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Maxime Riou

AUTEUR DE LA THÈSE / AUTHOR OF THESIS

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**Prins-Pinacol Synthesis of Bicyclo[3.3.1]nonanones and
Application towards the Total Synthesis of Papuaforin A**

TITRE DE LA THÈSE / TITLE OF THESIS

Louis Barriault

DIRECTEUR (DIRECTRICE) DE LA THÈSE / THESIS SUPERVISOR

CO-DIRECTEUR (CO-DIRECTRICE) DE LA THÈSE / THESIS CO-SUPERVISOR

EXAMINATEURS (EXAMINATRICES) DE LA THÈSE / THESIS EXAMINERS

Derrick L. Clive

Jeff Manthorpe

Rob Ben

William Ogilvie

Gary W. Slater

Le Doyen de la Faculté des études supérieures et postdoctorales / Dean of the Faculty of Graduate and Postdoctoral Studies

**Prins-Pinacol Synthesis of Bicyclo[3.3.1]nonanones and
Application towards the Total Synthesis of Papuaforin A**

by

Maxime Riou

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In Partial Fulfillment of the Requirements for the
Philosophiæ Doctor Degree in Chemistry

Candidate

Supervisor

Maxime Riou

Dr. Louis Barriault

Ottawa-Carleton Chemistry Institute
Faculty of Science
University of Ottawa

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Abstract

The present thesis concentrates on the development of the Prins-Pinacol mediated synthesis of bicyclo[3.3.1]nonanones and its application towards the total synthesis of papuaforin A. In addition, an exploratory study of the oxy-Cope/Claisen/ene cascade reaction and the total synthesis of (+)-isofregenedol are presented. These subjects are divided into four chapters.

The first part of this thesis describes the discovery and examination of a novel microwave-induced rearrangement of propargyl vinyl ethers delivering *cis*-bicyclic unsaturated lactones.

The methodological investigation of the Prins-Pinacol rearrangement oriented towards the construction of bicyclo[3.3.1]nonanones is discussed in Chapter 3. The synthesis of various precursors and the optimization of the key step are presented. The reactivity observed for the isopropylidene and benzylidene oxocarbenium precursors is then compared. The effect of the substitution of the alkene moiety and at the ring junction is also examined. The Prins-Pinacol rearrangement of complex Diels-Alder cycloadducts is described last.

The fourth chapter depicts the advancement towards the total synthesis papuaforin A. The synthesis of a model compound possessing the bicyclo[3.3.1]nonanone core of the natural product is first presented. The progress towards the actual total synthesis is discussed next.

Finally, the application of the gold(I)-catalyzed benzannulation of hydroxyenynes to the *de novo* synthesis of (+)-isofregenedol is described in Chapter 5.

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List of Abbreviations

18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
Ac	acetate
AIBN	2,2'-azobis(2-methyl)propionitrile
Aq.	aqueous
BBN	borabicyclo[3.3.1]nonane
brsm	based on recovered starting material
Bn	benzyl
br	broad
Bu	butyl
Bz	benzoate
cat.	catalytic or catalyst
Cy	cyclohexyl
DavePhos	2-Dicyclohexylphosphino-2'-(<i>N,N</i> -dimethylamino)biphenyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyano- <i>p</i> -benzoquinone
DET	diethyl tartrate
DIAD	diisopropyl azodicarboxylate
DIBAH	diisobutylaluminum hydride
DIPA	diisopropylamine
DMAP	<i>N,N</i> -4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DTBMP	2,6-di- <i>tert</i> -butyl-4-methylpyridine

d.r.	diastereomeric ratio
ee	enantiomeric excess
EI	electron ionization
equiv.	equivalent
Et	ethyl
GC	gas chromatography
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HMPA	hexamethylphosphoramide
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
<i>i</i> -Pr	isopropyl
IR	infrared
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
M ⁺	molecular ion
<i>m</i> -CPBA	<i>meta</i> -chloroperbenzoic acid
Me	methyl
mp	melting point
MS	molecular sieves or mass spectrometry
NBS	<i>N</i> -bromosuccinimide
<i>n</i> -BuLi	<i>n</i> -butyllithium
NIS	<i>N</i> -iodosuccinimide
NMR	nuclear magnetic resonance
NMO	4-methylmorpholine <i>N</i> -oxide
N-PSP	<i>N</i> -phenylselenophthalimide
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
PCC	pyridinium chlorochromate
PdCl ₂ (dppf)	[1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II)
Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)

Ph	phenyl
PhH	benzene
PhMe	toluene
PMB	<i>para</i> -methoxybenzyl
ppm	parts per million
PPTS	pyridinium <i>para</i> -toluenesulfonic acid
Pr	propyl
PPAP	polycyclic polyprenylated acylphloroglucinol
PTSA	<i>para</i> -toluenesulfonic acid
Quant.	quantitative
RCM	ring-closing metathesis
ROM	ring-opening metathesis
RT	room temperature
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
<i>t</i> -BuLi	<i>tert</i> -butyllithium
Tf	trifluoromethanesulfonyl (triflate)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPB	triisopropylbenzene
TLC	thin layer chromatography
TfOH	trifluoromethanesulfonic acid
TIPS	triisopropylsilyl
TM	transition metal
TMS	trimethylsilyl
TMSCl	chlorotrimethylsilane
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Tol	toluene or toluy
TPAP	tetra- <i>n</i> -propylammonium perruthenate
Ts	<i>para</i> -toluenesulfonyl

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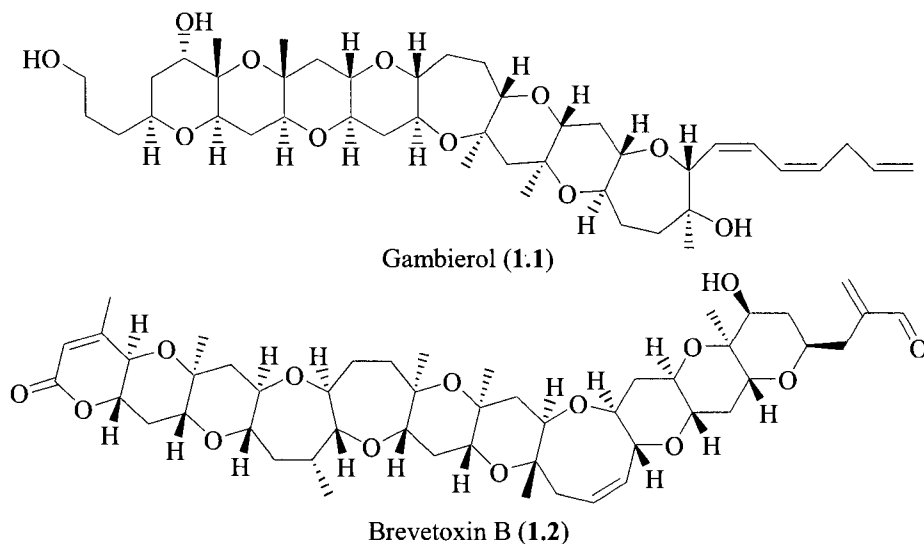
Introduction

Synthetic organic chemistry is undeniably one of the most important scientific disciplines. We are indeed, in our daily lives, literally surrounded by plentiful applications originating from research in that domain. Representative examples of these applications include pharmaceuticals, polymers, synthetic textiles and cosmetics.

From a scientific point of view, natural product synthesis is certainly the ultimate illustration of the power of synthetic organic chemistry. Since the first total synthesis was reported, early in the nineteenth century, tremendous advances have been realized in that field.¹ Nowadays, numerous total syntheses are realized every year. The synthesis of increasingly complex natural products is usually undertaken to demonstrate the value of new methodologies. It can however also be employed to confirm the structure, or to evaluate the biological properties of naturally occurring compounds. In any case, natural product synthesis promotes the development of innovative reactions and novel synthetic strategies. It is therefore considered to be an important motor of development in the field of organic chemistry.

Chemists have access today to a myriad of synthetic methods that allow them to construct almost any given organic molecule. Indeed, even extremely complex natural products such as gambierol (**1.1**)² and brevetoxin B (**1.2**)³ have successfully been synthesized (Figure 1.1).

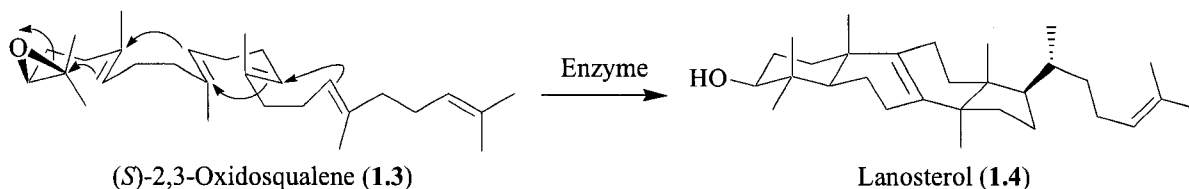
Figure 1.1 – Marine Natural Products Gambierol (1.1) and Brevetoxin B (1.2)



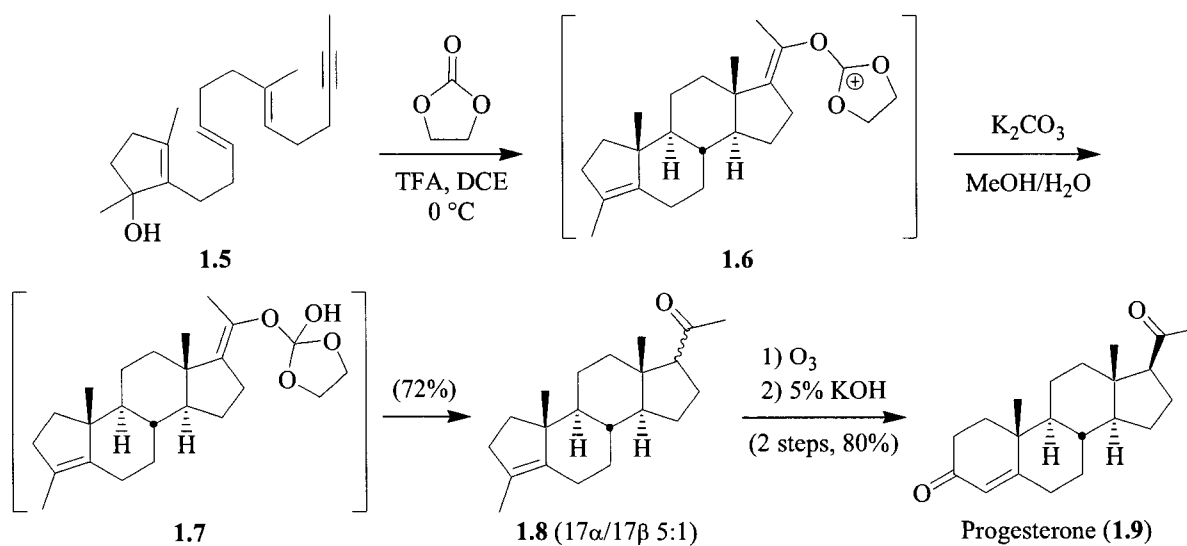
Cascade Reactions

In the course of the last decade, organic chemists have focused their attention on the efficacy of chemical syntheses. Several avenues have notably been explored in order to save the resources of our environment and to diminish the amount of waste produced by chemical processes. One of the most interesting ways of attaining that goal is the utilization of cascade reactions. As Tietze defines them, cascade reactions are “the transformation of two or more bond-forming reactions under identical reaction conditions, in which the latter transformations take place at the functionalities obtained in the former bond-forming reactions”.⁴

Even if they have only known a rapid development in recent years, cascade processes have been around for a long time. In fact, these reactions have been performed in living organisms ever since the appearance of life on Earth. For instance, Nature uses an enzyme-catalyzed cascade reaction to stereoselectively convert (*S*)-2,3-oxidosqualene (1.3) to lanosterol (1.4) (Scheme 1.1).⁵ Over the years, the elucidation of the biosynthesis of numerous steroids has stimulated the development of biomimetic strategies towards a variety of natural products

Scheme 1.1 – Biosynthesis of Lanosterol (1.4)

belonging to this category. A classical example of this type of approach is the utilization of an acid-mediated cyclization cascade to generate progesterone (**1.9**) (Scheme 1.2).⁶ This synthesis begins with the reaction of alcohol **1.5** with trifluoroacetic acid and ethylene carbonate. This results in a cascade of cyclizations that affords cationic intermediate **1.6**. Treatment of this intermediate with potassium carbonate yields intermediate **1.7**, which is hydrolyzed to provide ketone **1.8** as a mixture of epimers in 72% yield. The synthesis is then completed by the sequential ozonolysis of compound **1.8** and aldol condensation of the resulting triketone, which results in the formation of progesterone (**1.9**) in 80% overall yield. The synthesis of ketone **1.8** is an excellent illustration of the power of cascade reactions. Indeed, in a single chemical step (**1.5** $\rightarrow$ **1.8**), three rings and six stereocenters are generated with high stereoselectivity.

Scheme 1.2 – Total Synthesis of Progesterone (1.9) via an Electrophilic Cascade

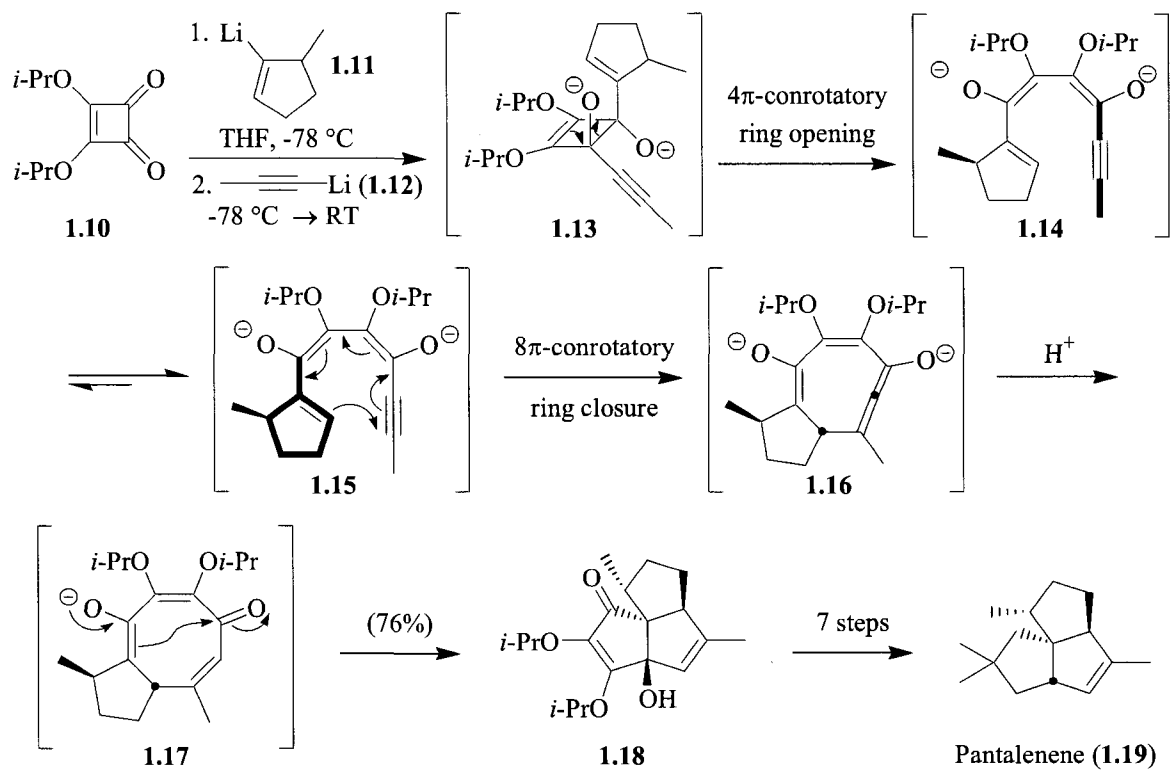
More recently, several research groups have taken advantage of the possibilities brought about by cascade reactions to develop novel transformations. To demonstrate the potential of these new methodologies, many researchers have also applied them to the synthesis of natural products. These cascade-reaction-based strategies can be classified into five main classes: nucleophilic (anionic) cascades, electrophilic (cationic) cascades, radical cascades, pericyclic cascades, and transition-metal-catalyzed cascades.^{4,7} In the following pages, each of these reaction types will be discussed briefly and illustrated by an application to total synthesis.

Nucleophilic (Anionic) Cascades

Nucleophilic cascades are the most common cascade reactions, and they include such well-known reactions as the Robinson annulation and double Michael reaction. These cascade reactions are triggered by the attack of a nucleophile (anionic or neutral) on an electrophilic site. The resulting intermediate then undergoes a series of transformations. The process is finally terminated by the addition of a proton or by the loss of an X^- group, which delivers the final product.⁴

In 2002, Paquette and co-workers employed an anionic cascade approach for the total synthesis of pantalenene (**1.19**), an angular triquinane (Scheme 1.3).⁸ In this case, the cascade reaction is initiated by the sequential addition of vinyl lithium species **1.11** and acetylide anion **1.12** to squarate ester **1.10**. Because of steric factors, these two additions occur in a *trans* fashion to give dianionic intermediate **1.13**. This is followed by a 4π -conrotatory ring opening, which is favored by the electrostatic repulsion between the two alkoxide ions. This leads to the formation of acyclic species **1.14**. This intermediate then equilibrates to more stable conformer **1.15**, in which the cyclopentene methyl group is pointing away from the dienolate. Intermediate **1.15** subsequently undergoes an 8π -conrotatory ring closure to generate strained cyclooctatetraene **1.16**. The allenolate group of intermediate **1.16** is then protonated selectively, because of strain release, to give ketone **1.17**. The sequence ends with a transannular aldol reaction that provides keto ester **1.18** in 76% overall yield. Pantalenene (**1.19**) is then synthesized from **1.18** in seven steps.

Scheme 1.3 – Total Synthesis of Pantalenene (1.19) via a Nucleophilic Cascade

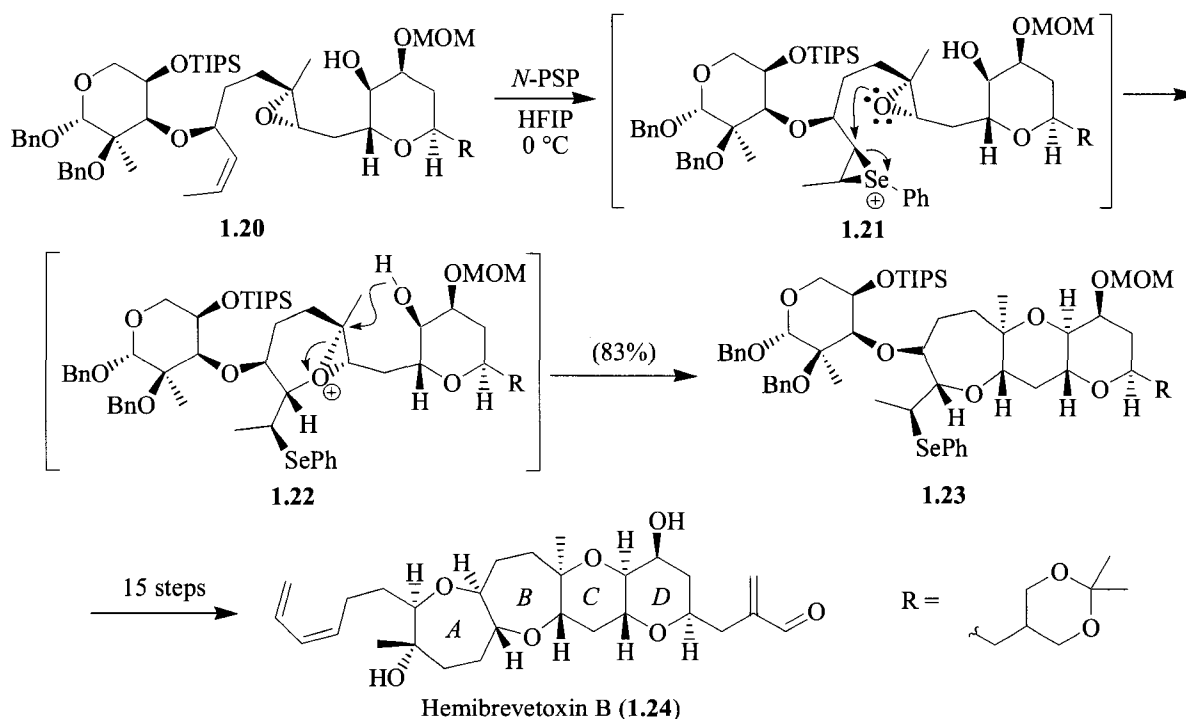


Electrophilic (Cationic) Cascades

In the case of electrophilic cascades, the first step involves the formation of a carbocation. This cationic species is most often generated by the addition of a Brønsted or Lewis acid to an alkene or epoxide, or by elimination of water from an alcohol. This carbocation then goes through a sequence of reactions that eventually leads to a final carbocation. The desired product is finally generated by elimination of a proton or by addition of another nucleophile.⁴

Several cationic cascades are triggered by the acid-catalyzed opening of epoxides. This type of process has for instance been employed by Holton and co-workers for the biomimetic total synthesis of hemibrevetoxin B (1.24) (Scheme 1.4).⁹ Their synthetic plan implied the formation of the B and C rings of the natural product through a double cyclization of epoxyalcohol 1.20. The cascade reaction was initiated by treatment of compound 1.20 with *N*-phenylselenophthalimide. This led to the formation of *epi*-selenonium ion 1.21, which was

Scheme 1.4 – Total Synthesis of Hemibrevetoxin B (1.24) via an Electrophilic Cascade



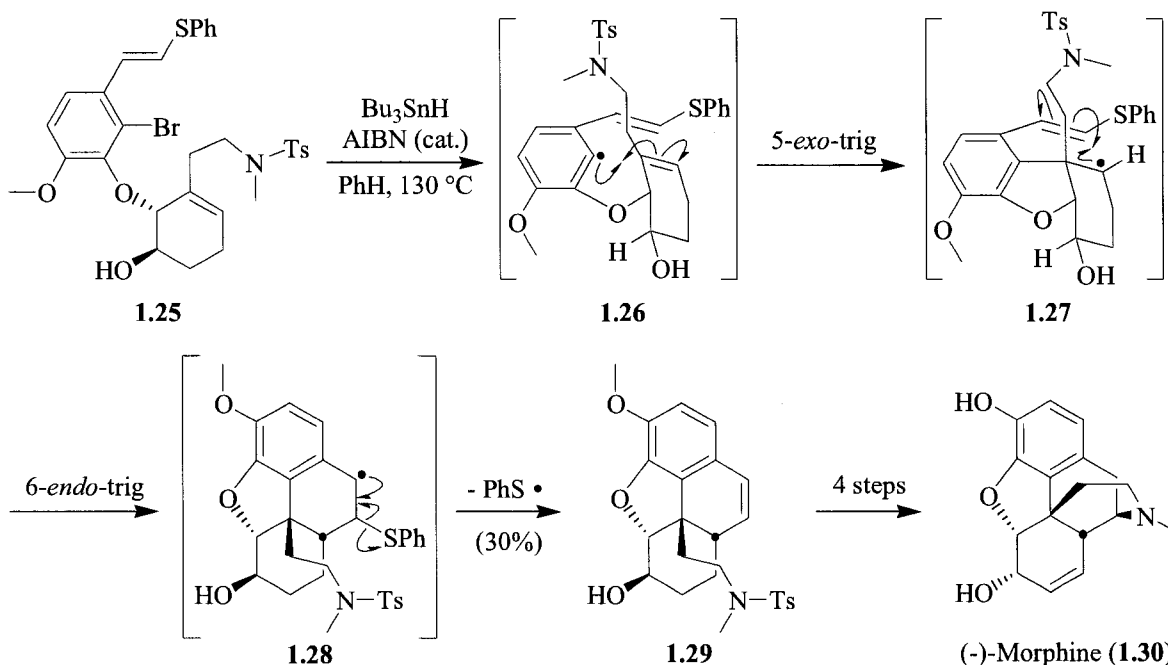
attacked by the oxygen atom of the epoxide to give bicyclic epoxonium **1.22**. A selective attack of the oxonium by the hydroxy group then afforded *trans*-fused oxepane **1.23**. Compound **1.23**, which bore the newly formed B and C rings, was generated in 83% overall yield. The total synthesis of hemibrevetoxin B (**1.24**) was then completed in fifteen steps by fusion of the A ring onto the tricyclic scaffold followed by elaboration of the side-chain.

Radical Cascades

For radical cascades, the first step of the sequence is the generation of a free radical. This can be carried out by employing halides, phenylthio or phenylselenium compounds as starting materials and stannanes or silanes as radical initiators. The resulting radical then undergoes a series of rearrangements that may include intramolecular or intermolecular additions and cyclizations. The cascade process ultimately leads to the formation of a final radical, which can be converted to the desired product by reduction, oxidation or atom transfer.⁴

In 2006, Parker and Fokas reported a formal synthesis of (-)-morphine (**1.30**) based on a radical cascade reaction (Scheme 1.5).¹⁰ This cascade process allowed the formation of two rings and the introduction of the quaternary stereocenter in a single chemical step. The reaction was initiated by refluxing a benzene solution of bromide **1.25** in the presence of tributyltin hydride and AIBN. This led to the formation of bicyclic aryl radical **1.26**, which then cyclized in a 5-*exo*-trig fashion to generate the first ring and the quaternary stereocenter. The resulting secondary radical (**1.27**) subsequently underwent a 6-*endo*-trig cyclization that delivered benzylic radical **1.28**. The elimination of the phenylsulfanyl radical finally led to the formation of compound **1.29**, which was obtained in 30% overall yield. Intermediate **1.29** could then be converted into (-)-morphine (**1.30**) via a four-step sequence.

Scheme 1.5 – Formal Synthesis of (-)-Morphine (1.30) via a Radical Cascade



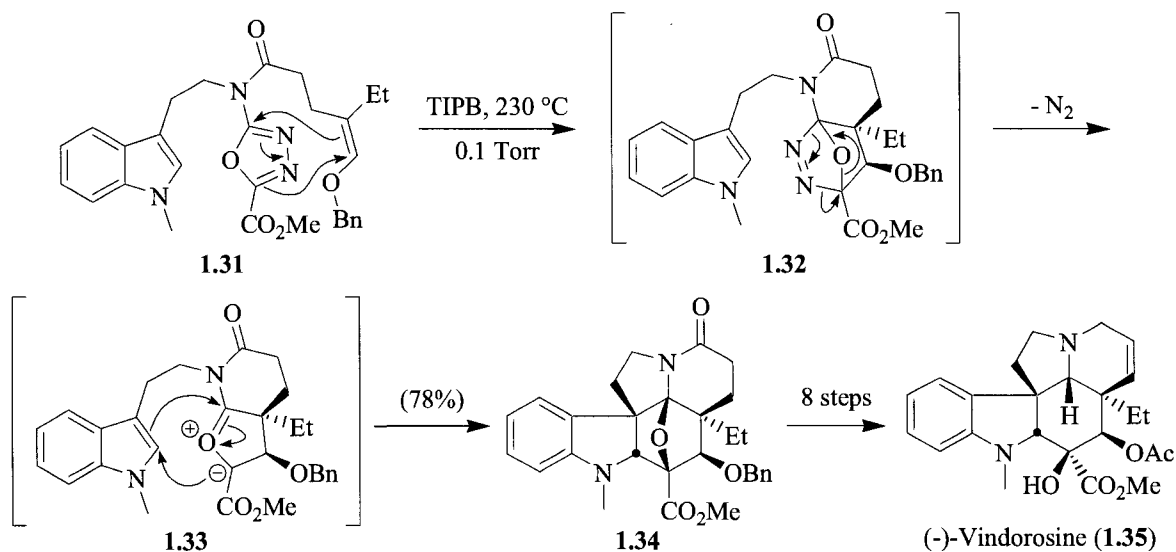
Pericyclic Cascades

Pericyclic cascades can be defined as the combination of pericyclic reactions with other transformations of the same type, or with non-pericyclic reactions. These processes can include sigmatropic rearrangements, cycloadditions, electrocyclizations and ene reactions. In

most cases, however, these cascades are composed of two successive cycloadditions, or of the combination of 1,3-dipolar cycloadditions with hetero-Diels-Alder reactions. Pericyclic cascades are usually initiated by heating the starting material at high temperatures under neutral conditions or in the presence of a Lewis acid.⁴

Boger and co-workers employed a hetero-Diels-Alder/1,3-dipolar cycloaddition cascade to construct the carbon skeleton of (-)-vindorosine (**1.35**) (Scheme 1.6).¹¹ Their strategy allowed the formation of the pentacyclic core of the natural product from substrate **1.31** in one step. This cascade reaction was triggered by heating a triisopropylbenzene solution of compound **1.31** at 230 °C. This induced an inverse-electron-demand Diels-Alder reaction between the oxadiazole ring and the benzyl enol ether that delivered pentacyclic intermediate **1.32**. The latter then underwent a retro [4+2] cycloaddition, which released molecular nitrogen and generated carbonyl ylide **1.33**. This intermediate was now set up for a 1,3-dipolar cycloaddition that stereoselectively generated hexacyclic product **1.34** in 78% overall yield. Precursor **1.31** being achiral, compound **1.34** was formed as a racemate. Nonetheless, resolution could efficiently separate the two enantiomers, and the desired one was further transformed into (-)-vindorosine (**1.35**) through an eight-step sequence.

Scheme 1.6 – Total Synthesis of (-)-Vindorosine (1.35) via a Pericyclic Cascade

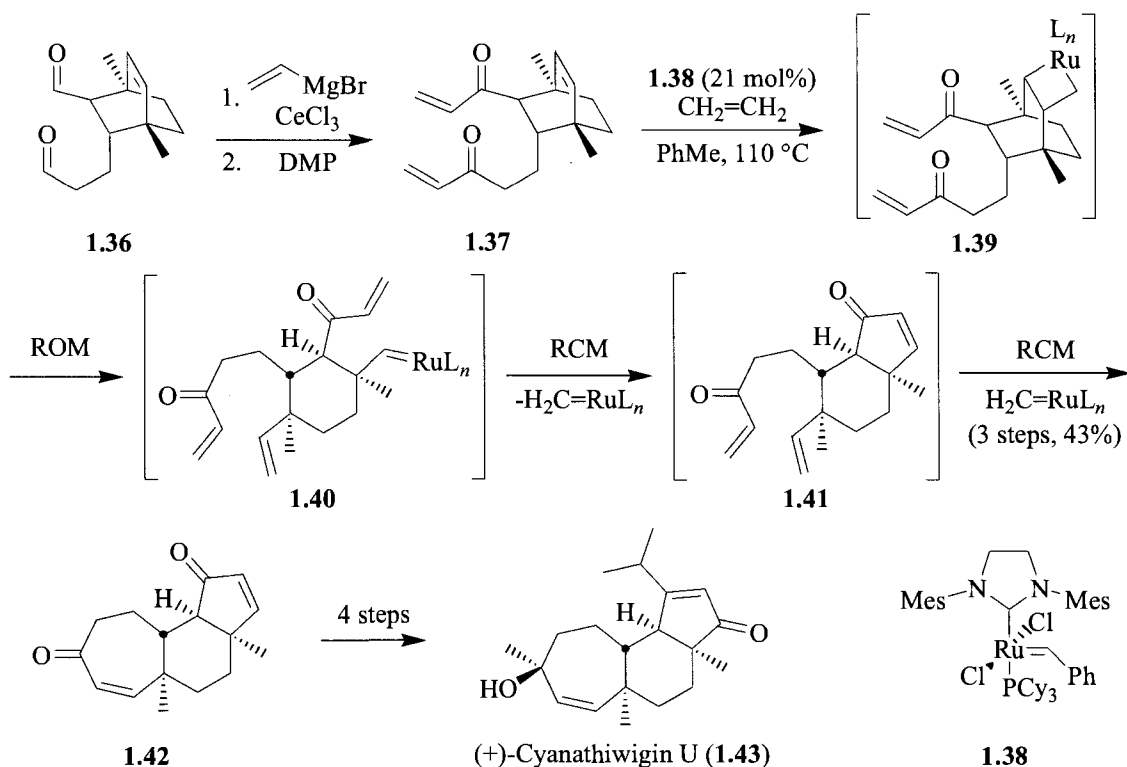


Transition-Metal-Catalyzed Cascades

The field of transition-metal-catalyzed cascades is presently in rapid development. Because of the many advantages they offer, these reactions are likely to become more and more important in the near future. Indeed, such cascade processes allow the creation of impressive molecular complexity in one step by using catalytic amounts of promoters.⁷ Most of these cascade processes are catalyzed by palladium and involve the combination of two Heck reactions, or of a Heck reaction and another cross-coupling reaction such as a Suzuki, Stille or Sonogashira. A considerable number of cascades also include rhodium- and ruthenium-catalyzed reactions. Rhodium is mostly employed in the formation of 1,3-dipoles from diazo compounds. Conversely, ruthenium-catalyzed cascades are generally based on metathesis.⁴

Pfeiffer and Phillips employed a metathesis-based cascade to construct the tricyclic core of (+)-cyanathiwiggin U (**1.43**) (Scheme 1.7).¹² Their strategy relied on a two-directional ring-

Scheme 1.7 – Total Synthesis of (+)-Cyanathiwiggin U (**1.43**) via a TM-Catalyzed Cascade



opening/ring-closing metathesis sequence, also known as a “ring-rearrangement metathesis”. First, chiral bicyclic dialdehyde **1.36** was synthesized via an asymmetric Diels-Alder reaction mediated by a chiral auxiliary. Compound **1.36** was then converted to dienone **1.37** via a straightforward two-step sequence. A solution of this dienone in toluene was refluxed under an atmosphere of ethylene in the presence of ruthenium carbene **1.38**. This induced a ring-opening metathesis that gave carbene intermediate **1.40**. This intermediate subsequently underwent a ring-closing metathesis that delivered intermediate **1.41**. This process concomitantly released the ruthenium carbene, which could then catalyze the ring-closing metathesis of intermediate **1.41** to finally afford tricyclic product **1.42**. The chiral tricycle was generated in 43% yield overall from dialdehyde **1.36**. Compound **1.42** was then further transformed into (+)-cyanathiwigin U (**1.43**) in four steps.

Over the years, some remarkable cascade reactions have also been investigated in the Barriault laboratory. The oxy-Cope/ene, oxy-Cope/ene/Claisen and oxy-Cope/Claisen/ene cascades will notably be looked at in Chapter 2. The Prins-Pinacol rearrangement will then be discussed exhaustively in Chapters 3 and 4.

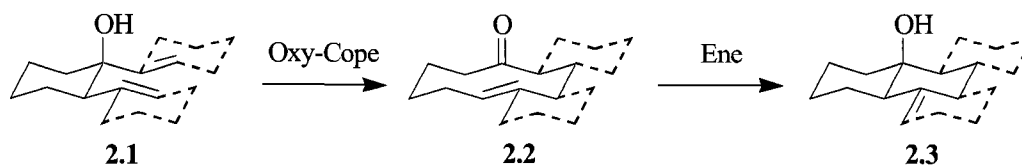
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New Variants of the Oxy-Cope/Claisen/Ene Cascade Reaction

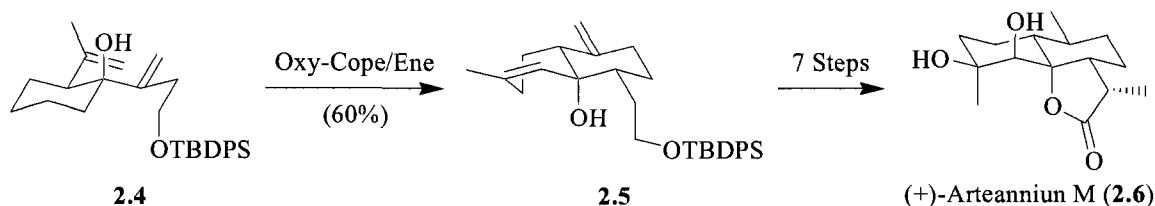
Introduction

Cascade reactions allow the stereoselective generation of several carbon-carbon bonds in a single chemical step, and therefore represent extremely valuable synthetic strategies.^{4,7,13} Their remarkable features render these reactions very attractive for the rapid construction of highly functionalized natural product frameworks. Notably, the challenging construction of the *trans*-decalin core of many terpenes and terpenoids has been achieved by employing a variety of cascade sequences. One of these reactions, the oxy-Cope/ene, has attracted the attention of many researchers, including the Barriault group.¹⁴ Indeed, in 2000, former Ph.D. student Jeff Warrington employed this method to generate diastereoselectively polycyclic enols **2.3** from 1,2-divinylcyclohexanols **2.1** (Scheme 2.1).¹⁵ In this reaction, the starting materials first undergo a [3,3] sigmatropic rearrangement that affords transient macrocyclic enones **2.2**, which are in turn converted to the desired *trans*-decalins. The usefulness of this cascade reaction was later demonstrated by former M.Sc. student Daniel Deon through an ingenious application to the total synthesis of sesquiterpene natural product (+)-arteannium M (**2.6**, Scheme 2.2).¹⁶ This sequence began by the two-step generation of cyclization precursor

Scheme 2.1 – The Oxy-Cope/Ene Cascade Reaction of 1,2-Divinylcyclohexanols



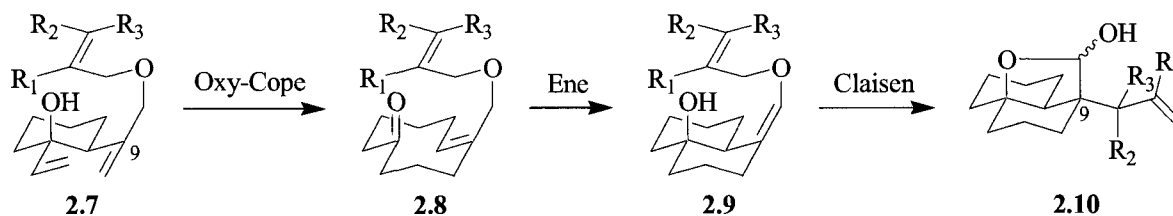
Scheme 2.2 – Total Synthesis of (+)-Arteannium M (2.6)



2.4 from (+)-limonene. The cascade reaction of compound **2.4** then gave diastereoselectively bicyclic alcohol **2.5**, which was further converted to arteannium M (**2.6**) in ten steps overall.

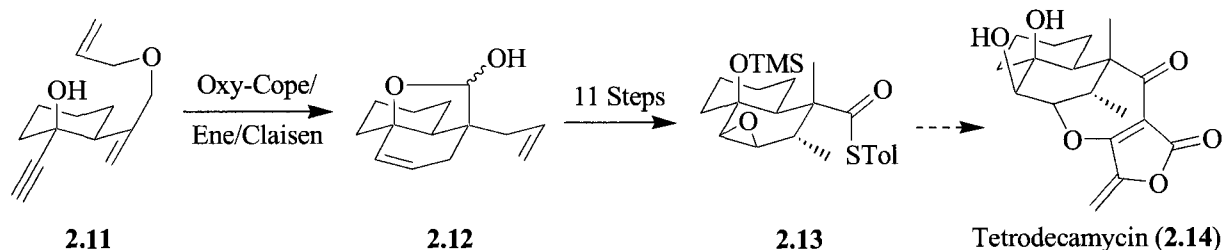
The scope of this methodology was further extended through a slight modification of the 1,2-divinylcyclohexanol substrates. Indeed, former Ph.D. student Irina Denissova found that addition of a strategically placed allyl ether group onto the cyclization precursors allowed a third pericyclic reaction to occur after the usual cascade (Scheme 2.3).¹⁷ In this novel reaction sequence, substrates **2.7** are first converted to macrocyclic enones **2.8** which in turn lead to the formation of alcohols **2.9**. These compounds are now perfectly arranged for a Claisen rearrangement to occur. This reaction thus affords the corresponding hydroxyaldehydes, which are isolated as lactols **2.10**. Overall, two rings, three sigma bonds, and a quaternary stereocenter at C₉ are generated during this cascade reaction.

Scheme 2.3 – The Oxy-Cope/Ene/Claisen Cascade Reaction



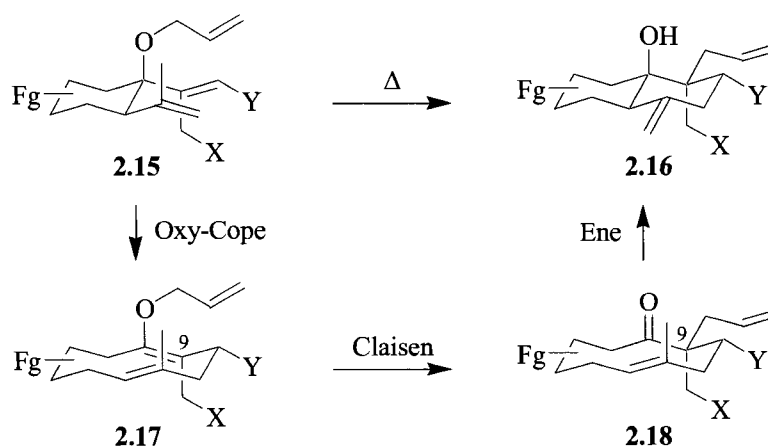
The oxy-Cope/ene/Claisen methodology was then applied to the synthesis of the C₇-C₁₅ *trans*-decalin segment of tetrodecamycin (**2.14**), a naturally occurring antibiotic (Scheme 2.4).¹⁸ Microwave irradiation of cyclohexanol precursor **2.11** initiated the cascade reaction, and the core of the natural product (**2.12**) was produced in 87% yield. Further elaboration of this carbon skeleton led to advanced *trans*-decalin intermediate **2.13** in eleven steps.

Scheme 2.4 – Oxy-Cope/Ene/Claisen Approach to Tetrodecamycin (**2.14**)



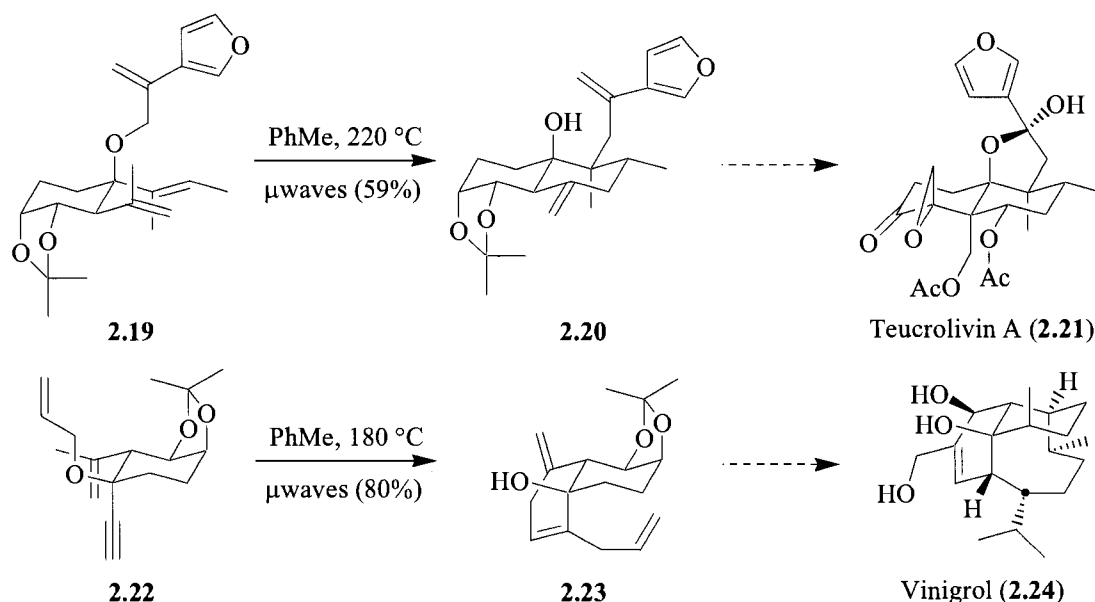
Another variation of the pericyclic reaction cascade was finally developed by former Ph.D. student Effiette Sauer. She determined that the order in which the ene and Claisen reactions occurred could simply be reversed by employing a cyclization precursor bearing an allylated tertiary alcohol (Scheme 2.5).¹⁹ In that innovative sequence, allyl ethers **2.15** first undergo the usual oxy-Cope rearrangement to give macrocyclic enol ethers **2.17**. The following Claisen reaction delivers macrocyclic enones **2.18** and concurrently generates the C₉ quaternary stereocenter. The final ene reaction then produces *trans*-decalins **2.16**.

Scheme 2.5 – The Oxy-Cope/Claisen/Ene Cascade Reaction



The oxy-Cope/Claisen/ene cascade is a powerful methodology that gives access to a large variety of *trans*-decalins **2.16** in high yield and diastereoselectivity. Moreover, precursors **2.15** are straightforwardly synthesized in four steps or less. This is therefore an ideal method for the construction of the *trans*-decalin core of numerous natural products. A few synthetic approaches based on this methodology were therefore considered (Scheme 2.6). The oxy-Cope/Claisen/ene reaction was notably applied successfully to the synthesis of the *trans*-decalin skeleton of teucrolivin A (**2.21**).²⁰ Moreover, microwave irradiation of precursor **2.22** allowed the efficient construction of the *cis*-decalin portion of vinigrol (**2.24**).²¹

Scheme 2.6 – Applications of the Oxy-Cope/Claisen/Ene Cascade in Synthesis



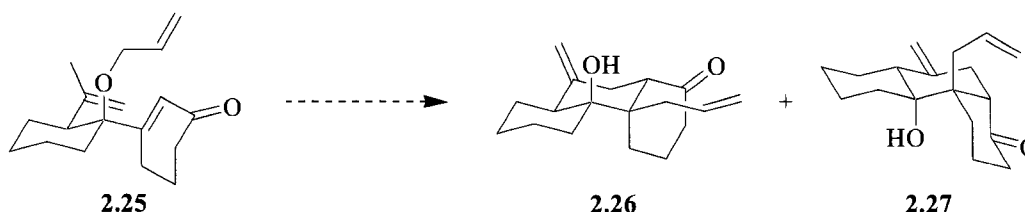
In order to extend further the possibilities brought about by the oxy-Cope/Claisen/ene cascade reaction, we proceeded to various exploratory studies. In the course of this work, some original cyclization precursors were synthesized and their reactivity was examined.

Oxy-Cope/Claisen/Ene Reaction of a Cyclohexenone-Bearing Precursor

We first envisaged the synthesis of **2.25**, a cyclization precursor containing a cyclohexenone ring (Scheme 2.7). Such a substrate was interesting because it could lead to a product bearing

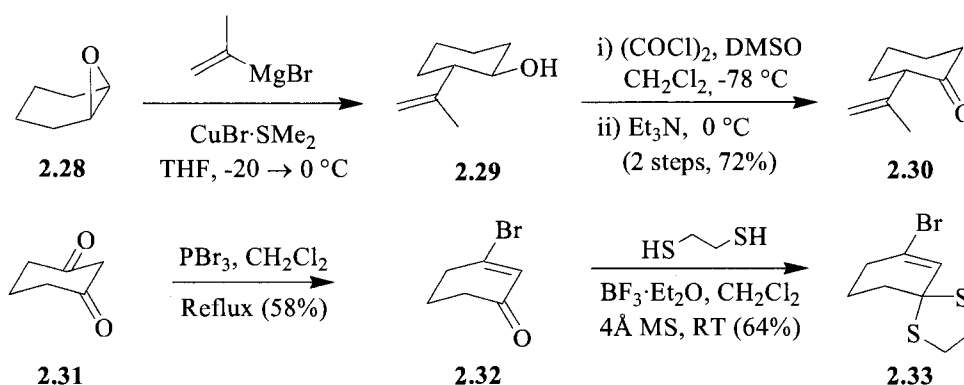
a ketone functionality, which could obviously serve as a synthetic handle for subsequent elaboration. According to the proposed mechanism, the pericyclic reaction cascade could lead to the formation of two tricyclic products, **2.26** and **2.27**.¹⁹

Scheme 2.7 – Proposed Oxy-Cope/Claisen/Ene Reaction of Substrate 2.25



In order to evaluate its behavior, substrate **2.25** was straightforwardly synthesized from compounds **2.30** and **2.33** (Scheme 2.8). Ketone **2.30** was obtained in two steps from epoxide **2.28**. Treatment of this epoxide with isopropenylmagnesium bromide in the presence of catalytic copper bromide, followed by Swern oxidation of crude alcohol **2.29**, gave compound **2.30** in 71% yield.^{22,23} Alkenyl bromide **2.33** was generated from diketone **2.31** in two steps. Reaction of this diketone with phosphorus tribromide first furnished bromoenone **2.32** in fair yield.²⁴ Thioketalization of the ketone then afforded **2.33** in 64% yield.²⁵

Scheme 2.8 – Syntheses of Ketone 2.30 and Alkenyl Bromide 2.33



Alkylation of ketone **2.30** with the lithium species derived from alkenyl bromide **2.33** delivered alcohol **2.34** as a single diastereomer in 40% yield (Scheme 2.9).²⁶ This alcohol was converted to allyl ether **2.35** in fair yield.¹⁹ Hydrolysis of the thioketal functionality of

2.35 then furnished cyclization precursor **2.25** in 47% yield.²⁷ Microwave irradiation of compound **2.25** at 220 °C resulted in the formation of tetracyclic compound **2.36** as a single diastereomer in 36% yield.¹⁹ Obviously, observed lactol **2.36** results from the intramolecular cyclization of hydroxyketone **2.27**. The tridimensional structure of polycyclic lactol **2.36** was established via crystallographic analysis (Figure 2.1).

Scheme 2.9 – Synthesis of 2.25 and Subsequent Oxy-Cope/Claisen/Ene Reaction

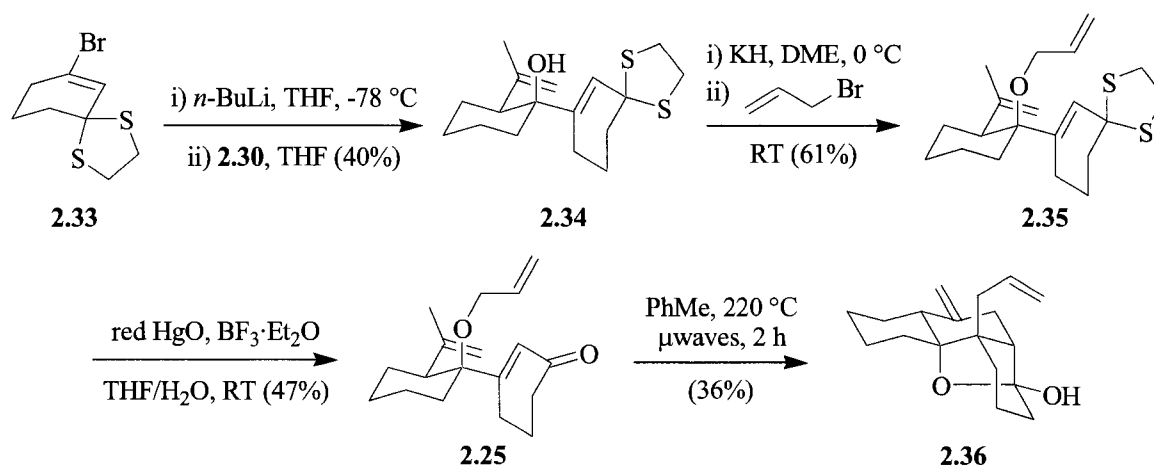
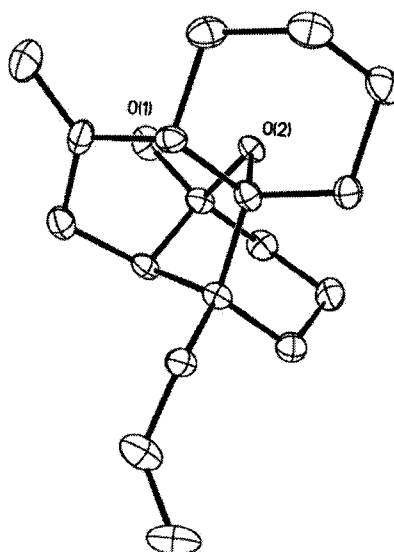
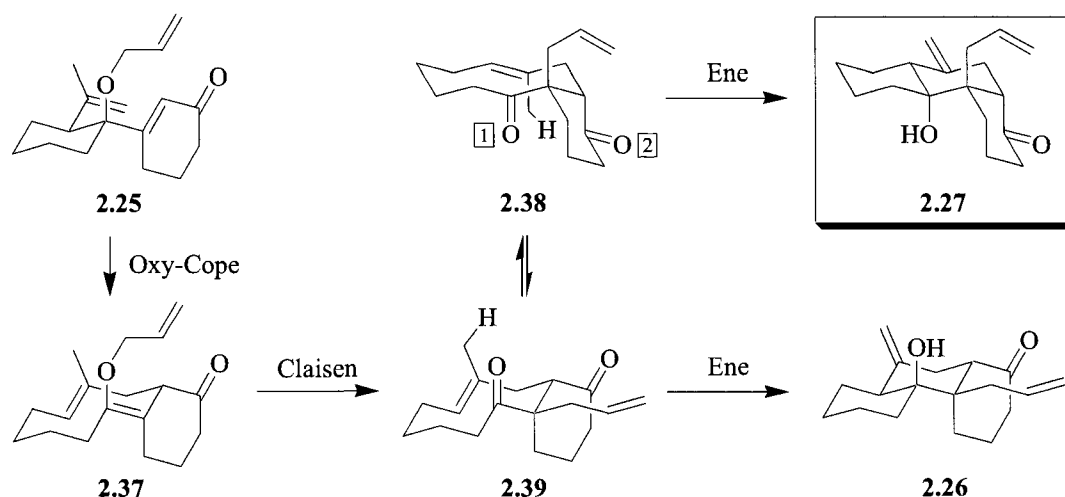


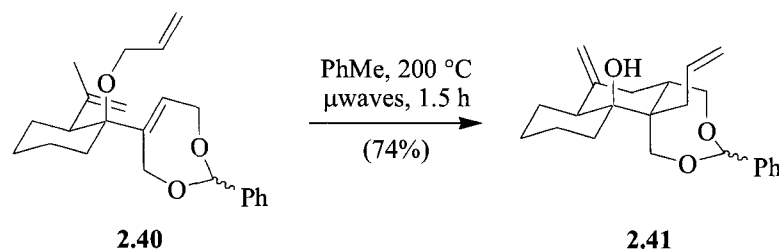
Figure 2.1 – X-Ray Crystallographic Structure of Lactol 2.36



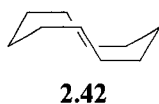
The formation of lactol **2.36** can be explained by the detailed mechanism illustrated in Scheme 2.10.^{19,28} According to that rationale, microwave irradiation of substrate **2.25** at 220 °C first triggers an oxy-Cope rearrangement that generates macrocyclic enol ether **2.37**. In general, the ring inversion of such an intermediate theoretically leads to an isomeric macrocycle. In this case, however, the presence of the cyclohexanone substructure prevents any ring inversion from taking. Since its conformation is locked, intermediate **2.37** has no choice but to undergo a Claisen rearrangement, which delivers enone **2.39**. This macrocyclic enone exists in equilibrium with conformer **2.38**. Assuming that the system obeys the Curtin-Hammett principle, the equilibrium between **2.38** and **2.39** is rapid and leads to two competing transannular ene reactions.²⁹ Upon cursory comparison of these reactions (**2.38** → **2.27** versus **2.39** → **2.26**), one would expect hydroxyketone **2.26** to be formed in preference to its diastereomer (**2.27**). Since it bears only one axial substituent, the transition state of the ene reaction leading to isomer **2.26** should be lower in energy. Indeed, former Ph.D. student Effiette Sauer observed, in a similar case, the selective formation of a product of type **2.26**.¹⁹ Microwave irradiation of substrate **2.40** at 200 °C produced alcohol **2.41** as a single diastereomer in 74% yield (Scheme 2.11). In the case of substrate **2.25**, however, the formation of hydroxyketone **2.26** was not observed. In order to explain this intriguing result, we examined in more detail the sterics and electronics of macrocyclic enones **2.38** and **2.39**.

Scheme 2.10 – Mechanism of the Oxy-Cope/Claisen/Ene Reaction of Substrate **2.25**



Scheme 2.11 – Oxy-Cope/Claisen/Ene Reaction of Substrate **2.40**

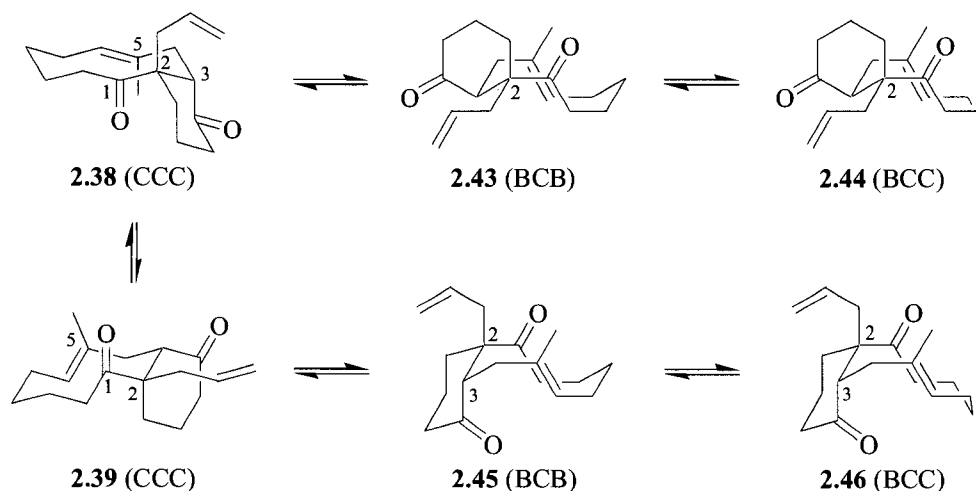
Computational data have demonstrated that, in the transition state of the transannular ene reaction, the macrocyclic enone (e.g. **2.38**) prefers to adopt a chair-chair-chair conformation, as illustrated in Scheme 2.10.²⁸ On the other hand, saturated ten-membered macrocycles such as cyclodecane are known to exist in a boat-chair-boat conformation in their ground state (Figure 2.2).³⁰ Taking this fact into consideration, we analyzed the alternative conformations

Figure 2.2 – Boat-Chair-Boat Conformation of Cyclodecane (**2.42**)

of the macrocyclic enones (Scheme 2.12). On the basis of steric effect analysis, intermediate **2.38**, having a chair-chair-chair conformation, should lead to a high energy transition state. In fact, **2.38** possesses axial substituents at C₂ and C₃ and pseudoaxial substituents at C₁ and C₂. It therefore experiences severe steric strain due to numerous 1,3-diaxial interactions. This steric tension is however reduced considerably when **2.38** is converted to a boat-chair-boat (**2.43**) or boat-chair-chair (**2.44**) conformation. Indeed, these two conformers bear only one pseudoaxial substituent at C₂ and do not suffer such unfavorable 1,3-diaxial interactions. They would thus lead to a lower energy transition state. In the case of **2.39**, no gain in stability is expected from a conversion to a boat-chair-boat (**2.45**) or boat-chair-chair (**2.46**) conformation. Intermediate **2.39** actually possesses one axial substituent at C₂, whereas **2.45** and **2.46** bear two pseudoaxial substituents (at C₂ and C₃). According to this brief analysis, it

is not obvious that conformers **2.43** or **2.44** are lower in energy than **2.45** or **2.46**. Therefore, the exclusive formation of lactol **2.36** can most likely not be explained by steric factors only.

*Scheme 2.12 – Possible Conformations of Macrocyclic Enones **2.38** and **2.39***



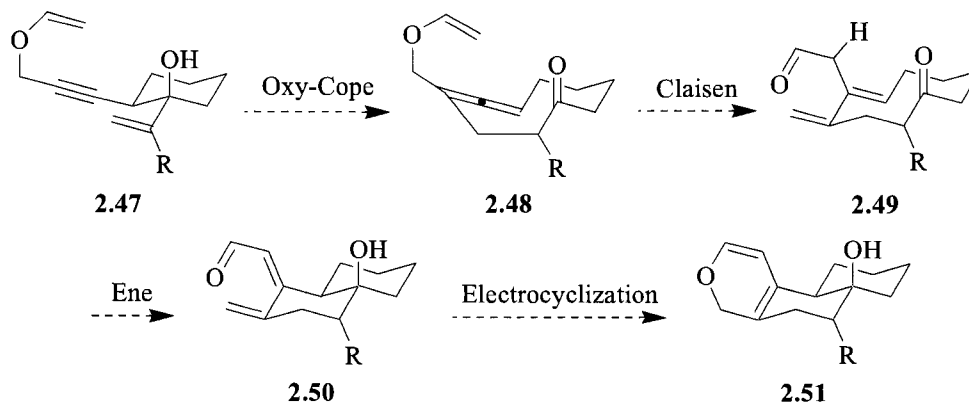
We then envisaged that the selectivity of the oxy-Cope/Claisen/ene reaction could have an electronic origin. A careful inspection of chair-chair-chair conformer **2.38** pointed up the close proximity of carbonyls 1 and 2 (Scheme 2.10). In this conformation, the donation of a lone pair by the oxygen of carbonyl 1 into the π system of carbonyl 2 seems likely. This process would probably result in the creation of a partial positive charge on the oxygen of carbonyl 1, which could accelerate the transannular ene reaction by lowering the energy of the transition state. In the case of conformer **2.39**, the two carbonyl groups are separated by a larger distance. As a result, no electronic interaction between the carbonyls is expected in this intermediate. According to this rationale, hydroxyketone **2.27** would be the sole product of the reaction, and this is what was observed experimentally.

In summary, the formation of lactol **2.36** showed that enone-containing compounds could be employed as substrates for the oxy-Cope/Claisen/ene reaction. However, this lactol could only be obtained in fair yield from simple precursor **2.25**. We consequently discontinued our investigation of this precursor and moved on to another type of substrate.

Attempted Synthesis of Pyrans via the Oxy-Cope/Claisen/Ene Cascade

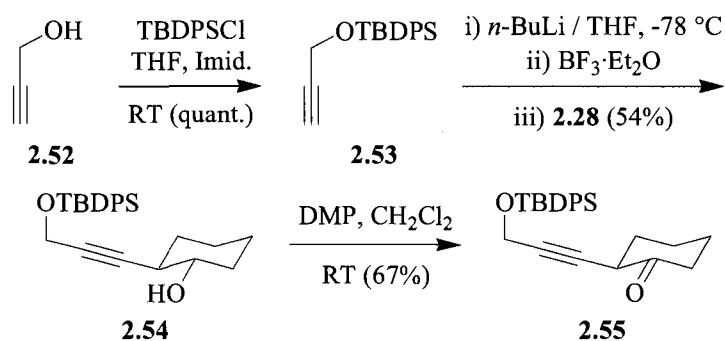
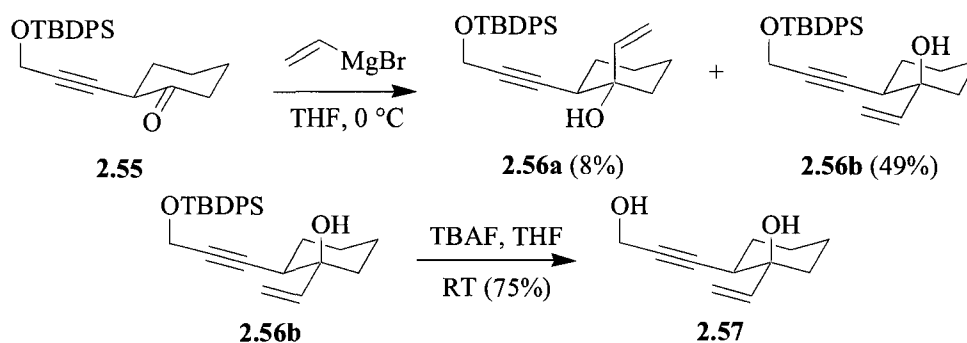
We envisioned that the oxy-Cope/Claisen/ene cascade could be employed to generate *trans*-decalins bearing a fused pyran ring, such as compound **2.51** (Scheme 2.13). According to our proposal, high temperature microwave irradiation of propargyl vinyl ethers **2.47** would first initiate an oxy-Cope rearrangement, yielding macrocyclic allenes **2.48**. These intermediates would then afford keto-aldehydes **2.49** after going through a Claisen shift. A subsequent ene reaction would generate dienaldehydes **2.50**, which would ultimately undergo a 6 π electron electrocyclization leading to the formation of pyrans **2.51**.

Scheme 2.13 – Proposed Formation of Pyrans through a Pericyclic Reaction Cascade

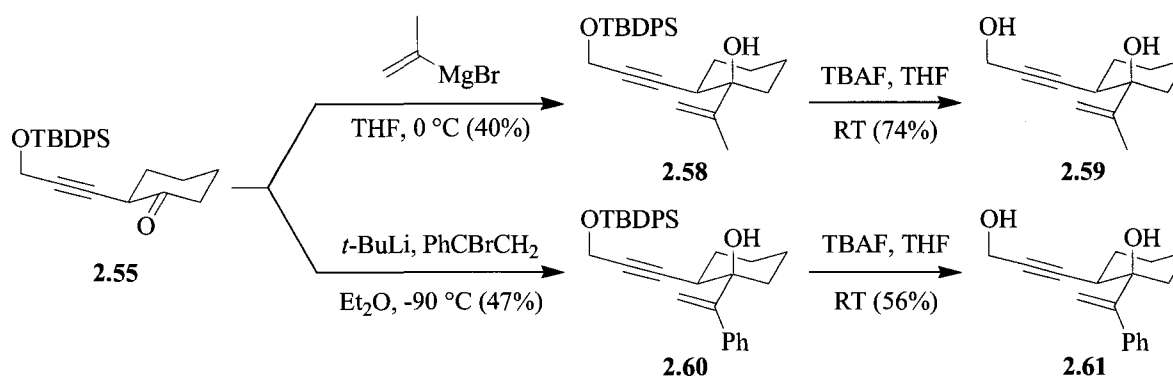


In order to verify the feasibility of the proposed reaction cascade, a few substrates of type **2.47** were generated. To this end, propargyl ketone **2.55** was first synthesized from epoxide **2.28** and alkyne **2.53** (Scheme 2.14). Alkyne **2.53** was formed by the quantitative silylation of propargyl alcohol **2.52**. The lithiated species derived from **2.53** was then reacted with epoxide **2.28** in the presence of boron trifluoride diethyl etherate, and propargyl alcohol **2.54** was obtained in 54% yield.³¹ Oxidation of the alcohol with Dess-Martin periodinane finally furnished ketone **2.55** in 67% yield.³²

Ketone **2.55** was first alkylated with vinylmagnesium bromide, yielding epimeric alcohols **2.56a** and **2.56b** in 57% overall yield (Scheme 2.15). Treatment of the desired epimer, **2.56b**, with tetra-*n*-butylammonium fluoride then afforded diol **2.57** in 75% yield.

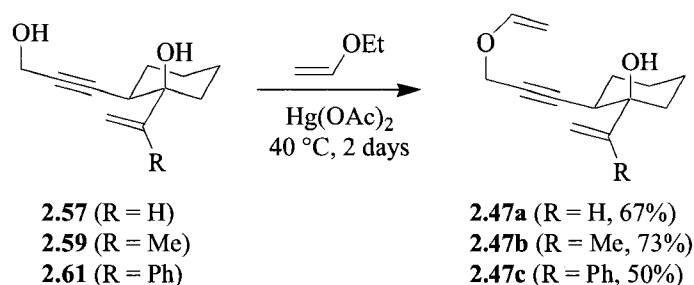
Scheme 2.14 – Synthesis of Propargyl Ketone **2.55**Scheme 2.15 – Synthesis of Diol **2.57**

Also, alkylation of ketone **2.55** with isopropenylmagnesium bromide furnished alcohol **2.58** as a sole epimer in low yield (Scheme 2.16). Moreover, reaction of the ketone with the lithiated species derived from α -bromostyrene afforded alcohol **2.60** as a single diastereomer

Scheme 2.16 – Synthesis of Diols **2.59** and **2.61**

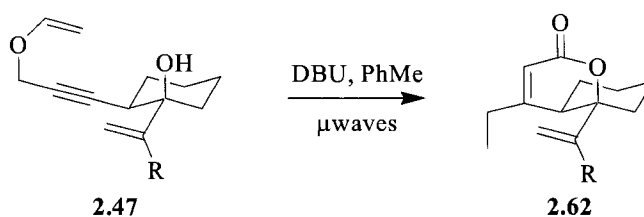
in 47% yield.²⁶ Alcohols **2.58** and **2.60** were then desilylated under the usual conditions to furnish respectively diols **2.59** and **2.61** in reasonable yields. Finally, diols **2.57**, **2.59** and **2.61** were converted to the corresponding propargyl vinyl ethers by treatment with ethyl vinyl ether and mercuric acetate (Scheme 2.17).³³ Substrates **2.47a-c** were obtained in yields ranging from 49 to 72%. The behavior of these three substrates under microwave irradiation was then examined (Table 2.1).

Scheme 2.17 – Synthesis of Propargyl Vinyl Ethers **2.47**



When propargyl vinyl ether **2.47a** was subjected to microwave irradiation at 180 °C in the presence of DBU³⁴, the expected pyran derivative was not formed. Instead, we were surprised to observe the formation α,β -unsaturated lactone **2.62a** in 71% yield (entry 1). Treatment of substrates **2.47b** and **2.47c** in the same conditions also led to the formation of

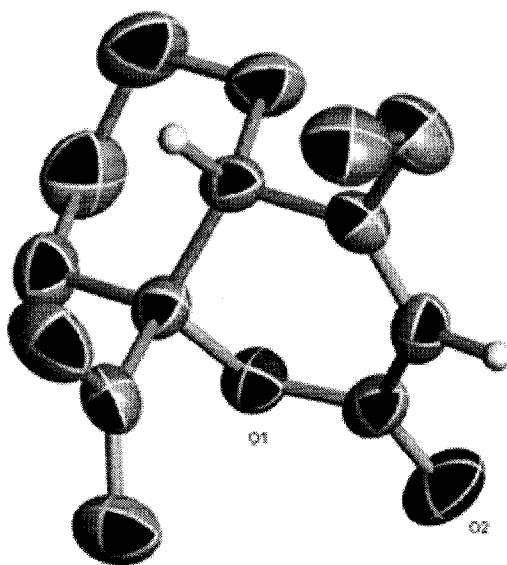
Table 2.1 – Rearrangement of Propargyl Vinyl Ethers **2.47**



Entry	Substrate	R	Temperature (°C)	Time (min)	Product	Yield (%)
1	2.47a	H	180	30	2.62a	71
2	2.47b	Me	200	30	2.62b	33
3	2.47c	Ph	180	60	2.62c	48

the corresponding unsaturated lactones, albeit in lower yield (entries 2-3). The structure of lactones **2.62** could not be established unambiguously by NMR spectroscopy. Fortunately, a single crystal of compound **2.62b** could be obtained, and X-ray crystallographic analysis established the tridimensional structure of this lactone (Figure 2.3).

Figure 2.3 – X-Ray Crystallographic Structure of Lactone 2.62b

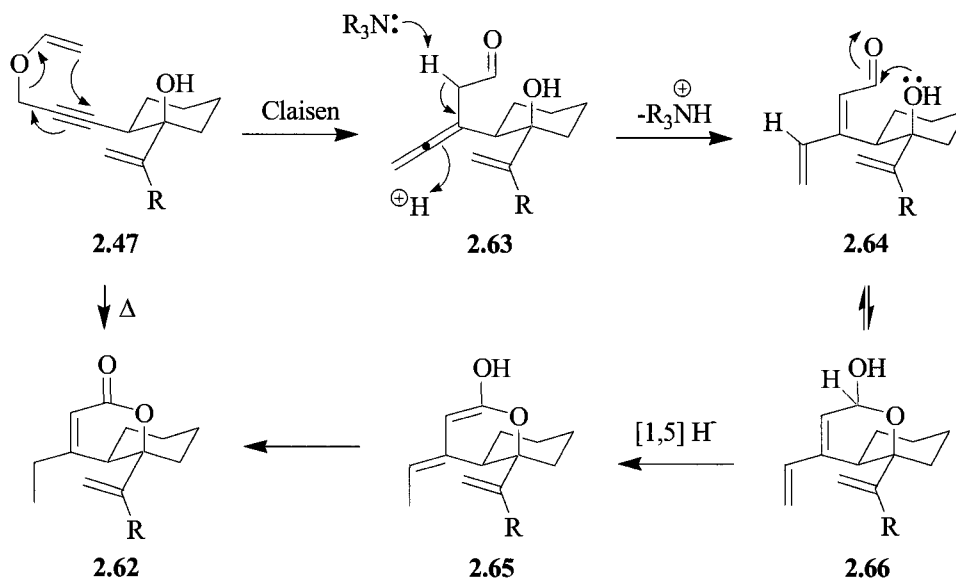


A proposed mechanism that accounts for the formation of lactones **2.62** is illustrated in Scheme 2.18. According to this rationale, propargyl vinyl ethers **2.47** would initially go through a Claisen rearrangement leading to allenes **2.63**. This could be followed by a formal [1,3] hydride shift yielding thermodynamically more stable 1,3-dienes **2.64**. Subsequent nucleophilic addition of the alcohol onto the aldehyde would in turn furnish six-membered lactol **2.66**. Obviously, this nucleophilic attack could also precede the [1,3] hydride shift. In any case, compound **2.66** would then undergo a [1,5] hydride shift leading to enol **2.65**, which, after tautomerization, would deliver the observed α,β -unsaturated lactones.

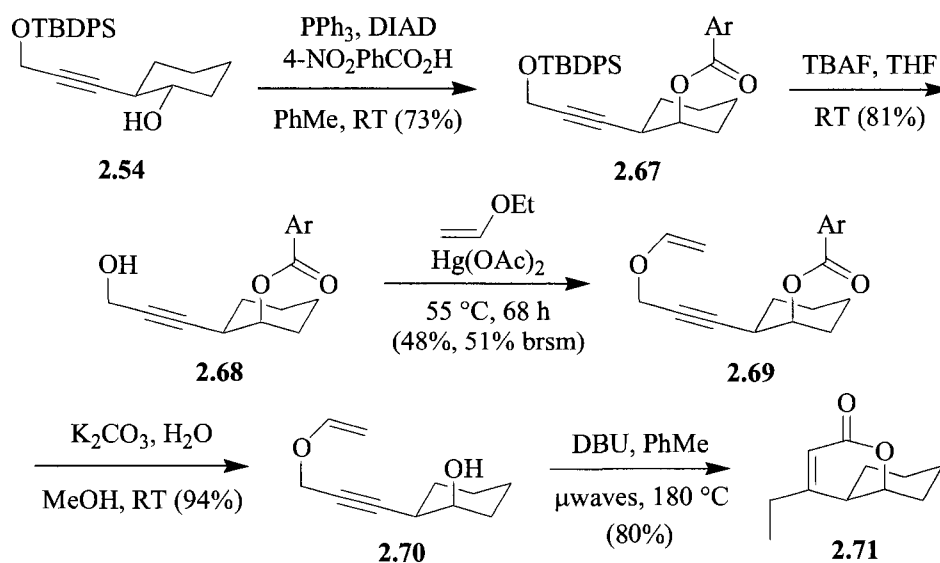
Interestingly, the alkenyl moieties of substrates **2.47** remained untouched during the reaction. We however suspected that the steric hindrance caused by these groups had a negative influence on the yield of formation of unsaturated lactones **2.62**. In order to verify that

supposition, we initiated the synthesis of a substrate lacking the alkenyl group. Propargyl vinyl ether **2.70** was thus synthesized in four steps from alcohol **2.54** (Scheme 2.19). First, the stereochemistry of the alcohol functionality was inverted through a Mitsunobu reaction, and 4-nitrobenzoate **2.67** was obtained in 73% yield.³⁵ Desilylation of this compound in the

Scheme 2.18 – Rationalization for the Formation of Lactones **2.62**



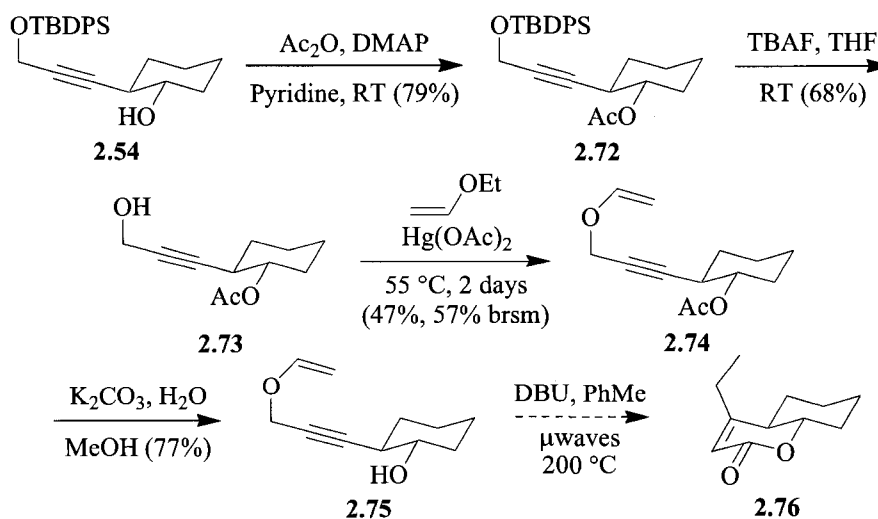
Scheme 2.19 – Synthesis and Subsequent Rearrangement of Substrate **2.70**



usual way efficiently produced alcohol **2.68**, which was then converted to the corresponding vinyl ether in 48% yield.³³ Hydrolysis of the benzoate ester finally delivered substrate **2.70** in high yield. This simple precursor was then irradiated with microwaves at 180 °C, and α,β -unsaturated lactone **2.71** was produced in 80% yield. This result seems to indicate that the presence of an alkenyl group on the alcohol carbon of compounds **2.47a-c** indeed impaired the formation of lactones **2.62a-c**.

We also wanted to verify the applicability of this novel rearrangement to the synthesis of *trans* bicyclic lactones. The synthesis of a substrate possessing an *anti* relationship between the side-chain and the alcohol was therefore undertaken. Precursor **2.75** was obtained from alcohol **2.54** in four steps (Scheme 2.20). The alcohol was first acetylated, delivering ester **2.72** in 79% yield. Desilylation of this compound, followed by etherification of the resulting alcohol afforded vinyl ether **2.74** in reasonable yield.³³ Ester hydrolysis finally afforded substrate **2.75** in good yield. When this compound was subjected to microwave irradiation, lactone **2.76** was not formed. The reaction rather led to the formation of a complex mixture of unseparable products. Consequently, the generation of *trans*-bicyclic lactones through this new reaction seems impracticable.

Scheme 2.20 – Synthesis and Attempted Rearrangement of Substrate **2.75**



Conclusion

In the course of the exploration studies described in this chapter, interesting results have been obtained. We first synthesized an enone-bearing substrate that successfully underwent the oxy-Cope/Claisen/ene cascade. The resulting lactol could moreover be characterized by crystallography. We also envisaged the generation of *trans*-decalins fused with a pyran ring through the same reaction cascade. However, when substrates **2.47a-c** were submitted to microwave irradiation, the unexpected formation of α,β -unsaturated lactones **2.62a-c** was observed. Moreover, irradiation of **2.70**, a substrate lacking the alkenyl group, led to the formation of the corresponding α,β -unsaturated lactone in higher yield. This new reaction could however not be applied to the synthesis of *trans*-bicyclic lactones.

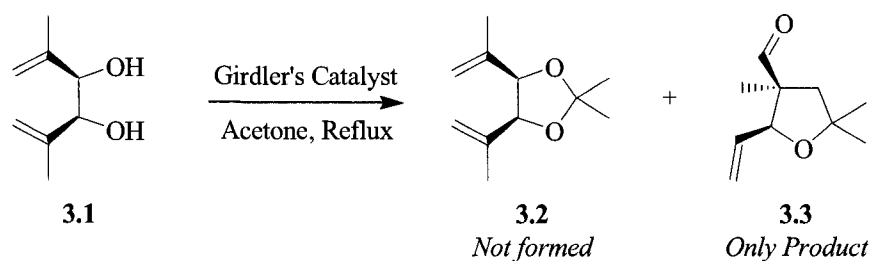
3

The Prins-Pinacol Rearrangement

Introduction

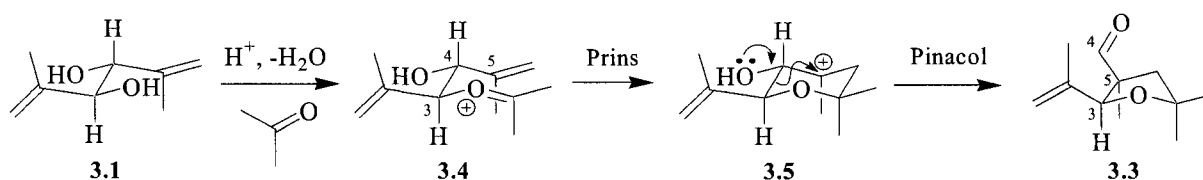
In the history of Science, major breakthroughs have often been made by mere chance. This applies particularly well to the field of synthetic organic chemistry. In fact, chance largely influenced early developments of this scientific discipline. When, in 1828, Wöhler attempted to synthesize ammonium cyanate from inorganic materials, he was surprised to obtain urea as the product of the reaction.¹ This unanticipated result was indeed the first organic reaction in History. Since then, several organic reactions have originated from fortuitous discoveries. For example, French chemist Mousset reported such an unexpected finding in 1969.³⁶ In the course of optimizing a protection procedure, he treated *meso* diol **3.1** with an activated montmorillonite (Girdler's catalyst; Al_2O_3 , 4 SiO_2 , H_2O + x H_2O) in acetone in order to generate isopropylidene **3.2** (Scheme 3.1). To his surprise, racemic tetrahydrofuran **3.3** was formed as the sole reaction product.³⁷ In a subsequent report, Mousset proposed a mechanism that accounts for the conversion of diol **3.1** to tetrahydrofuran **3.3**.³⁸ According to this rationale, tetrahydrofuran **3.3** results from a cationic cyclization followed by an oxygen-assisted ring contraction (Scheme 3.2). First, Lewis-acid-mediated condensation of acetone with one of the hydroxy groups of diol **3.1** leads to formation of oxocarbenium **3.4**. In the subsequent Prins cyclization, a nucleophilic attack of the alkene onto the oxocarbenium gives

Scheme 3.1 – First Observation of the Rearrangement



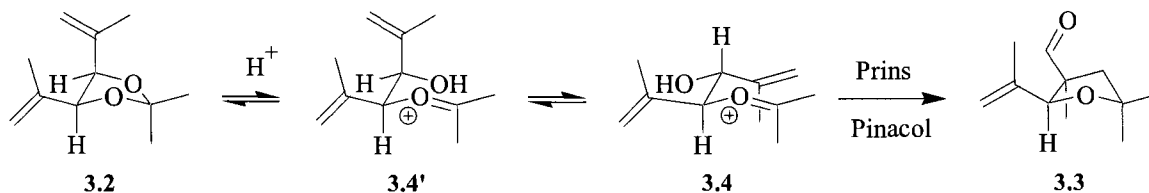
carbocation **3.5**. To end with, the newly formed carbenium ion undergoes an oxygen-assisted ring contraction. Through this bond reorganization, a lone pair of the exocyclic oxygen causes the migration of the C₃-C₄ bond. This bond being periplanar to the empty p orbital of the carbocation, a new C₃-C₅ bond is formed. Rearranged tetrahydrofuran **3.3** is therefore delivered. Importantly, the excellent stereoselectivity exhibited in this first example of the Prins-Pinacol reaction rendered it attractive for further developments.

Scheme 3.2 – Proposed Mechanism for the Rearrangement



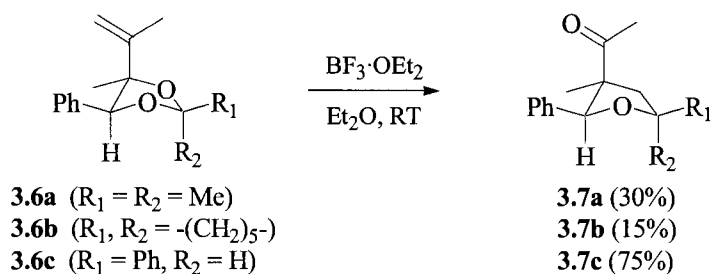
Mousset also hypothesized that acetonide **3.2** was formed as an intermediate in the course of the reaction.³⁹ To validate this supposition, compound **3.2** was treated with various Lewis acids (Scheme 3.3). This most probably led to the reversible formation of oxocarbenium **3.4'**, which, upon rotation, delivered conformer **3.4**. The latter then underwent the Prins-Pinacol

Scheme 3.3 – Reaction of Acetonide 3.2



rearrangement, and tetrahydrofuran **3.3** was obtained. This interesting result was further exploited in a systematic study of a variety of acetals and ketals.⁴⁰ In all cases, the benzylidene acetal gave the best results. For example, treatment of substrates of type **3.6** with boron trifluoride diethyl etherate at room temperature afforded corresponding tetrahydrofurans **3.7** (Scheme 3.4). As expected, benzylidene **3.6c** gave the best results (75% conversion), followed by isopropylidene **3.6a** (30%) and cyclohexylidene **3.6b** (15%).

Scheme 3.4 – Reaction of Some Acetals and Ketals

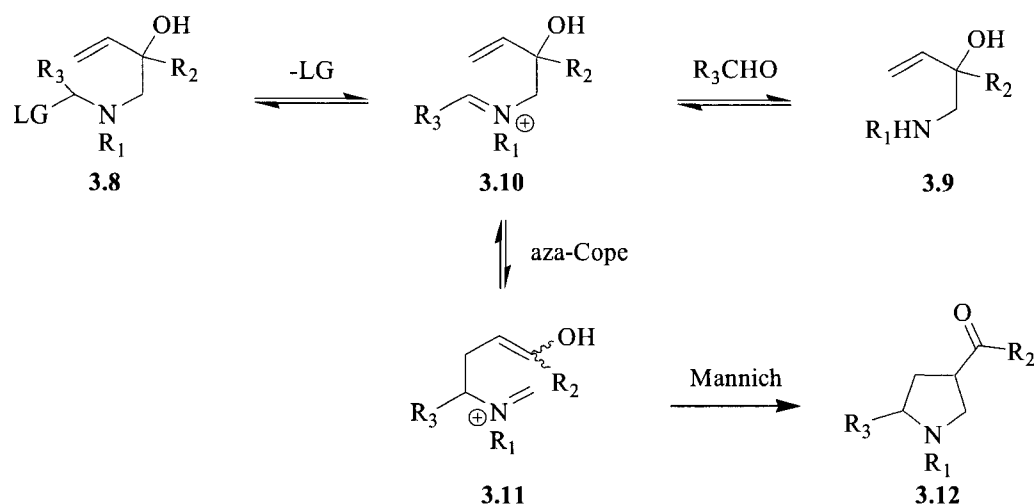


Mechanism and Stereoselectivity

After the rearrangement was originally observed, Mousset proposed that tetrahydrofurans of type **3.3** were probably formed through a Prins cyclization followed by a pinacolic rearrangement. Nonetheless, no experimental evidence gathered at that point could undeniably support this hypothetical mechanism. In the 1980s, Overman and co-workers were working on the development of a related transformation, the aza-Cope-Mannich tandem reaction. This synthetic strategy was employed for the concise synthesis of pyrrolidines (Scheme 3.5).⁴¹ In this reaction, iminium **3.10** can be generated either from amine **3.8** via nitrogen-assisted ejection of the leaving group or by condensation of amine **3.9** with an aldehyde. This iminium then undergoes a [3,3] sigmatropic rearrangement, which is commonly known as the aza-Cope reaction, and intermediate **3.11** is obtained. The following intramolecular Mannich reaction finally leads to desired pyrrolidine **3.12**. In a report published in 1987, Overman described the application of this tandem reaction to the synthesis of tetrahydrofurans. Employing conditions developed previously, isopropylidenes

3.13 were treated with tin(IV) chloride and the corresponding tetrahydrofurans were formed in high yields and complete stereoselectivity (Scheme 3.6).⁴²

Scheme 3.5 – The Aza-Cope-Mannich Tandem Reaction



According to Overman, three different mechanisms could account for the formation of tetrahydrofurans **3.14** (Figure 3.1).⁴³ Treatment of an allylic ketal such as **3.15** with a Lewis or a Brønsted acid first leads to corresponding oxocarbenium **3.16**. This intermediate can then follow three reaction pathways. A fragmentation of intermediate **3.16** yielding distinct species **3.19** and **3.20** is improbable, since an acyclic transition state could hardly explain the high degree of stereoselectivity observed for this rearrangement. Nevertheless, both Prins-Pinacol and oxonia-Cope-aldol mechanisms go through a cyclic transition state and could thus explain the observed stereochemistry. However, convincing experimental evidence supporting the Prins-Pinacol mechanism was obtained when the reaction was performed with

Scheme 3.6 – First Examples of the Rearrangement by Overman

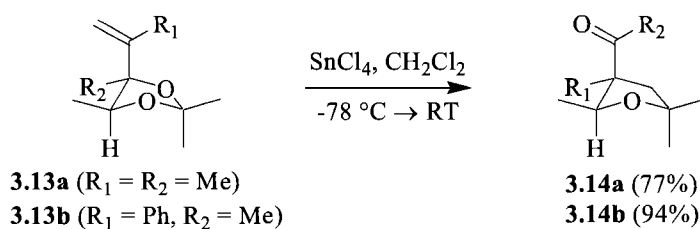
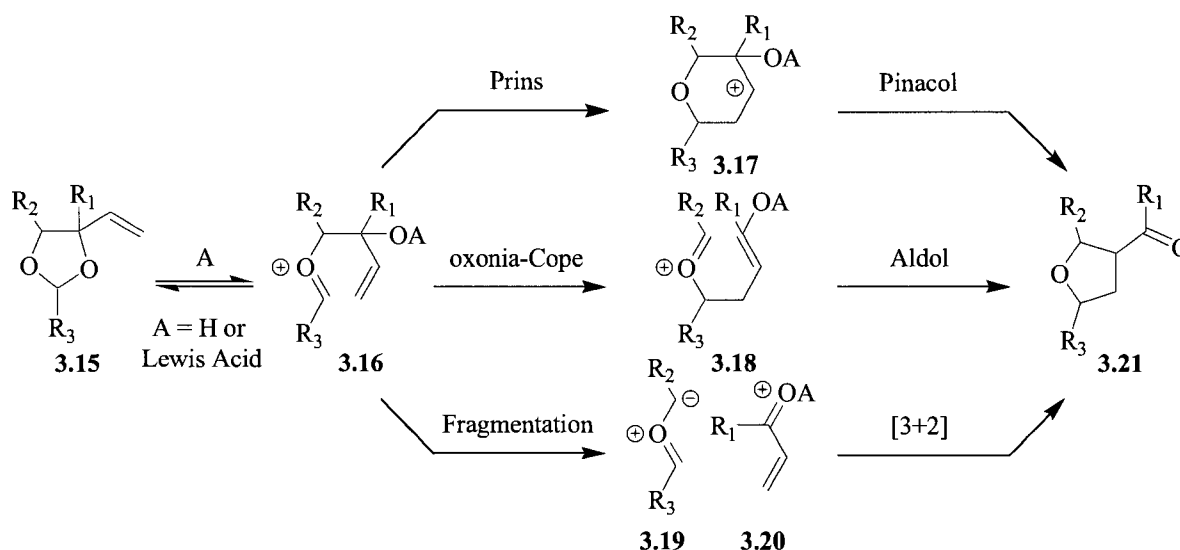
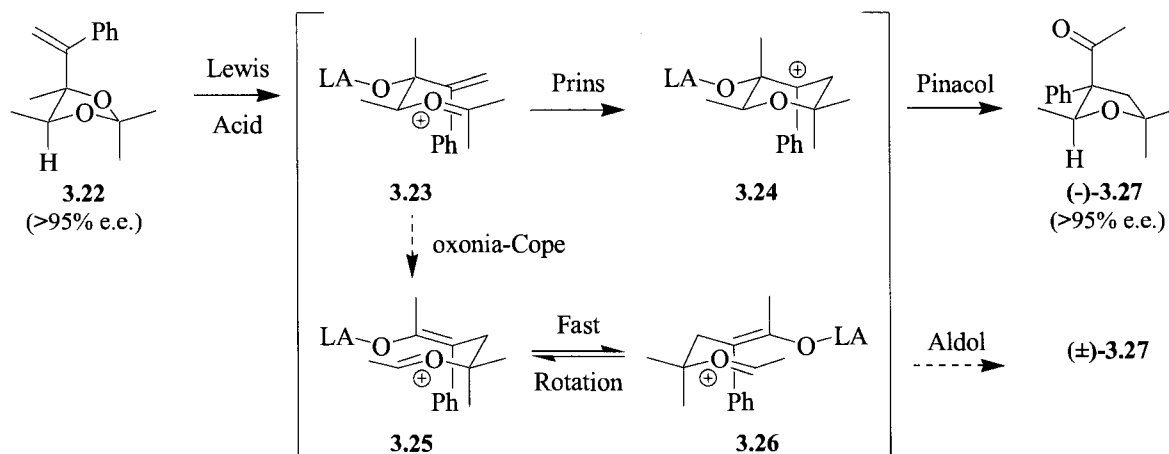


Figure 3.1 – Three Possible Mechanisms for the Rearrangement



enantioenriched ketal **3.22** (Scheme 3.7).⁴⁴ Upon treatment with a Lewis acid, the starting ketal is converted to related oxocarbenium **3.23**, which can undergo a [3,3] sigmatropic rearrangement to afford **3.25**. The rotation of the carbon-carbon bond within intermediate **3.25** is lower in energy than the aldol cyclization.⁴⁵ Therefore, a rapid equilibrium between **3.25** and **3.26** should be observed, and a racemic mixture of tetrahydrofurans **3.27** would be produced. On the other hand, a Prins cyclization going through a chair transition state gives cationic intermediate **3.24** without racemization. A pinacol ring contraction then delivers

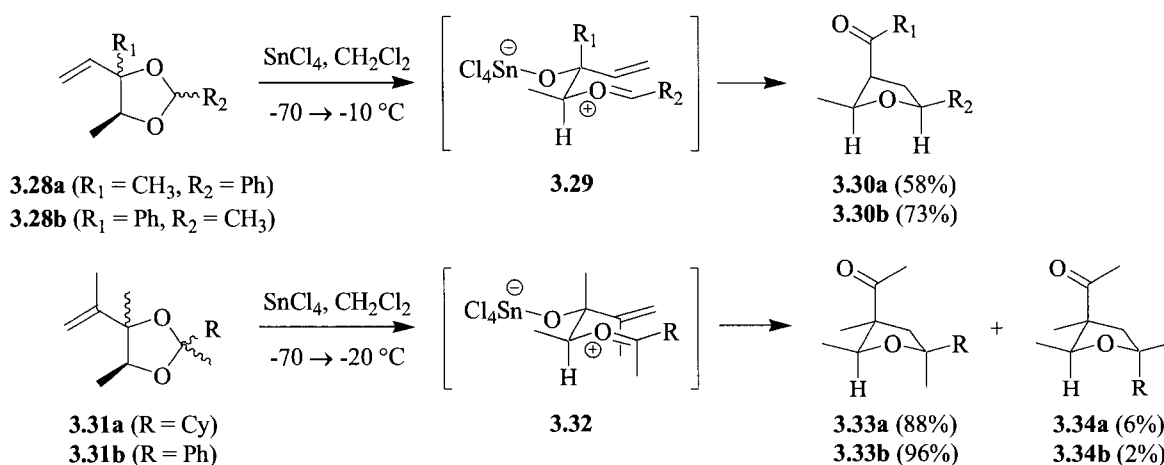
Scheme 3.7 – Comparison of Prins-Pinacol and Oxonia-Cope-Aldol Mechanisms



enantiomerically pure tetrahydrofuran **3.27**. Since no apparent loss of enantioselectivity was observed during this reaction, Overman preferred the Prins-Pinacol mechanism to its oxonia-Cope-Aldol counterpart. The Prins-Pinacol mechanism is now generally accepted.

As discussed above, stereoelectronic effects have a determining influence on the mechanism and stereoselectivity of the Prins-Pinacol rearrangement. However, steric effects are also involved in the stereochemical outcome of the reaction. For example, when treated with tin(IV) chloride, an isomeric acetal of type **3.28** generates the corresponding *E* oxocarbenium **3.29** (Scheme 3.8). This oxonium is thermodynamically more stable than the related *Z* oxocarbenium because the larger R_2 substituent occupies the pseudoequatorial position.⁴⁶ The subsequent Prins cyclization thus affords a cationic intermediate having an equatorial R_2 group. This explains the stereochemistry of resulting tetrahydrofuran **3.30**. Similarly, submission of isomeric ketal **3.31** to the reaction conditions results in the formation of *E* oxocarbenium **3.32**. In that case also, the larger substituent inherits the pseudoequatorial position.⁴⁷ Tetrahydrofuran **3.33**, bearing a large pseudoequatorial *R* group, is consequently the major product of the reaction. Obviously, the substituents of the ketal must be of different size in order to yield valuable epimeric ratios at the end of the reaction.

Scheme 3.8 – Influence of the Oxocarbenium Geometry



More evidence that the stereoselectivity observed in the Prins-Pinacol rearrangement is influenced by both electronic and steric effects was collected during an important study

dealing with isomerically pure allylic acetals (Table 3.1).⁴⁸ For this purpose, acetals **3.35** were generated from the corresponding *syn* diols whereas acetals **3.36** were synthesized from the related *anti* diols. When acetals **3.35** were treated with trifluoromethanesulfonic acid or tin(IV) chloride, tetrahydrofurans **3.37** were formed in preference to isomeric products **3.38** in all cases (entries 1-3). For these *syn* acetals, both electronic and steric effects seemed to favor the formation of **3.37**. In the *anti* series, however, the size of the R₂ substituent and the nucleophilicity of the alkene greatly influenced the stereochemistry of the resulting tetrahydrofuran. For instance, acetal **3.36a** containing a terminal vinyl group preferentially led to tetrahydrofuran **3.37**, as in the *syn* acetal series (entry 4). Nonetheless, a reversal of selectivity was observed when acetal **3.36b** bearing an isopropenyl group was submitted to the reaction conditions (entry 5). In addition, replacing the methyl group by a larger isopropyl group predominantly yielded tetrahydrofuran **3.38** (entry 6).

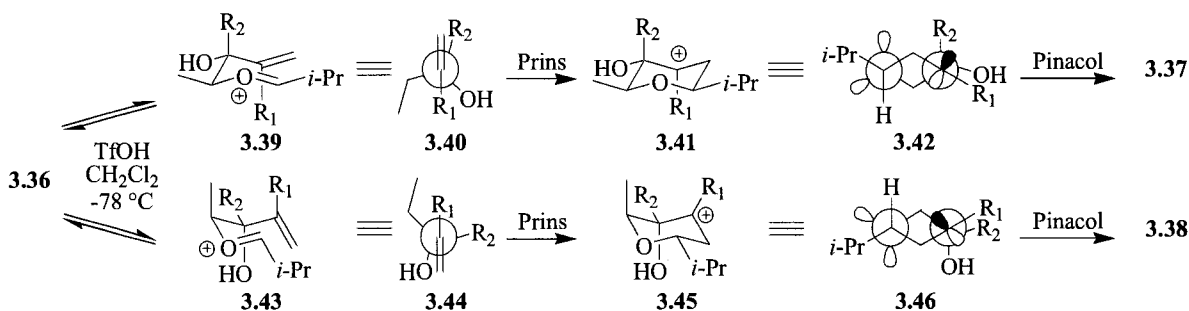
Table 3.1 – Prins-Pinacol Rearrangement of *Syn* and *Anti* Acetals

Entry	Acetal	R ₁	R ₂	% Conversion	3.37 : 3.38
1	3.35a	H	Me	90	>99 : 1
2	3.35b	Me	Me	88	97 : 3
3	3.35c	H	<i>i</i> -Pr	98	96 : 4
4	3.36a	H	Me	97	95 : 5
5	3.36b	Me	Me	96	14 : 86
6	3.36c	H	<i>i</i> -Pr	90	7 : 93

To explain those intriguing results, Overman and co-workers proposed the model depicted in Figure 3.2. According to this rationale, oxocarbenium **3.39** is preferred to conformer **3.43** when R₂ is small (e.g. Me) since the homoallylic methyl group occupies a pseudoequatorial position. However, an unfavorable overlap of the hydroxy $\sigma^*_{\text{C-O}}$ and the alkene $\pi_{\text{C-C}}$

molecular orbitals diminishes the nucleophilicity of the olefin. Nonetheless, the formation of cationic intermediate **3.41** is favored because the interaction between $\sigma^*_{\text{C-R}_2}$ and the empty p orbital increases as the new carbon-carbon bond is formed. Consequently, substrates having a less nucleophilic alkene group are believed to exhibit a later transition state during the Prins cyclization stage. The predominant production of tetrahydrofuran **3.37** from acetal **3.36a** therefore agrees with both steric and electronic evaluations. When the alkene component is substituted (e.g. $\text{R}_1 = \text{Me}$), oxocarbenium **3.43** becomes the favored conformer. The interaction between the hydroxy $\sigma^*_{\text{C-O}}$ and the alkene $\pi_{\text{C-C}}$ molecular orbitals is weakened, and overlap of alkene $\pi^*_{\text{C-C}}$ and $\sigma_{\text{C-R}_2}$ enhances the nucleophilicity of the olefin. Contrasting with cationic intermediate **3.41**, Prins cyclization product **3.45** suffers a destabilizing interaction between $\sigma_{\text{C-O}}$ and the empty p orbital. Accordingly, it is assumed that the Prins cyclization leading to **3.45** occurs through an early transition state. For that reason, a substrate bearing a more nucleophilic alkene group (e.g. **3.36b**) probably has an earlier transition state than one having a less nucleophilic olefin (e.g. **3.36a**) and thus leads preferentially to the formation of tetrahydrofuran **3.38**. To end with, when R_2 is larger than a methyl group (e.g. *i*-Pr), oxocarbenium **3.43** is preferred because this large group occupies a pseudoequatorial position. As a result, acetal **3.36c** mainly yields tetrahydrofuran **3.38**.

Figure 3.2 – Rationalization of the Stereoselectivity Observed for the Anti Acetals

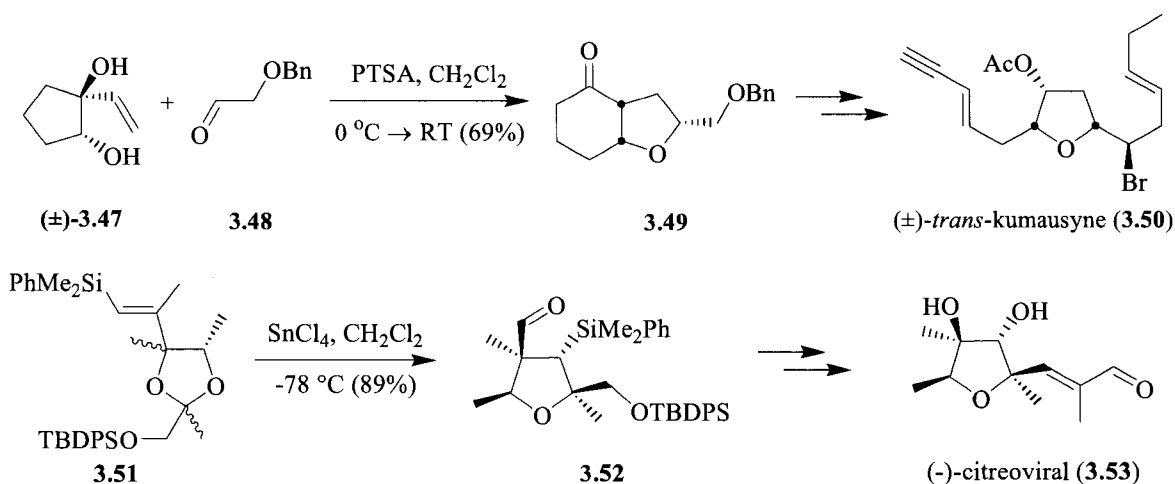


Applications in Synthesis

Overman and co-workers have been the major contributors in the development of the Prins-Pinacol development ever since their first report on this reaction in 1987. Overman notably took advantage of the remarkable stereoselectivity of the rearrangement to design innovative

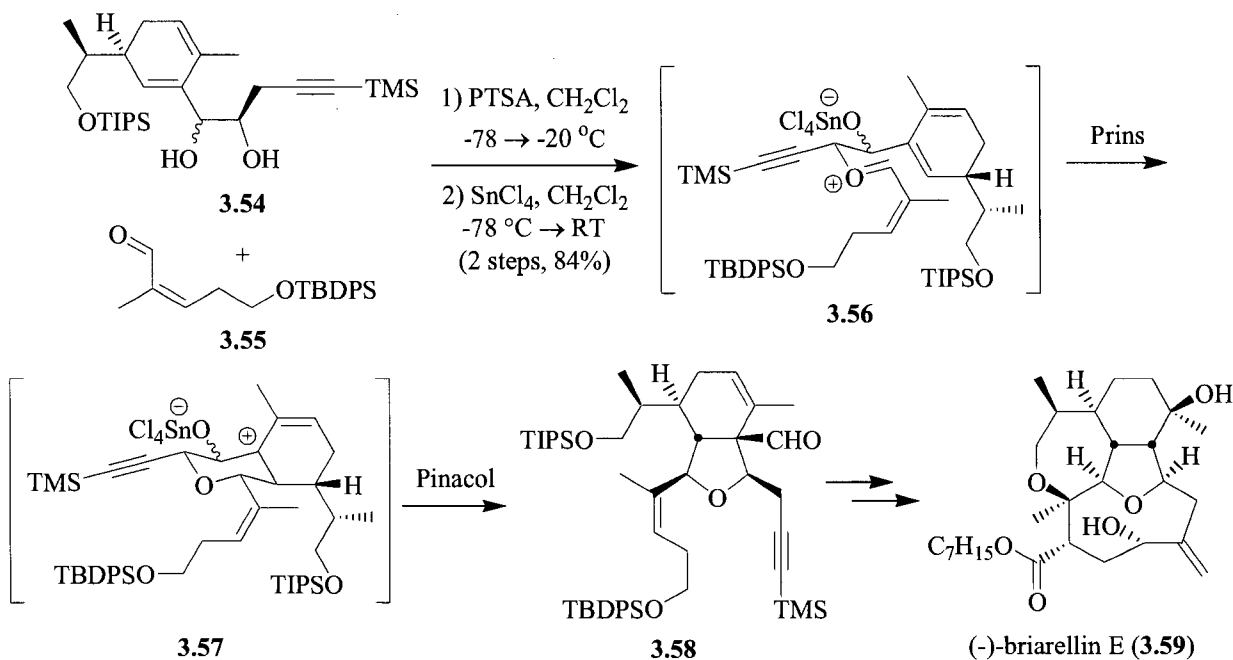
synthetic strategies. An elegant utilization of these approaches in total synthesis has given access to several natural products.⁴⁹ The rearrangement has mostly been employed to synthesize tetrahydrofuran-containing natural products such as ($\pm$)-*trans*-kumausyne (**3.50**) and (-)-citroviral (**3.53**) (Scheme 3.9).⁵⁰ The tetrahydrofuran cores of these molecules were constructed by using two variants of the methodology. In the case of compound **3.50**, the oxocarbenium ion was formed by condensation of allylic diol **3.47** with aldehyde **3.48**.⁵¹ The oxonium then underwent the Prins-Pinacol cascade to afford tetrahydrofuran **3.49** in 69% overall yield. The latter was further transformed into ($\pm$)-*trans*-kumausyne (**3.50**) in fourteen steps. In contrast, tetrahydrofuran **3.52** was obtained directly from allylic ketals **3.51**. Compound **3.52** was then converted to (-)-citroviral (**3.53**) in twelve steps.

Scheme 3.9 – Prins-Pinacol Synthesis of the Tetrahydrofuran Cores of **3.50** and **3.53**



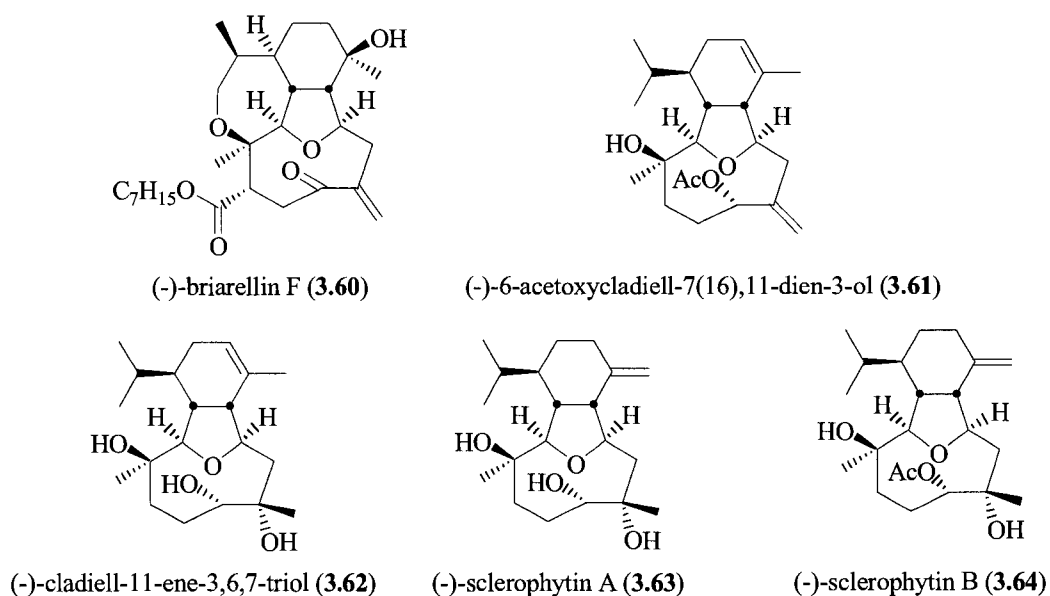
Additionally, the first total syntheses of numerous complex tetrahydrofuran-containing natural products of the C₂-C₁₁-cyclized cembranoid diterpene family were accomplished by using this methodology. For example, the bicyclic core of (-)-briarellin E (**3.59**) was assembled through the Prins-Pinacol condensation of chiral allylic diol **3.54** and aldehyde **3.55** (Scheme 3.10).⁵² Treatment with tin(IV) chloride brought about the formation of oxocarbenium **3.56**. Obviously, this oxonium was the preferred conformer since all its substituents occupied pseudoequatorial positions. As a result, the following Prins-Pinacol tandem reaction afforded tetrahydrofuran **3.58** as a single diastereomer in 84% overall yield.

Scheme 3.10 – Prins-Pinacol Synthesis of the Bicyclic Core of (-)-Briarellin E (3.59)



Desired natural product **3.59** could subsequently be obtained from tetrahydrofuran **3.58** in eighteen steps. Also, (-)-briarellin F (**3.60**) was obtained from **3.59** in one step (Figure 3.3). Furthermore, total syntheses of cladiellin diterpenes (-)-6-acetoxycladiell-7(16),11-dien-3-ol

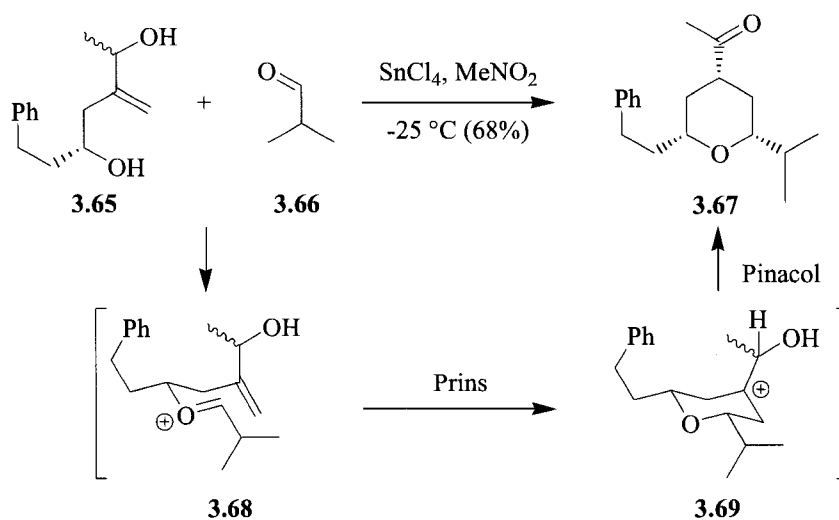
Figure 3.3 – Briarellin and Cladiellin Diterpenes Accessed by Total Synthesis



(**3.61**), (-)-cladiell-11-ene-3,6,7-triol (**3.62**), (-)-sclerophytin A (**3.63**) and (-)-sclerophytin B (**3.64**) could be achieved successfully by using the same strategy.⁵³

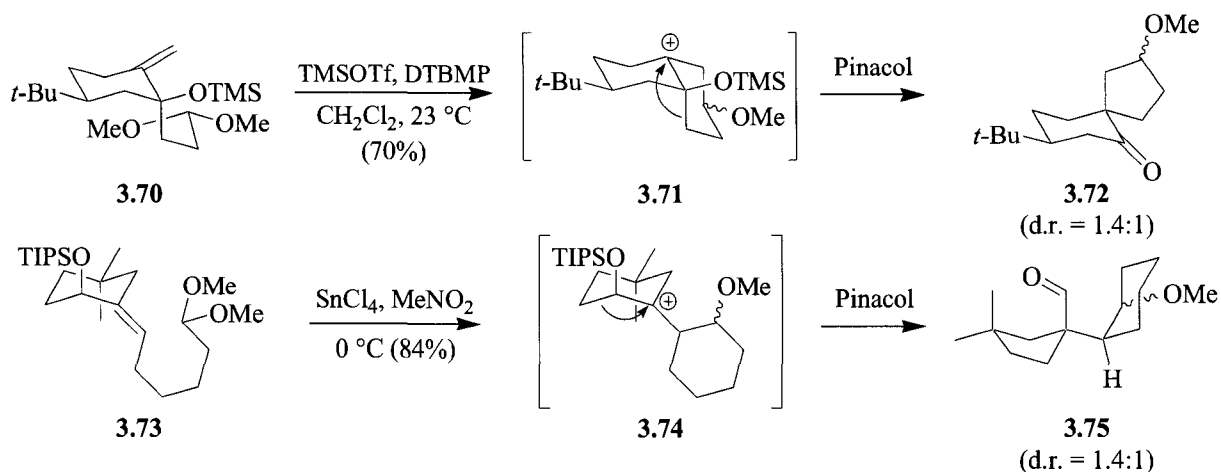
The Prins-Pinacol reaction has also been employed to construct molecules possessing a tetrahydropyran framework such as compound **3.67** (Scheme 3.11).⁵⁴ In that case, acid-mediated condensation of allylic diol **3.65** and aldehyde **3.66** first leads to formation of *E* oxocarbenium **3.68** having a pseudoequatorial side-chain. As usual, this oxonium then undergoes a Prins cyclization to afford corresponding cationic intermediate **3.69**. However, contrary to cyclic carbeniums involved in the production of tetrahydrofurans, the alcohol functionality of **3.69** is located outside the ring. Therefore, the pinacolic rearrangement induces an axial 1,2-hydride shift to generate ketone **3.67** in good yield.

Scheme 3.11 – Prins-Pinacol Synthesis of Tetrahydropyran Rings

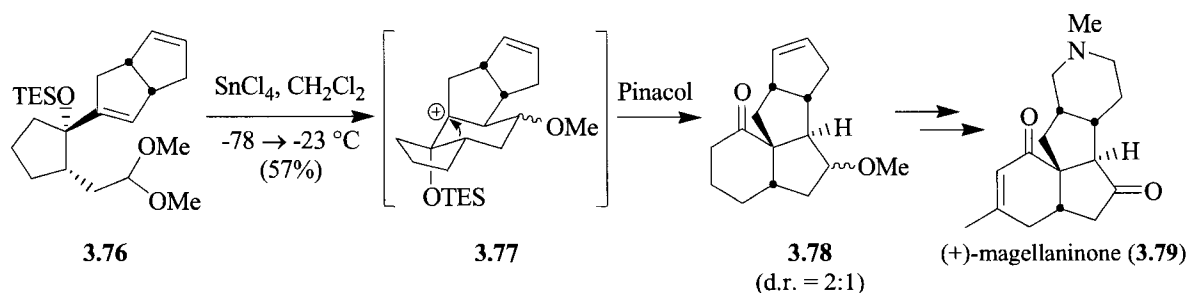


In addition to forming oxacyclic ring systems such as tetrahydrofurans and tetrahydropyrans, the Prins-Pinacol approach gives access to a wide range of molecules containing carbocyclic rings. For instance, several spirocyclic compounds such as **3.72** have been synthesized using this methodology (Scheme 3.12).⁵⁵ In this case, treatment of ketal **3.70** with TMSOTf generates cyclic carbenium **3.71**. During the subsequent pinacolic rearrangement, only the carbon-carbon bond that is periplanar to the vacant p orbital can migrate. Consequently, only spirocyclic ketone **3.72** is formed. This synthetic method can also lead to the formation

Scheme 3.12 – Prins-Pinacol Synthesis of Carbocyclic Ring Systems



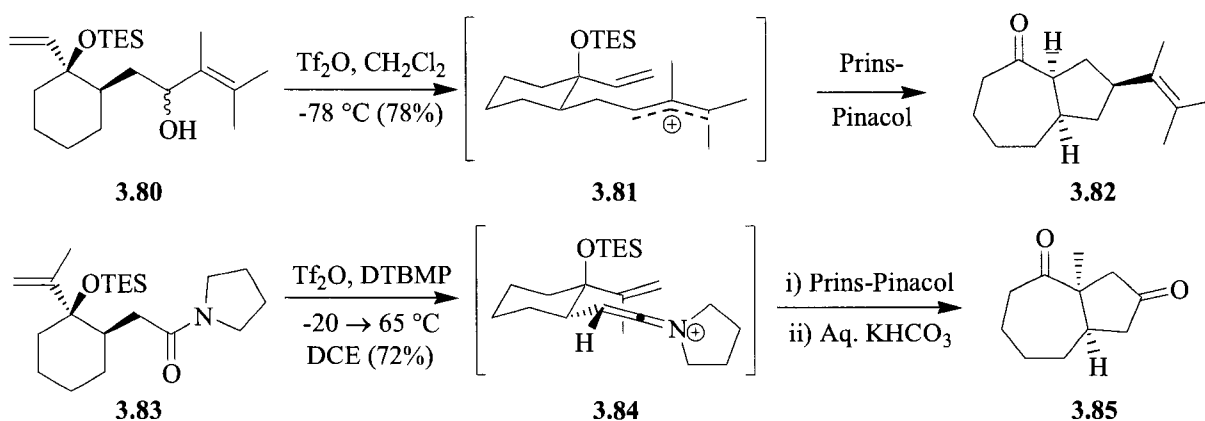
of molecules bearing attached rings.⁵⁶ For example, the ring contraction of cyclic carbenium **3.74** was facilitated by the good alignment of the migrating carbon-carbon bond with the empty p orbital. Consequently, aldehyde **3.75** was obtained in very good yield. Finally, the Prins-Pinacol rearrangement can be efficiently applied to the synthesis of *cis*-fused bicyclic compounds. The construction of the core of (+)-magellaninone (**3.79**) is an excellent illustration of this synthetic approach (Scheme 3.13).⁵⁷ In the course of this total synthesis, a ring-enlarging annulation of ketal **3.76** delivered carbocyclic core **3.78** in fair yield. The latter was then transformed into the desired natural product in fourteen steps.

Scheme 3.13 – Prins-Pinacol Synthesis of the Core of (+)-Magellaninone (**3.79**)

In most examples of the Prins-Pinacol rearrangement, the Prins cyclization is initiated by the formation of an oxocarbenium ion derived from an acetal or ketal. However, there are alternative methods to initiate the cyclization.⁵⁸ For instance, when allylic alcohol **3.80** is

treated with trifluoromethanesulfonic anhydride, allyl carbenium ion **3.81** is generated (Scheme 3.14). This carbocation can then undergo a Prins cyclization to afford the corresponding six-membered carbenium intermediate. The cascade reaction is then terminated by a pinacolic rearrangement of this carbocation, and *cis*-fused bicyclic ketone **3.82** is produced. Similarly, subjection of amide **3.83** to comparable conditions brings about the formation of keteniminium ion **3.84**. This intermediate can then go through the Prins-Pinacol cascade to yield a related iminium salt, which is hydrolyzed to afford diketone **3.85**.

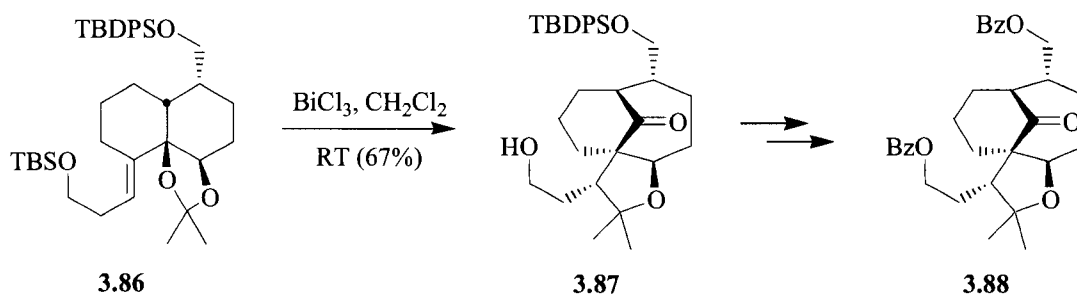
Scheme 3.14 – Alternative Cyclization Initiators



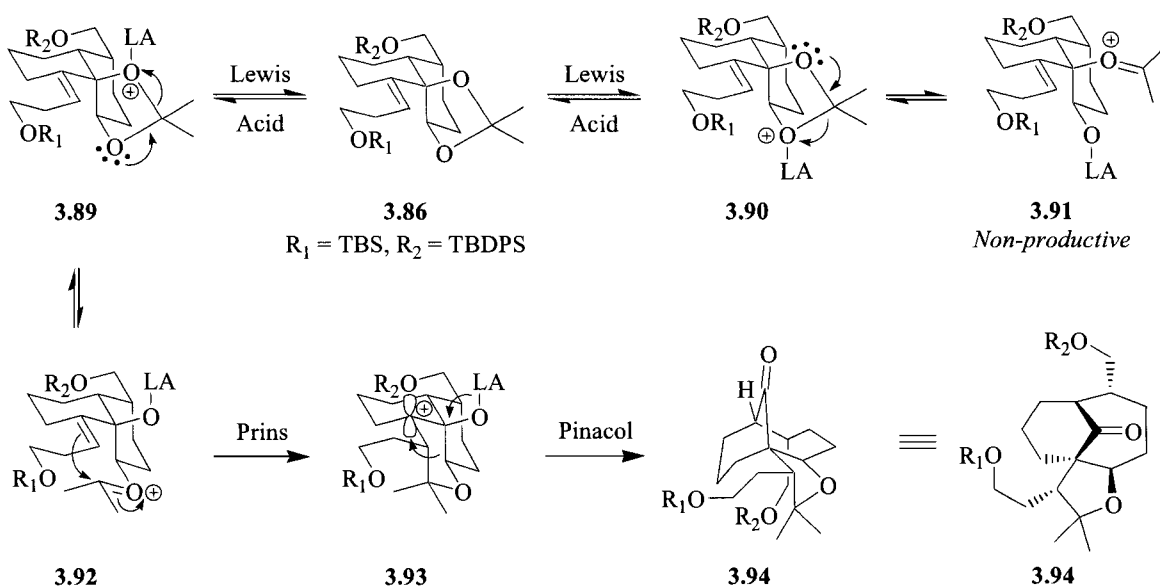
The Contribution of the Barriault Laboratory

In 2004, a novel application of the well-known Prins-Pinacol rearrangement was discovered in the laboratory of Professor Barriault. In the course of his efforts towards the synthesis of vinigrol, former Ph.D. student Louis Morency needed to remove the protecting group from isopropylidene **3.86** (Scheme 3.15).⁵⁹ After several unsuccessful attempts, compound **3.86** was treated with bismuth(III) chloride. As a result, the unexpected formation of bicyclo[4.3.1]decanone **3.87** was observed. The structure and stereochemistry of **3.87** were initially elucidated by NMR spectroscopy. They were subsequently confirmed by an X-ray crystallographic analysis of benzoate derivative **3.88**. A careful inspection of the structural features of **3.87** strongly suggested that the unanticipated reaction was indeed a Prins-Pinacol rearrangement. In fact, this result was the first example of a polycyclic bridged ketone being generated through such a reaction cascade. The proposed mechanism of formation of bridged

Scheme 3.15 – An Unanticipated Prins-Pinacol Rearrangement



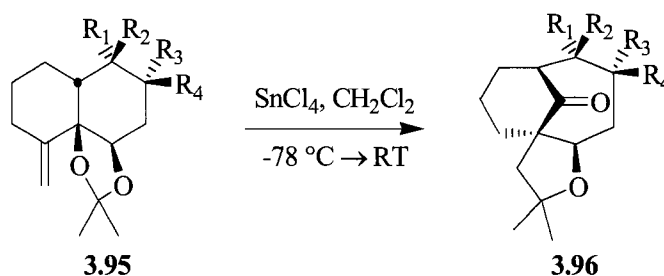
ketone **3.87** is illustrated in Scheme 3.16. In agreement with mechanistic investigations carried out by Overman and co-workers, treatment of isopropylidene **3.86** with a Lewis acid first produces a reactive oxocarbenium intermediate.^{43,44} Depending on which oxygen atom of the isopropylidene is activated by the Lewis acid (**3.89** vs **3.90**), both oxocarbeniums **3.91** and **3.92** are formed reversibly. In accordance with Baldwin rules, **3.91** cannot undergo a 5-*endo*-trig Prins cyclization because of poor orbital overlap.⁶⁰ However, the 6-*endo*-trig Prins cyclization of oxocarbenium **3.92** is favored and leads to cyclic carbenium **3.93**. Only one carbon-carbon bond of this carbocation is periplanar to the vacant p orbital. Hence, the following pinacolic rearrangement affords bicyclo[4.3.1]decanone **3.94** exclusively. Finally, Lewis-acid-mediated cleavage of the TBS protecting group delivers compound **3.87**.⁶¹

Scheme 3.16 – Mechanism of Formation for Bridged Ketone **3.87**

Significantly, this new application of the Prins-Pinacol rearrangement allows the introduction of considerable molecular complexity in the chemical system. Indeed, in a single synthetic step, a ring is enlarged, a tetrahydrofuran ring and a bridged ketone are formed, and two chiral centers are stereoselectively introduced.

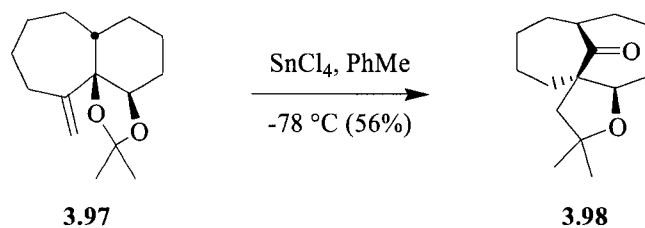
Shortly after its discovery, a systematic investigation of this variant of the Prins-Pinacol rearrangement was undertaken. Former M.Sc. students Roch Lavigne and Méline Girardin greatly contributed to the development of this methodology. Through his work, Roch Lavigne demonstrated that the reaction is general for bicyclo[4.3.1]decanones such as **3.96**. More specifically, several substituted substrates of type **3.95** were studied (Table 3.2) and it appeared that ring substitution has a positive influence on the reaction outcome.⁶² He also applied the rearrangement to the synthesis of bicyclo[4.4.1]undecanone **3.98** (Scheme 3.17).

Table 3.2 – Effect of the Substitution on the Formation of Bicyclo[4.3.1]decanones



Entry	R ₁	R ₂	R ₃	R ₄	Yield (%)
1	H	H	H	H	61
2	CH ₂ ODPS	H	H	H	86
3	CH ₂ OBn	H	CH ₂ OBn	H	81
4	CH ₂ OBn	H	H	CH ₂ OBn	85
5	H	CH ₂ OBn	CH ₂ OBn	H	90

Roch Lavigne further extended this methodology to the development of a Diels-Alder/Prins-Pinacol tandem reaction (Table 3.3).⁶² Through this reaction cascade, a Gassman dienophile (**3.99**) is first activated by the Lewis acid and then undergoes an ionic Diels-Alder reaction with diene **3.100**.⁶³ This cycloaddition generates intermediate **3.101**, which bears the alkene

Scheme 3.17 – Prins-Pinacol Synthesis of Bicyclo[4.4.1]undecanone **3.98**

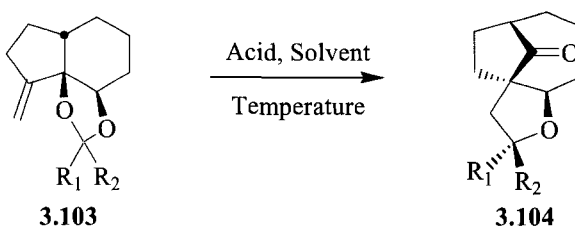
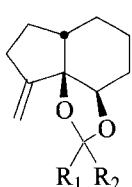
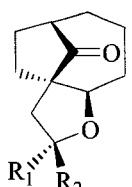
moiety required for the Prins cyclization. A Lewis-acid-mediated opening of the ketal functionality of intermediate **3.101** then triggers the Prins-Pinacol rearrangement, which finally delivers bicyclo[4.3.1]decanone **3.102**. This outstanding one-pot transformation results in the formation of four carbon-carbon bonds with concomitant introduction of up to five stereocontrolled chiral centers. During the optimization of this reaction, various Gassman dienophiles were examined. An excellent yield was observed when R_1 and R_2 were hydrogens (entry 1). However, increased substitution led to lower yields (entries 2-4).

Table 3.3 – Development of the Diels-Alder/Prins-Pinacol Tandem Reaction

Entry	R_1	R_2	Lewis Acid (equiv.)	Yield (%)
1	H	H	SnCl ₄ (1.0), TMSOTf (0.25)	96
2	Me	H	SnCl ₄ (1.0)	62
3	Me	Me	SnCl ₄ (3.0), TMSOTf (0.25)	44
4	-(CH ₂) ₄ -		SnCl ₄ (3.0), TMSOTf (0.25)	10

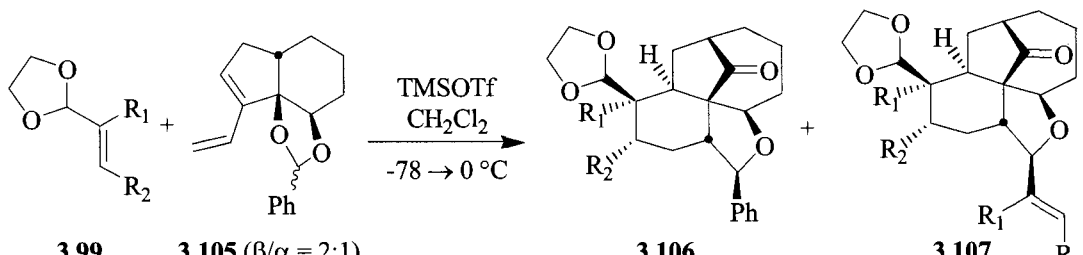
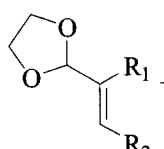
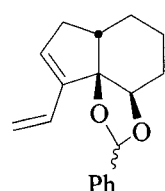
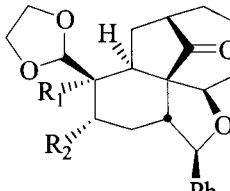
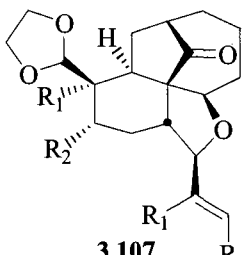
Mélina Girardin established that the Prins-Pinacol rearrangement could also be employed to generate bicyclo[4.2.1]nonanones such as **3.104** (Table 3.4).⁶⁴ She more particularly studied

Table 3.4 – Prins-Pinacol Synthesis of Bicyclo[4.2.1]nonanones

						
 3.103 $\xrightarrow[\text{Temperature}]{\text{Acid, Solvent}}$  3.104						
Entry	R ₁	R ₂	Acid	Solvent	Temperature (°C)	Yield (%)
1	Me	Me	TfOH	MeCN	0	94
2	H	Me	TMSOTf	CH ₂ Cl ₂	-78 → 0	90
3	H	Ph	TMSOTf	CH ₂ Cl ₂	-78	Quant.
4	H		TfOH	MeCN	-40 → 0	96

the effect of the nature of the ketal or acetal functionality on the outcome of the reaction. The utilization of different Lewis and Brønsted acids was also examined. Ultimately, the isopropylidene ketal (entry 1) and the ethylidene (entry 2), benzylidene (entry 3) and methallylidene (entry 4) acetals all afforded corresponding bridged ketone **3.104** in excellent yields. She then applied these findings to the Diels-Alder/Prins-Pinacol reaction (Table 3.5).

Table 3.5 – Further Development of the Diels-Alder/Prins-Pinacol Tandem Reaction

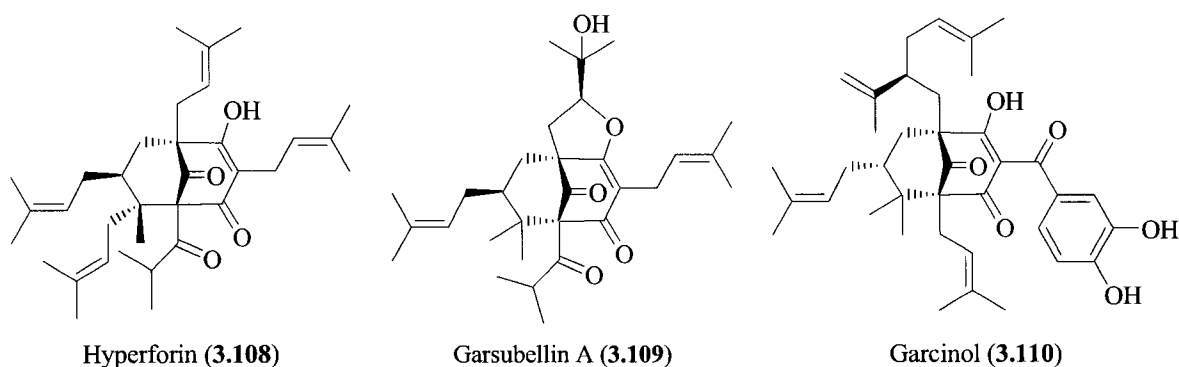
				
 3.99  3.105 (β/α = 2:1) $\xrightarrow[\text{-78} \rightarrow \text{0}^\circ\text{C}]{\text{TMSOTf, CH}_2\text{Cl}_2}$  3.106  3.107				
Entry	R ₁	R ₂	Yield 3.106 (%)	Yield 3.107 (%)
1	H	H	53	---
2	Me	H	38	17
3		-(CH ₂) ₄ -	37	19

Interestingly, when a mixture composed of Gassman dienophile **3.99** and diene **3.105** was treated with trimethylsilyl trifluoromethanesulfonate, two different bicyclo[4.2.1]nonanones (**3.106** and **3.107**) were formed. It was rationalized that bridged ketone **3.107** originated from a transacetalization of **3.105** with **3.99**, followed by the expected Diels-Alder/Prins-Pinacol tandem reaction. Employing an unsubstituted dienophile generated the desired product in fair yield (entry 1). However, substitution of the dienophile lowered the yield of **3.106** and increased the amount of byproduct formed (entries 2-3).

Prins-Pinacol Synthesis of Bicyclo[3.3.1]nonanones

As pointed out beforehand, the Prins-Pinacol reaction allows the rapid and stereocontrolled construction of highly functionalized polycyclic bridged ketones. Such impressive synthetic capabilities obviously render this rearrangement attractive for an application in total synthesis. Indeed, numerous natural products present a bicyclic bridged ketone in their framework. More particularly, several members of the polycyclic polyprenylated acylphloroglucinol (PPAP) family exhibiting a bicyclo[3.3.1]nonanone skeleton have been isolated and characterized in the recent years.⁶⁵ Hyperforin (**3.108**), garsubellin A (**3.109**) and garcinol (**3.110**) are representative of this class of natural products (Figure 3.4).

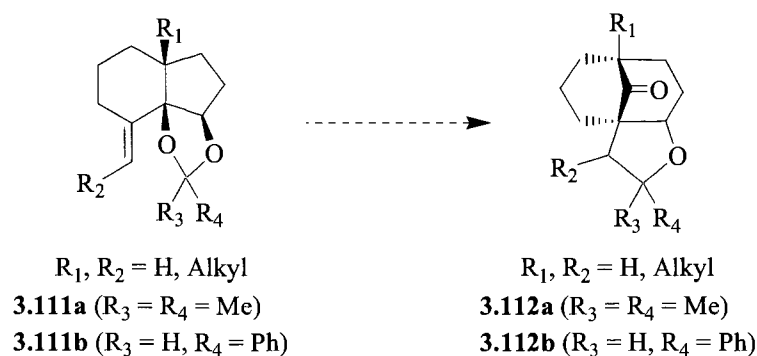
Figure 3.4 – PPAP Natural Products Possessing a Bicyclo[3.3.1]nonanone Core



Having in mind these synthetic considerations, we decided to examine the construction of model bicyclo[3.3.1]decanones **3.112** by employing the Prins-Pinacol methodology (Figure 3.5). We therefore synthesized and evaluated the reactivity of a series of bicyclo[4.3.0]nonane

Prins-Pinacol substrates bearing either an isopropylidene ketal (**3.111a**) or a benzylidene acetal (**3.111b**). Substitution at the ring junction and at the alkene was also examined.

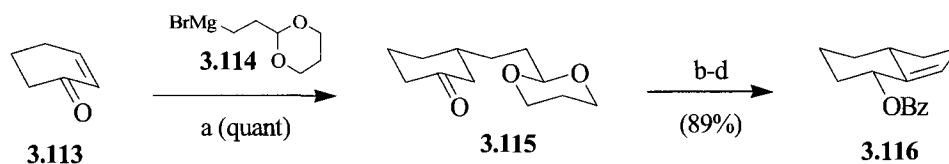
Figure 3.5 – General Structure of the Prins-Pinacol Precursors and Products



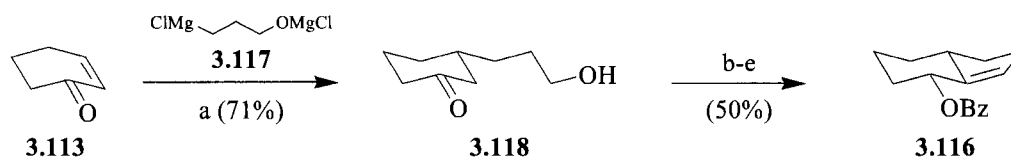
Evaluation of Isopropylidene Prins-Pinacol Precursors

The synthesis of the first Prins-Pinacol precursor began by the formation of benzoate **3.116** (Scheme 3.18). The initial copper-catalyzed conjugate addition of Grignard reagent **3.114** to cyclohexenone (**3.113**) quantitatively afforded ketone **3.115**.⁶⁶ This ketone then underwent an acid-mediated aldol cyclization that delivered the corresponding enone.⁶⁷ Due to its relative volatility, this compound was not purified. It was therefore directly reduced under the conditions developed by Luche to afford the related alcohol as a single diastereomer.⁶⁸ Yet again, this intermediate was used in the following step without purification to afford benzoate **3.116** in excellent overall yield. Undeniably, this first synthesis of compound **3.116** was very efficient. However, the cuprate addition step was rather unreliable and occasionally

Scheme 3.18 – Original Synthesis of Benzoate **3.116**



Reagents and conditions: (a) i. $\text{CuBr} \cdot \text{SMe}_2$, HMPA, TMSCl , THF, -78°C ; ii. **3.114**, THF, $-78^\circ\text{C} \rightarrow \text{RT}$; (b) 6N HCl , THF, RT; (c) NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, $\text{MeOH/Et}_2\text{O}$, 0°C ; (d) BzCl , Pyridine, DMAP, CH_2Cl_2 , RT.

Scheme 3.19 – Alternative Synthesis of Benzoate **3.116**

Reagents and conditions: (a) **3.117**, CuBr·SMc₂, THF, -20 °C → 0 °C; (b) i. (COCl)₂, DMSO, CH₂Cl₂, -78 °C; ii. Et₃N, 0 °C; (c) 6N HCl, THF, RT; (d) NaBH₄, CeCl₃·7H₂O, MeOH/Et₂O, 0 °C; (e) BzCl, Pyridine, DMAP, CH₂Cl₂, RT.

led to low conversions. In view of that, an alternative route was designed to access benzoate **3.116** (Scheme 3.19). This synthetic sequence also began with the copper-catalyzed conjugate addition of a Grignard reagent to enone **3.113**. For that purpose, organomagnesium compound **3.117** was prepared in one step from 3-chloropropanol.⁶⁹ The following 1,4-addition afforded primary alcohol **3.118** in 71% yield. Subsequent Swern oxidation afforded the corresponding aldehyde.²³ Because of the low stability of the crude product, the following aldol cyclization was performed without delay. Finally, transformation of the resulting enone into the desired benzoate was carried out in the same way as previously. Compound **3.116** was thus obtained in 50% overall yield from alcohol **3.118**. This alternative sequence was evidently lengthier and lower-yielding than the first route. However, no reliability problems were encountered in the 1,4-addition step. Moreover, because of the low cost of 3-chloropropanol, this route was more economical than the first one. For these reasons, variants of this route were employed for the synthesis of bicyclo[4.3.0]nonenes such as **3.116**.

The synthesis of Prins-Pinacol precursor **3.124** was completed in six steps from benzoate **3.116** (Scheme 3.20). An attempted dihydroxylation of **3.116** was performed at room temperature and failed to deliver *cis*-diol **3.119**. Nonetheless, employing more forcing conditions solved that difficulty, and the desired diol was obtained as a single diastereomer in 54% yield. Compound **3.119** was then reacted with 2-methoxypropene in the presence of PTSA, and isopropylidene **3.120** was produced in high yield. Cleavage of the benzyl ester under mildly basic conditions efficiently furnished alcohol **3.121**, which underwent a Dess-Martin oxidation to give ketone **3.122** in excellent yield.³² The *cis* relationship between the

hydrogen at the ring junction and the isopropylidene ketal was confirmed at that stage by crystallographic analysis (Figure 3.6). The final transformation of the ketone into a methylene group was completed in two steps. Indeed, alkylation of the ketone with methyllithium yielded tertiary alcohol **3.123**, which was eliminated by treatment with thionyl chloride and DMAP to furnish the desired Prins-Pinacol precursor in good yield.⁷⁰

Scheme 3.20 – Synthesis of Prins-Pinacol Precursor 3.124

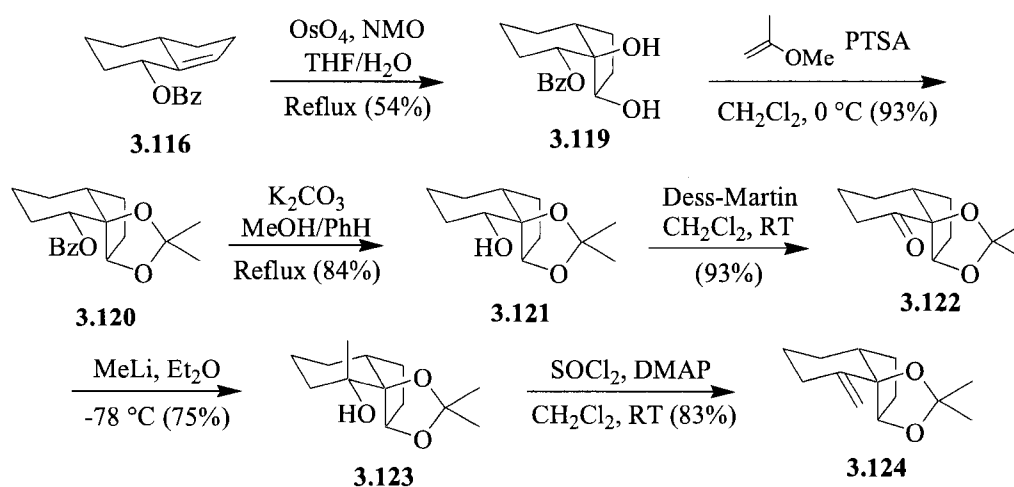
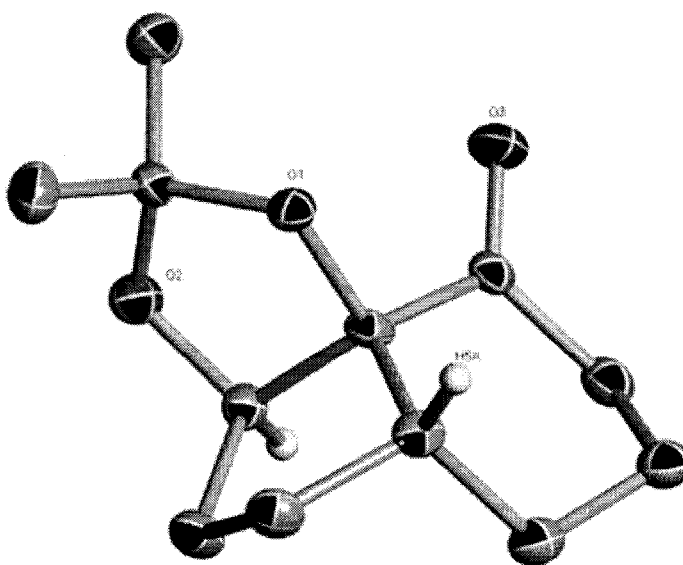
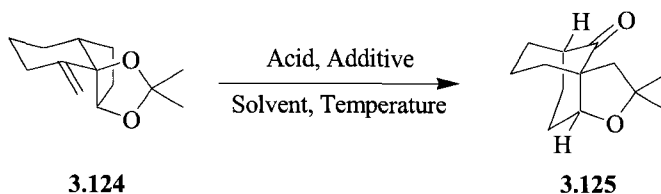


Figure 3.6 – X-Ray Crystallographic Structure of Ketone 3.122



Having alkene **3.124** in hand, the Prins-Pinacol rearrangement of a first bicyclo[4.3.0]nonane substrate was examined. A selection of Lewis acids was therefore investigated (Table 3.6). Treatment of alkene precursor **3.124** with zinc(II) bromide and dimethylaluminum chloride yielded no reaction (entries 1-2). Utilization of bismuth(III) and titanium(IV) chloride led to desired ketone **3.125**, albeit in poor yield (entries 3-4). Disappointed by these results, we turned to the conditions employed by Overman (tin tetrachloride in dichloromethane), but the

Table 3.6 – Optimization of the Prins-Pinacol Reaction of **3.124** with Lewis Acids



Entry	Acid (equiv.)	Additive (equiv.)	Solvent	Temperature (°C)	Yield (%)
1	ZnBr ₂ (1.2)	---	CH ₂ Cl ₂	RT	No reaction
2	Me ₂ AlCl (4.0)	---	CH ₂ Cl ₂	RT	No reaction
3	BiCl ₃ (2.0)	---	CH ₂ Cl ₂	RT	10
4	TiCl ₄ (1.2)	---	CH ₂ Cl ₂	-78	21
5	SnCl ₄ (1.2)	---	CH ₂ Cl ₂	-78 → RT	25
6	SnCl ₄ (1.2)	---	hexanes	-78 → RT	39
7	SnCl ₄ (1.2)	---	MeNO ₂	-20 → RT	45
8	SnCl ₄ (1.2)	---	PhCl	-20 → RT	49
9	SnCl ₄ (1.2)	---	PhMe	-78 → RT	55
10	GaCl ₃ (1.2)	---	CH ₂ Cl ₂	-78 → RT	30
11	GaCl ₃ (1.2)	---	PhMe	-78 → RT	55
12	TMSOTf (1.2)	---	CH ₂ Cl ₂	-78 → RT	34
13	TMSOTf (2.0)	---	PhMe	-78 → RT	37
14	SnCl ₄ (1.0)	TMSOTf (1.0)	CH ₂ Cl ₂	-78 → RT	31
15	SnCl ₄ (1.0)	TMSOTf (1.0)	CH ₂ Cl ₂	-78 → RT	36
16	SnCl ₄ (1.0)	2,2'-biphenol (2.0)	CH ₂ Cl ₂	-78 → RT	36
17	SnCl ₄ (1.0)	2,2'-biphenol (2.0)	PhMe	-78 → RT	57

desired ketone was obtained in 25% yield only (entry 5). Nonetheless, changing the solvent to hexanes significantly improved the yield (entry 6). Also, further increases in yield were observed when nitromethane, chlorobenzene and toluene were used (entries 7-9). Gallium(III) chloride behaved similarly to tin(IV) chloride (entries 10-11). Interestingly, these two Lewis acids exhibited a 25% yield enhancement when dichloromethane was replaced with toluene. This trend was however not followed with trimethylsilyl trifluoromethanesulfonate, which gave a maximal yield of 37% (entries 12-13). Combining tin(IV) chloride with trimethylsilyl trifluoromethanesulfonate had no impact on the reaction outcome (entries 14-15). Similarly, addition of a diol for coordination with SnCl_4 did not considerably improve the yield (entries 16-17).

In the course of his studies, Roch Lavigne reacted a Prins-Pinacol precursor with tin(IV) chloride in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), a hindered base. To his surprise, this additive prevented any reaction from occurring. He obtained the same result when TMSOTf was used.⁶² These experiments furnished evidence that our rearrangement is not promoted by a Lewis acid, but by traces of a protic acid present in the reaction mixture. For some substrates described by Overman, however, the presence of DTBMP is not detrimental to the Lewis-Acid-mediated Prins-Pinacol rearrangement.⁵⁵ This can be explained by the relative size of these acids. Bicyclo[4.3.0]nonane substrates such as **3.124** being more hindered than most precursors reported by Overman, the reaction might be catalyzed by a proton but not by a bulkier Lewis acid. For that reason, the reaction of **3.124** with a few Brønsted acids was examined (Table 3.7). Treatment with *p*-toluenesulfonic acid was unsuccessful (entry 1), but both methanesulfonic and trifluoromethanesulfonic acids brought about the formation of ketone **3.125** (entries 2-3). The observed yields, nonetheless,

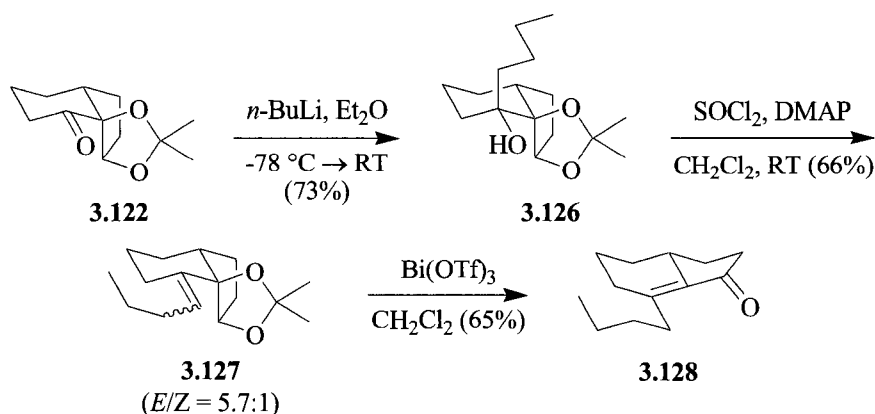
Table 3.7 – Optimization of the Prins-Pinacol Reaction of **3.124** with Brønsted Acids

Entry	Acid (equiv.)	Solvent	Temperature (°C)	Yield (%)
1	PTSA	CH_2Cl_2	0 $\rightarrow$ RT	No reaction
2	$\text{CH}_3\text{SO}_3\text{H}$ (4.0)	CH_2Cl_2	-78 $\rightarrow$ RT	33
3	TfOH (2.0)	MeCN	-20 $\rightarrow$ RT	52

were lower than with tin(IV) chloride. It appeared from optimization results that gallium(III) chloride and tin(IV) chloride were the best promoters for this Prins-Pinacol rearrangement. However, because solutions of tin(IV) chloride are commercially available, we decided to use this Lewis acid for further examination of the Prins-Pinacol rearrangement of bicyclo[4.3.0]nonane substrates.

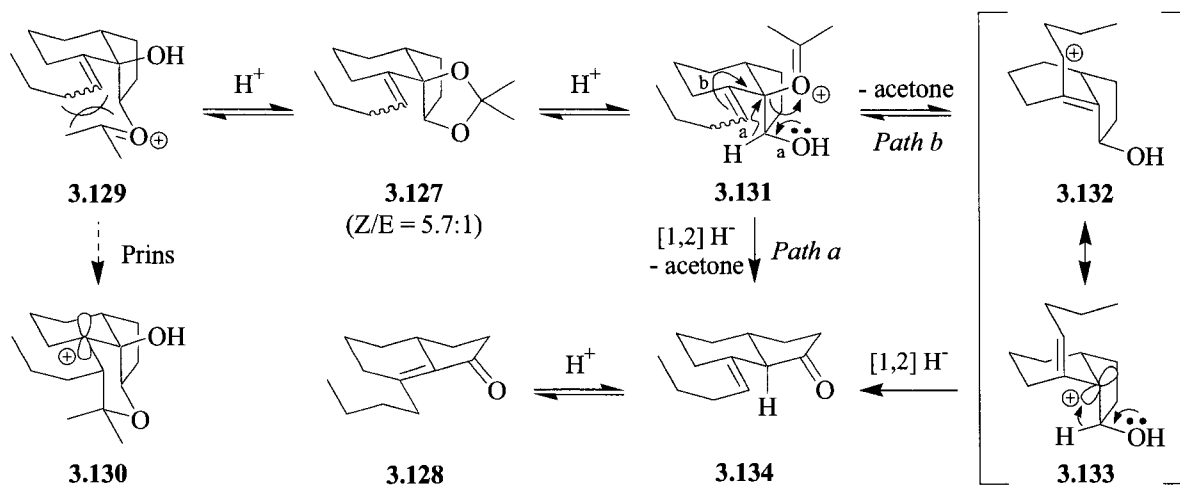
We then briefly studied the influence of alkene substitution. Prins-Pinacol precursor **3.127** was thus synthesized in two steps from ketone **3.122** (Scheme 3.21). Treatment of the ketone with *n*-butyllithium gave tertiary alcohol **3.126** as a single diastereomer in good yield. The stereochemistry of the new stereocenter was not determined and is assumed to be that illustrated in Scheme 3.21. The alcohol then underwent an elimination to yield alkene **3.127** as a mixture of geometrical isomers.⁷⁰ This precursor was then exposed to the optimized Prins-Pinacol conditions, but only starting material was recovered. Nonetheless, when alkene **3.127** was treated with bismuth(III) trifluoromethanesulfonate, enone **3.128** was formed in 65% yield. The formation of this enone was unexpected, but could be explained by the mechanism proposed in Scheme 3.22. As discussed earlier, the acid-mediated opening of isopropylidene substrates generates two distinct oxocarbenium ions that are in equilibrium. One of them can undergo the Prins cyclization, but the other is not productive and regenerates the starting material. In the case of substrate **3.127**, the steric hindrance caused by the alkene propyl chain most probably prevents the Prins cyclization (**3.129** $\rightarrow$ **3.130**) from occurring. Consequently, the competing loss of acetone from unproductive carbenium **3.131**

Scheme 3.21 – Effect of Substitution of the Alkene

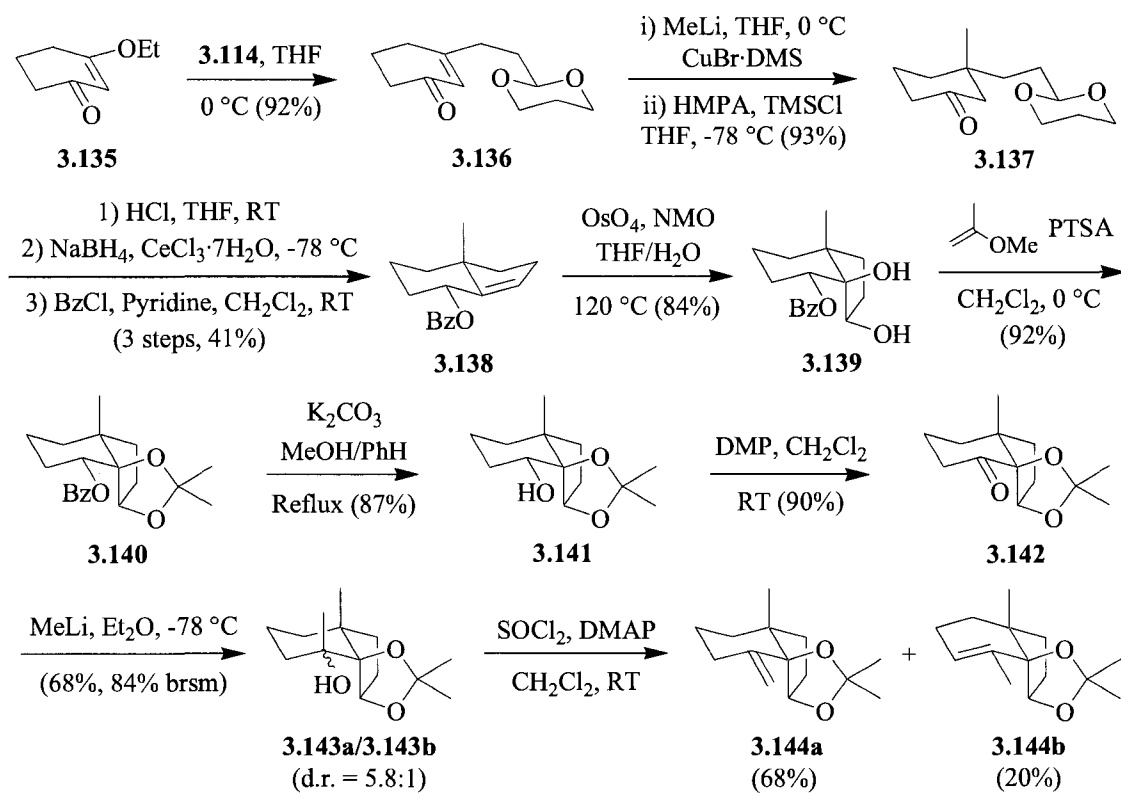
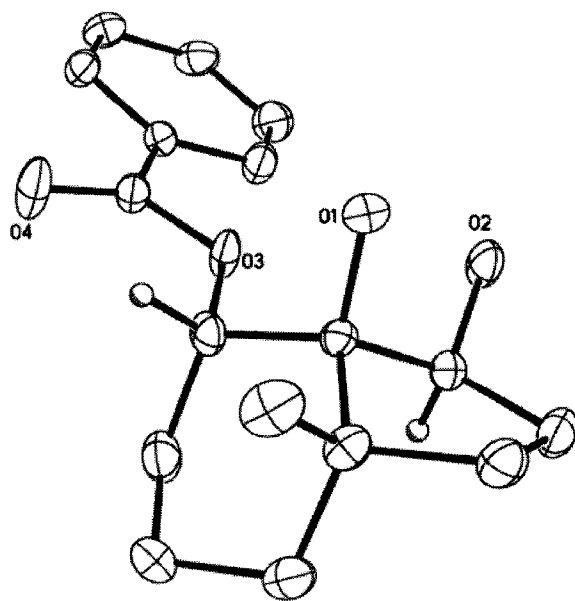


3.131 becomes the major reaction pathway. Ketone **3.134** can then be generated in two different ways. An oxygen-assisted [1,2] hydride shift concomitant with the departure of acetone gives **3.134** directly (path a). This ketone can also be formed in a stepwise fashion (path b). In that case, the expulsion of acetone initially generates tertiary allylic carbocation **3.132**, which then undergoes the [1,2] hydride shift to deliver ketone **3.134**. An acid-mediated conjugation of the alkene with the carbonyl finally delivers thermodynamically more stable enone **3.128**. After appropriate verification, we found that Overman indeed observed such a side-product in a similar system.⁷¹ It appeared from these results that substitution of the alkene might be a limitation of our methodology.

Scheme 3.22 – Proposed Mechanism of Formation for Enone 3.128

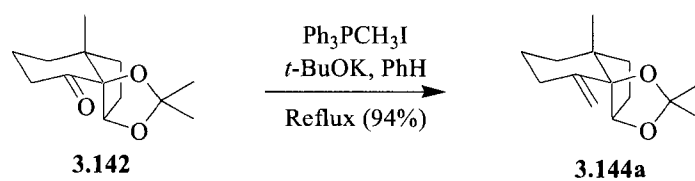


We then carried out a brief evaluation of the effect of the substitution at the ring junction. To this end, we synthesized a Prins-Pinacol precursor bearing a methyl group at this position. Indeed, alkene **3.144a** was constructed in eleven steps from enol ether **3.135** (Scheme 3.23). This enol ether was first converted to enone **3.136** through the high-yielding addition of organomagnesium reagent **3.114**.⁶⁷ Then, in a modification of the conditions developed by Spencer and co-workers, the copper-mediated conjugate addition of methyllithium to enone **3.136** yielded ketone **3.137** in near-quantitative yield.⁷² This ketone was transformed into benzoate **3.138** through the same three-step sequence as described previously. The following dihydroxylation required high temperatures, but afforded diol **3.139** as a single diastereomer in 84% yield. The *cis* relationship between the methyl at the ring junction and the diol was

Scheme 3.23 – Original Synthesis of Prins-Pinacol Precursor **3.144a**Figure 3.7 – X-Ray Crystallographic Structure of Diol **3.139**

confirmed at that stage by crystallographic analysis (Figure 3.7). Ketalization of the diol yielded isopropylidene **3.140** in good yield. This compound was then converted in high yield to ketone **3.142** by sequential ester hydrolysis and alcohol oxidation.³² Addition of methyllithium to this ketone afforded epimeric alcohols **3.143**. Elimination of these alcohols in the usual way yielded a mixture of exocyclic alkene **3.144a** and internal alkene **3.144b**.⁷⁰ Unfortunately, desired alkene **3.144a** could not be separated from the unwanted isomer. To generate selectively the exocyclic alkene, a direct olefination method was required. After a disappointing first exploration of the Wittig olefination, we turned to a method developed by Conia.⁷³ Using a modification of this methodology, isomerically pure alkene precursor **3.144a** could be obtained from ketone **3.142** in 94% yield (Scheme 3.24).

Scheme 3.24 – Improved Synthesis of Prins-Pinacol-Precursor **3.144a**



The Prins-Pinacol rearrangement of alkene **3.144a** was then examined (Table 3.8). When this precursor was treated with tin(IV) chloride in dichloromethane, desired bridged ketone **3.145** was obtained in 45% yield (entry 1). Changing the solvent for toluene had little effect on the

Table 3.8 – Prins-Pinacol Reaction of Substrate **3.144a**

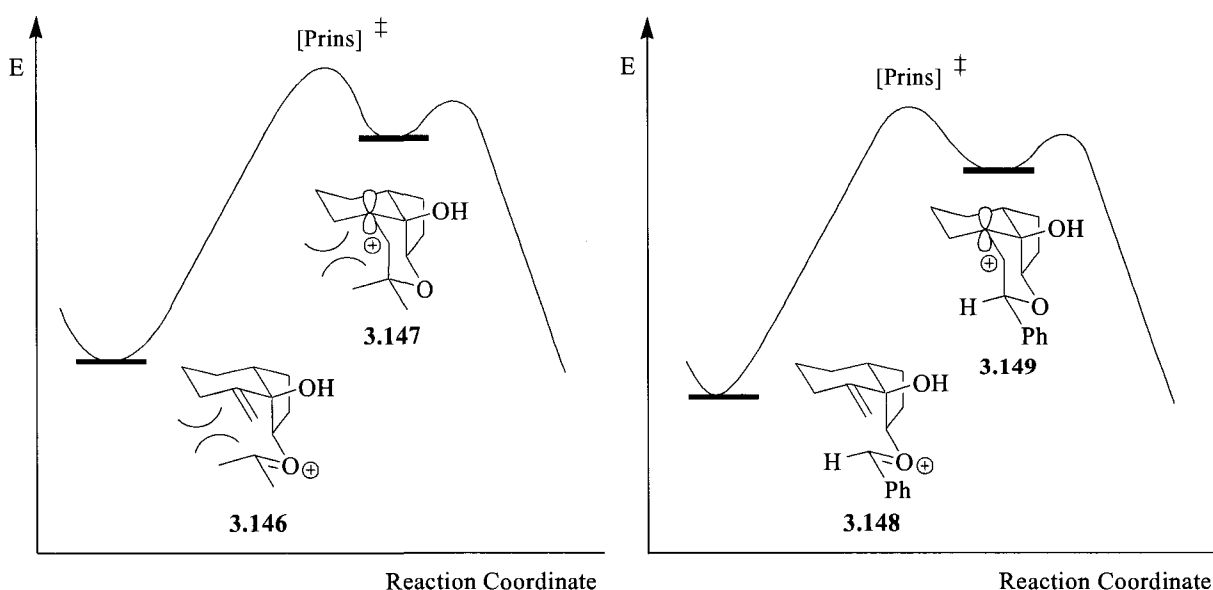
<chem>CC1(C)OC2(C)C(C)C(C)C2OC1=C</chem> $\xrightarrow[\text{Temperature}]{\text{Acid, Solvent}}$ <chem>CC1(C)OC2(C)C(C)C(C)C2OC1=O</chem>				
3.144a 3.145				
Entry	Acid (equiv.)	Solvent	Temperature (°C)	Yield (%)
1	SnCl ₄ (1.7)	CH ₂ Cl ₂	-78 → RT	45
2	SnCl ₄ (2.2)	PhMe	-78 → RT	49
3	TfOH (2.0)	MeCN	-20 → RT	78

yield (entry 2). These two results seemed to indicate that the presence of a small alkyl group at the ring junction has no significant influence on the Prins-Pinacol rearrangement. We were however pleased to see that treatment of **3.144a** with TfOH yielded the desired ketone in 78% yield (entry 3). Even though there was no obvious explanation for this surprisingly high yield, we decided to test both of these acids in all forthcoming Prins-Pinacol reactions.

Evaluation of a Benzylidene Prins-Pinacol Precursor

After the evaluation of a few substrates, we established that the Prins-Pinacol rearrangement of isopropylidene precursors led, as expected, to the formation of the corresponding bicyclo[3.3.1]nonanones. Nonetheless, the observed yields were considerably inferior to those previously reported for the synthesis of bicyclo[4.3.1]decanones and bicyclo[4.2.1]nonanones. In order to improve the effectiveness of the reaction, we turned to chemistry developed by Mousset in the 1970s. As pointed out at the beginning of the present chapter, he reported that the yield of the Prins-Pinacol reaction could be improved by replacing the isopropylidene ketal by a sterically less hindered benzylidene acetal.⁴⁰ This beneficial effect can be explained by comparing the transition states for these two precursors (Figure 3.8).

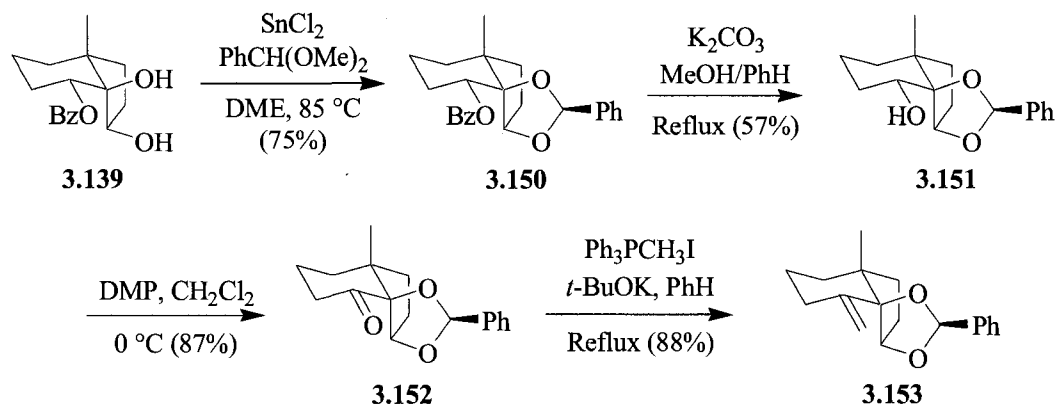
Figure 3.8 – Comparison of Transition State Energies for **3.146** and **3.148**



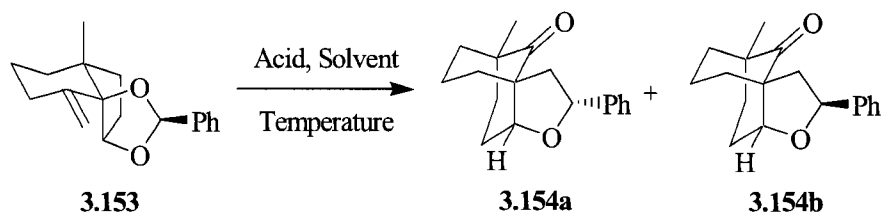
Because of the steric repulsion between the ketal and the six-membered ring, the productive oxocarbenium derived from an isopropylidene precursor (**3.146**) should be higher in energy than its benzylidene counterpart (**3.148**). This unfavorable steric interaction should indeed be avoided in **3.148** because of the pseudoequatorial orientation of the phenyl. Oxocarbenium **3.148** should also be stabilized by conjugation with the phenyl group. Consequently, the transition state energy for the Prins cyclization should be lower for the benzylidene substrate (**3.148** $\rightarrow$ **3.149**) than for the isopropylidene precursor (**3.146** $\rightarrow$ **3.147**), leading to improved reaction efficacy.

We therefore decided to examine the reactivity of a Prins-Pinacol precursor bearing a benzylidene acetal. Alkene substrate **3.153** was thus synthesized in four steps from diol **3.139** (Scheme 3.25). Treatment of this diol with benzylidene dimethyl acetal in the presence of catalytic stannous chloride yielded benzylidene **3.150** as the major component of an 8:1 mixture of epimers.⁷⁴ Subsequent hydrolysis of the ester, followed by oxidation of the alcohol and Conia olefination afforded the desired Prins-Pinacol precursor in good yield.^{32,73}

Scheme 3.25 – Synthesis of Prins-Pinacol Precursor **3.153**



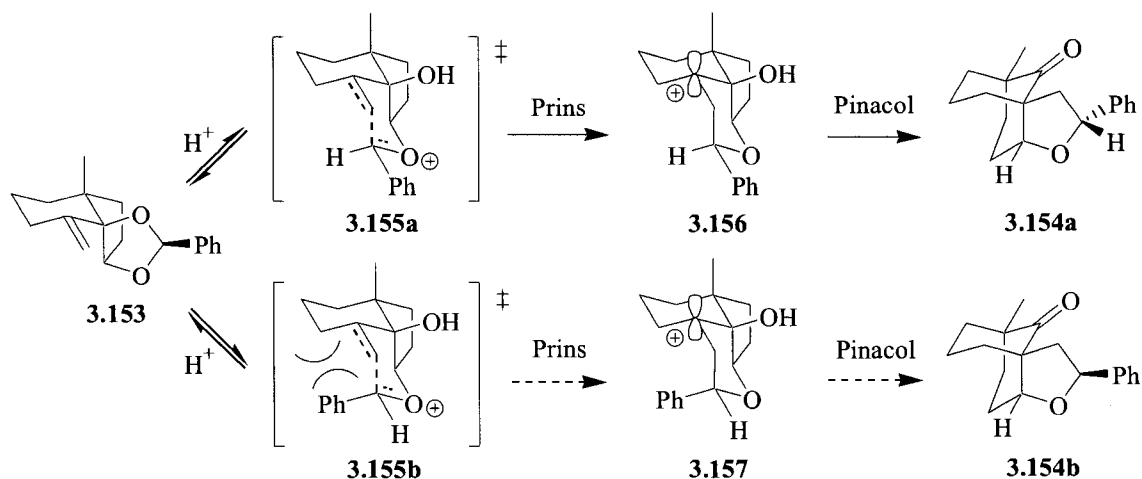
The Prins-Pinacol rearrangement of this substrate could then be evaluated (Table 3.9). Gratifyingly, treatment of alkene **3.153** with tin(IV) chloride in dichloromethane or toluene afforded ketone **3.154a** as a single diastereomer in near-quantitative yield (entries 1-2). The relative stereochemistry of this product was determined by 2D NMR experiments.⁷⁵

Table 3.9 – Prins-Pinacol Reaction of Substrate **3.153**

Entry	Acid (equiv.)	Solvent	Temperature (°C)	3.154a (%)	3.154b (%)
1	SnCl ₄ (1.2)	CH ₂ Cl ₂	-78 → RT	97	---
2	SnCl ₄ (1.2)	PhMe	-78 → RT	97	---
3	TfOH (2.0)	MeCN	-20 → RT	64	31

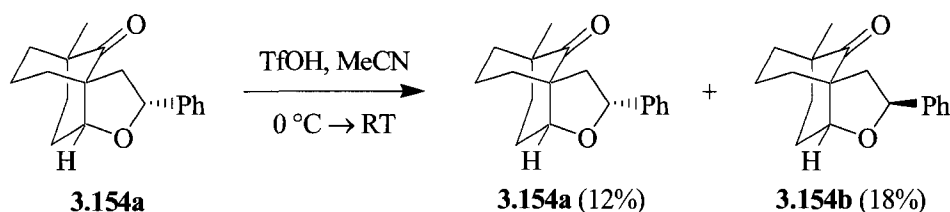
The complete stereoselectivity of this reaction can well be explained by comparing transition states **3.155** (Scheme 3.26). Addition of acid to alkene **3.153** brings about the reversible formation of these two intermediates. In order to minimize steric interactions, the bulky phenyl group will preferably occupy the pseudoequatorial position (**3.155a**) in the transition state. Consequently, only cyclic carbenium **3.156** will be formed and the following pinacol rearrangement will generate bridged ketone **3.154a** as the sole observed product. Nevertheless, when alkene **3.153** was treated with trifluoromethanesulfonic acid, a mixture

Scheme 3.26 – Rationale for the Stereoselectivity of the Prins-Pinacol Rearrangement



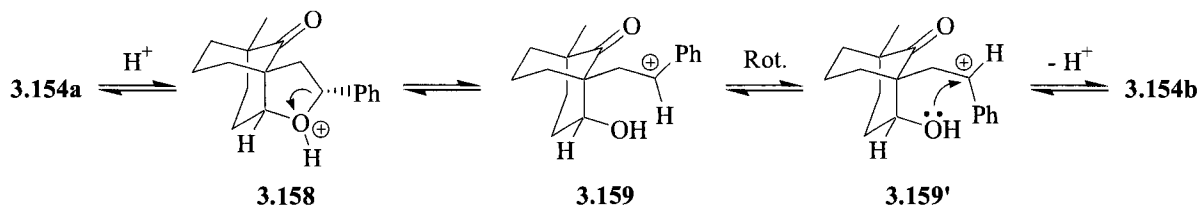
of epimers **3.154a** and **3.154b** was obtained in 95% overall yield (Table 3.9, entry 3). Since the typical stereoselectivity was not respected in that case, we suspected that minor epimer **3.154b** was formed through an acid-mediated epimerization of major epimer **3.154a**. In order to validate that hypothesis, we resubmitted major epimer **3.154a** to the reaction conditions (Scheme 3.27). After two hours of reaction, a mixture of epimers **3.154a** and **3.154b** was recovered, providing evidence that epimer **3.154b** results from epimerization of **3.154a**.

Scheme 3.27 – Formation of **3.154b** via Epimerization of **3.154a**



This epimerization most probably goes through an opening of the tetrahydrofuran ring (Scheme 3.28). According to this rationale, treatment of **3.154a** with strong acid first leads to the formation of oxonium **3.158**. This oxonium then opens to form benzylic carbenium ion **3.159**, which rotates to give intermediate **3.159'**. A subsequent intramolecular nucleophilic attack regenerates the tetrahydrofuran ring and epimer **3.154b** is delivered.

Scheme 3.28 – Rationalization for the Formation of **3.154b**

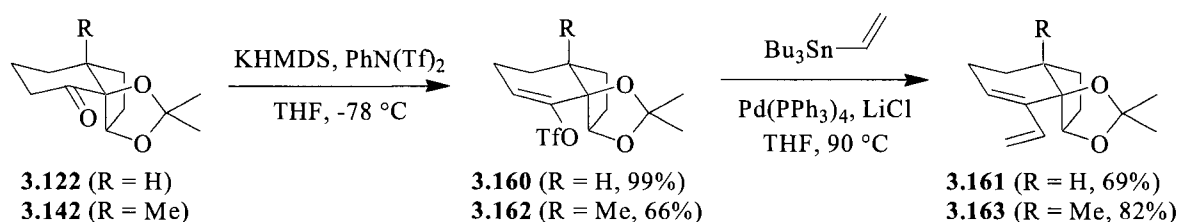


Importantly, the high yields obtained for alkene precursor **3.153** seem to corroborate the superiority of benzylidene acetals over isopropylidene ketals in our system. In this last case, the utilization of a benzylidene acetal almost doubled the yield of the rearrangement. This encouraging result prompted us to study the Prins-Pinacol rearrangement of Diels-Alder cycloadducts in order to construct complex bridged ketones having a bicyclo[3.3.1] skeleton.

Prins-Pinacol Rearrangement of Diels-Alder Cycloadducts

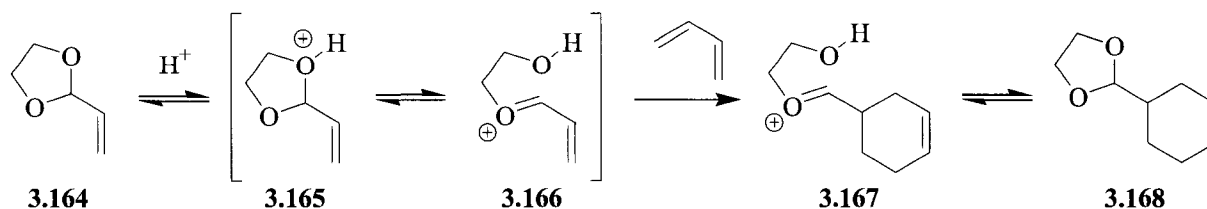
In this enterprise, our first objective has been to generate Diels-Alder adducts from isopropylidene precursors. To this end, dienes **3.161** and **3.163** were synthesized through a sequence developed by Roch Lavigne (Scheme 3.29).⁶² Ketones **3.122** and **3.142** were first converted to the corresponding vinyl triflates. Then, a Stille cross coupling with tributylvinyltin furnished the desired dienes in good overall yield.⁷⁶ These dienes could then be reacted with appropriate dienophile partners to generate the desired Diels-Alder products.

Scheme 3.29 – Synthesis of Dienes **3.161** and **3.163**



Since **3.161** and **3.163** are not activated dienes, we were particularly interested in using the powerful dienophiles developed by Gassman and co-workers.⁶³ In this system, acidic treatment of vinyl dioxolane **3.164** generates, under equilibrium, oxocarbenium **3.166** (Scheme 3.30). This diminishes the electron density at the alkene moiety and therefore lowers the energy of the LUMO of the dienophile. Consequently, the reaction of the diene occurs more rapidly with **3.166** than with **3.164**. The resulting cycloadduct is finally converted to compound **3.168** through regeneration of the dioxolane ring.

Scheme 3.30 – Diels-Alder Reaction with a Gassman Dienophile



Dienes **3.161** and **3.163** were reacted with various dienophiles in the presence of trimethylsilyl trifluoromethanesulfonate (Scheme 3.31). As a result, cycloadducts **3.171**-**3.174** were obtained in fair to good yields with excellent regio- and stereoselectivity. The tridimensional structure of *endo* adduct **3.171** was determined by crystallographic analysis (Figure 3.9). Two-dimensional NMR experiments did not allow the complete determination of the relative stereochemistry for cycloadducts **3.172**-**3.174**. Nonetheless, it was simple to

Scheme 3.31 – Formation of Prins-Pinacol Precursors via an Ionic Diels-Alder Reaction

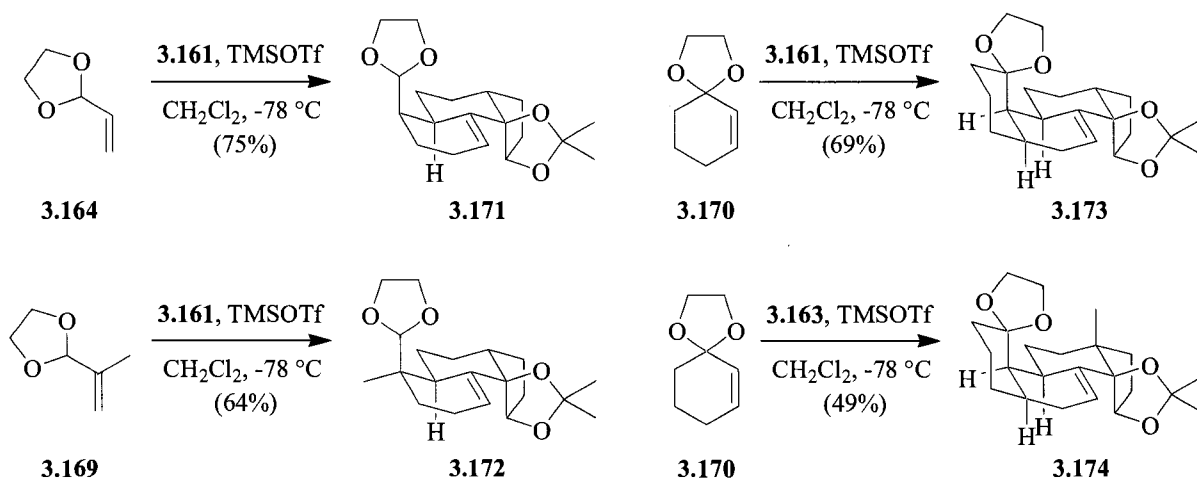
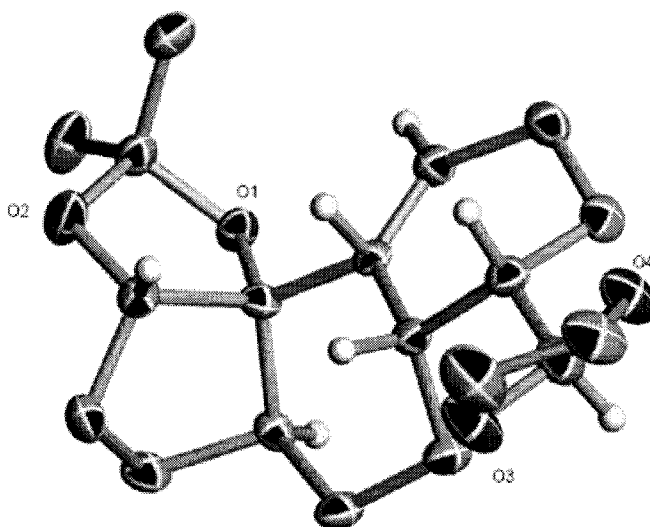


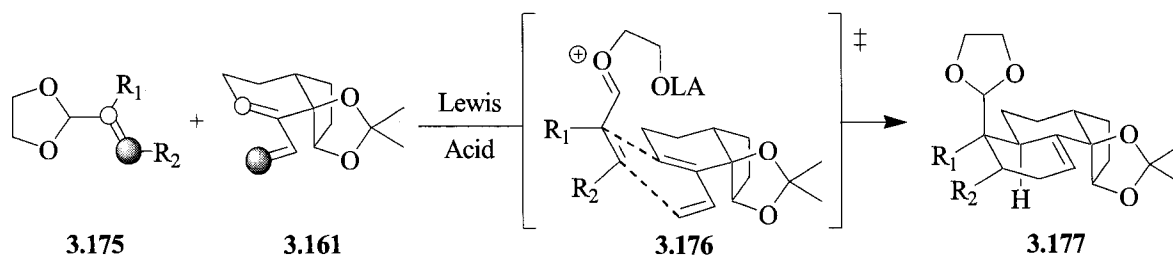
Figure 3.9 – X-Ray Crystallographic Structure of Cycloadduct 3.171



differentiate *endo* products from *exo* products by comparing their ^1H NMR spectra. Hence, a careful comparison of the ^1H spectra of adducts **3.172-3.174** with that of **3.171** allowed us to establish the *endo* configuration of these four compounds.

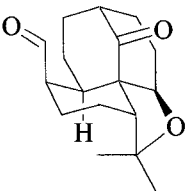
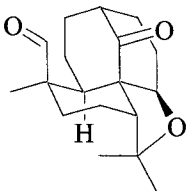
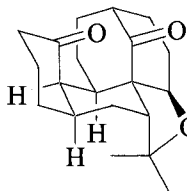
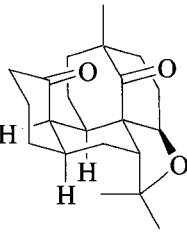
The high regioselectivity exhibited by these cycloadditions can obviously be explained by the preferential interactions between frontier molecular orbital coefficients of similar size, which result from the third term of the Klopman-Salem equation (Scheme 3.32).⁷⁷ Moreover, the observed regiochemistry corresponds to that reported in the literature for similar adducts.⁷⁸ The *endo* selectivity results from the favorable secondary orbital interactions between the diene and the carbonyl group of the dienophile. The high facial selectivity arises from the cage-like shape of the diene, which prevents the dienophile to approach from the bottom face of the molecule.

Scheme 3.32 – Origin of the High Regio- and Stereoselectivity of the Cycloaddition



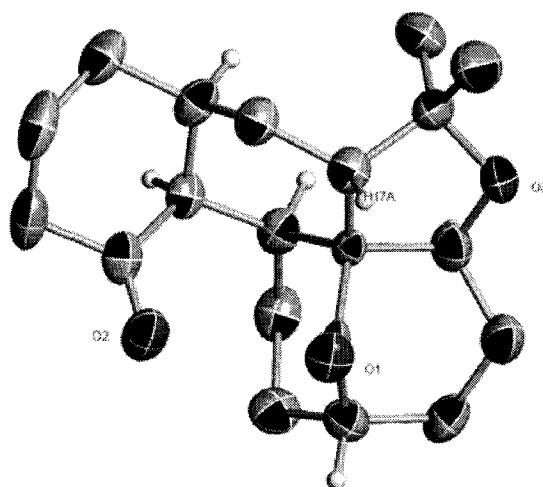
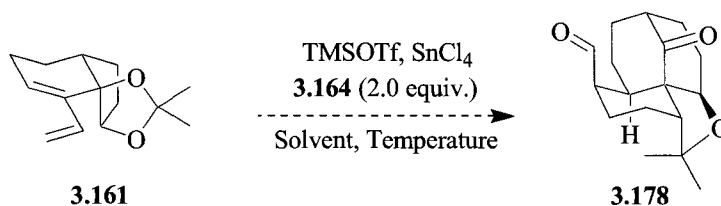
Having substrates **3.171-3.174** in hand, we proceeded to a brief inspection of their Prins-Pinacol rearrangement (Table 3.10). Treatment of alkene **3.171** with tin(IV) chloride in dichloromethane afforded bridged ketone **3.178** in a yield similar to that observed for the corresponding terminal alkene substrate **3.124** (entry 1). However, when the reaction was performed in chlorobenzene, the desired ketone was obtained in 67% yield (entry 2). Bridged ketone **3.179** was obtained in comparable yields, even though the proposed positive effect of chlorobenzene was not as accentuated (entries 3-4). Ketone **3.180** was also generated in similar yields (entries 5-6). Finally, ketone **3.181** was formed in fair yields with both tin tetrachloride and trifluoromethanesulfonic acid (entries 7-8). Overall, the yields obtained with precursors **3.171-3.174**, having a cyclic alkene, were analogous to those obtained for substrates bearing a terminal olefin. This seems to show that the increased structural rigidity

Table 3.10 – Prins-Pinacol Rearrangement of Diels-Alder Cycloadducts **3.171**-**3.174**

 3.178  3.179  3.180  3.181						
Entry	Alkene	Acid (equiv.)	Solvent	Temperature (°C)	Product	Yield (%)
1	3.171	SnCl ₄ (2.0)	CH ₂ Cl ₂	-78 → RT	3.178	28
2	3.171	SnCl ₄ (2.6)	PhCl	-20 → RT	3.178	67
3	3.172	SnCl ₄ (1.2)	CH ₂ Cl ₂	-78 → RT	3.179	29
4	3.172	SnCl ₄ (1.3)	PhCl	-20 → RT	3.179	49
5	3.173	SnCl ₄ (1.2)	CH ₂ Cl ₂	-78 → RT	3.180	30
6	3.173	SnCl ₄ (1.2)	PhCl	-20 → RT	3.180	66
7	3.174	SnCl ₄ (1.2)	PhCl	-20 → RT	3.181	53
8	3.174	TfOH (2.8)	MeCN	-20 → RT	3.181	46

of the cyclohexene ring does not substantially impair the Prins cyclization. In all cases, the dioxolane acetal was hydrolyzed, probably during the work-up of the reaction. Consequently, the Prins-Pinacol products were isolated as the corresponding aldehydes or ketones. Additionally, the structure and relative stereochemistry of ketone **3.180** were confirmed by crystallographic analysis (Figure 3.10). This information also validated the proposed tridimensional structure of alkene substrate **3.173**.

The Diels-Alder/Prins-Pinacol tandem reaction was also succinctly examined. Unfortunately, after a few attempts, we realized that the conditions developed by Roch Lavigne for this reaction were ineffective for bicyclo[4.3.0]nonane substrates bearing an isopropylidene ketal. These attempts are summarized in Table 3.11. In all cases, the reaction of diene **3.161** with dienophile **3.164** in the presence of trimethylsilyl trifluoromethanesulfonate and tin(IV) chloride led to decomposition of the starting material or to production of a mixture of several inseparable products.

Figure 3.10 – X-Ray Crystallographic Structure of Bridged Ketone **3.180**Table 3.11 – Attempted Diels-Alder/Prins-Pinacol Tandem Reaction of Diene **3.161**

Entry	Equiv. of SnCl ₄	Equiv. of TMSOTf	Solvent	Temperature (°C)	Result
1	2.0	0.25	CH ₂ Cl ₂	-78 → RT	Decomposition
2	1.0	1.0	PhCl	-20 → RT	Complex mixture
3	2.2	1.0	PhMe	-78 → RT	Decomposition

In view of these disappointing results, we decided to examine the rearrangement of Diels-Alder cycloadducts bearing a benzylidene acetal. We thus proceeded to the synthesis of diene **3.183** (Scheme 3.33). This diene was obtained in two steps from ketone **3.152**, and was then reacted with a series of Gassman dienophiles (Figure 3.11) in the presence of trimethylsilyl trifluoromethanesulfonate (Table 3.12).

Scheme 3.33 – Synthesis of Diene 3.183

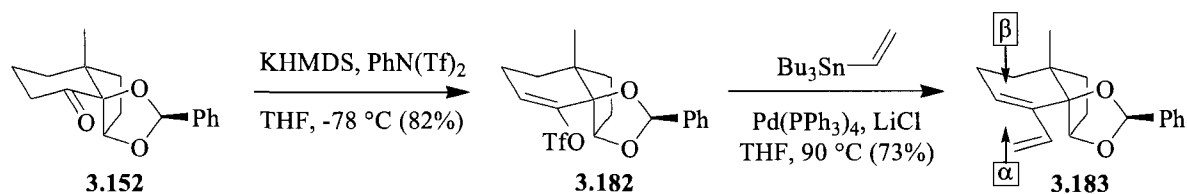


Figure 3.11 – Gassman Dienophiles Reacted with Diene 3.183

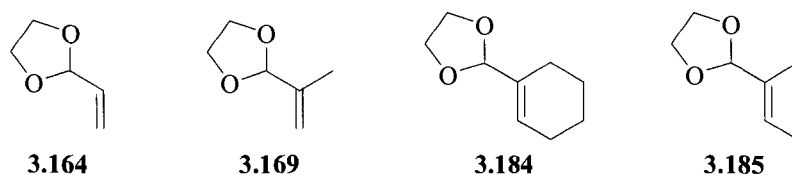
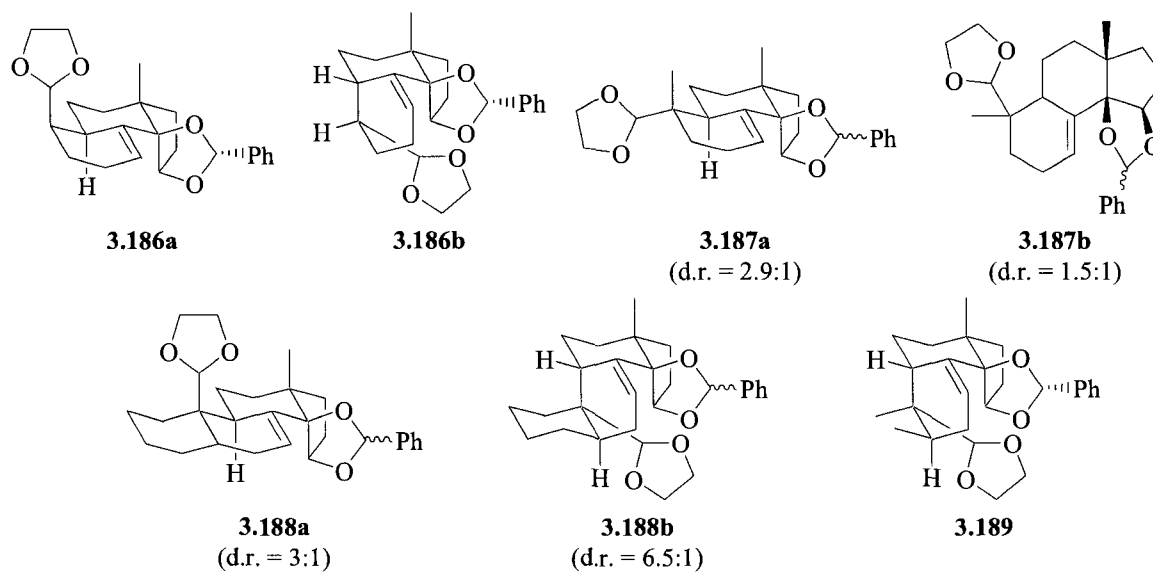


Table 3.12 – Prins-Pinacol Precursors Generated from Diene 3.183



Entry	Dienophile	Product (Yield in %) ^a
1	3.164	3.186a (34) 3.186b (40)
2	3.169	3.187a (32) 3.187b (57)
3	3.184	3.188a (29) 3.188b (32)
4	3.185	3.189 (49)

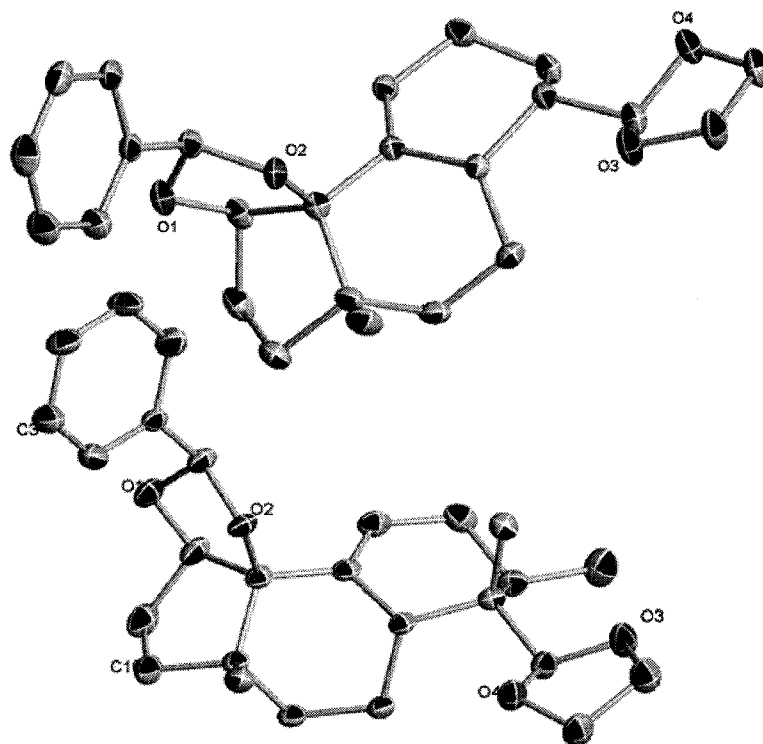
^aReaction conditions: 3.183 (1.0 equiv.), Dienophile (2.0 equiv.), TMSOTf (1.0 equiv.), CH₂Cl₂, -78 °C.

As described previously, the reaction of dienes **3.161** and **3.163** with various Gassman dienophiles provided each of the corresponding cycloadducts as a single diastereomer (Scheme 3.31). Compounds **3.171-3.174** were all *endo* products resulting from an approach of the dienophile from the less hindered β face of the diene (Scheme 3.33). In contrast, exposure of diene **3.183** to these dienophiles in the presence of TMSOTf led, in most cases, to the formation of diastereomeric mixtures. Indeed, treatment of this diene with dienophile **3.164** gave *endo* cycloadducts **3.186** as a 1.2:1 mixture of diastereomers in 74% yield (Table 3.12, entry 1). The major isomer, **3.186b**, came from an approach of the dienophile from the α face of **3.183**, whereas **3.186a** resulted from a β approach. A similar outcome was observed when **3.183** was treated with dienophile **3.184** (entry 3). In this case, diastereomeric *endo* products **3.188** were obtained as a 1.1:1 mixture in 61% overall yield. On the other hand, reaction of diene **3.183** with dienophile **3.169** afforded *exo* cycloadduct **3.187a** in 32% yield (entry 2). The relative stereochemistry of major diastereomer **3.187b** could unfortunately not be determined. Finally, treatment of the diene with dienophile **3.185** furnished *endo* cycloadduct **3.189** as a single diastereomer in 49% yield (entry 4). This compound also came from an approach of the dienophile from the α face. The apparent preference for the approach from the more hindered α face of the diene was unanticipated, since ionic Diels-Alder reactions performed previously yielded exclusively cycloadducts resulting from a β approach.^{62,64} This unexpected behavior could be caused by a complexation of the dioxolane acetal of the incoming dienophile with the benzyldiene acetal of **3.183** in the presence of the Lewis acid.

The tridimensional structure of cycloadduct **3.188b** was elucidated by two-dimensional NMR experiments⁷⁵ and those of products **3.186b** and **3.189** were determined by crystallographic analysis (Figure 3.12). Also, the tridimensional structures of adducts **3.186a**, **3.187a** and **3.188a** were deduced from those of the corresponding Prins-Pinacol products.⁷⁵

The lack of facial selectivity observed in the formation of Diels-Alder adducts **3.186-3.188** was not wished for, but it allowed us to examine more precursors than originally expected. The seven substrates were treated in the Prins-Pinacol conditions developed by Méline Girardin.⁶⁴ Treatment of substrate **3.186a** with trimethylsilyl trifluoromethanesulfonate gave

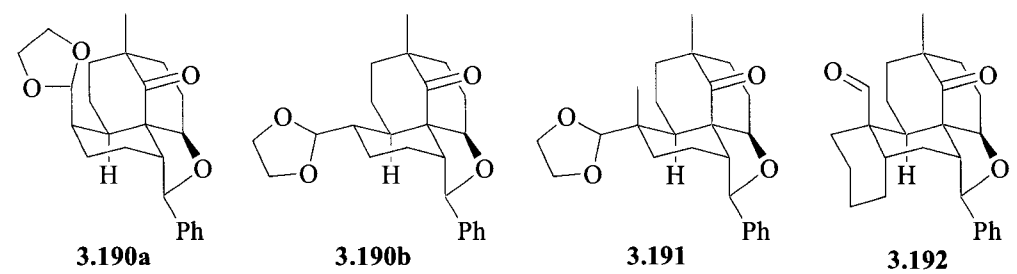
Figure 3.12 – X-Ray Crystallographic Structures of **3.186b** (top) and **3.189** (bottom)



bridged ketones **3.190** as a mixture of epimers in 45% yield (Table 3.13, entry 1). The formation of minor epimer **3.190b** most probably resulted from an epimerization consecutive to an acid-mediated opening of the dioxolane ring of **3.190a**. Importantly, the reaction of all cycloadducts resulting from an approach of the dienophile from the α face of the diene resulted in the formation of a complex mixture of inseparable products (entries 2, 4, 6-7). On the other hand, reaction of substrates **3.187a** and **3.188a** yielded the corresponding Prins-Pinacol products in good yields (entries 3, 5). This time, the dioxolane acetal survived the Prins-Pinacol conditions in all cases except for ketone **3.192**. As mentioned earlier, the tridimensional structure of each of these four Prins-Pinacol products was determined by two-dimensional NMR experiments.⁷⁵

The unsuccessful Prins-Pinacol rearrangement of substrates **3.186b**, **3.187b**, **3.188b** and **3.189** can be explained by the rationale depicted in Scheme 3.34. Upon treatment with acid, these substrates are converted to the corresponding oxocarbenium ions. Then, in order to undergo the Prins cyclization, the alkene moiety must be brought in close proximity with this

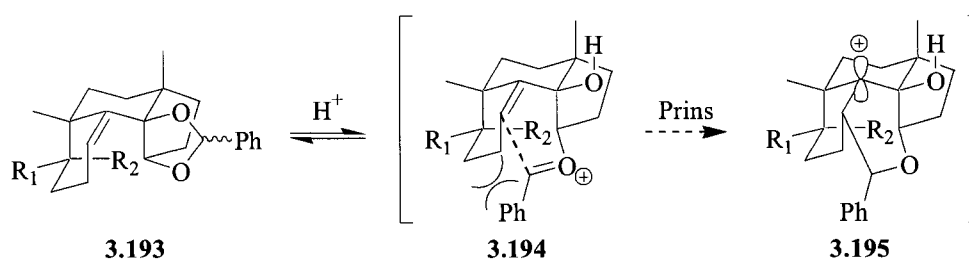
Table 3.13 – Prins-Pinacol Rearrangement of Diels-Alder Cycloadducts **3.186-3.189**

		
Entry	Substrate	Product (Yield in %) ^a
1	3.186a	3.190a (33) 3.190b (12)
2	3.186b	Complex mixture
3	3.187a	3.191 (62)
4	3.187b	Complex mixture
5	3.188a	3.192 (81)
6	3.188b	Complex mixture
7	3.189	Complex mixture

^aReaction conditions: TMSOTf (2.0 equiv.), CH₂Cl₂, -78 °C.

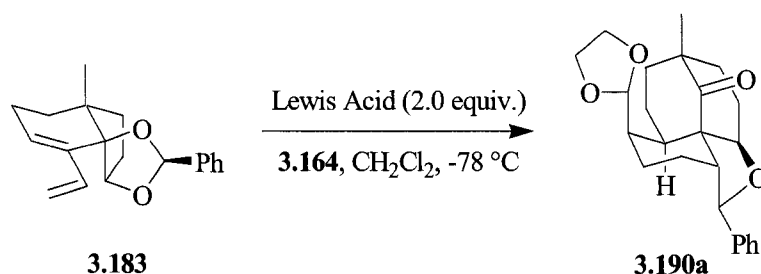
oxocarbenium. This is achieved by adopting a conformation of type **3.194**. However, in this case, the severe steric interactions existing between the oxocarbenium and the cyclohexene ring almost certainly prevent the formation of the new carbon-carbon sigma bond. No Prins cyclization can therefore take place, and no Prins-Pinacol product is generated. At that point, other background reactions most probably become competitive and lead to the formation of several unidentified products.

Scheme 3.34 – Rationale for the Unsuccessful Prins-Pinacol Rearrangement



Finally, the relatively high yields obtained for the rearrangement of cycloadducts bearing a benzylidene acetal led us to examine once more the Diels-Alder/Prins-Pinacol tandem reaction (Table 3.14). When diene **3.183** was treated with dienophile **3.164** in the presence of tin tetrachloride, the reaction stopped at the Diels-Alder stage and cycloadduct **3.186a** was isolated in 21% yield (entry 1). However, when this Lewis acid was replaced by trimethylsilyl trifluoromethanesulfonate, the desired bridged ketone, **3.190a**, was obtained in 20% yield (entry 2). Because the reaction did not go to completion, the experiment was repeated with increased amounts of the dienophile, but this resulted in the formation of complex mixtures of inseparable products (entries 3-4).

Table 3.14 – Diels-Alder/Prins-Pinacol Tandem Reaction of Diene **3.183**



Entry	Lewis Acid	Equiv. 3.164	Product (Yield in %)
1	SnCl ₄	1.2	3.186a (21)
2	TMSOTf	1.2	3.190a (20)
3	TMSOTf	1.5	Complex mixture
4	TMSOTf	2.0	Complex mixture

Conclusion

In the course of the methodology studies described in this chapter, a lot of information has been collected concerning the chemical behavior of bicyclo[4.3.0]nonane Prins-Pinacol precursors. A preliminary optimization of the Prins-Pinacol rearrangement of a simple isopropylidene substrate demonstrated that tin(IV) chloride and trifluoromethanesulfonic acid were the best promoters for the reaction. We then determined that substitution at the

ring junction had no noticeable effect on the reaction outcome. We also confirmed that alkene substitution inhibited the desired rearrangement and led to formation of an enone by-product. Additionally, we found that the utilization of Prins-Pinacol substrates bearing a benzylidene acetal greatly improved the yield of the reaction.

The reaction of dienes **3.161** and **3.163** with various Gassman dienophiles yielded Diels-Alder cycloadducts with excellent regio- and stereoselectivity. These isopropylidene substrates then underwent the Prins-Pinacol rearrangement to afford the corresponding bridged ketones in fair yields. In contrast, the Diels-Alder reaction of diene **3.183** with a choice of dienophiles unexpectedly afforded diastereomeric mixtures of the corresponding cycloadducts. All alkene precursors coming from an atypical α approach of the dienophile failed to deliver the desired bridged ketones. Nevertheless, benzylidene substrates possessing the typical stereochemistry gave the expected Prins-Pinacol products in fair to good yields. Finally, the Diels-Alder/Prins-Pinacol tandem reaction was attempted on dienes **3.161** and **3.183**, but with disappointing results.

Even though we were not satisfied in all aspects by the results obtained during its development, our methodology proved to be a reliable way to construct stereoselectively bicyclo[3.3.1]nonanone frameworks. We therefore decided to demonstrate the usefulness of this approach by an application to the total synthesis of a member of the polycyclic polyprenylated acylphloroglucinol family, papuaforin A.

4

Studies towards the Total Synthesis of Papuaforin A

Papuaforin A, a Natural Product

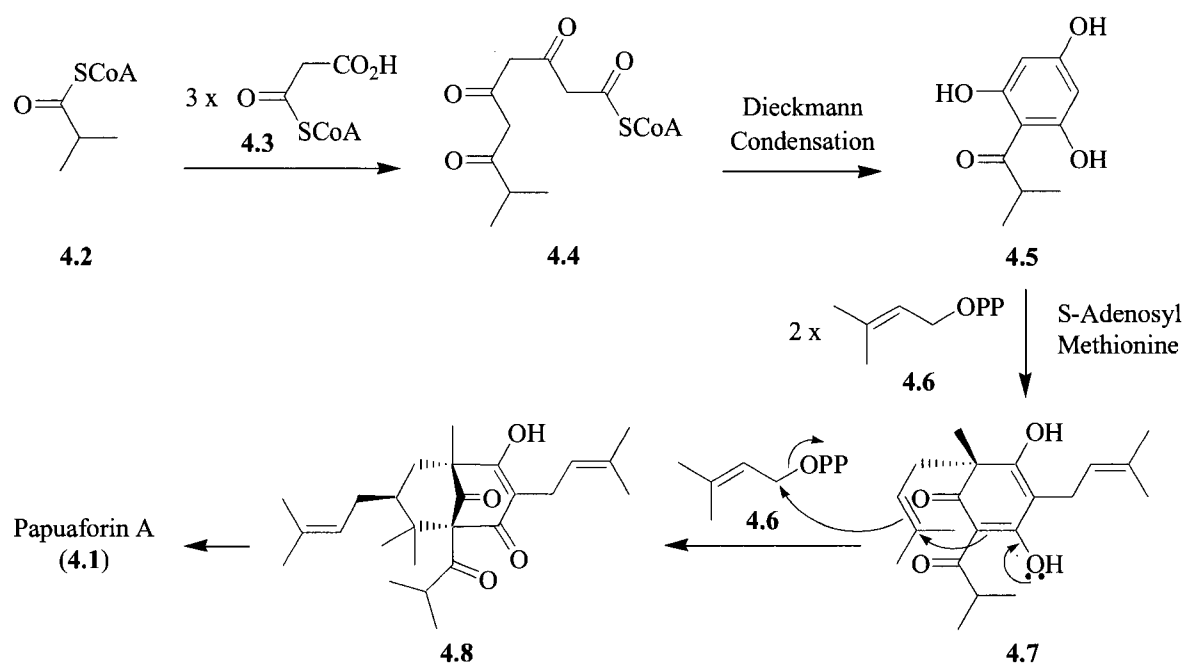
In 2001, during a systematic inspection of medicinal plants of Papua New Guinea, Sticher and co-workers reported the isolation of papuaforin A from the aerial parts of *Hypericum papuanum*, a shrub commonly found in mountainous areas of this country (Figure 4.1).⁷⁹ As illustrated on Figure 4.2, papuaforin A (**4.1**) exhibits complex structural characteristics.

Figure 4.1 – Hypericum papuanum Ridley (Guttiferae), Collected in Papua New Guinea



mediated methylation would then lead to monocyclic polyprenylated acylphloroglucinol **4.7**. Concomitant cyclization and prenylation would furnish bicyclic intermediate **4.8**, which would eventually be cyclized to generate the dimethylpyran ring of papuaforin A (**4.1**).

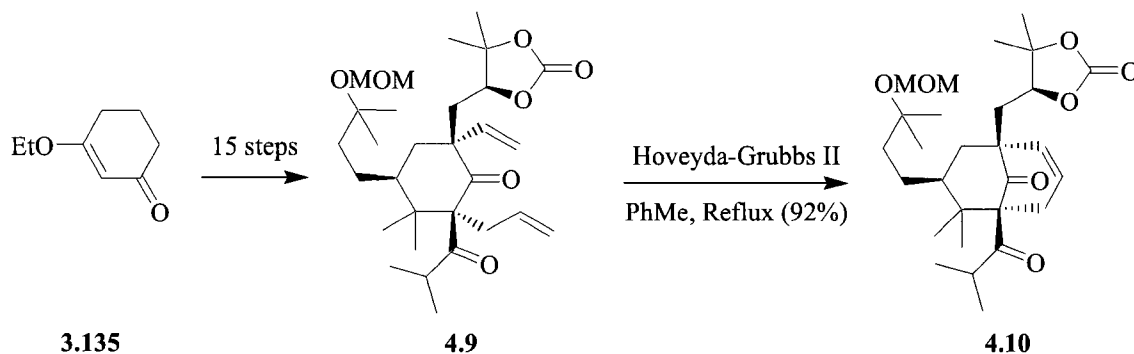
Scheme 4.1 – Putative Biosynthesis of Papuaforin A (4.1)



Selected Synthetic Approaches towards PPAPs

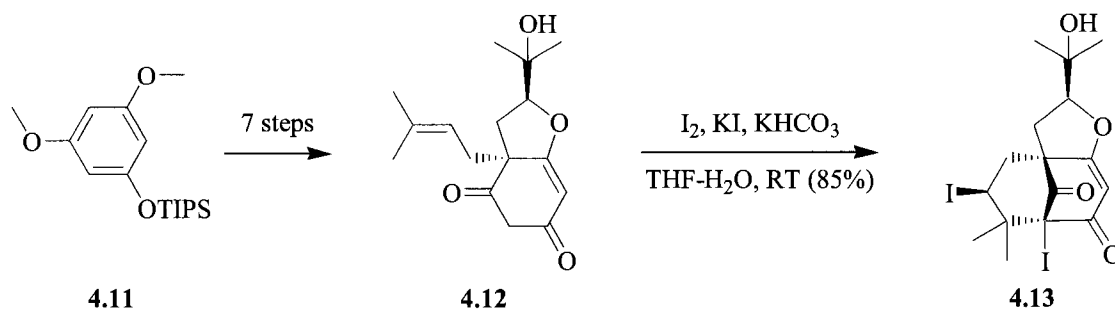
Because of their considerable structural complexity and often promising biological activity, many researchers have become interested in the total synthesis of type A PPAPs during the last decade. Amongst all these natural products, garsubellin A (**3.109**) has certainly been a target of choice, since at least eight research groups have reported synthetic efforts towards its synthesis. Two total syntheses have been reported thus far by Shibasaki (2005) and Danishefsky (2006).⁸¹ In their synthesis, Shibasaki and co-workers employed a ring-closing metathesis strategy to generate the bicyclo[3.3.1]nonanone core of the compound (Scheme 4.2). A fifteen-step sequence first gave access to diene **4.9**, which was treated with second generation Hoveyda-Grubbs catalyst to afford bridged ketone **4.10** in high yield. This advanced intermediate was then efficiently converted to garsubellin A (**3.109**) in seven steps.

Scheme 4.2 – Shibasaki's Ring-Closing Metathesis Approach



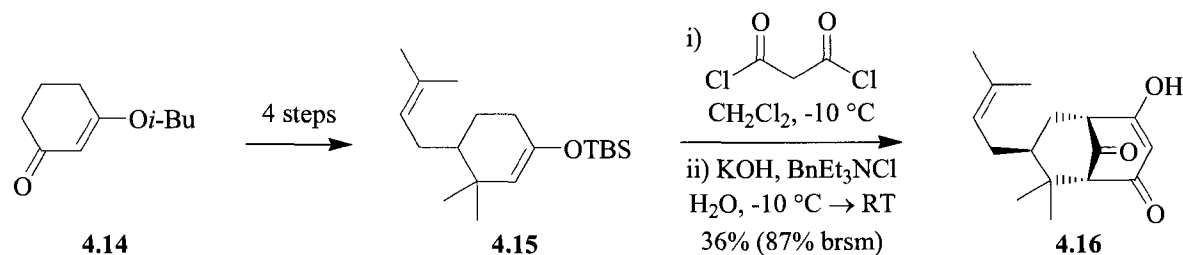
Interestingly, the synthetic strategy employed by Danishefsky was reminiscent of the biosynthetic pathways leading to polycyclic polyprenylated acylphloroglucinols. Indeed, a series of transformations including two formal prenylations afforded intermediate **4.12** from aromatic starting material **4.11** (Scheme 4.3). The bicyclo[3.3.1]nonanone skeleton of key intermediate **4.13** was then generated by an intramolecular iodocarbocyclization of the β -diketone with the prenyl chain of **4.12**. Tricyclic compound **4.13** was eventually transformed into garsubellin A (**3.109**) through a nine-step sequence.

Scheme 4.3 – Danishefsky's Iodocarbocyclization Approach



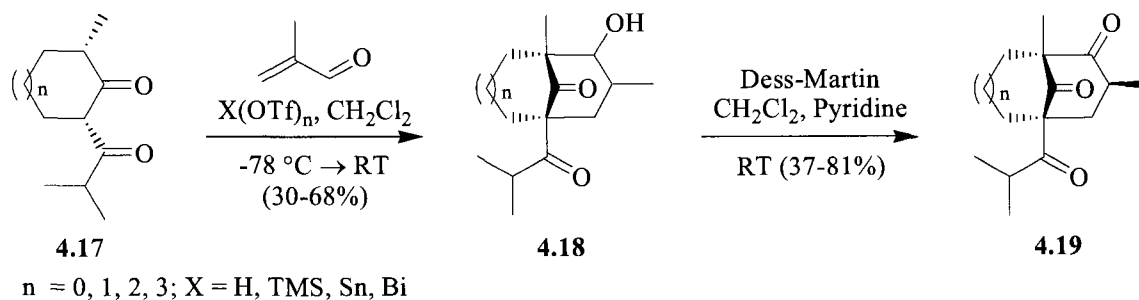
The Stoltz and Nicolaou research groups have also reported particularly interesting approaches to PPAPs. During a synthetic investigation directed towards garsubellin A, Stoltz and co-workers employed the Effenberger reaction to synthesize rapidly the bicyclo[3.3.1]nonanone skeleton of PPAPs.⁸² A four-step synthesis efficiently provided enol ether **4.15**, which was reacted with malonyl dichloride to give annulated product **4.16** as a single diastereomer (Scheme 4.4). Triketone **4.16** was only isolated in fair yield, but the unreacted

Scheme 4.4 – Stoltz's Approach to PPAPs



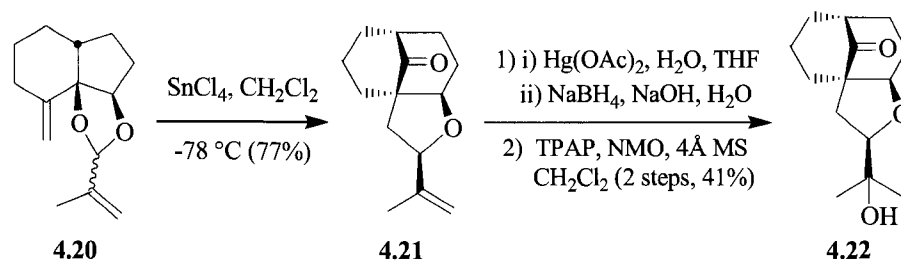
starting material was recovered as the keto form of **4.15** and could be recycled in the reaction sequence. More recently, Nicolaou reported a general method for the construction of bridged ketones via a Michael-aldol tandem reaction (Scheme 4.5).⁸³ By reacting simple 2-acylcycloalkanones of various ring sizes (**4.17**) with methacrolein and a catalytic amount of a Brønsted or Lewis acid, bicyclo[n.3.1]alkanones **4.18** were obtained in fair to good yields. Importantly, these reaction conditions allowed the simultaneous generation of the two bridgehead quaternary stereocenters. The subsequent oxidation of alcohol **4.18** with Dess-Martin periodinane then delivered triketone **4.19** as a single epimer.

Scheme 4.5 – Nicolaou's Michael-Aldol Approach to PPAPs



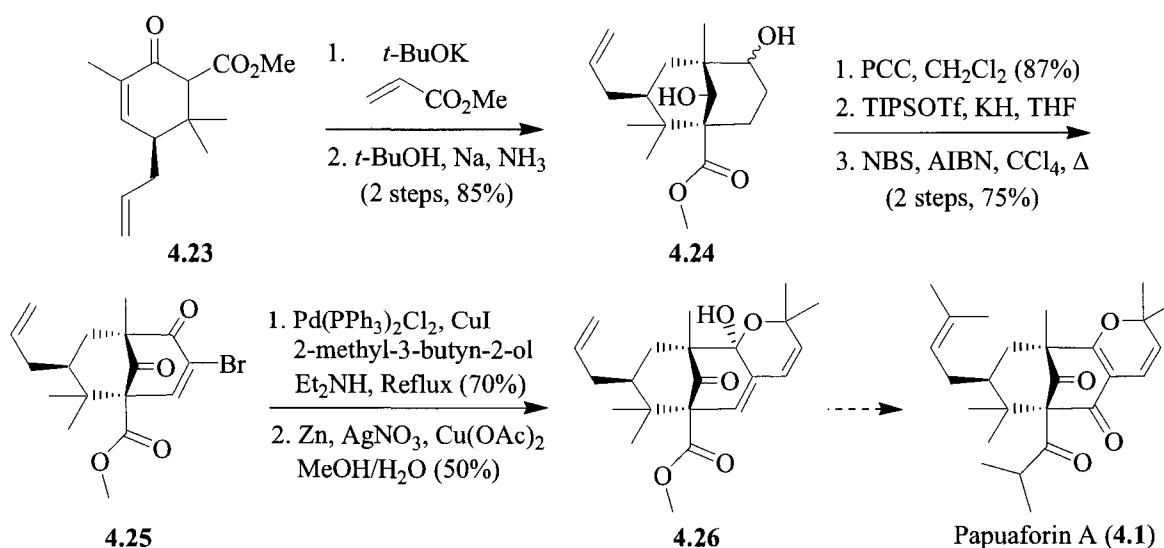
Former Barriault group member Méline Girardin used the Prins-Pinacol strategy to construct the core of garsubellin A (**3.109**).⁶⁴ To this end, a bicyclo[4.3.0]nonane precursor bearing a methallylidene acetal was synthesized (Scheme 4.6). When alkene substrate **4.20** was treated with tin(IV) chloride, bicyclo[3.3.1]nonanone **4.21** was produced in good yield. The tetrahydrofuran ring was further functionalized by introduction of the tertiary alcohol. Indeed successive oxymercuration and TPAP oxidation furnished keto-alcohol **4.22** in 41% overall yield.

Scheme 4.6 – Prins-Pinacol Synthesis of the Core of Garsubellin A (3.109)



Finally, earlier this year, the Kraus research group has reported an innovative strategy for the synthesis of the bicyclo[3.3.1]nonanone skeleton of papuaforin A (4.1), our molecule of interest.⁸⁴ In the key step of their synthesis, a Michael addition of methyl acrylate to keto ester 4.23 was followed by a cyclizative Birch reduction to afford bicyclic diol 4.24 in 85% yield (Scheme 4.7). Diol 4.24 was oxidized in high yield to the diketone, which was then converted to the corresponding silyl enol ether. The latter was treated with *N*-bromosuccinimide and catalytic AIBN in refluxing carbon tetrachloride to afford α -bromo enone 4.25 in good overall yield. Bromoenone 4.25 then underwent a Sonogashira coupling with 2-methyl-3-butyn-2-ol, giving the corresponding acetylenic ketone in 70% yield. The triple bond was then reduced to a *cis* double bond, and the resulting allylic alcohol

Scheme 4.7 – Kraus's Michael Addition/Birch Cyclizative Reduction Approach

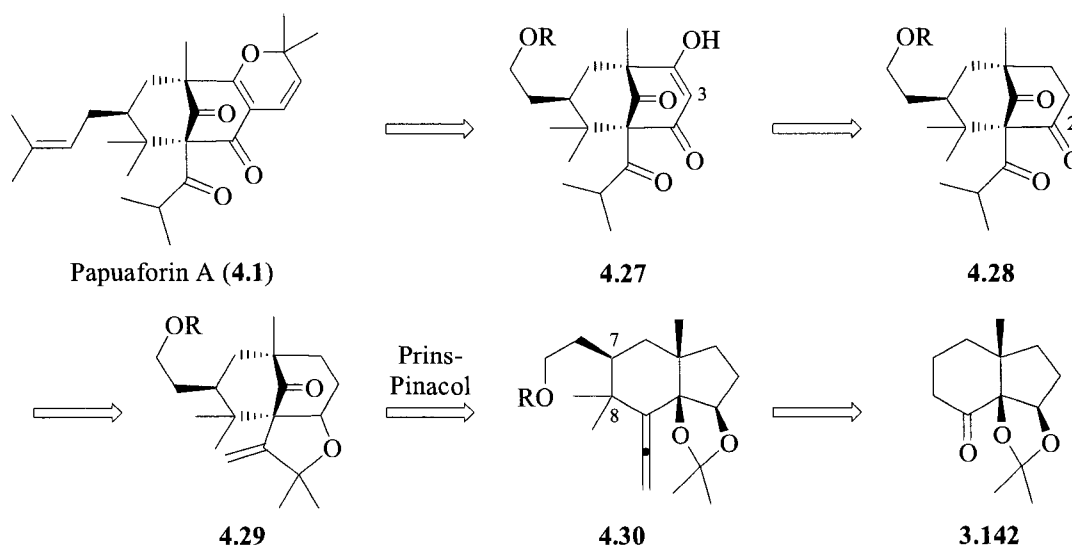


cyclized to provide hemiketal **4.26** in an acceptable yield of 50%. Advanced intermediate **4.26** was obtained in seven steps from readily available keto ester **4.23** in 19% overall yield. In order to attain papuaforin A (**4.1**), three problems remain to be tackled: the oxidative rearrangement of the tertiary allylic alcohol to the related enone, the formation of the isopropyl ketone, and the elaboration of the side-chain via cross-metathesis.

Synthesis of the Core of Papuaforin A via a Prins-Pinacol Strategy

We previously established that the Prins-Pinacol methodology provides a straightforward access to bicyclo[3.3.1]nonanones bearing a fused dimethyltetrahydrofuran ring. In order to fully demonstrate the potential of our method, we envisioned an application to the total synthesis of a PPAP natural product. We selected papuaforin A (**4.1**) as a synthetic target because of the relative simplicity of its two bridgehead quaternary centers. Indeed, we had already showed that the presence of a methyl group at the ring junction was well tolerated by the Prins-Pinacol rearrangement. Moreover, no total synthesis of this natural compound had yet been reported. After the appropriate retrosynthetic analysis (Scheme 4.8), we postulated

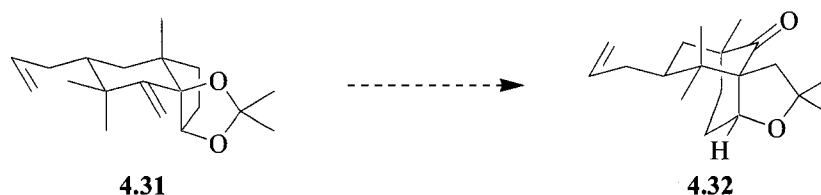
Scheme 4.8 – A Retrosynthetic Analysis of Papuaforin A (4.1)



that the desired natural product could be synthesized from ketone **3.142** in less than twenty steps. According to this retrosynthesis, papuaforin A (**4.1**) could come from pentaoxygenated compound **4.27** through a prenylation at C₃ followed by a 6 π electron electrocyclization. The latter could in turn come from the oxidation of triketone **4.28**. The bridgehead isobutyryl group and the ketone at C₂ of triketone **4.28** could be generated from tetrahydrofuran **4.29** by sequential alkene ozonolysis, dissolving metal reduction and alcohol oxidation. This tetrahydrofuran could be formed by a Prins-Pinacol rearrangement of allenic precursor **4.30**, which should be readily elaborated from ketone **3.142**.

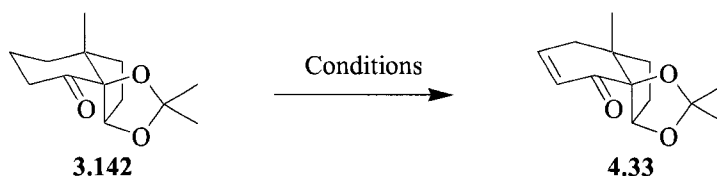
Before initiating the total synthesis, it was indispensable to prove the feasibility of the Prins-Pinacol rearrangement of an allenic substrate. Moreover, we were worried about the possible detrimental influence of the *gem*-dimethyl group at C₈ on this cascade reaction. We decided to address this concern first and consequently undertook the synthesis of model alkene substrate **4.31** in order to evaluate its reactivity (Scheme 4.9).

Scheme 4.9 – Reaction of Hindered Model Alkene Substrate 4.31



The first step in the synthesis of model alkene **4.31** was the formation of enone **4.33** from ketone **3.142**. Unfortunately, the oxidation of this ketone was not as simple as initially anticipated. The diverse experimental conditions attempted during the optimization of this reaction are summarized in Table 4.1. Palladium-mediated eliminations were first attempted, but no desired enone was produced (entries 1-2). Treatment of the ketone with IBX alone (entry 3) or in the presence of a co-oxidant (entry 4) furnished enone **4.33** in trace amounts only.⁸⁵ We then turned to selenium chemistry. Reaction of ketone **3.142** with phenylselenenyl chloride and sulfuryl chloride cleanly afforded the corresponding selenide.⁸⁶ However, treatment of the crude selenide with saturated aqueous sodium bicarbonate furnished the desired enone in 7% yield only (entry 5). Alternatively, the selenide was formed by reacting

Table 4.1 – Optimization of the Formation of Enone 4.33



Entry	Conditions	Yield (%)
1	NaHMDS, Pd(OAc) ₂ , <i>p</i> -benzoquinone, PhMe, 80 °C	No reaction
2	NaOMe, Pd(OAc) ₂ , <i>p</i> -benzoquinone, PhMe, 80 °C	No reaction
3	IBX, DMSO, 80 °C	Trace
4	IBX, NMO, DMSO, 80 → 100 °C	Trace
5	1. PhSeCl, SO ₂ Cl ₂ , Et ₂ O, RT; 2. NaHCO ₃ , CH ₂ Cl ₂ , H ₂ O, RT	7
6	1. PhSeCl, EtOAc, RT; 2. i) O ₃ , CH ₂ Cl ₂ , -78 °C, ii) Me ₂ S, RT	3-22
7	1. PhSeCl, EtOAc, RT; 2. NaIO ₄ , MeOH, H ₂ O, RT	13-38
8	1. PhSeCl, EtOAc, RT; 2. <i>m</i> -CPBA, NaHCO ₃ , EtOAc, 10 °C → RT	40

a solution of ketone **3.142** in ethyl acetate with phenylselenenyl chloride.⁸⁷ When the crude selenide was treated with ozone, enone **4.33** was obtained in up to 22% yield (entry 6). However, the oxidation step was unreliable and the isolated yields varied greatly. Oxidation of the crude selenide with sodium periodate led to formation of the enone in slightly better yields (entry 7).⁸⁷ Nonetheless, these conditions were plagued by the same reproducibility problem, as the yields varied from 13 to 38 percent. The selenide was also oxidized with *m*-chloroperbenzoic acid in the presence of aqueous sodium bicarbonate (entry 8).⁸⁸ On small scale (e.g. 25 mg), these conditions afforded enone **4.33** in 40% yield. Nevertheless, when the reaction was performed on larger scale (e.g. 100 mg), an unknown compound that could not be separated from **4.33** became the major product of the reaction.

Because of the poor reliability of the oxidation step, enone **4.33** could only be obtained in small amounts. We however managed to synthesize enough of this enone material to attempt a few conjugate addition reactions (Table 4.2). Copper mediated-addition of allylmagnesium bromide to enone **4.33** in the presence of chlorotrimethylsilane and HMPA gave no reaction

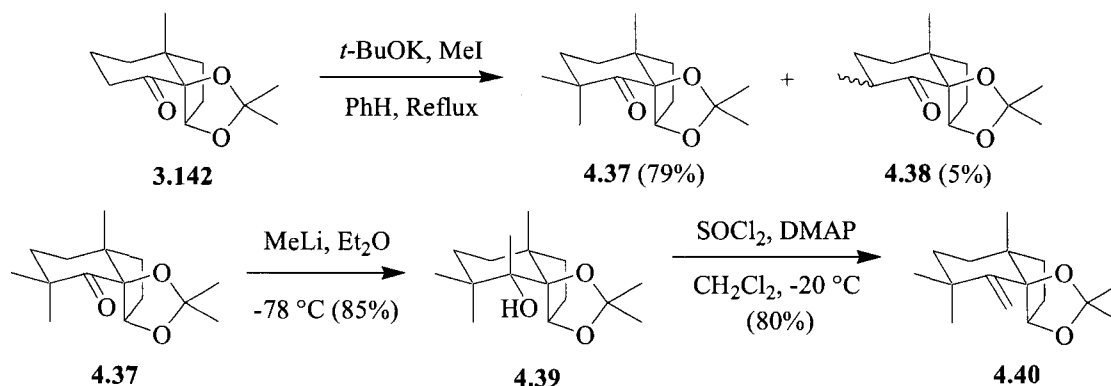
Table 4.2 – Attempted Conjugate Addition on Enone **4.33**

Entry	Conditions	Product(s)	Yield (%)
1	i) CuBr·SMe ₂ , 4.34 , THF, 0 °C ii) TMSCl, HMPA, 4.33 , THF, -78°C	4.33	--
2	CuBr·SMe ₂ , 4.34 , THF, -78°C	4.36a / 4.36b	22 / 11
3	4.34 , THF, -78°C	4.36a / 4.36b	33 / 23
4	4.34 , Et ₂ O, -78°C	4.36a / 4.36b	21 / 24

(entry 1). When the reaction was performed in the absence of additives, no 1,4-addition product was observed. Instead, epimeric alcohols **4.36** were recovered in 33% overall yield (entry 2). At that point, we realized that ketone **4.35** would probably be accessed more easily by an anionic oxy-Cope rearrangement of the allylic alcohol resulting from an axial attack. We therefore proceeded to 1,2-additions of allylmagnesium bromide to enone **4.33**. Unfortunately, no facial selectivity was observed when the reaction was executed in tetrahydrofuran (entry 3) or diethyl ether (entry 4). This can most likely be explained by the presence of a methyl at the ring junction. Indeed, an axial attack generates a severe 1,3-diaxial steric interaction between the methyl group and the incoming nucleophile in the transition state. Therefore, the equatorial attack becomes competitive and a mixture of epimeric alcohols is formed.

The non-reproducible yields observed for the formation of enone **4.33**, as well as the absence of facial selectivity in the generation of alcohols **4.36**, clearly demonstrated the impracticability of this route for the construction of model compound **4.31**. Therefore, this synthesis was abandoned and we decided to replace alkene **4.31** by a simpler model substrate. Compound **4.40** was consequently synthesized in three steps from ketone **3.142** (Scheme 4.10). Methylation of this ketone via treatment with potassium *tert*-butoxide and iodomethane brought about the formation of 8,8-dimethylketone **4.37** in good yield.⁸⁹

Scheme 4.10 – Synthesis of Model Alkene Substrate 4.40



Monomethylated ketone **4.38** was also produced in 5% yield. It could however simply be converted to **4.37** by resubmission to the reaction conditions. Olefination of the carbonyl was first attempted through the modified Conia conditions that we had already employed.⁷³ Nevertheless, the considerable steric hindrance caused by the *gem*-dimethyl drastically slowed down this reaction. For that reason, the addition-elimination method was employed, and alkene substrate **4.40** was generated in good yield over two steps.⁷⁰

The reactivity of this *gem*-dimethyl-bearing Prins-Pinacol precursor was then examined (Table 4.3). Treatment of **4.40** with tin(IV) chloride in dichloromethane afforded the corresponding bridged ketone in a disappointing 22% yield (entry 1). When the reaction was

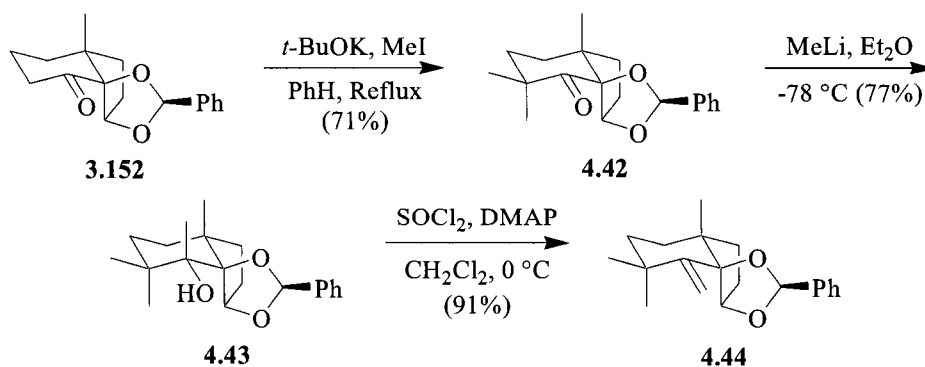
Table 4.3 – Prins-Pinacol Reaction of Substrate 4.40

Entry	Acid (equiv.)	Solvent	Temperature (°C)	Yield (%)
1	SnCl ₄ (1.2)	CH ₂ Cl ₂	-78 → 0	22
2	SnCl ₄ (2.2)	PhMe	-78 → 0	30
3	TfOH (2.0)	MeCN	-20 → RT	34

performed in toluene, a small increase of the yield was observed (entry 2). However, a maximal yield of 34% was obtained by using trifluoromethanesulfonic acid (entry 3). These low yields gave the impression that the presence of a *gem*-dimethyl at C₈ was detrimental to the Prins-Pinacol rearrangement. In fact, the average yield for this transformation was approximately twice as important for an analogous substrate lacking this bulky group (i.e. alkene **3.144a**). We hypothesized that the diminution of the yield could be explained by a concurrent [1,2] methyl shift occurring after the Prins cyclization and leading to unwanted side-products. By-products were indeed observed in some cases, but they could not be cleanly isolated and identified. Obviously, the yields observed for the rearrangement of model alkene substrate **4.40** were unsatisfactory. We therefore abandoned the idea of synthesizing a more complex allenic precursor having similar features. It was the end of our original synthetic plan.

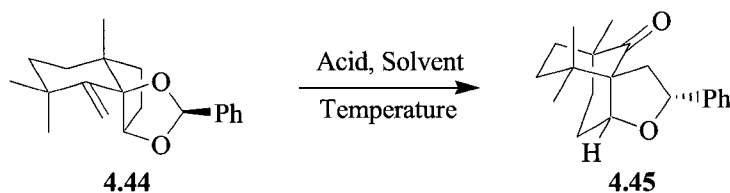
Nonetheless, it had been previously established that the Prins-Pinacol rearrangement is much more effective with a benzylidene acetal than with an isopropylidene ketal. We therefore decided to synthesize and evaluate the reactivity of an alkene precursor bearing a benzylidene acetal and a *gem*-dimethyl at C₈. For that purpose, model substrate **4.44** was generated in three steps from ketone **3.152**. Methylation of this ketone furnished 8,8-dimethylketone **4.42** in 71% yield.⁸⁹ The ketone was then converted to alkene **4.44** in good overall yield via the usual two-step sequence (Scheme 4.11).⁷⁰

Scheme 4.11 – Synthesis of Model Alkene Substrate **4.44**



We then evaluated the Prins-Pinacol rearrangement of that new substrate (Table 4.4). Treatment of alkene **4.44** with tin tetrachloride afforded bridged ketone **4.45** in a respectable yield of 75% (entry 1). As usual, a slight augmentation of the yield was observed when the reaction was performed in toluene (entry 2). Gratifyingly, the reaction of precursor **4.44** with trifluoromethanesulfonic acid delivered the desired ketone in 92% yield (entry 3). Replacement of the isopropylidene ketal with a benzylidene acetal most likely led to an increase of the rearrangement rate, which could explain the absence of side-products and the impressive yield improvement. This encouraging result confirmed that the *gem*-dimethyl-bearing bicyclo[3.3.1]nonanone core of papuaforin A could definitely be generated via a Prins-Pinacol rearrangement.

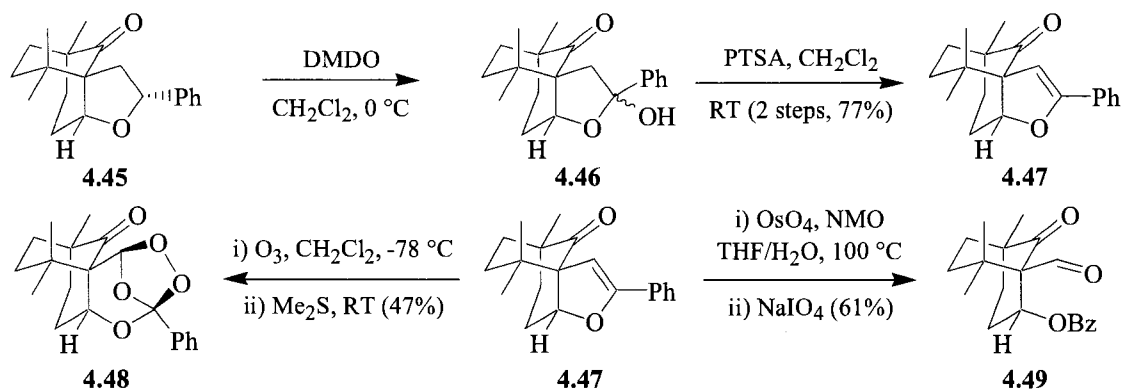
Table 4.4 – Prins-Pinacol Reaction of Substrate **4.44**



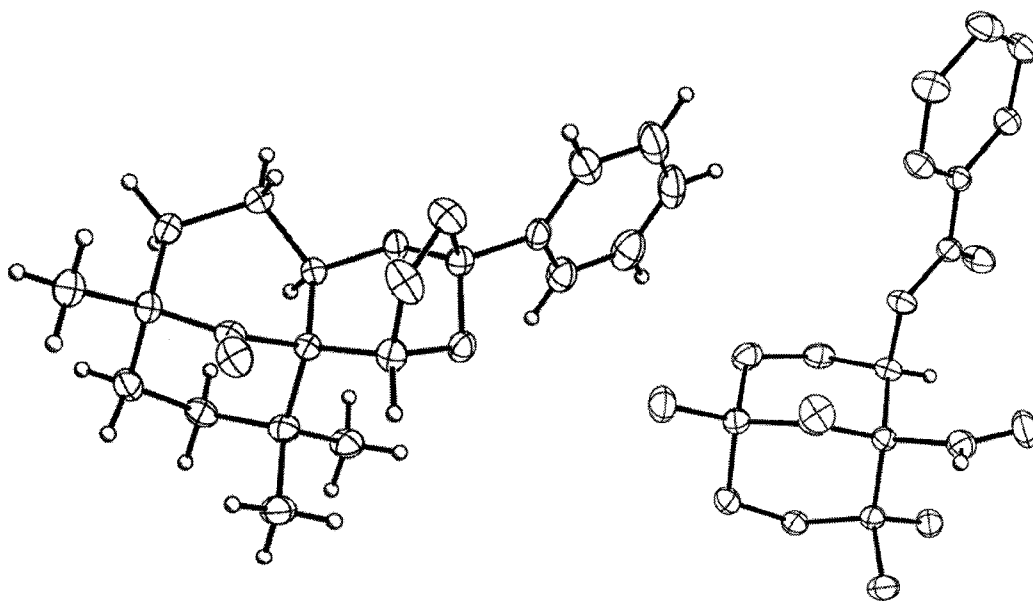
Entry	Acid (equiv.)	Solvent	Temperature (°C)	Yield (%)
1	SnCl ₄ (1.2)	CH ₂ Cl ₂	-78 → RT	75
2	SnCl ₄ (2.2)	PhMe	-78 → RT	81
3	TfOH (2.0)	MeCN	-20 → RT	92

Since the dissolving metal reduction that we had initially envisaged for the cleavage of the dimethyltetrahydrofuran was not applicable in the case of a 2-phenyltetrahydrofuran ring, an alternative ring-opening procedure was required. After analysis, we hypothesized that this transformation could be achieved through ozonolysis of the corresponding dihydrofuran ring. This dihydrofuran was therefore synthesized via a two-step sequence (Scheme 4.12). First, the tetrahydrofuran ring of compound **4.45** was oxidized at the benzylic carbon by treatment with dimethyldioxirane to afford lactol **4.46**.⁹⁰ The crude lactol was then reacted with *p*-toluenesulfonic acid and the desired elimination product was isolated in 77% overall yield. Cleavage of the enol ether double bond of compound **4.47** by ozonolysis was then attempted.

Scheme 4.12 – Cleavage of the 2-Phenyltetrahydrofuran Ring



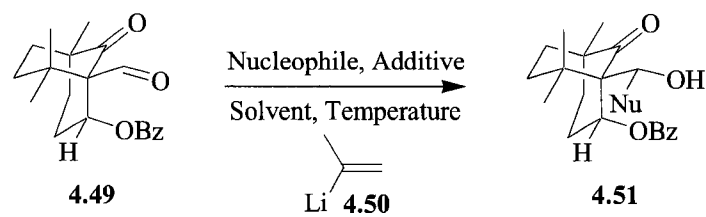
Unexpectedly, stable ozonide **4.48** was obtained as the sole reaction product in 47% yield. However, when **4.47** was subjected to the Lemieux-Johnson oxidative cleavage conditions, desired aldehyde **4.49** was smoothly delivered in 61% yield.⁹¹ The tridimensional structures of compounds **4.48** and **4.49** were confirmed by crystallographic analysis (Figure 4.3).

Figure 4.3 – X-Ray Crystallographic Structures of Compounds **4.48** (left) and **4.49** (right)

The cleavage of the 2-phenyltetrahydrofuran ring to generate compound **4.48** exposed two new synthetic handles that could be employed to further elaborate the model substrate. Indeed, the aldehyde could serve to introduce the required isopropyl chain, and the benzoate

could be converted to the requisite ketone. We thus examined the alkylation of the aldehyde functionality of compound **4.49** with isopropyl-containing nucleophiles (Table 4.5). Addition of excess isopropylmagnesium chloride at low temperatures yielded no reaction, even in the presence of cerium chloride (entries 1-2). Upon reflux in diethyl ether, however, a reaction was observed, but it yielded a complex mixture of inseparable products (entry 3). We then turned to isopropenyl lithium **4.50** in the hope its slightly smaller size would ease the reaction. Addition of an excess of this nucleophile at low temperature had no effect on compound **4.49** (entries 4-5).⁹² Also, employing HMPA as a co-solvent to enhance the nucleophilicity of the lithium species had no influence on the reaction outcome. This absence of reactivity of the aldehyde can most probably be explained by the severe steric hindrance caused by the neighboring *gem*-dimethyl and benzoate groups. The relative bulkiness of the nucleophiles prevented them from alkylating the other carbonyl functionalities as well.

Table 4.5 – Attempted Alkylation of Aldehyde **4.49**

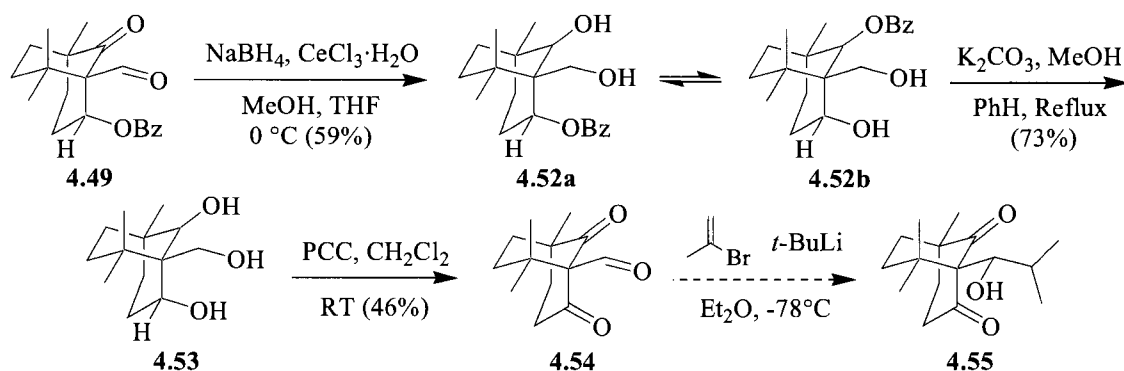


Entry	Nucleophile (equiv.)	Additive (equiv.)	Solvent	Temperature (°C)	Result
1	<i>i</i> -PrMgCl (5.0)	---	THF	-78 → RT	No reaction
2	<i>i</i> -PrMgCl (3.0)	CeCl ₃ (3.0)	THF	-78 → RT	No reaction
3	<i>i</i> -PrMgCl (5.0)	---	Et ₂ O	35	Complex mixture
4	4.50 (5.0)	---	THF	-78 → 0	No reaction
5	4.50 (5.0)	---	Et ₂ O	-78 → 0	No reaction
6	4.50 (3.0)	HMPA (20)	THF	-78 → 0	No reaction

In order to render the aldehyde more accessible for nucleophiles, we decided to remove the bulky benzoate group. A basic hydrolysis of the ester was thus attempted, but it only yielded decomposition of the starting material. The reduction of compound **4.49** with lithium

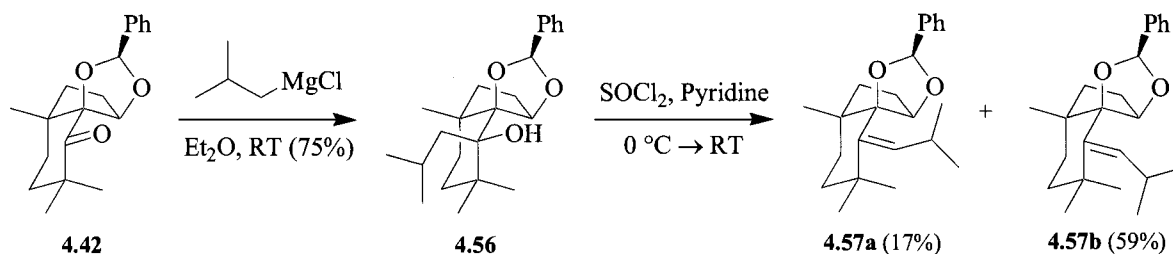
aluminum hydride led to a similar outcome. We thus hypothesized that a retro-aldol reaction triggered by the conversion of the benzoate to the corresponding alkoxide ion was probably responsible for this behavior. To circumvent this problem, a selective reduction of the ketone and aldehyde functionalities of **4.49** with sodium borohydride was carried out and the resulting diol was obtained as a dynamic mixture of **4.52a** and **4.52b** (Scheme 4.13). Subsequent cleavage of the ester in basic conditions afforded triol **4.53**, which was exhaustively oxidized to deliver diketoaldehyde **4.54** in fair overall yield. Unfortunately, alkylation of this diketoaldehyde with isopropenyl lithium **4.50** displayed no preference for the aldehyde site and a mixture of several inseparable products was generated.

Scheme 4.13 – Synthesis and Attempted Alkylation of Compound 4.54



At that point, we envisioned that a more efficient way to introduce the required alkyl group would probably be to carry out the Prins-Pinacol rearrangement of a substrate bearing an isopropyl-substituted alkene moiety. In order to synthesize the desired precursor, we employed the usual addition-elimination sequence (Scheme 4.14). Reaction of ketone **4.42**

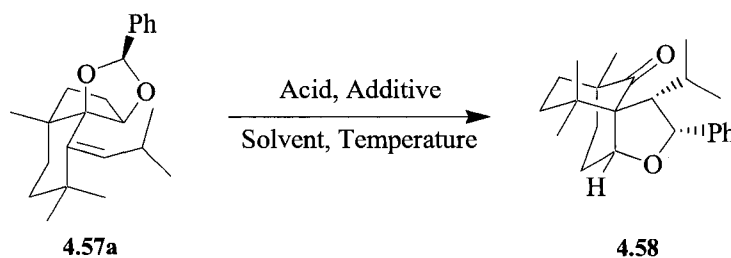
Scheme 4.14 – Synthesis of Isomeric Prins-Pinacol Precursors 4.57a and 4.57b



with excess isobutylmagnesium chloride afforded alcohol **4.56** as a single diastereomer in 75% yield. The relative stereochemistry of this intermediate was not determined and is assumed to be that illustrated in Scheme 4.14. The alcohol was then treated with thionyl chloride in pyridine, and a mixture of isomeric alkenes was recovered in 78% overall yield.⁹³

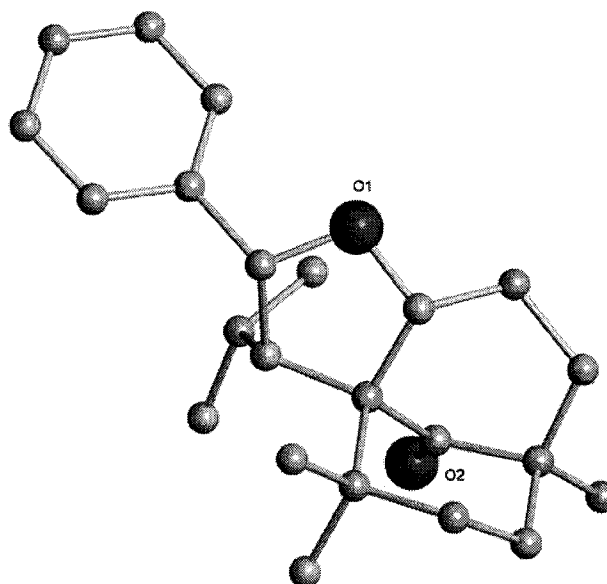
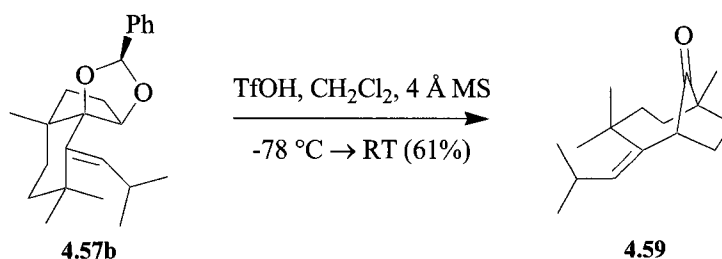
The Prins-Pinacol rearrangement of minor isomer **4.57a** was first inspected (Table 4.6). Surprisingly, treatment with tin(IV) chloride in toluene led to decomposition of the starting material (entry 1). Also, reaction with trifluoromethanesulfonic acid in acetonitrile yielded an inseparable mixture composed of bridged ketone **4.58** and an unidentified side-product (entry 2). However, when the reaction was performed at lower temperatures in dichloromethane, the desired product was obtained cleanly in 17% yield (entry 3). Furthermore, addition of molecular sieves to the reaction mixture resulted in a considerable augmentation of the yield (entry 4). The tridimensional structure of ketone **4.58** was determined by NMR spectroscopy and confirmed by crystallographic analysis (Figure 4.4).⁷⁵

Table 4.6 – Optimization of the Prins-Pinacol Reaction of Substrate **4.57a**

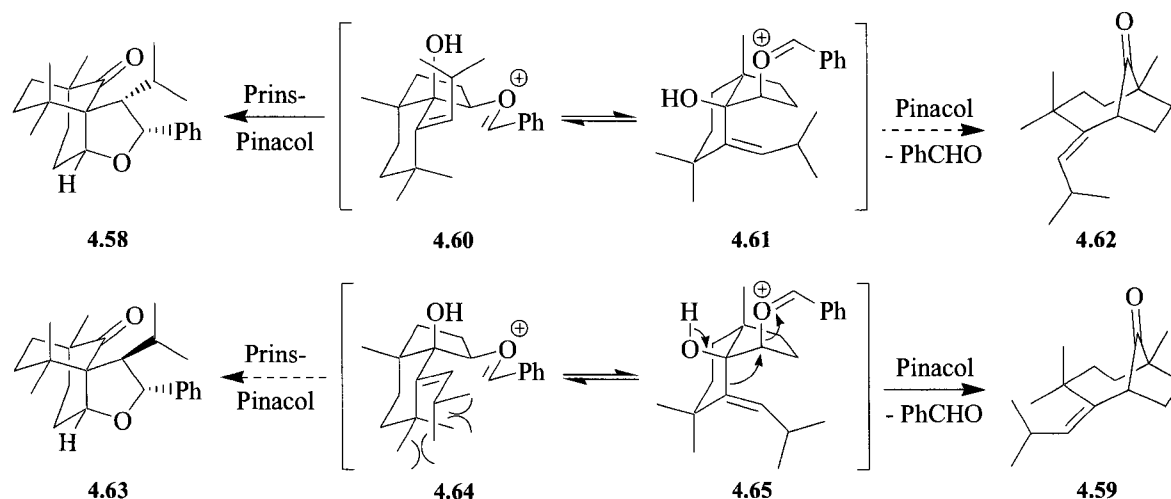


Entry	Acid (equiv.)	Additive	Solvent	Temperature (°C)	Yield (%)
1	SnCl ₄ (2.0)	---	PhMe	-78 → RT	Decomposition
2	TfOH (4.0)	---	MeCN	-20 → RT	Mixture
3	TfOH (2.0)	---	CH ₂ Cl ₂	-78	17
4	TfOH (2.0)	4 Å MS	CH ₂ Cl ₂	-78 → RT	58

The reactivity of major isomer **4.57b** was then examined. To our surprise, subjection of this alkene substrate to the optimized reaction conditions resulted in the exclusive formation of bicyclo[4.2.1]nonanone **4.59** in 61% yield (Scheme 4.15). The obvious reactivity difference

Figure 4.4 – X-Ray Crystallographic Structure of Bridged Ketone **4.58**Scheme 4.15 – Rearrangement of Alkene Substrate **4.57b**

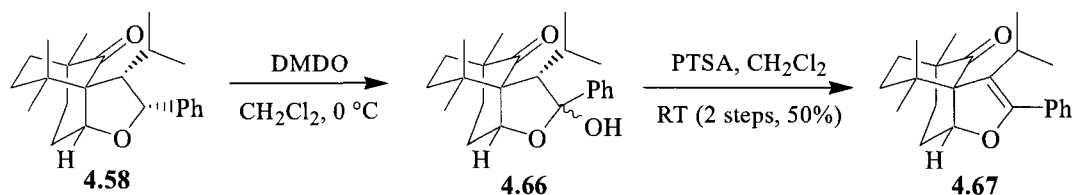
between substrates **4.57a** and **4.57b** can be well explained by the rationale depicted in Scheme 4.16. Treatment of minor isomer **4.57a** with trifluoromethanesulfonic acid results in the reversible generation of oxocarbenium **4.60**, which exists in equilibrium with conformer **4.61**. One can imagine the Prins-Pinacol reaction occurring faster than the conformational change. In that case, conformer **4.61** is not formed and the competing pinacolic rearrangement can never take place. On the other hand, assuming that the equilibrium between oxocarbeniums **4.60** and **4.61** is rapid, the system is under Curtin-Hammet conditions.²⁹ Therefore, the reaction pathway having the lowest transition state energy is preferred. In this case, the energy difference between the transition states is important enough for the Prins-Pinacol rearrangement to become the sole reaction pathway. More data

Scheme 4.16 – Rationalization of the Divergent Reactivity of Alkenes **4.57a** and **4.57b**

supporting the Curtin-Hammett hypothesis come from analysis of the behavior of major isomer **4.57b**. Treatment of this substrate in acidic conditions induces the formation of oxocarbenium **4.64**, which can reversibly be converted to conformer **4.65**. If the Prins-Pinacol reaction of **4.64** was faster than its conformational change, compound **4.63** would be produced during the reaction. Since this is not the case, we can assume that the equilibrium between conformers **4.64** and **4.65** is rapid and that the system obeys the Curtin-Hammett principle. The strong steric interactions existing between the *gem*-dimethyl and isopropyl groups of conformer **4.64** augment considerably the transition state energy of the Prins cyclization and thus prevent the Prins-Pinacol reaction from occurring. Because **4.65** does not experience these adverse steric effects, its pinacol rearrangement becomes the favored reaction pathway and bicyclo[4.2.1]nonanone **4.59** is the only product of the reaction.

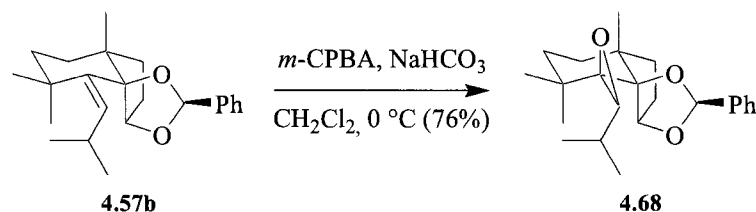
As we just saw, the introduction of the isopropyl group onto the 2-phenyltetrahydrofuran ring through a Prins-Pinacol rearrangement proved to be a valuable strategy. Considering the complexity of the precursor, bridged ketone **4.58** was obtained in relatively good yield. This compound was then converted to dihydrofuran **4.67** in 50% yield overall (Scheme 4.17).⁹⁰ The subsequent oxidative cleavage was attempted, but the results were inconclusive.⁹¹ Since only a minute amount of dihydrofuran **4.67** had been synthesized, this experiment could not be repeated. This situation emphasized a drawback that rendered our approach more difficult.

Scheme 4.17 – Synthesis of Dihydrofuran 4.67



Indeed, the isomer that led to the desired Prins-Pinacol rearrangement, **4.57a**, was obtained from alcohol **4.56** in only 17% yield. Therefore, a more efficient way to access alkene **4.57a** was required in order to render this strategy viable. Alcohol **4.56** was thus exposed to a few alternative elimination methods in the hope of obtaining a higher proportion of isomer **4.57a**. Unfortunately, treatment of alcohol **4.56** with the Burgess reagent or phosphorus oxychloride failed to deliver any elimination product.^{94,95} Moreover, attempted conversion of the tertiary alcohol to a mesylate or triflate leaving group was unsuccessful.⁹⁶ Disappointed by these results, we considered the isomerization of the unwanted isomer to desired **4.57a**. For that purpose, major isomer **4.57b** was first converted to the corresponding epoxide in 76% yield (Scheme 4.18).

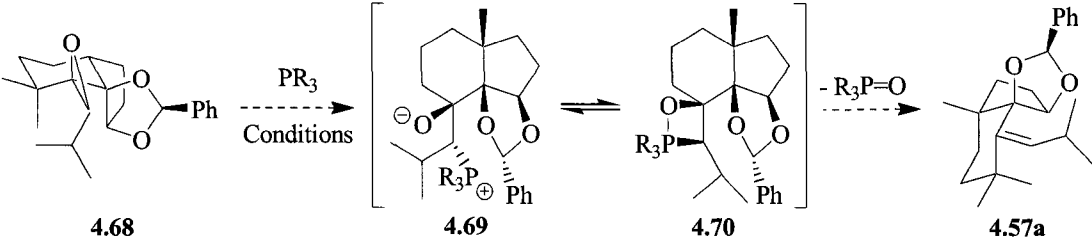
Scheme 4.18 – Synthesis of Epoxide 4.68



In the second stage of the olefin inversion sequence, a nucleophilic attack of a phosphine on the epoxide generates a betaine (e.g. **4.69**), which leads to the related oxaphosphetane (e.g. **4.70**). This intermediate then undergoes elimination of phosphine oxide and delivers the isomerized alkene. In our case, the reaction of epoxide **4.68** with various phosphines was examined (Table 4.7). When this epoxide was reacted with lithium diphenylphosphide and iodomethane, no reaction was observed (entry 1).⁹⁷ Treatment of **4.68** with tributylphosphine under reflux (entry 2) or microwave irradiation (entry 3) led to the same result. Addition of

lithium chloride to activate the epoxide had no effect on the outcome of the reaction (entry 4). Lastly, the use of the more nucleophilic trimethoxyphosphine also failed to deliver alkene **4.57a** (entry 5). We were not surprised by the lack of reactivity of epoxide **4.68**. In fact, the severe steric hindrance caused by the *gem*-dimethyl and isopropyl groups almost certainly prevented any nucleophilic attack of a phosphine onto the epoxide.

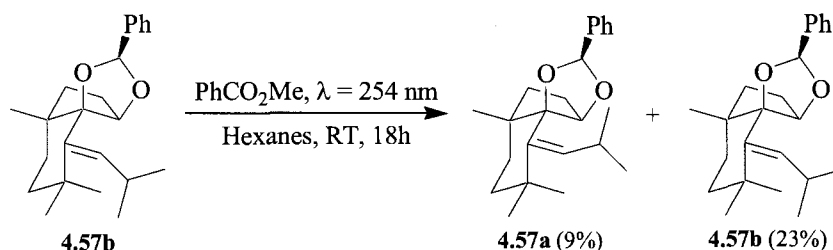
Table 4.7 – Attempted Generation of Alkene **4.57a** from Epoxide **4.68**



Entry	Conditions	Result
1	i) Ph ₂ PLi, THF, RT; ii) MeI, RT	4.68
2	PBu ₃ , PhMe, Reflux	4.68
3	PBu ₃ , PhMe, μ waves, 200 °C	4.68
4	PBu ₃ , LiCl, PhMe, μ waves, 200 °C	4.68
5	P(OMe) ₃ , LiCl, PhMe, μ waves, 200 °C	4.68

We also looked at the direct isomerization of alkene **4.57b**. When this compound was irradiated with ultraviolet light in the presence of a sensitizer, a mixture of **4.57a** and **4.57b** was obtained in 32% overall yield (Scheme 4.19). Obviously, we were pleased to finally gain

Scheme 4.19 – Isomerization of Alkene **4.57b** via Ultraviolet Irradiation

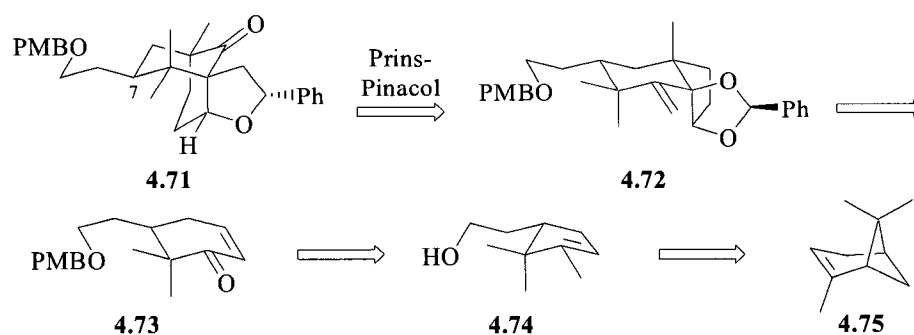


access to the desired isomer. On the other hand, **4.57a** was only obtained in poor yield and almost 70% of the initial mass was degraded during the reaction. This method was therefore not suitable for the conversion of **4.57b** to **4.57a**. We realized at that point that introducing the C₁ isobutyryl group of papuaforin A would be much more challenging than we initially imagined. Meanwhile, other aspects of the total synthesis also needed to be considered. Notably, a new strategy was required for the installation of the prenyl side-chain.

Introduction of the Prenyl Side-Chain of Papuaforin A

In the previous section, the synthesis and early elaboration of the core of papuaforin A were discussed. However, because our initial strategy for installing the side-chain at C₇ was unsuccessful, all compounds examined thus far lacked that important substituent. A new way of introducing the prenyl chain was therefore devised to remedy this problem. In order to validate this method, and to evaluate the potential influence of this substituent on the Prins-Pinacol rearrangement, we initiated the synthesis of a new analogue of papuaforin A. According to the retrosynthetic analysis illustrated in Scheme 4.20, analogue **4.71** would be generated through the Prins-Pinacol rearrangement of precursor **4.72**. This substrate would in turn be accessed from enone **4.73** via incorporation of the five-membered ring and elaboration of the benzylidene acetal. The enone would be derived from known alcohol **4.74** through sequential olefin cleavage and aldol condensation. Finally, the hydroxyethyl chain of compound **4.74** is generated through the oxidative rearrangement of α -pinene oxide, which is easily obtained from α -pinene (**4.75**). Given that both enantiomers of this starting material

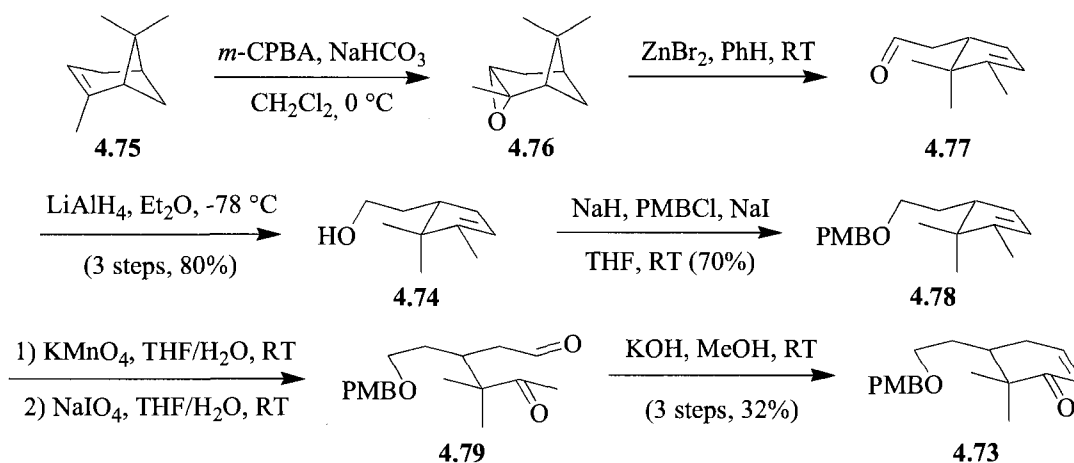
Scheme 4.20 – Retrosynthetic Analysis of Analogue 4.71



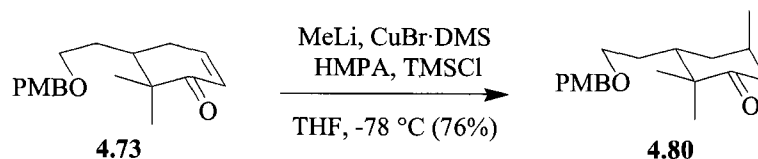
are commercially available, our approach could eventually lead to an enantiospecific total synthesis. Nonetheless, we preferred to use racemic α -pinene (**4.75**) for this model study because of its reasonable price.

Enone **4.73** was generated through a seven-step synthetic sequence developed by Méline Girardin in the course of her studies towards the synthesis of garsubellin A (**3.109**) (Scheme 4.21).⁶⁴ Treatment of α -pinene with *m*-CPBA furnished α -pinene oxide **4.76**, which underwent a rearrangement in the presence of zinc(II) bromide to afford aldehyde **4.77**.^{98,99} Reduction of the crude aldehyde with lithium aluminum hydride afforded, after purification, alcohol **4.74** in 80% overall yield. The alcohol was then protected with a *p*-methoxybenzyl group to afford **4.78** in 70% yield. Oxidative cleavage of the alkene was then performed using modified Lemieux-Johnson conditions.⁹¹ Indeed, we found that dihydroxylation of compound **4.78** was more effective with potassium permanganate than with its toxic and high-priced equivalent, osmium tetroxide.¹⁰⁰ Finally, treatment of the resulting keto-aldehyde with potassium hydroxide in methanol afforded enone **4.73** in 32% over three steps.¹⁰¹

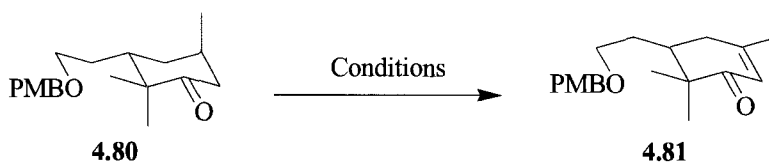
Scheme 4.21 – Synthesis of Enone **4.73**



Our next goal was to convert enone **4.73** to the corresponding 3-methylcyclohexenone. This was carried out in two steps. First, addition of lithium dimethylcuprate to enone **4.73** in the presence of chlorotrimethylsilane and HMPA produced ketone **4.80** in 76% yield (Scheme 4.22).⁷² We then examined the oxidation of **4.80** to the corresponding enone (Table 4.8).

Scheme 4.22 – Synthesis of Ketone **4.80**

Ketone **4.80** was first submitted to the conditions that were previously optimized for the oxidation of ketone **3.142**. In that case, however, treatment with phenylselenenyl chloride did not afford the corresponding selenide (entry 1).⁸⁶ Alternative conditions were therefore attempted. The reaction of **4.80** with palladium acetate and diethyl allyl phosphate afforded the desired enone in up to 53% yield (entry 2).¹⁰² Nonetheless, this reaction was unreliable and its efficiency decreased considerably as the scale increased. On the other hand, enone **4.81** was obtained rather reliably when the 2-bromoketone derived from **4.80** was submitted to forcing elimination conditions (entry 3).¹⁰³ Unfortunately, this reaction also led to disappointing yields.

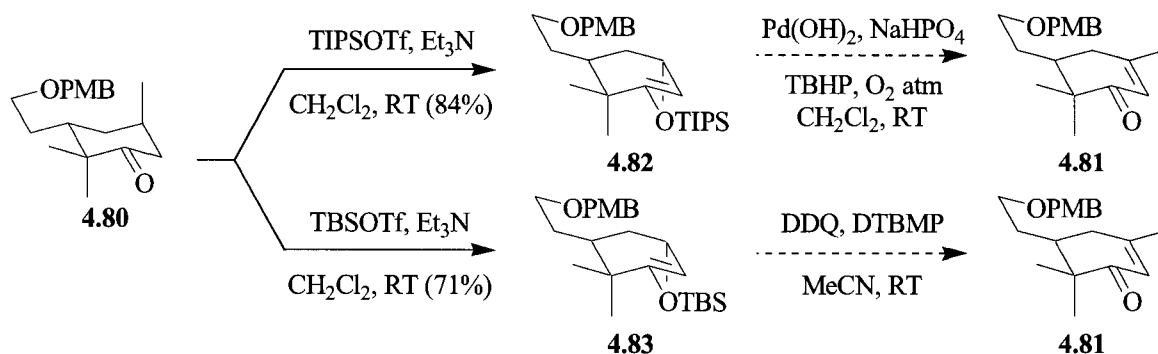
Table 4.8 – Optimization of the Formation of Enone **4.81**

Entry	Conditions	Yield (%)
1	1. PhSeCl, EtOAc, RT; 2. NaIO ₄ , MeOH, H ₂ O, RT	No reaction
2	Pd(OAc) ₂ , Diethyl allyl phosphate, Na ₂ CO ₃ , THF, 80 °C	12-53
3	1. CuBr ₂ , THF, RT; 2. LiBr, LiCO ₃ , DMF, Reflux	20-32

Finally, in the hope of generating enone **4.81** more effectively, the elimination of enol ethers derived from ketone **4.80** was briefly examined (Scheme 4.23). This ketone was first converted to triisopropylsilyl enol ether **4.82** in good yield. Then, employing a method developed by Corey, the enol ether was reacted with palladium(II) hydroxide and *tert*-butylhydroperoxide under an oxygen atmosphere, but no desired enone was produced.¹⁰⁴

Ketone **4.80** was also converted to the corresponding TBS enol ether in 71% yield.¹⁰⁴ However, oxidation of compound **4.83** with DDQ in the presence of DTBMP only yielded decomposition of the enol ether.¹⁰⁵

Scheme 4.23 – Attempted Elimination of Enol Ethers 4.82 and 4.83



Once again, the problematic formation of a crucial enone intermediate proved to be a major setback in the synthesis of a functionalized Prins-Pinacol precursor. Indeed, only a small quantity of enone **4.81** could be prepared (100 mg overall). For this reason, we decided to utilize readily available enone **4.73** for the exploration of the following steps of the synthesis. In this enterprise, the introduction of the five-membered ring was our first objective. This ring was incorporated through a three-step sequence developed for the generation of the Prins-Pinacol substrates presented in Chapter 3. First, using optimized conditions, a conjugate addition of the cuprate derived from Grignard reagent **3.117** onto enone **4.73** reproducibly furnished alcohol **4.84** in excellent yield (Scheme 4.24).⁶⁴ Subsequent Swern oxidation of this alcohol smoothly afforded keto-aldehyde **4.85**, but this compound could not be purified by chromatography because of its low stability. Therefore, the aldol cyclization of crude keto-aldehyde **4.85** was evaluated (Table 4.9).

Scheme 4.24 – Synthesis of Aldol Cyclization Precursor 4.85

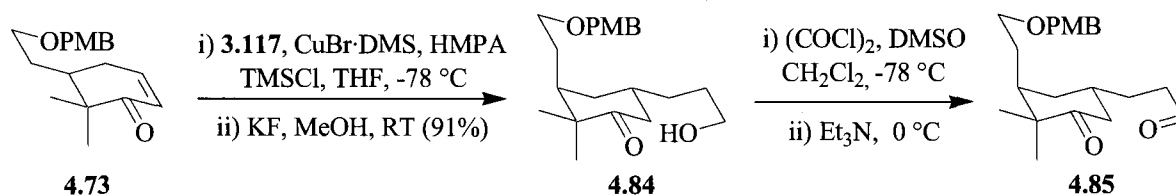
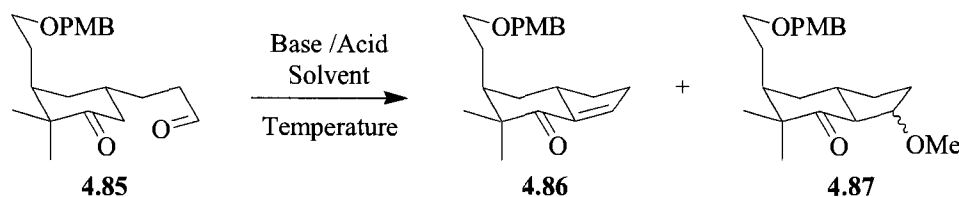


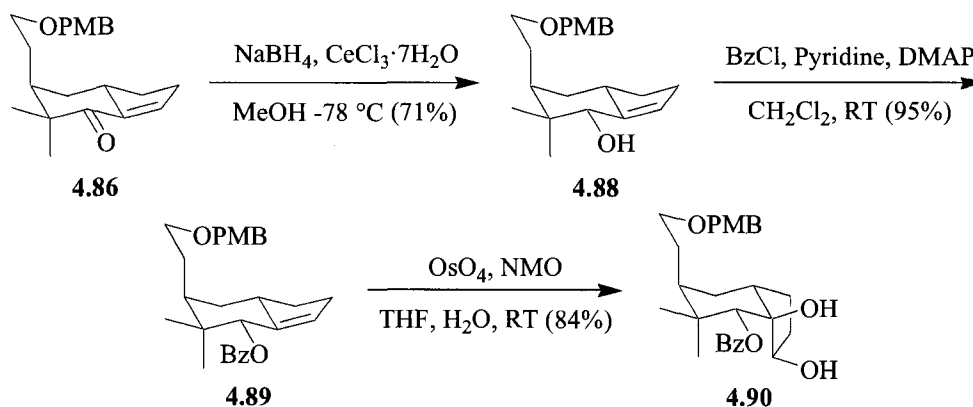
Table 4.9 – Aldol Condensation of Keto-Aldehyde **4.85**

Entry	Base / Acid	Solvent	Temperature (°C)	Yield 4.86 (%) ^a	Yield 4.87 (%) ^a
1	HCl	THF	RT	38-43	---
2	KOH	MeOH	65	16	21
3	KOH	THF	66	20	---

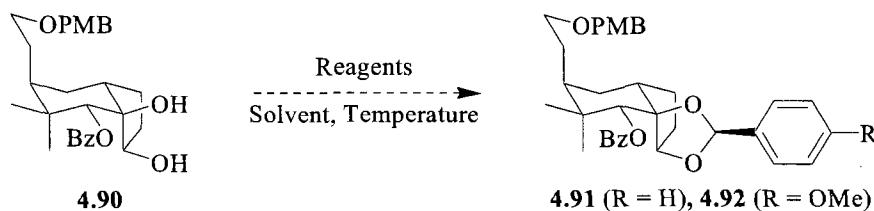
^aYield over two steps (Swern oxidation and aldol condensation).

On a small scale (e.g. 100 mg), the reaction of keto-aldehyde **4.85** with two equivalents of hydrochloric acid in tetrahydrofuran afforded enone **4.86** in about 40% yield (entry 1). Unfortunately, when this reaction was performed on a larger scale, keto-aldehyde **4.85** experienced degradation and no trace of the desired enone was observed. Since decomposition of the starting material was not previously observed on a substrate lacking the side-chain (**3.118**), we suspected that a reaction involving the *p*-methoxybenzyl protecting group occurred under these conditions. We therefore decided to perform the reaction under basic conditions. When keto-aldehyde **4.85** was treated with ten equivalents of potassium hydroxide in methanol, enone **4.86** was produced in 16% yield along with 21% of ketone **4.87** (entry 2).¹⁰¹ This ketone resulted from a conjugate addition of the solvent to enone **4.86**. In order to avoid the formation of that unwanted ketone, the reaction was carried out in tetrahydrofuran, and enone **4.86** was obtained as the sole product in 20% yield (entry 3).

The Luche reduction of enone **4.86** furnished allylic alcohol **4.88** in reasonable yield (Scheme 4.25). Importantly, the large-scale synthesis of this alcohol was conducted without purification from keto-alcohol **4.84** in 41% overall yield. This twofold augmentation of the yield suggests that a substantial proportion of enone **4.86** was lost during the purification stage. These losses could be related to the remarkable Michael acceptor character exhibited by this enone (Table 4.9, entry 2). Allylic alcohol **4.88** was then benzoylated the usual way

Scheme 4.25 – Synthesis of Diol **4.90**

to afford ester **4.89** in excellent yield. Dihydroxylation of the alkene moiety also proceeded very well and diol **4.90** was obtained in 84% yield. The relative stereochemistry of compounds **4.88-4.90** was determined by two-dimensional NMR experiments.⁷⁵ The subsequent acetalization of diol **4.90** was then attempted, but without success (Table 4.10).

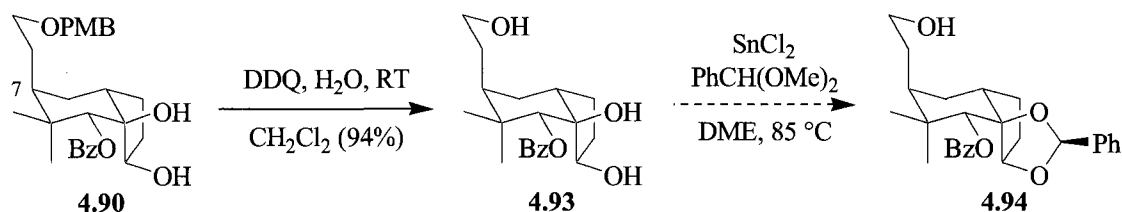
Table 4.10 – Attempted Acetalization of Diol **4.90**

Entry	Reagents (equiv.)	Solvent	Temperature (°C)	Result
1	PhCH(OMe) ₂ , (2.5), SnCl ₂ (0.6)	DME	85	Trace of 4.91 ?
2	PhCH(OMe) ₂ , (2.5), PTSA (0.2)	DMF	153	4.90
3	PhCHO (2.0), PTSA (0.05)	PhH	80	4.90
4	α,α-dibromotoluene (1.5)	Pyridine	115	4.90
5	4-MeO-C ₆ H ₄ CH(OMe) ₂ (1.5) SnCl ₂ (1.2)	DME	85	Decomposition
6	4-MeO-C ₆ H ₄ CHO (1.5) PTSA (0.05)	PhH	80	Decomposition

Diol **4.90** was first submitted to the standard acetalization procedure. Under these conditions, however, a mixture of three products was generated, and only a trace amount of what is believed to be benzylidene **4.91** was observed by NMR (entry 1).⁷⁴ Replacing stannous chloride with *p*-toluenesulfonic acid and heating at a higher temperature only yielded unreacted starting material (entry 2). The attempted acid-catalyzed condensation of diol **4.90** with benzaldehyde led to the same result (entry 3).¹⁰⁶ Also, no reaction was observed upon treatment of the diol with α,α -dibromotoluene in refluxing pyridine (entry 4).¹⁰⁷ We also attempted to synthesize acetal **4.92**. Nevertheless, treatment of diol **4.90** with *p*-anisaldehyde (entry 5) or *p*-anisaldehyde dimethyl acetal (entry 6) resulted in the production of complex mixtures.^{74,106} The formation of acetal **4.92**, even in trace amounts, was not observed under these conditions.

The unanticipated and disappointing behavior of diol **4.90** towards acetalization suggested a detrimental influence of the side-chain at C₇. The presence of this chain probably forces the bicyclic diol to adopt a conformation that prevents the desired acetalization from occurring. Therefore, in order to reduce the steric hindrance caused by the side-chain, we decided to withdraw the *p*-methoxybenzyl protecting group (Scheme 4.26). Diol **4.90** was thus reacted with DDQ, and triol **4.93** was obtained in 94% yield. The triol was then submitted to the standard acetalization conditions, but the formation of benzylidene **4.94** was not observed.

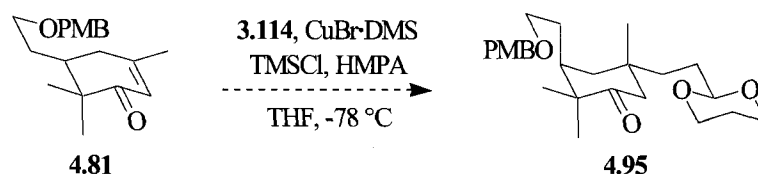
Scheme 4.26 – Attempted Acetalization of Triol **4.93**



Because of the unsuccessful acetalization of diol **4.90**, further exploration of that synthetic route had unfortunately to be suspended. We nonetheless chose to utilize the useful information gathered during the synthesis of this diol for the elaboration of Prins-Pinacol precursor **4.72** from enone **4.81**. As before, we planned to generate the five-membered ring of this substrate via a synthetic sequence involving a conjugate addition and an aldol

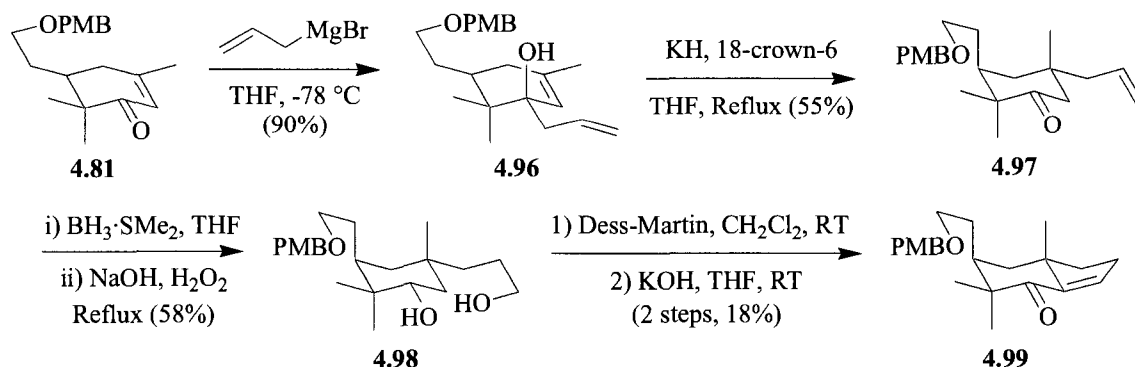
condensation. To this end, a conjugate addition of the cuprate derived from Grignard reagent **3.114** was first attempted (Scheme 4.27). Unfortunately, the reaction failed to deliver ketone **4.95**. The starting material could however be recovered almost completely. This lack of reactivity was probably related to the presence of a methyl at the β position of the enone.

Scheme 4.27 – Attempted Conjugate Addition on Enone **4.81**



An alternative way of forming the quaternary center at the ring junction was thus necessary. For this reason, the requisite three-carbon fragment was introduced through a two-step sequence developed by Méline Girardin (Scheme 4.28).⁶⁴ The initial 1,2-alkylation of enone **4.81** with allylmagnesium bromide afforded alcohol **4.96** as a single diastereomer in high yield. This was followed by an anionic oxy-Cope rearrangement of the alcohol.¹⁰⁸ The reaction was best achieved by treating **4.96** with potassium hydride and 18-crown-6 ether in refluxing tetrahydrofuran.⁶⁴ As a result, **4.97** was formed as a sole epimer in 55% yield. Three more steps were then required to form the five-membered ring. Hydroboration of alkene **4.97** under standard conditions reduced the ketone functionality as well, and diol **4.98** was obtained in reasonable yield. The relative stereochemistry of this compound was confirmed by two-dimensional NMR experiments.⁷⁵ This diol was then oxidized with Dess-

Scheme 4.28 – Synthesis of Enone **4.99**

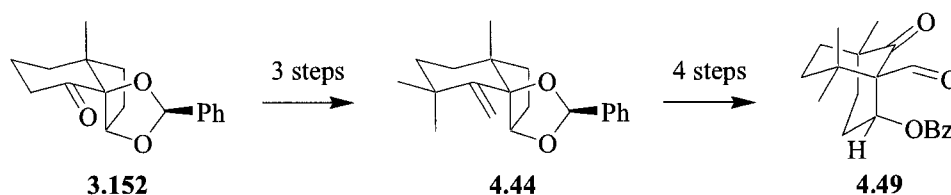


Martin periodinane to give the corresponding keto-aldehyde.³² Due to its relative instability, this compound was not chromatographed prior to the aldol condensation step. The crude keto-aldehyde was thus treated with a solution of potassium hydroxide in tetrahydrofuran, and enone **4.99** was generated in 18% yield over two steps. The whole five-step sequence was particularly low-yielding, since only 3.4 mg of enone **4.99** were produced starting from 100 mg of enone **4.81**. Considering the very small amount of enone **4.99** obtained and the questionable generation of the corresponding benzylidene acetal, the synthesis of Prins-Pinacol precursor **4.72** was abandoned. This unfortunate event also marked the end of our synthetic investigations towards papuaforin A.

Conclusion

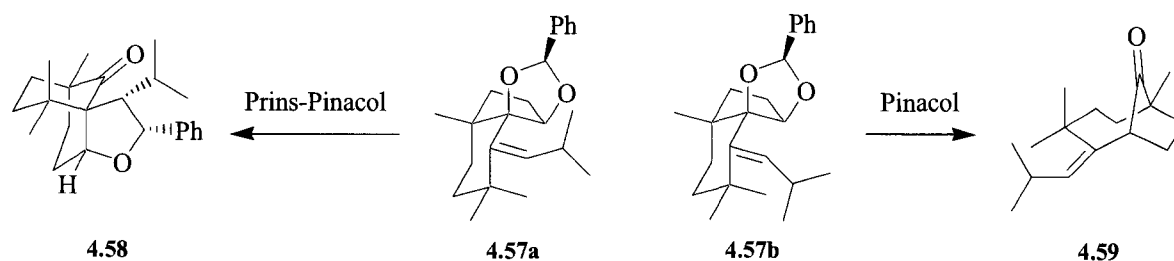
In the course of the synthetic investigations exposed in this chapter, a considerable volume of valuable information regarding the synthesis of papuaforin A (**4.1**) has been gathered. Our original synthetic strategy involved the construction of the core of this natural product via the Prins-Pinacol reaction of an allenic precursor bearing an isopropylidene ketal. A model study however demonstrated that the presence of a C₈ *gem*-dimethyl group seriously impaired the efficiency of the rearrangement of isopropylidene ketals. This unfortunately sealed the fate of our initial synthetic plan. We therefore considered the Prins-Pinacol rearrangement of a model benzylidene substrate (**4.44**), which provided in high yield and total stereoselectivity the bicyclo[3.3.1]nonanone skeleton of papuaforin A (**4.1**). The core of the natural product was further elaborated by cleaving the tetrahydrofuran ring. Advanced intermediate **4.49** was thus obtained in seven steps from ketone **3.152** (Scheme 4.29). Disappointingly, alkylation of the aldehyde functionality of compound **4.49** was unsuccessful due to the presence of two bulky neighboring groups. Nonetheless, the requisite alkyl group could be introduced via the

Scheme 4.29 – Summarized Generation of Advanced Intermediate **4.49**



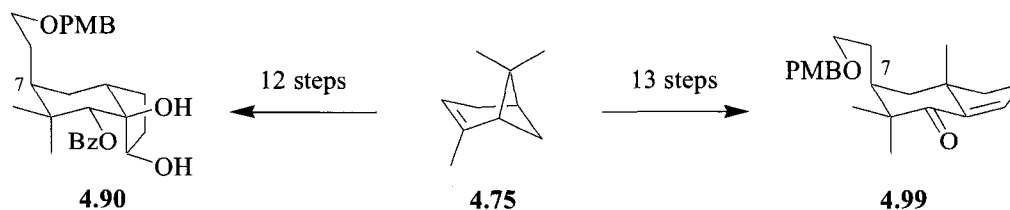
Prins-Pinacol reaction of **4.57a**, a precursor possessing an isopropyl-substituted alkene moiety (Scheme 4.30). Alkene **4.57a** was unfortunately formed as the minor component of a mixture. Moreover, the major isomer, alkene **4.57b**, exclusively underwent a pinacolic rearrangement to furnish unwanted bridged ketone **4.59**. Since all efforts to isomerize **4.57b** into **4.57a** failed, we realized that this approach was not suitable for our total synthesis.

Scheme 4.30 – Divergent Reactivity of Isomeric Alkenes 4.57a and 4.57b



Finally, a way of stereoselectively introducing the C₇ prenyl chain was examined. For that purpose, the synthesis of an analogue of papuaforin A (**4.71**) was undertaken. Early exploratory work gave access to model compound **4.90** in twelve steps from α -pinene **4.75** (Scheme 4.31). For reasons that are not yet understood, acetalization of diol **4.90** could however not be completed. The chemistry developed during the synthesis of **4.90** could nevertheless be employed in the construction of analogue **4.71**. Intermediate **4.99** was thus obtained in thirteen steps from α -pinene, but the poor efficacy of the synthetic sequence prevented further conversion of this enone to the corresponding Prins-Pinacol precursor.

Scheme 4.31 – Elaboration of two Side-Chain-Bearing Model Compounds from α -Pinene



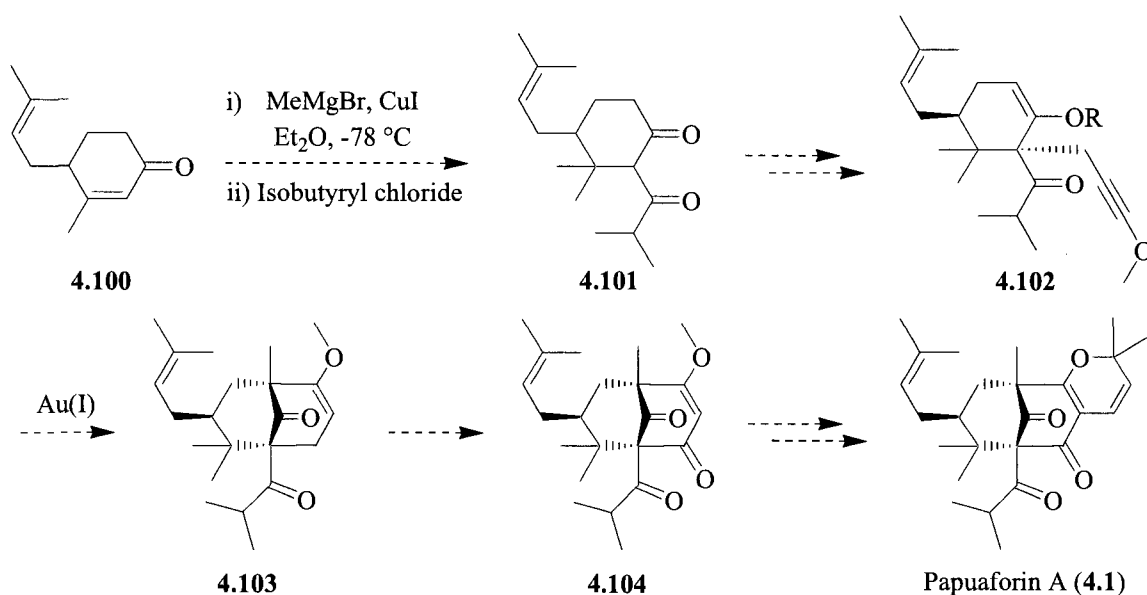
To sum up, the Prins-Pinacol rearrangement allowed the stereoselective generation of the bicyclo[3.3.1]nonanone core of papuaforin A (**4.1**) and the introduction of both bridgehead

quaternary stereocenters in a single chemical step. Unfortunately, important drawbacks related to the introduction of substituents onto the carbon skeleton were encountered. Notably, none of the two methods attempted for the generation of the C₁ isobutyryl group was satisfactory. Additionally, the presence of the C₇ side-chain thwarted the acetalization of elaborated diol **4.90**. These major flaws made us consider a completely different approach.

Outlook

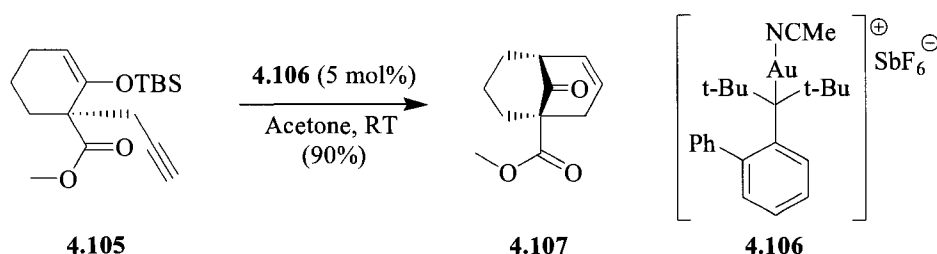
Inspired by recent publications on noble-metal-mediated formation of carbocycles, we envisioned that the bicyclo[3.3.1]nonanone skeleton of papuaforin A (**4.1**) could be generated via the gold-catalyzed 6-*endo*-dig cyclization of an enol ether on an alkyne. Our totally revised synthetic plan for the total synthesis of this natural product is illustrated in Scheme 4.32. The sequence would start with enone **4.100**, which could easily be converted to β -diketone **4.101**.⁸² Alkylation of **4.101** with 3-methoxypropyne, followed by formation of the silyl enol ether would afford cyclization precursor **4.102**. Treatment of this substrate with gold(I) would produce bridged ketone **4.103**, which would then be oxidized to trione **4.104**. Prenylation at C₃, followed by demethylation and electrocyclicization would ultimately furnish

Scheme 4.32 – Proposed Second-Generation Synthesis of Papuaforin A (**4.1**)



papuaforin A (**4.1**). In addition, the feasibility of the crucial gold-catalyzed cyclization step was demonstrated via a model study conducted recently by honors student Geneviève Bétournay and graduate student Francis Barabé. Preliminary results have indeed shown that treatment of simple substrate **4.105** with catalyst **4.106** at room temperature led to the formation of desired bicyclo[3.3.1]nonenone **4.107** in 90% yield (Scheme 4.33).^{109,110} This exciting result validated our proposed gold-catalyzed generation of bicyclo[3.3.1]nonanones. Besides, further optimization of this reaction will certainly result in the development of a valuable synthetic tool that will allow a straightforward total synthesis of papuaforin A.

Scheme 4.33 – Au(I)-Catalyzed Formation of Bicyclo[3.3.1]nonanone 4.107



This second-generation synthesis of bicyclo[3.3.1]nonanones was however not the first gold-catalyzed reaction to be developed in our laboratory. Indeed, a remarkable benzannulation of hydroxyenynes had already been developed in 2006 by Ph.D. student Christiane Grisé.¹¹¹ The value of this methodology was demonstrated through an application to synthesis, which was carried out in parallel with the synthetic investigations towards papuaforin A. This work resulted in the facile total synthesis of diterpene natural product (+)-isofregenedol.

5

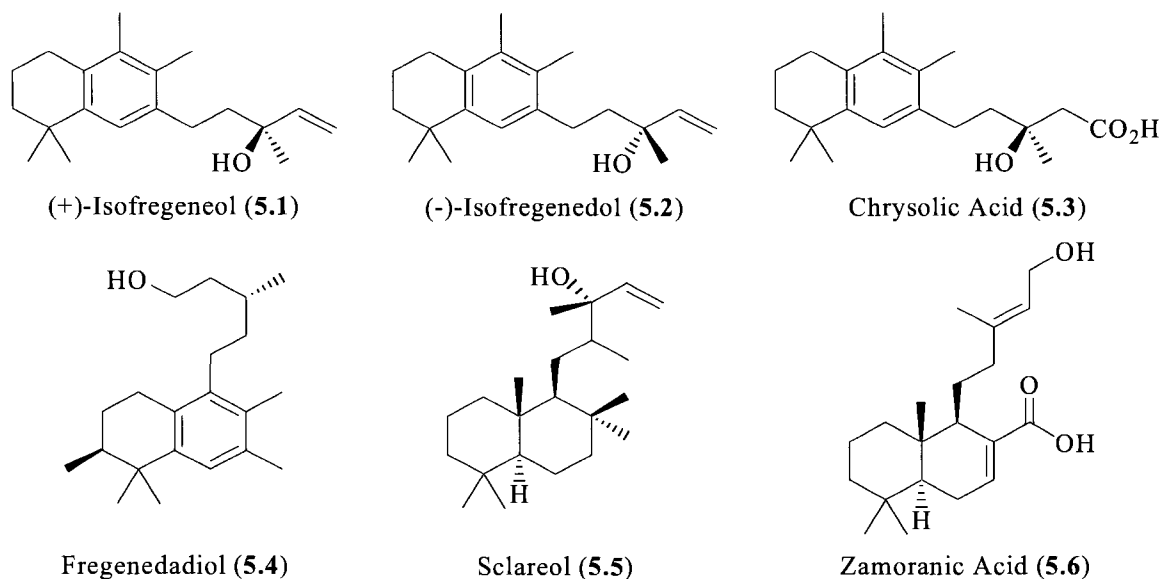
The Total Synthesis of (+)-Isofregenedol

Introduction

In 1991, Niemeyer and co-workers reported the isolation of a novel diterpene, (+)-isofregenedol (**5.1**), from the aerial parts of a Chilean flower, *Haplopappus parvifolius* (Figure 5.1).¹¹² NMR spectroscopy revealed that (+)-isofregenedol possesses a substituted tetrahydronaphthalene core. Also, on the basis of biogenetic hypotheses, the absolute configuration at C₁₃ was initially proposed to be *R* (**5.2**). Nonetheless, it was later established by means of synthesis that the absolute configuration at that center was *S*.¹¹³ Tetrahydronaphthalene skeletons are only encountered in a few naturally occurring products, most of them being members of the isofregenedane (e.g. **5.3**) and fregenedane (e.g. **5.4**) diterpenoid family. This type of carbon scaffold is also found in a number of medicinally active compounds.¹¹⁴

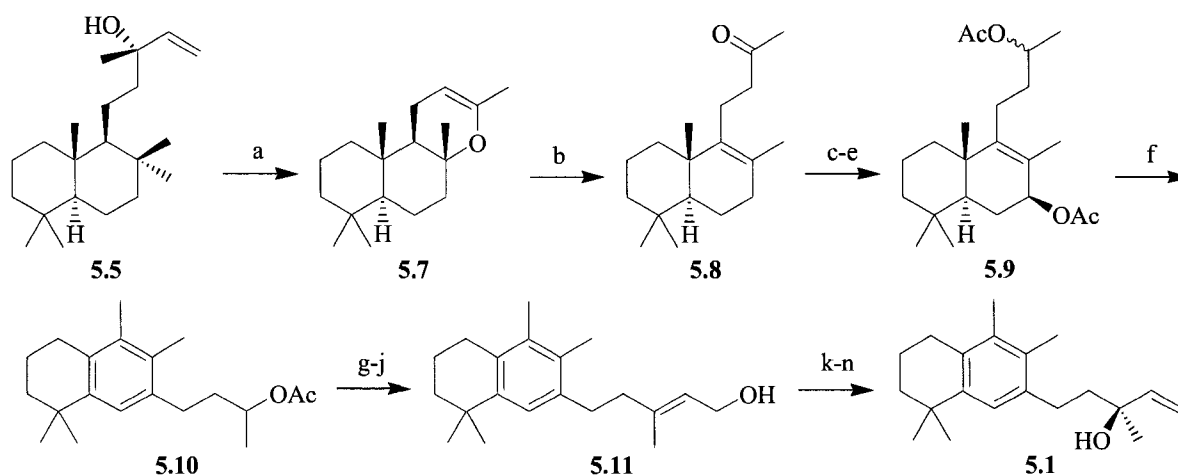
The prospective biological properties of (+)-isofregenedol, as well as its relatively complex structure, rendered it an attractive target for synthesis. Indeed, Marcos and co-workers have reported in 2003 the synthesis of this natural product via the cationic rearrangement of labdane diterpenes sclareol (**5.5**) and zamoranic acid (**5.6**).¹¹³ One of these syntheses is summarized in Scheme 5.1.

Figure 5.1 – Structures of Compounds 5.1-5.6



According to their strategy, sclareol (5.5), a complex natural product possessing five stereocenters, was transformed progressively into key intermediate 5.10 with loss of all stereochemical information. The required chiral center at C₁₃ was then introduced through a

Scheme 5.1 – Marcos' Synthesis of (+)-Isorefrenedol (5.1) from Sclareol (5.5)

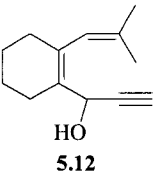
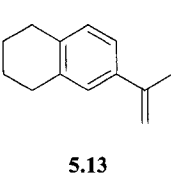
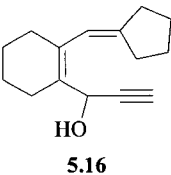
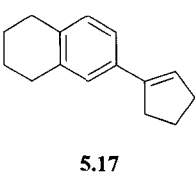
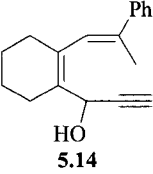
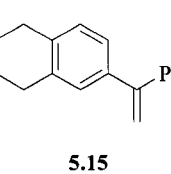
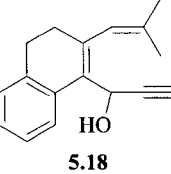
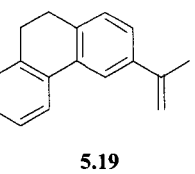


Reagents and conditions: (a) KMnO_4 , MgSO_4 , SiO_2 (65%); (b) HI , PhH , RT (98%); (c) Na_2CrO_4 , Ac_2O , AcONa , AcOH , 60 °C (65%); (d) LAH , THF (97%); (e) Ac_2O , Py (quant.); (f) HI , PhH , reflux (65%); (g) LAH (96%); (h) PCC , CH_2Cl_2 (90%); (i) $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COOMe}$, NaH (90%) (E/Z, 9:1); (j) DIBAH (90%); (k) L-(+)-DET, TBHP, $\text{Ti}(\text{i-PrO})_4$, -24 °C (90%); (l) TsCl , Py (75%); (m) Zn-Cu , ICu , THF (84%); (n) Zn , AcOH (80%).

lengthy route that led to (+)-isorefrenedol (**5.1**) in fourteen steps overall. Oxidation of sclareol (**5.5**) with KMnO_4 , followed by acid-mediated ring-opening of resulting pyran **5.7** afforded ketone **5.8** in good yield. The latter was then successively oxidized, reduced and esterified to yield diester **5.9** as a mixture of diastereomers. The key step of the synthesis consisted of an acid-mediated aromatization of the cyclohexene ring of **5.9**. The resulting tetrahydronaphthalene was obtained in a reasonable yield of 65%. An oxidation state adjustment of acetate **5.10** furnished the corresponding ketone. Introduction of the remaining carbon atoms by a Horner-Wadsworth-Emmons olefination, and reduction of the resulting ester afforded allylic alcohol **5.11**. Asymmetric epoxidation, followed by tosylation of the resulting alcohol gave the related tosylate in good yield. Finally, a $\text{S}_{\text{N}}2$ reaction, followed by reduction of the resulting iodide with zinc provided (+)-isorefrenedol (**5.1**). The natural product was obtained in 8% yield overall from sclareol (**5.5**). Importantly, this first synthesis of (+)-isorefrenedol allowed the determination of the absolute configuration at C_{13} . On the other hand, utilization of expensive natural products as starting materials unquestionably represented an important flaw. A straightforward total synthesis of this target was therefore desirable.

There are relatively few ways to build tetrahydronaphthalenes efficiently. These compounds have traditionally been synthesized by catalytic hydrogenation of naphthalenes, or via intramolecular Friedel-Crafts alkylations.¹¹⁵ Unfortunately, these methodologies experience regioselectivity problems, limited substrate scope and poor yields. In the last few years, however, innovative strategies have been developed to overcome the difficulty of constructing tetrahydronaphthalene frameworks. One of these alternative methods is the cycloisomerization of 1,5-enynes and 1,6-enynes, which allows the *de novo* assembly of aromatic rings and tetrahydronaphthalene skeletons. A good illustration of the possibilities brought about by this chemistry has been reported by Liu and co-workers in 2006.¹¹⁶ In this study, a variety of 4,6-dienyl-3-ols were treated with catalytic amounts of platinum(II) chloride to give tetrahydronaphthalenes in good to high yields (Table 5.1). However, this system tolerates substitution at the alkene moiety, but not at the alkyne site. The resulting tetrahydronaphthalenes are therefore substituted at a single position only. Hence, exploitation of this method for the total synthesis of isorefrenedol would most probably not be viable.

Table 5.1 – Liu's Pt(II)-Catalyzed Cyclization of 4,6-Dienyn-3-ols

Entry	Substrate ^a	Product	Yield	Entry	Substrate ^a	Product	Yield
1			78%	3			87%
2			86%	4			92%

^a Reaction Conditions: 5 mol% PtCl₂, PhMe, 80 °C, 30 minutes.

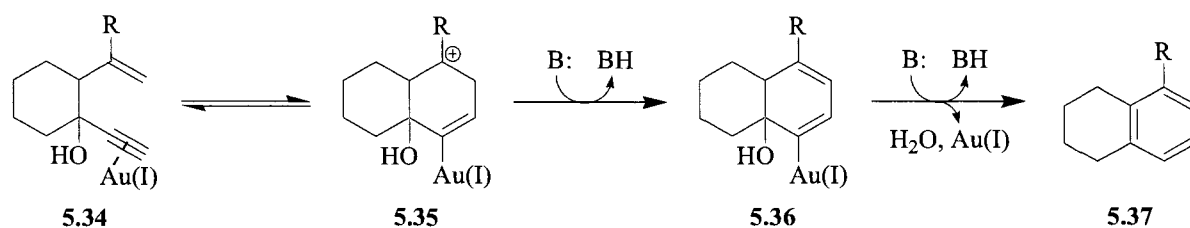
More recently, a novel gold-catalyzed benzannulation reaction has been reported by Ph.D. student Christine Grisé.¹¹¹ In this methodological work, treatment of 3-hydroxy-1,5-enynes **5.20** with catalytic amounts of triphenylphosphinegold(I) chloride and silver triflate led to the facile formation of tetrahydronaphthalenes **5.21** (Table 5.2). The low catalyst loadings and mild conditions employed, as well as the good to excellent yields obtained, rendered this reaction attractive for the synthesis of tetrahydronaphthalenes. In this system, substitution is well tolerated at both alkene and alkyne moieties. In fact, substitution at R₁ seems to be crucial for a successful reaction. Indeed, when R₁ was a hydrogen, compound **5.23** was obtained in 10% yield only (entry 1). Replacement of this hydrogen by a phenyl enhanced the yield to 84% (entry 2). Substitution of the alkyne seemed to have little effect on the efficiency of the reaction (entries 3-4). Substrate **5.30**, bearing a cyclic olefin, also proceeded in good yield (entry 5). At last, treatment of electron-rich furan **5.32** under the reaction conditions afforded benzofuran **5.33** in 57% yield (entry 6). These results bring out the capacity of this system to introduce substituents at specific positions of the arene. Since isofregenedol possesses three contiguous alkyl groups on its aromatic ring, we realized that this gold-catalyzed benzannulation would be ideal for the rapid construction of its core. Moreover, 3-hydroxy-1,5-enynes substrates could easily be synthesized from commercially available materials in two to four steps. The proposed mechanism of reaction is depicted in Scheme 5.2.¹¹¹ This postulated mechanistic pathway involves an initial interaction of the substrate with the gold catalyst that leads to the formation of Au(I) complex **5.34**. A 6-endo-

Table 5.2 – Au(I)-Catalyzed Benzannulation of 3-Hydroxy-1,5-enynes

Entry	Substrate	Product	Yield	Entry	Substrate	Product	Yield
1			10%	4			86%
2			84%	5			81%
3			77%	6			57%

dig cyclization of the latter gives **5.35**, which can be deprotonated to afford intermediate **5.36**. Finally, concomitant deauration and elimination of water yield tetrahydronaphthalene **5.37** as the only product of the reaction. This enyne cycloisomerization is remarkable, since it leads to the formation of an aromatic product. Indeed, metathesis, polycyclic or oxy-Cope products are habitually generated by such a reaction.

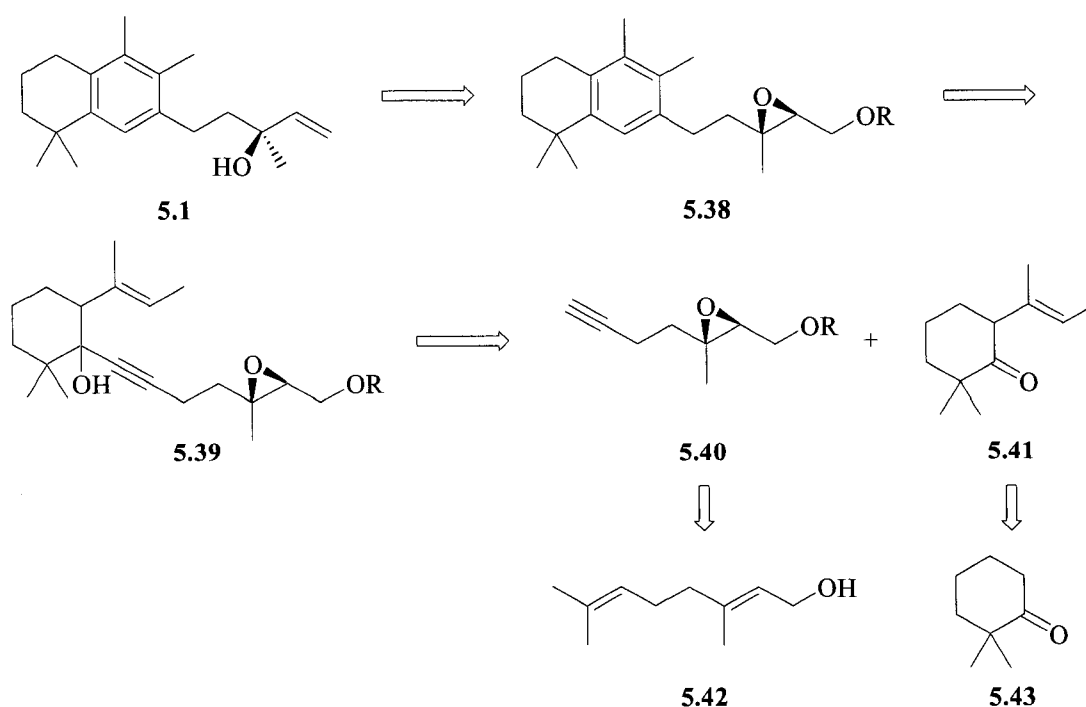
Scheme 5.2 – Proposed Mechanism for the Au(I)-Catalyzed Benzannulation



First Approach to (+)-Isofregenedol

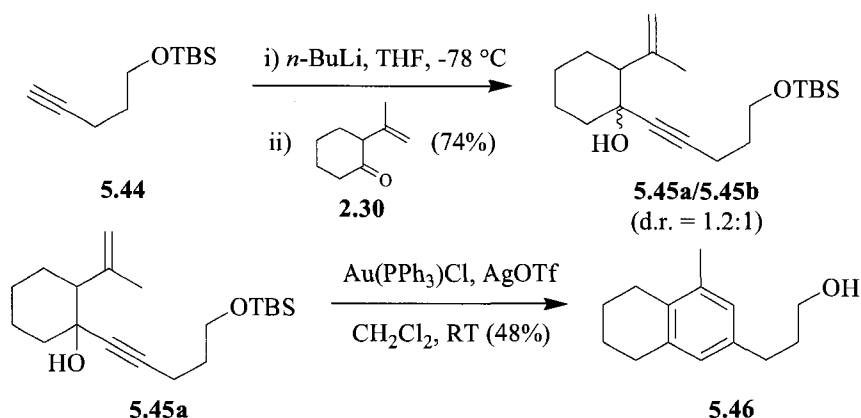
After inspection of the structure of (+)-isofregenedol, the construction of its tetrahydronaphthalene core employing the gold-catalyzed benzannulation described in table 5.2 was envisaged. According to a meticulous retrosynthetic analysis, it was decided that this natural product could most likely be synthesized from geraniol (**5.42**) and cyclohexanone **5.43** in as few as eight steps (Scheme 5.3). (+)-Isofregenedol (**5.1**) could come from elaboration of complex epoxide **5.38** by using chemistry analogous to that developed by Marcos and co-workers.¹¹³ This epoxide could in turn be generated by the key gold-catalyzed benzannulation of enyne **5.39**. The latter could most probably be obtained by alkylation of hindered ketone **5.41** with the lithium species derived from epoxyalkyne **5.40**. Notably, it was decided early on that elaboration of the side-chain should precede the junction of these two synthons to reduce the number of linear steps. Alkyne synthon **5.40** could thus be synthesized from geraniol (**5.42**) in four steps. An asymmetric epoxidation of this allylic alcohol would obviously give access to an enantioselective total synthesis. Finally, ketone **5.41** could be synthesized in one step from ketone **5.43** via a Buchwald-Hartwig coupling.

Scheme 5.3 – First Retrosynthetic Analysis of (+)-Isofregenedol (**5.1**)



Before applying this retrosynthetic plan to the actual total synthesis, a validation of the key step was indispensable. A short model study was thus performed to confirm that substitution of the alkyne with an alkyl chain would be compatible with the benzannulation reaction (Scheme 5.4). For this purpose, the lithium species derived from simple alkyne **5.44** was reacted with model ketone **2.30** to afford alcohols **5.45** as a 1.2:1 mixture of epimers in 74% yield. As anticipated, subjection of major epimer **5.45a** to the usual benzannulation conditions afforded tetrahydronaphthalene **5.46** as the sole product in an acceptable 48% yield.¹¹¹ Interestingly, this result indicated that silyl protecting groups could fall off in those conditions. More importantly, it demonstrated that the key step we envisioned in the retrosynthesis could realistically be carried out.

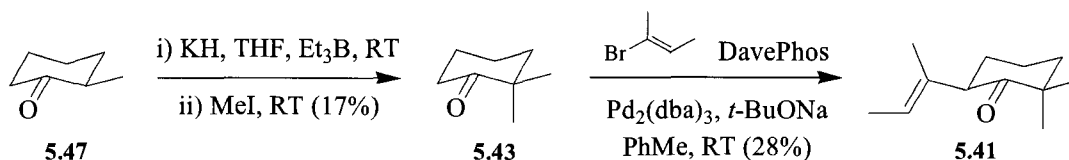
Scheme 5.4 – Validation of the Key Benzannulation Step



The total synthesis of (+)-isorefrenedol (**5.1**) commenced with the production of ketone **5.41**. This enterprise was however not as straightforward as it would seem at first glance. The high cost of commercially available ketone **5.43** (about \$ 265 per gram) led us to consider alternative ways to access this starting material. Ketone **5.43** was thus prepared from inexpensive 2-methylcyclohexanone **5.47** (Scheme 5.5). In accordance with a literature procedure, treatment of the potassium enolate of **5.47** with triethylborane, followed by addition of methyl iodide afforded ketone **5.43** in a disappointing 17% yield.¹¹⁷ The latter was nonetheless obtained as a single isomer. Ketone **5.43** was subsequently converted into ketone **5.41** in 28% yield using conditions developed by Buchwald and co-workers.¹¹⁸ This last reaction was however particularly unreliable and often yielded the desired ketone along

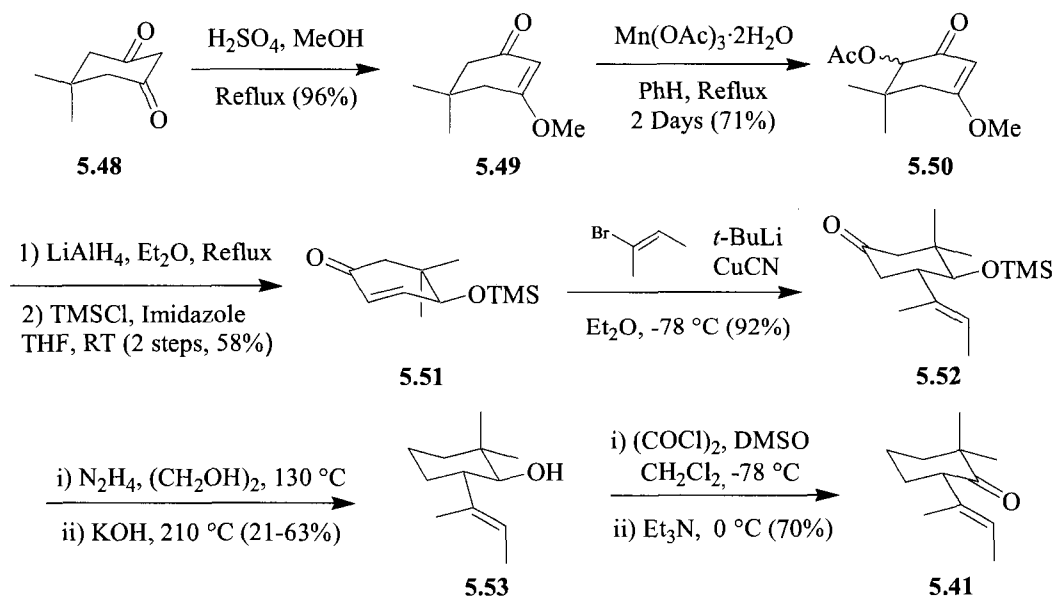
with inseparable byproducts. Since obtaining alkyne **5.41** in sufficient amounts and quality by this route was uncertain, an alternative synthetic sequence was investigated.

Scheme 5.5 – First Synthesis of Ketone **5.41**



The second route leading to ketone **5.41** was elaborated on the basis of a synthetic sequence developed by former Ph.D. student Irina Denisova (Scheme 5.6).¹¹⁹ Commercially available diketone **5.48** was first converted to enol ether **5.49** in high yield.¹²⁰ Subsequent radical-mediated incorporation of an acetate group via treatment with manganese(III) acetate hydrate delivered keto ester **5.50** in 71% yield.¹²¹ Compound **5.50** was then refluxed in the presence of excess lithium aluminum hydride to afford the crude rearranged alcohol, which was silylated to give compound **5.51** in good yield.¹¹⁹ Copper-mediated addition of *E*-2-bromobut-2-ene to **5.51** reproducibly afforded ketone **5.52** as a single diastereomer in excellent yield.¹¹⁹ A subsequent Wolff-Kishner reaction effected simultaneous reduction of

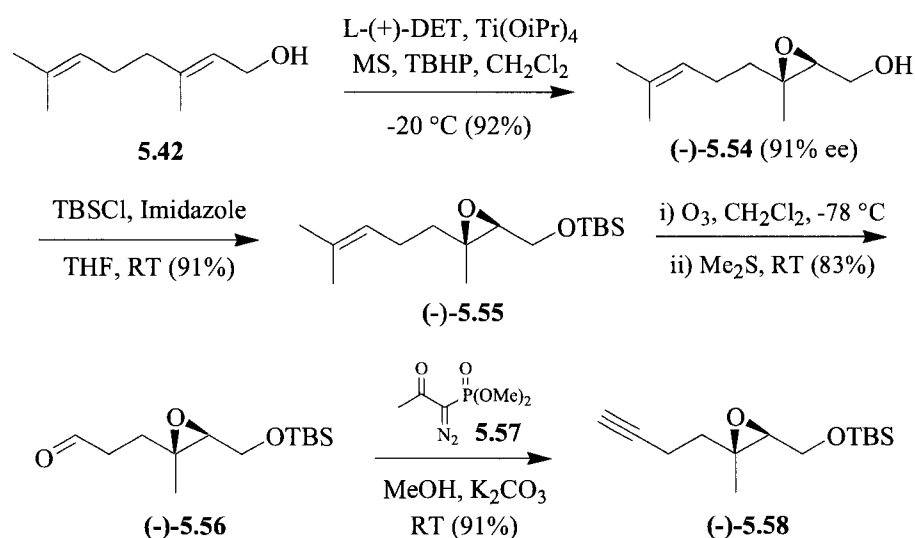
Scheme 5.6 – Second Synthesis of Ketone **5.41**



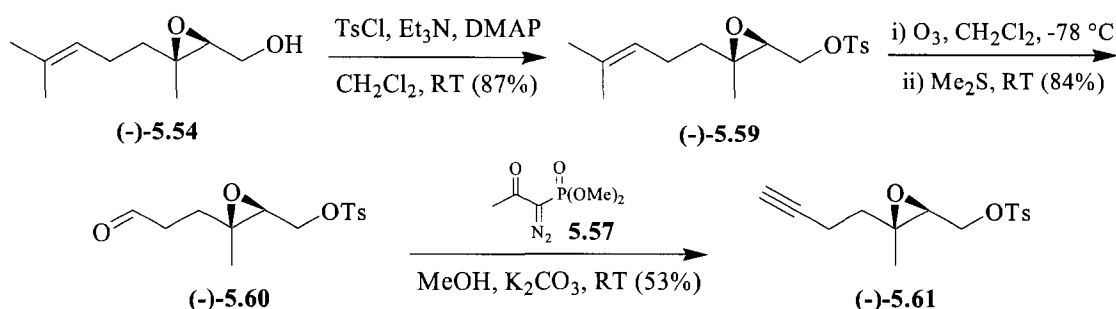
the carbonyl and removal of the TMS group to give alcohol **5.53**.¹²² This reaction did not reliably deliver the desired alcohol, as yields varied between 21 and 63%. However, a sufficient amount of intermediate **5.53** could be obtained to complete the preliminary synthetic exploration. Final Swern oxidation of the alcohol delivered pure ketone **5.41** in 70% yield.²³ Having ketone **5.41** in hand, the synthesis of elaborated alkynes of type **5.40** could be initiated.

Two alkyne synthons of type **5.40** were synthesized. Alkyne **5.58** had its hydroxy group silylated (Scheme 5.7), whereas **5.61** possessed a tosylate leaving group (Scheme 5.8). The hydroxy groups needed to be masked to simplify the alkylation and benzannulation steps. Protection with a silyl group was a safe choice because alkylation of ketone **5.41** and ensuing benzannulation would likely be successful according to the validation study shown in Scheme 5.4. A four-step synthetic sequence straightforwardly furnished alkyne **5.58** in good yield and high enantiomeric excess. First, Sharpless asymmetric epoxidation of geraniol (**5.42**) using L-diethyl tartrate yielded epoxygeraniol **5.54** in high yield with 91% ee.¹²³ Silylation of the latter, followed by ozonolysis of resulting alkene **5.55** afforded compound **5.56** in good yield. This aldehyde could then be converted to alkyne **5.58** in one step by treatment with modified Ohira reagent **5.57**.¹²⁴ On the other hand, incorporation of a tosylate

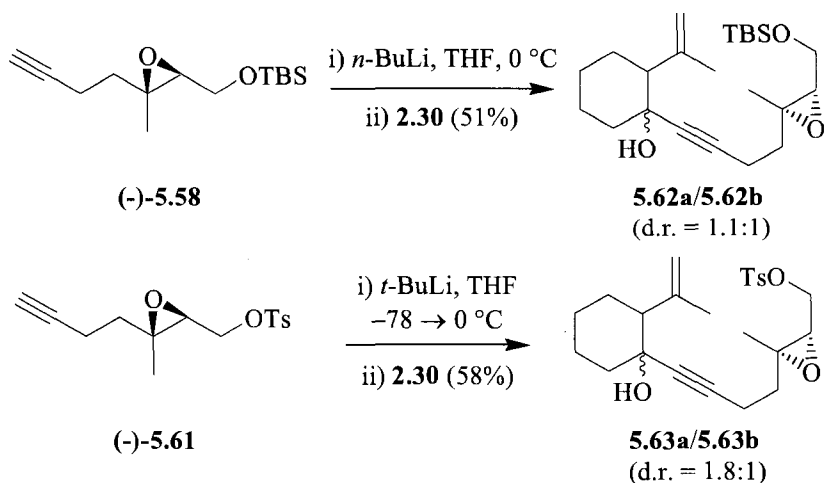
Scheme 5.7 – Synthesis of Alkyne Synthon **5.58**



group was more risky, since both the alkylation of ketone **5.41** and the following benzannulation could be compromised by the presence of such a leaving group. A successful reaction sequence would nonetheless shorten the synthesis, since a tosylation step is required towards the end of the synthetic sequence. Alkyne **5.61** was prepared in four steps from geraniol (Scheme 5.8). Tosylation of epoxygeraniol **5.54** gave compound **5.59** in 87% yield. Ozonolysis of the alkene, followed by treatment of aldehyde **5.60** with phosphonate **5.57** delivered alkyne **5.61** in good overall yield.¹²⁴

Scheme 5.8 – Synthesis of Alkyne Synthon **5.61**

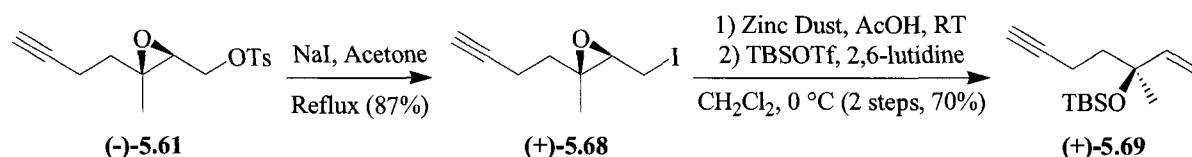
Given that ketone **5.41** could only be obtained in limited amounts, the alkylation step involving epoxyalkynes **5.58** and **5.61** was initially attempted on model ketone **2.30** (Scheme 5.9). Deprotonation of alkyne **5.58** with *n*-BuLi was done at 0 °C to ensure complete forma-

Scheme 5.9 – Alkylation of Model Ketone **2.30** with Alkynes **5.58** and **5.61**

in the reaction. For instance, following the formation of a gold complex of type **5.34**, the epoxide could have acted as a nucleophile and competed with the olefin. Its proximity could have allowed 5-*exo*-dig or 6-*endo*-dig attacks on the alkyne moiety. Of course, such cyclizations could have been followed by numerous events, which could have given several possible products. These unexpected results obviously led us to abandon the projected alkylation of ketone **5.41** with synthons **5.58** and **5.61**.

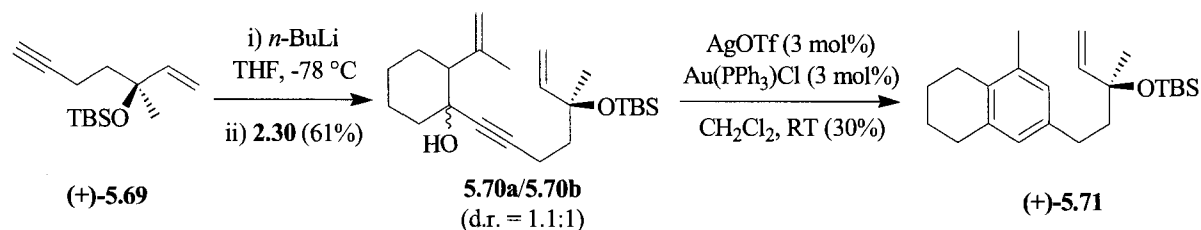
At that point, a small modification of the synthetic plan was considered. To avoid any unwanted reaction caused by the presence of an epoxide, this functionality was further transformed into a protected allylic alcohol. Alkyne synthon **5.69** was thus synthesized in three steps from tosylate **5.61** (Scheme 5.12). The tosylate was first refluxed in acetone in the presence of sodium iodide to generate the corresponding iodide in 87% yield.¹²⁵ Then, zinc reduction of iodide **5.68** followed by silylation of the resulting allylic alcohol gave alkyne synthon **5.69** in 70% yield overall.¹²⁶

Scheme 5.12 – Synthesis of Alkyne Synthon **5.69**



Again, alkylation with the lithium species derived from alkyne **5.69** was first attempted on model ketone **2.30** (Scheme 5.13). This reaction afforded isomeric alcohols **5.70** in 61% yield. Satisfyingly, submission of these alcohols to the usual benzannulation conditions cleanly gave desired tetrahydronaphthalene **5.71** in 30% yield. This preliminary result agreed

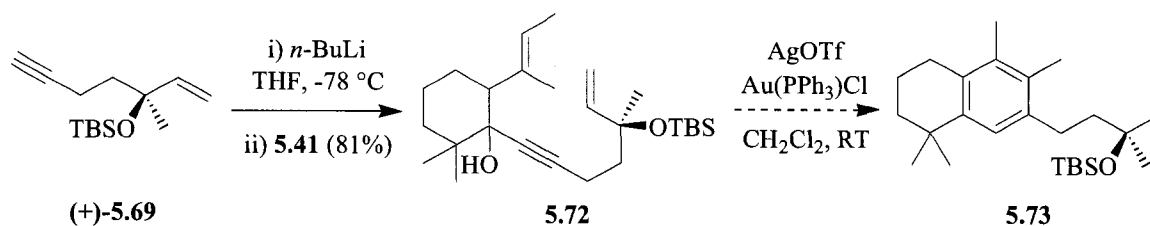
Scheme 5.13 – Alkylation of **2.30** with Alkyne **5.69** and Subsequent Benzannulation



with our supposition that epoxides interfered in the reaction. Moreover, it demonstrated that no racemization occurred during the benzannulation step. Indeed, the product of the reaction was optically active, as expected.

After that, the more complex ketone **5.41** was subjected to the same sequence of reactions (Scheme 5.14). Treatment of alkyne **5.69** with *n*-BuLi, followed by addition of ketone **5.41** afforded alcohol **5.72** as a single diastereomer in 81% yield. The relative stereochemistry of this compound could however not be determined by two-dimensional NMR. Disappointingly, treatment of alcohol **5.72** with AgOTf (3 mol%) and Au(PPh₃)Cl (3 mol%) did not afford desired tetrahydronaphthalene **5.73**. Rigorous inspection of the NMR spectrum of the crude reaction mixture revealed no trace of the desired product. Chromatographic purification of this mixture yielded an unidentified product that lacked the vinyl group.

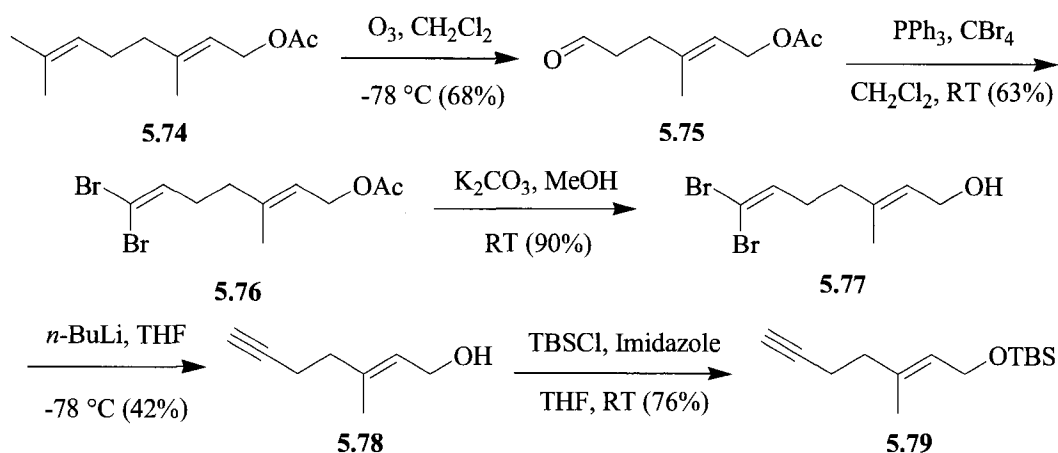
Scheme 5.14 – Alkylation of **5.41** with Alkyne **5.69** and Attempted Benzannulation



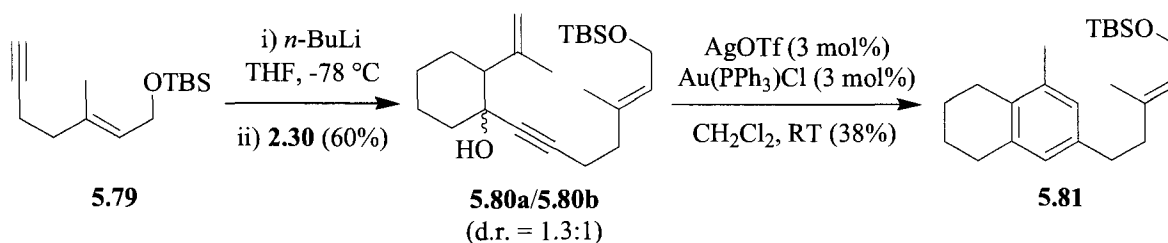
To explain this unexpected result, we hypothesized that the steric congestion exerted on the alkyne moiety by the neighboring *gem*-dimethyl group could probably prevent binding of the gold catalyst. In these circumstances, no benzannulation reaction would be possible and other background reactions could take place, possibly involving the vinyl group. It was thus postulated that a new alkyne synthon possessing a more hindered trisubstituted olefin instead of a vinyl group could be more suitable in this situation. One last alkyne synthon was therefore synthesized in a final effort to achieve the synthesis of the core via the benzannulation of functionalized enyne substrates.

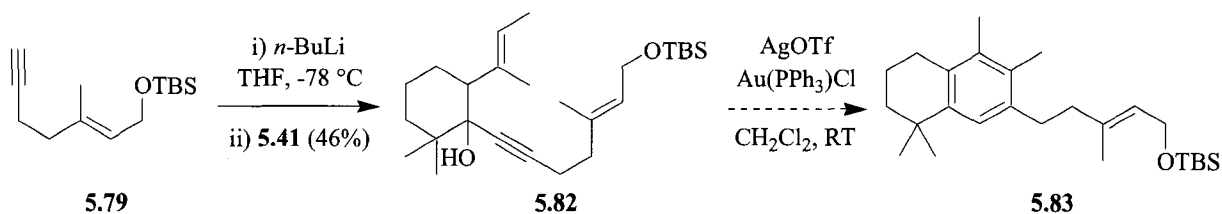
Alkyne synthon **5.79** was elaborated in five steps from geranyl acetate (**5.74**) (Scheme 5.15). Regioselective ozonolysis of **5.74**, followed by a Corey-Fuchs reaction of the resultant

aldehyde gave dibromoolefin **5.76** in 43% overall yield.¹²⁷ Basic hydrolysis of **5.76** furnished allylic alcohol **5.77** in excellent yield. Subsequent elimination with *n*-BuLi afforded enynol **5.78** in a non-optimized yield of 42%. Silylation of **5.78** finally yielded alkyne synthon **5.79** in 76% yield. Assuming successful alkylation and benzannulation, advanced intermediate **5.38** could be obtained from this synthon via successive deprotection, asymmetric epoxidation and tosylation.

Scheme 5.15 – Synthesis of Alkyne Synthon **5.79**

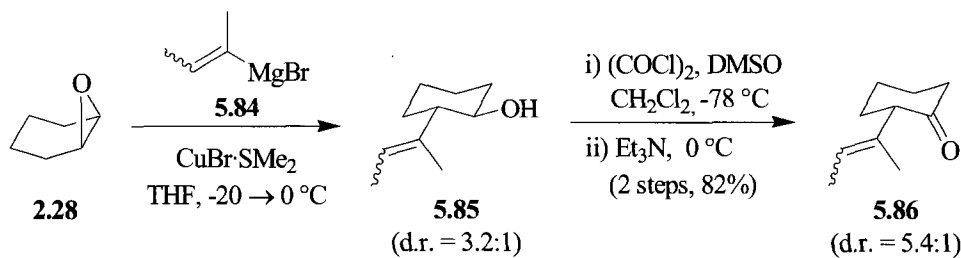
Following the usual procedure, alkylation of model ketone **2.30** with alkyne synthon **5.79** yielded isomeric alcohols **5.80** in 60% yield (Scheme 5.16). As anticipated, this mixture of alcohols was cleanly transformed into tetrahydronaphthalene **5.81** in 38% yield. Alkylation of ketone **5.41** led to the formation of alcohol **5.82** as a single diastereomer (Scheme 5.17). This compound was only obtained in fair yield due to a difficult separation from excess alkyne **5.79**. As for alcohol **5.72**, the relative stereochemistry of the two stereocenters of **5.82**

Scheme 5.16 – Alkylation of **2.30** with Alkyne **5.79** and Subsequent Benzannulation

Scheme 5.17 – Alkylation of **5.41** with Alkyne **5.79** and Attempted Benzannulation

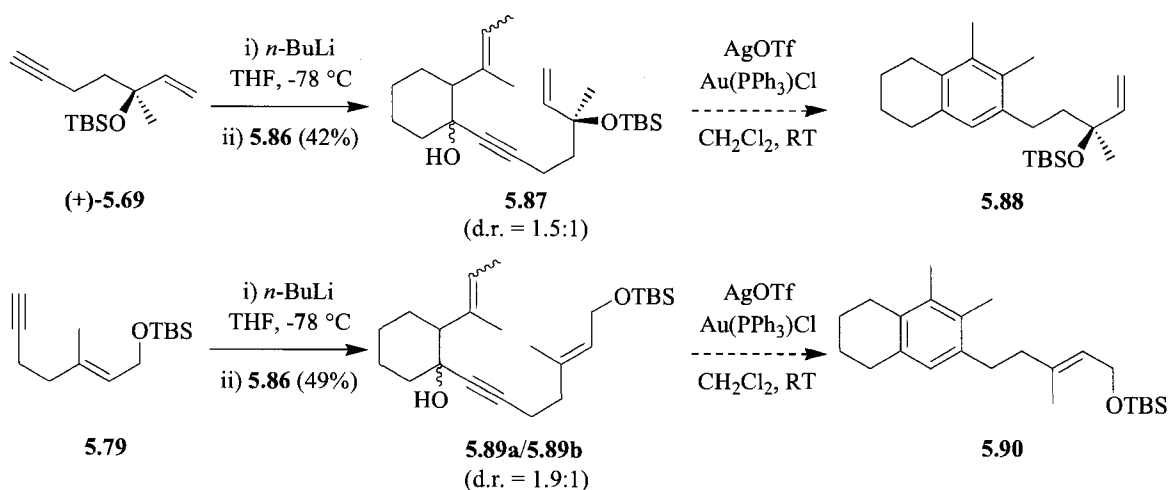
could not be determined by two-dimensional NMR experiments. Unfortunately, treatment of alcohol **5.82** with AgOTf (3 mol%) and $\text{Au(PPh}_3\text{)Cl}$ (3 mol%) afforded no trace of expected tetrahydronaphthalene **5.83**. All that could be isolated from the crude reaction mixture was an unidentified degradation product. This disappointing result showed that the degree of substitution of olefins comprised in synthons **5.69** and **5.79** had no influence on the outcome of the reaction. This result also seemed to support our previous hypothesis that the steric hindrance experienced by the alkyne moiety due to the proximity of the *gem*-dimethyl might prevent its binding to the bulky gold catalyst and therefore shut down the benzannulation. In the hope of circumventing this detrimental effect, we decided to examine the behavior of a substrate lacking the bulky *gem*-dimethyl group.

For this purpose, ketones **5.86** were synthesized in two steps from epoxide **2.28** (Scheme 5.18). Copper-catalyzed addition of Grignard reagent **5.84** to the epoxide yielded crude alcohols **5.85** as a mixture of geometrical isomers.²² Subsequent Swern oxidation of **5.85** afforded isomeric ketones **5.86** in 82% overall yield.²³

Scheme 5.18 – Synthesis of Ketones **5.86**

Ketones **5.86** were then reacted with the lithium species derived from alkynes **5.69** and **5.79** to afford respectively epimeric alcohols **5.87** and **5.89** in fair yields (Scheme 5.19). Again, treatment of alcohols **5.87** with AgOTf (3 mol%) and Au(PPh₃)Cl (3 mol%) did not give tetrahydronaphthalene **5.88**. Similarly, reaction of alcohols **5.89** with the gold catalyst failed to yield any desired product. In both cases, complex mixtures were recovered at the end of the reaction.

Scheme 5.19 – Attempted Benzannulation of Enynes **5.87** and **5.89**



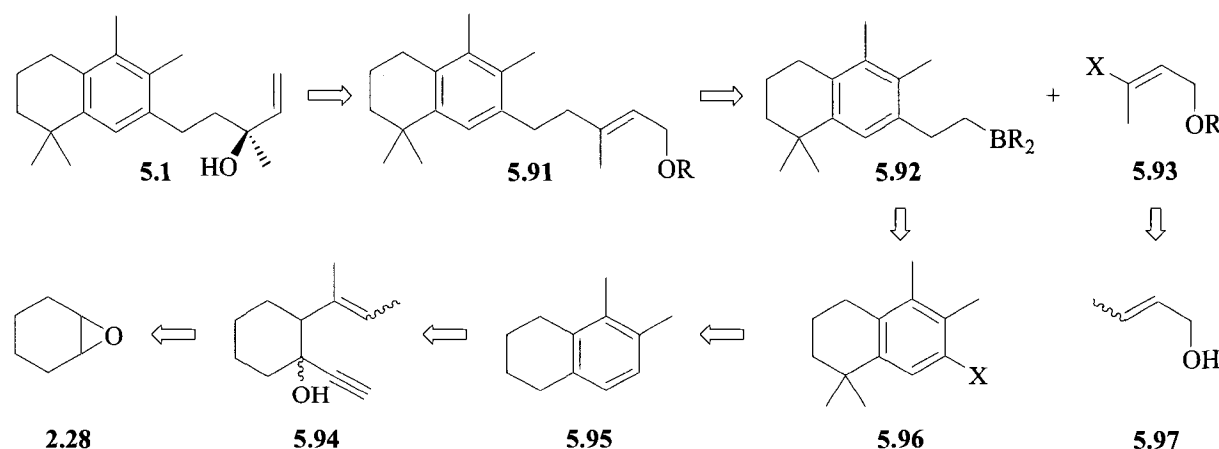
These results illustrated that the presence of an extra olefinic methyl group could, even in the absence of a *gem*-dimethyl substituent, prevent the benzannulation from occurring. Such results were surprising since substrates of type **5.20**, having a trisubstituted olefin, had already produced tetrahydronaphthalenes in very good yields (see Table 5.2, entry 5). Moreover, related enyne substrates **5.70** and **5.80** both underwent the desired reaction, albeit in fair yield.

Regardless of the cause of these unanticipated results, the second aromatic methyl group could not be incorporated. According to our synthetic plan, this methyl had to be introduced during the benzannulation step. Consequently, this approach to (+)-isorefrenedol (**5.1**) had to be abandoned, and a new synthetic strategy was designed.

Second Approach to (+)-Isofregenedol

After analyzing the difficulties encountered in the original synthetic sequence, a second retrosynthetic analysis was formulated. This new synthetic plan was designed to solve the major problems that were previously identified. As a consequence, no *gem*-dimethyl group would be present in the enyne precursor. Also, the side-chain of isofregenedol would be introduced and elaborated after the benzannulation step. Obviously, this new route would be less convergent and require more steps. Nonetheless, it should in all probability lead to the desired natural product. According to this retrosynthetic plan, (+)-isofregenedol (**5.1**) could come from elaboration of trisubstituted alkene **5.91** (Scheme 5.20). This alkene could in turn be generated by an alkyl Suzuki-Miyaura cross-coupling of borane **5.92** with alkenyl halide **5.93**. This halide could for example be synthesized from commercially available crotyl alcohol **5.97**. Borane **5.92** could come from aryl halide **5.96** by successive Stille cross-coupling and hydroboration reactions. This aryl halide could be accessed by introduction of the *gem*-dimethyl followed by halogenation of tetrahydronaphthalene **5.95**. The latter would naturally be obtained by benzannulation of simple enyne **5.94**. Finally, a simple three-step sequence should provide enyne **5.94** from commercially available cyclohexene oxide (**2.28**).

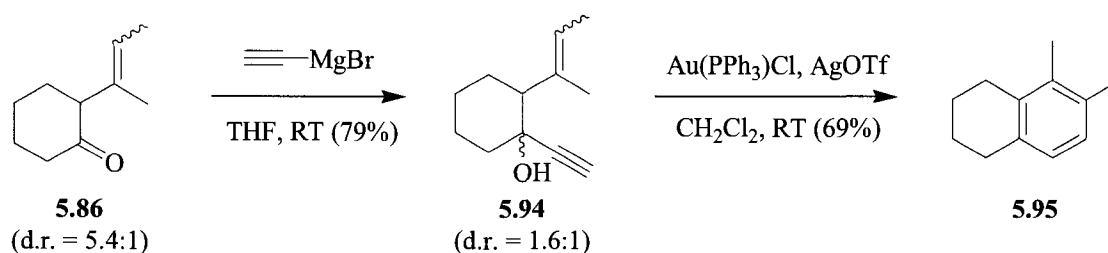
Scheme 5.20 – Second Retrosynthetic Analysis of (+)-Isofregenedol (**5.1**)



Application of the new synthetic plan to the total synthesis of (+)-isofregenedol (**5.1**) commenced with the synthesis of tetrahydronaphthalene **5.95** (Scheme 5.21). Addition of ethynylmagnesium bromide to ketones **5.86** indeed afforded epimeric alcohols **5.94** in 79%

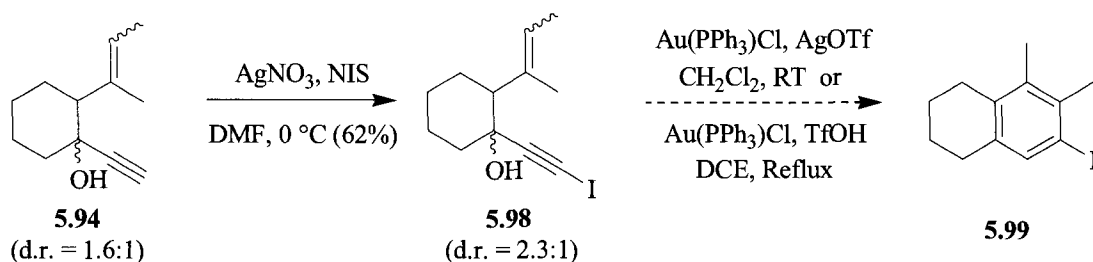
yield. Gratifyingly, submission these alcohols to the usual benzannulation conditions reproducibly yielded desired tetrahydronaphthalene **5.95** in good yield. Contrasting with unsuccessful substrates **5.87** and **5.89**, the absence of an elaborated alkyl chain on the alkyne moiety of **5.94** allowed the desired gold-catalyzed reaction to work beautifully. This encou-

Scheme 5.21 – Synthesis of Tetrahydronaphthalene **5.95**



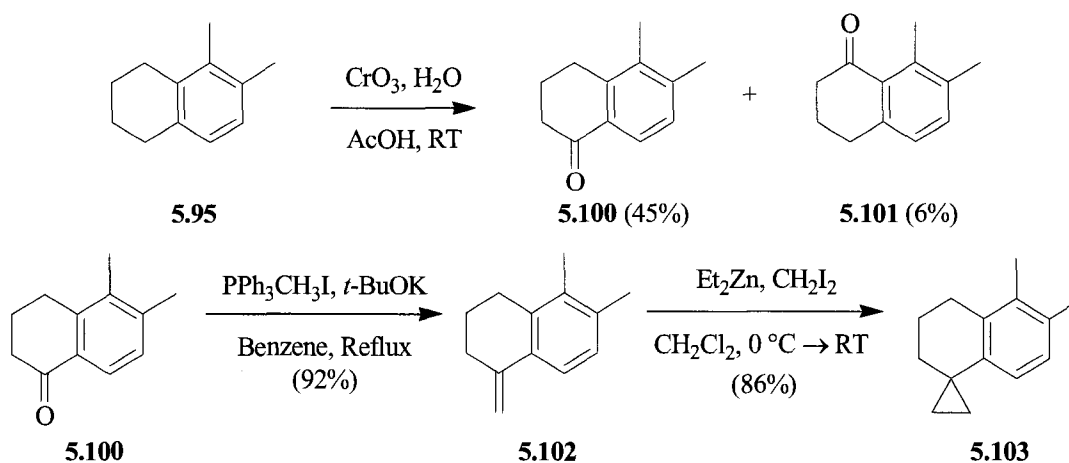
aging result led us to consider an immediate installation of the halogen atom at the required position of the arene through the benzannulation reaction. For this purpose, epimeric iodoalkynes **5.98** were synthesized in good yield from **5.94** by treatment with silver nitrate and *N*-iodosuccinimide (Scheme 5.22).¹²⁸ The benzannulation of iodoalkynes **5.98** was then attempted. Treatment of these substrates with AgOTf (10 mol%) and Au(PPh₃)Cl (10 mol%) afforded a complex mixture of products from which **5.99** was absent. Also, reaction with Au(PPh₃)Cl (5 mol%) and TfOH (5 mol%) in refluxing DCE led to the same result. This way of introducing the requisite halogen atom was thus abandoned. It was decided that this halogen atom would be installed by a more conventional electrophilic aromatic substitution reaction. However, the *gem*-dimethyl had to be introduced first, since a steric bias was required in order to favor the substitution at the required position.

Scheme 5.22 – Synthesis of Iodoalkynes **5.98** and Attempted Benzannulation

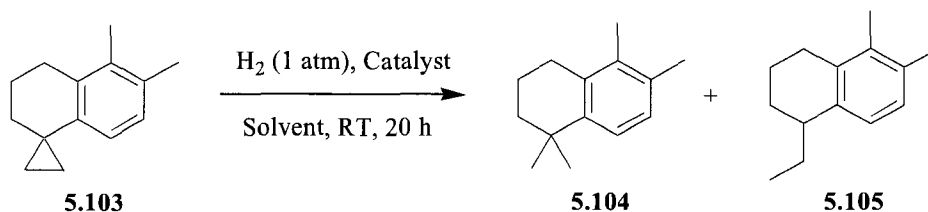


We first attempted to introduce the *gem*-dimethyl substituent by reduction of related cyclopropane **5.103**. This cyclopropane was synthesized from tetrahydronaphthalene **5.95** through a well established three-step sequence (Scheme 5.23). First, benzylic oxidation of **5.95** was performed with chromium(VI) oxide in acetic acid to deliver ketone **5.100** in 45% yield along with 6% of the minor regioisomer.¹²⁹ Subsequent olefination of the major ketone was carried out by using modified Conia conditions, and the corresponding alkene, **5.102**, was obtained in excellent yield.⁷³ This alkene was in turn submitted to standard Simmons-Smith conditions and cyclopropane **5.103** was produced in 86% yield.¹³⁰

Scheme 5.23 – Synthesis of Cyclopropane **5.103**

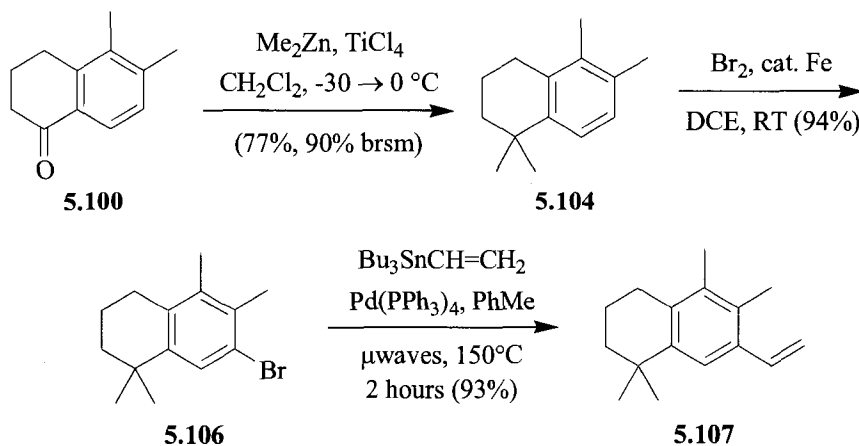


Metal-catalyzed hydrogenation of cyclopropane **5.103** was then attempted (Table 5.3). The most active hydrogenation catalyst, platinum (II) oxide, yielded some desired product. When a solution of **5.103** in methanol was treated with this catalyst under a hydrogen atmosphere, tetrahydronaphthalenes **5.104** and **5.105** were formed in comparable amounts (entry 1). The three components of the mixture were inseparable. Using ethanol as solvent led to increased conversion, but both **5.104** and **5.105** were produced again (entry 2).¹³¹ When the reaction was performed with palladium (II) hydroxide, only unwanted regioisomer **5.105** was observed in the crude reaction mixture. Using ethyl acetate as solvent led to an incomplete reaction (entry 3). However, treatment of an ethanolic solution of **5.103** with palladium (II) hydroxide afforded undesired regioisomer **5.105** in 87% yield (entry 4). Clearly, catalytic hydrogenation was not a good method to generate desired **5.104** and was thus abandoned.

Table 5.3 – Attempted Synthesis of Compound **5.104** by Catalytic Hydrogenation

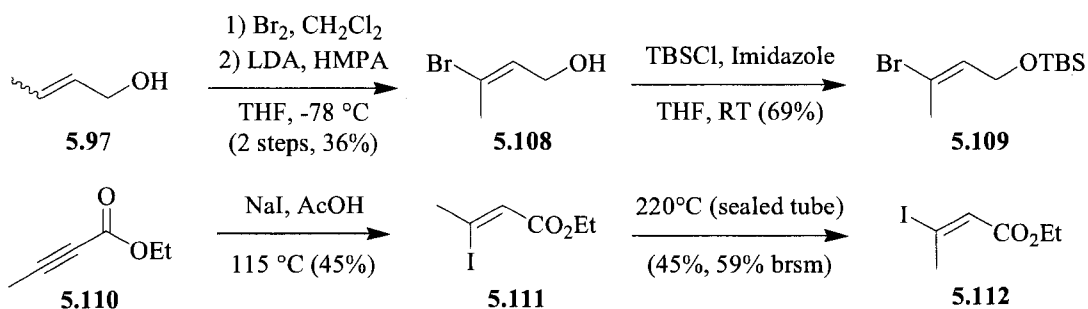
Entry	Catalyst (mol%)	Solvent	Product(s) (Yield)
1	PtO ₂ (10)	MeOH	5.103 / 5.104 / 5.105 (5:1:1.1)
2	PtO ₂ (10)	EtOH	5.103 / 5.104 / 5.105 (1:1.4:1.1)
3	Pd(OH) ₂ (10)	EtOAc	5.103 / 5.105 (2.7:1)
4	Pd(OH) ₂ (10)	EtOH	5.105 (87%)

Ultimately, the synthesis of desired tetrahydronaphthalene **5.104** was achieved by means of an exhaustive methylation methodology.¹³² The methylating agent employed in this method is TiMe_2Cl_2 , a reactive species generated *in situ* by adding dimethylzinc to a solution of titanium (IV) chloride in dichloromethane. Early attempts of bis-methylating ketone **5.100** using TiMe_2Cl_2 prepared from a solution of dimethylzinc in heptane were unsuccessful. However, when dimethylzinc in toluene was used instead, the reaction proceeded smoothly

Scheme 5.24 – Synthesis of Alkene **5.107**

to afford dimethylated tetrahydronaphthalene **5.104** in 77% yield (90% yield based on recovered starting material). As expected, bromination of the latter in the presence of a catalytic amount of iron powder yielded aryl bromide **5.106** as a single regioisomer in excellent yield.¹³³ The required vinyl group was then introduced via a Stille cross-coupling that necessitated unexpectedly forcing conditions.¹³⁴ Indeed, complete conversion could only be achieved by heating the reaction mixture at 150 °C for two hours in a microwave oven. Alkene **5.107** could nonetheless be obtained in an excellent yield of 93%. The following step consisted in the elongation of the side-chain of isofregenedol through an alkyl Suzuki-Miyaura cross-coupling reaction. At that point, two complementary alkenyl halide coupling partners of type **5.93** were synthesized. Both of these substrates were equivalent three-carbon units. Vinyl bromide **5.109** included a primary alcohol, whereas vinyl iodide **5.112** bore an ethyl ester. Synthon **5.109** was generated in three steps from crotyl alcohol **5.97** (Scheme 5.25). Successive bromination of alcohol **5.97** and regioselective elimination of HBr yielded adduct **5.108** in fair yield.¹³⁵ Subsequent silylation of the allylic alcohol afforded vinyl bromide **5.109** in 69% yield. Synthon **5.112** was synthesized in two steps from butynoate **5.110**. Initial treatment of this butynoate with sodium iodide in acetic acid afforded *cis*-vinyl iodide **5.111** in 45% yield.¹³⁶ The latter was then isomerized to *trans*-vinyl iodide **5.112** in fair yield by heating at high temperature in a sealed tube.^{137a}

Scheme 5.25 – Synthesis of the Alkenyl Halide Coupling Partners



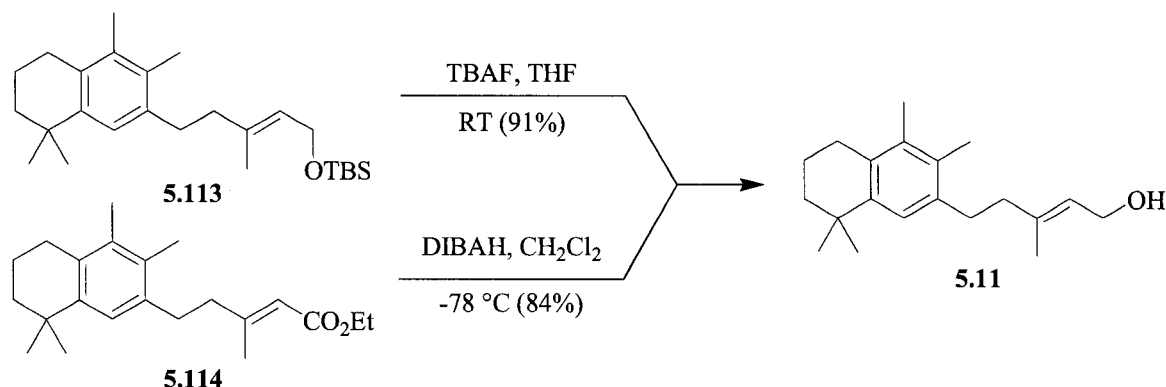
Having both alkenyl halide coupling partners in hand, the examination of the alkyl Suzuki-Miyaura cross-coupling reaction was initiated. The preliminary attempts were based on the chemistry developed by Ohba and co-workers during the course of their total synthesis of agelasimines A and B.¹³⁷ Following their procedure, treatment of alkene **5.107** with 9-BBN

in refluxing THF yielded the corresponding hydroboration product. This borane was then added to a solution of the remaining reagents, and the resulting reaction mixture was stirred at room temperature (Table 5.4). The reaction of vinyl bromide **5.109** was initially examined. An excess of 9-BBN (3 equiv.) was employed to ensure complete conversion of **5.107**, and the reaction mixture was stirred for 3.5 hours at room temperature, yielding silylated alcohol **5.113** in 24% yield (entry 1). Performing the reaction in the same conditions with vinyl iodide **5.112** led to formation of ester **5.114** in a comparable yield (entry 3). Heating the reaction at 50 °C had little effect on the yield (entry 4). However, when the reaction was heated at 80 °C for 2 hours, ester **5.114** was formed in a very respectable yield of 74% (entry 5). Treatment of vinyl bromide **5.109** under the same conditions also gave silylated alcohol **5.113** in 62% yield (entry 2). It is worth mentioning that the *E* geometry of coupling products **5.113** and **5.114** was confirmed by two-dimensional NMR experiments.⁷⁵

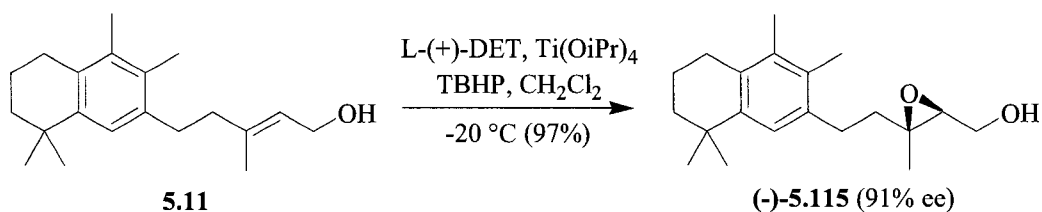
Table 5.4 – Optimization of the Alkyl Suzuki-Miyaura Reaction

Entry	Halide	Time (h)	T (°C)	Product	Yield (%)
1	5.109	3.5	22	5.113	24
2	5.109	2	80	5.113	62
3	5.112	3.5	22	5.114	17
4	5.112	15	50	5.114	22
5	5.112	2	80	5.114	74

As a result of this successful cross-coupling reaction, all the requisite carbon atoms had been incorporated in the skeleton of isofregenedol. The next goal was the conversion of compounds **5.113** and **5.114** into the corresponding allylic alcohol (Scheme 5.26). Removal

Scheme 5.26 – Synthesis of Allylic Alcohol **5.11**

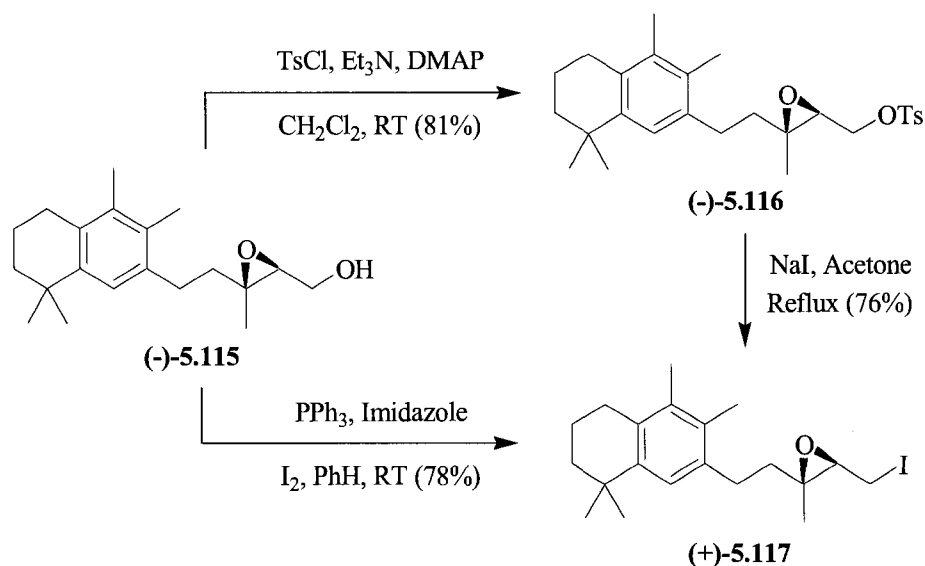
of the silyl protecting group from **5.113** yielded alcohol **5.11** in excellent yield. Reduction of ester **5.114** afforded the same product in 84% yield.^{137a} Since compound **5.11** had previously been synthesized by Marcos and co-workers in the course of their synthesis of (+)-isorefrenedol, a formal total synthesis of this natural product had been achieved at that point.¹¹³ We nevertheless decided to pursue the total synthesis in order to improve the last part of the synthetic sequence. As previously described, Sharpless asymmetric epoxidation of allylic alcohol **5.11** using L-diethyl tartrate led to the formation of alcohol **5.115** in near quantitative yield with 91% ee (Scheme 5.27).¹²³ This compound then had to be converted

Scheme 5.27 – Sharpless Asymmetric Epoxidation of Allylic Alcohol **5.11**

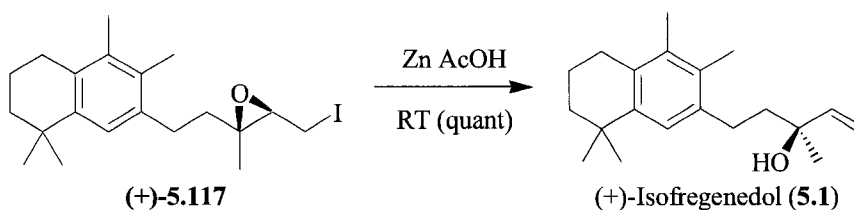
to the related iodide. For that purpose, alcohol **5.115** was transformed into tosylate **5.116** in good yield (Scheme 5.28). A subsequent S_N2 reaction yielded iodide **5.117** in 62% combined yield from alcohol **5.115**.¹²⁵ Alternatively, iodide **5.117** was prepared in a single step through an Appel reaction, increasing the yield to 78%.¹³⁸ Finally, treatment of iodide **5.117** with zinc dust in acetic acid delivered (+)-isorefrenedol (**5.1**) quantitatively (Scheme 5.29).¹²⁶ The spectroscopic properties for **5.1** were carefully scrutinized and proved to be identical to the

ones previously reported for authentic and synthetic samples of (+)-isofregenedol.^{112,113} Moreover, the optical rotation recorded for **5.1** agreed perfectly with that of the natural product.

Scheme 5.28 – Synthesis of Iodide **5.117**



Scheme 5.29 – Synthesis of (+)-Isofregenedol (**5.1**) from Iodide **5.117**



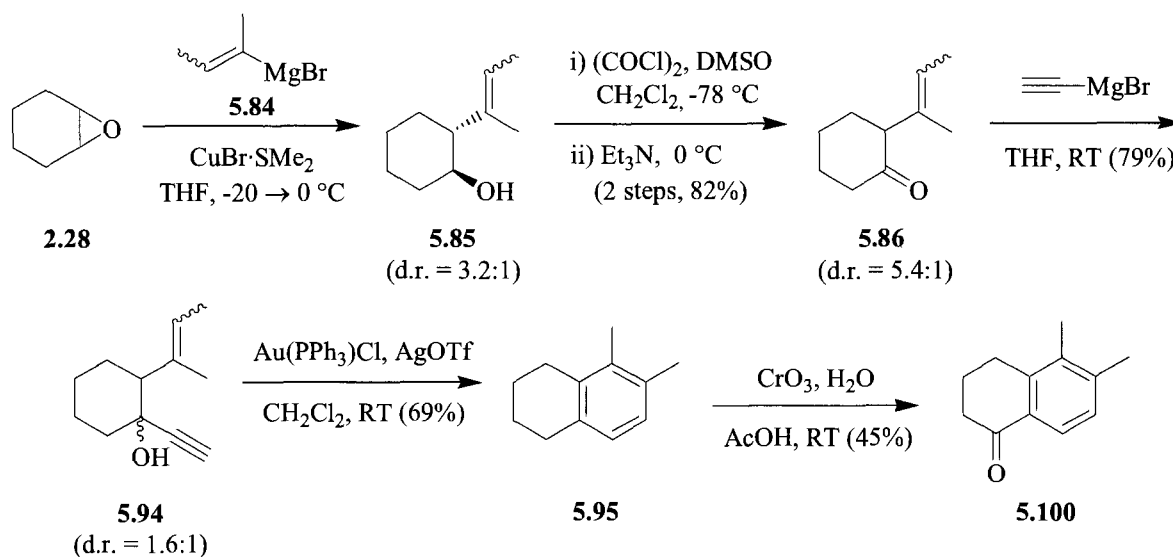
Conclusion

The total synthesis of (+)-isofregenedol (**5.1**) was completed in thirteen steps from commercially available cyclohexene oxide (**2.28**). This synthesis is summarized in Schemes 5.30 and 5.31. The natural product was obtained in 7% overall yield. A gold-catalyzed benzannulation reaction developed in the Barriault laboratory was employed to generate the tetrahydronaphthalene framework. Our original approach towards isofregenedol involved the

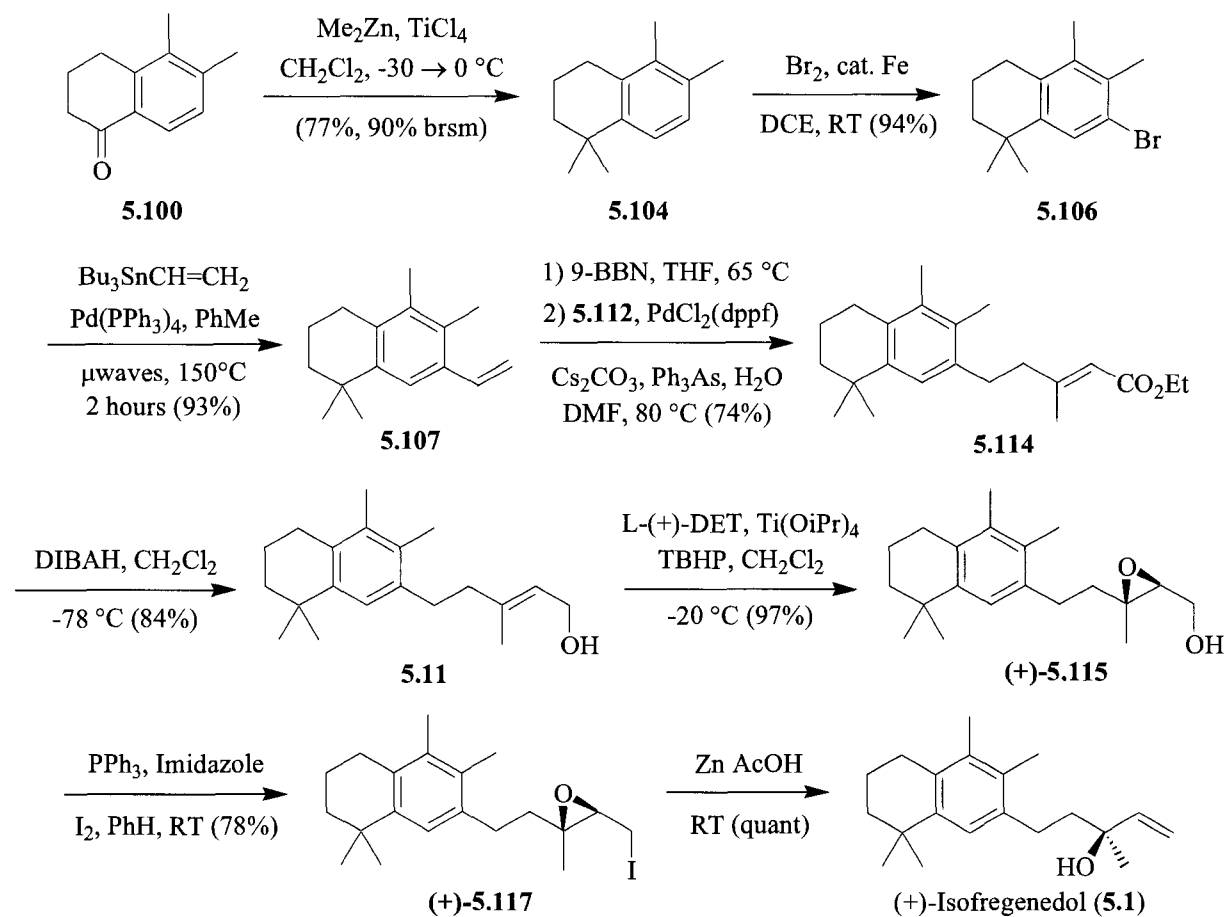
benzannulation of elaborated hydroxyenynes. In that enterprise, we first attempted the benzannulation of three model epoxide-bearing substrates (**5.62-5.64**). Unfortunately, no tetrahydronaphthalene product was observed in these cases. The epoxide functionality was thus replaced by two different silylated allylic alcohols. Model substrates **5.70** and **5.80**, possessing an isopropenyl group and lacking the *gem*-dimethyl, thus underwent the benzannulation successfully. Nonetheless, the required precursors, **5.72** and **5.82**, did not deliver any tetrahydronaphthalene product. We ultimately synthesized two model hydroxyenynes, **5.87** and **5.89**, that bore the required dimethylvinyl group but lacked the *gem*-dimethyl. Still, these substrates failed to generate any benzannulated product.

Since the initial strategy was not viable, we decided to modify our approach and to introduce the side-chain after the formation of the core. Fortunately, the tetrahydronaphthalene core was obtained in good yield from simple hydroxyenyne **5.94**. The requisite *gem*-dimethyl was then added through exhaustive methylation of benzylic ketone **5.100**. The carbon skeleton of the side-chain was elaborated in two stages. First, a vinyl group was introduced by a Stille coupling, and alkene **5.107** was obtained. Then, the borane derived from compound **5.107** was coupled with vinyl iodide **5.112** to furnish ester **5.114**. The latter was finally converted to the natural product through a series of functional group manipulations.

Scheme 5.30 – Summarized Total Synthesis of (+)-Isofregenedol (**5.1**) (Part I)



Scheme 5.31 – Summarized Total Synthesis of (+)-Isofregenedol (5.1) (Part II)



6

General Conclusion

Summary

In the last four years, three main research areas were explored. Our initial investigations of the oxy-Cope/Claisen/ene reaction resulted in the discovery of a novel rearrangement. Indeed, we found that high temperature microwave irradiation of propargyl vinyl ethers bearing a *syn* hydroxy group led to the formation of the corresponding *cis* bicyclic unsaturated lactones.

We subsequently examined the synthesis of bicyclo[3.3.1]nonanones via the Prins-Pinacol rearrangement. This methodological work showed that the benzyldiene acetal is a far better oxocarbenium precursor than the typical isopropylidene ketal. We found that substitution at the ring junction had no influence on the reaction efficiency. Also, the presence of a *gem*-dimethyl α to the alkene moiety significantly impaired the reaction of an isopropylidene precursor, but not that of a benzyldiene-bearing substrate. Similarly, we observed that the Prins-Pinacol rearrangement of a substituted alkene was possible only when a benzyldiene precursor was employed. In that particular case, only the *Z* alkene afforded the desired bridged ketone. The *E* isomer rather underwent a pinacolic rearrangement to afford the corresponding bicyclo[4.2.1]nonanone.

The generation of bicyclo[3.3.1]nonanones through the Diels-Alder/Prins-Pinacol tandem reaction was also attempted, but proved to be unsuccessful. The two reactions were therefore performed sequentially. Diene precursors bearing an isopropylidene ketal or benzylidene acetal were first reacted with various Gassman dienophiles to afford the corresponding Diels-Alder cycloadducts. These compounds then underwent the Prins-Pinacol rearrangement, and an array of complex polycyclic bridged ketones was formed. Once again, the benzylidene precursors underwent the reaction in better yields than their isopropylidene counterparts.

An application of this methodology to the total synthesis of papuaforin A was subsequently envisaged. In the course of our synthetic investigations, we synthesized a model compound having the bicyclo[3.3.1]nonanone skeleton of the natural product. This analogue of papuaforin A possessed the requisite *gem*-dimethyl and ring junction methyl groups. The model compound also bore an extra tetrahydrofuran ring, which was cleaved in a three-step sequence to expose two crucial synthetic handles. Unfortunately, the following introduction of the isobutyryl group via alkylation failed. An alternative method was thus devised, but it also failed to generate the required group.

We also considered a synthetic strategy that allowed the stereoselective introduction of the prenyl side-chain. Employing that approach, we obtained a functionalized bicyclic enone from α -pinene in thirteen steps. This advanced intermediate possessed the C₈ *gem*-dimethyl, the methyl at the ring junction, and a protected hydroxyethyl group that could be converted to the requisite prenyl side-chain. The bicyclic enone could however only be obtained in minute amounts and, for this reason, the synthesis could not be pursued further.

Finally, we achieved the first total synthesis of (+)-isofregenedol. In this synthesis, we applied the benzannulation methodology developed by Ph.D. student Christiane Grisé to the construction of the carbon skeleton of the natural product. The required hydroxyenyne substrate was first prepared in three steps from commercially available cyclohexene oxide. This precursor was benzannulated in 69% yield to furnish the tetrahydronaphthalene core. Nine additional steps were then required to conclude the construction of (+)-isofregenedol. The natural product was obtained in thirteen chemical steps in 7% overall yield.

Claims to Original Research

1. Discovery and succinct examination of a new rearrangement of propargyl vinyl ethers providing *cis*-bicyclic unsaturated lactones.
2. Methodological investigation of the Prins-Pinacol rearrangement oriented towards the synthesis of bicyclo[3.3.1]nonanones.
3. Demonstration of the superiority of the benzylidene acetal over the isopropylidene ketal as a precursor for the generation of oxocarbeniums.
4. Application of the methodology to the synthesis of the core of papuaforin A and investigations towards its total synthesis.
5. Application of the gold(I)-catalyzed benzannulation of hydroxyenynes to the first total synthesis of (+)-isofregenedol.

Publication from This Work

Lavigne, R. M. A.; Riou, M.; Girardin, M.; Morency, L.; Barriault, L. **"Synthesis of Highly Functionalized Bicyclo[m.n.1]alkanones via a Cationic Reaction Cascade"**, *Organic Letters*, **2005**, 7, 5921-5923.

Riou, M.; Barriault, L. **"De Novo synthesis of (+)-Isofregenedol"**, *The Journal of Organic Chemistry*, **2008**, 73, 7346-7349.

Poster Presentations from This Work

1. **"Studies Towards the Total Synthesis of Papuaforin A"** June 2007, Synthesis Day, University of Ottawa, Ontario, Canada.
2. **"Studies Towards the Total Synthesis of Papuaforin A"** August 2006, Synthesis Day, University of Ottawa, Ontario, Canada.
3. **"Synthesis of Highly Functionalized Bicyclo[3.3.1]nonanones by a Prins-Pinacol Rearrangement"** November 2005, Québec/Ontario Minisymposium in Synthetic and BioOrganic Chemistry, Ste-Adèle, Québec, Canada.

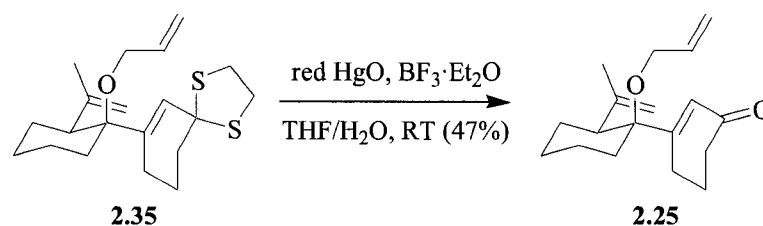
Experimental

General Information

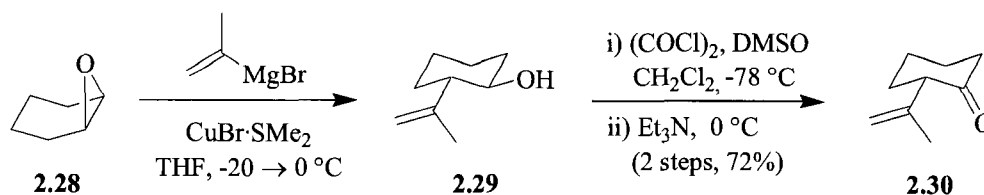
All reactions were performed under argon atmosphere in flame-dried glassware equipped with a magnetic stir bar and a rubber septum, unless otherwise indicated. All solvents were freshly distilled prior to use; diethyl ether and tetrahydrofuran over sodium and benzophenone; benzene, dichloromethane, 1,2-dichloroethane, dimethylformamide, ethyl acetate, pyridine, toluene and triethylamine over calcium hydride. All other commercially available reagents were used without purification, unless otherwise noted. Microwave reactions were performed using a CEM Discover 201A05 microwave oven. All reactions were monitored by thin layer chromatography (TLC) analysis of aliquots using glass sheets pre-coated (250 μm thickness) with ultra pure silica gel (60 Å, F₂₅₄) from SiliCycle. Thin layer chromatography plates were viewed under UV light and stained with phosphomolybdic acid or *p*-anisaldehyde staining solution. Column chromatography was carried out with 230-400 mesh silica gel (60 Å) from SiliCycle. For purification of compounds containing tertiary alcohol functionality, the silica gel was doped with 1% Et₃N. ¹H and ¹³C NMR spectra were recorded at room temperature in deuterated solvents on Bruker Avance 300 MHz, Bruker Avance 400 MHz, Bruker Avance 500 MHz, and Varian Inova 500 MHz spectrometers. IR spectra were recorded on a Bomem Michaelson 100 FTIR spectrometer and optical rotation

values were measured with a Perkin-Elmer Model 241 polarimeter. HRMS were obtained on a Kratos Analytical Concept IIH instrument operated by the University of Ottawa Mass Spectrometry Centre. Melting points were recorded on a Gallenkamp P 1106G melting point apparatus. Enantiomeric excesses were determined by HPLC. HPLC was performed on a Waters 2695 HPLC equipped with a ChiralCel OJ-H (4.6 x 250 mm) chiral column and a Waters 2996 photodiode array detector at isocratic elution (5% isopropanol/hexanes).

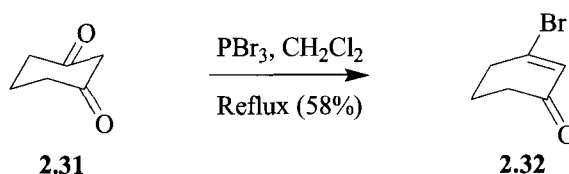
Experimental Procedures and Characterization of New Compounds



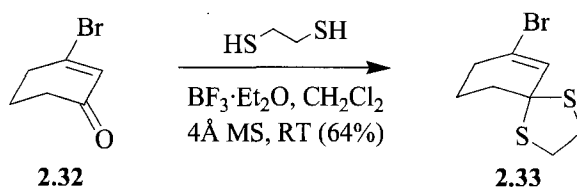
(±)-1'-Allyloxy-2'-isopropenylbicyclohexylen-3-one (**2.25**). To a solution of **2.35** (145 mg, 0.41 mmol) in THF (3 mL) at room temperature was added H₂O (1 mL). Red mercuric oxide (178 mg, 0.82 mmol) was then added, followed by the dropwise addition of BF₃·OEt₂ (110 μL, 0.87 mmol). After stirring for 50 minutes, the reaction mixture was quenched with saturated aqueous NaHCO₃ (5 mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 10 mL). Combined organics were dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (30% EtOAc/hexanes) to afford 53 mg of **2.25** as a pale yellow oil (47% yield): IR (neat) ν_{max} 2942, 2859, 1671, 1451 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.94 (1 H, s), 5.92-5.83 (m, 1 H), 5.33 (d, J = 17.3, 1.7 Hz, 1 H), 5.12 (dd, J = 10.7, 1.5 Hz, 1 H), 4.62 (s, 1 H), 4.52 (s, 1 H), 3.91-3.85 (m, 1 H), 3.68-3.62 (m, 1 H), 2.41-1.77 (m, 10 H), 1.72 (s, 3 H), 1.65-1.56 (m, 1 H), 1.32-1.15 (m, 4 H); ¹³C NMR (75 MHz, CDCl₃) δ 200.64 (C), 167.56 (C), 147.61 (C), 135.00 (CH), 125.88 (CH), 115.60 (CH₂), 113.40 (CH₂), 82.84 (C), 63.34 (CH₂), 55.00 (CH), 37.92 (CH₂), 30.83 (CH₂), 27.37 (CH₂), 27.17 (CH₂), 26.34 (CH₂), 23.00 (CH₂), 21.49 (CH₂), 21.41 (CH₃); HRMS m/z calculated for C₁₈H₂₆O₂ 274.1933 (M⁺), found 274.1868.



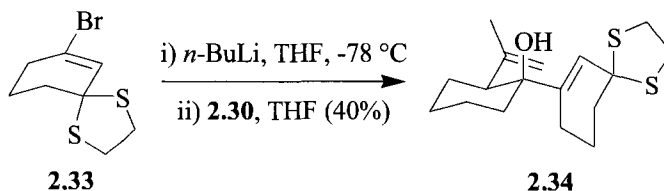
(±)-2-isopropenylcyclohexanone (2.30). *Step 1:* CuBr·SMe₂ (813 mg, 3.95 mmol) was placed in a flame-dried 500 mL round-bottom flask. THF (110 mL) was added and the suspension was cooled to -20 °C. Isopropenylmagnesium bromide (103 mL of a 0.5 M solution in THF, 51.50 mmol) was added dropwise and the resulting brown mixture was stirred for 15 minutes at -20 °C. Cyclohexene oxide **2.28** (4.00 mL, 39.53 mmol) was then added dropwise and the reaction mixture was warmed up to 0 °C. After stirring for 1 h at that temperature, it was quenched with saturated aqueous NH₄Cl (80 mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 80 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. Filtration and careful removal of the solvent gave crude alcohol **2.29**. *Step 2:* To a solution of oxalyl chloride (3.9 mL, 44.71 mmol) in CH₂Cl₂ (130 mL) at -78 °C was added DMSO (6.3 mL, 88.78 mmol) dropwise. The resulting solution was stirred for 20 minutes, and a solution of the crude alcohol in CH₂Cl₂ (20 mL) was added via cannula. The resulting cloudy mixture was stirred at -78 °C for 1.5 h, and Et₃N (26.5 mL, 190.13 mmol) was added dropwise. The reaction mixture was warmed up to 0 °C. After stirring for 1 h at that temperature, it was quenched with saturated aqueous NH₄Cl (100 mL). The aqueous layer was separated from the organic layer and extracted with CH₂Cl₂ (3 x 100 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford 3.93 g of **2.30** as a pale yellow oil (72% yield over 2 steps). Spectroscopic data for **2.30** were identical to that previously reported.¹⁵



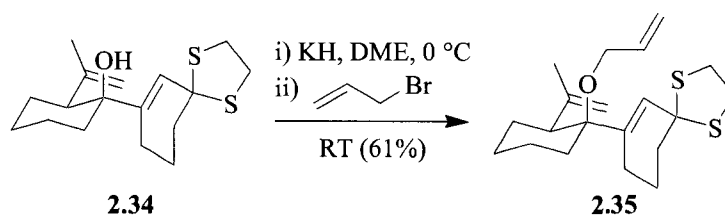
3-Bromocyclohex-2-enone (2.32). To a solution of cyclohexan-1,3-dione **2.31** (2.70 g, 24.08 mmol) in CH_2Cl_2 (240 mL) at room temperature was added dropwise phosphorus tribromide (4.60 mL, 48.43 mmol). The resulting mixture was then refluxed for 3 h. After cooling down to room temperature, the reaction was quenched with saturated aqueous NH_4Cl (100 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 100). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (30% EtOAc /hexanes) to afford 2.45 g of **2.32** as a pale yellow oil (58% yield). Spectroscopic data for **2.32** were identical to that previously reported.¹³⁹



7-Bromo-1,4-dithiaspiro[4.5]dec-6-ene (2.33). To a mixture of flame-dried 4 Å molecular sieves (450 mg), ethanedithiol (180 μL , 2.14 mmol) and $\text{BF}_3\cdot\text{OEt}_2$ (60 μL , 0.47 mmol) in CH_2Cl_2 (36 mL) at room temperature was added a solution of **2.32** (332 mg, 1.90 mmol) in CH_2Cl_2 (2 mL) dropwise via cannula. After stirring for 24 h, the reaction mixture was quenched with saturated aqueous NaHCO_3 (20 mL). The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 x 20 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% Et_2O /petroleum ether) to afford 304 mg of **2.33** as a pale yellow oil (64% yield). Spectroscopic data for **2.33** were identical to that previously reported.¹⁴⁰

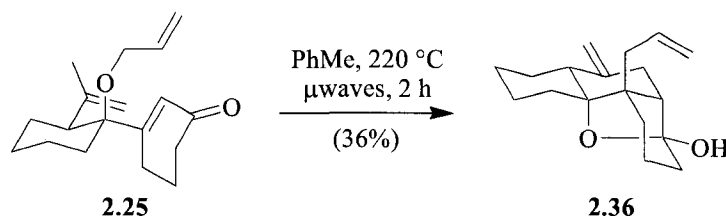


(±)-1-(1,4-Dithiaspiro[4.5]dec-6-en-7-yl)-2-isopropenylcyclohexanol (**2.34**). To a solution of *n*-BuLi (450 μ L of a 2.0 M solution in hexanes, 0.90 mmol) in THF (1 mL) at $-78\text{ }^{\circ}\text{C}$ was added a solution of **2.33** (113 mg, 0.45 mmol) in THF (1 mL). The yellow mixture was stirred at that temperature for 30 minutes. A solution of **2.30** (41 mg, 0.30 mmol) in THF (1 mL) was then added dropwise via cannula. The reaction mixture was stirred for 1 h at $-78\text{ }^{\circ}\text{C}$, and was quenched with saturated aqueous NH_4Cl (2 mL). After warming up to room temperature, The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were dried over MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% EtOAc /hexanes) to afford 37 mg of **2.34** as a yellow oil (40% yield). Spectroscopic data for **2.34** were identical to that previously reported.¹⁴¹

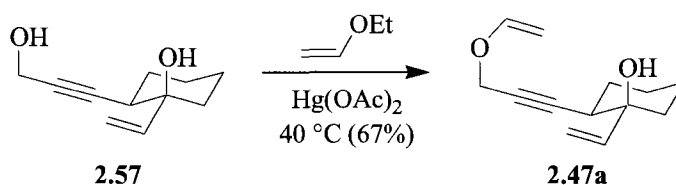


(±)-7-(1-Allyloxy-2-isopropenylcyclohexyl)-1,4-dithiaspiro[4.5]dec-6-ene (**2.35**). KH (60% in mineral oil, 413 mg, 6.18 mmol) was washed with dry hexanes (3 x 10 mL). The remaining solvent was removed under high vacuum and the flask was backfilled with argon. To a suspension of this freshly washed KH in DME (10 mL) at $0\text{ }^{\circ}\text{C}$ was added dry NaI (5 mg, 0.03 mmol). A solution of **2.34** (384 mg, 1.24 mmol) in DME (2 mL) was then added dropwise via cannula. After stirring for 5 minutes, allyl bromide (540 μ L, 6.24 mmol) was added dropwise. The resulting mixture was then stirred for 2 h at room temperature, and was quenched with saturated aqueous NH_4Cl (10 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 10 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes) to afford 264 mg of **2.35** as a yellow oil (61% yield): IR (neat) ν_{max} 2929, 2857, 1638, 1449 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.98-5.86 (m, 1 H), 5.66 (s, 1 H), 5.34 (dd, $J = 17.2, 1.8\text{ Hz}$, 1 H), 5.09 (dd, $J = 10.7, 1.7\text{ Hz}$, 1 H), 4.67 (s, 1 H), 4.57 (s, 1 H), 3.69-3.40 (m, 2 H), 3.38-

3.19 (m, 4 H), 2.15-1.73 (m, 13 H), 1.09-1.64 (m, 5 H); ^{13}C NMR (75 MHz, CDCl_3) δ 148.01 (C), 140.50 (C), 135.93 (CH), 127.17 (CH), 115.06 (CH_2), 112.88 (CH_2), 81.84 (C), 66.45 (C), 62.80 (CH_2), 54.76 (CH), 41.82 (CH_2), 40.29 (CH_2), 40.00 (CH_2), 31.15 (CH_2), 27.61 (CH_2), 26.61 (CH_2), 25.42 (CH_2), 23.15 (CH_2), 22.01 (CH_3), 21.78 (CH_2); HRMS m/z calculated for $\text{C}_{20}\text{H}_{30}\text{OS}_2$ 350.1738 (M^+), found 350.1735.

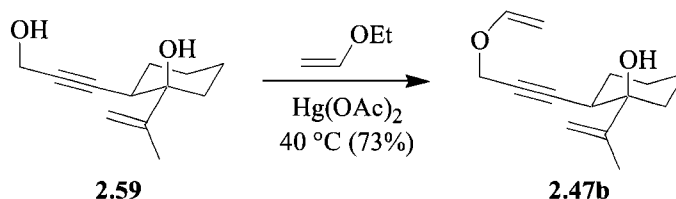


($\pm$)-4a-Allyl-4b-hydroxy-9-methylenedodecahydrophenanthrenone (**2.36**). A solution of **2.25** (50 mg, 0.182 mmol) in toluene (12 mL) was deoxygenated by bubbling argon through it for 20 minutes. The reaction mixture was then heated at 220 $^\circ\text{C}$ in the microwave oven for 2 h. After removal of the solvent, the residue was purified by silica gel column chromatography (20% EtOAc/hexanes) to afford 18 mg of **2.36** as a white solid (36% yield): mp 91-102 $^\circ\text{C}$; IR (neat) ν_{max} 3351 (br), 2937, 2861, 1641, 1443, 1185 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.84-5.70 (m, 1 H), 5.08 (s, 1 H), 5.03-5.01 (m, 2 H), 4.89 (s, 1 H), 2.97 (s, 1 H), 2.70-2.45 (m, 2 H), 2.27-2.09 (m, 1 H), 2.04-1.81 (m, 3 H), 1.78-1.37 (m, 11 H), 1.36-1.11 (m, 2 H); ^{13}C NMR (75 MHz, CDCl_3) δ 149.38 (C), 134.75 (CH), 118.05 (CH_2), 111.84 (CH_2), 106.67 (C), 85.90 (C), 49.66 (C), 49.49 (CH), 43.51 (CH), 37.11 (CH_2), 35.78 (CH_2), 31.87 (CH_2), 31.15 (CH_2), 28.52 (CH_2), 26.96 (CH_2), 25.62 (CH_2), 22.58 (CH_2), 20.58 (CH_2); HRMS m/z calculated for $\text{C}_{18}\text{H}_{26}\text{O}_2$ 274.1933 (M^+), found 274.1951. The tridimensional structure of this product was confirmed by X-ray crystallography.

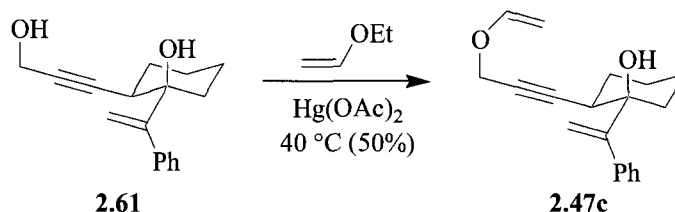


($\pm$)-1-Vinyl-2-(3-vinyloxypropynyl)-cyclohexanol (**2.47a**). To a Pyrex tube containing a solution of **2.57** (30 mg, 0.166 mmol) in ethyl vinyl ether (2 mL) was added $\text{Hg}(\text{OAc})_2$ (31 mg, 0.097

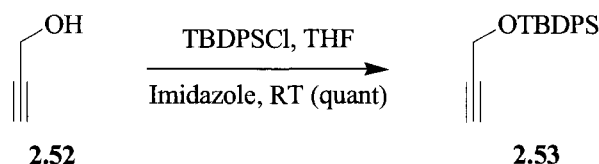
mmol). The tube was capped and the reaction mixture was heated at 40 °C for 48 h. After removal of the solvent, the residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford 23 mg of **2.47a** as a pale yellow oil (67% yield): IR (neat) $\nu_{\max}$ 3540 (br), 2937, 2863, 2233, 1638, 1614, 1442, 1184 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 6.40 (dd, $J = 14.3, 6.8$ Hz, 1 H), 5.88 (dd, $J = 17.2, 10.7$ Hz, 1 H), 5.29 (d, $J = 17.2$ Hz, 1 H), 5.09 (d, $J = 10.7$ Hz, 1 H), 4.35 (d, $J = 1.7$ Hz, 2 H), 4.25 (dd, $J = 14.3, 2.3$ Hz, 1 H), 4.09 (dd, $J = 6.8, 2.3$ Hz, 1 H), 2.46-2.41 (m, 1 H), 1.81-1.13 (m, 9 H); ^{13}C NMR (75 MHz, CDCl_3) δ 150.71 (CH), 144.93 (CH), 113.18 (CH_2), 88.47 (CH_2), 88.21 (C), 78.37 (C), 72.49 (C), 56.33 (CH_2), 39.67 (CH), 36.22 (CH_2), 28.33 (CH_2), 24.76 (CH_2), 21.04 (CH_2); HRMS m/z calculated for $\text{C}_{11}\text{H}_{14}\text{O}$ 162.1045 ($\text{M}^+ - \text{C}_2\text{H}_3\text{OH}$), found 161.9939.



(±)-1-Isopropenyl-2-(3-vinyloxypropynyl)-cyclohexanol (**2.47b**). To a Pyrex tube containing a solution of **2.59** (79 mg, 0.41 mmol) in ethyl vinyl ether (4 mL) was added $\text{Hg}(\text{OAc})_2$ (78 mg, 0.24 mmol). The tube was capped and the reaction mixture was heated at 40 °C for 40 h. After removal of the solvent, the residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford 65 mg of **2.47b** as a pale yellow oil (73% yield): IR (neat) $\nu_{\max}$ 3548 (br), 2938, 2863, 2230, 1639, 1619, 1447, 1359, 1319, 1189 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 6.39 (dd, $J = 14.3, 6.8$ Hz, 1 H), 5.10 (d, $J = 0.6$ Hz, 1 H), 4.86 (dd, $J = 1.4, 1.4$ Hz, 1 H), 4.34 (d, $J = 1.9$ Hz, 2 H), 4.25 (dd, $J = 14.3, 2.3$ Hz, 1 H), 4.09 (dd, $J = 6.8, 2.3$ Hz, 1 H), 2.69-2.62 (m, 1 H), 1.77 (s, 3 H), 1.73-1.44 (m, 7 H), 1.25-1.14 (m, 1 H); ^{13}C NMR (75 MHz, CDCl_3) δ 150.95 (C), 150.66 (CH), 110.85 (CH_2), 88.60 (CH_2), 88.25 (C), 78.12 (C), 75.34 (C), 56.53 (CH_2), 37.49 (CH), 35.52 (CH_2), 28.65 (CH_2), 25.40 (CH_2), 21.31 (CH_2), 19.80 (CH_3); HRMS m/z calculated for $\text{C}_{12}\text{H}_{16}\text{O}$ 176.1201 ($\text{M}^+ - \text{C}_2\text{H}_3\text{OH}$), found 176.1184.

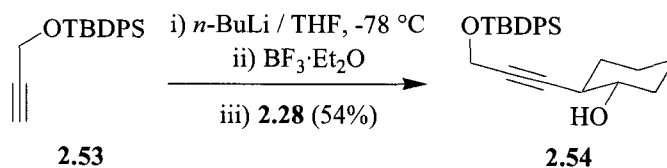


(±)-1-(1-Phenylvinyl)-2-(3-vinyloxypropynyl)-cyclohexanol (**2.47c**). To a Pyrex tube containing a solution of **2.61** (64 mg, 0.25 mmol) in ethyl vinyl ether (3 mL) was added Hg(OAc)_2 (48 mg, 0.15 mmol). The tube was capped and the reaction mixture was heated at 40 °C for 40 h. After removal of the solvent, the residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford 35 mg of **2.47c** as a pale yellow oil (50% yield): IR (neat) ν_{max} 3551, 2936, 2861, 2229, 1619, 1189 cm^{-1} ; ^1H NMR (300 MHz, acetone- d_6) δ 7.34-7.24 (m, 5 H), 6.47 (dd, J = 14.2, 6.8 Hz, 1 H), 5.60 (d, J = 2.0 Hz, 1 H), 4.92 (d, J = 2.0 Hz, 1 H), 4.43 (d, J = 1.9 Hz, 2 H), 4.30 (dd, J = 14.2, 2.0 Hz, 1 H), 4.05 (dd, J = 6.3, 2.0 Hz, 1 H), 3.33 (s, 1 H), 2.55-2.49 (m, 1 H), 1.85-1.54 (m, 6 H), 1.44-1.40 (m, 1 H), 1.14-1.00 (m, 1 H); ^{13}C NMR (75 MHz, CDCl_3) δ 156.45 (C), 150.77 (CH), 141.64 (C), 129.41 (CH), 128.05 (CH), 127.38 (CH), 114.84 (CH_2), 88.75 (CH_2), 88.72 (C), 79.27 (C), 75.47 (C), 56.59 (CH_2), 37.87 (CH), 35.95 (CH_2), 28.70 (CH_2), 24.99 (CH_2), 21.33 (CH_2); HRMS m/z calculated for $\text{C}_{17}\text{H}_{18}\text{O}$ 238.1358 ($\text{M}^+ - \text{C}_2\text{H}_3\text{OH}$), found 238.1332.

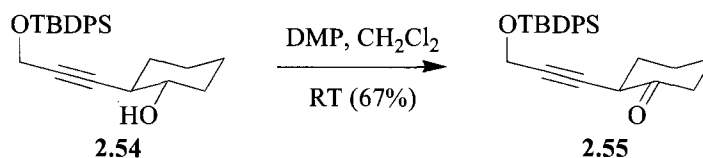


t-Butyldiphenylprop-2-ynyloxysilane (**2.53**). To a solution of propargyl alcohol **2.52** (3.10 mL, 53.25 mmol) in THF (300 mL) at room temperature were added TBDPSCl (15.00 mL, 58.61 mmol) and imidazole (12.69 g, 186.40 mmol). After stirring for 3 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (100 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 100 mL). Combined organics were dried over MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% then 20% EtOAc/hexanes) to afford 15.65 g of **2.53** as a

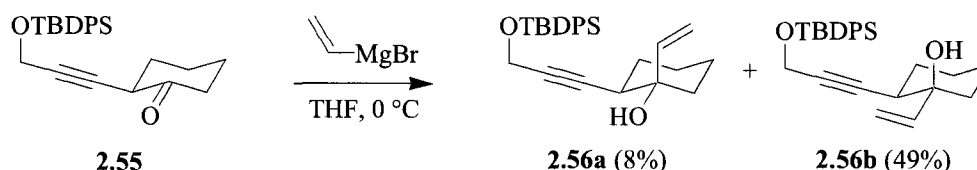
white solid (quantitative yield). Spectroscopic data for **2.53** were identical to that previously reported.¹⁴²



(±)-2-[3-(*t*-Butyldiphenylsilyloxy)-propynyl]-cyclohexanol (**2.54**). To a solution of **2.53** (12.00 g, 40.75 mmol) in THF (240 mL) at $-78\text{ }^\circ\text{C}$ was added *n*-BuLi (16.60 mL of a 2.46 M solution in hexanes, 40.84 mmol) over a 10-minute period. After stirring at -78 ° for 15 minutes, freshly distilled $\text{BF}_3 \cdot \text{OEt}_2$ (3.40 mL, 26.83 mmol) was added dropwise. The resulting solution was stirred at $-78\text{ }^\circ\text{C}$ for 15 minutes, and a solution of **2.28** (2.67 g, 27.20 mmol) in THF (10 mL) was added dropwise via cannula. The reaction mixture was then stirred at $-78\text{ }^\circ\text{C}$ for 2.5 h. After warming up to room temperature, it was quenched with saturated aqueous NH_4Cl (100 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 100 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% then 20% EtOAc /hexanes) to afford 5.75 g of **2.54** as a pale yellow oil (54% yield): IR (neat) ν_{max} 3415 (br), 2933, 2855, 1430, 1110 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.72-7.69 (m, 4 H), 7.45-7.34 (m, 6 H), 4.34 (d, $J = 1.8\text{ Hz}$, 2 H), 3.27 (ddd, $J = 9.8, 9.7, 4.0\text{ Hz}$, 1 H), 2.15-2.08 (m, 1 H), 1.96-1.83 (m, 3 H), 1.73-1.69 (m, 1 H), 1.62-1.57 (m, 1 H), 1.31-1.07 (m, 4 H), 1.03 (s, 9 H); ^{13}C NMR (75 MHz, CDCl_3) δ 135.94 (CH), 133.62 (C), 130.11 (CH), 127.99 (CH), 86.86 (C), 80.91 (C), 73.52 (CH), 53.05 (CH_2), 39.12 (C), 33.05 (CH_2), 30.90 (CH_2), 26.80 (CH_3), 24.92 (CH_2), 24.31 (CH_2), 19.23 (C); HRMS m/z calculated for $\text{C}_{21}\text{H}_{23}\text{O}_2\text{Si}$ 335.1467 ($\text{M}^+ - t\text{-Bu}$), found 335.1472.

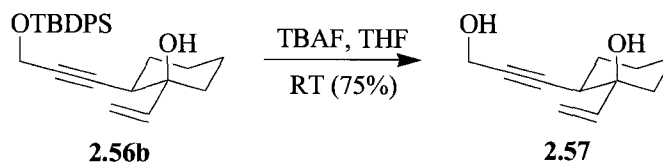


(±)-2-[3-(*t*-Butyldiphenylsilyloxy)-propynyl]-cyclohexanone (**2.55**). To a solution of **2.54** (3.29 g, 8.38 mmol) in CH₂Cl₂ (85 mL) at room temperature was added DMP (7.11 g, 16.76 mmol). The resulting cloudy mixture was stirred at room temperature for 3.5 h. Then, saturated aqueous NaHCO₃ (50 mL) and saturated aqueous Na₂SO₃ (50 mL) were added and the resulting biphasic mixture was stirred vigorously for 20 minutes. The aqueous layer was separated from the organic layer and extracted with CH₂Cl₂ (3 x 100 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% then 20% EtOAc/hexanes) to afford 2.18 g of **2.55** as a yellow oil (67% yield): IR (neat) $\nu_{\max}$ 2929, 2855, 1720, 1427, 1106 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.71-7.62 (m, 4 H), 7.44-7.33 (m, 6 H), 4.35 (d, *J* = 2.0 Hz, 2 H), 3.27-3.23 (m, 1 H), 2.61-2.52 (m, 1 H), 2.25-2.15 (m, 1 H), 2.05-1.89 (m, 1 H), 1.86-1.77 (m, 3 H), 1.65-1.59 (m, 2 H), 1.03 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 207.28 (C), 135.84 (CH), 133.52 (C), 130.07 (CH), 127.98 (CH), 83.60 (C), 82.22 (C), 53.07 (CH₂), 44.19 (C), 40.08 (CH₂), 34.34 (CH₂), 27.62 (CH₂), 26.80 (CH₃), 23.08 (CH₂), 19.27 (C); HRMS *m/z* calculated for C₂₁H₂₁O₂Si 333.1311 (M⁺ - *t*-Bu), found 333.1297.



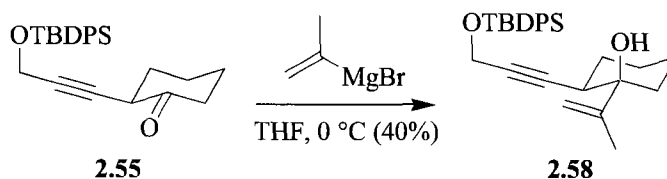
(±)-2-[3-(*t*-Butyldiphenylsilyloxy)-propynyl]-vinylcyclohexanol (**2.56**). To a solution of **2.55** (2.17 g, 5.56 mmol) in THF (56 mL) at 0 °C was added vinylmagnesium bromide (11.10 mL of a 1.0 M solution, 11.10 mmol) dropwise. The resulting yellow mixture was stirred at 0 °C for 3 h. After warming up to room temperature, it was quenched with saturated aqueous NH₄Cl (60 mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 60 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford 182 mg of **2.56a** (8% yield) and 1.13 g of **2.56b** (49% yield) as yellow oils. Epimer **2.56a**: IR (neat) $\nu_{\max}$ 3442 (br), 3071, 2932, 2858, 1589, 1428, 1112 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 7.71-7.70 (m,

4 H), 7.44-7.35 (m, 6 H), 6.19 (dd, $J = 17.3, 10.9$ Hz, 1 H), 5.32 (dd, $J = 17.3, 1.4$ Hz, 1 H), 5.13 (dd, $J = 10.9, 1.4$ Hz, 1 H), 4.33 (d, $J = 2.0$ Hz, 2 H), 2.48-2.46 (m, 1 H), 1.87-1.84 (m, 2 H), 1.75 (br, 1 H), 1.64-1.61 (m, 2 H), 1.50-1.33 (m, 4 H), 1.04 (s, 9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 135.53 (CH), 134.72 (CH), 133.23 (C), 129.65 (CH), 127.58 (CH), 113.75 (CH_2), 85.51 (C), 81.60 (C), 73.30 (C), 52.78 (CH_2), 40.68 (CH), 35.84 (CH_2), 28.47 (CH_2), 26.56 (CH_3), 23.16 (CH_2), 22.07 (CH_2), 19.02 (C); HRMS m/z calculated for $\text{C}_{23}\text{H}_{25}\text{O}_2\text{Si}$ 361.1618 ($\text{M}^+ - t\text{-Bu}$), found 361.1635. Epimer **2.56b**: IR (neat) ν_{max} 3359 (br), 2929, 2855, 2229, 1427, 1109 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.69-7.67 (m, 4 H), 7.44-7.34 (m, 6 H), 5.84 (dd, $J = 17.2, 10.7$ Hz, 1 H), 5.23 (d, $J = 17.3$ Hz, 1 H), 5.04 (d, $J = 10.7$ Hz, 1 H), 4.30 (d, $J = 1.8$ Hz, 2 H), 2.40-2.34 (m, 1 H), 1.77-1.58 (m, 4 H), 1.54-1.15 (m, 4 H), 1.02 (s, 9 H); ^{13}C NMR (75 MHz, CDCl_3) δ 145.08 (CH), 135.93 (CH), 133.56 (C), 130.09 (CH), 127.98 (CH), 113.00 (CH_2), 85.62 (C), 82.36 (C), 72.41 (C), 53.00 (CH_2), 39.69 (CH), 36.11 (CH_2), 28.32 (CH_2), 26.76 (CH_3), 24.80 (CH_2), 19.22 (CH_2), 17.97 (C); HRMS m/z calculated for $\text{C}_{23}\text{H}_{25}\text{O}_2\text{Si}$ 361.1624 ($\text{M}^+ - t\text{-Bu}$), found 361.1655.

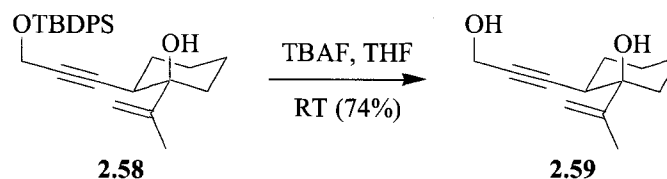


(±)-2-(3-Hydroxypropynyl)-vinylcyclohexanol (**2.57**). To a solution of **2.56b** (2.46 g, 5.88 mmol) in THF (60 mL) at room temperature was added TBAF (8.80 mL of a 1.0 M solution in THF, 8.80 mmol) dropwise. After stirring for 16 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL). The aqueous layer was separated from the organic layer and extracted with EtOAc (3 x 30 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (50% EtOAc/hexanes) to afford 790 mg of **2.57** as a white solid (75% yield): mp 51-53.5 °C; IR (neat) ν_{max} 3374 (br), 2936, 2863, 2225, 1447 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.88 (dd, $J = 17.3, 10.8$ Hz, 1 H), 5.27 (d, $J = 17.2$ Hz, 1 H), 5.06 (d, $J = 10.8$ Hz, 1 H), 4.16 (d, $J = 1.4$ Hz, 2 H), 3.61 (br, 1 H), 2.68 (br, 1 H), 2.39-2.34 (m, 1 H), 1.73-1.49 (m, 5 H), 1.45-1.17 (m, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 144.90 (CH), 113.25 (CH_2), 86.26 (C), 81.87 (C), 72.78 (C), 50.88

(CH₂), 39.42 (CH), 36.21 (CH₂), 28.45 (CH₂), 24.67 (CH₂), 21.08 (CH₂); HRMS *m/z* calculated for C₁₁H₁₄O 162.1045 (M⁺ - H₂O), found 161.9917.

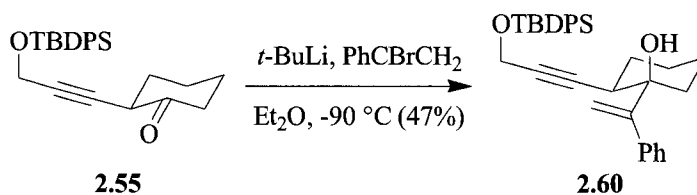


(±)-2-[3-(*t*-Butyldiphenylsilyloxy)-propynyl]-isopropenylcyclohexanol (2.58). To a solution of **2.55** (1.30 g, 3.33 mmol) in THF (35 mL) at 0 °C was added isopropenylmagnesium bromide (16.60 mL of a 0.5 M solution in hexanes, 8.30 mmol) dropwise. The resulting pale yellow solution was stirred at 0 °C for 1.5 h. After warming up to room temperature, it was quenched with saturated aqueous NH₄Cl (25 mL). The aqueous layer was separated from the organic layer and extracted with EtOAc (3 x 30 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% EtOAc/hexanes) to afford 580 mg of **2.58** as a pale yellow oil (40% yield): IR (neat) ν_{max} 3556, 2933, 2858, 2233, 1428, 1112 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.68-7.66 (m, 4 H), 7.42-7.33 (m, 6 H), 5.04 (s, 1 H), 4.82 (dd, *J* = 1.3, 1.3 Hz, 1 H), 4.27 (d, *J* = 1.9 Hz, 2 H), 2.62-2.56 (m, 1 H), 1.74 (d, *J* = 0.6 Hz, 3 H), 1.72-1.59 (m, 7 H), 1.50-1.45 (m, 1 H), 1.01 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 151.10 (C), 135.95 (CH), 133.65 (C), 130.14 (CH), 128.05 (CH), 110.76 (CH₂), 85.66 (C), 82.07 (C), 75.30 (C), 53.24 (CH₂), 37.50 (CH), 35.48 (CH₂), 28.67 (CH₂), 27.02 (CH₃), 25.48 (CH₂), 21.38 (CH₂), 19.84 (CH₃), 19.49 (C); HRMS *m/z* calculated for C₂₄H₂₇O₂Si 375.1780 (M⁺ - *t*-Bu), found 375.1789.



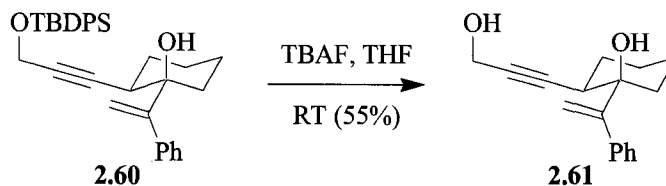
(±)-2-(3-Hydroxypropynyl)-isopropenylcyclohexanol (2.59). To a solution of **2.58** (550 mg, 1.27 mmol) in THF (13 mL) at room temperature was added TBAF (1.90 mL of a 1.0 M solution in THF, 1.90 mmol) dropwise. After stirring for 16 h, the reaction mixture was

quenched with saturated aqueous NH_4Cl (15 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 20 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (20% then 50% EtOAc /hexanes) to afford 184 mg of **2.59** as a pale yellow solid (74% yield): mp 74-76.5 °C; IR (neat) ν_{max} 3301 (br), 2933, 1646, 1441, 1361 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.10 (s, 1 H), 4.86 (s, 1 H), 4.22 (d, $J = 1.9$ Hz, 2 H), 2.67-2.62 (m, 1 H), 1.77 (s, 3 H), 1.75-1.13 (m, 8 H); ^{13}C NMR (75 MHz, CDCl_3) δ 151.07 (C), 110.80 (CH_2), 86.52 (C), 81.81 (C), 75.44 (C), 51.57 (CH_2), 37.37 (CH), 35.58 (CH_2), 28.79 (CH_2), 25.43 (CH_2), 21.33 (CH_2), 19.86 (CH_3); HRMS m/z calculated for $\text{C}_{12}\text{H}_{16}\text{O}$ 176.1201 ($\text{M}^+ - \text{H}_2\text{O}$), found 176.1185.

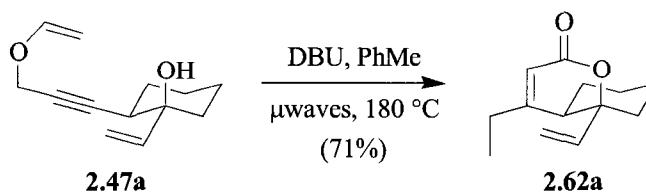


(±)-2-[3-(*t*-Butyldiphenylsilyloxy)-propynyl]-1-(1-phenylvinyl)-cyclohexanol (**2.60**). To a solution of α -bromostyrene (665 μL , 5.12 mmol) in Et_2O (20 mL) at -90 °C was added *t*-BuLi (5.10 mL of a 1.6 M solution in hexanes, 8.16 mmol) dropwise. The resulting orange solution was stirred at -90 °C for 1.5 h, and a solution of **2.55** (500 mg, 1.28 mmol) in Et_2O (2 mL) was added dropwise via cannula. The reaction mixture was stirred at -90 °C for 10 minutes, and was warmed up to -60 °C. After stirring at that temperature for 1 h, it was cooled down to -90 °C and quenched with H_2O (10 mL). Upon warming up to room temperature, the aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 10 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% EtOAc /hexanes) to afford 298 mg of **2.60** as a pale yellow oil (47% yield): IR (neat) ν_{max} 3555, 2932, 2858, 2225, 1428, 1112 cm^{-1} ; ^1H NMR (300 MHz, acetone-d_6) δ 7.78-7.71 (m, 4 H), 7.48-7.39 (m, 6 H), 7.36-7.32 (m, 2 H), 7.30-7.24 (m, 3 H), 5.59 (d, $J = 2.1$ Hz, 1 H), 4.91 (d, $J = 2.1$ Hz, 1 H), 4.40 (d, $J = 2.0$ Hz, 2 H), 3.09 (s, 1 H), 2.52-2.47 (m, 1 H), 1.81-1.53 (m, 6 H), 1.44-1.39 (m, 2 H), 1.04 (s, 9 H); ^{13}C NMR (75 MHz, CDCl_3) δ 156.65 (C), 141.85 (C), 135.99 (CH), 133.66 (C), 130.23 (CH),

129.48 (CH), 128.15 (CH), 128.05 (CH), 127.34 (CH), 114.73 (CH₂), 86.16 (C), 83.19 (C), 75.50 (C), 53.32 (CH₂), 27.80 (CH), 35.79 (CH₂), 28.70 (CH₂), 27.09 (CH₃), 25.09 (CH₂), 21.41 (CH₂), 19.57 (C); HRMS m/z calculated for C₂₉H₂₉O₂Si 437.1937 ($M^+ - t\text{-Bu}$), found 437.1915.

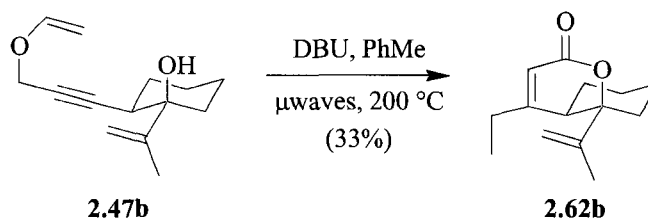


(±)-2-(3-Hydroxypropynyl)-isopropenylcyclohexanol (**2.61**). To a solution of **2.60** (260 mg, 0.52 mmol) in THF (5 mL) at room temperature was added TBAF (800 μL of a 1.0 M solution in THF, 0.80 mmol) dropwise. After stirring for 6 h, the reaction mixture was quenched with saturated aqueous NH₄Cl (5 mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 10 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (20% then 50% EtOAc/hexanes) to afford 74 mg of **2.61** as a pale yellow solid (55% yield): mp 75–78.5 °C; IR (neat) ν_{max} 3383 (br), 2935, 2863, 1489, 1442 cm⁻¹; ¹H NMR (300 MHz, acetone-d₆) δ 7.35–7.31 (m, 5 H), 5.61 (d, $J = 1.3$ Hz, 1 H), 4.93 (d, $J = 1.2$ Hz, 1 H), 4.21–4.19 (m, 2 H), 4.07–4.04 (m, 1 H), 3.27 (s, 1 H), 2.88–2.50 (m, 1 H), 1.86–1.60 (m, 6 H), 1.45–1.42 (m, 1 H), 1.15–0.99 (m, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 156.46 (C), 141.68 (C), 129.40 (CH), 128.08 (CH), 127.42 (CH), 114.89 (CH₂), 86.99 (C), 82.74 (C), 75.75 (C), 51.44 (CH₂), 37.68 (CH), 36.12 (CH₂), 28.83 (CH₂), 24.98 (CH₂), 21.38 (CH₂); HRMS m/z calculated for C₁₇H₁₈O 238.1358 ($M^+ - \text{H}_2\text{O}$), found 238.1349.



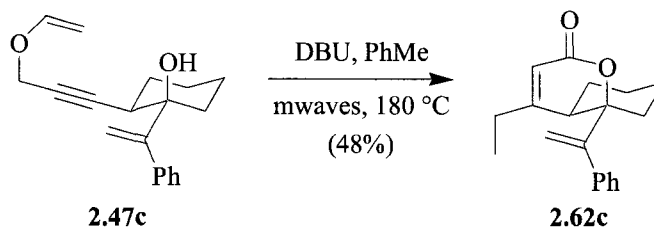
(±)-4-Ethyl-8a-vinyl-4a,5,6,7,8,8a-hexahydrochromen-2-one (**2.62a**). A solution of **2.47a** (14 mg, 0.068 mmol) and DBU (100 μL , 0.669 mmol) in toluene (12 mL) was deoxygenated by

bubbling argon through it for 20 minutes. The reaction mixture was then heated at 180 °C in the microwave oven for 30 minutes. After removal of the solvent, the residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford 10 mg of **2.62a** as a pale yellow oil (71% yield): IR (neat) $\nu_{\max}$ 2936, 2860, 1712, 1648, 1447, 1239 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.69 (dd, $J = 17.3, 11.0$ Hz, 1 H), 5.65 (t, $J = 1.5$ Hz, 1 H), 5.19 (d, $J = 17.3$ Hz, 1 H), 5.05 (d, $J = 11.0$ Hz, 1 H), 2.32-2.24 (m, 1 H), 2.17-2.09 (m, 1 H), 2.07-2.04 (m, 1 H), 2.02-1.93 (m, 1 H), 1.92-1.88 (m, 1 H), 1.79-1.70 (m, 1 H), 1.70-1.60 (m, 2 H), 1.43 (ddd, $J = 14.4, 14.3, 5.0$ Hz, 1 H), 1.28-1.18 (m, 2 H), 1.07 (t, $J = 7.4$ Hz, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 165.73 (C), 165.52 (C), 141.38 (CH), 114.39 (CH_2), 113.74 (CH), 81.47 (C), 43.06 (CH), 36.34 (CH_2), 28.85 (CH_2), 27.74 (CH_2), 24.25 (CH_2), 20.90 (CH_2), 10.55 (CH_3); IR (neat) $\nu_{\max}$ 2936, 2860, 1712, 1648, 1447, 1239 cm^{-1} , HRMS m/z calculated for $\text{C}_{13}\text{H}_{18}\text{O}_2$ 206.1307 (M^+), found 206.1320.

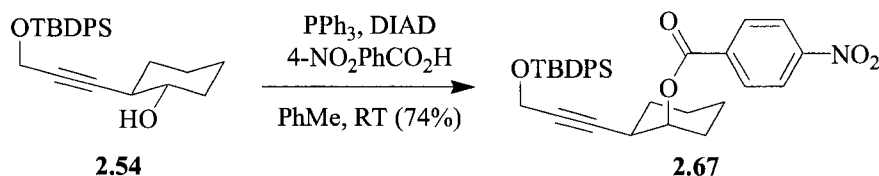


(±)-4-Ethyl-8a-isopropenyl-4a,5,6,7,8,8a-hexahydrochromen-2-one (**2.62b**). A solution of **2.47b** (24 mg, 0.109 mmol) and DBU (160 μL , 1.070 mmol) in toluene (12 mL) was deoxygenated by bubbling argon through it for 20 minutes. The reaction mixture was then heated at 200 °C in the microwave oven for 30 minutes. After removal of the solvent, the residue was purified by silica gel column chromatography (5% EtOAc/hexanes) to afford 8 mg of **2.62b** as a pale yellow solid (33% yield): mp 69-70 °C; IR (neat) $\nu_{\max}$ 2937, 2861, 1714, 1642, 1446, 1375, 1295, 1210 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.64 (t, $J = 1.6$ Hz, 1 H), 4.86 (s, 1 H), 4.95 (s, 1 H), 2.34-2.26 (m, 2 H), 2.22-2.13 (m, 1 H), 1.98-1.92 (m, 1 H), 1.91-1.88 (m, 1 H), 1.81-1.71 (m, 1 H), 1.68 (s, 3 H), 1.66-1.60 (m, 1 H), 1.50 (ddd, $J = 14.1, 13.5, 4.5$ Hz, 1 H), 1.30-1.19 (m, 3 H), 1.08 (t, $J = 7.4$ Hz, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 166.67 (C), 166.32 (C), 148.20 (C), 114.17 (CH), 112.32 (CH_2), 84.69 (C), 41.94 (CH), 36.37 (CH_2), 29.59 (CH_2), 28.20 (CH_2), 24.94 (CH_2), 21.58 (CH_2), 20.50 (CH_3), 11.00 (CH_3); HRMS m/z

calculated for $C_{13}H_{17}O_2$ 205.1229 ($M^+ - Me$), found 205.1287. The tridimensional structure of this product was confirmed by X-ray crystallography.

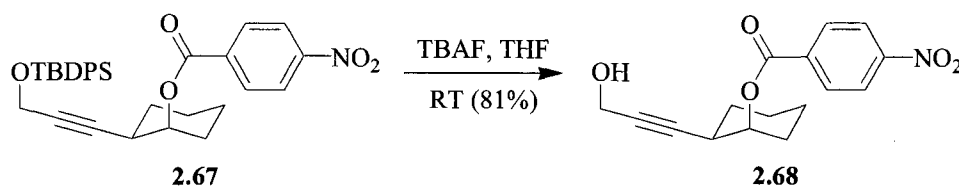


(±)-4-Ethyl-8a-(1-phenylvinyl)-4a,5,6,7,8,8a-hexahydrochromen-2-one (2.62c). A solution of **2.47c** (25 mg, 0.089 mmol) and DBU (130 μL , 0.869 mmol) in toluene (12 mL) was deoxygenated by bubbling argon through it for 20 minutes. The reaction mixture was then heated at 180 $^\circ\text{C}$ in the microwave oven for 1 h. After removal of the solvent, the residue was purified by silica gel column chromatography (5% EtOAc/hexanes) to afford 12 mg of **2.62c** as a pale yellow solid (48% yield): mp 77-78 $^\circ\text{C}$; IR (neat) ν_{max} 2936, 2859, 1718, 1647, 1443, 1237, 1211 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.30-7.27 (m, 3 H), 7.08-7.07 (m, 2 H), 5.67 (t, $J = 1.7$ Hz, 1 H), 5.52 (s, 1 H), 5.06 (s, 1 H), 2.18-2.10 (m, 1 H), 2.12-2.02 (m, 2 H), 1.88 (ddd, $J = 14.3, 12.7, 4.6$ Hz, 1 H), 1.81-1.76 (m, 1 H), 1.74-1.65 (m, 4 H), 1.27-1.14 (m, 2 H), 0.95 (t, $J = 7.3$ Hz, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 167.02 (C), 166.22 (C), 154.61 (C), 141.09 (C), 128.73 (CH), 128.35 (CH), 127.81 (CH), 117.02 (CH_2), 114.57 (CH), 84.48 (C), 42.65 (CH), 38.25 (CH_2), 29.42 (CH_2), 27.75 (CH_2), 24.77 (CH_2), 21.87 (CH_2), 10.37 (CH_3); HRMS m/z calculated for $C_{19}H_{22}O_2$ 282.1620 (M^+), found 282.1594.

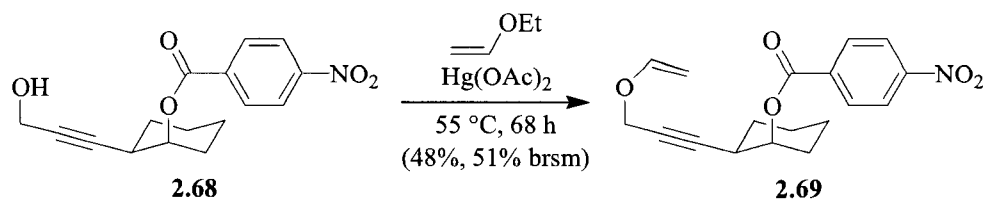


(±)-2-[3-(*t*-butyldiphenylsilyloxy)-propynyl]-cyclohexyl 4-nitrobenzoate (2.67). To a solution of **2.54** (50 mg, 0.13 mmol) in toluene (1.3 mL) at 0 $^\circ\text{C}$ were added PPh_3 (134 mg, 0.51 mmol) and 4-nitrobenzoic acid (85 mg, 0.51 mmol). DIAD (120 μL , 0.60 mmol) was added dropwise and the resulting yellow solution was stirred at room temperature for 17 h. After

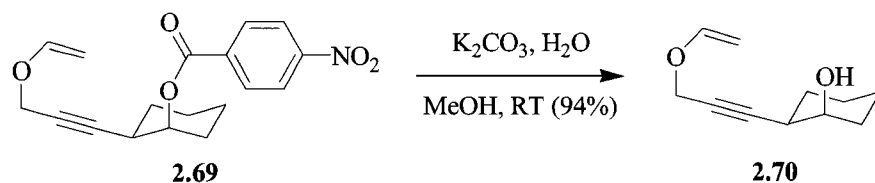
removal of most of the solvent, hexanes (1.5 mL) was added to precipitate out $\text{Ph}_3\text{P}=\text{O}$. The resulting mixture was filtered through celite, and the fritted glass funnel was rinsed with 1:1 Et_2O /hexanes (15 mL). The solvent was removed and the residue was purified by silica gel column chromatography (2% then 5% EtOAc /hexanes) to afford 51 mg of **2.67** as a pale yellow oil (74% yield): IR (neat) ν_{max} 2933, 2862, 1720, 1532, 1340, 1273 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.17 (s, 4 H), 7.68 (d, $J = 6.7$ Hz, 4 H), 7.41-7.37 (m, 2 H), 7.35-7.31 (m, 4 H), 5.07-5.04 (m, 1 H), 4.33 (s, 2 H), 3.04 (br, 1 H), 2.01-1.94 (m, 1 H), 1.89-1.83 (m, 1 H), 1.78-1.71 (m, 2 H), 1.69-1.63 (m, 2 H), 1.47-1.38 (m, 2 H), 1.00 (s, 9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 163.82 (C), 159.84 (C), 150.28 (C), 135.87 (C), 135.39 (CH), 133.09 (C), 130.63 (CH), 129.66 (CH), 127.57 (CH), 123.32 (CH), 84.28 (C), 81.16 (C), 52.81 (CH_2), 32.76 (CH), 29.23 (CH_2), 27.84 (CH_2), 26.51 (CH), 22.98 (CH_2), 21.69 (CH_2), 21.44 (CH_3); HRMS m/z calculated for $\text{C}_{28}\text{H}_{26}\text{NO}_5\text{Si}$ 484.1580 ($\text{M}^+ - t\text{-Bu}$), found 484.1638.



(±)-2-(3-hydroxypropynyl)-cyclohexyl 4-nitrobenzoate (**2.68**). To a solution of **2.67** (522 mg, 0.96 mmol) in THF (10 mL) at 0 °C was added TBAF (1.00 mL of a 1.0 M solution in THF, 1.00 mmol) dropwise. After stirring for 30 minutes at that temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL). The aqueous layer was separated from the organic layer and extracted with EtOAc (3 x 10 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (20% then 50% EtOAc /hexanes) to afford 237 mg of **2.68** as a pale yellow oil (81% yield): IR (neat) ν_{max} 3425 (br), 2938, 2862, 1727, 1533, 1348, 1276 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.29-8.26 (m, 2 H), 8.23-8.21 (m, 2 H), 5.12-5.10 (m, 1 H), 4.23 (d, $J = 2.0$ Hz, 2 H), 3.04 (br, 1 H), 2.01-1.85 (m, 2 H), 1.79-1.62 (m, 4 H), 1.50-1.36 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 163.94 (C), 150.32 (C), 135.82 (C), 130.61 (CH), 123.36 (CH), 85.01 (C), 80.99 (C), 73.84 (CH), 50.98 (CH_2), 32.80 (CH), 29.03 (CH_2), 27.97 (CH_2), 22.56 (CH_2), 21.93 (CH_2); HRMS m/z calculated for $\text{C}_9\text{H}_{12}\text{O}$ 136.0888 ($\text{M}^+ - 4\text{-NO}_2\text{PhCO}_2\text{H}$), found 136.0908.

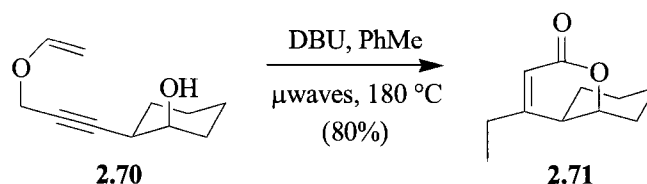


(±)-2-(3-vinyloxypropynyl)-cyclohexyl 4-nitrobenzoate (2.69). To a Pyrex tube containing a solution of **2.68** (207 mg, 0.68 mmol) in ethyl vinyl ether (6.8 mL) was added Hg(OAc)₂ (216 mg, 0.68 mmol). The tube was capped and the reaction mixture was heated at 55 °C for 68 h. After removal of the solvent, the residue was purified by silica gel column chromatography (10% then 20% EtOAc/hexanes) to afford 15 mg of unreacted **2.68** and 107 mg of **2.69** as a pale yellow solid (48% yield, 51% yield brsm): mp 76–77 °C; IR (neat) ν_{max} 2940, 2864, 1724, 1530, 1275 cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ 8.05–8.02 (m, 2 H), 7.86–7.83 (m, 2 H), 6.40 (dd, J = 14.3, 6.8 Hz, 1 H), 5.08 (ddd, J = 9.4, 4.2, 4.2 Hz, 1 H), 4.33 (dd, J = 14.3, 2.2 Hz, 1 H), 4.22 (d, J = 2.0 Hz, 2 H), 4.04 (dd, J = 6.8, 2.2 Hz, 1 H), 2.95 (br, 1 H), 2.04–1.97 (m, 1 H), 1.83–1.77 (m, 1 H), 1.68–1.53 (m, 3 H), 1.43–1.37 (m, 1 H), 1.24–1.10 (m, 2 H); ¹³C NMR (125 MHz, C₆D₆) δ 163.54 (C), 150.44 (CH), 150.28 (C), 135.47 (C), 130.36 (CH), 123.10 (CH), 87.72 (CH₂), 86.64 (C), 77.90 (C), 73.63 (CH), 55.92 (CH₂), 32.76 (CH), 29.02 (CH₂), 27.81 (CH₂), 22.80 (CH₂), 21.68 (CH₂); HRMS m/z calculated for C₁₆H₁₆NO₄ 286.1079 (M⁺ - C₂H₃O), found 286.1079.

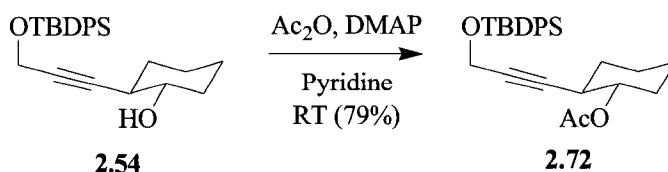


(±)-2-(3-Vinyloxypropynyl)-cyclohexanol (2.70). To a solution of **2.69** (41 mg, 0.124 mmol) in MeOH (1.5 mL) at room temperature were added H₂O (500 μ L) and K₂CO₃ (21 mg, 0.152 mmol). After stirring for 4 h, the reaction mixture was quenched with saturated aqueous NH₄Cl (1 mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 5 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (20% EtOAc/hexanes) to afford 21 mg of **2.70** as a

pale yellow oil (94% yield): IR (neat) $\nu_{\max}$ 3438 (br), 2933, 2862, 1614, 1183 cm^{-1} ; ^1H NMR (500 MHz, C_6D_6) δ 6.42 (dd, $J = 14.3, 6.8$ Hz, 1 H), 4.35 (dd, $J = 14.3, 2.2$ Hz, 1 H), 4.16 (d, $J = 2.0$ Hz, 2 H), 4.10 (dd, $J = 6.8, 2.2$ Hz, 1 H), 3.57 (br, 1 H), 2.69 (br, 1 H), 1.86-1.62 (m, 4 H), 1.61-1.49 (m, 2 H), 1.41-1.30 (m, 1 H), 1.20-1.07 (m, 2 H); ^{13}C NMR (125 MHz, C_6D_6) δ 150.52 (CH), 87.83 (C), 87.71 (CH_2), 78.48 (C), 69.27 (CH), 55.90 (CH_2), 36.07 (CH), 31.45 (CH_2), 31.45 (CH_2), 28.39 (CH_2), 22.41 (CH_2); HRMS m/z calculated for $\text{C}_{11}\text{H}_{14}\text{O}$ 162.1045 ($\text{M}^+ - \text{H}_2\text{O}$), found 161.9917.

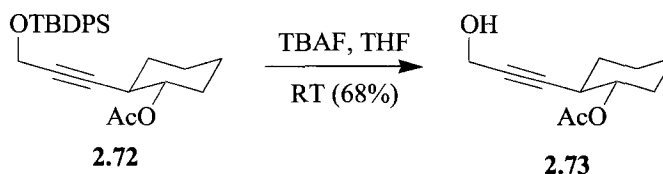


(±)-4-Ethyl-4a,5,6,7,8,8a-hexahydrochromen-2-one (**2.71**). A solution of **2.70** (17.3 mg, 0.096 mmol) and DBU (80 μL , 0.535 mmol) in toluene (12 mL) was deoxygenated by bubbling argon through it for 20 minutes. The reaction mixture was then heated at 180 $^\circ\text{C}$ in the microwave oven for 1 h. After removal of the solvent, the residue was purified by silica gel column chromatography (10% then 20% EtOAc/hexanes) to afford 13.8 mg of **2.71** as a white solid (80% yield): mp 51-53 $^\circ\text{C}$; IR (neat) $\nu_{\max}$ 2937, 2862, 1716, 1246 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.72 (s, 1 H), 4.43 (d, $J = 2.4$ Hz, 1 H), 2.35-2.27 (m, 1 H), 2.25-2.15 (m, 1 H), 2.10 (d, $J = 14.1$ Hz, 1 H), 2.03-2.00 (m, 1 H), 1.77 (d, $J = 8.3$ Hz, 2 H), 1.68-1.48 (m, 3 H), 1.32-1.20 (m, 2 H), 1.10 (t, $J = 7.4$ Hz, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 168.78 (C), 166.58 (C), 113.89 (CH), 76.11 (CH), 40.20 (CH), 30.17 (CH_2), 27.91 (CH_2), 27.14 (CH_2), 24.50 (CH_2), 20.12 (CH_2), 11.36 (CH_3); HRMS m/z calculated for $\text{C}_{11}\text{H}_{16}\text{O}_2$ 180.1150 (M^+), found 180.1165.



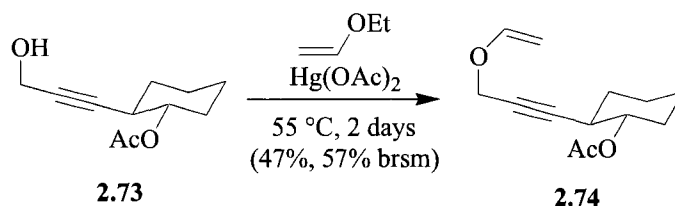
(±)-2-[3-(*t*-butyldiphenylsilyloxy)-propynyl]-cyclohexyl acetate (**2.72**). To a solution of **2.54** (715 mg, 1.82 mmol) in pyridine (8 mL) at 0 $^\circ\text{C}$ were added Ac_2O (210 μL , 2.22 mmol) and

DMAP (11 mg, 0.09 mmol). After stirring at room temperature for 19 h, the reaction mixture was quenched with 1 N HCl (5 mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 10 mL). Combined organics were washed with 1 N HCl (5 x 10 mL) and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford 624 mg of **2.72** as a colorless oil (79% yield): IR (neat) ν_{max} 3070, 2941, 2859, 2224, 1740, 1427, 1368, 1235 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.70-7.67 (m, 4 H), 7.42-7.35 (m, 6 H), 4.69 (ddd, J = 8.7, 8.7, 3.8 Hz, 1 H), 4.28 (d, J = 1.9 Hz, 2 H), 2.48-2.43 (m, 1 H), 2.01 (s, 3 H), 1.96-1.87 (m, 2 H), 1.66-1.59 (m, 2 H), 1.43-1.15 (m, 4 H), 1.03 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) δ 170.12 (C), 135.48 (CH), 133.18 (C), 129.62 (CH), 127.56 (CH), 85.67 (C), 79.79 (C), 74.05 (CH), 65.73 (CH₂), 52.77 (CH₂), 34.20 (CH), 29.93 (CH₂), 26.59 (CH₃), 23.68 (CH₂), 23.06 (CH₂), 21.10 (CH₃), 19.04 (C); HRMS m/z calculated for C₂₃H₂₅O₃Si 377.1573 (M⁺ - *t*-Bu), found 377.1571.

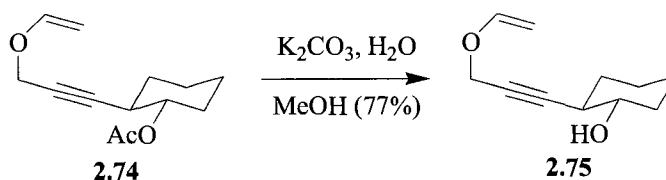


(±)-2-(3-hydroxypropynyl)-cyclohexyl acetate (**2.73**). To a solution of **2.72** (299 mg, 0.69 mmol) in THF (6 mL) at room temperature was added TBAF (1.00 mL of a 1.0 M solution in THF, 1.00 mmol) dropwise. After stirring for 7 h, the reaction mixture was quenched with saturated aqueous NH₄Cl (3 mL). The aqueous layer was separated from the organic layer and extracted with EtOAc (3 x 5 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (20% then 50% EtOAc/hexanes) to afford 92 mg of **2.73** as a colorless oil (68% yield): IR (neat) ν_{max} 3435 (br), 2939, 2863, 1738, 1449, 1376, 1241 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.76 (ddd, J = 9.2, 9.2, 4.1 Hz, 1 H), 4.20 (d, J = 2.0 Hz, 2 H), 2.48-2.44 (m, 1 H), 2.66 (s, 3 H), 2.00-1.93 (m, 2 H), 1.71-1.63 (m, 2 H), 1.50-1.42 (m, 1 H), 1.40-1.17 (m, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 170.61 (C), 86.29 (C), 79.77 (C), 74.24 (CH), 50.93 (CH₂), 34.55 (CH), 30.35

(CH₂), 30.20 (CH₂), 23.81 (CH₂), 23.23 (CH₂), 21.11 (CH₃); HRMS *m/z* calculated for C₉H₁₂O 136.0888 (M⁺ - AcOH), found 136.0867.

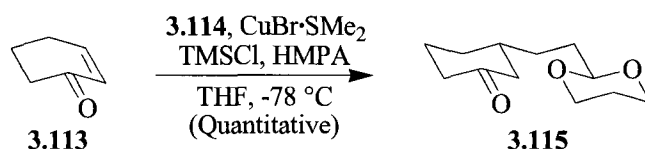


(±)-2-(3-vinyloxypropynyl)-cyclohexyl acetate (2.74). To a Pyrex tube containing a solution of **2.73** (92 mg, 0.47 mmol) in ethyl vinyl ether (5 mL) was added Hg(OAc)₂ (150 mg, 0.47 mmol). The tube was capped and the reaction mixture was heated at 55 °C for 41 h. After removal of the solvent, the residue was purified by silica gel column chromatography (10% then 20% EtOAc/hexanes) to afford 16 mg of unreacted **2.73** and 49 mg of **2.74** as a pale yellow oil (47% yield, 57% yield brsm): R(neat) ν_{max} 2940, 2864, 1735, 1614, 1374, 1234, 1188 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.40 (dd, *J* = 14.3, 6.8 Hz, 1 H), 4.74 (ddd, *J* = 9.0, 9.0, 3.7 Hz, 1 H), 4.33 (d, *J* = 1.9 Hz, 2 H), 4.25 (dd, *J* = 14.3, 2.3 Hz, 1 H), 4.07 (dd, *J* = 6.8, 2.3 Hz, 1 H), 2.51-2.46 (m, 1 H), 2.04 (s, 3 H), 1.97-1.94 (m, 2 H), 1.69-1.62 (m, 2 H), 1.50-1.42 (m, 1 H), 1.40-1.18 (m, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 170.76 (C), 150.78 (CH), 88.53 (CH₂), 77.32 (C), 76.49 (C), 74.54 (CH), 56.73 (CH₂), 34.95 (CH), 30.71 (CH₂), 30.71 (CH₂), 24.32 (CH₂), 23.70 (CH₂), 21.65 (CH₃); HRMS *m/z* calculated for C₁₁H₁₄O 162.1045 (M⁺ - AcOH), found 162.1035.

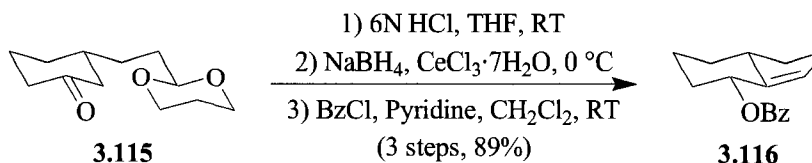


(±)-2-(3-Vinyloxy-propynyl)-cyclohexanol (2.75). To a solution of **2.74** (43 mg, 0.193 mmol) in MeOH (1 mL) at room temperature were added H₂O (1 mL) and K₂CO₃ (32 mg, 0.232 mmol). After stirring for 17 h, the reaction mixture was quenched with saturated aqueous NH₄Cl (1 mL). The aqueous layer was separated from the organic layer and extracted with EtOAc (3 x 5 mL). Combined organics were washed with saturated aqueous NaCl and dried

over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (20% EtOAc/hexanes) to afford 27 mg of **2.75** as a colorless oil (77% yield): IR (neat) ν_{max} 3416 (br), 2933, 2859, 1618, 1449, cm^{-1} ; ^1H NMR (500 MHz, C_6D_6) δ 6.35 (dd, $J = 14.3, 6.8$ Hz, 1 H), 4.28 (dd, $J = 14.3, 2.1$ Hz, 1 H), 4.10 (d, $J = 1.9$ Hz, 2 H), 4.03 (dd, $J = 6.8, 2.1$ Hz, 1 H), 2.37-2.33 (m, 1 H), 2.19-2.14 (m, 1 H), 1.97-1.90 (m, 2 H), 1.83-1.78 (m, 1 H), 1.47-1.11 (m, 4 H), 1.04-0.84 (m, 2 H); ^{13}C NMR (125 MHz, C_6D_6) δ 150.56 (CH), 89.04 (C), 87.68 (CH_2), 77.05 (C), 72.84 (CH), 55.97 (CH_2), 38.80 (CH), 33.02 (CH_2), 30.38 (CH_2), 24.41 (CH_2), 23.76 (CH_2); HRMS m/z calculated for $\text{C}_{11}\text{H}_{14}\text{O}$ 162.1045 ($\text{M}^+ - \text{H}_2\text{O}$), found 161.9895.

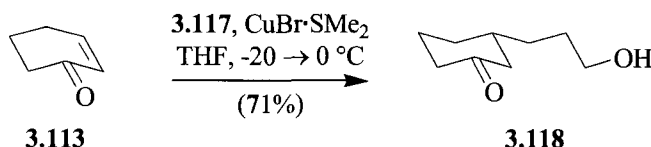


(±)-3-(2-[1,3]Dioxan-2-ylethyl)-cyclohexanone (**3.115**). To a suspension of magnesium turnings (1.12 g, 46.08 mmol) in THF (35 mL) was added 1,2-dibromoethane (260 μL , 3.00 mmol). The suspension was heated with a heat gun until bubbles evolved from the magnesium turnings. Then, a solution of 2-(2-bromo-ethyl)-[1,3]dioxane (5.98 g, 30.66 mmol) in THF (5 mL) was added dropwise via cannula, yielding a strongly exothermic reaction. Once the addition was over, the mixture was further refluxed for 1 h to ensure the complete formation of Grignard reagent **3.114**. This reagent was then cooled to room temperature. In a separate flask, a solution of cyclohexenone **3.113** (1.47 g, 15.29 mmol) in THF (30 mL) was cooled to -78°C , and $\text{CuBr} \cdot \text{SMe}_2$ (158 mg, 0.77 mmol) was added in one portion. TMSCl (5.80 mL, 45.70 mmol) and HMPA (5.30 mL, 30.46 mmol) were added dropwise. The Grignard solution was then added dropwise via cannula. After stirring at -78°C for 2.5 h, the reaction mixture was quenched with 5% aqueous H_2SO_4 (50 mL). Upon warming up to room temperature, the aqueous layer was separated from the organic layer and extracted with EtOAc (3 x 50 mL). Combined organics were washed with saturated aqueous NaHCO_3 and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (40% then 60% EtOAc/hexanes) to afford 3.25 g of **3.115** as a pale yellow oil (quantitative yield). Spectroscopic data for **3.115** were identical to that previously reported.⁶⁷

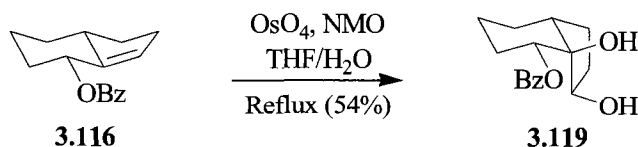


(±)-2,4,5,6,7,7a-hexahydro-1H-inden-4-yl benzoate (**3.116**). *Step 1*: Ketone **3.115** (3.25 g, 15.31 mmol) was dissolved in a 6N HCl solution in THF (80 mL) at room temperature. After being stirred at that temperature for 2 h, the reaction mixture was cooled to 0 °C and slowly neutralized by successive additions of 3 N aqueous NaOH (160 mL) and saturated aqueous NaHCO₃ (40 mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 200 mL). Combined organics were washed with H₂O (3 x 200 mL) and saturated aqueous NaCl (1 x 200 mL), and dried over MgSO₄. After filtration and careful removal of the solvent, the residue was passed through a silica gel plug (eluting with 30% Et₂O/petroleum ether). The solvent was carefully evaporated to deliver the crude enone. *Step 2*: This enone was dissolved in Et₂O (50 mL). MeOH (100 mL) was added and the solution was cooled down to 0 °C. CeCl₃·7H₂O (6.09 g, 16.35 mmol) was added and the mixture was stirred for 5 minutes. NaBH₄ (619 mg, 16.36 mmol) was then added and the reaction mixture was stirred at 0 °C for 1 h, at which point it was quenched with saturated aqueous NH₄Cl (50 mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 50 mL). Combined organics were washed with H₂O (4 x 50 mL) and saturated aqueous NaCl, and dried over MgSO₄. After filtration and careful removal of the solvent, the residue was passed through a silica gel plug (eluting with 50% Et₂O/petroleum ether). The solvent was carefully evaporated to deliver the crude alcohol. *Step 3*: This alcohol was dissolved in CH₂Cl₂ (150 mL). Benzoyl chloride (1.90 mL, 16.37 mmol), pyridine (3.97 mL, 49.09 mmol) and DMAP (40 mg, 0.33 mmol) were added, and the resulting mixture was stirred at room temperature for 15 h. It was then quenched with saturated aqueous NH₄Cl (50 mL). The aqueous layer was separated from the organic layer and extracted with CH₂Cl₂ (3 x 50 mL). Combined organics were washed with saturated aqueous NaCl and dried over MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes → 5% EtOAc/hexanes) to afford 3.30 g of **3.116** as a yellow oil (89% over 3 steps): IR (neat) $\nu_{\max}$ 2931, 2854, 1720, 1272, 1213, 1115 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.10-8.08 (m, 2 H), 7.54 (dd, *J* = 7.4, 7.4 Hz, 1 H), 7.43 (dd, *J* = 7.7, 7.7 Hz,

2 H), 5.54-5.51 (m, 1 H), 5.43 (dd, $J = 1.9, 1.9$ Hz, 1 H), 2.65-2.64 (m, 1 H), 2.38-2.26 (m, 2 H), 2.21-2.14 (m, 2 H), 1.95-1.92 (m, 1 H), 1.88-1.83 (m, 1 H), 1.48 (m, 3 H), 1.00 (dddd, $J = 12.7, 12.5, 12.2, 3.4$ Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.72 (C), 144.26 (C), 132.73 (CH), 130.41 (C), 129.51 (CH), 128.19 (CH), 119.78 (CH), 72.97 (CH), 45.75 (CH), 34.71 (CH_2), 32.88 (CH_2), 31.17 (CH_2), 30.28 (CH_2), 24.18 (CH_2); HRMS m/z calculated for $\text{C}_{16}\text{H}_{18}\text{O}_2$ 242.1317 (M^+), found 242.1280.

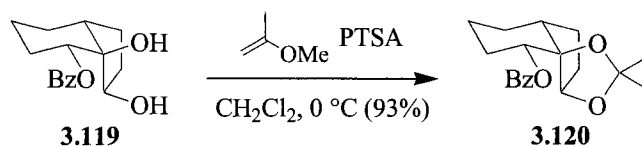


($\pm$)-3-(3-Hydroxypropyl)-cyclohexanone (**3.118**). A suspension of $\text{CuBr}\cdot\text{SMe}_2$ (802 mg, 3.90 mmol) in THF (90 mL) was cooled to $-20\text{ }^\circ\text{C}$. Grignard reagent **3.117** (0.29 M, 155.00 mL, 44.95 mmol) obtained from 3-chloropropanol (8.40 mL, 100.40 mmol), isopropylmagnesium chloride (1.63 M in THF, 61.35 mL, 100.00 mmol), magnesium turnings (3.60 g, 148.12 mmol) and 1,2-dibromoethane (340 μL , 3.93 mmol) in THF (100 mL) was added dropwise. The resulting mixture was stirred at $-20\text{ }^\circ\text{C}$ for 15 minutes. A solution of cyclohexenone **3.113** (3.75 g, 39.01 mmol) in THF (10 mL) was then added dropwise via cannula, and the mixture was warmed up to $0\text{ }^\circ\text{C}$. After stirring for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (100 mL). The aqueous layer was separated from the organic layer and extracted with EtOAc (3 x 100 mL). Combined organics were dried over MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (50% EtOAc/hexanes) to afford 4.41 g of **3.118** as a pale yellow oil (71%). Spectroscopic data for **3.118** were identical to that previously reported.¹⁴³



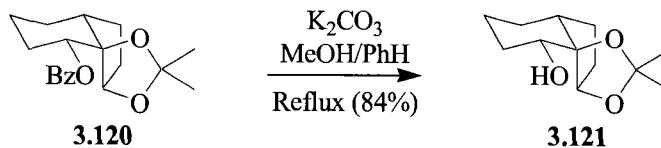
($\pm$)-3,3a-dihydroxyoctahydroinden-4-yl benzoate (**3.119**). To a stirred solution of **3.116** (6.26 g, 25.83 mmol) and H_2O (50 mL) in THF (250 mL) were added OsO_4 (4% in H_2O , 6.50 mL, 1.02 mmol) and NMO (6.05 g, 51.64 mmol). The reaction flask was covered with aluminum

foil and the mixture was refluxed for 18 h. After cooling to room temperature, it was quenched with saturated aqueous Na_2SO_3 (150 mL), and the resulting mixture was stirred for 20 minutes. The aqueous layer was separated from the organic layer and extracted with EtOAc (4 x 200 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (50% $\rightarrow$ 100% EtOAc/hexanes) to afford 3.89 g of **3.119** as a pale yellow solid (54% yield): mp 97-102 °C; IR (neat) ν_{max} 3473 (br), 3066, 2937, 1688, 1291 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.97-7.95 (m, 2 H), 7.55 (dd, $J = 7.4, 7.4$ Hz, 1 H), 7.43 (dd, $J = 7.9, 7.9$ Hz, 2 H), 5.25 (dd, $J = 11.3, 5.2$ Hz, 1 H), 4.65 (dd, $J = 9.0, 6.2$ Hz, 1 H), 3.47 (br, 1 H), 2.46-2.19 (m, 2 H), 2.18-2.12 (m, 2 H), 1.81-1.71 (m, 1 H), 1.67-1.51 (m, 3 H), 1.44 (dddd, $J = 13.1, 13.0, 12.8, 3.4, 3.1$ Hz, 1 H), 1.34-1.22 (m, 1 H), 1.07 (dddd, $J = 13.4, 13.0, 12.8, 3.7$ Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 166.51 (C), 132.99 (CH), 130.15 (C), 129.30 (CH), 128.43 (CH), 79.87 (CH), 79.79 (C), 72.83 (CH), 46.08 (CH), 29.87 (CH_2), 29.54 (CH_2), 28.49 (CH_2), 27.29 (CH_2), 22.62 (CH_2); HRMS m/z calculated for $\text{C}_9\text{H}_{14}\text{O}_2$ 154.0994 ($\text{M}^+ - \text{PhCO}_2\text{H}$), found 154.0961.

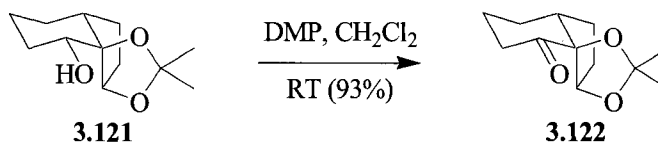


(±)-2,2-dimethyloctahydro-1,3-dioxacyclopenta[*c*]inden-9-yl benzoate (**3.120**). To a solution of **3.119** (16 mg, 0.058 mmol) in CH_2Cl_2 (1 mL) at 0 °C were added 2-methoxypropene (20 μL , 0.209 mmol) and PTSA (0.5 mg, 0.003 mmol). After stirring at 0 °C for 1 h, the reaction mixture was quenched with saturated aqueous NaHCO_3 (1 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (20% EtOAc/hexanes) to afford 17 mg of **3.120** as a yellow oil (93% yield): IR (neat) ν_{max} 2937, 2867, 1716, 1446, 1376, 1274 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.07-8.05 (m, 2 H), 7.54 (dddd, $J = 7.9, 7.2, 1.7, 1.3$ Hz, 1 H), 7.43 (dd, $J = 7.2, 7.2$ Hz, 2 H), 5.28-5.24 (m, 1 H), 4.82 (d, $J = 6.8$ Hz, 1 H), 2.25-2.00 (m, 5 H), 1.83-1.79 (m, 1 H), 1.73-1.65 (m, 3 H), 1.58-1.53 (m, 2 H), 1.44 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 165.99 (C), 133.40 (CH), 130.66 (C), 130.20 (CH), 128.80

(CH), 111.70 (C), 93.35 (C), 82.74 (CH), 76.73 (CH), 45.54 (CH), 31.72 (CH₂), 30.09 (CH₂), 29.46 (CH₂), 28.82 (CH₃), 27.98 (CH₃), 27.97 (CH₂), 20.49 (CH₂); HRMS m/z calculated for C₁₈H₂₁O₄ 301.1440 (M⁺ - Me), found 301.1438.

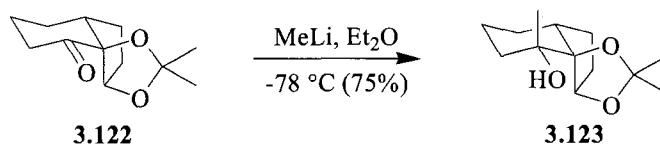


(±)-2,2-Dimethyloctahydro-1,3-dioxacyclopenta[c]inden-9-ol (**3.121**). To a solution of **3.120** (1.72 g, 5.44 mmol) in MeOH (60 mL) was added K₂CO₃ (5.40 g, 39.07 mmol). Benzene (40 mL) was then added. The mixture was refluxed for 6 h. After cooling down to room temperature, it was quenched with saturated aqueous NH₄Cl (50 mL). The aqueous layer was separated from the organic layer and extracted with EtOAc (4 x 50 mL). Combined organics were dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (40% then 60% EtOAc/hexanes) to afford 968 mg of **3.121** as a pale yellow solid (84% yield): mp 59-64 °C; IR (neat) ν_{max} 3488, 2930, 2865, 1451, 1363, 1211 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.69 (d, J = 7.3 Hz, 1 H), 3.82 (dd, J = 10.7, 4.7 Hz, 1 H), 2.21-2.13 (m, 1 H), 2.10-2.06 (m, 1 H), 2.04-1.94 (m, 2 H), 1.74 (dd, J = 14.6, 8.3 Hz, 1 H), 1.68-1.61 (m, 2 H), 1.59-1.49 (m, 1 H), 1.47 (s, 3 H), 1.45 (s, 3 H), 1.44-1.39 (m, 1 H), 1.34-1.19 (m, 2 H), 0.98-1.07 (m, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 110.96 (C), 96.64 (C), 81.15 (CH), 74.15 (CH), 45.41 (CH), 33.09 (CH₂), 31.91 (CH₂), 30.10 (CH₂), 29.15 (CH₂), 28.81 (CH₃), 28.48 (CH₃), 21.89 (CH₂); HRMS m/z calculated for C₁₁H₁₇O₃ 197.1178 (M⁺ - Me), found 197.1183.

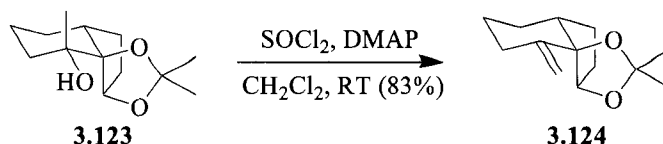


(±)-2,2-Dimethylhexahydro-1,3-dioxacyclopenta[c]inden-9-one (**3.122**). To a solution of **3.121** (936 mg, 4.41 mmol) in CH₂Cl₂ (50 mL) at 0 °C was added DMP (2.24 g, 5.28 mmol). The resulting cloudy white mixture was stirred at room temperature for 1 h. Then, saturated aqueous NaHCO₃ (30 mL) and saturated aqueous Na₂SO₃ (30 mL) were added and the

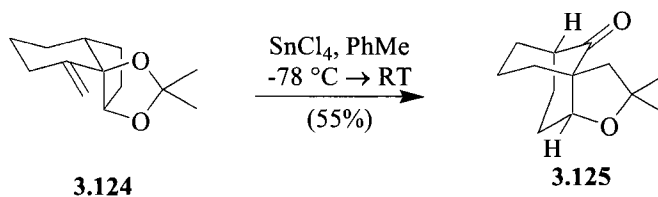
resulting biphasic mixture was stirred vigorously for 20 minutes. The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 x 60 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (20% then 40% EtOAc/hexanes) to afford 865 mg of **3.122** as a white solid (93% yield): mp 52-52.5 °C; IR (neat) ν_{max} 2934, 2857, 1721, 1455, 1379 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.76 (d, J = 6.5 Hz, 1 H), 2.56 (dddd, J = 14.0, 4.3, 4.2, 2.1 Hz, 1 H), 2.44-2.49 (m, 1 H), 2.26 (ddd, J = 14.0, 12.3, 5.3 Hz, 1 H), 2.16-2.02 (m, 3 H), 1.98-1.92 (m, 1 H), 1.87-1.81 (m, 3 H), 1.69 (dddd, J = 12.3, 9.4, 7.5, 3.9, 3.6 Hz, 1 H), 1.45 (s, 3 H), 1.39 (s, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 209.75 (C), 113.06 (C), 96.35 (CH), 84.40 (C), 50.29 (CH), 40.79 (CH_2), 32.18 (CH_2), 30.18 (CH_2), 28.36 (CH_2), 27.98 (CH_3), 27.50 (CH_3), 25.09 (CH_2); HRMS m/z calculated for $\text{C}_{12}\text{H}_{18}\text{O}_3$ 210.1256 (M^+), found 210.1204. The tridimensional structure of this product was confirmed by X-ray crystallography.



(±)-2,2,9-Trimethyloctahydro-1,3-dioxacyclopenta[c]inden-9-ol (3.123). To a solution of **3.122** (29 mg, 0.138 mmol) in Et_2O (2 mL) at -78 °C was added MeLi (430 μL of a 1.6 M solution in Et_2O , 0.688 mmol) dropwise. The reaction mixture was stirred at -78 °C for 30 minutes, and was warmed up to room temperature over 4 h. It was then quenched with saturated aqueous NH_4Cl (2 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (20% EtOAc/hexanes) to afford 24 mg of **3.123** as a white solid (75% yield): mp 70-74 °C; IR (neat) ν_{max} 3485, 2941, 1459, 1363, 1241 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.69 (d, J = 7.2 Hz, 1 H), 2.18-2.02 (m, 3 H), 1.78-1.89 (m, 2 H), 1.66-1.60 (m, 1 H), 1.59-1.55 (m, 2 H), 1.49 (s, 3 H), 1.46 (s, 3 H), 1.42-1.32 (m, 3 H), 1.30 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 110.75 (C), 97.37 (C), 81.71 (CH), 73.31 (C), 44.07 (CH), 39.74 (CH_2), 31.11 (CH_2), 29.93 (CH_2), 28.47 (CH_2), 28.36 (CH_3), 27.85 (CH_3), 24.35 (CH_3), 21.11 (CH_2); HRMS (EI) calculated for $\text{C}_{12}\text{H}_{19}\text{O}_3$ 211.1334 ($\text{M}^+ - \text{Me}$), found 211.1308.

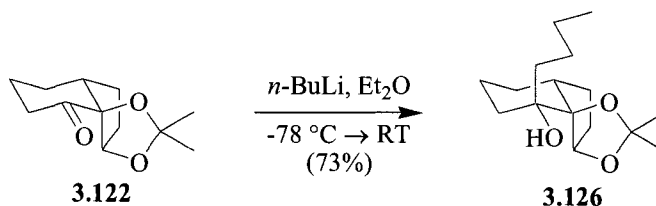


(±)-2,2-Dimethyl-9-methyleneoctahydro-1,3-dioxacyclopenta[*c*]indene (**3.124**). Thionyl chloride (140 μL , 1.93 mmol) was added dropwise to a solution of **3.123** (217 mg, 0.96 mmol) and DMAP (704 mg, 5.76 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The mixture was warmed up to room temperature and, after stirring for 1 h, was quenched with saturated aqueous NaHCO_3 (10 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 20 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% EtOAc /hexanes) to afford 135 mg of **3.124** as a pale yellow oil (68% yield): IR (neat) ν_{max} 2937, 2857, 1649, 1458, 1234 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.14 (d, $J = 2.2$ Hz, 1 H), 4.88 (s, 1 H), 4.59 (d, $J = 5.9$ Hz, 1 H), 2.42–2.36 (m, 1 H), 2.17–2.01 (m, 3 H), 1.91 (ddd, $J = 13.4, 11.6, 2.8$ Hz, 1 H), 1.78–1.66 (m, 3 H), 1.53 (d, $J = 2.6$ Hz, 1 H), 1.47 (s, 3 H), 1.42 (s, 3 H), 1.36–1.29 (m, 1 H), 1.26–1.17 (m, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 149.14 (C), 110.63 (C), 108.90 (CH_2), 94.63 (C), 84.23 (CH), 48.09 (CH), 34.56 (CH_2), 31.88 (CH_2), 29.64 (CH_2), 29.17 (CH_2), 28.72 (CH_3), 27.99 (CH_3), 26.77 (CH_2); HRMS m/z calculated for $\text{C}_{13}\text{H}_{20}\text{O}_2$ 208.1463 (M^+), found 208.1465.

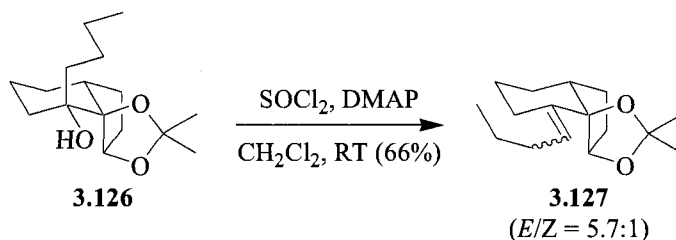


(±)-3,3-Dimethyl-4-oxatricyclo[6.3.1.0^{1,5}]dodecan-12-one (**3.125**). To a solution of SnCl_4 (70 μL of a 1.0 M solution in CH_2Cl_2 , 0.070 mmol) in toluene (500 μL) at -78 °C was added a solution of **3.124** (12 mg, 0.058 mmol) in toluene (500 μL) via cannula. The resulting solution was stirred at -78 °C for 1 h, warmed up to 0 °C, and stirred for 2 h at that temperature. Et_3N was added dropwise until complete discoloration, followed by saturated aqueous NaHCO_3 (1 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were dried over anhydrous MgSO_4 .

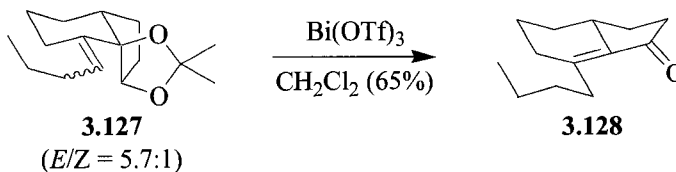
After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford 6.6 mg of **3.125** as a dark yellow oil (55% yield): IR (neat) $\nu_{\max}$ 2968, 2929, 2857, 1719, 1452, 1280 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.27 (dd, $J = 5.3, 5.3$ Hz, 1 H), 2.67 (d, $J = 12.7$ Hz, 1 H), 2.58-2.55 (m, 1 H), 2.24-2.15 (m, 2 H), 2.09-1.76 (m, 5 H), 1.55-1.50 (m, 3 H), 1.23 (s, 3 H), 1.22 (s, 3 H), 1.19 (d, $J = 12.7$ Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 217.44 (C), 84.69 (CH), 79.13 (C), 58.54 (C), 45.45 (CH), 44.40 (CH_2), 39.55 (CH_2), 34.45 (CH_2), 29.01 (CH_3), 28.25 (CH_3), 27.27 (CH_2), 27.00 (CH_2), 19.63 (CH_2); HRMS m/z calculated for $\text{C}_{13}\text{H}_{20}\text{O}_2$ 208.1463 (M^+), found 208.1446.



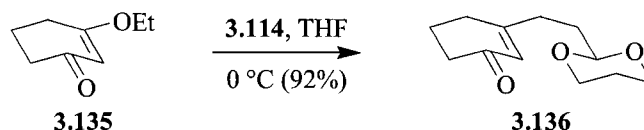
($\pm$)-9-Butyl-2,2-dimethyloctahydro-1,3-dioxacyclopenta[c]inden-9-ol (**3.126**). To a solution of **3.122** (62 mg, 0.29 mmol) in Et_2O (3 mL) at -78 $^\circ\text{C}$ was added $n\text{-BuLi}$ (660 μL of a 2.2 M solution in hexanes, 1.45 mmol) dropwise. After stirring at -78 $^\circ\text{C}$ for 30 minutes, the reaction mixture was warmed up to room temperature over 30 minutes. It was then quenched with saturated NH_4Cl (2 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (15% EtOAc/hexanes) to afford 57 mg of **3.126** as a colorless oil (73% yield): IR (neat) $\nu_{\max}$ 3502, 2945, 2869, 1458, 1375, 1238, 1159 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.71 (d, $J = 7.7$ Hz, 1 H), 2.20-2.02 (m, 3 H), 1.89-1.84 (m, 1 H), 1.81-1.75 (m, 1 H), 1.72-1.57 (m, 4 H), 1.48 (s, 3 H), 1.46 (s, 3 H), 1.39-1.28 (m, 4 H), 1.28-1.14 (m, 4 H), 1.08-1.00 (m, 1 H), 0.91 (t, $J = 7.1$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 110.66 (C), 98.53 (C), 81.82 (CH), 74.83 (C), 43.99 (CH), 34.69 (CH_2), 33.91 (CH_2), 31.20 (CH_2), 30.04 (CH_2), 28.74 (CH_2), 28.32 (CH_3), 28.00 (CH_3), 24.39 (CH_2), 23.21 (CH_2), 20.88 (CH_2), 14.05 (CH_3); HRMS m/z calculated for $\text{C}_{15}\text{H}_{25}\text{O}_3$ 253.1804 ($\text{M}^+ - \text{Me}$), found 253.1792.



(±)-9-Butylidene-2,2-dimethyloctahydro-1,3-dioxacyclopenta[*c*]indene (**3.127**). Thionyl chloride (30 μL , 0.413 mmol) was added dropwise to a solution of **3.126** (47 mg, 0.175 mmol) and DMAP (128 mg, 1.048 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The mixture was warmed up to room temperature and, after stirring for 1 h, was quenched with saturated aqueous NaHCO_3 (2 mL). The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford 29 mg of **3.127** as a pale yellow oil (66% yield). This was a 5.7:1 mixture of *E* and *Z* geometrical isomers. IR (neat) ν_{max} 2932, 2861, 1460, 1375, 1240, 1211 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) *major* δ 5.64 (*t*, J = 7.3 Hz, 1 H), 4.57 (*d*, J = 6.1 Hz, 1 H), 2.59–2.55 (*m*, 1 H), 2.23–1.99 (*m*, 5 H), 1.97–1.79 (*m*, 1 H), 1.75–1.61 (*m*, 3 H), 1.46 (*s*, 3 H), 1.40 (*s*, 3 H), 1.39–1.17 (*m*, 5 H), 0.88 (*t*, J = 7.3 Hz, 3 H) *minor* δ 5.72 (*t*, J = 4.2 Hz, 1 H), 4.76 (*d*, J = 7.3 Hz, 1 H), 2.37–2.36 (*m*, 1 H), 2.23–1.99 (*m*, 5 H), 1.97–1.79 (*m*, 1 H), 1.75–1.61 (*m*, 3 H), 1.57 (*s*, 3 H), 1.49 (*s*, 3 H), 1.39–1.17 (*m*, 5 H), 0.92 (*t*, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) *major* δ 138.20 (C), 122.54 (CH), 110.33 (C), 95.10 (C), 84.04 (CH), 48.00 (CH), 31.79 (CH_2), 29.71 (CH_2), 29.25 (CH_2), 29.00 (CH_2), 28.61 (CH_3), 28.07 (CH_3), 26.96 (CH_2), 25.99 (CH_2), 22.87 (CH_2), 13.77 (CH_3) *minor* δ 135.15, 127.49, 110.74, 90.50, 83.68, 43.71, 37.71, 31.27, 30.44, 28.75, 27.37, 26.66, 22.75, 22.24, 21.02, 13.95; HRMS m/z calculated for $\text{C}_{16}\text{H}_{26}\text{O}_2$ 250.1933 (M^+), found 250.1949.

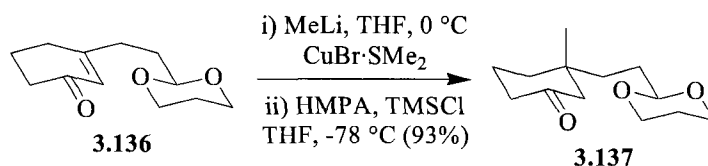


(±)-**7-Butyl-2,3,3a,4,5,6-hexahydroindenone (3.128)**. To a solution of **3.127** (10 mg, 0.040 mmol) in CH₂Cl₂ (400 µL) at room temperature was added Bi(OTf)₃ (28 mg, 0.043 mmol). After stirring for 1 h, the reaction mixture was quenched with saturated aqueous NaHCO₃ (1 mL). The aqueous layer was separated from the organic layer and extracted with CH₂Cl₂ (3 x 5 mL). Combined organics were dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% EtOAc/hexanes) to afford 5 mg of **3.128** as a yellow oil (65% yield): IR (neat) ν_{max} 2956, 2929, 2860, 1708, 1635, 1456 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 2.71-2.63 (m, 1 H), 2.52-2.47 (m, 1 H), 2.44-2.38 (m, 1 H), 2.26-2.20 (m, 2 H), 2.18-2.09 (m, 3 H), 2.01 (dddd, J = 8.2, 4.5, 3.9, 3.8 Hz, 1 H), 1.84-1.77 (m, 1 H), 1.54-1.42 (m, 1 H), 1.41-1.22 (m, 5 H), 1.07-0.99 (m, 1 H), 0.88 (t, J = 7.2 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 207.20 (C), 152.06 (C), 133.08 (C), 39.63 (CH), 38.84 (CH₂), 31.66 (CH₂), 30.98 (CH₂), 30.71 (CH₂), 29.41 (CH₂), 28.19 (CH₂), 22.68 (CH₂), 22.25 (CH₂), 13.87 (CH₃); HRMS m/z calculated for C₁₃H₂₀O 192.1514 (M⁺), found 192.1538.

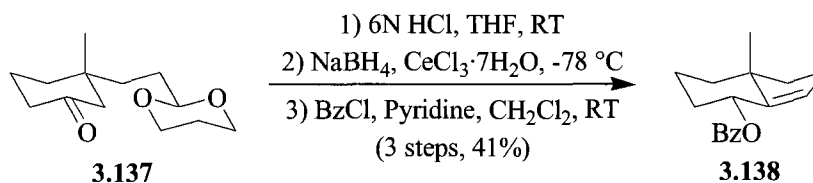


3-(2-[1,3]Dioxan-2-ylethyl)-cyclohex-2-enone (3.136). To a suspension of magnesium turnings (5.60 g, 230.36 mmol) in THF (100 mL) was added 1,2-dibromoethane (2.10 mL, 24.37 mmol). The suspension was heated with a heat gun until bubbles evolved from the magnesium turnings. Then, 2-(2-bromo-ethyl)-[1,3]dioxane (20.70 mL, 152.82 mmol) was added dropwise by syringe, yielding a strongly exothermic reaction. Once the addition was over, the mixture was further refluxed for 30 minutes to ensure the complete formation of Grignard reagent **3.114**. This reagent was then cooled to 35-40 °C and transferred to a 500 mL flame-dried flask using a large Teflon cannula. THF (60 mL) was added and the pale brown solution was cooled down to 0 °C. A solution of 3-ethoxycyclohex-2-enone **3.135** (11.90 g, 84.89 mmol) in THF (50 mL) was then added dropwise via cannula. After stirring at that temperature for 45 minutes, the reaction mixture was quenched with 5% aqueous H₂SO₄ (50 mL). The aqueous layer was separated from the organic layer and extracted with EtOAc (3 x 50 mL). Combined organics were washed with saturated aqueous NaHCO₃ and

dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (40% $\rightarrow$ 80% EtOAc/hexanes) to afford 16.45 g of **3.136** as a yellow oil (92% yield). Spectroscopic data for **3.136** were identical to that previously reported.⁶⁷

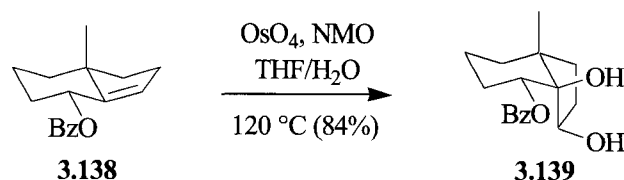


($\pm$)-3-(2-[1,3]Dioxan-2-ylethyl)-3-methylcyclohexanone (**3.137**). To a suspension of $\text{CuBr}\cdot\text{SMe}_2$ (14.10 g, 69.59 mmol) in THF (240 mL) at 0 $^\circ\text{C}$ was added MeLi (90.0 mL of a 1.5 M solution in Et_2O , 135.0 mmol) dropwise over a 15-minute period. After stirring at 0 $^\circ\text{C}$ for 15 minutes, the clear solution was cooled down to -78 $^\circ\text{C}$. TMSCl (21.10 mL, 189.89 mmol) and HMPA (11.90 mL, 68.40 mmol) were added dropwise. The mixture was then stirred for 5 minutes and a solution of **3.136** (8.00 g, 38.05 mmol) in THF (20 mL) was added dropwise via cannula. After stirring at -78 $^\circ\text{C}$ for 1 h, the reaction mixture was quenched by a slow addition of 1 N HCl (100 mL). Upon warming up to room temperature, the aqueous layer was separated from the organic layer and extracted with EtOAc (3 x 100 mL). Combined organics were washed with saturated aqueous NaHCO_3 and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (40% then 50% EtOAc/hexanes) to afford 8.04 g of **3.137** as a yellow oil (93% yield). Spectroscopic data for **3.137** were identical to that previously reported.⁶⁷

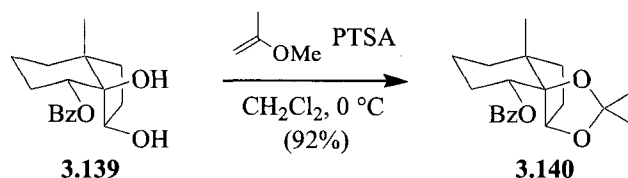


($\pm$)-7a-methyl-2,4,5,6,7,7a-hexahydro-1H-inden-4-yl benzoate (**3.138**). *Step 1:* Ketone **3.137** (12.19 g, 53.86 mmol) was dissolved in a 6N HCl solution in THF (280 mL) at room temperature. After being stirred at that temperature for 2 h, the mixture was cooled to 0 $^\circ\text{C}$ and slowly neutralized by successive additions of 6 N aqueous NaOH (280 mL) and

saturated aqueous NaHCO_3 (120 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 400 mL). Combined organics were washed with H_2O (3 x 400 mL) and saturated aqueous NaCl (1 x 400 mL), and dried over MgSO_4 . After filtration and careful removal of the solvent, the residue was passed through a silica gel plug (eluting with 30% Et_2O /petroleum ether). The solvent was evaporated carefully to deliver the crude enone. *Step 2:* This enone was dissolved in Et_2O (140 mL). MeOH (280 mL) was added and the solution was cooled down to $-78\text{ }^\circ\text{C}$. $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (16.05 g, 43.08 mmol) was added and the mixture was stirred for 5 minutes. NaBH_4 (1.63 g, 43.08 mmol) was then added and the reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 1 h. After warming up to room temperature, the reaction was quenched with saturated aqueous NH_4Cl (100 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 100 mL). Combined organics were washed with H_2O (3 x 200 mL) and saturated aqueous NaCl , and dried over MgSO_4 . After filtration and careful removal of the solvent, the residue was passed through a silica gel plug (eluting with 50% Et_2O /petroleum ether). The solvent was evaporated carefully to deliver the crude alcohol. *Step 3:* This alcohol was dissolved in CH_2Cl_2 (210 mL). Benzoyl chloride (7.50 mL, 64.61 mmol), pyridine (10.50 mL, 129.82 mmol) and DMAP (105 mg, 0.86 mmol) were added and the mixture was stirred at room temperature for 20 h. It was then quenched with saturated aqueous NH_4Cl (100 mL). The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 x 100 mL). Combined organics were washed with saturated aqueous NaCl and dried over MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes $\rightarrow$ 5% EtOAc /hexanes) to afford 5.63 g of **3.138** as a yellow oil (41% over 3 steps): IR (neat) ν_{max} 3062, 2934, 2864, 2849, 1720, 1602, 1451, 1312, 1273 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.09-8.07 (m, 2 H), 7.56-7.52 (m, 1 H), 7.45-7.41 (m, 2 H), 5.62-5.57 (m, 1 H), 5.38 (dd, J = 4.5, 2.2 Hz, 1 H), 2.40-2.32 (m, 1 H), 2.29-2.23 (m, 1 H), 2.22-2.17 (m, 1 H), 1.84 (ddd, J = 12.6, 8.2, 2.3 Hz, 1 H), 1.77-1.70 (m, 3 H), 1.46-1.25 (m, 3 H), 1.11 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.75 (C), 147.45 (C), 132.71 (CH), 130.43 (C), 129.48 (CH), 128.19 (CH), 118.80 (CH), 71.55 (CH), 48.07 (C), 41.23 (CH_2), 40.61 (CH_2), 33.43 (CH_2), 29.55 (CH_2), 23.33 (CH_3), 21.58 (CH_2); HRMS m/z calculated for $\text{C}_{17}\text{H}_{20}\text{O}_2$ 256.1463 (M^+), found 256.1486.

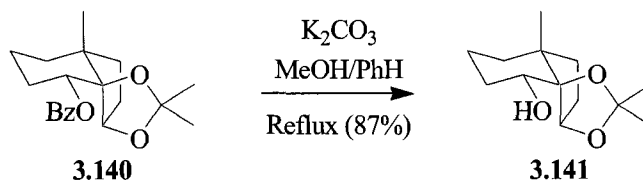


(±)-3,3a-dihydroxy-7a-methyloctahydroinden-4-yl benzoate (**3.139**). To a Pyrex tube containing a stirred solution of **3.138** (1.09 g, 4.23 mmol) in THF (20 mL) were added H₂O (8 mL), OsO₄ (4% in H₂O, 1.10 mL, 0.17 mmol) and NMO (992 mg, 8.47 mmol). The Pyrex tube was capped and covered with aluminum foil. The reaction mixture was heated at 120 °C for 19 h. After cooling to room temperature, it was quenched with saturated aqueous Na₂SO₃ (20 mL), and the resulting mixture was stirred for 20 minutes. The aqueous layer was separated from the organic layer and extracted with EtOAc (4 x 20 mL). Combined organics were dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (30% → 50% EtOAc/hexanes) to afford 1.03 g of **3.139** as a pale yellow solid (84% yield): mp 132.5-135 °C; IR (neat) ν_{max} 3479, 3065, 2941, 2868, 2250, 1968, 1920, 1714, 1601, 1451, 1281 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.96-7.94 (m, 2 H), 7.56-7.54 (m, 1 H), 7.53 (dd, J = 1.3, 1.3 Hz, 2 H), 5.22 (dd, J = 11.1, 5.4 Hz, 1 H), 4.84-4.80 (m, 1 H), 3.28 (s, 1 H), 2.29-2.21 (m, 1 H), 2.16-2.11 (m, 2 H), 1.91 (ddd, J = 12.3, 12.0, 8.0 Hz, 1 H), 1.65-1.53 (m, 4 H), 1.37-1.30 (m, 3 H), 1.11 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 166.46 (C), 132.92 (CH), 130.25 (C), 129.26 (CH), 128.41 (CH), 79.96 (C), 78.22 (CH), 73.71 (CH), 46.79 (C), 36.66 (CH₂), 35.29 (CH₂), 28.97 (CH₂), 28.77 (CH₂), 20.14 (CH₂), 19.45 (CH₃); HRMS m/z calculated for C₁₀H₁₆O₂ 168.1150 (M⁺ - BzOH), found 168.1152. The tridimensional structure of this compound was confirmed by X-ray crystallography.



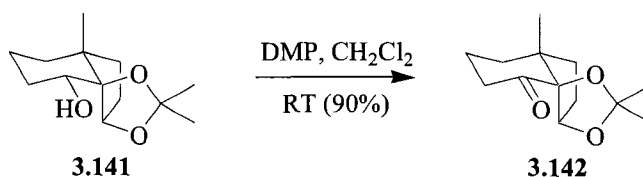
(±)-2,2,5a-trimethyloctahydro-1,3-dioxacyclopenta[c]inden-9-yl benzoate (**3.140**). To a solution of **3.139** (4.10 g, 14.12 mmol) in CH₂Cl₂ (140 mL) at 0 °C were added 2-methoxypropene (3.40 mL, 35.50 mmol) and PTSA (27 mg, 0.14 mmol). After stirring at 0 °C for 30 minutes,

the reaction mixture was quenched with saturated aqueous NaHCO_3 (50 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 50 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes then 5% EtOAc /hexanes) to afford 4.29 g of **3.140** as a pale yellow solid (92% yield): mp 103–105 °C; IR (neat) ν_{max} 3066, 2941, 2866, 1712, 1598, 1465, 1367, 1269 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.09–8.05 (m, 2 H), 7.54–7.51 (m, 1 H), 7.41 (dd, $J = 7.9, 7.5$ Hz, 2 H), 5.21 (dd, $J = 11.5, 5.1$ Hz, 1 H), 4.99 (d, $J = 7.7$ Hz, 1 H), 2.22–2.16 (m, 1 H), 2.15–2.08 (m, 1 H), 1.98 (ddd, $J = 12.3, 12.1, 8.2$ Hz, 1 H), 1.74 (dd, $J = 14.6, 8.2$ Hz, 1 H), 1.61–1.51 (m, 2 H), 1.42 (s, 3 H), 1.46–1.39 (m, 2 H), 1.37–1.23 (m, 2 H), 1.19 (s, 3 H), 1.15 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.56 (C), 132.76 (CH), 130.28 (C), 129.85 (CH), 128.18 (CH), 111.14 (C), 94.80 (C), 82.57 (CH), 75.27 (CH), 46.82 (C), 38.59 (CH_2), 35.52 (CH_2), 30.94 (CH_2), 30.24 (CH_2), 28.26 (CH_3), 28.10 (CH_3), 20.74 (CH_3), 19.18 (CH_2); HRMS m/z calculated for $\text{C}_{19}\text{H}_{23}\text{O}_4$ 315.1596 ($\text{M}^+ - \text{Me}$), found 315.1592.

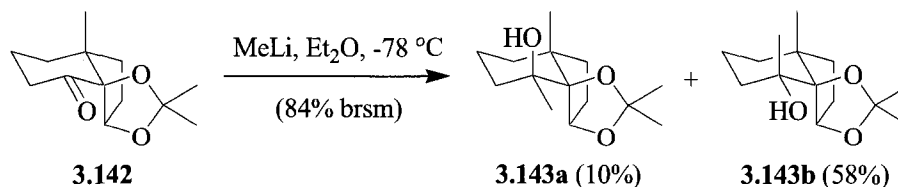


(±)-2,2,5a-Trimethyloctahydro-1,3-dioxacyclopenta[c]inden-9-ol (**3.141**). To a solution of **3.140** (4.29 g, 12.98 mmol) in MeOH (90 mL) was added K_2CO_3 (17.16 g, 124.16 mmol). Benzene (60 mL) was added. The mixture was refluxed for 16 h. After cooling down to room temperature, it was quenched with saturated aqueous NH_4Cl (50 mL). The aqueous layer was separated from the organic layer and extracted with EtOAc (4 x 50 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (30% then 60% EtOAc /hexanes) to afford 2.57 g of **3.141** as a white solid (87% yield): mp 96–97 °C; IR (neat) ν_{max} 3439, 2937, 2867, 1462, 1375, 1236 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.76 (d, $J = 7.6$ Hz, 1 H), 3.73 (dd, $J = 11.9, 4.9$ Hz, 1 H), 2.09–1.90 (m, 3 H), 1.76–1.50 (m, 3 H), 1.49 (s, 3 H), 1.45 (s, 3 H), 1.45–1.39 (m, 1 H), 1.36–1.32 (m, 2 H), 1.30–1.16 (m, 2 H), 1.06 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 110.55 (C), 97.34 (C), 81.37 (CH), 71.94 (CH), 46.21 (C), 38.60 (CH_2), 35.92

(CH₂), 33.26 (CH₂), 30.67 (CH₂), 28.34 (CH₃), 28.20 (CH₃), 20.51 (CH₃), 19.73 (CH₂); HRMS *m/z* calculated for C₁₂H₁₉O₃ 211.1334 (M⁺ - Me), found 211.1320.

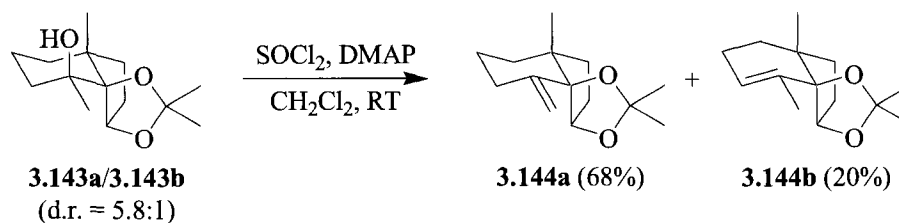


(±)-2,2,5a-Trimethylhexahydro-1,3-dioxacyclopenta[c]inden-9-one (3.142). To a solution of **3.141** (2.57 g, 11.36 mmol) in CH₂Cl₂ (120 mL) at 0 °C was added DMP (9.63 g, 22.70 mmol). The resulting cloudy white mixture was stirred at room temperature for 1.5 h. Then, saturated aqueous NaHCO₃ (60 mL) and saturated aqueous Na₂SO₃ (60 mL) were added and the resulting biphasic mixture was stirred vigorously for 20 minutes. The aqueous layer was separated from the organic layer and extracted with CH₂Cl₂ (3 x 120 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (20% then 40% EtOAc/hexanes) to afford 2.30 g of **3.142** as a white solid (90% yield): mp 81.5-82.5 °C; IR (neat) ν_{max} 2940, 2864, 1713, 1443, 1378, 1227 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.85 (d, *J* = 7.3 Hz, 1 H), 2.50-2.45 (m, 1 H), 2.37 (ddd, *J* = 13.6, 13.0, 5.9 Hz, 1 H), 2.30-2.22 (m, 1 H), 1.95-1.88 (m, 2 H), 1.86-1.73 (m, 3 H), 1.57-1.53 (m, 1 H), 1.52-1.47 (m, 1 H), 1.47 (s, 3 H), 1.46 (s, 3 H), 1.08 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 209.64 (C), 112.65 (C), 98.31 (C), 85.09 (CH), 52.79 (C), 40.10 (CH₂), 37.79 (CH₂), 34.83 (CH₂), 31.92 (CH₂), 27.50 (CH₃), 27.49 (CH₃), 22.94 (CH₂), 19.66 (CH₃); HRMS *m/z* calculated for C₁₂H₁₇O₃ 209.1178 (M⁺ - Me), found 209.1188.



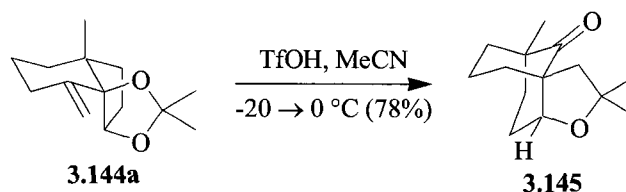
(±)-2,2,5a,9-Tetramethyloctahydro-1,3-dioxacyclopenta[c]inden-9-ol (3.143). To a solution of **3.142** (320 mg, 1.43 mmol) in Et₂O (15 mL) at -78 °C was added MeLi (5.7 mL of a 1.50 M solution in Et₂O, 8.55 mmol) dropwise. The reaction mixture was stirred at -78 °C for 1 h,

and was warmed up to room temperature over 2 h. It was then quenched with saturated aqueous NH_4Cl (10 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 10 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% EtOAc /hexanes) to afford 61 mg of unreacted **3.142**, 34 mg of **3.143a** as a pale yellow oil (10% yield) and 198 mg of **3.143b** as a white solid (58% yield). Total mass: 232 mg (68% yield, 84% yield brsm). Epimer **3.143a**: IR (neat) ν_{max} 3578, 3496, 2941, 2870, 1461, 1371, 1234, 1199, 1160, 1125 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.44 (d, $J = 7.3$ Hz, 1 H), 2.29 (br, 1 H), 2.09-1.93 (m, 2 H), 1.85-1.75 (m, 2 H), 1.64 (dd, $J = 14.4, 7.9$ Hz, 1 H), 1.51 (s, 3 H), 1.49 (s, 3 H), 1.40-1.36 (m, 1 H), 1.30-1.24 (m, 4 H), 1.22 (s, 3 H), 1.18 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 110.84 (C), 97.26 (C), 85.04 (CH), 72.57 (C), 45.70 (C), 39.89 (CH_2), 38.08 (CH_2), 36.74 (CH_2), 30.46 (CH_2), 28.57 (CH_3), 28.36 (CH_3), 27.86 (CH_3), 21.90 (CH_3), 16.88 (CH_2); HRMS m/z calculated for $\text{C}_{13}\text{H}_{21}\text{O}_3$ 225.1491 ($\text{M}^+ - \text{Me}$), found 225.1514. Epimer **3.143b**: mp 59-61 °C; IR (neat) ν_{max} 3496, 2937, 2870, 1461, 1371, 1234 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.80 (d, $J = 8.5$ Hz, 1 H), 2.08-1.94 (m, 3 H), 1.77 (dddd, $J = 7.3, 5.3, 4.9, 2.8$ Hz, 1 H), 1.73-1.64 (m, 1 H), 1.62-1.52 (m, 1 H), 1.50 (s, 3 H), 1.49-1.46 (m, 1 H), 1.45 (s, 3 H), 1.44-1.30 (m, 3 H), 1.28 (s, 3 H), 1.27-1.23 (m, 1 H), 1.06 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 111.07 (C), 97.63 (C), 84.11 (CH), 73.92 (C), 46.07 (C), 40.32 (CH_2), 39.86 (CH_2), 35.64 (CH_2), 29.78 (CH_2), 28.25 (CH_3), 28.19 (CH_3), 23.54 (CH_3), 21.10 (CH_3), 19.45 (CH_2); HRMS m/z calculated for $\text{C}_{13}\text{H}_{21}\text{O}_3$ 225.1491 ($\text{M}^+ - \text{Me}$), found 225.1499.



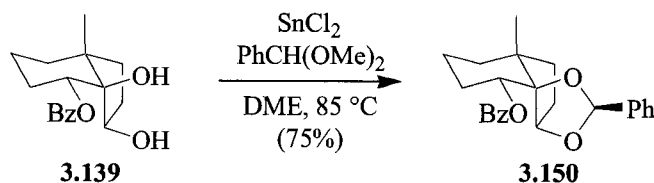
(±)-2,2,5a-Trimethyl-9-methyleneoctahydro-1,3-dioxacyclopenta[c]indene (**3.144**). Thionyl chloride (140 μL , 1.93 mmol) was added dropwise to a solution of **3.143a/3.143b** (5.8:1 mixture of epimers, 232 mg, 0.97 mmol) and DMAP (704 mg, 5.76 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The mixture was warmed up to room temperature and, after stirring for 40

minutes, was quenched with saturated aqueous NaHCO_3 (5 mL). The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% then 10% EtOAc/hexanes) to afford 188 mg of **3.144** as a pale yellow oil (88% yield). This was a 3.4:1 mixture of geometrical isomers: IR (neat) ν_{max} 2933, 2862, 1641, 1461, 1371, 1238 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) *major* δ 5.17 (d, $J = 2.0$ Hz, 1 H), 4.96 (t, $J = 2.0$ Hz, 1 H), 4.76 (d, $J = 3.8$ Hz, 1 H), 2.45-2.39 (m, 1 H), 2.27-2.13 (m, 1 H), 2.05-1.91 (m, 2 H), 1.75-1.68 (m, 2 H), 1.65-1.51 (m, 2 H), 1.49 (s, 3 H), 1.47 (s, 3 H), 1.45-1.34 (m, 2 H), 1.01 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) *major* δ 147.90 (C), 110.86 (C), 110.00 (CH_2), 96.66 (C), 84.86 (CH), 48.40 (C), 37.83 (CH_2), 36.22 (CH_2), 35.07 (CH_2), 31.51 (CH_2), 29.27 (CH_3), 28.09 (CH_3), 24.32 (CH_2), 19.18 (CH_3); HRMS m/z calculated for $\text{C}_{14}\text{H}_{22}\text{O}_2$ 222.1620 (M^+), found 222.1615.

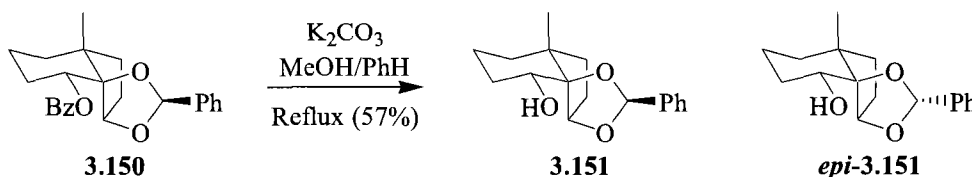


($\pm$)-3,3,8-Trimethyl-4-oxatricyclo[6.3.1.0^{1,5}]dodecan-12-one (**3.145**). To a solution of **3.144a** (27.5 mg, 0.124 mmol) in MeCN (1.5 mL) at $-20\text{ }^\circ\text{C}$ was added TfOH (25 μL , 0.283 mmol) dropwise. The resulting solution was stirred at $-20\text{ }^\circ\text{C}$ for 15 minutes, warmed up to room temperature, and stirred for 15 minutes at that temperature. Et_3N was added dropwise until complete discoloration, followed by saturated aqueous NaHCO_3 (1.5 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% EtOAc/hexanes) to afford 21.5 mg of **3.145** as a pale yellow oil (78% yield): IR (neat) ν_{max} 2972, 2925, 2850, 1716, 1449, 1375, 1289, 1156 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.25 (t, $J = 5.2$ Hz, 1 H), 2.74 (d, $J = 12.7$ Hz, 1 H), 2.34-2.21 (m, 1 H), 2.09-2.00 (m, 2 H), 1.95-1.75 (m, 5 H), 1.66-1.53 (m, 3 H), 1.23 (s, 3 H), 1.22 (s, 3 H), 1.00 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 217.48 (C), 84.83 (CH), 79.14 (C), 58.61 (C), 45.66 (C), 44.70 (CH_2), 42.21 (CH_2), 39.16 (CH_2),

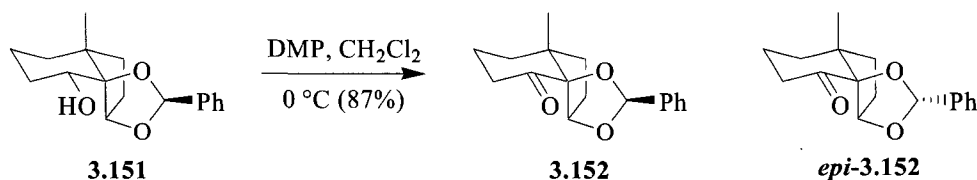
35.59 (CH₂), 28.99 (CH₃), 28.38 (CH₃), 26.78 (CH₂), 24.71 (CH₃), 20.41 (CH₂); HRMS *m/z* calculated for C₁₄H₂₂O₂ 222.1620 (M⁺), found 222.1625.



(±)-5a-methyl-2-phenyloctahydro-1,3-dioxacyclopenta[c]inden-9-yl benzoate (**3.150**). To a solution of **3.139** (52 mg, 0.18 mmol) in DME (2 mL) were added benzaldehyde dimethyl acetal (35 μL, 0.23 mmol) and SnCl₂ (4 mg, 0.02 mmol). The reaction mixture was then refluxed for 4 h. After cooling down to room temperature, it was quenched with saturated aqueous NaHCO₃ (2 mL). The aqueous layer was separated from the organic layer and extracted with CH₂Cl₂ (3 x 5 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (2% EtOAc/hexanes) to afford 51 mg of **3.150** as a white solid (75% yield). This was an 8:1 mixture of epimers: mp 105-106.5 °C; IR (neat) ν_{max} 2941, 2868, 1716, 1451, 1276, 1115 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) *major* δ 7.92-7.90 (m, 2 H), 7.46-7.45 (m, 1 H), 7.30-7.26 (m, 4 H), 7.03 (dd, *J* = 7.1, 7.1 Hz, 1 H), 6.91 (dd, *J* = 7.7, 7.7 Hz, 2 H), 5.93 (s, 1 H), 5.31 (dd, *J* = 12.0, 5.2 Hz, 1 H), 5.15 (d, *J* = 7.9 Hz, 1 H), 2.34-2.25 (m, 2 H), 1.93-1.83 (m, 2 H), 1.68-1.55 (m, 3 H), 1.47-1.42 (m, 1 H), 1.37 (ddd, *J* = 12.2, 12.2, 4.9 Hz, 2 H), 1.25 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) *major* δ 165.96 (C), 137.12 (C), 132.37 (CH), 130.32 (C), 129.70 (CH), 128.58 (CH), 127.84 (CH), 127.62 (CH), 126.35 (CH), 103.85 (CH), 93.78 (C), 82.22 (CH), 73.79 (CH), 47.84 (C), 40.65 (CH₂), 35.63 (CH₂), 30.82 (CH₂), 29.93 (CH₂), 20.48 (CH₃), 19.60 (CH₂); HRMS *m/z* calculated for C₂₄H₂₆O₄ 378.1831 (M⁺), found 378.1817.

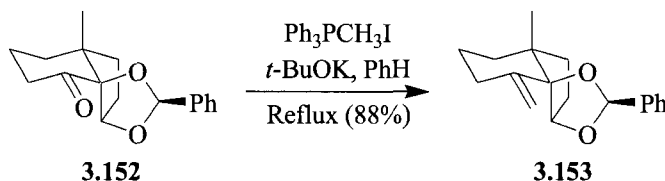


(±)-**5a-Methyl-2-phenyloctahydro-1,3-dioxacyclopenta[c]inden-9-ol (3.151)**. To a solution of **3.150** (2.03 g, 5.36 mmol) in MeOH (40 mL) was added K₂CO₃ (8.12 g, 58.75 mmol). Benzene (20 mL) was added. The mixture was refluxed for 16 h. After cooling down to room temperature, it was quenched with saturated aqueous NH₄Cl (20 mL). The aqueous layer was separated from the organic layer and extracted with EtOAc (4 x 50 mL). Combined organics were dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% then 20% EtOAc/hexanes) to afford 833 mg of **3.151** as a colorless oil (57% yield): IR (neat) $\nu_{\max}$ 3469 (br), 2941, 2870, 1457, 1395, 1223 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.53-7.50 (m, 2 H), 7.40-3.33 (m, 3 H), 5.94 (s, 1 H), 4.95 (d, J = 8.4 Hz, 1 H), 3.80 (dd, J = 12.0, 5.0 Hz, 1 H), 2.30-2.15 (m, 1 H), 2.08-2.02 (m, 1 H), 1.94 (br, 1 H), 1.86-1.77 (m, 2 H), 1.60-1.51 (m, 2 H), 1.47 (ddd, J = 13.3, 3.4, 3.4 Hz, 1 H), 1.43-1.35 (m, 1 H), 1.27 (dddd, J = 13.0, 13.0, 3.9, 3.9 Hz, 2 H), 1.15 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 137.56 (C), 129.38 (CH), 128.68 (CH), 126.13 (CH), 103.19 (CH), 95.36 (C), 81.67 (CH), 70.87 (CH), 46.95 (C), 40.91 (CH₂), 36.09 (CH₂), 32.13 (CH₂), 29.59 (CH₂), 20.50 (CH₃), 19.92 (CH₂); HRMS m/z calculated for C₁₇H₂₂O₃ 274.1569 (M⁺), found 274.1602. On large scale, *epi*-**3.151** was also obtained in minute amounts as a pink oil: IR (neat) $\nu_{\max}$ 3573, 3465 (br), 2948, 2872, 1458, 1401 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.54 (d, J = 7.7 Hz, 2 H), 7.39-7.32 (m, 3 H), 5.94 (s, 1 H), 4.90 (d, J = 8.1 Hz, 1 H), 3.88 (ddd, J = 10.4, 10.4, 5.1 Hz, 1 H), 2.31-2.22 (m, 1 H), 1.82-1.73 (m, 4 H), 1.67-1.58 (m, 2 H), 1.55-1.36 (m, 4 H), 0.91 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 137.81 (C), 128.97 (CH), 128.46 (CH), 125.96 (CH), 102.33 (CH), 94.27 (C), 82.01 (CH), 69.09 (CH), 46.90 (C), 38.48 (CH₂), 31.58 (CH₂), 31.24 (CH₂), 29.26 (CH₂), 21.04 (CH₃), 20.32 (CH₂); HRMS m/z calculated for C₁₇H₂₂O₃ 274.1569 (M⁺), found 274.1574.



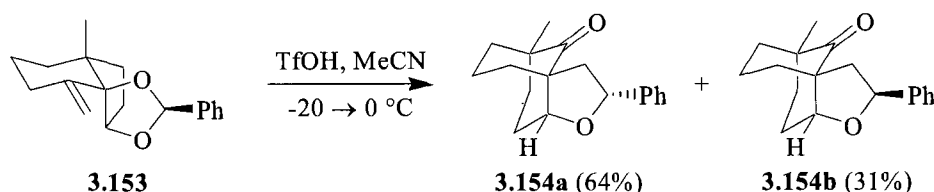
(±)-**5a-Methyl-2-phenylhexahydro-1,3-dioxacyclopenta[c]inden-9-one (3.152)**. To a solution of **3.151** (767 mg, 2.80 mmol) in CH₂Cl₂ (28 mL) at 0 °C was added DMP (2.40 g, 5.66 mmol). The resulting cloudy white mixture was stirred at that temperature for 2 h. Then, saturated

aqueous NaHCO_3 (15 mL) and saturated aqueous Na_2SO_3 (15 mL) were added and the resulting biphasic mixture was stirred vigorously for 20 minutes. The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 x 30 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (20% EtOAc/hexanes) to afford 665 mg of **3.152** as a pale yellow solid (87% yield): mp 95-96.5 °C; IR (neat) ν_{max} 2917, 2849, 1717, 1458 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.67-7.65 (m, 2 H), 7.39-7.34 (m, 3 H), 5.94 (s, 1 H), 5.08 (d, $J = 7.8$ Hz, 1 H), 2.58-2.51 (m, 1 H), 2.51-2.48 (m, 2 H), 1.98-1.85 (m, 4 H), 1.77 (ddd, $J = 13.3, 13.3, 4.6$ Hz, 1 H), 1.68 (dd, $J = 12.4, 8.5$ Hz, 1 H), 1.60 (dq, $J = 13.9, 2.9$ Hz, 1 H), 1.16 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 207.67 (C), 136.77 (C), 129.59 (CH), 128.25 (CH), 127.63 (CH), 105.97 (CH), 97.21 (C), 86.61 (CH), 52.88 (C), 40.08 (CH_2), 39.98 (CH_2), 35.08 (CH_2), 30.27 (CH_2), 22.15 (CH_2), 19.72 (CH_3); HRMS m/z calculated for $\text{C}_{17}\text{H}_{20}\text{O}_3$ 272.1412 (M^+), found 272.1412. On large scale, **epi-3.152** was also obtained in minute amounts as a pale yellow oil: IR (neat) ν_{max} 2952, 2876, 1720, 1458, 1386, 1222 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.33-7.28 (m, 5 H), 5.94 (s, 1 H), 5.23 (dd, $J = 8.5, 1.4$ Hz, 1 H), 2.84 (dddd, $J = 12.4, 8.5, 8.5, 8.5$ Hz, 1 H), 2.25-2.14 (m, 2 H), 2.11 (dd, $J = 12.8, 5.8$ Hz, 1 H), 1.98 (ddd, $J = 11.6, 11.6, 11.6$ Hz, 1 H), 1.93-1.73 (m, 3 H), 1.63-1.60 (m, 1 H), 1.53-1.49 (m, 1 H), 0.79 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.15 (C), 137.72 (C), 129.50 (CH), 128.42 (CH), 126.89 (CH), 104.59 (CH), 96.10 (C), 78.50 (CH), 49.15 (C), 37.55 (CH_2), 37.39 (CH_2), 31.31 (CH_2), 28.15 (CH_2), 22.49 (CH_2), 19.01 (CH_3); HRMS m/z calculated for $\text{C}_{17}\text{H}_{20}\text{O}_3$ 272.1412 (M^+), found 272.1413.



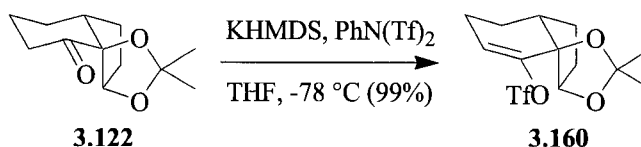
(±)-5a-Methyl-9-methylene-2-phenyloctahydro-1,3-dioxacyclopenta[c]indene (3.153). To a suspension of $\text{Ph}_3\text{PCH}_2\text{I}$ (233 mg, 0.58 mmol) in benzene (1.9 mL) at room temperature was added $t\text{-BuOK}$ (520 μL of a 1.0 M solution in THF, 0.52 mmol) dropwise. After stirring for 20 minutes, a solution of **3.152** (80 mg, 0.29 mmol) in benzene (1 mL) was added dropwise

via cannula. The reaction mixture was then refluxed for 30 minutes. After cooling down to room temperature, it was quenched with saturated aqueous NH_4Cl (3 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 10 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (20% then 40% benzene/hexanes) to afford 70 mg of **3.153** as a colorless oil (88% yield): IR(neat) ν_{max} 2937, 2868, 1648, 1458, 1395, 1218 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.53-7.49 (m, 2 H), 7.39-7.32 (m, 3 H), 5.97 (s, 1 H), 5.05 (dd, J = 2.6, 1.4 Hz, 1 H), 4.89 (dd, J = 2.2, 2.2 Hz, 1 H), 4.86 (d, J = 8.7 Hz, 1 H), 2.47 (dd, J = 13.8, 3.0 Hz, 1 H), 2.40-2.26 (m, 1 H), 2.10-2.01 (m, 1 H), 1.91-1.82 (m, 2 H), 1.63-1.43 (m, 5 H), 1.07 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.71 (C), 137.94 (C), 129.17 (CH), 128.23 (CH), 127.20 (CH), 110.77 (CH_2), 104.28 (CH), 95.22 (C), 85.78 (CH), 48.66 (C), 40.33 (CH_2), 36.63 (CH_2), 35.12 (CH_2), 29.70 (CH_2), 23.27 (CH_2), 19.69 (CH_3); HRMS m/z calculated for $\text{C}_{18}\text{H}_{22}\text{O}_2$ 270.1620 (M^+), found 270.1615.

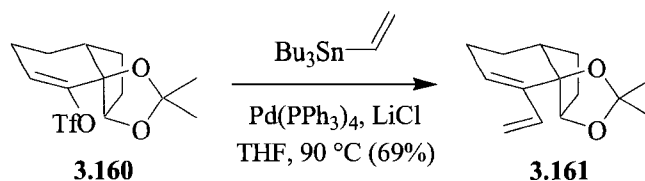


(±)-8-Methyl-3-phenyl-4-oxatricyclo[6.3.1.0^{1,5}]dodecan-12-one (3.154). To a solution of **3.153** (19.5 mg, 0.072 mmol) in MeCN (1 mL) at $-20\text{ }^\circ\text{C}$ was added TfOH (15 μL , 0.170 mmol) dropwise. The resulting solution was stirred at $-20\text{ }^\circ\text{C}$ for 15 minutes, warmed up to room temperature, and stirred for 15 minutes at that temperature. Et_3N was added dropwise until complete discoloration, followed by saturated aqueous NaHCO_3 (1 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% EtOAc/hexanes) to afford 12.5 mg of **3.154a** as a white solid (64% yield) and 6 mg of **3.154b** as a colorless oil (31% yield). Epimer **3.154a**: mp $65\text{--}66\text{ }^\circ\text{C}$; IR (neat) ν_{max} 2929, 2866, 1713, 1454, 1354 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.35-7.22 (m, 5 H), 4.75 (dd, J = 10.4, 5.7 Hz, 1 H), 4.24 (dd, J = 9.3, 5.3 Hz, 1 H), 2.64 (dd, J = 12.9, 10.4 Hz, 1 H), 2.26-2.15 (m, 2 H), 2.04-1.93 (m, 2 H), 1.90-1.75 (m, 3 H), 1.72 (dd, J = 13.0, 5.8 Hz, 1 H), 1.64-1.54 (m, 2 H), 1.41-1.31 (m, 1 H),

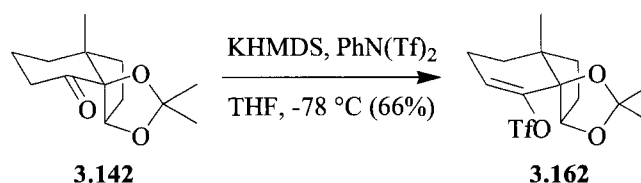
1.07 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 217.55 (C), 140.67 (C), 128.35 (CH), 127.76 (CH), 126.52 (CH), 85.94 (CH), 79.35 (CH), 57.85 (C), 45.57 (C), 43.05 (CH_2), 41.07 (CH_2), 40.14 (CH_2), 33.90 (CH_2), 27.61 (CH_2), 24.84 (CH_3), 19.00 (CH_2); HRMS m/z calculated for $\text{C}_{18}\text{H}_{22}\text{O}_2$ 270.1620 (M^+), found 270.1632. Epimer **3.154b**: IR (neat) ν_{max} 2926, 2851, 1714, 1453, 1377, 1048 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.33-7.28 (m, 4 H), 7.23-7.20 (m, 1 H), 4.86 (dd, $J = 9.7, 6.0$ Hz, 1 H), 4.48 (dd, $J = 6.9, 5.3$ Hz, 1 H), 3.10 (dd, $J = 12.2, 6.0$ Hz, 1 H), 2.24-2.12 (m, 1 H), 2.09-1.78 (m, 6 H), 1.65-1.56 (m, 3 H), 1.40 (dd, $J = 12.3, 9.7$ Hz, 1 H), 1.05 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 217.53 (C), 142.74 (C), 128.38 (CH), 127.26 (CH), 125.56 (CH), 86.35 (CH), 78.30 (CH), 58.67 (C), 45.56 (C), 42.47 (CH_2), 42.17 (CH_2), 38.59 (CH_2), 34.61 (CH_2), 26.57 (CH_2), 24.72 (CH_3), 20.61 (CH_2); HRMS m/z calculated for $\text{C}_{18}\text{H}_{22}\text{O}_2$ 270.1620 (M^+), found 270.1607.



(±)-2,2-dimethyl-3a,4,5,5a,6,7-hexahydro-1,3-dioxacyclopenta[c]inden-9-yl triflate (**3.160**). To a solution of KHMDS (1.42 g, 7.12 mmol) in THF (25 mL) at $-78\text{ }^\circ\text{C}$ was added dropwise a solution of **3.122** (825 mg, 3.96 mmol) in THF (5 mL) via cannula. The resulting yellow solution was stirred for 20 minutes and a solution of PhN(Tf)_2 (2.83 g, 7.92 mmol) in THF (10 mL) was added via cannula. After stirring at $-78\text{ }^\circ\text{C}$ for 30 minutes, the reaction mixture was warmed up to room temperature. The solvent was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (30% benzene/hexanes) to afford 1.34 g of **3.160** as a pale yellow oil (99% yield): IR (neat) ν_{max} 2939, 1417, 1373, 1212, 1144 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.07 (dd, $J = 5.1, 3.6$ Hz, 1 H), 4.57 (dd, $J = 5.0, 2.2$ Hz, 1 H), 2.51-2.46 (m, 1 H), 2.29-2.15 (m, 2 H), 2.03-1.87 (m, 3 H), 1.77-1.70 (m, 1 H), 1.60-1.56 (m, 2 H), 1.49 (s, 3 H), 1.41 (s, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 146.27 (C), 123.99 (CH), 122.42 (CF_3 , q, $J = 320$ Hz), 112.89 (C), 88.77 (C), 82.73 (CH), 46.05 (CH), 29.00 (CH_3), 28.95 (CH_2), 27.42 (CH_2), 26.85 (CH_3), 22.16 (CH_2), 21.56 (CH_2); HRMS m/z calculated for $\text{C}_{12}\text{H}_{14}\text{F}_3\text{O}_5\text{S}$ 327.0514 ($\text{M}^+ - \text{Me}$), found 327.0501.

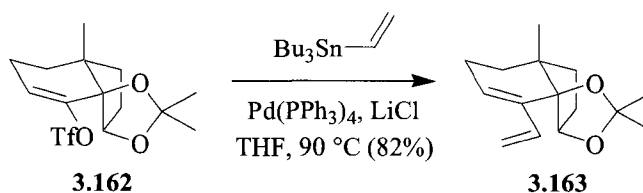


(±)-2,2-Dimethyl-9-vinyl-3a,4,5,5a,6,7-hexahydro-1,3-dioxacyclopenta[c]indene (**3.161**). To a Pyrex tube containing a stirred solution of **3.160** (1.34 g, 3.91 mmol) in THF (20 mL) were added Pd(PPh₃)₄ (46 mg, 0.04 mmol), tributylvinyltin (1.15 mL, 3.94 mmol) and LiCl (497 mg, 11.72 mmol). The Pyrex tube was capped, and the reaction mixture was heated at 90 °C for 2 days. After cooling down to room temperature, the mixture was diluted with hexanes (30 mL). It was then washed sequentially with H₂O (50 mL), 10% aqueous NH₄OH (30 mL), H₂O (50 mL) and saturated aqueous NaCl (50 mL). The organic layer was dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (0.5% EtOAc/benzene) to afford 595 mg of **3.161** as a pale yellow oil (69% yield): IR (neat) ν_{max} 2984, 2929, 1459, 1377, 1243, 1212 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.40 (ddd, J = 17.3, 10.8, 1.1 Hz, 1 H), 6.18 (dd, J = 5.3, 3.2 Hz, 1 H), 5.39 (dd, J = 17.3, 1.9 Hz, 1 H), 5.03 (dd, J = 10.8, 1.9 Hz, 1 H), 4.38 (dd, J = 4.0, 4.0 Hz, 1 H), 2.43-2.38 (m, 1 H), 2.15-2.07 (m, 1 H), 2.06-1.96 (m, 1 H), 1.95-1.89 (m, 1 H), 1.85-1.80 (m, 2 H), 1.72-1.65 (m, 1 H), 1.53 (s, 3 H), 1.63-1.52 (m, 1 H), 1.49-1.42 (m, 1 H), 1.41 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 135.51 (CH), 134.78 (C), 128.84 (CH), 114.03 (CH₂), 111.08 (C), 89.03 (C), 84.16 (CH), 43.40 (CH), 28.88 (CH₃), 28.79 (CH₂), 27.53 (CH₃), 26.80 (CH₂), 22.13 (CH₂), 21.19 (CH₂); HRMS m/z calculated for C₁₃H₁₇O₂ 205.1229 (M⁺ - Me), found 205.1257.



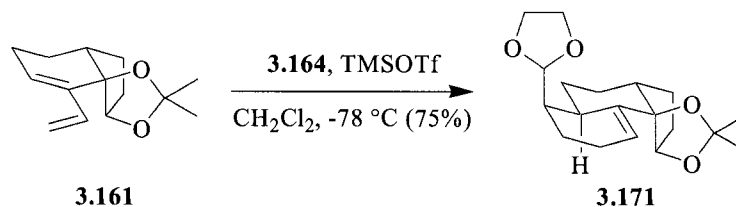
(±)-2,2,5a-trimethyl-3a,4,5,5a,6,7-hexahydro-1,3-dioxacyclopenta[c]inden-9-yl triflate (**3.162**). To a solution of KHMDS (80 mg, 0.40 mmol) in THF (1.2 mL) at -78 °C was added dropwise a solution of **3.142** (50 mg, 0.22 mmol) in THF (500 μ L) via cannula. The resulting yellow solution was stirred for 25 minutes and a solution of PhN(Tf)₂ (157 mg, 0.44 mmol)

in THF (500 μ L) was added via cannula. After stirring at -78°C for 30 minutes, the reaction mixture was warmed up to room temperature. The solvent was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (30% benzene/hexanes) to afford 52 mg of **3.162** as a pale yellow solid (66% yield): mp $41\text{--}44^{\circ}\text{C}$; IR (neat) ν_{max} 2991, 2941, 2870, 1673, 1418, 1246, 1203 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.06 (dd, $J = 5.5, 3.1$ Hz, 1 H), 4.65 (d, $J = 5.4$ Hz, 1 H), 2.34–2.25 (m, 1 H), 2.15–2.07 (m, 1 H), 1.99–1.90 (m, 1 H), 1.87–1.77 (m, 2 H), 1.67–1.60 (m, 1 H), 1.58–1.50 (m, 1 H), 1.47 (s, 3 H), 1.43 (s, 3 H), 1.45–1.40 (m, 1 H), 1.12 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 147.30 (C), 121.81 (CH), 118.23 (CF_3 , q, $J = 320$ Hz), 112.38 (C), 90.68 (C), 84.12 (CH), 45.90 (C), 36.97 (CH_2), 32.28 (CH_2), 28.66 (CH_2), 26.95 (CH_3), 26.57 (CH_3), 21.50 (CH_3), 20.81 (CH_2); HRMS m/z calculated for $\text{C}_{13}\text{H}_{16}\text{F}_3\text{O}_5\text{S}$ 341.0671 ($\text{M}^+ - \text{Me}$), found 341.0669.

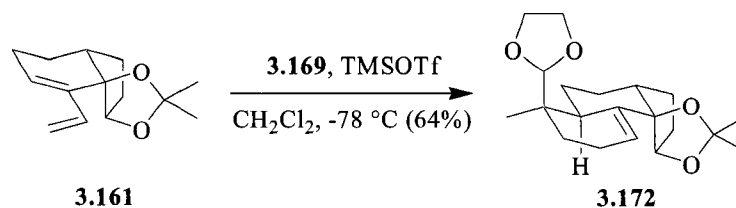


($\pm$)-2,2,5a-Trimethyl-9-vinyl-3a,4,5,5a,6,7-hexahydro-1,3-dioxacyclopenta[*c*]indene (**3.163**). To a Pyrex tube containing a stirred solution of **3.162** (52 mg, 0.146 mmol) in THF (1.5 mL) were added $\text{Pd(PPh}_3)_4$ (9 mg, 0.008 mmol), tributylvinyltin (45 μ L, 0.154 mmol) and LiCl (19 mg, 0.448 mmol). The Pyrex tube was capped, and the reaction mixture was heated at 90°C for 16 h. After cooling to room temperature, the mixture was diluted with hexanes (5 mL). It was then washed sequentially with H_2O (5 mL), 10% aqueous NH_4OH (3 mL), H_2O (5 mL) and saturated aqueous NaCl (5 mL). The organic layer was dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (3% EtOAc/benzene) to afford 28 mg of **3.163** as a yellow oil (82% yield): IR (neat) ν_{max} 3081, 2987, 2937, 2870, 1598, 1457, 1375, 1234, 1203 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.49 (dd, $J = 17.1, 10.7$ Hz, 1 H), 6.05–6.04 (m, 1 H), 5.31 (dd, $J = 17.1, 2.0$ Hz, 1 H), 5.01 (dd, $J = 10.7, 2.0$ Hz, 1 H), 4.51 (d, $J = 5.2$ Hz, 1 H), 2.20–2.13 (m, 1 H), 1.96–1.87 (m, 3 H), 1.78–1.72 (m, 1 H), 1.61–1.56 (m, 1 H), 1.48 (s, 3 H), 1.46 (s, 3 H), 1.44–1.42 (m, 1 H), 1.41–1.35 (m, 1 H), 1.10 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 138.18 (C), 137.40 (CH), 128.05 (CH), 114.37 (CH_2), 110.93 (C), 92.88 (C), 86.61 (CH), 43.47 (C),

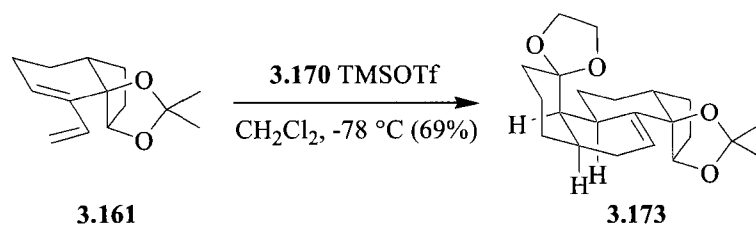
38.08 (CH₂), 33.94 (CH₂), 29.49 (CH₂), 28.25 (CH₃), 27.61 (CH₃), 21.65 (CH₂), 21.18 (CH₃); HRMS *m/z* calculated for C₁₅H₂₂O₂ 234.1620 (M⁺), found 234.1611.



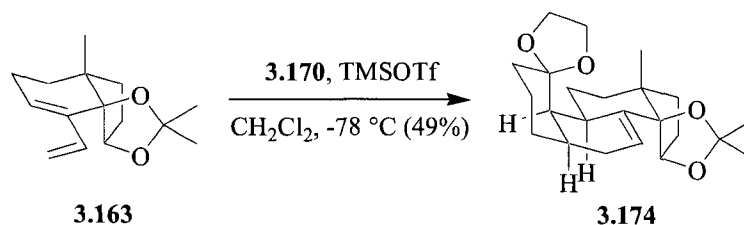
(±)-5-[1,3]Dioxolan-2-yl-10,10-dimethyl-1,2,2a,3,4,4a,5,6,7,11a-decahydro-9,11-dioxapentaleno [6a,1-a]naphthalene (**3.171**). To a solution of **3.161** (36 mg, 0.163 mmol) in CH₂Cl₂ (1.6 mL) at room temperature was added dienophile **3.164** (20 μL, 0.200 mmol). The resulting solution was cooled down to -78 °C and TMSOTf (30 μL, 0.166 mmol) was added dropwise. The mixture was stirred at -78 °C for 20 minutes. Et₃N was added dropwise until complete discoloration, followed by saturated aqueous NaHCO₃ (1 mL). After warming up to room temperature, the aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 5 mL). Combined organics were dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford 39 mg of **3.171** as a white solid (75% yield): mp 66-69 °C; IR (neat) ν_{max} 2934, 2866, 1456, 1377, 1366, 1239 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.89 (d, *J* = 3.9 Hz, 1 H), 4.74 (d, *J* = 7.2 Hz, 1 H), 4.57 (d, *J* = 6.5 Hz, 1 H), 3.98-3.91 (m, 2 H), 3.88-3.81 (m, 2 H), 2.18-2.06 (m, 4 H), 2.04-1.98 (m, 2 H), 1.85-1.75 (m, 2 H), 1.75-1.65 (m, 3 H), 1.46 (s, 3 H), 1.40 (s, 3 H), 1.30-1.23 (m, 4 H); ¹³C NMR (125 MHz, CDCl₃) δ 140.53 (C), 118.82 (CH), 110.18 (C), 105.90 (CH), 95.65 (C), 84.30 (CH), 64.66 (CH₂), 64.61 (CH₂), 48.56 (CH), 41.61 (CH), 37.14 (CH), 32.45 (CH₂), 29.64 (CH₂), 29.00 (CH₂), 28.87 (CH₃), 27.96 (CH₃), 27.74 (CH₂), 24.64 (CH₂), 19.41 (CH₂); HRMS *m/z* calculated for C₁₉H₂₈O₄ 320.1988 (M⁺), found 320.1985. Trace amounts of an epimer are present on the ¹H NMR spectrum. The tridimensional structure of the product was confirmed by X-ray crystallography.



(±)-5-[1,3]Dioxolan-2-yl-5,10,10-trimethyl-1,2,2a,3,4,4a,5,6,7,11a-decahydro-9,11-dioxapentaleno[6a,1-a]naphthalene (**3.172**). To a solution of **3.161** (40 mg, 0.182 mmol) in CH_2Cl_2 (1.8 mL) at room temperature was added dienophile **3.169** (23 mg, 0.202 mmol).¹⁴⁴ The resulting solution was cooled down to $-78\text{ }^\circ\text{C}$ and TMSOTf (35 μL , 0.193 mmol) was added dropwise. The mixture was stirred at $-78\text{ }^\circ\text{C}$ for 5 minutes. Et_3N was added dropwise until complete discoloration, followed by saturated aqueous NaHCO_3 (1 mL). After warming up to room temperature, the aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% EtOAc /hexanes) to afford 39 mg of **3.172** as a white solid (64% yield): mp $68\text{--}71\text{ }^\circ\text{C}$; IR (neat) ν_{max} 2937, 2867, 1453, 1379, 1366, 1240, 1212 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.84 (t, $J = 3.7\text{ Hz}$, 1 H), 4.66 (s, 1 H), 4.49 (d, $J = 5.7\text{ Hz}$, 1 H), 3.98–3.90 (m, 2 H), 3.88–3.81 (m, 2 H), 2.18–1.96 (m, 5 H), 1.89–1.82 (m, 1 H), 1.80–1.62 (m, 2 H), 1.53 (s, 3 H), 1.46–1.40 (m, 3 H), 1.37 (s, 3 H), 1.32–1.17 (m, 3 H), 0.86 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 139.94 (C), 117.25 (CH), 109.99 (C), 108.23 (CH), 95.71 (C), 84.12 (CH), 65.14 (CH_2), 64.84 (CH_2), 48.67 (CH), 43.66 (CH), 37.90 (C), 32.59 (CH_2), 29.60 (CH_2), 28.98 (CH_2), 28.87 (CH_2), 28.82 (CH_3), 27.87 (CH_3), 25.00 (CH_2), 21.10 (CH_2), 16.01 (CH_3); HRMS m/z calculated for $\text{C}_{20}\text{H}_{30}\text{O}_4$ 334.2144 (M^+), found 334.2148. Trace amounts of an epimer are present on the ^1H NMR spectrum.

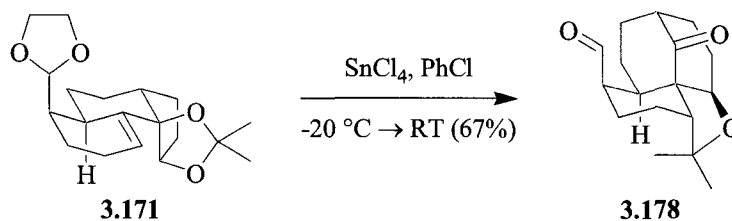


Cycloadduct 3.173. To a solution of **3.161** (56 mg, 0.254 mmol) in CH_2Cl_2 (2.5 mL) at room temperature was added dienophile **3.170** (71 mg, 0.460 mmol).¹⁴⁴ The resulting solution was cooled to $-78\text{ }^\circ\text{C}$ and TMSOTf (45 μL , 0.249 mmol) was added dropwise. The mixture was stirred at $-78\text{ }^\circ\text{C}$ for 1 h. Et_3N was added dropwise until complete discoloration, followed by saturated aqueous NaHCO_3 (1 mL). After warming up to room temperature, the aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% EtOAc /hexanes) to afford 63 mg of **3.173** as a white solid (69% yield): mp $105\text{--}107\text{ }^\circ\text{C}$; IR (neat) ν_{max} 2934, 2867, 1451, 1376, 1365, 1238, 1163 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.89 (dd, $J = 4.8, 2.1\text{ Hz}$, 1 H), 4.54 (d, $J = 6.6\text{ Hz}$, 1 H), 3.97–3.70 (m, 4 H), 2.36 (dddd, $J = 10.3, 8.1, 8.1, 2.5, 2.3\text{ Hz}$, 1 H), 2.19–2.04 (m, 4 H), 2.03–1.92 (m, 4 H), 1.79–1.64 (m, 5 H), 1.54 (dddd, $J = 13.3, 13.0, 13.0, 4.3, 4.3\text{ Hz}$, 1 H), 1.46 (s, 3 H), 1.42 (s, 3 H), 1.40–1.26 (m, 4 H), 1.15 (dddd, $J = 13.4, 13.3, 12.8, 3.9\text{ Hz}$, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 137.97 (C), 117.76 (CH), 110.95 (C), 110.44 (C), 95.87 (C), 84.67 (CH), 64.57 (CH_2), 63.56 (CH_2), 47.87 (CH), 43.51 (CH), 36.05 (CH), 33.21 (CH_2), 32.75 (CH_2), 32.23 (CH_2), 31.96 (CH), 30.68 (CH_2), 30.11 (CH_2), 29.82 (CH_2), 29.23 (CH_2), 29.20 (CH_3), 28.10 (CH_3), 23.22 (CH_2); HRMS m/z calculated for $\text{C}_{22}\text{H}_{32}\text{O}_4$ 360.2301 (M^+), found 360.2299.



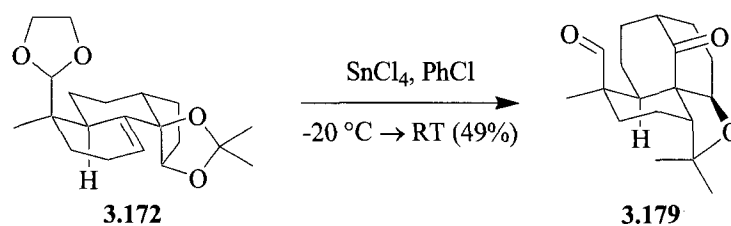
Cycloadduct 3.174. To a solution of **3.163** (28 mg, 0.119 mmol) in CH_2Cl_2 (1.2 mL) at room temperature was added dienophile **3.170** (43 mg, 0.279 mmol).¹⁴⁴ The resulting solution was cooled to $-78\text{ }^\circ\text{C}$ and TMSOTf (22 μL , 0.121 mmol) was added dropwise. The mixture was stirred at $-78\text{ }^\circ\text{C}$ for 30 minutes. Et_3N was added dropwise until complete discoloration, followed by saturated aqueous NaHCO_3 (1 mL). After warming up to room temperature, the aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the

solvent, the residue was purified by silica gel column chromatography (5% EtOAc/hexanes) to afford 22 mg of **3.174** as a pale yellow oil (49% yield): IR (neat) $\nu_{\max}$ 2937, 2866, 2248, 1457, 1379, 1238 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.87 (d, $J = 3.6$ Hz, 1 H), 4.71 (d, $J = 7.8$ Hz, 1 H), 3.99-3.86 (m, 4 H), 2.38-2.33 (m, 1 H), 2.22-1.98 (m, 5 H), 1.96-1.88 (m, 2 H), 1.79 (ddd, $J = 13.5, 13.4, 5.2$ Hz, 1 H), 1.73-1.70 (m, 1 H), 1.67-1.61 (m, 2 H), 1.60-1.47 (m, 3 H), 1.45 (s, 3 H), 1.42 (s, 3 H), 1.43-1.36 (m, 2 H), 1.35-1.23 (m, 2 H), 0.93 (s, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 136.48 (C), 119.68 (CH), 111.59 (C), 111.20 (C), 97.79 (C), 85.45 (CH), 65.14 (CH_2), 64.13 (CH_2), 47.96 (C), 43.80 (CH), 38.28 (CH_2), 36.95 (CH_2), 36.51 (CH), 33.66 (CH_2), 32.63 (CH), 31.85 (CH_2), 31.36 (CH_2), 30.14 (CH_2), 29.88 (CH_3), 29.52 (CH_2), 28.81 (CH_3), 23.83 (CH_2), 19.63 (CH_3); HRMS m/z calculated for $\text{C}_{23}\text{H}_{34}\text{O}_4$ 374.2457 (M^+), found 374.2435. Trace amounts of a stereoisomer are present on the ^1H NMR spectrum.



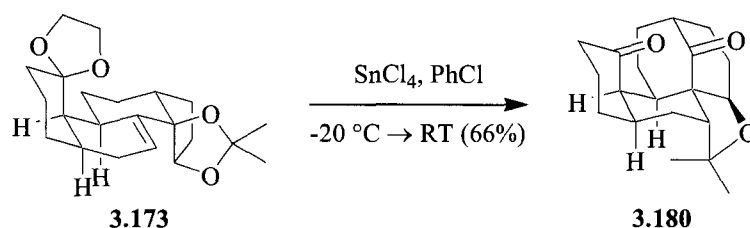
Prins-Pinacol adduct 3.178. To a solution of SnCl_4 (80 μL of a 1.0 M solution in CH_2Cl_2 , 0.080 mmol) in PhCl (400 μL) at $-20\text{ }^\circ\text{C}$ was added a solution of **3.171** (10 mg, 0.031 mmol) in PhCl (400 μL) via cannula. The resulting solution was stirred at $0\text{ }^\circ\text{C}$ for 1 h, warmed up to room temperature, and stirred for 1 h. Et_3N was added dropwise until complete discoloration, followed by saturated aqueous NaHCO_3 (1 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (40% EtOAc/hexanes) to afford 5.7 mg of **3.178** as a yellow oil (67% yield). This was a 7.3:1 mixture of epimers: IR (neat) $\nu_{\max}$ 3406, 2929, 2866, 1708, 1449, 1379, 1144 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) *major* δ 9.70 (d, $J = 4.3$ Hz, 1 H), 4.24 (dd, $J = 9.2, 5.1$ Hz, 1 H), 2.65-2.62 (m, 1 H), 2.61-2.57 (m, 2 H), 2.47-2.43 (m, 1 H), 2.41-2.33 (m, 1 H), 2.23-2.12 (m, 2 H), 1.97-1.89 (m, 1 H), 1.88-1.81 (m, 3 H), 1.80-1.69 (m, 2 H), 1.65 (dd, $J = 15.0, 5.1$ Hz, 1 H), 1.49-1.41 (m, 1 H), 1.33-1.28 (m, 1

H), 1.26 (s, 3 H), 1.16 (s, 3 H) *minor* δ 9.57 (d, J = 2.8 Hz, 1 H), 4.34 (dd, J = 11.0, 5.1 Hz, 1 H), 2.65-2.62 (m, 1 H), 2.61-2.57 (m, 2 H), 2.47-2.43 (m, 1 H), 2.41-2.33 (m, 1 H), 2.23-2.12 (m, 2 H), 1.97-1.89 (m, 1 H), 1.88-1.81 (m, 3 H), 1.80-1.69 (m, 2 H), 1.67-1.63 (m, 1 H), 1.49-1.41 (m, 1 H), 1.33-1.28 (m, 1 H), 1.24 (s, 3 H), 1.13 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) *major* δ 218.42 (C), 204.75 (CH), 85.98 (CH), 82.23 (C), 58.39 (C), 52.72 (CH), 46.34 (CH), 44.40 (CH), 43.39 (CH), 31.99 (CH_2), 29.09 (CH_3), 27.78 (CH_2), 25.92 (CH_2), 23.29 (CH_3), 22.92 (CH_2), 22.00 (CH_2), 18.61 (CH_2); HRMS m/z calculated for $\text{C}_{17}\text{H}_{24}\text{O}_3$ 276.1725 (M^+), found 276.1723.

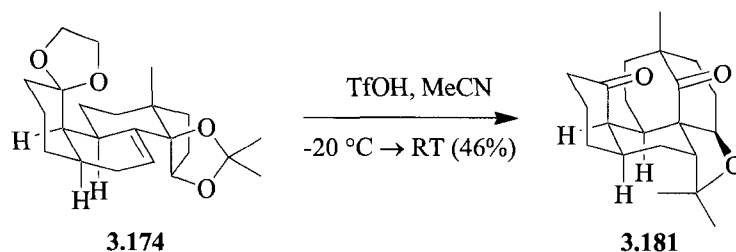


Prins-Pinacol adduct 3.179. To a solution of SnCl_4 (40 μL of a 1.0 M solution in CH_2Cl_2 , 0.040 mmol) in PhCl (400 μL) at $-20\text{ }^\circ\text{C}$ was added a solution of **3.172** (10.5 mg, 0.031 mmol) in CH_2Cl_2 (400 μL) via cannula. The resulting solution was stirred at $0\text{ }^\circ\text{C}$ for 1 h, warmed up to room temperature, and stirred for 1 h. Et_3N was added dropwise until complete discoloration, followed by saturated aqueous NaHCO_3 (1 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (20% EtOAc /hexanes) to afford 4.4 mg of **3.179** as a dark yellow oil (49% yield). This was a 6.1:1 mixture of epimers: IR (neat) ν_{max} 3409, 2934, 2870, 1715, 1449, 1384 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) *major* δ 9.59 (s, 1 H), 4.23 (dd, J = 8.7, 5.2 Hz, 1 H), 2.68 (t, J = 6.9 Hz, 1 H), 2.64-2.59 (m, 1 H), 2.24-2.10 (m, 4 H), 1.91-1.76 (m, 5 H), 1.46-1.27 (m, 3 H), 1.26 (s, 3 H), 1.20-1.17 (m, 1 H), 1.15 (s, 3 H), 1.05 (s, 3 H) *minor* δ 9.28 (s, 1 H), 4.30 (dd, J = 9.7, 5.2 Hz, 1 H), 2.70-2.67 (m, 1 H), 2.58-2.53 (m, 1 H), 2.24-2.10 (m, 4 H), 1.91-1.76 (m, 5 H), 1.46-1.27 (m, 3 H), 1.26 (s, 3 H), 1.20-1.7 (m, 1 H), 1.18 (s, 3 H), 1.02 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) *major* δ 218.01 (C), 205.48 (CH), 86.50 (CH), 82.02 (C), 59.43 (C), 52.97 (CH), 49.45 (C), 44.19 (CH), 44.09 (CH), 31.88 (CH_2), 31.26 (CH_2), 29.14 (CH_3), 27.68 (CH_2), 26.73 (CH_2), 23.30 (CH_3),

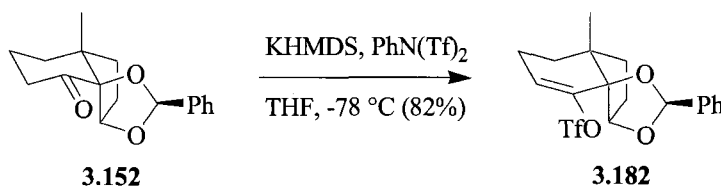
23.11 (CH₃), 18.40 (CH₂), 17.88 (CH₂) *minor* δ 220.32, 205.29, 86.59, 82.18, 65.70, 49.85, 45.39, 42.65, 32.17, 30.21, 28.98, 28.05, 25.82, 23.63, 19.59, 17.39, 15.68, 15.12; HRMS m/z calculated for C₁₈H₂₆O₃ 290.1882 (M⁺), found 290.1879.



Prins-Pinacol adduct 3.180. To a solution of SnCl₄ (40 μ L of a 1.0 M solution in CH₂Cl₂, 0.040 mmol) in PhCl (400 μ L) at -20 $^{\circ}$ C was added a solution of **3.173** (12.8 mg, 0.036 mmol) in PhCl (400 μ L) via cannula. The resulting solution was stirred at -20 $^{\circ}$ C for 1 h, warmed up to 0 $^{\circ}$ C, and stirred for 2 h at that temperature. Et₃N was added dropwise until complete discoloration, followed by saturated aqueous NaHCO₃ (1 mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 5 mL). Combined organics were dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (20% then 40% EtOAc/hexanes) to afford 7.5 mg of **3.180** as a yellow solid (66% yield): mp 120-130 $^{\circ}$ C; IR (neat) ν_{max} 3422, 2929, 2868, 1712, 1449, 1379, 1160 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.17 (dd, J = 11.2, 5.4 Hz, 1 H), 2.76-2.73 (m, 1 H), 2.70-2.66 (m, 2 H), 2.53-2.46 (m, 1 H), 2.36-2.13 (m, 6 H), 1.98-1.93 (m, 1 H), 1.92-1.85 (m, 3 H), 1.73 (dddd, J = 10.3, 8.4, 4.4, 4.0 Hz, 1 H), 1.54-1.48 (m, 2 H), 1.36 (dd, J = 15.2, 5.0 Hz, 1 H), 1.26 (d, J = 3.9 Hz, 1 H), 1.23 (s, 3 H), 1.14 (s, 3 H), 1.13-1.05 (m, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 213.78 (C), 211.46 (C), 87.47 (CH), 82.33 (C), 56.33 (C), 56.30 (C), 46.70 (CH), 43.04 (CH), 42.52 (CH₂), 41.87 (CH), 38.98 (CH), 32.13 (CH₂), 30.57 (CH₂), 28.84 (CH₃), 27.72 (CH₂), 25.42 (CH₂), 24.02 (CH₂), 23.97 (CH₃), 23.28 (CH₂), 22.62 (CH₂); HRMS m/z calculated for C₂₀H₂₈O₃ 316.2038 (M⁺), found 316.2018. The tridimensional structure of this product was confirmed by X-ray crystallography.

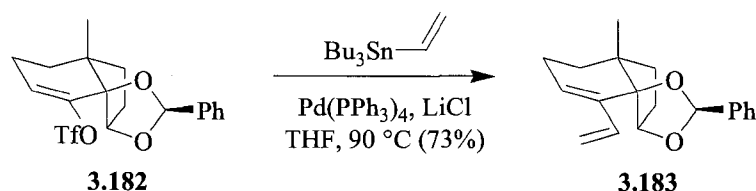


Prins-Pinacol adduct 3.181. To a solution of **3.174** (15 mg, 0.040 mmol) in MeCN (700 μL) at $-20\text{ }^{\circ}\text{C}$ was added TfOH (10 μL , 0.113 mmol). The resulting solution was allowed to warm up to room temperature over 40 minutes. Et_3N was added dropwise until complete discoloration, followed by saturated aqueous NaHCO_3 (1 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (20% EtOAc/hexanes) to afford 6.1 mg of **3.181** as a white solid (46% yield): mp $128.5\text{--}134\text{ }^{\circ}\text{C}$; IR (neat) ν_{max} 2921, 2858, 1712, 1453, 1371, 1309, 1164 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.16 (dd, $J = 11.0, 5.4\text{ Hz}$, 1 H), 2.75 (d, $J = 7.7\text{ Hz}$, 1 H), 2.68 (t, $J = 4.1\text{ Hz}$, 1 H), 2.37–2.15 (m, 5 H), 2.04–1.84 (m, 4 H), 1.66–1.56 (m, 3 H), 1.55–1.47 (m, 1 H), 1.42–1.38 (m, 1 H), 1.22 (s, 3 H), 1.18 (s, 3 H), 1.14 (s, 3 H), 1.12–0.97 (m, 2 H), 0.90–0.77 (m, 2 H); ^{13}C NMR (75 MHz, CDCl_3) δ 214.74 (C), 212.21 (C), 87.76 (CH), 83.26 (C), 67.31 (C), 56.81 (CH), 47.25 (CH), 43.99 (C), 43.13 (CH_2), 42.80 (CH), 40.69 (CH_2), 39.58 (CH), 34.63 (CH_2), 31.15 (CH_2), 29.47 (CH_3), 28.42 (CH_2), 25.78 (CH_3), 24.61 (CH_2), 24.57 (CH_2), 24.52 (CH_3), 23.88 (CH_2); HRMS m/z calculated for $\text{C}_{21}\text{H}_{30}\text{O}_3$ 330.2195 (M^+), found 330.2182.



($\pm$)-5a-methyl-2-phenyl-3a,4,5,5a,6,7-hexahydro-1,3-dioxacyclopenta-[c]inden-9-yl triflate (3.182). To a solution of KHMDS (52 mg, 0.261 mmol) in THF (500 μL) at $-78\text{ }^{\circ}\text{C}$ was added a solution of **3.152** (40 mg, 0.147 mmol) in THF (500 μL) via cannula. The resulting yellow solution was stirred for 20 minutes and a solution of PhN(Tf)_2 (103 mg, 0.288 mmol)

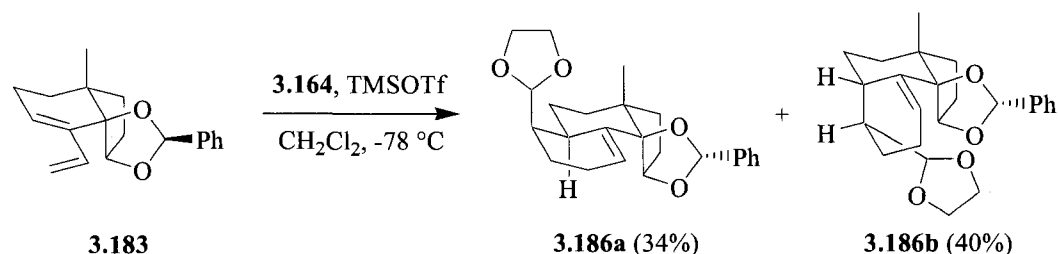
in THF (500 μ L) was added via cannula. After stirring at -78°C for 2 h, the reaction was warmed up to room temperature. The solvent was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (2% then 5% EtOAc/hexanes) to afford 49 mg of **3.182** as a pale yellow oil (82% yield): IR (neat) ν_{max} 3039, 2940, 2880, 1678, 1458, 1420, 1222, 1146 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.57-7.52 (m, 2 H), 7.37-7.34 (m, 3 H), 6.00 (dd, $J = 6.0, 2.4$ Hz, 1 H), 5.98 (s, 1 H), 4.90 (d, $J = 7.0$ Hz, 1 H), 2.43-2.34 (m, 1 H), 2.31-2.22 (m, 1 H), 2.16 (dddd, $J = 18.3, 5.6, 5.6, 2.7$ Hz, 1 H), 1.99 (dddd, $J = 15.0, 8.0, 1.3, 1.3$ Hz, 1 H), 1.90-1.82 (m, 1 H), 1.75-1.67 (m, 2 H), 1.46 (ddd, $J = 13.7, 4.5, 2.7$ Hz, 1 H), 1.22 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.06 (C), 136.31 (C), 129.51 (CH), 128.17 (CH), 127.04 (CH), 120.79 (CH), 118.35 (CF_3 , q, $J = 320.2$ Hz), 106.08 (CH), 90.32 (C), 86.16 (CH), 46.88 (C), 40.19 (CH_2), 32.63 (CH_2), 30.51 (CH_2), 21.26 (CH_2), 19.30 (CH_3); HRMS m/z calculated for $\text{C}_{18}\text{H}_{19}\text{OSF}_3$ 404.0905 (M^+), found 404.0870.



(±)-5a-Methyl-2-phenyl-9-vinyl-3a,4,5,5a,6,7-hexahydro-1,3-dioxo-cyclopenta[c]indene (3.183).

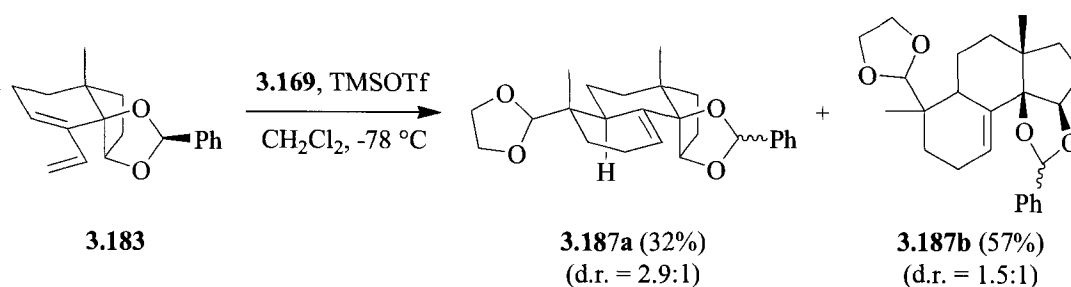
To a Pyrex tube containing a stirred solution of **3.182** (47 mg, 0.116 mmol) in THF (1.2 mL) were added $\text{Pd(PPh}_3)_4$ (7 mg, 0.006 mmol), tributylvinyltin (35 μ L, 0.120 mmol) and LiCl (15 mg, 0.354 mmol). The Pyrex tube was capped, and the reaction mixture was heated at 90°C for 16 h. After cooling to room temperature, the mixture was diluted with hexanes (5 mL). It was then washed sequentially with H_2O (5 mL), 10% aqueous NH_4OH (3 mL), H_2O (5 mL), and saturated aqueous NaCl (5 mL). The organic layer was dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (2% $\rightarrow$ 5% EtOAc/hexanes) to afford 24 mg of **3.183** as a pale yellow oil (73% yield): IR (neat) ν_{max} 3070, 3055, 2929, 2754, 2587, 1952, 1811, 1454, 1397, 1222 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.55-7.52 (m, 2 H), 7.39-7.33 (m, 3 H), 6.38 (ddd, $J = 17.5, 10.9, 0.9$ Hz, 1 H), 6.10-6.08 (m, 1 H), 6.01 (s, 1 H), 5.39 (dd, $J = 17.5, 1.5$ Hz, 1 H), 4.97 (dd, $J = 10.9, 1.5$ Hz, 1 H), 4.66 (d, $J = 6.8$ Hz, 1 H), 2.30-2.14 (m, 2 H), 2.02 (dddd, $J = 18.6, 5.4, 5.4, 2.3$ Hz, 1 H), 1.96-1.82 (m, 2 H), 1.68-1.61 (m, 2 H), 1.44-1.39 (m,

1 H), 1.18 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 137.43 (C), 137.38 (C), 135.95 (CH), 129.09 (CH), 128.30 (CH), 126.66 (CH), 126.47 (CH), 113.61 (CH_2), 105.20 (CH), 92.21 (C), 87.54 (CH), 44.53 (C), 41.03 (CH_2), 33.79 (CH_2), 30.63 (CH_2), 22.16 (CH_2), 20.21 (CH_3); HRMS m/z calculated for $\text{C}_{19}\text{H}_{22}\text{O}_2$ 282.1620 (M^+), found 282.1609.



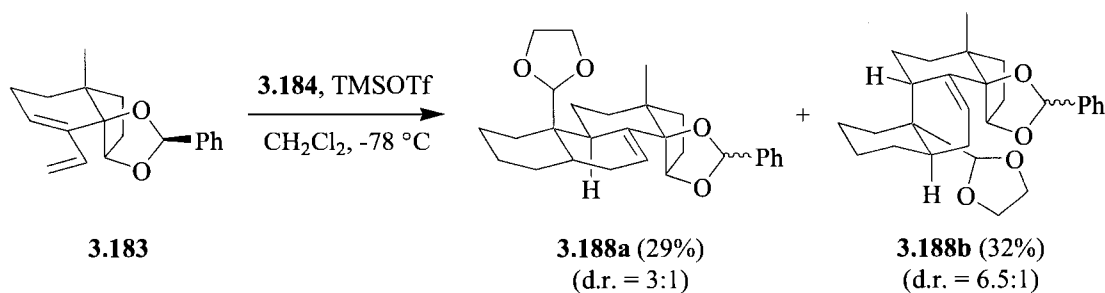
(±)-5-[1,3]Dioxolan-2-yl-2a-methyl-10-phenyl-1,2,2a,3,4,4a,5,6,7,11a-decahydro-9,11-dioxapentaleno[6a,1-a]naphthalene (**3.186**). To a solution of **3.183** (25 mg, 0.089 mmol) and dienophile **3.164** (18 mg, 0.180 mmol) in CH_2Cl_2 (1.8 mL) at $-78\text{ }^\circ\text{C}$ was added TMSOTf (15 μL , 0.083 mmol) dropwise. The mixture was stirred for 30 minutes at $-78\text{ }^\circ\text{C}$. Et_3N was added dropwise until complete discoloration, followed by saturated aqueous NaHCO_3 (2 mL). After warming to room temperature, the aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (2% then 5% EtOAc /hexanes) to afford 8.5 mg of **3.186a** as a pale yellow oil (34% yield) and 10 mg of **3.186b** a white solid (40% yield). Isomer **3.186a** was the major component of a mixture of three compounds: IR (neat) ν_{max} 2932, 2279, 1456, 1397, 1219, 1155, 1123 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.52-7.48 (m, 2 H), 7.38-7.32 (m, 3 H), 5.86 (d, $J = 4.9\text{ Hz}$, 1 H), 5.82 (s, 1 H), 4.76 (d, $J = 7.2\text{ Hz}$, 1 H), 4.69 (d, $J = 5.9\text{ Hz}$, 1 H), 3.99-3.92 (m, 2 H), 3.84 (m, 2 H), 2.22-2.00 (m, 5 H), 1.89-1.70 (m, 3 H), 1.69-1.56 (m, 2 H), 1.53-1.33 (m, 4 H), 1.00 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 138.18 (C), 136.53 (C), 129.24 (CH), 128.31 (CH), 126.79 (CH), 118.95 (CH), 105.99 (CH), 103.15 (CH), 96.08 (C), 85.24 (CH), 64.85 (CH_2), 64.81 (CH_2), 47.79 (C), 41.77 (CH), 37.44 (CH_2), 36.96 (CH), 35.26 (CH_2), 31.44 (CH_2), 24.96 (CH_2), 24.82 (CH_2), 19.91 (CH_2), 19.32 (CH_3); HRMS m/z calculated for $\text{C}_{24}\text{H}_{30}\text{O}_4$ 382.2144 (M^+), found 382.2122. Isomer **3.186b**: mp 135.5-136 $^\circ\text{C}$; IR (neat) ν_{max} 2940, 2873, 1458, 1402, 1220, 1136 cm^{-1} ; ^1H NMR (400 MHz, C_6D_6) δ 7.73-7.69 (m, 2 H), 7.26-7.17 (m, 3 H), 5.95 (s, 1 H), 5.83 (br, 1 H), 4.91 (d, $J = 4.8$

Hz, 1 H), 4.82 (d, $J = 7.2$ Hz, 1 H), 3.61-3.50 (m, 2 H), 3.49-3.41 (m, 2 H), 3.22 (dd, $J = 14.9, 9.1$ Hz, 1 H), 2.13-1.96 (m, 6 H), 1.67-1.49 (m, 2 H), 1.47 (s, 3 H), 1.45-1.17 (m, 5 H); ^{13}C NMR (100 MHz, C_6D_6) δ 139.50 (C), 138.02 (C), 129.00 (CH), 128.16 (CH), 127.29 (CH), 123.08 (CH), 105.72 (CH), 102.78 (CH), 92.25 (C), 84.37 (CH), 64.54 (CH_2), 64.46 (CH_2), 45.52 (C), 41.89 (CH), 39.70 (CH_2), 30.44 (CH_2), 29.94 (CH), 28.48 (CH_2), 25.57 (CH_2), 22.80 (CH_3), 22.15 (CH_2), 18.82 (CH_2); HRMS m/z calculated for $\text{C}_{24}\text{H}_{30}\text{O}_4$ 382.2144 (M^+), found 382.2156. The tridimensional structure of this product was confirmed by X-ray crystallography.

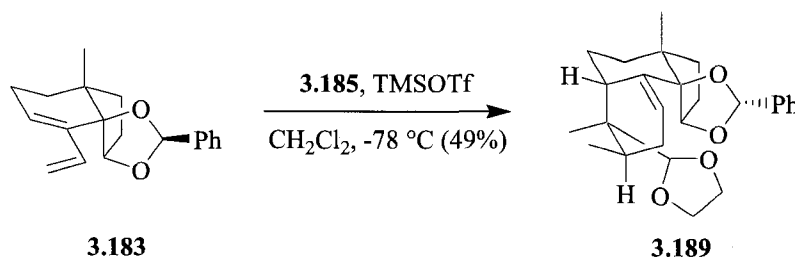


(±)-5-[1,3]Dioxolan-2-yl-2a,5-dimethyl-10-phenyl-1,2,2a,3,4,4a,5,6,7,11a-decahydro-9,11-dioxapentaleno-[6a,1-a]naphthalene (**3.187**). To a solution of **3.183** (40 mg, 0.142 mmol) and dienophile **3.169** (49 mg, 0.429 mmol) in CH_2Cl_2 (2.8 mL) at $-78\text{ }^\circ\text{C}$ was added TMSOTf (25 μL , 0.138 mmol) dropwise.¹⁴⁴ The mixture was stirred for 1.5 h at $-78\text{ }^\circ\text{C}$. Et_3N was added dropwise until complete discoloration, followed by saturated aqueous NaHCO_3 (2 mL). After warming to room temperature, the aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 x 10 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (2% then 5% EtOAc/hexanes) to afford 18 mg of **3.187a** as a colorless oil (32% yield) and 32 mg of **3.187b** as a white solid (57% yield). Isomer **3.187a** was a 2.9:1 mixture of epimers: IR (neat) 2938, 2871, 2766, 1457, 1395, 1222 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.52-7.46 (m, 4 H), 7.38-7.32 (m, 6 H), 5.95 (s, 1 H), 5.94 (s, 1 H), 5.84 (ddd, $J = 3.9, 3.9, 1.5$ Hz, 1 H), 5.78-5.77 (m, 1 H), 4.85 (d, $J = 8.9$ Hz, 1 H), 4.81-4.78 (m, 2 H), 4.67 (s, 1 H), 3.96-3.81 (m, 8 H), 2.24-2.23 (m, 2 H), 2.09-2.02 (m, 2 H), 2.01-1.97 (m, 3 H), 1.88-1.78 (m, 4 H), 1.77-1.66 (m, 2 H), 1.52-1.40 (m, 9 H), 1.38-1.19 (m, 4 H), 1.02 (s, 3 H), 0.99 (s, 3 H), 0.89 (s, 3 H), 0.83 (s, 3 H); ^{13}C NMR (100 MHz,

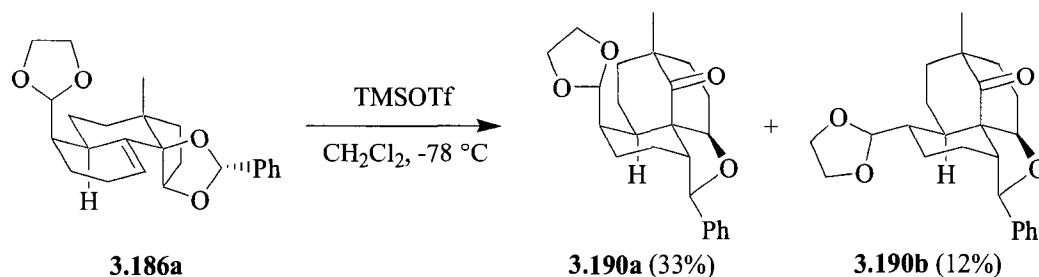
CDCl₃) δ 138.25 (C), 137.92 (C), 136.72 (C), 136.67 (C), 129.16 (CH), 129.07 (CH), 128.22 (CH), 128.22 (CH), 127.30 (CH), 127.07 (CH), 121.70 (CH), 120.11 (CH), 108.24 (CH), 107.75 (CH), 104.31 (CH), 104.00 (CH), 95.79 (C), 95.45 (C), 86.57 (CH), 85.44 (CH), 65.34 (CH₂), 65.23 (CH₂), 65.12 (CH₂), 64.98 (CH₂), 48.78 (C), 47.60 (C), 45.00 (CH), 41.46 (CH), 40.40 (CH₂), 40.15 (CH₂), 38.62 (C), 38.34 (C), 36.26 (CH₂), 35.42 (CH₂), 29.70 (CH₂), 29.50 (CH₂), 27.59 (CH₂), 26.02 (CH₂), 25.30 (CH₂), 23.66 (CH₂), 21.65 (CH₂), 21.52 (CH₂), 19.87 (CH₃), 19.80 (CH₃), 16.70 (CH₃), 16.26 (CH₃); HRMS m/z calculated for C₂₅H₃₂O₄ 396.2301 (M⁺), found 396.2314. Isomer **3.187b** was a 1.5:1 mixture of epimers: mp 115–117 °C; IR (neat) $\nu_{\max}$ 2938, 2880, 1455, 1397 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.53–7.50 (m, 2 H), 7.43–7.40 (m, 2 H), 7.27–7.37 (m, 6 H), 6.10 (s, 1 H), 5.91 (dd, J = 3.4, 3.4 Hz, 1 H), 5.64 (s, 1 H), 5.60 (dd, J = 3.2, 3.2 Hz, 1 H), 4.90 (d, J = 4.7 Hz, 1 H), 4.70 (s, 1 H), 4.67 (d, J = 4.4 Hz, 1 H), 4.66 (s, 1 H), 3.94–3.85 (m, 4 H), 3.84–3.79 (m, 4 H), 2.37 (dd, J = 9.2, 9.2 Hz, 1 H), 2.30 (dd, J = 8.3, 8.3 Hz, 1 H), 2.16–2.11 (m, 2 H), 2.03–1.98 (m, 2 H), 1.97–1.85 (m, 4 H), 1.84–1.66 (m, 4 H), 1.54–1.30 (m, 12 H), 1.28 (s, 3 H), 1.24 (s, 3 H), 0.89 (s, 3 H), 0.85 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 139.73 (C), 138.07 (C), 137.34 (C), 137.17 (C), 129.37 (CH), 128.54 (CH), 128.33 (CH), 128.06 (CH), 127.18 (CH), 126.47 (CH), 121.73 (CH), 120.53 (CH), 108.03 (CH), 107.51 (CH), 104.99 (CH), 102.56 (CH), 93.63 (C), 92.62 (C), 84.17 (CH), 83.58 (CH), 65.27 (CH₂), 65.23 (CH₂), 65.09 (CH₂), 64.97 (CH₂), 45.46 (C), 45.43 (C), 40.49 (CH₂), 39.79 (CH₂), 38.55 (CH), 37.92 (C), 37.87 (C), 36.37 (CH), 33.59 (CH₂), 30.74 (CH₂), 28.46 (CH₂), 28.25 (CH₂), 25.69 (CH₂), 24.21 (CH₂), 23.52 (CH₃), 23.33 (CH₂), 22.88 (CH₂), 22.82 (CH₃), 21.93 (CH₂), 21.93 (CH₂), 16.78 (CH₃), 16.48 (CH₃); HRMS m/z calculated for C₂₅H₃₂O₄ 396.2301 (M⁺), found 396.2319.



Cycloadducts 3.188. To a solution of **3.183** (48 mg, 0.170 mmol) and dienophile **3.184** (52 mg, 0.337 mmol) in CH₂Cl₂ (3.4 mL) at -78 °C was added TMSOTf (31 µL, 0.170 mmol) dropwise.¹⁴⁴ The mixture was stirred for 1 h at -78 °C. Et₃N was added dropwise until complete discoloration, followed by saturated aqueous NaHCO₃ (3 mL). After warming to room temperature, the aqueous layer was separated from the organic layer and extracted with CH₂Cl₂ (3 x 5 mL). Combined organics were dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (2% then 5% EtOAc/hexanes) to afford 21.5 mg of **3.188a** as a colorless oil (29% yield) 24 mg of **3.188b** as a white solid (32% yield). Isomer **3.188a** was a 3:1 mixture of epimers: IR (neat) $\nu_{\max}$ 2918, 2868, 1456, 1393, 1220 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.52-7.48 (m, 4 H), 7.38-7.31 (m, 6 H), 5.95 (s, 1 H), 5.93 (s, 1 H), 5.91-5.88 (m, 1 H), 5.83-5.80 (m, 1 H), 5.07 (br, 1 H), 5.04 (br, 1 H), 4.79 (d, *J* = 8.4 Hz, 1 H), 4.61 (d, *J* = 6.4 Hz, 1 H), 3.96-3.89 (m, 4 H), 3.88-3.82 (m, 4 H), 2.34-2.22 (m, 2 H), 2.20-2.14 (m, 2 H), 2.12-2.00 (m, 6 H), 1.88-1.69 (m, 10 H), 1.56-1.20 (m, 20 H), 1.01 (s, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 138.46, 137.81, 135.40, 128.95, 128.92, 128.19, 128.13, 128.03, 127.02, 126.49, 119.87, 118.05, 106.71, 106.63, 103.88, 103.53, 96.23, 95.43, 86.16, 86.11, 65.72, 65.09, 64.98, 64.87, 64.79, 47.40, 46.60, 40.52, 40.45, 40.16, 37.31, 36.45, 35.75, 34.52, 34.14, 33.88, 31.45, 31.21, 29.38, 28.21, 28.00, 26.89, 25.13, 24.78, 24.42, 22.96, 22.51, 22.12, 19.76, 19.22, 15.13, 13.99; HRMS *m/z* calculated for C₂₈H₃₆O₄ 436.2614 (M⁺), found 436.2609. Isomer **3.188b** was a 6.5:1 mixture of epimers: mp 55-57.5 °C: IR (neat) $\nu_{\max}$ 2928, 2866, 1457, 1394, 1223, 1112, 1068 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) *major* δ 7.55-7.51 (m, 2 H), 7.38-7.31 (m, 3 H), 5.99 (s, 1 H), 5.80 (ddd, *J* = 4.8, 2.5, 2.5 Hz, 1 H), 4.89 (s, 1 H), 4.49 (d, *J* = 7.5 Hz, 1 H), 3.89-3.72 (m, 4 H), 2.65-2.62 (m, 1 H), 2.42-2.35 (m, 1 H), 2.14-2.06 (m, 1 H), 1.87-1.74 (m, 4 H), 1.70-1.64 (m, 4 H), 1.60-1.37 (m, 4 H), 1.36-1.21 (m, 5 H), 1.18 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) *major* δ 137.54 (C), 135.26 (C), 128.81 (CH), 128.16 (CH), 126.50 (CH), 121.89 (CH), 105.20 (CH), 104.05 (CH), 93.72 (C), 89.28 (CH), 65.20 (CH₂), 64.03 (CH₂), 44.88 (C), 42.89 (CH₂), 41.03 (C), 38.11 (CH₂), 35.57 (CH), 34.52 (CH), 30.21 (CH₂), 29.75 (CH₂), 29.68 (CH₂), 26.03 (CH₂), 25.69 (CH₃), 24.12 (CH₂), 21.99 (CH₂), 20.69 (CH₂); HRMS *m/z* calculated for C₂₈H₃₆O₄ 436.2614 (M⁺), found 436.2623.

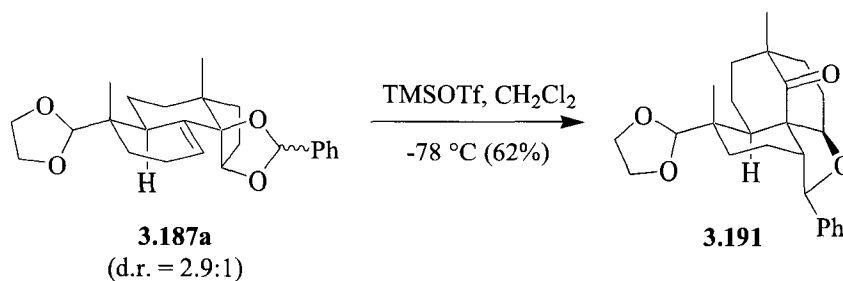


(±)-5-[1,3]Dioxolan-2-yl-2a,5,6-trimethyl-10-phenyl-1,2,2a,3,4,4a,5,6,7,11a-decahydro-9,11-dioxapentaleno[6a,1-a]naphthalene (**3.189**). To a solution of **3.183** (53 mg, 0.188 mmol) and dienophile **3.185** (48 mg, 0.375 mmol) in CH₂Cl₂ (3.8 mL) at -78 °C was added TMSOTf (35 μL, 0.192 mmol) dropwise.¹⁴⁴ The mixture was stirred at -78 °C for 1 h. Et₃N was added dropwise until complete discoloration, followed by saturated aqueous NaHCO₃ (3 mL). After warming to room temperature, the aqueous layer was separated from the organic layer and extracted with CH₂Cl₂ (3 x 5 mL). Combined organics were dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes/EtOAc, 49:1 then 19:1) to afford 38 mg of **3.189** as a pale yellow solid (49% yield): mp 130.5-133 °C; IR (neat) ν_{max} 2948, 2880, 2249, 1454, 1401, 1222 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.54-7.49 (m, 2 H), 7.37-7.32 (m, 3 H), 5.84 (d, J = 4.5 Hz, 1 H), 5.63 (s, 1 H), 4.89 (d, J = 4.7 Hz, 1 H), 4.66 (s, 1 H), 3.95-3.93 (m, 1 H), 3.89-3.74 (m, 3 H), 2.49 (dd, J = 9.4, 9.4 Hz, 1 H), 2.10-2.01 (m, 1 H), 1.98-1.84 (m, 3 H), 1.83-1.63 (m, 3 H), 1.61-1.42 (m, 3 H), 1.28 (s, 3 H), 1.26-1.13 (m, 1 H), 0.94 (d, J = 6.3 Hz, 3 H), 0.78 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 138.24 (C), 137.20 (C), 129.36 (CH), 128.33 (CH), 127.20 (CH), 121.63 (CH), 108.70 (CH), 102.60 (CH), 92.52 (C), 84.08 (CH), 65.22 (CH₂), 64.06 (CH₂), 45.38 (C), 40.46 (C), 39.82 (CH₂), 38.48 (CH), 32.13 (CH₂), 31.12 (CH₂), 28.42 (CH₂), 28.35 (CH), 22.73 (CH₃), 22.63 (CH₂), 16.57 (CH₃), 12.95 (CH₃); HRMS m/z calculated for C₂₆H₃₄O₄ 410.2457 (M⁺), found 410.2428. The tridimensional structure of this product was confirmed by X-ray crystallography.

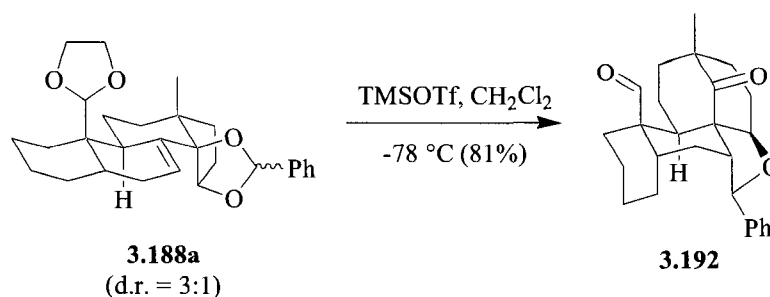


Prins-Pinacol adducts 3.190. To a solution of **3.186a** (21 mg, 0.055 mmol) in CH_2Cl_2 (600 μL) at -78°C was added TMSOTf (20 μL , 0.111 mmol) dropwise. The reaction mixture was stirred at -78°C for 1 h. Et_3N was added dropwise until complete discoloration, followed by saturated aqueous NaHCO_3 (1 mL). After warming to room temperature, the aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% then 10% EtOAc /hexanes) to afford 7 mg of **3.190a** as a pale yellow solid (33% yield) and 2.5 mg of **3.190b** as a pale yellow oil (12% yield). Epimer **3.190a**: mp $135\text{--}139^\circ\text{C}$; IR (neat) ν_{max} 2926, 2867, 1706, 1453, 1116 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.33–7.25 (m, 5 H), 4.65 (d, $J = 7.7$ Hz, 1 H), 4.57 (d, $J = 10.8$ Hz, 1 H), 4.24 (dd, $J = 10.8, 4.9$ Hz, 1 H), 3.92–3.88 (m, 1 H), 3.86–3.82 (m, 1 H), 3.77–3.68 (m, 2 H), 2.59–2.52 (m, 2 H), 2.33–2.23 (m, 1 H), 2.15–2.08 (m, 2 H), 2.05 (dd, $J = 13.9, 4.7$ Hz, 1 H), 1.95–1.90 (m, 1 H), 1.85–1.81 (m, 1 H), 1.77–1.71 (m, 3 H), 1.70–1.64 (m, 1 H), 1.54–1.50 (m, 1 H), 1.32–1.22 (m, 2 H), 1.06 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 219.95 (C), 139.80 (C), 128.37 (CH), 128.06 (CH), 127.07 (CH), 102.77 (CH), 88.85 (CH), 82.33 (CH), 64.90 (CH_2), 63.81 (CH_2), 57.48 (C), 46.87 (CH), 45.34 (C), 44.37 (CH), 43.88 (CH), 40.39 (CH_2), 34.00 (CH_2), 28.17 (CH_2), 25.27 (CH_3), 24.05 (CH_2), 22.45 (CH_2), 18.00 (CH_2); HRMS m/z calculated for $\text{C}_{24}\text{H}_{30}\text{O}_4$ 382.2144 (M^+), found 382.2165. Epimer **3.190b**: IR (neat) ν_{max} 2918, 2868, 1712, 1455 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.32–7.25 (m, 5 H), 4.85 (d, $J = 2.8$ Hz, 1 H), 4.46 (d, $J = 10.9$ Hz, 1 H), 4.34 (dd, $J = 11.6, 5.0$ Hz, 1 H), 3.97–3.89 (m, 2 H), 3.87–3.79 (m, 2 H), 2.44–2.38 (m, 1 H), 2.26 (dd, $J = 11.0, 4.6$ Hz, 1 H), 2.17–2.12 (m, 1 H), 2.11–2.06 (m, 1 H), 2.03 (dd, $J = 14.3, 4.6$ Hz, 1 H), 1.93 (d, $J = 15.6$ Hz, 1 H), 1.73 (ddd, $J = 14.1, 5.6, 2.4$ Hz, 1 H), 1.70–1.66 (m, 2 H), 1.64–1.59 (m, 3 H), 1.43–1.38 (m, 1 H), 1.35–1.28 (m, 1 H), 1.26–1.17 (m, 1 H), 1.06 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 218.28 (C), 139.50 (C), 128.19 (CH), 127.85 (CH), 126.71 (CH),

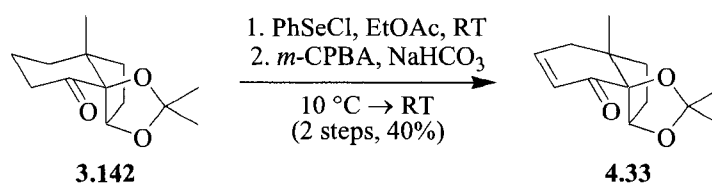
105.26 (CH), 85.58 (CH), 82.76 (CH), 64.97 (CH₂), 64.64 (CH₂), 59.60 (C), 45.34 (CH), 45.16 (C), 45.08 (CH), 39.46 (CH₂), 36.73 (CH), 33.13 (CH₂), 28.41 (CH₂), 24.60 (CH₃), 21.30 (CH₂), 20.48 (CH₂), 19.50 (CH₂); HRMS m/z calculated for C₂₄H₃₀O₄ 382.2144 (M⁺), found 382.2152.



Prins-Pinacol adduct 3.191. To a solution of **3.187a** (21 mg, 0.053 mmol) in CH₂Cl₂ (530 μ L) at -78 $^\circ$ C was added TMSOTf (20 μ L, 0.111 mmol) dropwise. The reaction mixture was stirred at -78 $^\circ$ C for 1 h. Et₃N was added dropwise until complete discoloration, followed by saturated aqueous NaHCO₃ (1 mL). After warming up to room temperature, the aqueous layer was separated from the organic layer and extracted with CH₂Cl₂ (3 x 5 mL). Combined organics were dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% then 10% EtOAc/hexanes) to afford 13 mg of **3.191** as colorless oil (62% yield): IR (neat) ν_{max} 2936, 2867, 1709, 1455 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.25 (m, 5 H), 4.69 (s, 1 H), 4.57 (d, J = 10.9 Hz, 1 H), 4.28 (dd, J = 10.9, 5.0 Hz, 1 H), 3.96-3.91 (m, 2 H), 3.91-3.81 (m, 2 H), 2.52-2.48 (m, 2 H), 2.15-2.04 (m, 3 H), 2.01 (ddd, J = 13.6, 13.6, 4.5 Hz, 1 H), 1.86-1.80 (m, 1 H), 1.76-1.69 (m, 3 H), 1.46 (ddd, J = 13.5, 13.5, 3.8 Hz, 1 H), 1.41-1.35 (m, 1 H), 1.30-1.20 (m, 2 H), 1.06 (s, 3 H), 0.85 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 220.43 (C), 140.25 (C), 128.73 (CH), 128.40 (CH), 127.43 (CH), 109.73 (CH), 88.92 (CH), 82.35 (CH), 65.63 (CH₂), 65.39 (CH₂), 58.22 (C), 48.44 (C), 45.44 (C), 44.66 (CH), 41.42 (C), 41.28 (CH₂), 34.50 (CH₂), 28.50 (CH₂), 28.14 (CH₂), 25.56 (CH₃), 18.55 (CH₂), 17.53 (CH₂), 17.12 (CH₃); HRMS m/z calculated for C₂₅H₃₂O₄ 396.2301 (M⁺), found 396.2300.

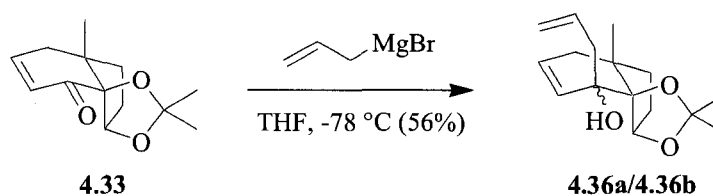


Prins-Pinacol adduct 3.192. To a solution of **3.188a** (22 mg, 0.050 mmol) in CH_2Cl_2 (500 μL) at $-78\text{ }^{\circ}\text{C}$ was added TMSOTf (20 μL , 0.111 mmol). The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h. Et_3N was added dropwise until complete discoloration, followed by saturated aqueous NaHCO_3 (2 mL). After warming to room temperature, the aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% then 10% EtOAc/hexanes) to afford 16 mg of **3.192** as a white solid (81% yield): mp $161\text{--}164\text{ }^{\circ}\text{C}$; IR (neat) ν_{max} 2926, 2866, 1725, 1710, 1455, 1051 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.38 (s, 1 H), 7.36–7.27 (m, 5 H), 4.69 (d, $J = 11.3$ Hz, 1 H), 4.27 (dd, $J = 12.1, 4.8$ Hz, 1 H), 2.53 (dd, $J = 11.3, 5.8$ Hz, 1 H), 2.34 (d, $J = 7.2$ Hz, 1 H), 2.11–1.96 (m, 5 H), 1.79–1.70 (m, 4 H), 1.50–1.45 (m, 2 H), 1.38–1.30 (m, 6 H), 1.28–1.14 (m, 2 H), 1.07 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 219.17 (C), 206.68 (CH), 138.96 (C), 128.34 (CH), 128.15 (CH), 126.79 (CH), 88.15 (CH), 81.29 (CH), 54.96 (C), 54.40 (C), 46.76 (CH), 44.80 (C), 44.32 (CH), 41.38 (CH_2), 32.80 (CH_2), 31.28 (CH), 29.04 (CH_2), 28.28 (CH_2), 24.77 (CH_3), 21.64 (CH_2), 21.64 (CH_2), 20.70 (CH_2), 18.45 (CH_2), 18.08 (CH_2), HRMS m/z calculated for $\text{C}_{26}\text{H}_{32}\text{O}_3$ 392.2351 (M^+), found 392.2329.



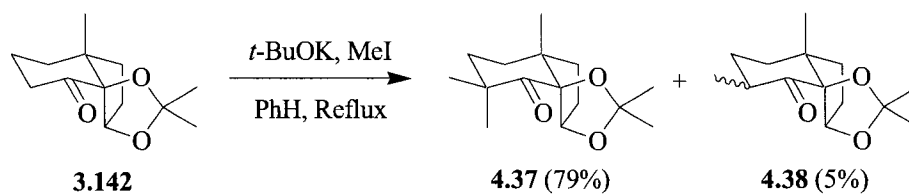
(±)-2,2,5a-Trimethyl-4,5,5a,6-tetrahydro-3aH-1,3-dioxacyclopenta[c]inden-9-one (**4.33**). *Step 1:* To a solution of **3.142** (25 mg, 0.111 mmol) in EtOAc (500 μL) at room temperature was

added a solution of PhSeCl (23 mg, 0.120 mmol) in EtOAc (600 μ L) via cannula. After stirring for 19 h, the reaction mixture was quenched with saturated aqueous NaHCO₃ (1 mL). The aqueous layer was separated from the organic layer and extracted with EtOAc (3 x 5 mL). Combined organics were washed with saturated NaHCO₃ and saturated aqueous NaCl, and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was passed through a short silica gel plug (eluting with 10% EtOAc/hexanes) to afford the corresponding selenide as a pale yellow solid. *Step 2:* To a stirred mixture of the selenide, saturated aqueous NaHCO₃ (1 mL) and AcOEt (1 mL) at 10 °C was added *m*-CPBA (77%, 40 mg, 0.178 mmol) in small portions over 15 minutes. The reaction mixture was then warmed up to room temperature over 1 h. The mixture was extracted with EtOAc (5 x 5 mL). Combined organics were dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by gel column chromatography (5% then 10% EtOAc/hexanes) to afford 10 mg of **4.33** as a pale yellow oil (40% yield over 2 steps): IR (neat) $\nu_{\max}$ 2936, 2874, 1683, 1463, 1378, 1238 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.77 (ddd, *J* = 10.1, 5.4, 2.9 Hz, 1 H), 6.05 (ddd, *J* = 10.1, 2.9, 1.1 Hz, 1 H), 4.73 (dd, *J* = 7.9, 1.4 Hz, 1 H), 2.42 (ddd, *J* = 19.8, 2.9, 2.9 Hz, 1 H), 2.24 (ddd, *J* = 19.8, 0.9, 0.8 Hz, 1 H), 2.13-2.06 (m, 1 H), 2.05-1.95 (m, 1 H), 1.82 (dddd, *J* = 14.4, 7.9, 1.7, 1.5 Hz, 1 H), 1.62 (s, 3 H), 1.51 (ddd, *J* = 12.4, 7.5, 1.8 Hz, 1 H), 1.48 (s, 3 H), 1.17 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 197.45 (C), 147.08 (CH), 128.12 (CH), 113.95 (C), 95.22 (C), 86.01 (CH), 48.66 (C), 37.43 (CH₂), 36.73 (CH₂), 32.37 (CH₂), 27.73 (CH₃), 27.60 (CH₃), 21.06 (CH₃); HRMS *m/z* calculated for C₁₂H₁₅O₃ 207.1021 (M⁺ - Me), found 207.1020.

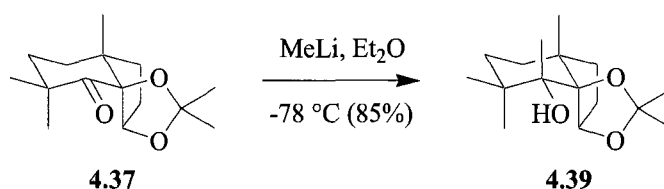


(±)-9-Allyl-2,2,5a-trimethyl-3a,4,5,5a,6,9-hexahydro-1,3-dioxacyclopenta[*c*]inden-9-ol (**4.36**). To a solution of **4.33** (18 mg, 0.081 mmol) in THF (1 mL) at -78 °C was added allylmagnesium bromide (200 μ L of a 1.0 M solution in THF, 0.200 mmol) dropwise. The resulting mixture was stirred for 1 h, and was quenched with saturated aqueous NH₄Cl (1 mL). After warming up to room temperature, the aqueous layer was separated from the organic layer and

extracted with Et₂O (3 x 5 mL). Combined organics were washed with brine and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (2% then 5% EtOAc/hexanes) to afford 7 mg of **4.36a** as a pale yellow oil (33% yield) and 5 mg of **4.36b** as a yellow oil (23% yield). Epimer **4.36a**: IR (neat) $\nu_{\max}$ 3525 (br), 2937, 1376, 1237 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.04-5.96 (m, 1 H), 5.86-5.82 (m, 1 H), 5.80-5.78 (m, 1 H), 5.14 (d, J = 10.3 Hz, 1 H), 5.10 (d, J = 17.4 Hz, 1 H), 4.53 (d, J = 6.5 Hz, 1 H), 2.71 (dd, J = 13.9, 5.8 Hz, 2 H), 2.25 (dd, J = 13.9, 8.4 Hz, 1 H), 2.14 (dd, J = 17.4, 4.4 Hz, 1 H), 2.05-1.97 (m, 2 H), 1.85-1.77 (m, 1 H), 1.70 (dd, J = 14.6, 8.0 Hz, 1 H), 1.53 (s, 3 H), 1.51 (s, 3 H), 1.19 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 134.63 (CH), 130.77 (CH), 129.31 (CH), 118.59 (CH₂), 111.34 (C), 97.65 (C), 84.92 (CH), 71.94 (C), 44.72 (C), 42.67 (CH₂), 40.01 (CH₂), 38.47 (CH₂), 31.10 (CH₂), 30.11 (CH₃), 28.92 (CH₃), 24.77 (CH₃); HRMS m/z calculated for C₁₆H₂₄O₃ (M⁺) 264.1725, found 264.1717. Epimer **4.36b**: IR (neat) $\nu_{\max}$ 3496 (br), 2938, 1637, 1461, 1377, 1238 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.96-5.85 (m, 1 H), 5.72 (ddd, J = 10.0, 5.5, 3.4 Hz, 1 H), 5.59 (ddd, J = 9.9, 2.7, 0.8 Hz, 1 H), 5.14-5.07 (m, 2 H), 4.65-4.64 (m, 1 H), 2.55 (dd, J = 13.9, 7.8 Hz, 1 H), 2.38 (ddd, J = 7.0, 7.0, 1.1 Hz, 1 H), 2.17-2.09 (m, 2 H), 2.08-1.97 (m, 3 H), 1.72-1.51 (m, 7 H), 1.47 (s, 6 H), 1.15 (s, 3 H), 0.91-0.82 (m, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 134.38 (CH), 133.10 (CH), 127.30 (CH), 118.65 (CH₂), 110.81 (C), 98.20 (C), 85.84 (CH), 73.88 (C), 44.03 (C), 42.37 (CH₂), 41.19 (CH₂), 39.67 (CH₂), 30.94 (CH₂), 28.05 (CH₃), 27.87 (CH₃), 25.01 (CH₃); HRMS m/z calculated for C₁₆H₂₄O₃ 264.1725 (M⁺), found 264.1724.

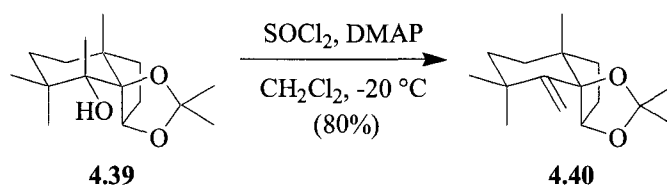


The reaction mixture turned cloudy yellow and was further refluxed for 2 h. After cooling down to room temperature, it was quenched with H₂O (5 mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 10 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% then 20% EtOAc/hexanes) to afford 352 mg of **4.37** as a pale yellow oil (79% yield) and 22 mg of **4.38** as a white solid (5% yield). Ketone **4.37**: IR (neat) $\nu_{\max}$ 2936, 2864, 1712, 1459, 1378, 1212 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.81 (d, J = 6.0 Hz, 1 H), 2.19-2.10 (m, 1 H), 1.90-1.77 (m, 4 H), 1.57-1.48 (m, 3 H), 1.46 (s, 3 H), 1.39 (s, 3 H), 1.12 (s, 3 H), 1.11 (s, 3 H), 1.08 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 21.34 (CH₃), 24.98 (CH₃), 26.45 (CH₃), 26.67 (CH₃), 27.08 (CH₃), 30.64 (CH₂), 30.78 (CH₂), 34.85 (CH₂), 38.44 (CH₂), 44.69 (C), 49.67 (C), 85.51 (CH), 96.55 (C), 112.53 (C), 213.89 (C); HRMS m/z calculated for C₁₅H₂₄O₃ 252.1725 (M⁺), found 252.1716. Ketone **4.38**: mp 68-70 °C; IR (neat) $\nu_{\max}$ 2934, 2866, 1719, 1458, 1378, 1238 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.81 (d, J = 7.3 Hz, 1 H), 2.49-2.41 (m, 1 H), 2.31-2.23 (m, 1 H), 1.95-1.85 (m, 2 H), 1.84-1.76 (m, 2 H), 1.59-1.47 (m, 3 H), 1.46 (s, 3 H), 1.38 (s, 3 H), 1.05-1.04 (m, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 210.84 (C), 112.52 (C), 98.94 (C), 85.58 (CH), 53.47 (C), 43.38 (CH), 37.88 (CH₂), 34.29 (CH₂), 32.26 (CH₂), 32.09 (CH₂), 27.80 (CH₃), 27.79 (CH₃), 19.71 (CH₃), 14.43 (CH₃); HRMS m/z calculated for C₁₃H₁₉O₃ 223.1334 (M⁺ - Me), found 223.1246.

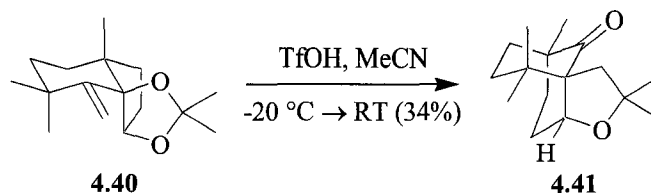


(±)-2,2,5a,8,8,9-Hexamethyloctahydro-1,3-dioxacyclopenta[c]inden-9-ol (**4.39**). To a solution of **4.37** (352 mg, 1.39 mmol) in Et₂O (14 mL) at -78 °C was added MeLi (4.60 mL of a 1.5 M solution in Et₂O, 6.90 mmol) dropwise. After stirring at that temperature for 30 minutes, the reaction mixture was warmed up to room temperature and quenched with saturated aqueous NH₄Cl (10 mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 10 mL). Combined organics were dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography

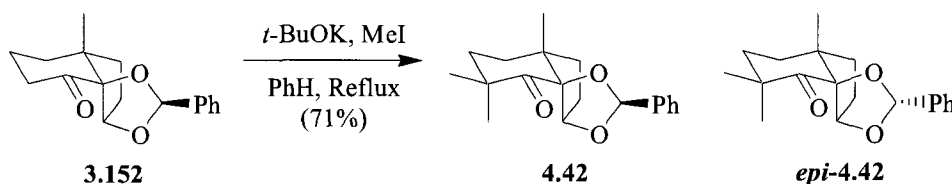
(5% then 10% EtOAc/hexanes) to afford 319 mg of **4.39** as a white solid (85% yield): mp 66-67 °C; IR (neat) $\nu_{\max}$ 3504 (br), 2941, 2866, 1461, 1377, 1241 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.90 (d, $J = 7.2$ Hz, 1 H), 2.05-1.97 (m, 1 H), 1.88-1.82 (m, 1 H), 1.62-1.50 (m, 4 H), 1.45 (s, 3 H), 1.44 (s, 3 H), 1.41-1.32 (m, 1 H), 1.29 (s, 3 H), 1.23-1.12 (m, 2 H), 1.06 (s, 3 H), 0.97 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 110.22 (C), 98.16 (C), 85.53 (CH), 77.80 (C), 45.77 (C), 39.72 (CH_2), 39.46 (C), 32.83 (CH_2), 30.69 (CH_2), 29.39 (CH_2), 28.41 (CH_3), 28.22 (CH_3), 28.22 (CH_3), 26.99 (CH_3), 22.85 (CH_3), 21.57 (CH_3); HRMS m/z calculated for $\text{C}_{15}\text{H}_{25}\text{O}_3$ 253.1804 ($\text{M}^+ - \text{Me}$), found 253.1840.



(±)-2,2,5a,8,8-Pentamethyl-9-methyleneoctahydro-1,3-dioxacyclopenta[c]indene (**4.40**). Thionyl chloride (20 μL , 0.275 mmol) was added dropwise to a solution of **4.39** (31 mg, 0.116 mmol) and DMAP (84 mg, 0.688 mmol) in CH_2Cl_2 (1.2 mL) at -20 °C. After stirring at that temperature for 25 minutes, the reaction mixture was warmed up to room temperature and quenched with saturated aqueous NaHCO_3 (1 mL). The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% EtOAc/hexanes) to afford 24 mg of **4.40** as a pale yellow oil (80% yield): IR (neat) $\nu_{\max}$ 2937, 2872, 1466, 1371, 1237, 1211 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.38 (d, $J = 1.5$ Hz, 1 H), 5.04 (d, $J = 1.5$ Hz, 1 H), 4.72 (d, $J = 6.5$ Hz, 1 H), 2.18-2.08 (m, 1 H), 1.89-1.80 (m, 3 H), 1.46 (s, 3 H), 1.39 (s, 3 H), 1.37-1.20 (m, 4 H), 1.14 (s, 3 H), 1.05 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.47 (C), 110.10 (CH_2), 109.83 (C), 96.59 (C), 86.50 (CH), 47.61 (C), 38.36 (CH_2), 37.43 (C), 36.71 (CH_2), 32.05 (CH_2), 31.66 (CH_3), 31.29 (CH_2), 28.54 (CH_3), 27.94 (CH_3), 27.47 (CH_3), 20.77 (CH_3); HRMS m/z calculated for $\text{C}_{16}\text{H}_{26}\text{O}_2$ 250.1933 (M^+), found 250.1954.

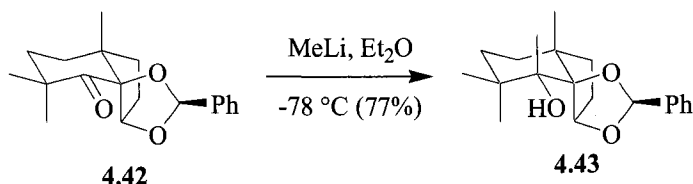


(±)-3,3,8,11,11-Pentamethyl-4-oxatricyclo[6.3.1.0^{4,5}]dodecan-12-one (**4.41**). To a solution of **4.40** (17.7 mg, 0.071 mmol) in MeCN (800 μL) at -20 $^{\circ}\text{C}$ was added TfOH (15 μL , 0.170 mmol) dropwise. The resulting solution was stirred at -20 $^{\circ}\text{C}$ for 20 minutes, warmed up to room temperature, and stirred for 40 minutes. Et₃N was added dropwise until complete discoloration, followed by saturated aqueous NaHCO₃ (1 mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 5 mL). Combined organics were dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (2% → 5% EtOAc/hexanes) to afford 6.1 mg of **4.41** as a yellow oil (34% yield): IR (neat) ν_{max} 2967, 2929, 2872, 1713, 1455, 1374 cm^{-1} ; ¹H NMR (500 MHz, CDCl₃) δ 4.38 (br, 1 H), 2.66 (d, J = 12.5 Hz, 1 H), 2.33-2.24 (m, 1 H), 2.16 (ddd, J = 14.1, 14.1, 6.5 Hz, 1 H), 1.98-1.91 (m, 1 H), 1.88-1.70 (m, 4 H), 1.45 (d, J = 12.5 Hz, 1 H), 1.30 (dd, J = 14.5, 6.4 Hz, 1 H), 1.21 (s, 3 H), 1.19 (s, 3 H), 1.05 (s, 3 H), 0.97 (s, 3 H), 0.69 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 217.16 (C), 81.70 (CH), 78.03 (C), 65.59 (C), 44.93 (C), 40.20 (C), 38.67 (CH₂), 38.00 (CH₂), 37.18 (CH₂), 35.98 (CH₂), 29.11 (CH₃), 29.05 (CH₃), 26.01 (CH₂), 25.58 (CH₃), 25.19 (CH₃), 25.08 (CH₃); HRMS m/z calculated for C₁₆H₂₆O₂ 250.1933 (M^{+}), found 250.1954.



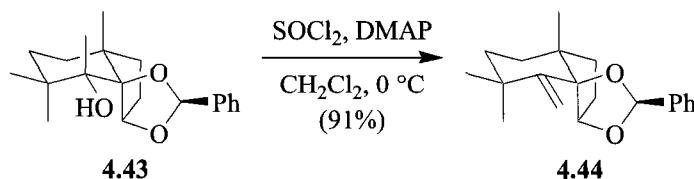
(±)-5a,8,8-Trimethyl-2-phenylhexahydro-1,3-dioxo-cyclopenta[c]inden-9-one (**4.42**). To a solution of **3.152** (267 mg, 0.98 mmol) in benzene (9 mL) was added *t*-BuOK (3.40 mL of a 1.0 M solution in THF, 3.40 mmol) dropwise. The brown resulting mixture was refluxed for 10 minutes, and a solution of MeI (310 μL , 4.98 mmol) in benzene (1 mL) was added dropwise via cannula. The reaction mixture turned pale brown and was further refluxed for

1.5 h. After cooling down to room temperature, it was quenched with H₂O (5 mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 10 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% EtOAc/hexanes) to afford 212 mg of **4.42** as a pale yellow solid (71% yield): mp 84.5-87.5 °C; IR (neat) $\nu_{\max}$ 2944, 2867, 1710, 1459, 1089 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.75 (dd, J = 7.8, 1.7 Hz, 2 H), 7.41-7.35 (m, 3 H), 5.92 (s, 1 H), 5.02 (d, J = 7.9 Hz, 1 H), 2.45-2.34 (m, 1 H), 1.97-1.79 (m, 4 H), 1.67 (dd, J = 13.2, 8.7 Hz, 1 H), 1.61-1.57 (m, 1 H), 1.49-1.44 (m, 1 H), 1.22 (s, 3 H), 1.19 (s, 3 H), 1.15 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 212.92 (C), 137.10 (C), 129.70 (CH), 128.40 (CH), 127.83 (CH), 106.02 (CH), 96.12 (C), 87.66 (CH), 50.79 (C), 44.62 (C), 40.56 (CH₂), 34.68 (CH₂), 30.58 (CH₂), 30.49 (CH₂), 27.02 (CH₃), 26.62 (CH₃), 20.97 (CH₃); HRMS m/z calculated for C₁₂H₁₈O 178.1358 (M⁺ - PhCO₂H), found 178.1347. On large scale, **epi-4.42** was also obtained in minute amounts as a white solid: mp 122-126 °C; IR (neat) $\nu_{\max}$ 2959, 2868, 1712, 1458, 1385, 1220 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 7.32-7.28 (m, 5 H), 5.91 (s, 1 H), 5.21 (dd, J = 8.6, 1.7 Hz, 1 H), 2.27-2.16 (m, 2 H), 1.99-1.91 (m, 1 H), 1.80-1.71 (m, 2 H), 1.65 (ddd, J = 14.2, 5.4, 2.0 Hz, 1 H), 1.55-1.52 (m, 1 H), 1.44 (ddd, J = 13.1, 5.2, 2.0 Hz, 1 H), 1.07 (s, 3 H), 1.06 (s, 3 H), 0.75 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 211.28 (C), 137.63 (C), 129.35 (CH), 128.20 (CH), 127.24 (CH), 105.01 (CH), 95.19 (C), 79.39 (CH), 48.00 (C), 45.11 (C), 37.48 (CH₂), 36.64 (CH₂), 29.19 (CH₂), 28.58 (CH₃), 28.32 (CH₂), 27.24 (CH₃), 19.31 (CH₃); HRMS (EI) calculated for C₁₉H₂₄O₃ 300.1725 (M⁺), found 300.1733.



(±)-5a,8,8,9-Tetramethyl-2-phenyloctahydro-1,3-dioxacyclopenta[c]inden-9-ol (**4.43**). To a solution of **4.42** (224 mg, 0.75 mmol) in Et₂O (7.5 mL) at -78 °C was added MeLi (2 mL of a 1.5 M solution in Et₂O, 3.00 mmol) dropwise. After stirring at that temperature for 30 minutes, the reaction mixture was warmed up to room temperature and quenched with

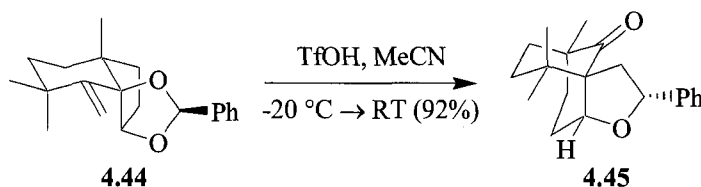
saturated aqueous NH_4Cl (5 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (2% then 4% EtOAc /hexanes) to afford 181 mg of **4.43** as a white solid (77% yield): mp 64.5–66.5 °C; IR (neat) ν_{max} 3587, 2941, 2868, 1459, 1386, 1218 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.54–7.52 (m, 2 H), 7.39–7.34 (m, 3 H), 5.92 (s, 1 H), 5.16 (d, J = 7.3 Hz, 1 H), 2.27–2.17 (m, 1 H), 1.81–1.71 (m, 3 H), 1.70–1.52 (m, 3 H), 1.32 (s, 3 H), 1.26–1.20 (m, 2 H), 1.18 (s, 3 H), 1.06 (s, 3 H), 1.01 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 138.36 (C), 128.84 (CH), 128.22 (CH), 126.18 (CH), 103.10 (CH), 97.45 (C), 85.43 (CH), 77.05 (C), 46.11 (C), 42.01 (CH_2), 38.92 (C), 32.94 (CH_2), 30.98 (CH_2), 28.51 (CH_2), 27.10 (CH_3), 22.32 (CH_3), 22.13 (CH_3), 21.81 (CH_3); HRMS m/z calculated for $\text{C}_{20}\text{H}_{28}\text{O}_3$ 316.2038 (M^+), found 316.2039.



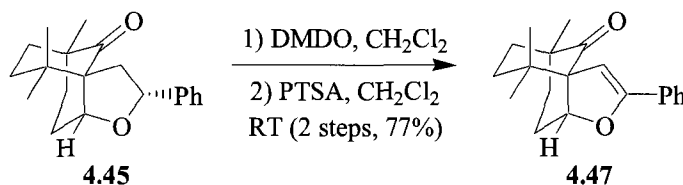
(±)-5a,8,8-Trimethyl-9-methylene-2-phenyloctahydro-1,3-dioxacyclopenta[c]indene (4.44).

Thionyl chloride (1.30 mL, 17.82 mmol) was added dropwise to a solution of **4.43** (2.77 g, 2.77 mmol) and DMAP (6.42 mg, 52.55 mmol) in CH_2Cl_2 (90 mL) at 0 °C. After stirring for 30 minutes at 0 °C, the reaction mixture was warmed up to room temperature and quenched with saturated aqueous NaHCO_3 (50 mL). The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 x 50 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (2% then 4% EtOAc /hexanes) to afford 2.38 g of **4.44** as a pale yellow oil (91% yield): IR (neat) ν_{max} 2940, 2871, 1629, 1455, 1393, 1220, 1143 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.08 (s, 3 H), 1.11 (s, 3 H), 1.17 (s, 3 H), 1.24–1.32 (m, 2 H), 1.53–1.60 (m, 2 H), 1.67–1.88 (m, 3 H), 2.27–2.36 (m, 1 H), 4.87 (d, J = 7.9 Hz, 1 H), 5.02 (d, J = 1.6 Hz, 1 H), 5.29 (d, J = 1.6 Hz, 1 H), 5.96 (s, 1 H), 7.32–7.38 (m, 3 H), 7.51–7.54 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 20.59 (CH_3), 28.37 (CH_3), 29.65 (CH_2), 31.37 (CH_2), 31.53 (CH_3), 35.33 (CH_2), 36.69 (C), 40.79 (CH_2), 47.50 (C), 87.66 (CH), 94.76 (C), 103.33

(CH), 110.65 (CH₂), 126.75 (CH), 128.09 (CH), 128.88 (CH), 137.57 (C), 153.52 (C); HRMS m/z calculated for C₂₀H₂₆O₂ 298.1933 (M⁺), found 298.1941.

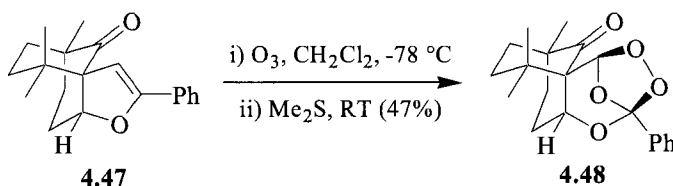


(±)-8,11,11-Trimethyl-3-phenyl-4-oxatricyclo[6.3.1.0^{1,5}]dodecan-12-one (**4.45**). To a solution of **4.44** (60 mg, 0.20 mmol) in MeCN (2 mL) at -20 °C was added TfOH (40 μL, 0.45 mmol) dropwise. The resulting solution was stirred at -20 °C for 45 minutes. Et₃N was added dropwise until complete discoloration, followed by saturated aqueous NaHCO₃ (2 mL). After warming up to room temperature, the aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 5 mL). Combined organics were dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% EtOAc/hexanes) to afford 55 mg of **4.45** as a white solid (92% yield): mp 112-116 °C; IR (neat) $\nu_{\max}$ 2963, 2925, 2863, 1714, 1459 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.32-7.26 (m, 4 H), 7.24-7.21 (m, 1 H), 4.71 (dd, J = 9.1, 7.6 Hz, 1 H), 4.42 (dd, J = 5.7, 5.7 Hz, 1 H), 2.69 (dd, J = 13.3, 9.1 Hz, 1 H), 2.32-2.25 (m, 1 H), 2.10 (ddd, J = 13.8, 13.8, 6.1 Hz, 1 H), 2.01 (dd, J = 13.4, 7.6 Hz, 1 H), 1.95-1.85 (m, 2 H), 1.85-1.70 (m, 2 H), 1.67-1.60 (m, 1 H), 1.31 (ddd, J = 14.4, 5.4, 1.7 Hz, 1 H), 1.14 (s, 3 H), 1.04 (s, 3 H), 0.78 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 216.66 (C), 141.53 (C), 128.15 (CH), 127.46 (CH), 126.51 (CH), 83.28 (CH), 79.99 (CH), 65.07 (C), 44.34 (C), 40.70 (C), 37.42 (CH₂), 36.27 (CH₂), 35.22 (CH₂), 34.52 (CH₂), 27.20 (CH₂), 25.62 (CH₃), 25.04 (CH₃), 24.432 (CH₃); HRMS m/z calculated for C₂₀H₂₆O₂ 298.1933 (M⁺), found 298.1909.



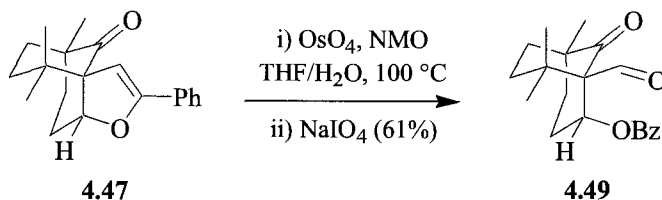
(±)-8,11,11-Trimethyl-3-phenyl-4-oxatricyclo[6.3.1.0^{1,5}]dodec-2-en-12-one (**4.47**). *Step 1:* To a solution of **4.45** (450 mg, 1.51 mmol) in CH₂Cl₂ (1.5 mL) at 0° C was added DMSO (90.6

mL of a 0.1 M solution in acetone, 9.06 mmol) dropwise. The resulting solution was stirred at 0 °C for 1 h. It was then warmed up to room temperature and stirred for 1 h. The reaction mixture was diluted with CH₂Cl₂ (50 mL) and dried over MgSO₄. After filtration, the solvent was removed under reduced pressure to deliver crude lactol **4.46**. *Step 2*: To a solution of this lactol in CH₂Cl₂ (15 mL) at room temperature were added PTSA (574 mg, 3.02 mmol) and 4 Å molecular sieves (450 mg). After stirring for 24 h, the cloudy reaction mixture was filtered through a fritted glass funnel. The reaction flask was rinsed with CH₂Cl₂ (15 mL). The filtrate was neutralized with saturated aqueous NaHCO₃ (20 mL). The aqueous layer was separated from the organic layer and extracted with CH₂Cl₂ (3 x 20 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% EtOAc/hexanes) to afford 344 mg of **4.47** as a white solid (77% yield over 2 steps): mp 78.5-79 °C; IR (neat) ν_{max} 2963, 2861, 1715, 1648, 1449, 1285 cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ 7.79-7.76 (m, 2 H), 7.23-7.13 (m, 3 H), 5.72 (s, 1 H), 4.81 (dd, *J* = 11.5, 5.1 Hz, 1 H), 1.95-1.91 (m, 1 H), 1.56-1.39 (m, 3 H), 1.34-1.26 (m, 3 H), 1.13 (s, 3 H), 0.98-0.95 (m, 1 H), 0.93 (s, 3 H), 0.91 (s, 3 H); ¹³C NMR (125 MHz, C₆D₆) δ 214.32 (C), 155.41 (C), 130.93 (C), 128.34 (CH), 128.09 (CH), 125.53 (CH), 94.09 (CH), 82.99 (CH), 70.48 (C), 43.67 (C), 41.92 (C), 38.45 (CH₂), 31.85 (CH₂), 30.86 (CH₂), 27.66 (CH₂), 24.93 (CH₃), 24.81 (CH₃), 22.26 (CH₃); HRMS *m/z* calculated for C₂₀H₂₄O₂ 296.1776 (M⁺), found 296.1791.



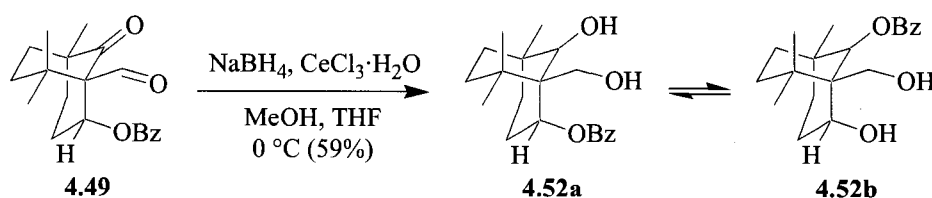
(±)-8,11,11-Trimethyl-3-phenyl-4-oxa-tricyclo[6.3.1.0^{1,5}]dodec-2-en-12-one (**4.48**). Through a solution of **4.47** (15 mg, 0.051 mmol) in CH₂Cl₂ (3 mL) at -78 °C was bubbled ozone for 5 minutes, at which point the solution turned clear blue. Oxygen was then bubbled through the solution for 5 minutes and the blue color disappeared. Me₂S (20 μL, 0.270 mmol) was added dropwise. The solution was warmed up to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (5%

EtOAc/hexanes) to afford 8.2 mg of **4.48** as a white solid (47% yield): mp 102-105 °C; IR (neat) $\nu_{\max}$ 2968, 2933, 2874, 1712, 1449, 1324, 1172, 1121 cm^{-1} ; ^1H NMR (500 MHz, C_6D_6) δ 8.04-8.01 (m, 2 H), 7.24-7.20 (m, 3 H), 6.52 (s, 1 H), 4.43 (dd, $J = 13.4, 3.8$ Hz, 1 H), 2.14 (dddd, $J = 13.4, 13.4, 13.4, 5.2$ Hz, 1 H), 1.92 (dddd, $J = 12.5, 4.2, 4.2, 4.2$ Hz, 1 H), 1.53 (ddd, $J = 14.3, 14.3, 5.3$ Hz, 1 H), 1.37-1.30 (m, 2 H), 1.25 (ddd, $J = 14.0, 14.0, 4.5$ Hz, 1 H), 1.17 (dddd, $J = 13.6, 1.8, 1.8, 1.8$ Hz, 1 H), 1.13 (s, 3 H), 1.04 (s, 3 H), 0.79 (s, 3 H), 0.68 (dddd, $J = 14.9, 1.8, 1.8, 1.8$ Hz, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 213.38 (C), 132.15 (C), 130.09 (CH), 128.08 (CH), 127.03 (CH), 116.29 (C), 102.23 (CH), 74.33 (CH), 57.70 (C), 44.02 (C), 42.55 (C), 39.21 (CH_2), 33.68 (CH_2), 31.37 (CH_2), 30.42 (CH_2), 25.88 (CH_3), 24.61 (CH_3), 21.26 (CH_3); HRMS m/z calculated for $\text{C}_{20}\text{H}_{24}\text{O}_3$ 312.1725 ($\text{M}^+ - \text{O}_2$), found 312.1687. The tridimensional structure of this product was confirmed by X-ray crystallography.



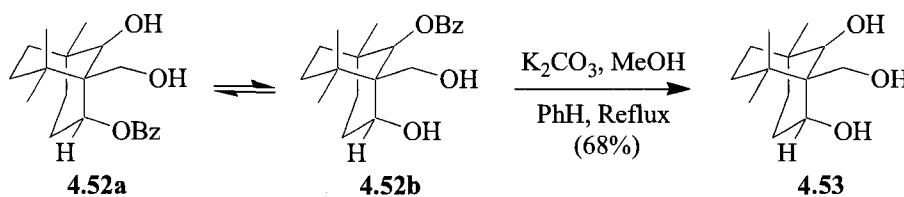
(±)-1-formyl-5,8,8-trimethyl-9-oxo-bicyclo[3.3.1]non-2-yl benzoate (**4.49**). To a Pyrex tube containing a stirred solution of **4.47** (256 mg, 0.86 mmol) in THF (6 mL) were added H_2O (1.5 mL), OsO_4 (4% in H_2O , 640 μL , 0.10 mmol) and NMO (302 mg, 2.58 mmol). The Pyrex tube was capped and covered with aluminum foil. The resulting mixture was heated at 100 °C for 29 h. This mixture was then cooled to room temperature, and NaIO_4 (736 mg, 3.44 mmol) was added. After stirring for 22 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL). The aqueous layer was separated from the organic layer and extracted with EtOAc (3 x 10 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% EtOAc/hexane) to afford 173 mg of **4.49** as a white solid (61% yield): mp 124-127 °C; IR (neat) $\nu_{\max}$ 2971, 2925, 2861, 1715, 1602, 1450, 1374, 1271, 1241, 1104 cm^{-1} ; ^1H NMR (400 MHz, C_6D_6) δ 10.62 (s, 1 H), 8.16-8.13 (m, 2 H), 7.09-7.05 (m, 1 H), 7.01-6.97 (m, 2 H), 6.33 (br, 1 H), 2.09-1.99

(m, 1 H), 1.91 (dd, $J = 16.1, 7.2$ Hz, 1 H), 1.80-1.70 (m, 2 H), 1.57 (ddd, $J = 6.4, 6.4, 2.4$ Hz, 1 H), 1.43-1.35 (m, 2 H), 1.06 (s, 3 H), 0.85 (s, 3 H), 0.75 (s, 3 H), 0.72-0.69 (m, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 214.63 (C), 202.20 (CH), 164.27 (C), 132.71 (CH), 130.12 (C), 129.53 (CH), 128.32 (CH), 77.21 (CH), 64.87 (C), 45.55 (C), 43.06 (C), 37.94 (CH_2), 36.90 (CH_2), 36.14 (CH_2), 26.46 (CH_2), 24.72 (CH_3), 24.31 (CH_3), 23.91 (CH_3); HRMS m/z calculated for $\text{C}_{18}\text{H}_{18}\text{O}_4$ 298.1205 ($\text{M}^+ - 2 \text{ Me}$), found 298.1908. The tridimensional structure of this product was confirmed by X-ray crystallography.

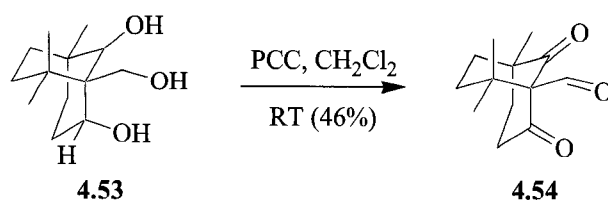


($\pm$)-9-hydroxy-1-hydroxymethyl-5,8,8-trimethyl-bicyclo[3.3.1]non-2-yl benzoate (**4.52a**) and ($\pm$)-8-hydroxy-1-hydroxymethyl-2,2,5-trimethyl-bicyclo[3.3.1]non-9-yl benzoate (**4.52b**). To a solution of **4.49** (14 mg, 0.043 mmol) in 1:1 MeOH/THF (1 mL) at 0°C was added $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (40 mg, 0.107 mmol). The resulting mixture was stirred for 10 minutes, and NaBH_4 (15 mg, 0.397 mmol) was added. The cloudy white reaction mixture was stirred at 0°C for 1.5 h, at which point it was quenched with saturated aqueous NH_4Cl (1 mL). The aqueous layer was separated from the organic layer and extracted with EtOAc (3 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (3:1:1 hexanes/ $\text{EtOAc}/\text{CH}_2\text{Cl}_2$) to afford 5.5 mg of **4.52a** (39% yield) and 2.8 mg of **4.52b** (20% yield) as colorless oils. Isomer **4.52a**: IR (neat) ν_{max} 3471 (br), 2915, 1698, 1451, 1285, 1119 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.06-8.01 (m, 2 H), 7.58 (tt, $J = 7.4, 1.3$ Hz, 1 H), 7.46 (dd, $J = 7.6, 7.6$ Hz, 2 H), 5.67 (br, 1 H), 4.11 (d, $J_{\text{AB}} = 12.6$ Hz, 1 H), 3.85 (s, 1 H), 3.58 (d, $J_{\text{AB}} = 12.6$ Hz, 1 H), 2.51 (br, 1 H), 2.29-2.19 (m, 1 H), 1.96-1.82 (m, 2 H), 1.78-1.62 (m, 4 H), 1.37 (s, 3 H), 1.27-1.23 (m, 1 H), 1.12 (s, 3 H), 0.97 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.67 (C), 133.37 (CH), 129.86 (C), 129.71 (CH), 128.60 (CH), 75.98 (CH), 75.87 (CH), 65.34 (CH_2), 47.18 (C), 39.43 (CH_2), 35.03 (C), 34.59 (CH_2), 34.31 (C), 29.25 (CH_3), 29.25 (CH_2), 28.50 (CH_3), 28.16 (CH_3), 27.85 (CH_2); HRMS m/z calculated for $\text{C}_{13}\text{H}_{22}\text{O}_2$ 210.1620 ($\text{M}^+ - \text{BzOH}$), found 210.1615. Isomer **4.52b**: IR (neat) ν_{max} 3493 (br),

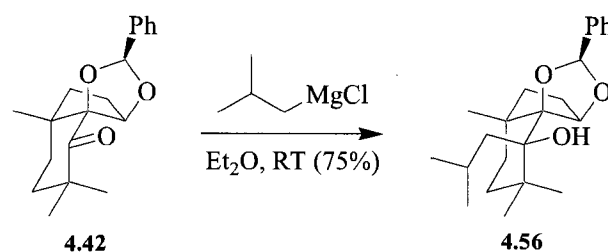
2926, 1698, 1451, 1282 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.06-8.01 (m, 2 H), 7.57 (t, J = 7.5 Hz, 1 H), 7.45 (dd, J = 7.7, 7.7 Hz, 2 H), 4.94 (d, J_{AB} = 12.2 Hz, 1 H), 4.72 (d, J_{AB} = 12.2 Hz, 1 H), 4.07 (br, 1 H), 3.95 (d, J = 4.2 Hz, 1 H), 3.90 (d, J = 3.5 Hz, 1 H), 2.25-2.05 (m, 1 H), 1.95-1.85 (m, 2 H), 1.82-1.71 (m, 1 H), 1.68-1.62 (m, 1 H), 1.44 (d, J = 2.3 Hz, 1 H), 1.41 (s, 3 H), 1.37-1.33 (m, 1 H), 1.26-1.17 (m, 2 H), 0.97 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.79 (C), 133.30 (CH), 129.86 (CH), 129.70 (CH), 128.60 (C), 128.55 (CH), 75.00 (C), 69.25 (CH), 68.35 (CH_2), 47.60 (C), 39.48 (CH_2), 35.14 (C), 33.84 (CH_2), 29.41 (CH_3), 29.28 (CH_2), 28.97 (CH_2), 28.40 (CH_3), 27.92 (CH_3); HRMS m/z calculated for $\text{C}_{13}\text{H}_{22}\text{O}_2$ 210.1620 ($\text{M}^+ - \text{BzOH}$), found 210.1633.



(±)-1-Hydroxymethyl-5,8,8-trimethyl-bicyclo[3.3.1]nonane-2,9-diol (4.53). To a solution of **4.52a/4.52b** (71 mg, 0.214 mmol) in MeOH (1 mL) was added K_2CO_3 (118 mg, 0.854 mmol). Benzene (1 mL) was added. The mixture was then refluxed for 1 h. After cooling down to room temperature, it was quenched with saturated aqueous NH_4Cl (2 mL). The aqueous layer was separated from the organic layer and extracted with EtOAc (4 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (50% EtOAc /hexanes) to afford 33 mg of **4.53** as a white solid (68% yield): mp 128-130.5 $^\circ\text{C}$; IR (neat) ν_{max} 3531 (br), 2932, 1450 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.33 (s, 1 H); 4.21 (d, J = 11.3 Hz, 1 H), 4.13 (s, 1 H), 3.86 (d, J = 11.3 Hz, 1 H), 3.55-2.95 (br, 2 H), 2.19-2.11 (m, 1 H), 2.08 (br, 1 H), 1.94-1.80 (m, 2 H), 1.77-1.70 (m, 1 H), 1.53-1.44 (m, 2 H), 1.27-1.19 (m, 5 H), 0.93 (s, 3 H), 0.81 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 76.34 (CH), 71.85 (CH), 65.72 (C), 46.16 (C), 39.11 (CH_2), 34.89 (C), 34.33 (CH_2), 33.39 (C), 31.17 (CH_2), 29.28 (CH_2), 28.75 (CH_3), 28.12 (CH_3), 26.97 (CH_3); HRMS m/z calculated for $\text{C}_{13}\text{H}_{22}\text{O}_2$ 210.1620 ($\text{M}^+ - \text{H}_2\text{O}$), found 210.1645.

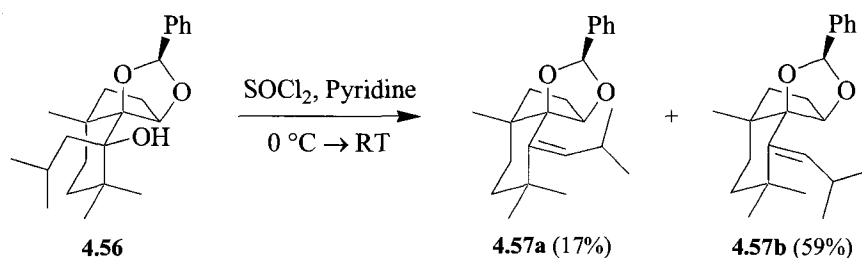


(±)-2,2,5-Trimethyl-8,9-dioxo-bicyclo[3.3.1]nonane-1-carbaldehyde (**4.54**). To a solution of **4.53** (10 mg, 0.044 mmol) in CH_2Cl_2 (1 mL) was added PCC (94 mg, 0.436 mmol). After stirring for 28 h, the black reaction mixture was filtered through a short pad of silica gel. The fritted glass funnel was then rinsed with CH_2Cl_2 (10 mL). After removal of the solvent, the residue was purified by silica gel column chromatography (10% then 20% EtOAc/hexanes) to afford 4.5 mg of **4.54** as a white solid (46% yield): mp 88-92 °C; IR ν_{max} (neat) 3059, 2969, 2932, 2863, 2755, 1740, 1716, 1682, 1456, 1256, 1155 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.60 (s, 1 H), 2.82 (ddd, $J = 10.3, 4.2, 1.1$ Hz, 1 H), 2.66 (ddd, $J = 18.7, 8.6, 3.5$ Hz, 1 H), 2.05-1.87 (m, 4 H), 1.84-1.77 (m, 1 H), 1.39 (ddd, $J = 14.2, 5.4, 1.5$ Hz, 1 H), 1.15 (s, 6 H), 1.13 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 210.68 (C), 206.74 (C), 195.31 (CH), 83.37 (C), 45.87 (C), 44.90 (C), 39.69 (CH_2), 37.76 (CH_2), 37.04 (CH_2), 31.88 (CH_2), 25.68 (CH_3), 23.56 (CH_3), 23.23 (CH_3); HRMS m/z calculated for $\text{C}_{12}\text{H}_{15}\text{O}_3$ 207.1021 ($\text{M}^+ - \text{Me}$), found 207.1003.



(±)-9-Isobutyl-5a,8,8-trimethyl-2-phenyloctahydro-1,3-dioxacyclopenta[c]inden-9-ol (**4.56**) To a solution of **4.42** (295 mg, 0.98 mmol) in Et_2O (10 mL) at room temperature was added isobutylmagnesium bromide (2.30 mL of a 1.7 M solution in Et_2O , 3.91 mmol) dropwise. After stirring for 1 hour, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 10 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (2%

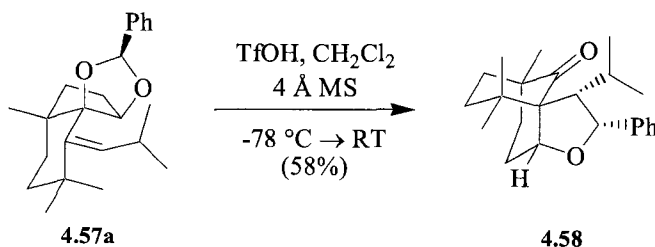
then 5% EtOAc/hexanes) to afford 266 mg of **4.56** as a white solid (75% yield): mp 53-55 °C; IR (neat) $\nu_{\max}$ 3588, 2952, 2867, 1463, 1386 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.49 (dd, $J = 7.5, 1.7$ Hz, 2 H), 7.36-7.30 (m, 3 H), 6.02 (s, 1 H), 4.63 (d, $J = 7.2$ Hz, 1 H), 2.30 (s, 1 H), 2.27-2.14 (m, 1 H), 2.10 (ddd, $J = 13.9, 13.9, 3.7$ Hz, 1 H), 1.82 (dd, $J = 15.0, 7.9$ Hz, 1 H), 1.76-1.69 (m, 1 H), 1.66-1.58 (m, 1 H), 1.57-1.53 (m, 1 H), 1.50-1.43 (m, 2 H), 1.39 (dd, $J = 14.6, 5.8$ Hz, 1 H), 1.32 (s, 3 H), 1.23 (ddd, $J = 14.2, 3.4, 3.4$ Hz, 1 H), 0.98 (s, 3 H), 0.88 (s, 3 H), 0.87-0.84 (m, 1 H), 0.79 (d, $J = 6.6$ Hz, 3 H), 0.42 (d, $J = 6.6$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 137.24 (C), 128.51 (CH), 127.82 (CH), 125.90 (CH), 102.51 (CH), 97.63 (C), 84.91 (CH), 78.53 (C), 46.14 (C), 42.25 (CH_2), 39.38 (CH), 39.31 (C), 31.71 (CH_2), 31.71 (CH_2), 29.85 (CH_2), 26.37 (CH_3), 25.07 (CH), 24.71 (CH_3), 24.62 (CH_3), 23.28 (CH_3), 23.01 (CH_3); HRMS m/z calculated for $\text{C}_{23}\text{H}_{34}\text{O}_3$ 358.2508 (M^+), found 358.2506.



(±)-9-Isobutylidene-5a,8,8-trimethyl-2-phenyl-octahydro-1,3-dioxo-cyclopenta[c]indene (4.57).

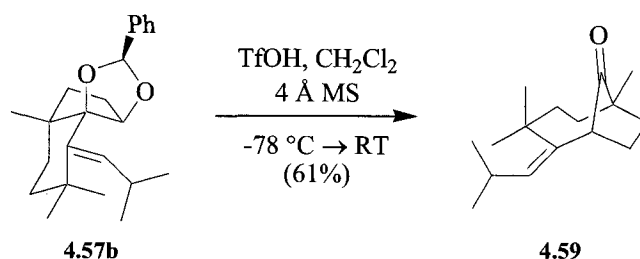
To a solution of **4.56** (345 mg, 0.96 mmol) in pyridine (10 mL) at room temperature was added freshly distilled thionyl chloride (350 μL , 4.80 mmol) dropwise. After stirring for 3 h, the reaction mixture was diluted with Et_2O (50 mL). The resulting solution was then washed with H_2O (3 x 50 mL) and saturated aqueous NaCl (1 x 50 mL). The organic layer was dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% $\rightarrow$ 30% benzene/hexanes) to afford 56 mg of **4.57a** as a white solid (17% yield) and 194 mg of **4.57b** as a pale yellow oil (59% yield). Isomer **4.57a**: mp 58-59.5 °C; IR (neat) $\nu_{\max}$ 3037, 2944, 2859, 1463, 1386, 1224 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.49-7.47 (m, 2 H), 7.34-7.27 (m, 3 H), 6.03 (s, 1 H), 5.18 (d, $J = 10.2$ Hz, 1 H), 4.70 (d, $J = 6.4$ Hz, 1 H), 2.87-2.80 (m, 1 H), 2.24-2.15 (m, 1 H), 1.90 (dd, $J = 14.7, 7.6$ Hz, 1 H), 1.78 (ddd, $J = 12.9, 12.9, 7.6$ Hz, 1 H), 1.66 (ddd, $J = 13.2, 13.2, 2.9$ Hz, 1 H), 1.59-1.55 (m, 1 H), 1.33 (ddd, $J = 13.7, 5.3, 3.1$ Hz, 1 H), 1.25-1.23 (m, 1 H), 1.21 (dd, $J = 5.4, 3.2$ Hz, 1 H), 1.18 (s, 3 H), 1.11 (s, 3 H), 1.02 (s, 3 H), 0.55 (d, $J = 6.5$ Hz, 3 H), 0.46

(d, $J = 6.5$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.48 (C), 138.24 (CH), 137.67 (C), 128.28 (CH), 127.79 (CH), 125.99 (CH), 103.56 (CH), 94.77 (C), 90.32 (CH), 47.61 (C), 42.61 (CH_2), 37.07 (C), 35.70 (CH_3), 33.30 (CH_2), 32.70 (CH_3), 31.54 (CH_3), 31.04 (CH_2), 26.06 (CH), 23.50 (CH_3), 23.23 (CH_3), 22.42 (CH_3); HRMS m/z calculated for $\text{C}_{23}\text{H}_{32}\text{O}_2$ 340.2402 (M^+), found 340.2390. Isomer **4.57b**: IR (neat) ν_{max} 2956, 2871, 1459, 1386, 1309, 1208 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.52-7.50 (m, 2 H), 7.36-7.34 (m, 3 H), 5.91 (s, 1 H), 5.48 (d, $J = 11.2$ Hz, 1 H), 4.69 (d, $J = 8.0$ Hz, 1 H), 2.92-2.85 (m, 1 H), 2.25-2.14 (m, 1 H), 1.87-1.80 (m, 2 H), 1.65-1.55 (m, 2 H), 1.48 (ddd, $J = 14.3, 4.2, 4.2$ Hz, 1 H), 1.41 (ddd, $J = 14.0, 14.0, 4.1$ Hz, 1 H), 1.26 (s, 3 H), 1.25 (s, 3 H), 1.23-1.18 (m, 1 H), 1.06 (s, 3 H), 0.94 (d, $J = 6.5$ Hz, 3 H), 0.86 (d, $J = 6.5$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 138.38 (C), 137.65 (C), 135.42 (CH), 129.13 (CH), 127.96 (CH), 127.45 (CH), 104.30 (CH), 95.54 (C), 88.56 (CH), 45.95 (C), 43.41 (CH_2), 39.22 (CH_2), 35.64 (C), 33.93 (CH_2), 30.93 (CH_3), 30.20 (CH_2), 29.06 (CH_3), 28.27 (CH), 24.63 (CH_3), 23.26 (CH_3), 23.02 (CH_3); HRMS m/z calculated for $\text{C}_{23}\text{H}_{32}\text{O}_2$ 340.2402 (M^+), found 340.2395.

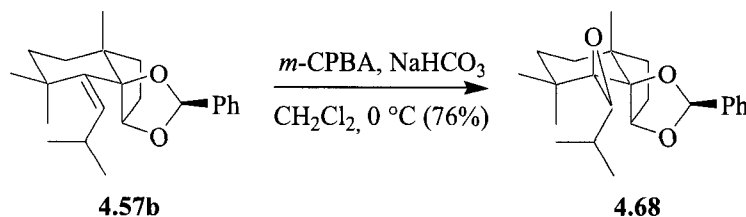


($\pm$)-2-Isopropyl-8,11,11-trimethyl-3-phenyl-4-oxa-tricyclo[6.3.1.0^{1,5}]dodecan-12-one (**4.58**). To a solution of **4.57a** (22.5 mg, 0.066 mmol) in CH_2Cl_2 (500 μL) at -78 $^\circ\text{C}$ was added TfOH (1.3 mL of a 0.1 M solution in CH_2Cl_2 , 0.130 mmol) dropwise. The resulting solution was stirred at -78 $^\circ\text{C}$ for 15 minutes. It was then warmed up to room temperature over 30 minutes and was further stirred for 1 h. Et_3N was added dropwise until complete discoloration, followed by saturated aqueous NaHCO_3 (1 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% $\rightarrow$ 30% benzene/hexanes) to afford 13 mg of **4.58** as a white solid (58% yield): mp 119.5-123.5 $^\circ\text{C}$; IR (neat) ν_{max} 2928, 2872, 1714, 1455 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.31-7.26 (m, 4 H), 7.21-7.18 (m, 1 H), 4.99 (d, $J = 6.1$ Hz, 1 H), 4.38

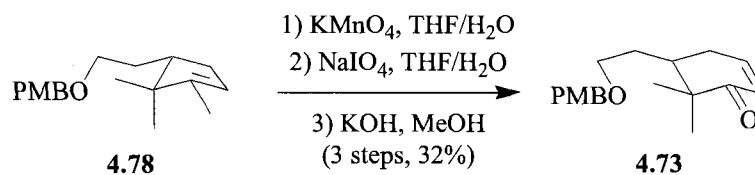
(dd, $J = 11.7, 4.9$ Hz, 1 H), 2.40 (dd, $J = 6.1, 2.2$ Hz, 1 H), 2.38-2.35 (m, 1 H), 2.25-2.20 (m, 1 H), 1.96-1.86 (m, 2 H), 1.76 (dddd, $J = 14.1, 2.7, 2.7, 2.7$ Hz, 1 H), 1.62 (ddd, $J = 13.5, 13.5, 4.7$ Hz, 1 H), 1.56-1.43 (m, 2 H), 1.20 (s, 3 H), 1.15 (dddd, $J = 14.4, 2.1, 2.1, 2.1$ Hz, 1 H), 1.05 (s, 3 H), 0.97 (d, $J = 7.2$ Hz, 3 H), 0.95 (s, 3 H), 0.48 (d, $J = 7.2$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 216.91 (C), 139.38 (C), 127.56 (CH), 126.58 (CH), 126.54 (CH), 82.76 (CH), 79.80 (CH), 67.20 (C), 54.28 (CH), 46.33 (C), 44.54 (C), 39.90 (CH_2), 33.50 (CH_2), 32.18 (CH_2), 28.13 (CH_2), 26.77 (CH_3), 26.27 (CH), 25.69 (CH_3), 23.81 (CH_3), 21.35 (CH_3), 20.92 (CH_3); HRMS m/z calculated for $\text{C}_{23}\text{H}_{32}\text{O}_2$ 340.2402 (M^+), found 340.2406. The tridimensional structure of this product was confirmed by X-ray crystallography.



($\pm$)-5-Isobutyridene-1,4,4-trimethyl-bicyclo[4.2.1]nonan-9-one (**4.59**). To a solution of **4.57b** (10 mg, 0.029 mmol) in MeCN (400 μL) at -78 $^\circ\text{C}$ was added TfOH (590 μL of a 0.1 M solution in MeCN, 0.059 mmol) dropwise. The resulting solution was stirred at -78 $^\circ\text{C}$ for 15 minutes. It was then warmed up to room temperature over 30 minutes and was further stirred for 30 minutes. Et_3N was added dropwise until complete discoloration, followed by saturated aqueous NaHCO_3 (1 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% EtOAc /hexanes) to afford 4.5 mg of **4.59** as a pale yellow oil (61% yield): IR (neat) ν_{max} 2960, 2929, 2870, 1743, 1457, 1383, 1121 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.38 (d, $J = 9.1$ Hz, 1 H), 2.79 (s, 1 H), 2.50-2.42 (m, 1 H), 2.39-2.30 (m, 2 H), 1.85 (dd, $J = 12.6, 9.4$ Hz, 1 H), 1.71-1.64 (m, 2 H), 1.45 (ddd, $J = 13.7, 3.8$ Hz, 1 H), 1.24-1.19 (m, 2 H), 1.09 (s, 3 H), 1.05 (s, 3 H), 0.99 (d, $J = 6.6$ Hz, 3 H), 0.89 (d, $J = 6.6$ Hz, 3 H), 0.76 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 218.25 (C), 136.02 (C), 134.85 (CH), 59.03 (CH), 40.40 (C), 36.48 (CH_2), 35.97 (CH_2), 35.46 (CH_2), 35.34 (C), 29.83 (CH_3), 29.44

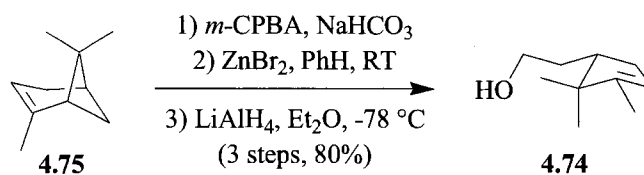


Epoxide 4.68. To a suspension of *m*-CPBA (77%, 40 mg, 0.18 mmol) and NaHCO₃ (20 mg, 0.24 mmol) in CH₂Cl₂ (500 μL) at 0 °C was added a solution of **4.57b** (40 mg, 0.12 mmol) in CH₂Cl₂ (700 μL) via cannula. After stirring at 0 °C for 1 h, the reaction mixture was warmed up to room temperature and quenched with 10% aqueous Na₂SO₃ (2 mL). The resulting biphasic mixture was stirred for 10 minutes. The aqueous layer was separated from the organic layer and extracted with CH₂Cl₂ (3 x 5 mL). Combined organics were dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (30% benzene/hexanes then 10% EtOAc/hexanes) to afford 32 mg of **4.68** as a white solid (76% yield): mp 84-86.5 °C; IR (neat) ν_{max} 2941, 2870, 1447, 1383 cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ 7.67 (d, *J* = 7.2 Hz, 2 H), 7.21-7.19 (m, 2 H), 7.13 (dd, *J* = 7.3 Hz, 1 H), 5.99 (s, 1 H), 4.87 (d, *J* = 8.1 Hz, 1 H), 2.82 (d, *J* = 10.0 Hz, 1 H), 2.02-1.84 (m, 3 H), 1.70-1.63 (m, 2 H), 1.44 (s, 3 H), 1.40 (dd, *J* = 13.8, 3.3 Hz, 1 H), 1.31-1.27 (m, 1 H), 1.14 (ddd, *J* = 14.0, 3.8, 3.8 Hz, 1 H), 1.04 (s, 3 H), 0.99 (dd, *J* = 3.8, 3.8 Hz, 1 H), 0.95-0.94 (m, 6 H), 0.85 (d, *J* = 6.6 Hz, 3 H); ¹³C NMR (100 MHz, C₆D₆) δ 138.12 (C), 128.53 (CH), 128.04 (CH), 126.39 (CH), 103.13 (CH), 92.24 (C), 87.15 (CH), 65.82 (C), 61.96 (CH), 46.46 (C), 41.36 (CH₂), 36.48 (CH₂), 35.23 (C), 31.51 (CH₂), 29.88 (CH₂), 29.05 (CH₃), 26.01 (CH), 25.08 (CH₃), 21.84 (CH₃), 20.32 (CH₃), 19.95 (CH₃); HRMS *m/z* calculated for C₂₃H₃₂O₃ 356.2351 (M⁺), found 356.2371.



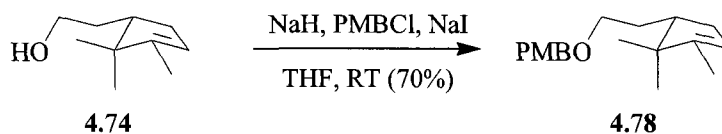
(±)-5-[2-(4-Methoxybenzyloxy)-ethyl]-6,6-dimethylcyclohex-2-enone (4.73). *Step 1:* To a solution of **4.78** (12.46 g, 45.41 mmol) in THF (450 mL) was added over 1 h a solution of KMnO₄ (12.20 g, 77.20 mmol) in H₂O (450 mL) using an addition funnel. The temperature

of the reaction was monitored and kept around 20 °C with a cold water bath. Once the addition was completed, the reaction mixture was stirred for an additional hour. This mixture was filtered through a filter paper and then through celite. The Buchner funnel was rinsed with EtOAc (250 mL). The phases of the filtrate were separated. The aqueous layer was extracted with EtOAc (4 x 400). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. Filtration and removal of the solvent delivered the corresponding diol. *Step 2:* To a solution of the crude diol in THF (650 mL) were added H₂O (150 mL) and NaIO₄ (14.57 g, 68.12 mmol). The resulting mixture was stirred at room temperature for 12 h. Saturated aqueous NaHCO₃ (250 mL) was then added, and the THF was evaporated under reduced pressure. The resulting aqueous layer was extracted with Et₂O (3 x 250 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. Filtration and removal of the solvent delivered the corresponding keto-aldehyde. *Step 3:* To the crude keto-aldehyde was added KOH (450 mL of a 1.0 M solution in MeOH). The resulting mixture was stirred at room temperature for 6.5 hours. Saturated aqueous NaCl (250 mL) was then added, and the solvent was evaporated under reduced pressure. The resulting aqueous layer was extracted with Et₂O (3 x 250 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10 then 15% EtOAc/hexanes) to afford 4.15 g of **4.73** as a yellowish oil (32% over 3 steps). Spectroscopic data for **4.73** were identical to that previously reported.⁶⁴



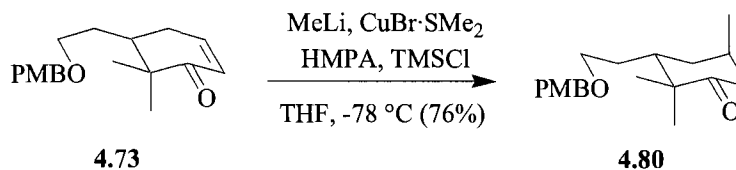
(±)-2-(2,5,5-Trimethylcyclopent-2-enyl)-ethanol (**4.74**). *Step 1:* To a suspension of *m*-CPBA (77%, 49.40 g, 220.42 mmol) and NaHCO₃ (23.10 g, 274.97 mmol) in CH₂Cl₂ (440 mL) at 0 °C was added a solution of α-pinene **4.75** (25 g, 183.50 mmol) in CH₂Cl₂ (40 mL) dropwise via cannula. After stirring at 0 °C for 1 h, the reaction mixture was quenched with 10% aqueous Na₂SO₃ (100 mL). The resulting mixture was warmed up to room temperature and stirred for 15 minutes. H₂O (100 mL) was added and the phases were separated. The organic

layer was washed with 5% aqueous Na_2SO_3 (100 mL). Combined aqueous layers were extracted with CH_2Cl_2 (2 x 200 mL). Combined organics were dried over anhydrous MgSO_4 . Filtration and removal of the solvent delivered the corresponding epoxide. *Step 2:* ZnBr_2 (4.12 g, 18.3 mmol) was flame-dried (molten) in a one-liter round-bottom flask. After cooling to room temperature, benzene (310 mL) was added. A solution of the crude epoxide in benzene (60 mL) was then added via cannula. After stirring for 16 h at room temperature, the reaction mixture was quenched with 10% aqueous AcOH (130 mL). The resulting mixture was diluted with Et_2O (200 mL). The organic layer was separated from the aqueous layer and washed with H_2O and saturated aqueous NaHCO_3 . It was then dried over anhydrous MgSO_4 . Filtration and careful removal of the solvent delivered the rearranged aldehyde. *Step 3:* To a solution of the crude aldehyde in Et_2O (900 mL) at -78°C was added LiAlH_4 (5.56 g, 146.50 mmol) in 3 portions. The resulting mixture was stirred at that temperature for 2 hours. 25% aqueous sodium tartrate (400 mL) was then added and the mixture was warmed up to room temperature. It was transferred to an erlenmeyer flask and stirred vigorously for 1 h, until the phases were easily separated. The aqueous layer was extracted with Et_2O (3 x 400 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% $\rightarrow$ 20% AcOEt /hexanes) to afford 22.59 g of **4.74** as a colorless oil (80% over 3 steps). Spectroscopic data for **4.74** were identical to that previously reported.⁶⁴

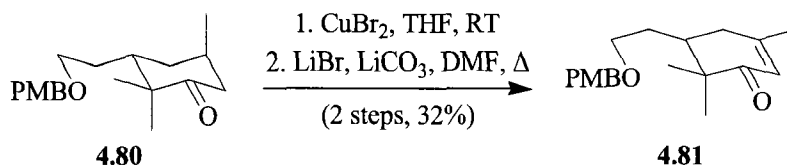


(±)-1-Methoxy-4-[2-(2,5,5-trimethylcyclopent-2-enyl)-ethoxymethyl]-benzene (**4.78**). To a solution of **4.74** (5.00 g, 32.41 mmol) in THF (160 mL) at room temperature was added NaH (60% in mineral oil, 3.24 g, 81.00 mmol) in 3 portions. After stirring for 5 minutes, PMBCl (3.28 mL, 32.46 mmol) and dry NaI (970 mg, 6.47 mmol) were added. The flask was covered with tin foil and the reaction mixture was stirred for 18 h. Saturated aqueous NH_4Cl (60 mL) was then added, and the THF was evaporated under reduced pressure. The resulting aqueous layer was extracted with Et_2O (3 x 60 mL). Combined organics were dried over

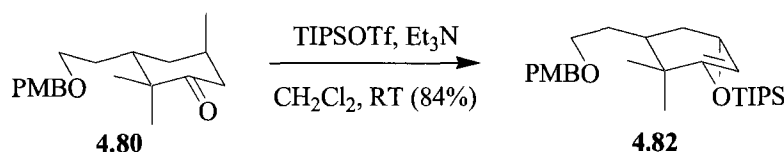
anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes $\rightarrow$ 50% CH_2Cl_2 /hexanes) to afford 6.21 g of **4.78** as a yellow oil (70% yield). Spectroscopic data for **4.78** were identical to that previously reported.⁶⁴



($\pm$)-3-[2-(4-Methoxybenzyloxy)-ethyl]-2,2,5-trimethylcyclohexanone (**4.80**). To a suspension of $\text{CuBr}\cdot\text{SMe}_2$ (861 mg, 4.19 mmol) in THF (26 mL) at 0 $^\circ\text{C}$ was added MeLi (5.60 mL of a 1.5 M solution in Et_2O , 8.40 mmol) dropwise. After stirring at 0 $^\circ\text{C}$ for 15 minutes, the clear solution was cooled down to -78 $^\circ\text{C}$. TMSCl (1.90 mL, 14.97 mmol) and HMPA (730 μL , 4.20 mmol) were added dropwise. The mixture was then stirred for 5 minutes and a solution of **4.73** (861 mg, 2.99 mmol) in THF (4 mL) was added dropwise via cannula. After stirring at -78 $^\circ\text{C}$ for 1 h, the reaction mixture was quenched by a slow addition of 1 N HCl (20 mL). Upon warming up to room temperature, the aqueous layer was separated from the organic layer and extracted with EtOAc (3 x 20 mL). Combined organics were washed with saturated aqueous NaHCO_3 and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford 697 mg of **4.80** as a pale yellow oil (76% yield): IR (neat) ν_{max} 2954, 2868, 1704, 1613, 1513, 1463, 1247, 1173 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.22 (d, J = 8.5 Hz, 2 H), 6.85 (d, J = 8.5 Hz, 2 H), 4.42 (d, J_{AB} = 11.5 Hz, 1 H), 4.37 (d, J_{AB} = 11.5 Hz, 1 H), 3.78 (s, 3 H), 3.45-3.36 (m, 2 H), 2.42 (dd, J = 13.0, 4.5 Hz, 1 H), 2.18-2.08 (m, 2 H), 1.85-1.78 (m, 2 H), 1.68-1.60 (m, 2 H), 1.37-1.23 (m, 1 H), 1.15 (s, 3 H), 0.99 (s, 3 H), 0.93 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 216.05 (C), 159.02 (C), 130.34 (C), 129.07 (CH), 113.63 (CH), 72.45 (CH_2), 68.36 (CH_2), 55.13 (CH_3), 47.99 (C), 45.04 (CH_2), 41.23 (CH), 32.46 (CH_2), 29.29 (CH), 29.09 (CH_2), 24.74 (CH_3), 20.95 (CH_3), 20.69 (CH_3); HRMS m/z calculated for $\text{C}_{19}\text{H}_{28}\text{O}_3$ 304.2038 (M^+), found 304.2036.

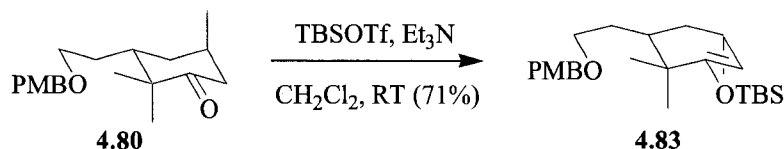


(±)-5-[2-(4-Methoxybenzyloxy)-ethyl]-3,6,6-trimethylcyclohex-2-enone (**4.81**). *Step 1*: To a solution of **4.80** (50 mg, 0.164 mmol) in THF (1.6 mL) at room temperature was added CuBr₂ (73 mg, 0.327 mmol). After stirring for 2 hours, the dark brown reaction mixture was quenched with H₂O (2 mL). The aqueous layer was separated from the organic layer and extracted with CH₂Cl₂ (3 x 5 mL). Combined organics were washed with H₂O (3 x 15 mL) and dried over anhydrous MgSO₄. After filtration, the solvent was removed under reduced pressure to deliver the crude bromide. *Step 2*: To a solution of the bromide in DMF (1 mL) were added dry LiBr (69 mg, 0.794 mmol) and dry LiCO₃ (59 mg, 0.798 mmol). The resulting mixture was refluxed for 2.5 hours. After cooling down to room temperature, it was quenched with H₂O (1 mL). The aqueous layer was separated from the organic layer and extracted with EtOAc (3 x 5 mL). Combined organics were washed with H₂O (3 x 15 mL) and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% then 20% EtOAc/hexanes) to afford 16 mg of **4.81** as a yellow oil (32% yield over 2 steps): IR (neat) ν_{max} 2967, 2929, 2861, 1667, 1511, 1245 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.23 (d, J = 8.6 Hz, 2 H), 6.86 (d, J = 8.6 Hz, 2 H), 5.76 (s, 1 H), 4.44 (d, J_{AB} = 11.6 Hz, 1 H), 4.38 (d, J_{AB} = 11.6 Hz, 1 H), 3.79 (s, 3 H), 3.51-3.43 (m, 2 H), 2.28 (dd, J = 18.6, 4.6 Hz, 1 H), 2.04 (dd, J = 19.1, 9.7 Hz, 1 H), 1.94-1.88 (m, 2 H), 1.86 (s, 3 H), 1.43-1.37 (m, 1 H), 1.11 (s, 3 H), 0.92 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 204.44 (C), 159.06 (C), 158.72 (C), 130.24 (C), 129.14 (CH), 124.71 (CH), 113.64 (CH), 72.43 (CH₂), 68.06 (CH₂), 55.14 (CH₃), 43.81 (C), 40.29 (CH₃), 33.71 (CH₂), 29.23 (CH₂), 23.89 (CH), 22.22 (CH₃), 18.82 (CH₃); HRMS m/z calculated for C₁₉H₂₆O₃ 302.1882 (M⁺), found 302.1882.



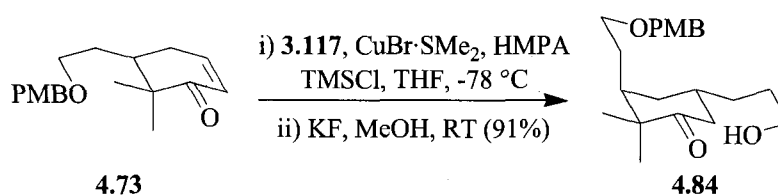
(±)-Triisopropyl-{5-[2-(4-methoxybenzyloxy)-ethyl]-3,6,6-trimethylcyclohexenyloxy}-silane

(4.82). To a mixture of **4.80** (27 mg, 0.09 mmol) and Et₃N (25 μ L, 0.18 mmol) in CH₂Cl₂ (1 mL) at 0 °C was added TIPSOTf (30 μ L, 0.11 mmol) dropwise. After stirring at 0 °C for 5 minutes, the reaction mixture was warmed up to room temperature and further stirred for 2h. It was then quenched with saturated aqueous NaHCO₃ (1 mL). The aqueous layer was separated from the organic layer and extracted with CH₂Cl₂ (3 x 5 mL). Combined organics were dried over MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes) to afford 34 mg of **4.82** as a colorless oil (84% yield): IR (neat) 2944, 2866, 1652, 1610, 1513, 1462, 1248 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.25 (d, J = 8.7 Hz, 2 H), 6.86 (d, J = 8.7 Hz, 2 H), 4.52-4.49 (m, 1 H), 4.46 (d, J_{AB} = 11.5 Hz, 1 H), 4.40 (d, J_{AB} = 11.5 Hz, 1 H), 3.79 (s, 3 H), 3.52-3.39 (m, 2 H), 2.23-2.16 (m, 1 H), 1.88-1.80 (m, 1 H), 1.59-1.53 (m, 1 H), 1.50-1.39 (m, 1 H), 1.40-1.27 (m, 2 H), 1.24-1.12 (m, 3 H), 1.09-1.05 (m, 18 H), 1.02-1.01 (m, 3 H), 0.93-0.90 (m, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 159.10 (C), 156.02 (C), 130.80 (C), 129.23 (CH), 113.76 (CH), 105.21 (CH), 72.62 (CH₂), 69.50 (CH₂), 55.29 (CH₃), 38.82 (C), 37.79 (CH₃), 31.06 (CH₂), 29.59 (CH₂), 27.18 (CH₃), 26.06 (CH), 22.24 (CH), 21.10 (CH), 18.24 (CH₃), 12.97 (CH₃); HRMS m/z calculated for C₂₀H₃₉O₂Si 339.2719 (M⁺ - PMB), found 339.2714.

**(±)-*t*-Butyl-{5-[2-(4-methoxybenzyloxy)-ethyl]-3,6,6-trimethylcyclohexenyloxy}-dimethylsilane**

(4.83). To a mixture of **4.80** (34 mg, 0.11 mmol) and Et₃N (30 μ L, 0.22 mmol) in CH₂Cl₂ (1.1 mL) at 0 °C was added TBSOTf (30 μ L, 0.13 mmol) dropwise. After stirring at 0 °C for 5 minutes, the reaction mixture was warmed up to room temperature and further stirred for 10 minutes. It was then quenched with saturated aqueous NaHCO₃ (1 mL). The aqueous layer was separated from the organic layer and extracted with CH₂Cl₂ (3 x 5 mL). Combined organics were dried over MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes) to afford 33 mg of **4.83** as a colorless oil (71% yield): IR (neat) $\nu_{\max}$ 2959, 2933, 2861, 1656, 1610, 1513, 1462, 1359, 1249, 1177, 1097 (br) cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ 7.38 (d, J = 8.7 Hz, 2 H), 6.92 (d, J

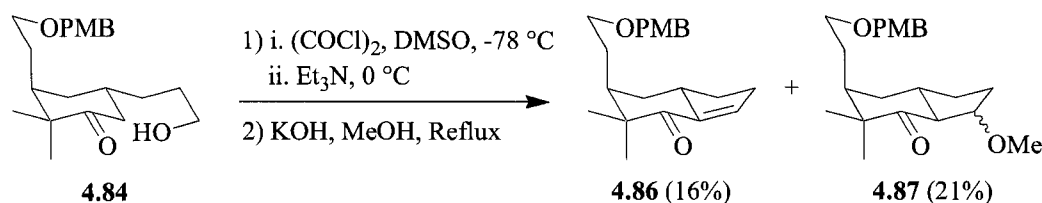
= 8.7 Hz, 2 H), 4.84 (d, J = 4.4 Hz, 1 H), 4.51 (d, J_{AB} = 11.7 Hz, 1 H), 4.44 (d, J_{AB} = 11.7 Hz, 1 H), 3.57-3.50 (m, 2 H), 3.41 (s, 3 H), 2.42-2.35 (m, 1 H), 2.06 (dtd, J = 14.7, 7.7, 2.5 Hz, 1 H), 1.90 (dddd, J = 10.6, 10.6, 2.7, 2.7 Hz, 1 H), 1.64 (ddd, J = 13.3, 10.3, 5.8 Hz, 1 H), 1.50 (ddd, J = 13.4, 3.5, 3.5 Hz, 1 H), 1.48-1.40 (m, 1 H), 1.33 (s, 3 H), 1.20-1.14 (m, 6 H), 1.10 (s, 9 H), 0.27 (s, 6 H); ^{13}C NMR (125 MHz, C_6D_6) δ 159.31 (C), 156.47 (C), 131.16 (C), 128.95 (CH), 113.72 (CH), 106.67 (CH), 72.45 (CH_2), 68.82 (CH_2), 54.40 (CH_3), 38.66 (C), 37.61 (CH), 30.95 (CH_2), 29.79 (CH_2), 27.43 (CH), 25.74 (CH_3), 22.09 (CH_3), 20.85 (CH_3), 18.17 (C), -4.50 (CH_3), -4.81 (CH_3); HRMS m/z calculated for $\text{C}_{17}\text{H}_{33}\text{O}_2\text{Si}$ 297.2250 ($\text{M}^+ - \text{PMB}$), found 297.2353.



(±)-5-(3-Hydroxypropyl)-3-[2-(4-methoxybenzyloxy)-ethyl]-2,2-dimethylcyclohexanone (4.84).

To a solution of **4.73** (3.80 g, 13.19 mmol) in THF (20 mL) at room temperature were added $\text{CuBr}\cdot\text{SMe}_2$ (3.25 g, 15.82 mmol), HMPA (4.60 mL, 26.44 mmol) and TMSCl (8.40 mL, 66.19 mmol). The resulting mixture was cooled to $-78\text{ }^\circ\text{C}$. Grignard reagent **3.117** (0.3 M, 110.0 mL, 33.0 mmol) obtained from 3-chloropropanol (8.40 mL, 100.40 mmol), isopropylmagnesium chloride (1.63 M in THF, 61.35 mL, 100.00 mmol), magnesium turnings (3.60 g, 148.12 mmol) and 1,2-dibromoethane (340 μL , 3.93 mmol) in THF (100 mL) was then added over a 20-minute period. After stirring at $-78\text{ }^\circ\text{C}$ for 1 h, the reaction mixture was warmed up to room temperature. Saturated aqueous NH_4Cl (50 mL) was added. Then, a solution of NH_4OH in saturated aqueous NH_4Cl (pH 8) was added until the biphasic mixture turned clear blue. The aqueous layer was separated from the organic layer and extracted with Et_2O (4 x 100 mL). Combined organics were washed with saturated aqueous NaCl , dried over anhydrous MgSO_4 , and concentrated. The crude silylated product was dissolved in MeOH (10 mL) and stirred with a catalytic amount of potassium fluoride for 1 h. The solution was concentrated and the residue was purified by silica gel column chromatography (40% then 60% EtOAc /hexanes) to afford 4.27 g of **4.84** as a pale yellow oil (91% yield): IR (neat) ν_{max} 3444 (br), 2934, 2866, 1699, 1613, 1513, 1464, 1248 cm^{-1} ; ^1H

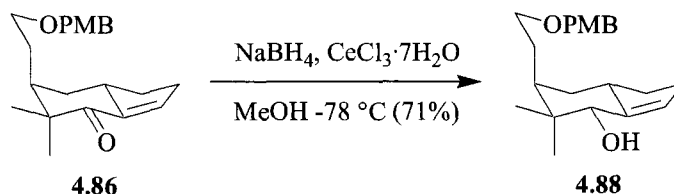
NMR (500 MHz, CDCl_3) δ 7.23 (d, $J = 8.6$ Hz, 2 H), 6.86 (d, $J = 8.6$ Hz, 2 H), 4.43 (d, $J_{\text{AB}} = 11.5$ Hz, 1 H), 4.36 (d, $J_{\text{AB}} = 11.5$ Hz, 1 H), 3.79 (s, 3 H), 3.57 (td, $J = 6.5, 1.2$ Hz, 2 H), 3.44-3.36 (m, 2 H), 2.44 (dd, $J = 13.9, 5.2$ Hz, 1 H), 2.20 (dd, $J = 13.9, 8.6$ Hz, 1 H), 1.96-1.88 (m, 1 H), 1.88-1.75 (m, 2 H), 1.73-1.61 (m, 2 H), 1.58-1.43 (m, 3 H), 1.31-1.23 (m, 3 H), 1.15 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 216.20 (C), 159.18 (C), 130.44 (C), 129.34 (CH), 113.80 (CH), 72.63 (CH_2), 68.34 (CH_2), 62.80 (CH_2), 55.31 (CH_3), 48.41 (C), 43.52 (CH_2), 41.38 (CH), 34.29 (CH), 31.47 (CH_2), 30.41 (CH_2), 30.12 (CH_2), 29.13 (CH_2), 24.91 (CH_3), 20.90 (CH_3); HRMS m/z calculated for $\text{C}_{13}\text{H}_{23}\text{O}_3$ 227.1647 ($\text{M}^+ - \text{PMB}$), found 227.1618.



(±)-6-[2-(4-Methoxybenzyloxy)-ethyl]-5,5-dimethyl-1,2,5,6,7,7a-hexahydroinden-4-one (4.86) and (±)-3-Methoxy-6-[2-(4-methoxybenzyloxy)-ethyl]-5,5-dimethyloctahydroinden-4-one (4.87).

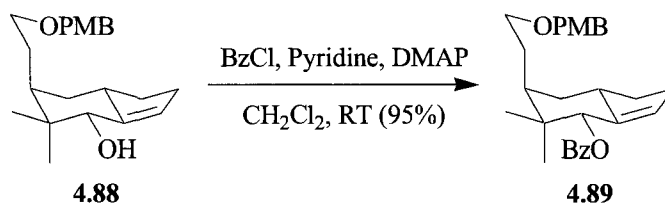
Step 1: To a solution of oxalyl chloride (15 μL , 0.172 mmol) in CH_2Cl_2 (1 mL) at -78°C was added DMSO (20 μL , 0.282 mmol) dropwise. The resulting solution was stirred for 20 minutes, and a solution of **4.84** (44 mg, 0.126 mmol) in CH_2Cl_2 (500 μL) was added via cannula. The resulting cloudy mixture was stirred at -78°C for 1.5 h, and Et_3N (90 μL , 0.646 mmol) was added dropwise. The reaction mixture was warmed up to 0°C . After stirring for 30 minutes at that temperature, it was quenched with saturated aqueous NH_4Cl (1 mL). The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 x 5 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After filtration, the solvent was removed under reduced pressure to deliver crude keto-aldehyde **4.85**. *Step 2:* To a solution of this keto-aldehyde in MeOH (1.3 mL) was added KOH powder (73 mg, 1.301 mmol). The resulting mixture was refluxed for 1 h. After cooling down to room temperature, it was diluted with Et_2O (2 mL) and quenched with saturated aqueous NaCl (2 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the

residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford 6.5 mg of **4.86** (16% yield over 2 steps) and 9.5 mg of **4.87** (21% yield over 2 steps) as pale yellow oils. Enone **4.86**: IR (neat) $\nu_{\max}$ 2931, 2859, 1681, 1613, 1513, 1462, 1248 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.23 (d, $J = 8.6$ Hz, 2 H), 6.86 (d, $J = 8.6$ Hz, 2 H), 6.51 (ddd, $J = 2.6, 2.6, 2.6$ Hz, 1 H), 4.43 (d, $J_{\text{AB}} = 11.5$ Hz, 1 H), 4.39 (d, $J_{\text{AB}} = 11.5$ Hz, 1 H), 3.79 (s, 3 H), 3.51-3.42 (m, 2 H), 3.01-2.96 (m, 1 H), 2.45-2.39 (m, 1 H), 2.37-2.29 (m, 1 H), 2.27-2.21 (m, 1 H), 1.94-1.89 (m, 1 H), 1.88-1.83 (m, 2 H), 1.71-1.63 (m, 1 H), 1.55-1.50 (m, 1 H), 1.42-1.35 (m, 1 H), 1.14 (s, 3 H), 1.08 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 205.31 (C), 159.19 (C), 143.62 (C), 138.15 (CH), 130.49 (C), 129.25 (CH), 113.79 (CH), 72.67 (CH_2), 68.39 (CH_2), 55.30 (C), 47.96 (CH_3), 43.00 (CH), 41.02 (CH), 34.34 (CH_2), 32.17 (CH_2), 30.32 (CH_2), 28.82 (CH_2), 27.42 (CH_3), 21.33 (CH_3); HRMS m/z calculated for $\text{C}_{21}\text{H}_{28}\text{O}_3$ 328.2038 (M^+), found 328.2034. Ketone **4.87**: IR (neat) $\nu_{\max}$ 2932, 2868, 1698, 1613, 1513, 1463, 1248, 1173, 1085 (br) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.21 (d, $J = 8.7$ Hz, 2 H), 6.85 (d, $J = 8.7$ Hz, 2 H), 4.43 (d, $J_{\text{AB}} = 11.6$ Hz, 1 H), 4.36 (d, $J_{\text{AB}} = 11.6$ Hz, 1 H), 4.30-4.28 (m, 1 H), 3.78 (s, 3 H), 3.48-3.44 (m, 1 H), 3.41-3.36 (m, 1 H), 3.24 (s, 3 H), 2.89 (d, $J = 8.4$ Hz, 1 H), 2.67-2.60 (m, 1 H), 1.98-1.91 (m, 1 H), 1.87-1.81 (m, 1 H), 1.79-1.70 (m, 1 H), 1.70-1.59 (m, 2 H), 1.54-1.48 (m, 1 H), 1.41-1.34 (m, 1 H), 1.25-1.13 (m, 2 H), 1.04 (s, 3 H), 1.02 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 215.36 (C), 159.01 (C), 130.32 (C), 129.06 (CH), 113.63 (CH), 82.95 (CH), 72.43 (CH_2), 68.34 (CH_2), 56.28 (CH_3), 55.13 (CH_3), 53.62 (CH), 48.07 (C), 39.15 (CH), 39.07 (CH), 30.16 (CH_2), 29.82 (CH_2), 28.15 (CH_2), 27.58 (CH_2), 22.05 (CH_3), 18.61 (CH_3); HRMS m/z calculated for $\text{C}_{21}\text{H}_{28}\text{O}_3$ 328.3028 ($\text{M}^+ - \text{MeOH}$), found 328.2039.



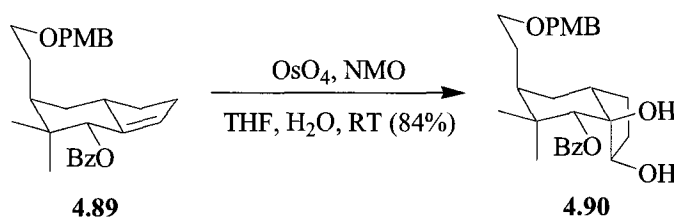
(±)-6-[2-(4-Methoxybenzyloxy)-ethyl]-5,5-dimethyl-2,4,5,6,7,7a-hexahydro-1H-inden-4-ol (**4.88**). To a solution of **4.86** (75 mg, 0.23 mmol) in MeOH (2.3 mL) at $-78\text{ }^\circ\text{C}$ was added $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (86 mg, 0.23 mmol). The resulting mixture was stirred for 5 minutes, and NaBH_4 (9 mg, 0.24 mmol) was added. The cloudy white reaction mixture was stirred at -78

°C for 30 minutes, at which point it was quenched with saturated aqueous NH_4Cl (2 mL). After warming up to room temperature, the aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (20% EtOAc /hexanes) to afford 54 mg of **4.88** as a yellow oil (71% yield): IR (neat) ν_{max} 3470 (br), 2928, 2858, 1613, 1513, 1463, 1247 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.24 (d, $J = 8.6$ Hz, 2 H), 6.86 (d, $J = 8.6$ Hz, 2 H), 5.43 (dd, $J = 1.9$ Hz, 1 H), 4.44 (d, $J_{\text{AB}} = 11.5$ Hz, 1 H), 4.40 (d, $J_{\text{AB}} = 11.5$ Hz, 1 H), 4.08 (d, $J = 1.7$ Hz, 1 H), 3.79 (s, 3 H), 3.48 (ddd, $J = 8.6, 8.6, 5.1$ Hz, 1 H), 3.43-3.39 (m, 1 H), 2.71 (br, 1 H), 2.39-2.25 (m, 2 H), 2.16-2.10 (m, 1 H), 1.94-1.88 (m, 1 H), 1.66-1.58 (m, 2 H), 1.55-1.52 (m, 2 H), 1.44-1.33 (m, 2 H), 1.07 (s, 3 H), 0.84 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.16 (C), 147.65 (C), 130.62 (C), 129.24 (CH), 120.26 (CH), 113.79 (CH), 74.79 (CH), 72.66 (CH_2), 69.58 (CH_2), 55.30 (CH_3), 43.76 (CH), 40.82 (CH), 39.71 (C), 32.55 (CH_2), 31.66 (CH_2), 31.45 (CH_2), 27.27 (CH_2), 24.89 (CH_3), 21.36 (CH_3); HRMS m/z calculated for $\text{C}_{13}\text{H}_{21}\text{O}_2$ 209.1542 ($\text{M}^+ - \text{PMB}$), found 209.1609.



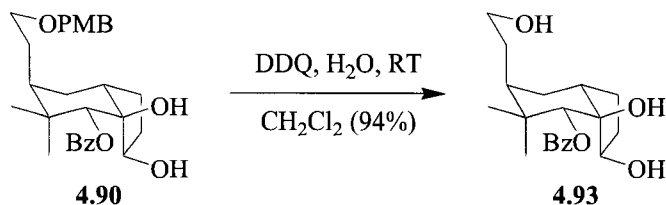
(±)-6-[2-(4-methoxybenzyloxy)-ethyl]-5,5-dimethyl-2,4,5,6,7,7a-hexahydro-1H-inden-4-yl benzoate (**4.89**). To a solution of **4.88** (308 mg, 0.93 mmol) in CH_2Cl_2 (9.3 mL) at room temperature were added benzoyl chloride (330 μL , 2.84 mmol), pyridine (450 μL , 5.59 mmol) and DMAP (57 mg, 0.47 mmol). After stirring for 5 days, the reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL). The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 x 10 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes $\rightarrow$ 2% EtOAc /hexanes) to afford 385 mg of **4.89** as a colorless oil (95% yield): IR (neat) ν_{max} 2929, 2857, 1721, 1612, 1513, 1451, 1271 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.08 (d, $J = 7.1$ Hz, 2 H), 7.55 (dd, $J = 7.4$ Hz, 1 H), 7.44 (dd, $J = 7.7, 7.7$ Hz, 2 H), 7.25 (d, $J = 8.6$ Hz, 2 H), 6.87 (d, $J = 8.6$ Hz, 2 H), 5.59 (d, $J = 1.7$ Hz,

1 H), 5.26 (dd, $J = 1.9, 1.9$ Hz, 1 H), 4.45 (d, $J_{AB} = 11.5$ Hz, 1 H), 4.41 (d, $J_{AB} = 11.5$ Hz, 1 H), 3.79 (s, 3 H), 3.54-3.44 (m, 2 H), 2.83 (br, 1 H), 2.35-2.24 (m, 2 H), 2.18-2.12 (m, 1 H), 2.03-1.97 (m, 1 H), 1.78-1.69 (m, 2 H), 1.67-1.64 (m, 1 H), 1.49-1.36 (m, 2 H), 1.08 (s, 3 H), 1.01 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.95 (C), 158.98 (C), 142.39 (C), 132.75 (CH), 130.48 (C), 130.30 (C), 129.50 (CH), 129.05 (CH), 128.25 (CH), 121.30 (CH), 113.62 (CH), 77.02 (CH), 72.40 (CH_2), 68.98 (CH_2), 55.14 (CH_3), 43.80 (CH), 40.75 (CH), 39.11 (C), 32.29 (CH_2), 31.50 (CH_2), 31.04 (CH_2), 27.17 (CH_2), 24.70 (CH_3), 22.65 (CH_3); HRMS m/z calculated for $\text{C}_{13}\text{H}_{19}\text{O}$ 191.1436 ($\text{M}^+ - \text{PMB} - \text{BzOH}$), found 191.1407.

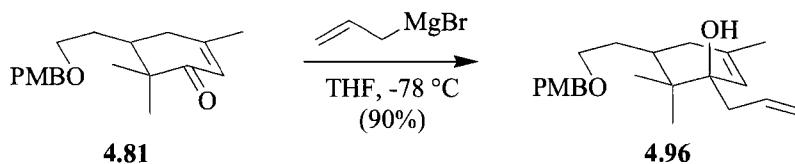


(±)-3,3a-dihydroxy-6-[2-(4-methoxybenzyloxy)-ethyl]-5,5-dimethyloctahydroinden-4-yl benzoate (**4.90**). To a Pyrex tube containing a stirred solution of **4.89** (84 mg, 0.193 mmol) in THF (2 mL) were added H_2O (1 mL), OsO_4 (4% in H_2O , 65 μL , 0.010 mmol) and NMO (45 mg, 0.384 mmol). The Pyrex tube was capped and covered with aluminum foil. The reaction mixture was heated at 80 °C for 17 h. After cooling to room temperature, it was quenched with saturated aqueous Na_2SO_3 (2 mL), and the resulting mixture was stirred for 20 minutes. The aqueous layer was separated from the organic layer and extracted with EtOAc (4 x 5 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (20% EtOAc/hexanes) to afford 76 mg of **4.90** as a pale brown oil (84% yield): IR (neat) ν_{max} 3446 (br), 2948, 2876, 1713, 1610, 1515, 1272, 1249, 1112 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.00 (d, $J = 7.4$ Hz, 2 H), 7.56 (dd, $J = 7.4, 7.4$ Hz, 1 H), 7.43 (dd, $J = 7.7, 7.7$ Hz, 2 H), 7.25 (d, $J = 8.5$ Hz, 2 H), 6.85 (d, $J = 8.5$ Hz, 2 H), 5.11 (s, 1 H), 4.47 (d, $J_{AB} = 11.5$ Hz, 1 H), 4.40 (d, $J_{AB} = 11.5$ Hz, 1 H), 4.02 (br, 1 H), 3.78 (s, 3 H), 3.58-3.51 (m, 1 H), 3.49-3.45 (m, 1 H), 3.35 (s, 1 H), 2.60 (d, $J = 4.4$ Hz, 1 H), 2.22-2.12 (m, 1 H), 2.02-1.81 (m, 5 H), 1.59-1.52 (m, 3H), 1.46-1.39 (m, 1 H), 1.06 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 166.62 (C), 158.97 (C), 133.16 (CH), 130.49 (C), 129.69 (C), 129.50 (CH), 129.04

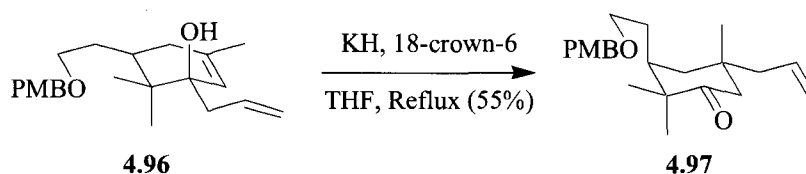
(CH), 128.51 (CH), 113.63 (CH), 82.57 (CH), 79.72 (C), 75.06 (CH), 72.37 (CH₂), 68.66 (CH₂), 55.14 (CH₃), 41.52 (CH), 37.88 (C), 35.01 (CH), 31.62 (CH₂), 28.41 (CH₂), 26.90 (CH₂), 26.42 (CH₂), 25.23 (CH₃), 22.13 (CH₃); HRMS m/z calculated for C₂₀H₂₇O₄ 331.1909 (M⁺ - OPMB), found 331.1855.



(±)-3,3a-dihydroxy-6-(2-hydroxy-ethyl)-5,5-dimethyl-octahydroinden-4-yl benzoate (**4.93**). To a solution of **4.90** (100 mg, 0.21 mmol) in CH₂Cl₂ (2.1 mL) were added H₂O (210 μL) and DDQ (73 mg, 0.32 mmol). After stirring at room temperature for 30 minutes, the reaction mixture was quenched with saturated aqueous NaHCO₃ (2 mL). The aqueous layer was separated from the organic layer and extracted with EtOAc (4 x 10 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (50% EtOAc/hexanes) to afford 70 mg of **4.93** as a white solid (94% yield): mp 66-68.5 °C; IR (neat) $\nu_{\max}$ 3408 (br), 2948, 2876, 1713, 1450, 1272, 1116 cm⁻¹; ¹H NMR (400 MHz, C₆D₆) δ 8.26-8.23 (m, 2 H), 7.20-7.03 (m, 3 H), 5.46 (d, J = 0.8 Hz, 1 H), 3.98 (ddd, J = 4.0, 4.0, 4.0 Hz, 1 H), 3.48-3.34 (m, 2 H), 3.28 (s, 1 H), 2.23-2.12 (m, 1 H), 2.07-1.87 (m, 3 H), 1.84-1.73 (m, 1 H), 1.71-1.50 (m, 5 H), 1.20 (s, 3 H), 1.18-1.11 (m, 1 H), 1.02 (s, 3 H); ¹³C NMR (100 MHz, C₆D₆) δ 166.38 (C), 132.96 (CH), 130.54 (C), 129.70 (CH), 128.63 (CH), 82.75 (CH), 79.49 (C), 75.21 (CH), 61.07 (CH₂), 42.02 (CH), 37.90 (C), 34.20 (CH), 32.31 (CH₂), 31.91 (CH₂), 26.91 (CH₂), 26.55 (CH₂), 25.53 (CH₃), 21.67 (CH₃); HRMS m/z calculated for C₂₀H₂₆O₄ 330.1831 (M⁺ - H₂O), found 330.1828.

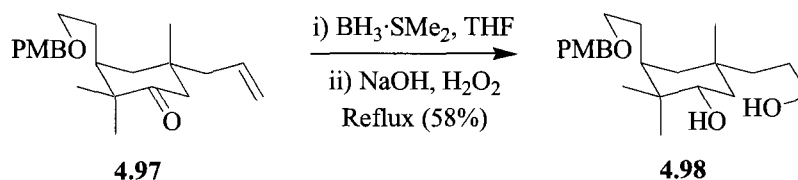


(±)-1-Allyl-5-[2-(4-methoxybenzyloxy)-ethyl]-3,6,6-trimethylcyclohex-2-enol (**4.96**). To a solution of **4.81** (44.5 mg, 0.147 mmol) in THF (1.5 mL) at -78 °C was added allylmagnesium bromide (440 µL of a 1.0 M solution in THF, 0.440 mmol) dropwise. After stirring at -78 °C for 30 minutes, the reaction mixture was quenched with saturated aqueous NH₄Cl (1 mL). Upon warming up to room temperature, the aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 5 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford 45.5 mg of **4.96** as a colorless oil (90% yield): IR (neat) $\nu_{\max}$ 3488 (br), 2975, 2914, 2857, 1612, 1513, 1439, 1363, 1301, 1247 cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ 7.37 (d, *J* = 8.7 Hz, 2 H), 6.92 (d, *J* = 8.7 Hz, 2 H), 6.18-6.10 (m, 1 H), 5.29 (s, 1 H), 5.19-5.12 (m, 2 H), 4.50 (d, *J*_{AB} = 11.7 Hz, 1 H), 4.45 (d, *J*_{AB} = 11.7 Hz, 1 H), 3.50-3.41 (m, 2 H), 3.40 (s, 3 H), 2.47 (dd, *J* = 13.3, 7.2 Hz, 1 H), 2.40 (dd, *J* = 13.3, 7.4 Hz, 1 H), 2.07-1.92 (m, 3 H), 1.61 (s, 3 H), 1.58-1.49 (m, 1 H), 1.39-1.34 (m, 1 H), 1.07 (s, 3 H), 0.95 (s, 3 H); ¹³C NMR (125 MHz, C₆D₆) δ 159.39 (C), 135.56 (CH), 132.73 (C), 131.01 (C), 129.08 (CH), 128.26 (CH), 117.36 (CH₂), 113.75 (CH), 75.61 (C), 72.43 (CH₂), 68.28 (CH₂), 54.42 (CH₃), 43.08 (CH₂), 39.35 (C), 36.60 (CH), 33.86 (CH₂), 30.11 (CH₂), 22.65 (CH₃), 20.95 (CH₃), 16.61 (CH₃); HRMS *m/z* calculated for C₂₂H₃₀O₂ 326.2246 (M⁺ - H₂O), found 326.2243.



(±)-5-Allyl-3-[2-(4-methoxybenzyloxy)-ethyl]-2,2,5-trimethylcyclohexanone (**4.97**). KH (30% in mineral oil, 71 mg, 0.531 mmol) was washed with dry hexanes (3 x 2 mL). The remaining solvent was removed under high vacuum and the flask was backfilled with argon. To a suspension of this freshly washed KH in THF (600 µL) at room temperature was added a solution of **4.96** (45.5 mg, 0.132 mmol) and 18-crown-6 (140 mg, 0.530 mmol) in THF (2 mL). The resulting mixture was refluxed for 30 minutes. After cooling down to room temperature, MeOH (100 µL) was added dropwise, followed by saturated aqueous NH₄Cl (2

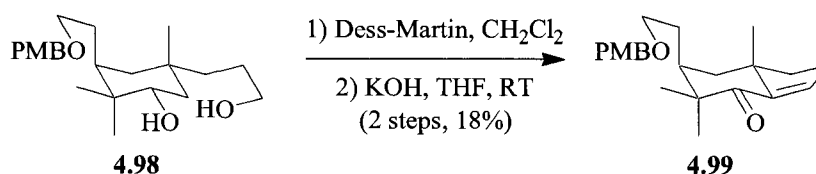
mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 10 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford 25 mg of **4.97** as a pale yellow oil (55% yield): IR (neat) $\nu_{\max}$ 3073, 2956, 2925, 2864, 1703, 1613, 1513, 1462, 1248, 1100 cm⁻¹; ¹H NMR (400 MHz, C₆D₆) δ 7.30 (d, J = 8.7 Hz, 2 H), 6.89 (d, J = 8.7 Hz, 2 H), 5.78-5.67 (m, 1 H), 5.09-5.01 (m, 2 H), 4.40 (d, J_{AB} = 11.7 Hz, 1 H), 4.36 (d, J_{AB} = 11.7 Hz, 1 H), 3.41-3.30 (m, 5 H), 2.21 (d, J = 13.4 Hz, 1 H), 2.16 (dd, J = 13.4, 2.3 Hz, 1 H), 1.96 (dd, J = 13.8, 7.6 Hz, 1 H), 1.88-1.77 (m, 3 H), 1.57 (ddd, J = 14.0, 3.5, 2.4 Hz, 1 H), 1.25 (s, 3 H), 1.22-1.14 (m, 1 H), 1.09 (dd, J = 13.4, 13.4 Hz, 1 H), 0.80 (s, 6 H); ¹³C NMR (125 MHz, C₆D₆) δ 212.93 (C), 159.42 (C), 133.92 (CH), 130.80 (C), 129.06 (CH), 117.74 (CH₂), 113.76 (CH), 72.48 (CH₂), 68.33 (CH₂), 54.42 (CH₃), 49.36 (CH₂), 47.04 (C), 41.95 (CH₂), 38.77 (CH), 37.86 (CH₂), 36.50 (C), 30.22 (CH₂), 28.02 (CH₃), 22.01 (CH₃), 18.98 (CH₃); HRMS m/z calculated for C₂₂H₃₂O₃ 344.2351 (M⁺), found 344.2337.



(±)-5-(3-Hydroxypropyl)-3-[2-(4-methoxybenzyloxy)-ethyl]-2,2,5-trimethylcyclohexanol (4.98**).**

To a solution of **4.97** (32.5 mg, 0.096 mmol) in THF (1 mL) at room temperature was added BH₃·SMe₂ (15 μ L, 0.158 mmol). After stirring for 1 h, the solution was cooled down to 0 °C. Aqueous 3 M NaOH (500 μ L) was added dropwise. This was followed by the dropwise addition of aqueous H₂O₂ (500 μ L). The resulting mixture was then refluxed for 1 h. After cooling down to room temperature, the aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 5 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (40% then 60% EtOAc/hexanes) to afford 20 mg of **4.98** as a colorless oil (58% yield): IR (neat) $\nu_{\max}$ 3416 (br), 2944, 2864, 1610, 1515, 1462, 1363, 1245 cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ 7.40 (d, J = 8.7 Hz, 2 H), 6.95 (d, J = 8.7 Hz, 2 H), 4.52 (d, J_{AB} = 11.7 Hz, 1 H), 4.47 (d, J_{AB} = 11.7 Hz, 1 H), 3.73-

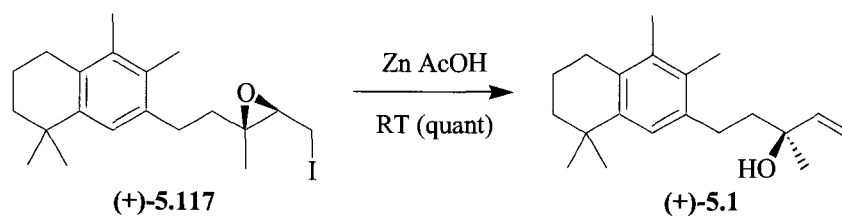
3.69 (m, 1 H), 3.64-3.51 (m, 3 H), 3.43 (s, 3 H), 3.38 (t, $J = 3.1$ Hz, 1 H), 2.62 (br, 2 H), 2.19-2.08 (m, 2 H), 2.03-1.97 (m, 1 H), 1.75 (ddd, $J = 14.7, 2.5, 2.5$ Hz, 1 H), 1.69-1.61 (m, 1 H), 1.56-1.48 (m, 2 H), 1.39-1.33 (m, 2 H), 1.30-1.16 (m, 1 H), 1.11 (dd, $J = 13.1, 13.1$ Hz, 1 H), 1.06 (s, 3 H), 0.89 (s, 3 H), 0.75 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 159.34 (C), 131.16 (C), 129.02 (CH), 113.77 (CH), 77.76 (CH), 72.42 (CH_2), 69.00 (CH_2), 63.11 (CH_2), 54.44 (CH_3), 41.11 (CH_2), 37.27 (C), 37.06 (CH_2), 35.66 (CH_2), 32.63 (C), 32.60 (CH), 30.24 (CH_2), 30.06 (CH_3), 27.43 (CH_2), 25.03 (CH_3), 19.59 (CH_3); HRMS m/z calculated for $\text{C}_{22}\text{H}_{34}\text{O}_3$ 346.2508 ($\text{M}^+ - \text{H}_2\text{O}$), found 346.2509.



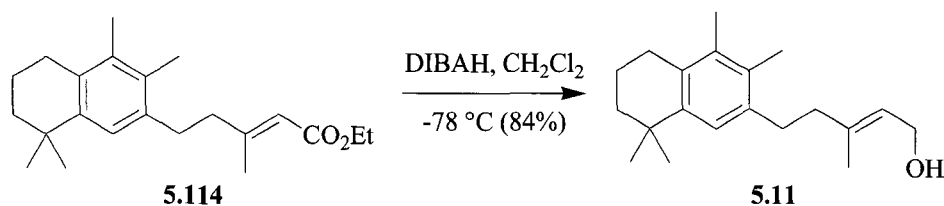
(±)-6-[2-(4-Methoxybenzyloxy)-ethyl]-5,5,7a-trimethyl-1,2,5,6,7,7a-hexahydroinden-4-one

(4.99). *Step 1:* To a solution of **4.98** (20 mg, 0.055 mmol) in CH_2Cl_2 (800 μL) at 0 °C was added DMP (105 mg, 0.248 mmol). The resulting cloudy white mixture was stirred at room temperature for 3.5 h. Then, saturated aqueous NaHCO_3 (500 μL) and saturated aqueous Na_2SO_3 (500 μL) were added and the resulting biphasic mixture was stirred vigorously for 20 minutes. The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 x 5 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After filtration, the solvent was removed under reduced pressure to deliver the crude keto-aldehyde. *Step 2:* To a solution of the crude product in THF (1 mL) was added KOH powder (56 mg, 1.00 mmol). The resulting suspension was stirred at room temperature for 17 h. It was then diluted with Et_2O (1 mL) and quenched with saturated aqueous NaCl (2 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% EtOAc /hexanes) to afford 3.4 mg of **4.99** as a yellow oil (18% yield over 2 steps): IR (neat) ν_{max} 2924, 2855, 1682, 1613, 1513, 1457, 1247 cm^{-1} ; ^1H NMR (500 MHz, C_6D_6) δ 7.34 (d, $J = 8.7$ Hz, 2 H), 6.92 (d, $J = 8.7$ Hz, 2 H), 6.32 (dd, $J = 3.4, 2.0$ Hz, 1 H), 4.48 (d, $J_{\text{AB}} = 11.8$ Hz, 1 H), 4.41 (d, $J_{\text{AB}} = 11.8$ Hz, 1 H),

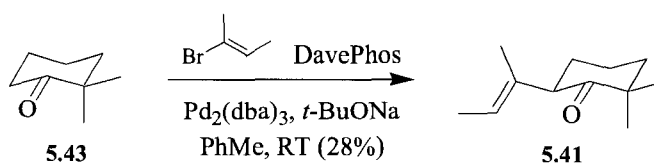
3.45-3.37 (m, 5 H), 2.23-2.16 (m, 1 H), 1.97 (dddd, $J = 8.2, 8.2, 8.2, 3.6$ Hz, 1 H), 1.89-1.82 (m, 2 H), 1.79-1.70 (m, 3 H), 1.51-1.40 (m, 1 H), 1.31 (s, 3 H), 1.22-1.15 (m, 1 H), 1.03 (s, 3 H), 1.01 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 204.94 (C), 159.42 (C), 149.97 (C), 135.02 (CH), 130.90 (C), 129.04 (CH), 113.76 (CH), 72.43 (CH_2), 68.22 (CH_2), 54.42 (CH_3), 46.91 (C), 43.84 (C), 43.70 (CH_2), 38.66 (CH_2), 38.06 (CH), 29.72 (CH_2), 29.60 (CH_2), 27.06 (CH_3), 24.21 (CH_3), 17.68 (CH_3); HRMS m/z calculated for $\text{C}_{14}\text{H}_{22}\text{O}$ 206.1671 ($\text{M}^+ - \text{OPMB}$), found 206.1711.



(+)-Isofregenedol (5.1). To a solution of **5.117** (94 mg, 0.23 mmol) in glacial AcOH (2.3 mL) was added zinc dust (196 mg, 3.00 mmol) in one portion. After stirring for 1 h, wet Et_2O (10 mL) was added and the resulting mixture was filtered through a fritted glass funnel. The funnel was rinsed with Et_2O (10 mL). The filtrate was washed successively with H_2O , saturated aqueous Na_2SO_3 , saturated aqueous NaHCO_3 , and saturated aqueous NaCl . It was then dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford 65 mg of **5.1** as a white solid (quantitative yield): mp 75-77 °C; $[\alpha]_D^{22} = +21$ (c 0.015, CHCl_3); IR (neat) ν_{max} 3408 (br), 2927, 2866, 1458, 1360, 1105 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.01 (s, 1 H), 5.99 (dd, $J = 17.3, 10.8$ Hz, 1 H), 5.27 (dd, $J = 17.3, 1.1$ Hz, 1 H), 5.12 (dd, $J = 10.8, 1.1$ Hz, 1 H), 2.68-2.58 (m, 4 H), 2.17 (s, 3 H), 2.12 (s, 3 H), 1.82-1.68 (m, 4 H), 1.60-1.57 (m, 2 H), 1.54 (s, 1 H), 1.34 (s, 3 H), 1.26 (s, 6 H); ^{13}C NMR (125 MHz, CDCl_3) δ 144.72 (CH), 143.10 (C), 137.38 (C), 134.87 (C), 132.33 (C), 131.28 (C), 124.85 (CH), 111.88 (CH_2), 73.25 (C), 43.28 (CH_2), 38.54 (CH_2), 33.62 (C), 31.85 (CH_3), 31.85 (CH_3), 28.85 (CH_2), 28.31 (CH_2), 27.85 (CH_3), 19.55 (CH_2), 15.53 (CH_3), 15.32 (CH_3); HRMS m/z calculated for $\text{C}_{20}\text{H}_{30}\text{O}$ 286.2297 (M^+), found 286.2296.

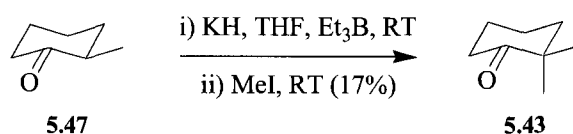


(*E*)-3-Methyl-5-(3,4,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-pent-2-enol (5.11). A solution of **5.114** (320 mg, 0.98 mmol) in CH_2Cl_2 (9.8 mL) was cooled to $-78\text{ }^{\circ}\text{C}$, and DIBALH (3.0 mL of a 1.0 M solution in CH_2Cl_2 , 3.00 mmol) was added dropwise over 5 minutes. After the mixture had been stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h, the reaction was quenched by adding a 5 M solution (4 mL) of AcOH in CH_2Cl_2 at $-78\text{ }^{\circ}\text{C}$. The resulting mixture was then stirred at room temperature, and 25% aqueous sodium tartrate (5 mL) and H_2O (4 mL) were sequentially added. The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 x 10 mL). Combined organics were washed successively with saturated aqueous NaHCO_3 and saturated aqueous NaCl. The aqueous layer was then dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (20% EtOAc/hexanes) to afford 236 mg of **5.11** as a pale yellow oil (84% yield): IR (neat) ν_{max} 3335 (br), 2927, 2866, 1668, 1473, 1458 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.00 (s, 1 H), 5.47 (td, $J = 6.9, 1.2$ Hz, 1 H), 4.16 (d, $J = 5.8$ Hz, 2 H), 2.73–2.70 (m, 2 H), 2.62 (t, $J = 6.5$ Hz, 2 H), 2.24–2.21 (m, 2 H), 2.19 (s, 3 H), 2.13 (s, 3 H), 1.83–1.78 (m, 2 H), 1.75 (s, 3 H), 1.60–1.58 (m, 2 H), 1.26 (s, 6 H), 1.14 (br, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 142.98 (C), 139.69 (C), 137.11 (C), 134.79 (C), 132.36 (C), 131.21 (C), 124.79 (CH), 123.26 (CH), 59.27 (CH_2), 40.69 (CH_2), 38.53 (CH_2), 33.61 (C), 33.03 (CH_2), 31.87 (CH_3), 31.87 (CH_3), 28.33 (CH_2), 19.56 (CH_2), 16.35 (CH_3), 15.55 (CH_3), 15.34 (CH_3); HRMS m/z calculated for $\text{C}_{20}\text{H}_{30}\text{O}$ 286.2297 (M^+), found 286.2284.



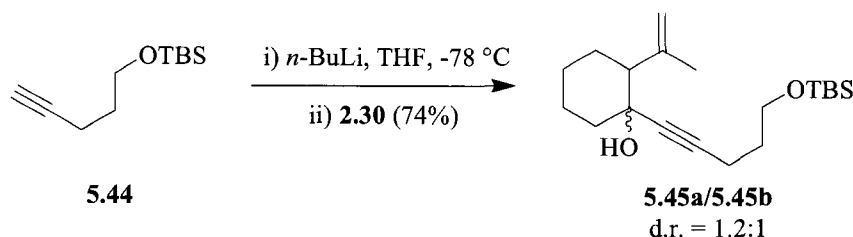
($\pm$)-2,2-Dimethyl-6-(1-methylpropenyl)-cyclohexanone (5.41). An oven-dried Schlenk tube equipped with a rubber septum was allowed to cool under an argon purge. The septum was

removed and the tube was charged with $\text{Pd}_2(\text{dba})_3$ (147 mg, 0.16 mmol), DavePhos (126 mg, 0.32 mmol) and **5.43** (531 mg, 4.21 mmol). Toluene (9 mL) was added and the mixture was stirred for 15 min at room temperature. 2-bromo-*cis*-2-butene (1.06 mL, 10.54 mmol) and *t*-BuONa (1.18 g, 10.53 mmol) were added. The Schlenk tube was capped with a septum, purged with argon, and additional toluene (10 mL) was added through the septum. After stirring for 2.5 h, the reaction mixture was diluted with Et_2O and quenched with saturated aqueous NH_4Cl (20 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 20 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% Et_2O /petroleum ether) to afford 213 mg of **5.41** as a yellow oil (28% yield): IR (neat) ν_{max} 2965, 2931, 2865, 1707, 1453 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.22-5.17 (m, 1 H), 3.18 (dd, J = 12.7, 5.4 Hz, 1 H), 1.97-1.83 (m, 2 H), 1.82-1.68 (m, 4 H), 1.60 (d, J = 6.6 Hz, 3 H), 1.55 (s, 3 H), 1.17 (s, 3 H), 1.02 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 215.54 (C), 134.51 (C), 121.02 (CH), 56.02 (CH), 45.60 (C), 41.45 (CH_2), 32.85 (CH_2), 25.64 (CH_3), 25.63 (CH_3), 21.47 (CH_2), 14.75 (CH_3), 13.35 (CH_3); HRMS m/z calculated for $\text{C}_{12}\text{H}_{20}\text{O}$ 180.1514 (M^+), found 180.1517.



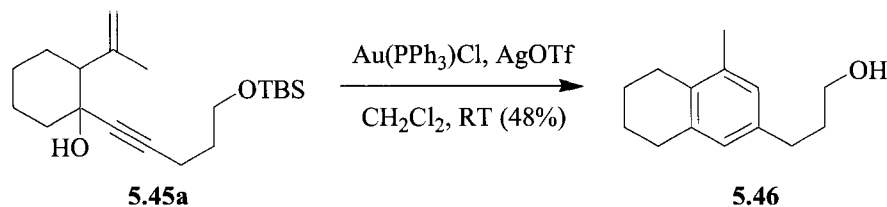
2,2-dimethylcyclohexanone (5.43). In the glovebox, dry KH (1.88 g, 46.87 mmol) was placed in a 500-mL flame-dried flask. The flask was cooled to 0 °C, and a solution of 2-methylcyclohexanone **5.47** (5.00 g, 44.58 mmol) was added dropwise, yielding moderate gas evolution. Triethylborane (56.0 mL of a 1 M solution in THF, 56.0 mmol) was then added over a 10-minute period. After stirring at room temperature for 12 h, MeI (8.40 mL, 134.63 mmol) was added dropwise. The resulting cloudy white mixture was stirred for 10 h, at which point it was poured into saturated aqueous NH_4Cl (100 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (2 x 100 mL). Combined organics were dried over MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes $\rightarrow$ 5% Et_2O /hexanes) to afford 931 mg of

5.43 as a colorless oil (17% yield). Spectroscopic data for **5.43** were identical to that of the commercially available compound.

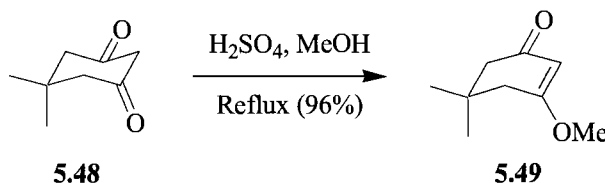


(±)-1-[5-(*t*-Butyldimethylsilyloxy)-pentynyl]-2-isopropenylcyclohexanol (5.45**). To a solution of **5.44** (287 mg, 1.45 mmol) in THF (6 mL) at -78 °C was added *n*-BuLi (650 μL of a 2.0 M solution in pentane, 1.30 mmol) dropwise. The resulting pale yellow solution was stirred at that temperature for 45 minutes.¹⁴⁵ A solution of ketone **2.30** (100 mg, 0.72 mmol) in THF (1.2 mL) was then added dropwise via cannula. After stirring at -78 °C for 40 minutes, the reaction mixture was quenched with saturated aqueous NH₄Cl (5 mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 10 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (2% then 4% EtOAc/hexanes) to afford 99 mg of **5.45a** (41% yield) and 80 mg of **5.45b** (33% yield) as colorless oils. Epimer **5.45a**: IR (neat) ν_{max} 3454, 2929, 2861, 2235, 1640, 1469, 1253, 1108 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.03 (s, 6 H), 0.87 (s, 9 H), 1.16-1.28 (m, 1 H), 1.45 (ddd, *J* = 12.6, 12.6, 4.5 Hz, 1 H), 1.59-1.73 (m, 7 H), 1.84 (s, 3 H), 1.99-2.04 (m, 1 H), 2.07-2.15 (m, 1 H), 2.28 (t, *J* = 7.2 Hz, 2 H), 2.60 (s, 1 H), 3.66 (t, *J* = 6.3 Hz, 2 H), 4.87-4.89 (m, 1 H), 4.93-4.95 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 145.75 (C), 114.69 (CH₂), 86.25 (C), 82.07 (C), 69.94 (C), 61.74 (CH₂), 56.30 (CH), 40.85 (CH₂), 31.77 (CH₂), 28.61 (CH₂), 25.93 (CH₃), 25.73 (CH₂), 24.05 (CH₂), 21.01 (CH₃), 18.33 (C), 15.19 (CH₂), -5.35 (CH₃); HRMS *m/z* calculated for C₁₆H₂₇O₂Si 279.1780 (*M*⁺ - *t*-Bu), found 279.1772. Epimer **5.45b**: IR (neat) ν_{max} 3568, 3469, 2933, 2857, 2233, 1637, 1469, 1249, 1104 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.94 (dd, *J* = 1.6, 1.6 Hz, 1 H), 4.79 (br, 1 H), 3.63 (t, *J* = 6.1 Hz, 2 H), 2.22 (t, *J* = 7.1 Hz, 2 H), 2.13 (dd, *J* = 12.8, 3.5 Hz, 1 H), 2.10-2.02 (m, 2 H), 1.94 (s, 3 H), 1.72-1.39 (m, 8 H), 1.26-1.16 (m, 1 H), 0.86 (s, 9 H), 0.02 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 148.54 (C), 111.97 (CH₂), 85.24 (C), 83.09 (C),**

67.04 (C), 61.63 (CH₂), 52.85 (CH), 40.14 (CH₂), 31.70 (CH₂), 26.85 (CH₂), 25.97 (CH₃), 25.94 (CH₃), 25.84 (CH₂), 20.75 (CH), 18.33 (C), 15.06 (CH₂), -5.32 (CH₃); HRMS m/z calculated for C₁₆H₂₇O₂Si 279.1780 (M⁺ - *t*-Bu), found 279.1769.

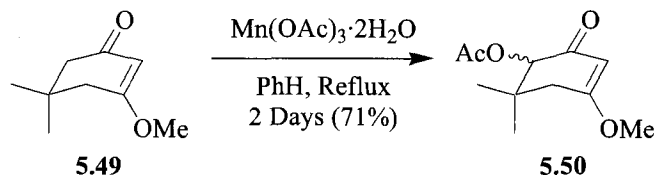


3-(4-Methyl-5,6,7,8-tetrahydronaphthalen-2-yl)propanol (5.46). AgOTf (1 mg, 0.004 mmol) and Au(PPh₃)Cl (2 mg, 0.004 mmol) were weighed in the glovebox and transferred to a flame-dried flask equipped with a magnetic stirrer. Then, a solution of **5.45a** (56 mg, 0.167 mmol) in CH₂Cl₂ (1.7 mL) was added via cannula. After stirring at room temperature for 15 h, the reaction mixture was filtered through celite. The fritted glass funnel was rinsed with Et₂O (10 mL), and the filtrate was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (20% EtOAc/hexanes) to afford 16.5 mg of **5.46** as a yellow oil (48% yield): IR (neat) $\nu_{\max}$ 3351 (br), 2925, 2857, 1610, 1580, 1481, 1450, 1435 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.82 (s, 1 H), 6.77 (s, 1 H), 3.67 (t, J = 6.4 Hz, 2 H), 2.73 (t, J = 6.2 Hz, 2 H), 2.61-2.56 (m, 4 H), 2.18 (s, 3 H), 1.90-1.71 (m, 6 H), 1.31 (br, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 138.48 (C), 137.14 (C), 136.64 (C), 133.08 (C), 127.29 (CH), 126.83 (CH), 62.57 (CH₂), 34.41 (CH₂), 31.61 (CH₂), 30.13 (CH₂), 26.43 (CH₂), 23.52 (CH₂), 22.98 (CH₂), 19.49 (CH₃); HRMS m/z calculated for C₁₄H₂₀O 204.514 (M⁺), found 204.1521.

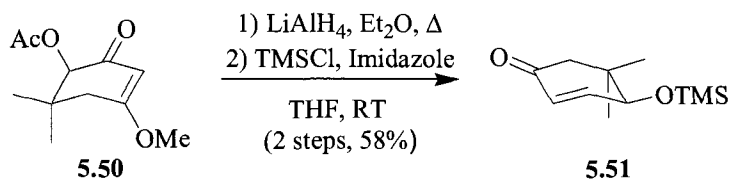


3-Methoxy-5,5-dimethylcyclohex-2-enone (5.49). To a solution of 5,5-dimethylcyclohexan-1,3-dione **5.48** (6.00g, 42.80 mmol) in MeOH (230 mL) was added concentrated H₂SO₄ (1 mL). The mixture was refluxed for 2 h. After cooling down to room temperature, most of the solvent was evaporated under reduced pressure. Saturated aqueous NaHCO₃ was then added

to the concentrate until the pH reached 8. The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 x 250 mL). Combined organics were dried over MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (50% EtOAc/hexanes) to afford 6.33 g of **5.49** as a yellow solid (96% yield). Spectroscopic data for **5.49** were identical to that of the commercially available compound.

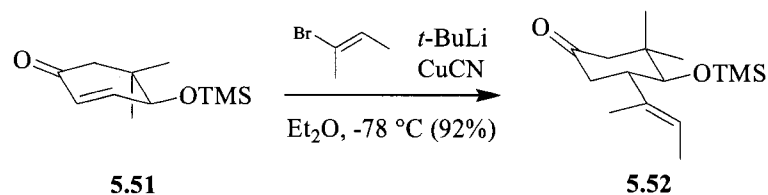


(±)-4-methoxy-6,6-dimethyl-2-oxocyclohex-3-enyl acetate (**5.50**). In a round-bottom flask equipped with a Dean-Stark trap, a suspension of $\text{Mn(OAc)}_3 \cdot 2\text{H}_2\text{O}$ (44.10 g, 164.49 mmol) in benzene (600 mL) was refluxed for 2 h. The mixture was then cooled to room temperature, and **5.49** (6.33 g, 41.08 mmol) was added. The resulting suspension was further refluxed for 2 days. After cooling down to room temperature, the mixture was diluted with AcOEt (600 mL). The organic layer was washed sequentially with 1 N HCl (1 L), saturated NaHCO_3 (1 L) and saturated aqueous NaCl (1 L). It was then dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (50% EtOAc/hexanes) to afford 6.18 g of **5.50** as a yellow oil (71% yield). Spectroscopic data for **5.50** were identical to that previously reported.¹⁴⁶



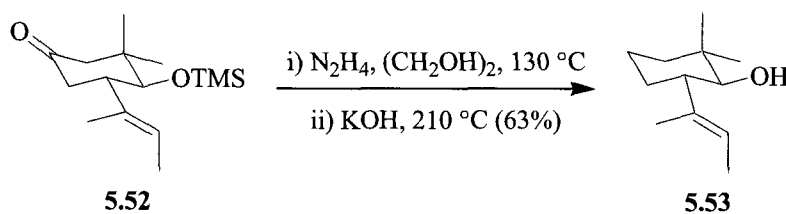
(±)-5,5-Dimethyl-4-trimethylsilyloxycyclohex-2-enone (**5.51**). To a suspension of LiAlH_4 (2.17 g, 57.18 mmol) in Et_2O (120 mL) at room temperature was added a solution of **5.50** (6.18 g, 29.14 mmol) in Et_2O (8 mL) dropwise via cannula. The resulting mixture was stirred at room temperature for 30 minutes and was then refluxed for 3 h. After cooling down to 0 °C, the reaction mixture was quenched by a dropwise addition of H_2O (40 mL) followed by

an addition of 10% aqueous solution H_2SO_4 (100 mL). The resulting suspension was stirred at room temperature for 3 h. The aqueous layer was separated from the organic layer and extracted with AcOEt (3 x 120 mL). Combined organics were washed with saturated aqueous NaHCO_3 and dried over anhydrous MgSO_4 . Filtration and removal of the solvent delivered the crude alcohol. To a solution of this alcohol in THF (90 mL) were added imidazole (1.98 g, 29.08 mmol) and TMSCl (3.70 mL, 29.15 mmol). After stirring at room temperature for 3 h, the reaction mixture was quenched with saturated aqueous NaCl (75 mL). The aqueous layer was separated from the organic layer and extracted with AcOEt (3 x 75 mL). Combined organics were dried over MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford **5.51** as a pale yellow solid (58% yield over 2 steps). Spectroscopic data for **5.51** were identical to that previously reported.¹¹⁹



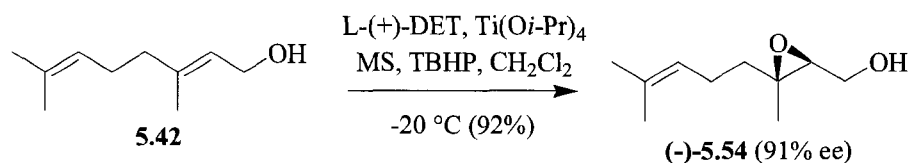
(±)-3,3-Dimethyl-5-(1-methylpropenyl)-4-trimethylsilanyloxycyclohexanone (**5.52**). Prior to any manipulation, Et_2O was degassed with argon for at least 30 minutes. To a solution of *trans*-2-bromobut-2-ene (2.11 mL, 19.93 mmol) in Et_2O (42 mL) at $-78\text{ }^\circ\text{C}$ was added *t*-BuLi (22.3 mL of a 1.7 M solution in pentane, 37.90 mmol) over a 10-minute period. The resulting cloudy solution was stirred at $-78\text{ }^\circ\text{C}$ for 2 h. A separate flame-dried flask was charged with CuCN (893 mg, 9.97 mmol) and dried under vacuum using a heat gun for at least 3 minutes. The flask was then carefully backfilled with argon. Et_2O (42 mL) was added and the resulting suspension was cooled to $-78\text{ }^\circ\text{C}$. The vinyl lithium solution was added to the CuCN suspension dropwise via cannula. The resulting pale brown mixture was stirred for 10 minutes at $-78\text{ }^\circ\text{C}$. The cold bath was removed and the reaction mixture was stirred for an additional 10 minutes, during which time it became slightly yellow. The solution was then cooled to $-78\text{ }^\circ\text{C}$ and, after 5 minutes, a solution of **5.51** (1.06 g, 4.98 mmol) in Et_2O (8 mL) was added dropwise via cannula. After stirring at $-78\text{ }^\circ\text{C}$ for 30 minutes, the reaction mixture was quenched with 100 mL a solution of NH_4OH in saturated aqueous NH_4Cl (pH 8). The

cold bath was removed and the mixture was stirred at room temperature for 1 h. The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 100 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% EtOAc/hexanes) to afford 1.24 g of **5.52** as a white solid (92% yield): mp 89-90.5°C; IR (neat) ν_{max} 2958, 2864, 1715, 1249, 1112 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.34-5.31 (m, 1 H), 3.69 (d, J = 10.0 Hz, 1 H), 2.48 (dddd, J = 13.2, 5.0, 5.0, 5.0 Hz, 1 H), 2.38 (ddd, J = 14.0, 13.2, 1.0 Hz, 1 H), 2.28 (d, J = 13.7 Hz, 1 H), 2.17 (ddd, J = 14.0, 4.6, 3.1 Hz, 1 H), 2.08 (dd, J = 13.6, 3.1 Hz, 1 H), 1.58-1.56 (m, 6 H), 0.99 (s, 3 H), 0.84 (s, 3 H), 0.05 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) δ 210.08 (C), 134.47 (C), 122.24 (CH), 78.39 (CH), 52.96 (CH₂), 50.29 (CH), 44.59 (CH₂), 39.25 (C), 29.50 (CH₃), 19.64 (CH₃), 13.27 (CH₃), 12.95 (CH₃), 0.55 (CH₃); HRMS m/z calculated for C₁₅H₂₈O₂Si 268.1859 (M⁺), found 268.1866.

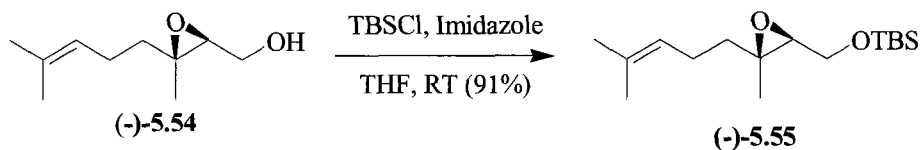


(±)-2,2-Dimethyl-6-(1-methylpropenyl)-cyclohexanol (5.53). A solution of **5.52** (50 mg, 0.19 mmol) in a 10-mL round-bottom flask was degassed by placing under high vacuum, with stirring, for 45 minutes. Hydrazine hydrate (45 μ L, 0.93 mmol) was added, and the flask was fitted with a reflux condenser. The atmosphere over the solution was replaced with argon (3 vacuum-refill cycles), and the mixture was heated at 130°C for 1 h. The reaction was cooled down to room temperature, and KOH (104 mg, 1.86 mmol) was added in one portion. The reaction mixture was heated at 210°C for 3 h and was then cooled back to room temperature. H₂O (3 mL) and Et₂O (2 mL) were added, and the resulting biphasic mixture was stirred for 30 minutes. The aqueous layer was separated from the organic layer and extracted with Et₂O (5 x 5 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (2% EtOAc/hexanes) to afford 21.5 mg of **5.53** as a pale

yellow oil (63% yield): mp 85.5-86.5 °C; IR (neat) ν_{max} 3563, 3501, 2969, 2927, 2863, 1446, 1393 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.39-5.35 (m, 1 H), 3.11 (dd, J = 10.5, 2.1 Hz, 1 H), 2.05-1.99 (m, 1 H), 1.60 (dd, J = 6.6, 0.8 Hz, 3 H), 1.57-1.52 (m, 5 H), 1.45-1.38 (m, 3 H), 1.35-1.26 (m, 1 H), 1.23-1.16 (m, 1 H), 1.01 (s, 3 H), 0.88 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 136.57 (C), 122.12 (CH), 76.69 (CH), 50.54 (CH), 39.43 (CH_2), 35.05 (C), 30.53 (CH_2), 29.71 (CH_3), 21.28 (CH_2), 18.10 (CH_3), 13.13 (CH_3), 11.69 (CH_3); HRMS m/z calculated for $\text{C}_{12}\text{H}_{22}\text{O}$ 182.1671 (M^+), found 182.1649.



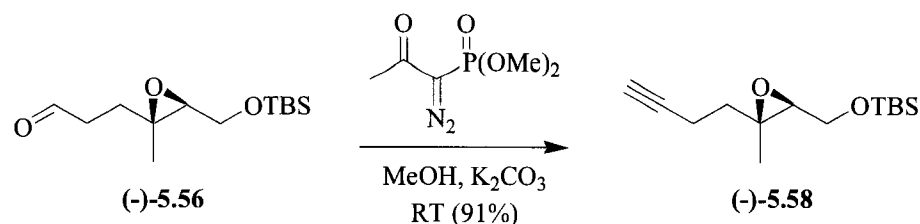
(-)-(2*S*,3*S*)-[3-Methyl-3-(4-methylpent-3-enyl)-oxiranyl]-methanol (5.54). A suspension of activated 4Å molecular sieves (200 mg) in CH_2Cl_2 (8 mL) was cooled to -10 °C. L-(+)-DET (80 μL , 0.47 mmol), Ti(Oi-Pr)_4 (100 μL , 0.34 mmol), and TBHP (1.80 mL, 9.90 mmol, 5.5 M in decane) were added sequentially. After 10 minutes of stirring, the mixture was cooled to -20 °C, and a solution of geraniol **5.42** (1.00 g, 6.48 mmol) in CH_2Cl_2 (3 mL) was added dropwise via cannula. After 1 h of stirring at -20 °C, the reaction mixture was warmed to 0 °C. It was stirred at that temperature for 5 minutes, and was then quenched by adding sequentially 4 mL of H_2O and 2 mL of 30% aqueous NaOH saturated with solid NaCl. After 10 minutes of vigorous stirring, the resulting mixture was partitioned between CH_2Cl_2 and H_2O . The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 x 10 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (50% $\rightarrow$ 80% EtOAc/hexanes) to afford 1.02 g of **5.54** as a pale yellow oil (92% yield). Spectroscopic data for **5.54** were identical to that previously reported.¹⁴⁷



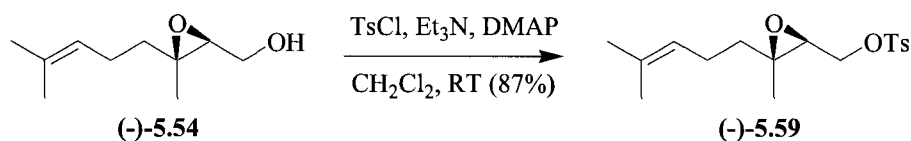
To a solution of **5.54** (500 mg, 2.94 mmol) in THF (30 mL) at room temperature were added TBSCl (576 mg, 3.82 mmol) and imidazole (600 mg, 8.81 mmol). After stirring for 2 h, the reaction mixture was quenched with saturated aqueous NH₄Cl (15 mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 15 mL). Combined organics were dried over MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes → 5% EtOAc/hexanes) to afford 759 mg of **5.55** as a pale yellow oil (91% yield). Spectroscopic data for **5.55** were identical to that previously reported.¹⁴⁸



Through a solution of **5.55** (705 mg, 2.48 mmol) in CH₂Cl₂ (25 mL) at -78 °C was bubbled ozone for 5 minutes, at which point the solution turned clear blue. Oxygen was then bubbled through the solution for 5 minutes and the blue color disappeared. Me₂S (910 μL, 12.39 mmol) was added dropwise. The solution was warmed up to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (20% EtOAc/hexanes) to afford 531 mg of **5.56** as a pale yellow oil (83% yield): $[\alpha]_D^{22} = -7$ (c 0.008, CH₂Cl₂); IR (neat) $\nu_{\max}$ 2955, 2930, 2857, 2721, 1727, 1463, 1256 cm⁻¹; ¹H NMR (400 MHz, C₆D₆) δ 9.29 (t, $J = 1.4$ Hz, 1 H), 3.69 (dd, $J = 5.3$ Hz, 2.0 Hz, 2 H), 2.83 (dd, $J = 5.3, 5.3$ Hz, 1 H), 1.92 (td, $J = 7.5, 1.3$ Hz, 2 H), 1.65-1.51 (m, 2 H), 1.04 (s, 9 H), 1.00 (s, 3 H), 0.14 (s, 3 H), 0.12 (s, 3 H); ¹³C NMR (100 MHz, C₆D₆) δ 199.38 (CH), 62.33 (CH₂), 62.25 (CH), 58.76 (C), 38.73 (CH₂), 29.92 (CH₂), 25.82 (CH₃), 18.22 (C), 16.76 (CH₃), -5.25 (CH₃), -5.52 (CH₃); HRMS m/z calculated for C₉H₁₇O₃Si 201.0947 (M⁺ - *t*-Bu), found 201.0947.

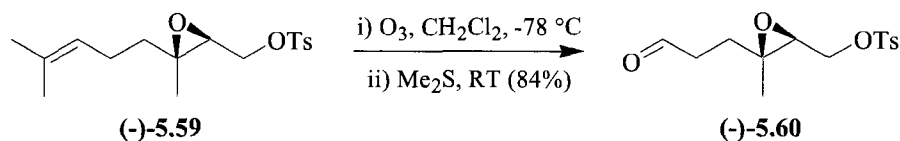


(-)-(2*S*,3*S*)-*t*-Butyl-(3-but-3-ynyl-3-methyloxiranylmethoxy)-dimethylsilane (5.58). To a solution of **5.56** (10 mg, 0.039 mmol) in MeOH (500 μL) was added K_2CO_3 (11 mg, 0.080 mmol). To this mixture was added a solution of dimethyl 1-diazo-2-oxopropyl phosphonate (9 mg, 0.047 mmol) in MeOH (500 μL) via cannula. After stirring at room temperature for 20 h, the reaction mixture was diluted with Et_2O (5 mL). The resulting solution was washed with saturated aqueous NaHCO_3 (3 mL) and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% EtOAc /hexanes) to afford 9 mg of **5.58** as an orange oil (91% yield): $[\alpha]_D^{22} = -1$ (c 0.009, CH_2Cl_2); IR (neat) ν_{max} 3313, 2955, 2930, 2857, 2123, 1473, 1255 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.76 (dd, $J_{\text{AB}} = 11.6$ Hz, $J_{\text{AX}} = 5.0$ Hz, 1 H), 3.69 (dd, $J_{\text{AB}} = 11.6$ Hz, $J_{\text{BX}} = 6.0$ Hz, 1 H), 2.96 (dd, $J = 5.3, 5.3$ Hz, 1 H), 2.27 (tdd, $J = 8.0, 2.7, 0.9$ Hz, 2 H), 1.94 (t, $J = 2.7$ Hz, 1 H), 1.86 (dt, $J = 13.9, 7.0$ Hz, 1 H), 1.69 (dt, $J = 13.9, 8.0$ Hz, 1 H), 1.27 (s, 3 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 83.45 (C), 68.83 (C), 63.19 (CH), 62.19 (CH_2), 59.59 (C), 37.13 (CH_2), 25.88 (CH), 18.32 (C), 16.58 (C), 14.42 (CH_2), -5.17 (CH_3), -5.33 (CH_3); HRMS m/z calculated for $\text{C}_{10}\text{H}_{17}\text{O}_2\text{Si}$ 197.0998 ($\text{M}^+ - t\text{-Bu}$), found 197.0990.



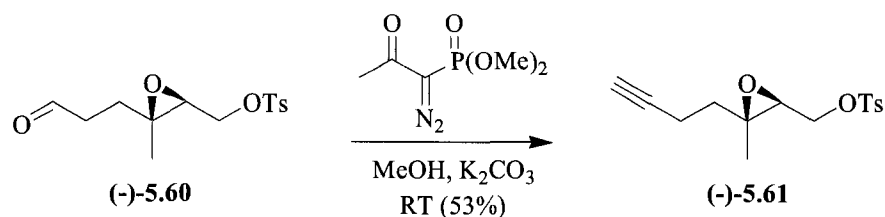
(-)-(2*S*,3*S*)-3-methyl-3-(4-methylpent-3-enyl)-oxiranylmethyl 4-toluenesulfonate (5.59). To a solution of tosyl chloride (158 mg, 0.83 mmol) and DMAP (22 mg, 0.18 mmol) in CH_2Cl_2 (5 mL) at room temperature was added a solution of **5.54** (101 mg, 0.59 mmol) in CH_2Cl_2 (1 mL) via cannula. Et_3N (210 μL , 1.51 mmol) was added and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was then quenched with saturated

aqueous NH_4Cl (3 mL). The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 x 10 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (20% EtOAc/hexanes) to afford 168 mg of **5.59** as a pale yellow oil (87% yield): $[\alpha]_D^{22} = -18$ (c 0.011, CH_2Cl_2); IR (neat) ν_{max} 2967, 2922, 2857, 1598, 1453, 1365, 1189 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.76 (d, $J = 8.0$ Hz, 2 H), 7.32 (d, $J = 8.0$ Hz, 2 H), 5.02–4.97 (m, 1 H), 4.11 (dd, $J_{\text{AB}} = 11.1$ Hz, $J_{\text{AX}} = 5.2$ Hz, 1 H), 4.05 (dd, $J_{\text{AB}} = 11.1$ Hz, $J_{\text{BX}} = 6.1$ Hz, 1 H), 2.93 (dd, $J = 5.7, 5.7$ Hz, 1 H), 2.41 (s, 3 H), 1.99 (dd, $J = 15.3, 7.6$ Hz, 2 H), 1.63 (s, 3 H), 1.62–1.56 (m, 1 H), 1.55 (s, 3 H), 1.42–1.35 (m, 1 H), 1.16 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.12 (C), 132.73 (C), 132.33 (C), 129.95 (CH), 127.96 (CH), 123.04 (CH), 68.67 (CH_2), 60.87 (C), 58.74 (CH), 37.97 (CH_2), 25.64 (CH_3), 23.48 (CH_2), 21.65 (CH_3), 17.64 (CH_3), 16.65 (CH_3); HRMS m/z calculated for $\text{C}_{10}\text{H}_{17}\text{O}$ 153.1279 ($\text{M}^+ - \text{OTs}$), found 153.1263.

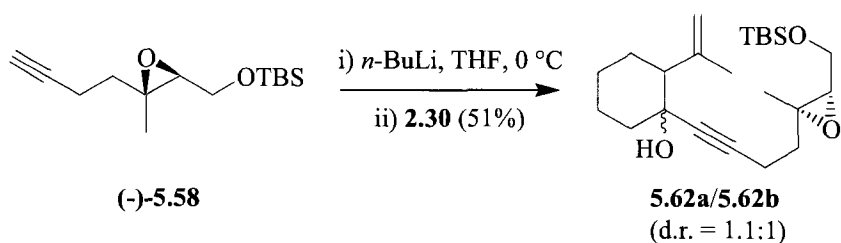


(-)-(2*S*,3*S*)-3-methyl-3-(3-oxopropyl)-oxiranylmethyl 4-toluenesulfonate (5.60). Through a solution of **5.59** (127 mg, 0.39 mmol) in CH_2Cl_2 (4 mL) at $-78\text{ }^\circ\text{C}$ was bubbled ozone for 5 minutes, at which point the solution turned clear blue. Oxygen was then bubbled through the solution for 5 minutes and the blue color disappeared. Me_2S (150 μL , 2.04 mmol) was added dropwise. The solution was warmed up to room temperature, the solvent was removed under reduced pressure and the residue was purified by gel column chromatography (20% then 50% EtOAc/hexanes) to afford 98 mg of **5.60** as a pale yellow oil (84% yield): $[\alpha]_D^{22} = -20$ (c 0.009, CH_2Cl_2); IR (neat) ν_{max} 2959, 2928, 2730, 1723, 1596, 1360, 1176 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 9.21 (t, $J = 1.2$ Hz, 1 H), 7.80 (d, $J = 8.6$ Hz, 2 H), 6.76 (d, $J = 8.6$ Hz, 2 H), 4.03 (dd, $J_{\text{AB}} = 11.3$ Hz, $J_{\text{AX}} = 5.2$ Hz, 1 H), 3.96 (dd, $J_{\text{AB}} = 11.3$ Hz, $J_{\text{BX}} = 6.1$ Hz, 1 H), 2.71 (dd, $J = 5.6, 5.6$ Hz, 1 H), 1.89 (s, 3 H), 1.79–1.74 (m, 2 H), 1.51–1.36 (m, 2 H), 0.80 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 199.10 (CH), 144.40 (C), 133.72 (C), 129.70 (CH),

127.94 (CH), 68.30 (CH₂), 59.36 (C), 58.10 (CH), 38.41 (CH₂), 29.30 (CH₂), 20.91 (CH₃), 16.49 (CH₃); HRMS m/z calculated for C₇H₁₁O₃ 143.0708 (M⁺ - Ts), found 143.0704.



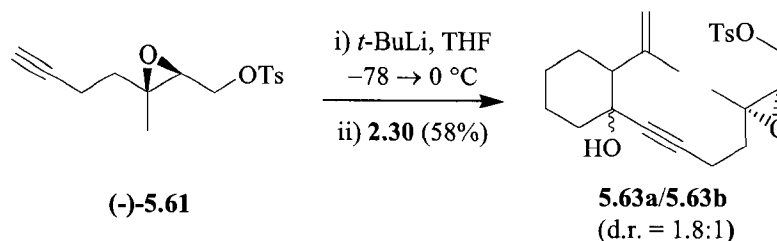
(-)-(2*S*,3*S*)-3-but-3-ynyl-3-methyloxiranylmethyl 4-toluenesulfonate (5.61). To a solution of **5.60** (94 mg, 0.32 mmol) in MeOH (2.2 mL) at room temperature was added K₂CO₃ (89 mg, 0.64 mmol). To this mixture was added a solution of dimethyl 1-diazo-2-oxopropyl phosphonate (73 mg, 0.38 mmol) in MeOH (1 mL) via cannula. After stirring at room temperature for 16 h, the reaction mixture was diluted with Et₂O (20 mL). The resulting solution was washed with saturated aqueous NaHCO₃ (10 mL) and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford 49 mg of **5.61** as a pale yellow oil (53% yield): $[\alpha]_D^{22} = -10$ (c 0.007, CH₂Cl₂); IR (neat) ν_{max} 3291, 2928, 2118, 1925, 1598, 1455, 1360 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.74 (d, $J = 8.2$ Hz, 2 H), 7.34 (d, $J = 8.2$ Hz, 2 H), 4.17 (dd, $J_{\text{AB}} = 11.3$ Hz, $J_{\text{AX}} = 5.0$ Hz, 1 H), 4.06 (dd, $J_{\text{AB}} = 11.3$ Hz, $J_{\text{BX}} = 6.2$ Hz, 1 H), 3.06 (dd, $J = 5.9, 5.2$ Hz, 1 H), 2.43 (s, 3 H), 2.23 (td, $J = 7.8, 2.5$ Hz, 2 H), 1.94 (t, $J = 2.7$ Hz, 1 H), 1.86-1.79 (m, 1 H), 1.67-1.57 (m, 1 H), 1.22 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 145.14 (C), 132.76 (C), 129.96 (CH), 127.99 (CH), 82.85 (C), 69.32 (CH), 68.44 (CH₂), 60.00 (C), 58.91 (CH), 36.51 (CH₂), 21.69 (CH₃), 16.46 (CH₃), 14.31 (CH₂); HRMS m/z calculated for C₈H₁₁O 123.0810 (M⁺ - OTs), found 123.0806.



(±)-1-[4-(3-Ethyl-2-methyloxiranyl)-butynyl]-2-isopropenylcyclohexanol (**5.62**). To a solution of **5.58** (43 mg, 0.17 mmol) in THF (1 mL) at 0 °C was added *n*-BuLi (100 µL of a 2.0 M solution in pentane, 0.20 mmol) dropwise. The resulting brown solution was stirred at that temperature for 30 minutes. A solution of ketone **2.30** (25 mg, 0.18 mmol) in THF (800 µL) was then added dropwise via cannula. After stirring at 0 °C for 1 h, the reaction mixture was quenched with saturated aqueous NH₄Cl (2 mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 10 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% EtOAc/hexanes) to afford 19 mg of **5.62a** (27% yield) and 17 mg of **5.62b** (24% yield) as pale yellow oils.

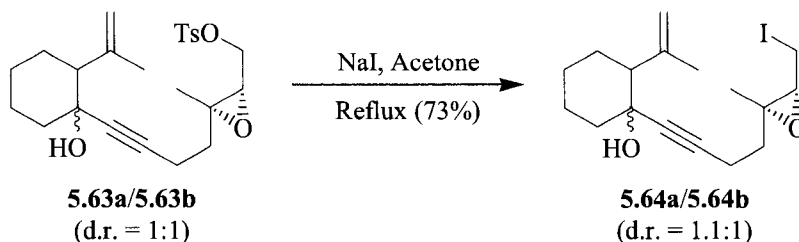
Epimer **5.62a**: IR (neat) $\nu_{\max}$ 3487 (br), 3077, 2932, 2857, 2236, 1639, 1471, 1385, 1256, 1128, 1072 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.95 (s, 1 H), 4.79 (s, 1 H), 3.79-3.74 (m, 1 H), 3.66 (ddd, *J* = 11.6, 5.7, 3.6 Hz, 1 H), 2.95-2.92 (m, 1 H), 2.25 (t, *J* = 7.3 Hz, 2 H), 2.15-2.12 (m, 2 H), 2.08-2.05 (m, 1 H), 1.93 (s, 3 H), 1.85-1.76 (m, 1 H), 1.72-1.50 (m, 6 H), 1.47-1.40 (m, 2 H), 1.24 (s, 3 H), 0.88 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 140.40 (C), 112.12 (CH₂), 85.68 (C), 82.43 (C), 67.03 (C), 63.24 (CH), 63.14 (CH), 62.23 (CH₂), 59.69 (C), 52.81 (CH₃), 40.06 (CH₂), 37.42 (CH₂), 26.79 (CH₂), 25.89 (CH₃), 25.80 (CH₂), 20.69 (CH₂), 18.31 (C), 16.65 (CH₃), 14.67 (CH₂), -5.17 (CH₃), -5.34 (CH₃); HRMS *m/z* calculated for C₁₉H₃₁O₃Si 335.2042 (M⁺ - *t*-Bu), found 335.1982.

Epimer **5.62b**: IR (neat) $\nu_{\max}$ 3465 (br), 3073, 2932, 2857, 2241, 1640, 1471, 1255, 1129 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.95 (s, 1 H), 4.88 (s, 1 H), 3.76 (ddd, *J* = 11.6, 4.7, 2.9 Hz, 1 H), 3.67 (ddd, *J* = 11.6, 5.7, 1.3 Hz, 1 H), 2.95-2.92 (m, 1 H), 2.63 (s, 1 H), 2.29 (t, *J* = 7.8 Hz, 2 H), 2.11-2.07 (m, 1 H), 2.03-1.99 (m, 1 H), 1.84 (s, 3 H), 1.80 (ddd, *J* = 7.6, 7.6, 2.6 Hz, 1 H), 1.75-1.65 (m, 4 H), 1.63-1.57 (m, 3 H), 1.45 (ddd, *J* = 12.6, 12.6, 3.8 Hz, 1 H), 1.25 (s, 3 H), 0.88 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 145.67 (C), 114.76 (CH₂), 85.53 (C), 82.54 (C), 69.94 (C), 63.12 (CH), 62.20 (CH₂), 59.67 (C), 56.24 (CH), 40.80 (CH₂), 37.45 (CH₂), 28.60 (CH₂), 25.88 (CH₃), 25.69 (CH₂), 24.02 (CH₂), 21.07 (CH₃), 18.31 (C), 16.68 (CH₃), 14.69 (CH₂), -5.18 (CH₃), -5.34 (CH₃); HRMS *m/z* calculated for C₁₉H₃₁O₃Si 335.2042 (M⁺ - *t*-Bu), found 335.1965.



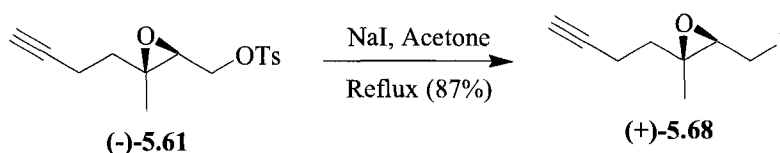
(±)-3-[4-(1-hydroxy-2-isopropenylcyclohexyl)-but-3-ynyl]-3-methyloxiranylmethyl 4-toluene-sulfonate (**5.63**). To a solution of **5.61** (36 mg, 0.122 mmol) in THF (500 μ L) at -78 °C was added *t*-BuLi (70 μ L of a 1.7 M solution in pentane, 0.119 mmol) dropwise. The resulting solution was allowed to warm up to 0 °C over 30 minutes. A solution of ketone **2.30** (11 mg, 0.082 mmol) in THF (500 μ L) was then added dropwise via cannula. After stirring at 0 °C for 1.5 h, the reaction mixture was quenched with saturated aqueous NH₄Cl (1 mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 5 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% then 20% EtOAc/hexanes) to afford 13 mg of **5.63a** (37% yield) and 7.5 mg of **5.63b** (21% yield) as pale yellow oils. Epimer **5.63a**: IR (neat) $\nu_{\max}$ 3543 (br), 3070, 2934, 2857, 2236, 1639, 1598, 1447, 1372, 1177 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, *J* = 8.2 Hz, 2 H), 7.34 (d, *J* = 8.2 Hz, 2 H), 4.95-4.94 (m, 1 H), 4.79 (s, 1 H), 4.18 (ddd, *J* = 11.2, 5.1, 5.1 Hz, 1 H), 4.04 (dd, *J* = 11.2, 6.2 Hz, 1 H), 3.07 (dd, *J* = 5.4, 5.4 Hz, 1 H), 2.43 (s, 3 H), 2.22 (t, *J* = 7.5 Hz, 2 H), 2.12 (dd, *J* = 12.8, 3.5 Hz, 1 H), 2.08-2.03 (m, 1 H), 1.92 (s, 3 H), 1.82-1.76 (m, 1 H), 1.71-1.41 (m, 8 H), 1.28-1.22 (m, 1 H), 1.20 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 148.28 (C), 145.14 (C), 132.72 (C), 129.95 (CH), 128.00 (CH), 112.23 (CH₂), 86.08 (C), 81.81 (C), 68.50 (CH₂), 67.12 (C), 60.11 (C), 58.87 (CH), 52.78 (CH), 40.09 (CH₂), 36.81 (CH₂), 26.77 (CH₂), 25.82 (CH₃), 25.77 (CH₂), 21.69 (CH₃), 20.67 (CH₂), 16.56 (CH₃), 14.54 (CH₂); HRMS *m/z* calculated for C₁₇H₂₅O₂ 261.1855 (M⁺ - OTs), found 261.1839. Epimer **5.63b**: IR (neat) $\nu_{\max}$ 3534 (br), 3070, 2930, 2857, 2237, 1640, 1598, 1447, 1367, 1177 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, *J* = 8.1 Hz, 2 H), 7.34 (d, *J* = 8.1 Hz, 2 H), 4.95 (q, *J* = 2.2 Hz, 1 H), 4.88-4.87 (m, 1 H), 4.17 (ddd, *J* = 11.2, 5.0, 1.2 Hz, 1 H), 4.05 (ddd, *J* = 11.2, 6.1, 1.3 Hz, 1 H), 3.07 (ddd, *J* = 5.6, 5.6, 1.8 Hz, 1 H), 2.44 (s, 3 H), 2.27 (t, *J* = 7.5 Hz, 2 H), 2.15-2.06 (m, 1 H), 2.04-1.98 (m, 1 H), 1.83 (s,

3 H), 1.78 (ddd, $J = 7.2, 7.2, 2.3$ Hz, 1 H), 1.73-1.41 (m, 9 H), 1.22 (d, $J = 0.9$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.58 (C), 145.15 (C), 132.71 (C), 129.95 (CH), 128.01 (CH), 114.79 (CH_2), 84.94 (C), 82.95 (C), 69.98 (C), 68.42 (CH_2), 60.11 (C), 58.78 (CH), 56.17 (CH), 40.81 (CH_2), 36.83 (CH_2), 28.61 (CH_2), 25.67 (CH_2), 24.02 (CH_2), 21.68 (CH_3), 21.14 (CH_3), 16.62 (CH_3), 14.35 (CH_2); HRMS m/z calculated for $\text{C}_{24}\text{H}_{32}\text{O}_5\text{Si}$ 432.1970 (M^+), found 432.1877.

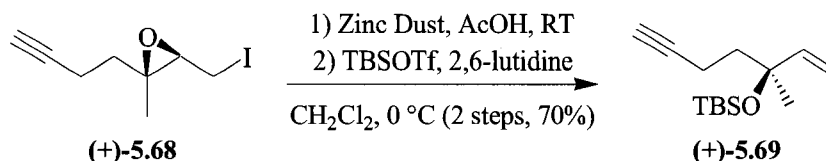


(±)-1-[4-(3-Iodomethyl-2-methyloxiranyl)-butynyl]-2-isopropenylcyclohexanol (**5.64**). To a solution of **5.63a/5.63b** (1:1 mixture of diastereomers, 71% pure, 116 mg, 0.19 mmol) in dry acetone (1.3 mL) was added dry NaI (86 mg, 0.57 mmol). The resulting mixture was refluxed for 3 h. After cooling down to room temperature, the solvent was evaporated under reduced pressure. The concentrate was diluted with H_2O (2 mL). The resulting mixture was extracted with Et_2O (3 x 5 mL). Combined organics were sequentially washed with H_2O , saturated aqueous Na_2SO_3 , saturated aqueous NaHCO_3 and saturated aqueous NaCl . The organic layer was then dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% then 10% EtOAc /hexanes) to afford 28 mg of **5.64a** (38% yield) and 26 mg of **5.64b** (35% yield) as colorless oils. Epimer **5.64a**: IR (neat) ν_{max} 3541 (br), 3076, 2934, 2853, 2236, 1638, 1447, 1386, 1285, 1172 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.97-4.95 (m, 1 H), 4.80 (s, 1 H), 3.30 (dd, $J = 9.9, 6.0$ Hz, 1 H), 3.15 (ddd, $J = 7.0, 6.0, 1.3$ Hz, 1 H), 2.99 (ddd, $J = 9.9, 8.1, 0.8$ Hz, 1 H), 2.26 (t, $J = 7.6$ Hz, 2 H), 2.16-2.11 (m, 2 H), 2.09-2.05 (m, 1 H), 1.93 (s, 3 H), 1.88-1.81 (m, 1 H), 1.72-1.59 (m, 4 H), 1.57-1.37 (m, 3 H), 1.26 (s, 3 H), 1.24-1.17 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 148.38 (C), 112.20 (CH_2), 85.81 (C), 82.29 (C), 67.08 (C), 63.36 (C), 62.33 (CH), 52.78 (CH), 40.06 (CH_2), 37.20 (CH_2), 26.80 (CH_2), 25.96 (CH_3), 25.80 (CH_2), 20.69 (CH_2), 15.77 (CH_3), 14.75 (CH_2), 2.11 (CH_2); HRMS m/z calculated for $\text{C}_{17}\text{H}_{25}\text{O}_2$ 261.1855 ($\text{M}^+ - \text{I}$), found 261.1886. Epimer **5.64b**: IR (neat) ν_{max} 3500 (br), 2932,

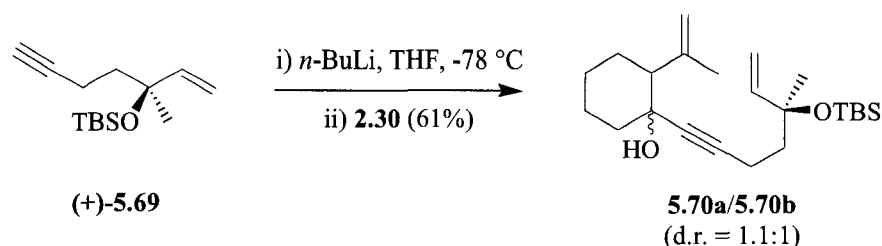
2857, 2239, 1639, 1446, 1386, 1327 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.96-4.94 (m, 1 H), 4.88 (s, 1 H), 3.31 (ddd, $J = 9.9, 6.0, 1.9$ Hz, 1 H), 3.17-3.13 (m, 1 H), 2.99 (ddd, $J = 9.6, 8.1, 1.1$ Hz, 1 H), 2.63 (d, $J = 2.1$ Hz, 1 H), 2.31 (t, $J = 7.7$ Hz, 2 H), 2.09 (dd, $J = 9.1, 6.7$ Hz, 1 H), 2.03-1.99 (m, 1 H), 1.90-1.82 (m, 4 H), 1.73-1.67 (m, 3 H), 1.66-1.53 (m, 4 H), 1.45 (ddd, $J = 12.6, 12.6, 3.7$ Hz, 1 H), 1.28 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.62 (C), 114.83 (CH_2), 85.30 (C), 82.74 (C), 69.96 (C), 63.34 (C), 62.35 (CH), 56.23 (CH), 40.78 (CH_2), 37.24 (CH_2), 28.59 (CH_2), 25.69 (CH_2), 24.04 (CH_2), 21.11 (CH_3), 15.77 (CH_3), 14.82 (CH_2), 2.05 (CH_2); HRMS m/z calculated for $\text{C}_{17}\text{H}_{25}\text{O}_2$ 261.1855 ($\text{M}^+ - \text{I}$), found 261.1781.



(+)-(2*S*,3*R*)-2-But-3-ynyl-3-iodomethyl-2-methyloxirane (5.68). To a solution of **5.61** (50 mg, 0.17 mmol) in dry acetone (1.2 mL) was added dry NaI (79 mg, 0.53 mmol). The resulting mixture was refluxed for 1.5 h. After cooling down to room temperature, the solvent was evaporated under reduced pressure. The concentrate was diluted with H_2O (1 mL). The resulting mixture was extracted with Et_2O (3 x 5 mL). Combined organics were sequentially washed with H_2O , saturated aqueous Na_2SO_3 , saturated aqueous NaHCO_3 and saturated aqueous NaCl . The organic layer was then dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% EtOAc /hexanes) to afford 37 mg of **5.68** as a colorless oil (87% yield): $[\alpha]_D^{22} = +21$ (c 0.03, CH_2Cl_2); IR (neat) ν_{max} 3294, 2959, 2928, 2118, 1429, 1386, 1179 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.31 (dd, $J = 10.0, 6.0$ Hz, 1 H), 3.16 (dd, $J = 8.1, 6.0$ Hz, 1 H), 2.99 (dd, $J = 10.0, 8.1$ Hz, 1 H), 2.28 (ddd, $J = 7.8, 7.8, 2.7$ Hz, 2 H), 1.97 (t, $J = 2.7$ Hz, 1 H), 1.93-1.86 (m, 1 H), 1.69 (ddd, $J = 13.9, 7.8, 7.8$ Hz, 1 H), 1.29 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 83.26 (C), 69.18 (CH), 63.29 (C), 62.39 (CH), 37.00 (CH_2), 15.65 (CH_3), 14.53 (CH_2), 1.90 (CH_2); HRMS m/z calculated for $\text{C}_8\text{H}_{11}\text{O}$ 123.0810 ($\text{M}^+ - \text{I}$), found 123.0805.



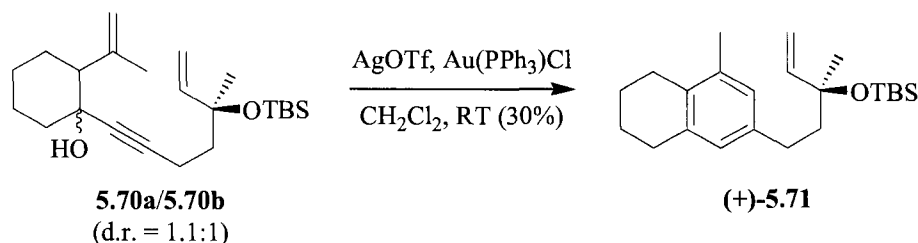
(+)-(1*S*)-*t*-Butyldimethyl-(1-methyl-1-vinylpent-4-ynyloxy)-silane (5.69). *Step 1:* To a solution of **5.68** (452 mg, 1.81 mmol) in glacial AcOH (9 mL) at room temperature was added zinc dust (904 mg, 13.83 mmol) in one portion. After stirring for 2 h, wet Et₂O (20 mL) was added and the resulting mixture was filtered through a fritted glass funnel. The funnel was rinsed with Et₂O (10 mL). The filtrate was sequentially washed with H₂O, saturated aqueous Na₂SO₃, saturated aqueous NaHCO₃ and saturated aqueous NaCl. It was then dried over anhydrous MgSO₄. Filtration and careful removal of the solvent delivered the crude allylic alcohol. *Step 2:* To a solution of the alcohol in CH₂Cl₂ (9 mL) at room temperature was added 2,6-lutidine (530 μL, 4.58 mmol) dropwise. The resulting solution was cooled to 0 °C and TBSOTf (830 μL, 3.62 mmol) was added dropwise. The reaction mixture was then warmed up to room temperature. After stirring for 1.5 h, it was diluted with CH₂Cl₂ (20 mL). The resulting solution was washed with saturated aqueous NaHCO₃ and saturated aqueous NaCl. It was then dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes) to afford 302 mg of **5.69** as a colorless oil (70% yield over 2 steps): $[\alpha]_D^{22} = +12$ (c 0.009, CH₂Cl₂); IR (neat) ν_{max} 3314, 2956, 2930, 2857, 2120, 1472, 1254, 1119 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.77 (dd, $J = 17.3, 10.7$ Hz, 1 H), 5.14 (dd, $J = 17.3, 1.5$ Hz, 1 H), 5.00 (dd, $J = 10.7, 1.5$ Hz, 1 H), 2.27-2.11 (m, 2 H), 1.88 (t, $J = 2.7$ Hz, 1 H), 1.78-1.68 (m, 2 H), 1.29 (s, 3 H), 0.86 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 144.42 (CH), 112.38 (CH₂), 85.11 (C), 74.79 (C), 67.50 (CH), 42.40 (CH₂), 27.37 (CH₃), 25.76 (CH₃), 18.18 (C), 13.12 (CH₂), -2.27 (CH₃); HRMS m/z calculated for C₁₀H₁₇OSi 181.1049 (M⁺ - *t*-Bu), found 181.1058.



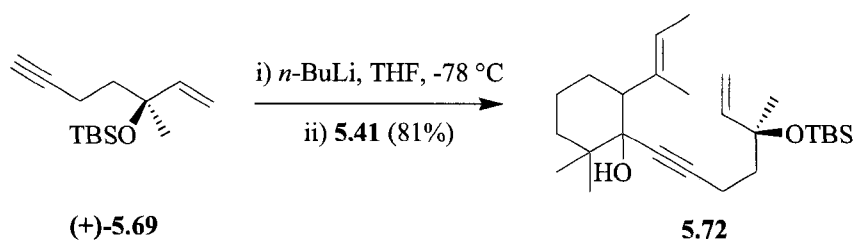
(±)-1-[5-(*t*-Butyldimethylsilanyloxy)-5-methylhept-6-enynyl]-2-isopropenylcyclohexanol (5.70).

To a solution of **5.69** (52 mg, 0.218 mmol) in THF (600 μ L) at $-78\text{ }^{\circ}\text{C}$ was added *n*-BuLi (120 μ L of a 1.4 M solution in pentane, 0.168 mmol) dropwise. The resulting solution was stirred at that temperature for 30 minutes. A solution of ketone **2.30** (15 mg, 0.109 mmol) in THF (500 μ L) was then added dropwise via cannula. After stirring at $-78\text{ }^{\circ}\text{C}$ for 15 minutes, the reaction mixture was warmed up to $0\text{ }^{\circ}\text{C}$. It was further stirred for 30 minutes at that temperature, and was quenched with saturated aqueous NH_4Cl (1 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (2% then 4% EtOAc /hexanes) to afford 13 mg of **5.70a** as a yellow oil (32% yield) and 12 mg of **5.70b** as a pale yellow oil (29% yield). Epimer **5.70a**: IR (neat) ν_{max} 3565 (br), 3083, 2931, 2856, 2235, 1639, 1462, 1370, 1254, 1177, 1118 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.76 (dd, $J = 17.3, 10.7$ Hz, 1 H), 5.12 (dd, $J = 17.3, 1.5$ Hz, 1 H), 4.98 (dd, $J = 10.7, 1.5$ Hz, 1 H), 4.95 (dd, $J = 1.6, 1.6$ Hz, 1 H), 4.79 (s, 1 H), 2.25–2.05 (m, 5 H), 1.95 (s, 3 H), 1.71–1.56 (m, 6 H), 1.54–1.39 (m, 2 H), 1.27 (m, 3 H), 1.21 (dd, $J = 12.6, 3.6$ Hz, 1 H), 0.85 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 148.45 (C), 144.58 (CH), 112.20 (CH_2), 111.79 (CH_2), 84.56 (C), 83.79 (C), 74.83 (C), 66.79 (C), 52.64 (CH), 42.49 (CH_2), 39.87 (CH_2), 27.32 (CH_3), 27.31 (CH_3), 26.70 (CH_2), 25.95 (CH_3), 25.76 (CH_3), 25.68 (CH_2), 20.59 (CH_2), 18.18 (C), 13.36 (CH_2), -2.67 (CH_3); HRMS m/z calculated for $\text{C}_{19}\text{H}_{31}\text{O}_2\text{Si}$ 319.2093 ($\text{M}^+ - t\text{-Bu}$), found 319.2071. Epimer **5.70b**: IR (neat) ν_{max} 3560, 3461 (br), 2929, 2857, 2233, 1637, 1462, 1371, 1253, 1116 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.77 (dd, $J = 17.3, 10.7$ Hz, 1 H), 5.13 (dd, $J = 17.3, 1.5$ Hz, 1 H), 4.99 (dd, $J = 10.7, 1.5$ Hz, 1 H), 4.94 (dd, $J = 2.4, 1.5$ Hz, 1 H), 4.87 (dd, $J = 1.7, 0.8$ Hz, 1 H), 2.60 (s, 1 H), 2.29–2.23 (m, 1 H), 2.21–2.14 (m, 1 H), 2.08 (dd, $J = 11.6, 4.1$ Hz, 1 H), 2.02–1.98 (m,

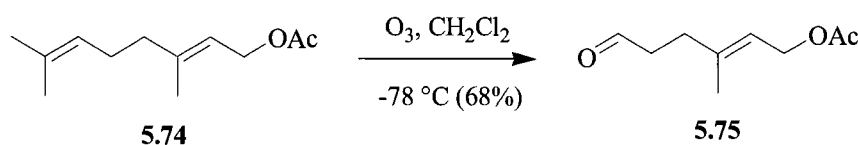
1 H), 1.84 (s, 3 H), 1.75-1.57 (m, 7 H), 1.44 (ddd, $J = 13.0, 12.3, 3.9$ Hz, 1 H), 1.28 (s, 3 H), 1.27-1.18 (m, 1 H), 0.86 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 145.65 (C), 144.53 (CH), 114.53 (CH_2), 112.25 (CH_2), 86.93 (C), 81.36 (C), 74.84 (C), 69.72 (C), 56.21 (CH), 42.51 (CH_2), 40.63 (CH_2), 28.41 (CH_2), 27.39 (CH_3), 27.36 (CH_3), 25.77 (CH_3), 25.57 (CH_2), 23.86 (CH_2), 20.78 (CH_3), 18.19 (C), 13.45 (CH_2), -2.27 (CH_3); HRMS m/z calculated for $\text{C}_{19}\text{H}_{31}\text{O}_2\text{Si}$ 319.2093 ($\text{M}^+ - t\text{-Bu}$), found 319.2085.



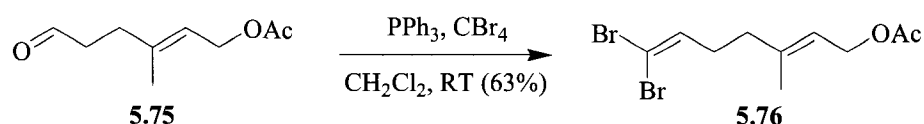
(+)-(1*R*)-*t*-Butyldimethyl-{1-methyl-1-[2-(4-methyl-5,6,7,8-tetrahydronaphthalen-2-yl)-ethyl]-allyloxy}-silane (5.71). AgOTf (0.5 mg, 0.002 mmol) and Au(PPh_3)Cl (1 mg, 0.002 mmol) were weighed in the glovebox and transferred to a flame-dried flask equipped with a magnetic stirrer. Then, a solution of **5.70a/5.70b** (1.1:1 mixture of epimers, 25 mg, 0.066 mmol) in CH_2Cl_2 (1 mL) was added via cannula. After stirring at room temperature for 1.5 h, the reaction mixture was filtered through celite. The fritted glass funnel was rinsed with Et_2O (10 mL), and the filtrate was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes) to afford 7 mg of **5.71** as a pale yellow oil (30% yield): $[\alpha]_D^{22} = +12$ (c 0.007, CH_2Cl_2); IR (neat) ν_{max} 2928, 2857, 1613, 1579, 1472, 1252, 1176, 1113 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.78 (s, 1 H), 6.72 (s, 1 H), 5.88 (dd, $J = 17.3, 10.7$ Hz, 1 H), 5.18 (dd, $J = 17.3, 1.5$ Hz, 1 H), 5.01 (dd, $J = 10.7, 1.5$ Hz, 1 H), 2.72 (t, $J = 6.1$ Hz, 2 H), 2.59-2.53 (m, 3 H), 2.51-2.45 (m, 1 H), 2.16 (s, 3 H), 1.82-1.78 (m, 2 H), 1.76-1.69 (m, 4 H), 1.33 (s, 3 H), 0.90 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.39 (CH), 139.60 (C), 136.88 (C), 136.38 (C), 132.58 (C), 127.06 (CH), 126.55 (CH), 111.73 (CH_2), 75.33 (C), 45.85 (CH_2), 29.95 (CH_2), 29.77 (CH_2), 27.44 (CH_3), 26.26 (CH_2), 25.83 (CH_3), 23.38 (CH_2), 22.83 (CH_2), 19.32 (CH_3), 18.25 (C), -2.12 (CH_3), -2.17 (CH_3); HRMS m/z calculated for $\text{C}_{19}\text{H}_{29}\text{OSi}$ 301.1988 ($\text{M}^+ - t\text{-Bu}$), found 301.1982.



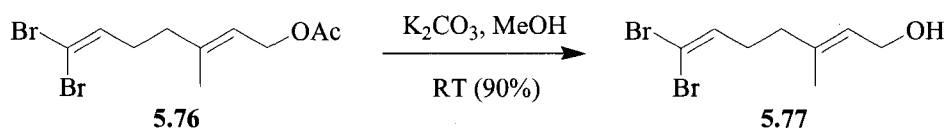
(±)-1-[5-(*t*-Butyldimethylsilanyloxy)-5-methylhept-6-enynyl]-2,2-dimethyl-6-(1-methylpropenyl)cyclohexanol (**5.72**). To a solution of **5.69** (109 mg, 0.458 mmol) in THF (500 μL) at $-78\text{ }^\circ\text{C}$ was added *n*-BuLi (330 μL of a 1.4 M solution in pentane, 0.462 mmol) dropwise. The resulting solution was stirred at that temperature for 30 minutes. A solution of ketone **5.41** (15 mg, 0.083 mmol) in THF (400 μL) was then added dropwise via cannula. After stirring at $-78\text{ }^\circ\text{C}$ for 30 minutes, the reaction mixture was warmed up to $0\text{ }^\circ\text{C}$. It was further stirred for 1.5 h at that temperature, and was quenched with saturated aqueous NH_4Cl (1 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes then 5% EtOAc /hexanes) to afford 28 mg of **5.72** as a yellow oil (81% yield): IR (neat) ν_{max} 3551 (br), 2980, 2858, 2238, 1462, 1384, 1253, 1177, 1118 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.78 (ddd, $J = 17.2, 10.7, 1.6\text{ Hz}$, 1 H), 5.36 (q, $J = 6.5\text{ Hz}$, 1 H), 5.14 (dd, $J = 17.2, 1.2\text{ Hz}$, 1 H), 4.99 (dd, $J = 10.7, 1.2\text{ Hz}$, 1 H), 2.32 (dd, $J = 12.9, 2.9\text{ Hz}$, 1 H), 2.29 (s, 1 H), 2.25 (dd, $J = 10.8, 5.7\text{ Hz}$, 1 H), 2.19 (dd, $J = 10.6, 6.0\text{ Hz}$, 1 H), 1.83–1.65 (m, 7 H), 1.61 (d, $J = 6.5\text{ Hz}$, 3 H), 1.50–1.47 (m, 2 H), 1.29 (s, 3 H), 1.25–1.23 (m, 2 H), 1.08 (s, 3 H), 0.99 (s, 3 H), 0.87 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.80 (CH), 136.38 (C), 124.21 (CH), 112.34 (CH_2), 87.34 (C), 81.54 (C), 75.04 (C), 74.58 (C), 51.95 (CH_3), 42.64 (CH_2), 39.05 (C), 37.84 (CH_2), 28.60 (CH_2), 27.56 (CH_3), 26.93 (CH_3), 25.94 (CH_3), 21.48 (CH_2), 20.04 (CH_3), 18.35 (C), 13.99 (CH_3), 13.67 (CH_2), 13.41 (CH_3), -2.10 (CH_3); HRMS m/z calculated for $\text{C}_{22}\text{H}_{37}\text{O}_2\text{Si}$ 361.2563 ($\text{M}^+ - t\text{-Bu}$), found 361.2577.



(E)-3-methyl-6-oxohex-2-enyl acetate (5.75). Through a solution of geranyl acetate **5.74** (5.59 g, 28.48 mmol) in CH_2Cl_2 (120 mL) at $-78\text{ }^\circ\text{C}$ was bubbled ozone for 2 h, at which point the solution turned clear blue. Oxygen was then bubbled through the solution for 10 minutes and the blue color disappeared. Me_2S (10.50 mL, 142.97 mmol) was added dropwise. The solution was warmed up to room temperature. After stirring for 1 h, the solvent was removed under reduced pressure and the residue was purified by gel column chromatography (20% $\rightarrow$ 50% Et_2O /hexanes) to afford 3.32 g of **5.75** as yellow oil (68% yield). Spectroscopic data for **5.75** were identical to that previously reported.^{127a}

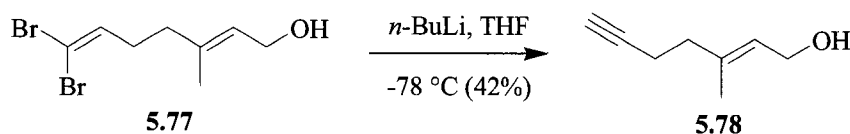


(E)-7,7-dibromo-3-methylhepta-2,6-dienyl acetate (5.76). To a solution of PPh_3 (21.40 g, 81.59 mmol) in CH_2Cl_2 (130 mL) at $0\text{ }^\circ\text{C}$ was added a solution of CBr_4 (12.90 g, 38.90 mmol) in CH_2Cl_2 (30 mL) dropwise via cannula. A solution of **5.75** (3.32 g, 19.51 mmol) in CH_2Cl_2 (30 mL) was then added dropwise, and the reaction mixture was warmed up to room temperature. After stirring for 3 h, the phosphonium salts were precipitated with pentane (120 mL) and filtered off through celite. Solvents were then removed *in vacuo* and the residue was purified by silica gel column chromatography (10% then 20% EtOAc /hexanes) to afford 3.96 g of **5.76** as a yellow oil (63% yield). Spectroscopic data for **5.76** were identical to that previously reported.^{127a}

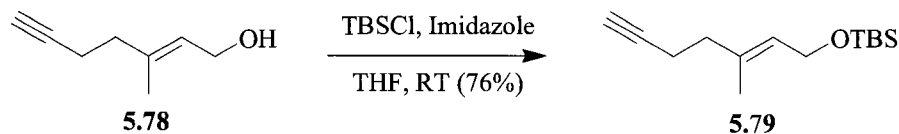


(E)-7,7-Dibromo-3-methylhepta-2,6-dienol (5.77). To a solution of **5.76** (3.96 mmol, 12.22 mmol) in MeOH (9 mL) at room temperature was added K_2CO_3 (844 mg, 6.11 mmol). After stirring for 1.5 h, the remaining K_2CO_3 was filtered off, and MeOH was evaporated under reduced pressure. The residue was dissolved in Et_2O (50 mL). The resulting solution was washed with saturated aqueous NH_4Cl and dried over MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (20%

EtOAc/hexanes) to afford 3.11 g of **5.77** as a yellow oil (90% yield). Spectroscopic data for **5.77** were identical to that previously reported.^{127a}

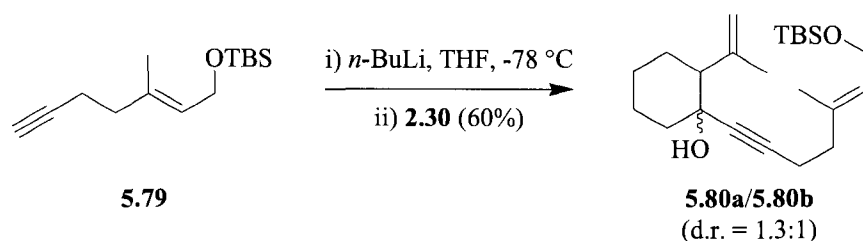


(E)-3-Methylhept-2-en-6-ynol (5.78). To a solution of **5.77** (3.11 g, 11.03 mmol) in THF (110 mL) at -78 °C was added *n*-BuLi (24.4 mL of a 1.4 M solution in pentane, 34.20 mmol) dropwise. After stirring at -78 °C for 30 minutes, the reaction mixture was warmed up to room temperature. It was further stirred at that temperature for 1 h, and was quenched with 4% aqueous HCl (20 mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 20 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% then 20% EtOAc/hexanes) to afford 576 mg of **5.78** as a yellow oil (42% yield): IR (neat) $\nu_{\max}$ 3397 (br), 2918, 2116, 1671, 1435 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.46-5.41 (m, 1 H), 4.13 (d, *J* = 6.8 Hz, 2 H), 2.31-2.27 (m, 2 H), 2.23-2.20 (m, 2 H), 1.93 (t, *J* = 2.5 Hz, 1 H), 1.66 (s, 3 H), 1.46 (br, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 137.52 (C), 124.68 (CH), 83.88 (C), 68.71 (CH), 59.23 (CH₂), 38.06 (CH₂), 17.21 (CH₂), 16.08 (CH₃); HRMS *m/z* calculated for C₈H₁₂ 124.0888 (M⁺), found 124.0865.



(E)-*t*-Butyldimethyl-(3-methylhept-2-en-6-ynyloxy)-silane (5.79). To a solution of **5.78** (350 mg, 2.82 mmol) in THF (28 mL) at room temperature were added TBSCl (510 mg, 3.38 mmol) and imidazole (576 mg, 8.46 mmol). After stirring for 15 h, the reaction mixture was quenched with saturated aqueous NH₄Cl (15 mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 15 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the

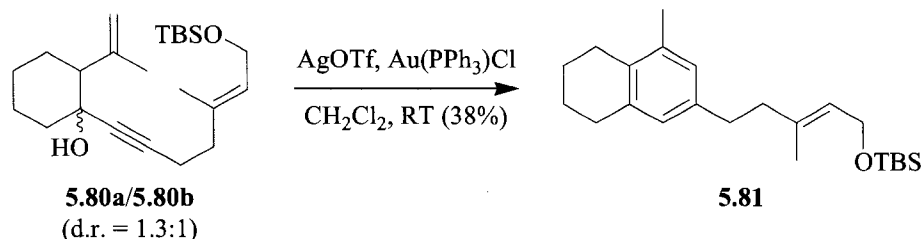
solvent, the residue was purified by silica gel column chromatography (2% then 4% EtOAc/hexanes) to afford 514 mg of **5.79** as a colorless oil (76% yield): IR (neat) $\nu_{\max}$ 3313, 2960, 2930, 2861, 2120, 1474, 1253, 1109 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.34 (tq, $J = 6.3, 1.3$ Hz, 1 H), 4.18 (dd, $J = 6.3, 0.8$ Hz, 2 H), 2.31–2.26 (m, 2 H), 2.23–2.19 (m, 2 H), 1.93 (t, $J = 2.5$ Hz, 1 H), 1.62 (s, 3 H), 0.88 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ 134.94 (C), 125.69 (CH), 84.10 (C), 68.52 (CH), 60.20 (CH_2), 38.19 (CH_2), 26.01 (CH_3), 18.43 (C), 17.27 (CH_2), 16.19 (CH_3), -5.05 (CH_3); HRMS m/z calculated for $\text{C}_{10}\text{H}_{17}\text{OSi}$ 181.1049 ($\text{M}^+ - t\text{-Bu}$), found 181.1054.



(±)-1-[7-(*t*-Butyldimethylsilanyloxy)-5-methylhept-5-enynyl]-2-isopropenylcyclohexanol (5.80**).**

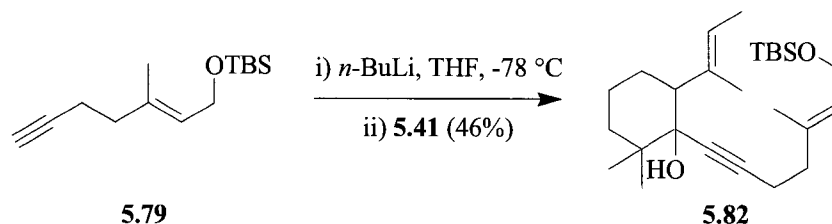
To a solution of **5.79** (76 mg, 0.319 mmol) in THF (1 mL) at $-78\text{ }^\circ\text{C}$ was added $n\text{-BuLi}$ (150 μL of a 1.8 M solution in pentane, 0.270 mmol) dropwise. The resulting solution was stirred at $-78\text{ }^\circ\text{C}$ for 30 minutes. A solution of ketone **2.30** (20 mg, 0.145 mmol) in THF (500 μL) was then added dropwise via cannula. After stirring at $-78\text{ }^\circ\text{C}$ for 30 minutes, the reaction mixture was warmed up to $0\text{ }^\circ\text{C}$. It was further stirred for 1 h at that temperature, and was quenched with saturated aqueous NH_4Cl (1 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes $\rightarrow$ 4% EtOAc/hexanes) to afford 18.5 mg of **5.80a** (34% yield) and 14 mg of **5.80b** (26% yield) as pale yellow oils. Epimer **5.80a**: IR (neat) $\nu_{\max}$ 3459 (br), 3466 (br), 3074, 2933, 2857, 2234, 1447, 1379, 1253, 1109 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.33 (tq, $J = 6.2, 1.3$ Hz, 1 H), 4.94 (dd, $J = 2.4, 1.5$ Hz, 1 H), 4.87 (dd, $J = 1.6, 0.8$ Hz, 1 H), 4.17 (dd, $J = 6.3, 0.7$ Hz, 2 H), 2.60 (s, 1 H), 2.34–2.30 (m, 2 H), 2.24–2.17 (m, 2 H), 2.08 (dd, $J = 11.3, 4.5$ Hz, 1 H), 2.04–1.98 (m, 1 H), 1.84 (s, 3 H), 1.74–1.52 (m, 8 H), 1.44 (ddd, $J = 12.5, 12.5, 4.1$ Hz, 1 H), 1.28–1.17 (m, 1 H), 0.88 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.78 (C),

135.12 (C), 125.68 (CH), 114.68 (CH₂), 86.04 (C), 82.44 (C), 69.93 (C), 60.20 (CH₂), 56.31 (CH), 40.85 (CH₂), 38.40 (CH₂), 28.58 (CH₂), 26.02 (CH₃), 25.74 (CH₂), 24.00 (CH₂), 20.99 (CH₃), 18.44 (C), 17.54 (CH₂), 16.08 (CH₃), -5.09 (CH₃); HRMS *m/z* calculated for C₂₃H₃₈OSi 358.2692 (M⁺ - H₂O), found 358.2683. Epimer **5.80b**: IR (neat) $\nu_{\max}$ 3568 (br), 3473 (br), 3082, 2933, 2854, 2241, 1641, 1447, 1382, 1253, 1109 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.31 (tq, *J* = 6.3, 1.2 Hz, 1 H), 4.95 (dd, *J* = 1.6, 1.6 Hz, 1 H), 4.79 (s, 1 H), 4.16 (dd, *J* = 6.3, 0.7 Hz, 2 H), 2.29-2.25 (m, 2 H), 2.17-2.05 (m, 5 H), 1.94 (s, 3 H), 1.72-1.57 (m, 2 H), 1.55 (s, 3 H), 1.54-1.50 (m, 2 H), 1.48-1.39 (m, 2 H), 1.27-1.17 (m, 1 H), 0.88 (s, 9 H), 0.05 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 148.55 (C), 135.23 (C), 125.55 (CH), 111.98 (CH₂), 85.59 (C), 83.00 (C), 77.34 (CH), 67.10 (C), 60.22 (CH₂), 52.80 (CH₃), 40.11 (CH₂), 38.42 (CH₂), 26.84 (CH₂), 26.03 (CH₃), 25.83 (CH₂), 20.74 (CH₂), 18.44 (C), 17.58 (CH₂), 16.19 (CH₃), -5.07 (CH₃); HRMS *m/z* calculated for C₂₃H₃₈OSi 358.2692 (M⁺ - H₂O), found 358.2699.

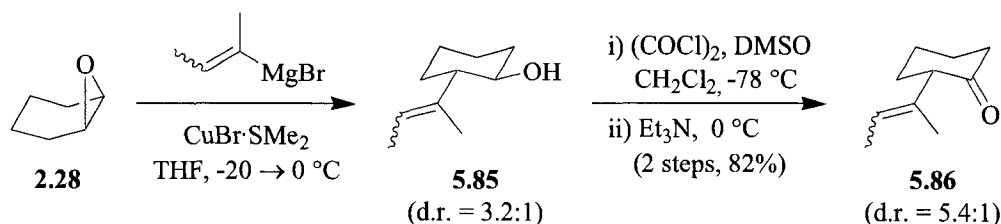


(*E*)-*t*-Butyldimethyl-[3-methyl-5-(4-methyl-5,6,7,8-tetrahydronaphthalen-2-yl)-pent-2-enyloxy]-silane (5.81). AgOTf (0.5 mg, 0.002 mmol) and Au(PPh₃)Cl (1 mg, 0.002 mmol) were weighed in the glovebox and transferred to a flame-dried flask equipped with a magnetic stirrer. Then, a solution of **5.80a/5.80b** (1.3:1 mixture of epimers, 22 mg, 0.058 mmol) in CH₂Cl₂ (1 mL) was added via cannula. After stirring at room temperature for 15 h, the reaction mixture was filtered through celite. The fritted glass funnel was rinsed with Et₂O (10 mL), and the filtrate was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (1% then 2% EtOAc/hexanes) to afford 8 mg of **5.81** as a pale yellow oil (38% yield): IR (neat) ν_{max} 2933, 2853, 1671, 1614, 1580, 1474, 1257, 1109 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.80 (s, 1 H), 6.75 (s, 1 H), 5.34 (t, *J* = 5.4 Hz, 1 H), 4.19 (d, *J* = 6.3 Hz, 2 H), 2.72 (t, *J* = 6.1 Hz, 2 H), 2.62-2.55 (m, 4 H), 2.27-2.23 (m, 2 H), 2.17 (s, 3 H), 1.83-1.78 (m, 2 H), 1.78-1.71 (m, 2 H), 1.66 (s, 3 H), 0.89 (s, 9 H), 0.05 (s, 6 H); ¹³C NMR

(100 MHz, CDCl₃) δ 138.98 (C), 137.02 (C), 136.79 (C), 136.51 (C), 132.94 (C), 127.18 (CH), 126.70 (CH), 124.51 (CH), 60.37 (CH₂), 41.72 (CH₂), 33.94 (CH₂), 30.12 (CH₂), 26.43 (CH₂), 26.05 (CH₃), 23.54 (CH₂), 22.99 (CH₂), 19.48 (CH₃), 18.46 (C), 16.55 (CH₃), -5.04 (CH₃); HRMS m/z calculated for C₁₉H₂₉OSi 301.1988 (M⁺ - *t*-Bu), found 301.2002.

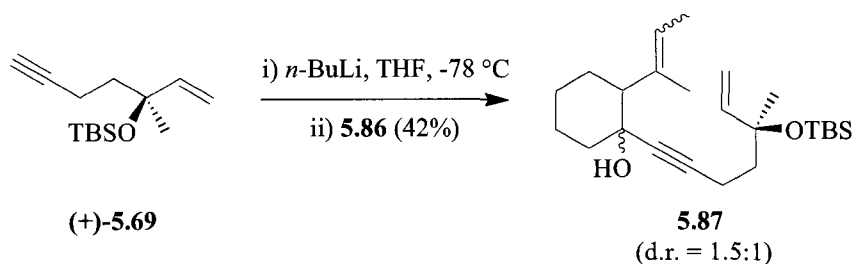


(±)-1-[7-(*t*-Butyldimethylsilyloxy)-5-methylhept-5-enynyl]-2,2-dimethyl-6-(1-methylpropenyl)cyclohexanol (**5.82**). To a solution of **5.79** (102 mg, 0.43 mmol) in THF (500 μ L) at -78 °C was added *n*-BuLi (220 μ L of a 1.8 M solution in pentane, 0.40 mmol) dropwise. The resulting solution was stirred at -78 °C for 30 minutes. A solution of ketone **5.41** (14 mg, 0.08 mmol) in THF (400 μ L) was then added dropwise via cannula. After stirring at -78 °C for 1 h, the reaction mixture was warmed up to 0 °C. It was further stirred for 30 minutes at that temperature, and was quenched with saturated aqueous NH₄Cl (1 mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 5 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes then 1% EtOAc/hexanes) to afford 15 mg of **5.82** as a colorless oil (46% yield): IR (neat) ν_{max} 3553, 2930, 2861, 2238, 1462, 1382, 1253, 1105 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.39-5.32 (m, 2 H), 4.17 (dd, J = 6.2, 0.7 Hz, 2 H), 2.35-2.25 (m, 4 H), 2.24-2.19 (m, 2 H), 1.84-1.73 (m, 1 H), 1.71 (t, J = 1.1 Hz, 3 H), 1.62-1.59 (m, 6 H), 1.50-1.44 (m, 3 H), 1.27-1.21 (m, 1 H), 1.08 (s, 3 H), 0.99 (s, 3 H), 0.88 (s, 9 H), 0.05 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 136.35 (C), 135.26 (C), 125.62 (CH), 124.24 (CH), 86.35 (C), 82.40 (C), 74.56 (C), 60.21 (CH₂), 51.90 (CH), 39.05 (C), 38.44 (CH₂), 37.78 (CH₂), 28.57 (CH₂), 26.90 (CH₃), 26.03 (CH₃), 21.48 (CH₂), 20.01 (CH₃), 18.44 (C), 17.56 (CH₂), 16.05 (CH₃), 13.96 (CH₃), 13.42 (CH₃), -5.05 (CH₃); HRMS m/z calculated for C₂₂H₃₇O₂Si 361.2563 (M⁺ - *t*-Bu), found 361.2573.



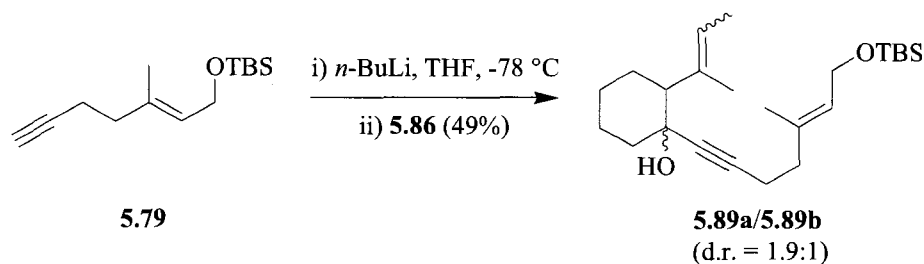
(±)-2-(1-Methylpropenyl)-cyclohexanol (**5.85**) and (±)-2-(1-methylpropenyl)-cyclohexanone (**5.86**). *Step 1*: CuBr·SMe₂ (545 mg, 2.65 mmol) was placed in a flame-dried 500 mL round-bottom flask. THF (73 mL) was added and the suspension was cooled to -20 °C. 1-methyl-1-isopropenylmagnesium bromide (69 mL of a 0.5 M solution in THF, 34.50 mmol) was added dropwise and the resulting brown mixture was stirred for 15 minutes at -20 °C. Cyclohexene oxide **2.28** (2.68 mL, 26.49 mmol) was then added dropwise and the reaction mixture was warmed up to 0 °C. After stirring for 1 h at that temperature, it was quenched with saturated aqueous NH₄Cl (50 mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 50 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. Filtration and careful removal of the solvent gave crude alcohol **5.85**. An aliquot was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford the alcohol as a pale yellow oil. This was a 3.2:1 mixture of geometrical isomers: IR (neat) ν_{max} 3420 (br), 2933, 2861, 2667, 1447, 1272 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) *major* δ 5.45 (qd, J = 6.7, 1.1 Hz, 1 H), 3.48-3.35 (m, 1 H), 2.40 (ddd, J = 10.0, 10.0, 3.6 Hz, 1 H), 2.07-2.01 (m, 1 H), 1.84-1.49 (m, 10 H), 1.39-1.16 (m, 4 H) *minor* δ 5.41-5.35 (m, 1 H), 3.48-3.35 (m, 1 H), 2.07-2.01 (m, 1 H), 1.84-1.49 (m, 11 H), 1.39-1.16 (m, 4 H); ¹³C NMR (100 MHz, CDCl₃) *major* δ 135.96 (C), 123.21 (CH), 70.94 (CH), 46.95 (CH), 34.25 (CH₂), 29.06 (CH₂), 25.70 (CH₂), 24.95 (CH₂), 19.08 (CH₃), 13.09 (CH₃) *minor* δ 136.43 (C), 122.00 (CH), 70.36 (CH), 56.31 (CH), 34.07 (CH₂), 29.98 (CH₂), 25.75 (CH₂), 24.92 (CH₂), 13.31 (CH₃), 12.24 (CH₃); HRMS m/z calculated for C₁₀H₁₈O 154.1358 (M⁺), found 154.1356. *Step 2*: To a solution of oxalyl chloride (3.5 mL, 40.12 mmol) in CH₂Cl₂ (240 mL) at -78 °C was added DMSO (5.6 mL, 78.91 mmol) dropwise. The resulting solution was stirred for 20 minutes, and a solution of the crude alcohol in CH₂Cl₂ (25 mL) was added via cannula. The resulting cloudy mixture was stirred at -78 °C for 1.5 h, and Et₃N (22.1 mL, 158.56 mmol) was added dropwise. The reaction mixture was warmed up to 0 °C. After stirring for 45 minutes at that temperature, it was quenched with saturated

aqueous NH_4Cl (100 mL). The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 x 100 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% EtOAc /hexanes) to afford 3.32 g of **5.86** as a pale yellow oil (82% yield over 2 steps). This was a 5.4:1 mixture of geometrical isomers: IR (neat) ν_{max} 2937, 2865, 1713, 1451, 1128 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) *major* δ 5.37 (qq, $J = 5.5, 1.3$ Hz, 1 H), 3.32 (ddd, $J = 5.7, 5.4, 0.9$ Hz, 1 H), 2.43–2.37 (m, 1 H), 2.37–2.23 (m, 1 H), 2.08–1.99 (m, 1 H), 1.95–1.88 (m, 2 H), 1.87–1.62 (m, 6 H), 1.45 (qd, $J = 6.8, 1.5$ Hz, 3 H) *minor* δ 5.21–5.17 (m, 1 H), 2.89 (dd, $J = 11.9, 5.4$ Hz, 1 H), 2.37–2.23 (m, 1 H), 2.08–1.99 (m, 1 H), 1.95–1.88 (m, 2 H), 1.87–1.62 (m, 7 H), 1.58–1.55 (m, 3 H); ^{13}C NMR (100 MHz, CDCl_3) *major* δ 210.33 (C), 133.52 (C), 122.09 (CH), 52.07 (CH), 42.18 (CH_2), 31.59 (CH_2), 27.04 (CH_2), 25.22 (CH_2), 20.69 (CH_3), 13.16 (CH_3) *minor* δ 211.66 (C), 133.99 (C), 121.34 (CH), 80.27 (CH), 42.18 (CH_2), 32.24 (CH_2), 27.51 (CH_2), 25.02 (CH_2), 14.68 (CH_3), 13.36 (CH_3); HRMS m/z calculated for $\text{C}_{10}\text{H}_{16}\text{O}$ 152.1201 (M^+), found 152.1201.



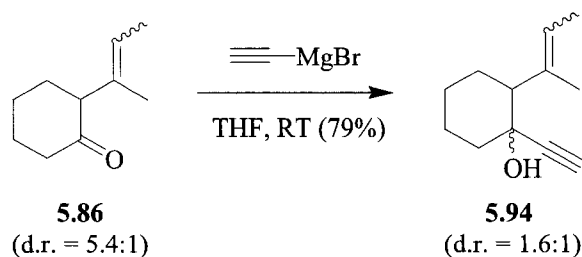
(±)-1-[5-(*t*-Butyldimethylsilanyloxy)-5-methylhept-6-enynyl]-2-(1-methylpropenyl)-cyclohexanol (**5.87**). To a solution of **5.69** (188 mg, 0.79 mmol) in THF (3 mL) at $-78\text{ }^\circ\text{C}$ was added $n\text{-BuLi}$ (300 μL of a 2.0 M solution in pentane, 0.60 mmol) dropwise. The resulting solution was stirred at $-78\text{ }^\circ\text{C}$ for 30 minutes. A solution of ketone **5.86** (60 mg, 0.39 mmol) in THF (1 mL) was then added dropwise via cannula. After stirring at $-78\text{ }^\circ\text{C}$ for 30 minutes, the reaction mixture was warmed up to $0\text{ }^\circ\text{C}$. It was further stirred for 30 minutes at that temperature, and was quenched with saturated aqueous NH_4Cl (2 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After

filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes $\rightarrow$ 2% EtOAc/hexanes) to afford 65 mg of **5.87** as a pale yellow oil (42% yield). This was mostly a 1.5:1 mixture of epimers: IR (neat) ν_{max} 3564, 3473, 2933, 2861, 2234, 1462, 1371, 1253, 1177, 1120 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) *major* δ 5.76 (dd, $J = 17.3, 10.7$ Hz, 1 H), 5.51 (qd, $J = 6.3, 1.0$ Hz, 1 H), 5.12 (dd, $J = 17.3, 1.5$ Hz, 1 H), 4.98 (dd, $J = 10.7, 1.5$ Hz, 1 H), 2.56 (dd, $J = 12.3, 3.1$ Hz, 1 H), 2.43 (s, 1 H), 2.30-2.05 (m, 3 H), 2.02-1.98 (m, 1 H), 1.82 (s, 3 H), 1.80-1.47 (m, 11 H), 1.28 (s, 3 H), 0.86 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H) *minor* δ 5.76 (dd, $J = 17.3, 10.7$ Hz, 1 H), 5.36-5.28 (m, 1 H), 5.12 (dd, $J = 17.3, 1.6$ Hz, 1 H), 4.98 (dd, $J = 10.7, 1.4$ Hz, 1 H), 2.61 (dd, $J = 12.7, 3.2$ Hz, 1 H), 2.30-2.05 (m, 3 H), 1.93-1.85 (m, 1 H), 1.82 (s, 3 H), 1.80-1.47 (m, 12 H), 1.26 (s, 3 H), 0.85 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.78, 144.69, 137.03, 135.45, 124.40, 121.73, 112.39, 112.32, 86.95, 84.32, 83.45, 82.31, 75.00, 71.02, 49.15, 46.50, 42.68, 42.62, 41.67, 40.77, 28.28, 27.55, 27.52, 27.46, 25.93, 25.87, 25.70, 24.11, 22.20, 21.15, 21.06, 18.34, 13.91, 13.83, 13.65, 13.61, -2.11; HRMS m/z calculated for $\text{C}_{24}\text{H}_{42}\text{O}_2\text{Si}$ 390.2954 (M^+), found 390.2980.



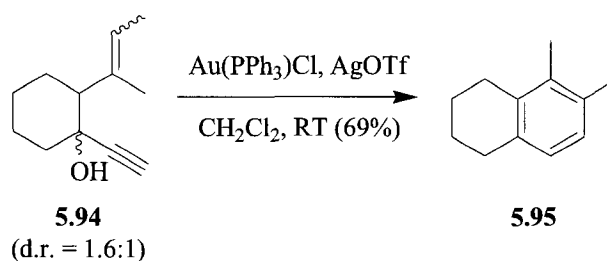
($\pm$)-1-[7-(*t*-Butyldimethylsilanyloxy)-5-methylhept-5-enynyl]-2-(1-methylpropenyl)-cyclohexanol (**5.89**). To a solution of **5.79** (188 mg, 0.79 mmol) in THF (2 mL) at -78°C was added *n*-BuLi (330 μL of a 2.0 M solution in pentane, 0.66 mmol) dropwise. The resulting solution was stirred at -78°C for 30 minutes. A solution of ketone **5.86** (40 mg, 0.26 mmol) in THF (0.6 mL) was then added dropwise via cannula. After stirring at -78°C for 30 minutes, the reaction mixture was warmed up to 0°C . It was further stirred for 30 minutes at that temperature, and was quenched with saturated aqueous NH_4Cl (1 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 5 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After

filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes $\rightarrow$ 2% EtOAc/hexanes) to afford 32.5 mg of **5.89a** (32% yield) and 17 mg of **5.89b** (17% yield) as pale yellow oils. Epimer **5.89a**: IR (neat) $\nu_{\max}$ 3568, 3473, 2933, 2857, 2234, 1671, 1462, 1382, 1253, 1109 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.51 (q, $J=5.9$ Hz, 1 H), 5.33 (br, 1 H), 4.16 (d, $J=5.7$ Hz, 2 H), 2.55 (dd, $J=12.2, 2.5$ Hz, 1 H), 2.43 (s, 1 H), 2.33-2.30 (m, 2 H), 2.20-2.17 (m, 2 H), 1.99 (d, $J=11.0$ Hz, 1 H), 1.81 (s, 3 H), 1.72-1.66 (m, 3 H), 1.63-1.60 (m, 7 H), 1.54-1.48 (m, 2 H), 1.28-1.17 (m, 1 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (125 MHz, CDCl_3) δ 135.24 (C), 135.00 (C), 125.47 (CH), 124.28 (CH), 85.77 (C), 83.02 (C), 70.85 (C), 60.03 (CH_2), 48.93 (CH), 40.61 (CH_2), 38.19 (CH_2), 28.07 (CH_2), 25.85 (CH_3), 25.68 (CH_2), 23.90 (CH_2), 20.98 (CH_3), 18.27 (C), 17.39 (CH_2), 15.91 (CH_3), 13.66 (CH_3), -5.27 (CH_3); HRMS m/z calculated for $\text{C}_{20}\text{H}_{33}\text{O}_2\text{Si}$ 333.2250 ($\text{M}^+ - t\text{-Bu}$), found 333.2228. Epimer **5.89b** was a mixture of geometrical isomers: IR (neat) $\nu_{\max}$ 3477 (br), 2933, 2856, 2238, 1471, 1378, 1253, 1112 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.37-5.29 (m, 2 H), 4.16 (d, $J=6.3$ Hz, 2 H), 2.61 (dd, $J=12.7, 3.3$ Hz, 1 H), 2.26-2.22 (m, 2 H), 2.17-2.12 (m, 2 H), 1.93-1.90 (m, 1 H), 1.85-1.78 (m, 1 H), 1.77 (t, $J=1.5$ Hz, 3 H), 1.75-1.60 (m, 4 H), 1.59 (s, 3 H), 1.53 (s, 3 H), 1.33-1.23 (m, 3 H), 0.88 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, CDCl_3) *major* δ 137.11 (C), 135.34 (C), 125.49 (CH), 121.71 (CH), 85.28 (C), 82.87 (C), 70.33 (C), 60.22 (CH_2), 46.46 (CH), 41.71 (CH_2), 38.49 (CH_2), 26.03 (CH_3), 25.91 (CH_2), 25.69 (CH_2), 22.20 (CH_3), 21.05 (CH_2), 18.46 (C), 17.69 (CH_2), 16.18 (CH_3), 13.89 (CH_3), -5.07 (CH_3); HRMS m/z calculated for $\text{C}_{20}\text{H}_{33}\text{O}_2\text{Si}$ 333.2250 ($\text{M}^+ - t\text{-Bu}$), found 333.2259.



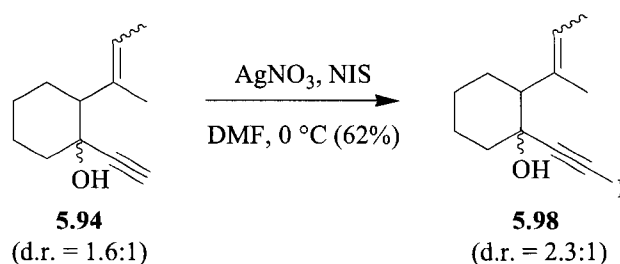
($\pm$)-1-Ethynyl-2-(1-methylpropenyl)-cyclohexanol (5.94**).** To a solution of **5.86** (3.61 g, 23.73 mmol) in THF (10 mL) at room temperature was added ethynylmagnesium bromide (190 mL of a 0.5 M solution in THF, 95.00 mmol). After stirring for 2 h, the reaction mixture was

cooled down to 0 °C. It was then quenched by the slow addition of saturated aqueous NH_4Cl (100 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 100 mL). Combined organics were washed with brine and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% EtOAc /hexanes) to afford 3.34 g of **5.94** as a colorless oil (79% yield). This was mostly a 1.6:1 mixture of epimers: IR (neat) ν_{max} 3544, 3160, 3307, 2936, 2861, 2108, 1447, 1147 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) *major* δ 5.54 (qd, J = 6.8, 1.2 Hz, 1 H), 2.59 (dd, J = 12.3, 3.0 Hz, 1 H), 2.57 (s, 1 H), 2.47 (s, 1 H), 2.10-2.06 (m, 1 H), 1.86-1.80 (m, 2 H), 1.79-1.68 (m, 4 H), 1.67-1.60 (m, 3 H), 1.57-1.52 (m, 2 H), 1.36-1.21 (m, 2 H); *minor* δ 5.36 (dddd, J = 6.9, 6.9, 5.4, 1.4 Hz, 1 H), 2.69 (dd, J = 12.5, 3.3 Hz, 1 H), 2.37 (s, 1 H), 1.99-1.95 (m, 1 H), 1.86-1.80 (m, 2 H), 1.79-1.68 (m, 4 H), 1.67-1.60 (m, 4 H), 1.57-1.52 (m, 2 H), 1.36-1.21 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) *major* δ 134.82 (C), 124.78 (CH), 86.57 (C), 74.24 (CH), 70.98 (C), 48.75 (CH), 40.30 (CH_2), 27.92 (CH_2), 25.56 (CH_2), 23.72 (CH_2), 20.90 (CH_3), 13.66 (CH_3); *minor* δ 136.62 (C), 122.05 (CH), 88, 23 (C), 70.66 (CH), 70.00 (C), 46.01 (CH), 41.15 (CH_2), 25.63 (CH_2), 25.33 (CH_2), 21.92 (CH_3), 20.61 (CH_2), 13.83 (CH_3); HRMS m/z calculated for $\text{C}_{12}\text{H}_{18}\text{O}$ 178.1358 (M^+), found 178.1371.



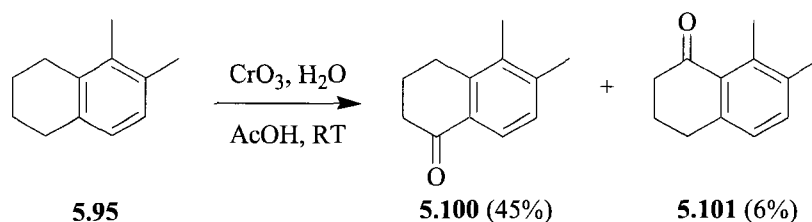
5,6-Dimethyl-1,2,3,4-tetrahydronaphthalene (5.95). AgOTf (388 mg, 1.51 mmol) and $\text{Au(PPh}_3\text{)Cl}$ (747 mg, 1.51 mmol) were weighed in the glovebox and transferred to a flame-dried flask equipped with a magnetic stirrer. CH_2Cl_2 (230 mL) was added. Then, a solution of **5.94** (4.48 g, 25.15 mmol) in CH_2Cl_2 (20 mL) was added via cannula. After stirring at room temperature for 21 h, the reaction mixture was filtered through celite. The fritted glass funnel was rinsed with Et_2O (50 mL), and the filtrate was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes) to afford 2.76 g of **5.95** as a colorless oil (69% yield): IR (neat) ν_{max} 2945, 2918, 2861, 1481, 1447 cm^{-1} ; ^1H NMR (400

MHz, CDCl_3) δ 6.93 (d, $J = 7.7$ Hz, 1 H), 6.85 (d, $J = 7.7$ Hz, 1 H), 2.75 (t, $J = 6.2$ Hz, 2 H), 2.66 (t, $J = 6.4$ Hz, 2 H), 2.26 (s, 3 H), 2.13 (s, 3 H), 1.86-1.78 (m, 2 H), 1.77-1.71 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 135.32 (C), 134.87 (C), 134.77 (C), 133.47 (C), 126.98 (CH), 126.45 (CH), 30.14 (CH_2), 27.33 (CH_2), 23.72 (CH_2), 22.84 (CH_2), 20.43 (CH_3), 14.81 (CH_3); HRMS m/z calculated for $\text{C}_{12}\text{H}_{16}$ 160.1252 (M^+), found 160.1267.

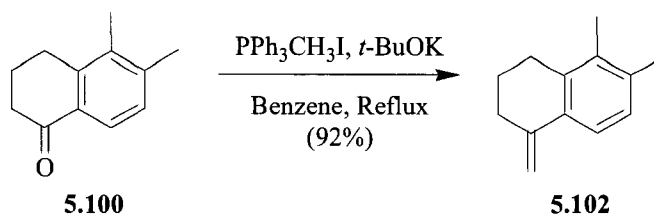


(±)-1-Iodoethynyl-2-(1-methylpropenyl)-cyclohexanol (5.98). Alcohols **5.94** (50 mg, 0.28 mmol) were dissolved in freshly distilled DMF (3.2 mL). The resulting solution was cooled down to 0 °C and the reaction flask was covered with tin foil. Then, NIS (76 mg, 0.34 mmol) and finely ground AgNO_3 (57 mg, 0.34 mmol) were added. The reaction mixture was kept in the dark and stirred for 4 h, at which point it was diluted with 1:1 Et_2O /hexanes (5 mL) and quenched with saturated aqueous Na_2SO_3 (3 mL). The thick reaction mixture was filtered over celite to remove the succinimide salts. It was then extracted with Et_2O (3 x 10 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (2% EtOAc /hexanes) to afford 52.5 mg of **5.98** as a pale yellow oil (62% yield). This was mostly a 2.3:1 mixture of epimers: IR (neat) ν_{max} 3453 (br), 2934, 2858, 2175, 1447, 1375, 1325, 1147 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) *major* δ 5.55 (qd, $J = 6.9, 0.4$ Hz, 1 H), 2.59-2.56 (m, 2 H), 2.10-2.07 (m, 1 H), 1.84-1.67 (m, 6 H), 1.66-1.49 (m, 6 H), 1.37-1.17 (m, 1 H) *minor* δ 5.39 (qd, $J = 6.8, 0.4$ Hz, 1 H), 2.67 (dd, $J = 12.5, 3.4$ Hz, 1 H), 1.97-1.93 (m, 1 H), 1.84-1.67 (m, 6 H), 1.66-1.49 (m, 6 H), 1.37-1.17 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) *major* δ 134.58 (C), 125.05 (CH), 97.27 (C), 72.41 (C), 49.09 (CH), 40.27 (CH_2), 27.96 (CH_2), 25.52 (CH_2), 23.77 (CH_2), 20.84 (CH_3), 13.66 (CH_3), 1.92 (C) *minor* δ 135.84 (C), 122.53 (CH), 98.89 (C), 72.06 (C), 46.02 (CH), 41.13 (CH_2), 25.58

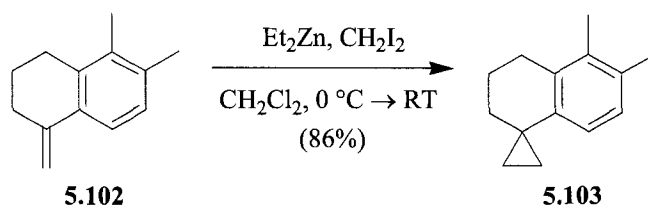
(CH₂), 25.31 (CH₂), 22.05 (CH₃), 20.65 (CH₂), 13.86 (CH₃), -0.50 (C); HRMS *m/z* calculated for C₁₂H₁₇O 304.0324 (M⁺), found 304.0324.



5,6-Dimethyl-3,4-dihydro-2H-naphthalenone (5.100) and **7,8-dimethyl-3,4-dihydro-2H-naphthalenone (5.101)**. A 10% aqueous CrO₃ acetic solution was prepared by mixing CrO₃ (2.34 g, 23.42 mmol), glacial AcOH (21.1 mL) and H₂O (1.1 mL) at room temperature. This solution was then added to a solution of **5.95** (750 mg, 4.68 mmol) in glacial AcOH (120 mL). The resulting dark brown reaction mixture was stirred at room temperature for 2.5 h. It was then diluted with H₂O (200 mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (4 x 100 mL). Combined organics were washed with H₂O and saturated aqueous NaHCO₃, and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% EtOAc/hexanes) to afford 370 mg of **5.100** as a pale yellow solid (45% yield) and 52.5 mg of **5.101** as a yellow oil (6% yield). Isomer **5.100**: mp 67-68.5 °C; IR (neat) $\nu_{\max}$ 2933, 2860, 1682, 1594, 1283 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.83 (d, *J* = 8.0 Hz, 1 H), 7.08 (d, *J* = 8.0 Hz, 1 H), 2.87 (t, *J* = 6.2 Hz, 2 H), 2.60-2.57 (m, 2 H), 2.32 (s, 3 H), 2.20 (s, 3 H), 2.15-2.09 (m, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 198.68 (C), 142.49 (C), 142.40 (C), 134.40 (C), 130.87 (C), 127.98 (CH), 124.52 (CH), 38.26 (CH₂), 26.88 (CH₂), 22.57 (CH₂), 21.13 (CH₃), 14.91 (CH₃); HRMS *m/z* calculated for C₁₂H₁₄O 174.1045 (M⁺), found 174.1044. Isomer **5.101**: IR (neat) $\nu_{\max}$ 2933, 2860, 1682, 1594, 1283 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.17 (d, *J* = 7.7 Hz, 1 H), 6.94 (d, *J* = 7.7 Hz, 1 H), 2.85 (t, *J* = 6.1 Hz, 2 H), 2.61 (t, *J* = 6.7 Hz, 2 H), 2.50 (s, 3 H), 2.26 (s, 3 H), 2.05-1.98 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 200.93 (CH), 143.20 (CH), 139.31 (CH), 136.20 (CH), 133.93 (CH), 131.96 (C), 125.84 (CH), 41.21 (CH₂), 30.87 (CH₂), 23.12 (CH₂), 20.53 (CH₃), 17.42 (CH₃); HRMS *m/z* calculated for C₁₂H₁₄O 174.1045 (M⁺), found 174.1062.

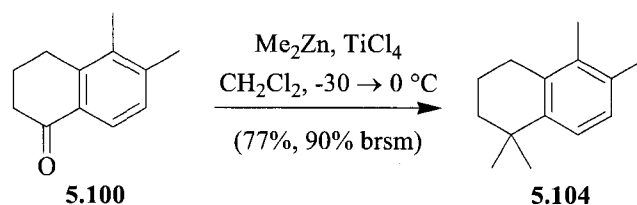


5,6-Dimethyl-1-methylene-1,2,3,4-tetrahydronaphthalene (5.102). To a suspension of $\text{Ph}_3\text{PCH}_3\text{I}$ (3.95 g, 9.76 mmol) in benzene (34 mL) at room temperature was added $t\text{-BuOK}$ (9.76 mL of a 1.0 M solution in THF, 9.76 mmol) dropwise. After stirring for 20 minutes, a solution of **5.100** (680 mg, 3.91 mmol) in benzene (5 mL) was added dropwise via cannula. The reaction mixture was then refluxed for 1.5 h. After cooling down to room temperature, it was quenched with saturated aqueous NH_4Cl (20 mL). The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 20 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes) to afford 619 mg of **5.102** as a white solid (92% yield): mp 56–57 °C; IR (neat) ν_{max} 2933, 2865, 1622, 1436, 1265 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.44 (d, $J = 8.0$ Hz, 1 H), 7.00 (d, $J = 8.0$ Hz, 1 H), 5.41 (s, 1 H), 4.40 (s, 1 H), 2.76 (t, $J = 6.4$ Hz, 2 H), 2.49 (dd, $J = 6.2, 5.9$ Hz, 2 H), 2.30 (s, 3 H), 2.16 (s, 3 H), 1.96–1.90 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.69 (C), 135.98 (C), 135.52 (C), 134.79 (C), 132.96 (C), 127.49 (CH), 121.80 (CH), 106.80 (CH_2), 32.94 (CH_2), 28.05 (CH_2), 24.12 (CH_2), 20.69 (CH_3), 15.09 (CH_3); HRMS m/z calculated for $\text{C}_{13}\text{H}_{16}$ 172.1252 (M^+), found 172.1260.



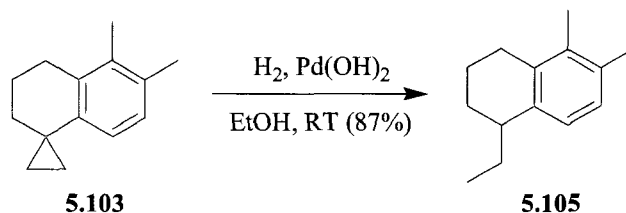
5',6'-Dimethylspiro[cyclopropane-1,1'-tetralin] (5.103). To a solution of **5.102** (318 mg, 1.85 mmol) in CH_2Cl_2 (4.6 mL) at 0 °C were added dropwise Et_2Zn (5.54 mL of a 1.0 M solution in hexanes, 5.54 mmol) and CH_2I_2 (890 μL , 11.04 mmol). The reaction mixture was allowed to warm up to room temperature over 5 h. It was then quenched with ice and partitioned

between CH_2Cl_2 (10 mL) and H_2O (10 mL). The resulting mixture was filtered through celite, and the fritted glass funnel was rinsed with CH_2Cl_2 (10 mL). The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 x 10 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes) to afford 297 mg of **5.103** as a white solid (86% yield): mp 58-59.5 °C; IR (neat) ν_{max} 2930, 2854, 1489, 1455, 1439 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.91 (d, J = 8.6 Hz, 1 H), 6.47 (d, J = 8.6 Hz, 1 H), 2.76 (t, J = 7.0 Hz, 2 H), 2.24 (s, 3 H), 2.14 (s, 3 H), 1.95-1.90 (m, 2 H), 1.61-1.59 (m, 2 H), 0.94-0.92 (m, 2 H), 0.75-0.73 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.29 (C), 135.69 (C), 134.51 (C), 132.79 (C), 127.46 (CH), 118.97 (CH), 34.74 (CH_2), 28.51 (CH_2), 22.52 (CH_2), 20.41 (CH_3), 19.41 (C), 18.50 (CH_2), 18.50 (CH_2), 15.10 (CH_3); HRMS m/z calculated for $\text{C}_{14}\text{H}_{18}$ 186.1409 (M^+), found 186.1412.

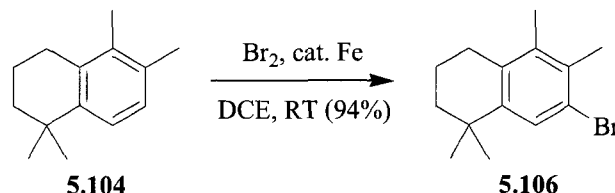


1,1,5,6-Tetramethyl-1,2,3,4-tetrahydro-naphthalene (5.104). To a solution of freshly distilled TiCl_4 (625 μL , 5.70 mmol) in CH_2Cl_2 (5 mL) at -30 °C was added Me_2Zn (5.7 mL of a 1.0 M solution in toluene, 5.70 mmol). The resulting orange mixture was stirred at that temperature for 10 minutes. A solution of **5.100** (450 mg, 2.58 mmol) in CH_2Cl_2 (2.2 mL) was then added dropwise via cannula. The dark red reaction mixture was slowly allowed to warm up to 0 °C over a period of about 2 h, and was then poured onto ice water. The aqueous layer was separated from the organic layer and extracted with Et_2O (3 x 20 mL). Combined organics were washed with saturated aqueous NaHCO_3 and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes then 10% EtOAc /hexanes) to afford 63 mg of unreacted **5.100** and 376 mg of **5.104** as a colorless oil (77% yield; 90% yield brsm): IR (neat) ν_{max} 2930, 2869, 1485, 1455, 1382, 1360 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.15 (d, J = 8.0 Hz, 1 H), 6.99 (d, J = 8.0 Hz, 1 H), 2.65 (t, J = 6.5 Hz, 2 H), 2.26 (s, 3 H), 2.14 (s, 3 H), 1.87-1.81 (m, 2 H),

1.64-1.61 (m, 2 H), 1.29 (s, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ 143.57 (C), 134.61 (C), 134.51 (C), 133.27 (C), 127.35 (CH), 123.89 (CH), 38.65 (CH_2), 33.88 (C), 32.06 (CH_3), 32.06 (CH_3), 28.35 (CH_2), 20.52 (CH_3), 19.67 (CH_2), 15.24 (CH_3); HRMS m/z calculated for $\text{C}_{14}\text{H}_{20}$ 188.1565 (M^+), found 188.1563.

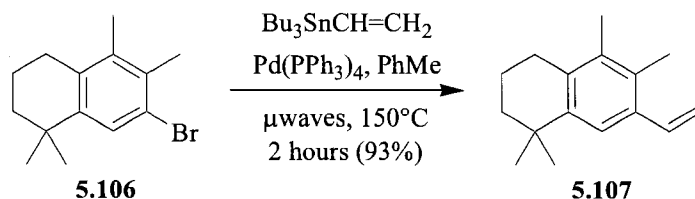


(±)-1-Ethyl-5,6-dimethyl-1,2,3,4-tetrahydronaphthalene (5.105). To a solution of **5.103** (10 mg, 0.054 mmol) in dry EtOH (800 μL) at room temperature was added $\text{Pd}(\text{OH})_2$ (3.8 mg, 0.0054 mmol). The resulting mixture was stirred under an atmosphere of hydrogen for 23 h. It was then filtered through a plug of celite, and the fritted glass funnel was rinsed with Et_2O (10 mL). After removal of the solvent, the residue was purified by silica gel column chromatography (hexanes) to afford 8.8 mg of **5.105** as a colorless oil (87% yield): IR (neat) ν_{max} 2933, 2869, 1481, 1455 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.95 (s, 2 H), 2.69-2.54 (m, 3 H), 2.25 (s, 3 H), 2.11 (s, 3 H), 1.88-1.80 (m, 1 H), 1.77-1.65 (m, 4 H), 1.59-1.50 (m, 1 H), 0.95 (t, $J = 7.4$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 139.04 (C), 135.10 (C), 134.47 (C), 133.25 (C), 126.83 (CH), 125.97 (CH), 39.46 (CH), 29.40 (CH_2), 27.37 (CH_2), 25.87 (CH_2), 20.33 (CH_3), 19.44 (CH_2), 14.83 (CH_3), 11.98 (CH_3); HRMS m/z calculated for $\text{C}_{14}\text{H}_{20}$ 188.1565 (M^+), found 188.1570.



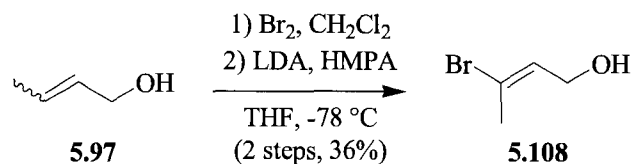
7-Bromo-1,1,5,6-tetramethyl-1,2,3,4-tetrahydronaphthalene (5.106). To a mixture of **5.104** (479 mg, 2.54 mmol) and iron powder (28 mg, 0.50 mmol) in 1,2-dichloroethane (20 mL) at 0 $^\circ\text{C}$ was added Br_2 (5.60 mL of a 0.50 M solution in CH_2Cl_2 , 2.80 mmol) dropwise. After warming up to room temperature, the reaction mixture was stirred for 15 h. It was then

quenched by the slow addition of cold H₂O (10 mL). The aqueous layer was separated from the organic layer and extracted with Et₂O (3 x 20 mL). Combined organics were dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes) to afford 637 mg of **5.106** as a colorless oil (94% yield): IR (neat) ν_{max} 2968, 2930, 2869, 1554, 1462, 1253 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.40 (s, 1 H), 2.57 (t, J = 6.5 Hz, 2 H), 2.36 (s, 3 H), 2.18 (s, 3 H), 1.83-1.78 (m, 2 H), 1.59-1.53 (m, 2 H), 1.25 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 145.34 (C), 136.61 (C), 133.93 (C), 132.61 (C), 128.17 (CH), 123.08 (C), 38.36 (CH₂), 33.98 (C), 31.88 (CH₃), 31.88 (CH₃), 28.49 (CH₂), 19.93 (CH₃), 19.49 (CH₂), 16.63 (CH₃); HRMS m/z calculated for C₁₄H₁₉Br 266.0670 (M⁺), found 266.0680.

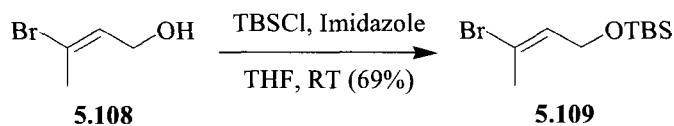


1,1,5,6-Tetramethyl-7-vinyl-1,2,3,4-tetrahydronaphthalene (5.107). A stirred solution of **5.106** (283 mg, 1.064 mmol), tributylvinyltin (560 μ L, 1.916 mmol), Pd(PPh₃)₄ (98 mg, 0.085 mmol) and toluene (7 mL) in a microwave cell was deoxygenated by bubbling argon through it for 15 minutes. The reaction mixture was heated at 150 °C in the microwave oven for 2 h. After cooling to room temperature, the mixture was diluted with hexanes (25 mL). It was then washed sequentially with H₂O (20 mL), 10% aqueous NH₄OH (20 mL), H₂O (20 mL), and saturated aqueous NaCl (20 mL). The organic layer was dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes) to afford 211 mg of **5.107** as a pale yellow oil (93% yield): IR (neat) ν_{max} 3085, 2960, 2926, 2865, 1816, 1622, 1466 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.32 (s, 1 H), 7.01 (dd, J = 17.3, 10.9 Hz, 1 H), 5.51 (dd, J = 17.3, 1.7 Hz, 1 H), 5.24 (dd, J = 10.9, 1.7 Hz, 1 H), 2.65 (t, J = 6.5 Hz, 2 H), 2.24 (s, 3 H), 2.15 (s, 3 H), 1.86-1.80 (m, 2 H), 1.64-1.61 (m, 2 H), 1.31 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 143.33 (C), 136.82 (CH), 135.16 (C), 134.72 (C), 134.46 (C), 130.88 (C), 122.11 (CH), 114.85 (CH₂), 38.70 (CH₂),

33.91 (C), 32.04 (CH₃), 32.04 (CH₃), 28.68 (CH₂), 16.69 (CH₂), 15.84 (CH₃), 15.62 (CH₃); HRMS m/z calculated for C₁₆H₂₂ 214.1721 (M⁺), found 214.1730.

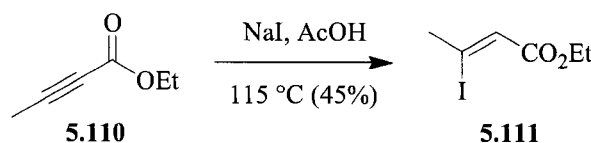


(*E*)-3-Bromobut-2-enol (5.108). *Step 1:* To a solution of crotyl alcohol **5.97** (2.00 mL, 23.44 mmol) in CHCl₃ (115 mL) at -10 °C was added Br₂ (1.20 mL, 23.35 mmol) dropwise. After stirring for 1.5 h, the reaction was quenched with saturated aqueous Na₂SO₃ (10 mL). The aqueous layer was separated from the organic layer and extracted with CH₂Cl₂ (3 x 10 mL). Combined organics were dried over MgSO₄. Filtration and removal of the solvent delivered the crude brominated alcohol. *Step 2:* To a solution of DIPA (8.40 mL, 59.93 mmol) in THF (80 mL) at -78 °C were added dropwise *n*-BuLi (37.0 mL of a 1.5 M solution in pentane, 55.5 mmol) and dry HMPA (1.70 mL, 9.77 mmol). A solution of the crude brominated alcohol in THF (20 mL) was then added to the reaction mixture over 1.5 h using a syringe pump. After stirring for an additional hour, the reaction was quenched at -78 °C with H₂O (100 mL). After warming up to room temperature, the aqueous layer was separated from the organic layer and extracted with AcOEt (4 x 100 mL). Combined organics were dried over MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (20% EtOAc/hexanes) to afford 1.28 g of **5.108** as a yellow oil (36% yield over 2 steps). Spectroscopic data for **5.108** were identical to that previously reported.^{135a}

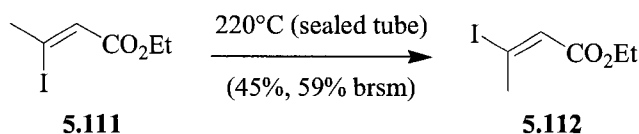


(*E*)-(3-Bromobut-2-enyloxy)-*t*-butyldimethylsilane (5.109). To a solution of **5.108** (1.28 g, 8.54 mmol) in THF (43 mL) were added TBSCl (1.42 g, 9.42 mmol) and imidazole (1.75 g, 25.71 mmol). After stirring at room temperature for 4 h, the reaction mixture was quenched with saturated aqueous NH₄Cl (20 mL). The aqueous layer was separated from the organic layer

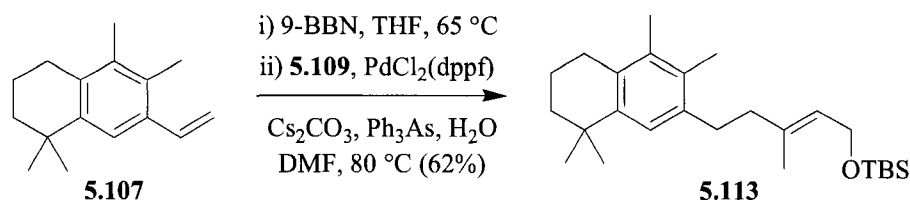
and extracted with Et₂O (3 x 20 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes then 2% EtOAc/hexanes) to afford 1.55 g of **5.109** as a colorless oil (69% yield). Spectroscopic data for **5.109** were identical to that previously reported.¹⁴⁹



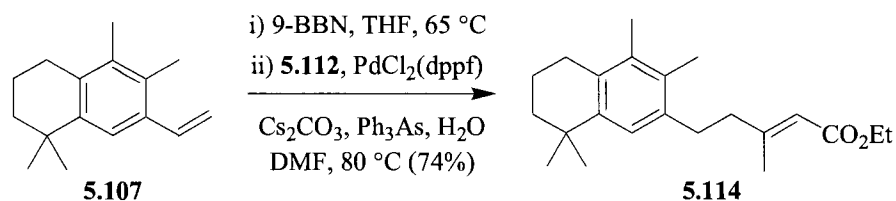
Ethyl (Z)-3-iodobut-2-enoate (5.111). An oil bath was preheated at 115 °C for 15 minutes. A flask containing a mixture of ethyl 2-butynoate **5.110** (1.31 g, 11.68), NaI (2.80 g, 18.68 mmol), and glacial AcOH (4.30 mL, 75.12 mmol) was placed in the oil bath, and the mixture was stirred for 1.5 h at 115 °C. The bath was removed and the brown mixture was transferred while hot to a separatory funnel containing H₂O (100 mL). The reaction flask was washed with H₂O (10 mL) and Et₂O (250 mL). The washings were added to the separatory funnel. The aqueous layer was separated from the organic layer and extracted with Et₂O (100 mL). Combined organics were washed with saturated aqueous NaHCO₃ (100 mL), 1 M aqueous Na₂S₂O₃ (100 mL) and saturated aqueous NaCl (100 mL). The aqueous layer was then dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was distilled from basic alumina (500 mg) to afford 1.26 g of **5.111** as a colorless oil (45% yield). Spectroscopic data for **5.111** were identical to that previously reported.¹³⁶



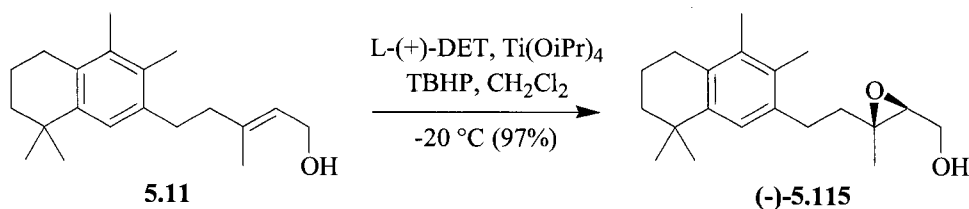
Ethyl (E)-3-Iodobut-2-enoate (5.112). Iodoalkene **5.111** (1.26 g, 5.27 mmol) was heated at 220 °C under argon in a sealed tube for 4 h. After cooling to room temperature, the brown oil was purified by silica gel column chromatography (20% then 40% CH₂Cl₂/hexanes) to afford 298 mg of unreacted **5.111** and 565 mg of **5.112** as a colorless oil (45% yield; 59% yield brsm). Spectroscopic data for **5.112** were identical to that previously reported.^{137a}



(*E*)-*t*-Butyldimethyl-[3-methyl-5-(3,4,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-pent-2-enyloxy]-silane (5.113**).** To 9-BBN (1.62 mL of a 0.5 M solution in THF, 0.81 mmol) was added dropwise a solution of **5.107** (58 mg, 0.27 mmol) in THF (500 μ L) over 2 minutes, and the mixture was heated under reflux for 1 h. In a separate flask, a solution of **5.109** (65 mg, 0.27 mmol) in DMF (500 μ L) was added to a stirred mixture of Cs₂CO₃ (177 mg, 0.54 mmol), PdCl₂(dppf)·CH₂Cl₂ (22 mg, 10 mol %), Ph₃As (8 mg, 10 mol %), DMF (1 mL) and H₂O (180 μ L, 36 equiv mol). The resulting mixture was stirred for 5 minutes. After addition of the above THF solution, the reaction mixture was heated at 80 °C for 2 h. After cooling down to room temperature, it was poured into H₂O (2 mL) and extracted with Et₂O (3 x 5 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% $\rightarrow$ 60% benzene/hexanes) to afford 67 mg of **5.113** as a colorless oil (62% yield): IR (neat) ν_{max} 2926, 2857, 1470, 1382, 1257, 1170 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.01 (s, 1 H), 5.37 (td, 6.3, 1.2 Hz, 1 H), 4.21 (d, J = 6.3 Hz, 2 H), 2.72-2.67 (m, 2 H), 2.86 (t, J = 6.4 Hz, 2 H), 2.22-2.18 (m, 5 H), 2.13 (s, 3 H), 1.84-1.77 (m, 2 H), 1.69 (s, 3 H), 1.61-1.58 (m, 2 H), 1.26 (s, 6 H), 0.90 (s, 9 H), 0.07 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 143.12 (C), 137.52 (C), 137.01 (C), 134.87 (C), 132.41 (C), 131.38 (C), 124.94 (CH), 124.45 (CH), 60.39 (CH₂), 40.94 (CH₂), 38.73 (CH₂), 33.78 (C), 33.22 (CH₂), 32.03 (CH₃), 28.49 (CH₂), 26.02 (CH₃), 19.74 (CH₂), 18.49 (C), 16.60 (CH₃), 15.70 (CH₃), 15.48 (CH₃), -5.02 (CH₃); HRMS m/z calculated for C₂₆H₄₄OSi 400.3161 (M⁺), found 400.3174.

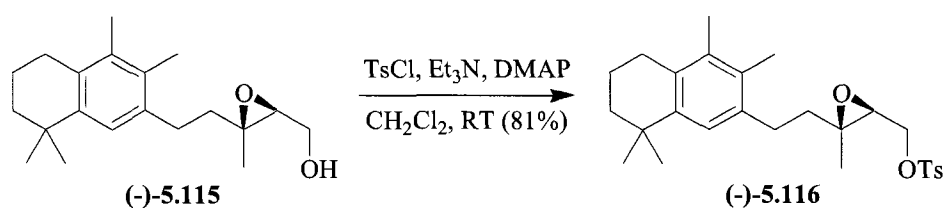


Ethyl (E)-3-methyl-5-(3,4,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-pent-2-enoate (5.114). To 9-BBN (2.12 mL of a 0.5 M solution in THF, 1.06 mmol) was added dropwise a solution of **5.107** (75.6 mg, 0.35 mmol) in THF (750 μ L) over 2 minutes, and the mixture was heated under reflux for 1 h. In a separate flask, a solution of **5.112** (85 mg, 0.35 mmol) in DMF (500 μ L) was added to a stirred mixture of Cs₂CO₃ (230 mg, 0.71 mmol), PdCl₂(dppf)·CH₂Cl₂ (29 mg, 10 mol %), Ph₃As (11 mg, 10 mol %), DMF (1 mL) and H₂O (230 μ L, 36 equiv mol). The resulting mixture was stirred for 5 minutes. After addition of the above THF solution, the reaction mixture was heated at 80 °C for 2 h. After cooling down to room temperature, it was poured into H₂O (3 mL) and extracted with Et₂O (3 x 5 mL). Combined organics were washed with saturated aqueous NaCl and dried over anhydrous MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% → 50% benzene/hexanes) to afford 86 mg of **5.114** as a white solid (74% yield): mp 73-76 °C; IR (neat) ν_{max} 2929, 2867, 1716, 1650, 1463, 1382, 1222, 1143 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.98 (s, 1 H), 5.72 (d, *J* = 1.0 Hz, 1 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 2.73-2.77 (m, 2 H), 2.61 (t, *J* = 6.5 Hz, 2 H), 2.31-2.35 (m, 2 H), 2.22 (d, *J* = 1.0 Hz, 3 H), 2.19 (s, 3 H), 2.13 (s, 3 H), 1.77-1.83 (m, 2 H), 1.53-1.60 (m, 2 H), 1.24-1.30 (m, 9 H); ¹³C NMR (100 MHz, CDCl₃) δ 166.86 (C), 159.56 (C), 143.31 (C), 136.45 (C), 135.09 (C), 132.81 (C), 131.26 (C), 124.97 (CH), 115.71 (CH), 59.52 (CH₂), 42.27 (CH₂), 38.67 (CH₂), 33.77 (C), 32.80 (CH₂), 31.99 (CH₃), 31.99 (CH₃), 28.49 (CH₂), 19.70 (CH₂), 19.05 (CH₃), 15.71 (CH₃), 15.48 (CH₃), 14.36 (CH₃); HRMS *m/z* calculated for C₂₂H₃₂O₂ 328.2402 (M⁺), found 328.2407.



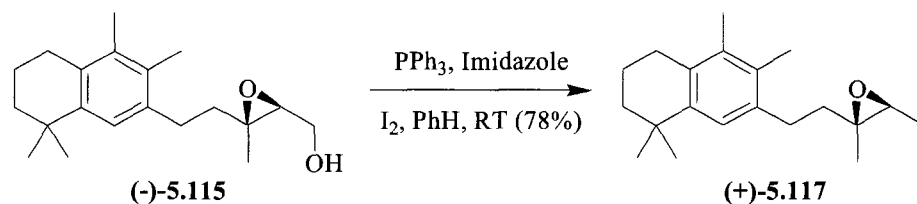
(-)-{3-Methyl-3-[2-(3,4,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-ethyl]-oxiranyl}-methanol (5.115). A suspension of activated 4Å molecular sieves (50 mg) and CH₂Cl₂ (3 mL) was cooled to -10 °C. L-(+)-DET (23 mg, 0.11 mmol, in 1 mL of CH₂Cl₂), Ti(Oi-Pr)₄ (21 mg, 0.07 mmol, in 1 mL of CH₂Cl₂), and TBHP (250 μ L, 1.38 mmol, 5.5 M in decane) were

added sequentially. After 10 min of stirring, the mixture was cooled to $-20\text{ }^{\circ}\text{C}$, and a solution of **5.11** (265 mg, 0.93 mmol) in CH_2Cl_2 (4.5 mL) was added dropwise via cannula. After 3 h of stirring at $-20\text{ }^{\circ}\text{C}$, the mixture was warmed to $0\text{ }^{\circ}\text{C}$. It was stirred at that temperature for 5 minutes, and was then quenched by adding sequentially 2 mL of H_2O and 1 mL of 30% aqueous NaOH saturated with solid NaCl. After 10 minutes of vigorous stirring, the resulting mixture was partitioned between CH_2Cl_2 and H_2O . The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 x 10 mL). Combined organics were dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (25% EtOAc/hexanes) to afford 271 mg of **5.115** as a pale yellow oil (97% yield): $[\alpha]_D^{22} = -5$ (c 0.035, CHCl_3); IR (neat) ν_{max} 3438 (br), 2925, 1472, 1384 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.99 (s, 1 H), 3.81-3.77 (m, 1 H), 3.70-3.65 (m, 1 H), 2.95 (dd, $J = 6.6, 4.4$ Hz, 1 H), 2.76-2.64 (m, 2 H), 2.61 (t, $J = 6.5$ Hz, 2 H), 2.17 (s, 3 H), 2.12 (s, 3 H), 1.88-1.84 (m, 1 H), 1.83-1.78 (m, 2 H), 1.75-1.69 (m, 1 H), 1.60-1.58 (m, 3 H), 1.38 (s, 3 H), 1.26 (s, 6 H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.11 (C), 136.32 (C), 134.99 (C), 132.60 (C), 131.20 (C), 124.76 (CH), 62.57 (CH), 61.22 (CH_2), 61.04 (C), 39.41 (CH_2), 38.51 (CH_2), 33.62 (C), 31.87 (CH_3), 31.86 (CH_3), 29.56 (CH_2), 28.31 (CH_2), 19.53 (CH_2), 16.75 (CH_3), 15.55 (CH_3), 15.33 (CH_3); HRMS m/z calculated for $\text{C}_{20}\text{H}_{30}\text{O}_2$ 302.2246 (M^+), found 302.2238; retention time: 16.82 minutes (minor enantiomer, 4.7%), 20.20 minutes (major enantiomer, 95.3%).



(-)-3-methyl-3-[2-(3,4,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-ethyl]-oxiranylmethyl 4-toluenesulfonate (5.116). To a solution of tosyl chloride (10 mg, 0.052 mmol) and DMAP (1 mg, 0.008 mmol) in CH_2Cl_2 (500 μL) at room temperature was added a solution of **5.115** (14 mg, 0.046 mmol) in CH_2Cl_2 (500 μL) via cannula. Et_3N (15 μL , 0.108 mmol) was then added and the mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (1 mL). The aqueous layer was separated from the

organic layer and extracted with CH_2Cl_2 (3 x 5 mL). Combined organics were washed with saturated aqueous NaHCO_3 and saturated aqueous NaCl , and dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford 17 mg of **5.116** as a pale yellow oil (81% yield): $[\alpha]_D^{22} = -25$ (c 0.016, CH_2Cl_2); IR (neat) ν_{max} 2930, 2867, 1598, 1455, 1361, 1178, cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.80 (d, $J = 8.1$ Hz, 2 H), 7.35 (d, $J = 8.1$ Hz, 2 H), 6.95 (s, 1 H), 4.15 (dd, $J_{\text{AB}} = 11.1$ Hz, $J_{\text{AX}} = 5.1$ Hz, 1 H), 4.07 (dd, $J_{\text{AB}} = 11.1$ Hz, $J_{\text{BX}} = 6.1$ Hz, 1 H), 2.99 (t, $J = 5.6$ Hz, 1 H), 2.67–2.59 (m, 4 H), 2.44 (s, 3 H), 2.14 (s, 3 H), 2.12 (s, 3 H), 1.82–1.66 (m, 4 H), 1.59–1.57 (m, 2 H), 1.28 (s, 3 H), 1.25 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 144.96 (C), 143.17 (C), 136.10 (C), 134.99 (C), 132.66 (C), 132.61 (C), 131.10 (C), 129.80 (CH), 127.85 (CH), 124.67 (CH), 68.47 (CH_2), 60.80 (C), 58.56 (CH), 38.96 (CH_2), 38.49 (CH_2), 33.61 (C), 31.86 (CH_3), 31.85 (CH_3), 29.53 (CH_2), 28.30 (CH_2), 21.54 (CH_3), 19.51 (CH_2), 16.68 (CH_3), 15.54 (CH_3), 15.30 (CH_3); HRMS m/z calculated for $\text{C}_{27}\text{H}_{36}\text{O}_4\text{S}$ 456.2334 (M^+), found 456.2356.



(+)-3-Iodomethyl-2-methyl-2-[2-(3,4,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-ethyl]-oxirane (5.117). To a solution of **5.115** (16.5 mg, 0.055 mmol) in benzene (1 mL) were added imidazole (20 mg, 0.294 mmol), PPh_3 (73 mg, 0.278 mmol) and I_2 (70 mg, 0.276 mmol). After stirring at room temperature for 3 h, the reaction was diluted with Et_2O (10 mL) and saturated aqueous NaHCO_3 (5 mL). To this mixture was added a solution of I_2 in Et_2O until the solution persisted in yellow-brown color. After addition of saturated aqueous Na_2SO_3 (5 mL), the mixture was extracted with Et_2O (3 x 10 mL). Combined organics were then dried over anhydrous MgSO_4 . After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (5% EtOAc hexanes) to afford 16 mg of **5.117** as a pale yellow oil (78% yield): $[\alpha]_D^{22} = +3$ (c 0.023, CHCl_3); IR (neat) ν_{max} 2927, 2865, 1457, 1384, 1174, 1143 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.00 (s, 1 H), 3.36 (dd, $J = 9.9, 6.0$ Hz, 1 H),

3.15 (dd, $J = 8.0, 6.1$ Hz, 1 H), 3.02 (dd, $J = 10.0, 8.4$ Hz, 1 H), 2.70 (t, $J = 8.6$ Hz, 2 H), 2.61 (t, $J = 6.4$ Hz, 2 H), 2.18 (s, 3 H), 2.13 (s, 3 H), 1.88-1.78 (m, 3 H), 1.73-1.66 (m, 1 H), 1.60-1.55 (m, 2 H), 1.37 (s, 3 H), 1.26 (s, 6 H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.16 (C), 136.36 (C), 134.94 (C), 132.58 (C), 131.13 (C), 124.63 (CH), 64.10 (C), 62.42 (CH), 39.40 (CH_2), 38.52 (CH_2), 33.63 (C), 31.87 (CH_3), 31.87 (CH_3), 29.93 (CH_2), 28.32 (CH_2), 19.53 (CH_2), 15.76 (CH_3), 15.55 (CH_3), 15.32 (CH_3), 2.34 (CH_2); HRMS m/z calculated for $\text{C}_{20}\text{H}_{29}\text{IO}$ 412.1263 (M^+), found 412.1237.

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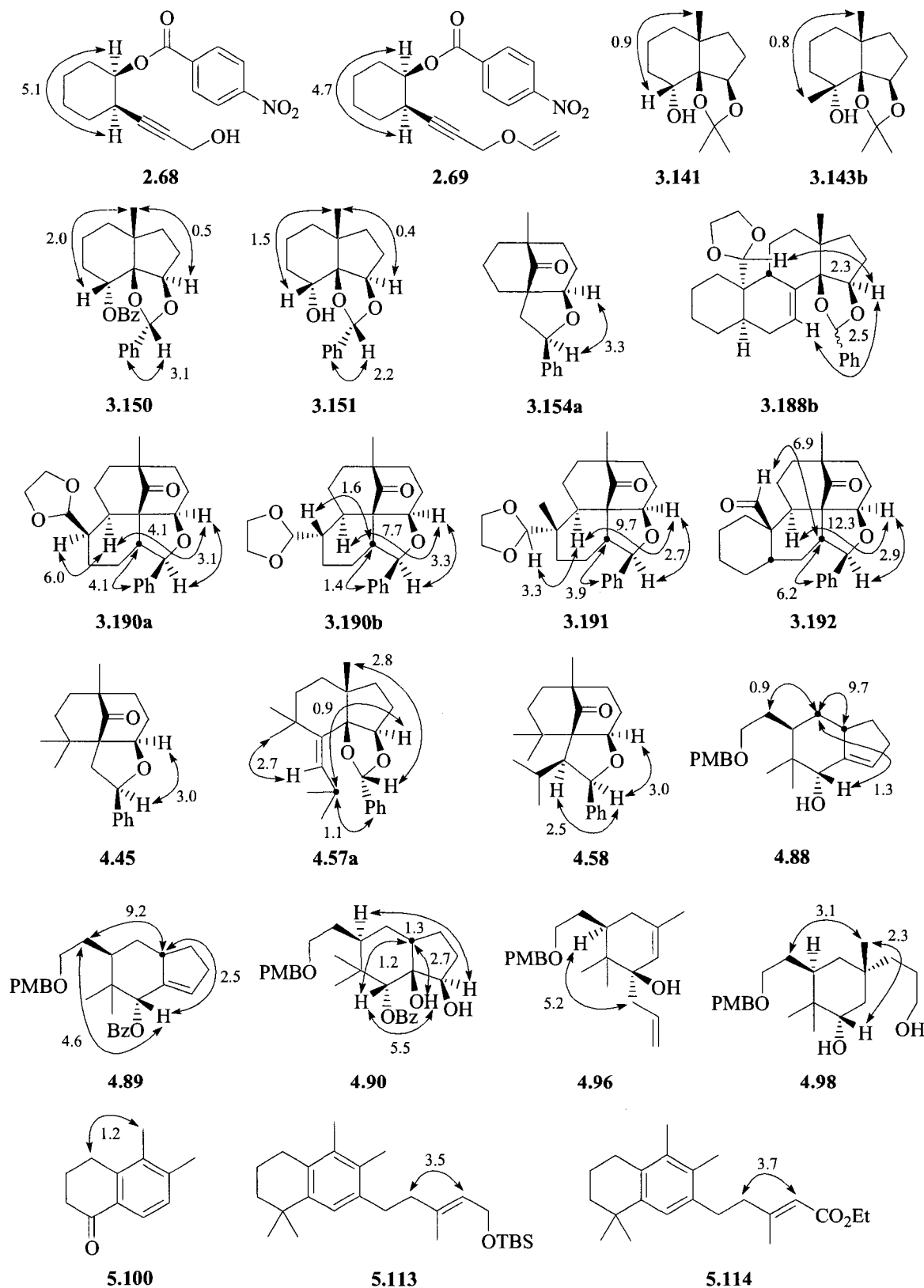
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Annex 1

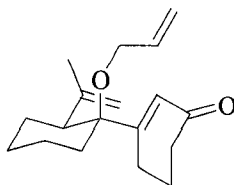
Stereochemical Elucidation via NOESY Experiments

Figure A1.1 - Summarized nOe Interactions (in %) for Selected Compounds



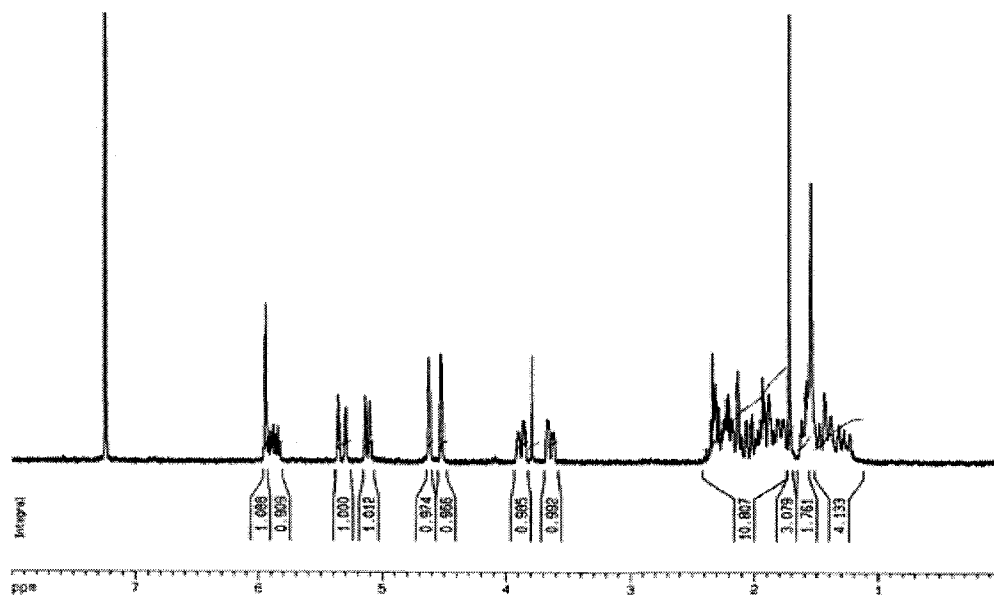
Annex 2

Nuclear Magnetic Resonance Spectra

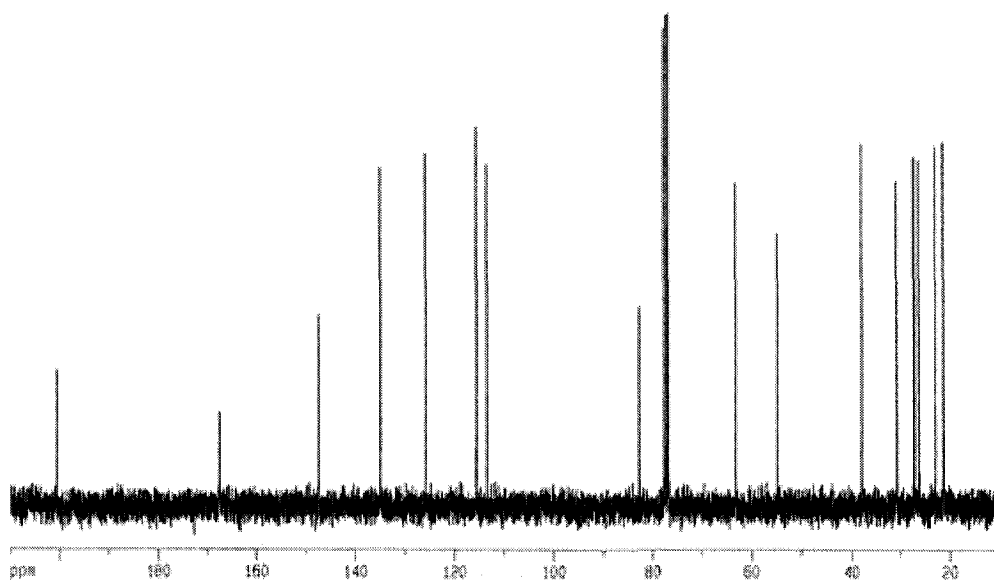


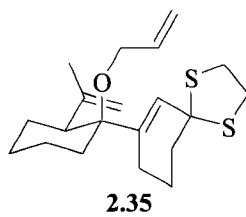
2.25

^1H NMR (CDCl_3 , 300 MHz)

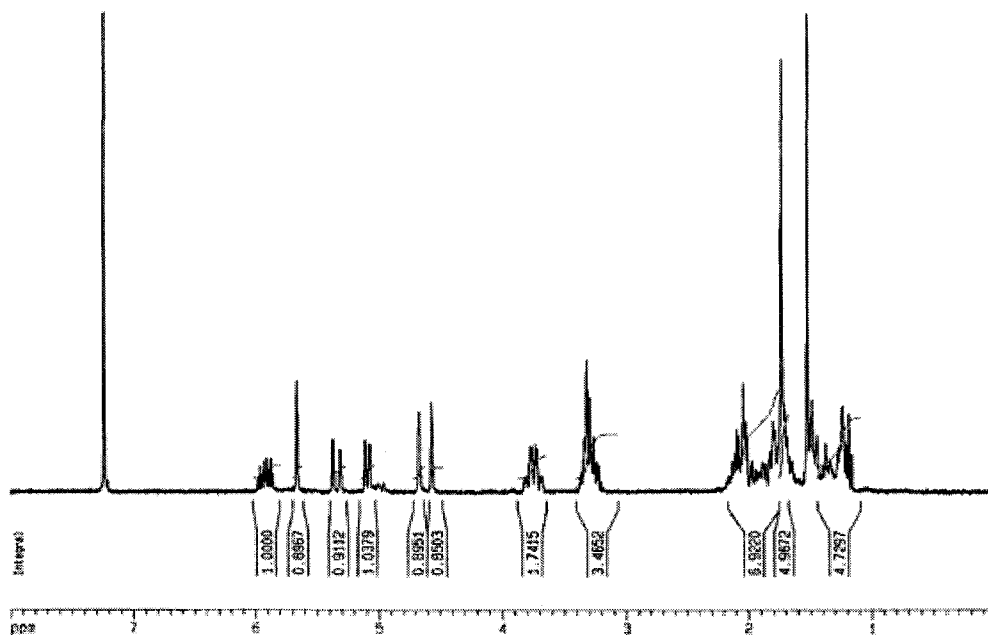


^{13}C NMR (CDCl_3 , 75 MHz)

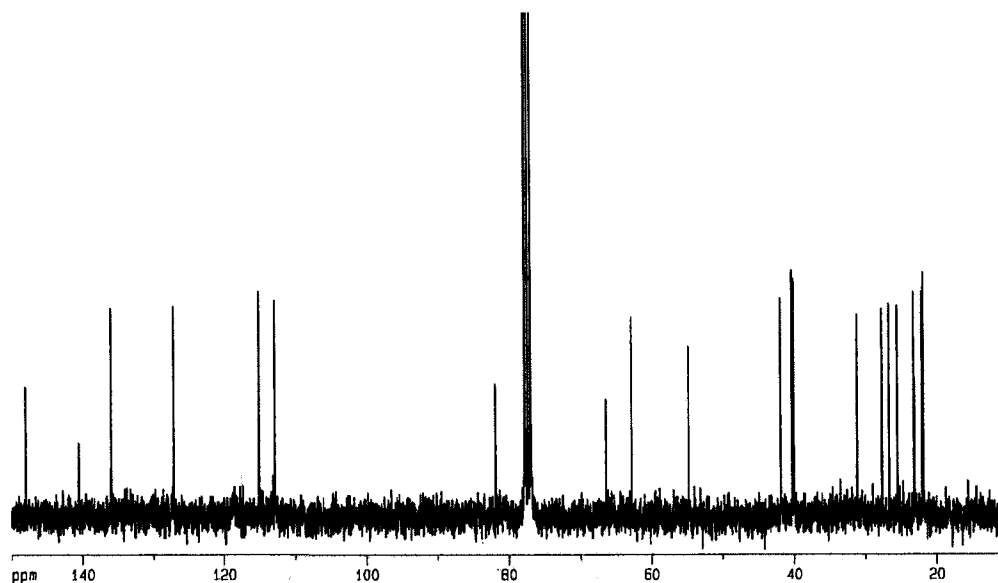


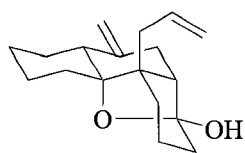


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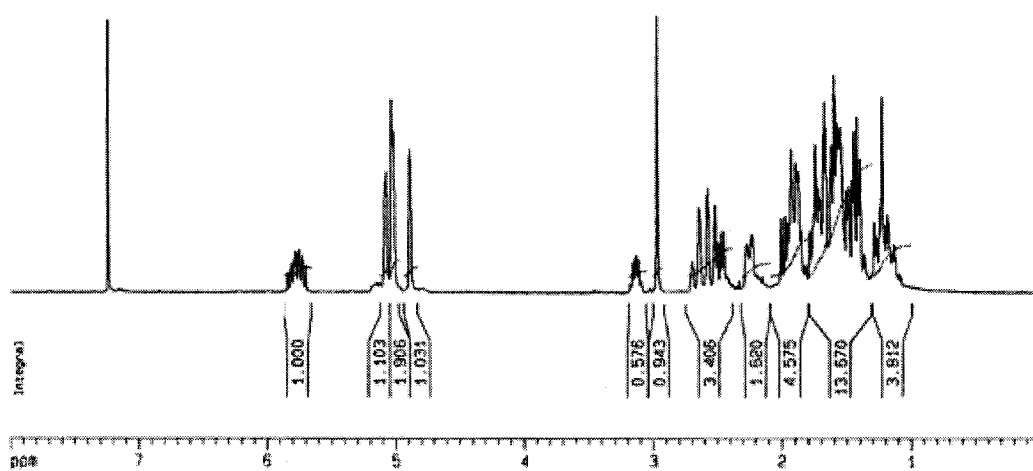
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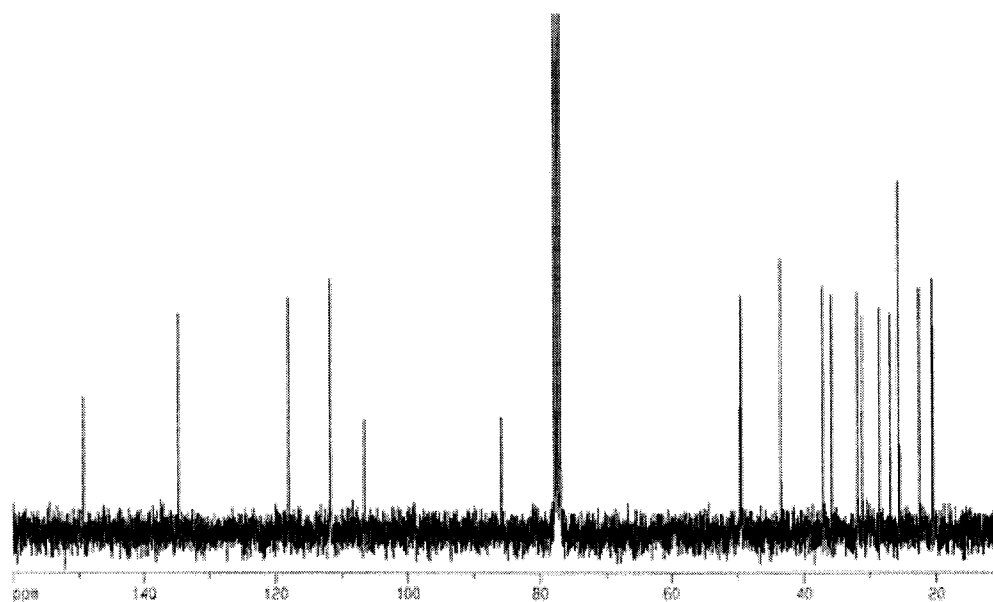


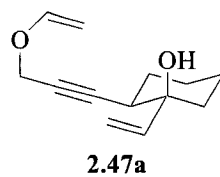
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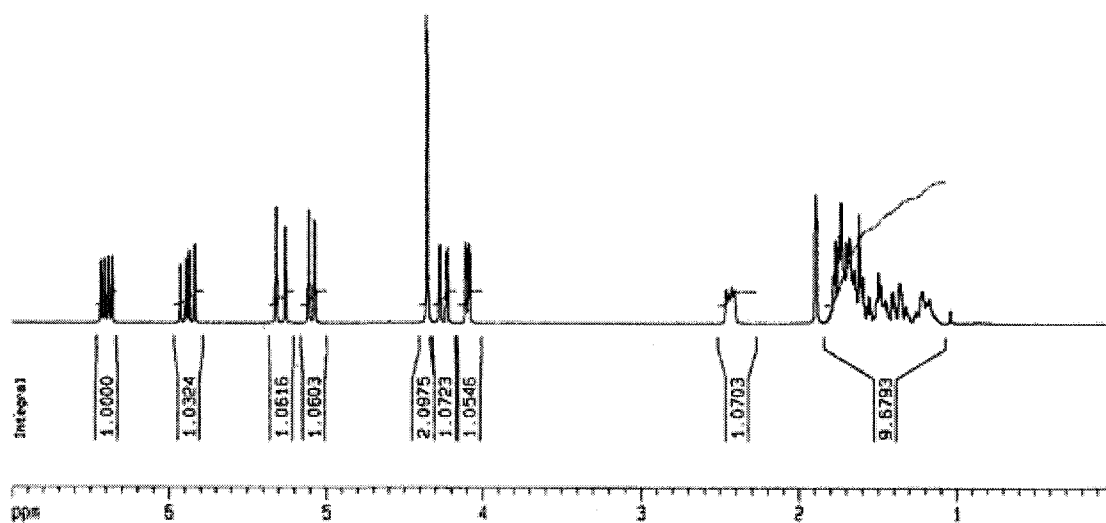


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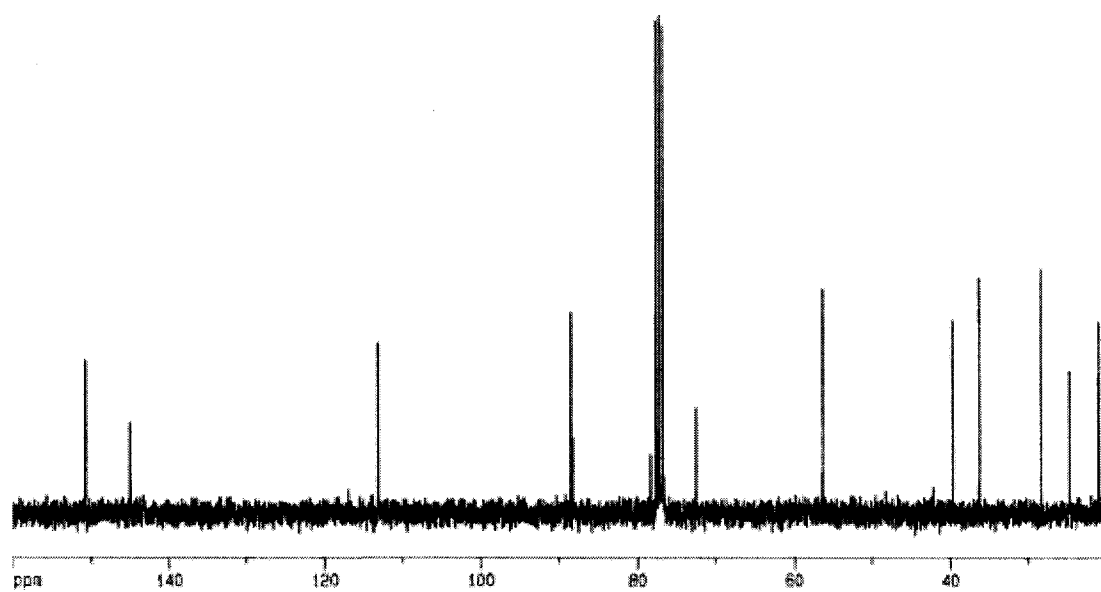


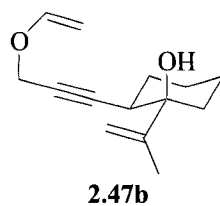


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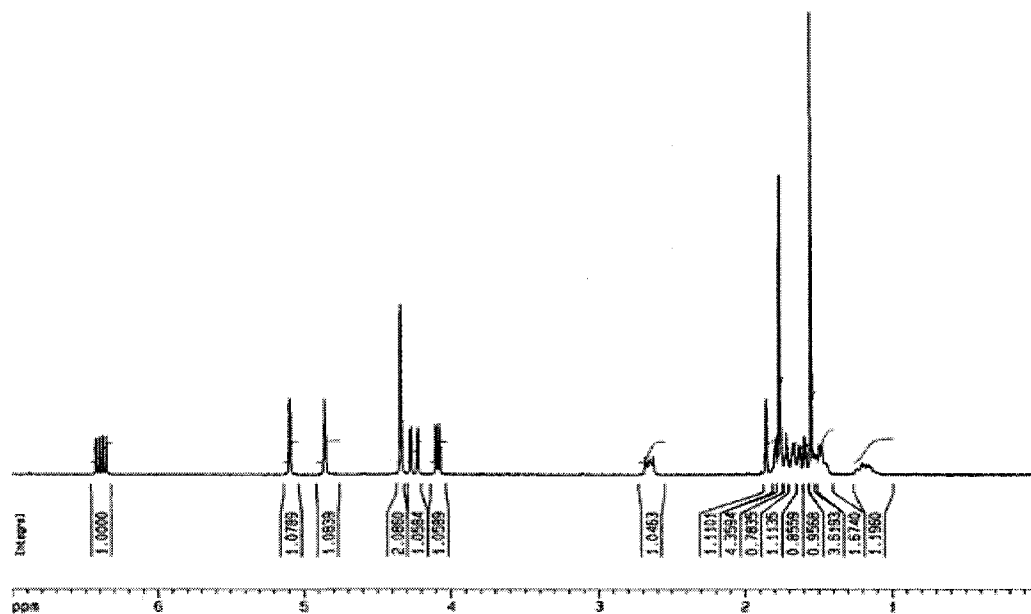


¹³C NMR (CDCl₃, 75 MHz)

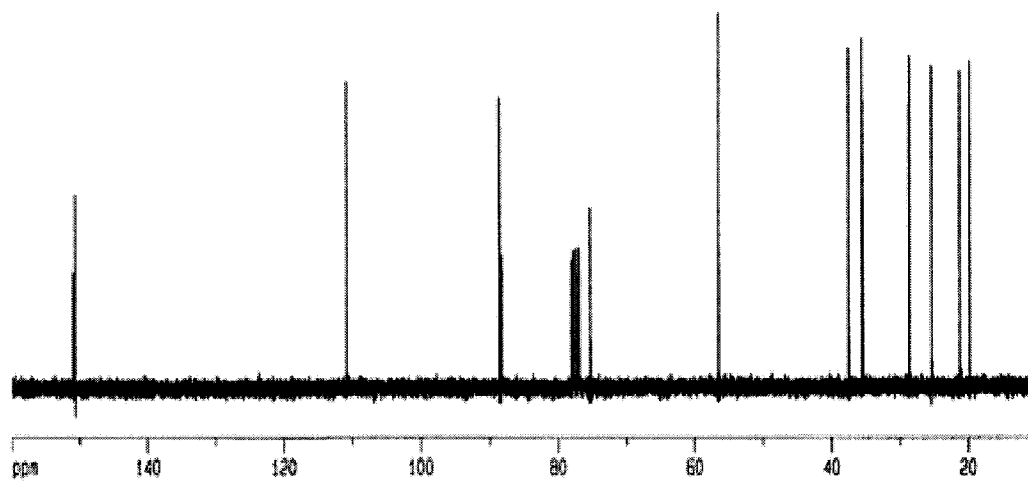


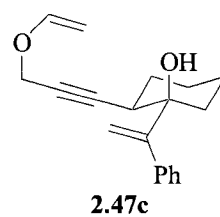


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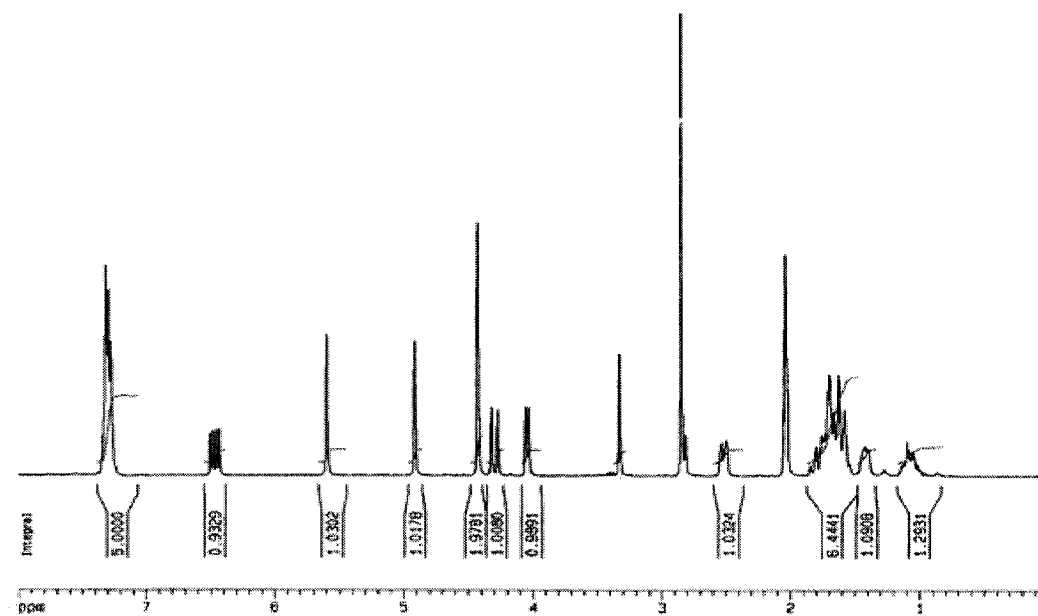


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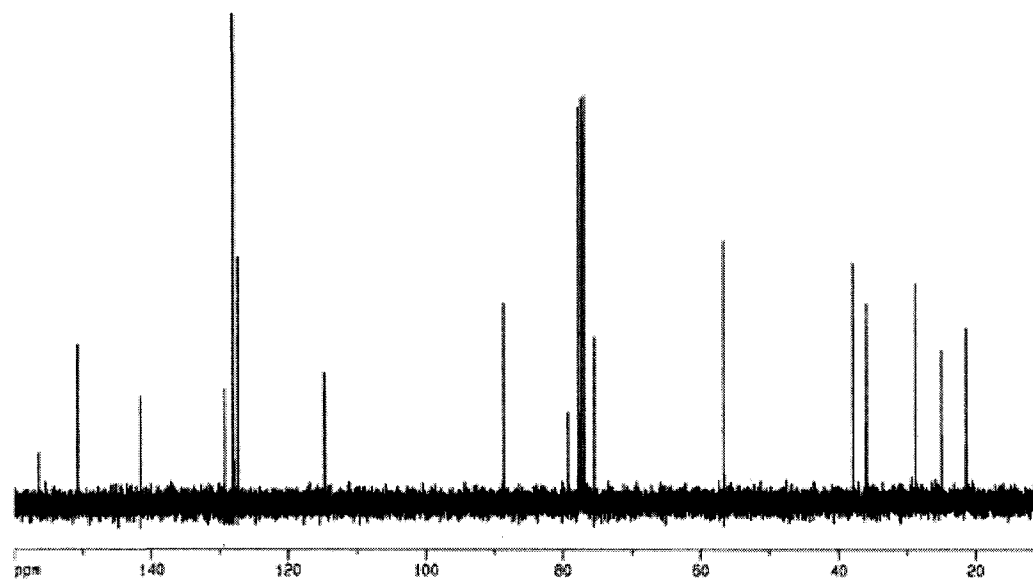


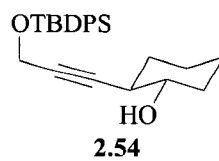


^1H NMR (acetone- d_6 , 300 MHz)

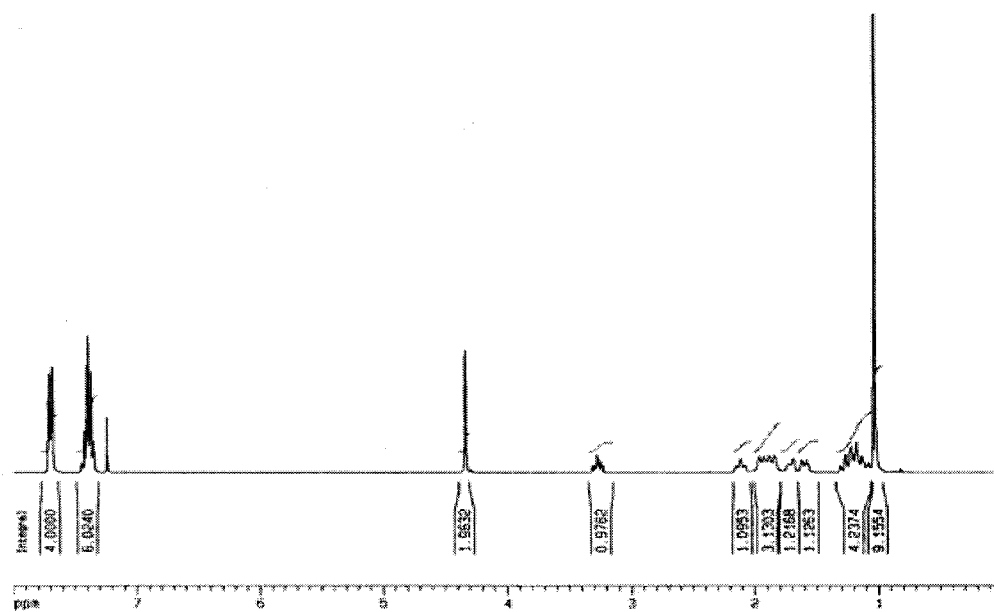


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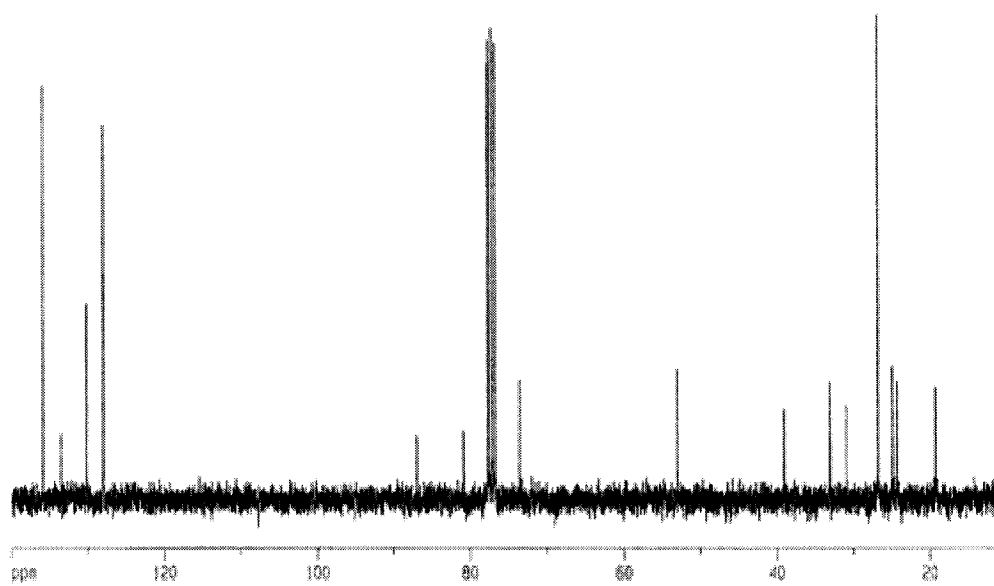


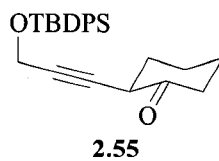


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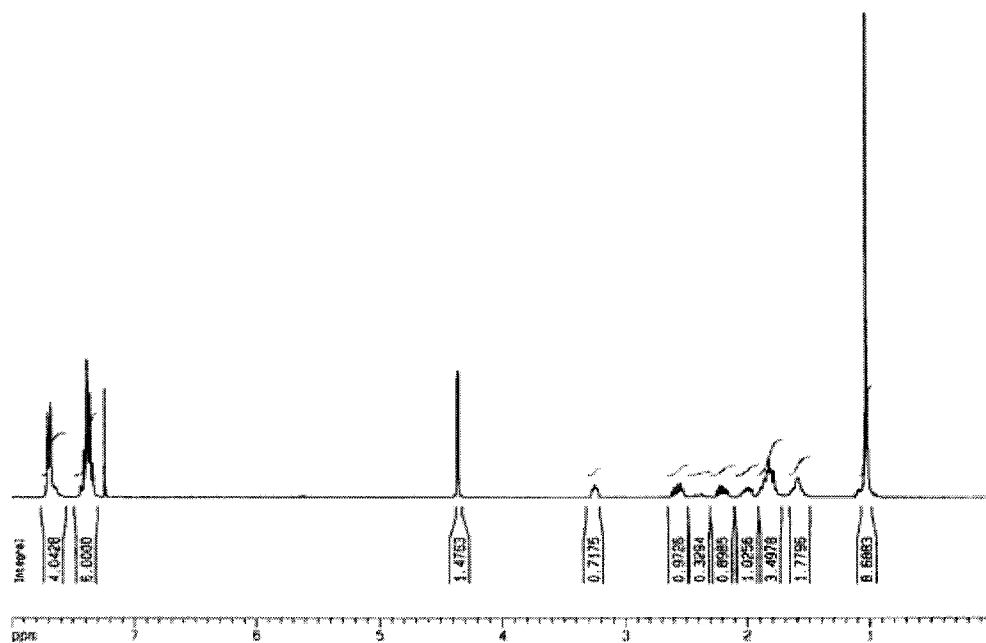


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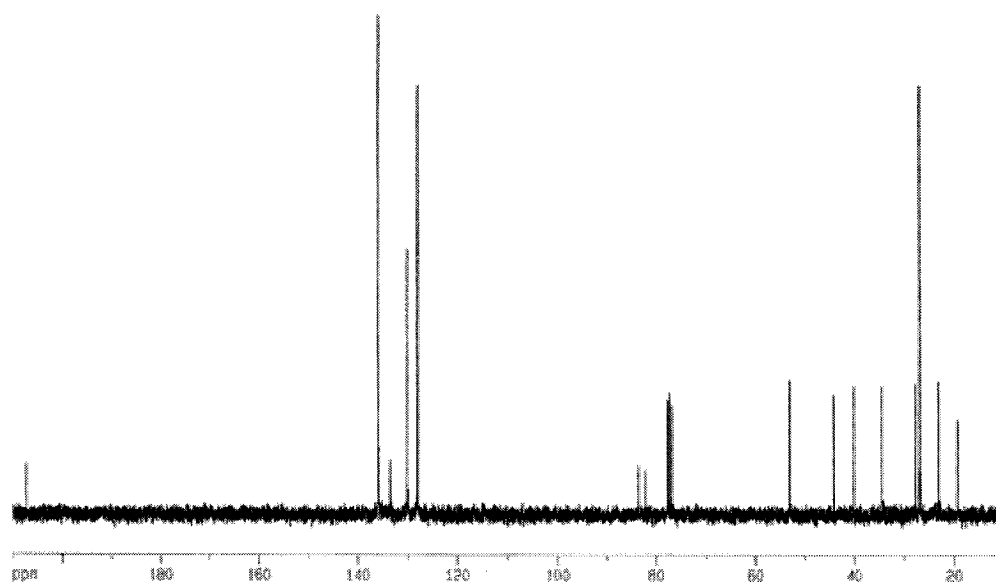


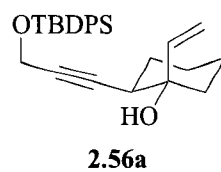


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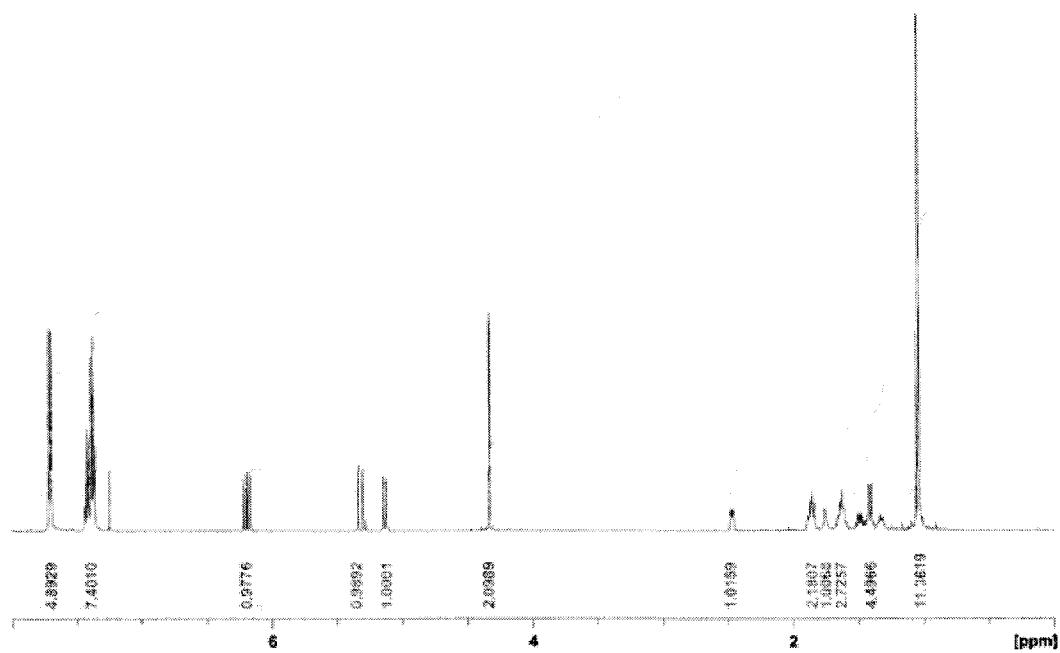


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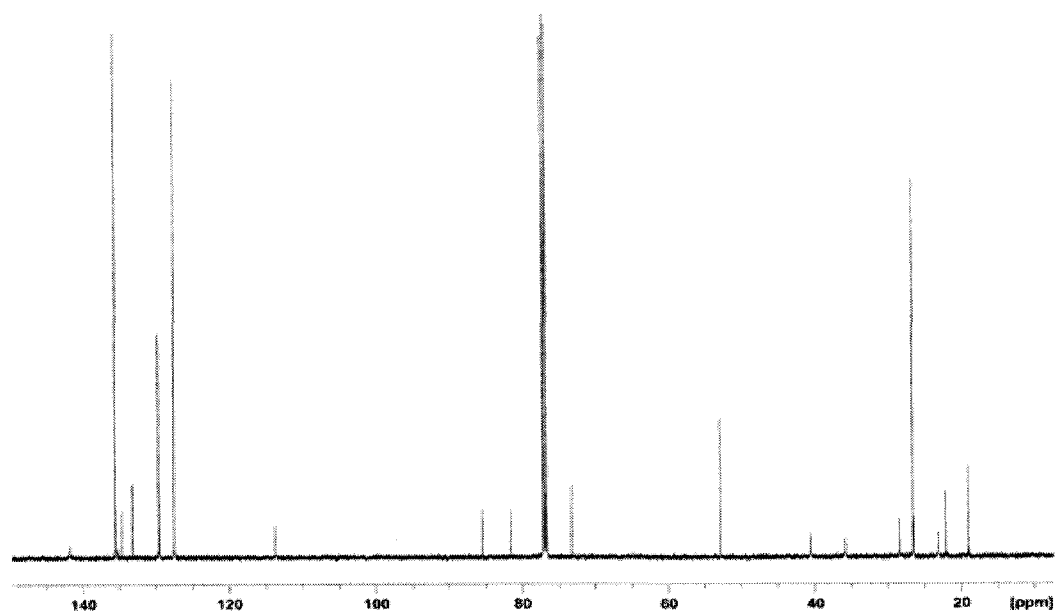


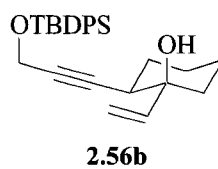


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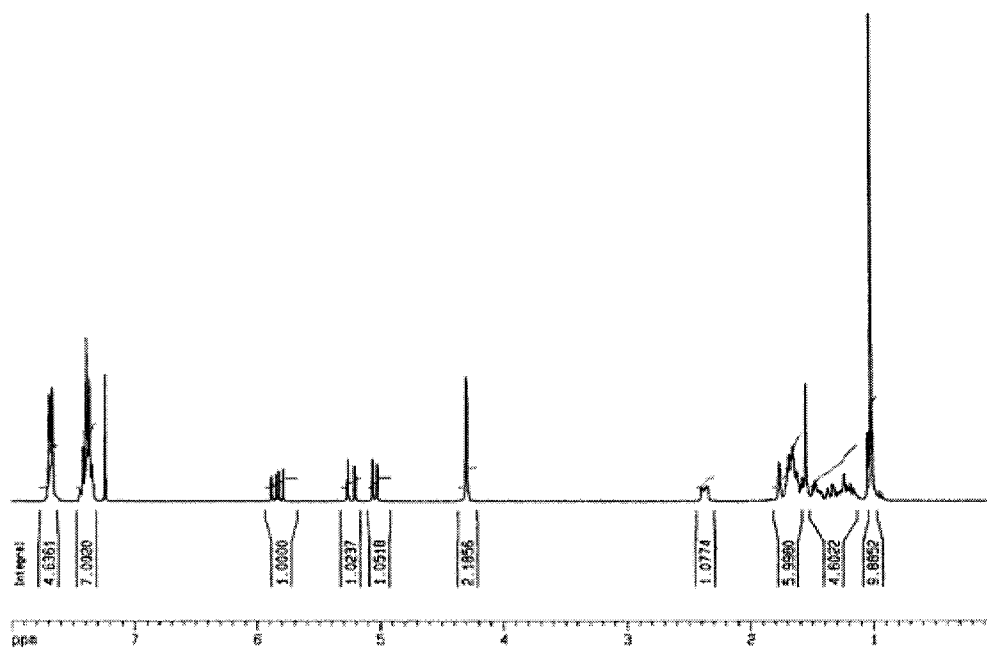


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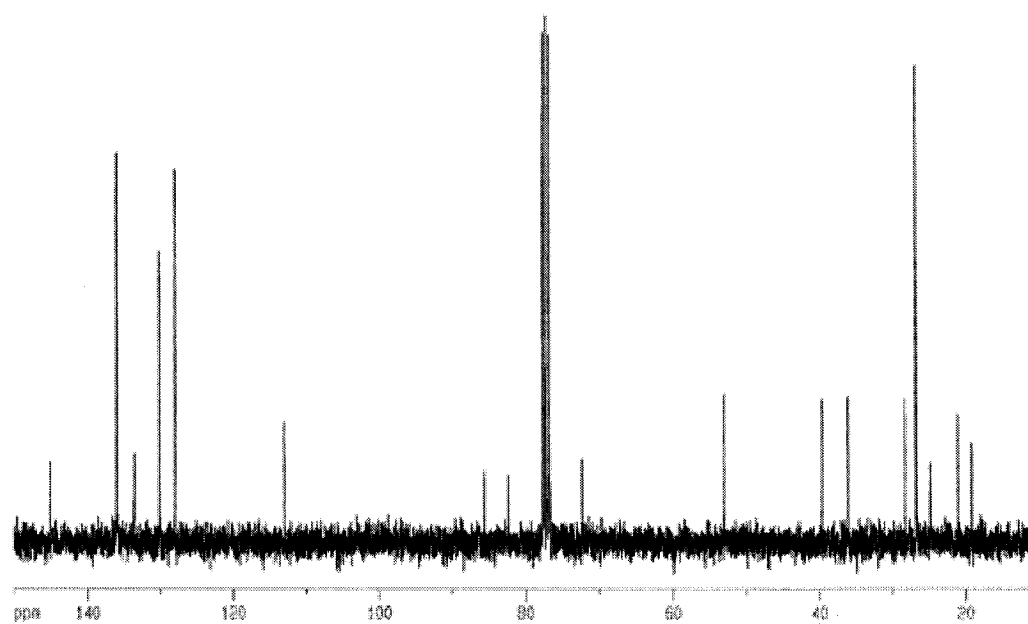


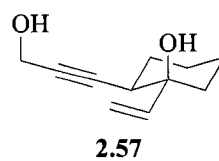


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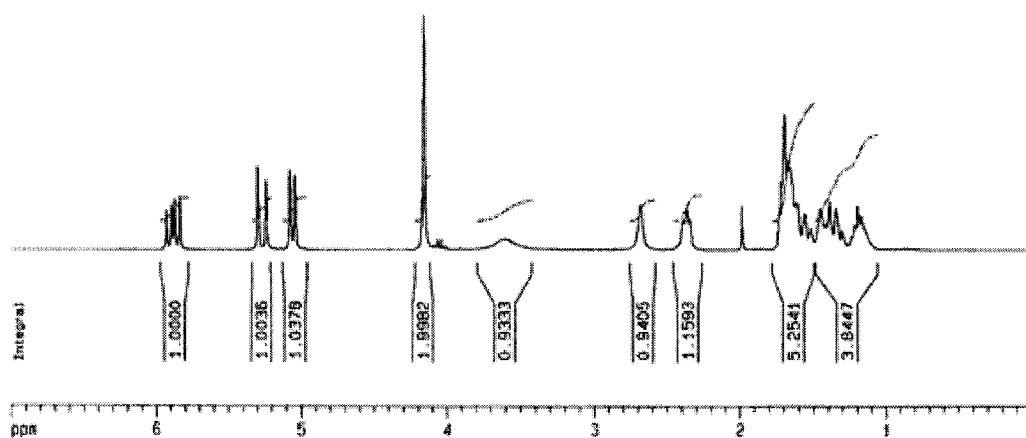


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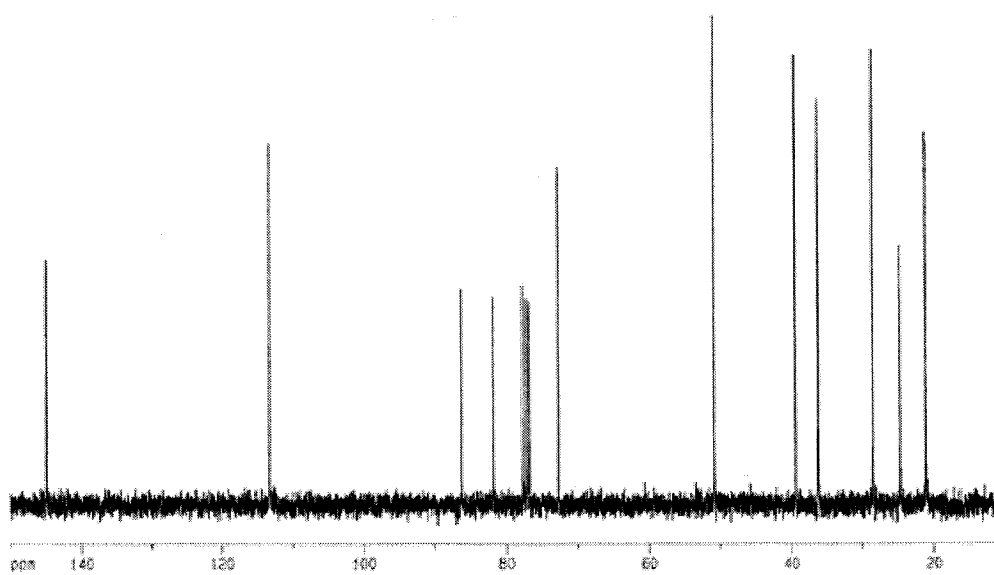


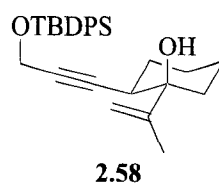


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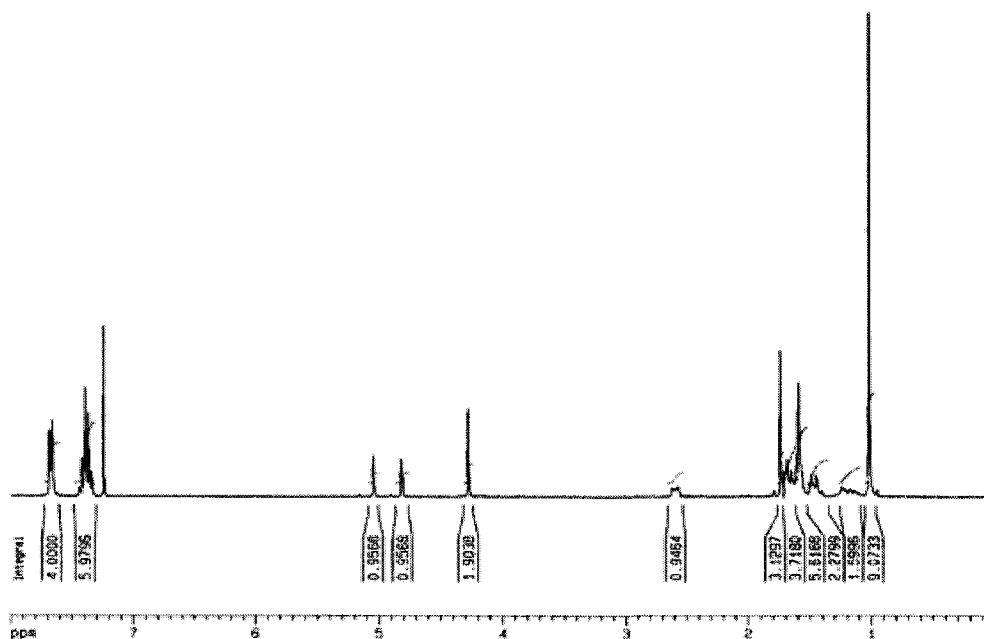


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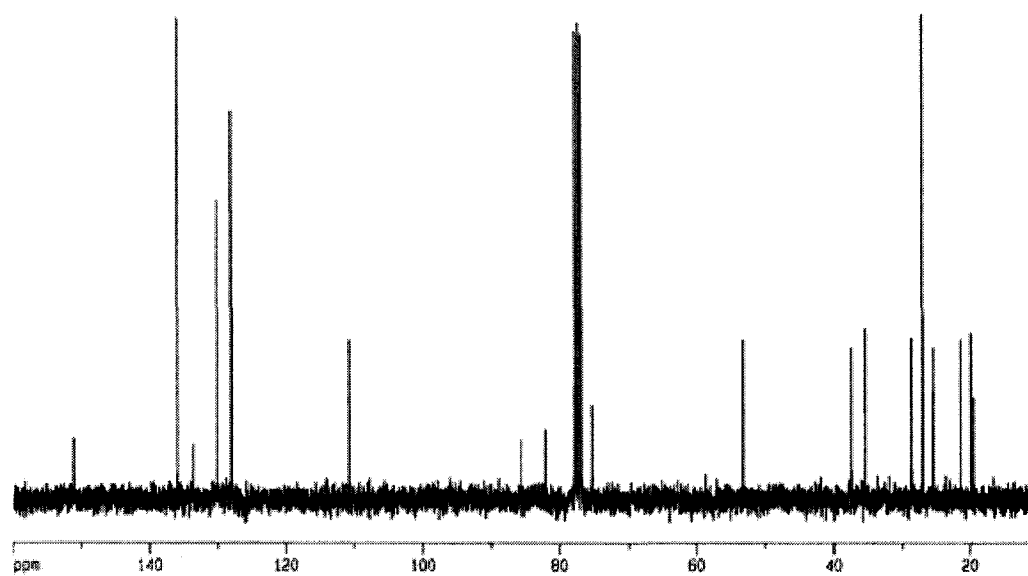


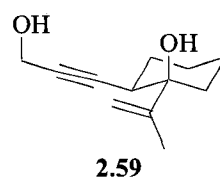


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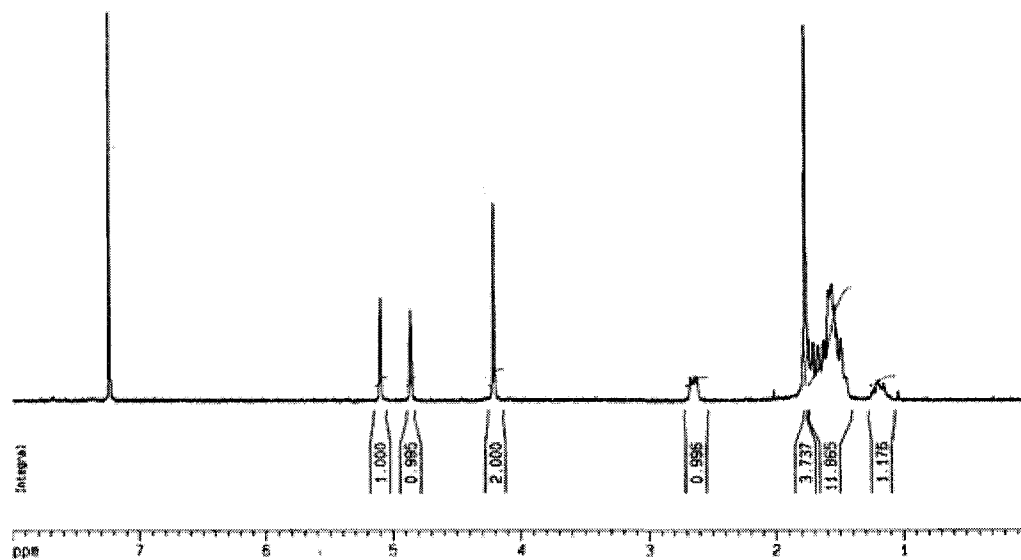


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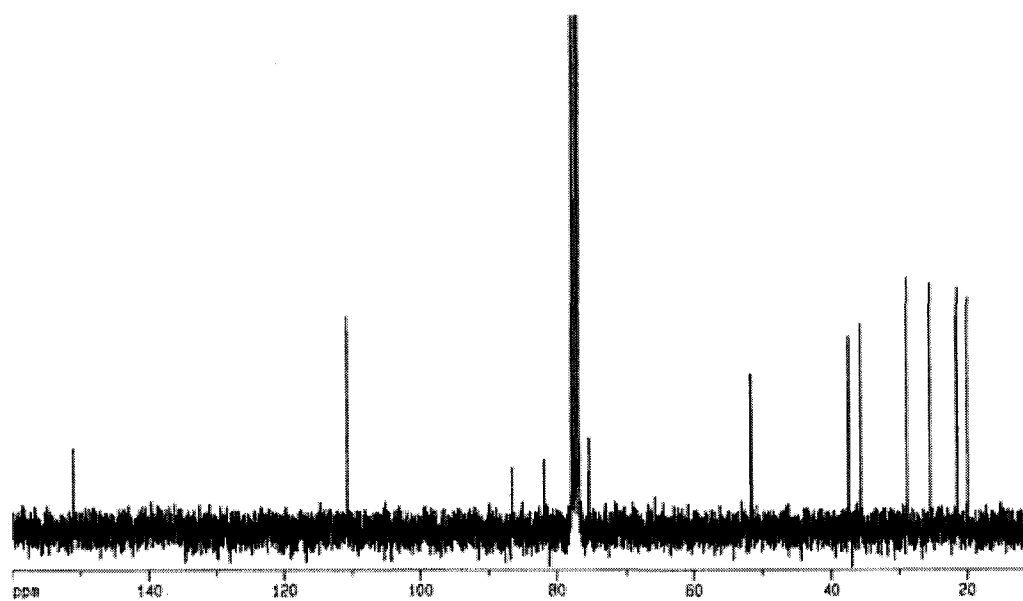


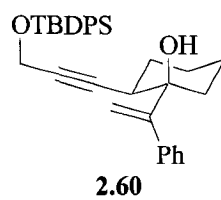


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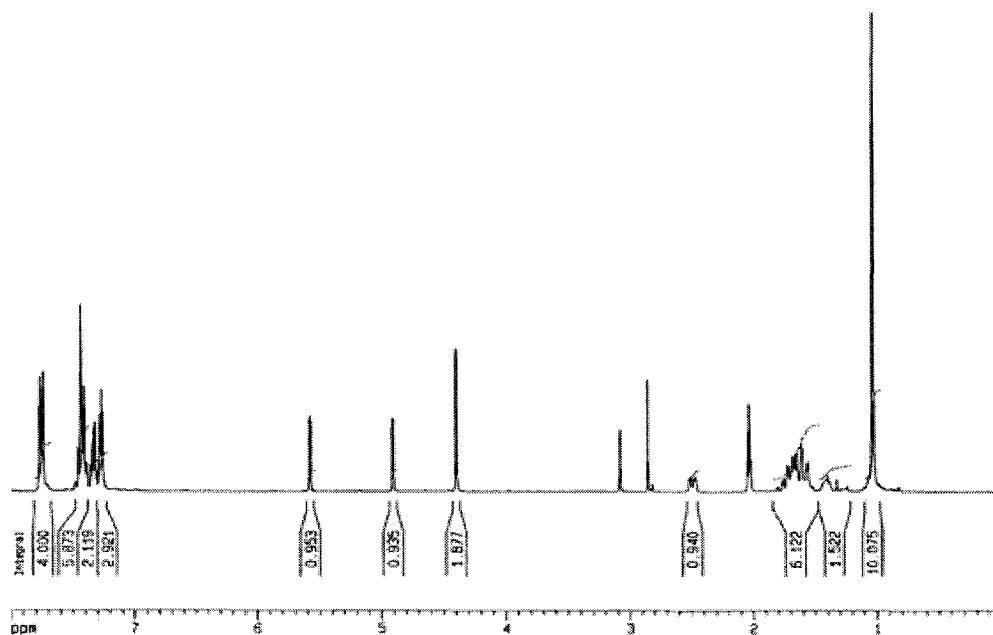


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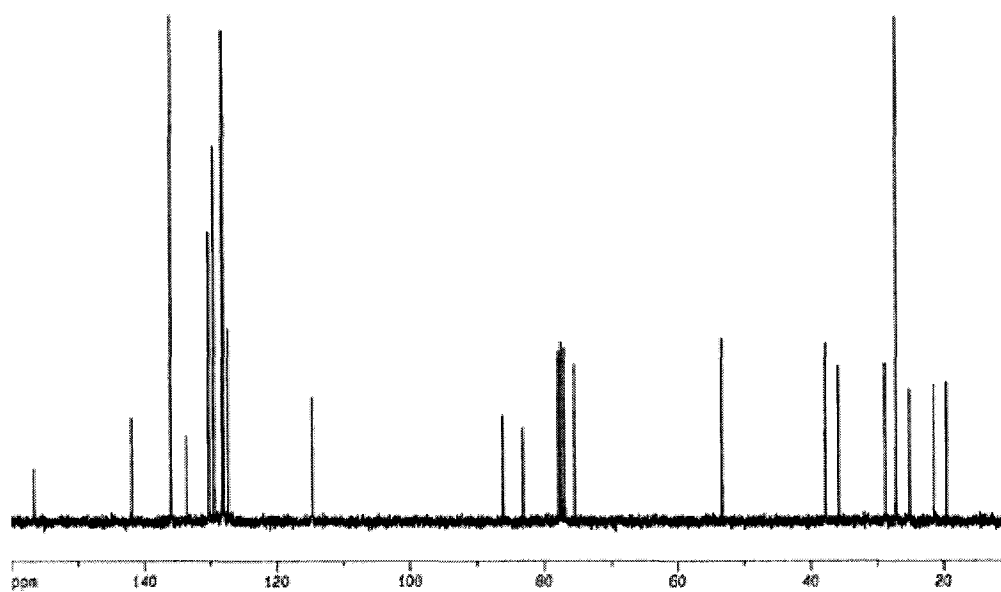


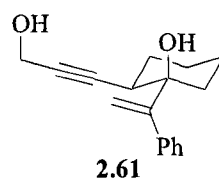


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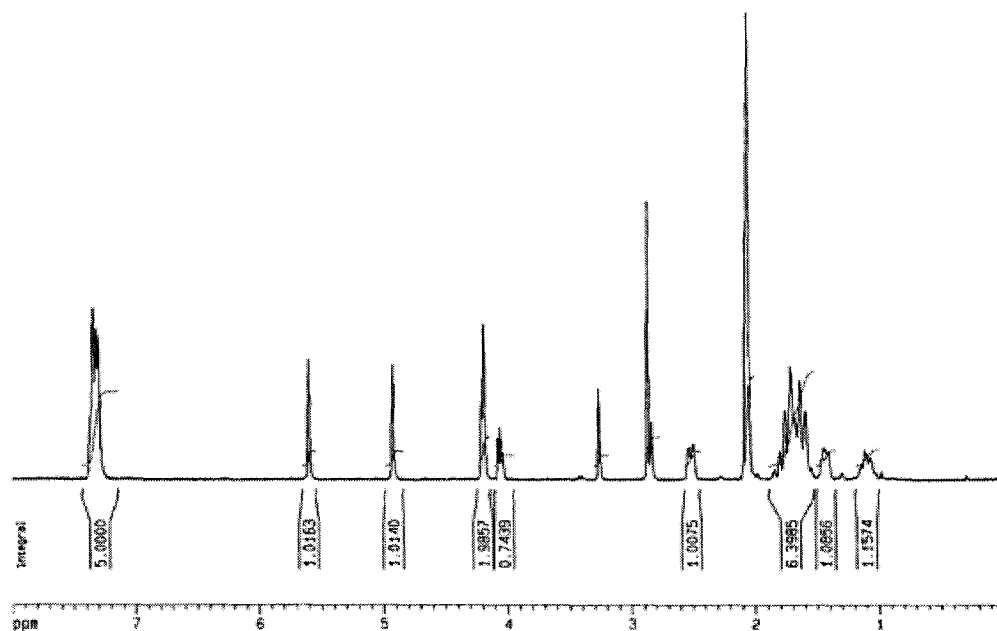


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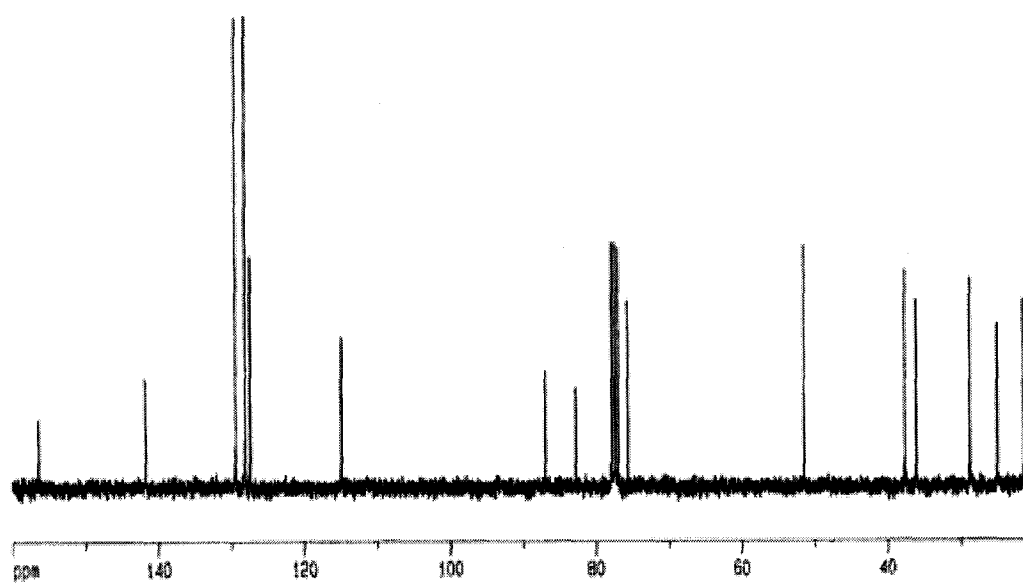


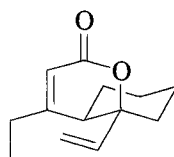


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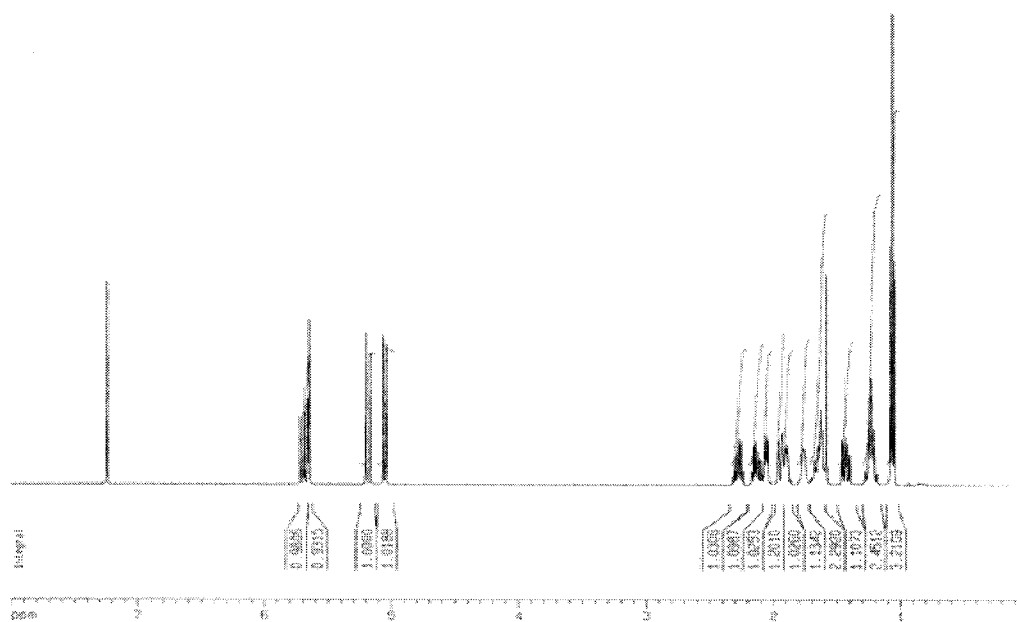


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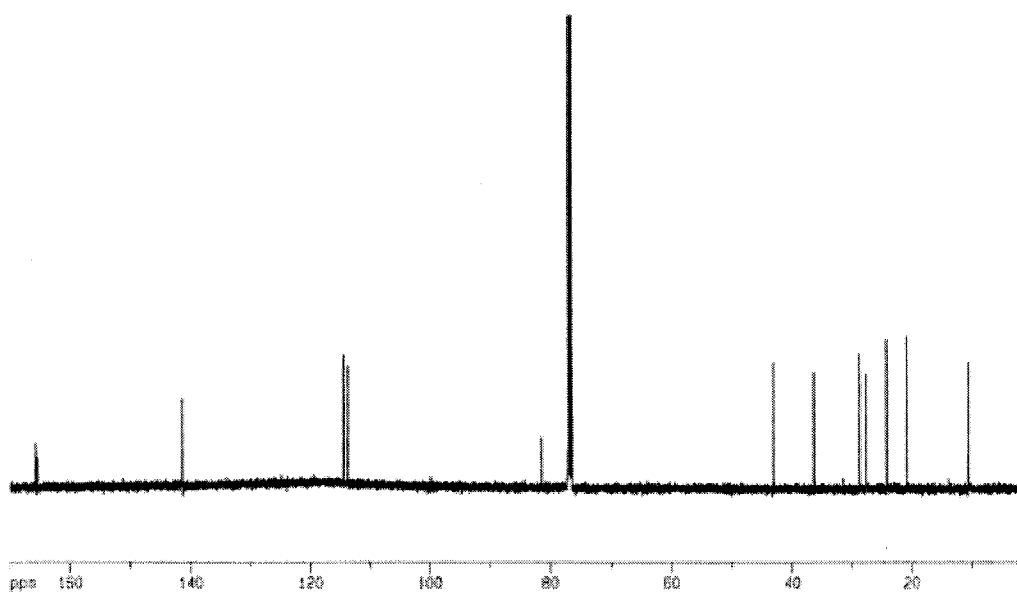


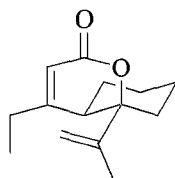
**2.62a**

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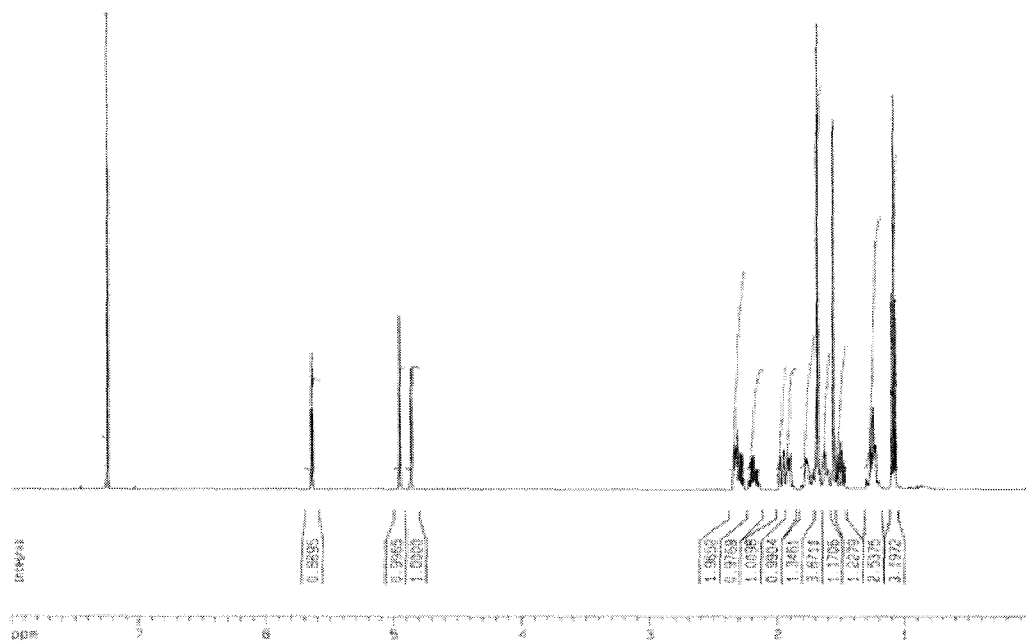
^{13}C NMR (CDCl_3 , 75 MHz)



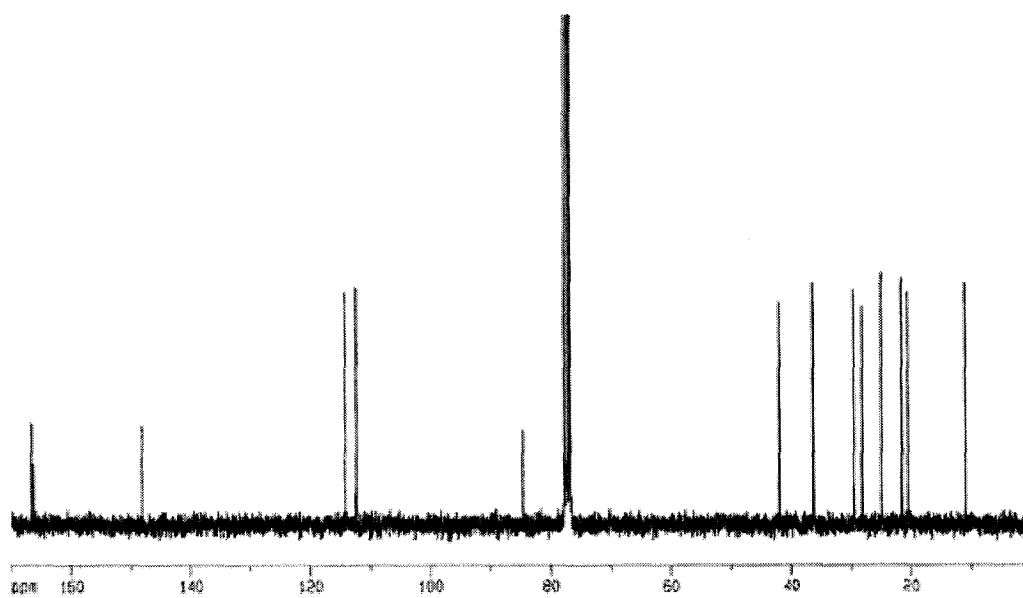


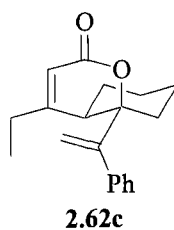
2.62b

^1H NMR (CDCl_3 , 500 MHz)

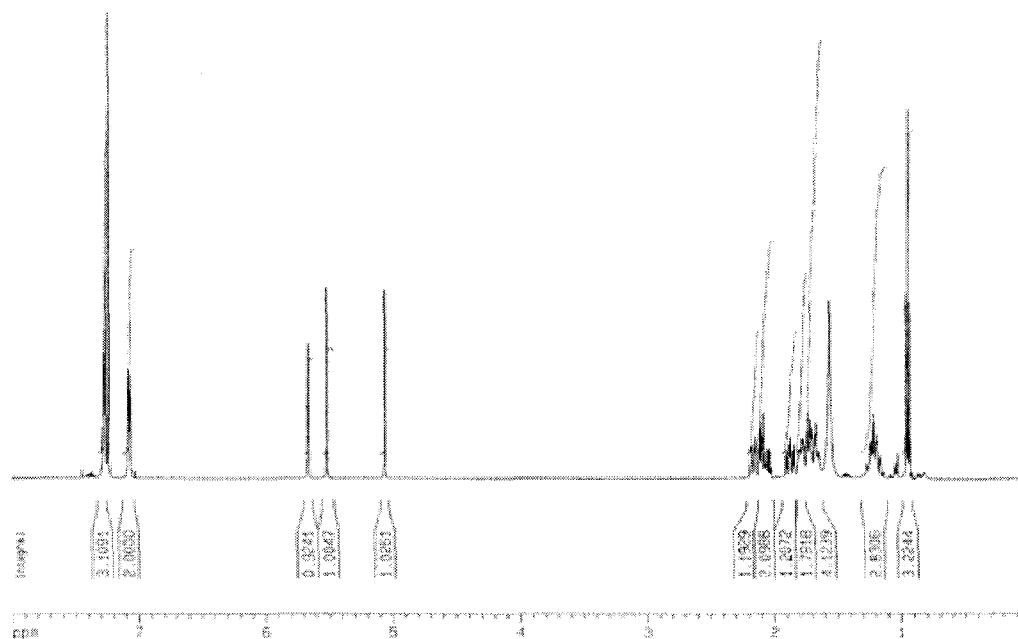


^{13}C NMR (CDCl_3 , 75 MHz)

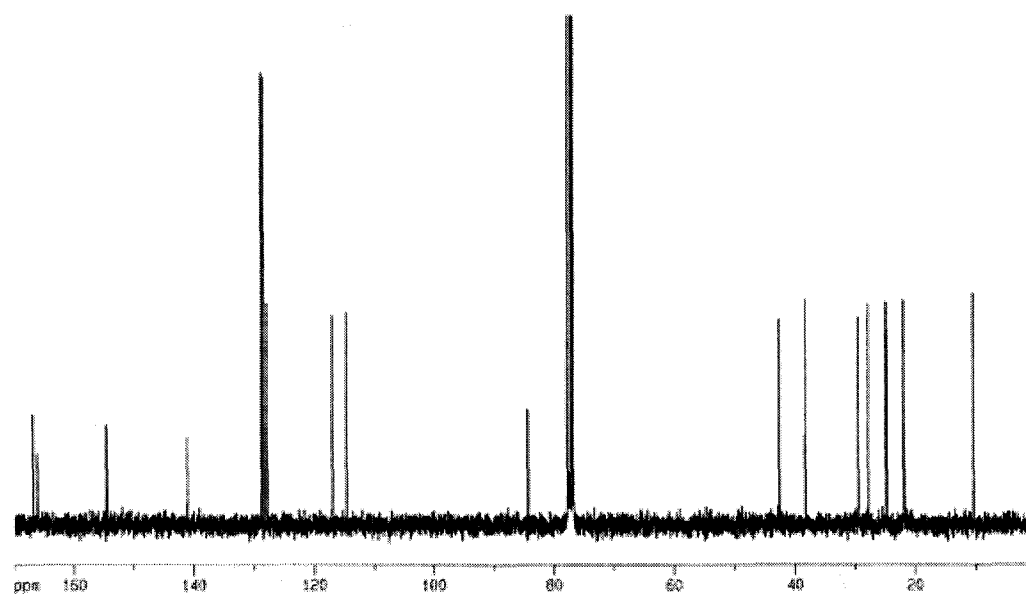


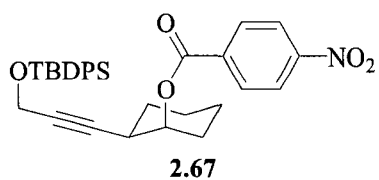


^1H NMR (CDCl_3 , 500 MHz)

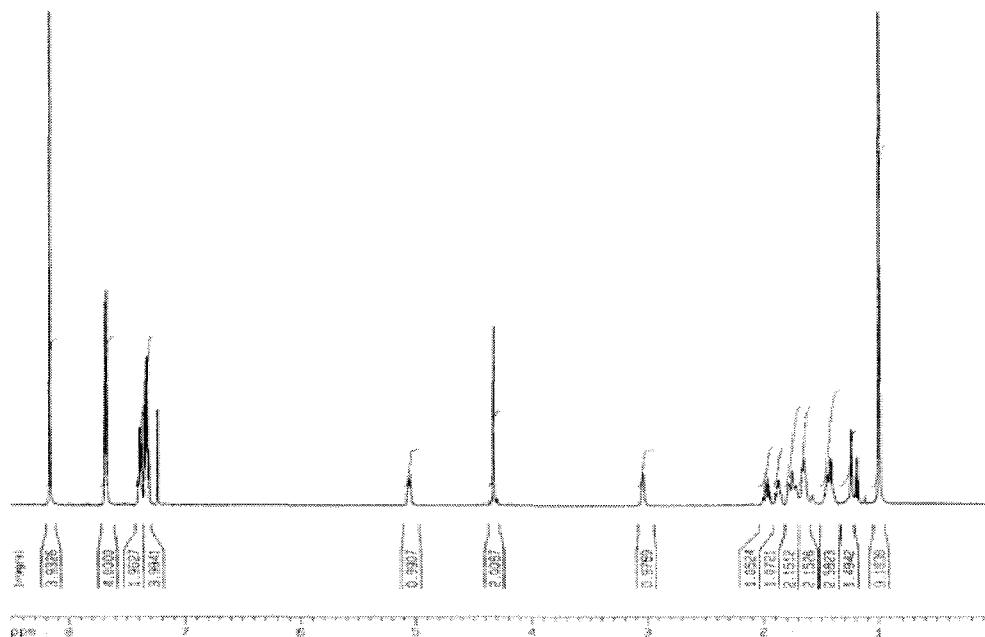


^{13}C NMR (CDCl_3 , 75 MHz)

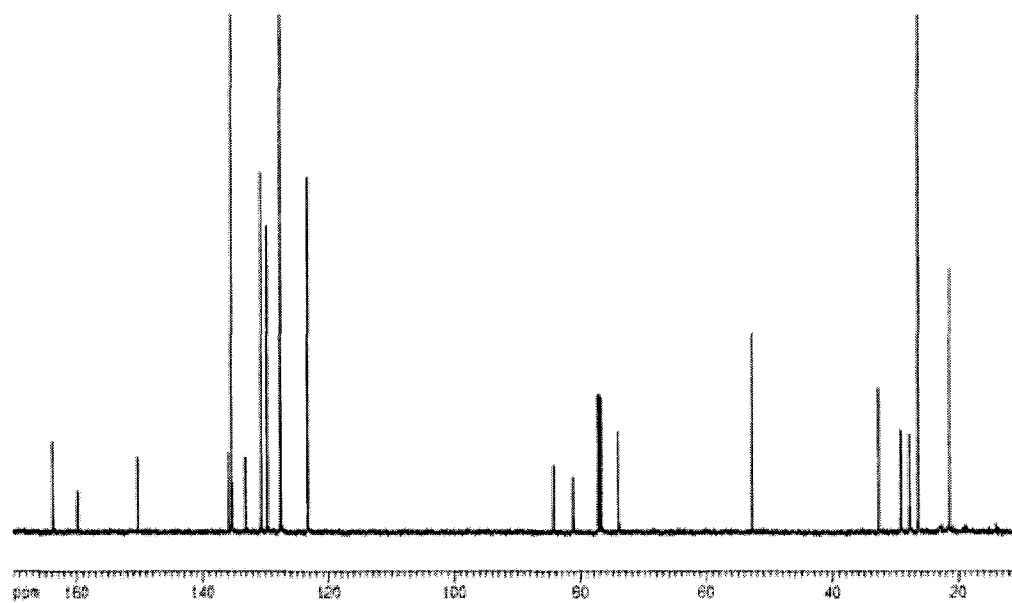


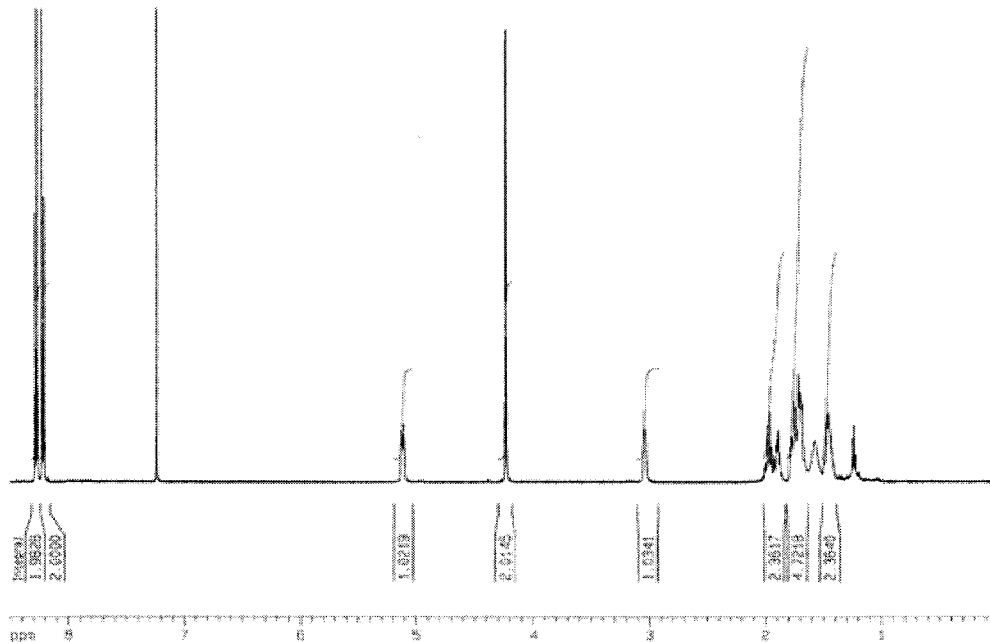


¹H NMR (CDCl₃, 500 MHz)

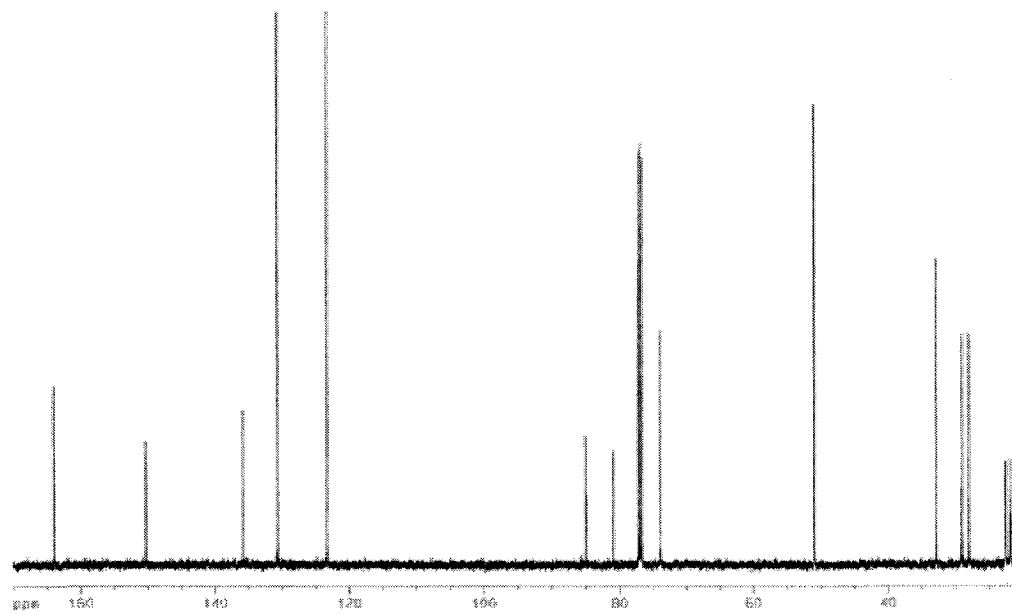


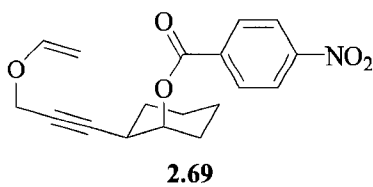
¹³C NMR (CDCl₃, 125 MHz)



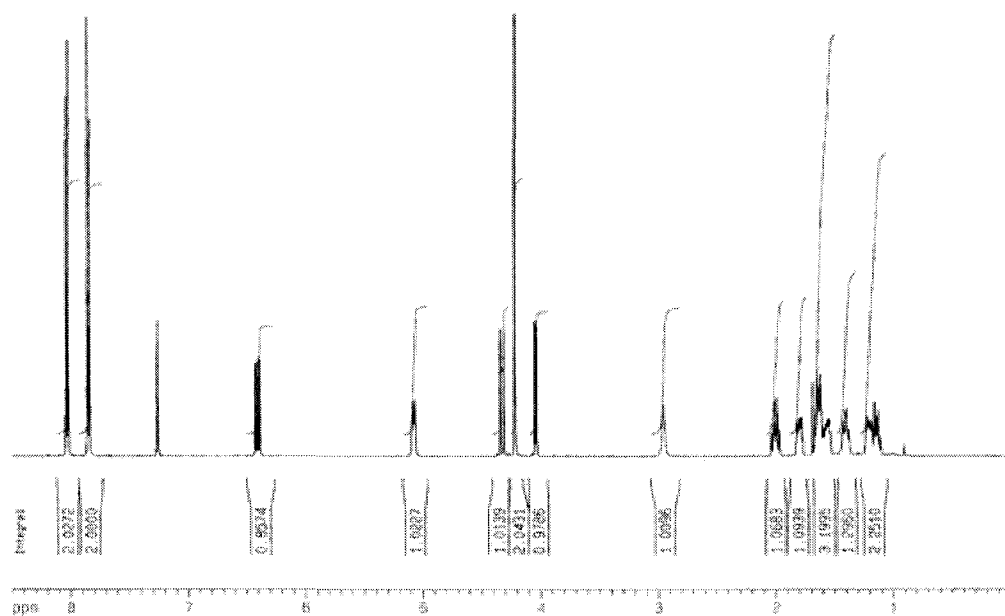
¹H NMR (CDCl₃, 500 MHz)

^{13}C NMR (CDCl_3 , 125 MHz)

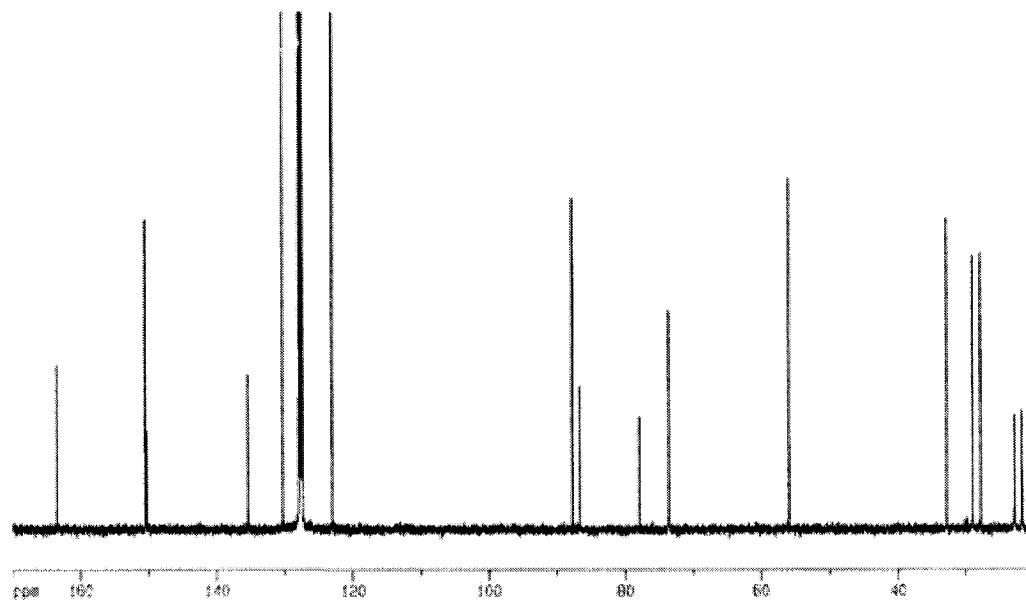


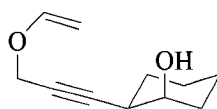


^1H NMR (C_6D_6 , 500 MHz)



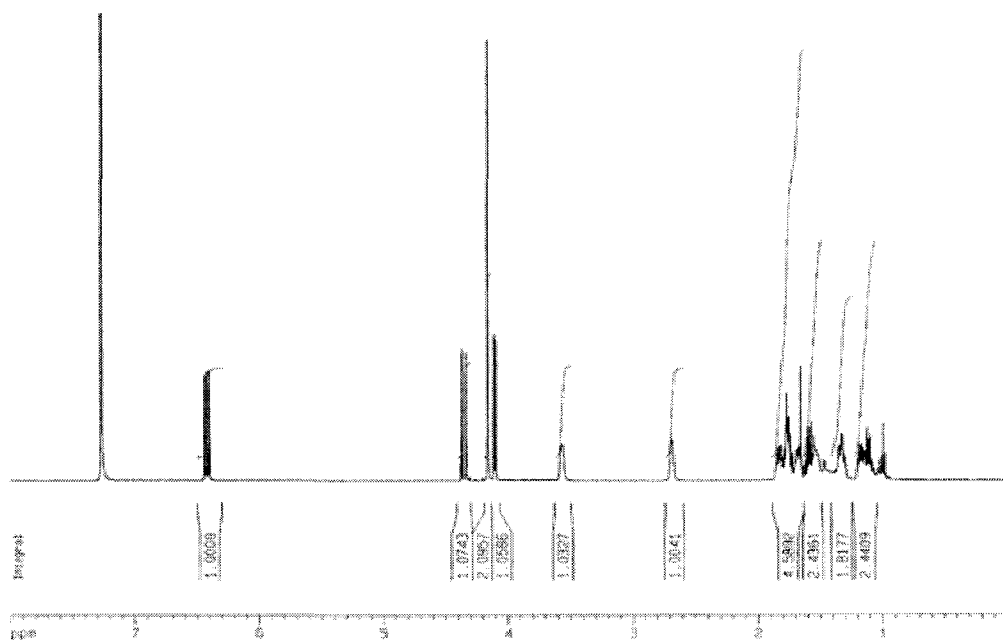
^{13}C NMR (C_6D_6 , 125 MHz)



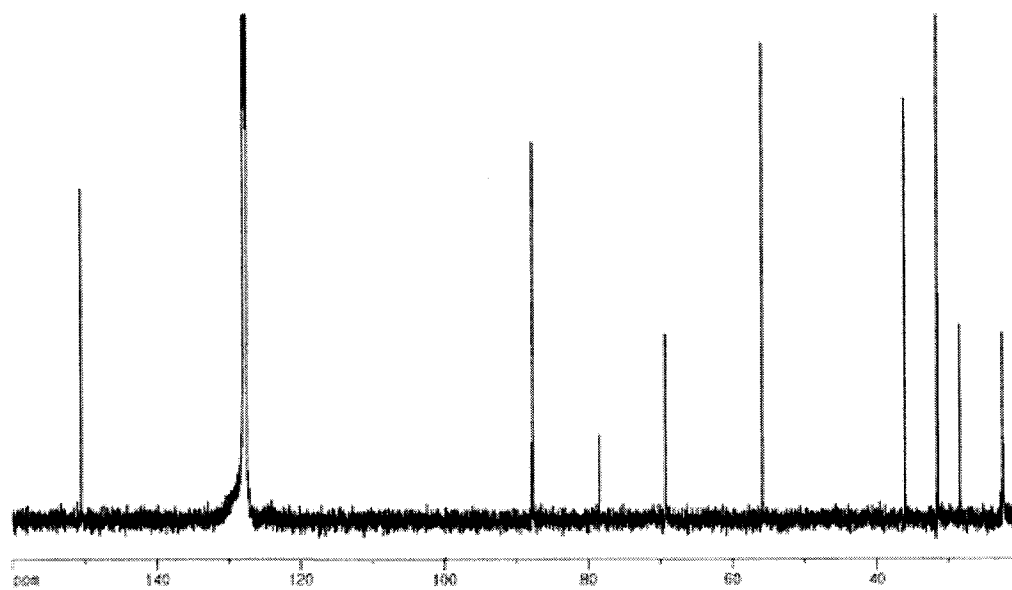


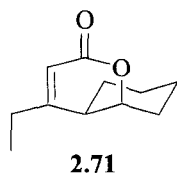
2.70

^1H NMR (C_6D_6 , 500 MHz)

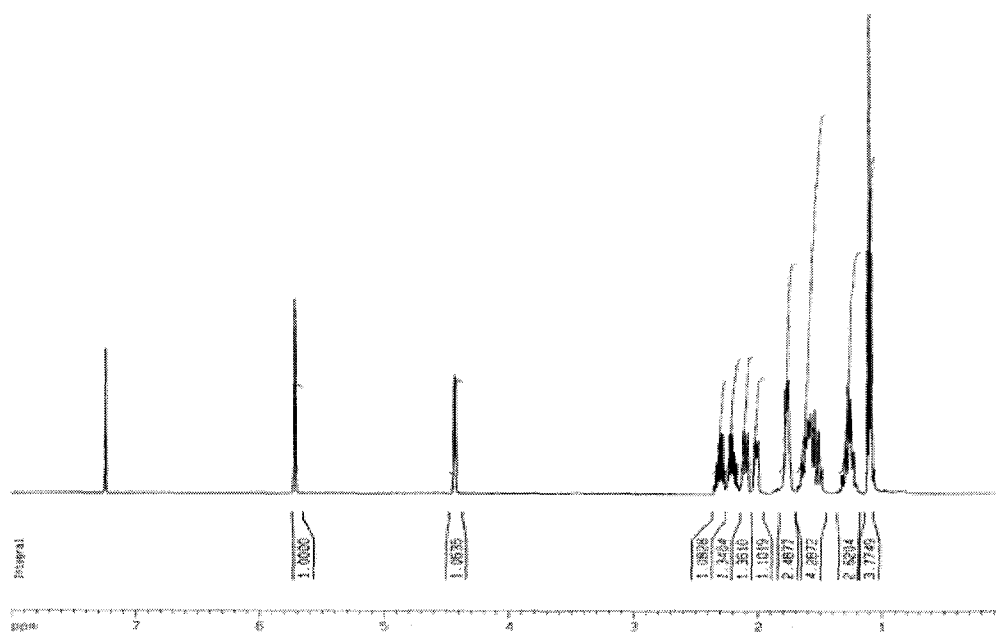


^{13}C NMR (C_6D_6 , 125 MHz)

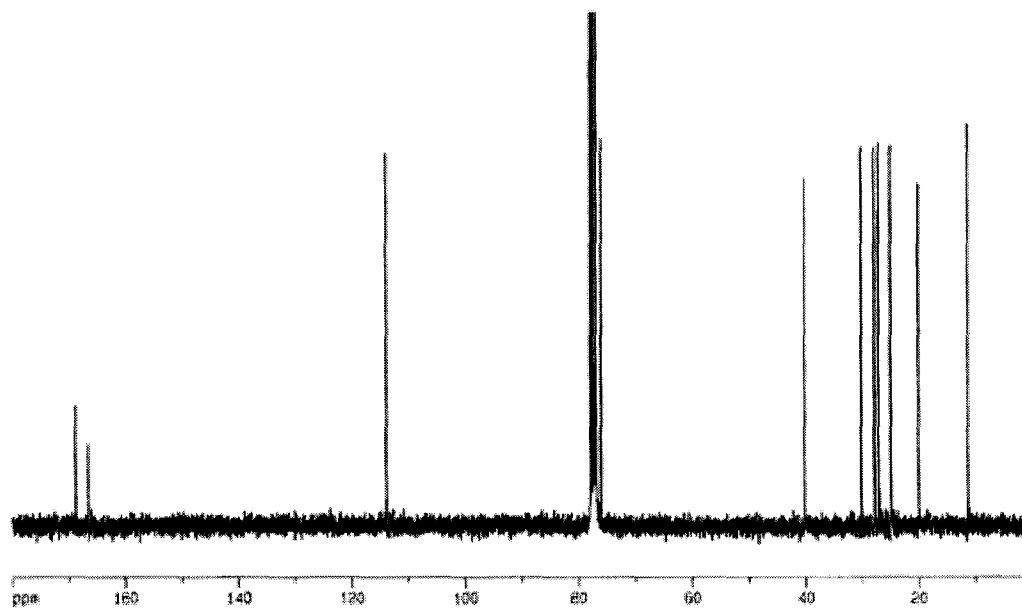


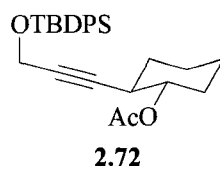


^1H NMR (CDCl_3 , 500 MHz)

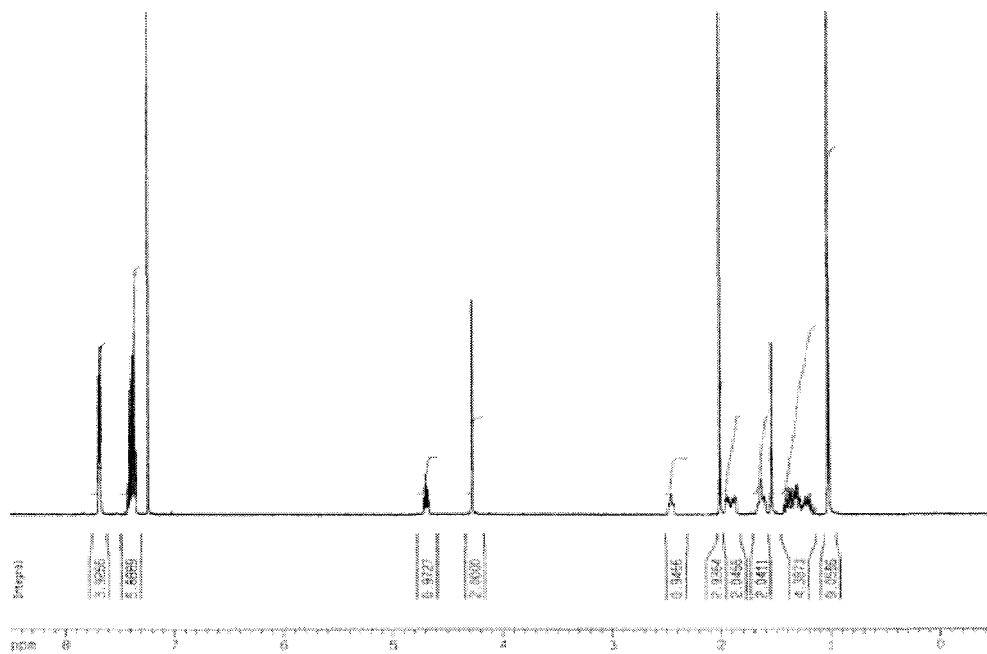


^{13}C NMR (CDCl_3 , 75 MHz)

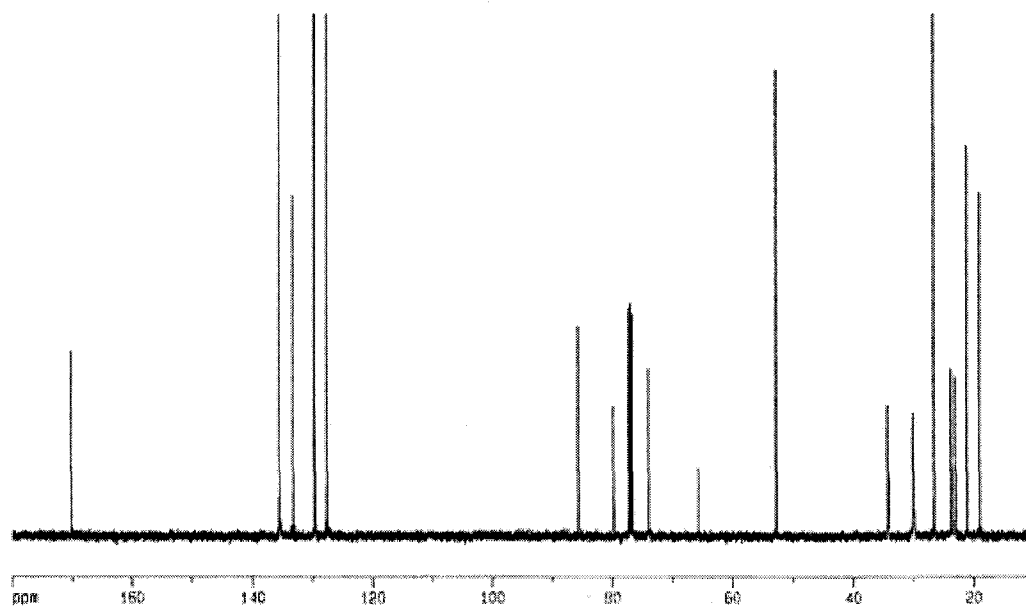


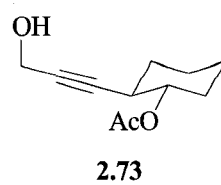


^1H NMR (CDCl_3 , 500 MHz)

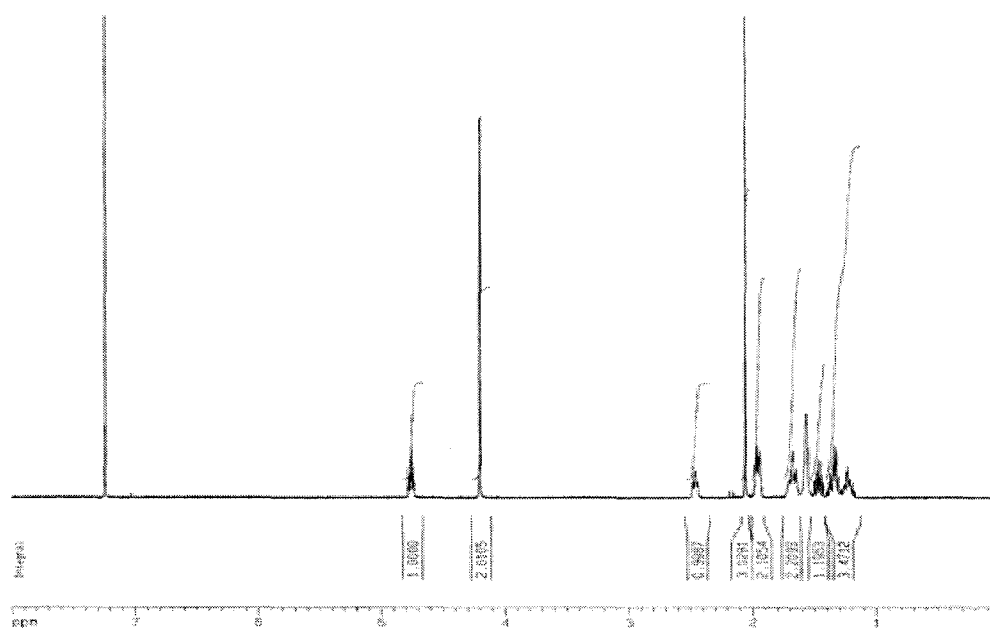


^{13}C NMR (CDCl_3 , 125 MHz)

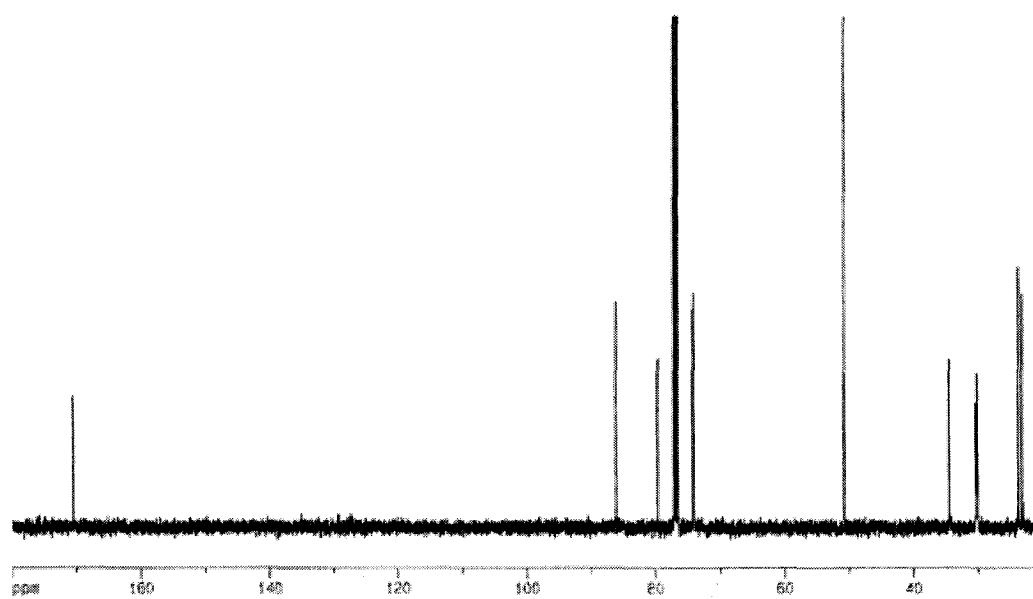


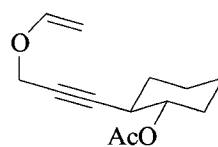


^1H NMR (CDCl_3 , 500 MHz)

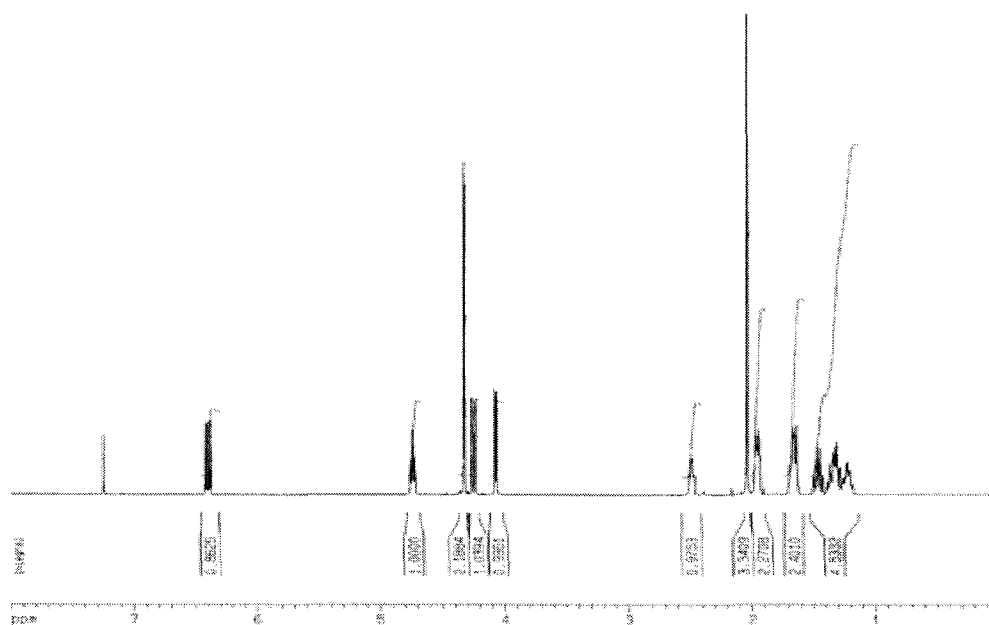
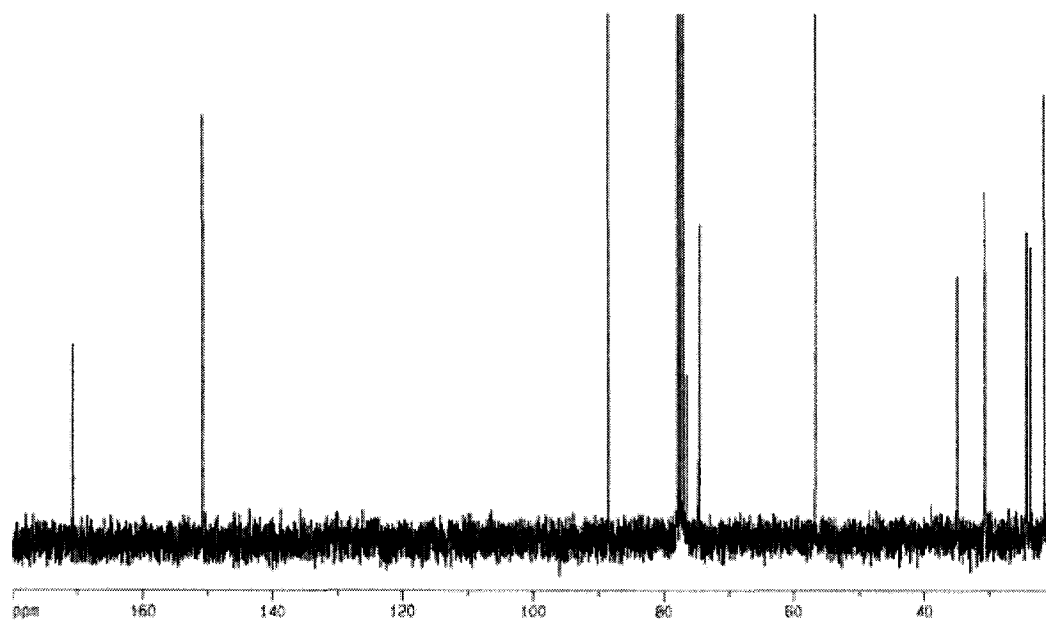


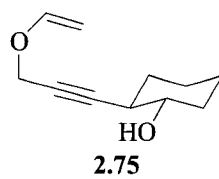
^{13}C NMR (CDCl_3 , 125 MHz)



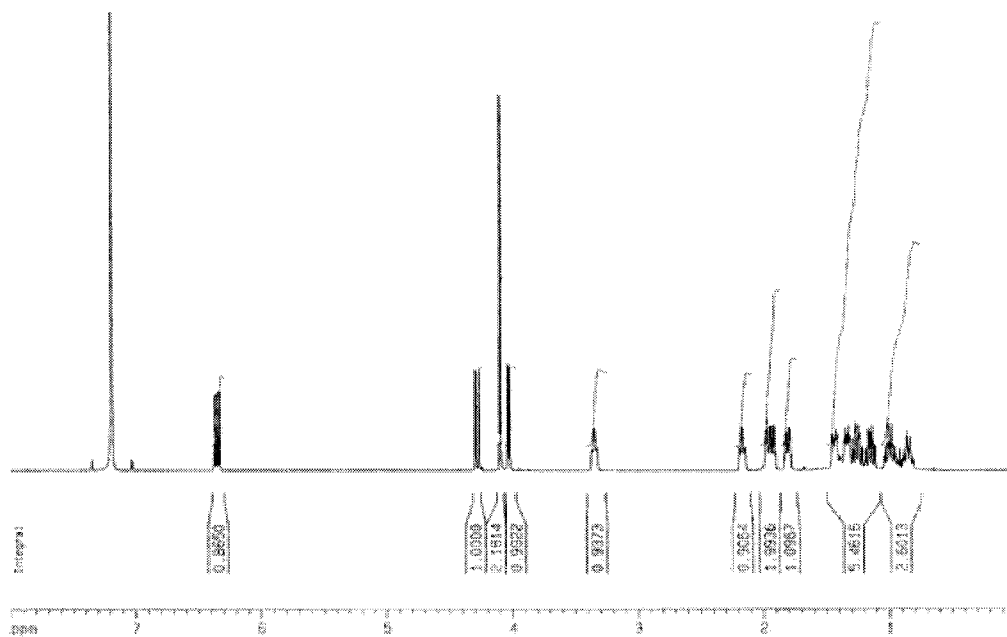


2.74

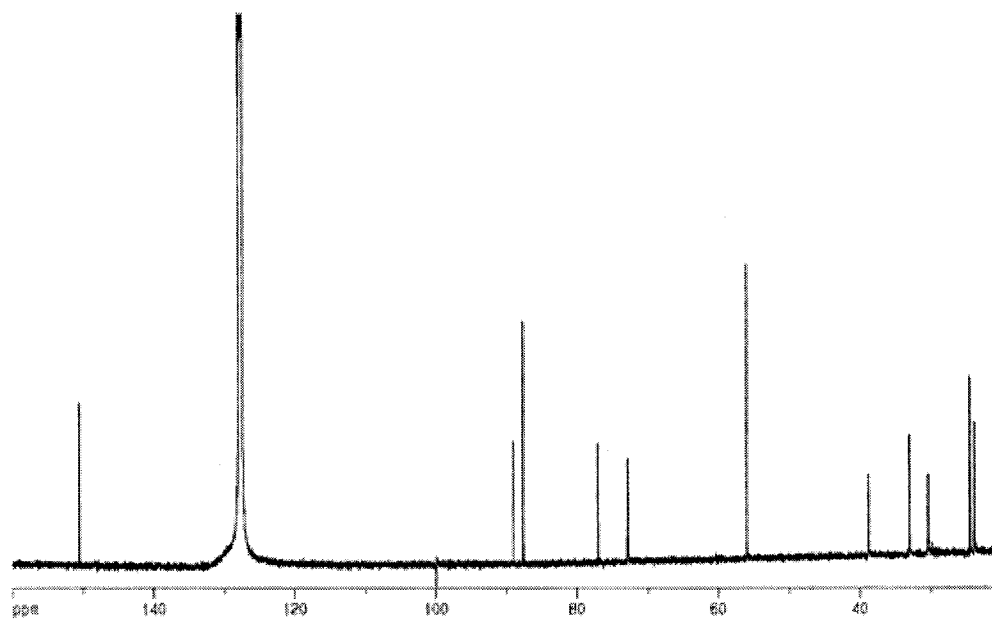
 ^1H NMR (CDCl_3 , 500 MHz) ^{13}C NMR (CDCl_3 , 75 MHz)

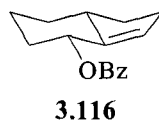


¹H NMR (C₆D₆, 500 MHz)

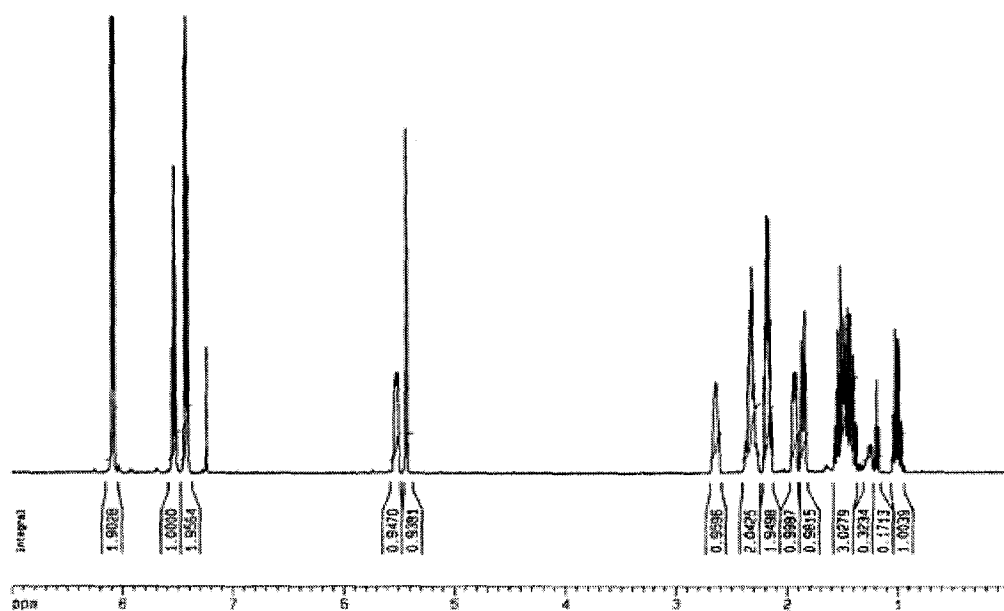


¹³C NMR (C₆D₆, 125 MHz)

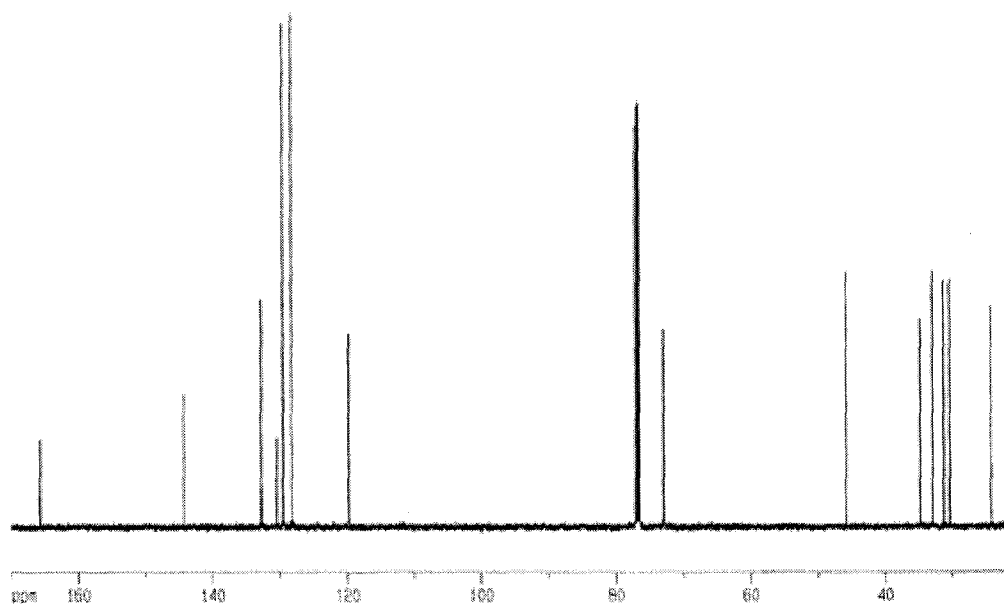


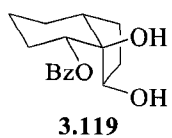


^1H NMR (CDCl_3 , 500 MHz)

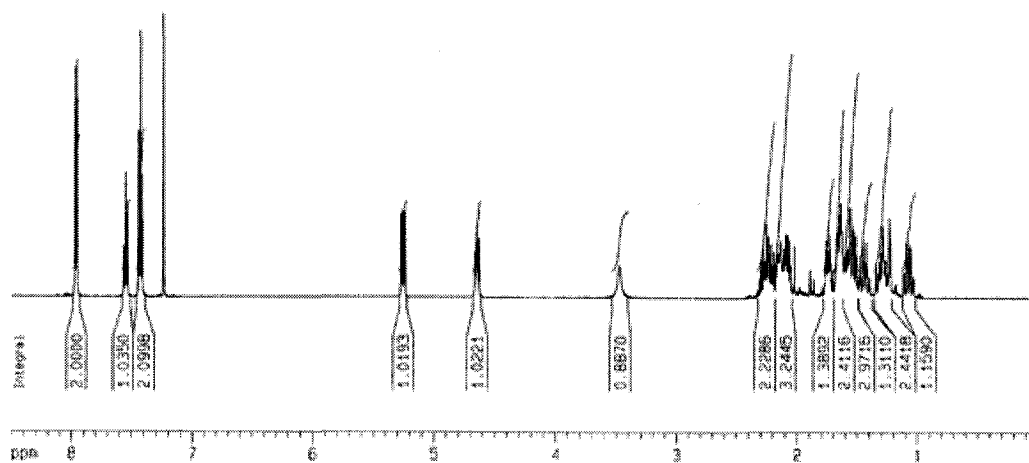


^{13}C NMR (CDCl_3 , 125 MHz)

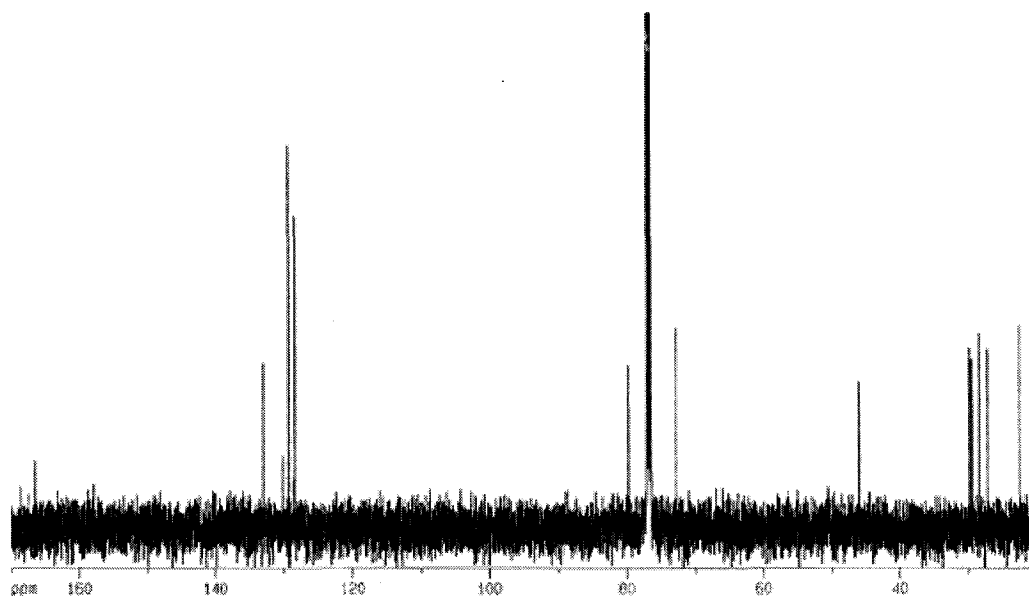


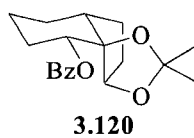


^1H NMR (CDCl_3 , 500 MHz)

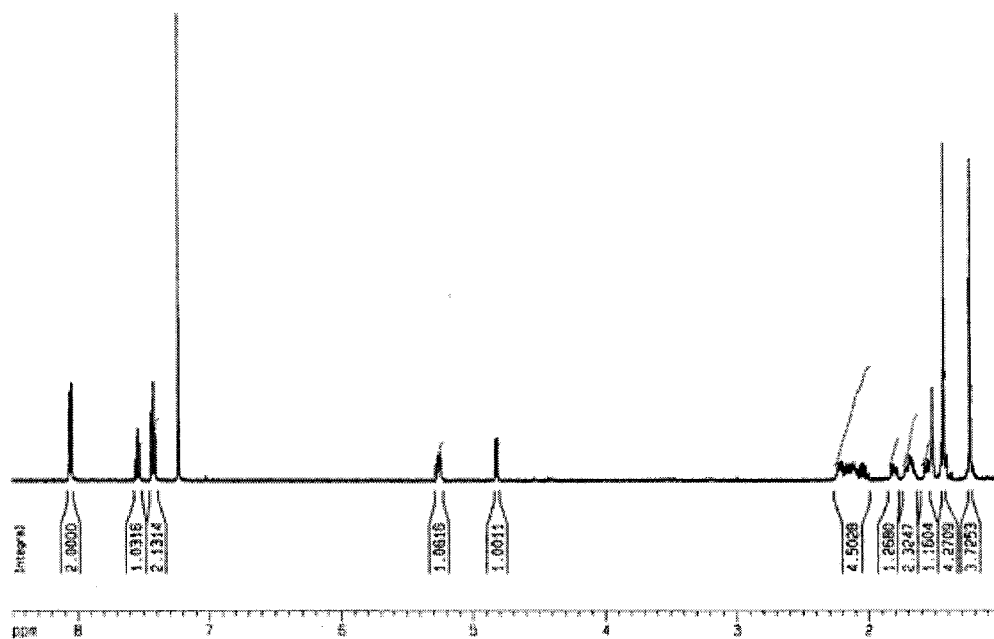


^{13}C NMR (CDCl_3 , 125 MHz)

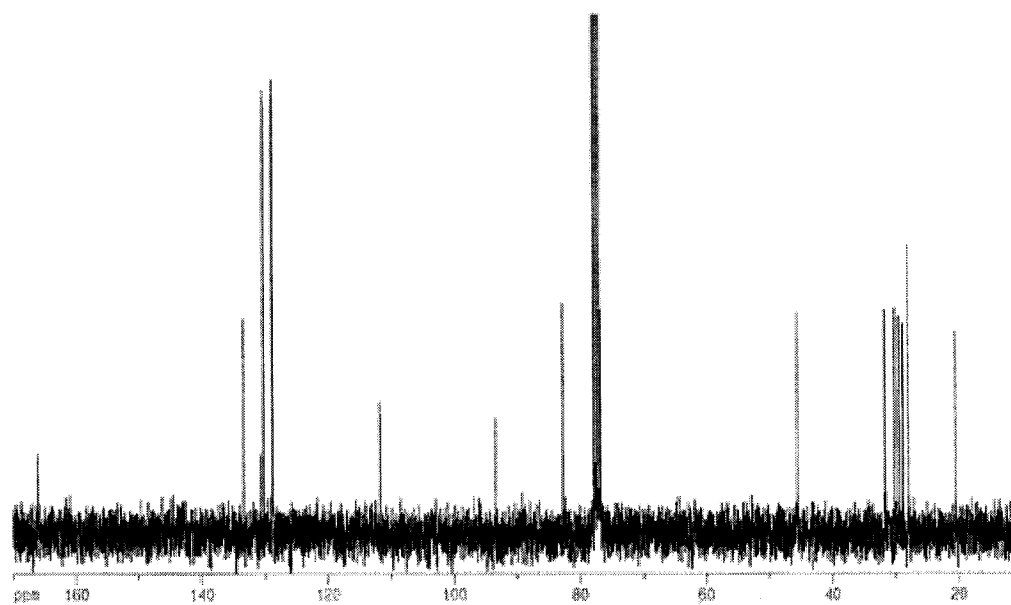


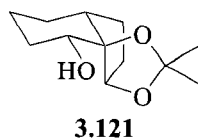


^1H NMR (CDCl_3 , 500 MHz)

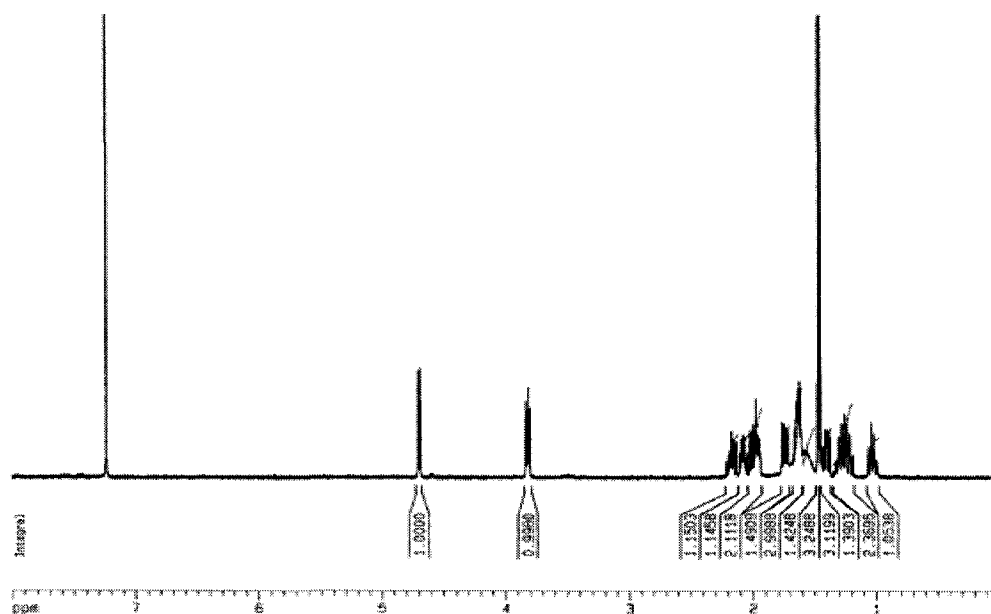


^{13}C NMR (CDCl_3 , 75 MHz)

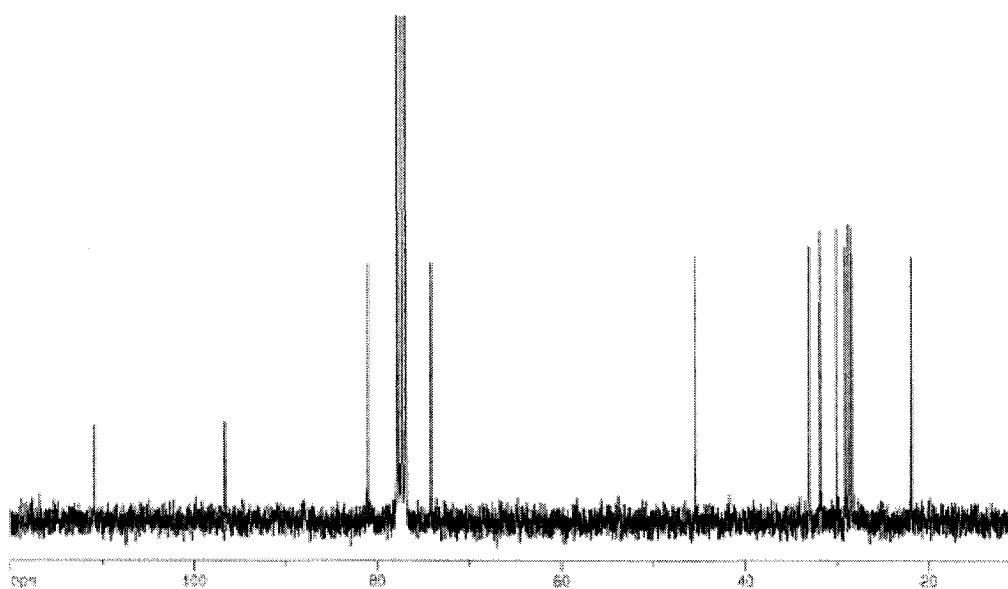


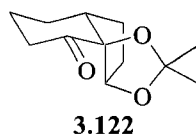


^1H NMR (CDCl_3 , 500 MHz)

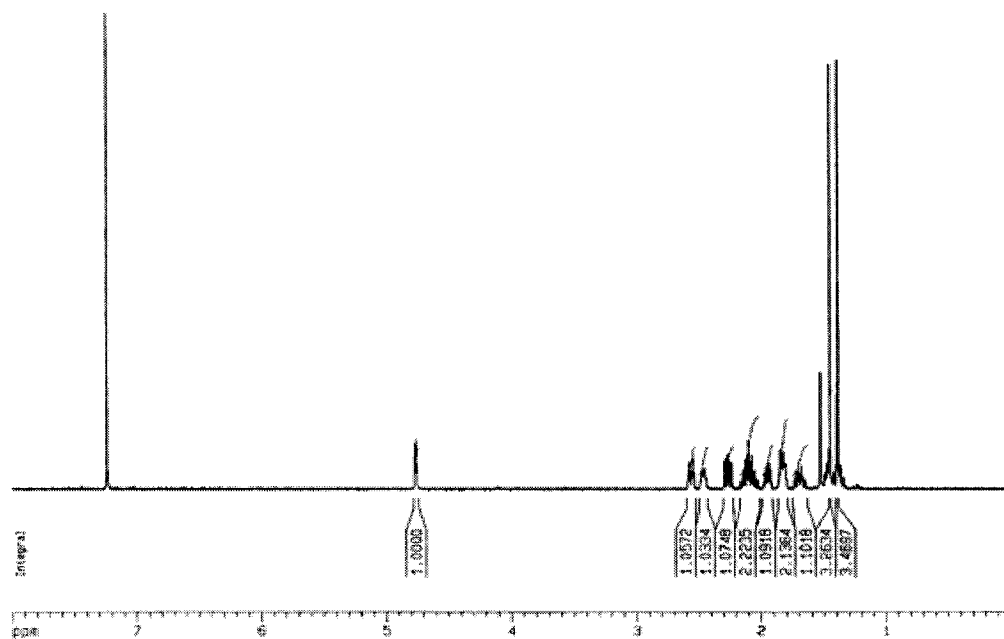


^{13}C NMR (CDCl_3 , 75 MHz)

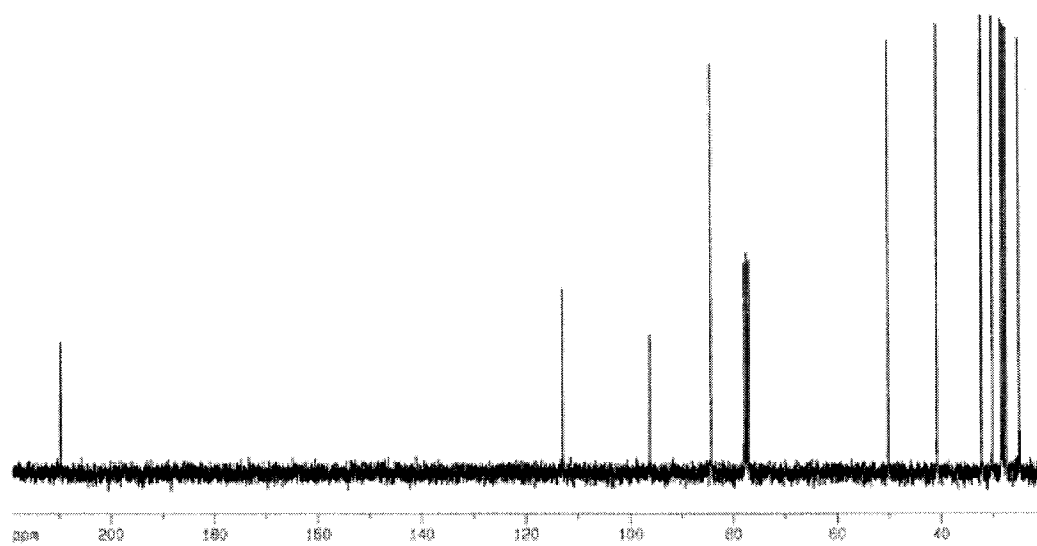


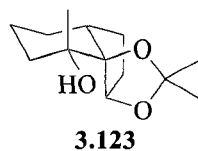


^1H NMR (CDCl_3 , 500 MHz)

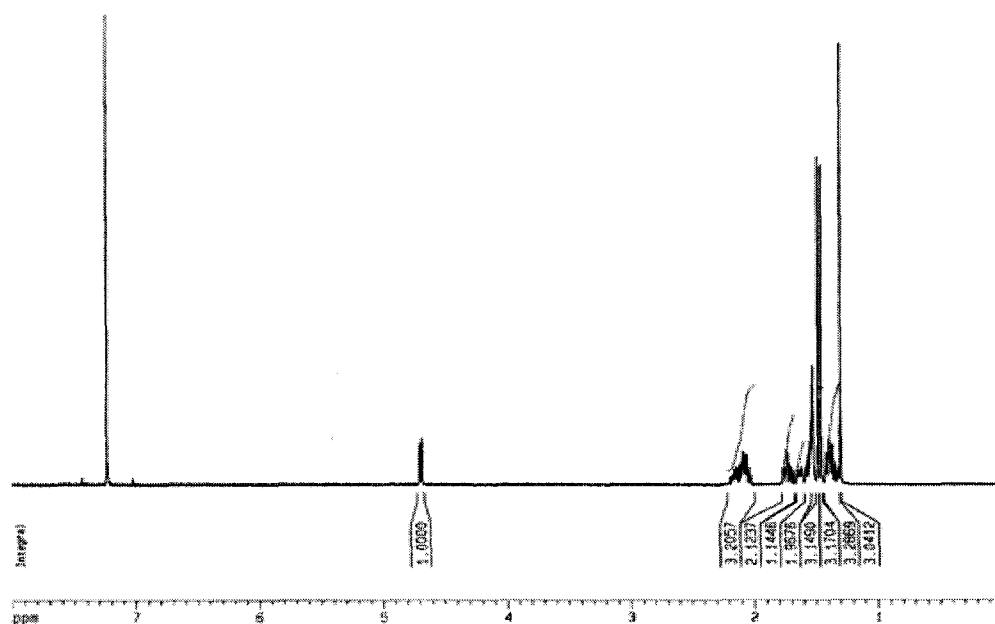


^{13}C NMR (CDCl_3 , 75 MHz)

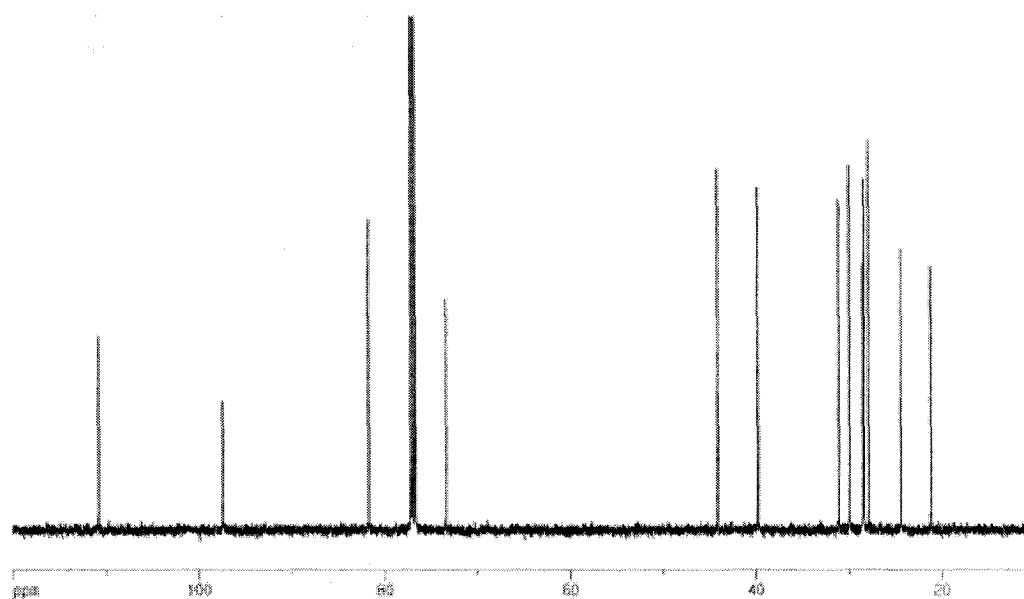


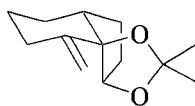
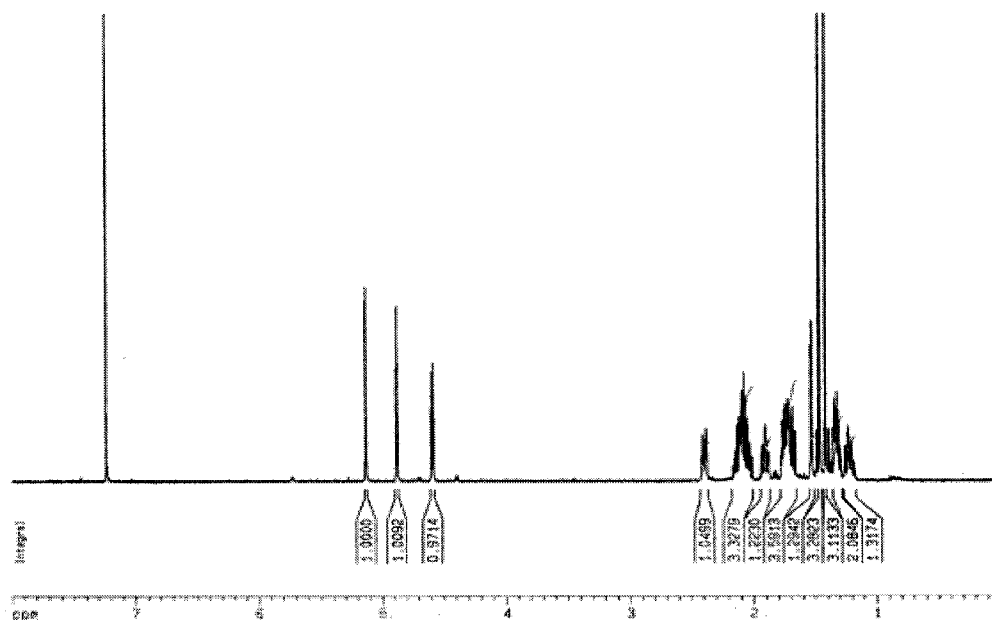
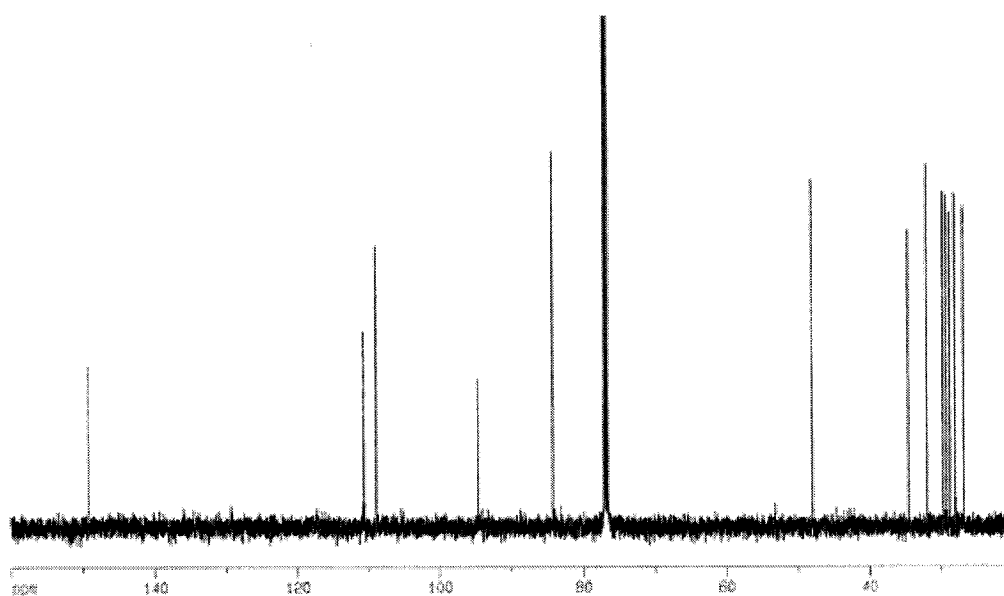


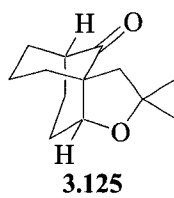
^1H NMR (CDCl_3 , 500 MHz)



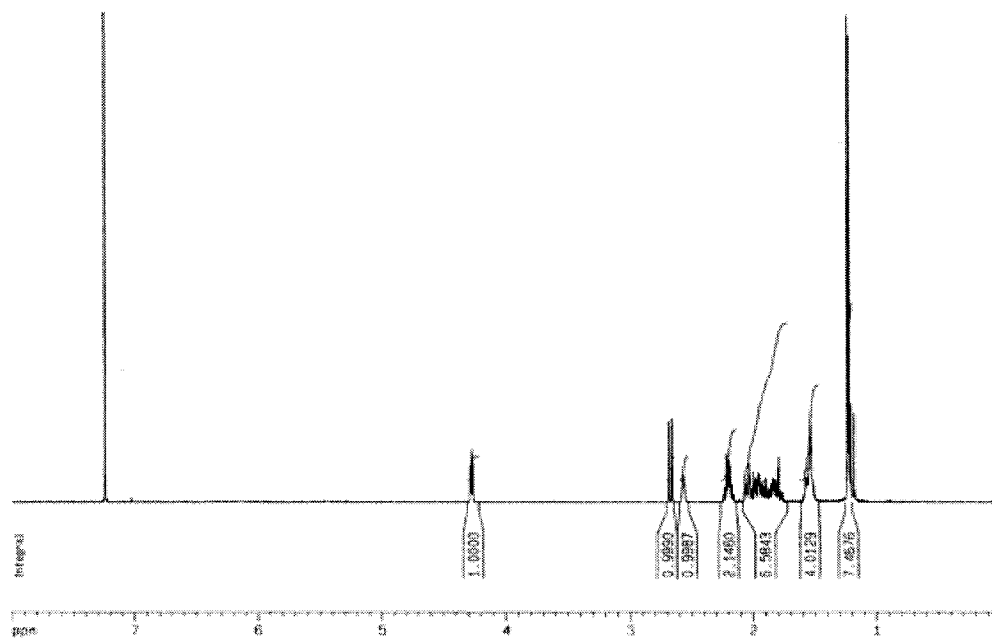
^{13}C NMR (CDCl_3 , 125 MHz)



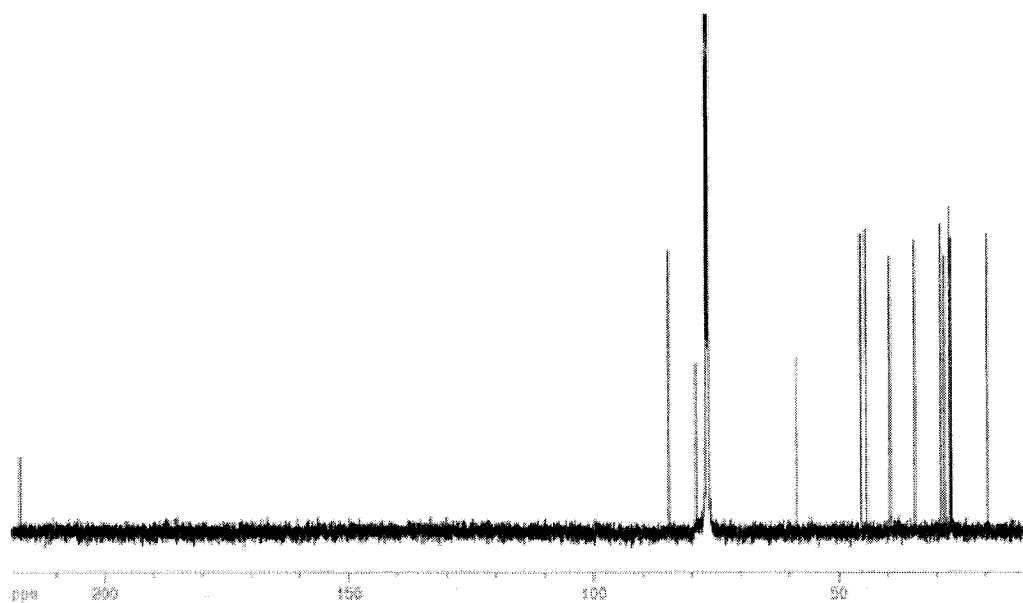
**3.124****¹H NMR (CDCl₃, 500 MHz)****¹³C NMR (CDCl₃, 125 MHz)**

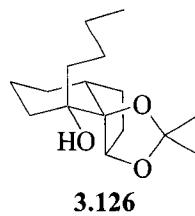


^1H NMR (CDCl_3 , 500 MHz)

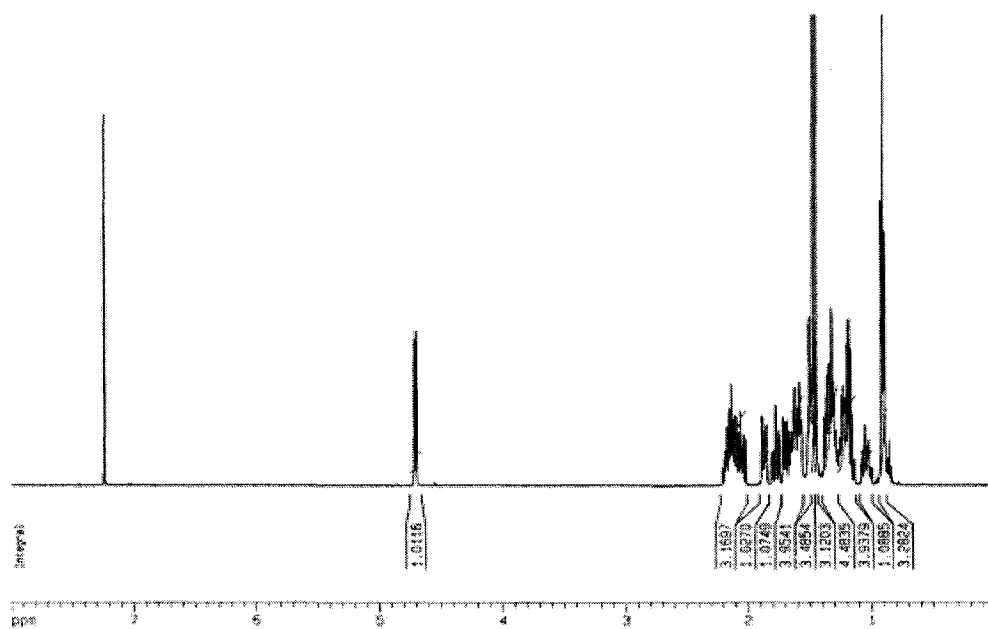


^{13}C NMR (CDCl_3 , 125 MHz)

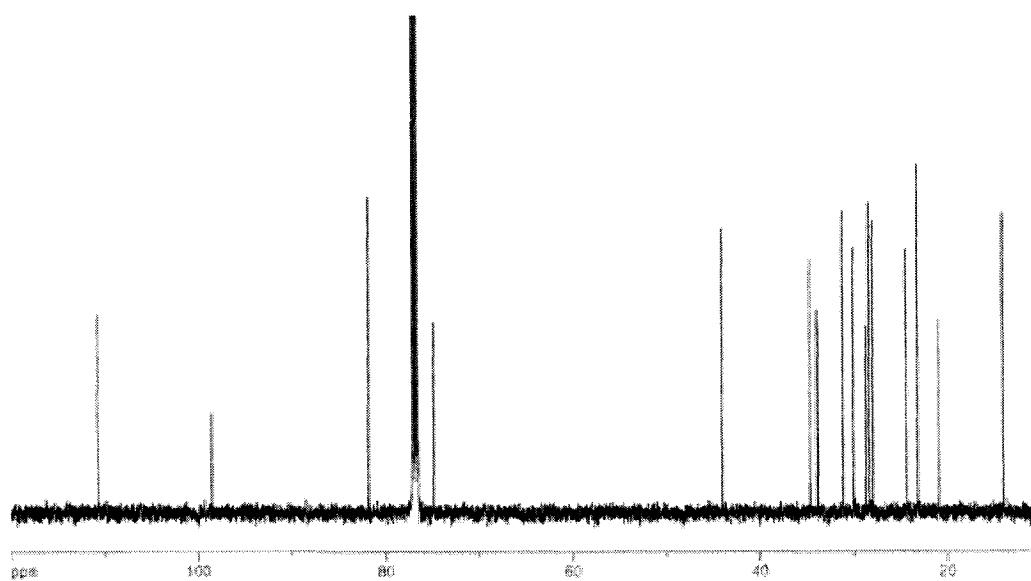


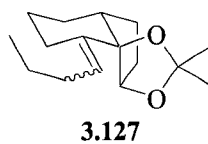


^1H NMR (CDCl_3 , 500 MHz)

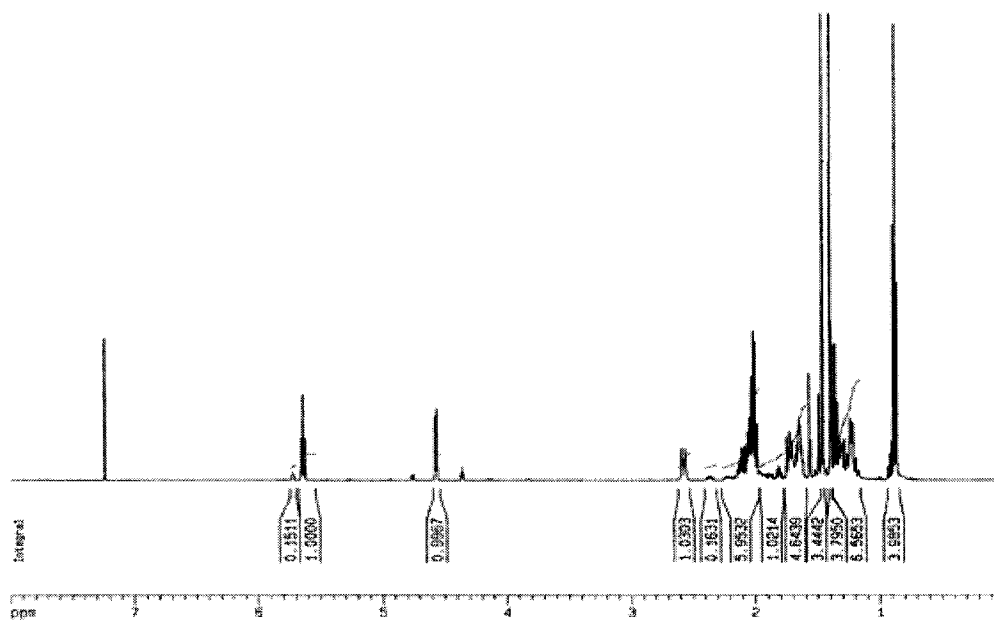


^{13}C NMR (CDCl_3 , 125 MHz)

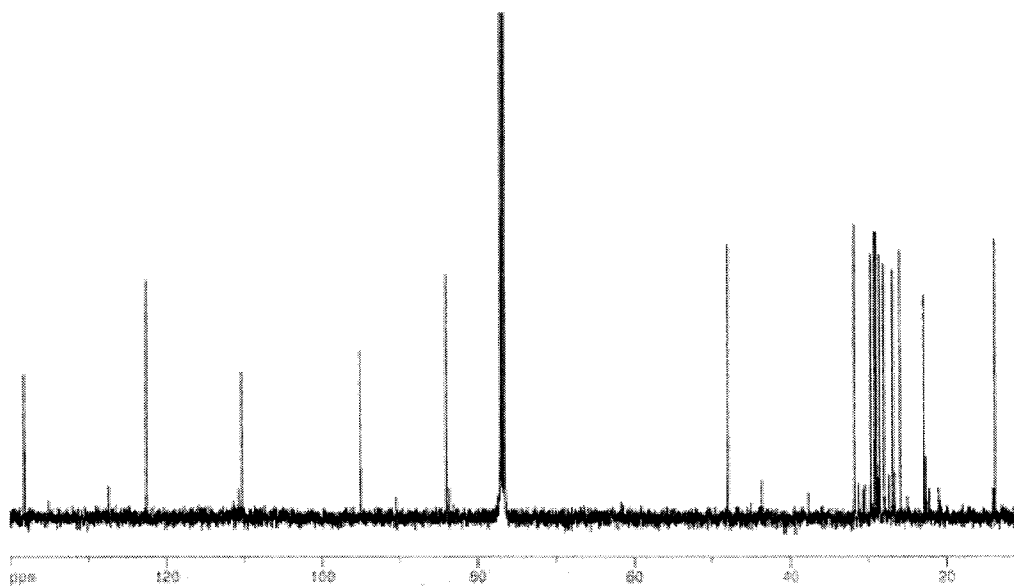


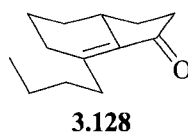


^1H NMR (CDCl_3 , 500 MHz)

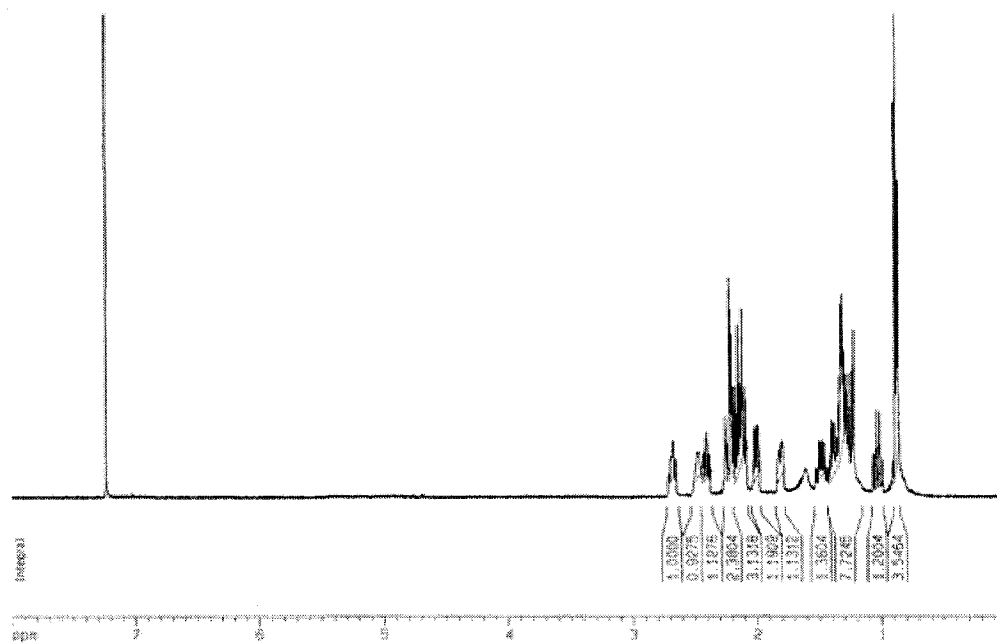


^{13}C NMR (CDCl_3 , 125 MHz)

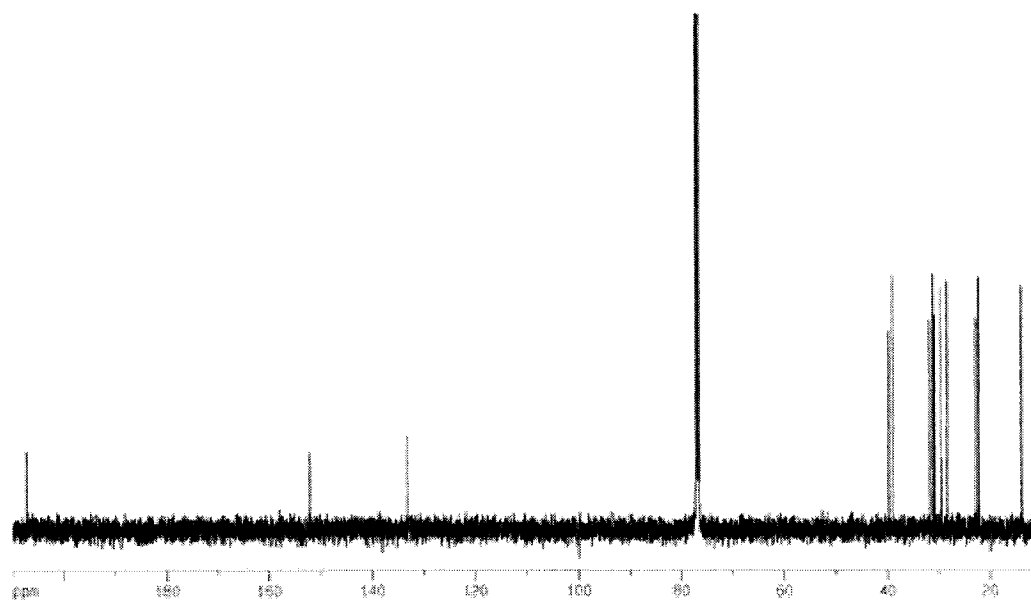


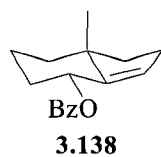


^1H NMR (CDCl_3 , 500 MHz)

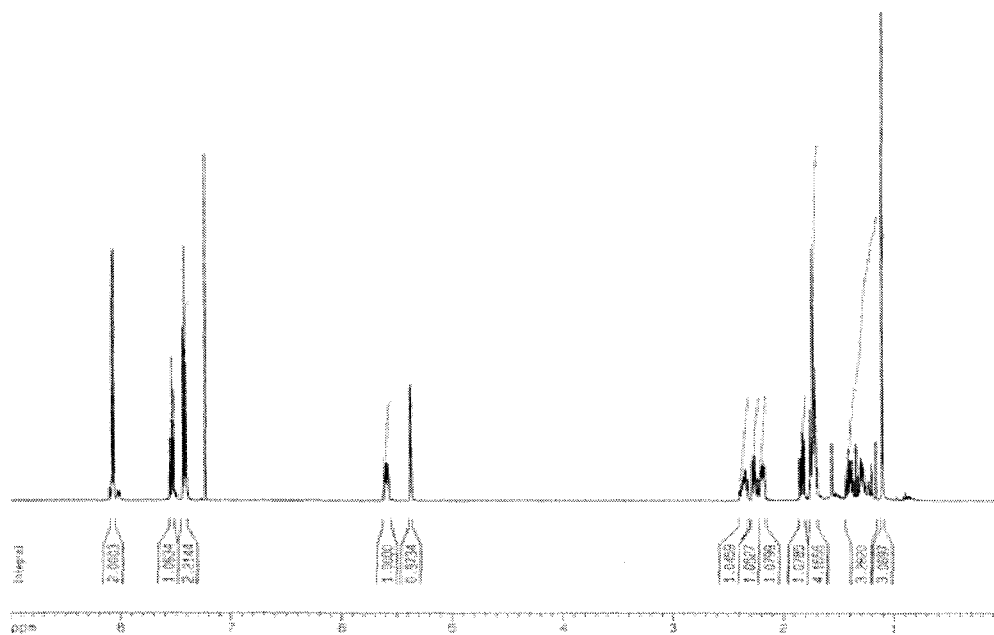


^{13}C NMR (CDCl_3 , 125 MHz)

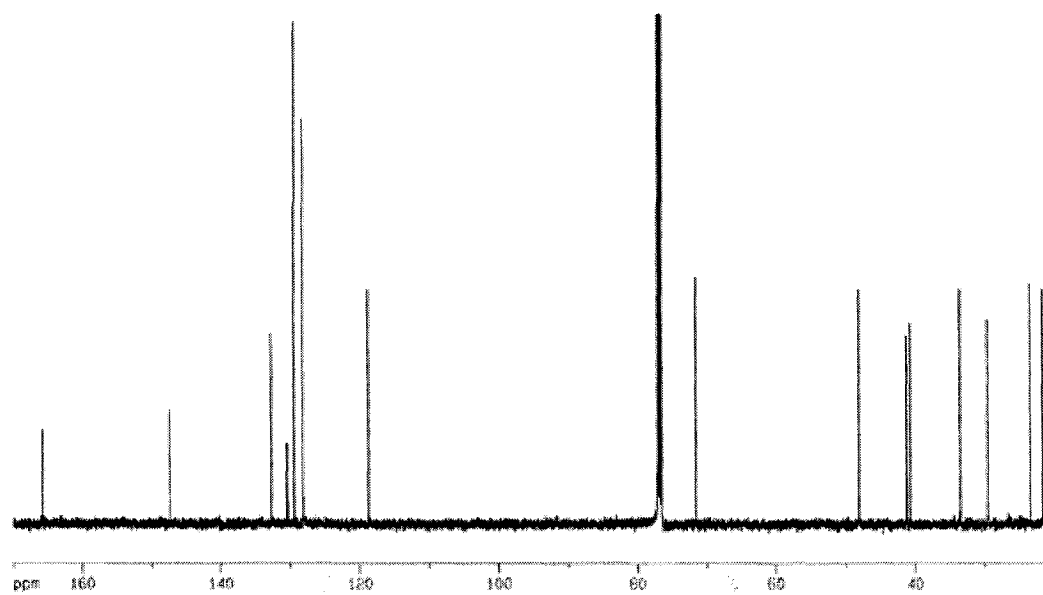


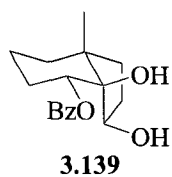


^1H NMR (CDCl_3 , 500 MHz)

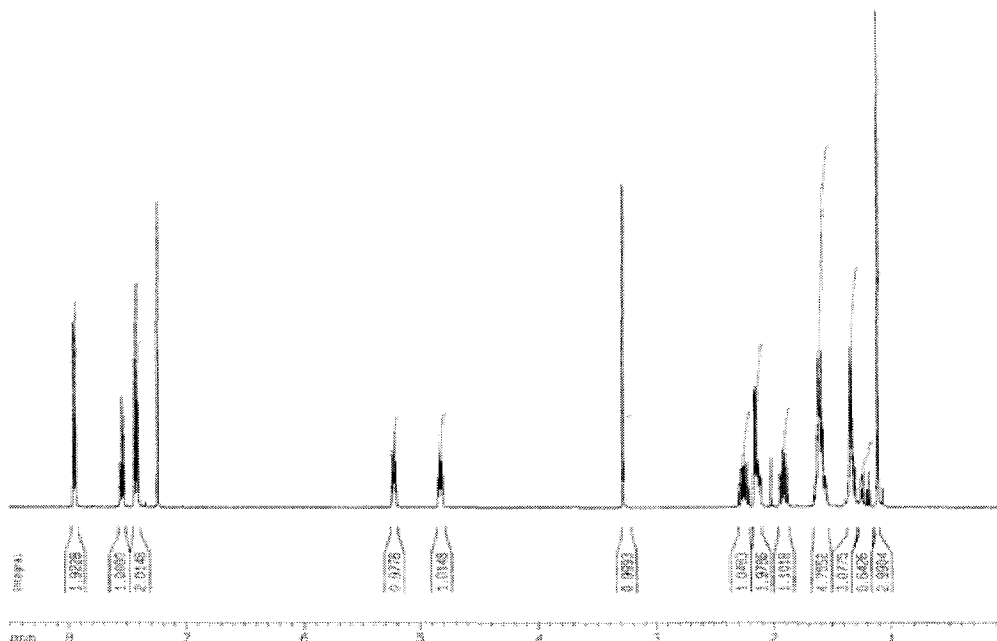


^{13}C NMR (CDCl_3 , 125 MHz)

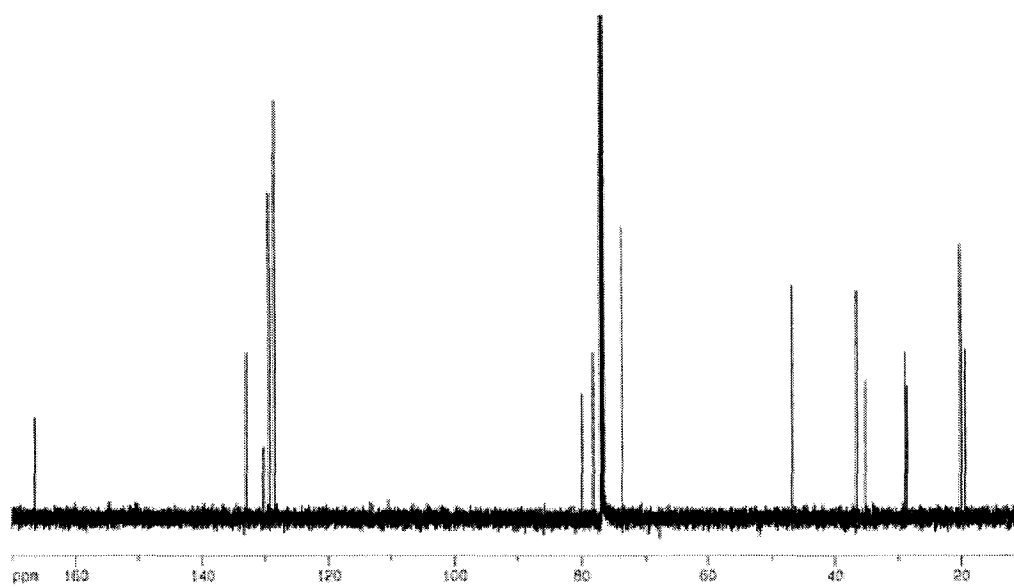


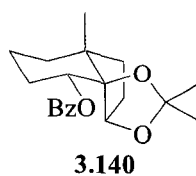


^1H NMR (CDCl_3 , 500 MHz)

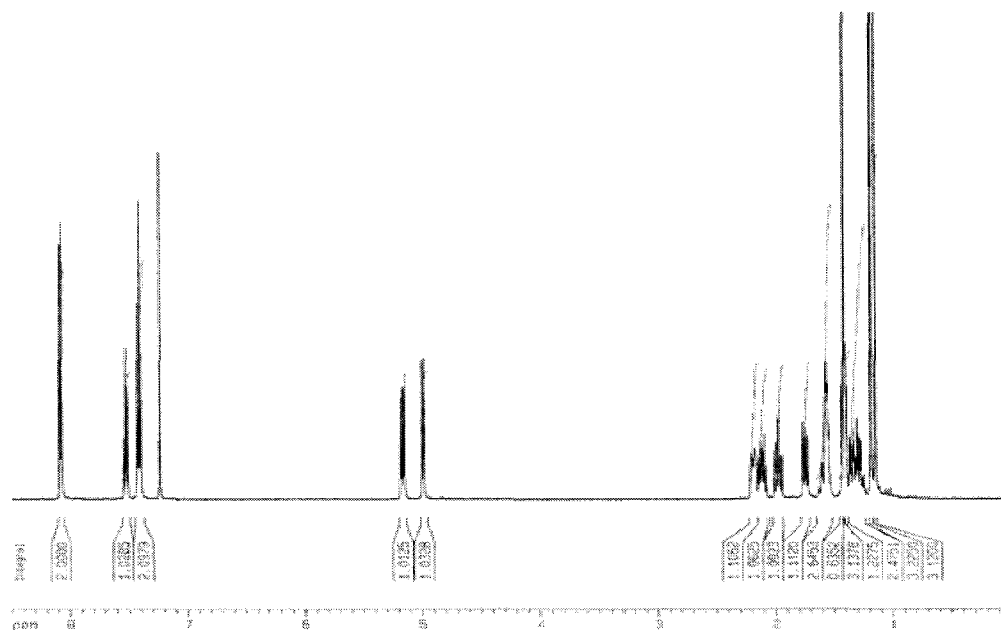


^{13}C NMR (CDCl_3 , 125 MHz)

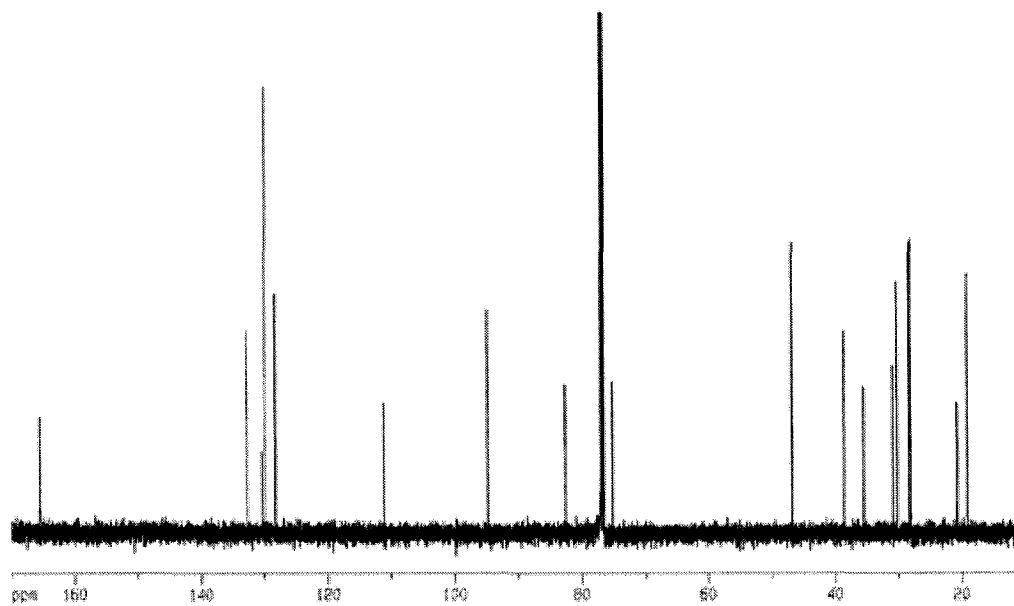


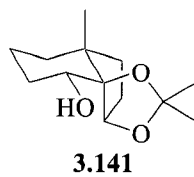


^1H NMR (CDCl_3 , 500 MHz)

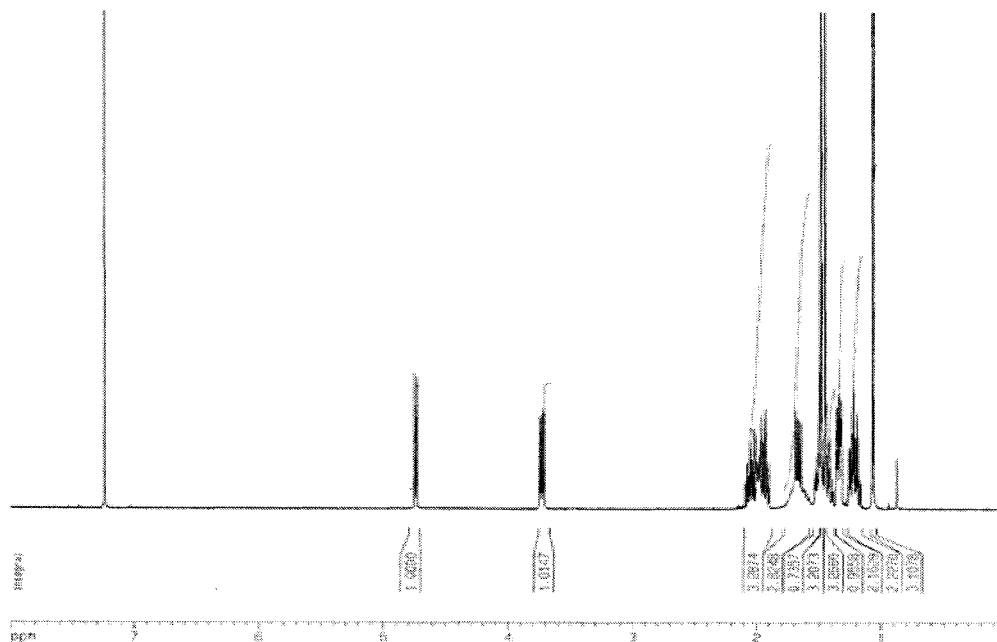


^{13}C NMR (CDCl_3 , 125 MHz)

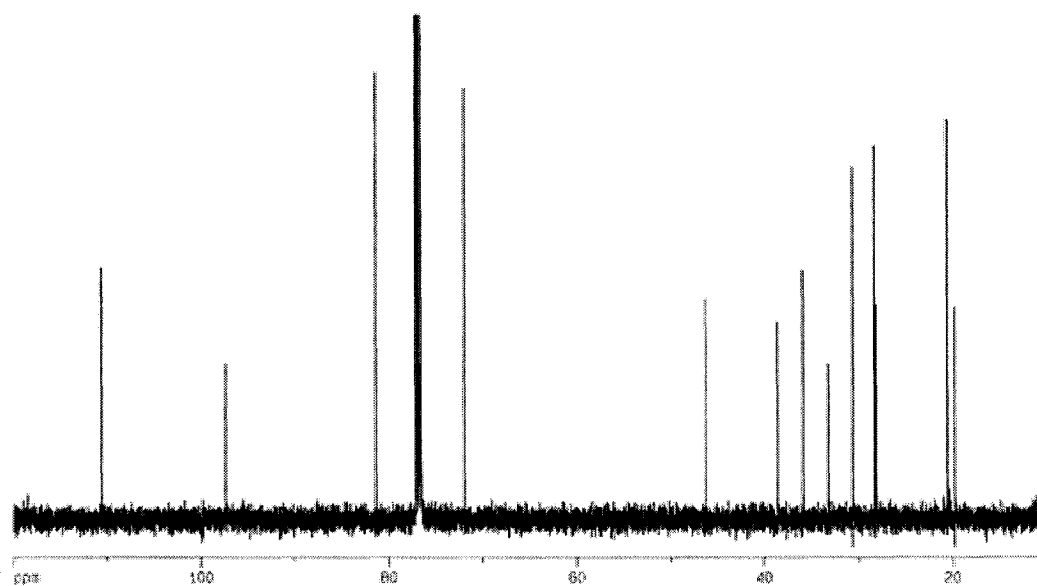


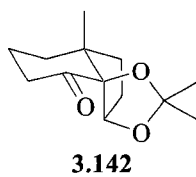


^1H NMR (CDCl_3 , 500 MHz)

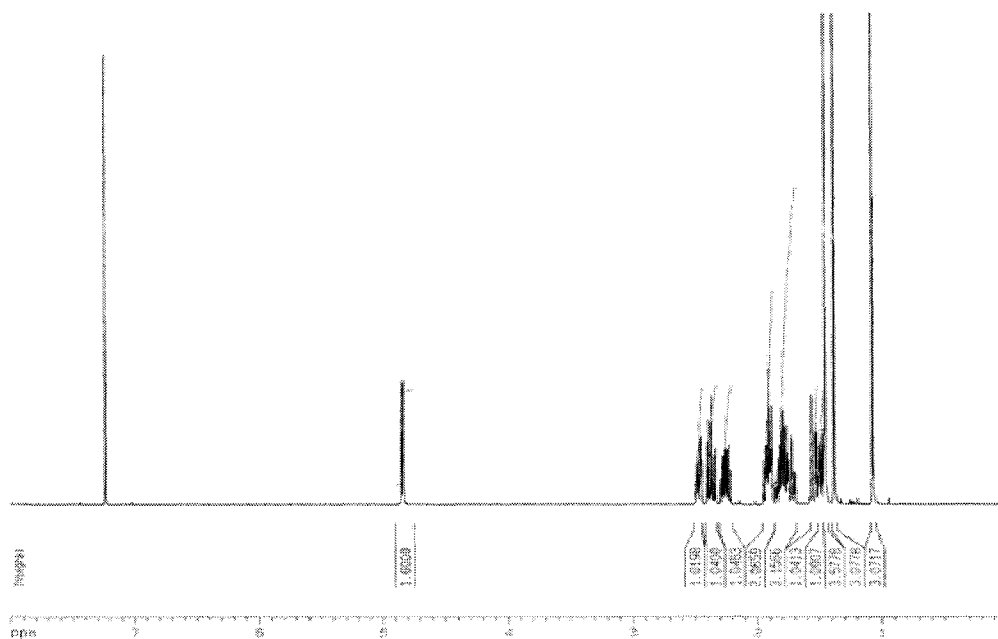


^{13}C NMR (CDCl_3 , 125 MHz)

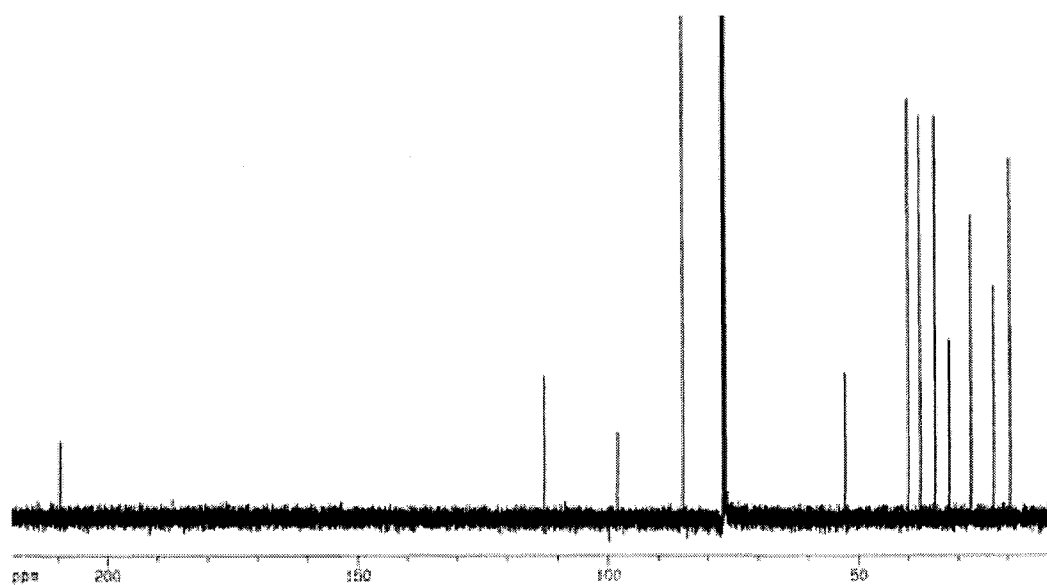


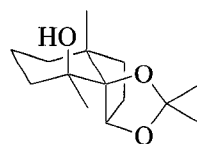


^1H NMR (CDCl_3 , 500 MHz)



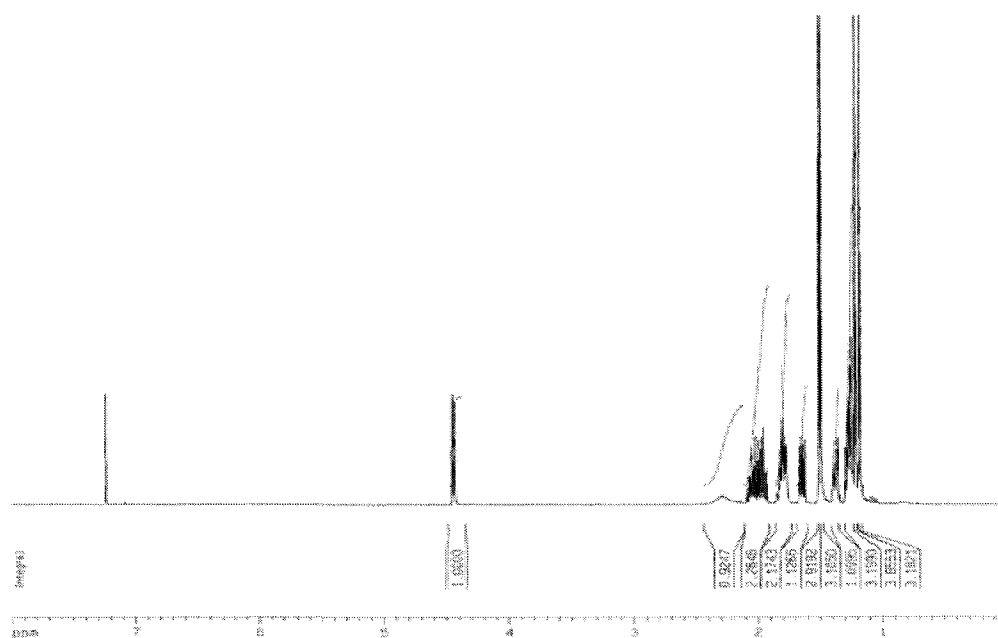
^{13}C NMR (CDCl_3 , 125 MHz)



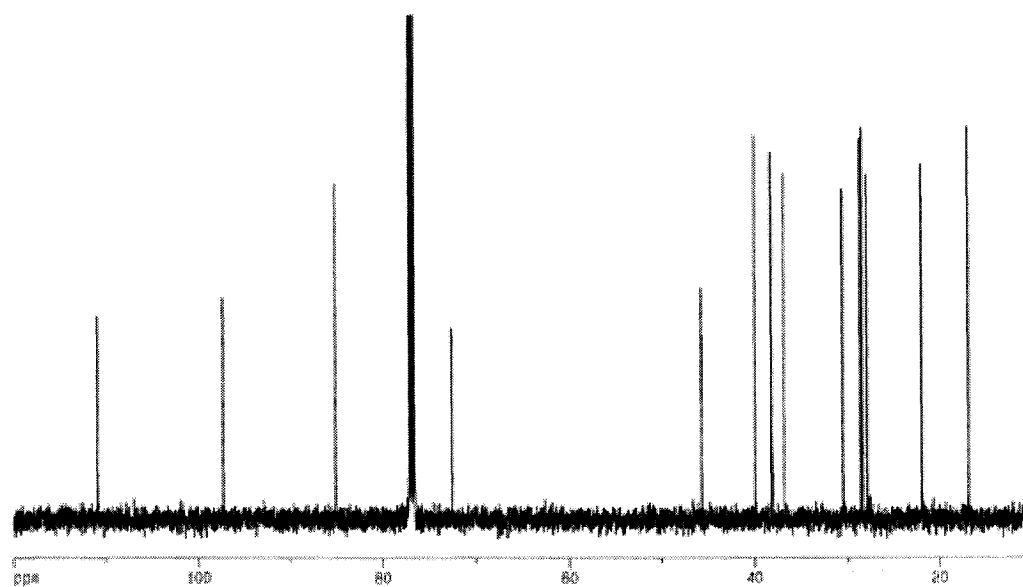


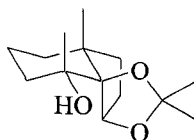
3.143a

^1H NMR (CDCl_3 , 500 MHz)



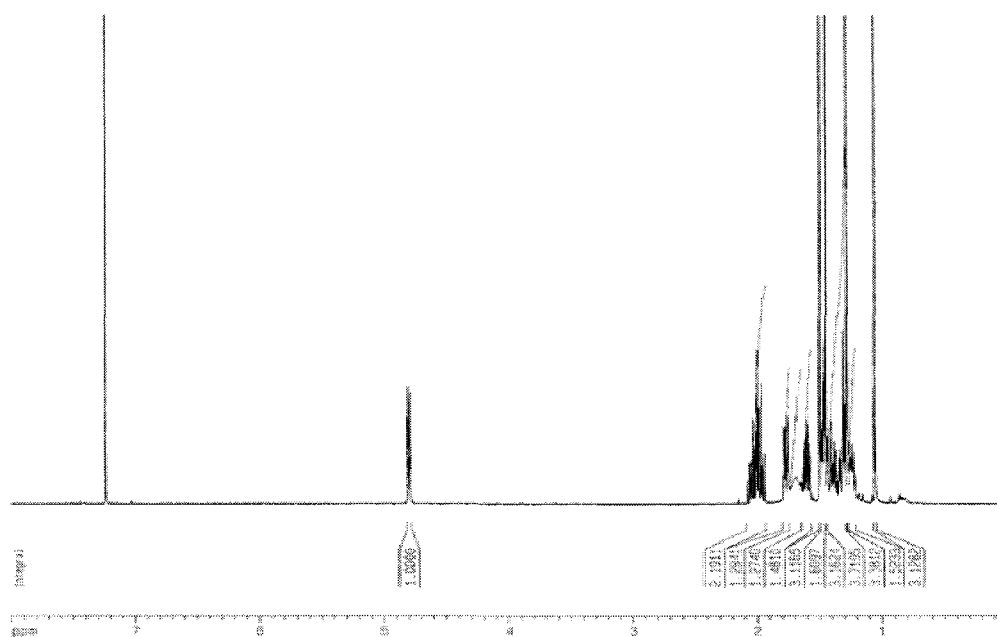
^{13}C NMR (CDCl_3 , 125 MHz)



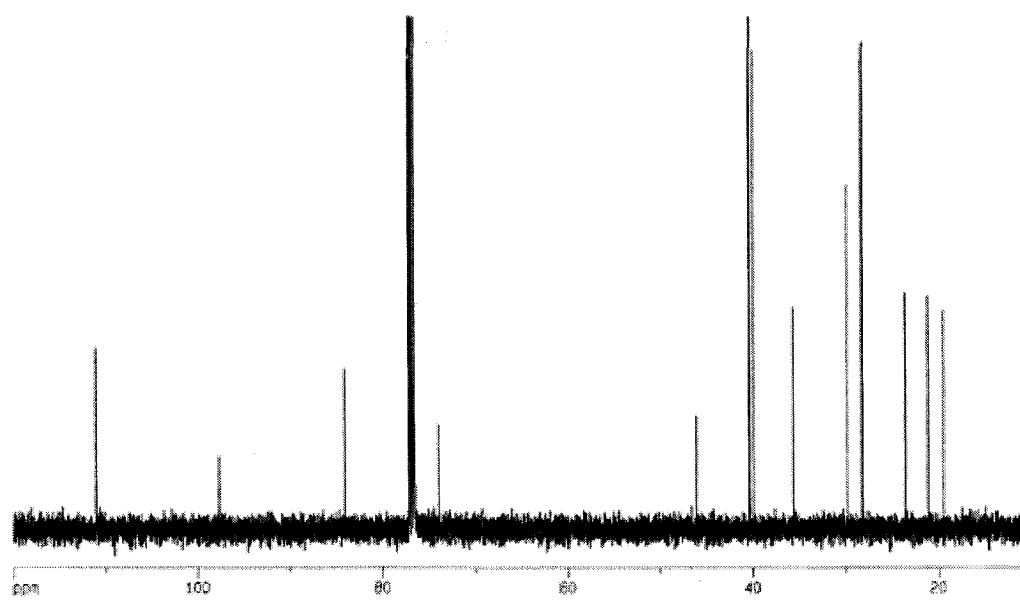


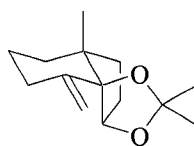
3.143b

^1H NMR (CDCl_3 , 500 MHz)

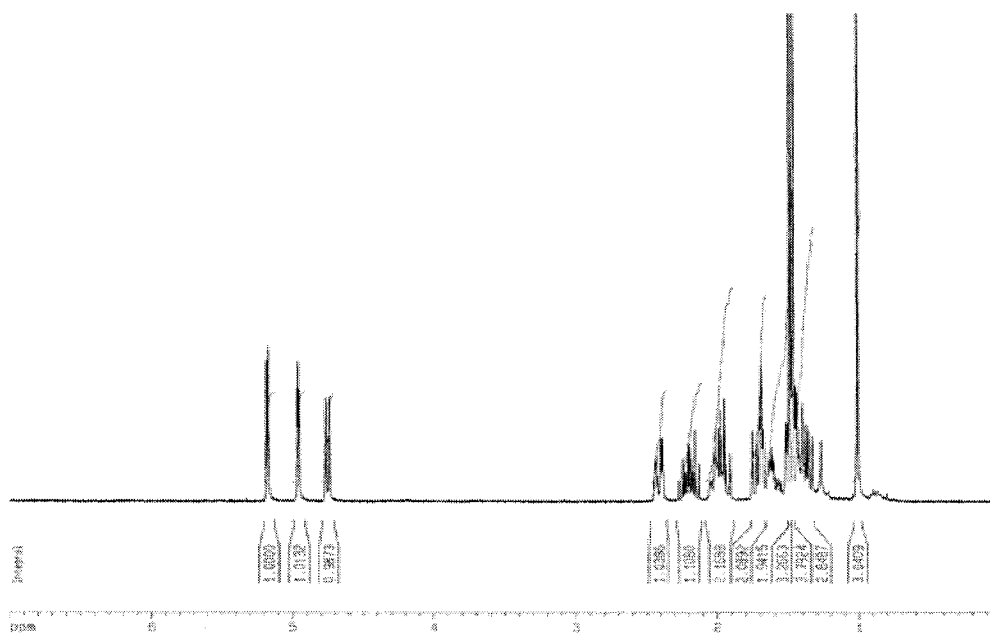


^{13}C NMR (CDCl_3 , 125 MHz)

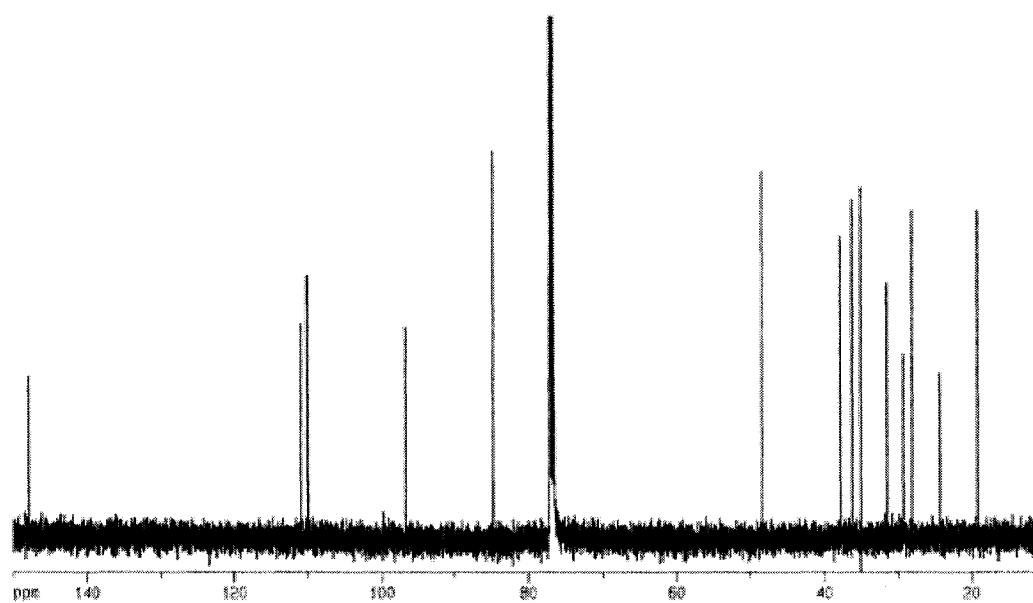


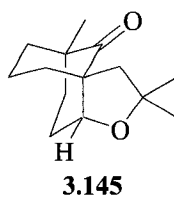
**3.144a**

^1H NMR (CDCl_3 , 300 MHz)

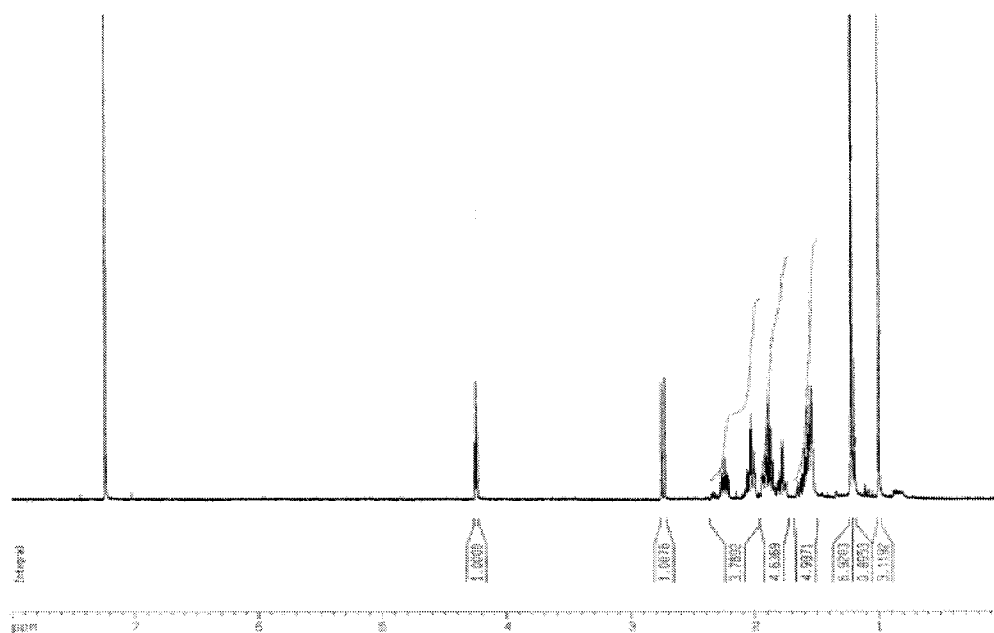


^{13}C NMR (CDCl_3 , 125 MHz)

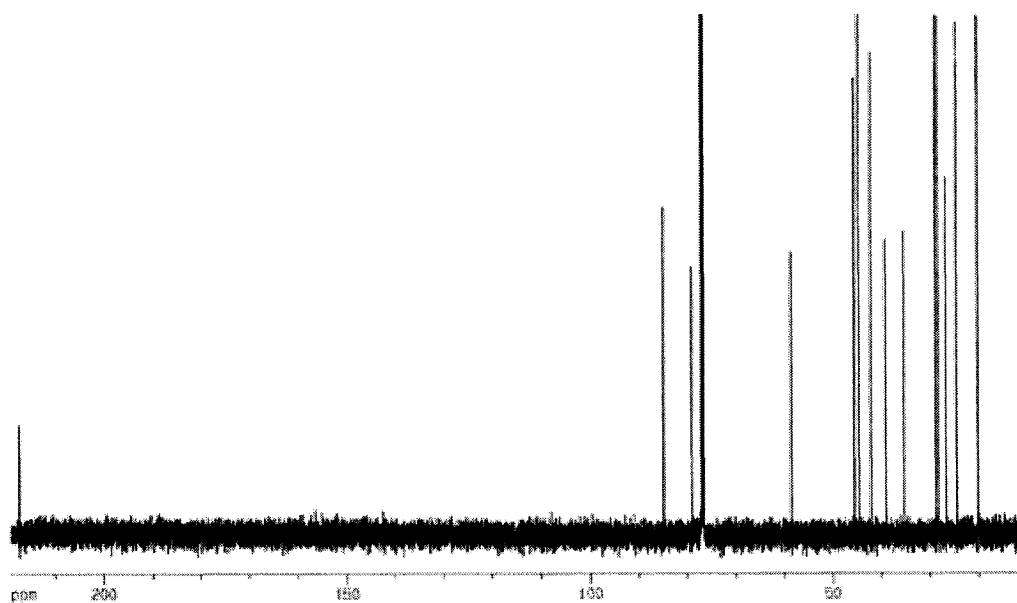


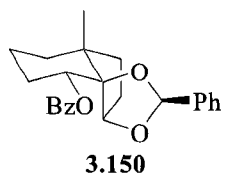


^1H NMR (CDCl_3 , 500 MHz)

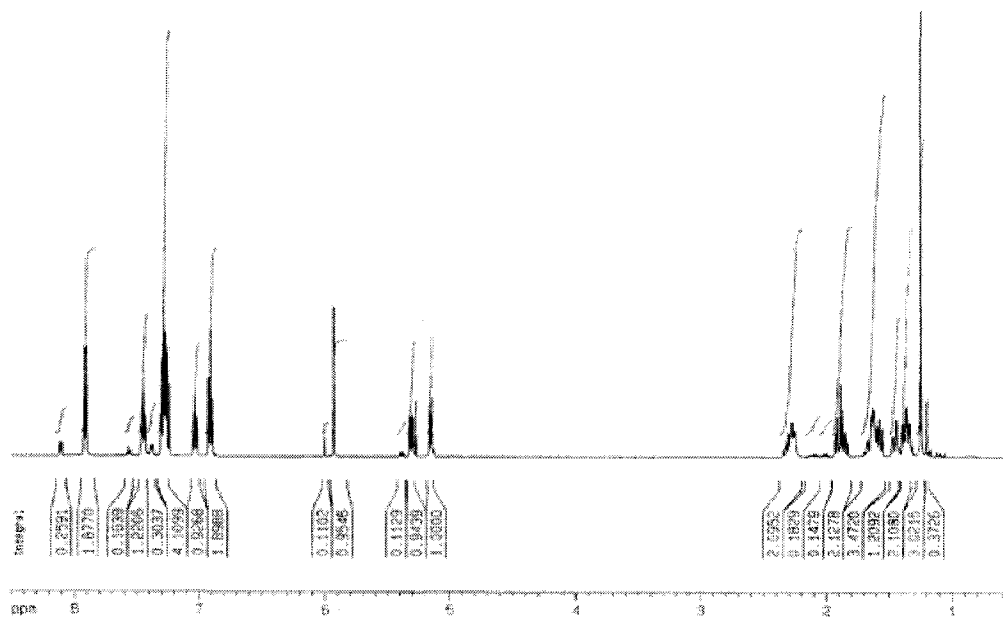


^{13}C NMR (CDCl_3 , 125 MHz)

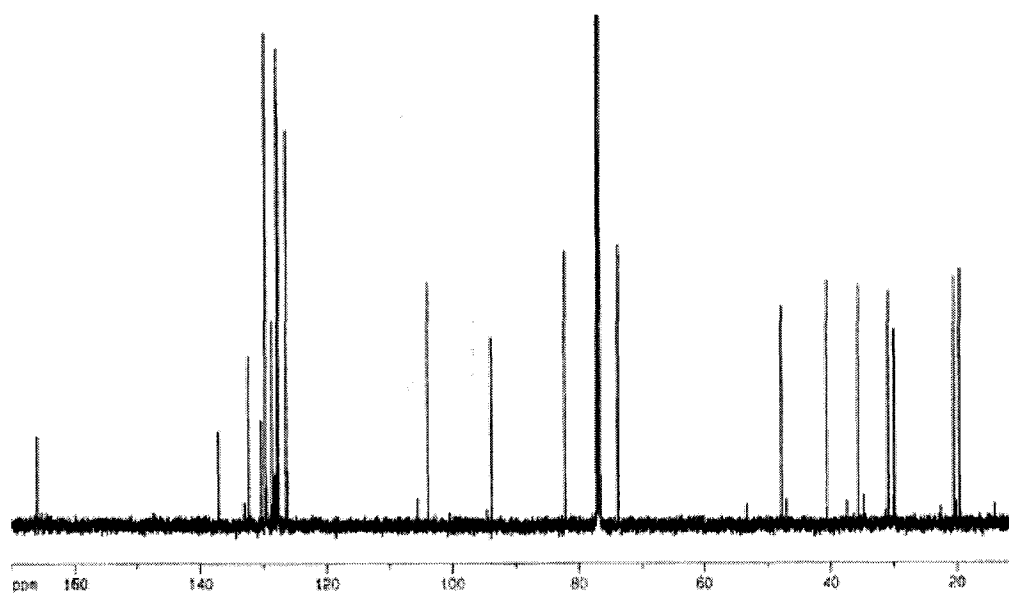


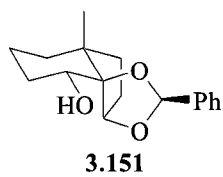


^1H NMR (CDCl_3 , 500 MHz)

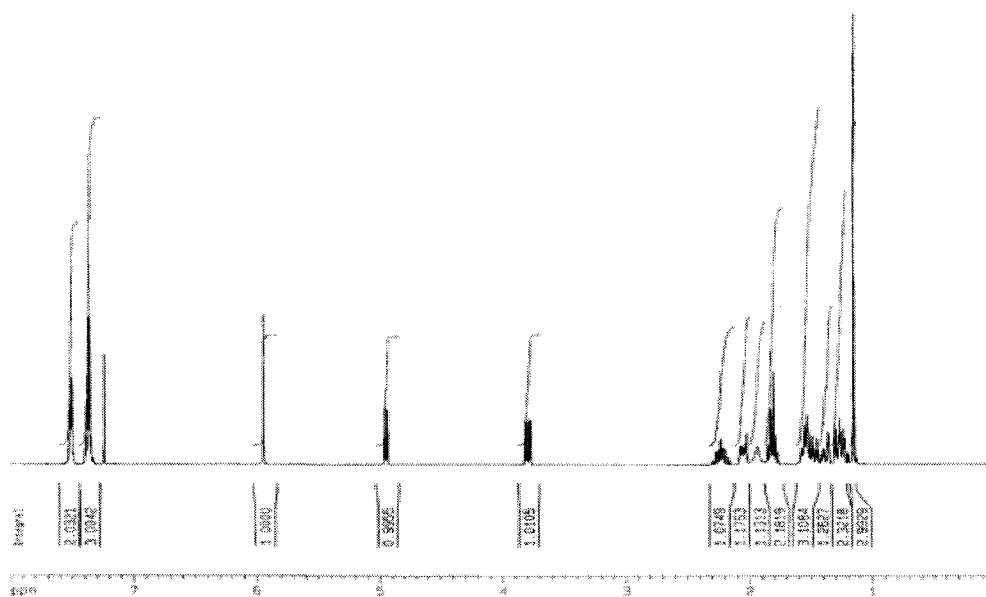


^{13}C NMR (CDCl_3 , 125 MHz)

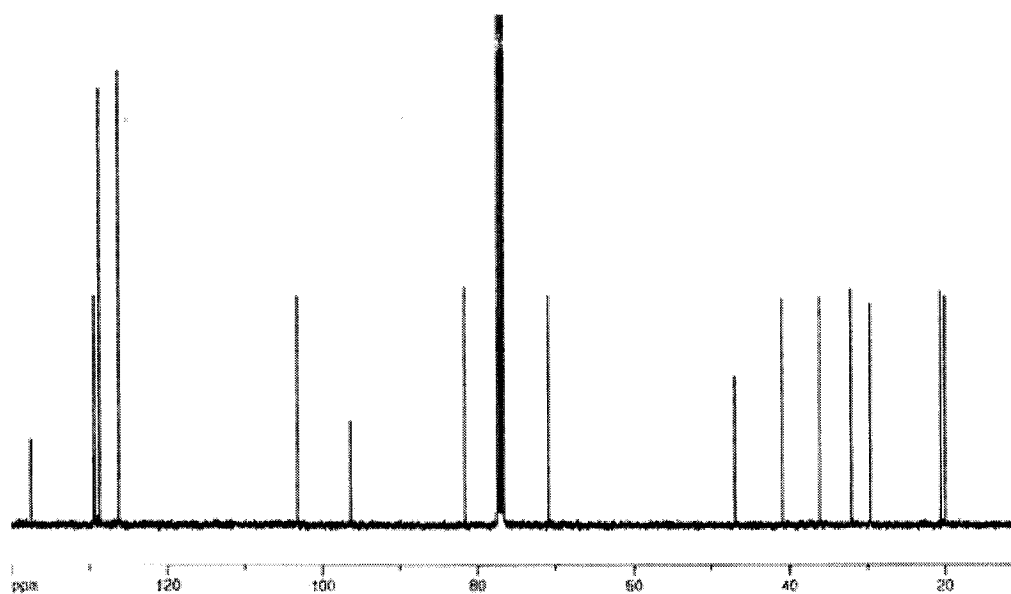


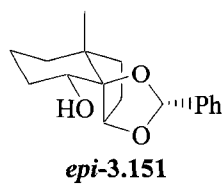


^1H NMR (CDCl_3 , 400 MHz)

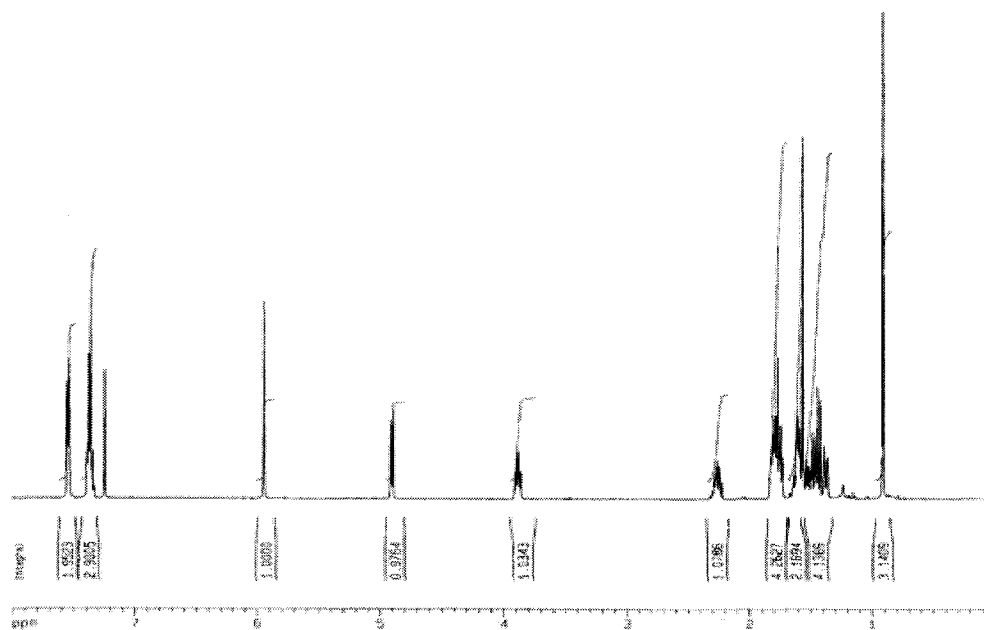


^{13}C NMR (CDCl_3 , 100 MHz)

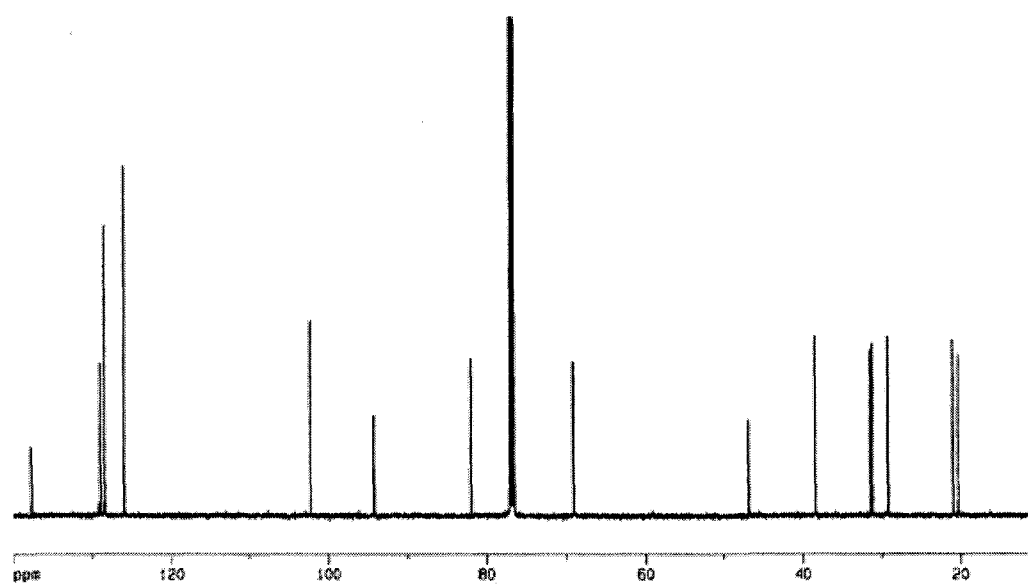


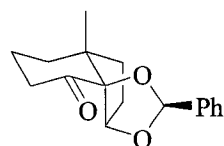


^1H NMR (CDCl_3 , 500 MHz)

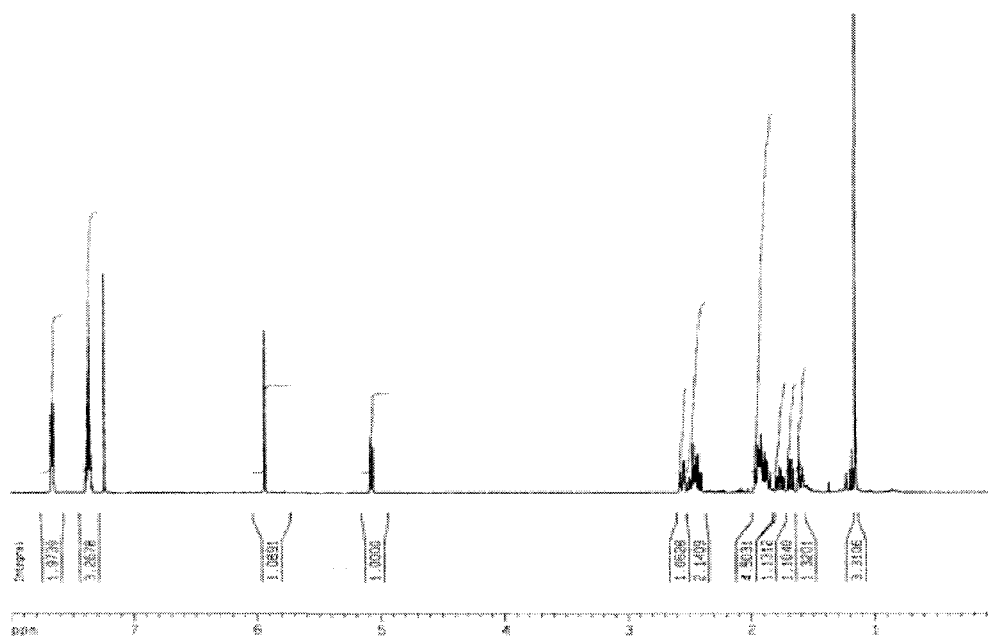
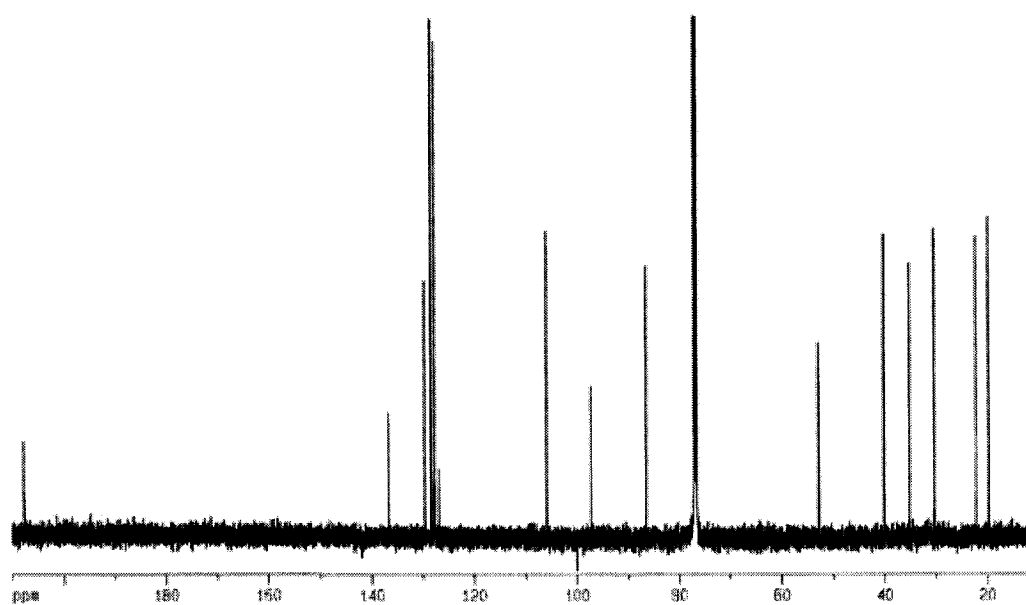


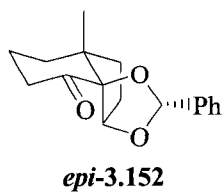
^{13}C NMR (CDCl_3 , 125 MHz)



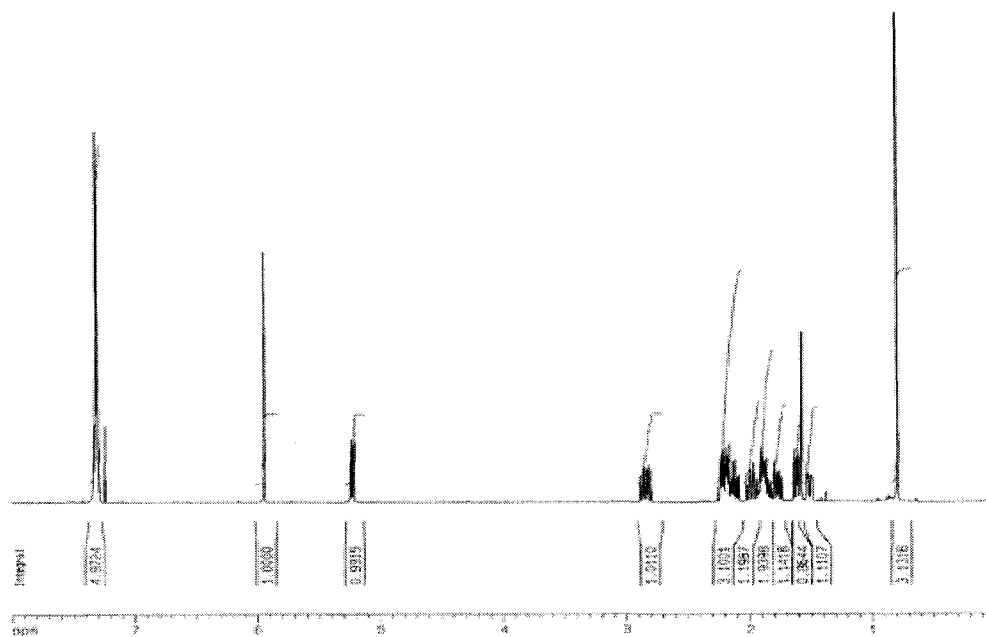


3.152

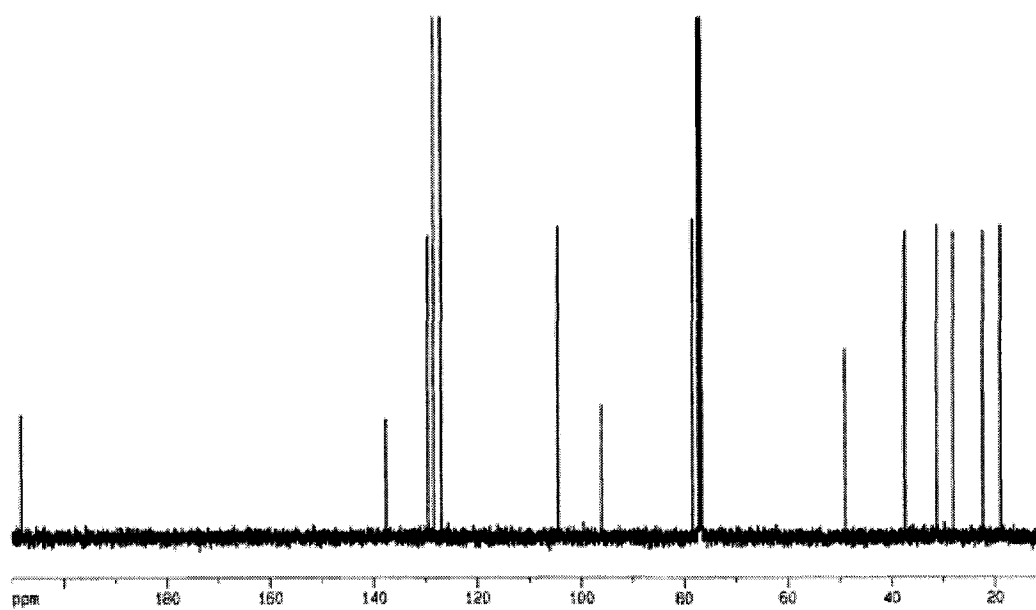
 ^1H NMR (CDCl_3 , 500 MHz) ^{13}C NMR (CDCl_3 , 125 MHz)

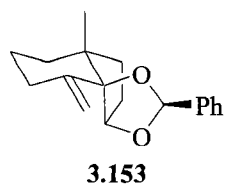


^1H NMR (CDCl_3 , 400 MHz)

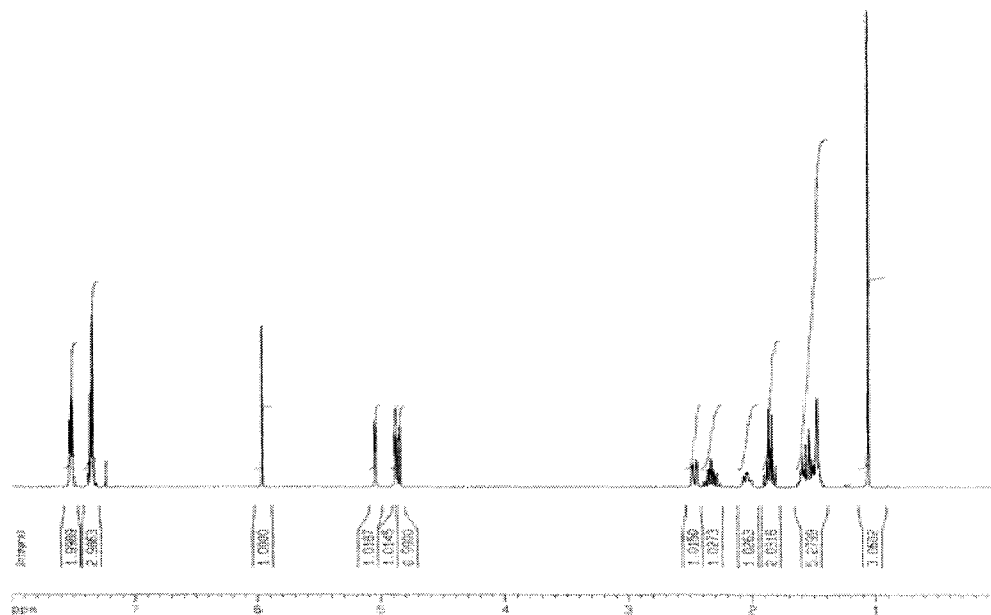


^{13}C NMR (CDCl_3 , 100 MHz)

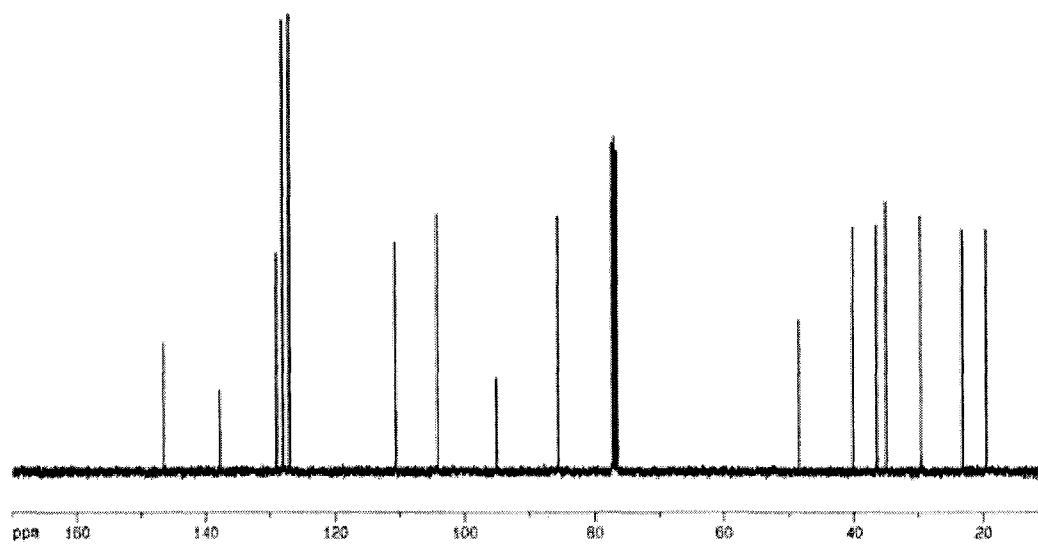


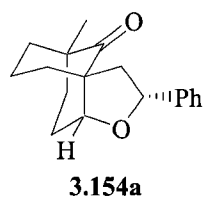


^1H NMR (CDCl_3 , 400 MHz)

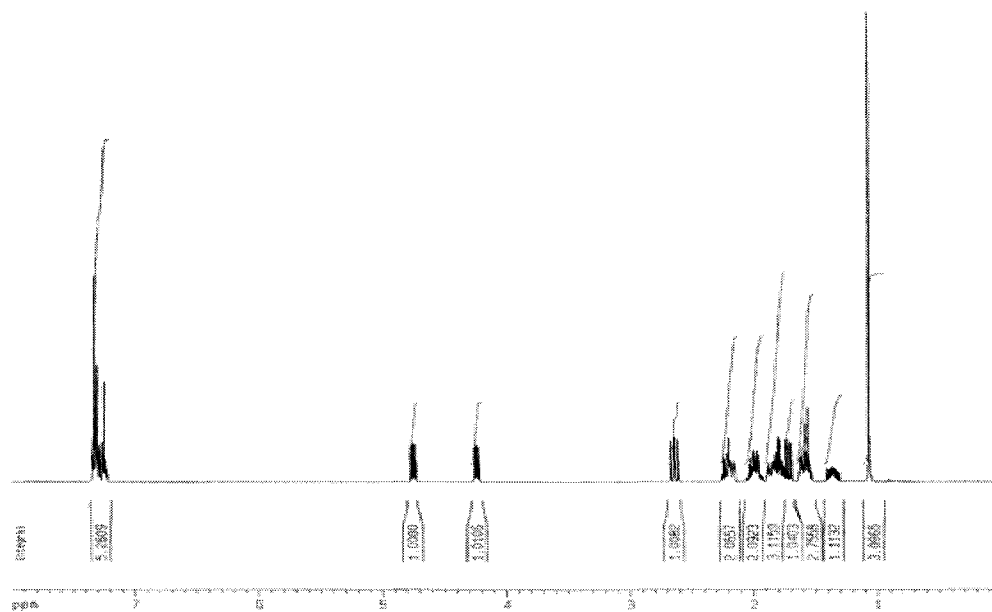


^{13}C NMR (CDCl_3 , 100 MHz)

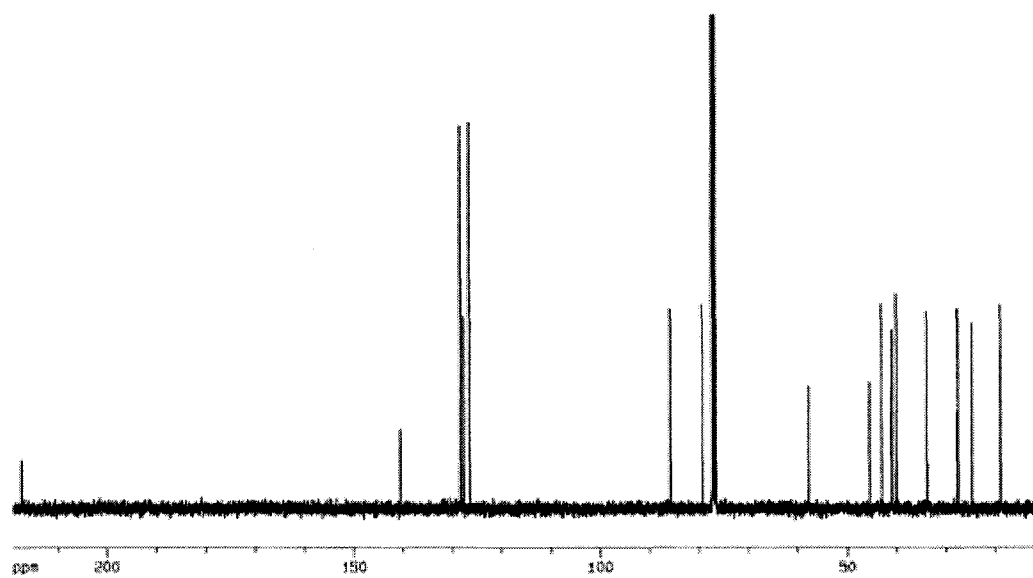


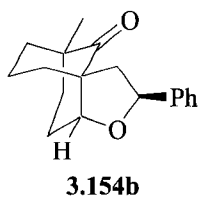


^1H NMR (CDCl_3 , 400 MHz)

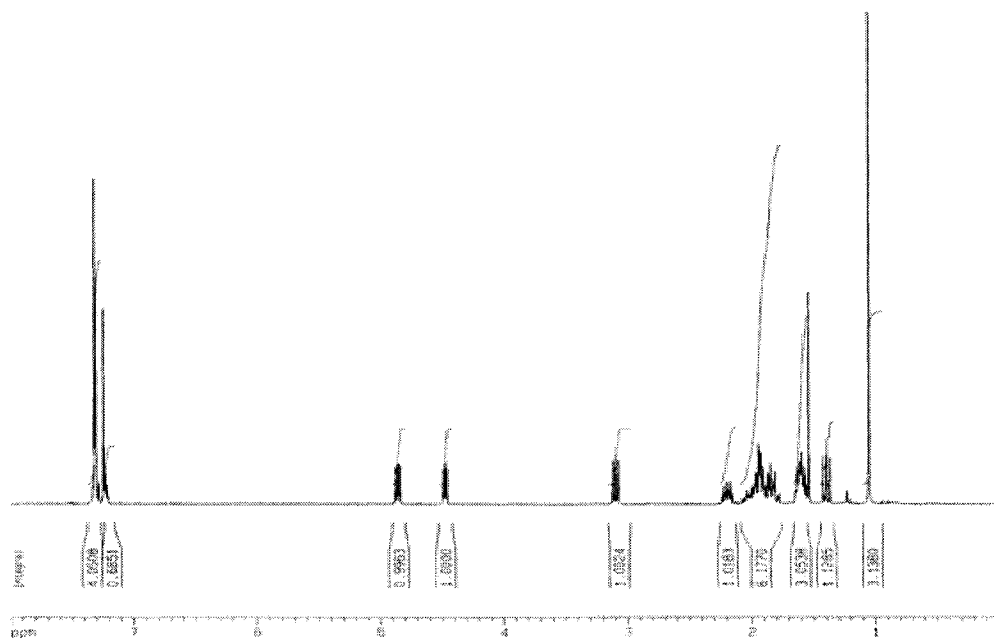


^{13}C NMR (CDCl_3 , 100 MHz)

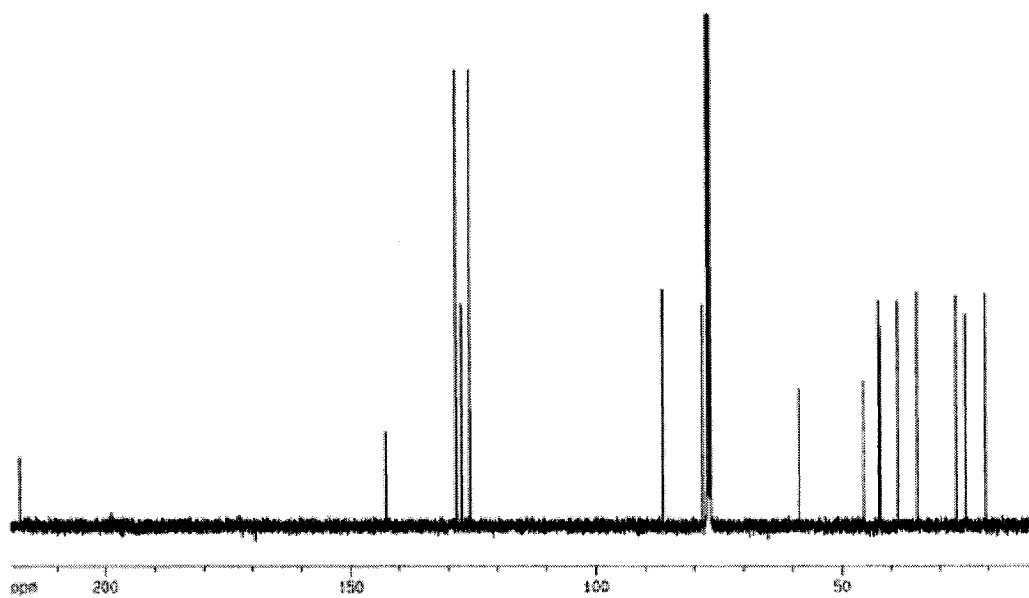


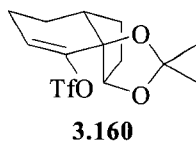


^1H NMR (CDCl_3 , 400 MHz)

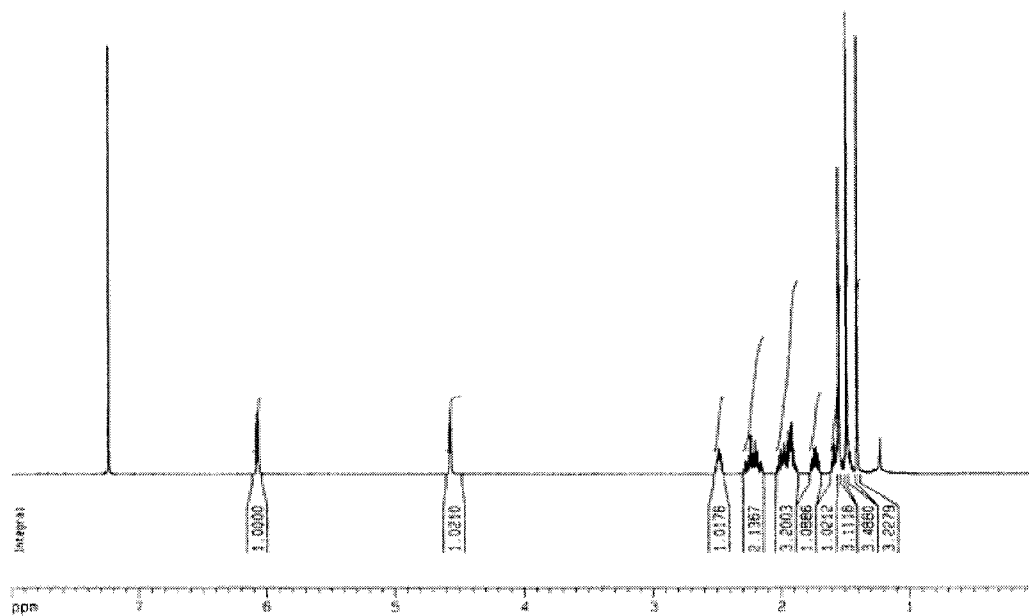


^{13}C NMR (CDCl_3 , 100 MHz)

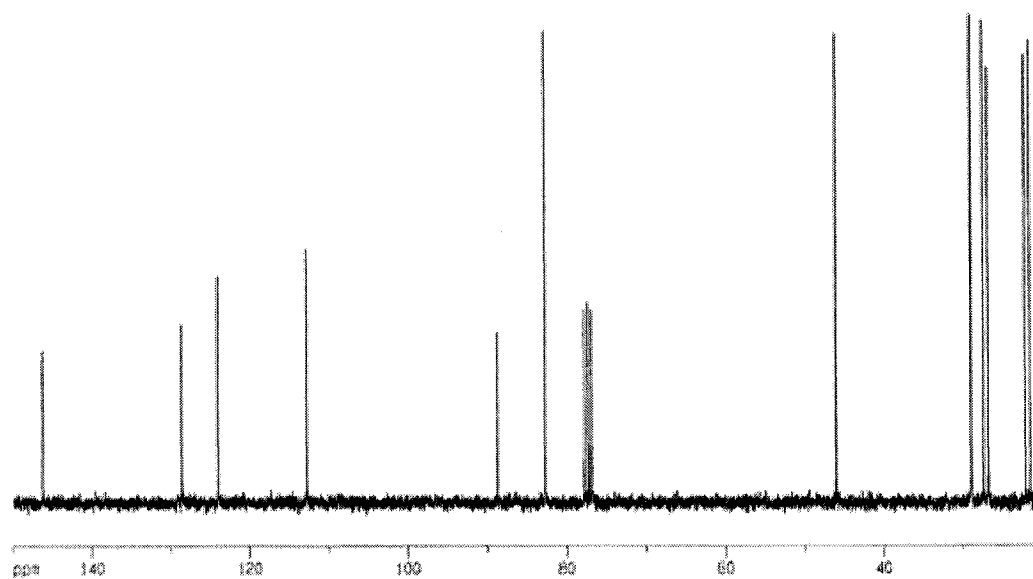


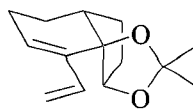


^1H NMR (CDCl_3 , 500 MHz)

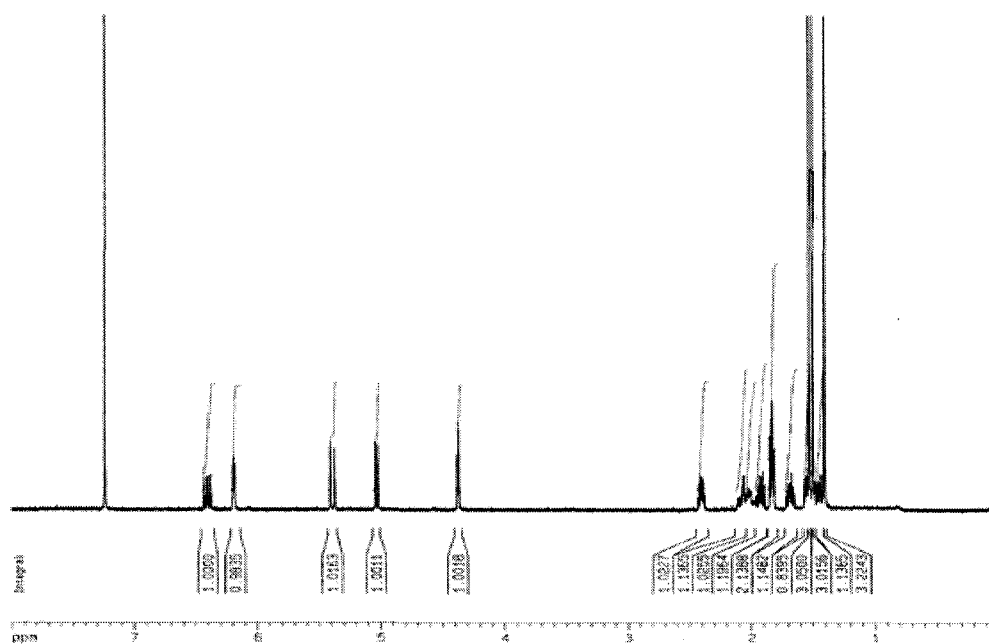
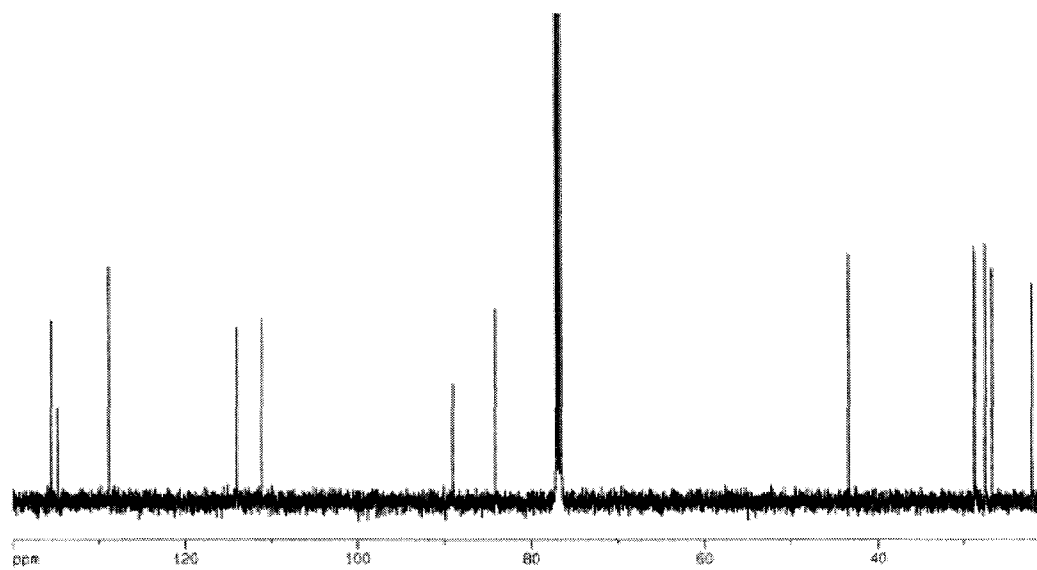


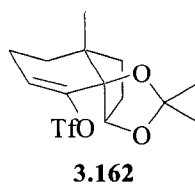
^{13}C NMR (CDCl_3 , 75 MHz)



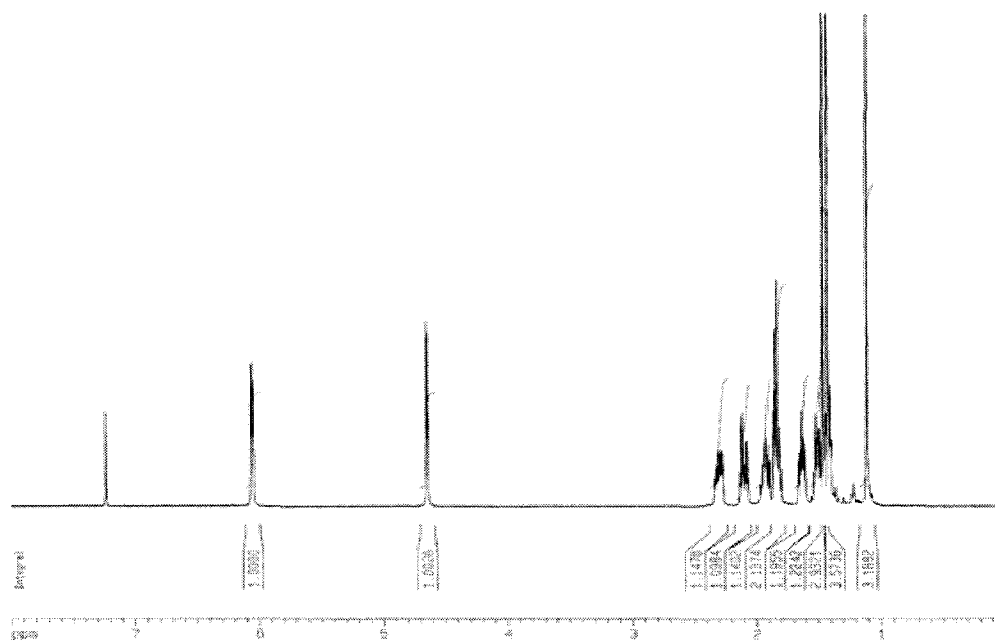


3.161

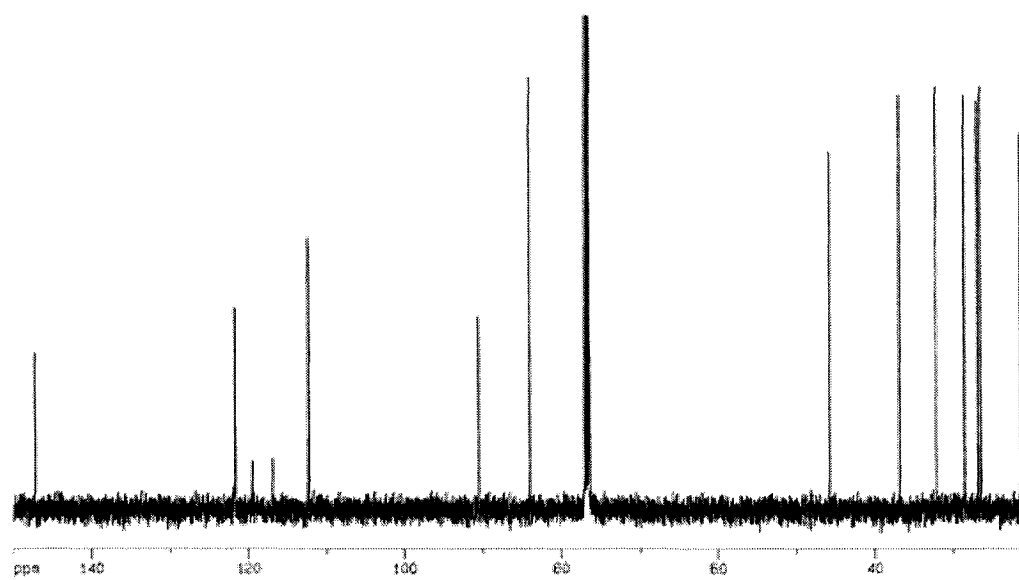
 ^1H NMR (CDCl_3 , 500 MHz) ^{13}C NMR (CDCl_3 , 125 MHz)

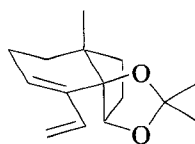


^1H NMR (CDCl_3 , 500 MHz)



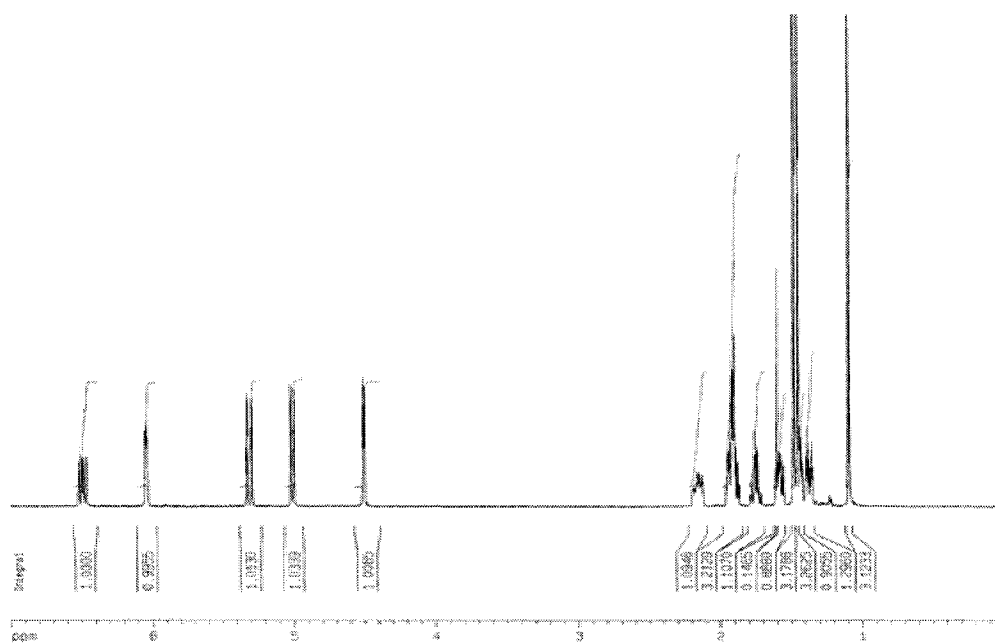
^{13}C NMR (CDCl_3 , 125 MHz)



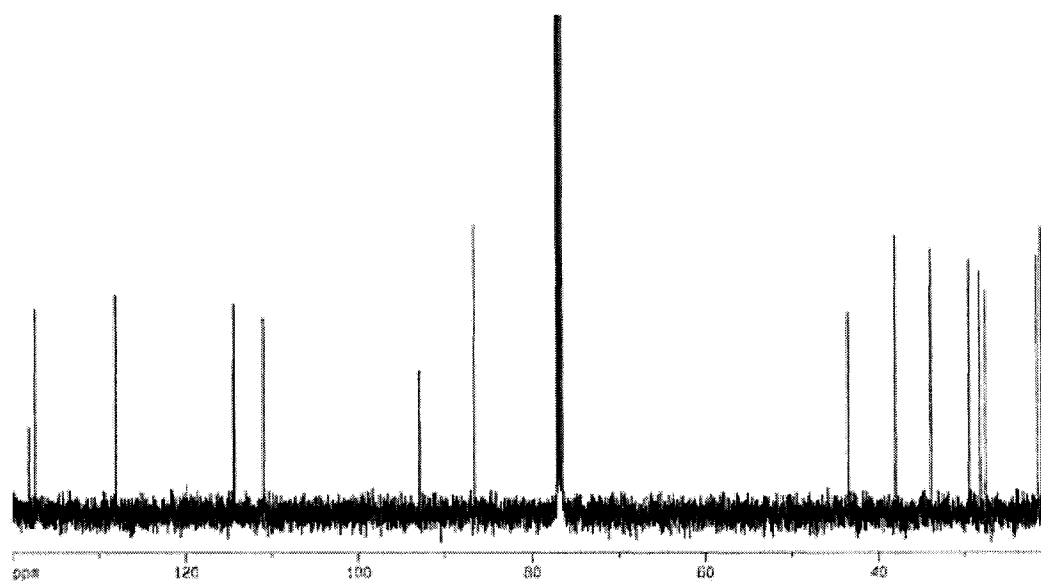


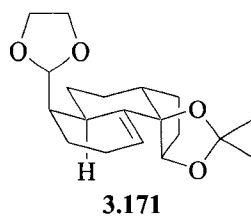
3.163

^1H NMR (CDCl_3 , 500 MHz)

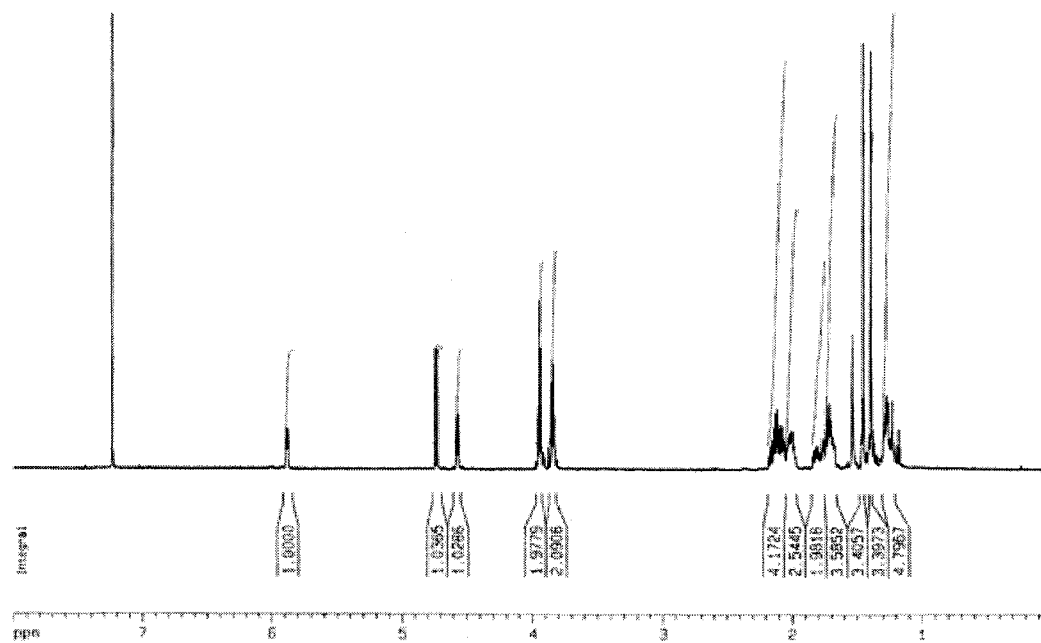


^{13}C NMR (CDCl_3 , 125 MHz)

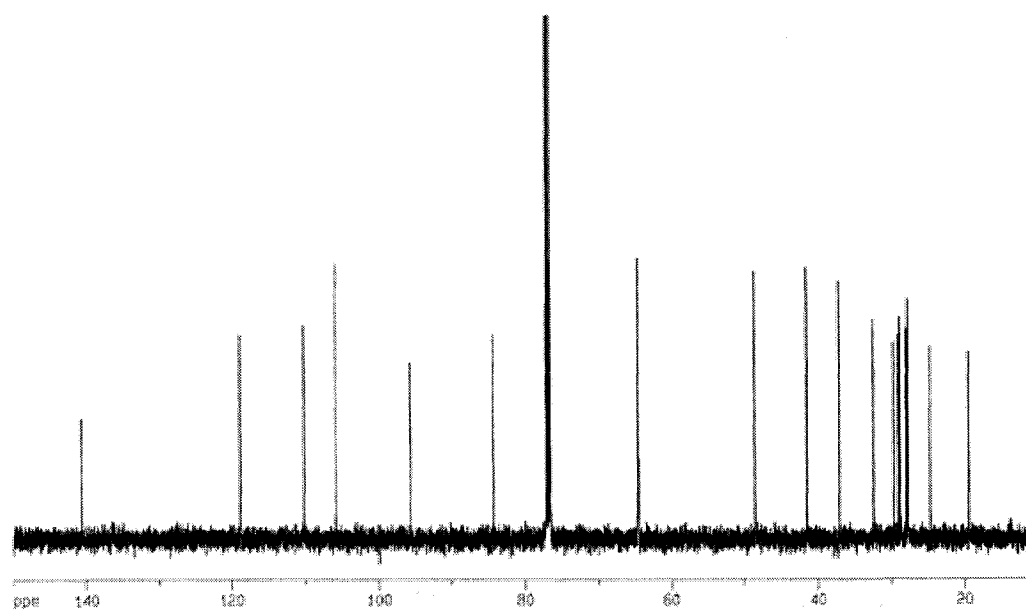


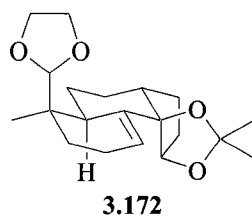


^1H NMR (CDCl_3 , 500 MHz)

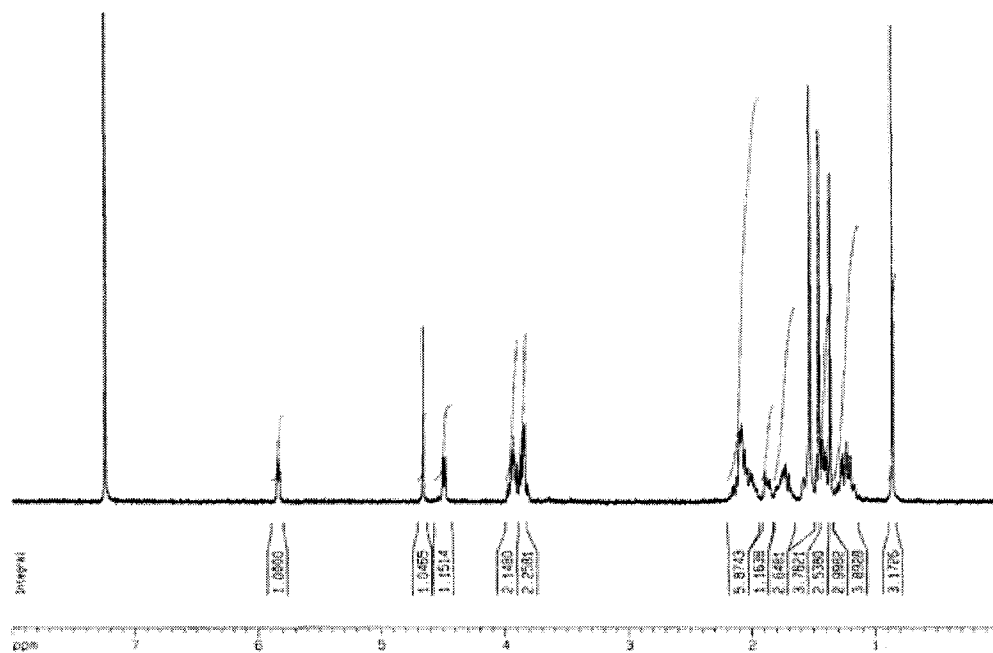


^{13}C NMR (CDCl_3 , 125 MHz)

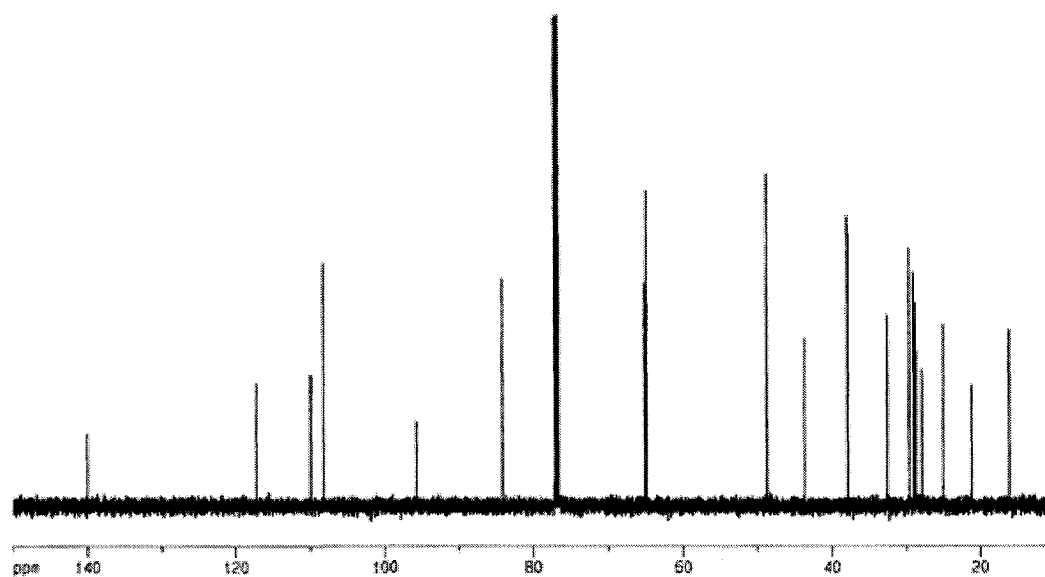


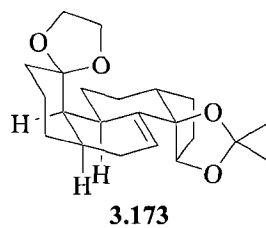


^1H NMR (CDCl_3 , 500 MHz)

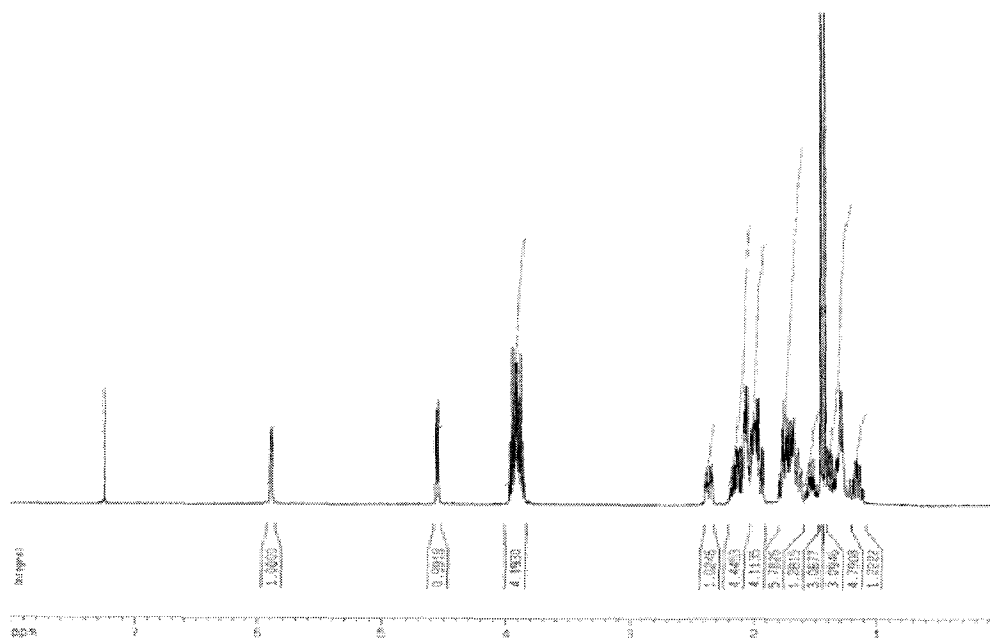


^{13}C NMR (CDCl_3 , 125 MHz)

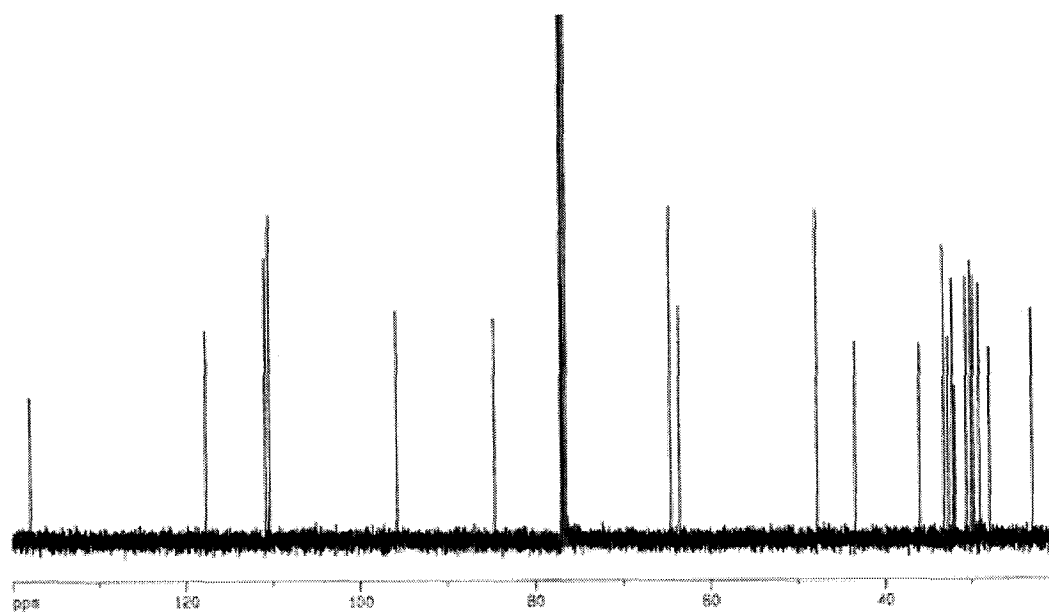


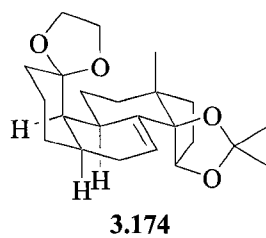


^1H NMR (CDCl_3 , 500 MHz)

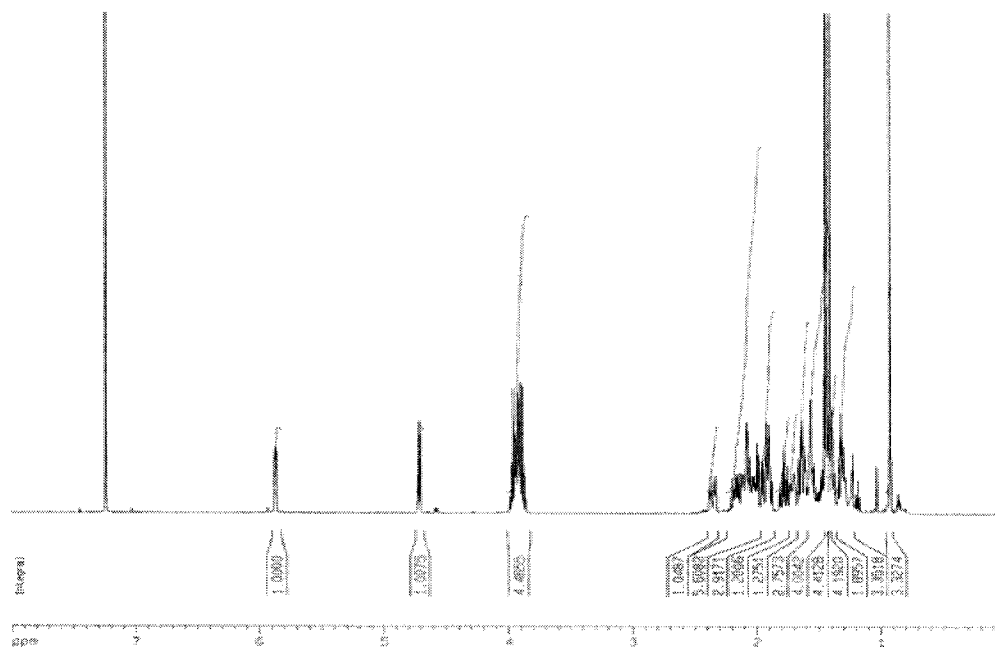


^{13}C NMR (CDCl_3 , 125 MHz)

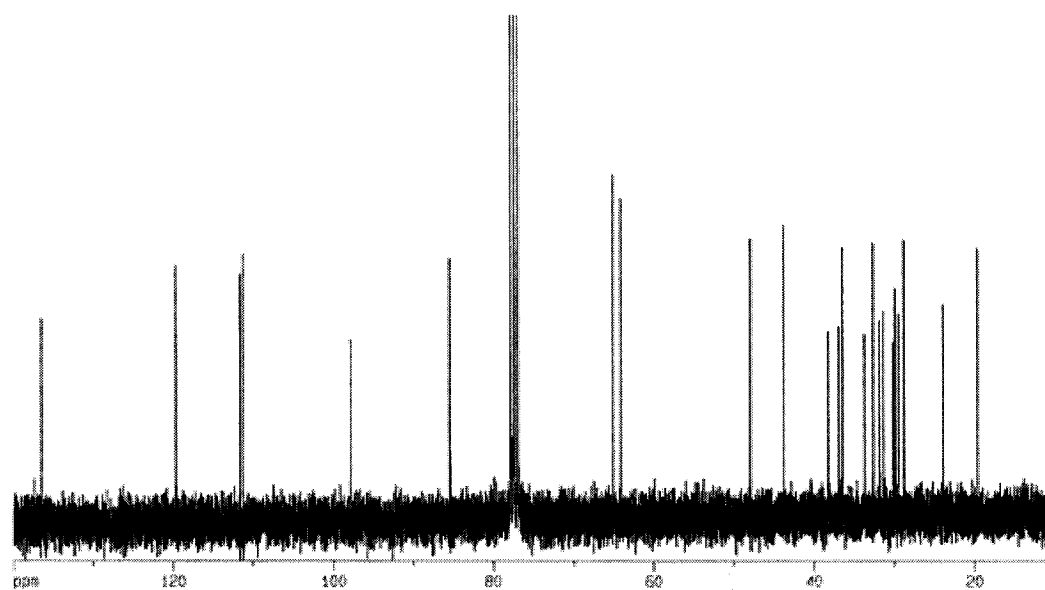




^1H NMR (CDCl_3 , 500 MHz)



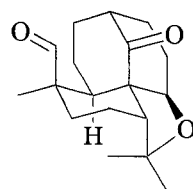
^{13}C NMR (CDCl_3 , 75 MHz)



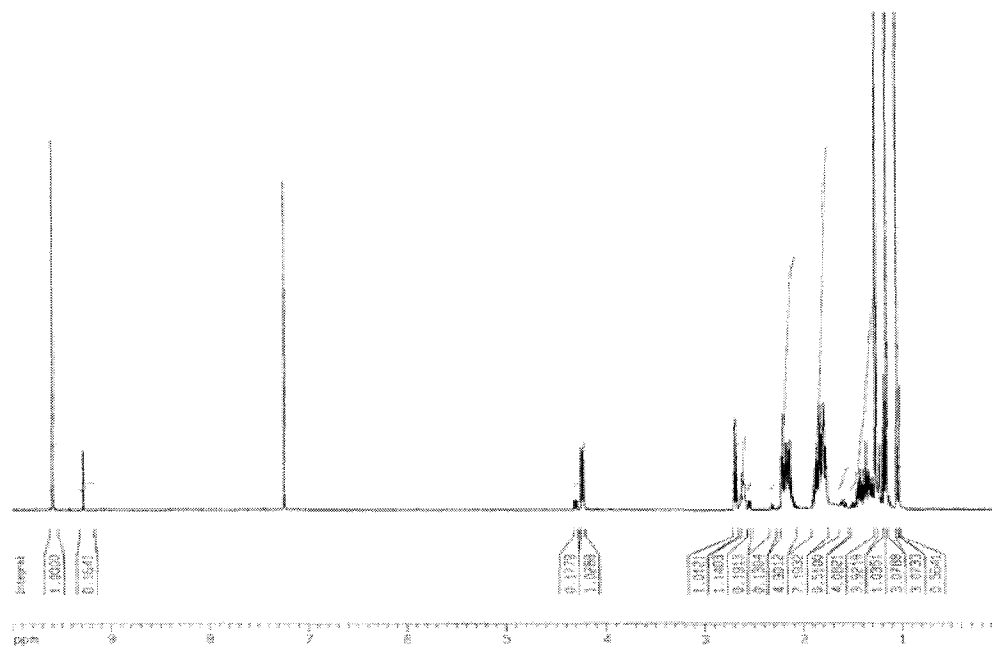
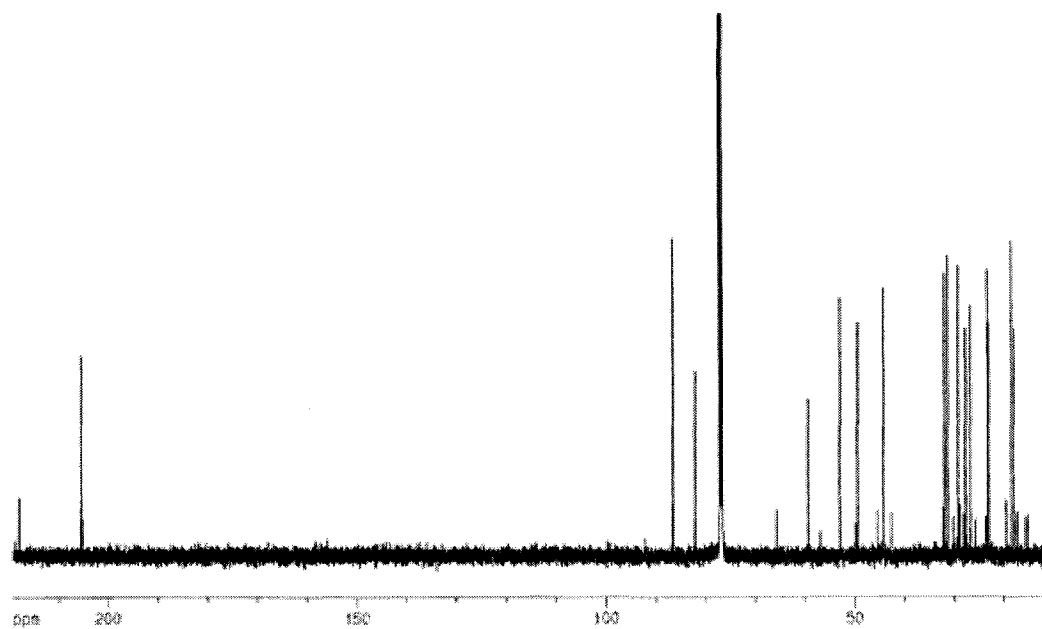


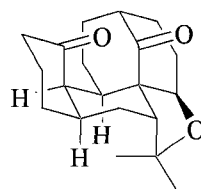
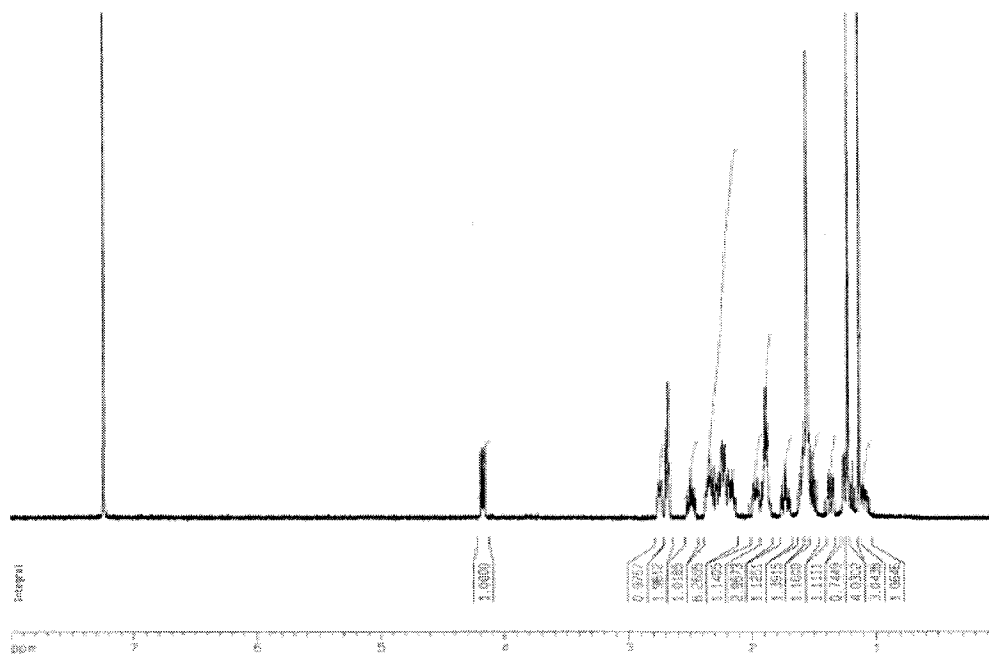
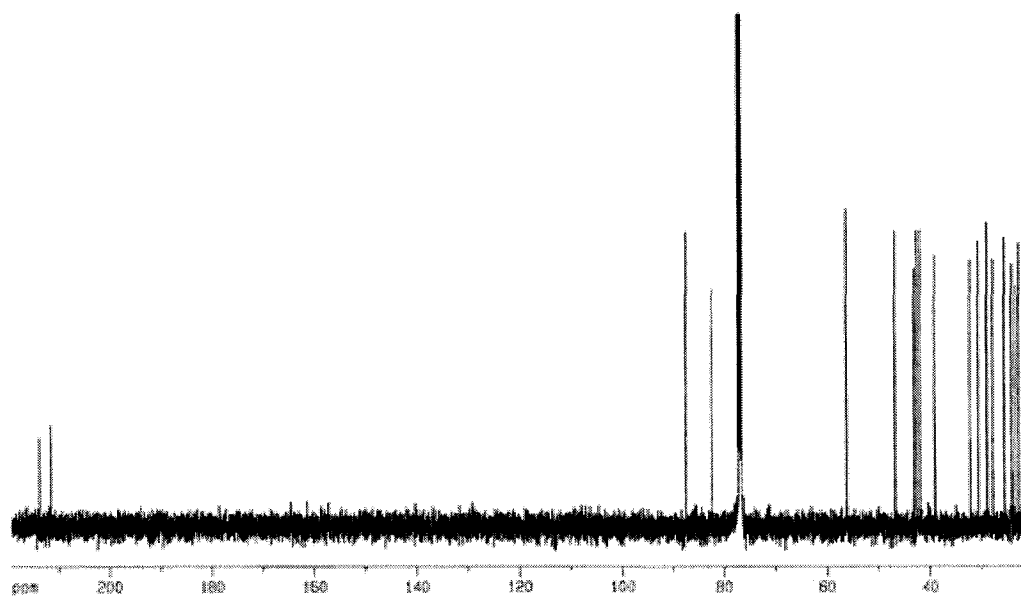
¹H NMR spectrum of compound 10 in CDCl₃. The spectrum shows several peaks in the aromatic region (6.5-7.5 ppm), a small peak at 4.7 ppm, and a large multiplet in the aliphatic region (1.2-2.0 ppm). Integration values are provided below the peaks.

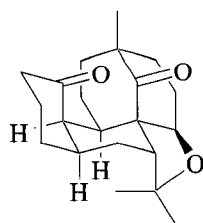
Chemical Shift (ppm)	Integration
7.45	1.000
7.35	0.998
6.55	5.1887
6.50	1.0711
2.00	3.1872
1.85	1.8291
1.75	1.7549
1.65	2.5008
1.55	1.6310
1.45	4.6286
1.35	3.3776
1.25	1.8851
1.15	1.4891
1.05	3.1822
1.00	1.3019



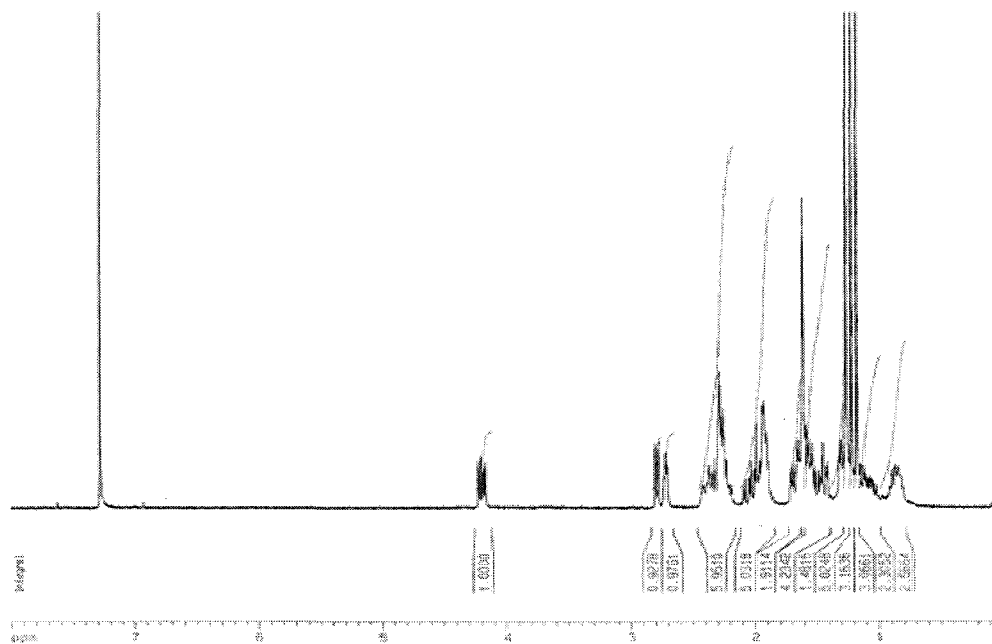
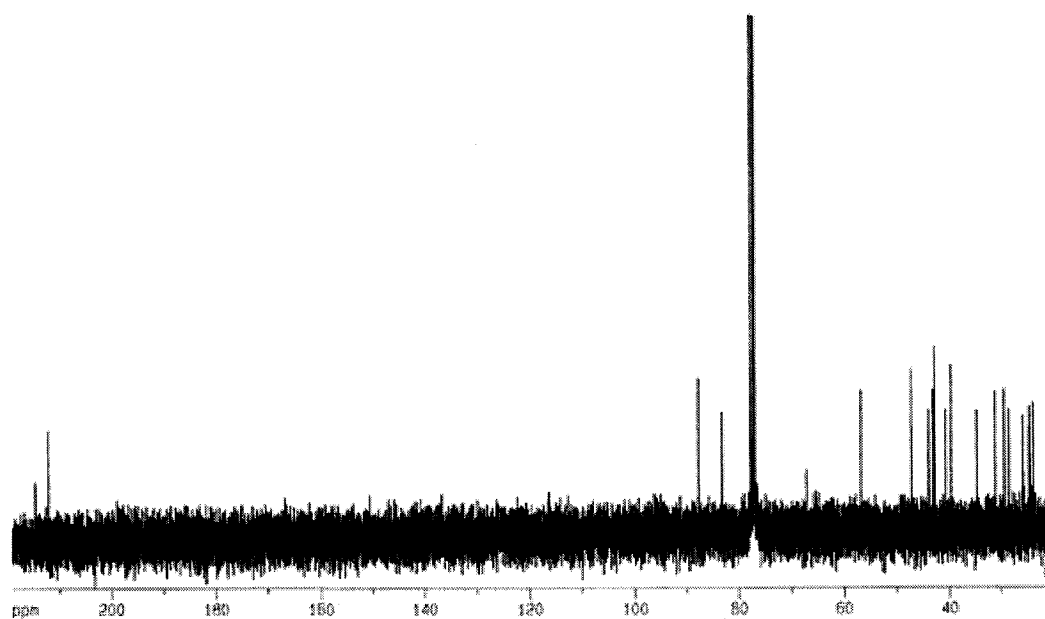
3.179

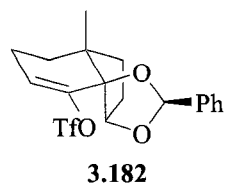
 ^1H NMR (CDCl_3 , 500 MHz) ^{13}C NMR (CDCl_3 , 125 MHz)

**3.180** **^1H NMR (CDCl₃, 500 MHz)** **^{13}C NMR (CDCl₃, 125 MHz)**

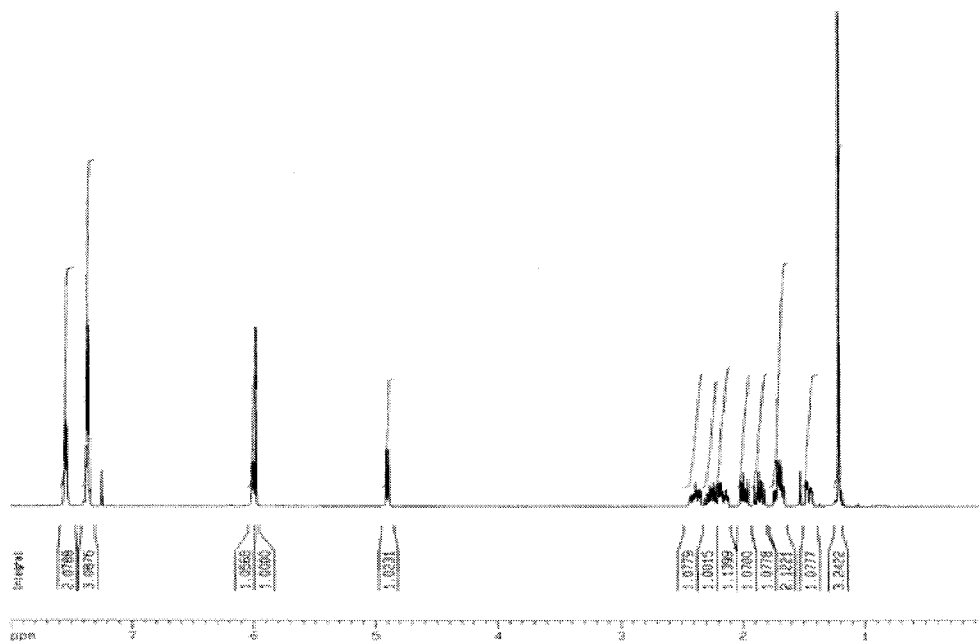


3.181

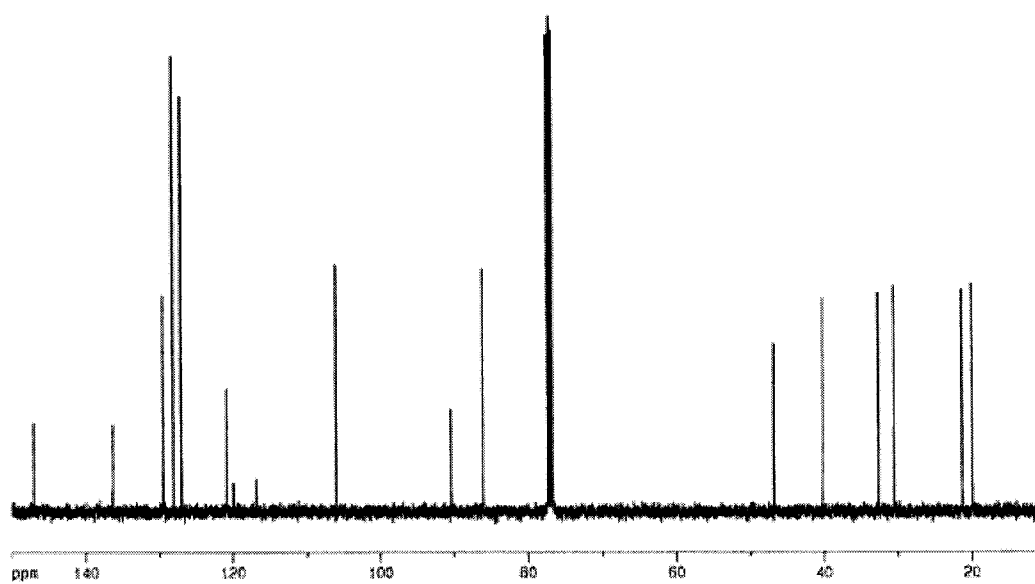
 ^1H NMR (CDCl_3 , 500 MHz) ^{13}C NMR (CDCl_3 , 75 MHz)

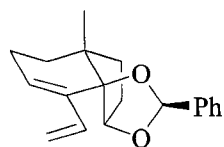


^1H NMR (CDCl_3 , 400 MHz)

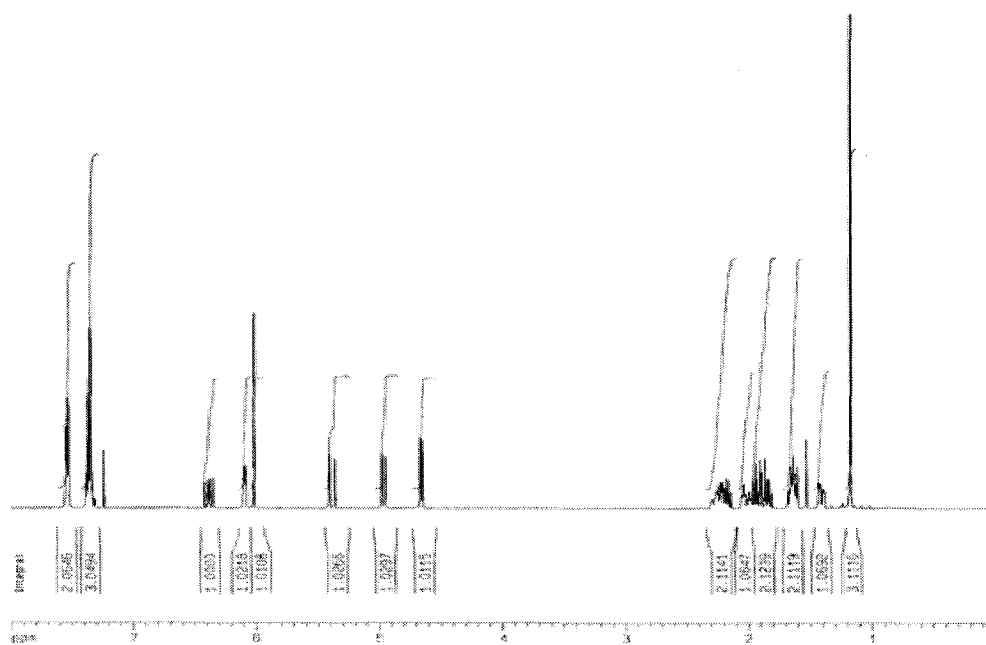
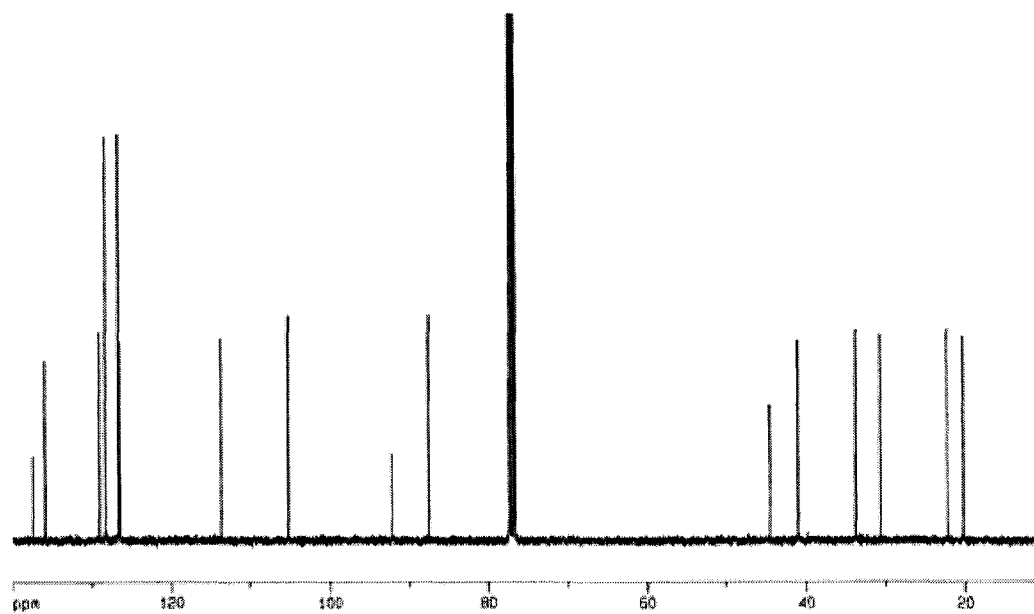


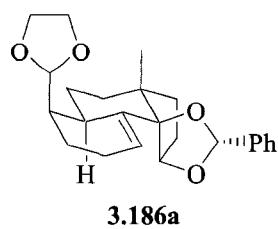
^{13}C NMR (CDCl_3 , 100 MHz)



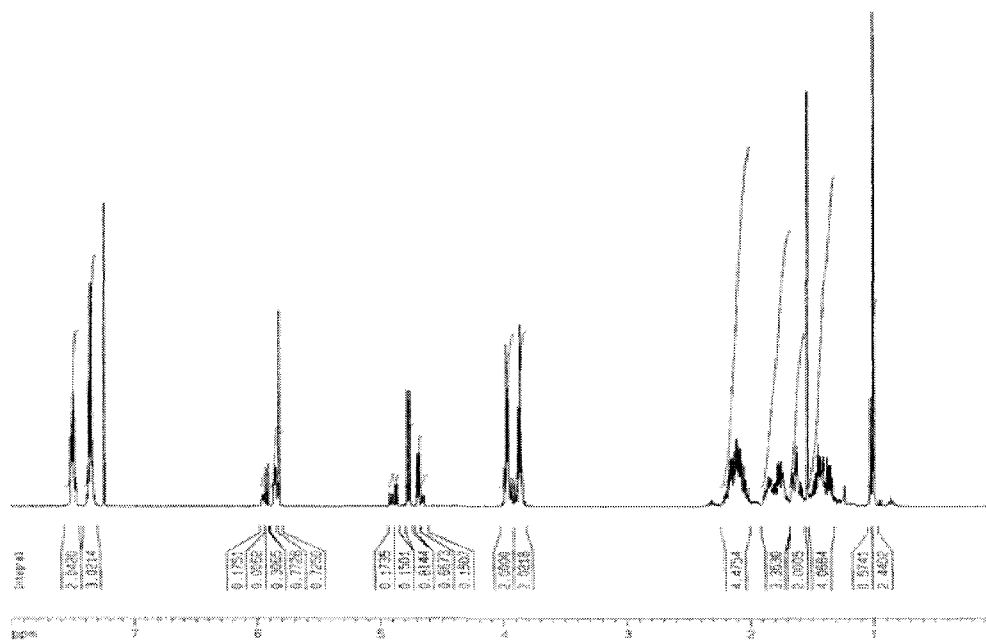


3.183

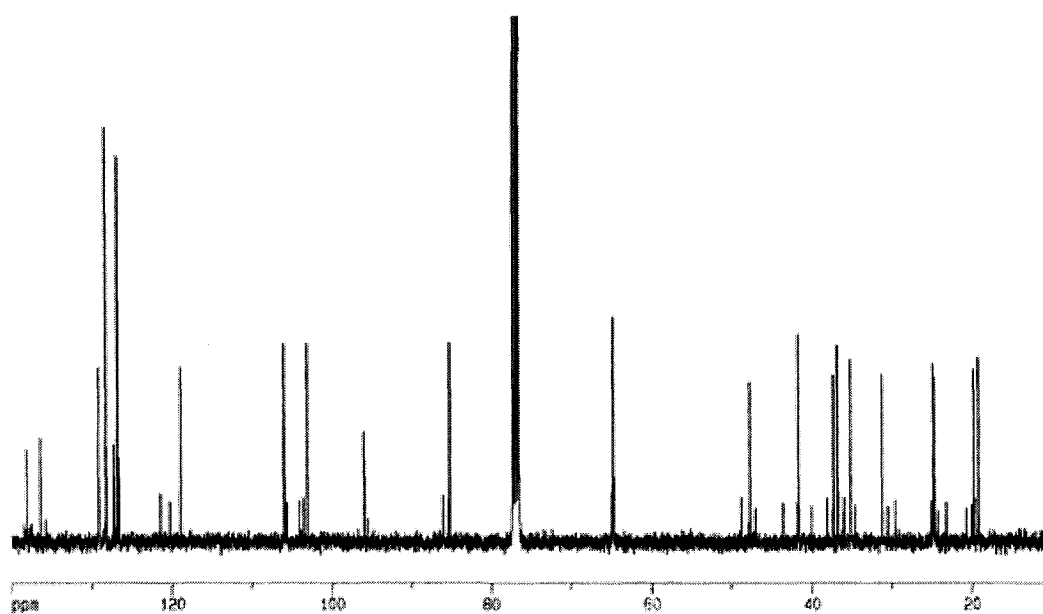
 ^1H NMR (CDCl_3 , 400 MHz) ^{13}C NMR (CDCl_3 , 100 MHz)

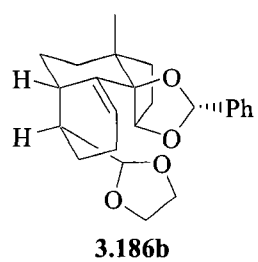


^1H NMR (CDCl_3 , 400 MHz)

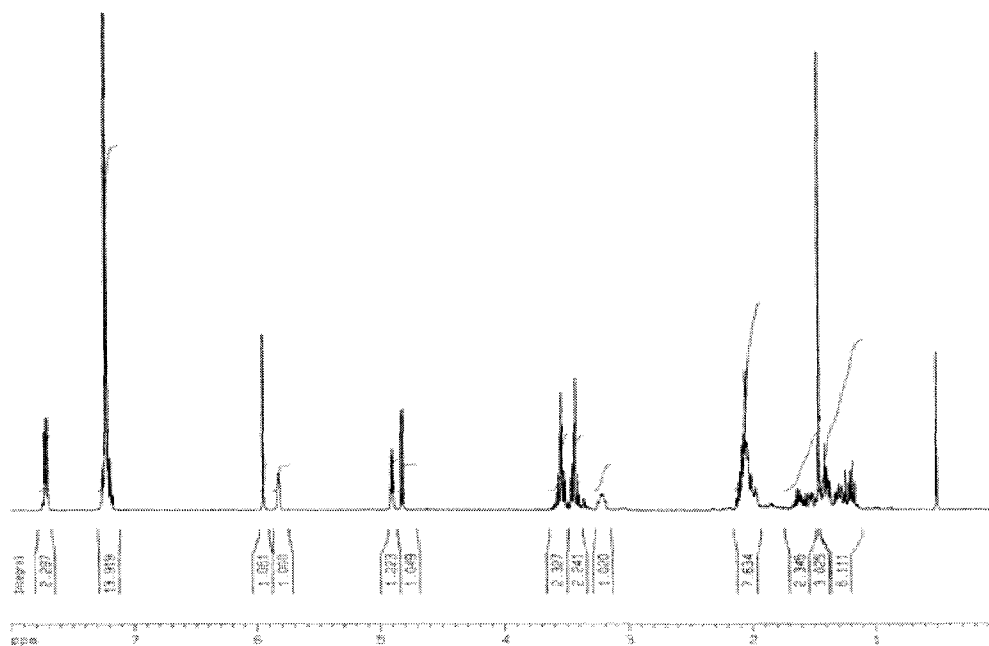


^{13}C NMR (CDCl_3 , 100 MHz)

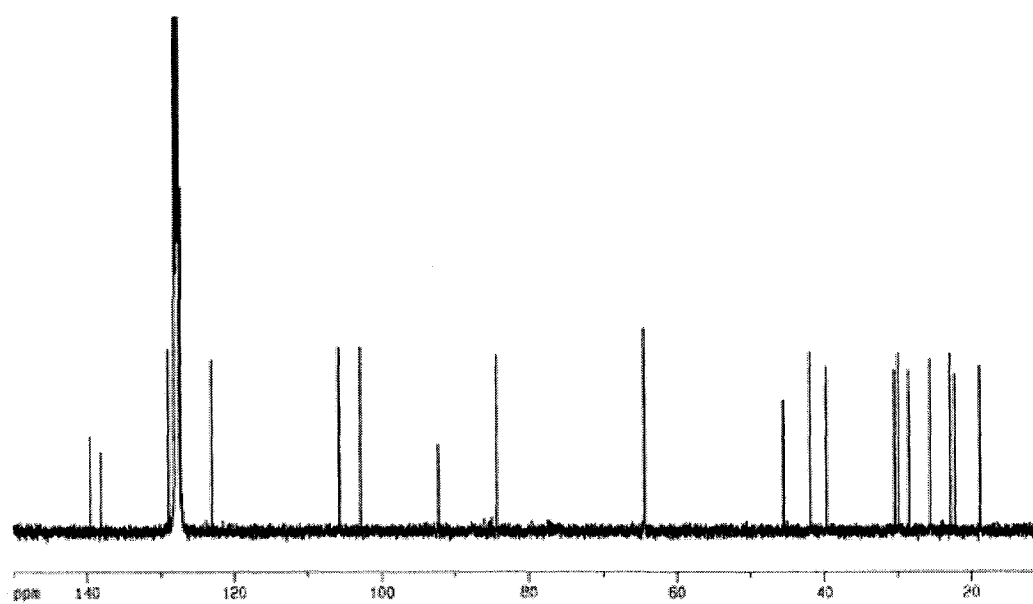


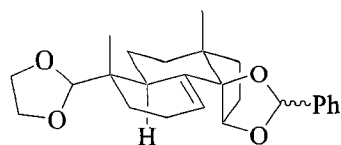


^1H NMR (C_6D_6 , 400 MHz)

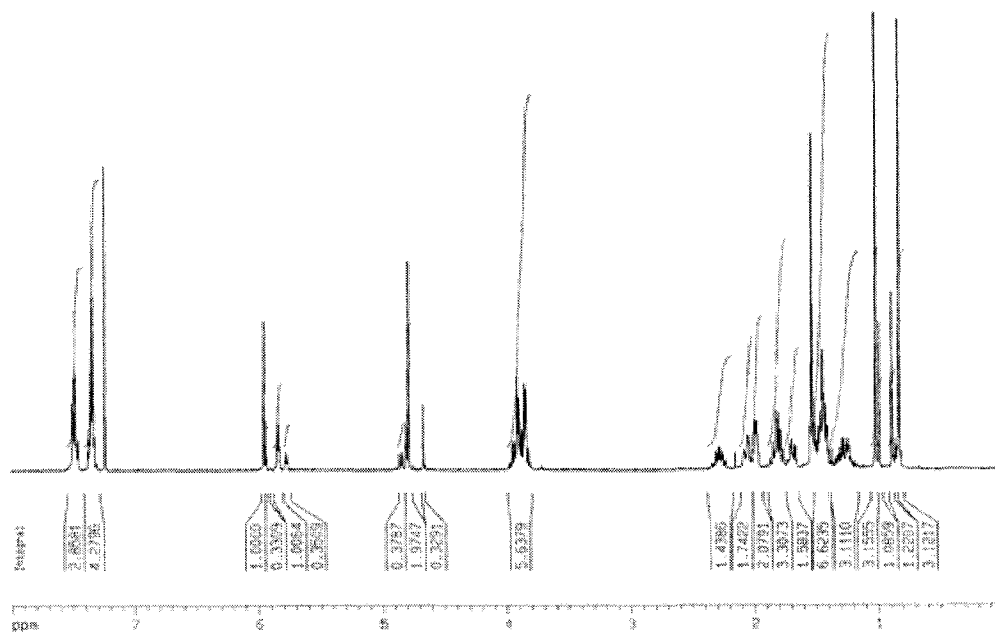


^{13}C NMR (C_6D_6 , 100 MHz)

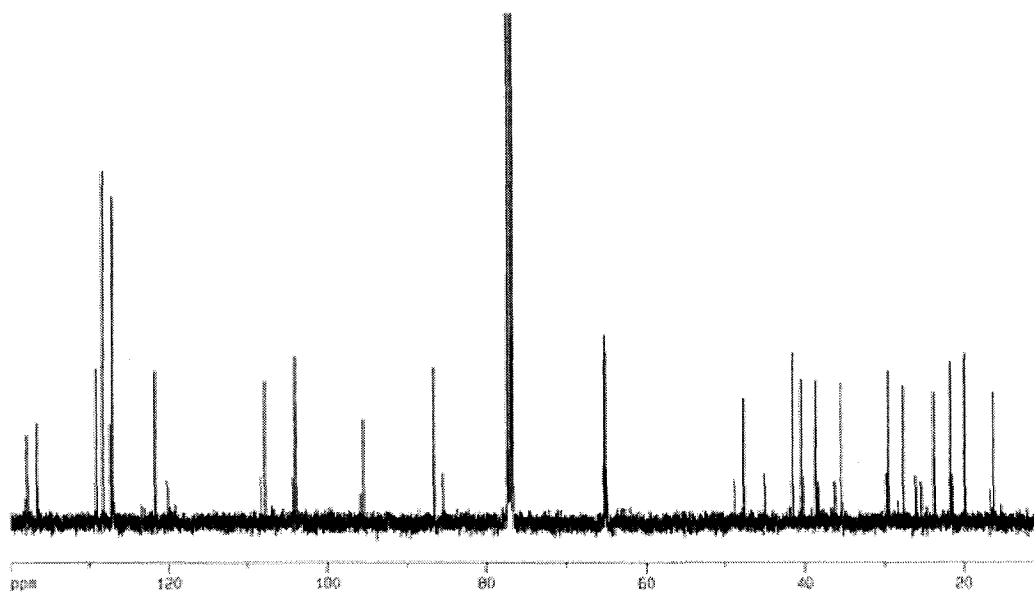


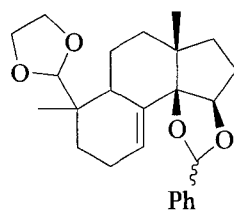
**3.187a**

¹H NMR (CDCl₃, 400 MHz)

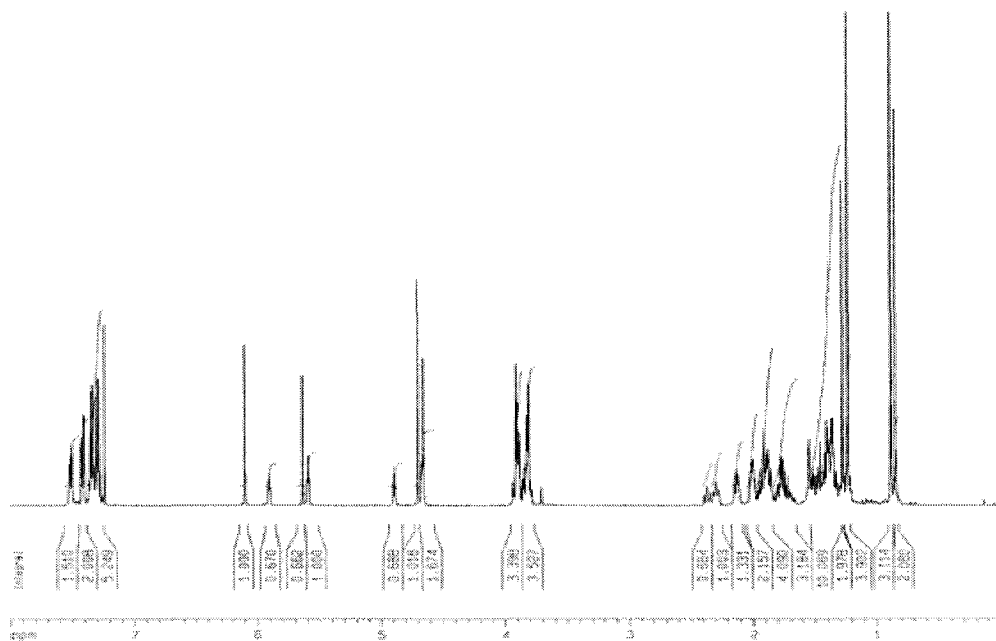


¹³C NMR (CDCl₃, 100 MHz)

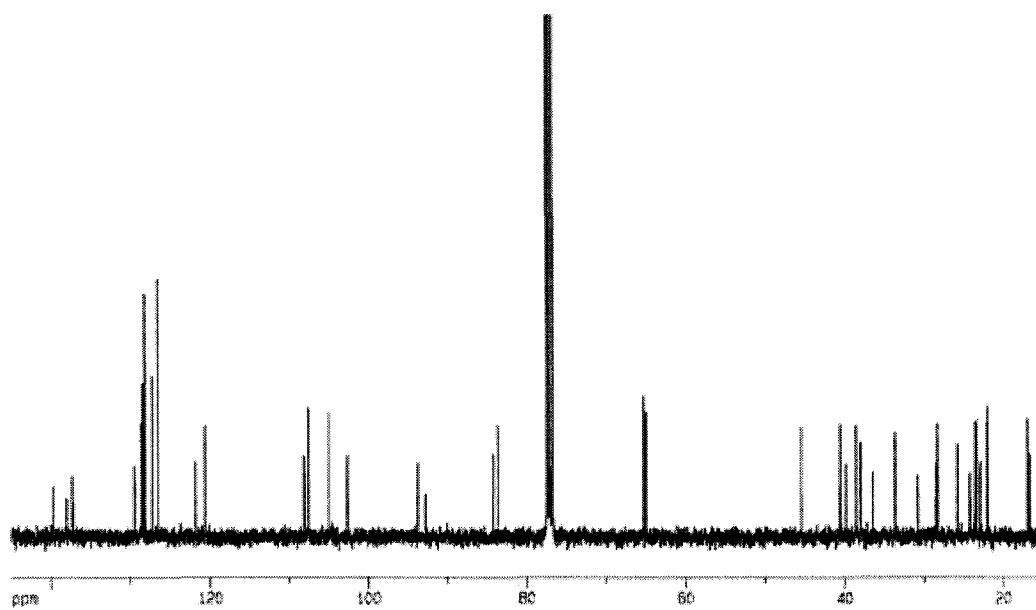


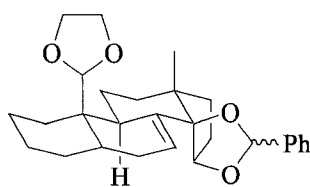
**3.187b**

^1H NMR (CDCl_3 , 400 MHz)

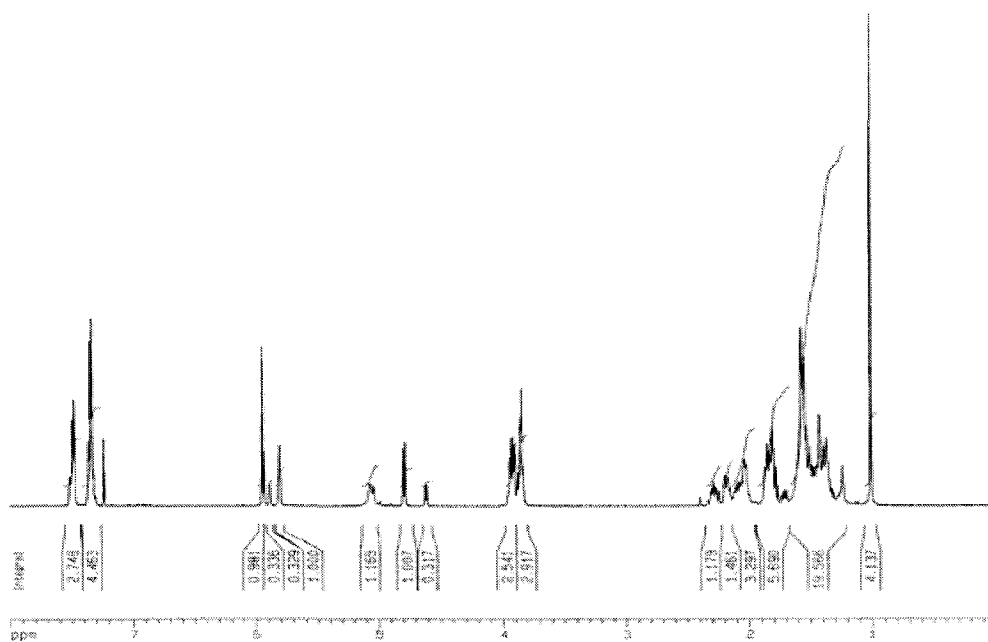


^{13}C NMR (CDCl_3 , 100 MHz)

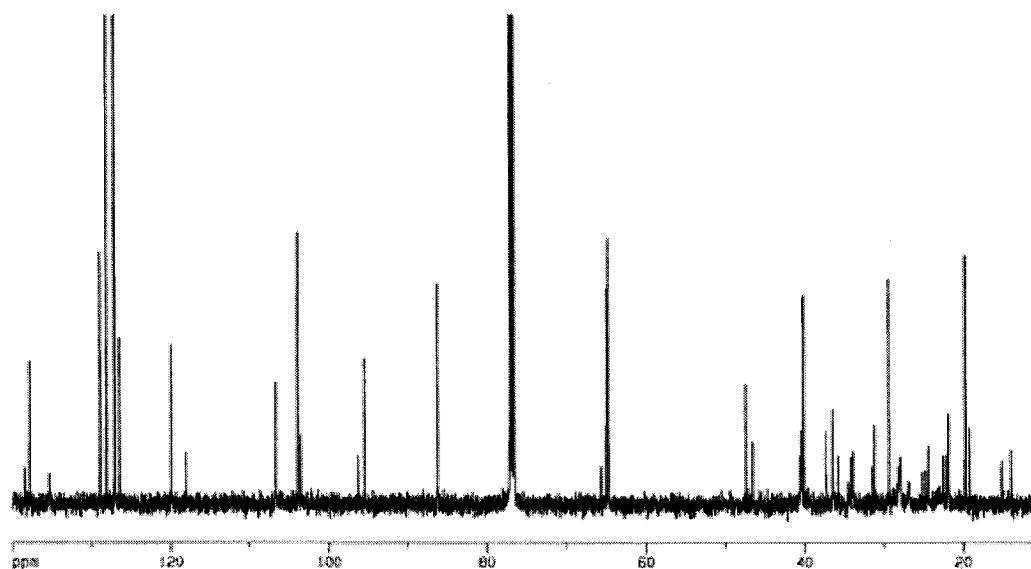


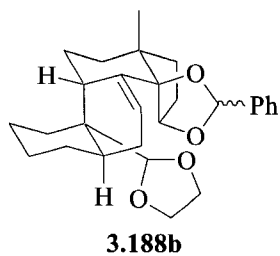
**3.188a**

¹H NMR (CDCl₃, 500 MHz)

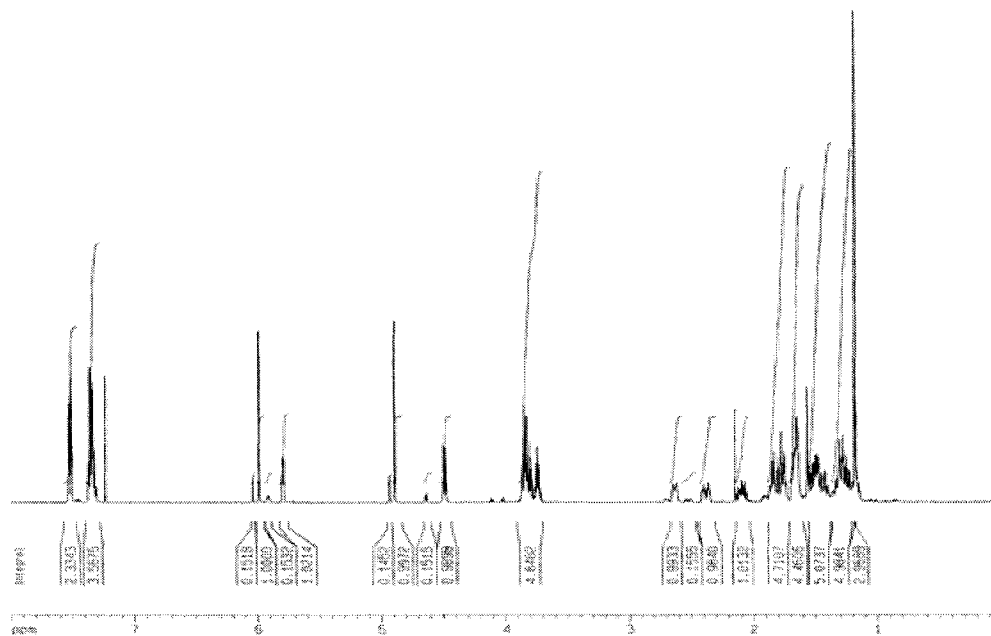


¹³C NMR (CDCl₃, 125 MHz)

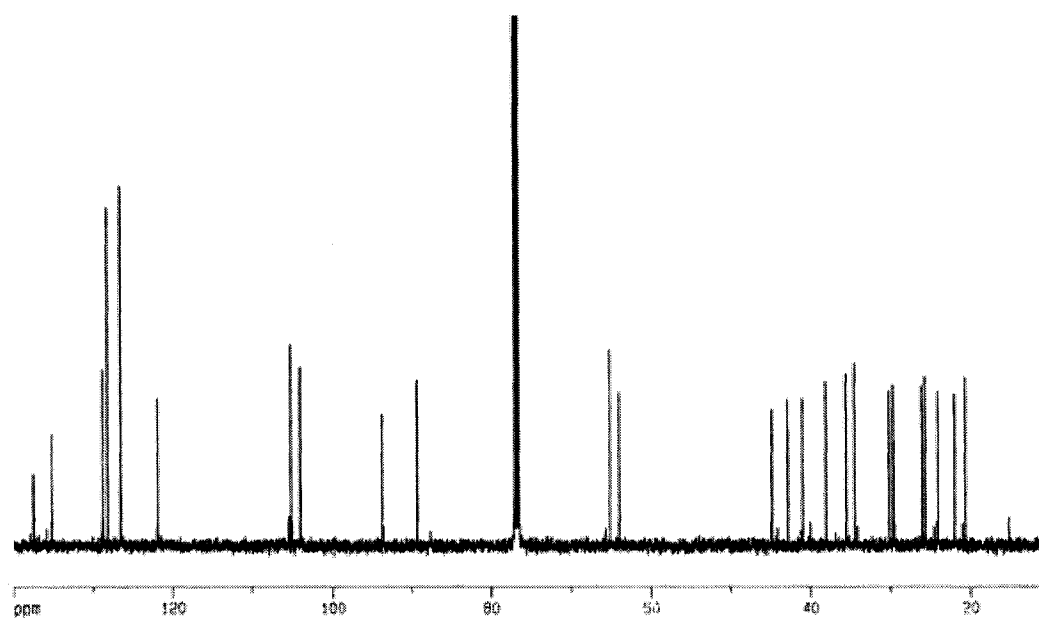


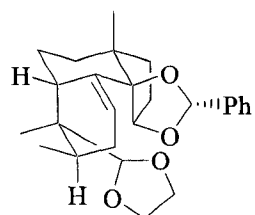


^1H NMR (CDCl_3 , 500 MHz)



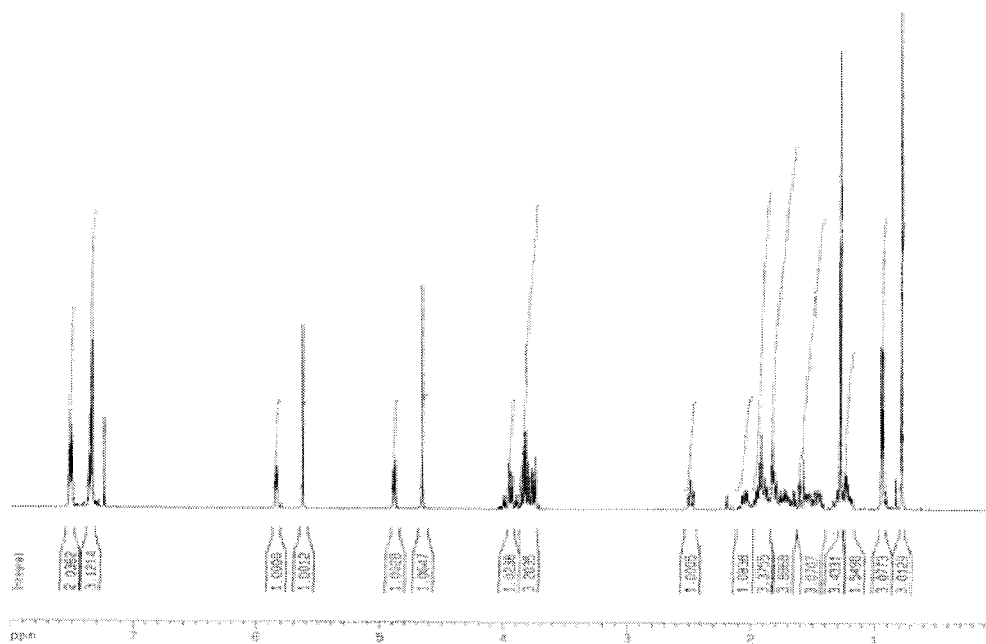
^{13}C NMR (CDCl_3 , 125 MHz)



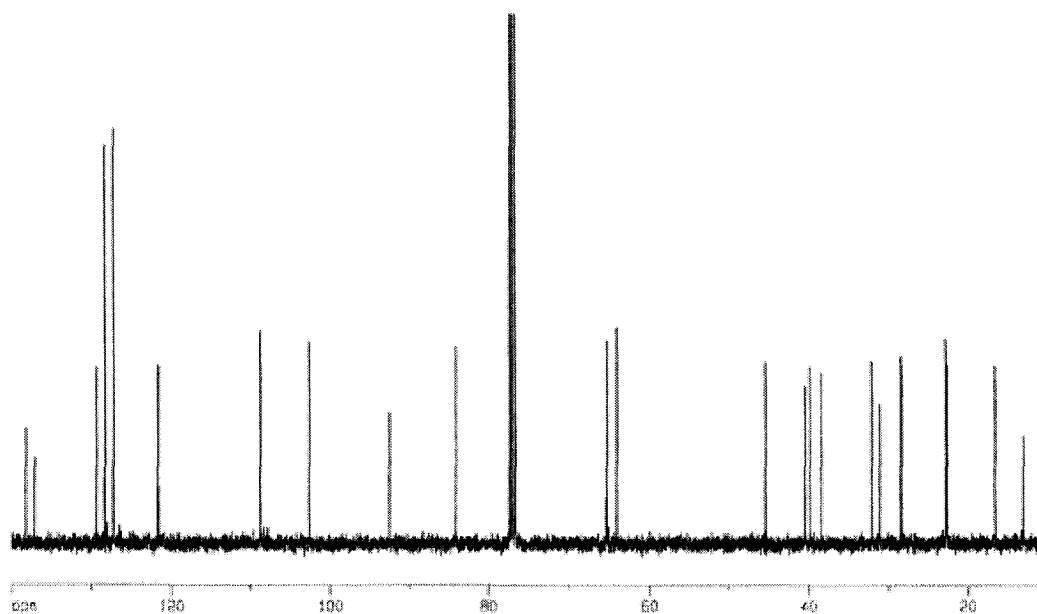


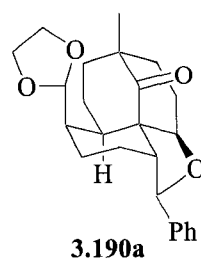
3.189

^1H NMR (CDCl_3 , 400 MHz)

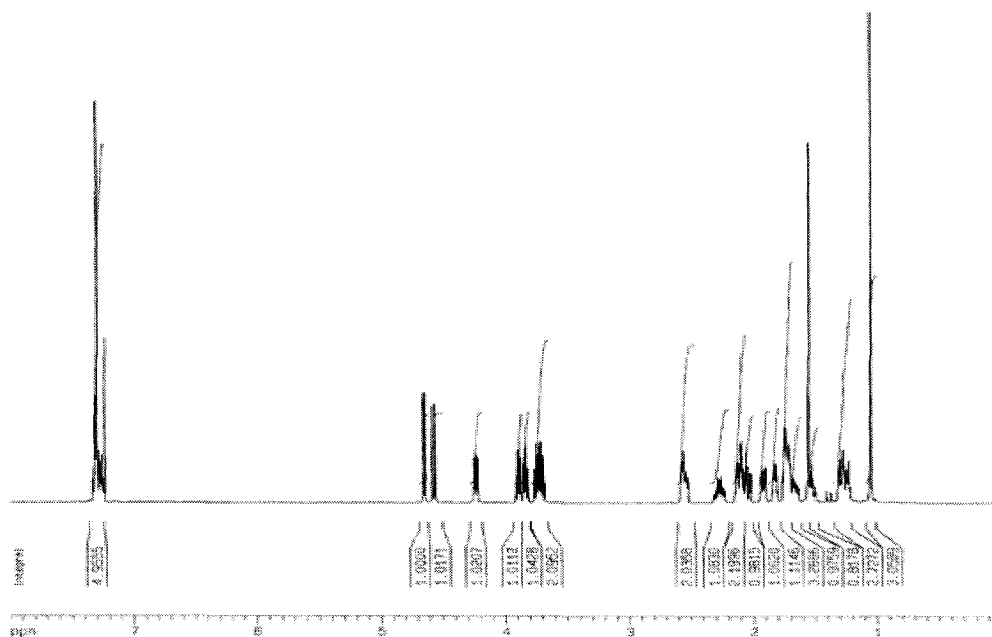


^{13}C NMR (CDCl_3 , 100 MHz)

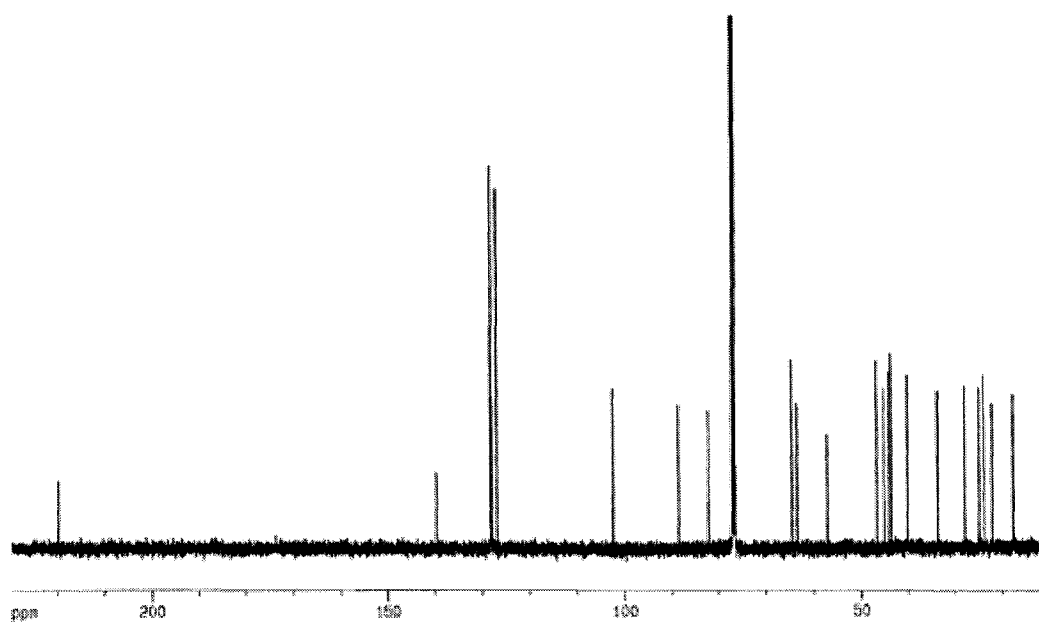


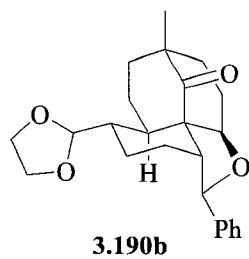


^1H NMR (CDCl_3 , 500 MHz)

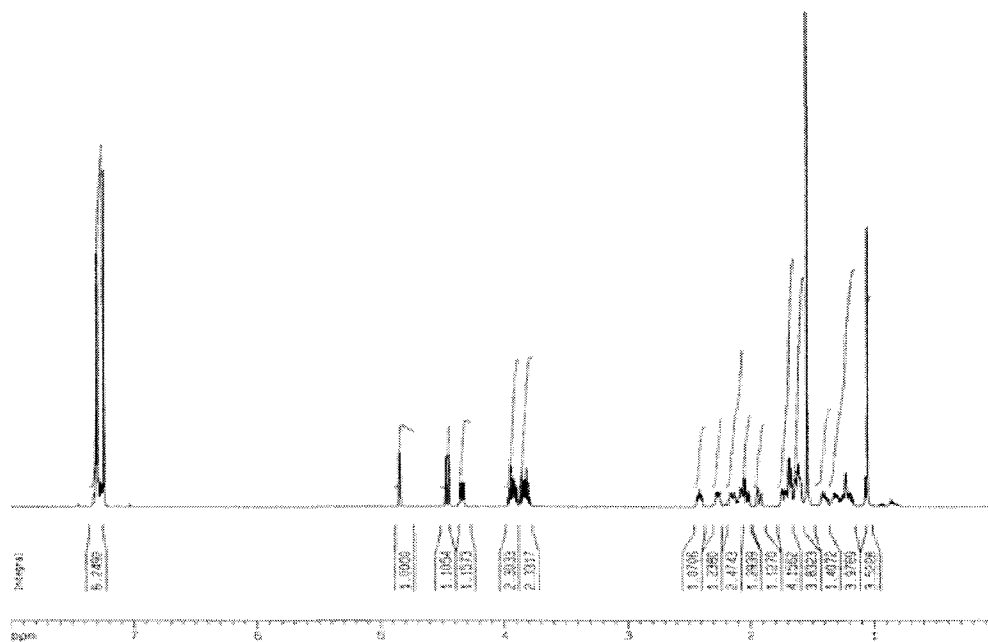


^{13}C NMR (CDCl_3 , 125 MHz)

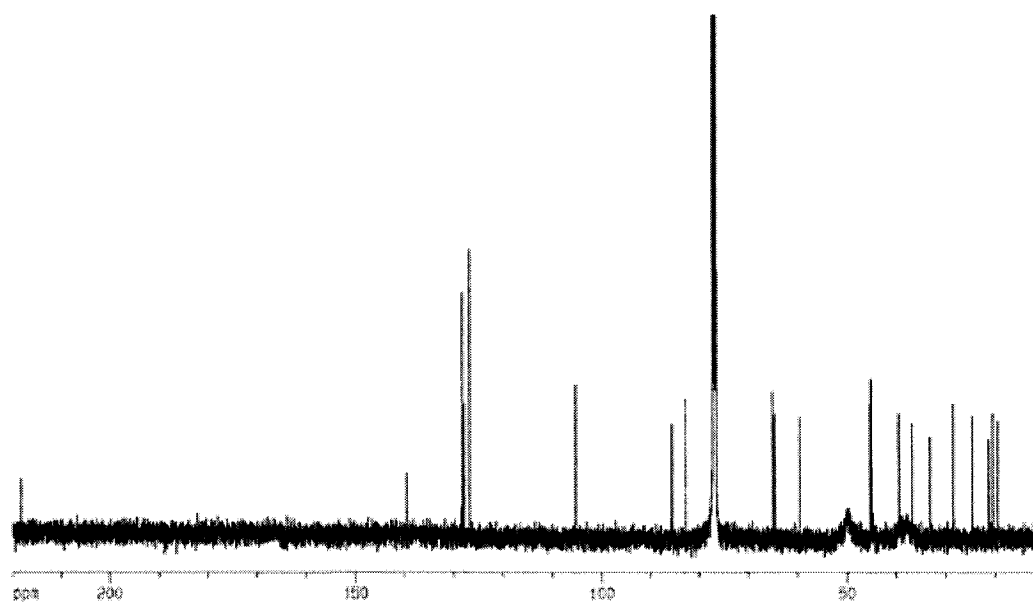


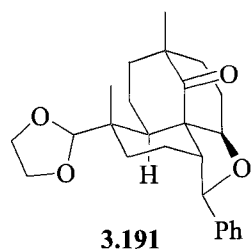


^1H NMR (CDCl_3 , 500 MHz)

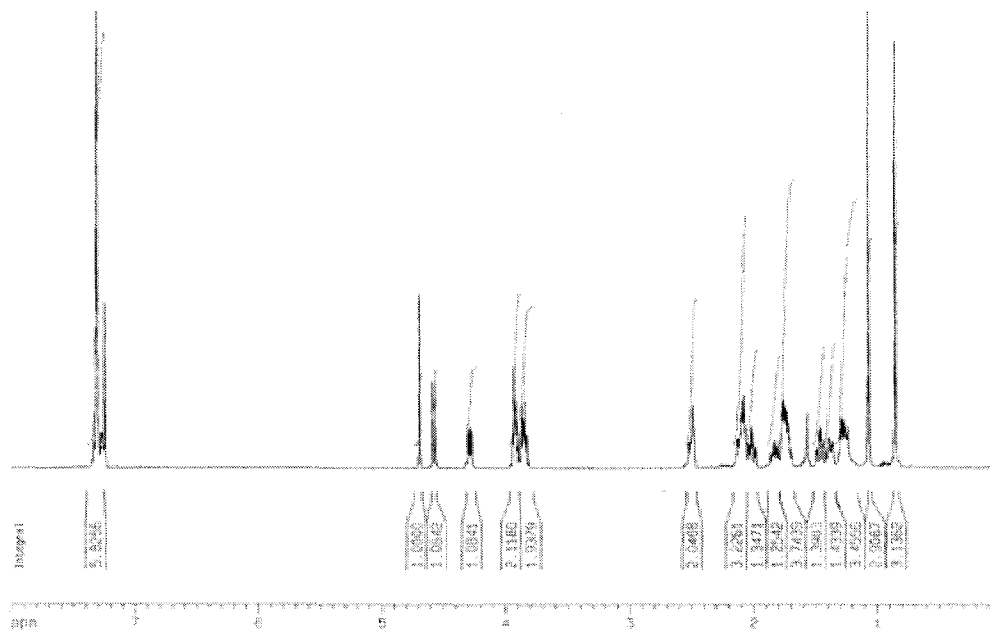


^{13}C NMR (CDCl_3 , 125 MHz)

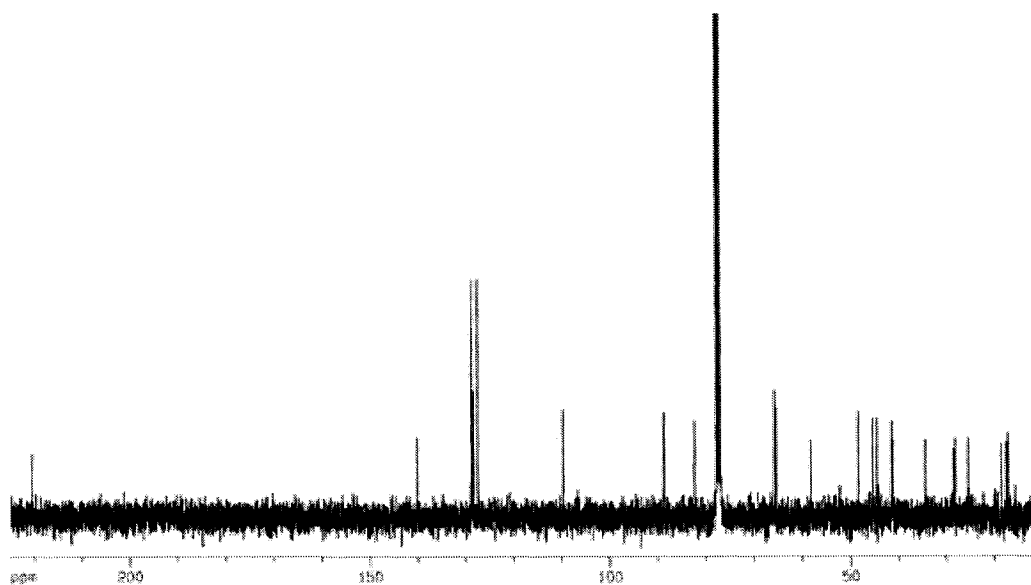


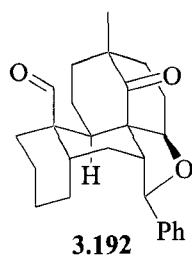


^1H NMR (CDCl_3 , 400 MHz)

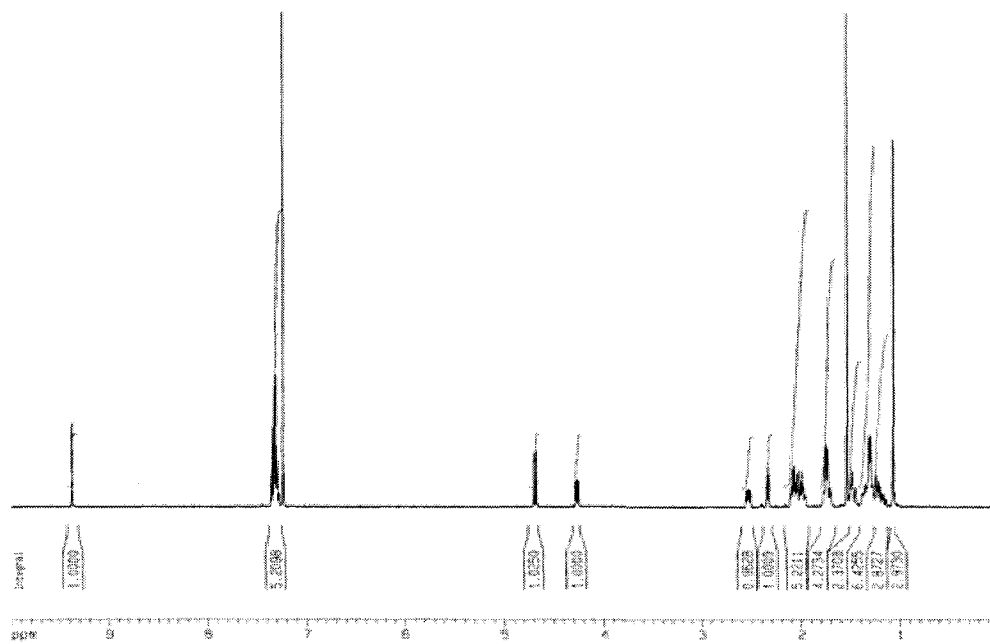


^{13}C NMR (CDCl_3 , 75 MHz)

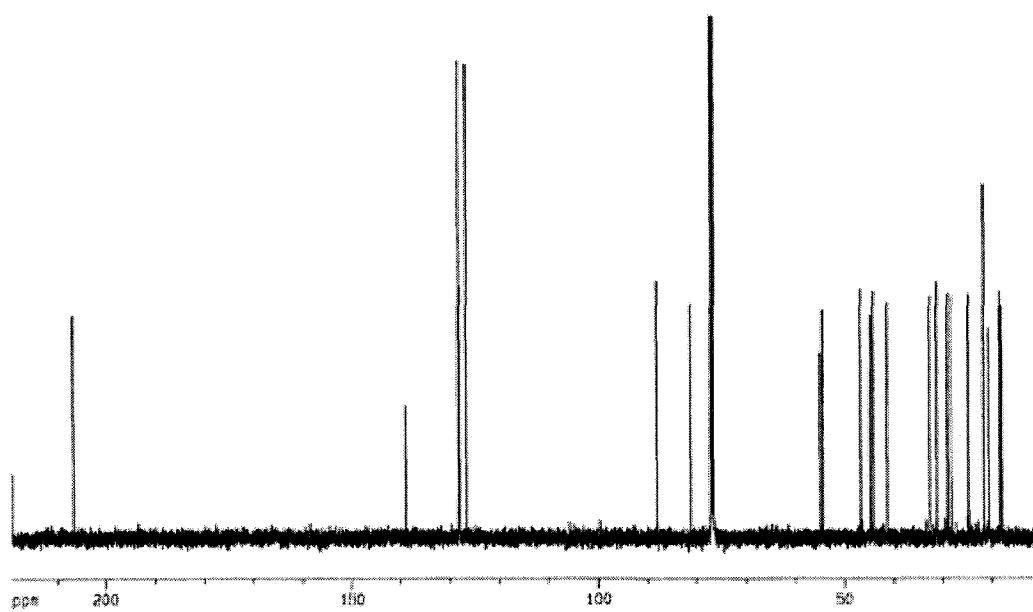


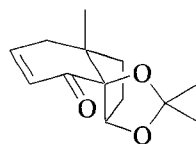


^1H NMR (CDCl_3 , 500 MHz)

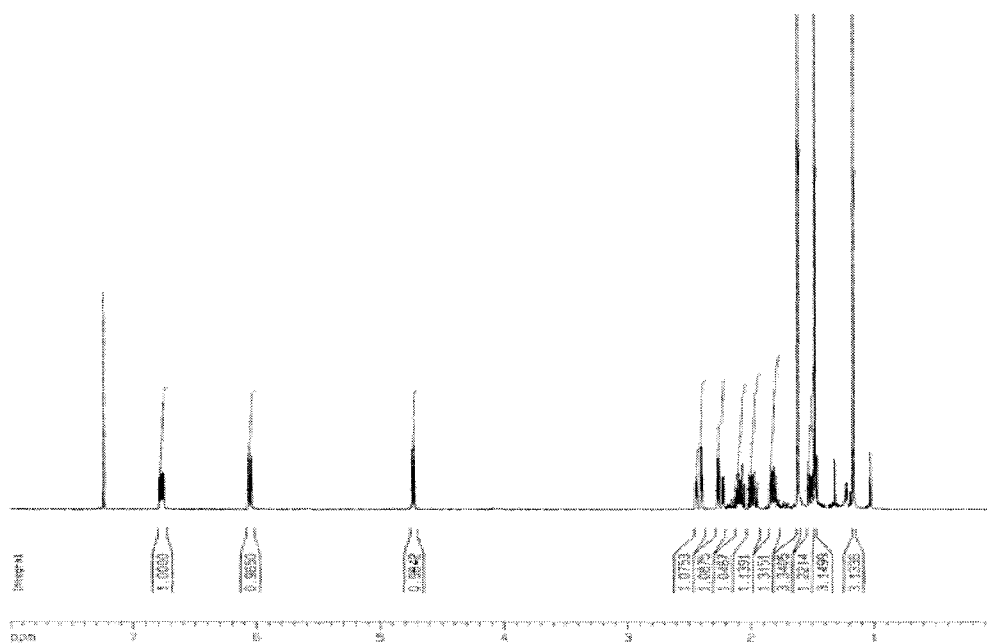
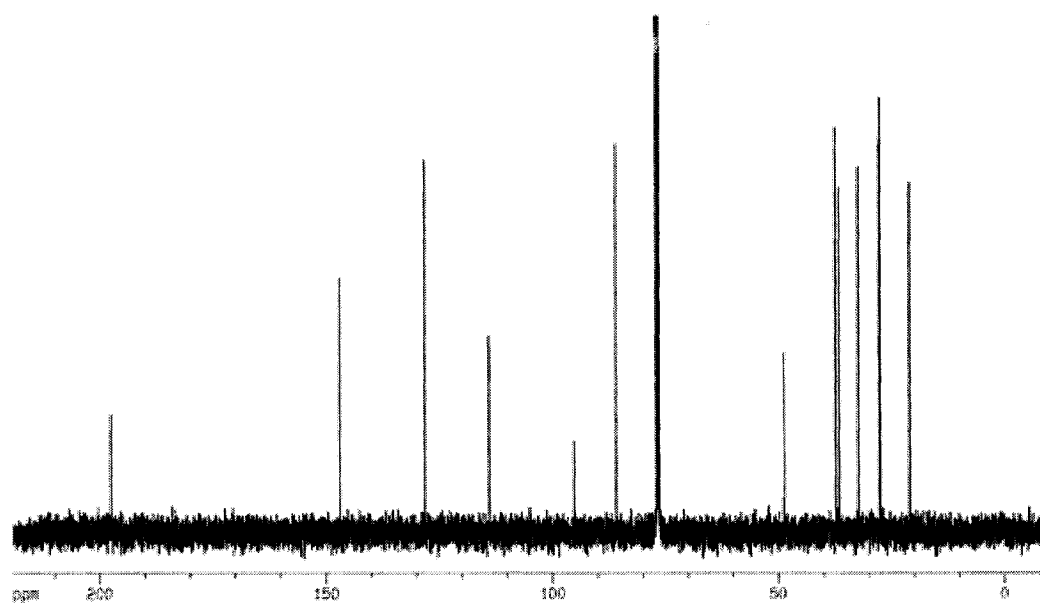


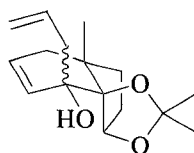
^{13}C NMR (CDCl_3 , 125 MHz)





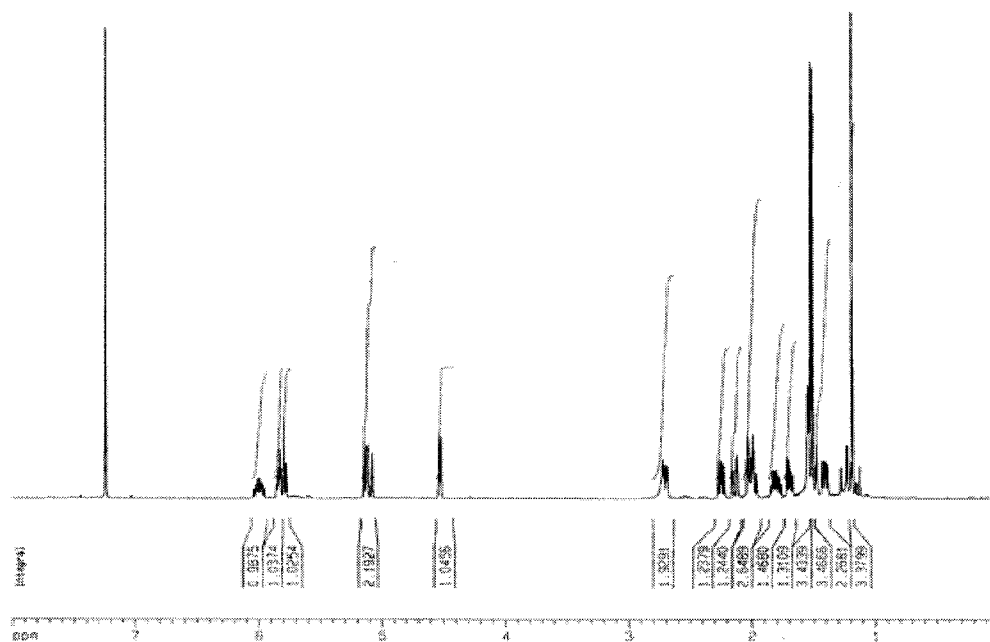
4.33

 ^1H NMR (CDCl_3 , 500 MHz) ^{13}C NMR (CDCl_3 , 125 MHz)

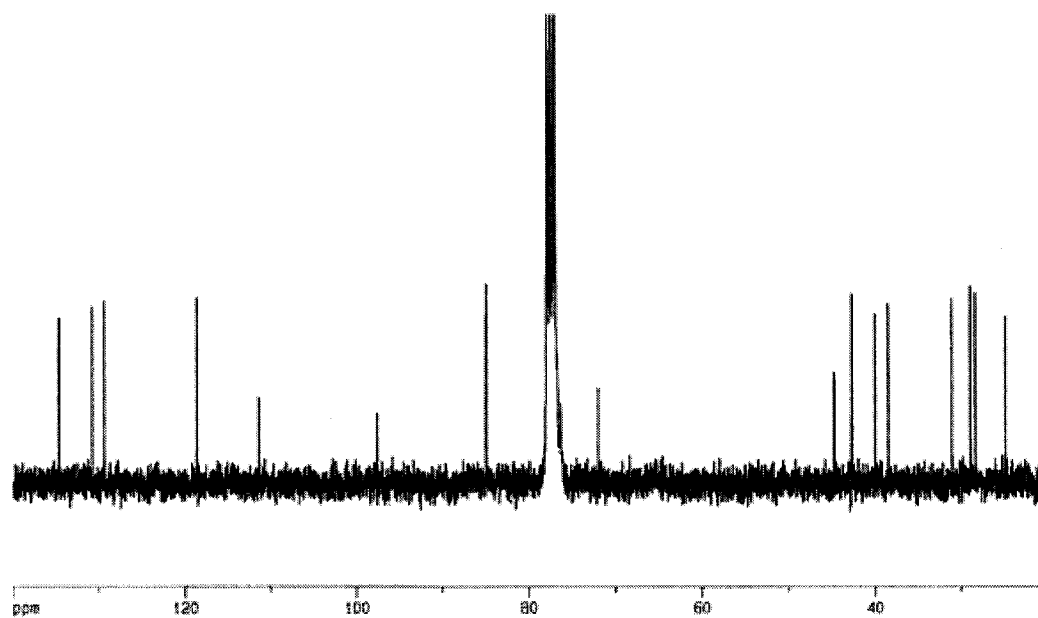


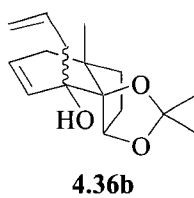
4.36a

¹H NMR (CDCl₃, 500 MHz)

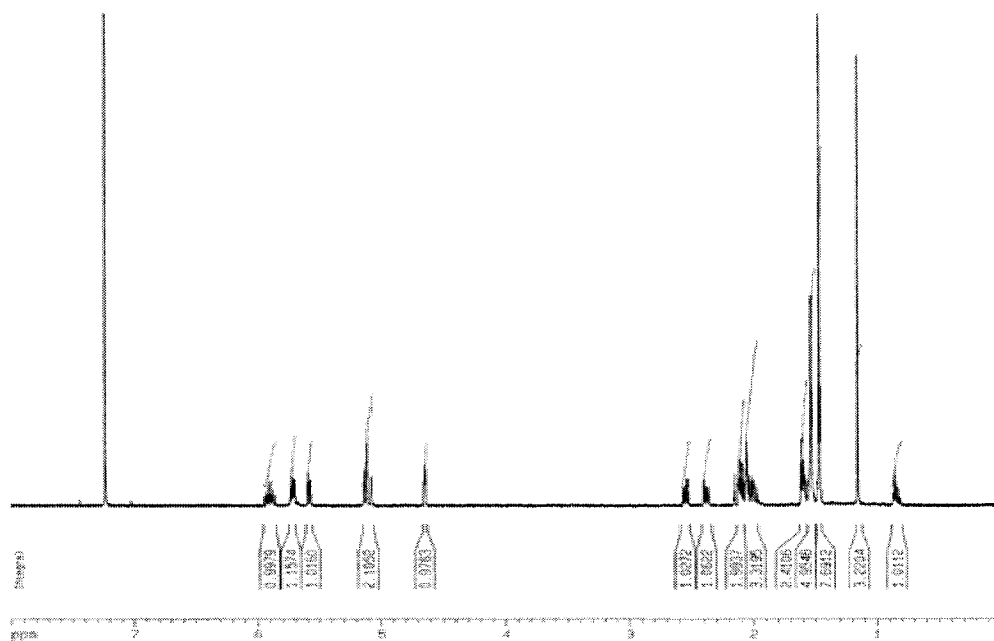


¹³C NMR (CDCl₃, 75 MHz)

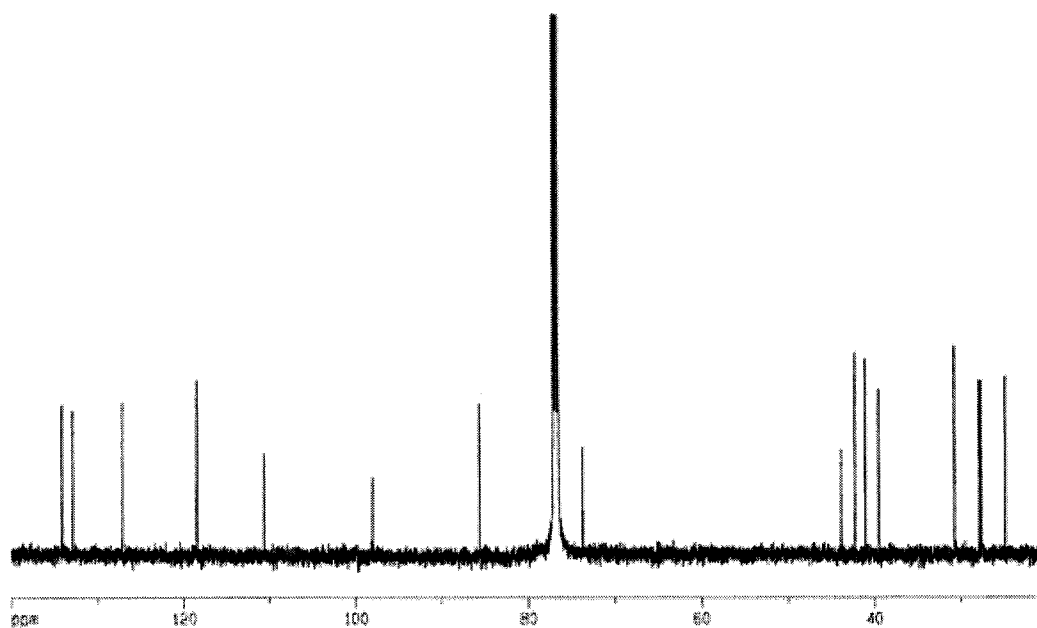


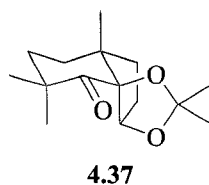


^1H NMR (CDCl_3 , 500 MHz)

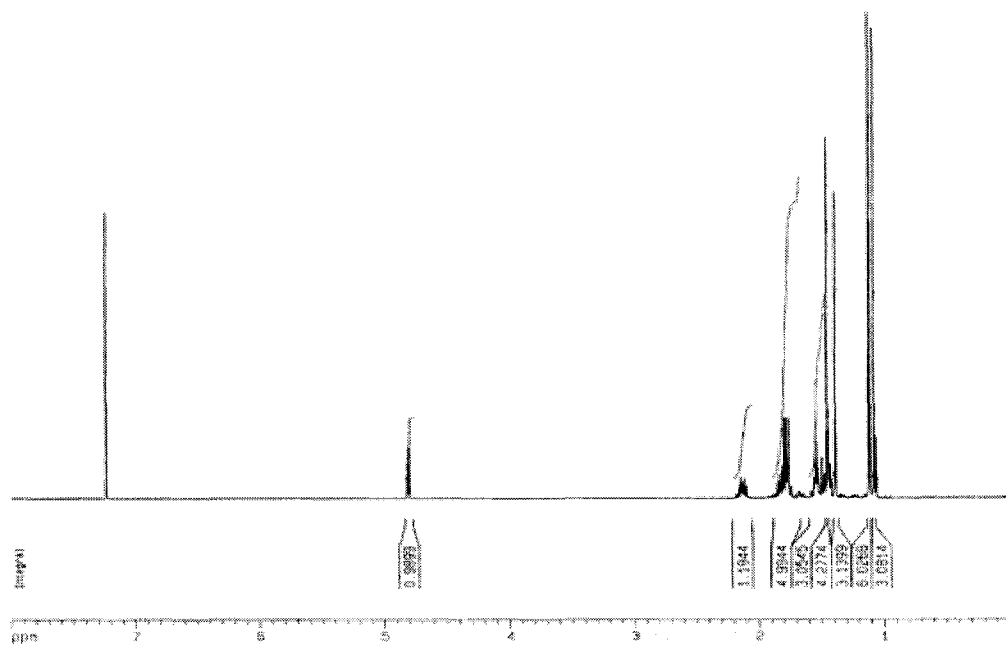


^{13}C NMR (CDCl_3 , 125 MHz)

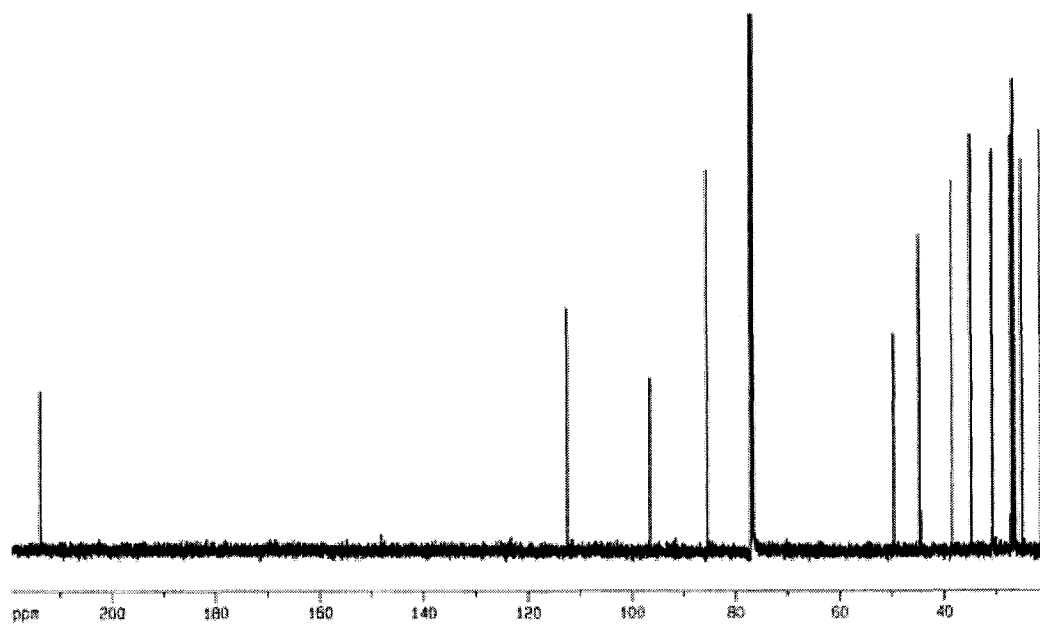




^1H NMR (CDCl_3 , 500 MHz)

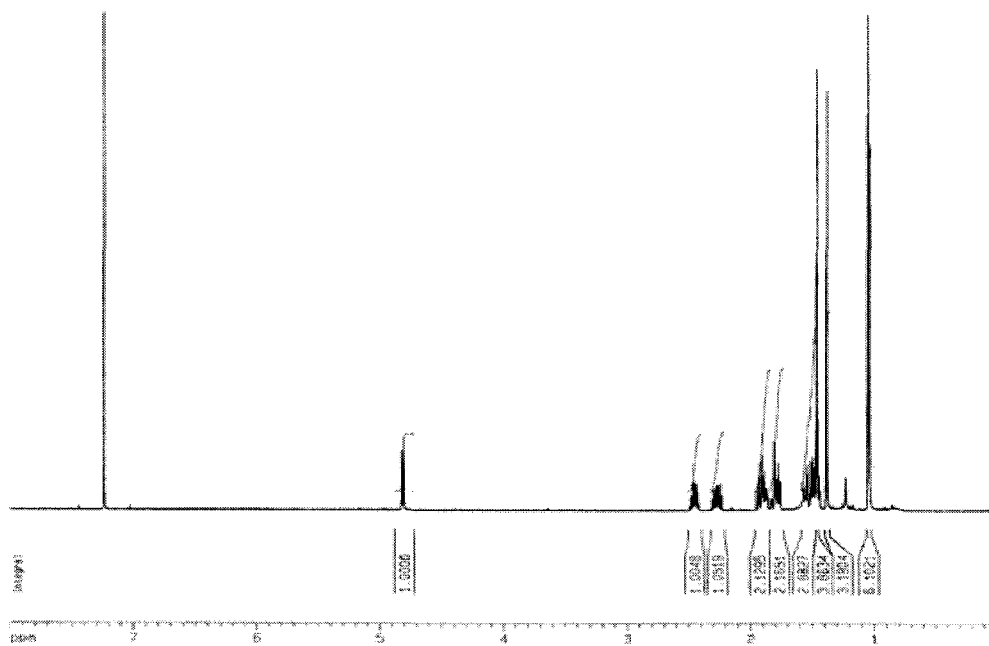


^{13}C NMR (CDCl_3 , 125 MHz)

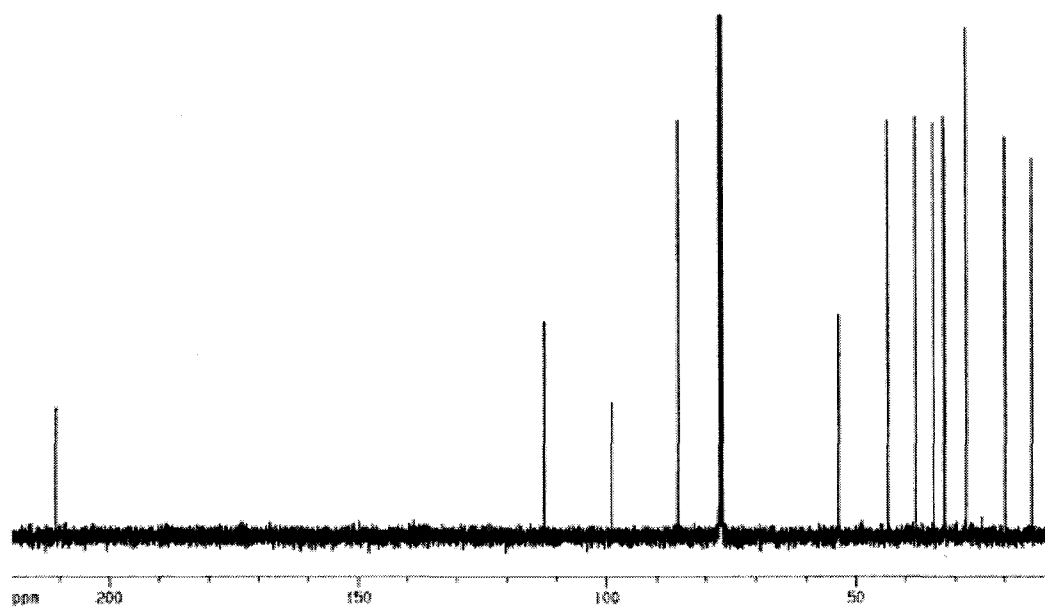


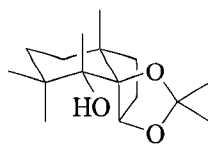


^1H NMR (CDCl_3 , 500 MHz)

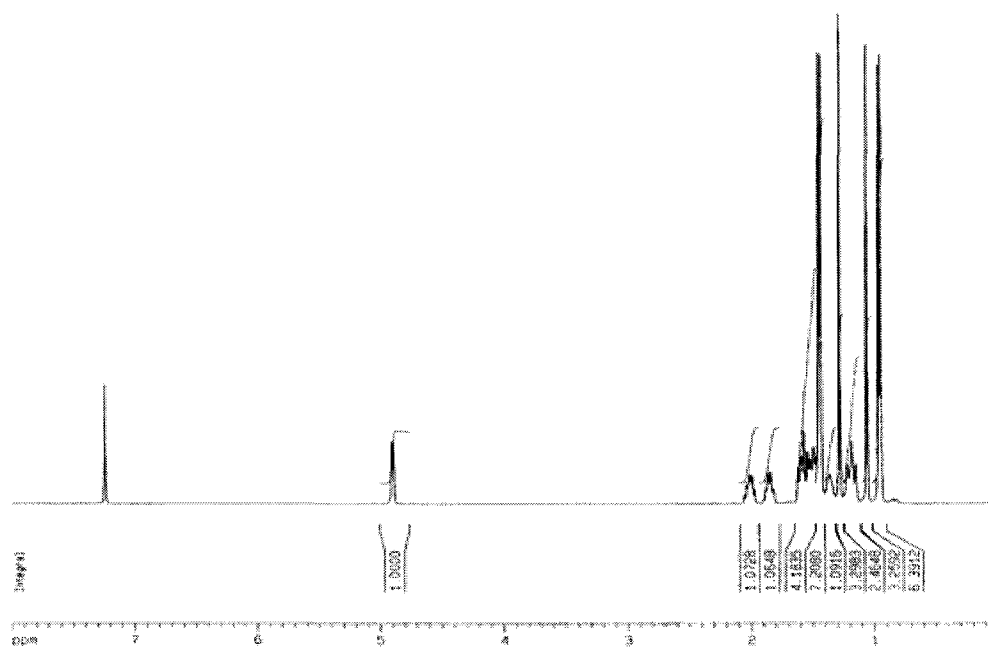
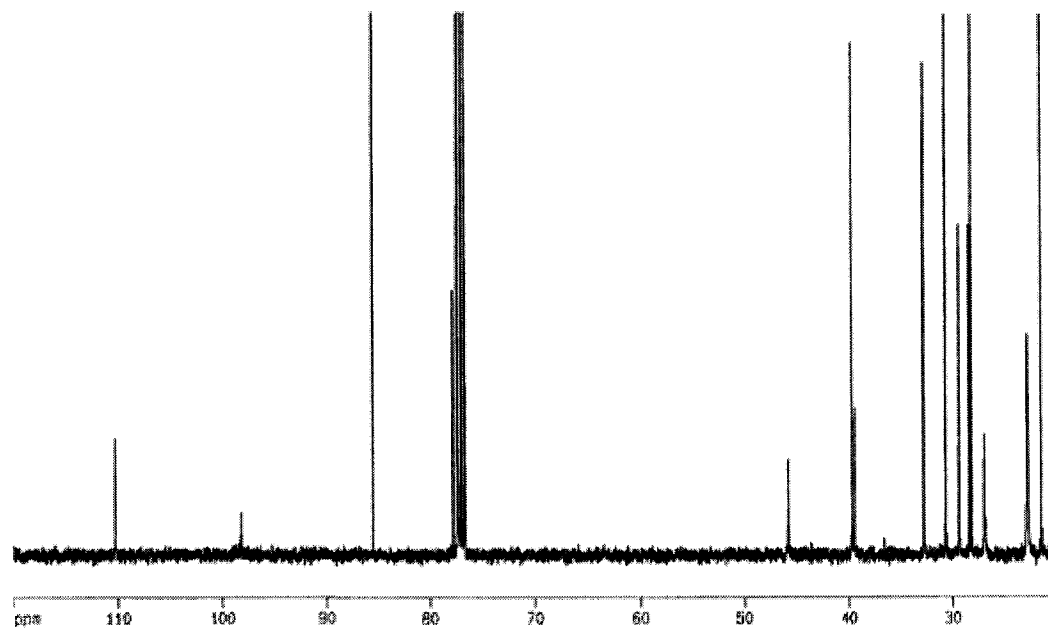


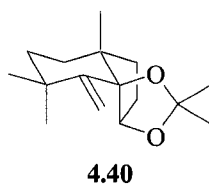
^{13}C NMR (CDCl_3 , 100 MHz)



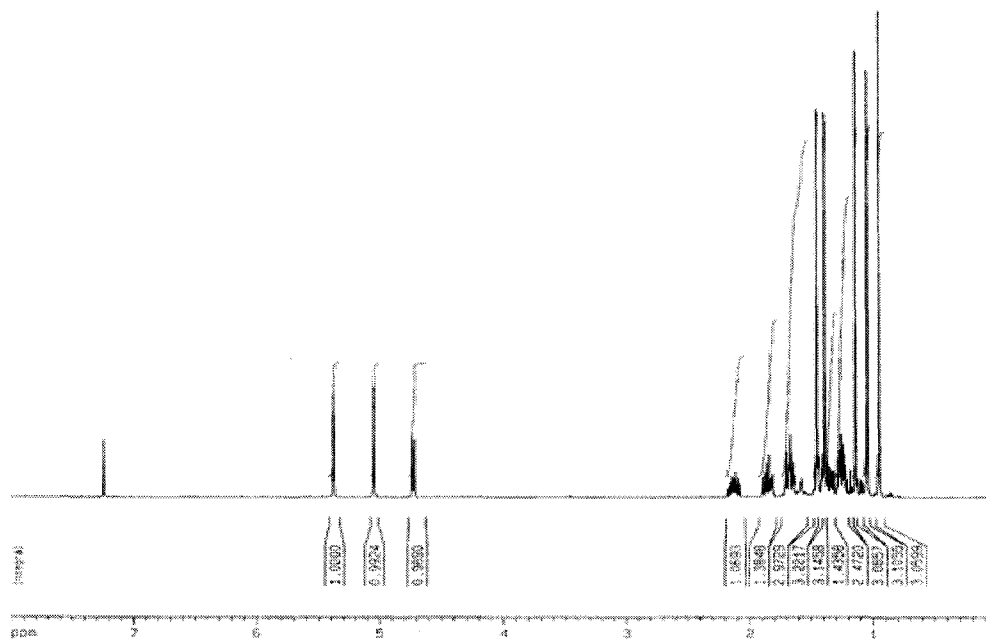


4.39

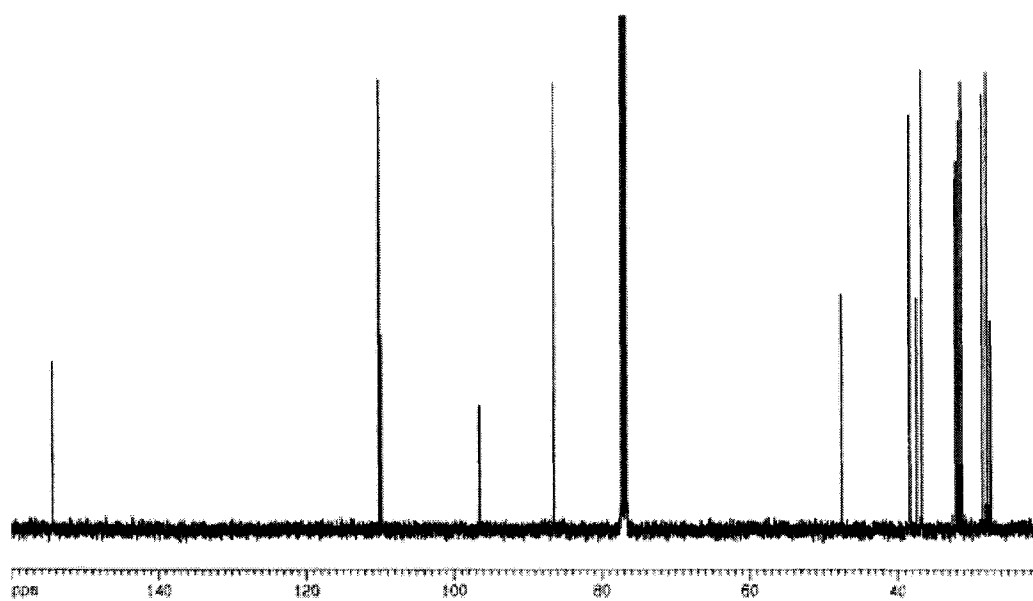
 ^1H NMR (CDCl_3 , 500 MHz) ^{13}C NMR (CDCl_3 , 100 MHz)

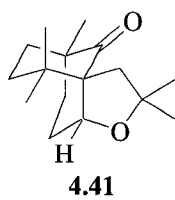


^1H NMR (CDCl_3 , 400 MHz)

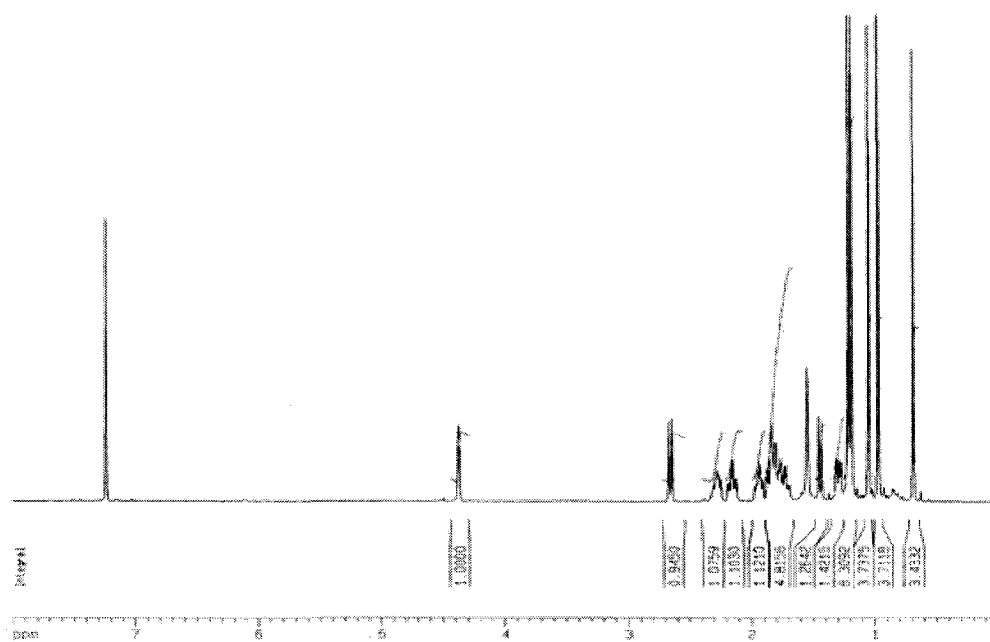


^{13}C NMR (CDCl_3 , 100 MHz)

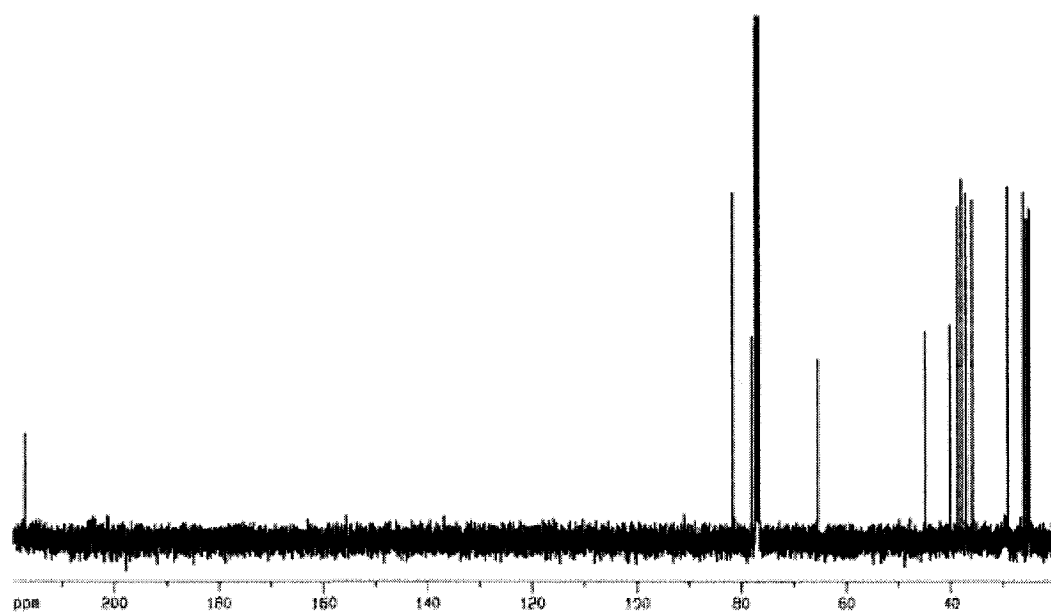


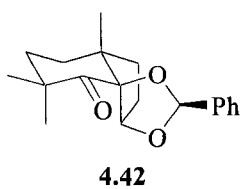


^1H NMR (CDCl_3 , 500 MHz)

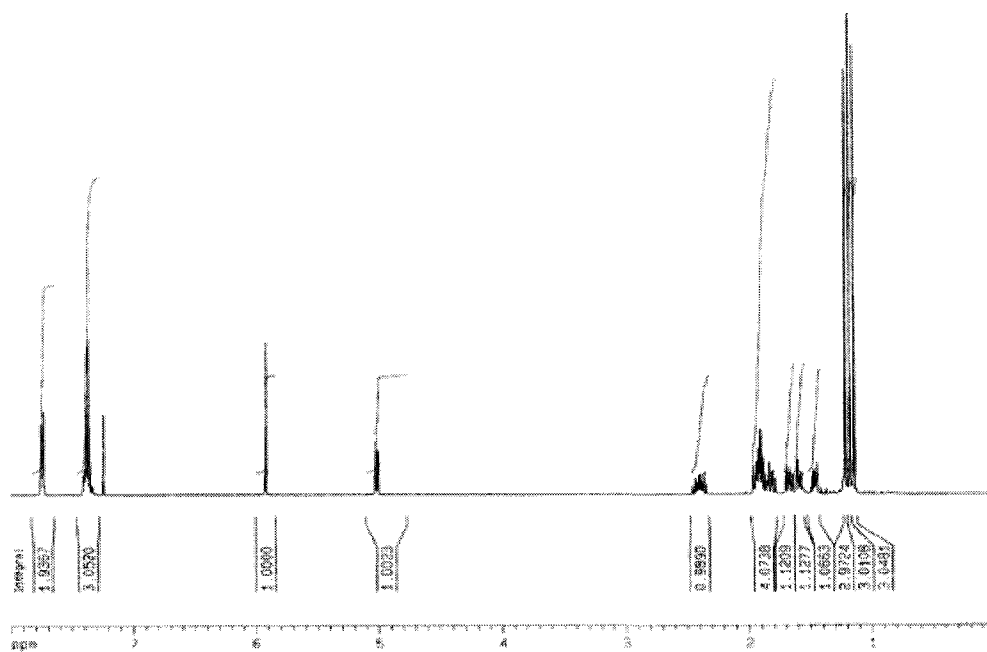


^{13}C NMR (CDCl_3 , 100 MHz)

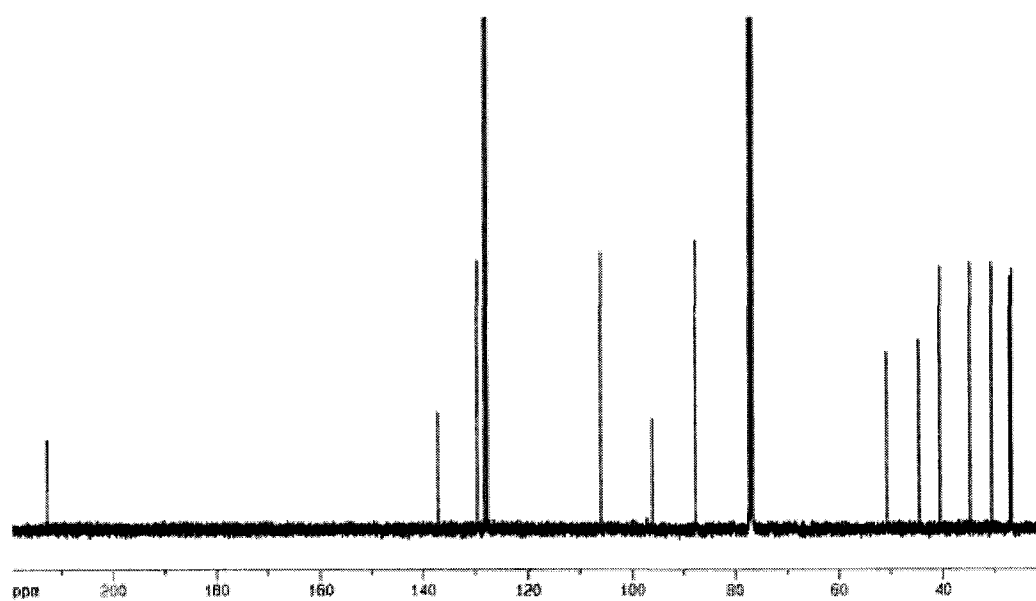


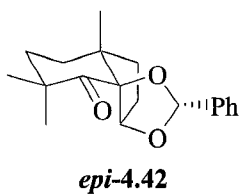


^1H NMR (CDCl_3 , 400 MHz)

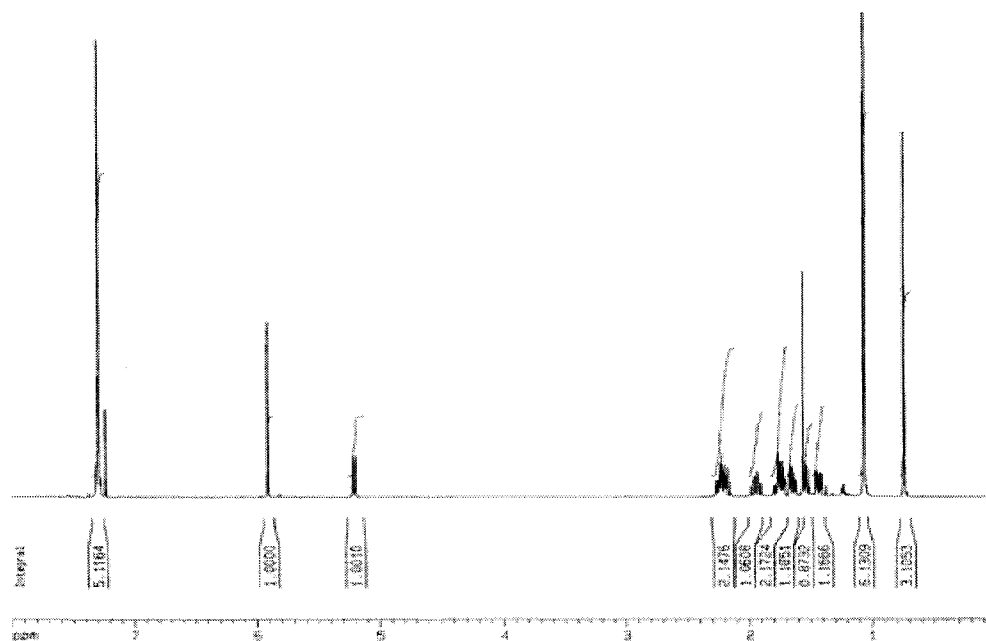


^{13}C NMR (CDCl_3 , 125 MHz)

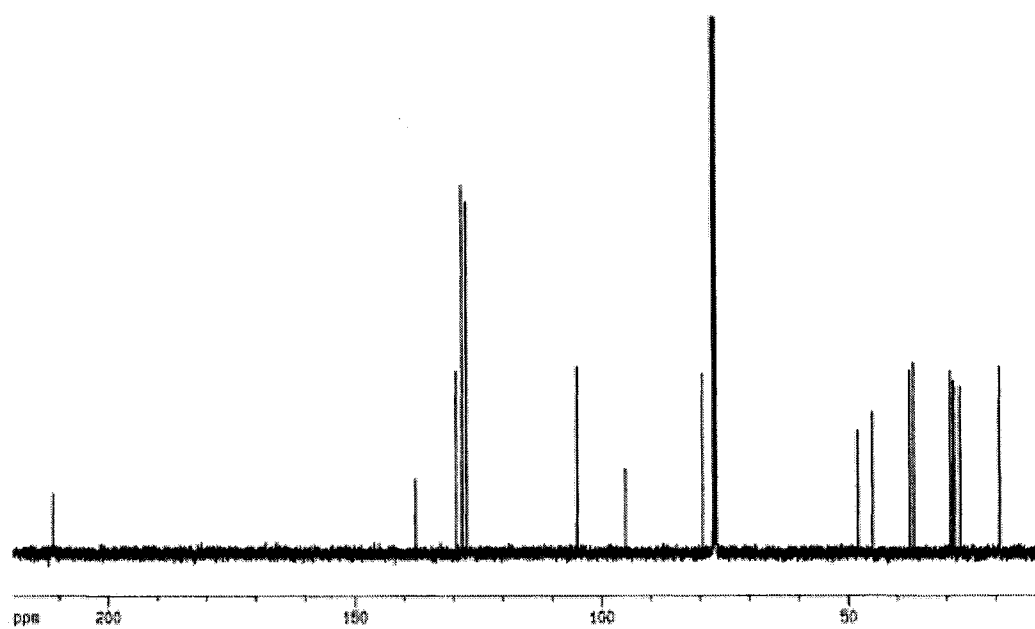


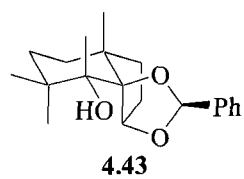


^1H NMR (CDCl_3 , 400 MHz)

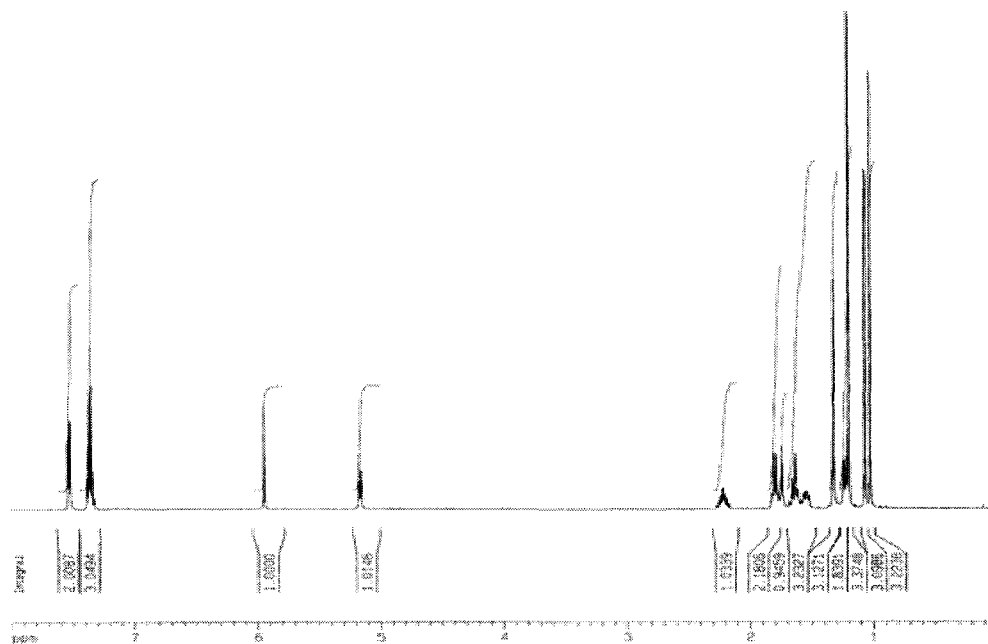


^{13}C NMR (CDCl_3 , 100 MHz)

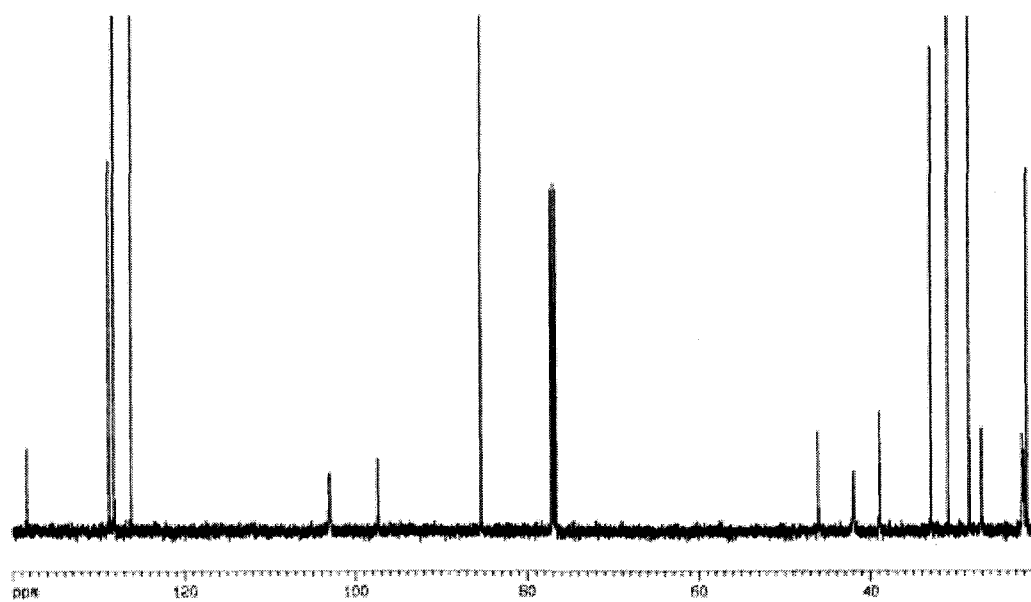


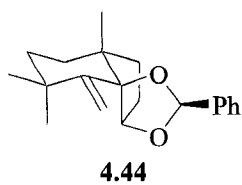


^1H NMR (CDCl_3 , 500 MHz)

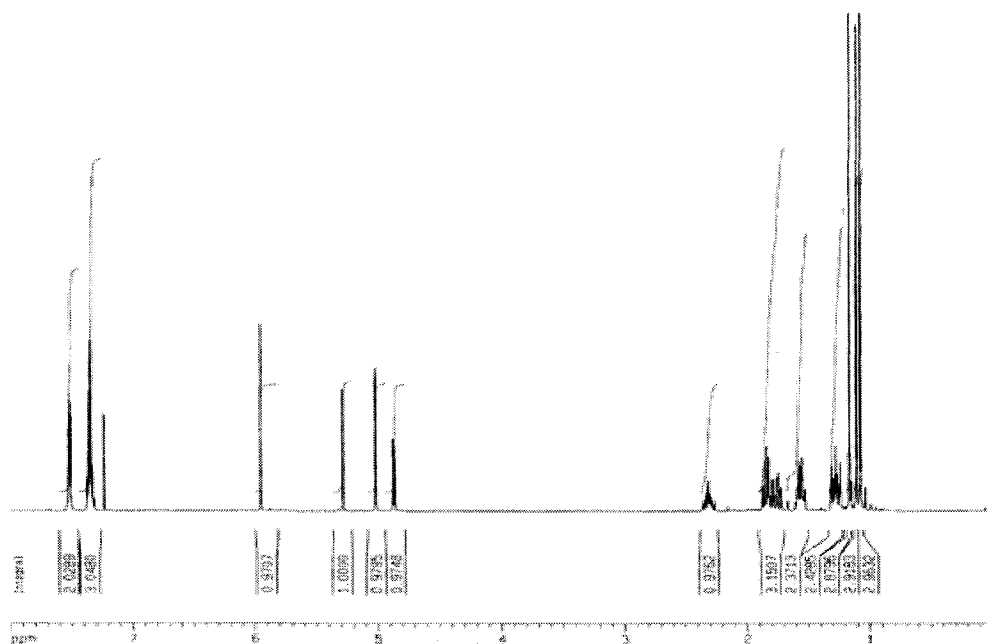


^{13}C NMR (CDCl_3 , 125 MHz)

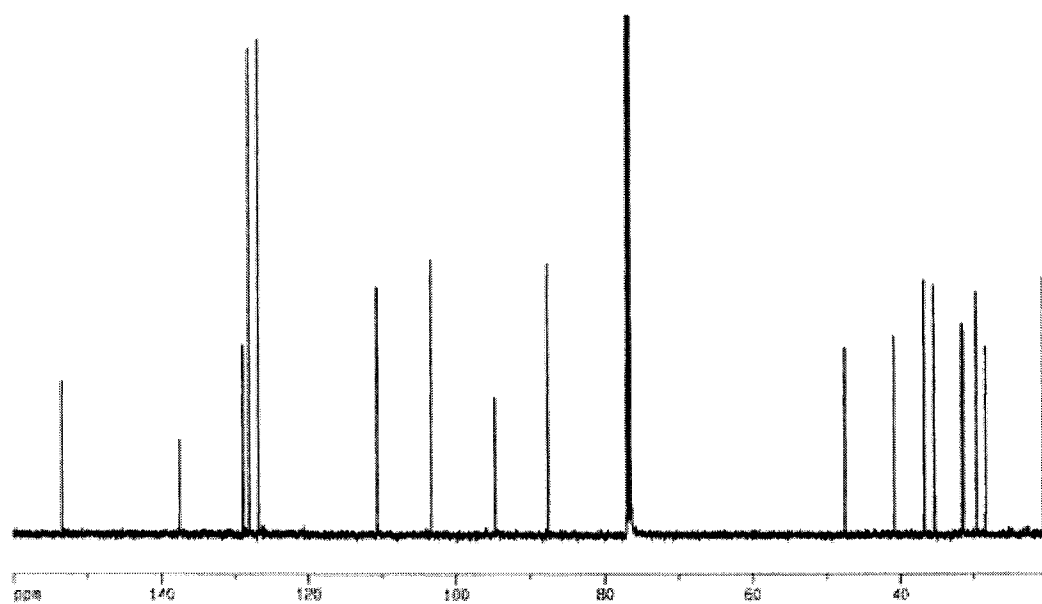


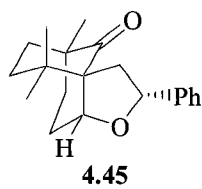


^1H NMR (CDCl_3 , 500 MHz)

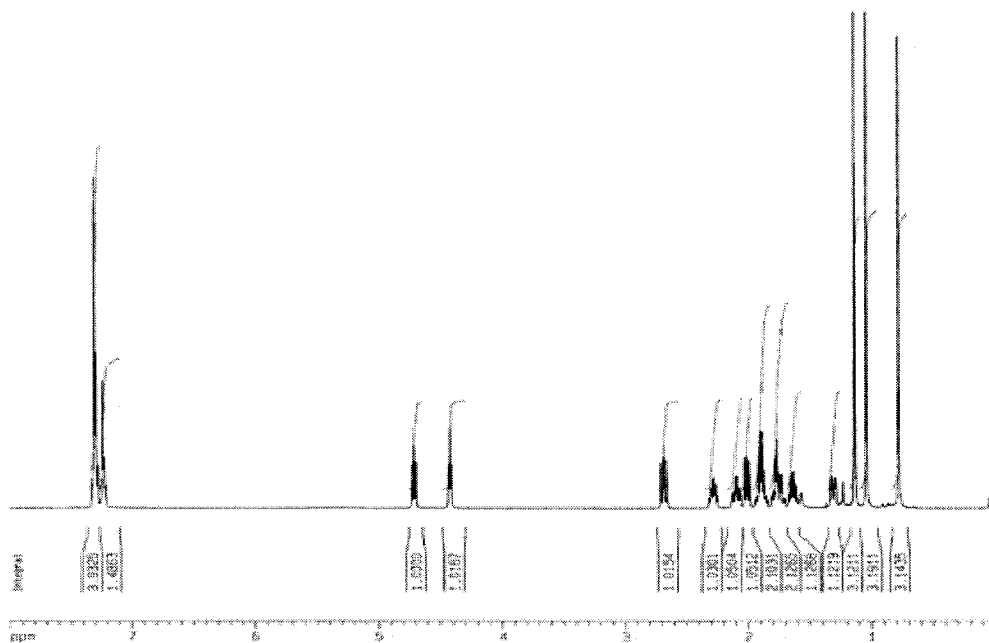


^{13}C NMR (CDCl_3 , 125 MHz)

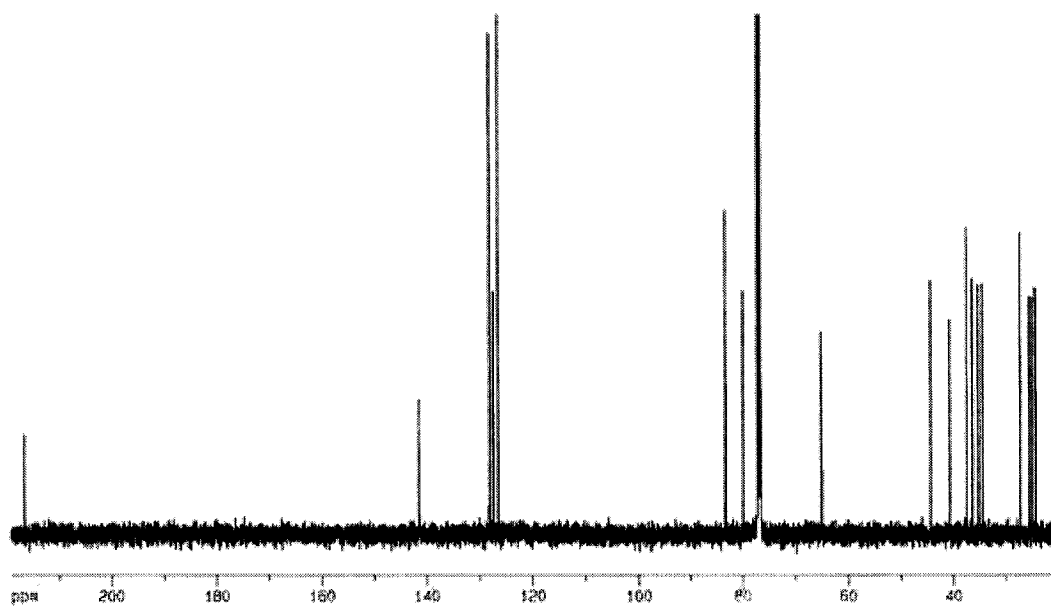


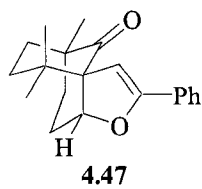


^1H NMR (CDCl_3 , 500 MHz)

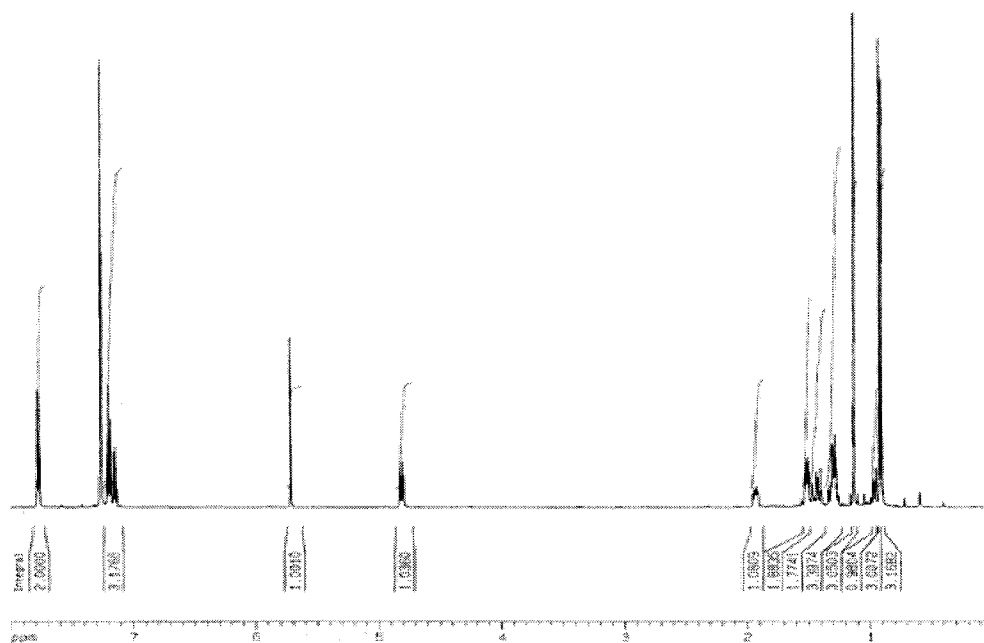


^{13}C NMR (CDCl_3 , 125 MHz)

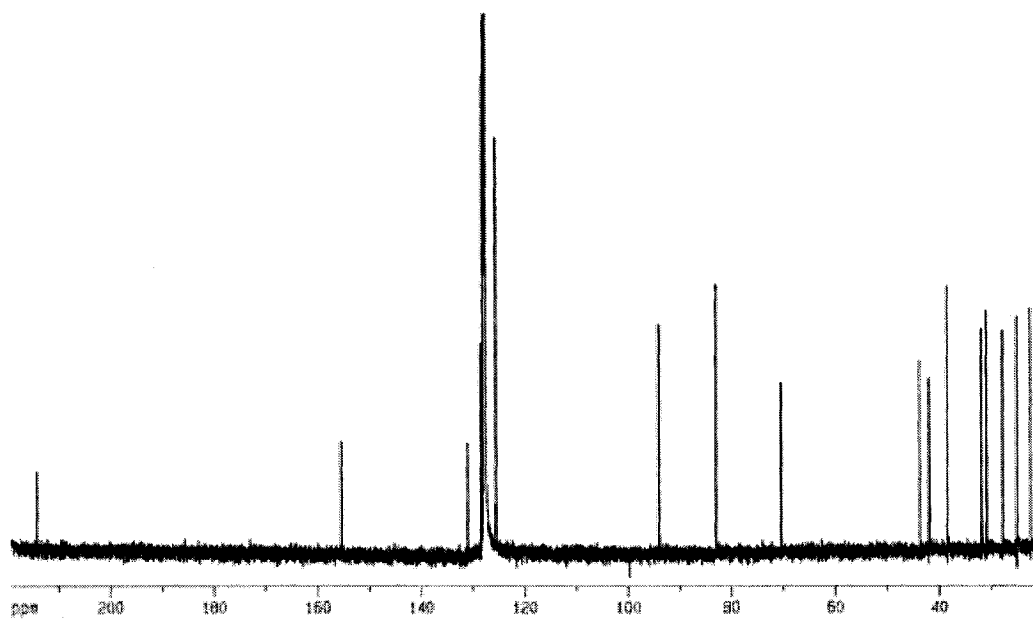


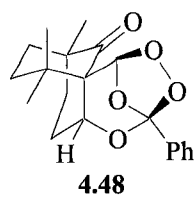


^1H NMR (C_6D_6 , 500 MHz)

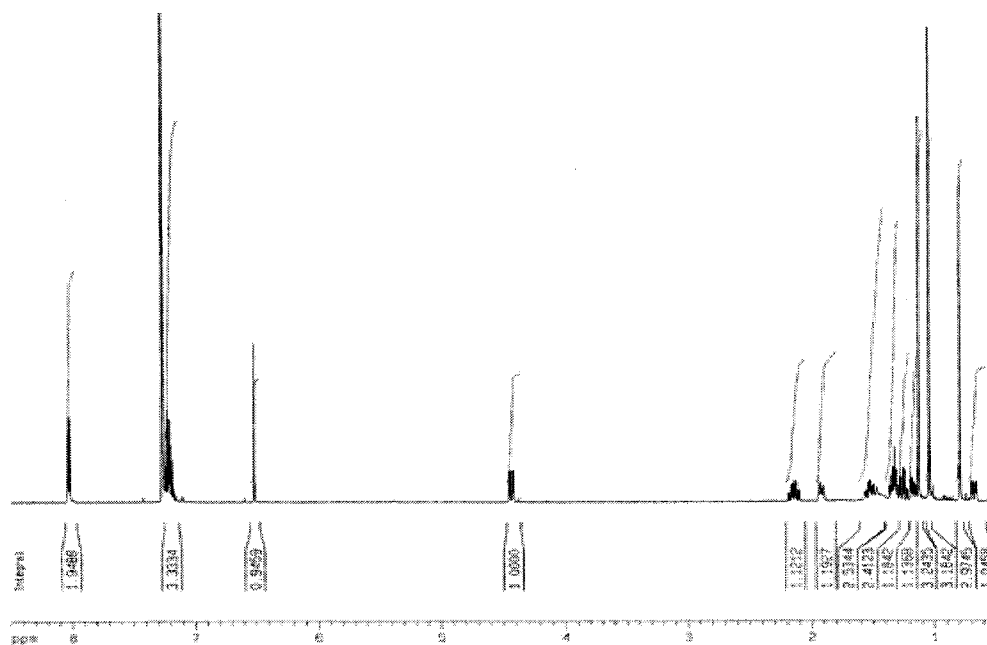


^{13}C NMR (C_6D_6 , 125 MHz)

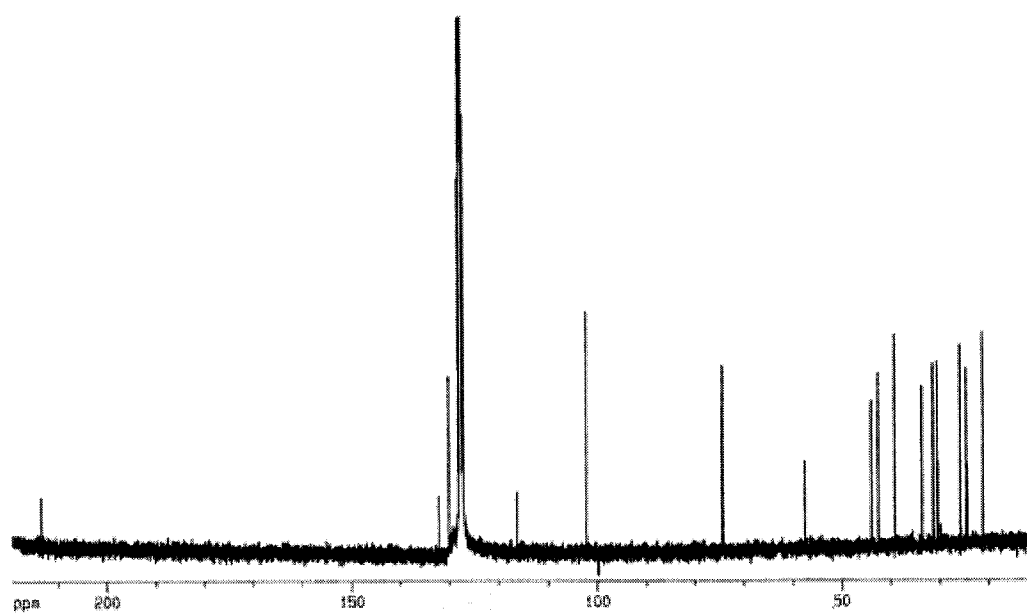


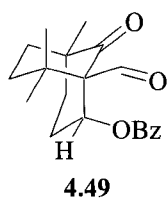


^1H NMR (C_6D_6 , 500 MHz)

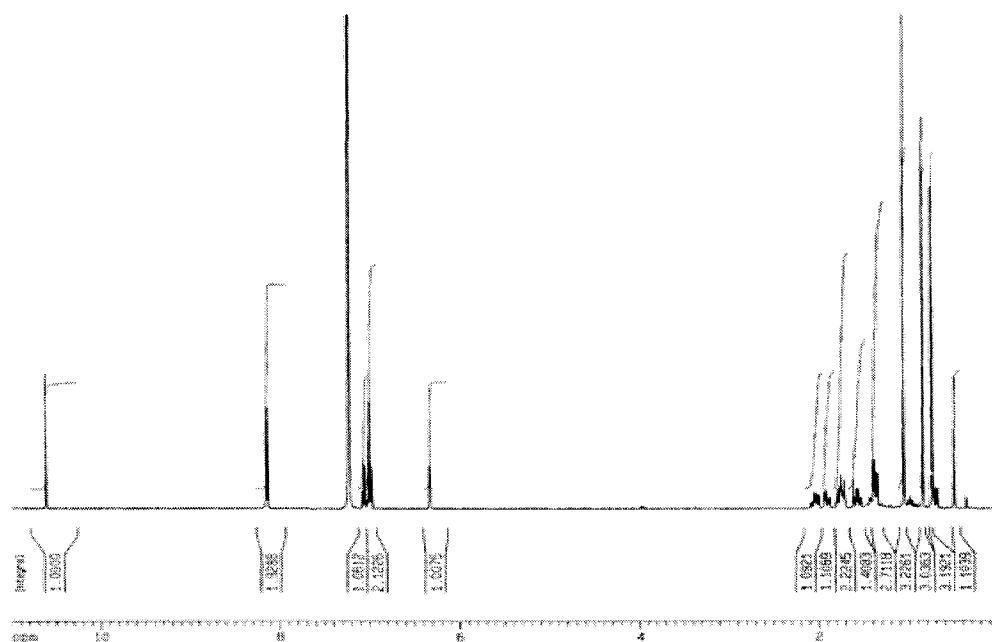


^{13}C NMR (C_6D_6 , 125 MHz)

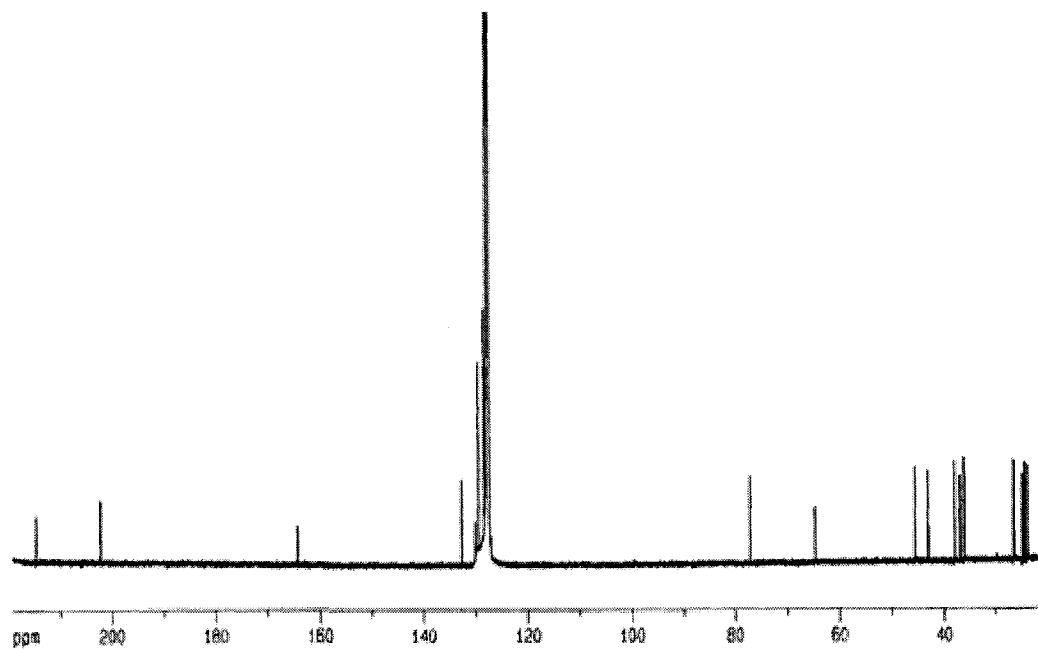


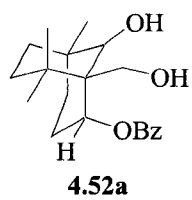


^1H NMR (C_6D_6 , 400 MHz)

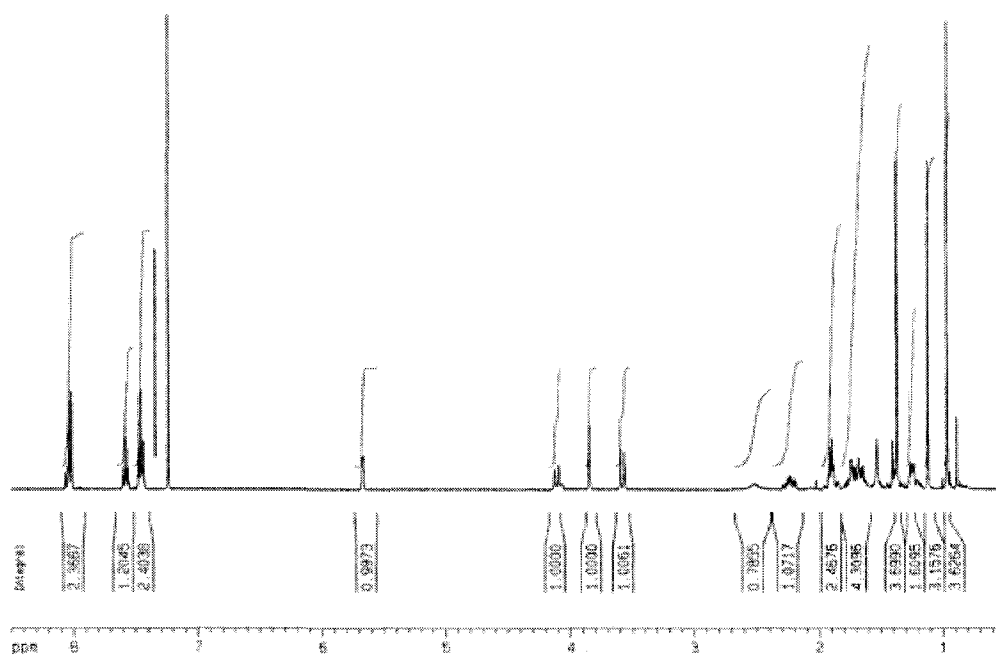


^{13}C NMR (C_6D_6 , 125 MHz)

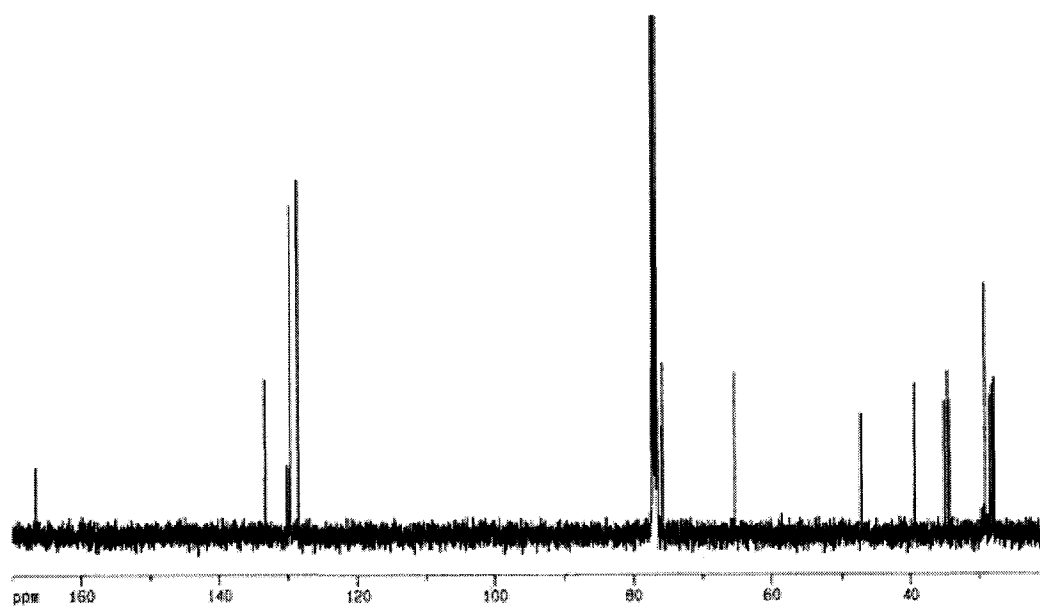


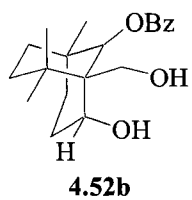


^1H NMR (CDCl_3 , 400 MHz)

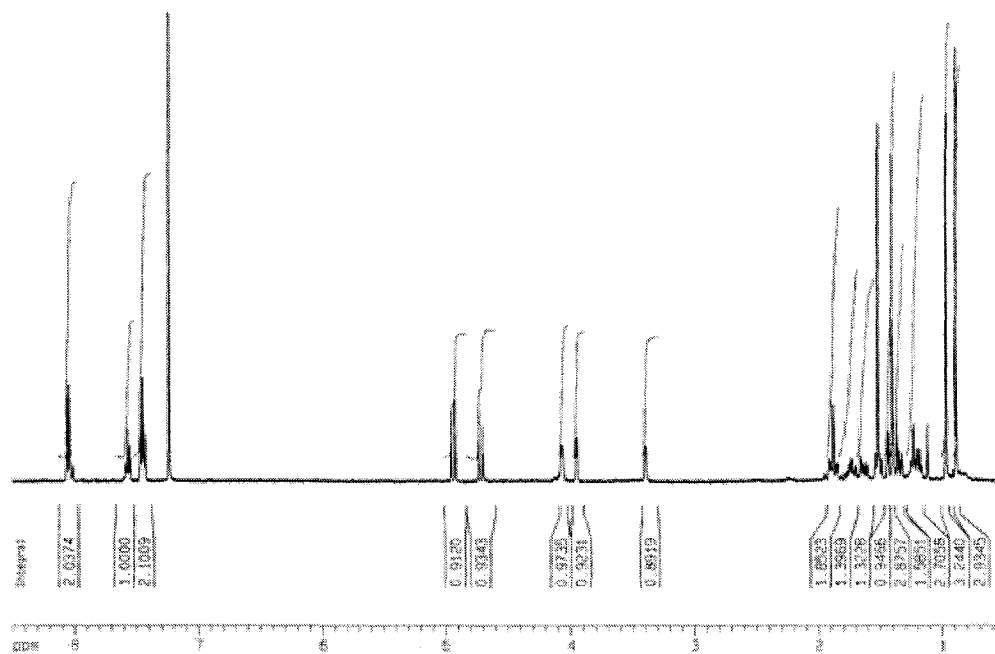


^{13}C NMR (CDCl_3 , 100 MHz)

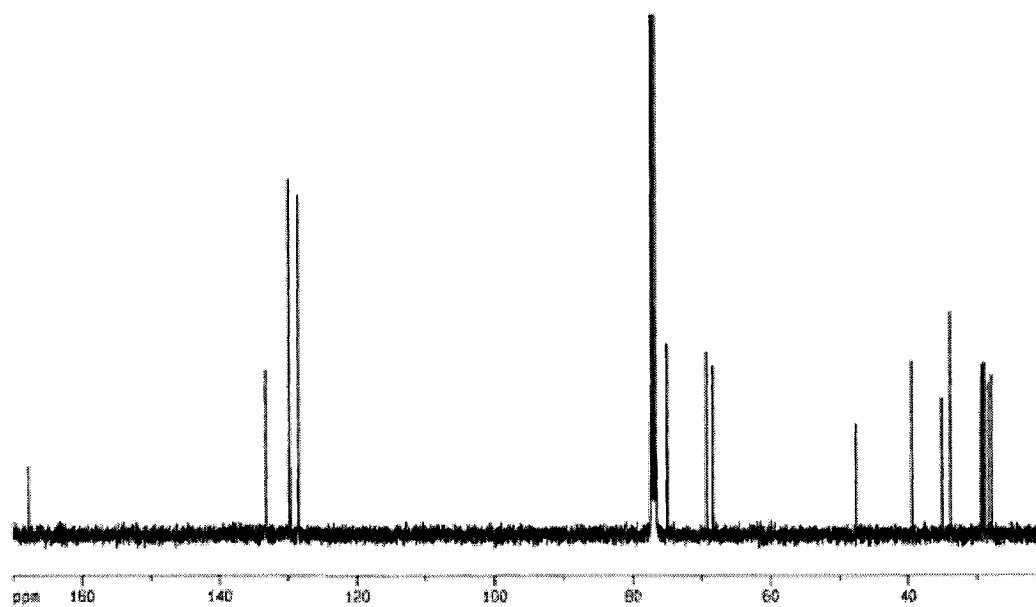


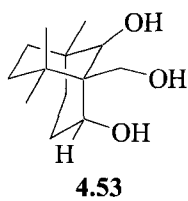


^1H NMR (CDCl_3 , 400 MHz)

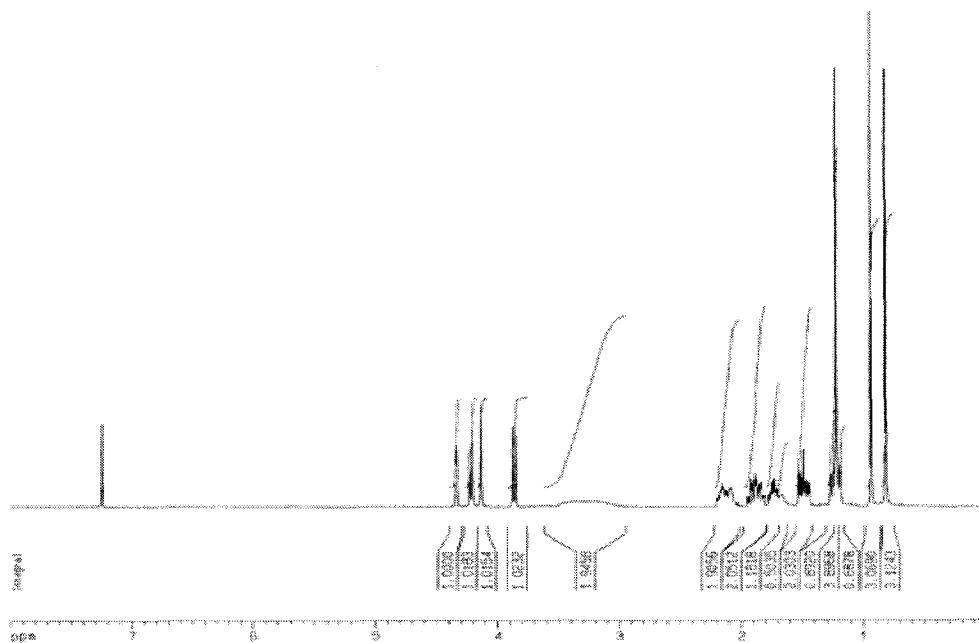


^{13}C NMR (CDCl_3 , 100 MHz)

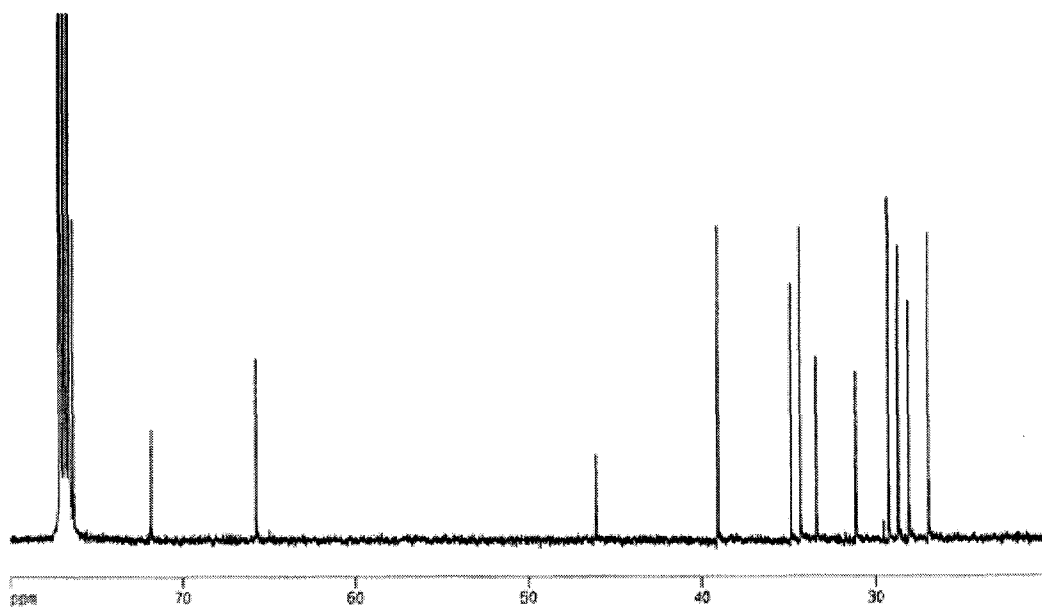


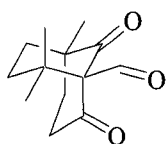


^1H NMR (CDCl_3 , 500 MHz)

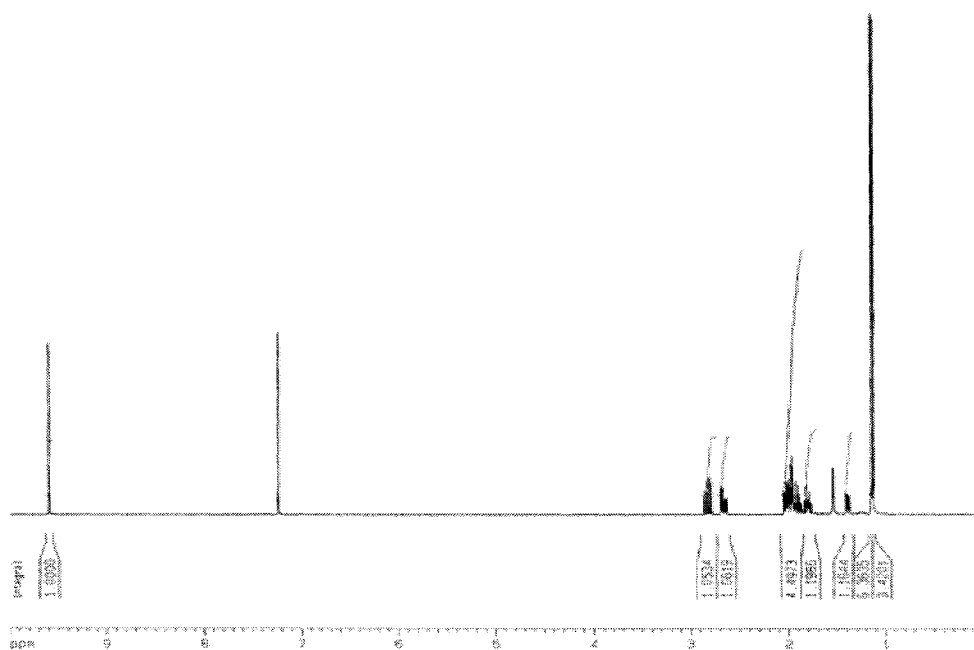


^{13}C NMR (CDCl_3 , 125 MHz)

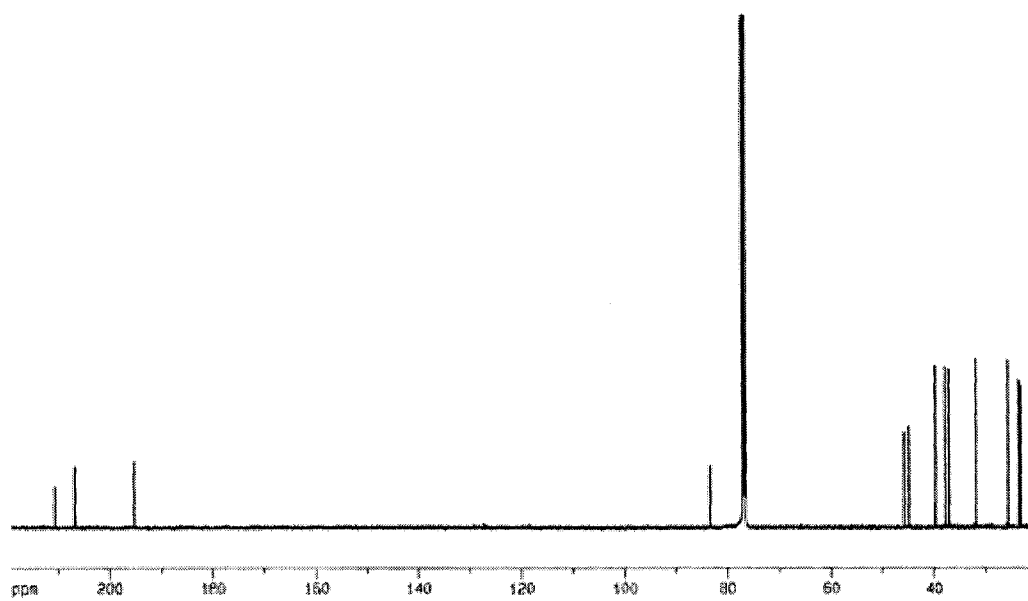


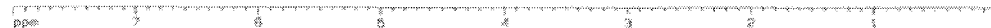


¹H NMR (CDCl₃, 500 MHz)

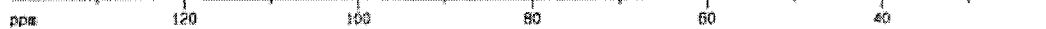


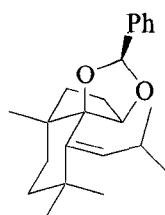
^{13}C NMR (CDCl_3 , 125 MHz)



¹H NMR (CDCl₃, 500 MHz)

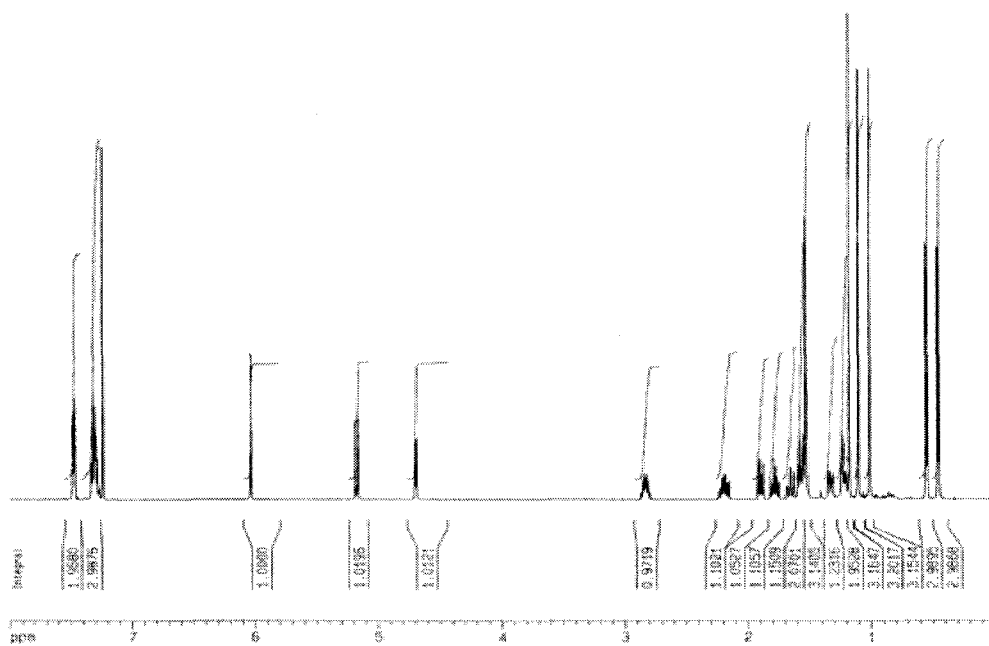
^{13}C NMR (CDCl₃, 125 MHz)



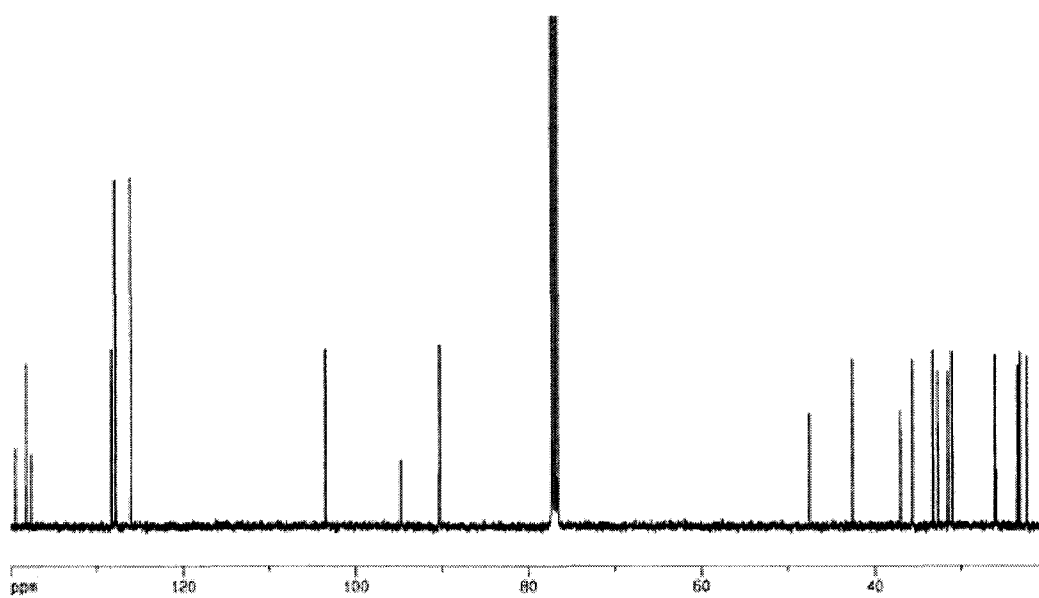


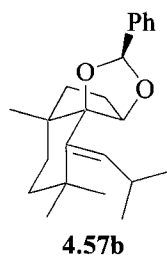
4.57a

^1H NMR (CDCl_3 , 500 MHz)

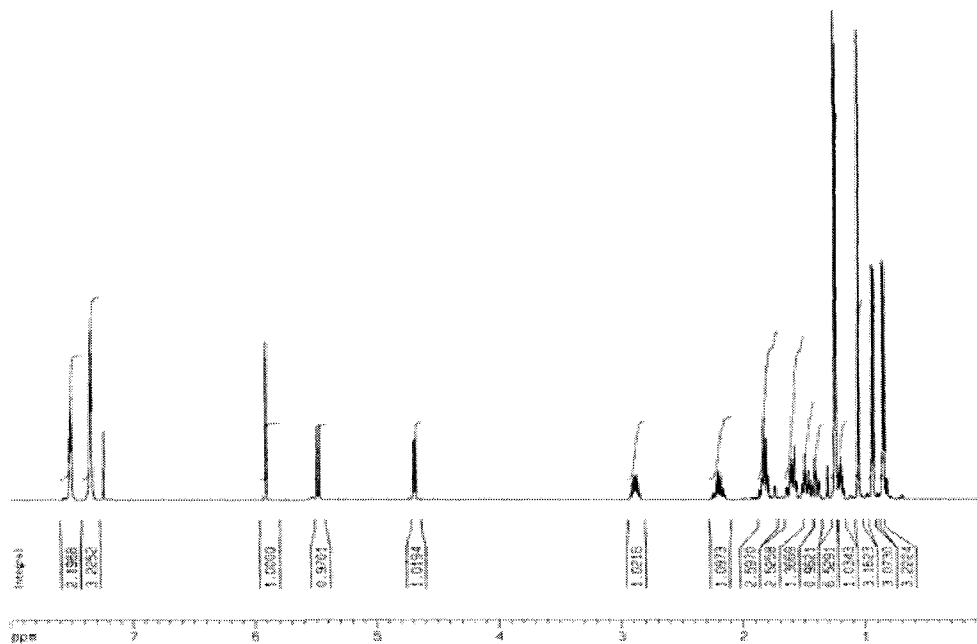


^{13}C NMR (CDCl_3 , 100 MHz)

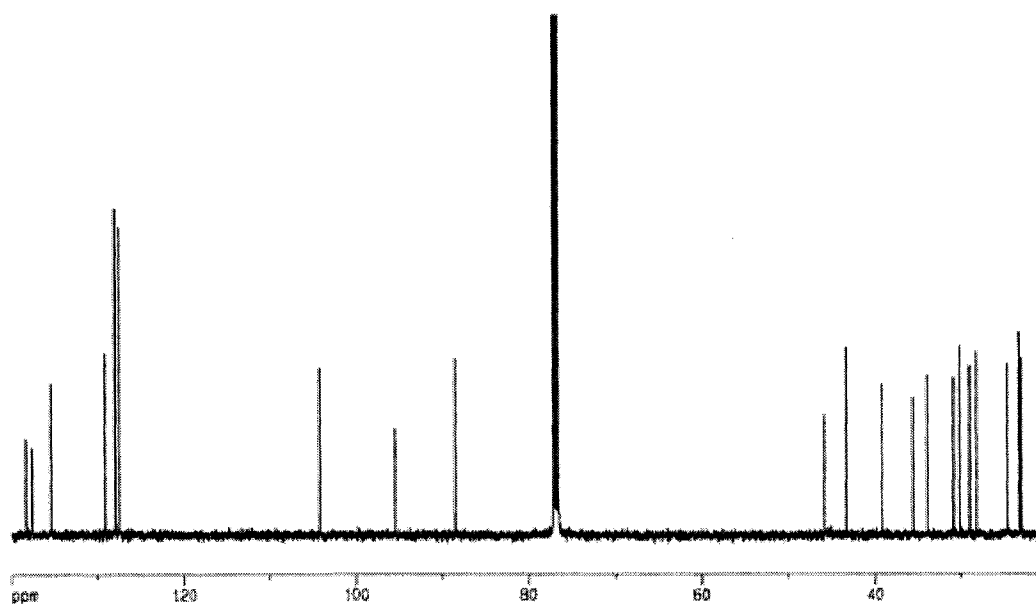


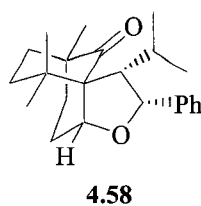


^1H NMR (CDCl_3 , 500 MHz)

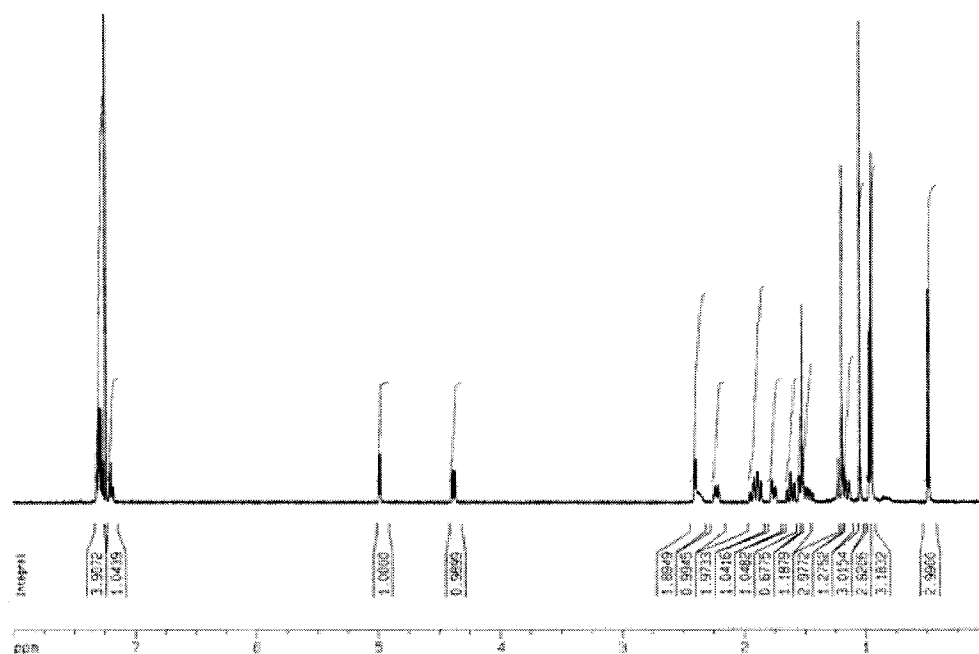


^{13}C NMR (CDCl_3 , 125 MHz)

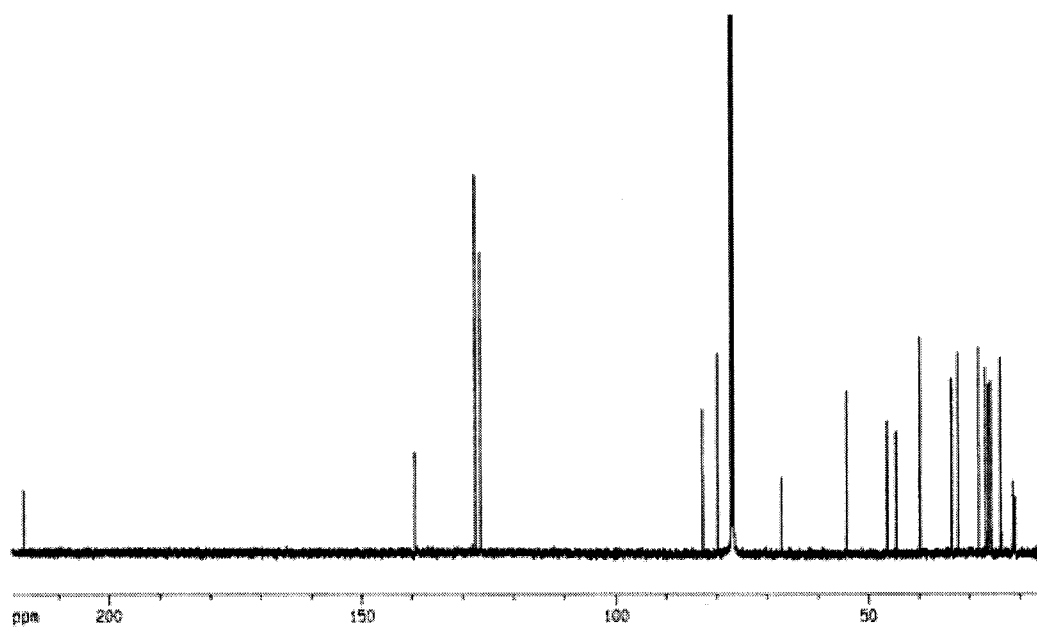


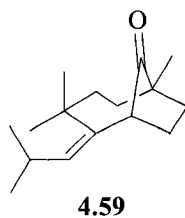


^1H NMR (CDCl_3 , 500 MHz)

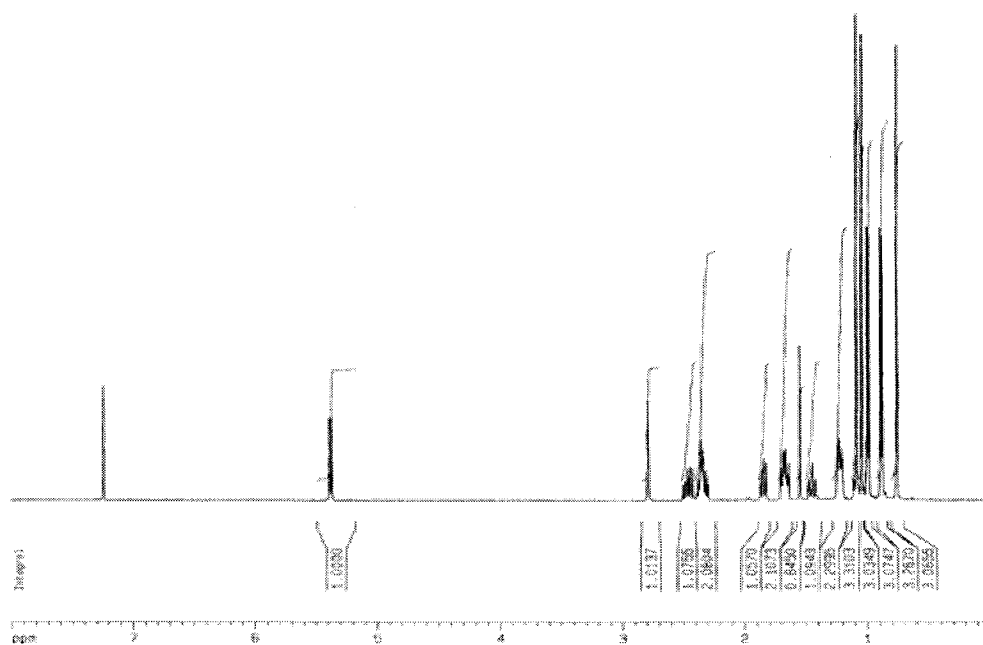


^{13}C NMR (CDCl_3 , 125 MHz)

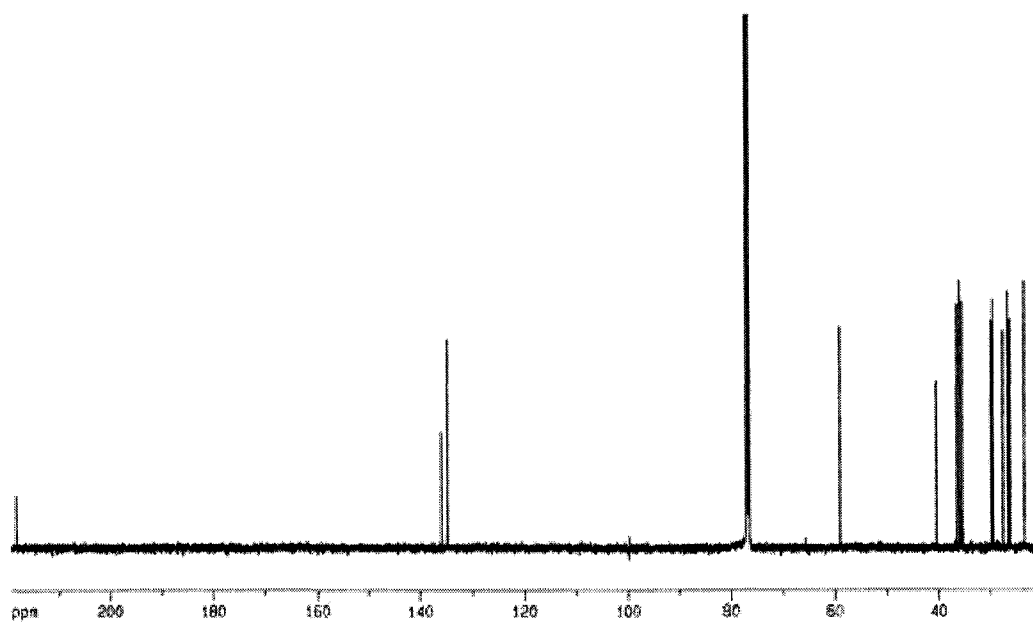


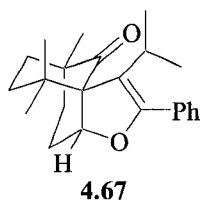


^1H NMR (CDCl_3 , 500 MHz)

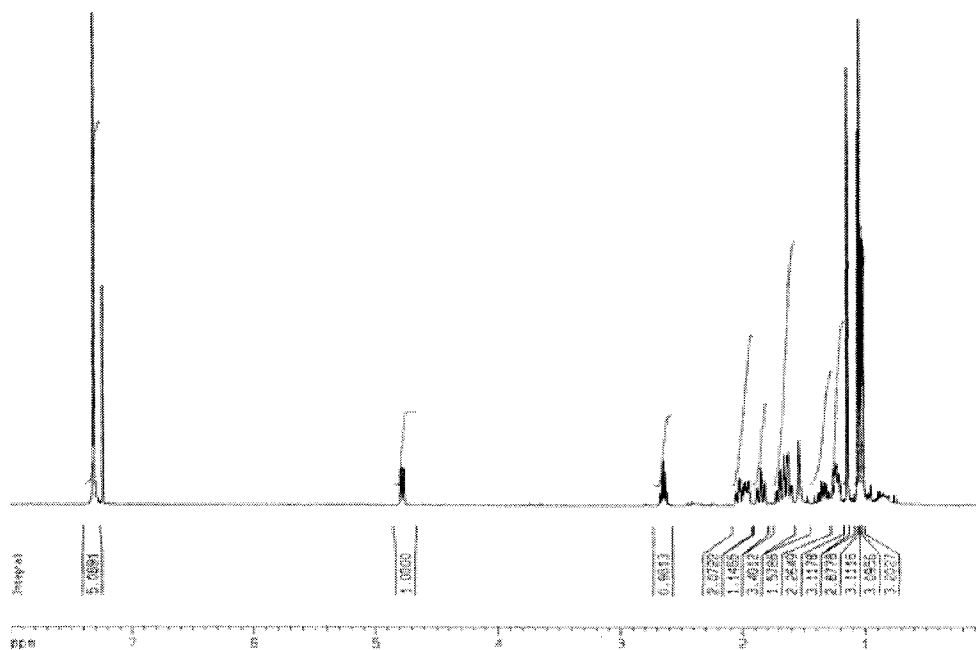


^{13}C NMR (CDCl_3 , 125 MHz)

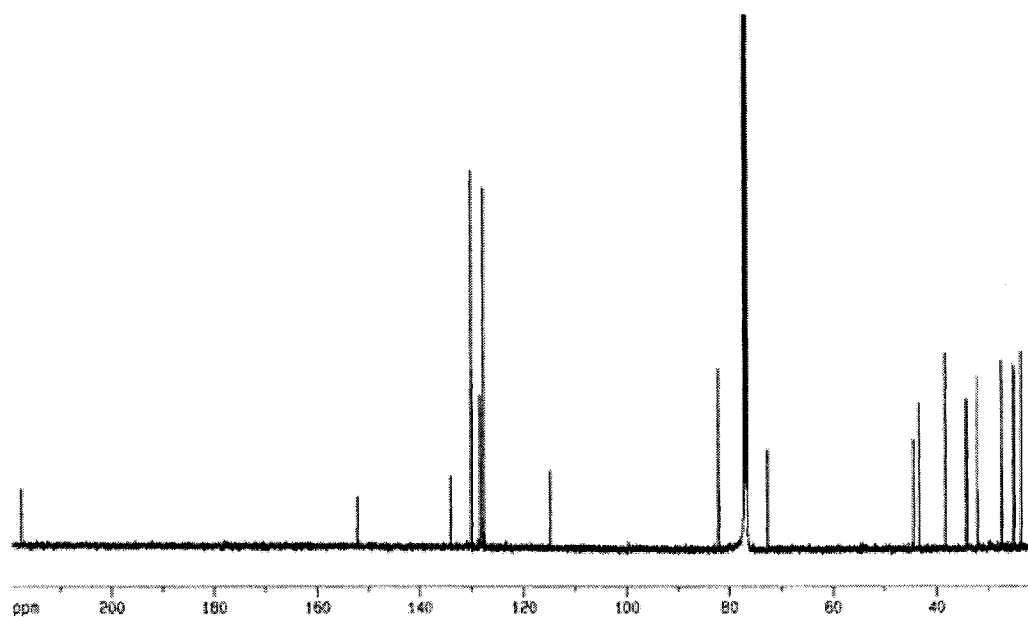


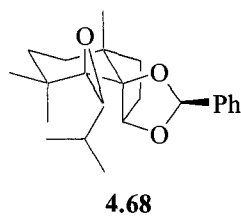


¹H NMR (CDCl₃, 500 MHz)

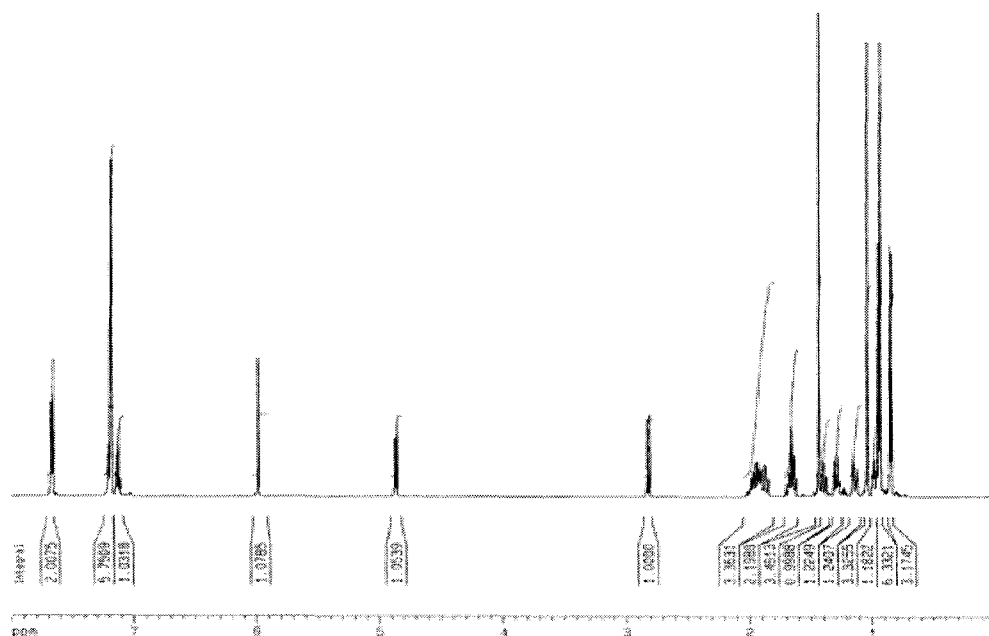


¹³C NMR (CDCl₃, 125 MHz)

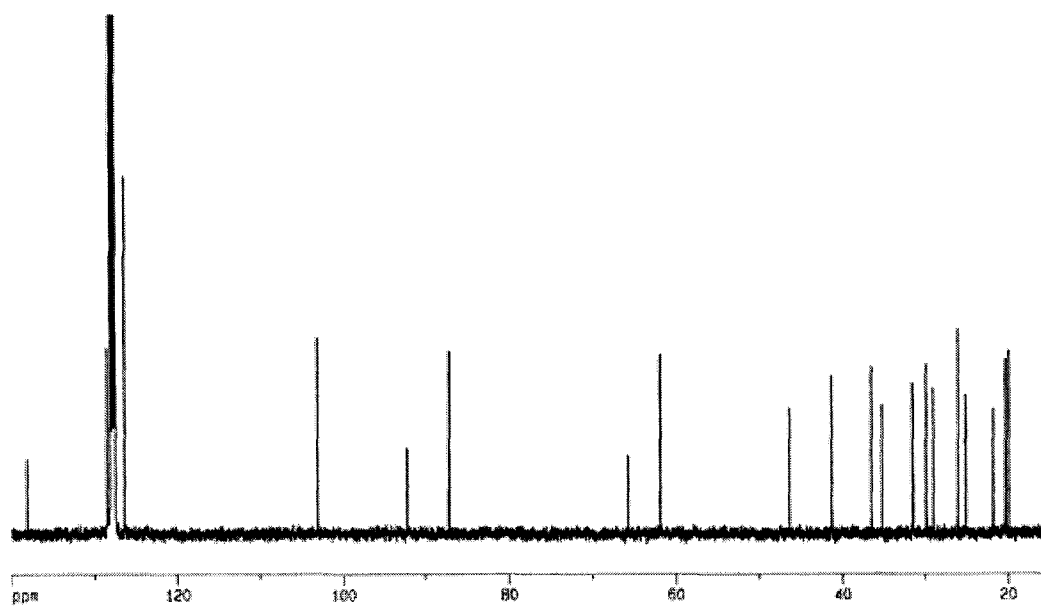


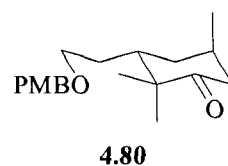


^1H NMR (C_6D_6 , 500 MHz)

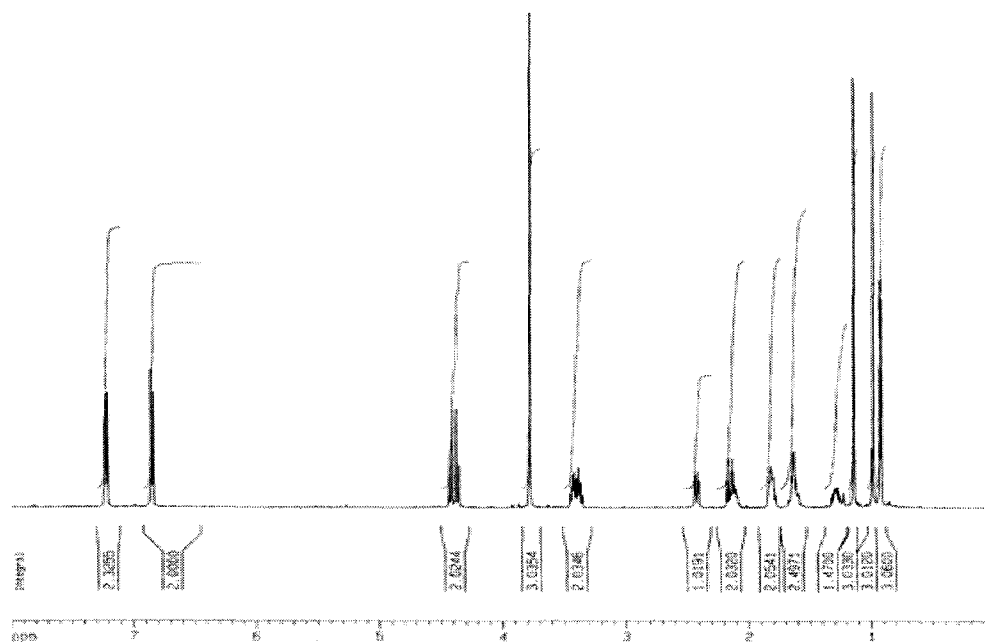


^{13}C NMR (C_6D_6 , 100 MHz)

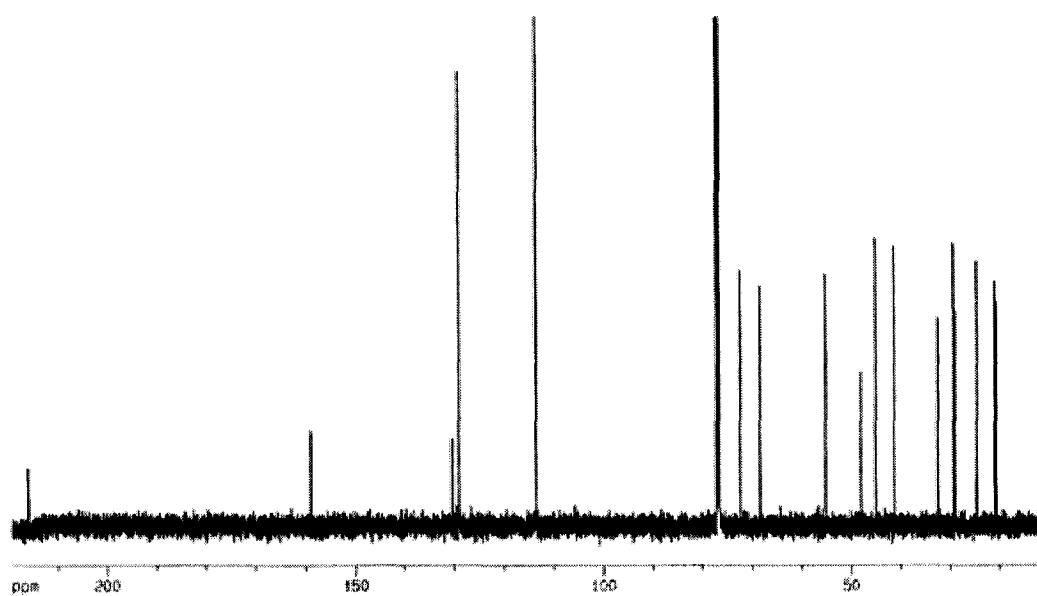


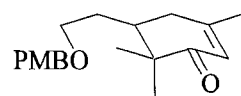


^1H NMR (CDCl_3 , 500 MHz)

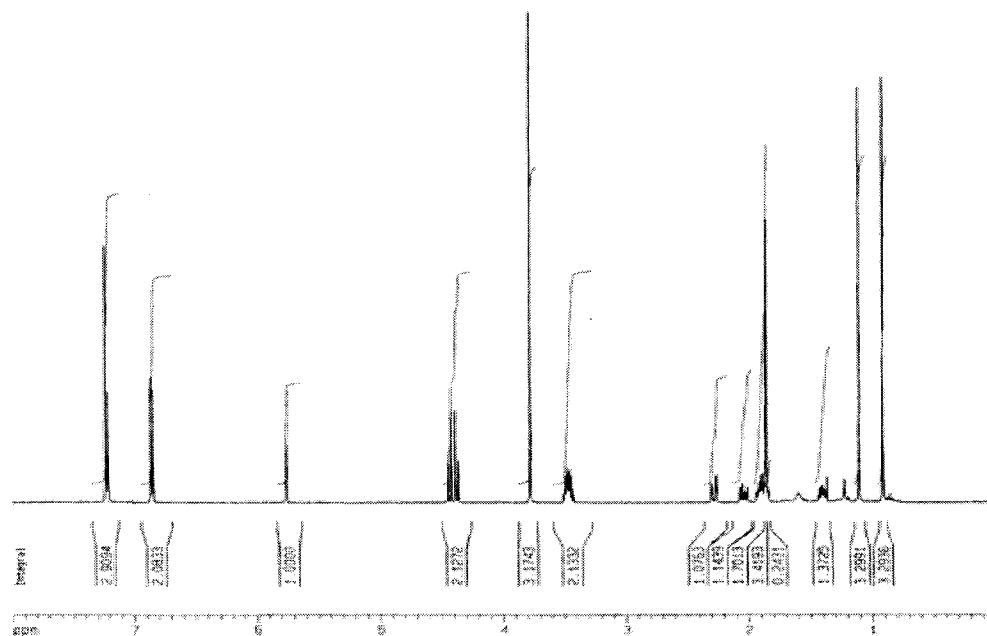
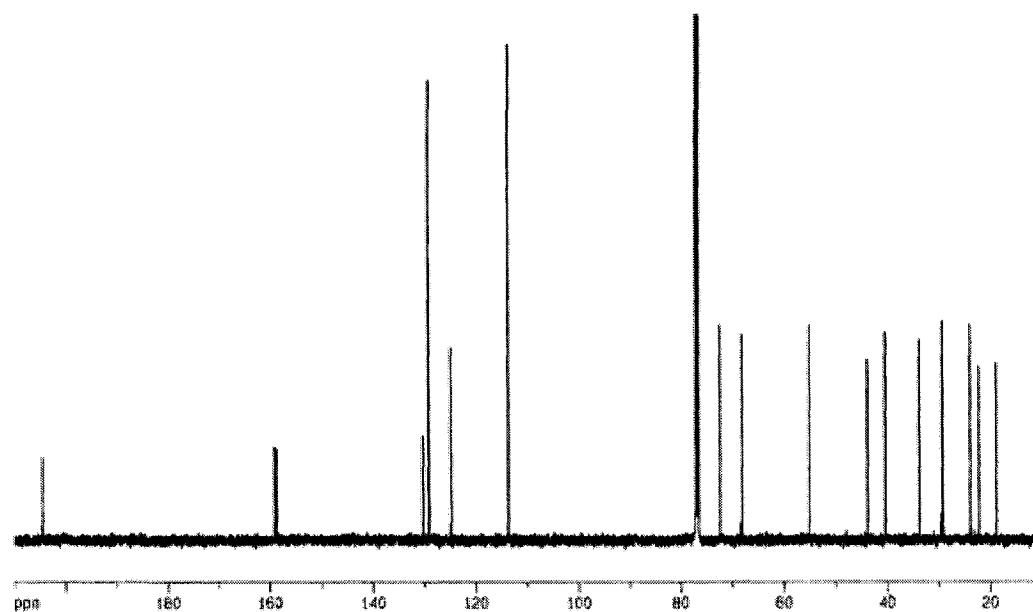


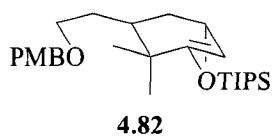
^{13}C NMR (CDCl_3 , 125 MHz)



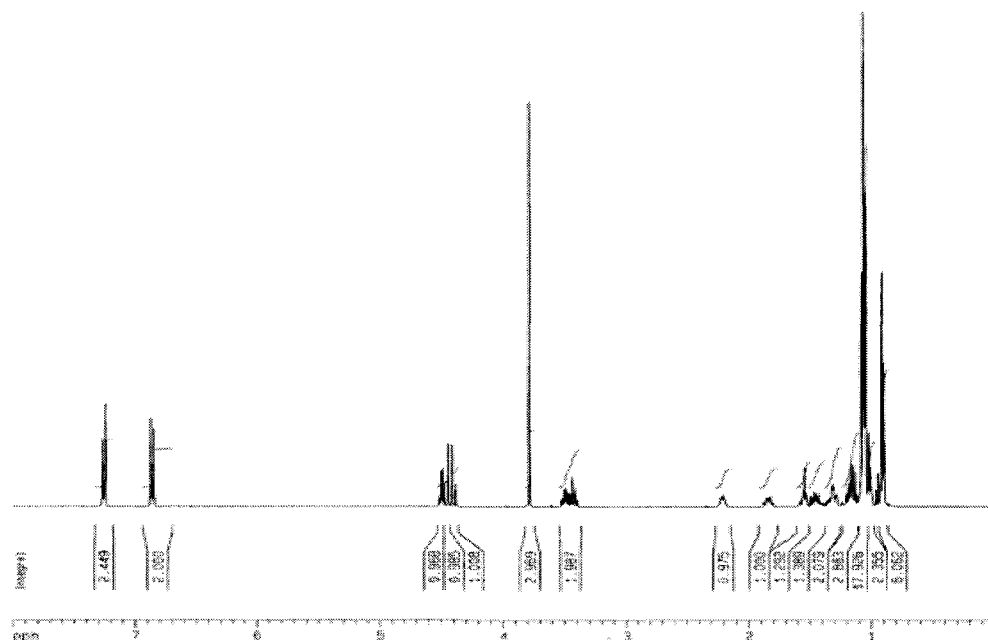


4.81

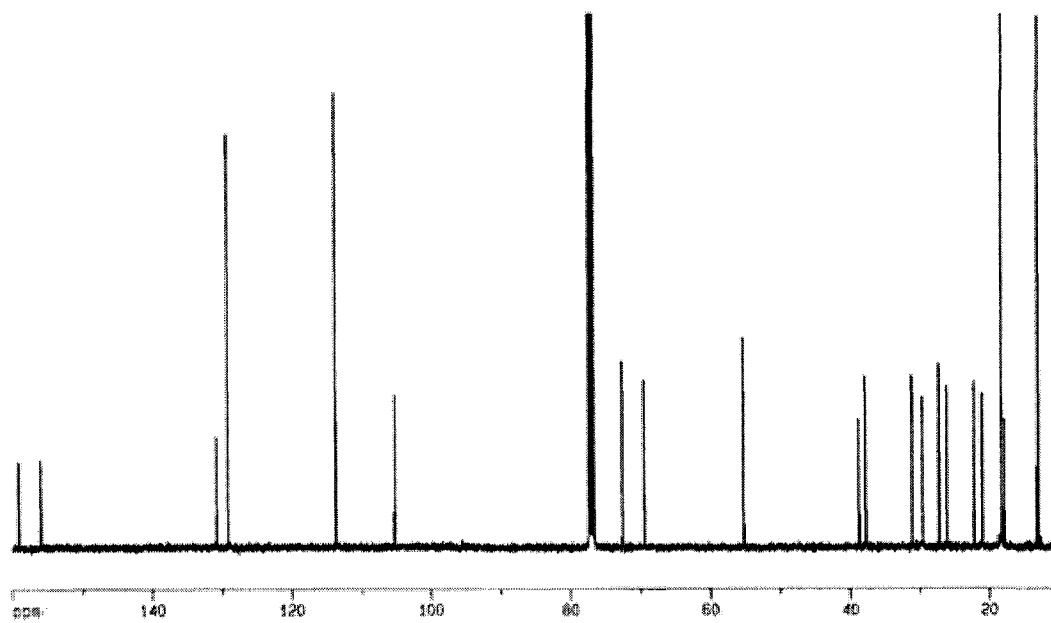
 ^1H NMR (CDCl_3 , 500 MHz) ^{13}C NMR (CDCl_3 , 125 MHz)

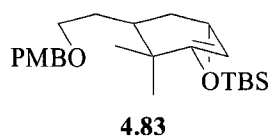


^1H NMR (CDCl_3 , 400 MHz)

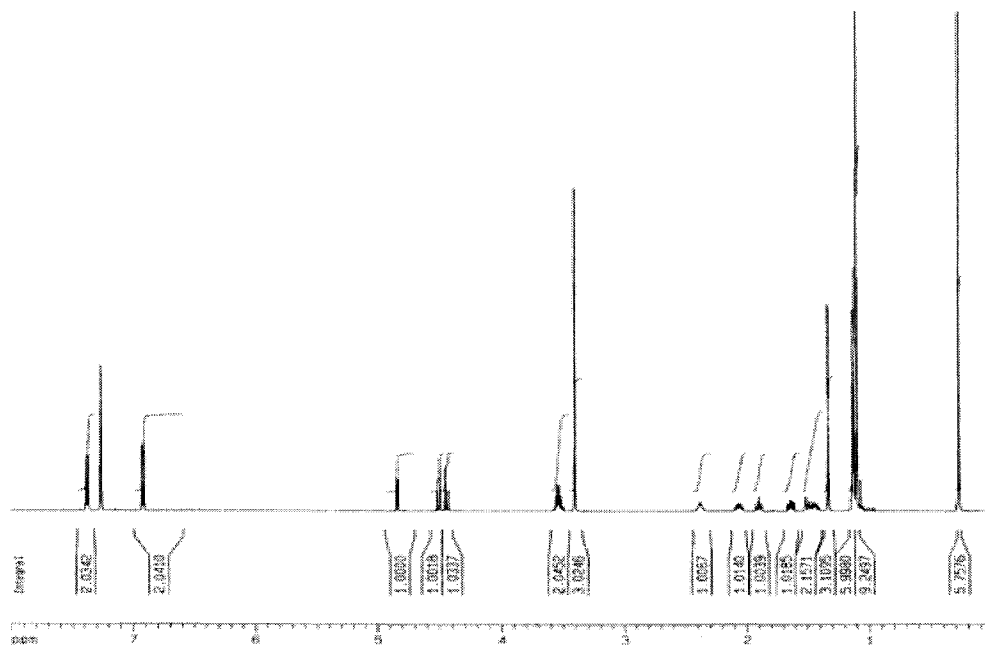


^{13}C NMR (CDCl_3 , 100 MHz)

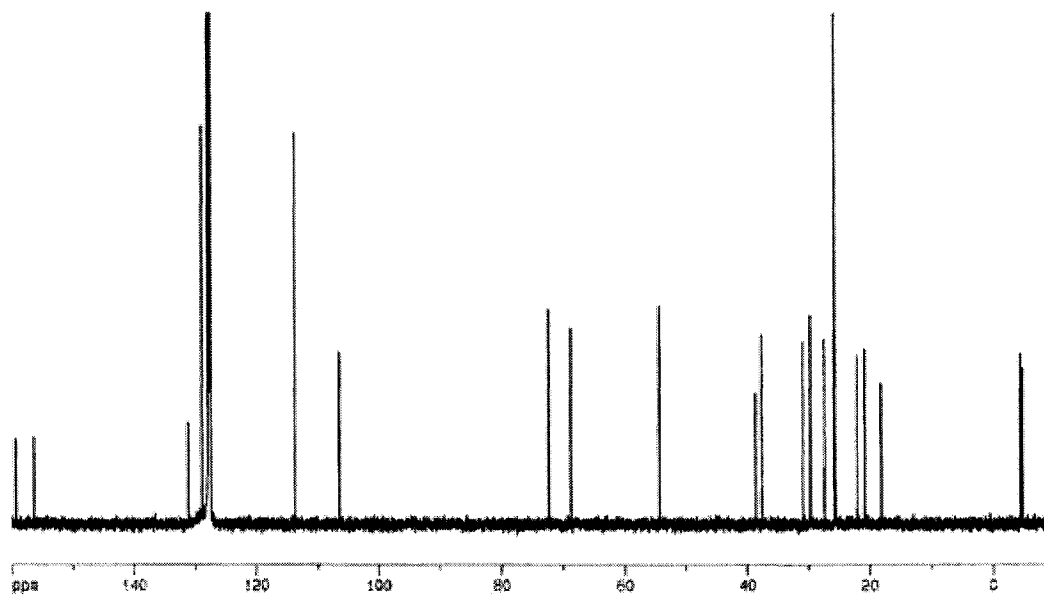


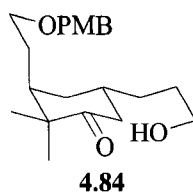


^1H NMR (C_6D_6 , 500 MHz)

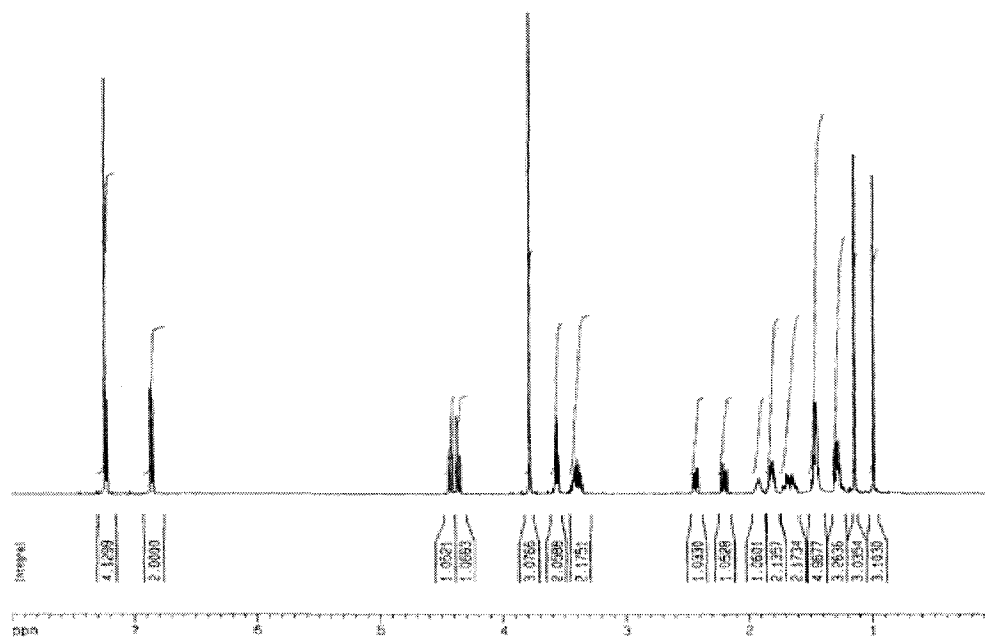


^{13}C NMR (C_6D_6 , 125 MHz)

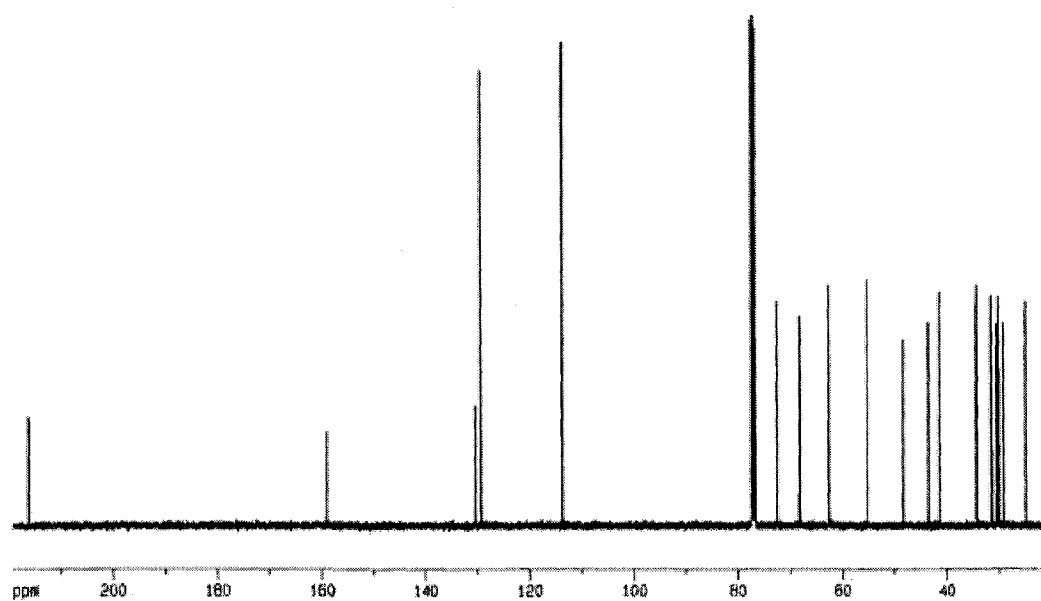


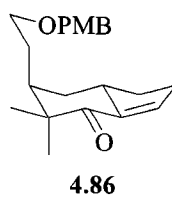


^1H NMR (CDCl_3 , 500 MHz)

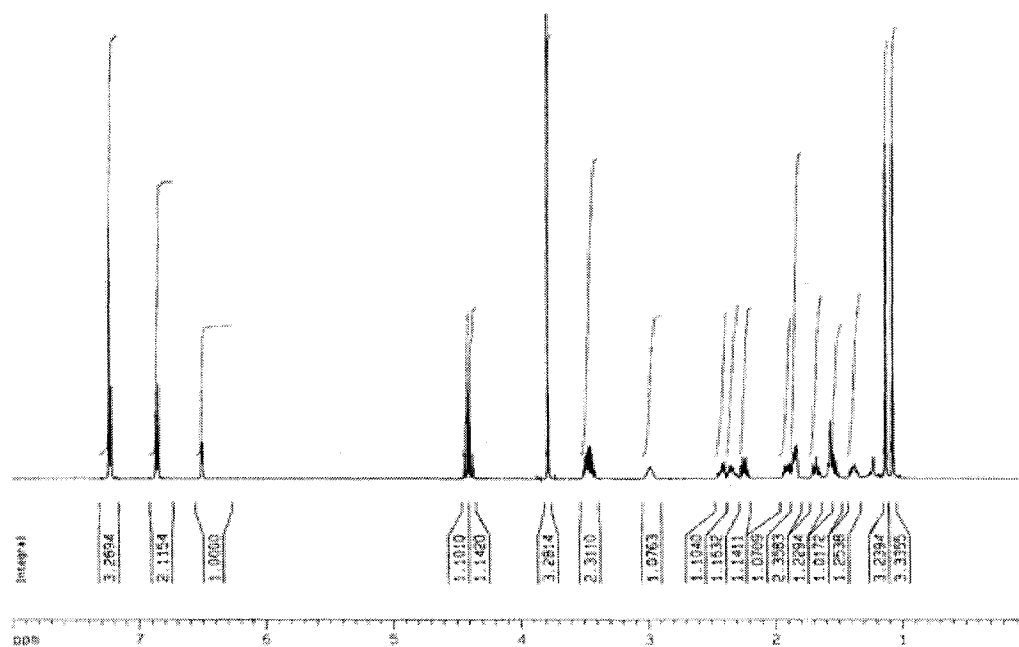


^{13}C NMR (CDCl_3 , 100 MHz)

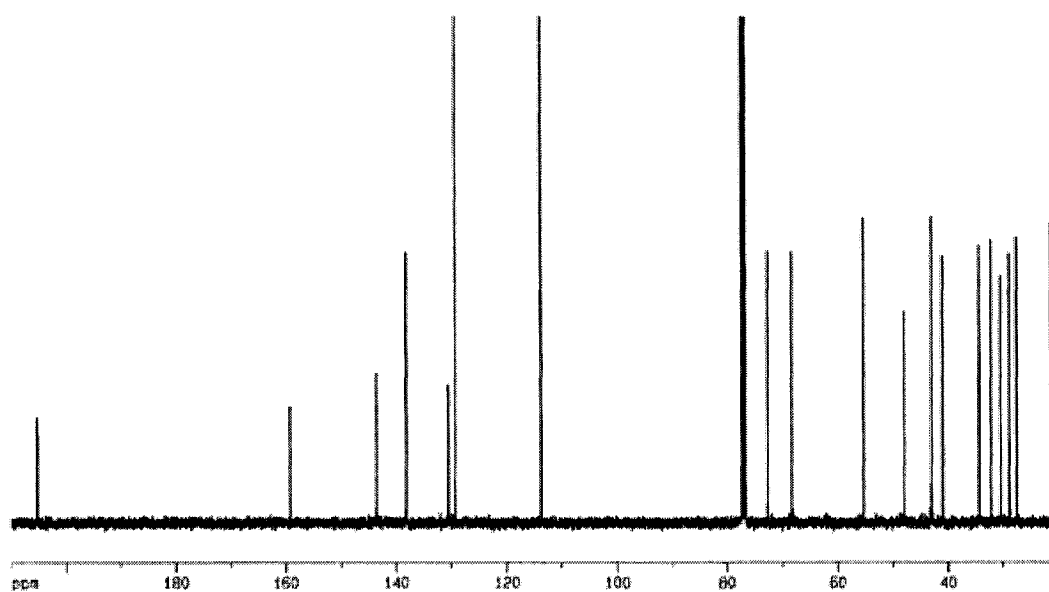


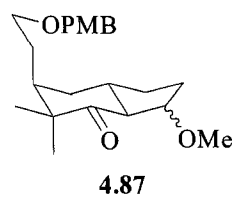


¹H NMR (CDCl₃, 500 MHz)

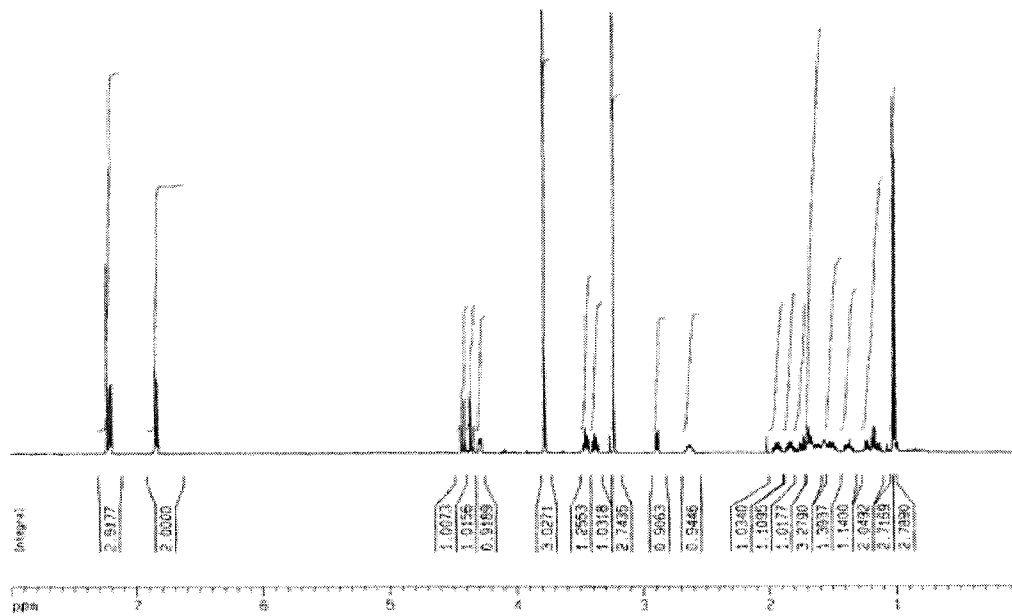


¹³C NMR (CDCl₃, 100 MHz)

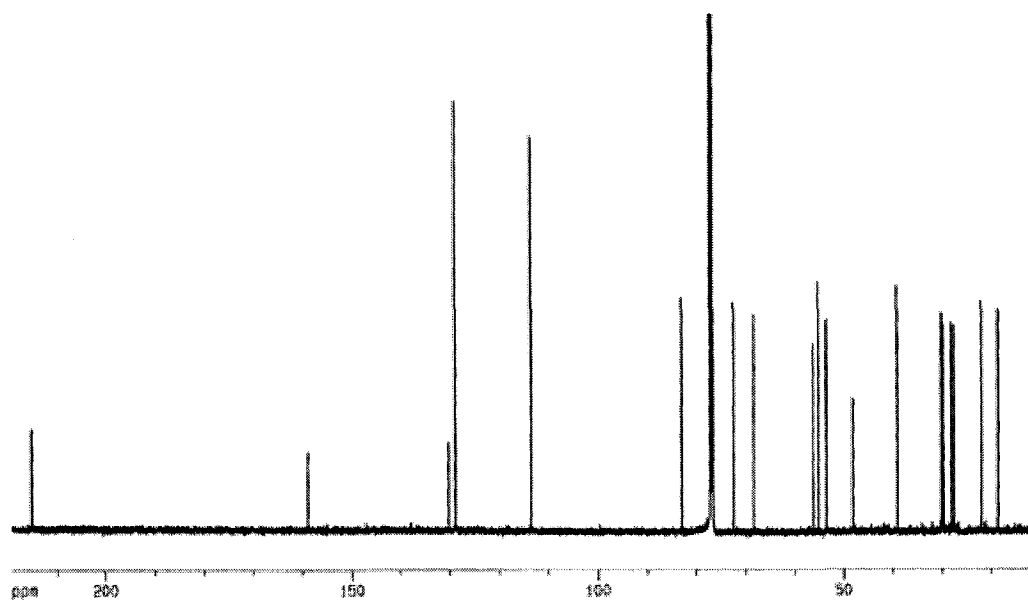


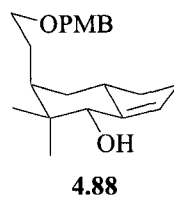


^1H NMR (CDCl_3 , 500 MHz)

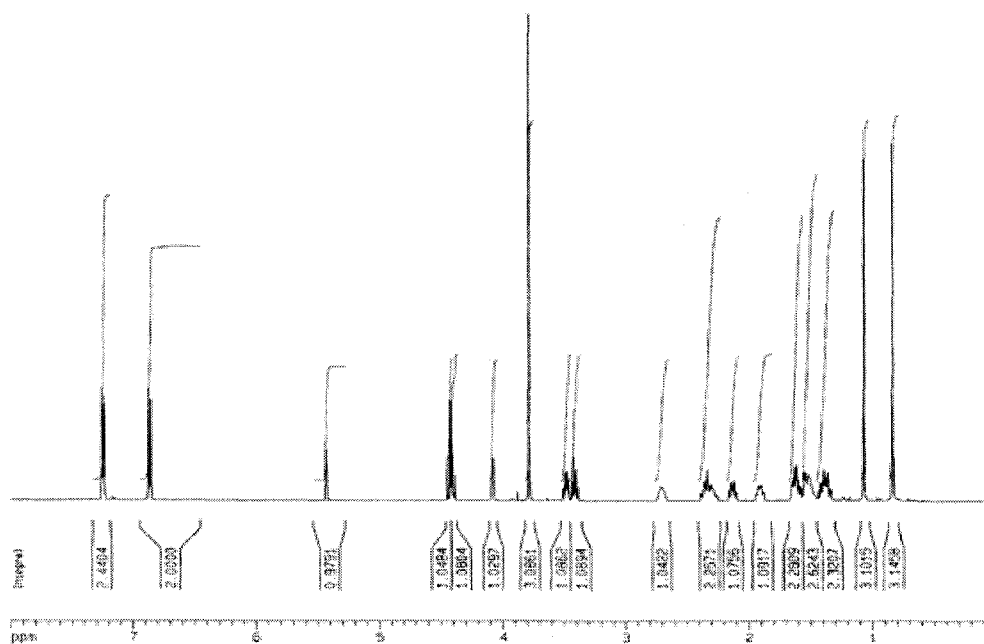


^{13}C NMR (CDCl_3 , 125 MHz)

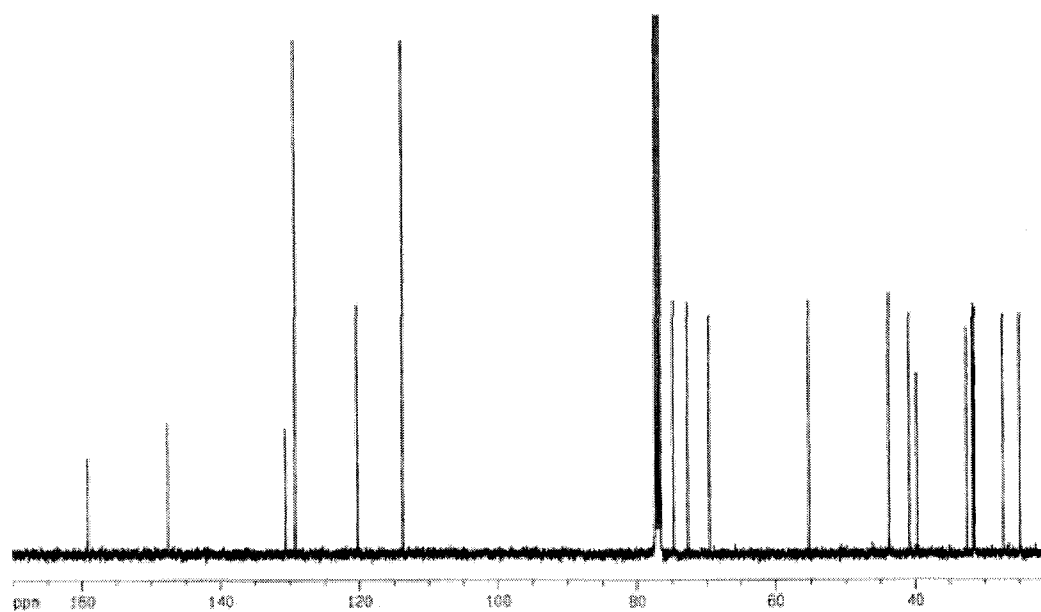


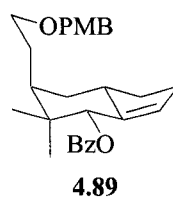


^1H NMR (CDCl_3 , 500 MHz)

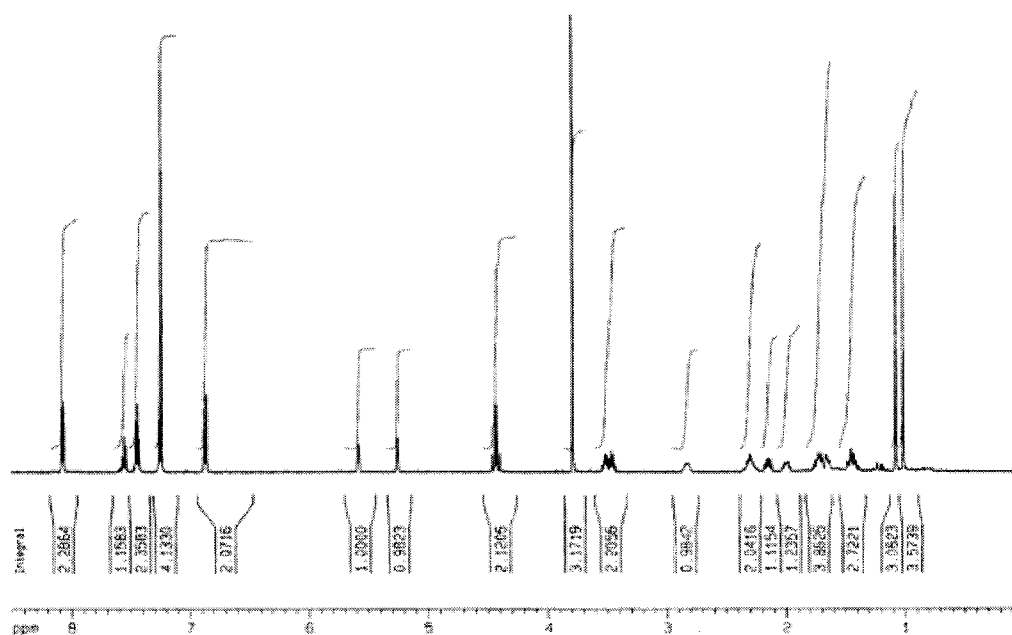


^{13}C NMR (CDCl_3 , 100 MHz)

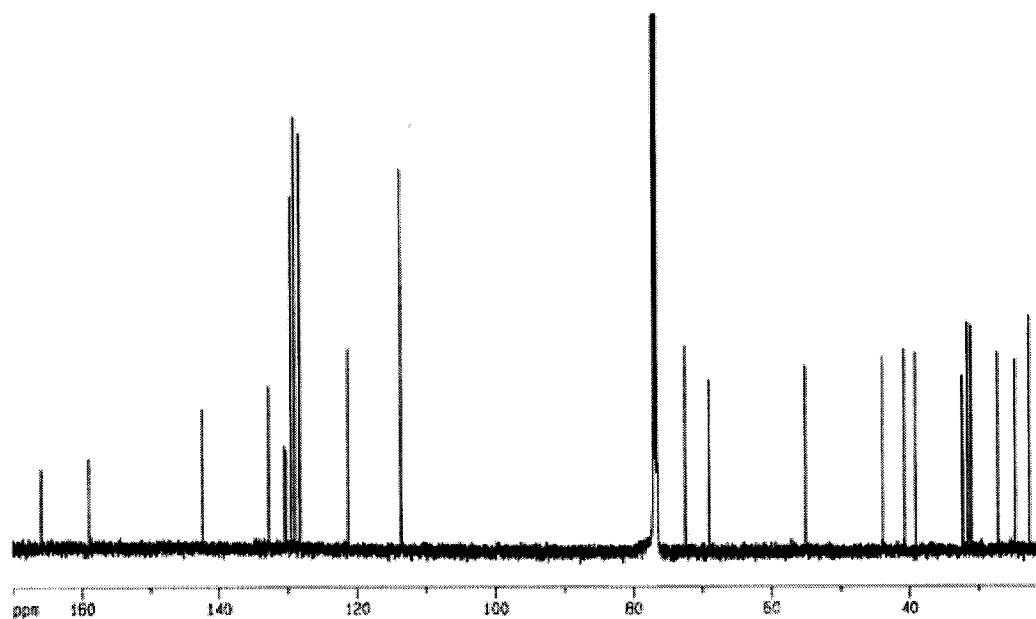


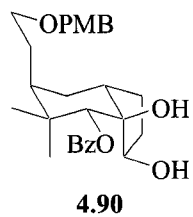


^1H NMR (CDCl_3 , 500 MHz)

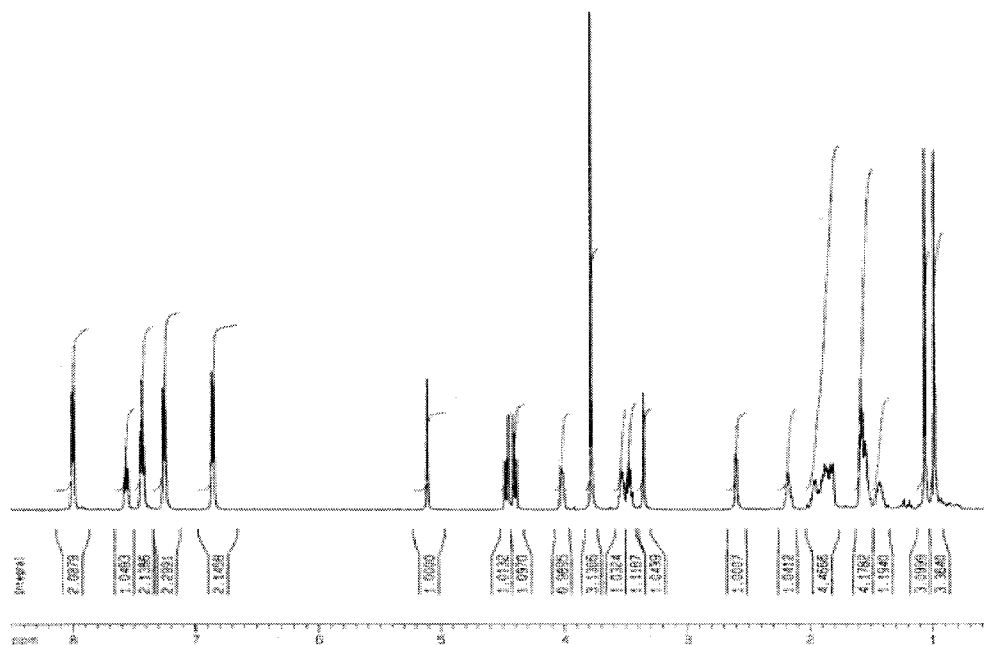


^{13}C NMR (CDCl_3 , 125 MHz)

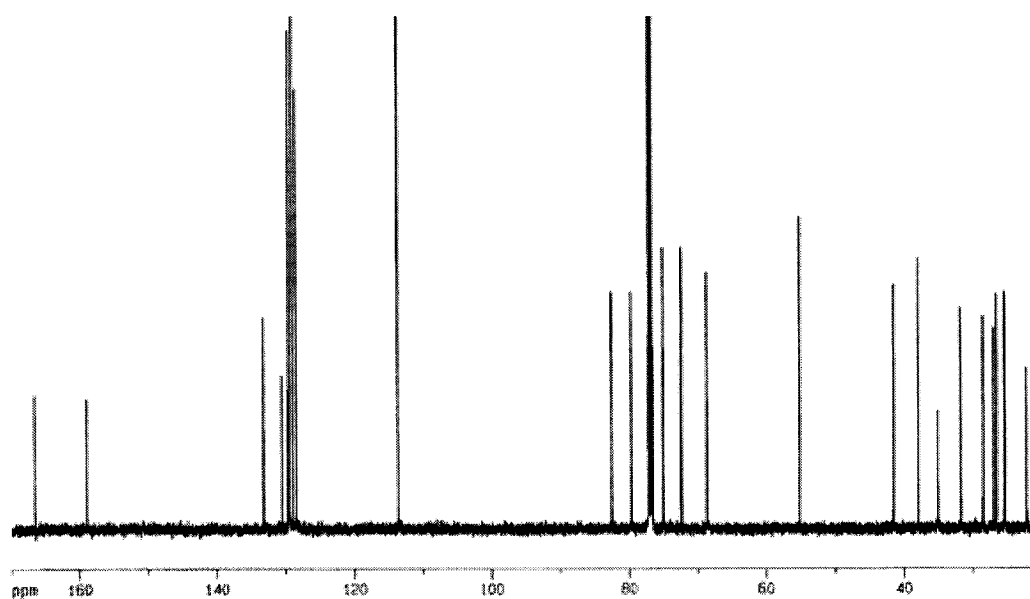




^1H NMR (CDCl_3 , 500 MHz)

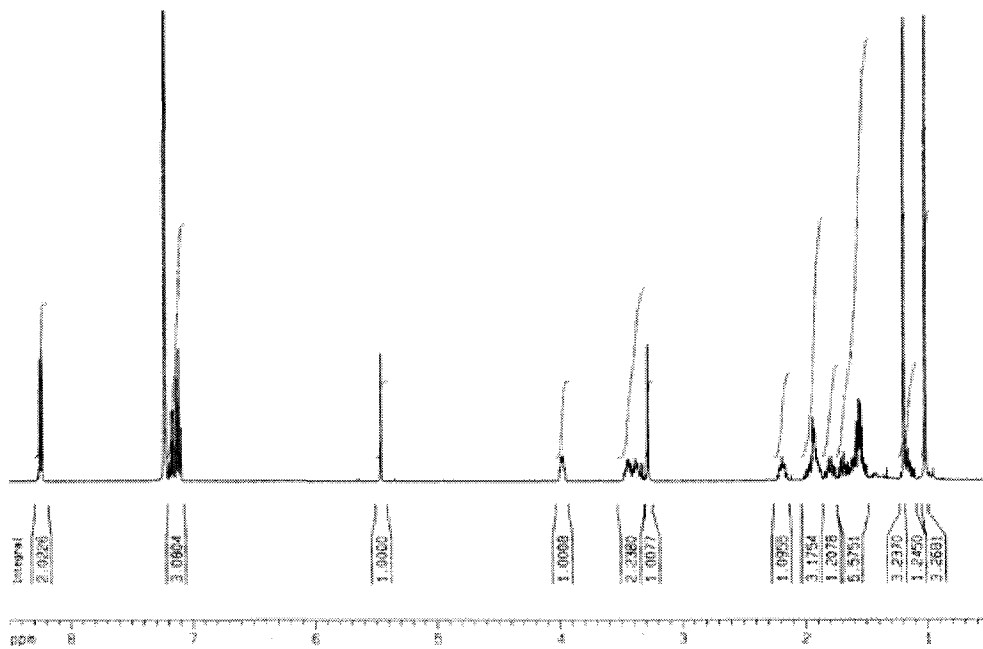


^{13}C NMR (CDCl_3 , 125 MHz)

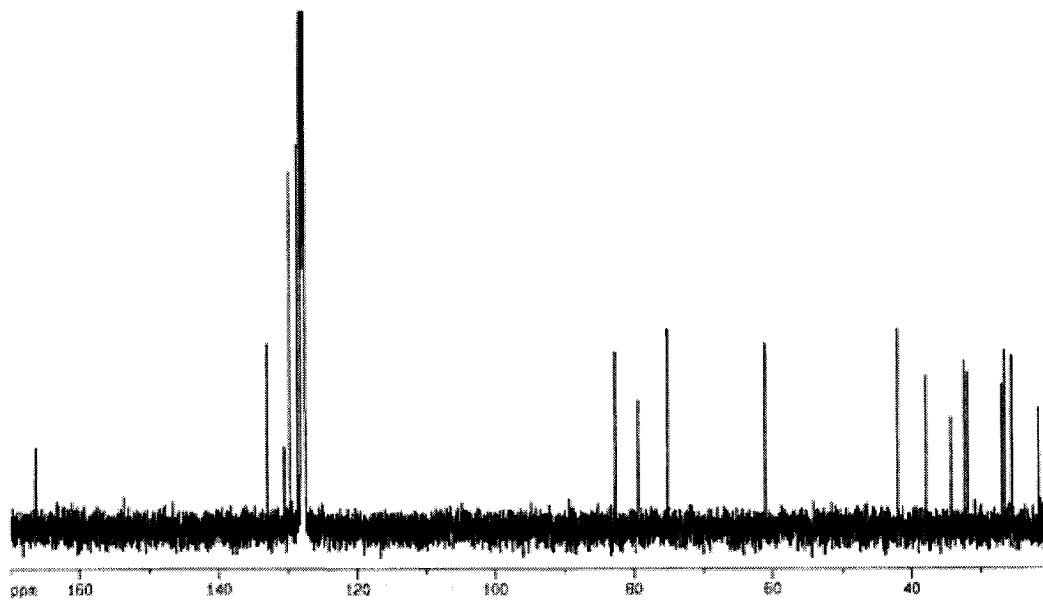


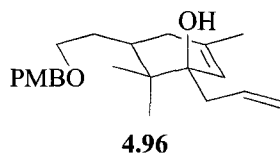


¹H NMR (C₆D₆, 400 MHz)

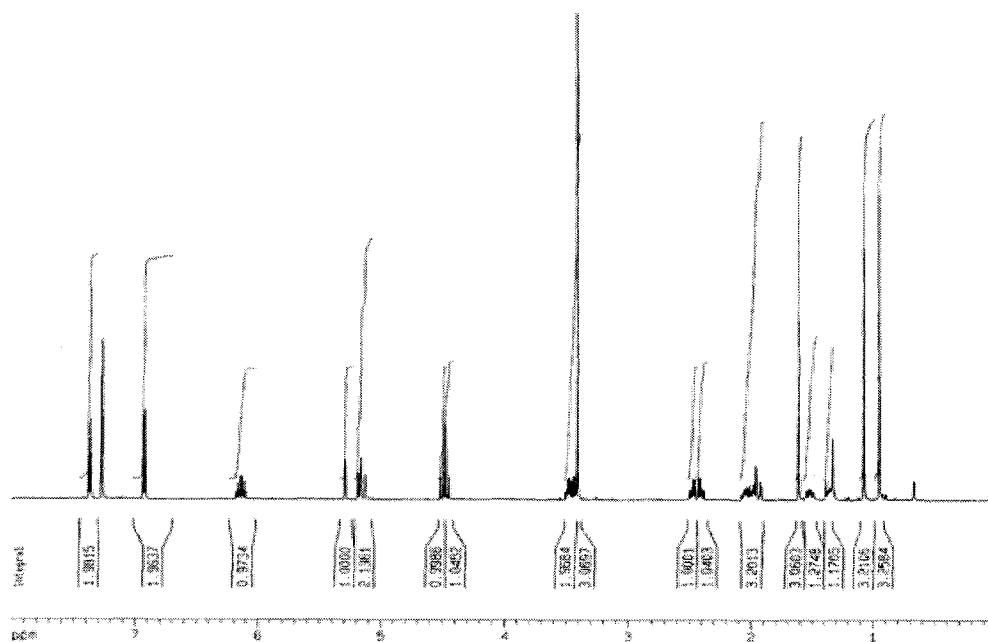


^{13}C NMR (C₆D₆, 100 MHz)

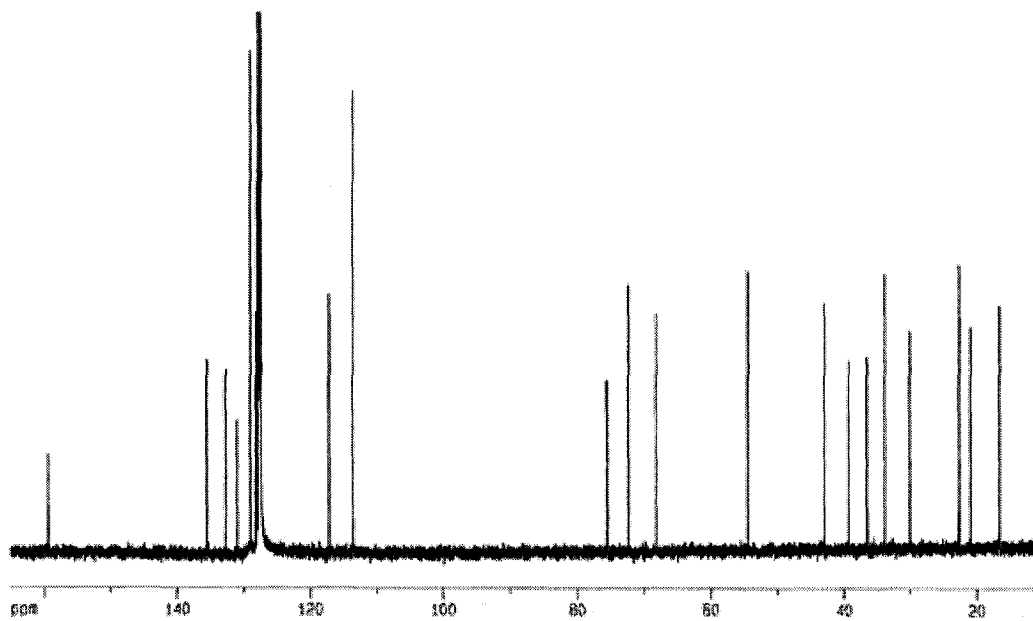


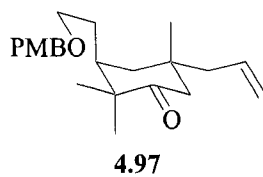


¹H NMR (C₆D₆, 500 MHz)

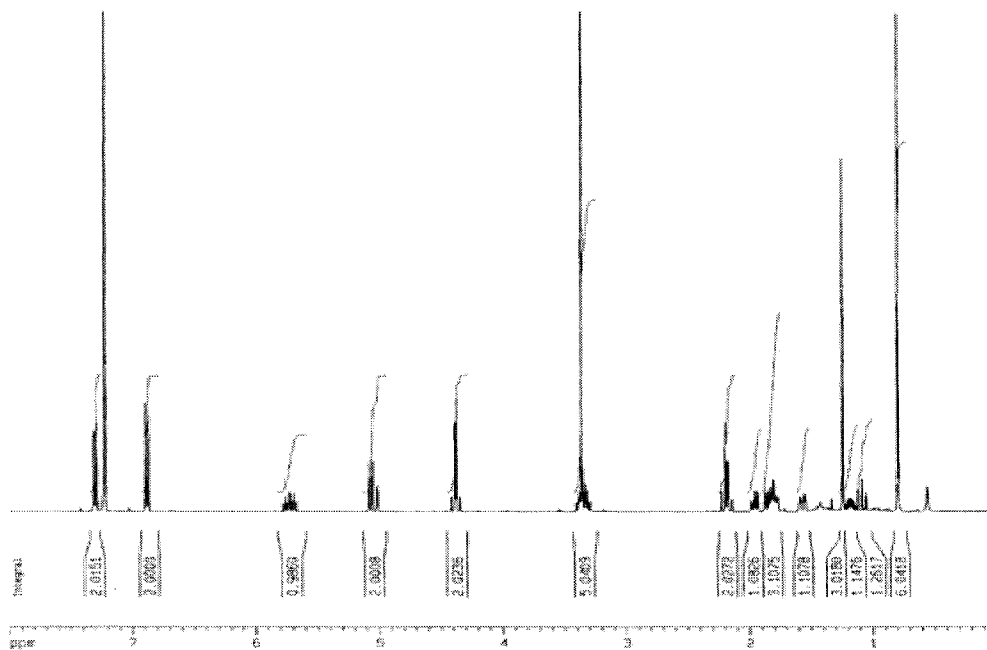


¹³C NMR (C₆D₆, 125 MHz)

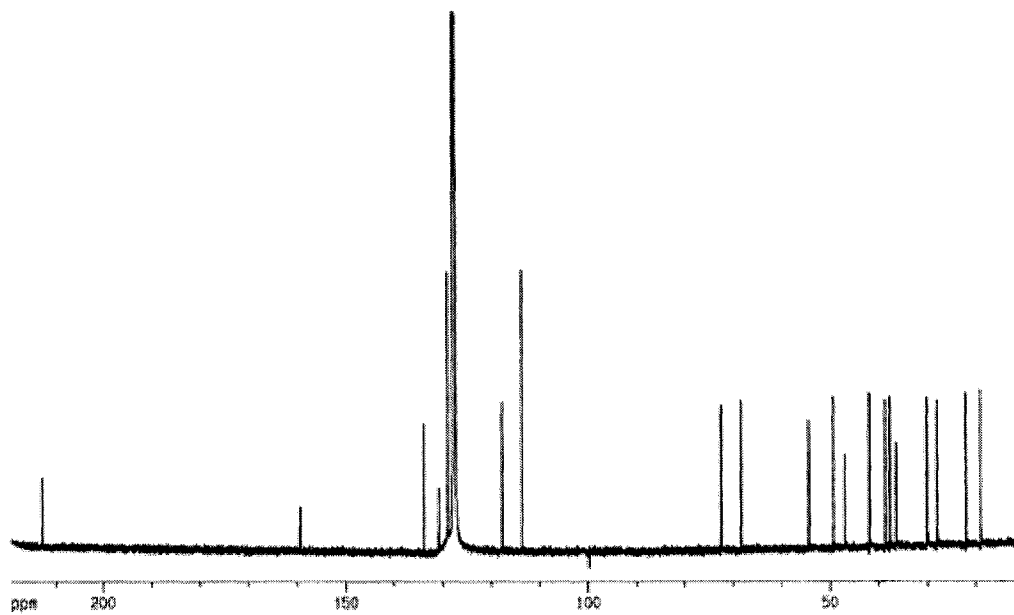


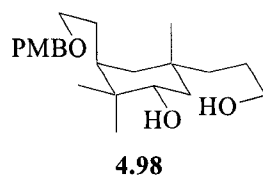


^1H NMR (C_6D_6 , 400 MHz)

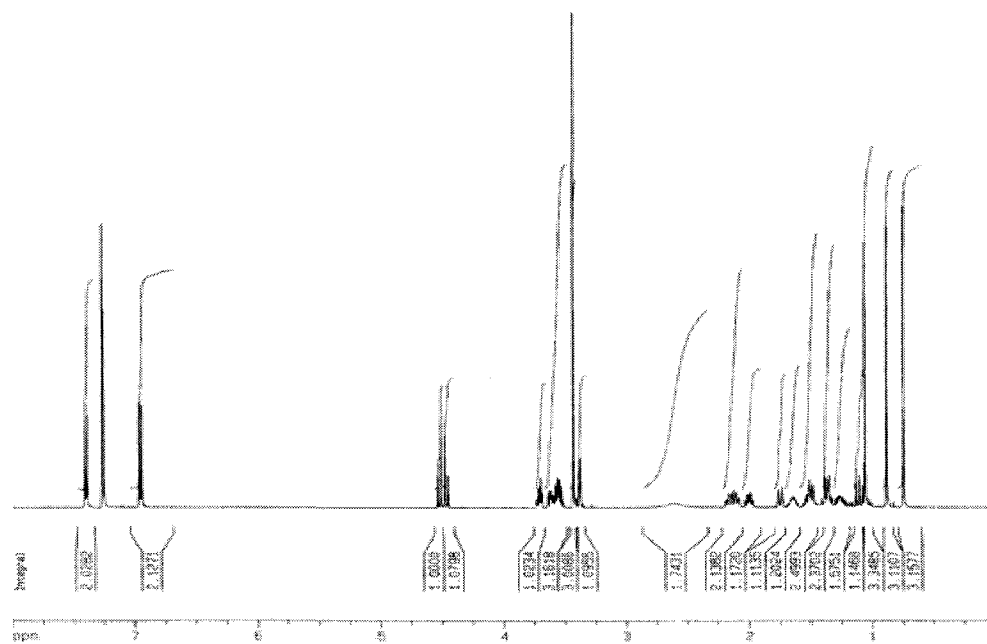


^{13}C NMR (C_6D_6 , 125 MHz)

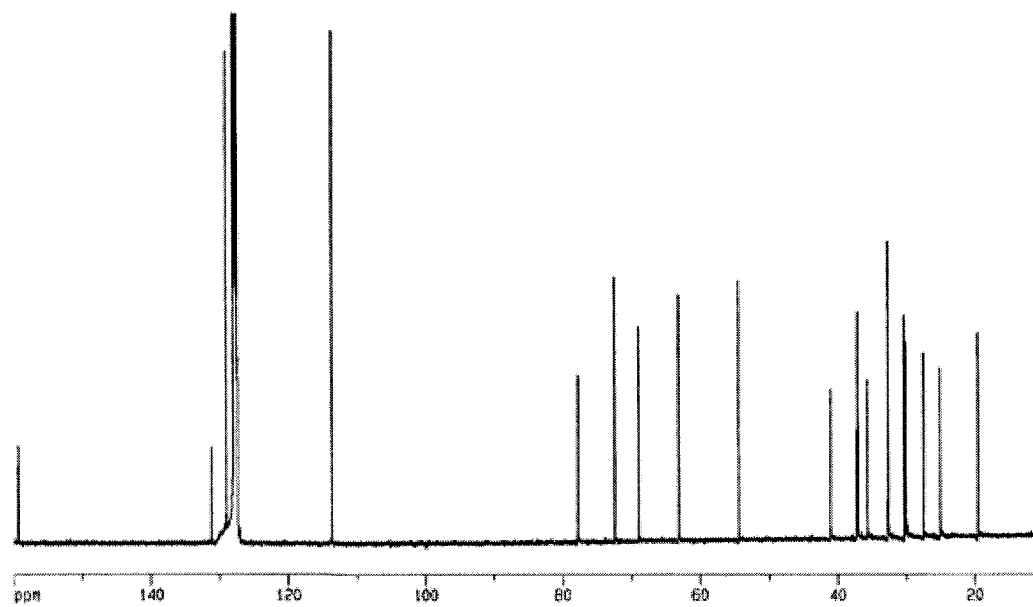


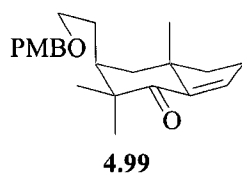


^1H NMR (C_6D_6 , 500 MHz)

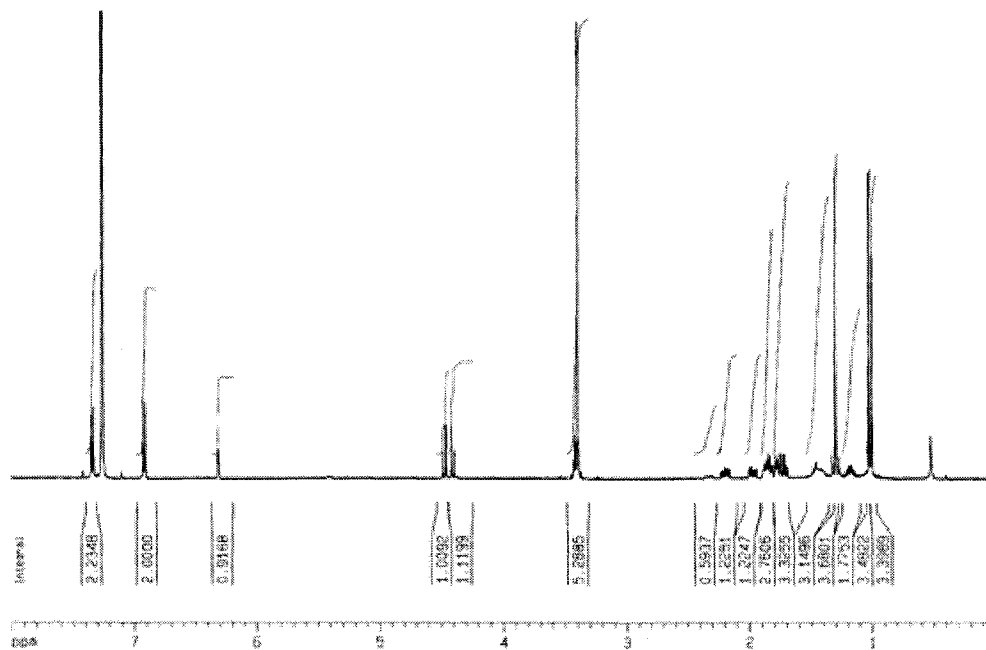


^{13}C NMR (C_6D_6 , 125 MHz)

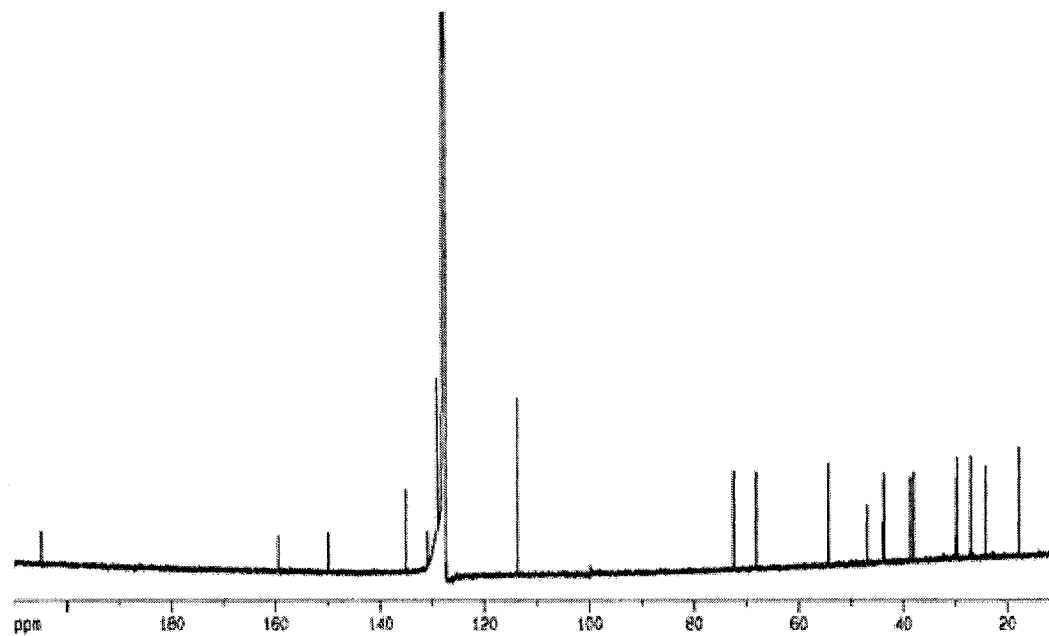


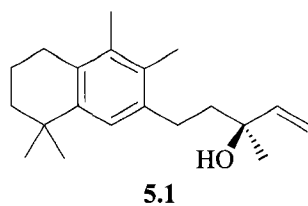


^1H NMR (C_6D_6 , 500 MHz)

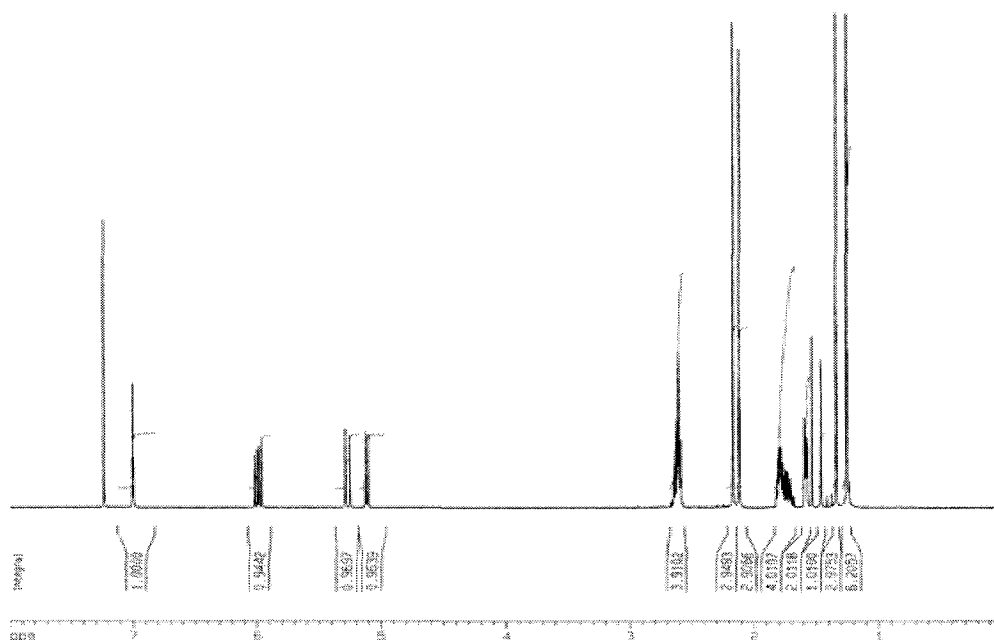


^{13}C NMR (C_6D_6 , 125 MHz)

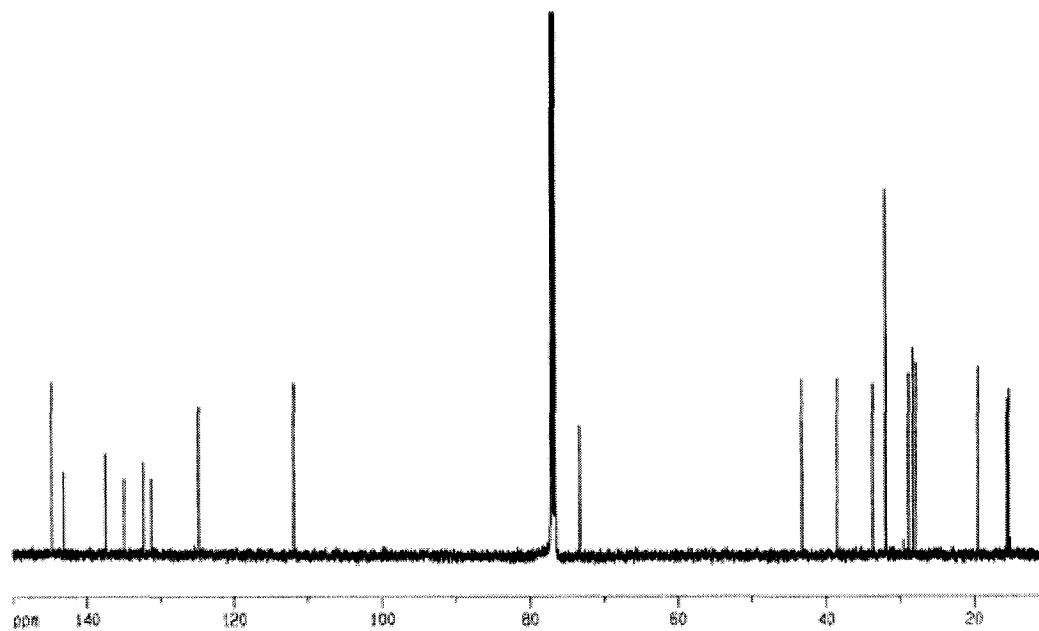


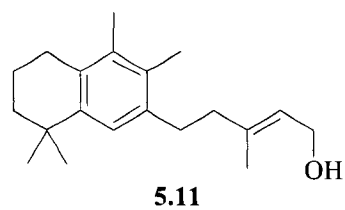


¹H NMR (CDCl₃, 500 MHz)

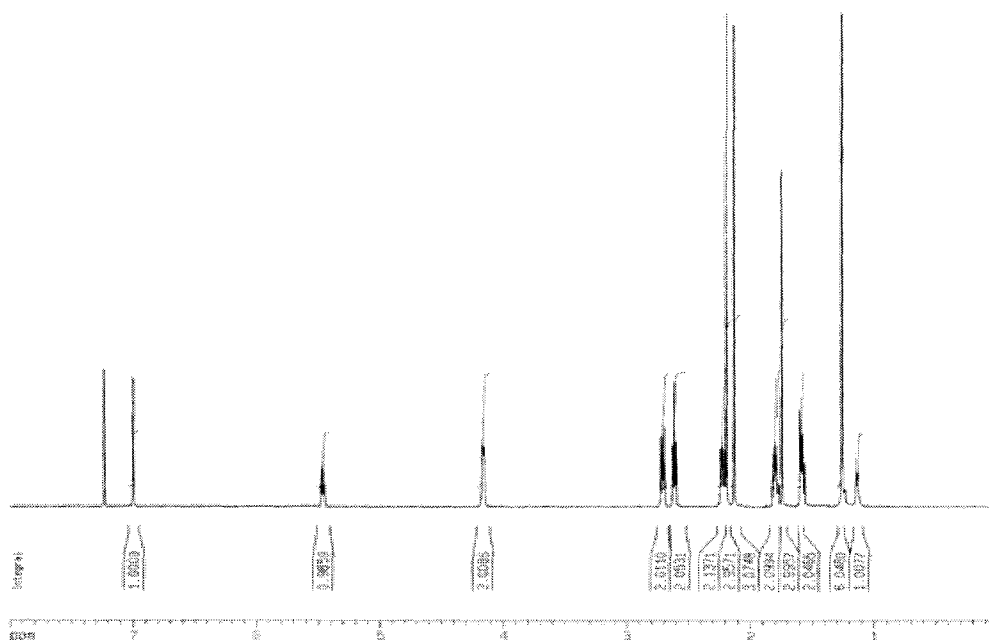


¹³C NMR (CDCl₃, 125 MHz)

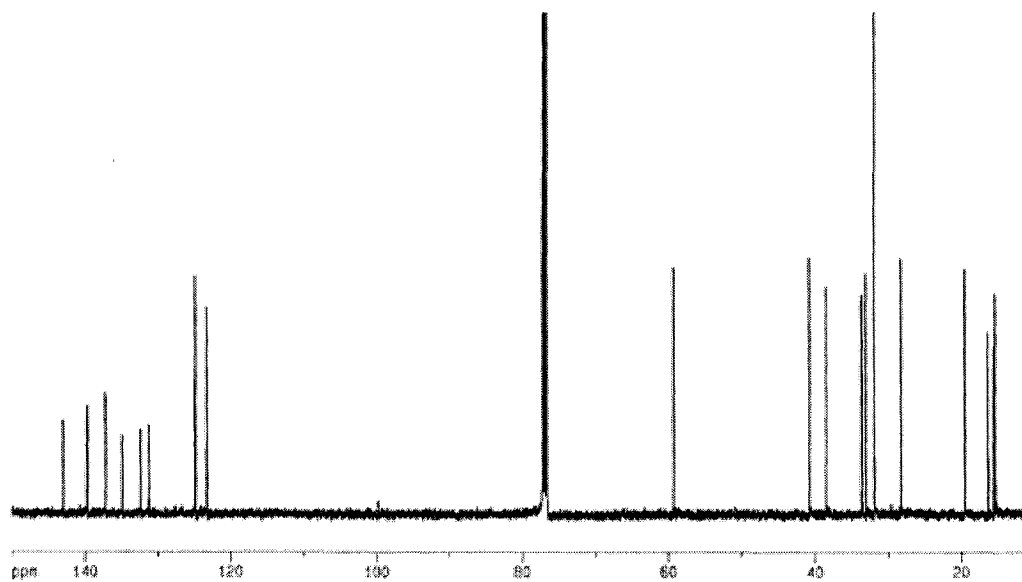


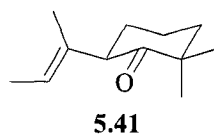


^1H NMR (CDCl_3 , 500 MHz)

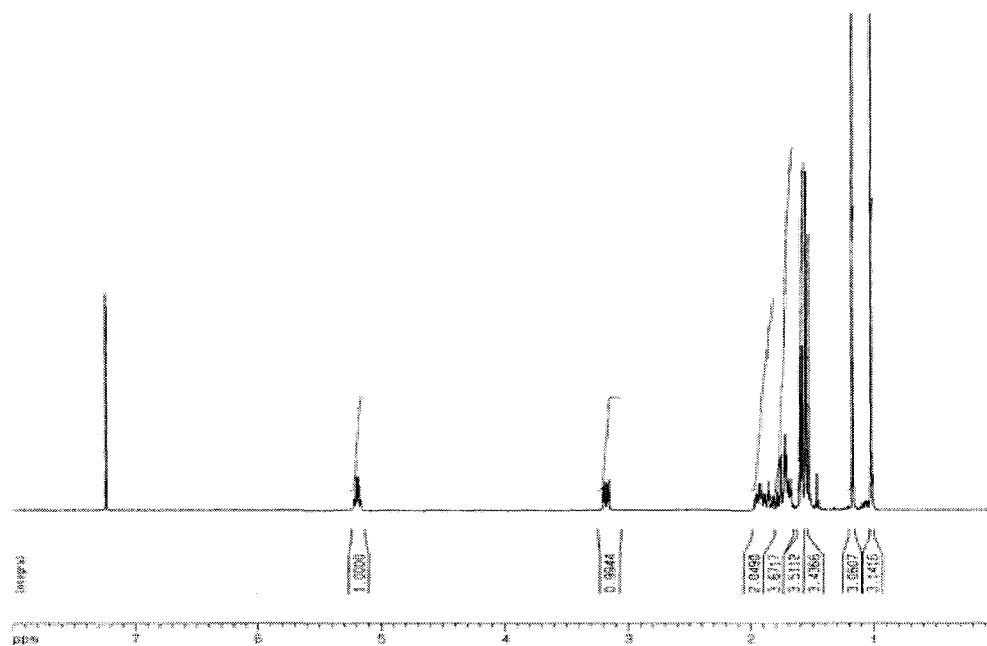


^{13}C NMR (CDCl_3 , 125 MHz)

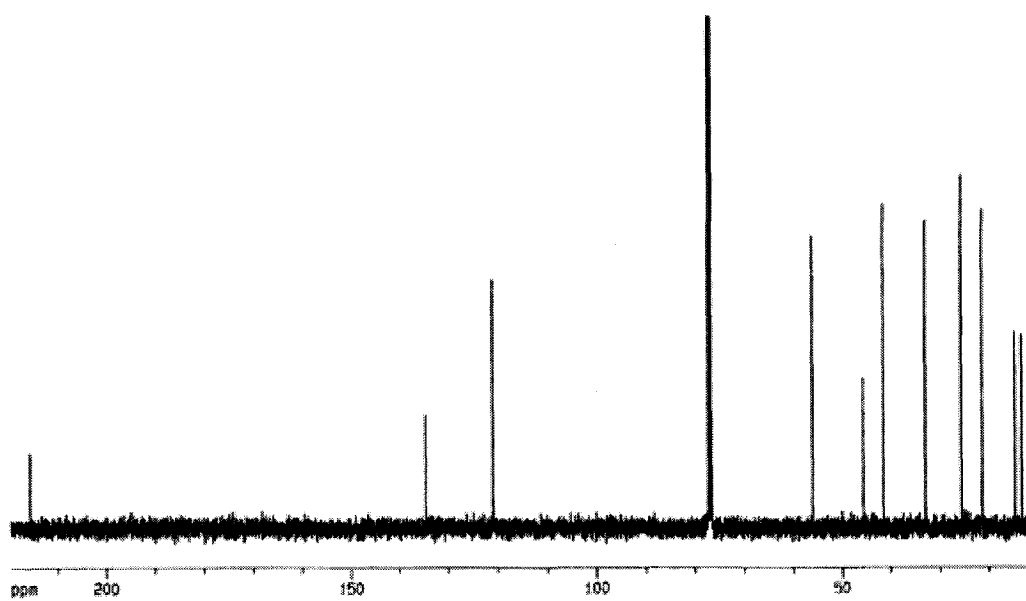


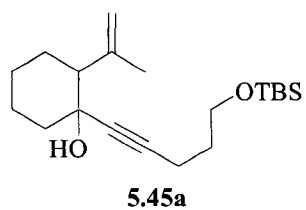


¹H NMR (CDCl₃, 400 MHz)

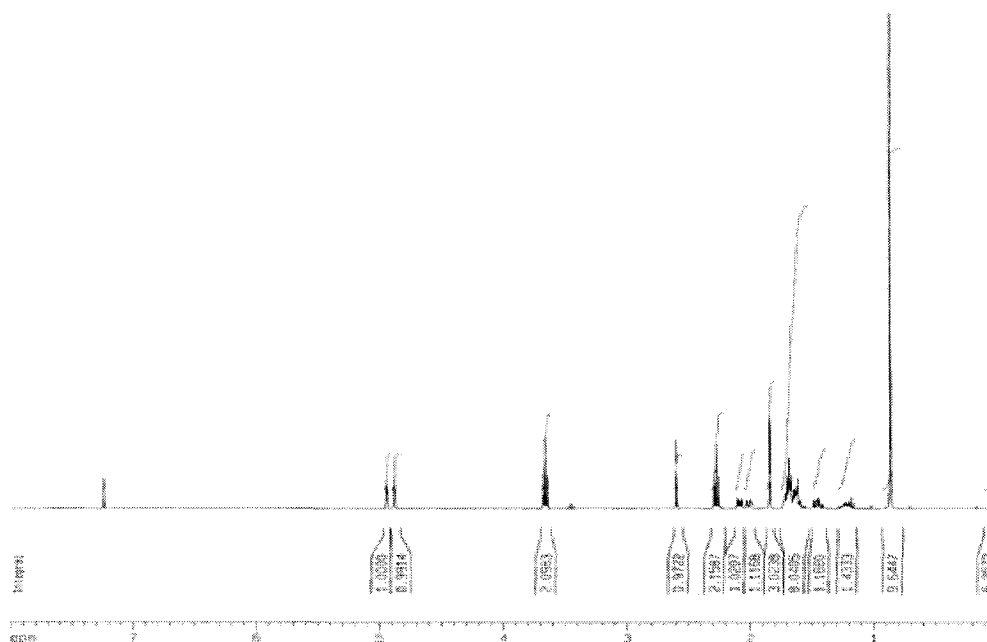


¹³C NMR (CDCl₃, 100 MHz)

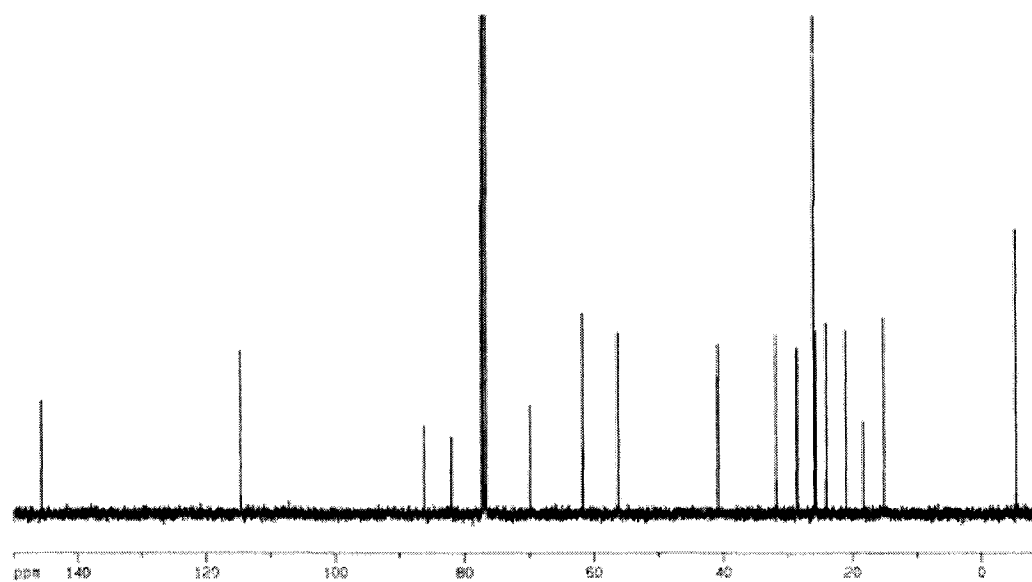


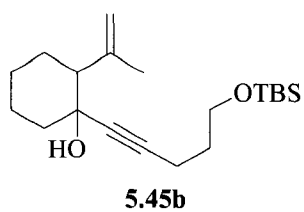


^1H NMR (CDCl_3 , 400 MHz)

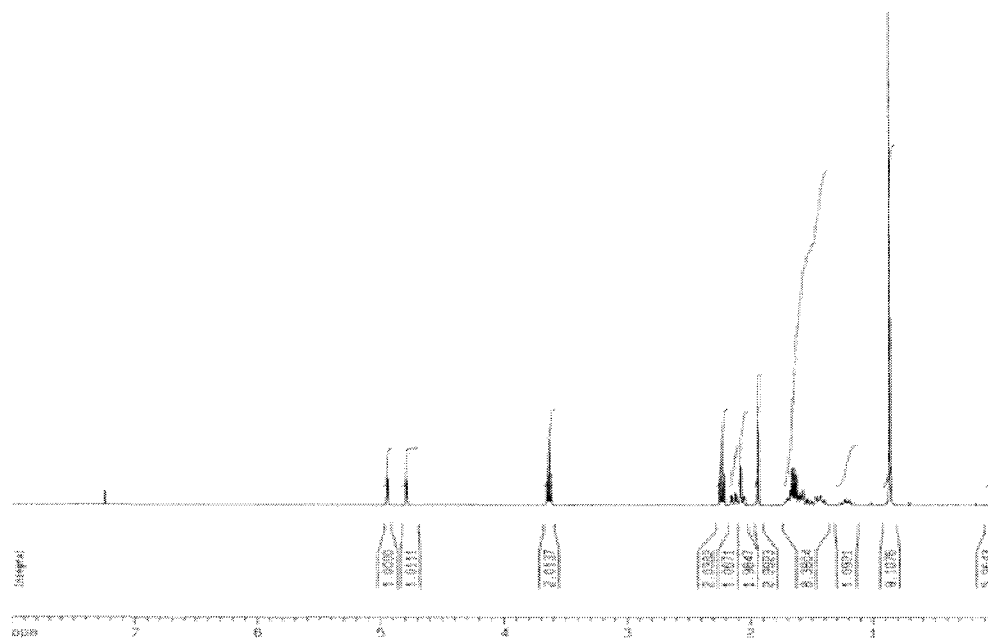


^{13}C NMR (CDCl_3 , 100 MHz)

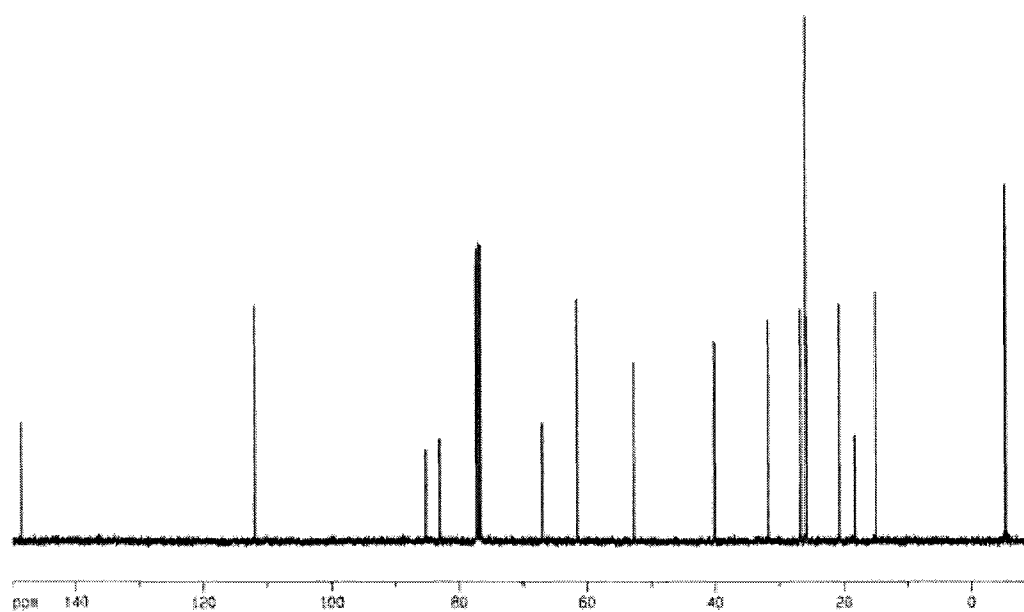


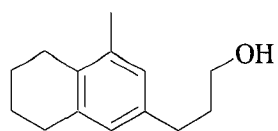
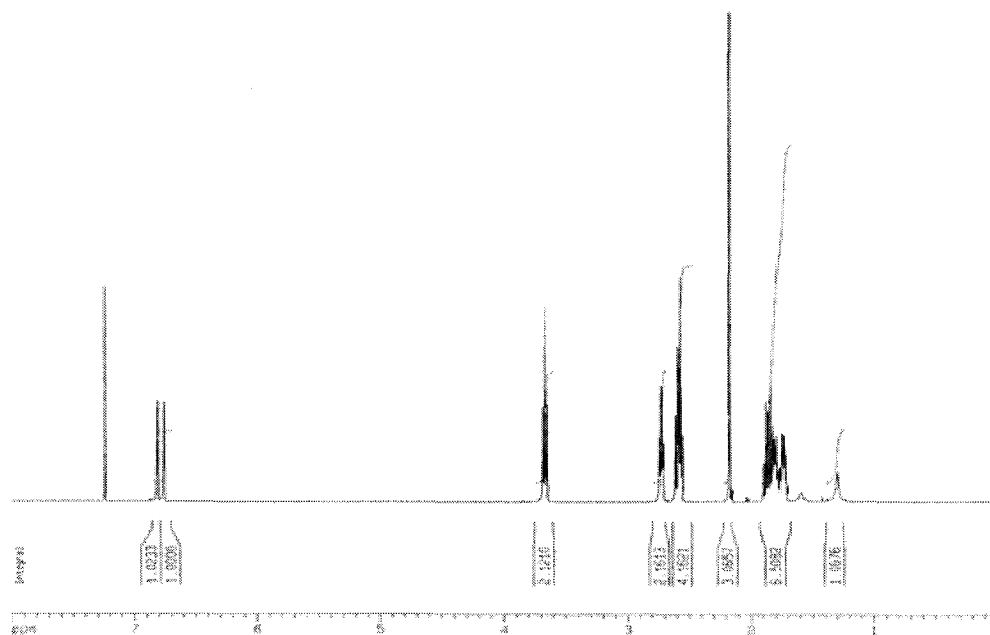
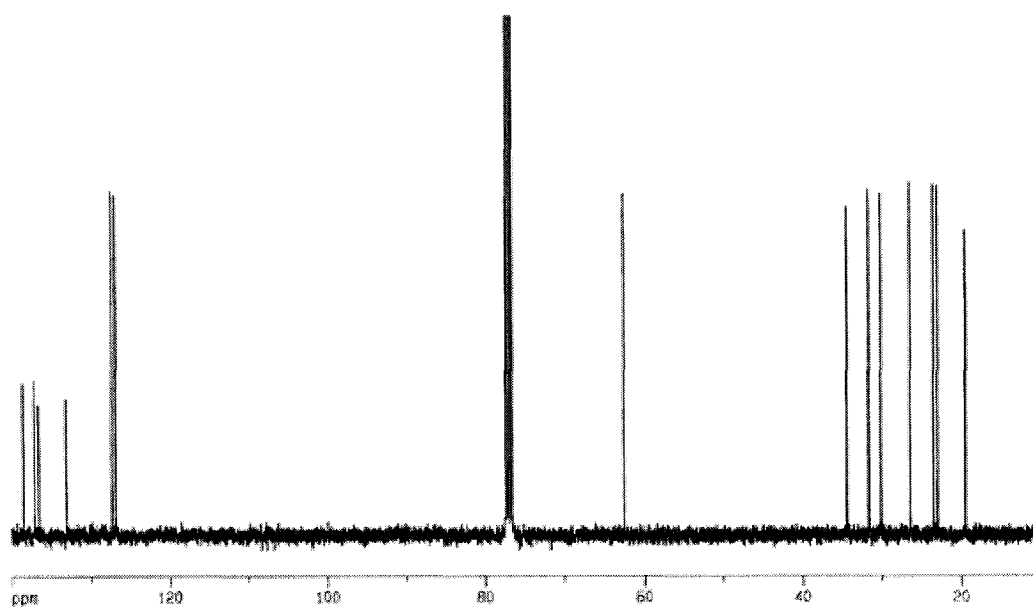


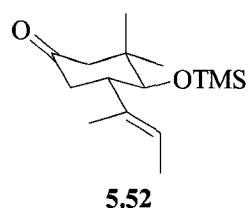
^1H NMR (CDCl_3 , 400 MHz)



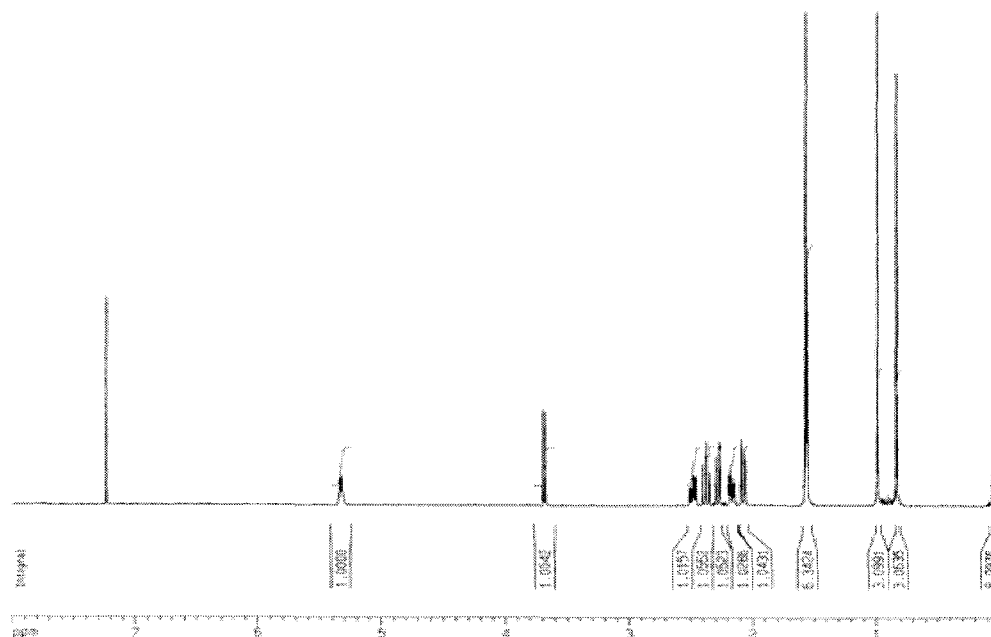
^{13}C NMR (CDCl_3 , 100 MHz)



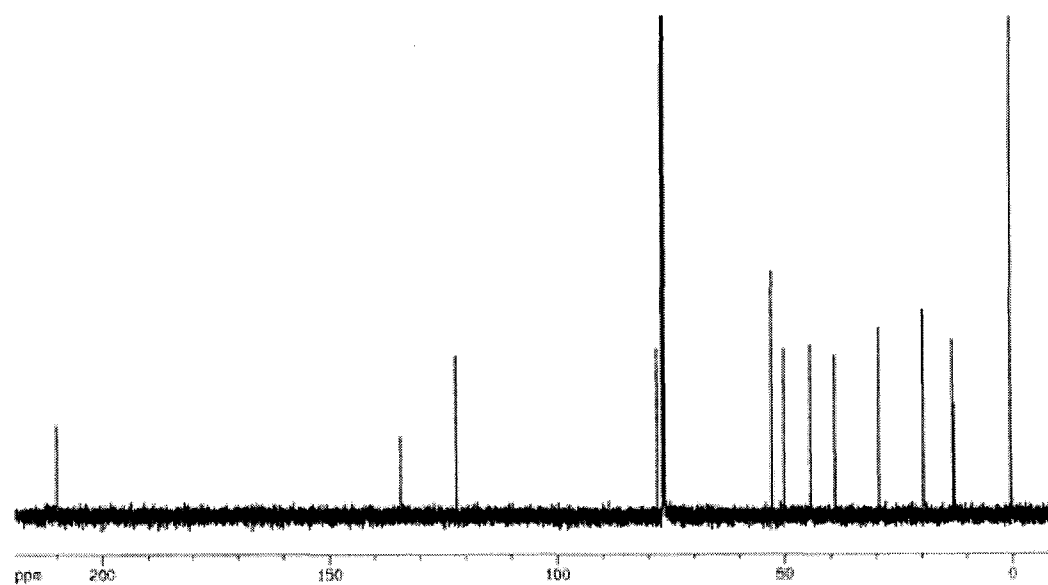
**5.46** **^1H NMR** (CDCl_3 , 400 MHz) **^{13}C NMR** (CDCl_3 , 100 MHz)

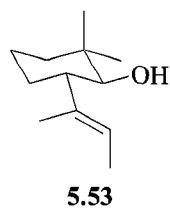


^1H NMR (CDCl_3 , 500 MHz)

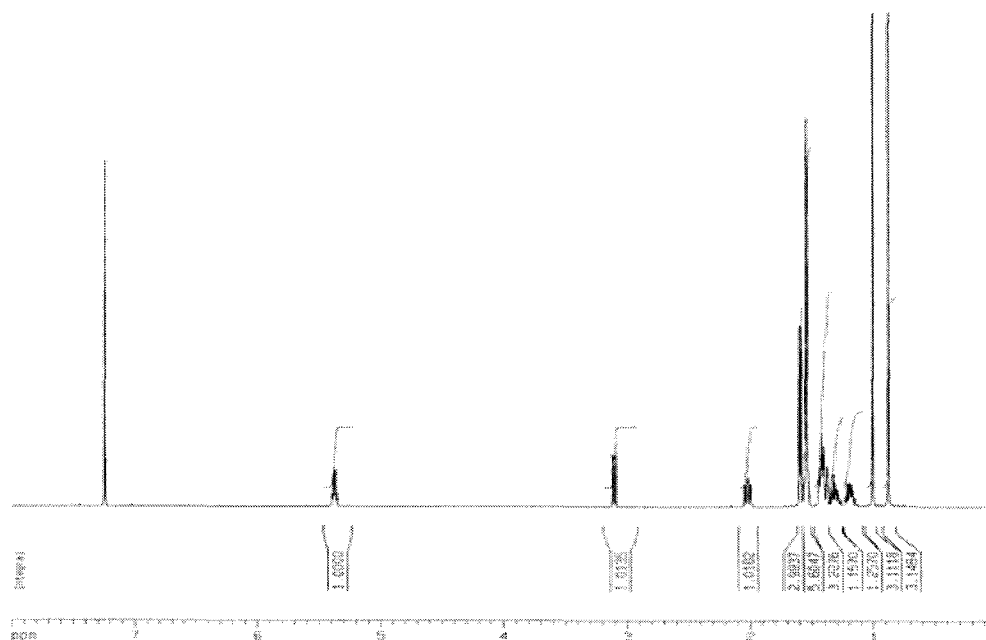


^{13}C NMR (CDCl_3 , 125 MHz)

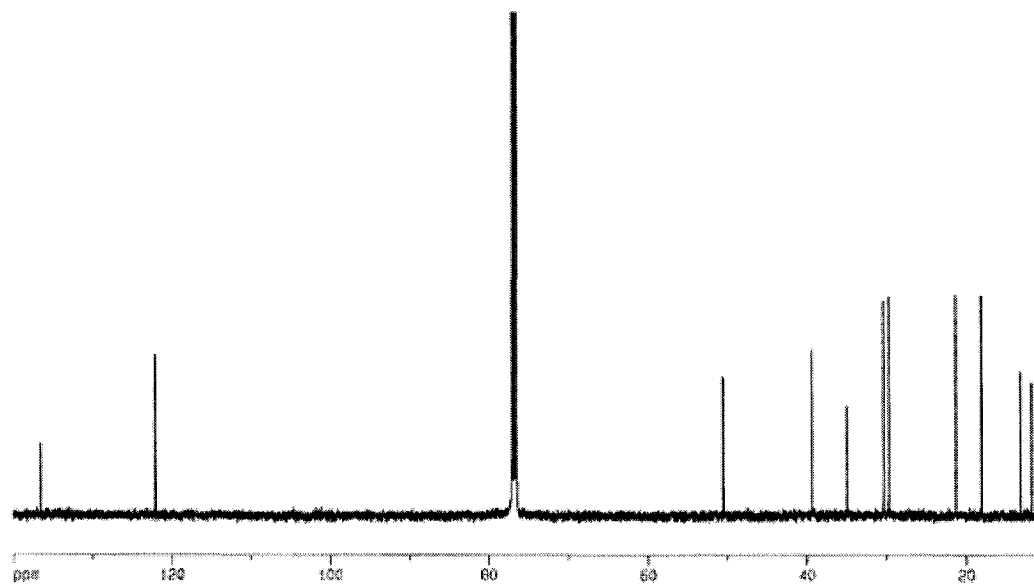


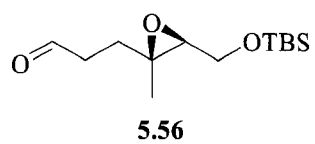


^1H NMR (CDCl_3 , 500 MHz)

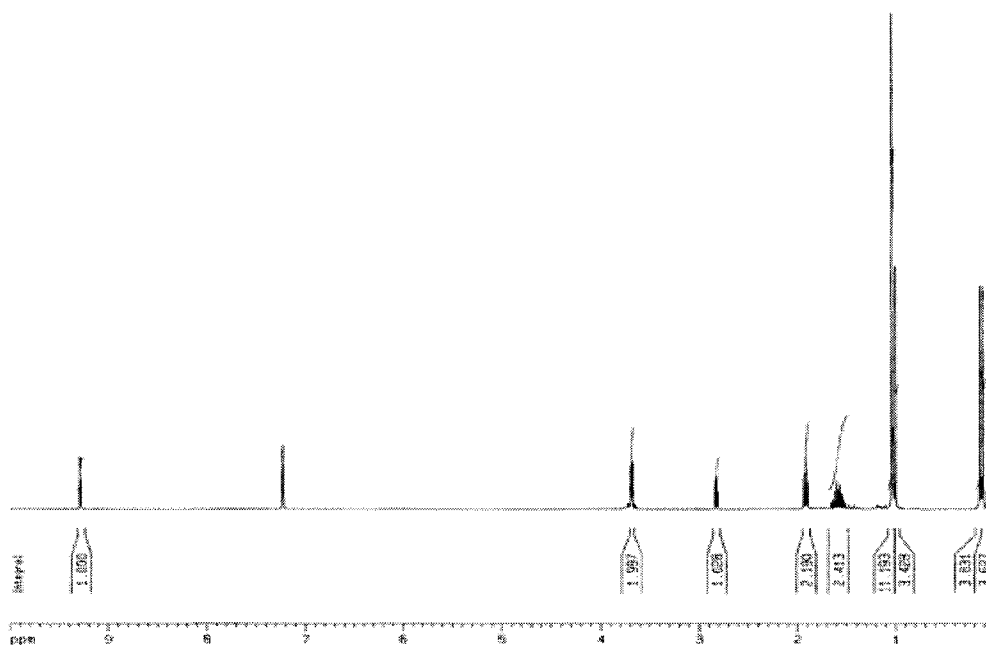


^{13}C NMR (CDCl_3 , 125 MHz)

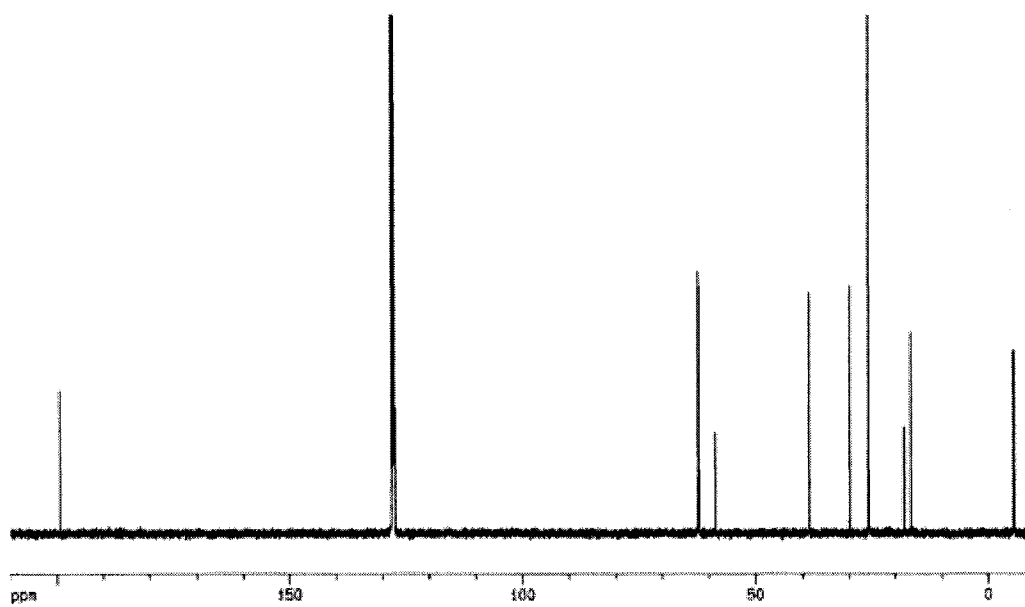


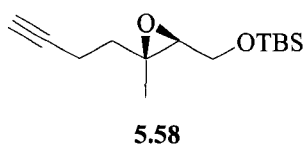


^1H NMR (C_6D_6 , 400 MHz)

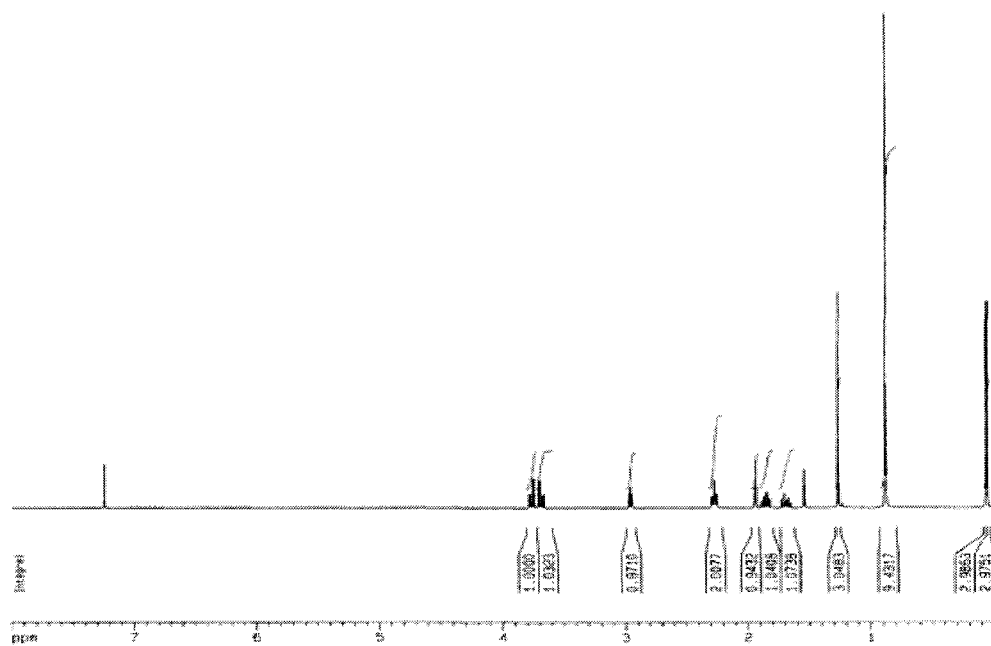


^{13}C NMR (C_6D_6 , 100 MHz)

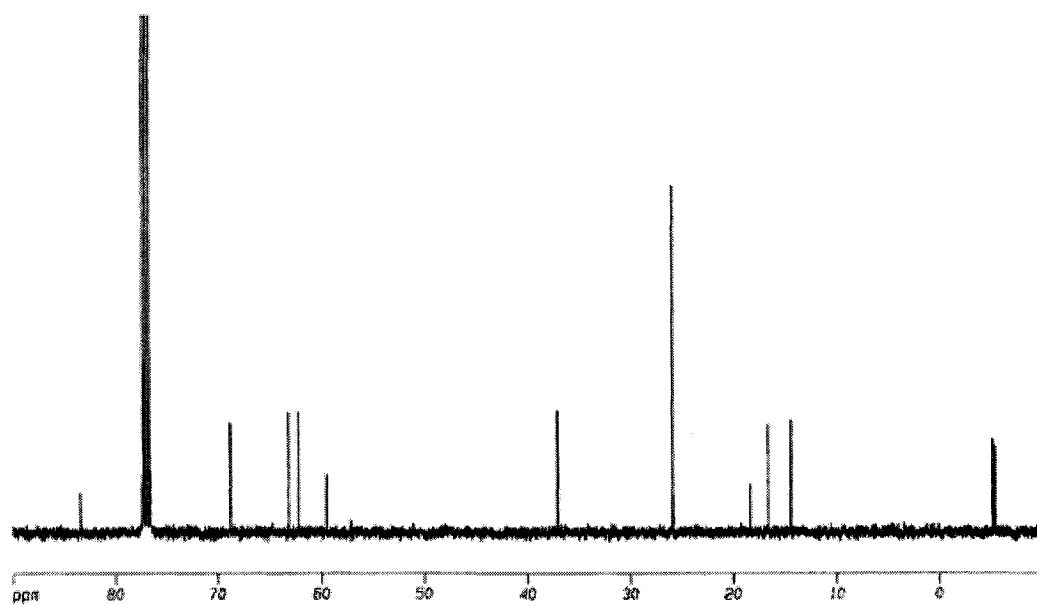


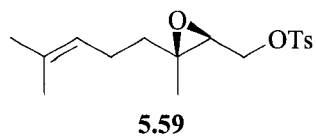


^1H NMR (CDCl_3 , 400 MHz)

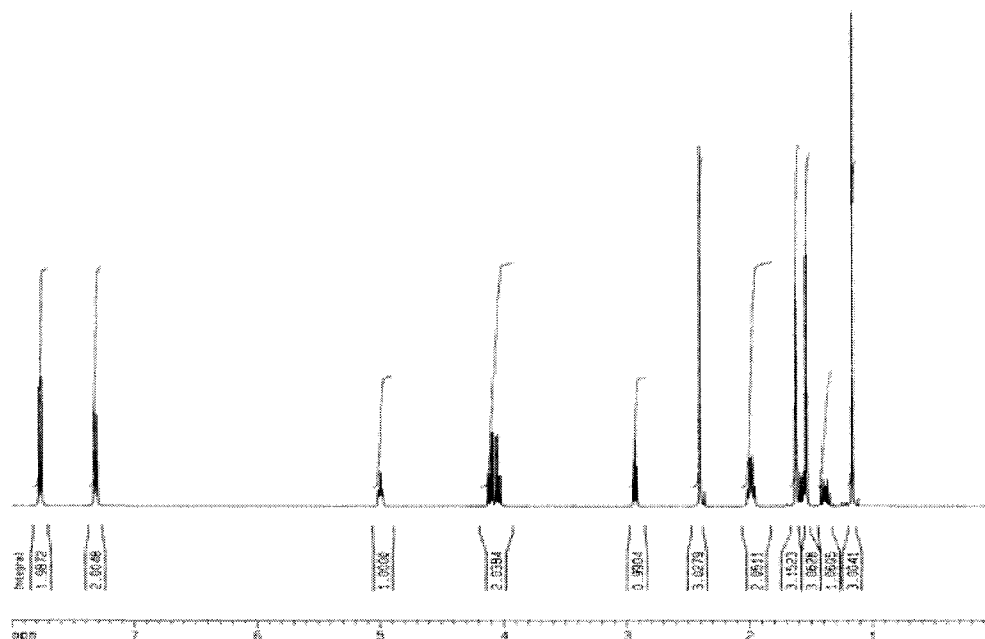


^{13}C NMR (CDCl_3 , 100 MHz)

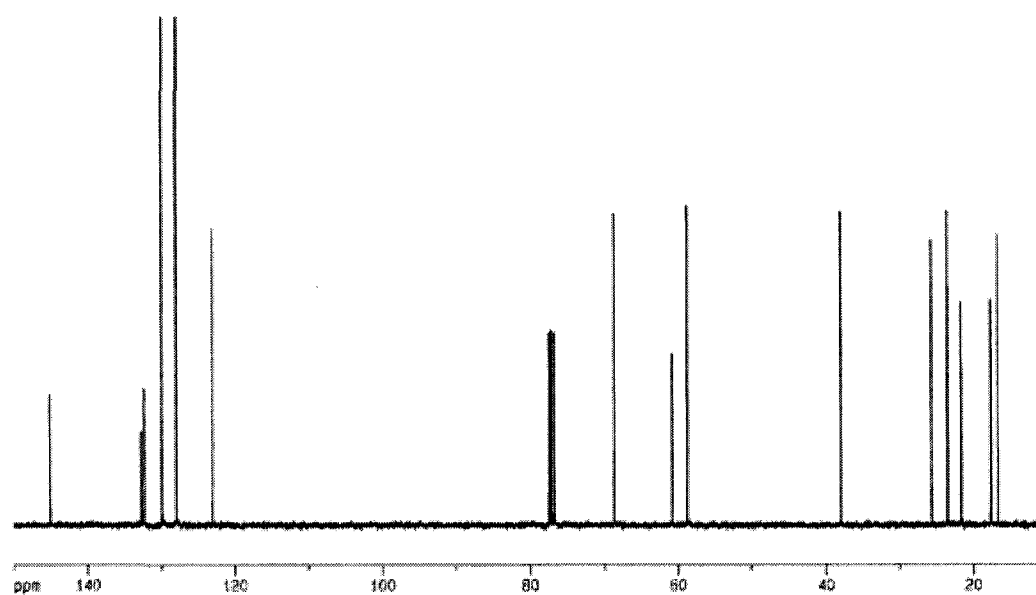


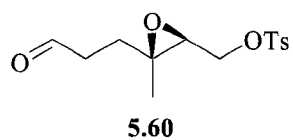


^1H NMR (CDCl_3 , 400 MHz)

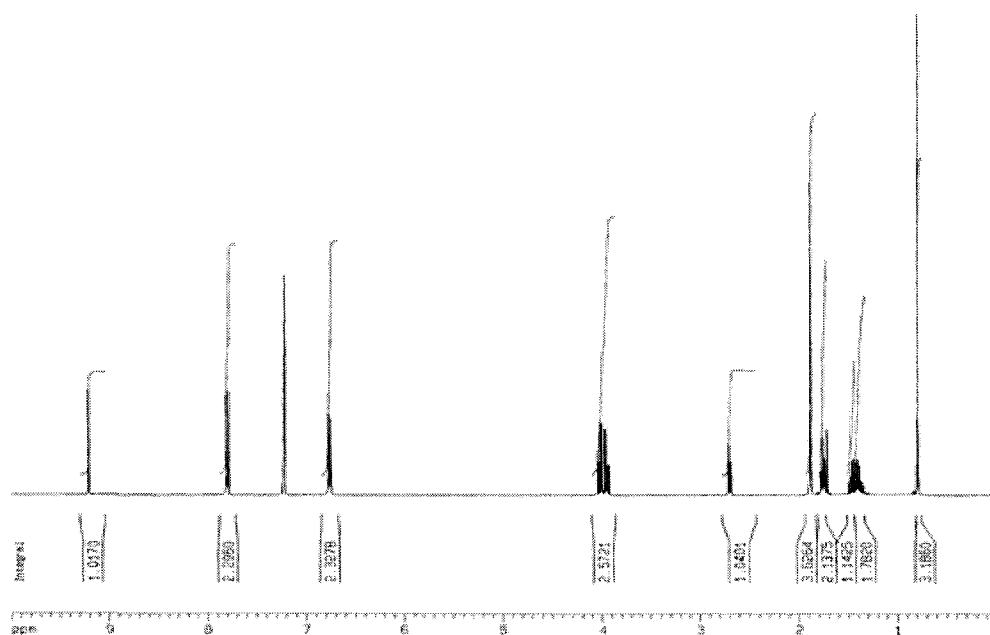


^{13}C NMR (CDCl_3 , 100 MHz)

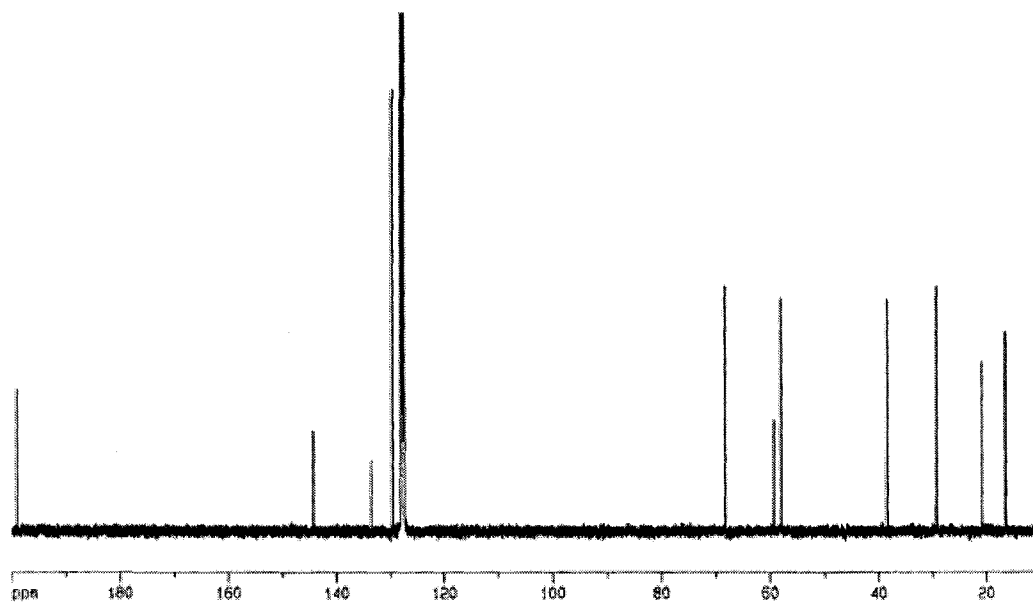


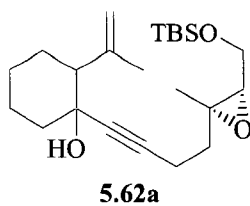


^1H NMR (CDCl_3 , 400 MHz)

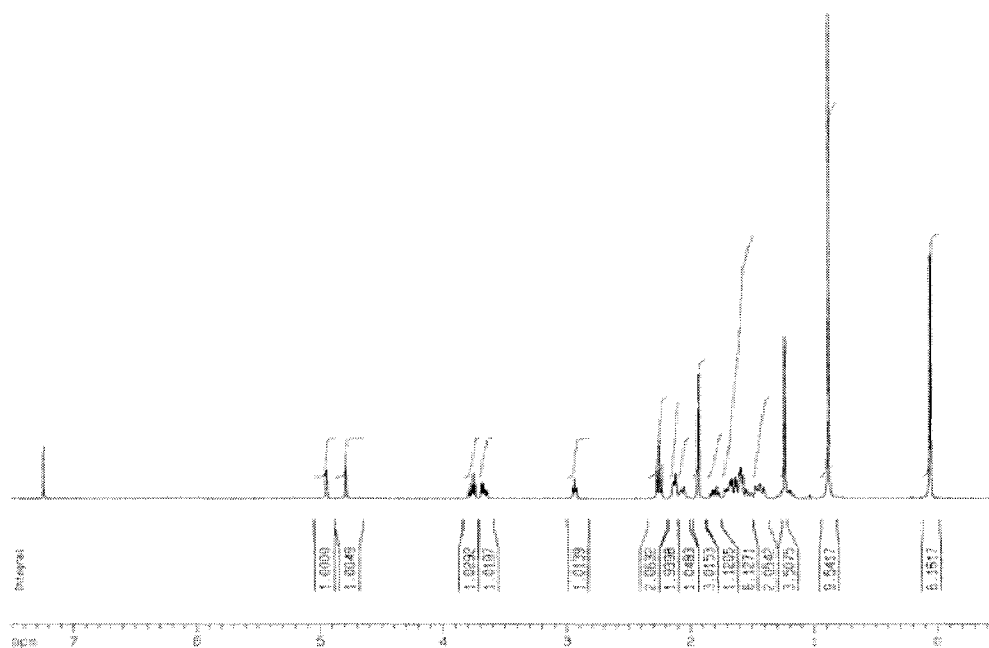


^{13}C NMR (CDCl_3 , 100 MHz)

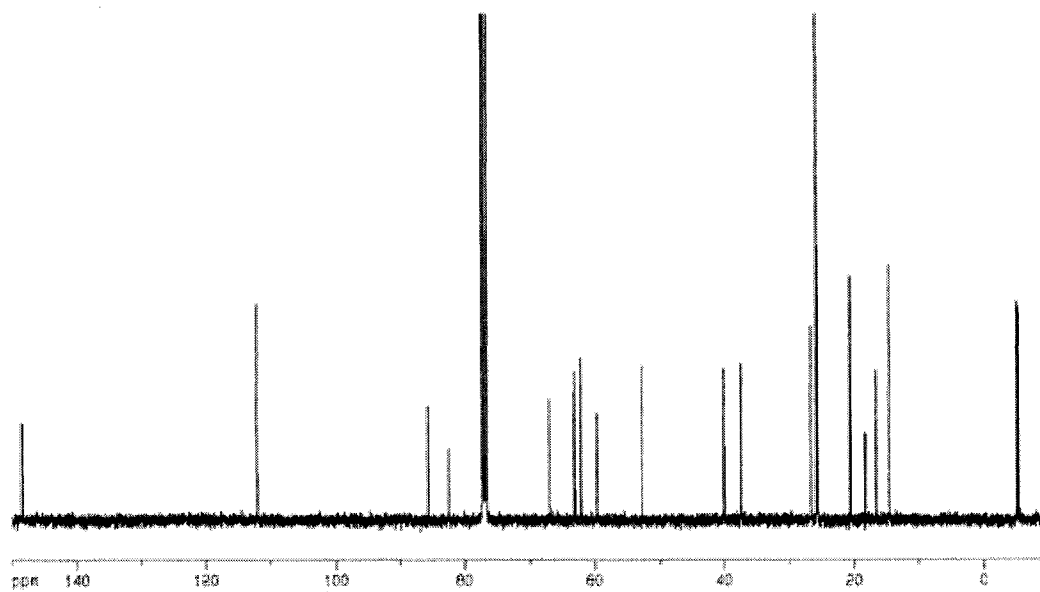


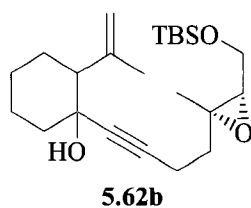


¹H NMR (CDCl₃, 400 MHz)

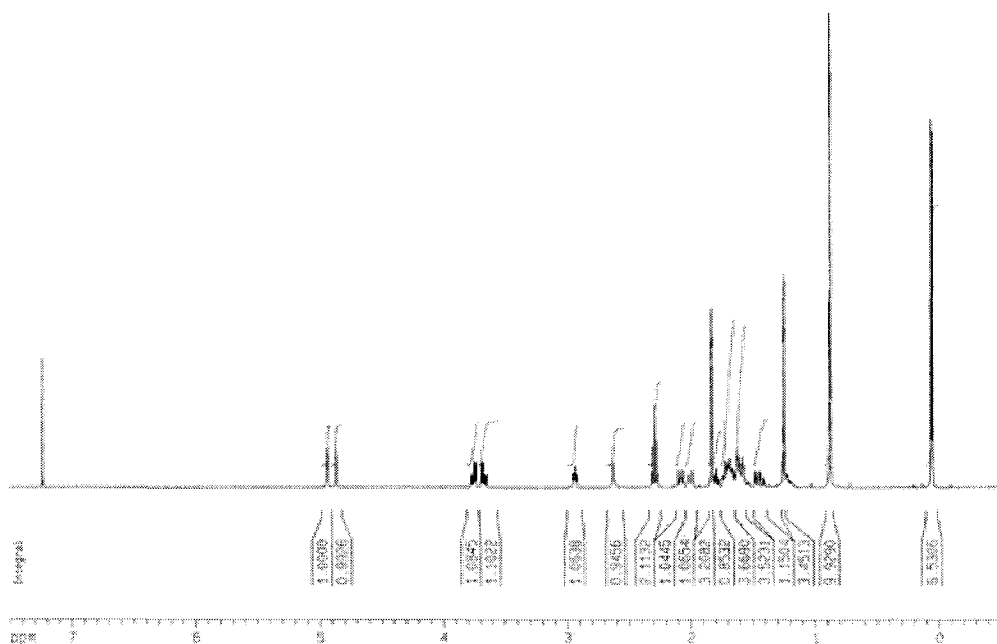


^{13}C NMR (CDCl_3 , 100 MHz)

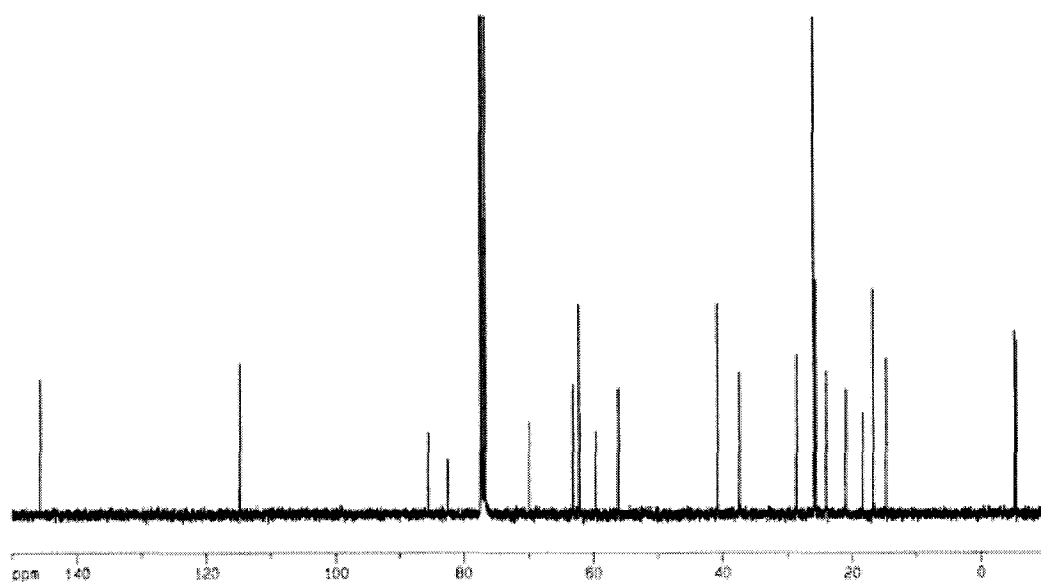


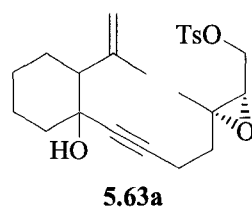


¹H NMR (CDCl₃, 400 MHz)

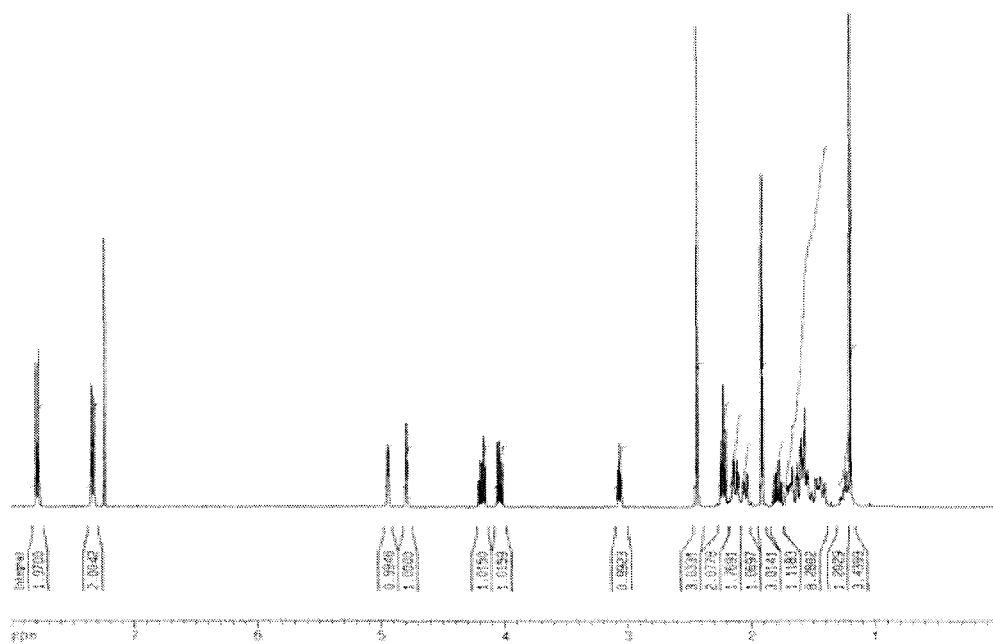


¹³C NMR (CDCl₃, 100 MHz)

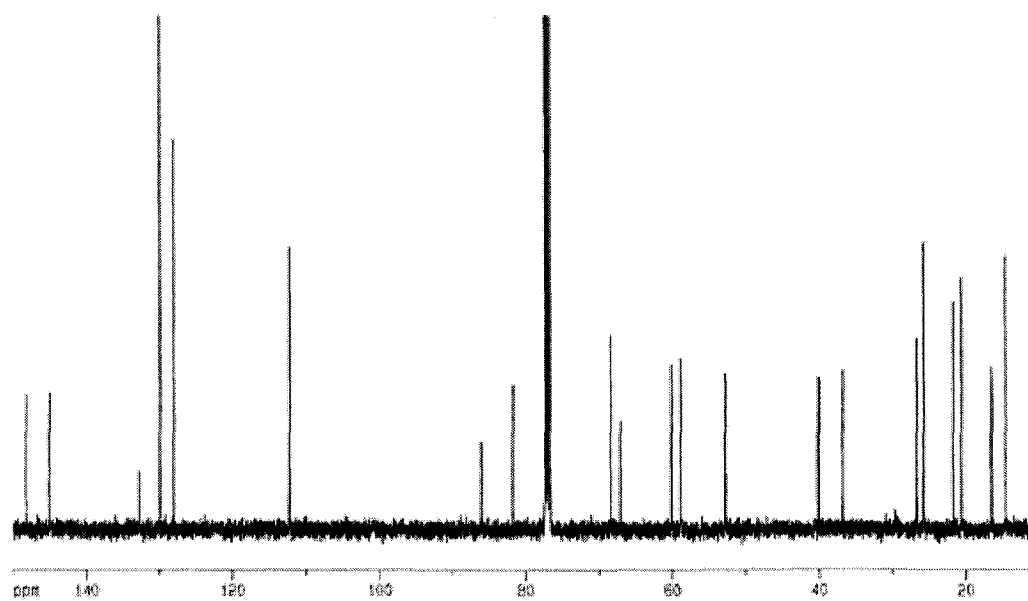


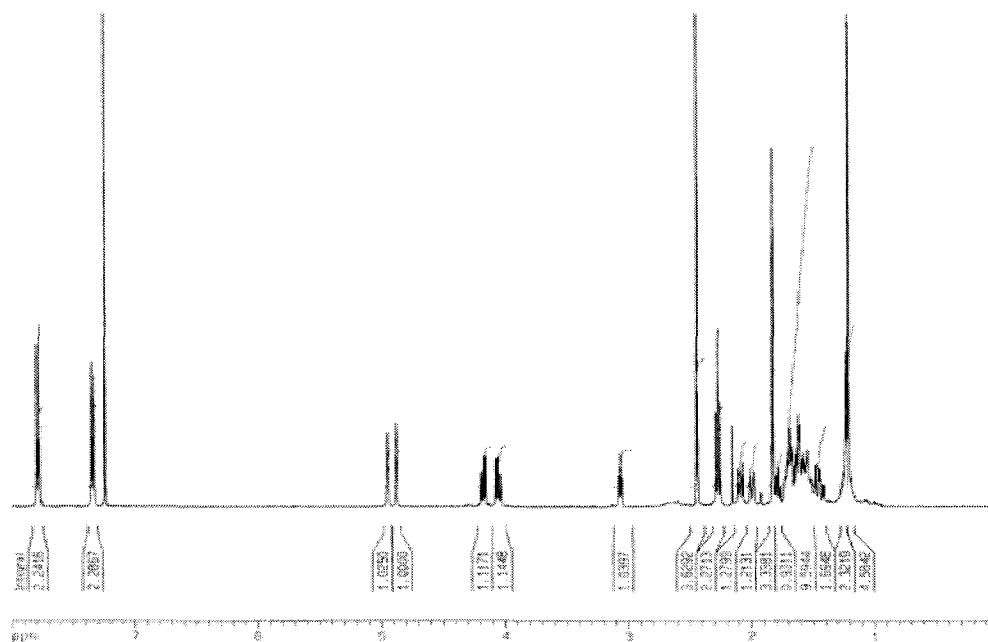


^1H NMR (CDCl_3 , 400 MHz)

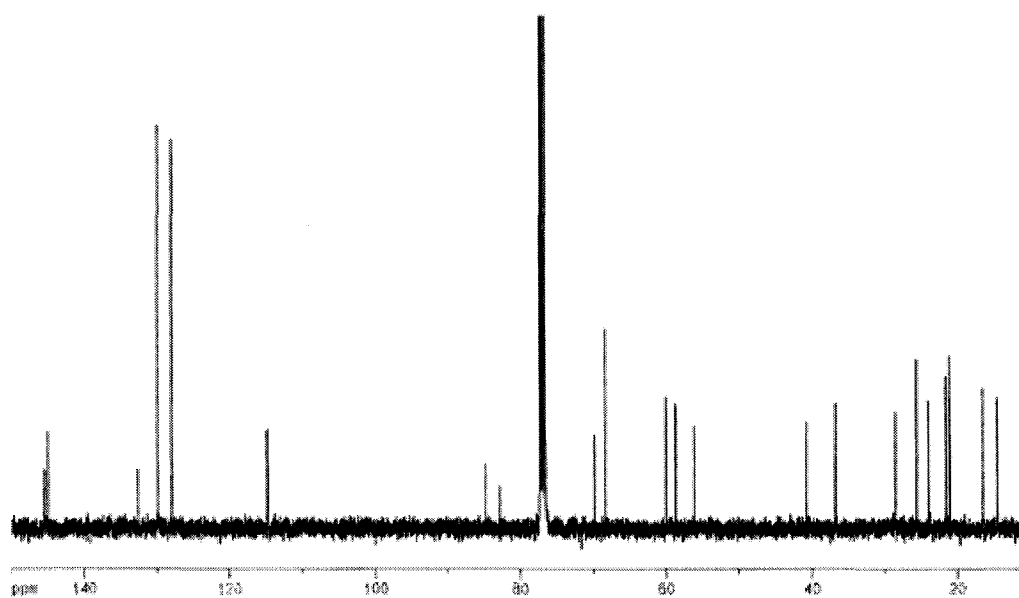


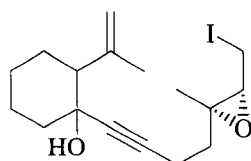
^{13}C NMR (CDCl_3 , 100 MHz)



¹H NMR (CDCl₃, 400 MHz)

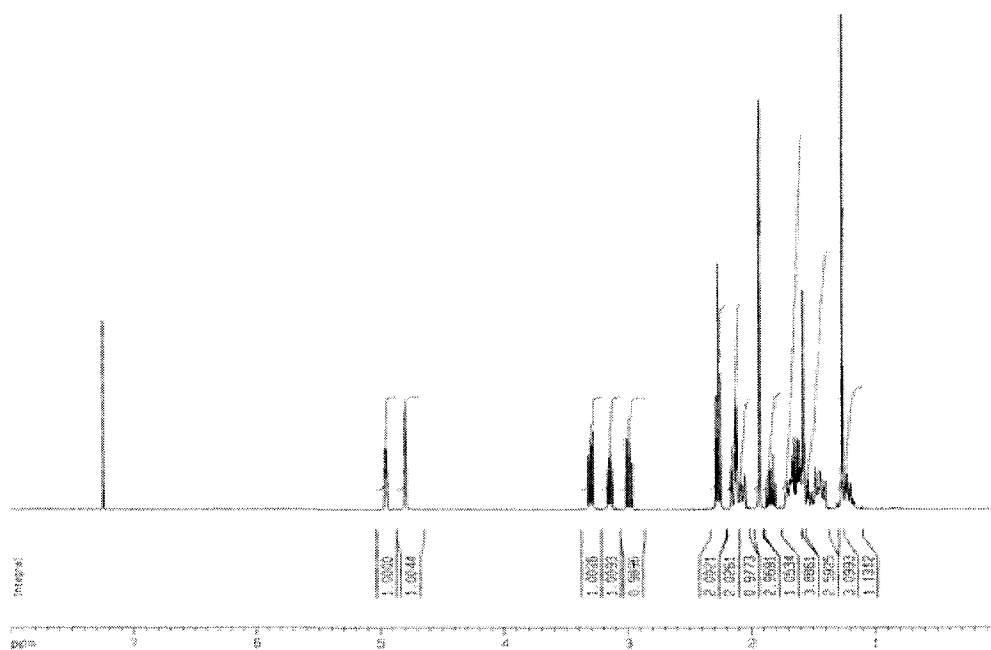
^{13}C NMR (CDCl_3 , 100 MHz)



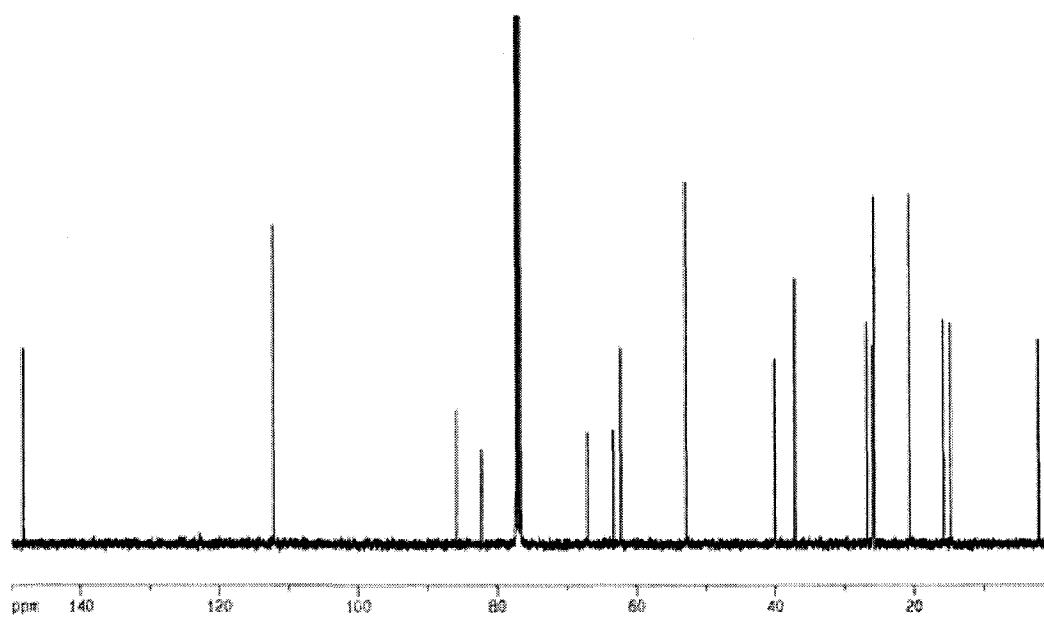


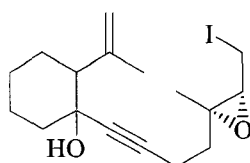
5.64a

^1H NMR (CDCl_3 , 400 MHz)



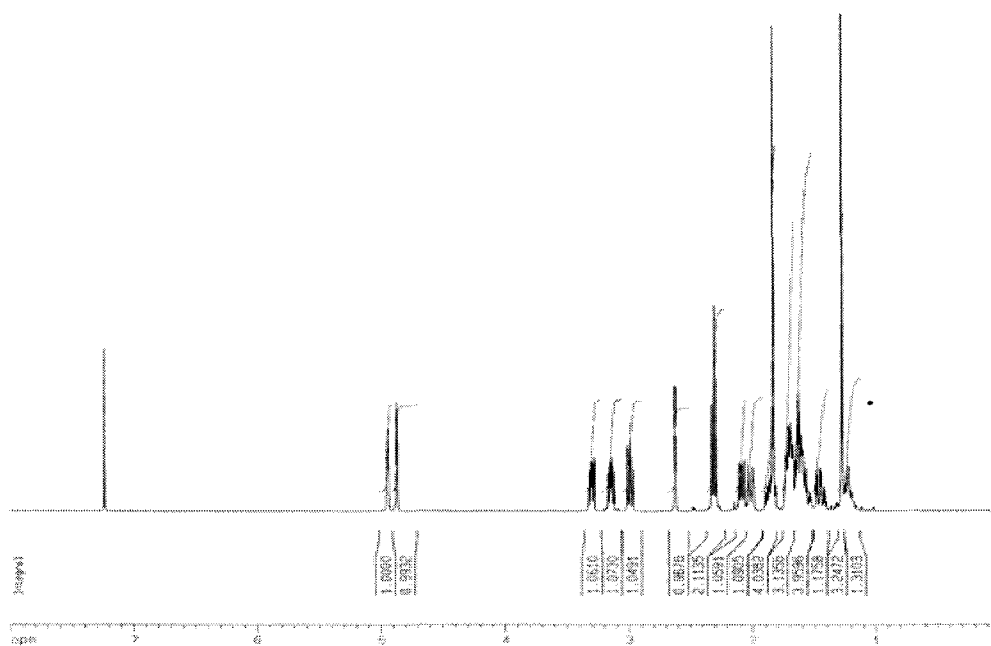
^{13}C NMR (CDCl_3 , 100 MHz)



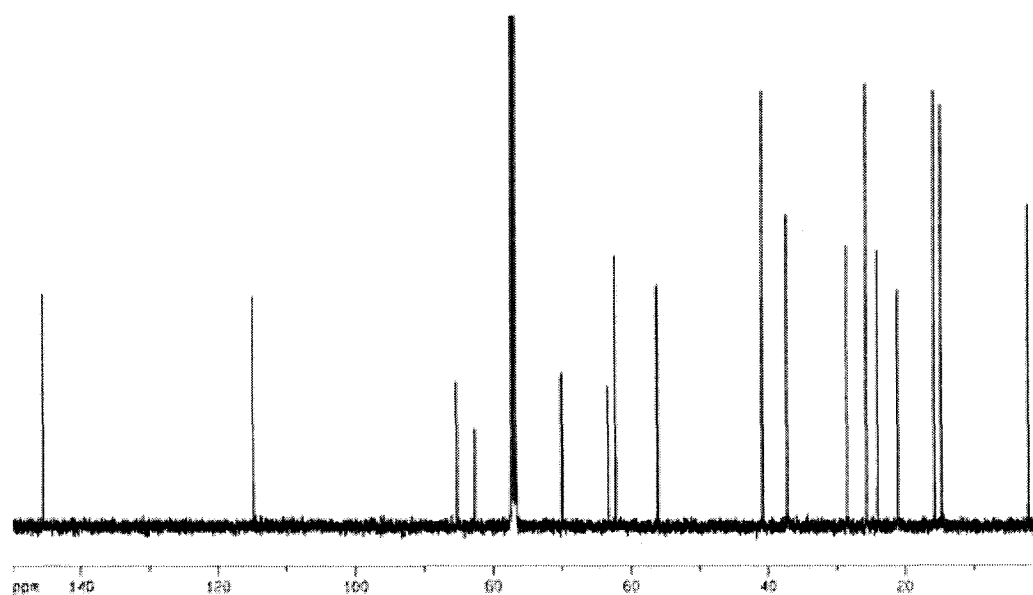


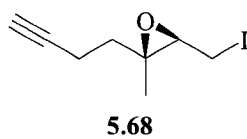
5.64b

^1H NMR (CDCl_3 , 400 MHz)

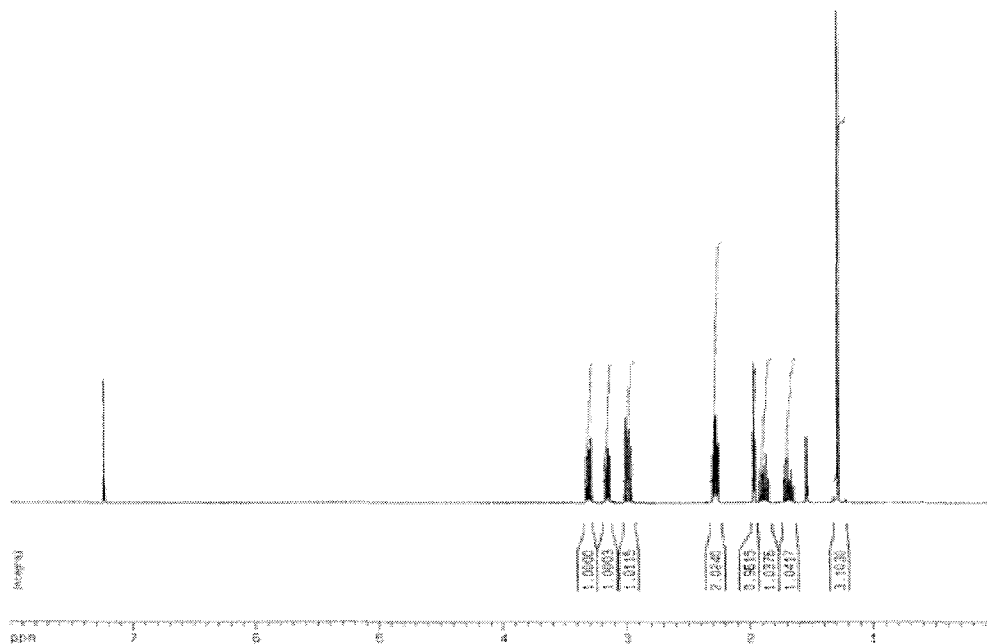


^{13}C NMR (CDCl_3 , 100 MHz)

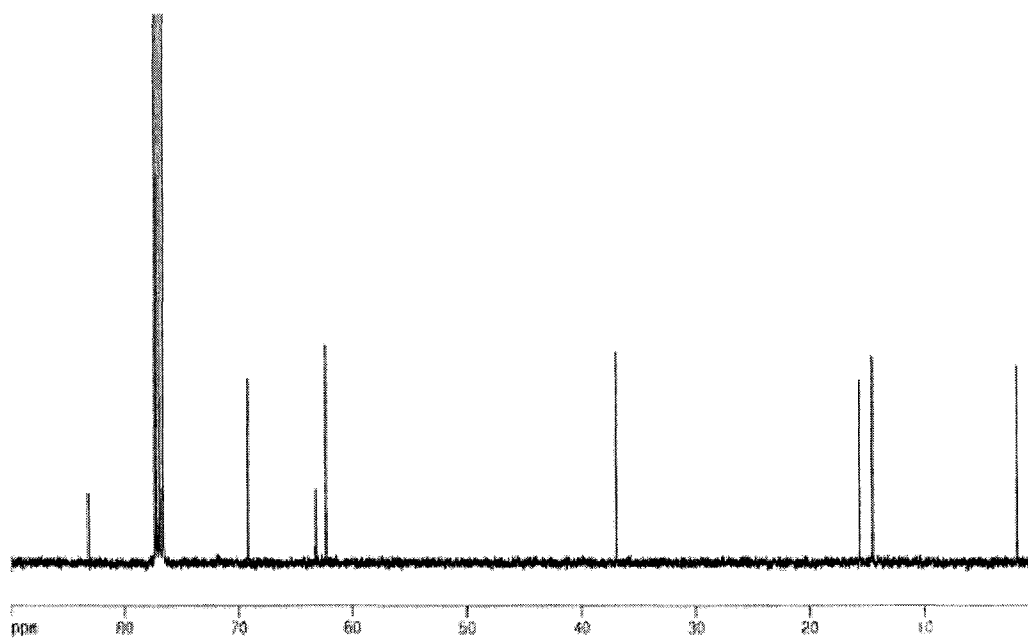


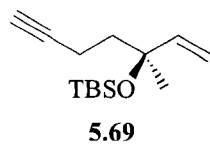


^1H NMR (CDCl_3 , 400 MHz)

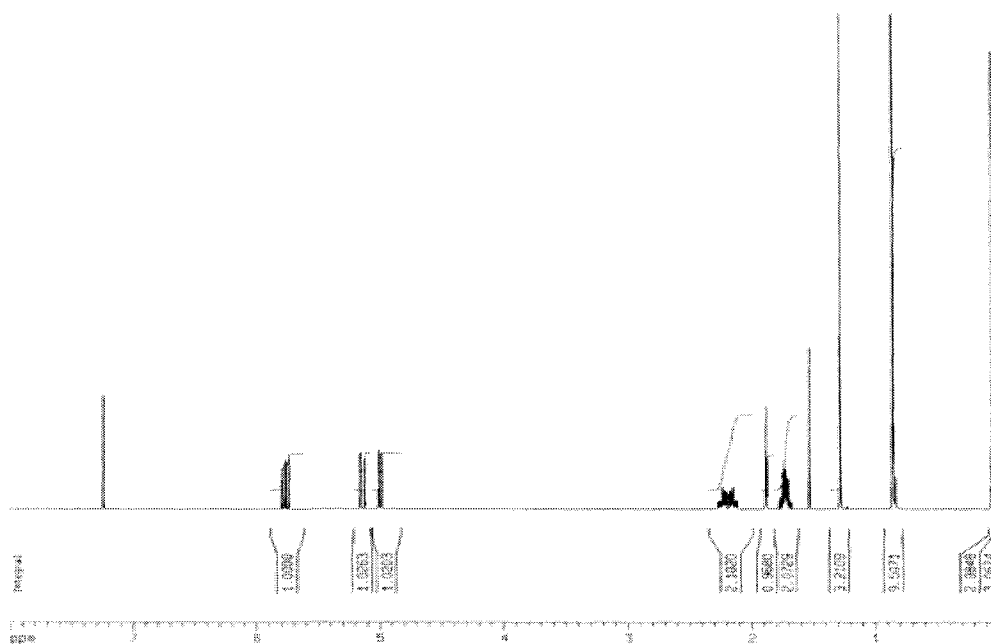


^{13}C NMR (CDCl_3 , 100 MHz)

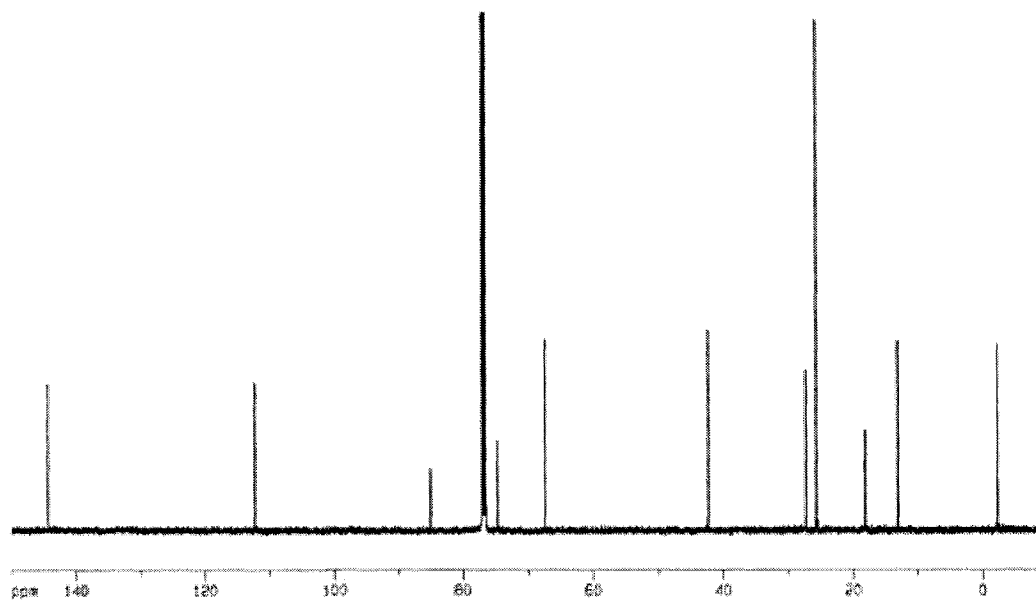


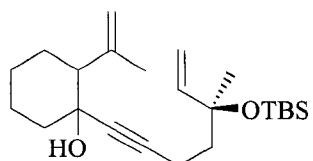


^1H NMR (CDCl_3 , 500 MHz)



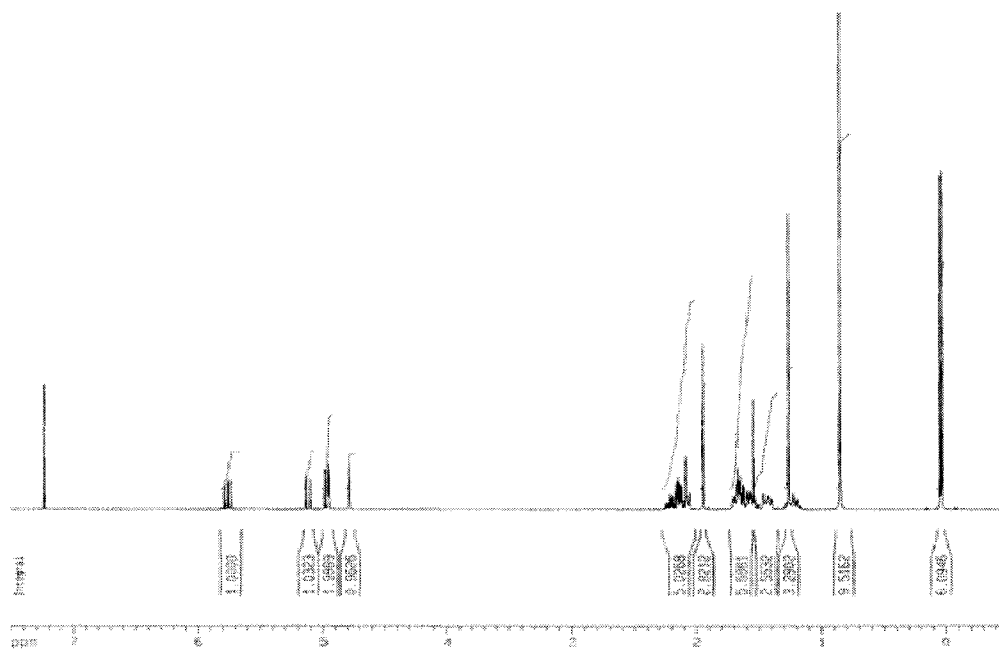
^{13}C NMR (CDCl_3 , 125 MHz)



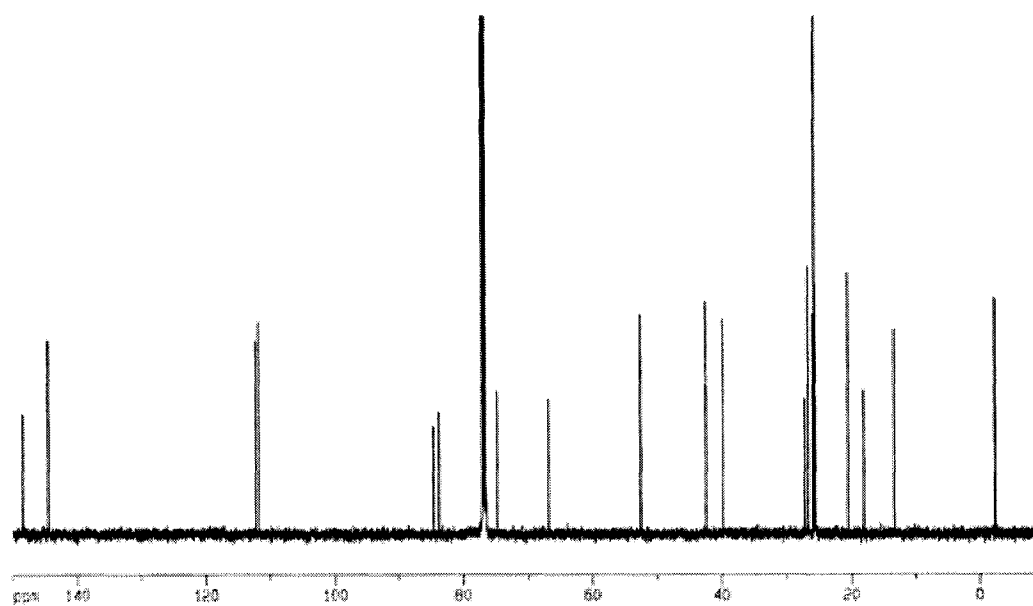


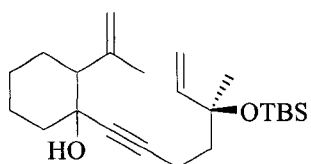
5.70a

^1H NMR (CDCl_3 , 500 MHz)



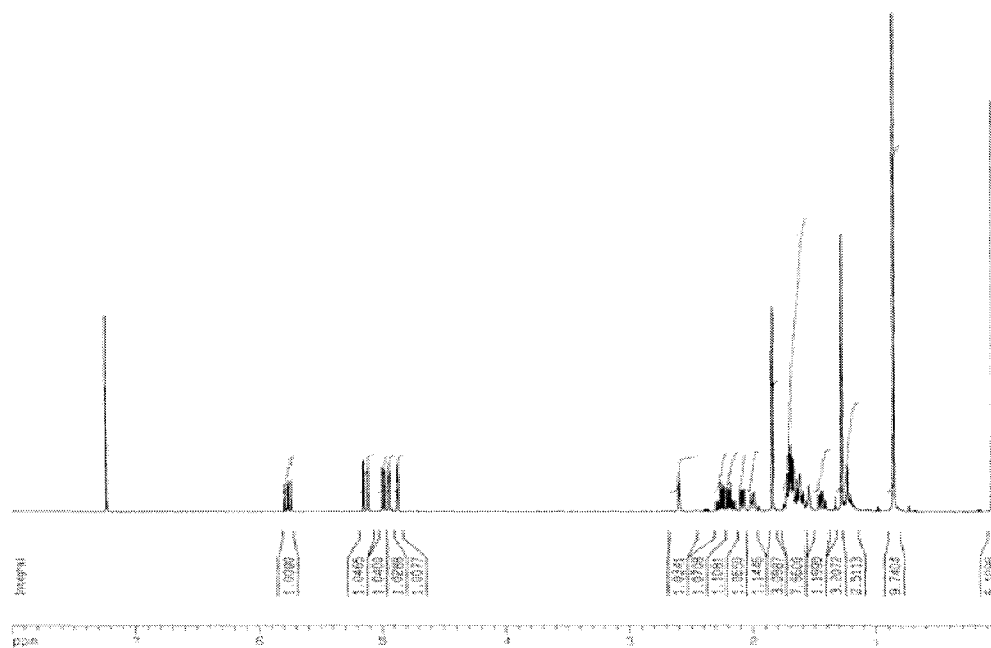
^{13}C NMR (CDCl_3 , 125 MHz)



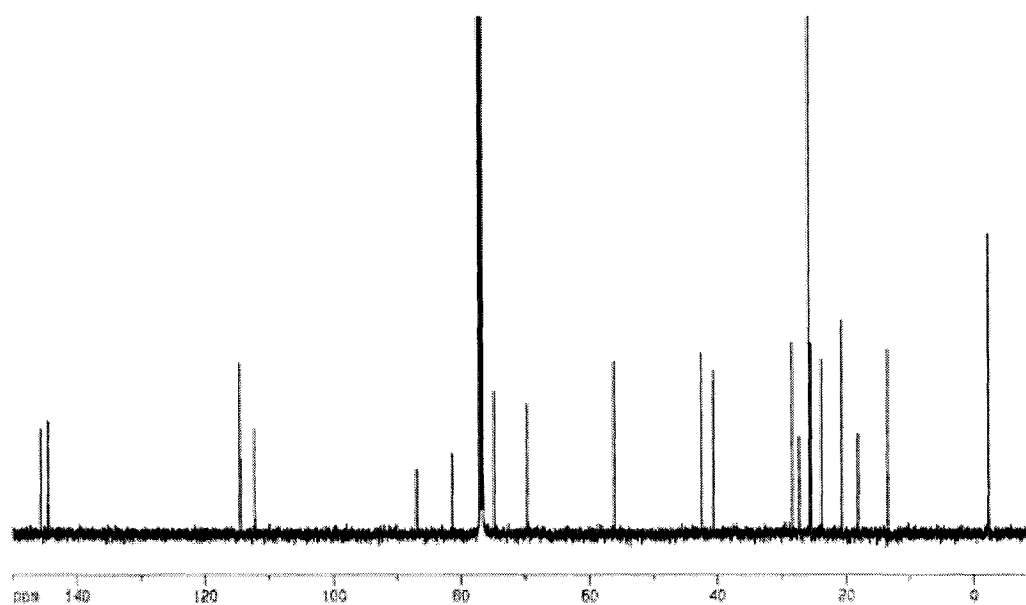


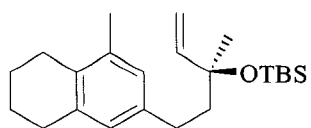
5.70b

^1H NMR (CDCl_3 , 500 MHz)



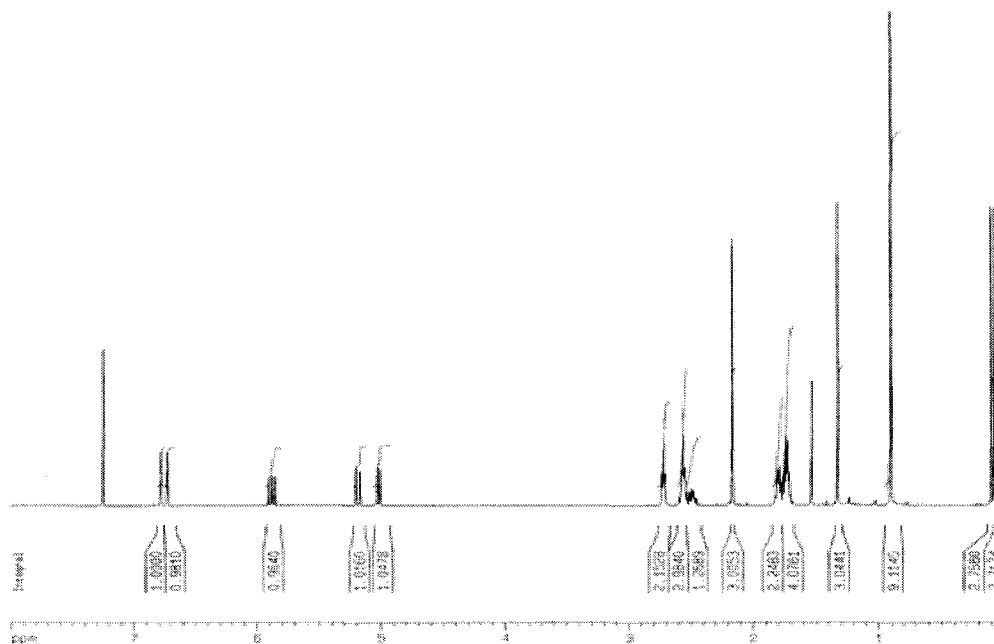
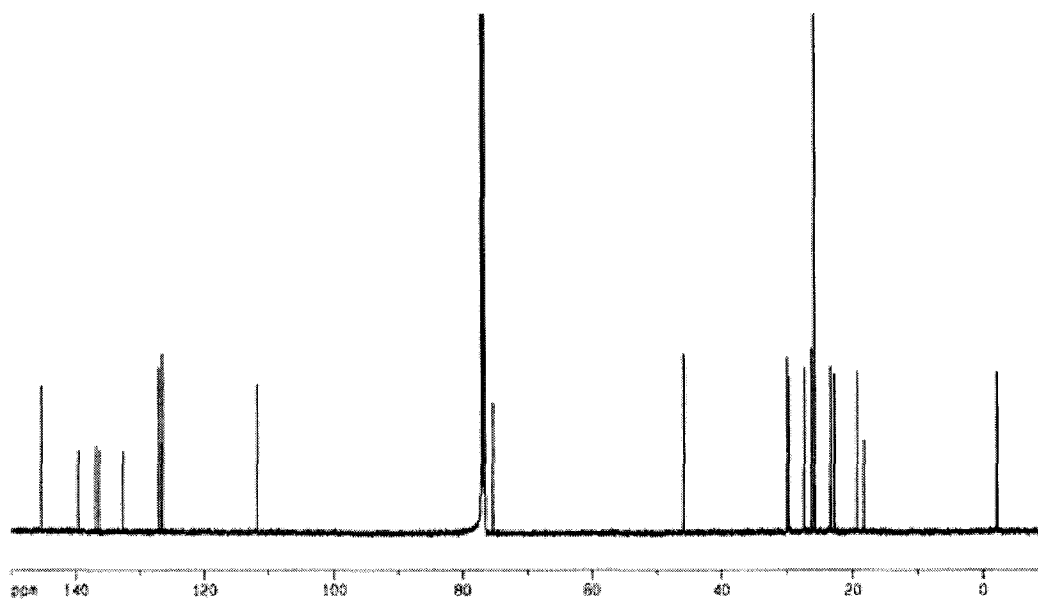
^{13}C NMR (CDCl_3 , 125 MHz)

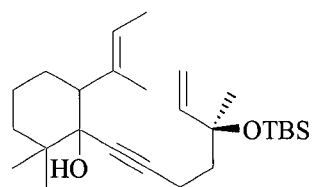




5.71

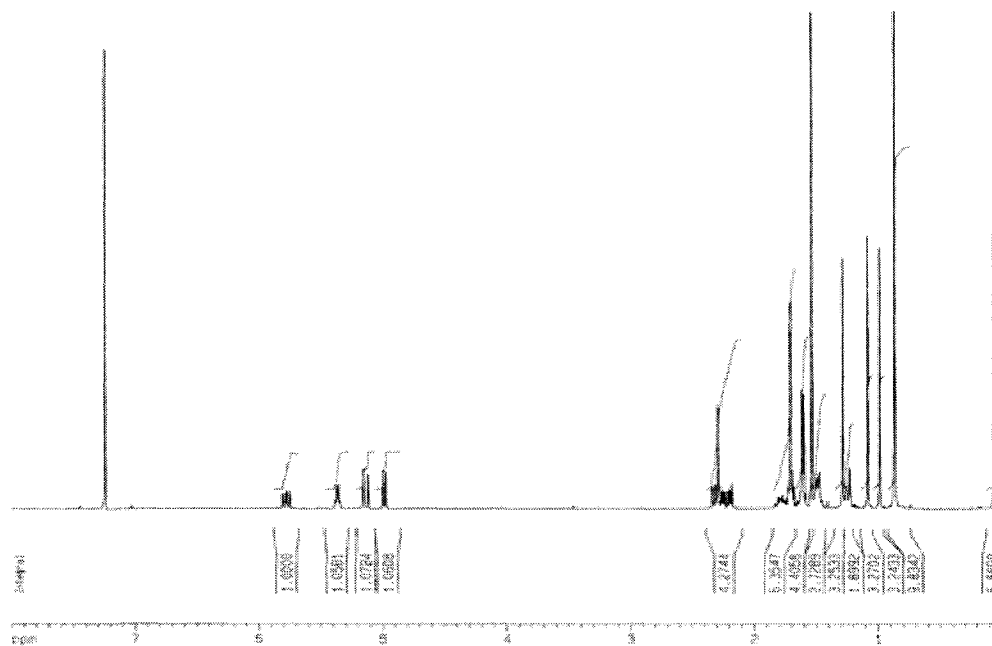
¹H NMR (CDCl₃, 500 MHz)

¹³C NMR (CDCl₃, 125 MHz)

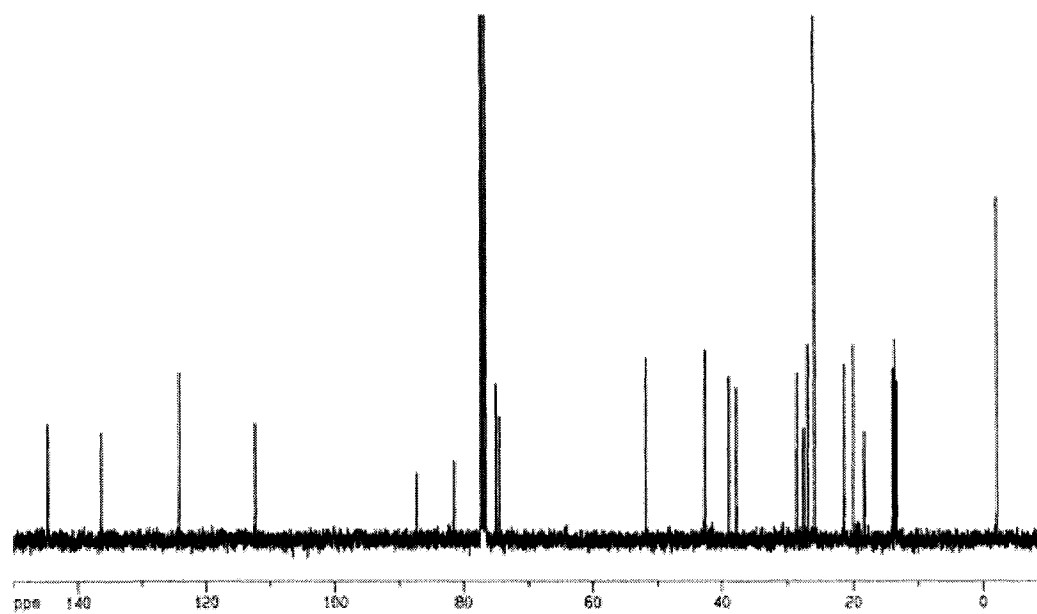


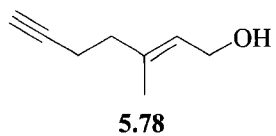
5.72

^1H NMR (CDCl_3 , 500 MHz)

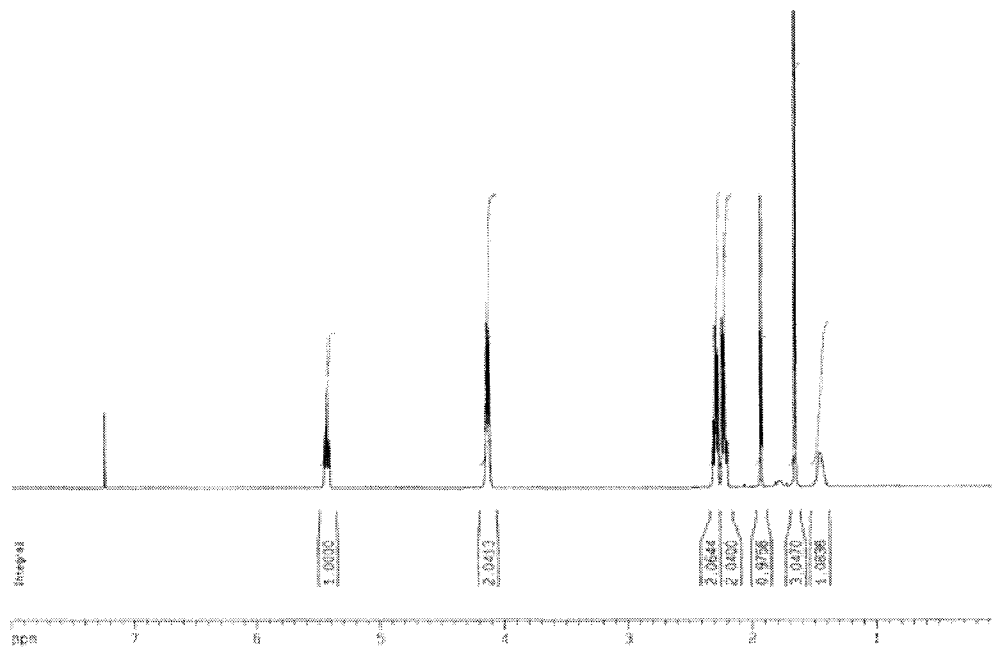


^{13}C NMR (CDCl_3 , 100 MHz)

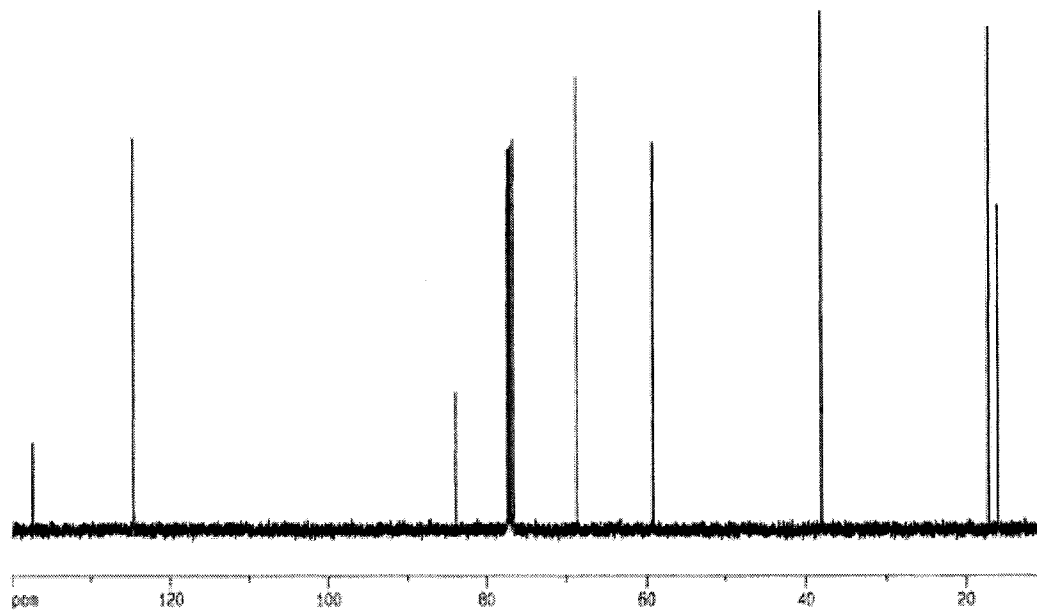


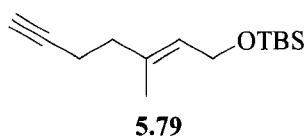


^1H NMR (CDCl_3 , 400 MHz)

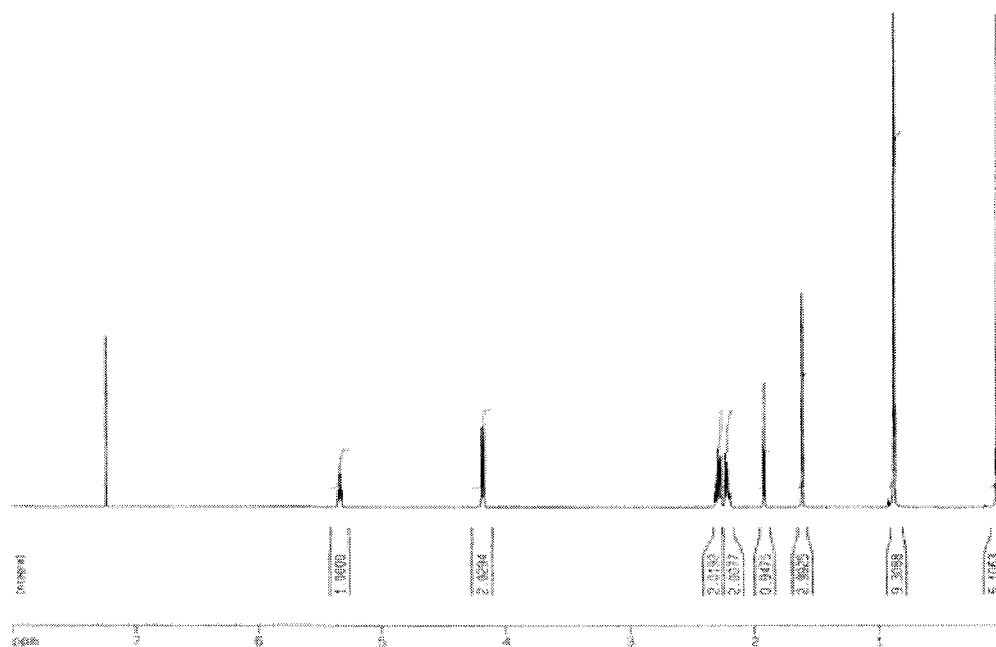


^{13}C NMR (CDCl_3 , 100 MHz)

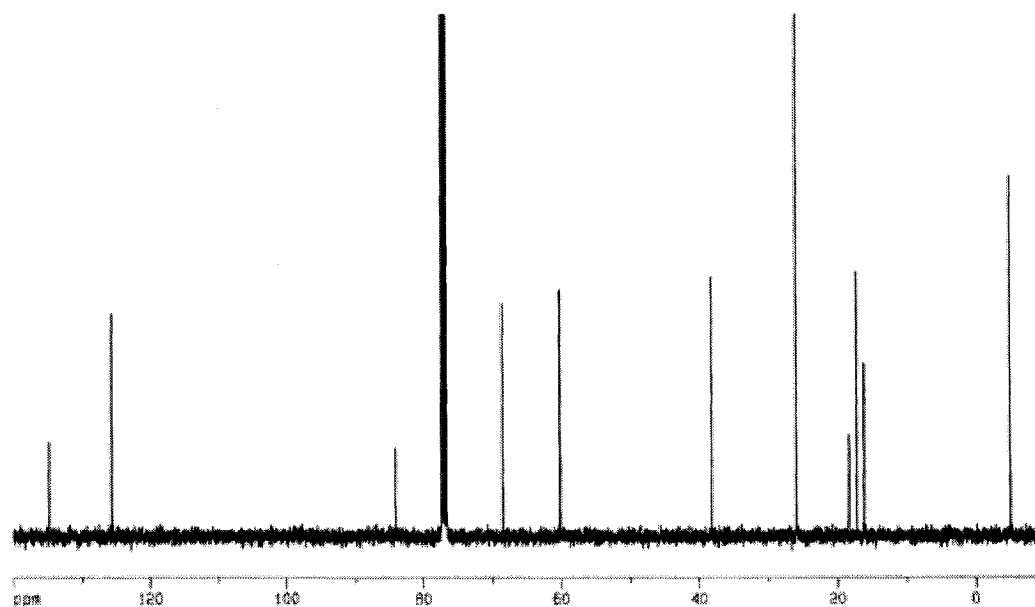


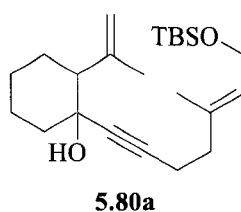


^1H NMR (CDCl_3 , 400 MHz)

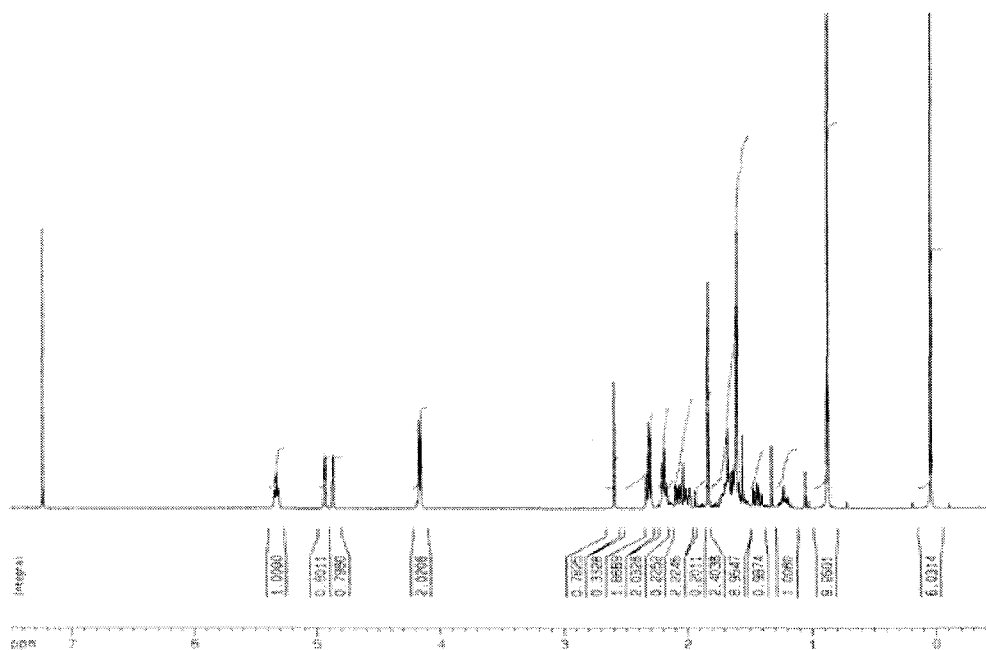


^{13}C NMR (CDCl_3 , 100 MHz)

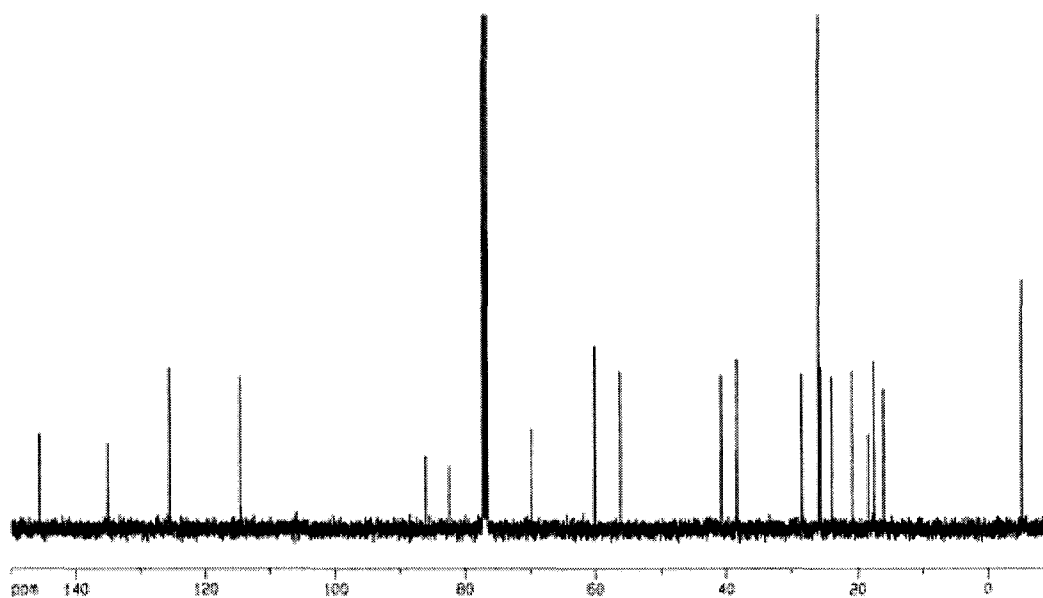


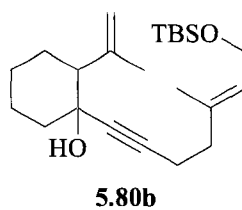


^1H NMR (CDCl_3 , 400 MHz)

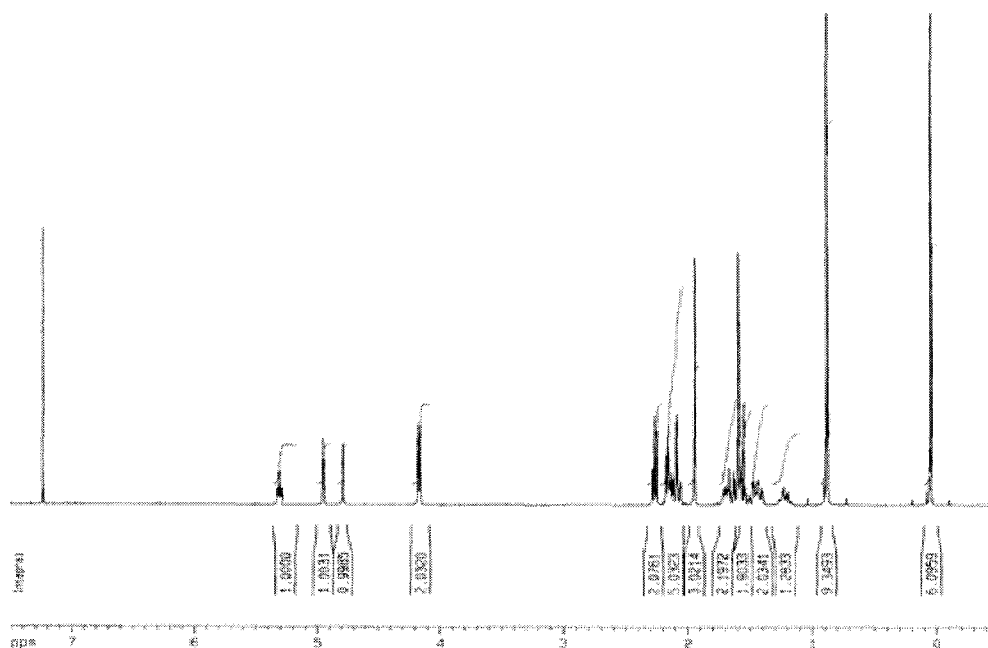


^{13}C NMR (CDCl_3 , 100 MHz)

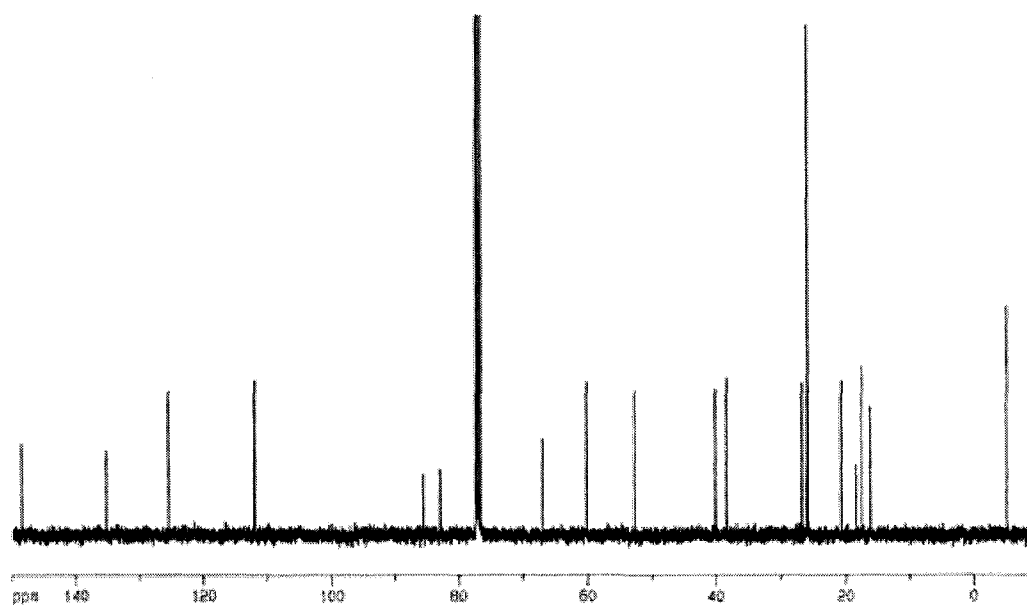


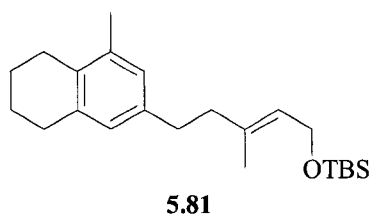


^1H NMR (CDCl_3 , 400 MHz)

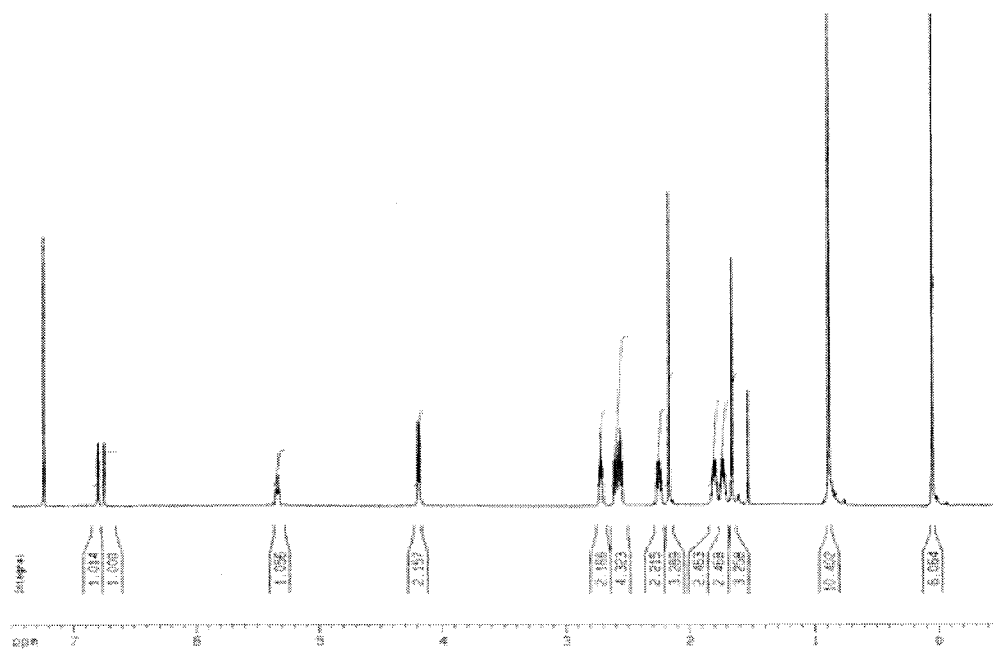


^{13}C NMR (CDCl_3 , 100 MHz)

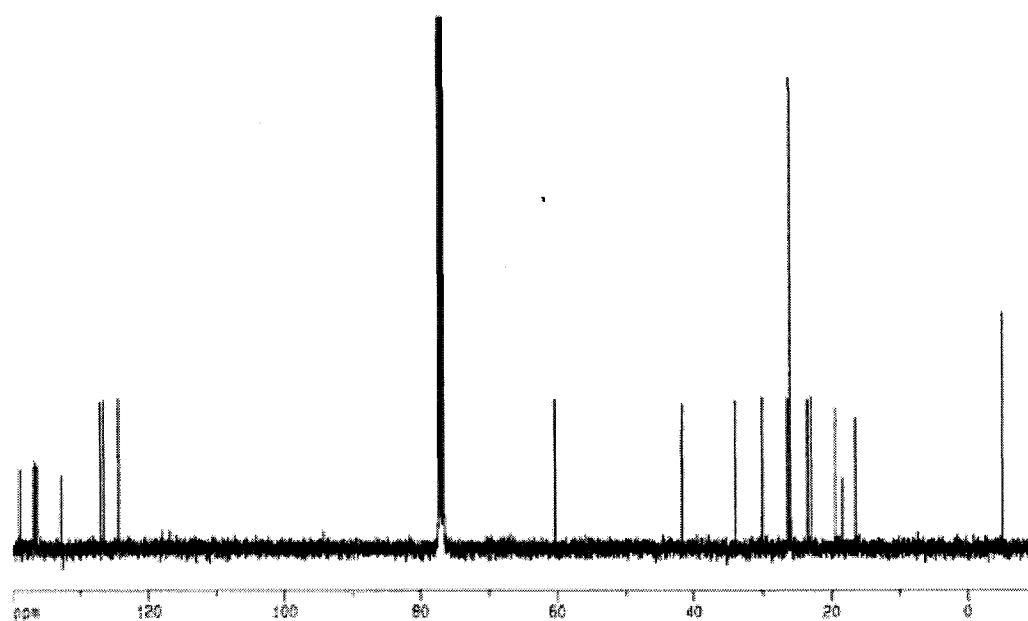


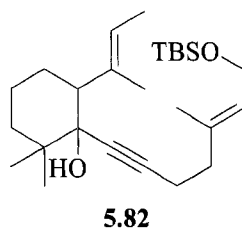


^1H NMR (CDCl_3 , 500 MHz)

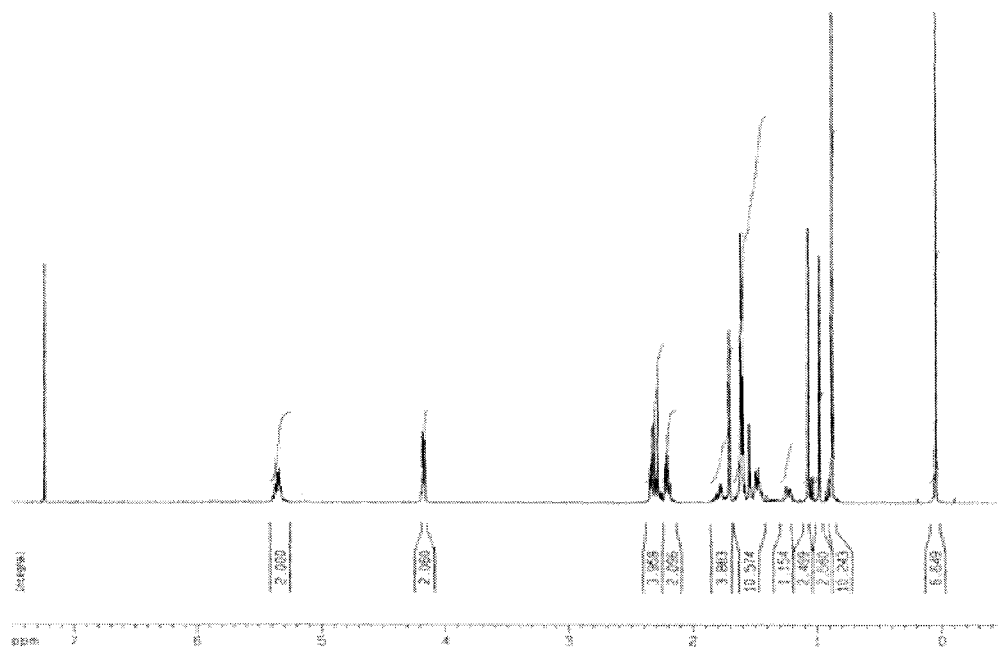


^{13}C NMR (CDCl_3 , 100 MHz)

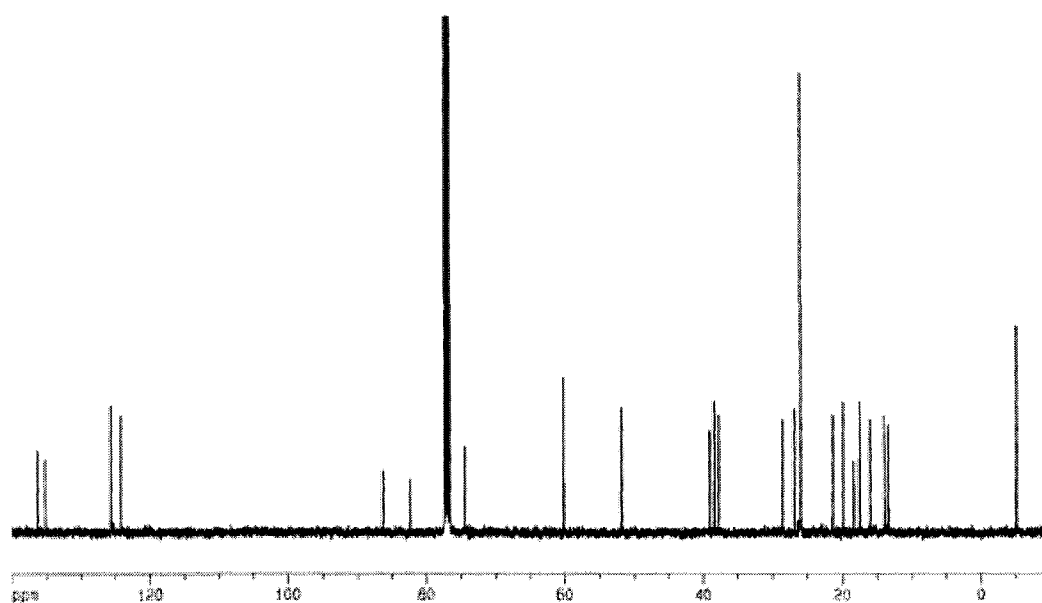


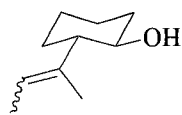


^1H NMR (CDCl_3 , 400 MHz)

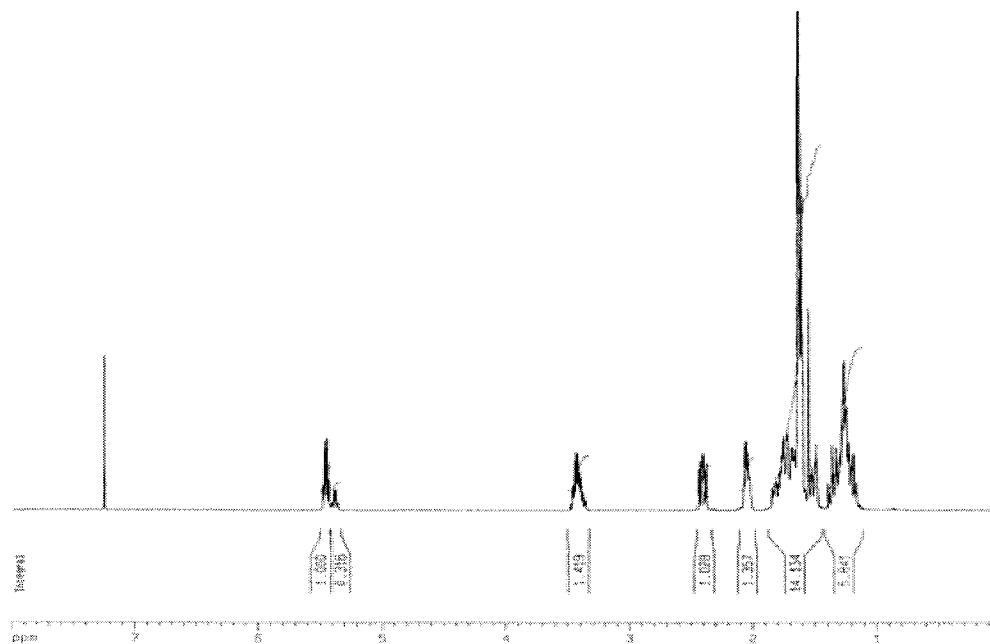
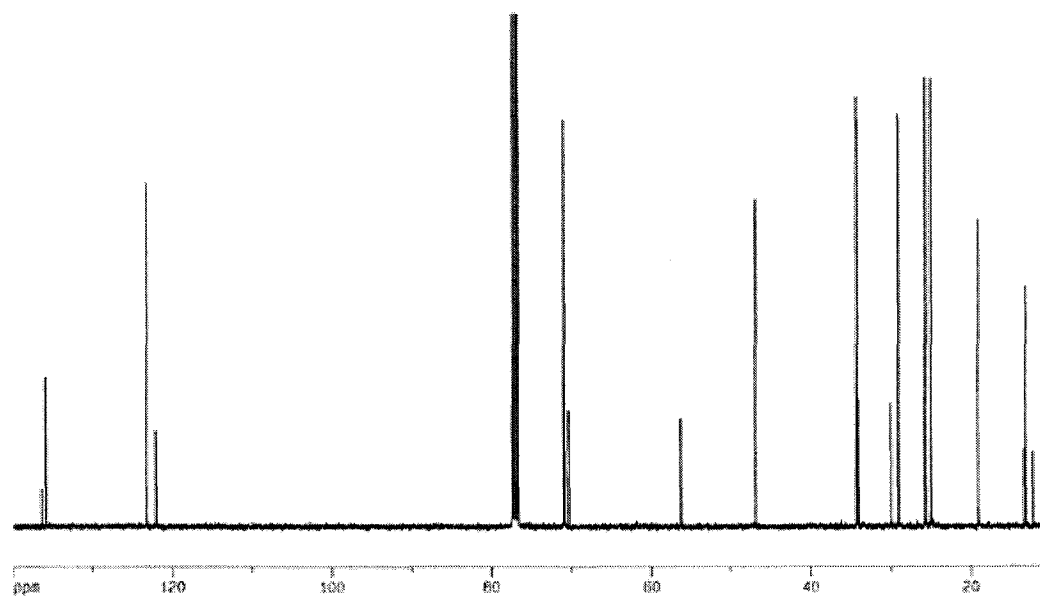


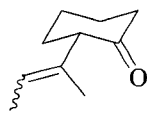
^{13}C NMR (CDCl_3 , 100 MHz)



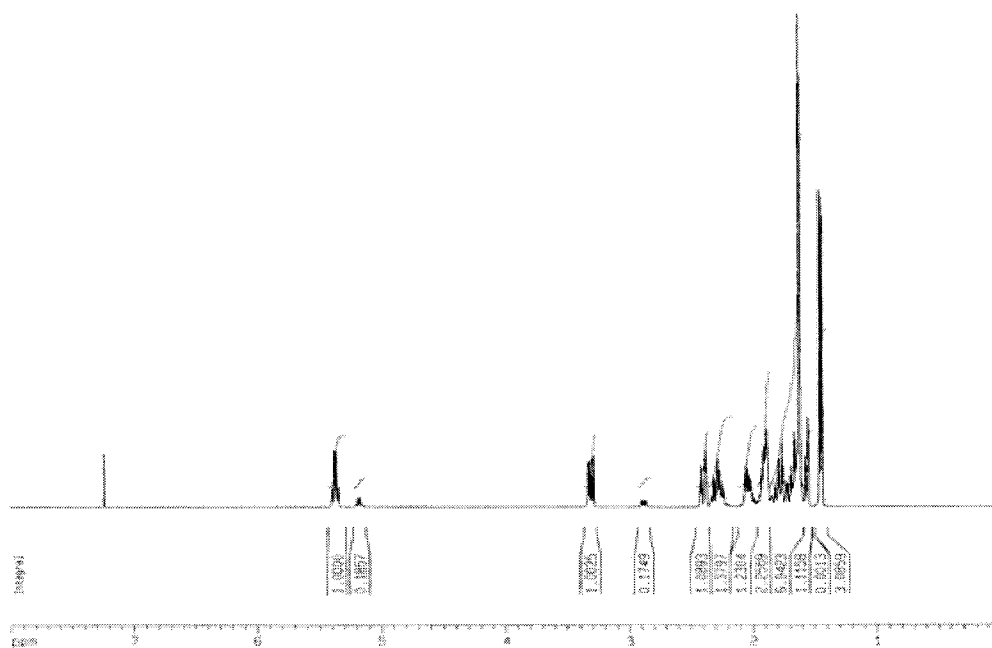
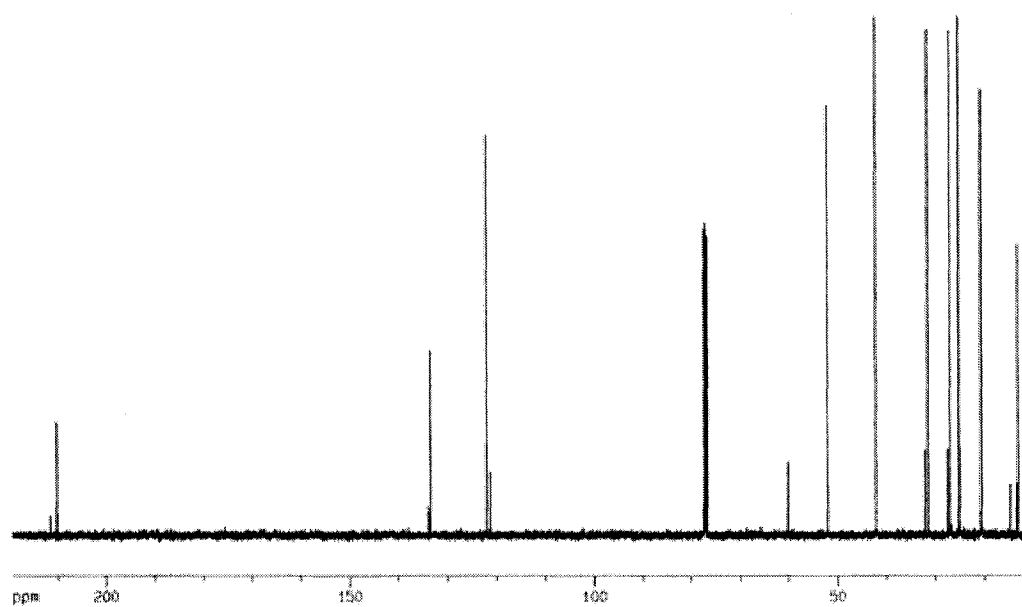


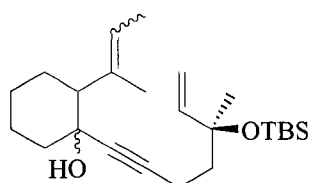
5.85

 ^1H NMR (CDCl_3 , 400 MHz) ^{13}C NMR (CDCl_3 , 100 MHz)

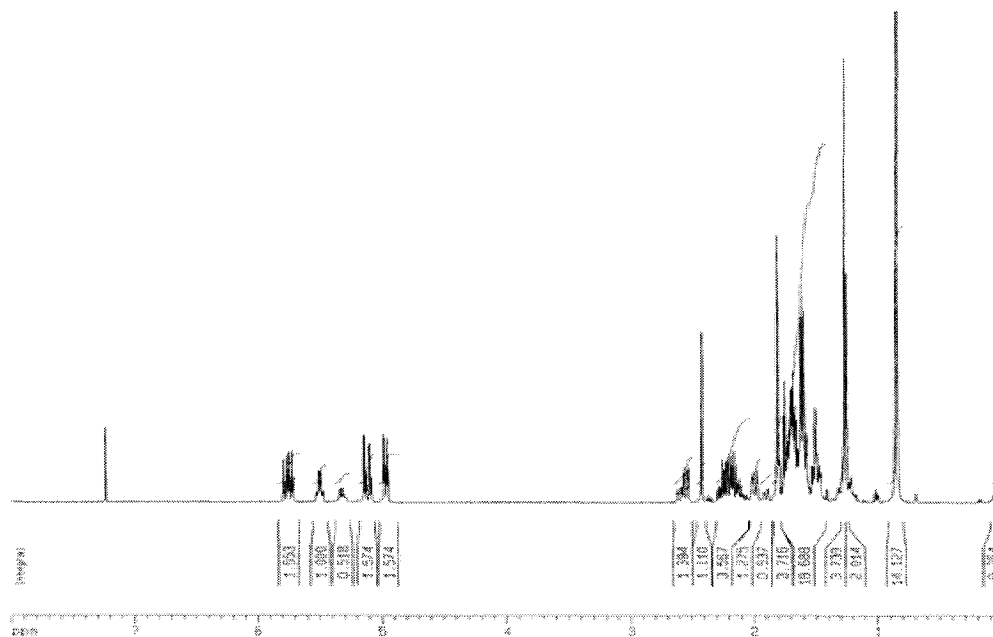
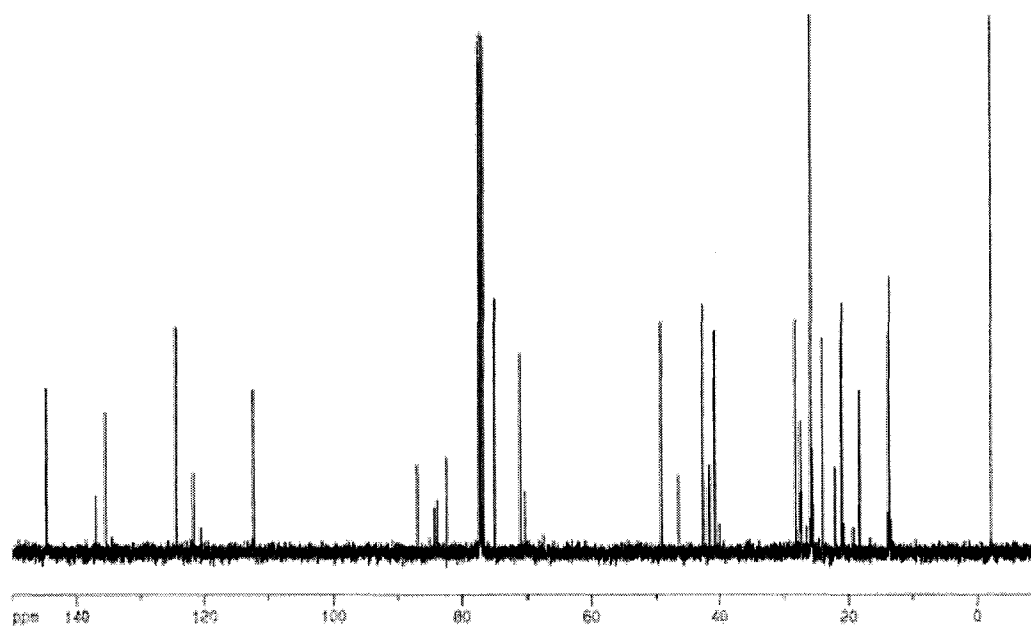


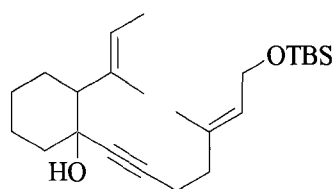
5.86

 ^1H NMR (CDCl_3 , 400 MHz) ^{13}C NMR (CDCl_3 , 100 MHz)

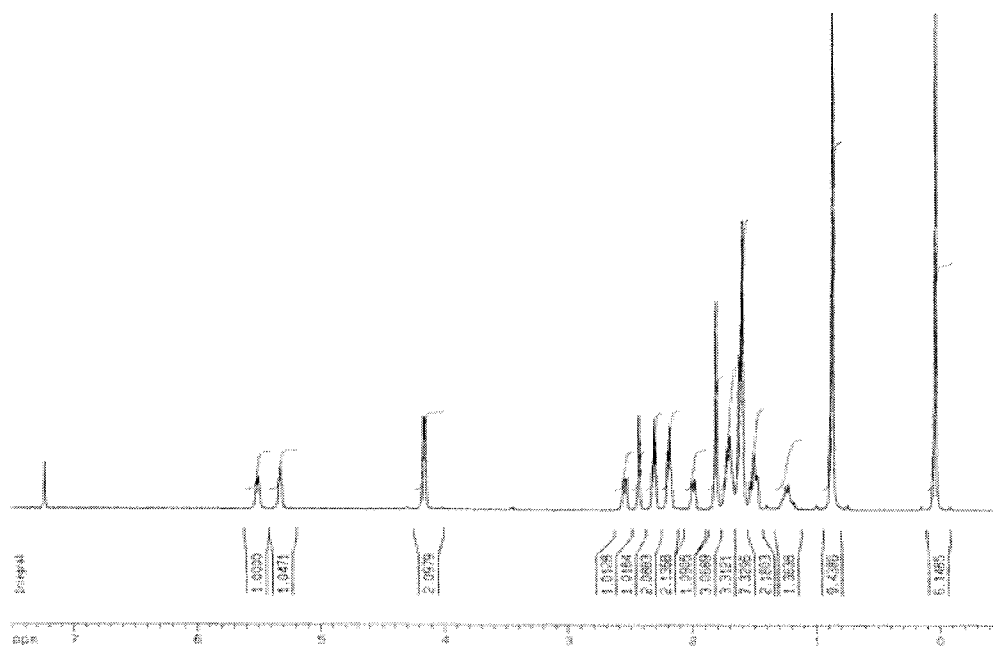


5.87

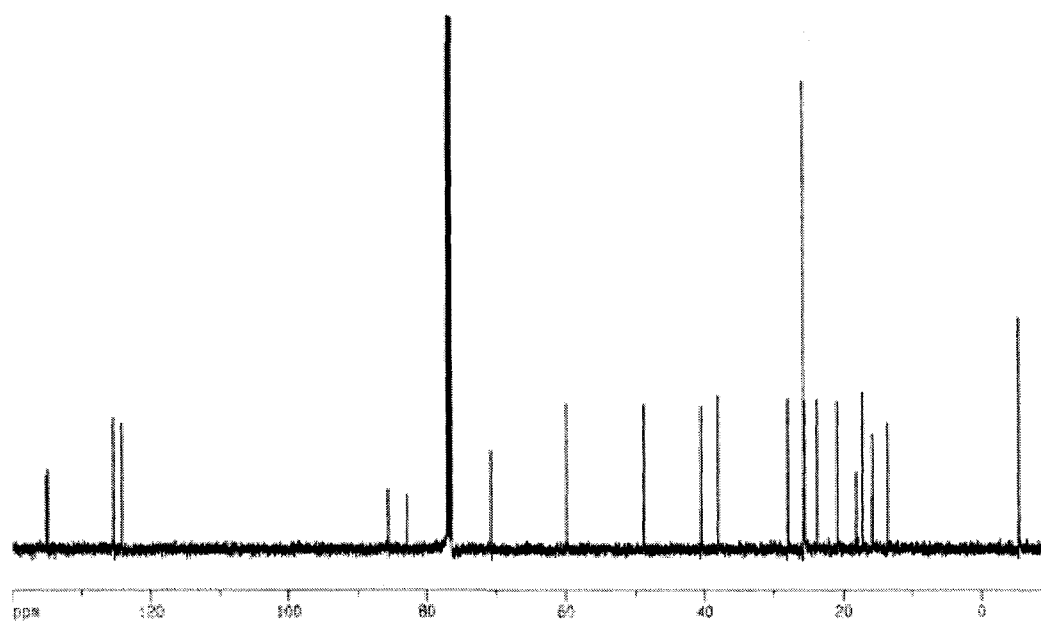
 ^1H NMR (CDCl_3 , 400 MHz) ^{13}C NMR (CDCl_3 , 100 MHz)

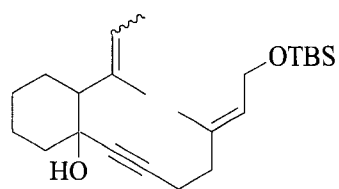
**5.89a**

^1H NMR (CDCl_3 , 500 MHz)

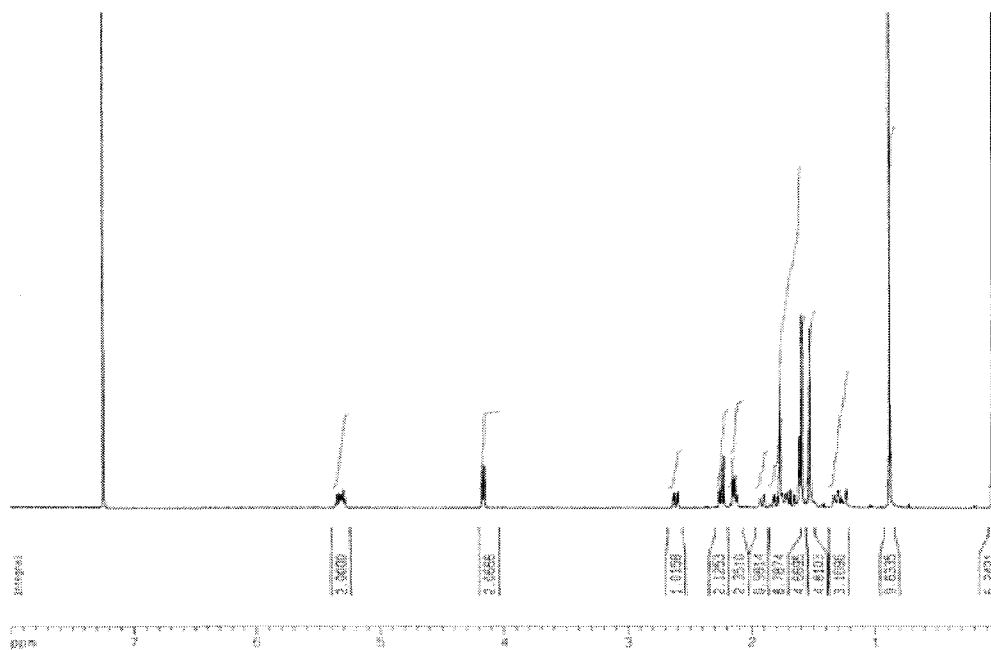


^{13}C NMR (CDCl_3 , 125 MHz)

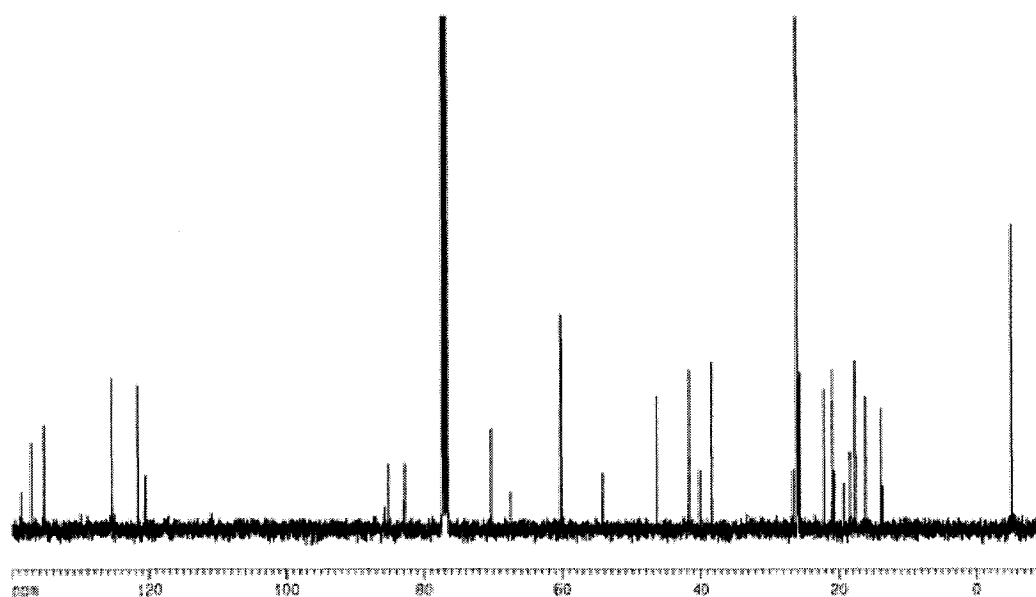


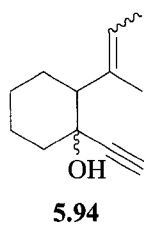
**5.89b**

^1H NMR (CDCl_3 , 400 MHz)

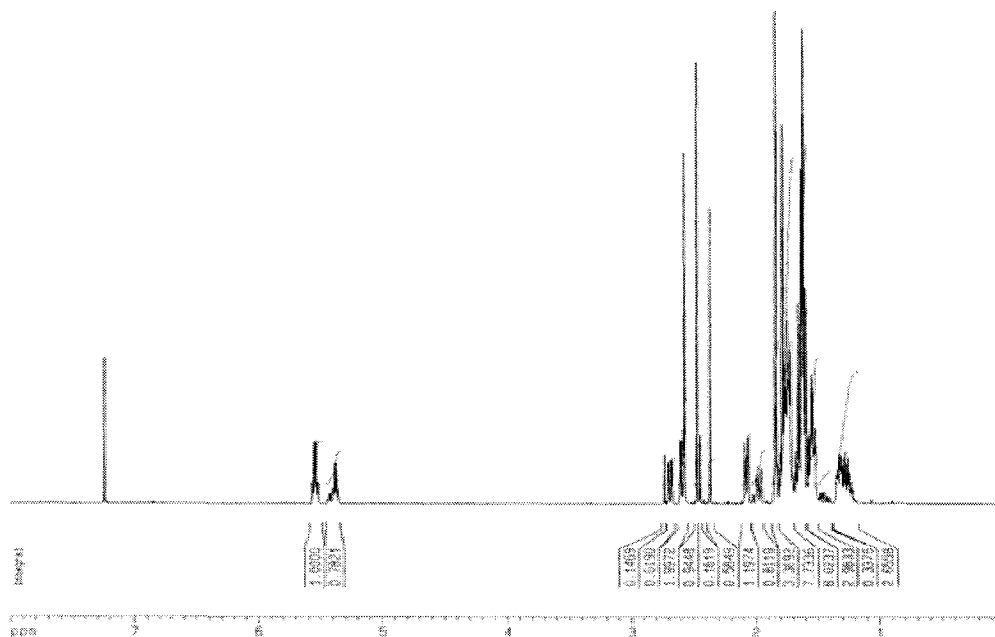


^{13}C NMR (CDCl_3 , 100 MHz)

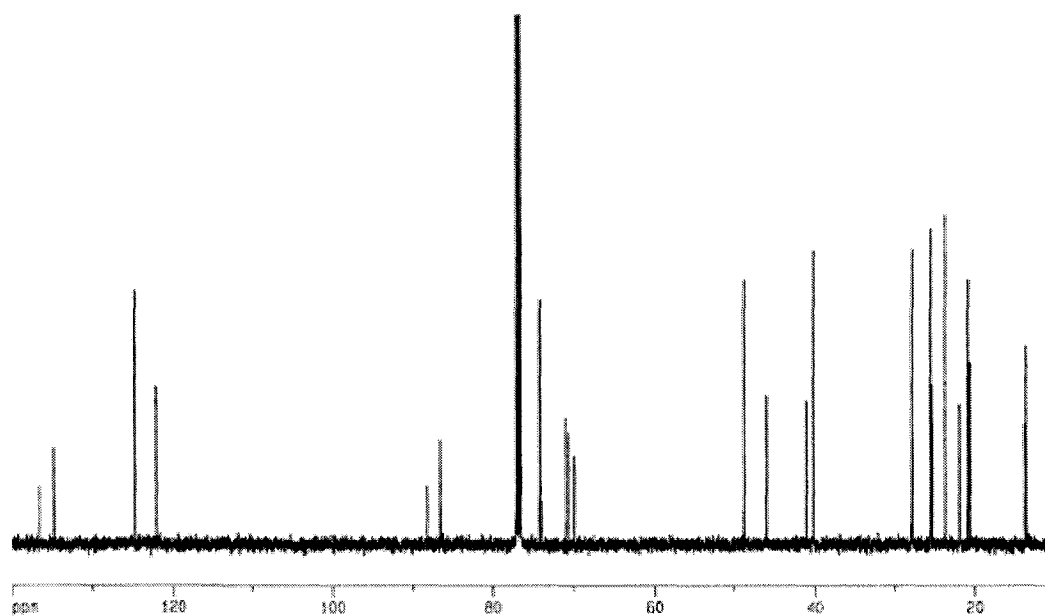


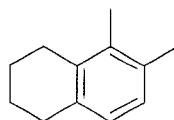


^1H NMR (CDCl_3 , 500 MHz)

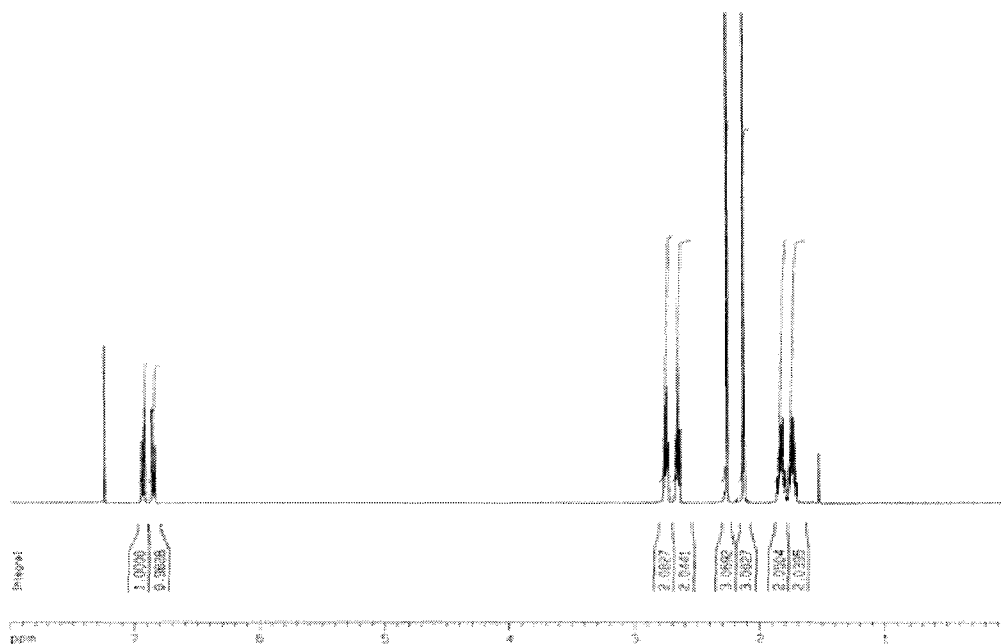
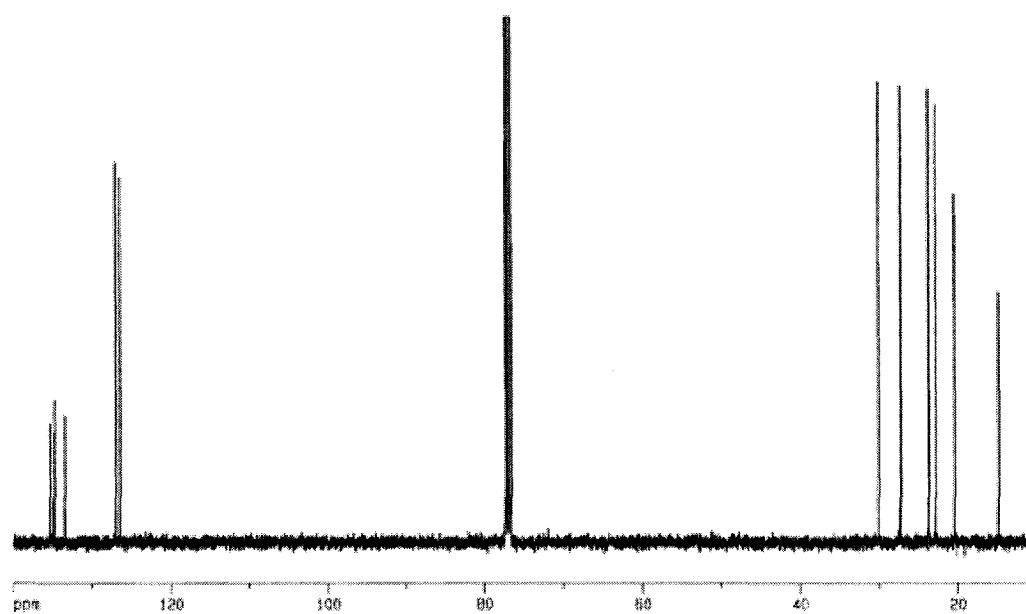


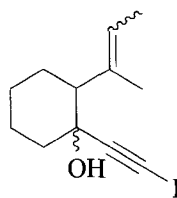
^{13}C NMR (CDCl_3 , 125 MHz)





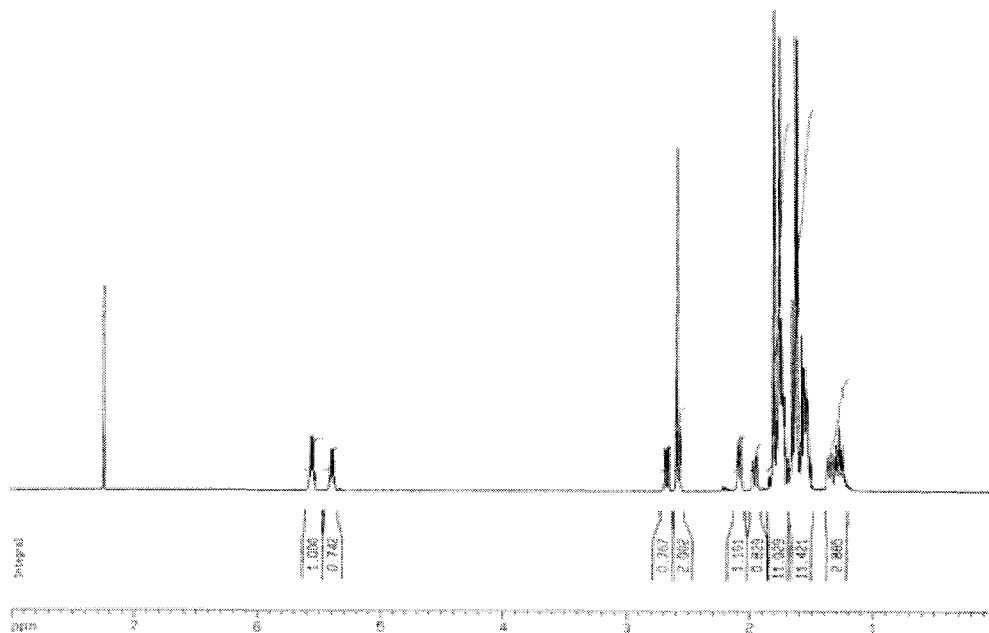
5.95

 ^1H NMR (CDCl_3 , 400 MHz) ^{13}C NMR (CDCl_3 , 100 MHz)

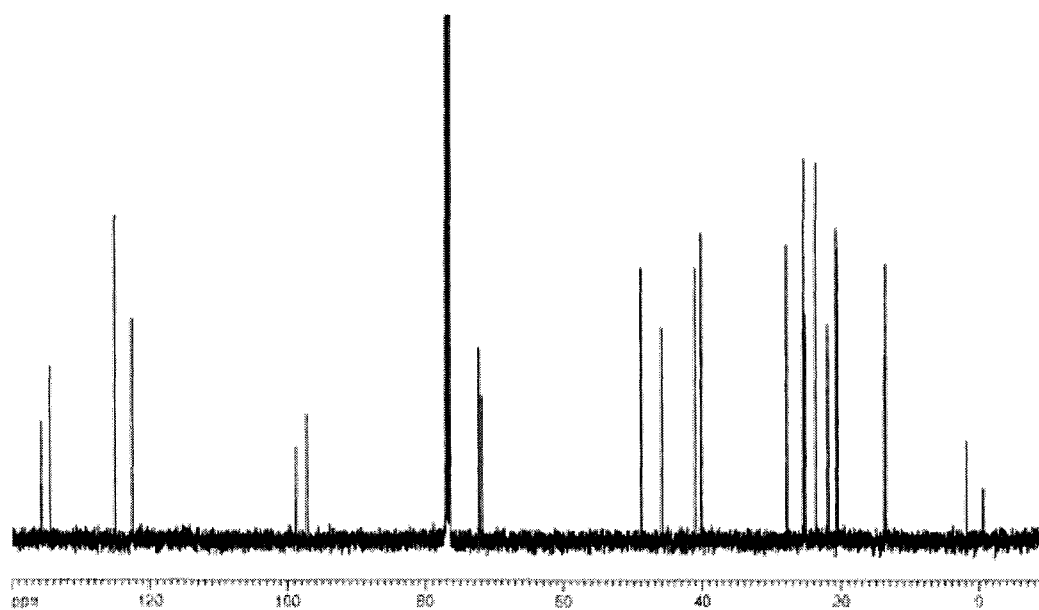


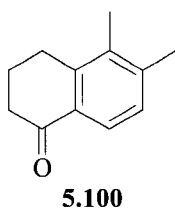
5.98

^1H NMR (CDCl_3 , 500 MHz)

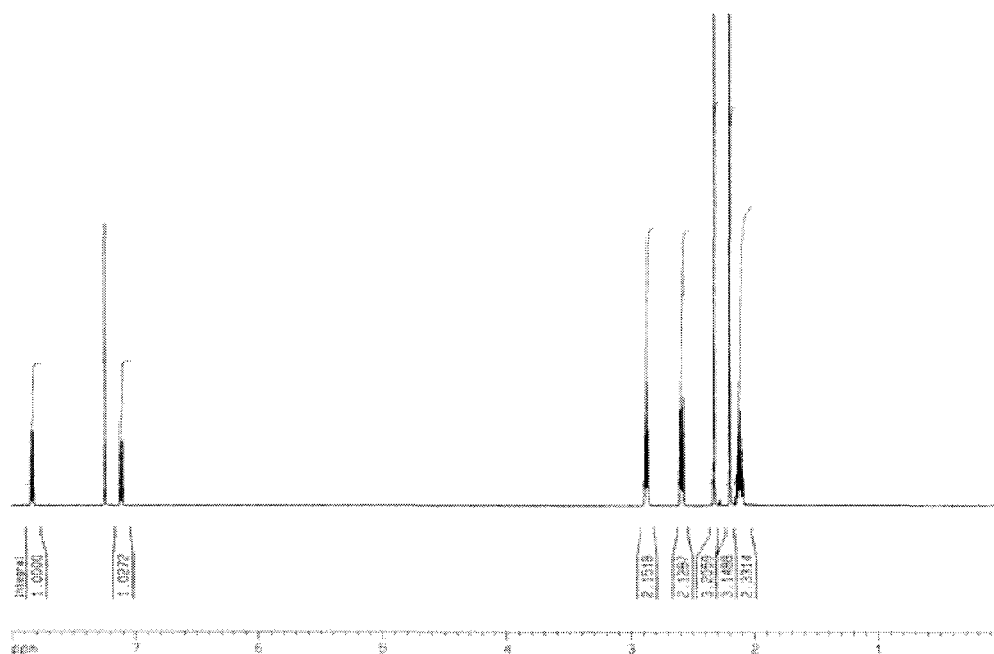


^{13}C NMR (CDCl_3 , 125 MHz)

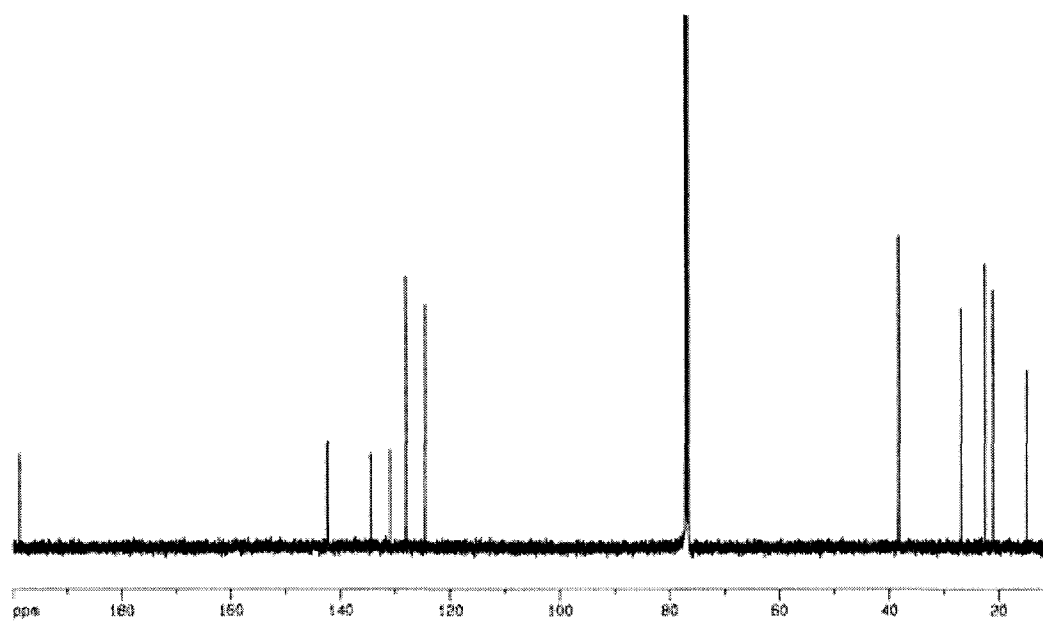


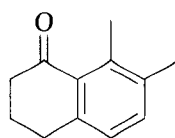
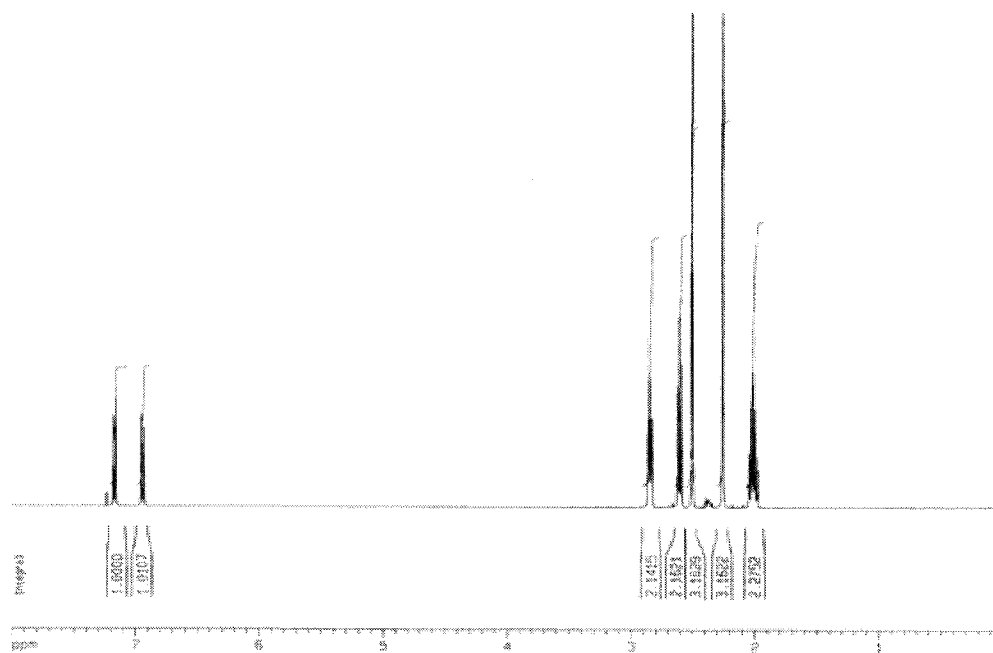
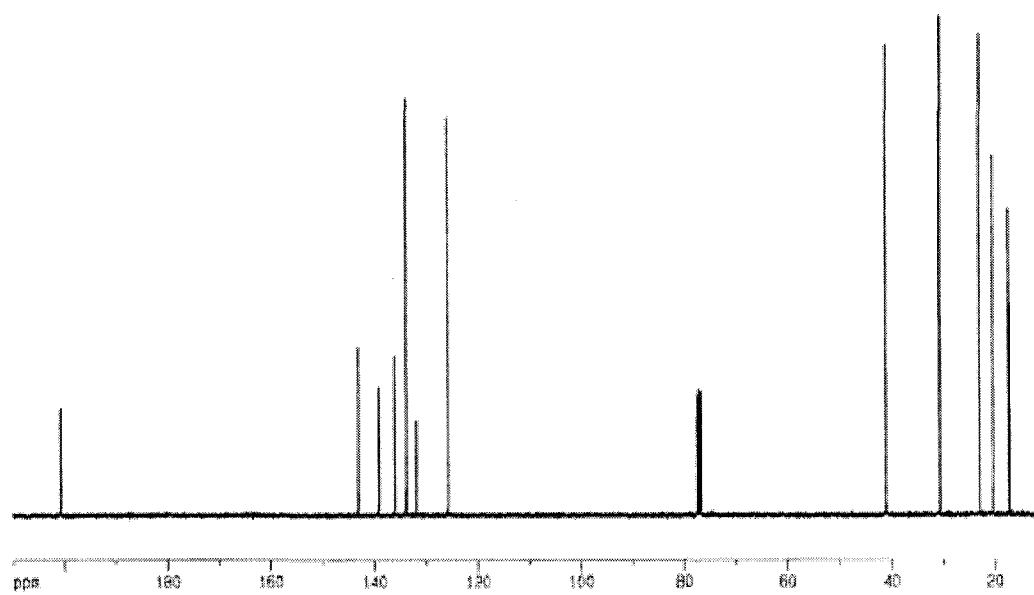


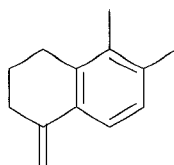
^1H NMR (CDCl_3 , 500 MHz)



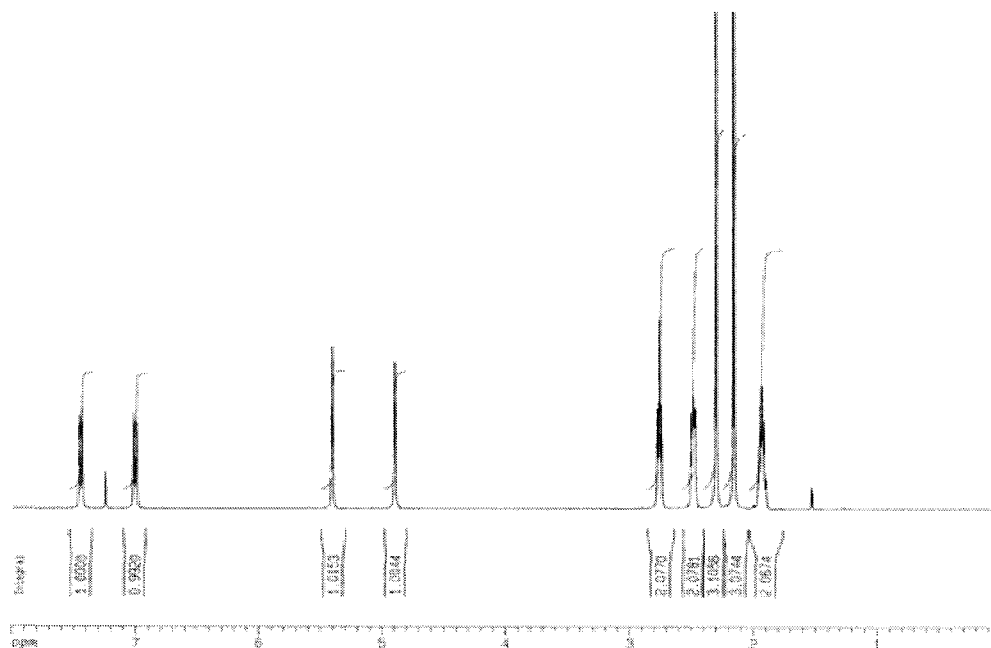
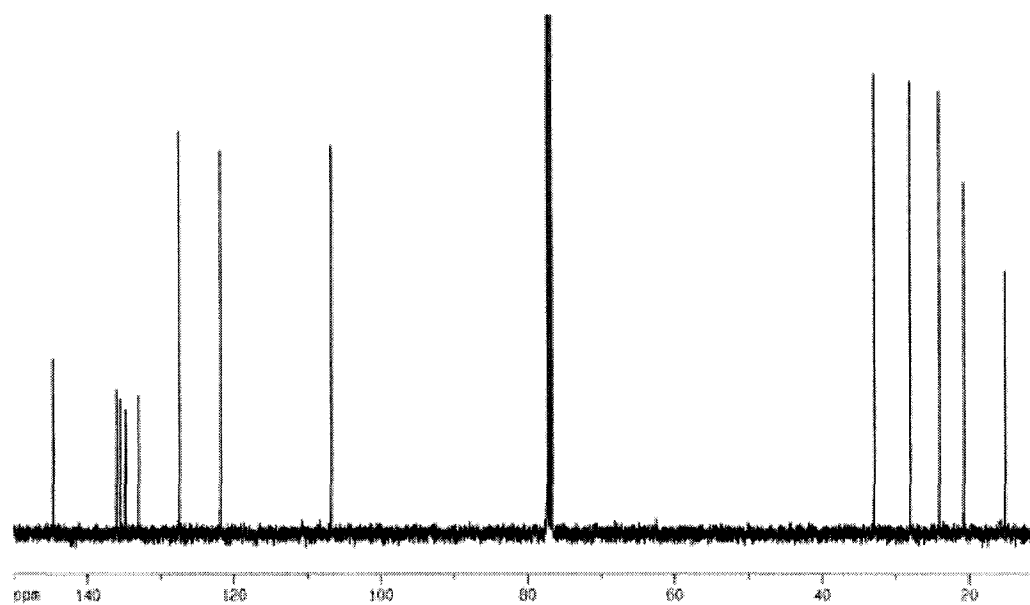
^{13}C NMR (CDCl_3 , 125 MHz)

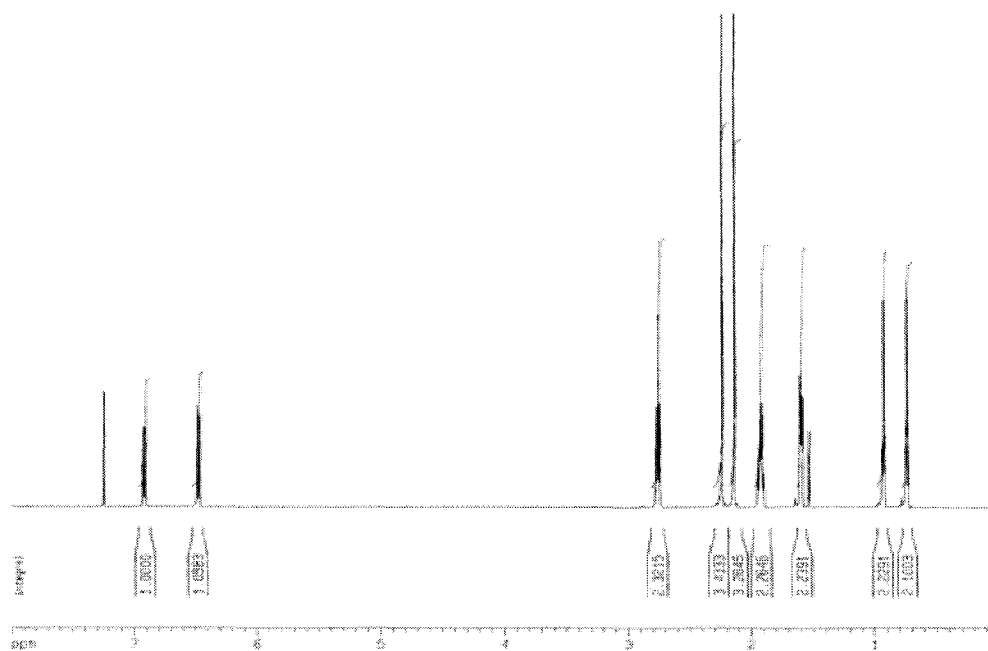


**5.101** **^1H NMR** (CDCl_3 , 400 MHz) **^{13}C NMR** (CDCl_3 , 100 MHz)

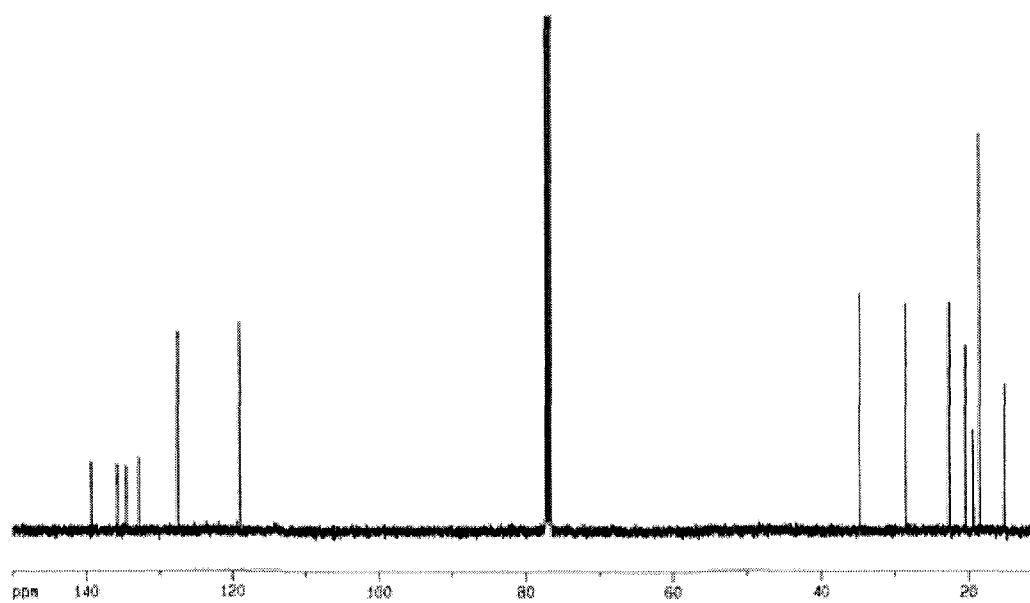


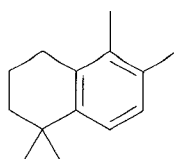
5.102

 ^1H NMR (CDCl_3 , 400 MHz) ^{13}C NMR (CDCl_3 , 100 MHz)

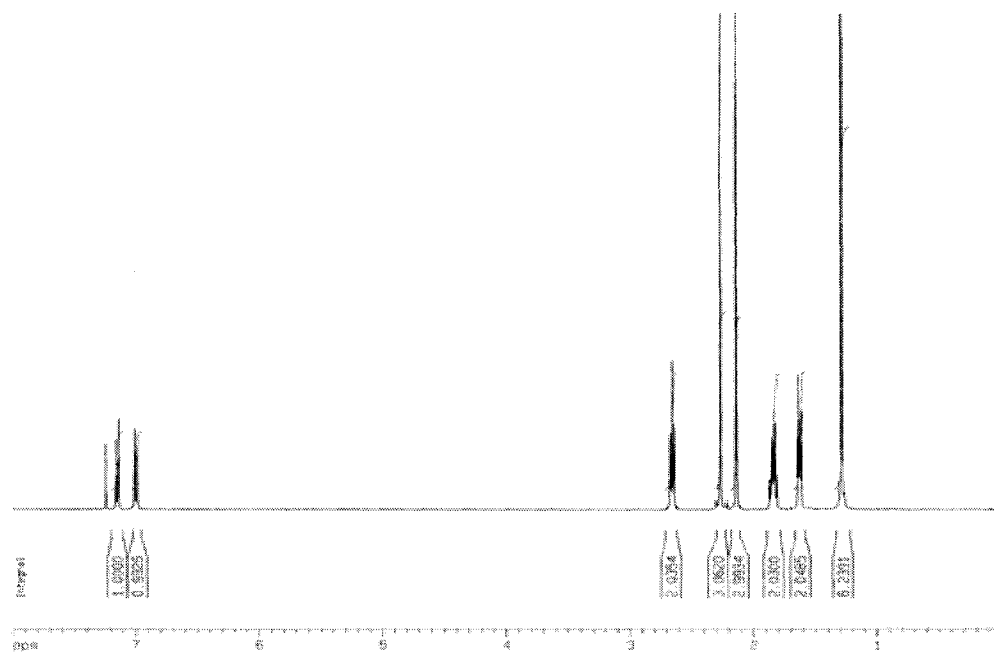
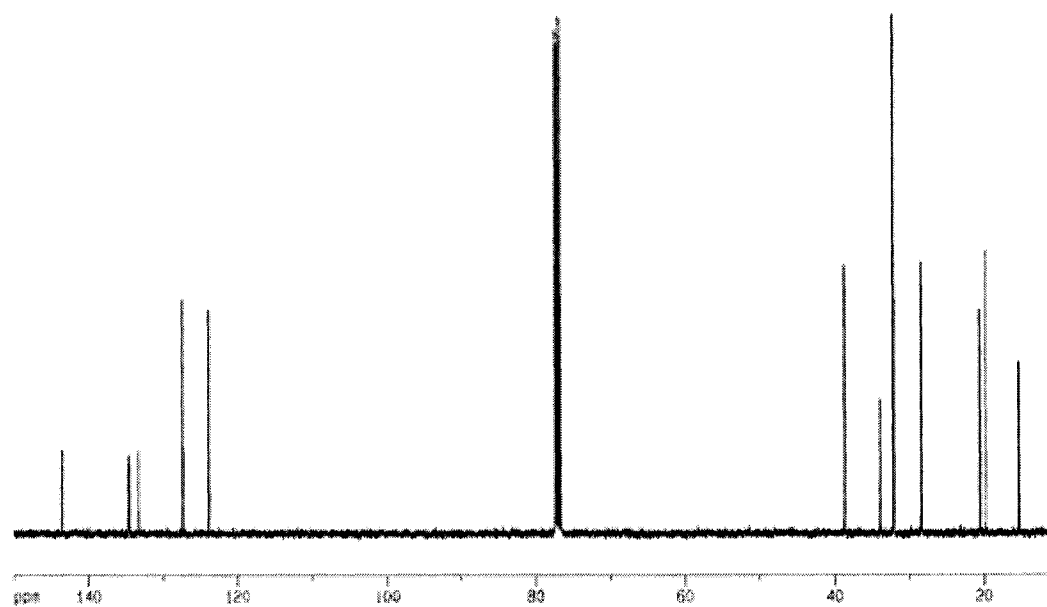
¹H NMR (CDCl₃, 500 MHz)

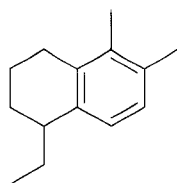
^{13}C NMR (CDCl_3 , 100 MHz)



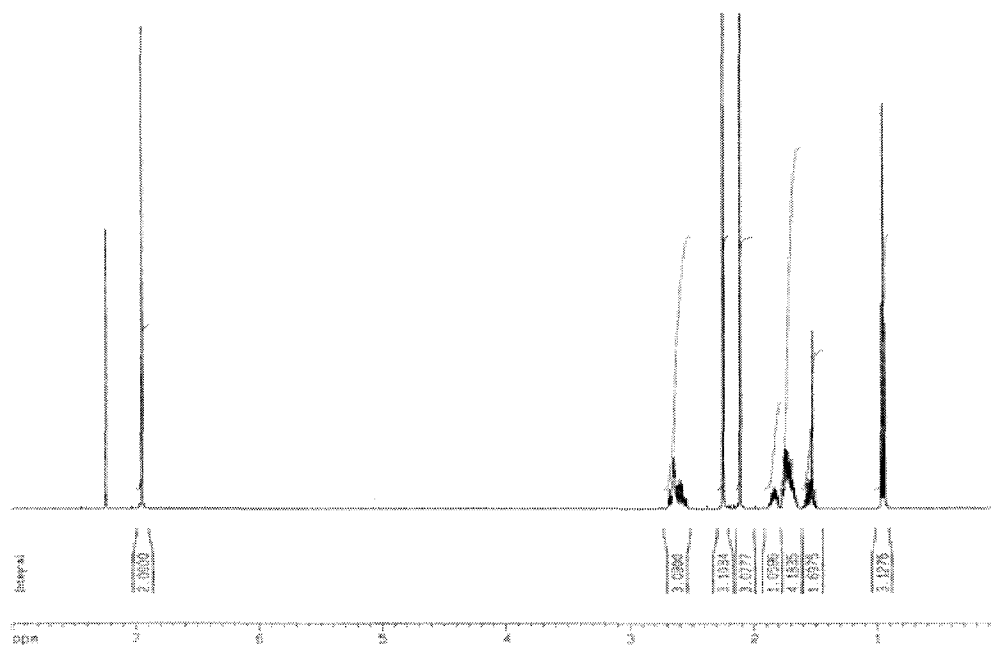
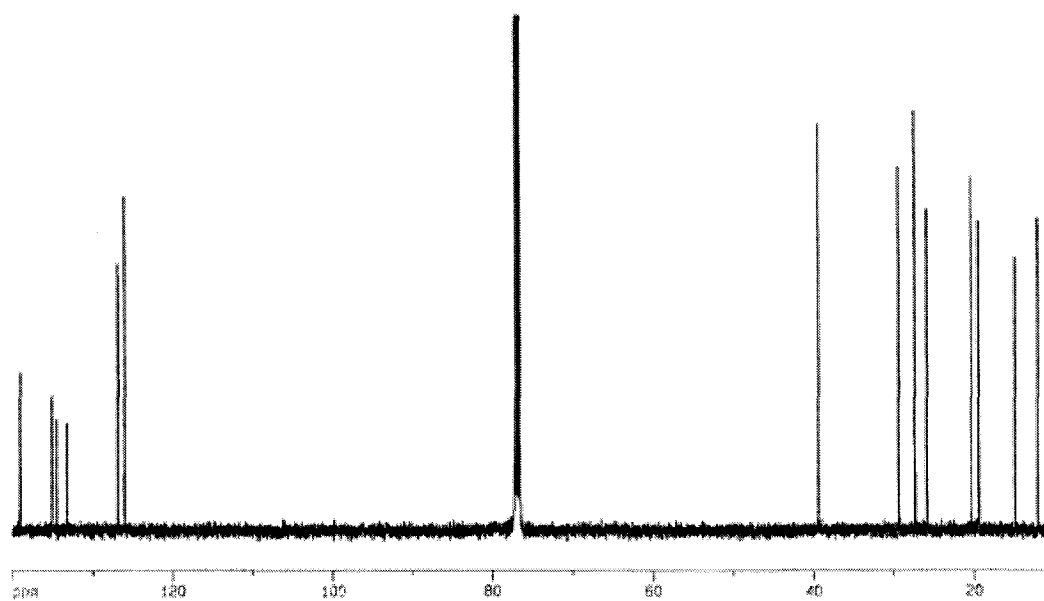


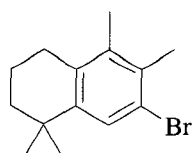
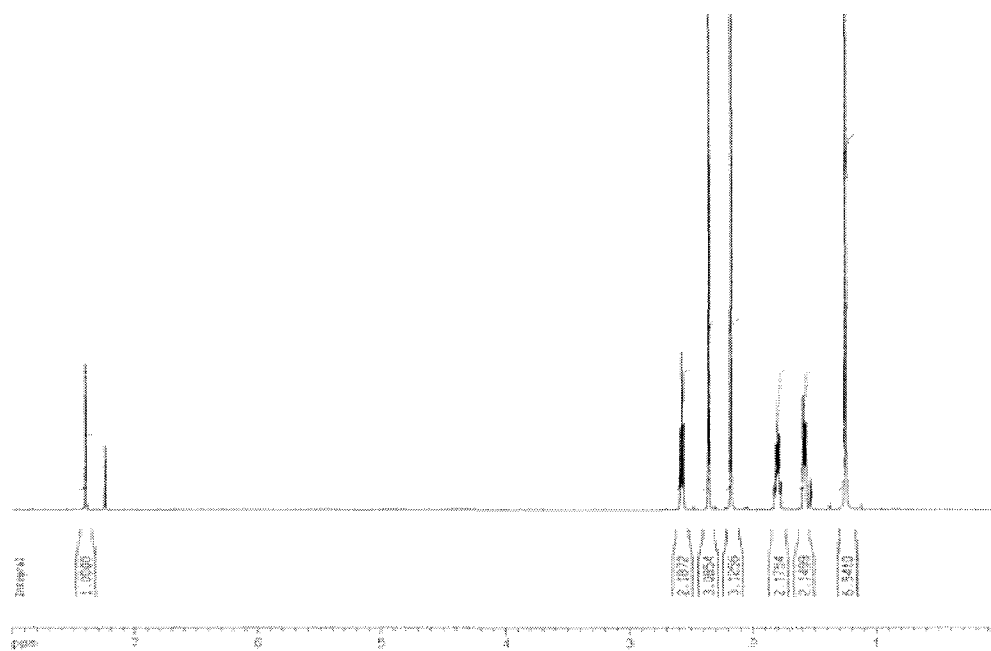
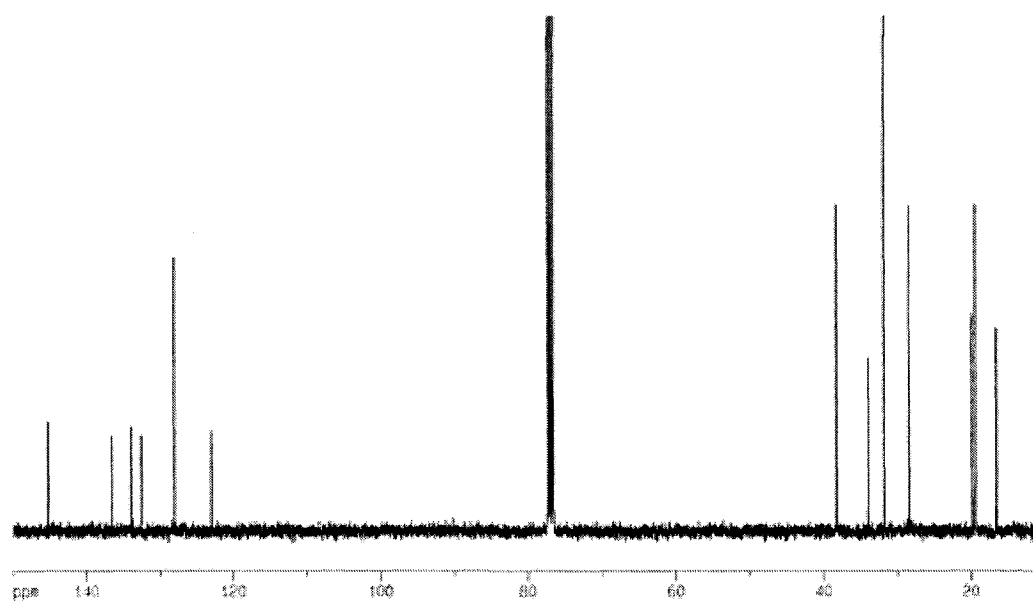
5.104

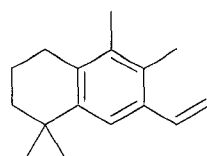
 ^1H NMR (CDCl_3 , 400 MHz) ^{13}C NMR (CDCl_3 , 100 MHz)



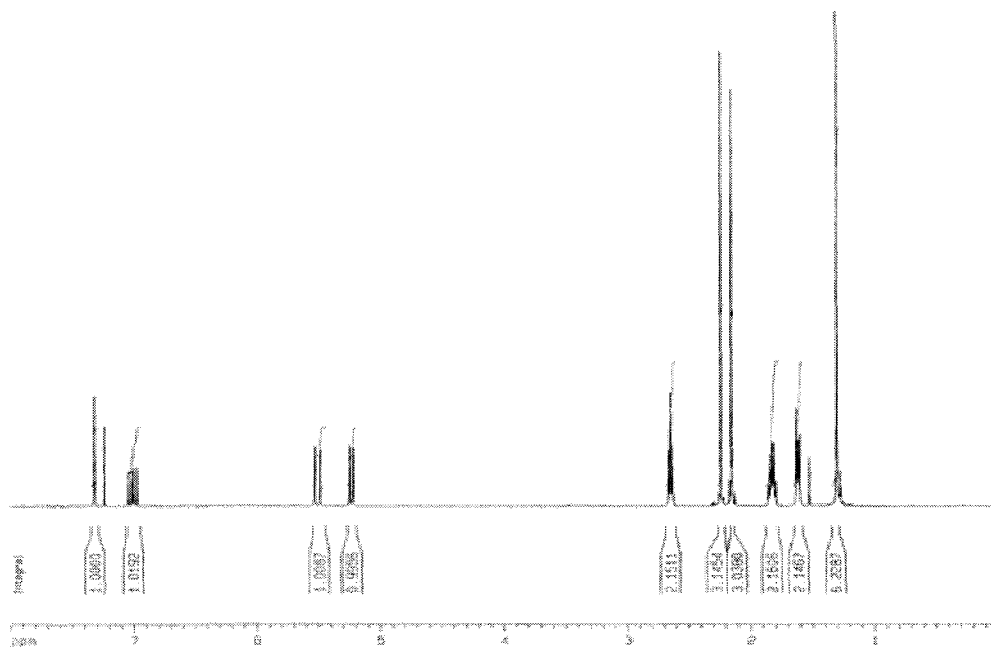
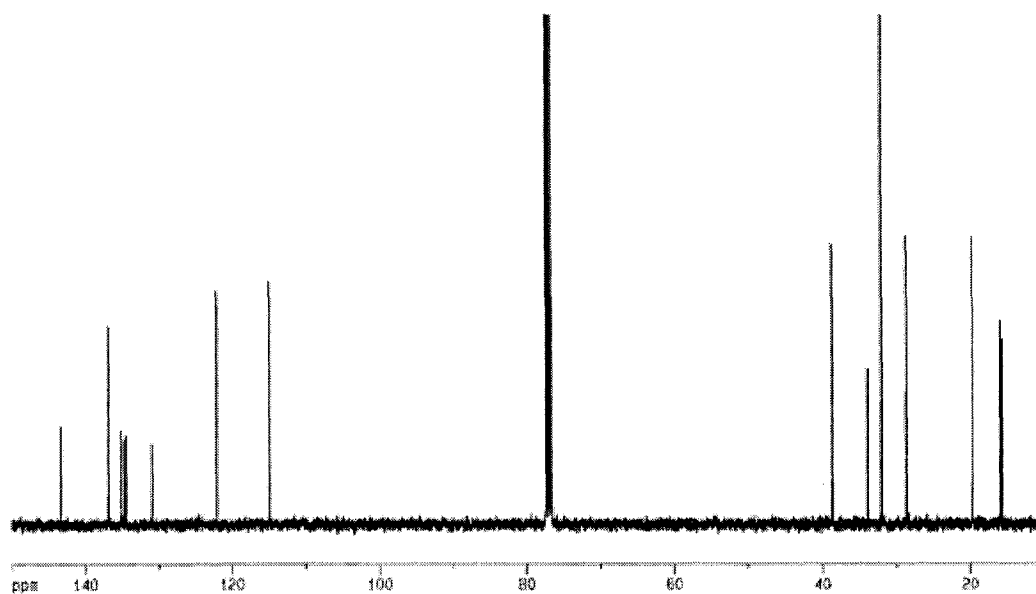
5.105

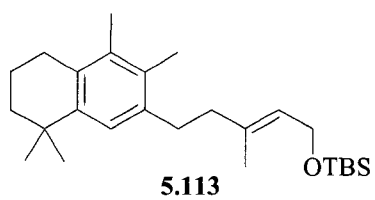
 ^1H NMR (CDCl_3 , 500 MHz) ^{13}C NMR (CDCl_3 , 125 MHz)

**5.106** **^1H NMR** (CDCl_3 , 500 MHz) **^{13}C NMR** (CDCl_3 , 100 MHz)

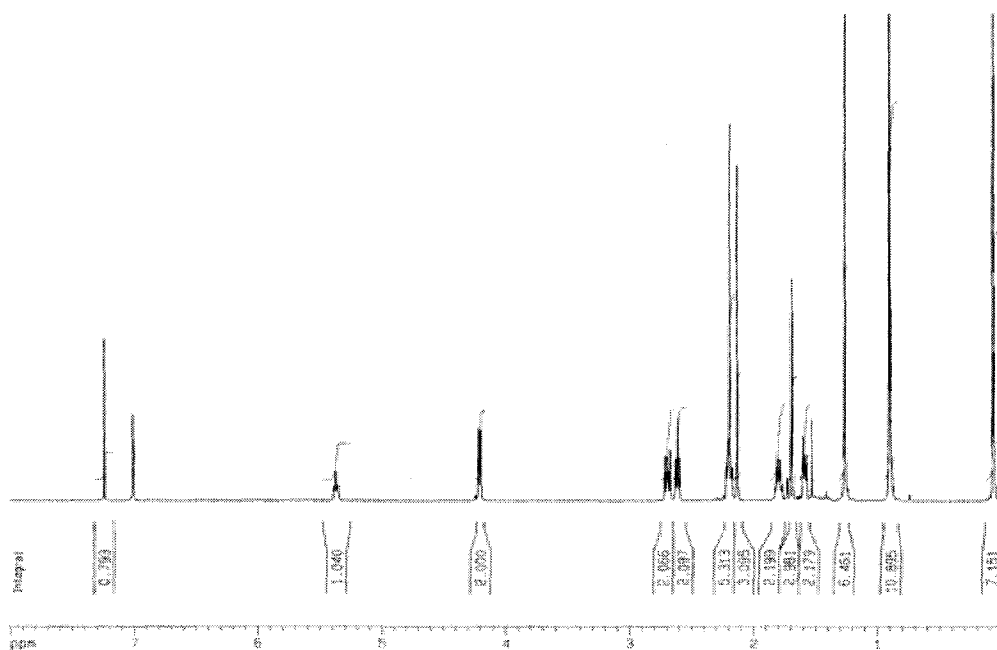


5.107

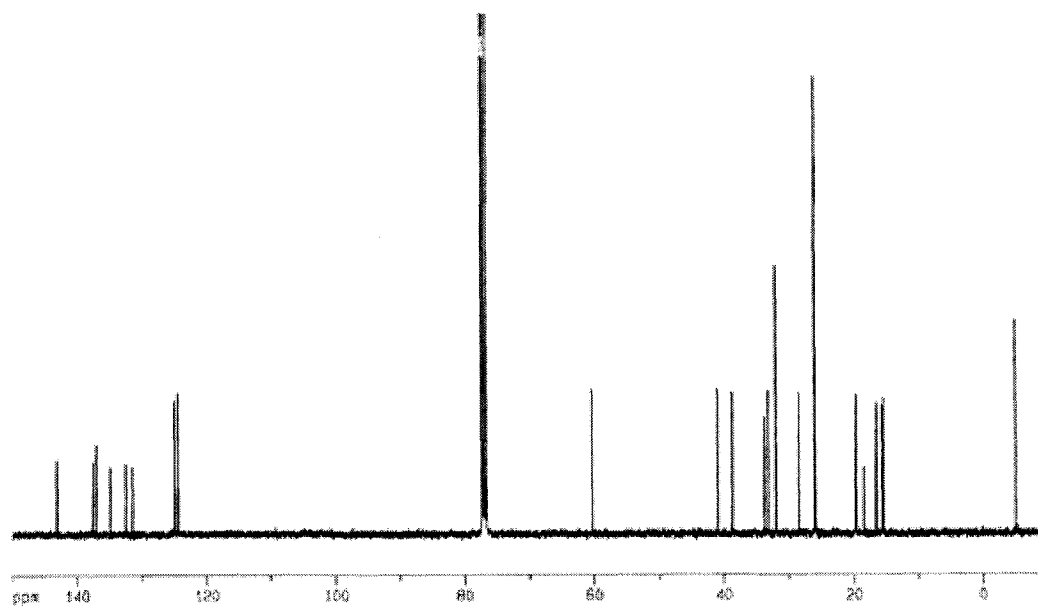
¹H NMR (CDCl₃, 400 MHz)¹³C NMR (CDCl₃, 100 MHz)

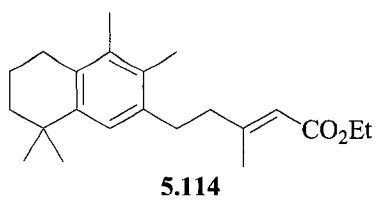


^1H NMR (CDCl_3 , 400 MHz)

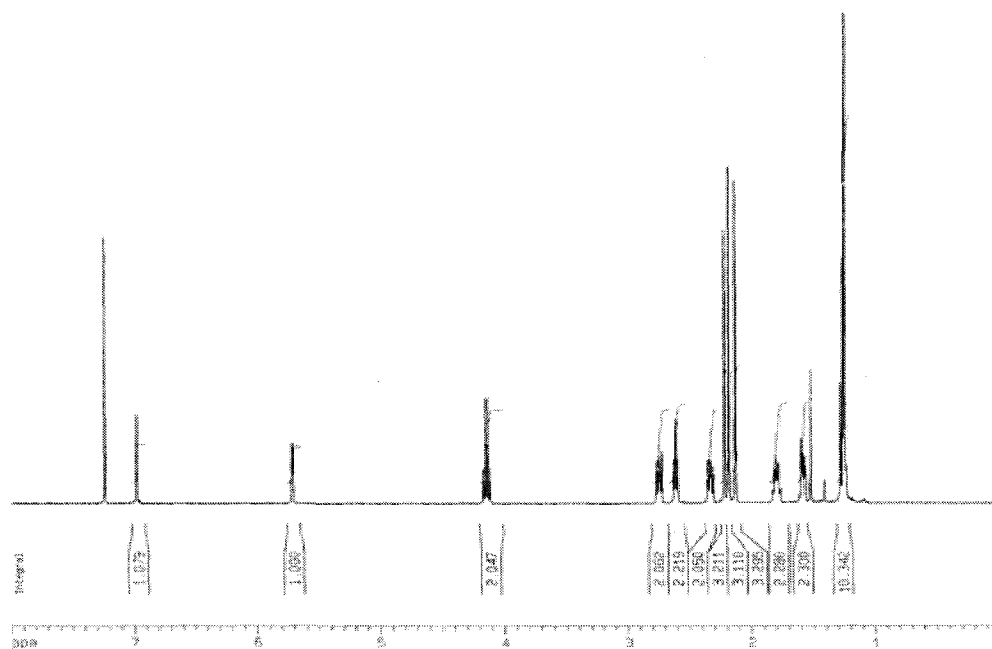


^{13}C NMR (CDCl_3 , 100 MHz)

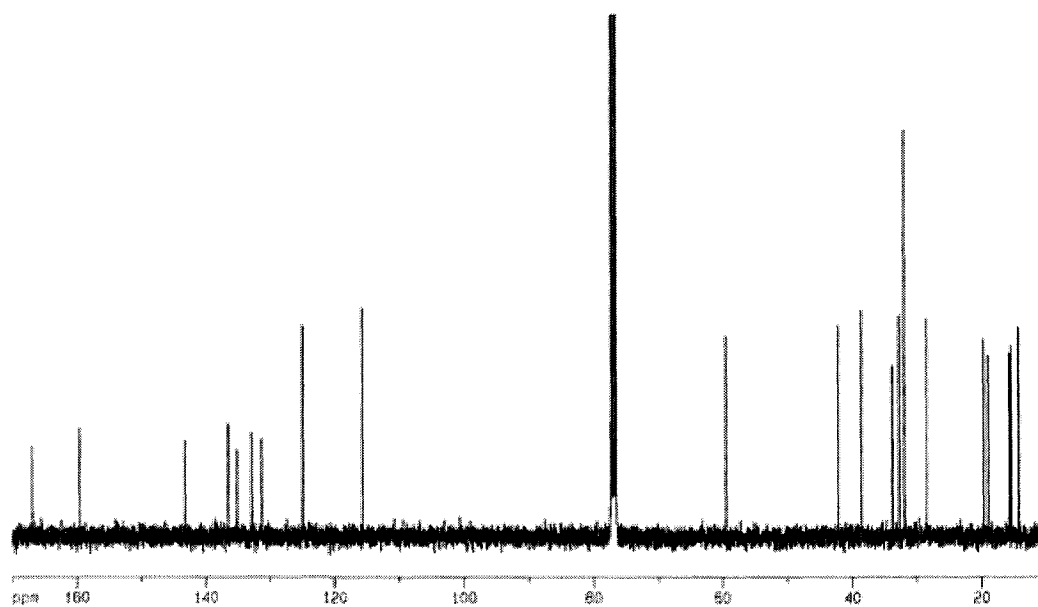


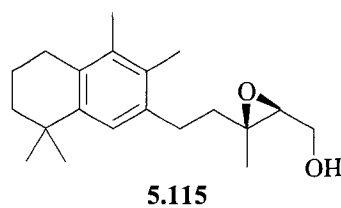


^1H NMR (CDCl_3 , 400 MHz)

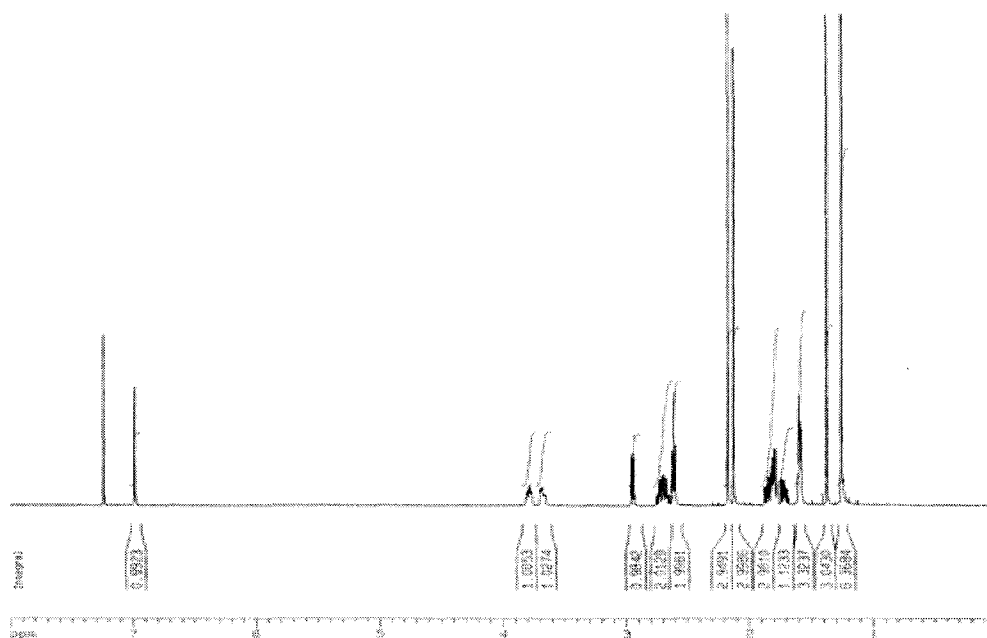


^{13}C NMR (CDCl_3 , 100 MHz)

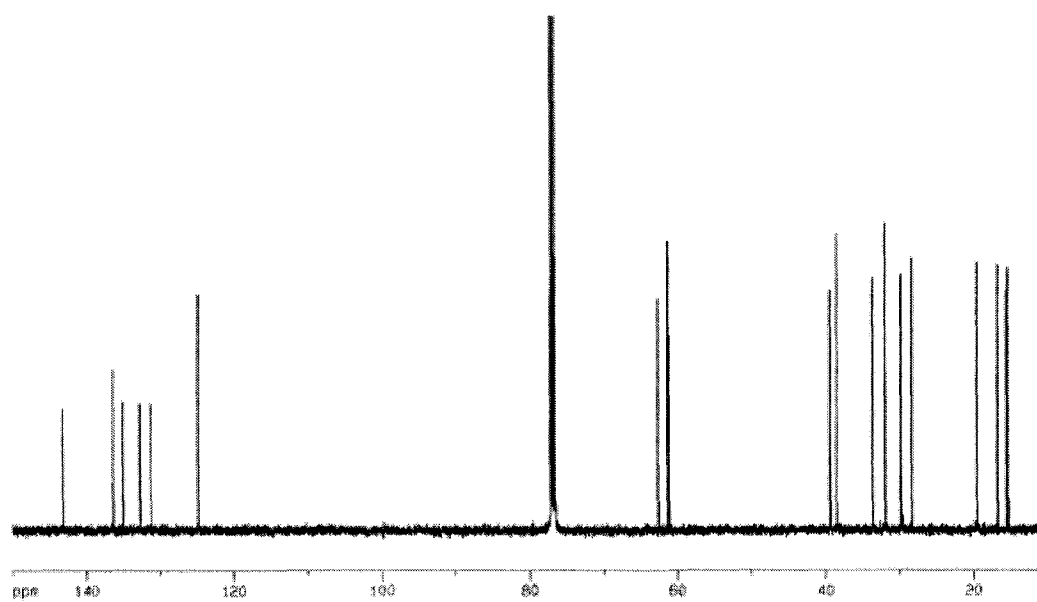


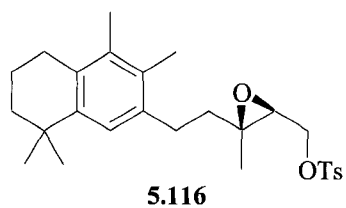


^1H NMR (CDCl_3 , 500 MHz)

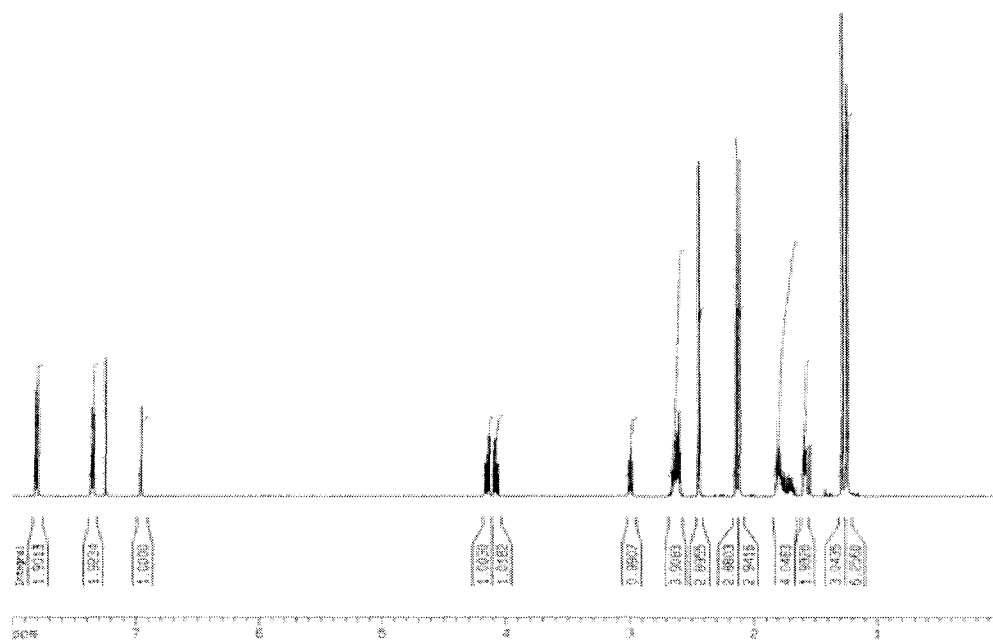


^{13}C NMR (CDCl_3 , 125 MHz)

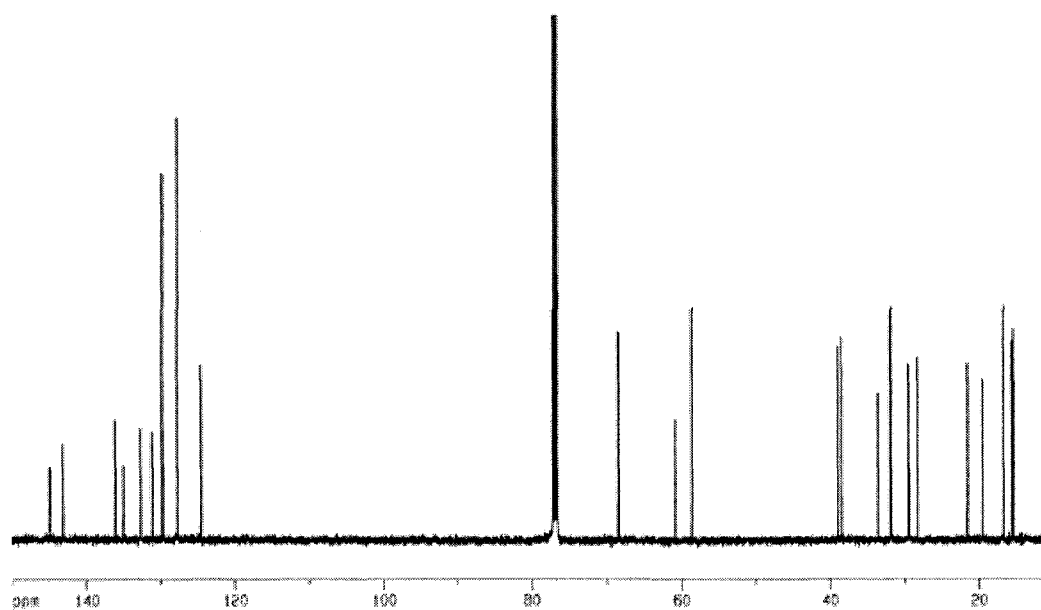


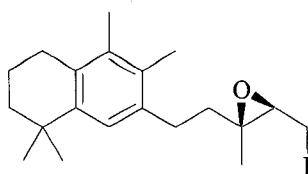


^1H NMR (CDCl_3 , 500 MHz)

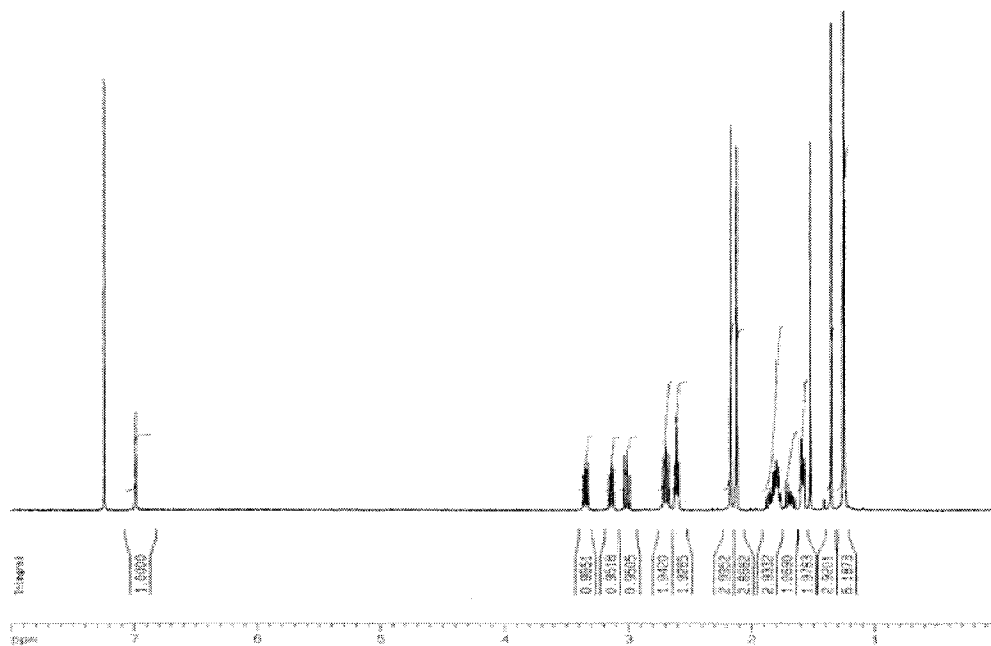


^{13}C NMR (CDCl_3 , 125 MHz)





5.117

 ^1H NMR (CDCl_3 , 500 MHz) ^{13}C NMR (CDCl_3 , 125 MHz)