/C, EtOH,) was performed, yielding a diastereomeric mixture of two products **2.77a** and **2.77b** (76:24) in which only the enyne was reduced (Scheme 2.10). The diastereomeric mixture was inseparable and the relative stereochemistries at the newly formed stereocentres were undefined. Reduction of the enyne was observed from ^{13}C NMR spectroscopy which revealed the disappearance of the alkene carbon signals at δ 149.1 and 118.5, as well as the alkyne carbon signals at δ 90.3 and 77.6. Performing the reaction at higher temperature and pressure (60 °C, 50 PSI) did not remove the 4-methoxybenzyl group.

The use of Lewis acid was investigated (Table 2.9). Treatment of **2.76** with trimethylsilyl iodide yielded a single product **2.78** in which the *tert*-butyldimethylsilyl only was removed (entry 1). When trifluoroacetic acid was used in conjunction with anisole as a carbonium ion trap,[53] the bis-alcohol **2.79** was obtained (entry 2). Boron trifluoride with triethylsilane provided a complex mixture (entry 3) whereas only starting materials were obtained if sodium cyanoborohydride was used as the nucleophile (entry 4). Aluminum chloride with ethanethiol provided **2.79** in which the silyl protecting group was removed in addition to the 4-methoxybenzyl group (entry 5), whereas when tin chloride was used, only starting materials were obtained (entry 6). The use of magnesium bromide with dimethylsulfide was more successful as **2.80** was obtained, albeit in only

31%, along with mostly starting material (entry 7). This required the use of at least 3 equivalents of Lewis acid, since the use of lower amounts provided decreased conversion. However, increasing the amounts of magnesium bromide and dimethylsulfide did not affect the yields and these were also found to be lowered on multigram scale.

Table 2.9 Lewis Acid Mediated Removal of the 4-Methoxybenzyl Group of 2.76



2.76

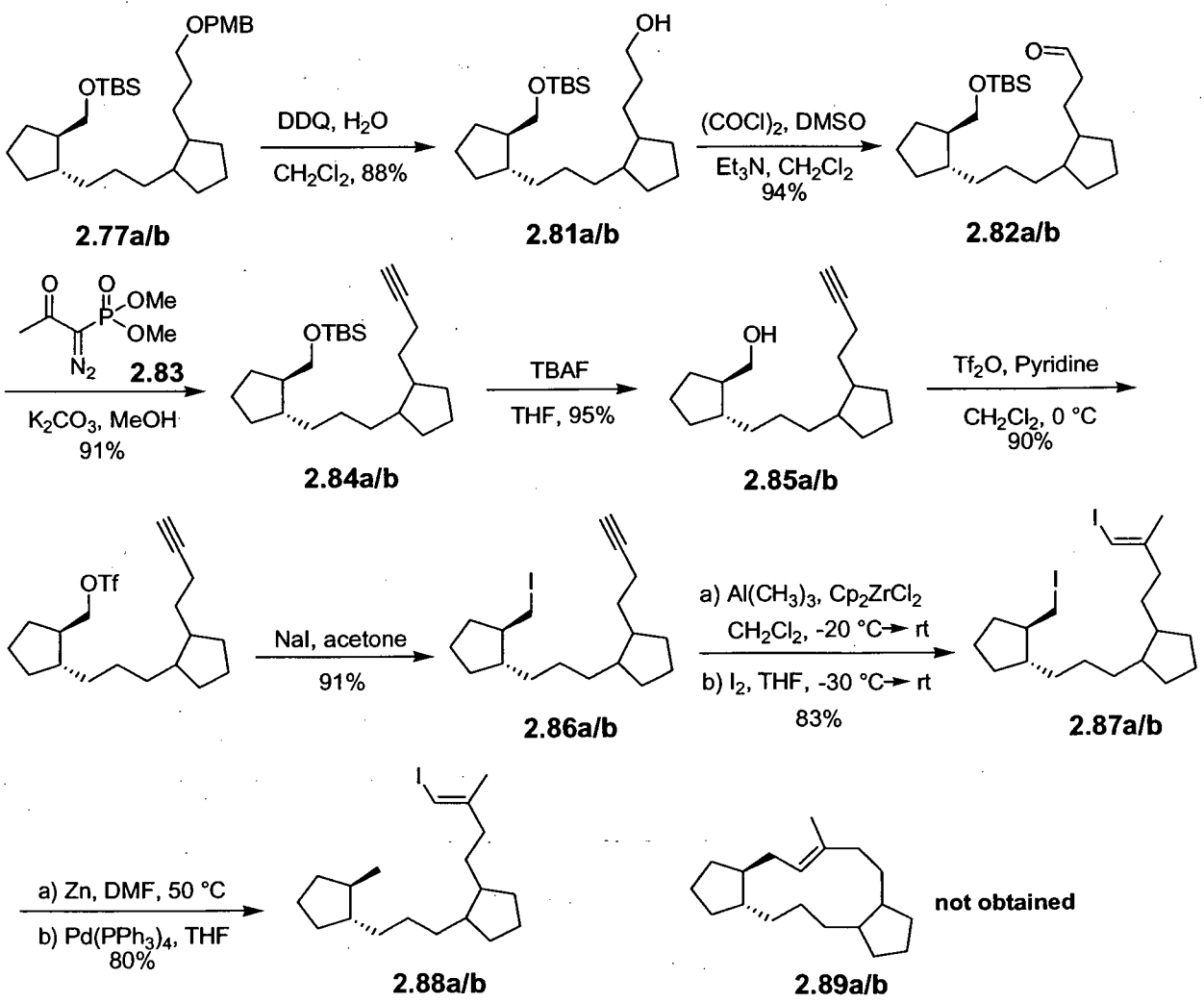
entry	LA (equiv.)	Nu (equiv.)	T (°C)	product	yield	Ref.[b]
1	TMSI		0	**2.78**	74%	J-40
2	TFA	anisole	rt	**2.79**	70%	J-41
3[c]	BF_3 (1.2)	TESH (2.4)	0	complex mixture	——	J-26
4[d]	BF_3 (1.1)	$NaCNBH_3$ (2)	rt→66	NR[a]	——	J-24
5	$AlCl_3$ (0.3)	EtSH (4)	rt	**2.79**	73%	J-36
6	$SnCl_2$ (0.35)	EtSH (4)	rt	NR[a]	——	J-37
7	$MgBr_2$ (3)	$(CH_3)_2S$ (10)	rt	**2.76, 2.80**	63%, 31%	J-23
8	BCl_3 (2)	$(CH_3)_2S$ (2)	rt	**2.79**	80%	J-39
9	BCl_3 (1.1)	$(CH_3)_2S$ (1.1)	0	**2.79, 2.80**	69%, 12%	J-42
10	BCl_3 (0.6)	$(CH_3)_2S$ (0.6)	-78→0	**2.76, 2.79, 2.80**	47%, 5%, 36%	J-44
11	BCl_3 (0.5)	$(CH_3)_2S$ (0.5)	-78→0	**2.76, 2.79, 2.80**	48%, 4%, 30%	J-44

[a] No Reaction. [b] Refers to laboratory notebook page. [c] Acetonitrile was used as solvent instead of CH_2Cl_2. [d] THF was used as solvent instead of CH_2Cl_2.

The use of a harder Lewis acid was examined. Hence, when 2 equivalents of boron chloride was used, **2.79** was obtained in which the silyl protecting was removed in addition to the 4-methoxybenzyl group. Close monitoring of the reaction revealed that the benzyloxy group was slightly more reactive under these conditions than the silyloxy group. Lowering the reaction temperature and using inferior amounts of boron chloride provided **2.80** (entry 9-11) along with starting material and **2.79**. Optimal conditions were found which minimized the quantity of **2.79** obtained. Hence, the use of substoichiometric amounts and slowly raising the reaction temperature from -78 to 0 °C provided the largest yield for **2.80** along with starting material **2.76** which could be recycled (entry 10). In addition, these conditions were successfully applied to a multigram scale (2.24 g).

Further functionalization of **2.80** was investigated. Swern-Moffatt oxidation of the alcohol in **2.80** and alkynylation of the resulting aldehyde provided products which were unstable upon standing at room temperature. The source of the instability was reasoned to originate from the enyne of **2.80**. Since the enyne functionality of **2.76** was suspected to be the cause of the dual problems with the oxidative removal of the 4-methoxybenzyl group and with further functionalization, a complementary substrate which did not contain this substrate was required.

Hence, the saturated analogues **2.77a** and **2.77b**, obtained from the hydrogenation of **2.76** (Scheme 2.11) as a 3.2:1 mixture of two inseparable diastereomers of unspecified stereochemistry, was subjected to treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, yielding **2.81a** and **2.81b**. The oxidative removal of the 4-methoxybenzyl group was confirmed from the ^{1}H NMR spectrum which revealed the disappearance of the aromatic proton signals in the ^{1}H NMR spectrum at δ 7.25 and δ 6.86 and of the proton signal corresponding to the methoxy at δ 3.78. The success of this reaction here validated the suggestion that the enyne was problematic for the oxidative removal of the 4-methoxybenzyl group. Additionally, the diastereomeric mixture **2.81a** and **2.81b** was used successfully in the further transformations of the synthetic sequence (Scheme 2.11).



Scheme 2.11 Elaboration of 2.77a/b and Attempted Negishi Intramolecular Cross-Coupling Reaction

Swern-Moffat oxidation of the alcohol in **2.81a** and **2.81b** provided the aldehyde diastereomeric mixture **2.82a** and **2.82b**, which showed the characteristic aldehyde proton signals in the ^{1}H NMR spectrum at δ 9.74, and carbonyl carbon signals in the ^{13}C NMR spectrum at δ 202.9. Additionally, a C=O stretching frequency of 1741 cm^{-1} was observed in the IR spectrum. Alkynylation of the resulting aldehyde using the Bestman-Ohira modification[54] of the Gilbert-Seyferth reagent[55] was then performed. Treatment of the aldehyde substrate with potassium carbonate and dimethyldiazo-2-oxopropylphosphonate **2.83** in methanol afforded the enyne diastereomeric mixture **2.84a** and **2.84b** in 70% yield. The spectral data for **2.84a** and **2.84b** supported the assigned structure. The IR spectrum showed an alkyne C-H stretching frequency of

3314 cm^{-1} and the ^1H NMR spectrum contained a proton singlet signal at δ 1.91 corresponding to the alkyne hydrogen. Subsequent fluoride deprotection of the silyl ether provided the alkynol diastereomeric mixture **2.85a** and **2.85b**, which was evidenced by the presence of an O-H stretching frequency of 3424 cm^{-1} in the IR spectrum. Triflation followed by substitution with sodium iodide yielded the iodide diastereomeric mixture **2.86a** and **2.86b** which was structurally confirmed by the presence of the iodomethylene proton singlet signal at δ 3.14 in the ^1H NMR spectrum. The diastereomeric mixture **2.86a** and **2.86b** was subjected to carboalumination conditions, followed by an iodine quench to provide the Negishi macrocyclization substrate as a diastereomeric mixture **2.87a** and **2.87b**. Evidence for the formation of the iodine quenched carboalumination products was obtained from the ^1H NMR spectrum which revealed a vinyl proton signal at δ 5.85 and a proton singlet signal for the vinyl methyl protons at δ 1.77.

At this stage the Negishi macrocyclization was attempted with the substrate mixture **2.87a** and **2.87b** using the similar reaction conditions that were attempted for the simplified substrate **2.23** (Zn, DMF, 50 °C, $Pd(PPh_3)_4$, THF). Reaction temperatures from room temperature to reflux (66 °C) were attempted, however no cross-coupling product **2.89** was observed as only the diastereomeric mixture **2.88a** and **2.88b** was isolated. This was evidenced from the ^1H NMR spectrum which revealed a vinyl proton singlet signal at δ 5.85 indicative of the unreacted vinyl iodide. Additionally, the presence of a methyl doublet signal at δ 0.95 and the disappearance of the iodomethylene proton signals at δ 3.35 and 3.11 were indicative of the zinc activation of **2.87a** and **2.87b**. No further experimentation with regard to reaction conditions was performed.

IV. Concluding Remarks

Although a general method for the stereospecific construction of macrocycles containing a trisubstituted alkene, which was the objective at the onset of the project, was not achieved, valuable lessons have been learned which deserve to be mentioned. It was understood early into the development of the project that the formation of alkenes by way of the cross-coupling of an organometallic sp^2 carbon with an electrophilic sp^3

carbon was not straightforward. The added concern of its use in macrocycle formation made this an even greater challenge. However, it was found that vinylzinc and vinylmagnesium reagents are suitable choices as the organometallic partner in the reaction. In terms of alkyl electrophile, alkyl bromides appear as the best choice with regards to balancing reactivity versus side product formation. Additionally, the choice of the catalytic system as well as the reaction conditions appear to be crucial and specific for the cross-coupling. A catalytic system (5 mol % $Pd(OAc)_2$, PCy_3) and the reaction conditions (NMP, 66 °C) were found which provided slightly over 50 % yield with a minimum amount of side product formation (entry 11, Table 2.5). The source of the lack of complete conversion is not completely understood, although an attempt was performed by way of varying the reaction conditions. With the subsequent work by Fu and co-workers on the development of the cross-coupling reaction between vinylorganometallics and alkyl electrophiles,[35,36,37,38] the work presented in here may at first be seen as no longer relevant. However, no method for the cross-coupling of vinylmagnesium reagents with alkyl electrophiles has been reported to date in the literature. Considering the ease for which vinylmagnesium reagents can be prepared or commercially purchased, this form of cross-coupling reaction may merit further attention. Hence, further optimizations to improve the reaction conversion would be useful. Extending this towards a tandem carboalumination/cross-coupling protocol may also be warranted.

An attempt in accessing unsaturated macrocycles by way of the intramolecular Negishi cross-coupling reaction was performed. Although it was shown that neopentyl iodides could be cross-coupled with vinyl iodides in the intermolecular stereospecific formation of trisubstituted alkenes using standard Negishi reaction conditions, the complementary intramolecular version proved to be problematic. This difficulty remains to be solved. However, reaction conditions (Zn, DMF, 50 °C) were found which allowed for the selective zinc activation of an alkyl iodide in the presence of a vinyl iodide contained within the substrate. This useful property allows for the formation of alkylzincs for substrates which contain a vinyl electrophile and can be employed further in a direct cyclization. Additional investigations in terms of developing suitable reaction conditions for the macrocyclic Negishi reaction may be useful.

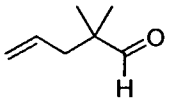
V. Experimental

Unless otherwise stated, all reactions were performed under a nitrogen atmosphere in flame-dried glassware. The glass syringes, Teflon® cannulae and stainless steel needles used for handling anhydrous solvents and reagents were oven dried, cooled in a dessicator, and flushed with dry nitrogen prior to use. Plastic syringes were flushed with dry nitrogen before use. Thin layer chromatography (TLC) was performed on DC-Fertigplatten SIL G-25 UV_{254} pre-coated TLC plates. Gas chromatographic (GC) analyses in a helium carrier gas were performed on an Agilent 6890 gas chromatograph, equipped with an Agilent 5973N mass selective detector. A Hewlett-Packard HP-5MS (30 m × 0.25 mm × 0.25 μm ID) fused silica capillary columns was used. Melting points were performed using a Mel-Temp II apparatus (Lab devices USA) and are uncorrected. Optical rotations of samples were performed using a Jasco model P1010 polarimeter at 589 nm (sodium 'D' Line). Infrared (IR) spectra were obtained using a Perkin-Elmer FT-IR spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded in deuterochloroform using either a Bruker AV-300 or a Bruker AV-400 spectrometer. Chemical shifts are reported in parts per million (ppm) and are referenced to the centreline of deuterochloroform (δ 7.24 ppm ^{1}H NMR, 77.0 ppm ^{13}C NMR). Coupling constants (J values) are given in Hertz (Hz). Low resolution mass spectra (LRMS) were recorded on either an Agilent 5973N mass selective detector, attached to an Agilent 6890 gas chromatograph for electron impact ionization (EI), a Kratos MS 80 spectrometer for desorption chemical ionization (CI) with the ionization gas noted, or a Agilent HP1100 spectrometer for electrospray ionization (ESI). Microanalyses were performed by the Microanalytical Laboratory at the University of British Columbia on a Carlo Erba Elemental Analyzer Model 1106 or a Fisions CHN-O Elemental Analyzer Model 1108.

All solvents and reagents were purified and dried using established procedures.[56] Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl under an atmosphere of dry argon. Methylene chloride, triethylamine, dimethyl sulfoxide, acetonitrile, pyridine, 1-methyl-2-pyrrolidinone, dimethylacetamide and dimethylsulfoxide were distilled from calcium hydride over an atmosphere of dry argon

or dry nitrogen. Trifluoromethanesulfonic anhydride was distilled from phosphorous pentaoxide over an atmosphere of dry nitrogen. Diisopropylamine was distilled from sodium hydroxide over an atmosphere of dry nitrogen. Dimethylformamide was dried by storing over 4 Å molecular sieves three times over three successive days. Solutions of *n*-butyllithium in hexanes were obtained from the Aldrich Chemical Co. and were standardized using the procedure of Burchat, Chong, and Nielsen.[57] Solutions of vinylmagnesium bromide, unless otherwise noted, were obtained from the Aldrich Chemical Co. and were standardized using the procedure of Lin and Paquette.[58] The promoter *p*-trifluoromethylstyrene was prepared by the Witig olefination of commercially available *p*-trifluoromethylbenzaldehyde as described by Giovannini and Knochel.[59] Elemental zinc was purified and made active prior to use by treatment with hydrochloric acid according to the method of Hauser and Breslow.[60] Aqueous chromic acid solution (Jones reagent) was prepared according to the procedure of Meinwald, Crandall and Hymans.[61] Dimethyldiazo-2-oxopropylphosphonate was prepared from toluenesulfonyl azide and dimethyl-2-oxopropylphosphonate according to the procedure of Callant, D'Haenens and Vandewall.[62] All other reagents were commercially available and were used without further purification.

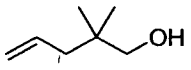
2,2-Dimethyl-4-pentenal (2.3)[63]



Isobutyraldehyde (34.0 mL, 0.341 mol, 1.5 equiv), allyl alcohol (15.5 mL, 0.227 mol, 1.0 equiv) and *p*-toluenesulfonic acid monohydrate (86.4 mg, 0.454 mmol, 0.02 equiv) in *p*-cymene (60 mL) were heated to reflux in a round bottom flask equipped with a Vigreux column and a Dean Stark trap for 40 h. The reaction mixture was distilled through the Vigreux column (120-127 °C) to yield 18.0 g (71 %) of **2.3** as a clear colourless liquid.

IR (neat): 2965, 2925, 1725, 1640 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.40 (s, 1H), 6.18-5.42 (m, 1H), 5.30-4.91 (m, 2H), 2.22 (d, *J*=7.1 Hz, 2H), 1.04 (s, 6H).

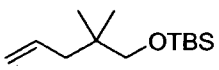
2,2-Dimethyl-4-pentenol (2.4)[64]



Sodium borohydride (7.54 g, 0.199 mol, 1.5 equiv) was added to methanol (900 mL) at 0°C and the mixture was stirred for 5 minutes. 2,2-dimethyl-4-pentenal (**2.3**) (14.9 g, 0.133 mol, 1 equiv) in methanol (40 mL) was added and the reaction mixture was warmed to rt and stirred at rt for 2 h. Water (1 L) was added and the mixture was extracted with ether (6 x 500 mL). The ether extracts were combined and washed with a saturated aqueous solution of sodium chloride (5 x 250 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear pale yellow liquid. The crude liquid was purified by distillation (143-145 °C) to yield 11.2 g (74 %) of **2.4** as a clear colourless liquid.

IR (neat): 3360, 2954, 1640 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.89-5.71 (m, 1H), 5.04-4.91 (m, 2H), 3.70 (s, 1H), 3.25 (s, 2H), 1.98 (d, *J*=7.3 Hz, 2H), 0.87 (s, 9H).

1-tert-Butyldimethylsiloxy-2,2-dimethyl-4-pentene (2.5)[65]

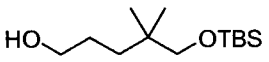


Triethylamine (18.13 mL, 130.0 mmol, 1.5 equiv) was added to a solution of 2,2-dimethyl-4-pentenol (**2.4**) (9.90 g, 86.7 mmol, 1 equiv), *tert*-butyldimethylsilyl chloride (15.68 g, 104.0 mmol, 1.2 equiv) and 4-dimethylaminopyridine (1.06 g, 8.67 mmol, 0.1 equiv) in methylene chloride at 0 °C and the reaction mixture was stirred at rt for 20 h. The mixture was then washed with water

(2 x 100 mL) and brine (1 x 100 mL), dried over magnesium sulfate and concentrated to yield a clear pale red liquid. The crude liquid was purified by column chromatography (hexanes) to yield 18.5 g (93 %) of **2.5** as a clear colourless liquid.

IR (neat): 3077, 2953, 1640 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.88-5.70 (m, 1H), 5.03-4.92 (m, 2H), 3.21 (s, 2H), 1.97 (d, *J*=7.6 Hz, 2H), 0.88 (s, 9H), 0.81 (s, 6H), 0.00 (s, 6H).

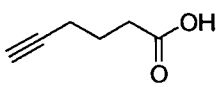
1-*tert*-Butyldimethylsiloxy-2,2-dimethyl-5-pentanol (2.6)[65]



Borane-THF complex (97.2 mL of a 1 M solution in THF, 97.2 mmol, 1 equiv) was added dropwise to a solution of 1-*tert*-butyldimethylsiloxy-2,2-dimethyl-4-pentene (**2.5**) (14.8 g, 64.8 mmol, 1 equiv) in THF (180 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 2.5 h. 3 M aqueous NaOH (65 mL) followed by 30% aqueous hydrogen peroxide (75 mL) were added to the mixture at 0 °C and stirring was continued for 1 h at rt. The mixture was extracted with ethyl acetate (3 x 100 mL), and the organic extracts were combined, washed with brine (1 x 50 mL), dried over magnesium sulfate and concentrated to yield a clear pale yellow oil. The crude oil was purified by column chromatography (1/4 ethyl acetate-hexanes) to yield 15.0 g (94 %) of **2.6** as a clear colourless oil.

IR (neat): 3338, 2955, 2875 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.61 (t, *J*=6.7 Hz, 2H), 3.24 (s, 2H), 1.57-1.45 (m, 2H), 1.41 (s, 1H), 1.30-1.21 (m, 2H), 0.88 (s, 9H), 0.83 (s, 6H), 0.01, (s, 6H).

Hex-5-ynoic acid (2.7)[66]

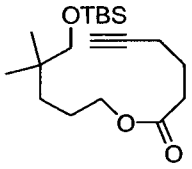


Chromic acid (11 mL of a 1 M aqueous solution, 11 mmol, 1.1 equiv) was added dropwise to a solution of 5-hexyn-1-ol (1.00g, 10.2 mmol, 1 equiv) in acetone until the green solution became and remained clear orange. The reaction mixture was back titrated with methanol (5 mL) to produce a green solution, and then the green precipitate was removed by vaccum filtration. The clear colourless filtrate was neutralized with sodium bicarbonate (7.0 g), filtered and concentrated to 10 mL. Ether (100 mL) was added and the solution was extracted with 3 M aqueous

sodium hydroxide (3 x 75 mL). The aqueous extracts were combined, acidified with concentrated hydrochloric acid (50 mL) and extracted with ether (3 x 100 mL). The organic extracts were combined, dried over magnesium sulfate and concentrated *in vacuo* to yield a clear pale green liquid. The crude liquid was purified by Kugelrohr distillation (85 °C at 9.5 mm Hg) to yield 0.96 g (84 %) of a clear colourless liquid.

IR (neat): 3299, 3105, 2946, 1706 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 10.20 (br s, 1H), 2.50 (t, *J*=7.3 Hz, 2H), 2.26 (dt, *J*=2.6, 6.9 Hz, 2H), 1.96 (t, *J*=2.6 Hz, 1H), 1.89-1.78 (m, 1H).

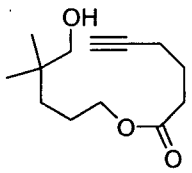
5-*tert*-Butyldimethylsiloxy-4,4-dimethylpentyl-5'-hexynoate (2.8)



1,3-Dicyclohexylcarbodiimide (1.64 g, 7.94 mmol, 1.2 equiv) was added in one portion to a solution of 1-*tert*-butyldimethylsiloxy-2,2-dimethyl-5-pentanol (**2.6**) (1.66g, 6.74 mmol, 1 equiv), hex-5-ynoic acid (**2.7**) (0.756 g, 6.74 mmol, 1 equiv) and 4-dimethylaminopyridine (89.0 mg, 0.794 mmol, 0.12 equiv) in methylene chloride (35 mL). The reaction mixture was stirred at rt for 1 h, after which silica gel (6 g) was added followed by concentration *in vacuo*. The residue was purified by column chromatography (1/19 ethyl acetate-hexanes) followed by Kugelrohr distillation (116-120 °C at 0.9 mm Hg) to yield 2.01 g (89 %) of a clear colourless liquid.

IR (neat): 3313, 2955, 2878, 2121, 1737 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.02 (t, *J*=6.8 Hz, 2H), 3.21 (s, 2H), 2.42 (t, *J*=7.4 Hz, 2H), 2.24 (dt, *J*=6.9, 2.6 Hz, 2H), 1.94 (t, *J*=2.6 Hz, 1H), 1.89-1.77 (m, 2H), 1.62-1.49 (m, 2H), 1.27-1.19 (m, 2H), 0.87 (s, 9H), 0.81 (s, 6H), 0.00 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 83.3, 71.3, 69.0, 65.4, 34.9, 34.7, 32.9, 25.8, 24.0, 23.6, 23.4, 18.2, 17.8, 5.6 ppm. Anal. Calcd for $C_{19}H_{36}O_3Si$: C, 67.01; H, 10.65. Found: C, 67.23; H, 10.72.

4,4-Dimethyl-5-hydroxypentyl-5'-hexynoate (2.9)

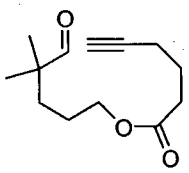


Tetrabutylammonium fluoride (10.0 mL of a 1 M solution in THF, 10.0 mmol, 2 equiv) was added to a solution of 5-*tert*-butyldimethylsiloxy-4,4-dimethylpentanyl-5'-hexynoate (**2.8**) (1.70 g, 4.99 mmol, 1 equiv)

in THF (125 mL) and the reaction mixture was stirred at rt for 20 h. The mixture was diluted with water (100 mL) and extracted with ether (3 x 100 mL). The ether extracts were combined, washed with brine (1 x 75 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (2/3 ethyl acetate-hexanes) followed by Kugelrohr distillation (146-150°C at 1.4 mmHg) to yield 1.07 g (95 %) of **2.9** as a clear colourless liquid.

IR (neat): 3454, 3300, 2958, 2880, 2119, 1734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.03 (t, *J*=6.9 Hz, 2H), 3.23 (s, 2H), 2.42 (t, *J*=7.4 Hz, 2H), 2.23 (dt, *J*=6.9, 2.6 Hz, 2H), 1.94 (t, *J*=2.6 Hz, 1H), 1.87-1.77 (m, 2H), 1.60-1.53 (m, 2H), 1.50 (br s, 1H), 1.29-1.22 (m, 2H), 0.85 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 83.3, 71.3, 69.1, 65.2, 34.8, 34.5, 32.9, 23.7, 23.6, 23.3, 17.8 ppm. Anal. Calcd for $C_{19}H_{36}O_3Si$: C, 68.99; H, 9.80. Found: C, 68.88; H, 9.84.

4,4-Dimethyl-5-oxopentyl-5'-hexynoate (2.10)

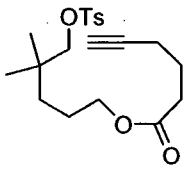


A solution of dimethylsulfoxide (0.392 mL, 5.52 mmol, 2.2 equiv) in methylene chloride (5 mL) was added to a solution of oxalyl chloride (0.241 mL, 2.77 mmol, 1.1 equiv) in methylene chloride (15 mL) at -78 °C and the reaction mixture was stirred at -78 °C for 30 min. A solution of 4,4-dimethyl-5-hydroxypentyl-5'-hexynoate (**2.9**) (0.569 g, 2.51 mmol, 1 equiv) in methylene chloride (5 mL) was added and the stirring was continued at -78 °C for 30 min before triethylamine (1.75 mL, 12.55 mmol, 5 equiv) was added dropwise. The reaction mixture was stirred for 30 min at 0 °C and then 1 h at rt. Water (30 mL) was added and the organic layer was separated and washed with 2N aqueous hydrochloric acid (30 mL), saturated aqueous sodium bicarbonate (30 mL), and brine (30 mL). The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow oil. The crude oil was purified by column chromatography (3/7 diethyl ether-petroleum ether) to yield 0.507 g (90 %) of **2.10** as a clear colourless liquid.

IR (neat): 3289, 2964, 2118, 1734, 1728 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.41 (s, 1H), 4.02 (t, *J*=5.9 Hz, 2H), 2.41 (t, *J*=7.5 Hz, 2H), 2.22 (dt, *J*=6.9, 2.44 Hz, 2H), 1.86-1.75 (m, 2H), 1.44-1.56 (m, 4H), 1.03 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.7,

173.0, 83.2, 69.1, 64.4, 45.5, 33.2, 32.8, 23.6, 23.5, 21.3, 17.8 ppm. LRMS (CI(+), ammonia) *m/z* (relative intensity): 242 (M^++18, 100). HRMS (CI(+), ammonia/methane): Calcd for $C_{13}H_{24}O_3N$ (M^++18): 242.1757. Found: 242.1768.

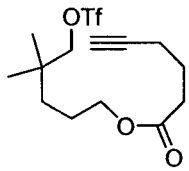
4,4-Dimethyl-5-(*p*-toluenesulfonate)hexanyl-5'-hexynoate (2.11)



Pyridine (86.5 µL, 1.07 mmol, 2 equiv) was added dropwise to a solution of 4,4-dimethyl-5-hydroxypentyl-5'-hexynoate (**2.9**) (121 mg, 0.535 mmol, 1 equiv) in methylene chloride (1 mL) followed by *p*-toluenesulfonyl chloride (112 mg, 0.588 mmol, 1.1 equiv) in 3 portions and the reaction mixture was stirred at rt for 48 h. Water (10 mL) was added and the mixture was extracted with diethyl ether (3 x 10 mL). The ether extracted were combined, washed with brine (1 x 10 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear colourless liquid. The crude liquid was purified by column chromatography (1/3 ethyl acetate-hexanes) to yield 179 mg (88 %) of **2.11** as a clear colourless liquid.

IR (neat): 3287, 2964, 2119, 1733, 1599 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J*=8.2 Hz, 2H), 7.33 (d, *J*=8.2 Hz, 2H), 3.96 (t, *J*=6.7 Hz, 2H), 3.64 (s, 2H), 2.42 (s, 3H), 2.41 (t, *J*=7.5 Hz, 2H), 2.23 (dt, *J*=7.0, 2.74 Hz, 2H), 1.94 (t, *J*=2.7 Hz, 1H), 1.85-1.76 (m, 2H), 1.41-1.50 (m, 2H), 1.26-1.19 (m, 2H), 0.84 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 144.7, 132.9, 129.8, 127.9, 83.2, 77.6, 69.1, 64.6, 34.4, 33.8, 32.8, 23.7, 23.5, 23.0, 21.6, 17.8 ppm. Anal. Calcd for $C_{20}H_{28}O_5$: C, 63.13; H, 7.42; S, 8.43. Found: C, 63.25; H, 7.25; S, 8.28.

4,4-Dimethyl-5-(trifluoromethanesulfonate)hexanyl-5'-hexynoate (2.12)

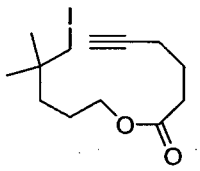


Pyridine (77.0 µL, 0.954 mmol, 1.3 equiv) was added to a solution of 4,4-dimethyl-5-hydroxypentyl-5'-hexynoate (**2.9**) (0.166 g, 0.734 mmol, 1 equiv) in methylene chloride (7 mL) at 0 °C followed by triflic anhydride (136 µL, 0.807 mmol, 1.1 equiv) dropwise and the reaction mixture was stirred at 0 °C for 30 minutes. The reaction mixture was diluted with methylene chloride (15 mL), washed with a 0.5 N aqueous solution of hydrochloric acid

(2 x 20 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (3/17 ethyl acetate-hexanes) to yield 0.236 g (90 %) of **2.12** as a clear pale yellow liquid.

IR (neat): 3306, 2967, 2120, 1734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.18 (s, 2H), 4.05 (t, *J*=6.5 Hz, 2H), 2.43 (t, *J*=7.5 Hz, 2H), 2.24 (dt, *J*=7.0, 2.7 Hz, 2H), 1.87-1.78 (m, 2H), 1.64-1.55 (m, 2H), 1.38-1.32 (m, 2H), 0.98 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 118.6 (q), 84.3, 83.2, 69.1, 64.4, 34.4, 34.3, 32.8, 23.6, 23.3, 23.0, 17.8 ppm. LRMS (CI(+), ammonia) *m/z* (relative intensity): 376 (M^++18, 100), 359 (M^++1, 1). HRMS (CI(+), ammonia/methane) *m/z* Calcd for $C_{14}H_{22}F_3O_5S$ (M^++1): 359.1141. Found: 359.1139.

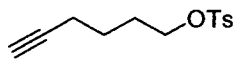
4,4-Dimethyl-5-iodohexanyl-5'-hexynoate (2.13)



Sodium iodide (35 mg, 0.23 mmol, 1.3 equiv) was added to a solution of 4,4-dimethyl-5-(trifluoromethanesulfonate)pentyl-5'-hexynoate (**2.12**) (70 mg, 0.19 mmol, 1 equiv) in acetone (2 mL) and the reaction mixture was stirred at rt for 4.5 h. Water (10 mL) was added and the reaction mixture was extracted with diethyl ether (3 x 10 mL). The ether extracts were combined, washed with brine (1 x 10 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a yellow liquid. The crude liquid was purified by column chromatography (1/19 ethyl acetate-hexanes) to yield 0.60 g (91 %) of **2.13** as a clear colourless liquid.

IR (neat): 3299, 2961, 2118, 1734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.04 (t, *J*=6.5 Hz, 2H), 3.11 (s, 2H), 2.43 (t, *J*=7.3 Hz, 2H), 2.24 (dt, *J*=7.0, 2.7 Hz, 2H), 1.87-1.78 (m, 2H), 1.59-1.50 (m, 2H), 1.38-1.32 (m, 2H), 0.98 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 83.2, 69.1, 64.6, 37.0, 33.1, 32.9, 27.1, 26.5, 23.6, 23.5, 17.8 ppm. LRMS (CI(+), ammonia) *m/z* (relative intensity): 354 (M^++18, 100). HRMS (CI(+), ammonia/methane) *m/z* Calcd for $C_{13}H_{25}INO_2$ (M^++18): 354.0930. Found: 354.0930.

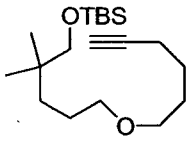
p-Toluenesulfonic acid hex-5-ynyl ester (2.14)[67]



Pyridine (1.67 mL, 20.6 mmol, 2.0 equiv) was added to a solution of 5-hexyn-1-ol (1.01 g, 10.3 mmol, 1 equiv) in methylene chloride (20 mL) at 0 °C, followed by *p*-toluenesulfonyl chloride (2.16 g, 11.3 mmol, 1.1 equiv) in 3 portions at 0 °C, and the reaction mixture was stirred at rt for 18 h. Water (50 mL) was added and the reaction mixture was extracted with diethyl ether (3 x 40 mL). The ether extracts were combined, washed with brine (1 x 50 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/19 ethyl acetate-hexanes) to yield 2.25 g (87 %) of **2.14** as a clear colourless liquid.

IR (neat): 3294, 1359 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, *J*=8.3 Hz, 2H), 7.35 (d, *J*=8.5 Hz, 2H), 4.06 (t, *J*=6.2 Hz, 2H), 2.45 (s, 3H), 2.17 (dt, *J*=6.8, 2.7 Hz, 2H), 1.92 (t, *J*=2.7 Hz, 1H), 1.81-1.75 (m, 2H), 1.58-1.53.

5-*tert*-Butyldimethylsiloxy-4,4-dimethylpentanylhex-5'-ynyl ether (2.15)

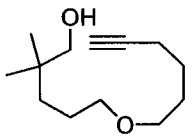


A solution of *tert*-butyldimethylsiloxy-2,2-dimethyl-5-pentanol (**2.6**) (2.20 g, 8.92 mmol, 1 equiv) in dimethylformamide (5 mL) was added dropwise to a slurry of 60% dispersion oil sodium hydride (0.482 g, 12.0 mmol, 1.35 equiv) in dimethylformamide (25 mL) and the mixture was stirred at 0 °C for 30 minutes. A solution of *p*-toluenesulfonic acid hex-5-ynyl ester (**2.14**) (2.25 g, 8.92 mmol, 1 equiv) in dimethylformamide (5 mL) was added and the reaction mixture was stirred at rt for 18 h. Water (100 mL) was added and the solution was extracted with diethyl ether (3 x 60 mL). The ether extracts were combined, washed with brine (2 x 30 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow oil. The crude oil was purified by column chromatography (1/33 ethyl acetate-hexanes) to yield 2.18 g (75 %) of **2.15** as a clear colourless oil.

IR (neat): 3315, 2953, 2857, 2120. ^1H NMR (400 MHz, $CDCl_3$): δ 3.40 (t, *J*=6.2 Hz, 2H), 3.34 (t, *J*=7.0 Hz, 2H), 3.21 (s, 2H), 2.20 (dt, *J*=6.7, 2.7 Hz, 2H), 1.92 (t, *J*=2.7 Hz, 1H), 1.71-1.45 (m, 6H), 1.23-1.17 (m, 2H), 0.87 (s, 9H), 0.80 (s, 6H), 0.00 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 84.4, 71.9, 71.5, 70.1, 68.3, 35.0, 34.9, 28.8, 25.9, 25.3,

24.4, 24.0, 18.3, 18.2, -5.5 ppm. LRMS (CI(+), ammonia) *m/z* (relative intensity): 345 (M^++19, 11), 344 (M^++18, 38), 327 (M^++1, 100). HRMS (CI(+), ammonia/methane) *m/z* Calc'd for $C_{19}H_{39}O_2Si$ (M^++1): 327.2720. Found: 327.2721.

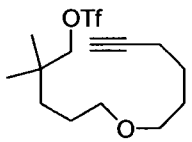
4,4-Dimethyl-5-hydroxypentylhex-5'-ynyl ether (2.16)



Tetrabutylammonium fluoride (5.42 mL of a 1 M solution in THF, 5.42 mmol, 2 equiv) was added to a solution of 5-*tert*-butyldimethylsiloxy-4,4-dimethylpentanylhex-5'-ynyl ether (**2.15**) (0.885 g, 2.71 mmol, 1 equiv) in THF (30 mL) and the reaction mixture was stirred at rt for 14 h. The mixture was diluted with water (50 mL) and extracted with ether (3 x 60 mL). The ether extracts were combined, washed with brine (1 x 30 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/3 ethyl acetate-hexanes) followed by Kugelrohr distillation (115-120°C at 0.9 mmHg) to yield 0.542 g (95 %) of **2.16** as a clear colourless liquid.

IR (neat): 3418, 3310, 2948, 2867, 2120 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.41 (t, *J*=6.4 Hz, 2H), 3.37 (t, *J*=6.6 Hz, 2H), 3.30 (s, 2H), 2.20 (dt, *J*=6.9, 2.7 Hz, 2H), 1.92 (t, *J*=2.7 Hz, 1H), 1.71-1.48 (m, 7H), 1.29-1.24 (m, 2H), 0.85 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 84.3, 71.6, 71.4, 70.3, 68.4, 34.9, 34.6, 28.7, 25.2, 24.1, 23.9, 18.2 ppm. Anal. Calcd for $C_{13}H_{22}O_3$: C, 73.54; H, 11.39. Found: C, 73.62; H, 11.54.

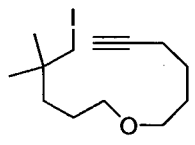
4,4-Dimethyl-5-(trifluoromethanesulfonate)pentanylhex-5'-ynyl ether (2.17)



Pyridine (0.131 mL, 1.62 mmol, 1.3 equiv) was added to a solution of 5-*tert*-butyldimethylsiloxy-4,4-dimethylpentanylhex-5'-ynyl ether (**2.15**) (0.265 g, 1.25 mmol, 1 equiv) in methylene chloride (12 mL) at 0°C followed by trifluoromethanesulfonic anhydride (231 µL, 1.37 mmol, 1.1 equiv) dropwise and the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with methylene chloride (25 mL), washed with a 0.5 N aqueous solution of hydrochloric acid (2 x 30 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/9 ethyl acetate-hexanes) to yield 0.408 g (95 %) of **2.12** as a clear colourless liquid.

IR (neat): 3307, 2947, 2865, 2118 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.19 (s, 2H), 3.40 (t, *J*=6.4 Hz, 2H), 3.37 (t, *J*=7.0 Hz, 2H), 2.20 (dt, *J*=6.9, 2.5 Hz, 2H), 1.92 (t, *J*=2.6 Hz, 2H) 1.72-1.47 (m, 5H), 1.38-1.31 (m, 2H), 0.98 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 120.8 (q), 84.7, 84.3, 70.9, 70.3, 68.4, 34.6, 34.4, 28.7, 25.2, 24.0, 23.4, 18.2 ppm. LRMS (CI(+), ammonia) m/z (relative intensity): 362 (M^++18, 100), 345 (M^++1, 6). HRMS (CI(+), ammonia/methane) m/z Calcd for $C_{14}H_{23}F_3O_4S$ (M^++1): 345.1347. Found: 345.1348.

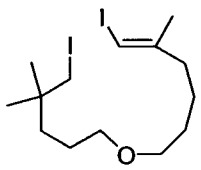
4,4-Dimethyl-5-iodopentanylhex-5-ynyl ether (2.18)



Sodium iodide (0.157 g, 1.05 mmol, 1.2 equiv) was added to a solution of 4,4-dimethyl-5-(trifluoromethanesulfonate)pentanylhex-5'-ynyl ether (**2.16**) (0.300 g, 0.871 mmol, 1.2 equiv) in acetone (9 mL) and the reaction mixture was stirred at rt for 3 h. Water (30 mL) was added and the mixture was extracted with diethyl ether (3 x 25 mL). The ether extracts were combined, washed with brine (1 x 20 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a yellow liquid. The crude liquid was purified by column chromatography (1/49 ethyl acetate-hexanes) to yield 0.269 g (96 %) of **2.18** as a clear pale yellow liquid.

IR (neat): 3303, 2944, 2860, 2117. ^1H NMR (400 MHz, $CDCl_3$): δ 3.41 (t, *J*=6.2 Hz, 2H), 3.37 (t, *J*=6.7 Hz, 2H), 3.14 (s, 2H), 2.21 (dt, *J*=7.1, 2.7 Hz, 2H), 1.93 (t, *J*=2.7 Hz, 1H), 1.72-1.45 (m, 6H), 1.37-1.31 (m, 2H), 1.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 84.4, 71.2, 70.2, 68.4, 37.2, 33.2, 28.8, 26.6, 25.2, 24.7, 24.2, 18.2 ppm. LRMS (CI(+), ammonia) *m/z* (relative intensity): 341 (M^++19, 17), 340 (M^++18, 100), 323 (M^++1, 15). HRMS (CI(+), ammonia/methane) m/z Calcd for $C_{13}H_{24}IO$ (M^++1): 323.0873. Found: 323.0871.

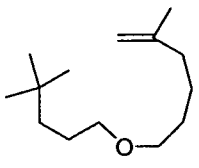
(*E*)-4,4-Dimethyl-5-iodopentanyl-6'-iodo-5'-methylhex-5'-enyl ether (2.23)



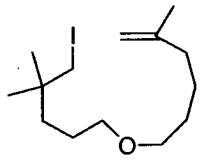
Trimethylaluminum (2.29 mL of a 2 M solution in hexanes, 4.57 mmol, 3 equiv) was added dropwise to a solution of bis(cyclopentadienyl)zirconium dichloride (0.444 g, 1.52 mmol, 1 equiv) in methylene chloride (17 mL) at -20 °C and the mixture was stirred at -20 °C for 10 minutes to yield a pale yellow solution. A solution of 4,4-dimethyl-5-iodopentanyl-5'-hexynyl ether (**2.18**) (0.491 g, 1.52 mmol, 1 equiv) in methylene chloride (2 mL) was added at -20 °C and the reaction mixture was stirred at rt for 3 h. The reaction mixture was then cooled to -30 °C and a solution of iodine (0.424 g, 1.67 mmol, 1.1 equiv) in THF (2 mL) was added dropwise. The reaction mixture was warmed to rt over 1 h, water (20 mL) was slowly added and the mixture was extracted with diethyl ether (3 x 20 mL). The ether extracts were combined, dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow oil. The oil was purified by column chromatography (1/4 ethyl acetate-hexanes) to yield 0.588 g (83 %) of **2.23** as a clear colourless liquid.

IR (neat): 2941, 2858, 1617 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.85 (s, 1H), 3.40-3.32 (m, 4H), 3.13 (s, 2H), 2.20 (t, *J*=6.7 Hz, 2H), 1.79 (s, 3H), 1.54-1.43 (m, 6H), 1.36-1.30 (m, 2H), 1.00 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.9, 74.7, 71.2, 70.1, 39.3, 37.2, 33.2, 29.1, 26.6, 24.6, 24.3, 24.2, 23.8 ppm. LRMS (CI(+), ammonia) m/z (relative intensity): 382 (M^++18, 100). HRMS (CI(+), ammonia/methane) m/z Calcd for $C_{14}H_{30}I_2NO$ (M^++18): 482.0417. Found: 482.0416.

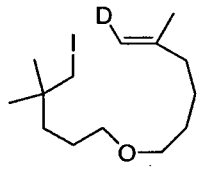
General Procedure for the Attempted Tandem Carboalumination-Negishi Cross-coupling Reactions of 4,4-Dimethyl-5-iodopentanylhex-5'-ynyl ether (2.18)



4,4-Dimethylpentanyl-5'-methylhex-5'-enyl ether (**2.24**)



4,4-Dimethyl-5-iodopentanyl-5'-methylhex-5'-enyl ether (**2.25**)



4,4-Dimethyl-5-iodopentanyl-6'-deutero-5'-methylhex-5'-enyl ether (**2.26**)

a) Reaction of 4,4-dimethyl-5-iodopentanylhex-5'-ynyl ether (**2.18**) using $Ni(acac)_2$ and Et_2Zn (entry 1, Table 2.2)

Trimethylaluminum in hexanes (198 µL of a 2 M solution in hexanes, 0.397 mmol, 3 equiv) was added dropwise to a solution of bis(cyclopentadienyl)zirconium dichloride (39 mg, 0.132 mmol, 1 equiv) in methylene chloride (1 mL) at -20 °C and the mixture was stirred at -20 °C for 10 minutes to yield a pale yellow solution. To this solution at -20 °C was added a solution of 4,4-dimethyl-5-iodopentanylhex-5'-ynyl ether (**2.18**) (43 mg, 0.132 mmol, 1 equiv) in methylene chloride (0.5 mL) and the reaction mixture was stirred at rt for 3 h. The reaction mixture was then cooled to -78 °C and diethylzinc (198 µL of a 1 M solution in hexane, 0.198 mmol, 1.5 equiv) was added dropwise and the mixture was warmed to rt over 30 minutes. The vinylzinc solution was added dropwise to a solution of nickel(II) acetylacetonate (2 mg, 0.0066 mmol, 0.05 equiv) in 1:3 NMP/THF (13 mL) at -78 °C and the reaction mixture was slowly warmed to rt over 1 h and then stirred at 80 °C for 3.5 h. A saturated aqueous solution of ammonium chloride (10 mL) was slowly added and the reaction mixture was extracted with diethyl ether (3 x 10 mL). The ether extracts were combined, washed with brine (10 mL), dried over magnesium sulfate and concentrated to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/49 ethyl acetate-hexanes) to yield 20 mg (70 %) of **2.24** as a clear colourless liquid.

b) Reaction of 4,4-dimethyl-5-iodopentanylhex-5'-ynyl ether (**2.18**) using Et_2Zn (entry 2, Table 2.2)

Trimethylaluminum in hexanes (188 µL of a 2 M solution in hexanes, 0.375 mmol, 3 equiv) was added dropwise to a solution of bis(cyclopentadienyl)zirconium dichloride (37 mg, 0.125 mmol, 1 equiv) in methylene chloride (1 mL) at -20 °C and the mixture was stirred at -20 °C for 10 minutes to yield a pale yellow solution. To this solution at -20 °C was added a solution of 4,4-dimethyl-5-iodopentanylhex-5'-ynyl ether (**2.18**) (40 mg, 0.125 mmol, 1 equiv) in methylene chloride (0.5 mL) and the reaction mixture was stirred at rt for 3 h. The reaction mixture was then cooled to -78 °C and diethylzinc (188 µL of a 1 M solution in hexane, 0.188 mmol, 1.5 equiv) was added dropwise and the mixture was warmed to rt over 30 minutes. The vinylzinc solution was added dropwise to a solution of 1:3 NMP/THF (13 mL) at -78 °C and the reaction mixture was slowly warmed to rt over 1 h and then stirred at 80 °C for 3.5 h. A saturated aqueous solution of ammonium chloride (10 mL) was slowly added and the reaction mixture was extracted with diethyl ether (3 x 10 mL). The ether extracts were combined, washed with brine (10 mL), dried over magnesium sulfate and concentrated to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/49 ethyl acetate-hexanes) to yield 34 mg (79 %) of **2.25** as a clear colourless liquid.

c) Reaction of 4,4-dimethyl-5-iodopentanylhex-5'-ynyl ether (**2.18**) using $Ni(acac)_2$ and Et_2Zn (entry 3, Table 2.2)

Trimethylaluminum in hexanes (188 µL of a 2 M solution in hexanes, 0.376 mmol, 3 equiv) was added dropwise to a solution of bis(cyclopentadienyl)zirconium dichloride (37 mg, 0.125 mmol, 1 equiv) in methylene chloride (1 mL) at -20 °C and the mixture was stirred at -20 °C for 10 minutes to yield a pale yellow solution. To this solution at -20 °C was added a solution of 4,4-dimethyl-5-iodopentanylhex-5'-ynyl ether (**2.18**) (40 mg, 0.125 mmol, 1 equiv) in methylene chloride (0.5 mL) and the reaction mixture was stirred at rt for 3 h. The reaction mixture was then cooled to -78 °C and diethylzinc (62.5 µL of a 1 M solution in hexane, 0.0625 mmol, 0.5 equiv) was added dropwise and the mixture was warmed to rt over 30 minutes. The vinylzinc solution was

added dropwise to a solution of nickel(II) acetylacetonate (2 mg, 0.0066 mmol, 0.05 equiv) in 1:3 NMP/THF (13 mL) at -78 °C and the reaction mixture was slowly warmed to rt over 1 h and then stirred at 80 °C for 3.5 h. A saturated aqueous solution of ammonium chloride (10 mL) was slowly added and the reaction mixture was extracted with diethyl ether (3 x 10 mL). The ether extracts were combined, washed with brine (10 mL), dried over magnesium sulfate and concentrated to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/49 ethyl acetate-hexanes) to yield 10 mg (37 %) of **2.24** as a clear colourless liquid and 10 mg (23 %) of **2.25** as a clear colourless liquid.

d) Reaction of 4,4-dimethyl-5-iodopentanylhex-5'-ynyl ether (**2.18**) using $Ni(acac)_2$ (entry 4, Table 2.2)

Trimethylaluminum in hexanes (192 µL of a 2 M solution in hexanes, 0.384 mmol, 3 equiv) was added dropwise to a solution of bis(cyclopentadienyl)zirconium dichloride (37 mg, 0.128 mmol, 1 equiv) in methylene chloride (1 mL) at -20 °C and the mixture was stirred at -20 °C for 10 minutes to yield a pale yellow solution. To this solution at -20 °C was added a solution of 4,4-dimethyl-5-iodopentanylhex-5'-ynyl ether (**2.18**) (41 mg, 0.128 mmol, 1 equiv) in methylene chloride (0.5 mL) and the reaction mixture was stirred at rt for 3 h. The vinylalane solution was added dropwise to a solution of nickel(II) acetylacetonate (2 mg, 0.0066 mmol, 0.05 equiv) in 1:3 NMP/THF (13 mL) at -78 °C and the reaction mixture was slowly warmed to rt over 1 h and then stirred at 80 °C for 3.5 h. A saturated aqueous solution of ammonium chloride (10 mL) was slowly added and the reaction mixture was extracted with diethyl ether (3 x 10 mL). The ether extracts were combined, washed with brine (10 mL), dried over magnesium sulfate and concentrated to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/49 ethyl acetate-hexanes) to yield 35 mg (82 %) of **2.25** as a clear colourless liquid.

e) Reaction of 4,4-dimethyl-5-iodopentanylhex-5'-ynyl ether (**2.18**) using $Ni(acac)_2$ and Et_2Zn (entry 5, Table 2.2)

Trimethylaluminum in hexanes (197 µL of a 2 M solution in hexanes, 0.395 mmol, 3 equiv) was added dropwise to a solution of bis(cyclopentadienyl)zirconium dichloride (39 mg, 0.132 mmol, 1 equiv) in methylene chloride (1 mL) at -20 °C and the mixture was stirred at -20 °C for 10 minutes to yield a pale yellow solution. To this solution at -20 °C was added a solution of 4,4-dimethyl-5-iodopentanylhex-5'-ynyl ether (**2.18**) (42 mg, 0.132 mmol, 1 equiv) in methylene chloride (0.5 mL) and the reaction mixture was stirred at rt for 3 h. The reaction mixture was then cooled to -78 °C and diethylzinc (198 µL of a 1 M solution in hexane, 0.198 mmol, 1.5 equiv) was added dropwise and the mixture was warmed to rt over 30 minutes. *n*-Butyllithium (8.3 µL of a 1.60 M solution in hexane, 0.013 mol, 0.1 equiv) was added dropwise to a solution of [1,1'-bis(diphenylphosphino)ferrocene]dichloronickel(II) (5 mg, 0.0066 mmol, 0.05 equiv) in THF (1 mL) and this mixture was stirred at rt for 15 min. This solution was then added to a solution of 1:3 NMP/THF (13 mL) at -78 °C followed by the dropwise addition of the vinylzinc solution, and the reaction mixture was slowly warmed to rt over 1 h and then stirred at 80 °C for 3.5 h. A saturated aqueous solution of ammonium chloride (10 mL) was slowly added and the reaction mixture was extracted with diethyl ether (3 x 10 mL). The ether extracts were combined, washed with brine (10 mL), dried over magnesium sulfate and concentrated to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/49 ethyl acetate-hexanes) to yield 18 mg (64 %) of **2.24** as a clear colourless liquid.

f) Reaction of 4,4-dimethyl-5-iodopentanylhex-5'-ynyl ether (**2.18**) using $Ni(acac)_2$ and Et_2Zn followed by quenching with deuterium oxide (entry 6, Table 2.2)

Trimethylaluminum in hexanes (165 µL of a 2 M solution in hexanes, 0.331 mmol, 3 equiv) was added dropwise to a solution of bis(cyclopentadienyl)zirconium dichloride (32 mg, 0.110 mmol, 1 equiv) in methylene chloride (1 mL) at -20 °C and the mixture was stirred at -20 °C for 10 minutes to yield a pale yellow solution. To this solution at -20 °C was added a solution of 4,4-dimethyl-5-iodopentanylhex-5'-ynyl ether

(**2.18**) (36 mg, 0.110 mmol, 1 equiv) in methylene chloride (0.5 mL) and the reaction mixture was stirred at rt for 3 h. The reaction mixture was then cooled to -78 °C and diethylzinc (165 µL of a 1 M solution in hexane, 0.165 mmol, 1.5 equiv) was added dropwise and the mixture was warmed to rt over 30 minutes. The vinylzinc solution was added dropwise to a solution of nickel(II) acetylacetonate (1 mg, 0.0050 mmol, 0.05 equiv) in 1:3 NMP/THF (11 mL) at -78 °C and the reaction mixture was slowly warmed to rt over 1 h and then stirred at 80 °C for 3.5 h. Deuterium oxide (5 mL) was slowly added and the reaction mixture was extracted with diethyl ether (3 x 10 mL). The ether extracts were combined, washed with brine (10 mL), dried over magnesium sulfate and concentrated to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/49 ethyl acetate-hexanes) to yield 18 mg (77 %) of **2.24** as a clear colourless liquid.

g) Reaction of 4,4-dimethyl-5-iodopentanylhex-5'-ynyl ether (**2.18**) using $Ni(acac)_2$ and Me_2Zn followed by quenching with deuterium oxide (entry 7, Table 2.2)

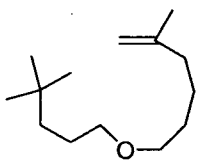
Trimethylaluminum in hexanes (314 µL of a 2 M solution in hexanes, 0.628 mmol, 3 equiv) was added dropwise to a solution of bis(cyclopentadienyl)zirconium dichloride (61 mg, 0.209 mmol, 1 equiv) in methylene chloride (1.6 mL) at -20 °C and the mixture was stirred at -20 °C for 10 minutes to yield a pale yellow solution. To this solution at -20 °C was added a solution of 4,4-dimethyl-5-iodopentanylhex-5'-ynyl ether (**2.18**) (68 mg, 0.209 mmol, 1 equiv) in methylene chloride (1 mL) and the reaction mixture was stirred at rt for 3 h. The reaction mixture was then cooled to -78 °C and dimethylzinc (157 µL of a 2 M solution in toluene, 0.314 mmol, 1.5 equiv) was added dropwise and the mixture was warmed to rt over 30 minutes. The vinylzinc solution was added dropwise to a solution of nickel(II) acetylacetonate (3 mg, 0.0105 mmol, 0.05 equiv) in 1:3 NMP/THF (20 mL) at -78 °C and the reaction mixture was slowly warmed to rt over 1 h and then stirred at 80 °C for 3.5 h. Deuterium oxide (5 mL) was slowly added and the reaction mixture was extracted with diethyl ether (3 x 10 mL). The ether extracts were combined, washed with brine (10 mL), dried over magnesium sulfate and concentrated to yield a clear yellow liquid. The crude liquid was purified by column

chromatography (1/49 ethyl acetate-hexanes) to yield 37 mg (82 %) of **2.26** as a clear colourless liquid.

h) Reaction of 4,4-dimethyl-5-iodopentanylhex-5'-ynyl ether (**2.18**) using Me_2Zn (entry 8, Table 2.2)

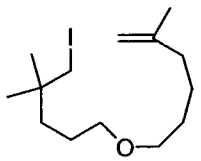
Trimethylaluminum in hexanes (330 µL of a 2 M solution in hexanes, 0.659 mmol, 3 equiv) was added dropwise to a solution of bis(cyclopentadienyl)zirconium dichloride (64 mg, 0.220 mmol, 1 equiv) in methylene chloride (1.8 mL) at -20 °C and the mixture was stirred at -20 °C for 10 minutes to yield a pale yellow solution. To this solution at -20 °C was added a solution of 4,4-dimethyl-5-iodopentanylhex-5'-ynyl ether (**2.18**) (71 mg, 0.220 mmol, 1 equiv) in methylene chloride (1 mL) and the reaction mixture was stirred at rt for 3 h. The reaction mixture was then cooled to -78 °C and dimethylzinc (165 µL of a 2 M solution in toluene, 0.330 mmol, 1.5 equiv) was added dropwise and the mixture was warmed to rt over 30 minutes. The vinylzinc solution was added dropwise to a solution of 1:3 NMP/THF (21 mL) at -78 °C and the reaction mixture was slowly warmed to rt over 1 h and then stirred at 80 °C for 3.5 h. A saturated aqueous solution of ammonium chloride (10 mL) was slowly added and the reaction mixture was extracted with diethyl ether (3 x 10 mL). The ether extracts were combined, washed with brine (10 mL), dried over magnesium sulfate and concentrated to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/49 ethyl acetate-hexanes) to yield 60 mg (80 %) of **2.26** as a clear colourless liquid.

4,4-Dimethylpentanyl-5'-methylhex-5'-enyl ether (**2.24**)



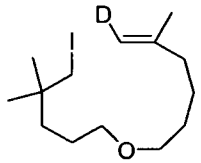
IR (neat): 2952, 2863, 1651 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.69-4.64 (m, 2H), 3.39 (t, *J*=6.4 Hz, 2H), 3.35 (t, *J*=7.0 Hz, 2H), 2.01 (t, *J*=7.3 Hz, 2H), 1.69 (s, 3H), 1.58-1.42 (m, 6H), 1.21-1.14 (m, 2H), 0.86 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.9, 109.8, 71.8, 70.7, 40.3, 37.6, 30.1, 29.4, 29.3, 25.0, 24.2, 22.3 ppm. LRMS (EI) m/z (relative intensity): 212 (M^+, 5).

4,4-Dimethyl-5-iodopentanyl-5'-methylhex-5'-enyl ether (**2.25**)



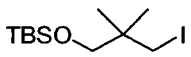
IR (neat): 2952, 2863, 1649 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.69-4.63 (m, 2H), 3.43-3.32 (m, 4H), 3.14 (s, 2H), 2.00 (t, *J*=7.1 Hz, 2H), 1.69 (s, 3H), 1.58-1.42 (m, 6H), 1.38-1.30 (m, 2H), 0.86 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.8, 109.8, 71.2, 70.8, 37.6, 37.2, 33.2, 29.3, 26.6, 24.7, 24.2, 24.1, 22.3 ppm. LRMS (EI) m/z (relative intensity): 338 (M^+, 1).

4,4-Dimethyl-5-iodopentanyl-6'-deutero-5'-methylhex-5'-enyl ether (**2.26**)



IR (neat): 2952, 2863, 1649 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.63 (s, 1H), 3.42-3.34 (m, 4H), 3.13 (s, 2H), 2.00 (t, *J*=7.4 Hz, 2H), 1.69 (s, 3H), 1.61-1.42 (m, 6H), 1.37-1.30 (m, 2H), 1.00 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.7, 109.6 (t, *J*= 23.7), 71.2, 70.8, 37.5, 37.2, 33.2, 29.3, 26.6, 24.7, 24.2, 24.1, 22.3 ppm. LRMS (EI) m/z (relative intensity): 339 (M^+, 1)

3-*tert*-Butyldimethylsiloxy-2,2-dimethyl-1-iodopropane (2.28)

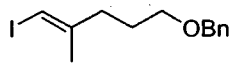


Pyridine (1.66 mL, 20.5 mmol, 1.3 equiv) was added dropwise to a solution of 3-*tert*-butyldimethylsiloxy-2,2-dimethyl-propan-1-ol (**2.27**) (3.46 g, 15.8 mmol, 1 equiv) in methylene chloride (160 mL) at 0 °C followed by the dropwise addition of trifluoromethansulfonic anhydride (2.93 mL, 17.4 mmol, 1.1 equiv) and the reaction mixture was stirred at 0 °C for 20 min. The reaction mixture was then diluted with methylene chloride (100 mL), washed with a 0.5 N aqueous solution of hydrochloric acid, dried over magnesium sulfate and concentrated *in vacuo* to yield a yellow liquid. The crude liquid was dissolved in acetone (160 mL), sodium iodide (2.61 g, 17.4 mmol, 1.1 equiv) was added and the reaction mixture was stirred at rt for 3 h. Water (100 mL) was added and the reaction mixture was extracted with diethyl ether (3 x 50 mL). The ether extracts were combined, washed with brine (1 x 50 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a yellow liquid. The crude liquid

was purified by column chromatography (hexanes) and by Kugelrohr distillation (109-111 °C at 20 mm Hg) to yield 3.39 g (65 %) of **2.28** as a clear colourless liquid.

IR (neat): 2929, 2956, 2888, 2857 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.33 (s, 2H), 3.20 (s, 2H), 0.98 (s, 6H), 0.88 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 69.8, 35.8, 25.9, 23.9, 20.9, 18.2, -5.5 ppm. LRMS (EI) m/z (relative intensity): 328 (M^+, 3).

5-Benzyloxy-1-iodo-2-methylpent-1-ene (2.31)



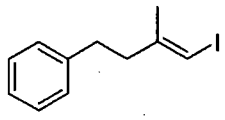
Trimethylaluminum in hexanes (23.0 mL of a 2 M solution in hexanes, 46.0 mmol, 3 equiv) was added dropwise to a solution of bis(cyclopentadienyl)zirconium dichloride (1.12 g, 3.83 mmol, 0.25 equiv) in methylene chloride (50 mL) at -20 °C and the mixture was stirred at -20 °C for 10 minutes to yield a pale yellow solution. A solution of 4-pentyn-1-ol (1.29 g, 15.3 mmol, 1 equiv) in methylene chloride (5 mL) was added dropwise at -20 °C and the reaction mixture was stirred at rt for 18 h. The reaction mixture was then cooled to -30 °C and a solution of iodine (4.26 g, 16.8 mmol, 1.1 equiv) in THF (25 mL) was added dropwise. The reaction mixture was warmed to 0 °C over 30 min and water (2.5 mL) was slowly added. The resulting slurry was diluted with hexanes (50 mL) and then filtered through a pad of Celite. The filtrate was washed with water (50 mL) and brine (50 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/3 ethyl acetate-hexanes) to yield 2.73 g (79 %) of (*E*)-5-iodo-4-methylpent-4-en-1-ol as a clear pale yellow liquid.

A solution of the 5-iodo-4-methylpent-4-en-1-ol (1.90 g, 8.40 mmol, 1 eq) in DMF (5 mL) was slowly added to a suspension of sodium hydride (0.840 g of a 60 % wt in mineral oil, 12.6 mmol, 1.5 eq) in DMF (10 mL) at 0 °C and the mixture was stirred at 0 °C for 45 min. Benzylbromide (1.50 mL, 12.6 mmol, 1.5 eq) was added dropwise at 0 °C and the reaction mixture was stirred for 45 min at 0 °C. The reaction mixture was diluted with ether (50 mL), washed with a 2N aqueous solution of hydrochloric acid (50 mL) followed by a saturated aqueous solution of sodium chloride (50 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude

liquid was purified by column chromatography (1/19 ethyl acetate-hexanes) to yield 2.45 g (92 %) of **2.31** as a clear colourless liquid.

IR (neat): 2942, 2855, 1618 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.38-7.24 (m, 5H), 5.86 (s, 1H), 4.47 (s, 2H), 3.43 (t, *J*=6.2 Hz, 2H), 2.29 (t, *J*=6.9 Hz, 2H), 1.82 (s, 3H), 1.79-1.67 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.5, 138.4, 128.4, 127.8, 127.6, 74.9, 73.0, 69.3, 36.1, 27.8, 23.8 ppm. LRMS (EI) m/z (relative intensity): 316 (M^+, 5).

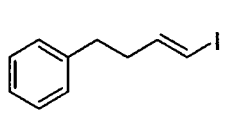
(*E*)-1-iodo-2-methyl-4-phenylbut-1-ene (2.33)



Trimethylaluminum in hexanes (15.4 mL of a 2 M solution in hexanes, 30.7 mmol, 2 equiv) was added dropwise to a solution of bis(cyclopentadienyl)zirconium dichloride (1.13 g, 3.85 mmol, 0.25 equiv) in methylene chloride (40 mL) at -20 °C and the mixture was stirred at -20 °C for 10 minutes to yield a pale yellow solution. A solution of 4-phenyl-1-butyne (**2.32**) (2.00 g, 15.4 mmol, 1 equiv) in methylene chloride (10 mL) was added dropwise at -20 °C and the reaction mixture was stirred at rt for 16 h. The reaction mixture was then cooled to -30 °C and a solution of iodine (4.30 g, 16.9 mmol, 1.1 equiv) in THF (25 mL) was added dropwise. The reaction mixture was warmed to 0 °C over 30 min, water (5 mL) was slowly added. The resulting slurry was diluted with hexanes (50 mL) and then filtered through a pad of Celite. The filtrate was washed with water (50 mL) and brine (50 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (hexanes) to yield 3.19 g (76 %) of **2.33** as a clear colourless liquid.

IR (neat): 3062, 2926, 2857, 1604 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.32-7.12 (m, 5H), 5.89 (s, 2H), 2.74 (t, *J*=7.90 Hz, 2H), 2.49 (t, *J*=7.90 Hz, 2H), 1.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.1, 147.2, 128.4, 128.3, 126.0, 75.4, 41.4, 34.3, 24.1. LRMS (EI) m/z (relative intensity): 272 (M^+, 2).

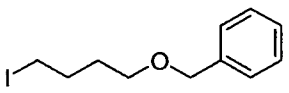
(*E*)-1-iodo-4-phenylbut-1-ene (2.34)[68]



diisobutylaluminum hydride (6.65 mL of a 1.0 M solution in hexanes, 6.65 mmol, 1 equiv) was added dropwise to a solution of 4-phenyl-1-butyne (**2.32**) (0.866 g, 6.65 mmol, 1 eq) in hexane (65 mL) at 0 °C and the reaction mixture was stirred at rt for 1 h, and then refluxed for 4 h. The reaction mixture was then cooled to -40 °C and a solution of iodine (1.69 g, 6.65 mmol, 1.1 equiv) in THF (5 mL) was added dropwise. The reaction mixture was warmed to rt over 30 h, water (20 mL) was slowly added and the mixture was extracted with ether (3 x 40 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (30 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield yellow liquid. The crude liquid was purified by column chromatography (hexanes) to yield 1.35 g (78 %) of **2.34** as a clear colourless liquid.

IR (neat): 3062, 3026, 2925, 1604 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.32-7.12 (m, 5H), 6.59-6.48 (m, 1H), 6.01 (dt, *J*=12.3, 1.5 Hz, 1H), 2.70 (t, *J*=7.7 Hz, 2H), 2.40-2.30 (m, 2H).

1-Benzyloxy-4-iodobutane (2.38)[69]

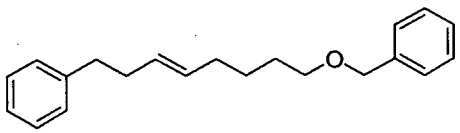


Iodine (1.59 g, 6.28 mmol, 1.1 eq) was added in one portion to a solution of imidazole (1.17 g, 17.1 mmol, 3 eq) and triphenylphosphine (1.65 g, 6.28 mmol, 1.1 equiv) in methylene chloride (35 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 10 min. A solution of 1-benzyloxybutan-4-ol (**2.37**) (1.03 g, 5.71 mmol, 1 equiv) in methylene chloride (15 mL) was added dropwise and the reaction mixture was stirred at rt overnight. A saturated aqueous solution of sodium thiosulfate (2 mL) was added, followed by water (15 mL) and the mixture was extracted with methylene chloride (2 x 15 mL). The methylene chloride extracts were combined, dried over magnesium sulfate and concentrated *in vacuo* to yield a yellow solid. The solid was triturated in petroleum ether (15 mL), filtered over a bed of Celite and the filtrate was concentrated *in vacuo* to yield a clear pale yellow liquid. The crude liquid was purified by column

chromatography (1/19 ethyl acetate-hexanes) to yield 1.48 g (89 %) of **2.38** as a clear colourless liquid.

IR (neat): 2856, 2792 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.37-7.23 (m, 5H), 4.48 (s, 2H), 3.48 (t, *J*=6.16 Hz, 2H), 3.20 (t, *J*=6.94 Hz, 2H), 1.99-1.87 (m, 2H), 1.76-1.65 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 128.4, 127.7, 127.6, 72.9, 69.0, 30.6, 30.4, 6.8. LRMS (EI) m/z (relative intensity): 274 (M^+, 6).

General Procedure for the Cross-Coupling Between Alkyl Iodides and Vinylzincs Obtained from Vinyl Iodides



(*E*)-8-Benzyloxy-1-phenyloct-3-ene
(**2.39**)

General procedure (Table 2.3)

n-Butyllithium (solution in hexanes) was added dropwise to a solution of the vinyl halide in 1:4 ether/THF (0.24 M) at -100 °C. A white precipitate formed immediately and stirring was continued at -100 °C for 20 min, after which a solution of the zinc halide in THF was added dropwise, and the reaction mixture was warmed to rt. The resulting vinylzinc solution was then added dropwise to a solution of the alkyl halide, the catalyst, and the additive in 1:1 NMP/THF (0.27 M) at -78 °C and the resulting reaction mixture was warmed to rt and stirred at this temperature until progression of the reaction cessed. A saturated aqueous solution of ammonium chloride was slowly added and the reaction mixture was extracted with diethyl ether. The ether extracts were combined, washed with brine, dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography.

a) Cross-coupling between (*E*)-1-iodo-4-phenylbut-1-ene (**2.34**) and 1-benzyloxy-4-iodobutane (**2.38**) using $Ni(acac)_2$ (entry 8, Table 2.3)

The general procedure was followed in which the vinylzinc was prepared from (*E*)-1-iodo-4-phenylbut-1-ene (**2.34**) (70 mg, 0.271 mmol, 1 equiv) in 1:4 ether/THF (1 mL) using *n*-butyllithium (0.197 mL of a 1.51 M solution in hexanes, 0.298 mmol, 1.1 equiv) and zinc chloride (41 mg, 0.298 mmol, 1.1 equiv). This vinylzinc solution was added to a solution containing 1-benzyloxy-4-iodobutane (**2.38**) (87 mg, 0.271 mmol, 1 equiv) and $Ni(acac)_2$ (7 mg, 0.0271 mmol, 0.1 equiv) in 1:1 NMP/THF (1 mL). Purification by column chromatography (hexanes) yielded 5 mg (6 %) of **2.39** as a clear colourless liquid.

b) Cross-coupling between (*E*)-1-iodo-4-phenylbut-1-ene (**2.34**) and 1-benzyloxy-4-iodobutane (**2.38**) using $Pd(OAc)_2$ and PCy_3 (entry 10, Table 2.3)

The general procedure was followed in which the vinylzinc was prepared from (*E*)-1-iodo-4-phenylbut-1-ene (**2.34**) (70 mg, 0.271 mmol, 1 equiv) in 1:4 ether/THF (1 mL) using *n*-butyllithium (0.184 mL of a 1.62 M solution in hexanes, 0.298 mmol, 1.1 equiv) and zinc chloride (41 mg, 0.298 mmol, 1.1 equiv). This vinylzinc solution was added to a solution containing 1-benzyloxy-4-iodobutane (**2.38**) (87 mg, 0.271 mmol, 1 equiv) $Pd(OAc)_2$ (6 mg, 0.0271 mmol, 0.1 equiv) and PCy_3 (15 mg, 0.0542 mmol, 0.2 equiv) in 1:1 NMP/THF (1 mL). Purification by column chromatography (hexanes) yielded 7 mg (9 %) of **2.39** as a clear colourless liquid.

c) Cross-coupling between (*E*)-1-iodo-4-phenylbut-1-ene (**2.34**) and 1-benzyloxy-4-iodobutane (**2.38**) using $Pd(OAc)_2$ and PCy_3 in which additional *n*-butyllithium is used (entry 12, Table 2.3)

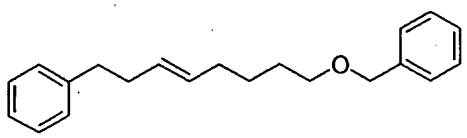
The general procedure was followed in which the vinylzinc was prepared from (*E*)-1-iodo-4-phenylbut-1-ene (**2.34**) (70 mg, 0.271 mmol, 1 equiv) in 1:4 ether/THF (1 mL) using *n*-butyllithium (0.368 mL of a 1.62 M solution in hexanes, 0.596 mmol, 1.1 equiv) and zinc chloride (41 mg, 0.298 mmol, 1.1 equiv). This vinylzinc solution was

added to a solution containing 1-benzyloxy-4-iodobutane (**2.38**) (87 mg, 0.271 mmol, 1 equiv) $Pd(OAc)_2$ (6 mg, 0.0271 mmol, 0.1 equiv) and PCy_3 (15 mg, 0.0542 mmol, 0.2 equiv) in 1:1 NMP/THF (1 mL). Purification by column chromatography (hexanes) yielded 5 mg (7 %) of **2.39** as a clear colourless liquid.

d) Cross-coupling between (*E*)-1-iodo-4-phenylbut-1-ene (**2.34**) and 1-benzyloxy-4-iodobutane (**2.38**) using additional $Pd(OAc)_2$ and PCy_3 (entry 13, Table 2.3)

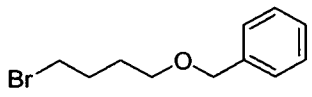
The general procedure was followed in which the vinylzinc was prepared from (*E*)-1-iodo-4-phenylbut-1-ene (**2.34**) (70 mg, 0.271 mmol, 1 equiv) in 1:4 ether/THF (1 mL) using *n*-butyllithium (0.184 mL of a 1.51 M solution in hexanes, 0.298 mmol, 1.1 equiv) and zinc chloride (41 mg, 0.298 mmol, 1.1 equiv). This vinylzinc solution was added to a solution containing 1-benzyloxy-4-iodobutane (**2.38**) (87 mg, 0.271 mmol, 1 equiv) $Pd(OAc)_2$ (18 mg, 0.0813 mmol, 0.1 equiv) and PCy_3 (45 mg, 0.163 mmol, 0.6 equiv) in 1:1 NMP/THF (1 mL). Purification by column chromatography (hexanes) yielded 5 mg (7 %) of **2.39** as a clear colourless liquid.

(*E*)-8-Benzyloxy-1-phenyloct-3-ene (**2.39**)



IR (neat): 3030, 2932, 2855, 1604 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.32-7.31 (m, 4H), 7.29-7.23 (m, 3H), 7.18-7.13 (m, 3H), 5.44-5.39 (m, 2H), 4.48 (s, 2H), 3.44 (t, *J*=6.5 Hz, 2H), 2.64 (t, *J*=7.8 Hz, 2H), 2.31-2.25 (m, 2H), 2.01-1.95 (m, 2H), 1.62-1.54 (m, 2H), 1.45-1.36 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 130.7, 129.7, 128.4, 128.3, 128.2, 127.6, 127.5, 125.7, 72.9, 70.3, 36.1, 34.4, 32.3, 29.2, 26.1. LRMS (EI) m/z (relative intensity): 294 (M^+, 16).

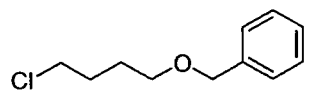
1-Benzyloxy-4-bromobutane (2.40)[70]



Phosphorous tribromide (1.00 mL, 5.55 mmol, 0.5 equiv) was added dropwise to a solution of 1-benzyloxybutan-4-ol (**2.37**) (2.00 g, 11.1 mmol, 1 equiv) and pyridine (0.100 mL, 1.24 mmol, 0.11 equiv) in ether (5 mL) at -30 °C and the reaction mixture was stirred at rt overnight. Water (15 mL) was slowly added and the mixture was extracted with ether (3 x 20 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride, dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/32 ethyl acetate-hexanes) to yield a clear colourless liquid. The liquid was further purified by Kugelrohr distillation (95-105 °C at 0.5 mm Hg) to yield 2.22 g (82 %) of **2.40** as a clear colourless liquid.

IR (neat): 2940, 2857, 2794 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.38-7.24 (m, 5H), 4.49 (s, 2H), 3.55 (t, *J*=6.5 Hz, 2H), 3.49 (t, *J*=6.1 Hz, 2H), 1.97-1.84 (m, 2H), 1.80-1.68 (m, 2H).

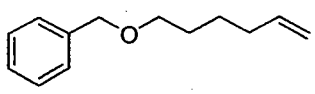
1-Benzyloxy-4-chlorobutane (2.41)[71]



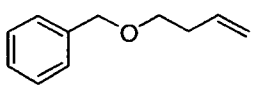
Thionyl chloride (0.81 mL, 11.1 mmol, 1 equiv) was added dropwise to a solution of 1-benzyloxybutan-4-ol (**2.37**) (2.00 g, 11.1 mmol, 1 equiv) and pyridine (0.200 mL, 1.24 mmol, 0.2 equiv) in ether (5 mL) at -30 °C and the reaction mixture was stirred at rt overnight. Water (15 mL) was slowly added and the mixture was extracted with ether (3 x 20 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride, dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/32 ethyl acetate-hexanes) to yield a clear colourless liquid. The liquid was further purified by Kugelrohr distillation (90-100 °C at 0.5 mm Hg) to yield 1.78 g (81 %) of **2.41** as a clear colourless liquid.

IR (neat): 2942, 2858, 2795 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.38-7.25 (m, 5H), 4.49 (s, 2H), 3.49 (t, *J*=6.5 Hz, 2H), 3.42 (t, *J*=6.1 Hz, 2H), 2.02-1.91 (m, 2H), 1.80-1.69 (m, 2H).

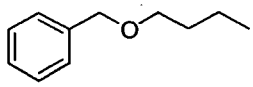
Cross-Coupling of Alkyl Halides 2.38, 2.40 and 2.41 with Vinylmagnesium Bromide



6-Benzyloxyhex-1-ene
(**2.42**)



4-Benzyloxybut-1-ene
(**2.43**)



4-Benzyloxybut-1-ene
(**2.44**)

General procedure (Table 2.4)

Vinylmagnesium bromide (1M solution in THF, 1.5 equiv) was added dropwise to a solution of the alkyl halide (1 equiv), palladium(II) acetate (0.05 equiv) and tricyclohexylphosphine (0.05 equiv) in NMP (0.18 M) and the reaction mixture was stirred at rt until progression of the reaction cessed. Methanol was added to quench the excess vinylmagnesium bromide and the reaction was concentrated *in vacuo* and the resulting solution was filtered through a plug of silica gel using *n*-pentane. A gas chromatography analysis was performed on this solution.

Cross-coupling of 1-benzyloxy-4-iodobutane (**2.38**) and vinylmagnesium bromide (entry 1, Table 2.4)

The general procedure was followed using vinylmagnesium bromide (0.517 mL of a 1.00 M solution in THF, 0.517 mmol, 1.5 equiv), 1-benzyloxy-4-iodobutane (**2.38**) (0.105 g, 0.345 mmol, 1.0 equiv), palladium(II) acetate (4 mg, 0.0172 mmol, 0.05 equiv) and tricyclohexylphosphine (5 mg, 0.0172 mmol, 0.05 equiv) in NMP (2 mL). The *n*-pentane solution used for the gas chromatography analysis was concentrated *in vacuo* to yield a clear yellow liquid upon which purification by rotary chromatography (1/32 ethyl acetate-hexanes) yielded 26 mg (39 %) of **2.42** as a clear colourless liquid, 15 mg

(27 %) of **2.43** as a clear colourless liquid, and 9 mg (15 %) of **2.44** as a clear colourless liquid.

6-Benzyloxyhex-1-ene (**2.42**)

IR (neat): 2935, 2858, 1641 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.24 (m, 5H), 5.87-5.71 (m, 1H), 5.04-4.90 (m, 2H), 4.49 (s, 2H), 3.46 (t, *J*=6.5 Hz, 2H), 2.10-2.00 (m, 2H), 1.68-1.57 (m, 2H), 1.55-1.41 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 138.6, 128.3, 127.6, 127.4, 114.5, 72.8, 70.2, 33.5, 29.2, 25.5. LRMS (EI) m/z (relative intensity): 190 (M^+, 7).

4-Benzyloxybut-1-ene (**2.43**)

IR (neat): 2959, 2935, 2856, 1641 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.37-7.24 (m, 5H), 5.94-5.79 (m, 1H), 5.16-5.03 (m, 2H), 4.53 (s, 2H), 3.54 (t, *J*=6.8 Hz, 2H), 2.45-2.35 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 135.2, 132.2, 127.6, 127.6, 127.5, 116.3, 72.8, 69.6, 34.2. LRMS (EI) m/z (relative intensity): 162 (M^+, 1).

1-Benzyloxybutane (**2.44**)

IR (neat): 2959, 2933, 2856 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.39-7.24 (m, 5H), 4.51 (s, 2H), 3.48 (t, *J*=6.8 Hz, 2H), 1.68-1.56 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 128.3, 127.6, 127.4, 72.8, 70.2, 31.8, 19.3, 13.9. LRMS (EI) m/z (relative intensity): 164 (M^+, 1).

Cross-Coupling of 1-Benzyloxy-4-bromobutane (2.40) with Vinylmagnesium Bromide: Dependence on Solvent and Temperature

General procedure (Table 2.5)

Vinylmagnesium bromide (1M solution in THF, 1.5 equiv) was added dropwise to a solution of 1-benzyloxy-4-bromobutane (**2.40**) (1 equiv), palladium(II) acetate (0.05,

0.20 or 0.30 equiv) and tricyclohexylphosphine (0.05, 0.20 or 0.30 equiv) in NMP, THF, DMAc, DMSO or DMF (0.18 M) and the reaction mixture was stirred at the required temperature until progression of the reaction cessed. Methanol was added to quench the excess vinylmagnesium bromide and the reaction was concentrated *in vacuo* and the resulting solution was filtered through a plug of silica gel using *n*-pentane. A gas chromatography analysis was performed on this solution.

Cross-Coupling of 1-Benzyloxy-4-bromobutane (2.40) with Vinylmagnesium Bromide: Investigating the Schlenk Equilibrium

General procedure (Table 2.6)

Vinylmagnesium bromide (1M solution in THF, 1.5 equiv) was added dropwise to a solution of 1-benzyloxy-4-bromobutane (**2.40**) (1 equiv), palladium(II) acetate (0.05 equiv), tricyclohexylphosphine (0.05 equiv) and the additive in NMP (0.18 M) and the reaction mixture was stirred at rt until progression of the reaction cessed. Methanol was added to quench the excess vinylmagnesium bromide and the reaction was concentrated *in vacuo* and the resulting solution was filtered through a plug of silica gel using *n*-pentane. A gas chromatography analysis was performed on this solution.

Cross-Coupling of 1-Benzyloxy-4-bromobutane (2.40) with Vinylmagnesium Bromide: Variation of the Catalyst System

General procedure (Table 2.7)

Vinylmagnesium bromide (1M solution in THF, 1.5 equiv) was added dropwise to a solution of 1-benzyloxy-4-bromobutane (**2.40**) (1 equiv) and with each component of the catalyst system (0.05 equiv each) in NMP (0.18 M) and the reaction mixture was stirred at rt until progression of the reaction cessed. Methanol was added to quench the excess vinylmagnesium bromide and the reaction was concentrated *in vacuo* and the resulting solution was filtered through a plug of silica gel using *n*-pentane. A gas chromatography analysis was performed on this solution.

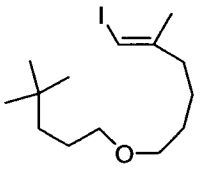
Cross-Coupling of 1-Benzyloxy-4-bromobutane (2.40) with Various Vinylorganometallics

General procedure (Table 2.8)

The vinylalane reagent solution was prepared by treating the corresponding alkyne material with diisobutylaluminum hydride (1 equiv) in refluxing hexane and then cooled before use. The methyl alanate reagent solution was prepared by treating the vinylalane reagent with methyllithium (1 equiv) at 0 °C.

The vinylorganometallic (1M solution in THF or hexane, 1.5 equiv) was added dropwise to a solution of 1-benzyloxy-4-bromobutane (**2.40**) (1 equiv) palladium(II) acetate (0.05 equiv) and tricyclohexylphosphine (0.05 equiv) in NMP (0.18 M) and the reaction mixture was stirred at rt until progression of the reaction cessed. Methanol was added to quench the excess vinylmagnesium bromide and the reaction was concentrated *in vacuo* and the resulting solution was filtered through a plug of silica gel using *n*-pentane. A gas chromatography analysis was performed on this solution.

(*E*)-4,4-Dimethylpentanyl-6'-iodo-5'-methylhex-5'-enyl ether (2.46)

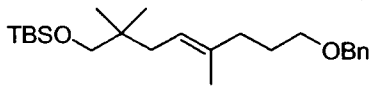


A solution of (*E*)-4,4-Dimethyl-5-iodopentanyl-6'-iodo-5'-methylhex-5'-enyl ether (**2.23**) (60 mg, 0.129 mmol, 1 equiv) in DMF (0.7 mL) was added to a solution of zinc (9 mg, 0.142 mmol, 1.1 equiv) in DMF (1 mL) and the reaction mixture was stirred at 50 °C for 2.5 h. The alkylzinc solution was cooled to rt and water was added. The reaction mixture was extracted with diethyl ether (3 x 10 mL), the ether extracts were combined, washed with brine (2 x 10 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a dark yellow liquid. The crude liquid was purified by column chromatography (1/49 ethyl acetate-hexanes) to yield 38 mg (88 %) of **2.46** as a clear colourless liquid.

IR (neat): 2941, 2858, 1617 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.85 (s, 1H), 3.41-3.31 (m, 4H), 2.20 (t, *J*=6.7 Hz, 2H), 1.80 (s, 3H), 1.59-1.42 (m, 6H), 1.21-1.12 (m, 2H), 0.86 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.9, 74.6, 71.9, 70.4, 40.2, 39.3,

30.1, 29.3, 29.1, 25.0,24.3, 23.7 ppm. LRMS (CI(+), ammonia) m/z (relative intensity): 329 (M^++18, 100).

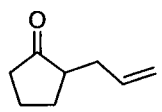
(*E*)-8-Benzyloxy-1-*tert*-butyldimethylsiloxy-2,2,5-trimethyloct-4-ene (2.48)



A solution of 3-*tert*-butyldimethylsiloxy-2,2-dimethyl-1-iodopropane (**2.28**) (101 mg, 0.308 mmol, 1 equiv) in DMF (1 mL) was added to a solution of zinc (22 mg, 0.338 mmol, 1.1 equiv) in DMF (3 mL) and the reaction mixture was stirred at 50 °C for 2.5 h. The alkylzinc solution was cooled to rt and then added dropwise to a solution of 5-benzyloxy-1-iodo-2-methylpent-1-ene (**2.31**) (97 mg, 0.308 mmol, 1 equiv) and tetrakis(triphenylphosphine)palladium (0) (71 mg, 0.0616 mmol, 0.2 equiv) in THF (5 mL). The reaction mixture was stirred at 50 °C for 1.5 h, after which a saturated aqueous solution of ammonium chloride (10 mL) was added and the reaction mixture was extracted with diethyl ether (3 x 10 mL). The ether extracts were combined, washed with brine (2 x 10 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a dark yellow liquid. The crude liquid was purified by column chromatography (1/49 ethyl acetate-hexanes) to yield 65 mg (54 %) of **2.48** as a clear colourless liquid.

IR (neat): 3030, 2942, 2855, 1618 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.39-7.24 (m, 5H), 5.19 (t, *J*=7.7 Hz, 1H), 4.56 (s, 2H), 3.45 (t, *J*=6.6 Hz, 2H), 3.21 (s, 2H), 2.08 (t, *J*=7.7 Hz, 2H), 1.91 (d, *J*=7.7 Hz, 2H), 1.79-1.66 (m, 2H), 1.59 (s, 3H), 0.89 (s, 9H), 0.80 (s, 6H), 0.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 138.3, 128.3, 127.7, 127.5, 121.4, 72.9, 71.4, 70.1, 36.5, 36.4, 33.6, 28.2, 25.9, 23.9, 18.3, 16.0, -5.5 ppm. LRMS (EI) m/z (relative intensity): 390 (M^+, 3).

2-Allylcyclopentanone (2.56)[72]

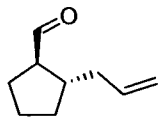


A solution of cyclopentanone (45.0 mL, 0.509 mol, 1 equiv), allyl alcohol (76.3 mL, 1.12 mol, 2.2 eq), 2,2-dimethoxypropane (68.8 mL, 0.560 mol, 1.1 eq) and *p*-toluenesulfonic acid monohydrate (0.484 g, 2.55 mmol, 0.005 eq) in benzene (200 mL) was heated at 100 °C so as to distill through a vigreux column the benzene/allyl alcohol azeotrope with a boiling point of 55-60 °C over a

period of 4 h. The temperature was slowly raised to 190 °C over 2.5 h at which time the distillation temperature of the distilling liquid was 95 °C. The reaction mixture was stirred overnight at 100 °C, and the resulting clear yellow solution was then purified by vacuum distillation (64-66 °C at 12 mmHg) to yield 41.15 g (65 %) of **2.56** as a clear colourless liquid.

IR (neat): 2965, 2879, 1741, 1641 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.81-5.66 (m, 1H), 5.08-4.96 (m, 2H), 2.53-2.43 (m, 1H), 2.35-1.90 (m, 6H), 1.87-1.67 (m, 1H), 1.61-1.47 (m, 1H).

(1*R, 2*S**)-2-Allylcyclopentanecarbaldehyde (2.55)**[73]

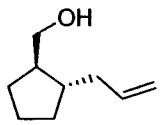


A solution of diphenyl(methoxymethyl)phosphine oxide (32.05 g, 0.108 mol, 1.2 equiv) in THF (500 mL) was added to a solution of lithium diisopropylamide, prepared from *n*-butyllithium (109.6 mL of a 1.38 M solution in hexanes, 0.151 mol, 1.4 equiv) and diisopropylamine (39.4 mL, 0.281 mol, 2.6 equiv) in THF (120 mL), at 0 °C. The reaction mixture was stirred for 30 min at 0 °C to yield a dark red solution, and a solution 2-allylcyclopentanone (**2.56**) (13.47 g, 0.108 mol, 1 eq) in THF (60 mL) was then added. The reaction mixture was stirred for 24 h at rt and 2 h at 50 °C. A saturated aqueous solution of ammonium chloride (100 mL) was added followed by water (200 mL), and the mixture was extracted with ether (3 x 300 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (75 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield an orange oil (18.1 g).

The crude product as a mixture of vinylether stereoisomers (**2.57**) was refluxed in 1:4 5% aqueous hydrochloric acid/THF (750 mL) for 40 min, after which a saturated aqueous solution of sodium bicarbonate (100 mL) was slowly added with stirring, and the mixture was extracted with ether (3 x 200 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (100 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a red oil. The oil was purified by column chromatography (1/19 ethyl acetate-hexanes) followed by vacuum distillation (82-84°C at 14 mmHg) to yield 9.08 g (61 %) of **2.55** as a clear colourless liquid.

IR (neat): 3078, 2958, 2710, 1724, 1641 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.58 (d, *J*=3.1 Hz, 1H), 5.82-5.63 (m, 1H), 5.07-4.95 (m, 2H), 2.44-2.32 (m, 1H), 2.24-1.49 (m, 8H), 1.38-1.24 (m, 1H).

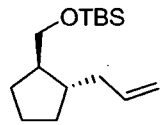
(1*R, 2*S**)-2-Allyl-1-(hydroxymethyl)cyclopentane (2.58)**



Sodium borohydride (3.72 g, 98.8 mmol, 1.5 equiv) was added to methanol (150 mL) at 0 °C and the mixture was stirred at 0 °C for 5 min. A solution of (1*R**, 2*S**)-2-Allylcyclopentanecarbaldehyde (**2.55**) (9.05 g, 65.5 mmo, 1 equiv) in methanol (50 mL) was added and the reaction mixture was stirred for 20 min at 0 °C and for 15 min at rt. The mixture was concentrated *in vacuo*, the residue was dissolved in ether (250 mL) and the solution was washed with water (300 mL). The aqueous layer was extracted with ether (3 x 150 mL), the ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (75 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear pale yellow oil. The crude oil was purified by column chromatography (3/97 methanol-chloroform) to yield 8.27 g (90 %) of **2.58x** as a clear colourless liquid.

IR (neat): 3333, 2948, 2869, 1640 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.85-5.69 (m, 1H), 5.03-4.90 (m, 2H), 3.62-3.38 (m, 2H), 2.23-2.12 (m, 1H), 2.04-1.92 (m, 1H), 1.84-1.17 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.9, 115.3, 66.5, 47.4, 41.6, 39.8, 32.3, 29.4, 24.2. LRMS (EI) m/z (relative intensity): 140 (M^+, 1).

(1*R, 2*S**)-2-Allyl-1-(*tert*-butyldimethylsilyloxymethyl)cyclopentane (2.59)**

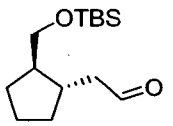


Triethylamine (9.39 mL, 67.4 mmol, 1.05 equiv) was added dropwise to a solution of (1*R**, 2*S**)-2-allyl-1-(hydroxymethyl)cyclopentane (**2.58**) (8.18 g, 58.3 mmol, 1 equiv), *tert*-butyldimethylsilyl chloride (9.67 g, 64.2 mmol, 1.1 equiv) and 4-(dimethylamino)pyridine (0.712 g, 5.83 mmol, 0.1 equiv) in methylene chloride (290 mL) at 0 °C, and the reaction mixture was stirred at rt for 1 h. Water (60 mL) was added and the methylene chloride layer was separated, dried over magnesium sulfate and concentrated *in vacuo* to yield a clear pale yellow oil. The oil

was purified by column chromatography (1/19 ethyl acetate-hexanes) to yield 13.93 g (94 %) of **2.59** as a clear colourless liquid.

IR (neat): 2953, 2858, 1641 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.83-5.65 (m, 1H), 5.01-4.94 (m, 2H), 3.53 (dd, *J*=9.6 Hz, 5.4 Hz, 1H), 3.43 (dd, *J*=9.6 Hz, 6.4 Hz, 1H), 2.28-2.17 (m, 1H), 2.00-1.88 (m, 1H), 1.80-1.14 (m, 8H), 0.87 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2, 114.9, 66.5, 47.3, 41.6, 39.9, 32.4, 30.9, 26.0, 24.3, 18.3, -5.3. LRMS (CI(+), ammonia) m/z (relative intensity): 272 (M^++18, 1), 255 (M^++1, 100).

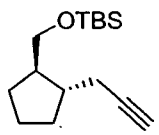
(1*R, 2*S**)-1-(*tert*-Butyldimethylsilyloxymethyl)-2-(2-oxoethyl)cyclopentane (2.60)**



Ozone was bubbled into a solution of (1*R**, 2*S**)-2-allyl-1-(*tert*-butyldimethylsilyloxymethyl)cyclopentane (**2.59**) (2.75 g, 10.8 mmol, 1 equiv) and Sudan III (0.031 g, 0.108 mmol, 0.01 equiv) in methylene chloride (120 mL) at -78 °C until the clear red solution became colourless. Triphenylphosphine (5.67 g, 21.6 mmol, 2 equiv) was added and the reaction mixture was stirred at rt for 5 h, after which the reaction mixture was concentrated *in vacuo* to yield a clear pale yellow oil. The oil was purified by column chromatography (1/19 ethyl acetate-hexanes), followed by Kugelrohr distillation (85-95 °C at 0.1 mmHg) to yield 2.17 g (78 %) of **2.60** as a clear colourless liquid.

IR (neat): 2953, 2858, 1727 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.72 (t, *J*=2.3 Hz, 1H) 3.57-3.44 (m, 2H), 2.68-2.51 (m, 1H), 2.37-2.26 (m, 1H), 2.15-2.00 (m, 1H), 1.96-1.84 (m, 1H), 1.76-1.49 (m, 4H), 1.39-1.13 (m, 2H), 0.86 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.0, 66.2, 49.9, 47.6, 36.9, 33.0, 28.7, 25.9, 24.3, 18.3, -5.4. LRMS (CI(+), ammonia) m/z (relative intensity): 273 (M^++17, 8), 257 (M^++1, 100).

(1*R, 2*S**)-1-(*tert*-Butyldimethylsilyloxymethyl)-2-propargylcyclopentane (2.53)**



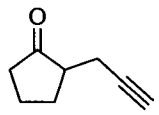
Method A (from **2.60**): Carbon tetrabromide (7.76 g, 23.4 mmol, 3 equiv) was added to a solution of triphenylphosphine (12.3 g, 46.8 mmol, 6 equiv) in methylene chloride (60 mL) at -15 °C and the mixture was stirred at -15 °C for 30 min. A solution of (1*R**, 2*S**)-1-(*tert*-

butyldimethylsilyloxymethyl)-2-(2-oxoethyl)cyclopentane (**2.60**) (3.98 g, 29.7 mmol, 1 equiv) in methylene chloride (20 mL) was added dropwise and the reaction mixture was stirred at 0 °C for 45 min. The dark red reaction mixture was concentrated *in vacuo* to yield a brown solid, which was triturated in hexanes (5 x 50 mL) and filtered. The filtrate was concentrated *in vacuo*, the resulting brown oil was passed through a plug of silica gel and the filtrate was concentrated *in vacuo* to yield a clear colourless oil (2.85 g). To this oil in THF (80 mL) at -78 °C was added *n*-butyllithium (18.5 mL of a 1.39 M solution in hexane, 25.7 mmol, 3.3 equiv) and the reaction mixture was stirred at -78 °C for 30 min, and at rt for 10 min. A saturated aqueous solution ammonium chloride (30 mL) was added and the mixture was extracted with ether (3 x 50 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (30 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear colourless oil. The crude oil was purified by column chromatography (1/19 ethyl acetate-hexanes) to yield 1.65 g (84 %) of **2.53** as a clear colourless liquid.

Method B (from **2.64**): Triethylamine (4.60 mL, 33.0, 1.05 equiv) was added dropwise to a solution of (1*R**, 2*S**)-1-(hydroxymethyl)-2-propargylcyclopentane (**2.64**) (4.34 g, 31.4 mmol, 1 equiv), *tert*-butyldimethylsilyl chloride (5.21 g, 34.5 mmol, 1.1 equiv) and 4-(dimethylamino)pyridine (0.384 g, 3.14 mmol, 0.1 equiv) in methylene chloride (160 mL) at 0 °C, and the reaction mixture was stirred at rt for 1 h. Water (60 mL) was added and the methylene chloride layer was separated, dried over magnesium sulfate and concentrated *in vacuo* to yield a clear pale yellow oil. The crude oil was purified by column chromatography (1/9 ethyl acetate-hexanes) to yield 7.49 g (94 %) of **2.53** as a clear colourless liquid.

IR (neat): 3314, 2954, 2858 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.57-3.46 (m, 2H), 2.38-2.10 (m, 2H), 1.89 (t, *J*=2.7 Hz, 1H), 1.87-1.28 (m, 8H), 0.87 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 83.9, 68.3, 66.4, 46.7, 41.1, 32.4, 29.3, 25.9, 24.3, 23.7, 18.3, -5.4. LRMS (CI(+), ammonia) m/z (relative intensity): 270 (M^++18, 9), 253 (M^++1, 100), 252 (M^+, 2). Anal. Calcd. for $C_{15}H_{28}OSi$: C, 71.36; H, 11.18. Found: C, 70.94; H, 11.48.

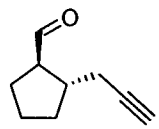
2-Propargylcyclopentanone (2.61)



Potassium carbonate (50.6 g, 0.366 mol, 2 equiv) was added to a solution of methyl-2-oxocyclopentane carboxylate (26.0 g, 0.183 mol, 1 equiv) in acetone (450 mL), followed by propargyl bromide (24.5 mL of a 80% solution in toluene, 0.220 mol, 1.2 equiv) and the reaction mixture was refluxed for 6 h. A saturated aqueous solution of sodium chloride (150 mL) was added, followed by water (150 mL), and the reaction mixture was extracted with ether (3 x 100 mL). The ether extracts were combined, dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow oil. To this oil in dimethyl sulfoxide (120 mL) was added water (3.3 mL, 0.183 mol, 1 equiv) and lithium chloride (15.5 g, 0.366 mol, 2 equiv) and the reaction mixture was refluxed for 2 h. Water (1 L) was added and the mixture was extracted with ether (4 x 300 mL). The ether extracts were combined, washed with water (2 x 500 mL) and with a saturated aqueous solution of sodium chloride (2 x 200 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a brown oil. The oil was purified by vacuum distillation (73-74 °C at 9 mmHg) to yield 14.46 g (65 %) of **2.61** as a clear colourless liquid.

IR (neat): 3290, 2966, 2880, 1742 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.59-2.49 (m, 1H), 2.39-2.20 (m, 4H), 2.18-2.00 (m, 2H), 1.93 (t, *J*=2.5 Hz, 1H), 1.86-1.72 (m, 2H). LRMS (EI) m/z (relative intensity): 122 (M^+, 3).

(1*R, 2*S**)-2-Propargylcyclopentanecarbaldehyde (2.63)**



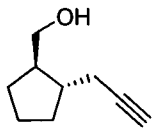
Dimethyl sulfoxide (175 mL) was added to sodium hydride (4.19 g of 95%, 166 mmol, 3 equiv) and the mixture was stirred at 75 °C for 1 h. A solution of (methoxymethyl)triphenylphosphium chloride (76.5 g, 216 mol, 3.9 equiv) in dimethyl sulfoxide (300 mL) was added dropwise via cannula to the reaction mixture at rt, followed by a solution of 2-propargylcyclopentanone (**2.61**) (6.75 g, 55.3 mmol, 1 equiv) in dimethyl sulfoxide (75 mL). The reaction mixture was stirred for 1.5 h at 70 °C, cooled to rt, and then extracted with hexanes (6 x 150 mL). The hexanes extracts were combined, washed with a saturated aqueous solution of ammonium chloride (100 mL), followed with a saturated aqueous solution of sodium

chloride (100 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield an orange oil (8.83 g).

The crude product as a mixture of vinylether stereoisomers (**2.62**) was refluxed in 1:4 5% aqueous hydrochloric acid/THF (425 mL) for 1 h, after which a saturated aqueous solution of sodium bicarbonate (100 mL) was slowly added with stirring, and the mixture was extracted with ether (3 x 100 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (50 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear pale yellow oil. The crude oil was purified by vacuum distillation (69-70 °C at 2.5 mmHg) to yield 4.85 g (64 %) of **2.63** as a clear colourless liquid.

IR (neat): 3292, 2958, 2872, 1722 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.62 (d, *J*=2.3 Hz, 1H), 2.59-2.48 (m, 1H), 2.40-2.22 (m, 3H), 1.92 (t, *J*=2.3 Hz, 1H), 1.93-1.77 (m, 3H), 1.75-1.36 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.2, 82.4, 69.5, 56.6, 39.2, 32.0, 26.6, 24.7, 23.2. LRMS (CI(+), ammonia) m/z (relative intensity): 154 (M^++18, 10), 137 (M^++1, 23).

(1*R, 2*S**)-1-(Hydroxymethyl)-2-propargylcyclopentane (2.64)**

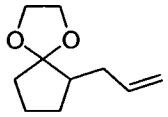


Sodium borohydride (1.91 g, 50.6 mmol, 1.5 equiv) was added to methanol (300 mL) at 0 °C and the mixture was stirred at 0 °C for 5 min. A solution of (1*R**, 2*S**)-2-propargylcyclopentanecarbaldehyde (**2.63**) (4.60 g, 33.7 mmo, 1 equiv) in methanol (55 mL) was added and the reaction mixture was stirred for 20 min at 0 °C and for 20 min at rt. The mixture was concentrated *in vacuo*, the residue was dissolved in ether (200 mL) and the solution was washed with water (200 mL). The aqueous layer was extracted with ether (3 x 100 mL), the ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (75 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear pale yellow oil. The crude oil was purified by column chromatography (3/97 methanol-chloroform) to yield 4.38 g (94 %) of **2.64** as a clear colourless liquid.

IR (neat): 3330, 3306, 2950, 2870 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.62-3.45 (m, 2H), 2.31-2.15 (m, 1H), 1.92 (t, *J*=2.5 Hz, 1H), 1.88-1.68 (m, 5H), 1.66-1.46 (m, 2H), 1.45-1.28 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 83.8, 68.7, 66.2, 46.9, 41.2, 32.4, 29.4,

24.1, 23.7. LRMS (CI(+), ammonia) m/z (relative intensity): 156 (M^++18, 8), 139 (M^++1, 18).

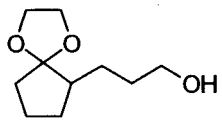
6-(2-Propenyl)-1,4-dioxaspiro[4.4]nonane (2.65)



Triethylamine (4.60 mL, 33.0, 1.05 equiv) was added dropwise to a solution of 2-allylcyclopentyl (**2.56**) (5.50 g, 44.3 mmol, 1 equiv), ethylene glycol (4.94 mL, 88.6 mmol, 2 equiv), and p-toluenesulfonic acid monohydrate (84.3 mg, 0.443 mmol, 0.01 equiv) in benzene (55 mL) was refluxed for 2 h under a Dean-Stark trap. A saturated aqueous solution of sodium bicarbonate (25 mL) was added, followed by water (100 mL), and the reaction mixture was extracted with ether (3 x 150 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (50 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear pale yellow oil. The oil was purified by vacuum distillation (74-75 °C at 2.5 mmHg) to yield 7.14 g (96 %) of **2.65** as a clear colourless liquid.

IR (neat): 2958, 2877, 1640 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.84-5.64 (m, 1H), 5.03-4.86 (m, 2H), 3.92-3.79 (m, 4H), 2.25-2.19 (m, 1H), 2.00-1.43 (m, 7H), 1.39-1.22 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.9, 117.9, 114.9, 64.6, 64.4, 45.7, 35.6, 33.5, 29.0, 20.5. LRMS (CI(+), ammonia) m/z (relative intensity): 170 (M^++2, 12), 169 (M^++1, 100).

6-(3-hydroxypropyl)-1,4-dioxaspiro[4.4]nonane (2.66)

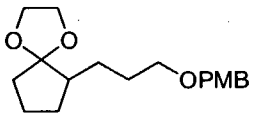


Borane-dimethyl sulfide complex (5.21 mL of a 10 M solution in dimethylsufide, 52.1 mmol, 1.2 equiv) was added dropwise to a solution of 6-(2-propenyl)-1,4-dioxaspiro[4.4]nonane (**2.65**) in THF (150 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 2 h. A 3 M aqueous solution of sodium hydroxide (45 mL) was added dropwise to the reaction mixture at 0 °C, followed by a 30% aqueous solution of hydrogen peroxide (50 mL), and the mixture was stirred at rt for 2 h. Water (200 mL) was added and the reaction mixture was extracted with ethyl acetate (3 x 100 mL). The ethyl acetate extracts were combined,

washed with a saturated aqueous solution of sodium chloride (50 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear colourless oil. The oil was purified by column chromatography (13/7 ethyl acetate-hexanes) to yield 7.25 g (90 %) of **2.66** as a clear colourless liquid.

IR (neat): 3423, 2942, 2873 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.90-3.77 (m, 4H), 3.55 (t, *J*=6.4 Hz, 2H), 2.15 (s, 1H), 1.91-1.78 (m, 2H), 1.72-1.40 (m, 7H), 1.33-1.13 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 118.1, 64.4, 64.3, 62.9, 45.7, 35.6, 31.3, 29.4, 24.9, 20.5. LRMS (EI) *m/z* (relative intensity): 186 (M^+, 11).

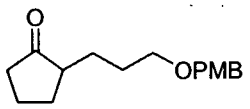
6-(3-(4-Methoxybenzyloxy)propyl)-1,4-dioxaspiro[4.4]nonane (2.67)



Potassium bis(trimethylsilyl)amide (101.5 mL of a 0.5 M solution in toluene, 52.8 mmol, 1.5 equiv) was added dropwise to a solution of 6-(3-hydroxypropyl)-1,4-dioxaspiro[4.4]nonane (**2.66**) (6.55 g, 35.2 mmol, 1 equiv) in THF (350 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 30 min. 4-methoxybenzyl chloride (5.25 mL, 38.7 mmol, 1.1 equiv) was added , followed by tetrabutylammonium iodide (1.30 g, 3.52 mmol, 0.1 equiv), and the reaction mixture was stirred at rt for 3 h. Water (200 mL) was added and the reaction mixture was extracted with ether (3 x 100 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (50 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear pale yellow oil. The oil was purified by column chromatography (1/9 ethyl acetate-hexanes) to yield 10.14g (94 %) of **2.67** as a clear colourless liquid.

IR (neat): 2948, 2871, 1613 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, *J*=8.6 Hz, 2H), 6.85 (d, *J*=8.6 Hz, 2H), 4.41 (s, 2H), 3.92-3.81 (m, 4H), 3.78 (s, 3H), 3.41 (t, *J*=6.6 Hz, 2H), 1.92-1.80 (m, 2H), 1.77-1.46 (m, 7H), 1.38-1.18 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 130.8, 129.2, 118.2, 113.7, 72.5, 70.5, 64.6, 64.4, 55.3, 46.0, 35.7, 29.4, 28.4, 25.4, 20.6. LRMS (EI) m/z (relative intensity): 306 (M^+, 11).

2-(3-(4-Methoxybenzyloxy)propyl)cyclopentanone (2.68)

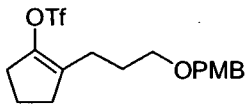


Method A (from **2.67**): Water (1.83 mL, 101.4 mmol, 6 equiv) and pyridinium p-toluenesulfonate monohydrate (0.321 g, 1.69 mmol, 0.1 equiv) were added to a solution of 6-(3-(4-methoxybenzyloxy)propyl)-1,4-dioxaspiro[4.4]nonane (**2.67**) (5.18 g, 16.9 mmol, 1 equiv) in acetone (190 mL), and the reaction mixture was refluxed for 3 h. The reaction mixture was concentrated *in vacuo* and the resulting clear pale yellow oil was dissolved in ether (100 mL). The ether solution was washed with a saturated aqueous solution of sodium bicarbonate (50 mL), followed with a saturated aqueous solution of sodium chloride (50 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear pale yellow oil. The crude oil was purified by column chromatography (1/4 ethyl acetate-hexanes) to yield 4.31g (97 %) of **2.68** as a clear colourless liquid.

Method B (from **2.71**): *n*-Butyllithium (44.7 mL of a 1.44 M solution in hexanes, 64.4 mmol, 1.1 equiv) was added to a solution of 2-cyclopentylidene-1,1-dimethylhydrazine (7.38 g, 58.5 mmol, 1 equiv) in THF (250 mL) at 0 °C and the reaction mixture was stirred at 0°C for 30 min. A solution of 3-(4-methoxybenzyloxy)propyl iodide (**2.71**) (17.9 g, 58.5 mmol, 1 equiv) in THF (50 mL) was added dropwise and the reaction mixture was slowly warmed to rt over 30 min and then stirred at rt for 2 h. An aqueous solution of 2 N sulfuric acid (125 mL, 125 mmol, 2.1 equiv) was added and the reaction mixture was further stirred for 1 h. The mixture was concentrated *in vacuo* to a volume of 150 mL and the resulting solution was extracted with ether (3 x 100 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium bicarbonate (100 mL), followed with a saturated aqueous solution of sodium chloride (100 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear pale yellow oil. The oil was purified by column chromatography (1/4 ethyl acetate-hexanes) to yield 9.10 g (59 %) of **2.68** as a clear colourless liquid.

IR (neat): 2941, 2861, 1734, 1613 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.23 (d, *J*=8.5 Hz, 2H), 6.84 (d, *J*=8.5 Hz, 2H), 4.39 (s, 2H), 3.77 (s, 3H), 3.42 (t, *J*=6.6 Hz, 2H), 2.30-1.25 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 221.1, 159.0, 130.6, 129.2, 113.7, 72.5, 69.9, 55.2, 48.9, 38.0, 29.5, 27.7, 26.3, 20.6. LRMS (EI) m/z (relative intensity): 306 (M^+, 11). Anal. Calcd for $C_{16}H_{22}OSi$: C, 73.25; H, 8.45. Found: C, 73.19; H, 8.72.

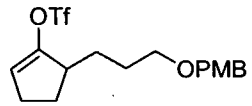
2-(3-(4-Methoxybenzyloxy)propyl)-1-trifluoromethanesulfonatecyclopent-1-ene (2.54)



n-Butyllithium (15.0 mL of a 1.37 M solution in hexanes, 20.6 mmol, 0.9 equiv) was added to a solution of diisopropylamine (3.21 mL, 22.9 mmol, 1 equiv) in THF (150 mL) at -78 °C and the reaction mixture was stirred at -78 °C for 1 h. This solution was then added dropwise via cannula to a solution of 2-(3-(4-methoxybenzyloxy)propyl)cyclopentanone (**2.68**) (6.00 g, 22.9 mmol, 1 equiv) in THF (80 mL) was added dropwise at 0 °C and the reaction mixture was stirred at rt for 15 h. The reaction mixture was then cooled to 0 °C, *N*-phenyltrifluoromethanesulfonimide (9.82 g, 27.5 mmol, 1.2 equiv) was added in 1 portion and stirring was continued for 1.5 h at rt. An aqueous solution of 2 N sodium hydroxide (150 mL) was added and the mixture was extracted with ether (3 x 100 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (100 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear pale yellow oil. The oil was purified by column chromatography (1/9 ethyl acetate-hexanes) to yield 7.53 g (83 %) of **2.54** as a clear colourless liquid and 0.585 g (7 %) of recovered **2.68**.

IR (neat): 2951, 2857, 1614 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, *J*=8.5 Hz, 2H), 6.86 (d, *J*=8.5 Hz, 2H), 4.41 (s, 2H), 3.79 (s, 3H), 3.41 (t, *J*=6.4 Hz, 2H), 2.57 (t, *J*=7.3 Hz, 2H), 2.32 (t, *J*=7.1 Hz, 2H), 2.21 (t, *J*=7.8 Hz, 2H), 1.98-1.87 (m, 2H), 1.74-1.63 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 142.5, 132.2, 130.5, 129.3, 118.5 (q, *J*=320.0 Hz), 113.7, 72.6, 69.4, 55.2, 30.7, 30.5, 27.1, 23.3, 19.4. LRMS (CI(+), ammonia) m/z (relative intensity): 413 (M^++19, 18), 412 (M^++18, 74). Anal. Calcd for $C_{17}H_{21}F_3O_5S$: C, 51.77; H, 5.37. Found: C, 51.63; H, 5.59.

5-(3-(4-Methoxybenzyloxy)propyl)-1-trifluoromethanesulfonatecyclopent-1-ene (2.69)

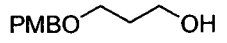


n-Butyllithium (0.865 mL of a 1.36 M solution in hexanes, 1.18 mmol, 1.1 equiv) was added to a solution of diisopropylamine (0.165 mL, 1.18 mmol, 1.1 equiv) in THF (6.5 mL) at -78 °C and the

reaction mixture was stirred at -78 °C for 1 h. A solution of 2-(3-(4-methoxybenzyloxy)propyl)cyclopentanone (**2.68**) (0.280 g, 10.7 mmol, 1 equiv) in THF (3.5 mL) was added dropwise and the reaction mixture was stirred at rt for 15 h. The reaction mixture was then cooled to 0 °C, *N*-phenyltrifluoromethanesulfonimide (9.82 g, 27.5 mmol, 1.2 equiv) was added in 1 portion and stirring was continued for 1.5 h at rt. An aqueous solution of 2 N sodium hydroxide (15 mL) was added and the mixture was extracted with ether (3 x 10 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (10 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear pale yellow oil. The oil was purified by column chromatography (1/9 ethyl acetate-hexanes) to yield 3.60 g (85 %) of **2.69** as a clear colourless liquid.

IR (neat): 2941, 2860, 1658 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, *J*=8.7 Hz, 2H), 6.87 (d, *J*=8.7 Hz, 2H), 5.61 (dd, *J*=4.5, 2.4 Hz, 1H), 4.42 (s, 2H), 3.79 (s, 3H), 3.44 (t, *J*=6.3 Hz, 2H), 2.90-2.75 (m, 1H), 2.39-2.28 (m, 2H), 2.25-2.11 (m, 1H), 1.80-1.50 (m, 4H), 1.43-1.29 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 152.0, 130.6, 129.2, 118.3 (q, *J*=320.7 Hz), 116.7, 113.8, 72.8, 69.8, 55.2, 42.8, 29.1, 27.4, 26.9, 26.6. LRMS (CI(+), ammonia) m/z (relative intensity): 413 (M^++19, 18), 412 (M^++18, 74).

3-(4-Methoxybenzyloxy)propan-1-ol (2.70)

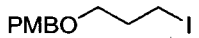


p-Anisaldehyde (18.3 mL, 150 mmol, 1 equiv) was added dropwise to a solution of 1,3-propanediol (11.4 g, 150 mmol, 1 equiv) and p-toluenesulfonic acid monohydrate (57.1 mg, 0.3 mmol, 0.002 equiv) in toluene (50 mL) and the reaction mixture was refluxed under a Dean-Stark trap for 2 h. The reaction mixture was cooled to 0 °C and diisobutylaluminum hydride (180 mL of a 1 M solution in hexanes, 180 mmol, 1.2 equiv) was added dropwise over a period of 15 min. The reaction mixture was then stirred at rt for 3 h, after which methanol (20 mL) in toluene (35 mL) was added carefully with cooling (ice-water bath) at rate to keep the temperature below 40 °C. The resulting slurry was stirred vigorously until the reaction mixture became granular. The solution was filtered through Celite, washed with toluene (200 mL), and the filtrate was concentrated to yield a clear yellow oil. The oil was

purified by vacuum distillation (140 °C at 0.6 mmHg) to yield 26.3 g (89 %) of **2.70** as a clear colourless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (d, *J*=8.9 Hz, 2H), 6.86 (d, *J*=8.9 Hz, 2H), 4.43 (s, 2H), 3.78 (s, 3H), 3.75 (t, *J*=5.4 Hz, 2H), 3.68 (t, *J*=5.8 Hz, 2H), 2.27 (s, 1H), 1.88-1.78 (m, 2H).

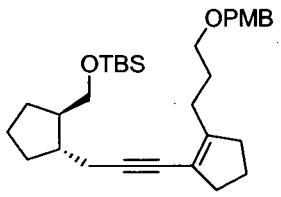
3-(4-Methoxybenzyloxy)propyl iodide (2.71)



Iodine (25.9 g, 102.0 mmol, 1.1 equiv) was added in one portion to a solution of imidazole (18.9 g, 278 mmol, 3 equiv) and triphenylphosphine (26.7 g, 102 mmol, 1.1 equiv) in methylene chloride (370 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 10 min. A solution of 3-(4-methoxybenzyloxy)propan-1-ol (**2.70**) (18.2 g, 92.7 mmol, 1 equiv) in methylene chloride (185 mL) was added over a period of 10 min and the reaction mixture was stirred for 2 h. A saturated aqueous solution of sodium thiosulfate (20 mL) was added, followed by water (200 mL) and the mixture was extracted with methylene chloride (2 x 100 mL). The methylene chloride extracts were combined, dried over magnesium sulfate and concentrated *in vacuo* to yield a yellow solid. The solid was triturated in hexanes (200 mL), filtered over a bed of Celite and the filtrate was concentrated *in vacuo* to yield a clear pale yellow oil. The oil was purified by vacuum distillation (144-145 °C at 0.3 mmHg) to yield 20.71 g (73 %) of **2.71** as a clear colourless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, *J*=8.5 Hz, 2H), 6.86 (d, *J*=8.5 Hz, 2H), 4.43 (s, 2H), 3.79 (s, 3H), 3.49 (t, *J*=5. 8 Hz, 2H), 3.27 (t, *J*=6.9 Hz, 2H), 2.10-2.01 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 130.3, 129.3, 113.8, 72.8, 69.3, 55.3, 33.5, 3.54.

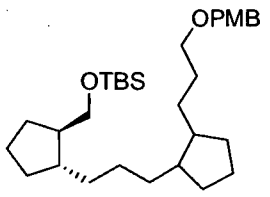
1-(3-((1*R, 2*S**)-2-(*tert*-Butyldimethylsilyloxymethyl)cyclopentyl)prop-1-ynyl)-2-(3-(4-methoxybenzyloxy)propyl)cyclopent-1-ene (2.76)**



A solution of 2-(3-(4-methoxybenzyloxy)propyl)-1-trifluoromethanesulfonatecyclopent-1-ene (**2.54**) (7.10 g, 18.0 mmol, 1 equiv) and tetrabutylammonium iodide (13.8 g, 37.8 mmol, 2.1 equiv) in DMF (180 mL) was added to tetrakis(triphenylphosphine)palladium(0) (2.08 g, 1.80 mmol, 0.1 equiv) and copper (I) iodide (1.71 g, 9.00 mmol, 0.5 equiv) and the reaction mixture was stirred for 10 min. A solution of (1*R**, 2*S**)-1-(*tert*-butyldimethylsilyloxymethyl)-2-propargylcyclopentane (**2.53**) (4.54 g, 18.0 mmol, 1 equiv) in DMF (180 mL) was added dropwise and the reaction mixture was stirred for 1.5 h. Water (500 mL) was added and the mixture was extracted with ether (3 x 400 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (2 x 200 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a dark brown oil. The oil was purified by column chromatography (1/19 ethyl acetate-hexanes) to yield 7.56 g (85 %) of **2.76** as a clear colourless liquid.

IR (neat): 2951, 2857, 1614 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, *J*=8.53 Hz, 2H), 6.85 (d, *J*=8.5 Hz, 2H), 4.42 (s, 2H), 3.78 (s, 3H), 3.58-3.45 (m, 2H), 3.42 (t, *J*=6.8 Hz, 2H), 2.52-2.27 (m, 8H), 1.85-1.67 (m, 8H), 1.63-1.30 (m, 4H), 0.87 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 149.1, 130.8, 129.2, 118.5, 113.7, 93.0, 77.6, 72.5, 70.0, 66.4, 55.2, 46.7, 41.5, 36.8, 35.2, 32.4, 29.5, 27.9, 26.8, 25.9, 24.9, 24.4, 22.4, 18.3, -5.4. *Anal.* Calcd for $C_{31}H_{48}O_3Si$: C, 74.64; H, 10.10. Found: C, 74.37; H, 9.82.

1-(3-((1*R, 2*S**)-2-(*tert*-Butyldimethylsilyloxymethyl)cyclopentyl)propyl)-2-(3-(4-methoxybenzyloxy)propyl)cyclopentane (2.77a, 2.77b)**

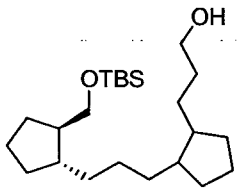


5 % palladium on charcoal (1.03 g, 0.483 mmol, 0.1 equiv) was added to a solution of 1-(3-((1*R**, 2*S**)-2-(*tert*-butyldimethylsilyloxymethyl)cyclopentyl)prop-1-ynyl)-2-(3-(4-methoxybenzyloxy)propyl)cyclopent-ene (**2.76**) (2.40 g, 4.83

mmol, 1 equiv) in ethanol (100 mL) and the reaction mixture was stirred under an atmosphere of hydrogen for 2.5 h. The reaction mixture was filtered through Celite and the filtrate was concentrated to yield clear pale yellow oil. The oil was purified by column chromatography (1/19 ethyl acetate-hexanes) to yield 2.19 g (90 %) of a 76:24 mixture of **2.77a** and **2.77b** (gas chromatography analysis) as a clear colourless liquid.

IR (neat): 2951, 2857, 1618 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J*=8.8 Hz, 2H), 6.86 (d, *J*=8.75 Hz, 2H), 4.42 (s, 2H), 3.78 (s, 3H), 3.53 (dd, *J*=9.7, 5.5 Hz, 1H), 3.45-3.36 (m, 3H), 1.82-1.00 (m, 27H), 0.88 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 130.8, 129.2, 72.5, 70.6, 66.8, 55.2, 48.0, 47.9, 46.0, 45.9, 45.8, 42.4, 42.1, 36.3, 36.2, 35.6, 35.5, 32.9, 32.8, 32.3, 32.2, 31.6, 30.2, 29.5, 28.8, 27.4, 26.0, 25.8, 24.4, 23.8, 22.5, 18.4, -5.3. LRMS (EI) m/z (relative intensity): 500 (M^+, 1).

1-(3-((1*R, 2*S**)-2-(*tert*-Butyldimethylsilyloxymethyl)cyclopentyl)propyl)-2-(3-hydroxypropyl)cyclopentane (2.81a, 2.81b)**

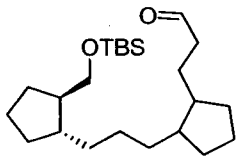


2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (1.08 g, 4.78 mmol, 1.2 equiv) was added to a solution of a 76:24 mixture of two diastereomers of 1-(3-((1*R**, 2*S**)-2-(*tert*-butyldimethylsilyloxymethyl)cyclopentyl)propyl)-2-(3-(4-methoxybenzyloxy)propyl)cyclopentane (**2.77a**, **2.77b**) (2.00 g, 3.98 mmol, 1 equiv) in methylene chloride (100 mL) and water (5 mL) and the reaction mixture was stirred for 1 h. Water (50 mL) was added and the mixture was extracted with methylene chloride (2 x 50 mL). The methylene chloride extracts were combined, washed with brine (50 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield an orange liquid. The crude liquid was purified by column chromatography (2/98 methanol-chloroform) to yield 1.34 g (88 %) of a 76:24 mixture of **2.81a** and **2.81b** (gas chromatography analysis) as a clear colourless liquid.

IR (neat): 3337, 2935, 2857 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.61 (t, *J*=5.62 Hz, 2H), 3.52 (dd, *J*=9.8, 5.4 Hz, 1H), 3.39 (dd, *J*=9.8, 6.9 Hz, 1H), 1.85-0.99 (m, 27H), 0.87 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 66.8, 63.4, 48.0, 47.9, 46.0, 45.8, 42.0, 36.3, 36.2, 35.7, 35.5, 32.9, 32.8, 32.3, 32.2, 31.8, 31.2, 29.5, 27.4, 26.0,

24.4, 23.8, 18.3, -5.3. LRMS (CI(+), ammonia) m/z (relative intensity): 400 (M^++18, 3), 383 (M^++1, 100).

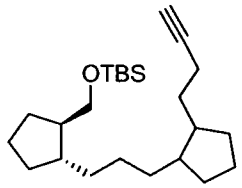
1-(3-((1*R, 2*S**)-2-(*tert*-Butyldimethylsilyloxymethyl)cyclopentyl)propyl)-2-(3-oxypropyl)cyclopentane (2.82a, 2.82b)**



A solution of dimethylsulfoxide (0.448 mL, 6.31 mmol, 2.2 equiv) in methylene chloride (5 mL) was added to a solution of oxalyl chloride (0.241 mL, 2.77 mmol, 1.1 equiv) in methylene chloride (35 mL) at -78 °C and the reaction mixture was stirred at -78 °C for 30 min. A solution of a 76:24 mixture of two diastereomers of 1-(3-((1*R**, 2*S**)-2-(*tert*-butyldimethylsilyloxymethyl)cyclopentyl)propyl)-2-(3-hydroxypropyl)cyclopentane (**2.81a**, **2.81b**) (2.00 g, 3.98 mmol, 1 equiv) in methylene chloride (10 mL) was added dropwise and the stirring was continued at -78 °C for 30 min before triethylamine (1.75 mL, 12.55 mmol, 5 equiv) was added dropwise. The reaction mixture was stirred for 30 min at 0 °C and then 1 h at rt. Water (30 mL) was added and the organic layer was separated and washed with 2N aqueous hydrochloric acid (30 mL), saturated aqueous sodium bicarbonate (30 mL), and brine (30 mL). The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/19 ethyl acetate-hexanes) to yield 1.02 g (94 %) of a 75:25 mixture of **2.82a** and **2.82b** (gas chromatography analysis) as a clear colourless liquid.

IR (neat): 2929, 2857, 2711, 1730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 3.51 (dd, *J*=9.8, 5.2 Hz, 1H), 3.39 (dd, *J*=9.8, 6.9 Hz, 1H), 2.48-2.30 (m, 2H), 1.89-1.00 (m, 24H), 0.86 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.9, 66.7, 48.0, 47.9, 45.9, 45.4, 43.1, 42.0, 36.2, 36.1, 35.5, 35.4, 32.8, 32.7, 32.2, 32.1, 32.0, 29.4, 27.3, 27.2, 25.9, 24.4, 23.7, 23.6, 18.3, -5.3. LRMS (CI(+), ammonia) m/z (relative intensity): 381 (M^++1, 36).

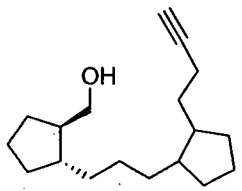
1-(3-((1*R, 2*S**)-2-(*tert*-Butyldimethylsilyloxymethyl)cyclopentyl)propyl)-2-but-3-ynylcyclopentane (2.84a, 2.84b)**



A solution of a 76:24 mixture of two diastereomers of 1-(3-((1*R**, 2*S**)-2-(*tert*-butyldimethylsilyloxymethyl)cyclopentyl)propyl)-2-(3-oxypropyl)cyclopentane (**2.82a**, **2.82b**) (0.678 g, 1.78 mmol, 1 equiv) in methanol (5 mL) was added to a solution of potassium carbonate (0.492 g, 3.56 mmol, 2.0 equiv) in methanol (15 mL), followed by a solution of dimethyldiazo-2-oxopropylphosphonate (**2.83**) (0.470 g, 2.67 mmol, 1.5 equiv) in methanol (5 mL), and the reaction mixture was stirred for 18 h. Water (35 mL) was added and the reaction mixture was extracted with hexanes (4 x 25 mL). The hexanes extracts were combined, dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (hexanes) to yield 0.605 g (90 %) of a 75:25 mixture of **2.84a** and **2.84b** (gas chromatography analysis) as a clear colourless liquid.

IR (neat): 3314, 2930, 2857, 2120 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.52 (dd, *J*=9.8, 5.5 Hz, 1H), 3.39 (dd, *J*=9.8, 7.0 Hz, 1H), 2.27-2.05 (m, 2H), 1.91 (t, *J*=2.5 Hz, 3H), 1.84-1.00 (m, 22H), 0.87 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 85.0, 67.9, 66.7, 48.0, 47.9, 45.7, 45.1, 42.0, 36.3, 36.2, 35.5, 35.4, 34.2, 32.9, 32.8, 32.3, 32.2, 31.9, 29.4, 27.3, 26.0, 24.4, 23.8, 22.5, 18.3, 17.5, -5.3.

2-But-3-ynyl-1-(3-((1*R, 2*S**)-2-(hydroxymethyl)cyclopentyl)propyl)cyclopentane (2.85a, 2.85b)**

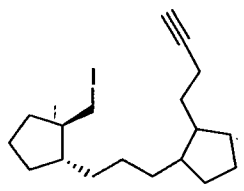


Tetrabutylammonium fluoride (2.65 mL of a 1 M solution in THF, 2.65 mmol, 1.5 equiv) was added to a solution of a 75:25 mixture of two diastereomers of 1-(3-((1*R**, 2*S**)-2-(*tert*-butyldimethylsilyloxymethyl)cyclopentyl)propyl)-2-but-3-ynylcyclopentane (**2.84a**, **2.84b**) (0.665 g, 1.77 mmol, 1 equiv) in THF (25 mL), and the reaction mixture was stirred for 2 h. Water (15 mL) was added and the reaction mixture was extracted with ether (3 x 10 mL). The ether extracts were combined, dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude

liquid was purified by column chromatography (2/9 ethyl acetate-hexanes) to yield 0.440 g (95 %) of a 78:22 mixture of **2.85a** and **2.85b** (gas chromatography analysis) as a clear colourless liquid.

IR (neat): 3349, 3310, 2948, 2867 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.58 (dd, *J*=10.4, 5.2 Hz, 1H), 3.44-3.34 (m, 1H), 2.26-2.00 (m, 2H), 1.89 (t, *J*=2.4 Hz, 3H), 1.84-1.00 (m, 23H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 84.9, 67.9, 66.6, 48.1, 48.0, 45.7, 45.6, 45.0, 49.9, 42.4, 42.3, 42.0, 41.6, 41.5, 36.1, 35.9, 35.4, 35.3, 34.1, 32.7, 32.6, 31.8, 30.2, 30.1, 29.7, 29.5, 29.4, 28.5, 28.4, 27.2, 24.3, 23.7, 22.4, 17.4.

2-But-3-ynyl-1-(3-((1*R, 2*S**)-2-(iodomethyl)cyclopentyl)propyl)cyclopentane (2.86a, 2.86b)**



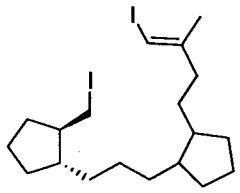
Pyridine (88.1 µL, 0.991 mmol, 1.3 equiv) was added to a solution of a 78:22 mixture of two diastereomers of 2-but-3-ynyl-1-(3-((1*R**, 2*S**)-2-(hydroxymethyl)cyclopentyl)propyl)cyclopentane (**2.85a, 2.85b**) (0.200 g, 0.762 mmol, 1 equiv) in methylene chloride (10 mL) at 0 °C, followed by trifluoromethanesulfonic anhydride (141 µL, 0.838 mmol, 1.1 equiv), and the reaction mixture was stirred at 0 °C for 15 min. The reaction mixture was diluted with methylene chloride (30 mL), washed with a 0.5 N aqueous solution of hydrochloric acid (2 x 20 mL), dried over magnesium sulphate and *in vacuo* to yield 0.288 g (96 %) of a 77:23 mixture of the two trifluoromethanesulfonate diastereomers (gas chromatography analysis) as a clear yellow liquid.

Sodium iodide (0.157 g, 1.05 mmol, 1.2 equiv) was added to a solution of the trifluoromethanesulfonate mixture in acetone (10 mL) and the reaction mixture was stirred for 3 h. Water (10 mL) was added and the reaction mixture was extracted with ether (3 x 10 mL). The ether extracts were combined, dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (2/49 ethyl acetate-hexanes) to yield 0.248 g (91 %) of a 77:23 mixture of **2.86a** and **2.86b** (gas chromatography analysis) as a clear colourless liquid.

IR (neat): 3309, 2932, 2857, 2120 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.58 (dd, *J*=10.4, 5.2 Hz, 1H), 3.44-3.34 (m, 1H), 2.26-2.00 (m, 2H), 1.89 (t, *J*=2.4 Hz, 3H), 1.84-1.00 (m,

23H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 84.9, 67.9, 66.6, 48.1, 48.0, 45.7, 45.6, 45.0, 49.9, 42.4, 42.3, 42.0, 41.6, 41.5, 36.1, 35.9, 35.4, 35.3, 34.1, 32.7, 32.6, 31.8, 30.2, 30.1, 29.7, 29.5, 29.4, 28.5, 28.4, 27.2, 24.3, 23.7, 22.4, 17.4.

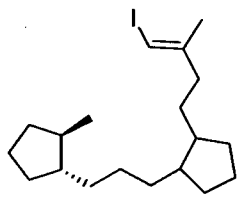
2-((*E*)-3-Methylbut-3-enyl-1-(3-((1*R, 2*S**)-2-(iodomethyl)cyclopentyl)propyl)cyclopentane (2.87a, 2.87b)**



Trimethylaluminum in hexanes (0.577 mL of a 2 M solution in hexanes, 1.15 mmol, 2 equiv) was added dropwise to a solution of bis(cyclopentadienyl)zirconium dichloride (0.169 g, 0.577 mmol, 1 equiv) in methylene chloride (6 mL) at -23 °C and the mixture was stirred at -23 °C for 10 minutes to yield a pale yellow solution. A solution of 2-but-3-ynyl-1-(3-((1*R**, 2*S**)-2-(iodomethyl)cyclopentyl)propyl)cyclopentane (**2.86a, 2.86b**) (0.215 mg, 0.577 mmol, 1 equiv) in methylene chloride (1 mL) was added dropwise at -20 °C and the reaction mixture was stirred at rt for 1 h. The reaction mixture was then cooled to -30 °C and a solution of iodine (0.161 g, 0.635 mmol, 1.1 equiv) in THF (1 mL) was added dropwise. The reaction mixture was warmed to 0 °C over 30 min, water (10 mL) was slowly added and the reaction mixture was extracted with ether (3 x 10 mL). The ether extracts were combined, washed with brine (10 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (hexanes) to yield 0.250 g (84 %) of a 76:24 mixture of **2.87a** and **2.87b** (gas chromatography analysis) as a clear colourless liquid.

IR (neat): 3055, 2934, 2857, 1619 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85 (s, 1H), 3.35 (dd, *J*=9.5, 4.4 Hz, 1H), 3.11 (dd, *J*=9.2, 8.3 Hz, 1H), 2.27-2.07 (m, 2H), 1.94-1.85 (m, 2H), 1.81 (s, 3H), 1.81-1.73 (m, 2H), 1.68-1.02 (m, 20 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.5, 148.4, 74.3, 47.9, 46.0, 45.9, 45.8, 45.4, 42.5, 42.3, 42.0, 41.9, 38.6, 35.5, 35.2, 35.2, 35.1, 33.7, 33.4, 33.3, 33.0, 32.9, 32.8, 32.3, 32.2, 32.1, 30.2, 30.1, 30.0, 29.6, 29.5, 27.7, 27.6, 27.2, 27.0, 24.0, 23.8, 23.4, 22.5, 14.6.

2-((*E*)-3-Methylbut-3-enyl-1-(3-((1*R, 2*S**)-2-methylcyclopentyl)propyl)cyclopentane (2.88a, 2.88b)**



A solution of a 76:24 mixture of two diastereomers of 2-((*E*)-3-methylbut-3-enyl-1-(3-((1*R**, 2*S**)-2-(iodomethyl)cyclopentyl)propyl)cyclopentane (**2.87a, 2.87b**) (51 mg, 0.100 mmol, 1 equiv) in DMF (0.5 mL) was added to a solution of zinc (7 mg, 0.100 mmol, 1.1 equiv) in DMF (1 mL) and the reaction was stirred at 50 °C for 2.5 h. The alkylzinc solution was cooled to rt and then added dropwise to a solution of tetrakis(triphenylphosphine)palladium (0) (6 mg, 0.005 mmol, 0.05 equiv) in THF (4 mL). The reaction mixture was stirred at rt for 1 h, and then refluxed for 4 h. A saturated aqueous solution of ammonium chloride (10 mL) was added and the reaction mixture was extracted with diethyl ether (3 x 5 mL). The ether extracts were combined, washed with brine (2 x 10 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a yellow liquid. The crude liquid was purified by column chromatography (hexanes) to yield 31 mg (80 %) of a 76:24 mixture of **2.88a** and **2.88b** (gas chromatography analysis) as a clear colourless liquid.

IR (neat): 3055, 2934, 2857, 1617 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.85 (s, 1H), 3.35 (dd, *J*=9.5, 4.4 Hz, 1H), 3.11 (dd, *J*=9.2, 8.3 Hz, 1H), 2.27-2.07 (m, 2H), 1.94-1.85 (m, 2H), 1.81 (s, 3H), 1.81-1.73 (m, 2H), 1.68-1.02 (m, 20 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.5, 148.4, 74.3, 47.9, 46.0, 45.9, 45.8, 45.4, 42.5, 42.3, 42.0, 41.9, 38.6, 35.5, 35.2, 35.2, 35.1, 33.7, 33.4, 33.3, 33.0, 32.9, 32.8, 32.3, 32.2, 32.1, 30.2, 30.1, 30.0, 29.6, 29.5, 27.7, 27.6, 27.2, 27.0, 24.0, 23.8, 23.4, 22.5, 14.6.

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Chapter Three

Fusicoccane Diterpenoids: Introduction and Previous Synthetic Approaches

I. Introduction

In 1828, Wöhler accidentally prepared urea from ammonium cyanate.[1] This event marked the beginning of organic synthesis, the construction of carbon based molecules. Considering that urea is an amino acid metabolite produced in the liver, this also marked the first total synthesis of a natural product. The synthesis of acetic acid from elemental carbon by Kolbe in 1845 followed.[2] This was significant since Kolbe was the first to use the word "synthesis" to describe the process of assembling a chemical compound from other substances. The turn of the century however saw the synthesis of slightly more complex natural products. This is manifested in the initial syntheses of the terpenes such of α-terpineol by Perkin in 1904,[3] camphor by Komppa in 1903 and by Perkin in 1904,[4] and tropinone by Robinson in 1917.[5] Throughout the history of organic synthesis, and organic chemistry in general, the study of natural products has usually provided the impetus to greater advances.[6] Synthetic organic chemists of today have to contend with molecules in which problems of stereochemistry and bond connection are of much higher complexities. Along with the development of tools for structure elucidation such as nuclear magnetic resonance, steadily improving chemical methods have made it possible to attack these ever emerging synthetic problems. Vice versa, the desire to construct intricate and complex molecules has spurred an attempt to develop new methodological processes of synthesis. Hence, the two main fields of synthetic organic chemistry, *methodological studies* and *total synthesis*, are intertwined and are influenced by the structural intricacies that are provided by Nature.

The motives for the synthesis of natural products in the laboratory may not be obvious, considering that Nature already provides them. However, the choice of a synthetic target can be dictated by subtle but important motives. In some cases, the compound is known to possess important biological activity of interest but is only available in small amounts from natural sources. In other cases, a total synthesis may be required to assign unambiguously the structure of a natural product. It is also possible to conduct a synthesis purely for the intellectual and practical challenge provided by a complex structure. These reasons for constructing complex natural products have spurred a final but important purpose. In many cases, the synthesis complex of a natural product becomes the motivation for the development of novel

methods. Frequently, it also provides for an improvement in methodology or the development of alternate processes to accomplish a specific transformation within the synthesis.[7]

II. Natural Products Containing a 5-8-5 Tricyclic Framework

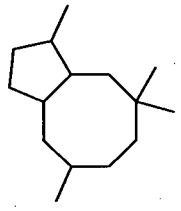
Although 8-membered rings are not as abundant as smaller sized rings, they do occur to a significant extent in nature, particularly in higher organisms.[8] Many of these cyclooctanoid natural products exist as terpenes, exhibiting interesting biological activity and their unusual structures have served as targets for numerous synthetic studies.

Terpenes are widely occurring natural product molecules which are formed from units of isoprene commonly linked in a head-to-tail fashion. This polymerization of isoprene, originally recognized by Wallach in 1887 and described as the "isoprene rule", was expanded as the "biogenetic isoprene rule" some 65 years later by Ruzicka to include stereospecific cyclization, rearrangement and dimerization reactions to account for the diversity that exists for terpenes.[9] The isoprene polymer natural products can also be functionalized during the course of their biosynthesis, producing oxygen containing terpenes described as "terpenoids". Mevalonic acid pyrophosphate is used as the isoprene source, which is converted to isopentenyl pyrophosphate (IPP) and its isomer dimethylallyl pyrophosphate (DMAPP). The enzymatic combination of a DMAPP isoprene unit with various amounts of IPP isoprene units form common acyclic hydrocarbon precursors to monoterpenes (2 isoprene units), sesquiterpenes (3 isoprene units), diterpenes (4 isoprene units), sesteterpenes (5 isoprene units) and triterpenes (6 isoprene units).

There are over a hundred known terpenoid natural products containing an 8-membered ring carbocycle in their structure.[8b] Characteristically, the 8-membered ring is fused or bridged to smaller 5- or 6-membered rings and contains other functionalities. The more typical examples are shown in Figure 3.1. There are a few examples of sesquiterpenoids, but the diterpenoids and sesteterpenoids are more widespread. The taxanes are common cyclooctane ring containing diterpenoids, whereas a distinctive 5-8-5 tricyclic skeleton is found in the widely occurring diterpenoid of the fusicoccane family and the ophiobolane sesteterpenoids. The following

discussion will focus on these two latter examples of 5-8-5 tricyclic containing terpenoids.

SESQUITERPENE:



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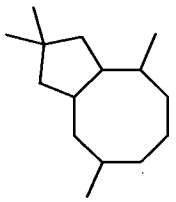

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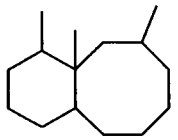

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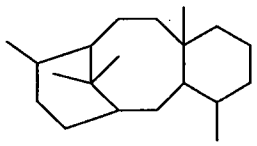
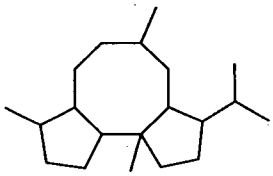
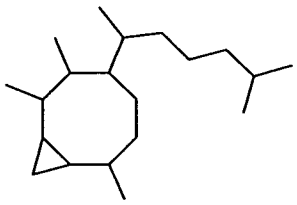


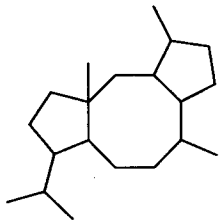
taxane



basmane

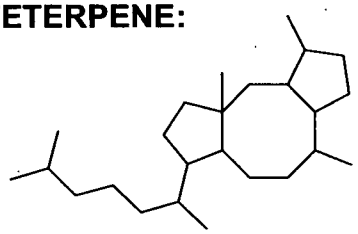


crenulane



fusicoccane

SESTETERPENE:



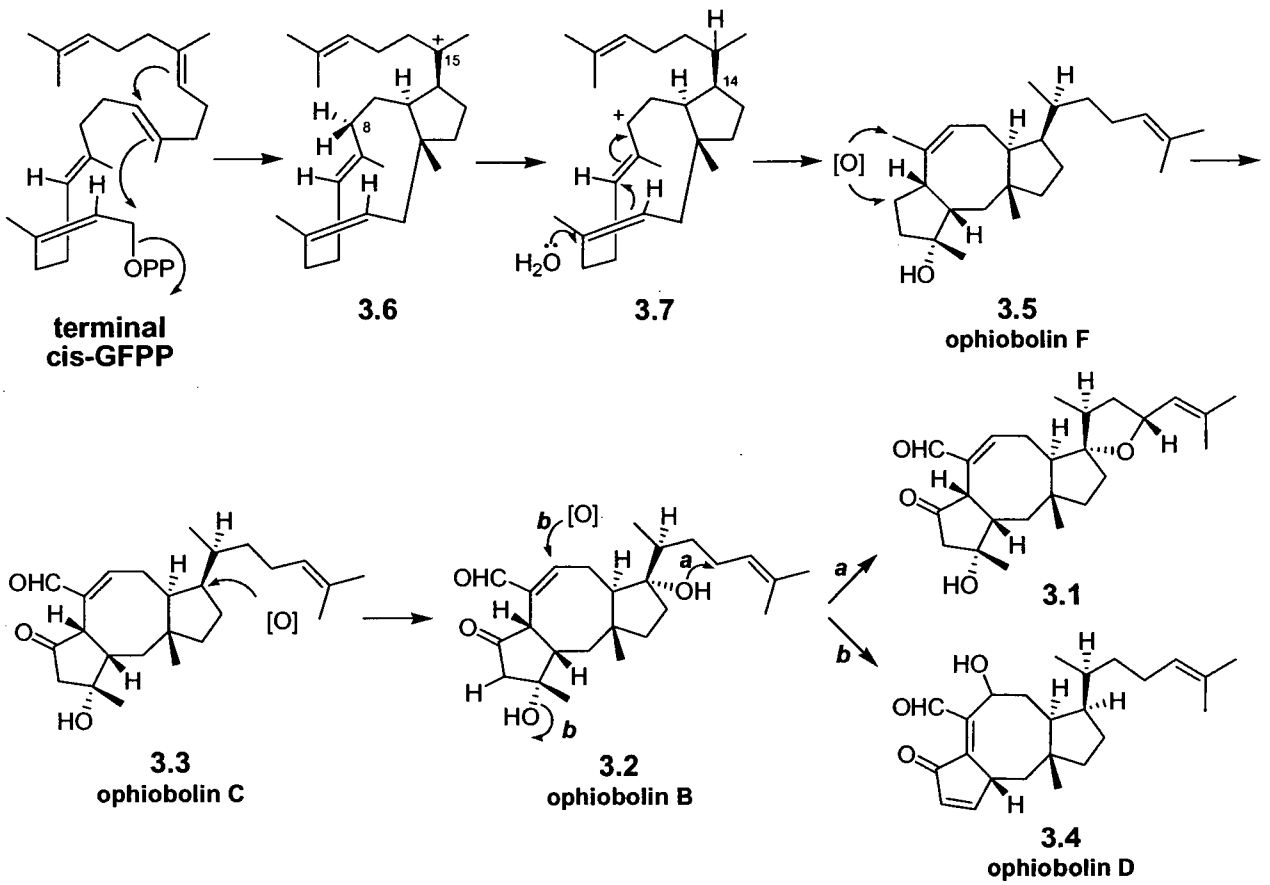
ophiobolane

Figure 3.1 Terpenoid Ring Systems Containing 8-Membered Carbocycles

A. Ophiobolanes

The first discovered sesteterpenoid, ophiobolin A (**3.1**),[10] was isolated from the plant pathogenic fungus *Bipolaris oryzae*[11,12] and its structure also revealed a formerly unknown 5-8-5 tricyclic ring system (see Scheme 3.1). Soon thereafter, the related ophiobolin B (**3.2**),[13] C (**3.3**),[14] D (**3.4**),[15,16] and F (**3.5**)[17] were isolated from other various

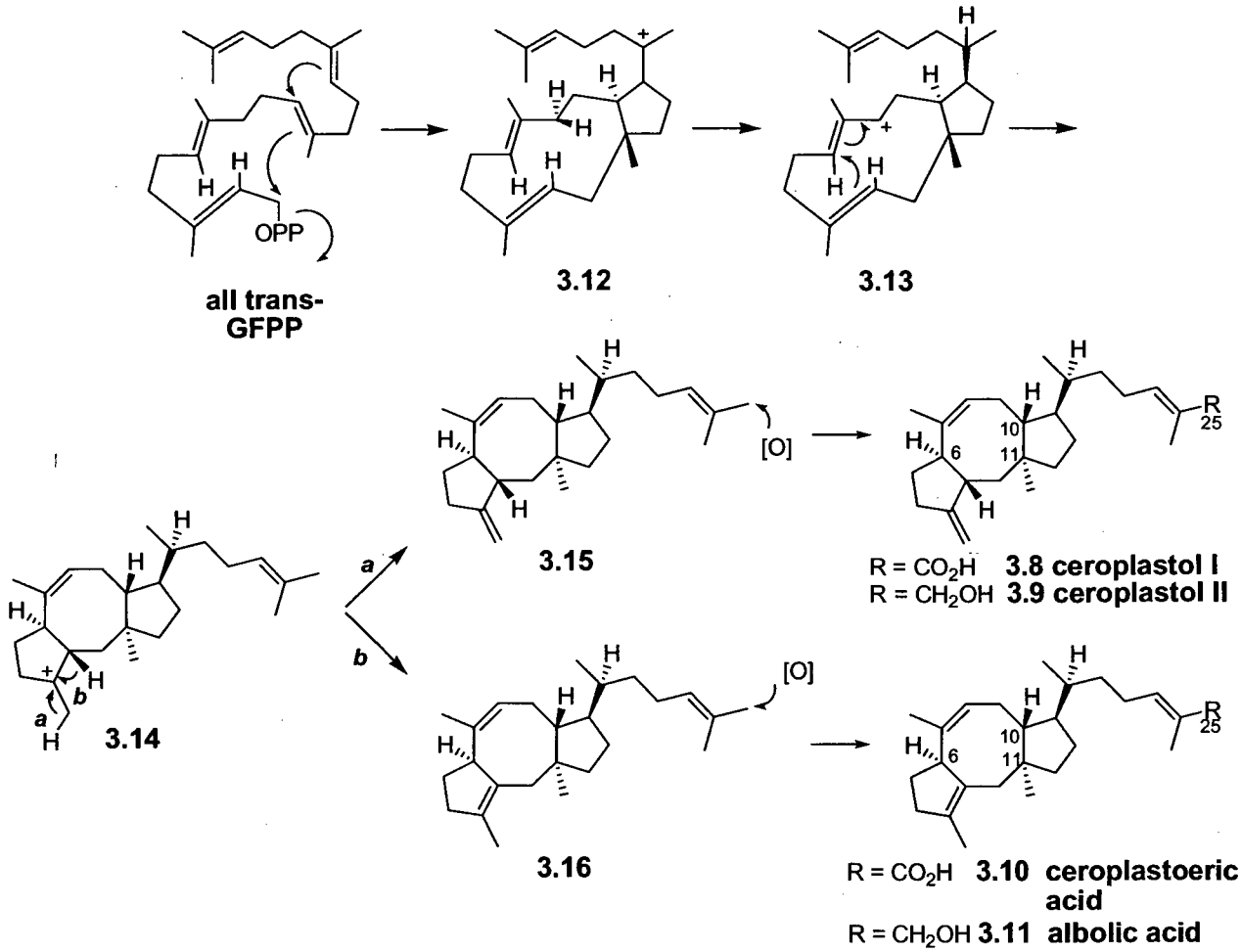
sources of *Bipolaris spp.* Currently, 23 biogenic analogues of ophiobolins have been identified, mostly from *Bipolaris spp.*, but also from other fungal sources such as *Cephalosporium caerulens* and *Aspergillus ustus*.[18] All of the ophiobolins show some pathogenic property towards a variety of plants, although their modes of action are diverse and not well understood.[18] Recently, the use of ophiobolin A as a calmodulin antagonist in plants and animals has also been investigated.[19]



Scheme 3.1 Major Biogenetic Pathways for the Ophiobolins

Due to the novel structural features of the ophiobolins, their biosynthesis has been extensively studied. ^{14}C labeled mevalonate feeding studies involving the natural source revealed the relative isoprenoid arrangements.[20,21] Biogenetically, the ophiobolin framework is thought to arise from *terminal cis*-GFPP (geranylfarnesyl pyrophosphate)

through a series of concerted cyclizations and a formal[i] 1,5-hydride shift.[22] Subsequent oxidation results in the variety of analogues (Scheme 3.1). The biogenetic pathways for all ophiobolins appear to arise from the common intermediate **3.7**. This can be assumed since the stereochemistry of the carbon centres around the ring fusions as well as that of C-14 are similar throughout the series.



Scheme 3.2 Major Biogenetic Pathways for the Ceroplastanes

The members of the ceroplastanes subfamily of ophiobolanes are distinguishable from the ophiobolins in that they differ in the stereochemistry at the ring junctions and have different oxidations state at C-25 (Scheme 3.2). These include ceroplastol I (**3.8**),[23] ceroplastol II (**3.9**),[24] ceroplasteric acid (**3.10**)[20] and albolic acid (**3.11**).[25] These

[i] It is important to note that arrow pushing is just a formalism and that the individual steps in these proposed biosynthetic pathways aren't necessarily as shown (i.e. the 1,5-hydride shift may actually involve selective deprotonation with concomitant hydride delivery).

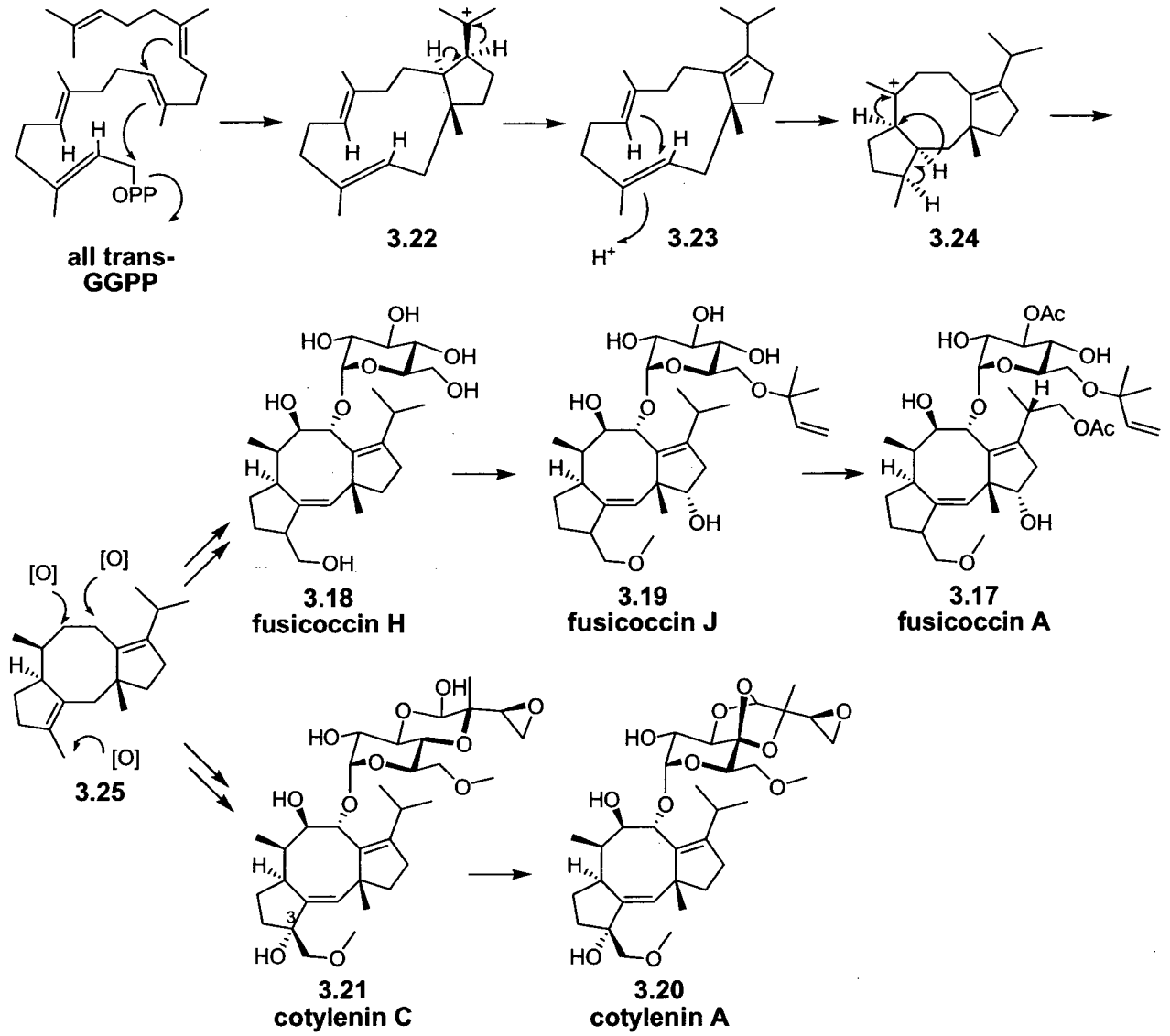
sesterterpenoids were isolated from wax secreted by the scale insect *Ceroplastes albolineatus*.[26] Rather than containing a *cis-trans* fusion between the three rings as for the ophiobolins, a *trans/trans* fusion is observed. Furthermore, the absolute configuration of the carbon centres C-6, C-10 and C-11 are inverted relative to the ophiobolin structures.

Considering the differences in the stereochemical configurations and that geranylfarnasol with *all-trans* olefin geometry was isolated from the same insect source, we can assume that the tricyclic framework arises from an *all trans*-GFPP.[27] Otherwise, the proposed biosynthesis follows a similar route, involving a formal 1,5-hydride shift. However, the second sequence of cyclizations is not initiated by hydroxide attack, and the resulting carbocation is quenched by E1 elimination. Depending on which proton eliminates, two possible products are formed; an exocyclic alkene (Scheme 3.2, path ***a***) or an endocyclic alkene (Scheme 3.2, path ***b***). Subsequent oxidation leads to the four ceroplastanes. Despite having interesting structural features and the similarities to the ophiobolins, their biological properties remain unexplored.

B. Fusicoccanes

Not long after the original discovery of the ophiobolane type of sesteterpenoids, a diterpenoid with a similar tricyclic ring structure was isolated from the peach and almond tree pathogenic fungus *Fusicoccum amygdali* (see Scheme 3.3).[28] The interest for this diterpenoid, named fusicoccin A (**3.17**), arose from the fact that it caused the wilting of the leaves and subsequent death of various plants. This results from activation of the plant's plasma membrane H^+-ATPase by binding with 14-3-3 proteins causing membrane hyperpolarization. Fusicoccin A was structurally elucidated, along with other congeners, of which the more important include fusicoccin H (**3.18**) and J (**3.19**).[29] This revealed them to be diterpenoids containing a 5-8-5 tricycle (a 5-membered carbocycle fused to an 8-membered carbocycle, itself fused to a second 5-membered carbocycle) with a glycoside moiety.[30] Another grouping of fusicoccane diterpenoids include the cotylenins isolated from *Cladosporium* sp. 501-7W.[31] These metabolites, which include cotylenin A (**3.20**) and cotylenin C (**3.21**), differ from the fusicoccins in the presence of a 3-hydroxyl substituent and different sugar moieties.[32] In addition to their various phytohormone action, the fusicoccins and the cotylenins are currently attracting

attention as the fusicoccin-binding 14-3-3 proteins are regarded to be the key proteins in intracellular signal transductions in both plants[33] and animals.[34] Furthermore, the cotylenins also show differentiation-inducing activity towards murine and human myeloid leukemia cells.[35]



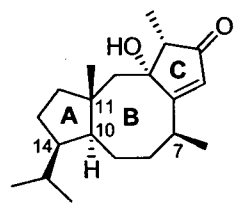
Scheme 3.3 Major Biogenetic Pathways for the Fusicoccins and the Cotylenins

The presence of an isoprenoid ether unit within the glycoside moiety of fusicoccin A led to the belief that the fusicoccins where originally rearranged sesteterpenoids. However the subsequent isolation of fusicoccin H, which does not contain this characteristic, strongly suggests that the biosynthesis for the fusicoccin originates from geranylpyrophosphate and they are therefore diterpenoid in origin. A number of

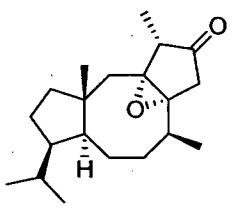
biosynthetic studies revealed a biogenetic pathway different from the ophiobolanes. All fusicoccane diterpenoids stem from an araneosenyl cation **3.22** intermediate originating from *all trans*-GGPP (geranylgeranyl pyrophosphate) in a similar fashion as for the ceroplastanes. However, the subsequent steps involve a 1,2-hydride shift to form the 11-5 bicyclic (+)-δ-araneosene (**3.23**), followed by further cyclization and two consecutive 1,2-hydride shifts to form (+)-fusicocca-2,10(14)-diene **3.23**. A number of oxidations and glycosidation leads to the fusicoccins, whereas the cytolenins require the additional C-3 hydroxylation.

A large amount of the more recently discovered fusicoccane diterpenoids have been isolated from plant sources, most notably liverworts. The first fusicoccane diterpenoid to be isolated from such a source, anadensin (**3.26**), was obtained from the liverwort *Anastrepta orcadensis* in 1983 (Figure 3.2).[36] Its structural characteristics include a stereochemical arrangement about the ring junctions which differs from that of the fusicoccins and the cytolenins and a stereodefined C-14 isopropyl reminiscent of the ophiobolins. This stereochemical arrangement about the A- and B-rings was subsequently found in diterpenoids isolated from other liverworts sources. Fusicogigantone A (**3.27**),[37] fusicogigantone B (**3.28**),[37] fusicogigantepoxide A (**3.29**)[37] and fusicogigantepoxide B (**3.30**),[37b] isolated from the east Malaysian liverwort *Pleurozia gigantea*, show similar structural features and differ only in the oxidation arrangement about the C-ring.

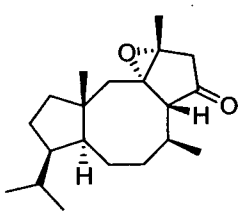
Novel C_{35} terpenoids were isolated from the Panamanian liverwort *Plagiochila moritziana*.[38] These included plagiosporolide A (**3.31**), B (**3.32**), C (**3.33**) and D (**3.34**), and are the result of a combination of a diterpenoid fusicoccane fragment and a sesquiterpenoid eudesmanolide fragment.[39] The plagiospirolide terpenoids were thought to most likely be the result of a biosynthetic Diels-Alder Reaction between these two fragments. This was substantiated by the isolation of fusicoccadiene (**3.35**),[35b] most likely the dienophile for the process, and which contained the similar arrangement about the A- and B-rings as anadensin.



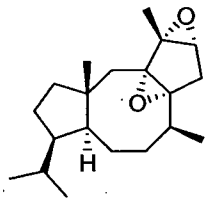
3.26
anadensin



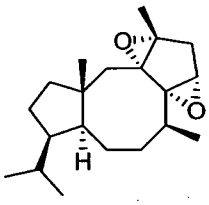
3.27
fusicogigantone A



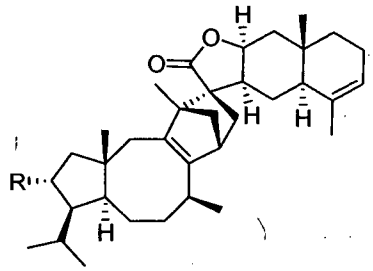
3.28
fusicogigantone B



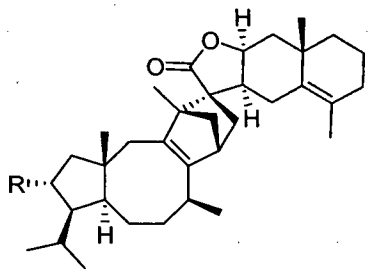
3.29
fusicogigantepoxide A



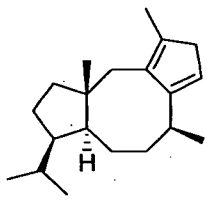
3.30
fusicogigantepoxide B



R = H **3.31 plagiospirolide A**
= OH **3.33 plagiospirolide C**



R = H **3.32 plagiospirolide B**
= OH **3.34 plagiospirolide D**

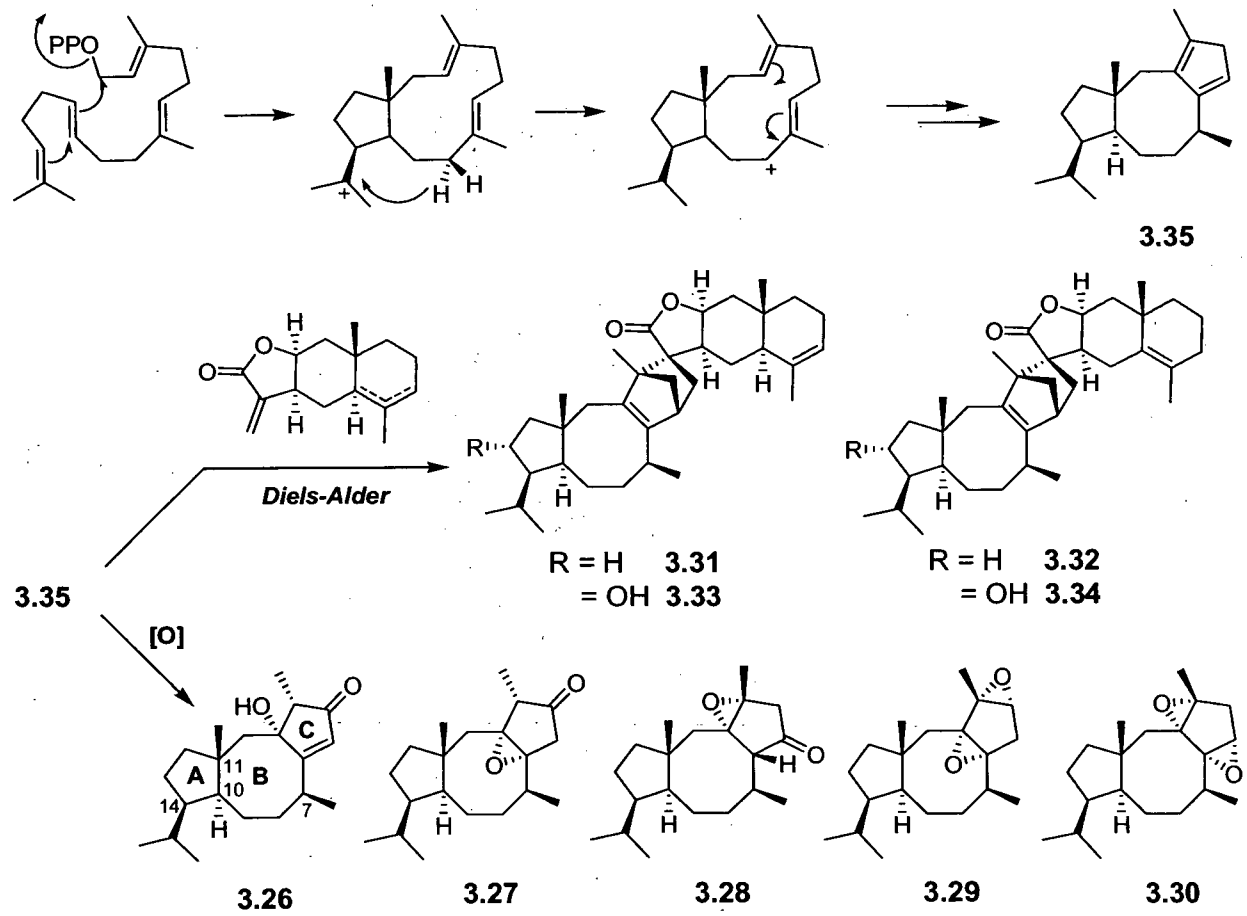


3.35
fusicoccadiene

Figure 3.2 Fusicoccane Diterpenoids with Similar Arrangements about the A-B Ring System

Aside from the structural similarities, there is strong evidence for anadensin, the fusicogigantones, the fusicogigantepoxides and the plagiospirolides to arise from a common fusicoccadiene intermediate. Anadensin exists in natural sources which contain fusicogigantones and fusicogiganepoxides as well.[38,40] In fact, treatment of fusicogigantone A with lithium diisopropylamide yields anadensin.[38] A biomimetic synthesis has also been achieved for anadensin, the fusicogigantone and the fusicogigantepoxide by way of oxidation of fusicoccadiene (*vide infra*).[37b] Similarly, a Diels-Alder biomimetic synthesis has been accomplished using fusicoccadiene as the dieneophile for the plagiospirolides (*vide infra*).[41] The possible biogenetic pathways for the formation of fusicoccadiene have not been extensively studied. However, it is not unreasonable to propose a biogenetic pathway from GGPP similar to the ophiobolanes, involving a series of concerted cyclizations and with a formal 1,5-hydride shift (Scheme

3.4). This would account for the difference in unsaturation in the A-ring compared to the fusicoccins.



Scheme 3.4 Possible Biogenetic Pathways for Anadensin, the Fusicogigantones, the Fusicogigantepoxides and the Plagiospirolides

The hypoestenones (Figure 3.3) are also fusicoccane diterpenoids isolated from the Arabian liverwort *Hypoestes forskalei*, and are comprised of hypoestenone (**3.36**), deoxyhypoestenone (**3.37**) and dehydrohypoestenone (**3.38**).[42] The further interest in these compounds stem from the use of the natural source as an east African traditional remedy against high blood pressure and various other chest diseases.[43] They also show modest antimicrobial activity against a range of microbe organisms.[44] The hypoestenones contain a unique stereochemistry at C-11 compared to all other fusicoccanes which are epimeric at this position.

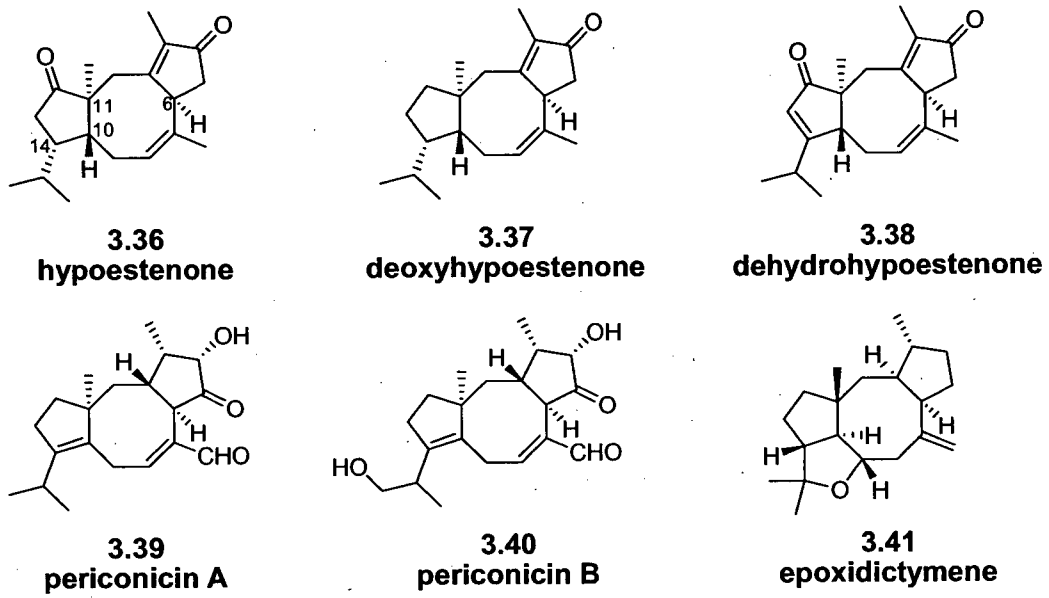


Figure 3.3 Hypoestenones, Periconicins and Epoxydictymene Structures

Periconicin A (**3.39**) and B (**3.40**) (Figure 3.3) were recently isolated from the endophytic fungus *Periconia* sp. OBW-15.[45] The periconicins exhibited significant antibacterial activity against both Gram-positive and Gram-negative bacteria.[44] They also showed activity against fungal agents of human mycosis in addition to the usual fusicoccane plant growth regulatory activity.[46]

A last fusicoccane diterpenoid is included here due to its complex structure and consequently its interest in its total synthesis. Epoxydictymene (**3.41**), a metabolite of the brown algae *Dictyota dichotoma*, is a structurally interesting fusicoccane since it features a 5-8-5-5 tetracycle containing a strained *trans*-fused 5-5 ring system.[47] It is the only example of a tetracyclic fusicoccane and one of four terpene natural products to contain such a 5-5 *trans*-fusion.[48] It is also the only fusicoccane example from a marine source.

III. Previous Relevant Synthetic Approaches

Due to the large variety of natural products containing a 5-8-5 tricyclic framework, the following should be considered only as a brief overview on constructing such ring systems. Focus will be placed on the total synthesis of fusicoccanes which contain a particular stereorelationship around the A and B rings. This includes specifically anadensin, the fusicogigantones, the fusicogigantepoxides and the

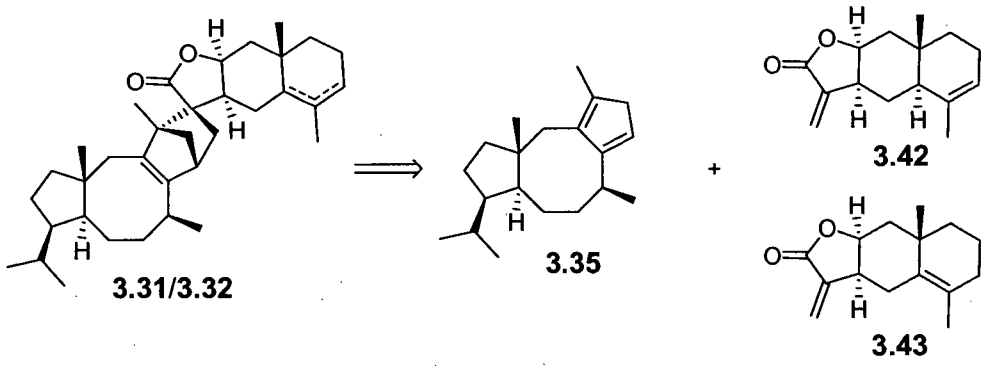
plagiospirolides. A brief description on the total synthesis of ophiobolanes, as well as other generalized approaches to 5-8-5 tricyclic frameworks will also be presented in a second part.

A. Synthesis of Fusicoccanes

The synthesis of fusicoccanes originating from liverwort sources (exemplified in Figure 3.2) is described below. Specifically, these fusicoccanes structurally include fused bicycles containing a methyl in a *cis* relationship with an isopropyl within a cyclopentyl ring system. An overview of their total synthesis is described below with particular attention to the structural arrangement about the cyclopentyl fragment of interest.

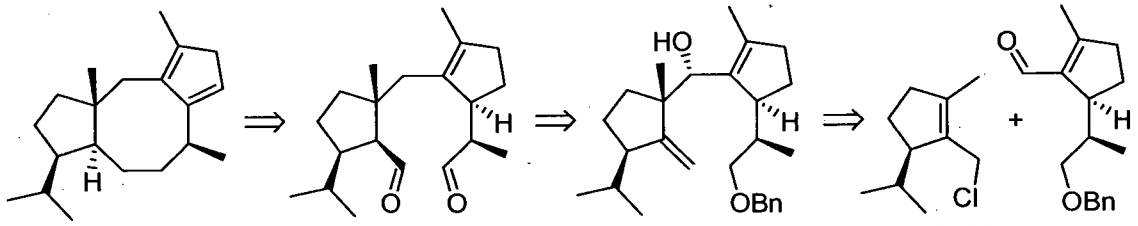
i) Plagiospirolides A and B

Although the plagiospirolides are not explicitly fusicoccane diterpenes in nature, focus will be directed towards the synthesis of the fusicoccadiene fragment (**3.35**). This is widely thought to be an intermediate in the biosynthetic Diels-Alder formation of these C_{35} terpenoids (*vide supra*). The asymmetric syntheses of plagiospiroides A (**3.31**) and plagiospirolide B (**3.32**) has been reported only once by means of a biomimetic approach by Takeshita and co-workers.[49] These terpenoids were constructed through Diels-Alder reactions between the sesquiterpenoids, diplophyllolide A (**3.42**) and diplophyllin (**3.43**), and fusicoccadiene (**3.35**) (Scheme 3.5).



Scheme 3.5 Biomimetic Diels-Alder Approach to Plagiospirolides A and B[49]

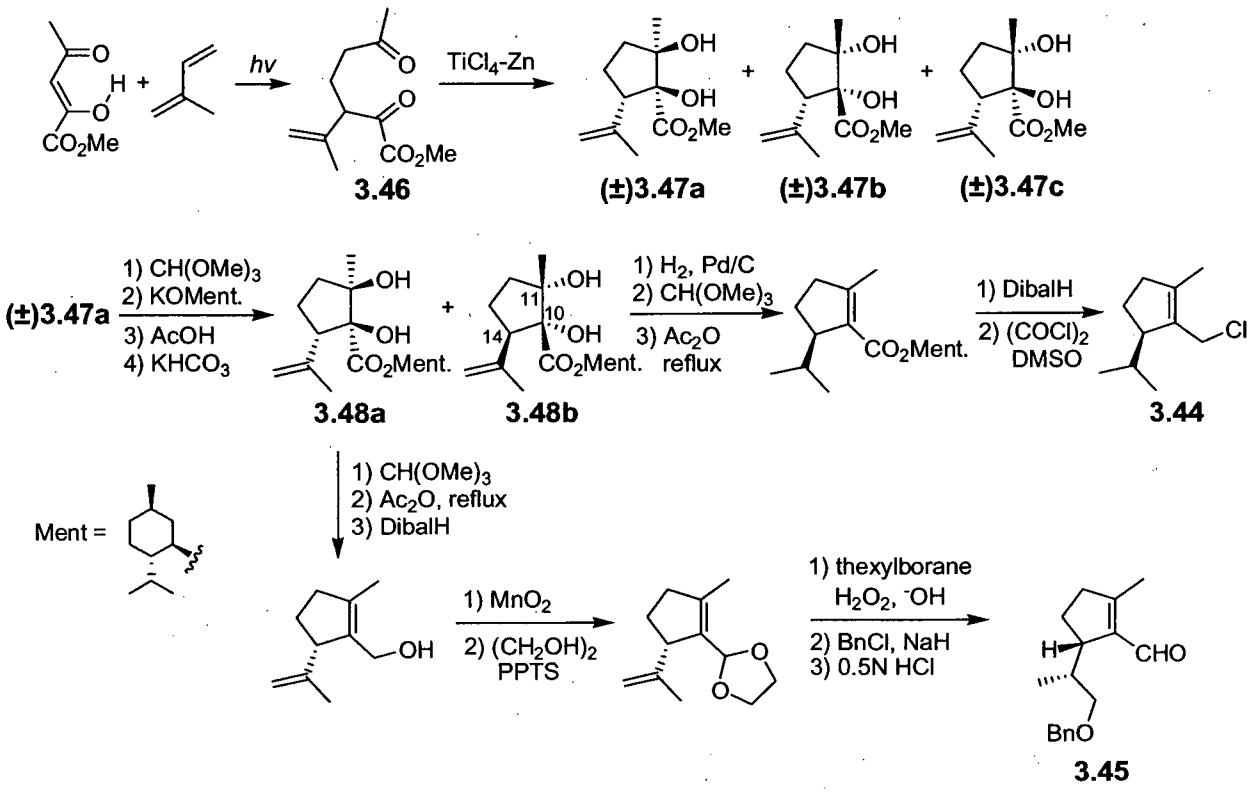
Retrosynthetic analysis of **3.35** suggested two C-C disconnections about the 8-membered ring to give two cyclopentenyl fragments **3.44** and **3.45** (Scheme 3.6). The first disconnection provides a dialdehyde. Synthetically, this bond is formed by a reductive cyclization. Bond formation in the case of the second disconnection involves a chromium-mediated condensation.



3.35 **3.44** **3.45**

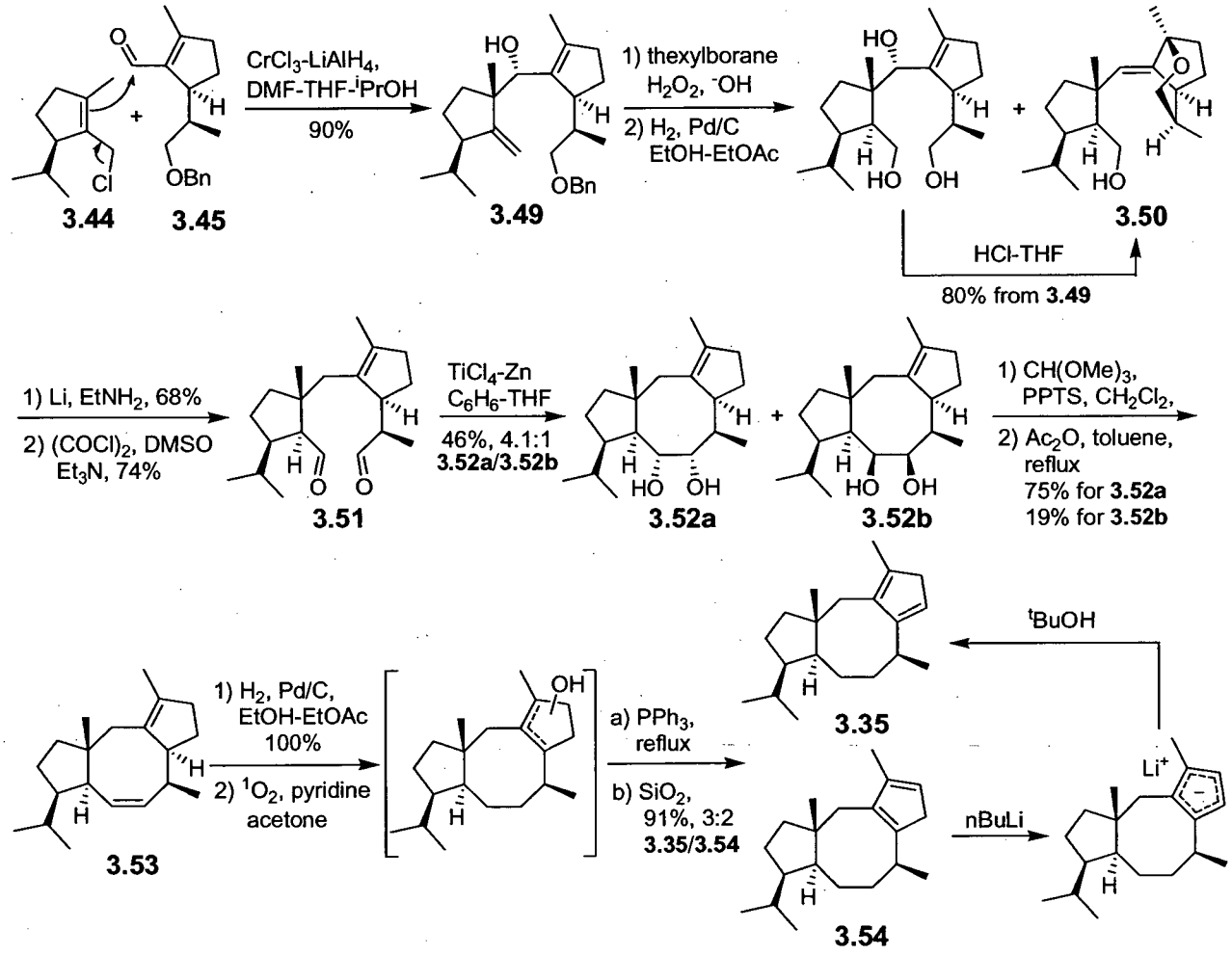
Scheme 3.6 Retrosynthetic Analysis for Fusicoccadiene 3.35[49]

The cyclopentenyl fragments, **3.44** and **3.45**, were both synthesized by the use of a common route originating from the reductive cyclization[50] of photoadduct **3.46** (Scheme 3.7). The desired racemic diol **(±)3.47a** was derivatized as the two diastereomeric methyl esters **3.48a** and **3.48b**, which were resolved by fractional recrystalization. The cyclopentenyl fragment **3.44** was subsequently prepared from **3.48b** by means of standard manipulations, and likewise, **3.45** was obtained from **3.48a**.



Scheme 3.7 Synthesis of the Cyclopentenyl Fragments 3.44 and 3.45[49]

The two cyclopentenyl fragments were coupled using chromium(II) chloride to produce the allylic alcohol **3.49** in 90% yield (Scheme 3.8). Hydroboration with thexylborane followed by removal of the benzyl group under hydrogenation conditions resulted in a mixture of the expected diol and cyclized ether **3.50**. Treatment of the mixture with hydrochloric acid afforded exclusively **3.50** which was then reductively converted to the diol under Birch conditions and then oxidized to the dialdehyde cyclization substrate **3.51**. A titanium(II)-mediated reductive cyclization followed,[50] which produced a 4:1 mixture of cis-glycols **3.52a** and **3.52b**. These glycols were individually converted into diene **3.53** via an Eastwood-Ando reductive elimination[51] of the intermediate orthoformates. Hydrogenation of the cyclooctene alkene was then performed which also resulted in isomerization of the cyclopentene to produce a 5:3 mixture of alkenes. Oxidation of this mixture with singlet oxygen, followed by reduction with triphenylphosphine and dehydration with silica gel, afforded a mixture of cyclopentadienes **3.35** and **3.54** in a 3:2 ratio. Treating the mixture with butyllithium and quenching with t-butanol afforded exclusively **3.35**, which equilibrated back to a 3:2 ratio of **3.35** and **3.54** when heated above 80 °C.



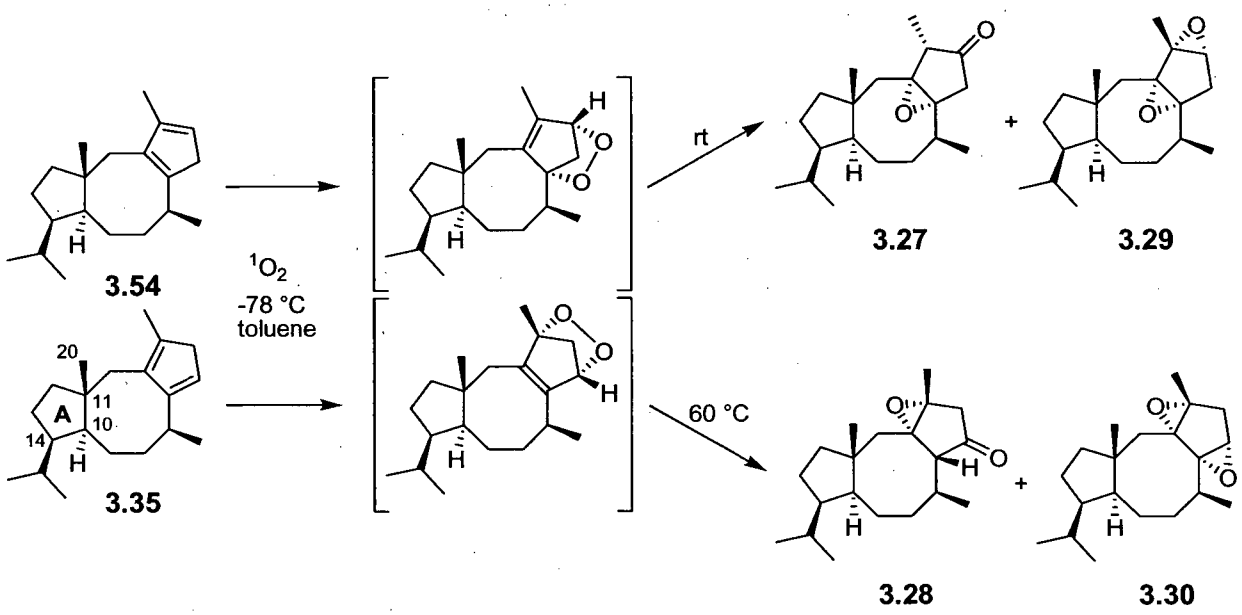
Scheme 3.8 Synthesis of Fusicoccadiene 3.35[49]

When the equilibrium mixture of **3.35** and **3.54** was heated with either **3.42** or **3.43**, plagiospirolide A or B was obtained as the major products (Scheme 3.5). This completed the only total synthesis to date for these diterpenoids.

ii) Fusigicogantones, fusicogigantepoxides and anadensin

Fusicocadiene **3.35** and its isomer **3.54** were also subsequently used in a total synthesis of the fusicogigantones, the fusicogigantepoxides and a formal synthesis of anadensin.[52] The equilibrium mixture of **3.35** and **3.54** was oxygenated with singlet oxygen generated by tetraphenylporphin under an oxygen atmosphere at -78 °C to produce two endoperoxides (Scheme 3.9). These intermediates then rearranged to a

mixture of **3.27**, **3.28**, **3.29**, and **3.30** upon heating. Since anadensin had previously been formed from fusicogigantone A (**3.27**), this also constituted a formal synthesis of anadensin (*vide supra*).[37a]



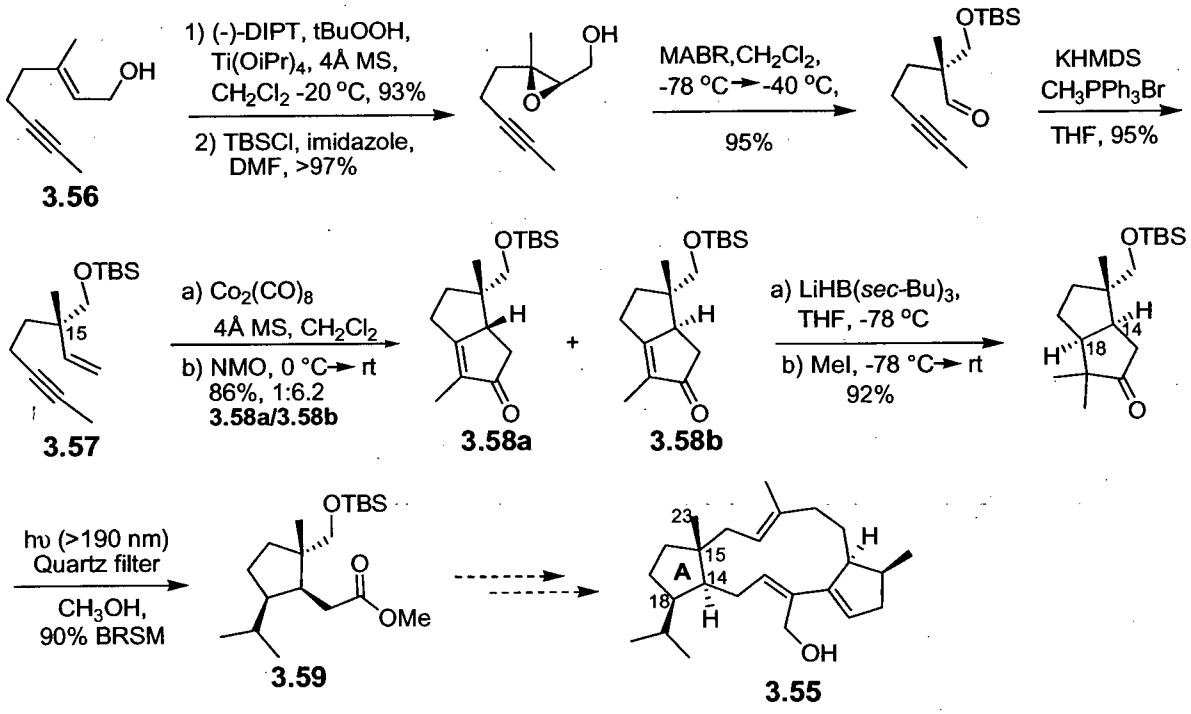
Scheme 3.9 Synthesis of the Fusicogigantones and the Fusicogigantepoxides[52]

It is worth taking note of the stereochemical considerations about the A-ring in the synthesis of the plagiospirolides, the fusicogigantone, the fusicogigantepoxide and anadensin. This synthetic challenge involves forming a cyclopentyl structural motif containing a *cis* relationship between the isopropyl group at C-14 and the C-20 methyl in the A-ring. This difficulty was overcome by resolving the two enantiomers of **3.48** in order to first set the isopropyl stereochemistry (Scheme 3.7). The remaining stereocentres about the A-ring, at C-10 and C-11 were then set by chemical relay from the C-14 isopropyl. The chromium(II) mediated condensation of the two cyclopentenyl fragments resulted in the approach of the electrophile opposite the isopropyl (Scheme 3.8). Hydroboration of the alkene in **3.49** also resulted in the reagent approach opposite the isopropyl group.

iii) Nitiol

The cyclopentyl structural motif containing three contiguous stereochemical centres has also recently been handled in our laboratory in a synthetic approach to nitiol

(**3.55**).[53] The A-ring of nitiol was prepared by way of the Sharpless epoxidation of allylic alcohol **3.56**, followed by a Lewis acid mediated stereoselective siloxyepoxide rearrangement and olefination to form enyne **3.57** (Scheme 3.10). A Pauson-Khand reaction, hydride reduction of the resulting enone followed by quenching with iodomethane, and an α-carbonyl photofragmentation resulted in the advanced cyclopentyl intermediate **3.59**.



Scheme 3.10 Synthesis of the A-ring Fragment of Nitiol[53]

The stereoselectivity of the Pauson-Khand reaction was dictated by the C-15 quaternary stereocentre, which in turn ensured a *cis* arrangement between the isopropyl at C-18 and the alkyl substituent at C-14. To the best of our knowledge, these are the only two examples (syntheses of **3.35** and **3.59**) which require the construction of a cyclopentyl containing three contiguous stereocentres (specifically involving the methyl and an isopropyl centres) in such an arrangement.

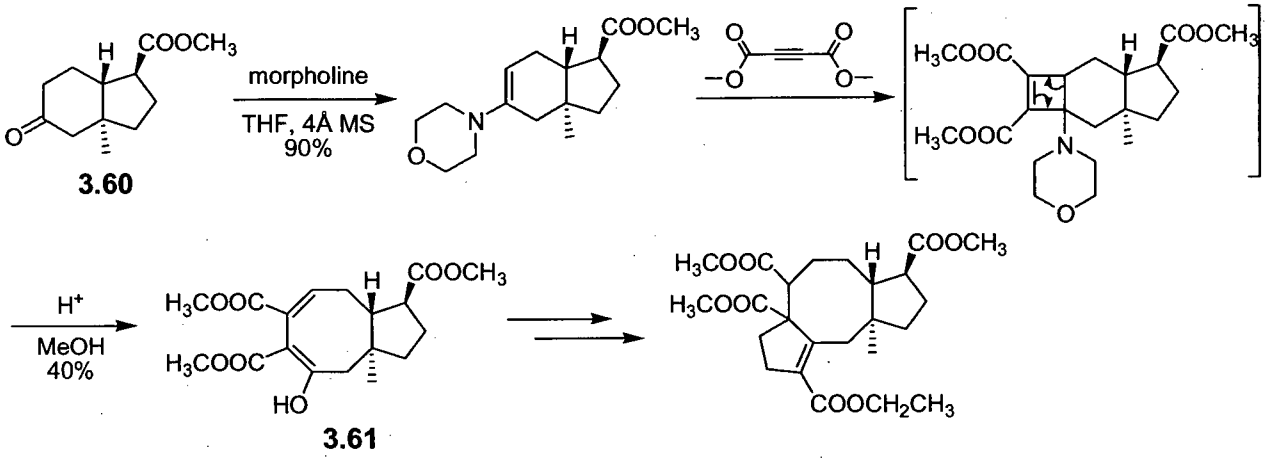
B. Generalized Approach to 5-8-5 Tricyclic Frameworks

The following description serves as a brief overview of the methods developed to construct 5-8-5 tricyclic frameworks in general. Despite the interesting aspects in the

formation of such tricycles as that present in the ophiobolane and fusicoccane diterpenoids, only a few examples of completed total syntheses have been presented in the literature. However, a number of approaches in the preparation of the tricyclic core have been reported. In a general sense, these have focused around the formation of the cyclooctanoid central ring as the key synthetic challenge. A number of strategies have been employed and an attempt to categorize these various approaches has been made here.

i) Approaches involving Cycloadditions/Fragmentations

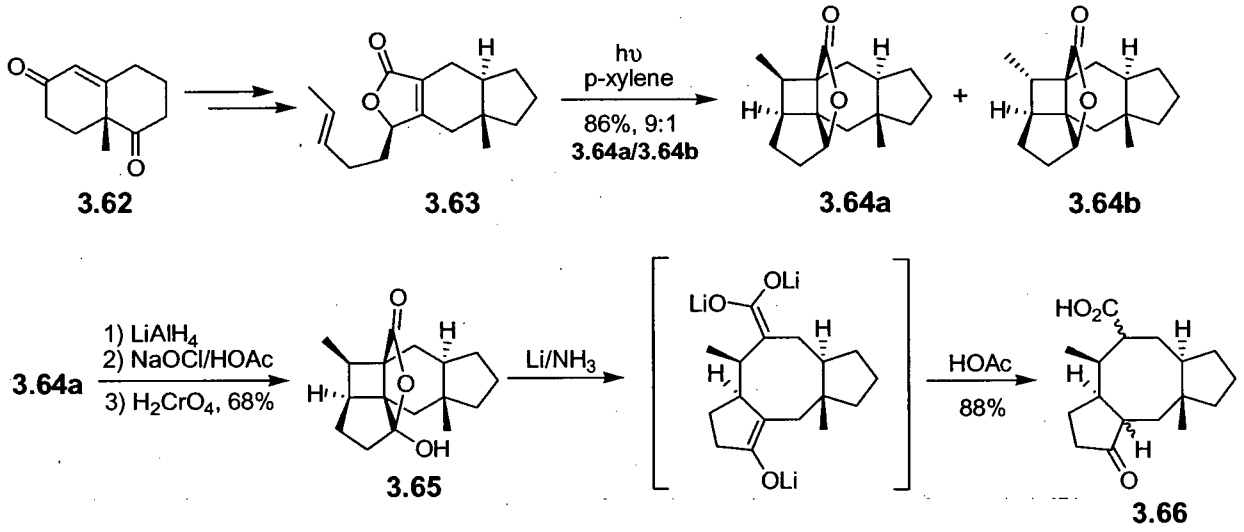
The first synthetic approach to the 5-8-5 tricyclic framework was reported in 1977.[54] In a synthesis of the ophiobolin nucleus by Dauben and co-workers, a [2+2] cycloaddition followed by a retro [2+2] fragmentation was utilized (Scheme 3.11). This involved treating the morpholine enamine of **3.60** with dimethyl acetylenedicarboxylate. The portion containing a 6-membered carbocycle fused to a 4-membered ring in the resulting tricycle underwent a rearrangement followed by hydrolysis upon treatment with acidic methanol to yield **3.61**. Further elaboration yielded a tricyclic framework resembling the ophiobolin ring skeleton.



Scheme 3.11 Synthesis of the Ophiobolin Nucleus[54]

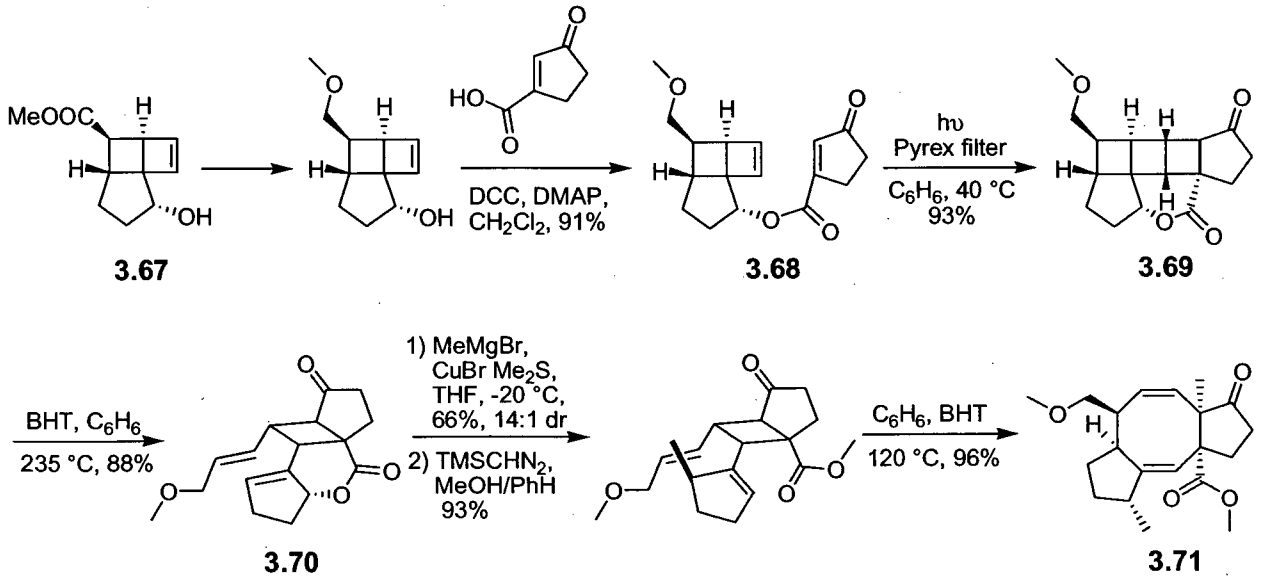
The cycloaddition followed by a fragmentation strategy used by Dauben and co-workers has subsequently been employed in a number of syntheses of the ophiobolanes and fusicoccanes to form the cyclooctanoid portion. Coates and co-workers subsequently reported an intramolecular [2+2] of hydrindenes followed by a radical fragmentation approach to these ring systems[55]. Hydrindene **3.63** was prepared

in 14 steps from the Wieland-Mischer ketone **3.62** (Scheme 3.12). Light irradiation resulted in the photocycloaddition to yield **3.64a** along with the minor diastereomer **3.64b**. A sequence of reduction and oxidations produced **3.65,** which was reductively cleaved to **3.66** with lithium in ammonia to form a 5-8-5 tricyclic framework. A number of examples were presented. However little control of the diastereoselectivity of the fragmentation process was possible, and a number of isomers were obtained.



Scheme 3.12 Intramolecular [2+2]-Photocycloaddition/Radical Fragmentation of Hydrindenes Approach Towards 5-8-5 Ring Systems[55]

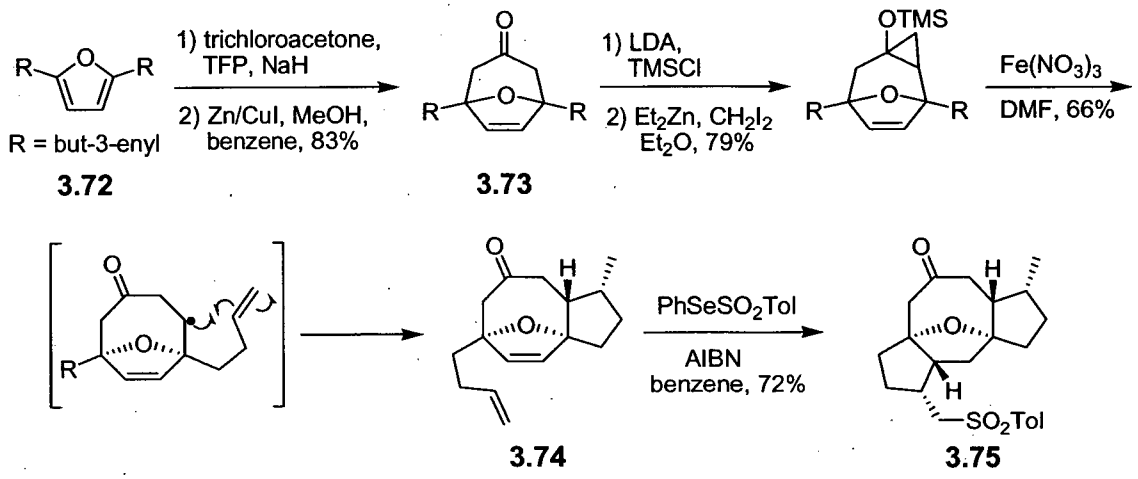
Snapper and co-workers have reported an approach to the fusicoccane ring system involving a regio- and stereoselective intermolecular [2+2]-photocycloaddition between functionalized cyclobutenes and cyclopentenones, followed by the thermal fragmentation of the resulting photoadducts (Scheme 3.13).[56] Manipulation of cyclobutene **3.67** and esterification leads to the cycloaddition substrate **3.68**. Subjection of **3.68** to pyrex filtered light radiation promotes an intramolecular [2+2]-photocycloaddition, providing the highly strained photoadduct **3.69**. Thermolysis of the photoadduct resulted in dialkenyl cyclobutane **3.70**. This was followed by methyl organocuprate S_N2' nucleophilic addition to the allylic lactone and a thermally promoted Cope rearrangement to form cyclooctadiene **3.71**. Formally, **3.71** is the result of a [2+2], retro-[2+2] sequence from **3.68** followed by hydrolysis.



Scheme 3.13 Intramolecular [2+2]-Photocycloaddition/Thermal Fragmentation Approach Towards 5-8-5 Ring Systems[56]

The stereochemical issues in the thermal fragmentation of photoadduct **3.69** result from a chair-like diradical intermediate which leads to **3.70**. This is followed by the Cope rearrangement which proceeds through a stereoselective boat-like conformation. Hence, a 5-8-5 tricyclic ring system is produced with stereochemistry and functionality in place to access a number of fusicoccanes and ophiobolanes.

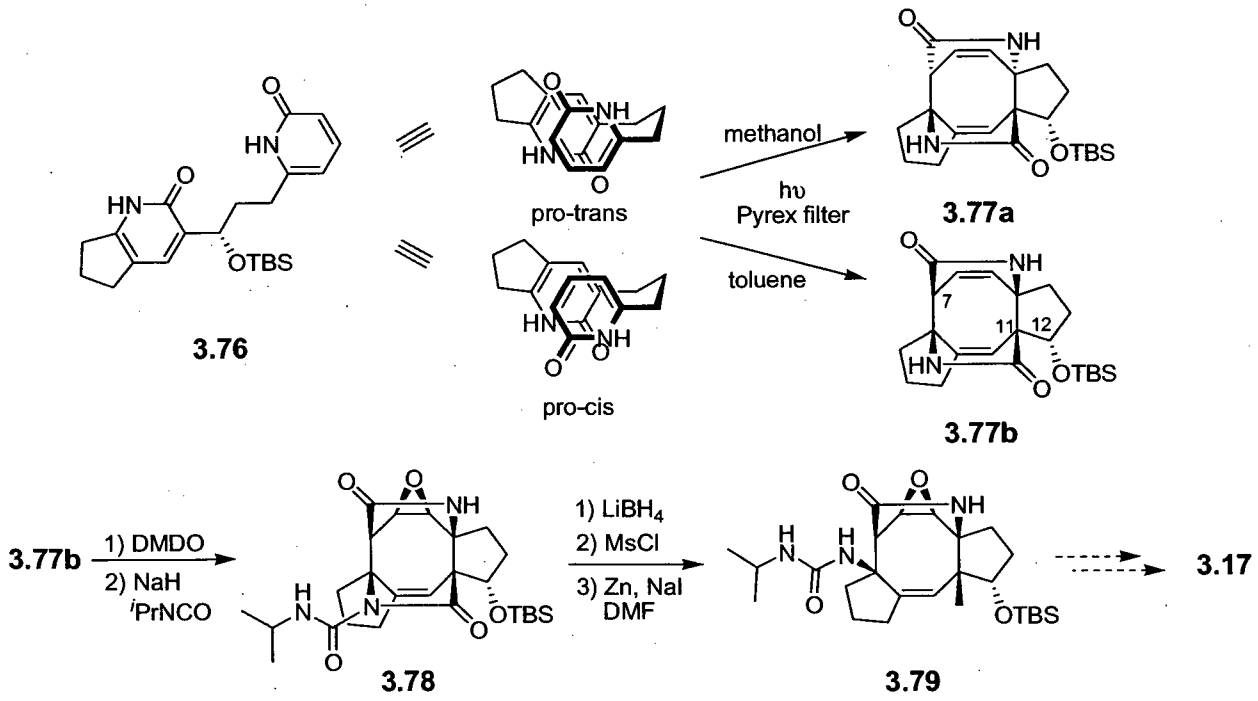
A recent strategy was reported by Simpkins and co-workers.[57] This approach involved a [4+3] cycloaddition to form a 7-membered ring, followed by a concomitant Saegusa fragmentation and radical cyclization onto an unsaturated appendage to form an 8-5 bicycle (Scheme 3.14). The furan **3.72** was subjected to a [4+3] cycloaddition using the enolate of trichloroacetone in the presence of 2,2,3,3-tetrafluoropropan-1-ol (TFP), followed by dehalogenation to yield the oxa-bridged bicyclic ketone **3.73**. Cyclopropanation of the silylenol ether of **3.73** was followed by radical fragmentation using a modified Saegusa protocol. A *5-exo-trig* cyclization of the resulting radical onto the butenyl appendage ensued to form **3.74**. The remaining 5-membered ring was then formed by a second promoted *5-exo-trig* cyclization yielding **3.75**.



Scheme 3.14 Saegusa Radical Fragmentation/Annulation Approach Towards 5-8-5 Ring Systems[57]

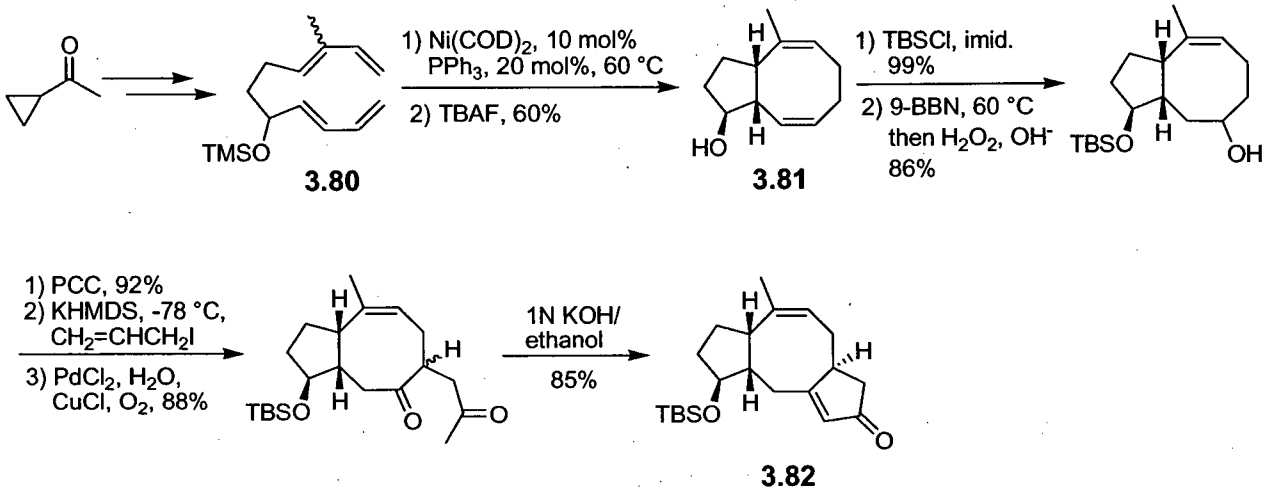
The remaining two examples of this section involve [4+4]-cycloadditions in order to obtain the 5-8-5 tricycle cyclooctanoid ring directly. Sieburth and co-workers have developed an intramolecular [4+4]-photocycloaddition of 2-pyridinones (Scheme 3.15).[58] The photocycloaddition substrate **3.76**, which contained a pyridinone tethered to a pyrindinone, was subjugated to pyrex filtered light radiation. This could proceed by way of two conformations wherein the 2-pyridinone rings could be in either a pro-*trans* or pro-*cis* arrangement, resulting in **3.77a** or **3.77b** respectively. In cases where the photocycloaddition was performed on *N*-methylated substrates, the *trans* product predominated, this resulting from less overall steric interactions than for the *cis* product. However, in the absence of *N*-methylation, a solvent dependence was observed. In non-polar solvents, the *cis* product **3.77b** was obtained, whereas in polar solvents, **3.77a** was formed. This strongly suggests a hydrogen bonding effect between the pyridinones which is favored in the pro-*cis* conformation. The *cis* product **3.77b** contained the desired stereochemical arrangement between C-7 and C-11 observed in the fusicoccin diterpenoids (see Scheme 3.3). However, **3.77b** underwent an irreversible Cope rearrangement at ambient temperature and a second reaction was required in order to arrest the rearrangement. Treatment of the crude **3.77b** with dimethyl dioxirane at low temperature (0-5 °C) resulted in a chemo- and stereoselective epoxidation. Deprotonation and chemoselective addition of isopropyl isocyanate produced **3.78**. This was followed by lithium borohydride reduction of the activated

amide and deoxygenation of the resulting alcohol to form **3.79** as an advanced intermediate in an approach to the synthesis of fusicoccin A (**3.17**).



Scheme 3.15 Intramolecular [4+4]-Photocycloaddition of Tethered 2-Pyridinones Approach Towards Fusicoccin Ring System[58]

Wender and co-workers have also employed a [4+4]-cycloaddition in which the cyclooctanoid ring is obtained directly with no need for further modifications.[59] Hence a bis-diene **3.80** was prepared in 6 steps from commercially available cyclopropyl methyl ketone (Scheme 3.16). The key [4+4] cycloaddition was promoted using catalytic Ni^0 to produce mostly **3.81** after desilylation, along with a small amount of the endo alcohol epimer. Hydroboration and further manipulations allowed for the appendage of a second cyclopentane ring after base treatment of the diketone **3.82**. Hence, **3.82** was proposed as an advanced intermediate in the possible synthesis of a number of ophiobolanes and fusicoccanes.

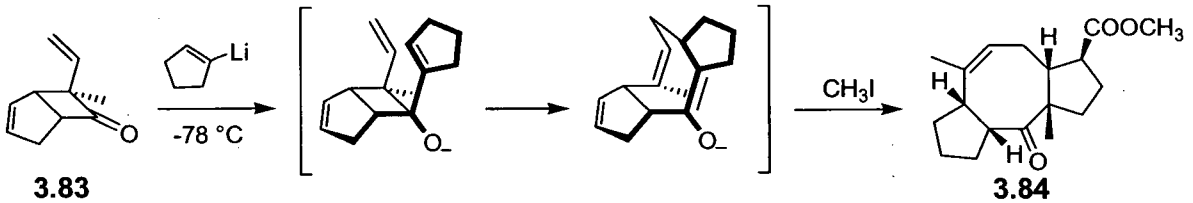


3.80 **3.81** **3.82**

Scheme 3.16 [4+4] Cycloaddition Approach to the Ophiobolanes and Fusicoccanes[59]

ii) Approaches involving [3,3]-sigmatropic rearrangements

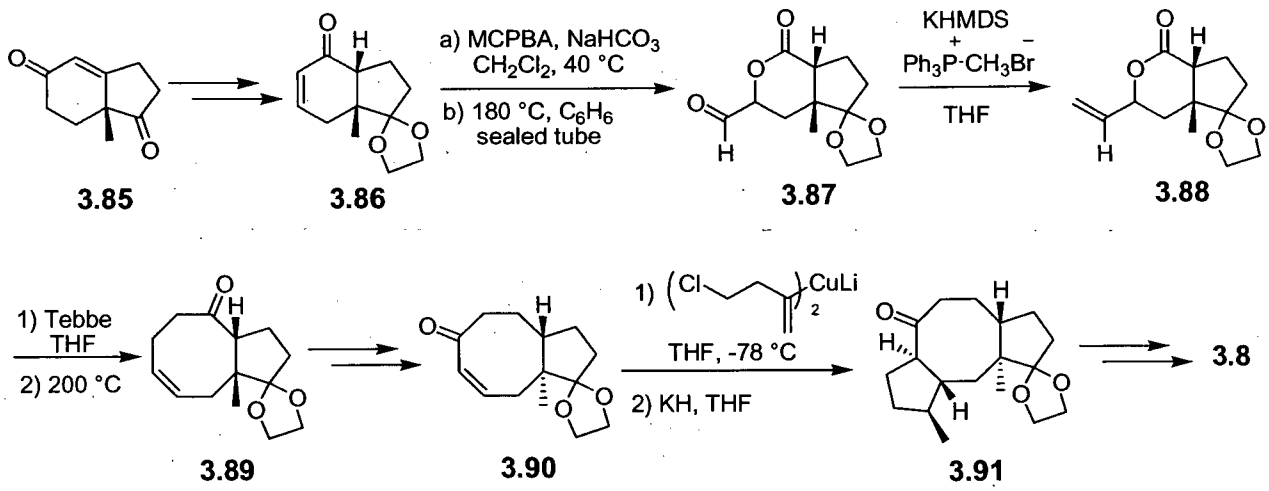
Paquette and co-workers have reported an anionic oxy-Cope rearrangement approach to the ophiobolin ring system.[60] The [3.2.0]-bicycle **3.83**, obtained as a 7:3 mixture with its epimer from the [2+2] cycloaddition of methyl vinyl ketene and cyclopentadiene, was treated with 1-cyclopentenyllithium (Scheme 3.17). This resulted in exo facial attack and the intermediate was easily predisposed to the anionic oxy-Cope rearrangement due to the low activation energy required in the relief of the 4-membered ring strain energy. Addition of iodomethane resulted in a single isomer **3.84**. The stereochemical consideration of the four ring junction stereocentres follows from the anticipated boat-like transition state of the sigmatropic rearrangement and from the sterically controlled addition during the methylation of the enolate anion. Hence, this process allows for a rapid entry to the 5-8-5 tricyclic systems.



3.83 **3.84**

Scheme 3.17 Anionic Oxy-Cope Rearrangement Approach to the Ophiobolanes and Fusicoccanes[60]

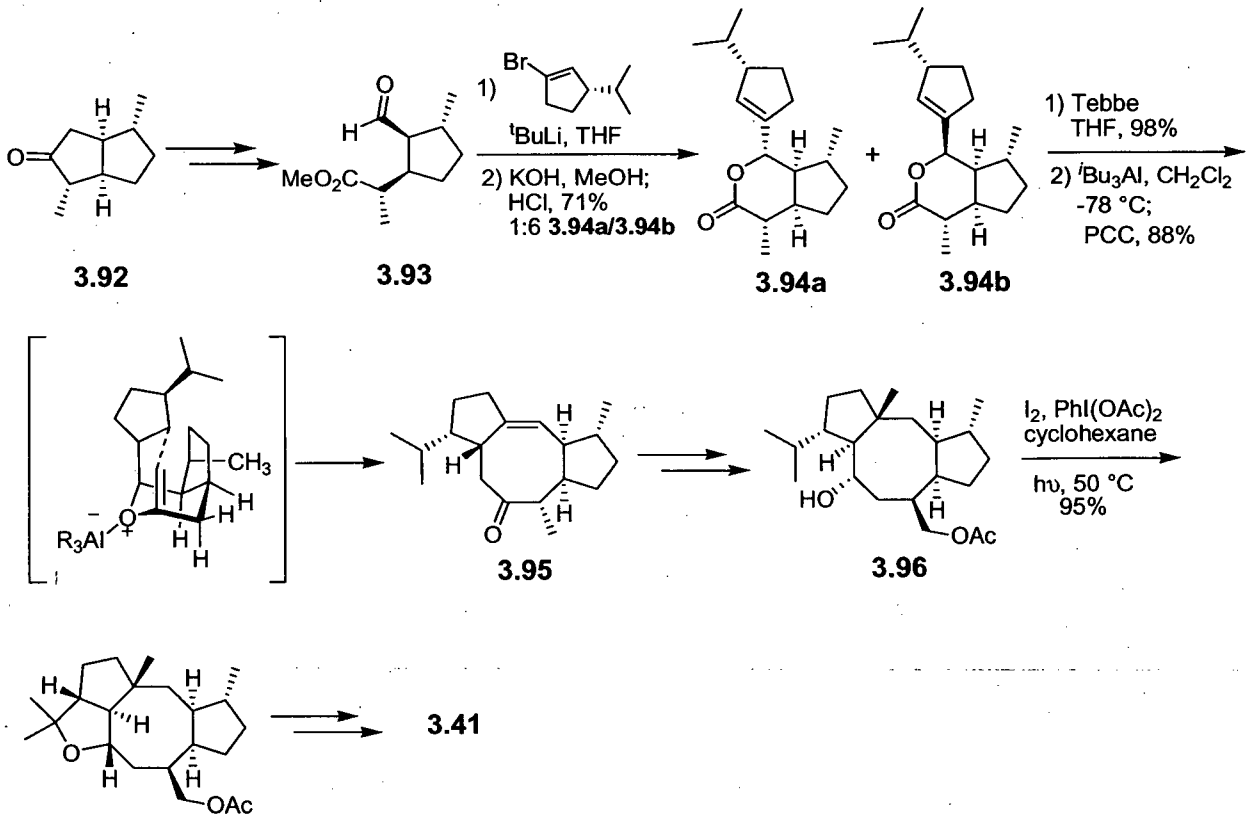
Subsequently, Paquette and co-workers have used a 2-carbon intercalation protocol of a cyclohexenone to form the cyclooctanoid ring in a synthesis of (+)-ceroplastol I (**3.8**).[61] This process makes use of a tandem Tebbe olefination and Claisen ring expansion process (Scheme 3.18). The cyclohexenone **3.86**, obtained in four steps from the Hajos-Parrish ketone **3.85**, was heated in the presence of a peracid to form **3.87** via the rearrangement of an intermediate epoxylactone. A Wittig olefination followed to produce **3.88**. A Tebbe olefination was followed by a subsequent Claisen rearrangement at elevated temperature to form the 5-8 bicycle **3.89**. The remaining ring was appended via a conjugate addition to enone **3.90**, obtained in five steps from **3.89**, followed by annulation yielding **3.91**. Subsequent functional group manipulations produced ceroplastol I (**3.8**) in an additional 5 steps.



Scheme 3.18 Synthesis of Ceroplastol I using a Claisen Rearrangement Procedure[61]

This approach was also used in a synthesis of the structurally more complex synthesis (+)-epoxydictymene (**3.41**) by Paquette and co-workers.[62] The Claisen rearrangement precursor was prepared from a cyclopentenyllithium addition to **3.93**, which in turn was easily prepared in three steps from known enantiopure **3.92** (Scheme 3.19). This provided a 1:6 mixture of **3.94a** and **3.94b** after lactonization. The tandem Tebbe olefination and Claisen ring expansion process using **3.94b** followed in which use of tributylaluminum allowed for the key rearrangement to proceed at low temperature. The stereochemical outcome was rationalized by a chair-like conformation in the transition state providing **3.95** as a single diastereomer. A number

of manipulations provided **3.96**, which was then subjected to an alkoxy-directed radical cyclization to form the tetracyclic framework. This was then converted to (+)-epoxydictymene (**3.41**) in a further three steps.



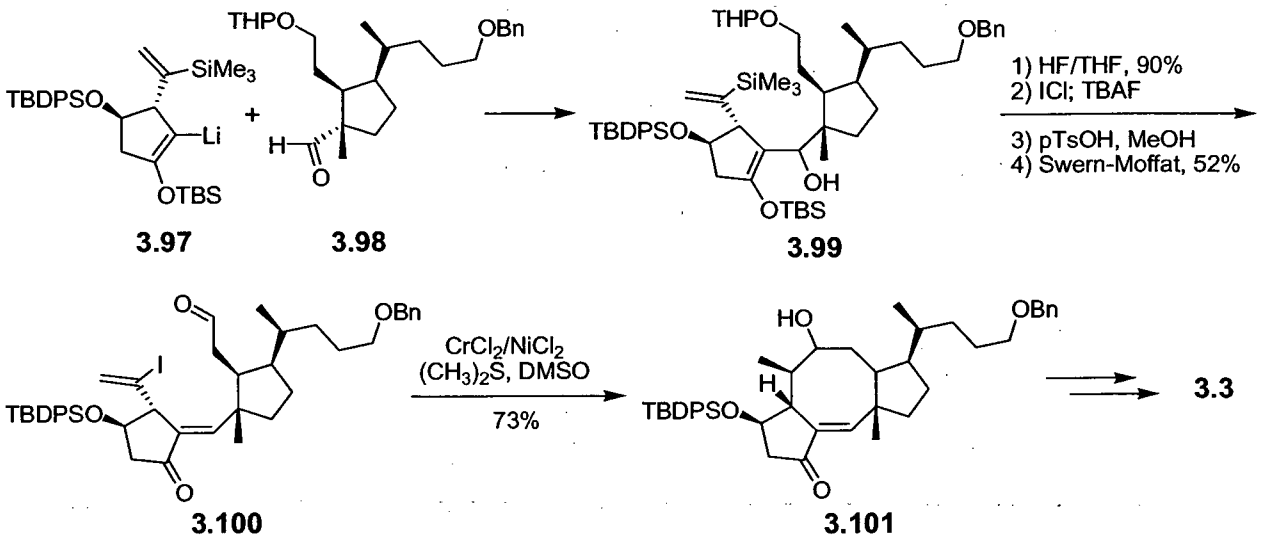
3.92 **3.93** **3.94a** **3.94b** **3.95** **3.96** **3.41**

Scheme 3.19 Total Synthesis of (+)-Epoxydictymene Using a Claisen Rearrangement Procedure[62]

iii) Approaches involving acyclic cyclizations

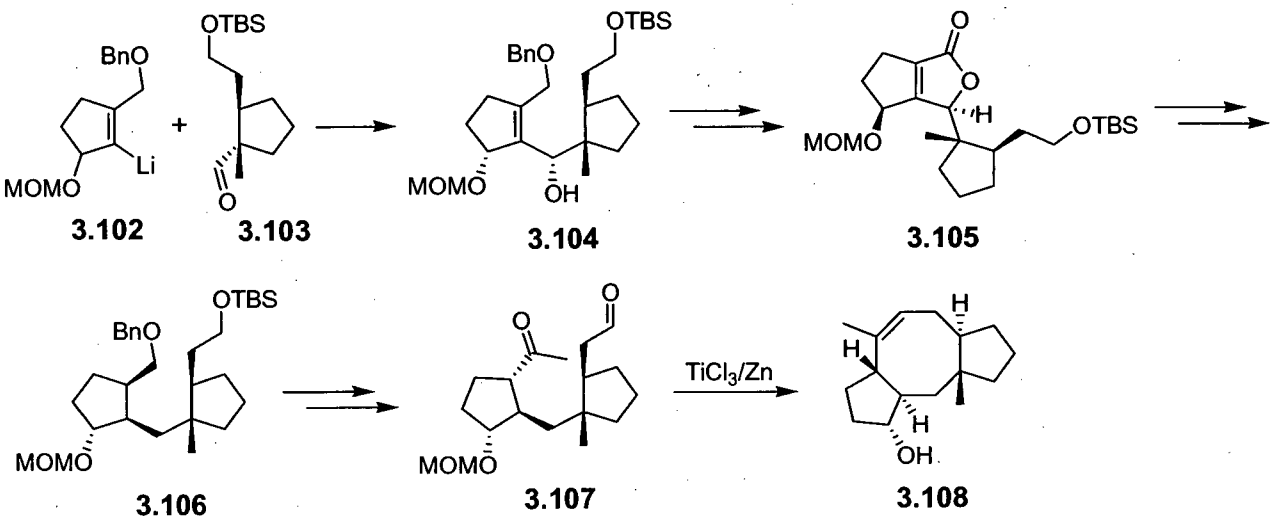
The majority of acyclic cyclization approaches have involved the intermolecular coupling of two tethered cyclopentyl ring through reductive methods. Although this appears as the simplest method to synthesize the tricyclic framework, the formation on an 8-membered ring from an acyclic precursor is a formidable challenge. This is primarily due to unfavorable torsional strain and transannular interactions engendered in the cyclization process. Kishi and co-workers were the first to present such an approach in their synthesis of (+)-ophiobolin C (**3.3**) in which a Ni(II)/Cr(II) mediated intramolecular reductive coupling procedure was employed to form the cyclooctanoid

ring (Scheme 3.20).[63] The two tethered cyclopentyl rings were coupled by the addition of vinyllithium **3.97** to the aldehyde **3.98**. The vinylogous hemiacetal **3.99** was hydrolyzed to the *E*-enone, followed by iododesilylation, deprotection and oxidation to produce **3.100**. The key cyclization step was accomplished using chromium chloride and catalytic nickel chloride yielding a single unspecified diastereomer **3.101**. A couple of additional functional group manipulations yielded (+)-ophiobolin C (**3.3**).



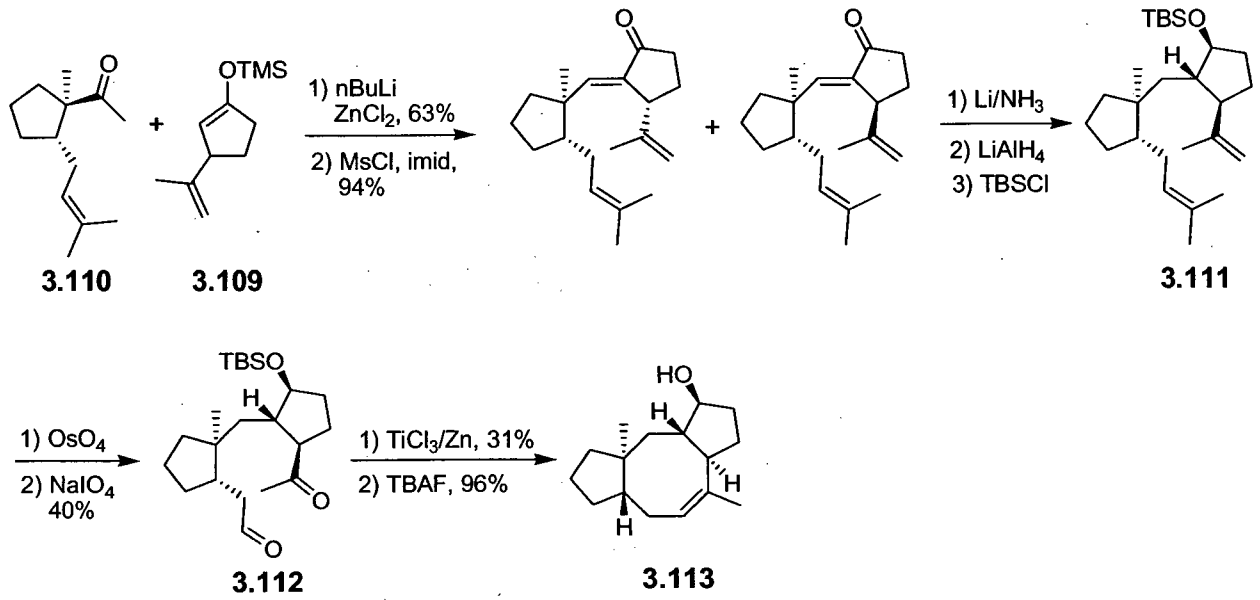
Scheme 3.20 Synthesis of (+)-Ophiobolin C Using a Ni(II)/Cr(II) Intramolecular Reductive Coupling[63]

In addition to the above approach of using a Ni(II)/Cr(II) mediated reductive coupling of tethered cyclopentanes, Dauben and co-workers[64] as well as Snider and co-workers[65] have both used a titanium mediated reductive coupling in essentially a similar approach for the synthesis of the ceroplastin nucleus. In Dauben's synthesis, vinyllithium **3.102** was added to the aldehyde **3.103** (Scheme 3.21). A mixture of diastereomers were obtained which were subsequently separated and each carried through to produce a number of 5-8-5 tricyclic frameworks. For simplicity, only one sequence is shown. The coupling product **3.104** was cyclized into a bicyclic lactone **3.105**. This allowed for diastereoselective hydrogenation, eventually producing **3.106**. Further functionalization produced the keto aldehyde **3.107** which cyclized to the ceroplastin nucleus **3.108** in approximately 50% yield using titanium trichloride.



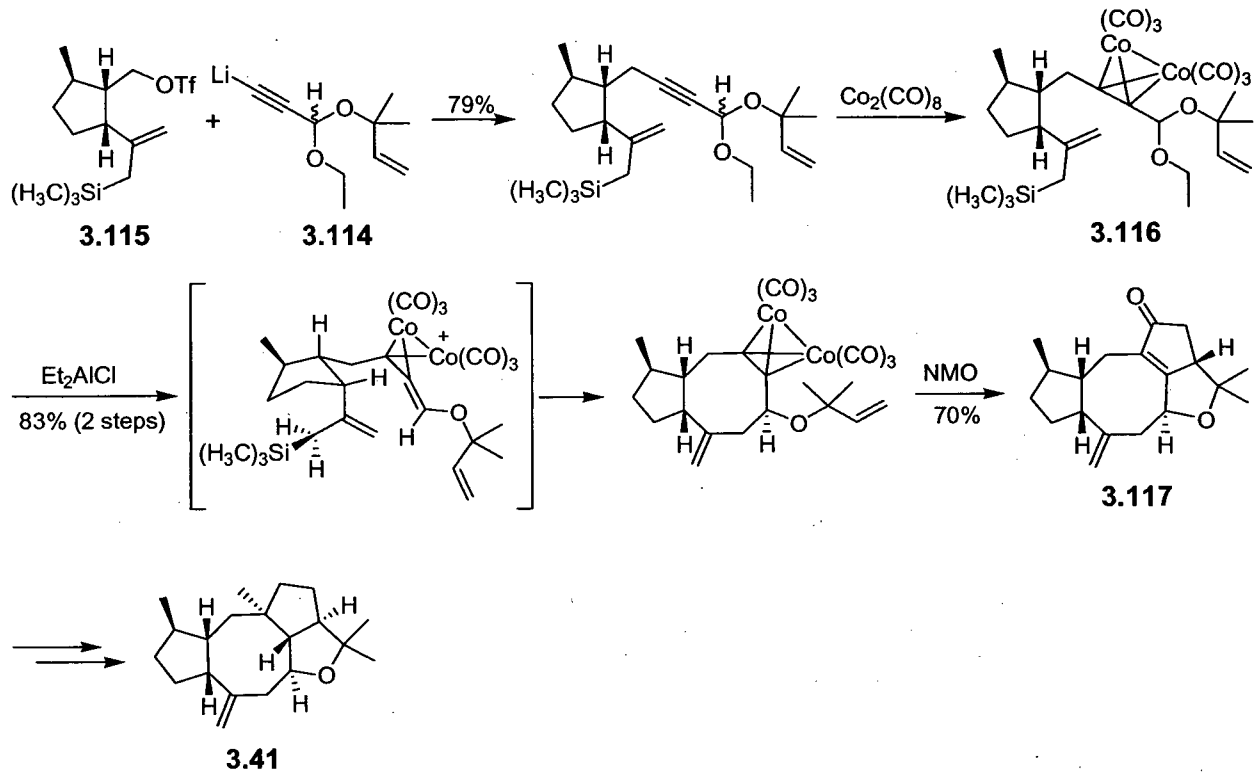
Scheme 3.21 Synthesis of the Ceroplastin Nucleus Using a Titanium Intramolecular Reductive Coupling (Dauben)[64]

Snider and co-workers used a similar approach which differed mostly in the construction of the cyclopentyl fragments (Scheme 3.22). Hence, silyl enol ether **3.109** was added in an aldol fashion to the aldehyde **3.110**. Diastereomers are produced since racemic **3.109** was used. Lithium/ammonia reduction followed by further ketone reduction provided a mixture of eight stereoisomers in varying amounts. The major products obtained are shown and, although the sequence was performed on each of the two, only one is shown for simplicity. The keto aldehyde **3.112** was produced from diene **3.111**, and the Ti(III)/Zn mediated reductive intramolecular coupling was carried out in 31% yield. Finally, deprotection produced **3.113**.



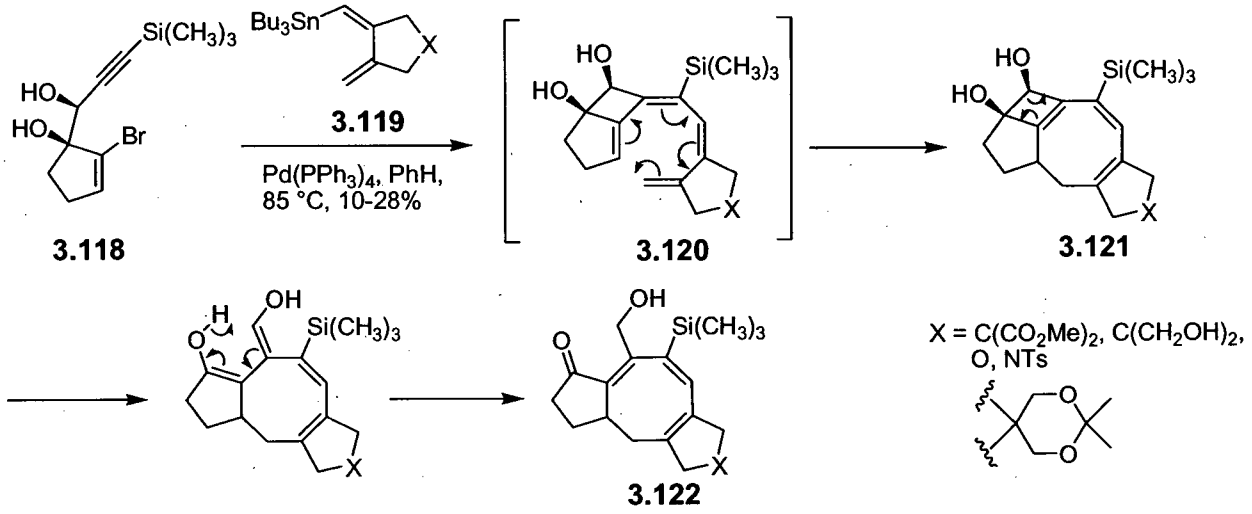
Scheme 3.22 Synthesis of the Ceroplastin Nucleus Using a Titanium Intramolecular Reductive Coupling (Snider)[65]

In an efficient total synthesis of (+)-epoxydictymene (**3.41**), Schreiber and co-workers made use of a cobalt mediated Nicholas reaction to append the cyclooctanoid ring to a cyclopentyl ring, followed by a Pauson-Khand reaction to form the remaining fused rings (Scheme 3.23).[66] The Nicholas reaction cyclopentyl substrate **3.116** was prepared by adding the lithium anion of **3.114** to the cyclopentyltriflate **3.115** followed by dicobalt octacarbonyl treatment. Addition of a Lewis acid promoted the Nicholas cyclization to form the cyclooctanoid ring. Oxidative initiation of the Pauson-Khand cyclization yielded **3.117** which was subsequently functionalized into (+)-epoxydictymene (**3.41**).



Scheme 3.23 Total Synthesis of (+)-Epoxydictymene Using a Nicholas Cyclization/Pauson-Khand Procedure[66]

Suffert and Salem have recently made use of a tandem cyclopalladation/ electrocyclization to form a 5-8-5 tricyclic framework.[67] This procedure in essence employs a similar strategy as the above examples in that two cyclopentyl units are joined together followed by cyclization to form the central cyclooctane ring. However the coupling process is performed in tandem with the cyclization process, which itself involves an 8π-electrocyclization (Scheme 3.24). Hence, the cyclopentenyl bromide **3.118** was treated with catalytic Pd^0, initiating a 4-*exo*-dig carbopallation and followed by a Stille cross-coupling with the vinyl tin **3.119**, to yield **3.120** as an intermediate. The intermediate then underwent a concerted conrotatory 8π-electrocyclization to form the cyclooctanoid ring in **3.121**. Further 4 π-conrotatory ring opening and a 1,5-hydride transfer produced the observed product **3.122**. Although only a yield range of 10-28% was obtained depending on the nature of the vinyl tin cyclopentyl substrate, the tricyclic framework is essentially constructed in a single step from two simple cyclopentyl units.



Scheme 3.24 Synthesis of 5-8-5 Tricyclic Frameworks Using a Carbopalladation/Electrocyclization Approach[67]

IV. Concluding Remarks

A number of fusicoccane diterpenoids and ophiobolane sesteterpenoids have been isolated and characterized in the last 40 years. Their action as plant growth regulators has been widely recognized. A wide variety of other biological properties for these terpenoids have only been more recently explored. However, aside from the plant growth regulation properties, little else is known about the biological activity of the liverwort fusicoccane diterpenoids of the anadensin subfamily (Figure 3.2). A number of approaches to forming the 5-8-5 tricyclic core of the fusicoccanes have been presented in this chapter. The key step in all approaches presented involve the formation of the 8-membered ring. Surprisingly, the synthesis of the diterpenoids derived from fusicoccadiene (**3.35**) by Takeshita and co-workers (Scheme 3.7 and Scheme 3.8) is the only synthesis for members of the anadensin subfamily. As in the other syntheses presented, the formation of the 8-membered B ring was a key challenge in the synthesis. However, the A ring cyclopentyl containing a *cis* relationship between the isopropyl group at C-14 and the C-20 methyl also presented an important synthetic challenge.

V. References

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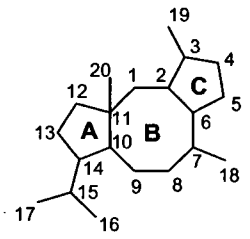
Chapter Four

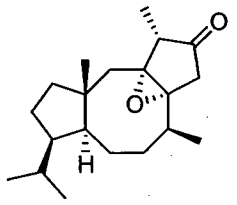
Synthetic Approach to the Fusicoccane Diterpenoids

I. Proposal

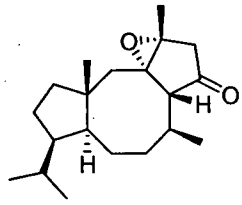
Since the first examples of fusicoccane diterpenoid based natural products 40 years ago, a number of fusicoccanes have been discovered from a variety of natural sources.[1] Surprisingly, a relatively low number of total syntheses for these types of natural products exist in the literature. Attention was initially drawn to them, especially the liverwort subset of these (Figure 4.1), by the commonality of the structural motif around the A-ring fragment. This structural motif is comprised of a cyclopentane ring system which contains three contiguous stereocentres. Specifically, there exists a *cis* relationship between the isopropyl group at C-14 and the C-20 methyl group. Our laboratory has been previously engaged in the construction of this cyclopentyl structural motif as part of the synthesis of the A-ring fragment of nitiol.[2] The synthetic challenges of establishing the remote C-7 methyl stereocentre and the formation of the 8-membered B-ring provided additional interest. Throughout this chapter, the natural product numbering shown in the fusicoccane skeleton in Figure 4.1, as well as the lettering for the representative ring systems will be used to discuss all synthetic intermediates towards the fusicoccane diterpenoids.[3]



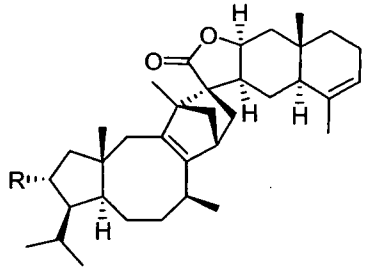
fusicoccane skeleton



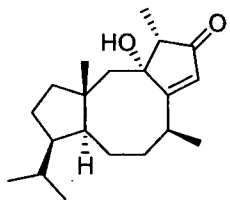
fusicogigantone A



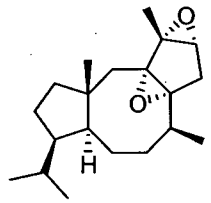
fusicogigantone B



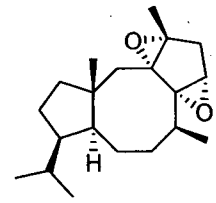
R = H **Plagiospirolide A**
= OH **Plagiospirolide C**



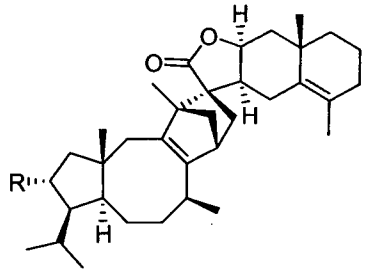
anadensin



fusicogigantepoxide A

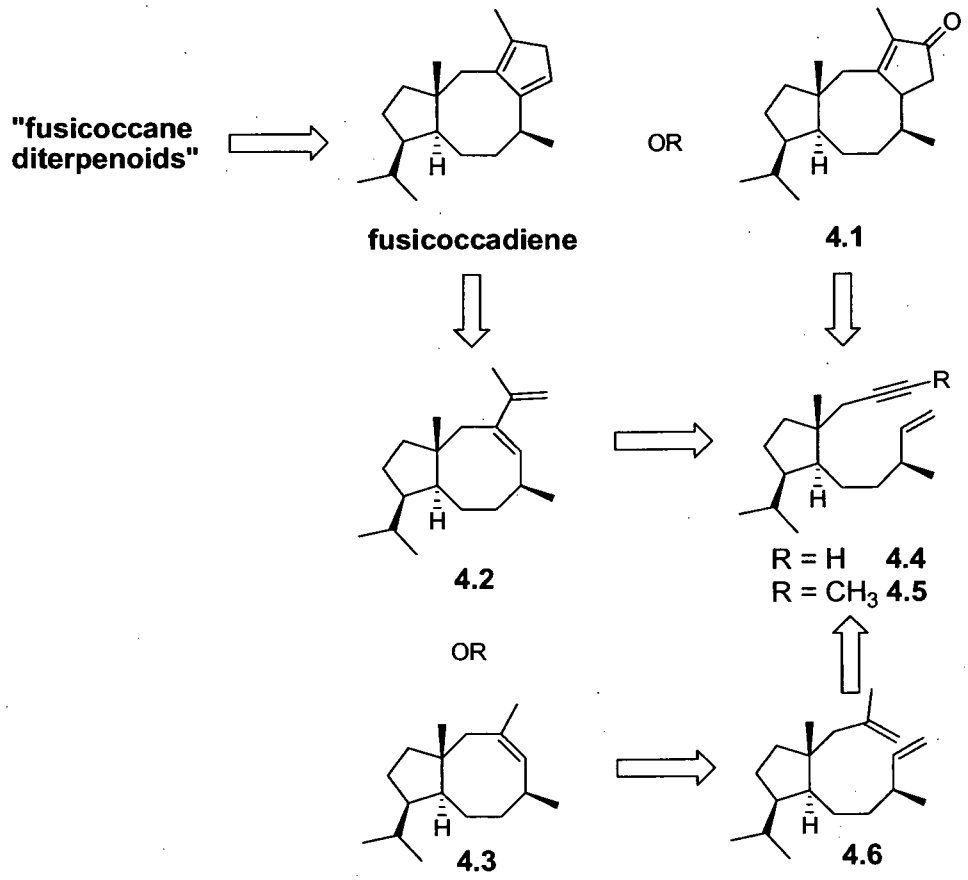


fusicogigantepoxide B



R = H **Plagiospirolide B**
= OH **Plagiospirolide D**

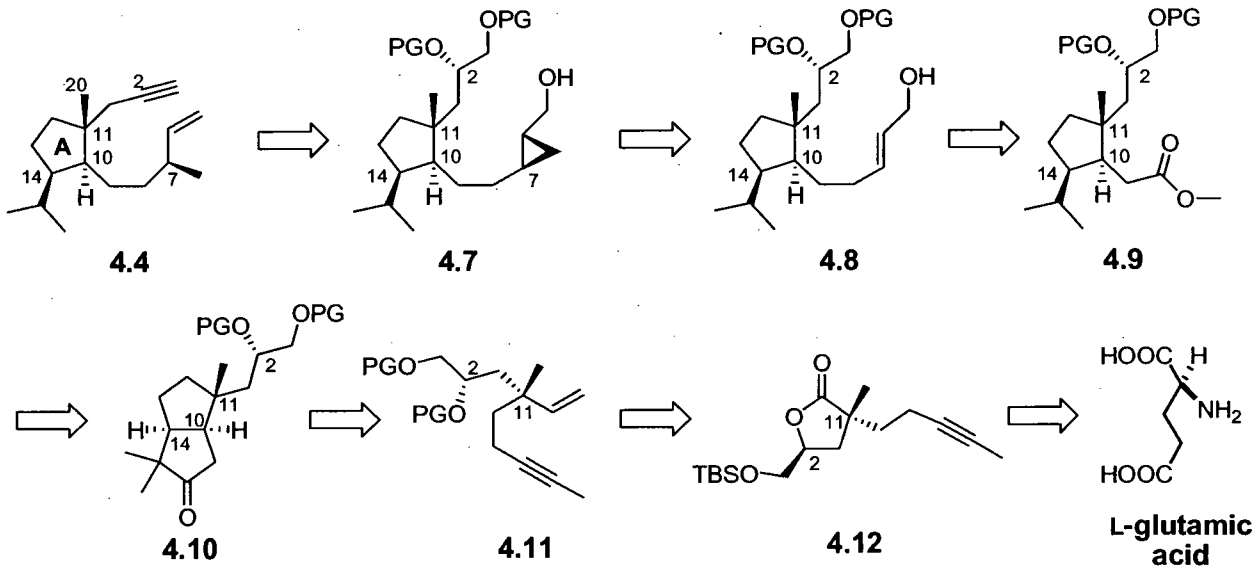
Figure 4.1 Selected Examples of Fusicoccane Diterpenoids



Scheme 4.1 Retrosynthetic Analysis of the 5-8-5 Ring System of the Fusicoccane Diterpenoids

The goal of the project was to synthesize a number of fusicoccane diterpenoids with the similar structural motifs around the A- and B-rings. It was believed that this could be achieved from the synthesis of a common advanced intermediate which would require manipulation of the C-ring fragment only. Hence, the 5-8-5 tricyclic intermediate **4.1** or fusicoccadiene (Scheme 4.1) were envisioned to be suitable advanced intermediates. Fusicoccadiene has not previously been isolated from any natural sources but is thought to be a natural precursor in the biosynthesis of the fusicogigantone and the fusicogigantepoxide diterpenoids as well as the plagiospirolide higher order terpenoids (Figure 4.1). This has been demonstrated by the previous biomimetic syntheses of each of these compounds from fusicoccadiene.[4] Although to date anadensin (Figure 4.1) has not been known to be biosynthesized from fusicoccadiene, it was hypothesized that this may possibly be produced similarly. In fact, anadensin has previously been derivatized from fusicogigantone A.[5]

Fusicoccadiene was proposed to be a retrosynthetic precursor to the 5-8 ring systems **4.2** or **4.3**. Synthetically, these are products of either ring closing enyne metathesis or ring closing diene metathesis of enyne **4.5** or diene **4.6** respectively. On the other hand, the 5-8-5 intermediate **4.1** is the synthetic product of a Pauson-Khand cycloaddition reaction of enyne **4.5**. Since diene **4.6** and enyne **4.5** can be obtained directly from enyne **4.4**, the initial goal was the synthesis of enyne **4.4**. Thereafter, three options for the formation of the 8-membered B-ring could be persued: Pauson-Khand cycloaddition, ring closing diene metathesis or ring closing enyne metathesis.



Scheme 4.2 Retrosynthetic Analysis of Enyne 4.4

A retrosynthetic analysis of enyne **4.4** was devised based on our previous knowledge for the formation of cyclopentyl structural motifs containing a *cis* relationship between the isopropyl group at C-14 and the C-20 methyl in the A-ring (Scheme 4.2). The stereochemistry of the C-7 methyl was to be introduced by way of cyclopropyl derivative **4.7** via an asymmetric cyclopropanation of allylic alcohol **4.8** followed by a fragmentation reaction. Allylic alcohol **4.8** could be simplified to ester **4.9**, which is the Norrish Type I fragmentation product of the bicyclopentanone **4.10**. The bicyclopentanone **4.10** in turn may be derived from Pauson-Khand [2+2+1] cycloaddition[6] of enyne substrate **4.11**. Functional group interconversion leads to

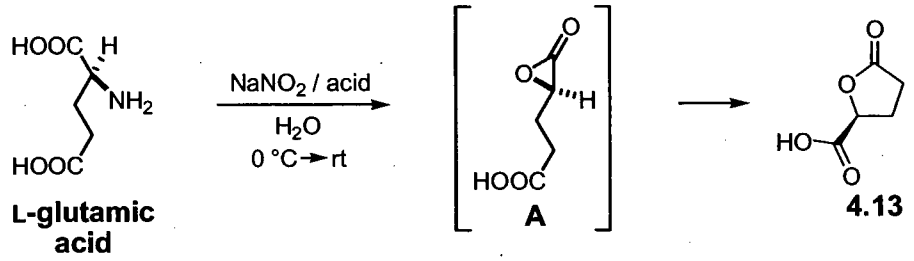
lactone **4.12**, which itself may derived from commercially available and inexpensive L-glutamic acid (1 kg costs $ 46.50 CAD)[7]. Hence, the three contiguous stereocentres around the A-ring would be formed through the use of chemical relay from the asymmetric carbon of L-glutamic acid.

II. Synthesis of Lactone 4.12

(*S*)-(+)-4-(*tert*-Butyldimethylsilyl)oxymethyl-γ-butyrolactone (**4.15**) is a known compound that has previously been synthesized from L-glutamic acid (Scheme 4.2).[8] Lactone **4.12** should be obtainable from two sequential alkylation reactions with the appropriate electrophiles. The reported synthesis of **4.15** by Bhat and co-workers involved diazotization of L-glutamic acid, followed by the chemoselective reduction of the carboxylic acid function to the alcohol **4.14** and silylation to produce lactone **4.15** in an overall yield of 45%. These steps were repeated and modified accordingly to the scale of the reaction and the description which follows will relate to these modifications.

Various literature examples report the use of either sulfuric acid[9] or hydrochloric acid[10] along with sodium nitrite in the diazotization reaction of L-glutamic acid. In either case, the reported yields are roughly similar (~55%). In our case (Table 4.1), the formation of **4.13** was initially performed using sulfuric acid and sodium nitrite to generate the nitrous acid (entry 1). However, on scale up we noticed a yield decrease (entry 2), markedly due to difficulties in recrystallizations. When hydrochloric acid was used instead (entry 3), the yield was found to be higher (by about 10%) but more importantly the recrystallization was found to occur with greater ease. Residual sulfuric acid, when this is the acid source, appears to interfere with the formation of a recrystallizable solid after removal of the solvents, as a viscous oil is often obtained.

Table 4.1 Scale-up of Formation of 4.13

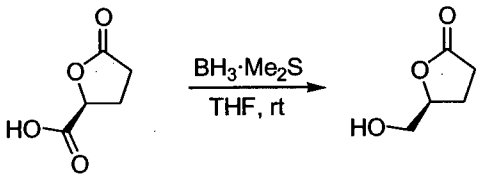


entry	amount of L-glutamic acid (g)	acid	yield 4.13	amount of 4.13 (g)	Ref.[a]
1	73.5	H_2SO_4	46%	30.1	M-30
2	147	H_2SO_4	38%	49.4	M-33
3	73.5	HCl	55%	35.7	M-35

[a] Refers to laboratory notebook page.

The chemoselective reduction of **4.13** was executed on a much larger scale than previously reported (Table 4.2).[11] It has been noted elsewhere that **4.14** has a propensity to decompose when heated, which makes the purification by heated distillation problematic at larger scales, resulting in lower yields.[9a] However, the reduction of **4.13** was found to remain excellent with no additional decomposition on scales of up to 30.1 g.

Table 4.2 Scale-up of Formation of 4.14 from 4.13

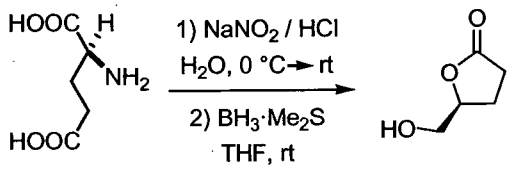


entry	amount of 4.13 (g)	yield 4.14	amount of 4.14 (g)	Ref.[a]
1	10.6	92%	8.70	M-36
2	25.5	94%	21.5	M-38
3	30.1	94%	25.1	M-32

[a] Refers to laboratory notebook page.

Subsequently, it was found that the difficulties in the recrystallization of **4.13** could be circumvented since the crude acid could be used in the subsequent step. This in fact made the sequence less labour intensive and led to improved overall yields (Table 4.3). The yield remained about the same even as the scale was increased up to 110 g.

Table 4.3 Scale-up of Formation of 4.14 Directly from L-glutamic acid



L-glutamic acid **4.14**

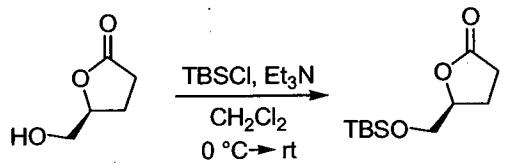
entry	amount of 4.13 (g)	yield 4.14	amount of 4.14 (g)	Ref.[a]
1	27.1	69%	14.7	M-40
2	110	65%	56.8	O-21

[a] Refers to laboratory notebook page.

The protection of the alcohol **4.14** was again performed on larger scale than that previously reported (Table 4.4).[11] The concentration was found to be a factor since at the reported concentration of 1.5 M a large amount of insoluble salts made stirring inefficient. Hence, when the concentration was reduced by one half or more, these salts were soluble and near quantative yields were obtained on reaction scales of up to 44.0 g.

It is important to highlight that the synthesis of **4.15** from L-glutamic acid was easily produced on large scale (up to 110 g) with a total yield in the 60% range and with a minimum amount of purification. Since, as mentioned above, the crude carboxylic acid **4.13** could be reduced efficiently without purification, the alcohol **4.14** was purified by distillation, and the lactone **4.15** required only filtration through a plug of silica gel after aqueous workup, the purification requirements for the synthetic sequence was amenable to large scale.

Table 4.4 Scale-up of Formation of 4.15



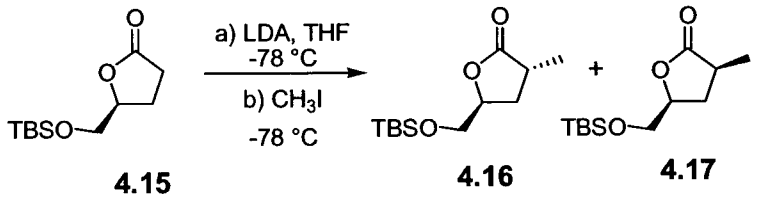
4.14 **4.15**

entry	amount of 4.14 (g)	concentration (M)	yield 4.15	amount of 4.15 (g)	Ref.[a]
1	8.60	1.5	84%	14.3	M-37
2	21.5	0.75	95%	40.3	M-39
3	44.0	0.32	97%	85.0	O-21

[a] Refers to laboratory notebook page.

With the lactone **4.15** in hand, the stage was set for the two step alkylation sequence to set the stereodefined quaternary centre at C-11. The procedure for the methylation of a similar compound[12] (in which the silyl ether is substituted as a trityl ether) was followed (LDA, THF, -78 °C, iodomethane) to yield a 9:1 mixture (GC analysis) of **4.16** and **4.17** on a 0.988 g scale (Table 4.5). This alkylation procedure was found to be acceptable at large scale as no appreciable difference in yield was obtained on a variety of reaction scales. The literature reference relating to this alkylation argued that the pendant trityl group had a steric directing effect in this alkylation and it was reasoned that this should also be true in the case of a silyl group, hence the tentative assignment of **4.16** as the major product. In any case, this is not of any direct importance since the deprotonation in a subsequent alkylation for either **4.16** or **4.17** would lead to the same enolate intermediate. In fact, if a 9:1 mixture of lactones **4.16** and **4.17** was treated with lithium diisopropylamide at -78 °C in THF, stirred for 30 minutes at that temperature, and quenched with water, a 1.1:1 mixture of diastereomers was obtained (GC analysis). Therefore, purification of the reaction mixture again required only filtration through a plug of silica gel, since the mixture of lactones **4.16** and **4.17** could be used in the subsequent alkylation. It was however reasoned that this subsequent alkylation would, for the same reason as stated above, be directed by the silyl substituent to provide the desired alkylation product as the major compound.

Table 4.5 Scale-up of Formation of 4.16 and 4.17

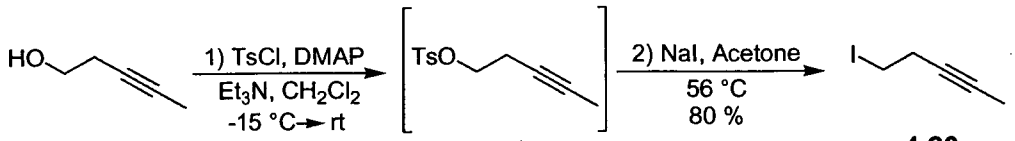


4.15 **4.16** **4.17**

entry	amount of 4.15 (g)	yield 4.16 and 4.17	amount of 4.16 and 4.17 (g)	Ref.[a]
1	0.988	88%	0.919	M-41
2	2.50	88%	2.33	N-01
3	35.3	89%	33.2	N-13
4	85.0	93%	84.0	O-30

[a] Refers to laboratory notebook page.

The subsequent alkylation proved to be more difficult and required an extensive study (Table 4.6). The known 5-iodo-pent-2-yne[13] (**4.20**) was synthesized as the required electrophile from 3-pentyn-1-ol (**4.18**) via the tosylate **4.19** (Scheme 4.4). Although **4.19** could be purified by column chromatography to produce an analytically pure sample, the crude product was found to be acceptable in the next step to produce the iodide **4.20** that could be purified by simple distillation under atmospheric pressure. This simplified the process to produce the iodide. This sequence was run on 40 g of alcohol.



4.18 **4.19** **4.20**

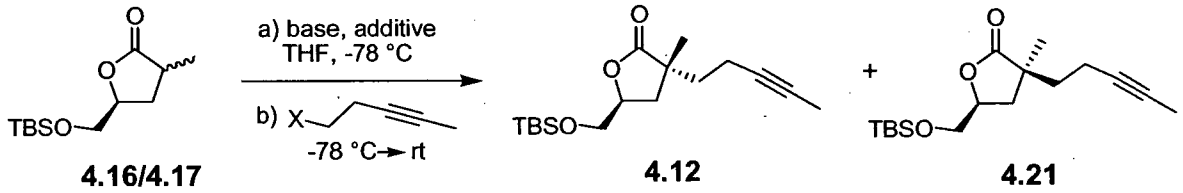
Scheme 4.3 Synthesis of 5-iodo-pent-2-yne (4.20) from 3-pentyn-1-ol

Initially, the alkylation was attempted by adding a solution of a 9:1 mixture of lactones **4.16** and **4.17** to a solution of KHMDS in THF at -78 °C, followed by the addition of the tosylate **4.19** as the electrophile and slow warming to ambient temperature. No reaction product was obtained and the lactones **4.16** and **4.17** were

recovered in 75% yield and essentially a 1:1 mixture (entry 1). It did appear however that the electrophile was consumed completely during the course of the reaction as none was recovered. The same result was obtained when 0.1 equivalent of potassium iodide was employed in order to catalytically generate **4.20** *in situ* (entry 2). No reaction was observed either when **4.20** was employed as the substrate with KHMDS (entry 3) or LDA (entry 4). It was reasoned that the generated lithium enolate could act as a base and cause the electrophile to undergo an E_2 elimination to generate a conjugated enyne. It was subsequently found that the addition of HMPA provided the desired product **4.12** at -78 °C, albeit only in 28%, along with a small amount of the diastereomer **4.21**, and an essentially 1:1 mixture of **4.16** and **4.17** in 51% (entry 5). The diastereomers **4.12** and **4.21** could be separated and each displayed two alkynyl carbons in the ^{13}C NMR spectrum at δ 77.8 and 76.3 in the case of **4.12**, and δ 78.1 and 76.1 in the case of **4.21**. The relative stereochemistry of each was confirmed through selective NOE experiments (Figure 4.2). The forward and reverse NOE's between H-2 and H-12 (in **4.12**) and between H-2 and H-20 (in **4.21**) were particularly diagnostic.

Careful optimization showed that slowly raising the reaction temperature after the addition of the electrophile was found to increase the yield of **4.12** to 54% (entry 6). Increasing the amount of LDA (entry 7) or HMPA (entry 8) was found to have no effect on the yield. It appeared that LDA however was the only effective base since the use of LHMDS (entry 9), KDA (entry 10) or KHMDS (entry 11) provided no alkylation products, although the electrophile was consumed in each of these cases. Finally, inverse addition of the enolate solution to a solution of the electrophile at -78 °C (entry 12) or substituting a bromide for the iodide electrophile (entry 13) gave lower yields.

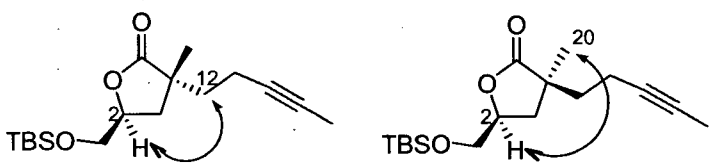
Table 4.6 Optimization of the Reaction Conditions for the Synthesis of 4.12



4.16/4.17 **4.12** **4.21**

entry	X	base (equiv.)	additive (equiv.)	yield 4.12	yield 4.21	yield 4.16/4.17	Ref.[a]
1	OTs	KHMDS (1.1)	____	0%	0%	75%	M-42
2	OTs	KHMDS (1.1)	KI (0.1)	0%	0%	77%	M-42
3	I	KHMDS (1.1)	____	0%	0%	86%	M-44
4	I	LDA (1.1)	____	0%	0%	NI[b]	M-45
5[c]	I	LDA (1.1)	HMPA (2.2)	28%	4%	51%	M-46
6	I	LDA (1.1)	HMPA (2.2)	54%	6%	31%	N-02
7	I	LDA (2.2)	HMPA (2.2)	51%	4%	27%	N-04
8	I	LDA (1.1)	HMPA (3.3)	51%	5%	35%	N-06
9	I	LHMDS (1.1)	HMPA (2.2)	0%	0%	NI[b]	N-16
10	I	KDA (1.1)	HMPA (2.2)	0%	0%	NI[b]	N-17
11	I	KHMDS (1.1)	HMPA (2.2)	0%	0%	NI[b]	N-03
12[d]	I	LDA (1.1)	HMPA (2.2)	28%	7%	50%	N-18
13	Br	LDA (1.1)	HMPA (2.2)	8%	2%	77%	N-22

[a] Refers to laboratory notebook page. [b] Not Isolated: compounds **4.16** and **4.17** were not recovered from the reaction mixture although TLC analysis showed that no reaction occurred. [c] The reaction temperature in entry 5 was kept at -78 °C after the addition of **4.20** rather than slow warming to room temperature. [d] Entry 12 involved the inverse addition of the enolate solution of **4.16/4.17** to a solution of **4.20** at -78 °C.



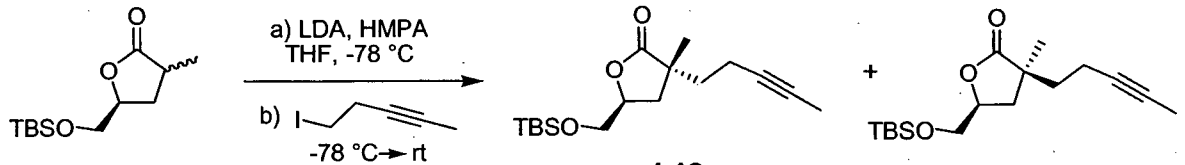
4.12 **4.21**

Figure 4.2 Diagnostic NOE's for 4.12 and 4.21

One more experimental note is worth mentioning. It was reasoned that if the alkyne of **4.20** could be treated with $Co_2(CO)_8$ and transformed into its alkyne-cobalt complex, E_2 elimination would be less likely, and the resulting alkylation product could be deprotected to yield **4.12**. The alkyne-cobalt complex of **4.20** was prepared and isolated using standard conditions ($Co_2(CO)_8$, toluene, rt), and then used as the electrophile as in entry 6 of Table 4.6. However, no reaction was observed, even as the reaction was stirred at room temperature overnight, and in fact **4.20** was recovered if the crude reaction mixture was treated with cerric ammonium nitrate. Presumably, the steric interference of the large cobalt complex renders the electrophile unreactive towards the alkylation.

All of the preceding reactions were performed on a scale of 100 mg. Applying the reaction conditions of entry 6 (Table 4.6) to larger scales of up to 85 g was found to provide slightly lowered yields of **4.12** but the ratio of **4.12** to **4.21** as well as the yield based on recoverable starting material remained similar (Table 4.7). Therefore, the akylation on 85.0 g scale was favoured since the unreacted **4.16** and **4.17** could be recycled in any case. This yield was found to be quite acceptable considering the difficulty. The asymmetric construction of quaternary carbon stereocentres remains a formidable challenge in organic synthesis.[14]

Table 4.7 Scale-up of Formation of 4.12



4.16/4.17 **4.12** **4.21**

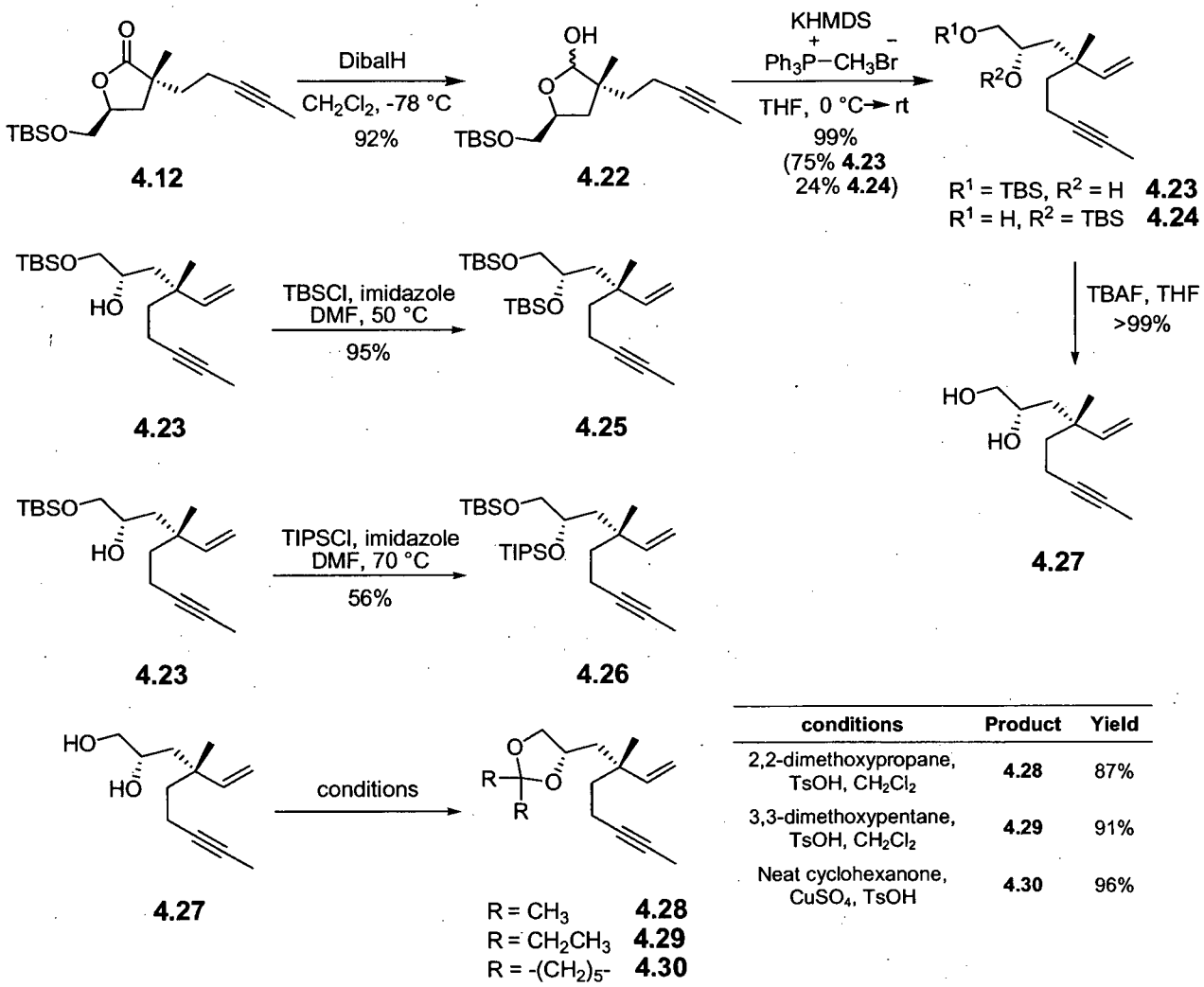
entry	amount of 4.16/4.17 (g)	yield 4.12[a]	amount of 4.12 (g)	Ref.[b]
1	0.100	54% (80%)	0.0682	N-02
2	2.50	47% (79%)	1.29	N-07
3	35.3	43% (74%)	19.3	N-20
4	85.0	36% (80%)	38.9	O-46

[a] yield in parenthesis refers to yield based on recovered starting materials **4.16/4.17**. [b] Refers to laboratory notebook page.

III. Pauson-Khand and Norrish Type I Reactions

A. Synthesis of Pauson-Khand Substrates

With the lactone substrate **4.12** in hand, focus turned to the elaboration towards the A-ring. The required Pauson-Khand substrate of the type **4.11** could be obtained via reduction of **4.12** to the lactol, followed by olefination and protection.



conditions	Product	Yield
2,2-dimethoxypropane, TsOH, CH_2Cl_2	**4.28**	87%
3,3-dimethoxypentane, TsOH, CH_2Cl_2	**4.29**	91%
Neat cyclohexanone, $CuSO_4$, TsOH	**4.30**	96%

Scheme 4.4 Synthesis of Pauson-Khand Substrates

Hence, lactone **4.12** was reduced to the lactol **4.22** using diisobutylaluminum hydride in methylene chloride (Scheme 4.4). An inseparable but inconsequential mixture of an approximately 3.6:1 ratio (GC analysis) of two diastereomers was

obtained. The spectral data for **4.22** supported the assigned structure. The IR spectrum showed a broad O-H stretching frequency of 3413 cm^{-1}. The ^{13}C NMR spectrum of the diastereomeric mixture contained signals at δ 104.0 or δ 102.8 for each of the two diastereomer lactol carbons.

The Wittig olefination of the lactol **4.22** with the ylide generated from the *n*-butyllithium deprotonation of methyltriphenylphosphonium bromide provided **4.23** in 76% yield. However, it was found that a minimum of 3.8 equivalents of the Wittig reagent was required. When the ylide was generated from the deprotonation of methyltriphenylphosphonium bromide using potassium bis(trimethylsilyl)amide on the other hand, only 2.1 equivalents were necessary. This was preferred on large scale due to cost and to the fact that the workup was uncomplicated by the removal of larger amounts of phosphonium salts. The expected product **4.23** was obtained in 74% yield. The presence of a C=C stretching frequency of 1637 cm^{-1}, three vinyl proton signals in the ^{1}H NMR spectrum at δ 5.63, 5.00, 4.90, and two alkene carbon signals in the ^{13}C NMR spectrum at δ 146.1 and 112.7 supported the assigned structure. In addition, **4.24** was also obtained in 25% yield, which resulted from the transfer of the *tert*-butyldimethylsilyl substituent between the oxygens under the basic conditions.[i] The assigned structure was also supported by the presence of a C=C stretching frequency of 1637 cm^{-1}, three vinyl proton signals in the ^{1}H NMR spectrum at δ 5.61, 5.02, 4.89, and two alkene carbon signals in the ^{13}C NMR spectrum at δ 145.7 and 113.0. This was not of much concern since it was subsequently deduced during the course of our synthetic planning that both **4.23** and **4.24** were useful (*vide infra*) and hence a near quantitative yield (99%) of useable material was obtained.

The secondary hydroxyl group of the enyne **4.23** was protected as a *tert*-butyldimethylsilyl derivative prior to the Pauson-Khand reaction. This reaction did require some optimization. Difficulties arose from the steric hindrance of placing a second adjacent *tert*-butyldimethylsilyl substituent. However, suitable conditions (TBSCl, imidazole, DMF, 50 °C) were found which provided **4.25** in 95% yield.

Producing a diversity of Pauson-Khand substrates differing in the hydroxyl protecting groups, in particular substrates which contained large protecting groups, was subsequently desired (*vide infra*). The secondary hydroxyl group of the enyne **4.23** was protected as its triisopropylsilyl derivative using similar conditions as for **4.25** (TIPSCl,

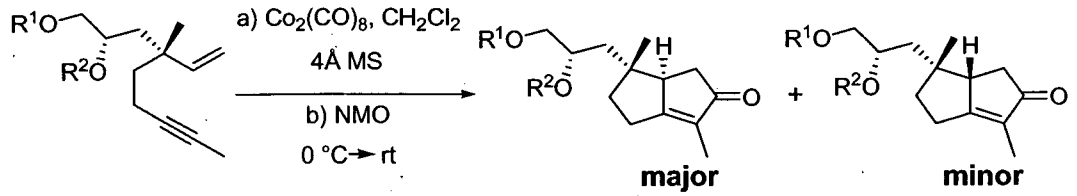
[i] **4.24** was also obtained in 8% yield in the case were *n*-butyllithium was used as the base.

imidazole, DMF, 70 °C), providing **4.26**, although in only 56% yield.[ii] In addition to silyl protected hydroxyls, producing substrates in which the diol was protected as ketals was also desired. Hence, the mixture of **4.23** and **4.24** was treated with a fluoride ion source (TBAF, THF, rt) to yield the **4.27** in near quantitative yield (>99%). This was followed by converting the diol **4.27** under standard conditions to the isopropylidene ketal **4.28** (2,2-dimethoxypropane, TsOH, CH_2Cl_2) in 87%, the isopentylidene ketal **4.29** (3,3-dimethoxypentane, TsOH, CH_2Cl_2) in 91%, and the cyclohexylidene ketal **4.30** (cyclohexanone, $CuSO_4$, TsOH) in 96%.

B. Pauson-Khand [2+2+1] Cycloadditions

A number of Pauson-Khand reaction substrates were now at our disposal. This reaction has been previously performed in our laboratory using similar substrates[2] and hence slight modifications of previously optimized conditions ($Co_2(CO)_8$, 4Å mol. sieves, CH_2Cl_2, NMO, rt)[15] were used (Table 4.8).[16]

Table 4.8 Pauson-Khand [2+2+1] Cycloadditions

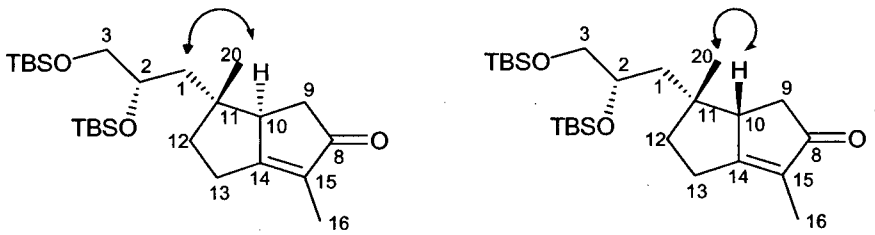


entry	substrate	R^1	R^2	yield[a]	dr[b] (major:minor)	product (major/minor)	Ref.[c]
1	**4.25**	TBS	TBS	81%	2.5:1	**4.31/4.32**	N-26
2	**4.26**	TBS	TIPS	86%	2.8:1	**4.33/4.34**	N-34
3	**4.28**	$-C(CH_3)_2-$		89%	5.9:1	**4.35/4.36**	N-35
4	**4.29**	$-C(CH_2CH_3)_2-$		80%	1.3:1	**4.37/4.38**	N-26
5	**4.30**	-C(cyclohexyl)-		74%	2.2:1	**4.39/4.40**	N-39

[a] Combined yield (major+minor). [b] Determined by GC analysis. [c] Refers to laboratory notebook page.

[ii] A large amount of the product in which the two silyloxy groups are exchanged was also obtained.

When enyne **4.25** was converted to its $Co_2(CO)_6$ complex, followed by treatment with excess (6 equivalents) of *N*-methylmorpholine oxide (NMO) to initiate the cyclization process, a mixture of two diastereomeric Pauson-Khand products **4.31** and **4.32** were obtained in 81% yield and in a ratio of 2.5:1. The diastereomers were easily separable using flash chromatography such that structure elucidation could be performed on each. The spectral data for **4.31** was in complete agreement with the assigned structure. The IR spectrum showed a C=O stretching frequency of 1709 cm^{-1} and a C=C stretching frequency of 1670 cm^{-1}, indicating an enone moiety. The ^{13}C NMR spectrum contained a signal at δ 210.9 corresponding to the carbonyl carbon, and pairs of signals at δ 183.0 and δ 132.3 corresponding to the vinyl carbons. Likewise for the minor diastereomer **4.32**, the IR spectrum showed a C=O stretching frequency of 1710 cm^{-1} and a C=C stretching frequency of 1670 cm^{-1} corresponding to the enone moiety. The ^{13}C NMR spectrum contained a signal at δ 211.0 assigned to the carbonyl carbon, and pairs of signals at δ 183.7 and δ 132.2 for the vinyl carbons. The structures were further elucidated through analysis of their 2D NMR data (HMQC and HMBC). The relative stereochemistry of each diastereomer was confirmed through selective NOE experiments. The forward and reverse NOE's between H_5 and H_{11} (in **4.31**) and between H_5 and H_{10} (in **4.32**) were particularly diagnostic (Figure 4.3).



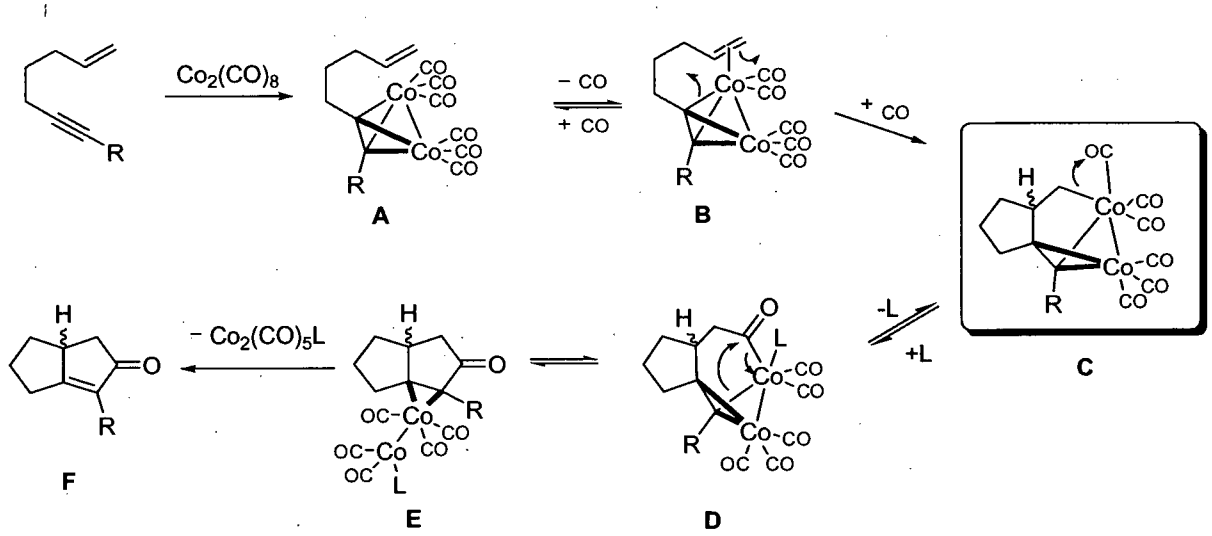
4.31 **4.32**

Figure 4.3 Diagnostic NOE's for 4.31 and 4.32

An attempt to understand the mechanism of the reaction pathway and the stereodefining factors was considered in order to establish whether this modest diastereoselectivity could be improved upon. The mechanistic pathway for the Pauson-Khand intramolecular cycloaddition has been widely studied and is fairly well understood.[17] It has been previous noted in the literature that gem-dialkyl substitution on the alkyl chain connecting the alkene and alkyne not only enhances the rate of the reaction,[18] but also that a stereocentre at the allylic position of the enyne may control

the configuration of the forming ring junction.[17b,c] Hence our substrates of the type **4.11** (Scheme 4.2) were potentially well disposed in terms of reactivity as well as diastereoselectivity.

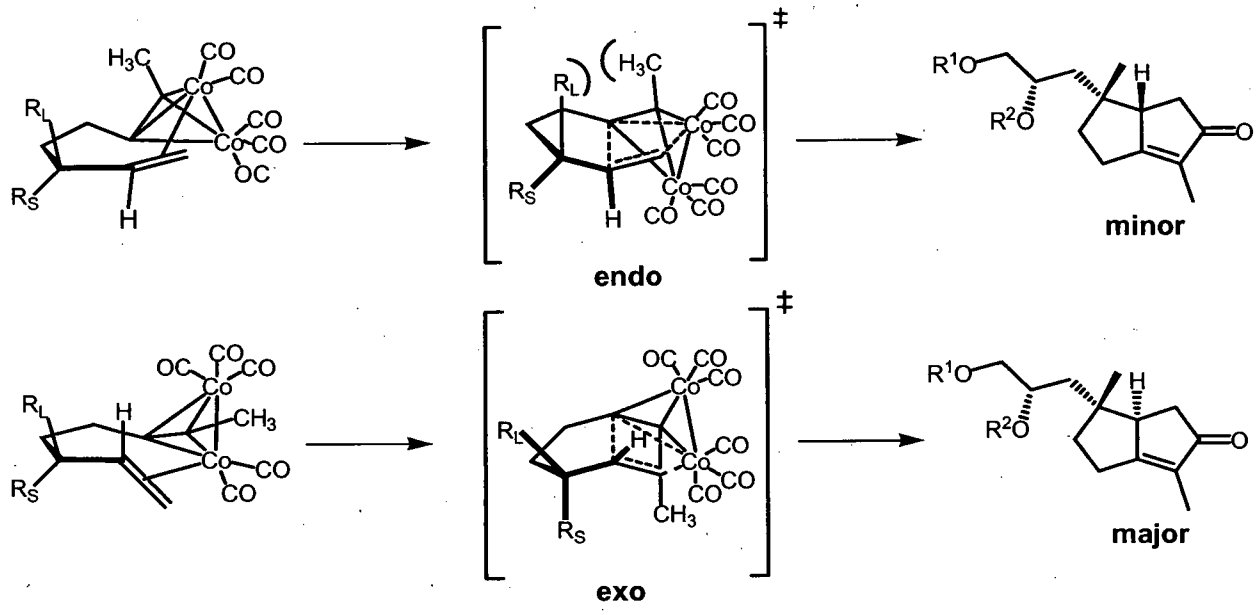
The generally accepted mechanistic pathway for the intramolecular Pauson-Khand reaction is as shown in Scheme 4.5. Upon formation of the alkyne-cobalt complex (**A**), the first step involves decarbonylation to form a coordinatively unsaturated cobalt centre followed by a ligand exchange of the olefin for CO to form complex **B**. The decarbonylation can be promoted either thermally or oxidatively. This is followed by an irreversible insertion reaction of the π-complexed olefin (**B**) into a cobalt-carbon bond, which leads to cobaltacycle **C**. This insertion step is likely rate-limiting and the product-determining step in terms of the stereochemical outcome of the reaction. The next step involves insertion of CO into a Co-Csp^3 bond, forming intermediate **D**. Reductive elimination follows, forming **E**, followed by subsequent loss of the dicobaltcarbonyl fragment, producing the bicyclo[3.3.0]octenone product **F**.



Scheme 4.5 Proposed Mechanism for the Intramolecular Pauson-Khand Reaction

Magnus and co-workers have reported that allylic substitution affects the diastereoselectivity of the reaction.[17b,c] An analysis of the structure of the transition state for the non-reversible step (**B** to **C**) is required in order to understand the potential stereoselective outcome of the reaction. With the assumption that the transition state for the reaction approximates the intermediate **C**, the following analysis was performed with respect to our system (Scheme 4.6). The newly formed 5-membered cobaltacycle

in **C** is assumed to be *cis*-fused, since the corresponding *trans*-fusion is unacceptably strained. Two such *cis*-fused cobaltacycles are therefore possible if there exists a stereocentre at the allylic position. The preferred cobaltacycle is the one in which the large group (R_L) is placed on the exo face of the forming bicycle (labeled **exo** in Scheme 4.6) such that there is no unfavorable 1,4-pseudo diaxial steric interaction with the methyl group placed on the endo face. This results in a 1,2-stereoselection in which the R_L is placed on the same face of the product bicycle as the ring fusion hydrogen.



Scheme 4.6 Proposed Source of the 1,2-Stereoselection in the Pauson-Khand: 1,4-Pseudo Diaxial Steric Interaction

Additionally, in accordance with the work of Magnus and co-workers,[17b,c] the steric interaction of the gem-dialkyl group with the forming cobaltacycle in the transition state must also be considered (Figure 4.4). In the case in which R_L is placed on the exo face (labeled **exo** in Figure 4.4), it is eclipsing the ring fusion hydrogen. This is a more favorable transition state than if it were placed on the endo face (labeled **endo** in Figure 4.3), in which it is eclipsing a methylene carbon of the forming cobaltacycle ring. This again results in a similar 1,2-stereoselection in which the R_L is placed on the same face of the product bicycle as the ring fusion hydrogen.

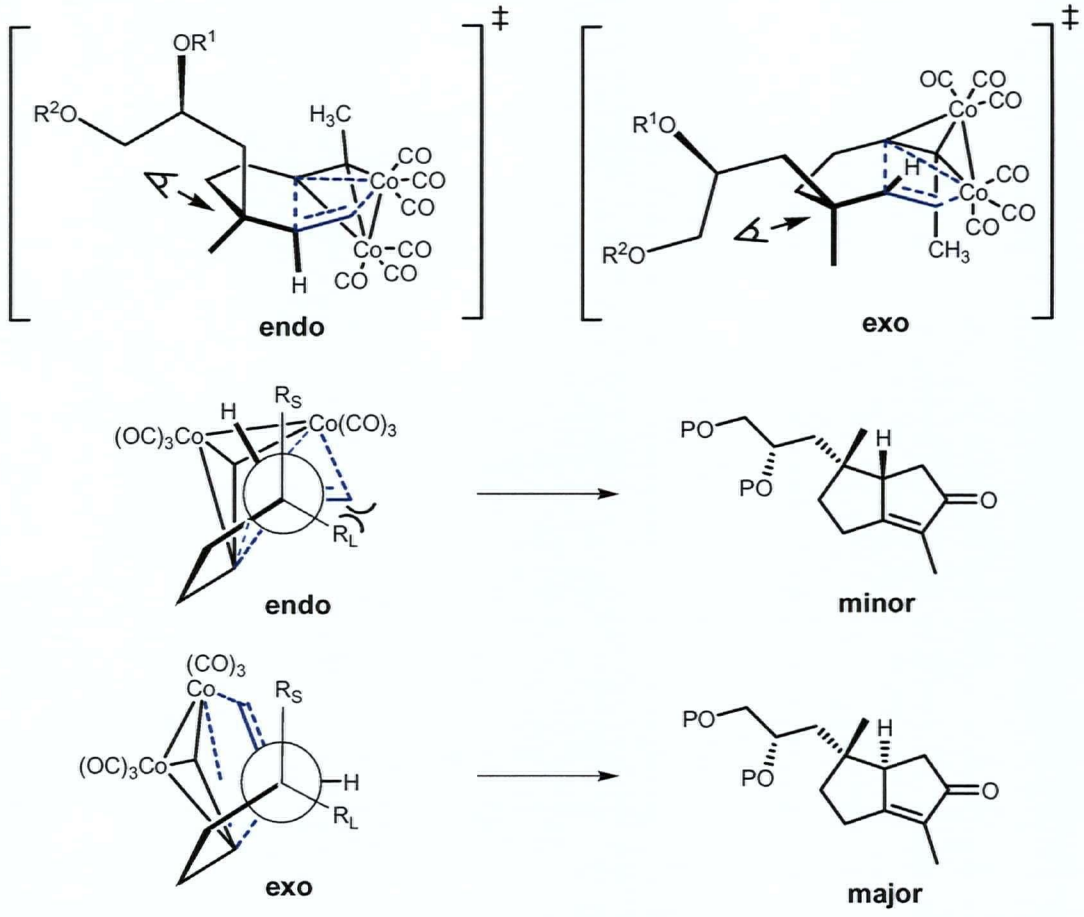


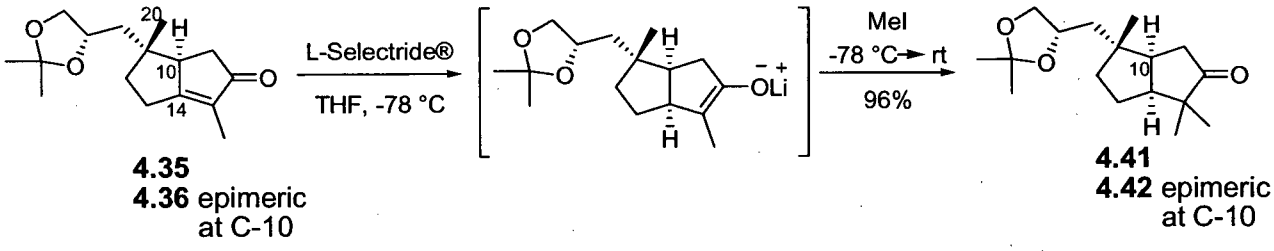
Figure 4.4 Proposed Source of the 1,2-Stereoselection in the Pauson-Khand Reaction of Compounds of the Type 4.11

With the above analysis in mind, the differentiating factors of the two gem-dialkyl substituents in **4.25** are enough to provide the moderate diastereoselective outcome observed for the Pauson-Khand reaction. Since the diastereoselection is the result of steric interactions, it was rationalized that substituting the silyl protecting groups of **4.25** with other substituents (which ideally provide larger steric interactions) would affect the product ratio. However, when **4.26**, in which the secondary hydroxyl is protected as a triisopropylsilyl ether instead of a *tert*-butyldimethylsilyl ether, was subjected to the same reaction conditions, only a slight increase in diastereoselective ratio was observed (Table 4.8). It was reasoned that the silyl substituents are too far from the diastereodefining centres, and consequently the diastereoselectivity is more a result of the effects of the difference between a methyl and an alkyl substituted methylene of the gem-dialkyl substituents. Interestingly, when the isopropylidene ketal **4.28** was used, a much higher ratio of 5.9:1. Presumably, the additional factors of tying up the diol as a ring provides for increased steric interactions, possibly by limiting the degree of

rotational freedom into a conformation in which these interactions are more pronounced. The source of this increase in diastereoselection is not well understood and would require further studies. Surprisingly, when the isopropylidene ketal **4.29** was used, an almost insignificant diastereoselective ratio of 1.3:1 was obtained. Also, when the cyclohexylidene ketal **4.30** was used, which was believed to provide greater steric interaction, a 2.2:1 ratio was obtained. We are unable to provide an explanation for the anomaly of these last two results with respect to that for **4.28**. We decided however to proceed with the Pauson-Khand reaction using the isopropylidene ketal **4.28**, as this result was found to be reproducible on a variety of reaction scales. For analytical purposes, the resulting diastereomeric mixture **4.35/4.36** was found to be separable on small scale (<0.5 g) using rotary chromatography. This was found to be difficult on larger scale, and the unseparated mixture was subsequently carried forward in the next step.

In order to verify the relative stereochemistry of each diastereomers, **4.35** and **4.36** were each deprotected (HCl, H_2O/THF, rt) and the resulting spectroscopic analysis of each of the diols were compared to those obtained from the silyl deprotection of **4.31** and **4.32** (TBAF, THF, rt). The same was performed for the diastereomeric mixtures **4.37/4.38** and **4.39/4.40**. In a similar manner, the diastereomeric mixture **4.33/4.34** was desilylated and compared.

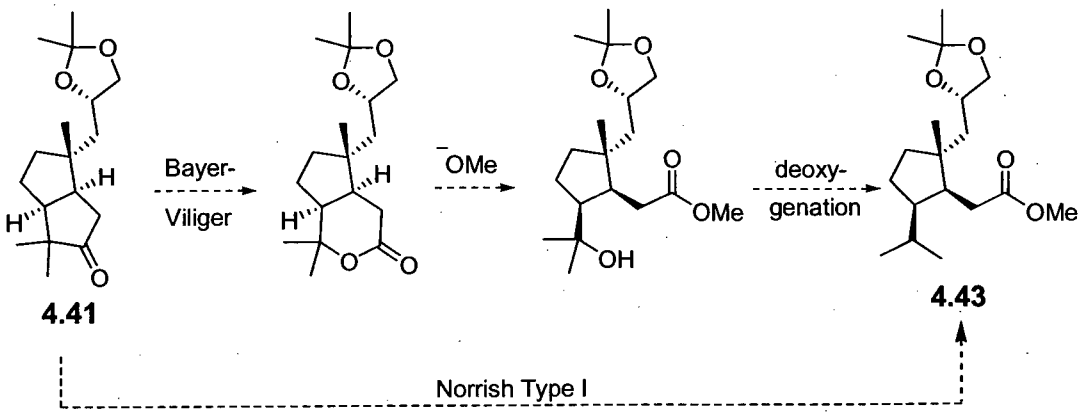
A bicyclic structure of the type **4.10** (Scheme 4.2) was now in hand. The required cyclopentyl structural motif of the type **4.9** containing a *cis* relationship between the isopropyl group at C-14 and the C-20 methyl in the A-ring was achievable using the following transformations. The diastereomeric mixture **4.35/4.36** was treated with lithium tri-*sec*-butylborohydride (L-Selectride®) in THF at -78 °C to form the desired enolate regioselectively. This enolate was subsequently trapped with methyl iodide to yield **4.41** and **4.42**, which were separable at this stage (Scheme 4.7). The structures were confirmed through analysis of the spectral data. The IR spectrum of **4.41** showed a C=O stretching frequency of 1737 cm^{-1} which is consistent with an aliphatic ketone (compared to 1709 cm^{-1} for the enone starting material). The ^1H NMR spectrum contained signals at δ 1.02 (s, 3H) and δ 1.00 (s, 3H) corresponding to the *gem*-dimethyl moiety. The ^{13}C NMR spectrum contained a signal at δ 222.9 (ketone carbon) and lacked any olefinic carbon signals.



Scheme 4.7 Formation of 4.41/4.42 from enones 4.35/4.36

C. Norrish Type I Reactions

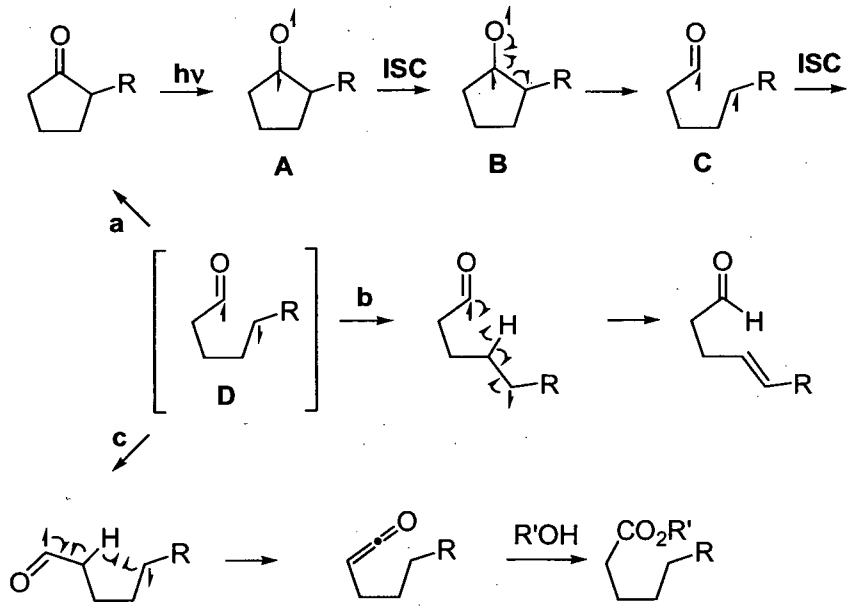
With **4.41** in hand, a fragmentation protocol for the cleavage of the cyclopentanone ring was required. The Norrish type I reaction[19] has previously been employed in your laboratory for a similar fragmentation in the synthesis of Nitiol.[2] This is complementary to a more obvious protocol in which the cyclopentanone is regioselectively oxidized to the lactone under Bayer-Villiger conditions, followed by methanolysis and deoxygenation (Scheme 4.8). However, through the use of the Norrish type I reaction, this process is performed in a single step, and circumvents the challenge of a tertiary alcohol deoxygenation.[20]



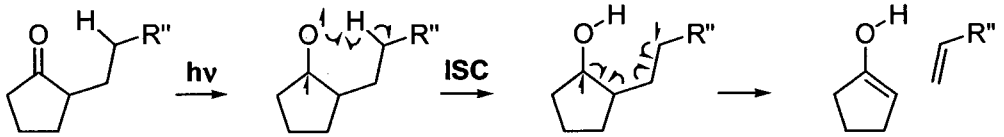
Scheme 4.8 Possible Fragmentation Routes to Form 4.43 from 4.41

The Norrish type I reaction involves the photorearrangement of cycloalkanones to unsaturated aldehydes or ketenes.[iii] Photon absorption is followed by a homolytic cleavage of a bond α to the excited carbonyl function. A triplet biradical species is produced which, after intersystem crossing, results in disproportionation and/or cyclization products. If the photolysis is performed in a nucleophilic solvent such as amines or alcohols, the disproportionation ketene product results in amides or esters. A common side reaction involves radical abstraction of hydrogens γ to the acyl radical, a competitive process known as the Norrish type II reaction.

Norrish type I mechanism



Norrish type II mechanism



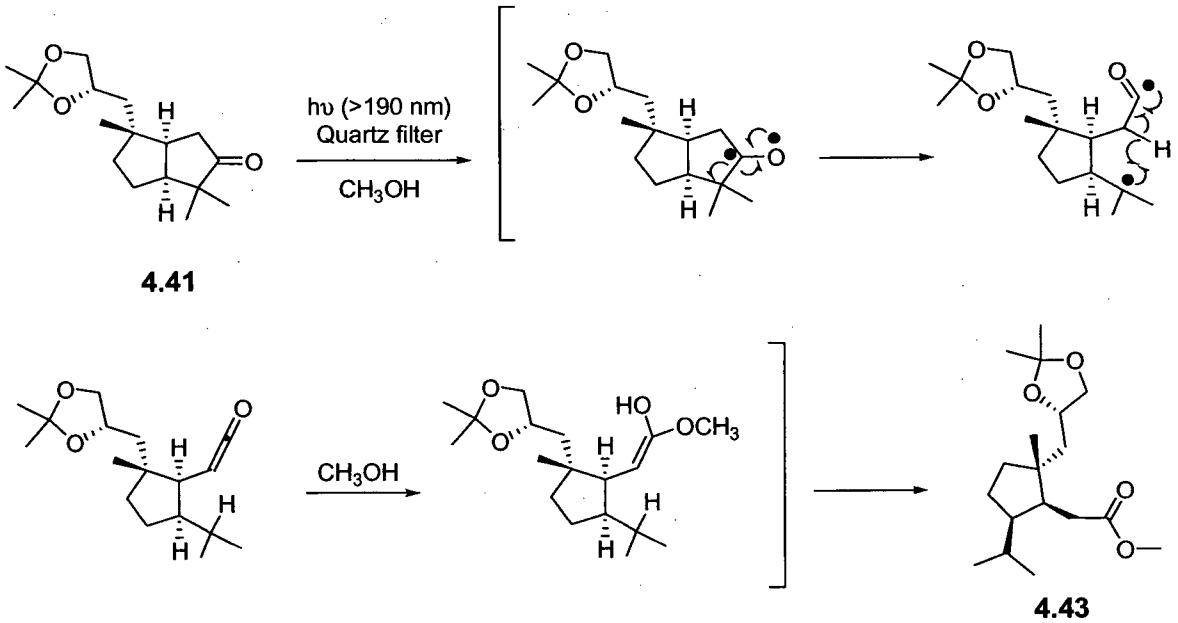
Scheme 4.9 Norrish Mechanistic Pathways for Cyclic Alkanones

Mechanistically, the Norrish type I reaction involves the n→π* excitation of the carbonyl function of an alkanone from the ground state (S_0) to the excited singlet state (S_1), forming a ketal radical **A** (Scheme 4.9). The α-cleavage occurs after intersystem

[iii] Discussion of the Norrish type I reaction is limited here to cycloalkanone cases, although the same is applicable to non-cyclic examples. Furthermore, only intramolecular pathways are discussed.

crossing to the more reactive triplet state (T_1) **B**. The more substituted α-bond is cleaved (which parallels radical stability) to yield a triplet biradical **C**. Intersystem crossing provides a reactive singlet biradical **D** which can undergo three reactivity pathways. Recyclization can occur (path **a**) to form the cyclic alkanone which is unproductive unless epimerization of the α-stereocentre is desired. If the reaction is carried out in a non-polar solvent, disporportionation can occur to yield a γ,δ unsaturated aldehyde (path **b**). If the reaction is however performed in a nucleophilic solvent such as methanol, alkyl radical abstraction of the α-hydrogen results in a transient ketene (path **c**) which then undergoes solvent attack to produce an ester after tautomerization.

In addition, further complications can arise from a competitive process from cleavage of a bond β to the excited carbonyl function. This Norrish type II mechanism involves the radical abstraction of a γ-hydrogen by the excited triplet state alkanone **B** to yield a biradical species **E**. Further fragmentation results in an alkene and a ketone (after tautomerization). This process is only important if the γ-hydrogen lies in the plane of the carbonyl functionality.



4.41 **4.43**

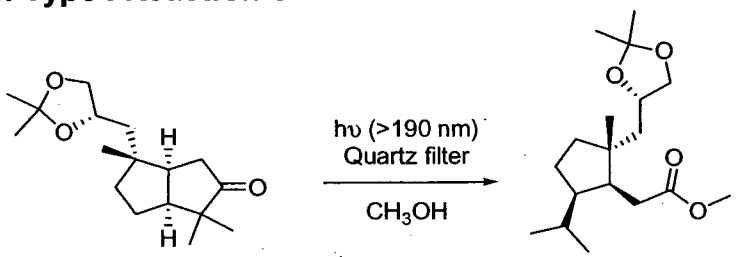
Scheme 4.10 Norrish Type I Reaction for 4.41

If we wish to produce the photofragmentation product **4.43**, this requires predominance of path **c** over the competitive processes (Scheme 4.10). Path **b** can be minimized by performing the reaction in methanol. And since the substrate **4.41**

contains no γ-hydrogens which lie in the same plane as the carbonyl functionality, the Norrish type II process is also minimized.

Compound **4.41** was dissolved in dry methanol which had been sparged with argon for 30 minutes, placed in quartz filtered reaction vessel and subjected to UV light (λ ≥ 190 nm) (Table 4.9). If the reaction was left until completion, the methyl ester **4.43** was obtained in 41% yield, along with unidentified baseline decomposition material (entry 1). Slight reaction time optimizations were required as we found that decreasing the length of exposure from 12 hours to 5.5 hours resulted in a yield of 65%, along with the starting material **4.41** in 6%, which could be recycled (entry 2). Decreasing the substrate concentration from 0.03 M to 0.015 M provided less decomposition as **4.43** was obtained in 70%, along with **4.41** in 9% (entry 4)

Table 4.9 Norrish Type I Reaction of 4.41



4.41 **4.43**

entry	reaction time (h)	concentration (M)	yield 4.43[a]	yield 4.41	Ref.[b]
1	12	0.03	41% (41%)	0%	N-40
2	5.5	0.03	65% (69%)	6%	N-40
3	4.5	0.03	58% (68%)	18%	N-40
4	5.5	0.015	70% (76%)	9%	O-06

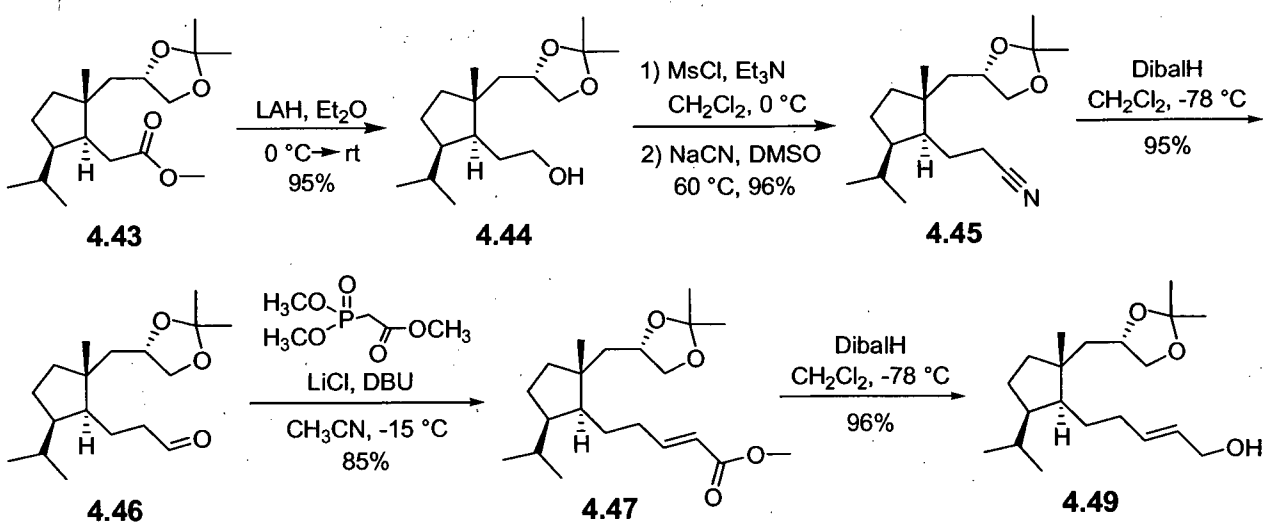
[a] Yield in parenthesis refers to yield based on recovered starting materials **4.41**. [b] Refers to laboratory notebook page.

Evidence for the formation of a methyl ester was obtained from the presence of an ester carbonyl C=O stretching frequency of 1740 cm^{-1} in the IR spectrum, of a methyl ester singlet proton signals in the ^1H NMR spectrum at δ 3.65, and of an ester carbonyl carbon signal in the ^{13}C NMR spectrum at δ 174.8. The cleavage reaction was further confirmed by the presence of two distinctive isopropyl $-CH_3$ doublet signals at δ 0.86 and δ 0.84. The relative stereochemistry around the cyclopentyl A-ring was

confirmed through X-ray crystallography (Figure 4.4, Appendix C) of the product obtained from reduction of the methyl ester and displacement of the resulting alcohol with cyanide (*vide infra*).

IV. Elaboration of 4.43 and Stereoselective Formation of the C-7 Methyl

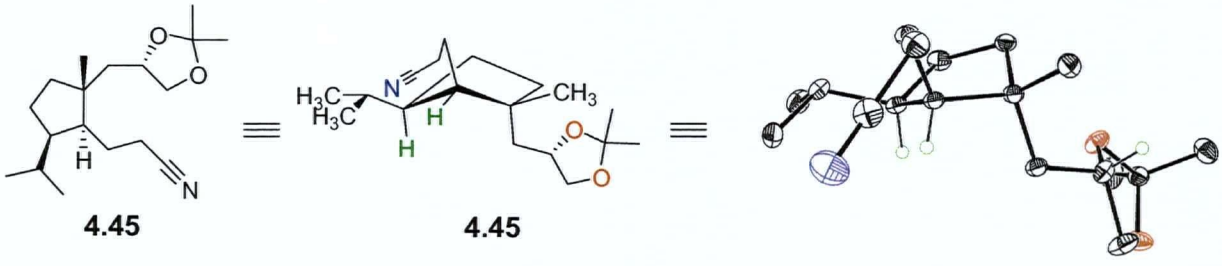
Having formed the cyclopentyl A-ring containing the *cis* relationship between the isopropyl group at C-14 and the C-20 methyl, we focused on the elaboration of the ester **4.43** towards the enyne **4.4** (Scheme 4.2). This specifically required homologation of the ester to the required carbon chain length while stereoselectively implementing the C-7 methyl. As we had decided that the C-7 methyl could be introduced stereoselectively by way of an asymmetric cyclopropanation of an allylic alcohol, we focused on the synthesis of the substrate **4.49** (Scheme 4.11).



Scheme 4.11 Elaboration of the ester 4.43 to the allylic alcohol 4.49

Hence, the ester **4.43** was reduced to the alcohol **4.44** using lithium aluminum hydride in near quantitative yield. This was markedly evidenced from the presence of an O-H stretching frequency of 3424 cm^{-1} in the IR spectrum, and the disappearance of the methyl ester proton signal in the ^{1}H NMR spectrum at δ 3.65 and the ester carbonyl carbon signal in the ^{13}C NMR spectrum at δ 174.8. A one carbon homologation was then performed by treating the alcohol **4.44** with methanesulfonyl chloride and

triethylamine, and then displacing the resulting mesylate with sodium cyanide. The mesylate intermediate was not isolated as we found that direct treatment of the crude reaction mixture with sodium cyanide resulted in a near quantitative yield of 96%. Formation of the nitrile **4.45** was observed from the presence of a C≡N stretching frequency of 2240 cm^{-1} in the IR spectrum, and of the nitrile carbon signal in the ^{13}C NMR spectrum at δ 119.9. Structural evidence was further confirmed by X-ray crystallography (Figure 4.4, Appendix C), which also allowed for the verification of the stereochemistry around the cyclopentyl A-ring from the earlier Norrish type I reaction.



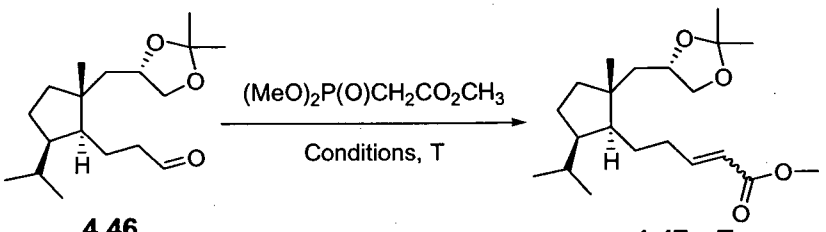
4.45 **4.45**

Figure 4.5 X-ray Crystal Structure of 4.45

The nitrile **4.45** was then reduced to the aldehyde **4.46** using diisobutylaluminum hydride at -78 °C. This transformation was confirmed by the appearance of an aldehyde C=O stretching frequency of 1727 cm^{-1} in the IR spectrum, an aldehyde proton signal at δ 9.71 in the ^{1}H NMR spectrum, and an aldehyde carbon at δ 202.2. The Horner-Wadsworth-Emmons olefination reaction[21] of the aldehyde **4.46** with trimethylphosphonoacetate (Table 4.10) using KHMDS as base resulted in an inseparable mixture of the *E* and *Z* stereoisomers in a 76:24 ratio (GC analysis) (entry 1). The same reaction was performed using the Masamune-Roush conditions (LiCl, DBU, CH_3CN, 0 °C)[22] to give a much improved *E*/*Z* ratio of 97:3 in a similar overall yield (entry 2). Lowering the reaction temperature to -15 °C provided essentially only the *E* stereoisomer (entry 3). Evidence for the homologation reaction was observed from the presence of an ester C=O stretching frequency of 1728 cm^{-1} and a C=C stretching frequency of 1657 cm^{-1} in the IR spectrum. The ^{1}H NMR spectrum showed the presence of vinyl proton signals at δ 6.94 and δ 5.79 and the ^{13}C NMR spectrum showed the presence of olefinic carbon signals at δ 149.5 and δ 120.7 and an ester carbonyl carbon signal at δ 167.1.

The *E* and *Z* stereoisomers were differentiated by comparing the coupling constants of the vinyl proton at the α carbon position of the unsaturated ester to the β vinyl proton in the two cases (Figure 4.5). The coupling constant for the vinyl proton signal corresponding to the minor product was found to be 9.3 Hz whereas that corresponding to the major product was found to be 15.6 Hz. The coupling constant for vinyl protons of a C=C double bond of *E* stereochemistry is usually found to be between 12-18 Hz, whereas that for those of *Z* stereochemistry is found to be between 6-12 Hz.[23] It is also well precedented that using the Masamune-Roush conditions for the Horner-Wadsworth-Emmons olefination reaction provides predominantly the *E* stereoisomer.[22]

Table 4.10 Horner-Wadsworth-Emmons Olefination Reaction of the Aldehyde 4.46



4.46

4.47 ***E***
4.48 ***Z***

entry	conditions	T (°C)	yield 4.47/4.48	ratio 4.47/4.48[a]	Ref.[b]
1	KHMDS, THF	0	93%	76:24	O-17
2	LiCl, DBU, CH_3CN	0	90%	97:3	O-31
3	LiCl, DBU, CH_3CN	-15	94%	>99:1	P-17

[a] Determined by GC analysis. [b] Refers to laboratory notebook page.

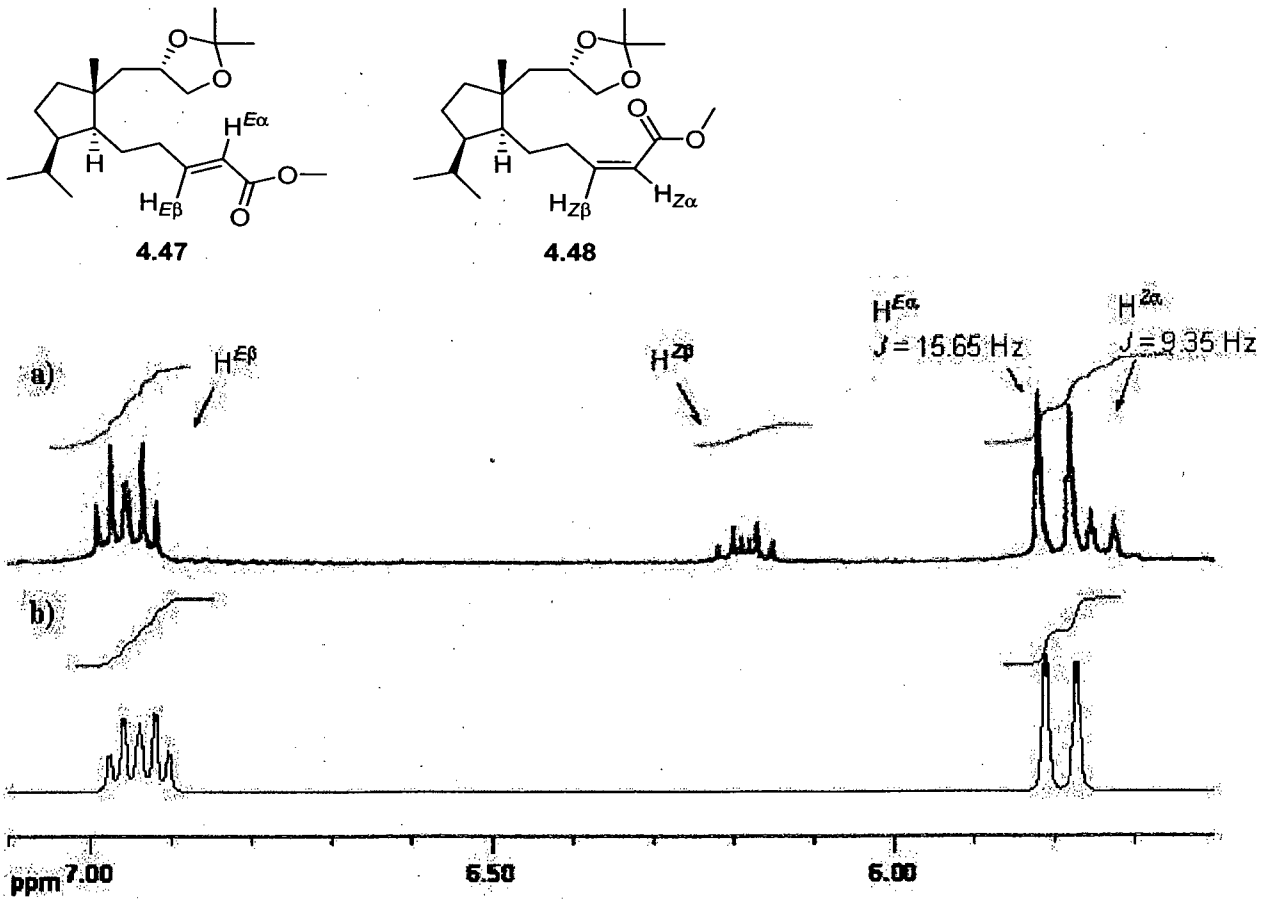
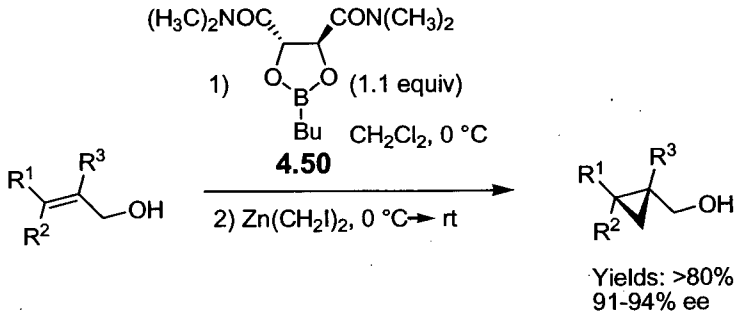


Figure 4.6 NMR Spectrum for a 3.2:1 Mixture of 4.47 and 4.48 (a) entry 1, Table 4.9) and for a >99:1 Mixture (b) entry 3, Table 4.9)

The unsaturated ester **4.47** was then reduced to the allylic alcohol **4.49** with diisobutylaluminum hydride at -78 °C in a near quantitative yield (Scheme 4.11). Evidence for the reduction was observed as an O-H stretching frequency of 3414 cm^{-1} in the IR spectrum, and the disappearance of the methyl ester proton signal in the ^{1}H NMR spectrum at δ 3.69 and the ester carbonyl carbon signal in the ^{13}C NMR spectrum at δ 167.1.

With the allylic alcohol **4.49** in hand, we could now focus on the asymmetric cyclopropanation which would eventually lead to the isolated C-7 methyl group. The method developed by Charette and co-workers for the asymmetric cyclopropanation of allylic alcohols was chosen as this appeared most suited to our system.[24] This involves a Simmons-Smith type cyclopropanation reaction using a zinc reagent in the presence of an amphoteric bifunctional chiral dioxaborolane ligand. The procedure involves the conversion of allylic alcohols to substituted cyclopropylmethanols in both high yields and enantiomeric excesses (Scheme 4.12). The dioxaborolane ligand **4.50** is prepared

from butylboronic acid and *N,N,N',N*-tetramethyltartaric acid diamide. Since either the (*R,R*) or the (*S,S*) enantiomers of tetramethyltartaric acid diamide are commercially available, either enantiomers of the resulting cyclopropylmethanol are accessible. The design of the dioxaborolane relies on the presence of an acidic (boron) and basic (amide) site that allows the simultaneous complexation of the acidic halomethylzinc reagent and the basic allylic metal alkoxide.



Scheme 4.12 Asymmetric Cyclopropanation Reaction of Allylic Alcohols Using a Chiral Dioxaborolane Ligand Developed by Charette and Co-Workers[24]

An analysis of the stereodefining transition state was required in order to determine which dioxaborolane ligand enantiomer was required in our system. The modeled transition state proposed by Charette and co-workers (Figure 4.6)[24c] results from the reaction of the alkoxide derived from the allylic alcohol and the dioxaborolane to produce the ate complex. The butyl substituent is assumed to occupy the less congested pseudoequatorial position and the allylic alkoxide the pseudoaxial position due to chelation. In as such, the complex accommodates the simultaneous coordination of the zinc reagent to both the carbonyl amide of the dioxaborolane ligand and to the allylic alkoxide oxygen. Methylene delivery then occurs when the allylic chain is in its most stable conformation. Consequentially, this model predicts that the use of the dioxaborolane ligand **4.50** derived from (*S,S*)-(-)-*N,N,N',N'*-tetramethyltartaric acid diamide should provide the cyclopropylmethanol **4.51** with the required stereochemistry as shown (Figure 4.6).

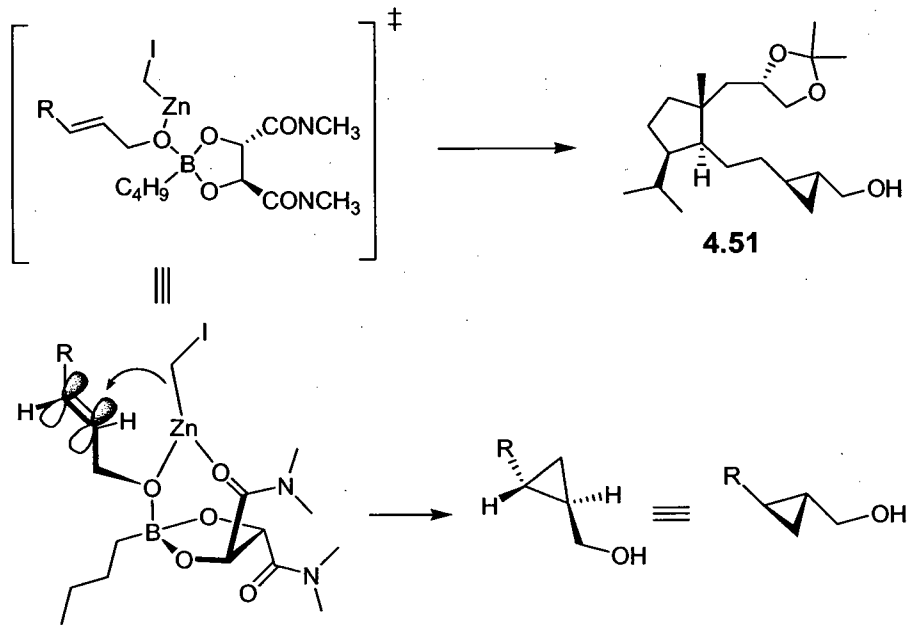


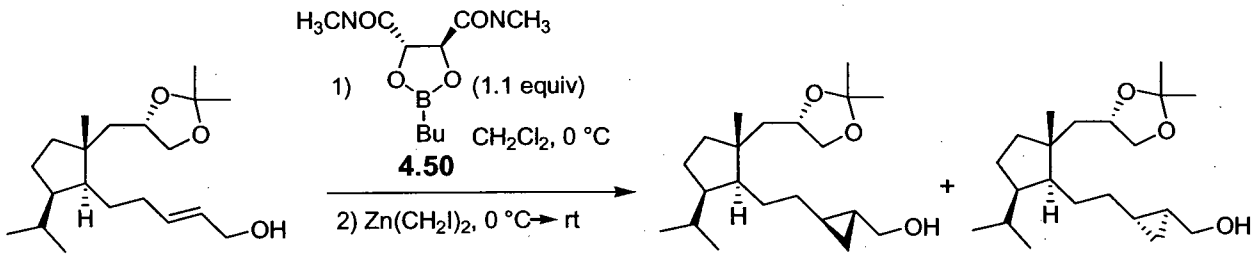
Figure 4.7 Proposed Transition State For The Enantioselective Cyclopropanation of Allylic Alcohol 4.49[24c]

Hence, a solution of allylic alcohol **4.49** and the dioxaborolane **4.50** was added dropwise to a methylene chloride solution of the $Zn(CH_2I)_2$ reagent, preformed from diiodomethane and diethylzinc, at 0 °C and stirred for 3 hours at ambient temperature. The yield and the diastereoselectivity were found to be both quite satisfying. Reproducible yields of 97% were obtained, and only trace amounts of the minor diastereomer was detected. The formation for the cyclopropylmethanol product was confirmed from the IR spectrum which showed the disappearance C=C stretching frequency of 1670 cm^{-1}, as well as for the vinyl proton signals at δ 5.71-5.54 in the ^1H NMR spectrum and for the olefinic carbon signals at δ 133.3 and δ 128.9 in the ^{13}C NMR spectrum. Moreover, the presence of cyclopropyl protons signals were observed in the ^1H NMR spectrum at δ 0.62-0.49 and at δ 0.37-0.22, and cyclopropyl carbon signals were observed in the ^{13}C NMR spectrum at δ 21.3, δ 17.7 and at δ 9.8.

However, we found that if the reaction scale was increased, the diastereoselectivity decreased substantially (Table 4.10). The minor diastereoisomer **4.52** could not be separated from the major, but its appearance in the reaction mixture could be observed from the GC/MS spectrum as a peak with a slightly longer retention time but which represented a compound with the same molecular weight. Additionally, the ^1H NMR and ^{13}C NMR spectra of the mixture showed additional signals attributed to

the minor diastereoisomer **4.52**. Most significant was the presence of differentiable signals for the protons of the alcohol carbon and for the cyclopropyl protons in the ^1H NMR spectrum.

Table 4.11 Enantioselective Cyclopropanation of Allylic Alcohol 4.49

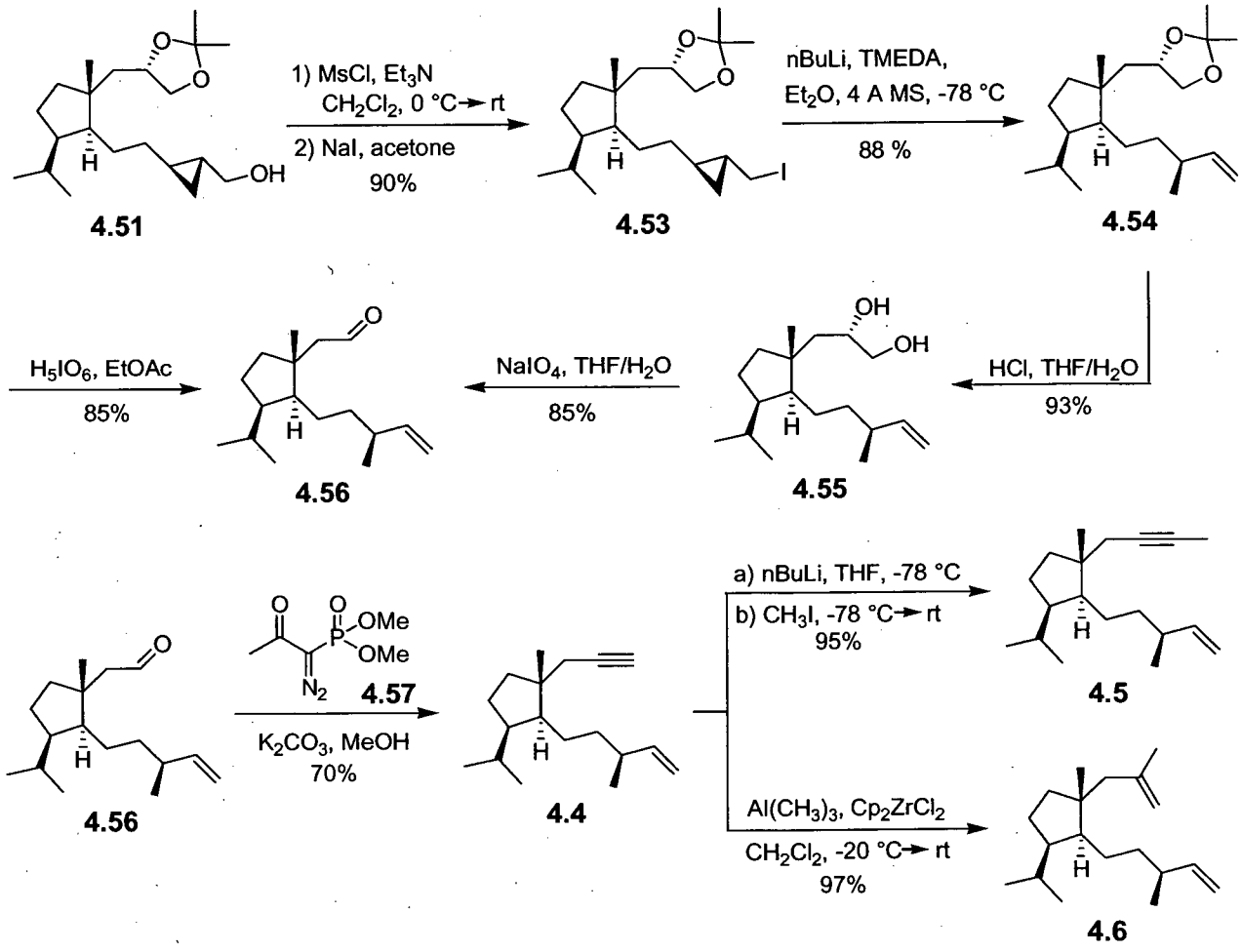


4.49 **4.51** **4.52**

entry	amount of 4.49 (mg)	yield 4.51/4.52	ratio 4.51/4.52[a]	Ref.[b]
1	73.9	97%	97:3	P-24
2	161	97%	95:5	R-23
3	200	91%	95:5	Q-30
4	350	96%	90:10	Q-08
5	753	97%	70:30	O-44

[a] Determined by GC analysis. [b] Refers to laboratory notebook page.

The diastereoselectivity for the reaction was found to remain comparable for a scale of up to 200 mg. Upon increasing this scale, the product ratio decreased significantly. Henceforth, the reaction was not performed on scales larger than 200 mg, since we found that the diastereomeric mixture was not seperable, and purifications at later stages in the synthetic sequence were problematic. The reason for this apparent scale dependence was not probed. Charette and co-workers have however noted the exothermic nature of the formation of the zinc alkoxide for this procedure on larger scales (> 8 mmol), which even sometimes led to violent explosions.[24c]



Scheme 4.13 Synthesis of Enynes 4.4 and 4.5, and Diene 4.6 from Cyclopropylmethanol 4.51

A procedure for the fragmentation of the cyclopropylmethanol of **4.51** was now required. There exists a few methods for this fragmentation type by way of a cyclopropylcarbinyl radical.[25] However, we found that the anionic method developed by Charette and co-workers was best suited to our system.[26] This required conversion of the alcohol **4.51** to the iodide **4.53** via the mesylate intermediate (Scheme 4.13). The mesylate was found to be acid sensitive. Therefore the crude product obtained after workup was treated directly with sodium iodide in acetone solvent to produce the iodide **4.53** in 90% overall yield. Evidence for the formation of the iodide **4.53** was obtained from the disappearance of the O-H stretch at 3441 cm^{-1} in the IR spectrum. The fragmentation was initiated by treatment of the iodide **4.53** with *n*-butyllithium in the presence of *N,N,N',N'*-tetramethylethylenediamine at -78 °C, and quenching the reaction at -78 °C with water, to yield **4.54** in 86 % yield. Control of the reaction

mixture temperature was important since, if allowed to increase above -78 °C, addition to iodobutane, formed from the lithium-iodide exchange, was observed. The reaction yielded excellent regiocontrol as only one product was essentially obtained. The formation of alkene **4.54** was noted from the IR spectrum which showed the presence of a C=C stretch at 1640 cm^{-1}. The ^1H NMR spectrum showed the presence of the protons for the newly formed methyl as a singlet at δ 0.97 and for vinyl proton signals at δ 5.67 and δ 4.96-4.86. The ^{13}C NMR spectrum furthermore showed the presence of olefinic carbon signals at δ 149.5 and δ 120.7.

With the C-7 methyl group in place, attention was now focused on the ketal deprotection of the diol and alkynylation of the resulting aldehyde. The isopropylidene ketal of **4.54** was originally hydrolyzed (1N HCl, THF/H_2O) and the resulting glycol **4.55** was oxidatively cleaved ($NaIO_4$, THF/H_2O) in 93% and 85% yield respectively. We subsequently found that use of the periodic acid hydrate in ethyl acetate[27] efficiently performed this 2 step hydrolytic cleavage sequence in one pot to provide **4.56** in an improved overall yield of 85% (over two steps). The presence of an aldehyde was confirmed by the occurrence of a C=O stretching frequency of 1722 cm^{-1} in the IR spectrum, an aldehydic proton signal at δ 9.78 in the ^1H NMR spectrum, and a carbonyl carbon signal at δ 203.8 in the ^{13}C NMR spectrum.

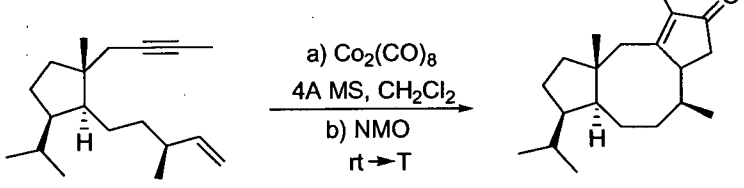
The aldehyde **4.56** was transformed to the terminal alkyne using the Bestmann-Ohira modification[28] of the Gilbert-Seyferth reagent.[29] Treatment of the aldehyde substrate with potassium carbonate and dimethyldiazo-2-oxopropylphosphonate **4.57** in methanol afforded the enyne **4.4** in 70% yield. The spectral data for **4.4** supported the assigned structure. The IR spectrum showed an alkyne C-H stretching frequency of 3312 cm^{-1} and the ^1H NMR spectrum contained a signal at δ 1.94 corresponding to the alkyne hydrogen. The enyne **4.5** was obtained from the methylation of enyne **4.4**, which was evidenced from the presence of a singlet signal at δ 1.05 representative of the added methyl group. The diene **4.6** was also obtained from the enyne **4.4** via a methylalumination reaction.[30] This was observed from the ^1H NMR spectrum which showed the appearance of a vinyl proton signals at δ 4.79 and 4.62. The ^{13}C NMR spectrum also showed the appearance of alkene signals at δ 144.0 and 113.8.

V. Formation of the 8-Membered B-Ring

With the preparation of the enynes **4.4** and **4.5** and of the diene **4.6** accomplished, attention was focused on the formation of the 8-membered B-ring. The synthesis of 8-membered carbocycles has for long remained a challenge due to the unfavourable entropic factors and transannular interactions associated with their preparation.[31] However, the development of a number of recent metal-mediated synthetic methodologies has expanded the scope of the synthesis of medium-sized rings.[32]

It was envisioned that the enyne **4.5** could be used in a Pauson-Khand reaction to form the remaining B- and C-rings in a single transformation. Until recently, the intramolecular Pauson-Khand reaction has been restricted to the preparation of bicycle[3.3.0]octenones and bicycle[4.3.0]nonenones. However, Lovely and co-workers have recently demonstrated the preparation of bicycles containing 7- and 8-membered rings using the Pauson-Khand reaction.[33] Similar reaction conditions ($Co_2(CO)_8$, 4Å mol. sieves, CH_2Cl_2, NMO, rt)[14] were applied to enyne **4.5** (Table 4.11). However, only the starting material **4.5** was recovered after 34 hours in a near quantitative yield after treatment of the resulting crude $Co_2(CO)_6$-alkyne complex with cerric ammonium nitrate (entry 1). An attempt to perform the reaction at higher temperature led to decomposition (entry 2).

Table 4.12 Attempted Pauson-Khand [2+2+1] Cycloadditions of Enyne 4.5



4.5 **4.1**

entry	T	result	Ref.[c]
1	rt	NR[a] (98% recovered **4.5**)[b]	P-32
2	40 °C	decomposition	P-33

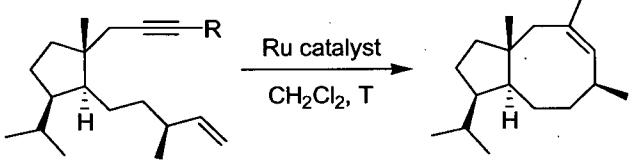
[a] No Reaction. [b] **4.5** was isolated after treatment of the resulting crude $Co_2(CO)_6$ complex with cerric ammonium nitrate. [c] Refers to laboratory notebook page.

In consideration of the failure of enyne **4.5** to undergo Pauson-Khand cyclization, the use of ring closing metathesis was then considered for the formation of the B-ring. A number of recent examples have demonstrated the utility of this method of cyclization in the synthesis of 8-membered rings.[34] Mori and co-workers have recently demonstrated the use of ring closing enyne metathesis reactions[35] in the formation of 8-membered rings.[36] The use of enyne metathesis has been applied to the total synthesis of natural products containing 7-membered rings.[37] It is important to note that, to the best of our knowledge, no examples have been previously reported on the use of enyne metathesis in the synthesis of natural products containing an 8-membered ring. Mori and co-workers reported that in general, the formation of 8-membered rings were unsuccessful unless heteratoms or rings were present in the enyne to restrict conformational freedom in the starting material, thereby reducing the entropy loss in the transition state.

An initial investigation of the ring closing enyne metathesis was performed using the substrate **4.5** (Table 4.13). The use of the Grubbs ruthenium catalyst **4.57** provided no reaction (entry 1). However, trace amounts of the cyclized product were observed when the reaction was performed in refluxing methylene chloride (entry 2). The presence of trace amounts of **4.2** was confirmed through the use of GC/MS analysis of the reaction mixture which revealed the presence of a peak in the GC trace corresponding to a compound having a molecular weight of 260. The use of the Grubbs ruthenium catalyst **4.58** in refluxing methylene chloride provided for an improved yield of 19% (entry 3). However, increasing the reaction temperature to 80 °C provided for a lowered yield of 8% and with only 24% recovered **4.5**, the remaining mass balance appearing to be dimerization products according to GC/MS analysis (entry 4). An improved yield of 53% for the cyclized product **4.2** was obtained with complete conversion of the starting material **4.5** when the reaction was performed in refluxing methylene chloride with higher catalyst loading (30 mol %) (entry 5). The remaining mass balance was attributed to a mixture of dimerization products and the cross metathesis products of **4.2** with styrene origination from the benzylidene catalyst according to GC/MS and ^{1}H NMR analyses. In addition to the mass spectral analysis, evidence for the cyclization was observed from the appearance of a vinyl proton doublet signal at δ 5.40 and two vinyl proton singlet signals at δ 5.01 and at δ 4.87 in the ^{1}H NMR spectrum and of four vinyl carbon signals at δ 153.1, δ 149.2, δ 111.8 and δ 111.2

in the ^{13}C NMR spectrum.[38] Moreover, the disappearance of the alkyne carbon signals of **4.5** in the ^{13}C NMR spectrum at δ 78.0 and at δ 76.5 was also observed.

Table 4.13 Ring Closing Enyne Metathesis of Enyne 4.5

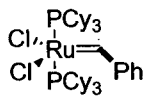


SM

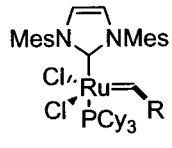
R = CH_3 **4.5**
= TMS **4.62**
= OTIPS **4.63**

product

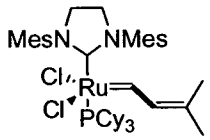
R = CH_3 **4.2**
= TMS **4.64**
= OTIPS **4.65**



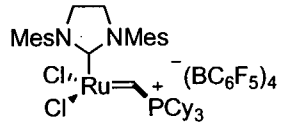
4.57



R = Ph **4.58**
= H **4.60**



4.59



4.61

entry	enyne	T	Ru catalyst	mol %	yield product[a]	Yield SM[b]	Ref[c]
1	**4.5**	rt	**4.57**	5	——	99%	P-36
2	**4.5**	40 °C	**4.57**	5	trace	84%	P-36
3	**4.5**	40 °C	**4.58**	5	19%	65%	R-37
4[d]	**4.5**	80 °C	**4.58**	10	8%	24%	R-39
5	**4.5**	40 °C	**4.58**	30	53%	——	R-35
6[e]	**4.5**	40 °C	**4.58**	10	trace	NI[f]	R-40
7[g,h]	**4.5**	40 °C	**4.58**	10	——	——	Q-44
8	**4.5**	40 °C	**4.59**	20	trace	NI[f]	R-36
9[d]	**4.5**	80 °C	**4.59**	10	——	NI[f]	R-38
10	**4.5**	40 °C	**4.60**	20	trace	NI[f]	R-41
11	**4.5**	40 °C	**4.61**	20	trace	NI[f]	R-49
12	**4.62**	40 °C	**4.58**	20	——	45%	R-32
13	**4.63**	40 °C	**4.58**	20	——	NI[f]	R-33

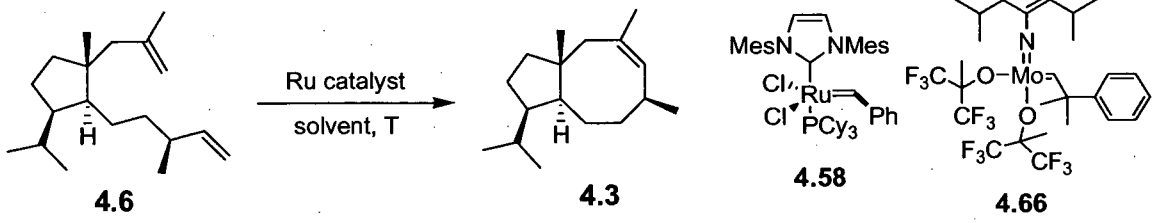
[a] Cyclized Product: Refers to either **4.2**, **4.64**, **4.65**. [b] Starting Material: Refers to either **4.5**, **4.62**, **4.63**. [c] Refers to laboratory notebook page. [d] The reaction was performed in toluene. [e] The ruthenium catalyst **4.59** was added to the reaction mixture over a period of 2 hours. [f] Not Isolated: the starting material enyne **4.5** was not recovered from the reaction mixture although NMR analysis showed that most of the reaction mixture was composed of the enyne. [g] The reaction was performed under a balloon atmosphere of ethylene. [h] Product resulting from the cross metathesis of the alkyne and ethylene was obtained in 70% yield .

The incomplete conversion of starting material observed in most of the cases (entries 2, 3 and 4) led to the belief that the ruthenium catalyst may be decomposing or rendered inactive during the course of the cyclization reaction. Slow addition of a solution of **4.58** in methylene chloride over a period of 2 hours in order to minimize the loss of the catalyst during the course of the cyclization, resulted in mostly unreacted **4.5** (entry 6). Mori and co-workers have reported the beneficial effect of performing the reaction under an atmosphere of ethylene in certain cases.[36b] However, when the reaction was performed with ethylene, the only obtainable product was that resulting from the cross enyne metathesis reaction of the alkyne of **4.5** with ethylene.

A number of other ruthenium catalysts were screened for their reactivity in the cyclization of **4.5**. Nonetheless, **4.59**, **4.60** and **4.61** each lead to the formation of only trace amounts of **4.2** at best (entries 8-11). Additionally, the silyl substituted enyne **4.62** and the silyloxy substituted enyne **4.63** did not yield any cyclization products.

Although there exists few examples for the formation of 8-membered rings by way of ring closing metathesis of a diene substrate, the synthesis of dactylol by Fürstner and co-workers was of particular interest.[39] This made use of a ring closing metathesis reaction to form an 8-membered ring fused to a cyclopentane under the influence of the Schrock molebdenum complex **4.66**. The success of the cyclization was attributed to the conformational constraint of the cyclopentane and the structural similarity to **4.6** led to the belief that this may be a viable route to forming the 8-membered ring. However the reaction proved unsuccessful using either the Grubbs ruthenium catalyst **4.58** or the Schrock molybdenum catalyst **4.66** (Table 4.14).

Table 4.14 Attempted Ring Closing Metathesis of Diene 4.6



4.6 **4.3** **4.58** **4.66**

entry	Ru catalyst	mol %	solvent	T	yield 4.3	Yield 4.6	Ref[a]
1	**4.58**	5	CH_2Cl_2	40 °C	____	NI[b]	R-44
2	**4.58**	5	Toluene	80 °C	____	NI[b]	R-46
3	**4.66**	5	Hexane	50 °C	____	NI[b]	R-47

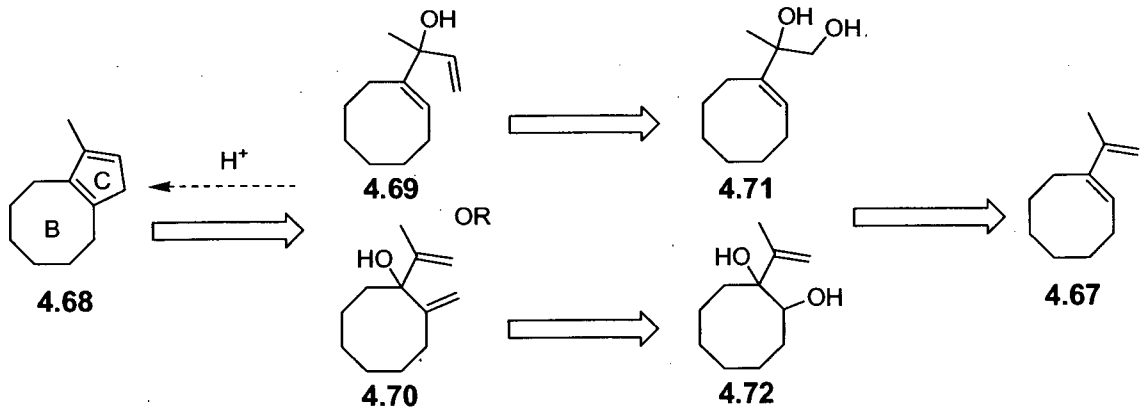
[a] Refers to laboratory notebook page. [b] Not Isolated: the starting material diene **4.6** was not recovered from the reaction mixture although NMR analysis showed that most of the reaction mixture was composed of the diene.

Hence, whereas the Pauson-Khand [2+2+1] cycloaddition of enyne **4.5** or the ring closing metathesis of diene **4.6** did not yield cyclization products, the ring closing enyne metathesis of **4.5** was the only cyclization method attempted which provided for the formation of the 8-membered B-ring, albeit in only moderate yield. Using 30 mol % of the Grubbs catalyst **4.58** at 40 °C produced the desired diene **4.2** in 53% yield (Table 4.13, entry 5). It was hoped that the conformational constraints provided by the presence of the A-ring cyclopentane ring would allow to overcome the unfavourable entropic factors and transannular interactions associated with the formation of the cyclooctane ring. This appears to be true in the case of the ring closing enyne metathesis only. However a high catalyst loading is required for the reaction to proceed to completion. The required high catalyst loading is a consequence of a low catalyst turnover in the system. Additional studies would be essential in order to solve the cause for the low catalyst turnover and would provide valuable information towards improving the reaction yield.

VI. Formation of the C-ring: Further Model Studies

During the course of attempted ring closing enyne metathesis reactions, synthetic material was completely consummed. Hence, further progression in the synthesis of the targets could not be accomplished without repeating the complete synthetic sequence. However, the preparation of the known 8-membered ring compound (*E*)-1-(prop-1-en-2-yl)cyclooct-1-ene **4.67**[40] to model the enyne metathesis product **4.6** was performed with the goal of demonstrating the synthetic sequence for the formation of the C-ring in fusicoccadiene.

In any case, the formation of the C-ring[iv] in a model such as **4.68** could be envisioned by being prepared from an acid-catalyzed cyclodehydration reaction[41] analogous to the Nazarov cyclization[42] of either dienols **4.69** or **4.70**. The two dienols retrosynthetically lead to the diols **4.71** and **4.72** respectively, of which both may be reduced to the diene **4.67**.

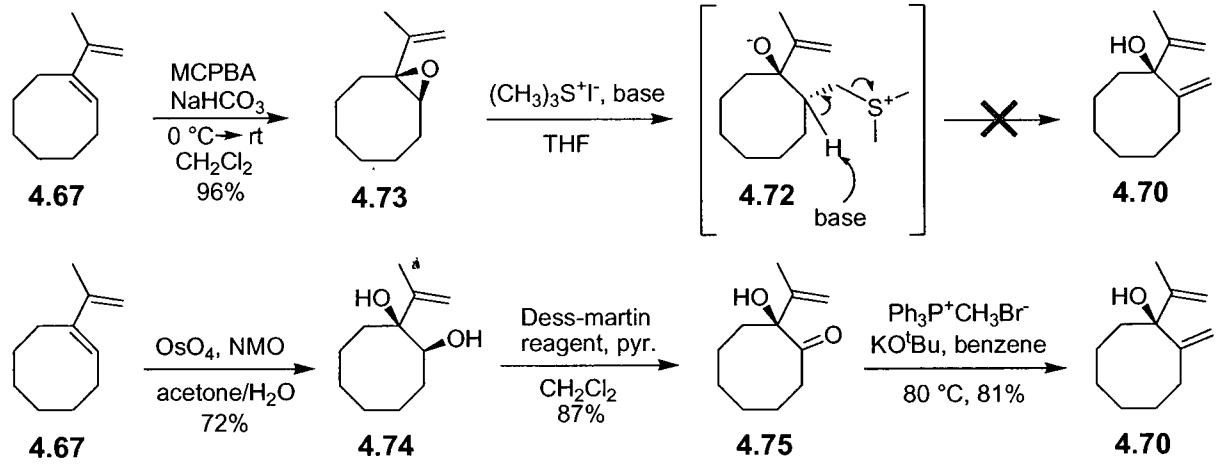


Scheme 4.14 Retrosynthetic Analysis of the 5-8-5 Ring System in the model compound 4.68

The diene **4.67** was treated under standard epoxidation conditions (MCPBA, $NaHCO_3$, CH_2Cl_2). Epoxidation occurred at the more electron rich ring alkene to produce **4.73** in near quantitative yields (Scheme 4.15). This was evidenced from the ^1H NMR spectrum which revealed the disappearance of the triplet vinyl proton signal observed for **4.67** at δ 5.82 and the appearance of a doublet of doublet at δ 3.04 for a proton attached to the to the epoxide carbon.

[iv] The same ring nomenclature used for the fusicoccadiene is used in the model substrate. Hence, the 8-membered ring is labeled as the B-ring and the 5-membered ring is labeled as the C-ring.

In order to obtain the dienol **4.70**, the use of a methylide ylide was contemplated. This would undergo a nucleophilic substitution with the epoxide, followed by an elimination to produce the doubly allylic alcohol. Alcaraz and co-workers have reported a procedure for the conversion of epoxides into allylic alcohols using dimethylsulfonium methylide.[43] The reaction requires the use of two equivalents of the sulfonium methylide, the first equivalent adding as a nucleophile to the epoxide, and the second acting as a base to eliminate dimethylsulfide and producing the allylic alcohol (see Scheme 4.15). The conditions reported (3 equiv trimethylsulfonium iodide, 2.9 equiv nBuLi, THF, -10 °C, 30 min, then **4.72**, -10 °C→rt) were first applied to the allylic epoxide **4.73**. However, only starting was recovered in a near quantitative yield. Performing the reaction at higher temperature or with larger amounts of the sulfonium ylide did not assist in producing any product. Neither did varying the base used to prepare the sulfonium ylide (KHMDS) or using a variety of Lewis acids (LiCl, $AlMe_3$, $AlCl_3$, BF_3, BCl_3). No example of the addition of dimethylsulfonium methylide was reported for 1,1,2-trisubstituted epoxides, and it was reasoned that steric interactions hindered the addition. This was validated through subsequent experimentations (*vide infra*).



Scheme 4.15 Synthesis of Dienol 4.70

The diene **4.67** was also dihydroxylated using osmium tetraoxide. In a similar manner to the epoxidation of the same compound (*vide supra*), the osmylation occurred predominantly at the more electron rich ring alkene to produce **4.74** in good yield (Scheme 4.15). Formation of the diol was evidenced by the occurrence of a large and

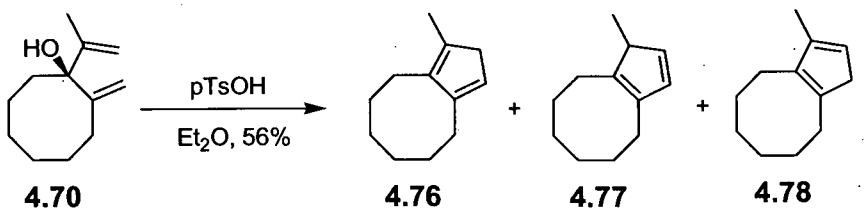
broad O-H stretching frequency of 3424 cm^{-1} in the IR spectrum. Further evidence for the chemoselective dihydroxylation was obtained from the ^1H NMR spectrum which revealed the disappearance of the triplet vinyl proton signal observed for **4.67** at δ 5.82 and the appearance of a multiplet at δ 4.08-4.00 for a proton attached to the hydroxyl-bearing carbon.

Swern-Moffatt (DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, 30 min, then **4.74**, 1 h, then Et_3N, rt, 4 h) or perruthenate oxidation condition (0.2 equiv TPAP, 1.05 equiv NMO, 3Å mol. sieves) did not yield any oxidation products as only the starting material **4.74** was recovered. Steric hinderance at the reactive centre was assumed to be the cause for the lack of reactivity. However the use of the Dess-Martin periodinane[44] did allow for the formation of **4.75** in good yield. The presence of a C=O stretching frequency of 1699 cm^{-1} and of a carbonyl carbon signal in the ^{13}C NMR spectrum at δ 217.2 supported the assigned structure.

The standard Wittig olefination conditions (triphenylphosphonium bromide, nBuLi, THF) did not provide for the methylenation of the ketone in **4.75**. It was subsequently found that the use of potassium *t*-butoxide in refluxing benzene did however provide the desired dienol **4.70**. Evidence for the olefination reaction was obtained from the ^{13}C NMR spectrum which revealed the appearance of two additional alkene carbon signals at δ 153.1 and δ 111.4 as well as the disappearance of the carbonyl carbon signal in the ^{13}C NMR spectrum at δ 217.2.

With the dienol **4.70** in hand, the cyclodehydration reaction was attempted. Initial exposure of of **4.70** to a catalytic amount of sulfuric acid (10 mol %) led to the formation of decomposition products. Gratifyingly, treatment of **4.70** with a catalytic amount of p-toluenesulfonic acid (10 mol %) in diethyl ether produced, after 18 h at ambient temperature, a less polar spot by TLC analysis which was further found to be a mixture of three isomers of the same molecular weight by GC/MS analysis in a ratio of 51:34:15 (Scheme 4.16). The three isomeric products were not separable by column chromatography and the above mentioned ratio remains unassigned for the three isomeric products. The cyclodehydration reaction was evidenced from the disappearance of the O-H stretch at 3483 cm^{-1} in the IR spectrum. Further evidence was revealed from the disappearance of the terminal vinyl proton signals in the ^1H NMR spectrum at δ 5.32, δ 5.00, δ 4.95 and δ 4.84, and the appearance of the vinyl C-ring

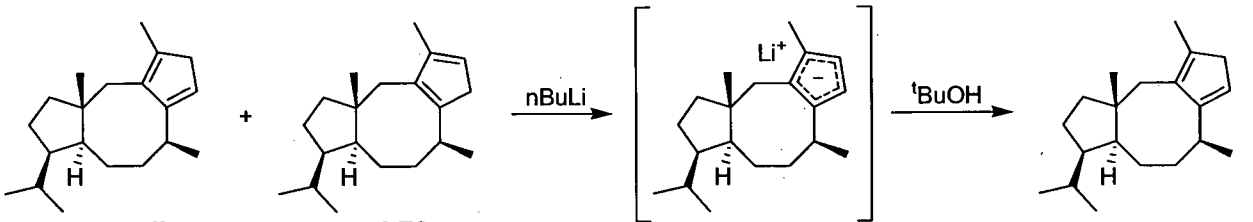
cyclopentadiene protons at δ 5.92-5.76. No further optimizations were performed for the cyclodehydration reaction.



4.70 **4.76** **4.77** **4.78**

Scheme 4.16 Cyclodehydration Reaction of Dienol 4.70

The formation of a mixture of three cyclopentadiene isomers in the cyclodehydration reaction of dienol **4.70** was of little concern. Takeshita and co-workers have previously shown the preparation of fusicoccadiene as the sole product from a mixture of two cyclopentadiene isomers via the protonation of the corresponding cyclopentadienide with *tert*-butyl alcohol (Scheme 4.17).[4] The main concern described in this section was to validate the possibility of forming the cyclopentadiene C-ring from **4.2**.



fusicoccadiene **4.79** **fusicoccadiene**

3 : 1

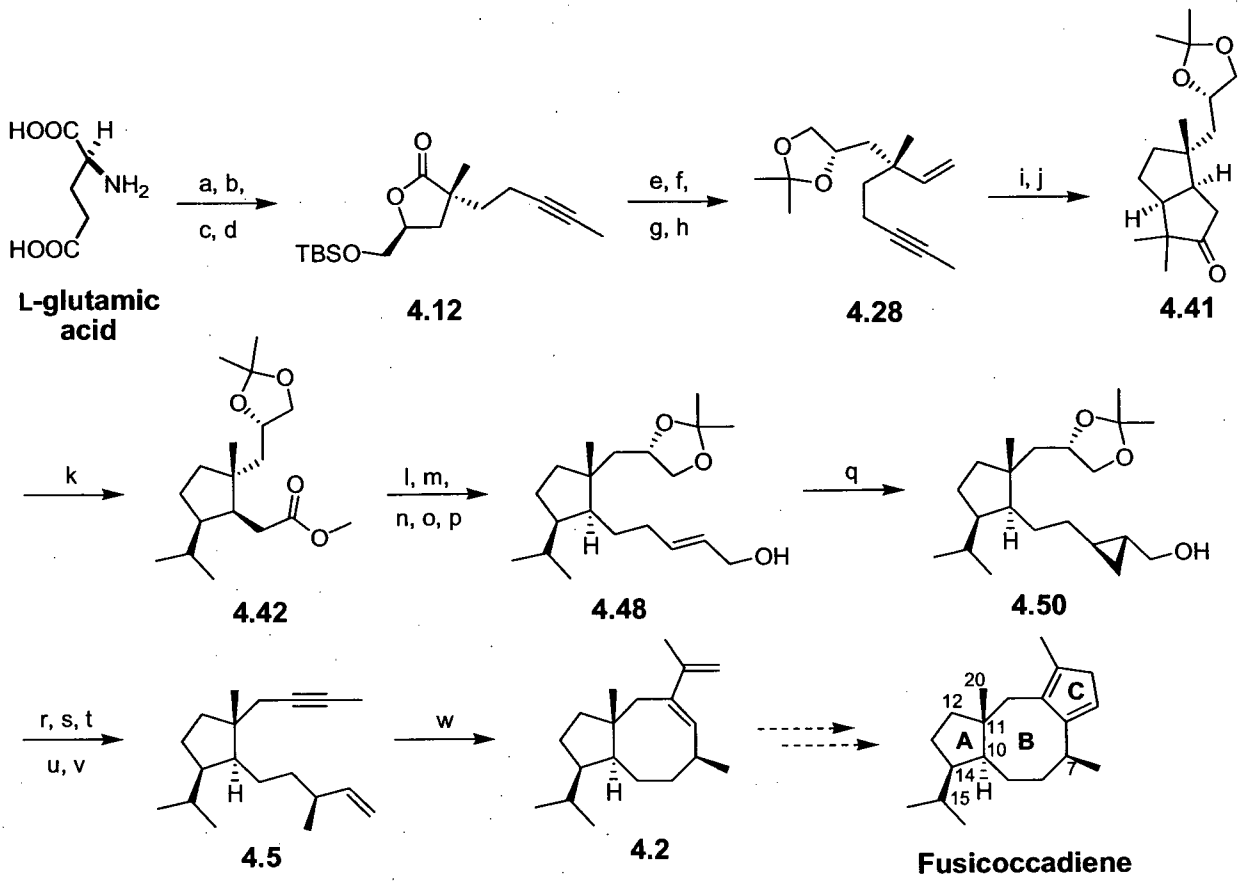
Scheme 4.17 Formation of Fusicoccadiene from a Mixture of Cyclopentadiene Isomers[4]

VII. Concluding Remarks

The work described in this part of the thesis involved the progress towards the synthesis of enantiomeric fusicoccadiene as a source for the accessibility of a number of fusicoccane diterpenoids listed in Figure 4.1. The A- and B-ring portions were constructed which included the installation of the four stereocentres of fusicoccadiene. This was manifested as the enyne metathesis product **4.2** (Scheme 4.17). Due to the difficulties in the cyclization reactions to form the B-ring which exhausted the available synthetic material, further progress towards fusicoccadiene was not achieved. Rather, a model study was performed to demonstrate the possibility of transforming **4.2** into fusicoccadiene. Further work will require the elaboration of **4.2** to fusicoccadiene accordingly to the sequence established in the model study.

Highlights of the synthetic approach includes the preparation of the functionalized cyclopentane A-ring through the use of a stereoselective Pauson-Khand [2+2+1] cycloaddition to establish the C-10 and C-14 stereocentres followed by the Norrish Type I reaction, the asymmetric cyclopropanation reaction to establish the remote C-7 stereocentre, and the formation of the 8-membered B-ring using ring closing enyne metathesis. Efficient use of chemical relay from the asymmetric carbon of L-glutamic acid (C-2) to establish the C-11 stereocentre deserves mention since this further allowed the selective creation of the C-10 and C-14 stereocentres. Hence the three contiguous stereocentres about the cyclopentane A-ring are derived from an inexpensive chiral pool reagent.

The synthesis of the advanced intermediate **4.2** was achieved in 21 steps from the known (*S*)-(+)-4-(*tert*-butyldimethylsilyl)oxymethyl-γ-butyrolactone (**4.15**). The synthesis of fusicoccadiene from **4.2** would require an additional 4 steps according to model studies performed. This synthesis compares favourably to that previously reported by Takeshita and co-workers[4] which required 30 synthetic operations from known starting materials.



(a) $NaNO_2$/HCl, H_2O, 0 °C → rt; BH_3•SMe_2, THF, rt, 65%; (b) TBSCl, Et_3N, CH_2Cl_2, 0 °C → rt, 97%; (c) LDA, THF, -78 °C, 30 min, then CH_3I, -78 °C, 93%; (d) LDA, HMPA, THF, -78 °C, 1h, then 5-iodopent-2-yne **4.20**, -78 °C → rt, 54% (80% BRSM); (e) Dibal-H, CH_2Cl_2, -78 °C, 92%; (f) KHMDS, methyltriphenylphosphonium bromide, THF, 0 °C → rt, 99%; (g) TBAF, THF, rt, >99%; (h) 2,2-dimethoxypropane, TsOH, CH_2Cl_2, rt, 87%; (i) $Co_2(CO)_8$, 4 Å MS, CH_2Cl_2, rt, 1 h, then NMO, 0 °C → rt, 89% (5.9:1 **4.35**/**4.36**); (j) L-Selectride®, THF, -78 °C, 30 min, then CH_3I, -78 °C → rt, 96%; (k) hv (> 190 nm), quartz filter, CH_3OH, 70% (76% BRSM); (l) LAH, Et_2O, 0 °C → rt, 95%; (m) MsCl, Et_3N, CH_2Cl_2, 0 °C; NaCN, DMSO, 60 °C, 96%; (n) Dibal-H, CH_2Cl_2, -78 °C, 95%; (o) Trimethylphosphonoacetate, DBU, CH_3CN, -15 °C, 85%; (p) Dibal-H, CH_2Cl_2, -78 °C, 95%; (q) dioxaborolane **4.50**, CH_2Cl_2, 0 °C, then cannulate to a solution of $Zn(CH_2I)_2$, 0 °C → rt, 97%; (r) MsCl, Et_3N, CH_2Cl_2, 0 °C → rt; NaI, acetone, rt, 90%; (s) nBuLi, TMEDA, 4 Å MS, Et_2O, -78 °C, 88%; (t) H_5IO_6, EtOAc, rt, 85%; (u) **4.57**, K_2CO_3, CH_3OH, rt, 70%; (v) nBuLi, THF, -78 °C, then CH_3I, -78 °C → rt, 95%; (w) **4.58** (30 mol%), CH_2Cl_2, 40 °C, 53%.

Scheme 4.18 Asymmetric Synthesis of the Advanced Intermediate 4.2 and Proposed Construction of Fusicoccadiene

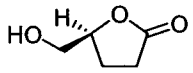
VIII. Experimental

Unless otherwise stated, all reactions were performed under a nitrogen atmosphere in flame-dried glassware. The glass syringes, Teflon® cannulae and stainless steel needles used for handling anhydrous solvents and reagents were oven dried, cooled in a dessicator, and flushed with dry nitrogen prior to use. Plastic syringes were flushed with dry nitrogen before use. Thin layer chromatography (TLC) was performed on DC-Fertigplatten SIL G-25 UV_{254} pre-coated TLC plates. Gas chromatographic (GC) analyses in a helium carrier gas were performed on an Agilent 6890 gas chromatograph, equipped with an Agilent 5973N mass selective detector. A Hewlett-Packard HP-5MS (30 m × 0.25 mm × 0.25 μm ID) fused silica capillary columns was used. Melting points were performed using a Mel-Temp II apparatus (Lab devices USA) and are uncorrected. Optical rotations of samples were performed using a Jasco model P1010 polarimeter at 589 nm (sodium 'D' Line). Infrared (IR) spectra were obtained using a Perkin-Elmer FT-IR spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded in deuterochloroform using either a Bruker AV-300 or a Bruker AV-400 spectrometer. Chemical shifts are reported in parts per million (ppm) and are referenced to the centreline of deuterochloroform (δ 7.24 ppm ^{1}H NMR, 77.0 ppm ^{13}C NMR). Coupling constants (J values) are given in Hertz (Hz). Low resolution mass spectra (LRMS) were recorded on either an Agilent 5973N mass selective detector, attached to an Agilent 6890 gas chromatograph for electron impact ionization (EI), a Kratos MS 80 spectrometer for desorption chemical ionization (CI) with the ionization gas noted, or a Agilent HP1100 spectrometer for electrospray ionization (ESI). Microanalyses were performed by the Microanalytical Laboratory at the University of British Columbia on a Carlo Erba Elemental Analyzer Model 1106 or a Fisions CHN-O Elemental Analyzer Model 1108.

All solvents and reagents were purified and dried using established procedures.[45] Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl under an atmosphere of dry argon. Dichloromethane, triethylamine, hexamethylphosphoramide, triisopropylsilyl chloride, dimethyl sulfoxide, acetonitrile, trimethylphosphonoacetate, 1,8-diazabicyclo[5.4.0]undec-7-ene, *N,N,N',N'*-tetramethylethylenediamine, and trimethylsilyl chloride were distilled from calcium

hydride over an atmosphere of dry argon or dry nitrogen. Diisopropylamine was distilled from sodium hydroxide over an atmosphere of dry nitrogen. Toluene was distilled from sodium over an atmosphere of dry argon. *N,N*-Dimethylformamide was purified by drying over 4Å molecular sieves. Methanol and cyclohexanone were distilled from magnesium sulfate over an atmosphere of dry nitrogen. Methanesulfonyl chloride was distilled from phosphorus pentoxide under an atmosphere of dry nitrogen. Solutions of *n*-butyllithium in hexanes were obtained from the Aldrich Chemical Co. and were standardized using the procedure of Burchat, Chong, and Nielsen.[46] Solutions of potassium bis(trimethylsilyl)amide and lithium bis(trimethylsilyl)amide in toluene were freshly prepared by dissolution of the potassium or sodium salt, available from the Aldrich Chemical Co. and standardized via titration from diphenylacetic acid.[47] 3,3-Dimethoxypentane was prepared according to the procedure of Schmid and Bradley.[48] (4*S-trans*)-2-Butyl-*N,N,N',N'*-tetramethyl[1,3,2]dioxaborolane-4,5-dicarboxamide was prepared from [(2-)-*N,O,O'*[2,2'-iminobis[ethanolato]]]-2-butylboron and (*S, S*)-(-)-*N,N,N',N'*-tetramethyltartaric acid according to the procedure of Charette and Lebel.[49] Dimethyldiazo-2-oxopropylphosphonate was prepared from toluenesulfonyl azide and dimethyl-2-oxopropylphosphonate according to the procedure of Callant, D'Haenens and Vandewall.[50] The Dess-Martin periodinane reagent was prepared according to the procedure of Boeckman, Shao and Mullins.[51] All other reagents were commercially available and were used without further purification.

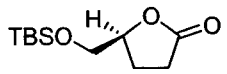
(*S*)-(+)-4-Hydroxymethyl-γ-Butyrolactone (4.14)[52]



A 2 N aqueous solution of hydrochloric acid (450 mL, 0.900 mol, 1.20 equiv.) was added to a solution of L-glutamic acid (110.3 g, 0.750 mmol, 1 equiv) in water (750 mL) at 0 °C followed by the dropwise addition of a solution of sodium nitrite (62.1 g, 0.900 mol, 1.20 equiv) in water (450 mL) at 0 °C over a period of 2 h using a pressure equalizing dropping funnel, and the reaction mixture was stirred at rt overnight. The reaction mixture was concentrated *in vacuo* to a white paste, which was taken up in boiling ethyl acetate (1 L). Anhydrous magnesium sulfate (50 g) was added and the reaction mixture was stirred for 1 h, filtered and concentrated *in vacuo* to yield a clear yellow oil (73.2 g). Borane-dimethyl sulfide complex (63.8 mL, 0.638 mol, 0.85 equiv) was added dropwise to a solution of the crude oil in THF (750 mL) at 0 °C over a period of 30 min using a pressure equalizing dropping funnel, and the reaction mixture was stirred at rt for 4 h. The reaction mixture was quenched by the slow dropwise addition of methanol (300 mL), and the solvents were removed by distillation at atmosphere to yield a yellow liquid. The crude liquid was purified by vacuum distillation (125-127 °C at 0.08 mmHg) to yield 56.8 g (65 %) of **4.14** as a clear colourless liquid.

$[\alpha]_D^{25.1}$ = +55.28 ± 0.08 (c 0.259, $CHCl_3$). IR (neat): 3423, 2942, 2877, 1767 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.62-4.54 (m, 1H), 3.84 (dd, J=11.2, 3.1 Hz, 1H), 3.63 (dd, J=11.2, 3.1 Hz, 1H), 2.72 (s, 1H), 2.65-2.40 (m, 2H), 2.27-2.05 (m, 2H).

(*S*)-(+)-4-(*tert*-Butyldimethylsilyl)oxymethyl-γ-butyrolactone (4.15)[53]

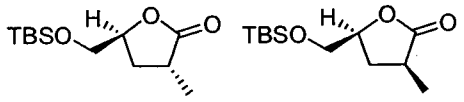


Triethylamine (79.9 mL, 0.573 mol, 1.50 equiv) was added to a solution of (S)-(+)-4-hydroxymethyl-γ-butyrolactone (**4.14**) (44.4 g, 0.382 mol, 1 equiv), *tert*-butyldimethylsilyl chloride (63.4 g, 0.421 mol, 1.1 equiv) and 4-dimethylaminopyridine (4.67 g, 38.2 mmol, 0.10 equiv) in methylene chloride (1.20 L) at 0 °C and the reaction mixture was stirred at rt overnight. The reaction mixture was washed with water (2 x 300 mL) and a saturated aqueous solution of sodium chloride (100 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear

colourless liquid. The crude liquid was purified by column chromatography (1/7 ethyl acetate-hexanes) to yield 85.0 g (97 %) of **4.15** as a clear colourless liquid.

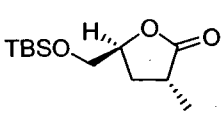
$[\alpha]_D^{25.5}$ = +13.50 ± 0.05 (c 0.199, $CHCl_3$). IR (neat): 2931, 2858, 1780 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.60-4.53 (m, 1H), 3.84 (dd, J=11.2, 3.1 Hz, 1H), 3.66 (dd, J=11.2, 3.1 Hz, 1H), 2.66-2.37 (m, 2H), 2.32-2.08 (m, 2H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

(2*R*, 4*S*)-4-(*tert*-Butyldimethylsilyl)oxymethyl-2-methyl-γ-butyrolactone (4.16)
(2*S*, 4*S*)-4-(*tert*-Butyldimethylsilyl)oxymethyl-2-methyl-γ-butyrolactone (4.17)



n-Butyllithium (264 mL of a 1.54 M solution in hexane, 0.406 mol, 1.1 equiv) was added dropwise to a solution of diisopropylamine (56.9 mL, 0.406 mol, 1.1 equiv) in THF (450 mL) at -78 °C and the reaction mixture was stirred at -78 °C for 1 h. A solution of (S)-(+)-4-(*tert*-butyldimethylsilyl)oxymethyl-γ-butyrolactone (**4.15**) (85.0 g, 0.369 mol, 1 equiv) in THF (800 mL) was added dropwise and stirring was further continued for 30 min. Iodomethane (23.0 mL, 0.369 mol, 1 equiv) was added dropwise and the reaction mixture was stirred at -78 °C for 30 min. A saturated aqueous solution of ammonium chloride (400 mL) was added and the mixture was extracted with ether (3 x 300 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (200 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear colourless liquid. The crude liquid was purified by column chromatography (1/7 ethyl acetate-hexanes) to yield 84.0 g (93 %) of a 90:10 mixture of **4.16** and **4.17** (gas chromatography analysis) as a clear colourless liquid. Further purification of an analytical sample by column chromatography (1/7 ethyl acetate-hexanes) was performed to yield an analytically pure sample of **4.16** as a clear colourless liquid and **4.17** as a clear colourless liquid.

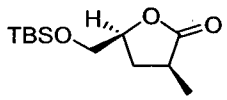
(2*R*, 4*S*)-4-(*tert*-Butyldimethylsilyl)oxymethyl-2-methyl-γ-butyrolactone (**4.16**):



$[\alpha]_D^{27.9}$ = +20.70 ± 0.08 (c 0.179, $CHCl_3$). IR (neat): 2955, 2933, 2859, 1774 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.52-4.43 (m, 1H),

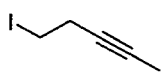
3.79 (dd, J=11.2, 3. 3 Hz, 1H), 3.63 (dd, J=11.2, 3.3 Hz, 1H), 2.81-2.63 (m, 1H), 2.41-2.30 (m, 1H), 1.96-1.83 (m, 1H), 1.22 (d, J=7.3 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 180.2, 77.6, 65.0, 34.2, 32.2, 25.8, 18.2, 16.3, -5.6. LRMS (EI) m/z (relative intensity): 244 (M^+, 0.1).

(2*S*, 4*S*)-4-(*tert*-Butyldimethylsilyl)oxymethyl-2-methyl-γ-butyrolactone (**4.17**):



$[\alpha]_D^{20.2}$ = +8.34 ± 0.03 (c 1.30, $CHCl_3$). IR (neat): 2955, 2931, 2858, 1775 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.45-4.34 (m, 1H), 3.79 (dd, J=11.4, 3.9 Hz, 1H), 3.66 (dd, J=11.2, 3.9 Hz, 1H), 2.72-2.56 (m, 1H), 2.40-2.28 (m, 1H), 1.82-1.69 (m, 1H), 1.23 (d, J=7.8 Hz, 3H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 179.4, 78.2, 63.9, 35.3, 31.9, 25.7, 18.2, 15.4, -5.5. LRMS (EI) m/z (relative intensity): 244 (M^+, 0.2).

5-iodopent-2-yne (4.20)[54]



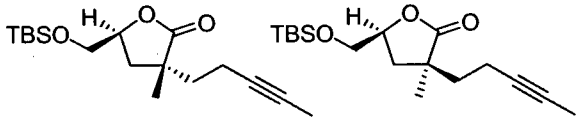
3-pentyn-1-ol (39.8 g, 0.473 mol, 1 equiv) in methylene chloride (300 mL) was added dropwise to a solution of *p*-toluenesulfonyl chloride (94.7 g, 0.947 mol, 1.05 g) 4-dimethylaminopyridine (11.6 g, 94.6 mmol, 0.20 equiv) and triethylamine (79.1 mL, 0.568 mol, 1.20 equiv) in methylene chloride (650 mL) at -15 °C over a period of 20 min. The reaction mixture was warmed to rt over a period of 1 h and stirred at rt for 1 h. Water (500 mL) was added and the reaction mixture was extracted with methylene chloride (2 x 200 mL). The methylene chloride extracts were combined, dried over magnesium sulfate and concentrated *in vacuo* to yield a yellow liquid. The crude liquid was filtered through a plug of silica gel, washed with methylene chloride (2 x 100 mL), and the filtrate was concentrated *in vacuo* to yield a clear yellow liquid. Sodium iodide (172.2 g, 1.18 mol, 2.5 equiv) was added in 1 portion to a solution of the yellow liquid in acetone (800 mL) and the reaction mixture was stirred at 51 °C for 3 h. The reaction mixture was cooled to 0 °C and the precipitated white sodium *p*-toluenesulfonate was removed by filtration, washed with ether (3 x 100 mL) and the filtrate was concentrated at atmospheric pressure to yield a yellow liquid. The crude yellow liquid was dissolved in ether (200 mL), washed with a saturated aqueous solution of sodium thiosulfate (50 mL) and water (150 mL), dried over magnesium

sulfate and concentrated at atmospheric pressure to yield a yellow liquid. The crude liquid was purified by vacuum distillation (62-63 °C at 16 mmHg) to yield 73.7 g (80 %) of **4.20** as a clear colourless liquid.

IR (neat): 2963, 2917, 2853, 1436, 1249, 1173 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.18 (t, J=7.5, 2H), 2.74-2.64 (m, 2H), 1.76 (t, J=3.7 Hz, 1H).

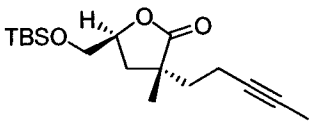
(2*R*, 4*S*)-4-(*tert*-Butyldimethylsilyl)oxymethyl-2-methyl-2-(pent-3-yne)-γ-butyrolactone (4.12)

(2*S*, 4*S*)-4-(tert-Butyldimethylsilyl)oxymethyl-2-methyl-2-(pent-3-yne)-γ-butyrolactone (4.21)



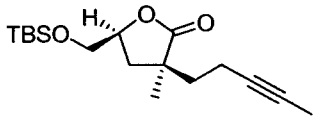
n-Butyllithium (102 mL of a 1.46 M solution in hexane, 0.149 mol, 1.1 equiv) was added dropwise to a solution of diisopropylamine (20.9 mL, 0.149 mol, 1.1 equiv) in THF (300 mL) at -78 °C and the reaction mixture was stirred at -78 °C for 1 h. A solution of a 90:10 mixture of (2*R*, 4*S*)-4-(*tert*-butyldimethylsilyl)oxymethyl-2-methyl-γ-butyrolactone (**4.16**) and (2*S*, 4*S*)-4-(*tert*-butyldimethylsilyl)oxymethyl-2-methyl-γ-butyrolactone (**4.17**) (33.0 g, 0.135 mol, 1 equiv) and hexamethylphosphoramide (51.7 mL, 0.297 mol, 2.2 equiv) in THF (175 mL) was added dropwise, and stirring was continued at -78 °C for 45 min. A solution of 5-iodo-pent-2-yne (26.2 g, 0.135 mol, 1 equiv) in THF (175 mL) was added and stirring was continued at –78 °C for 1 h. The reaction mixture was then warmed to –20 °C over 1 h, stirred at –20 °C for 1 h, and then at rt for 1 h. A saturated aqueous solution of ammonium chloride (200 mL) was added and the mixture was extracted with ether (3 x 150 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (100 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear colourless liquid. The crude liquid was purified by column chromatography (1/19 ethyl acetate-hexanes) to yield 18.2 g (43 %) of **4.12** as a clear colourless liquid, 1.93 g (5 %) of **4.21** as a clear colourless liquid, and 13.9 g (42 %) of recovered 1:1 mixture of **4.16** and **4.17** as a clear colourless liquid.

(2*R*, 4*S*)-4-(*tert*-Butyldimethylsilyl)oxymethyl-2-methyl-2-(pent-3-yne)-γ-butyrolactone (**4.12**):



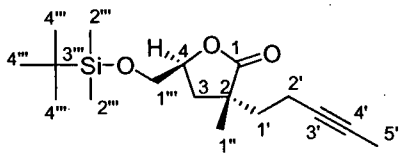
$[\alpha]_D^{28.4}$ = +6.5 ± 0.3 (c 0.097, $CHCl_3$). IR (neat): 2930, 2858, 1769, 1463, 1255, 1188, 1112, 832, 780 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.48-4.39 (m, 1H), 3.79 (dd, J=11.4, 3.66 Hz, 1H), 3.62 (dd, J=11.4, 3.7 Hz, 1H), 2.22-2.10 (m, 2H), 2.21 (dd, J=13.1, 7.3 Hz, 1H), 1.95 (dd, J=13.1, 8.5 Hz, 1H), 1.75 (t, J=7.9 Hz, 2H), 1.71 (t, J=2.6 Hz, 3H), 1.22 (s, 3H), 0.84 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 180.8, 77.8, 76.9, 76.3, 64.1, 43.4, 37.2, 35.8, 25.7, 23.3, 18.2, 14.3, 3.3, -5.4, -5.5. LRMS (EI) m/z (relative intensity): 310 (M^+, 0.2). Anal. Calcd for $C_{12}H_{24}O_3Si$: C, 65.76; H, 9.74. Found: C, 65.81; H, 9.84.

(2*S*, 4*S*)-4-(*tert*-Butyldimethylsilyl)oxymethyl-2-methyl-2-(pent-3-yne)-γ-butyrolactone (**4.21**):



$[\alpha]_D^{20.4}$ = +15.10 ± 0.05 (c 0.910, $CHCl_3$). IR (neat): 2930, 2858, 1772, 1462, 1255, 1201, 1175, 1107, 838, 780 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.48-4.39 (m, 1H), 3.79 (dd, J=11.3, 3.7 Hz, 1H), 3.65 (dd, J=11.3, 4.1 Hz, 1H), 2.27-2.03 (m, 2H), 2.16 (dd, J=12.7, 9.8 Hz, 1H), 1.88 (dd, J=12.7, 6.5 Hz, 1H), 1.78 (t, J=7.8 Hz, 2H), 1.70 (t, J=2.6 Hz, 3H), 1.21 (s, 3H), 0.84 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 180.7, 78.1, 76.9, 76.1, 64.0, 43.5, 36.4, 35.3, 25.7, 22.8, 18.2, 14.2, 3.3, -5.4, -5.5. LRMS (EI) m/z (relative intensity): 310 (M^+, 0.1).

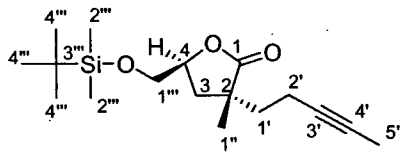
Table 4.15 Selected NMR Data for (2*R*, 4*S*)-4-(*tert*-butyldimethylsilyl)oxymethyl-2-methyl-2-(pent-3-yne)-γ-butyrolactone (4.12)



Carbon No.	^{13}C δ (ppm)[a]	Mult.	^{1}H δ (ppm) (mult J (Hz))[b,c,d]	HMBC Correlations[e]
1	180.8	Q		$H_{3\alpha}$;$H_{3\beta}$;$H_{1'}$; $H_{1"}$
2	43.4	Q		$H_{3\alpha}$;$H_{3\beta}$;$H_{1'}$;$H_{1"}$
3	35.8	CH_2	$H_{3\alpha}$: 2.21 (dd, 13.1, 7.3)	$H_{1'}$;$H_{1"}$
			$H_{3\beta}$: 1.95 (dd, 13.1, 8.5)	
4	76.9	CH_3	4.48-4.39 (m, 1H)	$H_{3\alpha}$;$H_{3\beta}$;$H_{1'''a}$
1'	37.2	CH_2	1.75 (t, 7.9)	$H_{3\alpha}$;$H_{3\beta}$;$H_{2'}$;$H_{1"}$
2'	14.3	CH_2	2.22-2.10 (m)	$H_{1'}$
3'	77.8	Q		$H_{1'}$
4'	76.3	Q		$H_{5'}$
5'	3.3	CH_3	1.71 (t, 2.6)	
1"	23.3	CH_3	1.21 (s)	$H_{3\beta}$;$H_{1'}$
1'''	64.1	CH_2	$H_{1'''a}$: 3.79 (dd, 11.3, 3.7)	$H_{3\beta}$
			$H_{1'''b}$: 3.65 (dd, 11.3, 4.1)	
2'''	-5.4; -5.5	CH_3	0.03 (s), 0.02 (s)	$H_{2'''}$
3'''	18.2	Q		$H_{4'''}$
4'''	25.7	CH_3	0.84 (s)	$H_{4'''}$

[a] Recorded at 75 MHz. [b] Recorded at 400 MHz. [c] Assignments based on HMQC data.
[d] Methylene protons are designated α and β depending on the ring face.
[e] Only those correlations which could be unambiguously assigned are recorded.

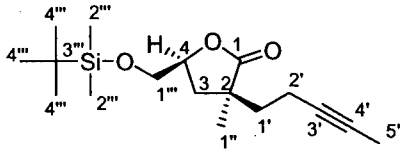
Table 4.16 Selected NOE Data for (2*R*, 4*S*)-4-(*tert*-butyldimethylsilyl)oxymethyl-2-methyl-2-(pent-3-yne)-γ-butyrolactone (4.12)



Proton No.[a]	1H δ (ppm) (mult J (Hz))[b,c]	NOE Correlation[d]
H_4	4.48-4.39 (m, 1H)	$H_{3\alpha}$;$H_{3\beta}$;$H_{1'''a}$;$H_{1'''b}$;$H_{2'}$
$H_{1'''a}$	3.79 (dd, J=11.27, 3.66 Hz, 1H)	H_4;$H_{1'''b}$; $H_{3\beta}$
$H_{1'''b}$	3.62 (dd, J=11.27, 3.66 Hz, 1H)	H_4;$H_{1'''b}$;$H_{3\alpha}$;$H_{3\beta}$
$H_{1''}$	1.22 (s, 3H)	$H_{1'}$;$H_{2'}$;$H_{3\beta}$

[a] Methylene protons are designated α and β depending on the ring face.
[b] Recorded at 400 MHz. [c] Assignments based on HMQC and HMBC.
[d] Only those correlations which could be unambiguously assigned are recorded.

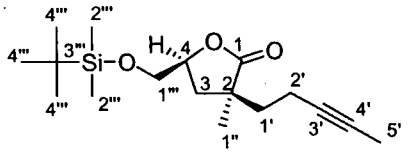
Table 4.17 Selected NMR Data for (2*S*, 4*S*)-4-(*tert*-butyldimethylsilyl)oxymethyl-2-methyl-2-(pent-3-yne)-γ-butyrolactone (4.21)



Carbon No.	^{13}C δ (ppm)[a]	Mult.	^{1}H δ (ppm) (mult J (Hz))[b,c,d]	HMBC Correlations[e]
1	180.7	Q		$H_{3\alpha}$;$H_{3\beta}$;$H_{1'}$; $H_{1''}$
2	43.5	Q		$H_{3\alpha}$;$H_{3\beta}$;$H_{1'}$;$H_{1''}$
3	35.3	CH_2	$H_{3\alpha}$: 2.16 (dd, 12.7, 9.8)	$H_{1'}$;$H_{1''}$
			$H_{3\beta}$: 1.88 (dd, 12.7, 6.5)	
4	76.9	CH_3	4.48-4.39 (m, 1H)	$H_{3\alpha}$;$H_{3\beta}$;$H_{1'''a}$;$H_{1'''b}$
1'	36.4	CH_2	1.78 (t, 7.8)	$H_{3\alpha}$;$H_{3\beta}$;$H_{2'}$;$H_{1''}$;
2'	14.2	CH_2	2.27-2.03 (m)	$H_{1'}$
3'	78.1	Q		$H_{1'}$
4'	76.1	Q		$H_{5'}$
5'	3.3	CH_3	1.70 (t, 2.6)	
1''	22.8	CH_3	1.21 (s)	$H_{3\beta}$;$H_{1'}$
1'''	64.0	CH_2	$H_{1'''a}$: 3.79 (dd, 11.3, 3.7)	$H_{3\beta}$
			$H_{1'''b}$: 3.65 (dd, 11.3, 4.1)	
2'''	-5.4; -5.5	CH_3	0.03 (s), 0.02 (s)	$H_{2'''}$
3'''	18.2	Q		$H_{4'''}$
4'''	25.7	CH_3	0.84 (s)	$H_{4'''}$

[a] Recorded at 75 MHz. [b] Recorded at 400 MHz. [c] Assignments based on HMQC data.
[d] Methylene protons are designated α and β depending on the ring face.
[e] Only those correlations which could be unambiguously assigned are recorded.

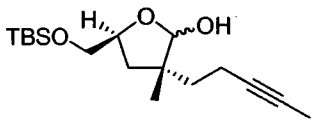
Table 4.18 Selected NOE Data for (2*S*, 4*S*)-4-(*tert*-butyldimethylsilyl)oxymethyl-2-methyl-2-(pent-3-yne)-γ-butyrolactone (4.21)



Proton No.[a]	1H δ (ppm) (mult J (Hz))[b,c]	NOE Correlation[d]
H_4	4.48-4.39 (m, 1H)	$H_{3\alpha}$;$H_{3\beta}$;$H_{1'''a}$;$H_{1'''b}$
$H_{1'''a}$	3.79 (dd, J=11.27, 3.66 Hz, 1H)	H_4;$H_{1'''b}$
$H_{1'''b}$	3.65 (dd, J=11.27, 4.11 Hz, 1H)	H_4;$H_{1'''b}$;$H_{1'''a}$;$H_{1'''b}$
$H_{1''}$	1.21 (s, 3H)	H_4;$H_{1'}$;$H_{2'}$;$H_{3\beta}$

[a] Methylene protons are designated α and β depending on the ring face.
[b] Recorded at 400 MHz. [c] Assignments based on HMQC and HMBC.
[d] Only those correlations which could be unambiguously assigned are recorded.

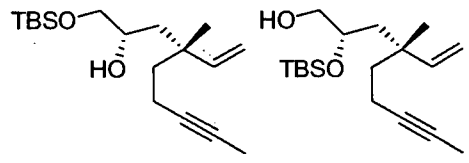
(2*R*, 4*S*)-4-(*tert*-Butyldimethylsilyl)oxymethyl-2-methyl-2-(pent-3-yne)-γ-butyrolactol (4.22)



Diisobutylaluminum hydride (67.6 mL of a 1.00 M solution in hexane, 67.6 mmol, 1 equiv) was added dropwise to a solution of (2*R*, 4*S*)-4-(*tert*-butyldimethylsilyl)oxymethyl-2-methyl-2-(pent-3-yne)-γ-butyrolactone (**4.12**) (21.1 g, 67.6 mmol, 1 equiv) in methylene chloride (675 mL) at -78 °C and the reaction mixture was stirred at -78 °C for 1 h. A saturated aqueous solution of basic ammonium chloride (16.9 mL) was added slowly and the reaction mixture was warmed to rt over 10 min and stirred at rt for 1 h. Magnesium sulfate (7.24 g) was added and the reaction mixture was filtered through Celite and concentrated *in vacuo* to yield a clear colourless liquid. The crude liquid was purified by column chromatography (1/9 ethyl acetate-hexanes) to yield 19.4 g (92 %) of a 3.6:1 mixture of the two diastereomers of **4.22** (GC analysis) as a clear colourless liquid.

IR (neat): 3413, 2930, 2858 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.96 (d, J=3.1 Hz, 0.20H), 4.77 (d, J=8.9 Hz, 0.80H), 4.32-4.23 (m, 1H), 3.76 (dd, J=10.8, 2.5 Hz, 0.85H), 3.65 (d, J=11.3, 3.66 Hz, 1H), 3.64-3.59 (m, 0.36), 3.43 (dd, J=10.8, 1.93 Hz, 0.80H), 2.19-2.07 (m, 2H), 1.81-1.45 (m, 7H), 1.03 (s, 2.37H), 0.99 (s, 0.65H), 0.90 (s, 7H), 0.87 (s, 2H), 0.08 (s, 4.58H), 0.04 (s, 1.46H). ^{13}C NMR (75 MHz, CDCl3): δ 104.0, 102.8, 79.1, 78.9, 78.1, 75.5, 66.0, 64.3, 48.0, 45.8, 38.3, 37.6, 34.4, 26.0, 25.8, 23.8, 19.0, 18.3, 14.3, 3.4, -5.3, -5.5, -5.7. LRMS (EI) m/z (relative intensity): 312 (M^+, 0.2). Anal. Calcd for $C_{17}H_{32}O_3Si$: C, 65.34; H, 10.32. Found: C, 65.02; H, 10.54.

(2*S*, 4*R*)-1-*tert*-Butyldimethylsilyloxy-2-hydroxy-4-methyl-4-vinyl-7-nonyne (4.23)
(2*S*, 4*R*)-2-*tert*-Butyldimethylsilyloxy-1-hydroxy-4-methyl-4-vinyl-7-nonyne (4.24)

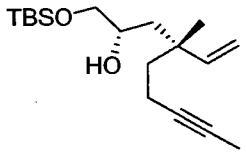


Method A (using *n*-butyllithium as base): *n*-Butyllithium (97.6 mL of a 1.60 M solution in hexane, 0.156 mol, 3.8 equiv) was added to a solution of methyltriphenylphosphonium bromide (58.8 g, 0.164 mol, 4 equiv) in THF (300 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 30 min. A solution of (2*R*, 4*S*)-4-(*tert*-butyldimethylsilyl)oxymethyl-2-

methyl-2-(pent-3-yne)-γ-butyrolactol (**4.22**) (12.8 g, 41.1 mmol, 1 equiv) in THF (110 mL) was added dropwise via canulla and the reaction mixture was warmed to rt and stirred at rt for 2 h. A saturated aqueous solution of ammonium chloride (100 mL) was added and the mixture was extracted with ether (3 x 50 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (50 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield an orange oil with a white solid which was triturated in petroleum ether (100 mL). The solid was filtered, washed with petroleum ether (3 x 50 mL), and the filtrate was concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/19 ethyl acetate-hexanes) to yield 9.70 g (76 %) of **4.23** as a clear colourless liquid and 1.04 g (8%) of **4.24** as a clear colourless liquid.

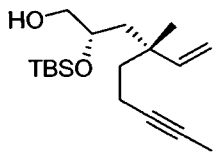
Method B (using potassium bis(trimethylsilyl)amide as base): Potassium bis(trimethylsilyl)amide (248 mL of a 0.50 M solution in toluene, 0.124 mol, 2.0 equiv) was added to a solution of methyltriphenylphosphonium bromide (46.6 g, 0.130 mol, 2.1 equiv) in THF (400 mL) at 0 °C and the reaction mixture was stirred at 0°C for 30 min. A solution of (2*R*, 4*S*)-4-(*tert*-butyldimethylsilyl)oxymethyl-2-methyl-2-(pent-3-yne)-γ-butyrolactol (**4.22**) (19.4 g, 41.1 mmol, 1 equiv) in THF (220 mL) was added dropwise via canulla and the reaction mixture was warmed to rt and stirred at rt for 1 h. A saturated aqueous solution of ammonium chloride (100 mL) was added and the mixture was extracted with ether (3 x 100 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (50 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield an orange oil with a white solid which was triturated in petroleum ether (100 mL). The solid was filtered, washed with petroleum ether (3 x 50 mL), and the filtrate was concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/19 ethyl acetate-hexanes) to yield 14.2 g (74 %) of **4.23** as a clear colourless liquid and 4.89 g (25%) of **4.24** as a clear colourless liquid.

(2*S*, 4*R*)-1-*tert*-Butyldimethylsilyloxy-2-hydroxy-4-methyl-4-vinyl-7-nonyne (**4.23**):



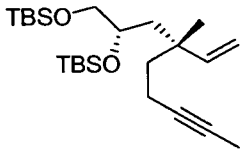
$[\alpha]_D^{20.2}$ = -10.7 ± 0.2 (c 0.620, $CHCl_3$). IR (neat): 3564, 3083, 2931, 2858, 1637 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.63 (dd, J=17.4, 10.7 Hz, 1H), 5.00 (dd, J=10.7, 0.9 Hz, 1H), 4.90 (dd, J=17.4, 0.9 Hz, 1H), 3.69-3.60 (m, 1H), 3.45 (dd, J=9.7, 3.7 Hz, 1H), 3.27 (dd, J=9.7, 8.2 Hz, 1H), 2.40 (s, 1H), 2.04-1.96 (m, 2H), 1.71 (t, J=2.6 Hz, 3H), 1.59-1.51 (m, 2H), 1.39 (dd, J=14.5, 7.5 Hz, 1H), 1.27 (J=14.5, 2.9 Hz, 1H), 1.03 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (75 MHz, CDCl3): δ 146.1, 112.7, 79.6, 75.1, 68.9, 68.0, 43.5, 41.1, 39.1, 25.8, 22.0, 18.2, 13.8, 3.4, -5.4. LRMS (CI, ammonia) m/z (relative intensity): 328 (M^+ + 18, 43), 311 (M^+ + 1, 30), 310 (M^+, 0.6). Anal. Calcd for $C_{18}H_{34}O_2Si$: C, 69.62; H, 11.03. Found: C, 69.41; H, 11.03.

(2*S*, 4*R*)-2-*tert*-Butyldimethylsilyloxy-1-hydroxy-4-methyl-4-vinyl-7-nonyne (**4.24**):



$[\alpha]_D^{20.4}$ = -8.15 ± 0.05 (c 0.485, $CHCl_3$). IR (neat): 3456, 3082, 2931, 2858, 1637 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.61 (dd, J=17.6, 10.8 Hz, 1H), 5.02 (dd, J=10.8, 1.1 Hz, 1H), 4.89 (dd, J=17.6, 1.1 Hz, 1H), 3.79-3.71 (m, 1H), 3.56 (dd, J=11.1, 3.5 Hz, 1H), 3.35 (dd, J=11.1, 5.0 Hz, 1H), 2.04-1.93 (m, 2H), 1.74 (t, J=2.5 Hz, 3H), 1.70-1.42 (m, 5H), 1.00 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (75 MHz, CDCl3): δ 145.7, 113.0, 79.4, 75.3, 70.4, 67.3, 45.5, 41.9, 38.8, 25.8, 21.3, 18.0, 13.7, 3.4, -4.3. LRMS (CI, ammonia) m/z (relative intensity): 328 (M^+ + 18, 21), 311 (M^+ + 1, 35), 310 (M^+, 0.6).

(2*S*, 4*R*)-1,2-di-*tert*-Butyldimethylsilyloxy-4-methyl-4-vinyl-7-nonyne (4.25)

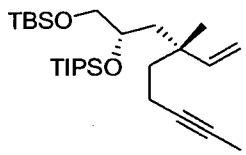


tert-Butyldimethylsilyl chloride (64.2 mg, 0.426 mmol, 1.15 equiv) was added to a solution of (2*S*, 4*R*)-1-*tert*-butyldimethylsilyloxy-2-hydroxy-4-methyl-4-vinyl-7-nonyne (**4.23**) (115 mg, 0.370 mmol, 1.0 equiv) in dimethylformamide (2.0 mL), followed by imidazole (63.0 mg, 0.925 mmol, 2.5 equiv) and the reaction mixture was stirred at 50 °C for 4 h. Water (5 mL) was added and the reaction mixture was extracted with ether (4 x 5 mL).

The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (5 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/99 ethyl acetate-hexanes) to yield 149 mg (95 %) of **4.25** as a clear colourless liquid.

$[\alpha]_D^{26.3}$ = -4.98 ± 0.10 (0.104, $CHCl_3$). IR (neat): 3083, 2936, 1637 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.62 (dd, J=17.8, 10.5 Hz, 1H), 4.97 (dd, J=10.5, 1.3 Hz, 1H), 4.89 (dd, J=17.8, 1.3 Hz, 1H), 3.77-3.67 (m, 1H), 3.42 (dd, J=11.1, 3.5 Hz, 1H), 3.29 (dd, J=11.1, 5.0 Hz, 1H), 2.05-1.94 (m, 2H), 1.74 (t, J=2.7 Hz, 3H), 1.66 (dd, J=13.1, 2.5 Hz, 1H), 1.58-1.49 (m, 2H), 1.32 (dd, J=13.1, 4.6 Hz, 1H), 1.00 (s, 3H), 0.85 (s, 9H), 0.84 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 145.7, 112.5, 79.5, 75.2, 70.7, 67.3, 45.6, 41.9, 38.9, 25.8, 21.4, 18.1, 18.0, 13.7, 3.4, -5.4. LRMS (CI, ammonia) m/z (relatve intensity): 442 (M^+ + 18, 20), 425 (M^+ + 1, 20), 424 (M^+, 0.4).

(2*S*, 4*R*)-1-*tert*-Butyldimethylsilyloxy-2-triisopropylsiloxy-4-methyl-4-vinyl-7-nonyne (4.26)

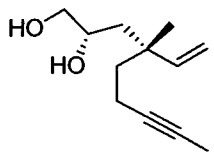


Triisopropylsilyl chloride (82.6 µL, 0.386 mmol, 1.2 equiv) was added to a solution of (2S, 4R)-1-*tert*-butyldimethylsilyloxy-2-hydroxy-4-methyl-4-vinyl-7-nonyne (**4.23**) (100 mg, 0.322 mmol, 1.0 equiv) in dimethylformamide (2.0 mL), followed by imidazole (54.8 mg, 0.805 mmol, 2.5 equiv) and the reaction mixture was stirred at 70 °C for 1 day. Water (5 mL) was added and the reaction mixture was extracted with ether (4 x 5 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (5 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (hexanes) to yield 84.2 mg (56 %) of **4.26** as a clear colourless liquid.

$[\alpha]_D^{27.2}$ = -4.09 ± 0.10 (0.153, $CHCl_3$). IR (neat): 3083, 2936, 1637 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.63 (dd, J=17.5, 10.8 Hz, 1H), 5.00 (dd, J=10.8, 1.2 Hz, 1H), 4.87 (dd, J=17.5, 1.2 Hz, 1H), 3.82-3.73 (m, 1H), 3.48 (dd, J=9.9, 4.9 Hz, 1H), 3.39 (dd, J=9.9, 5.9 Hz, 1H), 2.05-1.93 (m, 2H), 1.74 (t, J=2.5 Hz, 3H), 1.57-1.48 (m, 3H), 1.36 (dd, J=14.1, 5.5 Hz, 1H), 1.04-1.00 (m, 24H), 0.85 (s, 9H), 0.00 (s, 3H), -0.01 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): 146.4, 112.4, 79.8, 75.1, 71.2, 67.7, 45.9, 42.0, 39.0,

25.9, 21.6, 18.3, 18.0, 13.7, 13.0, 11.9, 3.5, -5.4. LRMS (CI, ammonia) m/z (relatve intensity): 484 (M^+ + 18, 18), 467 (M^+ + 1, 25).

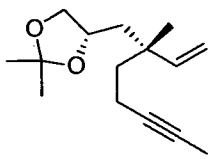
(2*S*, 4*R*)-1,2-Dihydroxy-4-methyl-4-vinyl-7-nonyne (4.27)



Tetrabutylammonium fluoride (30.9 mL of a 1.0 M solution THF, 30.9 mmol, 1.2 equiv) was added to a solution containing a mixture of (2*S*, 4*R*)-1-*tert*-butyldimethylsilyloxy-2-hydroxy-4-methyl-4-vinyl-7-nonyne (**4.23**) (14.2 g, 45.7 mmol, 0.74 equiv) and (2S, 4R)-2-*tert*-butyldimethylsilyloxy-1-hydroxy-4-methyl-4-vinyl-7-nonyne (**4.24**) (4.89 g, 15.7 mmol, 0.26 equiv) in THF (300 mL) and the reaction mixture was stirred at rt for 15 min. Water (100 mL) was added and the mixture was extracted with ether (3 x 50 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (50 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/19 methanol-chloroform) to yield 5.05 g (>99 %) of **4.27** as a clear colourless liquid.

$[\alpha]_D^{28.7}$ = -20.30 ± 0.03 (c 0.778, $CHCl_3$). IR (neat): 3382, 3082, 2920, 1636 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.69 (dd, J=17.5, 11.0 Hz, 1H), 5.05 (dd, J=11.0, 1.2 Hz, 1H), 4.96 (dd, J=17.5, 1.2 Hz, 1H), 3.82-3.71 (m, 1H), 3.52 (dd, J=11.8, 3.3 Hz, 1H), 3.34 (dd, J=10.8, 8.1 Hz, 1H), 2.11 (s, 2H), 2.08-1.96 (m, 2H), 1.74 (t, J=2.7 Hz, 3H), 1.65-1.53 (m, 2H), 1.46 (dd, J=14.6, 7.3 Hz, 1H), 1.36 (dd, J=14.6, 3.1 Hz, 1H), 1.04 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 146.0, 113.0, 79.5, 75.4, 69.3, 67.5, 43.8, 40.5, 39.0, 22.4, 13.8, 3.4. Anal. Calcd for $C_{12}H_{24}O_3Si$: C, 73.44; H, 10.27. Found: C, 73.17; H, 10.47.

(2*S*, 4*R*)-1,2-*O*-Isopropylidene-4-methyl-4-vinyl-7-nonyne-1,2-diol (4.28)

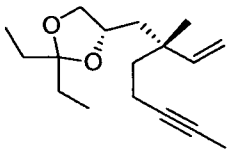


2,2-Dimethoxypropane (7.91 g, 64.3 mmol, 2.5 equiv) was added to a solution of (2*S*, 4*R*)-1,2-dihydroxy-4-methyl-4-vinyl-7-nonyne (**4.27**) (5.05 g, 25.7 mmol, 1 equiv) and p-toluenesulfonic acid monohydrate (0.489 g, 2.57 mmol, 0.10 equiv) in methylene chloride (130 mL) and the reaction mixture was stirred at rt overnight. A saturated aqueous solution of sodium bicarbonate (50 mL) was added and the mixture was extracted with methylene chloride

(2 x 50 mL). The methylene chloride extracts were combined, washed with a saturated aqueous solution of sodium chloride (50 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/19 ethyl acetate-hexanes) to yield 5.30 g (87 %) of **4.28** as a clear colourless liquid.

$[\alpha]_D^{25.8}$ = -3.78 ± 0.09 (0.161, $CHCl_3$). IR (neat): 3083, 2985, 2936, 1637 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.58 (dd, J=17.3, 10.8 Hz, 1H), 4.98 (dd, J=10.8, 1.2 Hz, 1H), 4.88 (dd, J=17.3, 1.16 Hz, 1H), 4.06-3.89 (m, 2H), 3.31 (t, J=7.9 Hz, 1H), 2.02-1.92 (m, 2H), 1.70 (t, J=2.5 Hz, 3H), 1.69-1.63 (m, 1H), 1.55-1.38 (m, 3H), 1.32 (s, 3H), 1.27 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 145.4, 113.0, 108.0, 79.4, 75.1, 73.1, 70.5, 44.4, 41.2, 38.8, 26.8, 25.9, 21.5, 13.7, 3.4. LRMS (ESI) m/z (relative intensity): 259.3 ($M^+ + Na^+$, 100). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.63; H, 10.43.

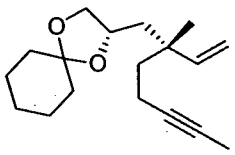
(2*S*, 4*R*)-1,2-*O*-Isopentylidene-4-methyl-4-vinyl-7-nonyne-1,2-diol (4.29)



3,3-Dimethoxypentane (168 mg, 1.27 mmol, 2.5 equiv) was added to a solution of (2*S*, 4*R*)-1,2-dihydroxy-4-methyl-4-vinyl-7-nonyne 12 (100 mg, 0.509 mmol, 1 equiv) and p-toluenesulfonic acid monohydrate (9.7 mg, 0.051 mmol, 0.10 equiv) in methylene chloride (2.5 mL) and the reaction mixture was stirred at rt overnight. A saturated aqueous solution of sodium bicarbonate (5 mL) was added and the mixture was extracted with methylene chloride (2 x 10 mL). The methylene chloride extracts were combined, washed with a saturated aqueous solution of sodium chloride (10 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/29 ethyl acetate-hexanes) to yield 0.123 g (91 %) of **4.29** as a clear colourless liquid.

IR (neat): 3083, 2972, 2937, 1637 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.60 (dd, J=17.5, 10.8 Hz, 1H), 5.00 (dd, J=10.8, 1.2 Hz, 1H), 4.90 (dd, J=17.5, 1.2 Hz, 1H), 4.07-3.90 (m, 2H), 3.30 (t, J=7.8 Hz, 1H), 2.05-1.95 (m, 2H), 1.72 (t, J=2.5 Hz, 3H), 1.70-1.40 (m, 8H), 1.01 (s, 3H), 0.85 (t, J=7.5 Hz, 3H), 0.84 (t, J=7.5 Hz, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 145.5, 113.0, 112.1, 79.5, 75.2, 73.4, 71.1, 44.1, 41.3, 38.9, 30.0, 29.9, 21.7, 13.8, 8.2, 7.9, 3.4. LRMS (ESI) m/z (relative intensity): 287.2 ($M^+ + Na^+$, 100).

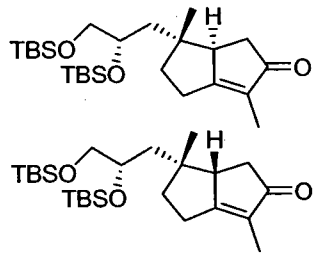
(2*S*, 4*R*)-1,2-*O*-Cyclohexylidene-4-methyl-4-vinyl-7-nonyne-1,2-diol (4.30)



Copper(I) chloride (212 mg, 2.14 mmol, 3.5 equiv) and p-toluenesulfonic acid monohydrate (5.8 mg, 0.031 mmol, 0.10 equiv) were added to a solution of (2*S*, 4*R*)-1,2-dihydroxy-4-methyl-4-vinyl-7-nonyne 12 (120 mg, 0.611 mmol, 1 equiv) in cyclohexanone (3 mL) containing 4 Å molecular sieves (90.0 mg) and the reaction mixture was stirred at rt overnight. The reaction mixture was filtered, washed with ether (10 mL) and the filtrate was concentrated *in vacuo* to yield a brown liquid. The crude liquid was purified by column chromatography (1/19 ethyl acetate-hexanes) to yield 0.162 g (96 %) of **4.30** as a clear colourless liquid.

IR (neat): 3082, 2936, 2860, 1637, 1449, 1365, 1165, 1109, 1006, 936 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.61 (dd, J=17.5, 10.8 Hz, 1H), 5.00 (dd, J=10.8, 1.0 Hz, 1H), 4.90 (dd, J=17.5, 1.0 Hz, 1H), 4.09-3.91 (m, 2H), 3.34 (t, J=7.8 Hz, 1H), 2.06-1.96 (m, 2H), 1.73 (t, J=2.5 Hz, 3H), 1.72-1.30 (m, 14H), 1.02 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 145.6, 113.0, 108.8, 79.5, 75.2, 72.7, 70.1, 44.3, 41.3, 38.9, 36.6, 35.4, 25.2, 24.0, 23.9, 13.8, 3.4. LRMS (ESI) m/z (relative intensity): 299.4 ($M^+ + Na^+$, 100).

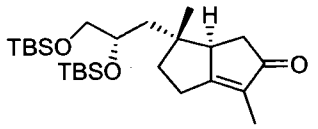
[3.3.0]-(5*R*, 6*R*)-6-((2*S*)-2,3-di-*tert*-Butyldimethylsilyloxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (4.31)
[3.3.0]-(5*S*, 6*R*)-6-((2*S*)-2,3-di-*tert*-Butyldimethylsilyloxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (4.32)



A solution of (2*S*, 4*R*)-1,2-di-*tert*-butyldimethylsilyloxy-4-methyl-4-vinyl-7-nonyne (**4.25**) (600 mg, 1.41 mmol, 1 equiv) in methylene chloride (30 mL) was added to 4 Å molecular sieves (6.00 g) followed by dicobalt octacarbonyl (531 mg, 1.55 mmol, 1.10 equiv) in 1 portion and the reaction mixture was stirred at rt for 1 h. 4-Methylmorpholine N-oxide (1.49 g, 12.7 mol, 9.0 equiv) was added in 3 portion to the reaction mixture at 0 °C and the reaction mixture was stirred at rt overnight. The reaction mixture was filtered through a plug of silica gel, the silica gel was washed with ether (100 mL) and the filtrate was concentrated to yield a clear brown liquid. The crude liquid was purified by column chromatography (1/9 ethyl acetate-

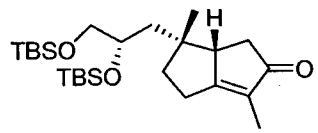
hexanes) to yield 530 mg (83 %) of a 71:29 mixture of the two diastereomers **4.31** and **4.32** (gas chromatography analysis) as a clear colourless liquid. Further purification by rotary chromatography (1/13 ethyl acetate-hexanes) was performed to yield 347 mg (54 %) of **4.31** as a clear colourless liquid and 173 mg (27 %) of **4.32** as a clear colourless liquid.

[3.3.0]-(5*R*, 6*R*)-6-((2*S*)-2,3-di-*tert*-Butyldimethylsilyloxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**4.31**):



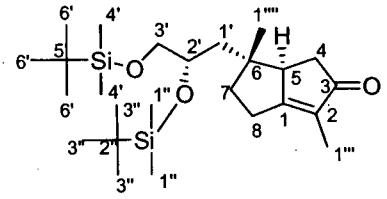
IR (neat): 2931, 2858, 1709, 1670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.79-3.71 (m, 1H), 3.54 (dd, J=9.7, 4.9 Hz, 1H), 3.28 (dd, J=9.7, 7.3 Hz, 1H), 2.67 (m, 1H), 2.59-2.39 (m, 2H), 2.36 (dd, J=14.2, 7.6, 1H), 2.04 (dd, J=14.2, 3.0 Hz, 1H), 1.98-1.79 (m, 3H), 1.67 (s, 3H), 1.46 (dd, J=14.2, 7.6 Hz, 1H), 0.86 (s, 9H), 0.85 (s, 9H), 0.64 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 210.8, 182.9, 132.2, 71.1, 67.5, 54.1, 46.2, 39.9, 36.6, 25.8, 25.7, 24.1, 18.1, 17.8, 17.7, 8.1, -3.7, -4.4, -5.4, -5.5. LRMS (EI) m/z (relative intensity): 452 (M^+, 6).

[3.3.0]-(5*S*, 6*R*)-6-((2*S*)-2,3-di-*tert*-Butyldimethylsilyloxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**4.32**):



IR (neat): 2931, 2858, 1709, 1670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.79-3.69 (m, 1H), 3.49 (dd, J=9.7, 4.8 Hz, 1H), 3.21 (dd, J=9.7, 7.3 Hz, 1H), 2.64 (m, 1H), 2.53-2.34 (m, 3H), 2.32 (dd, J=18.1, 6.4, 1H), 2.07 (dd, J=18.1, 2.9 Hz, 1H), 1.66 (s, 3H), 1.66-1.54 (m, 2H), 1.31 (d, J=14.2 Hz, 1H), 1.11 (s, 3H), 0.85 (s, 9H), 0.84 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.00, -0.01 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 210.8, 183.5, 132.0, 70.9, 67.5, 56.7, 40.5, 37.1, 35.4, 34.8, 25.7, 25.6, 25.2, 24.3, 18.0, 17.8, 8.0, -3.7, -4.6, -5.4, -5.5. LRMS (EI) m/z (relative intensity): 452 (M^+, 2).

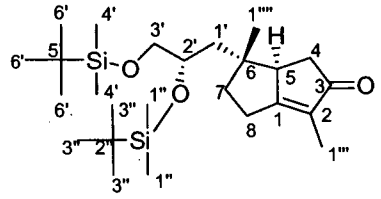
Table 4.19 Selected NMR Data for [3.3.0]-(5*R*, 6*R*)-6-((2*S*)-2,3-di-*tert*-butyldimethylsilyloxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (4.31)



Carbon No.	^{13}C δ (ppm)[a]	Mult.	^{1}H δ (ppm) (mult J (Hz))[b,c,d]	HMBC Correlations[e]
1	182.9	Q		H_8;$H_{7\beta}$;$H_{4\alpha}$; $H_{1''''}$
2	132.2	Q		$H_{1''''}$
3	210.8	Q		$H_{4\alpha}$; $H_{4\beta}$; $H_{1''}$
4	36.6	CH_2	$H_{4\alpha}$: 2.36 (dd, 14.2, 7.6)	H_8
			$H_{4\beta}$: 2.04 (dd, 14.2, 3.0)	
5	54.1	CH	2.59-2.32 (m)	H_8;$H_{7\alpha}$;$H_{4\alpha}$;$H_{4\beta}$;$H_{1'}$;$H_{1''''}$
6	46.2	Q		$H_{4\beta}$;H_5;$H_{7\alpha}$;$H_{7\beta}$;H_8;$H_{1'}$;$H_{1''''}$
7	39.9	CH_2	1.98-1.79 (m)	H_8;$H_{1'}$;$H_{1''''}$
8	24.1	CH_2	2.59-2.32 (m)	$H_{4\alpha}$;$H_{4\beta}$;H_7;$H_{1''''}$
1'	34.8	CH_2	$H_{1'a}$: 1.98-1.79 (m)	$H_{2'}$;$H_{1''''}$;
			$H_{1'b}$: 1.31 (d, 14.2)	
2'	67.5	CH	3.28 (dd, 9.7, 7.3)	$H_{1'}$;$H_{3'a}$;$H_{3'b}$;$H_{1''''}$
3'	71.1	CH_2	$H_{3'a}$: 3.79-3.71 (m)	$H_{2'}$;$H_{4'}$
			$H_{3'b}$: 3.54 (dd, J=9.7, 4.9)	
4'	-5.4; -5.5	CH_3	0.00 (s), -0.01 (s)	$H_{4'}$
5'	17.7	Q		$H_{4'}$;$H_{6'}$
6'	25.7	CH_3	0.84 (s)	$H_{6'}$
1''	-3.7; -4.4	CH_3	0.06 (s), 0.05 (s)	$H_{1''}$
2''	17.8	Q		$H_{1''}$;$H_{3''}$
3''	25.8	CH_3	0.85 (s)	$H_{3''}$
1'''	8.1	CH_3	1.67 (s)	
1''''	18.1	CH_3	1.11 (s)	$H_{4\beta}$;H_5;$H_{7\alpha}$;$H_{7\beta}$;$H_{1'}$

[a] Recorded at 75 MHz. [b] Recorded at 400 MHz. [c] Assignments based on HMQC data.
[d] Methylene protons are designated α and β depending on the ring face.
[e] Only those correlations which could be unambiguously assigned are recorded.

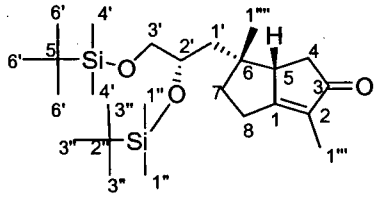
Table 4.20 Selected NOE Data for [3.3.0]-(5*R*, 6*R*)-6-((2*S*)-2,3-di-*tert*-butyldimethylsilyloxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (4.31)



Proton No.[a]	1H δ (ppm) (mult J (Hz))[b,c]	NOE Correlation[d]
H_5	2.59-2.32 (m, 1H)	$H_{4\alpha}$;$H_{7\alpha}$;$H_{1'a}$;$H_{1'b}$
$H_{1''''}$	0.64 (s)	$H_{4\beta}$;$H_{7\beta}$;$H_{1'a}$;$H_{1'b}$
$H_{1'a}$	1.98-1.79 (m, 1H)	H_5;$H_{7\alpha}$;$H_{7\beta}$;H_2';$H_{1''''}$
$H_{1'b}$	1.46 (dd, 14.2, 7.62, 1H)	H_5;$H_{7\alpha}$;$H_{7\beta}$;H_2';$H_{1''''}$

[a] Methylene protons are designated α and β depending on the ring face.
[b] Recorded at 400 MHz. [c] Assignments based on HMQC and HMBC.
[d] Only those correlations which could be unambiguously assigned are recorded.

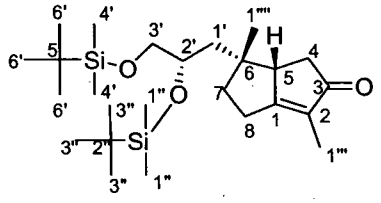
Table 4.21 Selected NMR Data for [3.3.0]-(5*S*, 6*R*)-6-((2*S*)-2,3-di-*tert*-butyldimethylsilyloxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (4.32)



Carbon No.	^{13}C δ (ppm)[a]	Mult.	^{1}H δ (ppm) (mult J (Hz))[b,c,d]	HMBC Correlations[e]
1	183.5	Q		H_8;$H_{7\beta}$;$H_{4\alpha}$; $H_{1'''}$
2	132.0	Q		$H_{1'''}$
3	210.8	Q		$H_{4\alpha}$; $H_{4\beta}$; $H_{1''}$
4	35.4	CH_2	$H_{4\alpha}$: 2.32 (dd, 18.1, 6.4)	H_8
			$H_{4\beta}$: 2.07 (dd, 18.1, 2.9)	
5	56.7	CH	2.64 (m)	H_8;$H_{7\alpha}$;$H_{4\alpha}$;$H_{4\beta}$;$H_{1'}$;$H_{1''''}$
6	40.5	Q		$H_{4\beta}$;H_5;$H_{7\alpha}$;$H_{7\beta}$;H_8;$H_{1'}$;$H_{1''''}$
7	37.1	CH_2	1.98-1.79 (m)	H_8;$H_{1'}$;$H_{1'''}$
8	24.3	CH_2	2.53-2.34 (m)	$H_{4\alpha}$;$H_{4\beta}$;H_7;$H_{1'''}$
1'	34.8	CH_2	$H_{1'a}$: 1.98-1.79 (m)	$H_{2'}$;$H_{1''''}$;
			$H_{1'b}$: 1.46 (dd, 14.2, 7.62)	
2'	67.5	CH	3.28 (dd, 9.7, 7.3)	$H_{1'}$;$H_{3'a}$;$H_{3'b}$;$H_{1''''}$
3'	70.9	CH_2	$H_{3'a}$: 3.79-3.71 (m)	$H_{2'}$;$H_{4'}$
			$H_{3'b}$: 3.54 (dd, J=9.7, 4.9)	
4'	-5.4; -5.5	CH_3	0.03 (s), 0.02 (s)	$H_{4'}$
5'	17.8	Q		$H_{4'}$;$H_{6'}$
6'	25.7	CH_3	0.85 (s)	$H_{6'}$
1''	-3.7; -4.6	CH_3	0.06 (s), 0.05 (s)	$H_{1''}$
2''	18.0	Q		$H_{1''}$;$H_{3''}$
3''	25.6	CH_3	0.86 (s)	$H_{3''}$
1'''	8.0	CH_3	1.67 (s)	
1''''	25.2	CH_3	1.11 (s)	$H_{4\beta}$;H_5;$H_{7\alpha}$;$H_{7\beta}$;$H_{1'}$

[a] Recorded at 75 MHz. [b] Recorded at 400 MHz. [c] Assignments based on HMQC data.
[d] Methylene protons are designated α and β depending on the ring face.
[e] Only those correlations which could be unambiguously assigned are recorded.

Table 4.22 Selected NOE Data for [3.3.0]-(5*S*, 6*R*)-6-((2*S*)-2,3-di-*tert*-butyldimethylsilyloxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (4.32)

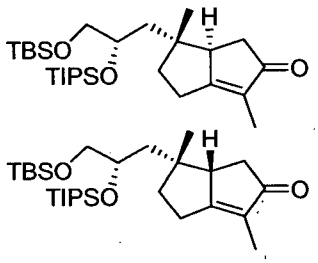


Proton No.[a]	1H δ (ppm) (mult J (Hz))[b,c]	NOE Correlation[d]
H_5	2.53-2.34 (m, 1H)	$H_{4\beta}$;$H_{7\beta}$;$H_{1''''}$
$H_{1''''}$	1.11 (s)	$H_{4\beta}$;$H_{7\beta}$;$H_{1'a}$;$H_{1'b}$
$H_{1'a}$	1.98-1.79 (m, 1H)	$H_{7\alpha}$;$H_{7\beta}$;$H_{2'}$;$H_{1''''}$
$H_{1'b}$	1.46 (dd, 14.2, 7.62, 1H)	$H_{7\alpha}$;$H_{7\beta}$;$H_{2'}$;$H_{1''''}$

[a] Methylene protons are designated α and β depending on the ring face.
[b] Recorded at 400 MHz. [c] Assignments based on HMQC and HMBC.
[d] Only those correlations which could be unambiguously assigned are recorded.

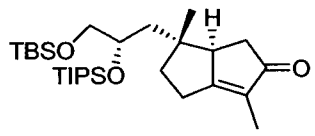
[3.3.0]-(5*R*, 6*R*)-6-((2*S*)-3-*tert*-Butyldimethylsilyloxy-2-triisopropylsiloxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (4.33)

[3.3.0]-(5*S*, 6*R*)-6-((2*S*)-3-*tert*-Butyldimethylsilyloxy-2-triisopropylsiloxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (4.34)



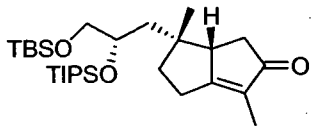
A solution of (2*S*, 4*R*)-1-*tert*-butyldimethylsilyloxy-2-triisopropylsiloxy-4-methyl-4-vinyl-7-nonyne (**4.26**) (62 mg, 0.13 mmol, 1.0 equiv) in methylene chloride (2.5 mL) was added to 4 Å molecular sieves (620 mg) followed by dicobalt octacarbonyl (50 mg, 0.15 mmol, 1.1 equiv) in 1 portion and the reaction mixture was stirred at rt for 1 h. 4-Methylmorpholine N-oxide (141 mg, 1.20 mol, 9.0 equiv) was added in 3 portion to the reaction mixture at 0 °C and the reaction mixture was stirred at rt overnight. The reaction mixture was filtered through a plug of silica gel, the silica gel was washed with ether (10 mL) and the filtrate was concentrated to yield a clear brown liquid. The crude liquid was purified by column chromatography (1/9 ethyl acetate-hexanes) to yield 56.7 mg (86 %) of a 74:26 mixture of the two diastereomers **4.33** and **4.34** (gas chromatography analysis) as a clear colourless liquid. Further purification by rotary chromatography (1/13 ethyl acetate-hexanes) was performed to yield 41.2 mg (63 %) of **4.33** as a clear colourless liquid and 14.3 mg (22 %) of **4.34** as a clear colourless liquid.

[3.3.0]-(5*R*, 6*R*)-6-((2*S*)-3-*tert*-Butyldimethylsilyloxy-2-triisopropylsiloxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**4.33**):



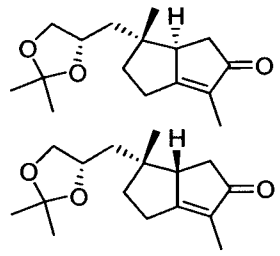
IR (neat): 2931, 2858, 1709, 1670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.80-3.71 (m, 1H), 3.57 (dd, J=9.7, 4.9 Hz, 1H), 3.28 (dd, J=9.4, 7.2 Hz, 1H), 2.61 (m, 1H), 2.59-2.40 (m, 2H), 2.36 (dd, J=14.1, 7.6, 1H), 2.04 (dd, J=14.1, 3.0 Hz, 1H), 2.00-1.79 (m, 3H), 1.66 (s, 3H), 1.46 (dd, J=14.2, 7.6 Hz, 1H), 1.08-1.02 (m, 21H), 0.85 (s, 9H), 0.64 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 210.9, 182.9, 132.1, 71.0, 67.5, 54.0, 45.9, 39.9, 36.5, 25.8, 25.7, 24.1, 18.1, 17.8, 17.7, 13.2, 11.7, 8.1, -5.4, -5.5. LRMS (ESI) m/z (relative intensity): 517.4 ($M^+ + Na^+$, 100).

[3.3.0]-(5*S*, 6*R*)-6-((2*S*)-3-*tert*-Butyldimethylsilyloxy-2-triisopropylsiloxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**4.34**):



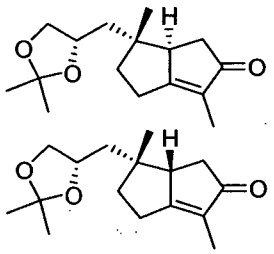
IR (neat): 2930, 2860, 1709, 1668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.79-3.69 (m, 1H), 3.51 (dd, J=9.7, 4.8 Hz, 1H), 3.20 (dd, J=9.5, 7.1 Hz, 1H), 2.64 (m, 1H), 2.52-2.33 (m, 3H), 2.32 (dd, J=18.0, 6.2, 1H), 2.07 (dd, J=18.0, 2.9 Hz, 1H), 1.66 (s, 3H), 1.66-1.52 (m, 2H), 1.31 (d, J=14.1 Hz, 1H), 1.11 (s, 3H), 1.10-1.03 (m, 21H), 0.84 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 211.0, 183.4, 132.1, 71.1, 67.5, 56.6, 40.1, 37.2, 35.6, 34.6, 25.7, 25.6, 25.1, 24.5, 18.0, 17.9, 13.0, 11.9, 8.0, -5.4, -5.5. LRMS (ESI) m/z (relative intensity): 517.4 ($M^+ + Na^+$, 100).

[3.3.0]-(5*R*, 6*R*)-6-((2*S*)-2,3-*O*-Isopropylidene-2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (4.35)
[3.3.0]-(5*S*, 6*R*)-6-((2*S*)-2,3-*O*-Isopropylidene-2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (4.36)



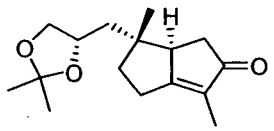
A solution of (2*S*, 4*R*)-1,2-*O*-isopropylidene-4-methyl-4-vinyl-7-nonyne-1,2-diol (**4.28**) (5.10 g, 21.6 mmol, 1 equiv) in methylene chloride (430 mL) was added to 4 Å molecular sieves (51.0 g) followed by dicobalt octacarbonyl (8.12 g, 23.7 mmol, 1.10 equiv) in 1 portion and the reaction mixture was stirred at rt for 1 h. 4-Methylmorpholine N-oxide (22.8 g, 0.194 mol, 9.0 equiv) was added in 3 portion to the reaction mixture at 0 °C and the reaction mixture was stirred at rt overnight. The reaction mixture was filtered through a plug of silica gel, the silica gel was washed with ether (500 mL) and the filtrate was concentrated to yield a clear brown liquid. The crude liquid was purified by column chromatography (1/9 ethyl acetate-hexanes) to yield 5.09 g (89 %) of a 86:14 mixture of the two diastereomers **4.35** and **4.36** (gas chromatography analysis) as a clear colourless liquid. Further purification of an analytical sample by column chromatography (1/19 ethyl acetate-hexanes) was performed to yield an analytically pure sample of **4.35** as a clear colourless liquid.

[3.3.0]-(5*R*, 6*R*)-6-((2*S*)-2,3-*O*-Isopropylidene-2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**4.35**) and [3.3.0]-(5*S*, 6*R*)-6-((2*S*)-2,3-*O*-Isopropylidene-2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**4.36**) (5.2:1 mixture):



IR (neat): 2985, 2933, 1706, 1668 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.18-3.93 (m, 2H), 3.42 (t, J=7.6 Hz, 0.84H), 3.35 (t, J=7.7 Hz, 0.16H), 2.75-2.25 (4H), 2.10-1.55 (m, 8H), 1.35 (s, 5.03H), 1.29 (s, 2.52H), 1.10 (s, 0.48H), 0.65 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 210.7, 210.5, 183.0 182.6, 132.5, 132.0, 108.8, 108.6, 73.6, 73.1, 70.5, 70.3, 56.3, 53.5, 45.1, 41.1, 40.7, 39.9, 37.4, 36.7, 35.5, 35.0, 26.9, 26.8, 25.8, 25.4, 24.4, 24.0, 18.1, 8.2. LRMS (EI) m/z (relative intensity): 264 (M^+, 27).

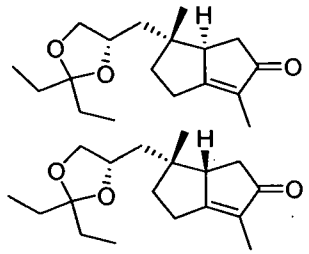
[3.3.0]-(5*R*, 6*R*)-6-((2*S*)-2,3-*O*-Isopropylidene-2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**4.35**):



$[\alpha]_D^{20.7}$ = -48.47 ± 0.08 (c 0.303, $CHCl_3$). IR (neat): 2985, 2933, 1706, 1668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.18-4.10 (m, 1H), 4.01 (dd, J=7.8, 5.9 Hz, 1H), 3.42 (t, J=7.6 Hz, 1H), 2.70 (m, 1H), 2.59-2.29 (m, 3H), 2.04 (dd, J=18.1, 2.9 Hz, 1H), 1.97-1.78 (m, 2H), 1.74-1.57 (m, 2H), 1.64 (s, 3H), 1.34 (s, 3H), 1.29 (s, 3H), 0.64 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 210.6, 182.4, 132.6, 108.8, 73.6, 70.3, 53.5, 45.1, 41.1, 40.0, 36.8, 27.0, 25.8, 24.0, 18.1, 8.2. LRMS (EI) m/z (relative intensity): 264 (M^+, 5). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.52; H, 9.28.

[3.3.0]-(5*R*, 6*R*)-6-((2*S*)-2,3-*O*-Isopentylidene-2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (4.37)

[3.3.0]-(5*S*, 6*R*)-6-((2*S*)-2,3-*O*-Isopentylidene-2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (4.38)

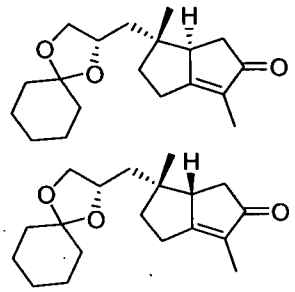


A solution of (2*S*, 4*R*)-1,2-*O*-isopentylidene-4-methyl-4-vinyl-7-nonyne-1,2-diol (**4.29**) (120 mg, 0.454 mmol, 1 equiv) in methylene chloride (9 mL) was added to 4 Å molecular sieves (1.20 g) followed by dicobalt octacarbonyl (171 mg, 0.499 mmol, 1.10 equiv) in 1 portion and the reaction mixture was stirred at rt for 1 h. 4-Methylmorpholine N-oxide (479 mg, 4.09 mol, 9.0 equiv) was added in 3 portion to the reaction mixture at 0 °C and the reaction mixture was stirred at rt overnight. The reaction mixture was filtered through a plug of silica gel, the silica gel was washed with ether (25 mL) and the filtrate was concentrated to yield a clear brown liquid. The crude liquid was purified by column chromatography (1/9 ethyl acetate-hexanes) to yield 112 mg (84 %) of a 57:43 mixture of the two diastereomers **4.36** and **4.37** (gas chromatography analysis) as a clear colourless liquid.

IR (neat): 2987, 2933, 1707, 1670 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.20-3.92 (m, 2H), 3.42 (t, J=7.4 Hz, 0.55H), 3.35 (t, J=7.4 Hz, 0.45H), 2.73-2.21 (4H), 2.11-1.43 (m, 12H), 1.35 (s, 3H), 1.10 (s, 3H), 0.65 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 210.7, 210.5, 183.0 182.6, 132.5, 132.0, 108.8, 108.6, 73.6, 73.1, 70.5, 70.3, 56.3, 53.5, 45.1, 41.1, 40.7, 39.9, 37.4, 36.7, 35.5, 35.0, 26.9, 26.8, 25.8, 25.4, 24.4, 24.0, 18.1, 8.2. LRMS (EI) m/z (relative intensity): 292 (M^+, 11).

[3.3.0]-(5*R*, 6*R*)-6-((2*S*)-2,3-*O*-Cycohexylidene-2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (4.39)

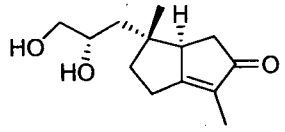
[3.3.0]-(5*S*, 6*R*)-6-((2*S*)-2,3-*O*-Cycohexylidene-2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (4.40)



A solution of (2*S*, 4*R*)-1,2-*O*-cyclohexylidene-4-methyl-4-vinyl-7-nonyne-1,2-diol (**4.30**) (140 mg, 0.506 mmol, 1 equiv) in methylene chloride (10 mL) was added to 4 Å molecular sieves (1.40 g) followed by dicobalt octacarbonyl (191 mg, 0.557 mmol, 1.10 equiv) in 1 portion and the reaction mixture was stirred at rt for 1 h. 4-Methylmorpholine N-oxide (534 mg, 4.09 mol, 9.0 equiv) was added in 3 portion to the reaction mixture at 0 °C and the reaction mixture was stirred at rt overnight. The reaction mixture was filtered through a plug of silica gel, the silica gel was washed with ether (25 mL) and the filtrate was concentrated to yield a clear brown liquid. The crude liquid was purified by column chromatography (1/9 ethyl acetate-hexanes) to yield 122 mg (79%) of a 69:31 mixture of the two diastereomers **4.39** and **4.40** (gas chromatography analysis) as a clear colourless liquid.

IR (neat): 2986, 2932, 1706, 1671 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.22-3.92 (m, 2H), 3.43 (t, J=7.4 Hz, 0.59H), 3.34 (t, J=7.4 Hz, 0.41H), 2.75-2.22 (4H), 2.13-1.35 (m, 14H), 1.35 (s, 3H), 1.10 (s, 3H), 0.65 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 210.7, 210.5, 183.0 182.6, 132.5, 132.0, 108.8, 108.6, 73.6, 73.1, 70.5, 70.3, 56.3, 53.5, 45.1, 41.1, 40.7, 39.9, 37.4, 36.7, 35.5, 35.0, 26.9, 26.8, 25.8, 25.4, 24.4, 24.0, 18.1, 8.2. LRMS (EI) m/z (relative intensity): 304 (M^+, 4).

[3.3.0]-(5*R*, 6*R*)-6-((2*S*)- 2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one



Method A (treatment of **4.31** with tetrabutylammonium fluoride): Tetrabutylammonium fluoride (0.464 mL of a 1.0 M solution in THF, 0.464 mmol, 3.0 equiv) was added to a solution of [3.3.0]-(5*R*, 6*R*)-6-((2*S*)-2,3-di-*tert*-butyldimethylsilyloxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**4.31**) (70 mg, 0.155 mmol, 1 equiv) in THF (2 mL) and the reaction mixture was stirred for 1 h. Water (3 mL) was added and the mixture was extracted with ether (6 x

5mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (5 mL), dried over sodium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/9 methanol-chloroform) to yield 34 mg (99 %) of [3.3.0]-(5*R*, 6*R*)-6-((2*S*)- 2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one as a clear colourless liquid.

Method B (treatment of **4.33**/**4.34** with tetrabutylammonium fluoride): Tetrabutylammonium fluoride (0.230 mL of a 1.0 M solution in THF, 0.230 mmol, 3.0 equiv) was added to a solution of a 74:26 mixture of [3.3.0]-(5*R*, 6*R*)-6-((2*S*)-3-*tert*-butyldimethylsilyloxy-2-triisopropylsiloxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**4.33**) and [3.3.0]-(5*S*, 6*R*)-6-((2*S*)-3-*tert*-butyldimethylsilyloxy-2-triisopropylsiloxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**4.34**) (38 mg, 0.0768 mmol, 1 equiv) in THF (1 mL) and the reaction mixture was stirred for 1 h. Water (3 mL) was added and the mixture was extracted with ether (6 x 5mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (5 mL), dried over sodium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. A gas chromatography analysis was performed on this solution.

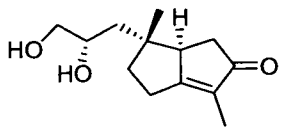
Method C (treatment of **4.35** with 1N hydrochloric acid): A 1N aqueous solution of hydrochloric acid (0.110 mL) was added to a solution of [3.3.0]-(5*R*, 6*R*)-6-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**4.35**) (21 mg, 0.0794 mmol, 1 equiv) in THF (0.44 mL) and the reaction mixture was stirred for 6 h. Solid sodium bicarbonate (50 mg) was added, followed by sodium sulfate (50 mg). The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to yield a clear colourless liquid. The crude liquid was purified by column chromatography (1/9 methanol-chloroform) to yield 16 mg (92 %) of [3.3.0]-(5*R*, 6*R*)-6-((2*S*)- 2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one as a clear colourless liquid.

Method D (treatment of **4.37**/**4.38** with 1N hydrochloric acid): A 1N aqueous solution of hydrochloric acid (0.110 mL) was added to a solution of a 57:43 mixture of [3.3.0]-(5*R*, 6*R*)-6-((2*S*)-2,3-*O*-isopentylidene-2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**4.37**) and [3.3.0]-(5*S*, 6*R*)-6-((2*S*)-2,3-*O*-isopentylidene-2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**4.38**) (21 mg, 0.0794 mmol, 1 equiv) in THF (0.44 mL) and the reaction mixture was stirred for 6 h. Solid sodium bicarbonate (50 mg) was added, followed by sodium sulfate (50 mg). The

reaction mixture was filtered and the filtrate was concentrated *in vacuo* to yield a clear colourless liquid. A gas chromatography analysis was performed on this solution.

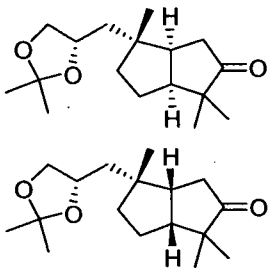
Method E (treatment of **4.39/4.40** with 1N hydrochloric acid): A 1N aqueous solution of hydrochloric acid (0.110 mL) was added to a solution of a 69:31 mixture of [3.3.0]-(5*R*, 6*R*)-6-((2*S*)-2,3-*O*-cycohexylidene-2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**4.39**) and [3.3.0]-(5*S*, 6*R*)-6-((2*S*)-2,3-*O*-cycohexylidene-2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**4.40**) (21 mg, 0.0794 mmol, 1 equiv) in THF (0.44 mL) and the reaction mixture was stirred for 6 h. Solid sodium bicarbonate (50 mg) was added, followed by sodium sulfate (50 mg). The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to yield a clear colourless liquid. A gas chromatography analysis was performed on this solution.

[3.3.0]-(5*R*, 6*R*)-6-((2*S*)-2,3-*O*-Isopropylidene-2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**4.35**):



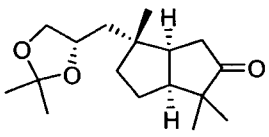
$[\alpha]_D^{20.7}$ = -36.41 ± 0.09 (c 0.213, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87-3.75 (m, 1H), 3.55 (dd, J=10.9, 3.0 Hz, 1H), 3.36 (dd, J=10.9, 7.9 Hz, 1H), 3.28-2.90 (m, 2H), 2.70 (m, 1H), 2.59-2.29 (m, 3H), 2.06 (dd, J=18.1, 2.9 Hz, 1H), 1.97-1.80 (m, 2H), 1.64 (s, 3H), 1.53-1.46 (m, 2H), 0.67 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 211.5, 183.6, 132.4, 69.9, 67.7, 53.9, 44.1, 41.1, 40.1, 36.8, 24.3, 17.9, 8.2. LRMS (EI) m/z (relative intensity): 224 (M^+, 9).

[3.3.0]-(1*R*, 5*S*, 6*R*)-6-((2*S*)-2,3-*O*-Isopropylidene-2,3-dihydroxypropyl)-2,2,6-trimethylbicyclononan-3-one (4.41):
[3.3.0]-(1*S*, 5*R*, 6*R*)-6-((2*S*)-2,3-*O*-Isopropylidene-2,3-dihydroxypropyl)-2,2,6-trimethylbicyclononan-3-one (4.42):



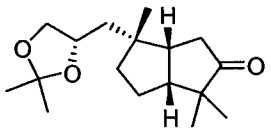
L-Selectride® (16.0 mL of a 1.0 M solution in THF, 16.0 mmol, 1.05 equiv) was added dropwise to a solution of a 5.2:1 mixture of [3.3.0]-(5*R*, 6*R*)-6-(2',3'-*O*-isopropylidene-2',3'-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**4.35**) and [3.3.0]-(5*S*, 6*R*)-6-(2',3'-*O*-isopropylidene-2',3'-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**4.36**) (4.03 g, 15.2 mmol, 1 equiv) in THF (150 mL) at -78 °C and the reaction mixture was stirred at -78 °C for 30 min. Iodomethane (0.996 mL, 16.0 mmol, 1.05 equiv) was added dropwise and the reaction mixture was warmed to rt over 30 min, followed by stirring at rt overnight. Water (100 mL) was added and the mixture was extracted with ether (3 x 50 mL). The ether extracts were combined, washed with a 2N aqueous solution of sodium hydroxide (50 mL) and a saturated aqueous solution of sodium chloride (50 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear colourless liquid. The crude liquid was purified by column chromatography (1/19 ethyl acetate-hexanes) to yield 3.45 g (81 %) of **4.41** as a clear colourless liquid and 0.639 g (15 %) of **4.42** as a white solid.

[3.3.0]-(1*R*, 5*S*, 6*R*)-6-((2*S*)-2,3-*O*-Isopropylidene-2,3-dihydroxypropyl)-2,2,6-trimethylbicyclononan-3-one (**4.41**)



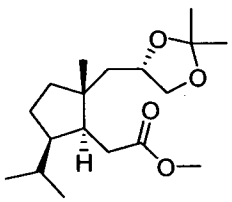
$[\alpha]_D^{22.4}$ = +58.15 ± 0.09 (c 0.367, $CHCl_3$). IR (neat): 2932, 1737 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.19-4.11 (m, 1H), 4.04 (dd, J=7.92 5.79 Hz, 1H), 3.44 (t, J=7.92 Hz, 1H), 2.47-2.24 (m, 3H), 2.06-1.98 (m, 1H), 1.82-1.64 (m, 3H), 1.52-1.33 (m, 3H), 1.37 (s, 3H), 1.33 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 222.9, 108.4, 73.7, 70.7, 52.8, 49.7, 46.9, 45.5, 43.3, 37.6, 37.4, 26.9, 25.9, 25.5, 23.2, 19.7. Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.42; H, 10.19.

[3.3.0]-(1*S*, 5*R*, 6*R*)-6-((2*S*)-2,3-*O*-Isopropylidene-2,3-dihydroxypropyl)-2,2,6-trimethylbicyclononan-3-one (**4.42**)



m.p. = 68-70 °C (ethyl acetate-hexanes). $[\alpha]_D^{23.9}$ = +62.15 ± 0.01 (c 0.893, $CHCl_3$). IR (KBr): 2971, 2932, 2872, 1729 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.15-4.05 (m, 1H), 4.01 (dd, J=7.62 5.80 Hz, 1H), 3.40 (t, J=7.62 Hz, 1H), 2.55-2.44 (m, 1H), 2.36-2.22 (m, 2H), 1.98-1.28 (m, 7H), 1.34 (s, 3H), 1.31 (s, 3H), 1.04 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 222.6, 108.5, 74.1, 70.5, 51.8, 49.9, 48.1, 43.6, 42.6, 37.6, 36.8, 26.9, 26.7, 26.5, 25.9, 24.6, 19.7. LRMS (ESI) m/z (relative intensity): 281.3 (M^+ + 1, 100).

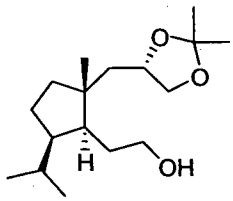
(1*R*, 2*S*, 3*R*)-3-Isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methyl-2-methylethanoatecyclopentane (4.43)



A solution of [3.3.0]-(1*R*, 5*S*, 6*R*)-6-((2*S*)-2,3-*O*-Isopropylidene-2,3-dihydroxypropyl)-2,2,6-trimethylbicyclononan-3-one (**4.41**) (1.48 g, 5.28 mmol, 1 equiv) in methanol (350 mL) in a quartz reaction vessel was irradiated with light from a 450-W Hanovia medium pressure mercury lamp for 5.5 h, after which the reaction mixture was concentrated *in vacuo* to yield a clear colourless liquid. The crude liquid was purified by column chromatography (1/19 ethyl acetate-hexanes) to yield 1.15 g (70 %) of **4.43** as a clear colourless liquid, and 0.133 g (9 %) of **4.41** as a clear colourless liquid.

$[\alpha]_D^{25.1}$ = +22.20 ± 0.02 (0.645, $CHCl_3$). IR (neat): 2953, 2872, 1740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.17-4.06 (m, 2H), 3.65 (s, 3H), 3.42 (t, J=7.16 Hz, 1H), 2.27-2.04 (m, 3H), 1.81-1.69 (m, 3H), 1.65-1.54 (m, 2H), 1.47-1.29 (m, 2H), 1.37 (s, 3H), 1.33 (s, 3H), 1.25-1.12 (m, 1H), 0.89 (s, 3H), 0.86 (d, J=5.82 Hz, 3H), 0.84 (d, J=5.82 Hz, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 174.8, 108.0, 73.9, 70.8, 51.6, 49.7, 45.8, 45.2, 44.2, 36.9, 30.5, 29.7, 27.5, 26.9, 25.9, 22.7, 22.0, 21.7. Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.09; H, 10.34.

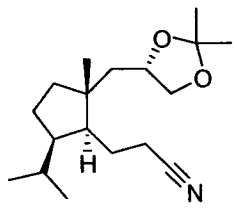
(1*R*, 2*S*, 3*R*)-2-(2-Hydroxyethyl)-3-isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methylcyclopentane (4.44)



Lithium aluminum hydride (0.425 g, 11.2 mmol, 1 equiv) was added to a solution of (1*R*, 2*S*, 3*R*)-3-isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methyl-2-methylethanoatecyclopentane (**4.43**) (3.50 g, 11.2 mmol, 1 equiv) in ether (75 mL) at 0 °C and the reaction mixture was stirred at rt for 30 min. The reaction mixture was then cooled to 0 °C and quenched by the slow dropwise addition of a saturated aqueous solution of sodium potassium tartrate (40 mL). The biphasic mixture was then stirred at rt for 15 min and then extracted with ether (2 x 75 mL). The ether extracts were combined, washed with water (40 mL) and a saturated aqueous solution of sodium chloride (40 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear colourless liquid. The crude liquid was purified by column chromatography (1/3 ethyl acetate-hexanes) to yield 3.04 g (95 %) of 31 as a clear colourless liquid.

$[\alpha]_D^{28.3}$ = +20.09 ± 0.06 (0.410, $CHCl_3$). IR (neat): 3424, 2954 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.14-4.04 (m, 1H), 4.02 (dd, J=7.92, 5.82 Hz, 1H), 3.72-3.63 (m, 1H), 3.59-3.50 (m, 1H), 3.40 (t, J=7.9, Hz, 1H), 1.86-1.48 (m, 9H), 1.45-1.15 (m, 3H), 1.36 (s, 3H), 1.32 (s, 3H), 0.96 (s, 3H), 0.85 (s, 3H), 0.83 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 108.2, 73.8, 70.7, 63.2, 49.8, 45.6, 44.3, 44.0, 37.1, 29.3, 28.4, 27.0, 26.9, 25.9, 23.5, 22.4, 21.7. Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.79; H, 11.34. Found: C, 71.82; H, 11.43.

(1*R*, 2*S*, 3*R*)-2-(2-Cyanoethyl)-3-isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methylcyclopentane (4.45)

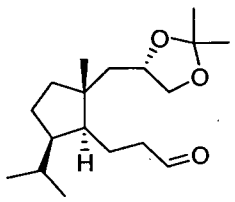


Methanesulfonyl chloride (0.910 mL, 11.8 mmol, 1.1 equiv) was added to a solution of (1*R*, 2*S*, 3*R*)-2-(2-hydroxyethyl)-3-isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methylcyclopentane (**4.44**) (3.04 g, 10.7 mmol, 1 equiv) and triethylamine (2.24 mL, 16.1 mmol, 1.5 equiv) in methylene chloride (100 mL) at 0 °C and the reaction mixture was stirred at rt for 5 h. The reaction mixture was concentrated *in vacuo* and the crude solid was dissolved in dimethyl sulfoxide (100 mL).

Sodium cyanide (1.57 g, 32.1 mmol, 3 equiv) was added and the reaction mixture was stirred at 60 °C overnight. Water (100 mL) was added and the mixture was extracted with ether (4 x 50 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (2 x 50 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear colourless liquid. The crude liquid was purified by column chromatography (1/9 ethyl acetate-hexanes) to yield 3.00 g (96 %) of **4.45** as a clear colourless liquid.

m.p. = 50-51 °C (ethyl acetate-hexanes). $[\alpha]_D^{22.4}$ = +15.24 ± 0.03 (0.315, $CHCl_3$). IR (KBr): 2986, 2946, 2873, 2240 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.16-4.07 (m, 1H), 4.04 (dd, J=7.61, 5.79 Hz, 1H), 3.42 (t, J=7.61 Hz, 1H), 2.48-2.38 (m, 1H), 2.37-2.26 (m, 1H), 1.80-1.15 (m, 11H), 1.37 (s, 3H), 1.33 (s, 3H), 1.01 (s, 3H), 0.88 (d, J=5.20 Hz, 3H), 0.87 (d, J=5.20 Hz, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 119.9, 108.4, 73.5, 70.7, 50.1, 47.8, 45.7, 44.4, 37.1, 29.4, 27.1, 26.9, 25.8, 23.5, 22.2, 21.8, 21.2, 17.8. LRMS (EI) m/z (relative intensity): 293 (M^+, 1).

(1*R*, 2*S*, 3*R*)-3-Isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methyl-2-(3-oxopropyl)cyclopentane (4.46)

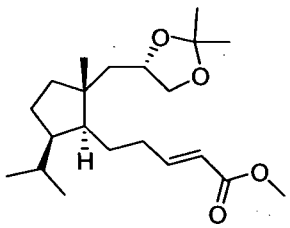


Diisobutylaluminum hydride (8.54 mL of a 1.0 M solution in hexanes, 8.54 mmol, 1.15 equiv) was added dropwise to a solution of (1*R*, 2*S*, 3*R*)-2-(2-cyanoethyl)-3-isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methylcyclopentane (**4.45**) (2.18 g, 7.43 mmol, 1 equiv) in methylene chloride (75 mL) at -78 °C and the reaction mixture was stirred at -78 °C for 1 h. A saturated aqueous solution of basic ammonium chloride (2.5 mL) was added slowly and the reaction mixture was warmed to rt over 10 min and stirred at rt for 1 h. Magnesium sulfate (1.00 g) was added and the reaction mixture was filtered through Celite and concentrated *in vacuo* to yield a clear colourless liquid. The crude liquid was purified by column chromatography (1/9 ethyl acetate-hexanes) to yield 2.08 g (95 %) of **4.46** as a clear colourless liquid.

$[\alpha]_D^{27.1}$ = +19.27 ± 0.01 (0.885, $CHCl_3$). IR (neat): 2954, 2871, 1727 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 4.10-4.02 (m, 1H), 3.99 (dd, J=7.61, 5.79 Hz, 1H), 3.38 (t, J=7.61 Hz, 1H), 2.58-2.47 (m, 1H), 2.44-2.32 (m, 1H), 1.75-1.14 (m, 11H), 1.33 (s, 3H), 1.29 (s, 3H), 0.96 (s, 3H), 0.82 (d, J=6.70 Hz, 3H), 0.80 (d, J=6.70 Hz, 3H).

^{13}C NMR (75 MHz, CDCl3): δ 202.2, 108.1, 73.7, 70.7, 50.2, 48.2, 45.9, 45.0, 44.4, 37.1, 29.3, 27.0, 26.9, 25.8, 23.4, 22.3, 21.8, 17.0. Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88. Found: C, 72.84; H, 11.01.

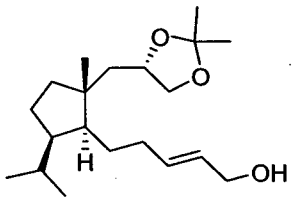
(1*R*, 2*S*, 3*R*)-3-Isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-2-((*E*)-5-methoxy-5-oxopent-3-enyl)-1-methylcyclopentane (4.47)



Trimethylphosphonoacetate (0.670 mL, 4.14 mmol, 1.25 equiv) was added to a suspension of lithium chloride (0.281 g, 6.62 mmol, 2 equiv) in acetonitrile (20 mL) followed by a 1,8-diazabicyclo[5.4.0]undec-7-ene (0.552 mL, 3.64 mmol, 1.1 equiv), and the mixture was cooled to -15 °C. A solution of (1*R*, 2*S*, 3*R*)-3-isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methyl-2-(3-oxopropyl)cyclopentane (**4.46**) (0.982 g, 3.31 mmol, 1 equiv) in acetonitrile (15 mL) was added dropwise and the reaction mixture was stirred at -15 °C for 1 h. Water (25 mL) was added and the reaction mixture was extracted with ether (3 x 50 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (20 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear colourless liquid. The crude liquid was purified by column chromatography (1/9 ethyl acetate-hexanes) to yield 1.10 g (94 %) of **4.47** as a clear colourless liquid.

$[\alpha]_D^{23.7}$ = +19.58 ± 0.01 (0.237, $CHCl_3$). IR (neat): 2953, 2870, 1728, 1657, 1436, 1379, 1369, 1270, 1212, 1168, 1060, 863 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.94 (m, 1H), 5.79 (dd, J=15.65, 1.46 Hz, 1H), 4.13-3.99 (m, 2H), 3.69 (d, J=1.64 Hz, 3H), 3.40 (dt, J=7.61, 1.52 Hz, 1H), 2.34-2.22 (m, 1H), 2.19-2.05 (m, 1H), 1.74-1.12 (m, 11H), 1.36 (s, 3H), 1.32 (s, 3H), 0.99 (s, 3H), 0.84 (d, J=6.40 Hz, 3H), 0.81 (d, J=6.40 Hz, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 167.1, 149.5, 120.7, 108.1, 73.8, 70.8, 51.3, 50.3, 48.4, 46.0, 44.3, 37.2, 33.1, 29.4, 27.2, 26.9, 25.8, 23.4, 23.3, 22.3, 21.9. Anal. Calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.29. Found: C, 71.36; H, 10.36.

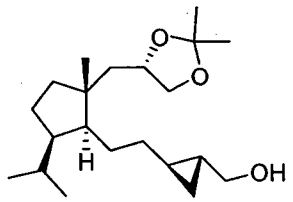
(1*R*, 2*S*, 3*R*)-2-(5-Hydroxypent-3-enyl)-3-isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methylcyclopentane (4.49)



Diisobutylaluminum hydride (12.5 mL of a 1.0 M solution in hexanes, 12.5 mmol, 2.2 equiv) was added dropwise to a solution of (1*R*, 2*S*, 3*R*)-3-isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-2-((*E*)-5-methoxy-5-oxopent-3-enyl)-1-methylcyclopentane (**4.47**) (2.00 g, 5.67 mmol, 1 equiv) in methylene chloride (50 mL) at -78 °C and the reaction mixture was stirred at -78 °C for 20 min, after which a saturated aqueous solution of sodium potassium tartrate (20 mL) was slowly added dropwise. The biphasic mixture was then stirred at rt for 1.5 h and extracted with ethyl acetate (3 x 50 mL). The ethyl acetate extracts were combined, washed with a saturated aqueous solution of sodium chloride (50 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear colourless liquid. The crude liquid was purified by column chromatography (1/3 ethyl acetate-hexanes) to yield 1.76 g (96 %) of **4.49** as a clear colourless liquid.

$[\alpha]_D^{22.1}$ = +22.16 ± 0.09 (0.389, $CHCl_3$). IR (neat): 3414, 2953, 2869, 1670, 1468, 1379, 1369, 1247, 1217, 1060, 670, 867 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.70-5.54 (m, 2H), 4.13-3.98 (m, 4H), 3.41 (dt, J=7.68, 1.88 Hz, 1H), 2.18-1.90 (m, 2H), 1.75-1.26 (m, 11H), 1.36 (s, 3H), 1.32 (s, 3H), 1.25-1.10, 0.98 (s, 3H), 0.83 (d, J=6.63 Hz, 3H), 0.81 (d, J=6.63 Hz, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 133.3, 129.0, 108.0, 74.0, 70.8, 63.6, 50.3, 48.2, 46.0, 44.2, 37.2, 33.1, 29.4, 27.2, 26.9, 25.8, 24.4, 23.3, 22.3, 21.9. Anal. Calcd for $C_{20}H_{36}O_3$: C, 74.03; H, 11.18. Found: C, 73.75; H, 11.25.

(1*R*, 2*S*, 3*R*)-2-(2-((1*S*, 2*S*)-2-(Hydroxymethyl)cyclopropyl)ethyl)-3-isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methylcyclopentane (4.51)

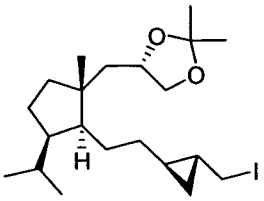


Diiodomethane (0.200 mL, 2.48 mmol, 5.0 equiv) was added dropwise to a solution of diethyl zinc (0.127 mL, 1.24 mmol, 2.5 equiv) in methylene chloride (2 mL) at 0°C. The reaction mixture was stirred at 0 °C for 10 min and a solution of (1*R*, 2*S*, 3*R*)-2-(5-hydroxypent-3-enyl)-3-isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methylcyclopentane (**4.49**) (0.161 g, 0.496 mmol, 1 equiv) and (4S-*trans*)-2-butyl-

N,N,N',N'-tetramethyl[1,3,2]dioxaborolane-4,5-dicarboxamide (0.139 g, 0.570 mmol, 1.15 equiv) in methylene chloride (4 mL) was added dropwise via cannula. The reaction mixture was stirred at rt for 3 h, after which water (5 mL) was added and the mixture was extracted with ethyl acetate (3 x 25 mL). The ethyl acetate extracts were combined, washed with a saturated aqueous solution of sodium chloride (2 x 15 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/3 ethyl acetate-hexanes) to yield 0.162 g (97 %) of **4.51** as a clear colourless liquid.

$[\alpha]_D^{23.7}$ = +22.67 ± 0.14 (0.271, $CHCl_3$). IR (neat): 3441, 2952, 2869, 1468, 1378, 1369, 1246, 1062, 867 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.12-3.95 (m, 2H), 3.39 (m, 3H), 1.76-1.08 (m, 15H), 1.35 (s, 3H), 1.31 (s, 3H), 0.95 (s, 3H), 0.83 (d, J=6.57 Hz, 3H), 0.81 (d, J=6.57 Hz, 3H), 0.60-0.52 (m, 1H), 0.37-0.22 (m, 2H). ^{13}C NMR (75 MHz, CDCl3): δ 107.9, 74.0, 70.8, 67.0, 50.3, 48.4, 46.0, 44.3, 37.2, 34.7, 29.5, 27.2, 26.9, 25.8, 24.7, 23.3, 22.3, 21.9, 21.3, 21.3, 17.7, 9.8. LRMS (EI) m/z (relative intensity): 338 (M^+, 1).

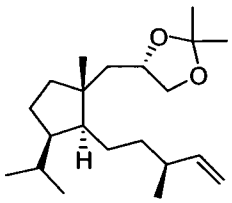
(1*R*, 2*S*, 3*R*)-2-(2-((1*S*, 2*S*)-2-(Iodomethyl)cyclopropyl)ethyl)-3-isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methylcyclopentane (4.53)



Methanesulfonyl chloride (0.521 mL, 6.74 mmol, 1.5 equiv) was added to a solution of (1*R*, 2*S*, 3*R*)-2-(2-((1*S*, 2*S*)-2-(hydroxymethyl)cyclopropyl)ethyl)-3-isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methylcyclopentane (**4.51**) (1.52 g, 4.50 mmol, 1 equiv) and triethylamine (1.88 mL, 13.5 mmol, 3.0 equiv) in methylene chloride (45 mL) at 0 °C and the reaction mixture was stirred at rt for 1 h. The reaction mixture was concentrated *in vacuo* and the crude solid was dissolved in acetone (45 mL). Sodium iodide (6.06 g, 40.4 mmol, 9 equiv) was added and the reaction mixture was stirred at rt for 1 h. A saturated aqueous solution of sodium bicarbonate (15 mL) was added, followed by a saturated aqueous solution of sodium thiosulfate (15 mL), and the mixture was extracted with ether (3 x 15 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (2 x 10 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/19 ethyl acetate-hexanes) to yield 1.80 mg (90 %) of **4.53** as a clear colourless liquid.

$[\alpha]_D^{23.7}$ = +10.58 ± 0.16 (0.124, $CHCl_3$). IR (neat): 2953, 2868, 1468, 1378, 1368, 1216, 1171, 1060, 868 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.12-3.98 (m, 2H), 3.40 (t, J=7.58 Hz, 1H), 3.19-3.05 (m, 2H), 1.74-0.97 (m, 14H), 1.36 (s, 3H), 1.32 (s, 3H), 0.96 (s, 3H), 0.84 (d, J=6.57 Hz, 3H), 0.82 (d, J=6.57 Hz, 3H), 0.65-0.57 (m, 2H), 0.46-0.39 (m, 1H). ^{13}C NMR (75 MHz, CDCl3): δ 107.9, 74.0, 70.9, 50.4, 48.7, 46.1, 44.3, 37.2, 35.0, 29.6, 27.3, 26.9, 25.9, 24.6, 23.5, 23.3, 22.3, 22.0, 18.0, 14.1. Anal. Calcd for $C_{21}H_{37}O_2I$: C, 56.25; H, 8.32. Found: C, 56.33; H, 8.41.

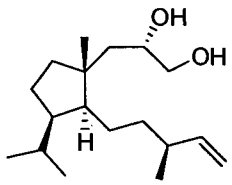
(1*R*, 2*S*, 3*R*)-3-Isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methyl-2-((3*S*)-3-methylpent-4-enyl)cyclopentane (4.54)



N,N,N',N'-tetramethylethylenediamine (75.7 µL, 0.502 mmol, 1.5 equiv) was added to a solution of (1*R*, 2*S*, 3*R*)-2-(2-((1*S*, 2*S*)-2-(iodomethyl)cyclopropyl)ethyl)-3-isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methylcyclopentane (**4.53**) (0.150 g, 0.335 mmol, 1 equiv) and 4 Å molecular sieves (0.185 g) in diethyl ether (4 mL), and the reaction mixture was cooled to -78 °C. To this mixture was added n-butyllithium (0.332 mL of a 1.51 M solution in hexanes, 0.502 mmol, 1.5 equiv) dropwise and the reaction mixture was stirred at -78 °C for 30 min. Water (5 mL) was added and the reaction mixture was warmed to rt over 20 min, after which it was extracted with ether (3 x 10 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (5 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/19 ethyl acetate-hexanes) to yield 95 mg (88 %) of **4.54** as a clear colourless liquid.

$[\alpha]_D^{26.0}$ = +19.42 ± 0.11 (0.297, $CHCl_3$). IR (neat): 2955, 2869, 1640 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.67 (m, 1H), 4.96-4.86 (m, 2H), 4.13-4.00 (m, 2H), 3.41 (t, J=7.61 Hz, 1H), 2.10-1.96 (m, 1H), 1.73-1.08 (m, 13H), 1.37 (s, 3H), 1.33 (s, 3H), 0.97 (s, 3H), 0.96 (s, 3H), 0.83 (d, J=6.55 Hz, 3H), 0.81 (d, J=6.55 Hz, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 144.7, 112.4, 107.8, 74.0, 70.8, 50.4, 49.2, 46.1, 44.2, 38.6, 37.9, 37.2, 29.5, 27.2, 26.9, 25.8, 23.2, 22.4, 22.2, 21.9, 20.1. LRMS (EI) m/z (relative intensity): 322 (M^+, 2).

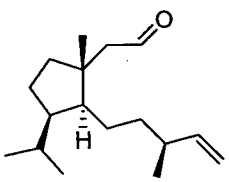
(1*R*, 2*S*, 3*R*)-3-isopropyl-1-((2*S*)-2,3-dihydroxypropyl)-1-methyl-2-((3*S*)-3-methylpent-4-enyl)cyclopentane (4.55)



A 1N aqueous solution of hydrochloric acid (0.674 mL, 0.674 mmol, 2.5 equiv) was added to a solution of (1*R*, 2*S*, 3*R*)-3-isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methyl-2-((3*S*)-3-methylpent-4-enyl)cyclopentane (**4.54**) (87 mg, 0.270 mmol, 1 equiv) in THF (1.5 mL) and the reaction mixture was stirred for 24 h. A saturated aqueous solution of sodium bicarbonate (10 mL) was added and the reaction mixture was extracted with ether (3 x 10 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (10 mL), dried over sodium sulfate and concentrated *in vacuo* to yield a clear colourless liquid. The crude liquid was purified by column chromatography (1/19 methanol-chloroform) to yield 71 mg (93 %) of **4.55** as a clear colourless liquid.

$[\alpha]_D^{21.4}$ = +0.73 ± 0.09 (0.214, $CHCl_3$). IR (neat): 3363, 2953, 2869, 1640, 1467, 1381, 1366, 1064, 910 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.67 (ddd, J=17.54, 10.25, 7.57 Hz, 1H), 4.96-4.86 (m, 2H), 3.83-3.75 (m, 1H), 3.56-3.49 (m, 1H), 3.39-3.31 (m, 1H), 2.60 (br s, 1H), 2.46 (br s, 1H), 2.09-1.98 (m, 1H), 1.74-1.12 (m, 13H), 1.04 (s, 3H), 0.96 (d, J=6.75 Hz, 3H), 0.83 (d, J=6.60 Hz, 3H), 0.81 (d, J=6.60 Hz, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 144.8, 112.5, 70.2, 68.1, 50.4, 48.8, 45.4, 44.7, 38.7, 38.0, 37.8, 29.5, 27.3, 23.4, 22.4, 22.3, 21.9, 20.2. LRMS (ESI) m/z (relative intensity): 305.4 (M^+ + Na^+, 65), 282.4 (M^+, 67).

(1*R*, 2*S*, 3*R*)-3-Isopropyl-1-methyl-2-((3*S*)-3-methylpent-4-enyl)-1-(2-oxoethyl)cyclopentane (4.56)



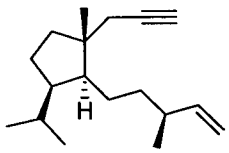
Method A (treatment of **4.54** with periodic acid): periodic acid (0.899 g, 3.94 mmol, 1.2 equiv) was added to a solution of (1*R*, 2*S*, 3*R*)-3-isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methyl-2-((3*S*)-3-methylpent-4-enyl)cyclopentane (**4.54**) (1.06 g, 3.29 mmol, 1 equiv) in in ethyl acetate (35 mL) and the reaction mixture was stirred for 3 h. The reaction mixture was filtered through Celite® and the filtrate was concentrated to

yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/19 ethyl acetate-hexanes) to yield 0.700 g (85 %) of **4.56** as a clear colourless liquid.

Method B (treatment of **4.55** with sodium periodate): Sodium periodate (0.927 g, 4.33 mmol, 2.0 equiv) was added in 1 portion to a solution of (1*R*, 2*S*, 3*R*)-3-isopropyl-1-((*S*)-2,3-dihydroxypropyl)-1-methyl-2-((*S*)-3-methylpent-4-enyl)cyclopentane (**4.55**) (0.612 g, 2.17 mmol, 1.0 equiv) in water (5 mL) and THF (20 mL) and the reaction mixture was stirred for 30 min. Water was added and the reaction mixture was extracted with ether (3 x 20 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (20 mL), dried over sodium sulfate and concentrated *in vacuo* to yield a clear colourless liquid. The crude liquid was purified by column chromatography (1/19 ethyl acetate-hexanes) to yield 0.460 g (85 %) of **4.56** as a clear colourless liquid.

$[\alpha]_D^{22.3}$ = +3.6 ± 0.2 (c 0.192, $CHCl_3$). IR (neat): 2956, 2870, 2727, 1722, 1640 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.78 (t, J=2.98 Hz, 1H), 5.65 (ddd, J=17.67, 10.27, 7.58 Hz, 1H), 4.96-4.85 (m, 2H), 2.40 (dd, J=14.97, 3.34 Hz, 1H), 2.26 (dd, J=14.97, 3.34 Hz, 1H), 2.08-1.96 (m, 1H), 1.76-1.65 (m, 2H), 1.58-1.10 (m, 9H), 1.14 (s, 3H), 0.96 (d, J=6.99 Hz, 3H), 0.87-0.79 (m, 6H). ^{13}C NMR (75 MHz, CDCl3): δ 203.8, 144.5, 112.6, 55.5, 50.5, 49.2, 48.8, 44.5, 38.7, 37.8, 37.4, 29.6, 27.3, 23.6, 22.2, 21.9, 20.2.

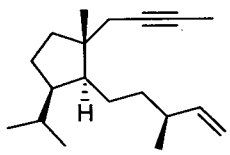
(1*R*, 2*S*, 3*R*)-3-Isopropyl-1-methyl-2-((3*S*)-3-methylpent-4-enyl)-1-(prop-2-ynyl)cyclopentane (4.4)



A solution of (1*R*, 2*S*, 3*R*)-3-isopropyl-1-methyl-2-((3*S*)-3-methylpent-4-enyl)-1-(2-oxoethyl)cyclopentane (**4.56**) (0.445 g, 1.78 mmol, 1 equiv) in methanol (5 mL) was added to a solution of potassium carbonate (0.491 g, 3.55 mmol, 2.0 equiv) in methanol (10 mL), followed by a solution of dimethyldiazo-2-oxopropylphosphonate (0.470 g, 2.67 mmol, 1.5 equiv) in methanol (5 mL), and the reaction mixture was stirred for 12 h. Water (15 mL) was added and the reaction mixture was extracted with hexanes (4 x 5 mL). The hexanes extracts were combined, dried over magnesium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (hexanes) to yield 0.373 g (85 %) of **4.4** as a clear colourless liquid.

$[\alpha]_D^{20.8}$ = +2.39 ± 0.18 (c 0.298, $CHCl_3$). IR (neat): 3312, 2955, 2870, 2117, 1640 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.74 (ddd, J=17.4, 10.3, 7.6 Hz, 1H), 4.97-4.86 (m, 2H), 2.22 (dd, J=16.8, 2.4 Hz, 1H), 2.09 (dd, J=16.6, 2.4 Hz, 1H), 1.94 (t, 2.6 Hz, 1H), 1.74-1.12 (m, 12 H), 1.09 (s, 3H), 0.97 (d, J=6.7 Hz, 3H), 0.85 (d, J=2.3 Hz, 3H), 0.83 (d, J=2.3 Hz, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 144.9, 112.4, 83.5, 69.4, 50.7, 47.7, 38.7, 37.6, 36.3, 32.4, 29.6, 27.5, 23.1, 22.2, 22.1, 20.2. LRMS (EI) m/z (relative intensity): 246 (M^+, 1).

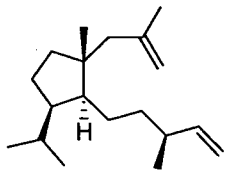
(1*R*, 2*S*, 3*R*)-1-(But-2-ynyl)-3-isopropyl-1-methyl-2-((3*S*)-3-methylpent-4-enyl)cyclopentane (4.5)



n-Butyllithium (0.537 mL of a 1.36 M solution in hexanes, 0.730 mmol, 1.2 equiv) was added dropwise to a solution of (1*R*,2*S*,3*R*)-1-(prop-2-ynyl)-3-isopropyl-1-methyl-2-((3*S*)-3-methylpent-4-enyl)cyclopentane (**4.4**) (0.150 g, 0.609 mmol, 1 equiv) in THF (6 mL) at -78 °C, and the reaction mixture was stirred at -78 °C for 30 min. iodomethane (0.0493 mL, 0.791 mmol, 1.3 equiv) was added dropwise and the reaction mixture was warmed to rt over 30 min and stirred at rt overnight. A saturated aqueous solution of ammonium chloride (10 mL) was added and the reaction mixture was extracted with ether (3 x 10 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (10 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear colourless liquid. The crude liquid was purified by column chromatography (hexanes) to yield 0.151 g (95 %) of **4.5** as a clear colourless liquid.

$[\alpha]_D^{20.0}$ = +3.90 ± 0.14 (c 0.103, $CHCl_3$). IR (neat): 2954, 2869, 1640 cm^{-1}. ^1H NMR (300 MHz, CDCl3): δ 5.69 (ddd, J=17.6, 10.3, 7.4 Hz, 1H), 4.98-4.86 (m, 2H), 2.18-1.96 (m, 3H), 1.78 (t, 2.5 Hz, 3H), 1.70-1.00 (m, 11 H), 1.05 (s, 3H), 0.97 (d, J=6.7 Hz, 3H), 0.84 (m, 6H). ^{13}C NMR (75 MHz, CDCl3): δ 145.0, 112.4, 78.0, 76.5, 50.7, 47.8, 45.8, 38.7, 37.6, 36.4, 32.9, 29.6, 27.6, 23.3, 22.6, 22.3, 22.1, 20.2, 3.5. LRMS (EI) m/z (relative intensity): 260 (M^+, 1). Anal. Calcd for $C_{19}H_{32}$: C, 87.62; H, 12.38. Found: C, 87.84; H, 12.44.

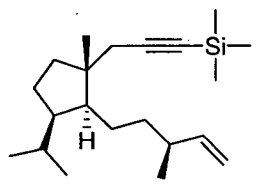
(1*R*, 2*S*, 3*R*)-3-Isopropyl-1-methyl-2-((3*S*)-3-methylpent-4-enyl)-1-(2-methylprop-2-enyl)cyclopentane (4.6)



Trimethylaluminum (0.254 mL of a 2.0 M solution in hexame, 0.507 mmol, 2.5 equiv) was added dropwise to a slurry of bis(cyclopentadienyl)zirconium dichloride (18 mg, 0.061 mmol, 0.3 equiv) in methylene chloride (1.5 mL) at -20 °C to produce a clear pale yellow solution. The reaction mixture was stirred at -20 °C for 10 min, and a solution of (1*R*, 2*S*, 3*R*)-1-(but-2-ynyl)-3-isopropyl-1-methyl-2-((3*S*)-3-methylpent-4-enyl)cyclopentane (**4.5**) (50.0 mg, 0.203 mmol, 1.0 equiv) in methylene chloride (0.5 mL) was added dropwise to the reaction mixture at -20 °C. The reaction mixture was stirred at rt for 16 h, after which excess trimethylaluminum was destroyed by the slow dropwise addition of water (1 mL). The resulting slurry was diluted with hexanes (5 mL) and the solution was filtered through Celite.® The filtrate was washed with water (5 mL), the water layer was separated and extracted with hexanes (1 x 5 mL), the organic layers were combined, dried over magnesium sulfate and concentrated *in vacuo* to yield a clear colourless liquid. The crude liquid was purified by column chromatography (hexanes) to yield 51.7 mg (97 %) of **4.6** as a clear colourless liquid.

$[\alpha]_D^{21.0}$ = +4.87 ± 0.19 (c 0.113, $CHCl_3$). IR (neat): 3074, 2957, 2869, 1640 cm^{-1}. ^1H NMR (300 MHz, CDCl3): δ 5.69 (ddd, *J*=17.5, 10.2, 7.5 Hz, 1H), 5.02-4.86 (m, 2H), 4.79 (s, 1H), 4.62 (s, 1H), 2.15 (d, *J*=13.4 Hz, 1H), 1.92 (d, *J*=13.4 Hz, 1H), 2.11-1.95 (m, 1H), 1.80-0.79 (m, 11H), 1.76 (s, 3H), 0.99 (s, 3H), 0.97 (d, *J*=6.7, 3 H), 0.84 (m, 6H). ^{13}C NMR (75 MHz, CDCl3): δ 145.0, 144.4, 113.8, 112.4, 50.3, 48.0, 45.8, 38.8, 38.0, 29.7, 27.3, 25.3, 23.7, 22.6, 22.4, 22.0, 20.2, 1.0. LRMS (EI) m/z (relative intensity): 262 (M^+, 1).

(1*R*, 2*S*, 3*R*)-3-Isopropyl-1-methyl-2-((3*S*)-3-methylpent-4-enyl)-1-(3-(trimethylsilyl)prop-2-ynyl)cyclopentane (4.62)

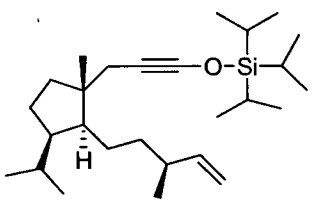


n-Butyllithium (73.0 µL of a 1.52 M solution in hexanes, 0.111 mmol, 1.1 equiv) was added dropwise to a solution of (1*R*,2*S*,3*R*)-1-(prop-2-ynyl)-3-isopropyl-1-methyl-2-((3*S*)-3-methylpent-4-

enyl)cyclopentane (**4.4**) (25 mg, 0.101 mmol, 1 equiv) in THF (1.5 mL) at -78 °C, and the reaction mixture was stirred at -78 °C for 30 min. Trimethylsilyl chloride (38.6 µL, 0.304 mmol, 3 equiv) was added dropwise and the reaction mixture was stirred at -78 °C for 2 h. A saturated aqueous solution of ammonium chloride (2 mL) was added and the reaction mixture was extracted with ether (3 x 5 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride (5 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear colourless liquid. The crude liquid was purified by column chromatography (hexanes) to yield 32 mg (99 %) of **4.5** as a clear colourless liquid.

$[\alpha]_D^{20.0}$ = +4.95 ± 0.29 (c 0.093, $CHCl_3$). IR (neat): 2954, 2869, 1640 cm^{-1}. ^1H NMR (300 MHz, CDCl3): δ 5.69 (ddd, J=17.6, 10.3, 7.5 Hz, 1H), 4.99-4.87 (m, 2H), 2.23 (d, J=16.9, 1H), 2.09 (d, J=16.9, 1H), 2.09-1.99 (m, 1H), 1.70-1.04 (m, 11 H), 1.07 (s, 3H), 0.97 (d, J=6.7 Hz, 3H), 0.84 (m, 6H), 0.13 (s, 9H). ^{13}C NMR (75 MHz, CDCl3): δ 144.9, 112.4, 106.8, 85.8, 50.7, 47.7, 45.9, 38.6, 37.7, 36.6, 33.9, 29.6, 27.6, 23.3, 22.4, 22.2, 22.1, 20.2, 0.2. LRMS (EI) m/z (relative intensity): 318 (M^+, 1).

(1*R*, 2*S*, 3*R*)-3-Isopropyl-1-methyl-2-((3*S*)-3-methylpent-4-enyl)-1-(3-(triisopropylsilyloxy)prop-2-ynyl)cyclopentane (4.63)

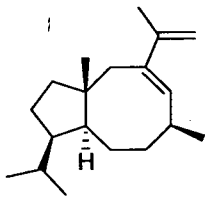


Lithium bis(trimethylsilyl)amide (0.121 mL of a 1.0 M solution in THF, 0.121 mmol, 1.2 eq) was added dropwise to a solution of (1*R*,2*S*,3*R*)-1-(prop-2-ynyl)-3-isopropyl-1-methyl-2-((3*S*)-3-methylpent-4-enyl)cyclopentane (**4.4**) (25 mg, 0.101 mmol, 1 equiv) in THF (0.8 mL) at -78 °C, and the reaction mixture was stirred at -78 °C for 10 min. A solution of lithium *tert*-butylhydroperoxide prepared from the addition of lithium bis(trimethylsilyl)amide (0.131 mL of a 1.0 M solution in THF, 0.131 mmol, 1.3 eq) to a solution of *tert*-butylhydroperoxide (24 µL of a 5 M solution in decane, 0.121 mmol, 1.2 equiv) in THF (0.8 mL) at -78 °C was then added dropwise and the reaction mixture was allowed to warm to 0 °C over 0.5 h, and stirred at 0 °C for 3 h. The resulting reaction mixture was cooled to -78 °C before triisopropylsilyl chloride (35.5 µL, 0.131 mmol, 1.3 equiv) was added dropwise and the reaction mixture was stirred at 0 °C for 0.5 h. The reaction mixture was diluted with hexanes (5 mL), washed with a saturated aqueous solution of sodium bicarbonate (5 mL), followed by a

saturated aqueous solution of sodium chloride (5 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear colourless liquid. The crude liquid was purified by column chromatography (hexanes) to yield 18 mg (41 %) of **4.63** as a clear colourless liquid and 17 mg (67 %) of **4.4** as a clear colourless liquid.

IR (neat): 2954, 2869, 1640 cm^{-1}. ^1H NMR (300 MHz, CDCl3): δ 5.69 (ddd, J=17.6, 10.3, 7.5 Hz, 1H), 4.99-4.87 (m, 2H), 2.23 (d, J=16.9, 1H), 2.09 (d, J=16.9, 1H), 2.09-1.99 (m, 1H), 1.70-1.04 (m, 11 H), 1.07 (s, 3H), 0.97 (d, J=6.7 Hz, 3H), 0.84 (m, 6H), 0.13 (s, 9H). ^{13}C NMR (75 MHz, CDCl3): δ 144.9, 112.4, 106.8, 85.8, 50.7, 47.7, 45.9, 38.6, 37.7, 36.6, 33.9, 29.6, 27.6, 23.3, 22.4, 22.2, 22.1, 20.2, 0.2. LRMS (ESI) m/z (relative intensity): 441.4 (M^+ + Na^+, 69).

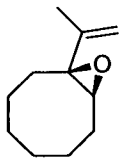
[6.3.0]-(1*R*, 5*S*, 8*S*, 9*R*)-1,5-Dimethyl-9-isopropyl-3-(prop-1-en-2-yl)bicycloundec-2-ene (4.2)



Ruthenium [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(phenylmethylene) (trichlorohexylphosphine) (68 mg, 0.0807 mmol, 30 mol %) was added in one portion to a solution of (1*R*, 2*S*, 3*R*)-1-(but-2-ynyl)-3-isopropyl-1-methyl-2-((3*S*)-3-methylpent-4-enyl)cyclopentane (**4.5**) (70 mg, 0.269 mmol, 1 equiv) in methylene chloride and the reaction mixture was refluxed for 18 h. Triethylamine (0.5 mL) was then added, the reaction mixture was concentrated *in vacuo* to yield a dark red coloured liquid. The crude liquid was purified by column chromatography (hexanes) to yield 37 mg (53 %) of **4.2** as a clear colourless liquid.

$[\alpha]_D^{21.0}$ = +8.87 ± 0.15 (c 0.100, $CHCl_3$). IR (neat): 3089, 2926, 2854, 1637 cm^{-1}. ^1H NMR (300 MHz, CDCl3): δ 5.40 (d, J=9.4 Hz, 1H), 5.01 (s, 1H), 4.87 (s, 1H), 2.64-2.54 (m, 1H), 2.15-2.08 (m, 2H), 1.90 (s, 3H), 1.70-1.00 (m, 11 H), 1.05 (s, 3H), 0.97 (d, J=6.7 Hz, 3H), 0.84 (m, 6H). ^{13}C NMR (75 MHz, CDCl3): δ 153.1, 149.2, 111.8, 111.2, 78.0, 76.5, 50.7, 47.8, 45.8, 38.7, 37.6, 36.4, 32.9, 29.6, 27.6, 23.3, 22.6, 22.3, 22.1, 20.2, 3.5. LRMS (EI) m/z (relative intensity): 260 (M^+, 1).

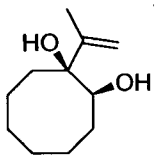
(1*S, 8*S**)-1-(Prop-1-en-2-yl)-9-oxa-bicyclo[6.1.0]nonane (4.73)**



Sodium bicarbonate (9.07 mL of a 0.5 M aqueous solution, 45.4 mmol, 2.1 equiv) was added to a solution of (*E*)-1-(prop-1-en-2-yl)cyclooct-1-ene (3.24 g, 21.6 mmol, 1 equiv) in methylene chloride (215 mL) at 0 °C, followed by 3-chloroperbenzoic acid (3.91 g, 22.6 mmol, 1.05 equiv) and the reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was washed with water (40 mL) and brine (40 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear colourless liquid. The crude liquid was purified by column chromatography (1/19 ethyl acetate-hexanes) to yield 3.47 g (96 %) of **4.73** as a clear colourless liquid.

IR (neat): 2931, 2855, 1650 cm^{-1}. ^1H NMR (300 MHz, CDCl3): δ 5.01-4.96 (m, 2H), 3.04 (dd, *J*=9.8, 4.2 Hz, 1H), 2.20-2.10 (m, 2H), 1.76 (s, 3H), 1.65-1.26 (d, *J*=13.4 Hz, 10H). ^{13}C NMR (75 MHz, CDCl3): δ 143.6, 114.3, 64.4, 62.1, 28.2, 27.7, 26.5, 26.3, 25.7, 25.2, 18.7. LRMS (EI) m/z (relative intensity): 166 (M^+, 6).

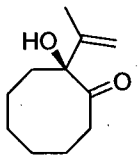
(1*S, 2*S**)-1-(Prop-1-en-2-yl)cyclooctane-1,2-diol (4.74)**



4-Methylmorpholine *N*-oxide (0.445 g, 3.80 mmol, 1.9 equiv) was added to a solution of (*E*)-1-(prop-1-en-2-yl)cyclooct-1-ene (0.300 g, 2.00 mmol, 1 equiv) in 8:1 acetone/water (4 mL) followed by a osmium tetroxide (1.00 mL of a 0.1 M solution in *t*-butanol, 0.100 mmol, 0.05 equiv) and the reaction was stirred for 16 hr. A 10 % aqueous solution of sodium bisulfate (5 mL) was added, and the reaction mixture was saturated with sodium chloride and extracted with ethyl acetate (3 x 5 mL). The ethyl acetate extracts were combined, washed with a saturated aqueous solution of sodium chloride (5 mL), dried over sodium sulfate and concentrated *in vacuo* to yield a dark red coloured liquid. The crude liquid was purified by column chromatography (1/3 ethyl acetate-hexanes) to yield 0.265 g (72 %) of **4.74** as a clear colourless liquid.

IR (neat): 3446, 2922, 2855, 1640 cm^{-1}. ^1H NMR (300 MHz, CDCl3): δ 5.01-4.96 (m, 2H), 4.08-4.00 (m, 1H), 2.62 (s, 1H), 2.20-2.04 (m, 1H), 1.90-1.18 (m, 15H), 1.79 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 150.0, 110.9, 78.8, 73.3, 32.4, 30.5, 27.5, 26.7, 24.2, 20.9, 19.6. LRMS (EI) m/z (relative intensity): 184 (M^+, 6).

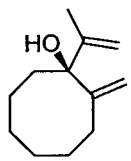
(1*S)-2-Hydroxy-2-(prop-1-en-2-yl)cyclooctanone (4.75)**



Dess-Martin periodinane (241 mg, 0.568 mmol, 1.1 equiv) was added to a solution of 1-(prop-1-en-2-yl)cyclooctane-1,2-diol (**4.74**) (95 mg, 0.516 mmol, 1 equiv) and pyridine (0.209 mL, 2.58 mmol, 5 equiv) in methylene chloride (5 mL) and the reaction mixture was stirred for 6 h. A 1.5 M solution of sodium thiosulfate (5 mL) was added followed by a saturated aqueous solution of sodium bicarbonate (5 mL) and the reaction mixture was extracted with methylene chloride (3 x 5 mL). The methylene chloride extracts were combined, dried over sodium sulfate and concentrated *in vacuo* to yield a clear yellow liquid. The crude liquid was purified by column chromatography (1/19 ethyl acetate-hexanes) to yield 82 mg (87 %) of **4.76** as a clear colourless liquid.

IR (neat): 3474, 2931, 2858, 1699, 1637 cm^{-1}. ^1H NMR (300 MHz, CDCl3): δ 5.10 (s, 1H), 5.00 (s, 1H), 4.18 (s, 1H), 2.84 (dt, *J*=12.4, 3.8 Hz, 1H), 2.60-2.47 (m, 1H), 2.10 (dt, *J*=12.4, 3.8 Hz, 1H), 2.02-1.53 (m, 9H), 1.46-1.19 (m, 2H), 0.98-0.81 (m, 1H). ^{13}C NMR (75 MHz, CDCl3): δ 217.2, 145.8, 113.9, 82.2, 35.3, 30.4, 30.1, 25.3, 24.3, 22.5, 18.2. LRMS (EI) m/z (relative intensity): 182 (M^+, 2).

2-Methylene-1-(prop-1-en-2-yl)cyclooctanol (4.70)



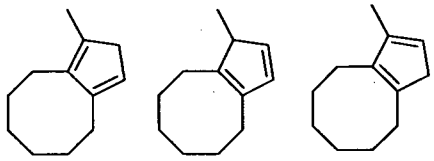
Methyltriphenylphosphonium bromide (320 mg, 0.896 mmol, 2.2 equiv) was added to a solution of potassium *t*-butoxide (96 mg, 0.855 mmol, 2.1 equiv) in benzene (3 mL) and the reaction mixture was stirred at 80 °C for 2 h. Water (6 mL) was added and the reaction mixture was extracted with hexane (3 x 6 mL). The hexane extracts were combined, dried over magnesium sulfate and concentrated *in vacuo* to yield an orange liquid. The crude liquid was purified by column chromatography (chloroform) to yield 59 mg (81 %) of **4.69** as a clear colourless liquid.

IR (neat): 3483, 2926, 2854, 1637 cm^{-1}. ^1H NMR (300 MHz, CDCl3): δ 5.32 (s, 1H), 5.00 (s, 1H), 4.95 (s, 1H), 4.84 (s, 1H), 2.33-2.17 (m, 2H), 1.93-1.30 (m, 13 H), 1.71 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 153.1, 149.2, 111.4, 111.2, 79.1, 35.3, 30.4, 30.1, 25.3, 24.3, 22.5, 18.2. LRMS (EI) m/z (relative intensity): 180 (M^+, 5).

(4*S)-1,4-dimethyl-4,5,6,7,8,9-hexahydro-2*H*-cyclopenta[8]annulene (4.76)**

(4*S)-1,4-dimethyl-4,5,6,7,8,9-hexahydro-1*H*-cyclopenta[8]annulene (4.77)**

(4*S)-3,9-dimethyl-4,5,6,7,8,9-hexahydro-1*H*-cyclopenta[8]annulene (4.78)**



p-Toluenesulfonic acid monohydrate (12 mg, 0.0655 mmol, 0.1 equiv) was added to a solution of 2-methylene-1-(prop-1-en-2-yl)cyclooctanol (**4.70**) (118 mg, 0.655 mmol, 1 equiv) in ether (7 mL) and the reaction mixture was stirred for 18 h. A saturated aqueous solution of sodium bicarbonate (5 mL) was added and the reaction mixture was extracted with ether (2 x 5 mL). The ether extracts were combined, washed with a saturated aqueous solution of sodium chloride, dried over magnesium sulfate and concentrated *in vacuo* to yield an clear yellow liquid. The crude liquid was purified by column chromatography (hexanes) to yield 65 mg (56 %) of an inseparable 51:34:15 mixture of the three isomers **4.76**, **4.77** and **4.78** (gas chromatography analysis, unassigned) as a clear colourless liquid.

IR (neat): 3483, 2926, 2854, 1637 cm^{-1}. ^{1}H NMR (300 MHz, CDCl3): δ 5.92-5.76 (m, 1.81 H), 2.85-2.73 (m, 1.23 H), 2.45-1.18 (m, 15H). ^{13}C NMR (75 MHz, CDCl3): δ 153.1, 149.2, 111.4, 111.2, 79.1, 35.3, 30.4, 30.1, 25.3, 24.3, 22.5, 18.2. LRMS (EI) m/z (relative intensity): 180 (M^{+}, 5).

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Afterword

The following brief section is meant to summarize the general achievement of the work presented in this thesis as well as its contribution to the field of science in general. The reader may refer to the concluding remarks in the relevant chapters (Chapter Two IV, and Chapter Four VII) for detailed summaries.

The field of synthetic organic chemistry can be divided superficially into two branches: target oriented synthesis (the total synthesis of important and useful organic molecules); method oriented synthesis (the development of practical methods and reactions). Both branches of synthetic organic chemistry have been touched upon in the work presented herein.

In the first part, a general method for the stereospecific construction of macrocycles containing a trisubstituted alkene was originally proposed with the goal of applying this to the synthesis of a number of natural products. The importance and practicability of transition metal catalyzed carbon-carbon bond forming cross-coupling reactions have been widely recognized in the past 30 years. In fact, its importance stems from the recognition that such reactions address the twin issues of selectivity and atom economy, which renders industrial and medicinal molecules more accessible. It was expected early into the development of the project that the formation of alkenes by way of the cross-coupling of an organometallic sp^2 carbon with an electrophilic sp^3 carbon was not straightforward. In fact, this cross-coupling was the least understood of the possible combinations of such reactions. The added concern of its use in macrocycle formation made our task an even greater challenge. However, suitable reaction conditions, using a palladium based catalytic system, were found which allowed for the cross-coupling of vinylzinc or vinylmagnesium reagents with alkyl bromides, albeit in modest yields. To the best of our knowledge, this represented at the time of study the first methodological work relating to transition metal catalyzed cross-coupling reaction between vinylorganometallics and alkyl electrophiles. With the subsequent work reported by Fu and co-workers on the development of various forms of such a reaction, further attempts at improving the modest yields were temporarily abandoned. However, it is important to note that no method for the cross-coupling of vinylmagnesium reagents with alkyl electrophiles has yet been reported in the literature. Considering that many vinylmagnesium reagents can be prepared or commercially purchased, this form of cross-coupling reaction merits further attention.

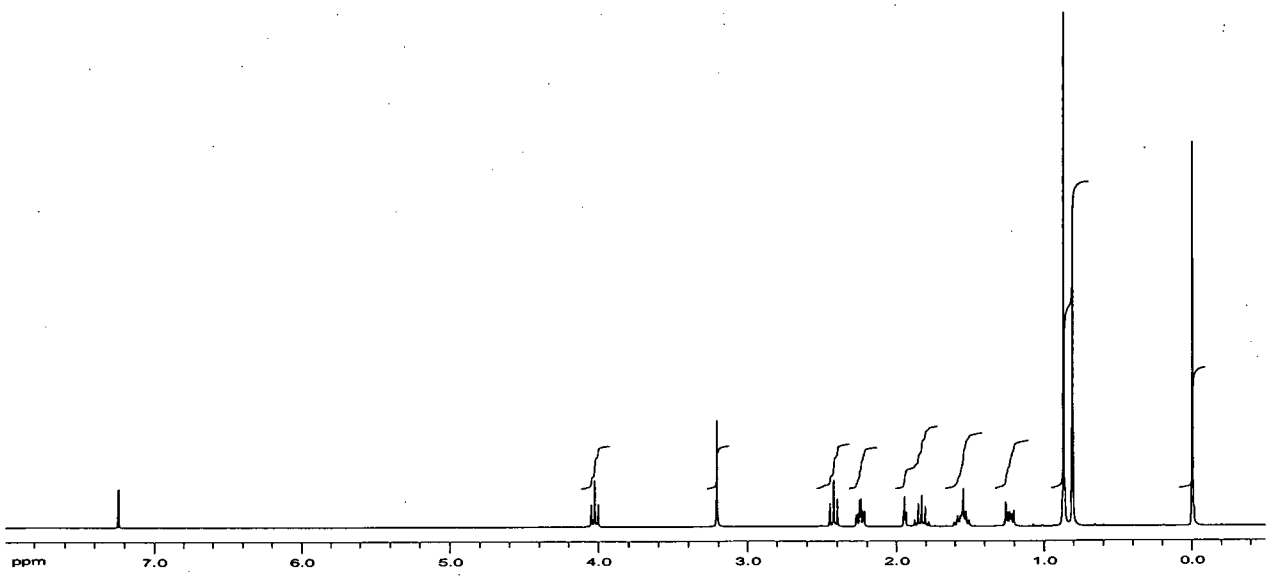
In the second part, an asymmetric synthetic approach towards fusicoccadiene was presented as a source for the accessibility of a number of fusicoccane diterpenoids. The phytohormone properties exhibited by a number of fusicoccane diterpenoids and their potential use for agricultural purposes, are obvious reasons for exploration into their synthesis. In addition, the recent interest for which a number of these natural products have been found regarding human 14-3-3 protein binding activity is an additional motive regarding medicinal purposes. However, a rather less obvious but equally important reason is the use of the synthesis as a testing ground for methods recently developed in our laboratory. The synthesis of the A-ring of fusicoccadiene was achieved using the Pauson-Khand/Norrish Type 1 sequence in order to overcome the stereochemical challenge posed by the three contiguous stereocentres. Additionally, theses stereocentres were all established through the use of chemical relay from the chirality of L-glutamic acid. The challenge with regards to the formation of the 8-membered B-ring was of particular interest. Whereas cyclization using the Pauson-Khand reaction as well as the more common ring closing diene metathesis reaction were unsuccessful, the lesser used ring closing enyne metathesis proved effective. To the best of our knowledge, this appears to be the first example of ring closing enyne metathesis in the context of a total synthesis of a cyclooctanoid containing natural product.

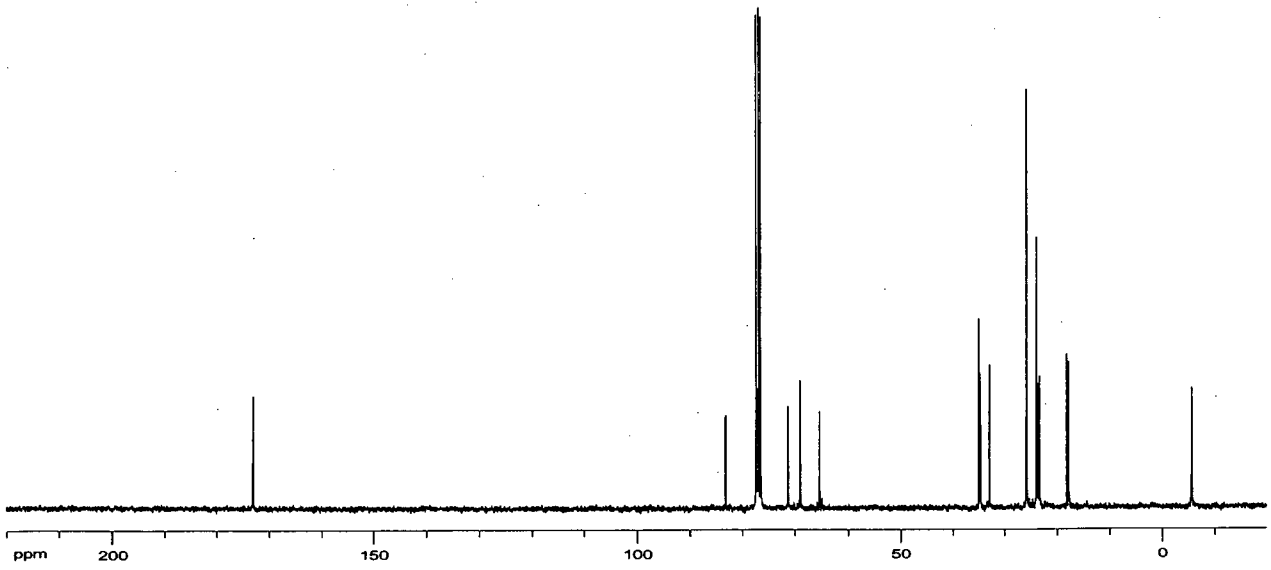
It is the hope of the author that the details of the scientific research intailed in this thesis will facilitate further development of the cross-coupling of vinylmagnesium reagents with alkyl electrophiles as well as the synthetic access to natural products of the fusicoccane diterpenoid family.

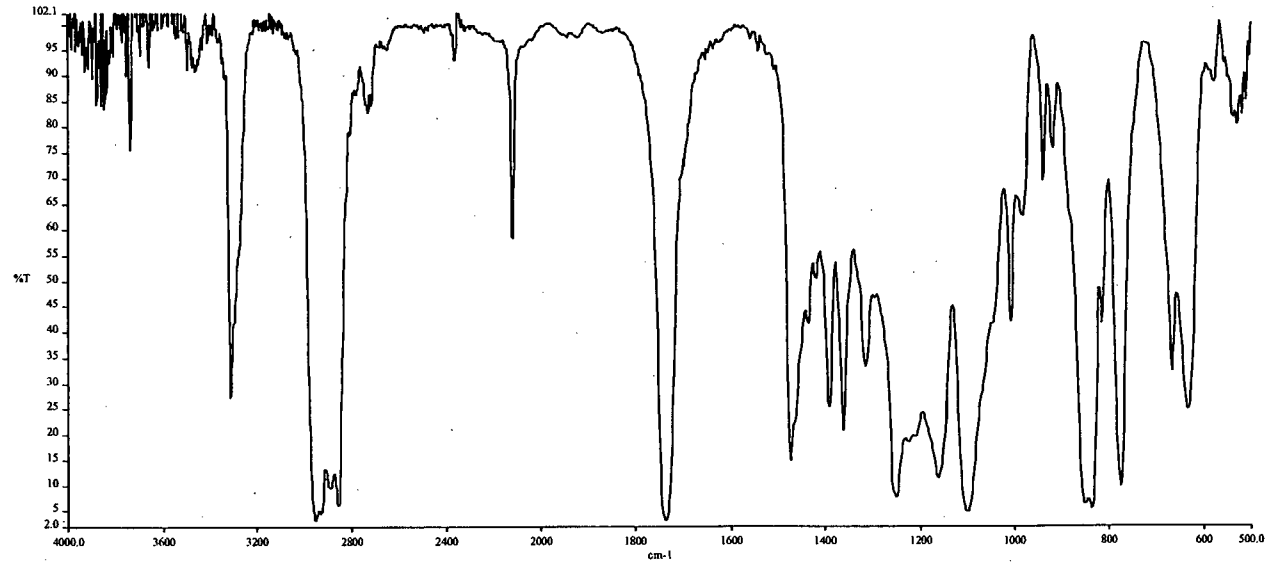
Appendix A

Selected Spectra for Chapter Two

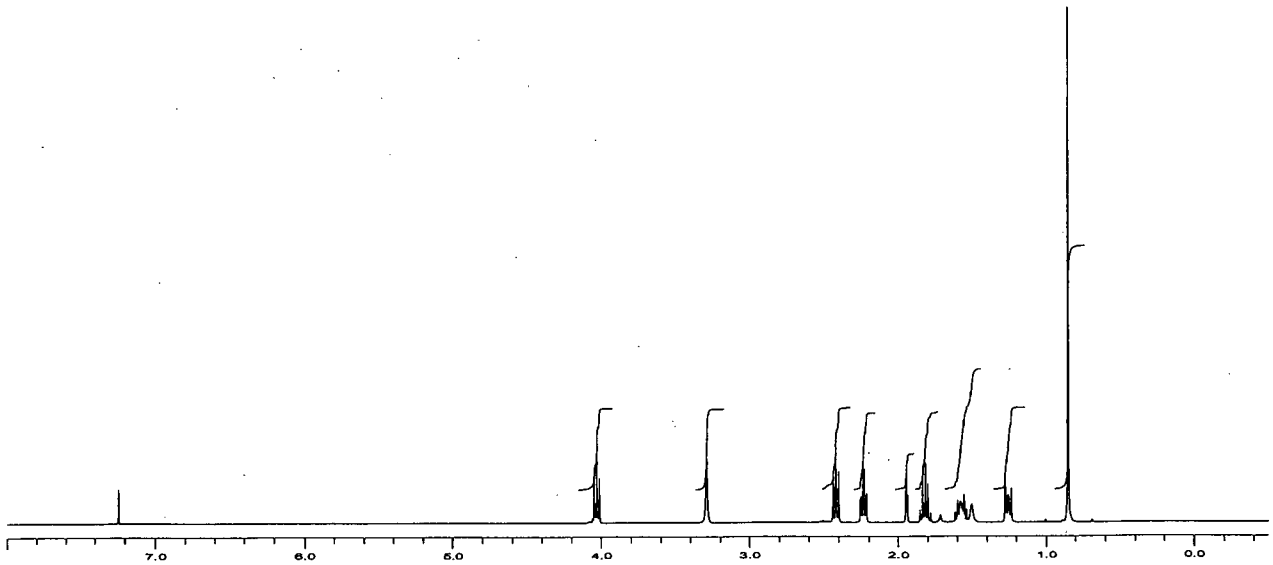
5-*tert*-Butyldimethylsiloxy-4,4-dimethylpentyl-5'-hexynoate (**2.8**)

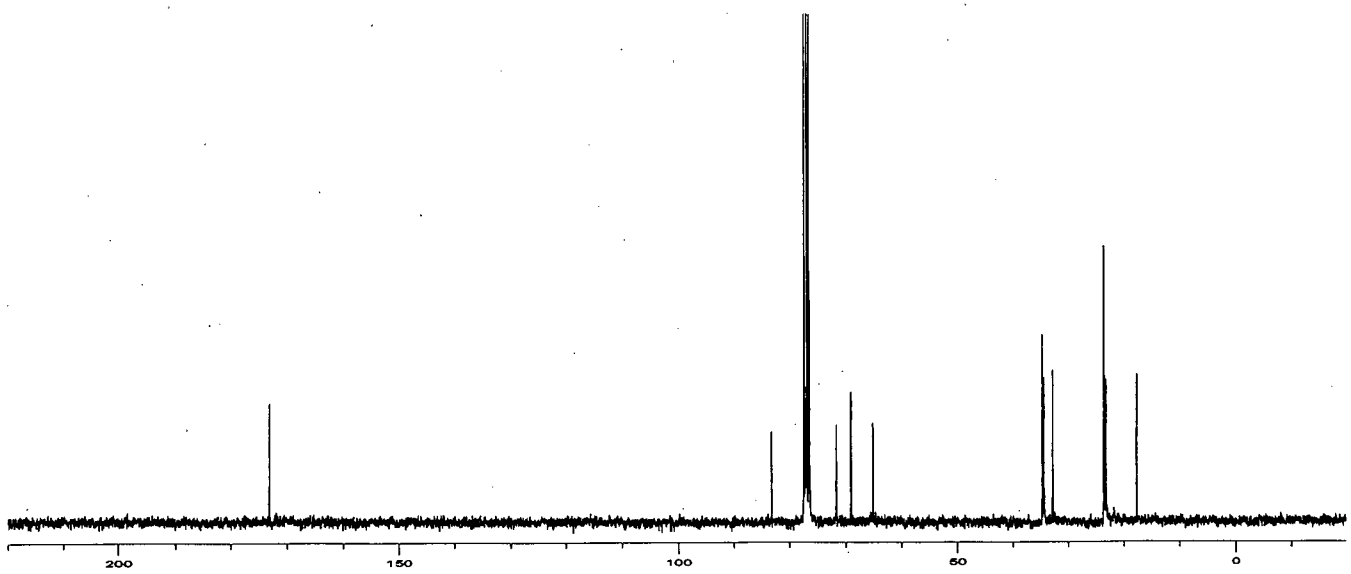


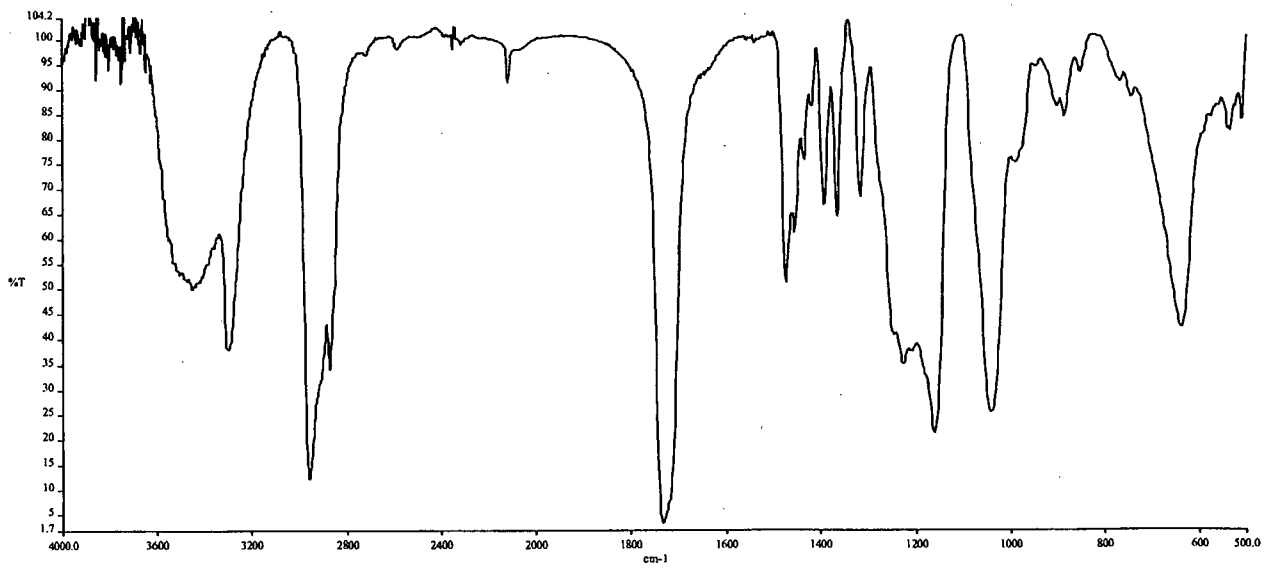




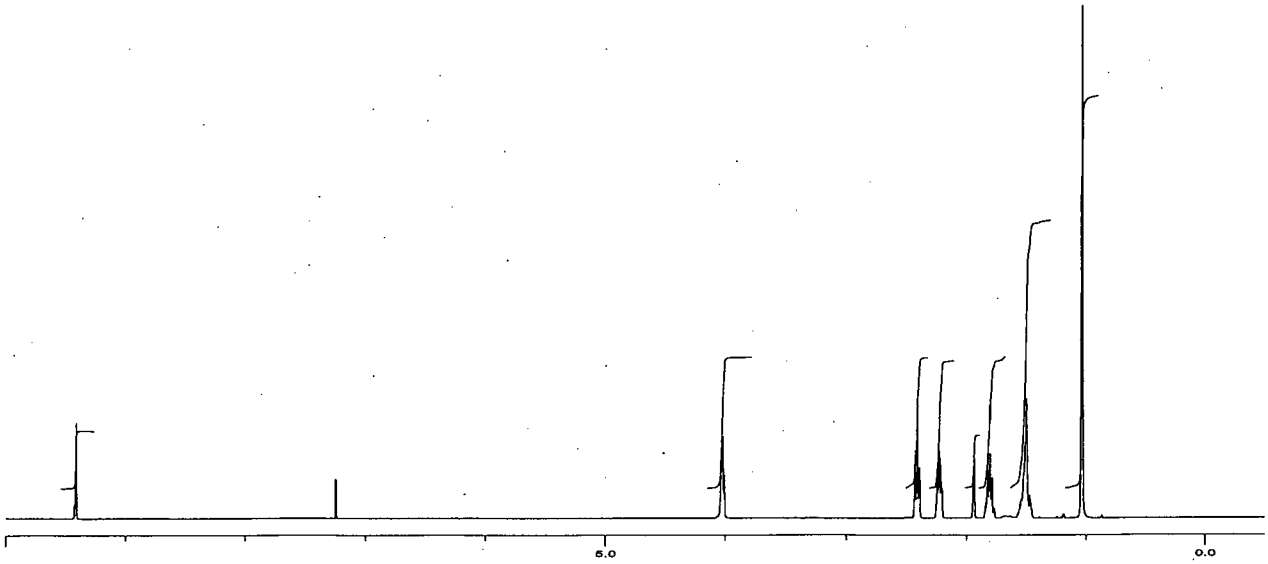
4,4-Dimethyl-5-hydroxypentyl-5'-hexynoate (**2.9**)

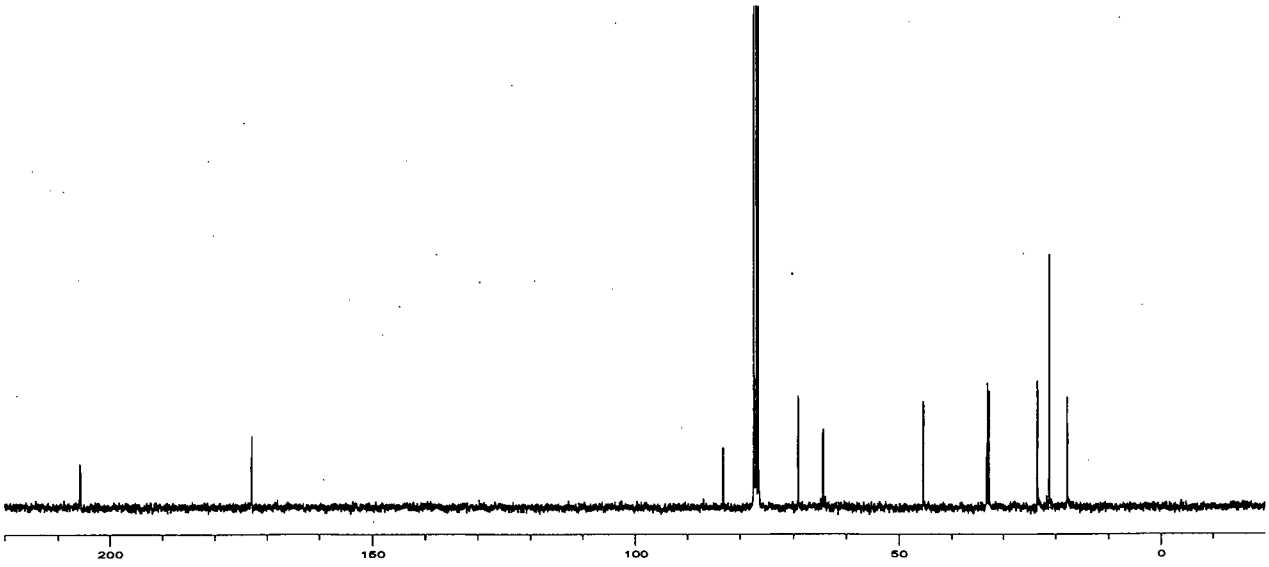


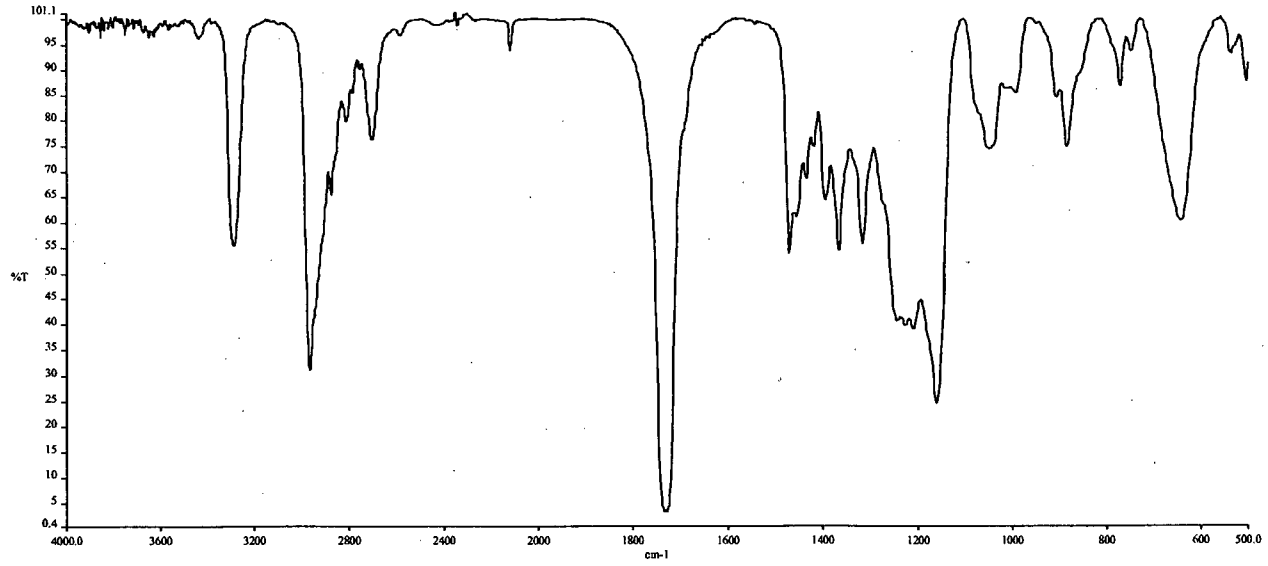




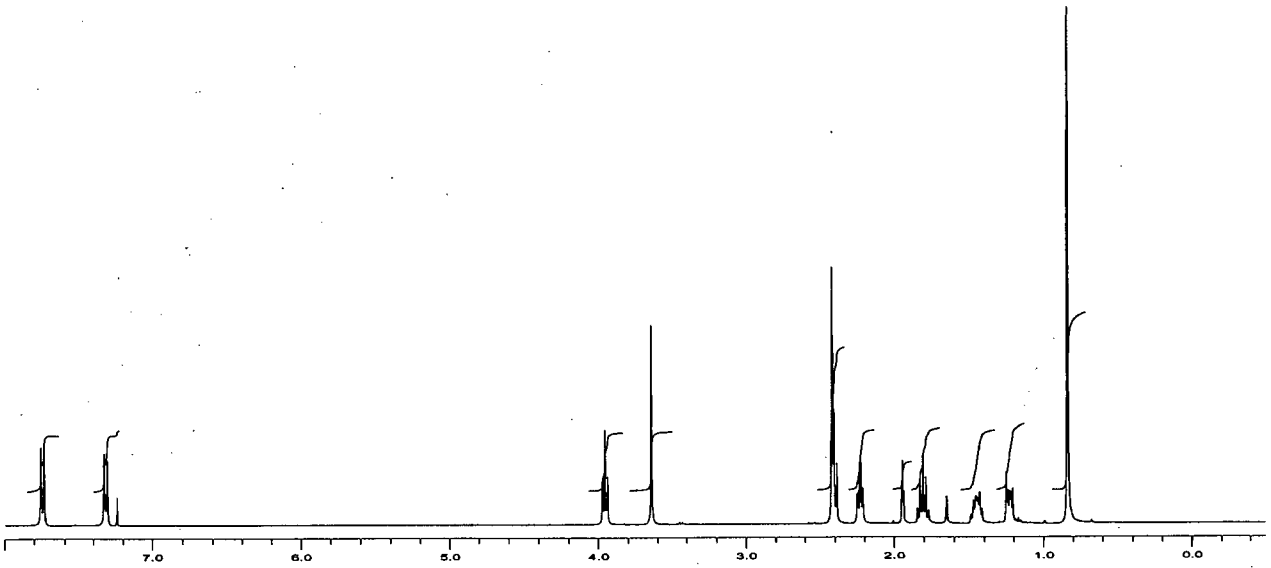
4,4-Dimethyl-5-oxopentyl-5'-hexynoate (**2.10**)

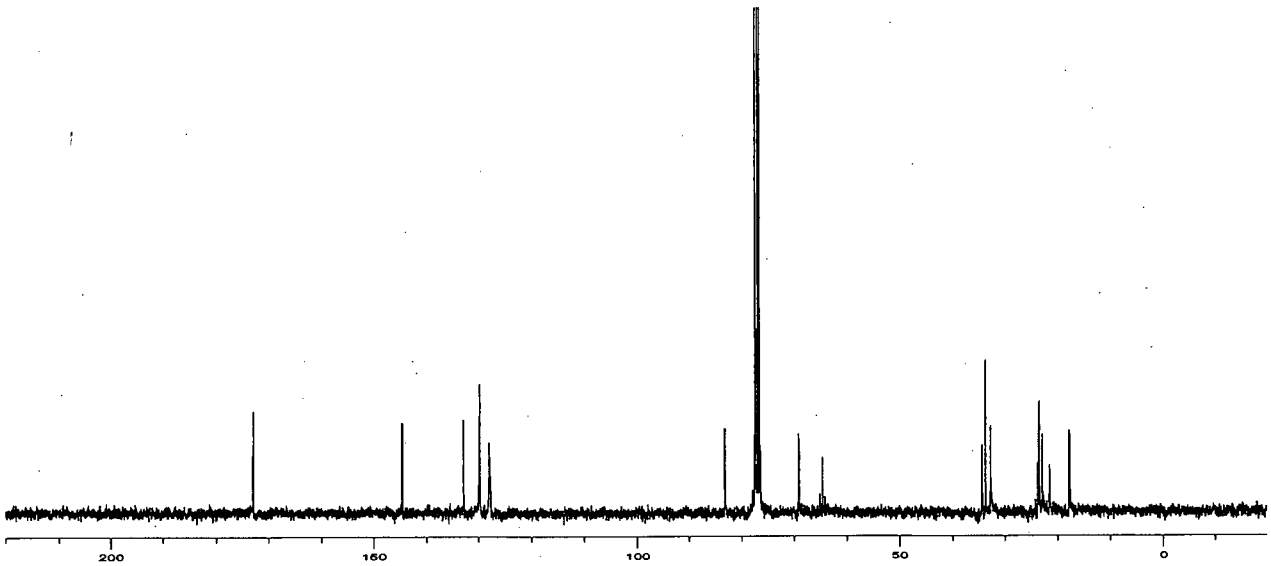


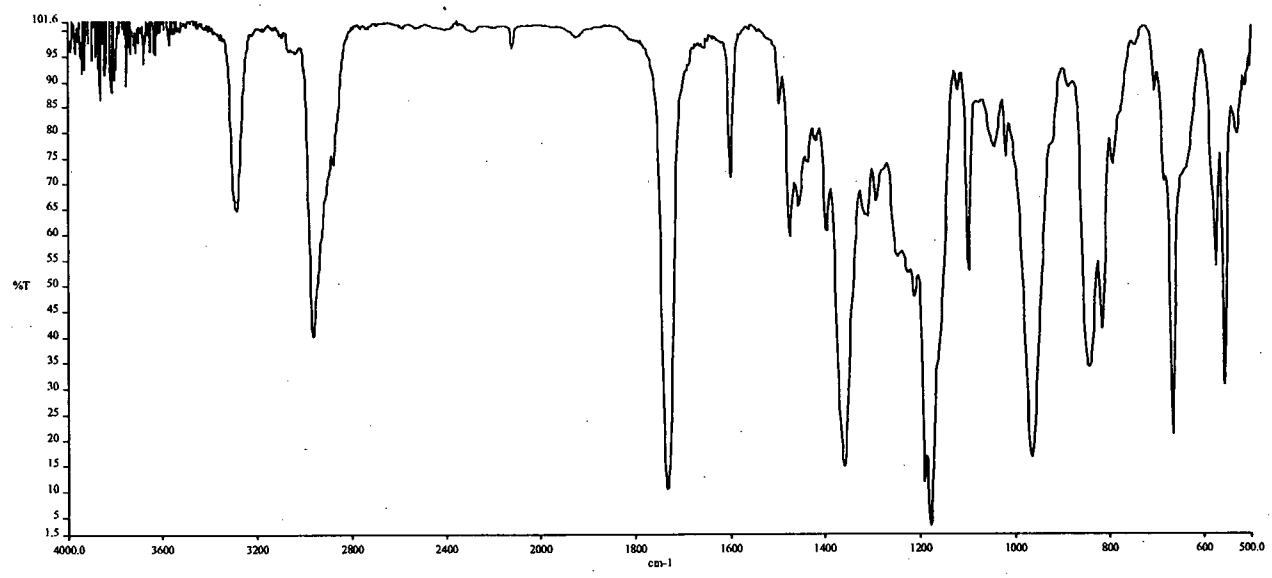




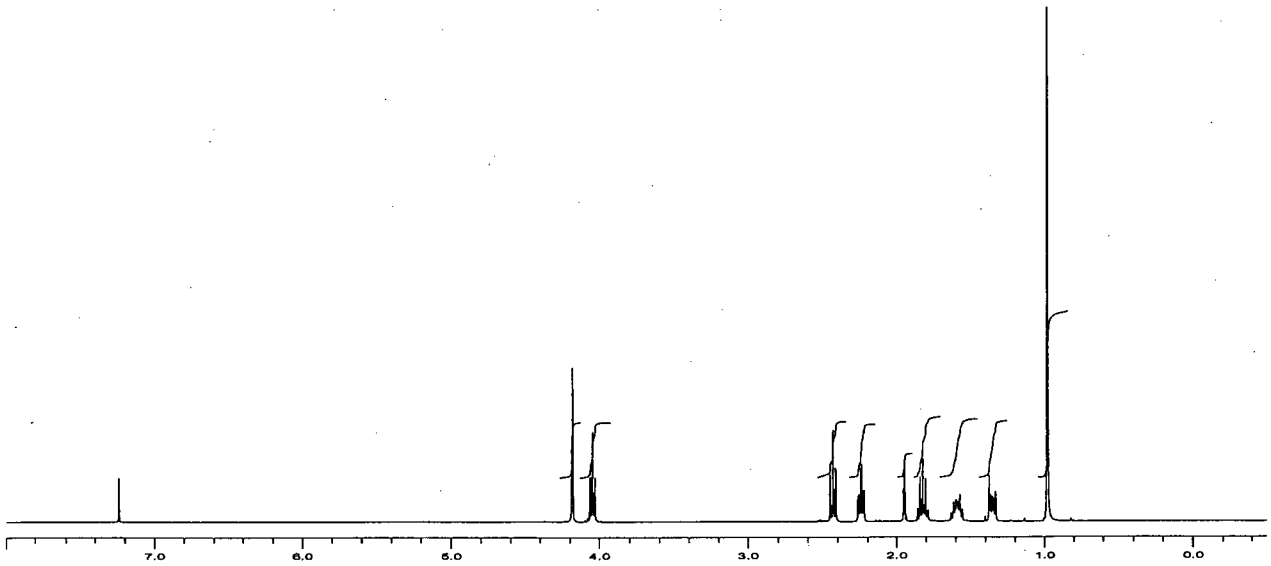
4,4-Dimethyl-5-(*p*-toluenesulfonate)hexanyl-5'-hexynoate (**2.11**)

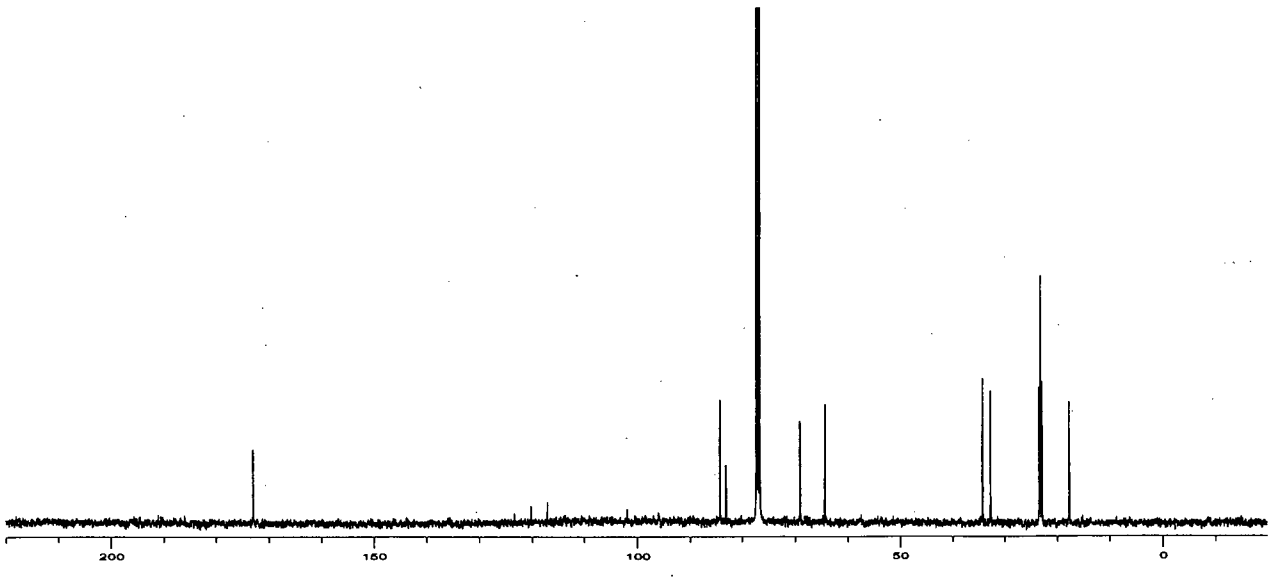


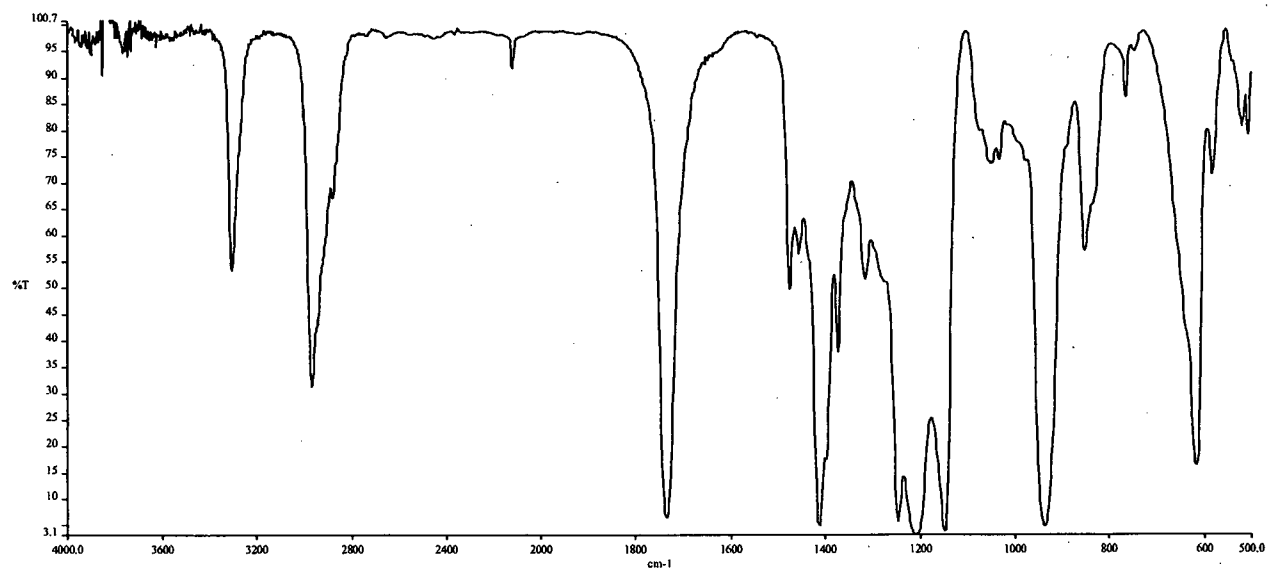




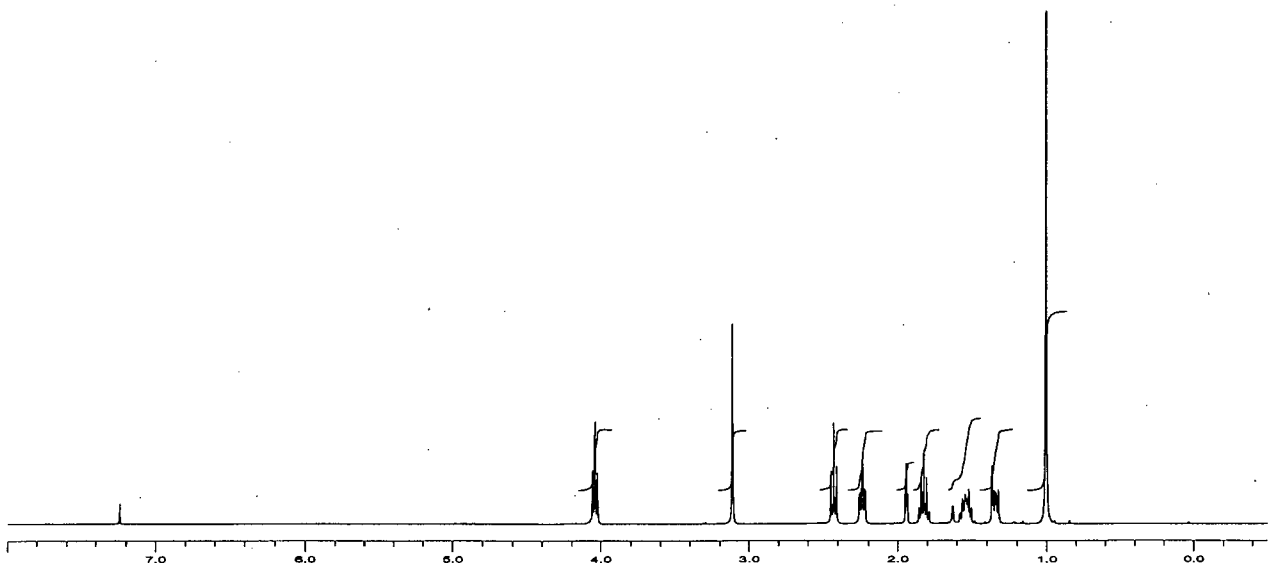
4,4-Dimethyl-5-(trifluoromethanesulfonate)hexanyl-5'-hexynoate (**2.12**)

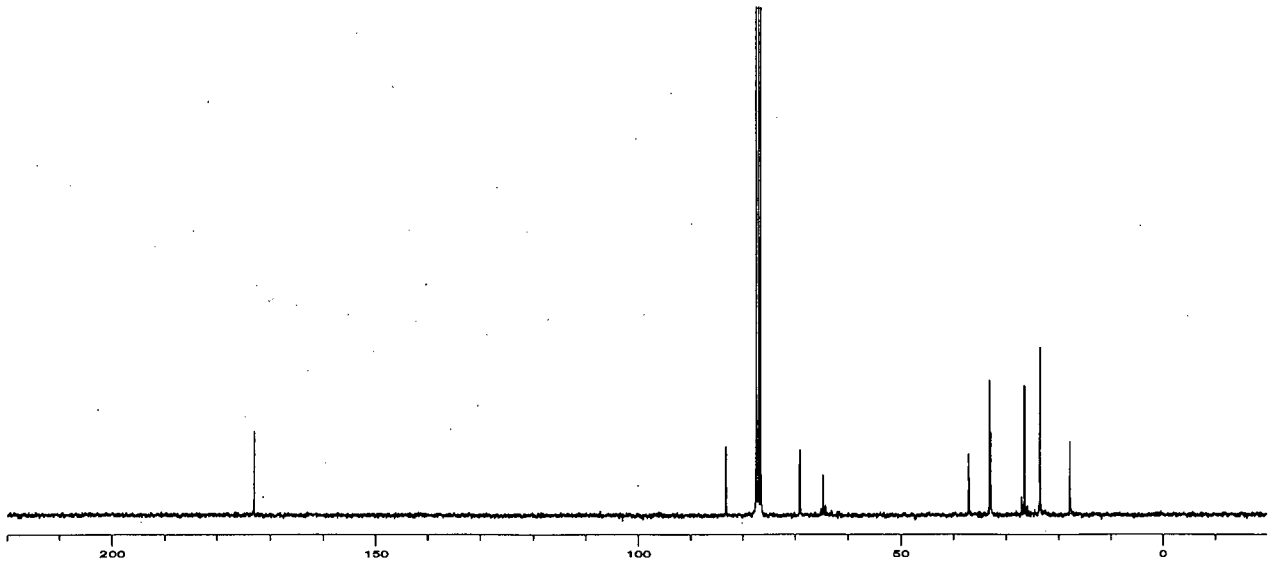


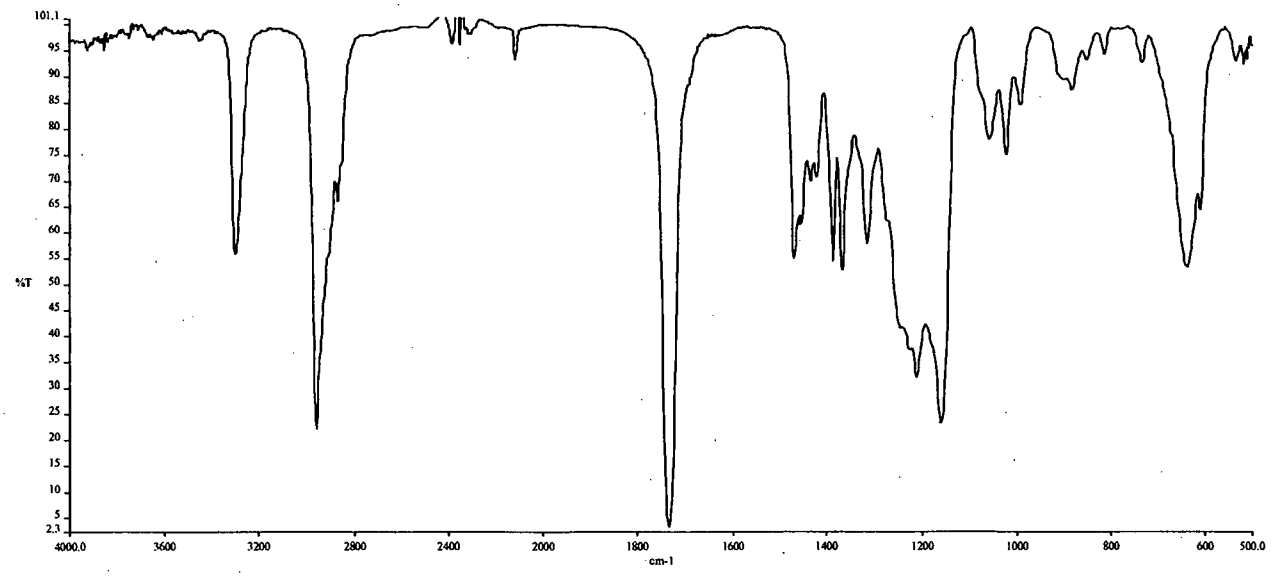




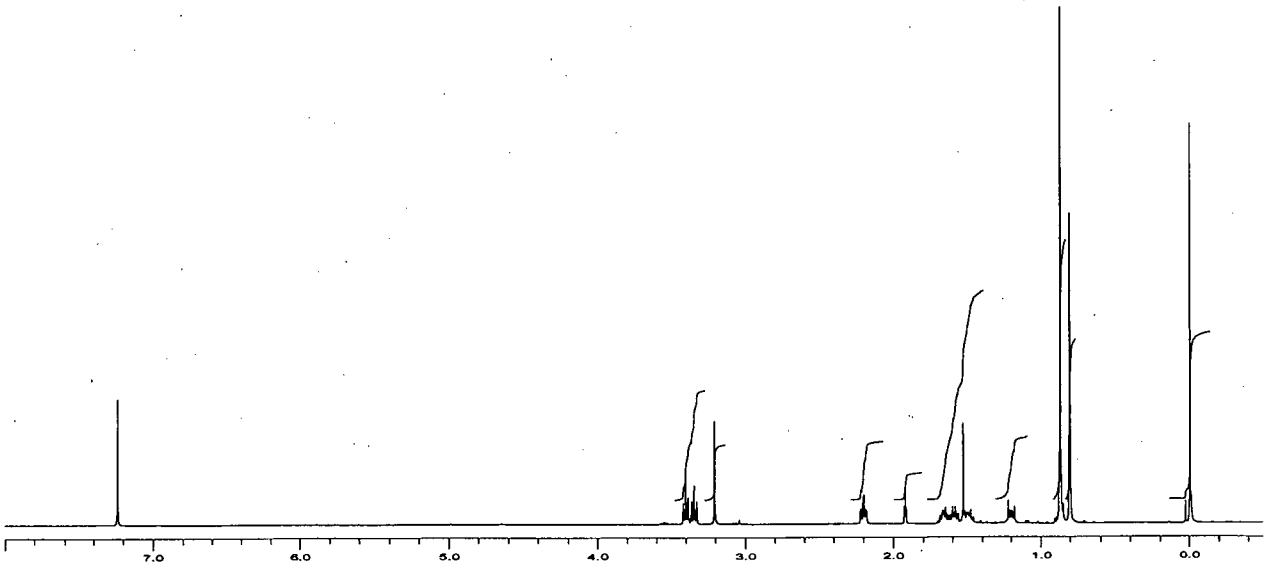
4,4-Dimethyl-5-iodohexanyl-5'-hexynoate (**2.13**)

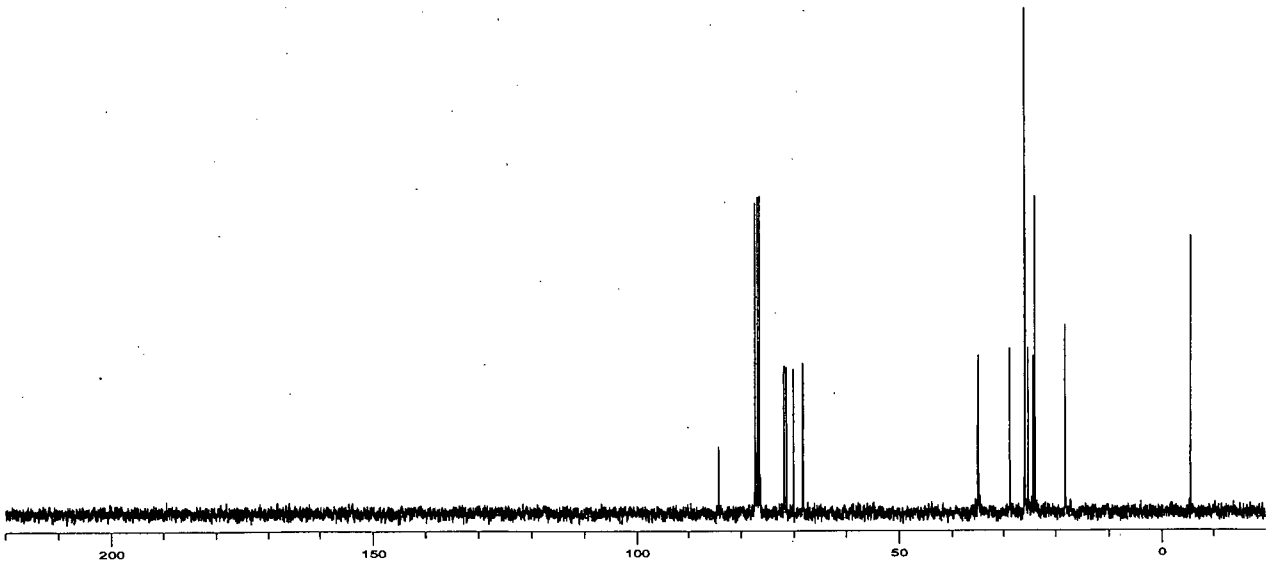


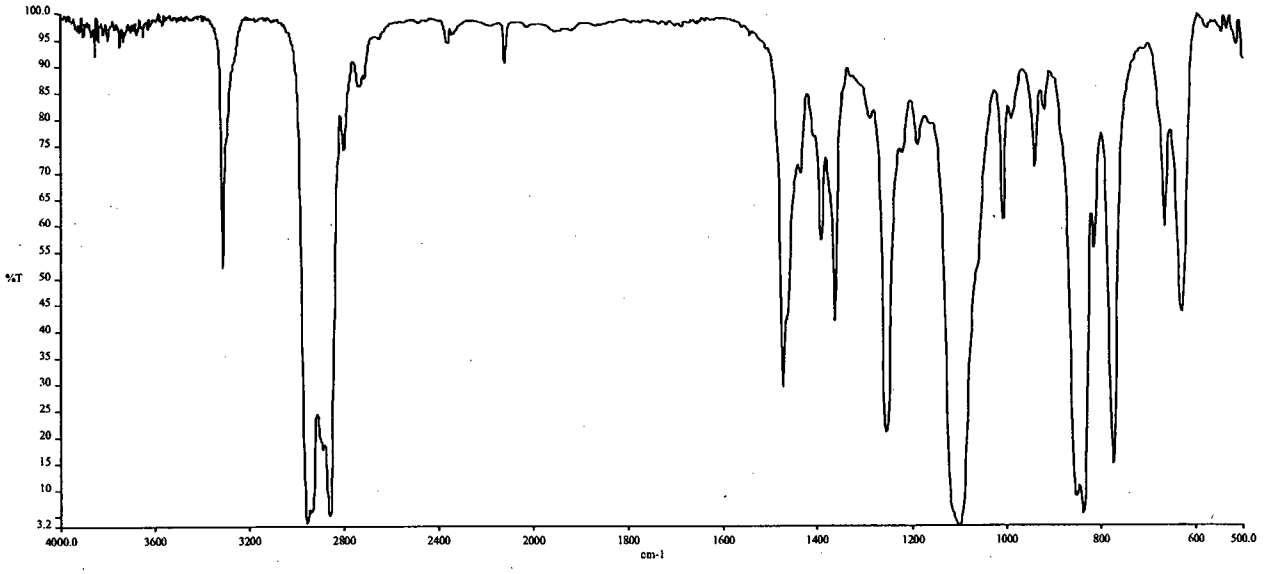




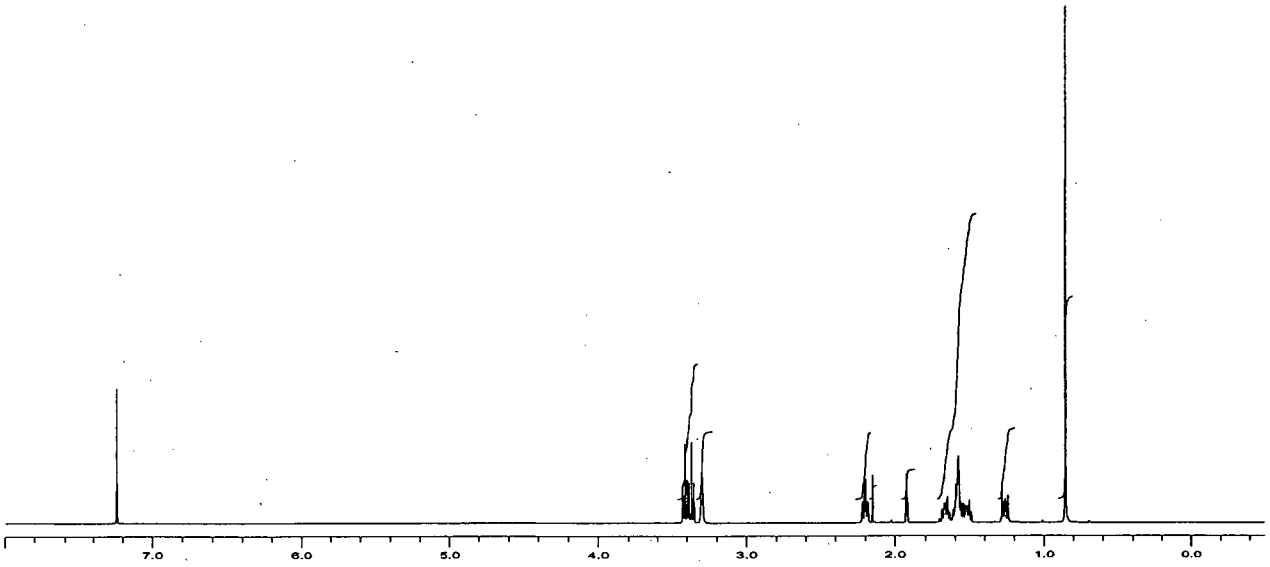
5-*tert*-Butyldimethylsiloxy-4,4-dimethylpentanylhex-5'-ynyl ether (**2.15**)

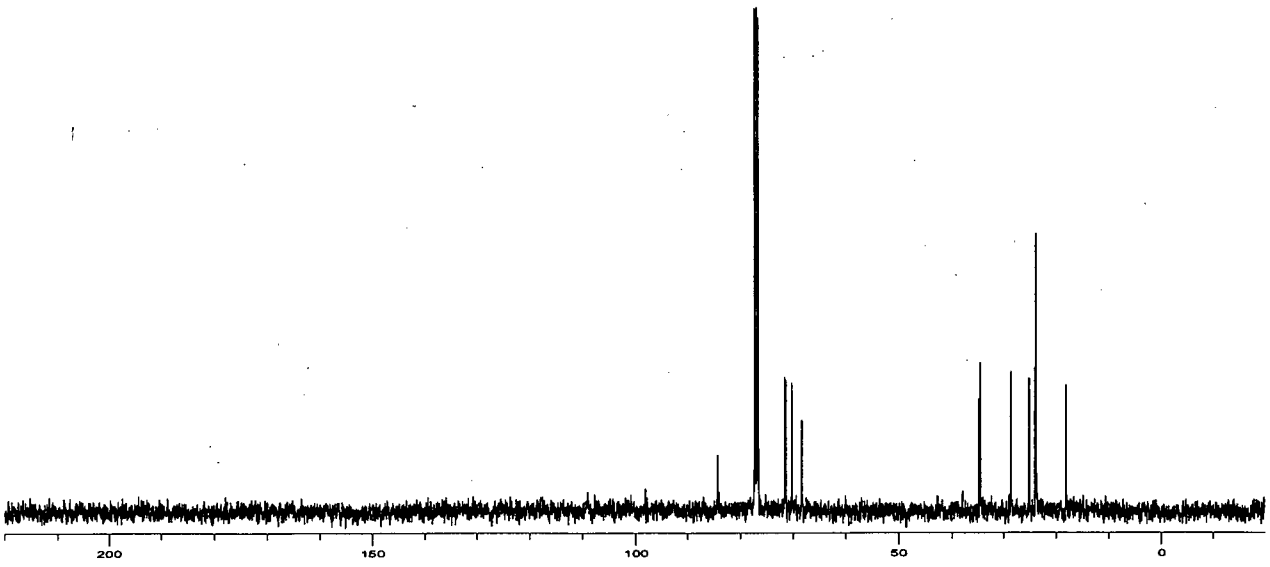


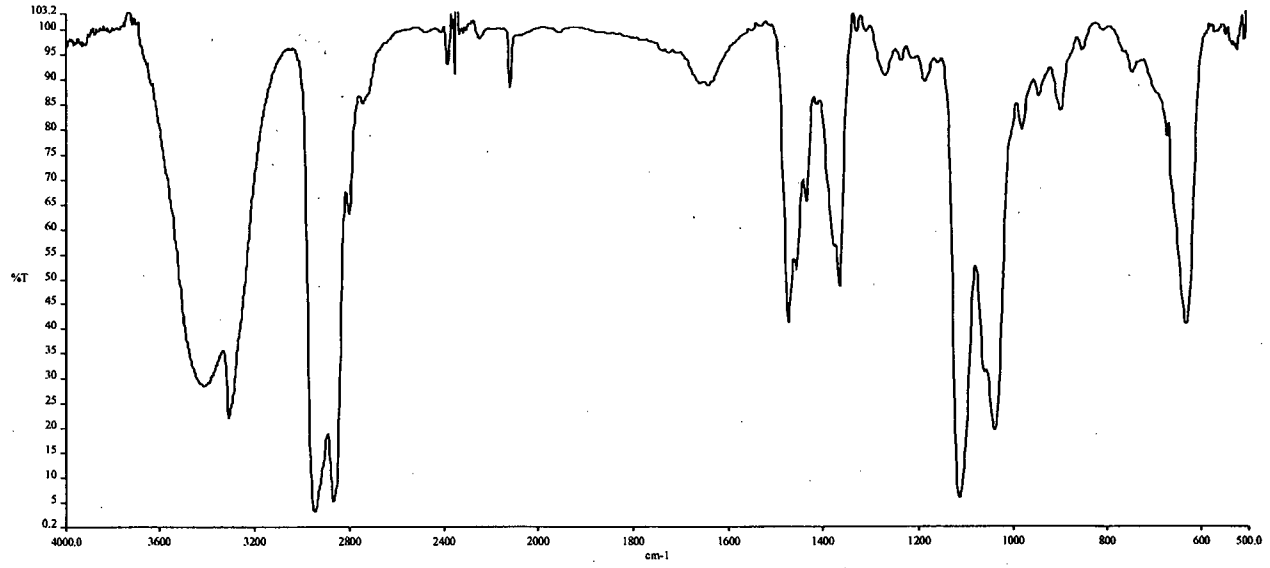




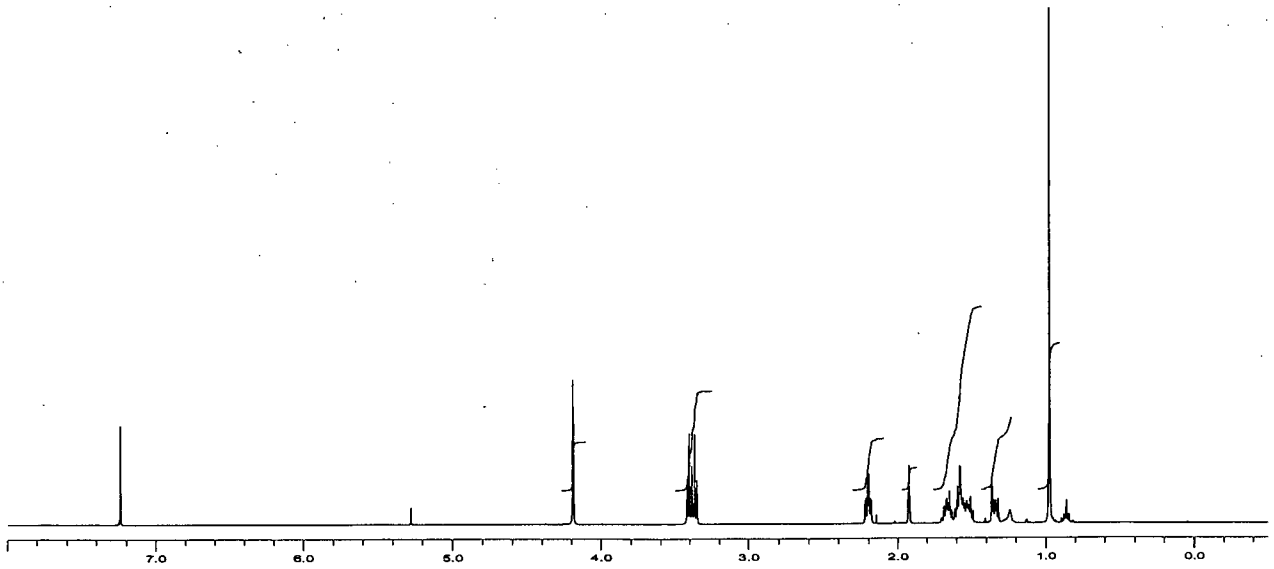
4,4-Dimethyl-5-hydroxypentylhex-5'-ynyl ether (**2.16**)

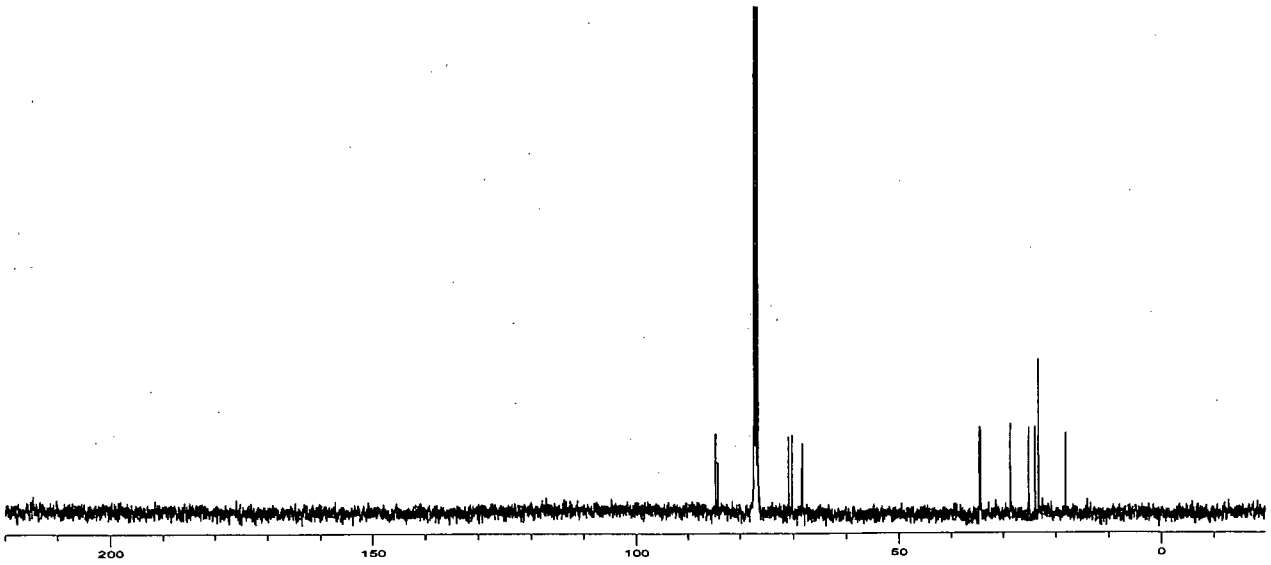


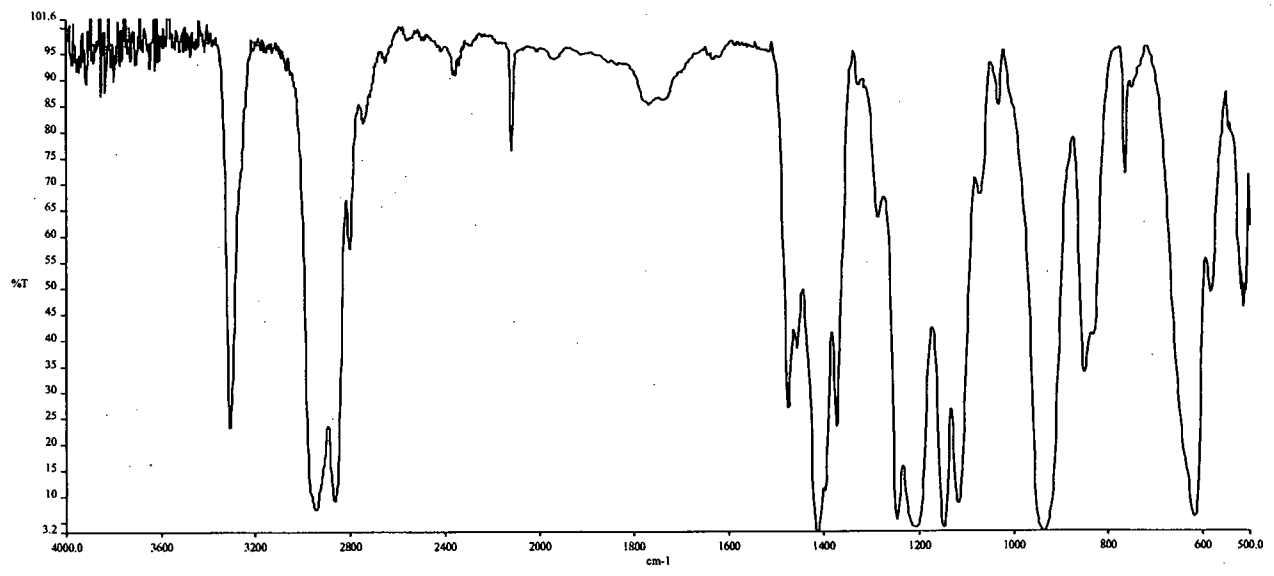




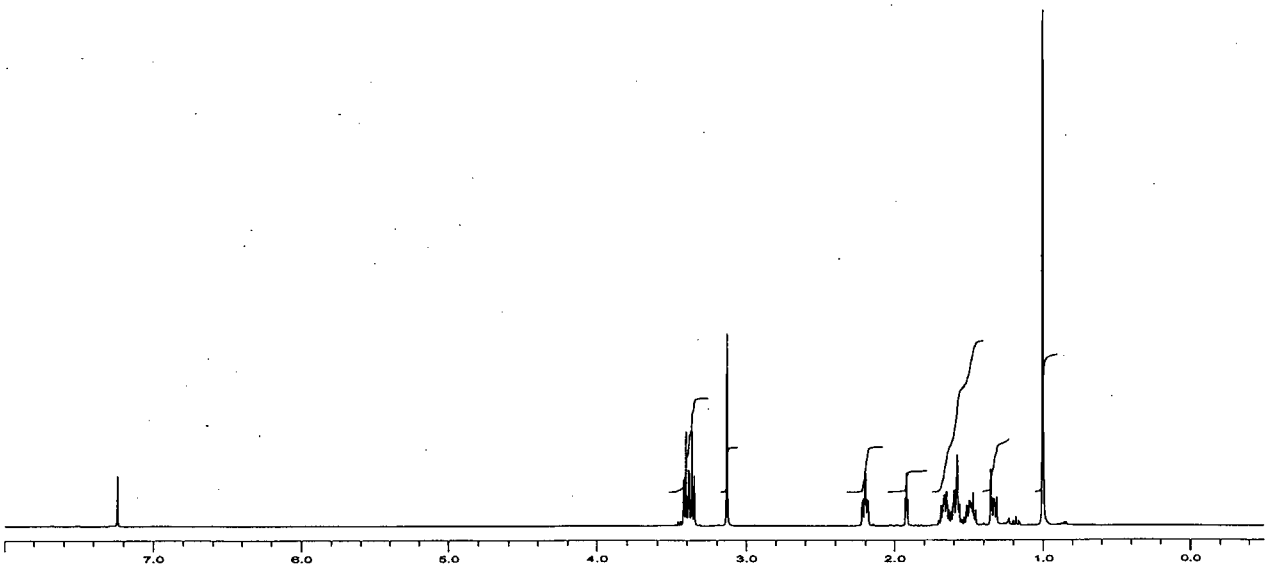
4,4-Dimethyl-5-(trifluoromethanesulfonate)pentanylhex-5'-ynyl ether (**2.17**)

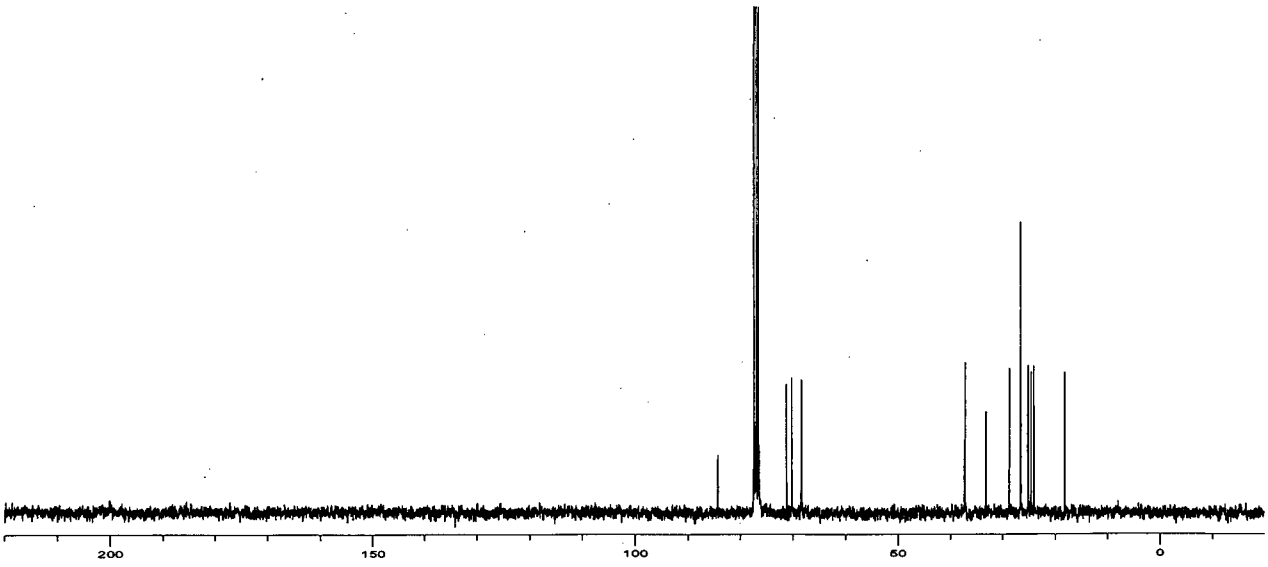


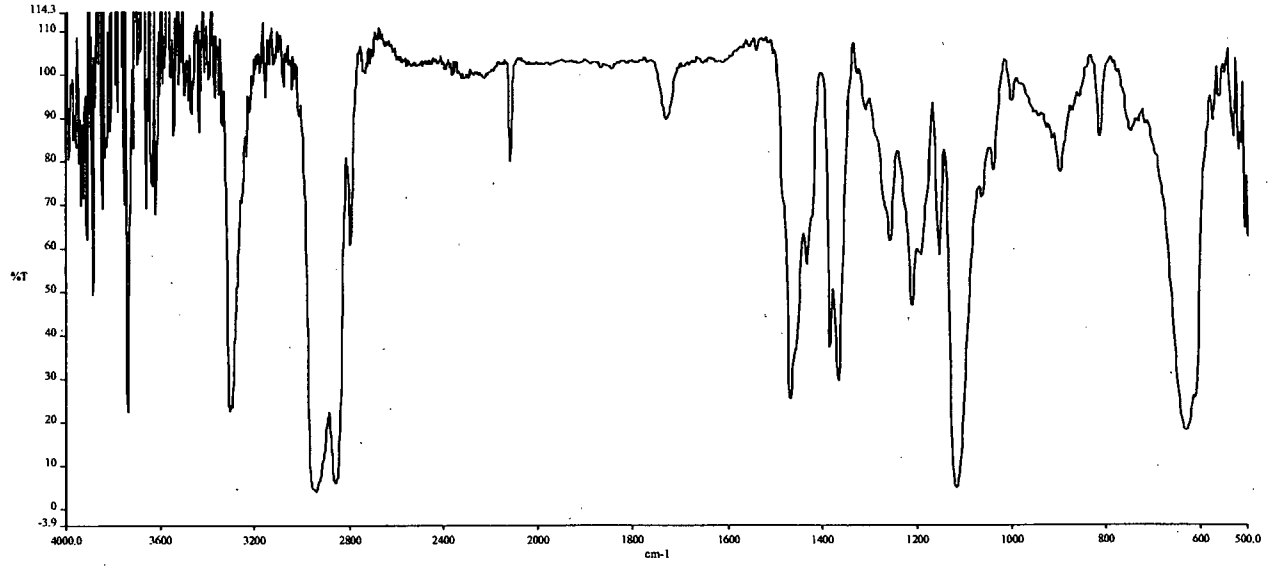




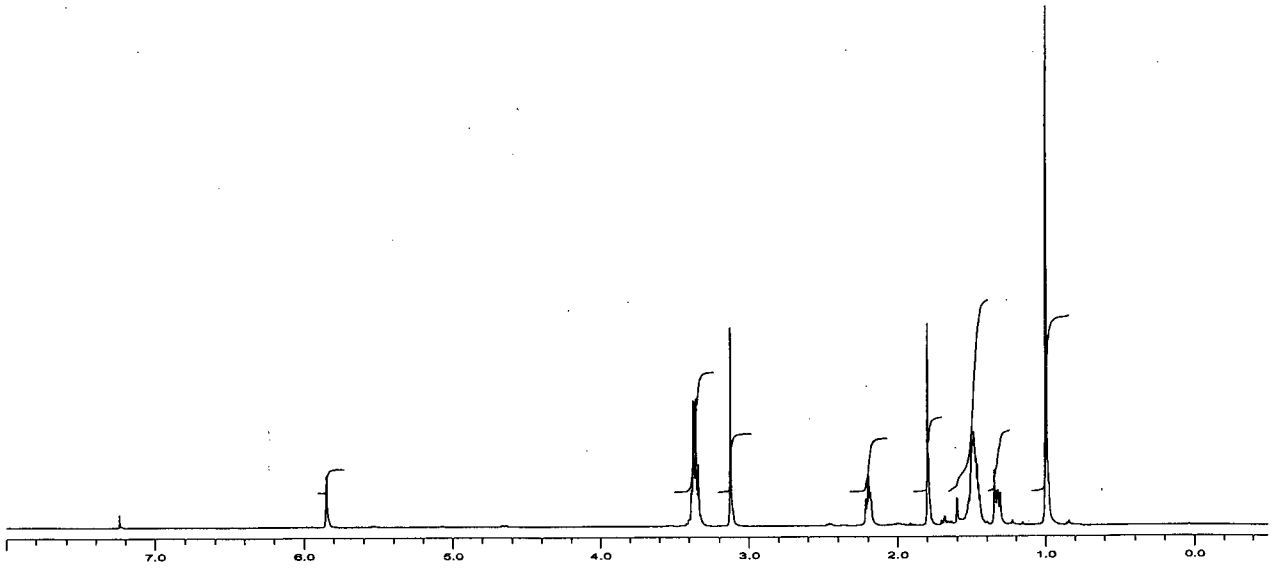
4,4-Dimethyl-5-iodopentanylhex-5-ynyl ether (**2.18**)

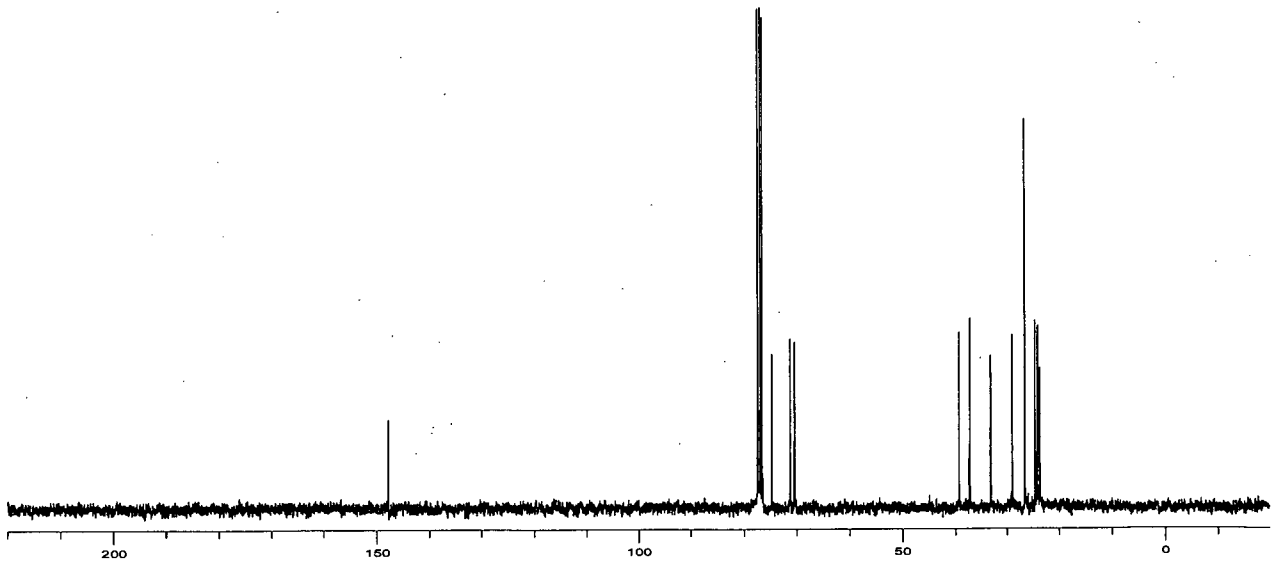


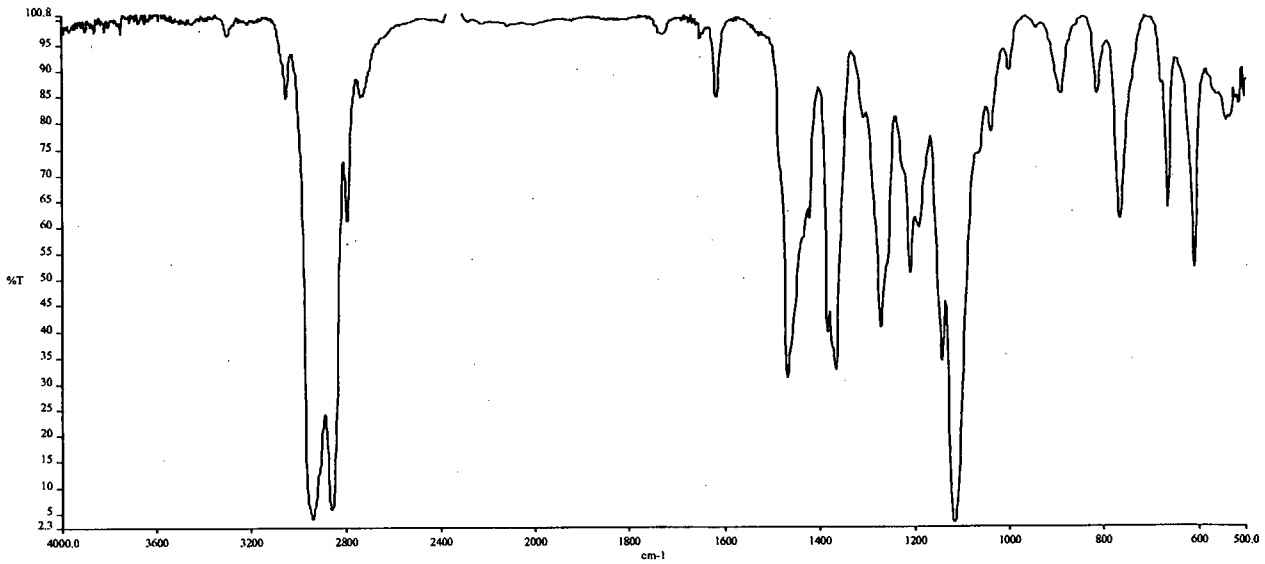




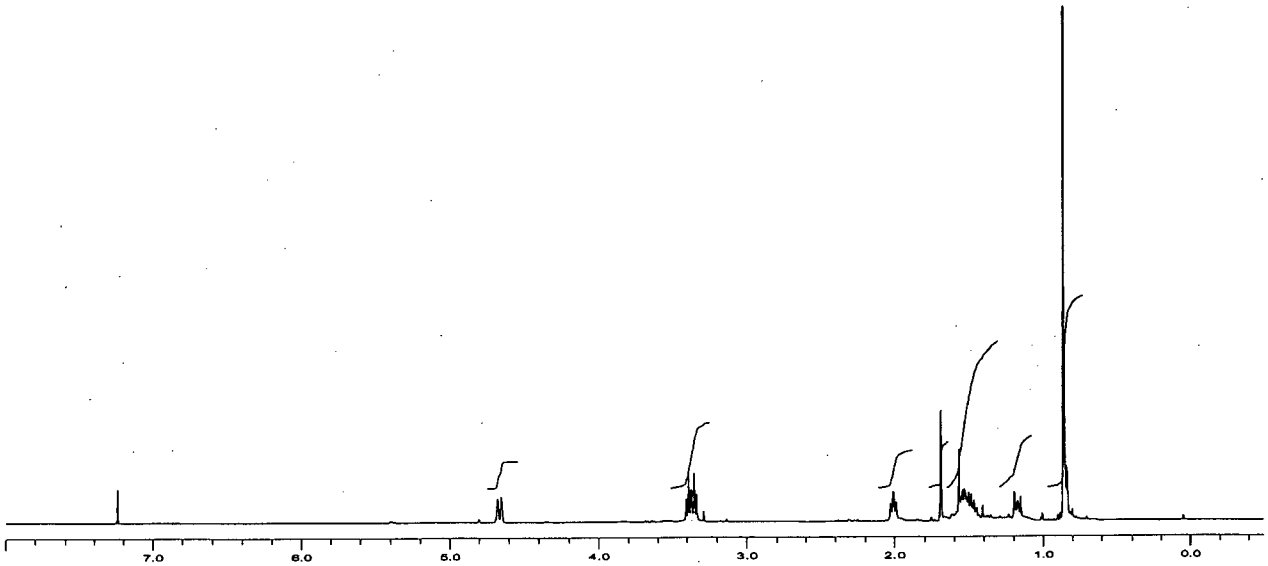
(*E*)-4,4-Dimethyl-5-iodopentanyl-6'-iodo-5'-methylhex-5'-enyl ether (**2.23**)

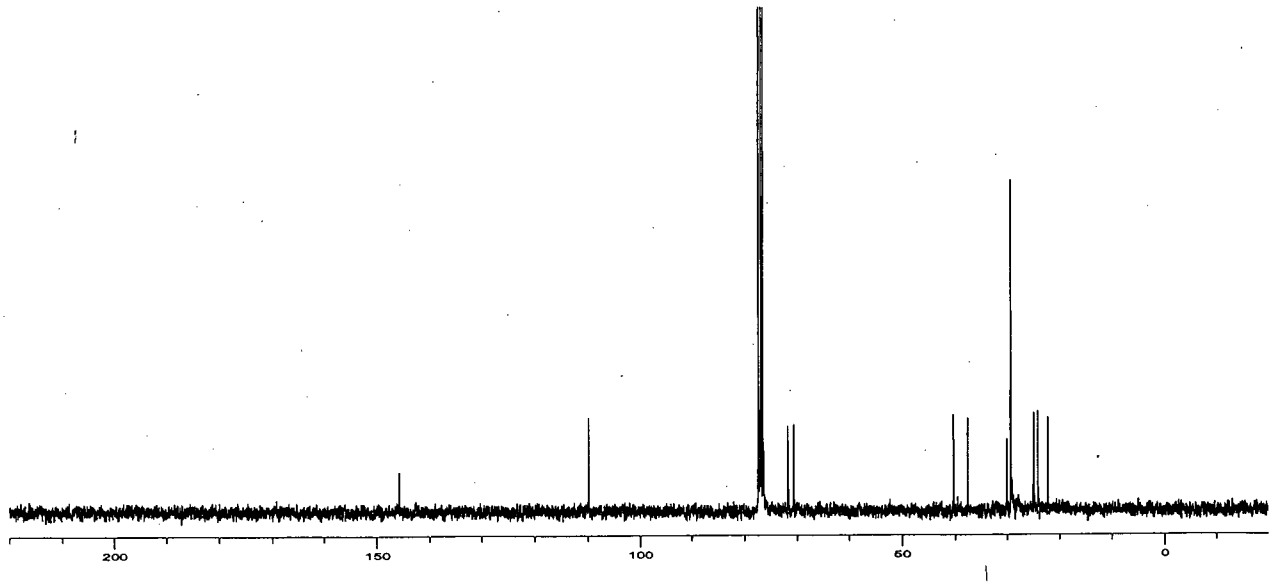


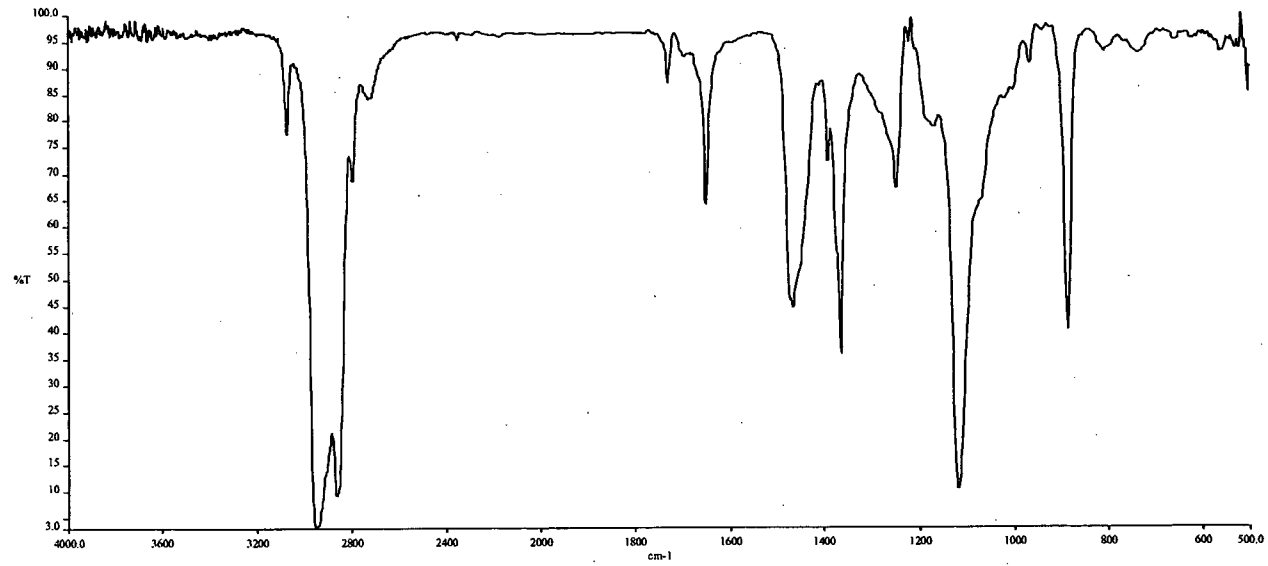




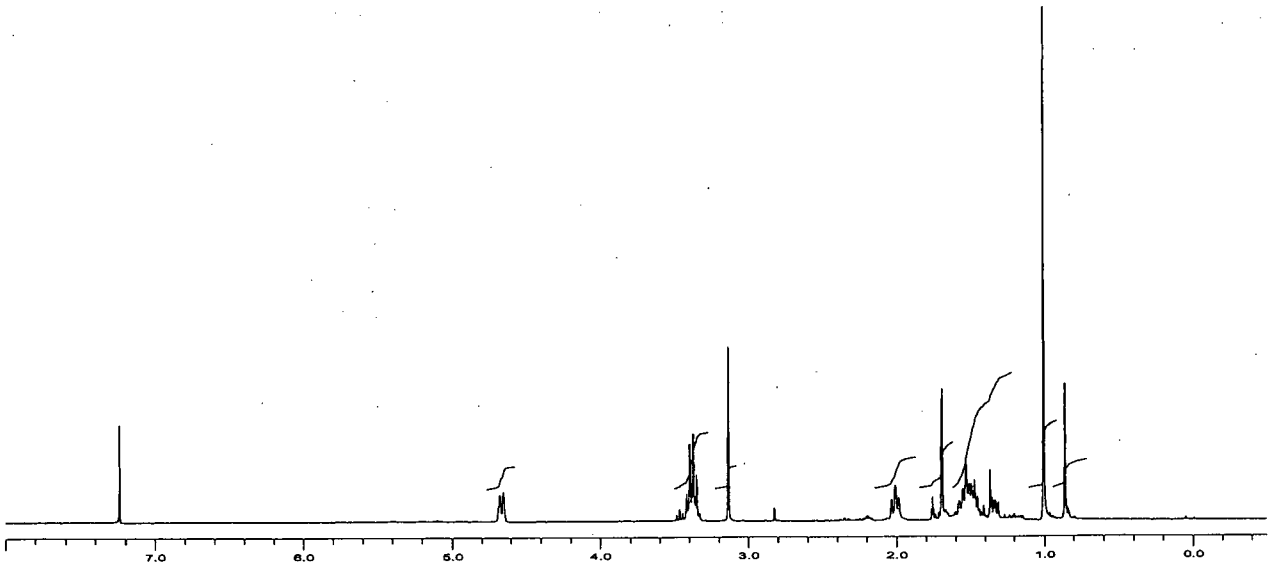
4,4-Dimethylpentanyl-5'-methylhex-5'-enyl ether (**2.24**)

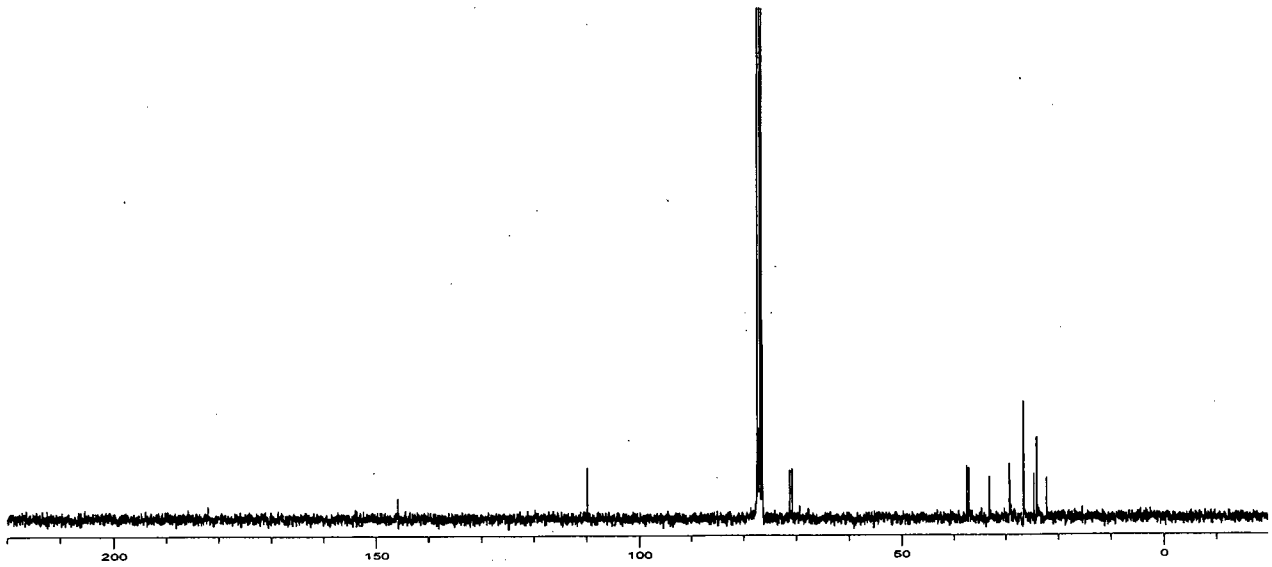


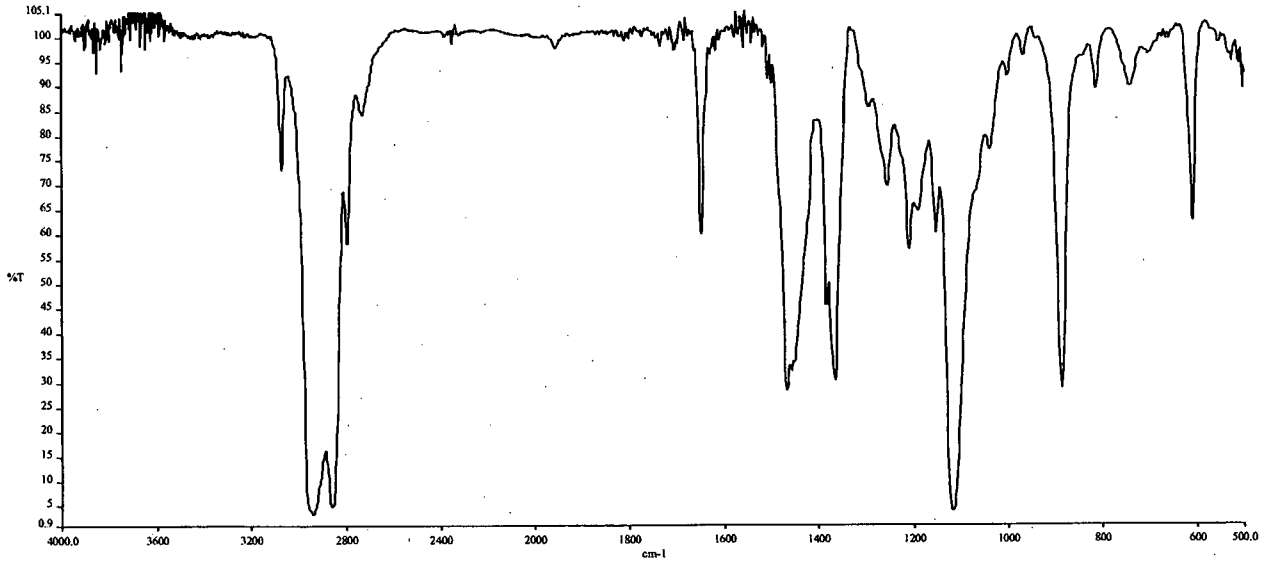




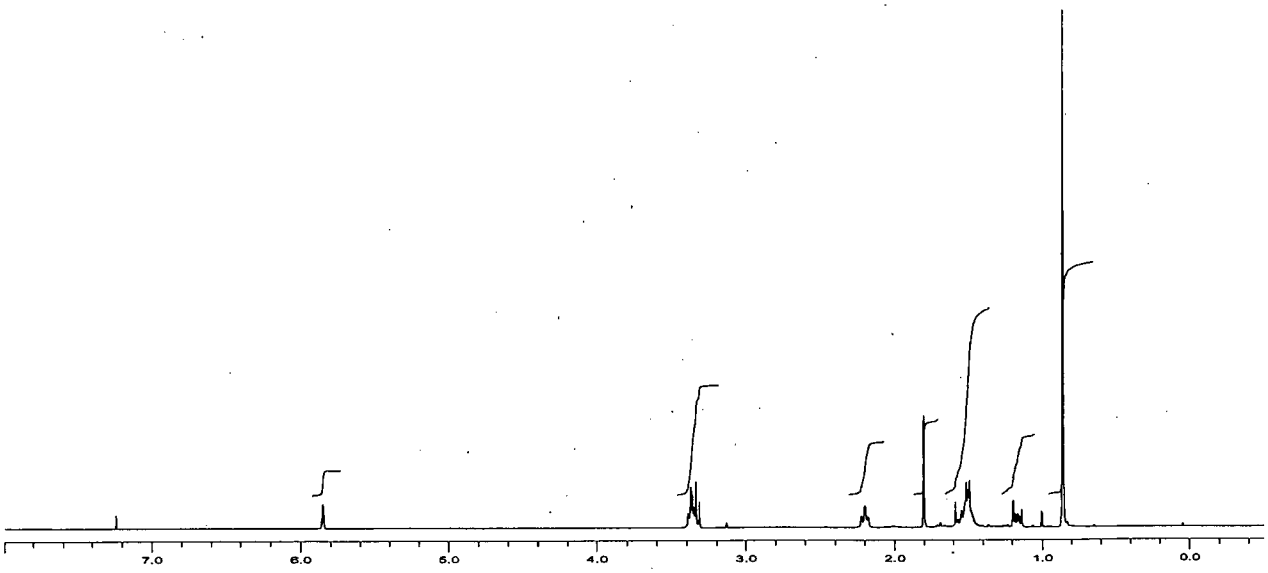
4,4-Dimethyl-5-iodopentanyl-5'-methylhex-5'-enyl ether (**2.25**)

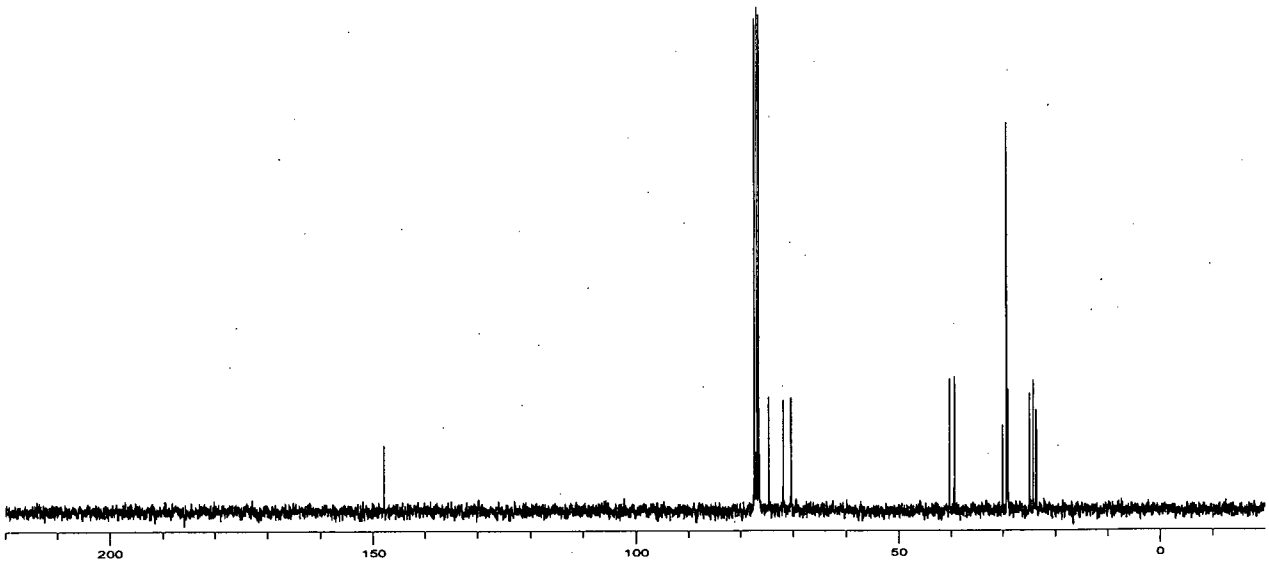


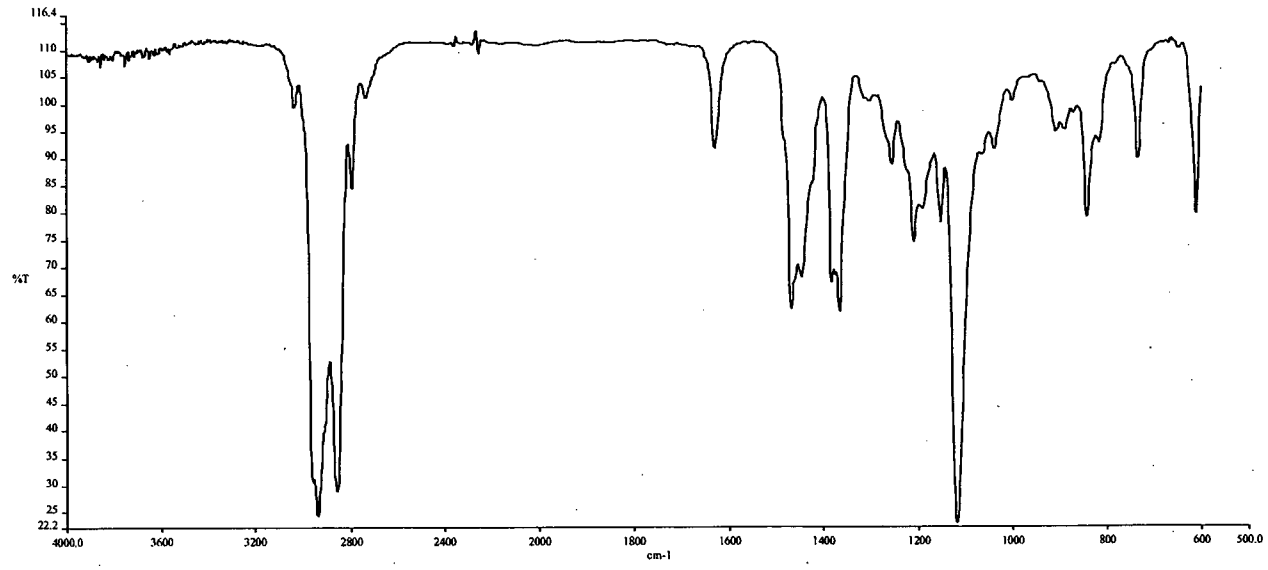




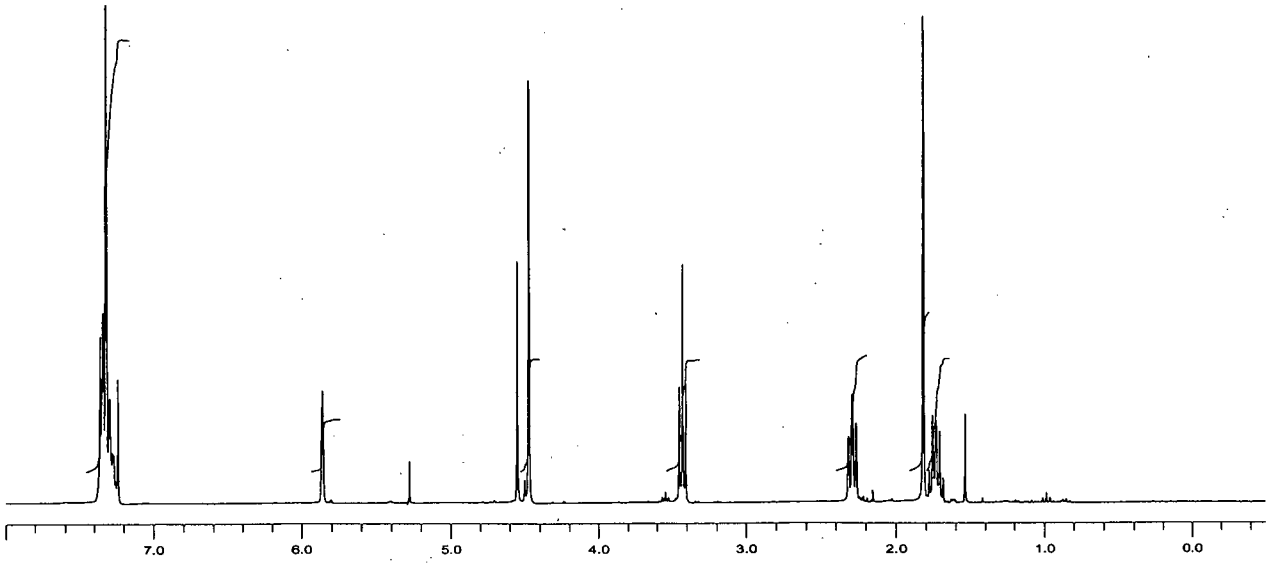
4,4-Dimethyl-5-iodopentanyl-6'-deutero-5'-methylhex-5'-enyl ether (**2.26**)

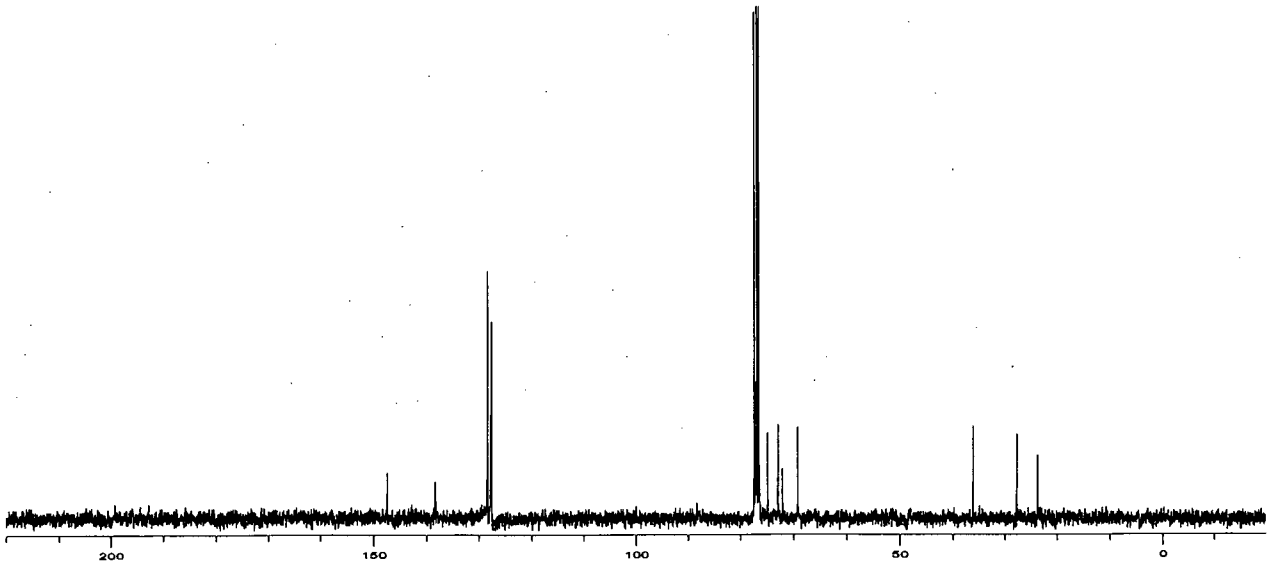


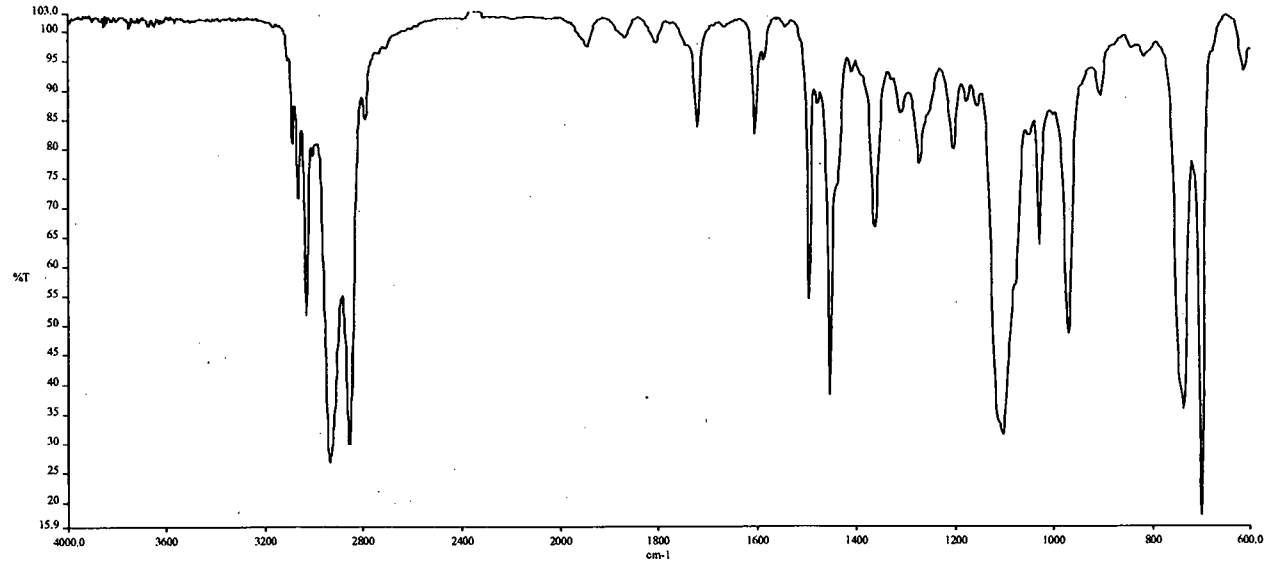




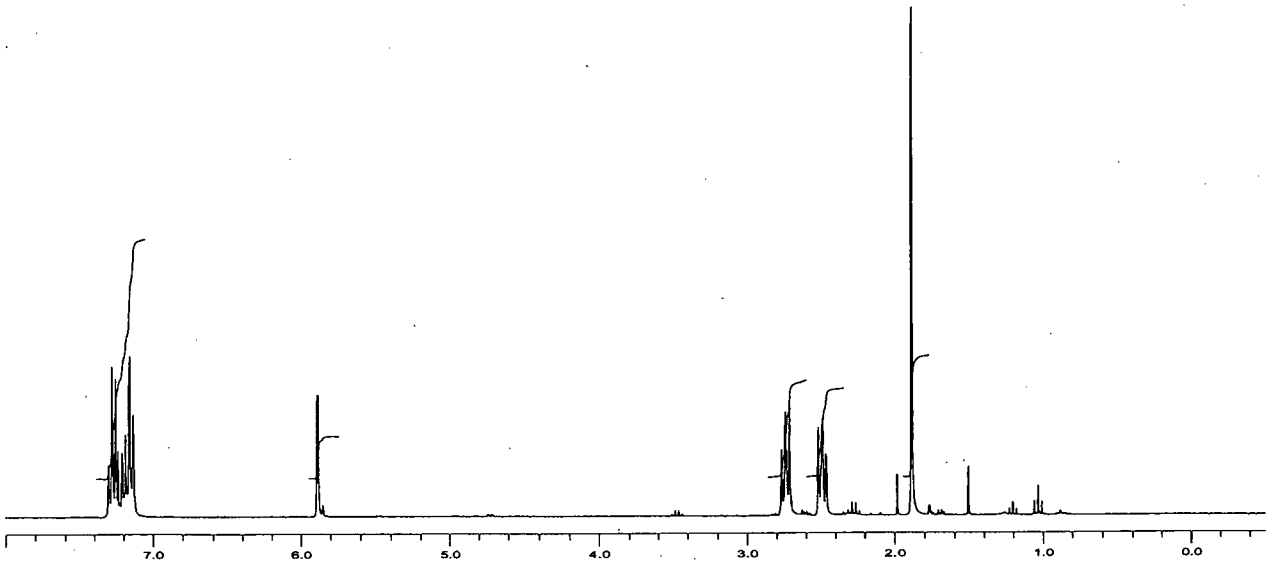
(*E*)-5-Benzyloxy-1-iodo-2-methylpent-1-ene (**2.31**)

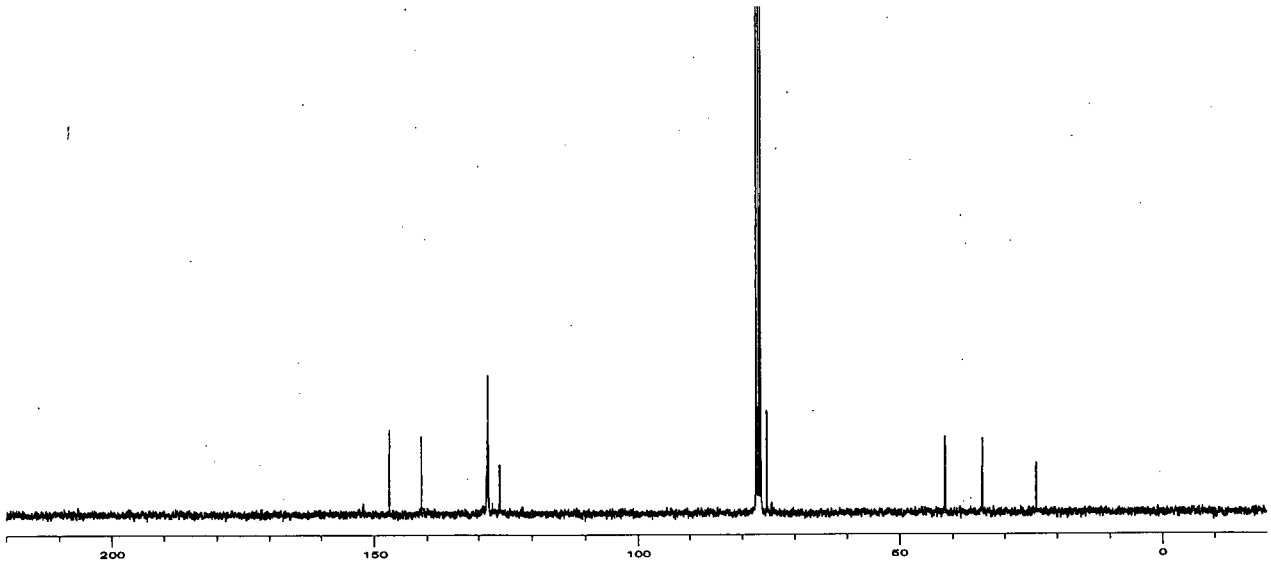


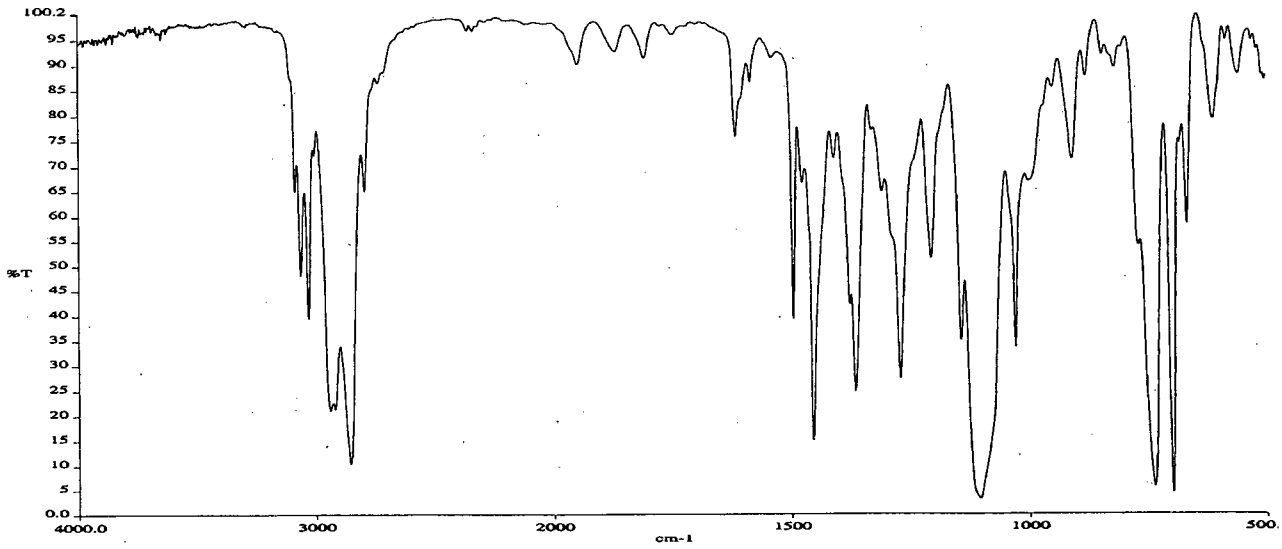




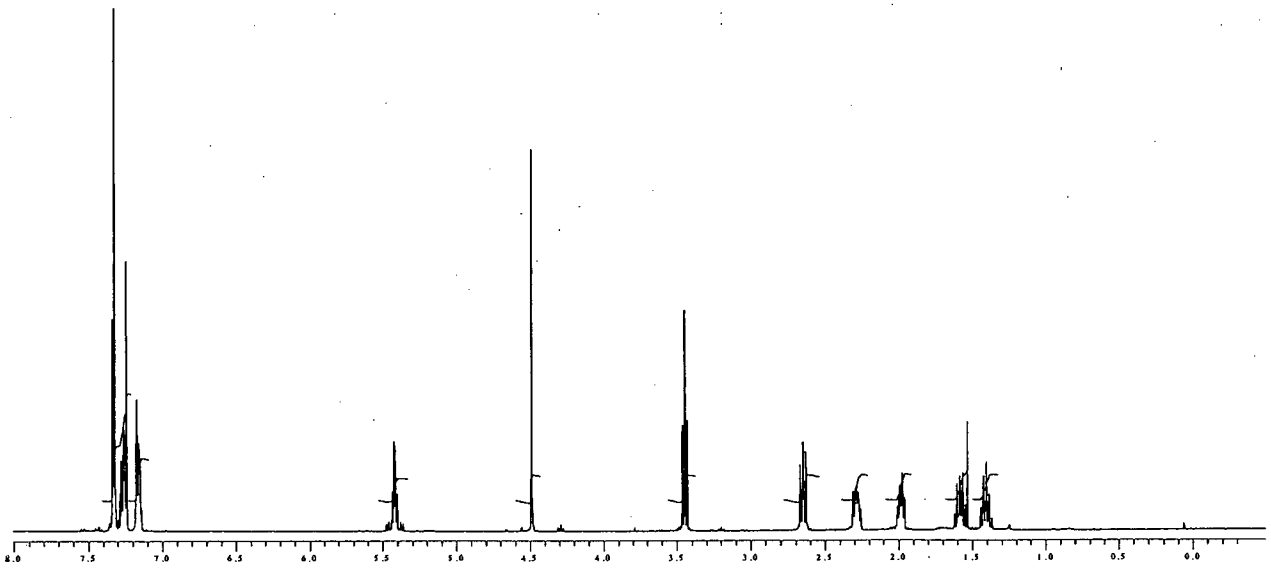
(*E*)-1-iodo-2-methyl-4-phenylbut-1-ene (**2.33**)

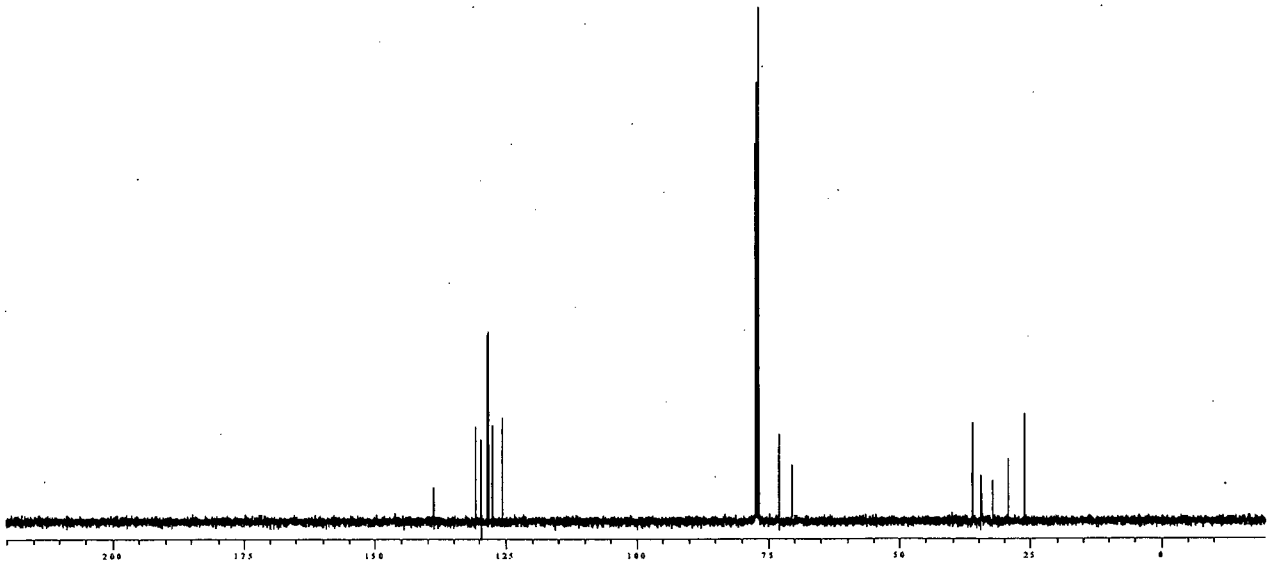


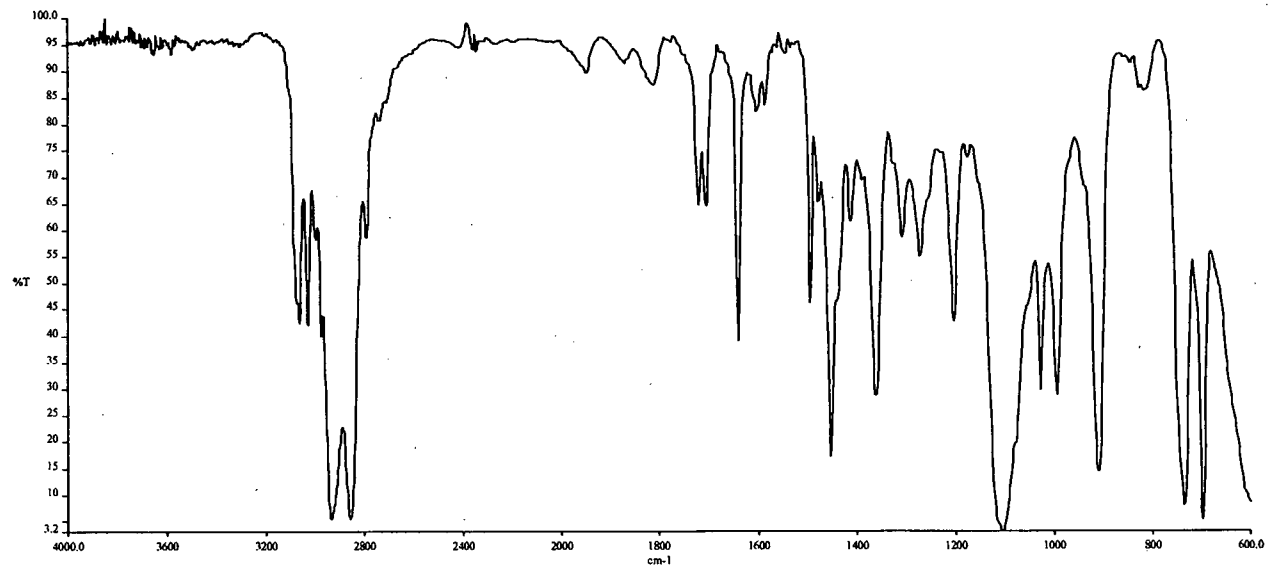




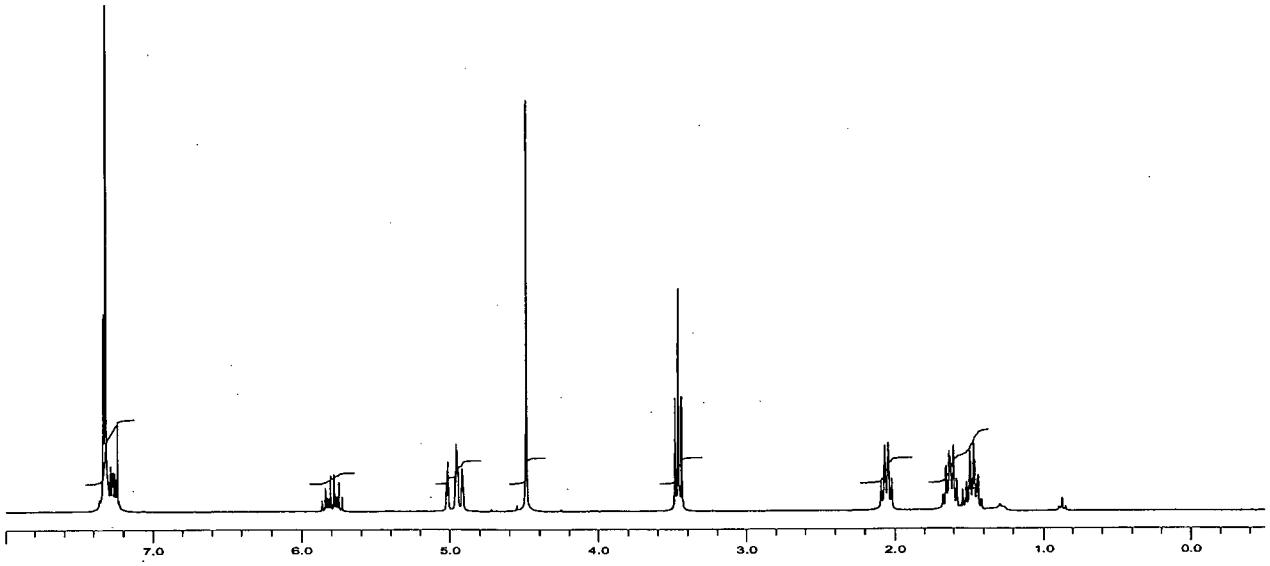
(*E*)-8-Benzyloxy-1-phenyloct-3-ene (**2.39**)

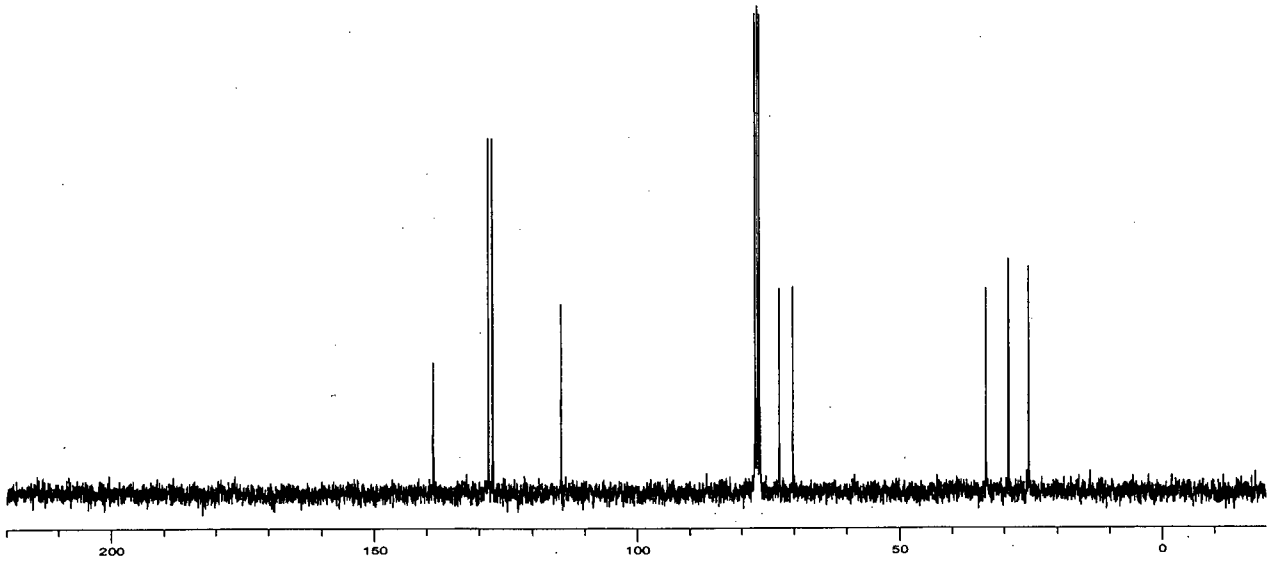


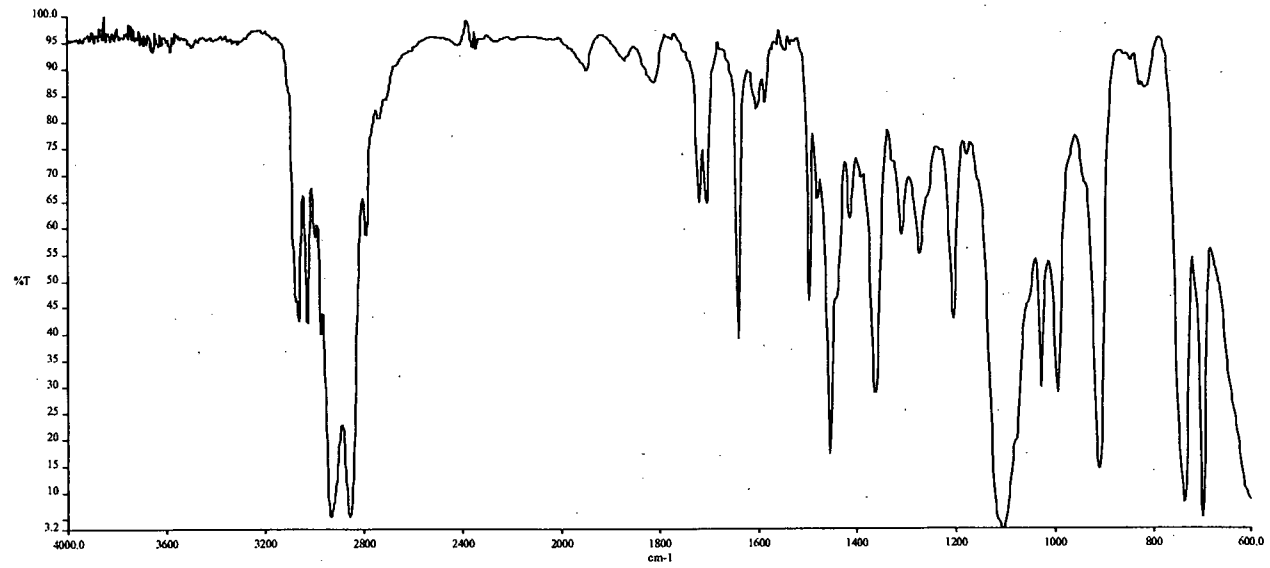




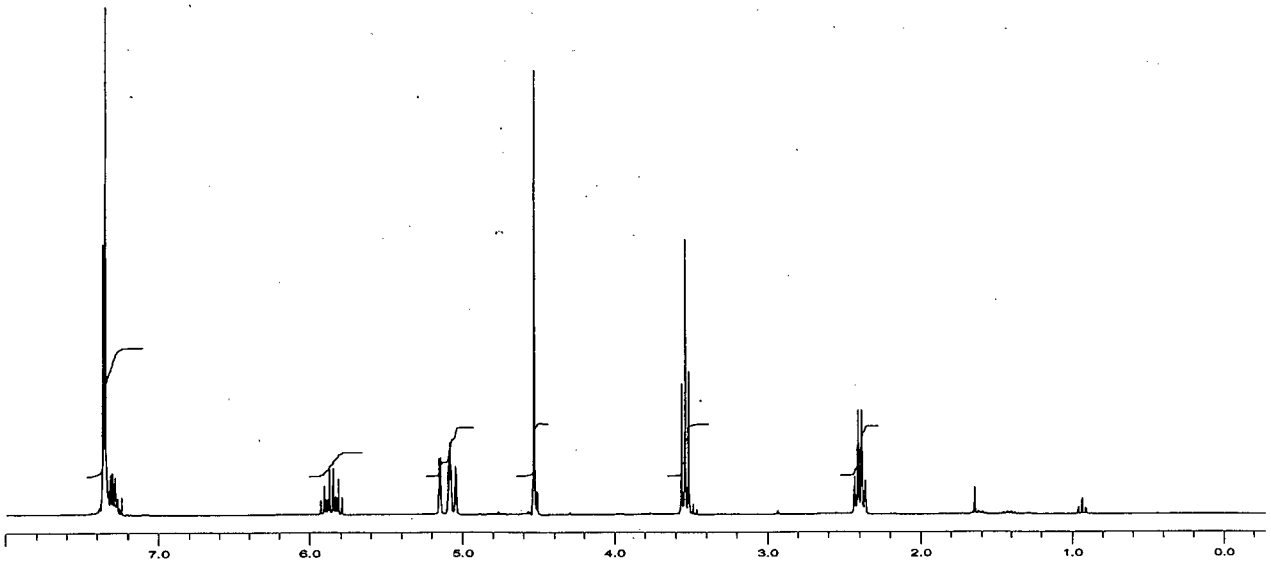
6-Benzyloxyhex-1-ene (**2.42**)

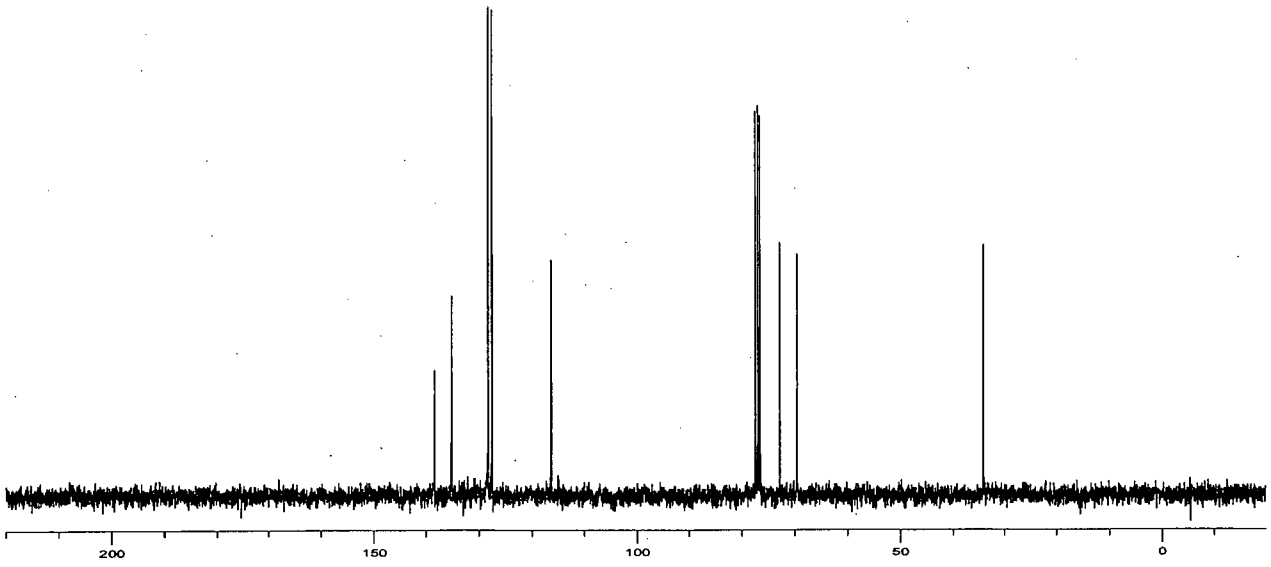


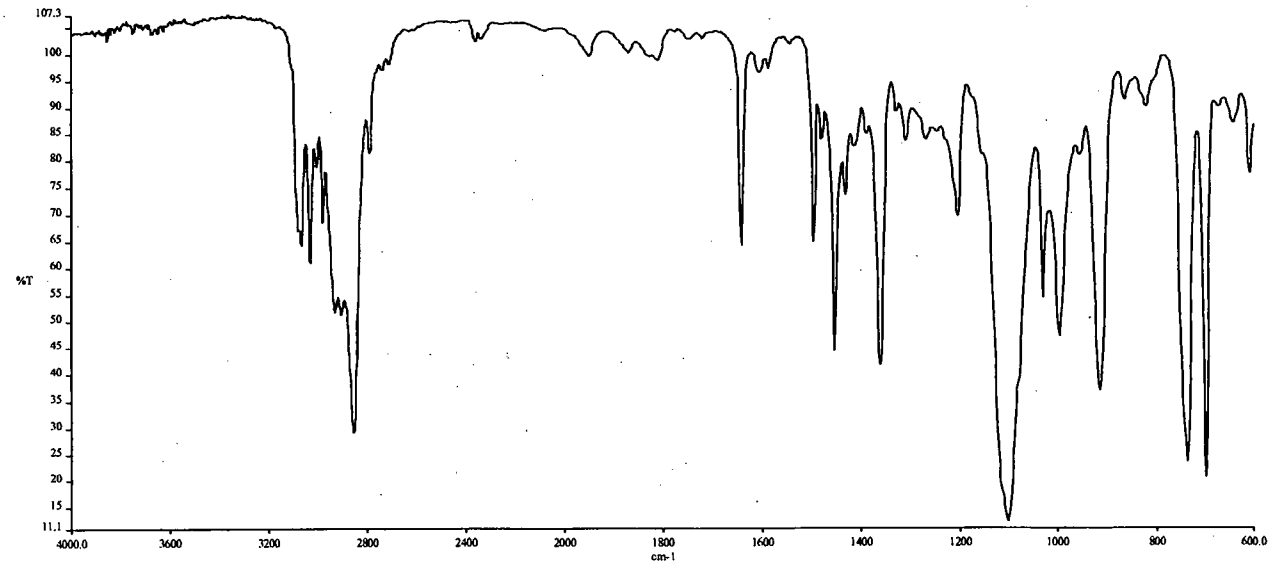




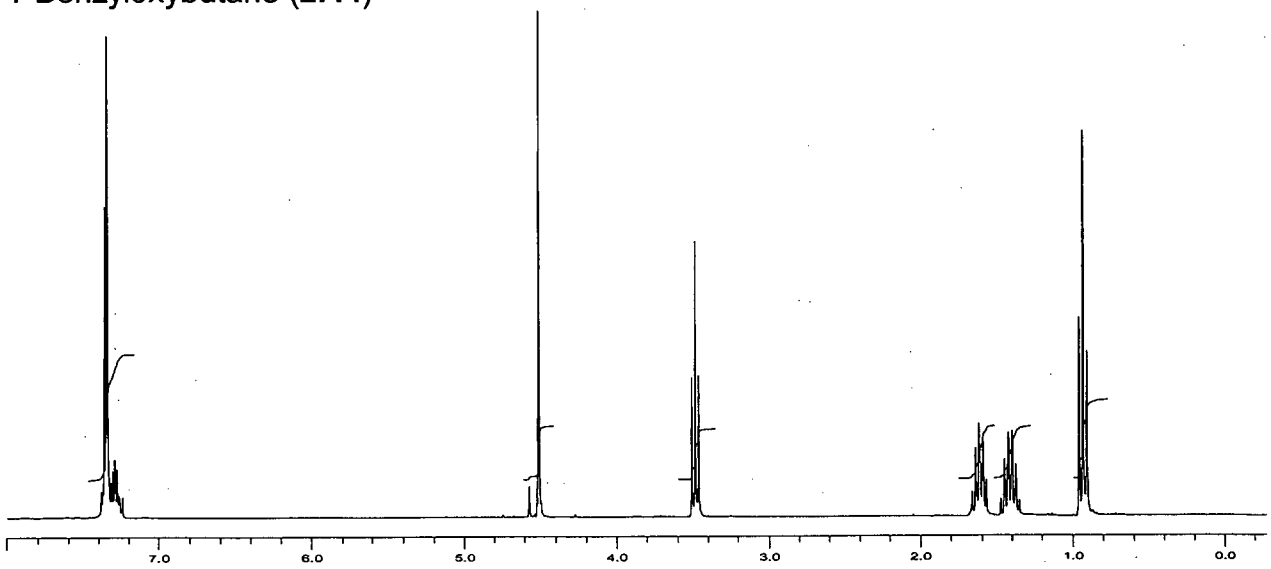
4-Benzyloxybut-1-ene (**2.43**)

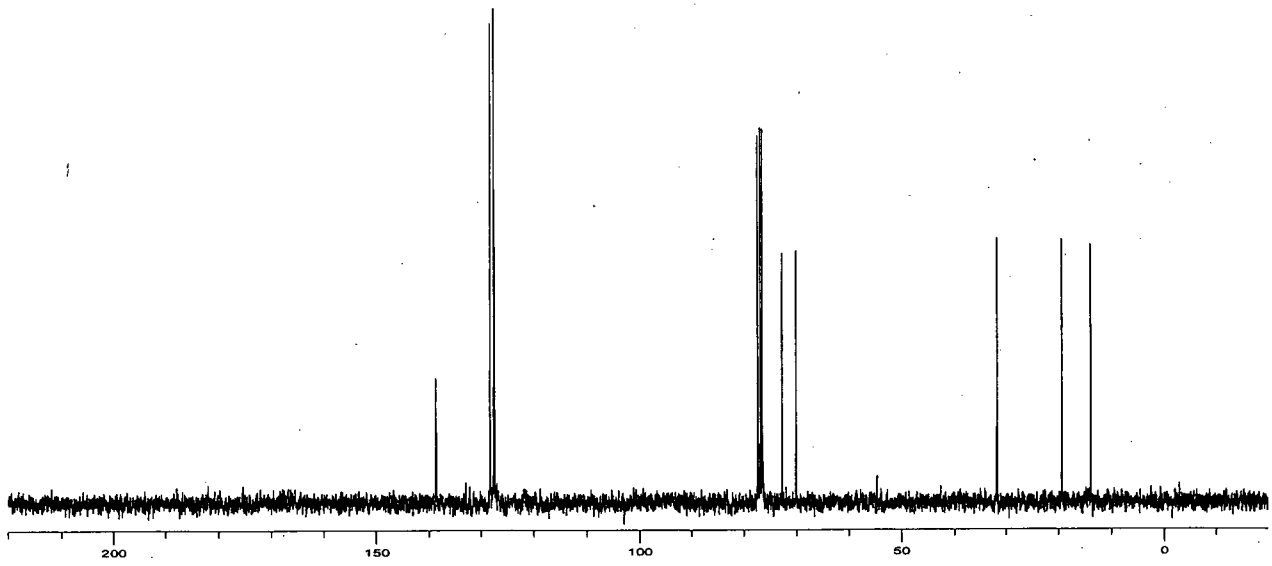


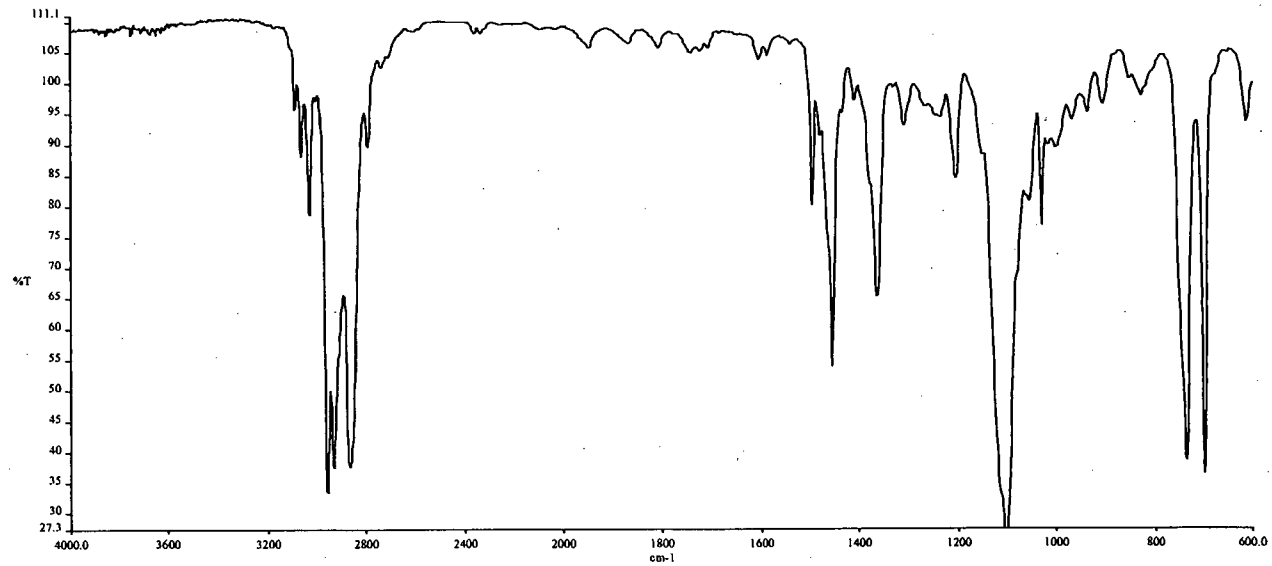




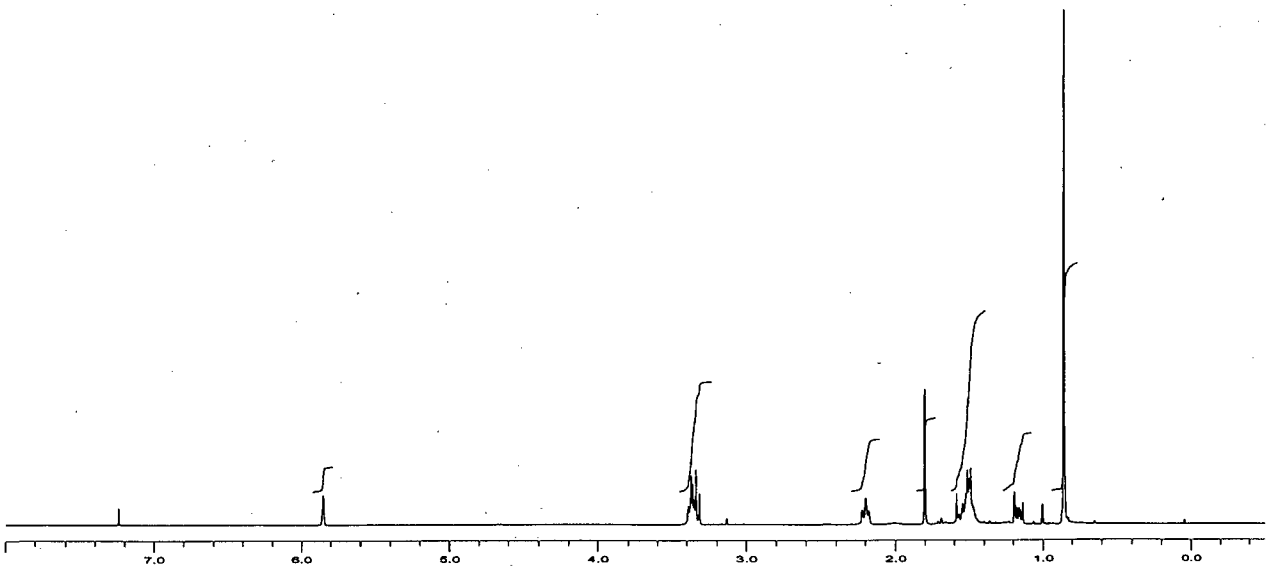
1-Benzyloxybutane (**2.44**)

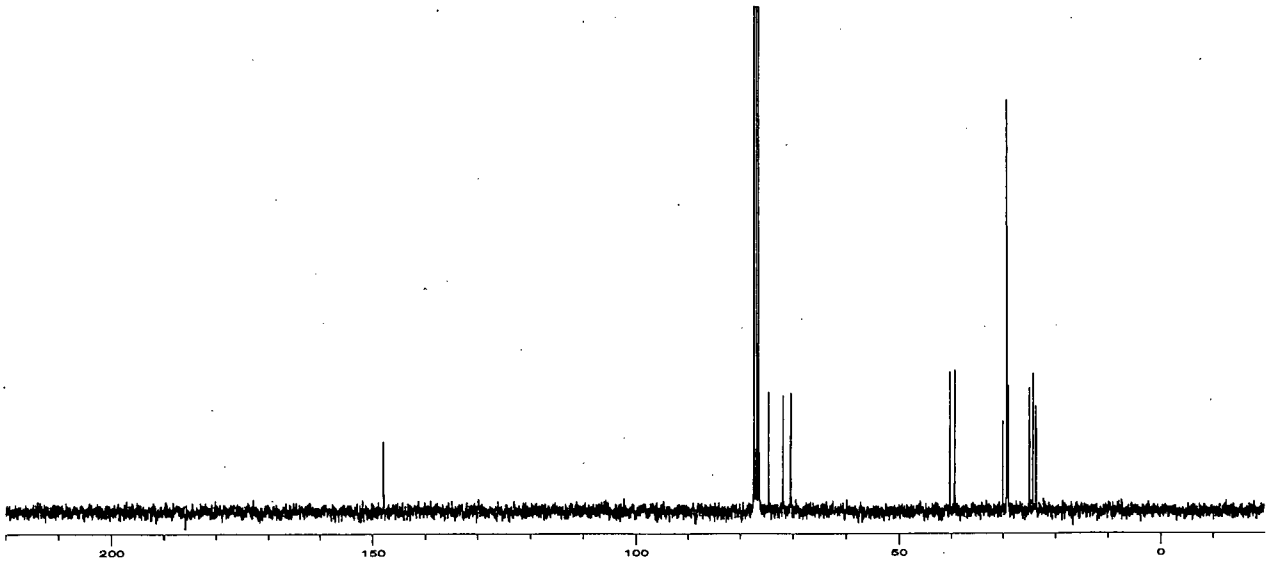


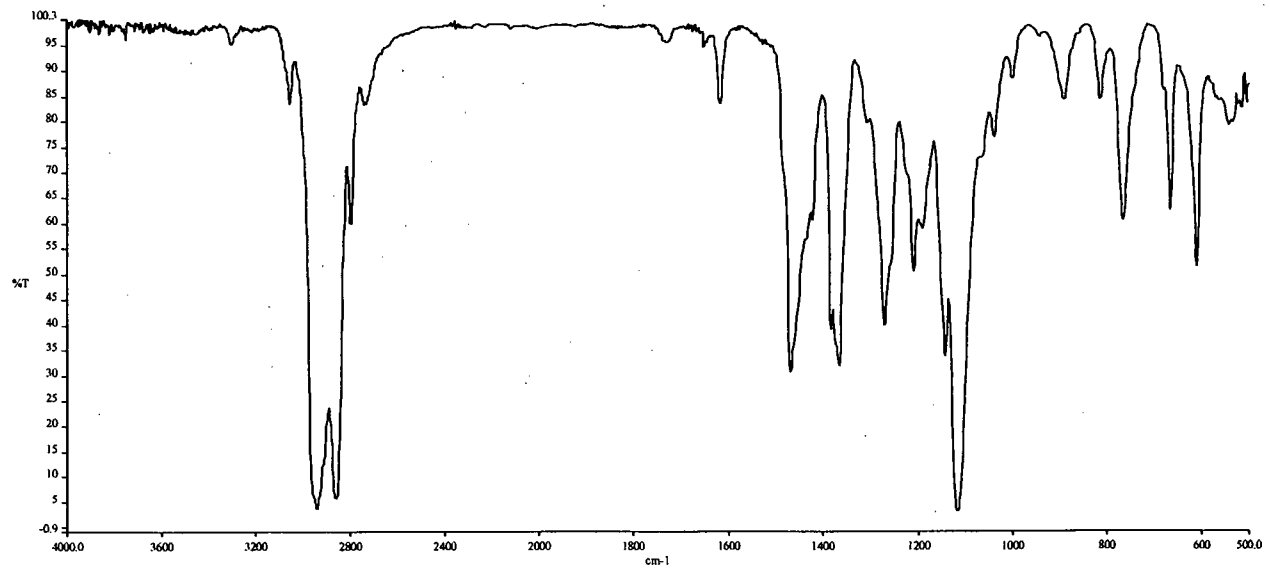




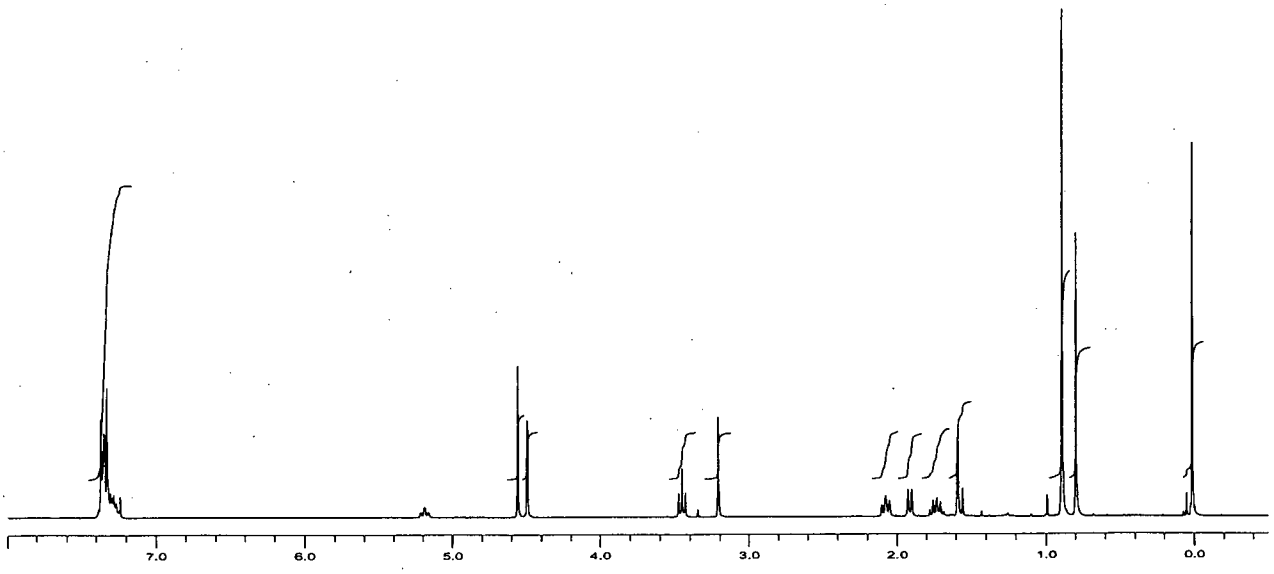
(*E*)-4,4-Dimethylpentanyl-6'-iodo-5'-methylhex-5'-enyl ether (**2.46**)

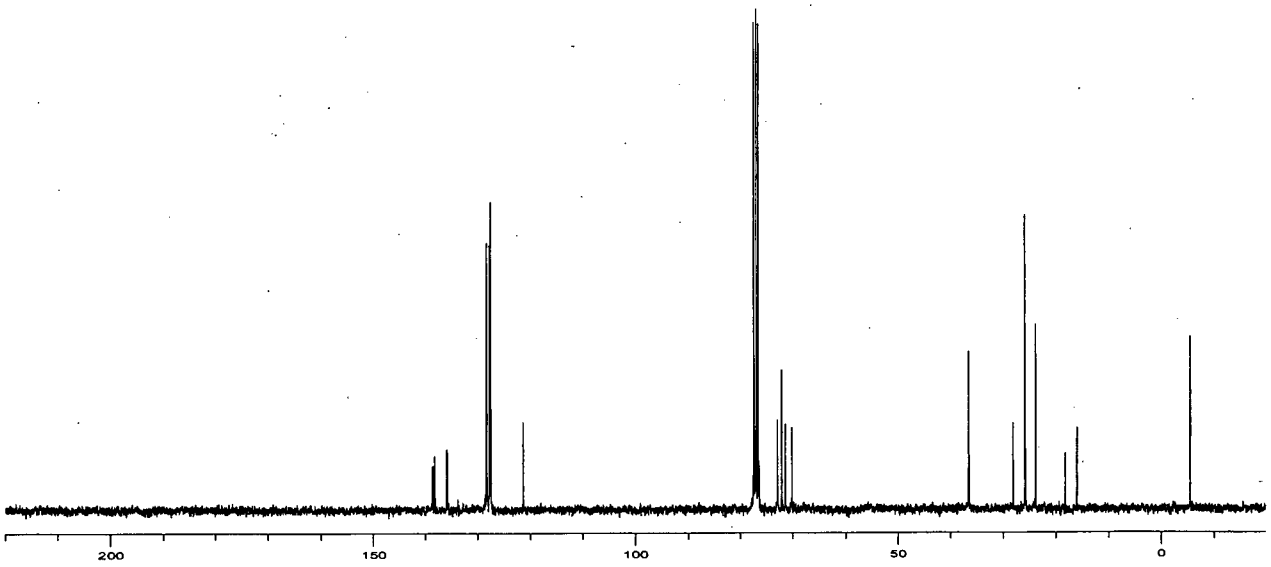


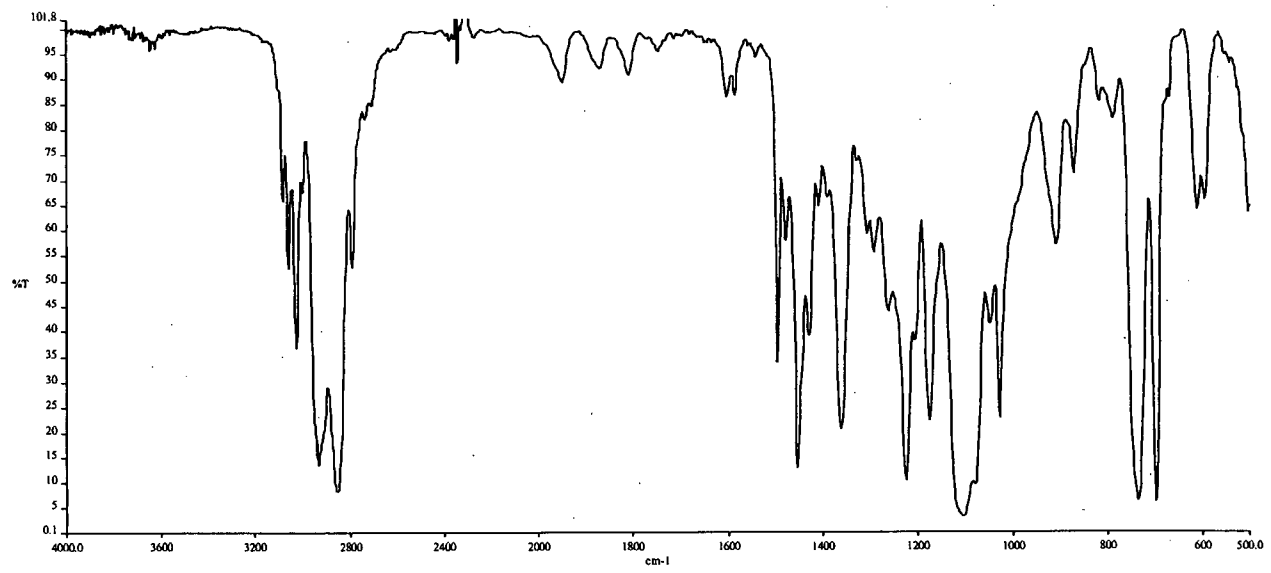




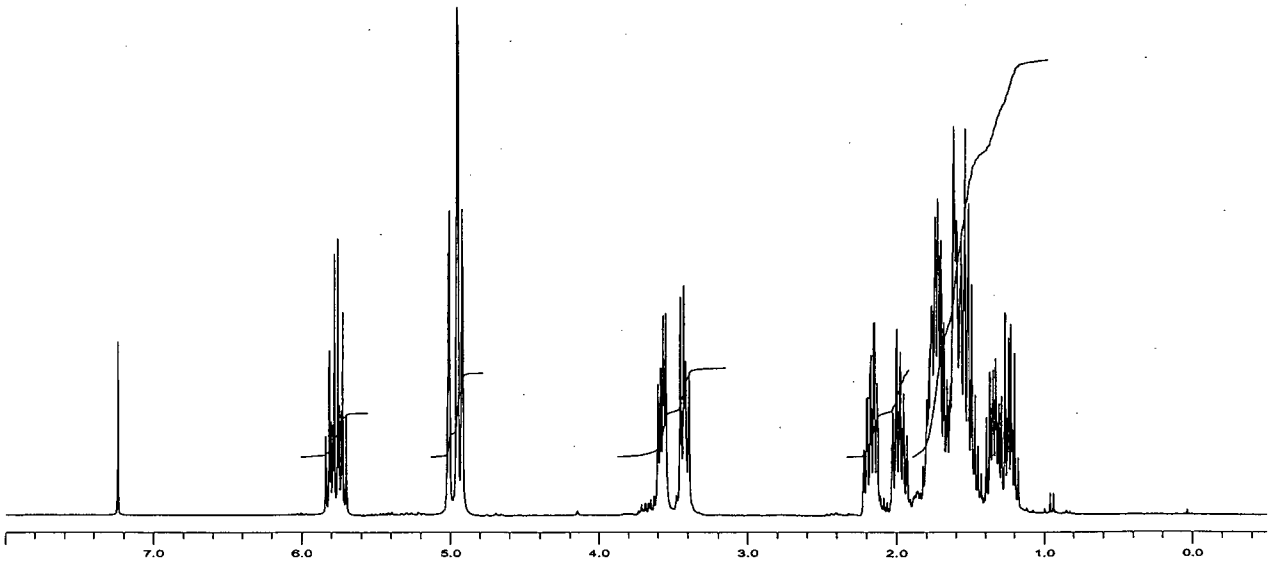
(*E*)-8-Benzyloxy-1-*tert*-butyldimethylsiloxy-2,2,5-trimethyloct-4-ene (**2.48**)

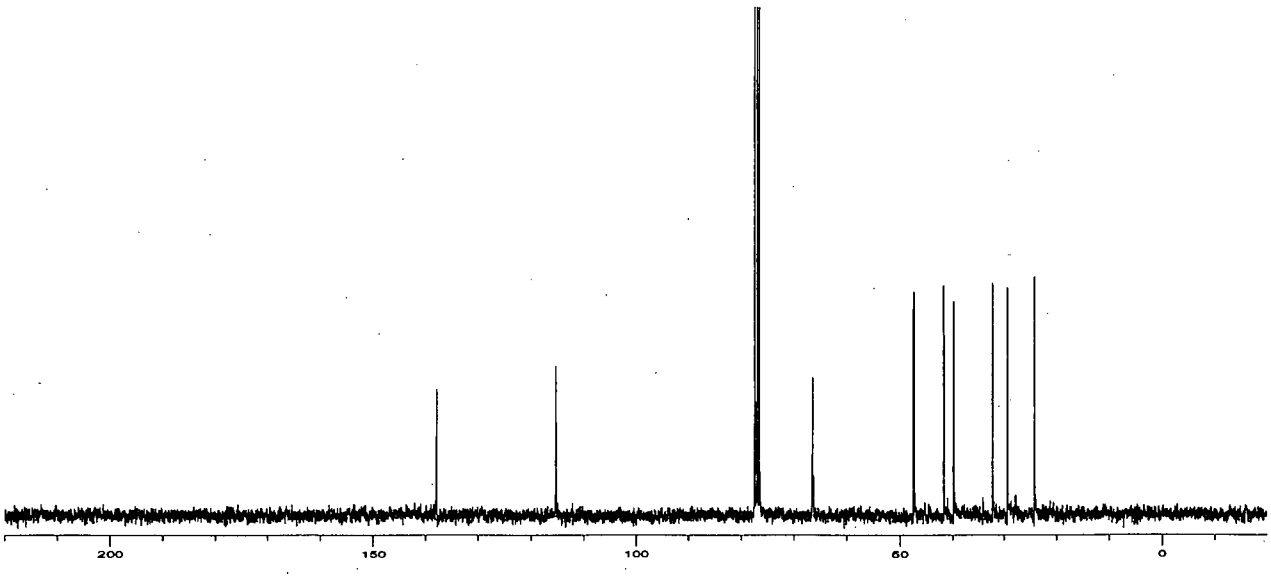


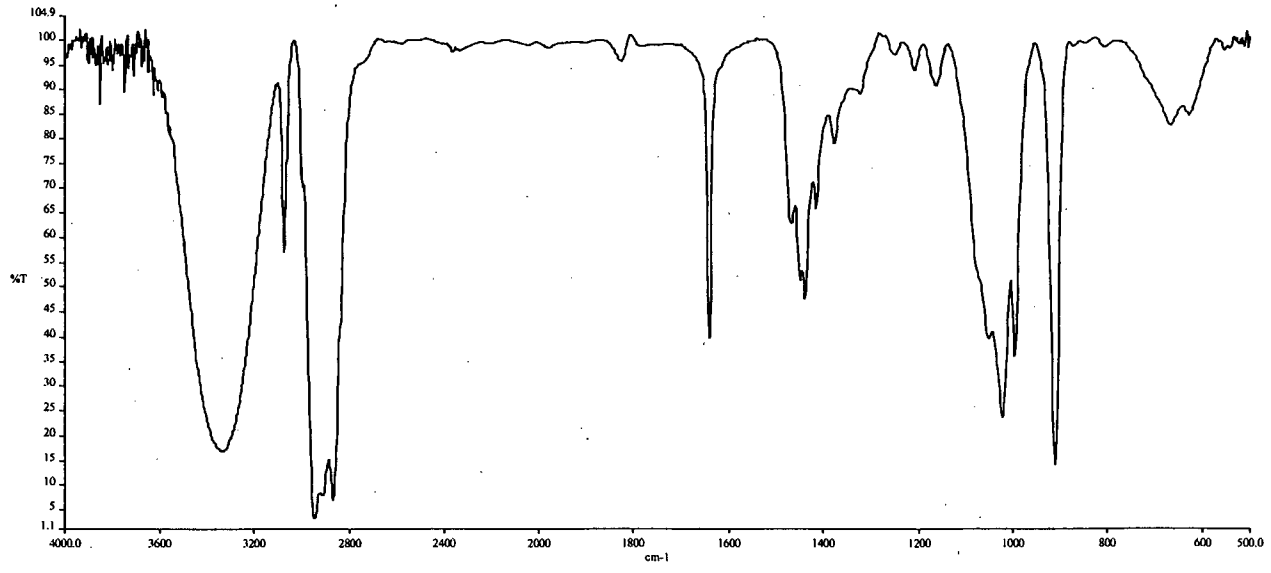




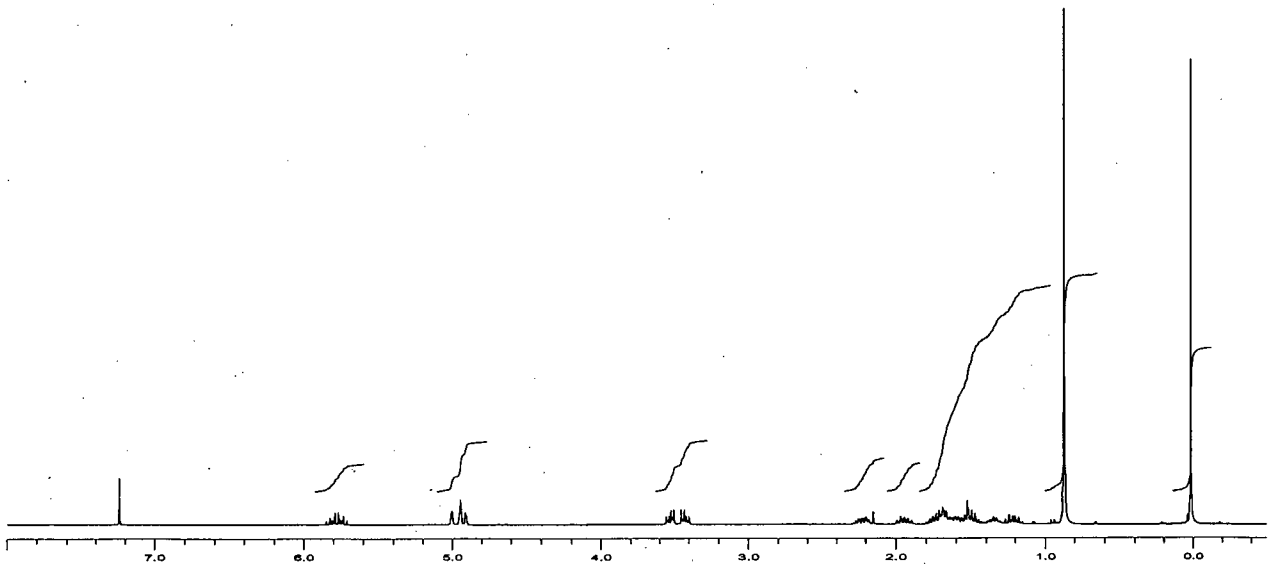
(1*R**, 2*S**)-2-Allyl-1-(hydroxymethyl)cyclopentane (**2.58**)

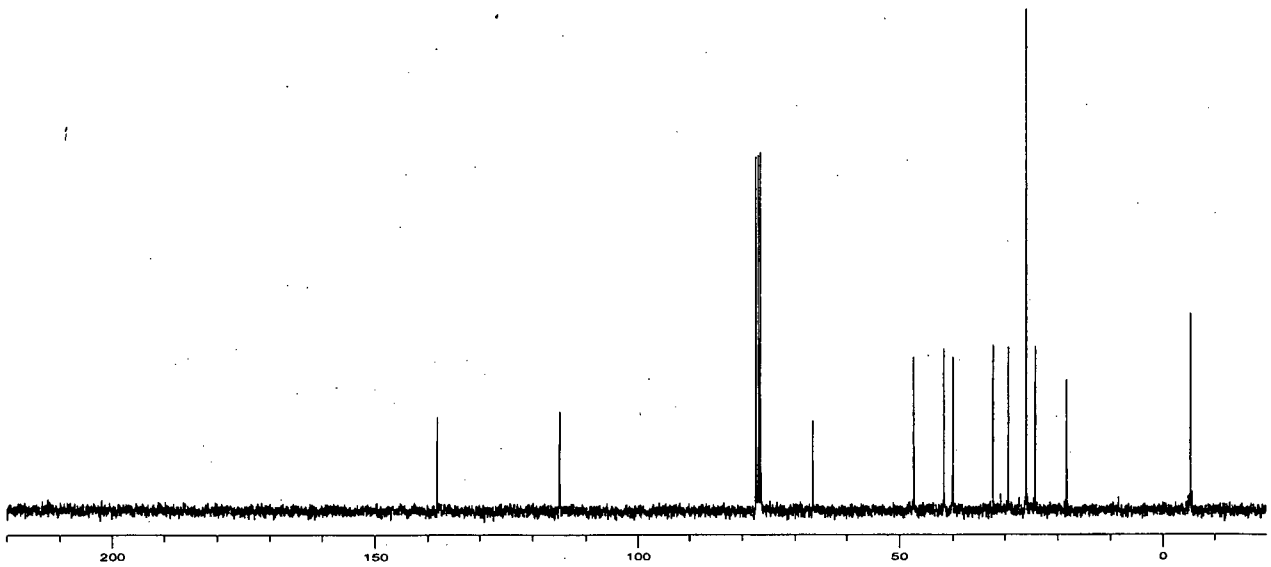


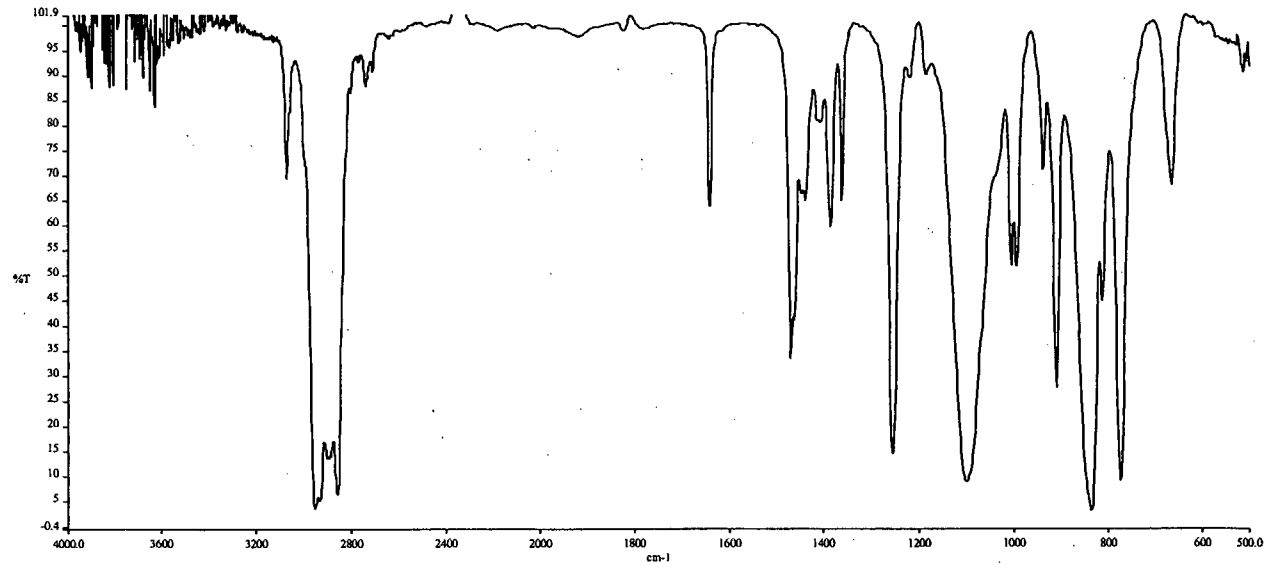




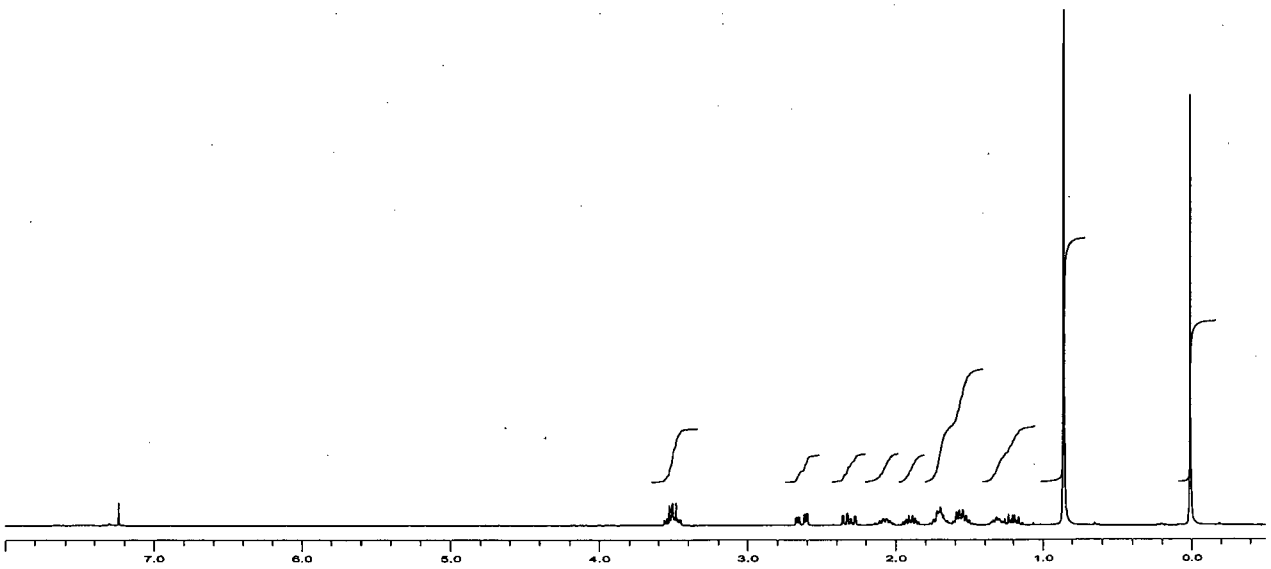
(1*R**, 2*S**)-2-Allyl-1-(*tert*-butyldimethylsilyloxymethyl)cyclopentane (**2.59**)

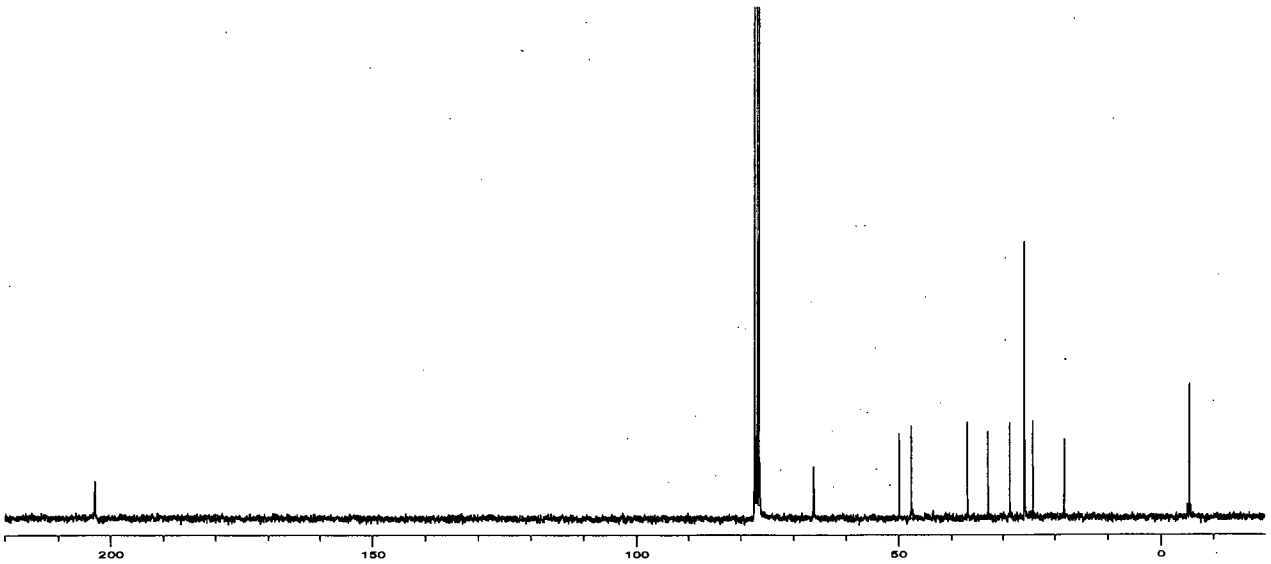


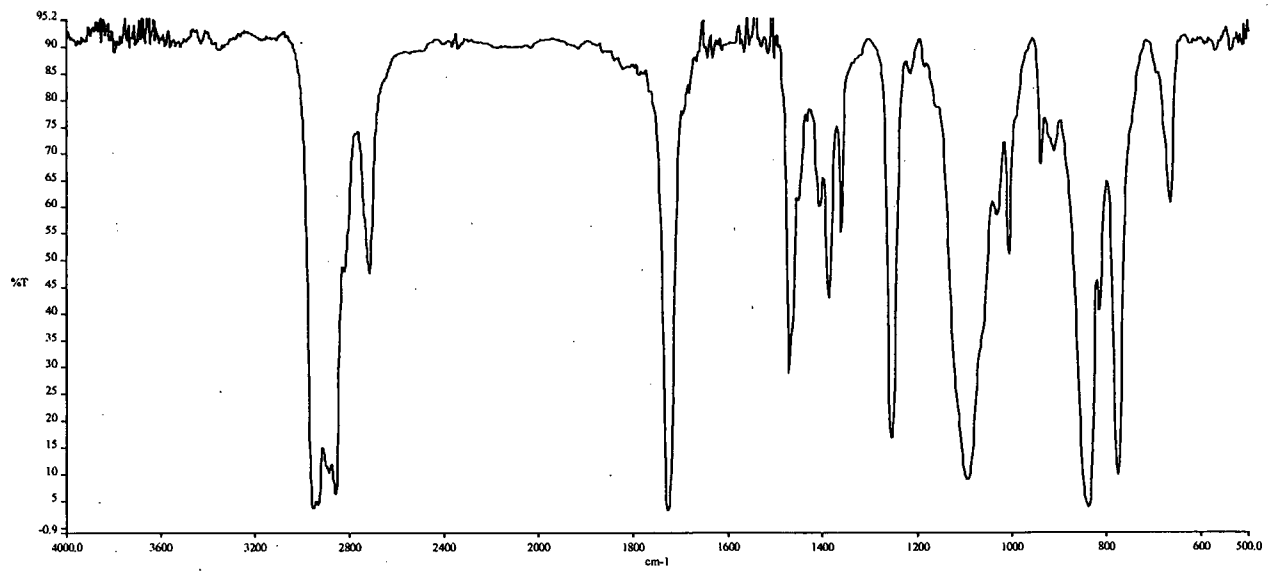




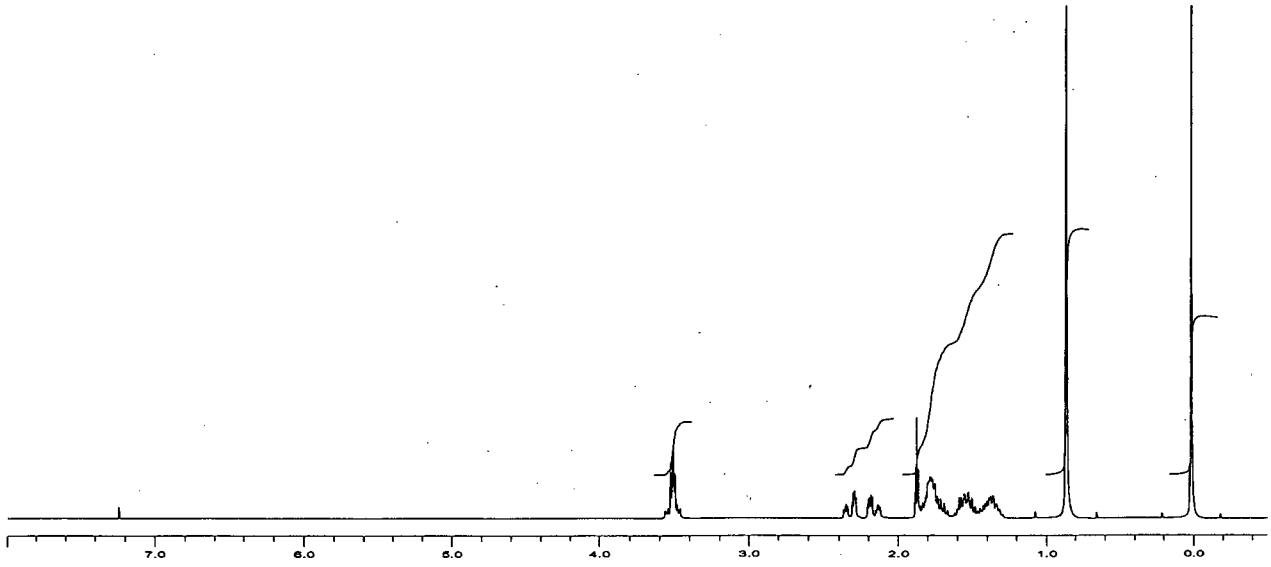
(1*R**, 2*S**)-1-(*tert*-Butyldimethylsilyloxymethyl)-2-(2-oxoethyl)cyclopentane (**2.60**)

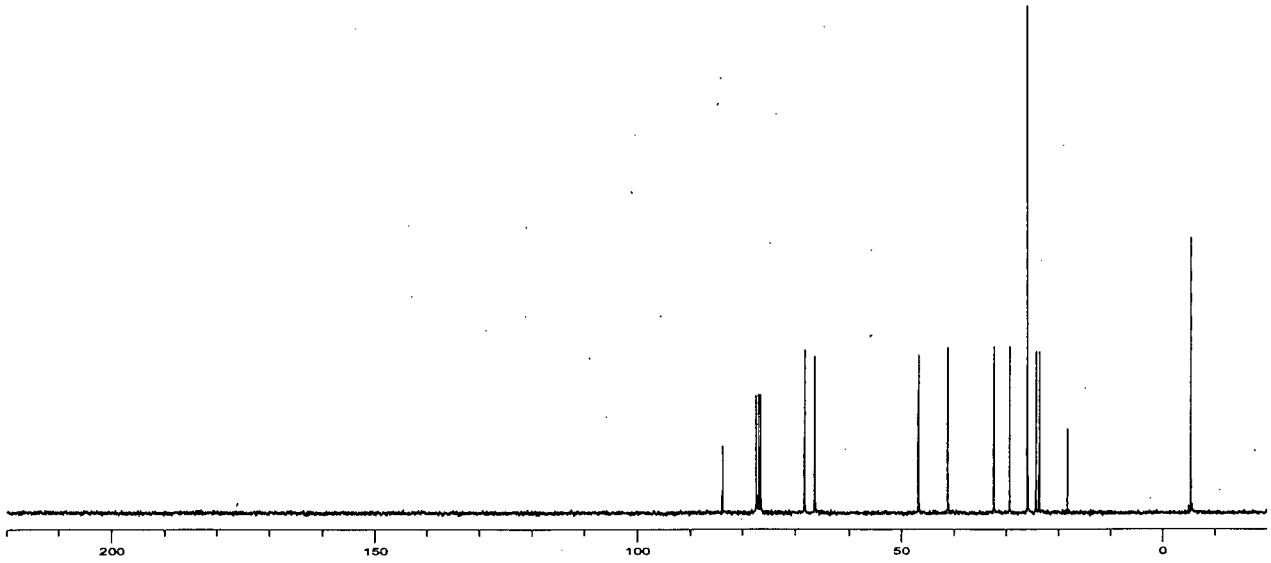


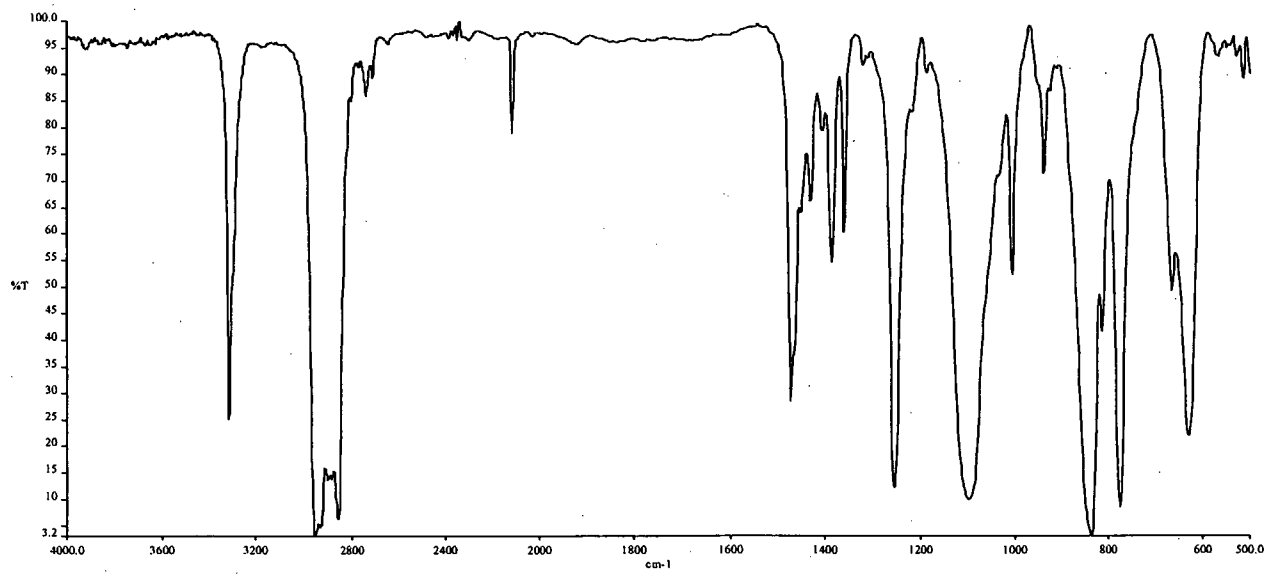




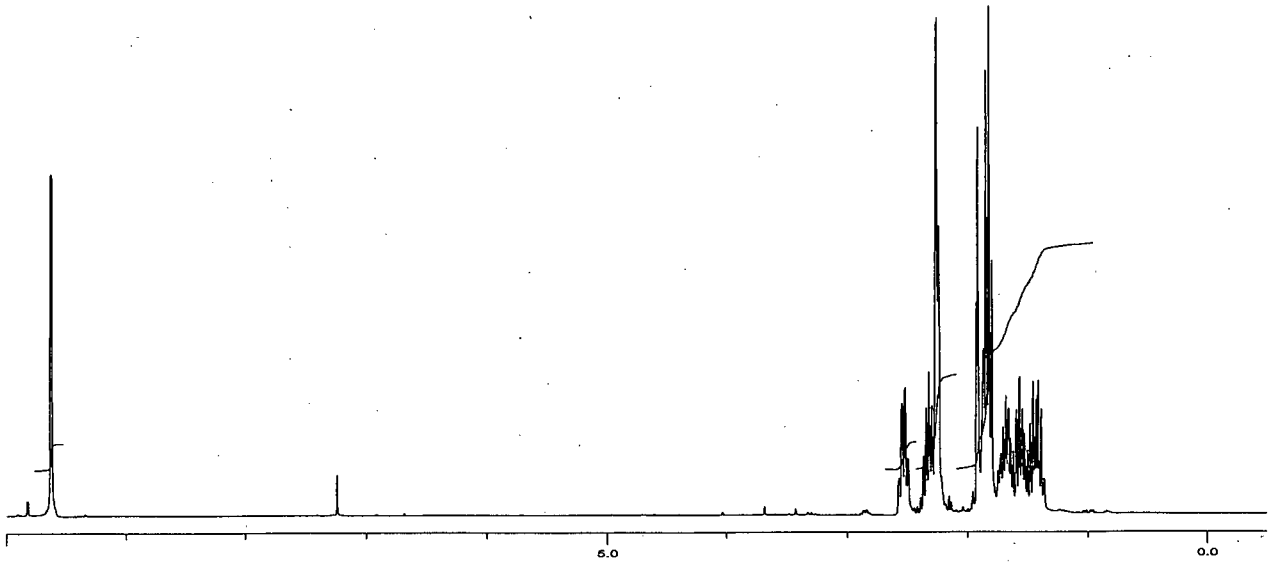
(1*R**, 2*S**)-1-(*tert*-Butyldimethylsilyloxymethyl)-2-propargylcyclopentane (**2.53**)

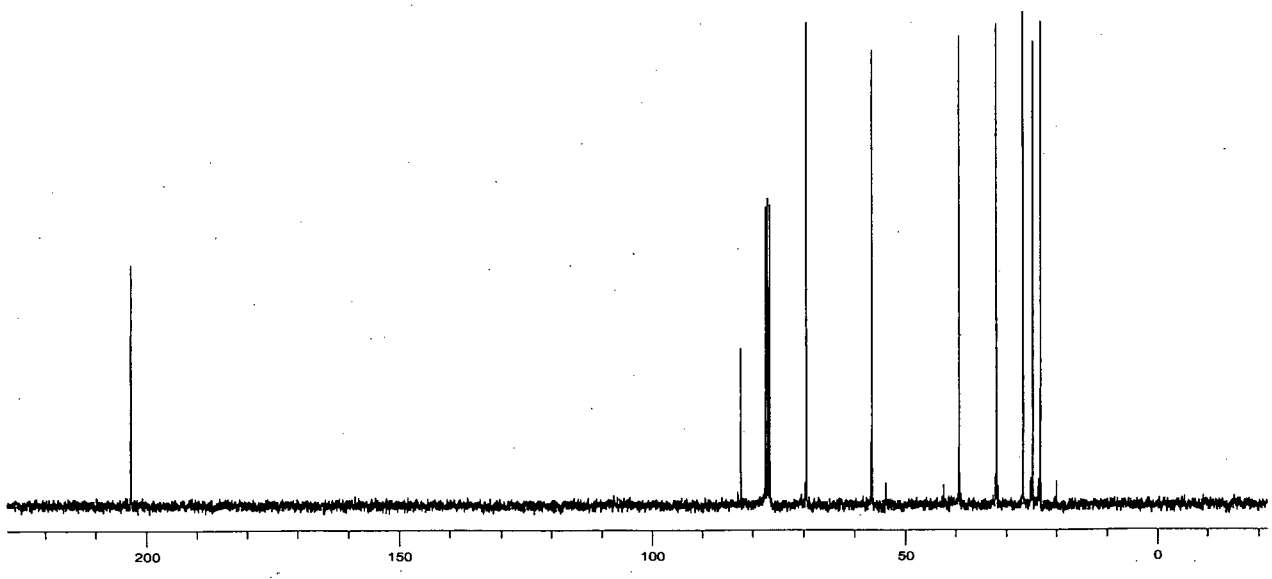


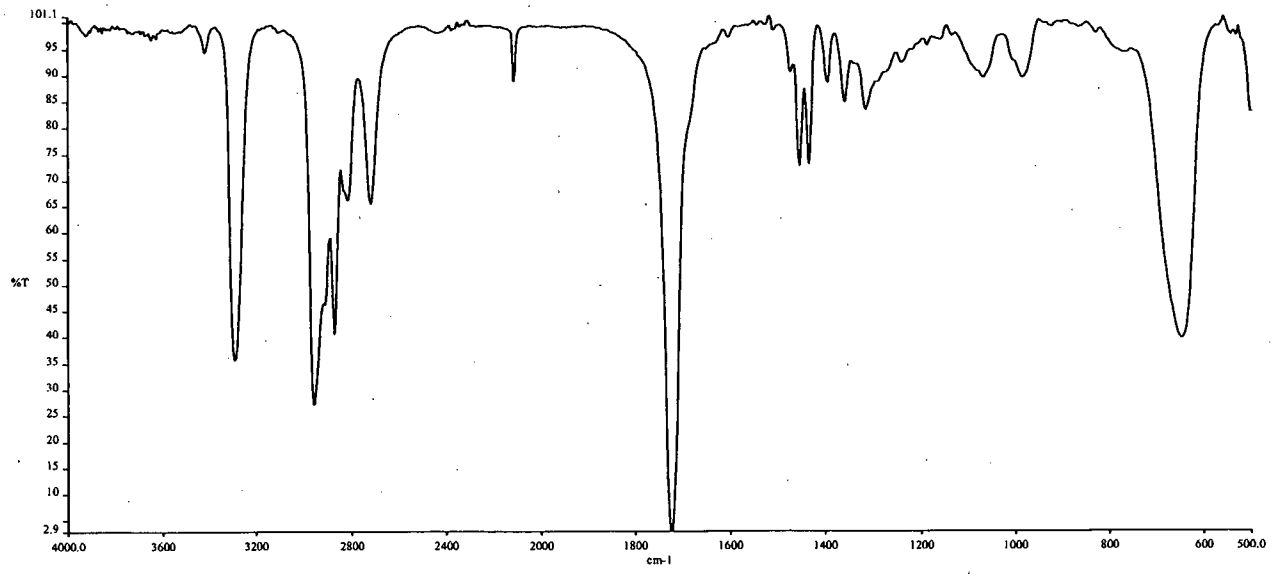




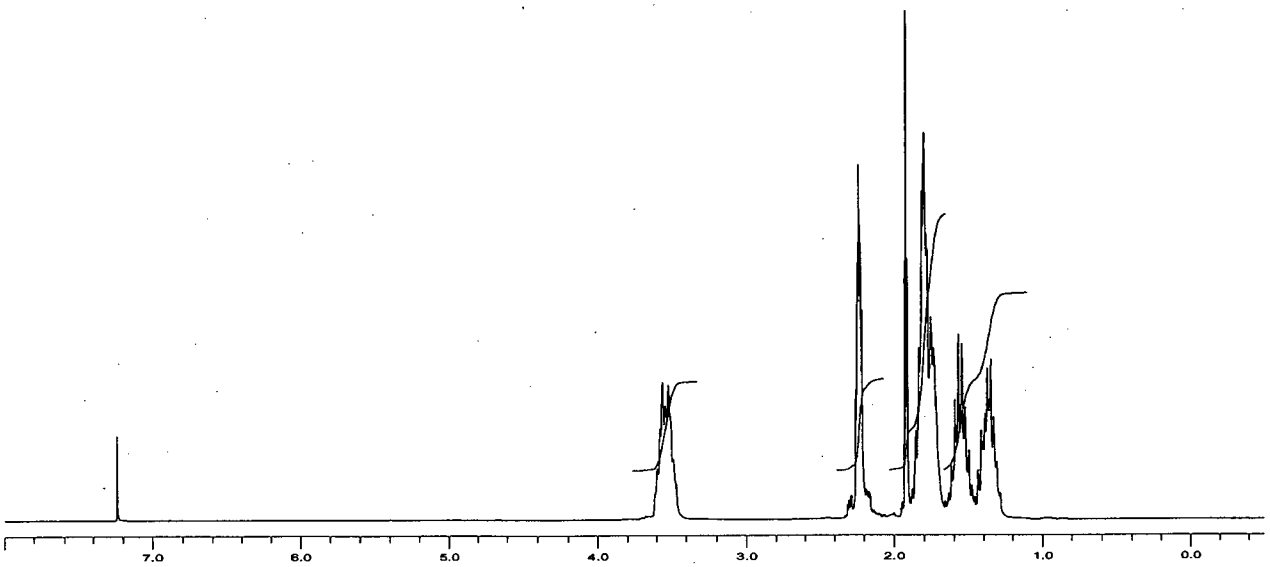
(1*R**, 2*S**)-2-Propargylcyclopentanecarbaldehyde (**2.63**)

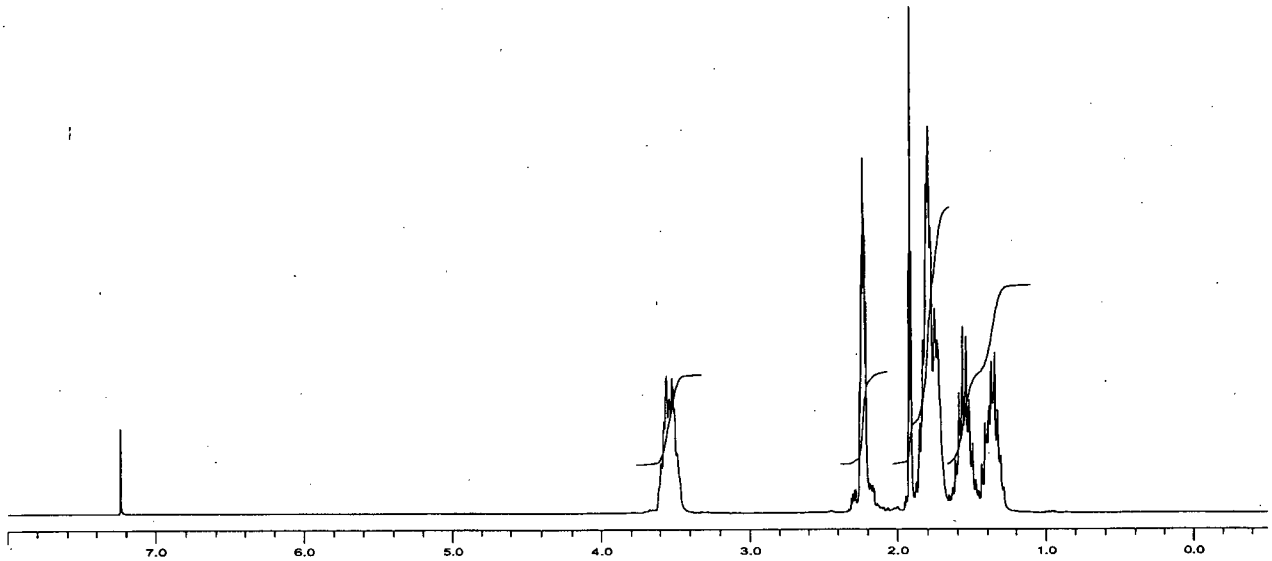


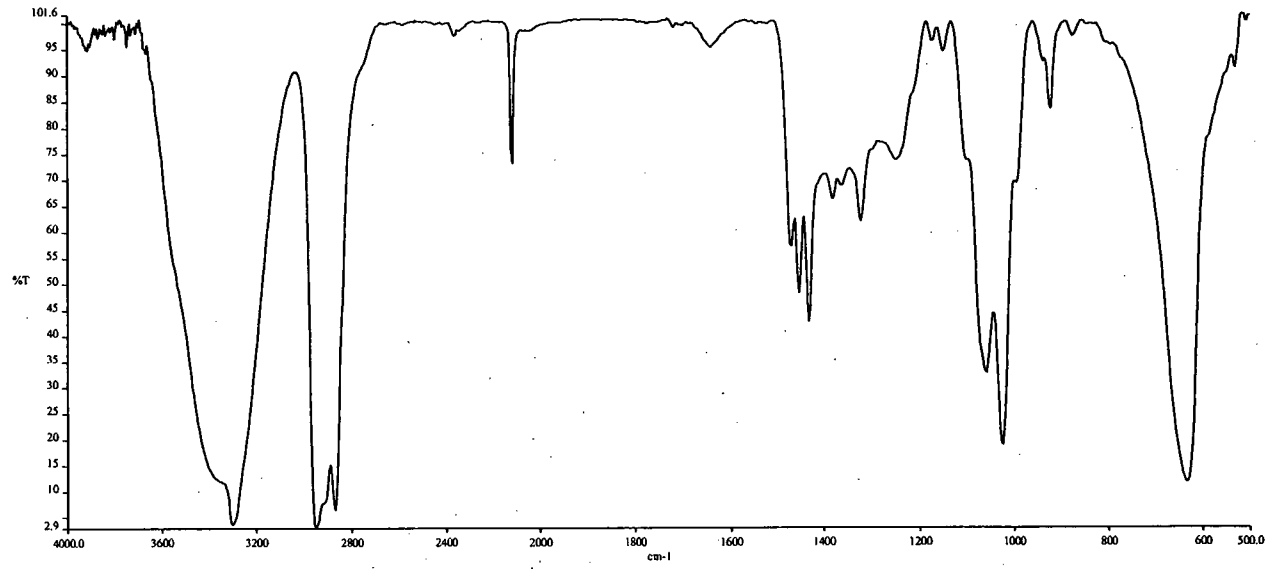




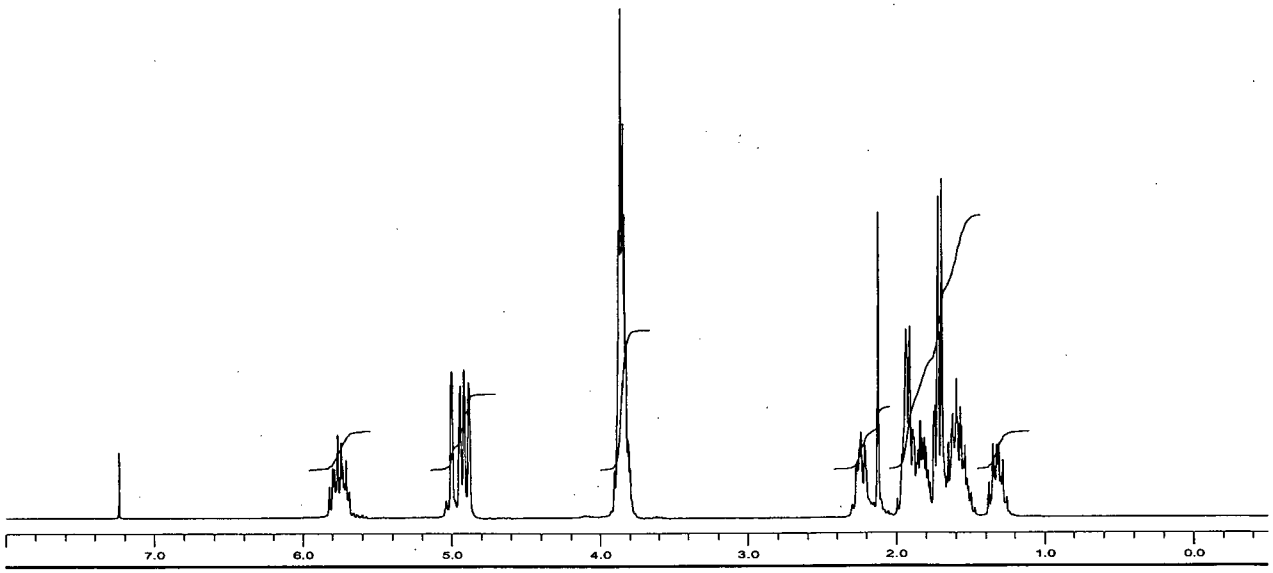
(1*R**, 2*S**)-1-(Hydroxymethyl)-2-propargylcyclopentane (**2.64**)

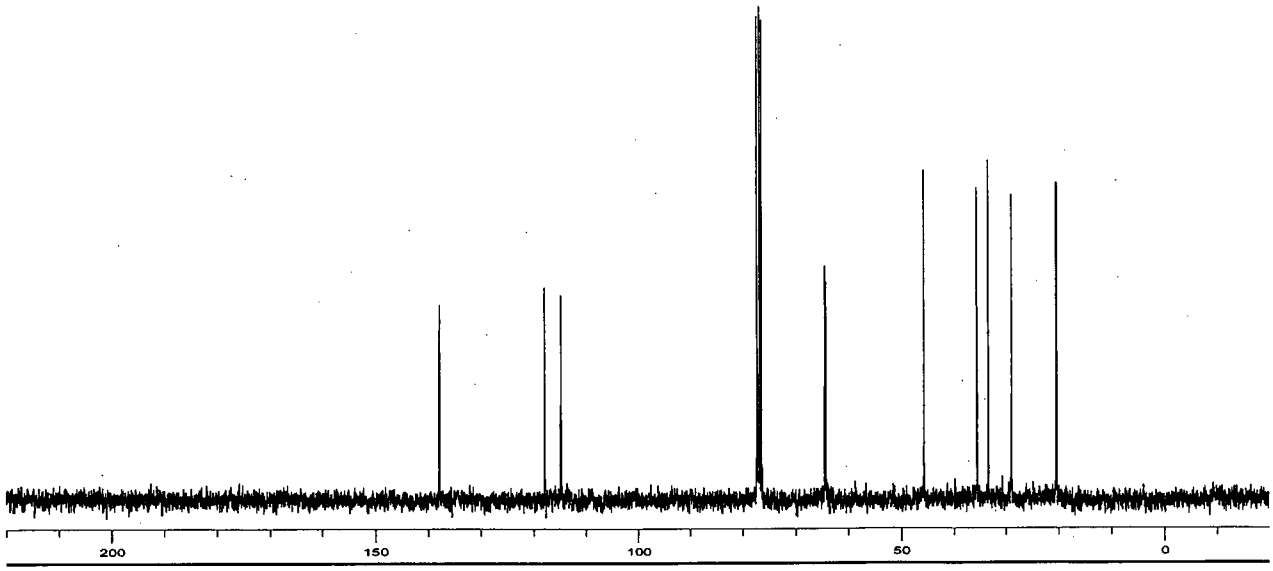


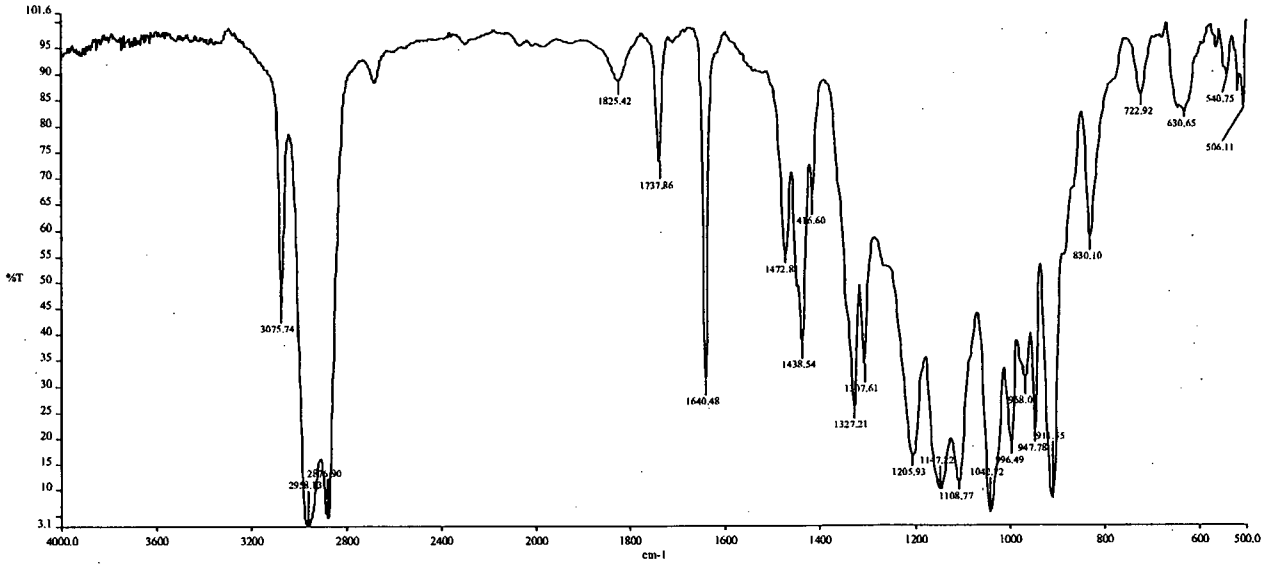




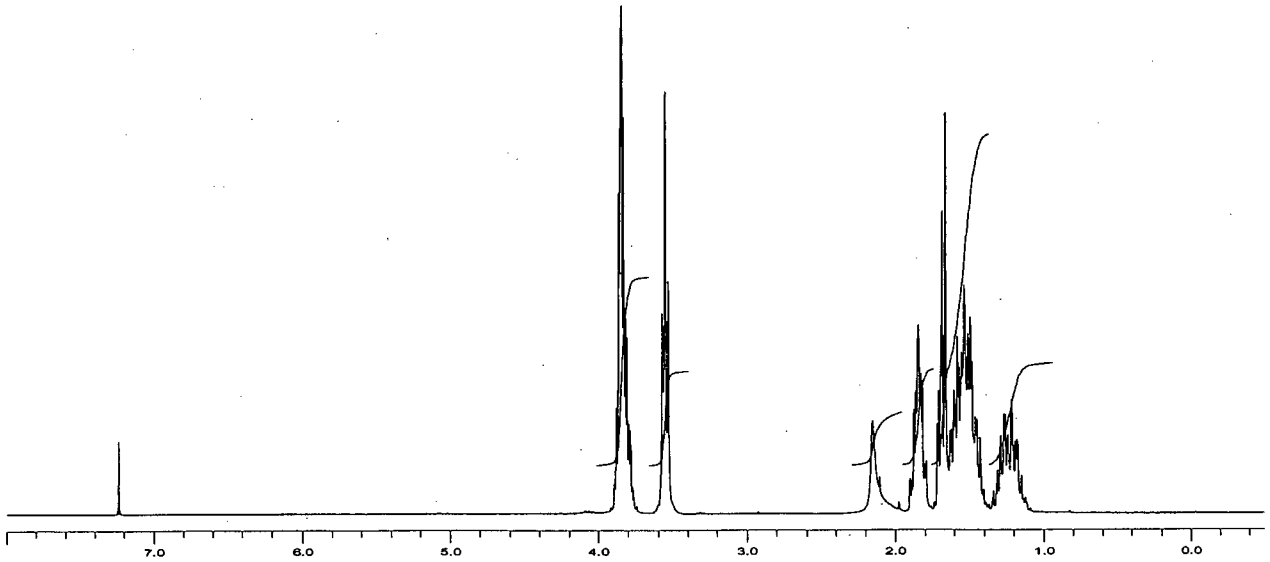
6-(2-Propenyl)-1,4-dioxaspiro[4.4]nonane (**2.65**)

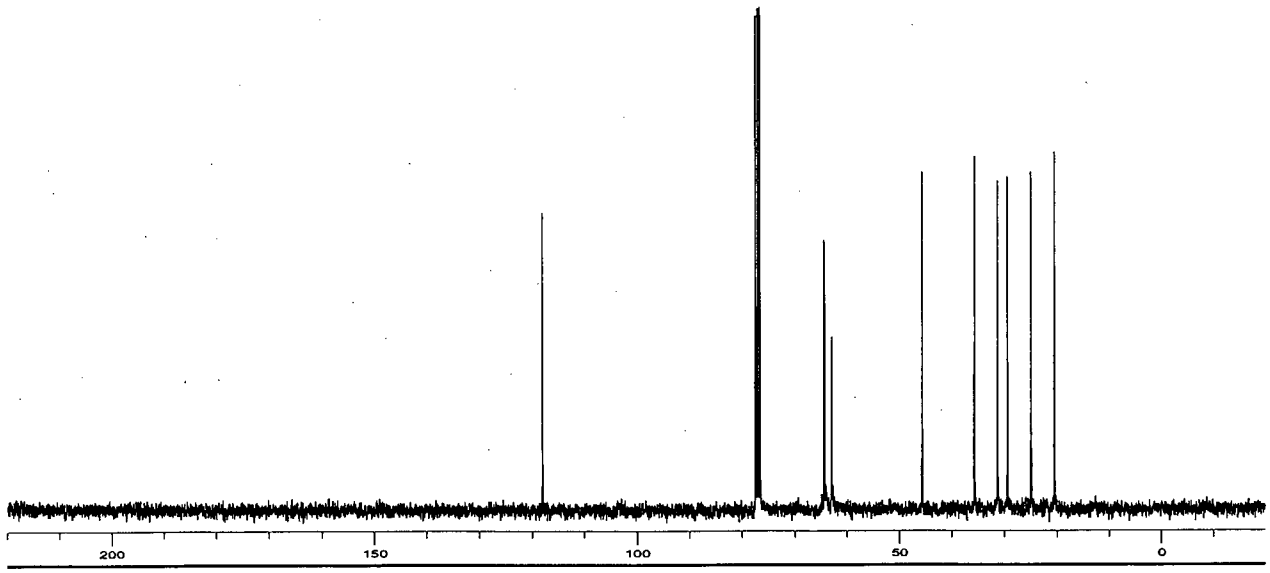


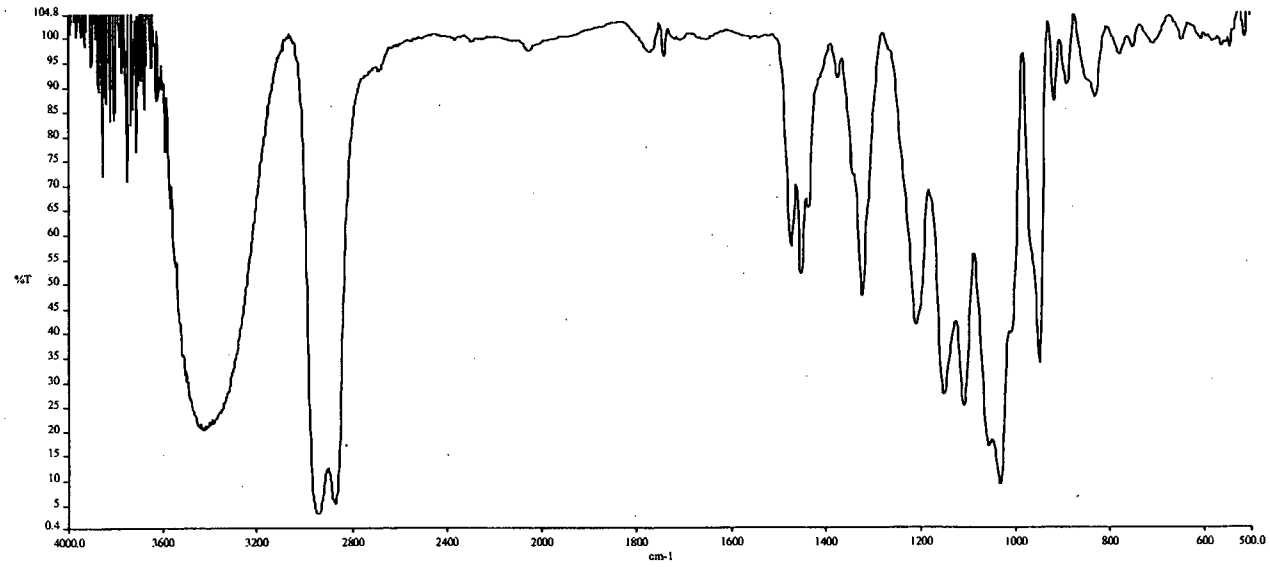




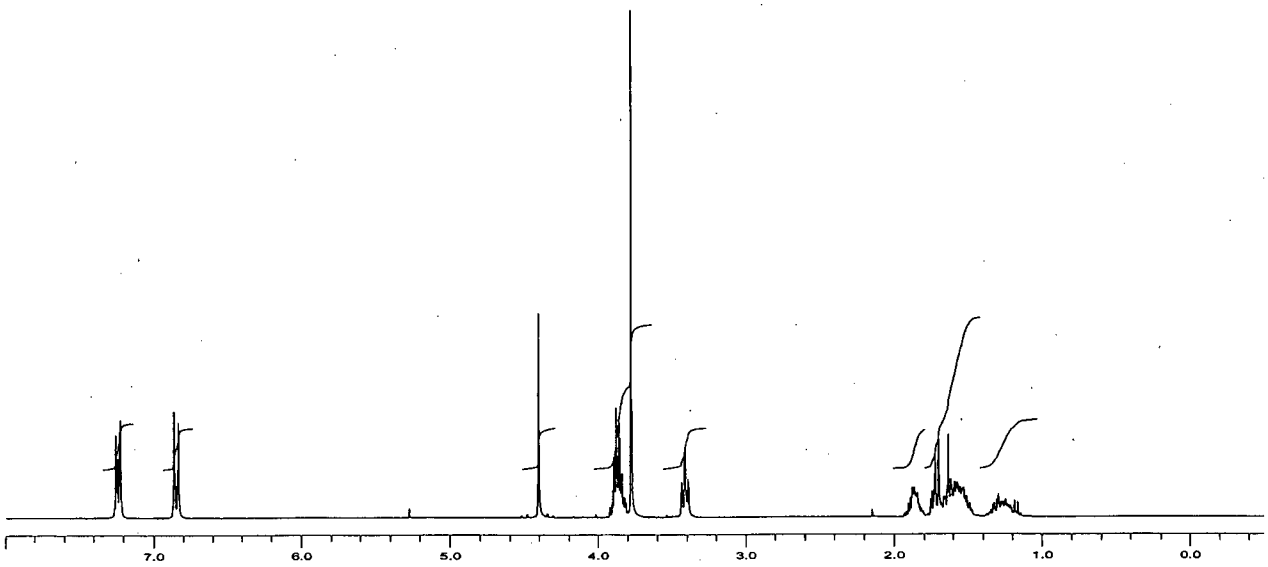
6-(3-hydroxypropyl)-1,4-dioxaspiro[4.4]nonane (**2.66**)

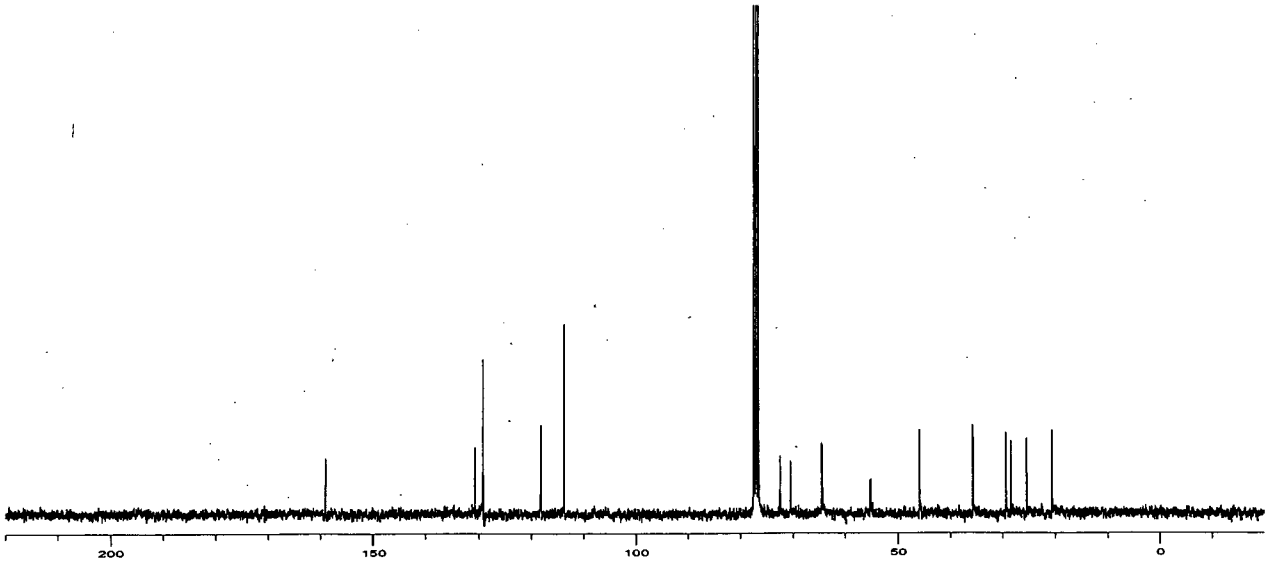


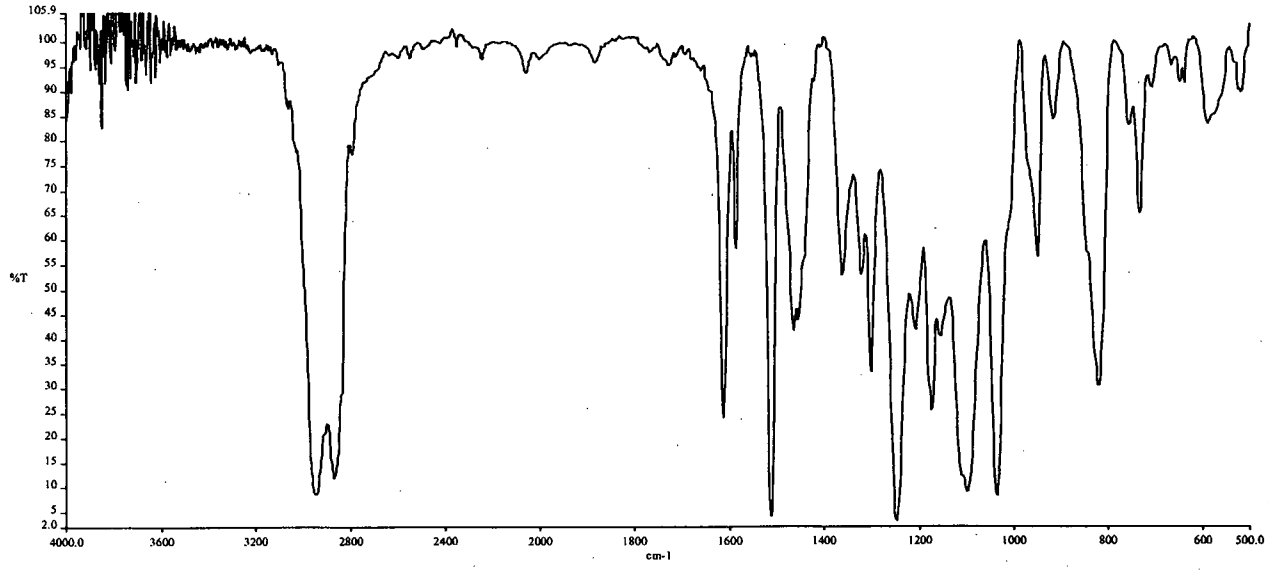




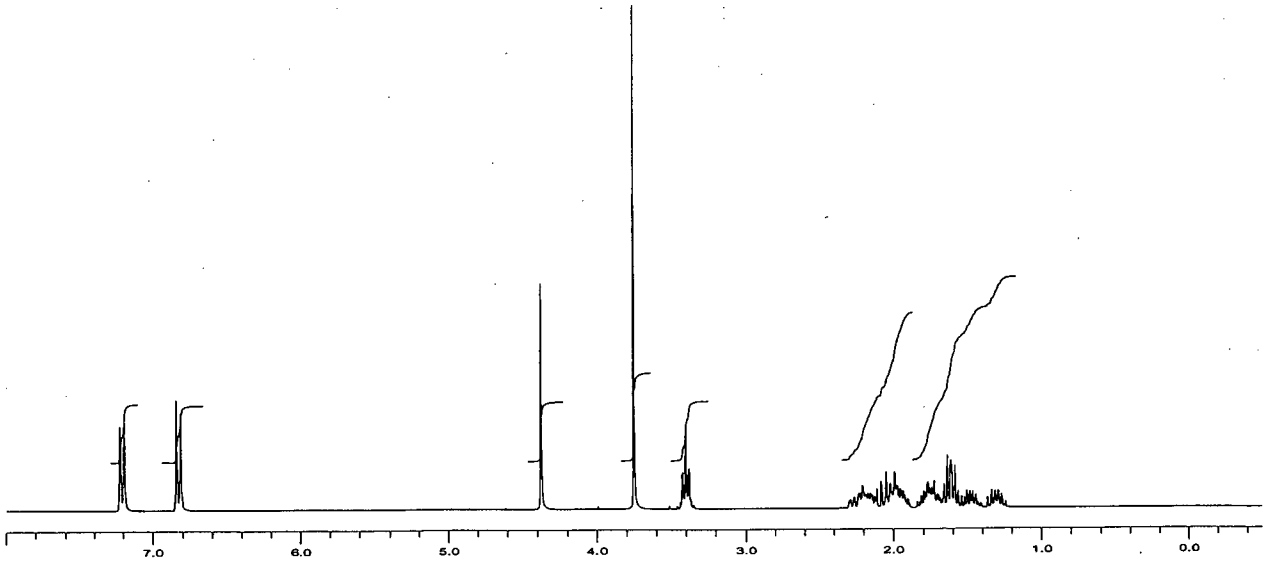
6-(3-(4-Methoxybenzyloxy)propyl)-1,4-dioxaspiro[4.4]nonane (**2.67**)

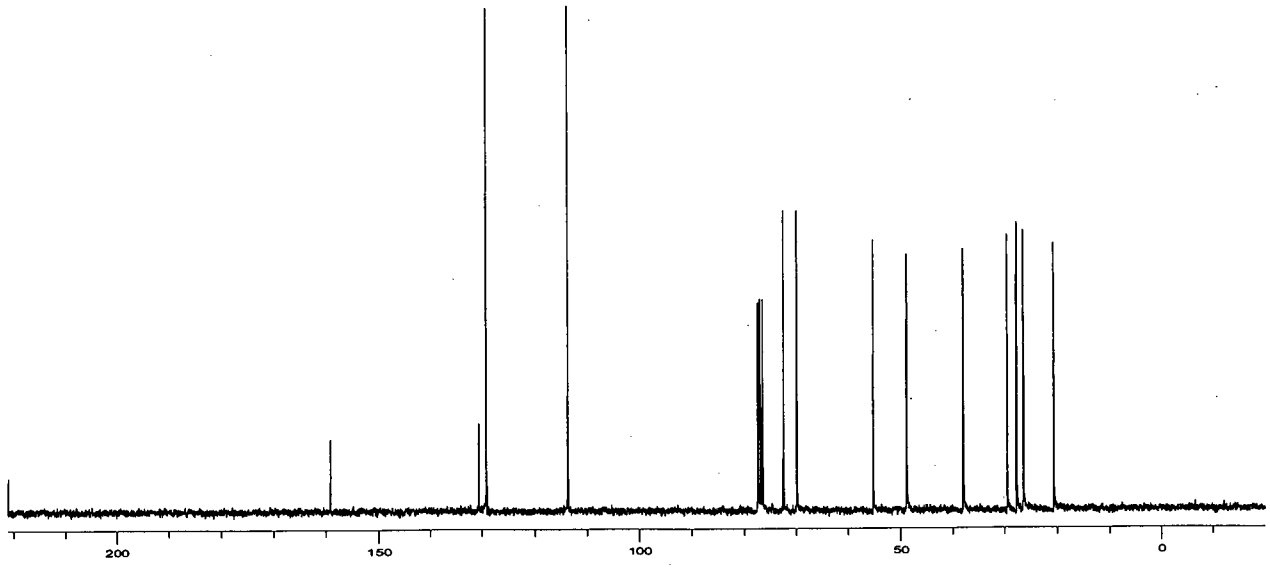


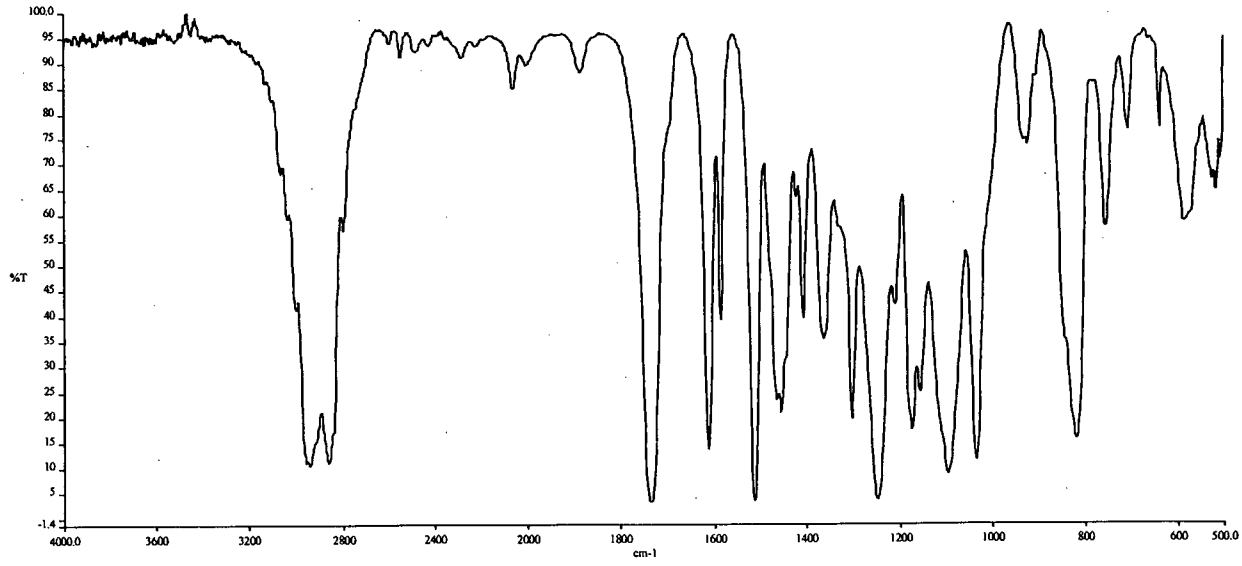




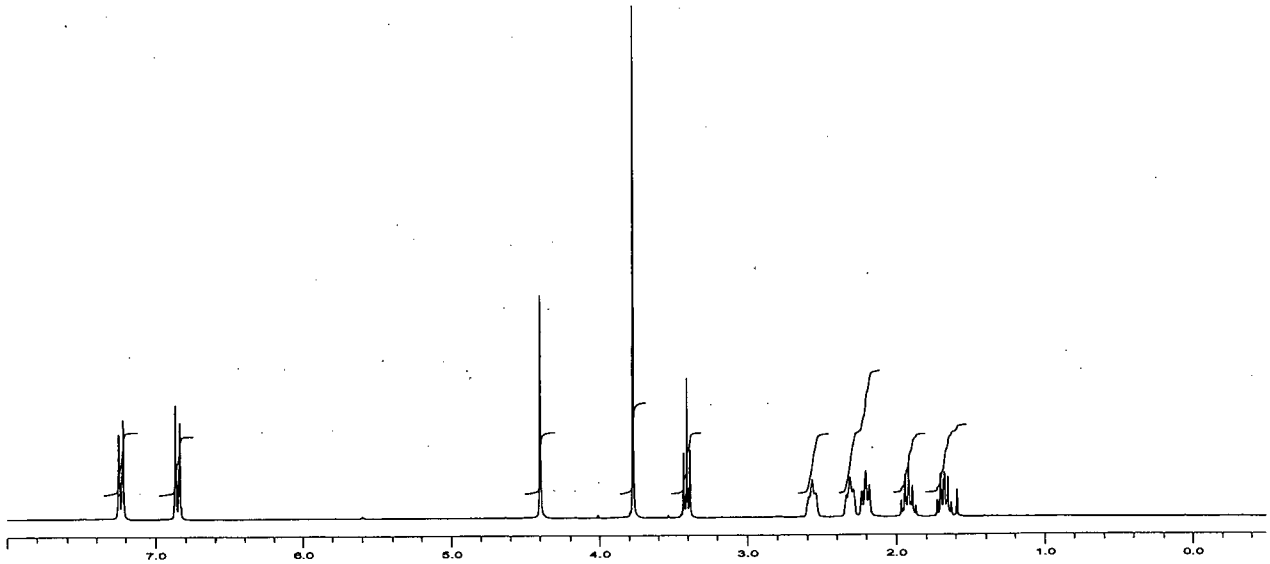
2-(3-(4-Methoxybenzyloxy)propyl)cyclopentanone (**2.68**)

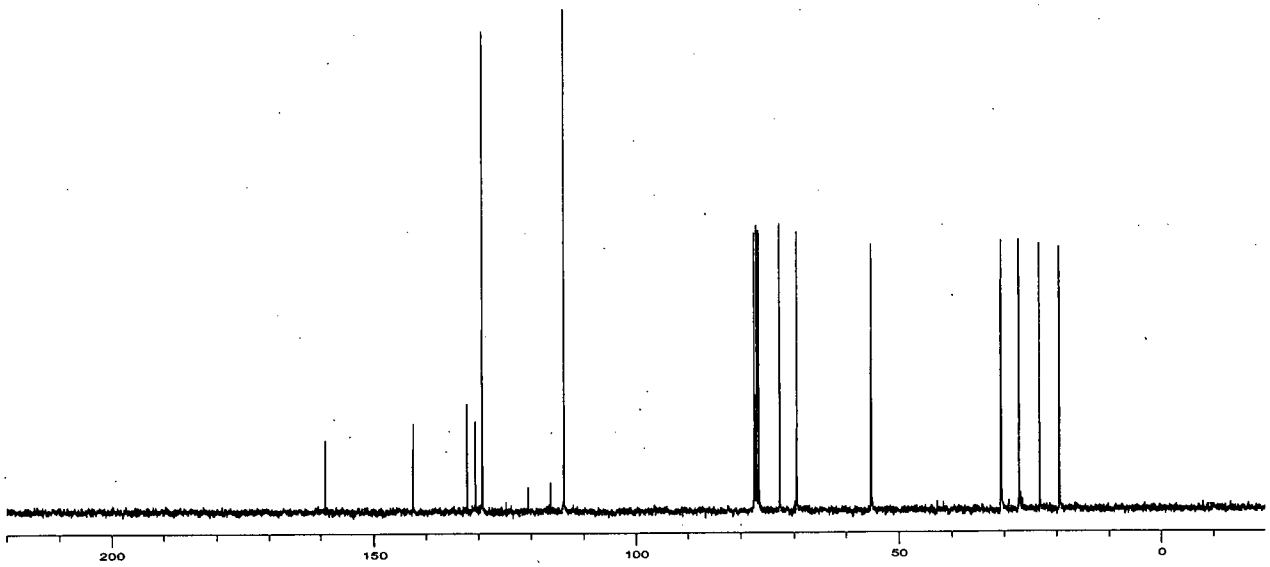


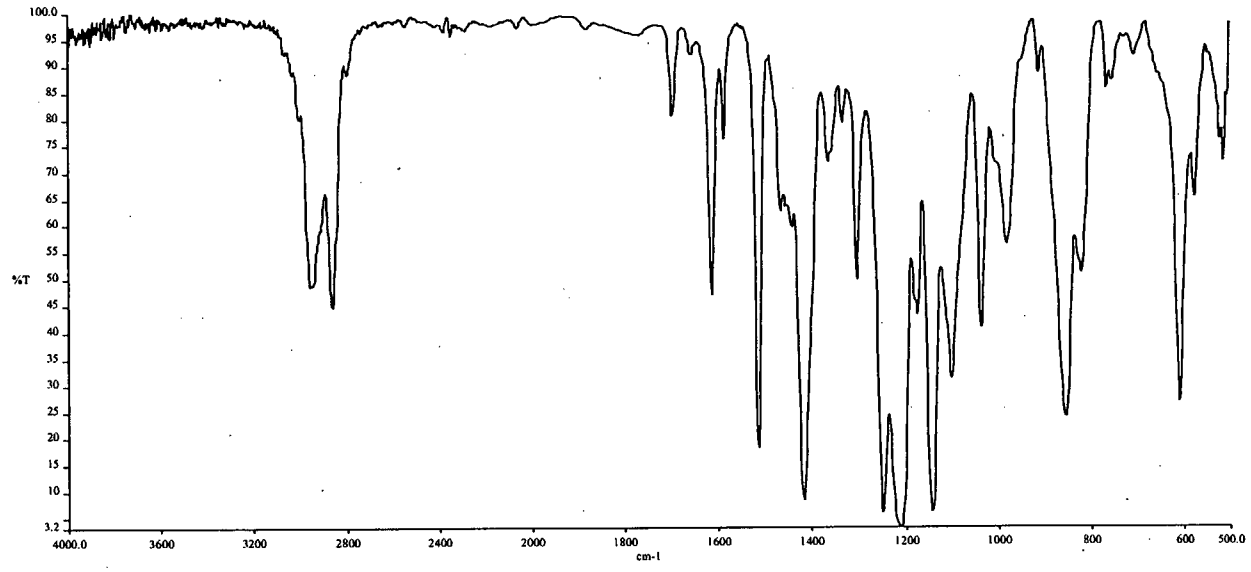




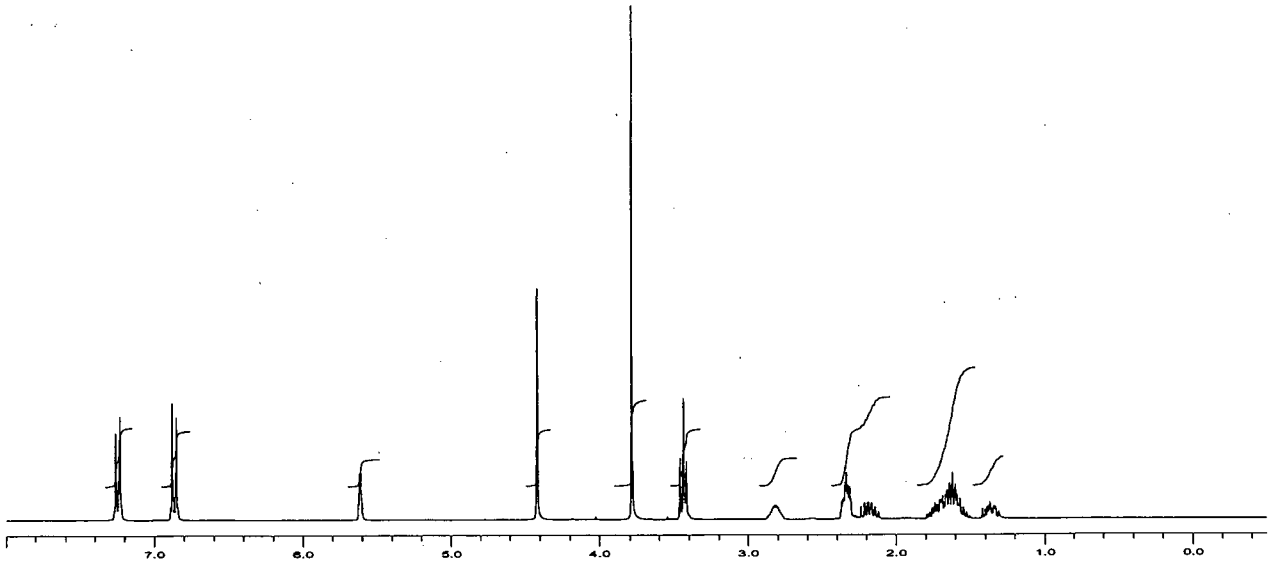
2-(3-(4-Methoxybenzyloxy)propyl)-1-trifluoromethanesulfonatecyclopent-1-ene (**2.54**)

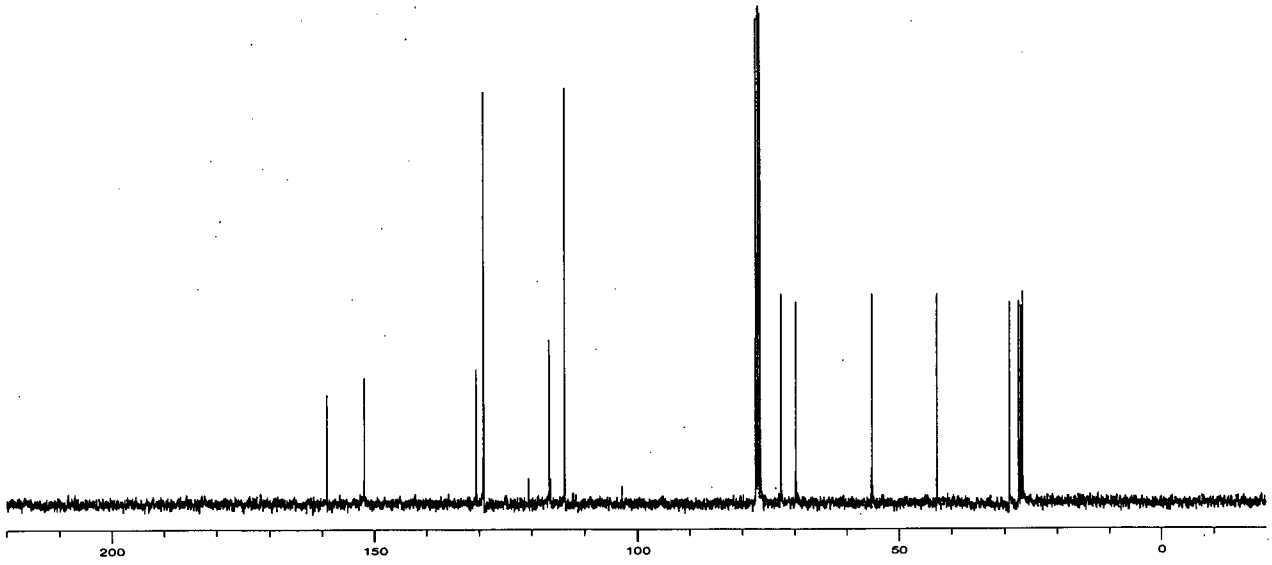


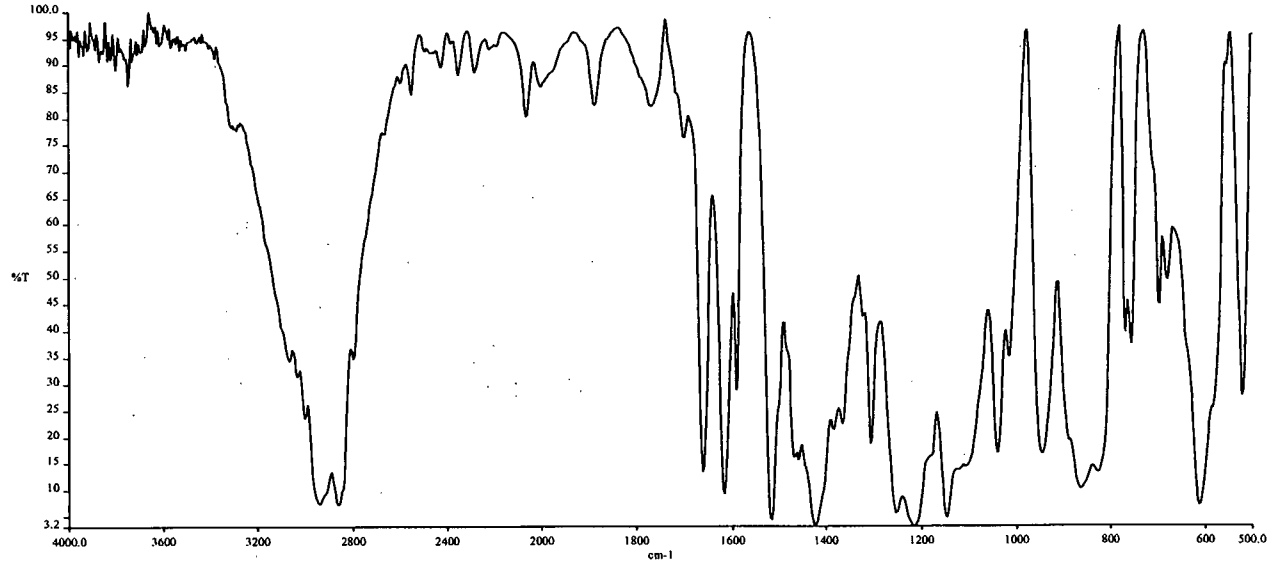




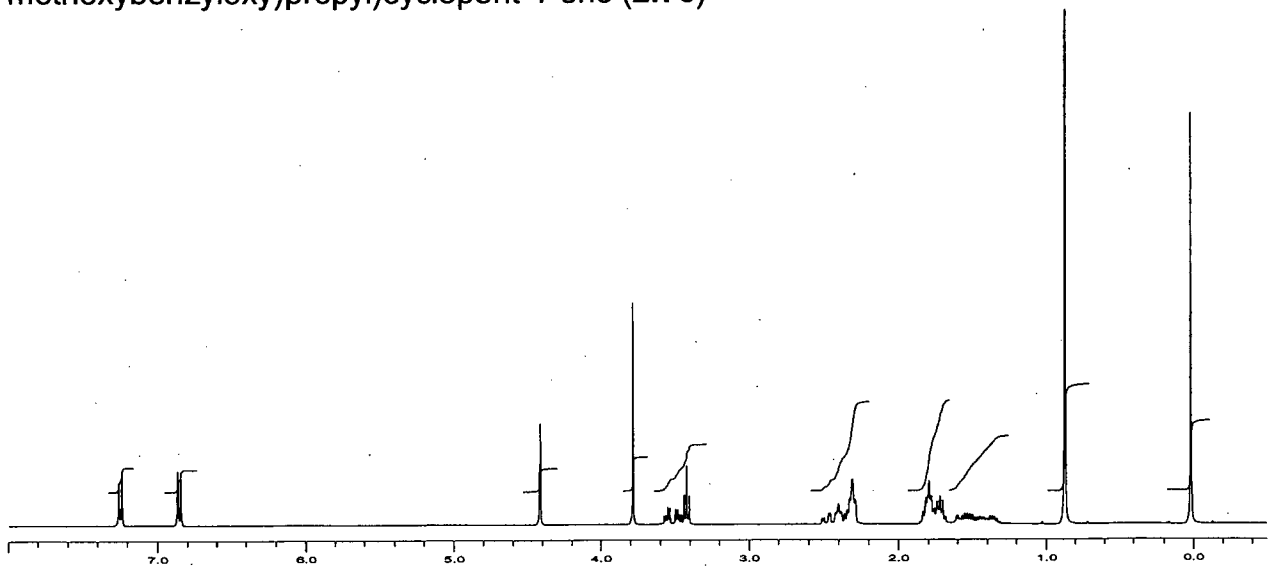
5-(3-(4-Methoxybenzyloxy)propyl)-1-trifluoromethanesulfonatecyclopent-1-ene (**2.69**)

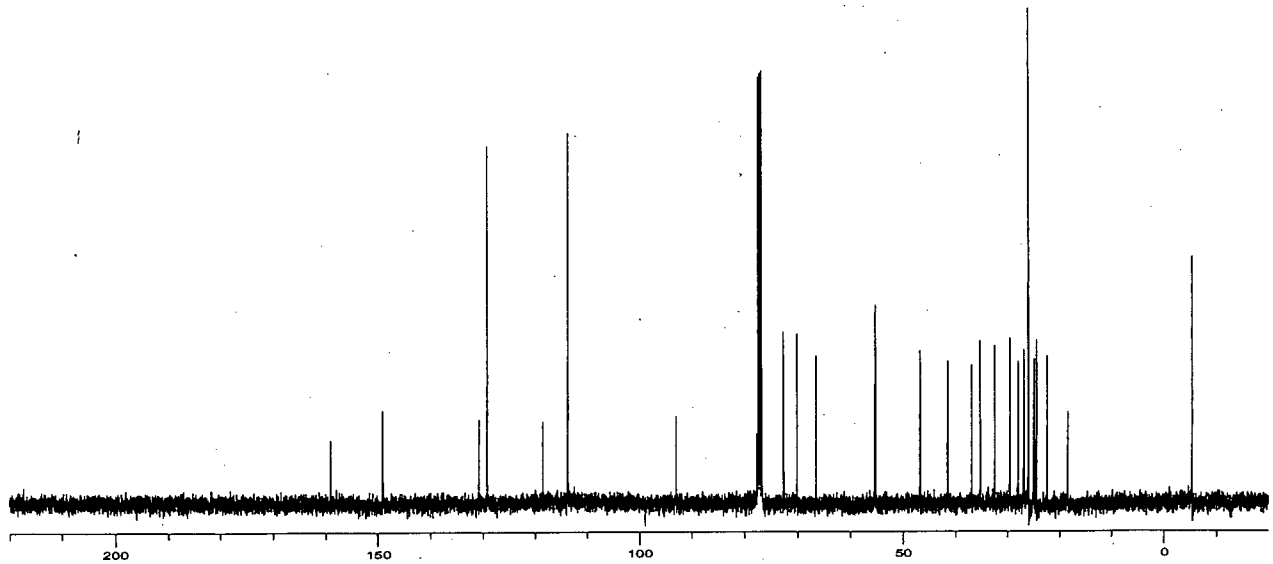


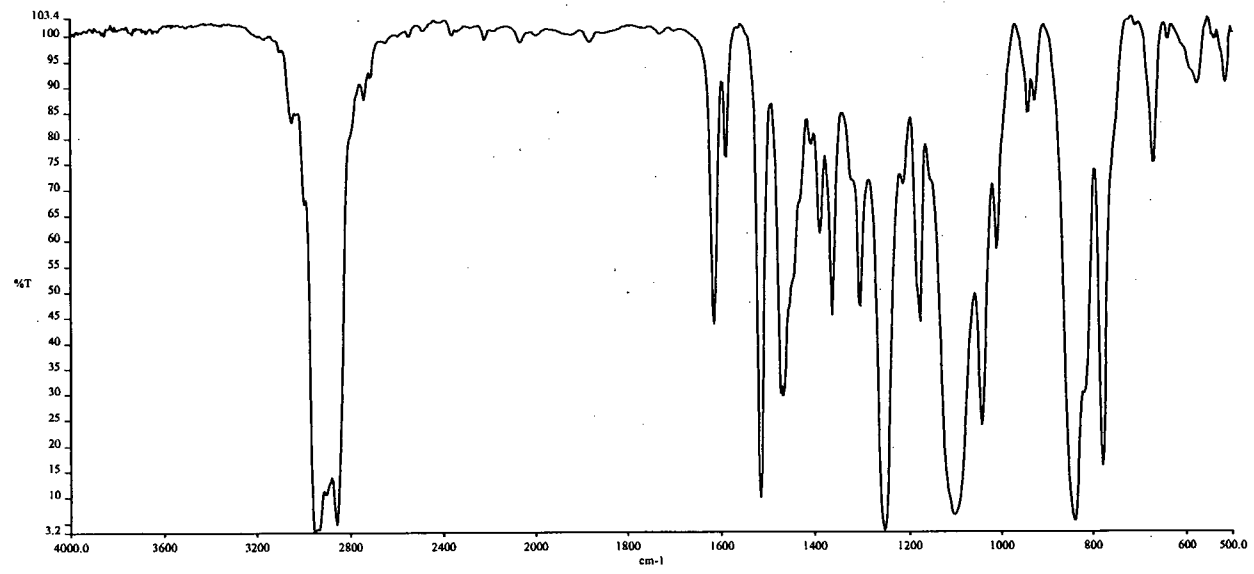




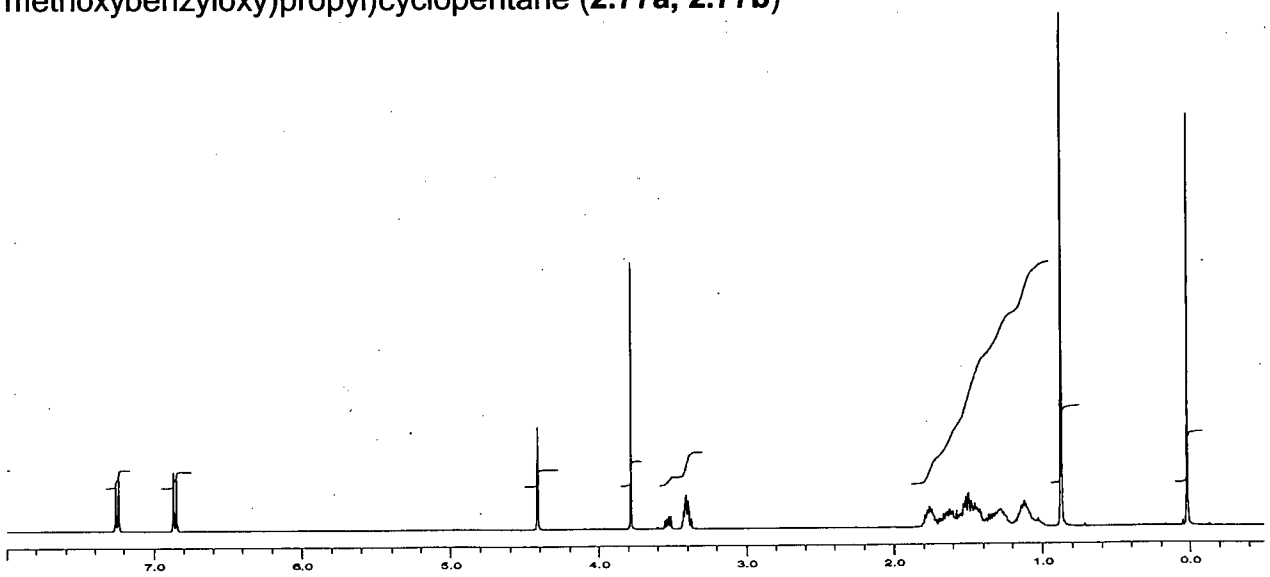
1-(3-((1*R**, 2*S**)-2-(*tert*-Butyldimethylsilyloxymethyl)cyclopentyl)prop-1-ynyl)-2-(3-(4-methoxybenzyloxy)propyl)cyclopent-1-ene (**2.76**)

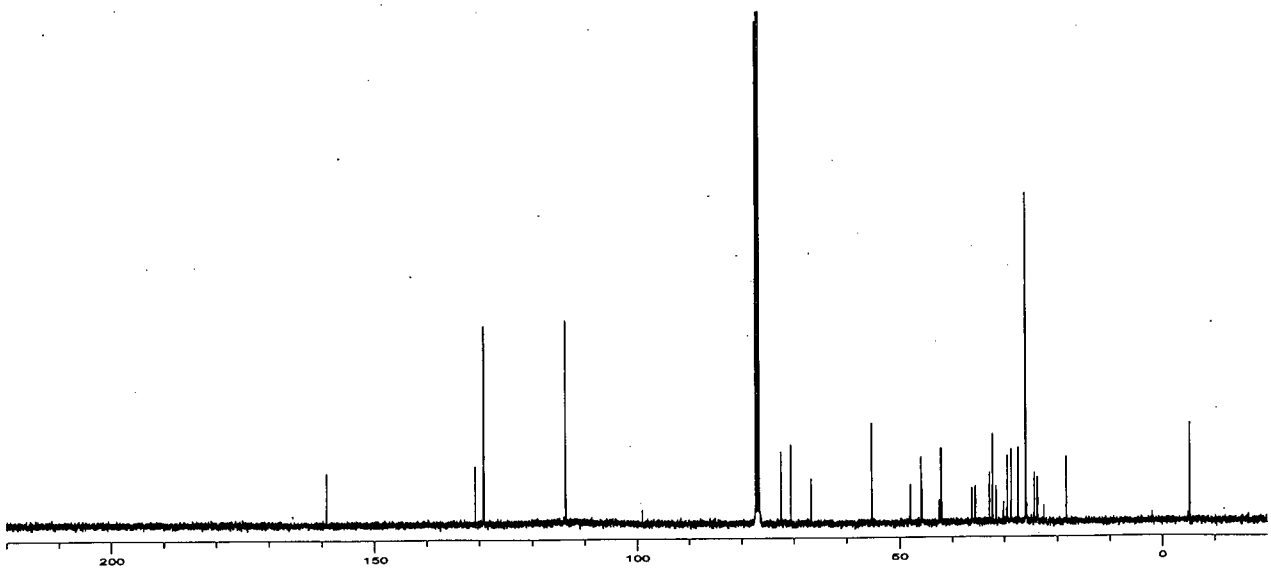


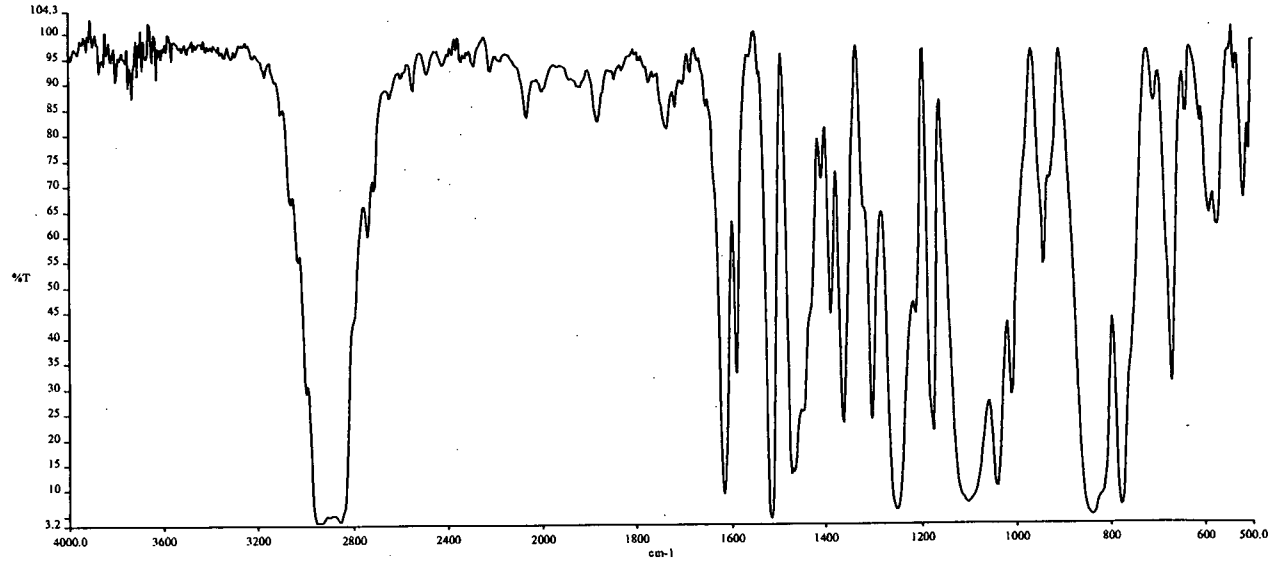




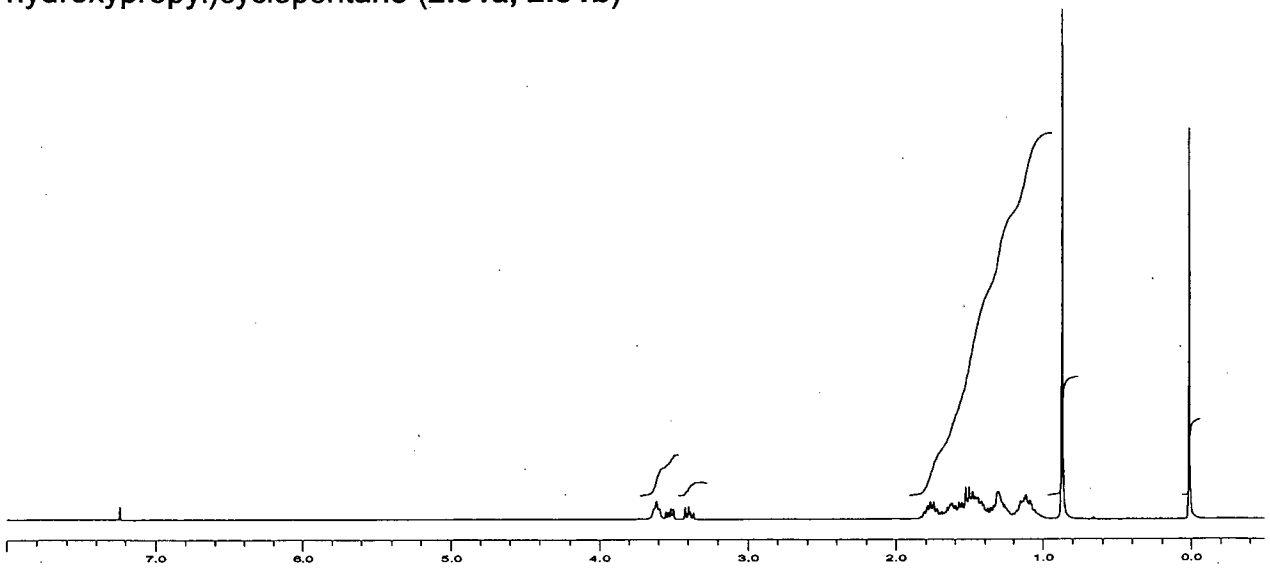
1-(3-((1*R**, 2*S**)-2-(*tert*-Butyldimethylsilyloxymethyl)cyclopentyl)propyl)-2-(3-(4-methoxybenzyloxy)propyl)cyclopentane (**2.77a, 2.77b**)

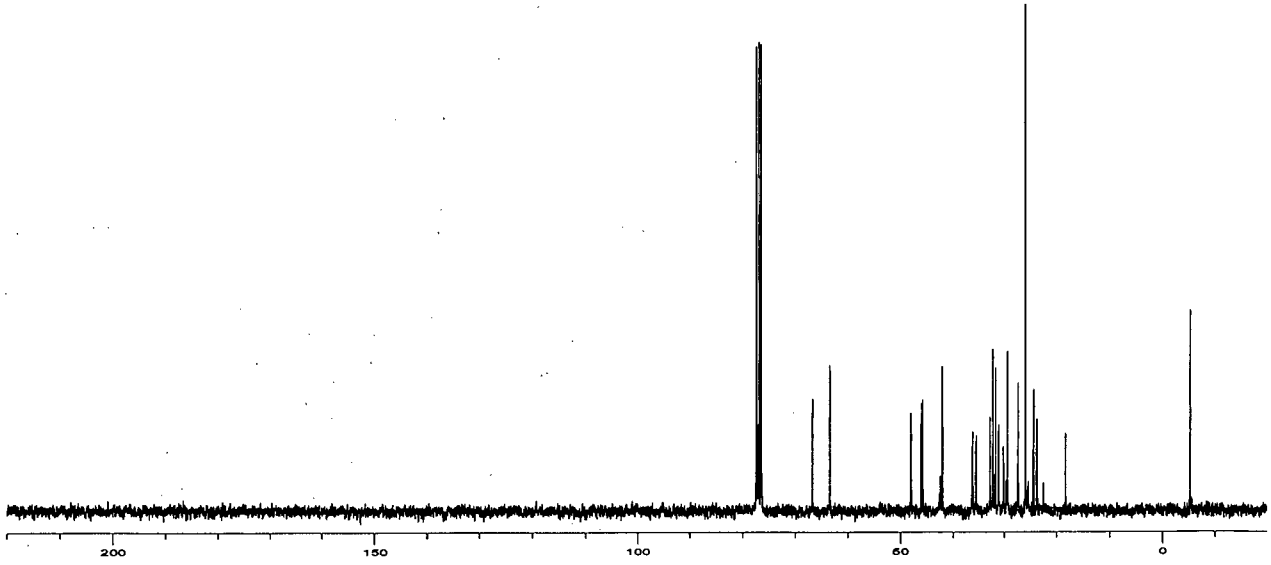


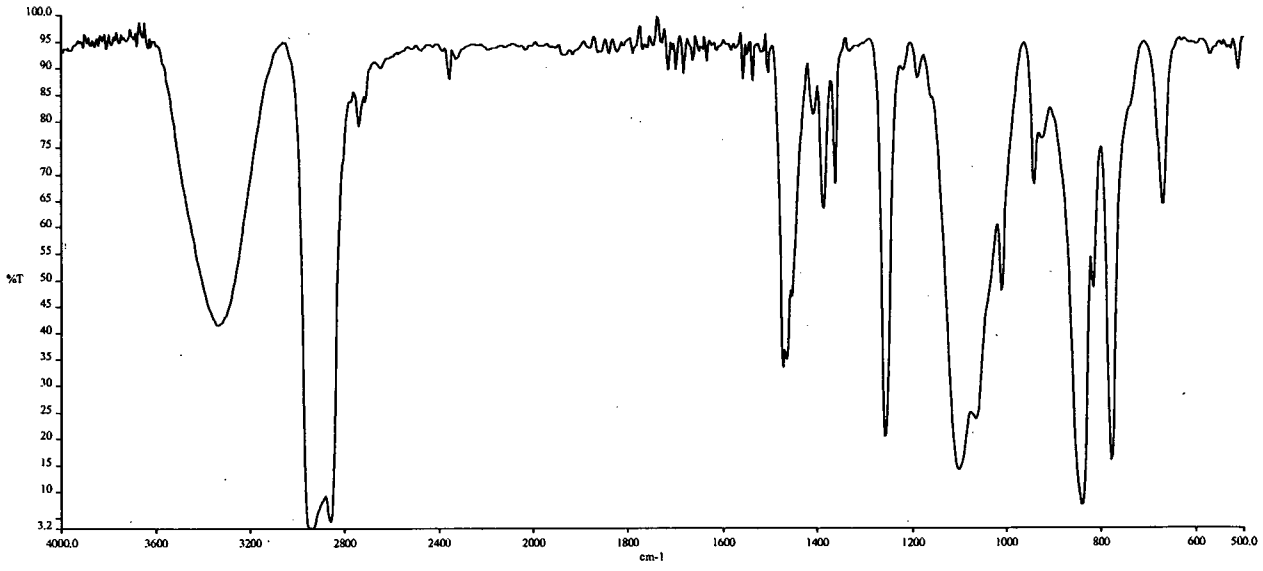




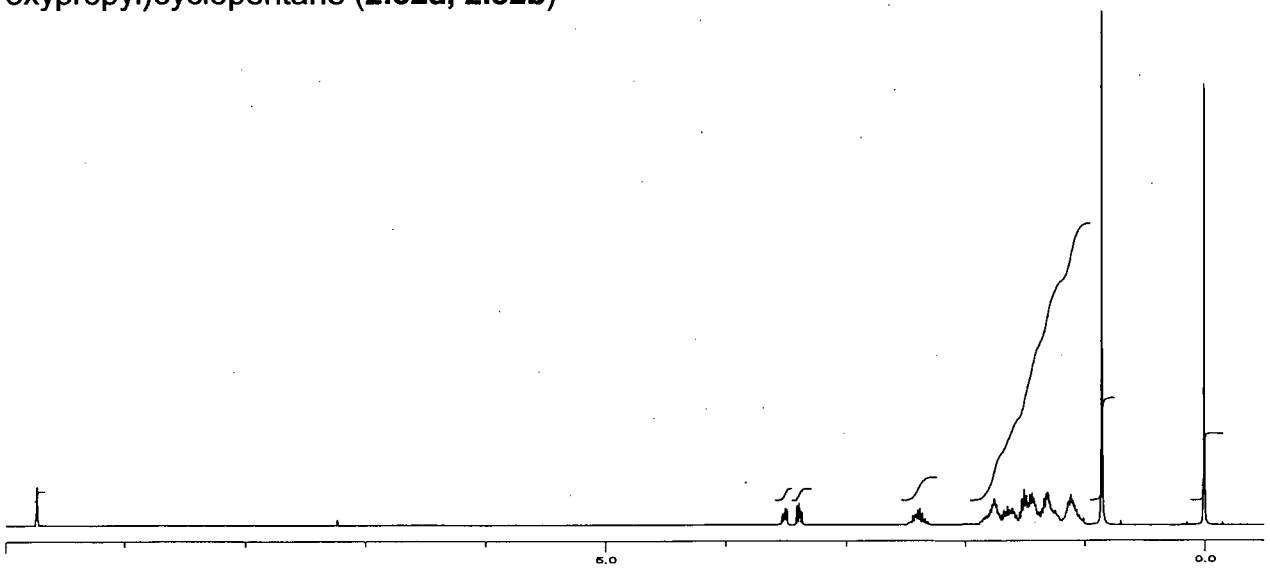
1-(3-((1*R**, 2*S**)-2-(*tert*-Butyldimethylsilyloxymethyl)cyclopentyl)propyl)-2-(3-hydroxypropyl)cyclopentane (**2.81a, 2.81b**)

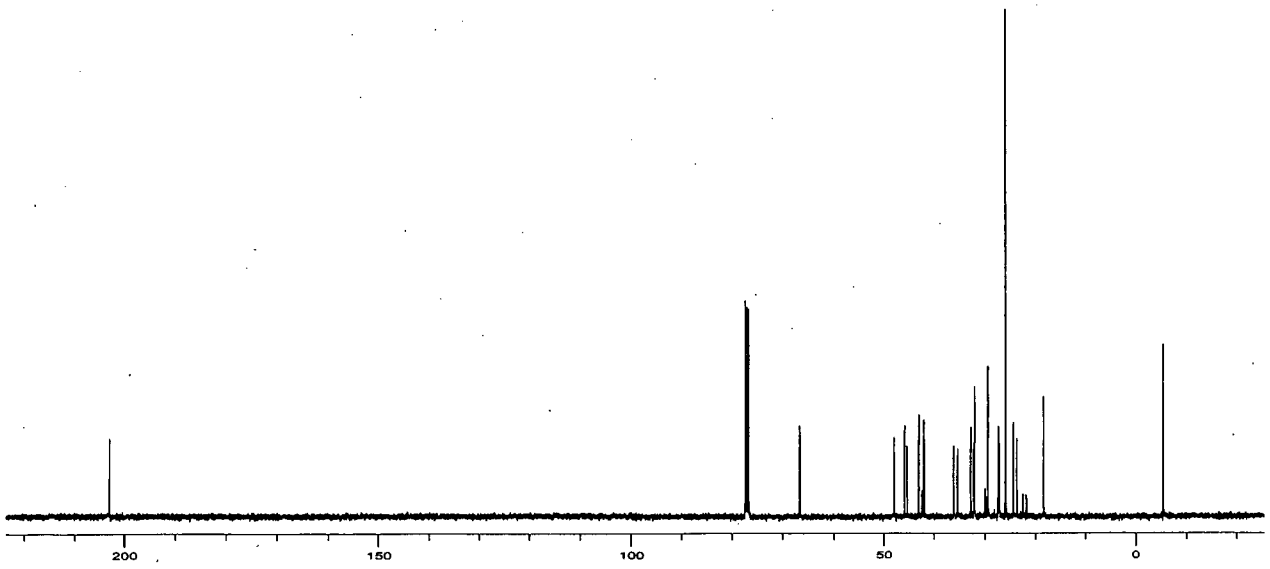


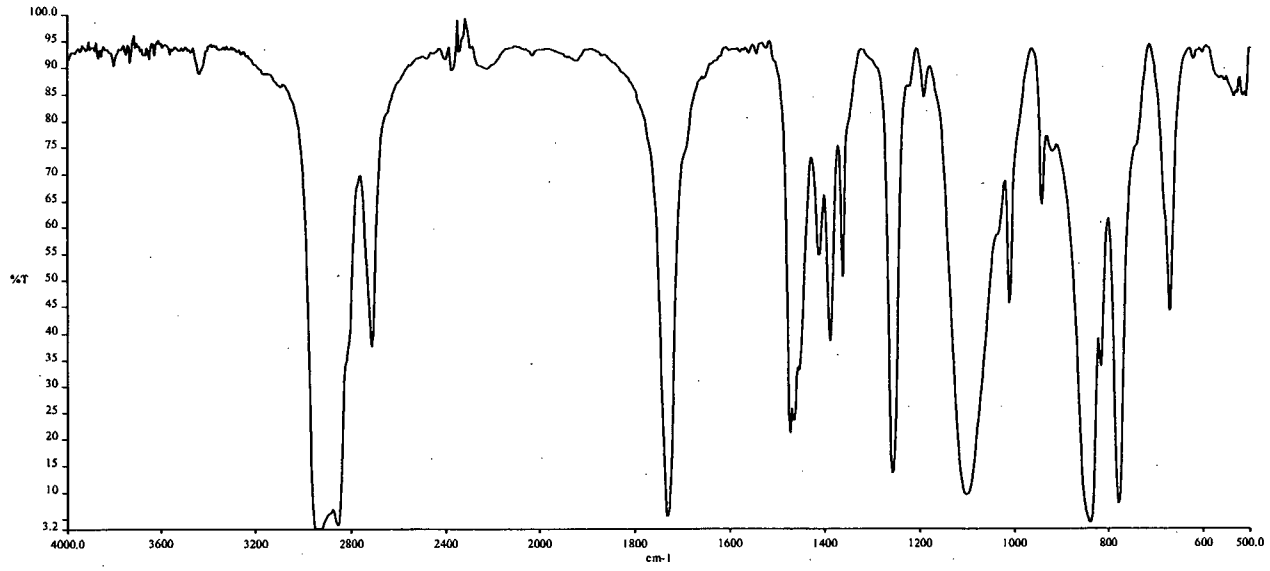




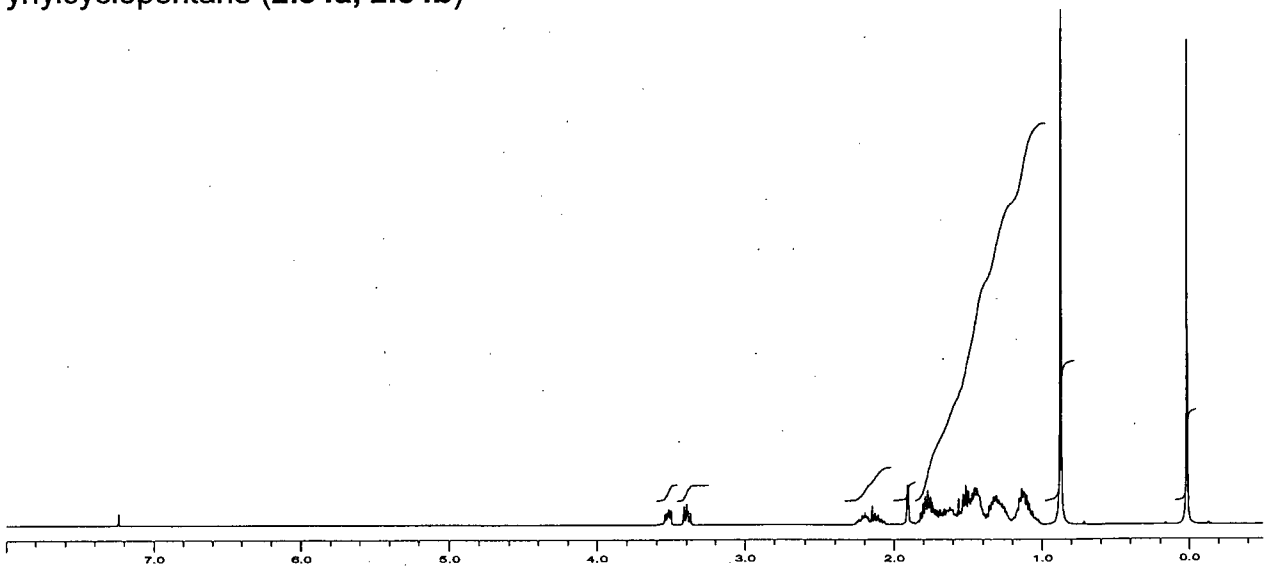
1-(3-((1*R**, 2*S**)-2-(*tert*-Butyldimethylsilyloxymethyl)cyclopentyl)propyl)-2-(3-oxypropyl)cyclopentane (**2.82a, 2.82b**)

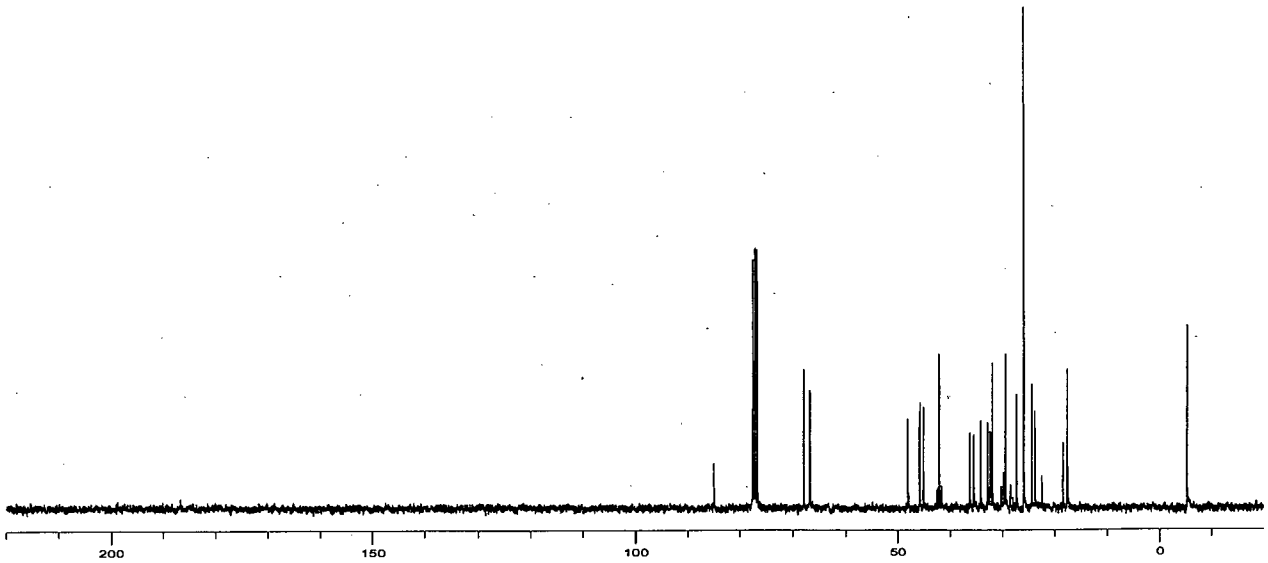


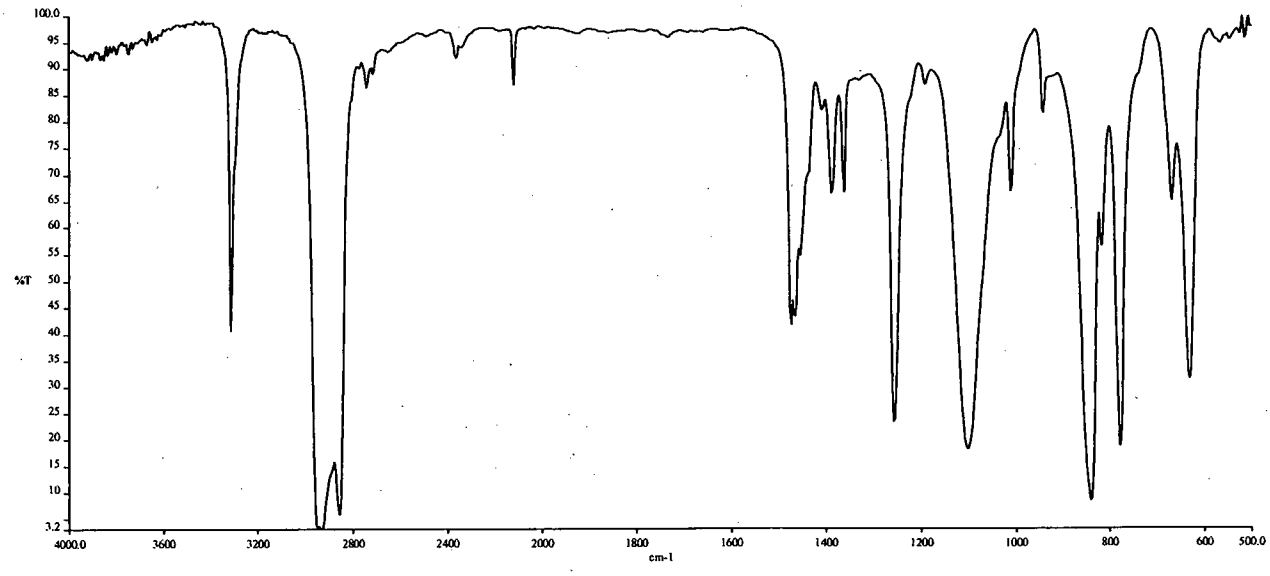




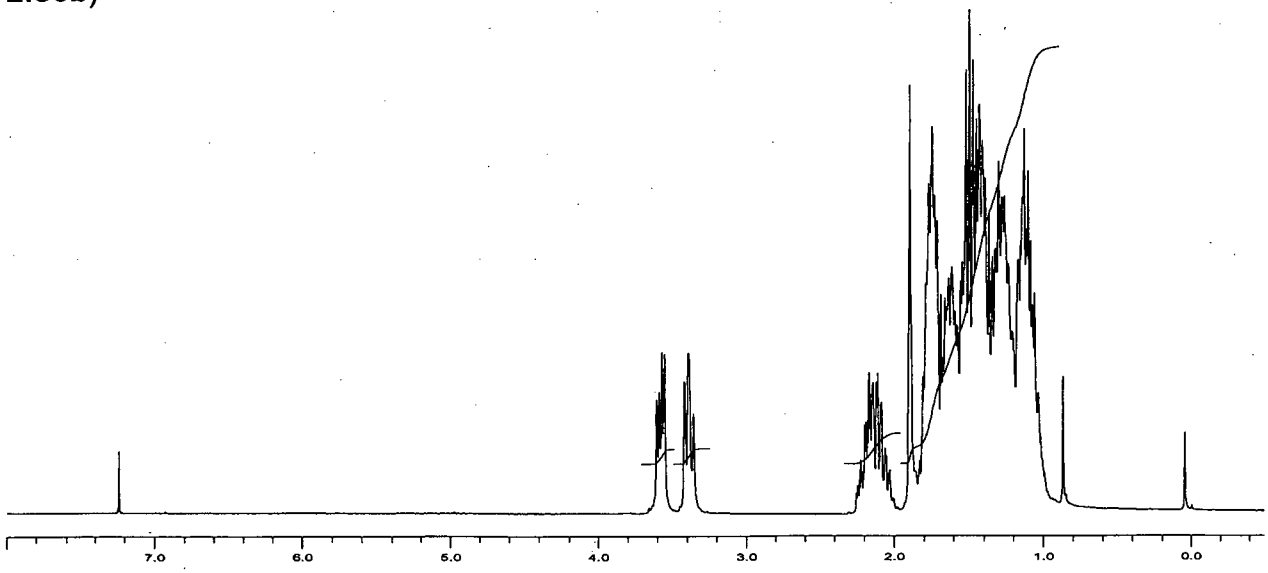
1-(3-((1*R**, 2*S**)-2-(*tert*-Butyldimethylsilyloxymethyl)cyclopentyl)propyl)-2-but-3-ynylcyclopentane (**2.84a, 2.84b**)

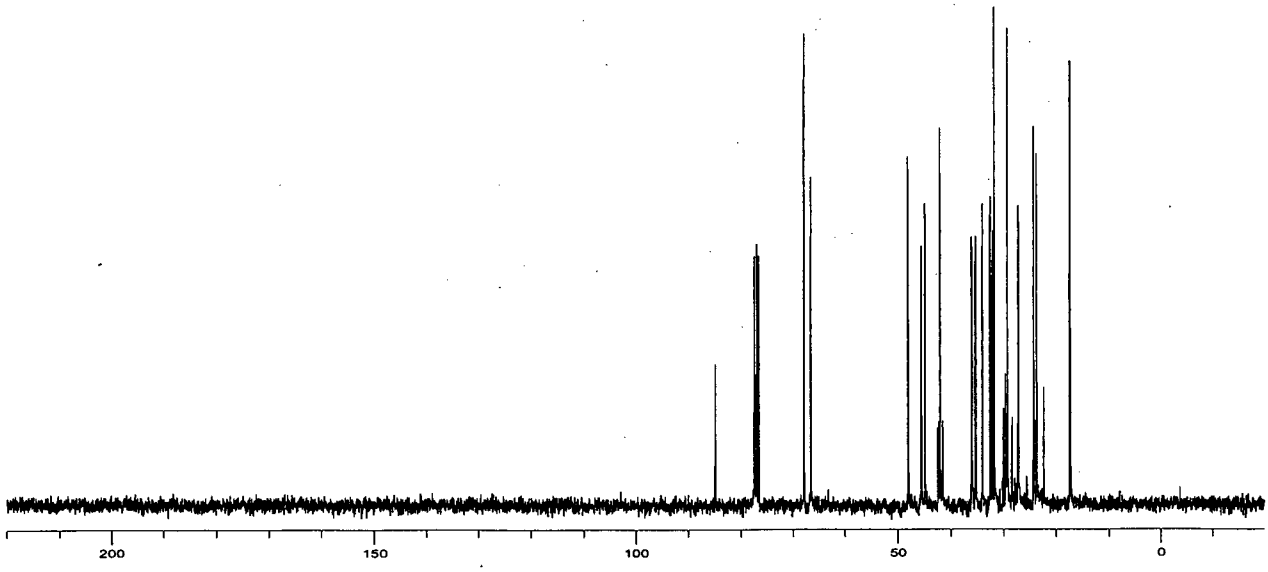


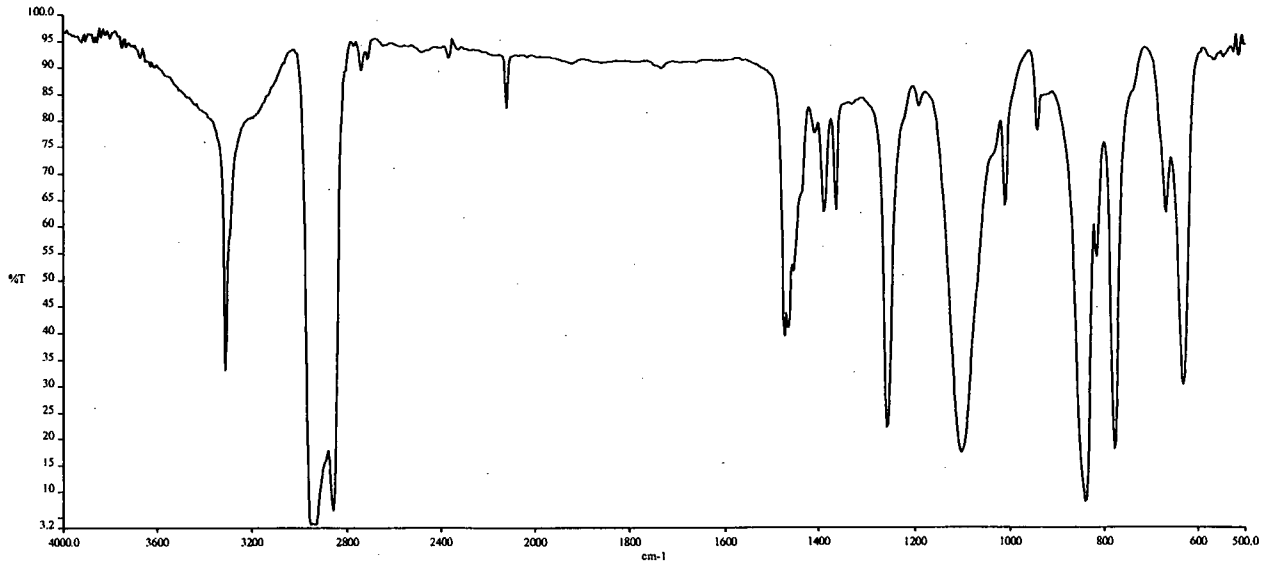




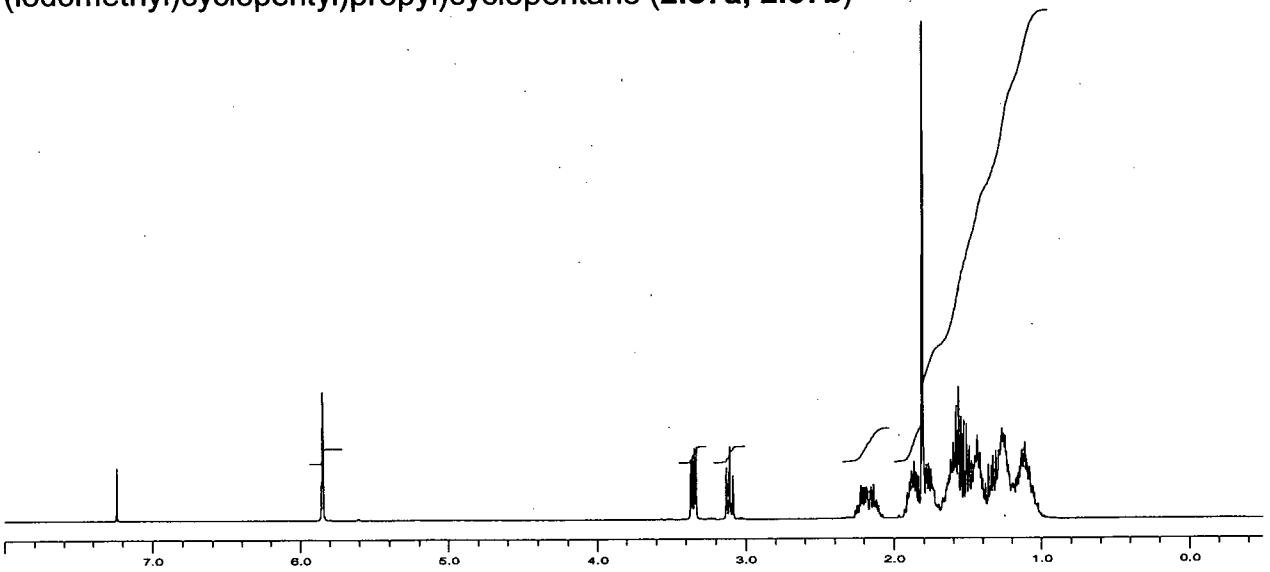
2-But-3-ynyl-1-(3-((1*R**, 2*S**)-2-(hydroxymethyl)cyclopentyl)propyl)cyclopentane (**2.85a, 2.85b**)

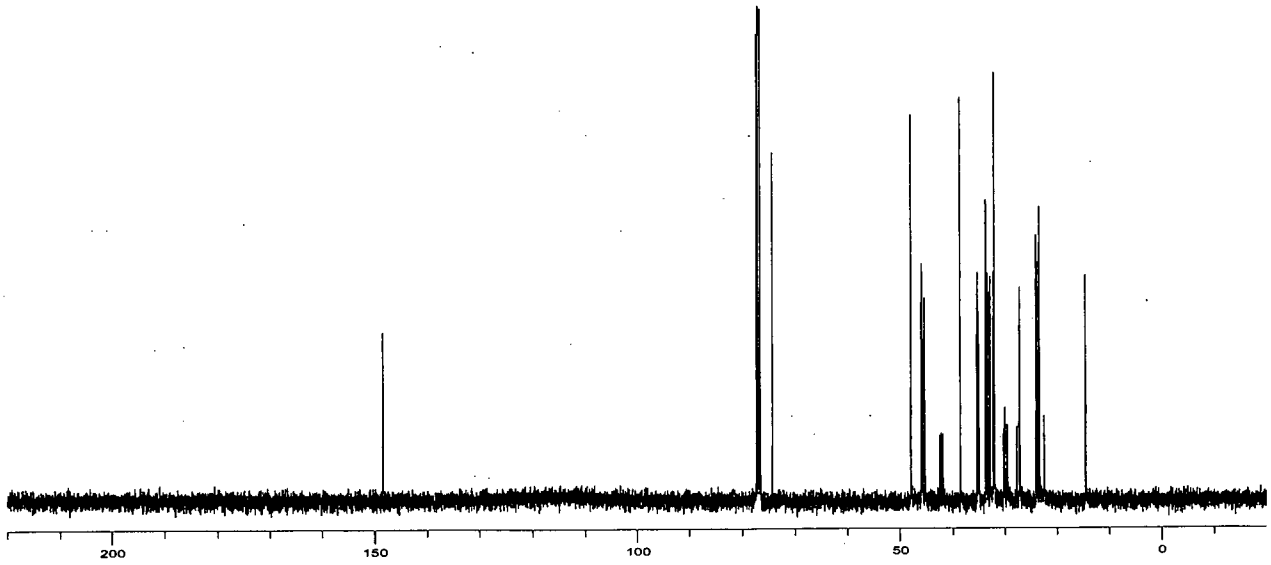


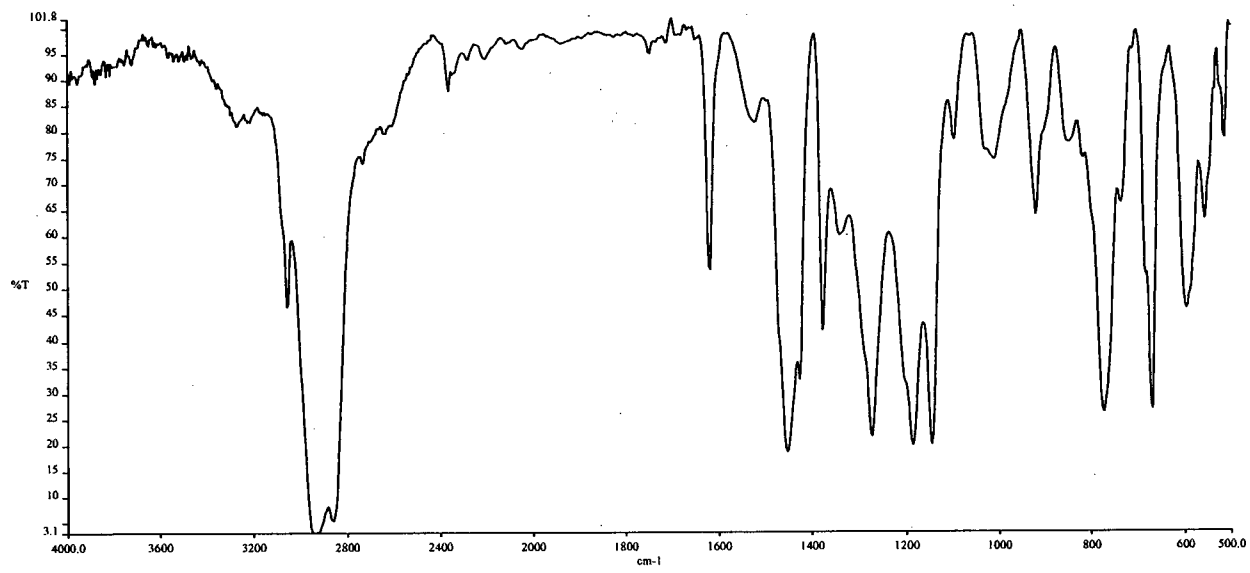




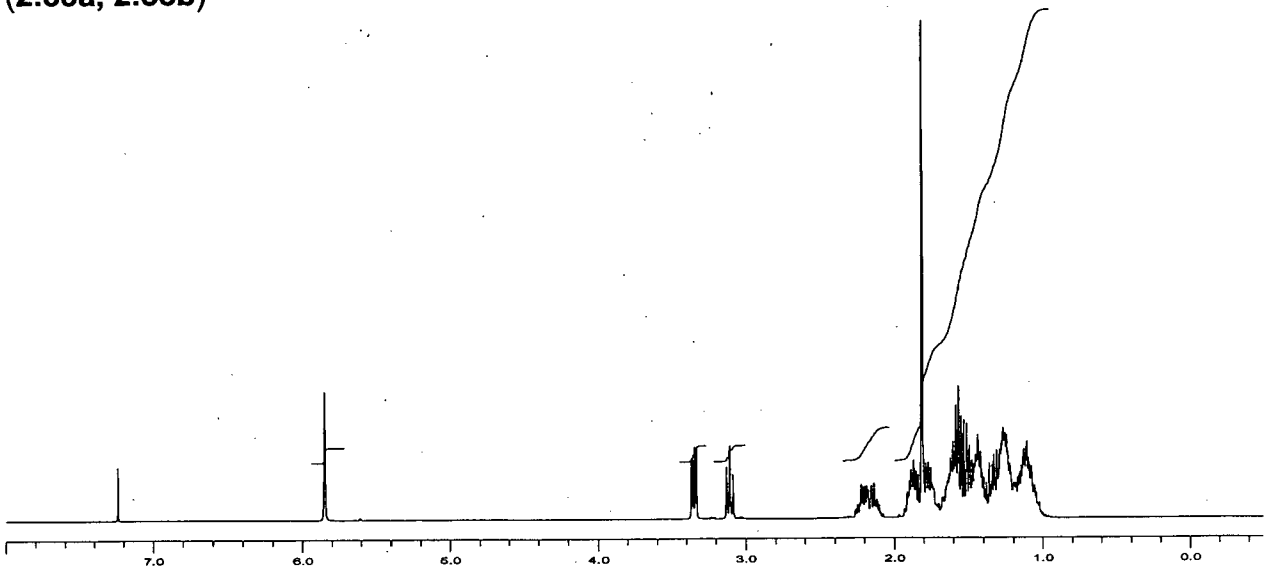
2-((*E*)-3-Methylbut-3-enyl-1-(3-((1*R**, 2*S**)-2-(iodomethyl)cyclopentyl)propyl)cyclopentane (**2.87a, 2.87b**)

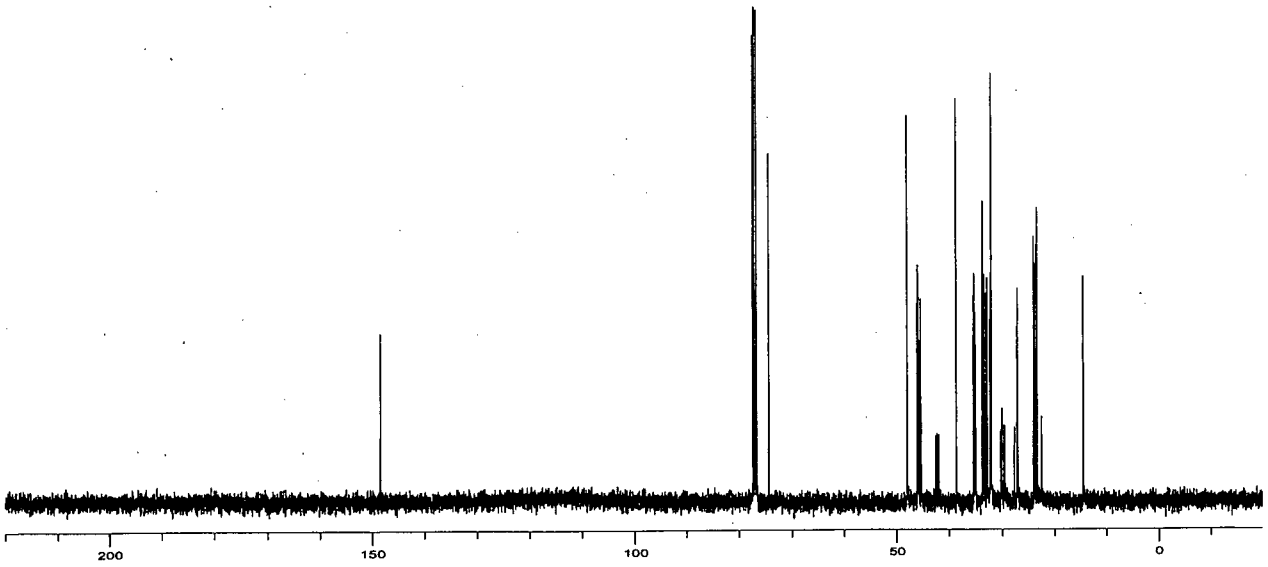


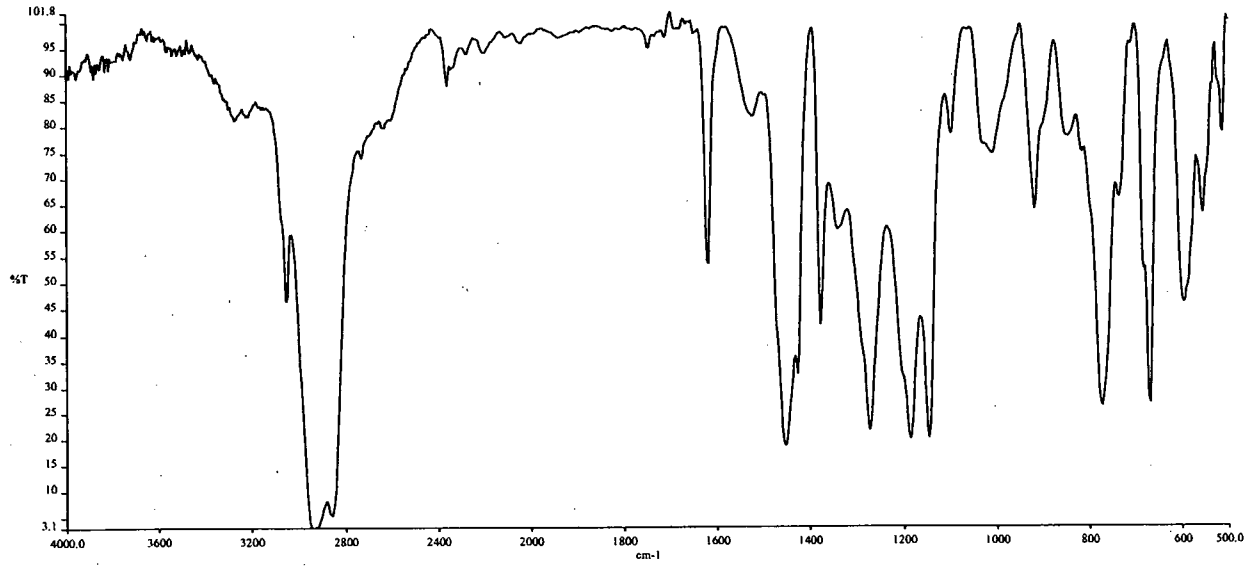




2-((*E*)-3-Methylbut-3-enyl-1-(3-((1*R**, 2*S**)-2-methylcyclopentyl)propyl)cyclopentane (**2.88a, 2.88b**)



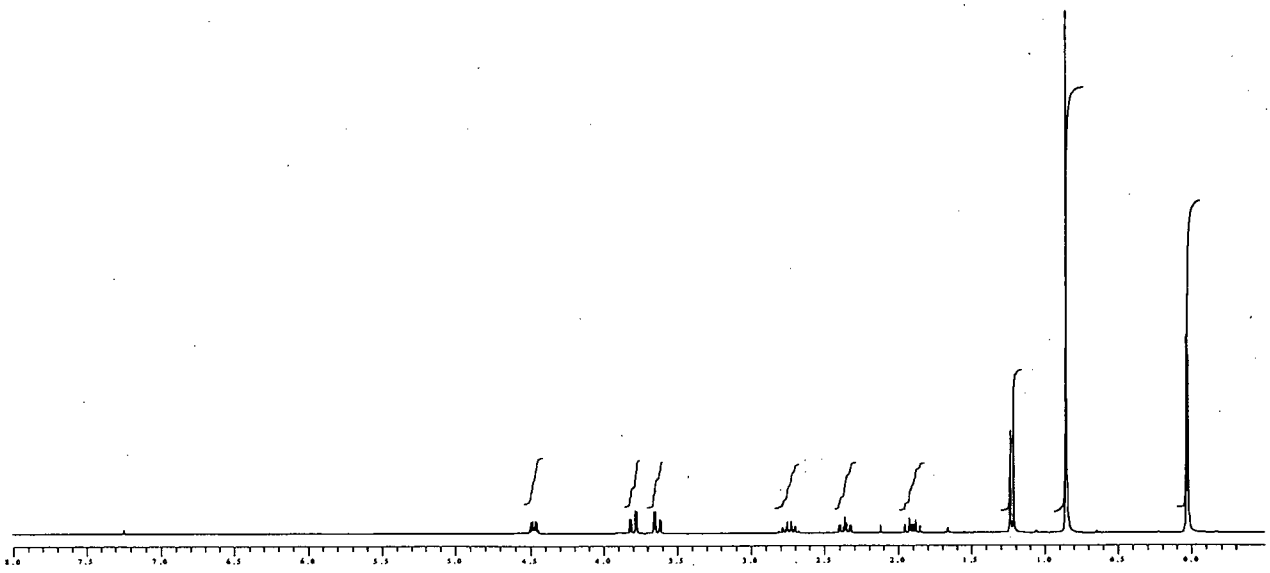


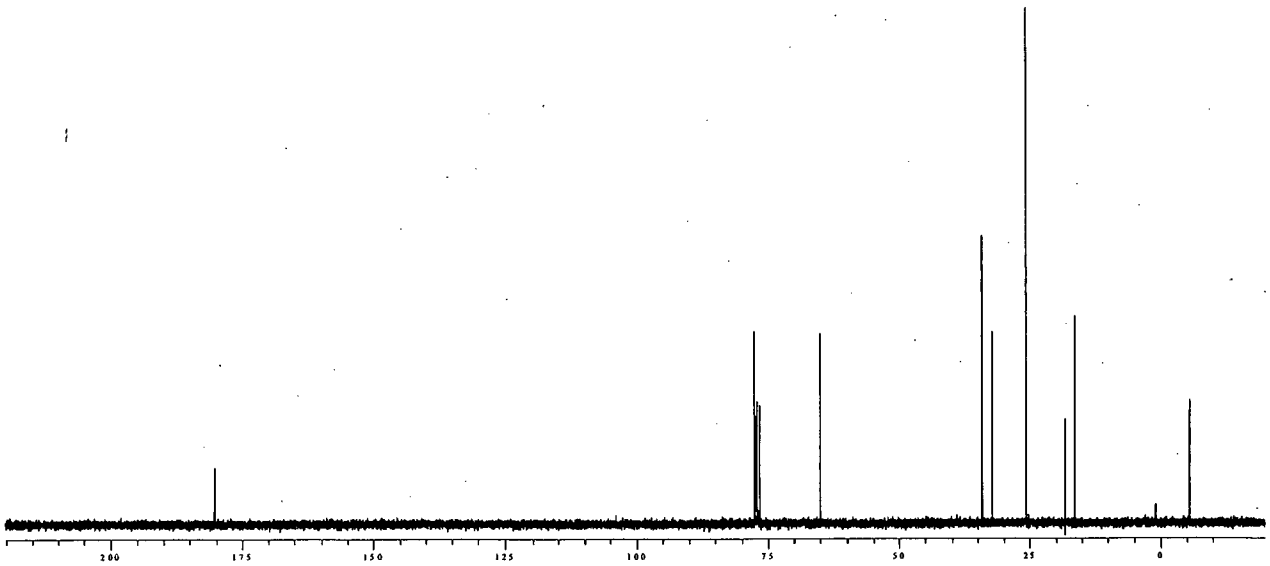


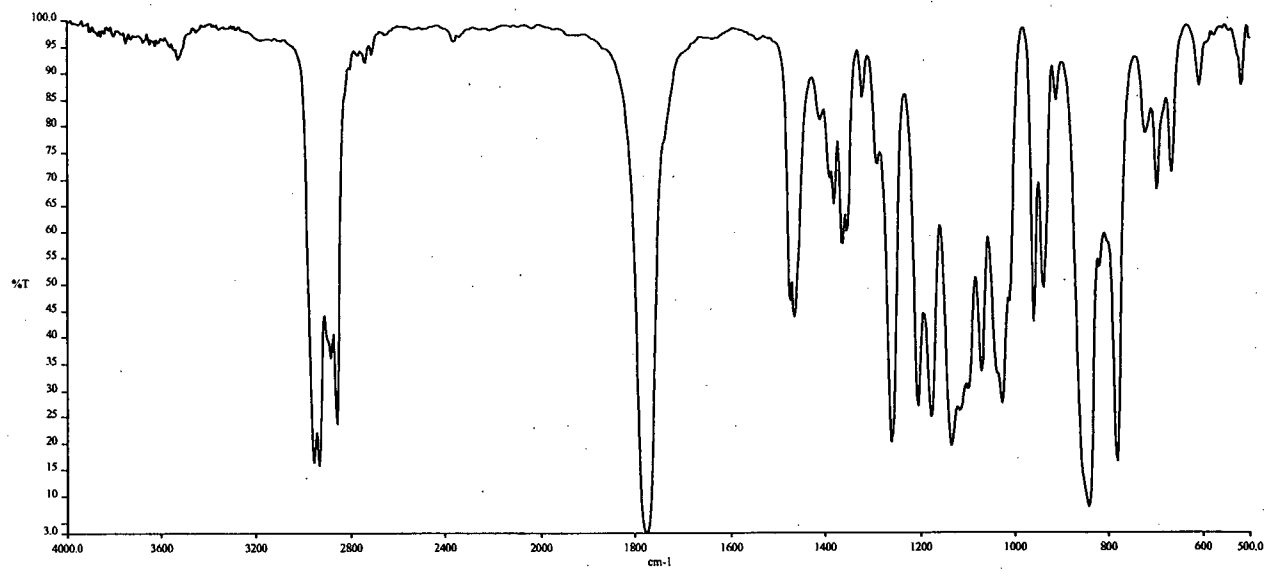
Appendix B

Selected Spectra for Chapter Four

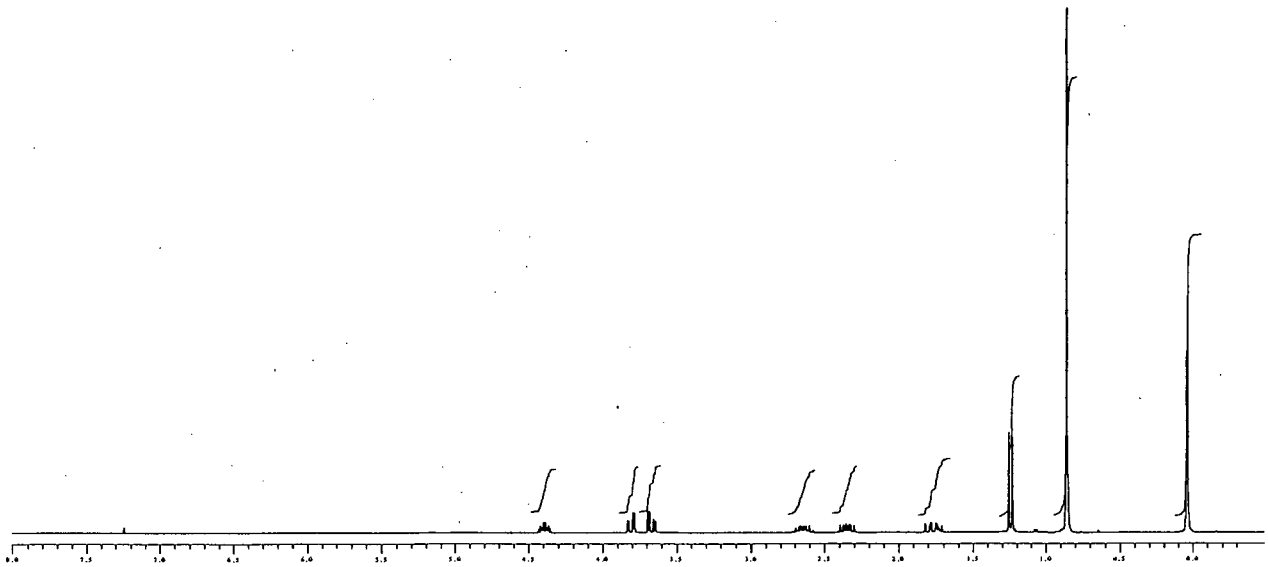
(2*R*, 4*S*)-4-(*tert*-Butyldimethylsilyl)oxymethyl-2-methyl-γ-butyrolactone (**4.16**)

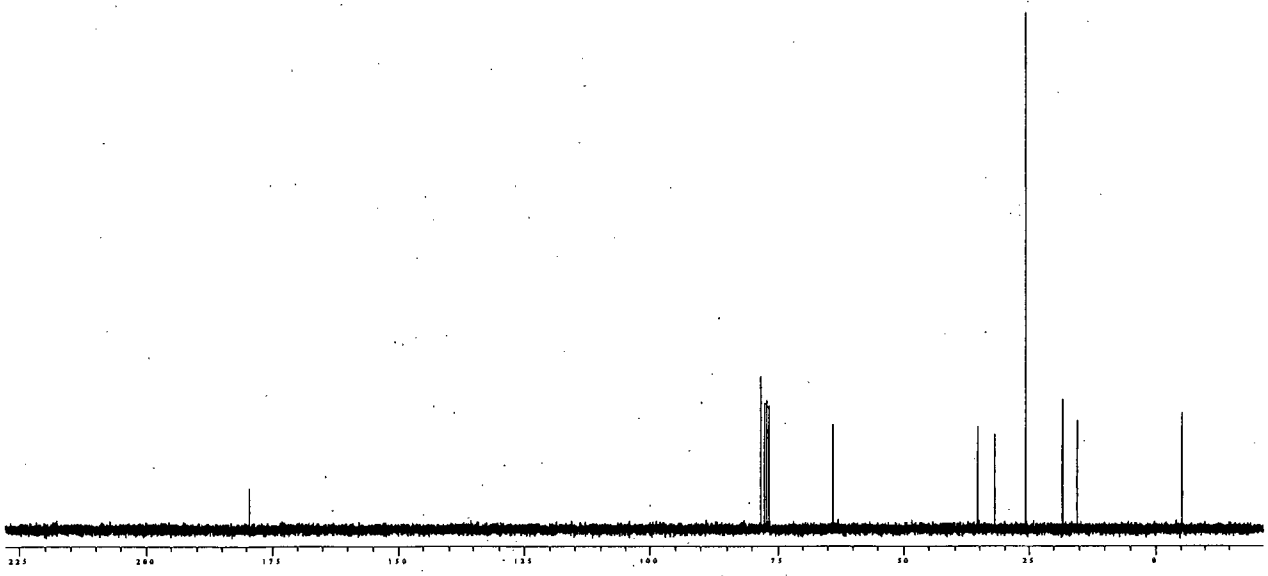


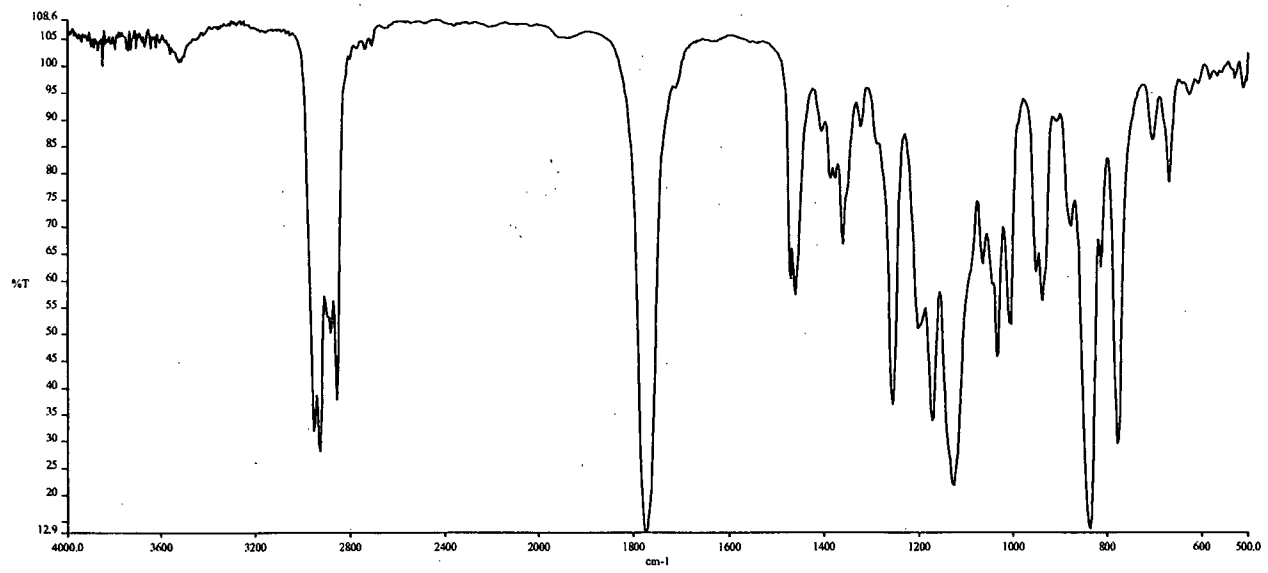




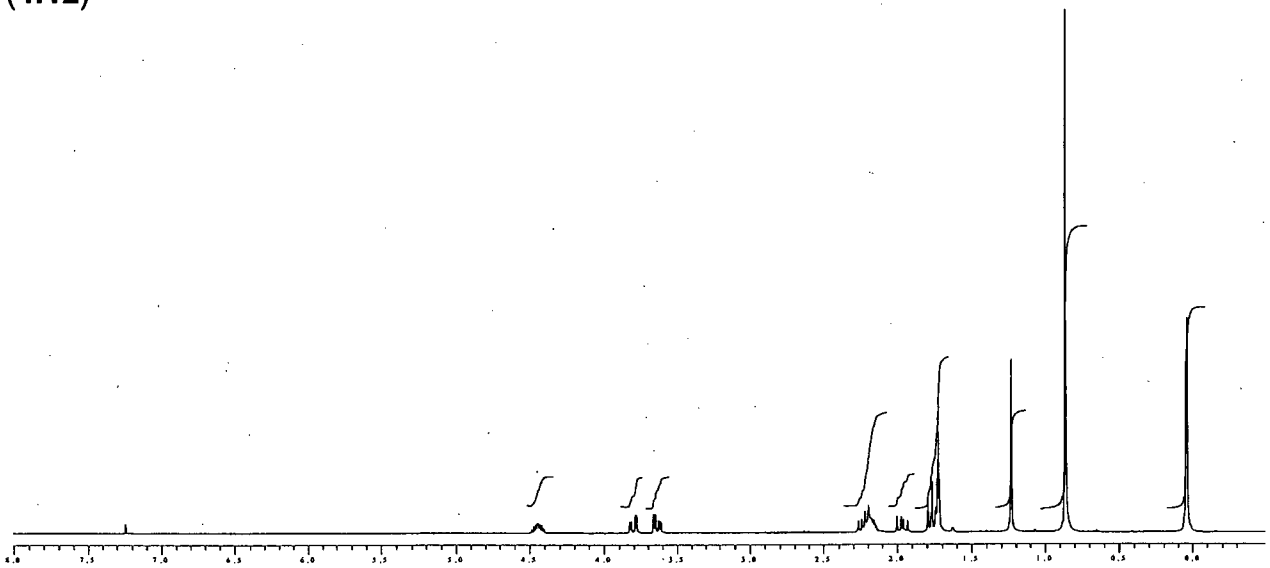
(2*S*, 4*S*)-4-(*tert*-Butyldimethylsilyl)oxymethyl-2-methyl-γ-butyrolactone (**4.17**)

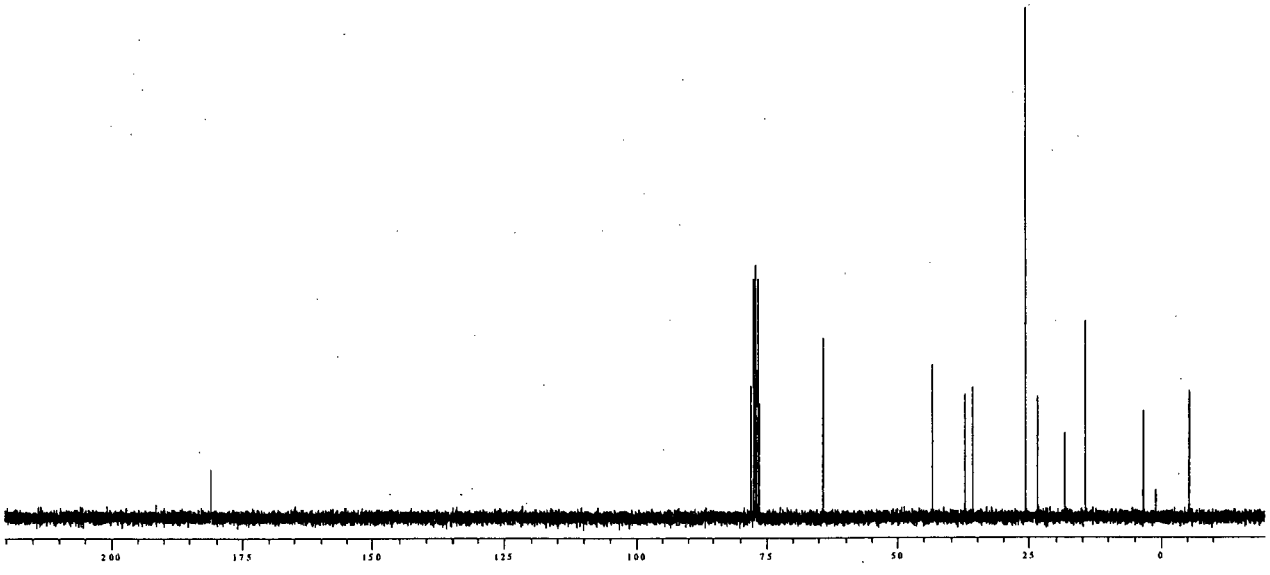


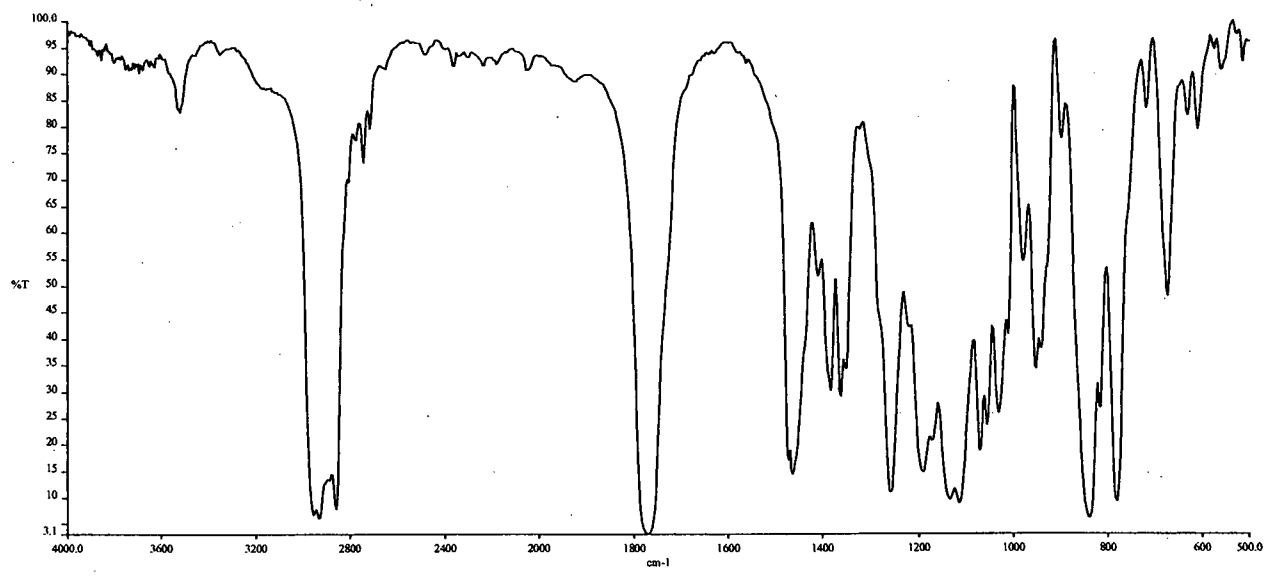




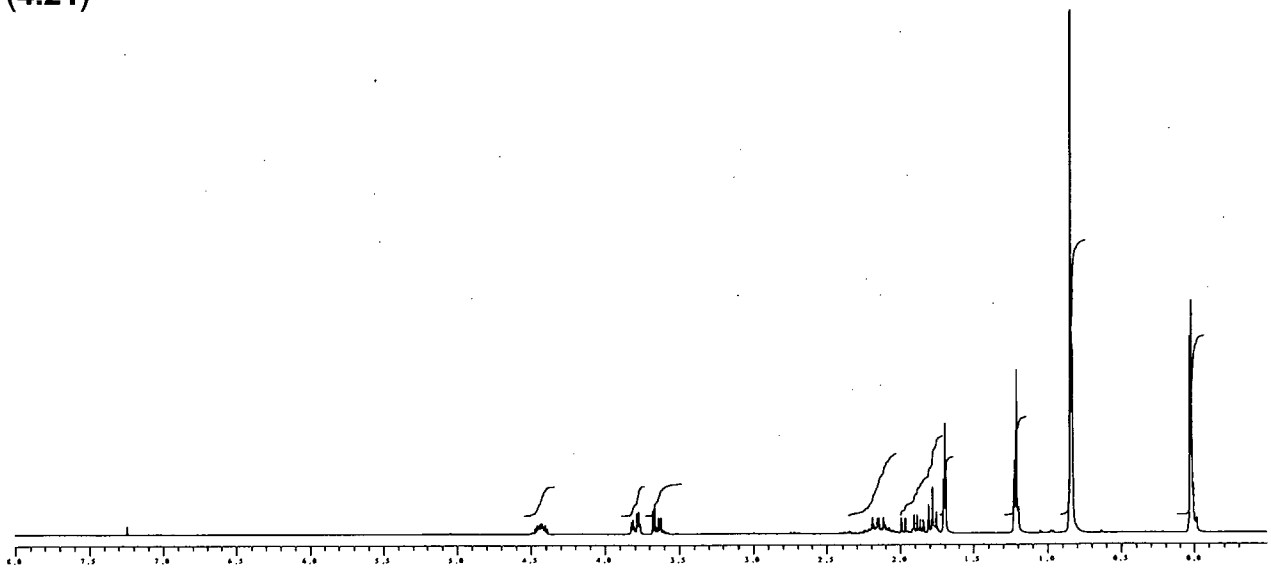
(2*R*, 4*S*)-4-(*tert*-Butyldimethylsilyl)oxymethyl-2-methyl-2-(pent-3-yne)-γ-butyrolactone (**4.12**)

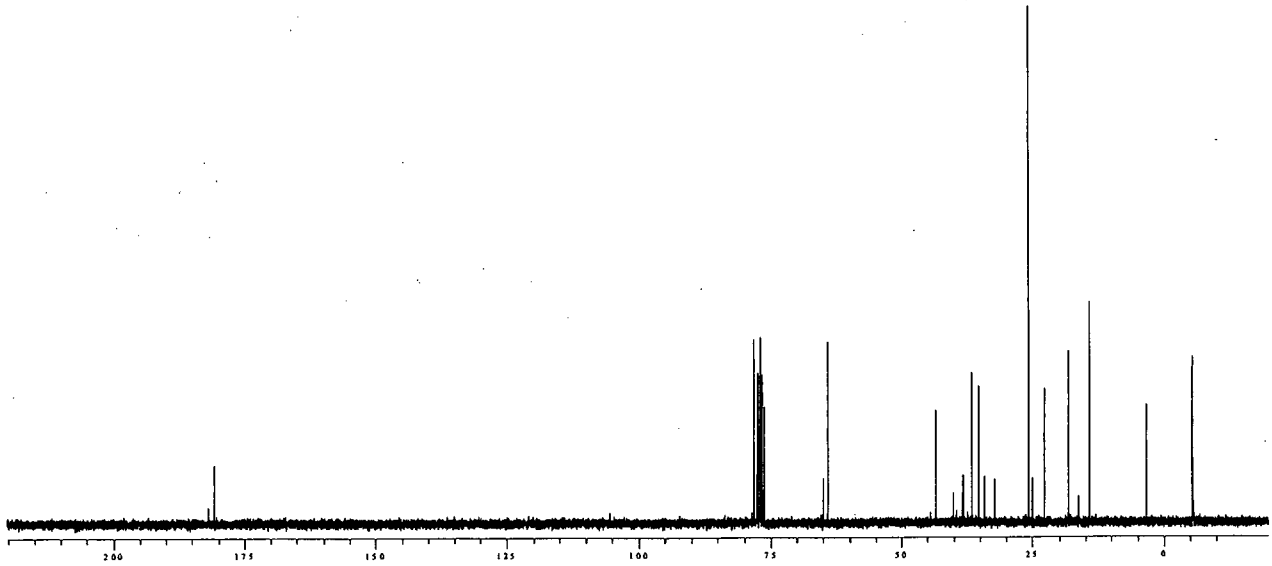


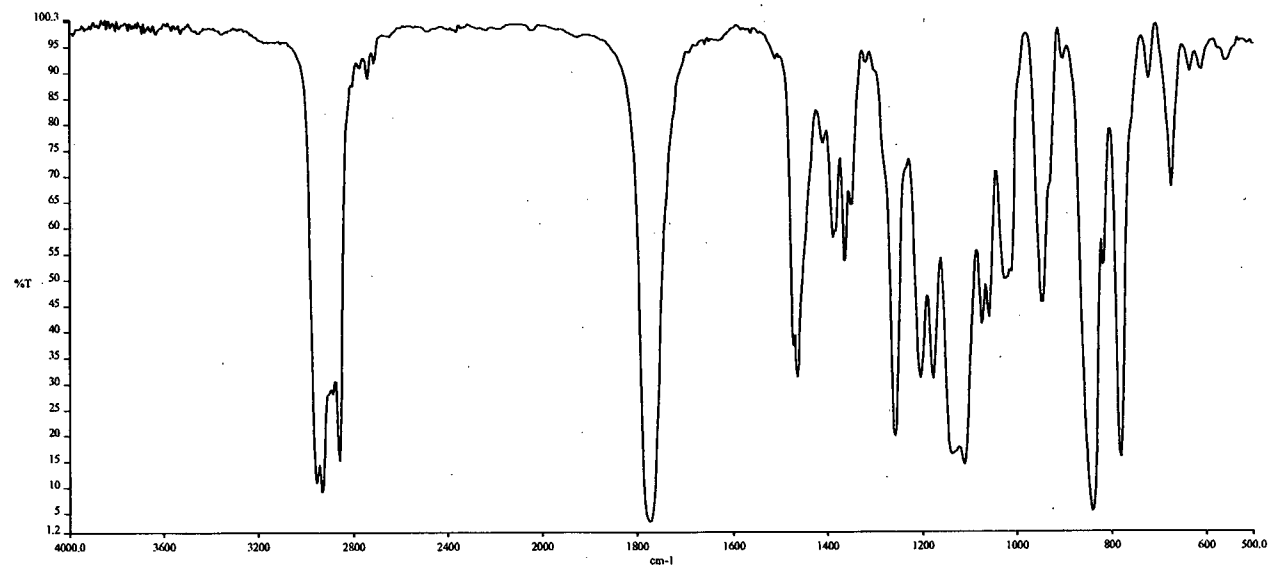




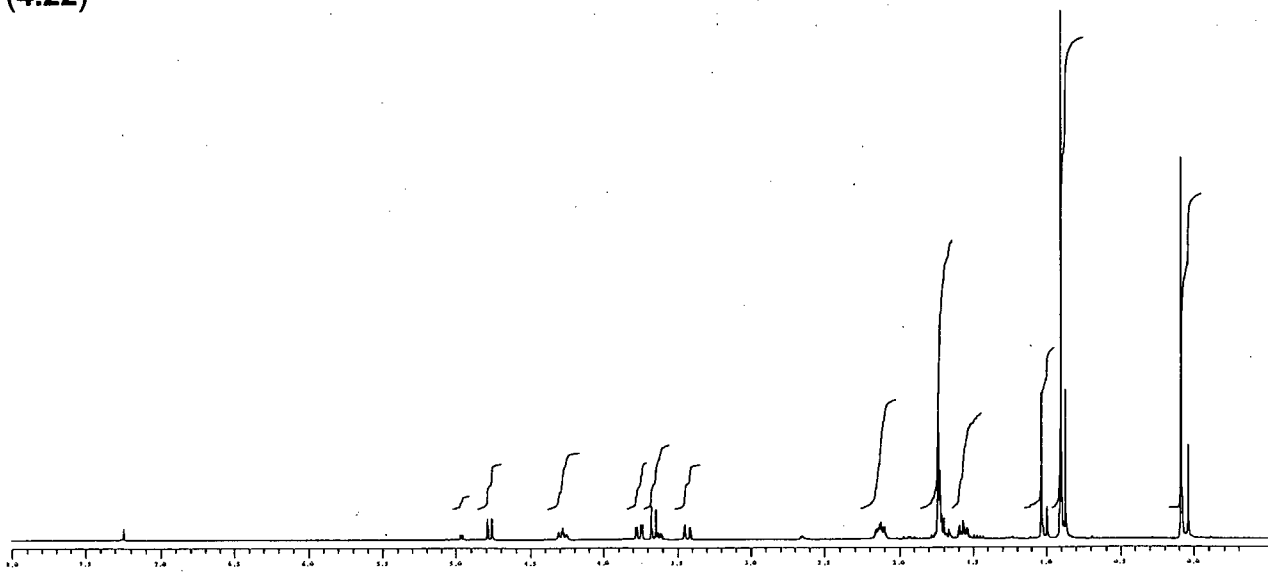
(2*S*, 4*S*)-4-(tert-Butyldimethylsilyl)oxymethyl-2-methyl-2-(pent-3-yne)-γ-butyrolactone (**4.21**)

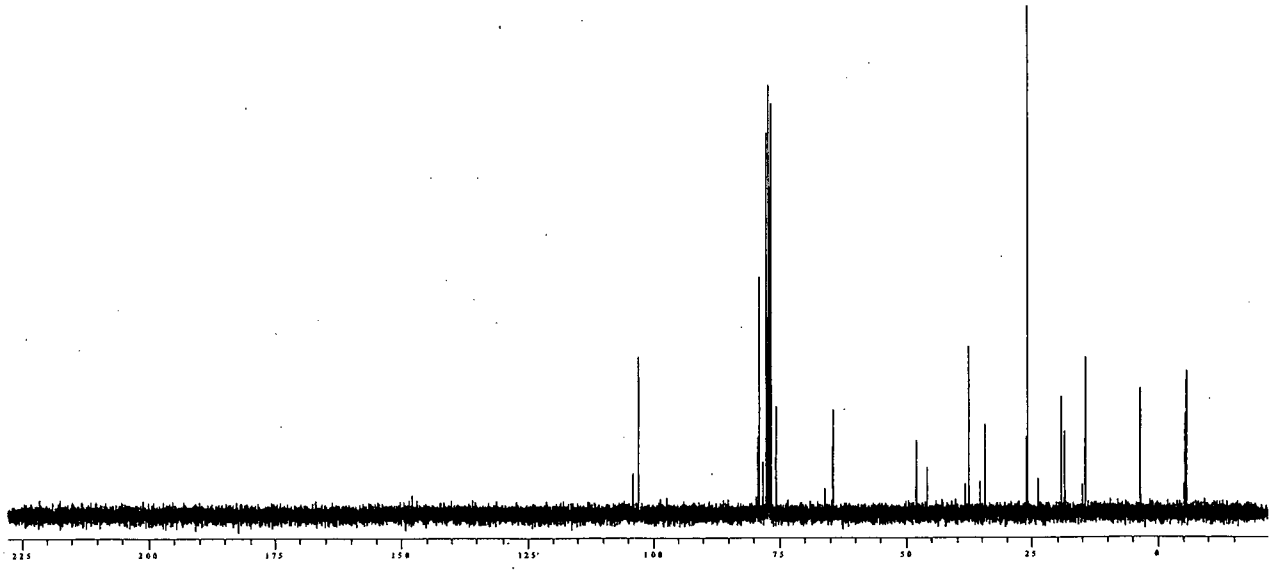


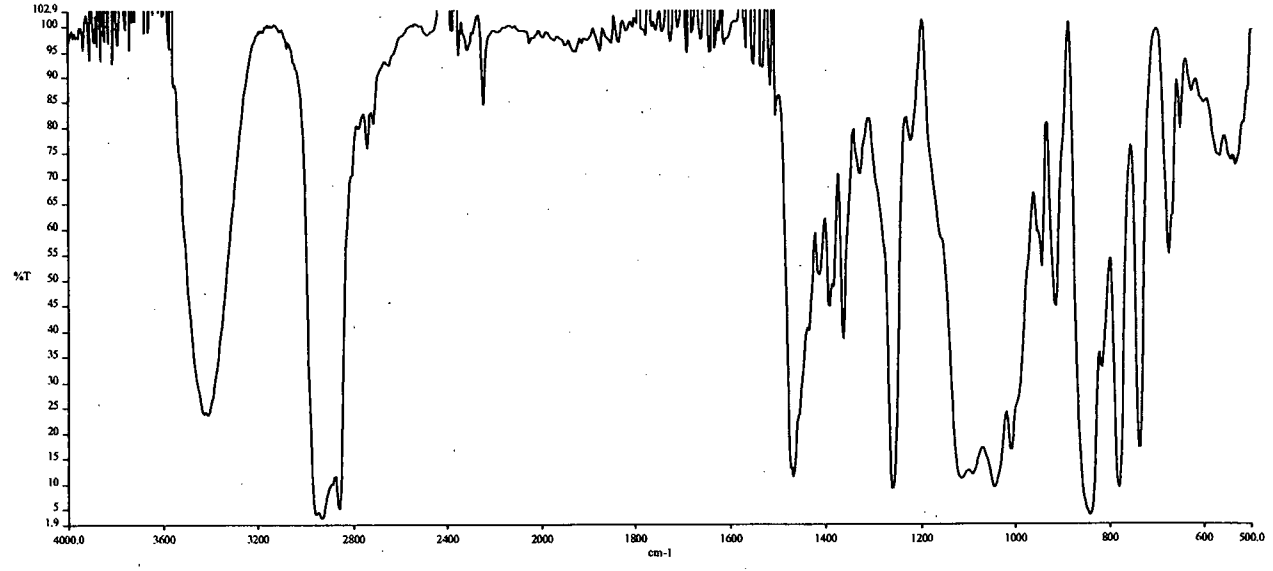




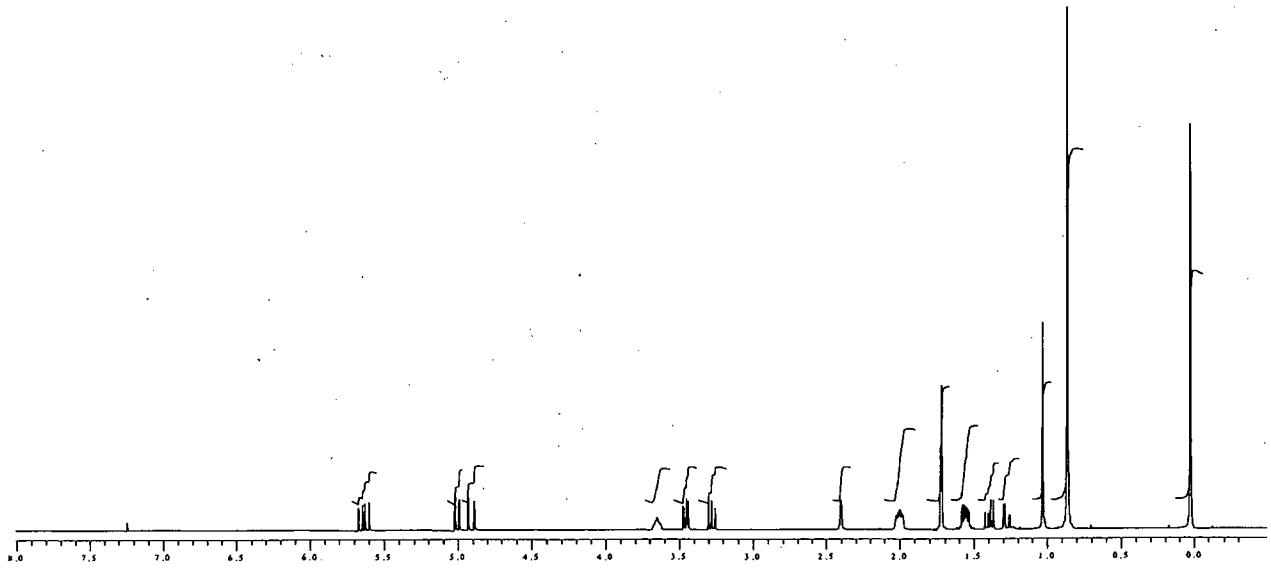
(2*R*, 4*S*)-4-(*tert*-Butyldimethylsilyl)oxymethyl-2-methyl-2-(pent-3-yne)-γ-butyrolactol (**4.22**)

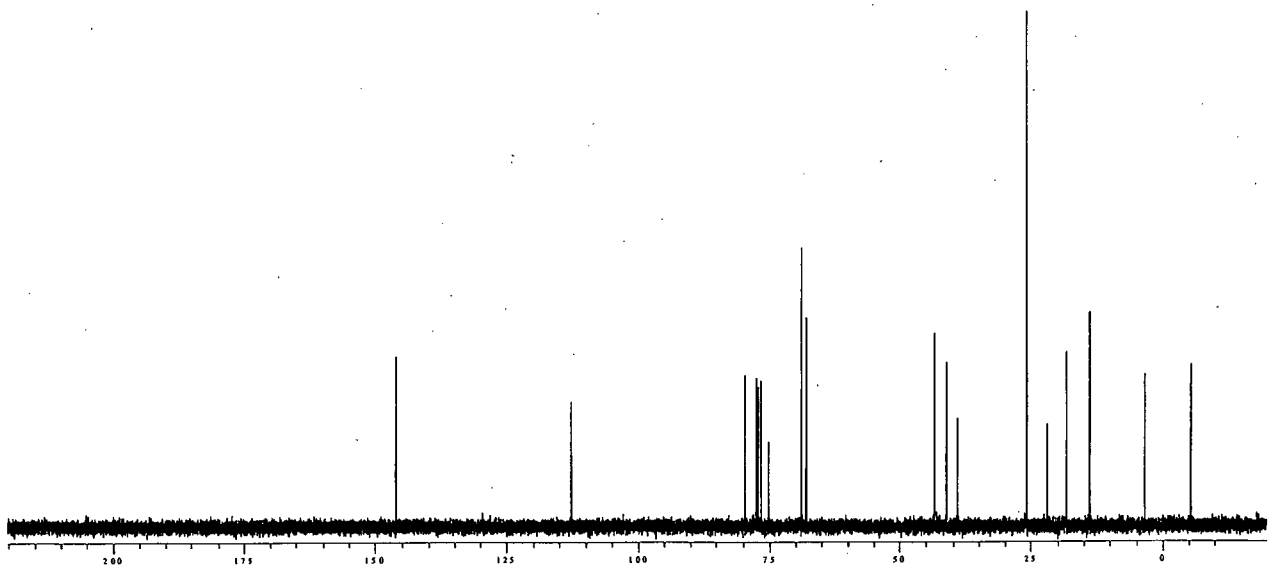


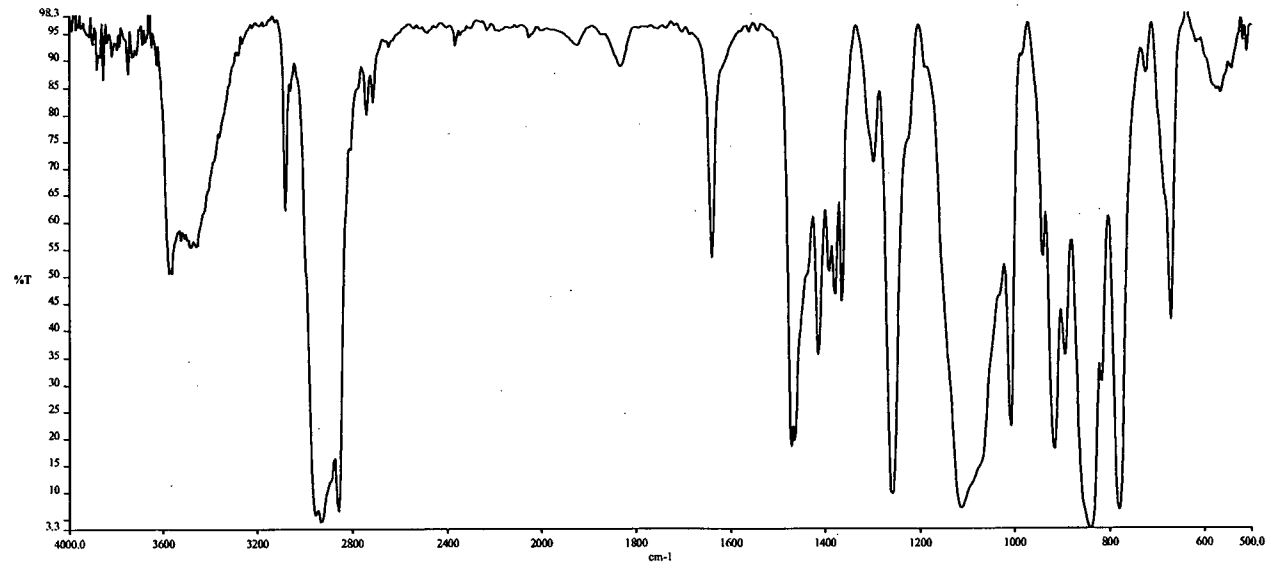




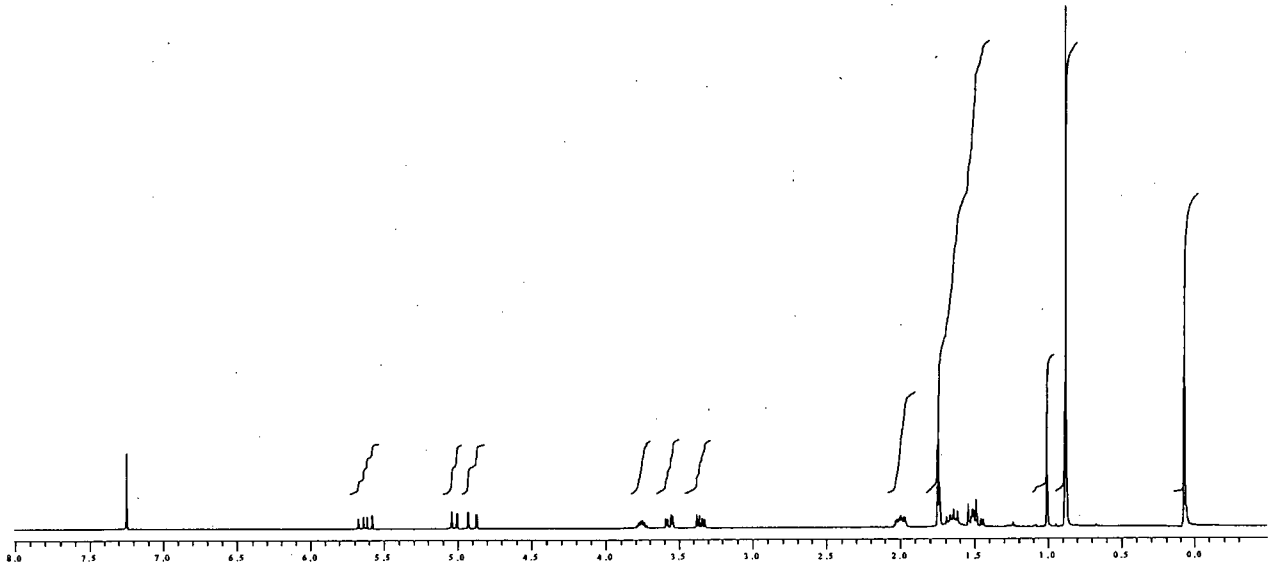
(2*S*, 4*R*)-1-*tert*-Butyldimethylsilyloxy-2-hydroxy-4-methyl-4-vinyl-7-nonyne (**4.23**)

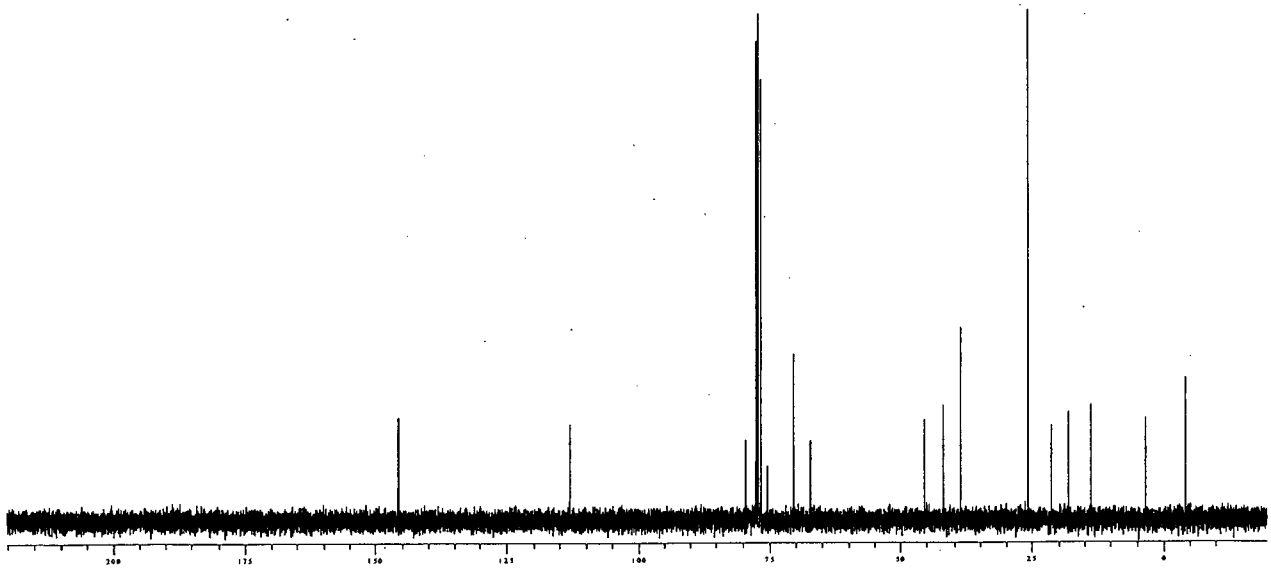


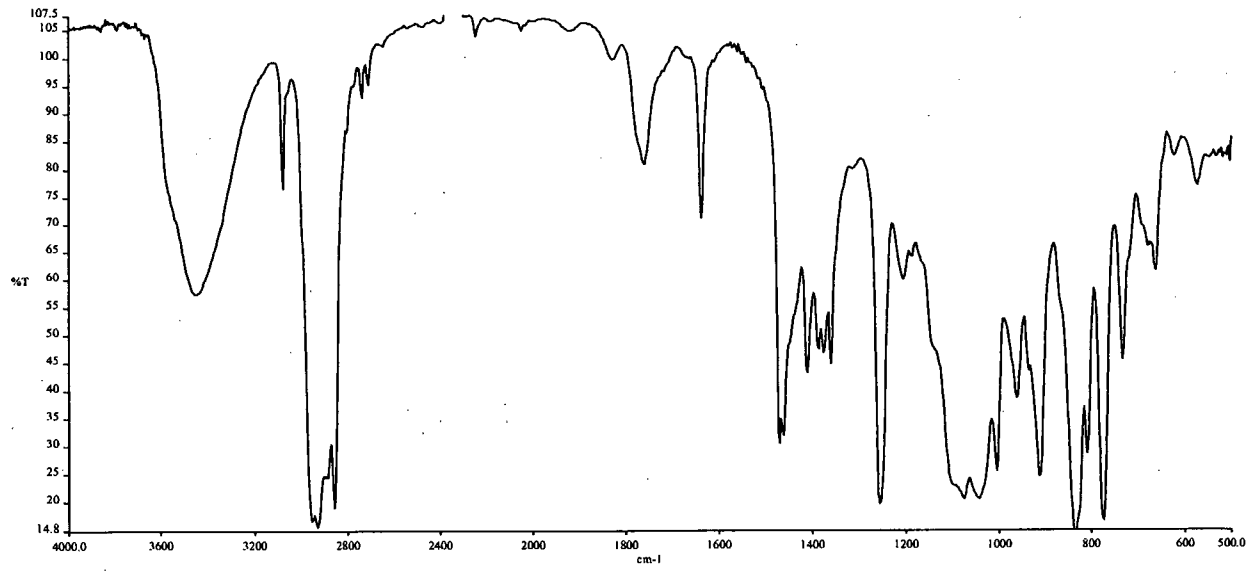




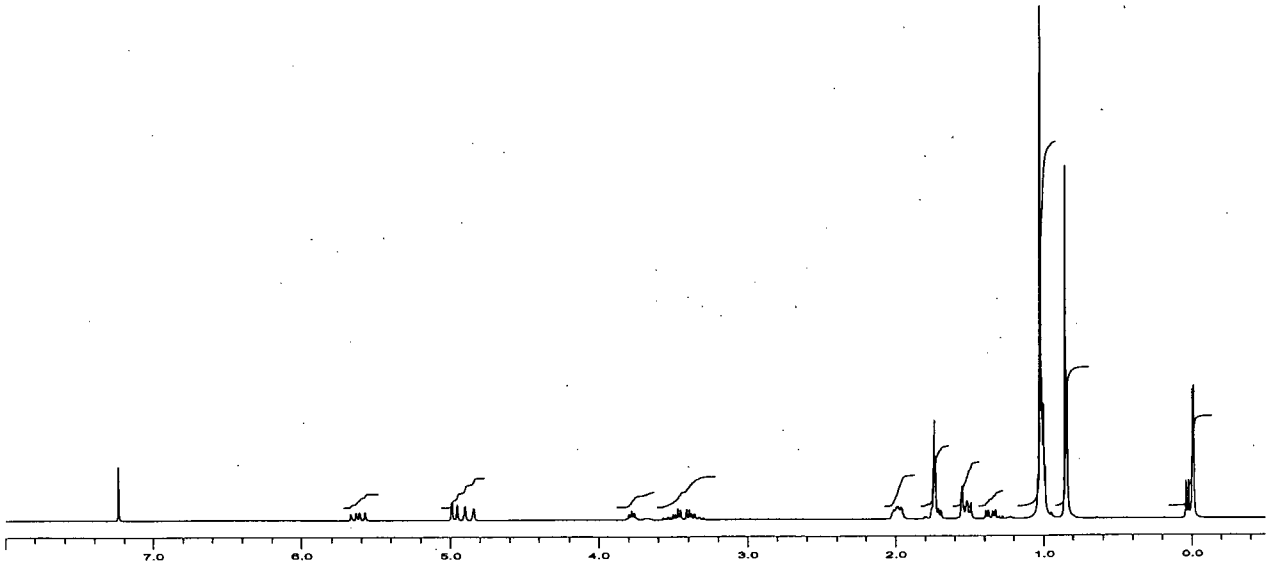
(2*S*, 4*R*)-2-*tert*-Butyldimethylsilyloxy-1-hydroxy-4-methyl-4-vinyl-7-nonyne (**4.24**)

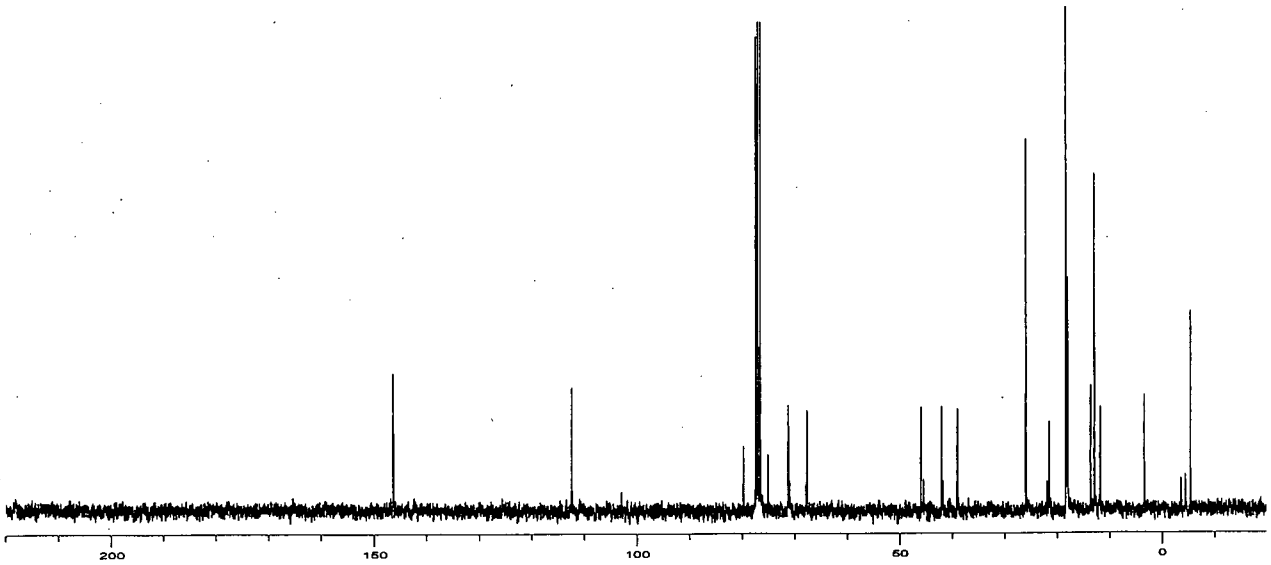


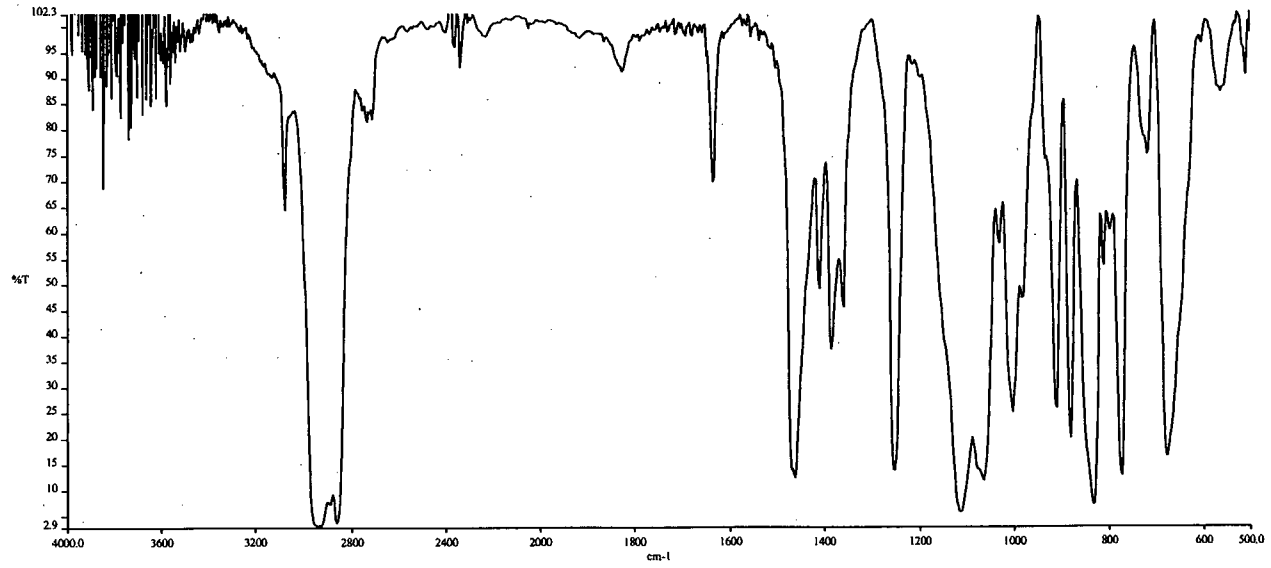




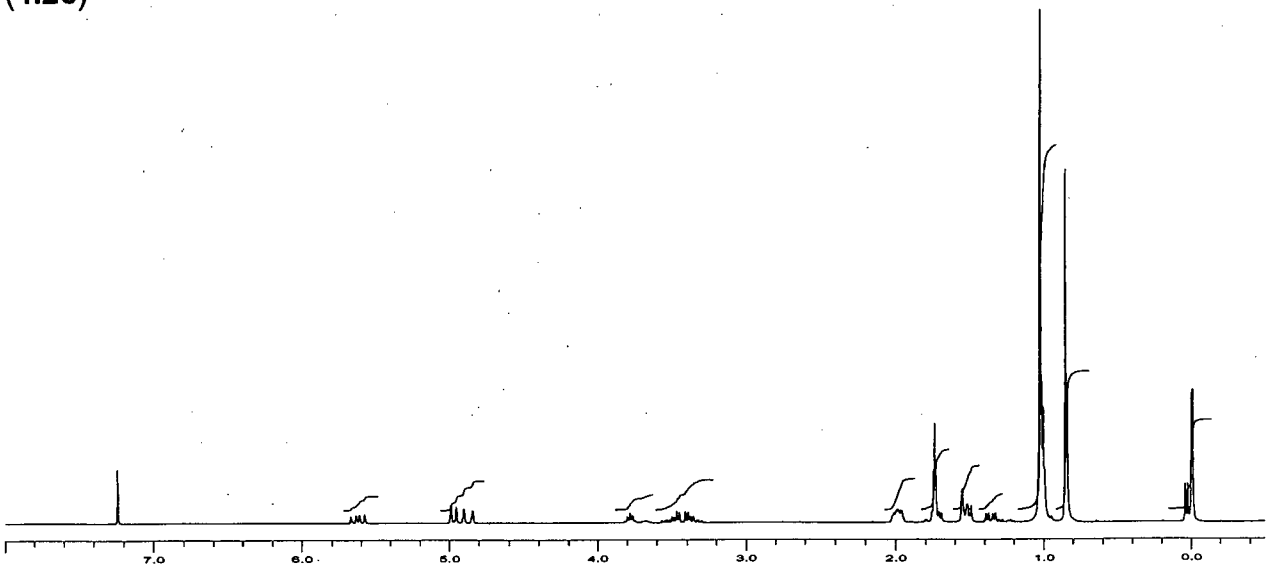
(2*S*, 4*R*)-1,2-di-*tert*-Butyldimethylsilyloxy-4-methyl-4-vinyl-7-nonyne (**4.25**)

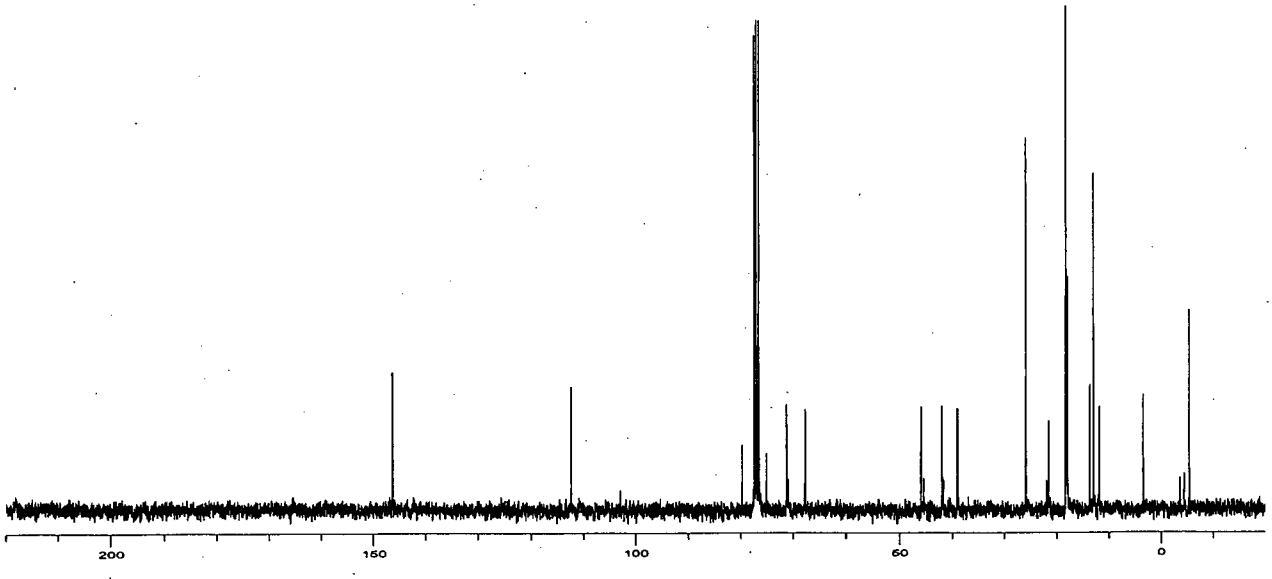


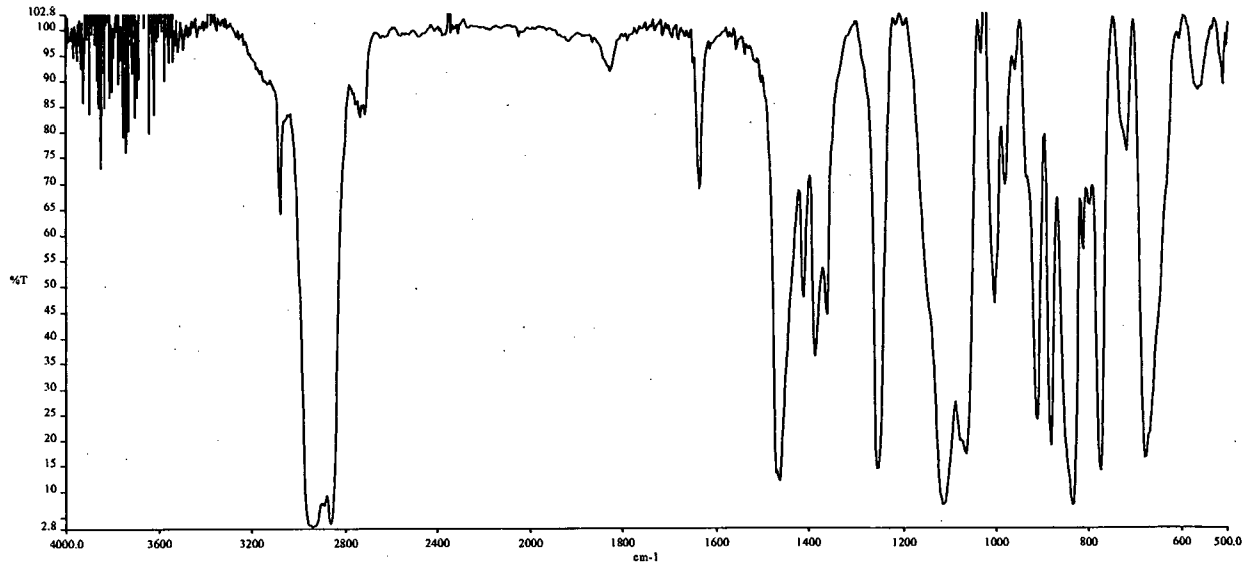




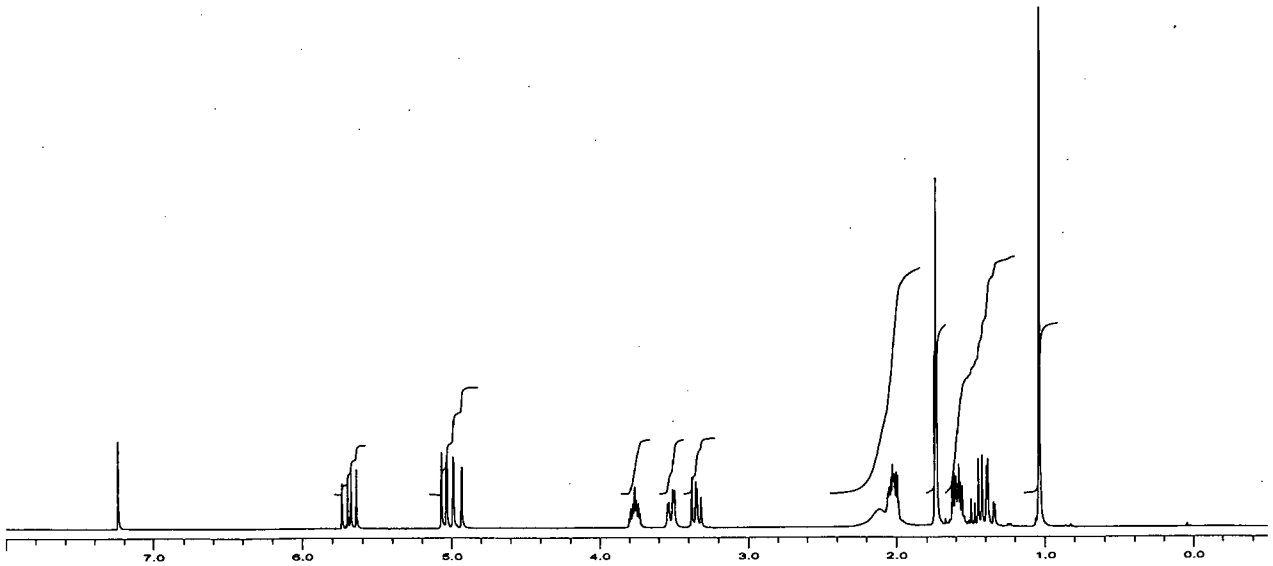
(2*S*, 4*R*)-1-*tert*-Butyldimethylsilyloxy-2-triisopropylsiloxy-4-methyl-4-vinyl-7-nonyne (**4.26**)

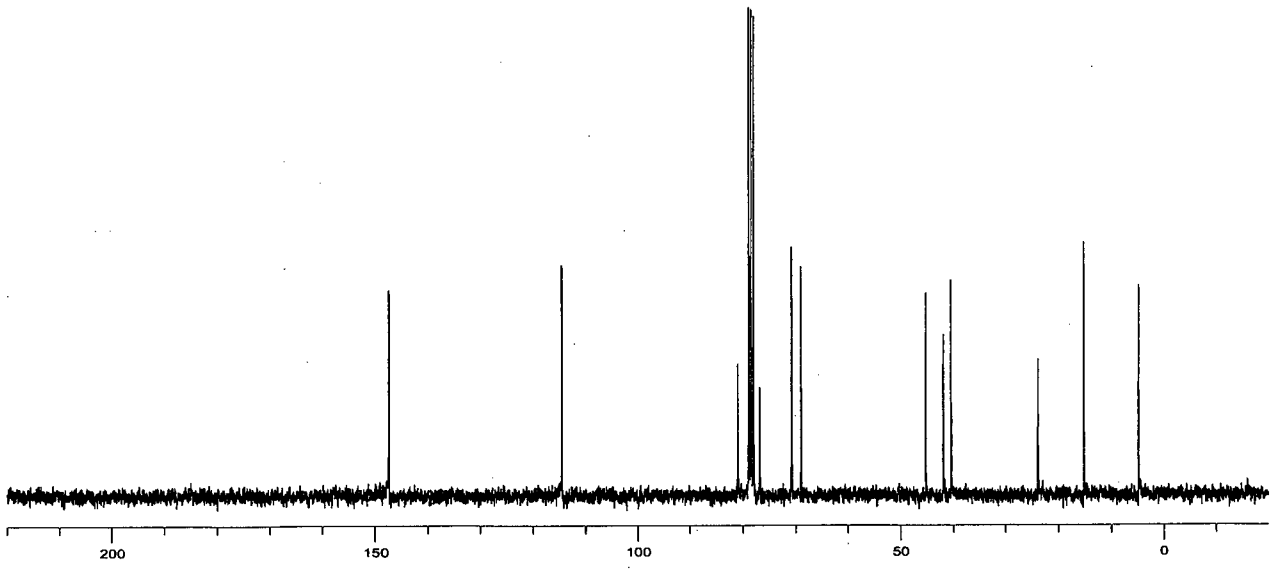


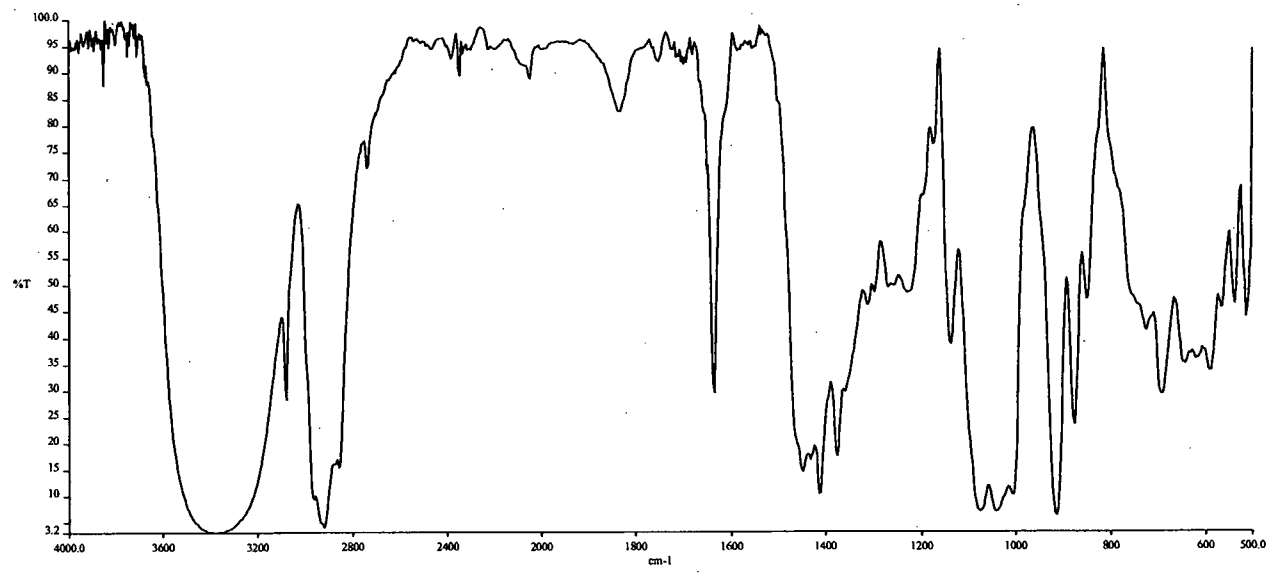




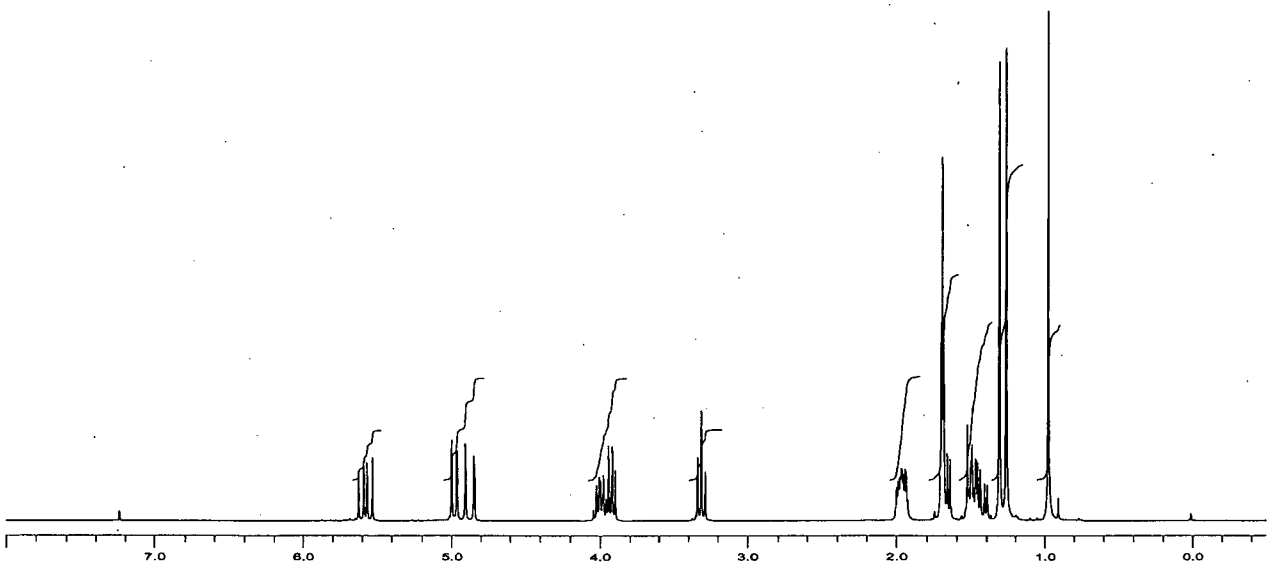
(2*S*, 4*R*)-1,2-Dihydroxy-4-methyl-4-vinyl-7-nonyne (**4.27**)

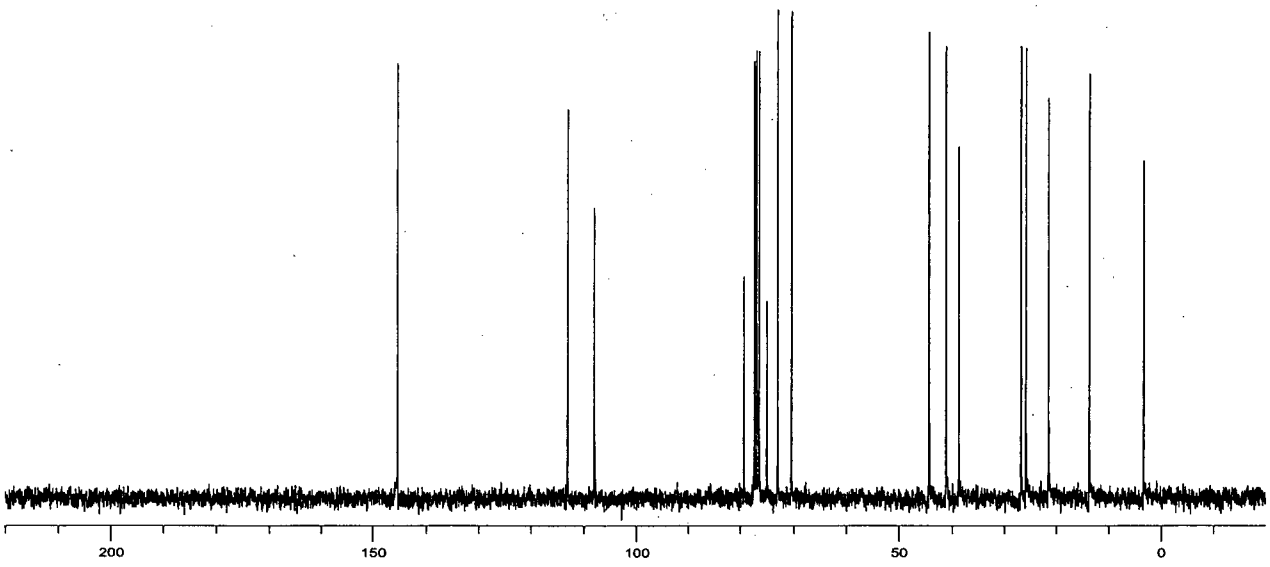


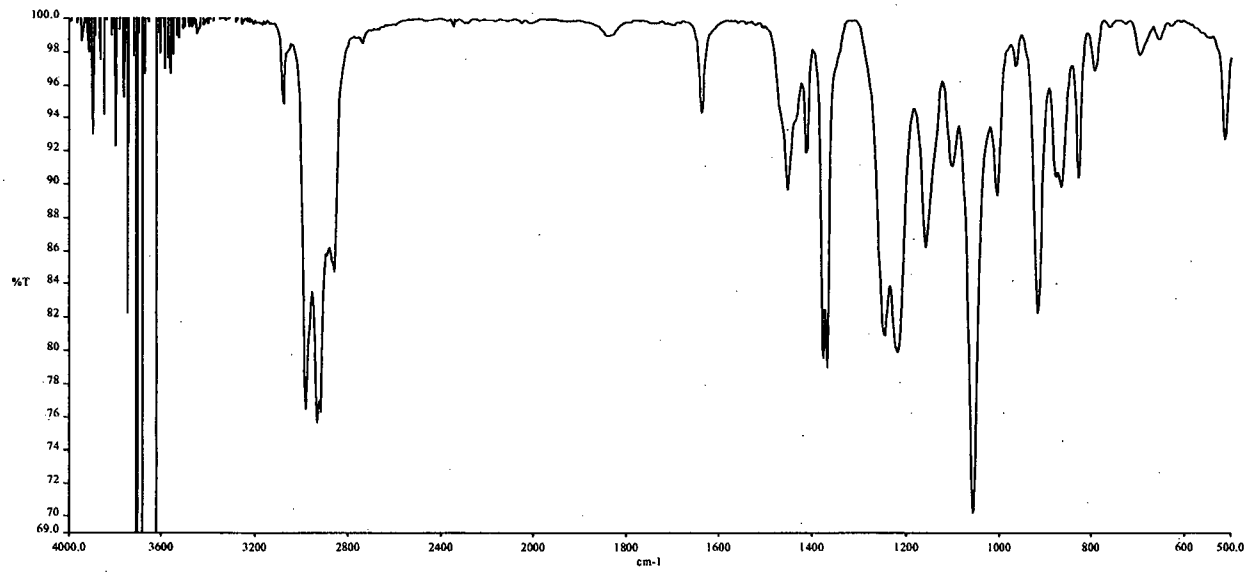




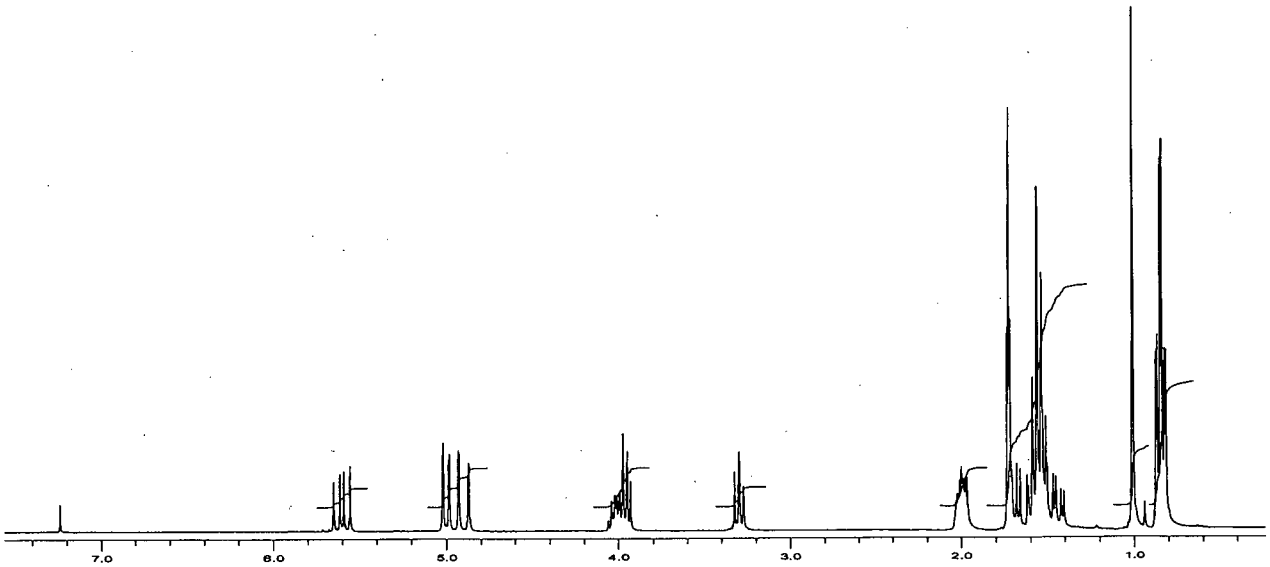
(2*S*, 4*R*)-1,2-*O*-Isopropylidene-4-methyl-4-vinyl-7-nonyne-1,2-diol (**4.28**)

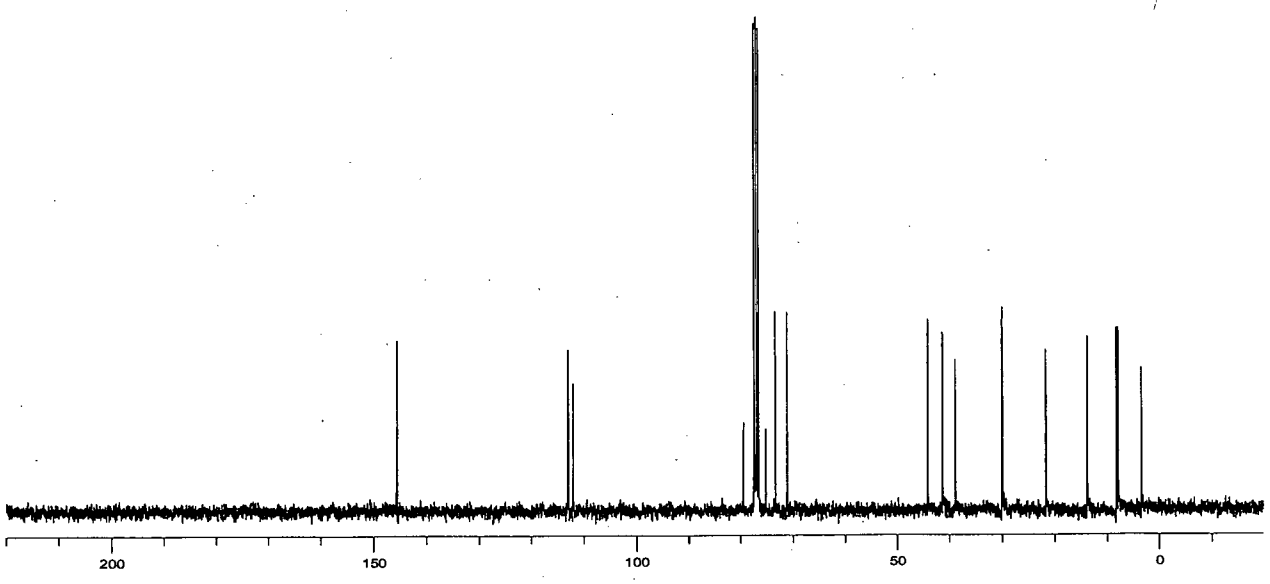


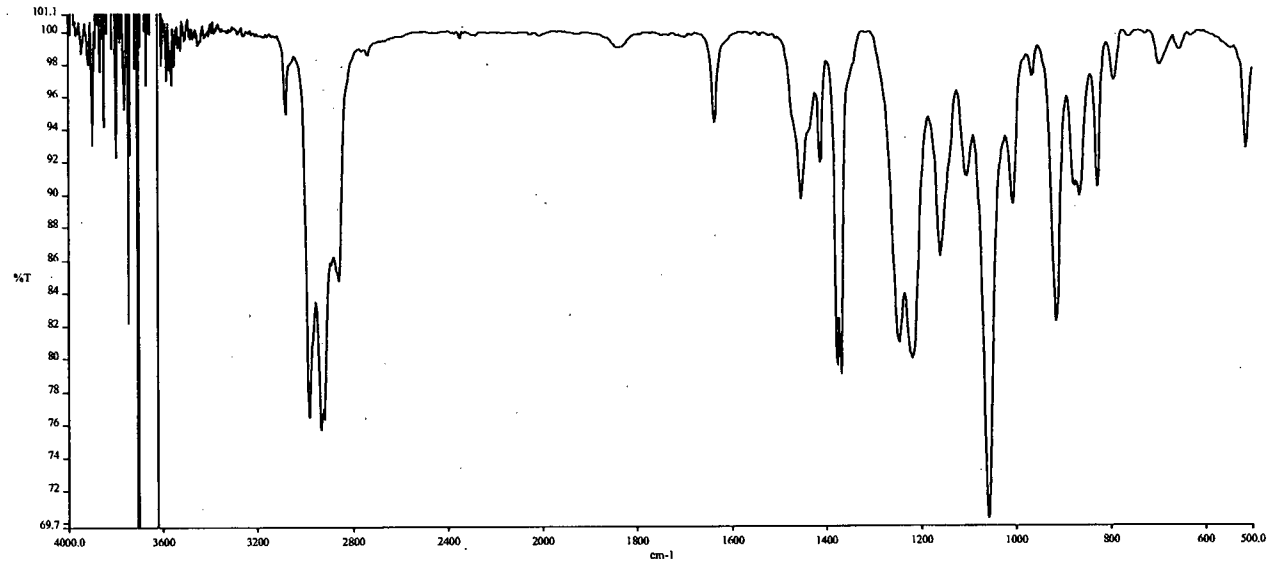




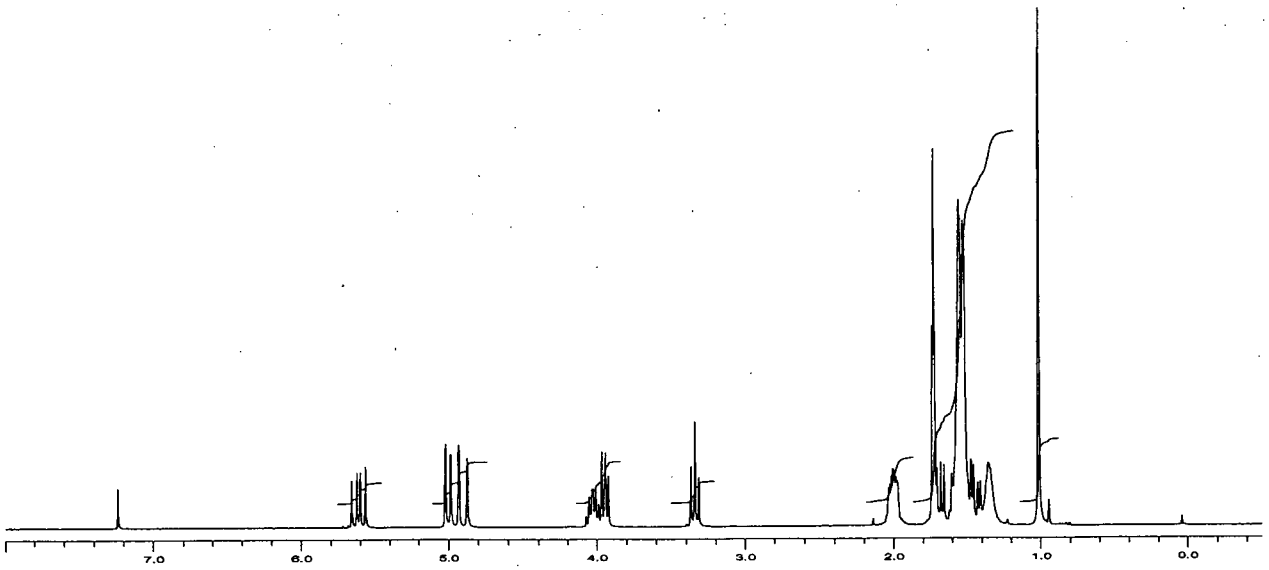
(2*S*, 4*R*)-1,2-*O*-Isopentylidene-4-methyl-4-vinyl-7-nonyne-1,2-diol (**4.29**)

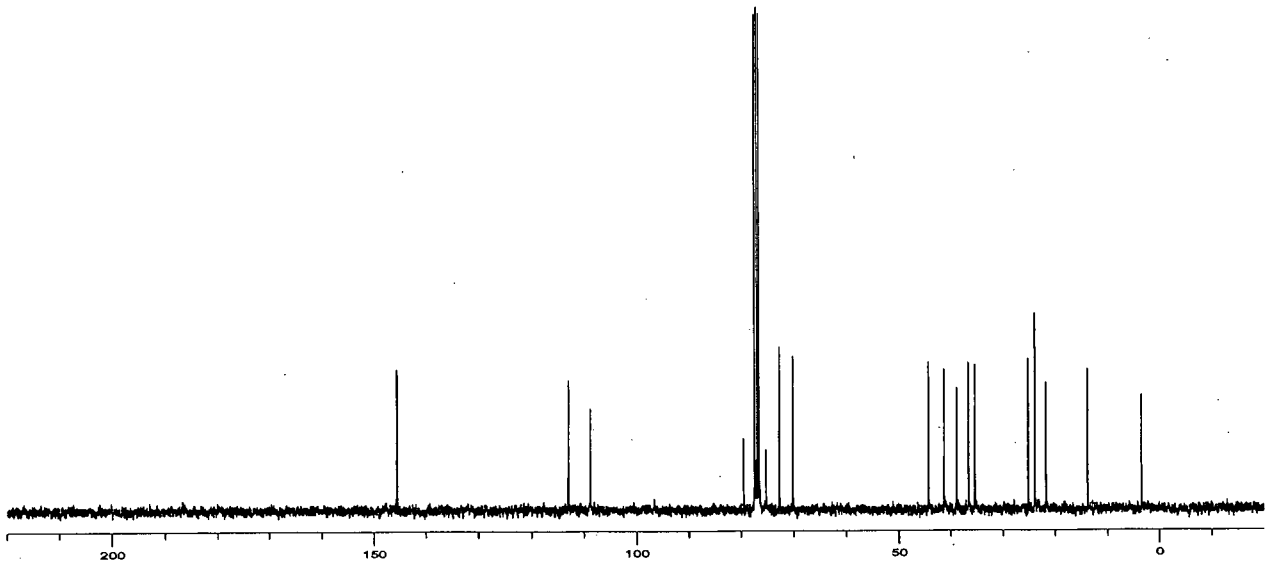


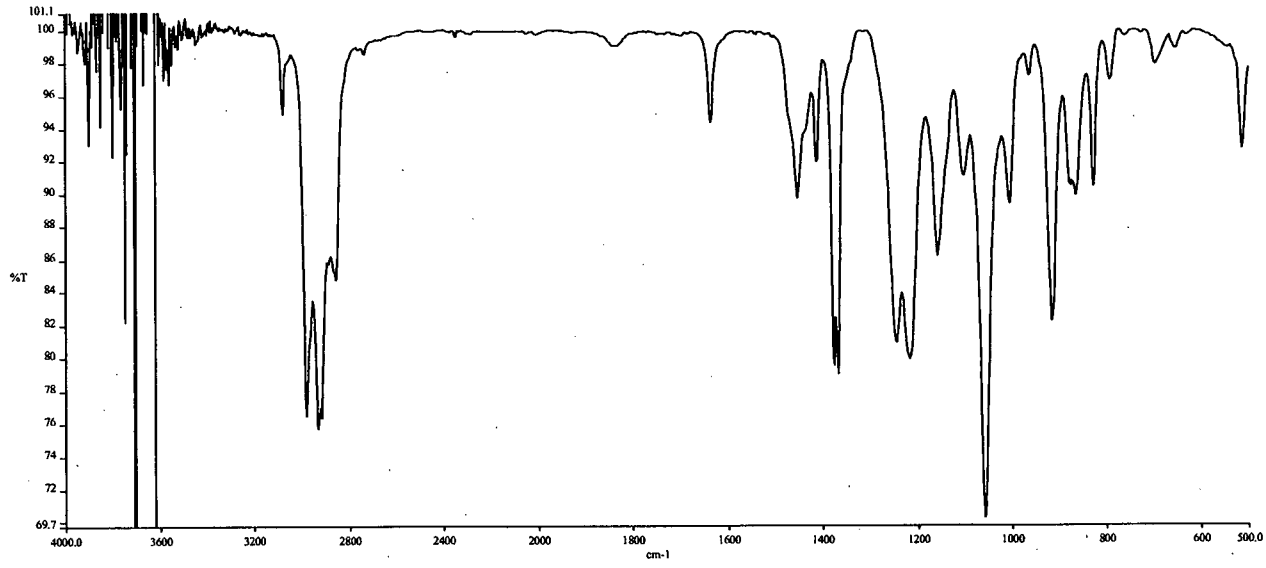




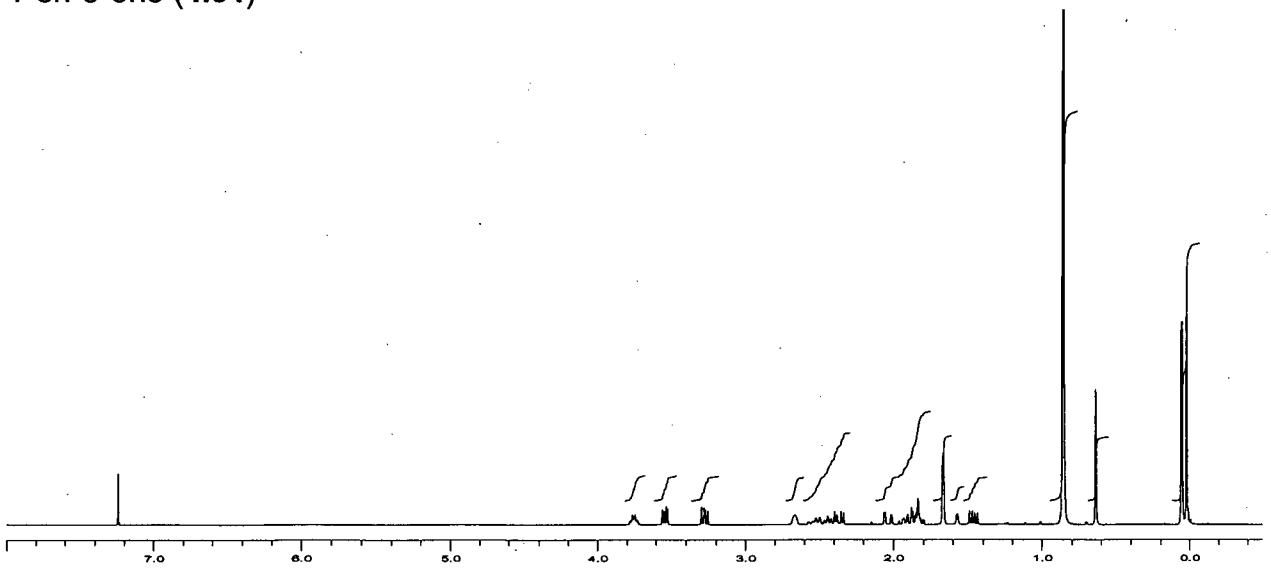
(2*S*, 4*R*)-1,2-*O*-Cyclohexylidene-4-methyl-4-vinyl-7-nonyne-1,2-diol (**4.30**)

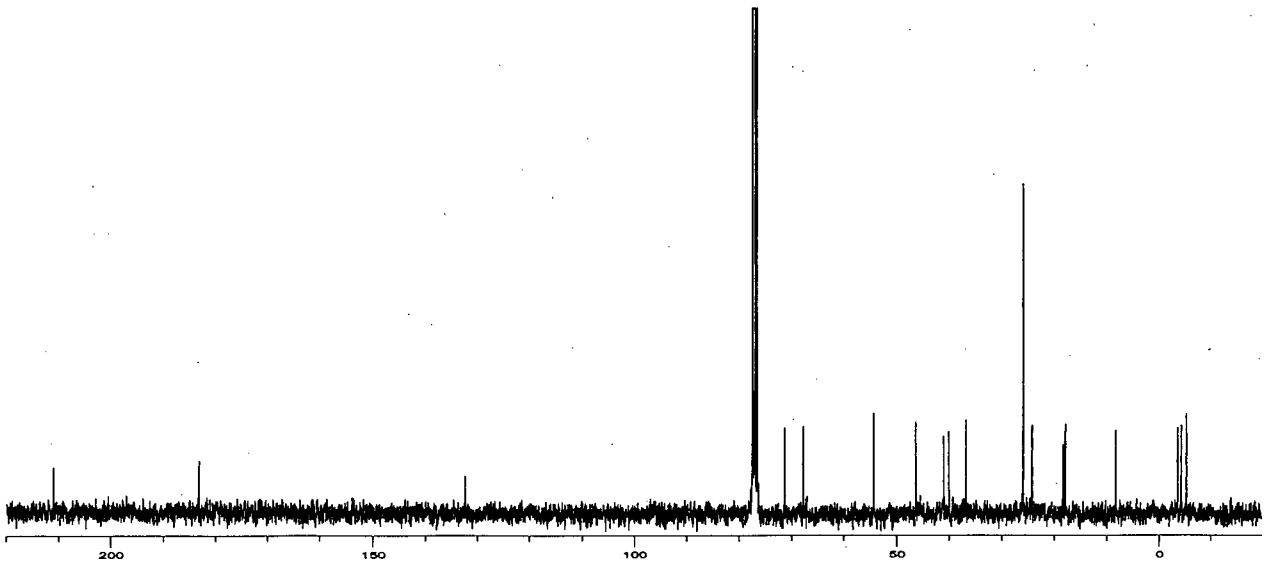


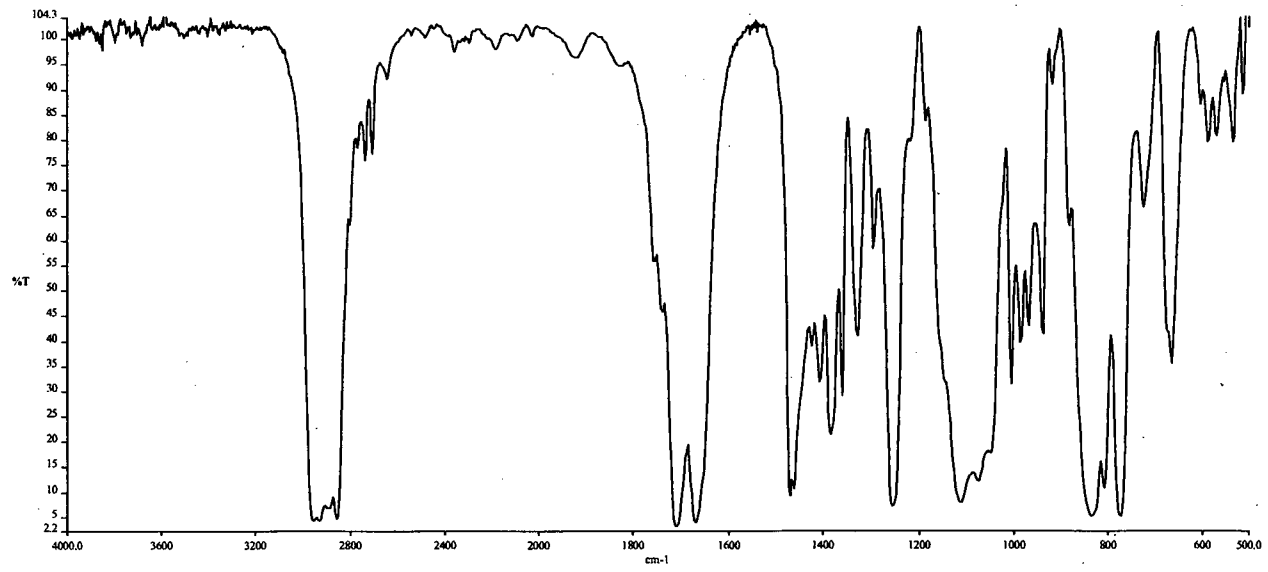




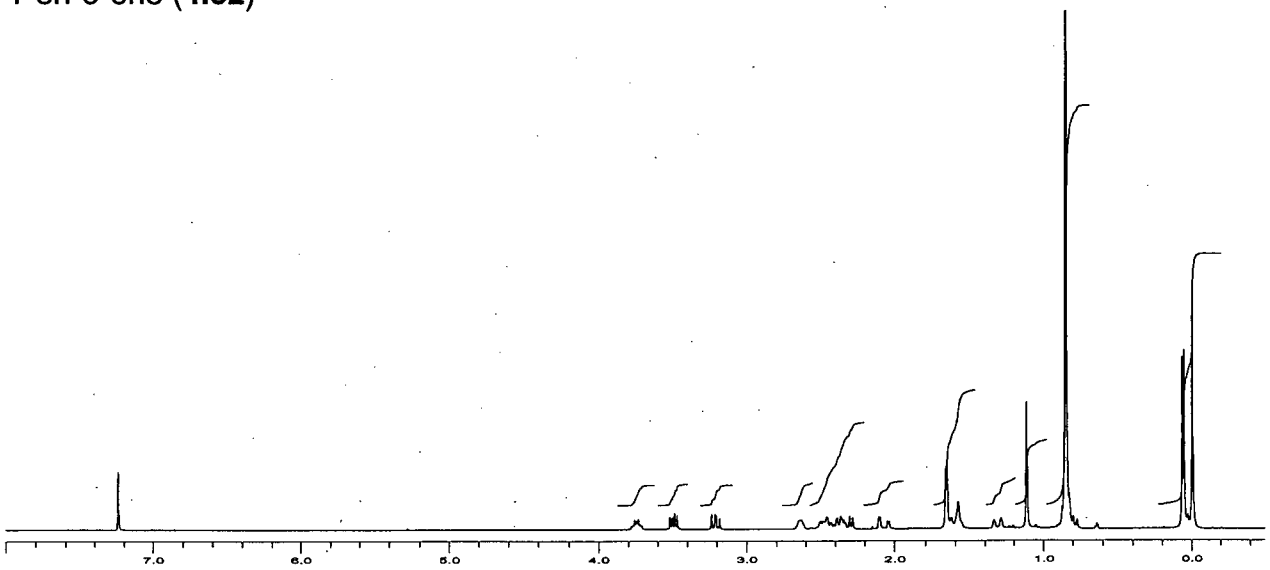
[3.3.0]-(5*R*, 6*R*)-6-((2*S*)-2,3-di-*tert*-Butyldimethylsilyloxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**4.31**)

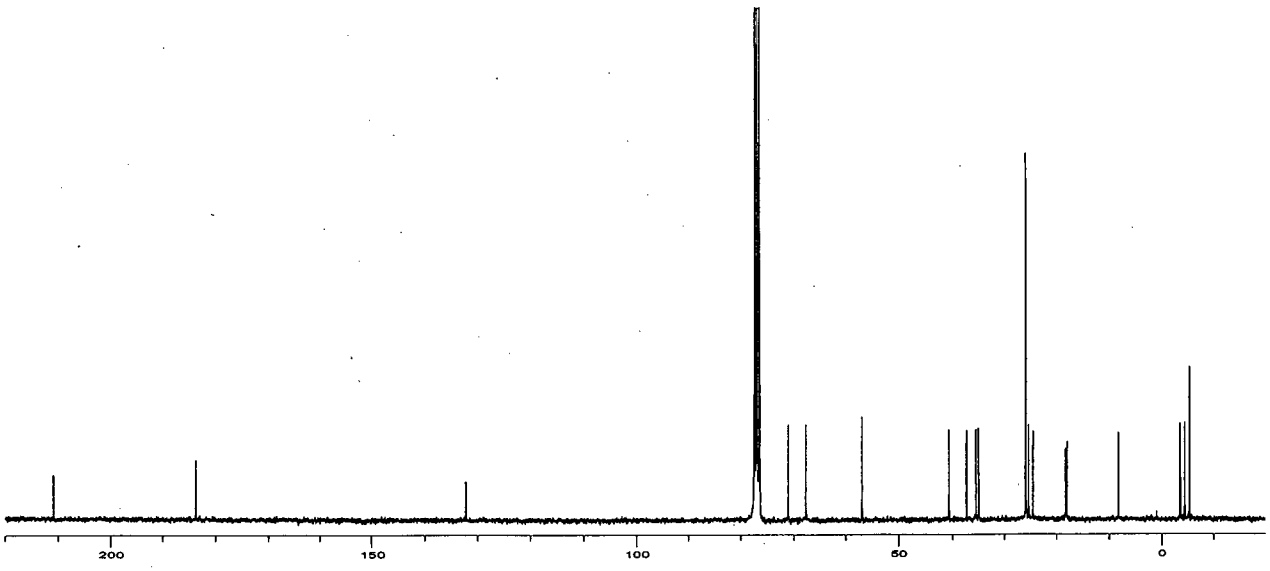


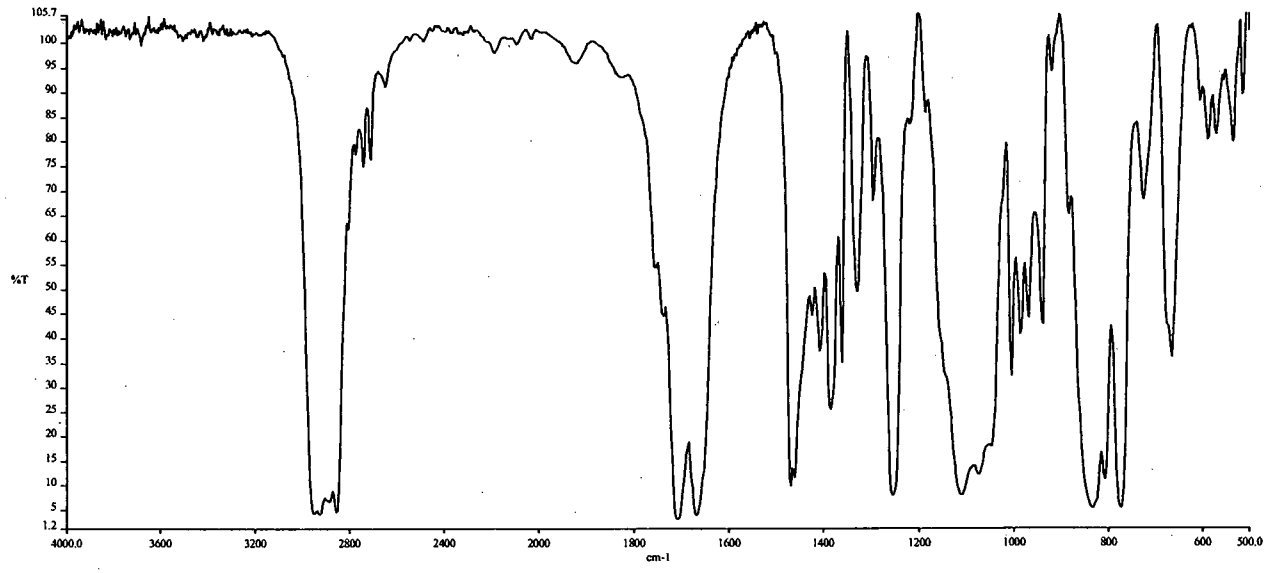




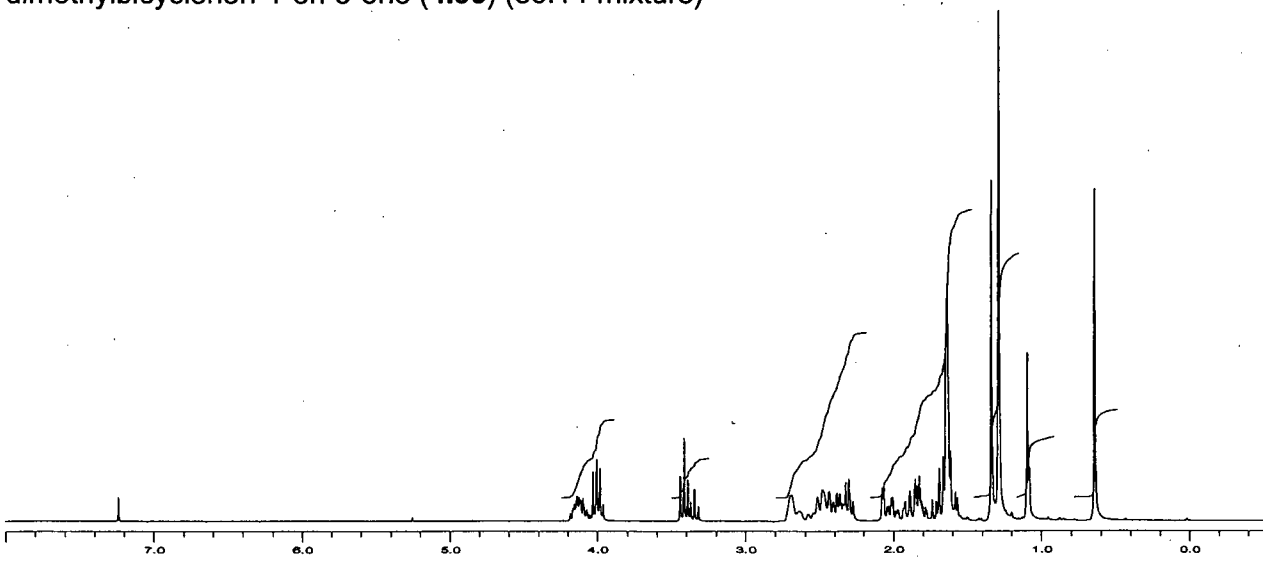
[3.3.0]-(5*S*, 6*R*)-6-((2*S*)-2,3-di-*tert*-Butyldimethylsilyloxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**4.32**)

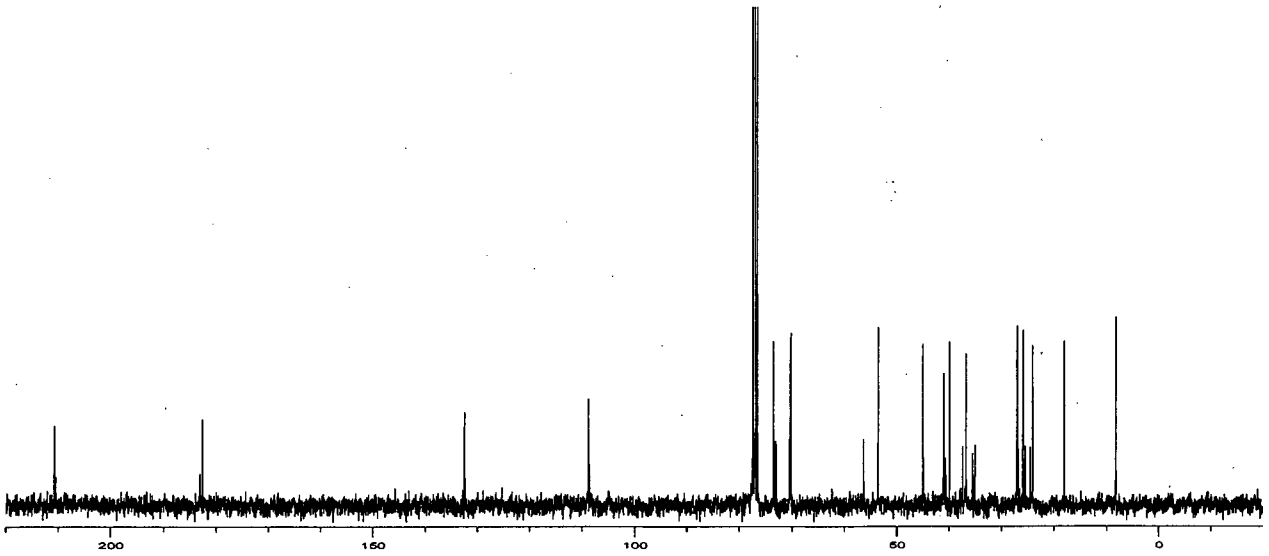


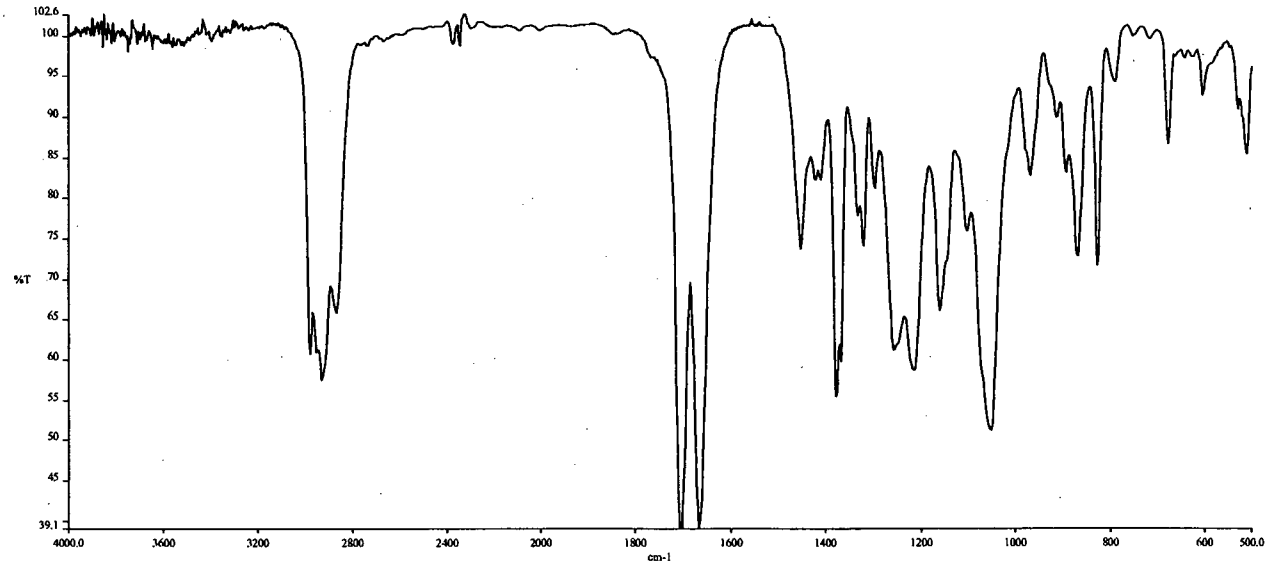




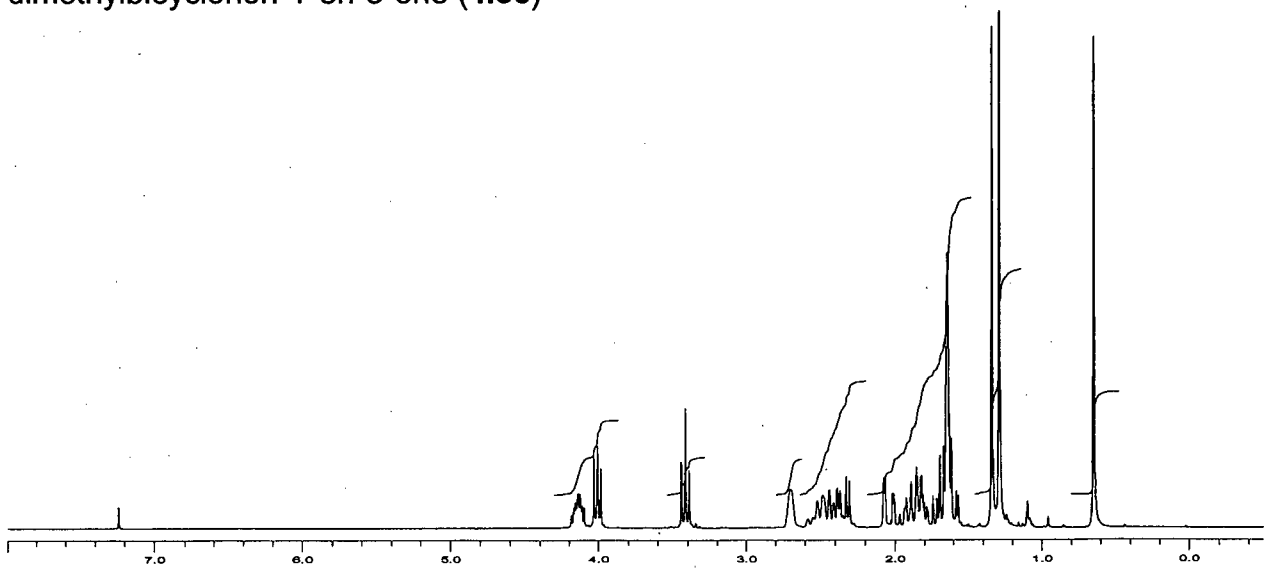
[3.3.0]-(5*R*, 6*R*)-6-((2*S*)-2,3-*O*-Isopropylidene-2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**4.35**) and [3.3.0]-(5*S*, 6*R*)-6-((2*S*)-2,3-*O*-Isopropylidene-2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**4.36**) (86:14 mixture)

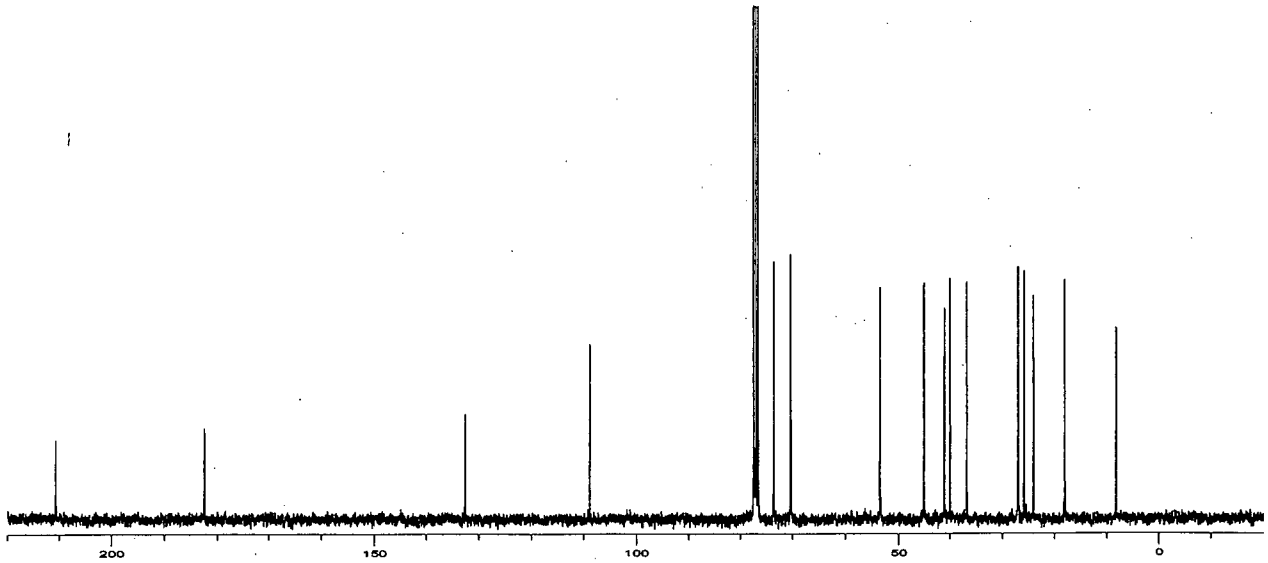


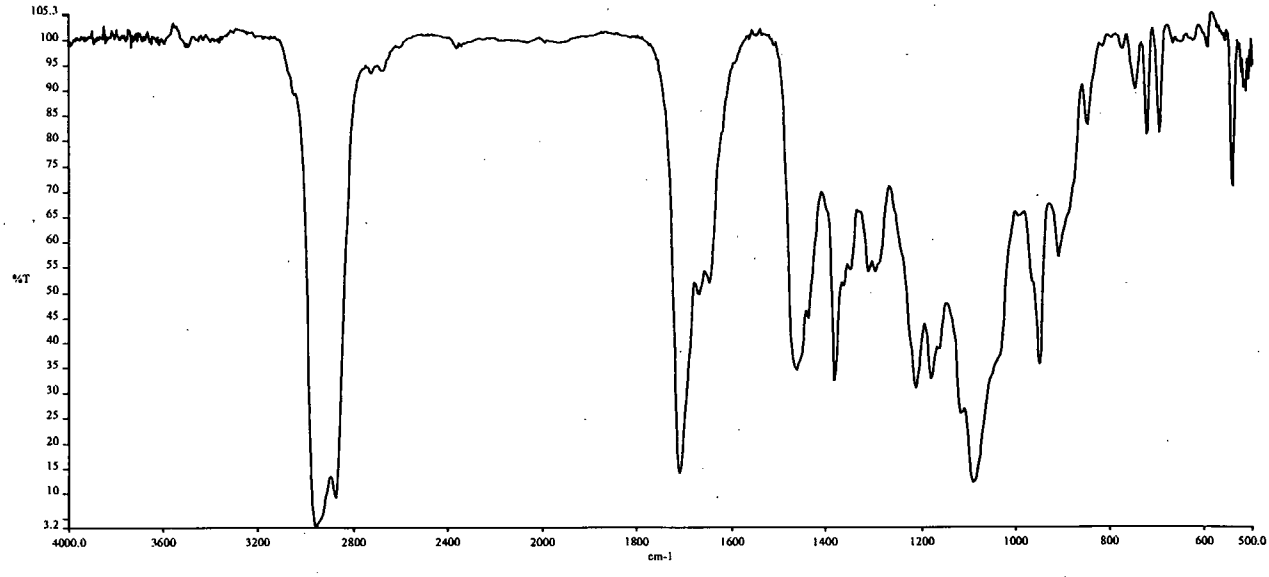




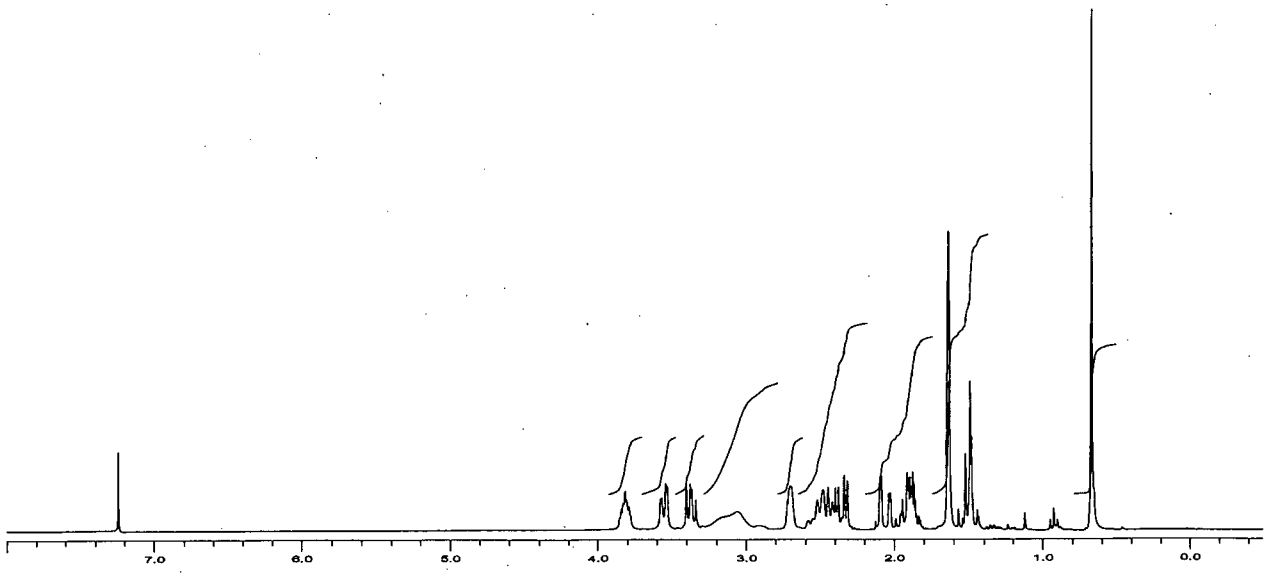
[3.3.0]-(5*R*, 6*R*)-6-((2*S*)-2,3-*O*-Isopropylidene-2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**4.35**)

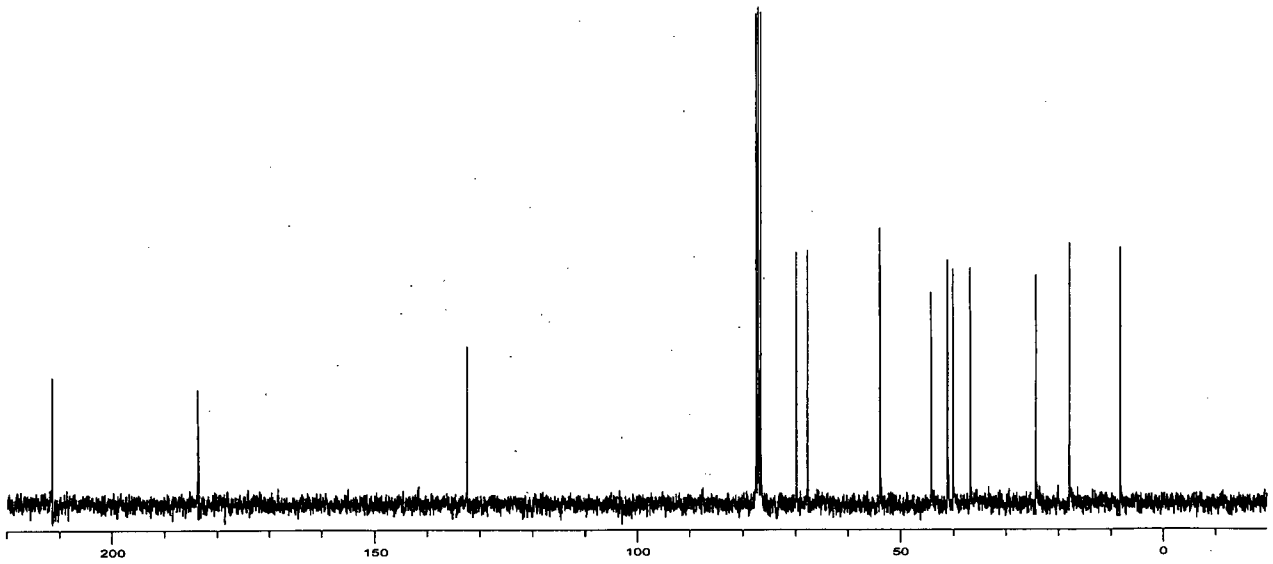


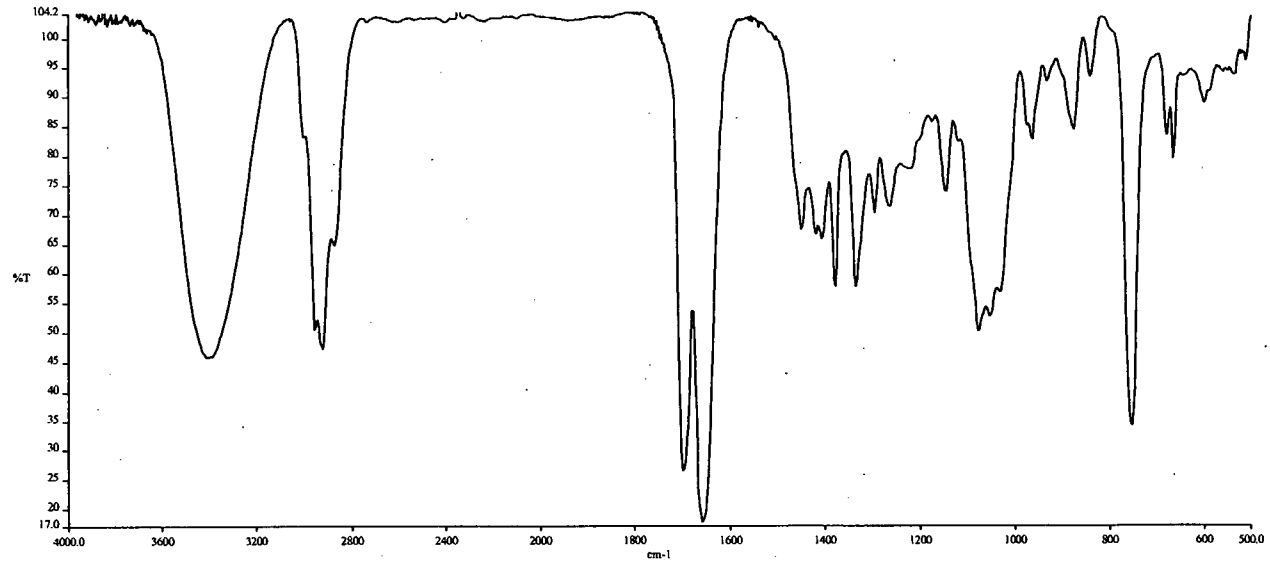




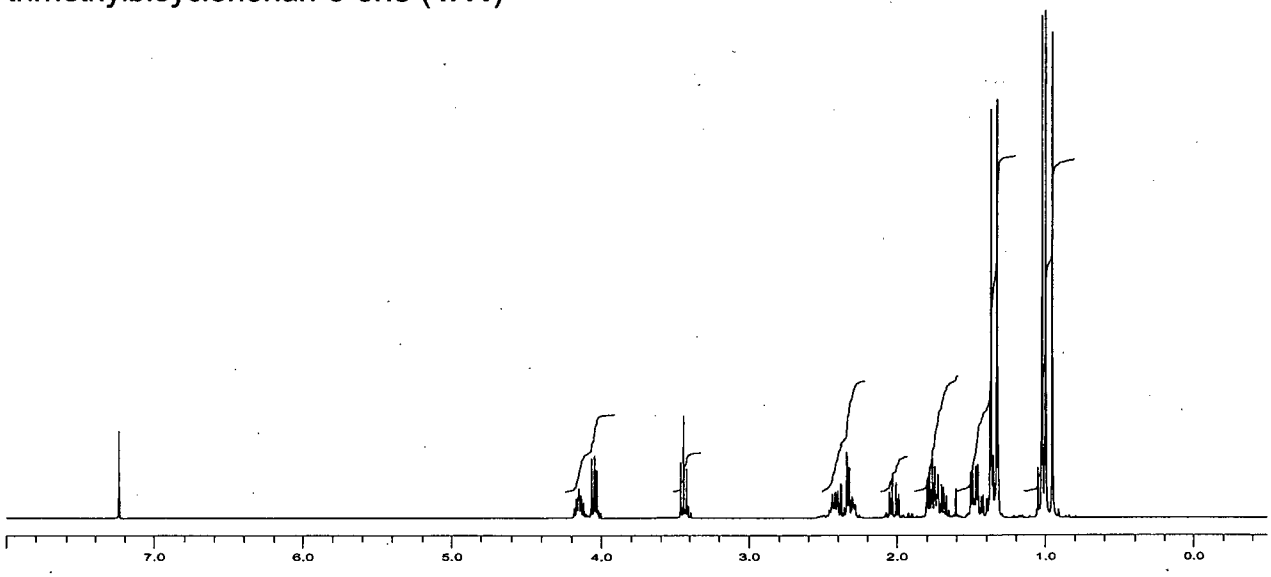
[3.3.0]-(5*R*, 6*R*)-6-((2*S*)- 2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one

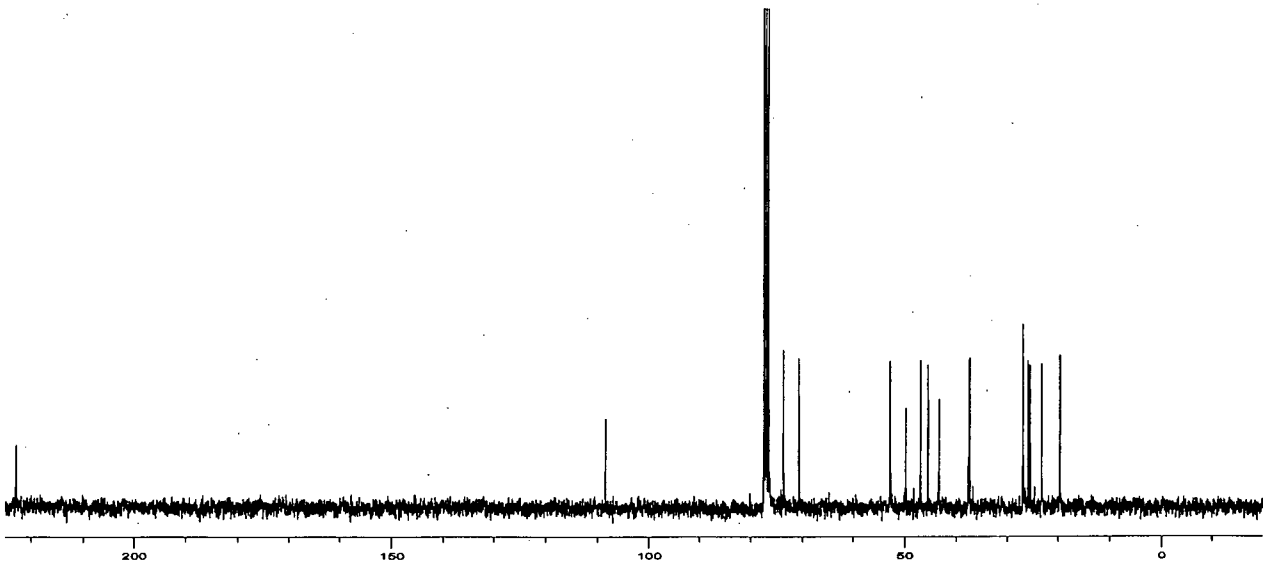


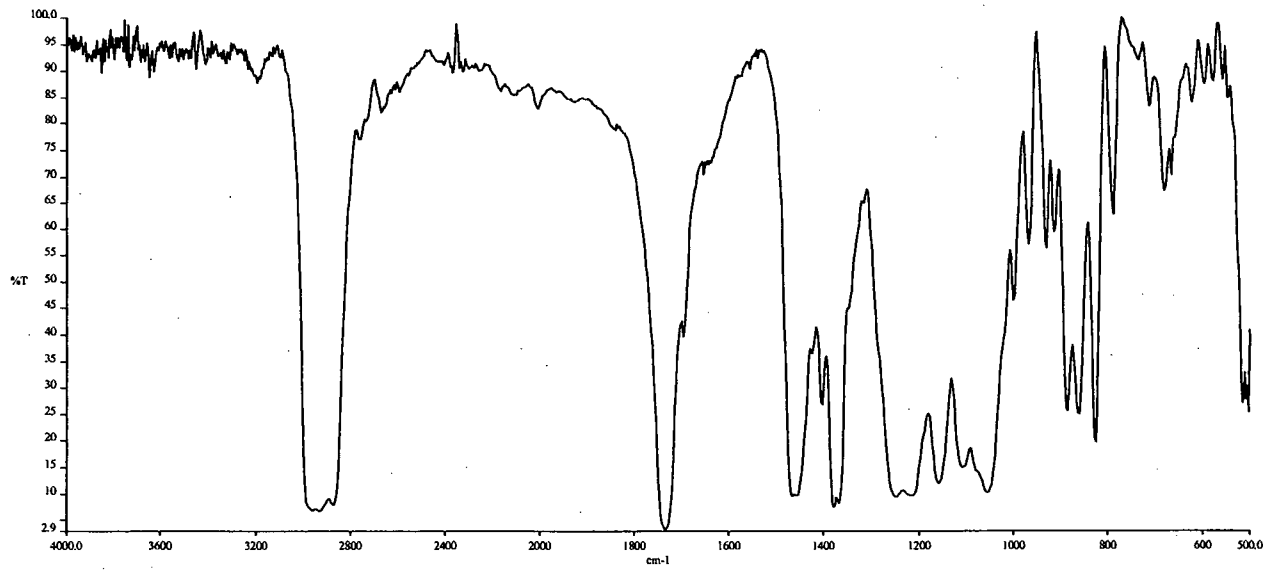




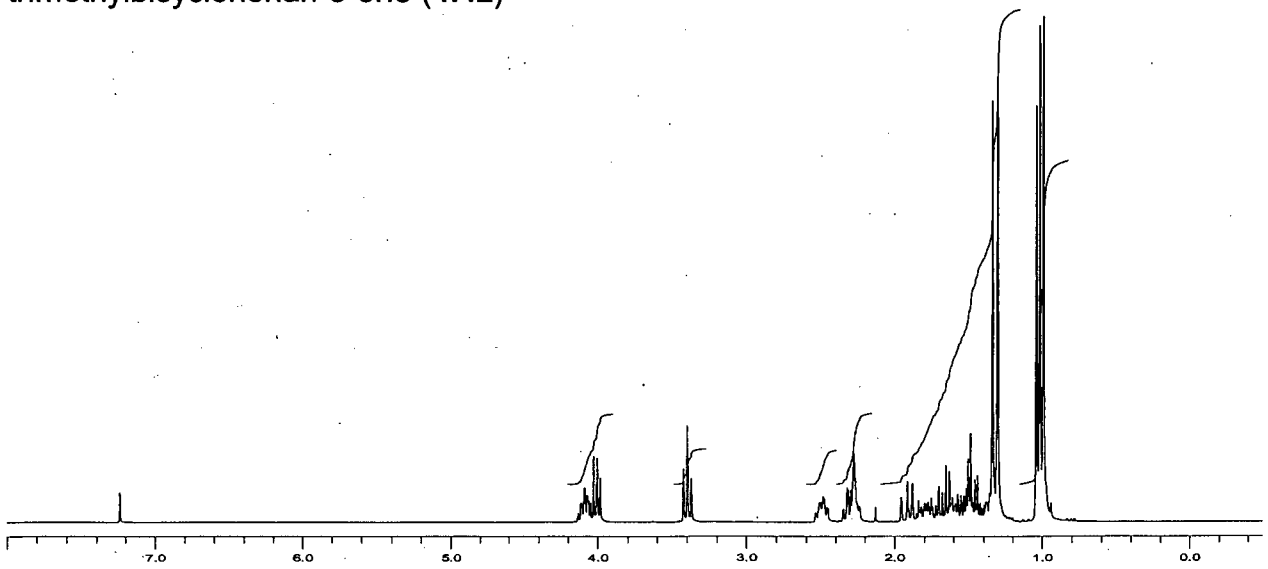
[3.3.0]-(1*R*, 5*S*, 6*R*)-6-((2*S*)-2,3-*O*-Isopropylidene-2,3-dihydroxypropyl)-2,2,6-trimethylbicyclononan-3-one (**4.41**)

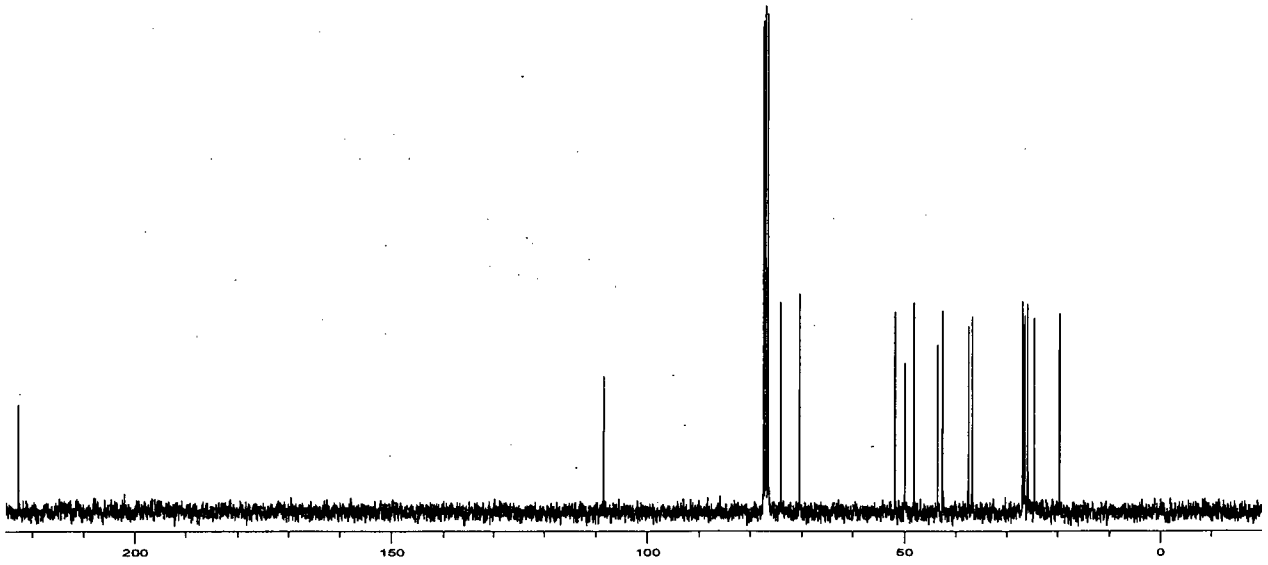


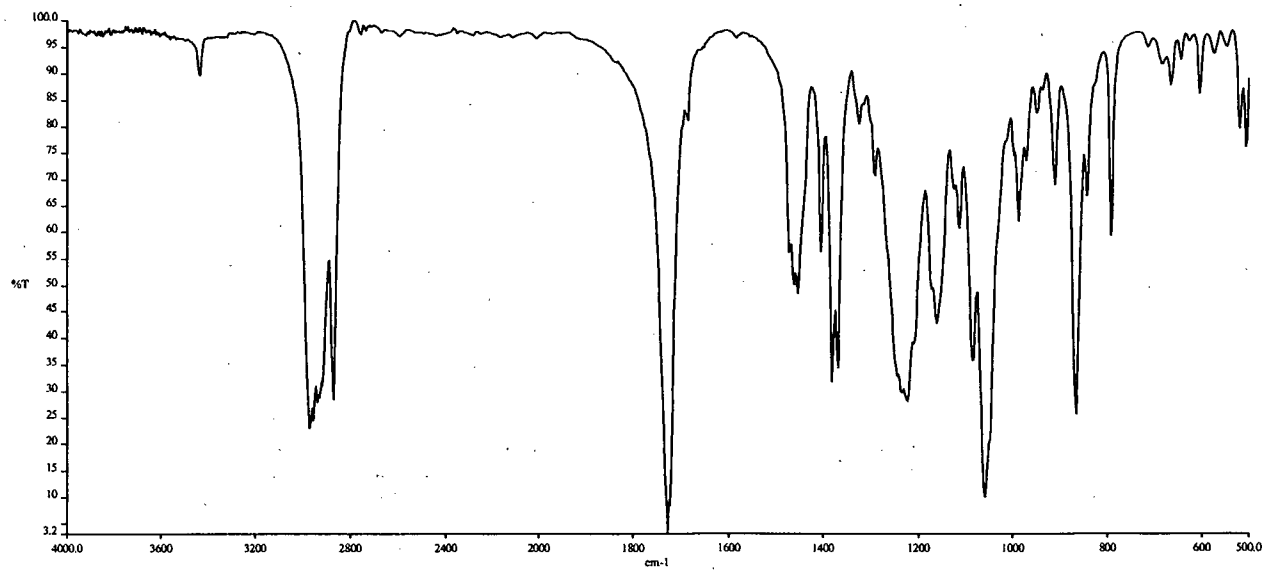




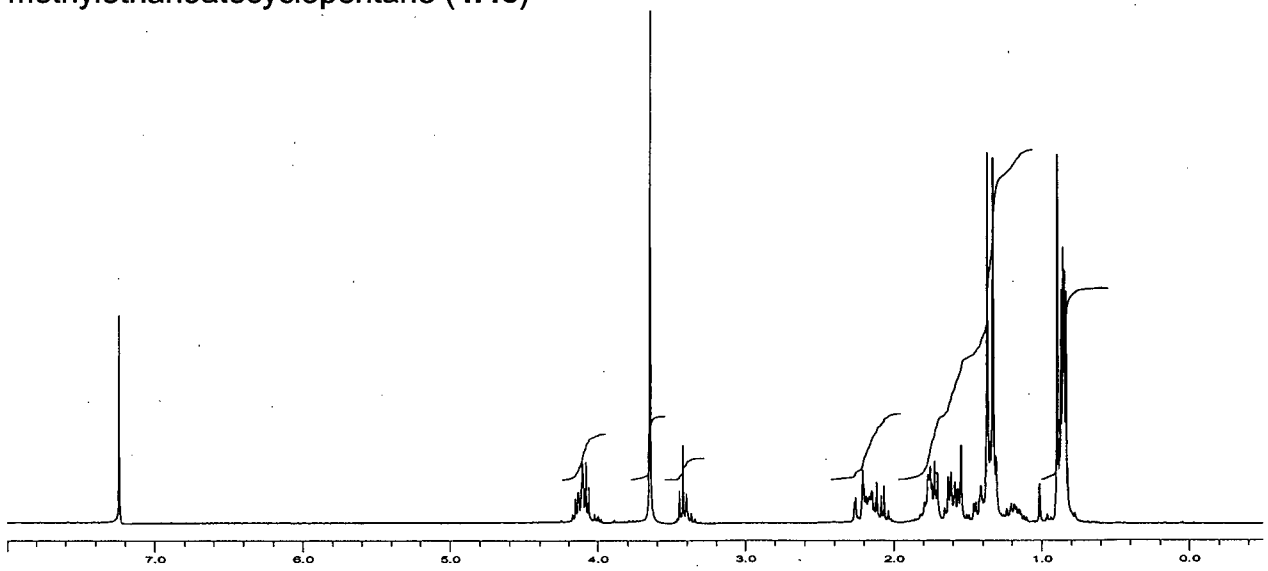
[3.3.0]-(1*S*, 5*R*, 6*R*)-6-((2*S*)-2,3-*O*-Isopropylidene-2,3-dihydroxypropyl)-2,2,6-trimethylbicyclononan-3-one (**4.42**)

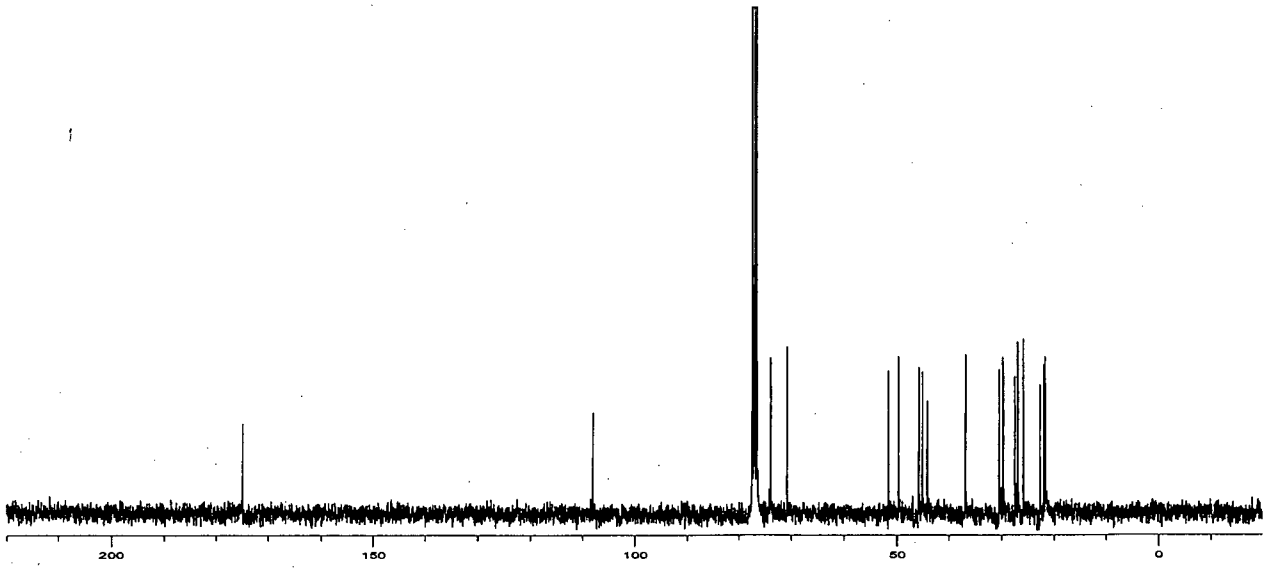


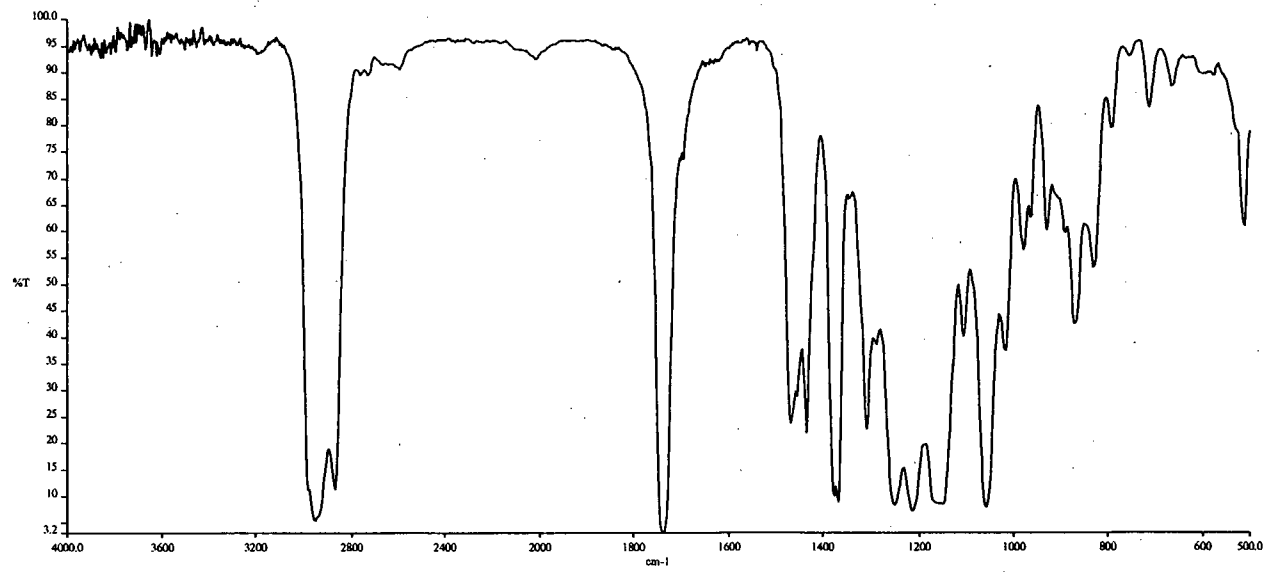




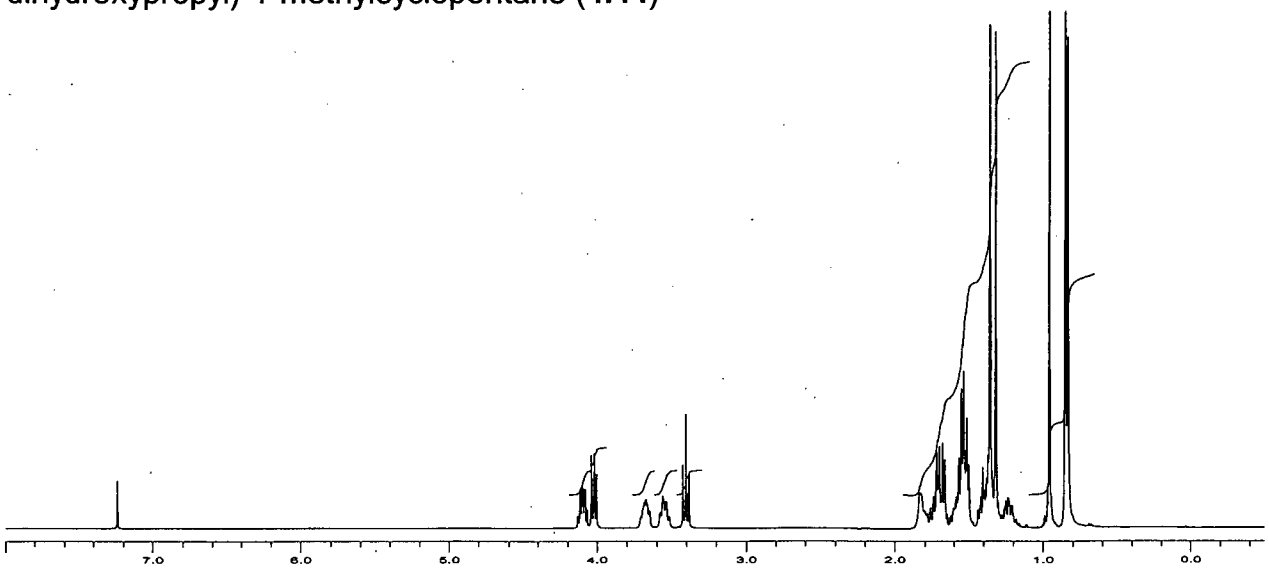
(1*R*, 2*S*, 3*R*)-3-Isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methyl-2-methylethanoatecyclopentane (**4.43**)

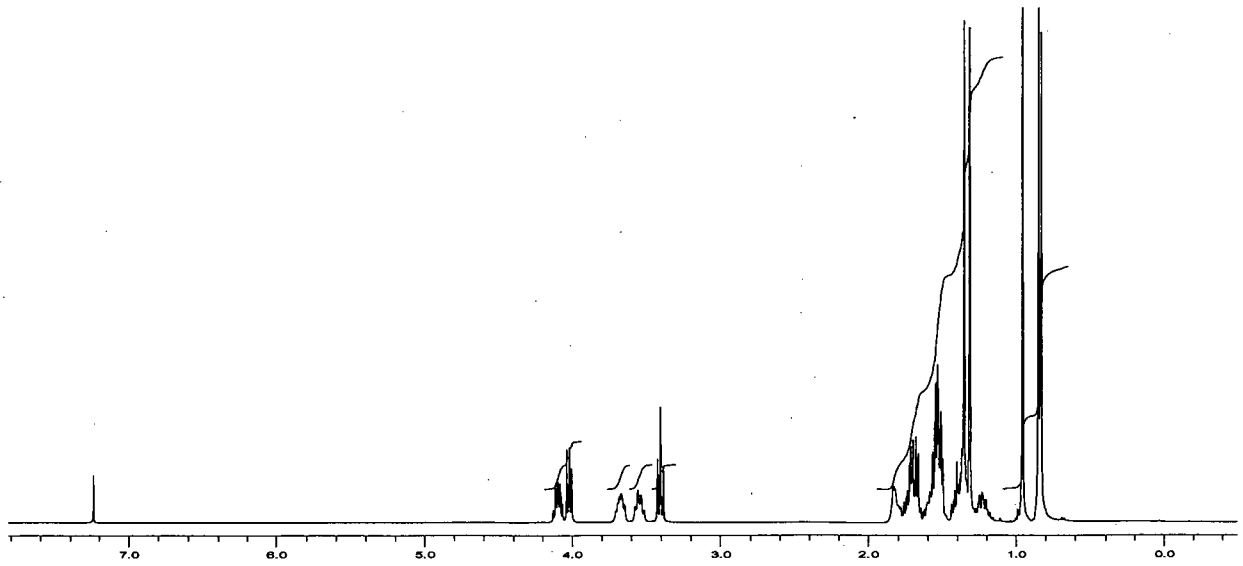


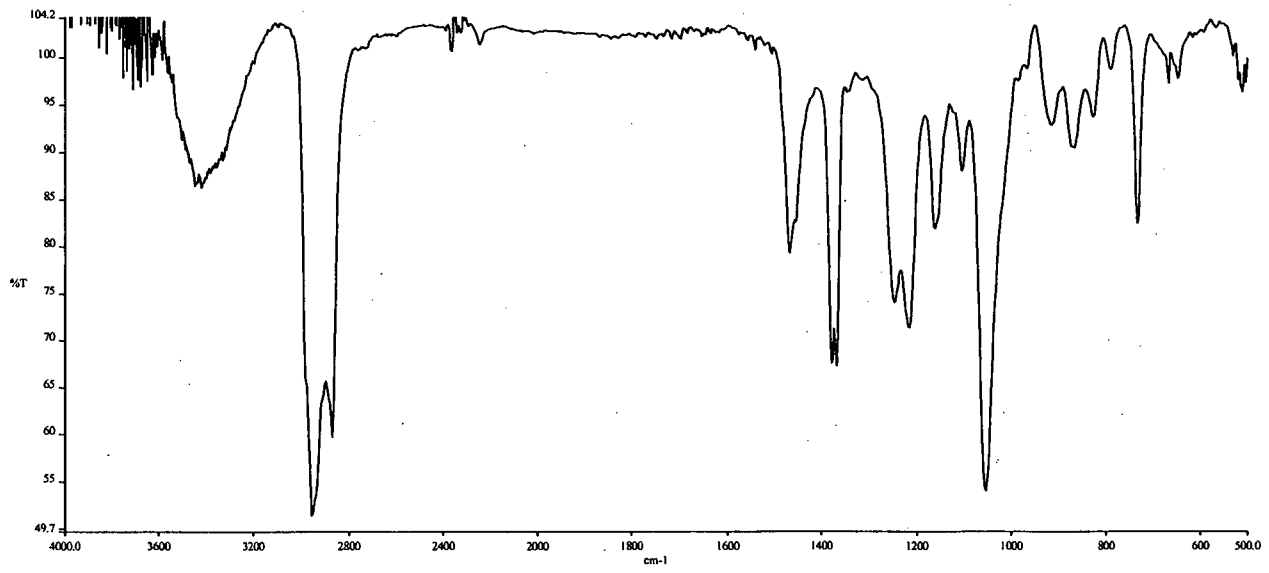




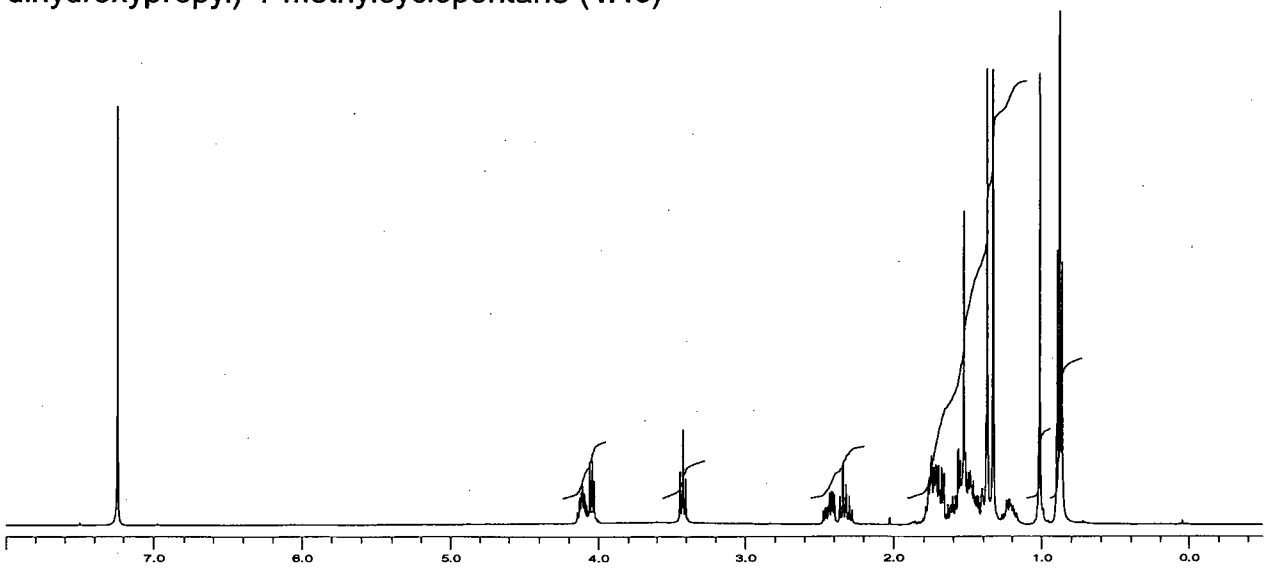
(1*R*, 2*S*, 3*R*)-2-(2-Hydroxyethyl)-3-isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methylcyclopentane (**4.44**)

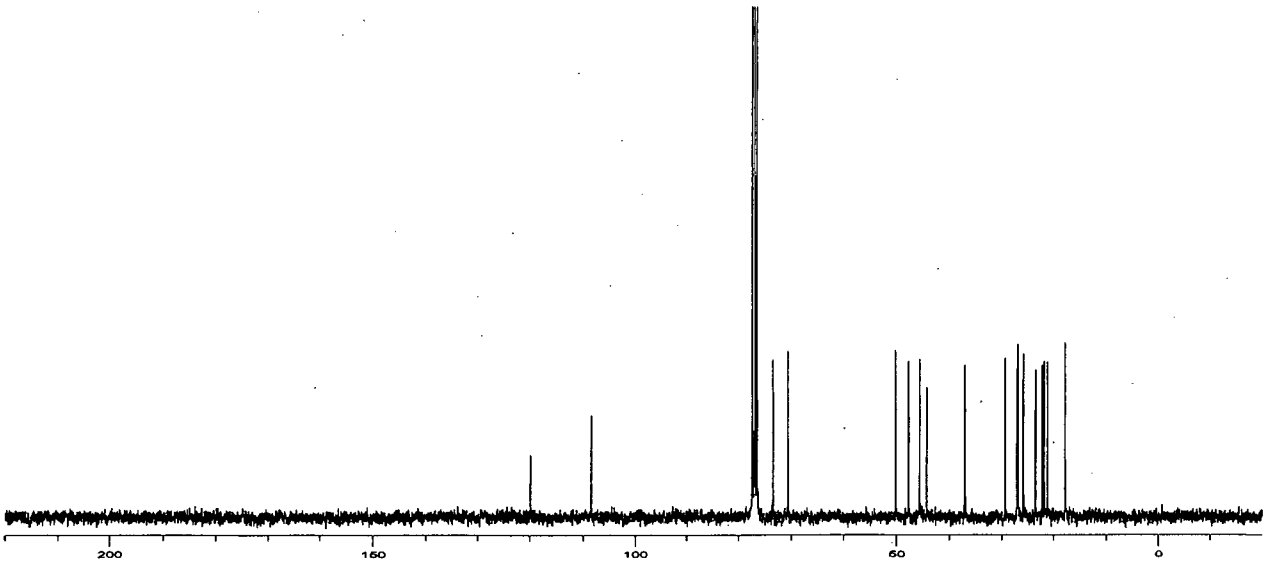


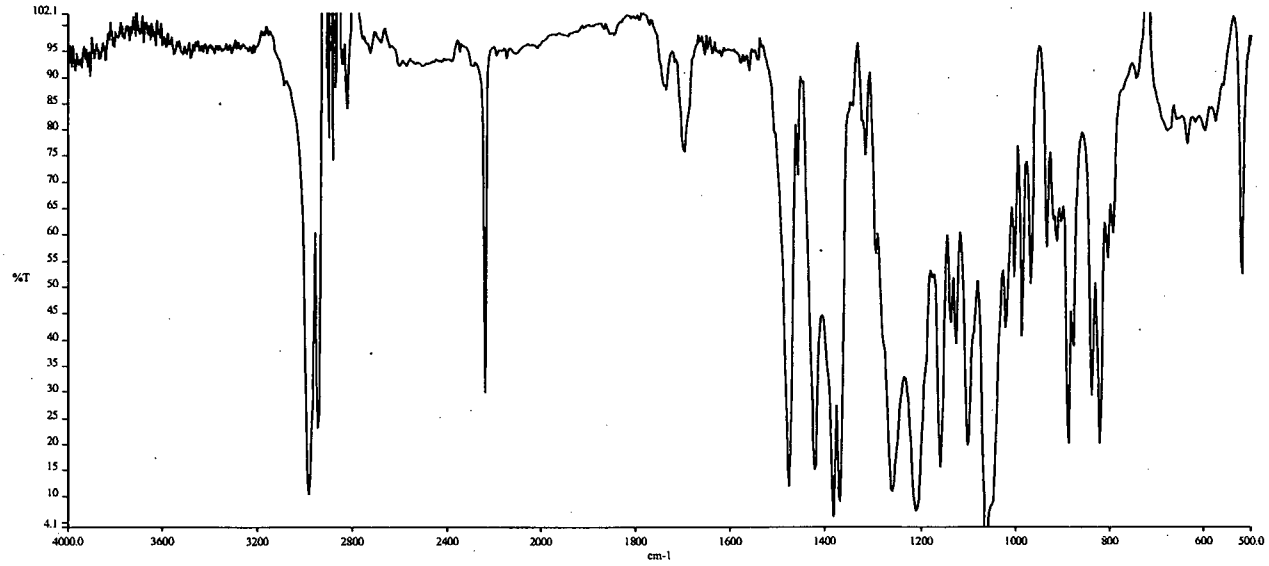




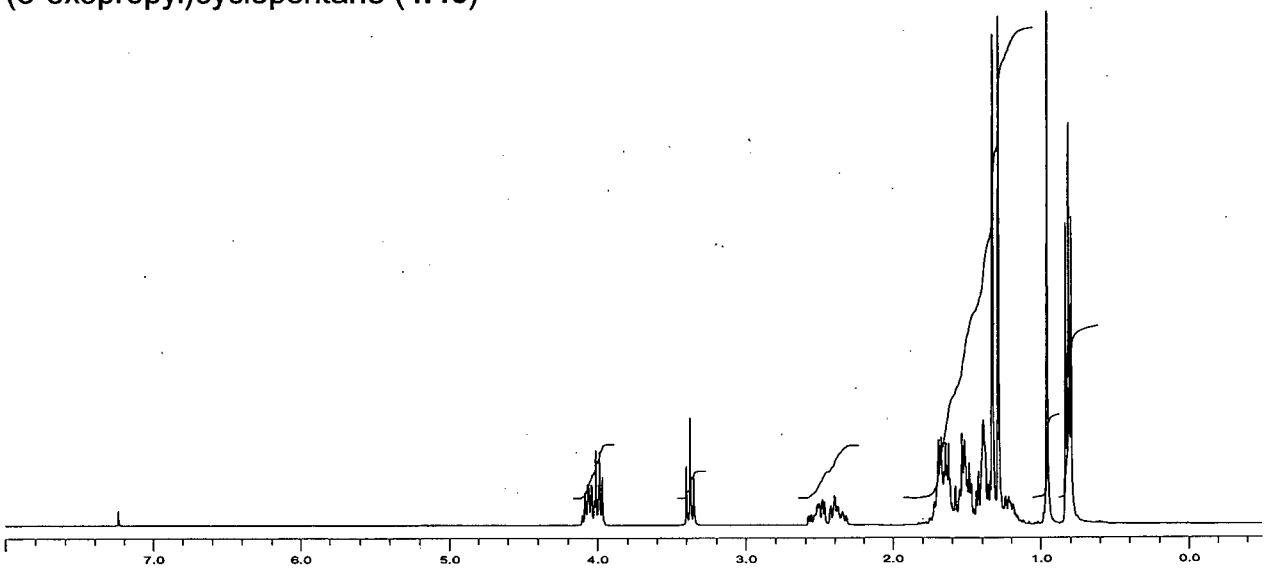
(1*R*, 2*S*, 3*R*)-2-(2-Cyanoethyl)-3-isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methylcyclopentane (**4.45**)

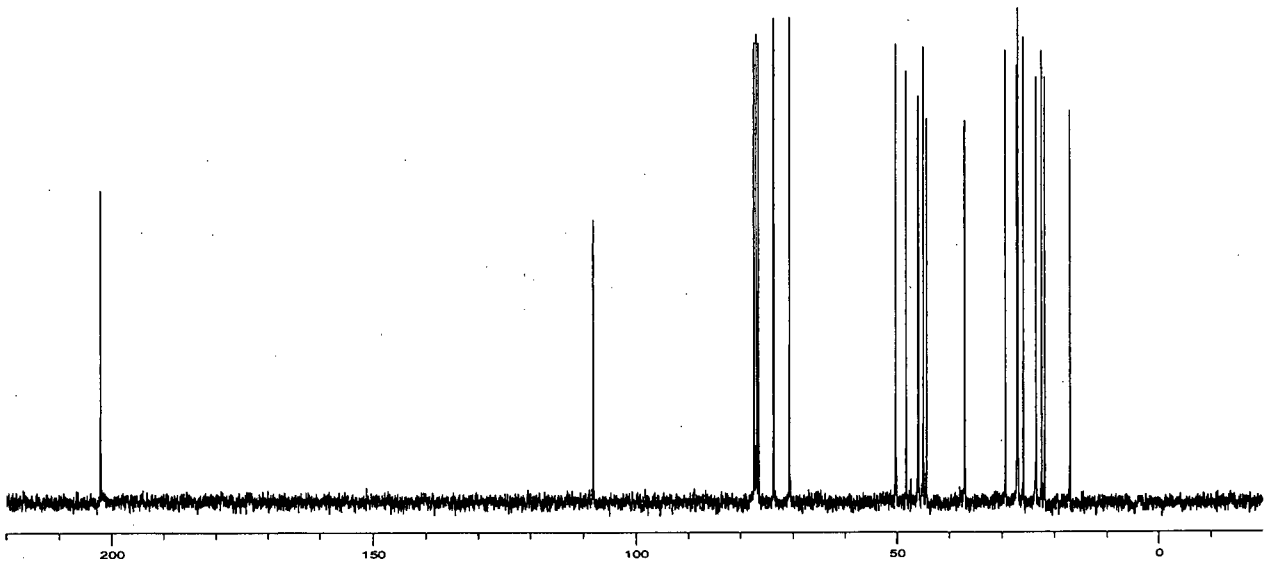


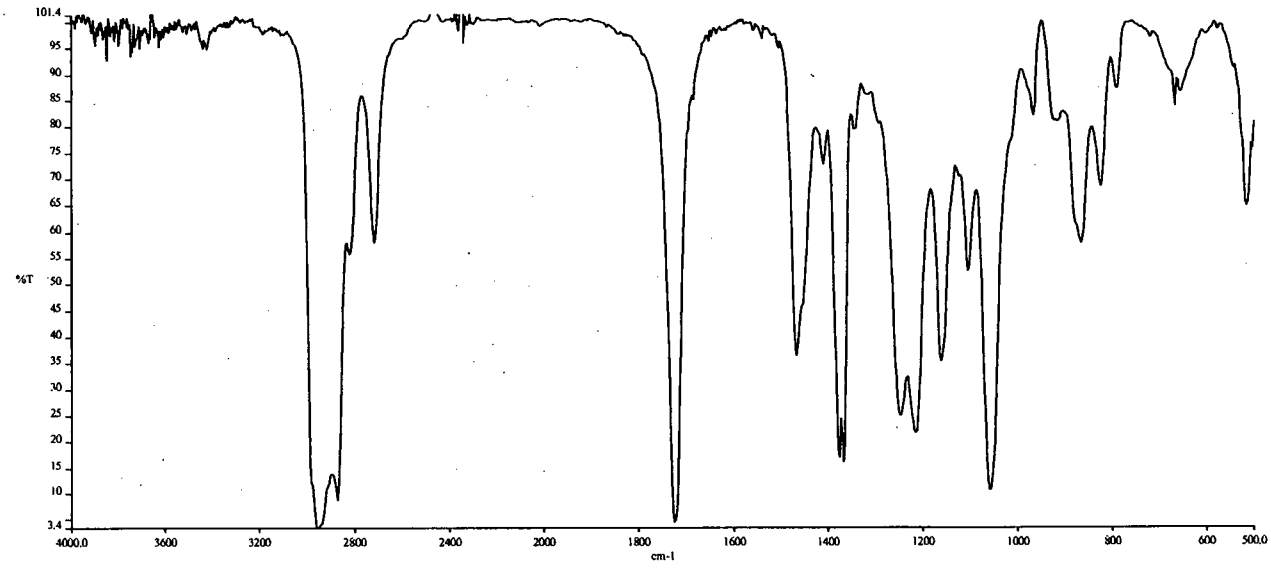




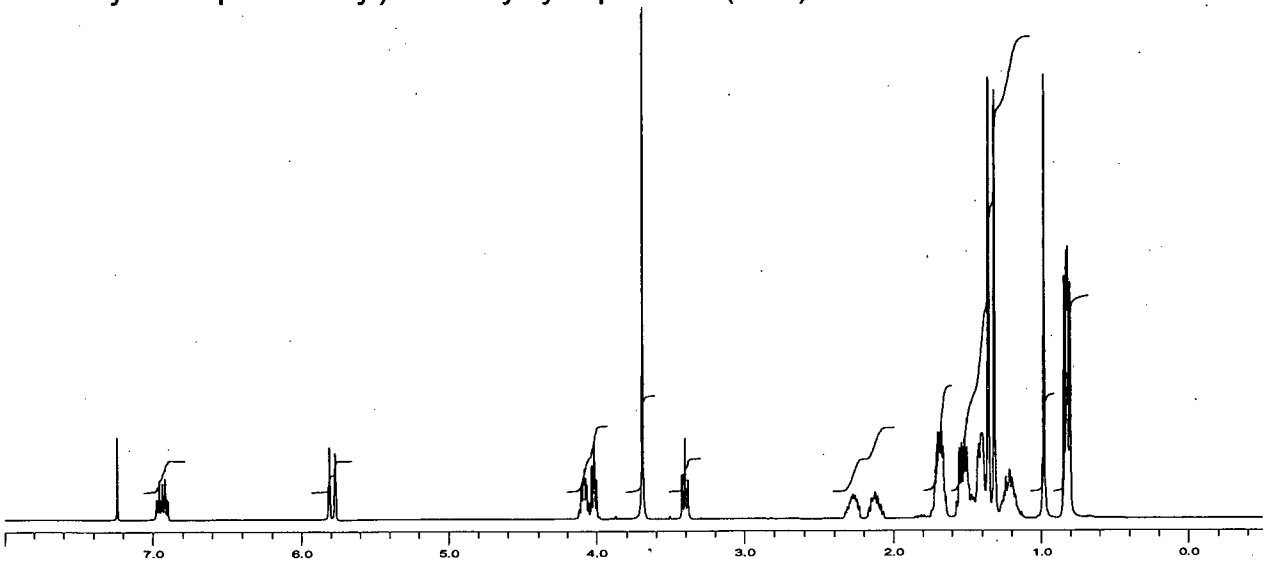
(1*R*, 2*S*, 3*R*)-3-Isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methyl-2-(3-oxopropyl)cyclopentane (**4.46**)

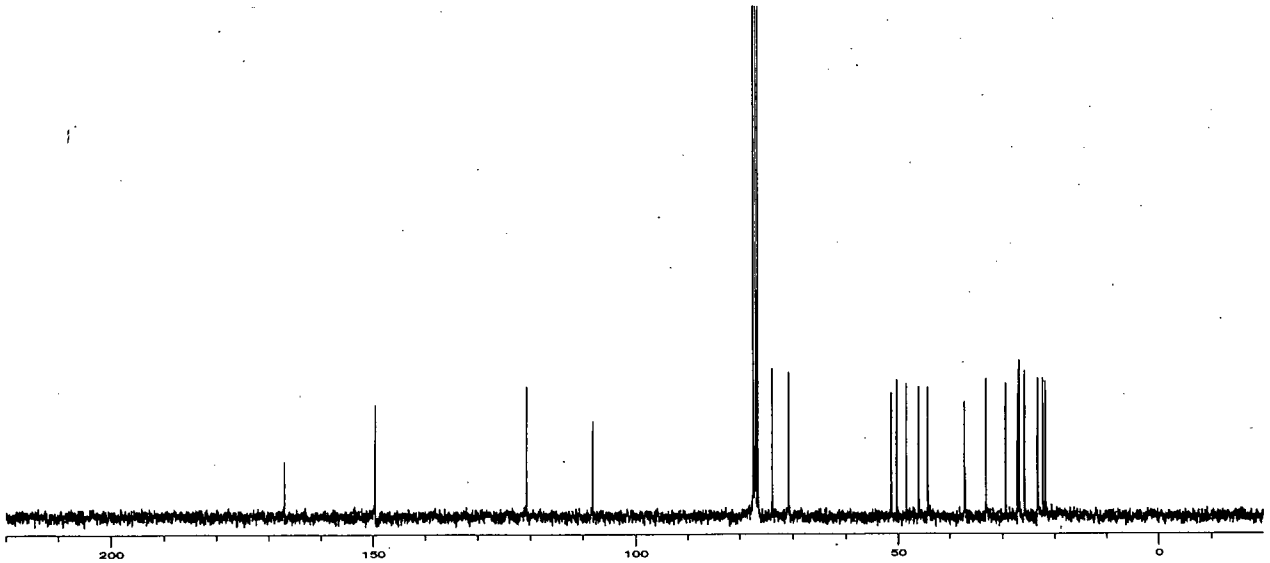


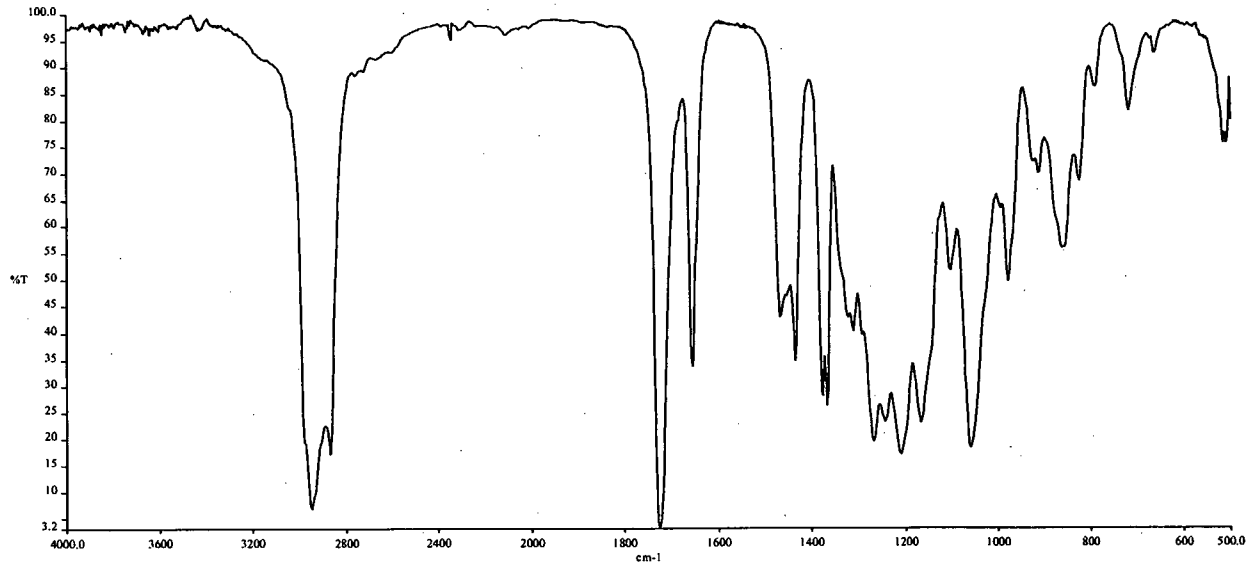




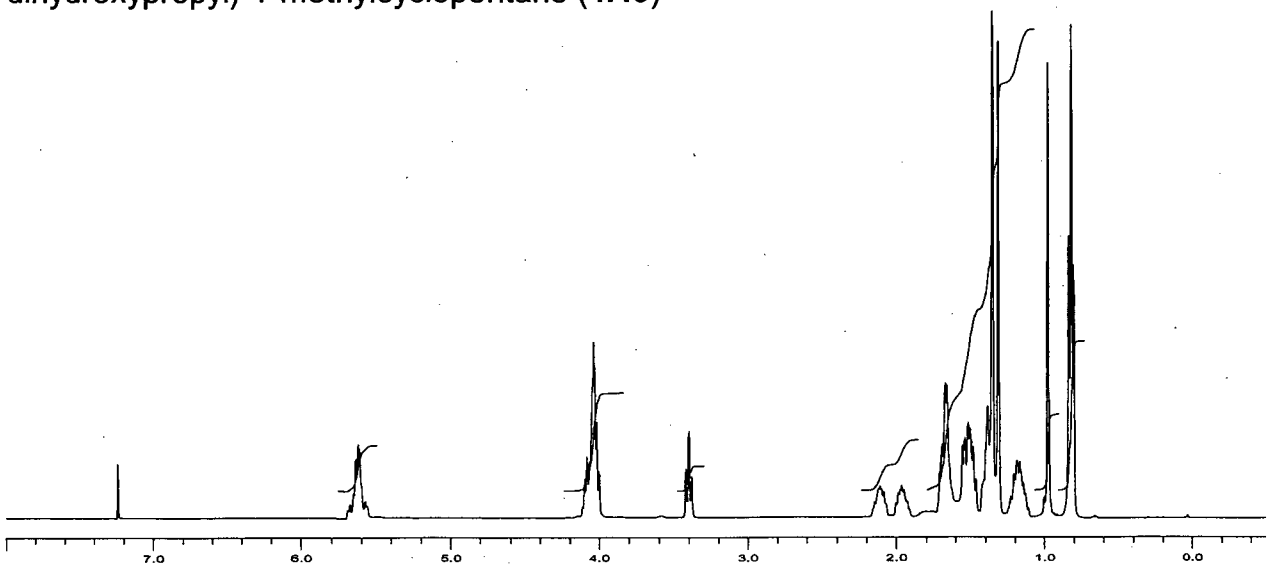
(1*R*, 2*S*, 3*R*)-3-Isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-2-((*E*)-5-methoxy-5-oxopent-3-enyl)-1-methylcyclopentane (**4.47**)

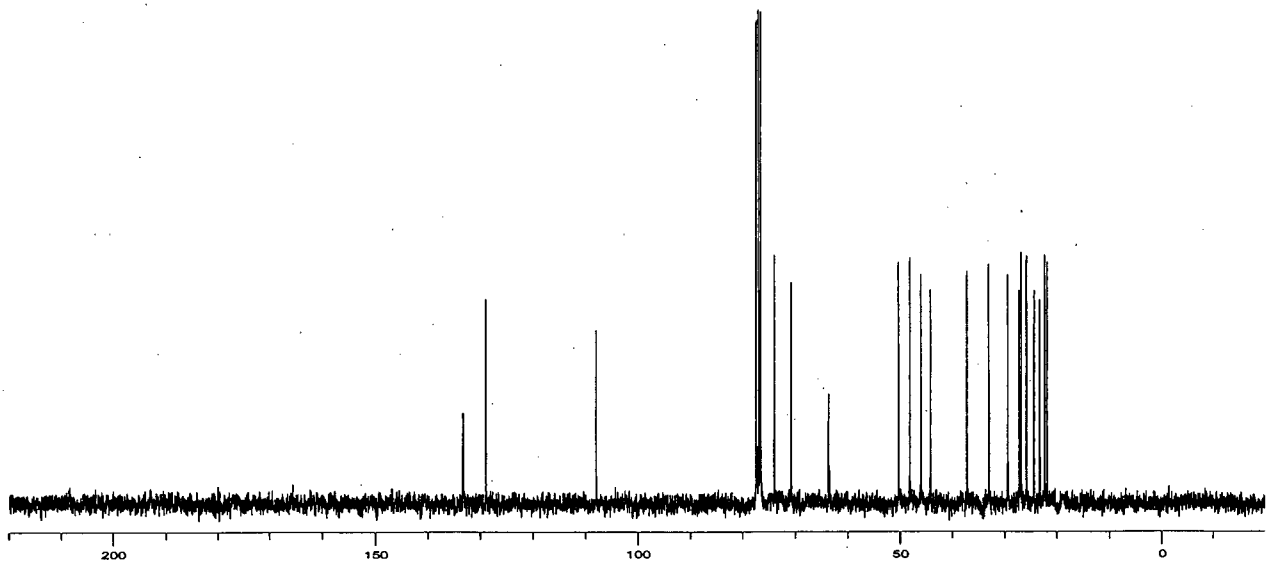


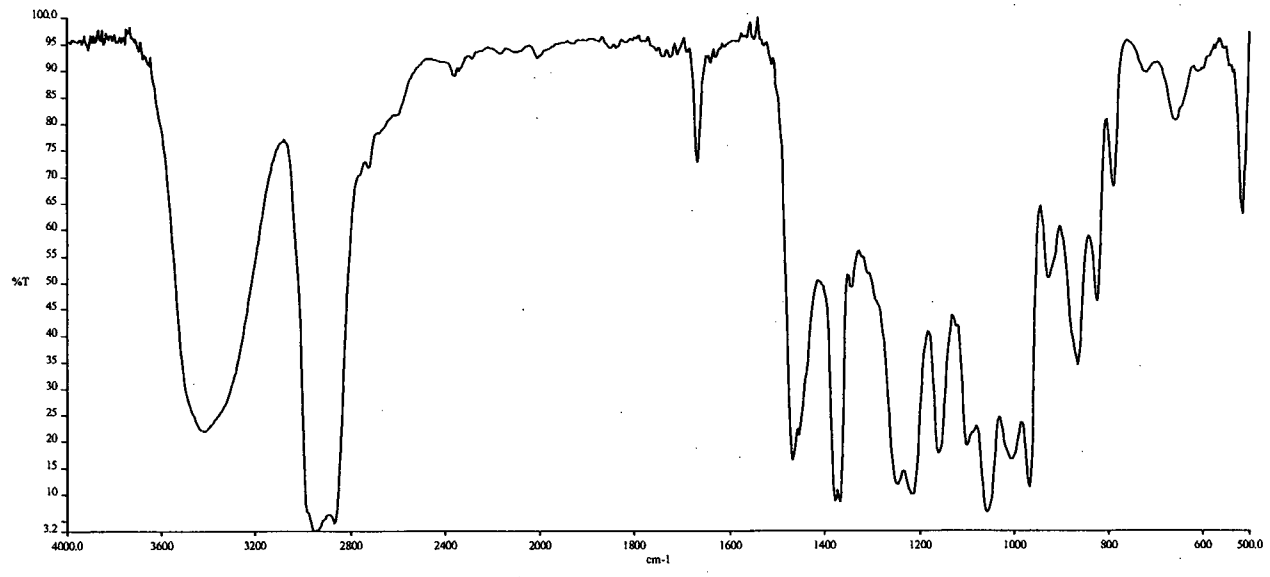




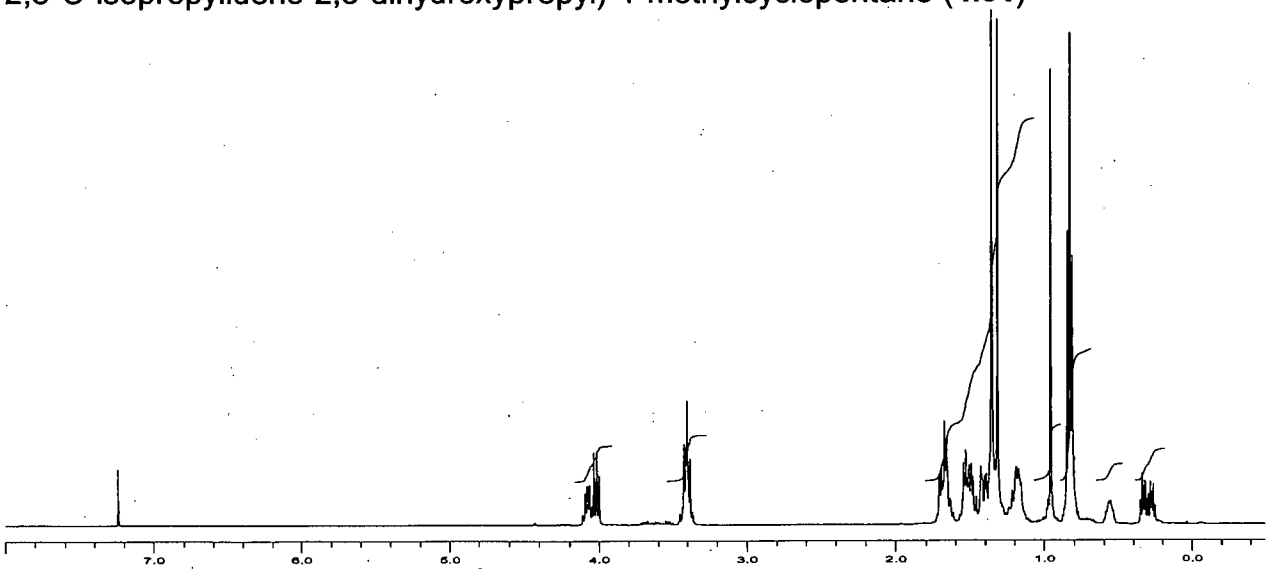
(1*R*, 2*S*, 3*R*)-2-(5-Hydroxypent-3-enyl)-3-isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methylcyclopentane (**4.49**)

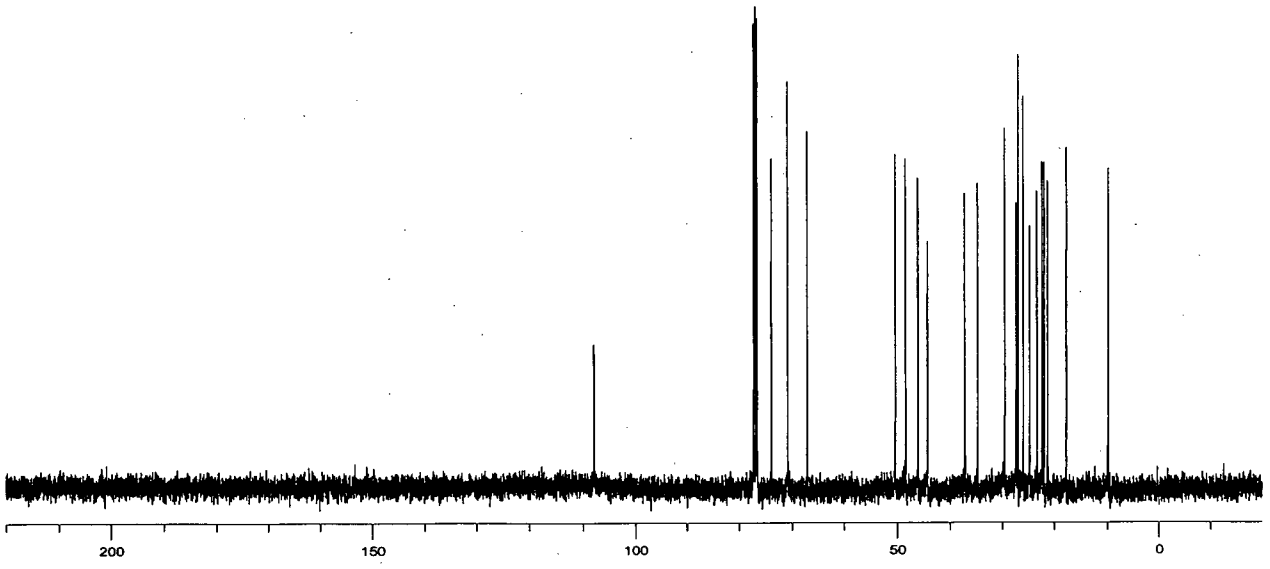


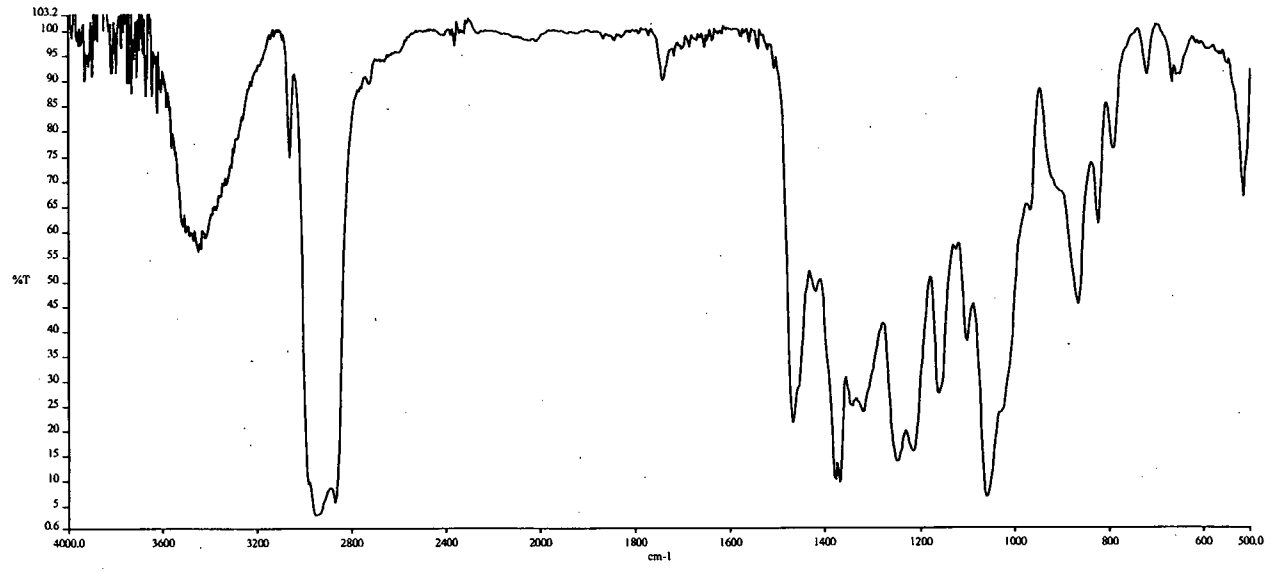




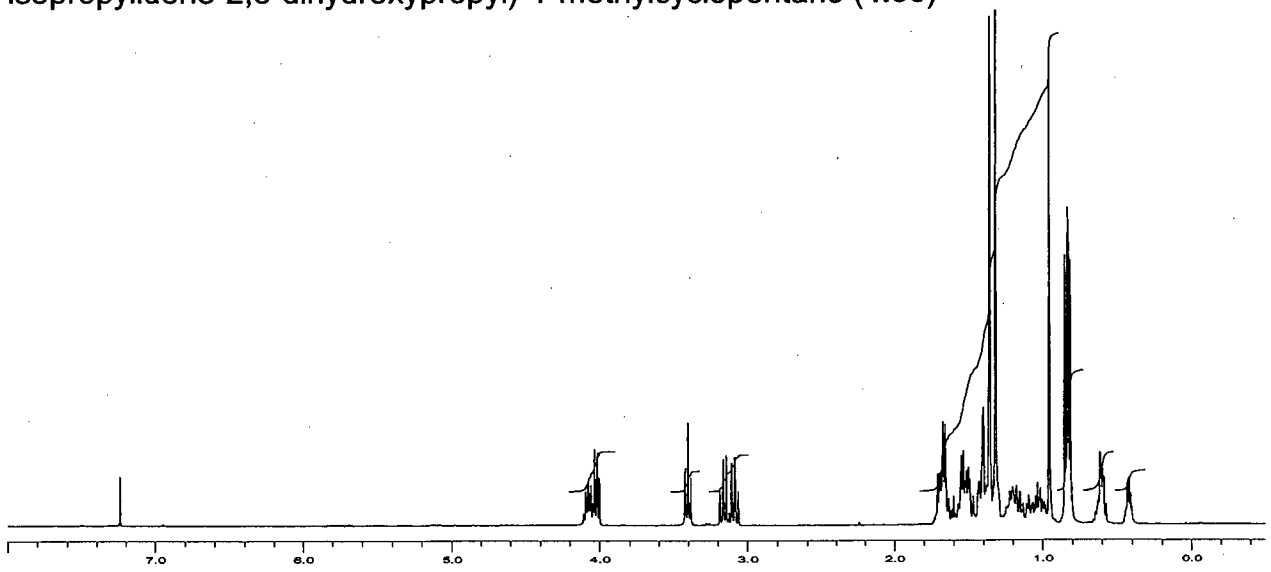
(1*R*, 2*S*, 3*R*)-2-(2-((1*S*, 2*S*)-2-(Hydroxymethyl)cyclopropyl)ethyl)-3-isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methylcyclopentane (**4.51**)

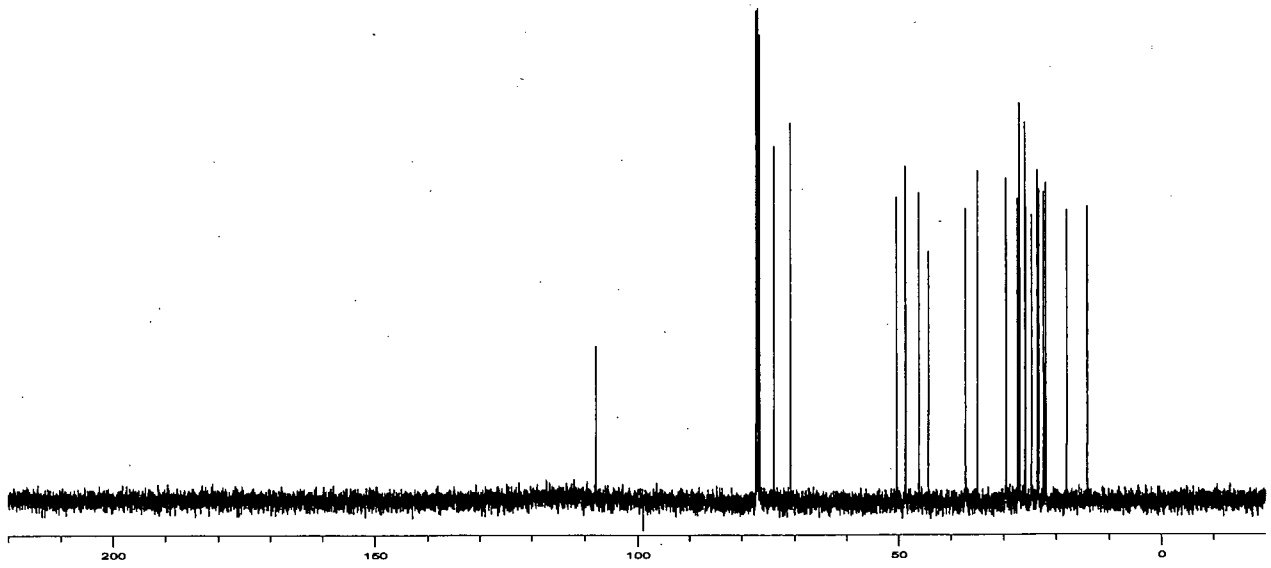


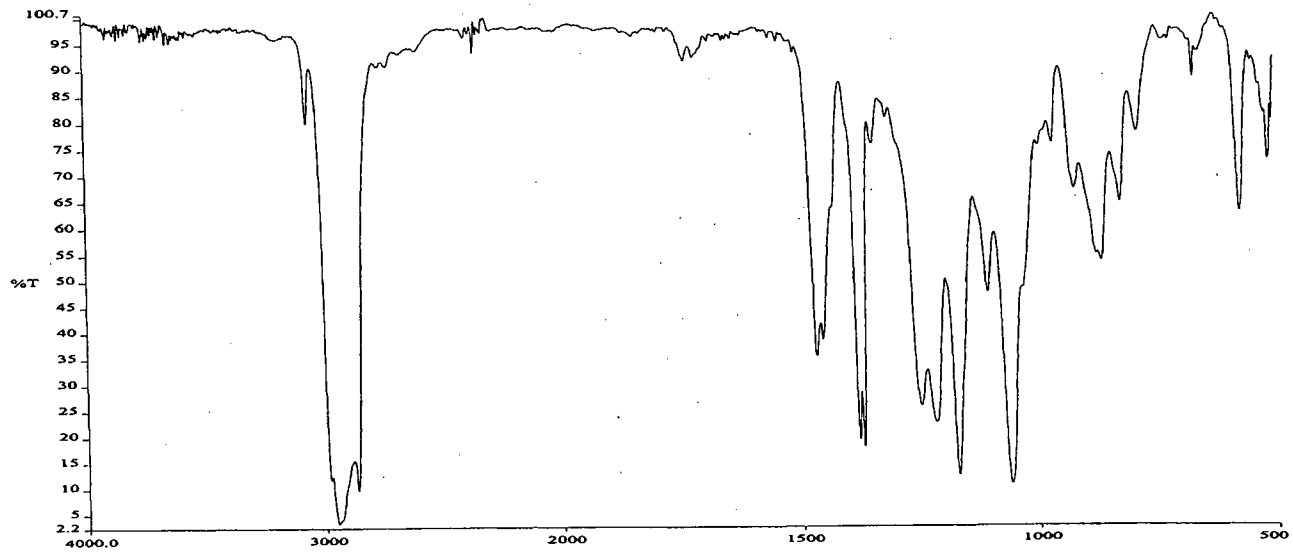




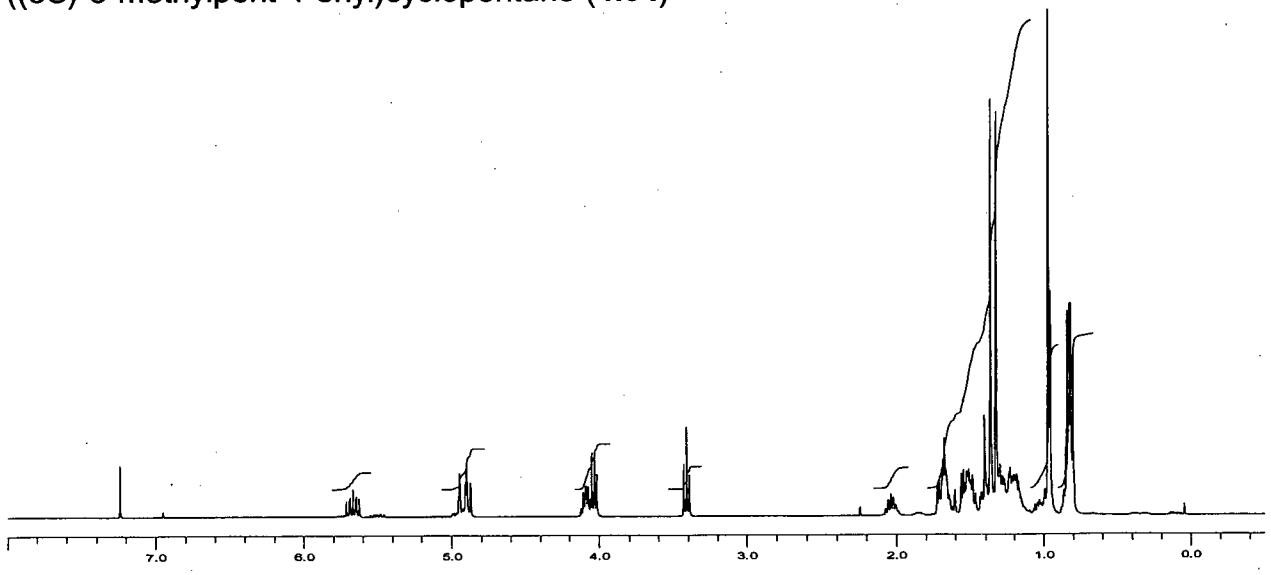
(1*R*, 2*S*, 3*R*)-2-(2-((1*S*, 2*S*)-2-(Iodomethyl)cyclopropyl)ethyl)-3-isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methylcyclopentane (**4.53**)

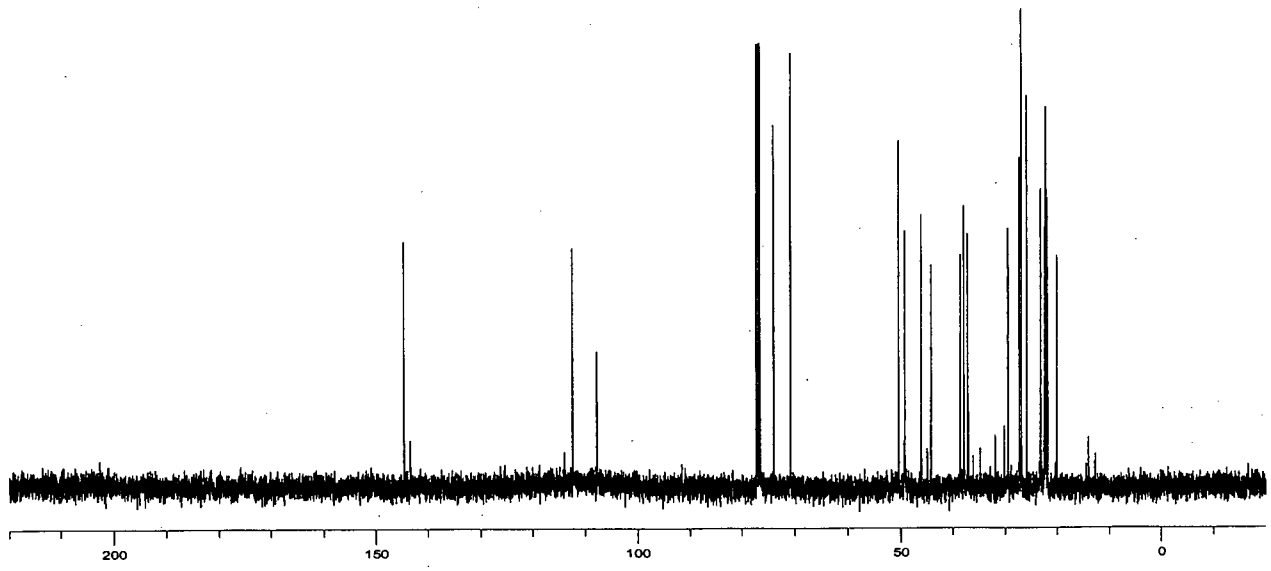


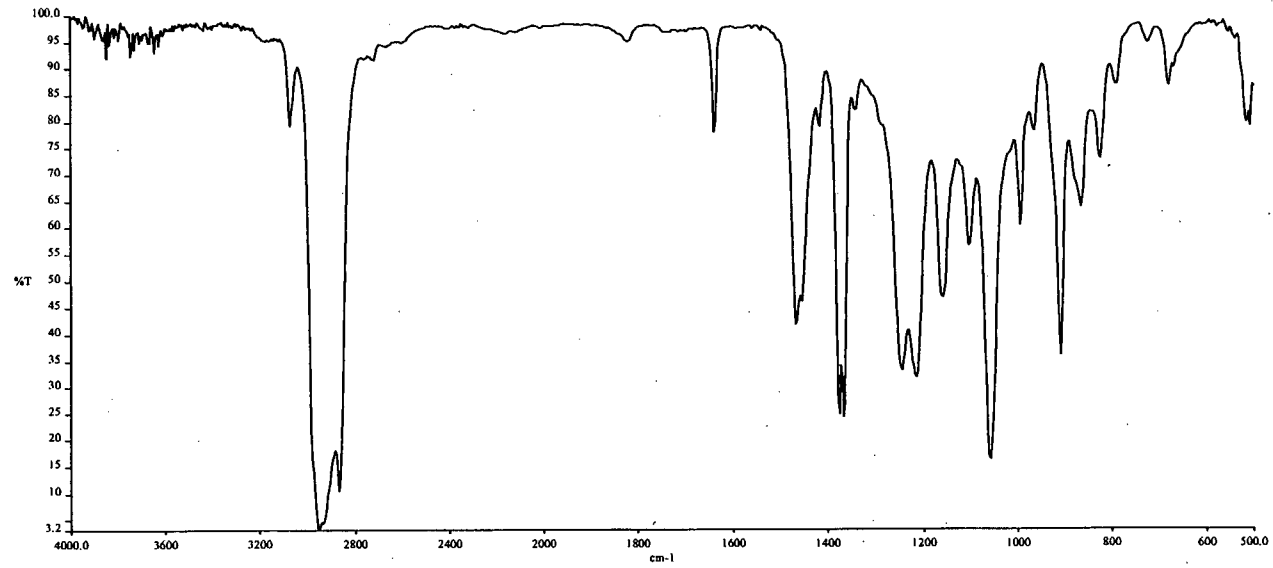




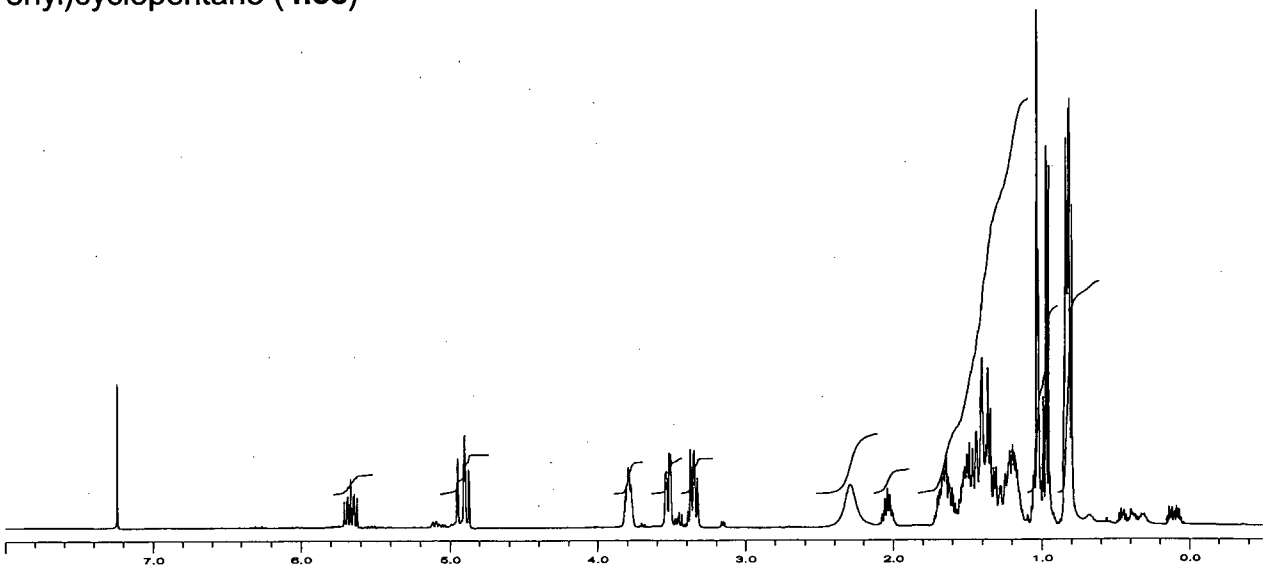
(1*R*, 2*S*, 3*R*)-3-Isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methyl-2-((3*S*)-3-methylpent-4-enyl)cyclopentane (**4.54**)

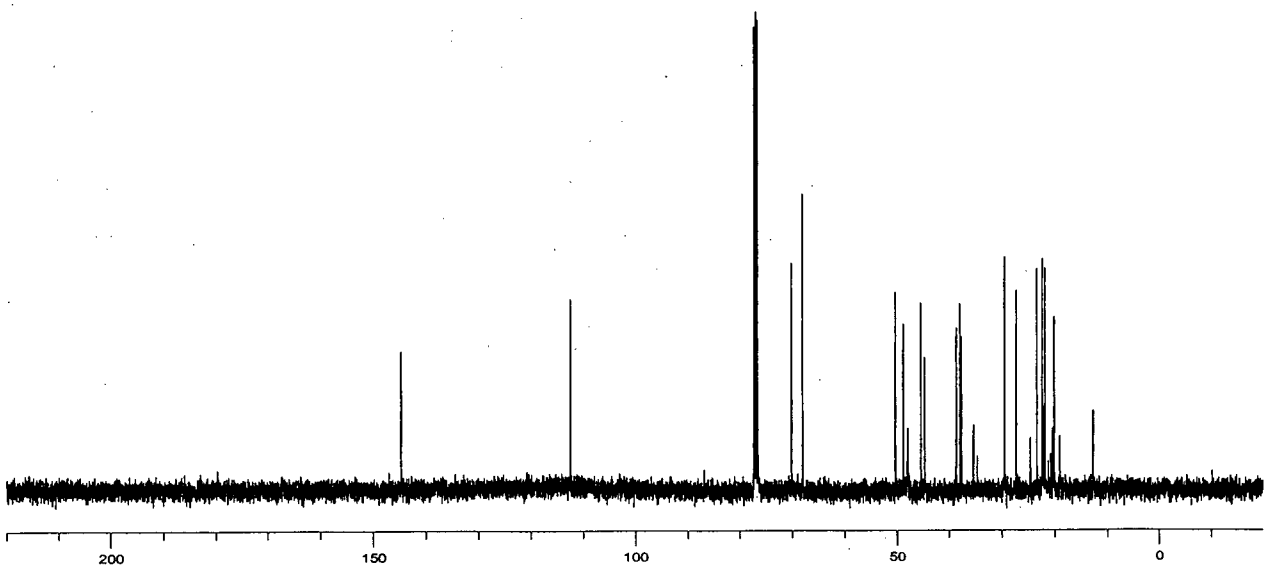




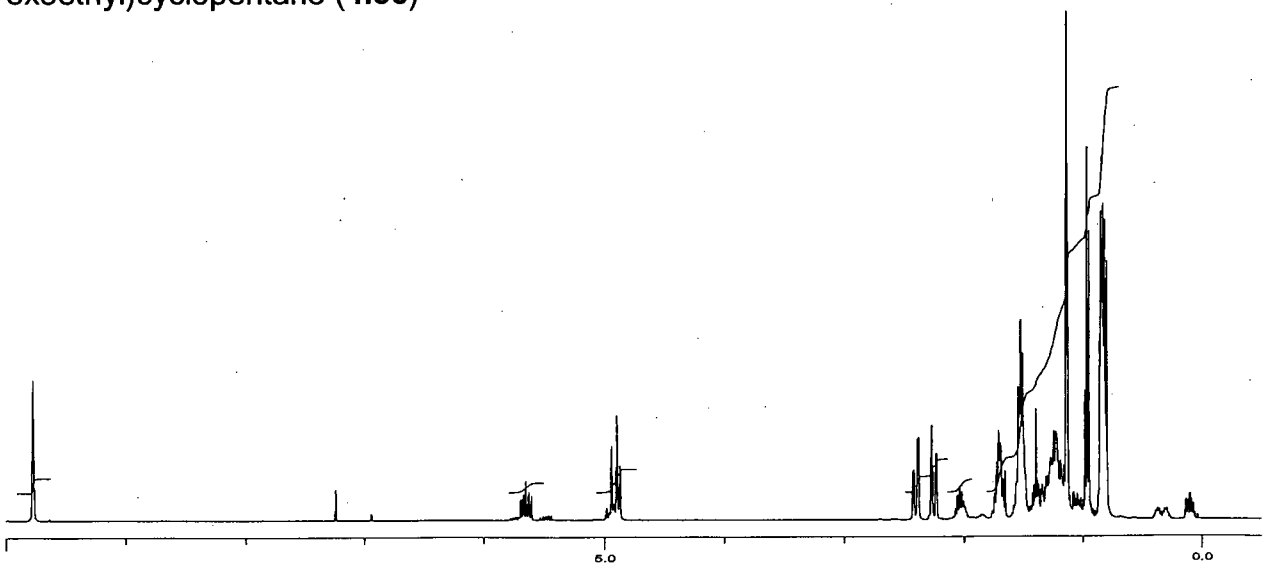


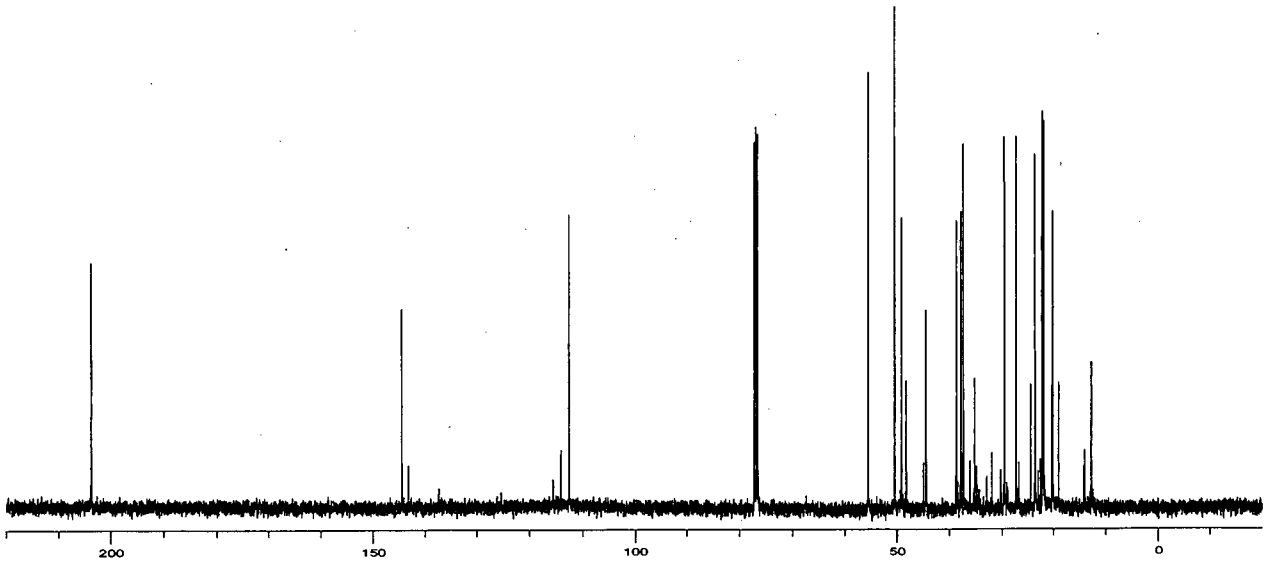
(1*R*, 2*S*, 3*R*)-3-isopropyl-1-((2*S*)-2,3-dihydroxypropyl)-1-methyl-2-((3*S*)-3-methylpent-4-enyl)cyclopentane (**4.55**)

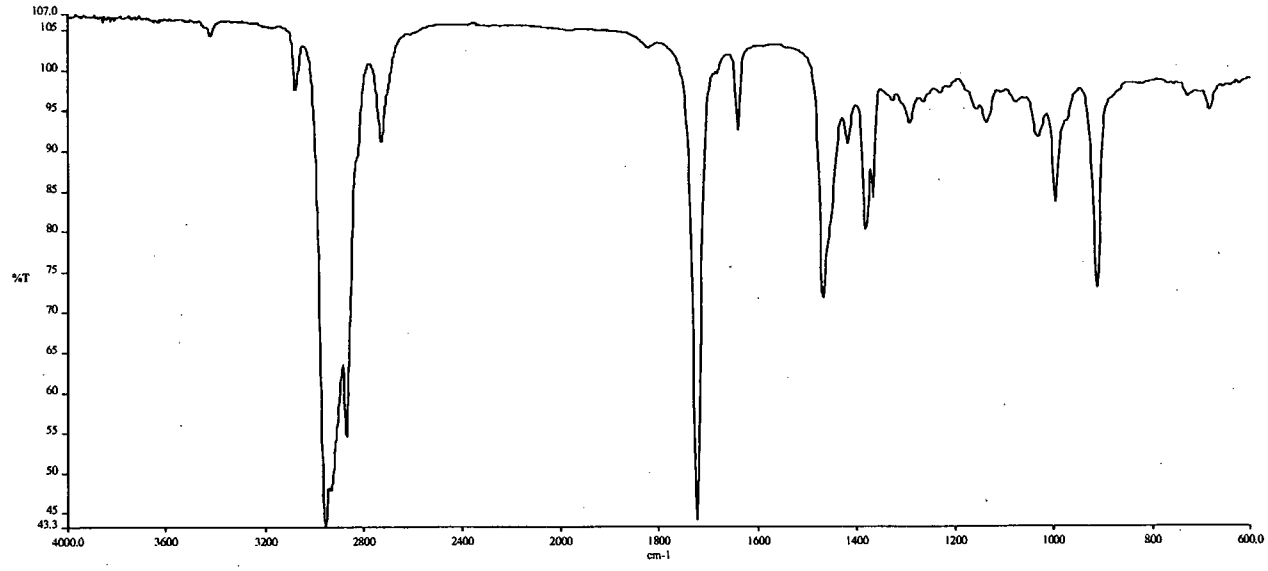




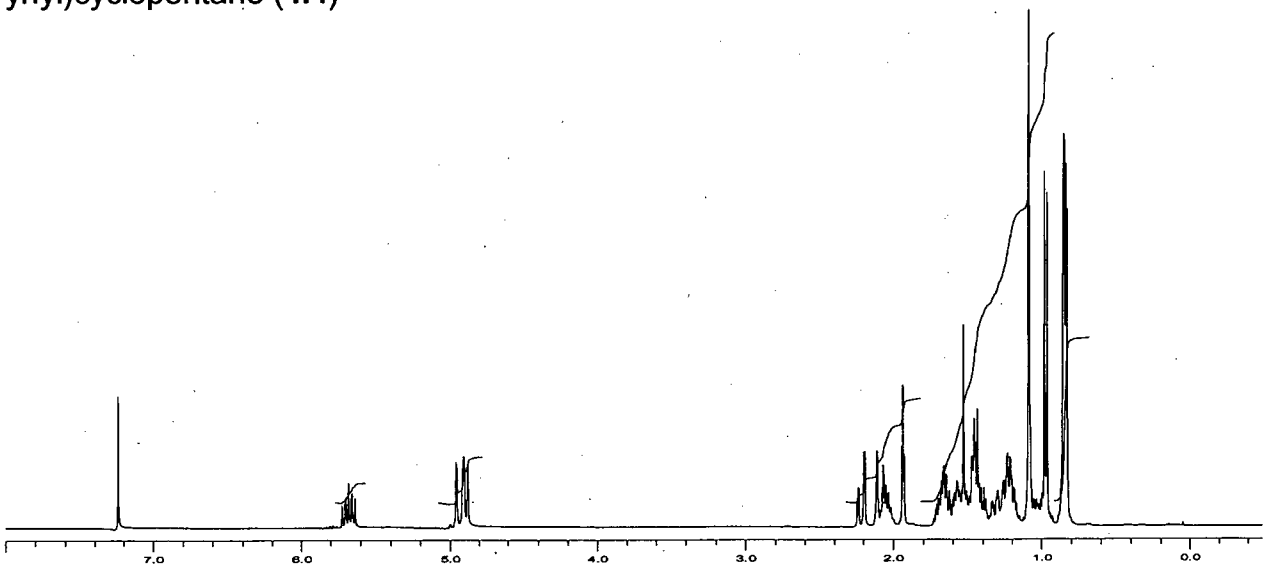
(1*R*, 2*S*, 3*R*)-3-Isopropyl-1-methyl-2-((3*S*)-3-methylpent-4-enyl)-1-(2-oxoethyl)cyclopentane (**4.56**)

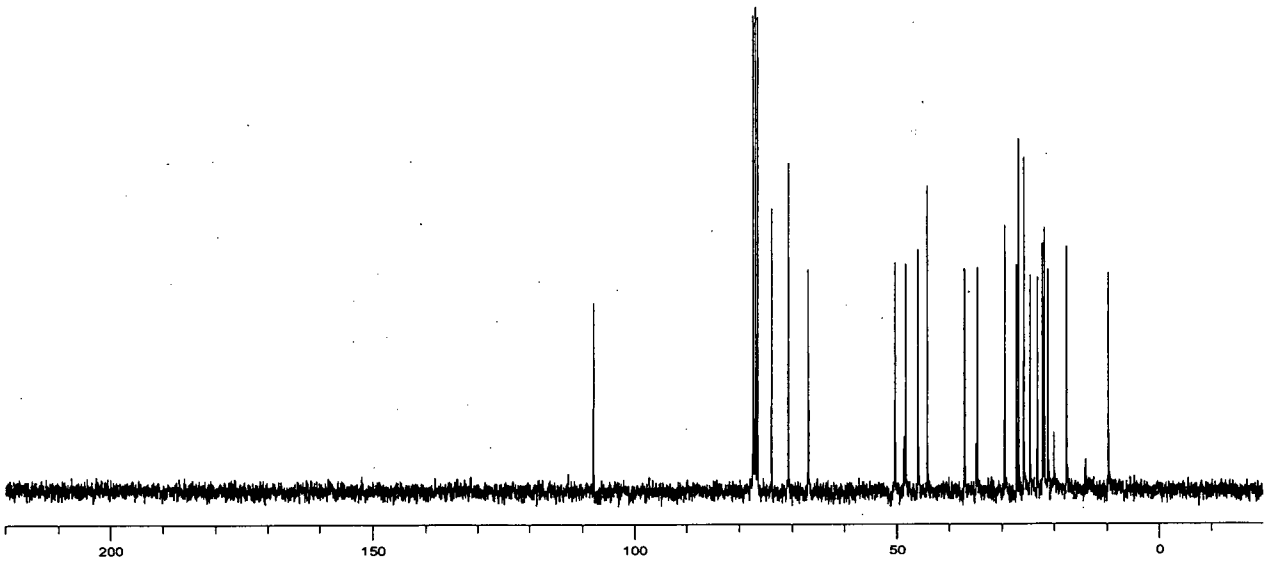


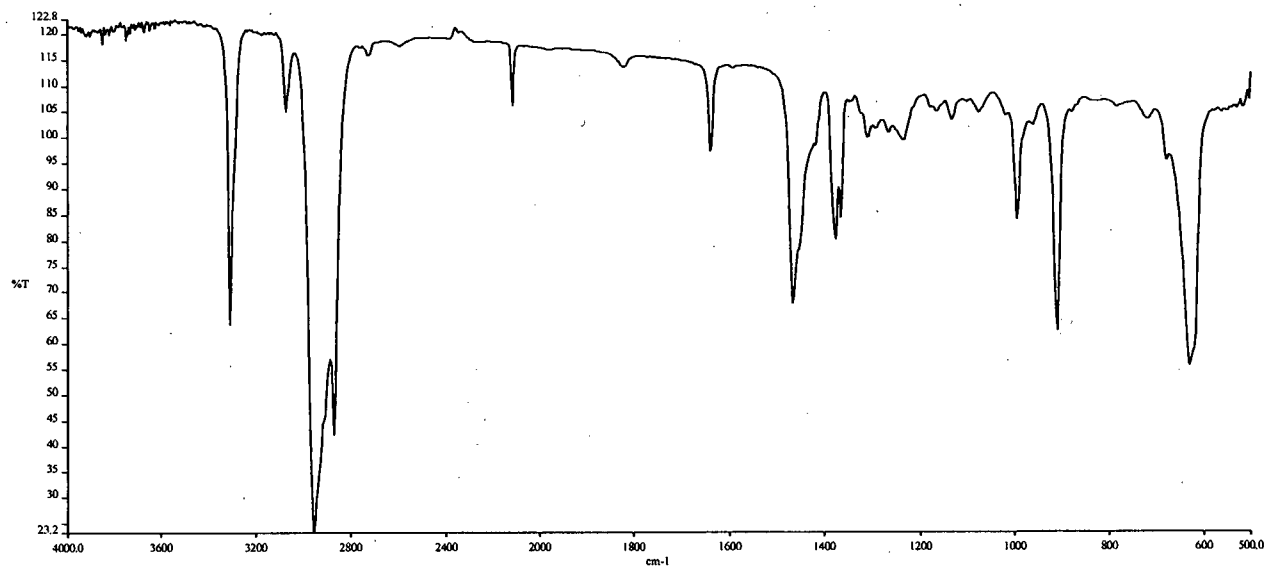




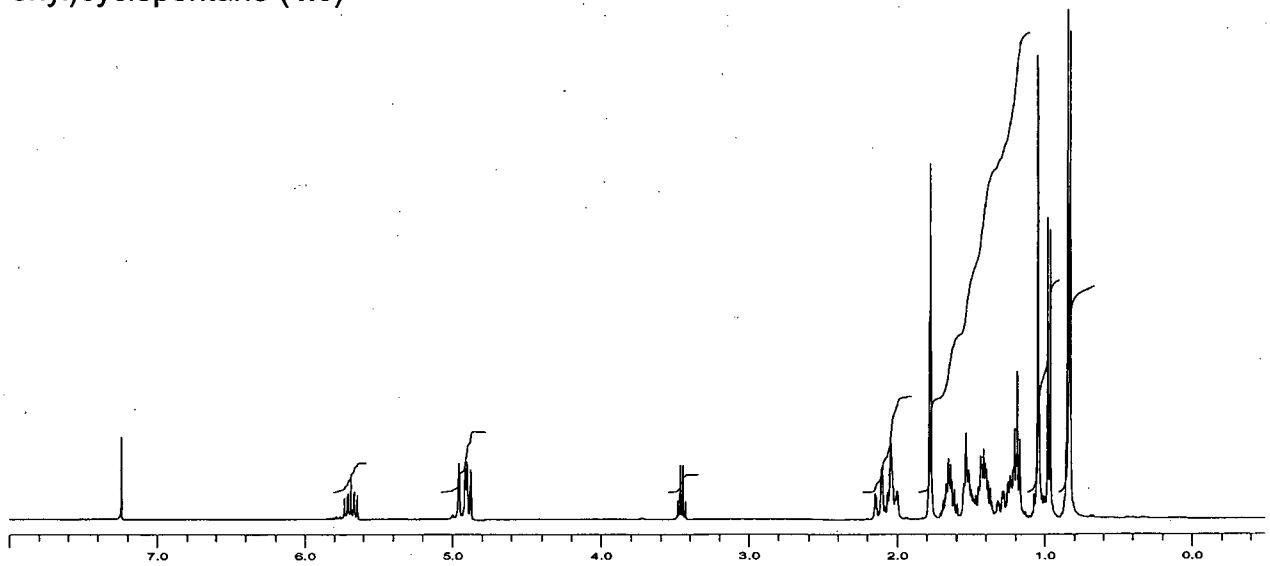
(1*R*, 2*S*, 3*R*)-3-Isopropyl-1-methyl-2-((3*S*)-3-methylpent-4-enyl)-1-(prop-2-ynyl)cyclopentane (**4.4**)

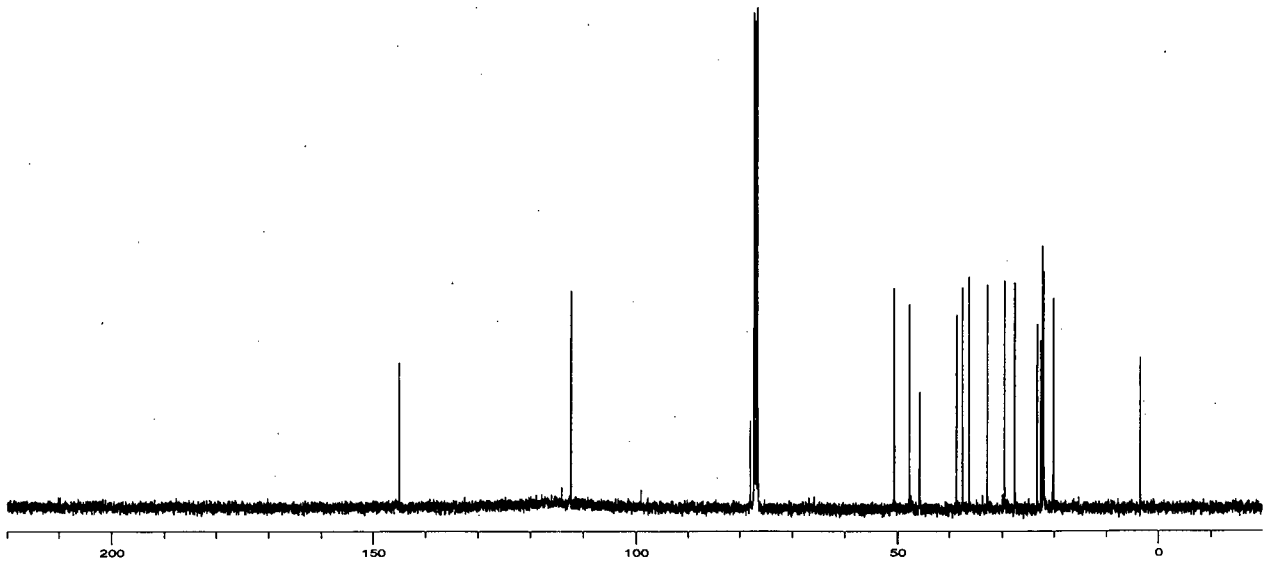


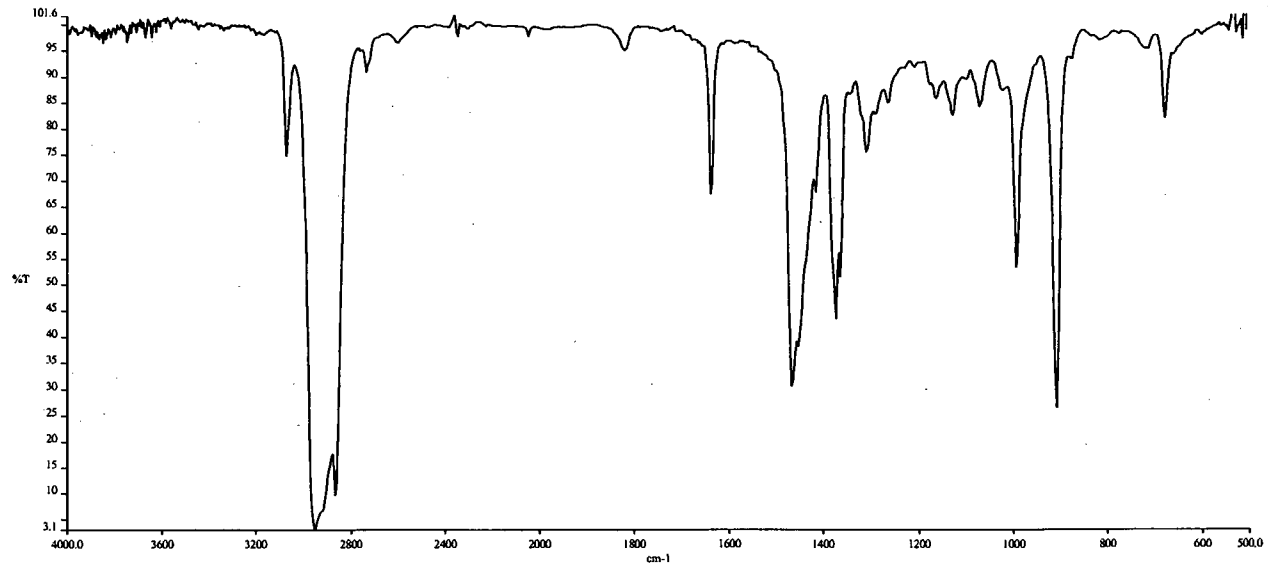




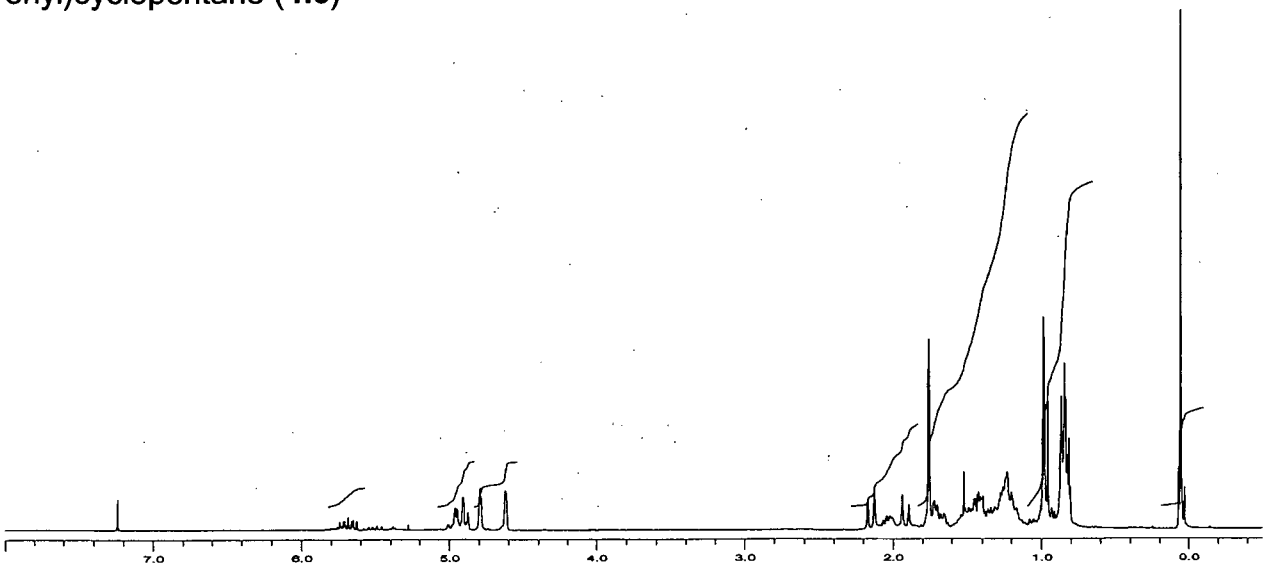
(1*R*, 2*S*, 3*R*)-1-(But-2-ynyl)-3-isopropyl-1-methyl-2-((3*S*)-3-methylpent-4-enyl)cyclopentane (**4.5**)

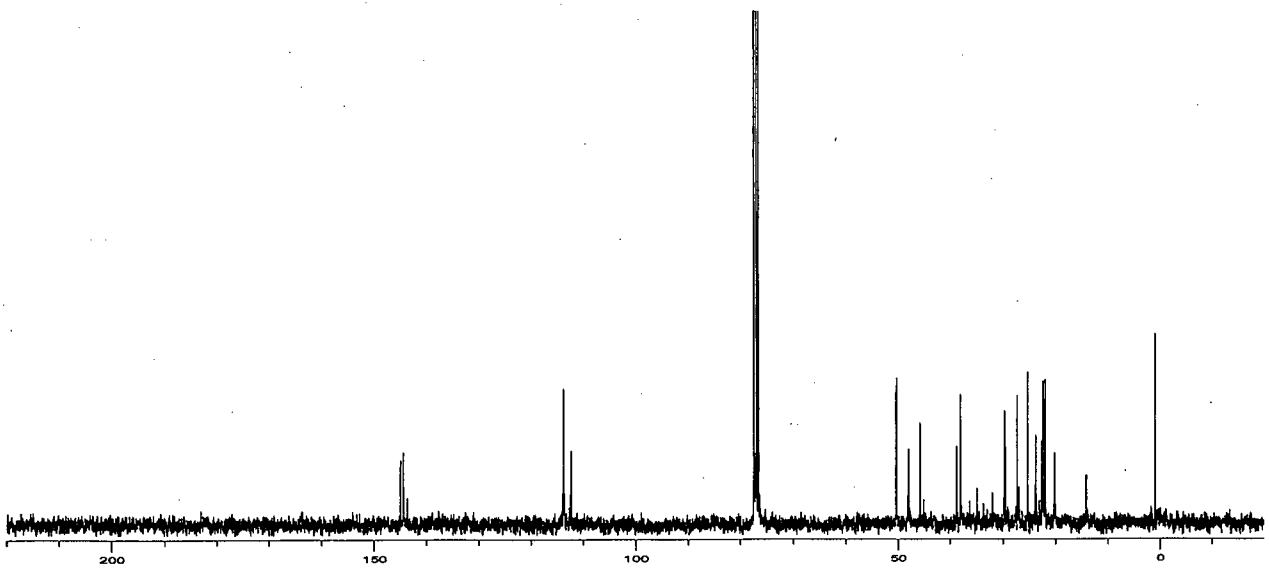


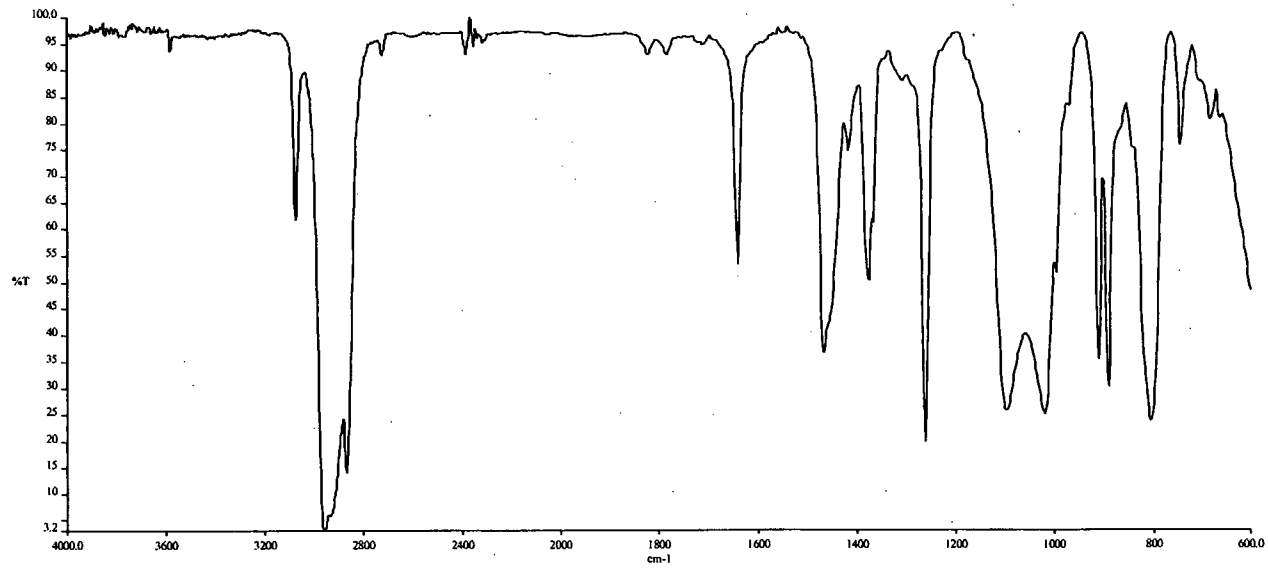




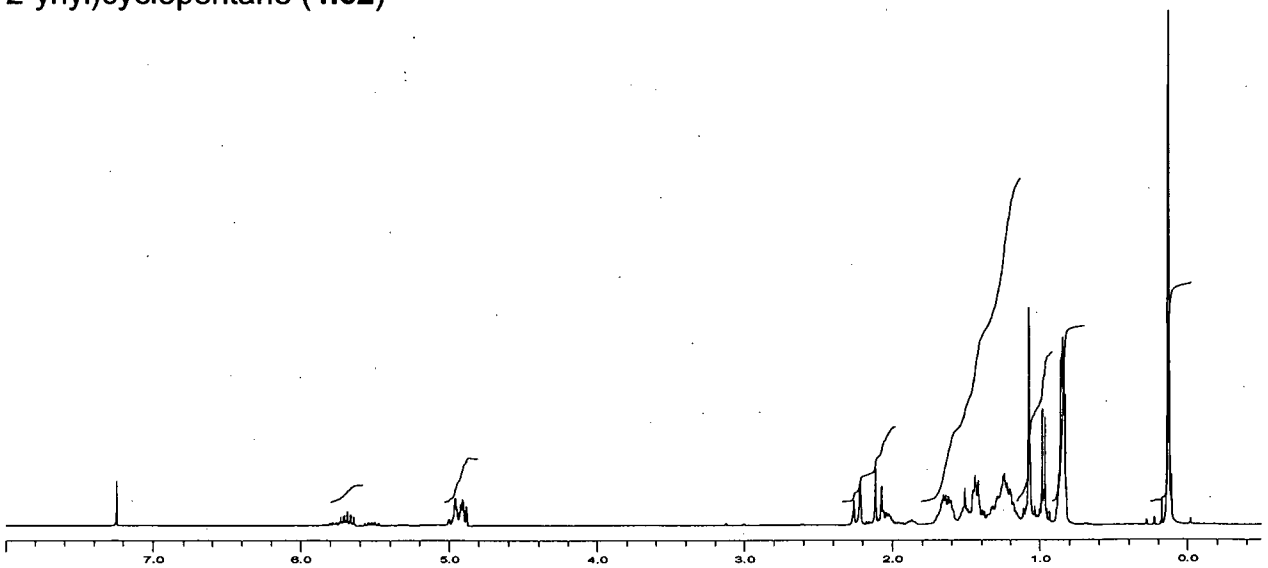
(1*R*, 2*S*, 3*R*)-3-Isopropyl-1-methyl-2-((3*S*)-3-methylpent-4-enyl)-1-(2-methylprop-2-enyl)cyclopentane (**4.6**)

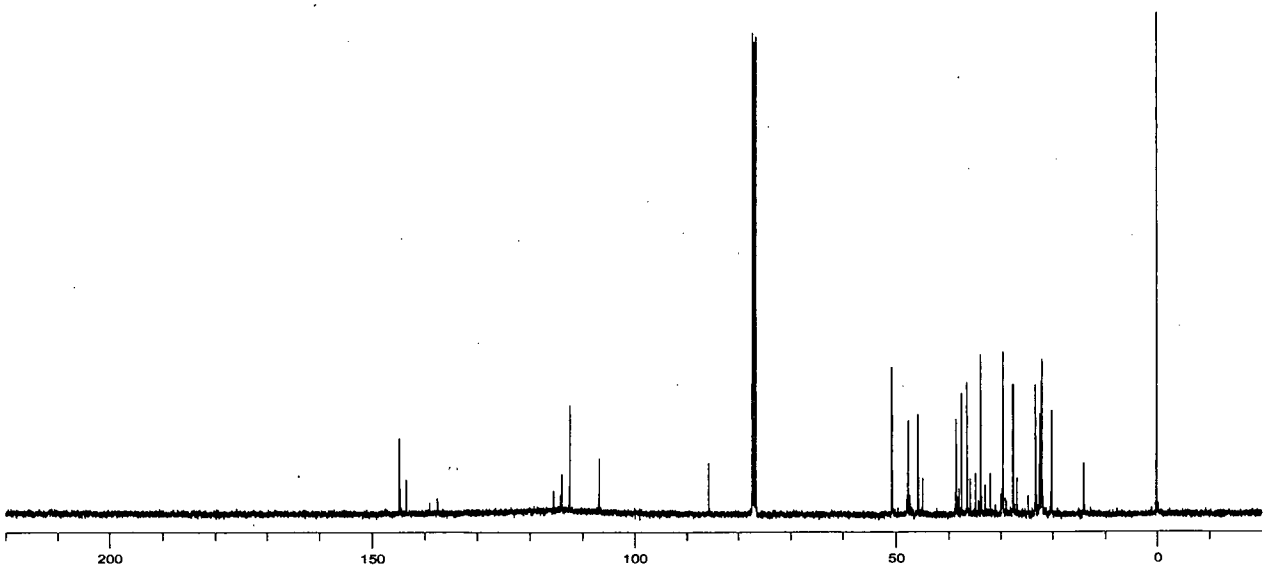


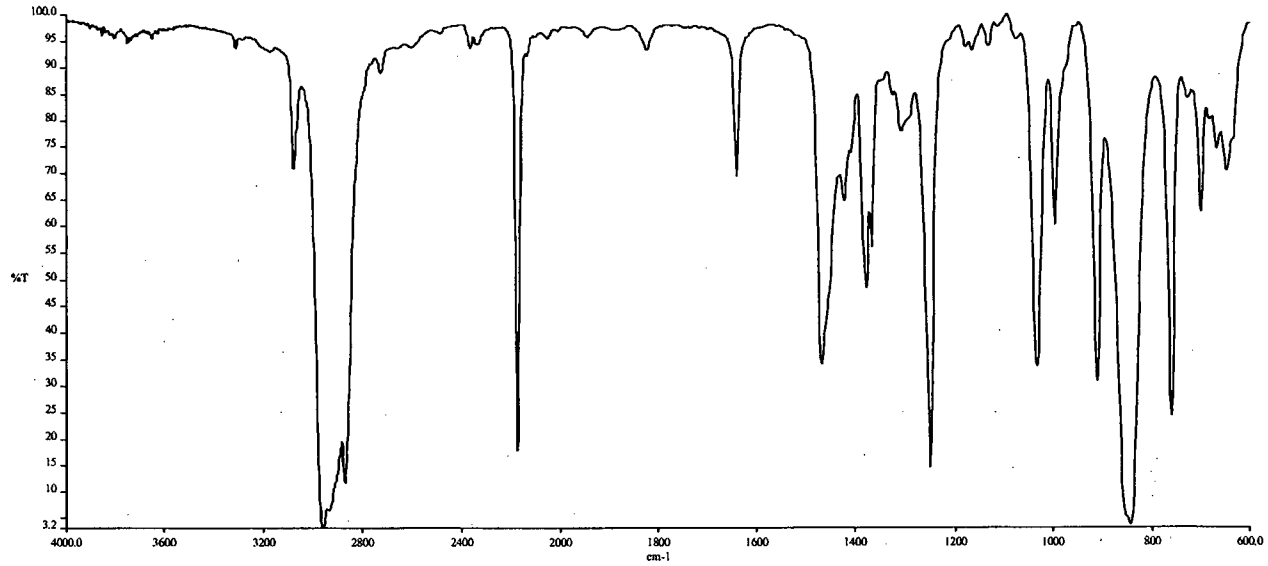




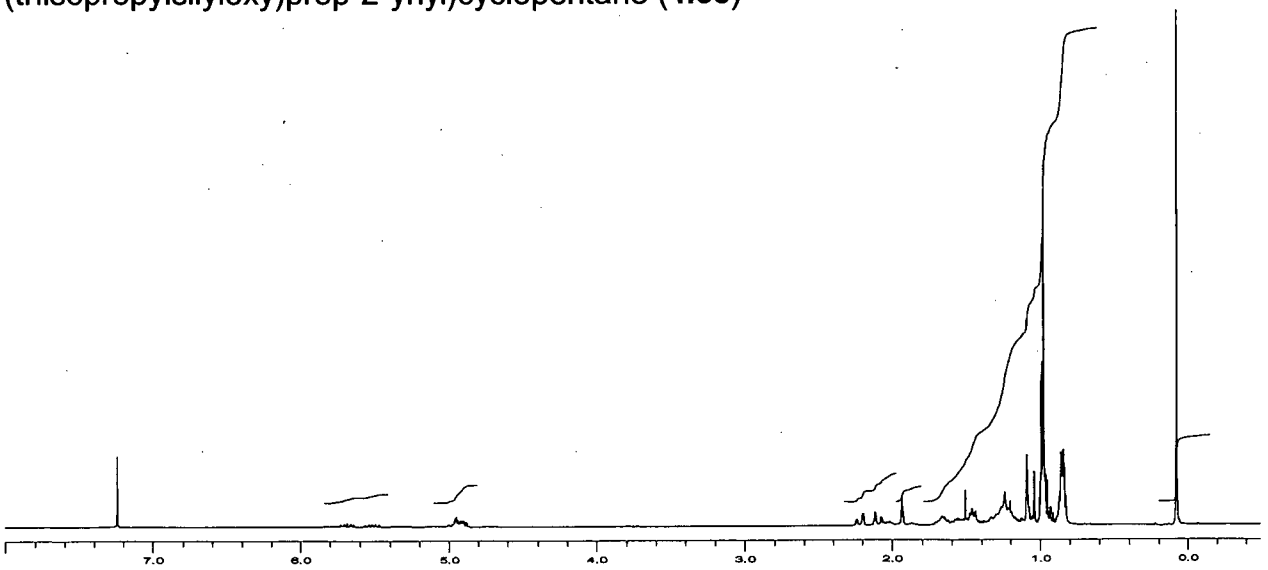
(1*R*, 2*S*, 3*R*)-3-Isopropyl-1-methyl-2-((3*S*)-3-methylpent-4-enyl)-1-(3-(trimethylsilyl)prop-2-ynyl)cyclopentane (**4.62**)

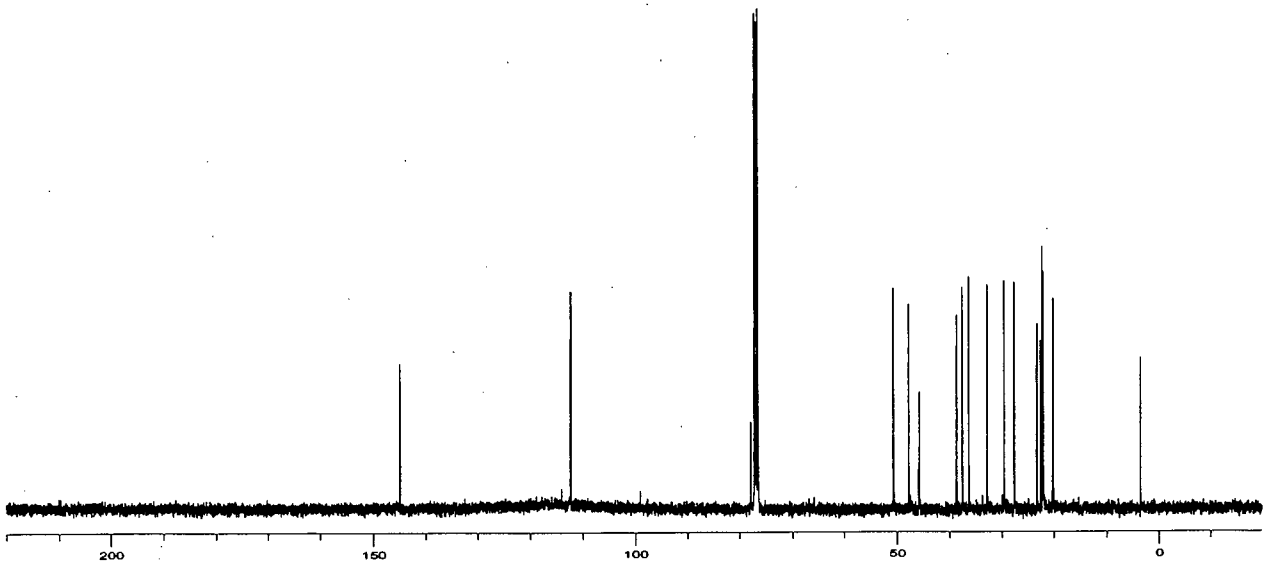


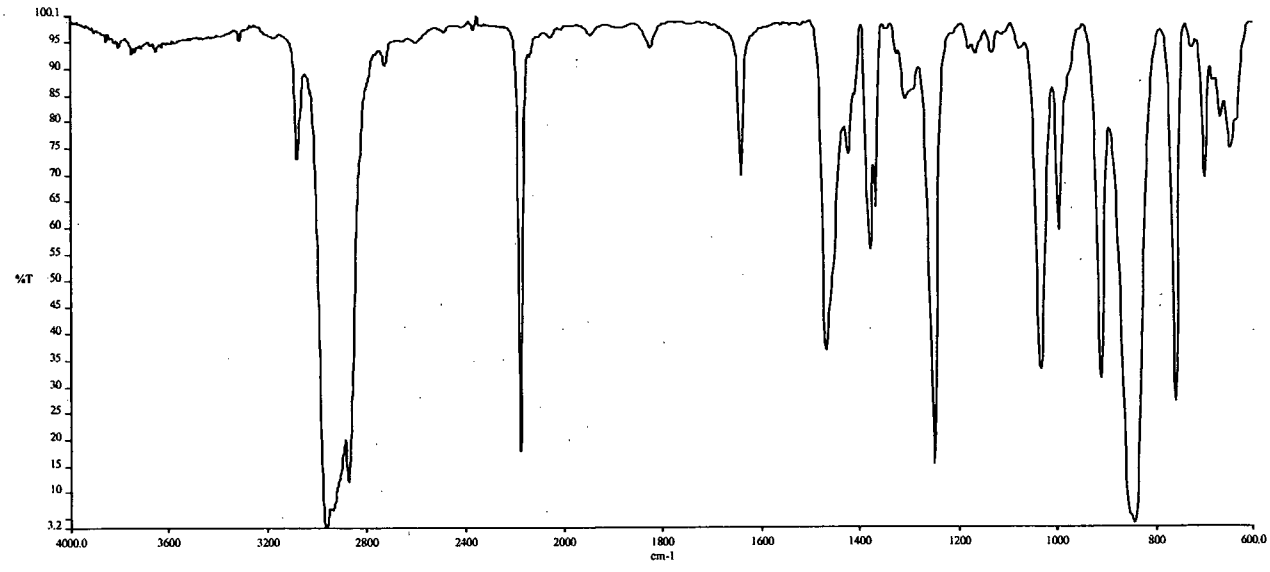




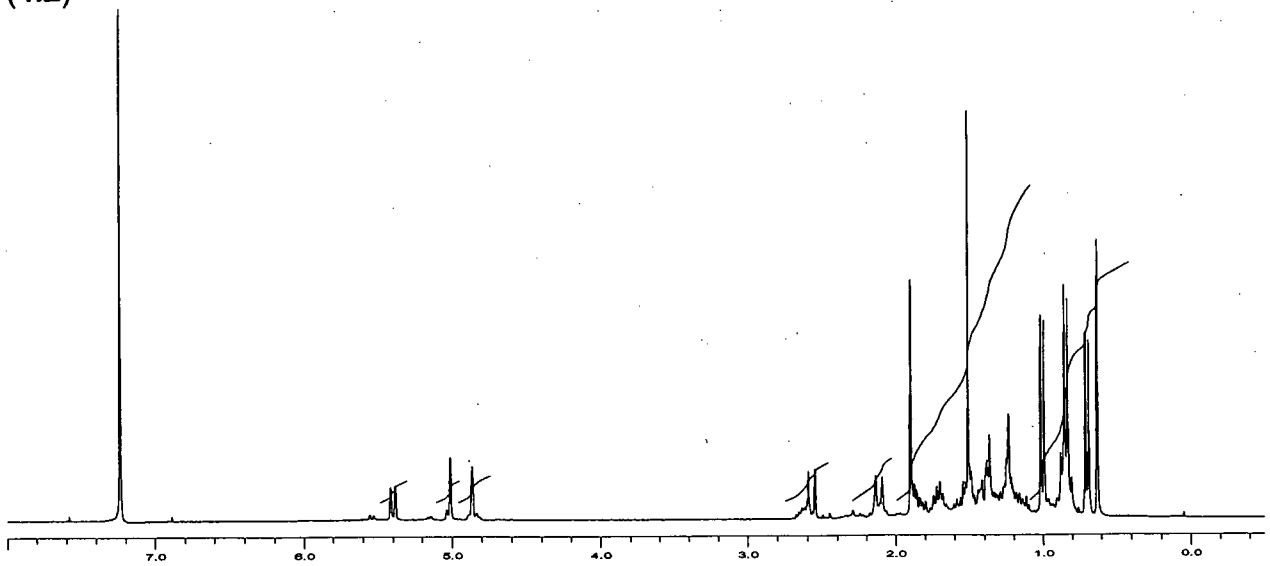
(1*R*, 2*S*, 3*R*)-3-Isopropyl-1-methyl-2-((3*S*)-3-methylpent-4-enyl)-1-(3-(triisopropylsilyloxy)prop-2-ynyl)cyclopentane (**4.63**)

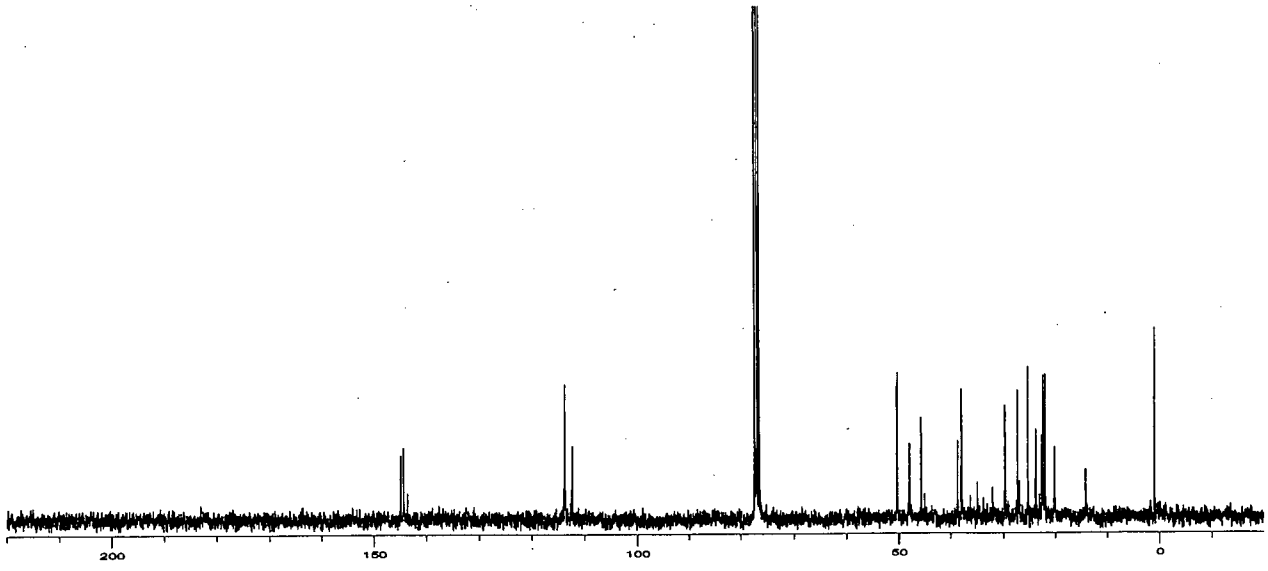


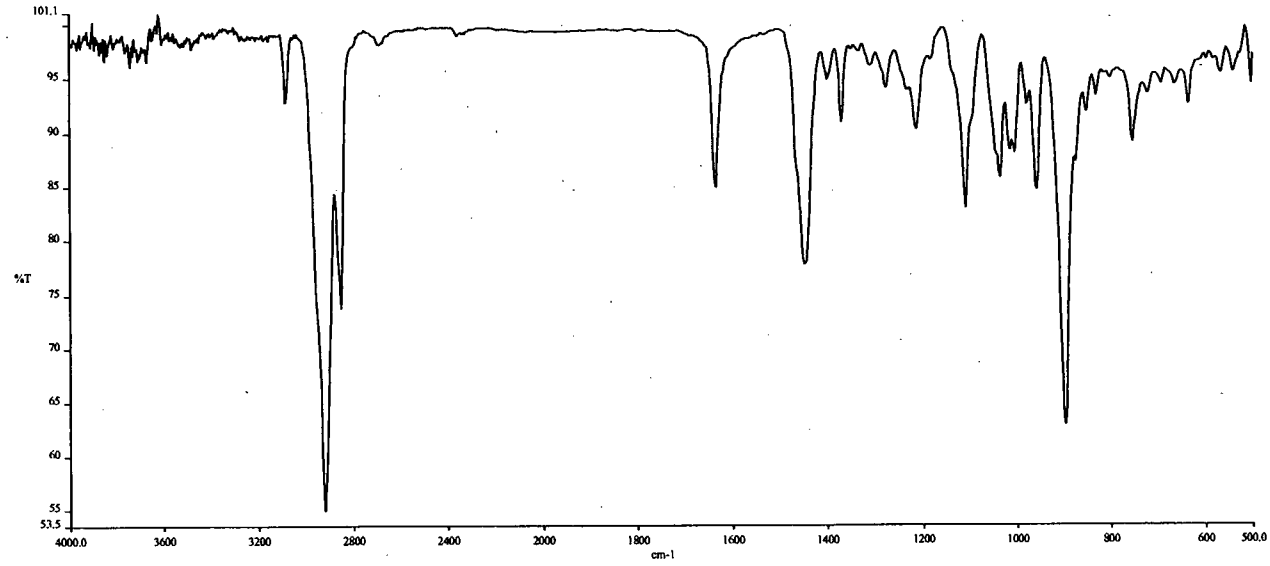




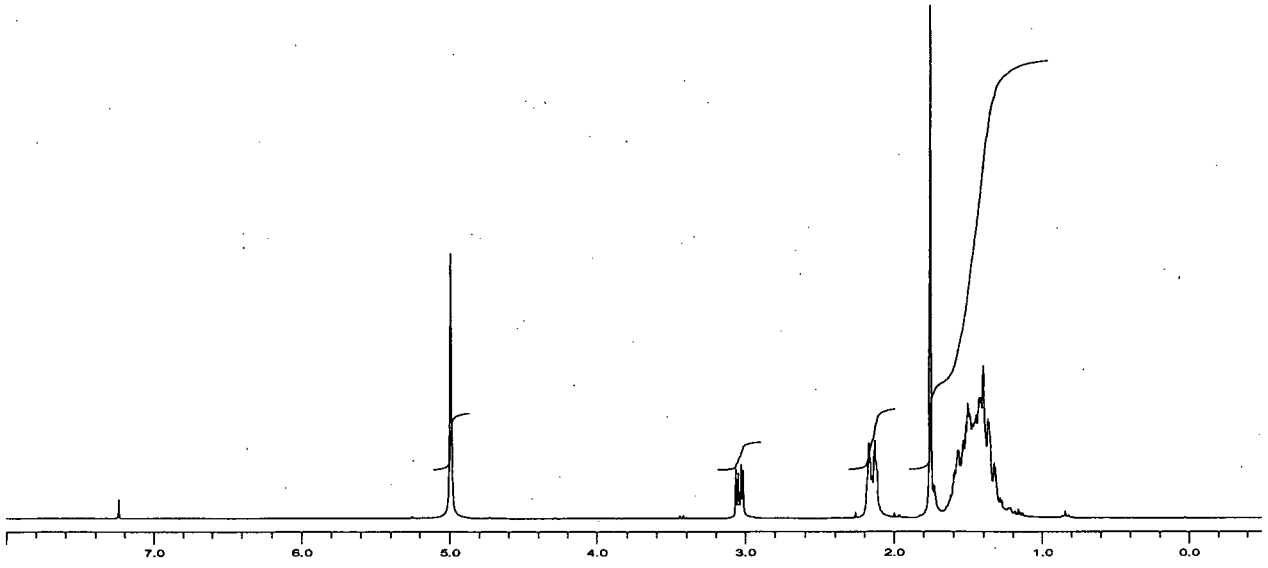
[6.3.0]-(1*R*, 5*S*, 8*S*, 9*R*)-1,5-Dimethyl-9-isopropyl-3-(prop-1-en-2-yl)bicycloundec-2-ene (**4.2**)

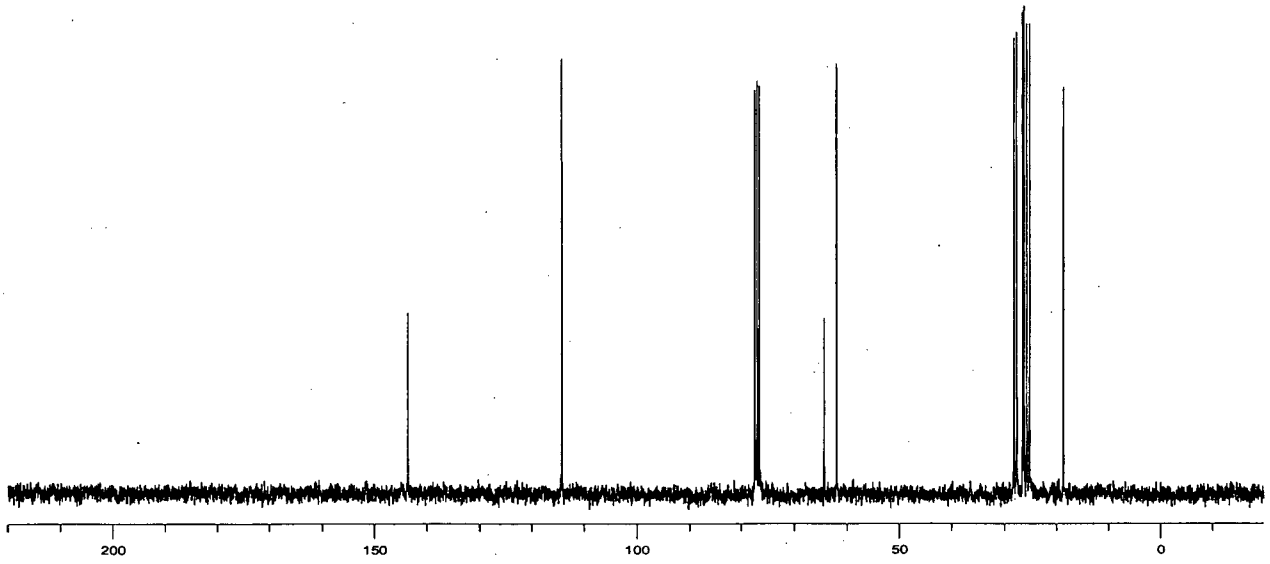


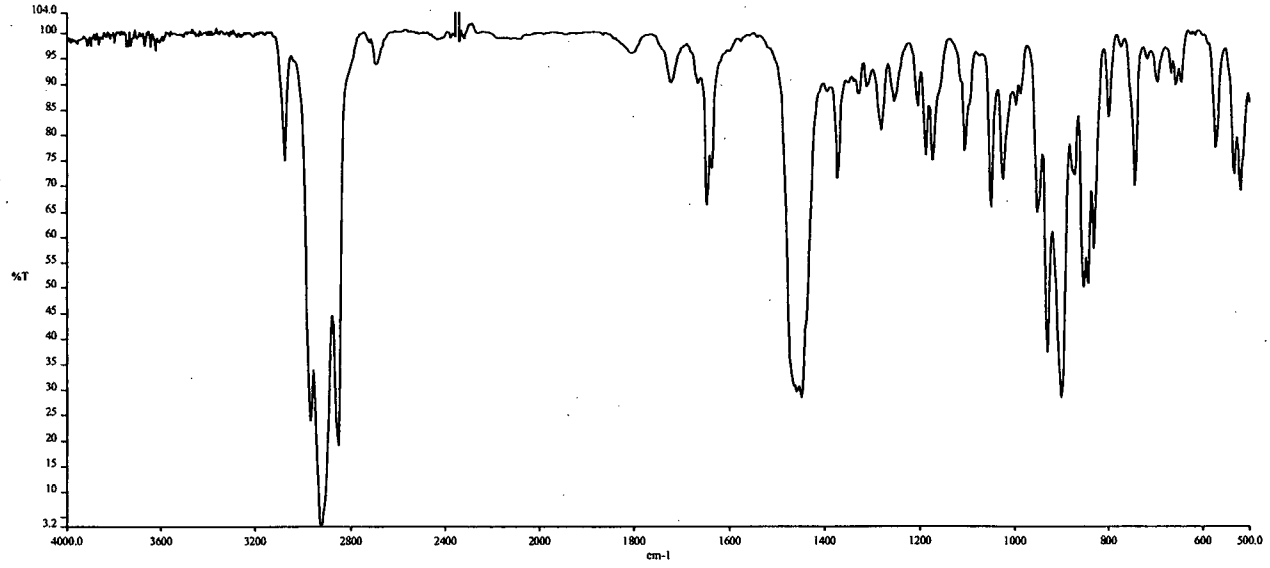




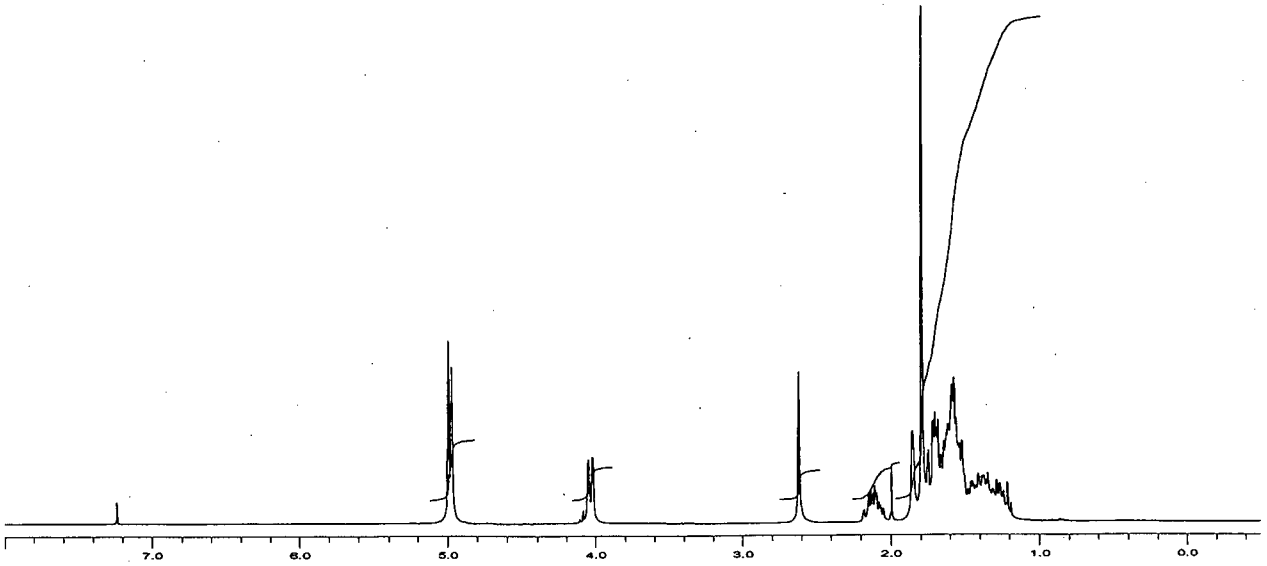
(1*S**, 8*S**)-1-(Prop-1-en-2-yl)-9-oxa-bicyclo[6.1.0]nonane (**4.73**)

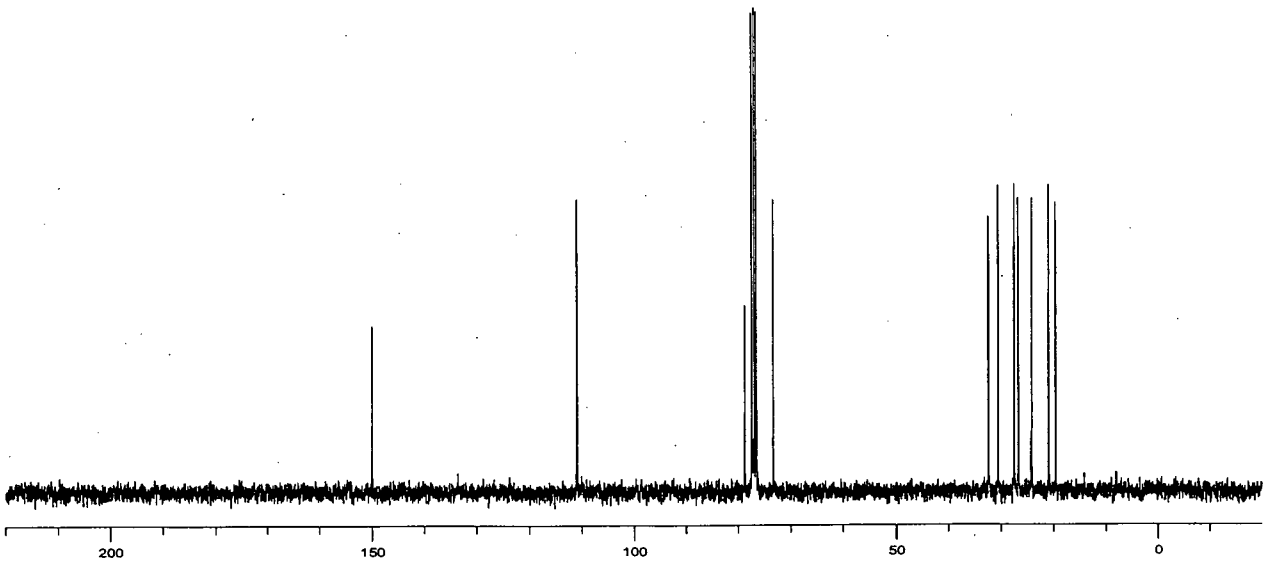


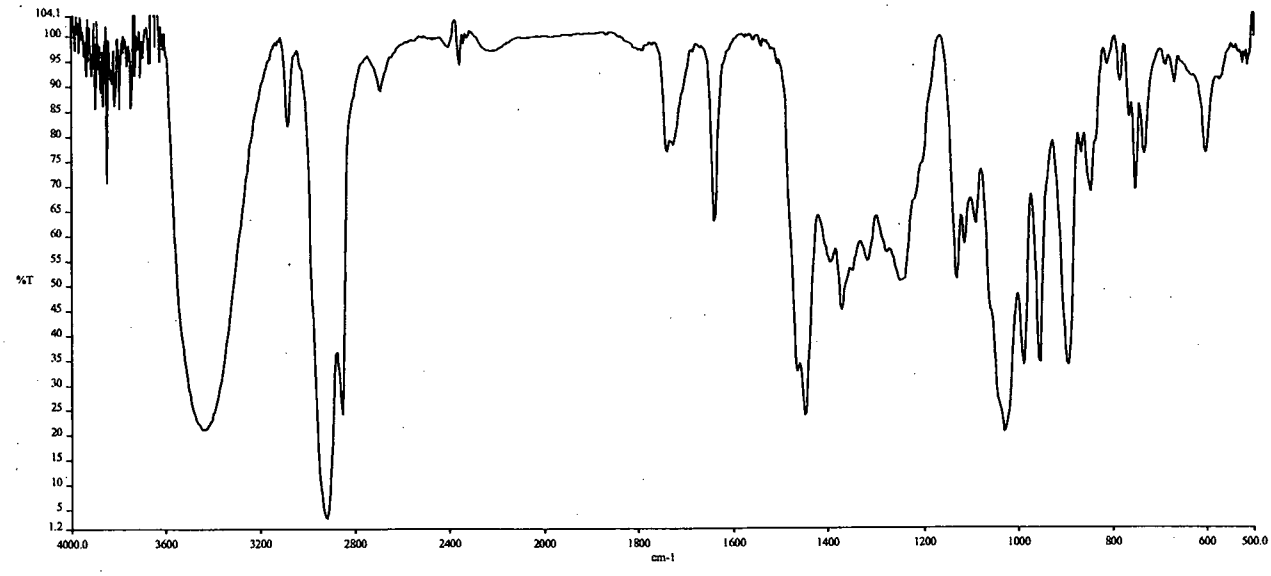




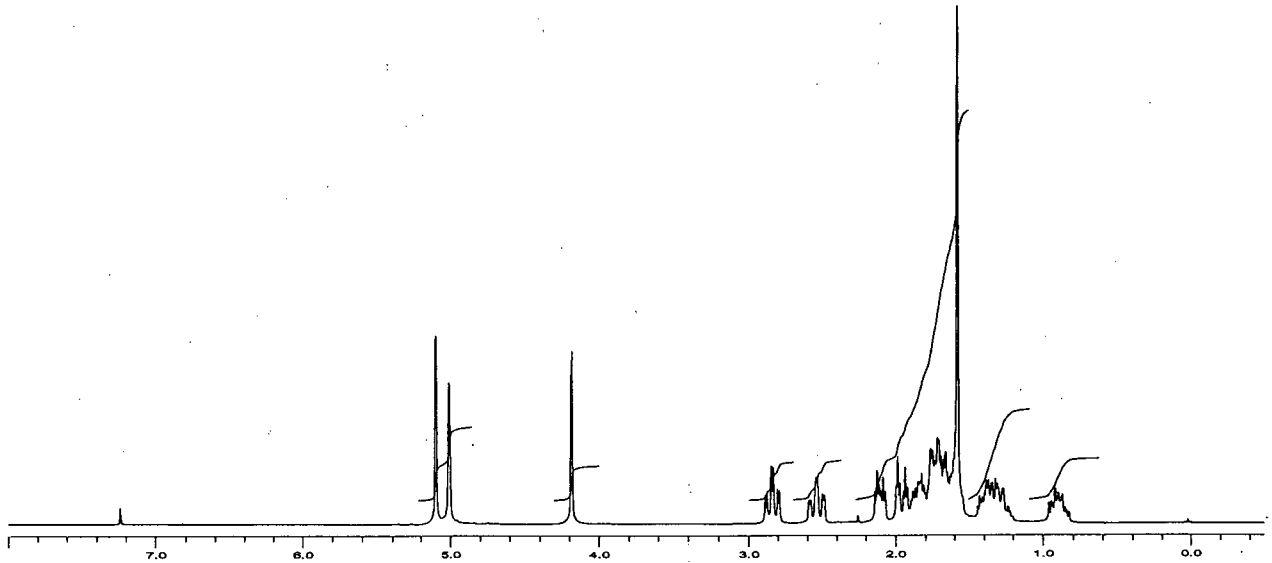
(1*S**, 2*S**)-1-(Prop-1-en-2-yl)cyclooctane-1,2-diol (**4.74**)

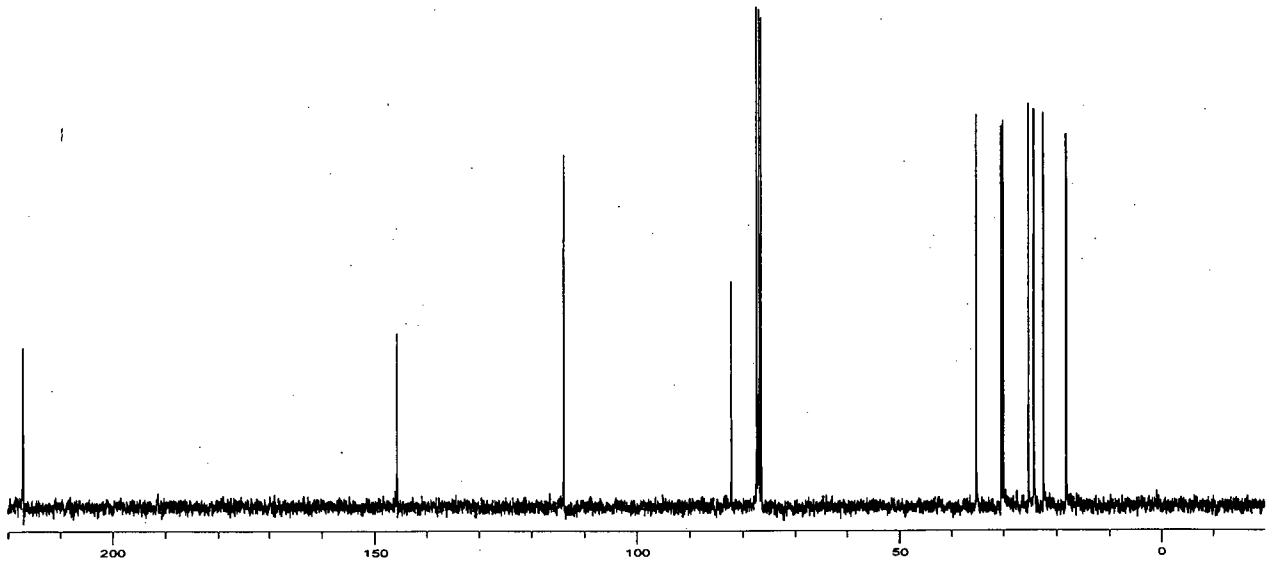


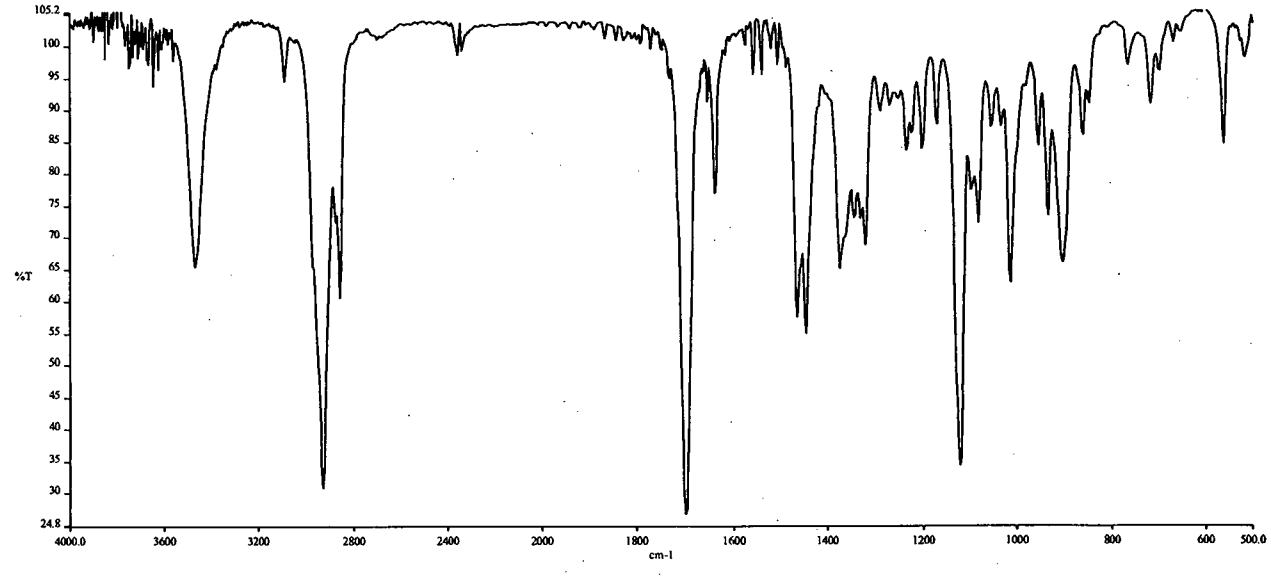




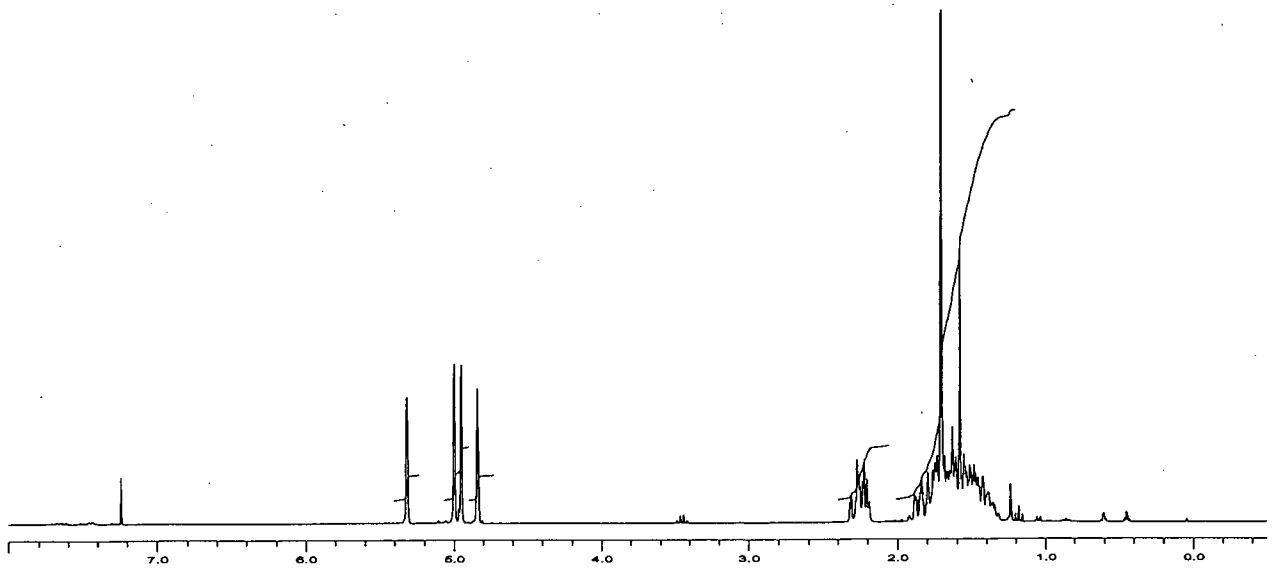
(1*S**)-2-Hydroxy-2-(prop-1-en-2-yl)cyclooctanone (**4.75**)

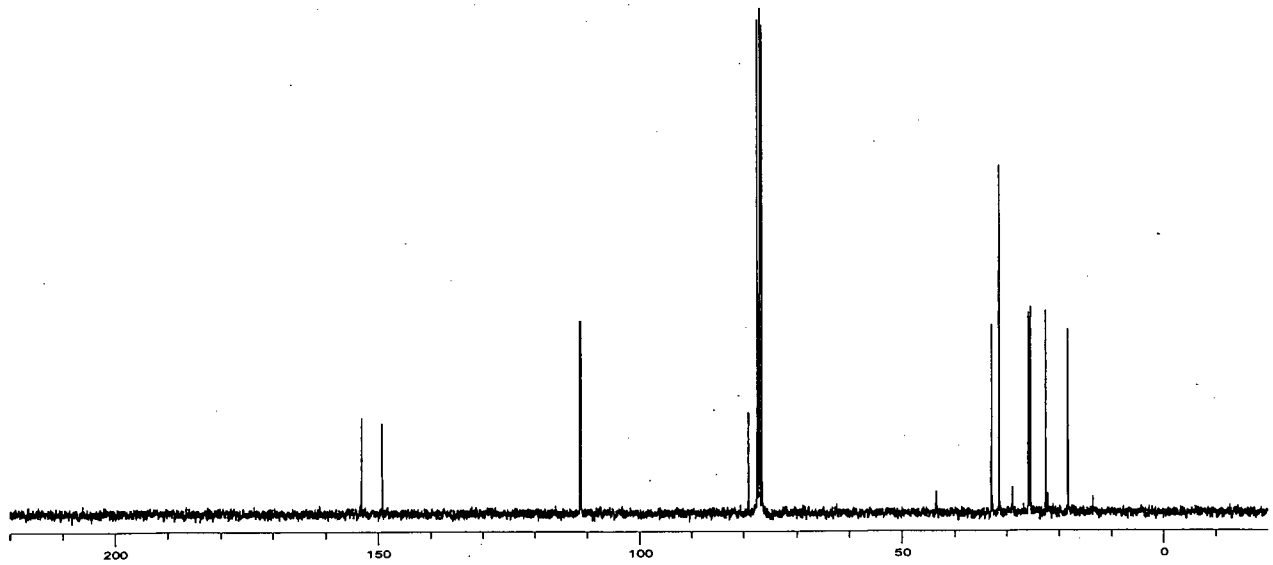


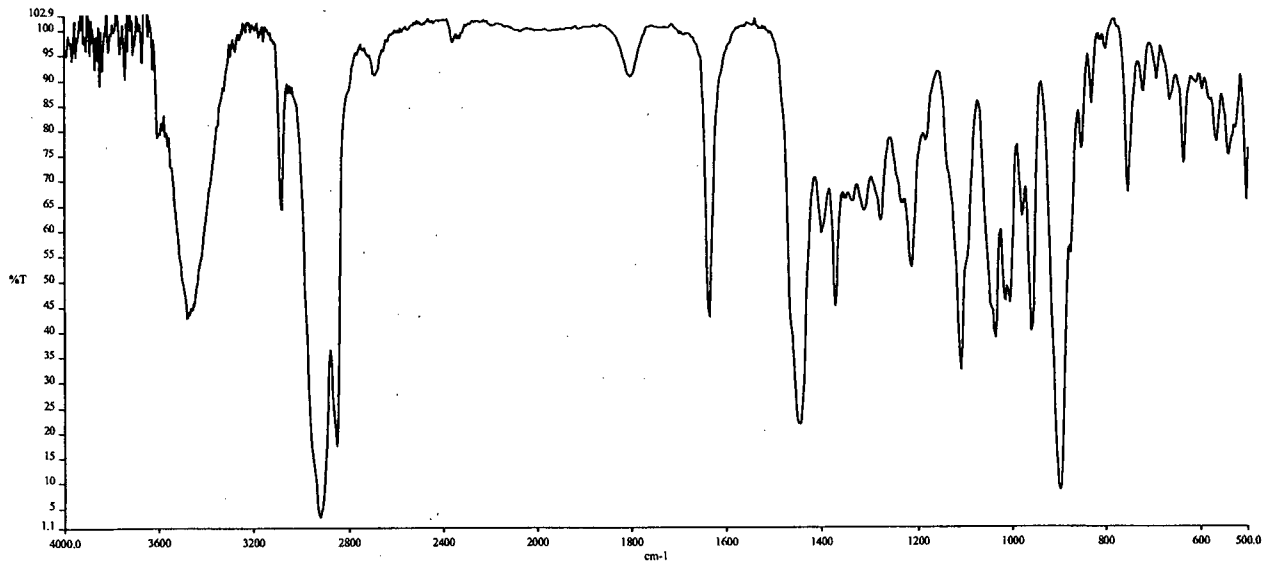




2-Methylene-1-(prop-1-en-2-yl)cyclooctanol (**4.70**)







Appendix C

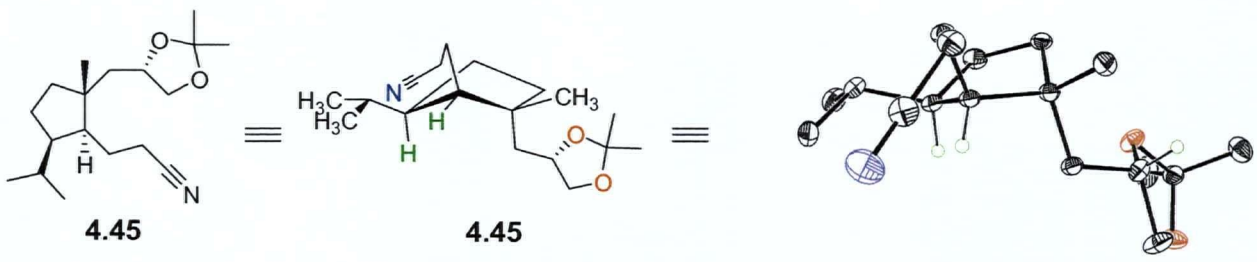
X-ray Crystallography Data

I. General Considerations

Suitable crystals were selected and mounted on a glass fiber using Paratone-N oil or an acceptable substitute and freezing to -100 °C. All measurements were made on a Bruker X8 diffractometer with graphite monochromated Mo-Kα radiation. Crystallographic data and some details of structural refinement appear in Table AC.1. In each case the data were processed[1] and corrected for Lorentz and polarization effects and absorption. Neutral atom scattering factors for all non-hydrogen atoms were taken from the *International Tables for X-ray Crystallography.*[2,3] All structures were solved by direct methods[4] and expanded using Fourier techniques.[5] All non-hydrogen atoms were refined anisotropically.

For further details reagarding the data files for **4.45**, please contact the Professional Officer of the UBC X-ray Structural Laboratory, Dr. Brian O. Patrick.

Table AC.1 Crystallographic Data and Structure Refinement for 4.45



4.45 **4.45**

(1*R*, 2*S*, 3*R*)-2-(2-Cyanoethyl)-3-isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methylcyclopentane (4.45)	
Formula	$C_{18}H_{31}NO_2$
FW	293.44
Colour, habit	colourless, needle
Crystal size, mm	0.25 x 0.10 x 0.05
Crystal system	monoclinic
Space group	$P\,2_1$ (#4)
a, Å	8.700(1)
b, Å	10.448(2)
c, Å	13.264(2)
β, deg	96.00(1)
V, Å^3	869.7(2)
Z	2
D_{calc}, g/cm^3	1.121
F(000)	324.00
μ(MoKα), cm^{-1}	0.72
transmission factors	0.7107 - 1.0000
$2\theta_{max}$, deg	50.6
total no. of reflns	14377
no. of unique reflns	3932
R (F^2, all data)	0.054
R_w (F^2, all data)	0.115
R (F, I >2σ(I))	0.045
R_w (F, I >2σ(I))	0.109
goodness of fit indicator	1.04

Bruker X8 diffractometer, $R = \Sigma||F_o|-|F_c||/\Sigma|F_o|$; $R_W = (\Sigma w(|F_o^2| - |F_c^2|)^2 / \Sigma w|F_o^2|^2)^{1/2}$.

II. References

1. SAINT. Version 6.02. Bruker AXS Inc., Madison, Wisconsin, USA. (1999).

2. *International Tables for X-Ray Crystallography*; Kluwer Academic: Boston, MA, 1992; Vol. C, pp 200-206.

3. *International Tables for X-Ray Crystallography*; Kynoch Press: Birmingham, U. K. (present distributer Kluwer Academic: Boston, MA), 1974; Vol. IV, pp 99-102.

4. Altomare, A.; Burla, M. C.; Cammali, G.; Cascarano, M.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, A. *SIR97: a new tool for crystal structure determination and refinement,* 1999.

5. Beurskens, P. T.; Admiraal, G.; Beurskens, G.; Bosman, W. P.; de Gelder, R.; Israel, R.; Smits, J. M. M. *DIRDIF94; The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory*; University of Nijmegen: The Netherlands, 1994.